ENANTIOSELECTIVE REACTIONS OF PALLADIUM ENOLATES

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Dedicated to my daughter

Marie Elise

Abstract

Synthetic efforts directed at preparing certain target molecules highlight deficiencies in the synthetic technology currently available to chemists. Enolates are among the most important synthetic intermediates for synthesis, but general means for enolate functionalizations are not available for many transformations. In order to address these limitations in synthetic technology, novel enantioselective transformations are developed and applied to total syntheses of biologically active natural products.

First, to address the challenge of generating all-carbon quaternary stereocenters, a palladium-catalyzed allylic alkylation reaction is discovered and optimized for allyl enol carbonate and silyl enol ether substrate classes. Certain enolate precursors are not accessible using these substrates, and therefore a method employing racemic allyl β-ketoester substrates is developed. In addition to solving the problem of regiospecific enolate generation, these transformations are conceptually interesting due to the stereoablative enantioconvergent mechanism.

Studies of the mechanism of the above transformation suggest the intermediacy of a chiral palladium enolate. Since enolate functionalization reactions are valuable to synthetic chemistry and general protocols are rare, different electrophiles are explored in addition to the allyl electrophiles used in quaternary center formation. These studies lead to the discovery of enantioselective protonation reactions generating tertiary stereocenters.

To demonstrate the importance of enantioselective enolate functionalization reactions in synthesis, the allylic alkylation reaction is applied in the total synthesis of cassiol and the formal synthesis of platencin.

Enantioselective Reactions of Palladium Enolates

Table of Contents

Abstract iv

Table of Contents v

List of Figures xvi

List of Schemes xxxix

List of Tables xlvii

List of Abbreviations l

CHAPTER 1 ***1***

Natural Products and Pharmaceuticals as Inspiration for the Development of Enantioselective Catalysis

1.1 Introduction 1

1.2 Historical Overview of Enantioselective Methods 2

1.3 Recent Developments in Enantioselective Catalysis 7

1.3.1 β-Enamino Amide Hydrogenations—Januvia® 8

1.3.2 $C(sp^3)$–$C(sp^3)$ Cross-Coupling—Fluvirucinine A_1 12

1.3.3 Intramolecular Heck Cyclizations—Minfiensine 15

1.3.4 Indole Friedel–Crafts Alkylations—Flustramine B 17

1.3.5 Pictet–Spengler Cyclizations—Harmicine 19

1.3.6 Phase Transfer Alkylations—Indacrinone 21

1.3.7 Pd-Catalyzed Enolate Alkylation—Cyanthiwigin F 23

1.3.8 Trimethylenemethane Cyclizations—Marcfortine B 25

1.4 Outlook 28

1.5 Notes and References 30

CHAPTER 2 ***38***

Enantioselective Allylic Alkylations of Ketone Enolates: Catalyst Development and Allyl Enol Carbonate and Silyl Enol Ether Substrates

2.1 Introduction 38

2.2 Screening and Optimization....42

2.2.1 Initial Screening of Chiral Ligands....42

2.2.2 Optimization of Reaction Parameters....44

2.2.3 Fine Tuning of Phosphinooxazoline Ligands....47

2.3 Substrate Scope....52

2.3.1 Asymmetric Allylation of Allyl Enol Carbonates 52

2.3.2 Asymmetric Allylation of Silyl Enol Ethers 52

2.4 Synthetic Applications....59

2.5 Miscellaneous Alkylations Using the Pd•PHOX System....62

2.5.1 Synthesis of Tertiary Stereocenters from Acyclic Enolate Precursors 62

2.5.2 Application of the Pd•PHOX Catalyst System to Propargylation....63

2.5.3 Substrates Proceeding via Weakly Basic Enolates....64

2.6 Summary....65

2.7 Notes and References for Text....67

2.8 Experimental Section 78

2.8.1 Materials and Methods 78

2.8.2 Synthesis of PHOX Ligands 81

2.8.2.1 General Procedures for Synthesis of PHOX Ligands 81

2.8.2.2 Characterization Data for New PHOX Ligands....83

2.8.3 Synthesis of Allyl Enol Carbonates 100

2.8.3.1 General Procedures for the Synthesis of Allyl Enol Carbonates 100

2.8.3.2 Characterization Data for Allyl Enol Carbonates....103

2.8.4 Synthesis of Silyl Enol Ethers 112

2.8.4.1 General Procedure for the Synthesis of Silyl Enol Ethers from Cycloalkanones 112

2.8.4.2 Characterization Data for Cycloalkanone Silyl Enol Ethers 113

2.8.5 Enantioselective Allylic Alkylation Methods 116

2.8.5.1 General Procedures for Asymmetric Tsuji Allylation 116

2.8.5.2 Characterization Data for Ketones Prepared by Enantioselective Alkylation 119

2.8.5.3 Procedure for Asymmetric Propargylation 128

2.8.5.4 Methods for Determination of Enantiomeric Excess 129

2.8.6 Preparation and Characterization of Derivatives 131

2.8.6.1 Preparation and Characterization of Semicarbazone Derivatives 131

2.8.6.2 X-Ray Structures of Semicarbazones **161** and **162** 134

2.8.6.3 Preparation and Characterization of α-Quaternary Ketone Derivatives 140

2.8.7 Preparation and Characterization of [(PHOX)Pd(allyl)][PF_6] Salt 147

2.8.8 Notes and References for Experimental Section 152

APPENDIX 1 ***155***

Spectra Compounds Relevant to Chapter 2

CHAPTER 3 ***312***

Enantioselective Allylic Alkylations of Ketone Enolates: β-Ketoester Substrates

3.1 Introduction 312

3.2 Asymmetric Alkylation with Racemic Allyl β-Ketoesters 314

3.2.1 Initial Explorations 314

3.2.2 Substrate Syntheses 317

3.2.3 Results of Enantioselective Ketone Alkylation with Allyl β-Ketoester Substrates 319

3.2.4 Cascade Reactions Generating Multiple Quaternary Stereocenters 322

3.2.5 Substrates Containing Five-Membered Rings 323

3.3 Mechanistic Insights 324

3.3.1 The Outer-Sphere Mechanism Proposed by Helmchen 324
3.3.2 Experimental Evidence Consistent with an Inner-Sphere Mechanism 326
3.4 Summary 338
3.5 Notes and References for Text 339
3.6 Experimental Section 350
3.6.1 Materials and Methods 350
3.6.2 Substrate Compounds 352
3.6.2.1 General Procedures for the Synthesis of Allyl β-Ketoesters 352
3.6.2.2 Characterization Data for β-Ketoester Substrates 356
3.6.3 Enantioselective Alkylations 387
3.6.3.1 General Procedure for Enantioselective Decarboxylative Alkylation 387
3.6.3.2 Characterization Data for Ketone Products 388
3.6.3.3 Methods for Determination of Enantiomeric Excess 410
3.6.3.4 Allylation with a Substituted Allyl Carbonate 413
3.6.4 Mechanistic Experiments 414
3.6.4.1 Nonlinear Experiments 414
3.6.4.2 Kinetics Experiments 416
3.6.4.3 Deuterium Labeling Experiments 420
3.6.4.4 ^{31}P NMR Studies 427
3.6.5 Notes and References for Experimental Section 444

APPENDIX 2 ***446***

Spectra Compounds Relevant to Chapter 3

CHAPTER 4 ***585***

Computational Study of the Mechanism of the Enantioselective Tsuji Allylation

4.1 Introduction 585

4.2 Mechanistic Experiments and Computations 588
4.3 Notes and References for Text 591
4.4 Experimental Section 594
4.4.1 Materials and Methods 594
4.4.2 Experimental Procedures for Allylic Alkylation 595
4.4.3 Atomic Coordinates for Calculated Complexes 599
4.4.4 Notes and References for Experimental Section 617

CHAPTER 5 ***618***

Enantioselective Tsuji Allylations

5.1 Introduction 618
5.1.1 Background and Significance 618
5.1.2 History 620
5.2 Allyl Enol Carbonates 622
5.2.1 Synthesis of Cyclic Ketones 622
5.2.2 Synthesis of Acyclic Ketones and Aldehydes 625
5.3 Silyl Enol Ethers 631
5.3.1 Carbocyclic Ketones 631
5.3.2 Dioxanones 632
5.4 Allyl β-Ketoesters 634
5.5 Synthetic Applications of Enantioenriched Cycloalkanones 641
5.5.1 Applications in Target-Directed Synthesis 641
5.5.1.1 Total Synthesis of (+)-Dichroanone 641
5.5.1.2 Formal Synthesis of Oxybutynin 642
5.5.1.3 Progress toward Zoanthenol 644
5.5.1.4 Total Synthesis of Cyanthiwigin F 646
5.5.1.5 Total Synthesis of Laurencenone B and Elatol 647

5.5.1.6 Formal Synthesis of Quinic Acid 648
5.5.1.7 Total Synthesis of Carissone 649
5.5.1.8 Total Synthesis of Cassiol 650
5.5.2 Methodological Applications 651
5.5.2.1 α-Fluorinated Cycloalkanones 651
5.5.2.2 Cascade Reactions to Generate Enolates 656
5.5.2.3 Intercepted Alkylation with Conjugate Acceptors 657
5.5.3 Miscellaneous Applications 659
5.6 Mechanism of Allylation Reactions 661
5.7 Conclusions 664
5.8 Notes and References 666

CHAPTER 6 ***675***

Enantioselective Protonations

6.1 Introduction 675
6.2 Important Factors in Achieving Enantioselective Protonation 676
6.3 Enantioselective Protonation in Enzymatic Systems 678
6.3.1 Decarboxylase Enzymes 678
6.3.2 Esterase Enzymes 681
6.4 Strategic Approaches to Nonenzymatic Enantioselective Protonation 683
6.4.1 General Considerations 683
6.4.2 Enantioselective Protonation by Means of Chiral Proton Donor 684
6.4.3 Enantioselective Protonation by Means of Chiral Brønsted Base 695
6.4.4 Enantioselective Hydrogen Atom Transfer 706
6.5 Conclusion 707
6.6 Notes and References 709

CHAPTER 7 ***714***

Catalytic Enantioselective Decarboxylative Protonation

7.1 Introduction 714

7.2 Enantioselective Protonation with Formic Acid as Proton Donor 716

7.2.1 Discovery and Optimization of Reaction Conditions 716

7.2.2 Results of Enantioselective Protonation 720

7.2.3 Enantioselective Protonation with Other Enolate Precursors 722

7.2.4 Deuterium Labeling Experiments 723

7.2.5 Summary of Enantioselective Protonation Methodology Using Formic Acid 724

7.3 Homogeneous Enantioselective Protonation 725

7.3.1 Background 725

7.3.2 Screening of Alternate Proton Donors 726

7.3.3 Results of Homogeneous Enantioselective Protonation 729

7.3.4 Preliminary Kinetic Studies 732

7.4 Summary 734

7.5 Notes and References for Text 736

7.6 Experimental Section 739

7.6.1 Materials and Methods 739

7.6.2 Experimental Data Relevant to the Formic Acid Protocol 741

7.6.2.1 Optimization of Reaction Conditions for Formic Acid Protocol 741

7.6.2.2 Syntheses of Substrate Compounds 743

7.6.2.3 Characterization Data for Substrate Compounds 746

7.6.2.4 Enantioconvergent Decarboxylative Protonation Using Formic Acid 755

7.6.2.5 Deuterium Labeling Experiments 764

7.6.3 Experimental Data Relevant to the Meldrum's Acid Protocol 767

7.6.3.1 Screening of Alternate Proton Donors 767

7.6.3.2 Enantioconvergent Decarboxylative Protonation Using Meldrum's Acid 770

7.6.4 Kinetic Studies for the Enantioconvergent Protonation with Meldrum's Acid 778

7.6.5 Notes and References for Experimental Section 779

APPENDIX 3 ***782***

Spectra Compounds Relevant to Chapter 7

CHAPTER 8 ***828***

Catalytic Enantioselective Stereoablative Reactions

8.1 Introduction 828

8.2 Examples of Stereoablative Enantioselective Reactions 830

8.2.1 Kinetic Resolutions 830

8.2.1.1 Oxidation of Racemic Alcohols 830

8.2.1.2 Oxidation of Sulfoxides and Sulfides 832

8.2.1.3 Hydrogenation of Alkenes 833

8.2.2 Desymmetrizations 834

8.2.3 Enantioconvergent Reactions 835

8.2.3.1 Dynamic Kinetic Resolution 835

8.2.3.2 Deracemization 836

8.2.3.3 Destruction/Construction Sequences 838

8.3 Conclusions 844

8.4 Notes and References 845

CHAPTER 9 ***849***

Enantioselective Total Synthesis of (+)-Cassiol

9.1 Introduction 849

9.2 Retrosynthetic Analysis 850

9.3 Total Synthesis of (+)-Cassiol 851

9.3.1 Enantioselective Alkylation with Vinylogous Esters 851
9.3.2 Preparation of the Cyclohexenone Core 852
9.3.3 Preparation of the Sidechain Synthon 854
9.3.4 Fragment Coupling 855
9.4 Summary 855
9.5 Notes and References for Text 857
9.6 Experimental Section 861
9.6.1 Materials and Methods 861
9.6.2 Experimental Procedures and Characterization Data 863
9.6.3 Comparison Tables for Properties of Synthetic and Natural Cassiol 879
9.6.4 Notes and References for Experimental Section 881

APPENDIX 4 ***882***

Spectra Compounds Relevant to Chapter 9

CHAPTER 10 ***908***

Enantioselective Formal Synthesis of Platencin

10.1 Introduction 908
10.2 Retrosynthetic Analysis 909
10.3 Initial Studies toward Platencin 910
10.4 Revised Retrosynthesis 911
10.5 Implementation of the Revised Strategy—Formal Synthesis of Platencin 912
10.6 Summary 915
10.7 Notes and References for Text 916
10.8 Experimental Section 921
10.8.1 Materials and Methods 921
10.8.2 Experimental Procedures and Characterization Data 922

10.8.3 X-Ray Structure of Diketone 751 943

10.8.4 Notes and References for Experimental Section 952

APPENDIX 5 ***954***

Spectra Compounds Relevant to Chapter 10

APPENDIX 6 ***989***

Optimized Large-scale Procedure for Preparation of t-Bu-PHOX

A6.1 Procedure 989

A6.1.1 2-Bromo-*N*-[(1*S*)-1-hydroxymethyl-2,2-dimethylpropyl]-benzamide 989

A6.1.2 2-(2-Bromophenyl)-4-(1,1-dimethylethyl)-4,5-dihydro-(4*S*)-oxazole 992

A6.1.3 4-(1,1-dimethylethyl)-2-[2-(diphenylphosphino)phenyl]-4,5-dihydro-(4*S*)-oxazole ((*S*)-tert-ButylPHOX) 993

A6.2 Notes 995

A6.3 Discussion 1001

A6.4 References 1004

APPENDIX 7 ***1006***

Optimized Large-Scale Procedure for Enantioselective Tsuji Allylation

A7.1 Procedure 1006

A7.1.1 1-Methyl-2-oxo-cyclohexanecarboxylic acid 2-propenyl ester 1006

A7.1.2 (2*S*)-2-Methyl-2-(2-propen-1-yl)-cyclohexanone 1009

A7.1.3 Enrichment of (2*S*)-2-methyl-2-(2-propen-1-yl)-cyclohexanone via (2*E*)-2-[(2*S*)-2-methyl-2-(2-propenyl)cyclohexylidene]-hydrazinecarboxamide 1011

A7.2 Notes 1013

A7.3 Discussion 1020

A7.4 References 1025

NOTEBOOK CROSS-REFERENCE ***1029***

SUBJECT INDEX ***1032***

COMPREHENSIVE BIBLIOGRAPHY ***1036***

ABOUT THE AUTHOR ***1075***

LIST OF FIGURES

CHAPTER 2

Figure 2.1. Representations of semicarbazones **161** and **162**.....134

Figure 2.2. Representation of [Pd(II)(allyl)PHOX]•PF_6 salt **165**.....148

Figure 2.3. Representation of the unit cell of [Pd(II)(allyl)PHOX]•PF_6 salt **165**.....149

APPENDIX 1

Figure A1.1 ^{1}H NMR of compound **125** (300 MHz, $CDCl_3$).....156

Figure A1.2 IR of compound **125** (NaCl/film).....157

Figure A1.3 ^{13}C NMR of compound **125** (75 MHz, $CDCl_3$).....157

Figure A1.4 ^{1}H NMR of compound **126** (300 MHz, $CDCl_3$).....158

Figure A1.5 IR of compound **126** (NaCl/film).....159

Figure A1.6 ^{13}C NMR of compound **126** (75 MHz, $CDCl_3$).....159

Figure A1.7 ^{1}H NMR of compound **127** (300 MHz, $CDCl_3$).....160

Figure A1.8 IR of compound **127** (NaCl/film).....161

Figure A1.9 ^{13}C NMR of compound **127** (75 MHz, $CDCl_3$.....161

Figure A1.10 ^{1}H NMR of compound **128** (300 MHz, $CDCl_3$).....162

Figure A1.11 IR of compound **128** (NaCl/film).....163

Figure A1.12 ^{13}C NMR of compound **128** (75 MHz, $CDCl_3$).....163

Figure A1.13 ^{1}H NMR of compound **129** (300 MHz, $CDCl_3$).....164

Figure A1.14 IR of compound **129** (NaCl/film).....165

Figure A1.15 ^{13}C NMR of compound **129** (75 MHz, $CDCl_3$).....165

Figure A1.16 ^{1}H NMR of compound **130** (300 MHz, $CDCl_3$).....166

Figure A1.17 IR of compound **130** (NaCl/film).....167

Figure A1.18 ^{13}C NMR of compound **130** (75 MHz, $CDCl_3$).....167

Figure A1.19 ^{1}H NMR of compound **131** (300 MHz, $CDCl_3$).....168

Figure A1.20 IR of compound **131** (NaCl/film) 169

Figure A1.21 ^{13}C NMR of compound **131** (75 MHz, $CDCl_3$) 169

Figure A1.22 ^{1}H NMR of compound **132** (300 MHz, $CDCl_3$) 170

Figure A1.23 IR of compound **132** (NaCl/film) 171

Figure A1.24 ^{13}C NMR of compound **132** (75 MHz, $CDCl_3$) 171

Figure A1.25 ^{1}H NMR of compound **135** (300 MHz, $CDCl_3$) 172

Figure A1.26 IR of compound **135** (NaCl/film) 173

Figure A1.27 ^{13}C NMR of compound **135** (75 MHz, $CDCl_3$) 173

Figure A1.28 ^{1}H NMR of compound **136** (500 MHz, $CDCl_3$) 174

Figure A1.29 IR of compound **136** (NaCl/film) 175

Figure A1.30 ^{13}C NMR of compound **136** (125 MHz, $CDCl_3$) 175

Figure A1.31 ^{1}H NMR of compound **137** (300 MHz, $CDCl_3$) 176

Figure A1.32 IR of compound **137** (NaCl/film) 177

Figure A1.33 ^{13}C NMR of compound **137** (75 MHz, $CDCl_3$) 177

Figure A1.34 ^{1}H NMR of compound **138** (500 MHz, $CDCl_3$) 178

Figure A1.35 IR of compound **138** (NaCl/film) 179

Figure A1.36 ^{13}C NMR of compound **138** (125 MHz, $CDCl_3$) 179

Figure A1.37 ^{1}H NMR of compound **139** (300 MHz, $CDCl_3$) 180

Figure A1.38 IR of compound **139** (NaCl/film) 181

Figure A1.39 ^{13}C NMR of compound **139** (75 MHz, $CDCl_3$) 181

Figure A1.40 ^{1}H NMR of compound **140** (300 MHz, $CDCl_3$) 182

Figure A1.41 IR of compound **140** (NaCl/film) 183

Figure A1.42 ^{13}C NMR of compound **140** (75 MHz, $CDCl_3$) 183

Figure A1.43 ^{1}H NMR of compound **141** (300 MHz, $CDCl_3$) 184

Figure A1.44 IR of compound **141** (NaCl/film) 185

Figure A1.45 ^{13}C NMR of compound **141** (75 MHz, $CDCl_3$) 185

Figure A1.46 ^{1}H NMR of compound **142** (500 MHz, $CDCl_3$) 186

Figure A1.47 IR of compound **142** (NaCl/film) 187

Figure A1.48 ^{13}C NMR of compound **142** (125 MHz, $CDCl_3$) 187

Figure A1.49 ^{1}H NMR of compound **143** (300 MHz, $CDCl_3$) 188

Figure A1.50 IR of compound **143** (NaCl/film) 189

Figure A1.51 ^{13}C NMR of compound **143** (75 MHz, $CDCl_3$) 189

Figure A1.52 ^{1}H NMR of compound **145** (500 MHz, $CDCl_3$) 190

Figure A1.53 IR of compound **145** (NaCl/film) 191

Figure A1.54 ^{13}C NMR of compound **145** (125 MHz, $CDCl_3$) 191

Figure A1.55 ^{1}H NMR of compound **146** (500 MHz, $CDCl_3$) 192

Figure A1.56 IR of compound **146** (NaCl/film) 193

Figure A1.57 ^{13}C NMR of compound **146** (125 MHz, $CDCl_3$) 193

Figure A1.58 ^{1}H NMR of compound **187** (300 MHz, $CDCl_3$) 194

Figure A1.59 IR of compound **187** (NaCl/film) 195

Figure A1.60 ^{13}C NMR of compound **187** (75 MHz, $CDCl_3$) 195

Figure A1.61 ^{1}H NMR of compound **188** (300 MHz, $CDCl_3$) 196

Figure A1.62 IR of compound **188** (NaCl/film) 197

Figure A1.63 ^{13}C NMR of compound **188** (75 MHz, $CDCl_3$) 197

Figure A1.64 ^{1}H NMR of compound **189** (300 MHz, $CDCl_3$) 198

Figure A1.65 IR of compound **189** (NaCl/film) 199

Figure A1.66 ^{13}C NMR of compound **189** (75 MHz, $CDCl_3$) 199

Figure A1.67 ^{1}H NMR of compound **105** (300 MHz, $CDCl_3$) 200

Figure A1.68 IR of compound **105** (NaCl/film) 201

Figure A1.69 ^{13}C NMR of compound **105** (75 MHz, $CDCl_3$) 201

Figure A1.70 ^{1}H NMR of compound **124** (300 MHz, $CDCl_3$) 202

Figure A1.71 IR of compound **124** (NaCl/film) 203

Figure A1.72 ^{13}C NMR of compound **124** (75 MHz, $CDCl_3$) 203

Figure A1.73 ^{1}H NMR of compound **210** (300 MHz, $CDCl_3$) 204

Figure A1.74 IR of compound **210** (NaCl/film) 205

Figure A1.75 ^{13}C NMR of compound **210** (75 MHz, $CDCl_3$) 205

Figure A1.76 ^{1}H NMR of compound **211** (300 MHz, $CDCl_3$) 206

Figure A1.77 IR of compound **211** (NaCl/film) 207

Figure A1.78 ^{13}C NMR of compound **211** (75 MHz, $CDCl_3$) 207

Figure A1.79 ^{1}H NMR of compound **212** (300 MHz, $CDCl_3$) 208

Figure A1.80 IR of compound **212** (NaCl/film) 209

Figure A1.81 ^{13}C NMR of compound **212** (75 MHz, $CDCl_3$) 209

Figure A1.82 ^{1}H NMR of compound **213** (300 MHz, $CDCl_3$) 210

Figure A1.83 IR of compound **213** (NaCl/film) 211

Figure A1.84 ^{13}C NMR of compound **213** (75 MHz, $CDCl_3$) 211

Figure A1.85 ^{1}H NMR of compound **214** (300 MHz, $CDCl_3$) 212

Figure A1.86 IR of compound **214** (NaCl/film) 213

Figure A1.87 ^{13}C NMR of compound **214** (75 MHz, $CDCl_3$) 213

Figure A1.88 ^{1}H NMR of compound **215** (300 MHz, $CDCl_3$) 214

Figure A1.89 IR of compound **215** (NaCl/film) 215

Figure A1.90 ^{13}C NMR of compound **215** (75 MHz, $CDCl_3$) 215

Figure A1.91 ^{1}H NMR of compound **216** (300 MHz, $CDCl_3$) 216

Figure A1.92 IR of compound **216** (NaCl/film) 217

Figure A1.93 ^{13}C NMR of compound **216** (75 MHz, $CDCl_3$) 217

Figure A1.94 ^{1}H NMR of compound **217** (300 MHz, $CDCl_3$) 218

Figure A1.95 IR of compound **217** (NaCl/film) 219

Figure A1.96 ^{13}C NMR of compound **217** (75 MHz, $CDCl_3$) 219

Figure A1.97 ^{1}H NMR of compound **218** (300 MHz, $CDCl_3$) 220

Figure A1.98 IR of compound **218** (NaCl/film) 221

Figure A1.99 ^{13}C NMR of compound **218** (75 MHz, $CDCl_3$) 221

Figure A1.100 ^{1}H NMR of compound **219** (300 MHz, $CDCl_3$) 222

Figure A1.101 IR of compound **219** (NaCl/film) 223

Figure A1.102 ^{13}C NMR of compound **219** (75 MHz, $CDCl_3$) 223

Figure A1.103 ^{1}H NMR of compound **220** (300 MHz, $CDCl_3$) 224

Figure A1.104 IR of compound **220** (NaCl/film) 225

Figure A1.105 ^{13}C NMR of compound **220** (75 MHz, $CDCl_3$) 225

Figure A1.106 ^{1}H NMR of compound **182** (300 MHz, $CDCl_3$) 226

Figure A1.107 IR of compound **182** (NaCl/film) 227

Figure A1.108 ^{13}C NMR of compound **182** (75 MHz, $CDCl_3$) 227

Figure A1.109 ^{1}H NMR of compound **185** (300 MHz, $CDCl_3$) 228

Figure A1.110 IR of compound **185** (NaCl/film) 229

Figure A1.111 ^{13}C NMR of compound **185** (75 MHz, $CDCl_3$) 229

Figure A1.112 ^{1}H NMR of compound **190** (300 MHz, $CDCl_3$) 230

Figure A1.113 IR of compound **190** (NaCl/film) 231

Figure A1.114 ^{13}C NMR of compound **190** (75 MHz, $CDCl_3$) 231

Figure A1.115 ^{1}H NMR of compound **191** (300 MHz, $CDCl_3$) 232

Figure A1.116 IR of compound **191** (NaCl/film) 233

Figure A1.117 ^{13}C NMR of compound **191** (75 MHz, $CDCl_3$) 233

Figure A1.118 ^{1}H NMR of compound **193** (300 MHz, $CDCl_3$) 234

Figure A1.119 IR of compound **193** (NaCl/film) 235

Figure A1.120 ^{13}C NMR of compound **193** (75 MHz, $CDCl_3$) 235

Figure A1.121 ^{1}H NMR of compound **194** (300 MHz, $CDCl_3$) 236

Figure A1.122 IR of compound **194** (NaCl/film) 237

Figure A1.123 ^{13}C NMR of compound **194** (75 MHz, $CDCl_3$) 237

Figure A1.124 ^{1}H NMR of compound **196** (300 MHz, $CDCl_3$) 238

Figure A1.125 IR of compound **196** (NaCl/film) 239

Figure A1.126 ^{13}C NMR of compound **196** (75 MHz, $CDCl_3$) 239

Figure A1.127 ^{1}H NMR of compound **209** (300 MHz, $CDCl_3$) 240

Figure A1.128 IR of compound **209** (NaCl/film) 241

Figure A1.129 ^{13}C NMR of compound **209** (75 MHz, $CDCl_3$) 241

Figure A1.130 ^{1}H NMR of compound **110** (300 MHz, $CDCl_3$) 242

Figure A1.131 IR of compound **110** (NaCl/film) 243

Figure A1.132 ^{13}C NMR of compound **110** (75 MHz, $CDCl_3$) 243

Figure A1.133 ^{1}H NMR of compound **222** (300 MHz, C_6D_6) 244

Figure A1.134 IR of compound **222** (NaCl/film) 245

Figure A1.135 ^{13}C NMR of compound **222** (75 MHz, C_6D_6) 245

Figure A1.136 ^{1}H NMR of compound **223** (300 MHz, $CDCl_3$) 246

Figure A1.137 IR of compound **223** (NaCl/film) 247

Figure A1.138 ^{13}C NMR of compound **223** (75 MHz, $CDCl_3$) 247

Figure A1.139 ^{1}H NMR of compound **224** (300 MHz, $CDCl_3$) 248

Figure A1.140 IR of compound **224** (NaCl/film) 249

Figure A1.141 ^{13}C NMR of compound **224** (75 MHz, $CDCl_3$) 249

Figure A1.142 ^{1}H NMR of compound **225** (300 MHz, $CDCl_3$) 250

Figure A1.143 IR of compound **225** (NaCl/film) 251

Figure A1.144 ^{13}C NMR of compound **225** (75 MHz, $CDCl_3$) 251

Figure A1.145 ^{1}H NMR of compound **226** (300 MHz, $CDCl_3$) 252

Figure A1.146 IR of compound **226** (NaCl/film) 253

Figure A1.147 ^{13}C NMR of compound **226** (75 MHz, $CDCl_3$) 253

Figure A1.148 ^{1}H NMR of compound **106** (300 MHz, $CDCl_3$) 254

Figure A1.149 IR of compound **106** (NaCl/film) 255

Figure A1.150 ^{13}C NMR of compound **106** (75 MHz, $CDCl_3$) 255

Figure A1.151 ^{1}H NMR of compound **148** (300 MHz, $CDCl_3$) 256

Figure A1.152 IR of compound **148** (NaCl/film) 257

Figure A1.153 ^{13}C NMR of compound **148** (75 MHz, $CDCl_3$) 257

Figure A1.154 ^{1}H NMR of compound **149** (300 MHz, $CDCl_3$) 258

Figure A1.155 IR of compound **149** (NaCl/film) 259

Figure A1.156 ^{13}C NMR of compound **149** (75 MHz, $CDCl_3$) 259

Figure A1.157 ^{1}H NMR of compound **150** (300 MHz, $CDCl_3$) 260

Figure A1.158 IR of compound **150** (NaCl/film) 261

Figure A1.159 ^{13}C NMR of compound **150** (75 MHz, $CDCl_3$) 261

Figure A1.160 ^{1}H NMR of compound **151** (300 MHz, $CDCl_3$) 262

Figure A1.161 IR of compound **151** (NaCl/film) 263

Figure A1.162 ^{13}C NMR of compound **151** (75 MHz, $CDCl_3$) 263

Figure A1.163 ^{1}H NMR of compound **227** (300 MHz, $CDCl_3$) 264

Figure A1.164 IR of compound **227** (NaCl/film) 265

Figure A1.165 ^{13}C NMR of compound **227** (75 MHz, $CDCl_3$) 265

Figure A1.166 ^{1}H NMR of compound **153** (300 MHz, $CDCl_3$) 266

Figure A1.167 IR of compound **153** (NaCl/film) 267

Figure A1.168 ^{13}C NMR of compound **153** (75 MHz, $CDCl_3$) 267

Figure A1.169 ^{1}H NMR of compound **154** (300 MHz, $CDCl_3$) 268

Figure A1.170 IR of compound **154** (NaCl/film) 269

Figure A1.171 ^{13}C NMR of compound **154** (75 MHz, $CDCl_3$) 269

Figure A1.172 ^{1}H NMR of compound **155** (300 MHz, $CDCl_3$) 270

Figure A1.173 IR of compound **155** (NaCl/film) 271

Figure A1.174 ^{13}C NMR of compound **155** (75 MHz, $CDCl_3$) 271

Figure A1.175 ^{1}H NMR of compound **98** (300 MHz, $CDCl_3$) 272

Figure A1.176 IR of compound **98** (NaCl/film) 273

Figure A1.177 ^{13}C NMR of compound **98** (75 MHz, $CDCl_3$) 273

Figure A1.178 ^{1}H NMR of compound **156** (300 MHz, $CDCl_3$) 274

Figure A1.179 IR of compound **156** (NaCl/film) 275

Figure A1.180 ^{13}C NMR of compound **156** (75 MHz, $CDCl_3$) 275

Figure A1.181 ^{1}H NMR of compound **157** (300 MHz, $CDCl_3$) 276

Figure A1.182 IR of compound **157** (NaCl/film) 277

Figure A1.183 ^{13}C NMR of compound **157** (75 MHz, $CDCl_3$) 277

Figure A1.184 ^{1}H NMR of compound **158** (300 MHz, $CDCl_3$) 278

Figure A1.185 IR of compound **158** (NaCl/film) 279

Figure A1.186 ^{13}C NMR of compound **158** (75 MHz, $CDCl_3$) 279

Figure A1.187 ^{1}H NMR of compound **163** (300 MHz, $CDCl_3$) 280

Figure A1.188 IR of compound **163** (NaCl/film) 281

Figure A1.189 ^{13}C NMR of compound **163** (75 MHz, $CDCl_3$) 281

Figure A1.190 ^{1}H NMR of compound **164** (300 MHz, $CDCl_3$) 282

Figure A1.191 IR of compound **164** (NaCl/film) 283

Figure A1.192 ^{13}C NMR of compound **164** (75 MHz, $CDCl_3$) 283

Figure A1.193 ^{1}H NMR of compound **192** (300 MHz, $CDCl_3$) 284

Figure A1.194 IR of compound **192** (NaCl/film) 285

Figure A1.195 ^{13}C NMR of compound **192** (75 MHz, $CDCl_3$) 285

Figure A1.196 ^{1}H NMR of compound **197** (300 MHz, $CDCl_3$) 286

Figure A1.197 IR of compound **197** (NaCl/film) 287

Figure A1.198 ^{13}C NMR of compound **197** (75 MHz, $CDCl_3$) 287

Figure A1.199 ^{1}H NMR of compound **186** (300 MHz, $CDCl_3$) 288

Figure A1.200 IR of compound **186** (NaCl/film) 289

Figure A1.201 ^{13}C NMR of compound **186** (75 MHz, $CDCl_3$) 289

Figure A1.202 ^{1}H NMR of compound **159** (300 MHz, $CDCl_3$) 290

Figure A1.203 IR of compound **159** (NaCl/film) 291

Figure A1.204 ^{13}C NMR of compound **159** (75 MHz, $CDCl_3$) 291

Figure A1.205 ^{1}H NMR of compound **161** (300 MHz, $CDCl_3$) 292

Figure A1.206 IR of compound **161** (NaCl/film) 293

Figure A1.207 ^{13}C NMR of compound **161** (75 MHz, $CDCl_3$) 293

Figure A1.208 ^{1}H NMR of compound **162** (300 MHz, $CDCl_3$) 294

Figure A1.209 IR of compound **162** (NaCl/film) 295

Figure A1.210 ^{13}C NMR of compound **162** (75 MHz, $CDCl_3$) 295

Figure A1.211 ^{1}H NMR of compound **166** (300 MHz, $CDCl_3$) 296

Figure A1.212 IR of compound **166** (NaCl/film) 297

Figure A1.213 ^{13}C NMR of compound **166** (75 MHz, $CDCl_3$) 297

Figure A1.214 ^{1}H NMR of compound **168** (300 MHz, $CDCl_3$) 298

Figure A1.215 IR of compound **168** (NaCl/film) 299

Figure A1.216 ^{13}C NMR of compound **168** (75 MHz, $CDCl_3$) 299

Figure A1.217 ^{1}H NMR of compound **169** (300 MHz, $CDCl_3$) 300

Figure A1.218 IR of compound **169** (NaCl/film) 301

Figure A1.219 ^{13}C NMR of compound **169** (75 MHz, $CDCl_3$) 301

Figure A1.220 ^{1}H NMR of compound **170** (300 MHz, $CDCl_3$) 302

Figure A1.221 IR of compound **170** (NaCl/film) 303

Figure A1.222 ^{13}C NMR of compound **170** (75 MHz, $CDCl_3$) 303

Figure A1.223 ^{1}H NMR of compound **171** (300 MHz, $CDCl_3$) 304

Figure A1.224 IR of compound **171** (NaCl/film) 305

Figure A1.225 ^{13}C NMR of compound **171** (75 MHz, $CDCl_3$) 305

Figure A1.226 ^{1}H NMR of compound **172** (300 MHz, $CDCl_3$) 306

Figure A1.227 IR of compound **172** (NaCl/film) 307

Figure A1.228 ^{13}C NMR of compound **172** (75 MHz, $CDCl_3$) 307

Figure A1.229 ^{1}H NMR of compound **173** (300 MHz, $CDCl_3$) 308

Figure A1.230 IR of compound **173** (NaCl/film) 309

Figure A1.231 ^{13}C NMR of compound **173** (75 MHz, $CDCl_3$) 309

Figure A1.232 ^{1}H NMR of compound **165** (300 MHz, $CDCl_3$) 310

Figure A1.233 IR of compound **165** (NaCl/film) 311

Figure A1.234 ^{13}C NMR of compound **165** (75 MHz, $CDCl_3$) 311

CHAPTER 3

Figure 3.1. Plot of k_{obs} vs. concentration of Pd(PHOX) complex for allyl enol carbonate 330

Figure 3.2. Plot of *i*-Pr-PHOX ee vs. product ee 330

Figure 3.3. Plot of allyl enol carbonate ^{1}H NMR integral vs. time (s) 331

Figure 3.4. Plot of allyl β-ketoester ^{1}H NMR integral vs. time (s) 331

Figure 3.5. Comparison of sterically varied products formed at 25 °C in THF 332

Figure 3.6. ^{31}P NMR collected during the enantioselective allylation reaction: Spectrum A: Pd•PHOX complex (18.8 ppm) and excess PHOX ligand (–5.9 ppm) prior to addition of substrate; Spectrum B: After addition of substrate (±)-**107**, during reaction; Spectrum C: After complete consumption of substrate 336

Figure 3.7. X-Ray structure of $[Pd(II)(allyl)PHOX]^+[PF_6]^-$ EtOH adduct 337

Figure 3.8. Plot of k_{obs} vs. concentration of (*S*)-*t*-Bu-PHOX. 419

APPENDIX 2

Figure A2.1 ^{1}H NMR of compound **241** (300 MHz, $CDCl_3$) 447

Figure A2.2 IR of compound **241** (NaCl/film) 448

Figure A2.3 ^{13}C NMR of compound **241** (75 MHz, $CDCl_3$) 448

Figure A2.4 ^{1}H NMR of compound **244** (300 MHz, $CDCl_3$) 449

Figure A2.5 IR of compound **244** (NaCl/film) 450

Figure A2.6 ^{13}C NMR of compound **244** (75 MHz, $CDCl_3$) 450

Figure A2.7 ^{1}H NMR of compound **237** (300 MHz, $CDCl_3$) 451

Figure A2.8 IR of compound **237** (NaCl/film) 452

Figure A2.9 ^{13}C NMR of compound **237** (75 MHz, $CDCl_3$) 452

Figure A2.10 ^{1}H NMR of compound **242** (300 MHz, $CDCl_3$) 453

Figure A2.11 ^{13}C NMR of compound **242** (75 MHz, $CDCl_3$) 454

Figure A2.12 ^{1}H NMR of compound **107** (300 MHz, $CDCl_3$) 455

Figure A2.13 IR of compound **107** (NaCl/film) 456

Figure A2.14 ^{13}C NMR of compound **107** (75 MHz, $CDCl_3$) 456

Figure A2.15 ^{1}H NMR of compound **248** (300 MHz, $CDCl_3$) 457

Figure A2.16 IR of compound **248** (NaCl/film) 458

Figure A2.17 ^{13}C NMR of compound **248** (75 MHz, $CDCl_3$) 458

Figure A2.18 ^{1}H NMR of compound **250** (300 MHz, $CDCl_3$) 459

Figure A2.19 IR of compound **250** (NaCl/film) 460

Figure A2.20 ^{13}C NMR of compound **250** (75 MHz, $CDCl_3$) 460

Figure A2.21 ^{1}H NMR of compound **252** (300 MHz, $CDCl_3$) 461

Figure A2.22 IR of compound **252** (NaCl/film) 462

Figure A2.23 ^{13}C NMR of compound **252** (75 MHz, $CDCl_3$) 462

Figure A2.24 ^{1}H NMR of compound **254** (300 MHz, $CDCl_3$) 463

Figure A2.25 IR of compound **254** (NaCl/film) 464

Figure A2.26 ^{13}C NMR of compound **254** (75 MHz, $CDCl_3$) 464

Figure A2.27 ^{1}H NMR of compound **256** (300 MHz, $CDCl_3$) 465

Figure A2.28 IR of compound **256** (NaCl/film) 466

Figure A2.29 ^{13}C NMR of compound **256** (75 MHz, $CDCl_3$) 466

Figure A2.30 ^{1}H NMR of compound **258** (300 MHz, $CDCl_3$) 467

Figure A2.31 IR of compound **258** (NaCl/film) 468

Figure A2.32 ^{13}C NMR of compound **258** (75 MHz, $CDCl_3$) 468

Figure A2.33 ^{1}H NMR of compound **260** (300 MHz, $CDCl_3$) 469

Figure A2.34 IR of compound **260** (NaCl/film) 470

Figure A2.35 ^{13}C NMR of compound **260** (75 MHz, $CDCl_3$) 470

Figure A2.36 ^{1}H NMR of compound **306** (300 MHz, $CDCl_3$) 471

Figure A2.37 IR of compound **306** (NaCl/film) 472

Figure A2.38 ^{13}C NMR of compound **306** (75 MHz, $CDCl_3$) 472

Figure A2.39 ^{1}H NMR of compound **307** (300 MHz, $CDCl_3$) 473

Figure A2.40 IR of compound **307** (NaCl/film) 474

Figure A2.41 ^{13}C NMR of compound **307** (75 MHz, $CDCl_3$) 474

Figure A2.42 ^{1}H NMR of compound **308** (300 MHz, $CDCl_3$) 475

Figure A2.43 IR of compound **308** (NaCl/film) 476

Figure A2.44 ^{13}C NMR of compound **308** (75 MHz, $CDCl_3$) 476

Figure A2.45 ^{1}H NMR of compound **293** (300 MHz, $CDCl_3$) 477

Figure A2.46 IR of compound **293** (NaCl/film) 478

Figure A2.47 ^{13}C NMR of compound **293** (75 MHz, $CDCl_3$) 478

Figure A2.48 ^{1}H NMR of compound **309** (300 MHz, $CDCl_3$) 479

Figure A2.49 IR of compound **309** (NaCl/film) 480

Figure A2.50 ^{13}C NMR of compound **309** (75 MHz, $CDCl_3$) 480

Figure A2.51 ^{1}H NMR of compound **310** (300 MHz, $CDCl_3$) 481

Figure A2.52 ^{13}C NMR of compound **310** (75 MHz, $CDCl_3$) 482

Figure A2.53 ^{1}H NMR of compound **311** (300 MHz, $CDCl_3$) 483

Figure A2.54 IR of compound **311** (NaCl/film) 484

Figure A2.55 ^{13}C NMR of compound **311** (75 MHz, $CDCl_3$) 484

Figure A2.56 ^{1}H NMR of compound **312** (300 MHz, $CDCl_3$) 485

Figure A2.57 IR of compound **312** (NaCl/film) 486

Figure A2.58 ^{13}C NMR of compound **312** (75 MHz, $CDCl_3$) 486

Figure A2.59 ^{1}H NMR of compound **317** (300 MHz, $CDCl_3$) 487

Figure A2.60 ^{13}C NMR of compound **317** (75 MHz, $CDCl_3$) 488

Figure A2.61 ^{1}H NMR of compound **318** (300 MHz, $CDCl_3$) 489

Figure A2.62 IR of compound **318** (NaCl/film) 490

Figure A2.63 ^{13}C NMR of compound **318** (75 MHz, $CDCl_3$) 490

Figure A2.64 ^{1}H NMR of compound **321** (500 MHz, $CDCl_3$) 491

Figure A2.65 ^{13}C NMR of compound **321** (126 MHz, $CDCl_3$) 492

Figure A2.66 ^{1}H NMR of compound **323** (300 MHz, $CDCl_3$) 493

Figure A2.67 ^{13}C NMR of compound **SI27** (75 MHz, $CDCl_3$) 494

Figure A2.68 ^{1}H NMR of compound **271** (300 MHz, $CDCl_3$).....495

Figure A2.69 IR of compound **271** (NaCl/film).....496

Figure A2.70 ^{13}C NMR of compound **271** (75 MHz, $CDCl_3$).....496

Figure A2.71 ^{1}H NMR of first diastereomer of compound **273** (500 MHz, $CDCl_3$).....497

Figure A2.72 ^{13}C NMR of first diastereomer of compound **273** (125 MHz, $CDCl_3$).....498

Figure A2.73 ^{1}H NMR of second diastereomer of compound **273** (500 MHz, $CDCl_3$).....499

Figure A2.74 ^{13}C NMR of second diastereomer of compound **273** (125 MHz, $CDCl_3$).....500

Figure A2.75 ^{1}H NMR of compound **326** (300 MHz, $CDCl_3$).....501

Figure A2.76 IR of compound **326** (NaCl/film).....502

Figure A2.77 ^{13}C NMR of compound **326** (75 MHz, $CDCl_3$).....502

Figure A2.78 ^{1}H NMR of compound **327** (300 MHz, $CDCl_3$).....503

Figure A2.79 IR of compound **327** (NaCl/film).....504

Figure A2.80 ^{13}C NMR of compound **327** (75 MHz, $CDCl_3$).....504

Figure A2.81 ^{1}H NMR of compound **328** (300 MHz, $CDCl_3$).....505

Figure A2.82 IR of compound **328** (NaCl/film).....506

Figure A2.83 ^{13}C NMR of compound **328** (75 MHz, $CDCl_3$).....506

Figure A2.84 ^{1}H NMR of compound **329** (300 MHz, $CDCl_3$).....507

Figure A2.85 IR of compound **329** (NaCl/film).....508

Figure A2.86 ^{13}C NMR of compound **329** (75 MHz, $CDCl_3$).....508

Figure A2.87 ^{1}H NMR of compound **330** (300 MHz, $CDCl_3$).....509

Figure A2.88 IR of compound **330** (NaCl/film).....510

Figure A2.89 ^{13}C NMR of compound **330** (75 MHz, $CDCl_3$).....510

Figure A2.90 ^{1}H NMR of compound **331** (300 MHz, $CDCl_3$).....511

Figure A2.91 IR of compound **331** (NaCl/film).....512

Figure A2.92 ^{13}C NMR of compound **331** (75 MHz, $CDCl_3$).....512

Figure A2.93 ^{1}H NMR of compound **332** (300 MHz, $CDCl_3$).....513

Figure A2.94 IR of compound **332** (NaCl/film).....514

Figure A2.95 ^{13}C NMR of compound **332** (75 MHz, $CDCl_3$) 514

Figure A2.96 ^{1}H NMR of compound **333** (300 MHz, $CDCl_3$) 515

Figure A2.97 IR of compound **333** (NaCl/film) 516

Figure A2.98 ^{13}C NMR of compound **333** (75 MHz, $CDCl_3$) 516

Figure A2.99 ^{1}H NMR of compound **106** (300 MHz, $CDCl_3$) 517

Figure A2.100 IR of compound **106** (NaCl/film) 518

Figure A2.101 ^{13}C NMR of compound **106** (75 MHz, $CDCl_3$) 518

Figure A2.102 ^{1}H NMR of compound **235** (300 MHz, $CDCl_3$) 519

Figure A2.103 IR of compound **235** (NaCl/film) 520

Figure A2.104 ^{13}C NMR of compound **235** (75 MHz, $CDCl_3$) 520

Figure A2.105 ^{1}H NMR of compound **249** (300 MHz, $CDCl_3$) 521

Figure A2.106 IR of compound **249** (NaCl/film) 522

Figure A2.107 ^{13}C NMR of compound **249** (75 MHz, $CDCl_3$) 522

Figure A2.108 ^{1}H NMR of compound **251** (300 MHz, $CDCl_3$) 523

Figure A2.109 IR of compound **251** (NaCl/film) 524

Figure A2.110 ^{13}C NMR of compound **251** (75 MHz, $CDCl_3$) 524

Figure A2.111 ^{1}H NMR of compound **253** (300 MHz, $CDCl_3$) 525

Figure A2.112 IR of compound **253** (NaCl/film) 526

Figure A2.113 ^{13}C NMR of compound **253** (75 MHz, $CDCl_3$) 526

Figure A2.114 ^{1}H NMR of compound **153** (300 MHz, $CDCl_3$) 527

Figure A2.115 IR of compound **153** (NaCl/film) 528

Figure A2.116 ^{13}C NMR of compound **153** (75 MHz, $CDCl_3$) 528

Figure A2.117 ^{1}H NMR of compound **255** (300 MHz, $CDCl_3$) 529

Figure A2.118 IR of compound **255** (NaCl/film) 530

Figure A2.119 ^{13}C NMR of compound **255** (75 MHz, $CDCl_3$) 530

Figure A2.120 ^{1}H NMR of compound **257** (300 MHz, $CDCl_3$) 531

Figure A2.121 IR of compound **257** (NaCl/film) 532

Figure A2.122 ^{13}C NMR of compound **257** (75 MHz, $CDCl_3$).....532

Figure A2.123 ^{1}H NMR of compound **259** (300 MHz, $CDCl_3$).....533

Figure A2.124 IR of compound **259** (NaCl/film).....534

Figure A2.125 ^{13}C NMR of compound **259** (75 MHz, $CDCl_3$).....534

Figure A2.126 ^{1}H NMR of compound **261** (300 MHz, $CDCl_3$) 535

Figure A2.127 IR of compound **261** (NaCl/film).....536

Figure A2.128 ^{13}C NMR of compound **261** (75 MHz, $CDCl_3$).....536

Figure A2.129 ^{1}H NMR of compound **150** (300 MHz, $CDCl_3$).....537

Figure A2.130 IR of compound **150** (NaCl/film).....538

Figure A2.131 ^{13}C NMR of compound **150** (75 MHz, $CDCl_3$).....538

Figure A2.132 ^{1}H NMR of compound **155** (300 MHz, $CDCl_3$).....539

Figure A2.133 IR of compound **155** (NaCl/film).....540

Figure A2.134 ^{13}C NMR of compound **155** (75 MHz, $CDCl_3$).....540

Figure A2.135 ^{1}H NMR of compound **262** (300 MHz, $CDCl_3$).....541

Figure A2.136 IR of compound **262** (NaCl/film).....542

Figure A2.137 ^{13}C NMR of compound **262** (75 MHz, $CDCl_3$).....542

Figure A2.138 ^{1}H NMR of compound **149** (300 MHz, $CDCl_3$).....543

Figure A2.139 IR of compound **149** (NaCl/film).....544

Figure A2.140 ^{13}C NMR of compound **149** (75 MHz, $CDCl_3$).....544

Figure A2.141 ^{1}H NMR of compound **98** (300 MHz, $CDCl_3$).....545

Figure A2.142 IR of compound **98** (NaCl/film).....546

Figure A2.143 ^{13}C NMR of compound **98** (75 MHz, $CDCl_3$).....546

Figure A2.144 ^{1}H NMR of compound **157** (300 MHz, $CDCl_3$).....547

Figure A2.145 IR of compound **157** (NaCl/film).....548

Figure A2.146 ^{13}C NMR of compound **157** (75 MHz, $CDCl_3$).....548

Figure A2.147 ^{1}H NMR of compound **263** (300 MHz, $CDCl_3$).....549

Figure A2.148 ^{13}C NMR of compound **263** (75 MHz, $CDCl_3$).....550

Figure A2.149 ^{1}H NMR of compound **148** (300 MHz, $CDCl_3$) 551

Figure A2.150 IR of compound **148** (NaCl/film) 552

Figure A2.151 ^{13}C NMR of compound **148** (75 MHz, $CDCl_3$) 552

Figure A2.152 ^{1}H NMR of compound **264** (300 MHz, $CDCl_3$) 553

Figure A2.153 IR of compound **264** (NaCl/film) 554

Figure A2.154 ^{13}C NMR of compound **264** (75 MHz, $CDCl_3$) 554

Figure A2.155 ^{1}H NMR of compound **265** (300 MHz, $CDCl_3$) 555

Figure A2.156 ^{13}C NMR of compound **265** (75 MHz, $CDCl_3$) 556

Figure A2.157 ^{1}H NMR of compound **266** (300 MHz, $CDCl_3$) 557

Figure A2.158 IR of compound **266** (NaCl/film) 558

Figure A2.159 ^{13}C NMR of compound **266** (75 MHz, $CDCl_3$) 558

Figure A2.160 ^{1}H NMR spectrum of compound **267** (500 MHz, $CDCl_3$) 559

Figure A2.161 ^{13}C NMR spectrum of compound **267** (126 MHz, $CDCl_3$) 560

Figure A2.162 ^{1}H NMR spectrum of compound **268** (300 MHz, $CDCl_3$) 561

Figure A2.163 ^{13}C NMR spectrum of compound **268** (75 MHz, $CDCl_3$) 562

Figure A2.164 ^{1}H NMR of compound **272** (300 MHz, $CDCl_3$) 563

Figure A2.165 IR of compound **272** (NaCl/film) 564

Figure A2.166 ^{13}C NMR of compound **272** (75 MHz, $CDCl_3$) 564

Figure A2.167 ^{1}H NMR of compound **335** (300 MHz, $CDCl_3$) 565

Figure A2.168 ^{13}C NMR of compound **335** (75 MHz, $CDCl_3$) 566

Figure A2.169 ^{1}H NMR of compound **274** (300 MHz, $CDCl_3$) 567

Figure A2.170 IR of compound **274** (NaCl/film) 568

Figure A2.171 ^{13}C NMR of compound **274** (75 MHz, $CDCl_3$) 568

Figure A2.172 ^{1}H NMR of compound **275** (300 MHz, $CDCl_3$) 569

Figure A2.173 IR of compound **275** (NaCl/film) 570

Figure A2.174 ^{13}C NMR of compound **275** (75 MHz, $CDCl_3$) 570

Figure A2.175 ^{1}H NMR of compound **276** (300 MHz, $CDCl_3$) 571

Figure A2.176 IR of compound **276** (NaCl/film) 572

Figure A2.177 ^{13}C NMR of compound **276** (75 MHz, $CDCl_3$) 572

Figure A2.178 ^{1}H NMR of compound **278** (300 MHz, $CDCl_3$) 573

Figure A2.179 IR of compound **278** (NaCl/film) 574

Figure A2.180 ^{13}C NMR of compound **278** (75 MHz, $CDCl_3$) 574

Figure A2.181 ^{1}H NMR of compound **279** (300 MHz, $CDCl_3$) 575

Figure A2.182 IR of compound **279** (NaCl/film) 576

Figure A2.183 ^{13}C NMR of compound **279** (75 MHz, $CDCl_3$) 576

Figure A2.184 ^{1}H NMR of compound **280** (300 MHz, $CDCl_3$) 577

Figure A2.185 IR of compound **280** (NaCl/film) 578

Figure A2.186 ^{13}C NMR of compound **280** (75 MHz, $CDCl_3$) 578

Figure A2.187 ^{1}H NMR of compound **281** (300 MHz, $CDCl_3$) 579

Figure A2.188 IR of compound **281** (NaCl/film) 580

Figure A2.189 ^{13}C NMR of compound **281** (75 MHz, $CDCl_3$) 580

Figure A2.190 ^{1}H NMR of compound **294** (300 MHz, $CDCl_3$) 581

Figure A2.191 IR of compound **294** (NaCl/film) 582

Figure A2.192 ^{13}C NMR of compound **294** (75 MHz, $CDCl_3$) 582

Figure A2.193 ^{1}H NMR of compound **295** (300 MHz, $CDCl_3$) 583

Figure A2.194 IR of compound **295** (NaCl/film) 584

Figure A2.195 ^{13}C NMR of compound **295** (75 MHz, $CDCl_3$) 584

CHAPTER 4

Figure 4.1. X-ray crystal structure for π-allyl complex **114**, with PF_6 as the counter ion (i.e., **165**) 587

Figure 4.2. Relevant internal coordinates (Å) and thermodynamic energies of intermediates and transition states in this study (some atoms from the enolate and PHOX ligand are omitted from the figures for clarity) 589

Figure 4.3. Summary of energy pathway $\Delta E + E_{solv}$ for the enantioselective Tsuji Allylation reaction 590

CHAPTER 7

Figure 7.1. Diallyl Meldrum's acid by-product of protonation 732

Figure 7.2. Plot of substrate **293** ^{1}H NMR integral vs time 733

APPENDIX 3

Figure A3.1 ^{1}H NMR of compound **329** (300 MHz, $CDCl_3$) 783

Figure A3.2 IR of compound **329** (NaCl/film) 784

Figure A3.3 ^{13}C NMR of compound **329** (75 MHz, $CDCl_3$) 784

Figure A3.4 ^{1}H NMR of compound **241** (300 MHz, $CDCl_3$) 785

Figure A3.5 IR of compound **241** (NaCl/film) 786

Figure A3.6 ^{13}C NMR of compound **241** (75 MHz, $CDCl_3$) 786

Figure A3.7 ^{1}H NMR of compound **293** (300 MHz, $CDCl_3$) 787

Figure A3.8 IR of compound **293** (NaCl/film) 788

Figure A3.9 ^{13}C NMR of compound **293** (75 MHz, $CDCl_3$) 788

Figure A3.10 ^{1}H NMR of compound **98** (300 MHz, $CDCl_3$) 789

Figure A3.11 IR of compound **98** (NaCl/film) 790

Figure A3.12 ^{13}C NMR of compound **98** (75 MHz, $CDCl_3$) 790

Figure A3.13 ^{1}H NMR of compound **640** (300 MHz, $CDCl_3$) 791

Figure A3.14 IR of compound **640** (NaCl/film) 792

Figure A3.15 ^{13}C NMR of compound **640** (75 MHz, $CDCl_3$) 792

Figure A3.16 ^{1}H NMR of compound **498** (300 MHz, $CDCl_3$) 793

Figure A3.17 IR of compound **498** (NaCl/film) 794

Figure A3.18 ^{13}C NMR of compound **498** (75 MHz, $CDCl_3$) 794

Figure A3.19 ^{1}H NMR of compound **629** (300 MHz, $CDCl_3$) 795

Figure A3.20 IR of compound **629** (NaCl/film) 796

Figure A3.21 ^{13}C NMR of compound **629** (75 MHz, $CDCl_3$) 796

Figure A3.22 ^{1}H NMR of compound **643** (300 MHz, $CDCl_3$) 797

Figure A3.23 IR of compound **643** (NaCl/film) 798

Figure A3.24 ^{13}C NMR of compound **643** (75 MHz, $CDCl_3$) 798

Figure A3.25 ^{1}H NMR of compound **644** (300 MHz, $CDCl_3$) 799

Figure A3.26 IR of compound **644** (NaCl/film) 800

Figure A3.27 ^{13}C NMR of compound **644** (75 MHz, $CDCl_3$) 800

Figure A3.28 ^{1}H NMR of compound **646** (300 MHz, $CDCl_3$) 801

Figure A3.29 IR of compound **646** (NaCl/film) 802

Figure A3.30 ^{13}C NMR of compound **646** (75 MHz, $CDCl_3$) 802

Figure A3.31 ^{1}H NMR of compound **648** (300 MHz, $CDCl_3$) 803

Figure A3.32 IR of compound **648** (NaCl/film) 804

Figure A3.33 ^{13}C NMR of compound **648** (75 MHz, $CDCl_3$) 804

Figure A3.34 ^{1}H NMR of compound **650** (300 MHz, $CDCl_3$) 805

Figure A3.35 IR of compound **650** (NaCl/film) 806

Figure A3.36 ^{13}C NMR of compound **650** (75 MHz, $CDCl_3$) 806

Figure A3.37 ^{1}H NMR of compound **107** (300 MHz, $CDCl_3$) 807

Figure A3.38 IR of compound **107** (NaCl/film) 808

Figure A3.39 ^{13}C NMR of compound **107** (75 MHz, $CDCl_3$) 808

Figure A3.40 ^{1}H NMR of compound **318** (300 MHz, $CDCl_3$) 809

Figure A3.41 IR of compound **318** (NaCl/film) 810

Figure A3.42 ^{13}C NMR of compound **318** (75 MHz, $CDCl_3$) 810

Figure A3.43 ^{1}H NMR of compound **631** (300 MHz, $CDCl_3$) 811

Figure A3.44 ^{13}C NMR of compound **631** (75 MHz, $CDCl_3$) 812

Figure A3.45 ^{1}H NMR of compound **682** (300 MHz, $CDCl_3$) 813

Figure A3.46 ^{13}C NMR of compound **682** (75 MHz, $CDCl_3$) 814

Figure A3.47 ^{1}H NMR of compound **258** (300 MHz, $CDCl_3$) 815

Figure A3.48 IR of compound **258** (NaCl/film) 816

Figure A3.49 ^{13}C NMR of compound **258** (75 MHz, $CDCl_3$) 816

Figure A3.50 ^{1}H NMR of compound **676** (300 MHz, $CDCl_3$) 817

Figure A3.51 ^{1}H NMR of compound **207** (300 MHz, $CDCl_3$) 818

Figure A3.52 ^{1}H NMR of compound **221** (300 MHz, $CDCl_3$) 819

Figure A3.53 ^{1}H NMR of compound **639** (300 MHz, $CDCl_3$) 820

Figure A3.54 ^{1}H NMR of compound **674** (300 MHz, $CDCl_3$) 821

Figure A3.55 ^{1}H NMR of compound **675** (300 MHz, $CDCl_3$) 822

Figure A3.56 ^{13}C NMR of compound **675** (75 MHz, $CDCl_3$) 823

Figure A3.57 ^{1}H NMR of compound **97** (300 MHz, $CDCl_3$) 824

Figure A3.58 ^{1}H NMR of compound **641** (300 MHz, $CDCl_3$) 825

Figure A3.59 ^{1}H NMR of compound **649** (300 MHz, $CDCl_3$) 826

Figure A3.60 ^{1}H NMR of compound **638** (300 MHz, $CDCl_3$) 827

CHAPTER 9

Figure 9.1. Structures of (+)-cassiol and (–)-cassioside 849

APPENDIX 4

Figure A4.1 ^{1}H NMR spectrum of compound **731** (500 MHz, $CDCl_3$) 883

Figure A4.2 ^{1}H NMR spectrum of compound **733** (500 MHz, $CDCl_3$) 884

Figure A4.3 ^{13}C NMR spectrum of compound **733** (126 MHz, $CDCl_3$) 885

Figure A4.4 ^{1}H NMR spectrum of compound **321** (500 MHz, $CDCl_3$) 886

Figure A4.5 ^{13}C NMR spectrum of compound **321** (126 MHz, $CDCl_3$) 887

Figure A4.6 ^{1}H NMR spectrum of compound **267** (500 MHz, $CDCl_3$) 888

Figure A4.7 ^{13}C NMR spectrum of compound **267** (126 MHz, $CDCl_3$) 889

Figure A4.8 ^{1}H NMR spectrum of compound **322** (500 MHz, $CDCl_3$) 890

Figure A4.9 ^{13}C NMR spectrum of compound **322** (126 MHz, $CDCl_3$) 891

Figure A4.10 ^{1}H NMR spectrum of compound **323** (300 MHz, $CDCl_3$) 892

Figure A4.11 ^{13}C NMR spectrum of compound **323** (75 MHz, $CDCl_3$) 893

Figure A4.12 ^{1}H NMR spectrum of compound **268** (300 MHz, $CDCl_3$) 894

Figure A4.13 ^{13}C NMR spectrum of compound **268** (75 MHz, $CDCl_3$) 895

Figure A4.14 ^{1}H NMR spectrum of compound **472** (500 MHz, $CDCl_3$) 896

Figure A4.15 ^{13}C NMR spectrum of compound **472** (75 MHz, $CDCl_3$) 897

Figure A4.16 ^{1}H NMR spectrum of compound **473** (300 MHz, $CDCl_3$) 898

Figure A4.17 ^{13}C NMR spectrum of compound **473** (75 MHz, $CDCl_3$) 899

Figure A4.18 ^{1}H NMR spectrum of compound **474** (500 MHz, $CDCl_3$) 900

Figure A4.19 ^{13}C NMR spectrum of compound **474** (75 MHz, $CDCl_3$) 901

Figure A4.20 ^{1}H NMR spectrum of compound **729** (500 MHz, C_6D_6) 902

Figure A4.21 ^{13}C NMR spectrum of compound **729** (75 MHz, C_6D_6) 903

Figure A4.22 ^{1}H NMR spectrum of compound **270** (500 MHz, D_2O) 904

Figure A4.23 ^{13}C NMR spectrum of compound **270** (126 MHz, D_2O) 905

Figure A4.24 ^{1}H NMR spectrum of compound **270** (500 MHz, $CDCl_3$) 906

Figure A4.25 ^{13}C NMR spectrum of compound **270** (126 MHz, $CDCl_3$) 907

CHAPTER 10

Figure 10.1. Structures of the antibiotics platencin (**737**) and platensimycin (**738**) 908

Figure 10.2. ORTEP plot of dione **751** derived from X-ray crystallographic analysis (nonhydrogen atoms are shown with ellipsoids at 50% probability) 914

Figure 10.3 Representations of diketone **751** 947

Figure 10.4 Anisotropic displacement parameters ($Å^2$ x 10^4) for **751** (CCDC 686706). 951

APPENDIX 5

Figure A5.1 ^{1}H NMR of compound **747** (300 MHz, C_6D_6) 955

Figure A5.2 IR of compound **747** (NaCl/film)..... 956

Figure A5.3 ^{13}C NMR of compound **747** (75 MHz, C_6D_6)..... 956

Figure A5.4 ^{1}H NMR of compound **760** (500 MHz, C_6D_6) 957

Figure A5.5 IR of compound **760** (NaCl/film)..... 958

Figure A5.6 ^{13}C NMR of compound **760** (125 MHz, C_6D_6) 958

Figure A5.7 ^{1}H NMR of compound **761** (500 MHz, C_6D_6) 959

Figure A5.8 IR of compound **761** (NaCl/film)..... 960

Figure A5.9 ^{13}C NMR of compound **761** (125 MHz, C_6D_6) 960

Figure A5.10 ^{1}H NMR of compound **743** (500 MHz, $CDCl_3$)..... 961

Figure A5.11 ^{13}C NMR of compound **743** (125 MHz, $CDCl_3$) 962

Figure A5.12 ^{1}H NMR of compound **744** (500 MHz, $CDCl_3$)..... 963

Figure A5.13 ^{13}C NMR of compound **744** (125 MHz, $CDCl_3$) 964

Figure A5.14 ^{1}H NMR of compound **742** (500 MHz, $CDCl_3$)..... 965

Figure A5.15 ^{13}C NMR of compound **742** (125 MHz, $CDCl_3$) 966

Figure A5.16 ^{1}H NMR of compound **763** (500 MHz, $CDCl_3$)..... 967

Figure A5.17 ^{13}C NMR of compound **763** (125 MHz, $CDCl_3$) 968

Figure A5.18 ^{1}H NMR of compound **748** (500 MHz, $CDCl_3$)..... 969

Figure A5.19 ^{13}C NMR of compound **748** (125 MHz, $CDCl_3$) 970

Figure A5.20 ^{1}H NMR of compound **741** (500 MHz, $CDCl_3$)..... 971

Figure A5.21 ^{13}C NMR of compound **741** (125 MHz, $CDCl_3$) 972

Figure A5.22 ^{1}H NMR of compound **767** (500 MHz, $CDCl_3$)..... 973

Figure A5.23 ^{13}C NMR of compound **767** (125 MHz, $CDCl_3$) 974

Figure A5.24 ^{1}H NMR of compound **753** (500 MHz, $CDCl_3$)..... 975

Figure A5.25 ^{13}C NMR of compound **753** (125 MHz, $CDCl_3$) 976

Figure A5.26 ^{1}H NMR of compound **754** (500 MHz, $CDCl_3$)..... 977

Figure A5.27 ^{13}C NMR of compound **754** (125 MHz, $CDCl_3$) 978

Figure A5.28 ^{1}H NMR of compound **750** (500 MHz, $CDCl_3$)..... 979

Figure A5.29 ^{13}C NMR of compound **750** (125 MHz, $CDCl_3$).....980

Figure A5.30 ^{1}H NMR of compound **749** (500 MHz, $CDCl_3$).....981

Figure A5.31 ^{13}C NMR of compound **749** (125 MHz, $CDCl_3$).....982

Figure A5.32 ^{1}H NMR of compound **751** (500 MHz, $CDCl_3$).....983

Figure A5.33 ^{13}C NMR of compound **751** (125 MHz, $CDCl_3$).....984

Figure A5.34 ^{1}H NMR of compound **740** (500 MHz, $CDCl_3$).....985

Figure A5.35 ^{13}C NMR of compound **740** (125 MHz, $CDCl_3$).....986

Figure A5.36 ^{1}H NMR of compound **756** (500 MHz, $CDCl_3$).....987

Figure A5.37 ^{13}C NMR of compound **756** (125 MHz, $CDCl_3$).....988

APPENDIX 6

Figure A6.1 PHOX derivatives prepared via this protocol 1003

APPENDIX 7

Figure A7.1 Ketones prepared via enantioselective decarboxylative allylation.....1022

Figure A7.1 Synthetic targets accessed via enantioselective decarboxylative allylation 1023

Figure A7.2 (a) Derivatives of 2-allyl-2-methylcyclohexanone. (b) Spirocycles accessible via ring-closing metathesis. (c) Cleavage of dioxanones to access acyclic products. 1024

LIST OF SCHEMES

CHAPTER 1

Scheme 1.1. Enantioselective Diels–Alder cycloaddition and enantioselective ketone reduction en route to prostaglandins 3

Scheme 1.2. a) Enantioselective enamide hydrogenation toward α-amino acids; b) Enantioselective alkene epoxidation toward Crixivan®; c) Enantioselective isomerization of an allyl amine toward menthol 5

Scheme 1.3. Enantioselective intramolecular aldol condensation toward steroids 6

Scheme 1.4. Convergent application of various enantioselective methods toward the synthesis of phorboxazole B 7

Scheme 1.5. Enantioselective hydrogenation of a β-enamino amide toward the synthesis of Januvia® 10

Scheme 1.6. Enantioselective C(sp^3)–C(sp^3) cross-couplings toward fluvirucinine A1 14

Scheme 1.7. Enantioselective intramolecular Heck reaction toward minfiensine 16

Scheme 1.8. Enantioselective Friedel–Crafts alkylation toward flustramine B 18

Scheme 1.9. Enantioselective Pictet–Spengler cyclization toward harmicine 20

Scheme 1.10. Phase-transfer alkylation toward indacrinone 22

Scheme 1.11. Pd-catalyzed enolate alkylations toward cyanthiwigin F 24

Scheme 1.12. a) Pd-catalyzed TMM-[3 + 2]-cycloaddition toward marcfortine B b) Enantioselective TMM-cyclization 27

CHAPTER 2

Scheme 2.1. Trost's allylic alkylation with prochiral nucleophiles 40

Scheme 2.2. Tsuji's allylic alkylation methods 41

Scheme 2.3. Regiochemical fidelity in Tsuji's palladium-catalyzed alkylation 42

Scheme 2.4. Inactivity of (*S*)-*t*-Bu-PHOX oxide as an allylation catalyst 45

Scheme 2.5. Determination of absolute stereochemistry 54

Scheme 2.6. General catalytic cycle for silyl enol ether alkylation 56

Scheme 2.7. Allylation with Pd(II)PF_6 salt **165** 58

Scheme 2.8. Useful derivatives of enantioenriched cyclic ketones 60

Scheme 2.9. Enantioenriched cyclic ketones in the synthesis of natural products 61

CHAPTER 3

Scheme 3.1. Enantioselective allylation of allyl enol carbonates and silyl enol ethers 313

Scheme 3.2. Non-selective enolization leads to product mixtures 314

Scheme 3.3. Asymmetric decarboxylative allylation with an allyl β-Ketoester 315

Scheme 3.4. Stereoablative enantioconvergent catalysis 317

Scheme 3.5. Methods for the synthesis of racemic quaternary β-ketoesters 318

Scheme 3.6. Conversion of ketone **268** to the natural products (+)-carissone (**269**) and (+)-cassiol (**270**) 322

Scheme 3.7. Enantioselective cascade allylations generating two quaternary centers 323

Scheme 3.8. Helmchen's outer-sphere mechanism for asymmetric allylation of prochiral allyl electrophiles 326

Scheme 3.9. Proposed inner-sphere mechanism for asymmetric alkylation of prochiral enolate nucleophiles 328

Scheme 3.10. Crossover experiments with deuterated allyl enol carbonates 334

CHAPTER 4

Scheme 4.1. The enantioselective Tsuji allylation 586

Scheme 4.2. The enantioselective Tsuji allylation mechanism studied in this work 587

CHAPTER 5

Scheme 5.1. a) Enantioselective allylic alkylation with stabilized enolates b) Enantioselective allylic alkylation with unstabilized enolates 619

Scheme 5.2. Tsuji allylation reactions 620

Scheme 5.3. Regiochemical fidelity in the Tsuji allylation 621

Scheme 5.4. Enantioenriched cycloalkanones produced from allyl enol carbonates 623

Scheme 5.5. Enantioenrichment of ketone (–)-**106** via the semicarbazone derivative 623

Scheme 5.6. Enantioenriched cycloalkanones produced from allyl enol carbonates 625

Scheme 5.7. Enantioenriched ketones produced from (*Z*)-enol carbonates 626

Scheme 5.8. Reactivity differences for (*E*)- and (*Z*)-enol carbonates 627

Scheme 5.9. Allylic alkylation from isomeric silyloxy substituted allyl enol carbonates 628

Scheme 5.10. Allylic alkylation to form α-silyloxy aldehydes and ketones 629

Scheme 5.11. Regiochemical fidelity with acyloxy enol carbonates 630

Scheme 5.12. Allylic alkylation to form α-acyloxy ketones 630

Scheme 5.13. Enantioenriched cycloalkanones produced from silyl enol ethers 632

Scheme 5.14. Enantioselective alkylation using dioxanone derived enol silanes 634

Scheme 5.15. Non-selective enolization leads to mixtures of allylated products 635

Scheme 5.16. Enantioselective decarboxylative allylation with an allyl β-ketoester 636

Scheme 5.17. Enantioenriched cycloalkanones prepared from allyl β-ketoesters 637

Scheme 5.18. Enantioselective cascade allylation generating two quaternary stereocenters 638

Scheme 5.19. Vinylogous thioesters prepared from allyl β-ketoesters 639

Scheme 5.20. Allylation in the presence of a pendent 1,3-diester 640

Scheme 5.21. Alkylation of vinylogous esters and thioesters with the Pd•PHOX catalyst system 640

Scheme 5.22. Enantioselective Tsuji allylation in the total synthesis of (+)-dichroanone 641

Scheme 5.23. Enantioselective formal synthesis of (*S*)-oxybutynin 643

Scheme 5.24. Progress toward the total synthesis of zoanthenol 645

Scheme 5.25. Total synthesis of cyanthiwigin F via double enantioselective alkylation.....647

Scheme 5.26. Total syntheses of laurencenone B and elatol.....648

Scheme 5.27. Formal synthesis of quinic acid.....648

Scheme 5.28. Enantioselective synthesis of carissone.....650

Scheme 5.29. Enantioselective total synthesis of cassiol.....651

Scheme 5.30. Enantioenriched α-fluoroketones derived from allyl β-ketoesters.....652

Scheme 5.31. Enantioenriched α-fluorocycloalkanones prepared from allyl β-ketoesters.....653

Scheme 5.32. Enantioenriched α-fluorocycloalkanones prepared from silyl enol ethers.....654

Scheme 5.33. Alkylation with pseudoenantiomeric ligands.....654

Scheme 5.34. Alkylation using fluorinated enol carbonates.....655

Scheme 5.35. Alkylation reactions relatively unaffected by ligand-to-metal ratio.....656

Scheme 5.36. Asymmetric ring-expanding allylation.....657

Scheme 5.37. Interrupted allylic alkylation.....659

Scheme 5.38. a) Transformations of ketone (–)-**106** b) Ring-closing metathesis to form a spirocycle.....660

Scheme 5.39. Stork–Danheiser type transformations of vinylogous thioester (*R*)-**51**.....661

Scheme 5.40. Useful derivatives of enantioenriched dioxanones.....661

Scheme 5.41. a) Trost's crossover experiment b) Stoltz' crossover experiment.....662

Scheme 5.42. Possible catalytic cycle for decarboxylative allylation.....663

CHAPTER 6

Scheme 6.1. Enantioselective tautomerization of an isolated enol.....678

Scheme 6.2. Enzymatic decarboxylative protonation with wild-type and mutant decarboxylases.....679

Scheme 6.3. Enzymatic oxidation/decarboxylation/protonation/oxidation cascade.....681

Scheme 6.4. Enzymatic hydrolysis of enol acetates.....682

Scheme 6.5. Kim's enolate protonation.....685

Scheme 6.6. Eames's enolate protonation 685

Scheme 6.7. Rouden's decarboxylative protonation 686

Scheme 6.8. Donohoe's partial pyrrole reduction 687

Scheme 6.9. Rueping's quinoline reduction/protonation 688

Scheme 6.10. Yamamoto's enol silane protonation 689

Scheme 6.11. Yanagisawa's lithium enolate protonation 689

Scheme 6.12. Yanagisawa's enol silane protonation 690

Scheme 6.13. Levacher's enol silane protonation 691

Scheme 6.14. Deng's conjugate addition/protonation 692

Scheme 6.15. Tan's conjugate addition/protonation 693

Scheme 6.16. Hénin/Muzart Norrish type II fragmentation/protonation 693

Scheme 6.17. Fu's addition of hydrazoic acid to ketenes followed by Curtius rearrangement .. 694

Scheme 6.18. Fu's Addition of alcohols to ketenes 696

Scheme 6.19. Rovis' protonation of chloroenolates 697

Scheme 6.20. Scheidt's protonation of homoenolate equivalents 697

Scheme 6.21. Frost's Rh-catalyzed conjugate addition/protonation 699

Scheme 6.22. Sibi's Rh-catalyzed conjugate addition/protonation 699

Scheme 6.23. Hayashi's Rh-catalyzed conjugate addition/protonation 700

Scheme 6.24. Conjugate addition/protonation with a nitrogen nucleophile catalyzed by palladium 700

Scheme 6.25. Divergent pathway consisting of β-hydride elimination, hydride transfer, and protonation 701

Scheme 6.26. Friedel–Crafts-type conjugate addition followed by enantioselective protonation 702

Scheme 6.27. Trauner's Nazarov cyclization/enantioselective protonation 703

Scheme 6.28. Stoltz' palladium-catalyzed decarboxylative protonation reactions 704

Scheme 6.29. Kanai and Shibasaki's gadolinium-catalyzed protonation reactions 706

Scheme 6.30. Radical conjugate addition followed by enantioselective H-atom transfer 707

CHAPTER 7

Scheme 7.1. Interception of the putative Pd-enolate intermediate 715

Scheme 7.2. Initial attempts at enantioselective protonation.....716

Scheme 7.3. Enantioselective protonation with allyl enol carbonate and silyl enol ether substrates.....723

Scheme 7.4. Acetoacetic ester synthesis vs alkylation/decarboxylation sequence.....724

Scheme 7.5. Pd-catalyzed enantioselective decarboxylative allylation and protonation of racemic allyl β-ketoesters 725

Scheme 7.6. Proposed catalytic cycle for enantioselective protonation.....734

CHAPTER 8

Scheme 8.1. Strategies for enantioselective catalysis.....829

Scheme 8.2. Stoltz' oxidative kinetic resolution of secondary alcohols 831

Scheme 8.3. Stoltz' stereoablative kinetic resolution with recycle.....831

Scheme 8.4. OKR in the Stoltz synthesis of (+)-amurensinine 832

Scheme 8.5. Jackson's oxidation of sulfoxides and sulfides.....833

Scheme 8.6. Noyori's reductive kinetic resolution 834

Scheme 8.7. Stoltz' desymmetrization of meso diol **696**.....834

Scheme 8.8. Andersson's epoxide desymmetrization.....835

Scheme 8.9. Bäckvall's dynamic kinetic resolution of alcohols 836

Scheme 8.10. Williams' deracemization of benzylic alcohols 837

Scheme 8.11. Stoltz' stereoablative enantioconvergent ketone alkylation 838

Scheme 8.12. Stoltz' cascade asymmetric allylation generating two quaternary stereocenters ..839

Scheme 8.13. Stoltz' stereoablative enantioconvergent protonation 840

Scheme 8.14. Vedejs' enantioselective enolate protonation 840

Scheme 8.15. Hénin and Muzart's photolytic stereoablative process 841

Scheme 8.16. Fu's enantioconvergent Negishi coupling 842

Scheme 8.17. Stoltz' stereoablative oxindole functionalization 843

Scheme 8.18. Trost's doubly-stereoconvergent allylic alkylation 843

CHAPTER 9

Scheme 9.1. Retrosynthetic analysis of (+)-cassiol (**270**) 850

Scheme 9.2. Enantioselective synthesis of alcohol (–)-**474** 853

Scheme 9.3. Synthesis of vinyl iodide **729** 855

Scheme 9.4. Preparation of (+)-cassiol (**270**) 855

CHAPTER 10

Scheme 10.1. Retrosynthetic analysis of platencin (**737**) 910

Scheme 10.2. Investigations of the Tsuji allylation 911

Scheme 10.3. Revised retrosynthesis of the platencin core 912

Scheme 10.4. Assembly of the bicyclo[2.2.2]octadione scaffold 913

Scheme 10.5. Formal synthesis of platencin 914

APPENDIX 6

Scheme A6.1 Amino acid reduction and amide bond formation 989

Scheme A6.1 Oxazoline formation 992

Scheme A6.2 C–P cross-coupling 993

APPENDIX 7

Scheme A7.1 Substrate synthesis 1007

Scheme A7.2 Enantioselective decarboxylative allylation 1009

Scheme A7.3 Increase of ee by means of semicarbazone derivative..... 1011

LIST OF TABLES

CHAPTER 2

Table 2.1. Initial ligand screen 44

Table 2.2. Effect of concentration on asymmetric allylation 46

Table 2.3. Effect of solvent on asymmetric allylation 47

Table 2.4. Effect of phosphinooxazoline sterics on asymmetric allylation 49

Table 2.5. Effect of phosphine electronics on asymmetric allylationa 50

Table 2.6. Effect of varied heteroatom chelates on asymmetric allylation 51

Table 2.7. Substrate scope for asymmetric allylation of allyl enol carbonates 53

Table 2.8. Substrate scope for asymmetric allylation of silyl enol ethers 57

Table 2.9. Enantioselective allylation of enol carbonates and silyl enol ethers not contained in a ring 63

Table 2.10. Enantioselective propargylation 64

Table 2.11. Asymmetric alkylation via stabilized allyl enol carbonates 65

Table 2.12. Methods used for the determination of enantiomeric excess 129

Table 2.13. Crystal data and structure refinement for semicarbazone **161** (CCDC 246585) 134

Table 2.14. Crystal data and structure refinement for semicarbazone **162** (CCDC 248956) 137

Table 2.15. Crystal data and structure refinement for [Pd(II)(allyl)PHOX]•PF_6 (CCDC 245187) 149

CHAPTER 3

Table 3.1. Temperature effects in decarboxylative allylation of allyl β-ketoesters 316

Table 3.2. Enantioconvergent decarboxylative allylation of α-Substituted 2-carboxyallylcyclohexanones 319

Table 3.3. Enantioconvergent decarboxylative allylation of β-ketoesters with substituted carbocycles and allyl fragments 321

Table 3.4. Enantioconvergent decarboxylative allylation of β-ketoesters containing five-membered rings 324

Table 3.5. Effect of water on asymmetric alkylation 333

Table 3.6. Methods used for determining product ee 410

CHAPTER 7

Table 7.1. Effect of basic additives on enantioselecitve protonation 717

Table 7.2. Effect of other additives on enantioselective protonation 717

Table 7.3. Effect of palladium source on enantioselective protonation 718

Table 7.4. Effect of solvent on enantioselective protonation 718

Table 7.5. Ligand screen for enantioselective protonation 719

Table 7.6. Optimization of relative amounts of HCO_2H and 4ÅMS 720

Table 7.7. Enantioconvergent decarboxylative protonations with formic acid 721

Table 7.8. Screening of achiral proton donors 727

Table 7.9. Screening of Meldrum's acid derivatives 729

Table 7.10. Homogeneous enantioconvergent decarboxylative protonations with Meldrum's acid 731

Table 7.11. Methods for the determination of enantiomeric excess (formic acid conditions) 763

Table 7.12. Optimization of chiral ligand (Meldrum's acid conditions) 769

Table 7.13. Methods for the determination of enantiomeric excess (Meldrum's acid conditions) 777

CHAPTER 9

Table 9.1. Enantioselective alkylation of vinylogous esters 852

Table 9.2. Comparison of ^{1}H NMR data for synthetic, literature, and natural (+)-cassiol 879

Table 9.3. Comparison of ^{13}C NMR data for synthetic, literature, and natural (+)-cassiol 879

Table 9.4. Comparison of IR data for synthetic, literature, and natural (+)-cassiol 880

Table 9.5. Comparison of HRMS data for synthetic, literature, and natural (+)-cassiol 880

Table 9.6. Comparison of optical rotation data for synthetic, literature, and natural (+)-cassiol 880

CHAPTER 10

Table 10.1 Crystal data and structure refinement for diektone **751** (CCDC 686706). 944

Table 10.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **751** (CCDC 686706).. 949

Table 10.3 Bond lengths [Å] and angles [°] for **751** (CCDC 686706). 950

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LIST OF ABBREVIATIONS

Å	Ångstrom
$[\alpha]_D$	specific rotation at wavelength of sodium D line
Ac	acetyl
app.	apparent
aq	aqueous
Ar	aryl
atm	atmosphere
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bp	boiling point
br	broad
Bu	butyl
n-Bu	*n*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
c	concentration for specific rotation measurements
°C	degrees Celsius (centigrade)
calc'd	calculated
cat.	catalytic
CCDC	Cambridge Crystallographic Data Centre
CI	chemical ionization
comp.	complex
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone

DCE	dichloroethane
dec.	decomposition
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FAB	fast atom bombardment
g	gram(s)
GC	gas chromatography
h	hour(s)
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
$h\nu$	light
Hz	Hertz
IR	infrared (spectroscopy)
J	coupling constant
λ	wavelength
L	liter
L_n	L-type ligand
m	multiplet or milli
m	meta

m/z	mass to charge ratio
μ	micro
M	metal or molar
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
mp	melting point
MS	molecular sieves
n	nano
N	normal (normality)
NMR	nuclear magnetic resonance
o	ortho
p	para
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PhH	benzene
ppm	parts per million
i-Pr	isopropyl
Py	pyridine
q	quartet
ref	reference
R_f	retention factor
s	singlet or selectivity factor
sat.	saturated
t	triplet
TBAF	tetrabutylammonium fluoride

TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl (trifyl)
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl (tosyl)
X	anionic ligand or halide

CHAPTER 1

Natural Products and Pharmaceuticals as Inspiration for the Development of Enantioselective Catalysis[†]

1.1 INTRODUCTION

Biologically active natural products and pharmaceuticals often contain particularly challenging structural features and functionalities in terms of synthesis. Perhaps the greatest difficulties are those caused by issues of stereochemistry. A useful strategy for synthesizing such molecules is to devise methods of bond formation that provide opportunities for using enantioselective catalysis. In using this tactic, the desire for a particular target structure ultimately drives the development of catalytic methods. New enantioselective catalytic methods contribute to a greater fundamental understanding of how bonds can be constructed and lead to valuable synthetic technologies that are useful for a variety of applications. The lack of methods available for installing functionalities or structural motifs during chemical synthesis can at first be frustrating. However, retrosynthetic analysis,[1] a way of viewing the target molecule as a series of structurally

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[†] This review was written in collaboration with Michael R. Krout and a similar version has been published. See: Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Nature* **2008**, *455*, 323–332.

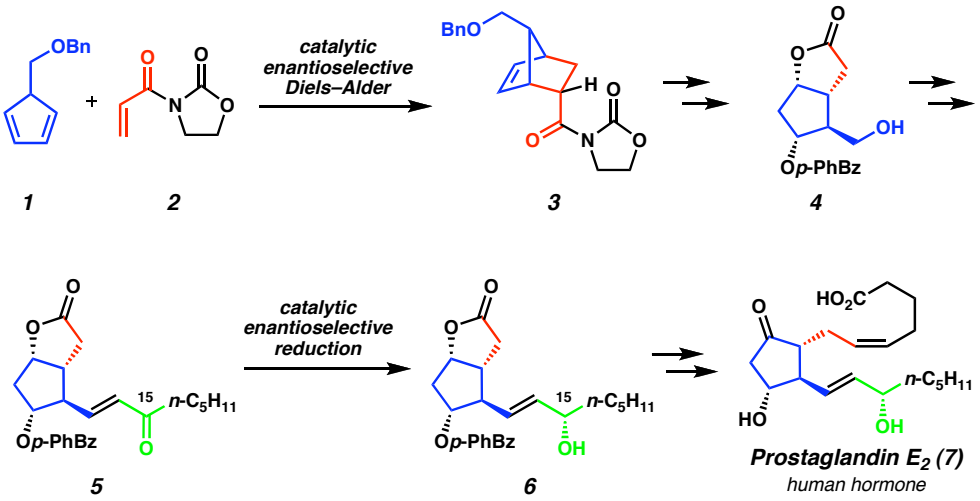
simpler precursors, can greatly aid in planning how to generate a valuable chemical substance. Despite this, difficulties in preparing materials enriched in a particular enantiomer persist because of the limited number of catalytic enantioselective transformations available.[2] One fruitful strategy is to design a synthesis that depends on a bond-forming reaction for which there is no known enantioselective variant. This approach thus provides the impetus for developing novel transformations and leads to a greater understanding of methods of bond construction and catalysis. Herein, several recent examples of novel catalytic enantioselective transformations are described in order to illustrate the effectiveness of this strategy for preparing important structural motifs found in biologically active molecules. Each of these transformations has contributed not only an effective means of generating a particular target structure but also a useful new tool for a variety of applications in synthetic chemistry.

1.2 HISTORICAL OVERVIEW OF ENANTIOSELECTIVE METHODS

To provide an overview of established catalytic enantioselective methods that have been developed for total synthesis, several notable examples of enantioselective reactions in total synthesis are highlighted in Scheme 1.1 through Scheme 1.4. In each of these cases, the target molecules posed particular challenges that had yet to be solved by enantioselective catalysis. Although, in some instances (e.g., the Diels–Alder reaction, Scheme 1.1), the methods were developed before their first application in total synthesis, the demonstrated value of the transformation highlighted the need for enantioselective variants. Following the development of the [4 + 2] cycloaddition reaction in the 1920s,[3]

studies of this transformation elucidated several key facets of the stereochemical outcome of the reaction (e.g., the "endo rule," regioselectivity, and diastereoselectivity). These intrinsic stereochemical control elements proved useful when the Diels–Alder reaction was first featured in a total synthesis with Stork's stereocontrolled synthesis of cantharidin[4] in 1951. Subsequently, the thermal Diels–Alder reaction was used for several total syntheses, perhaps most famously in Woodward's landmark synthesis of reserpine.[5] Enantioselectivity in this transformation remained elusive, however, and perhaps was considered unattainable at the time.

Scheme 1.1. Enantioselective Diels–Alder cycloaddition and enantioselective ketone reduction en route to prostaglandins



One key practical improvement in the Diels–Alder reaction was the discovery that Lewis acids markedly increased the reaction rate.[6] Many laboratories sought to exploit this and to develop asymmetric versions of the Diels–Alder reaction catalyzed by chiral Lewis acids, culminating in a report of the first highly enantioselective catalytic Diels–Alder reaction in 1979.[7] The interface between reaction development, study of the mechanism, and synthesis is readily apparent from the multitude of chiral Diels–Alder

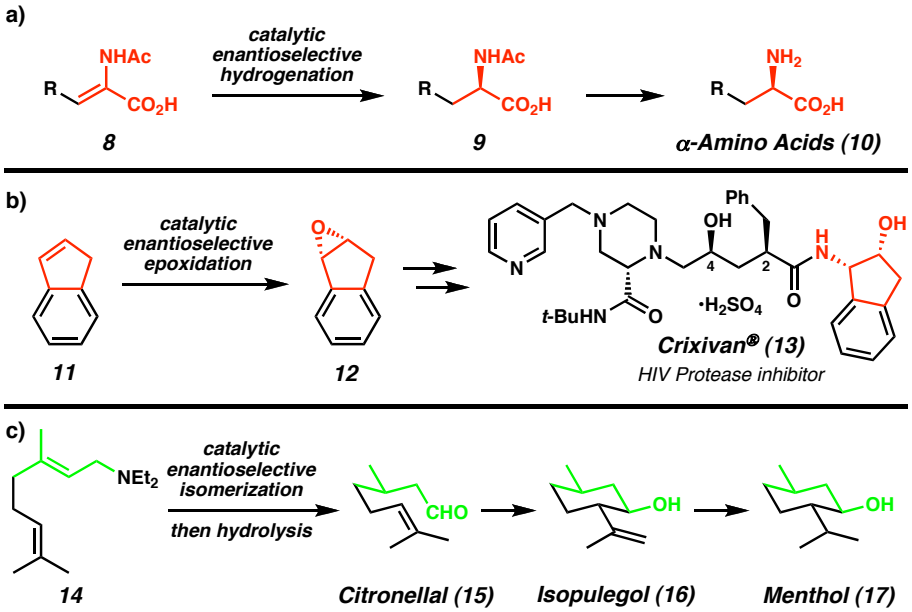
catalysts and accompanying enantioselective total syntheses that have been reported.[8] These successes validate the extensive efforts directed at realizing this important goal.

Other methods were developed to address more general problems in synthesis (e.g., synthesis of chiral alcohols by means of enantioselective ketone reduction, Scheme 1.1); however, the key structures are embedded in a variety of important natural products and pharmaceutical compounds. In the case of Corey's approach to the synthesis of prostaglandins,[9] first reported in the 1960s, control of the configuration of the side chain allylic alcohol at C15 required stoichiometric chiral reducing agents until a solution to this long-standing problem was found in the 1980s.[10] Interestingly, the oxazaborolidine catalyst discovered in these explorations has had other varied applications in synthesis and catalysis,[11] demonstrating the versatility of privileged molecular frameworks[12] for enantioselective catalysis.

The practical application of enantioselective catalysis is apparent in myriad industrial applications (e.g., Scheme 1.2), for which the limits of catalysis must be examined to minimize costs. Important industrial applications include the synthesis of chiral building blocks (e.g., amino acids[13] (**10**)), novel biologically active pharmaceuticals (e.g., Crixivan[14] (indinavir sulfate, **13**)), and commodity chemicals (cheap chemicals sold in bulk) with various important uses (e.g., menthol[15] (**17**)). Only the most efficient methods are feasible for large-scale industrial synthesis, and in many ways these protocols represent the pinnacle of modern enantioselective catalysis.[16] A viable commercial operation must account for more than simply effective asymmetric induction; factors including turnover frequency, catalyst availability, catalyst recovery, catalyst toxicity, and feasible large-scale handling procedures must all be considered for industrial

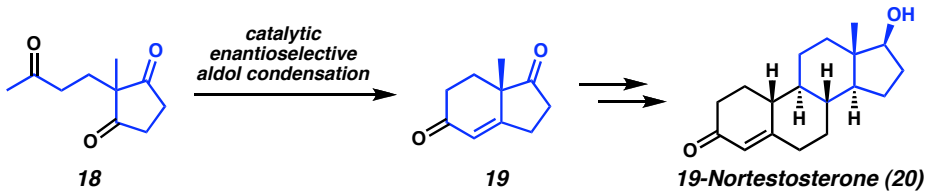
applications. These daunting challenges underscore the demand for increasingly efficient catalyst systems.

Scheme 1.2. a) Enantioselective enamide hydrogenation toward α-amino acids; b) Enantioselective alkene epoxidation toward Crixivan®; c) Enantioselective isomerization of an allyl amine toward menthol



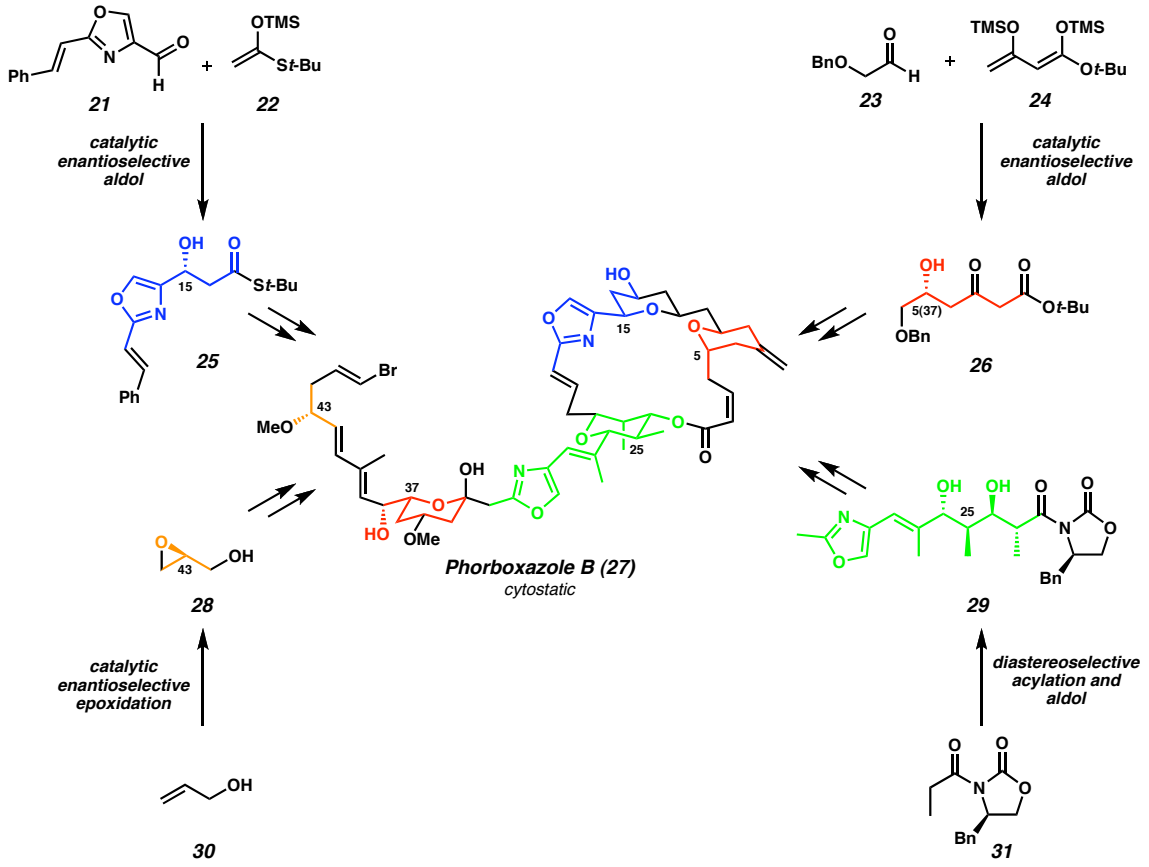
To maximize the usefulness of the stereochemistry attained by these key asymmetric transformations, subsequent diastereoselective reactions may be used to control the formation of many stereocenters based on a single enantioselective transformation (e.g., Scheme 1.3). The Hajos–Parrish ketone (**19**), first prepared in the context of steroid synthesis, has been used extensively in other synthetic efforts and has proved to be a versatile chiral-pool starting material.[17] The amino acid catalyst system developed for this intramolecular aldol condensation provided a sound basis for the recent use of organic molecules as catalysts for a variety of enantioselective transformations (see subsection 1.3.4).

Scheme 1.3. Enantioselective intramolecular aldol condensation toward steroids



The use of several different enantioselective reactions to prepare enantioenriched fragments of complex molecules improves efficiency through convergency. The importance of this strategy is shown by the variety of extraordinarily complex polyketide natural products that have been prepared through asymmetric intermolecular aldol reactions (e.g., phorboxazole B[18] (**27**), Scheme 1.4). The challenging structure of these molecules has required the development of several related protocols to address the subtle differences in substitution patterns and functionality present in substrates, and, despite many successes, studies are ongoing.[19]

Scheme 1.4. Convergent application of various enantioselective methods toward the synthesis of phorboxazole B



1.3 RECENT DEVELOPMENTS IN ENANTIOSELECTIVE CATALYSIS

In this section, recent representative developments made by using this approach — that is, by using target structures to inspire the development of enantioselective catalysts — for the construction of biologically important target molecules are described. Most of these methods involve the formation of a carbon–carbon bond, the fundamental structure of organic molecules. These cases were selected to illustrate some of the latest developments in enantioselective catalysis for complex molecule synthesis. Special

attention has been given to reactions that address some of the most important challenges in synthetic chemistry today: increasing functional-group tolerance, generating new carbocyclic and heterocyclic rings, and forming all-carbon quaternary stereocenters. The examples are also intended to show the important symbiosis between total synthesis and method development, and to show that improvements in one branch of synthetic chemistry have an impact on the others.

1.3.1 β-ENAMINO AMIDE HYDROGENATIONS—JANUVIA®

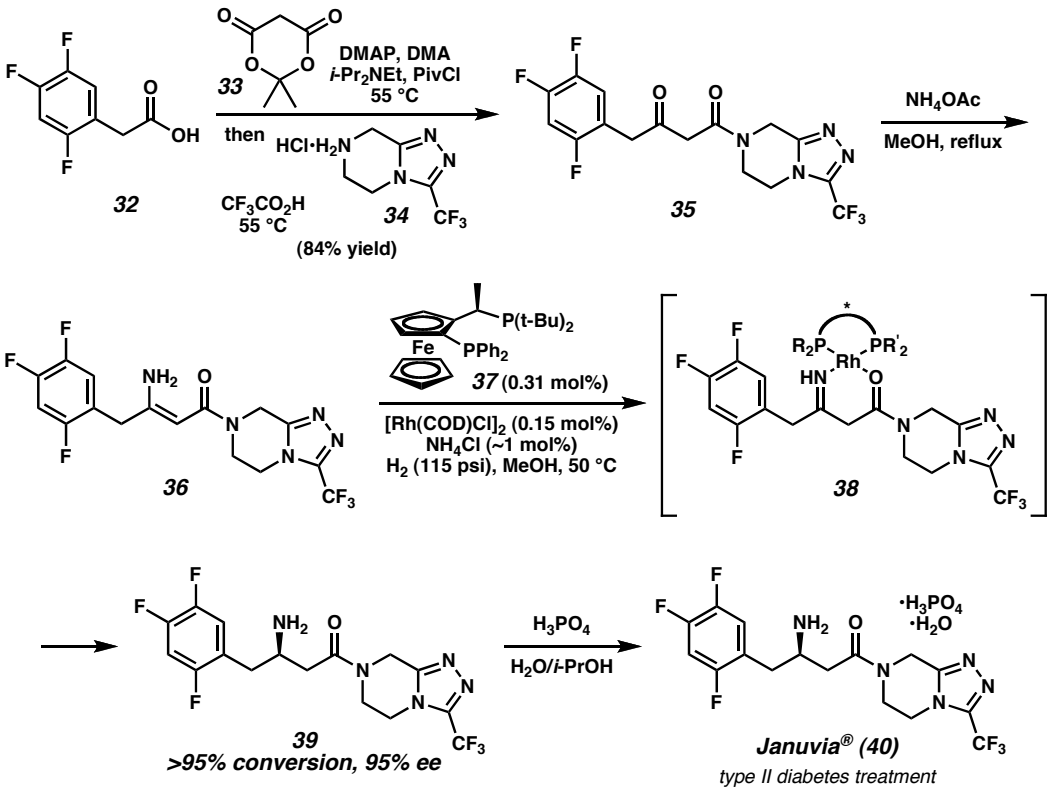
Catalytic enantioselective hydrogenation has become one of the most effective and powerful methods for the synthesis of chiral α-amino acids for numerous applications.[13] Over the past decade, the usefulness of the homologous building blocks, β-amino acids, in pharmaceutical, agrochemical, β-peptide, and natural substances has become evident, highlighting the need for a general and effective means for their preparation.[20] Undoubtedly, the implementation of a catalytic asymmetric hydrogenation of *N*-acyl-β-enamino esters seemed to be the most efficient pathway toward their synthesis, although initial investigations achieved poor selectivities.[21] Additional syntheses using the chiral pool, auxiliaries, and more recently the catalytic asymmetric generation of C–C and C–N bonds have been successful in satisfying the increased demand for β-amino acids.[20b] These valuable methods allow flexible strategies for the synthesis of a variety of analogs; however, most examples are limited by the requirement for further chemical manipulation that is often necessary to produce the functionality of the desired β-amino acids.

Despite initial difficulties, the asymmetric hydrogenation of *N*-acyl-β-enamino esters has been developed into a useful method over the past 15 years.[22] This fruitful endeavor has demonstrated that several transition metal and ligand combinations are competent for preparing *N*-acyl-β-amino acids with good-to-excellent enantioselectivities. A notable drawback to this strategy, however, is the requirement for the seemingly indispensable *N*-acyl group on the β-enamino esters; this group is needed for metal chelation, which improves reactivity and selectivity. The introduction of this moiety often produces enamine alkene isomers that can be difficult to separate, and, importantly, the individual isomers are typically hydrogenated with differing rates and selectivities. Moreover, these difficulties are magnified by the necessary removal of this group, a seemingly cumbersome artifact of an otherwise powerful strategy. Nonetheless, this advance has allowed a variety of β-amino acids to be prepared.[20b]

An innovative solution to this problem was demonstrated by a group at Merck en route to synthesizing Januvia (sitagliptin phosphate; **40**, Scheme 1.5), which has recently been approved by the United States Food and Drug Administration for the treatment of type II diabetes.[23] The optimal target contains an unfunctionalized β-amino amide. A strategy was sought to install this moiety directly by asymmetric hydrogenation of unsubstituted β-enamino ester and amide derivatives[24] (e.g., **36**). A traditional hydrogenation route for the production of amino acids is a proven, cost-effective method for the synthesis of chiral building blocks. The industrial infrastructure is already in place to realize this goal; however, in this case, the reduction of unprotected β-enamino acids was not effective with existing chiral catalysts. A crucial component in addressing such limitations was Merck's high-throughput screening facility, which allowed rapid

screening of catalyst structures and reaction conditions (an essential component for the success of any asymmetric catalytic process).[25] One potential complication for this hydrogenation strategy was avoided when it was observed that the preparation of the β-enamino ester and amide substrates (e.g., **35** → **36**) proceeded with complete selectivity for the *Z*-isomer, presumably owing to hydrogen bonding in the products.

Scheme 1.5. Enantioselective hydrogenation of a β-enamino amide toward the synthesis of Januvia®



During the screening, a survey of transition metals and ligands revealed that rhodium complexes of the Josiphos (e.g., **37**, Scheme 1.5) family of ligands efficiently catalyze the hydrogenation of a variety of substrates to give high yields with excellent enantioselectivities. The remarkable functional-group tolerance of this catalyst allowed the strategic implementation of this asymmetric transformation as the penultimate step of the synthesis, thereby maximizing the usefulness of the process and materials. Thus,

phenylacetic acid derivative **32** was converted into β-ketoamide **35** in a one-pot procedure via acylation of Meldrum's acid (**33**), followed by treatment with triazole salt **34**.[26] Exposure to ammonium acetate converted this into β-enamino amide **36** as a single enamine isomer. Hydrogenation of amide **36** in the presence of 0.30 mol% of rhodium(I) and ligand **37** provided β-amino amide **39** in >95% conversion and 95% enantiomeric excess. Subsequent recrystallization and salt formation with phosphoric acid gave Januvia® (**40**). Efforts to optimize efficiency and examine the mechanism of the asymmetric process revealed that reactivity and selectivity were dependent on the pH of the reaction solution.[27] It was found that ~1 mol% of a mild acid (i.e., ammonium chloride) was essential for the reaction to proceed reproducibly on a large scale. In addition, it was observed that hydrogenation of a related substrate under identical conditions with a deuterium gas atmosphere resulted in deuterium incorporation at the β-position only, suggesting that an imine is an intermediate (**38**) and that an enamine–imine tautomerization process plays an important part in the mechanism.[24] Interestingly, intermediates such as **38** have a striking similarity to asymmetric β-carbonyl hydrogenations pioneered by Noyori and co-workers.[28]

This example demonstrates the development of asymmetric catalysis into a state-of-the-art science through maximizing the efficiency by minimizing unnecessary functionality, by using atom economy, and by using extremely active catalysts. Moreover, the development of the catalyst system for the synthesis of Januvia exemplifies the continued need for subtly different catalysts to meet new synthetic demands. Building on the experience obtained during the development of a highly

efficient enamide reduction toward α-amino acids, such large-scale industrial synthesis of important β-amino acids has been a relatively rapid process.

1.3.2 $C(sp^3)$–$C(sp^3)$ CROSS-COUPLINGS—FLUVIRUCININE A_1

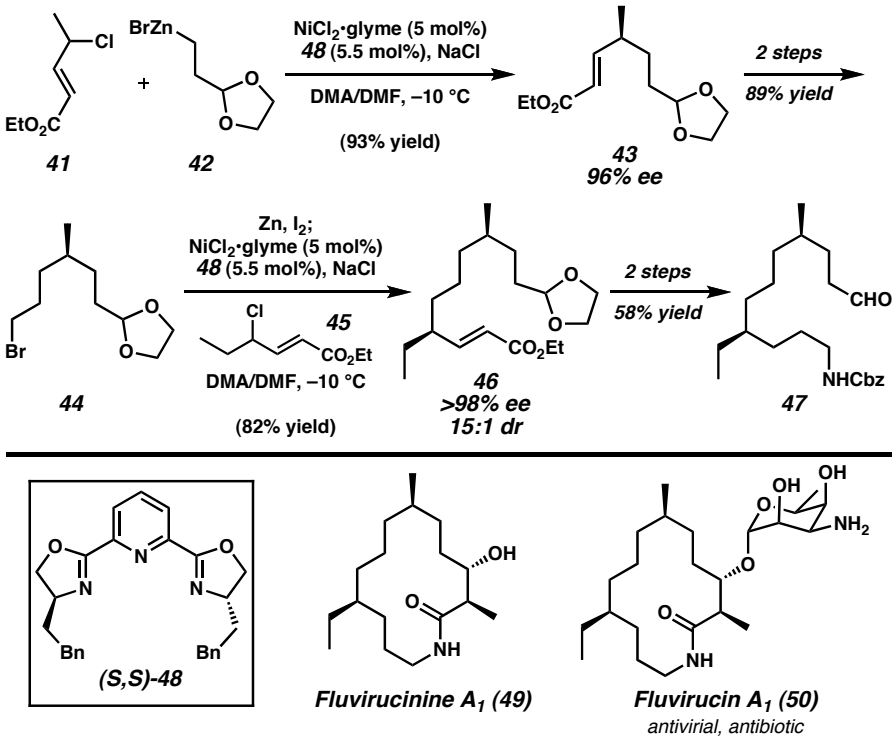
Transition metal-catalyzed cross-coupling reactions have been used extensively for constructing C–C bonds and, consequently, have had a substantial effect on the field of complex molecule synthesis.[29] The predominance of palladium and nickel catalysts in cross-coupling technologies and their extraordinary functional-group tolerance increases the efficiency of this process by allowing a large degree of functionalization before coupling. Moreover, the efficacy of this cross-coupling strategy for streamlining synthesis has allowed retrosynthetic analyses that had been thought impossible with standard, nonmetal reactions. Until recently, however, most cross-coupling methods involved $C(sp^2)$–$C(sp^2)$ or $C(sp^2)$–C(sp) centers, limiting the application potential. Two crucial issues associated with expanding the substrate scope to include $C(sp^3)$–$C(sp^3)$ couplings are the relatively low reactivity of alkyl halides toward oxidative addition and the propensity of σ-alkyl organometallic complexes to undergo rapid β-hydrogen elimination reactions.[30] Practical solutions to this problem were first presented by Suzuki and Knochel, followed more recently by Fu.[30b,31] In general, the reaction scope now encompasses a variety of primary and secondary halides and pseudohalides as the electrophilic component, with organoboranes, boronic acids, alkylmagnesium halides, and alkylzinc halides as the nucleophilic component.[30b] Although perhaps not developed in the context of a particular target molecule, progress in these cross-coupling methods

has allowed retrosynthetic disconnections that were not practical previously. Asymmetric cross-coupling protocols could, in turn, allow the direct formation of remote stereocenters in relatively unfunctionalized molecules.

Early examples of catalytic asymmetric cross-coupling reactions involving $C(sp^3)$–$C(sp^2)$ centers were explored by Kumada and co-workers in the late 1970s and produced moderate enantioselectivities.[32] Despite these initial reports and the subsequent evolution of cross-coupling methods and asymmetric catalysis, a deficiency in the development of catalytic asymmetric methods for $C(sp^3)$–$C(sp^3)$ couplings existed until Fu and co-workers[33] reported an asymmetric Negishi coupling in 2005. Before this report, researchers in the Fu laboratory observed the proficiency of tridentate pybox ligands (e.g., **48**, Scheme 1.6) at enabling the room temperature nickel-catalyzed Negishi coupling of symmetric secondary alkyl bromides and iodides.[34] It was postulated that the tridentate nature of pybox ligands prevented the undesired β-hydrogen-elimination pathway, which would require a vacant coordination site. Reaction optimization facilitated the development of several asymmetric variations that generate challenging stereocenters applicable to complex molecule synthesis, as demonstrated in Fu's formal total synthesis of fluvirucinine A_1 (**49**), the aglycon of the macrolactam antibiotic fluvirucin A_1 (**50**).[35] A key nickel(II)-catalyzed asymmetric cross-coupling of racemic allylic chloride **41** and alkylzinc reagent **42** in the presence of (*S*,*S*)-**48** generated γ-disubstituted enone **43** in an excellent yield and 96% enantiomeric excess. Elaboration over two steps to a bromide (**44**), followed by conversion to the alkylzinc form and a second nickel(II)-catalyzed asymmetric Negishi cross-coupling with racemic allylic chloride **45**, provided the ester **46** in a good yield and with >98% enantiomeric excess

and a 15:1 ratio of diastereomers. A subsequent two-step conversion to the aldehyde **47** intersected Suh's synthesis of fluvirucinine A_1 (**49**).[36] This method exemplifies the efficiency of the $C(sp^3)$–$C(sp^3)$ cross-coupling and presents a creative solution to the particularly difficult challenge of remote stereochemical control.

Scheme 1.6. Enantioselective $C(sp^3)$–$C(sp^3)$ cross-couplings toward fluvirucinine A_1



At present, most examples of this technology require a stabilizing group adjacent to the site of the putative carbon-centered radical. Eliminating this condition would further improve the utility of this asymmetric cross-coupling method. In addition, stereogenic organometallic coupling partners (e.g., secondary alkylzinc reagents) have not yet been reported in this asymmetric transformation. A potential goal for this synthetic method would be the combination of a racemic secondary alkyl halide and a racemic secondary alkylmetal reagent to form vicinal stereocenters along an alkyl chain with high levels of enantioselectivity and diastereoselectivity.

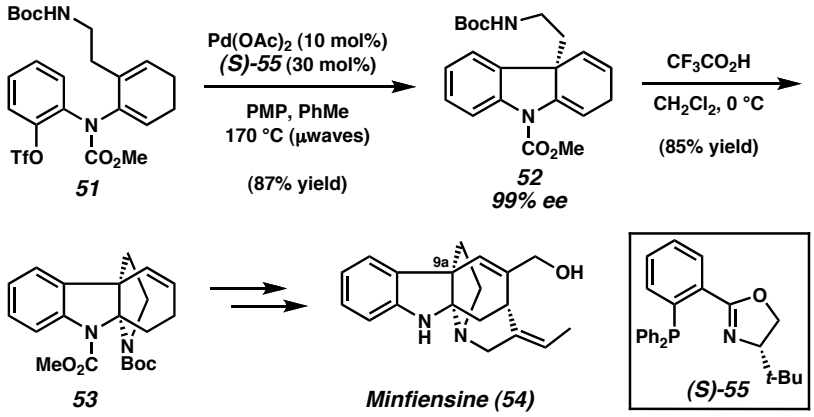
1.3.3 INTRAMOLECULAR HECK CYCLIZATIONS—MINFIENSINE

The enantioselective generation of all-carbon quaternary stereocenters is a considerable challenge for synthetic chemists.[37] As quaternary stereocenters are found in many natural product structures, convenient enantioselective methods for their formation would be useful. One such method is the Heck reaction,[38] in which a palladium(0) catalyst promotes the vinylation of an aryl halide, vinyl halide, or trifluoromethane sulfonate. The large body of literature on palladium catalysis and mechanisms,[29] as well as an ever-growing collection of chiral ligands for transition-metal catalysis, greatly increased the potential of using this method to carry out asymmetric catalysis. In addition, many synthetic endeavors using diastereoselective or nonstereoselective intramolecular Heck reactions have been reported,[39] increasing the significance of an enantioselective process. In 1989, the laboratories of Shibasaki[40] and Overman[41] independently reported the first variants of an intramolecular catalytic asymmetric Heck reaction. Initial levels of enantioselectivity were moderate; however, subsequent optimizations realized good-to-excellent selectivities in the generation of tertiary and all-carbon quaternary stereocenters.[42]

Indole alkaloids encompass a large number of natural and pharmaceutical substances with a wide range of biological activities.[43] The plant alkaloid minfiensine (**54**, Scheme 1.7) is a compelling example of the all-carbon quaternary stereocenter motif in biologically active natural products. Minfiensine and related alkaloids have been used in traditional

medicines and have promising anticancer activity.[44] The intriguing polycyclic structure and biological relevance of minfiensine prompted the Overman laboratory[45] to explore a catalytic enantioselective Heck reaction to generate the sole quaternary stereocenter at C9a. It was discovered that the palladium-catalyzed intramolecular Heck reaction of dienyl aryl trifluoromethane sulfonate **51** in the presence of the phosphinooxazoline ligand (*S*)-**55** under microwave conditions produced indoline **52** in good yield and with 99% enantiomeric excess. Subsequent acid-promoted carbamate cyclization produced the tricyclic core of minfiensine (**53**), which was then converted to the natural product. The efficiency and selectivity of the catalytic asymmetric Heck reaction facilitated completion of the target, where the remaining stereocenters are derived from this initial transformation.

Scheme 1.7. Enantioselective intramolecular Heck reaction toward minfiensine



Despite numerous examples of the asymmetric Heck reaction in total synthesis,[42] there are several features that could be improved. Reactions typically require high temperatures and relatively high catalyst loadings, and the development of chiral ligands that greatly increase the reactivity of the transition metal while maintaining an adequate

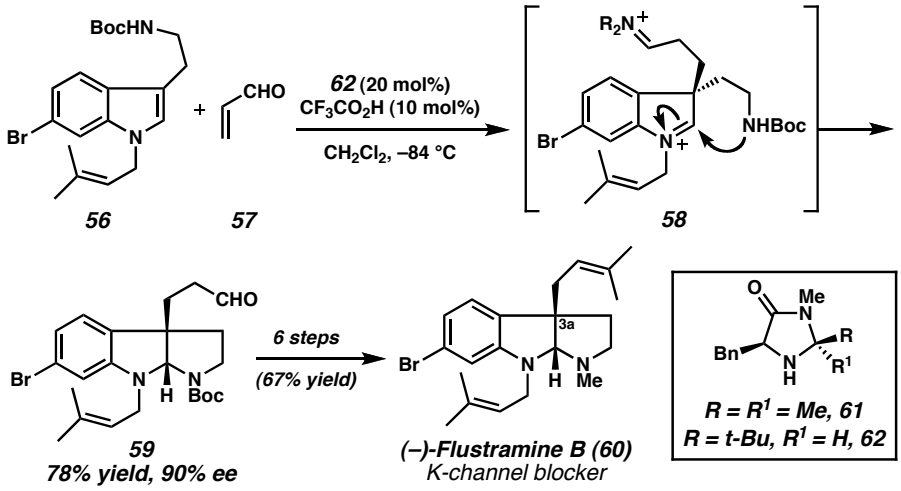
asymmetric environment would be greatly beneficial. As most enantioselective Heck reactions use an sp^2-hybridized organohalide component, another frontier lies in the application of unactivated alkyl carbon electrophiles that have β-hydrogens in both intramolecular and intermolecular cases, an area currently in its infancy.[46]

1.3.4 INDOLE FRIEDEL–CRAFTS ALKYLATIONS—FLUSTRAMINE B

Numerous methods have been developed for the generation of substituted indoles;[47] however, enantioselective indole functionalization has been far less explored. To address the deficiencies in the indole functionalization literature, Jørgensen[48] and MacMillan[49] independently developed strategies for asymmetric Friedel–Crafts alkylation of conjugate acceptors with electron-rich heteroaromatics. MacMillan's method uses a secondary amine catalyst (**61**, Scheme 1.8) that facilitates the LUMO-lowering activation of α,β-unsaturated aldehydes for a variety of transformations.[50] Although imidazolidinone **61** was a sufficient catalyst for the Friedel–Crafts alkylation of pyrroles, generating good yields and excellent enantioselectivities,[49] application of less-activated indole substrates resulted in sluggish reactivity with considerably diminished selectivities.[51] Kinetic investigations of iminium-catalyzed reactions revealed that the overall reaction rate was influenced by the efficiency of formation for both the iminium ion and the C–C bond, prompting the development of a modified imidazolidinone catalyst (**62**). This refinement minimized the steric bulk around one face of the catalyst, thereby exposing the lone pair of electrons on the secondary amine nitrogen. This structural change translated into

increased reactivity that enabled the asymmetric Friedel–Crafts alkylation of a variety of indoles with good-to-excellent yields and very high enantioselectivities.[51]

Scheme 1.8. Enantioselective Friedel–Crafts alkylation toward flustramine B



Pyrroloindoline alkaloids are a family of polyindole alkaloids of diverse structural complexity and biological relevance.[52] Diastereoselective syntheses of the core of these compounds have focused on the control of the C3a all-carbon quaternary stereocenter as a key design element.[53] With a powerful and mild indole alkylation method in hand, MacMillan and co-workers[54] devised a cascade strategy for the catalytic asymmetric preparation of the C3a stereocenter and the pyrroloindoline core of the potassium-channel blocker (–)-flustramine B (**60**, Scheme 1.8) in one step. In this key transformation, tryptamine derivative **56** and 2-propenal (acrolein, **57**), in the presence of catalyst **62**, underwent the asymmetric Friedel–Crafts alkylation to provide iminium intermediate **58**. Subsequent carbamate cyclization and hydrolysis to regenerate the catalyst provided the core (**59**) with a good yield and 90% enantiomeric excess. Importantly, this allowed completion of (–)-flustramine B (**60**) in just six steps and with

good overall yield, highlighting the efficiency of this cascade approach. It is noteworthy that this strategy also has the potential to be applied to the synthesis of various polycyclic indolines such as the diazonamide family of cytotoxic alkaloids.[54] It is also interesting to note that both the intramolecular Heck reaction (see subsection 1.3.3) and the indole Friedel–Crafts alkylation can generate similar indoline structural motifs despite the markedly different bond-connecting strategies of these reactions. The success of these dissimilar strategies allows a great deal of flexibility in the planning of syntheses.

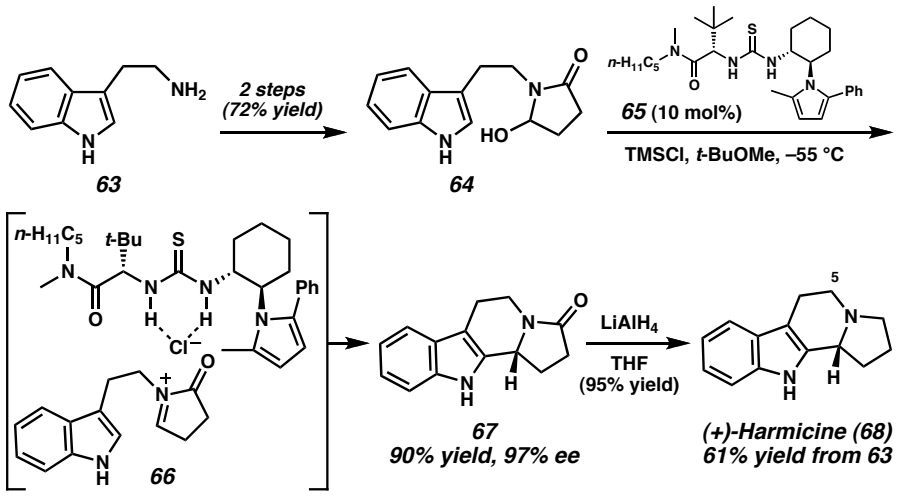
Iminium-activation methods with chiral amine catalysts have been successful for numerous transformations, but catalyst loading, turnover frequency, and excesses of certain reagents limit the large-scale industrial application of these methods. In addition, in some cases, the organic catalyst may be more difficult to remove from the reaction products than a metal catalyst. However, the typically air- and moisture-stable reaction conditions, low cost of some catalysts, and often metal-free conditions are attractive. The variety of asymmetric transformations (some proceeding through substantially different reaction pathways) that have been realized with chiral amine catalysts so far indicates a burgeoning field in which there are many useful enantioselective catalysts.

1.3.5 PICTET–SPENGLER CYCLIZATIONS—HARMICINE

Since the intramolecular cyclization of an aromatic ring onto an iminium species was reported by Pictet and Spengler in 1911,[55] this transformation has been of great use in the synthesis of many important alkaloid natural products.[56] Indeed, the need for asymmetric

variants of this reaction was recognized, and several diastereoselective protocols have been devised.[56] A common approach to diastereoselective Pictet–Spengler cyclization has been to use tryptophan derivatives to control the stereochemistry of the cyclization. However, using this type of technique for the synthesis of a natural product such as harmicine (**68**, Scheme 1.9), which is active against the disease leishmaniasis, necessitates the removal of the stereocontrol element at C5, following the diastereoselective cyclization. Nonetheless, Allin and co-workers[57] proved this to be a viable method in 2007. This particular structure, however, highlighted a challenge for enantioselective catalysis and an opportunity to improve synthetic efficiency.

Scheme 1.9. Enantioselective Pictet–Spengler cyclization toward harmicine



When considering prospects for asymmetric induction, Jacobsen and Taylor considered activated *N*-acyl-iminium ions as a template and reasoned that a chiral thiourea derivative might be effective in promoting cyclization.[58] In practice, these Brønsted acids,[58] as well as other Brønsted acids investigated later by other groups,[59] proved to be excellent catalysts for enantioselective indole annulations with in situ-generated *N*-acyl-iminium species (e.g., **66**, Scheme 1.9). In later studies by Jacobsen

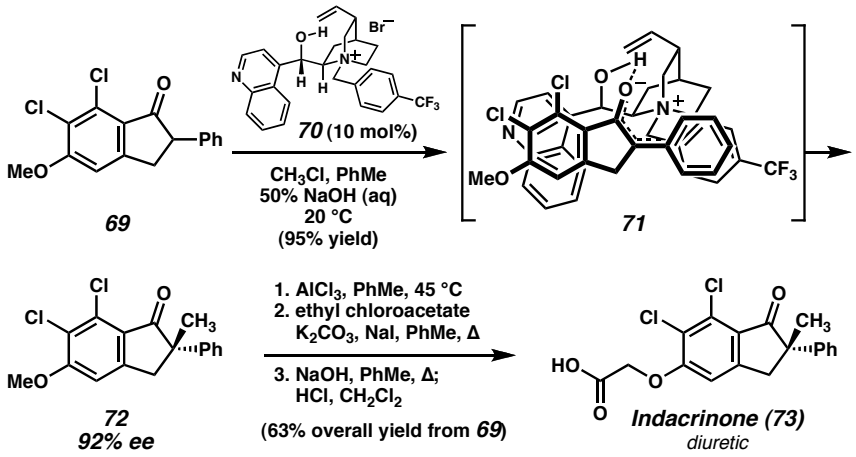
and co-workers, it was found that hydroxylactams (e.g., **64**) are convenient precursors to *N*-acyl-iminium ions, which in turn enable access to various polycyclic structures.[60] Given this effective protocol, an efficient catalytic asymmetric synthesis of harmicine (**68**) was realized in four steps from tryptamine (**63**). Several mechanistic experiments have suggested that asymmetric induction is controlled by a complex of the Brønsted acid catalyst (**65**) and a chloride counterion closely associated with the iminium ion (e.g., **66**) that effectively blocks approach to one face of the electrophile, providing annulated products (e.g., **67**) with excellent enantiomeric excesses. This insight into the remarkable mechanism of this transformation has led to a related C–C bond-forming process using oxocarbenium ions.[61] Further exploitation of this unusual proposed catalyst–anion interaction could lead to a variety of other asymmetric addition reactions, such as intermolecular alkylation of *N*-acyl-iminium ions. In common with the history of the Diels–Alder reaction (see section 1.2), the exploration of the Pictet–Spengler cyclization has provided a useful method to access many heterocyclic structures embedded in alkaloid natural products using a classical reaction with well-established synthetic applications.

1.3.6 PHASE TRANSFER ALKYLATIONS—INDACRINONE

Enolate alkylations exemplify the fundamental usefulness of the carbonyl group for C–C bond formation. Strategies to induce asymmetry in these reactions have included chiral auxiliaries and chiral ligands, although few examples are catalytic. A particularly challenging class of product targets are all-carbon quaternary stereocenters adjacent to carbonyl groups. One example of an important target bearing this motif is the diuretic

drug candidate indacrinone (**73**, Scheme 1.10).[62] Given the lack of efficient methods for synthesizing this structure, researchers at Merck envisaged an enantioselective phase-transfer alkylation method based on a quaternary ammonium salt derived from a naturally occurring cinchona alkaloid (e.g., **70**). In the event, readily prepared indanone **69** was methylated, producing ketone **72** with 95% yield and 92% enantiomeric excess, and **72** was then converted to indacrinone (**73**) in three additional steps.

Scheme 1.10. Phase-transfer alkylation toward indacrinone



Although successful in achieving enantioselective enolate alkylation, the mechanism for this process seems to be complex;[63] however, enantiofacial selectivity in the alkylation event may be rationalized through the hypothetical transition state **71** (Scheme 1.10). Three key interactions are thought to control selectivity: a hydrogen bond between the enolate oxygen and the catalyst hydroxyl group, and two π-system stacking interactions between the four aromatic rings. Perhaps as a consequence of the complex mechanism, the range of substrates for enolate alkylation is limited, and other solutions to this problem are still needed. However, these initial results have led to several related catalytic enantioselective reactions using cinchoninium salts or related organic

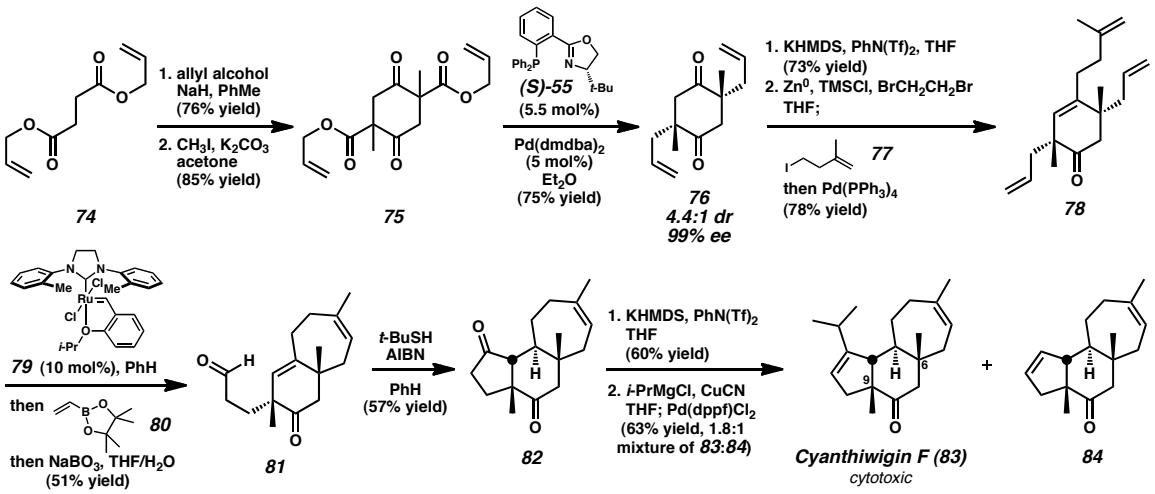
ammonium complexes as catalysts.[64] The discovery of these useful catalysts has provided not only an alternative to related transformations using metal catalysts but also a means of accessing chiral environments that are simply not possible with metal-based catalysts. Moreover, eliminating metal waste materials is attractive from an industrial and environmental standpoint. Ultimately, the studies directed toward an enantioselective synthesis of indacrinone demonstrate the versatility of privileged catalysts developed for the synthesis of target molecules for a range of other applications.

1.3.7 PD-CATALYZED ENOLATE ALKYLATION—CYANTHIWIGIN F

A recent case of enantioselective enolate alkylation is the synthesis of cyanthiwigin F (**83**, Scheme 1.11), a cytotoxic natural product from a sea sponge. The cyanthiwigin family is composed of more than 30 diterpenoids, most of which bear two quaternary stereocenters, at C6 and C9, and a syn relationship of the methyl groups in the central ring. These core stereochemical elements are a complicating factor for a convergent strategy that might seek to couple the five- and seven-membered ring portions and subsequently form the six-membered ring. To avoid this difficulty, Enquist and Stoltz chose instead to address these two central stereocenters at an early stage and append the five- and seven-membered rings to the assembled cyclohexane.[65] Accordingly, a synthetic strategy was devised that involved a one-pot double-enantioselective enolate alkylation reaction to form both quaternary stereocenters simultaneously. Although such enantioselective alkylations have proved difficult, recent studies have identified palladium catalysts that might provide a solution to this problem and enable the synthesis

of a variety of targets containing quaternary carbon stereocenters, including the cyanthiwigins.[66]

Scheme 1.11. Pd-catalyzed enolate alkylations toward cyanthiwigin F



The implementation of this retrosynthetic strategy began with a Claisen–Dieckmann sequence that converted diallyl succinate (**74**, Scheme 1.11) to bis(β-ketoester) **75** as a 1:1 mixture of racemic and meso diastereomers. On exposure to the catalyst derived from $Pd(dmdba)_2$ and phosphinooxazoline ligand (*S*)-**55**,[66] each stereoisomer of **75** was transformed to bis(allylated) ketone **76** with 75% yield and 99% enantiomeric excess as a 4.4:1 mixture of diastereomers. With both quaternary centers in place, elaboration of this stereochemically rich core structure to the natural product was achieved in six further steps. Enol triflate formation and Negishi coupling (**76** + **77** → **78**) preceded a tandem ring-closing metathesis–cross-metathesis sequence with Grubbs' ruthenium catalyst **79**.[67] Aldehyde–alkene radical cyclization generated the final ring of the cyanthiwigin core (**81** → **82**), and enol triflate formation and palladium-catalyzed cross-coupling formed (–)-cyanthiwigin F (**83**), together with reduction product **84**. Choosing to confront the difficult stereochemical elements of the cyanthiwigin structure at an early stage led to a

direct synthetic route proceeding in nine steps from diallyl succinate. This strategy was made possible by the intriguing reaction mechanism of the enantioselective decarboxylative allylation, in which all three stereoisomers of bis(β-ketoester) **75** were converted to a specific stereoisomer of product (**76**) with high selectivity, through a stereoablative process.[68] In addition, of the nine steps required for the synthesis, seven form C–C bonds, and four form *multiple* C–C bonds. Directly addressing the carbon framework of the target molecule and the stereochemical challenges embedded within ultimately led to an efficient synthetic sequence for this important molecule.

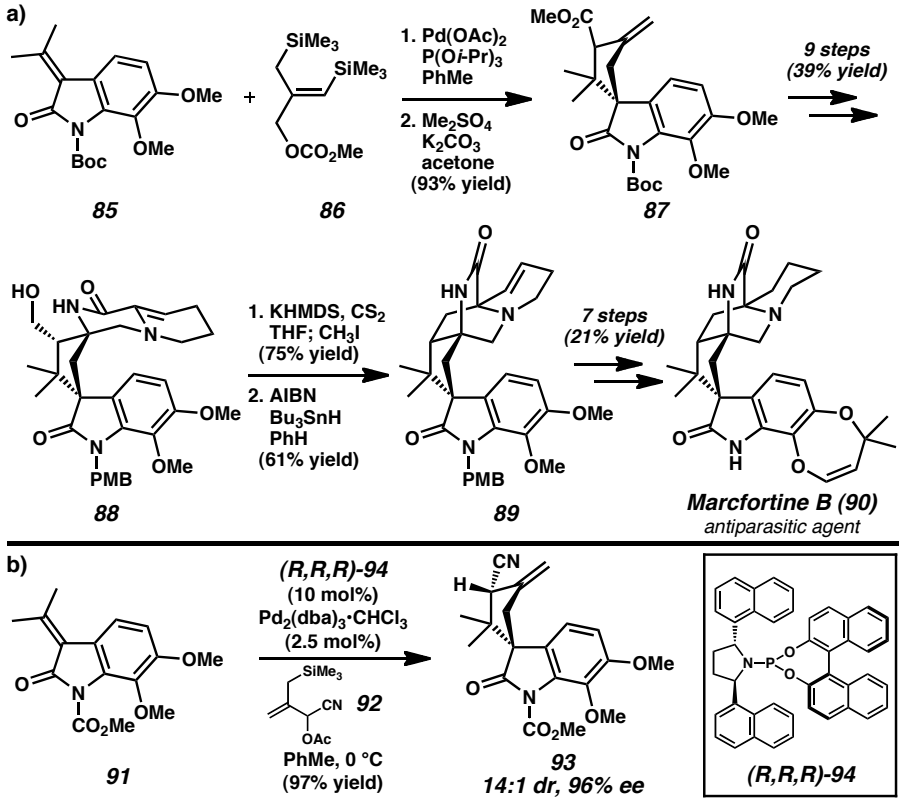
Recently, the proposed chiral palladium enolate was shown to be intercepted by allyl or proton electrophiles (the development of this reaction will be a major component of this thesis; see Chapters 6 and 7).[66,69] Although the synthesis of cyanthiwigin F demonstrates the versatility of allyl moieties for further derivatization, the direct use of alternative electrophiles would provide a more general and direct method for transition metal-mediated enolate functionalization.[70]

1.3.8 TRIMETHYLENEMETHANE CYCLIZATIONS—MARCFORTINE B

Of the many fundamental approaches to the formation of five-membered rings from acyclic precursors, the [3 + 2] cycloaddition is among the most convergent strategies. A useful method of achieving such a cyclization is via a trimethylenemethane (TMM) intermediate.[71] This interesting non-Kekulé molecule was first prepared and studied through photolytic decomposition of a cyclic diazene precursor. However, the free diyl is prone to several undesired reaction pathways and does not lend itself to asymmetric

catalysis. Despite this, intramolecular diyl-trapping reactions are valuable methods of cyclopentane formation.[71] Recognizing the synthetic utility of TMM, Trost and coworkers developed an array of 2-(trimethylsilyl)-2-propenyl acetate reagents that generate a metal•TMM complex when exposed to a palladium catalyst.[72] A recent application of this transformation in total synthesis is the approach to marcfortine B (**90**, Scheme 1.12a), a member of a family of antiparasitic agents.[73] The strategy used sought to forge the [2.2.2]bicycle via an intramolecular radical cyclization and install the spiro all-carbon quaternary stereocenter by the cycloaddition of oxindole **85** with TMM precursor **86**. In the event, an excellent yield was observed for the annulation reaction yielding spirooxindole **87** as a 1:1 mixture of diastereomers. Over the course of nine additional steps, spirocycle **87** was transformed into amide **88**. Preparation of the xanthate derivative of alcohol **88** allowed radical cyclization, generating the challenging [2.2.2]bicycle **89**. Seven further steps produced (±)-marcfortine B (**90**).

Scheme 1.12. a) Pd-catalyzed TMM-[3 + 2]-cycloaddition toward marcfortine B b) Enantioselective TMM-cyclization



Although this strategy demonstrated several intriguing ring-forming reactions, an asymmetric synthesis of **90** would require an enantioselective variant of the key TMM-[3 + 2] cycloaddition, a goal that has remained elusive.[74] The first asymmetric palladium-catalyzed [3 + 2] cycloaddition with various bis(phosphine) ligands was reported by Ito and co-workers,[75] but with only moderate enantiomeric excess (up to 78%) and diastereomeric ratio (up to 4:1 trans:cis). Thereafter, Trost and co-workers explored bulky monodentate phosphoramidite ligands (e.g., (*R*,*R*,*R*)-**94**, Scheme 1.12b) for the transformation and observed very high enantioselectivity for the first time.[76] Of particular interest is the enantioselective addition of substituted TMM reagents to functionalized oxindole derivatives.[76b] The use of oxindole **91** and TMM-precursor **92** in

the palladium-catalyzed cyclization with ligand (*R*,*R*,*R*)-**94** yielded spirooxindole **93** with 14:1 diastereomeric ratio and 96% enantiomeric excess for the major diastereomer. Although a completed asymmetric synthesis of marcfortine B (**90**) from intermediate **93** has not been reported, many of the key functional groups are in place and the challenging spiroquaternary stereocenter has been installed (cf. **87** and **93**). The development of this valuable asymmetric transformation highlights the ongoing efforts to devise new and useful techniques for the construction of important molecules.

1.4 OUTLOOK

The representative synthetic efforts presented here demonstrate the crucial interplay between target-directed synthesis and the development of novel reaction methods. Although many useful asymmetric technologies are currently available, the specific challenges posed by important natural products and pharmaceutical compounds highlight deficiencies in the current technology. Envisaging strategies to construct these relevant molecules through means beyond the current arsenal of enantioselective transformations will aid the evolution of both synthetic planning and reaction development. The symbiotic relationship between total synthesis and method development can continue to expand the understanding of synthetic strategy and catalysis on both fundamental and practical levels.

Despite the substantial advances that have been made so far, significant challenges remain for both multistep synthesis and catalysis. In addition to improvements to

efficiency and selectivity, better reactivity and handling stability are constantly required to implement and improve industrial processes for existing methods. Exceptionally reliable methods will aid in the discovery of new biologically active compounds by using high-throughput combinatorial screening techniques that are well established in the pharmaceutical industry, although these techniques are limited by the number of readily accessible chiral building blocks. Existing methods may be improved by identifying systems with better functional-group tolerances that might obviate the need for protecting and masking groups. Similarly, known privileged chiral frameworks may be modified to control chiral space more effectively for especially challenging transformations, a technique conspicuously successful for Trost's TMM cyclizations (see subsection 1.3.8).

Overall, creative solutions are required to address specific organic transformations that remain significant impediments to efficient syntheses, namely forming multiple stereocenters and rings, forming multiple C–C bonds, generating vicinal quaternary stereocenters, and achieving C–H and C–C functionalization reactions. Cyclic structures often present particular challenges owing to the unique strain and steric elements imparted by their connectivity. As a result, many highly strained or complex polycyclic structures are daunting targets for synthesis. Finally, the discovery of new natural products will undoubtedly result in new challenges for synthetic chemistry and catalysis.

In this thesis, examples of the development of useful enantioselective transformations for the synthesis of natural products will be presented. These reactions were initially conceived as solutions to synthetic problems in the context of total synthesis efforts and have led to various derivative applications and methodologies with broad utility.

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Chem. Soc. **2007**, *129*, 12396–12397. (c) Trost, B. M.; Silverman, S. M.; Stambuli, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 12398–12399.

CHAPTER 2

Enantioselective Allylic Alkylations of Ketone Enolates: Catalyst Development and Allyl Enol Carbonate and Silyl Enol Ether Substrates[†]

2.1 INTRODUCTION

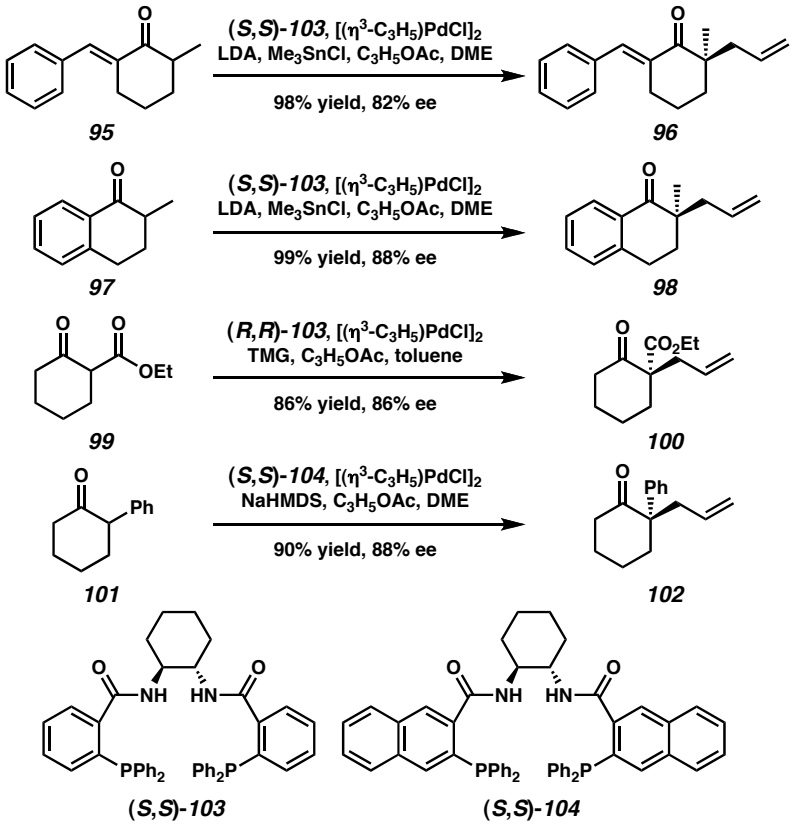
The catalytic asymmetric synthesis of all-carbon quaternary stereocenters stands as a significant challenge in synthetic chemistry.[1] Despite the demanding sterics of quaternary stereocenter formation, a number of useful catalytic transformations, including Diels–Alder,[2] Heck,[3] cyclopropanation,[4] alkylation,[5] acylation,[6] desymmetrization,[7] and pericyclic[8] reactions, have been successful in generating these moieties. Although palladium-catalyzed enantioselective allylic alkylation chemistry has long been an important tool for organic synthesis, only relatively recently has palladium(II) π-allyl chemistry been used for the formation of quaternary stereocenters.[9] The vast majority of palladium-catalyzed allylic alkylations studied by Trost, Helmchen, Pfaltz, and others form tertiary stereocenters by the attack of stabilized (e.g., malonate)

[†] This work was performed in collaboration with Douglas C. Behenna, John A. Enquist, Jr., Andrew M. Harned, Akihiko Iwashita, Michael R. Krout, Samantha R. Levine, Sandy Ma, Smaranda C. Marinescu, Ryan M. McFadden, Zoltán Novák, Krastina V. Petrova, Jennifer L. Roizen, Masaki Seto, Nathaniel H. Sherden, Kousuke Tani, Scott C. Virgil, and David E. White. Portions of this work have been published as indicated by references in the text.

anions on prochiral 1,3-disubstituted allyl fragments.[9] Helmchen has shown that such reactions with palladium phosphinooxazoline (PHOX) complexes typically occur via an outer-sphere malonate attack at the allyl termini.[10] Although allylic alkylation mediated by other metals, especially copper,[11] has successfully generated quaternary centers on prochiral allyl groups, to our knowledge this mode of reactivity has not been realized with palladium.[12]

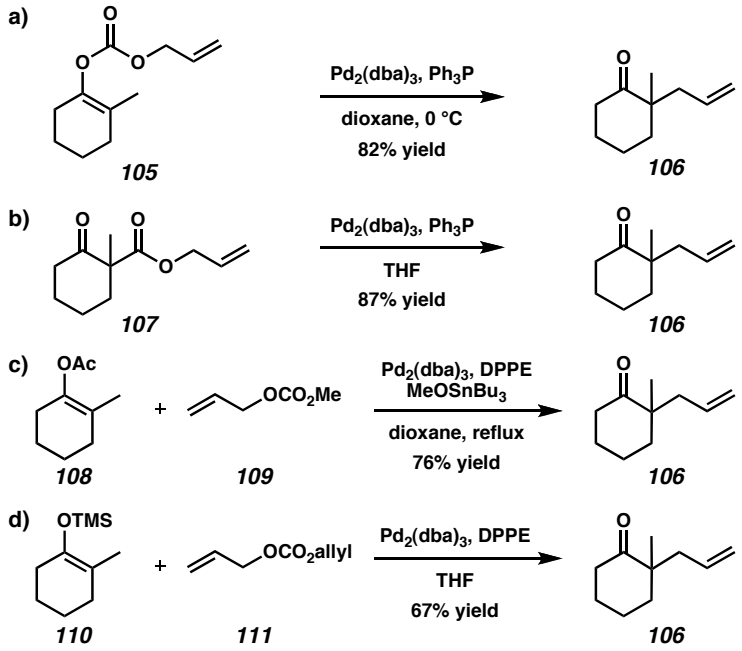
An alternative, less common strategy in allylic alkylation is the use of prochiral nucleophiles. A quaternary stereocenter may be formed on the prochiral nucleophile when it possesses three distinct substituents. Such reactions require a remote chiral ligand to discriminate between the prochiral faces of an incoming nucleophile, and thus may seem a more challenging strategy. However, Hayashi,[13] Ito,[14] and Trost[15] have demonstrated the asymmetric allylation of prochiral enolates derived from 1,3-dicarbonyl compounds. Trost and co-workers demonstrated that diamine-derived ligands **103** and **103**, which were designed to project bulk forward of the allyl fragment due to their large bite angle, are able to favor one face of the in situ-generated ketone enolate (Scheme 2.1).[16,17,18] These reactions represented a significant advance in asymmetric allylation technology by forming quaternary stereocenters with excellent yield and good ee. However, the substrate scope of these reactions was limited by the restriction that the ketones must contain either a single acidic site (e.g., ketone **95** and tetralone **97**) or two α-sites that have a large difference in acidity (e.g., β-ketoester **99** and α-phenyl ketone **101**).[1d] These limitations prevented direct access to simple α-quaternary ketones, such as 2-allyl-2-methylcyclohexanone (**106**), a cyclohexanone derivative not known as a single enantiomer prior to our work.[19]

Scheme 2.1. Trost's allylic alkylation with prochiral nucleophiles



We were confronted by these limitations during studies toward the synthesis of several natural products.[20] A survey of the literature revealed that the nonenantioselective alkylation reactions developed by Tsuji in the early 1980s had the proper reactivity and selectivity to form quaternary stereocenters in the presence of less substituted ketone α-sites of similar acidity. Allyl enol carbonate and allyl β-ketoester substrates contain both the latent enolate and allyl fragments (Scheme 2.2a and b).[21] Alternatively, enol acetates and silyl enol ethers may serve as enolate precursors in intermolecular reactions with allyl carbonates (Scheme 2.2c and d).[22] These alkylations have the advantage that the reaction occurs under nearly neutral conditions and often at mild temperatures. Despite these advantages, these alkylation reactions had been utilized rarely during the intervening twenty years between 1983 and the time we began research in 2003.[23,24]

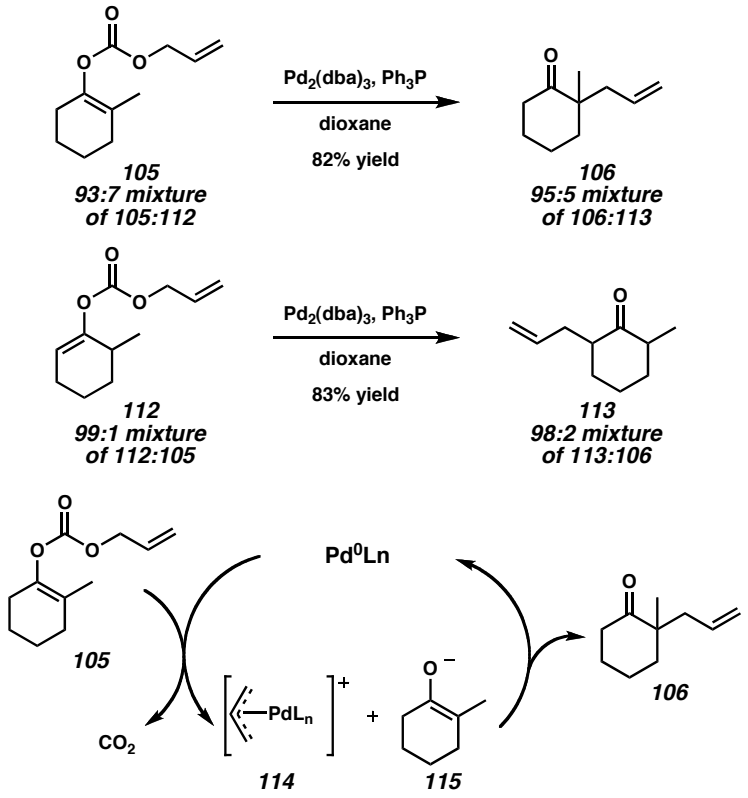
Scheme 2.2. Tsuji's allylic alkylation methods



Our analysis of Tsuji's alkylation reaction showed it to be an ideal candidate for asymmetric catalysis. These high yielding alkylation methods are a clear case of ligand-accelerated catalysis, occurring only in the presence of phosphine ligands.[25] Of additional interest was the regiochemical fidelity observed in the alkylation reactions (Scheme 2.3). Tsuji demonstrated that both the tetrasubstituted allyl enol carbonate isomer **105** and the trisubstituted allyl enol carbonate isomer **112** undergo reaction to give allylated ketones **106** and **113** in ratios essentially unchanged from that of the substrates.[21a] These reactions were believed to proceed via oxidative addition of Pd to the allyl fragment followed by loss of CO_2 to give [Pd(II)(allyl)] complex **114** and enolate **115**. However, the details involving the recombination of the ion pair to give cyclohexanone **106** and Pd(0) were unclear at the time of Tsuji's original reports.[26,27] Coupled with the ability to purify the stable enolate precursors, we believed that the regiochemical fidelity afforded in the palladium-catalyzed reaction would provide direct

access to enantioenriched α-quaternary ketones if a suitable chiral ligand could be found.[28]

Scheme 2.3. Regiochemical fidelity in Tsuji's palladium-catalyzed alkylation



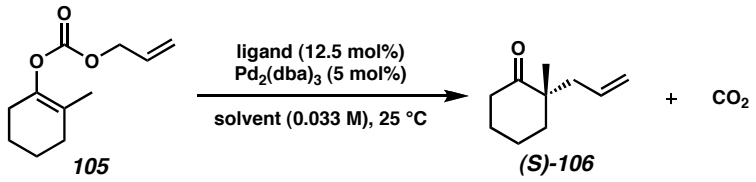
2.2 SCREENING AND OPTIMIZATION

2.2.1 INITIAL SCREENING OF CHIRAL LIGANDS

Our initial goal was to show that a chiral ligand could transmit useful levels of asymmetric induction in the reaction while maintaining the important property of enolate regiochemical fidelity found in the nonenantioselective system. We chose allyl enol carbonate **105** as a test substrate to evaluate the effect of various ligands (Table 2.1). Although allyl enol carbonates are less common than the other enolate precursors

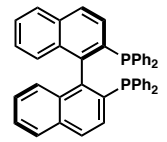
explored by Tsuji, they allowed us to add a single, achiral reagent to our catalyst system without extraneous initiators or counterions that might affect enantioselectivity, whereas silyl enol ether, enol acetate, and β-ketoester substrates did not. In accord with Tsuji's reports, we performed our initial trials in dioxane. Due to the prevalence of bis(phosphine) ligands in asymmetric catalysis, we began with several privileged bis(phosphine) ligands, but found that only Trost's ligand **103** gave significant ee. However, commercially available (*R*)-QUINAP (**120**), a chelating N/P-type ligand,[29] gave more uniform ee with other ethereal solvents (cf. entries 5 and 6 in dioxane and THF). Encouraged, we quickly found that the phosphinooxazoline (PHOX) class of N/P-type ligands also provided excellent reactivity and promising levels of enantioselectivity. The ready availability of numerous amino acid-derived PHOX ligands[30] allowed us to rapidly identify that bulkier aliphatic groups on the oxazoline provided higher levels of enantioinduction, with (*S*)-*t*-Bu-PHOX (**55**) providing α-quaternary ketone **106** in 86% ee when dioxane was used as solvent. Additionally, we observed slightly higher ee in reactions with (*R*)-*i*-Pr-PHOX (**122**) and (*S*)-*t*-Bu-PHOX (**55**) when THF was used as solvent (83% and 88% ee, respectively).[31] Having attained satisfying levels of enantioselectivity and selectivity in forming ketone **106**, we began a more thorough investigation of reaction conditions.

Table 2.1. Initial ligand screen

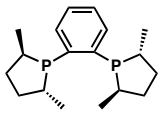


105 *(S)-106*

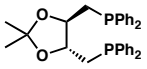
		dioxane			THF		
entry	ligand	time (h)	% yield[a]	% ee[b]	time (h)	% yield[a]	% ee[b]
1	*(R)-BINAP (116)*	5	92	5[c]	5	76	2[c]
2	*(R,R)-Me-DUPHOS (117)*	5	61	0	5	66	0
3	*(R,R)-DIOP (118)*	2	91	2[c]	2	59	2[c]
4	*(R)-MOP (119)*	3	93	18	3	47	13
5	*(R,R)-Trost ligand (103)*	2	97	46[c]	5	92	64[c]
6	*(R)-QUINAP (120)*	2	98	61	2	97	61
7	*(R)-Ph-PHOX (121)*	2	95	62[c]	2	95	65[c]
8	*(S)-Bn-PHOX (122)*	3	96	65	5	94	63
9	*(R)-i-Pr-PHOX (123)*	3	96	82[c]	2	95	83[c]
10	*(S)-t-Bu-PHOX (55)*	2	95	86	2	96	88



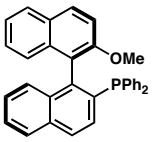
(R)-BINAP (116)



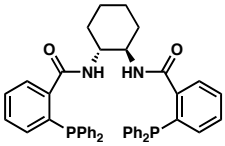
(R,R)-Me-DUPHOS (117)



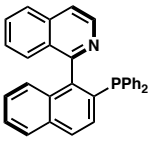
(R,R)-DIOP (118)



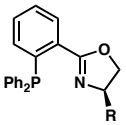
(R)-MOP (119)



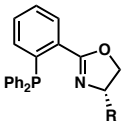
(R,R)-Trost ligand (103)



(R)-QUINAP (120)



R = Ph
(R)-Ph-PHOX (121)
R = i-Pr
(R)-i-Pr-PHOX (122)



R = Bn
(S)-Bn-PHOX (123)
R = t-Bu
(S)-t-Bu-PHOX (55)

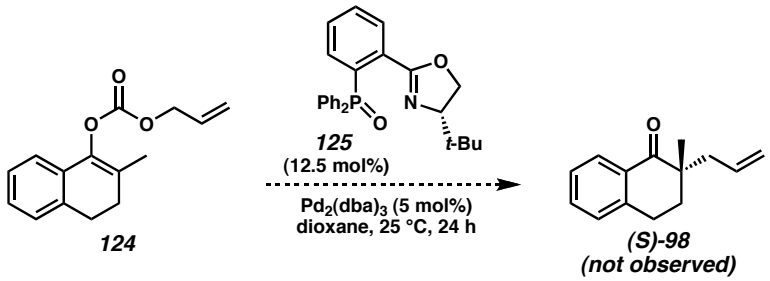
[a] GC yield of **106** relative to internal standard (tridecane). [b] Enantiomeric excess measured by chiral GC. [c] (*R*)-**106** produced as the major product.

2.2.2 OPTIMIZATION OF REACTION PARAMETERS

The straightforward experimental procedure for asymmetric alkylation provided several opportunities to optimize the reaction. One important experimental parameter was found to be complexation time for the (*S*)-*t*-Bu-PHOX (**55**) and tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$). A 30 min complexation time

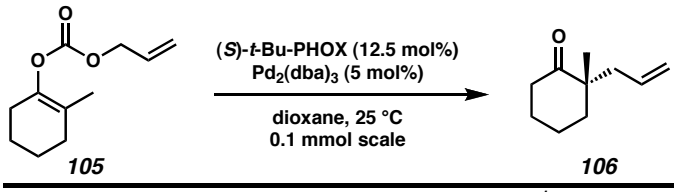
resulted in a balance between short complexation times (e.g., 5 min), in which lower yields but complete consumption of the substrate were observed, and longer complexation times (e.g., 1–3 h) in which poor conversion was observed. Long complexation times seemed to be complicated by adventitious amounts of O_2 that readily oxidized the ligated PHOX molecule at phosphorus, thereby preventing significant consumption of the starting material.[27] We have independently synthesized (*S*)-*t*-Bu-PHOX oxide (**125**) and found that when used as a ligand for the conversion of tetralone-derived allyl enol carbonate **124** to ketone **98** no reaction was observed (Scheme 2.4).[32]

Scheme 2.4. Inactivity of (S)-t-Bu-PHOX oxide as an allylation catalyst



We also investigated the effect of concentration on the reaction (Table 2.2). At higher concentrations, significantly lower yields were observed, as well as slightly decreased ee. No further increase in enantioselectivity was observed below 0.03 M.

Table 2.2. Effect of concentration on asymmetric allylation



105 ***106***

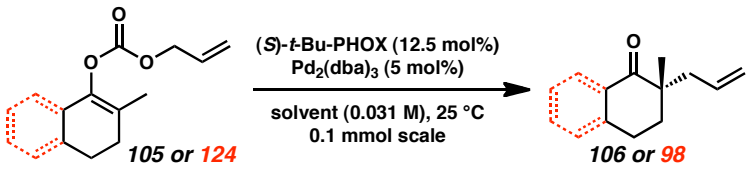
entry[a]	concentration (M)	time (h)	% yield[b]	% ee[c]
1	0.500	3	81	82
2	0.250	2	90	84
3	0.125	2	94	84
4[d]	0.063	2	99	85
5	0.031	2	95	86

[a] Data reported are the average of three trials. [b] GC yield relative to internal standard (tridecane).
[c] Enantiomeric excess measured by chiral GC. [d] Data reported are the average of two trials.

Encouraged by our initial discovery that reactions in THF gave better levels of enantioinduction than those in dioxane, we undertook a more thorough study of solvent effects on the reaction (Table 2.3). Many of the ethereal solvents investigated gave good results. Diethyl ether, *t*-butyl methyl ether (TBME), and diisopropyl ether all provided good yields and slightly higher ee than reactions in THF with allyl enol carbonate **105** (entries 3–5). However, the methyl tetralone-derived allyl enol carbonate **124** yielded products with substantially lower ee in diethyl ether and TBME. The poor solubility of the catalyst system in these less-coordinating ethereal solvents occasionally led to incomplete conversion, a disadvantage that outweighed the slight increase in ee. Interestingly, several non-ethereal solvents also performed well in the reaction. Reactions in benzene and toluene gave similar yield and enantioselectivity to those in THF (entries 8 and 9). The reaction tolerated carbonyl-containing solvents: ethyl acetate (entry 10) provided good yields and enantioselectivity in the asymmetric allylation, while acetone (entry 11) afforded inferior yield and enantioinduction. Interestingly, triethylamine produced a level of enantioselectivity equal to that observed with the best

ethereal solvents, albeit with lower yield (entry 12). Halogenated solvents fared poorly in the reaction, suffering from low conversion and yield (entries 13–15). Overall, we were intrigued by the variety of solvents with vastly different properties that performed equally well.

Table 2.3. Effect of solvent on asymmetric allylation



			106[a]		98[a,b]	
entry	solvent	time (h)	% yield[c]	% ee[d]	time (h)	% ee[e]
1	dioxane	2	95	86	1	87
2	tetrahydrofuran	2	96	88	1	88
3	diethyl ether	2	98	89	1	80
4	*t*-butyl methyl ether	2	98	89	1	78
5	diisopropyl ether	2	95	89	–	–
6	anisole	3	82	81	–	–
7	1,2-dimethoxyethane	2	72	56	–	–
8	benzene	2	99	88	1	89
9	toluene	2	99	88	1	87
10	ethyl acetate	2	97	86	–	–
11	acetone	3	26	60	–	–
12	triethylamine	2	72	89	–	–
13	fluorobenzene	3	58	51	–	–
14	dichloromethane	3	42	13	–	–
15	chloroform	6	0	NA	–	–

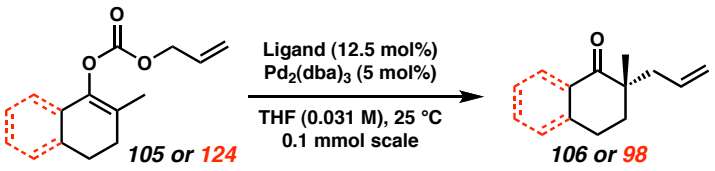
[a] Data reported are the average of three trials. [b] All reactions proceeded to complete conversion except entries 13–15. [c] GC yield relative to internal standard (tridecane). [d] Enantiomeric excess measured by chiral GC. [e] Enantiomeric excess measured by chiral HPLC.

2.2.3 FINE TUNING OF PHOSPHINOOXAZOLINE LIGANDS

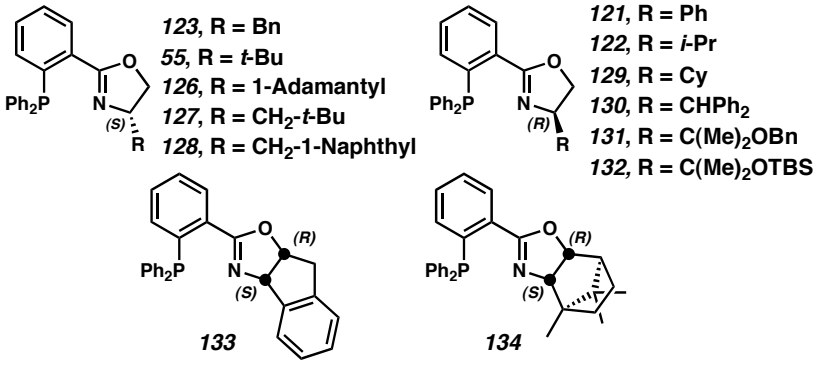
A substantial effort was undertaken to improve the enantioselectivity of the reaction by modifying the PHOX ligand structure (Table 2.4).[33] Hoping to continue the trend of increasing enantioselectivity initially noted in moving from *i*-Pr- to *t*-Bu-PHOX (entries 2 and 4), we undertook the synthesis of numerous PHOX ligands with varied sterics and

evaluated these ligands in the reaction of allyl enol carbonates **105** and **124**. In general, ligands bearing saturated substituents performed better than those with aryl groups in terms of ee. Moving the steric bulk away from the oxazoline framework by inserting a methylene group (i.e., ligand **127**, entry 6) substantially lowered enantioselectivity. Of particular note are the L-serine-derived ligands **131** and **132** (entries 10 and 11),[34] which allowed access to the enantiomeric *R* product series with nearly the same level of enantioselectivity as that observed with (*S*)-*t*-Bu-PHOX (**55**), but without the need for more costly (*R*)-*tert*-leucine.[35] The known *cis*-1-amino indan-2-ol-derived ligand **133** and borneol-derived ligand **134**, both with uniquely shaped substituents, gave slightly lower enantioselectivity relative to *t*-Bu-PHOX (**55**).[36] It is noteworthy that regardless of the shape or type of the substituent on the PHOX ligand, the ketone products contained quaternary stereocenters with a consistent sense of configuration (e.g., (*S*)-PHOX ligands provide (*S*)-**106**). With *t*-Bu-PHOX (**55**) established as the optimal steric framework, we next considered the electronics of the ligand.[37]

Table 2.4. Effect of phosphinooxazoline sterics on asymmetric allylation



entry	ligand	product[a]	% ee[b]	entry	ligand	product[a]	% ee[b]
1	*121*	*106*	65 (*R*)	8	*129*	*106*	83 (*R*)
2	*122*	*106*	83 (*R*)	9	*130*	*106*	69 (*R*)
3	*123*	*106*	63 (*S*)	10	*131*	*98*	85 (*R*)
4	*55*	*106*	88 (*S*)	11	*132*	*98*	85 (*R*)
5[c]	*126*	*98*	78 (*S*)	12	*133*	*98*	79 (*S*)
6	*127*	*98*	59 (*S*)	13	*134*	*98*	81 (*S*)
7	*128*	*106*	41 (*S*)				

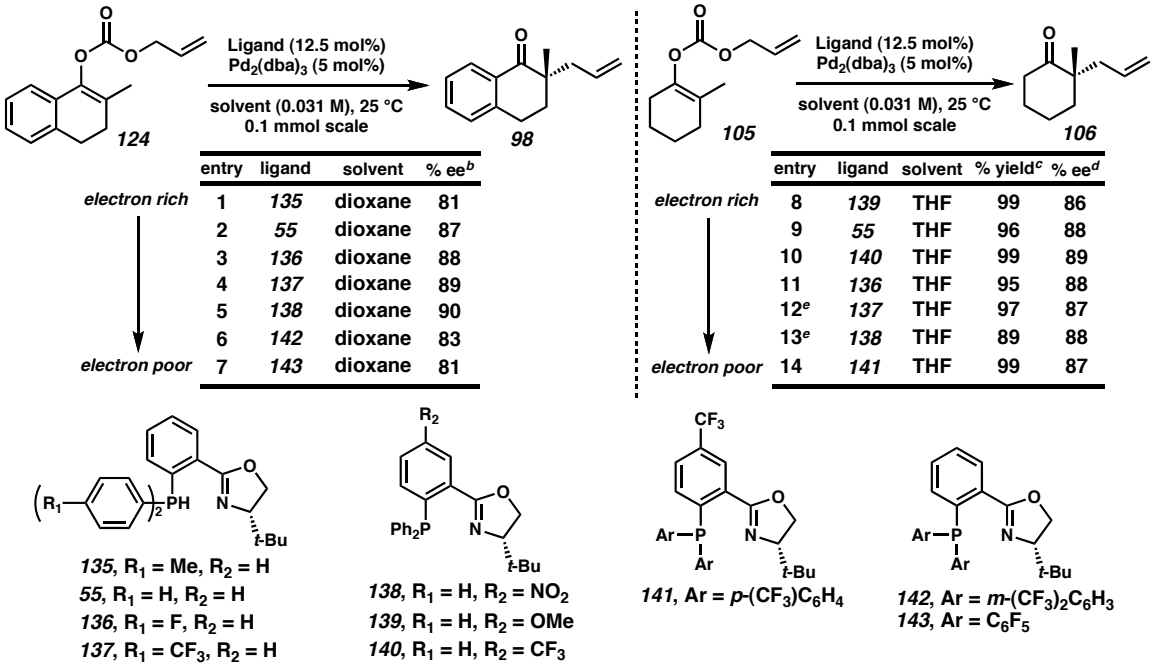


[a] All reactions proceeded to complete conversion. [b] Enantiomeric excess measured by chiral HPLC or GC. [c] Reaction run at 0.2 M in dioxane.

A number of *t*-Bu-PHOX derivatives were synthesized to probe the importance of phosphine electronics (Table 2.5). We investigated ligands ranging from electron rich to electron poor phosphines with allyl enol carbonates **124** and **105** (entries 1–7 and 8–14, respectively). The electronic perturbation had no significant effect on reaction yield, but ligands bearing electron withdrawing groups (especially CF_3 groups) gave a significant increase in the *rate* of reaction with allyl enol carbonate substrates.[33a] Further, electron releasing *para* substituents on the phenyl rings tended to lower the ee of the product relative to that observed with (*S*)-*t*-Bu-PHOX (entries 1 and 8). When tetralone-derived allyl enol carbonate **124** was used as the substrate, a slight increase in enantioselectivity was observed with electron withdrawing substitution at the *p*-phenyl positions (entries 3–

5). However, enantioselectivity decreased significantly with extremely electron poor PHOX ligands (entries 6 and 7). This trend was not apparent in the enantioselectivity with cyclohexyl-derived allyl enol carbonate **105** (entries 8–14). These results suggest a subtle interplay between ligand and substrate electronics.

Table 2.5. Effect of phosphine electronics on asymmetric allylation[a]



	entry	ligand	solvent	% ee[b]
electron rich	1	*135*	dioxane	81
	2	*55*	dioxane	87
	3	*136*	dioxane	88
	4	*137*	dioxane	89
	5	*138*	dioxane	90
	6	*142*	dioxane	83
electron poor	7	*143*	dioxane	81

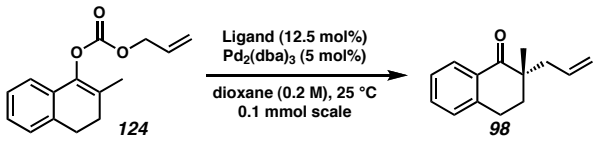
	entry	ligand	solvent	% yield[c]	% ee[d]
electron rich	8	*139*	THF	99	86
	9	*55*	THF	96	88
	10	*140*	THF	99	89
	11	*136*	THF	95	88
	12[e]	*137*	THF	97	87
	13[e]	*138*	THF	89	88
electron poor	14	*141*	THF	99	87

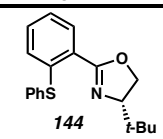
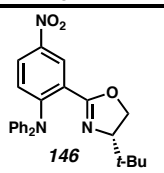
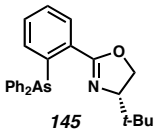
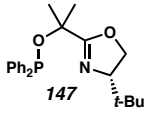
[a] All reactions proceeded to complete conversion. [b] Enantiomeric excess measured by chiral HPLC. [c] GC yield relative to internal standard (tridecane). [d] Enantiomeric excess measured by chiral GC. [e] Data reported are the average of two trials.

As a final investigation into the PHOX ligand structure, we prepared a number of non-N/P mixed chelates based on the phenyl oxazoline skeleton of the PHOX ligands. As mentioned above, the phosphine oxide of *t*-Bu-PHOX (**125**) was inactive as a catalyst (Scheme 2.4). A sulfur analogue (**144**) also failed to catalyze the reaction (Table 2.6, entry 1).[38] Moving down the periodic table from phosphorus, the arsenic analogue of *t*-Bu-PHOX (**145**) had excellent activity as a catalyst, but gave tetralone **98** in only moderate ee (entry 2). A nitrogen analogue (**146**) showed little catalytic activity, and the

small amount of product produced was nearly racemic (entry 3). As a final derivative that maintains the six-membered chelation, but changes the hybridization of the backbone atoms involved, a known phosphinite ligand, SimplePHOX (**147**), was found to give only moderate ee (entry 4).[39]

Table 2.6. Effect of varied heteroatom chelates on asymmetric allylation



entry	ligand	% conversion	% ee[b]	entry	ligand	% conversion	% ee[b]
1	 *144*	0[a]	ND	3	 *146*	<5[a]	7
2	 *145*	99[a]	52	4	 *147*	87[c]	56

[a] Conversion estimated by TLC analysis. [b] Enantiomeric excess measured by chiral HPLC. [c] Trial performed with allyl enol carbonate **105**. Conversion measured by GC relative to internal standard (tridecane). Enantiomeric excess measured by chiral GC.

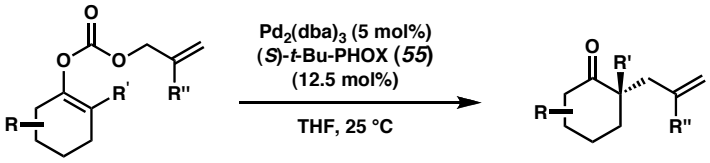
Although some electron deficient derivatives of *t*-Bu-PHOX did provide slightly better enantioselectivity with certain substrates, ultimately this slight improvement did not offset the added difficulty in synthesizing substituted PHOX ligands.[33] Our studies clearly showed that N/P chelates were particularly effective at inducing high levels of asymmetry in the allylation. As a result, we retained the use of (*S*)-*t*-Bu-PHOX (**55**) in our optimized conditions for exploring the scope of the reaction.

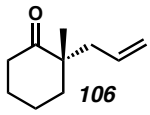
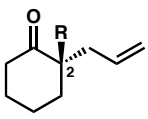
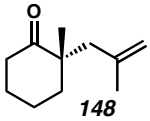
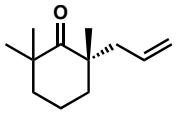
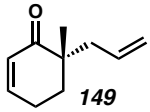
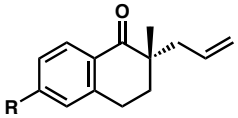
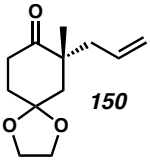
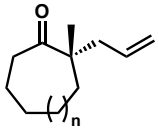
2.3 SUBSTRATE SCOPE

2.3.1 ASYMMETRIC ALLYLATION OF ALLYL ENOL CARBONATES

We have successfully employed a variety of allyl enol carbonates in our asymmetric Tsuji allylation (Table 2.7).[40] The allyl group may be substituted at the internal position resulting in slightly higher levels of asymmetric induction (entry 4). The cyclic portion may be unsaturated (entry 5), substituted (entries 6–11), appended (entries 12 and 13), or enlarged (entries 14 and 15). Among these variations, several are particularly noteworthy: the presence of a conjugate acceptor enone (entry 5) does not lead to Michael addition products, highlighting the essentially neutral reaction conditions; quaternary stereocenters may be synthesized vicinal to preexisting fully substituted carbons (entry 8); the temperature may be lowered in order to improve enantioselectivity when highly reactive substrates are employed (entries 12 and 13), although the reaction time increases significantly.[41] Overall, we were pleased to find that a wide range of functionalized enantioenriched cycloalkanones were accessible by this method.

Table 2.7. Substrate scope for asymmetric allylation of allyl enol carbonates



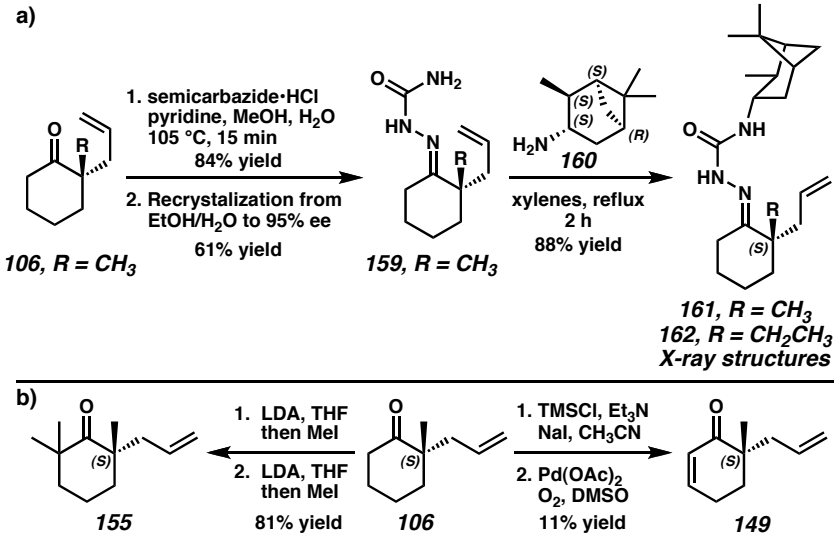
entry	product[a]	% yield[b]	% ee[c]	entry	product[a]	% yield[b]	% ee[c]
1		85	87	7	 ***151***, R = CH_2CH_3	96	92
2[d]		85	88 (96)[e]	8[g]	***152***, R = *t*-Bu	55[h]	82
3[f]	***106***	90	89	9	***153***, R = CH_2Ph	96	85
				10	***154***, R = $(CH_2)_3OBn$	87	88
4[g]	 ***148***	89	91	11	 ***155***	94	92
5	 ***149***	91	89	12[i]	 ***98***, R = H	87	91
				13[i]	***156***, R = OCH_3	94	91
6	 ***150***	87	86	14	 ***157***, n = 1	81	87
				15	***158***, n = 2	90	79

[a] Reactions were performed using 1.0 mmol of substrate in THF (0.033 M in substrate) at 25 °C with 2.5 mol% $Pd_2(dba)_3$ and 6.25 mol% (*S*)-*t*-Bu-PHOX (**55**), unless otherwise noted. Each reaction is complete in 1–10 h. [b] Isolated yields. [c] Measured by chiral GC or HPLC. [d] Performed on 5.1 mmol scale. [e] In parentheses is the % ee after one recrystallization of the corresponding semicarbazone. [f] Reaction performed at 12 °C (GC yield). [g] Performed with 5 mol% $Pd_2(dba)_3$ and 12.5 mol% (*S*)-**55**. [h] Isolated yield after conversion to the corresponding diketone via Wacker oxidation. [i] Performed at 10 °C.

At the time of our investigations, 2-allyl-2-methylcyclohexanone (**106**) was not known in enantioenriched form. Consequently, we wished to determine the absolute stereochemistry for several of our substrates (Scheme 2.5). To definitively assign the absolute stereochemistry of the newly formed quaternary stereocenter, we prepared the corresponding semicarbazone **159**. This derivative is highly crystalline, and recrystallization from EtOH/H_2O or toluene produced material of near enantiopurity (>98% ee).[42,43] Treatment of the semicarbazone with amine **160** of known absolute stereochemistry in refluxing xylenes gave the substituted semicarbazone **161**. Amino-substituted semicarbazone **161** also proved to be crystalline and amenable to single-

crystal X-ray analysis when recrystallized from acetone.[44] As the absolute stereochemistry of the isopinocampheylamine portion of semicarbazone **161** was known, the quaternary stereocenter set during the alkylation could be assigned *S* configuration. An analogous sequence was performed to prepare ethyl quaternary semicarbazone **162**, which confirmed that it, too, is of *S* configuration.[44] Having established the absolute configuration of the parent alkylation product, ketone (*S*)-**106** could be transformed in a straightforward manner to trimethyl ketone **155** and enone **149** (Scheme 2.5b), compounds also available directly by asymmetric alkylation (see Table 2.7). These transformations confirmed that the alkylation reaction forms ketone **155** and enone **149** with the same sense of absolute configuration. Finally, the *S* configuration of tetralone **98** was confirmed by comparison with literature data.[16b] Based on the consistent sense of enantiofacial selectivity, the stereochemistries of the remaining allylation products in Table 2.7 were inferred by analogy.

Scheme 2.5. Determination of absolute stereochemistry



Our use of allyl enol carbonates enabled direct access to α-quaternary ketones with multiple acidic sites. However, allyl enol carbonates are rarely encountered in the literature, and the synthesis of isomerically pure enol carbonates[45] often required the synthesis of silyl enol ethers. Since Tsuji had used silyl enol ethers in his non-enantioselective allylation, we contemplated adapting our conditions such that silyl enol ethers could be employed directly.

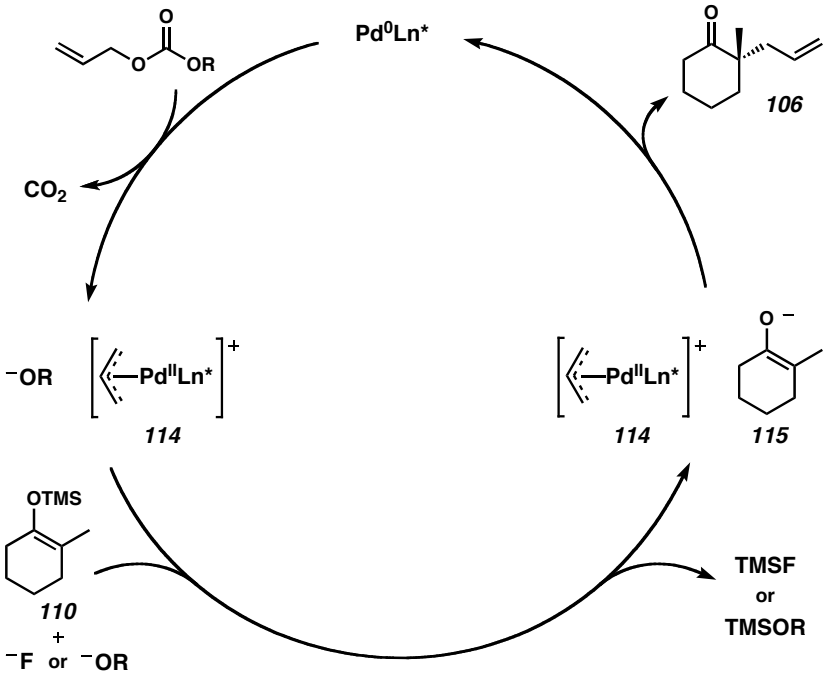
2.3.2 ASYMMETRIC ALLYLATION OF SILYL ENOL ETHERS

Silyl enol ethers are commonly encountered enolate equivalents. Unlike allyl enol carbonates, silyl enol ethers render the alkylation reaction intermolecular, with the enolate precursor and allyl fragment introduced separately. We discovered in our initial studies that silyl enol ethers were not sufficiently nucleophilic to react with the [Pd(II)(allyl)] fragment under our reaction conditions at 25 °C. However, we found that the reaction could be initiated in the presence of tetra-*n*-butylammonium difluorotriphenylsilicate (TBAT), a commercially available dry fluoride source.

The use of TBAT as an initiator complicated the proposed catalytic cycle (Scheme 2.6). In the case of allyl enol carbonates, the oxidative addition to allyl carbonate **105** and rapid decarboxylation led directly to the enolate/[Pd(II)(allyl)] ion pair, which could collapse directly to the product (Scheme 2.3). For the intermolecular reaction, we primarily used diallyl carbonates as allyl precursors, although mixed carbonates were also effective. Oxidative addition of allyl carbonates occurred readily at 25 °C to give [Pd(II)(allyl)] species **114**, CO_2, and an alkoxide. The addition of TBAT immediately generated the enolate, which we imagined would react with palladium complex **114** by

the same enantioselective mechanism observed with allyl enol carbonates. A substoichiometric amount of TBAT was sufficient, as the alkoxide formed in the reaction is also capable of providing the enolate in situ. In principle, it should be possible for the small amount of allyl alkoxide generated from oxidative addition to initiate the reaction.[46] In practice, we found that 35 mol% TBAT was usually sufficient to ensure complete conversion of the silyl enol ether (**110**). Having developed an effective means of silyl enol ether activation, we attempted asymmetric alkylation with a range of tetrasubstituted silyl enol ethers.

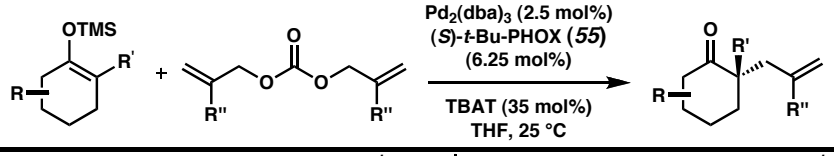
Scheme 2.6. General catalytic cycle for silyl enol ether alkylation

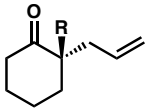
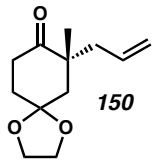
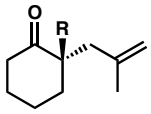
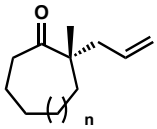


Gratifyingly, alkylation of the silyl enol ether substrates occurred with levels of enantioinduction similar to those observed for the allyl enol carbonate substrates and over a similar range of substrates (Table 2.8). Specifically, methyl- and ethyl-substituted quaternary ketones were produced with the same ee observed in the allyl enol carbonate

reactions (entries 1 and 2). Tertiary ether stereocenters were accessible from an α-oxygenated silyl enol ether, albeit with moderate enantioselectivity (entry 3). In addition to diallyl carbonate, dimethallyl carbonate served as a suitable allyl fragment precursor (entries 4 and 5). Interestingly, 2-allyl-2-methallylcyclohexanone (**164**), bearing only a remote methyl group to engender chirality, formed in 91% ee. As with the reactions of allyl enol carbonates, substitution about the ring and larger ring sizes were tolerated as well (entries 6–8).[47]

Table 2.8. Substrate scope for asymmetric allylation of silyl enol ethers



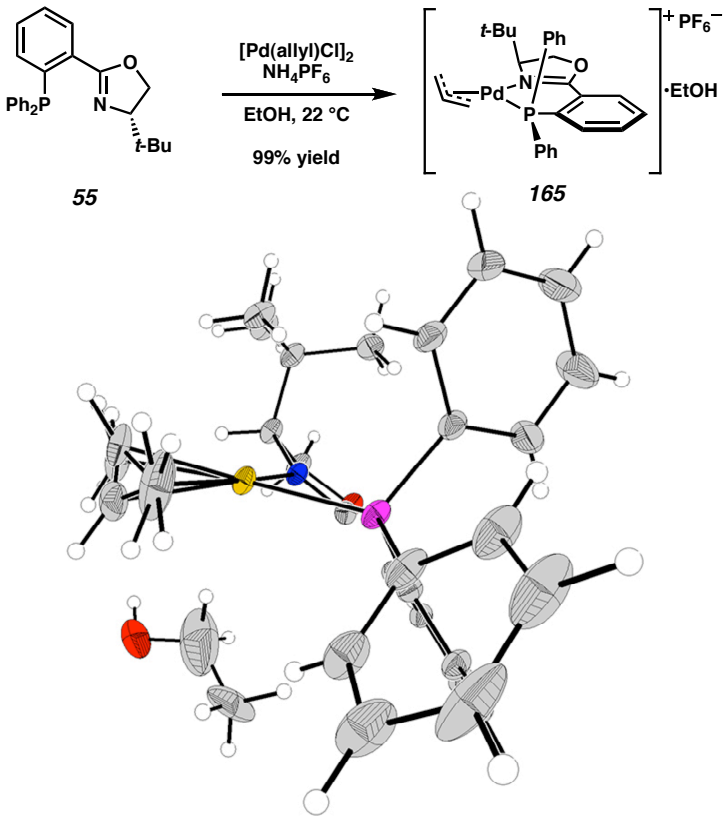
entry	product[a]		% yield[b]	% ee[c]	entry	product[a]		% yield[b]	% ee[c]
1		***106***, R = CH_3	95	87	6		***150***	99	81
2		***151***, R = CH_2CH_3	96	92					
3		***163***, R = OBn	83	59					
4[d]		***148***, R = CH_3	79	91	7		***157***, n = 1	94	86
5[d]		***164***, R = allyl	82	91	8		***158***, n = 2	96	79

[a] Reactions were performed using 1.0 mmol of substrate in THF (0.033 M in substrate) at 25 °C with 2.5 mol% $Pd_2(dba)_3$, 6.25 mol% (*S*)-*t*-Bu-PHOX (**55**), diallyl carbonate (1.05 equiv), and TBAT (35 mol%) unless otherwise noted. Each reaction was complete in 2–5 h. [b] Isolated yields. [c] Measured by chiral GC or HPLC. [d] Reaction performed with dimethallyl carbonate (1.05 equiv).

In addition to the flexibility afforded by the intermolecular reaction of silyl enol ethers and diallyl carbonates, the use of silyl enol ethers as a means to generate enolates independent of the allyl fragment allowed the catalytic cycle to commence at the stage of a [Pd(II)(allyl)] complex **165** (Scheme 2.7). Upon mixing (*S*)-*t*-Bu-PHOX, $[Pd(allyl)Cl]_2$, and NH_4PF_6 in ethanol,[48] $[Pd(II)(allyl)PHOX]^+[PF_6]^-$ salt **165** readily precipitated and this solid could be recrystallized and characterized crystallographically

as a partial EtOH adduct.[49] The complex (**165**) served as an active catalyst in the enol silane variant of our enantioselective alkylation reaction, giving good yield and nearly identical product ee compared to that observed with the in situ-generated catalyst. The Pd(II)PF_6 salt **165** has several practical advantages: it is an air stable, nonhygroscopic solid that may be stored indefinitely. Moreover, using the preformed [Pd(allyl)PHOX] catalyst obviated the introduction of dibenzylideneacetone (dba), which often complicated the purification of the α-quaternary ketone products.[50]

*Scheme 2.7. Allylation with Pd(II)PF_6 salt **165***



2.4 SYNTHETIC APPLICATIONS

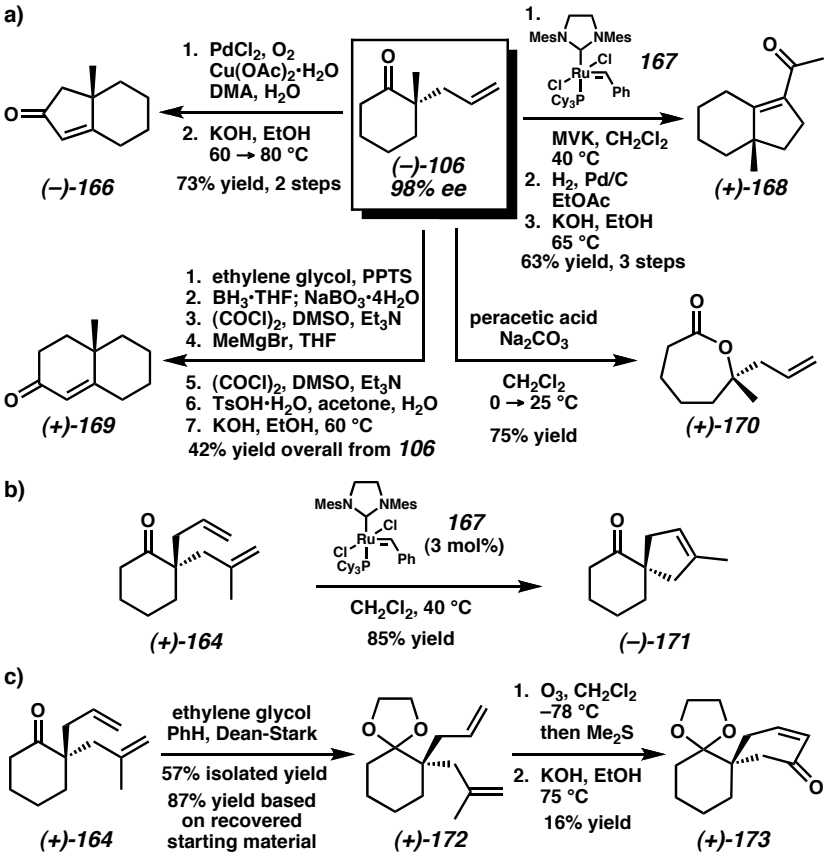
The α-quaternary cycloalkanones produced in the asymmetric Tsuji alkylation are highly useful chiral building blocks. Each substrate contains at least two functional groups, a ketone and an olefin, for further manipulation. Moreover, the preceding section has demonstrated these allylation reactions to be highly functional group tolerant. The application of this suite of allylation reactions to the catalytic asymmetric synthesis of natural products is an ongoing topic of research in our laboratories.[24]

To further demonstrate the utility of these products, we transformed ketone (*S*)-**106** into several familiar cyclic frameworks (Scheme 2.8a). Wacker oxidation of (*S*)-**106** followed by aldol condensation gave enone **166** in good yield. Another functionalized [6-5] skeleton was formed in a three-step sequence by olefin cross-metathesis with methyl vinyl ketone catalyzed by Grubbs' second-generation Ru-complex **167**,[51] olefin hydrogenation, and aldol condensation under basic conditions to afford exocyclic enone **168**. Carbocyclic [6-6] ring systems were accessible as well; multistep elaboration of the allyl group afforded an intermediate diketone, which underwent aldol condensation to enone **169** in 42% overall yield. Enone **169**, which has been classically produced by Robinson annulation, has been used extensively in synthesis.[52] As a final transformation of (*S*)-**106**, we executed a Baeyer–Villiger oxidation with peracetic acid to give caprolactone **170**. This transformation demonstrates the conversion of our enantioenriched quaternary stereocenter into a latent tertiary alcohol with defined absolute stereochemistry and entry into acyclic systems.[47]

Carbocyclic spiro compounds represent a particularly challenging subclass of quaternary stereocenters. In addition to the fused cyclic skeletons above, allyl methallyl

ketone **164** was used as an entry into the synthesis of ring systems containing spiro quaternary stereocenters. Ketone **164** could be treated with Grubbs' second generation catalyst (**167**) in dichloromethane to give a good yield of the spiro[4.5]ketone **171** (Scheme 2.8b). Spiro[5.5]enone **173** was produced in modest yield by treatment of ketone **164** with standard ketal protection conditions, followed by ozonolysis, and exposure to base (Scheme 2.8c).

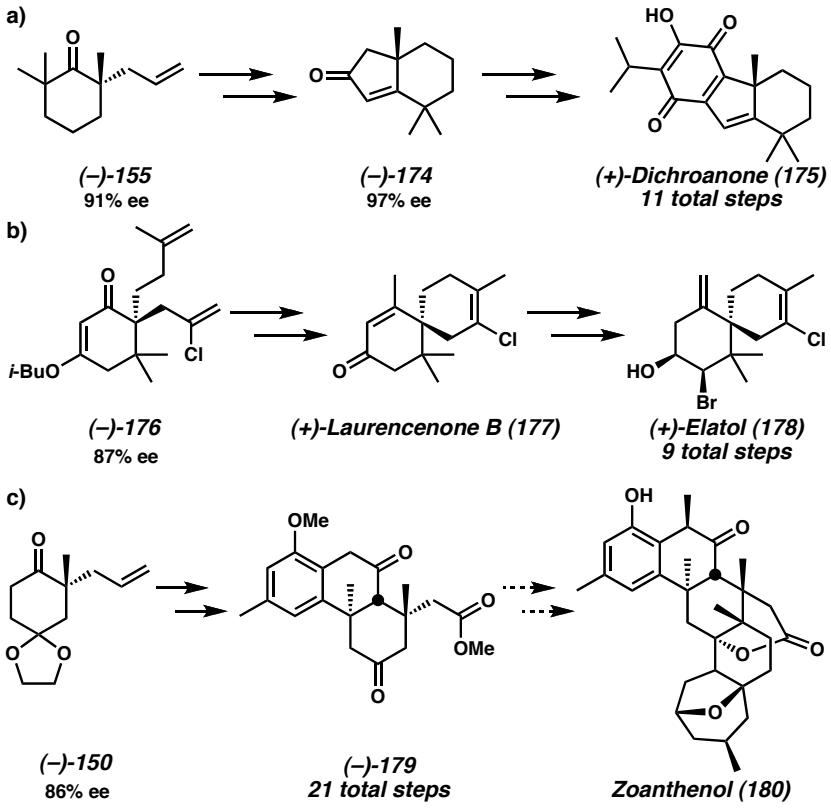
Scheme 2.8. Useful derivatives of enantioenriched cyclic ketones



Similar tactics have enabled the use of the enantioselective Tsuji allylation in a number of synthetic efforts.[24] Ketone (*S*)-**155** (Scheme 2.9a) was readily converted to enone **174**, which could be recrystallized via the semicarbazone derivative to 97% ee. Enantioenriched enone **174** was then elaborated to the natural product dichroanone (**175**)

in seven additional steps.[24a] A strategy comprising enantioselective allylation and ring-closing metathesis was employed to synthesize the spirocyclic natural products laurencenone B (**177**) and elatol (**178**) from vinylogous ester **176** (Scheme 2.9b).[24c] An ongoing effort toward the preparation of the marine alkaloid zoanthenol (**180**) featured α-quaternary ketone **150** as a key synthon for the preparation of the ABC tricyclic substructure (**179**) of the target molecule (Scheme 2.9c).[24b]

Scheme 2.9. Enantioenriched cyclic ketones in the synthesis of natural products

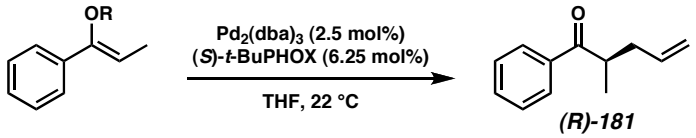


2.5 MISCELLANEOUS ALKYLATIONS USING THE PD•PHOX SYSTEM

2.5.1 SYNTHESIS OF TERTIARY STEREOCENTERS FROM ACYCLIC ENOLATE PRECURSORS

Although we have principally employed our asymmetric allylation for the synthesis of fully substituted stereocenters, the mild and nearly neutral conditions of the reaction are well suited for the synthesis of tertiary stereocenters α to carbonyls (Table 2.9).[40d,40g] Such stereocenters are prone to epimerization and over alkylation under the strongly basic conditions traditionally used for enolate generation.[53] We found that the allyl enol carbonate **182** underwent allylation to form phenyl ketone (*R*)-**181** in 67% ee (entry 1). In analogy to the results of Hou and co-workers,[18d] we found that the addition of AgBr gave a significant increase in the ee of the product (entry 2). Both TMS (**183**)[54] and TBS (**184**)[55] enol ethers were competent enolate precursors when TBAT was used as an initiator (entries 3 and 4). Unlike the tetrasubstituted silyl enol ethers, CsF proved to be the optimal fluoride source for the less-substituted silyl enol ethers, resulting in noticeably higher ee (entry 5). Unfortunately, the use of AgBr in the presence of CsF greatly reduced reactivity and only slightly increased enantioselectivity (entry 6). Similarly, the use of ethyl ether as a solvent increased enantioselectivity at the cost of lowered yield (entry 7). Although our allylation methods have provided tertiary stereocenters in only moderate ee, we have recently disclosed a decarboxylative protonation of quaternary allyl β-ketoesters based on a similar catalyst system that provides access to tertiary stereocenters α to ketones in excellent ee.[56]

Table 2.9. Enantioselective allylation of enol carbonates and silyl enol ethers not contained in a ring



(R)-181

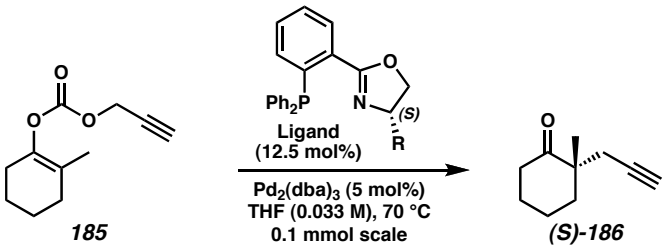
entry	R	additive	% yield[a]	% ee[b]	entry	R	additive	% yield[a]	% ee[b]
1	CO_2allyl (*182*)	none	79	67	5[d]	TMS (*183*)	CsF[f]	79	77
2	CO_2allyl (*182*)	AgBr[c]	75	79	6[d]	TMS (*183*)	CsF[f] AgBr[c]	20	79
3[d]	TMS (*183*)	TBAT[e]	60	62					
4[d]	TBS (*184*)	TBAT[e]	82	73	7[d,g]	TMS (*183*)	CsF[f]	38	82

[a] Isolated yield from reactions with 0.092 mmol of substrate in THF (0.092 M) with 2.5 mol% $Pd_2(dba)_3$ and 6.25 mol% (*S*)-*t*-Bu-PHOX (**55**), unless otherwise noted. [b] Measured by chiral HPLC. [c] Reaction with 40 mol% additive. [d] Reaction performed with diallyl carbonate (1.05 equiv). [e] Reaction with 35 mol% additive. [f] Reaction with 48 mol% additive. [g] Performed in Et_2O solvent.

2.5.2 APPLICATION OF THE PD•PHOX CATALYST SYSTEM TO PROPARGYLATION

In addition to allylation, we also explored propargylation of enol carbonates with the Pd•PHOX catalyst system (Table 2.10).[57] Our preliminary studies found that propargylation of enol carbonate **185** required significantly higher temperatures than are needed for allylation.[58] Additionally, the optimal structure of the PHOX ligand is significantly different for propargylation than for allylation. Moving the bulk of the *t*-Bu group away from the oxazoline by insertion of a methylene group gave (*S*)-**186** with higher ee (entries 1 and 2). Unlike allylation (cf. Table 2.4), PHOX ligands prepared from phenylalanine derivatives gave higher enantioselectivity than those prepared from saturated amino acids, with the 9-anthracenylalanine derivative (**189**) giving the highest level of enantioselectivity (entry 7, Table 2.10). Although still preliminary, these studies suggest that the Pd•PHOX catalyst system may find use outside allylation reactions.[56]

Table 2.10. Enantioselective propargylation



185 *(S)-186*

entry	ligand	% yield[a]	% ee[b]	entry	ligand	% yield[a]	% ee[b]
1	*55*, R = *t*-Bu	84	12	4	*128*, R = CH_2-1-Naphthyl	57	37
2	*127*, R = CH_2-*t*-Bu	83	32	5	*187*, R = CH_2-2-Naphthyl	71	26
				6	*188*, R = CH_2-(3,5-di-*t*-Bu-Ph)	94	25
3	*123*, R = CH_2Ph	54	26	7	*189*, R = CH_2-9-Anthracenyl	80	44

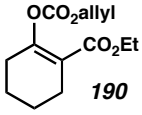
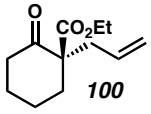
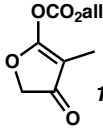
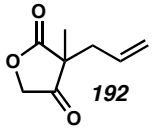
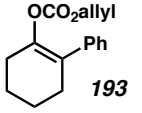
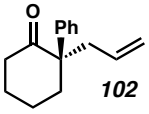
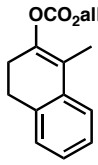
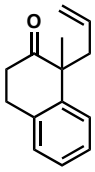
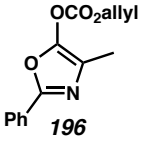
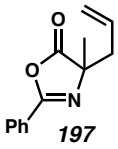
[a] GC yield relative to internal standard (tridecane). [b] Enantiomeric excess measured by chiral GC. In all cases, (*S*)-**186** was the major enantiomer.

2.5.3 SUBSTRATES PROCEEDING VIA WEAKLY BASIC ENOLATES

The alkylation of substrates derived from ketones of unusually low pK_a (i.e., stabilized enolates) as a group gave by far the lowest levels of enantioselectivity we have observed with the Pd•PHOX catalyst system (Table 2.11). Despite the low selectivity, these substrates gave consistently excellent chemical yields of the allylated products. It is noteworthy that the β-ketoester (entries 1 and 2) and α-phenyl ketone (entries 3 and 4) derived enolates that gave excellent enantioselectivity with Trost's earlier asymmetric allylation reactions[15,16b] failed to give useful levels of enantioinduction under our conditions. An oxazole (**196**), designed with the intention of executing an enantioselective synthesis of α,α-disubstituted amino acids, also underwent allylation with little enantioselectivity, presumably due to the stability of the intermediate aromatic enolate (entry 5). The orthogonality of the substrate scope, in terms of asymmetric induction, between our method and Trost's early reports may be indicative of

fundamentally different mechanisms underlying the two allylation reactions as has been an important piece of evidence in our mechanistic hypothesis.[26,59]

Table 2.11. Asymmetric alkylation via stabilized allyl enol carbonates

entry	substrate	product	% yield[a]	% ee[b]
1	 **190**	 **100**	89	24[c]
2	 **191**	 **192**	87	2
3	 **193**	 **102**	99	11[c]
4	 **194**	 **195**	93	0
5	 **196**	 **197**	89	2

[a] Isolated yield from reactions with 1.0 mmol of substrate in THF (0.033 M) at 25 °C with 2.5 mol% $Pd_2(dba)_3$ and 6.25 mol% (*S*)-*t*-Bu-PHOX (**55**). Each reaction was complete in 2 h. [b] Measured by chiral GC or HPLC. [c] Absolute stereochemistry of products assigned by analogy.

2.6 SUMMARY

In order to address a significant deficiency in the asymmetric alkylation literature, we have developed a strategy to prepare enantioenriched cycloalkanones in high yield. This work provides direct access to valuable enantioenriched α-quaternary ketones from readily accessible enolate precursors. Critical to our success was the use of enolate precursors, which can be converted to enolates under mild conditions, and the use of a chiral catalyst that exhibited the enolate isomeric fidelity found in Tsuji's non-enantioselective system. The reactivity and enantioselectivity of the alkylation reactions have proven to be quite general with respect to substrate steric bulk, ring size, unsaturation, and diverse functional groups. We have demonstrated the relevance of the α-quaternary ketones produced in the reaction by their conversion to a number of

carbocyclic chiral building blocks, including several spiro quaternary motifs, as well as in the asymmetric synthesis of the natural products dichroanone, laurencenone B, and elatol and an approach to zoanthenol.[24] Studies directed toward further development of the scope of this reaction and catalyst system are ongoing.[26,56] Additionally, the continued application of our asymmetric alkylation as a key enantiodetermining step in natural products synthesis will be reported in due course.[24]

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7173–7175. (g) Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833–4840. (h) Tsuji, Y.; Funato, M.; Ozawa, M.; Ogiyama, H.; Kajita, S.; Kawamura, T. *J. Org. Chem.* **1996**, *61*, 5779–5787. (i) Rayabarapu, D. K.; Tunge, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13510–13511.

28. For our initial communications concerning this chemistry, see: (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045. (b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924–6927. (c) Seto, M.; Roizen, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6873–6876. (d) We have recently reviewed the development of the enantioselective variants of these reactions to date by our lab and others. See: Mohr, J. T.; Stoltz, B. M. *Chem.–Asian J.* **2007**, *2*, 1476–1491.

29. For a review of chiral N/P ligands in asymmetric catalysis, see: Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497–537.

30. (a) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000,** *33*, 336–345. (b) Williams, J. M. J. *Synlett* **1996**, 705–710, and references therein. (c) Peer, M.; de Jong, J. C.; Kiefer, M.; Langer, T.; Rieck, H.; Schell, H.; Sennhenn, P.; Sprinz, J.; Steinhagen, H.; Wiese, B.; Helmchen, G. *Tetrahedron* **1996**, *52*, 7547–7583. (d) For a recent review of oxazoline-containing ligands, see: Hargaden, G. C.; Guiry, P. J. *Chem. Rev.* **2009**, *109*, 2505–2550.

31. THF also offers the practical advantage of being easier to obtain pure and dry than dioxane. THF also simplified the isolation of volatile ketones like **106**.

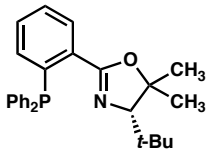
32. We have studied the ^{31}P NMR spectra of the reaction at length, and we believe that phosphine oxide **125** is produced as a catalyst decomposition product. Ligand **55** does not oxidize significantly in the absence of Pd. See the following chapter.

33. As a result of our desire to generate a large variety of PHOX ligands, we adapted a procedure for C–P bond formation disclosed by Buchwald and co-workers for the

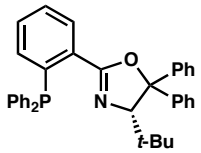
synthesis of PHOX ligands, see: (a) Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. *Org. Lett.* **2007**, *9*, 2529–2531. (b) Krout, M. R.; Mohr, J. T.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 181–193. (c) Gelman, D.; Jiang, L.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2315–2318.

34. Synthesized in analogy to PHOX ligands prepared by Helmchen, see ref 30c.

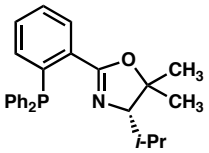
35. We have previously prepared the similar ligands **198** and **199**. In our prototypical reaction (**105** → **106**) 86% and 79% ee product was formed, respectively, with complete substrate conversion. A recent publication from another laboratory has put forth the related ligand **200**, which is available from valine, as an alternative to *t*-Bu-PHOX. The authors report comparable levels of enantioinduction with fluorinated enol silane substrates. See: Bélanger, É.; Pouliot, M.-F.; Paquin, J.-F. *Org. Lett.* **2009**, *11*, 2201–2204.



198



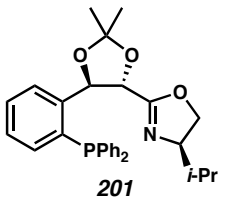
199



200

36. Wiese, B.; Helmchen, G. *Tetrahedron Lett.* **1998**, *39*, 5727–5730.

37. Trudeau and Morken synthesized PHOX-type ligand **201** as well as some structurally related ligands. These were tested it in a decarboxylative alkylation with carbonate substrate **124**, providing ketone **98** in up to 59% ee. See: Trudeau, S.; Morken, J. P. *Tetrahedron* **2006**, *62*, 11470–11476.



201

38. Dawson, G. J.; Frost, C. G.; Martin C. J.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 7793–7796.

39. Smidt, S. P.; Menges, F.; Pfaltz, A. *Org. Lett.* **2004**, *6*, 2023–2026.

40. Subsequent to our initial report on asymmetric allylation, several related reports have appeared: (a) For a collected review, see ref 28. (b) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846–2847. (c) Nakamura, M.; Hajra, A.; Endo, K.; Nakamura, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 7248–7251. (d) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180–17181. (e) Burger, E. C.; Barron, B. R.; Tunge, J. A. *Synlett* **2006**, 2824–2826. (f) Trost, B. M.; Bream, R. N.; Xu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3109–3112. (g) Trost, B. M.; Xu, J.; Reichle, M. *J. Am. Chem. Soc.* **2007**, *129*, 282–283. (h) Bélanger, É.; Cantin, K.; Messe, O.; Tremblay, M.; Paquin, J.-F. *J. Am. Chem. Soc.* **2007**, *129*, 1034–1035. (i) Schulz, S. R.; Blechert, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 3966–3970. (j) Bélanger, É.; Houzé, C.; Guimond, N.; Cantin, K.; Paquin, J.-F. *Chem. Commun.* **2008**, 3251–3253. (k) Ref 37. (l) Ref 35.

41. Goodwin, N. T. Application of iminium activation technologies to natural product synthesis: total syntheses of the spiculisporic acids, progress toward the total synthesis of cylindrocyclophane F, and a formal synthesis of cylindrocyclophane A. PhD thesis, California Institute of Technology, Pasadena, CA, 2006.

42. The recrystallization of semicarbazone derivatives as a means to increase the ee of our products has proven to be of general use with the α-quaternary ketones and their derivatives. For an example, see: ref 24a.

43. For an optimized procedure for recrystallization via the semicarbazone, see: Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 194–211.

44. See the experimental section (section 2.8) for details.

45. While isomerically pure enol carbonates and silyl enol ethers were desired for substrate characterization and to maximize the yield of α-quaternary ketone, it should be noted that this is not required for the allylation reaction. The less substituted enolate precursors are cleanly transformed to 2,6-substituted ketones, which are typically readily removed by chromatography, and have no effect on the ee of the desired product.

46. Sodium and potassium methoxide (1 equiv) could be used directly as silyl enol ether activators. However, lower yields (14% and 36%, respectively) and slightly lower ee (81% and 80%, respectively) were observed.

47. Silyl enol ethers of dioxanones have been useful for the preparation of a number of compounds bearing a tertiary oxygen moiety. For examples, see ref 28c.

48. For procedure, see: Liu, S.; Müller, J. F. K.; Neuburger, M.; Schaffner, S.; Zehnder, M. *J. Organomet. Chem.* **1997**, *549*, 283–293.

49. PF_6^- counterions removed for clarity. Two out of four of the crystallographically unique [Pd(allyl)PHOX] complexes in the unit cell crystallized with a molecule of ethanol. The *endo*- and *exo*-allyl isomers were present in equal electron density and are modeled as a superposition of the two isomers.

50. In some cases we have encountered difficulty in separating the cycloalkanone products from the residual dba introduced with the palladium source. As a practical consideration, it is often useful to employ bis(di(3,5-dimethoxybenzylidene)acetone)palladium(0) ($Pd(dmdba)_2$) or tris(di(4-methoxybenzylidene)acetone)dipalladium(0) ($Pd_2(pmdba)_3$) as the source of palladium because of the difference in polarity of dmdba and pmdba relative to dba. We have observed no difference in the effectiveness of these two catalyst precursors in terms of reactivity and enantioselectivity.

51. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.

52. For representative examples, see: (a) Boger, D. L. Key Ring Forming Reactions. *Modern Organic Synthesis: Lecture Notes*, TSRI Press: La Jolla, CA, 1999; pp 273–281. (b) Revial, G.; Pfau, M. *Organic Syntheses*; Wiley & Sons: New York, 1998; Collect. Vol. 9, pp 610–618, and references therein.

53. Under our conditions we found that negligible racemization of α-aryl ketone **181** was observed when allowed to remain under the reaction conditions for an additional 12 h.

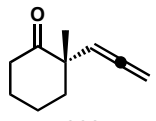
54. Muñoz-Muñiz, O.; Quintanar-Audelo, M.; Juaristi, E. *J. Org. Chem.* **2003**, *68*, 1622–1625.

55. Trimitsis, G.; Beers, S.; Ridella, J.; Carlon, M.; Cullin, D.; High, J.; Brutts, D. *J. Chem. Soc., Chem. Commun.* **1984**, 1088–1089.

56. (a) Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11348–11349. (b) Marinescu, S. C.; Nishimata, T.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2008**, *10*, 1039–1042.

57. For examples of propargylation of similar enolates, see: (a) Matsuda, I.; Komori, K.-i.; Itoh, K. *J. Am. Chem. Soc.* **2002**, *124*, 9072–9073. (b) Bienaymé, H. *Tetrahedron Lett.* **1994**, *35*, 7383–7386. (c) Bienaymé, H. *Tetrahedron Lett.* **1994**, *35*, 7387–7390.

58. In addition to α-propargylated ketone **186**, trace amounts of (*S*)-allene **202** are produced in 56% ee with ligand **127**.



202

59. For a computational discussion of the mechanism of this reaction, see: Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard, W. A., III. *J. Am. Chem. Soc.* **2007**, *129*, 11876–11877.

2.8 EXPERIMENTAL SECTION

2.8.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Tetrabutylammonium difluorotriphenylsilicate (TBAT) was purchased from Sigma-Aldrich and azeotropically dried five times from acetonitrile prior to use. Bis(di(3,5-dimethoxybenzylidene)acetone)palladium(0) ($Pd(dmdba)_2$), alkyl halides, triethylsilyl chloride, diallyl carbonate, Select-fluor®, pimelic acid, and all other ketone starting materials were purchased from Sigma-Aldrich and used as received, unless otherwise noted. Commercial 3-methylcyclohex-2-en-1-one, cyclohex-2-en-1-one, and NaH (60% dispersion in mineral oil) were purchased from Acros and used as received. Dimethallyl carbonate was purchased from Alfa Aesar and used as received. Trimethylsilyl chloride (TMSCl) and triethylamine were purchased from Sigma-Aldrich and distilled from sodium hydride immediately prior to use. Sodium iodide was dried by heating at 90 °C (2 torr) for 12 h. Molecular sieves were purchased from Aldrich as activated 5 μm powder and stored in a 120 °C drying oven until immediately prior to use unless otherwise noted. Ligands (*R,R*)-Trost Ligand (**103**), (*R*)-BINAP (**116**), (*R,R*)-Me-DUPHOS (**117**), (*R,R*)-DIOP (**118**), (*R*)-MOP (**119**), (*R*)-QUINAP (**120**), (*R*)-*i*-Pr-PHOX (**122**), (1*S*,2*R*)-*cis*-1-amino-indan-2-ol, and tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) were purchased from Strem and stored in a glovebox until immediately before use. (*R*)-Ph-PHOX (**121**) and (*S*)-Bn-PHOX (**123**) were prepared by the method of

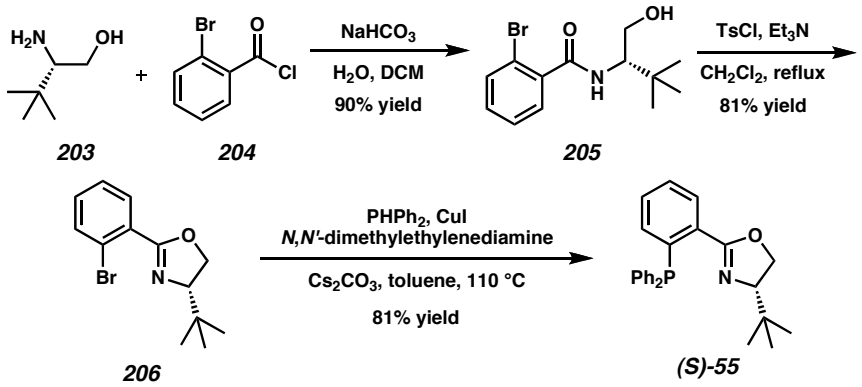
Helmchen.[60] (*S*)-*tert*-Leucine was purchased from Aldrich or Degussa and used as received. Other chiral amino acids were purchased from Chem-Impex International and reduced to the corresponding amino alcohols according to literature precedent,[61] unless otherwise noted. Methallyl chloroformate was prepared by the method of Kirby.[62] Ruthenium olefin metathesis catalysts were generously donated by Materia and stored under argon in a dessicator jar at –20 °C until just prior to use.

Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, $KMnO_4$ or CAM staining. ICN Silica gel (particle size 0.032–0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing chiralcel AD, OD-H, or OJ columns (4.6 mm × 25 cm) obtained from Daicel Chemical Industries, Ltd., with visualization at 254 nm. Analytical chiral GC was performed with an Agilent 6850 GC utilizing a Chiraldex G-TA (30.0 m x 0.25 mm) column (1.0 mL/min He carrier gas flow). Analytical achiral GC was performed with an Agilent 6850 GC utilizing an Agilent DB-WAX (30.0 m × 0.25 mm) column (1.0 mL/min He carrier gas flow). Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz, respectively) or a Varian Inova 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept. = septet, m = multiplet, comp. m = complex multiplet, app. = apparent, br

s = broad singlet. Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). ^{19}F NMR spectra were recorded on a Varian Mercury 300 spectrometer at 282 MHz, and are reported relative to the external standard F_3CCO_2H (δ –76.53 ppm) or $CFCl_3$ (δ 0.0 ppm). ^{31}P NMR spectra were recorded on a Varian Mercury 300 spectrometer at 121 MHz, and are reported relative to the external standard H_3PO_4 (δ 0.0 ppm). Temperature controlled ^{1}H NMR kinetic experiments were performed on a Varian Inova 500 MHz. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number.

2.8.2 SYNTHESIS OF PHOX LIGANDS

2.8.2.1 GENERAL PROCEDURES FOR SYNTHESIS OF PHOX LIGANDS



Amide 205: To a solution of (*S*)-*t*-leucinol (**203**)[61] (3.57 g, 30.5 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) was added a solution of Na_2CO_3 (9.70 g, 91.5 mmol, 3.0 equiv) in water (75.0 mL). To the vigorously stirred biphasic mixture was added 2-bromobenzoyl chloride (**204**, 4.58 mL, 35.1 mmol, 1.15 equiv) in a dropwise manner. After 12 h ambient temperature, the layers were separated, and aqueous layer extracted with CH_2Cl_2 (2 x 50 mL). The combined organics were treated with KOH (15 mL of a 1 M methanolic solution) for 15 min, neutralized with 3 M HCl, and water (50 mL) was added. The layers were separated, and the aqueous layer extracted with CH_2Cl_2 (2 x 50 mL). The combined organics were dried (Na_2SO_4), evaporated, and the residue chromatographed (25→35% acetone in hexanes on SiO_2) to give amide **205** (8.19 g, 89.5% yield): mp 50–51 °C from acetone/hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.54 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.34 (app. dt, *J* = 7.4, 1.1 Hz, 1H), 7.26 (app. dt, *J* = 7.7, 1.8 Hz, 1H), 6.24 (bd, *J* = 8.1 Hz, 1H), 4.05 (m, 1H), 3.93 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.66 (dd, *J* = 11.4, 7.5 Hz, 1H), 2.68 (br s, 1H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 137.9, 133.3, 131.2, 129.7, 127.6, 119.0, 62.9, 60.2,

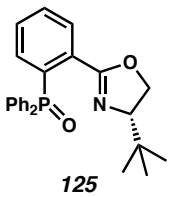
33.8, 27.1; IR (Neat Film NaCl) 3245, 3070, 2963, 1640, 1557 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{13}H_{19}NO_2Br$ $[M + H]^+$: 300.0599, found 300.0590; $[\alpha]_D^{29}$ +20.19 (*c* 2.38, methanol).

Phenyloxazoline 206:[60] A solution of amide **205** (8.10 g, 27.0 mmol, 1.0 equiv), tosyl chloride (6.69 g, 35.1 mmol, 1.3 equiv), triethylamine (18.7 mL, 135.0 mmol, 5.0 equiv) in CH_2Cl_2 (200 mL) in a rb flask equipped with a reflux condenser was heated at 55 °C for 22 h. Water (28 mL) was added and heating was continued at 75 °C for 2 h. The reaction mixture was cooled, the layers separated, and the aqueous layer extracted with CH_2Cl_2 (2 x 25 mL). The combined organics were dried (Na_2SO_4), evaporated, and the residue chromatographed (5% EtOAc in Hexanes on SiO_2) to give phenyloxazoline **206** (6.19 g, 81.2% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (app. dt, *J* = 8.7, 1.7 Hz, 2H), 7.33 (app. dt, *J* = 7.7, 1.5 Hz, 1H), 7.26 (m, 1H), 4.38 (dd, *J* = 10.5, 8.9 Hz, 1H), 4.25 (app. t, *J* = 8.3 Hz, 1H), 4.10 (dd, *J* = 10.2, 8.1 Hz, 1H), 1.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 133.6, 131.4, 131.2, 130.2, 127.0, 121.8, 76.6, 69.0, 34.0, 25.9; IR (Neat Film NaCl) 2956, 1661, 1478, 1354, 1099, 1022, 963 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{13}H_{17}NOBr$ $[M + H]^+$: 282.0493, found 282.0488; $[\alpha]_D^{29}$ –48.32 (*c* 3.77, hexane).

(*S*)-*t*-Bu-PHOX (55): A mixture of CuI (338.3 mg, 1.77 mmol, 0.125 equiv), diphenylphosphine (4.64 mL, 26.7 mmol, 1.88 equiv), *N*,*N*'-dimethylethylenediamine (1.32 mL, 12.4 mmol, 0.875 equiv) in toluene (60 mL) was stirred for 20 min at ambient temperature. At this point, phenyloxazoline **206** (4.00 g, 14.2 mmol, 1.0 equiv), cesium carbonate (17.4 g, 53.3 mmol, 3.75 equiv), and toluene (60 mL) were added, the flask sealed and heated to 110 °C with stirring. The reaction mixture became deep red after

~15 min of heating. After 6 h, the reaction mixture was allowed to cool to ambient temperature, filtered, and washed with CH_2Cl_2 (2 x 50 mL). Evaporation of the solvent and chromatography (3→7% Et_2O in Hexanes on SiO_2) afforded the known[60] (*S*)-*t*-Bu-PHOX (4.48 g, 81.4% yield).

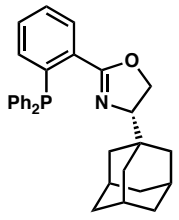
2.8.2.2 CHARACTERIZATION DATA FOR NEW PHOX LIGANDS



125

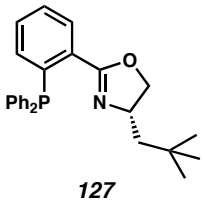
(*S*)-*t*-Bu-PHOX oxide (125, Scheme 2.4): To a solution of (*S*)-*t*-Bu-PHOX (150 mg, 0.387 mmol, 1.00 equiv) in THF (2.5 mL) was added a 5% aqueous H_2O_2 solution (1.94 mL). After 15 min the reaction mixture was diluted with EtOAc (5 mL) and brine (5 mL), washed with 10% aqueous Na_2CO_3 (5 mL) and brine (5 mL), dried ($MgSO_4$), and purified by flash chromatography on silica gel (5% MeOH in CH_2Cl_2) to give (*S*)-*t*-Bu-PHOX oxide **125** (149.3 mg, 96% yield) as a white foam: R_f 0.47 (10% MeOH in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (ddd, *J* = 7.5, 3.9, 1.2 Hz, 1H), 7.81-7.33 (comp. m, 7H), 7.52-7.31 (comp. m, 7H), 3.84 (dd, *J* = 8.1, 8.1 Hz, 1H), 3.57 (dd, *J* = 9.9, 9.9 Hz, 1H), 3.41 (dd, *J* = 9.9, 8.4 Hz, 1H), 0.77 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 135.0 (d, *J* = 10.1 Hz), 133.7 (d, *J* = 107.1 Hz), 133.3 (d, *J* = 107.1 Hz), 132.6, 132.4-131.0 (7 lines), 130.8 (d, *J* = 8.6 Hz), 130.3 (d, *J* = 11.7 Hz), 138.2 (app. dd, *J* = 12.3, 1.4 Hz), 75.9, 68.8, 33.6, 25.8; ^{31}P NMR (121 MHz, $CDCl_3$) δ 30.3; IR (Neat Film NaCl) 3057, 2957, 2903, 2868, 2217, 1664, 1589, 1565, 1477, 1438, 1356, 1337, 1307,

1248, 1201, 1119, 1108, 1067, 1028, 963, 930, 905 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{25}H_{27}O_2NP$ $[M]^+$: 404.1779, found 404.1799; $[\alpha]_D^{27.6}$ –69.3 (*c* 1.96, CH_2Cl_2).



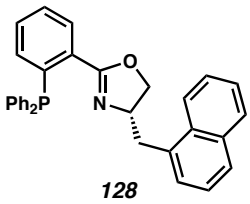
126

(*S*)-(Adamant-1-yl)-PHOX (126, Table 2.4, entry 5): Prepared by general procedure 1 from 2-(1-adamantyl)-glycine[63] in 71% yield as a white solid; mp 163–164 ºC; R_f = 0.59 (5:1 Hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (m, 1H), 7.40-7.20 (m, 12H), 6.85 (m, 1H), 4.11 (t, *J* = 9.0 Hz, 1H), 4.03 (t, *J* = 9.0 Hz, 1H), 3.73 (t, *J* = 9.0 Hz, 1H), 1.85 (m, 3H), 1.68-1.46 (m, 6H), 1.44-1.34 (m, 3H), 1.24-1.14 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4 (d, J_{CP} = 3 Hz), 138.8-138.3 (6 lines), 134.4 (d, J_{CP} = 21 Hz), 134.1, 133.4 (d, J_{CP} = 20 Hz), 132.0 (d, J_{CP} = 20 Hz), 130.3, 129.7 (d, J_{CP} = 3 Hz), 128.5-128.0 (7 lines), 76.8, 66.8, 38.2, 37.0, 35.3, 28.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ –5.67; IR (Neat Film NaCl) 3053, 2902, 2848, 1651, 1586, 1477, 1434, 1346, 1248, 1089, 1044, 1026, 963, 744, 696 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{31}H_{33}NOP$ $[M + H]^+$: 466.2300, found 466.2309; $[\alpha]_D^{27}$ –31.8 (*c* 0.48, $CHCl_3$).



127

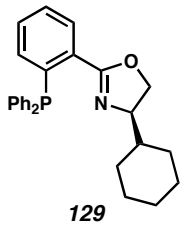
(*S*)-Neopentyl-PHOX (127, Table 2.4, entry 6; Table 2.10, entry 2): Prepared by general procedure 1 from D-neopentyl-glycine in 73% yield as a white solid; mp 83-86 ºC; R_f = 0.52 (5:1 Hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (ddd, J = 7.8, 3.6, 1.5 Hz, 1H), 7.38-7.23 (m, 12H), 6.84 (ddd, J = 7.8, 4.5, 1.5 Hz, 1H), 4.25 (dd, J = 9.3, 8.1 Hz, 1H), 4.03 (m, 1H), 3.58 (t, J = 8.1 Hz, 1H), 1.52 (dd, J = 14.1, 4.5 Hz, 1H), 0.93 (dd, J = 14.1, 8.1 Hz, 1H), 0.84 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0 (d, J_{CP} = 3 Hz), 138.7 (d, J_{CP} = 25 Hz), 137.9 (d, J_{CP} = 12 Hz), 137.8 (d, J_{CP} = 10 Hz), 134.3 (d, J_{CP} = 21 Hz), 133.9 (d, J_{CP} = 21 Hz), 133.5 (d, J_{CP} = 2 Hz), 131.8 (d, J_{CP} = 18 Hz), 130.3, 129.8 (d, J_{CP} = 3 Hz), 128.6-128.3 (6 lines), 127.9, 73.9, 64.0, 49.7, 30.0, 29.8; ^{31}P NMR (121 MHz, $CDCl_3$) δ –3.95; IR (Neat Film NaCl) 3054, 2955, 1652, 1586, 1476, 1434, 1355, 1248, 1089, 1035, 968, 742, 697 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{26}H_{29}NOP$ [M + H]$^+$: 402.1987, found 402.2002; $[\alpha]_D^{26}$ –6.9 (*c* 1.03, $CHCl_3$).



128

(*S*)-(Naphth-1-ylmethyl)-PHOX (128, Table 2.4, entry 7; Table 2.10, entry 4): Prepared by general procedure 1 (*S*)-3-(1-napthyl)-alanine in 54% yield as a white amorphous solid; R_f = 0.29 (25% Et_2O in Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (m, 1H), 7.91 (m, 1H), 7.85 (m, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.56-7.45 (m, 2H), 7.42-

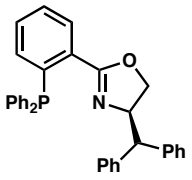
7.28 (m, 13H), 7.16 (m, 1H), 6.87 (m, 1H), 4.55 (m, 1H), 3.97 (t, J = 8.4 Hz, 1H), 3.86 (dd, J = 8.4, 7.2 Hz, 1H), 3.44 (dd, J = 14.4, 4.2 Hz, 1H), 2.39 (dd, J = 14.4, 10.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1 (d, J_{CP} = 3 Hz), 138.9 (d, J_{CP} = 25 Hz), 137.84 (d, J_{CP} = 10 Hz), 137.79 (d, J_{CP} = 12 Hz), 134.5 (d, J_{CP} = 21 Hz), 134.0, 133.82 (d, J_{CP} = 21 Hz), 133.80, 133.5 (d, J_{CP} = 3 Hz), 131.9, 131.3 (d, J_{CP} = 17 Hz), 130.6, 130.0 (d, J_{CP} = 3 Hz), 128.8-128.4 (6 lines), 127.9, 127.2, 126.6, 126.0, 125.6, 125.4, 123.8, 71.7, 66.7, 38.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ –3.59; IR (Neat Film NaCl) 3052, 2962, 1651, 1585, 1511, 1476, 1434, 1354, 1216, 1089, 1037, 963, 745, 697 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{32}H_{27}NOP$ $[M + H]^+$: 472.1830, found 472.1835; $[\alpha]_D^{24}$ +29.7 (*c* 0.50, $CHCl_3$).



129

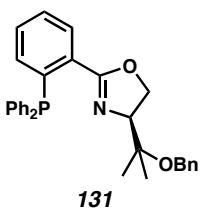
(*S*)-Cyclohexyl-PHOX (129, Table 2.4, entry 8): Prepared by general procedure 1 from (*R*)-cyclohexyl-glycine[64] in 68% yield as a white solid; mp 122-124 ºC; R_f = 0.57 (20% EtOAc in Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (ddd, J = 7.7, 4.1, 1.7 Hz, 1H), 7.27 (m, 13H), 6.82 (ddd, J = 7.7, 4.1, 1.1 Hz, 1H), 4.12 (ddd, J = 14.6, 9.1, 1.4 Hz, 1H), 3.85 (t, J = 8.3 Hz, 1H), 3.81 (t, J = 8.5 Hz, 1H), 1.60 (m, 4H), 1.28 (d, J = 13.5 Hz, 1H), 1.05 (m, 4H), 0.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7 (d, J_{CP} = 3 Hz), 139.0-138.0 (6 lines), 134.5 (d, J_{CP} = 21 Hz), 133.8, 133.7 (d, J_{CP} = 20 Hz), 131.8 (d, J_{CP} = 19 Hz), 130.4, 129.8 (d, J_{CP} = 3 Hz), 128.6-128.0 (7 lines), 71.2, 70.1, 42.7, 29.4, 29.0, 26.4, 26.1, 26.0; ^{31}P NMR (121 MHz, $CDCl_3$) δ –4.21; IR (Neat Film NaCl) 3053, 2923,

2852, 1651, 1478, 1434, 1356, 1089, 1044, 964, 908 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{27}H_{28}NOP$ [M^+]: 413.1909, found 413.1923; $[\alpha]_D^{25}$ +47.9 (*c* 0.175, $CHCl_3$).



130

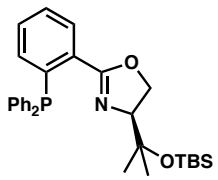
(*R*)-Benzhydryl-PHOX (130, Table 2.4, entry 9): Prepared by general procedure 1 from (*R*)-3,3-diphenyl-alanine in 89% yield as a white amorphous solid; R_f = 0.45 (5:1 Hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (m, 1H), 7.38-7.13 (m, 22H), 6.88 (m, 1H), 4.92 (q, *J* = 9.0 Hz, 1H), 4.13 (dd, *J* = 9.3, 9.0 Hz, 1H), 3.79 (t, *J* = 9.0 Hz, 1H), 3.72 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 142.2, 142.1, 138.8 (d, J_{CP} = 25 Hz), 138.0-137.7 (3 lines), 134.1 (d, J_{CP} = 21 Hz), 133.9 (d, J_{CP} = 21 Hz), 133.7 (d, J_{CP} = 2 Hz), 131.7 (d, J_{CP} = 19 Hz), 130.5, 130.0 (d, J_{CP} = 3 Hz), 128.7-128.2 (9 lines), 128.0, 126.5, 126.2, 71.1, 70.1, 56.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ –5.22; FTIR (Neat Film NaCl) 3056, 3026, 2895, 1649, 1598, 1584, 1494, 1477, 1451, 1434, 1356, 1091, 1029, 909, 741 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{34}H_{29}NOP$ [M + H]$^+$: 498.1987, found 498.1963; $[\alpha]_D^{24}$ +10.4 (*c* 1.00, $CHCl_3$).



131

(*S*)-(2-(Benzyloxy)propan-2-yl)-PHOX (131, Table 2.4, entry 10): The aryl bromide was prepared from L-serine using the analogous procedure reported by

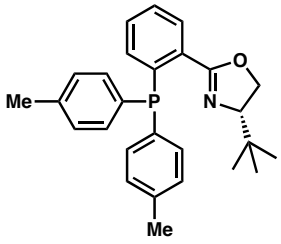
Helmchen.[60] Coupling was achieved by general procedure 1 in 75% yield as a colorless viscous oil; R_f = 0.45 (5:1 Hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (ddd, J = 7.5, 3.6, 1.2 Hz, 1H), 7.41-7.19 (m, 17H), 6.88 (ddd, J = 7.5, 4.2, 0.9 Hz, 1H), 4.43-4.23 (m, 4H), 4.15 (dd, J = 9.6, 7.8 Hz, 1H), 1.21 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8 (d, J_{CP} = 3 Hz), 139.5, 139.1-138.3 (5 lines), 134.4 (d, J_{CP} = 21 Hz), 134.2, 133.5 (d, J_{CP} = 20 Hz), 131.6 (d, J_{CP} = 19 Hz), 130.5, 129.9 (d, J_{CP} = 3 Hz), 128.6-128.1 (6 lines), 127.14, 127.12, 76.9, 74.9, 68.5, 63.9, 23.9, 19.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ –5.51; IR (Neat Film NaCl) 3067, 2973, 2905, 1649, 1586, 1478, 1434, 1352, 1248, 1155, 1091, 1065, 1027, 964, 743, 697 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{31}H_{31}NO_2P$ [M + H]$^+$: 480.2092, found 480.2078; $[\alpha]_D^{26}$ –2.0 (*c* 1.03, $CHCl_3$).



132

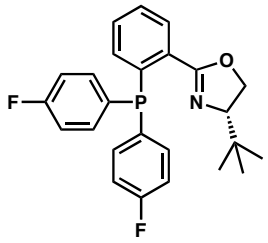
(*S*)-(2-(*tert*-Butyldimethylsilyloxy)propan-2-yl)-PHOX (132, Table 2.4, entry 11): The aryl bromide was prepared from L-serine using the analogous procedure reported by Helmchen.[60] Coupling was achieved by general procedure 1 in 84% yield as a white solid; mp 104-106 ºC; R_f = 0.62 (5:1 HexanesEtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (ddd, J = 7.5, 3.6, 1.2 Hz, 1H), 7.40-7.20 (m, 12H), 6.88 (ddd, J = 7.5, 3.9, 0.9 Hz, 1H), 4.32 (dd, J = 7.5, 6.6 Hz, 1H), 4.09 (dd, J = 10.2, 7.5 Hz, 1H), 4.02 (dd, J = 10.2, 6.6 Hz, 1H), 1.15 (s, 3H), 0.86 (s, 3H), 0.78 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 139.0-138.3 (6 lines), 134.3 (d, J_{CP} = 21 Hz), 134.2, 133.5 (d, J_{CP} = 20 Hz), 131.9 (d, J_{CP} = 19 Hz), 130.4, 129.8 (d, J_{CP} = 3 Hz), 128.5-128.0 (5 lines),

76.8, 74.9, 68.7, 28.7, 25.7, 23.9, 17.9, –2.2, –2.3; ^{31}P NMR (121 MHz, $CDCl_3$) δ –5.99; IR (Neat Film NaCl) 3054, 2955, 2929, 2856, 1652, 1586, 1472, 1434, 1353, 1251, 1162, 1091, 1058, 835, 774, 743, 696 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{30}H_{39}NO_2PSi$ [M + H]$^+$: 504.2488, found 504.2469; $[\alpha]_D^{26}$ +19.8 (*c* 1.16, $CHCl_3$).



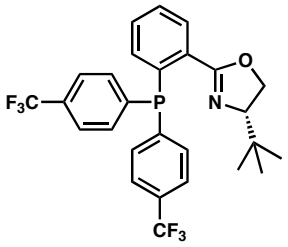
135

(*S*)-4-*tert*-Butyl-2-(2-(di-*p*-tolylphosphino)phenyl)-4,5-dihydrooxazole (135, Table 2.5, entry 1): Prepared by general procedure 1 using (*p*-Tol)$_2$PH in 73% yield as a colorless viscous oil; R_f = 0.39 (10% EtOAc in Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (ddd, *J* = 7.5, 3.6, 1.5 Hz, 1H), 7.33 (m, 1H), 7.26 (m, 1H), 7.23-7.05 (m, 8H), 6.89 (ddd, *J* = 7.5, 4.2, 1.5 Hz, 1H), 4.06 (dd, *J* = 10.2, 8.4 Hz, 1H), 3.98 (t, *J* = 8.3 Hz, 1H), 3.85 (dd, *J* = 10.2, 7.8 Hz, 1H), 2.33 (s, 3H), 2.32 (s, 3H), 0.75 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0 (d, J_{CP} = 3 Hz), 139.3 (d, J_{CP} = 25 Hz), 138.4, 138.1, 135.0-134.7 (4 lines), 134.3 (d, J_{CP} = 21 Hz), 133.9, 133.6 (d, J_{CP} = 20 Hz), 131.9 (d, J_{CP} = 20 Hz), 130.2, 129.9 (d, J_{CP} = 3 Hz), 129.2 (d, J_{CP} = 7 Hz), 129.0 (d, J_{CP} = 7 Hz), 127.8, 76.5, 68.3, 33.6, 25.7, 21.3, 21.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ –6.98; IR (Neat Film NaCl) 2953, 1653, 1496, 1476, 1394, 1353, 1306, 1248, 1185, 1134, 1089, 1024, 967, 805, 743 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{27}H_{30}NOP$ [M$^+$]: 415.2065, found 415.2065; $[\alpha]_D^{25}$ –58.8 (*c* 2.23, $CHCl_3$).



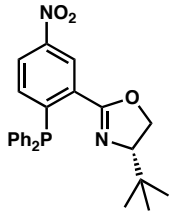
136

(*S*)-2-(2-(bis(4-fluorophenyl)phosphino)phenyl)-4-*tert*-butyl-4,5-dihydrooxazole (136, Table 2.5, entries 3 and 11): Prepared by Helmchen's Grignard method[60] in 14% yield as a colorless oil; R_f = 0.50 (5% Et_2O in hexanes developed twice); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (ddd, *J* = 7.0, 3.0, 1.0 Hz, 1H), 7.39 (ddd, *J* = 8.0, 8.0, 1.5 Hz, 1H), 7.31 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 7.26-7.14 (comp. m, 4H), 7.01 (app. dt, *J* = 13.0, 8.5 Hz, 4H), 6.83 (ddd, *J* = 7.5, 4.0, 1.0 Hz, 1H), 4.12 (dd, *J* = 10.0, 8.5 Hz, 1H), 4.03 (dd, *J* = 8.0, 8.0 Hz, 1H), 3.90 (dd, *J* = 10.0, 8.0 Hz, 1H), 0.74 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3 (d, $J_{C\text{-}F}$ = 247.5 Hz), 163.1 (d, $J_{C\text{-}F}$ = 246.5 Hz), 162.3, 138.6 (d, $J_{C\text{-}P}$ = 25.3 Hz), 136.1 (dd, $J_{C\text{-}P}$ = 22.5 Hz, $J_{C\text{-}F}$ = 8.1 Hz), 135.3 (dd, $J_{C\text{-}P}$ = 21.9 Hz, $J_{C\text{-}F}$ = 8.1 Hz), 134.1 (dd, $J_{C\text{-}P}$ = 12.5, $J_{C\text{-}F}$ = 4.1 Hz), 134.0 (dd, $J_{C\text{-}P}$ = 10.4 Hz, $J_{C\text{-}F}$ = 4.0 Hz), 133.9, 131.7 (d, $J_{C\text{-}P}$ = 20.0 Hz), 130.5, 130.0 (d, $J_{C\text{-}P}$ = 2.9 Hz), 128.3, 115.6 (dd, $J_{C\text{-}F}$ = 18.6 Hz, $J_{C\text{-}P}$ = 7.6 Hz), 115.5 (dd, $J_{C\text{-}F}$ = 18.6 Hz, $J_{C\text{-}P}$ = 7.6 Hz) 76.8, 68.3, 33.6, 25.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ –8.2 (app. t, *J* = 3.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ –113.6, –114.1; IR (Neat Film NaCl) 2955, 2904, 2868, 1653, 1587, 1494, 1392, 1354, 1336, 1225, 1159, 1091, 1039, 1025, 966, 827, 744 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{25}H_{25}ONPF_2$ $[M + H]^+$: 424.1642, found 424.1622; $[\alpha]_D^{26.4}$ –17.7 (*c* 0.53, CH_2Cl_2).



137

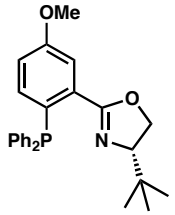
(*S*)-2-(2-(Bis(4-(trifluoromethyl)phenyl)phosphino)phenyl)-4-*tert*-butyl-4,5-dihydrooxazole (137, Table 2.5, entries 4 and 12): Prepared by general procedure 1 using (p-$CF_3Ph)_2PH$ in 75% yield as a white amorphous powder; R_f = 0.44 (10% EtOAc in Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (ddd, J = 7.5, 3.9, 1.2 Hz, 1H), 7.62-7.50 (m, 4H), 7.44 (m, 1H), 7.40-7.28 (m, 5H), 6.82 (ddd, J = 7.5, 3.9, 0.9 Hz, 1H), 4.20 (dd, J = 10.2, 8.4 Hz, 1H), 4.06 (t, J = 8.4 Hz, 1H), 3.93 (dd, J = 10.2, 8.4 Hz, 1H), 0.69 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8 (d, J_{CP} = 3 Hz), 143.4-143.2 (m), 136.7 (d, J_{CP} = 24 Hz), 134.4 (d, J_{CP} = 21 Hz), 134.2, 133.7 (d, J_{CP} = 20 Hz), 132.0 (d, J_{CP} = 20 Hz), 130.74, 130.65 (q, J_{CF} = 32 Hz), 130.5 (q, J_{CF} = 32 Hz), 129.9 (d, J_{CP} = 3 Hz), 128.9, 125.3-124.9 (m), 124.1 (q, J_{CF} = 271 Hz,), 77.0, 68.4, 33.6, 25.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ –7.29; ^{19}F NMR (282 MHz, $CDCl_3$) δ –63.23, –63.28; IR (Neat Film NaCl) 2958, 1653, 1606, 1480, 1396, 1324, 1166, 1128, 1106, 1061, 1017, 831, 700 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{27}H_{24}NOPF_6$ [M^+]: 523.1500, found 523.1494; $[\alpha]_D^{25}$ –21.1 (*c* 2.26, $CHCl_3$).



138

(*S*)-4-*tert*-Butyl-2-(2-(diphenylphosphino)-5-nitrophenyl)-4,5-dihydrooxazole

(138, Table 2.5, entries 5 and 13): Prepared by a modification of Andreas' method[65] in 8% yield as a red oil; R_f = 0.57 (25% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 3.0, 3.0 Hz, 1H), 8.07 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.40-7.29 (comp. m, 6H), 7.29-7.18 (comp. m, 4H), 7.04 (dd, *J* = 8.5, 3.0 Hz, 1H), 4.15 (dd, *J* = 10.0, 8.5 Hz, 1H), 4.04 (dd, *J* = 9.0, 8.0 Hz, 1H), 3.90 (dd, *J* = 9.5, 8.0 Hz, 1H), 0.72 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7 (d, *J* = 3.8 Hz), 148.6 (d, *J* = 33.0 Hz), 147.4, 137.2 (d, *J* = 12.0 Hz), 136.9 (d, *J* = 8.5 Hz), 135.1 (d, *J* = 1.4 Hz), 134.3 (d, *J* = 21.5 Hz), 133.6 (d, *J* = 20.5 Hz), 132.7 (d, *J* = 18.6 Hz), 129.2-128.6 (6 lines), 124.4 (d, *J* = 1.9 Hz), 124.1, 77.2, 68.6, 33.6, 25.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ –3.4; IR (Neat Film NaCl) 3071, 2956, 2904, 2868, 1656, 1522, 1478, 1434, 1346, 1118, 1086, 1026, 970, 913, 742, 696 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{25}H_{26}O_3N_2P$ $[M + H]^+$: 433.1681, found 433.1702; $[\alpha]_D^{26.4}$ – 16.2 (*c* 0.87, $CHCl_3$).

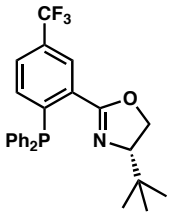


139

(*S*)-4-*tert*-Butyl-2-(2-(diphenylphosphino)-5-methoxyphenyl)-4,5-dihydrooxazole

(139, Table 2.5, entry 8): Prepared by general procedure 1 using 2-bromo-5-

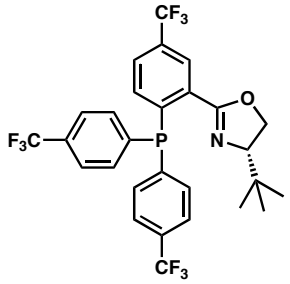
methoxybenzoyl chloride[66] in 72% yield as a white amorphous powder; R_f = 0.61 (25% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (t, *J* = 2.9 Hz, 1H), 7.34-7.18 (m, 10H), 6.84 (ddd, *J* = 8.7, 2.4, 0.6 Hz, 1H), 6.78 (ddd, *J* = 8.7, 3.3, 0.6 Hz, 1H), 4.13 (dd, *J* = 10.2, 8.4 Hz, 1H), 4.03 (t, *J* = 8.1 Hz, 1H), 3.92 (dd, *J* = 10.2, 8.1 Hz, 1H), 3.82 (s, 3H), 0.73 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5 (d, J_{CP} = 3 Hz), 159.4, 139.0 (d, J_{CP} = 13 Hz), 138.7 (d, J_{CP} = 10 Hz), 135.8, 134.1 (d, J_{CP} = 20 Hz), 133.41 (d, J_{CP} = 33 Hz), 133.36 (d, J_{CP} = 20 Hz), 129.3 (d, J_{CP} = 22 Hz), 128.3-128.0 (6 lines), 116.5, 114.9 (d, J_{CP} = 4 Hz), 76.7, 68.3, 55.3, 33.6, 25.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ –10.1; IR (Neat Film NaCl) 3069, 2956, 2903, 1654, 1594, 1561, 1479, 1434, 1354, 1336, 1297, 1224, 1181, 1093, 1050, 1022, 973, 744, 697 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{26}H_{28}NO_2P$ [M^+]: 417.1858, found 417.1844; $[\alpha]_D^{25}$ –48.8 (*c* 2.11, $CHCl_3$).



140

(*S*)-4-*tert*-Butyl-2-(2-(diphenylphosphino)-5-(trifluoromethyl)phenyl)-4,5-dihydrooxazole (140, Table 2.5, entry 10): Prepared by general procedure 1 from 2-bromo-5-trifluoromethylbenzoyl chloride[67] in 77% yield as a white powder; mp 98-100 ºC; R_f = 0.45 (10% EtOAc in Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (m, 1H), 7.51 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.38-7.18 (m, 10H), 6.99 (dd, *J* = 8.1, 3.3 Hz, 1H), 4.12 (dd, *J* = 10.2, 8.4 Hz, 1H), 4.03 (t, *J* = 8.4 Hz, 1H), 3.90 (dd, *J* = 10.2, 8.4 Hz, 1H), 0.72 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4 (d, J_{CP} = 3 Hz), 144.2 (d, J_{CP} = 30 Hz), 137.7 (d, J_{CP} = 12 Hz), 137.3 (d, J_{CP} = 9 Hz), 134.6, 134.3 (d, J_{CP} = 21 Hz), 133.6 (d, J_{CP} = 20 Hz), 132.2

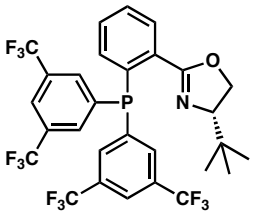
(d, J_{CP} = 19 Hz), 130.1 (q, J_{CF} = 33 Hz), 128.9-128.4 (6 lines), 126.6-126.3 (m), 123.7 (q, J_{CF} = 271 Hz), 77.0 (d, J_{CP} = 1 Hz), 68.4, 33.6, 25.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ –6.55 (J_{PF} = 2 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ –63.36; IR (Neat Film NaCl) 3071, 2957, 1655, 1478, 1434, 1407, 1357, 1343, 1326, 1302, 1262, 1244, 1174, 1131, 1080, 969, 744, 696 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{26}H_{25}NOPF_3$ [M$^+$]: 455.1626, found 455.1646; $[\alpha]_D^{25}$ –36.3 (*c* 2.39, $CHCl_3$).



141

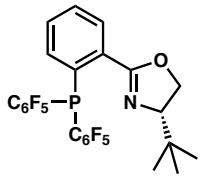
(*S*)-2-(2-(Bis(4-(trifluoromethyl)phenyl)phosphino)-5-(trifluoromethyl)phenyl)-4-*tert*-butyl-4,5-dihydrooxazole (141, Table 2.5, entry 14): Prepared by general procedure 1 using (*p*-$CF_3Ph)_2PH$ in 74% yield as a white amorphous powder; R_f = 0.63 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (m, 1H), 7.64-7.54 (m, 5H), 7.39-7.27 (m, 4H), 6.95 (dd, *J* = 7.8, 3.0 Hz, 1H), 4.25 (dd, *J* = 10.2, 8.7 Hz, 1H), 4.09 (t, *J* = 8.7 Hz, 1H), 3.95 (dd, *J* = 10.2, 8.7 Hz, 1H), 0.69 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7 (d, J_{CP} = 4 Hz), 142.6-141.7 (6 lines), 134.7-133.6 (5 lines), 132.4 (d, J_{CP} = 20 Hz), 131.1 (q, J_{CF} = 32 Hz), 130.9 (q, J_{CF} = 32 Hz), 127.0 (q, J_{CF} = 3 Hz), 126.7-126.4 (6 lines), 125.6-125.1 (8 lines), 123.9 (q, J_{CF} = 271 Hz), 123.5 (q, J_{CF} = 271 Hz), 77.3 (d, J_{CP} = 1 Hz), 68.6, 33.5, 25.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ –6.57; ^{19}F NMR (282 MHz, $CDCl_3$) δ –63.33, –63.39, –63.53; IR (Neat Film NaCl) 2960, 1657, 1606, 1479, 1397,

1324, 1169, 1129, 1107, 1082, 1061, 1017, 832, 700 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{28}H_{24}F_9NOP$ $[M + H]^+$: 592.1452, found 592.1480; $[\alpha]_D^{24}$ –16.0 (*c* 2.56, $CHCl_3$).



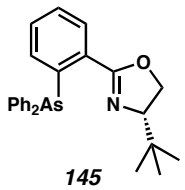
142

(*S*)-2-(2-(Bis(3,5-bis(trifluoromethyl)phenyl)phosphino)phenyl)-4-*tert*-butyl-4,5-dihydrooxazole (142, Table 2.5, entry 6): Prepared by Helmchen's Grignard method[60] in 6% yield as a colorless oil; R_f = 0.29 (5% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (ddd, *J* = 7.5, 4.0, 1.5 Hz, 1H), 7.86 (app. d, *J* = 11.0 Hz, 2H), 7.64 (app. dd, *J* = 21.0, 6.0 Hz, 4H), 7.53 (ddd, *J* = 7.0, 7.0, 1.0, 1H), 7.42 (ddd, *J* = 7.5, 7.5 1.0 Hz, 1H), 6.77 (ddd, *J* = 7.5, 3.5, 1.0 Hz, 1H), 4.28 (dd, *J* = 10.0, 8.5 Hz, 1H), 4.12 (dd, *J* = 9.0, 9.0 Hz, 1H), 3.91 (dd, *J* = 10.5, 9.0 Hz, 1H), 0.68 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4 (d, *J* = 3.4 Hz), 141.9 (d, *J* = 13.9 Hz), 141.8 (d, *J* = 11.9 Hz), 134.8 (d, *J* = 23.9 Hz), 134.0, 133.7 (d, *J* = 19.1 Hz), 133.2 (d, *J* = 21.5 Hz), 131.8 (app. dq, *J* = 31.5, 4.8 Hz), 131.3, 130.0 (d, *J* = 2.9 Hz), 129.8, 123.1 (q, *J* = 271.8 Hz), 122.7 (app. d of septets, *J* = 25.3, 3.3 Hz), 77.1, 68.7, 33.4, 25.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ –6.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ –63.9 (2 peaks); HRMS (FAB) *m/z* calc'd for $C_{29}H_{23}ONPF_{12}$ $[M + H]^+$: 660.1325, found 660.1328; $[\alpha]_D^{26.2}$ –5.0 (*c* 0.35, $CHCl_3$).



143

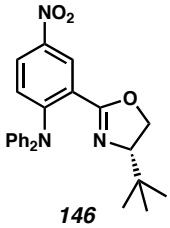
(*S*)-4-*tert*-Butyl-2-(2-(diperfluorophenylphosphino)phenyl)-4,5-dihydrooxazole (143, Table 2.5, entry 7): Prepared by Helmchen's Grignard method[60] in 13% yield as a colorless oil; R_f = 0.39 (2.5% Et_2O in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (ddd, *J* = 7.4, 4.8, 1.3 Hz, 1H), 7.51 (app. tt, *J* = 7.5, 1.3 Hz, 1H), 7.41 (app. tt, *J* = 7.7, 1.3 Hz, 1H), 7.16 (dd, *J* = 7.7, 3.5 Hz, 1H), 4.35 (dd, *J* = 10.1, 8.8 Hz, 1H), 4.18 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.93 (dd, *J* = 10.1, 8.8 Hz, 1H), 0.75 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3 (d, *J* = 5.0 Hz), 132.5, 130.9, 129.7 (2 peaks), 129.6, 77.3, 69.1, 33.6, 25.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ –54.7 (app. quintet, *J* = 38.1 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ –130.6 (app. t, *J* = 27.5 Hz), –131.1 (app. t, *J* = 27.5 Hz), –151.9 (app. t, *J* = 18.6 Hz), –152.4 (app. t, *J* = 21.2 Hz), –161.8 (app. t, *J* = 18.0 Hz), –162.0 (app. t, *J* = 15.0 Hz); IR (Neat Film NaCl) 2962, 2908, 2872, 1654, 1516, 1476, 1382, 1360, 1287, 1139, 1087, 1052, 978, 908, 834, 740 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{25}H_{17}ONPF_{10}$ $[M + H]^+$: 568.0888, found 568.0868; $[\alpha]_D^{26.2}$ –6.3 (*c* 0.56, CH_2Cl_2).



145

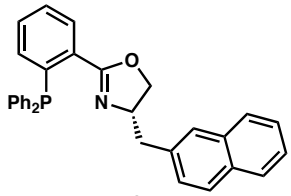
(*S*)-4-*tert*-Butyl-2-(2-(diphenylarsino)phenyl)-4,5-dihydrooxazole (145, Table 2.6, entry 2): Prepared by Helmchen's S_NAr method[60] in 40% yield using lithium diphenylarsine generated by lithium reduction of triphenylarsine as a colorless oil; R_f =

0.42 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.37 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 7.34-7.23 (comp. m, 10H), 7.01 (dd, *J* = 8.0, 1.0, 1H), 4.15 (dd, *J* = 9.5, 8.0 Hz, 1H), 4.04 (dd, *J* = 8.5, 8.5 Hz, 1H), 3.88 (dd, *J* = 10.5, 9.0 Hz, 1H), 0.75 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 141.9 (2 peaks), 141.5, 134.6, 134.0, 133.7, 131.8, 130.6, 129.5, 128.4 (2 peaks), 128.0, 127.9, 76.7, 68.3, 33.6, 25.7; IR (Neat Film NaCl) 3066, 3052, 2955, 2903, 2867, 1652, 1480, 1433, 1354, 1336, 1306, 1253, 1132, 1088, 1024, 967, 903, 736, 696 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{25}H_{27}ONAs$ $[M + H]^+$: 432.1309, found 432.1290; $[\alpha]_D^{25.6}$ –33.8 (*c* 1.47, $CHCl_3$).



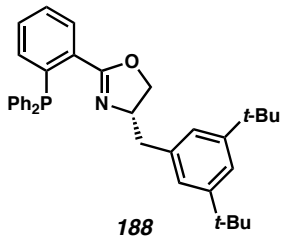
146

(*S*)-4-*tert*-Butyl-2-(2-(diphenylamino)-5-nitrophenyl)-4,5-dihydrooxazole (146, Table 2.6, entry 3): Prepared by a modification of Zhu's method[68] in 18% yield as a red oil; R_f = 0.45 (10% Et_2O in hexanes developed thrice); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (d, *J* = 3.0 Hz, 1H), 8.13 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.28 (app. t, *J* = 7.5 Hz, 4H), 7.09 (app. t, *J* = 7.5, 2H), 7.09 (d, *J* = 9.0 Hz, 1H), 7.03 (app. d, *J* = 7.5 Hz, 4H), 3.77 (dd, *J* = 8.5, 8.5 Hz, 1H), 3.59 (dd, *J* = 10.0, 8.5 Hz, 1H), 3.24 (dd, *J* = 10.0, 8.0 Hz, 1H), 0.80 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3, 151.8, 146.6, 141.8, 129.4, 128.6, 126.6, 126.5, 124.6, 124.3, 123.3, 75.0, 68.7, 33.6, 25.9; IR (Neat Film NaCl) 2958, 2904, 2868, 1647, 1588, 1574, 1518, 1490, 1333, 1299, 1278, 1116, 968, 912, 860, 751, 695 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{25}H_{26}O_3N_3$ $[M + H]^+$: 416.1974, found 416.1969; $[\alpha]_D^{25.6}$ +203.9 (*c* 0.55, $CHCl_3$).



187

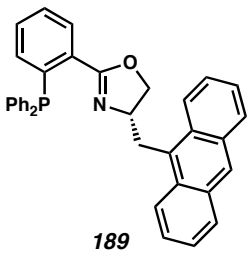
(*S*)-(Napth-2-ylmethyl)-PHOX (187, Table 2.10, entry 5): Prepared by general procedure 1 from 3-(2-napthyl)-alanine in 71% yield as a white amorphous solid; R_f = 0.24 (25% Et_2O in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (m, 1H), 7.82-7.72 (m, 3H), 7.53 (br s, 1H), 7.49-7.27 (m, 14H), 7.23 (m, 1H), 6.88 (m, 1H), 4.46 (m, 1H), 4.05 (dd, J = 9.0, 8.7 Hz, 1H), 3.83 (dd, J = 9.0, 7.5 Hz, 1H), 3.08 (dd, J = 14.1, 5.1 Hz, 1H), 2.30 (dd, J = 14.1, 9.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0 (d, J_{CP} = 3 Hz), 138.9 (d, J_{CP} = 25 Hz), 137.0-137.7 (3 lines), 135.6, 134.4 (d, J_{CP} = 21 Hz), 133.8 (d, J_{CP} = 21 Hz), 133.5 (d, J_{CP} = 2 Hz), 133.4, 132.1, 131.4 (d, J_{CP} = 18 Hz), 130.5, 129.9 (d, J_{CP} = 3 Hz), 128.7-127.4 (12 lines), 125.9, 125.4, 71.4, 67.7, 41.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ –4.05; FTIR (Neat Film NaCl) 3052, 1651, 1508, 1476, 1434, 1354, 1217, 1090, 1027, 964, 817, 743, 697 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{32}H_{27}NOP$ $[M + H]^+$: 472.1830, found 472.1845; $[\alpha]_D^{25}$ +42.7 (*c* 0.50, $CHCl_3$).



188

(*R*)-(3,5-Di-*tert*-butylbenzyl)-PHOX (188, Table 2.10, entry 6): Prepared by general procedure 1 from (*R*)-3-(3,5-di-*tert*-butylphenyl)-alaninol[69] in 55% yield as a

colorless viscous oil; R_f = 0.52 (5:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (m, 1H), 7.40-7.28 (m, 13H), 6.92 (d, *J* = 1.8 Hz, 2H), 6.86 (m, 1H), 4.33 (m, 1H), 4.00 (t, *J* = 8.7 Hz, 1H), 3.78 (dd, *J* = 8.7, 7.5 Hz, 1H), 2.95 (dd, *J* = 13.8, 4.2 Hz, 1H), 2.01 (dd, *J* = 13.8, 10.2 Hz, 1H), 1.30 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9 (d, J_{CP} = 3 Hz), 150.8, 138.9 (d, J_{CP} = 25 Hz), 137.9 (d, J_{CP} = 12 Hz), 137.8 (d, J_{CP} = 10 Hz), 137.2, 134.4 (d, J_{CP} = 21 Hz), 134.0 (d, J_{CP} = 21 Hz), 133.4 (d, J_{CP} = 3 Hz), 131.5 (d, J_{CP} = 17 Hz), 130.5, 130.0 (d, J_{CP} = 3 Hz), 128.8-128.4 (6 lines), 127.9, 123.3, 120.3, 71.6, 68.1, 41.6, 34.7, 31.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ –3.60; IR (Neat Film NaCl) 2963, 1649, 1598, 1477, 1434, 1361, 1248, 1090, 1027, 965, 742, 696 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{36}H_{41}NOP$ $[M + H]^+$: 534.2926, found 534.2905; $[\alpha]_D^{25}$ –49.3 (*c* 0.36, $CHCl_3$).



189

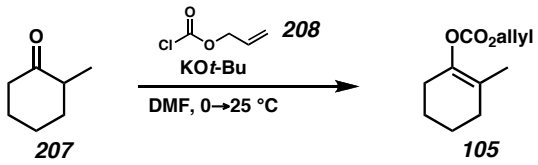
(*S*)-(Anthracen-9-ylmethyl)-PHOX (189, Table 2.10, entry 7): Prepared by general procedure 1 from 3-(9-anthracenyl)-alanol[69] in 42% yield as a yellow powder; mp 165-169 ºC; R_f = 0.38 (5:1 Hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.16 (m, 2H), 7.99 (m, 2H), 7.94 (m, 1H), 7.55-7.29 (comp. m, 16H), 6.88 (m, 1H), 4.63 (m, 1H), 3.92 (dd, *J* = 9.0, 6.3 Hz, 1H), 3.77 (dd, *J* = 14.7, 4.5 Hz, 1H), 3.68 (t, *J* = 9.0 Hz, 1H), 3.17 (dd, *J* = 14.7, 10.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3 (d, J_{CP} = 3 Hz), 138.9 (d, J_{CP} = 25 Hz), 138.1 (d, J_{CP} = 10 Hz), 137.8 (d, J_{CP} = 13 Hz), 134.6 (d, J_{CP} = 21 Hz), 133.8 (d, J_{CP} = 21 Hz), 133.5 (d, J_{CP} = 3 Hz), 131.5, 130.7, 130.2, 130.0,

129.2, 128.9-128.5 (6 lines), 128.0, 126.5, 125.8, 124.9, 124.5, 71.2, 67.8, 32.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ –3.57; IR (Neat Film NaCl) 3051, 2961, 1648, 1476, 1434, 1353, 1092, 1032, 956, 742, 696 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{36}H_{29}NOP$ [M^+]: 521.1909, found 521.1905; $[\alpha]_D^{26}$ –5.1 (*c* 0.20, $CHCl_3$).

2.8.3 SYNTHESIS OF ALLYL ENOL CARBONATES

2.8.3.1 GENERAL PROCEDURES FOR THE SYNTHESIS OF ALLYL ENOL CARBONATES

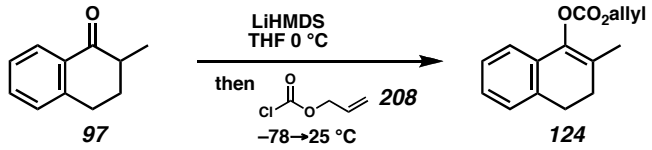
General Procedure 2:



Allyl 2-methylcyclohex-1-enyl carbonate (105, Table 2.7, entries 1–3):[70] To a solution of potassium *t*-butoxide (5.88 g, 52.5 mmol, 1.05 equiv) in DMF (100 mL) was added 2-methylcyclohexanone (**207**, 6.13 mL, 50 mmol, 1.0 equiv). After 12 h, the reaction mixture was cooled in an ice bath and allyl chloroformate (**208**, 6.4 mL, 60 mmol, 1.2 equiv) was added in a dropwise fashion. After an additional 30 min in the ice bath and 15 min at 25 °C, the reaction mixture was quenched into water (250 mL), extracted with 2:1 CH_2Cl_2:hexanes (4 x 125 mL), dried ($MgSO_4$), and evaporated. Chromatography (2.5→4% Et_2O in hexanes on SiO_2) afforded the allyl enol carbonate **105** (4.49 g, 46% yield) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (ddt, *J* = 17.4, 10.5, 5.6 Hz, 1H), 5.36 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.26 (dq, *J* = 10.2, 1.2 Hz, 1H),

4.63 (dt, *J* = 5.7, 1.4 Hz, 2H), 2.13 (m, 2H), 2.02 (m, 2H), 1.70 (m, 2H), 1.59 (m, 2H), 1.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 142.2, 131.5, 120.8, 118.8, 68.5, 30.0, 26.6, 23.1, 22.3, 15.7; IR (Neat Film NaCl) 3936, 1755, 1275, 1239, 1037 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{16}O_3$ [M]$^+$: 196.1100, found 196.1092.

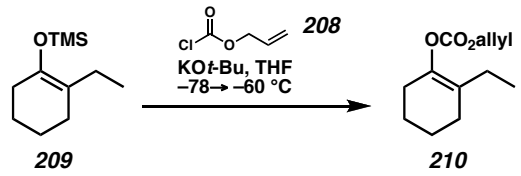
General Procedure 3:



Allyl 2-methyl-3,4-dihydronaphthalen-1-yl carbonate (124, Table 2.7, entry 12):[71] To a cooled (0 °C) solution of LiHMDS (17.16 mmol, 1.1 equiv) in THF (37 mL) was added 2-methyl-1-tetralone (**97**, 2.37 mL, 15.6 mmol, 1.0 equiv) in a dropwise manner over 15 min. After an additional 1.5 h at 0 °C, the enolate solution was added dropwise over 15 min to a –78 °C solution of allyl chloroformate (**208**, 2.0 mL, 18.7 mmol, 1.2 equiv) in THF (80 mL). The reaction mixture was allowed to warm to 25 °C in a Dewar vessel over 8 h. At which time, the reaction was quenched into CH_2Cl_2 (100 mL) and half-saturated aq NH_4Cl (100 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 50 mL). The organic fractions were washed with brine (100 mL), and dried (Na_2SO_4). Evaporation of the solvents under reduced pressure, and chromatography (2→5% Et_2O in Hexanes on SiO_2) afforded the allyl enol carbonate **124** (3.34 g, 88% yield) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.08 (m, 4H), 6.01 (ddt, *J* = 17.7, 10.4, 5.6 Hz 1H), 5.41 (dq, *J* = 17.3, 1.5 Hz, 1H), 5.32 (dd, *J* = 10.2, 1.0 Hz, 1H), 4.72 (dt, *J* = 6.3, 1.4 Hz, 2H), 2.87 (t, *J* = 8.0 Hz, 2H), 2.40 (t, *J* = 8.0 Hz, 2H), 1.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 140.6, 135.2, 131.3, 130.8, 127.3,

127.0, 126.4, 124.4, 119.9, 119.1, 68.9, 28.8, 27.4, 16.5; IR (Neat Film NaCl) 2935, 2833, 1760, 1239 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{15}H_{16}O_3$ $[M]^+$: 244.1100, found 244.1098.

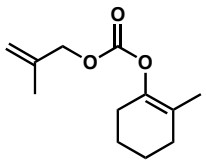
General Procedure 4:



Allyl 2-ethylcyclohex-1-enyl carbonate (210, Table 2.7, entry 7):[72] To a solution of (2-ethylcyclohex-1-enyloxy)trimethylsilane (**209**, vide infra) (1.50 g, 7.56 mmol, 1.0 equiv) in THF (14 mL) cooled to –78 °C was added a solution of potassium *t*-butoxide (0.933 g, 8.32 mmol, 1.1 equiv) in THF (8 mL) in a dropwise fashion over 2 min. The reaction mixture was maintained at –60 °C for 2.5 h, at which time allyl chloroformate (**208**, 847 μL, 7.93 mmol, 1.05 equiv) in THF (3 mL) was added. After 1 h at –50 °C, the reaction mixture was poured into a mixture of CH_2Cl_2 (20 mL) and half-saturated aqueous NH_4Cl (20 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The organic fractions were washed with water (50 mL), brine (50 mL), and dried (Na_2SO_4). Evaporation of the solvents under reduced pressure followed by chromatography on (2% Et_2O in Hexanes on SiO_2) and heating (room temperature to 105 °C) at 2 torr in a kugelrohr distillation apparatus afforded the allyl enol carbonate (**210**, 0.944 g, 59% yield) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddt, *J* = 17.4, 10.5, 5.6 Hz, 1H), 5.37 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.27 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.64 (dt, *J* = 5.7, 1.5 Hz, 2H), 2.16 (m, 2H), 2.05 (m, 2H), 1.99 (q, *J* = 7.8, 2H), 1.70 (m, 2H),

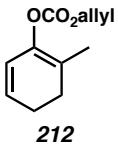
1.61 (m, 2H), 0.4 (t, J = 7.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 141.7, 131.5, 126.3, 118.8, 68.5, 27.2, 26.6, 23.0, 22.9, 22.3, 11.9; IR (Neat Film NaCl) 2936, 1754, 1239 cm^{-1}; HRMS (EI) m/z calc'd for $C_{12}H_{18}O_3$ [M]$^+$: 210.1256, found 210.1255.

2.8.3.2 CHARACTERIZATION DATA FOR ALLYL ENOL CARBONATES



211

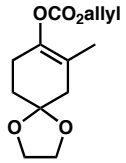
2-Methylallyl 2-methylcyclohex-1-enyl carbonate (211, Table 2.7, entry 4): Prepared by general procedure 4 from 2-methylcyclohexanone and methallyl chloroformate[62] in 16% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (s, 1H), 4.96 (s, 1H), 4.57 (s, 2H), 2.16 (m, 2H), 2.034 (br s, 2H), 1.79 (s, 3H), 1.77-1.58 (m, 4H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 142.2, 139.4, 120.9, 113.4, 71.1, 30.1, 26.6, 23.1, 22.3, 19.3, 15.8; IR (Neat Film NaCl) 2926, 1755, 1236 cm^{-1}; HRMS (EI) m/z calc'd for $C_{12}H_{18}O_3$ [M]$^+$: 210.1256, found 210.1259.



212

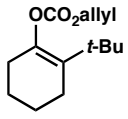
Allyl 2-methylcyclohexa-1,5-dienyl carbonate (212, Table 2.7, entry 5): Prepared by general procedure 3 from 6-methyl-cyclohex-2-en-1-one[73] in 45% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (ddt, J = 17.1, 10.5, 5.7 Hz, 1H), 5.75 (m, 2H), 5.39 (dq, J = 17.1, 1.5 Hz, 1H), 5.29 (d, J = 10.5, 1.2 Hz, 1H), 4.67 (app. dt, J = 5.7, 1.5

Hz, 2H), 2.42 (br s, 4H), 1.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 140.4, 131.3, 126.1, 122.7, 120.0, 119.1, 68.8, 28.2, 22.4, 15.7; IR (Neat Film NaCl) 2933, 1760, 1260 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{14}O_3$ $[M]^+$: 194.0943, found 194.0938.



213

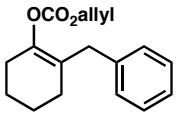
Allyl 7-methyl-1,4-dioxaspiro[4.5]dec-7-en-8-yl carbonate (213, Table 2.7, entry 6): Prepared by general procedure 4 from 2-methyl-1,4-cyclohexanedione monoethylene ketal[74] in 31% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddt, *J* = 17.1, 10.5, 5.7 Hz, 1H), 5.41 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.28 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.65 (app. dt, *J* = 5.7, 1.5 Hz, 2H), 3.97 (m, 4H), 2.37 (m, 2H), 2.30 (br s, 2H), 1.87 (app. t, *J* = 6.6 Hz, 2H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 141.3, 131.4, 119.0, 118.5, 107.3, 68.6, 64.5, 39.9, 31.3, 25.3, 15.8; IR (Neat Film NaCl) 2919, 1756, 1250 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{13}H_{19}O_5$ $[M + H]^+$: 255.1232, found 255.1227.



214

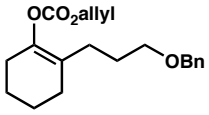
Allyl 2-*tert*-butylcyclohex-1-enyl carbonate (214, Table 2.7, entry 8): Prepared by general procedure 4 from 2-*tert*-butylcyclohexanone in 18% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddt, *J* = 17.3, 10.4, 5.7 Hz, 1H), 5.38 (d, *J* = 17.4 Hz, 1H), 5.27 (d, *J* = 10.5 Hz, 1H), 5.65 (app. dt, *J* = 5.7, 1.2 Hz, 2H), 2.19 (m, 2H), 2.10 (m, 2H), 1.63 (m, 4H), 1.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 142.1, 131.6, 130.7,

118.9, 68.4, 34.8, 29.4, 28.1, 26.4, 23.1, 22.7; IR (Neat Film NaCl) 2926, 1754, 1241 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{14}H_{22}O_3$ $[M]^+$: 238.1569, found 238.1566.



215

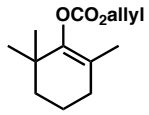
Allyl 2-benzylcyclohex-1-enyl carbonate (215, Table 2.7, entry 9): Prepared by general procedure 2 from 2-benzylcyclohexanone in 52% yield as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.16 (m, 5H), 5.95 (ddt, *J* = 17.3, 10.4, 5.7 Hz, 1H), 5.38 (dq, *J* = 17.3, 1.5 Hz, 1H), 5.28 (dq, *J* = 10.2,1.2 Hz, 1H), 4.66 (app. dt, *J* = 5.7, 1.2 Hz, 2H), 3.35 (s, 2H), 2.27 (app. t, *J* = 6.3 Hz, 2H), 1.95 (m, 2H), 1.73 (m, 2H), 1.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 143.1, 139.3, 131.4, 128.8, 128.3, 126.0, 123.9, 119.0, 68.6, 36.0, 27.5, 26.7, 23.0, 22.2; IR (Neat Film NaCl) 2937, 1754, 1702, 1648, 1600, 1239 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{20}O_3$ $[M]^+$: 272.1413, found 272.1416.



216

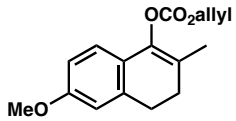
Allyl 2-(3-(benzyloxy)propyl)cyclohex-1-enyl carbonate (216, Table 2.7, entry 10): Prepared by general procedure 2 from 2-(3-(benzyloxy)propyl)cyclohexanone[75] in 48% yield as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.26 (comp. m, 5H), 5.92 (ddt, *J* = 17.1, 10.5, 5.7 Hz, 1H), 5.35 (app. dq, *J* = 17.1, 1.5 Hz, 1H), 5.25 (app. dq, *J* = 10.5, 1.1 Hz, 1H), 4.60 (app. dt, *J* = 5.7, 0.9 Hz, 2H), 4.49 (s, 2H), 3.44 (t, *J* = 6.6 Hz, 2H), 2.11 (comp. m, 6H), 1.64 (comp. m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 142.6, 138.7, 131.5, 128.3, 127.6, 127.4, 124.3, 118.8, 72.7, 70.0, 68.5, 27.7, 27.3, 26.6,

26.5, 23.0, 22.3; IR (Neat Film NaCl) 2924, 1754, 1240 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{20}H_{27}O_4$ $[M + H]^+$: 331.1909, found 331.1907.



217

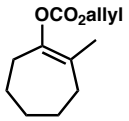
Allyl 2,6,6-trimethylcyclohex-1-enyl carbonate (217, Table 2.7, entry 11): Prepared by general procedure 3 from 2,2,6-trimethylcyclohexanone in 59% yield as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 5.96 (m, 1H), 5.38 (d, *J* = 17.4 Hz, 1H), 5.28 (d, *J* = 10.5 Hz, 1H), 4.65 (d, *J* = 6.9 Hz, 2H), 2.05 (t, *J* = 5.4 Hz, 2H), 1.56 (m, 4H), 1.49 (s, 3H), 1.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 147.9, 131.6, 120.7, 118.8, 68.5, 39.2, 34.9, 31.1, 26.7, 19.1, 16.5; IR (Neat Film NaCl) 2935, 1759, 1238 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{13}H_{20}O_3$ $[M]^+$: 224.1413, found 224.1418.



218

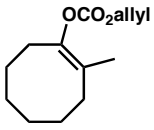
Allyl 6-methoxy-2-methyl-3,4-dihydronaphthalen-1-yl carbonate (218, Table 2.7, entry 13): Prepared by general procedure 3 from 2-methyl-6-methoxy-1-tetralone[76] in 88% yield as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.04 (m, 1H), 6.70 (m, 2H), 5.98 (ddt, *J* = 17.1, 10.4, 5.7 Hz 1H), 5.42 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.32 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.71 (dt, *J* = 5.7, 1.2 Hz, 2H), 3.78 (s, 3H), 2.84 (t, *J* = 7.8 Hz, 2H), 2.38 (t, *J* = 8.1 Hz, 2H), 1.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 153.1, 140.4, 137.2, 131.3, 123.9, 121.4, 121.1, 119.1, 113.7, 110.9, 68.9, 55.2, 28.8, 27.8, 16.3; IR (Neat

Film NaCl) 2933, 1758, 1237 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{16}H_{18}O_4$ $[M]^+$: 274.1205, found 274.1213.



219

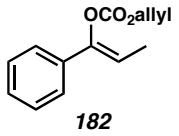
Allyl 2-methylcyclohept-1-enyl carbonate (219, Table 2.7, entry 14): Prepared by general procedure 4 from 2-methylcycloheptanone in 36% yield as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddt, *J* = 17.1, 10.5, 5.7 Hz 1H), 5.37 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.28 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.65 (app. dt, *J* = 6.0, 1.5 Hz, 2H), 2.33 (m, 2H), 2.10 (m, 2H), 1.70-1.54 (m, 6H), 1.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 146.2, 131.5, 125.5, 118.8, 68.5, 32.8, 32.5, 31.0, 25.7, 25.3, 18.3; IR (Neat Film NaCl) 2925, 1753, 1255, 1226 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1253.



220

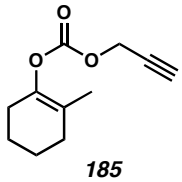
Allyl 2-methylcyclooct-1-enyl carbonate (220, Table 2.7, entry 15): Prepared by general procedure 4 from 2-methylcyclooctanone in 28% yield as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (m, 1H), 5.39 (d, *J* = 16.5 Hz, 1H), 5.29 (d, *J* = 10.5 Hz, 1H), 4.66 (d, *J* = 5.4 Hz, 2H), 2.34 (app. t, *J* = 5.7 Hz, 2H), 2.15 (app. t, *J* = 5.4 Hz, 2H), 1.59 (s, 3H), 1.64-1.48 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 143.7, 131.5, 123.0,

118.8, 68.5, 31.4, 29.7, 28.7, 28.4, 26.6, 25.6, 15.5; IR (Neat Film NaCl) 2927, 1754, 1227 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{13}H_{20}O_3$ $[M]^+$: 224.1413, found 224.1419.



182

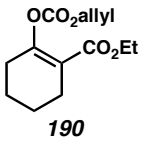
(*Z*)-Allyl 1-phenylprop-1-enyl carbonate (182, Table 2.9, entries 1–2): Prepared by general procedure 3 from propiophenone in 69% yield as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46-7.43 (m, 2H), 7.37-7.26 (m, 3H), 6.04-5.85 (m, 2H), 5.44-5.28 (m, 2H), 4.71 (dt, *J* = 5.7, 1.5 Hz, 2H), 1.80 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 150.7, 147.2, 134.6, 131.1, 128.4, 128.1, 119.0, 68.9, 11.2; IR (Neat Film NaCl) 3061, 2920, 1760, 1673, 1496, 1446, 1366, 1227, 1186, 966, 765, 693 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{13}H_{14}O_3$ $[M]^+$: 218.0943, found 218.0938.



185

2-Methylcyclohex-1-enyl prop-2-ynyl carbonate (185, Table 2.10): A 50 mL flask equipped with a septum was flame-dried under vacuum and cooled under dry nitrogen. To this was added methyllithium in Et_2O (1.6 M, 7.5 mL, 12.0 mmol, 1.10 equiv) followed by dry Et_2O (10 mL). To this solution was added a solution of trimethyl(2-methylcyclohex-1-enyloxy)silane (vide infra) (2.003 g, 10.9 mmol, 1.00 equiv) in Et_2O (5 mL) at 0 ºC and the resulting colorless solution was stirred for 1.5 h at ambient temperature to afford a solution of lithium enolate in Et_2O.

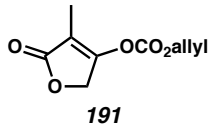
To a solution of propargyl chloroformate (1.18 mL, 12.0 mmol, 1.10 equiv) in Et_2O (10 mL) was added the above lithium enolate solution at 0 ºC. The resulting mixture was stirred and warmed to 10 ºC over 1 h. The resulting mixture was poured into saturated aq NH_4Cl and extracted with Et_2O twice. The combined organic layers were washed with water, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude oil. The crude residue was purified by SiO_2 chromatography (2 → 10% Et_2O in hexanes) to give propargyl enol carbonate **185** (733 mg, 35% yield) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 4.75 (d, J = 2.4 Hz, 2H), 2.53 (t, J = 2.4 Hz, 1H), 2.20-2.11 (m, 2H), 2.07-2.00 (m, 2H), 1.76-1.66 (m, 2H), 1.66-1.56 (m, 2H), 1.57 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 142.3, 121.1, 76.9, 75.7, 55.4, 30.0, 26.5, 23.1, 22.3, 15.8; IR (Neat Film NaCl) 3295, 2937, 2862, 2130, 1756, 1709, 1439, 1376, 1275, 1250, 1220, 1045 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{14}O_3$ $[M]^+$: 194.0943, found 194.0939.



190

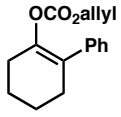
Ethyl 2-(allyloxycarbonyloxy)cyclohex-1-enecarboxylate (190, Table 2.11, entry 1): Prepared by general procedure 2 from ethyl 2-oxocyclohexanecarboxylate in 78% yield as a light yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 5.96 (ddt, J = 17.1, 10.5, 5.7 Hz, 1H), 5.39 (ddt, J = 17.1, 1.5, 1.5 Hz, 1H), 5.28 (ddt, J = 10.5, 1.5, 1.2 Hz, 1H), 4.67 (ddd, J = 5.7, 1.2, 1.2 Hz, 2H), 4.15 (q, J = 7.2 Hz, 2H), 2.44-2.34 (m, 2H), 2.32-2.24 (m, 2H), 1.80-1.58 (comp. m, 4H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 154.8, 152.2, 131.2, 119.2, 118.3, 69.0, 60.5, 28.6, 25.1, 21.9, 21.5, 14.0; IR (Neat Film NaCl) 3087, 1983, 2942, 2866, 1760, 1715, 1666, 1449, 1368, 1233, 1189, 1081, 1056,

1035, 994, 946, 767 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{13}H_{18}O_5$ $[M]^+$: 254.1154, found 254.1153.



191

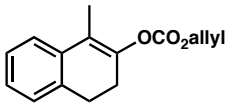
Allyl 4-methyl-5-oxo-2,5-dihydrofuran-3-yl carbonate (191, Table 2.11, entry 2): Prepared by a modification of general procedure 2 from 3-methyltetronic acid using Et_3N as the base and THF as solvent in 79% yield as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddt, *J* = 17.1, 10.2, 6.0 Hz, 1H), 4.93 (ddt, *J* = 17.1, 2.7, 1.2 Hz, 1H), 5.37 (ddt, *J* = 10.2, 2.1, 0.9 Hz, 1H), 5.07 (q, *J* = 1.8 Hz, 2H), 4.74 (ddd, *J* = 6.0, 1.2, 0.9 Hz, 2H), 1.81 (t, *J* = 1.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 163.4, 150.2, 130.0, 120.8, 109.4, 70.3, 67.5, 6.9; IR (Neat Film NaCl) 3089, 2958, 2931, 1774, 1702, 1446, 1392, 1360, 1330, 1240, 1132, 1079, 1025, 945, 889, 775, 754 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_9H_{11}O_5$ $[M + H]^+$: 199.0606, found 199.0600.



193

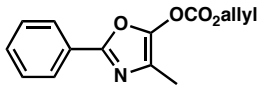
Allyl 2-phenylcyclohex-1-enyl carbonate (193, Table 2.11, entry 3): Prepared by general procedure 2 from 2-phenylcyclohexanone in 43% yield as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.18 (comp. m, 5H), 5.80 (ddt, *J* = 17.4, 10.5, 5.4 Hz, 1H), 5.20 (ddt, *J* = 17.4, 1.8, 1.2 Hz, 1H), 5.18 (ddt, *J* = 10.5, 1.5, 1.2 Hz, 1H), 5.02 (ddd, *J* = 5.7, 1.5, 1.5 Hz, 2H), 2.46-2.38 (m, 2H), 2.37-2.30 (m, 2H), 1.90-1.72 (comp. m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 143.4, 138.8, 131.3, 128.1, 127.6, 126.8, 125.9,

118.4, 68.4, 30.1, 27.1, 22.8, 22.5; IR (Neat Film NaCl) 3081, 3057, 3024, 2938, 2862, 1753, 1687, 1601, 1492, 1444, 1367, 1238, 1178, 1091, 1036, 941, 784, 760, 700 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{16}H_{18}O_3$ $[M]^+$: 258.1256, found 258.1256.



194

Allyl 1-methyl-3,4-dihydronaphthalen-2-yl carbonate (194, Table 2.11, entry 4): Prepared by general procedure 2 from 2-tetralone in 59% yield as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29-7.11 (comp. m, 4H), 6.00 (ddt, *J* = 17.1, 10.2, 6.0 Hz, 1H), 5.43 (ddt, *J* = 17.1, 1.8, 1.2 Hz, 1H), 5.33 (ddt, *J* = 10.2, 1.5, 1.2 Hz, 1H), 4.72 (ddd, *J* = 6.0, 1.5, 1.2 Hz, 2H), 2.97 (t, *J* = 7.8 Hz, 2H), 2.55 (tq, *J* = 8.1, 1.5 Hz, 2H), 2.00 (t, *J* = 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 145.9, 135.0, 134.1, 131.2, 127.1, 126.6, 126.5, 123.4, 119.7, 119.2, 68.9, 28.7, 26.0, 10.9; IR (Neat Film NaCl) 3021, 2993, 2944, 2891, 2836, 1757, 1674, 1488, 1451, 1365, 1304, 1279, 1246, 1217, 1181, 1157, 1031, 1018, 986, 943, 782, 760 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{15}H_{16}O_3$ $[M]^+$: 244.1100, found 244.1095.



196

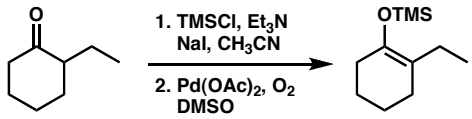
Allyl 4-methyl-2-phenyloxazol-5-yl carbonate (196, Table 2.11, entry 5): Prepared by a modification of Leplawy's procedure[77] in 96% yield as a colorless oil that solidifies on standing; mp 37.5-39 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97-7.90 (m, 2H), 7.45-7.38 (comp. m, 3H), 5.99 (ddt, *J* = 17.4, 10.5, 5.7 Hz, 1H), 5.45 (ddt, *J* = 17.4, 1.5,

1.2 Hz, 1H), 5.36 (ddt, *J* = 10.5, 1.2, 1.2 Hz, 1H), 4.78 (ddd, *J* = 6.0, 1.2, 1.2 Hz, 2H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 155.0, 151.6, 146.2, 130.5 (2C), 128.9, 127.3, 126.1, 120.6, 70.7, 10.5; IR (Neat Film NaCl) 3066, 2930, 1786, 1669, 1554, 1490, 1450, 1367, 1213, 1082, 1069, 1026, 992, 939, 774, 711, 692 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{14}H_{13}O_4N$ [M]$^+$: 259.0845, found 259.0855.

2.8.4 SYNTHESIS OF SILYL ENOL ETHERS

2.8.4.1 GENERAL PROCEDURE FOR THE SYNTHESIS OF SILYL ENOL ETHERS FROM CYCLOALKANONES

General Procedure 5:

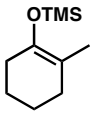


221 ***209***

(2-Ethylcyclohex-1-enyloxy)trimethylsilane (209, Table 2.8, entry 2):[78] To a solution of NaI (15.0 g, 100 mmol, 1.25 equiv) in CH_3CN (125 mL) were added 2-ethylcyclohexanone (**221**, 10.1 g, 80 mmol, 1.0 equiv), Et_3N (14.0 mL, 100 mmol, 1.25 equiv), and finally TMSCl (11.6 mL, 91.2 mmol, 1.14 equiv) in a dropwise fashion. After 1 h, pentane (75 mL) was added, the biphasic mixture was stirred for 2 min, and the pentane decanted. After additional pentane extractions (5 x 75 mL), the combined pentane fractions were washed with water (2 x 50 mL) and brine (1 x 50 mL), and then dried (Na_2SO_4). Evaporation under reduced pressure gave the crude silyl enol ether (12.0 g) as an 80:20 mixture (NMR) of isomers favoring the tetrasubstituted silyl enol ether. An oxygen balloon was affixed to a flask containing a solution of the crude silyl enol

ether (6.0 g) and $Pd(OAc)_2$ (338.9 mg, 1.51 mmol) in DMSO (250 mL). The reaction mixture darkened and became heterogeneous. After 48 h, ^{1}H NMR analysis of an aliquot indicated less than 2% of the undesired isomer, and the reaction mixture was poured into a separatory funnel containing pentane (300 mL), water (300 mL), and ice (200 g). The layers were separated and the aqueous layer extracted with pentane (3 x 200 mL). The pentane fractions were washed with water (2 x 100 mL) and brine (100 mL), and then dried (Na_2SO_4). Evaporation and chromatography (2% Et_2O in Hexanes on SiO_2) afforded the pure silyl enol ether (**209**, 3.21 g, 41% yield) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08-1.90 (comp. m, 6H), 1.62 (m, 2H), 1.54 (m, 2H), 0.92 (t, J = 7.8 Hz, 3H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 117.4, 30.4, 27.0, 23.7, 23.1, 22.9, 12.2, 0.7; IR (Neat Film NaCl) 2961, 2933, 1680, 1252, 922, 843 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{22}OSi$ $[M]^+$: 198.1440, found 198.1436.

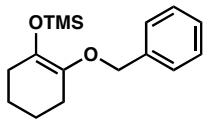
2.8.4.2 CHARACTERIZATION DATA FOR CYCLOALKANONE SILYL ENOL ETHERS



110

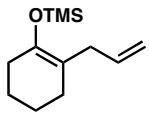
Trimethyl(2-methylcyclohex-1-enyloxy)silane (110, Table 2.8, entries 1 and 4): Prepared by general procedure 5 from 2-methylcyclohexanone. The initial 10:1 mixture favoring the tetrasubstituted isomer was purified by fractional distillation with a spinning band column[79] to give silyl enol ether **110** (84% yield) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (m, 2H), 1.94 (m, 2H), 1.64 (m, 2H), 1.58-1.49 (comp. m, 5H), 0.16

(s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 111.8, 30.3, 30.1, 23.8, 23.0, 16.3, 0.7; IR (Neat Film NaCl) 2930, 1688, 1252, 1185, 843 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{10}H_{20}OSi$ $[M]^+$: 184.1284, found 184.1275.



222

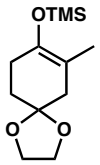
(2-(Benzyloxy)cyclohex-1-enyloxy)trimethylsilane (222, Table 2.8, entry 3): Prepared by general procedure 5 from 2-(benzyloxy)cyclohexanone[80] in 11% yield as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6) δ 7.40 (d, *J* = 7.2 Hz, 2H), 7.19 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 4.77 (s, 2H), 2.12-1.98 (comp. m, 4H), 1.39 (app. quintet, *J* = 3.3 Hz, 4H), 0.25 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 139.9, 136.9, 135.5, 128.8, 128.2, 128.0, 71.3, 30.8, 27.1, 23.9, 23.7, 1.2; IR (Neat Film NaCl) 3065, 3032, 2934, 2860, 2841, 1694, 1497, 1454, 1343, 1250, 1245, 1195, 1122, 1017, 930, 860, 844, 750, 698 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{16}H_{24}O_2Si$ $[M]^+$: 276.1546, found 276.1545.



223

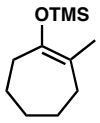
(2-Allylcyclohex-1-enyloxy)trimethylsilane (223, Table 2.8, entry 5): Prepared by general procedure 5 from 2-allylcyclohexanone in 59% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (ddt, *J* = 16.8, 9.9, 6.9 Hz, 1H), 4.99 (ddt, *J* = 16.5, 2.1, 1.8 Hz, 1H), 4.95 (ddt, *J* = 9.6, 2.1, 1.5 Hz, 1H), 2.77 (app. d, *J* = 6.6 Hz, 2H), 2.14-1.88 (comp. m, 4H), 1.75-1.42 (comp. m, 4H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 136.9, 114.6, 113.5, 34.8, 30.4, 27.5, 23.7, 23.0, 0.7; IR (Neat Film NaCl) 3077, 2931,

2838, 1682, 1638, 1448, 1433, 1355, 1252, 1204, 1168, 948, 905, 888, 844, 753 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{22}OSi$ $[M]^+$: 210.1440, found 210.1449.



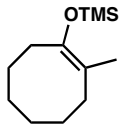
224

Trimethyl(7-methyl-1,4-dioxaspiro[4.5]dec-7-en-8-yloxy)silane (224, Table 2.8, entry 6): Prepared by general procedure 5 from 2-methyl-1,4-cyclohexanedione monoethylene ketal[74] in 51% yield as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 3.96 (br s, 4H), 2.21 (comp. m, 4H), 1.79 (app. t, *J* = 6.9 Hz, 2H), 1.54 (s, 3H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 108.9, 108.0, 64.4, 39.9, 31.7, 28.7, 16.2, 0.7; IR (Neat Film NaCl) 2956, 1691, 1252 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{22}O_3Si$ $[M]^+$: 242.1338, found 242.1334.



225

Trimethyl(2-methylcyclohept-1-enyloxy)silane (225, Table 2.8, entry 7): Prepared by general procedure 5 from 2-methylcycloheptanone in 39% yield as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 2.23 (app. t, *J* = 5.4 Hz, 2H), 2.01 (app. t, *J* = 5.1 Hz, 2H), 1.66 (m, 2H), 1.59 (s, 3H), 1.56-1.45 (comp. m, 4H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 116.9, 35.1, 32.7, 31.6, 26.5, 25.5, 18.7, 0.6; IR (Neat Film NaCl) 2921, 1678, 1251, 1171, 892, 842 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{22}OSi$ $[M]^+$: 198.1440, found 198.1439.



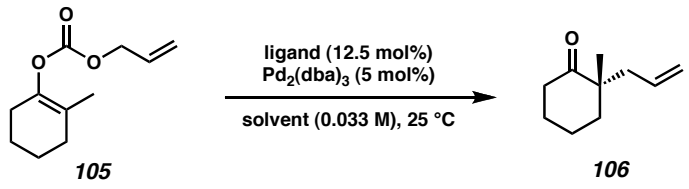
226

Trimethyl(2-methylcyclooct-1-enyloxy)silane (226, Table 2.8, entry 8): Prepared by general procedure 5 (pyridine substituted for Et_3N) from 2-methylcyclooctanone in 29% yield as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 2.21 (m, 2H), 2.05 (m, 2H), 1.61-1.44 (comp. m, 8H), 1.57 (s, 3H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 113.5, 31.7, 28.9, 28.8, 26.7, 26.3, 15.8, 0.8; IR (Neat Film NaCl) 2924, 1678, 1251 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{24}OSi$ $[M]^+$: 212.1597, found 212.1590.

2.8.5 ENANTIOSELECTIVE ALLYLIC ALKYLATION METHODS

2.8.5.1 GENERAL PROCEDURES FOR ASYMMETRIC TSUJI ALLYLATION

General Procedure 9: 0.1 mmol Optimization Reactions of Allyl Enol Carbonates

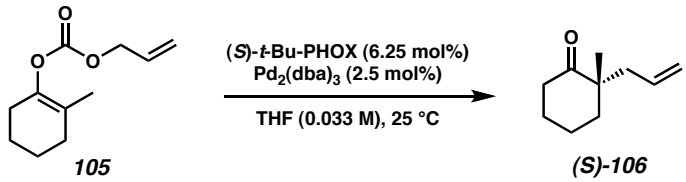


105 ***106***

A 1 dram vial equipped with a magnetic stir bar was flame dried under vacuum. After cooling under dry argon, $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol, 0.05 equiv) and ligand (0.0125 mmol, 0.125 equiv) were added. After the vial was flushed with argon, solvent (3.0 mL) was added, and the contents were stirred at 25 °C for 30 min, at which time tridecane (12.25 μL) and allyl enol carbonate **105** (19.6 mg, 0.1 mmol, 1.0 equiv) were

added by syringe. When the reaction was complete by TLC, the reaction mixture was diluted with hexanes (5 mL), filtered through a small plug of silica gel and analyzed by GC. GC yield determined on DB-WAX column (70 °C initial temp, 5 °C/min ramp to 180 °C), tridecane retention time = 7.000 min, ketone **106** retention time = 12.309 min.

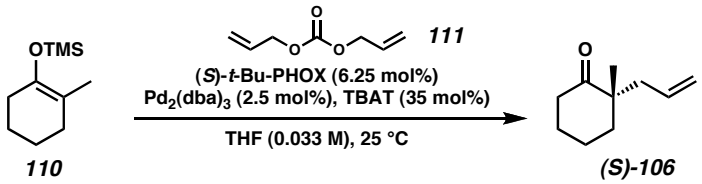
General Procedure 10: 1.0 mmol Preparative Reactions of Allyl Enol Carbonates



A 50 mL round-bottom flask equipped with a magnetic stir bar was flame dried under vacuum. After cooling under dry argon, $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol, 0.025 equiv) and (*S*)-*t*-Bu-PHOX (**55**, 24.2 mg, 0.0625 mmol, 0.0625 equiv) were added. After the flask was flushed with argon, THF (30 mL) was added, and the contents were stirred at 25 °C for 30 min, at which time allyl enol carbonate **105** (196.2 mg, 1.0 mmol, 1.0 equiv) was added by syringe in one portion. When the reaction was complete by TLC (2 h), the reaction mixture was evaporated under reduced pressure and the residue chromatographed (2→3% Et_2O in pentane on SiO_2) to afford (*S*)-2-allyl-2-methylcyclohexanone ((*S*)-**106**) (129.6 mg, 85.1% yield, 87% ee) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75–5.61 (m, 1H), 5.05 (s, 1H), 5.01 (m, 1H), 2.40–2.31 (comp. m, 3H), 2.21 (dd, *J* = 13.8, 7.5 Hz, 1H), 1.78 (comp. m, 5H), 1.56 (m, 1H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.4, 133.7, 117.9, 48.4, 41.9, 38.8, 38.5, 27.4, 22.6, 21.0; IR (Neat Film NaCl) 2934, 2865, 1707, 1451, 912 cm^{-1}; HRMS (EI) *m/z*

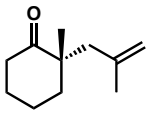
calc'd for $C_{10}H_{16}O$ $[M]^+$: 152.1201, found 152.1204; $[\alpha]_D^{21}$ –49.64 (*c* 2.38, hexane, 98% ee).

General Procedure 11: 1.0 mmol Preparative Reactions of Cycloalkanone Silyl Enol Ethers



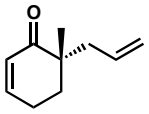
A 50 mL round-bottom flask equipped with a magnetic stir bar was flame dried under vacuum. After cooling under dry argon, $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol, 0.025 equiv), (*S*)-*t*-Bu-PHOX (**55**, 24.2 mg, 0.0625 mmol, 0.0625 equiv), and TBAT (189 mg, 0.35 mmol, 0.35 equiv) were added. After the flask was flushed with argon, THF (30 mL) was added, and the contents were stirred at 25 °C for 30 min, at which time diallyl carbonate (**111**, 150.6 μL, 1.05 mmol, 1.05 equiv) and trimethyl(2-methylcyclohex-1-enyloxy)silane (**110**, 184.35 mg, 1.0 mmol, 1.0 equiv) were added sequentially by syringe in one portion. When the reaction was complete by TLC (2 h), the reaction mixture was evaporated under reduced pressure and the residue chromatographed (2→3% Et_2O in pentane on SiO_2) to afford ketone (*S*)-**106** (144.3 mg, 94.8% yield, 87% ee).

2.8.5.2 CHARACTERIZATION DATA FOR KETONES PREPARED BY ENANTIOSELECTIVE ALKYLATION



148

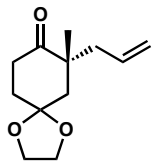
2-Methyl-2-(2-methylallyl)cyclohexanone (148, Table 2.7, entry 4; Table 2.8, entry 4): Reaction time: from allyl enol carbonate, 8 h, performed with 5 mol% $Pd_2(dba)_3$, 12.5 mol% (*S*)-**55**; from silyl enol ether, 4 h, performed with dimethallyl carbonate and 2.5 mol% $Pd_2(dba)_3$, 6.25 mol% (*S*)-**55**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.81 (s, 1H), 4.64 (s, 1H), 2.52 (m, 1H), 2.48 (d, *J* = 13.5 Hz, 1H), 2.36 (app. dt, *J* = 14.7, 6.0 Hz, 1H), 2.25 (d, *J* = 13.8 Hz, 1H), 1.94-1.53 (comp. m, 6H), 1.65 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.8, 142.2, 114.7, 48.7, 45.4, 40.0, 38.9, 27.6, 24.3, 23.3, 21.1; IR (neat) 2927, 1707 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{18}O$ $[M]^+$: 166.1358, found 166.1358; $[\alpha]_D^{27}$ –26.42 (*c* 1.85, hexane, 90% ee).



(S)-149

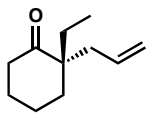
(*S*)-6-Allyl-6-methylcyclohex-2-enone (149, Table 2.7, entry 5): Reaction time: from allyl enol carbonate, 1 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (app. dt, *J* = 10.2, 4.2 Hz, 1H), 5.91 (app. dt, *J* = 10.2, 2.1 Hz, 1H), 5.72 (m, 1H), 5.07 (m, 1H), 5.02 (d, *J* = 9.3 Hz, 1H), 2.35 (m, 3H), 2.16 (dd, *J* = 13.8, 7.5, Hz, 1H), 1.91 (dt, *J* = 13.8, 6.0 Hz, 1H), 1.74 (dt, *J* = 13.8, 6.0 Hz, 1H), 1.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 148.8, 134.0, 128.4, 118.0, 44.4, 40.9, 32.9, 23.1, 21.6; IR (Neat Film NaCl) 2927, 1673 cm^{-1};

HRMS (EI) *m/z* calc'd for $C_{10}H_{14}O$ $[M]^+$: 150.1045, found 150.1039; $[\alpha]_D^{26}$ +14.62 (*c* 1.56, hexane, 89% ee).



150

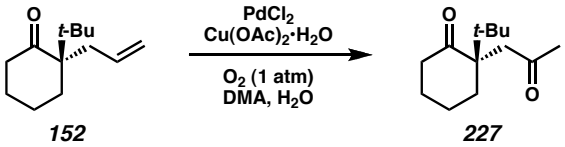
7-Allyl-7-methyl-1,4-dioxaspiro[4.5]decan-8-one (150, Table 2.7, entry 6; Table 2.8, entry 6; Scheme 2.9c): Reaction time: from allyl enol carbonate, 1 h; from silyl enol ether, 2 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67 (ddt, *J* = 17.1, 10.5, 7.2 Hz, 1H), 5.07 (br s, 1H), 5.02 (app. d, *J* = 9.3 Hz, 1H), 3.99 (app. d, *J* = 1.5 Hz, 4H), 2.57 (app. t, *J* = 6.3 Hz, 1H), 2.42 (m, 2H), 2.00 (d, *J* = 13.8 Hz, 1H), 1.98 (app. t, *J* = 7.2 Hz, 1H), 1.75 (d, *J* = 14.1 Hz, 1H), 1.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.9, 133.7, 118.4, 107.6, 64.4, 64.3, 47.5, 44.3, 42.7, 35.7, 34.5, 23.9; IR (Neat Film NaCl) 2964, 1710, 1116 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1255; $[\alpha]_D^{29}$ –7.99 (*c* 2.41, hexane, 86% ee).



151

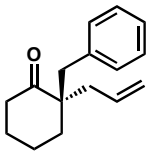
(*S*)-2-allyl-2-ethylcyclohexanone (151, Table 2.7, entry 7; Table 2.8, entry 2): Reaction time: from allyl enol carbonate, 2 h; from silyl enol ether, 3 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66 (m, 1H), 5.02 (m, 2H), 2.47-2.18 (m, 4H), 1.90-1.60 (m, 7H), 1.46 (ddd, *J* = 21.6, 15.0, 7.2 Hz, 1H), 0.75 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.0, 134.2, 117.6, 51.6, 39.2, 38.5, 36.0, 27.2, 27.1, 20.7, 7.8; IR (Neat Film NaCl)

2937, 1703 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{18}O$ $[M]^+$: 166.1358, found 166.1362; $[\alpha]_D^{28}$ +28.58 (*c* 1.51, hexane, 92% ee).



152 *227*

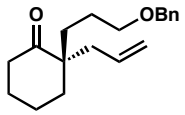
2-*tert*-Butyl-2-(2-oxopropyl)cyclohexanone (227, Table 2.7, entry 8): Allylation reaction time: from allyl enol carbonate, 10 h. Isolated yield determined by Wacker oxidation (vide infra) of ketone **152** and isolation of **227**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.29 (d, *J* = 18.0 Hz, 1H), 2.58 (app. dt, *J* = 16.2, 4.8 Hz, 1H), 2.34 (d, *J* = 17.7 Hz, 1H), 2.23 (dd, *J* = 11.1, 6.0 Hz, 1H), 2.18-2.00 (m, 2H), 2.07 (s, 3H), 1.92-1.60 (comp. m, 4H), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.5, 207.6, 53.0, 51.3, 43.2, 36.6, 31.6, 30.5, 27.7, 24.0, 23.9; IR (Neat Film NaCl) 2955, 1716, 1692, 1372, 1171 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{13}H_{22}O_2$ $[M]^+$: 210.1620, found 210.1615; $[\alpha]_D^{28}$ +132.01 (*c* 1.38, hexane, 81% ee).



153

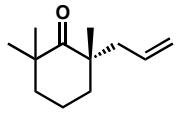
2-Allyl-2-benzylcyclohexanone (153, Table 2.7, entry 9): Reaction time: from allyl enol carbonate, 2 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (comp. m, 3H), 7.12 (comp. m, 2H), 5.74 (ddt, *J* = 17.2, 10.1, 7.2 Hz, 1H), 5.12-5.03 (m, 2H), 2.91 (s, 2H), 2.46 (m, 2H), 2.28 (d, *J* = 7.2 Hz, 2H), 1.86-1.65 (comp. m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.1, 137.5, 133.7, 130.6, 127.9, 126.3, 118.2, 52.5, 40.8, 39.6, 39.2, 35.5, 26.8, 20.8; IR (Neat

Film NaCl) 2937, 1704, 1638, 1602 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{16}H_{20}O$ $[M]^+$: 228.1514, found 228.1514; $[\alpha]_D^{28}$ –12.34 (*c* 2.07, hexane, 85% ee).



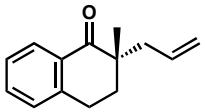
154

2-Allyl-2-(3-(benzyloxy)propyl)cyclohexanone (154, Table 2.7, entry 10): Reaction time: from allyl enol carbonate, 2 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.26 (comp. m, 5H), 5.68 (m, 1H), 5.06 (s, 1H), 5.01 (m, 1H), 4.84 (s, 2H), 3.44 (app. t, *J* = 6.3 Hz, 2H), 2.32 (comp. m, 4H), 1.88-1.24 (comp. m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.8, 138.5, 133.9, 128.3, 127.5, 127.5, 117.8, 72.8, 70.5, 51.2, 39.2, 39.0, 36.4, 31.2, 27.1, 23.8, 20.7; IR (Neat Film NaCl) 2926, 1703, 1102 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{19}H_{27}O_2$ $[M + H]^+$: 287.2011, found 287.2001; $[\alpha]_D^{27}$ +24.19 (*c* 2.73, hexane, 88% ee).



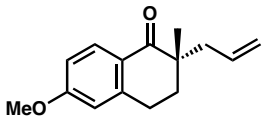
(S)-155

(*S*)-2-Allyl-2,6,6-trimethylcyclohexanone (155, Table 2.7, entry 11; Scheme 2.9a): Reaction time: from allyl enol carbonate, 1 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (m, 1H), 5.01 (m, 2H), 2.33 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.18 (dd, *J* = 13.8, 7.8 Hz, 1H), 1.82-1.53 (comp. m, 6H), 1.11 (s, 3H), 1.09 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.8, 134.6, 117.9, 47.6, 44.4, 43.9, 39.7, 36.8, 27.8, 27.2, 25.5, 17.7; IR (Neat Film NaCl) 2933, 1697, 1463 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{20}O$ $[M]^+$: 180.1514, found 180.1521; $[\alpha]_D^{27}$ –35.69 (*c* 2.15, hexane, 92% ee).



(S)-98

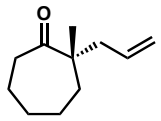
(*S*)-2-Allyl-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (98, Table 2.7, entry 12): Reaction time: from allyl enol carbonate, 2 h, 10 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.45 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.29 (app. t, *J* = 7.2 Hz, 1H), 7.21 (app. d, *J* = 7.5 Hz, 1H), 5.85–5.71 (m, 1H), 5.10 (s, 1H), 5.05 (s, 1H), 2.97 (t, *J* = 6.3 Hz, 2H), 2.46 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.27 (ddt, *J* = 14.0, 7.5, 1.2 Hz, 1H), 2.07 (ddd, *J* = 13.4, 7.2, 6.0 Hz 1H), 1.89 (ddd, *J* = 14.0, 6.9, 5.7 1H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 143.2, 133.9, 133.0, 131.5, 128.6, 127.9, 126.5, 118.1, 44.5, 41.0, 33.2, 25.3, 21.8; IR (Neat Film NaCl) 3073, 2930, 1682, 1455, 1220, 916, 742 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{14}H_{16}O$ $[M]^+$: 200.1201, found 200.1194; $[\alpha]_D^{27}$ –18.59 (*c* 2.08, hexane, 88% ee).



156

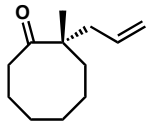
2-Allyl-6-methoxy-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (156, Table 2.7, entry 13): Reaction time: from allyl enol carbonate, 8 h, 10 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.7 Hz, 1H), 6.82 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.66 (d, *J* = 2.4 Hz, 1H), 5.78 (m, 1H), 5.09 (s, 1H), 5.04 (m, 1H), 3.84 (s, 3H), 3.93 (app. t, *J* = 6 Hz, 2H), 2.45 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.25 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.05 (m, 1H), 1.87 (m, 1H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 163.3, 145.7, 134.1, 130.4, 125.1,

118.0, 113.2, 112.2, 55.4, 44.3, 41.3, 33.4, 25.7, 22.0; IR (Neat Film NaCl) 2931, 1672, 1601, 1256 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{15}H_{18}O_2$ $[M]^+$: 230.1307, found 230.1313; $[\alpha]_D^{26}$ –13.71 (*c* 1.5, hexane, 89% ee).



157

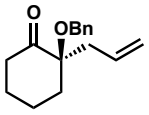
2-Allyl-2-methylcycloheptanone (157, Table 2.7, entry 14; Table 2.8, entry 7): Reaction time: from allyl enol carbonate, 6 h; from silyl enol ether, 2 h. ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (ddt, *J* = 16.8, 10.2, 7.5, 1H), 5.02 (m, 2H), 2.59 (app. dt, *J* = 11.1, 2.7 Hz, 1H), 2.42 (app. t, *J* = 9.0 Hz, 1H), 2.24 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.16 (dd, *J* = 13.8, 7.8 Hz, 1H), 1.78-1.30 (comp. m, 8H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.4, 133.8, 117.9, 50.8, 43.6, 40.6, 36.6, 30.6, 26.4, 24.4, 22.3; IR (Neat Film NaCl) 2930, 1702, 1458 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{18}O$ $[M]^+$: 166.1358, found 166.1360; $[\alpha]_D^{28}$ –34.70 (*c* 1.52, hexane, 87% ee).



158

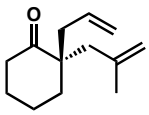
2-Allyl-2-methylcyclooctanone (158, Table 2.7, entry 15; Table 2.8, entry 8): Reaction time: from allyl enol carbonate, 2 h; from silyl enol ether, 3 h. ^1H NMR (300 MHz, $CDCl_3$) δ 5.67 (m, 1H), 5.04 (app. d, *J* = 1.2 Hz, 1H), 5.00 (app. d, *J* = 8.1 Hz, 1H), 2.59 (m, 1H), 2.29 (m, 2H), 2.12 (dd, *J* = 14.1, 7.7 Hz, 1H), 2.01 (m, 1H), 1.83-1.70 (comp. m, 3H), 1.61-1.32 (comp. m, 5H), 1.18 (m, 1H), 1.01 (s, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 220.3, 133.9, 117.8, 50.1, 42.0, 36.8, 33.5, 30.4, 25.9, 24.8, 24.3, 19.8; IR (Neat Film NaCl) 2929, 1699 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{20}O$ $[M]^+$: 180.1514, found 180.1508; $[\alpha]_D^{26}$ –21.22 (*c* 1.56, hexane, 79% ee).



163

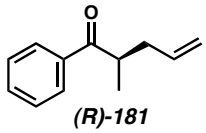
2-Allyl-2-(benzyloxy)cyclohexanone (163, Table 2.8, entry 3): Reaction time: from silyl enol ether, 3 h. ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.25 (comp. m, 5H), 5.83 (dddd, *J* = 16.5, 10.8, 6.9, 6.9 Hz, 1H), 5.15 (app. ddd, *J* = 16.5, 3.0, 1.5 Hz, 1H), 5.13 (app. d, *J* = 10.8 Hz, 1H), 4.54 (d, *J* = 11.1 Hz, 1H), 4.16 (d, *J* = 11.1 Hz, 1H), 2.85-2.68 (m, 2H), 2.42-2.24 (comp. m, 3H), 2.13-1.95 (comp. m, 2H), 1.76-1.44 (comp. m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.5, 138.2, 132.8, 128.4, 127.5, 127.3, 118.3, 82.1, 65.3, 39.5, 37.8, 36.0, 27.9, 20.6; IR (Neat Film NaCl) 3068, 3032, 2942, 2864, 1715, 1640, 1498, 1454, 1433, 1384, 1311, 1254, 1157, 1121, 1085, 1060, 1028, 997, 970, 915, 735, 696 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{16}H_{20}O_2$ $[M]^+$: 244.1463, found 244.1455; $[\alpha]_D^{28.3}$ +47.3 (*c* 2.38, hexanes, 59% ee).



164

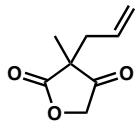
2-Allyl-2-(2-methylallyl)cyclohexanone (164, Table 2.8, entry 5; Scheme 2.8b & c): Reaction time: from silyl enol ether, 5 h, performed with dimethallyl carbonate. ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (dddd, *J* = 16.5, 10.8, 7.5, 7.2 Hz, 1H), 5.00 (dddd, *J* = 16.5, 2.1, 1.2, 1.2 Hz, 1H), 5.01 (dddd, *J* = 10.2, 2.1, 1.5, 1.5 Hz, 1H), 4.82 (app. ddd, *J* =

2.7, 1.2, 1.2 Hz, 1H), 4.66 (app. ddd, J = 3.0, 0.9, 0.9 Hz, 1H), 2.56-2.28 (comp. m, 6H), 1.91-1.66 (comp. m, 6H), 1.64 (app. ddd, J = 0.9, 0.9, 0.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.5, 142.1, 134.1, 118.0, 115.0, 51.5, 43.0, 39.9, 39.5, 36.5, 27.1, 24.3, 20.9; IR (Neat Film NaCl) 3075, 2938, 2865, 1704, 1640, 1453, 1376, 1312, 1206, 1124, 1062, 997, 913, 894 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{13}H_{20}O$ [M]$^+$: 192.1514, found 192.1514; $[\alpha]_D^{29.3}$ +3.9 (*c* 3.52, hexanes, 91% ee).



(R)-181

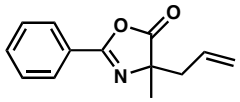
(*R*)-2-Methyl-1-phenylpent-4-en-1-one (181, Table 2.9):[81] Purified by preparative TLC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 7.2 Hz, 2H), 7.55 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 5.77 (m, 1H), 5.00 (m, 2H), 3.52 (app. sextet, J = 6.9 Hz, 1H), 2.54 (m, 1H), 2.19 (m, 1H), 1.21 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.6, 136.4, 135.9, 133.0, 128.5, 116.7, 40.5, 37.7, 17.1; IR (Neat Film NaCl) 3078, 2976, 2933, 1682, 1642, 1448, 1209, 976, 917, 704 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{14}O$ [M]$^+$: 174.1045, found 174.1048; $[\alpha]_D^{27.0}$ –38.1 (*c* 1.73, hexanes, 70% ee).



192

3-Allyl-3-methylfuran-2,4(3*H*,5*H*)-dione (192, Table 2.11, entry 2): Purified by flash chromatography (SiO_2, 2→12% EtOAc in hexanes). 87% yield, 2% ee. R_f = 0.20 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62 (dddd, J = 17.7, 9.6, 7.5,

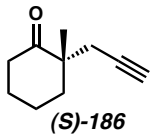
7.2 Hz, 1H), 5.13 (app. ddd, J = 9.6, 1.8, 0.9 Hz, 1H), 5.12 (app. ddd, J = 17.1, 1.5, 0.9 Hz, 1H), 4.59 (d, J = 17.1 Hz, 1H), 4.44 (d, J = 17.4 Hz, 1H), 2.53-2.37 (m, 2H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.9, 176.6, 130.1, 121.1, 72.5, 45.6, 40.2, 19.0; IR (Neat Film NaCl) 3543, 3083, 2983, 2939, 2877, 1803, 1758, 1642, 1454, 1436, 1378, 1341, 1231, 1122, 1065, 1043, 998, 912, 664 cm^{-1}; HRMS (EI) m/z calc'd for $C_8H_{10}O_3$ $[M]^+$: 154.0630, found 154.0626.



197

4-Allyl-4-methyl-2-phenyloxazol-5(4*H*)-one (197, Table 2.11, entry 5): Purified by flash chromatography (SiO_2, 4→7% Et_2O in hexanes). 89% yield, 2% ee. R_f = 0.39 (25% Et_2O in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (ddd, J = 7.2, 1.5, 1.2 Hz, 2H), 7.57 (tt, J = 7.8, 1.2 Hz, 1H), 7.48 (ddd, J = 7.8, 6.9, 1.5 Hz, 2H), 5.67 (dddd, J = 17.1, 9.9, 7.5, 6.9 Hz, 1H), 5.18 (dddd, J = 17.1, 1.5, 1.5, 1.5 Hz, 1H), 5.11 (dddd, J = 10.2, 1.5, 0.9, 0.9 Hz, 1H), 2.64 (dddd, J = 13.8, 6.9, 0.9, 0.9 Hz, 1H), 2.57 (dddd, J = 13.8, 7.5, 1.2, 1.2 Hz, 1H), 1.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2, 159.8, 132.7, 130.8, 128.7, 127.9, 125.9, 120.4, 69.7, 42.3, 23.2; IR (Neat Film NaCl) 3078, 2982, 2934, 1819, 1655, 1581, 1493, 1451, 1321, 1293, 1177, 1094, 1071, 1005, 930, 889, 780, 700 cm^{-1}; HRMS (EI) m/z calc'd for $C_{13}H_{13}O_2N$ $[M]^+$: 215.0946, found 215.0938.

2.8.5.3 PROCEDURE FOR ASYMMETRIC PROPARGYLATION



(S)-186

(*S*)-2-Methyl-2-(prop-2-ynyl)cyclohexanone (186, Table 2.10): A 50 mL two-neck rb flask containing a stirbar was equipped with a three-way stopcock, flame dried under vacuum, and cooled under dry nitrogen. To this was added $Pd_2(dba)_3$ (11.4 mg, 0.0125 mmol, 0.05 equiv) and (*S*)-*t*-Bu-PHOX (**55**, 12.5 mg, 0.0313 equiv). The flask was evacuated and backfilled with dry nitrogen twice. THF (15 mL) was then added and the mixture was stirred for 30 min at 25 ºC. To the resulting yellow solution was added propargyl enol carbonate **185** (97.1 mg, 0.50 mmol) and then this mixture was stirred at 70 ºC. After the reaction was complete (~1 h), the resulting mixture was concentrated *in vacuo*. Flash chromatography gave propargyl ketone **186** (64.3 mg, 86% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.55-2.29 (comp. m, 4H), 1.99 (t, J = 2.7 Hz, 1H), 1.98-1.65 (comp. m, 6H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.9, 81.1, 70.7, 47.8, 38.5, 37.8, 27.6, 27.3, 22.3, 21.1; IR (Neat Film NaCl) 3292, 2936, 2865, 2117, 1709, 1451, 1425, 1377, 1314, 1128, 1075 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{10}H_{14}O$ $[M]^+$: 150.1045, found 150.1044; $[\alpha]_D^{25}$ +0.74 (*c* 1.50, $CHCl_3$, 31% ee).

2.8.5.4 METHODS FOR DETERMINATION OF ENANTIOMERIC EXCESS

Table 2.12. Methods used for the determination of enantiomeric excess

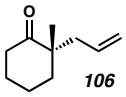
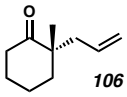
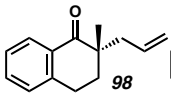
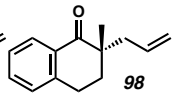
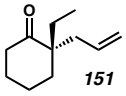
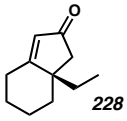
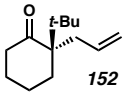
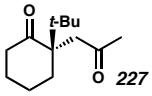
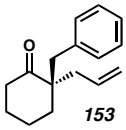
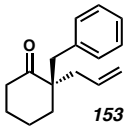
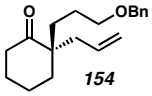
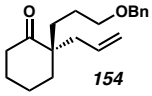
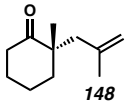
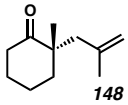
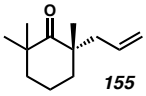
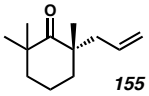
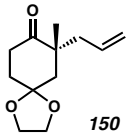
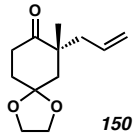
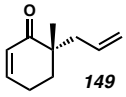
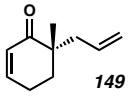
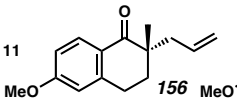
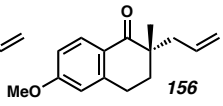
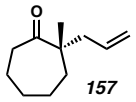
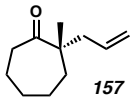
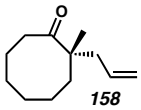
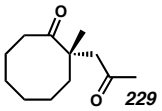
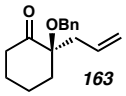
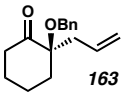
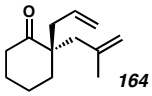
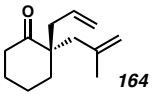
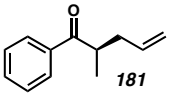
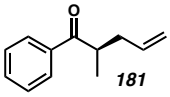
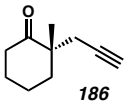
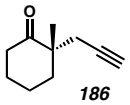
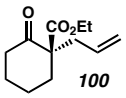
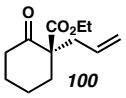
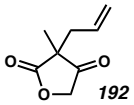
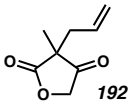
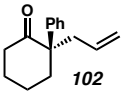
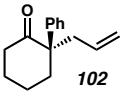
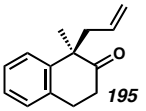
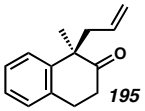
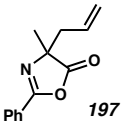
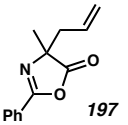
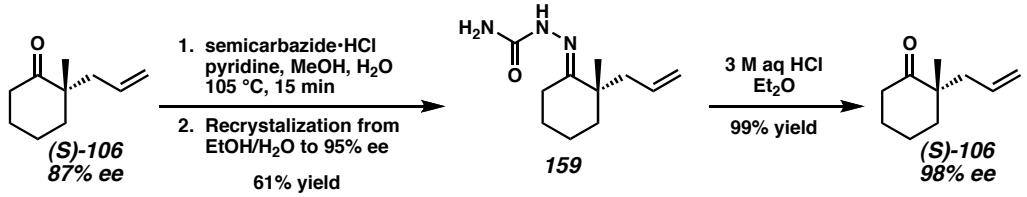
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1	 ***106***	 ***106***	GC, G-TA 100 °C isotherm	11.13	12.74	88
2	 ***98***	 ***98***	HPLC Chiracel OD-H 0.1% IPA in heptane isocratic, 0.7 mL/min	19.97	21.48	92
3	 ***151***	 ***228***	GC, G-TA 100 °C isotherm	14.52	13.35	92
4	 ***152***	 ***227***	GC, G-TA 110 °C isotherm	63.65	62.01	82
5	 ***153***	 ***153***	HPLC Chiracel OJ 2% EtOH in hexane isocratic, 1.0 mL/min	19.81	13.82	85
6	 ***154***	 ***154***	HPLC Chiralpak AD 0.75% IPA in hexane isocratic, 1.0 mL/min	11.95	13.80	88
7	 ***148***	 ***148***	GC, G-TA 100 °C isotherm	15.76	17.65	92
8	 ***155***	 ***155***	GC, G-TA 80 °C isotherm	25.48	27.90	92
9	 ***150***	 ***150***	GC, G-TA 120 °C isotherm	26.90	28.64	86
10	 ***149***	 ***149***	GC, G-TA 100 °C isotherm	15.31	18.04	90

Table 2.12. (continued)

entry	product	compound assayed	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
11	 **156**	 **156**	HPLC Chiracel OJ 1% EtOH in hexane isocratic 1.0 mL/min	11.38	10.16	91
12	 **157**	 **157**	GC, G-TA 110 °C isotherm	9.88	10.68	87
13	 **158**	 **229**	GC, G-TA 110 °C isotherm	63.25	61.94	79
14	 **163**	 **163**	HPLC Chiracel OB-H 0.2% EtOH in hexane isocratic, 1.0 mL/min	13.56	16.96	59
15	 **164**	 **164**	GC, G-TA 95 °C isotherm	49.77	47.98	91
16	 **181**	 **181**	HPLC Chiracel OD-H 0.1% IPA in heptane isocratic, 0.7 mL/min	21.63	25.04	70
17	 **186**	 **186**	GC, B-DM 90 °C isotherm	21.8	23.0	31
18	 **100**	 **100**	GC, G-TA 120 °C isotherm	15.55	16.66	24
19	 **192**	 **192**	GC, G-TA 100 °C isotherm	19.67	21.64	2
20	 **102**	 **102**	HPLC Chiracel OJ 0.1% IPA in hexane isocratic, 1.0 mL/min	7.76	8.59	11
21	 **195**	 **195**	HPLC Chiracel OJ 3% IPA in hexane isocratic, 1.0 mL/min	9.03	7.38	0
22	 **197**	 **197**	HPLC Chiracel OD-H 2% IPA in hexane isocratic, 1.0 mL/min	6.61	5.40	2

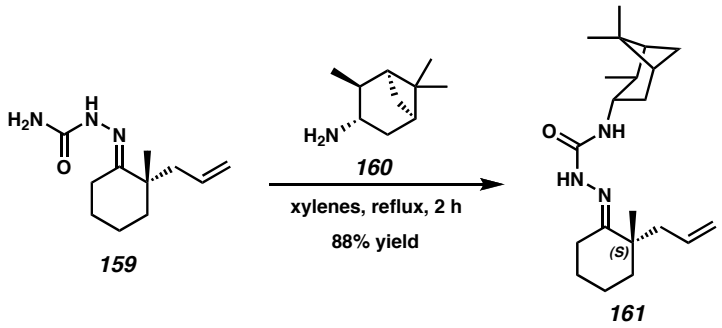
2.8.6 PREPARATION AND CHARACTERIZATION OF DERIVATIVES

2.8.6.1 PREPARATION AND CHARACTERIZATION OF SEMICARBAZONE DERIVATIVES



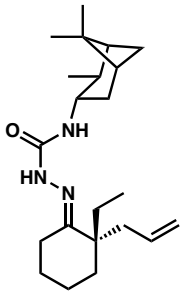
Semicarbazone 159 (Scheme 2.5):[82] To a solution of ketone (*S*)-**106** (661.4 mg, 4.34 mmol, 1.0 equiv) of 88% ee in pyridine (1.22 mL), water (3.0 mL), and MeOH (8.0 mL) was added semicarbazide•HCl (848.1 mg, 7.60 mmol, 1.75 equiv). The reaction mixture was heated at 105 °C for 15 min, cooled, diluted with water (10 mL), filtered, and dried to give semicarbazone **159** (763 mg, 84% yield). The semicarbazone **159** (3.10 g, 14.8 mmol, 87% ee) was suspended in EtOH/water (35/65 v/v 355 mL) and warmed to 90 °C. When all the material had dissolved, heating was discontinued, and the flask allowed to cool in the heating bath. After 8 h, crystals were filtered and dried giving the enantioenriched semicarbazone (1.894 g, 61% yield, 95% ee). Recrystalization of this material in EtOH/water (30/70 v/v 175 mL) by the same procedure gave semicarbazone **159** (1.692 g, 89% yield, 98% ee) as white crystals; mp 188–189 °C (EtOH/water); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (br s, 1H), 5.73 (m, 1H), 5.05 (s, 1H), 5.00 (app. d, J = 3.3 Hz, 1H), 2.40-2.11 (comp. m, 4H), 1.71-1.44 (comp. m, 6H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 156.8, 134.6, 117.2, 42.9, 41.5, 38.6, 25.9, 24.5, 22.5, 21.0; IR (Neat Film NaCl) 3465, 3195, 1693, 1567, 1478 cm^{-1}; HRMS (CI, CH_4) m/z calc'd for $C_{11}H_{20}N_3O$ $[M + H]^+$: 210.1606, found 210.1599; $[\alpha]_D^{28}$ –50.35 (*c* 2.60, MeOH).

To a biphasic mixture of Et_2O (30 mL) and 3 M aq HCl (3.0 mL) was added the enriched semicarbazone **159** (1.00 g, 4.77 mmol, 1.0 equiv). The reaction mixture was stirred vigorously for 2 h and then quenched with saturated aq $NaHCO_3$ (40 mL). The layers were separated, and aqueous layer extracted with Et_2O (4 x 30 mL). The combined organics were washed with brine (30 mL), dried ($MgSO_4$), and concentrated to give ketone **106** (718.2 mg, 98.9% yield).



(isopinocampheylamine)-Semicarbazone 161 (Scheme 2.5): To a solution of the semicarbazone **159** (100 mg, 0.43 mmol, 1.0 equiv) in xylenes (1.0 mL) was added (1*S*,2*S*,3*S*,5*R*)-(+)-isopinocampheylamine (**160**, 76.2 μL, 0.45 mmol, 1.05 equiv). The reaction mixture was refluxed for 2 h, cooled, and concentrated. Chromatography (10→50% EtOAc in Hexanes on SiO_2) afforded the (isopinocampheylamine)-semicarbazone **161** (130.5 mg, 87.8% yield). mp 131-133 °C from acetone; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (br s, 1H), 6.08 (bd, *J* = 8.7 Hz, 1H), 5.77 (m, 1H), 5.06 (s, 1H), 5.01 (s, 1H), 4.18 (m, 1H), 2.63 (app. tdd, *J* = 9.9, 3.6, 2.4 Hz, 1H), 2.45-2.13 (comp. m, 4H), 1.96 (m, 1H), 1.82 (m, 2H), 1.74-1.41 (comp. m, 8H), 1.23 (s, 3H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.11 (s, 3H), 1.10 (s, 3H), 0.89 (d, *J* = 9.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 155.5, 134.9, 117.0, 48.0, 47.8, 46.8, 43.0, 41.6, 41.5, 38.5, 38.3,

37.8, 35.3, 28.0, 25.9, 24.5, 23.4, 22.4, 21.0, 20.8; IR (Neat Film NaCl) 3400, 3189, 3074, 2929, 1672, 1526 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{21}H_{36}N_3O$ $[M + H]^+$: 346.2858, found 346.2874; $[\alpha]_D^{27}$ –18.9 (*c* 0.53, hexane). The semicarbazone was recrystallized from $EtOH/H_2O$ to provide suitable crystals for X-ray analysis (vide infra).



162

(isopinocampheylamine)-Semicarbazone 162 (Scheme 2.5). Prepared in an analogous manner to **161**. mp 145-146 °C from acetone; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 21.3 Hz, 1H), 6.07 (d, *J* = 4.4 Hz, 1H), 5.86-5.72 (m, 1H), 5.08-5.04 (m, 1H), 5.00 (s, 1H), 4.23-4.12 (m, 1H), 2.68-2.55 (m, 1H), 2.46-2.34 (m, 2H), 2.30 (d, *J* = 7.5 Hz, 2H), 2.12-2.00 (m, 1H), 1.98-1.90 (m, 1H), 1.88-1.40 (comp. m, 11H), 1.22 (s, 3H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.05 (s, 3H), 0.88 (d, *J* = 9.6 Hz, 1H), 0.77 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 154.4, 135.3, 116.7, 48.0, 47.9, 46.8, 44.2, 41.7, 39.9, 38.3, 37.9, 35.6, 35.3, 28.1, 28.0, 25.6, 23.4, 22.6, 20.8, 20.7, 7.8; IR (Neat Film NaCl) 3402, 3194, 3074, 2930, 1672, 1526 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{22}H_{37}N_3O$ $[M]^+$: 359.2937, found 359.2940; $[\alpha]_D^{29}$ –4.43 (*c* 0.38, hexane). The semicarbazone was recrystallized from acetone to provide suitable crystals for X-ray analysis (vide infra).

2.8.6.2 X-RAY STRUCTURES OF SEMICARBAZONES 161 AND 162

*Figure 2.1. Representations of semicarbazones **161** and **162***

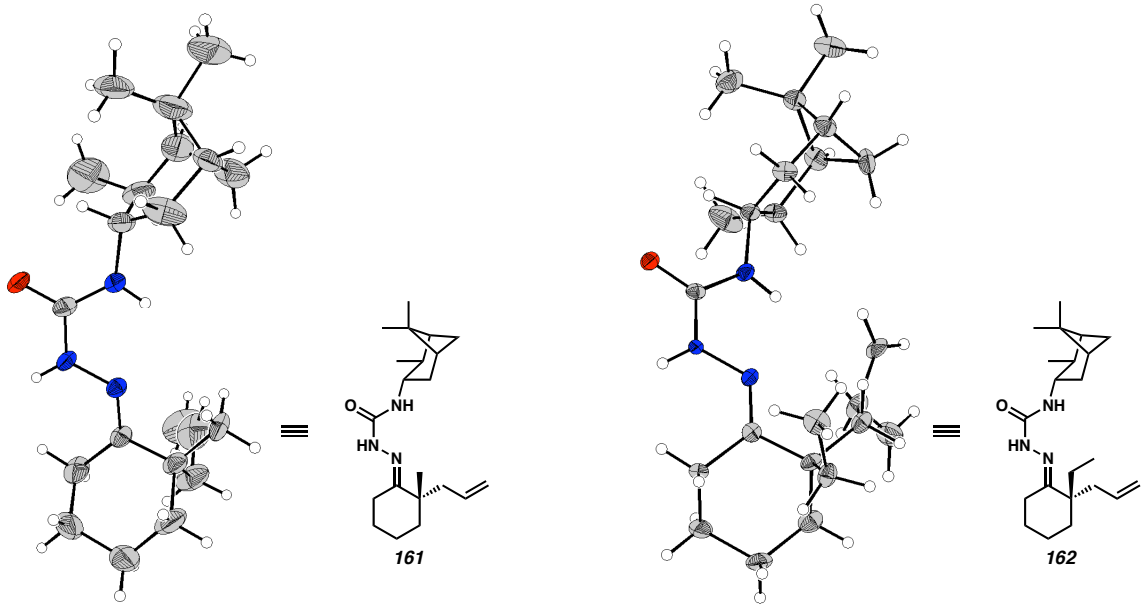


*Table 2.13. Crystal data and structure refinement for semicarbazone **161** (CCDC 246585)*

Empirical formula	$C_{21}H_{35}N_3O$
Formula weight	345.52
Crystallization solvent	Ethanol/water
Crystal habit	Fragment
Crystal size	0.41 x 0.37 x 0.24 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker SMART 1000
Wavelength	0.71073 Å MoKα
Data Collection Temperature	100(2) K
θ range for 7110 reflections used in lattice determination	2.31 to 24.12°

Table 2.13. (continued)

Unit cell dimensions	a = 23.1170(16) Å b = 13.6467(9) Å β = 90.396(2)° c = 13.2060(9) Å
Volume	4166.0(5) $Å^3$
Z	8
Crystal system	Monoclinic
Space group	C2
Density (calculated)	1.102 Mg/m^3
F(000)	1520
θ range for data collection	1.73° to 33.55°
Completeness to θ = 33.55°	81.9%
Index ranges	$-29 \le h \le 34$, $-20 \le k \le 20$, $-18 \le l \le 17$
Data collection scan type	ω scans at 4 ϕ settings
Reflections collected	30377
Independent reflections	12571 [R_{int}= 0.0616]
Absorption coefficient	0.068 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9838 and 0.9726

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2

Table 2.13. (continued)

Data / restraints / parameters	12571 / 64 / 486
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	1.972
Final R indices [$I > 2\sigma(I)$, 5761 reflections]	R1 = 0.0873, *w*R2 = 0.1490
R indices (all data)	R1 = 0.1657, *w*R2 = 0.1573
Type of weighting scheme used	Sigma
Weighting scheme used	$w = 1 / \sigma^2(Fo^2)$
Max shift/error	0.002
Average shift/error	0.000
Absolute structure parameter	0.4(16)
Largest diff. peak and hole	0.630 and –0.361 e.Å^{-3}

Special Refinement Details

The data are weak and the structure is disordered in the allyl of molecule B. These two factors combine to produce a final structure that falls short of the desired quality. Nevertheless, the quality is sufficient to determine the relative stereochemistry around C1 and, given the known stereochemistry of another chiral center, the absolute conformation can be deduced. Care should be taken when including these results in a publication. The allylic fragments were restrained to have similar geometry and the anisotropic displacement factors of the B molecule allyl fragment (only) were restrained to tend towards isotropic behavior.

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances,

angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

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*Table 2.14. Crystal data and structure refinement for semicarbazone **162** (CCDC 248956)*

Empirical formula	$C_{22}H_{37}N_3O$
Formula weight	359.55
Crystallization solvent	Acetone
Crystal habit	Fragment
Crystal size	0.39 x 0.37 x 0.24 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker SMART 1000
Wavelength	0.71073 Å MoKα
Data collection temperature	100(2) K
θ range for 13615 reflections used	
in lattice determination	2.25° to 21.58°
Unit cell dimensions	a = 13.4105(11) Å
	b = 13.4433(11) Å
	c = 24.353(2) Å
Volume	4390.4(6) $Å^3$
Z	8
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Density (calculated)	1.088 Mg/m^3
F(000)	1584
θ range for data collection	1.67° to 28.34°

Table 2.14. (continued)

Completeness to θ = 28.34°	94.5%
Index ranges	–17 ≤ h ≤ 17, –17 ≤ k ≤ 17, –32 ≤ l ≤ 30
Data collection scan type	ω scans at 5 ϕ settings
Reflections collected	63444
Independent reflections	10086 [R_{int}= 0.0909]
Absorption coefficient	0.067 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9841 and 0.9744

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	10086 / 447 / 570
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	2.208
Final R indices [I>2σ(I), 6214 reflections]	R1 = 0.0842, *w*R2 = 0.1195
R indices (all data)	R1 = 0.1330, *w*R2 = 0.1224
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.000
Average shift/error	0.000
Absolute structure parameter	0.6(17)
Largest diff. peak and hole	0.271 and -0.287 e.$Å^{-3}$

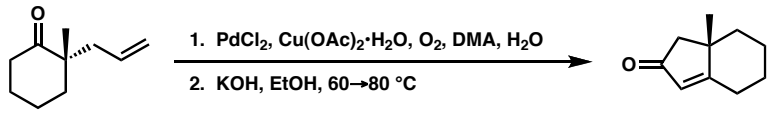
Special Refinement Details

The diffraction intensities fall off sharply past $2\theta = 40^{o}$, presumably because the structure is disordered. The asymmetric unit contains two molecules (hydrogen bonded to each other and of the same configuration) disordered in different ways. Molecule A is disordered about the terminal carbon (C11) of the allyl ligand (see figures 1 and 2). Both orientations were modeled, including riding hydrogen atoms, with the only restraint being a total occupancy of 1.0 for C11A and C11C. Molecule B is disordered in the camphene moiety, C13B-C22B. The disorder manifests as a rotation of the camphene around the N3B-C13B bond (see figures 3 and 4). Both orientations were restrained to have geometry similar to the corresponding part of the A molecule, using the SAME command. Additional restraints were imposed in this portion of molecule B as follows: 1) SIMU – to restrained bonded atoms to have similar displacement parameters, and 2) ISOR – to restrain the anisotropic displacement parameters, U_{ij}, to approximate isotropic behavior without placing restraint on the refined value of the isotropic U.

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

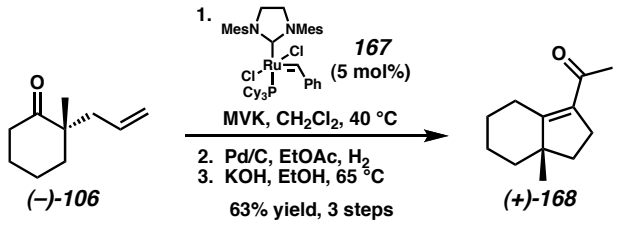
All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles, and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

2.8.6.3 PREPARATION AND CHARACTERIZATION OF α-QUATERNARY KETONE DERIVATIVES



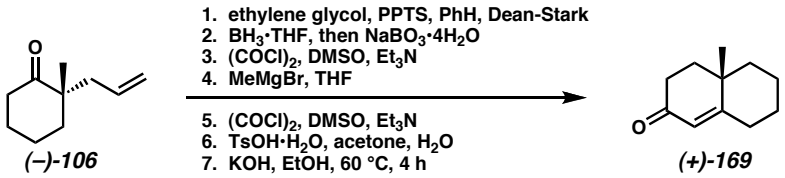
(–)-7a-Methyl-5,6,7,7a-tetrahydro-1*H*-inden-2(4*H*)-one (166, Scheme 2.8a):[83] To a solution of ketone **106** (98% ee, 304.4 mg, 2.0 mmol, 2.0 equiv) in dimethylacetamide (2.8 mL) and water (0.4 mL) was added $PdCl_2$ (53.1 mg, 1.2 mmol, 0.15 equiv), $Cu(OAc)_2 \bullet H_2O$ (217.9 mg, 1.20 mmol, 0.60 equiv). An oxygen balloon was attached. After 24 h of vigorous stirring at 25 °C the reaction mixture was chromatographed (5→25 % EtOAc in Hexanes on SiO_2). To a solution of the resulting diketone in EtOH (30 mL) was added KOH (3.4 mL of a 50 mg/mL ethanolic solution), and the reaction mixture was heated at 60 °C for 6 h. The temperature was increased to 80 °C and additional KOH (200 mg) was added. After 4 h the reaction was cooled and concentrated. The resulting residue was partitioned between EtOAc (30 mL) and water (20 mL) and acidified to pH 2 with 3 M aq HCl. The layers were separated, and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. Chromatography (10→30% Et_2O in pentane on SiO_2) afforded enone **166** (219.1 mg, 72.9% overall yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (s, 1H), 2.62 (br d, J = 12.0 Hz, 1H), 2.35 (dt, J = 13.5, 5.4 Hz, 1H), 2.27 (dd, J = 18.3, 0.9 Hz, 1H), 2.17 (d, J = 18.6 Hz, 1H), 2.26-1.88 (m, 2H), 1.64 (m, 2H), 1.36 (m, 2H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 188.6, 126.0, 52.1, 43.1, 40.6, 27.9, 27.8, 24.0, 21.8; IR (Neat Film NaCl) 2934, 1713, 1622, 1221 cm^{-1};

HRMS (EI) *m/z* calc'd for $C_{10}H_{14}O$ [M]$^+$: 150.1045, found 150.1041; $[\alpha]_D^{27}$ –44.86 (*c* 3.55, hexane, 98% ee).



(+)-1-(7a-Methyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-3-yl)ethanone (168, Scheme 2.8a):[84,85] To a solution of ketone **106** (98% ee, 152.2 mg, 1.0 mmol, 1.0 equiv) and methyl vinyl ketone (208.1 μL, 2.5 mmol, 2.5 equiv) in CH_2Cl_2 (5 mL) was added Grubbs' 2nd generation catalyst (**167**)[86] (42.4 mg, 0.05 mmol, 0.05 equiv). The reaction mixture was heated at 40 °C for 18 h, cooled to 25 °C, and concentrated. Chromatography (20% EtOAc in hexanes on SiO_2) gave the enone (152.1 mg 78.3% yield), which was dissolved in EtOAc (12 mL) and treated with 10% Pd/C (30 mg) under an atmosphere of hydrogen gas for 12 h. The system was purged with argon, filtered through a small pad of silica gel, and concentrated. To a solution of the crude diketone in EtOH (12 mL) was added KOH (2.0 mL of a 50 mg/mL ethanolic solution). The reaction mixture was heated to 65 °C for 8 h, cooled to 25 °C, concentrated, and the residue partitioned between EtOAc (10 mL) and 1 M aq HCl (10 mL) The layers were separated, the aqueous layer extracted with Et_2O (3 x 25 mL), and the combined organics were washed with saturated $NaHCO_3$ (25 mL), then brine (25 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (10→15 % Et_2O in hexanes on SiO_2) gave enone **168** (112.4 mg, 81% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.32 (d, *J* = 14.7 Hz, 1H), 2.59 (m, 2H), 2.23 (s, 3H), 2.01 (app. t, *J* = 13.5 Hz, 1H), 1.82 (m, 3H), 1.59 (m, 3H),

1.43-1.23 (m, 2H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.2, 162.2, 131.9, 48.6, 41.5, 39.0, 30.9, 30.5, 27.1, 25.2, 22.9, 22.0; IR (Neat Film NaCl) 2931, 1678, 1654, 1614, 1357 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{10}H_{18}O$ $[M]^+$: 178.1358, found 178.1355; $[\alpha]_D^{27}$ +82.9 (*c* 3.26, hexane, 98% ee).



(+)-4a-Methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (169, Scheme 2.8a):[87]

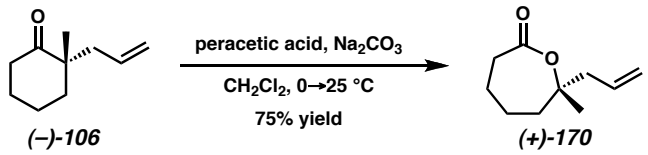
A solution of ketone **106** (98% ee, 1.23 g, 8.11 mmol, 1.0 equiv), ethylene glycol (1.8 mL), pyridinium *p*-toluenesulfonate (PPTS, 0.6 g), and benzene (45 mL) was refluxed for 22 h in a Dean-Stark apparatus. The reaction mixture was cooled, poured into saturated aq $NaHCO_3$ (50 mL), the aq layer extracted with 1:1 hexanes:Et_2O (2 x 20 mL). The combined organics were washed with brine (2 x 15 mL), dried ($MgSO_4$), concentrated, and chromatographed to give the ketal (1.59 g). The ketal in THF (15 mL) was added dropwise to a cooled (–25 °C) solution of BH_3•THF (20.3 mmol, 2.5 equiv) in THF (100 mL), and after 4 h was allowed to warm to 25 °C overnight. The reaction mixture was then cooled to –10 °C and water (25 mL) was slowly added, followed by $NaBO_3$•$4H_2O$ (4.99 g, 32.4 mmol, 4.0 equiv), and the reaction mixture was allowed to warm to 25 °C. After 48 h, the reaction mixture was partitioned between water (100 mL) and EtOAc (100 mL), the layers separated, the aq layer extracted with EtOAc (5 x 75 mL), and the organic fractions were dried (Na_2SO_4). Evaporation of the solvents under reduced pressure, and

chromatography (20→40% EtOAc in hexanes on SiO_2) gave the primary alcohol (1.50 g, 87% yield).

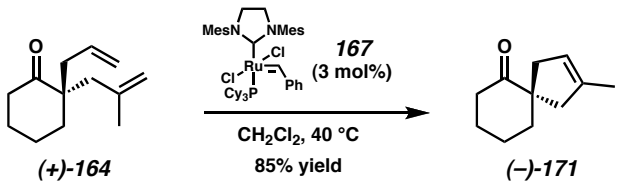
To a cooled (–78 °C) solution of DMSO (479.0 μL, 6.72 mmol, 1.6 equiv) in CH_2Cl_2 (45 mL) was added oxalyl chloride (475.2 μL, 5.45mmol, 1.3 equiv). After 45 min, the primary alcohol (900 mg, 4.19 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added in a dropwise manner. After an additional 30 min, Et_3N (2.32 mL, 16.8 mmol, 4.0 equiv) was added, the reaction mixture warmed to 25 °C, and quenched with half-saturated aq $NaHCO_3$. The aq layer was extracted with CH_2Cl_2 (3 x 30 mL), the combined organics dried ($MgSO_4$), and solvents evaporated. This crude aldehyde in THF (45 mL) was cooled to –10 °C, treated with methyl magnesium bromide (3 M soln in Et_2O, 8.40 mmol, 2.0 equiv), quenched with water (20 mL) and saturated aq NH_4Cl (20 mL), extracted CH_2Cl_2 (4 x 20 mL), dried ($MgSO_4$), and solvents evaporated. The resulting crude secondary alcohol was resubmitted to the Swern oxidation conditions described above to give a crude methyl ketone. A solution of the methyl ketone in acetone (45 mL) and water (0.7 mL) was treated with $TsOH•H_2O$ (60 mg), and heated at 50 °C for 4 h. The reaction mixture was then concentrated and chromatographed (7.5→20% EtOAc in hexanes on SiO_2) to give the diketone (515.8 mg, 68% yield for 4 steps).

To a solution of KOH (300 mg 5.36 mmol, 1.91 equiv) in EtOH (40 mL) was added the diketone (510.0 mg, 2.80 mmol, 1.0 equiv) dissolved in EtOH (15 mL), and the reaction mixture heated at 60 °C for 4 h. The reaction was quenched with acetic acid (306 μL, 5.36 mmol, 1.91 equiv), concentrated and chromatographed (5→20% Et_2O in hexanes on SiO_2) to give enone **169** (334.2 mg, 73% yield, 42% overall yield for 7 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (s, 1H), 2.56-2.22 (m, 4H), 1.92-1.64 (m, 6H), 1.44-

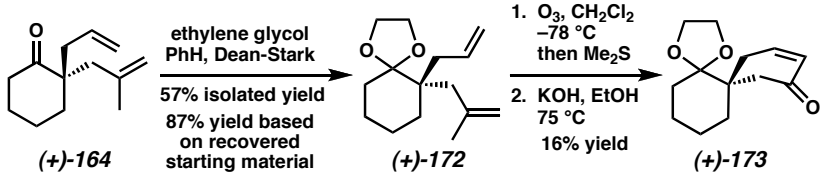
1.30 (m, 2H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 170.5, 124.1, 41.5, 38.0, 35.9, 34.0, 32.7, 27.1, 22.0, 21.7; IR (Neat Film NaCl) 2930, 1678 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{16}O$ $[M]^+$: 164.1201, found 164.1196; $[\alpha]_D^{28}$ +216.2 (*c* 1.05, EtOH, 98% ee).



(+)-7-Allyl-7-methyloxepan-2-one (170, Scheme 2.8a):[88] To a cooled (0 °C) solution of ketone **106** (98% ee, 152.2 mg, 1.0 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added Na_2CO_3 (593.6 mg, 5.6 mmol, 5.6 equiv) and peracetic acid (800 μL of a 32% solution in acetic acid). The reaction mixture was maintained at 0 °C for 9 h, then allowed to warm to 25 °C for an additional 12 h, diluted with saturated aq $NaHCO_3$, and the organic layer dried (Na_2SO_4). Chromatography (5→20% EtOAc in hexanes on SiO_2) afforded lactone **170** (125.6 mg, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (m, 1H), 5.15 (m, 1H), 5.11 (app. d, *J* = 8.4 Hz, 1H), 2.78-2.61 (m, 2H), 2.51 (dd, *J* = 13.8, 7.2 Hz, 1H), 2.42 (dd, *J* = 14.1, 7.5 Hz, 1H), 1.86-1.62 (m, 6H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 132.8, 119.0, 82.7, 46.7, 38.4, 37.3, 24.8, 23.8, 23.3; IR (Neat Film NaCl) 2936, 1717, 1172 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{10}H_{16}O_2$ $[M]^+$: 168.1150, found 168.1154; $[\alpha]_D^{27}$ +20.58 (*c* 3.46, hexane, 98% ee).



(–)-2-methylspiro[4.5]dec-2-en-6-one (171, Scheme 2.8b): To a sparged (Ar, 5 min) solution of ketone **164** (91% ee, 526 mg, 2.73 mmol, 1.00 equiv) in CH_2Cl_2 (56 mL) was added the 2nd generation Grubbs catalyst (**167**)[86] (69.6 mg, 0.082 mmol, 0.03 equiv) and the reaction was heated at 40 °C for 10 h. The reaction mixture was cooled to ambient temperature, concentrated, and the residue purified by flash chromatography (1→2% Et_2O in hexanes on SiO_2) to give spiro[4.5]ketone **171** (381 mg, 85% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 5.14 (m, 1H), 2.86-2.71 (m, 2H), 2.44-2.35 (m, 2H), 2.17 (dddd, *J* = 16.2, 5.4, 4.2, 2.1 Hz, 1H), 2.02 (ddd, *J* = 16.5, 3.0, 1.2 Hz, 1H), 1.88-1.68 (comp. m, 6H), 1.67-1.64 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.3, 137.5, 121.1, 56.3, 45.7, 41.9, 40.3, 39.4, 27.2, 22.2, 16.4; IR (Neat Film NaCl) 3042, 2930, 2860, 1710, 1666, 1438, 1338, 1312, 1207, 1129, 1056, 1019, 899, 853, 838, 807 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{16}O$ $[M]^+$: 164.1201, found 164.1201; $[\alpha]_D^{27.1}$ –21.7 (*c* 2.65, CH_2Cl_2, 91% ee).



(+)-6-Allyl-6-(2-methylallyl)-1,4-dioxaspiro[4.5]decane (172, Scheme 2.8c): A solution of ketone **164** (91% ee, 1.27 g, 6.60 mmol, 1.0 equiv), ethylene glycol (1.8 mL), pyridinium *p*-toluenesulfonate (PPTS, 0.600 g), and benzene (80 mL) was refluxed for 15

h in a Dean-Stark apparatus. The reaction mixture was cooled, poured into saturated aq $NaHCO_3$ (20 mL), and diluted with H_2O (30 mL) and CH_2Cl_2 (30 mL). The aqueous layer extracted with CH_2Cl_2 (3 x 30 mL). The combined organics were dried (Na_2SO_4), concentrated, and purified by flash chromatography (1→2% Et_2O in hexanes on SiO_2) to give ketal **172** (889 mg, 57% yield) plus recovered **164** (433.3 mg, 34% recovery). ^1H NMR (300 MHz, $CDCl_3$) δ 6.02 (dddd, *J* = 16.2, 11.1, 7.2, 7.2 Hz, 1H), 4.95 (app. ddd, *J* = 15.9, 1.8, 1.8 Hz, 1H), 4.95 (app. ddd, *J* = 11.1, 1.2, 1.2 Hz, 1H), 4.85 (app. ddd, *J* = 4.2, 2.4, 1.5 Hz, 1H), 4.78-4.71 (m, 1H), 3.98-3.84 (comp. m, 4H), 2.43-2.17 (comp. m, 4H), 1.82 (s, 3H), 1.67-1.40 (comp. m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 136.9, 114.9, 114.8, 112.9, 64.4, 64.1, 45.0, 39.4, 38.1, 33.1, 30.5, 25.6, 23.4, 20.7; IR (Neat Film NaCl) 3073, 2936, 2882, 1638, 1452, 11374, 1275, 1215, 1173, 1089, 1060, 1026, 957, 892 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{15}H_{24}O_2$ $[M]^+$: 236.1776, found 236.1779; $[\alpha]_D^{26.7}$ +5.0 (*c* 2.71, CH_2Cl_2, 91% ee).

(+)-Spiro[5.5]ketone 173 (Scheme 2.8c): Through a cooled (–78 °C) solution of ketal **172** (441 mg, 1.86 mmol, 1.00 equiv) in CH_2Cl_2 (40 mL) was bubbled a stream of ozone until the reaction mixture turned blue. The reaction mixture was quenched with dimethyl sulfide (0.50 mL), allowed to warm to ambient temperature, and concentrated to an oil. This residue was dissolved in EtOH (35 mL), treated with an ethanolic KOH solution (3.0 mL of 50 mg/mL), and heated to 75 °C for 3 h. The reaction mixture was cooled to ambient temperature, neutralized with acetic acid, concentrated, and purified by flash chromatography (5→25% EtOAc in hexanes on SiO_2) to give spiro[5.5]ketone **173** (65.7 mg, 16% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (ddd, *J* = 10.2, 5.7, 2.7 Hz, 1H), 5.98 (app. dd, *J* = 9.9, 3.0 Hz, 1H), 4.02-3.87 (comp. m, 4H), 2.66 (ddd, *J* = 19.2,

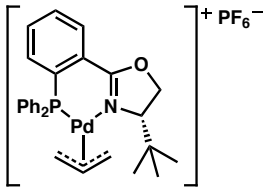
2.7, 2.7 Hz, 1H), 2.64 (d, J = 16.2 Hz, 1H), 2.46 (d, J = 15.9 Hz, 1H), 2.33 (ddd, 19.2, 6.0, 1.5 Hz, 1H) 1.68-1.50 (comp. m, 6H), 1.48-1.34 (comp. m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 148.1, 128.5, 111.1, 65.0 (2C), 44.7, 43.3, 31.5, 31.1, 30.1, 23.1, 20.4; IR (Neat Film NaCl) 2935, 2865, 1677, 1448, 1389, 1346, 1253, 1179, 1142, 1101, 1063, 1022, 961, 909, 885, 736 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{13}H_{17}O_3$ [(M + H) – H_2]$^+$: 221.1178, found 221.1185; $[\alpha]_D^{28.1}$ +27.9 (*c* 1.13, CH_2Cl_2, 91% ee).

For conversion of ketone (–)-**155** to (+)-dichroanone (**175**), see ref 89.

For preparation of ketone (–)-**176** and conversion to the natural products laurencenone B (**177**) and (+)-elatol (**178**), see ref 90.

For conversion of ketone (–)-**150** to the ABC tricycle (**179**) toward the natural product zoanthenol (**180**), see ref 91.

2.8.7 PREPARATION AND CHARACTERIZATION OF [(PHOX)PD(ALLYL)][PF_6] SALT

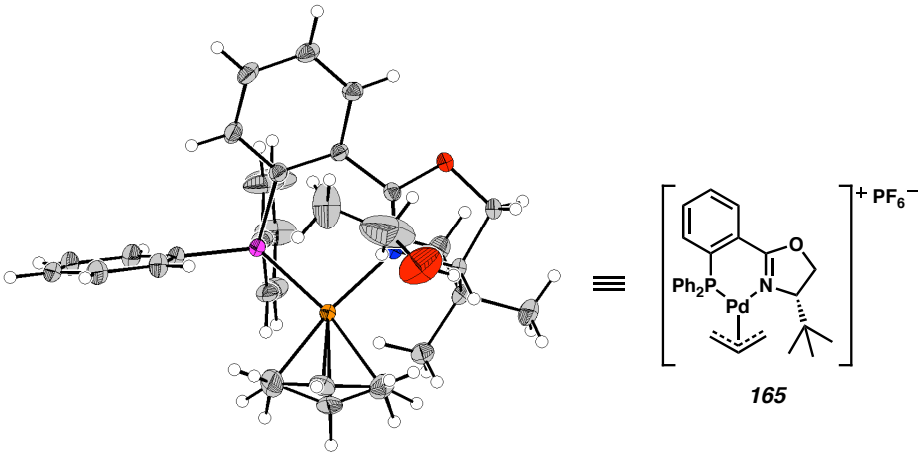


165

[Pd(allyl)PHOX]•PF_6 salt 165 (Scheme 2.7). Prepared using Zehnder's method[92] with (*S*)-*t*-Bu-PHOX as a mixture of *endo*- and *exo*-isomers (ca. 60:40 ratio) in quantitative yield as a light yellow powder. mp (EtOH) 152-154 °C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (app. ddd, J = 7.7, 4.1, 1.1 Hz, 0.6H), 8.24 (app. ddd, J = 7.7,

4.4, 1.1 Hz, 0.4H), 7.74-7.42 (comp. m, 8H), 7.39-7.11 (comp. m, 4H), 7.04-6.87 (comp m, 1H), 5.96-5.82 (m, 0.4H), 5.82-5.67 (m, 0.6H), 4.96-4.86 (comp. m, 1H), 4.68 (app. q, J = 9.9 Hz, 1H), 4.49 (app. dt, J = 11.3, 3.9 Hz, 1H), 4.19 (app. dt, J = 10.2, 4.4 Hz, 1H), 4.03 (app. dd, J = 14.3, 9.4 Hz, 0.6H), 3.63-3.48 (comp. m, 1H), 3.32 (app. d, J = 6.6 Hz, 0.4H), 3.16 (app. d, J = 12.7 Hz, 0.4H), 2.77 (app. d, J = 12.1 Hz, 0.6H), 0.64 (s, 3.5H), 0.56 (s, 5.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9-164.8 (3 peaks), 134.9, 134.8, 134.0-133.3 (7 peaks), 132.9-132.6 (4 peaks), 132.2-132.1 (3 peaks), 131.8 (app. d, J = 2.3 Hz), 130.2-128.8 (13 peaks), 128.5-127.8 (5 peaks), 127.3, 122.4 (app. d, J = 6.0 Hz), 122.4, 83.3-79.4 (6 peaks), 69.8, 69.7, 58.6, 54.1, 54.0, 34.3, 25.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ 22.7 (d, J = 118.1 Hz), –143.8 (sept., $J_{P\text{-}F}$ = 711.0 Hz); IR (Neat Film from $CDCl_3$, NaCl) 3062, 2964, 2872, 2271, 1971, 1899, 1826, 1621, 1584, 1568, 1482, 1437, 1372, 1315, 1249, 1211, 1145, 1121, 1100, 1060, 1028, 958, 913, 836, 778, 732, 697, 678 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{28}H_{31}ONPPd$ $[M]^+$: 534.1178, found 534.1182; $[\alpha]_D^{27.1}$ +256.6 (*c* 3.72, CH_2Cl_2).

Figure 2.2. Representation of [Pd(II)(allyl)PHOX]•PF6 salt ***165***



165

*Figure 2.3. Representation of the unit cell of [Pd(II)(allyl)PHOX]•PF6 salt **165***

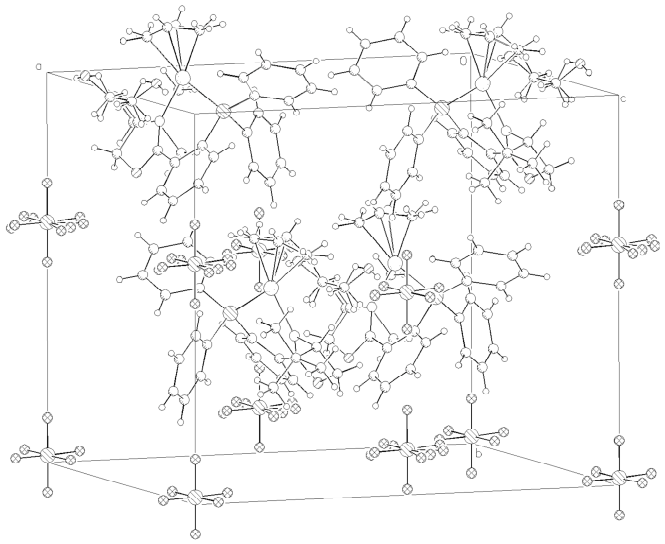


Table 2.15. Crystal data and structure refinement for [Pd(II)(allyl)PHOX]•PF6 (CCDC 245187)

Empirical formula	$[C_{28}H_{31}NOPPd]^+ PF_6^- \bullet \frac{1}{2}C_2H_5OH$
Formula weight	702.91
Crystallization solvent	Ethanol
Crystal habit	Fragment
Crystal size	0.35 x 0.34 x 0.23 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker SMART 1000	
Wavelength	0.71073 Å MoKα	
Data Collection Temperature	100(2) K	
θ range for 15322 reflections used in		
lattice determination	2.31° to 41.00°	
Unit cell dimensions	a = 17.5183(6) Å	
	b = 15.7792(5) Å	β = 107.0990(10)°
	c = 11.3736(4) Å	

Table 2.15. (continued)

Volume	3004.98(18) $Å^3$
Z	4
Crystal system	Monoclinic
Space group	C2
Density (calculated)	1.554 Mg/m^3
F(000)	1428
θ range for data collection	1.77 to 42.31°
Completeness to θ = 42.31°	85.0 %
Index ranges	$-32 \le h \le 32$, $-28 \le k \le 29$, $-20 \le l \le 15$
Data collection scan type	ω scans at 3 ϕ settings of 2θ = –28° and 2 at 2θ = –59°
Reflections collected	28501
Independent reflections	15572 [R_{int}= 0.0351]
Absorption coefficient	0.787 mm^{-1}
Absorption correction	SADABS
Max. and min. transmission	0.8397 and 0.7702

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	15572 / 1 / 408
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	1.343
Final R indices [I > 2σ(I), 13582 reflections]	R1 = 0.0373, *w*R2 = 0.0725

Table 2.15. (continued)

R indices (all data)	R1 = 0.0459, *w*R2 = 0.0748
Type of weighting scheme used	Sigma
Weighting scheme used	$w = 1 / \sigma^2(Fo^2)$
Max shift/error	0.004
Average shift/error	0.000
Absolute structure parameter	–0.019(13)
Largest diff. peak and hole	1.422 and –0.710 e.Å^{-3}

Special Refinement Details

The propyl ligand, C26-C27-C28, is disordered in two alternate orientations, differing by "up-down" positions for C27. Additional disorder is observed in one PF_6 counterion and an included solvent molecule, modeled as ethanol hydrogen bonded to a fluorine of one counterion.

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles, and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

2.8.8 NOTES AND REFERENCES FOR EXPERIMENTAL SECTION

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APPENDIX 1

Spectra of Compound Relevant to Chapter 2

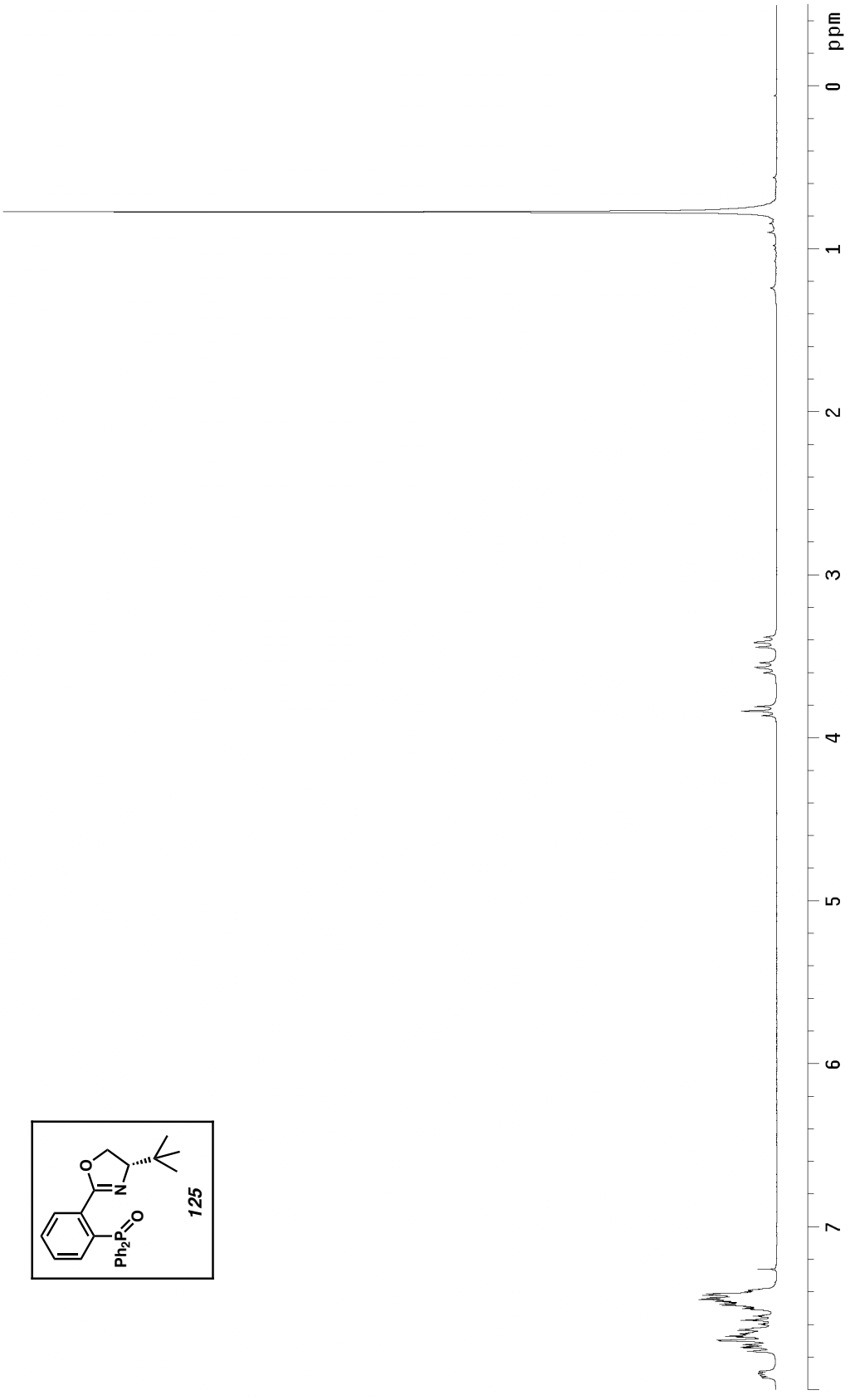


Figure A1.1 ^{1}H *NMR of compound* ***125*** *(300 MHz,* $CDCl_3$*)*

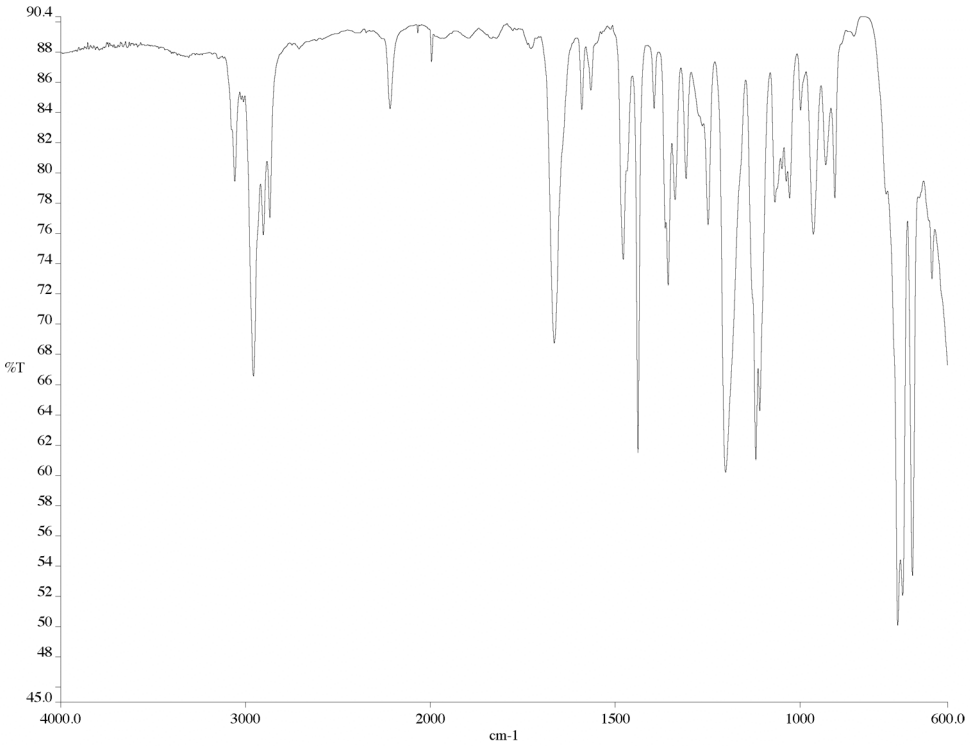


*Figure A1.2 IR of compound **125** (NaCl/film)*

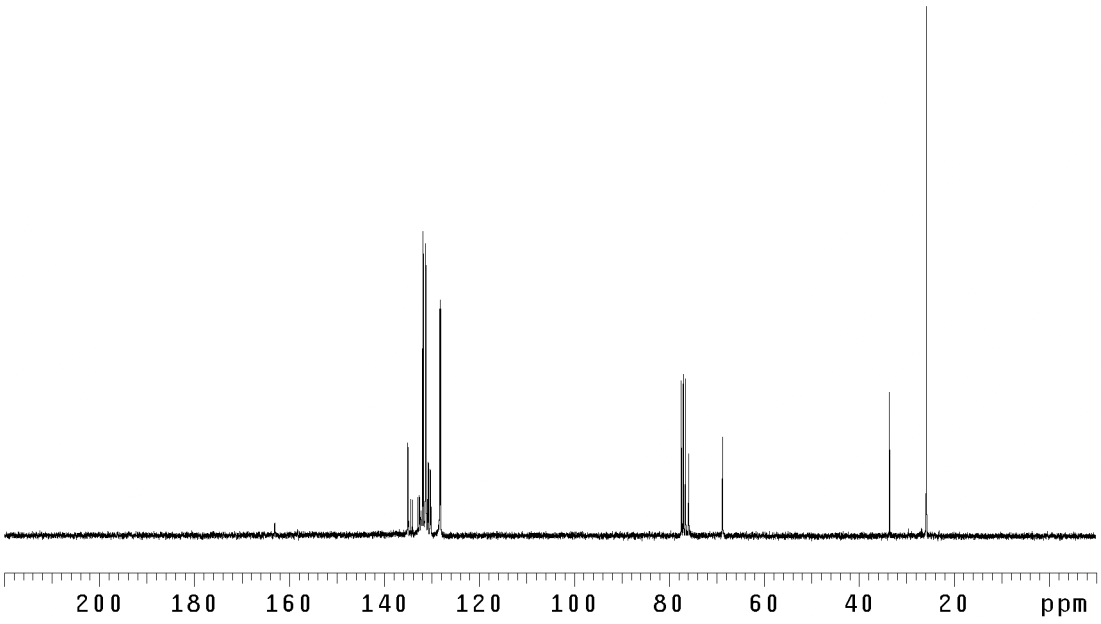
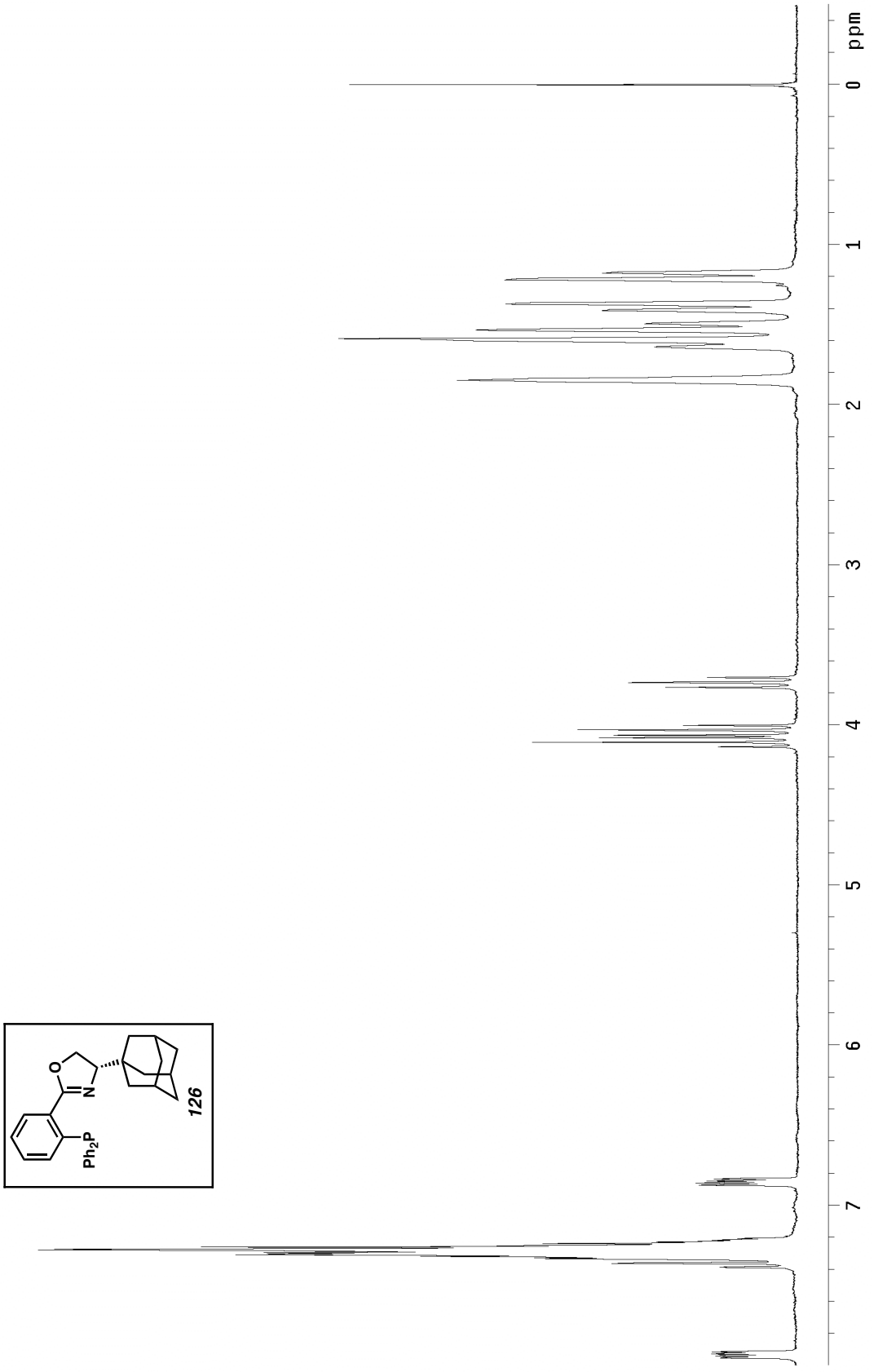


*Figure A1.3 ^{13}C NMR of compound **125** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
N
Ph2P
126

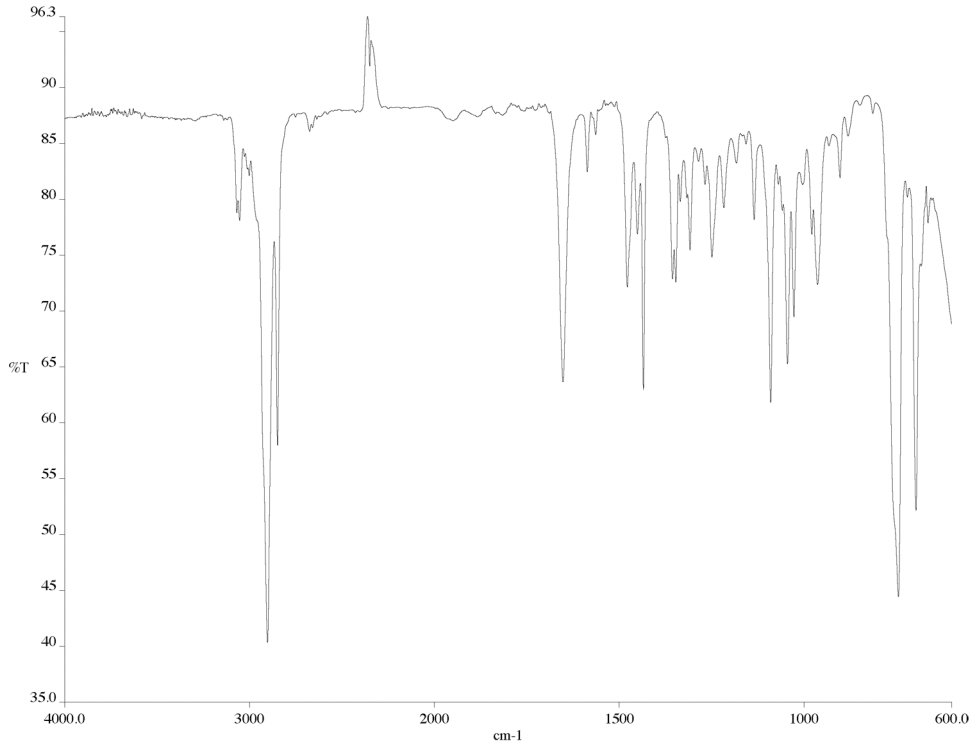


*Figure A1.5 IR of compound **126** (NaCl/film)*

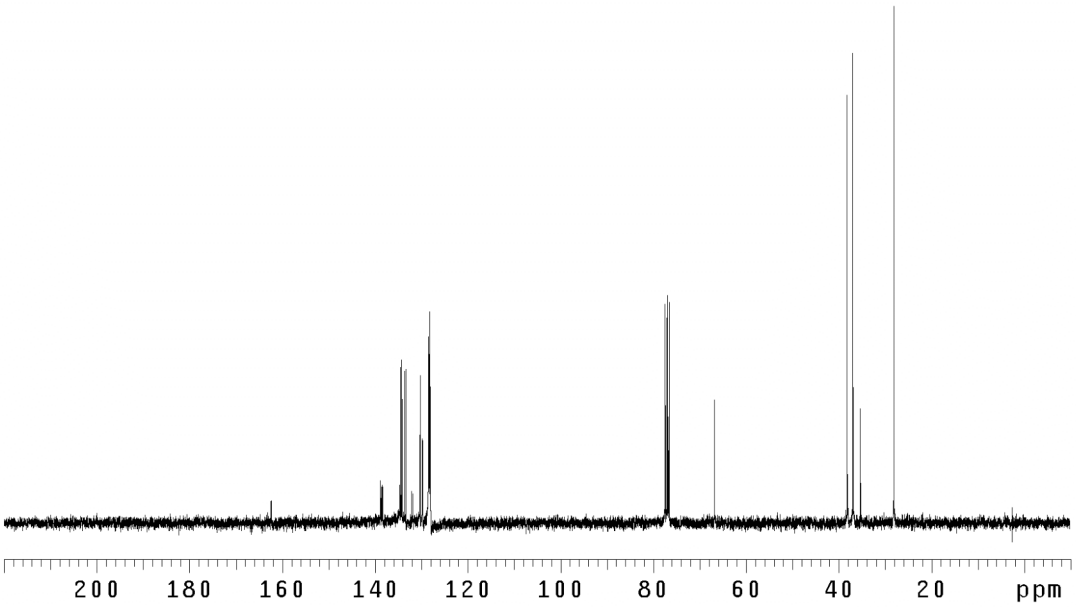
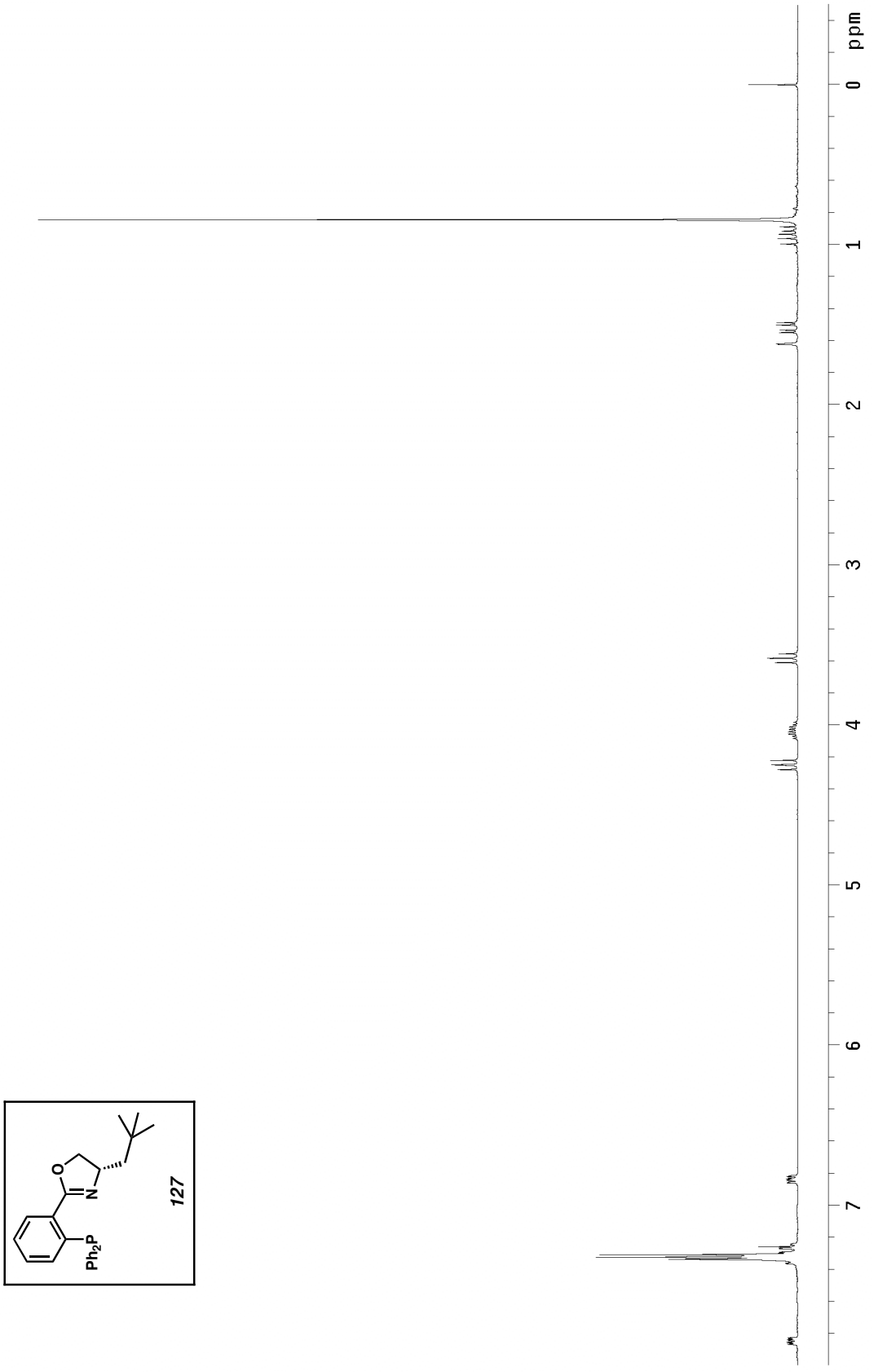


*Figure A1.6 ^{13}C NMR of compound **126** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
N
Ph_2P
127

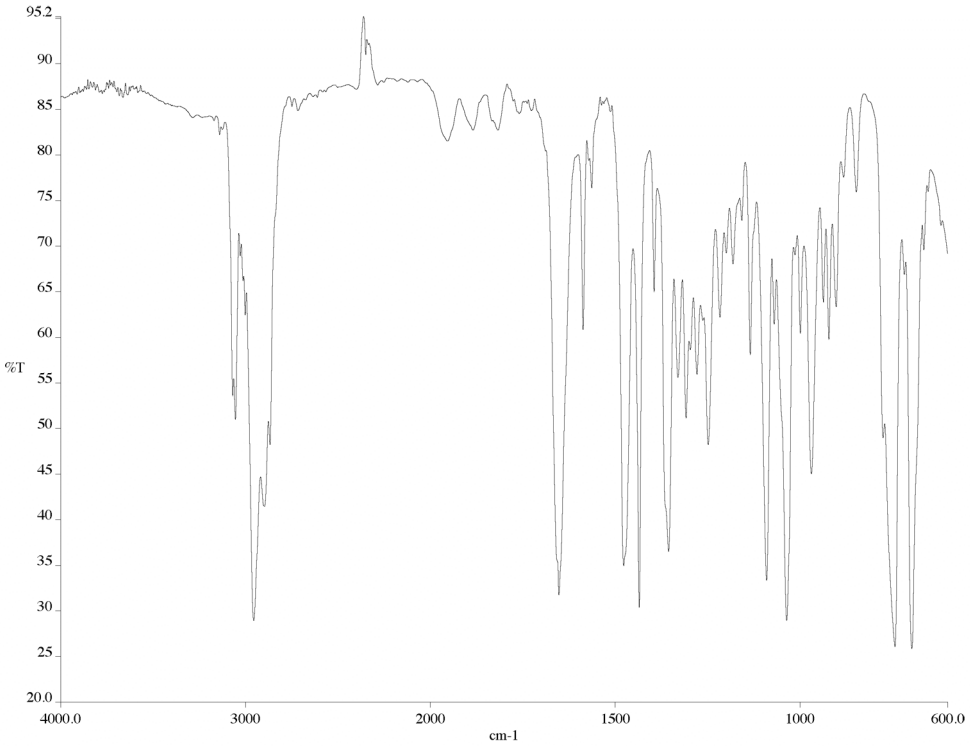


*Figure A1.8 IR of compound **127** (NaCl/film)*

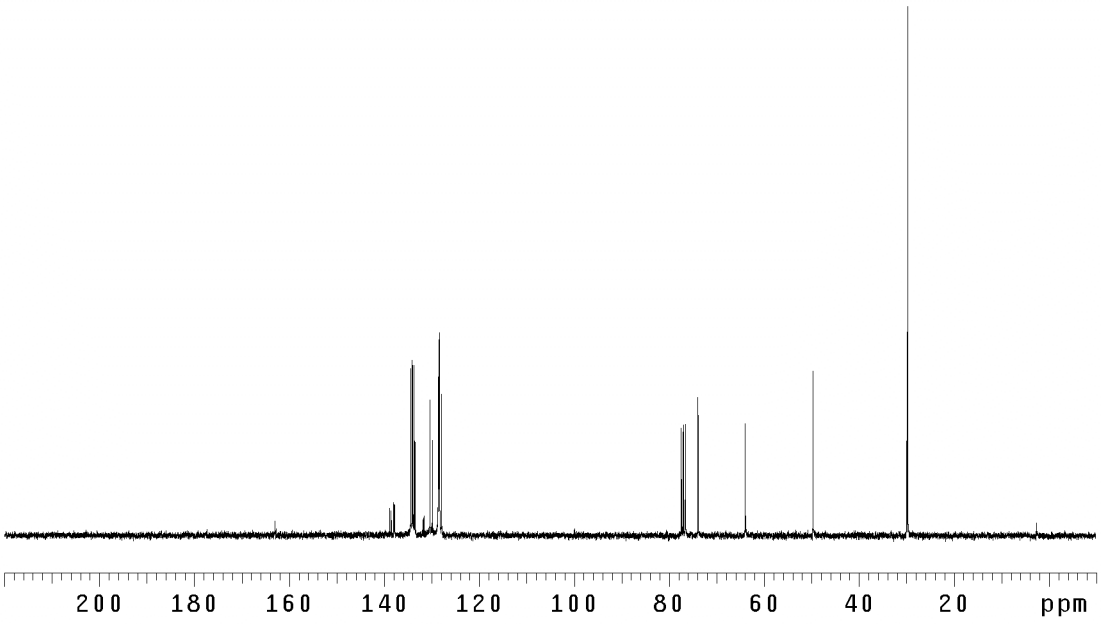
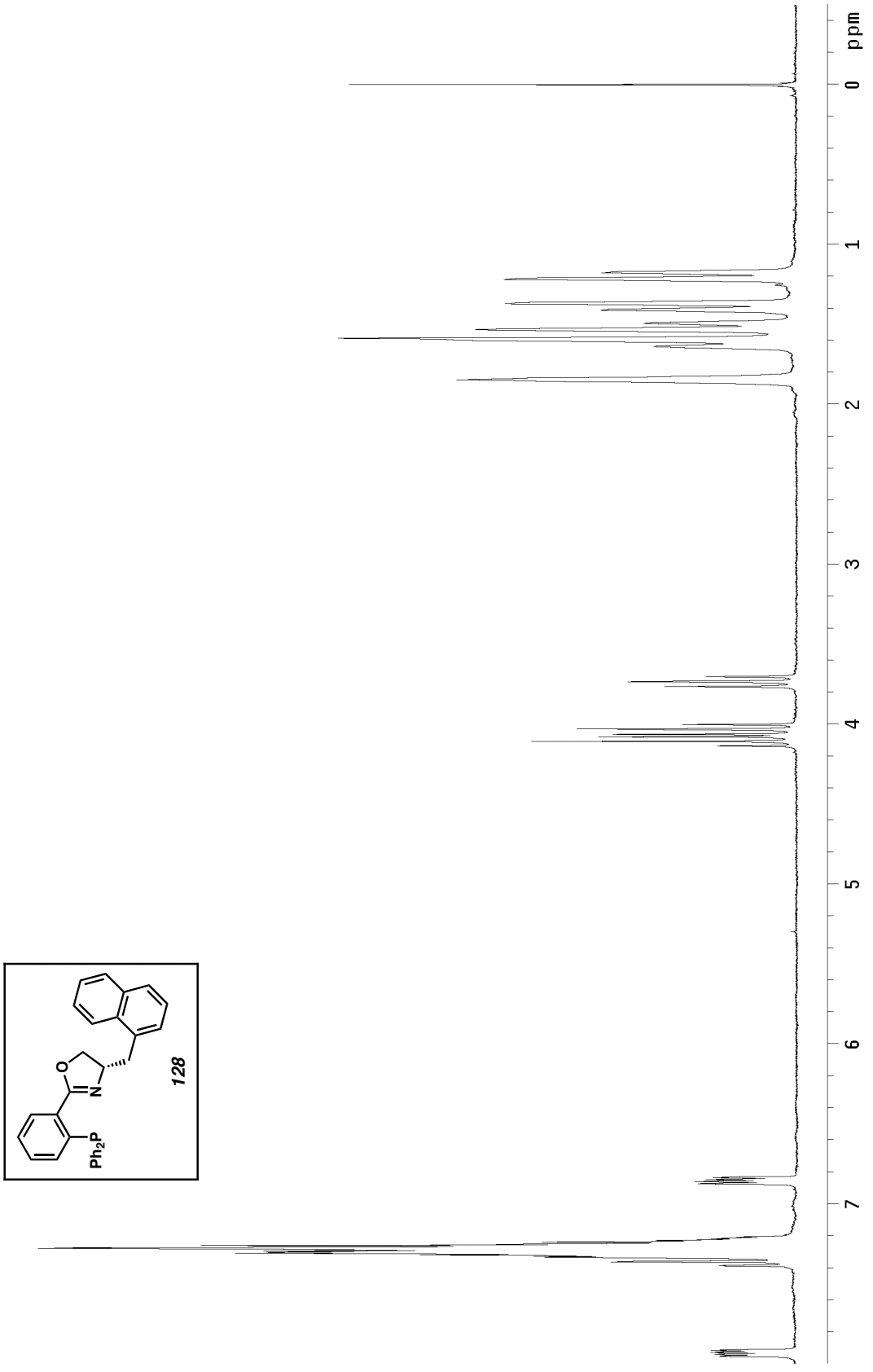


*Figure A1.9 ^{13}C NMR of compound **127** (75 MHz, $CDCl_3$*


ppm
0
1
2
3
4
5
6
7
O
N
Ph2P
128

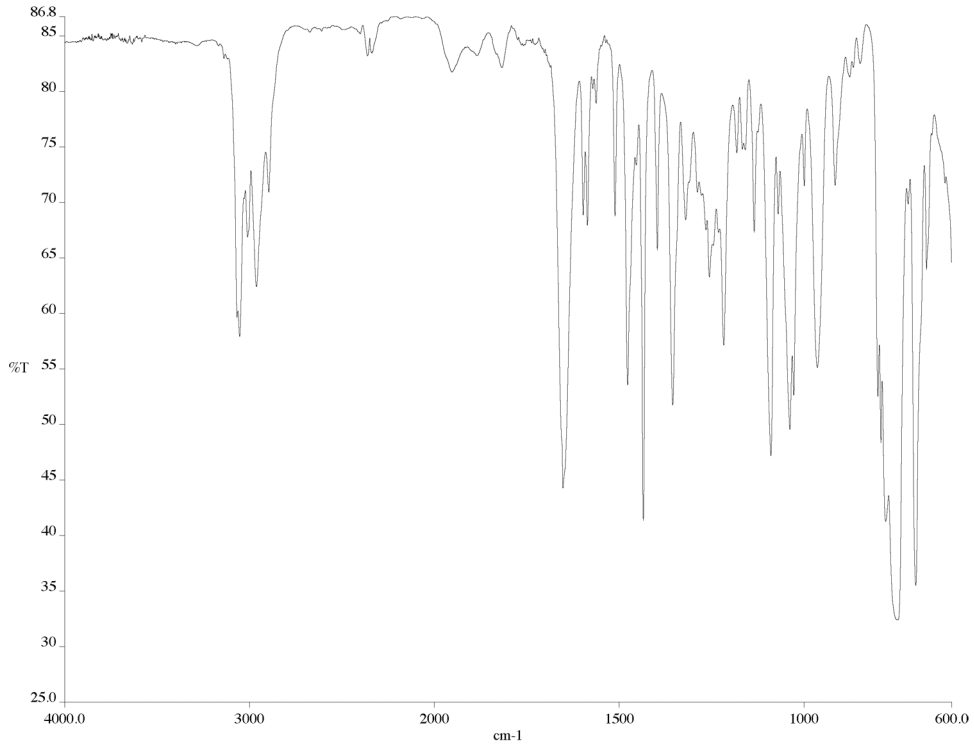


*Figure A1.11 IR of compound **128** (NaCl/film)*

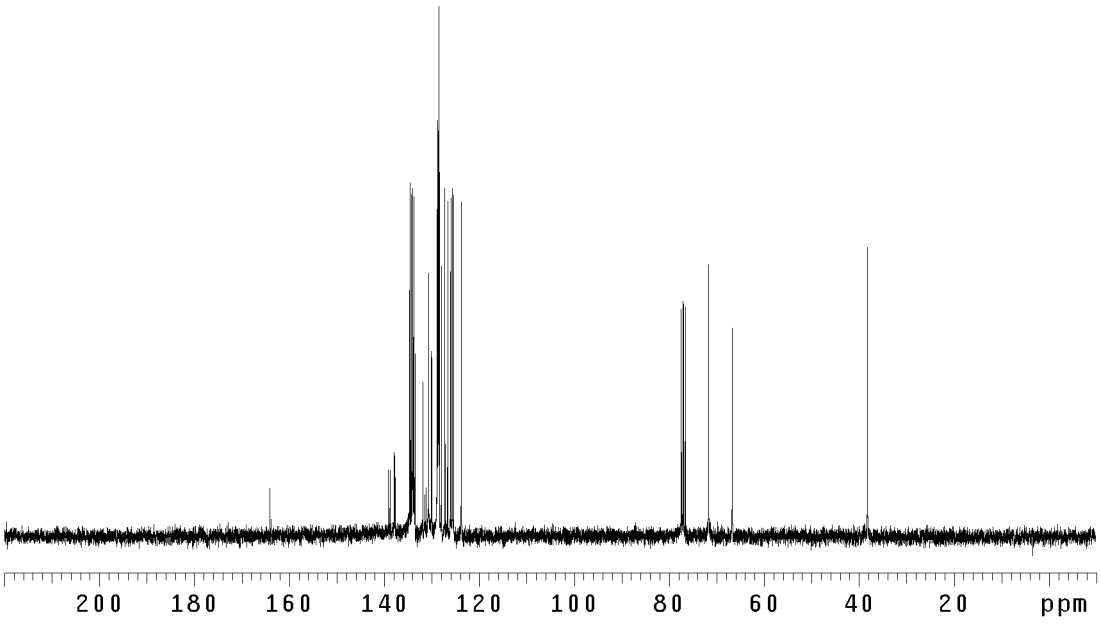
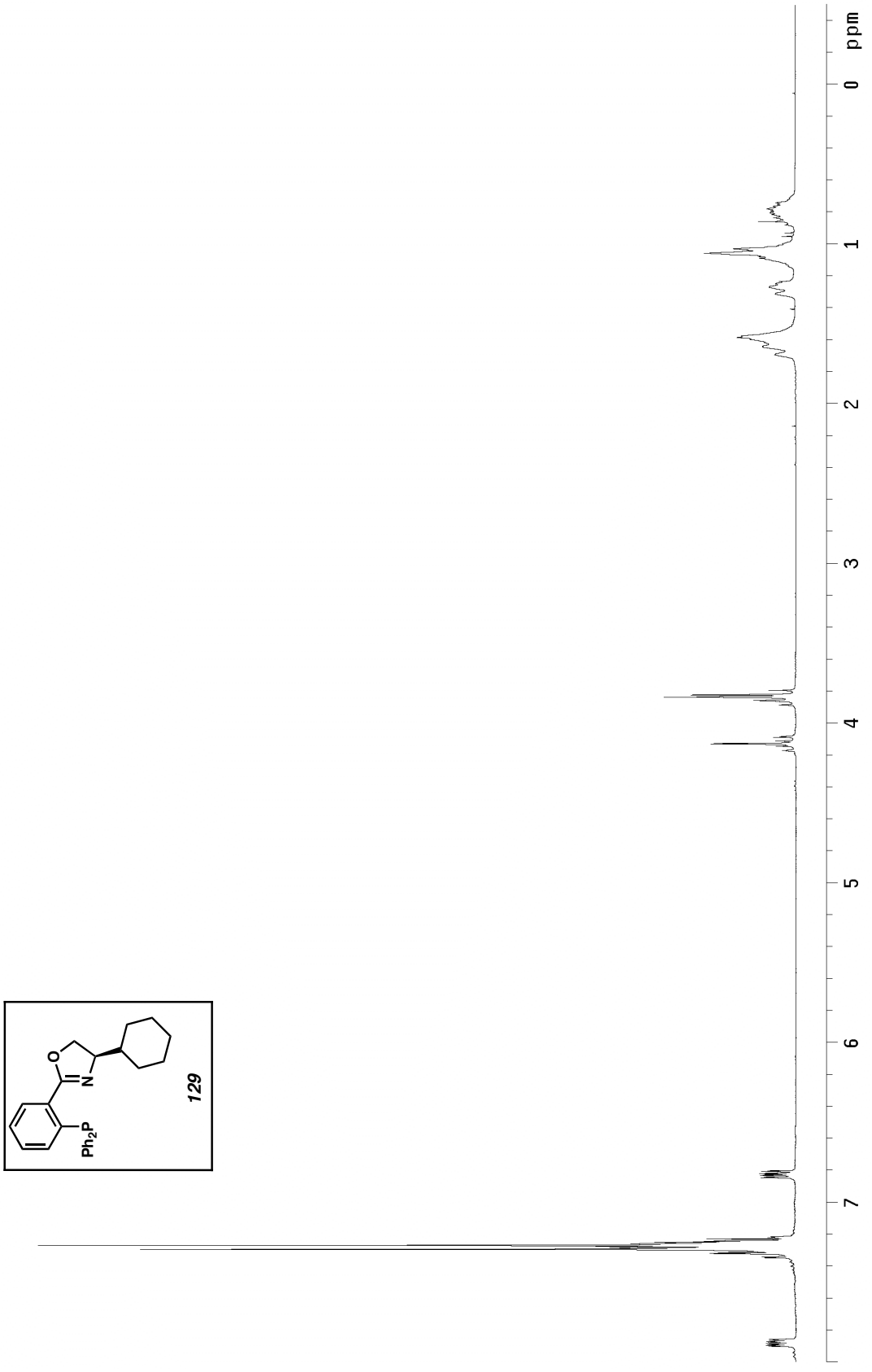


*Figure A1.12 ^{13}C NMR of compound **128** (75 MHz, $CDCl_3$)*


O
N
Ph2P
129
ppm
0
1
2
3
4
5
6
7

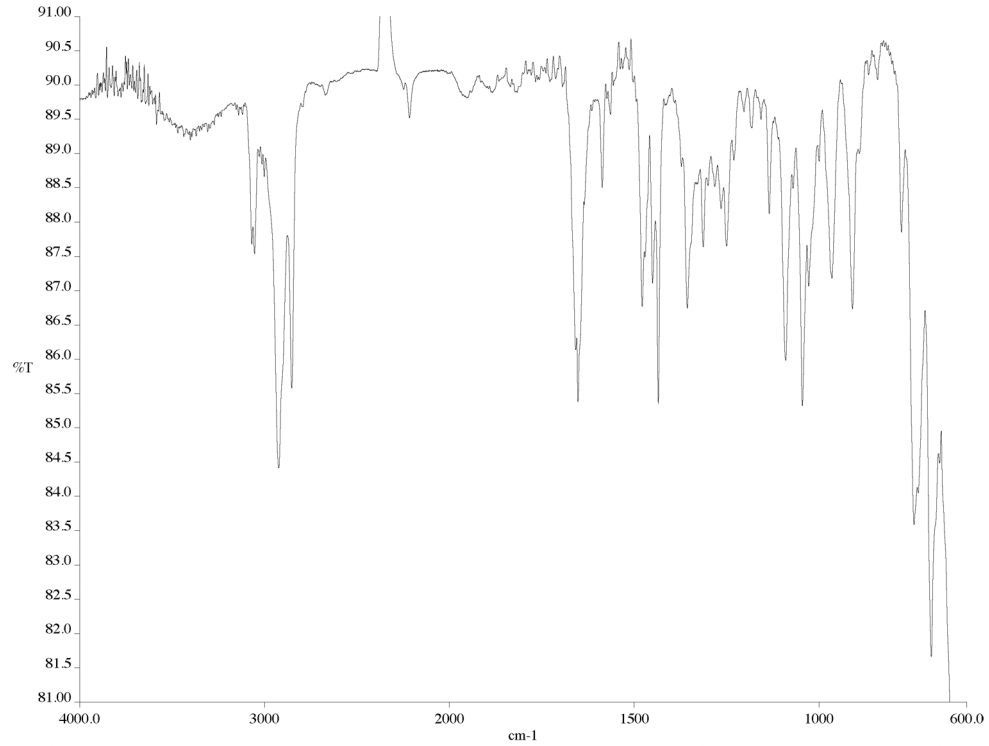


*Figure A1.14 IR of compound **129** (NaCl/film)*

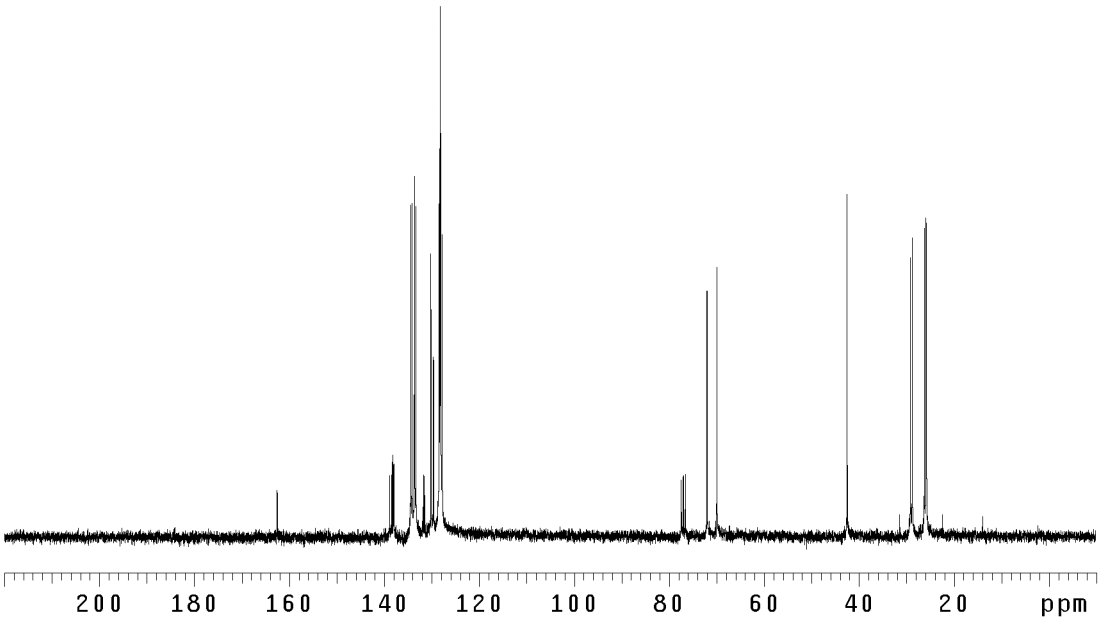
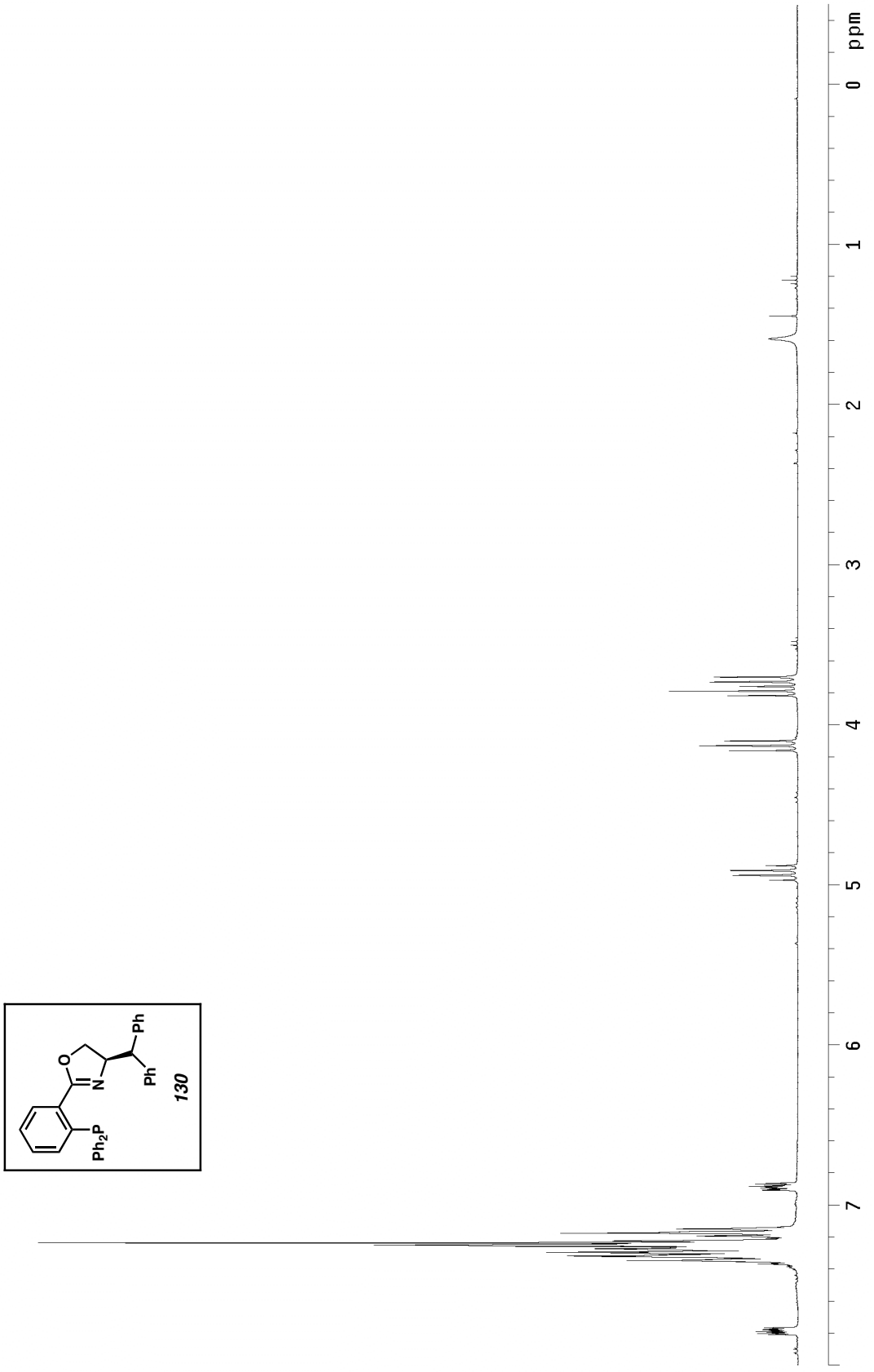


*Figure A1.15 ^{13}C NMR of compound **129** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
N
Ph
Ph
Ph2P
130

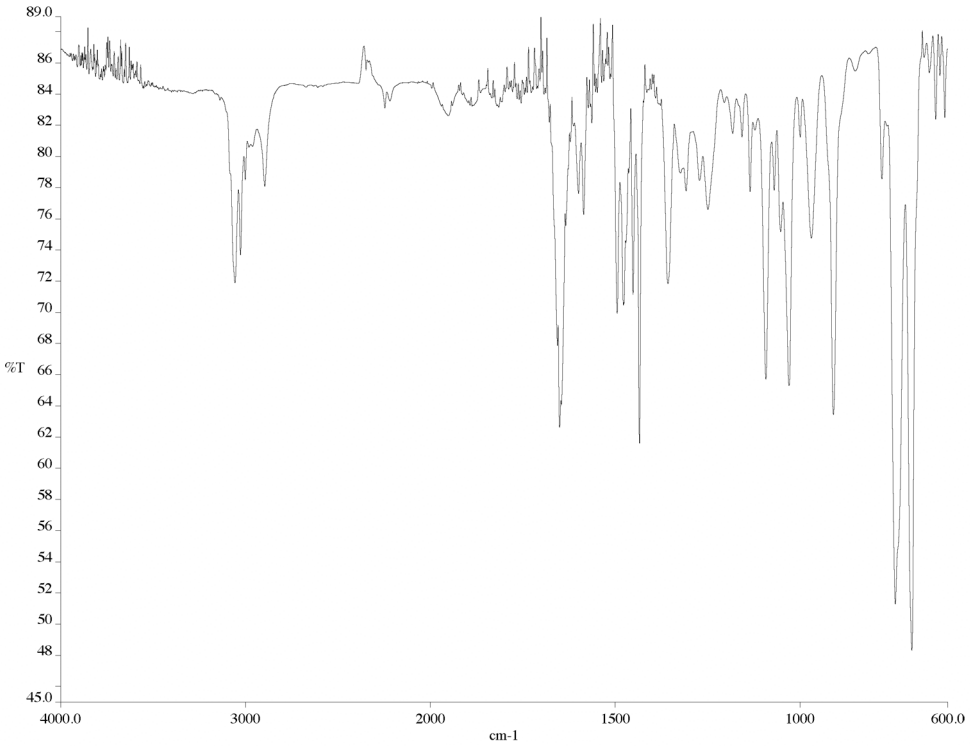


*Figure A1.17 IR of compound **130** (NaCl/film)*

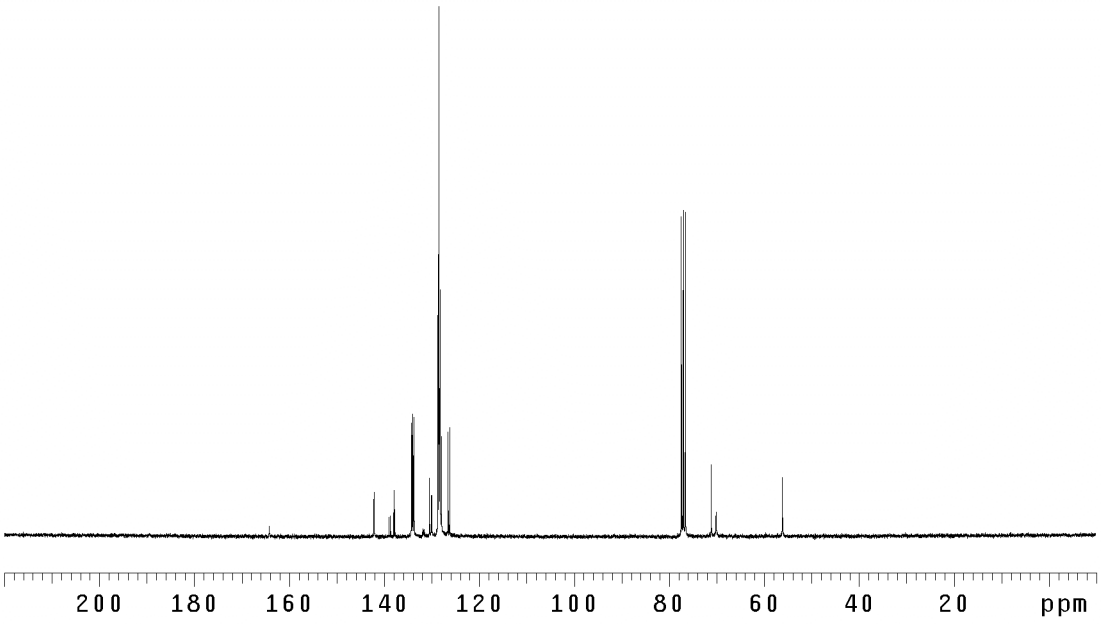
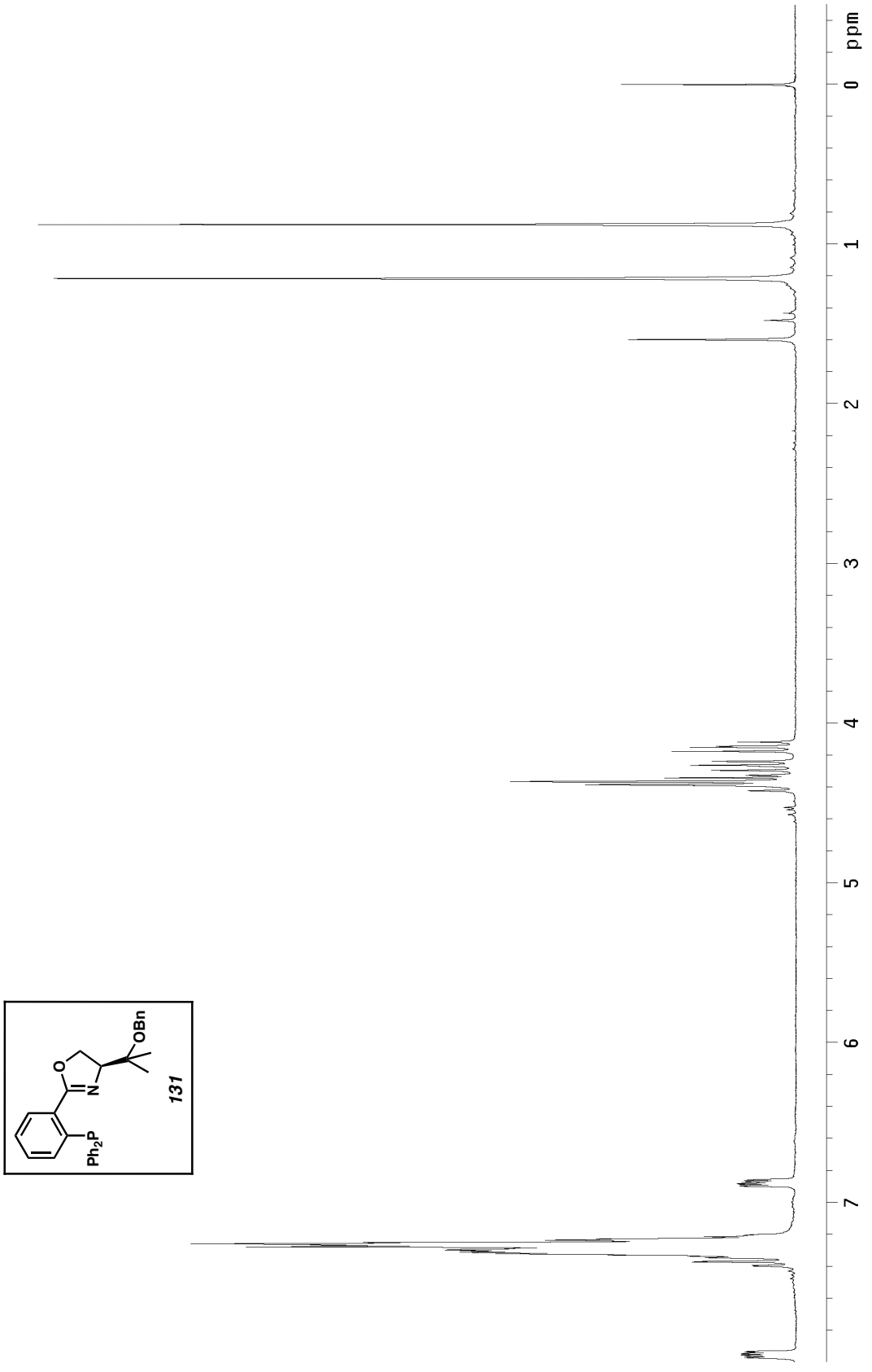


*Figure A1.18 ^{13}C NMR of compound **130** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
OBn
O
N
Ph2P
131

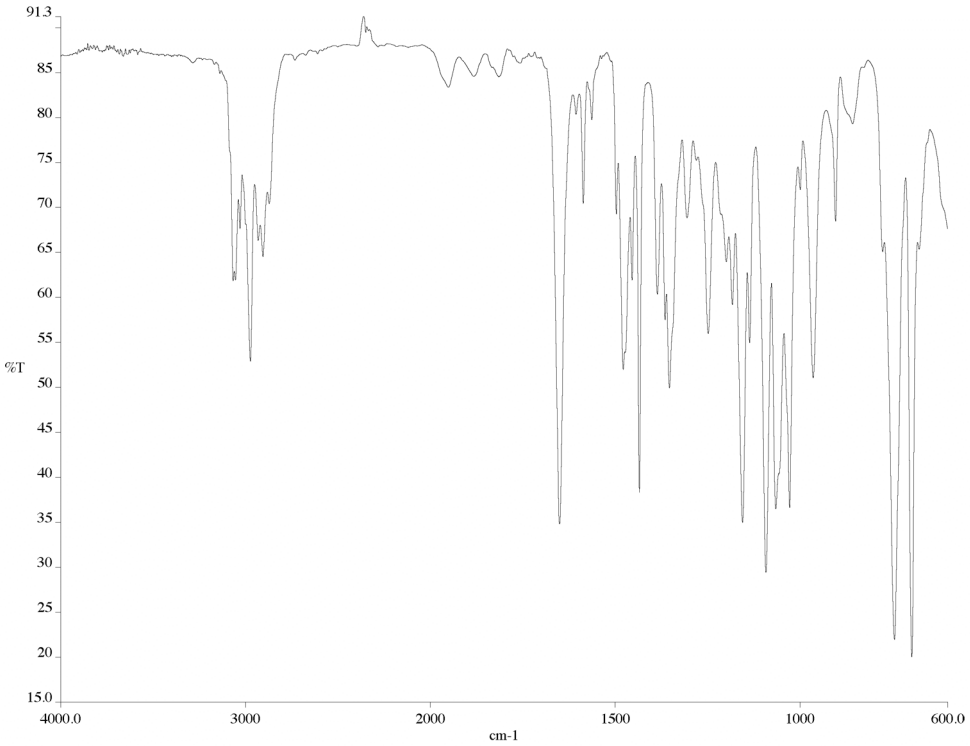


*Figure A1.20 IR of compound **131** (NaCl/film)*

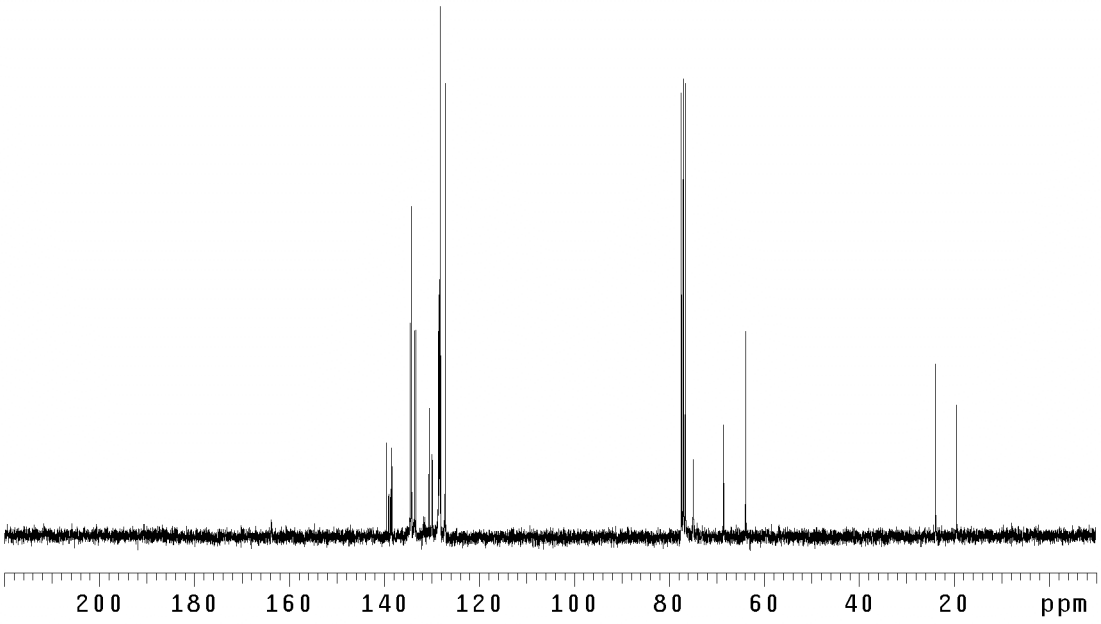
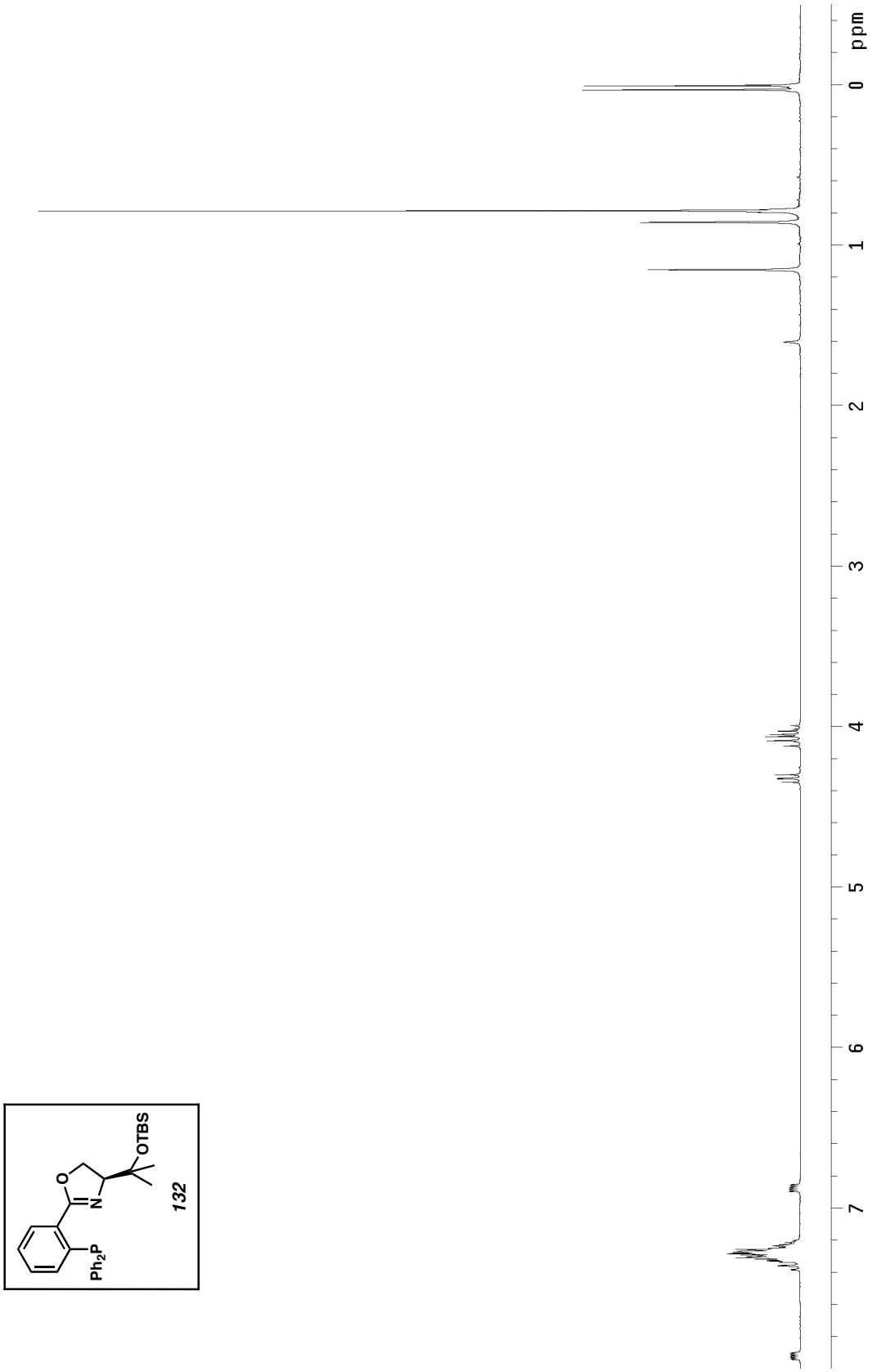


*Figure A1.21 ^{13}C NMR of compound **131** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
OTBS
O
N
Ph2P
132

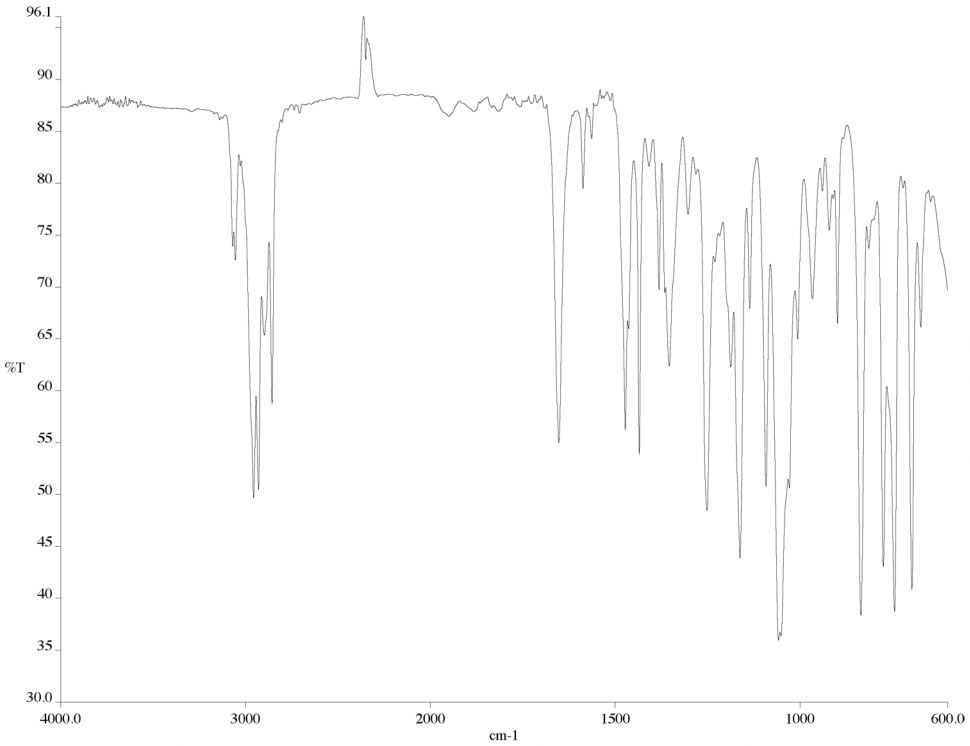


*Figure A1.23 IR of compound **132** (NaCl/film)*

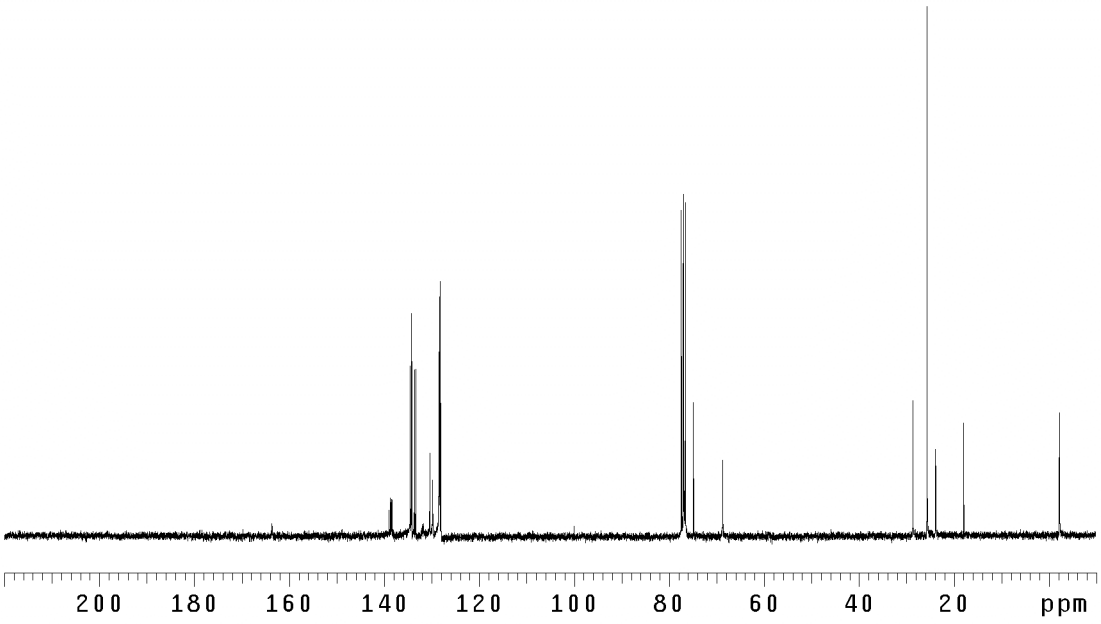
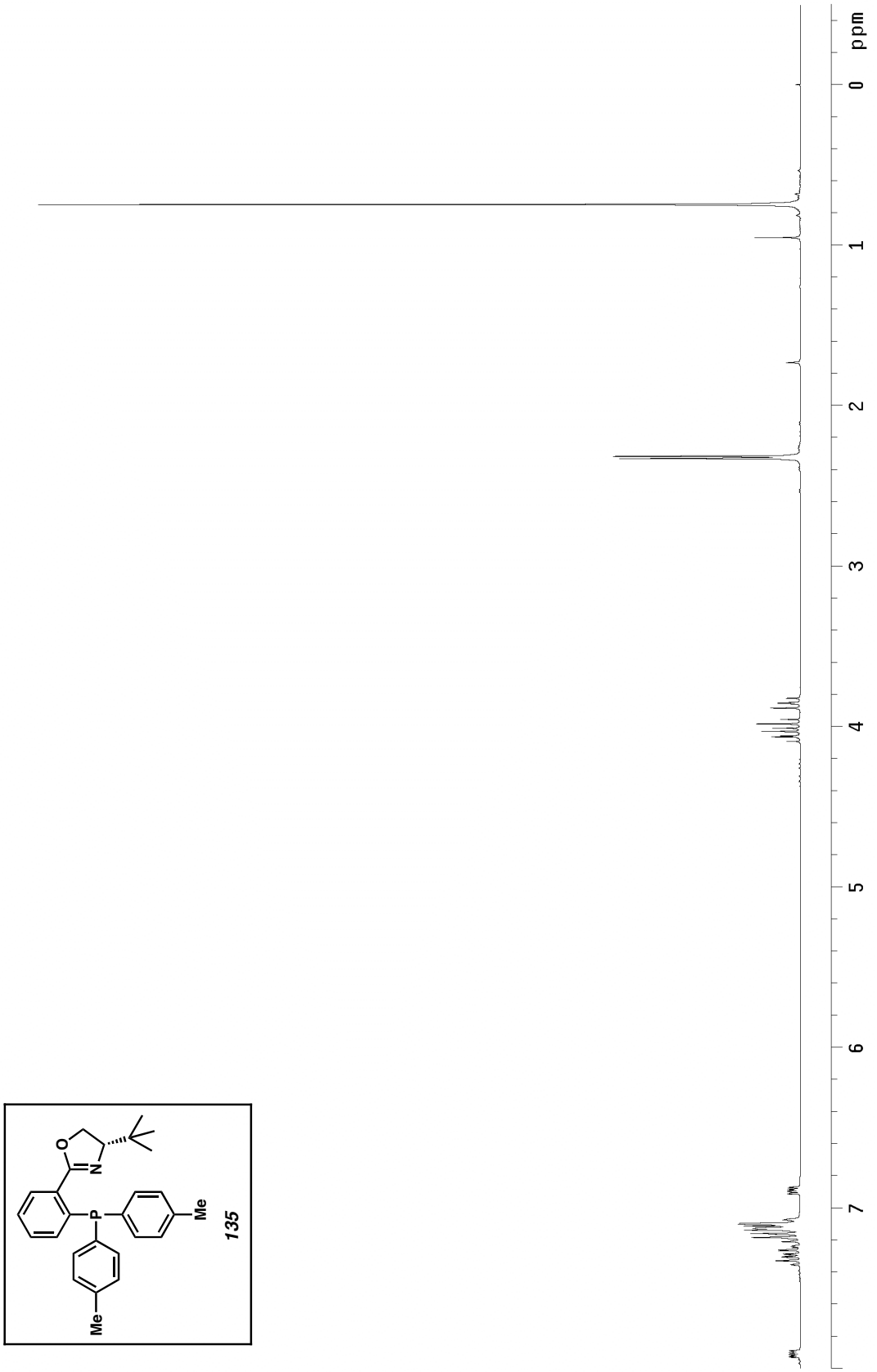


*Figure A1.24 ^{13}C NMR of compound **132** (75 MHz, $CDCl_3$)*



135

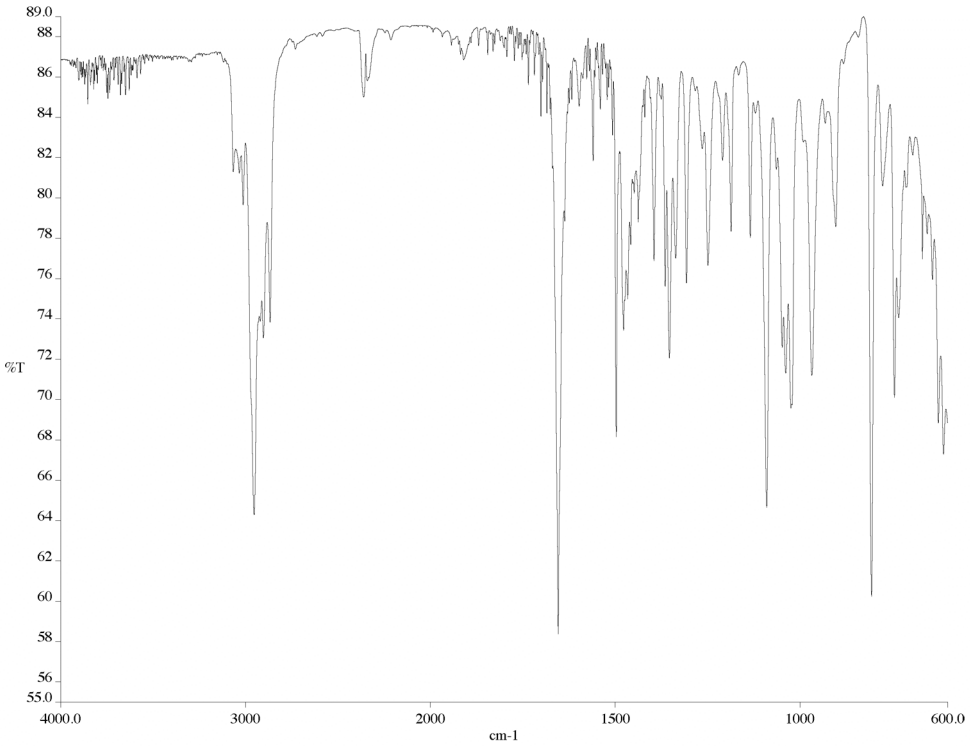


*Figure A1.26 IR of compound **135** (NaCl/film)*

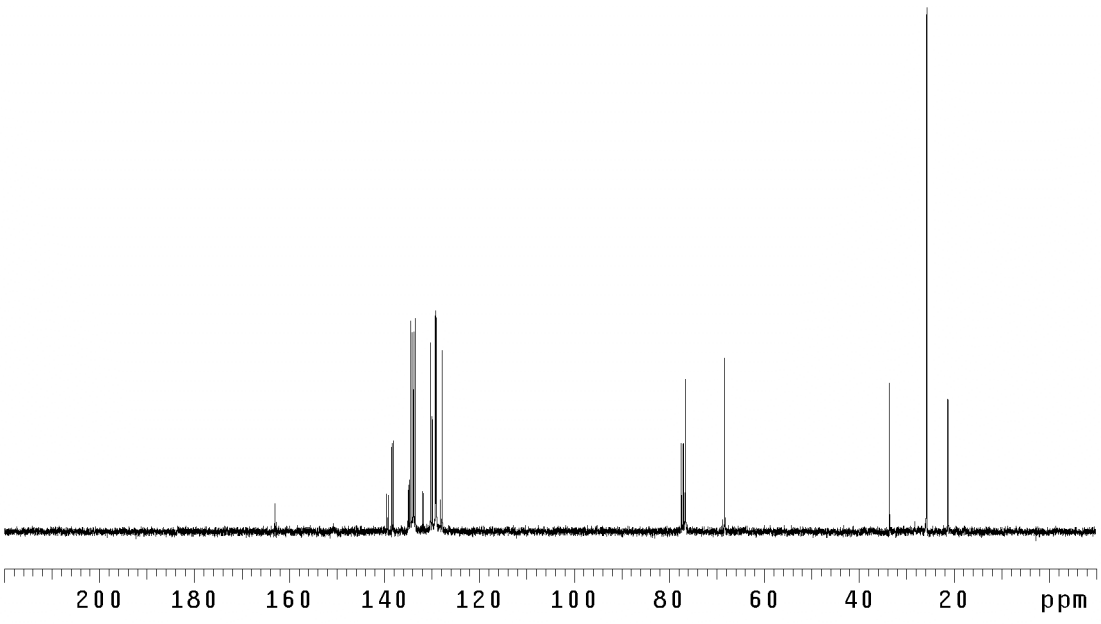
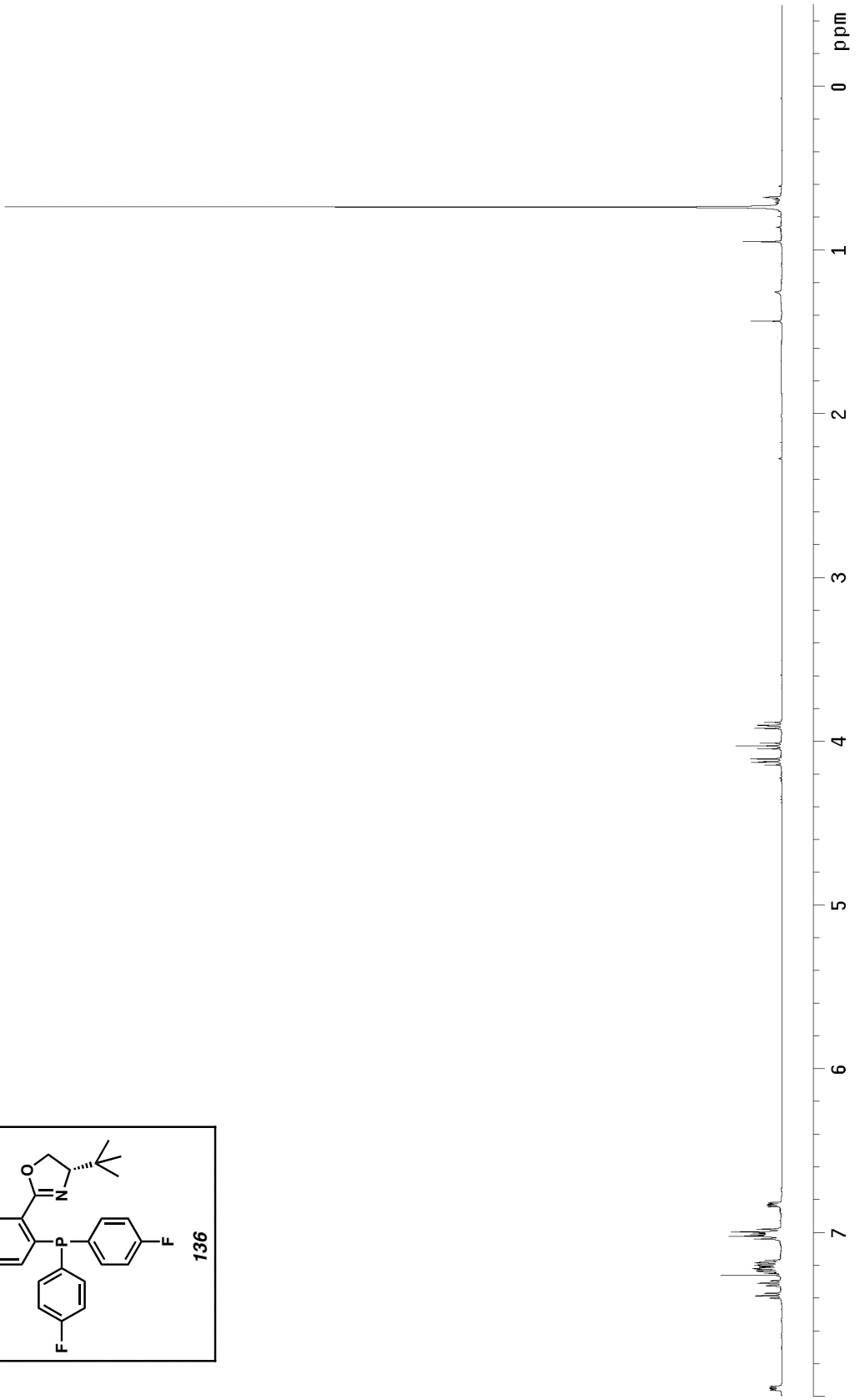
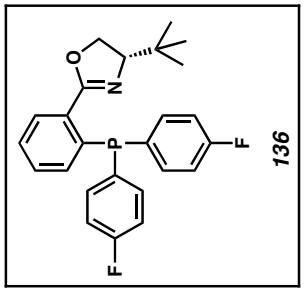


*Figure A1.27 ^{13}C NMR of compound **135** (75 MHz, $CDCl_3$)*





136

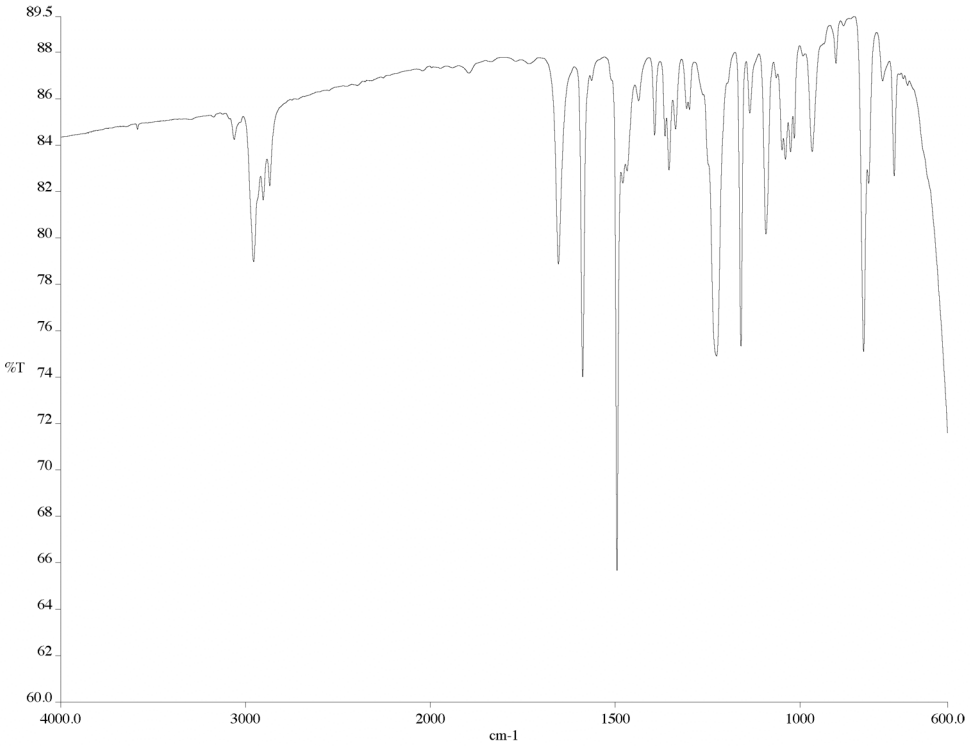


*Figure A1.29 IR of compound **136** (NaCl/film)*

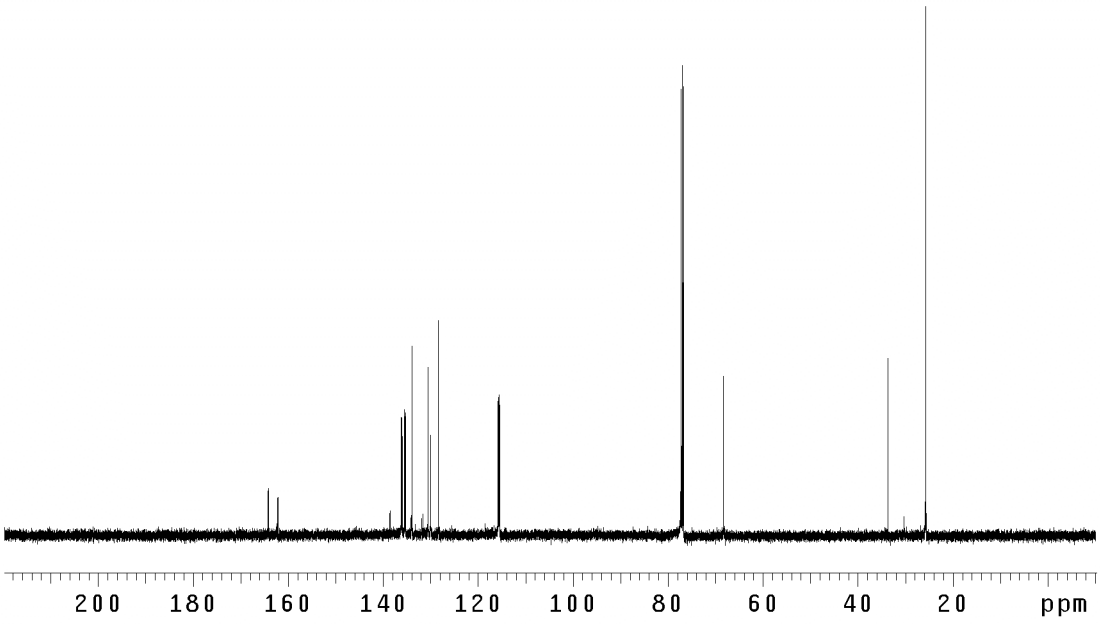
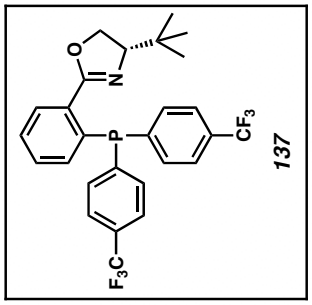
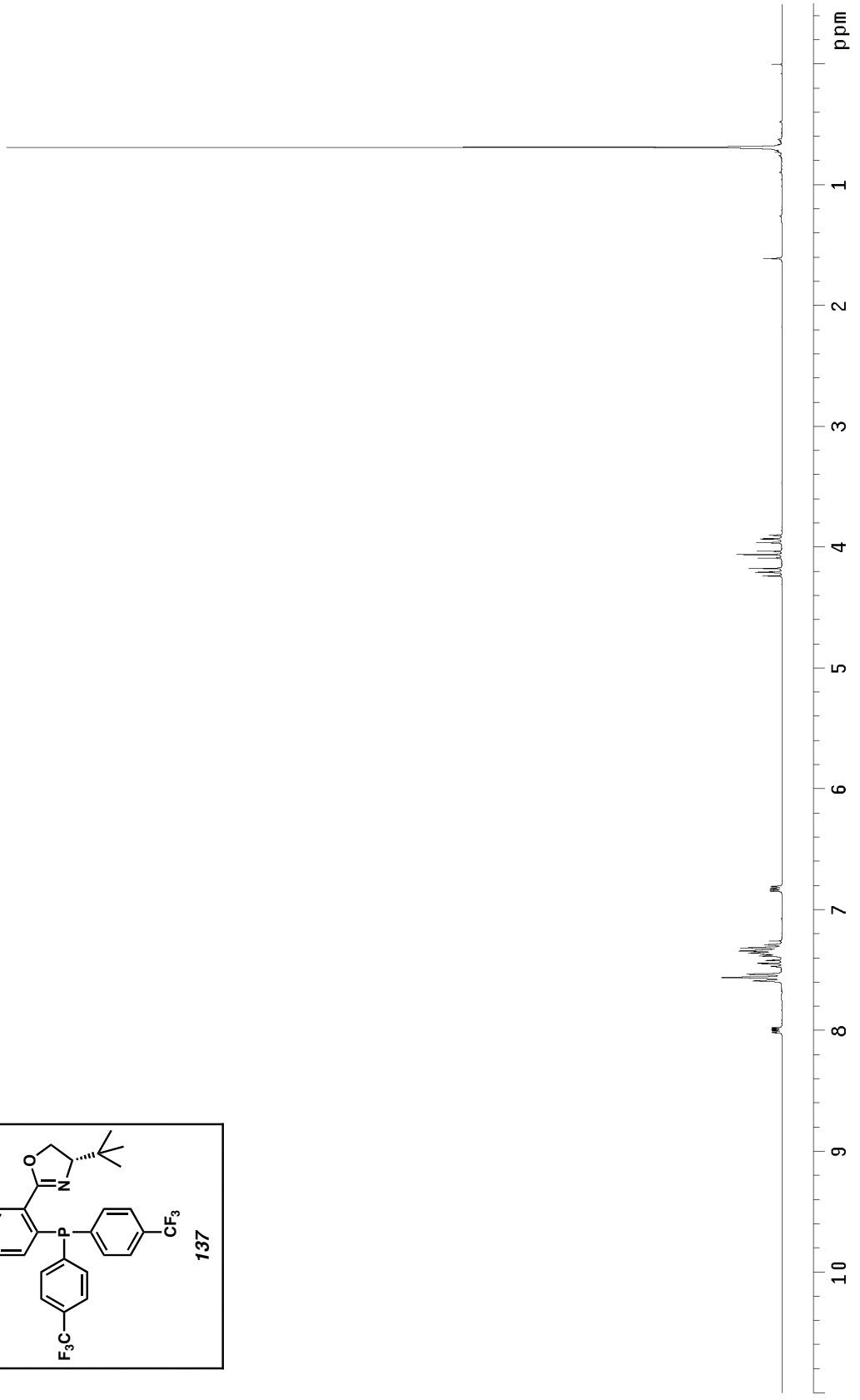


*Figure A1.30 ^{13}C NMR of compound **136** (125 MHz, $CDCl_3$)*



137



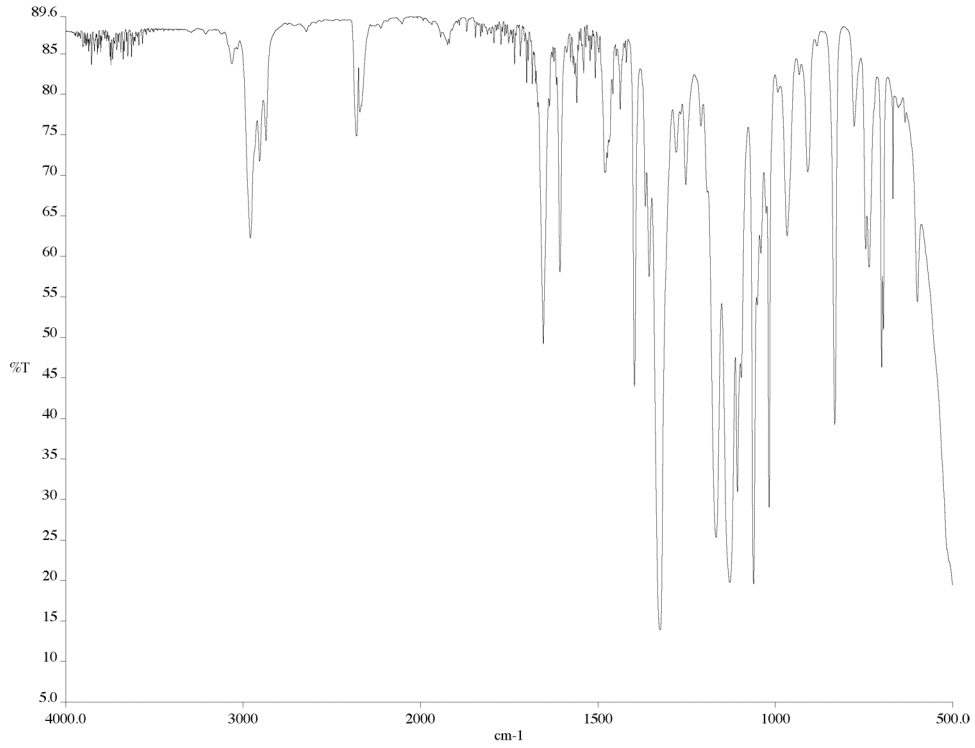


*Figure A1.32 IR of compound **137** (NaCl/film)*

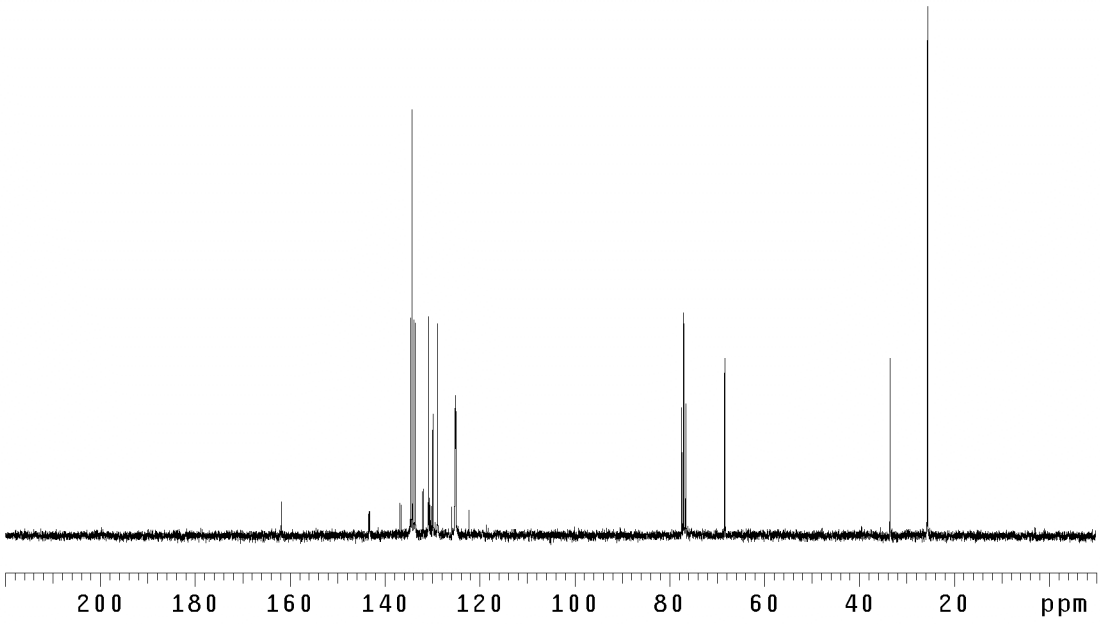
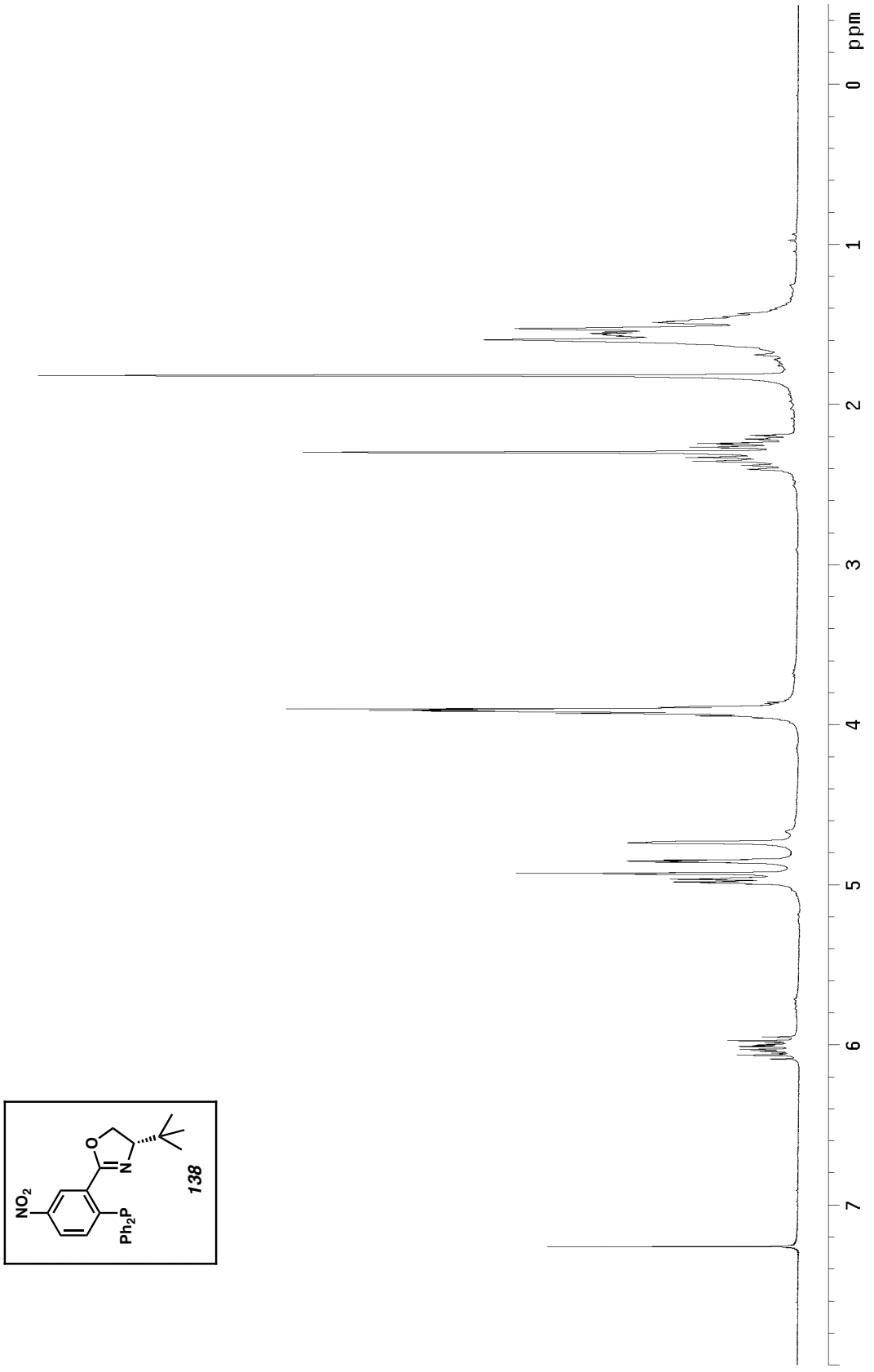


*Figure A1.33 ^{13}C NMR of compound **137** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
NO2
Ph2P
O
N
138

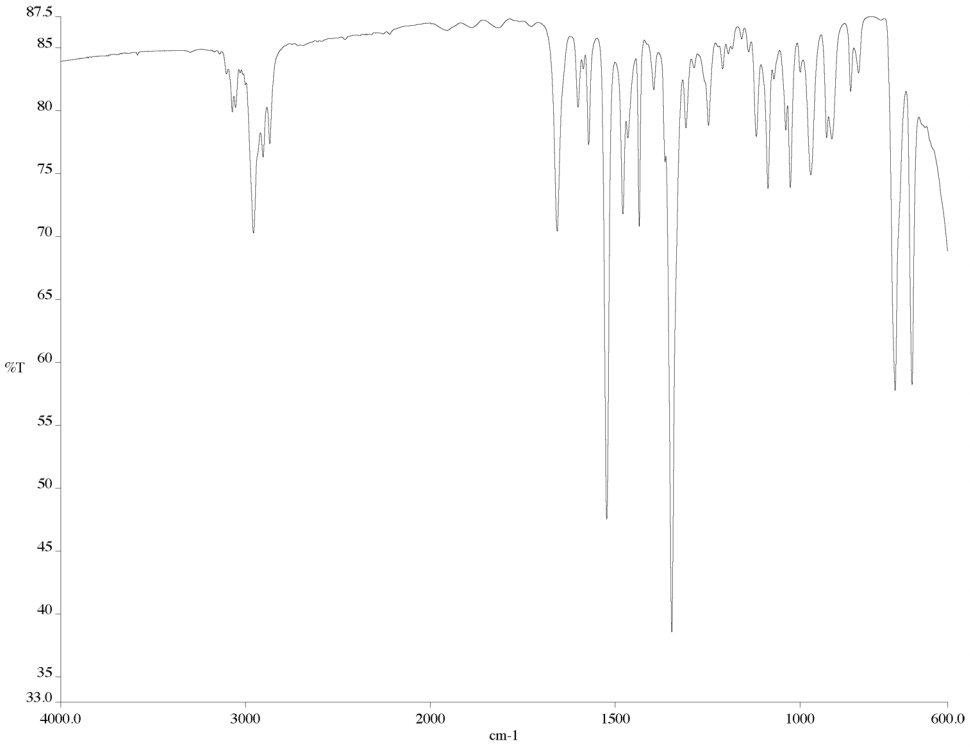


*Figure A1.35 IR of compound **138** (NaCl/film)*

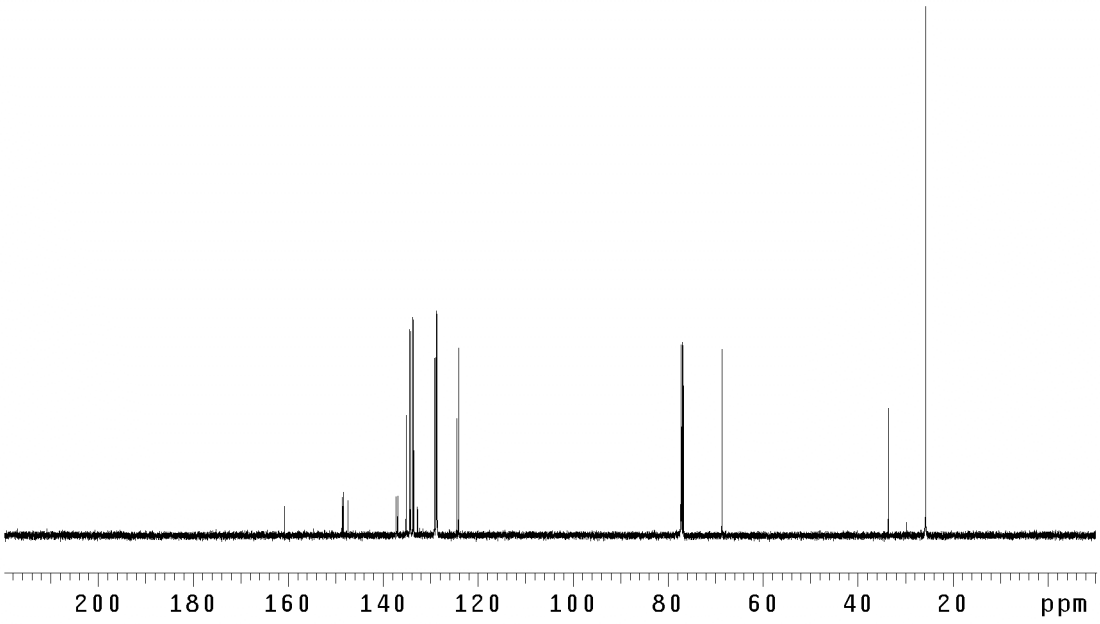
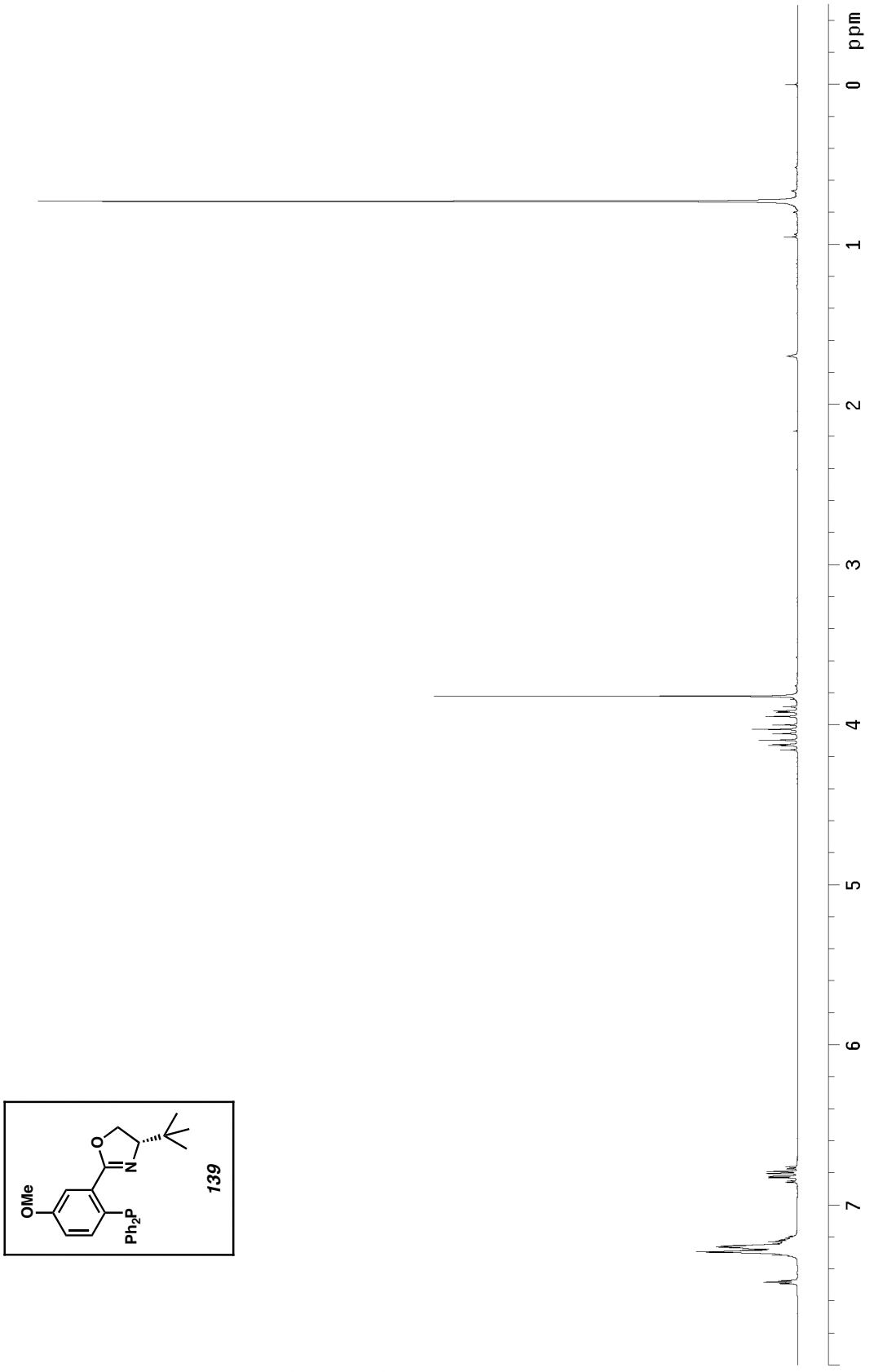


*Figure A1.36 ^{13}C NMR of compound **138** (125 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
OMe
Ph2P
O
N
139

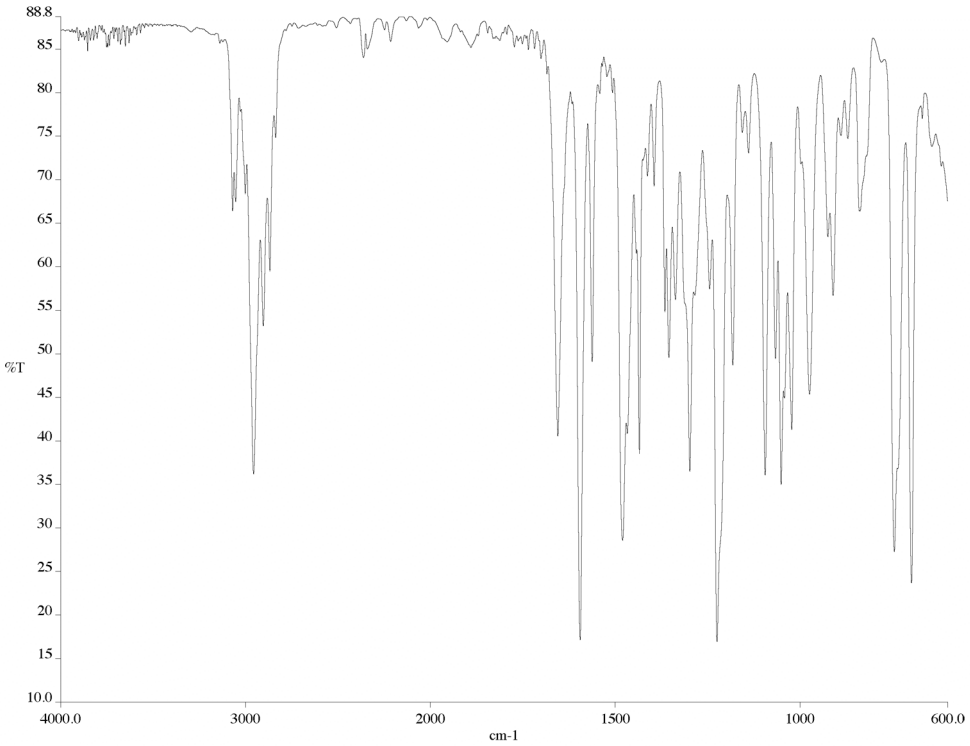


*Figure A1.38 IR of compound **139** (NaCl/film)*

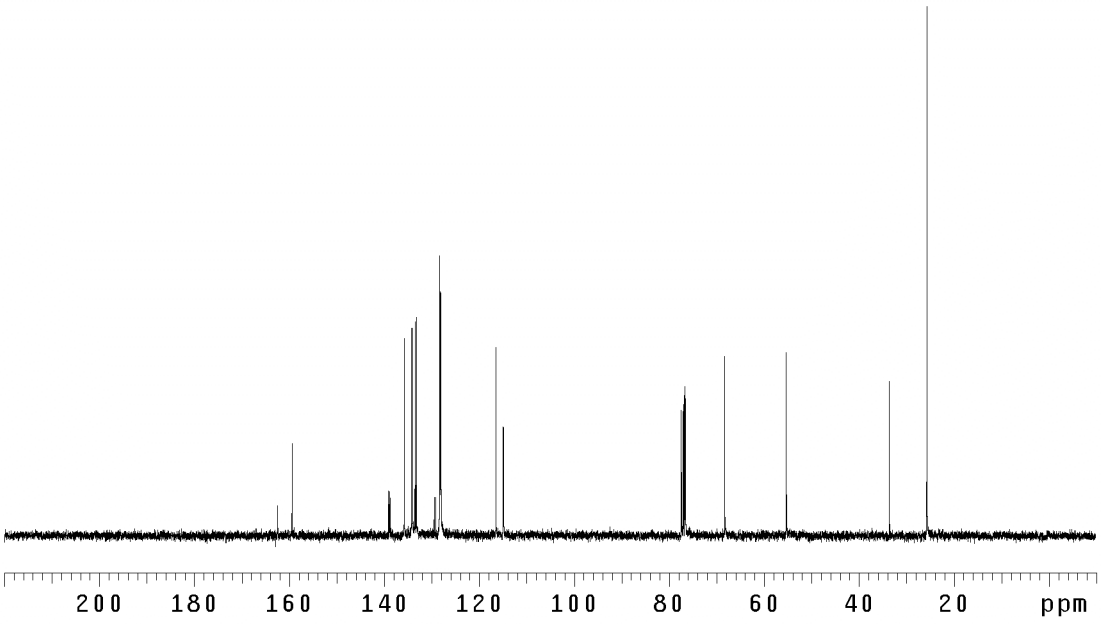


*Figure A1.39 ^{13}C NMR of compound **139** (75 MHz, $CDCl_3$)*

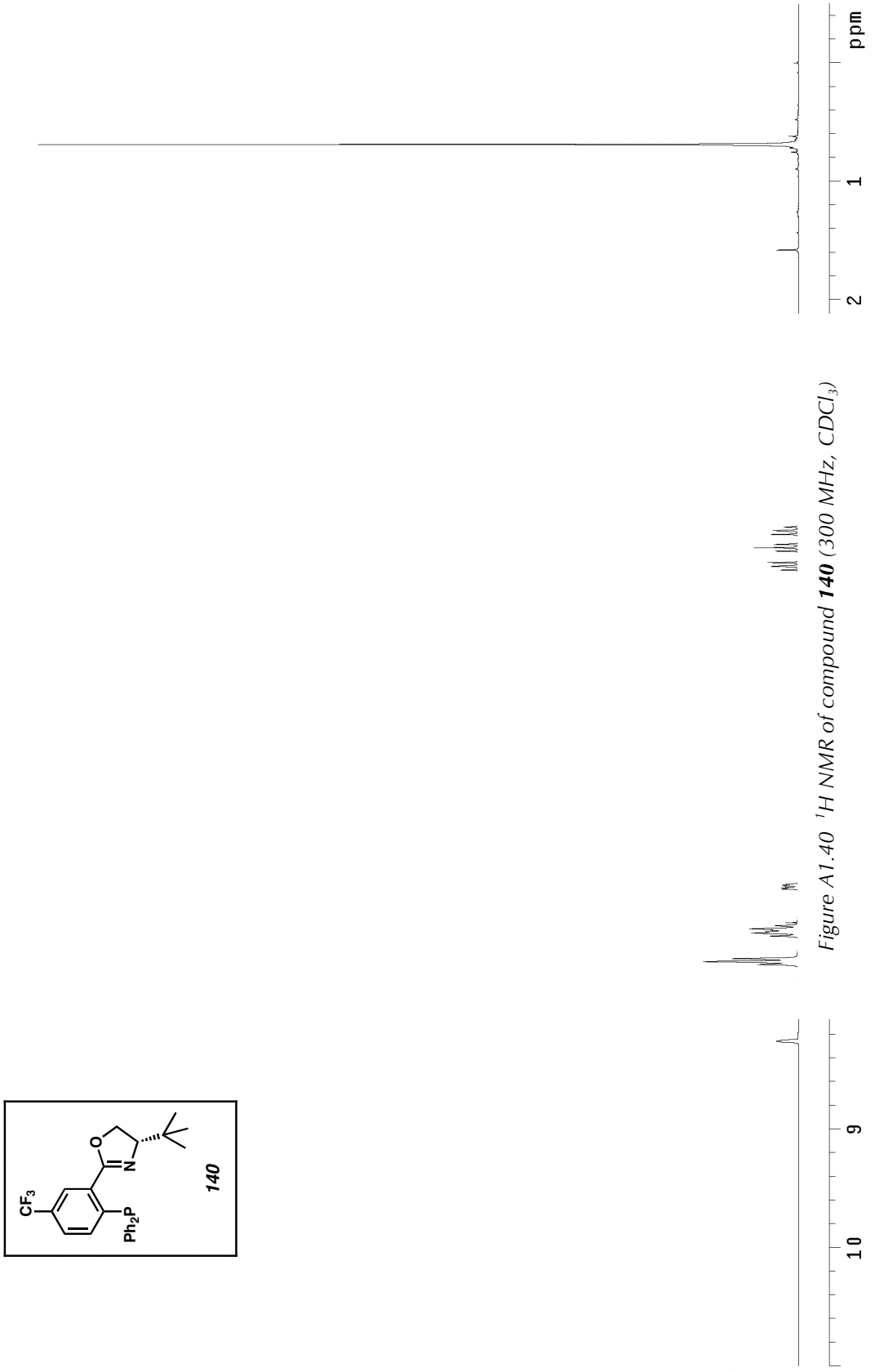


*Figure A1.40 ^{1}H NMR of compound **140** (300 MHz, $CDCl_3$)*

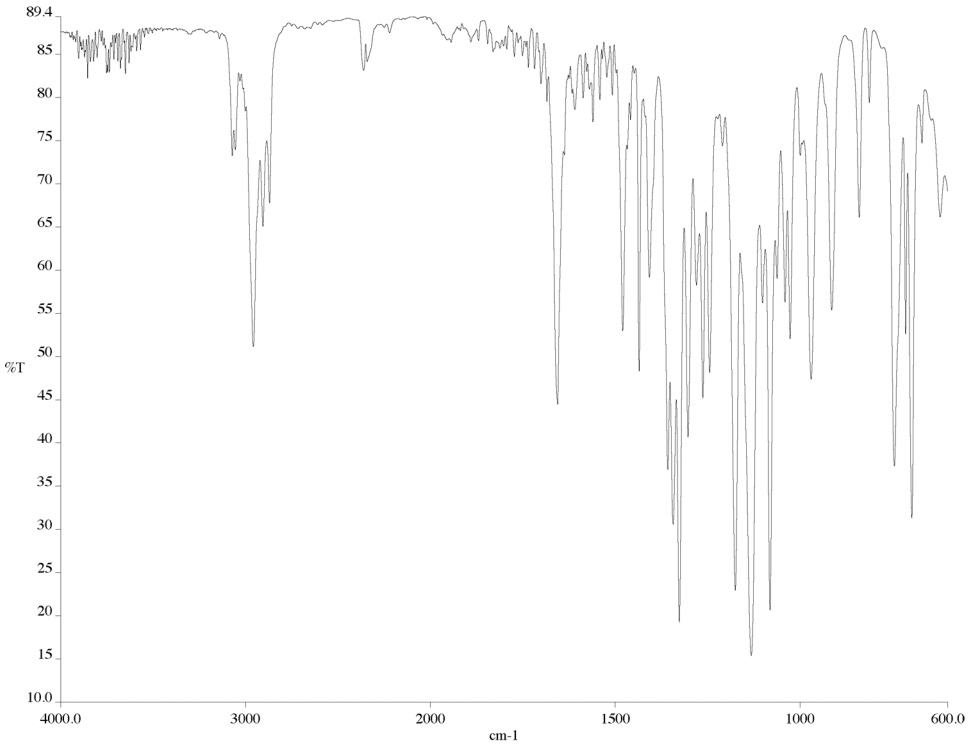


*Figure A1.41 IR of compound **140** (NaCl/film)*

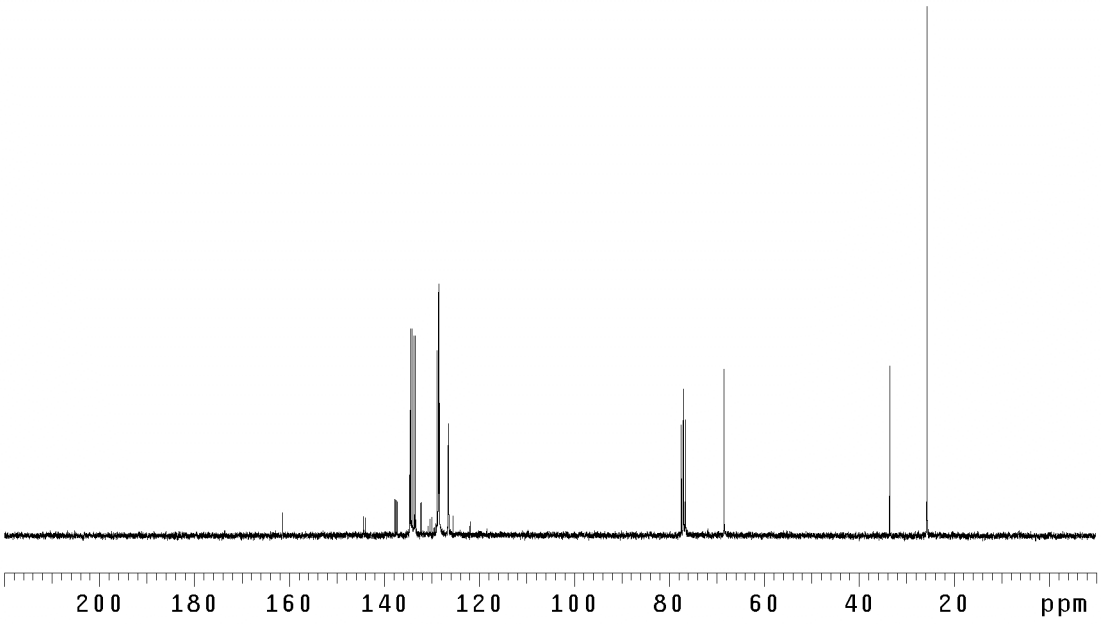
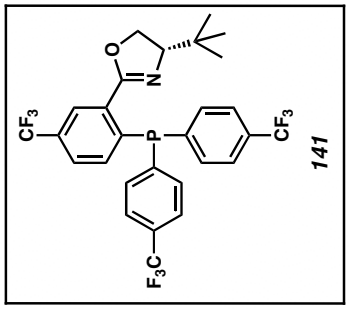


*Figure A1.42 ^{13}C NMR of compound **140** (75 MHz, $CDCl_3$)*



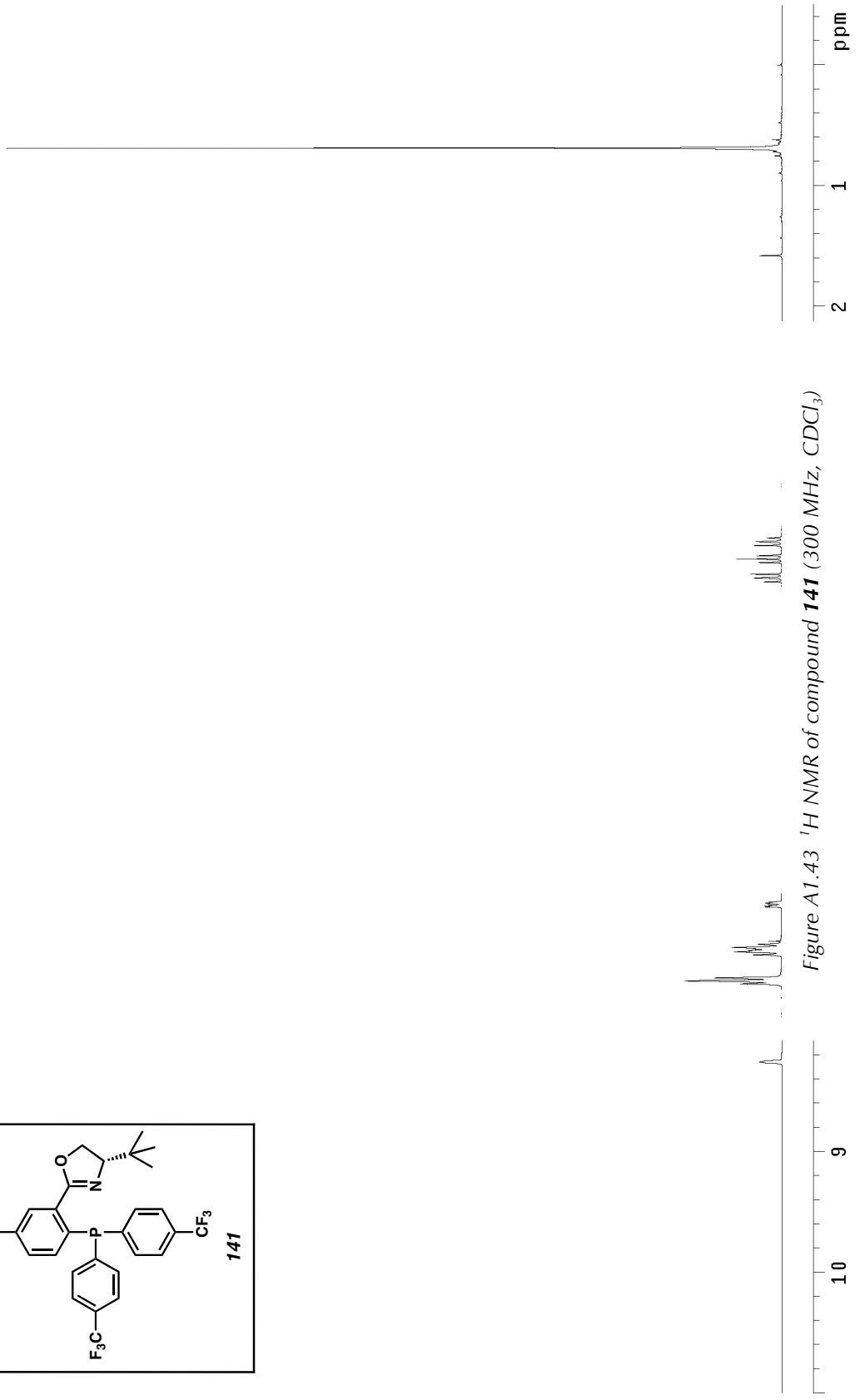


*Figure A1.43 ^{1}H NMR of compound **141** (300 MHz, $CDCl_3$)*

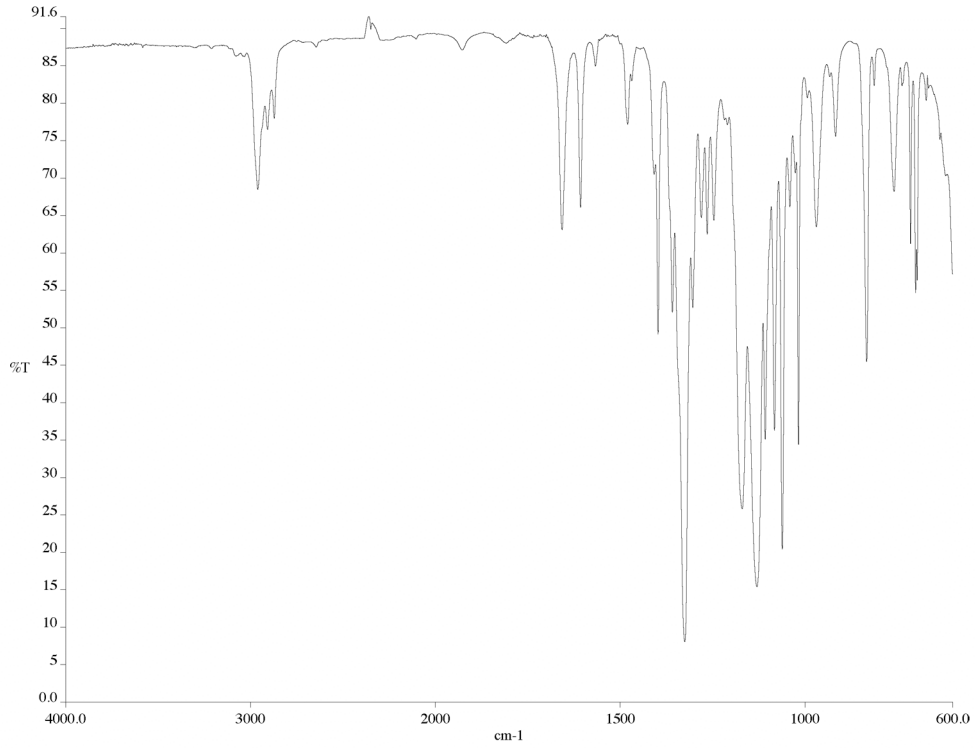


*Figure A1.44 IR of compound **141** (NaCl/film)*

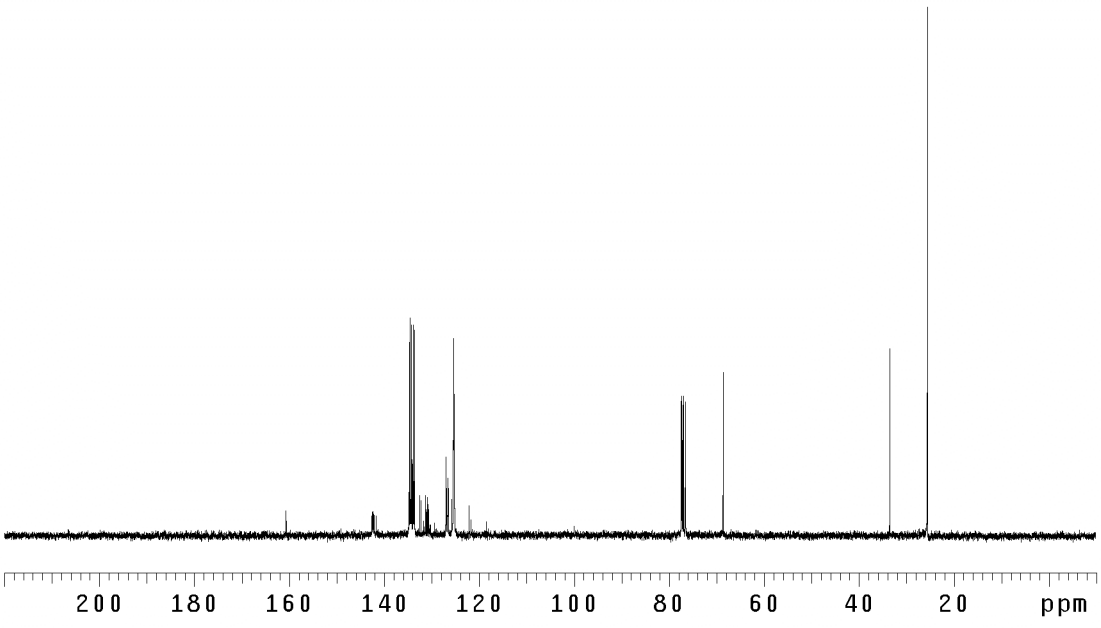
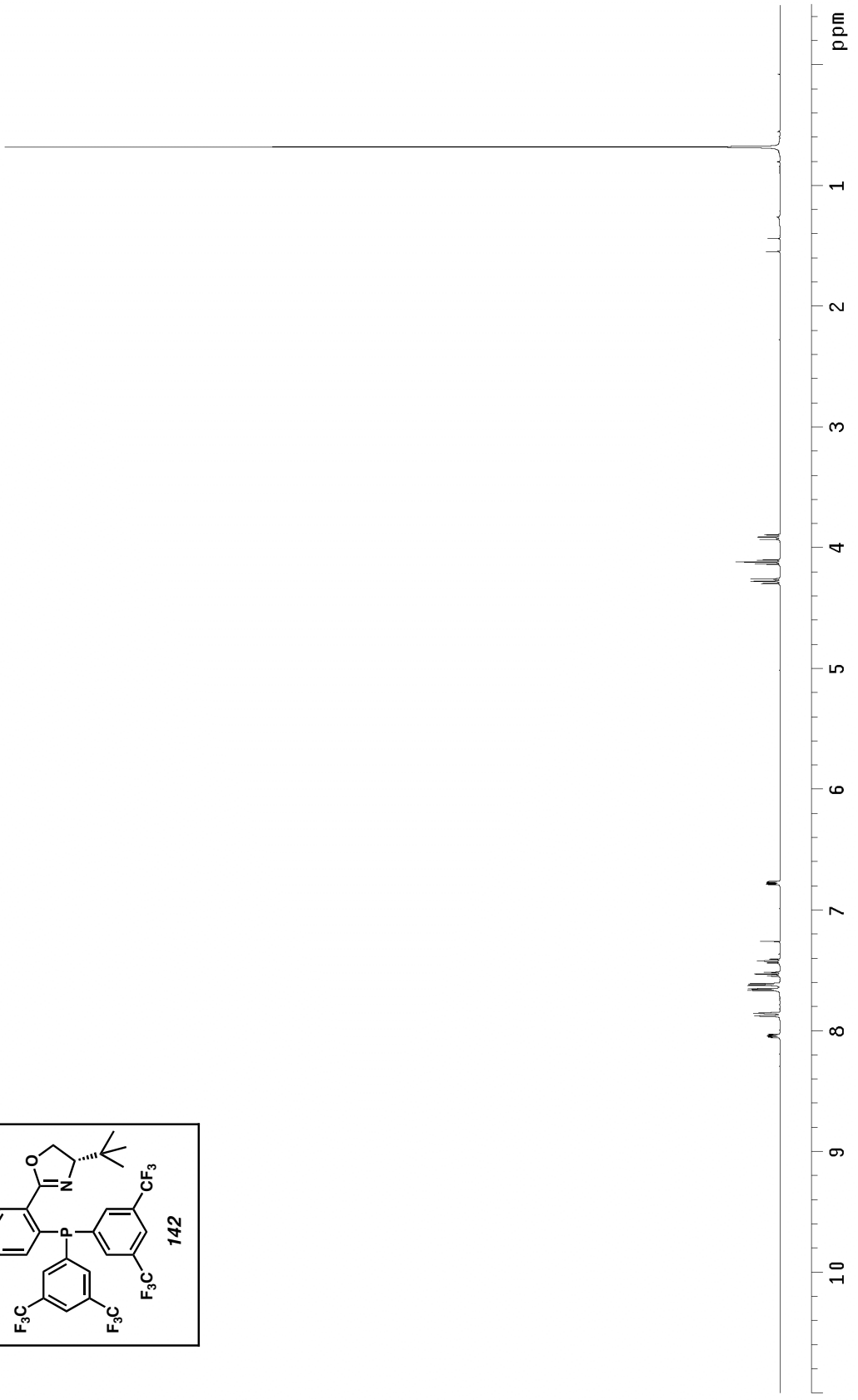
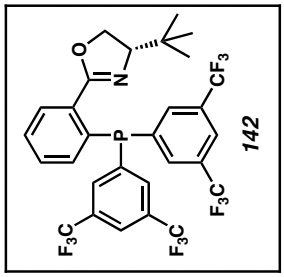


*Figure A1.45 ^{13}C NMR of compound **141** (75 MHz, $CDCl_3$)*





142

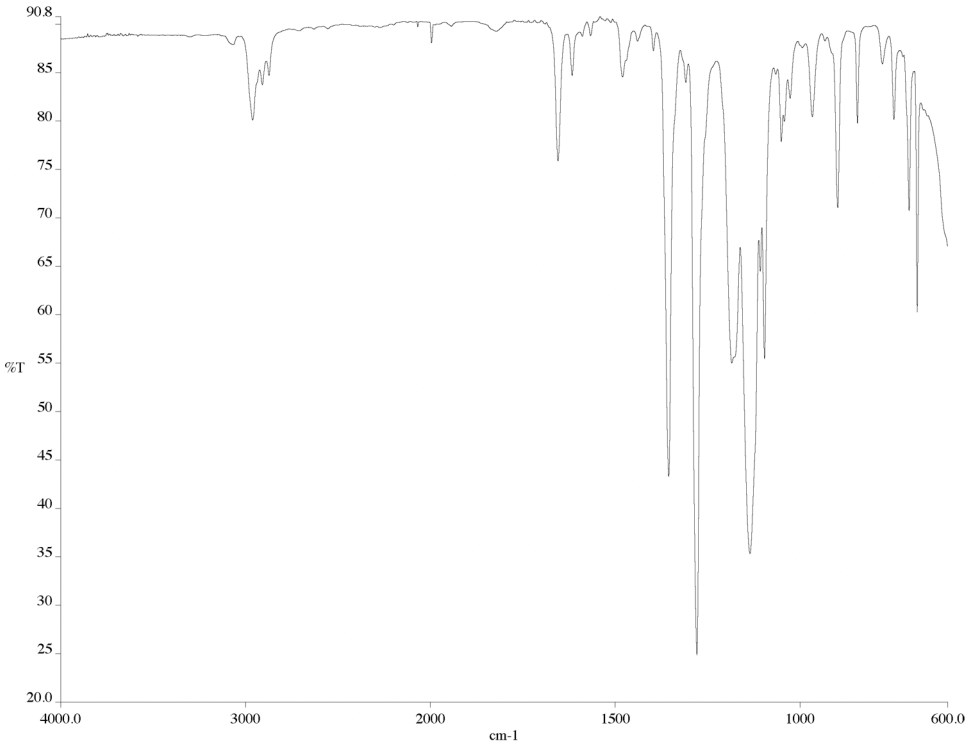


*Figure A1.47 IR of compound **142** (NaCl/film)*

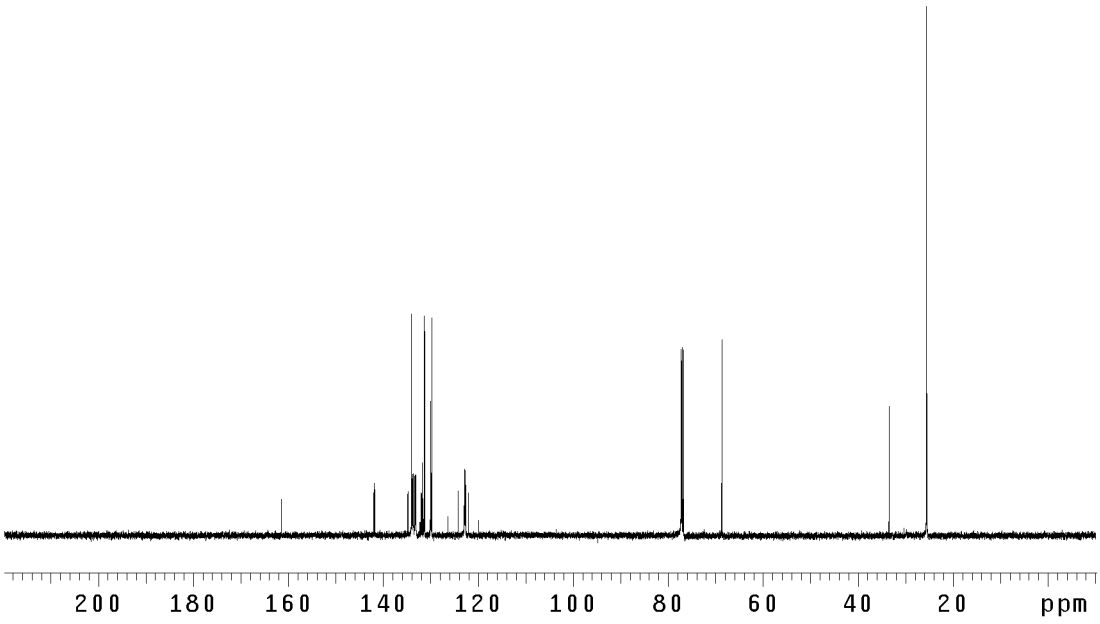
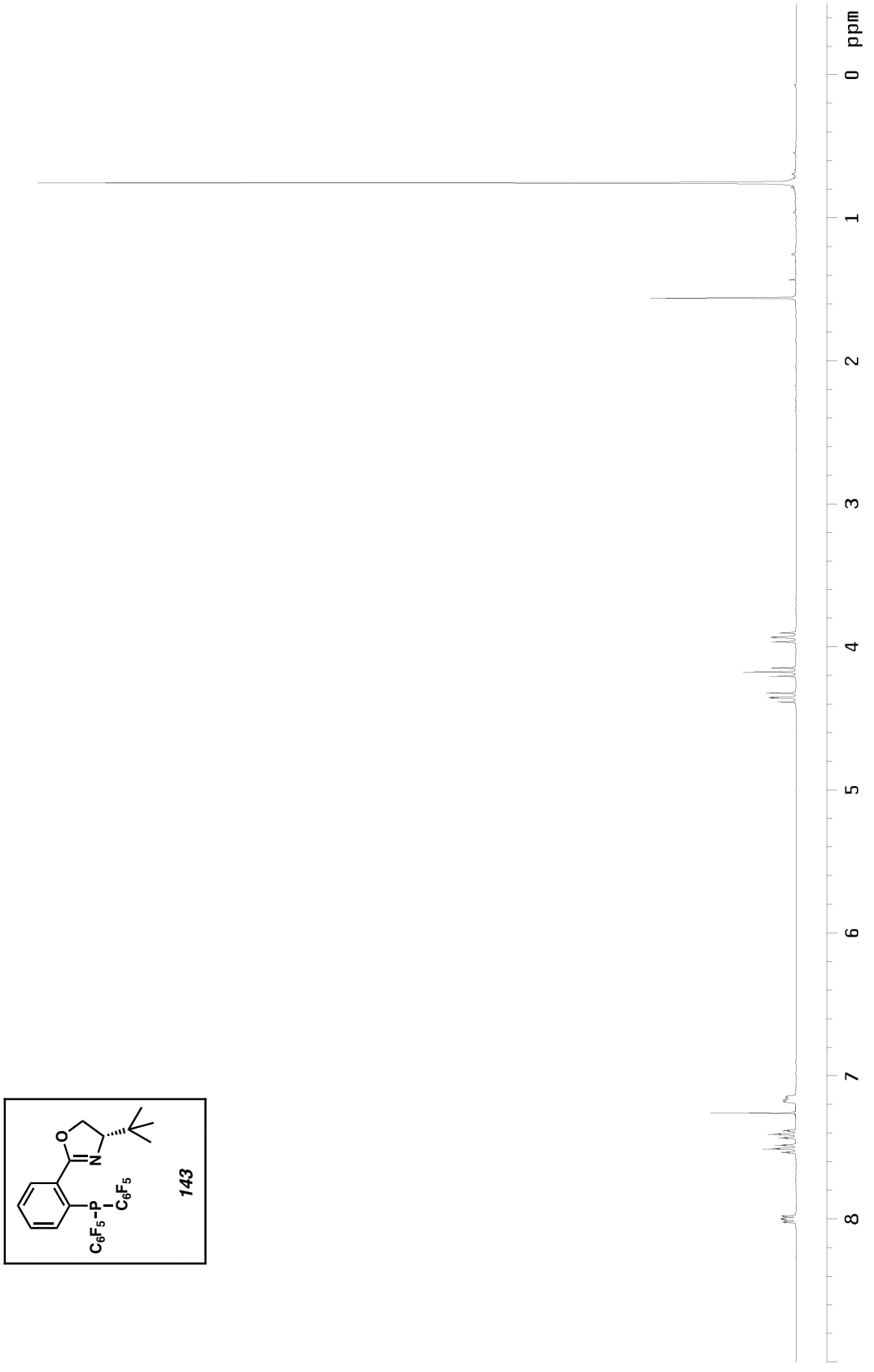


*Figure A1.48 ^{13}C NMR of compound **142** (125 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
8
O
N
C_6F_5–P–C_6F_5
143

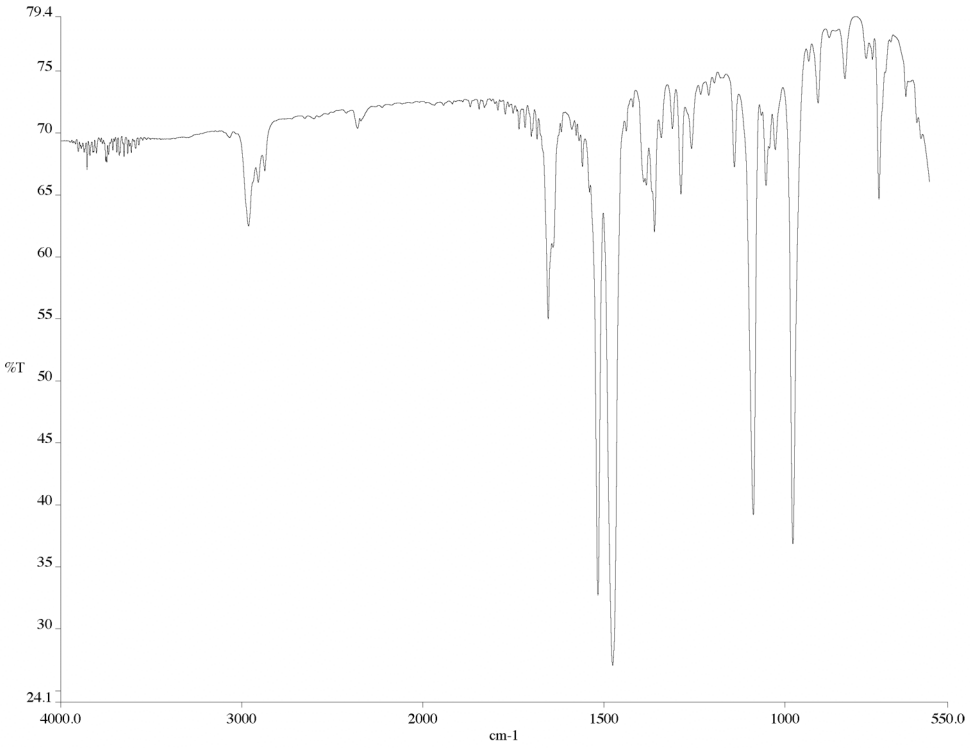


*Figure A1.50 IR of compound **143** (NaCl/film)*

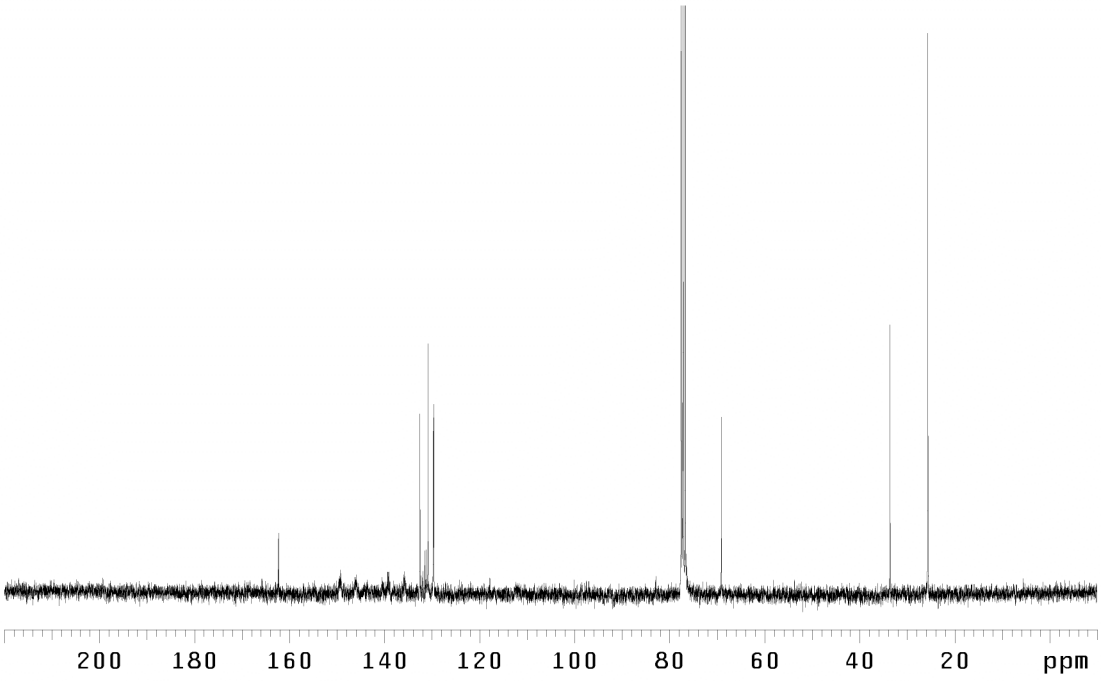
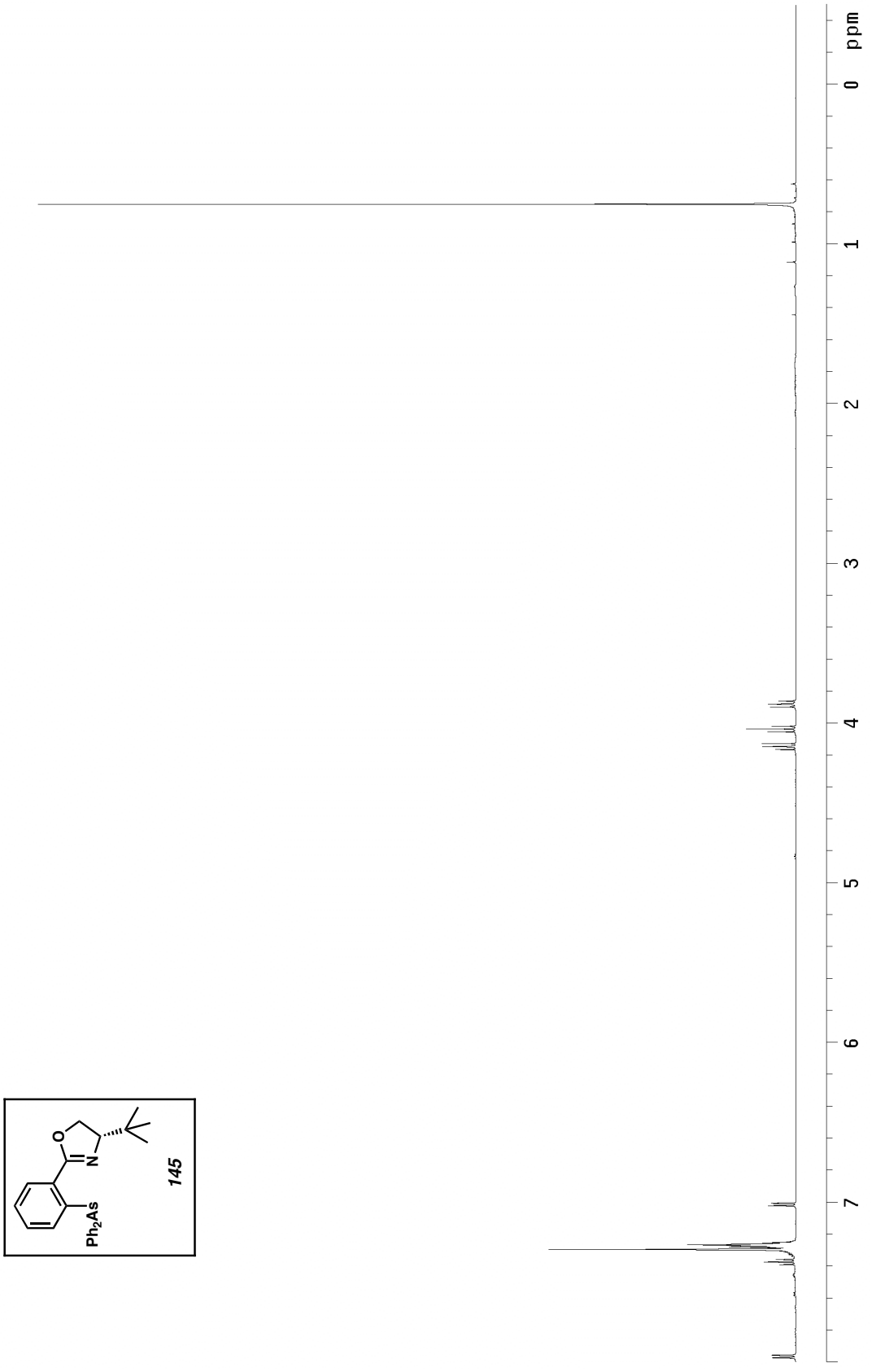


*Figure A1.51 ^{13}C NMR of compound **143** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
N
Ph2As
145

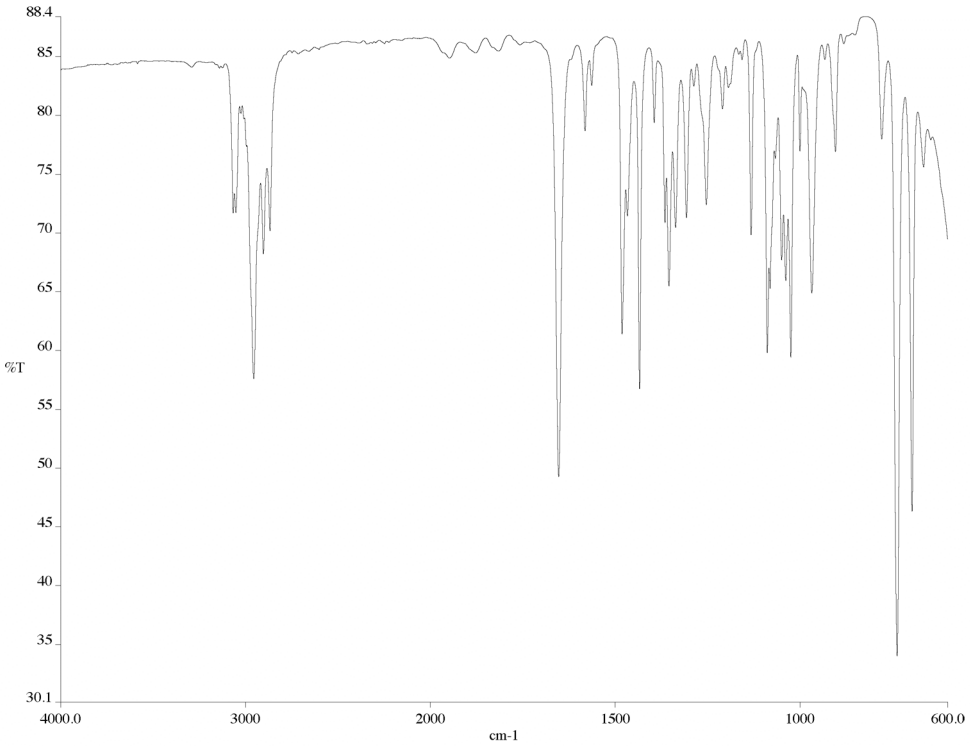


*Figure A1.53 IR of compound **145** (NaCl/film)*

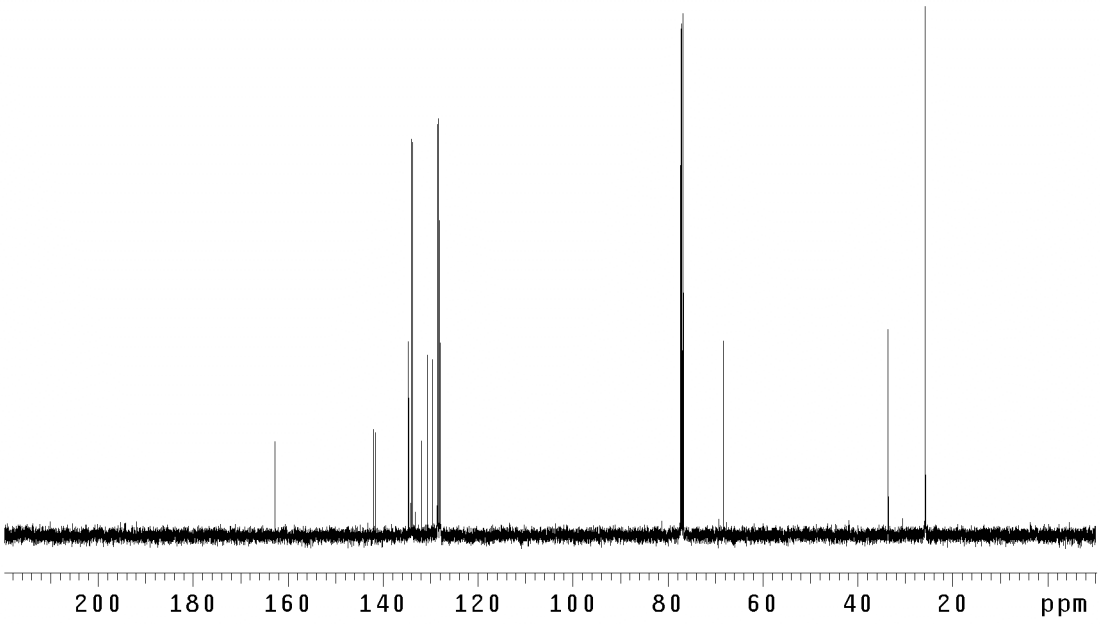
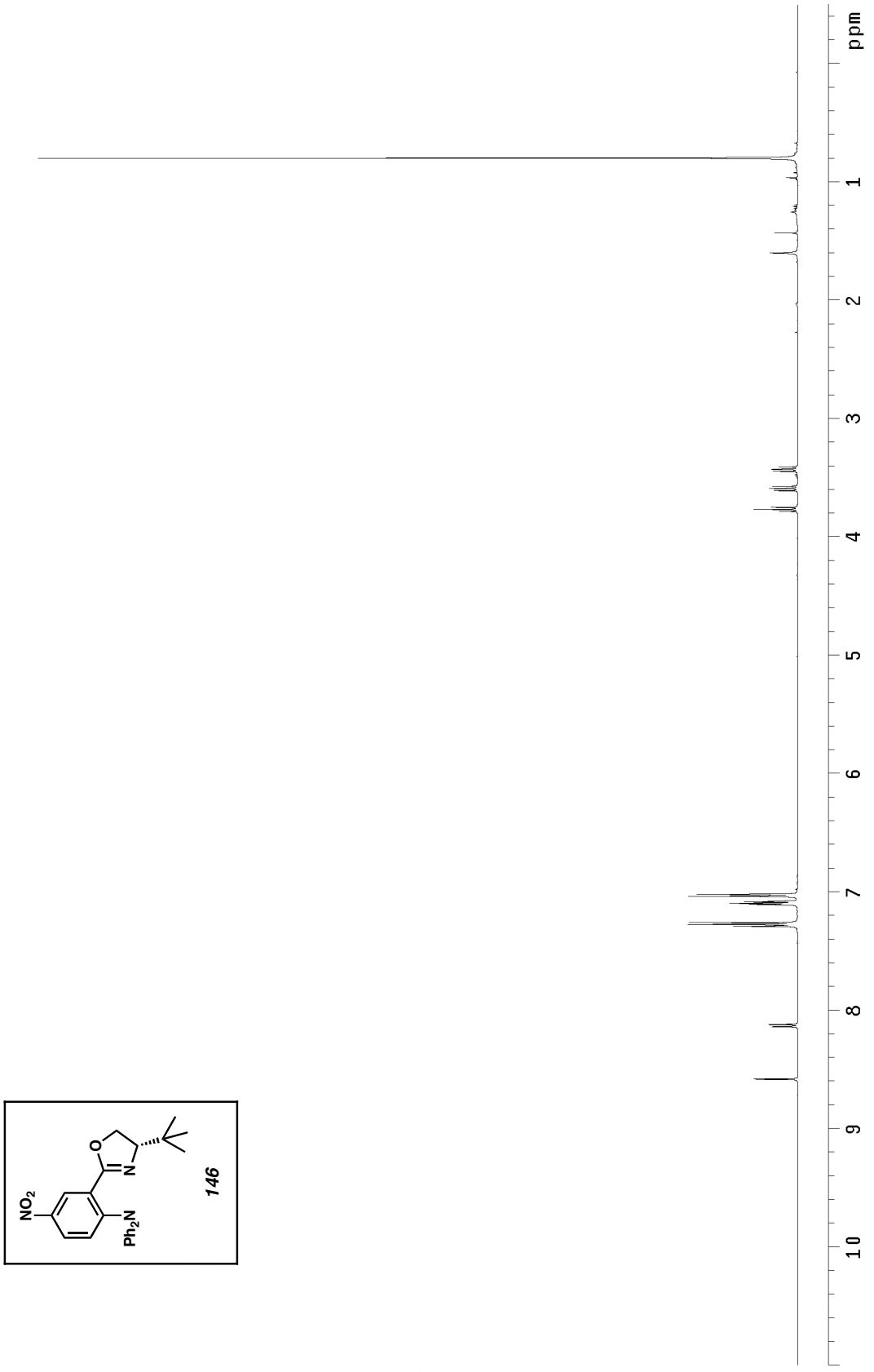


*Figure A1.54 ^{13}C NMR of compound **145** (125 MHz, $CDCl_3$)*


ppm
1
2
3
4
5
6
7
8
9
10
O
N
NO2
Ph2N
146

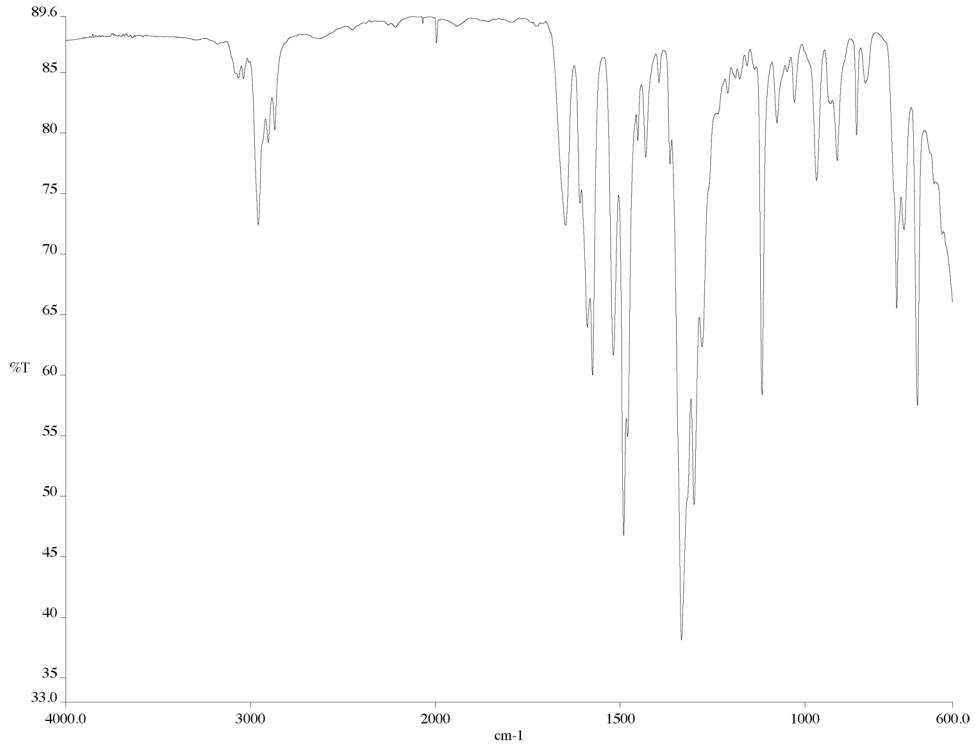


*Figure A1.56 IR of compound **146** (NaCl/film)*

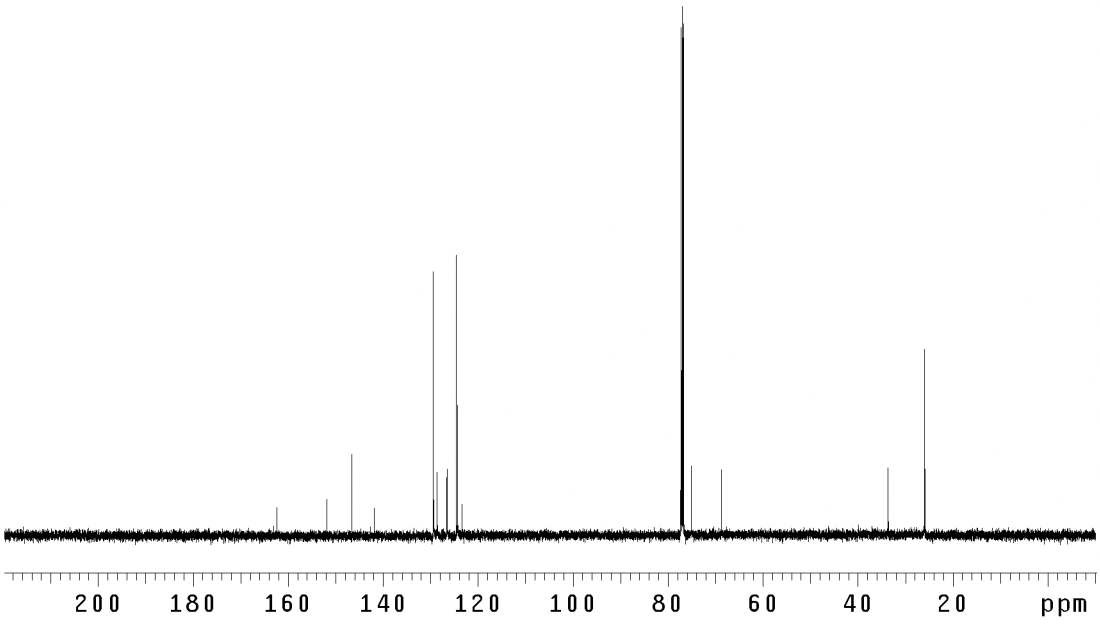
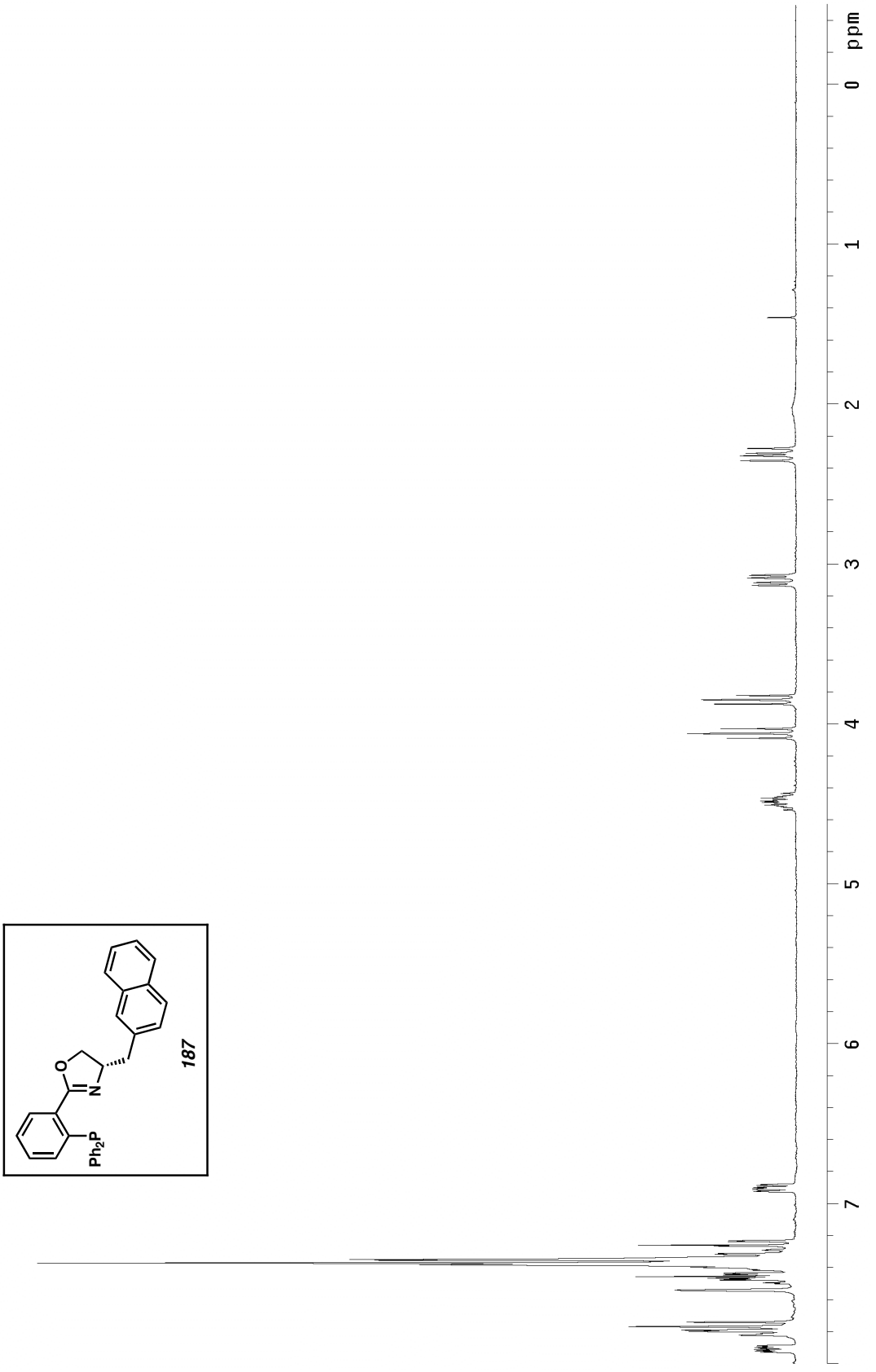


*Figure A1.57 ^{13}C NMR of compound **146** (125 MHz, $CDCl_3$)*


O
N
Ph_2P
187
ppm
0
1
2
3
4
5
6
7

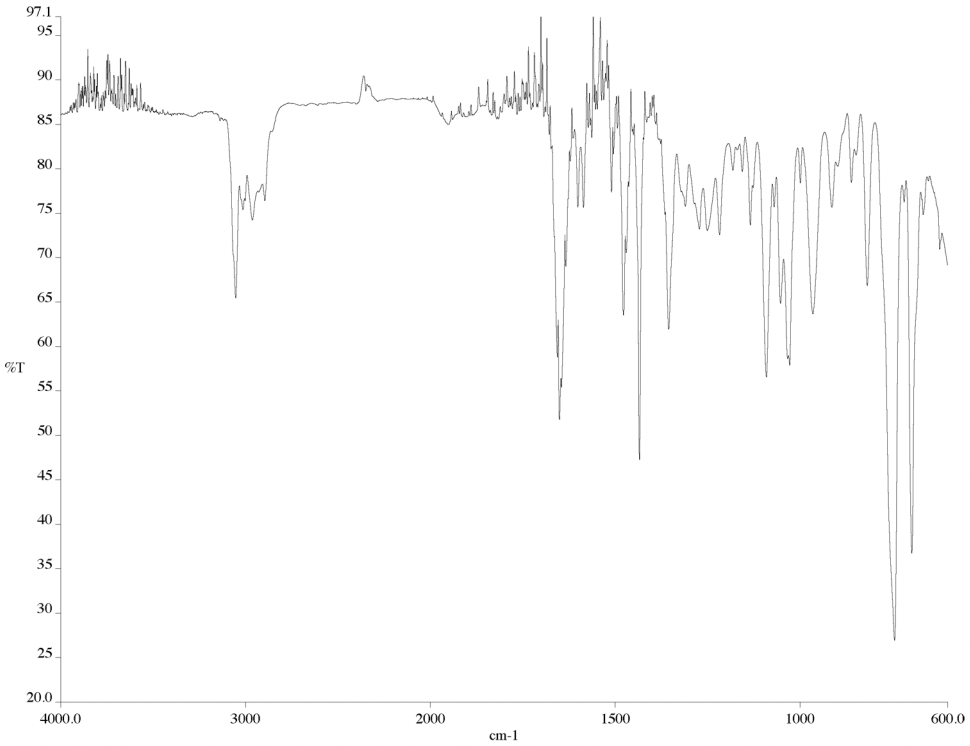


*Figure A1.59 IR of compound **187** (NaCl/film)*

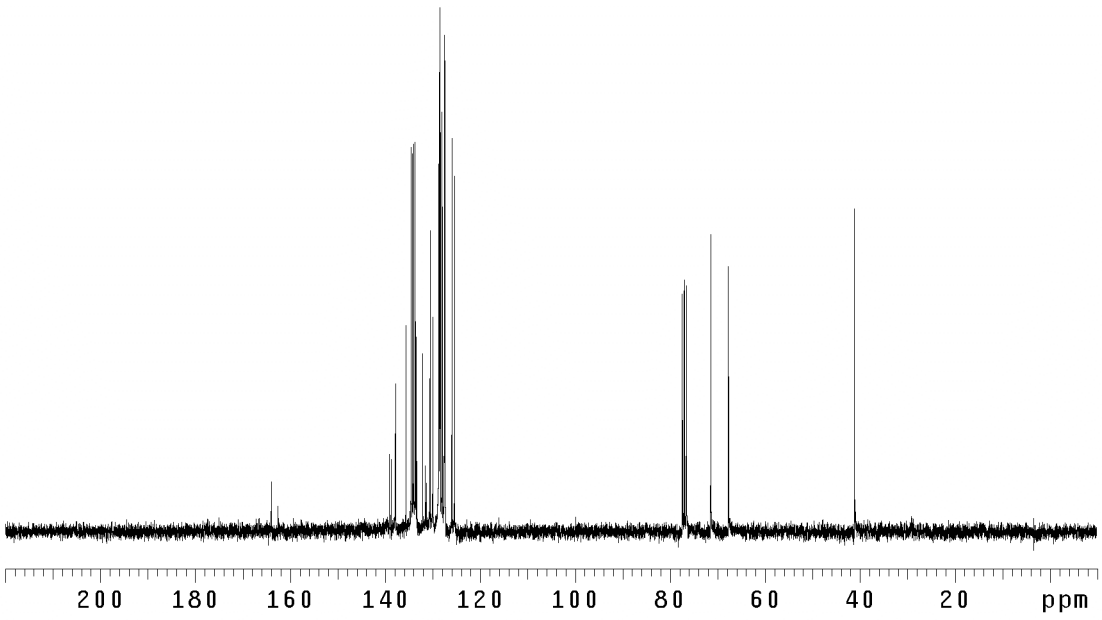
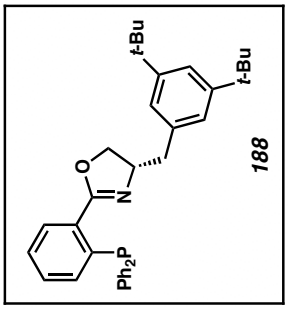
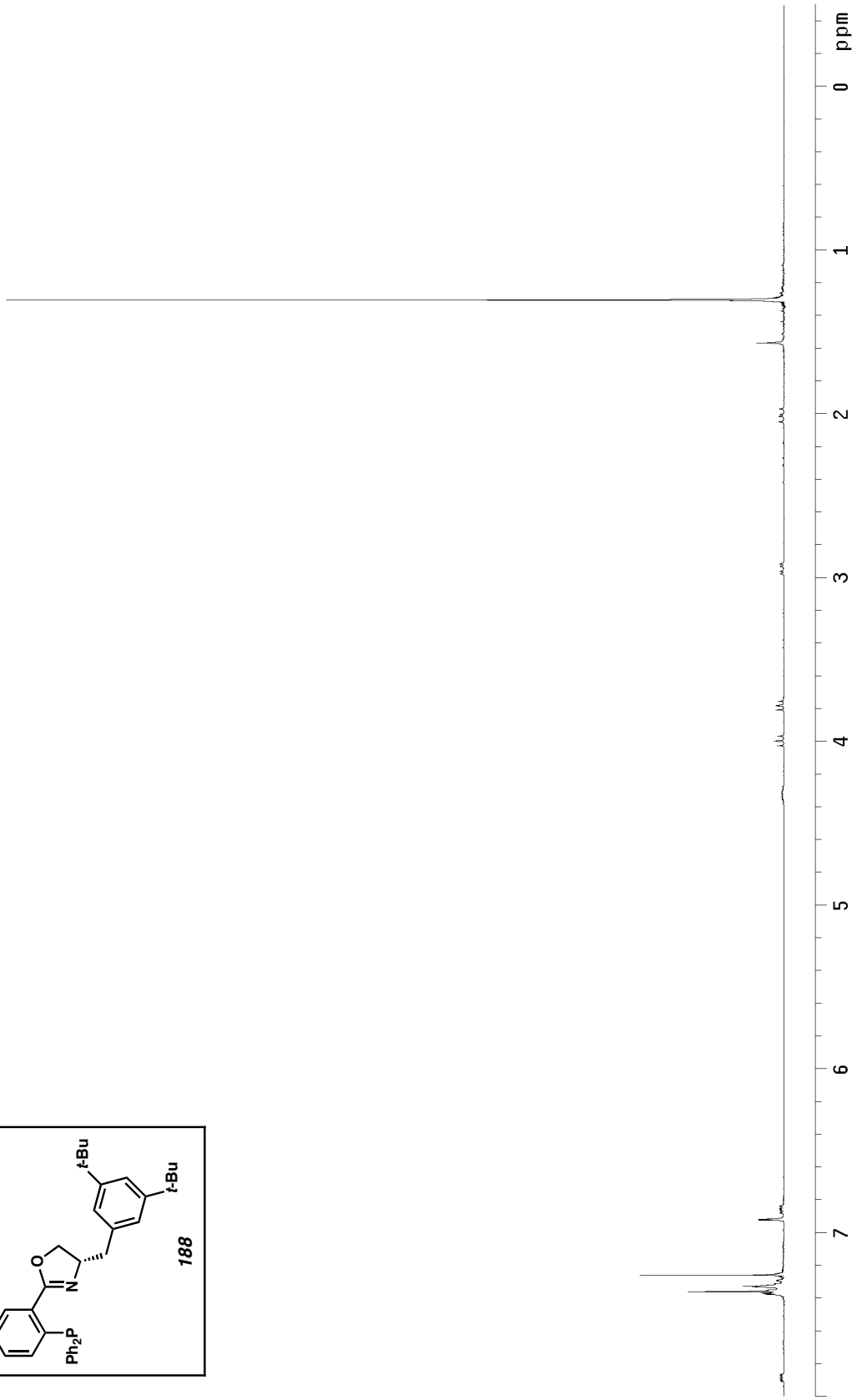


*Figure A1.60 ^{13}C NMR of compound **187** (75 MHz, $CDCl_3$)*


t-Bu
t-Bu
O
N
Ph2P
188


ppm
0
1
2
3
4
5
6
7

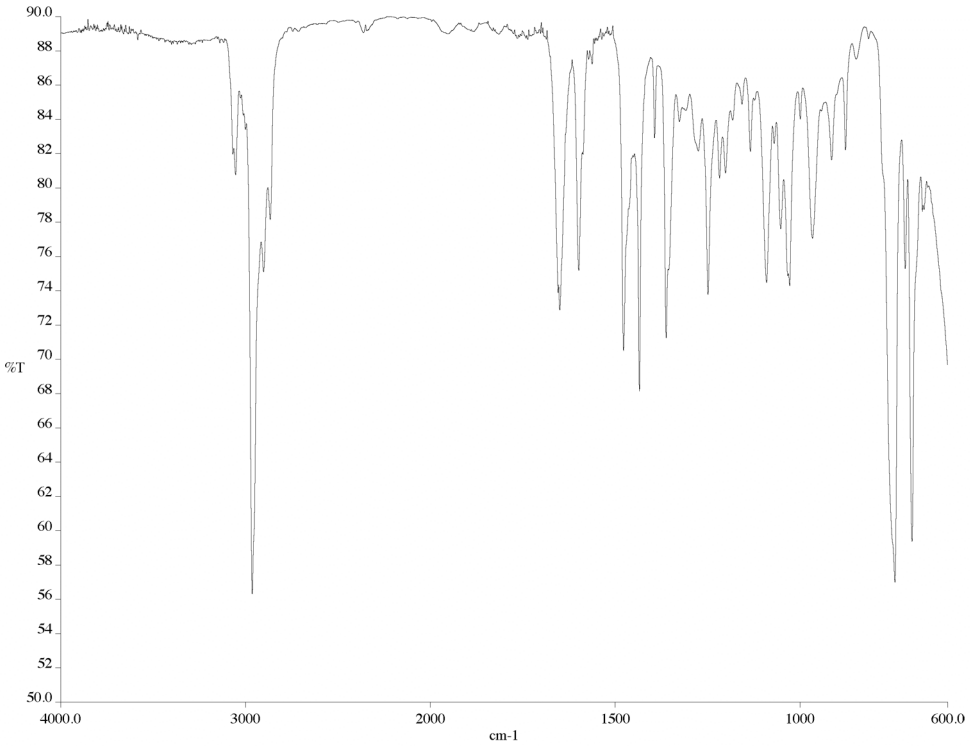


*Figure A1.62 IR of compound **188** (NaCl/film)*

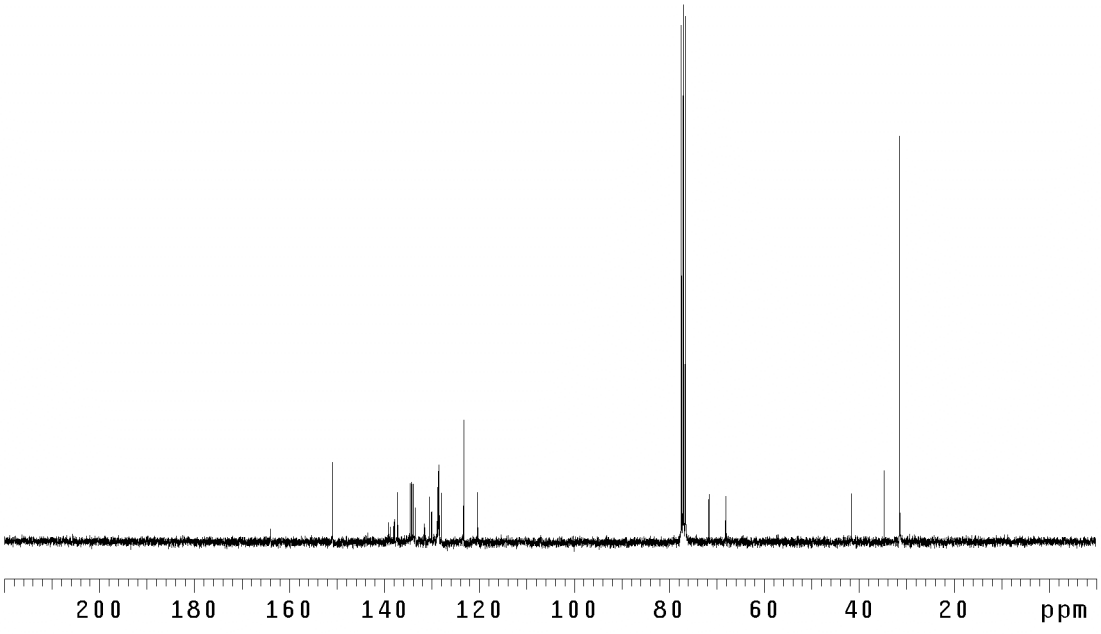
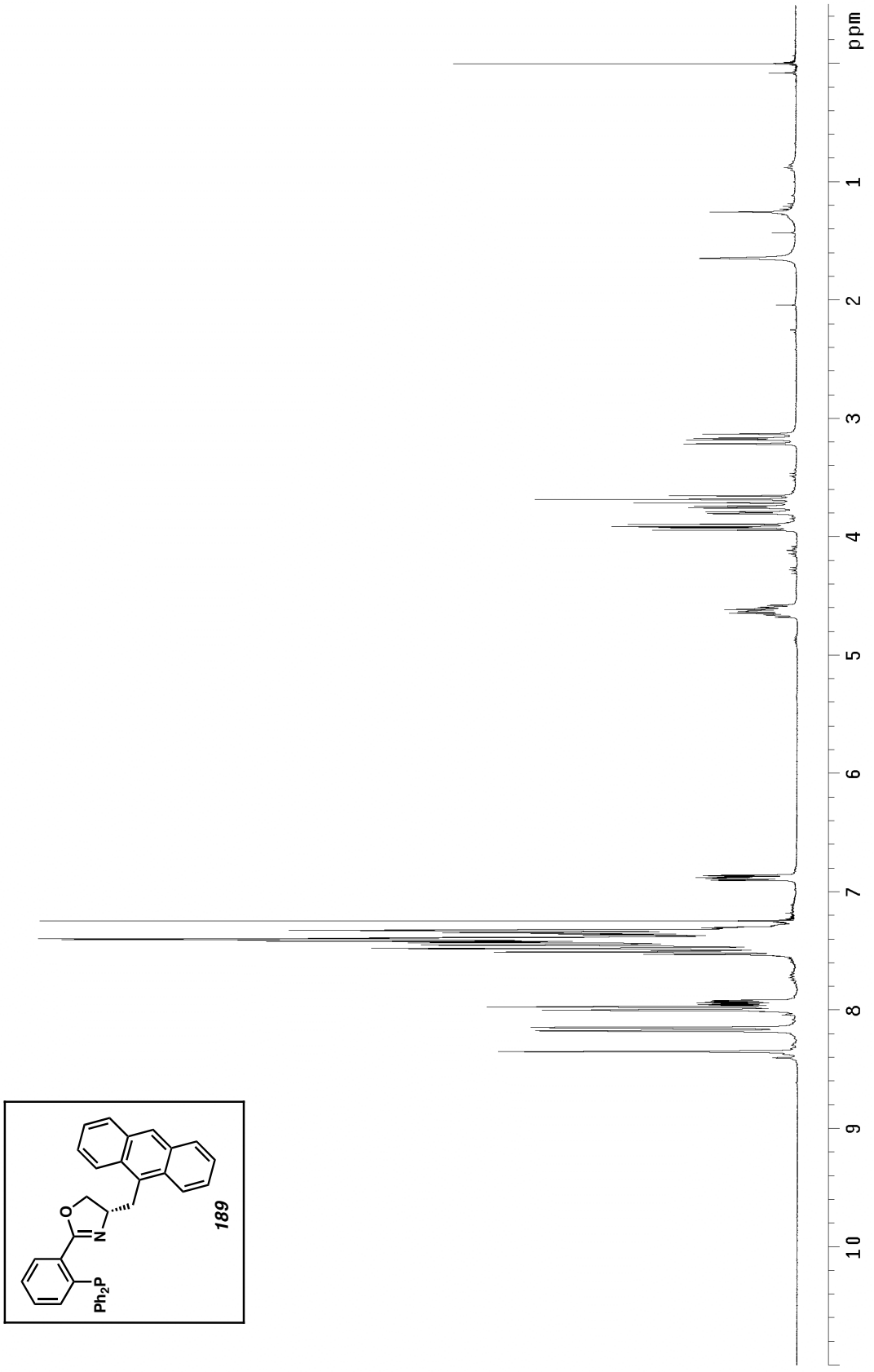


*Figure A1.63 ^{13}C NMR of compound **188** (75 MHz, $CDCl_3$)*


ppm
1
2
3
4
5
6
7
8
9
10
O
N
Ph2P
189

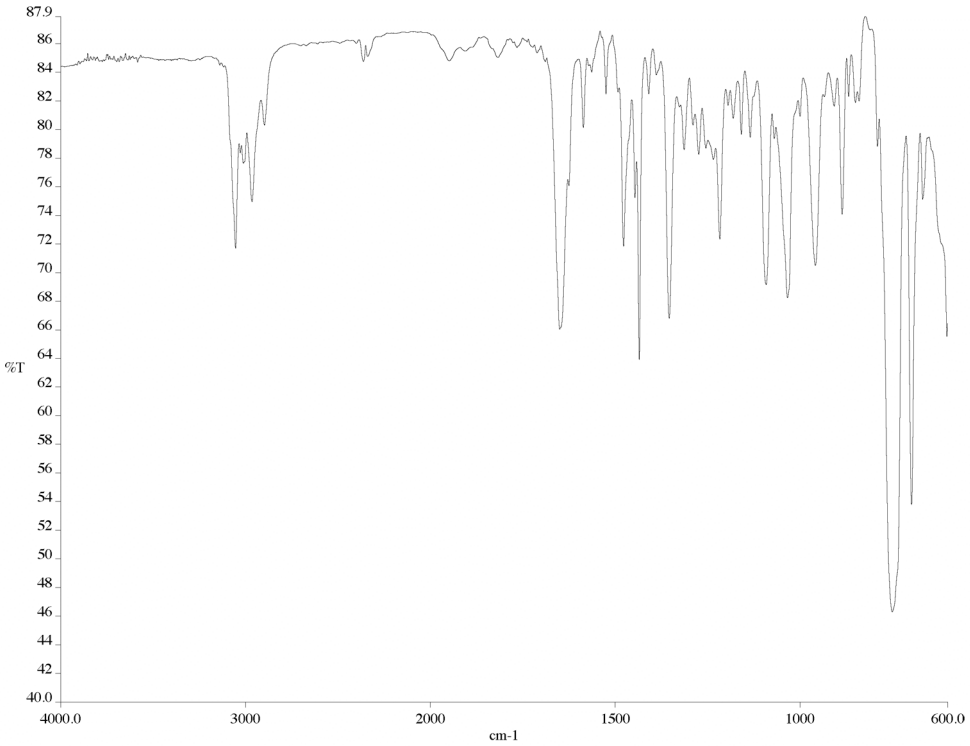


*Figure A1.65 IR of compound **189** (NaCl/film)*

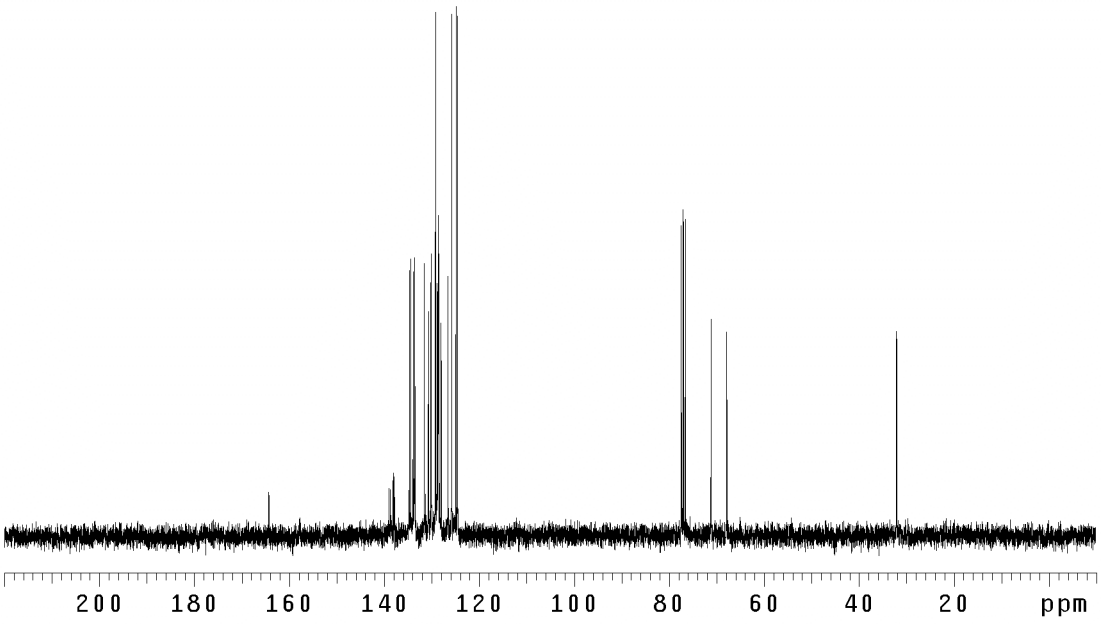
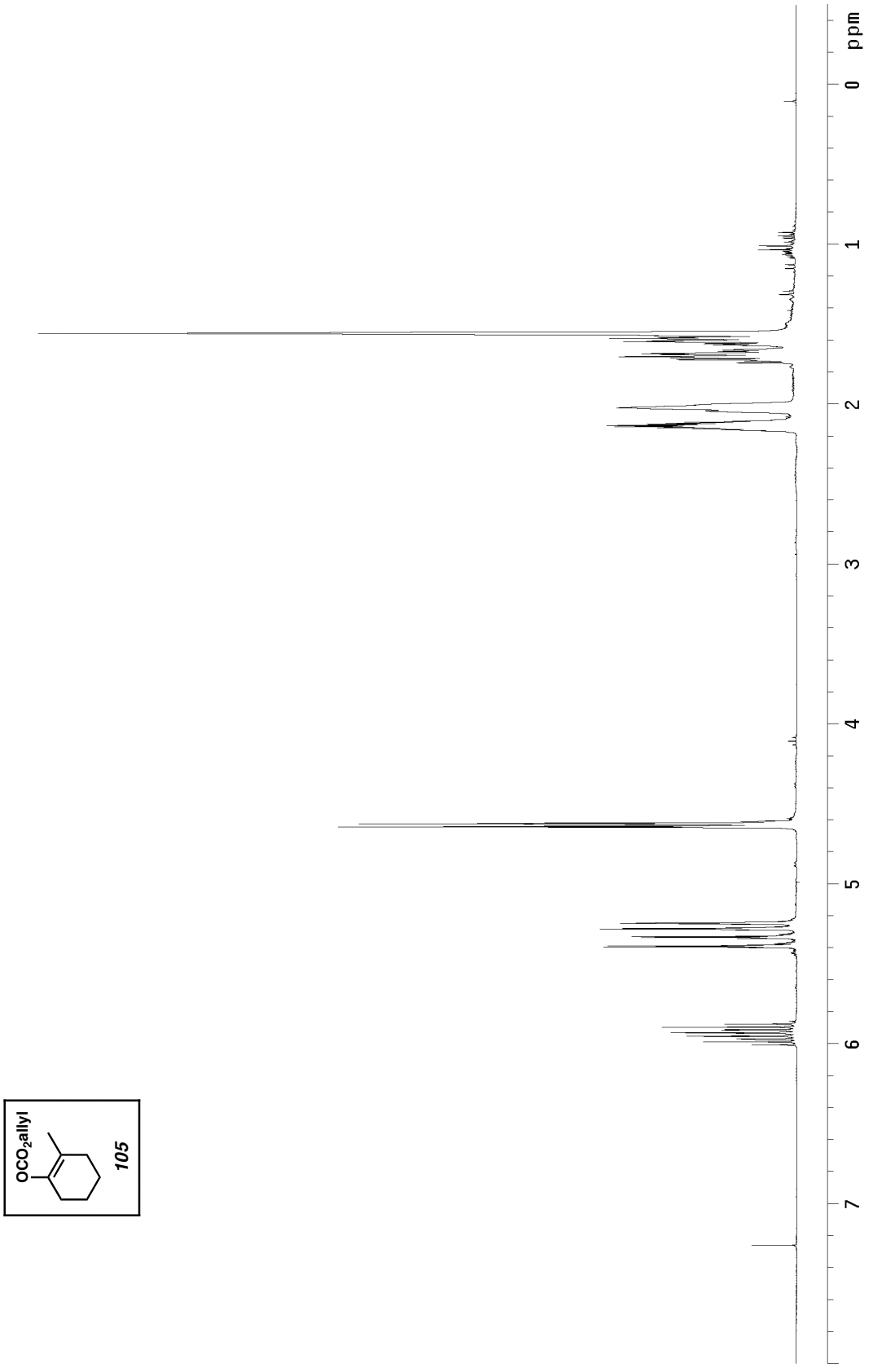


*Figure A1.66 ^{13}C NMR of compound **189** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
OCO2allyl
105

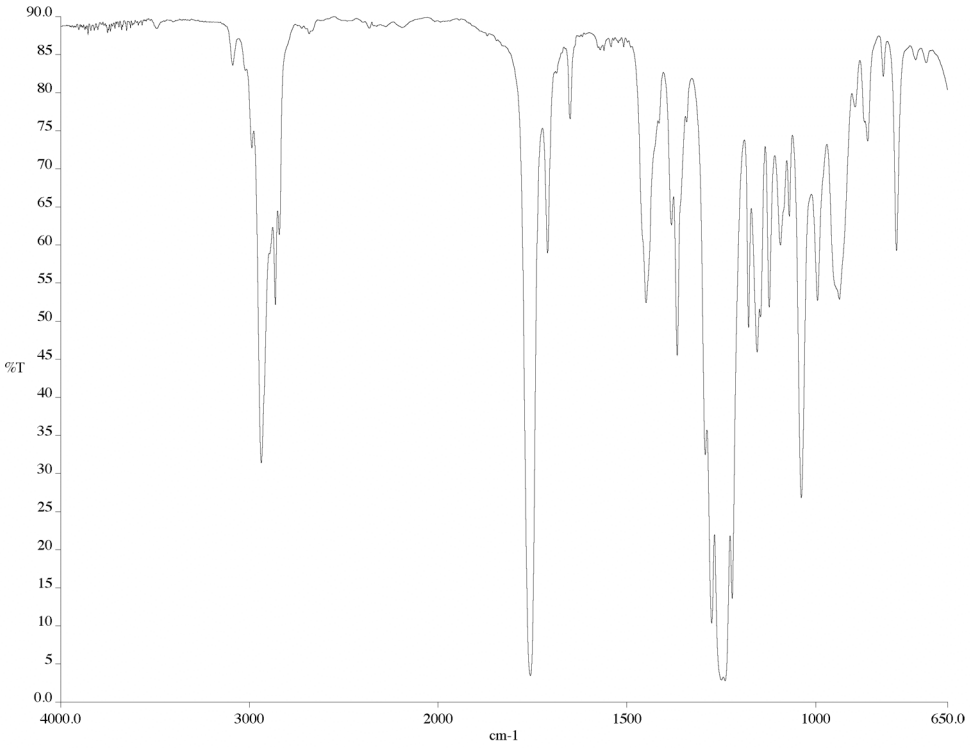


*Figure A1.68 IR of compound **105** (NaCl/film)*

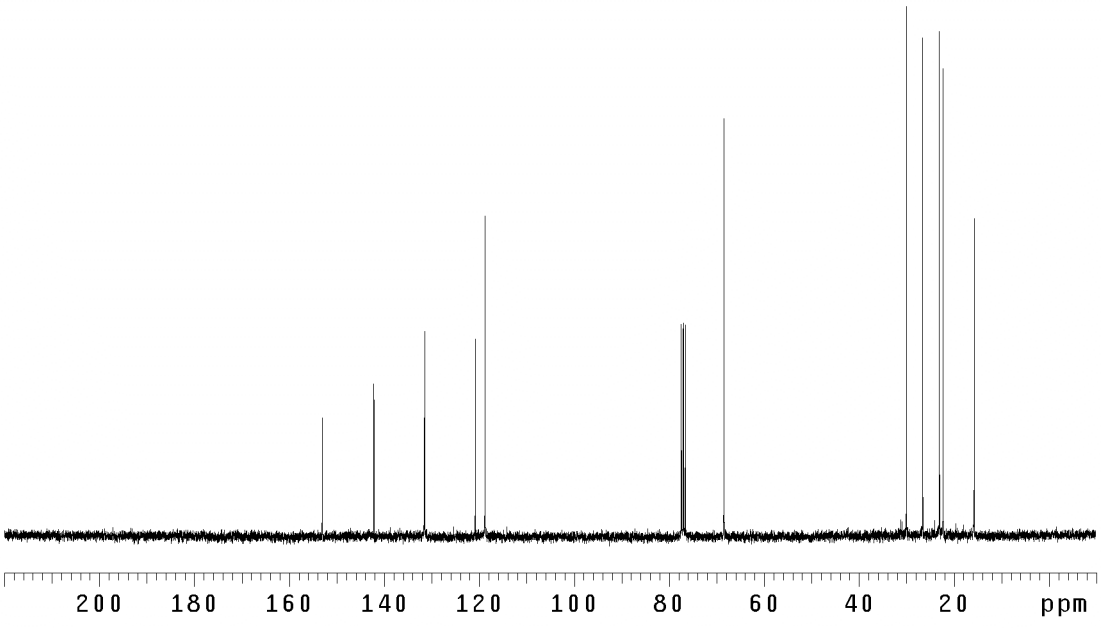
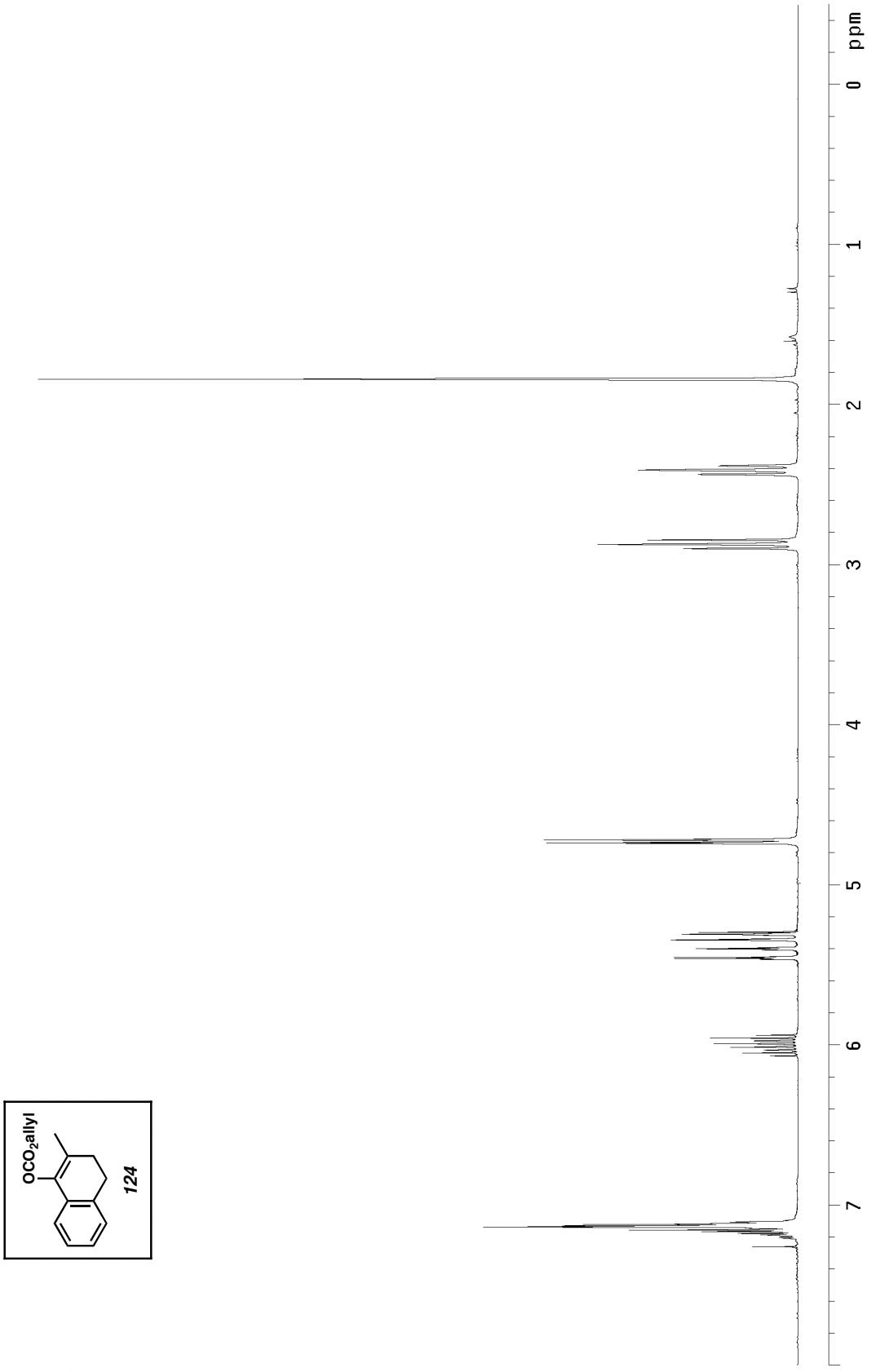


*Figure A1.69 ^{13}C NMR of compound **105** (75 MHz, $CDCl_3$)*


OCO2allyl
124
ppm
0
1
2
3
4
5
6
7

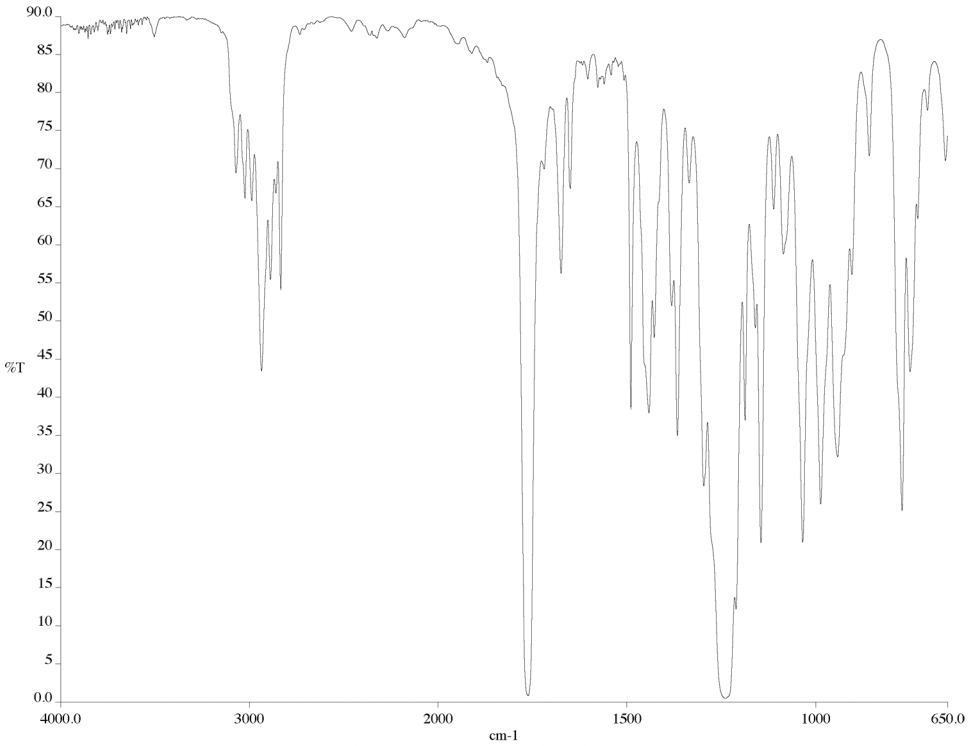


*Figure A1.71 IR of compound **124** (NaCl/film)*

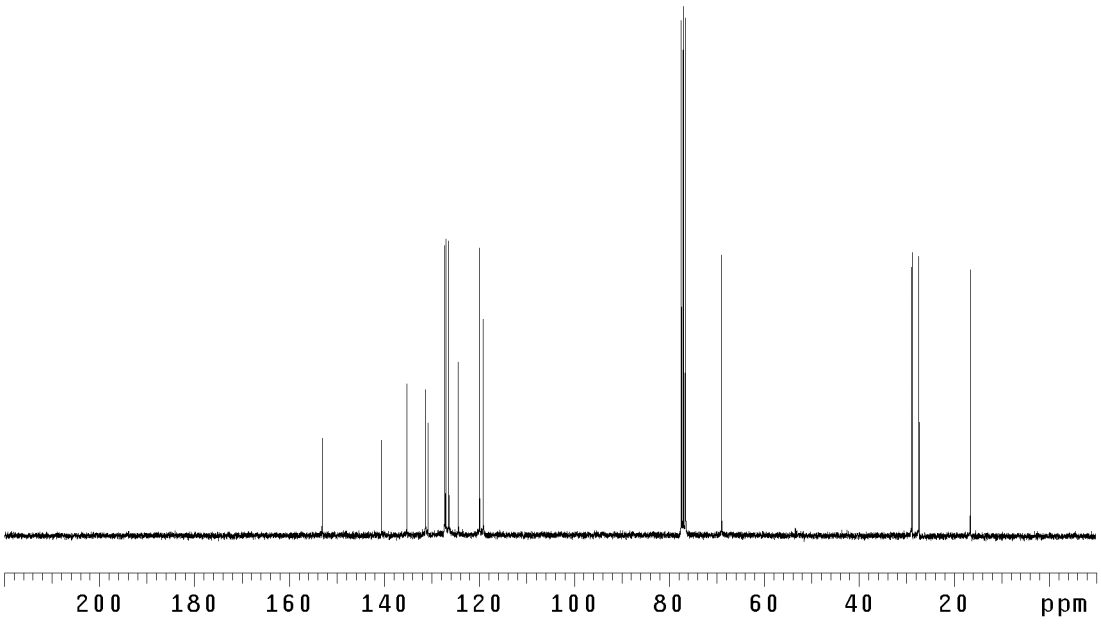
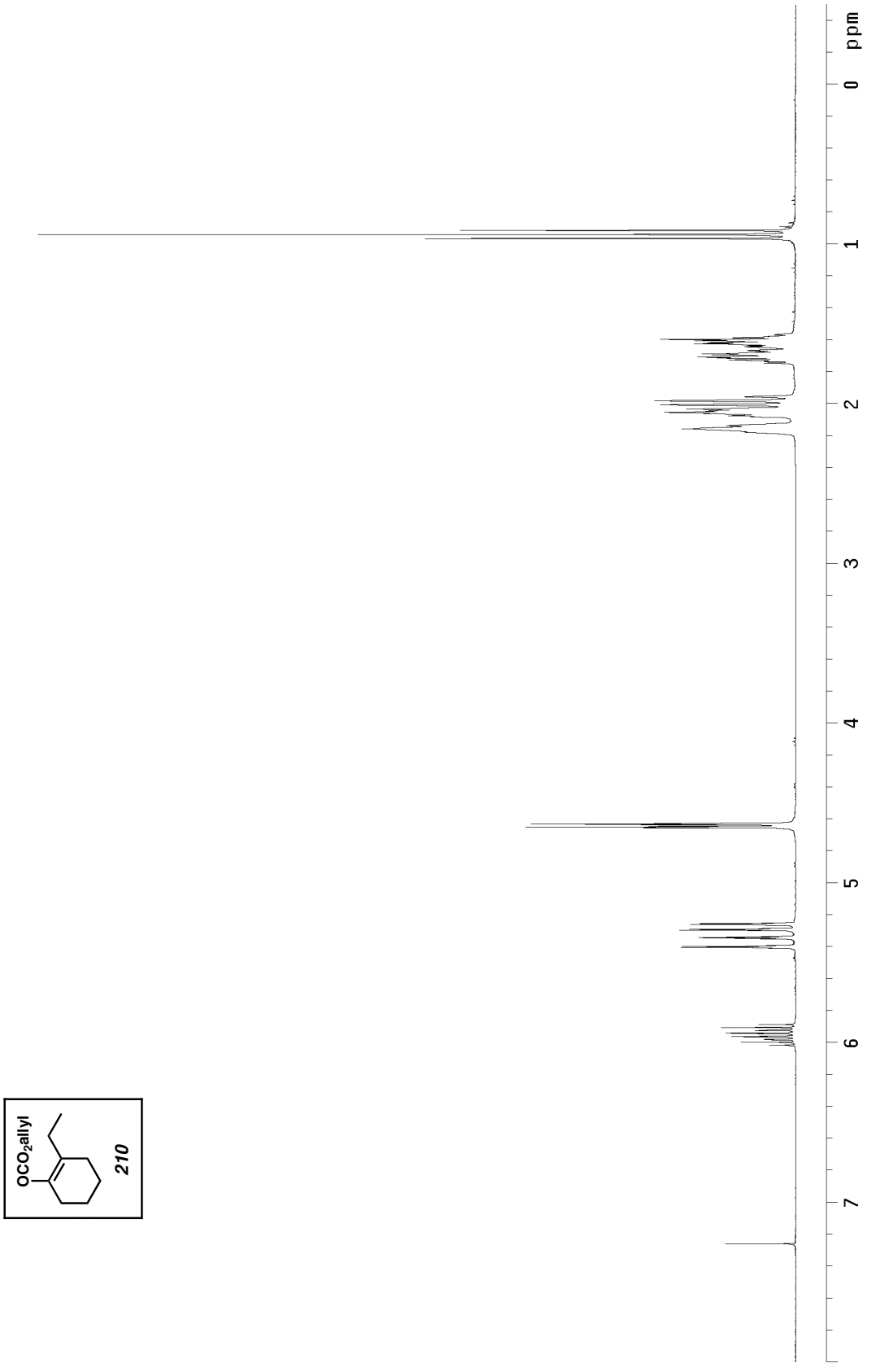


*Figure A1.72 ^{13}C NMR of compound **124** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
OCO2allyl
210

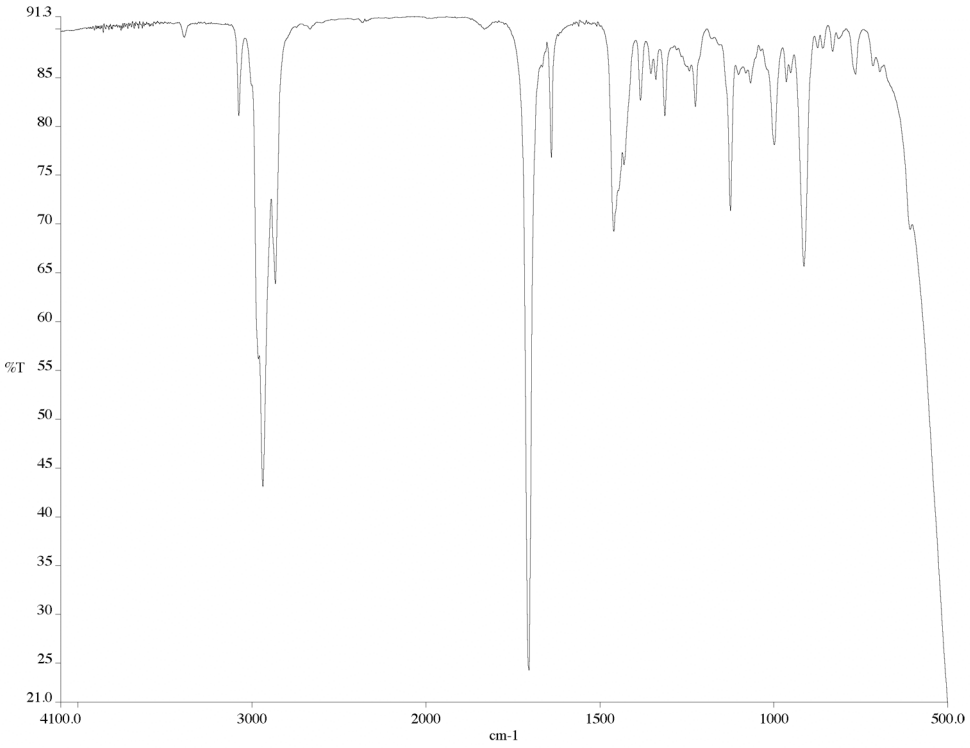


*Figure A1.74 IR of compound **210** (NaCl/film)*

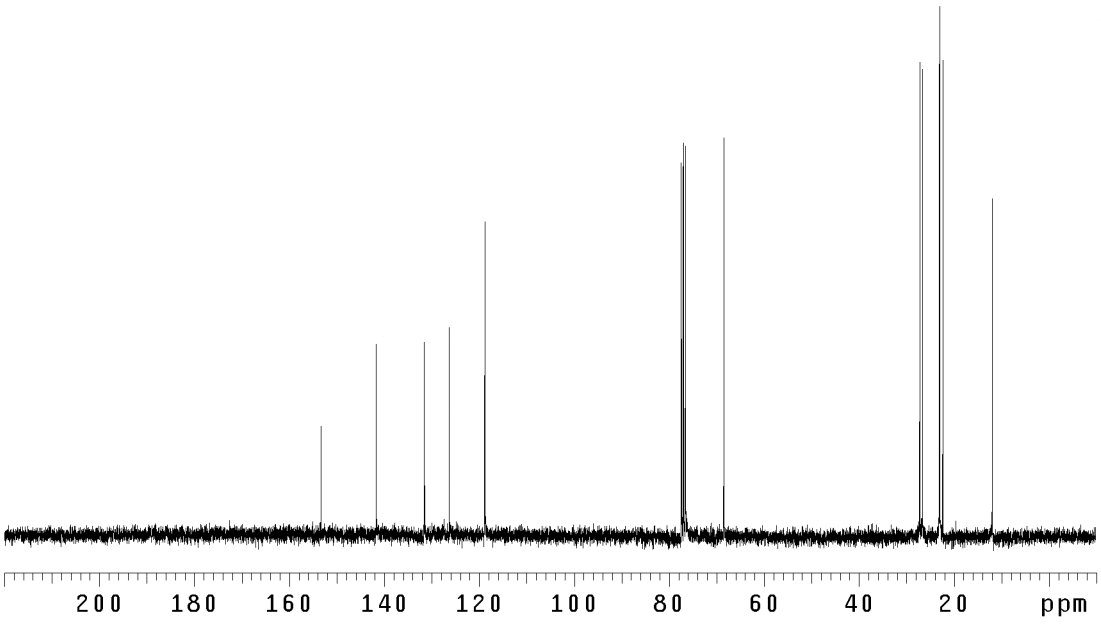


*Figure A1.75 ^{13}C NMR of compound **210** (75 MHz, $CDCl_3$)*

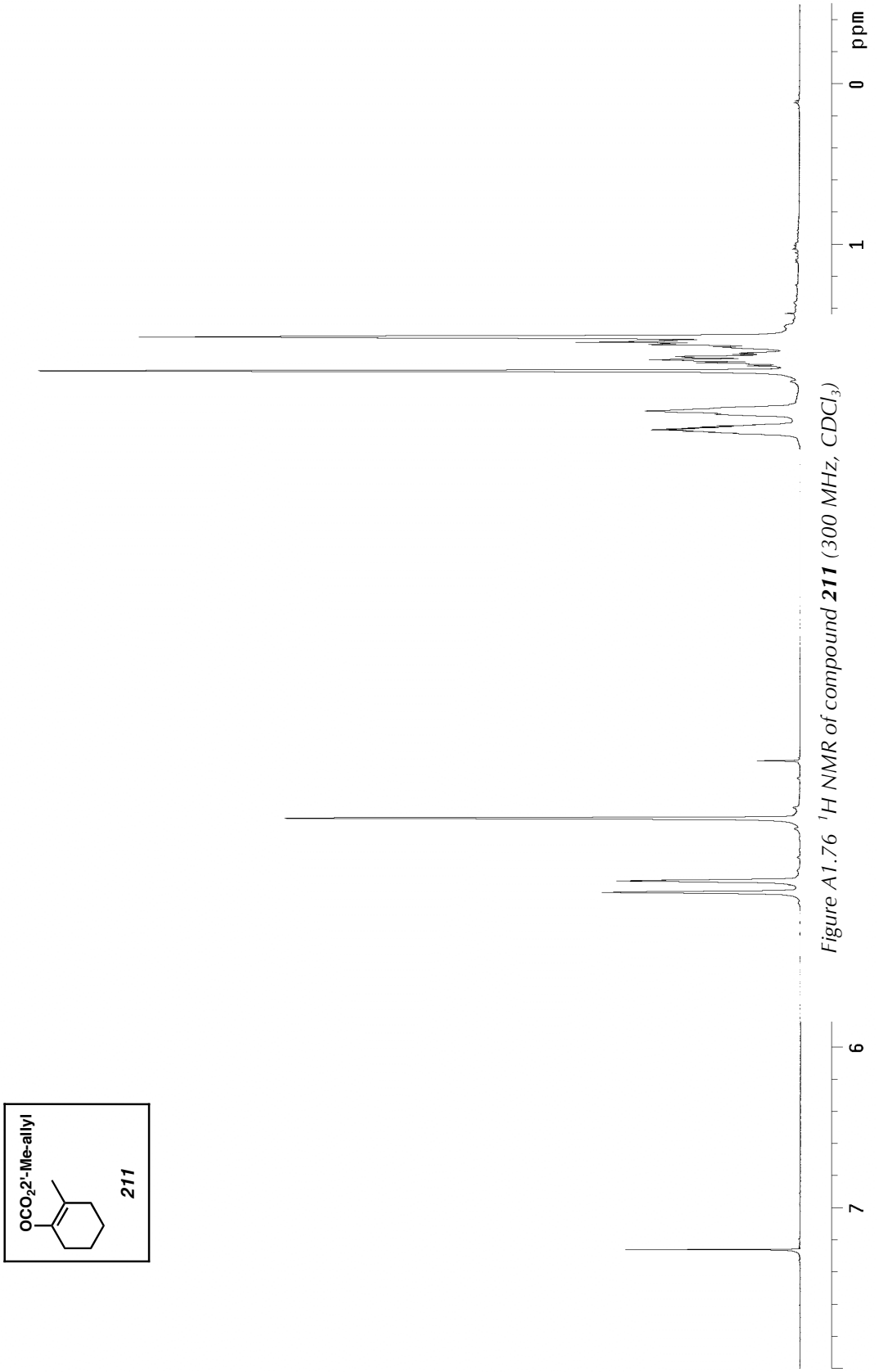


*Figure A1.76 ^1H NMR of compound **211** (300 MHz, $CDCl_3$)*

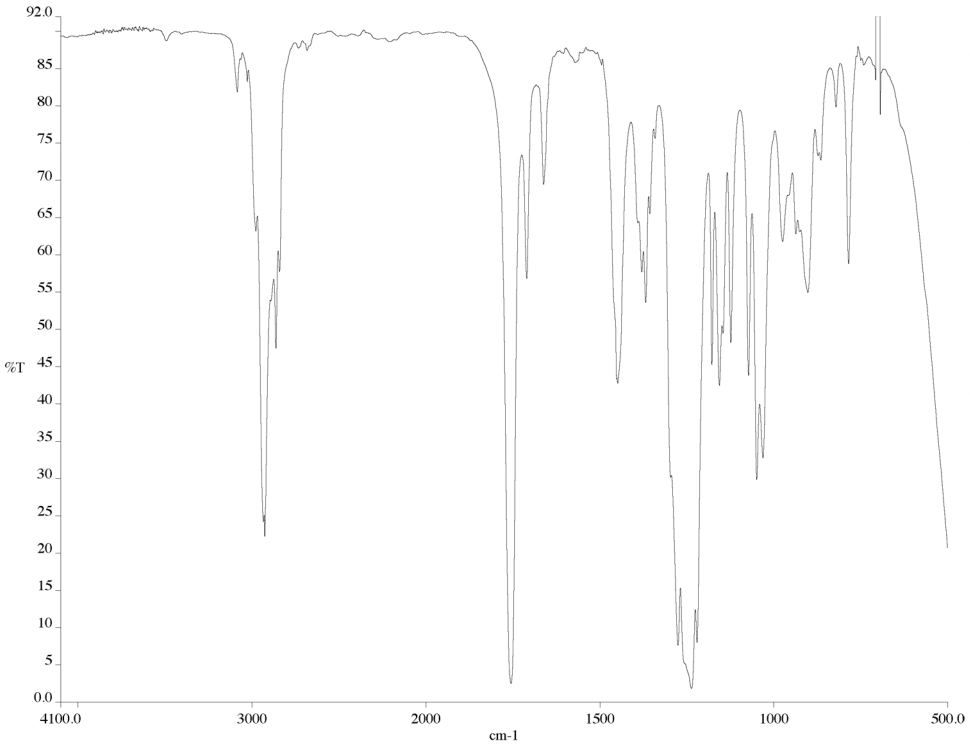


*Figure A1.77 IR of compound **211** (NaCl/film)*

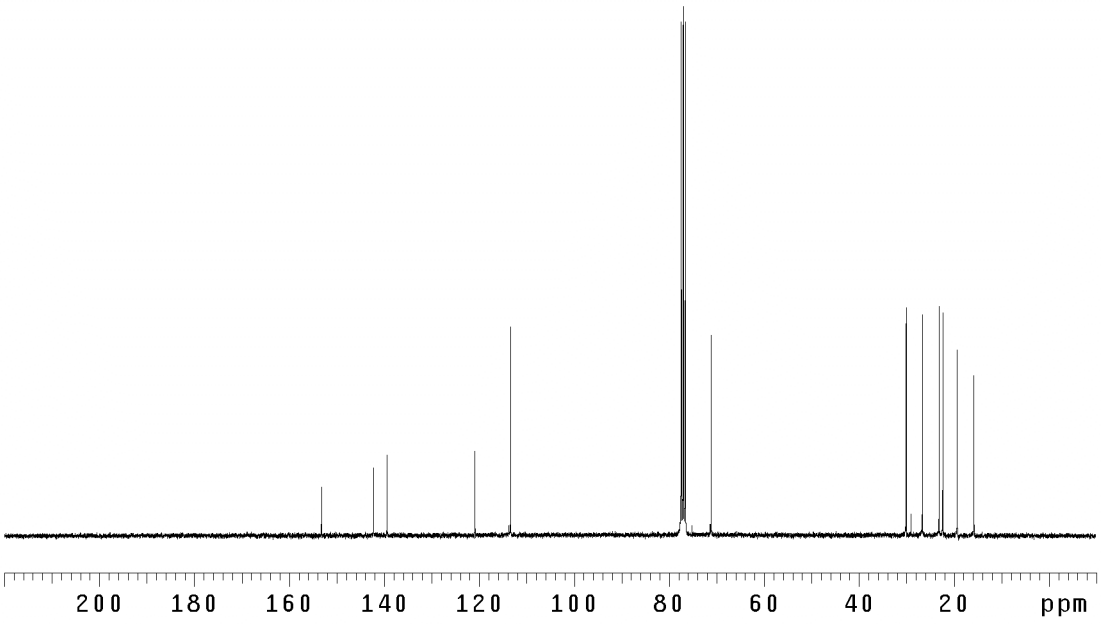


*Figure A1.78 ^{13}C NMR of compound **211** (75 MHz, $CDCl_3$)*

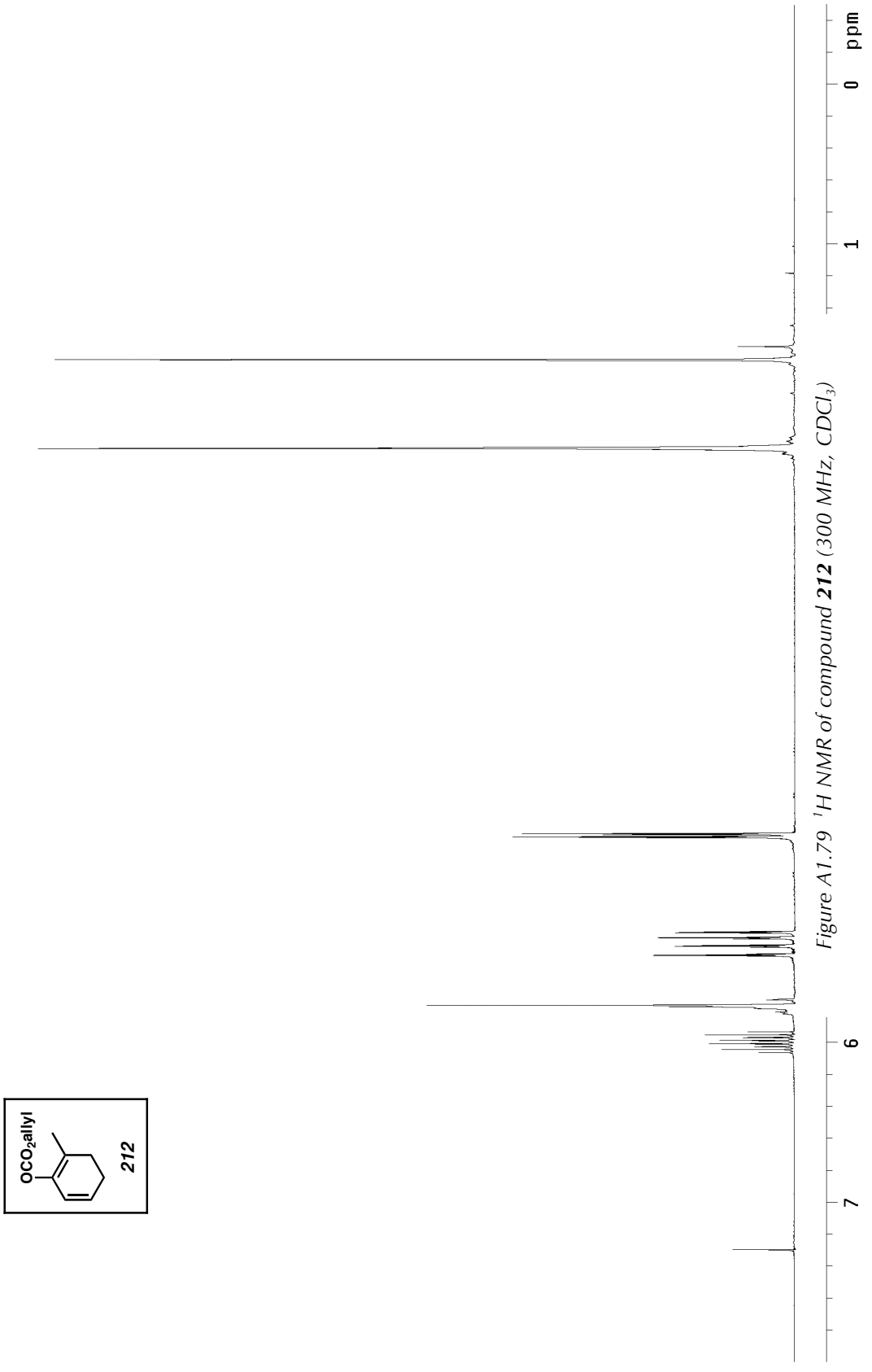


*Figure A1.79 ^1H NMR of compound **212** (300 MHz, $CDCl_3$)*

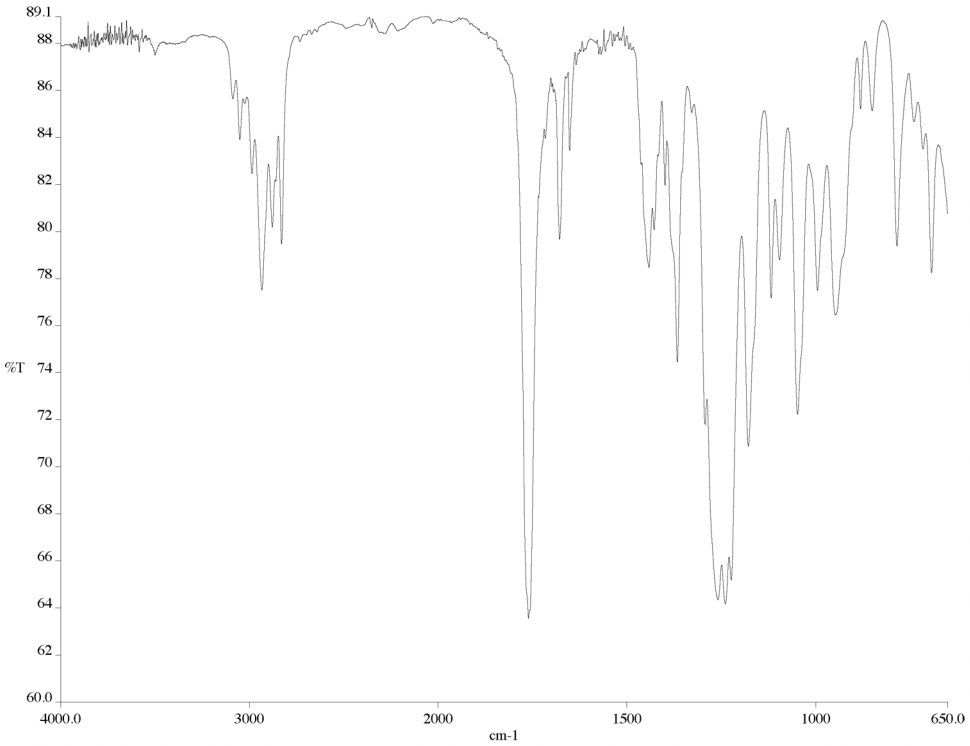


*Figure A1.80 IR of compound **212** (NaCl/film)*

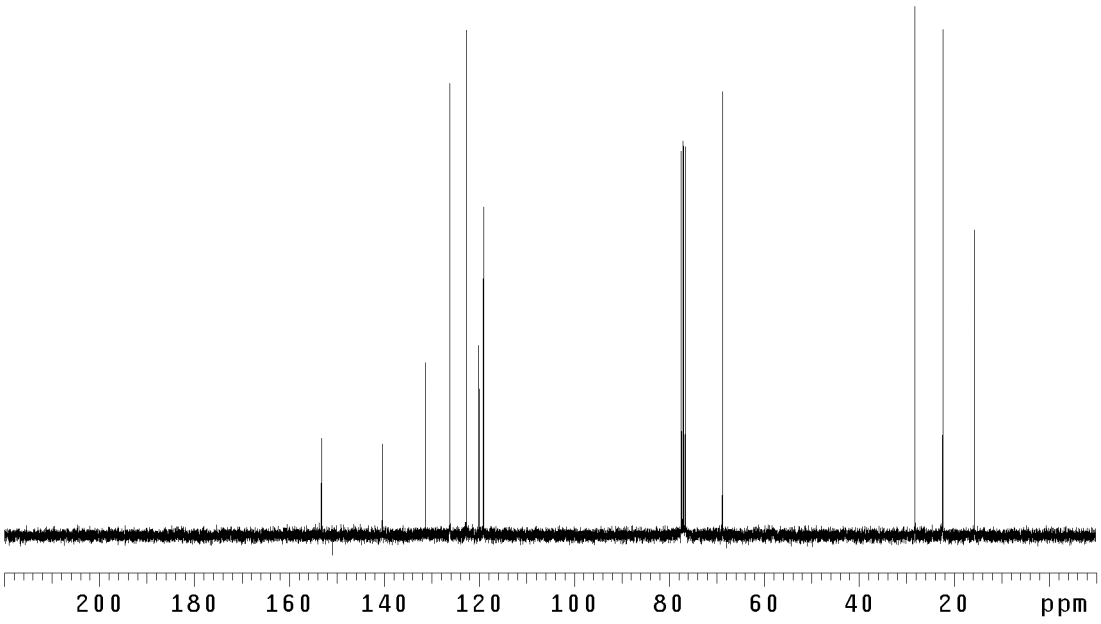


*Figure A1.81 ^{13}C NMR of compound **212** (75 MHz, $CDCl_3$)*

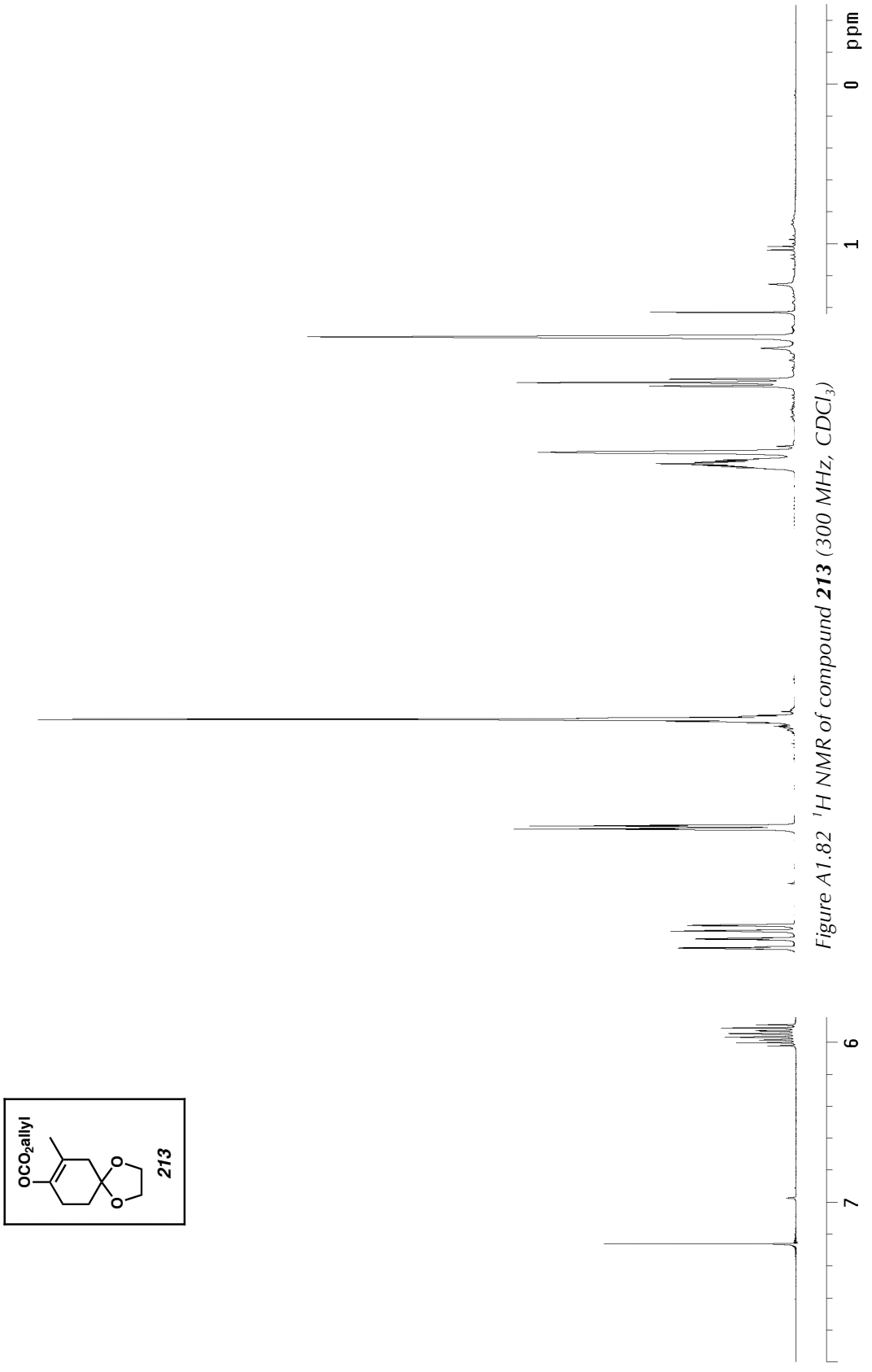


*Figure A1.82 ^1H NMR of compound **213** (300 MHz, $CDCl_3$)*

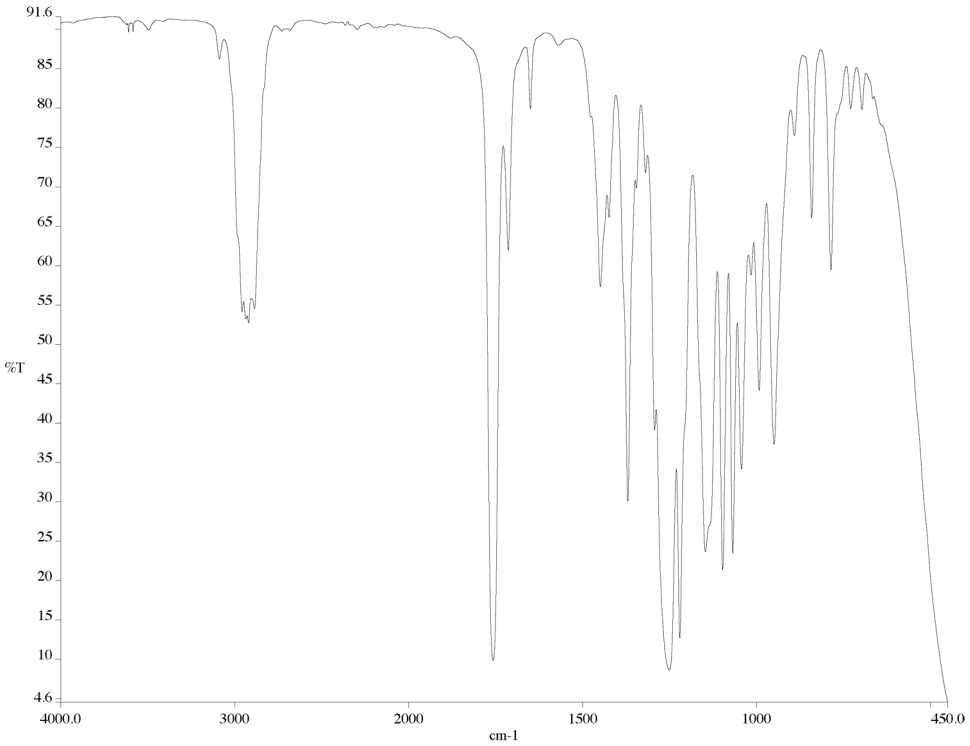


*Figure A1.83 IR of compound **213** (NaCl/film)*

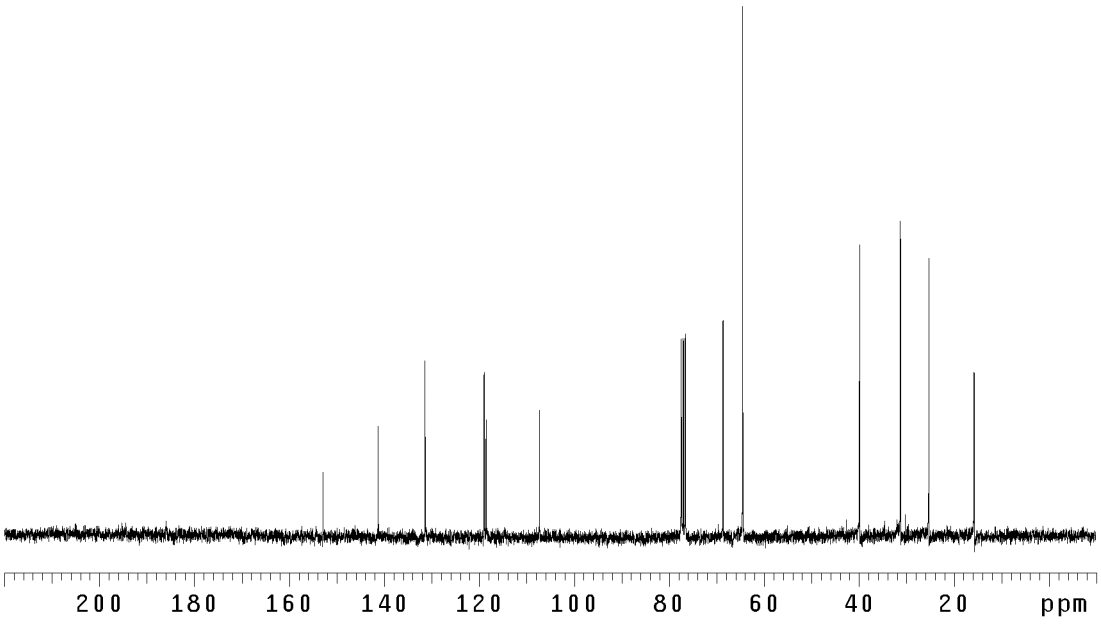
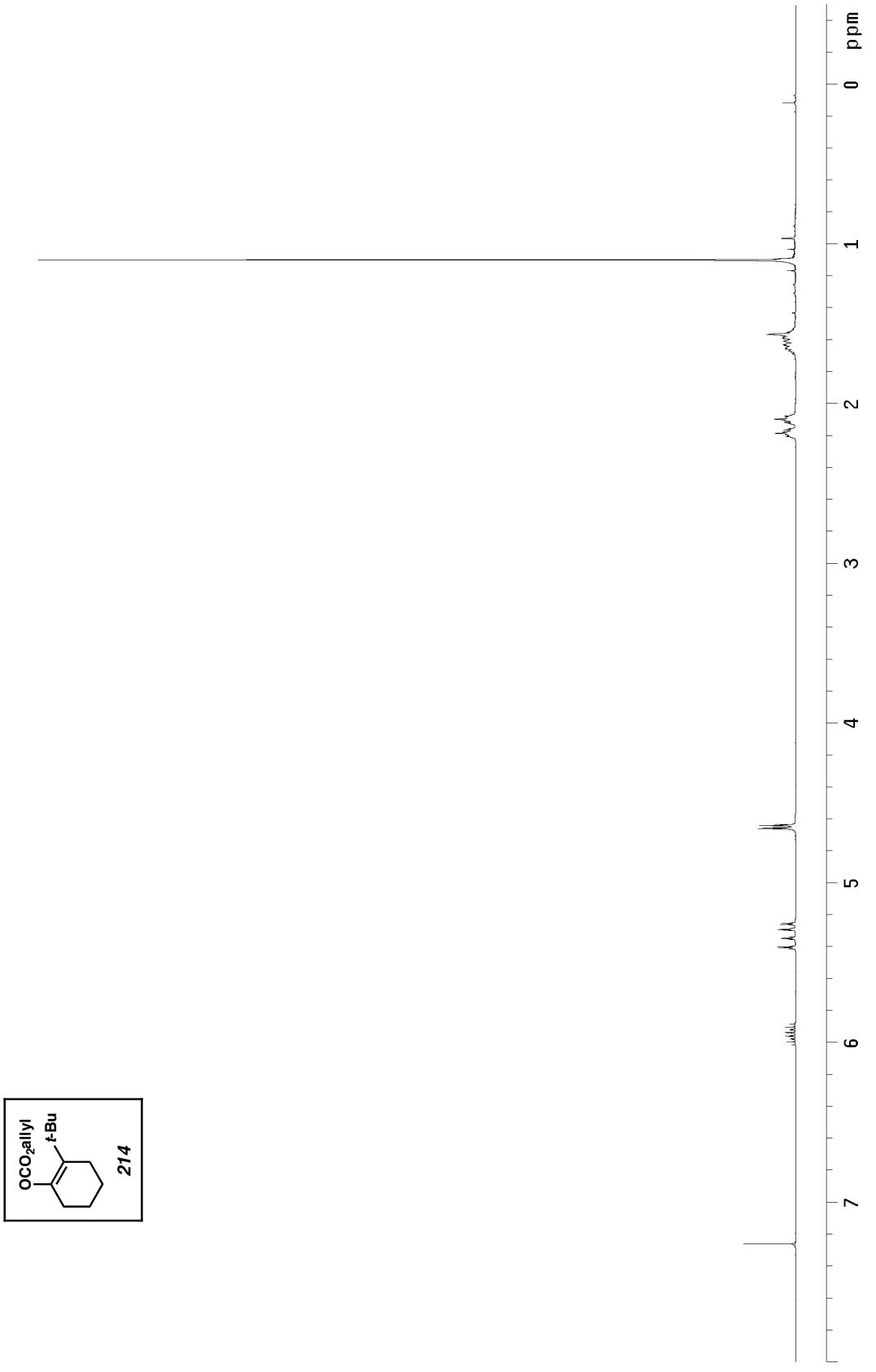


*Figure A1.84 ^{13}C NMR of compound **213** (75 MHz, $CDCl_3$)*


OCO2allyl
t-Bu
214
ppm
0
1
2
3
4
5
6
7

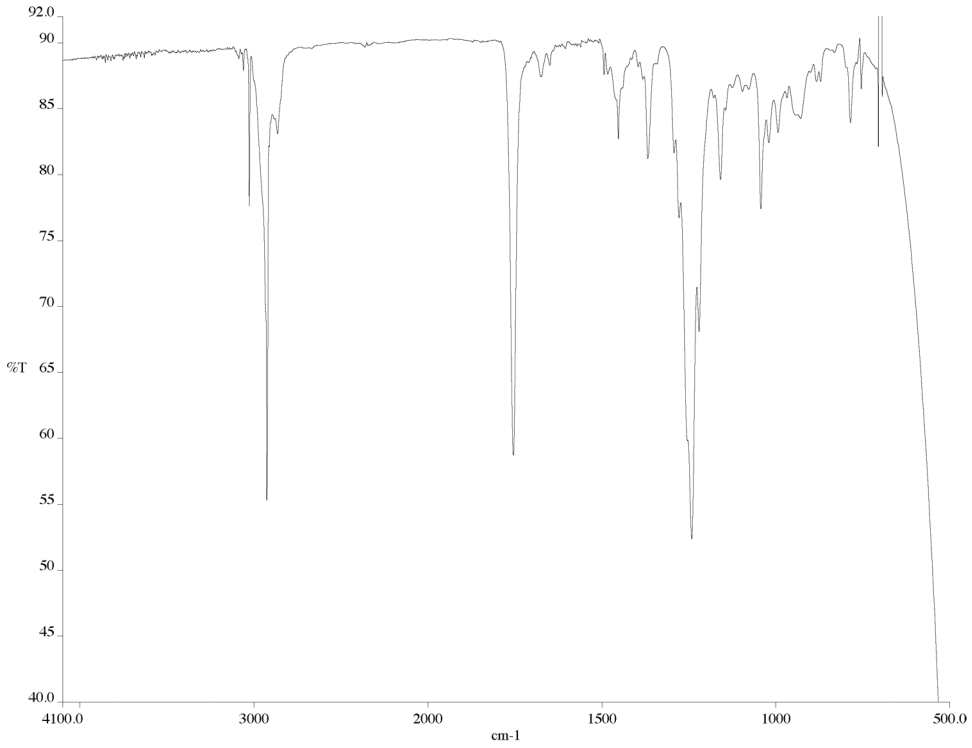


*Figure A1.86 IR of compound **214** (NaCl/film)*

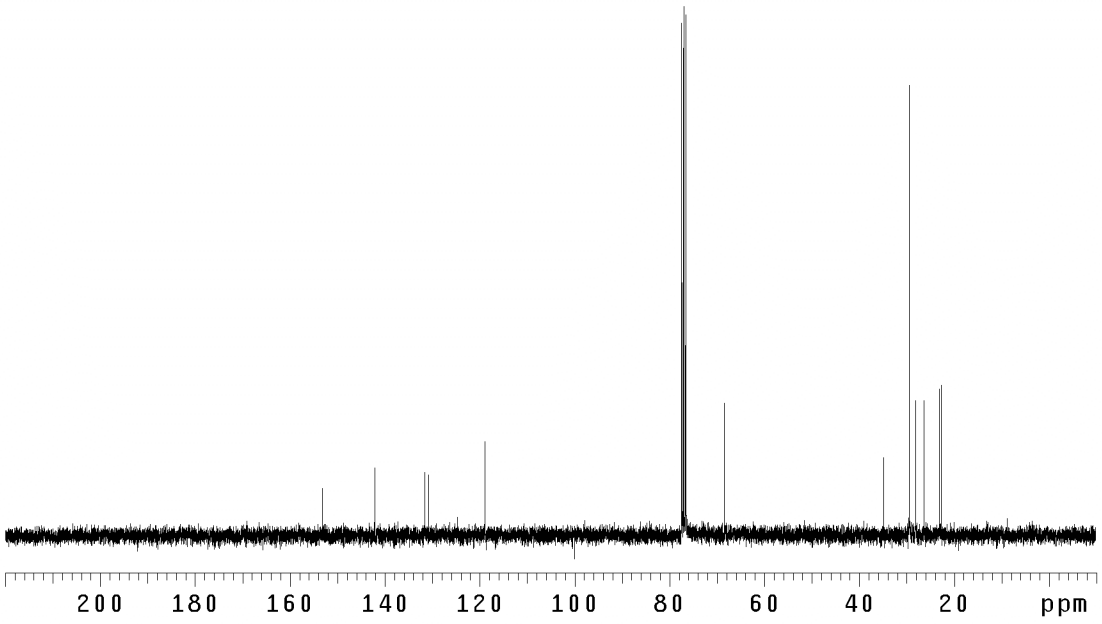
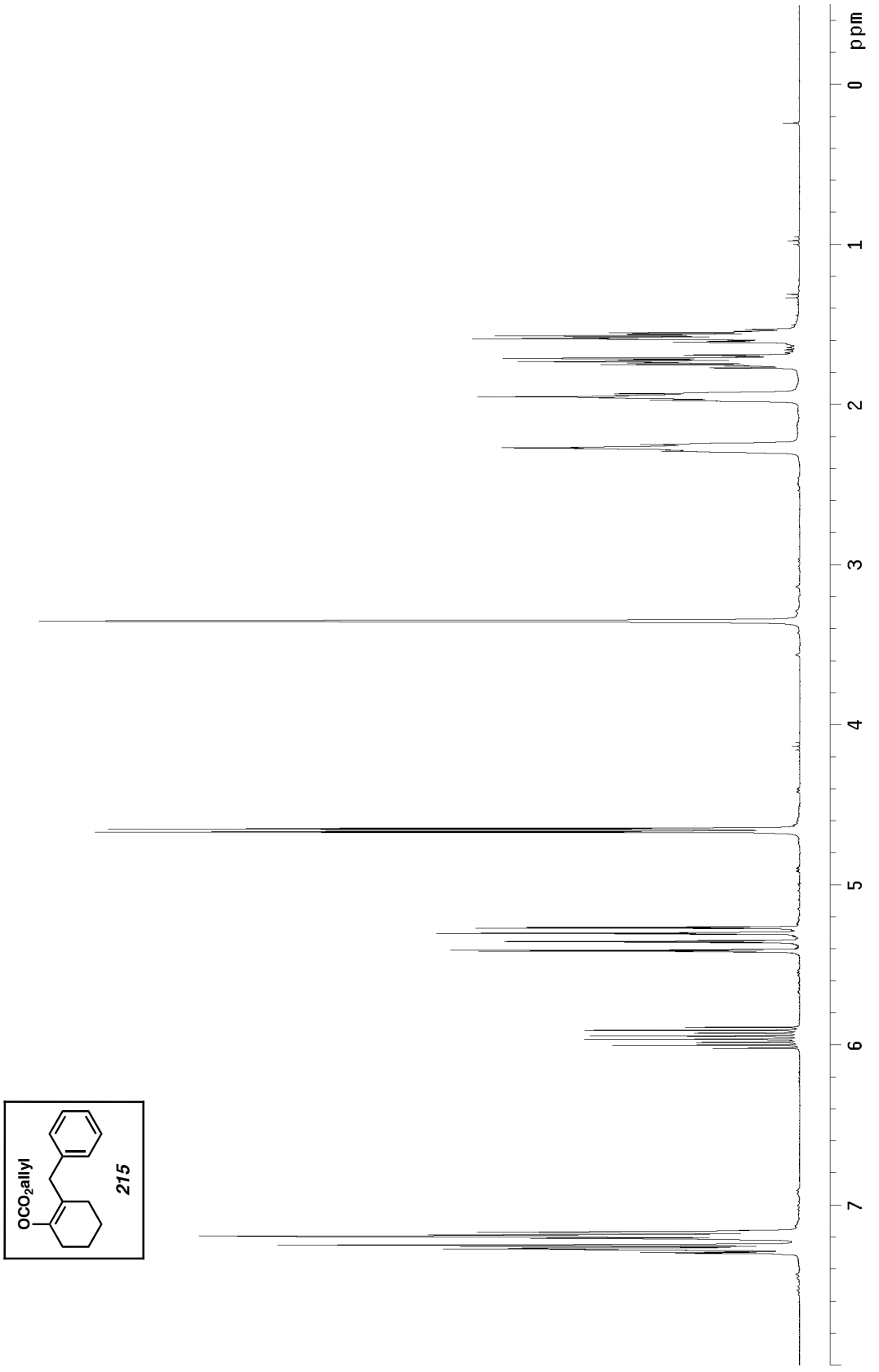


*Figure A1.87 ^{13}C NMR of compound **214** (75 MHz, $CDCl_3$)*


OCO2allyl
215
ppm
0
1
2
3
4
5
6
7

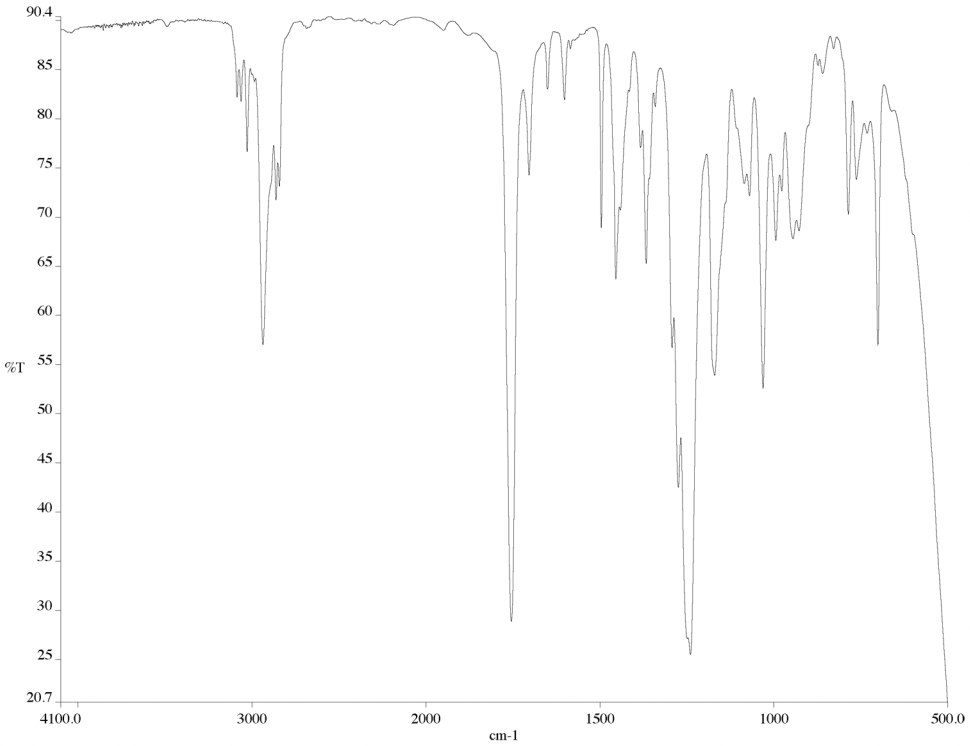


*Figure A1.89 IR of compound **215** (NaCl/film)*

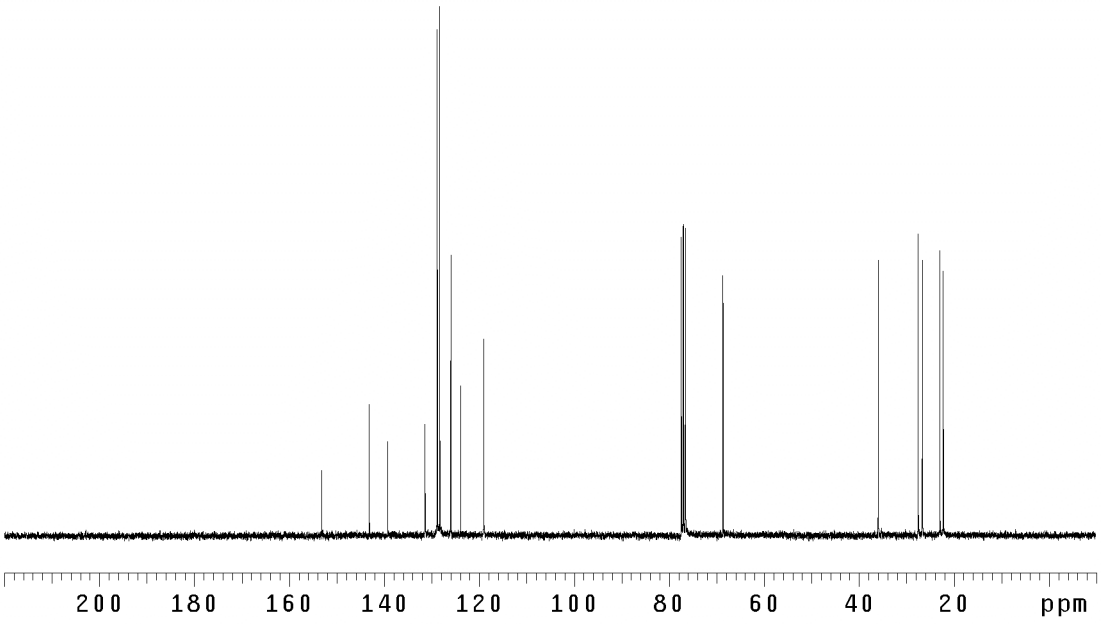
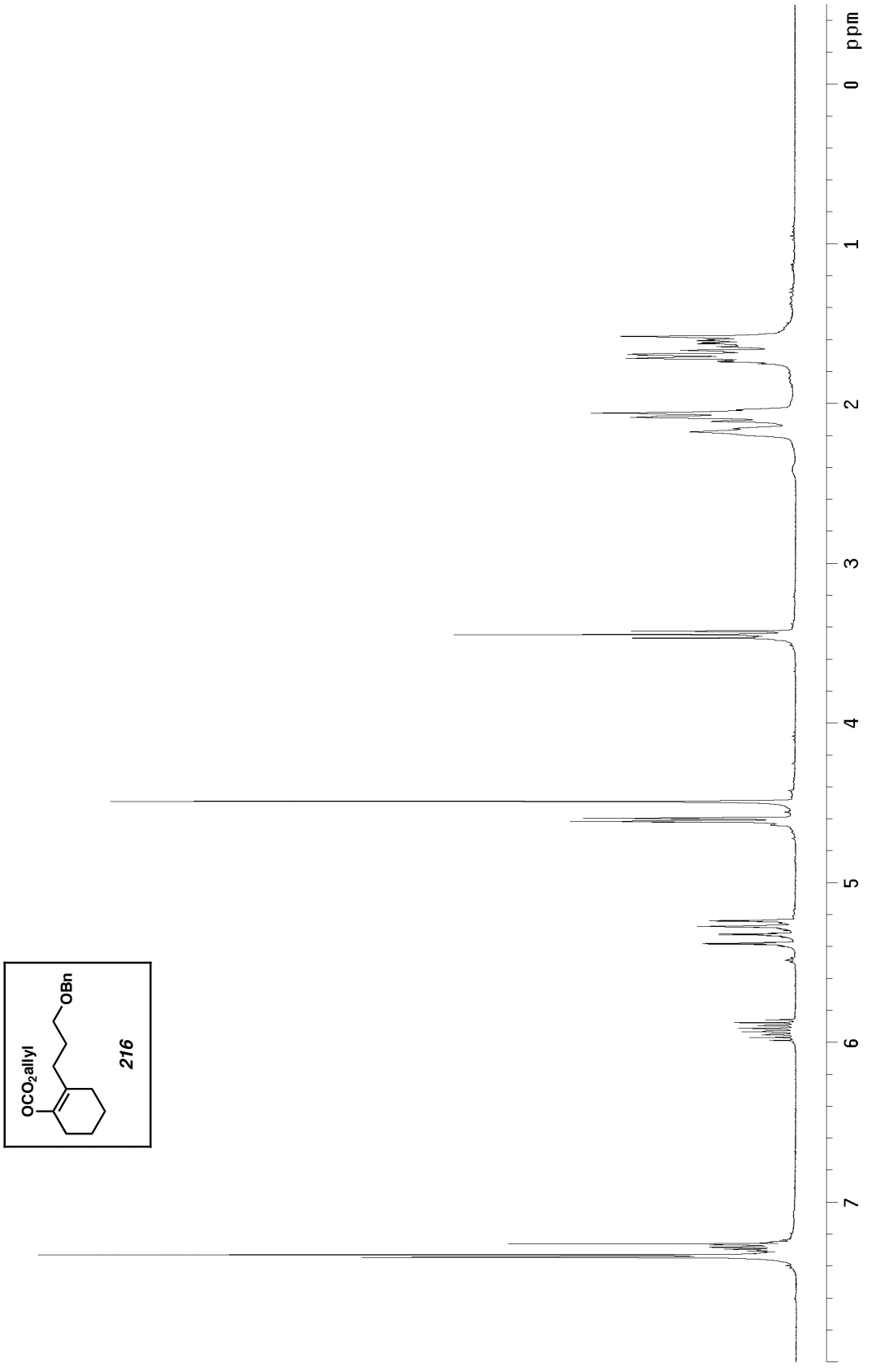


*Figure A1.90 ^{13}C NMR of compound **215** (75 MHz, $CDCl_3$)*


OCO2allyl
OBn
216
ppm
0
1
2
3
4
5
6
7

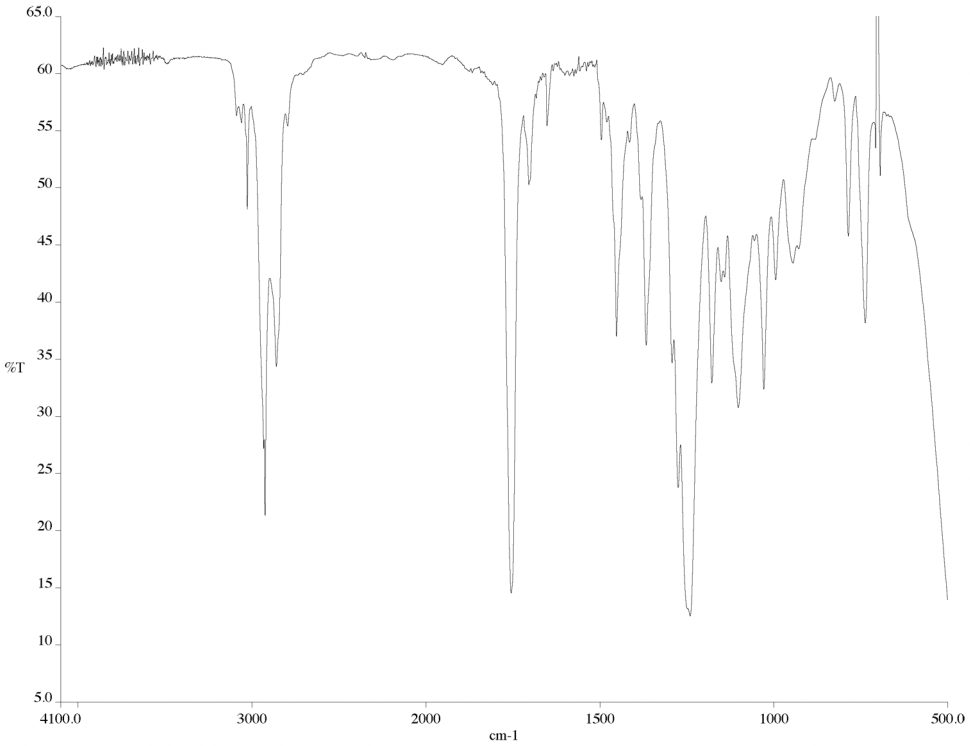


*Figure A1.92 IR of compound **216** (NaCl/film)*

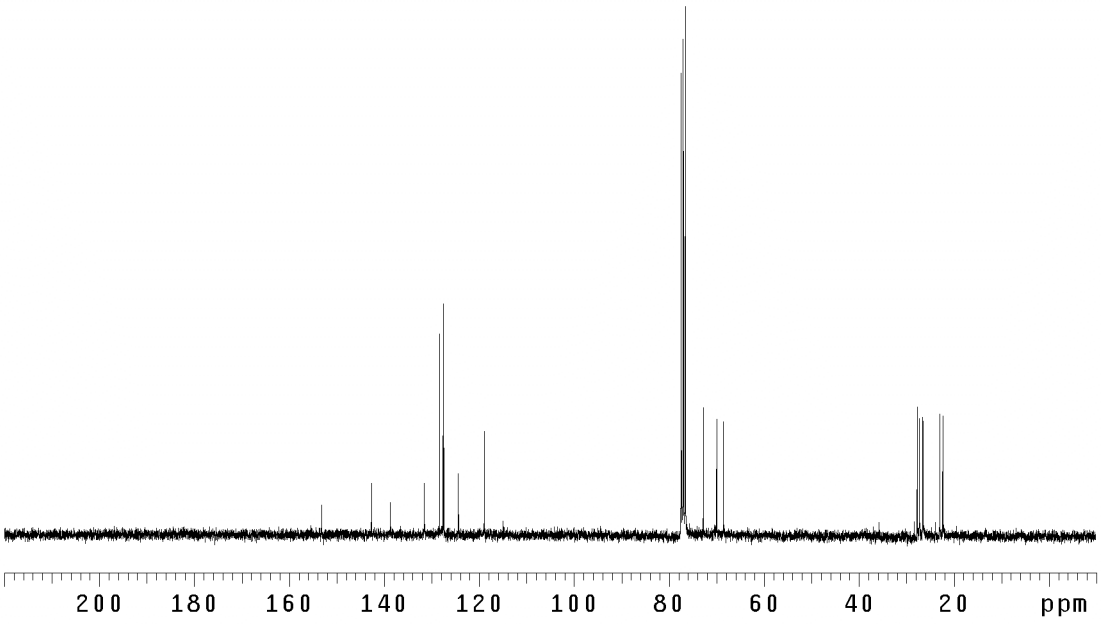
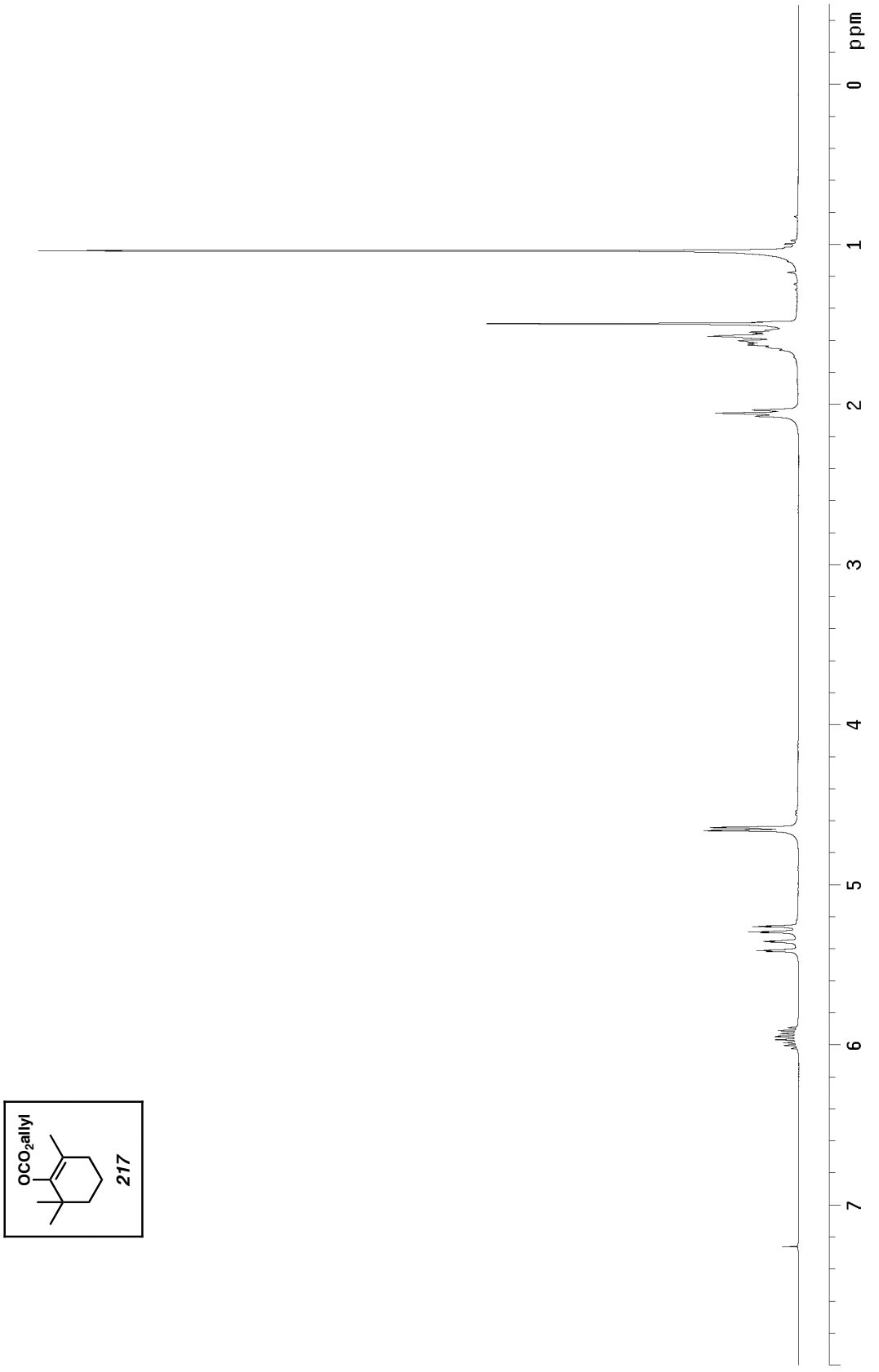


*Figure A1.93 ^{13}C NMR of compound **216** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
OCO2allyl
217

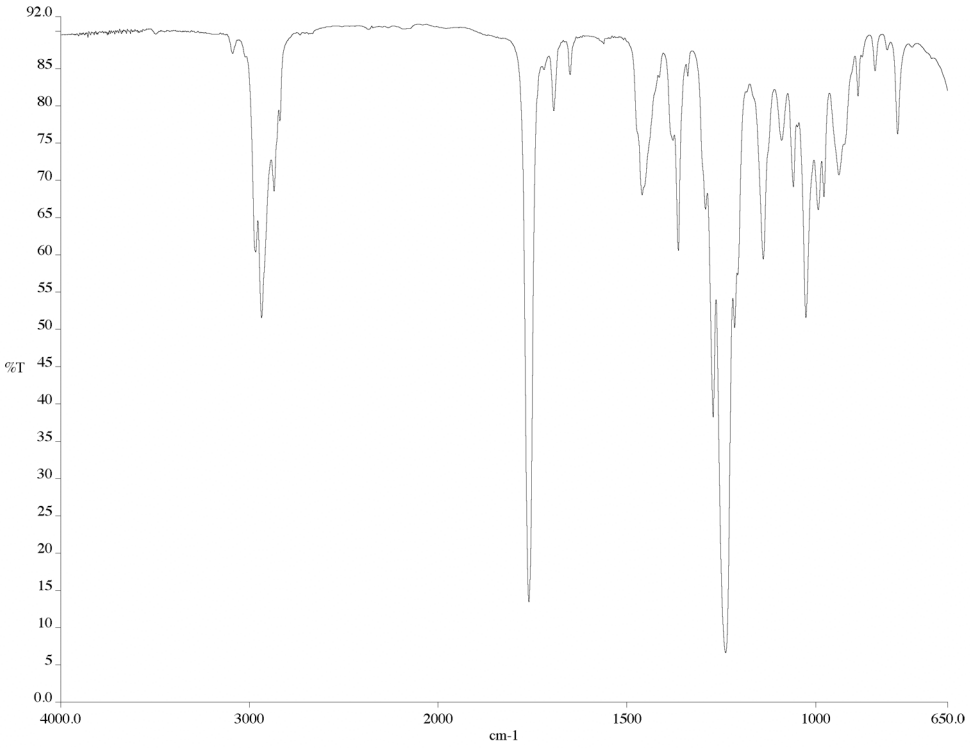


*Figure A1.95 IR of compound **217** (NaCl/film)*

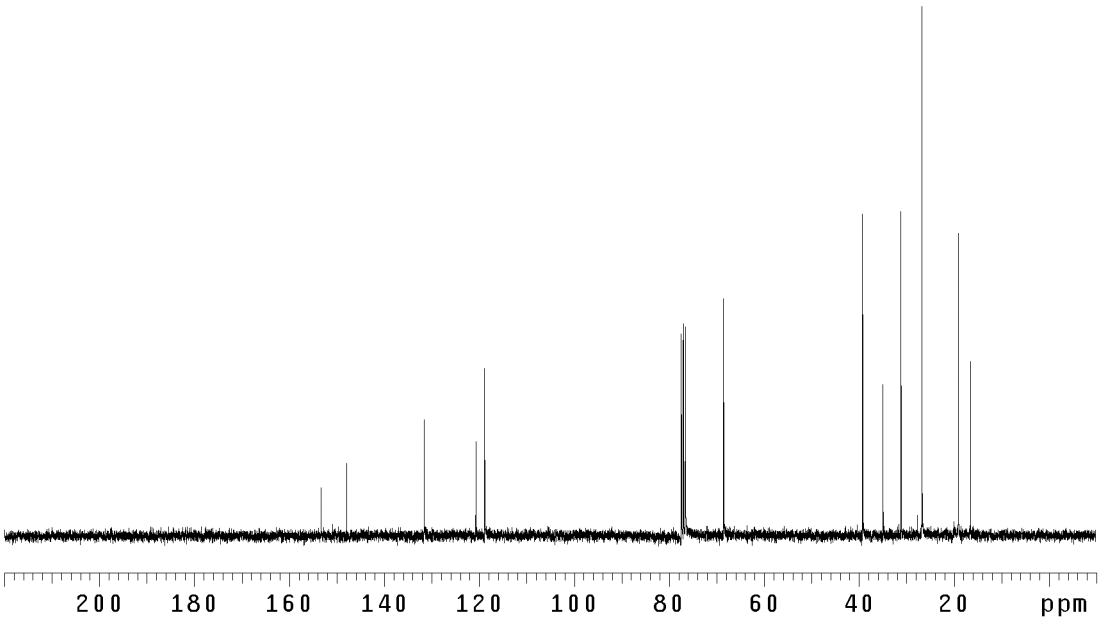
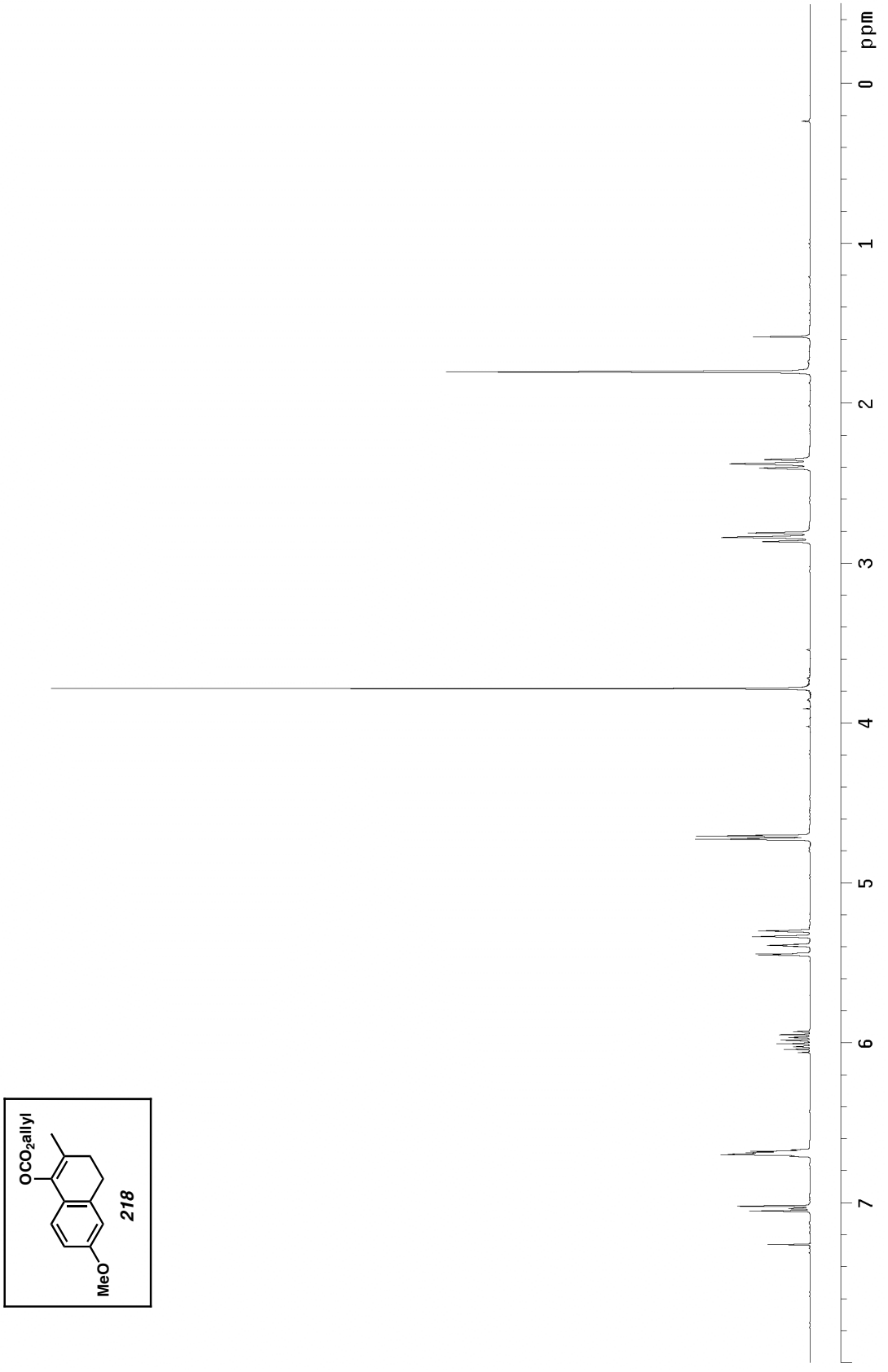


*Figure A1.96 ^{13}C NMR of compound **217** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
OCO2allyl
MeO
218

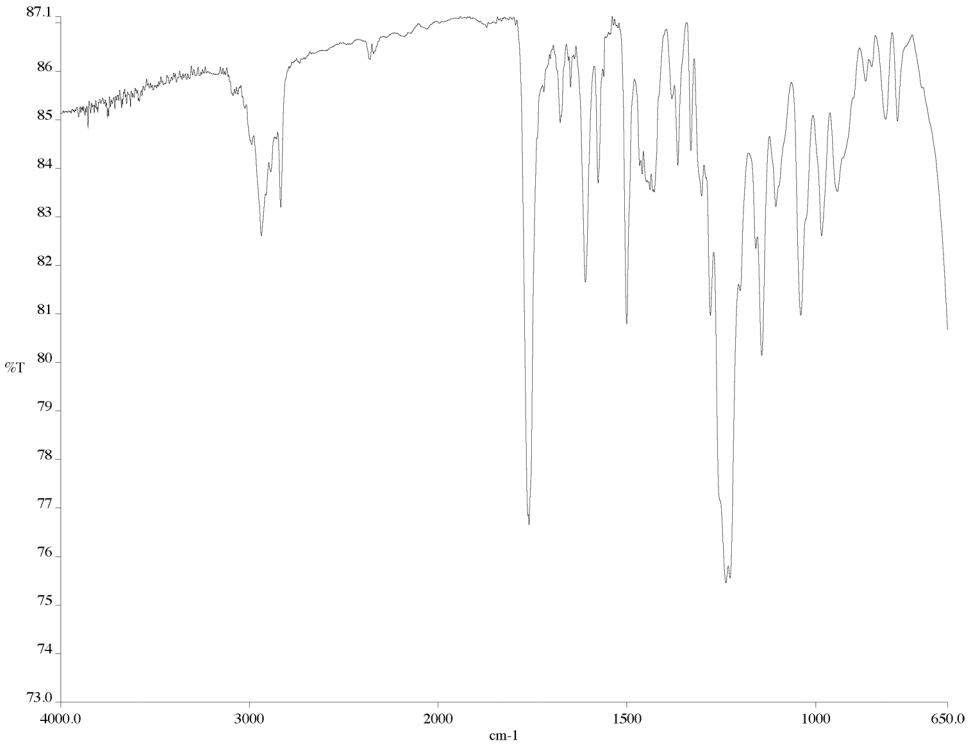


*Figure A1.98 IR of compound **218** (NaCl/film)*

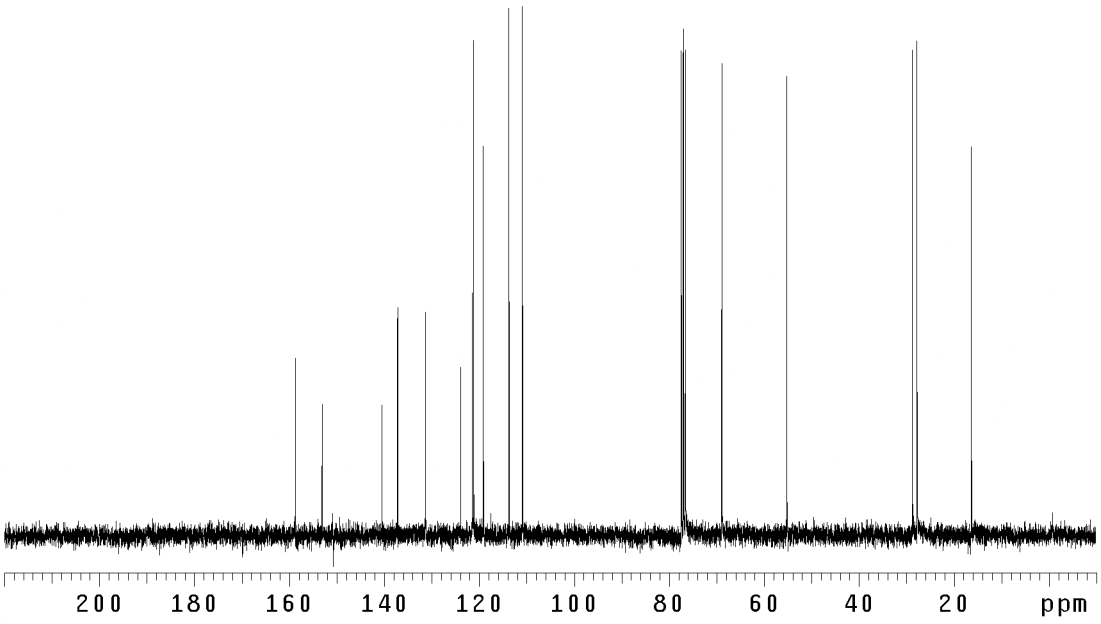
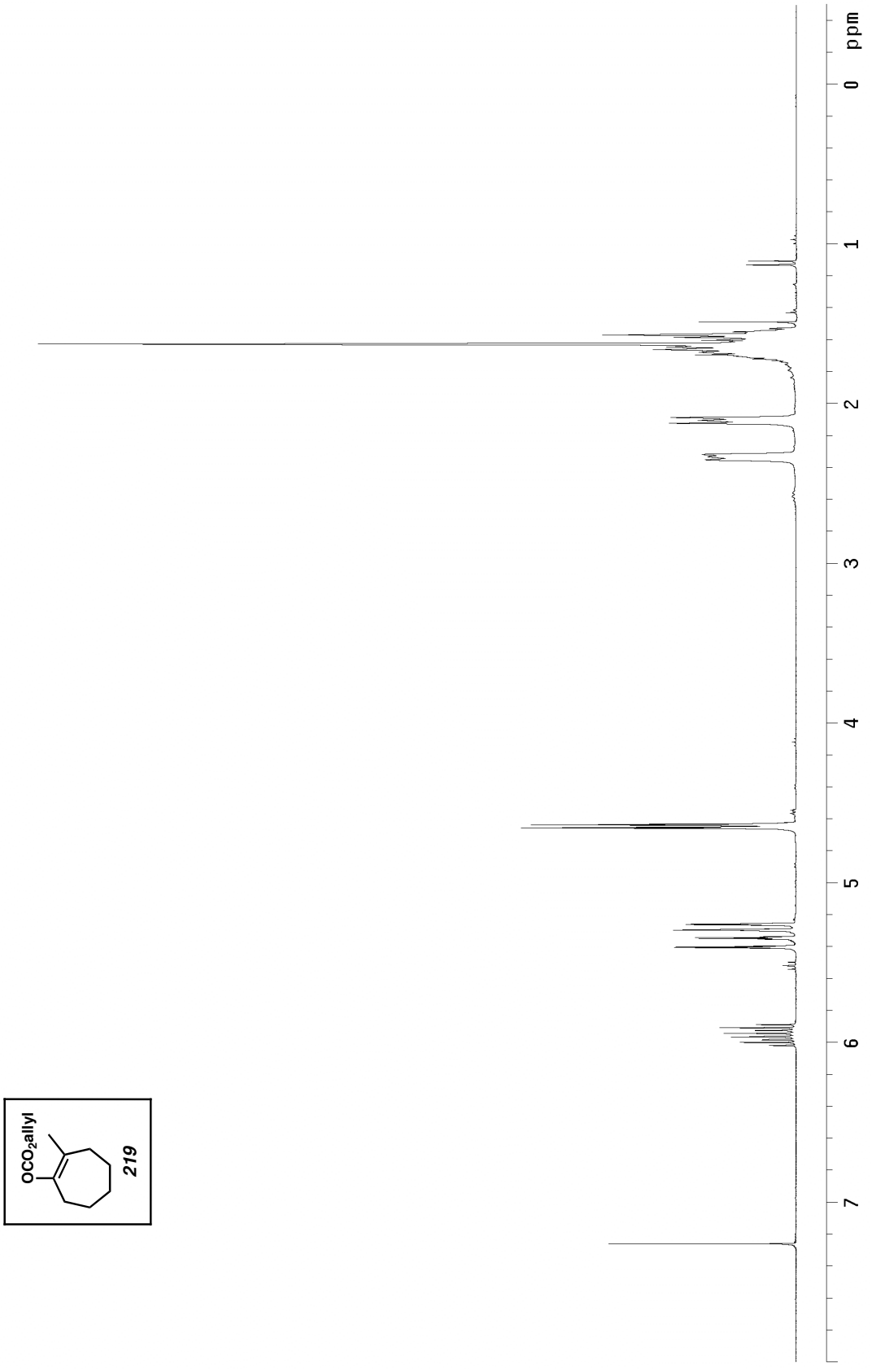


*Figure A1.99 ^{13}C NMR of compound **218** (75 MHz, $CDCl_3$)*


OCO2allyl
219
ppm
0
1
2
3
4
5
6
7

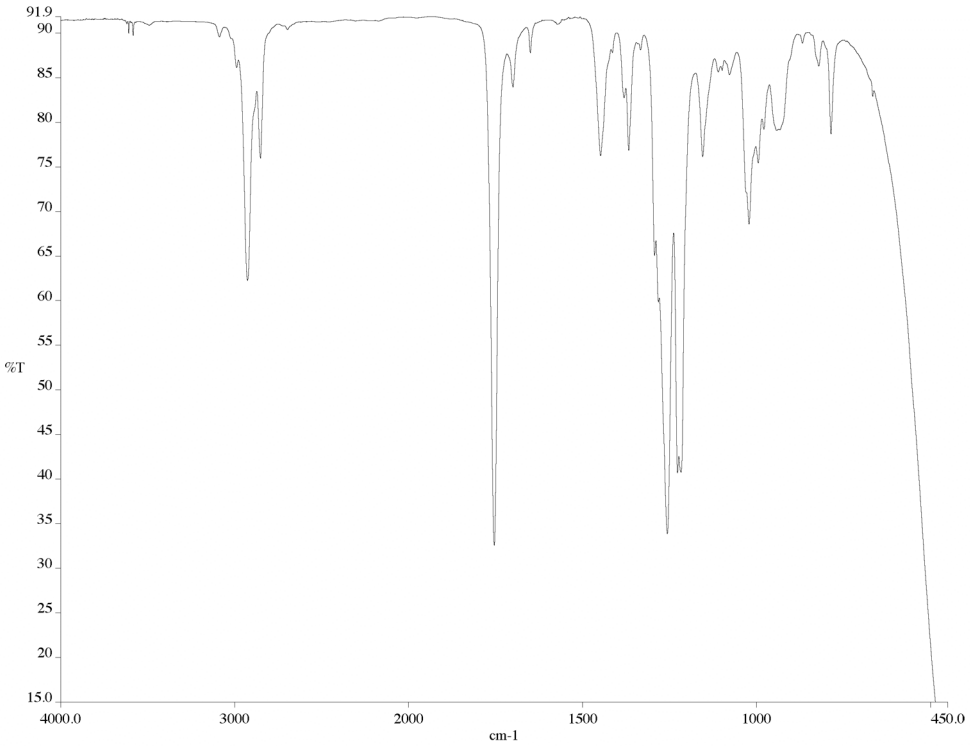


*Figure A1.101 IR of compound **219** (NaCl/film)*

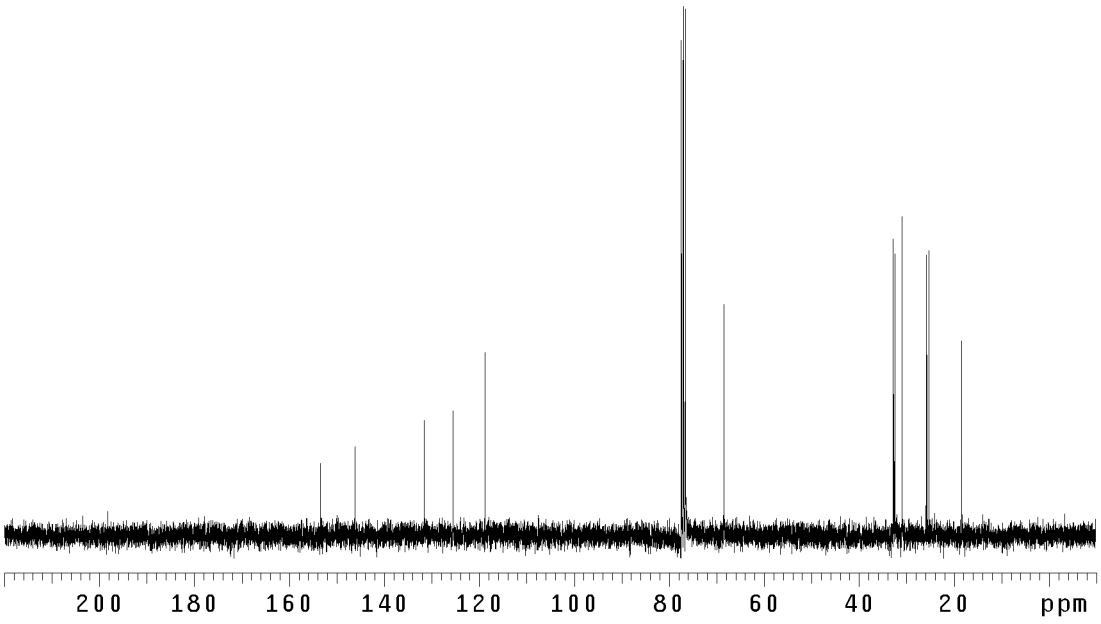
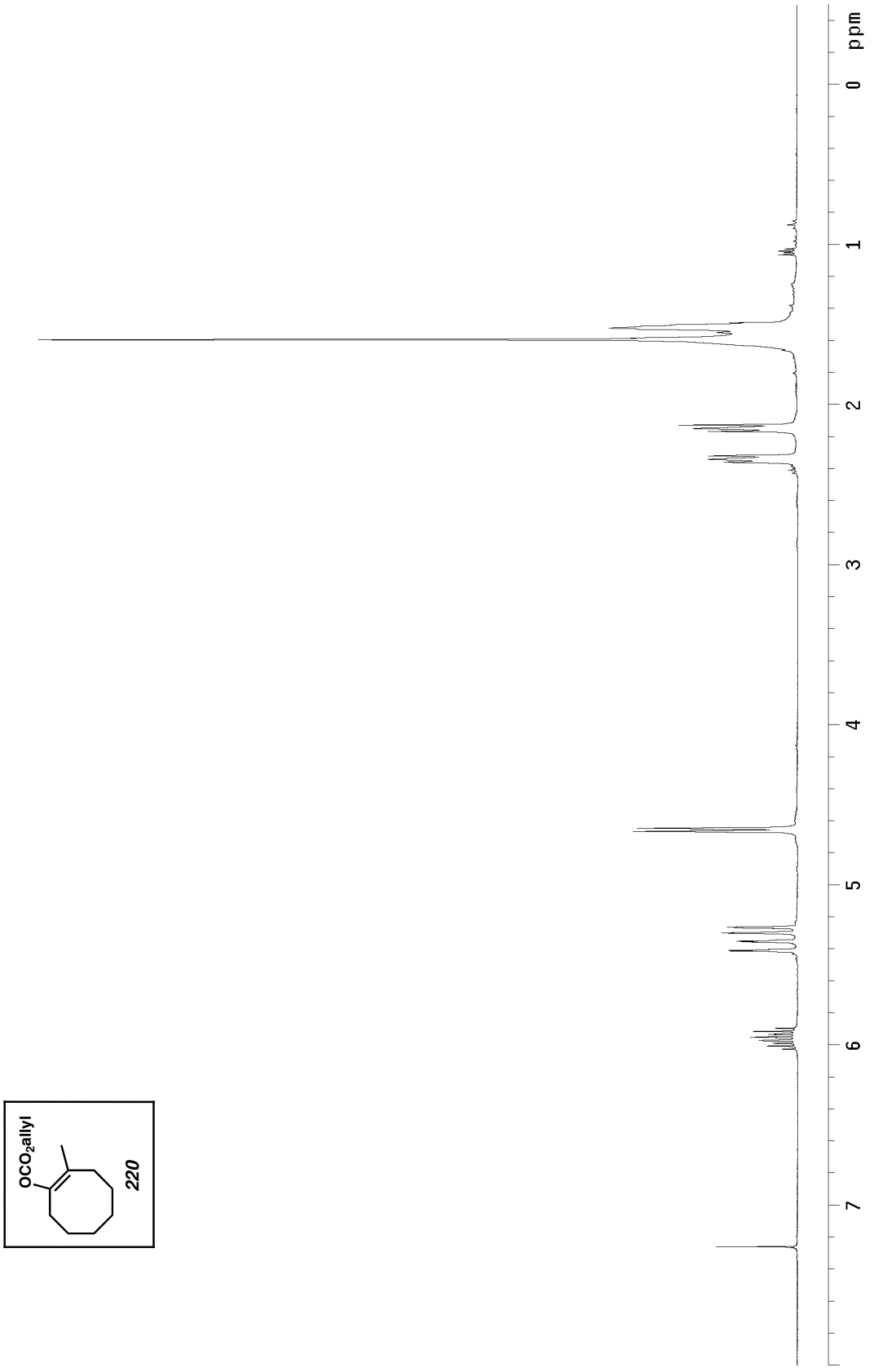


*Figure A1.102 ^{13}C NMR of compound **219** (75 MHz, $CDCl_3$)*


OCO2allyl
220
ppm
0
1
2
3
4
5
6
7

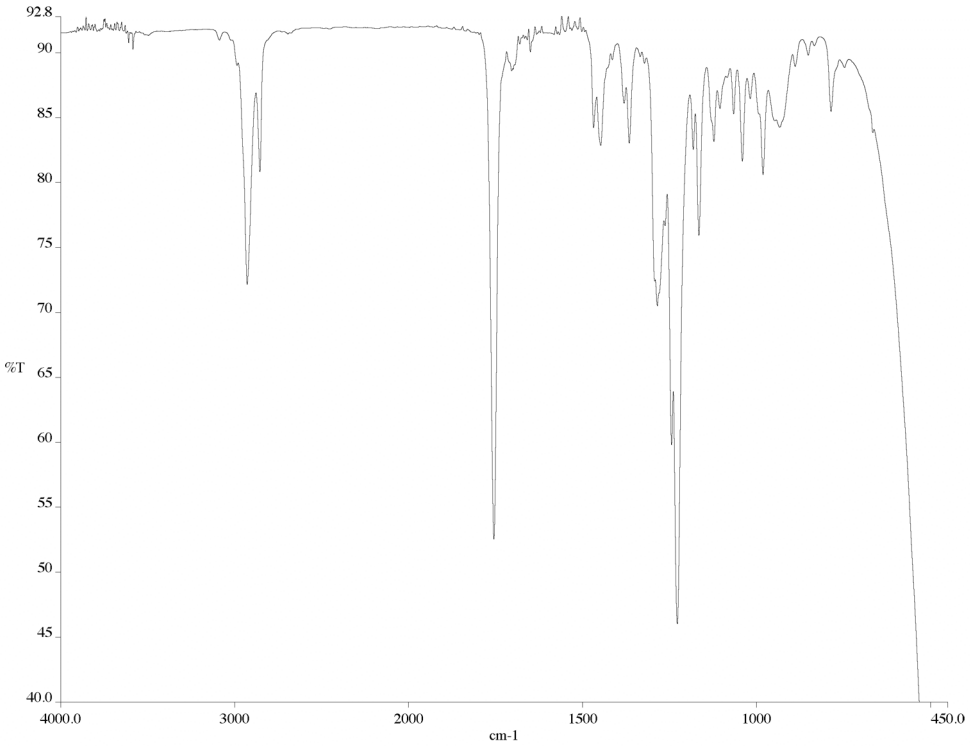


*Figure A1.104 IR of compound **220** (NaCl/film)*

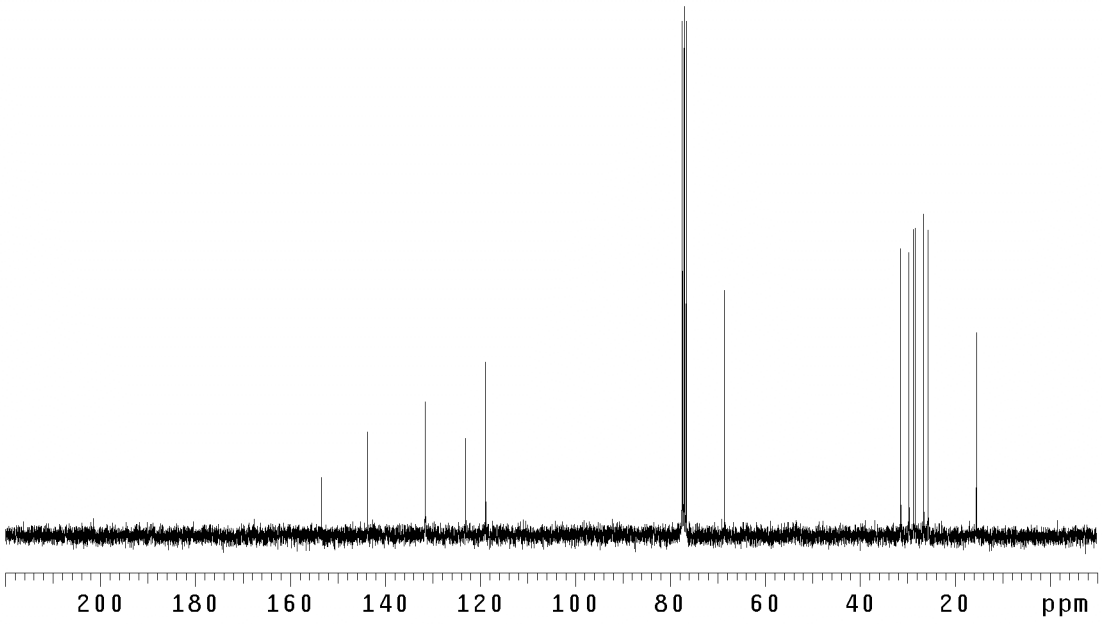
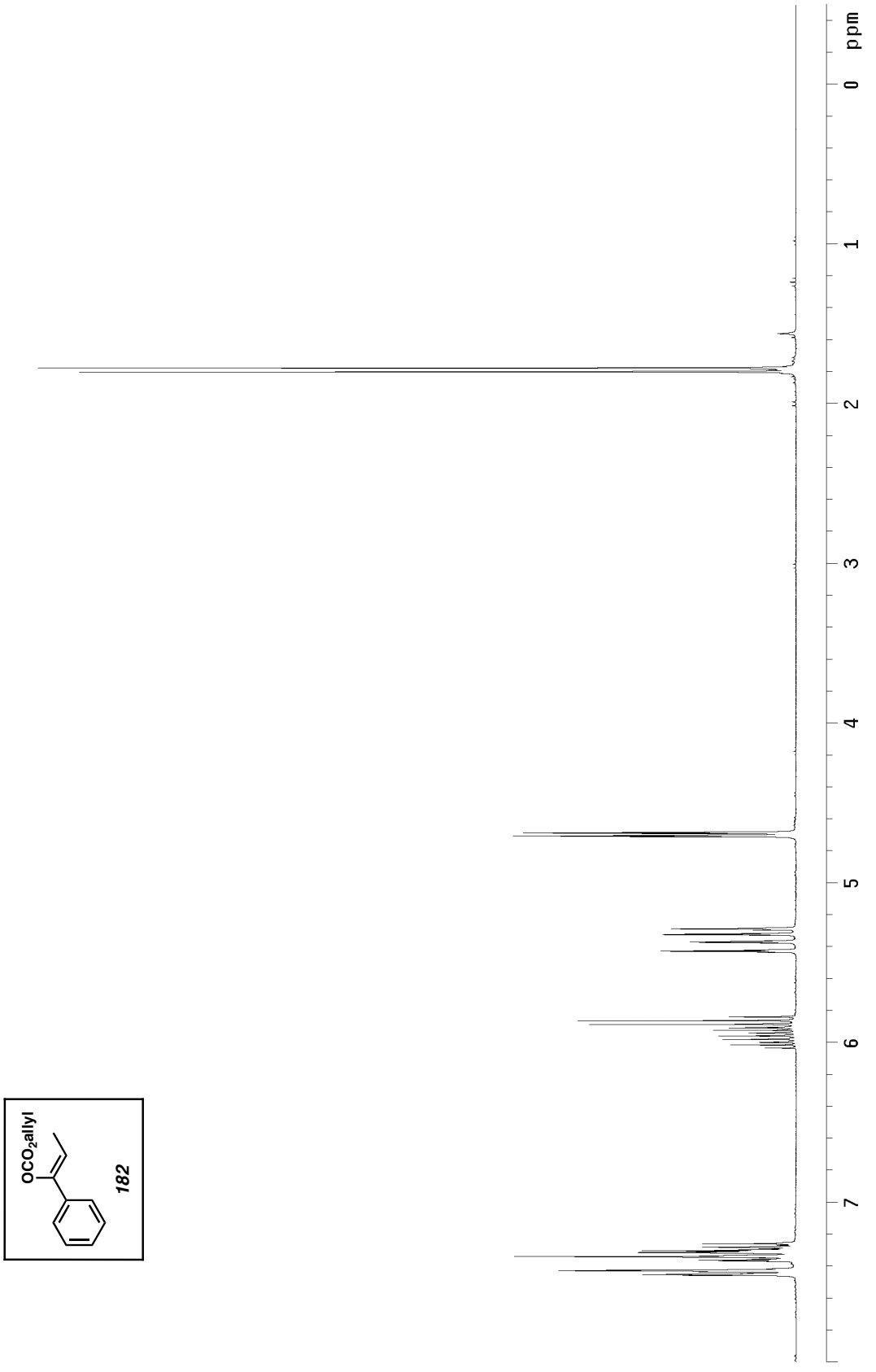


*Figure A1.105 ^{13}C NMR of compound **220** (75 MHz, $CDCl_3$)*


OCO2allyl
182
ppm
0
1
2
3
4
5
6
7

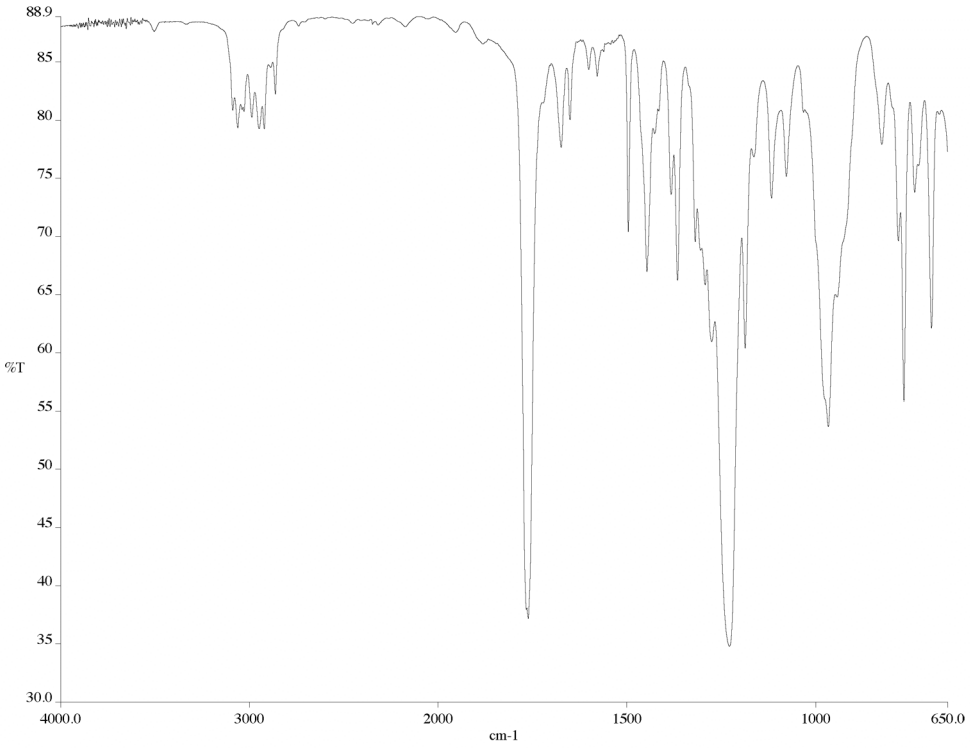


*Figure A1.107 IR of compound **182** (NaCl/film)*

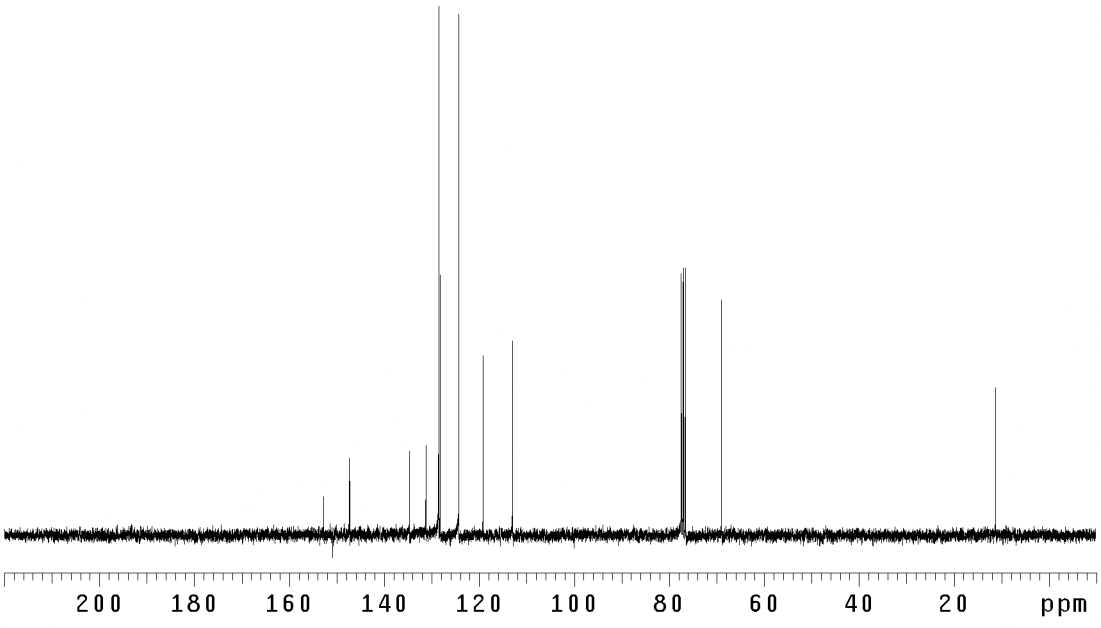


*Figure A1.108 ^{13}C NMR of compound **182** (75 MHz, $CDCl_3$)*

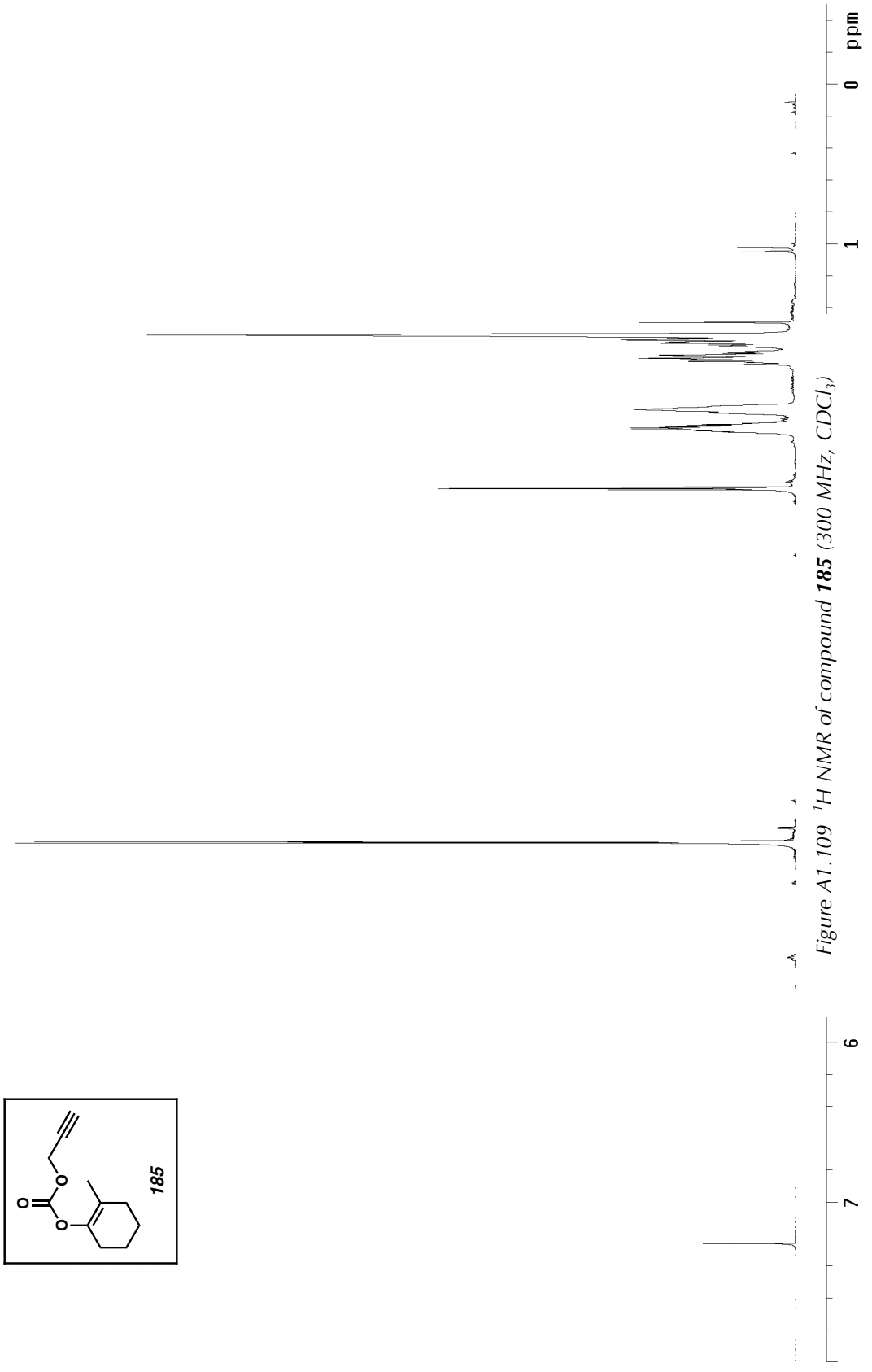


*Figure A1.109 ^1H NMR of compound **185** (300 MHz, $CDCl_3$)*

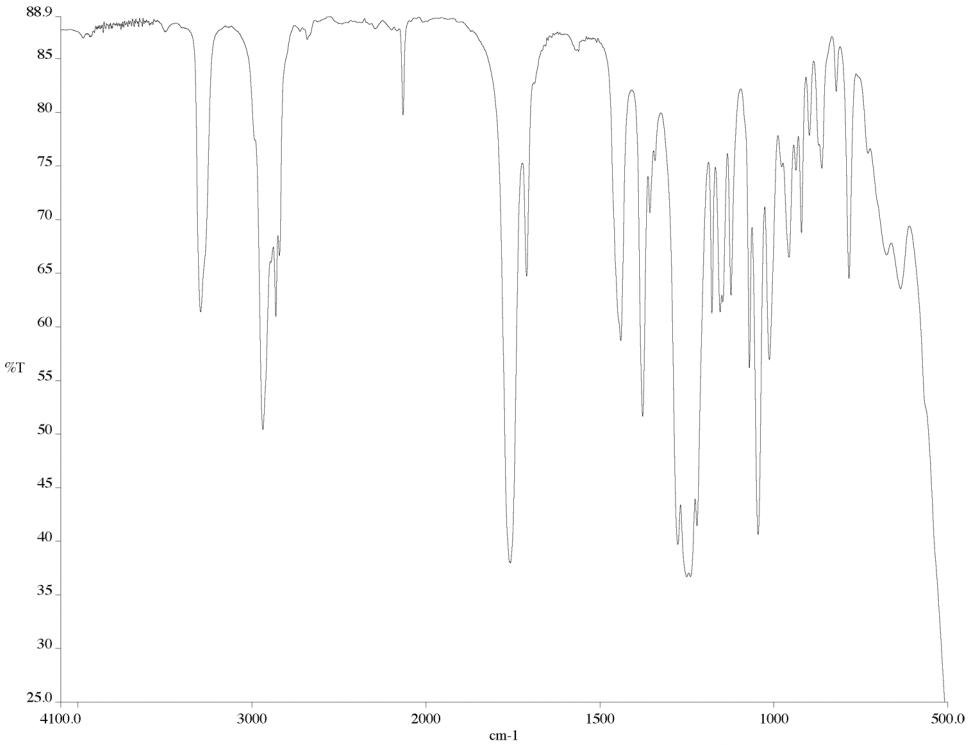


*Figure A1.110 IR of compound **185** (NaCl/film)*

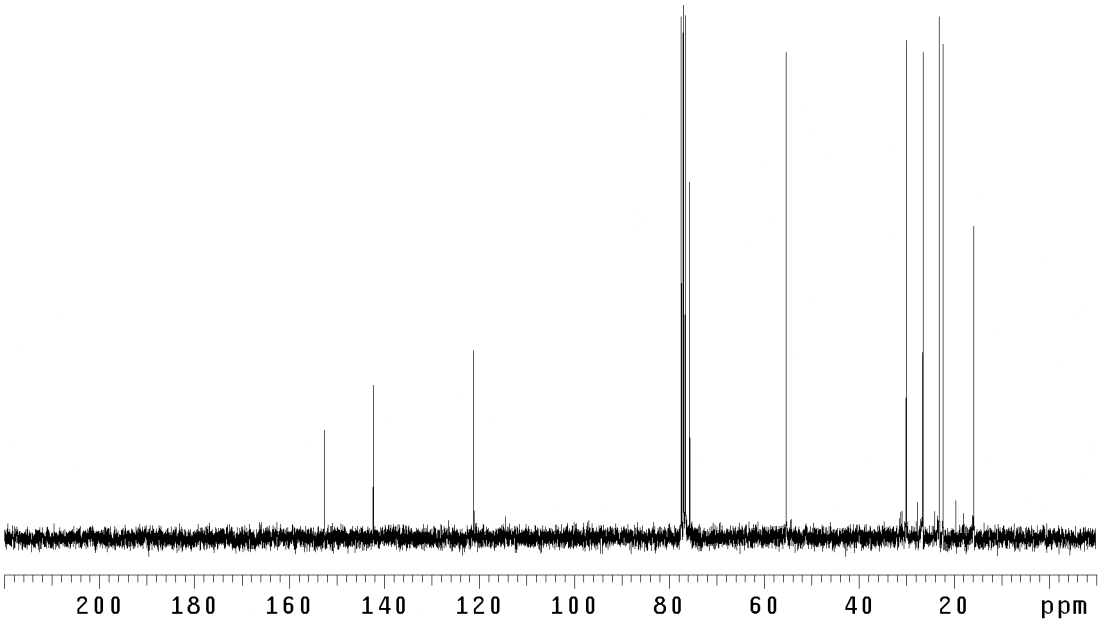


*Figure A1.111 ^{13}C NMR of compound **185** (75 MHz, $CDCl_3$)*

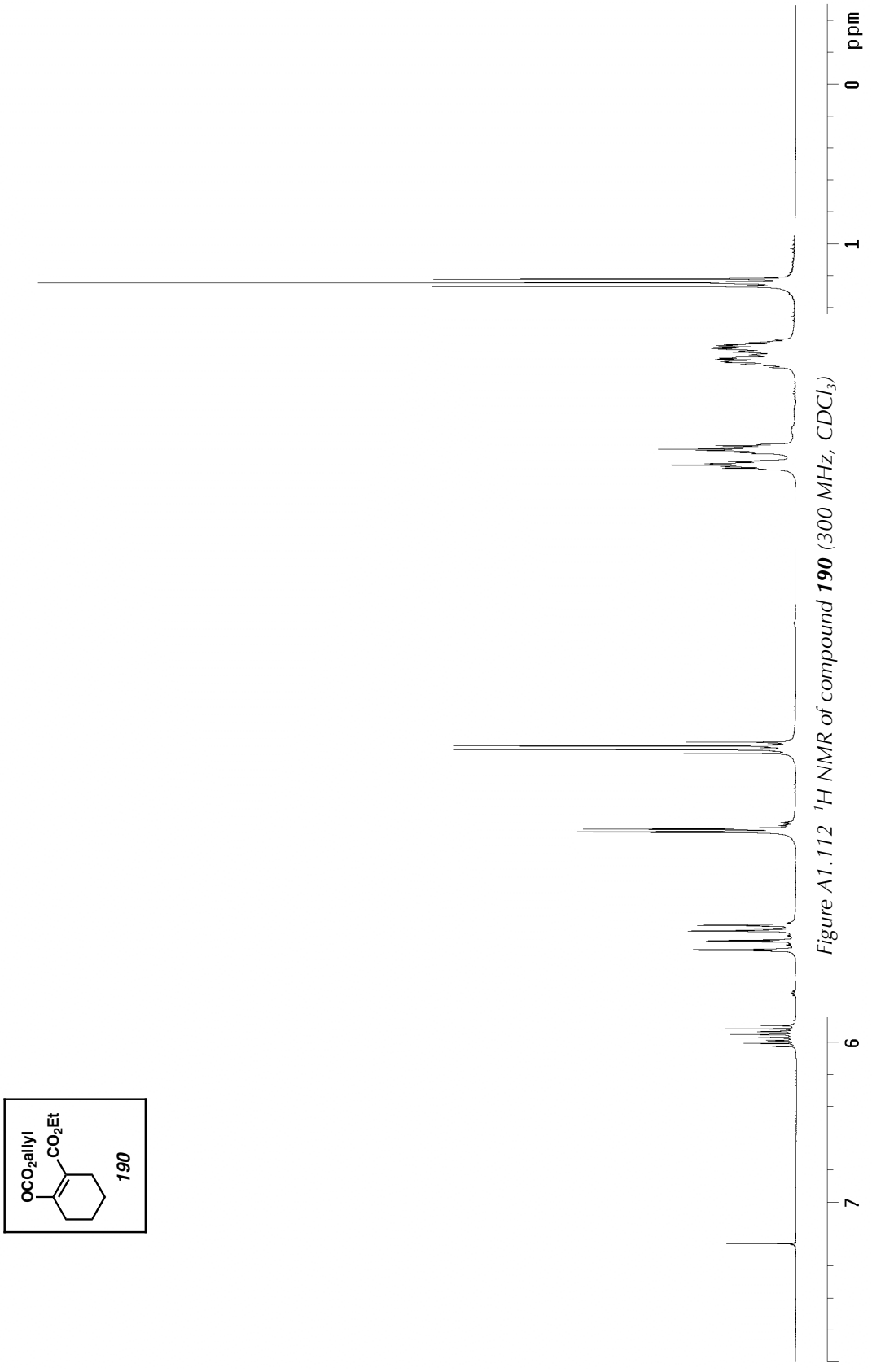


Figure A1.112 ^{1}H *NMR of compound* ***190*** *(300 MHz,* $CDCl_3$*)*

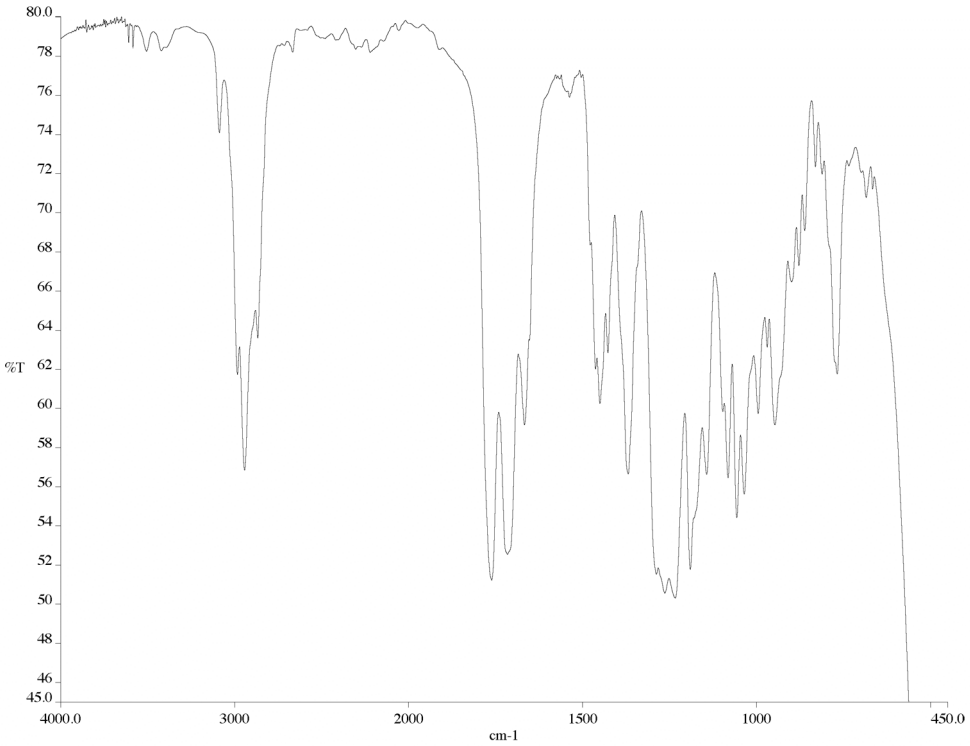


*Figure A1.113 IR of compound **190** (NaCl/film)*

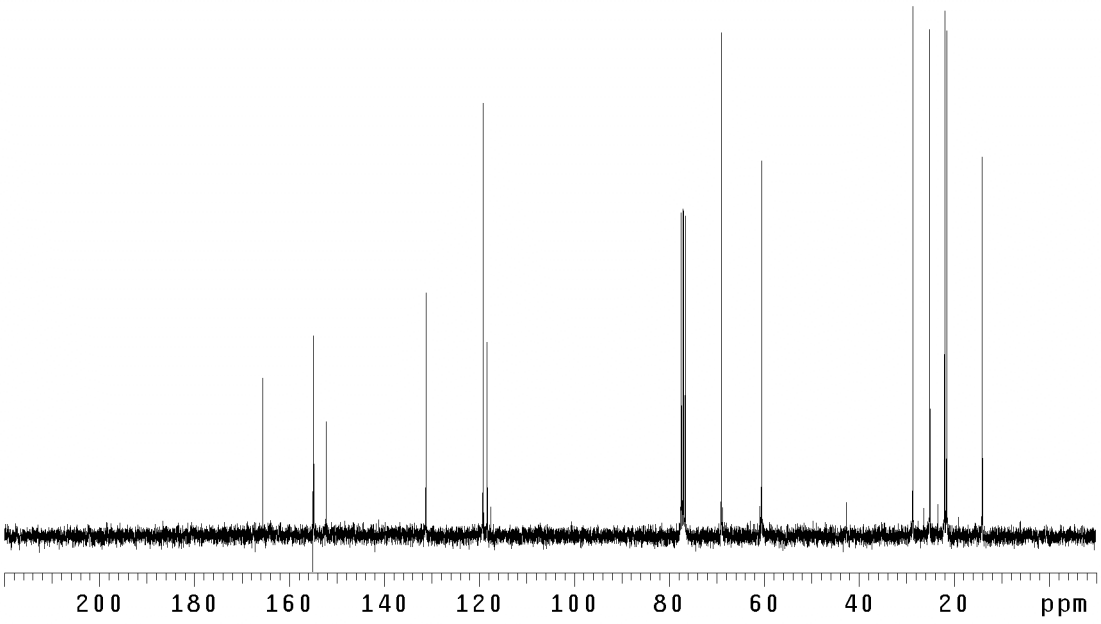


*Figure A1.114 ^{13}C NMR of compound **190** (75 MHz, $CDCl_3$)*

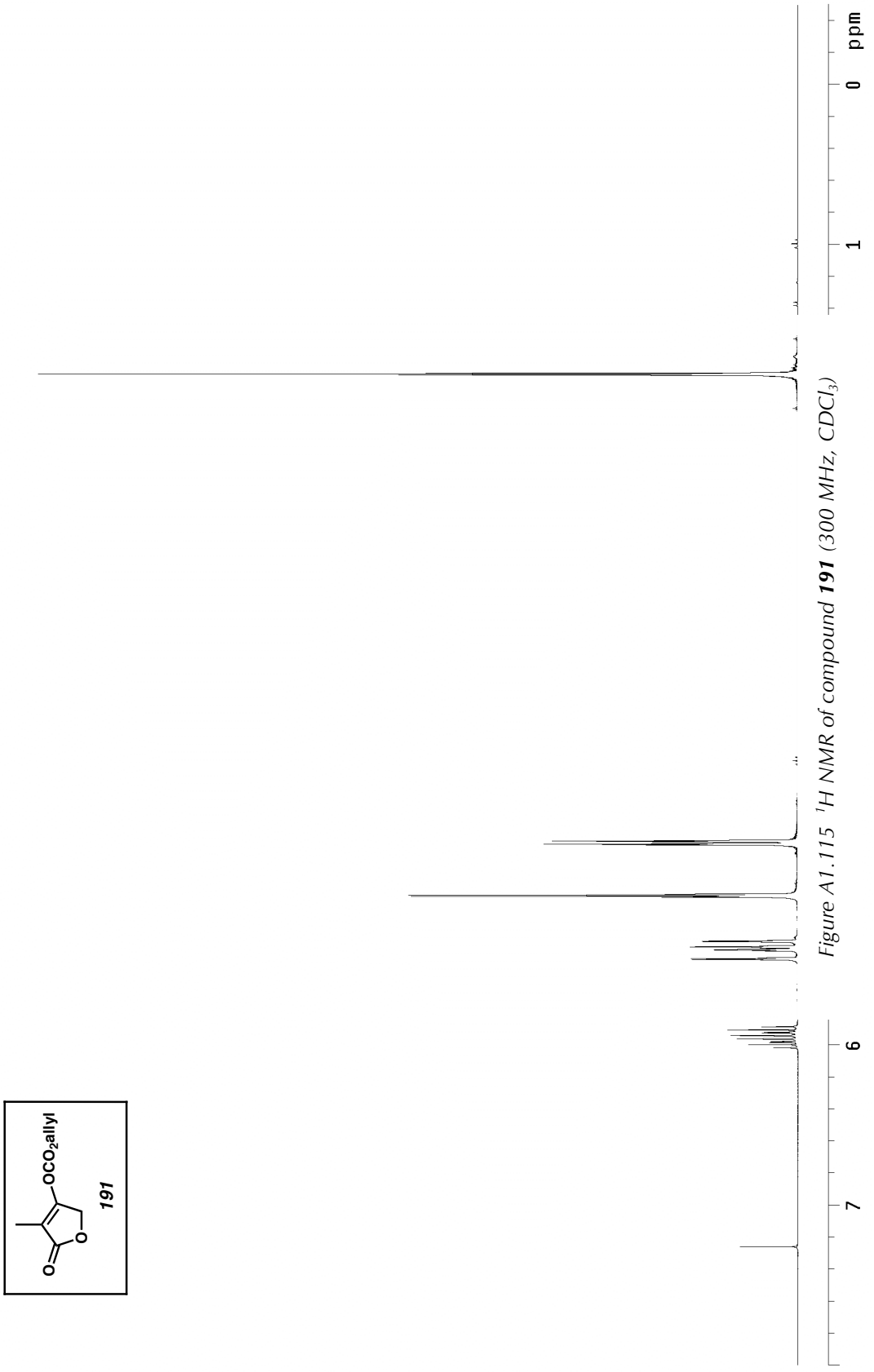


*Figure A1.115 ^1H NMR of compound **191** (300 MHz, $CDCl_3$)*

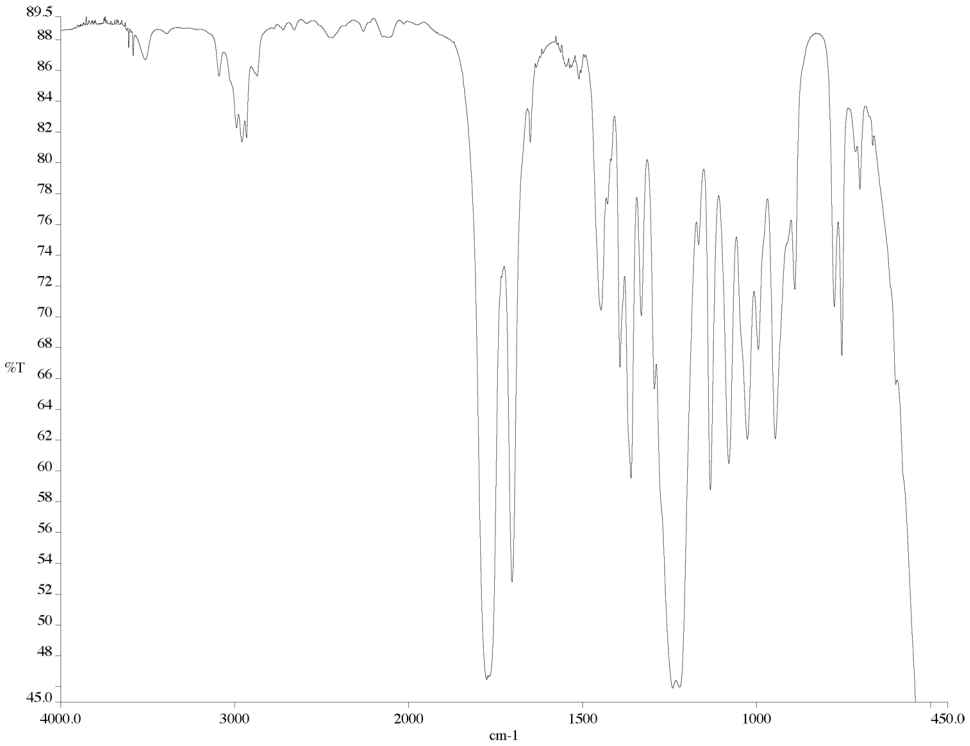


*Figure A1.116 IR of compound **191** (NaCl/film)*

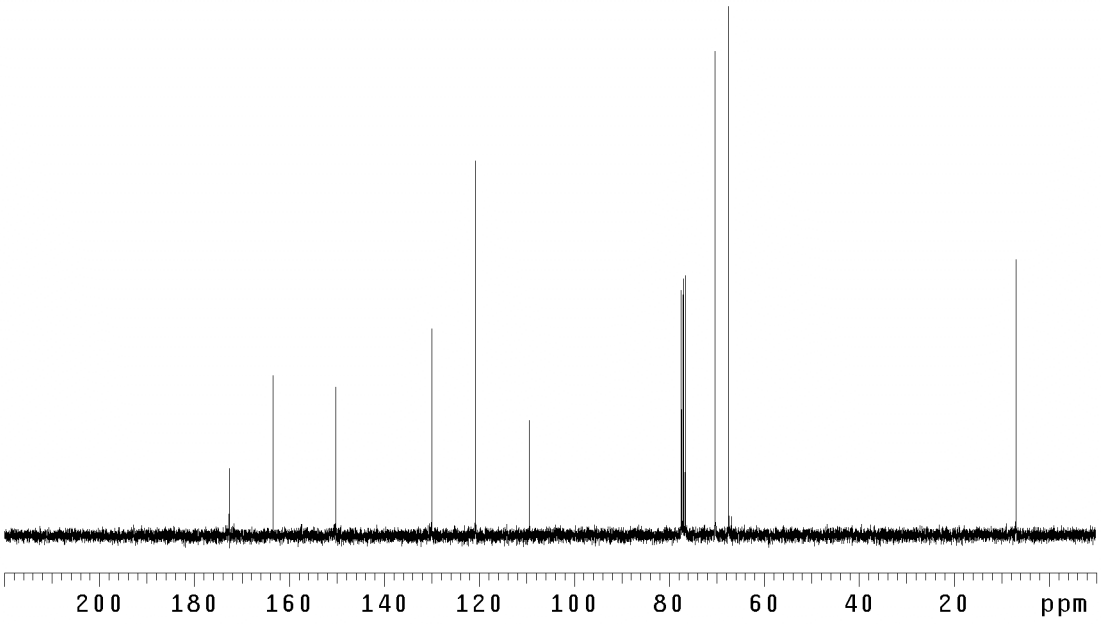
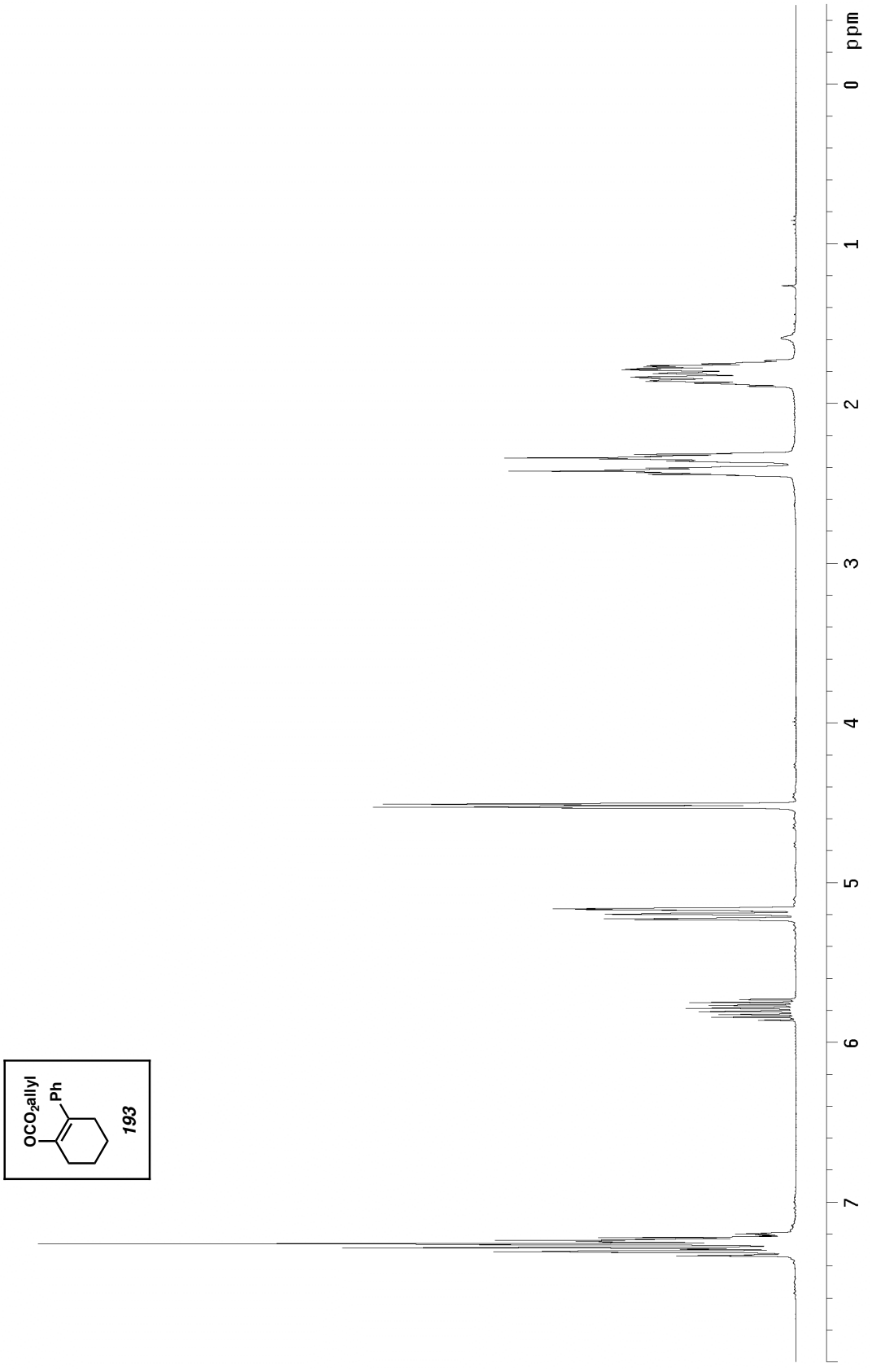


*Figure A1.117 ^{13}C NMR of compound **191** (75 MHz, $CDCl_3$)*


OCO2allyl
Ph
193
ppm
0
1
2
3
4
5
6
7

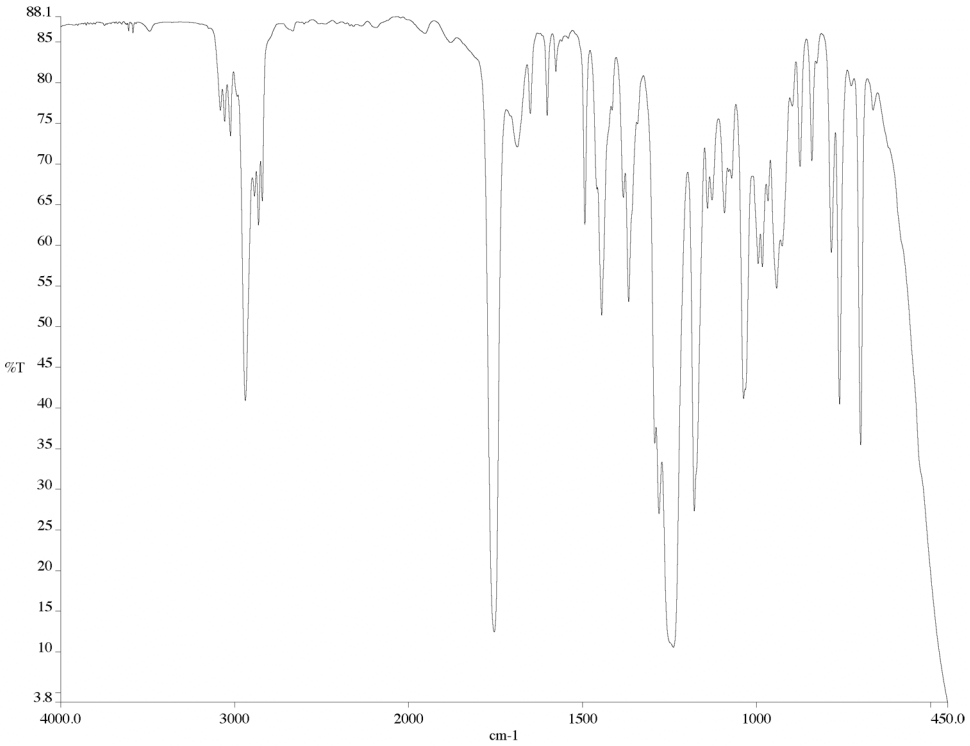


*Figure A1.119 IR of compound **193** (NaCl/film)*

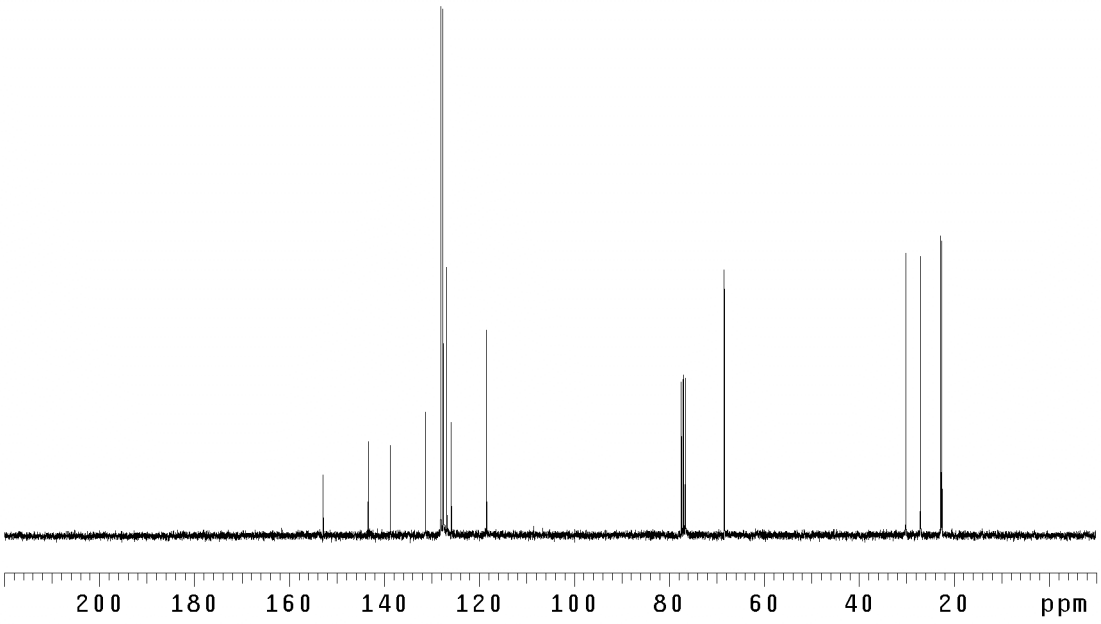
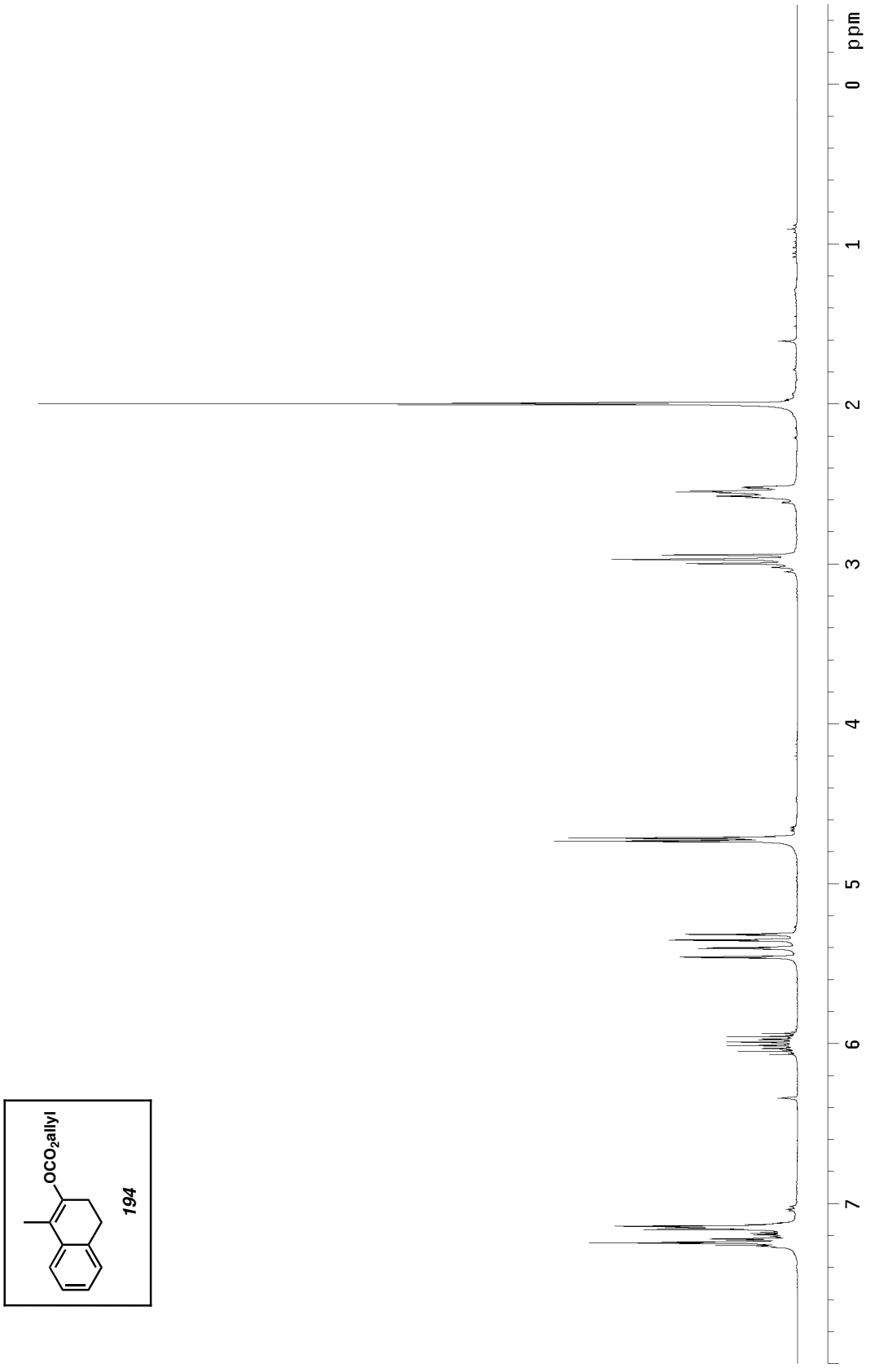


*Figure A1.120 ^{13}C NMR of compound **193** (75 MHz, $CDCl_3$)*


OCO2allyl
194
ppm
0
1
2
3
4
5
6
7

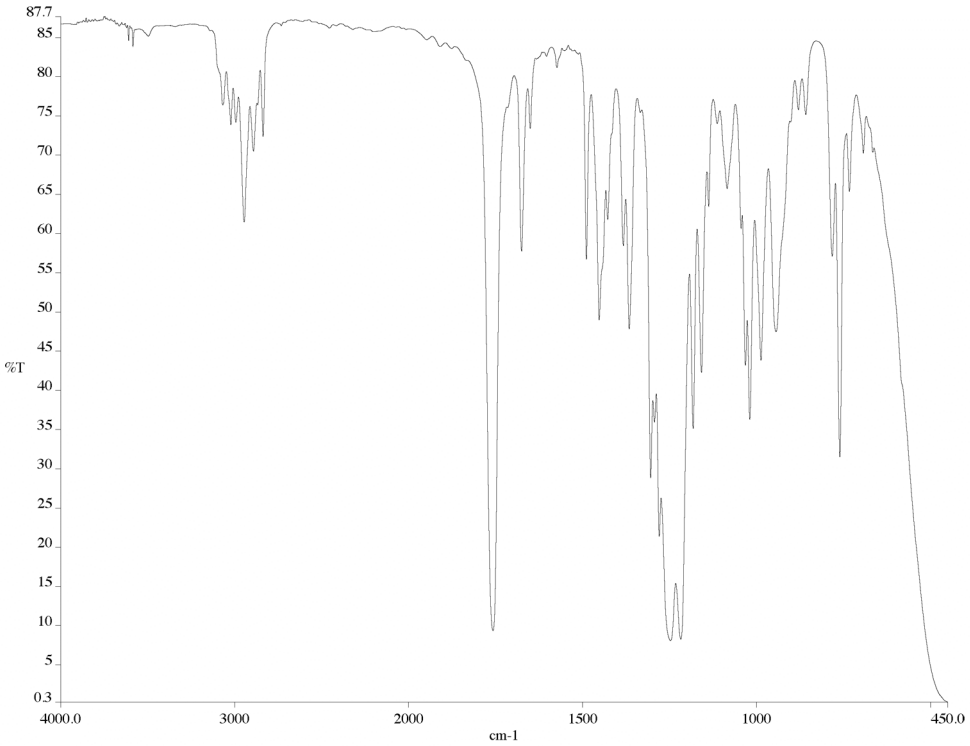


*Figure A1.122 IR of compound **194** (NaCl/film)*

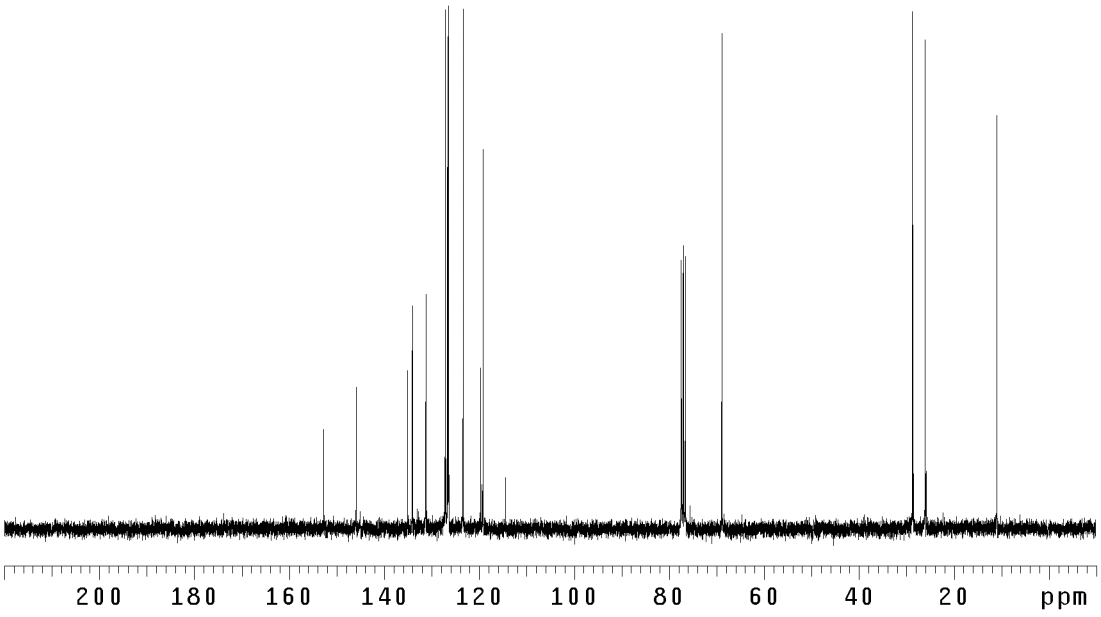
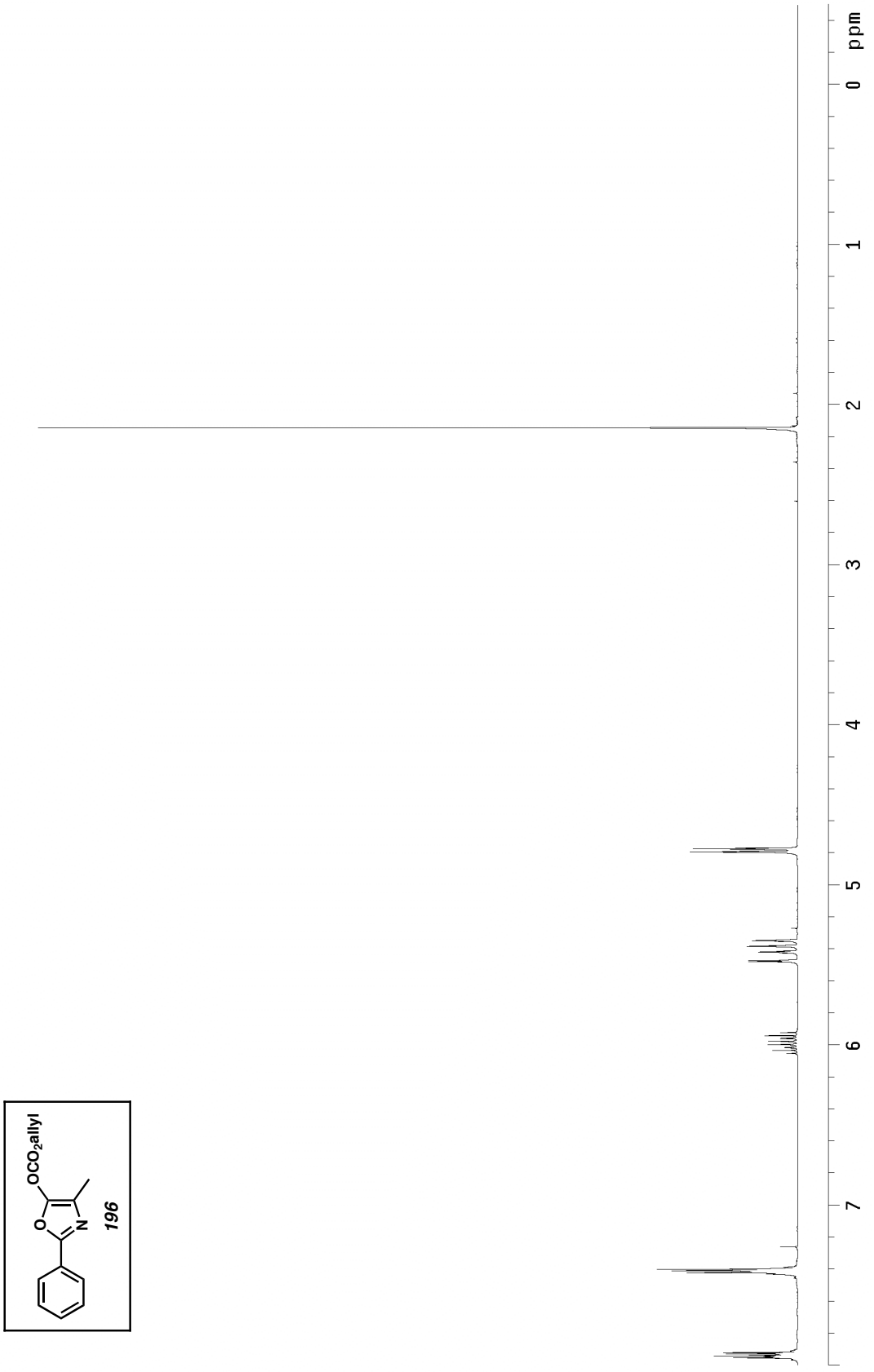


*Figure A1.123 ^{13}C NMR of compound **194** (75 MHz, $CDCl_3$)*


OCO2allyl
O
N
196
ppm
0
1
2
3
4
5
6
7

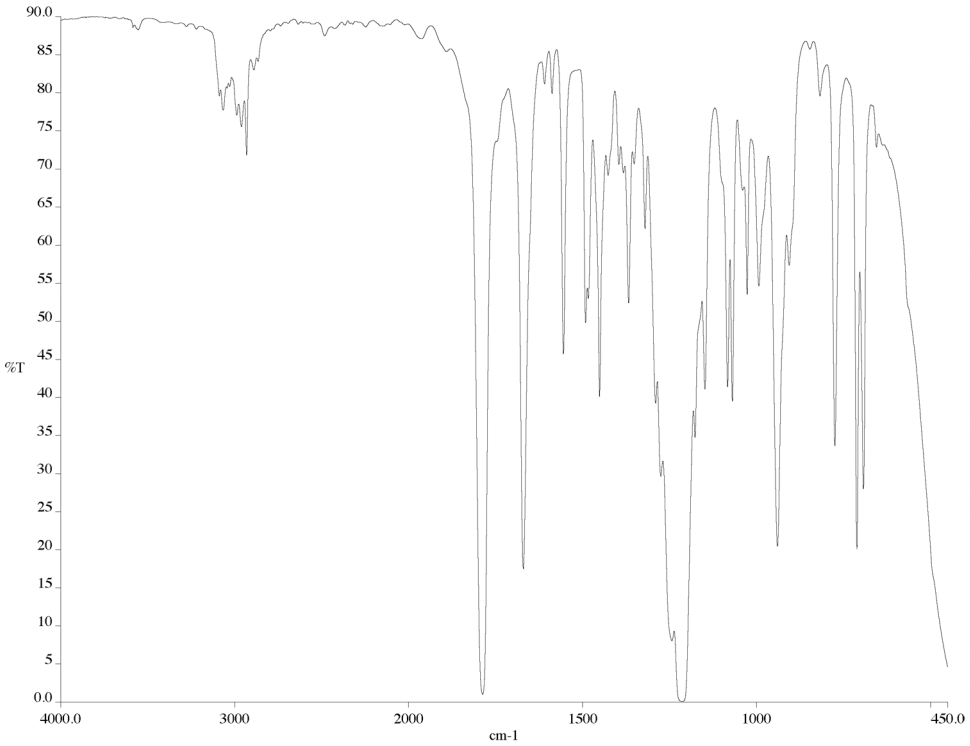


*Figure A1.125 IR of compound **196** (NaCl/film)*

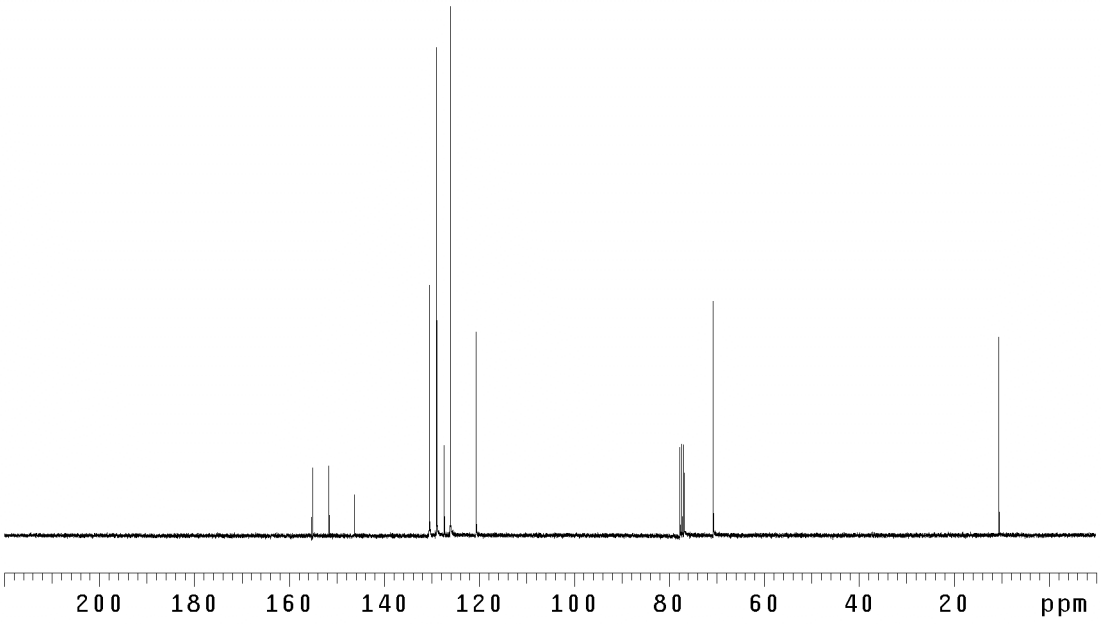


*Figure A1.126 ^{13}C NMR of compound **196** (75 MHz, $CDCl_3$)*

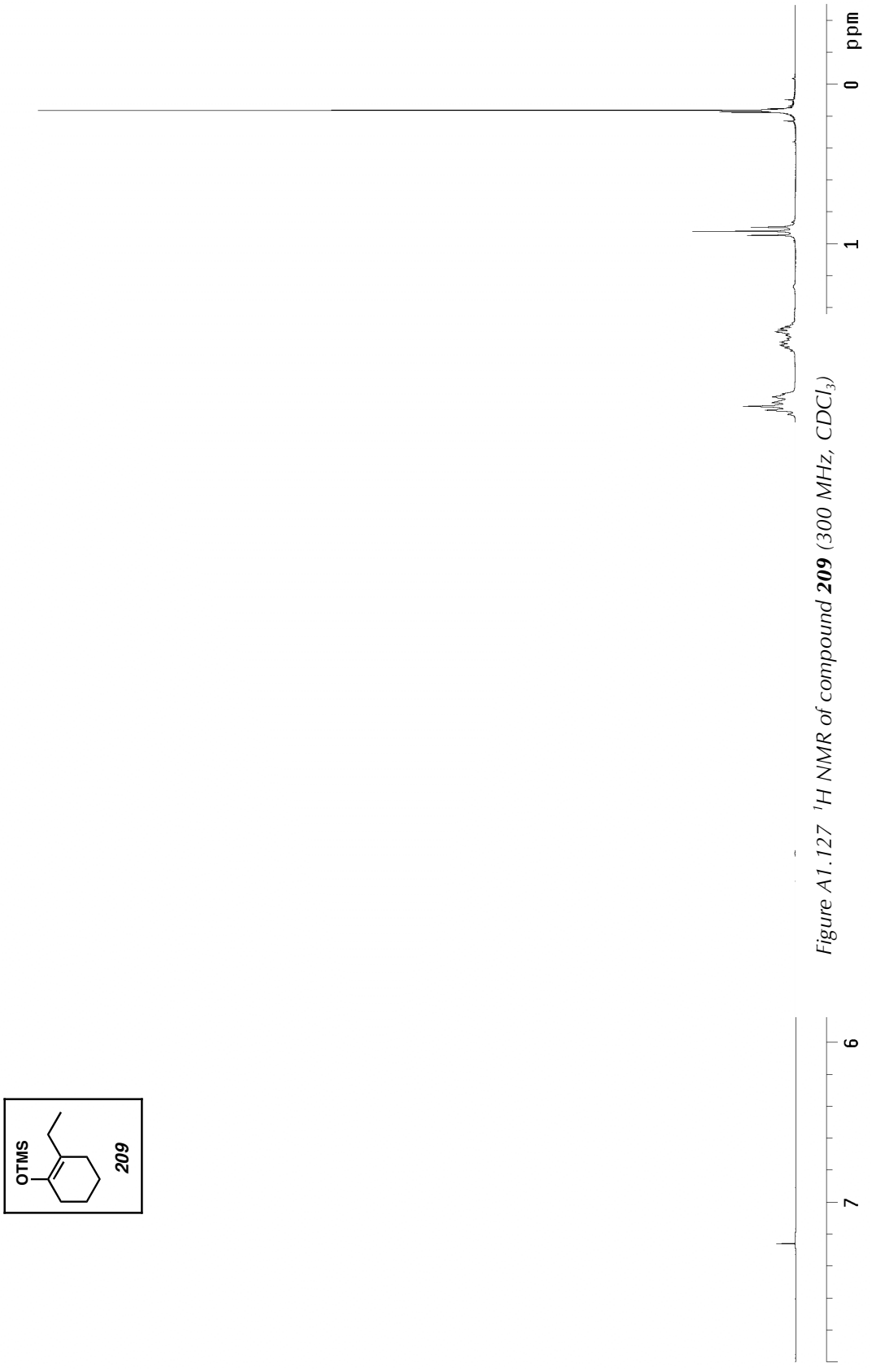


*Figure A1.127 ^1H NMR of compound **209** (300 MHz, $CDCl_3$)*

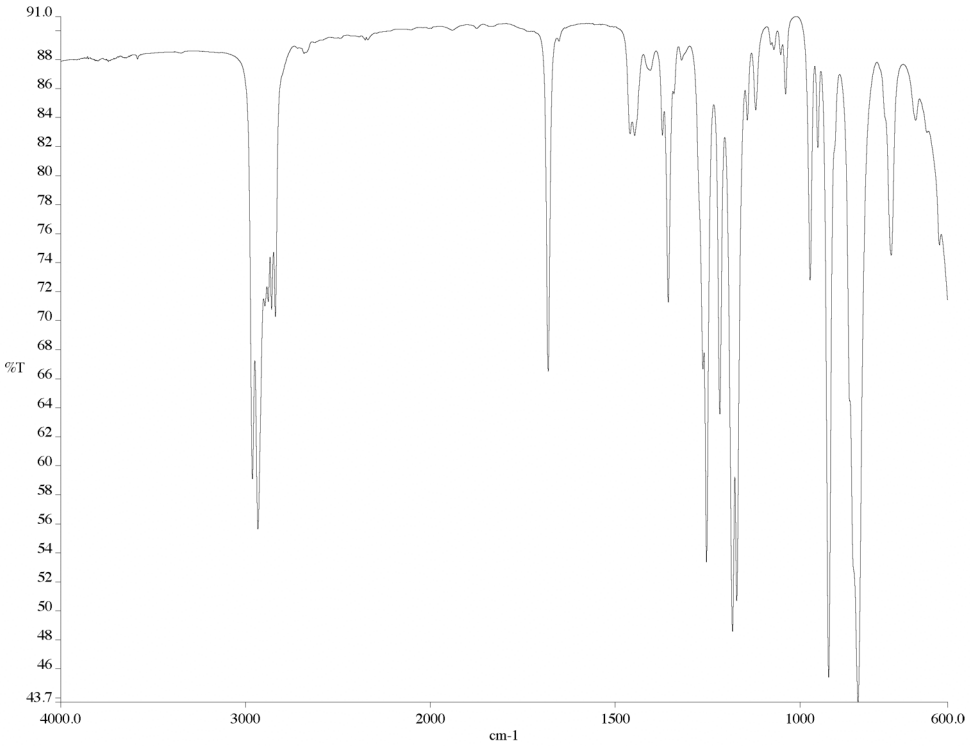


*Figure A1.128 IR of compound **209** (NaCl/film)*

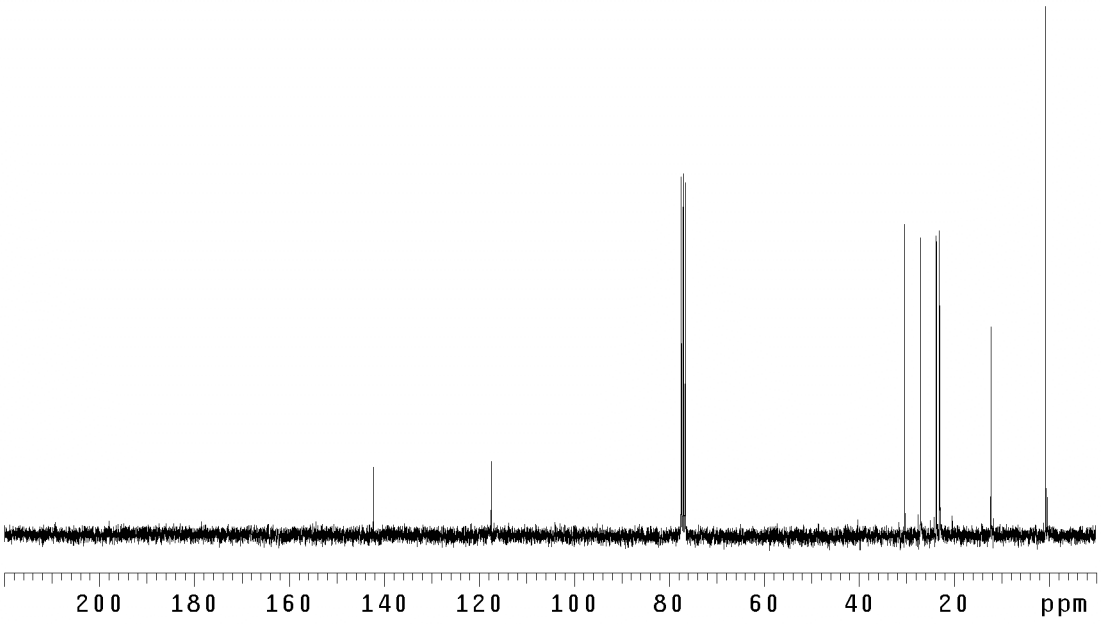
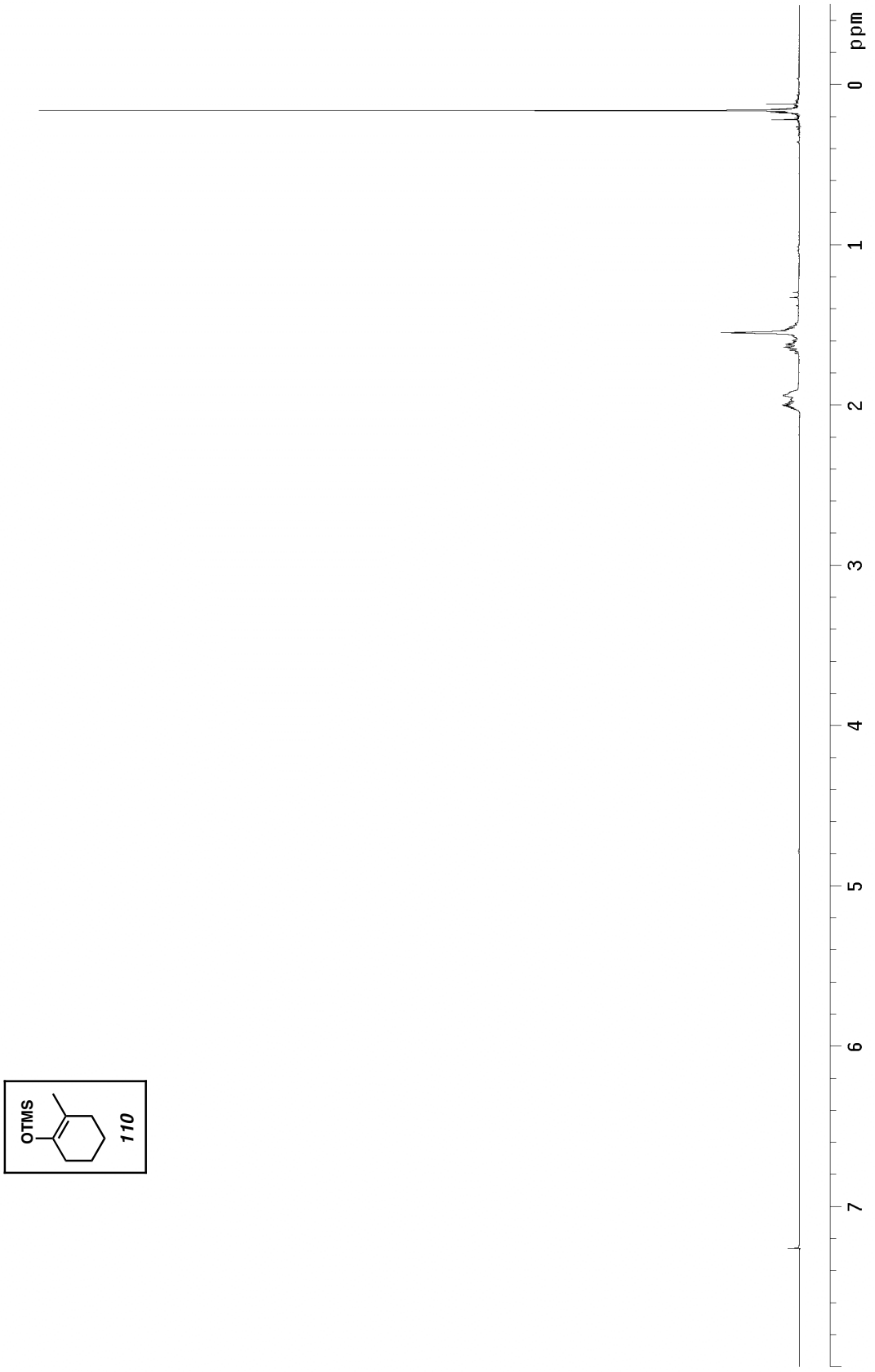


*Figure A1.129 ^{13}C NMR of compound **209** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
OTMS
110

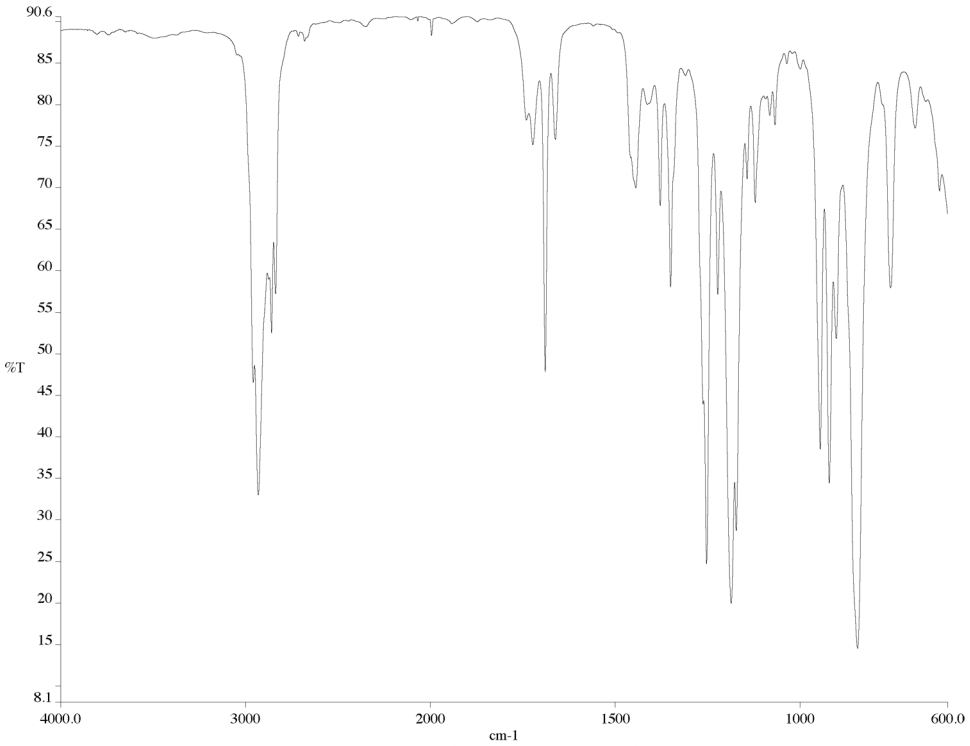


*Figure A1.131 IR of compound **110** (NaCl/film)*

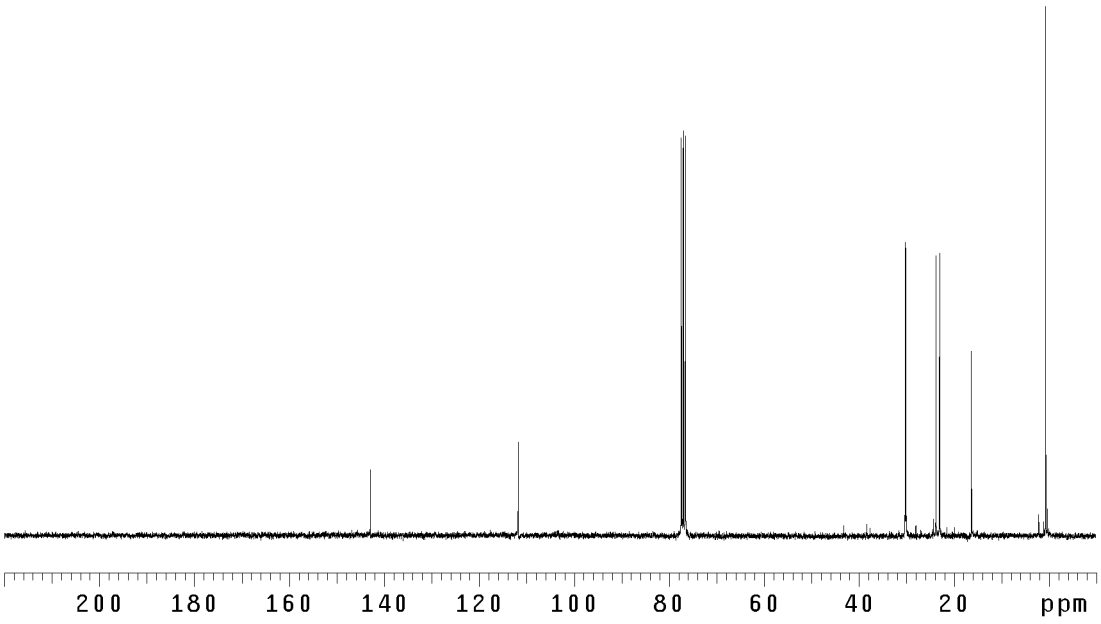
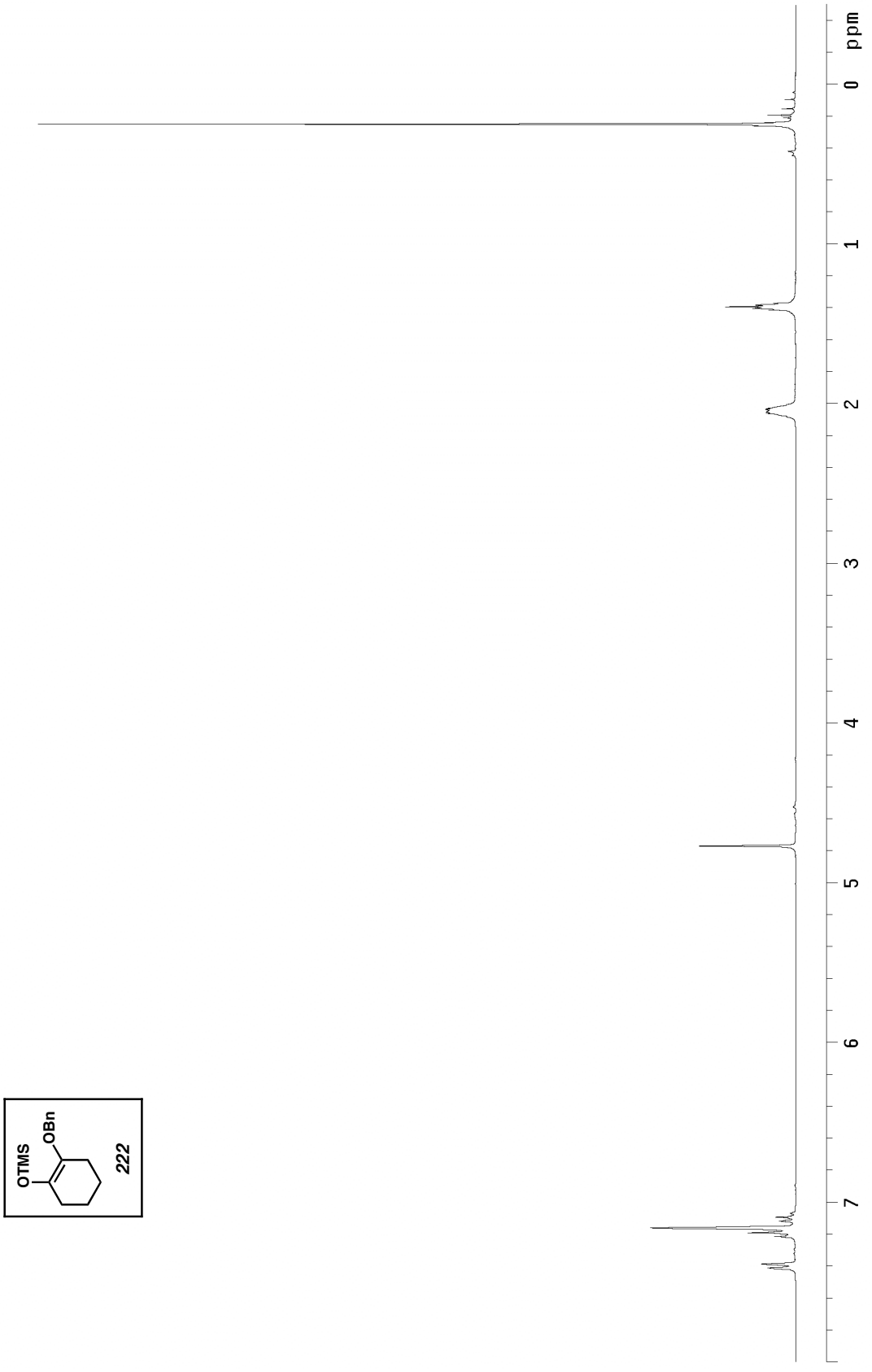


*Figure A1.132 ^{13}C NMR of compound **110** (75 MHz, $CDCl_3$)*


OTMS
OBn
222
ppm
0
1
2
3
4
5
6
7

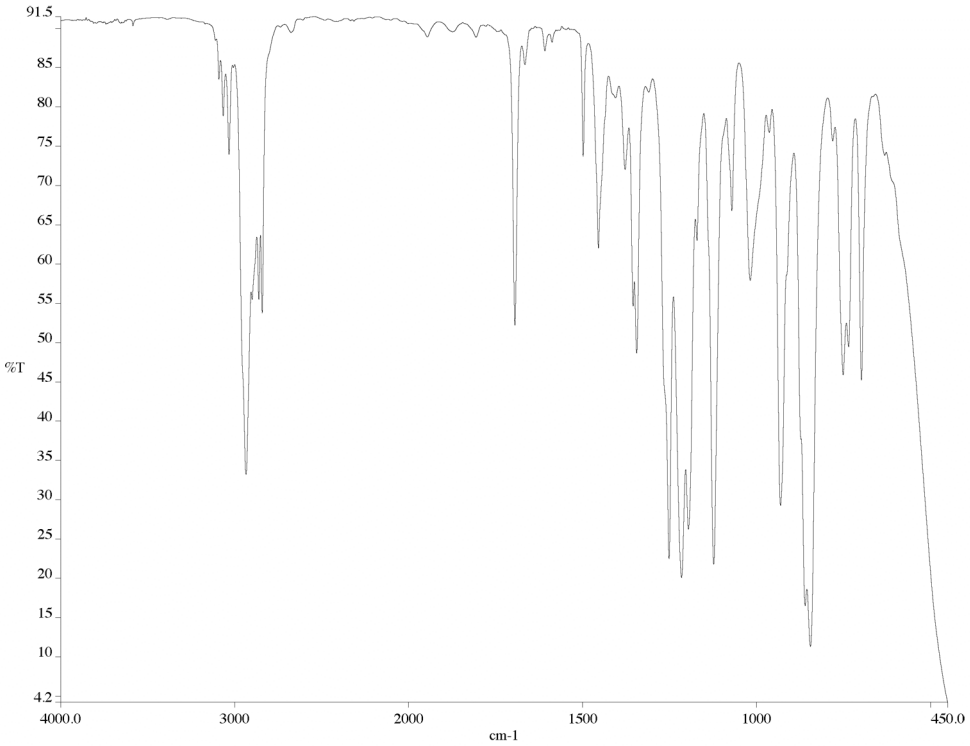


*Figure A1.134 IR of compound **222** (NaCl/film)*

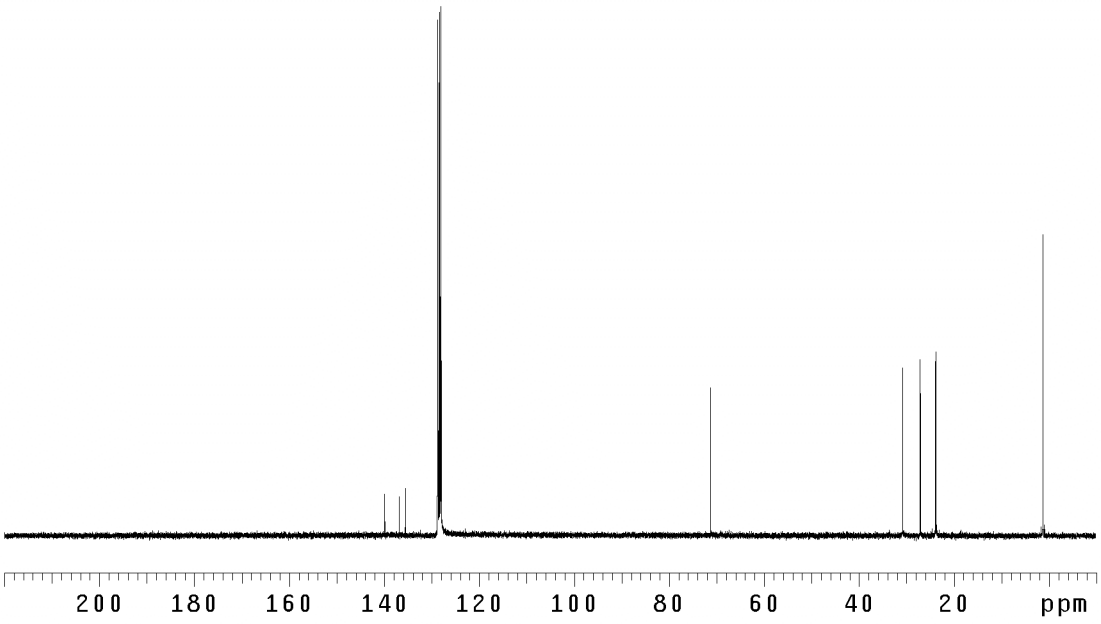
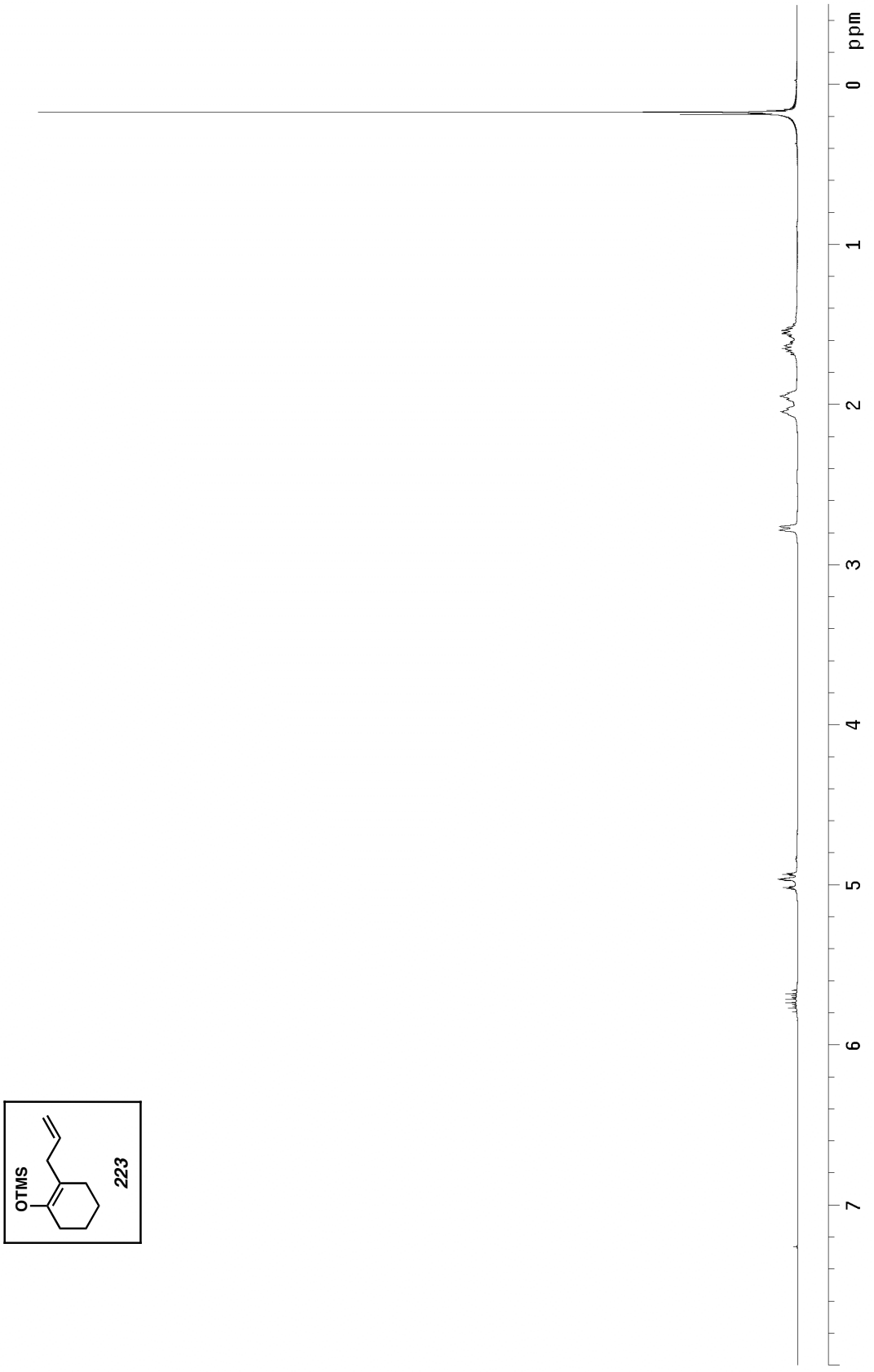


*Figure A1.135 ^{13}C NMR of compound **222** (75 MHz, C_6D_6)*


OTMS
223
ppm
0
1
2
3
4
5
6
7

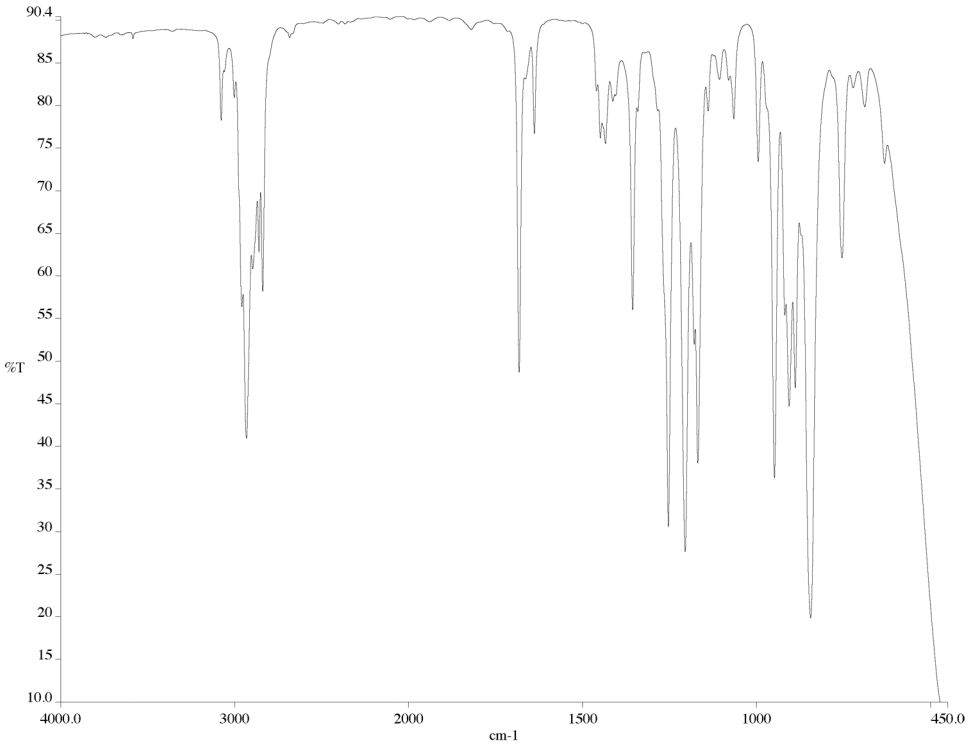


*Figure A1.137 IR of compound **223** (NaCl/film)*

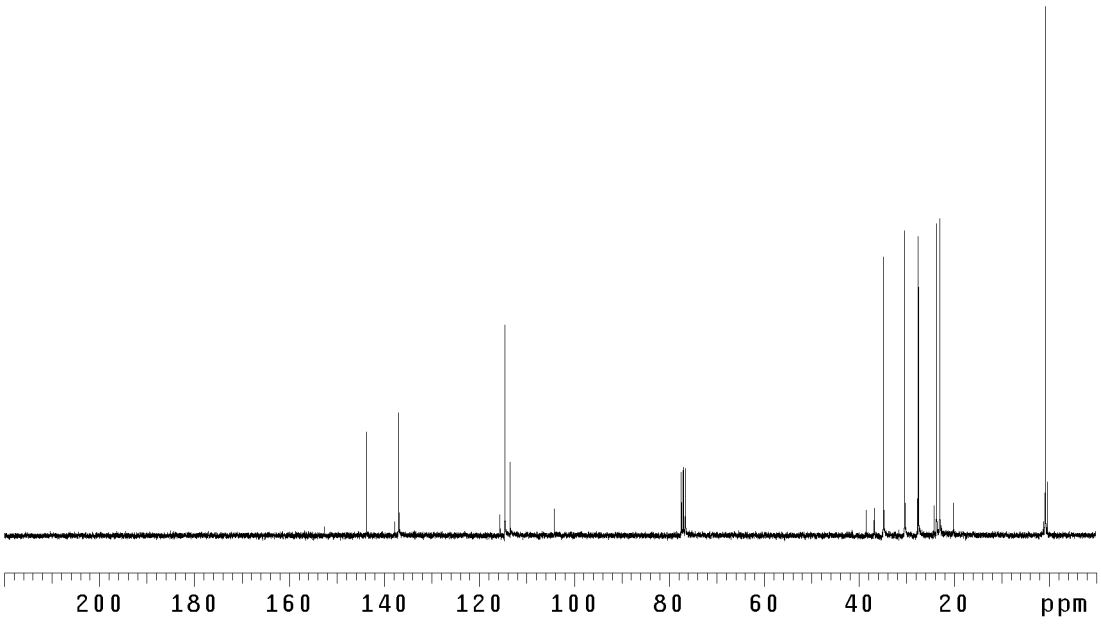
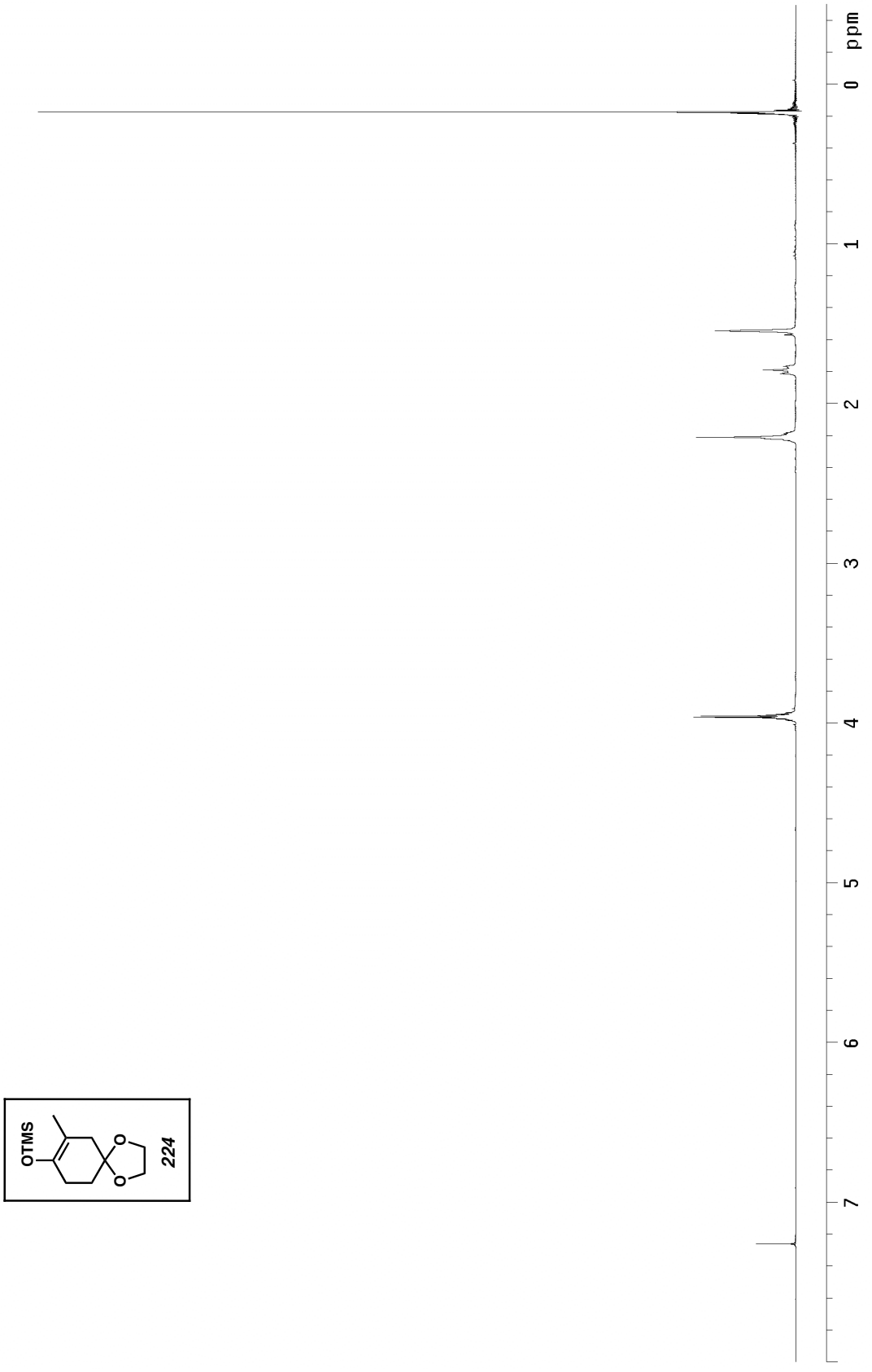


*Figure A1.138 ^{13}C NMR of compound **223** (75 MHz, $CDCl_3$)*


OTMS
224
ppm
0
1
2
3
4
5
6
7

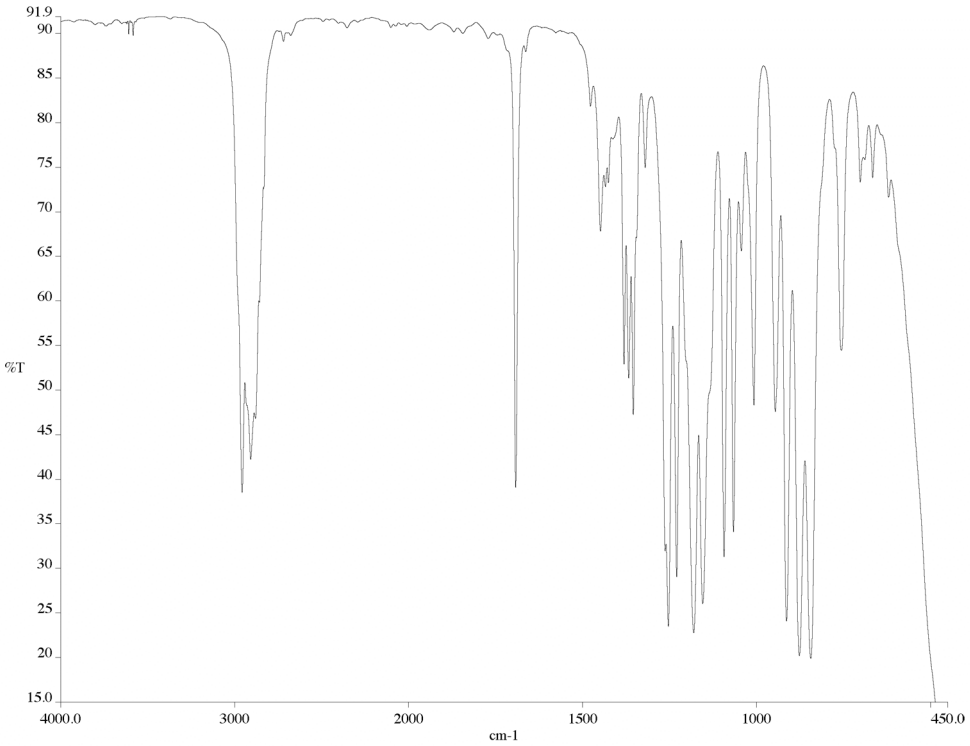


*Figure A1.140 IR of compound **224** (NaCl/film)*

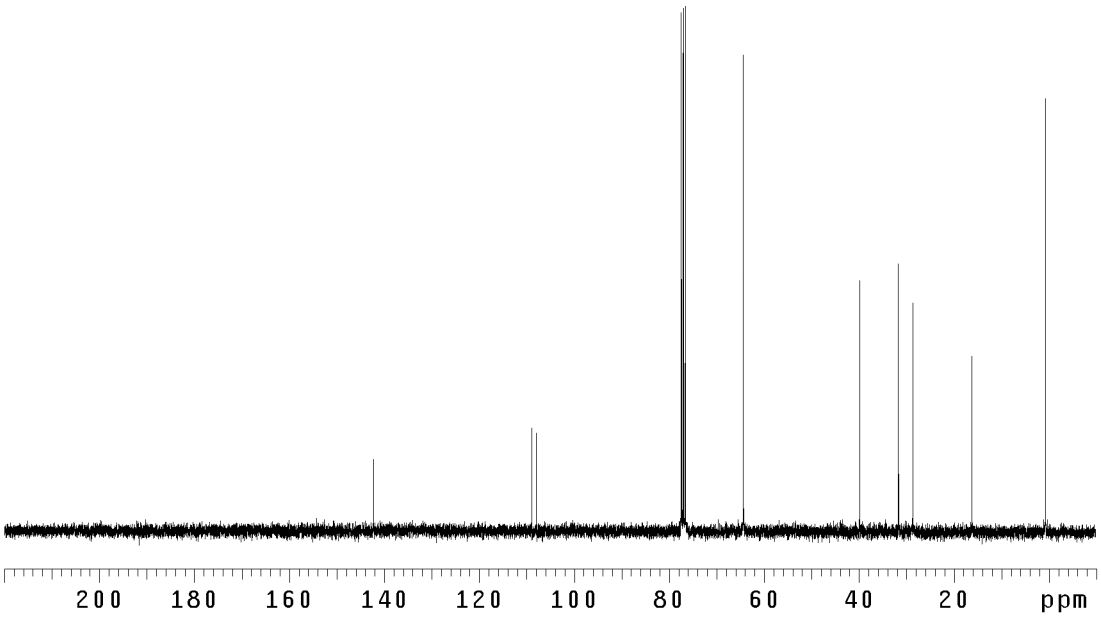
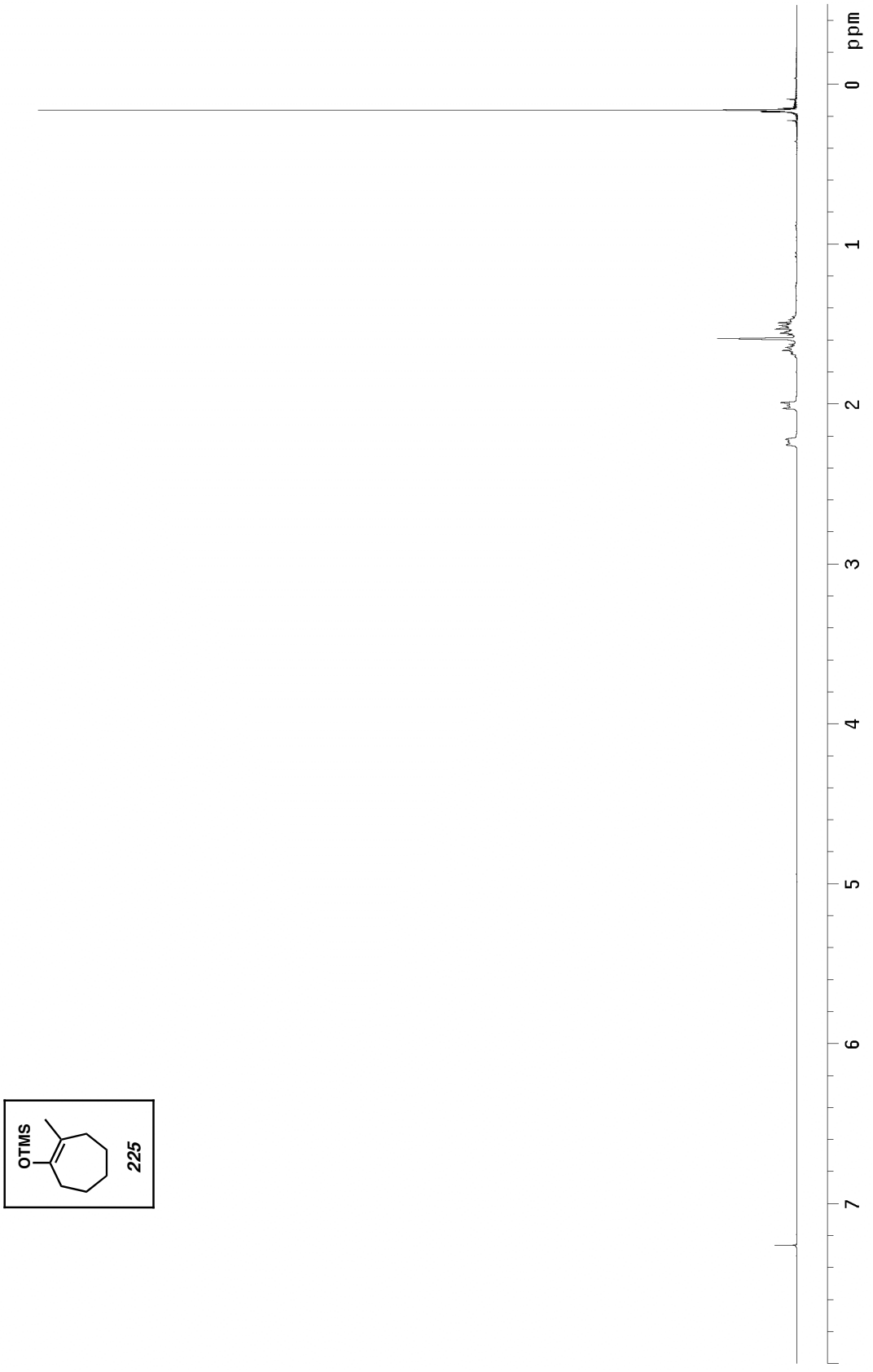


*Figure A1.141 ^{13}C NMR of compound **224** (75 MHz, $CDCl_3$)*


OTMS
225
ppm
0
1
2
3
4
5
6
7

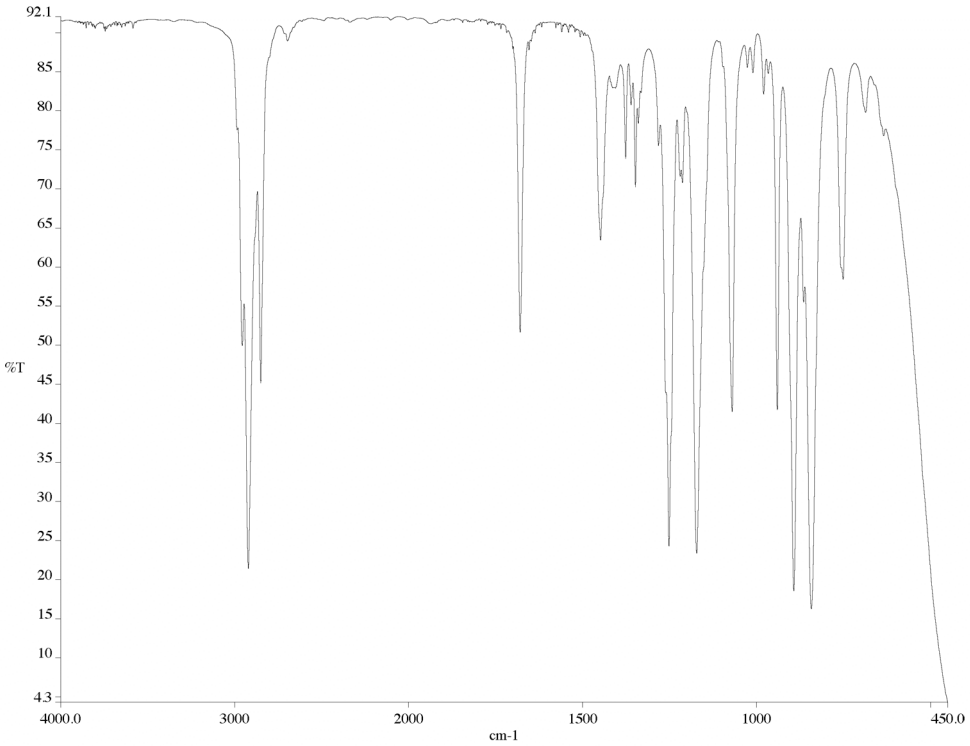


*Figure A1.143 IR of compound **225** (NaCl/film)*

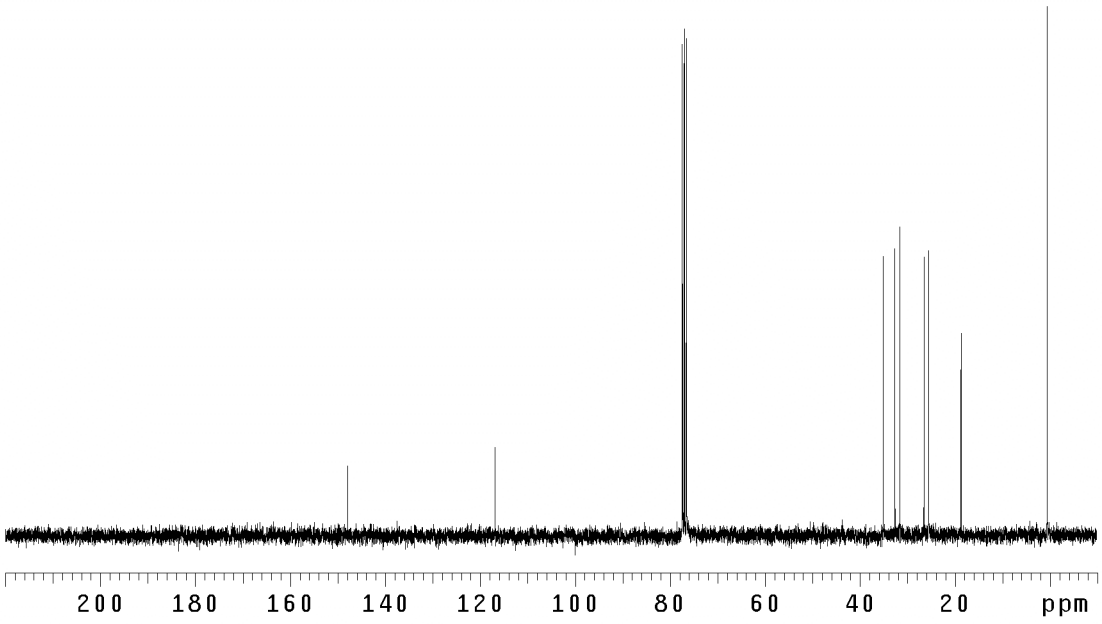
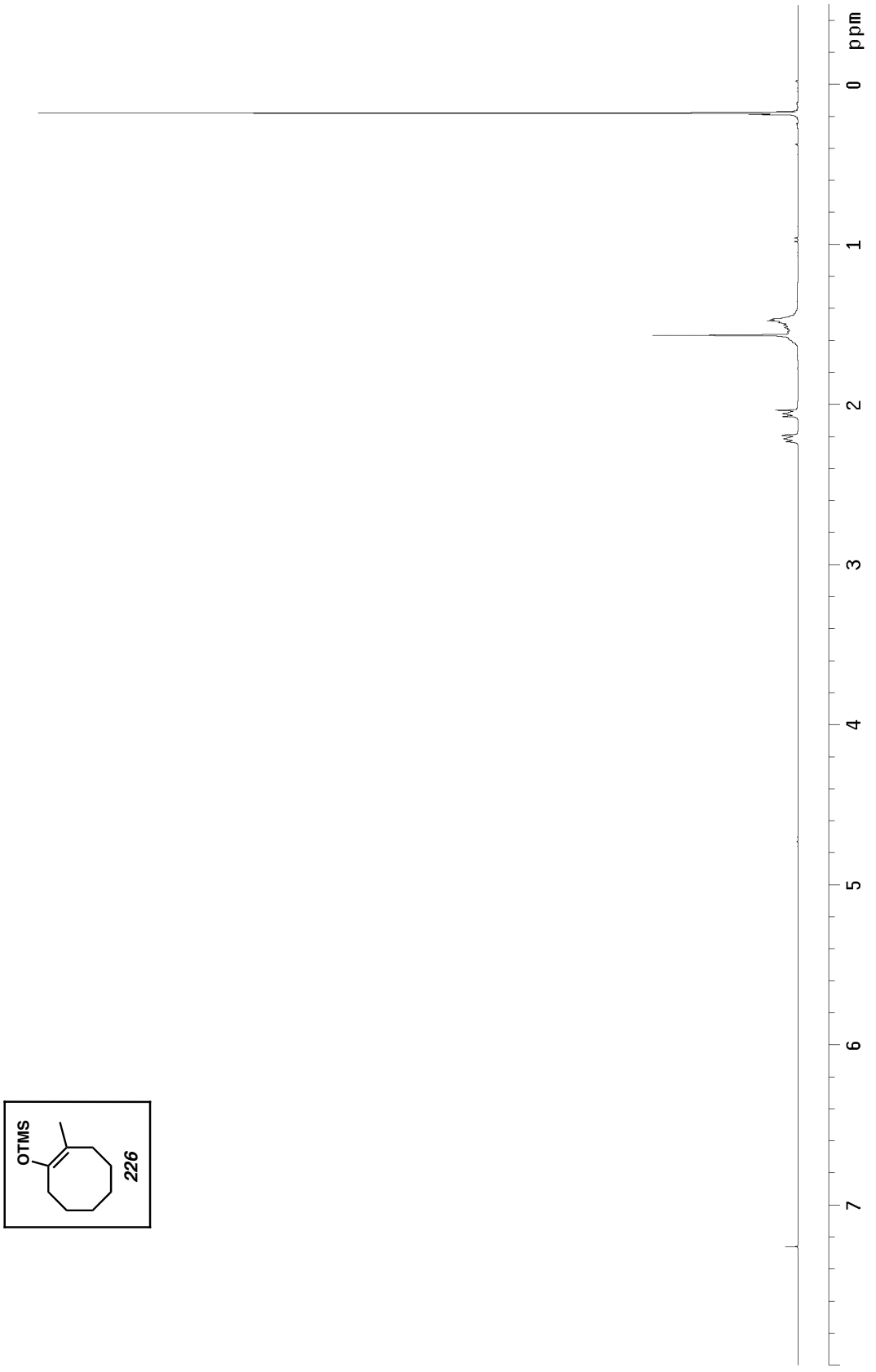


*Figure A1.144 ^{13}C NMR of compound **225** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
OTMS
226

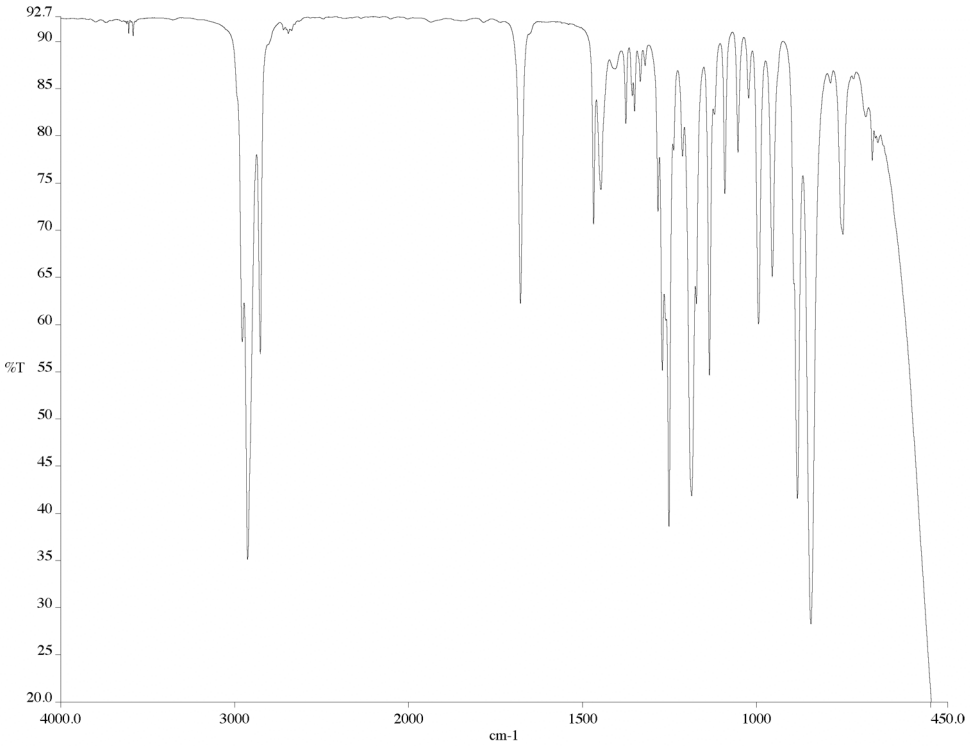


*Figure A1.146 IR of compound **226** (NaCl/film)*

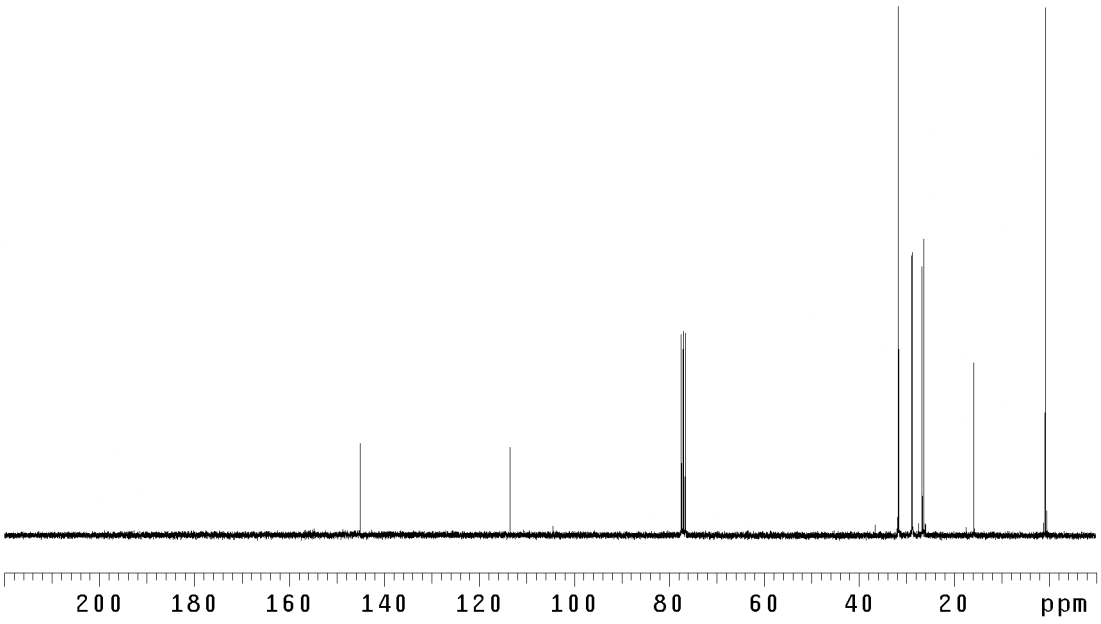
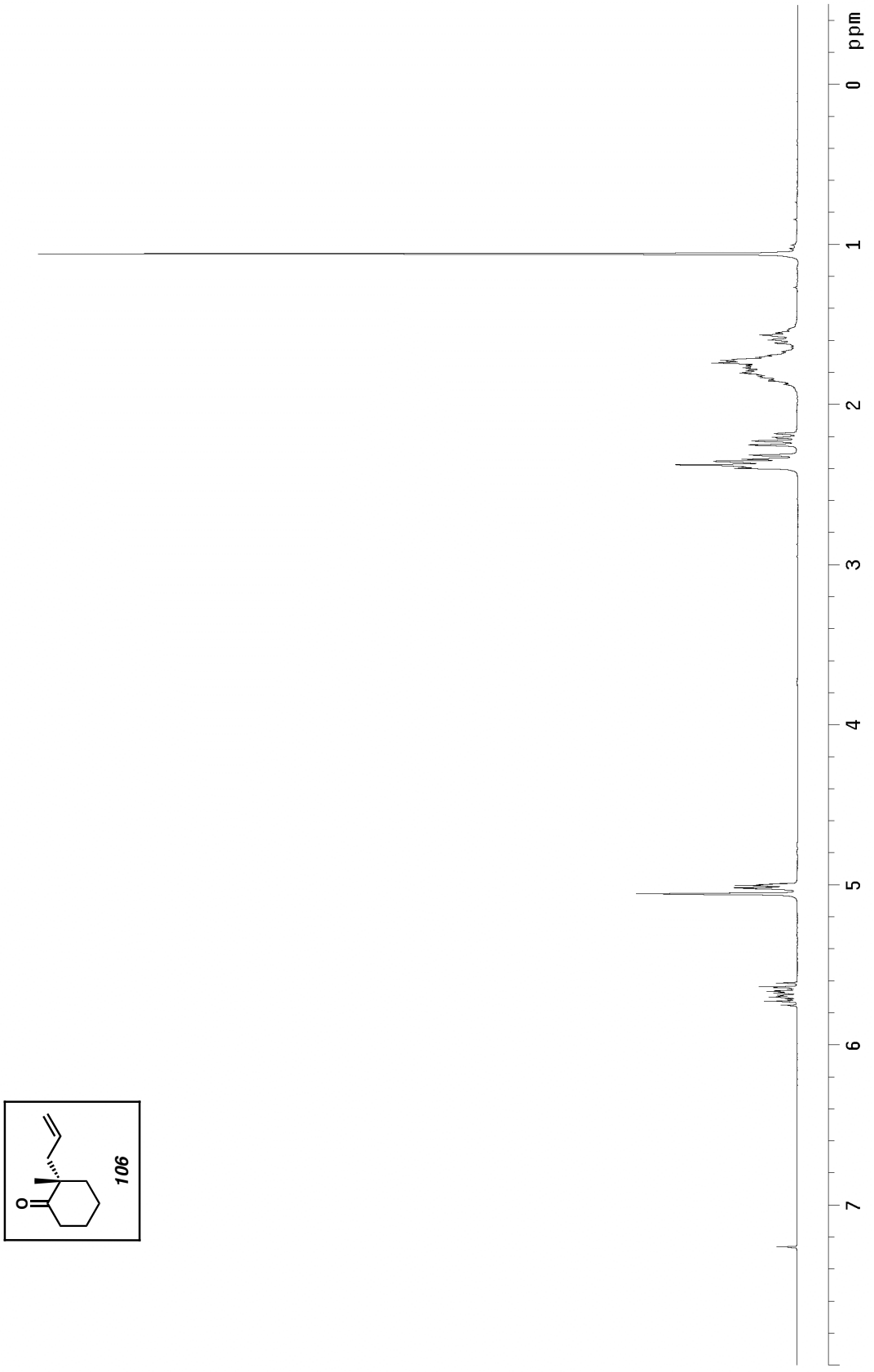


*Figure A1.147 ^{13}C NMR of compound **226** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
106

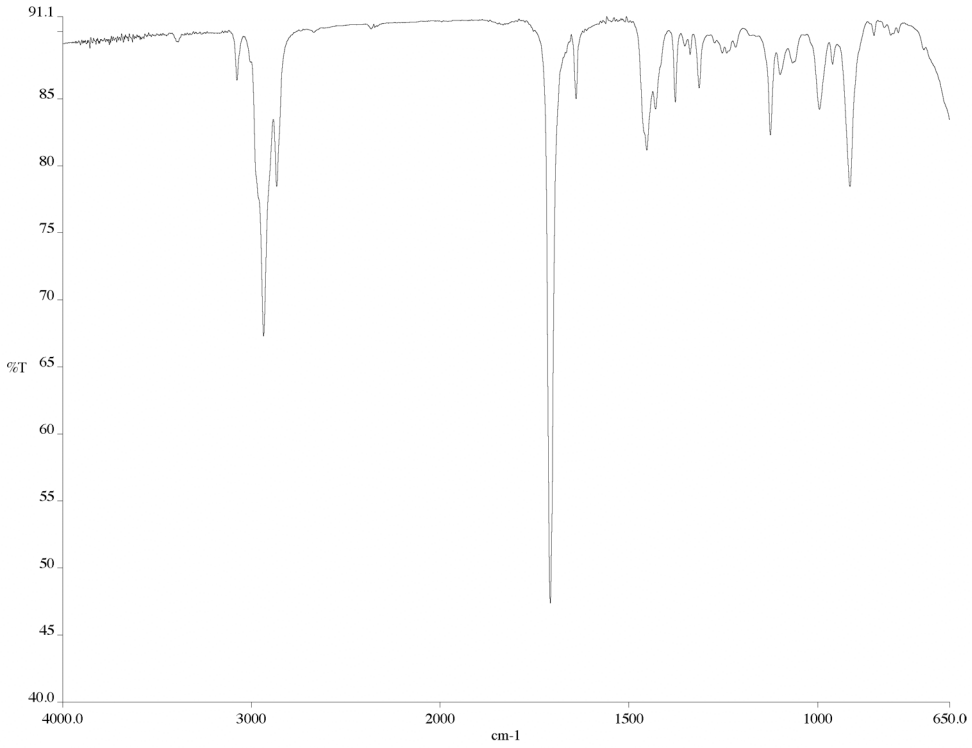


*Figure A1.149 IR of compound **106** (NaCl/film)*

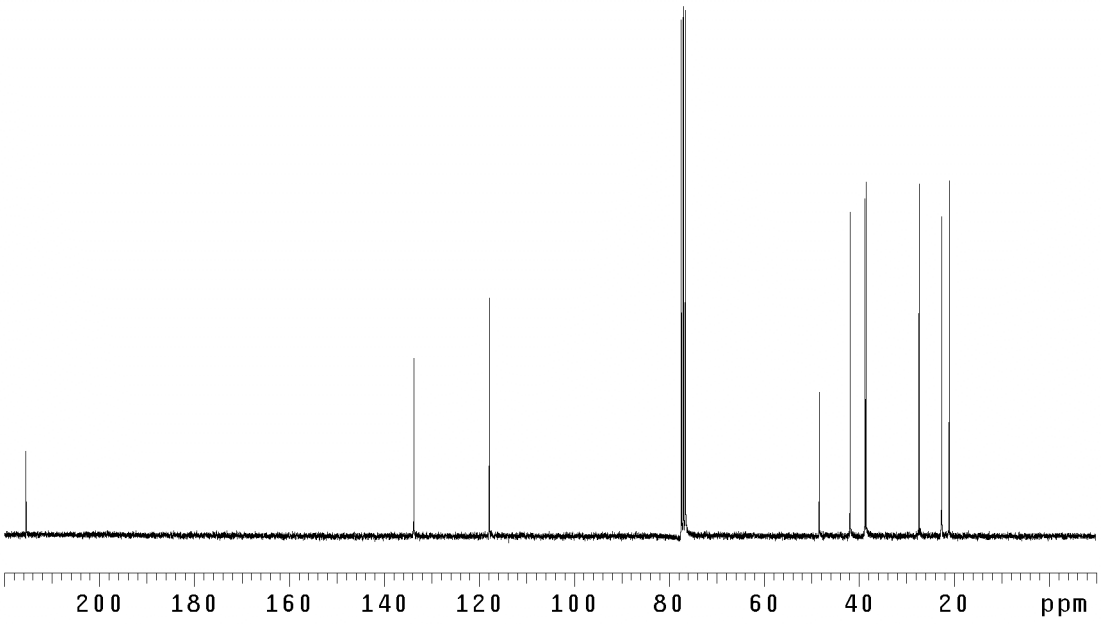
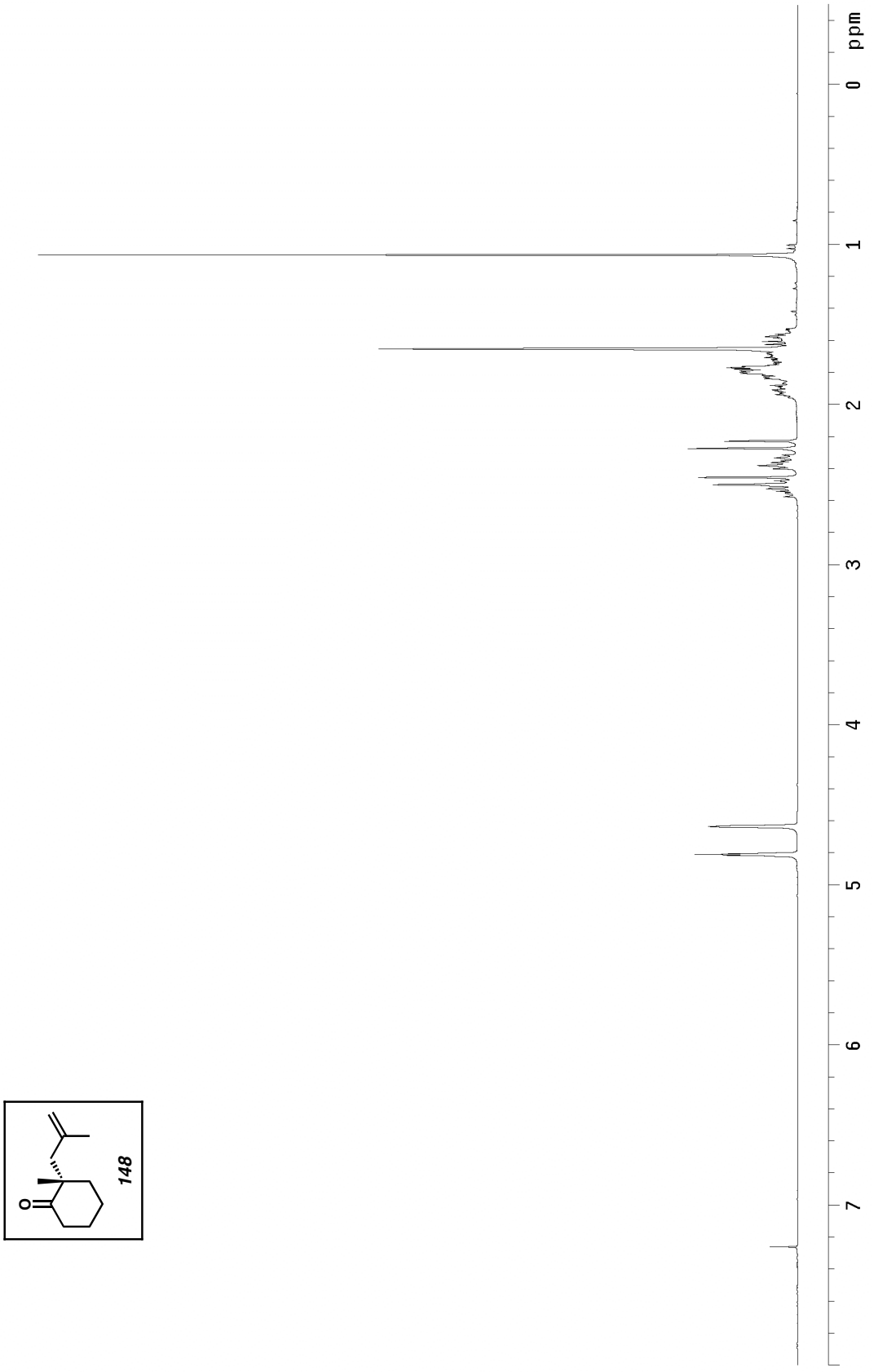


*Figure A1.150 ^{13}C NMR of compound **106** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
148

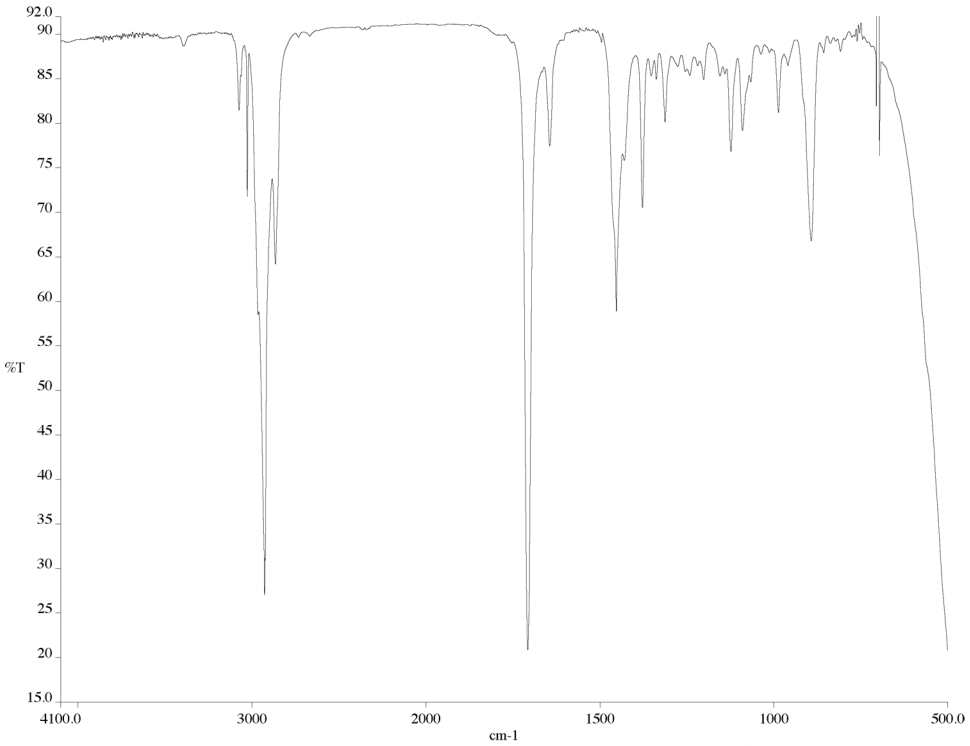


*Figure A1.152 IR of compound **148** (NaCl/film)*

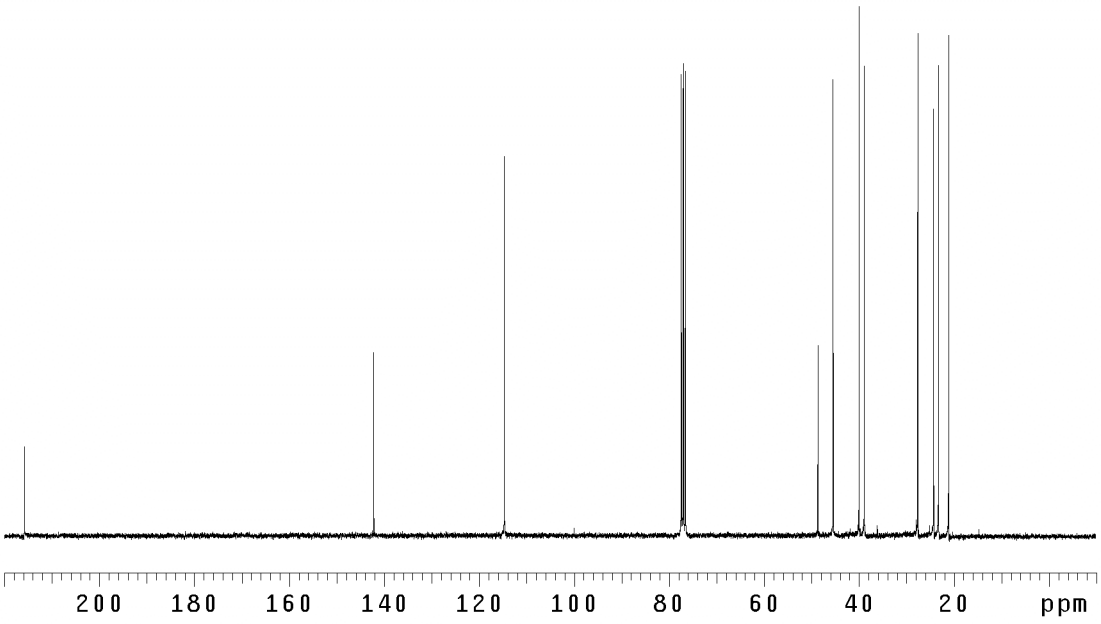
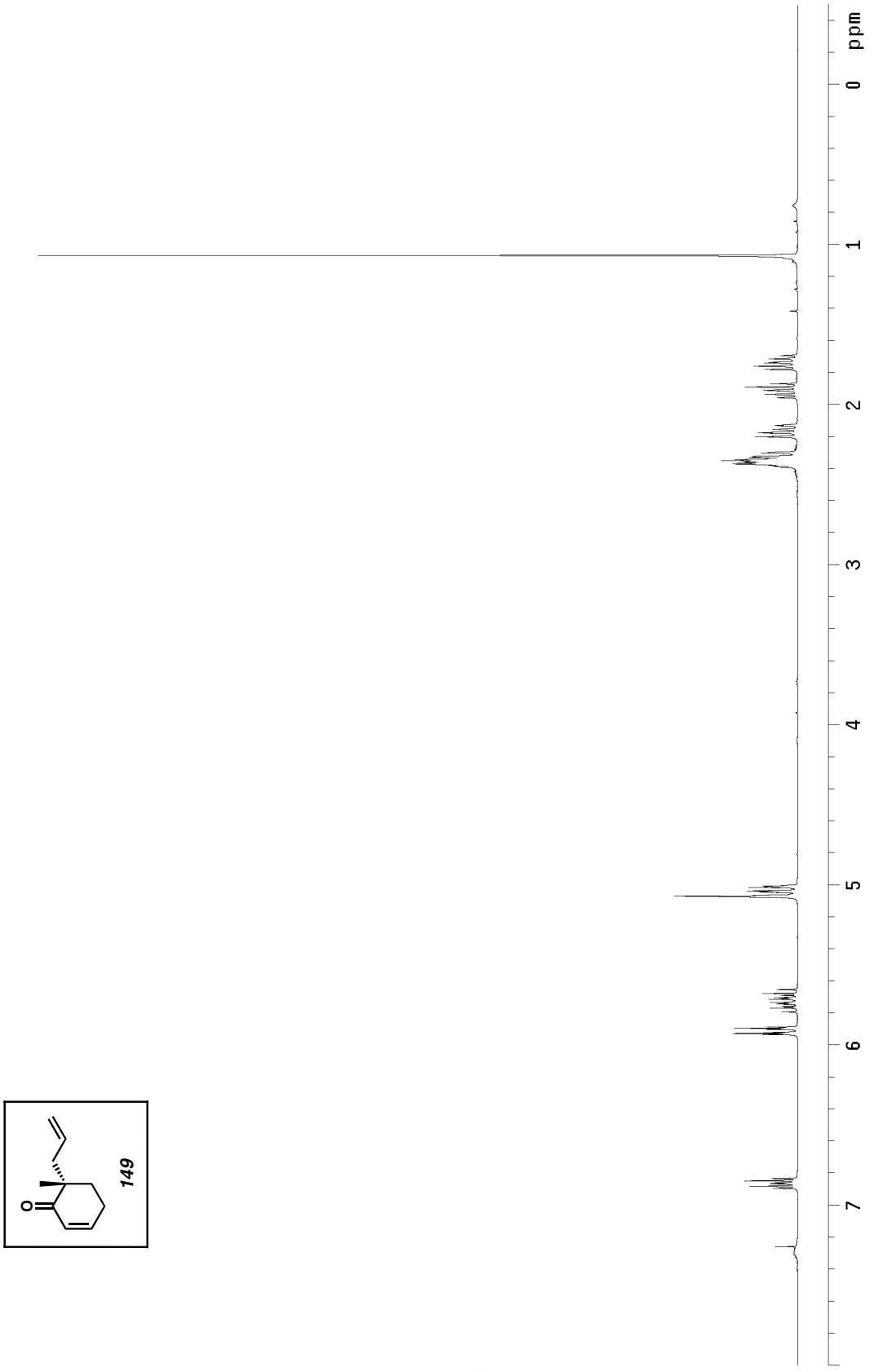


*Figure A1.153 ^{13}C NMR of compound **148** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
149

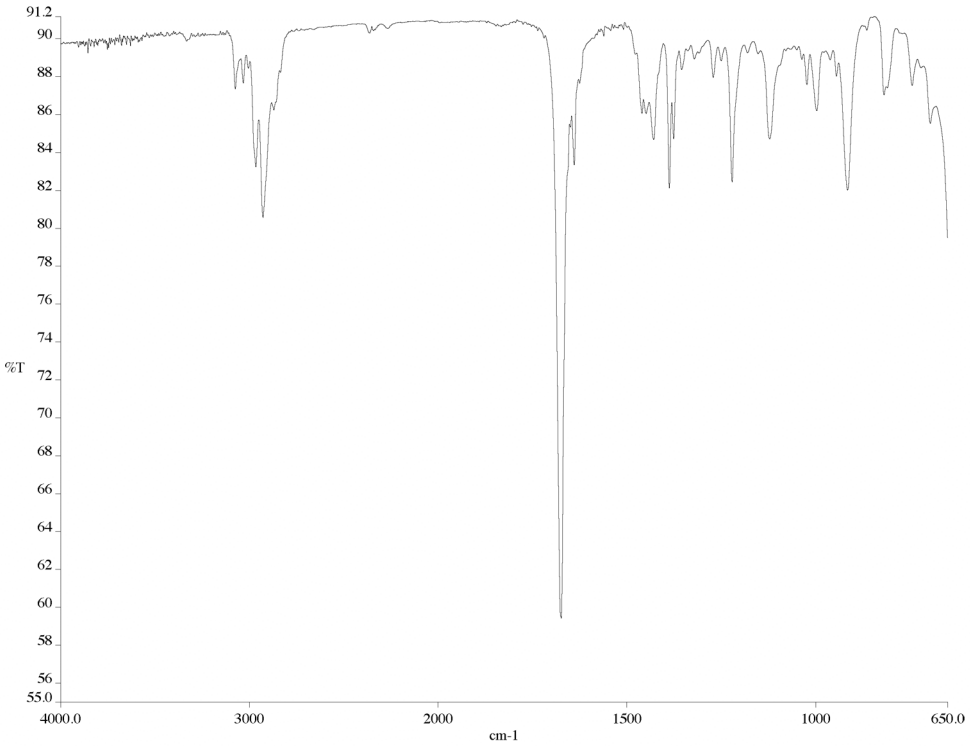


*Figure A1.155 IR of compound **149** (NaCl/film)*

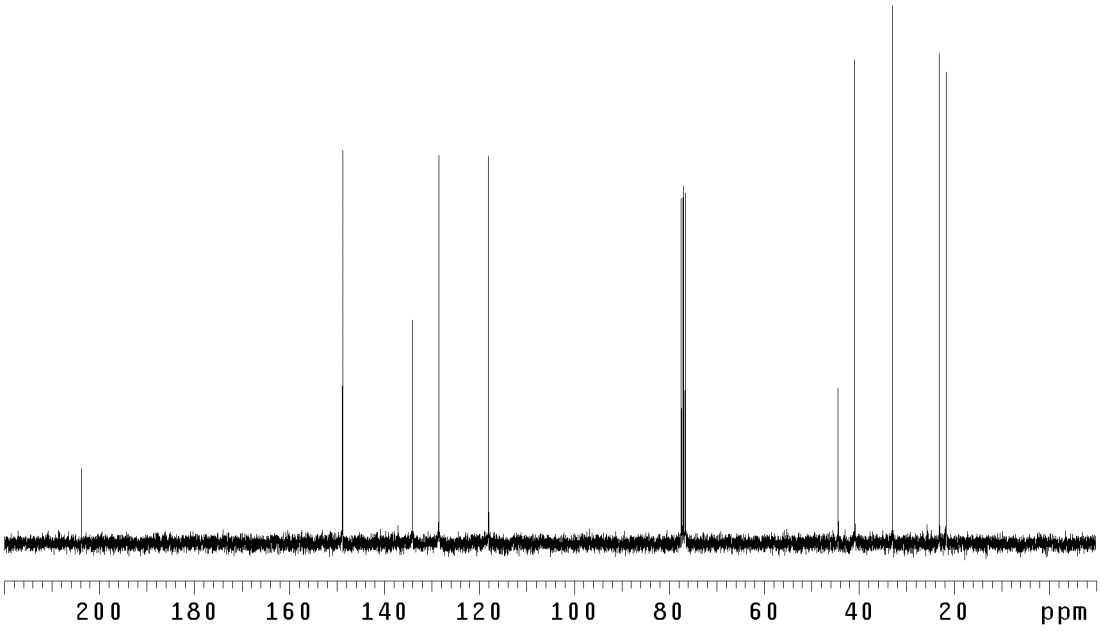
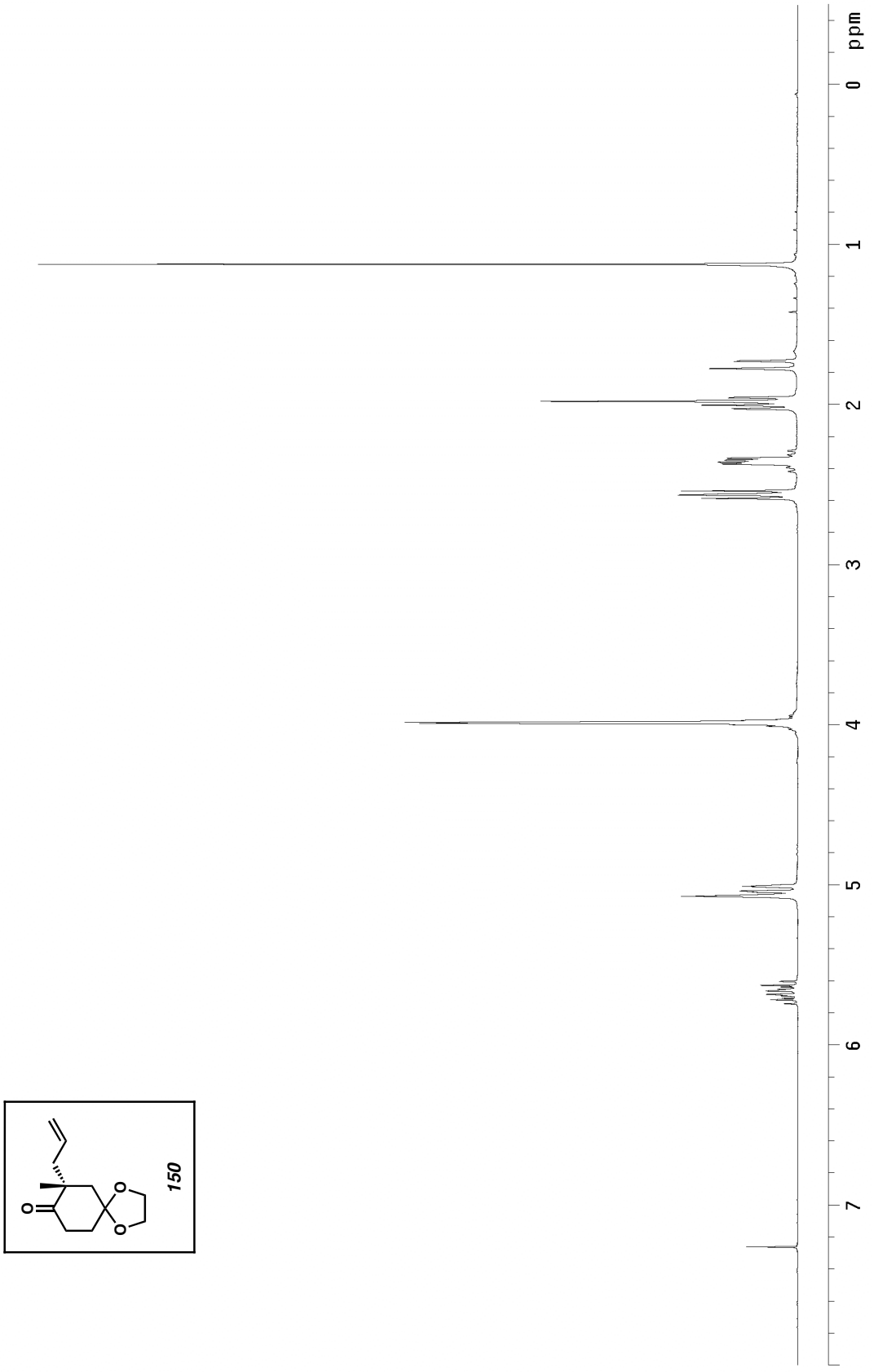


*Figure A1.156 ^{13}C NMR of compound **149** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
O
O
150

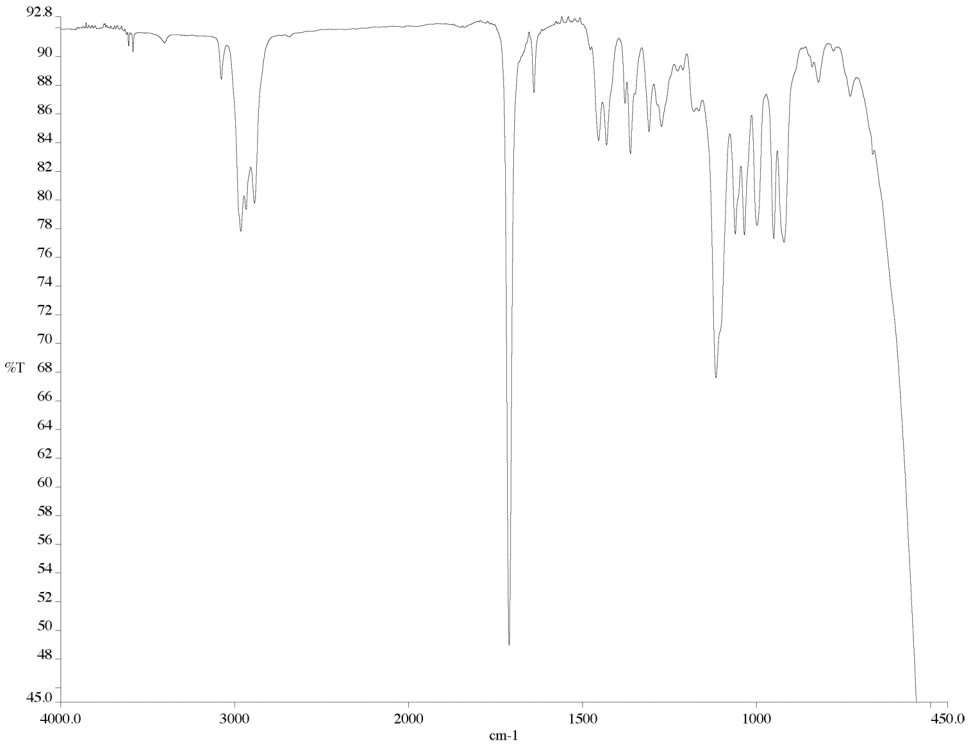


*Figure A1.158 IR of compound **150** (NaCl/film)*

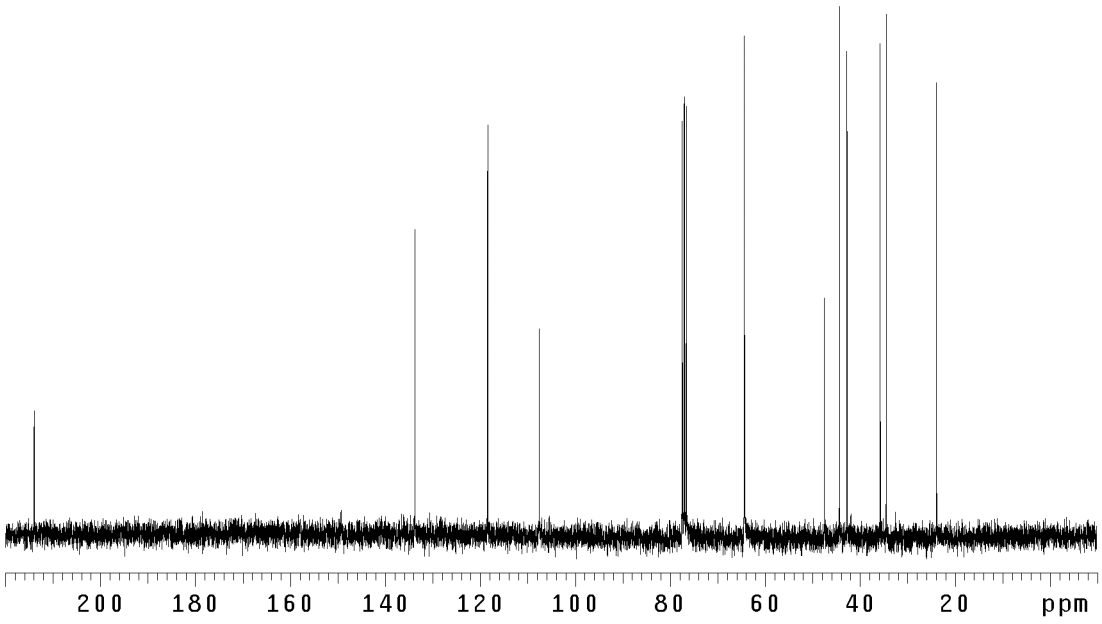
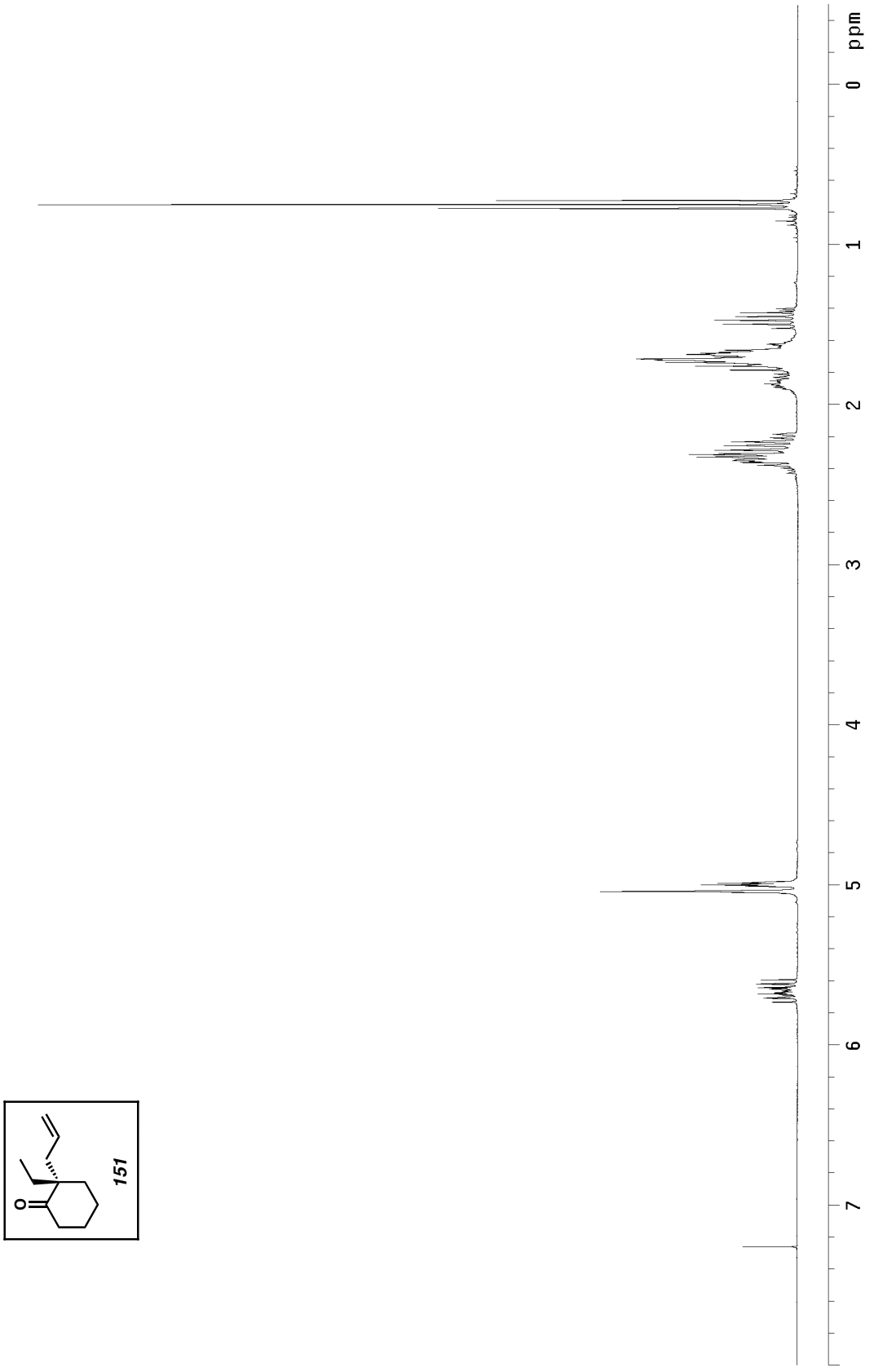


*Figure A1.159 ^{13}C NMR of compound **150** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
151

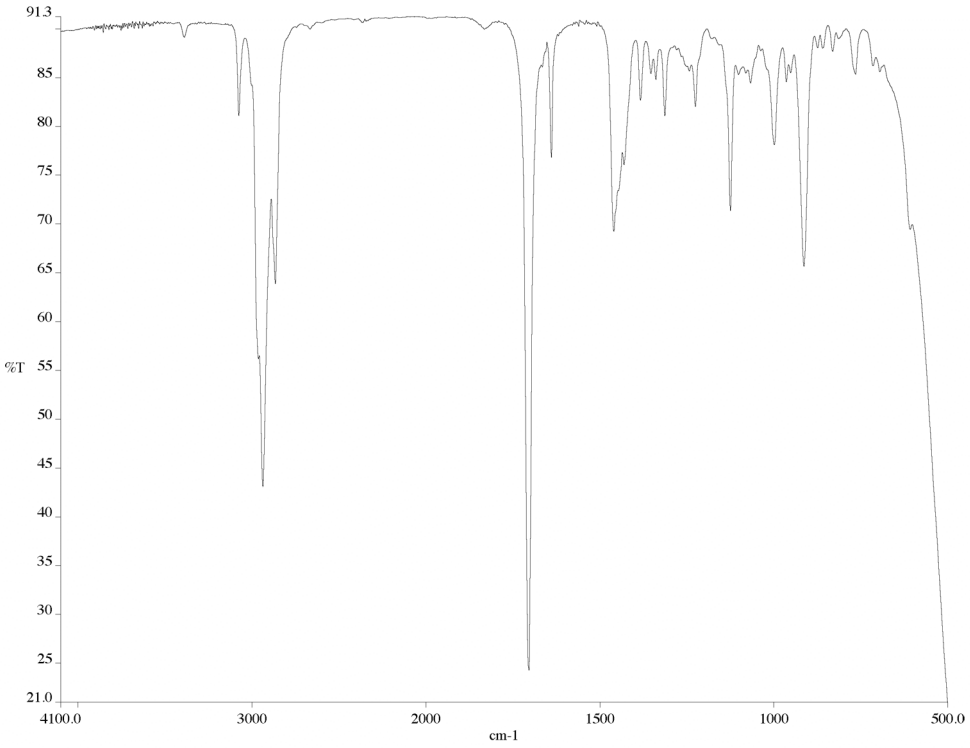


*Figure A1.161 IR of compound **151** (NaCl/film)*

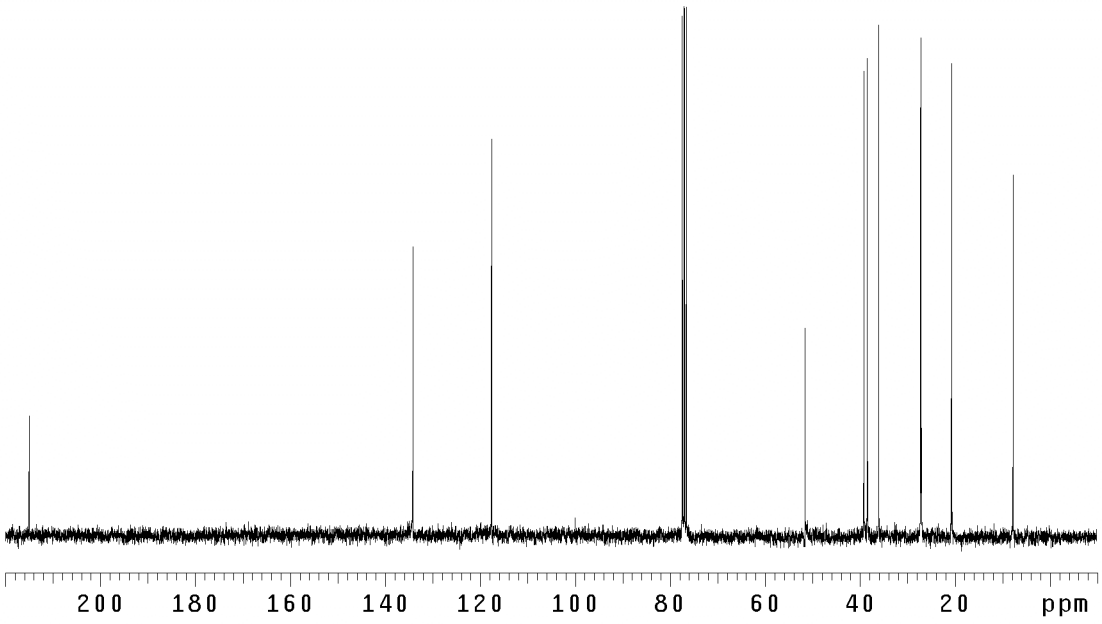
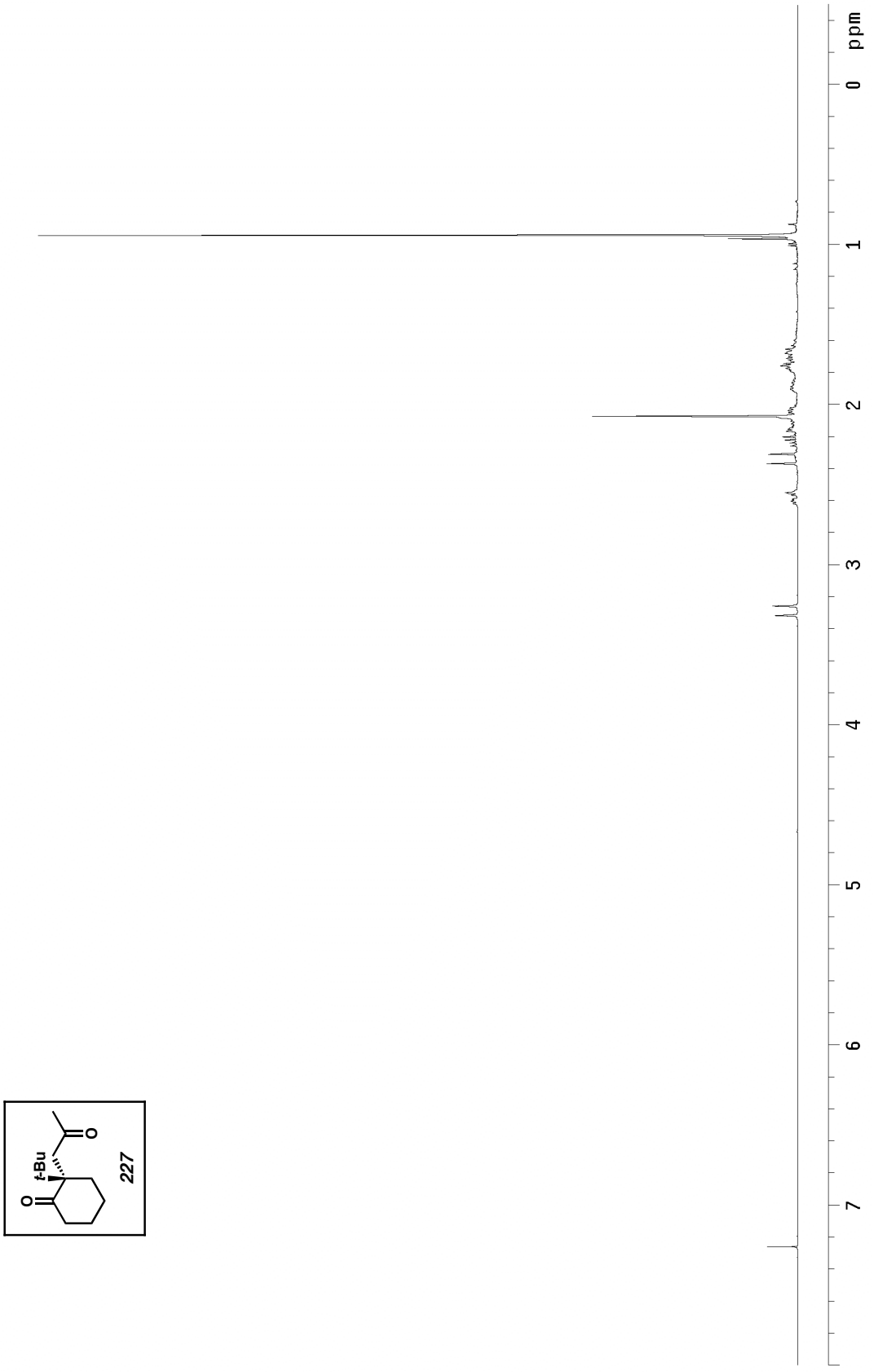


*Figure A1.162 ^{13}C NMR of compound **151** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
t-Bu
O
227

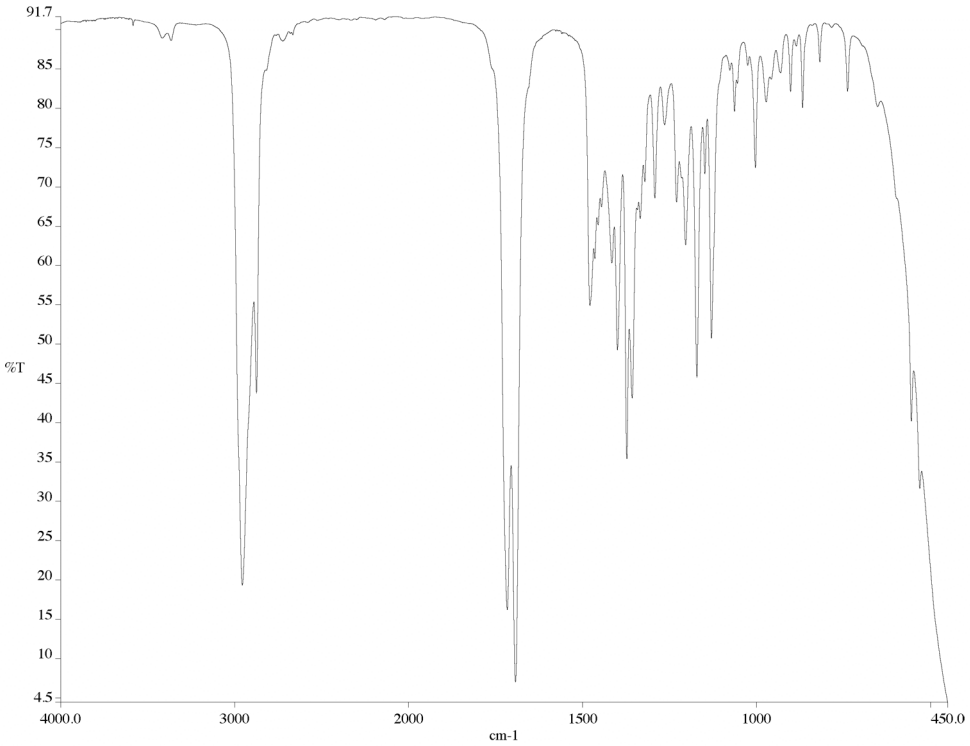


*Figure A1.164 IR of compound **227** (NaCl/film)*

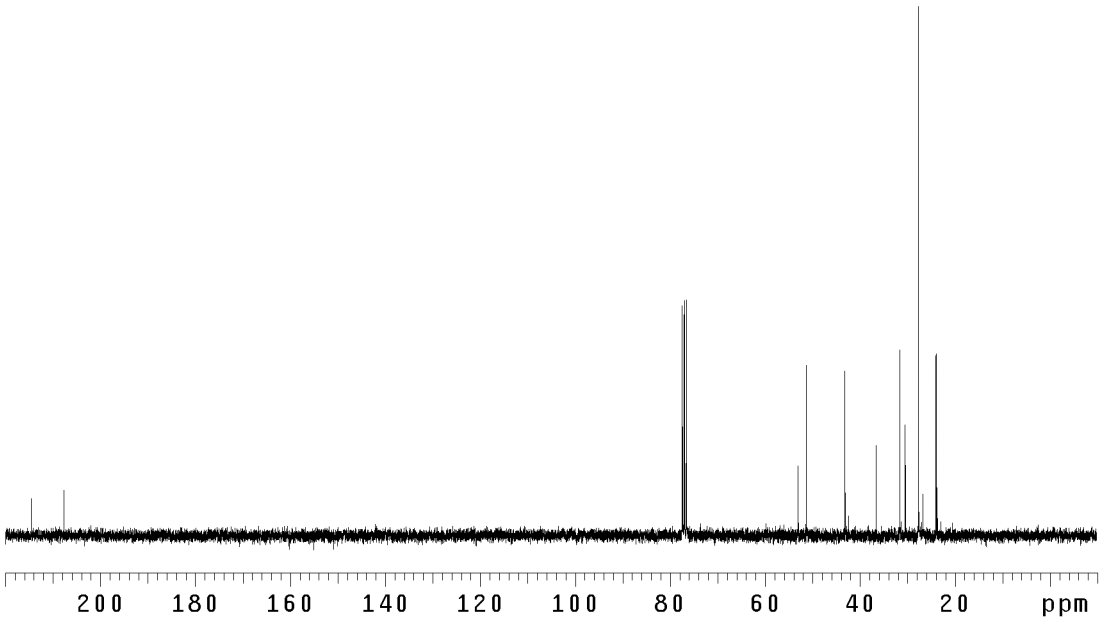
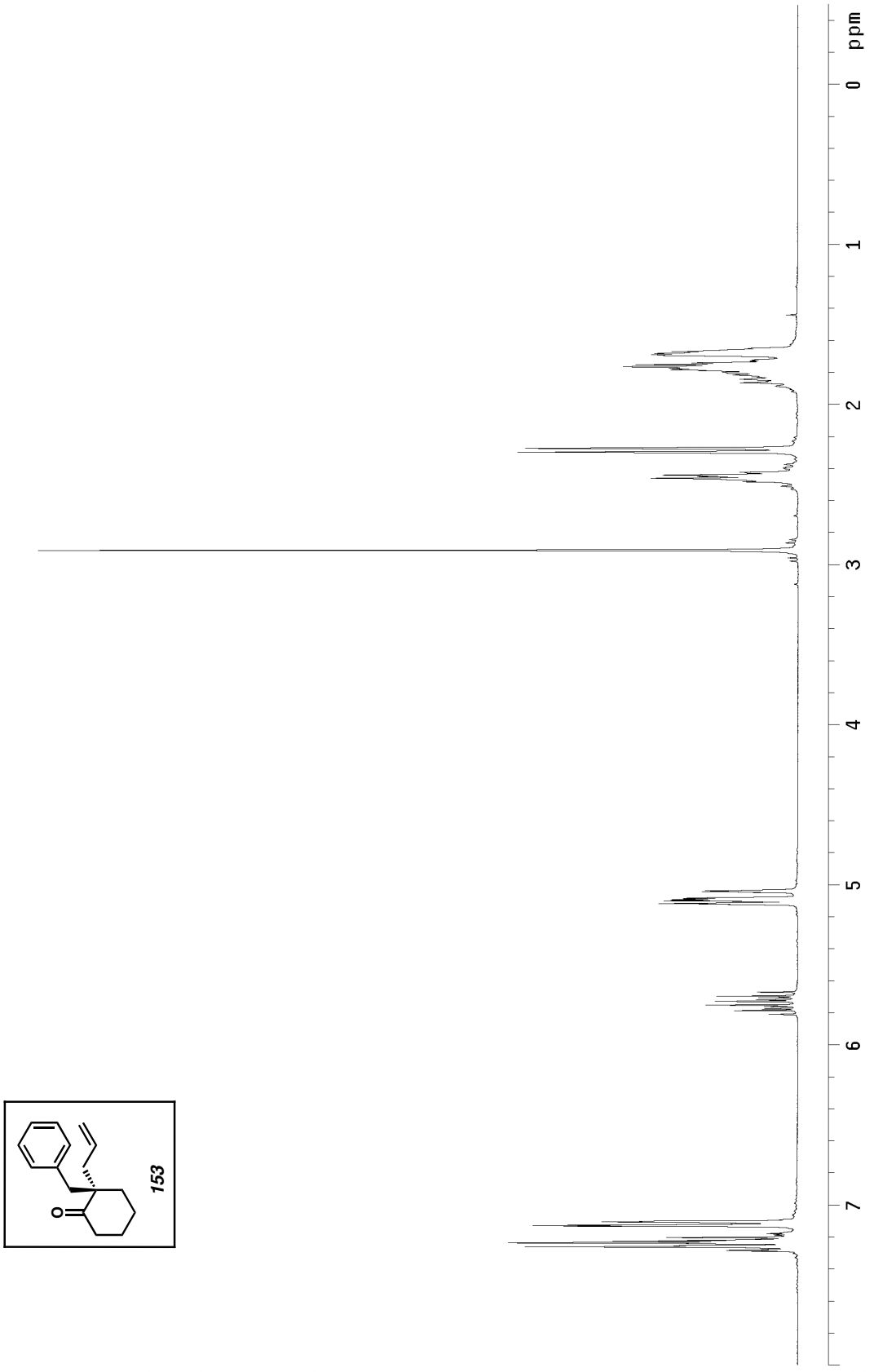


*Figure A1.165 ^{13}C NMR of compound **227** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
153

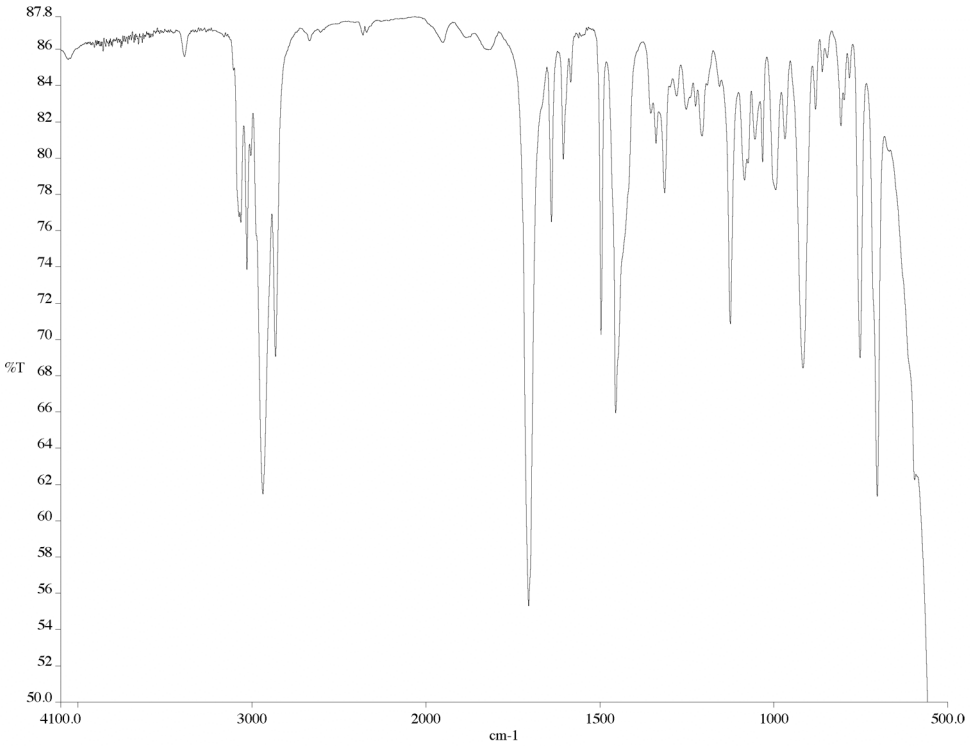


*Figure A1.167 IR of compound **153** (NaCl/film)*

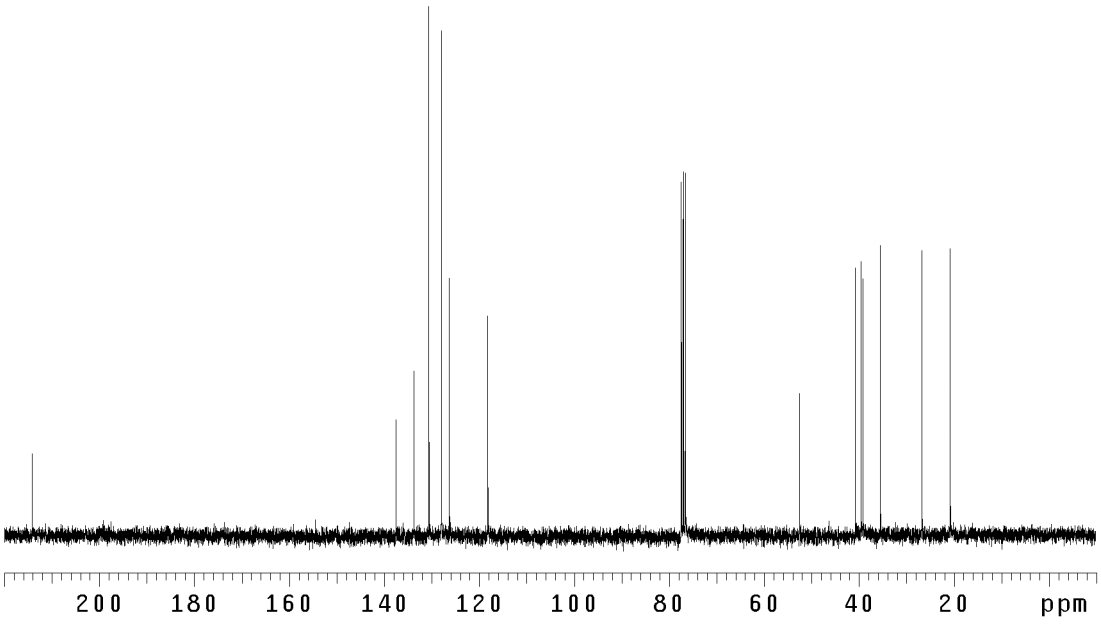
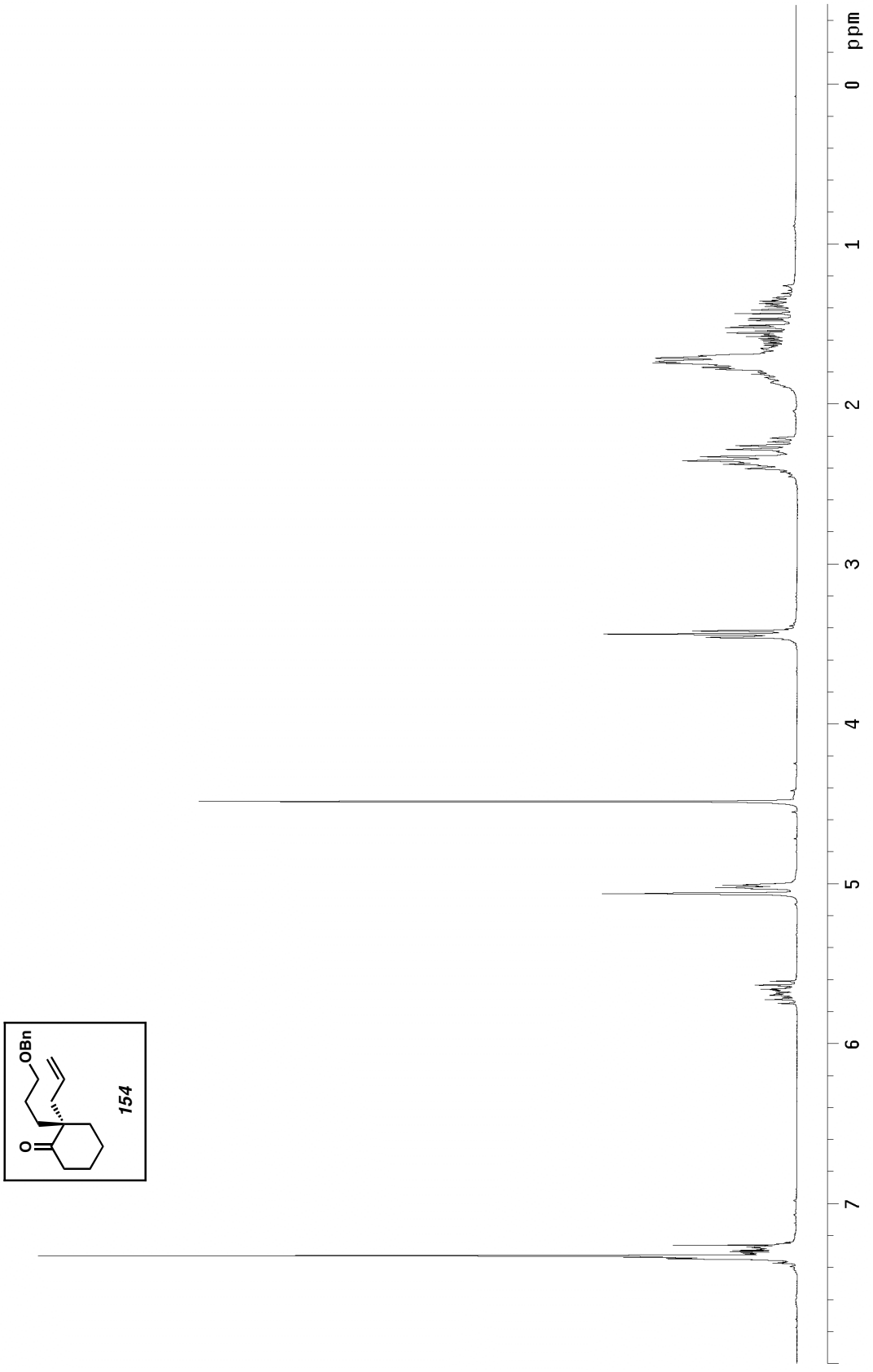


*Figure A1.168 ^{13}C NMR of compound **153** (75 MHz, $CDCl_3$)*


OBn
O
154
ppm
0
1
2
3
4
5
6
7

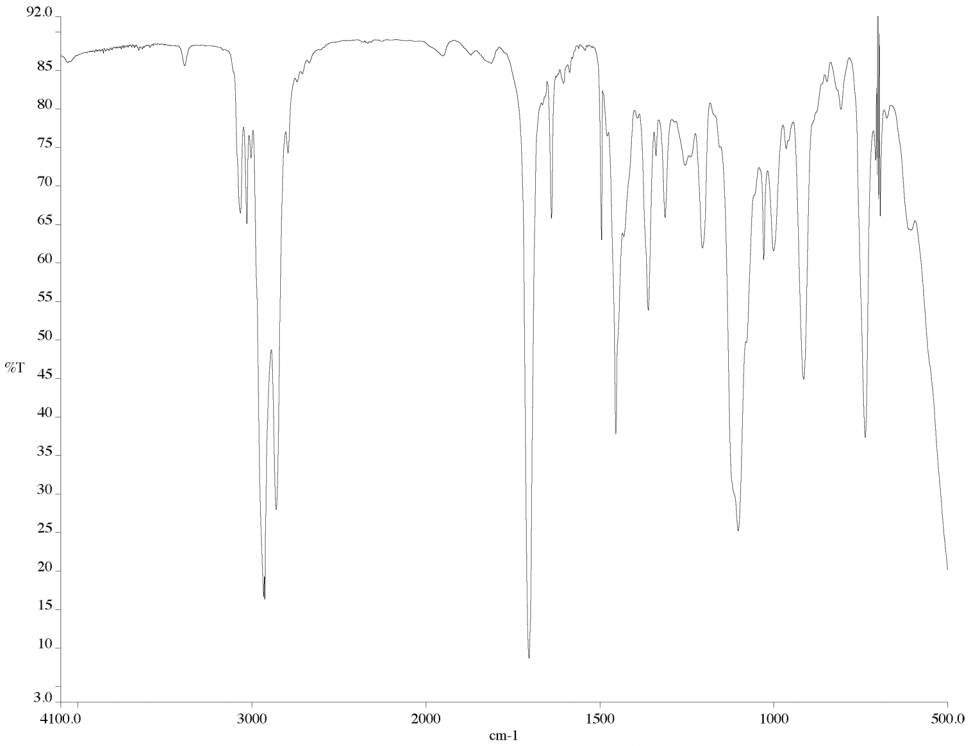


*Figure A1.170 IR of compound **154** (NaCl/film)*

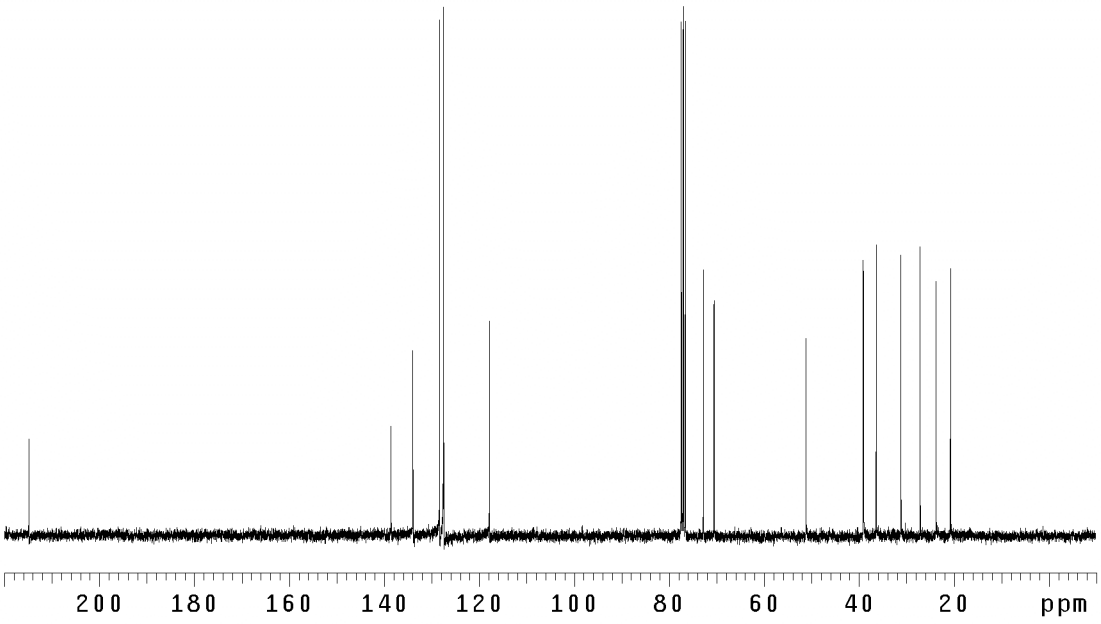
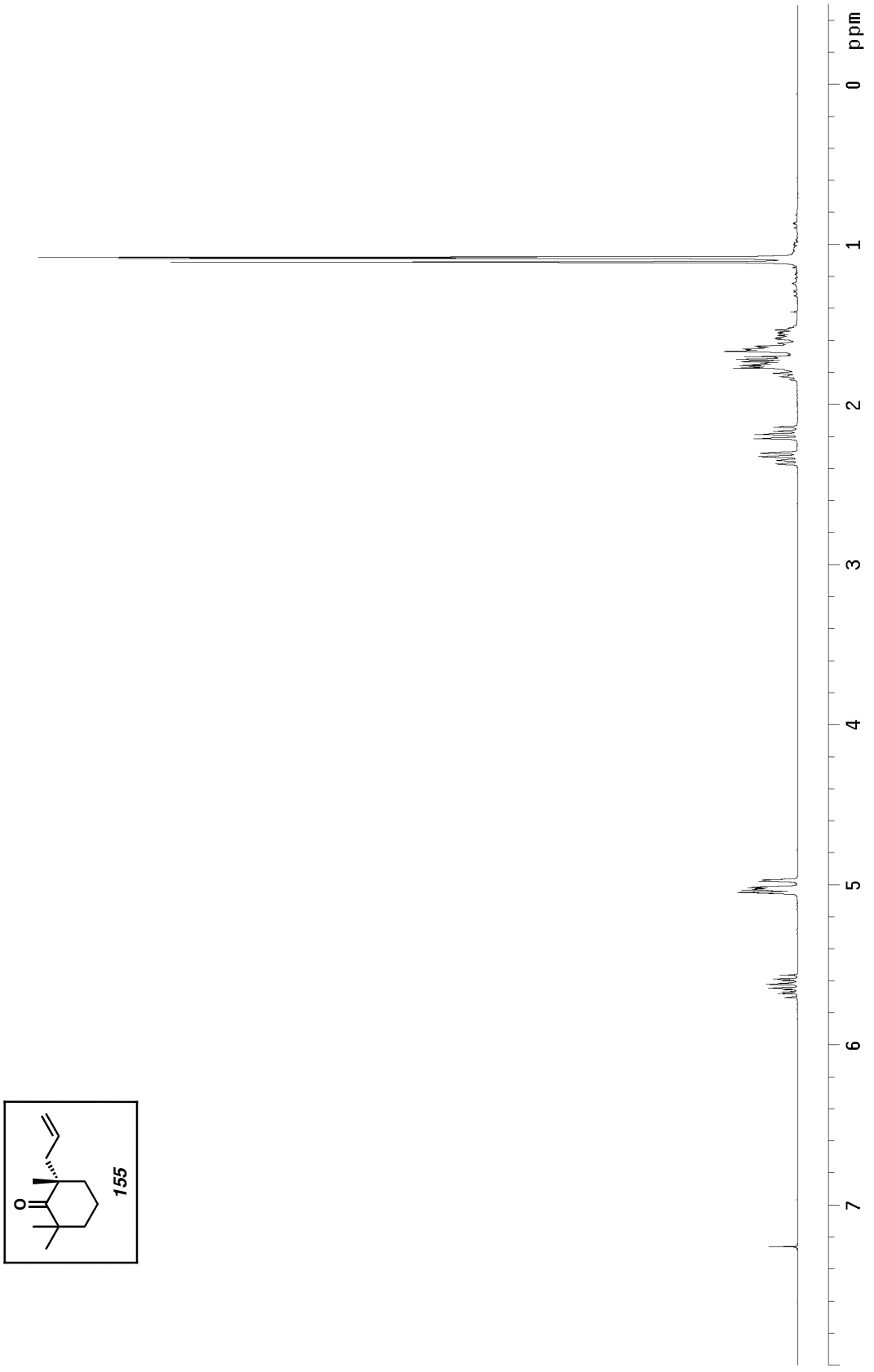


*Figure A1.171 ^{13}C NMR of compound **154** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
155

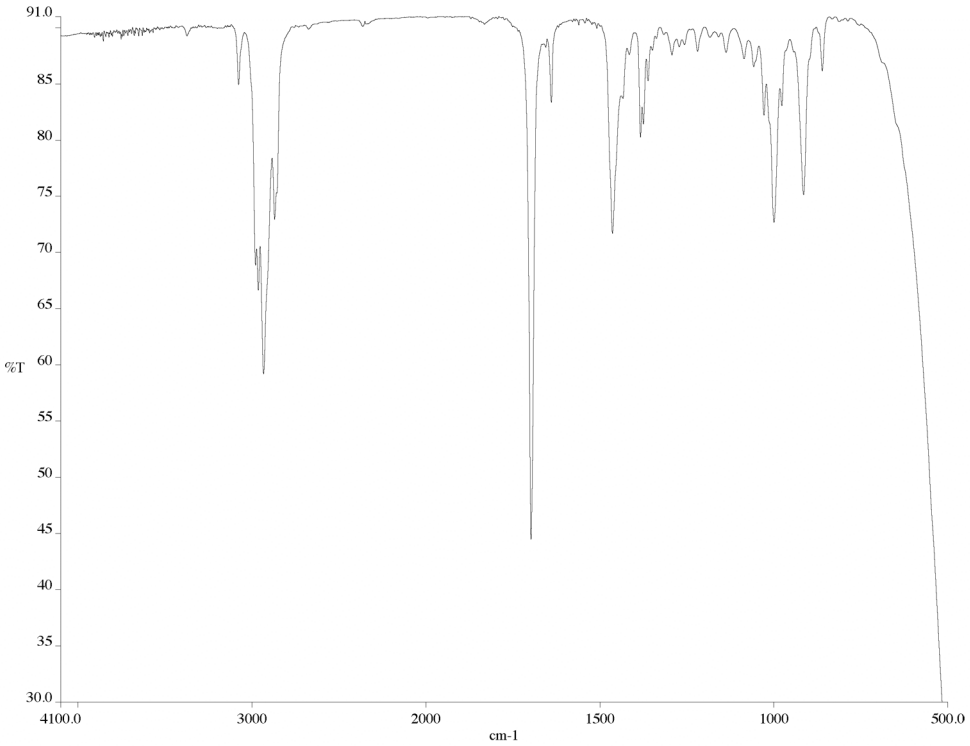


*Figure A1.173 IR of compound **155** (NaCl/film)*

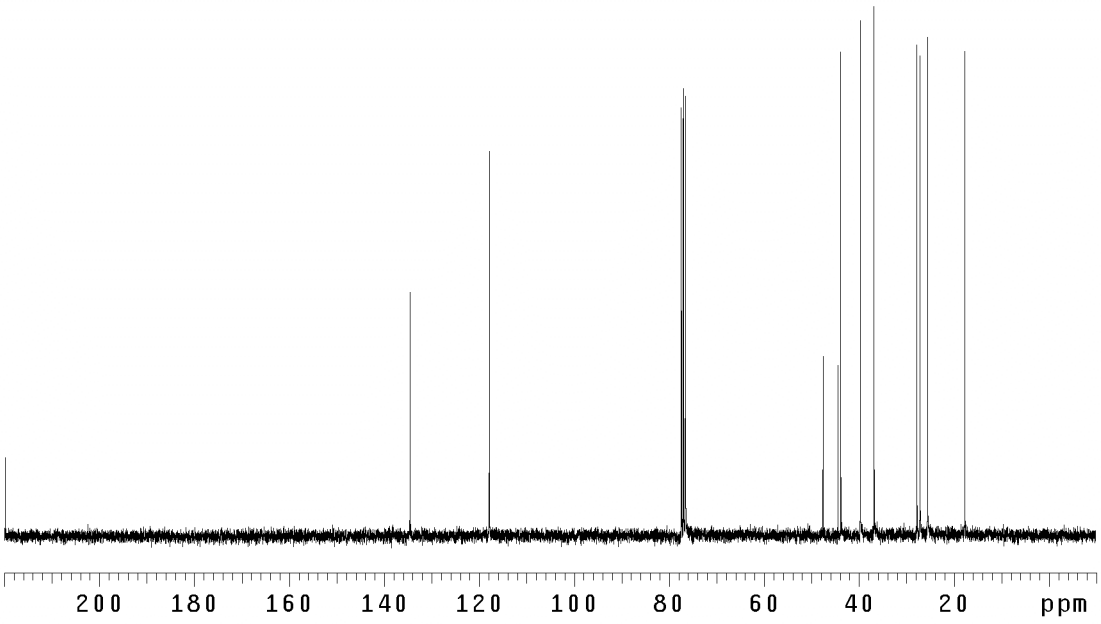
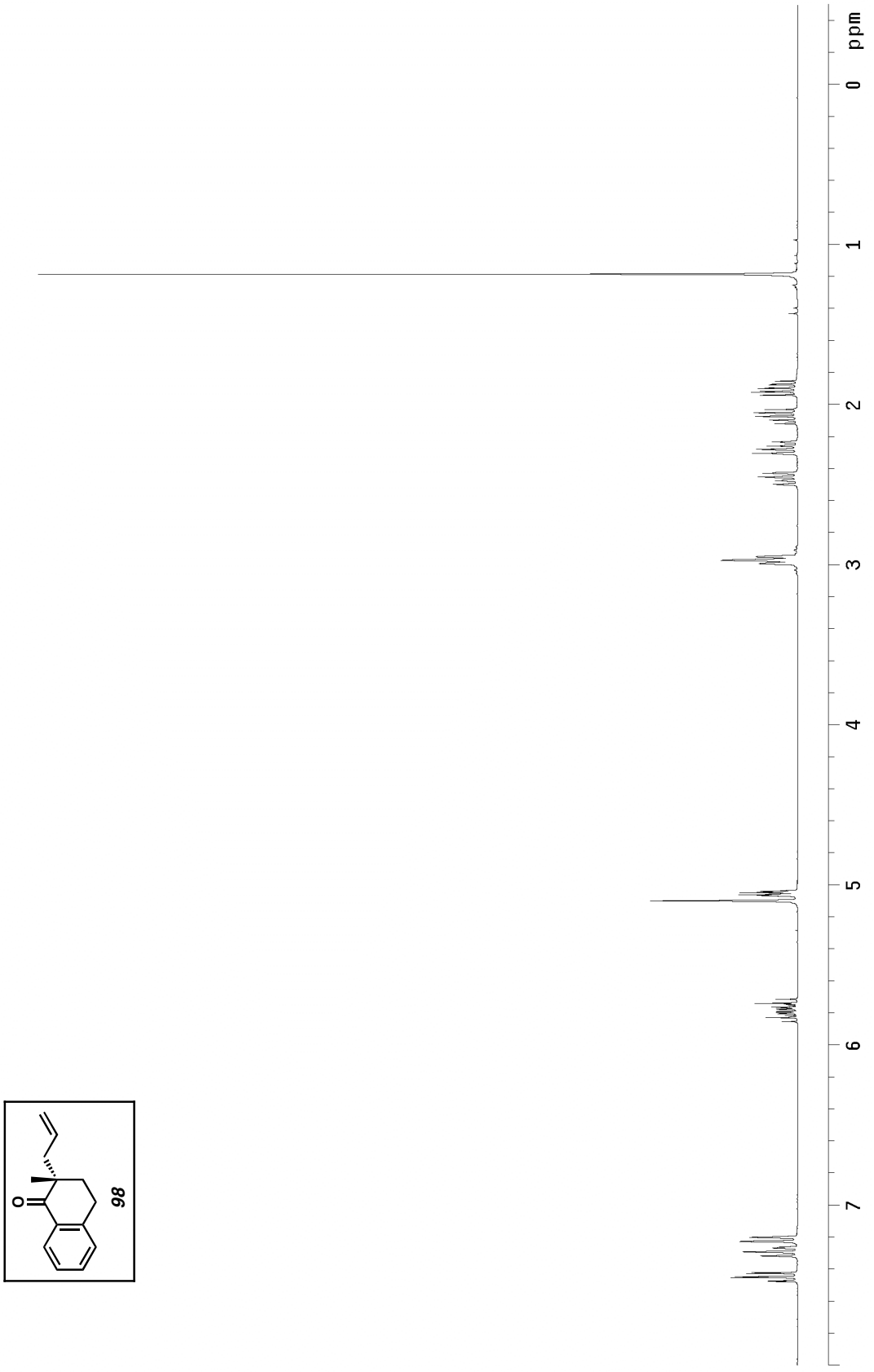


*Figure A1.174 ^{13}C NMR of compound **155** (75 MHz, $CDCl_3$)*


O
98
ppm
0
1
2
3
4
5
6
7

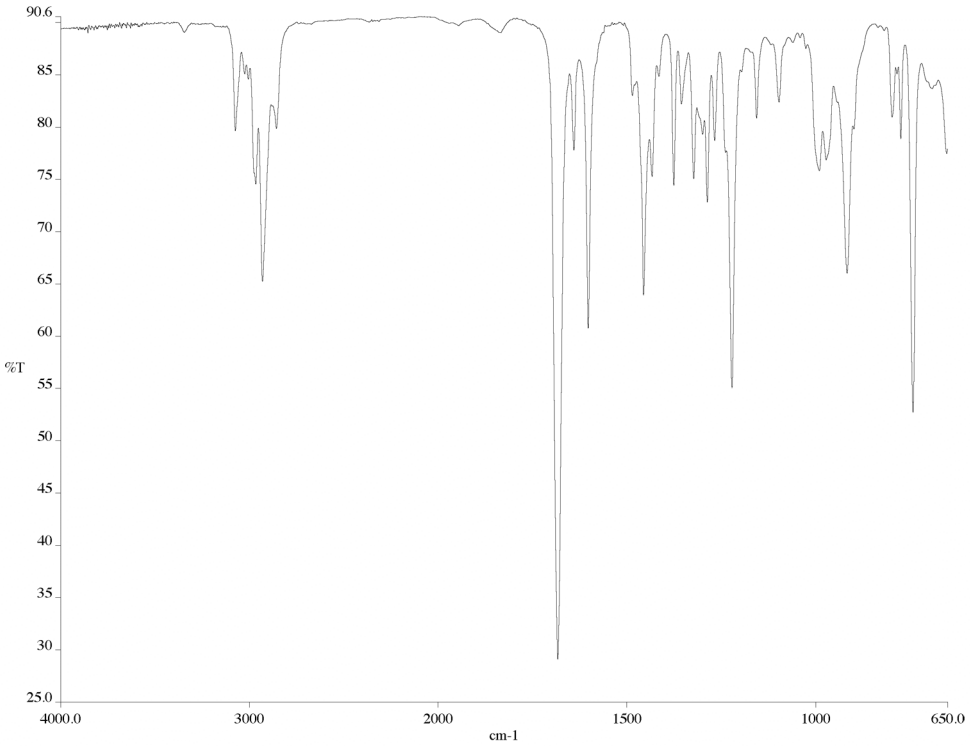


*Figure A1.176 IR of compound **98** (NaCl/film)*

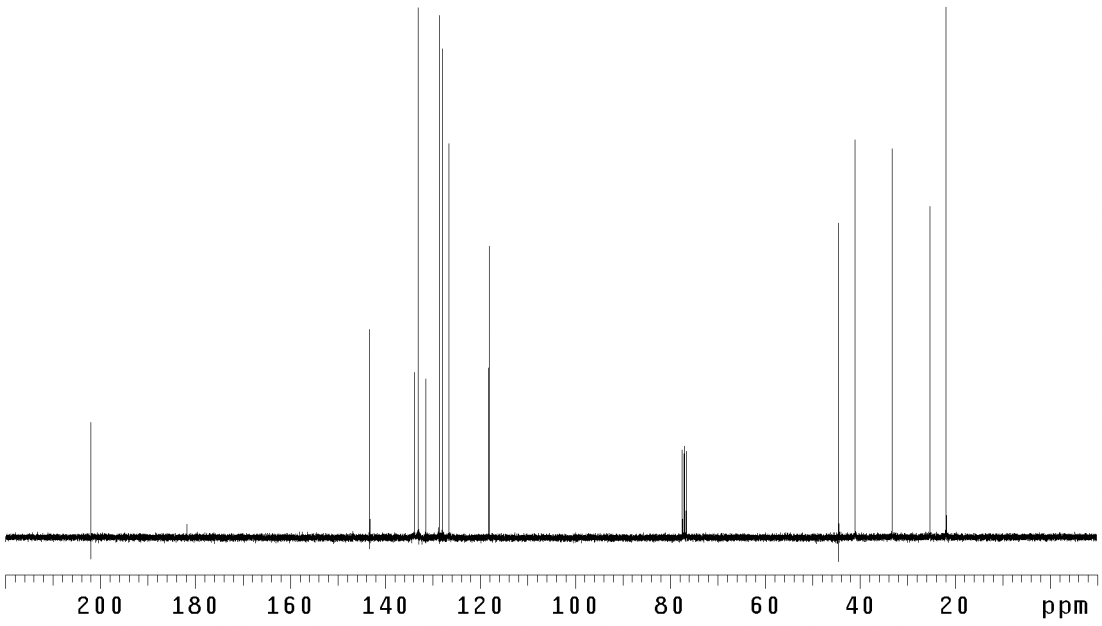
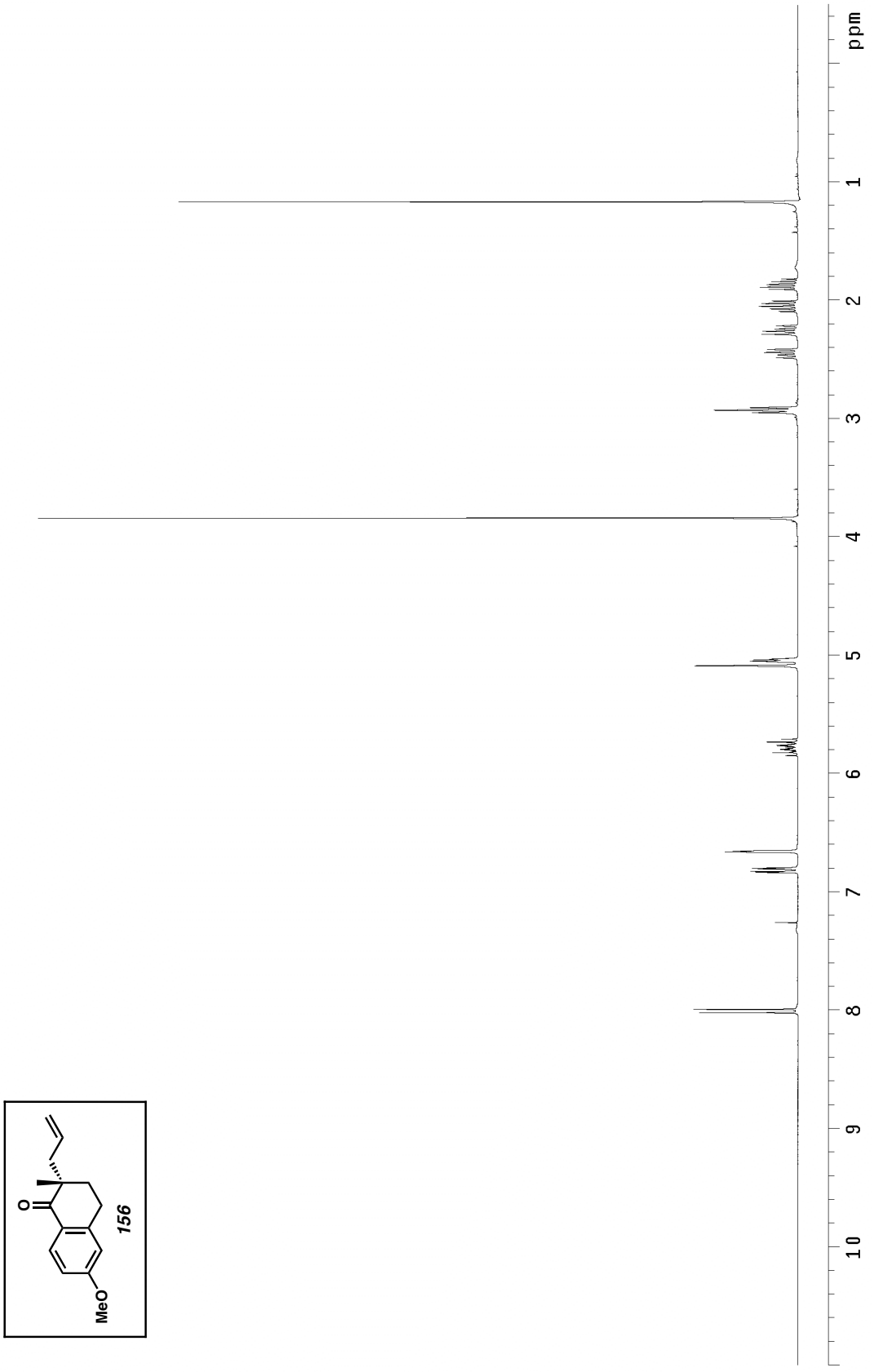


*Figure A1.177 ^{13}C NMR of compound **98** (75 MHz, $CDCl_3$)*


ppm
1
2
3
4
5
6
7
8
9
10
O
MeO
156

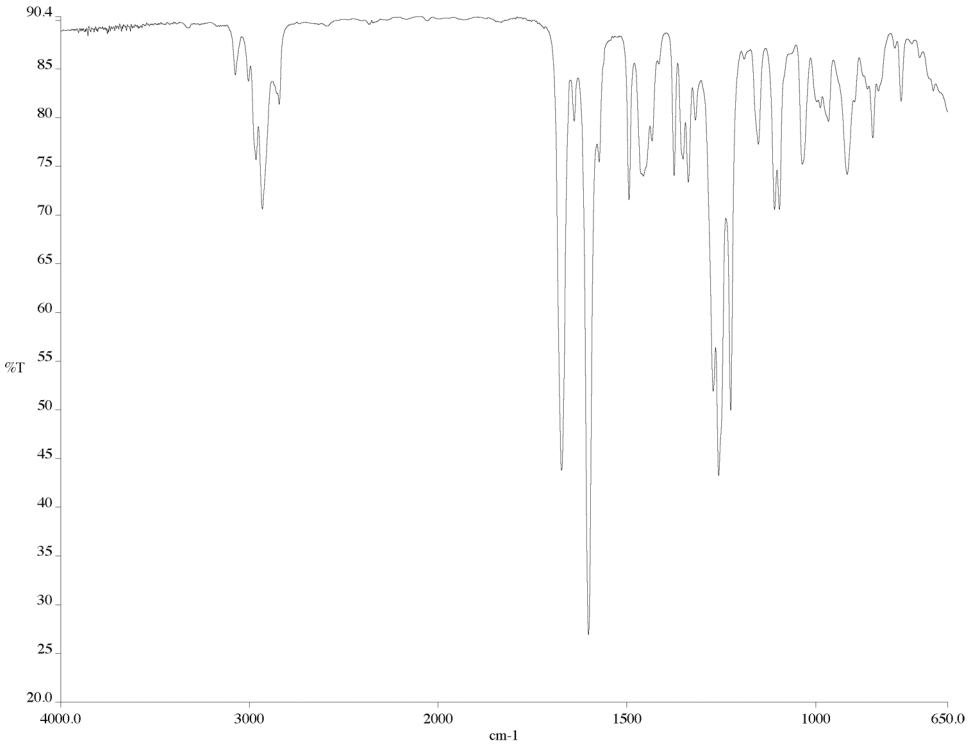


*Figure A1.179 IR of compound **156** (NaCl/film)*

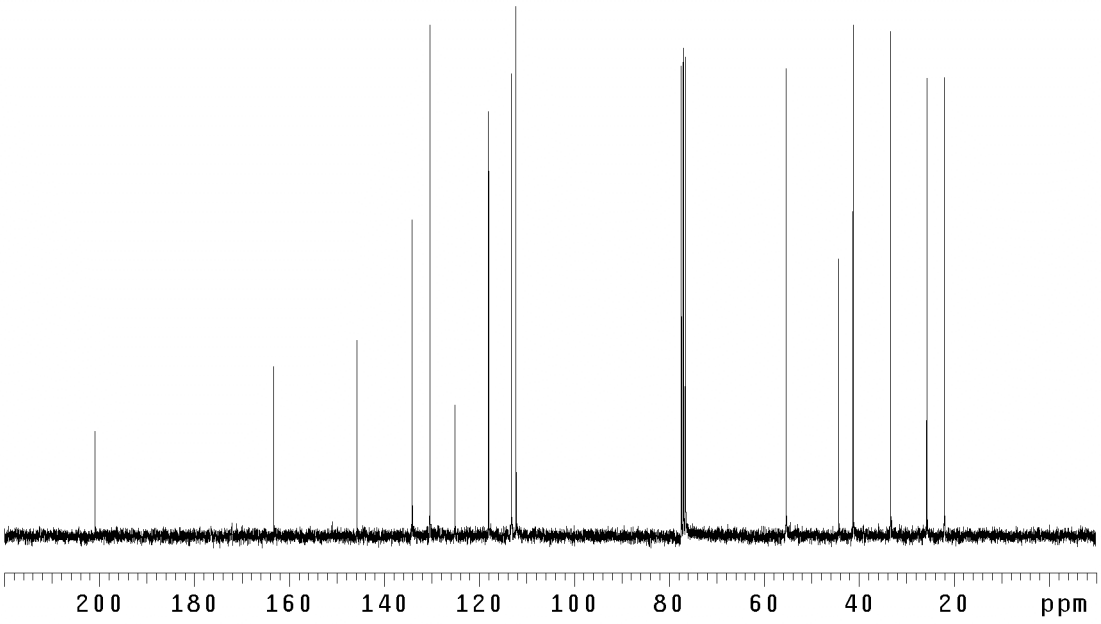
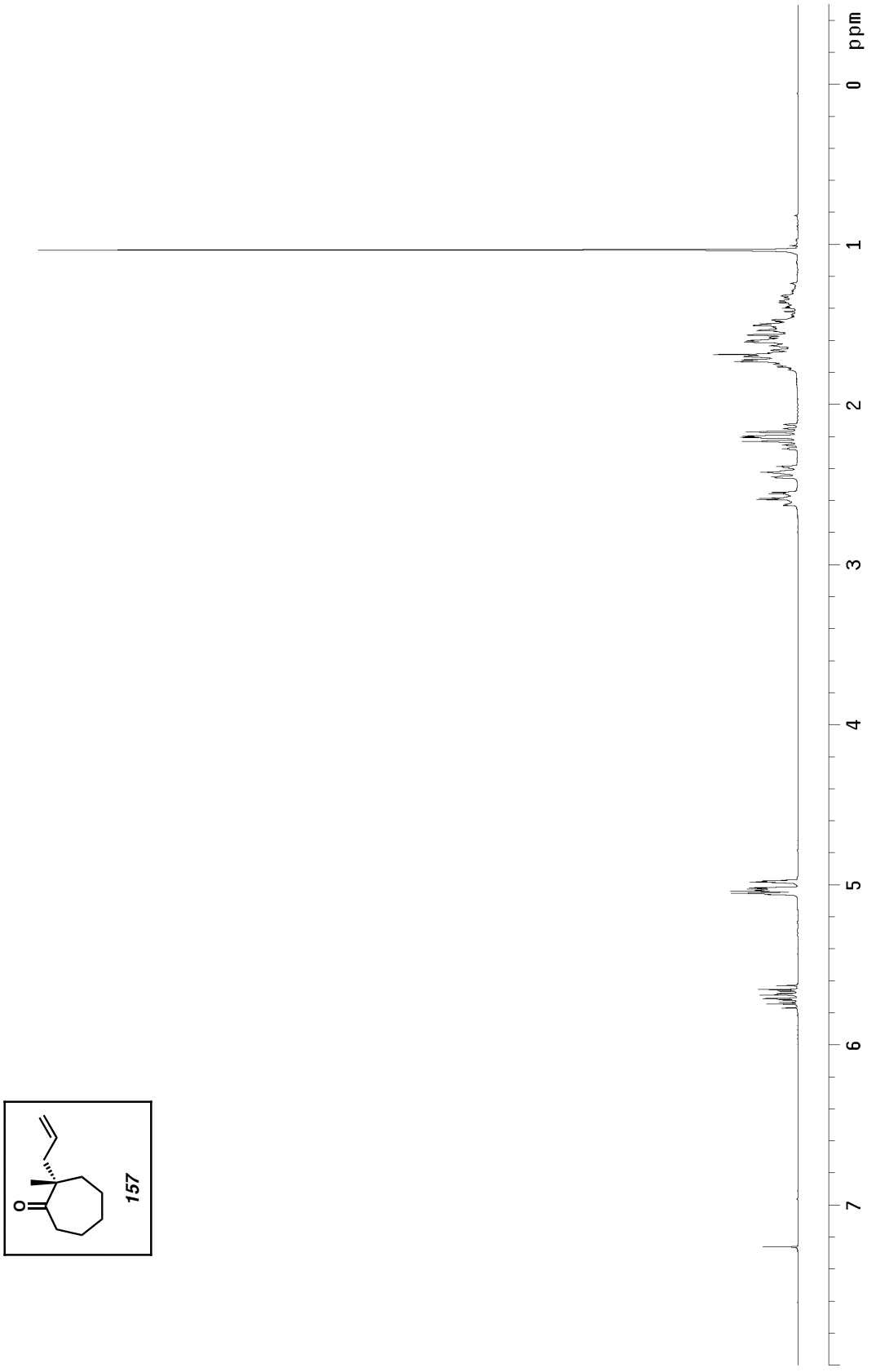


*Figure A1.180 ^{13}C NMR of compound **156** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
157

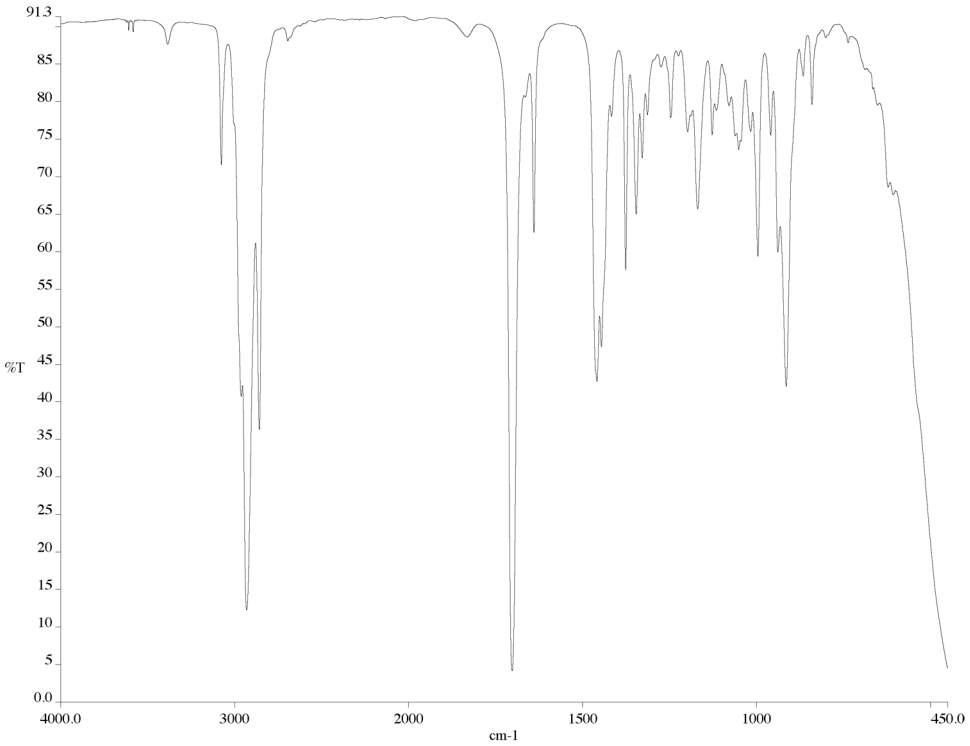


*Figure A1.182 IR of compound **157** (NaCl/film)*

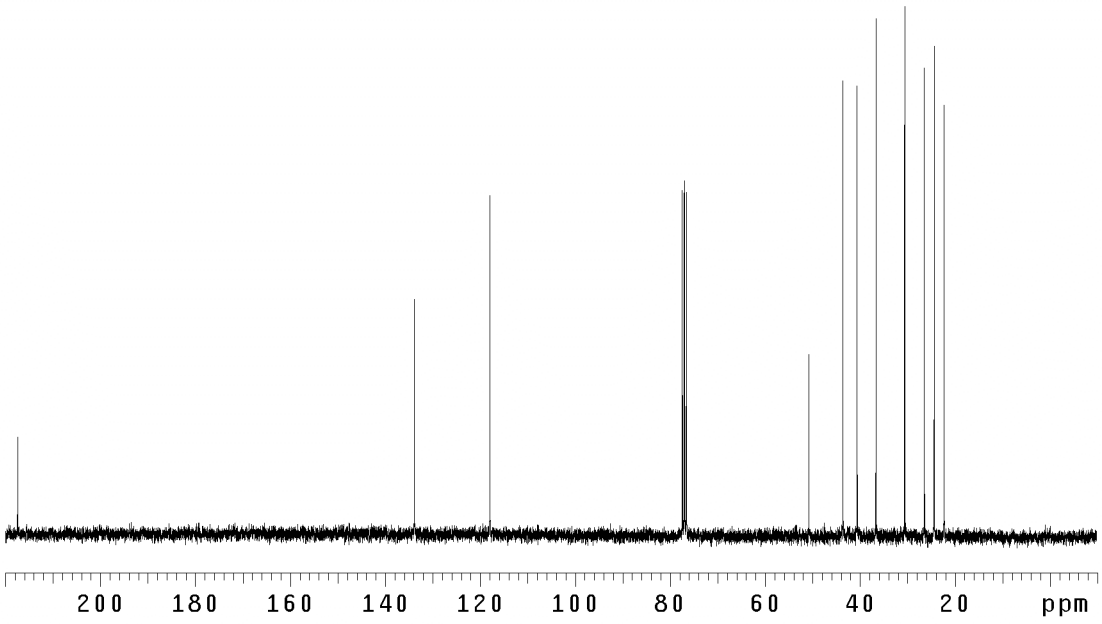
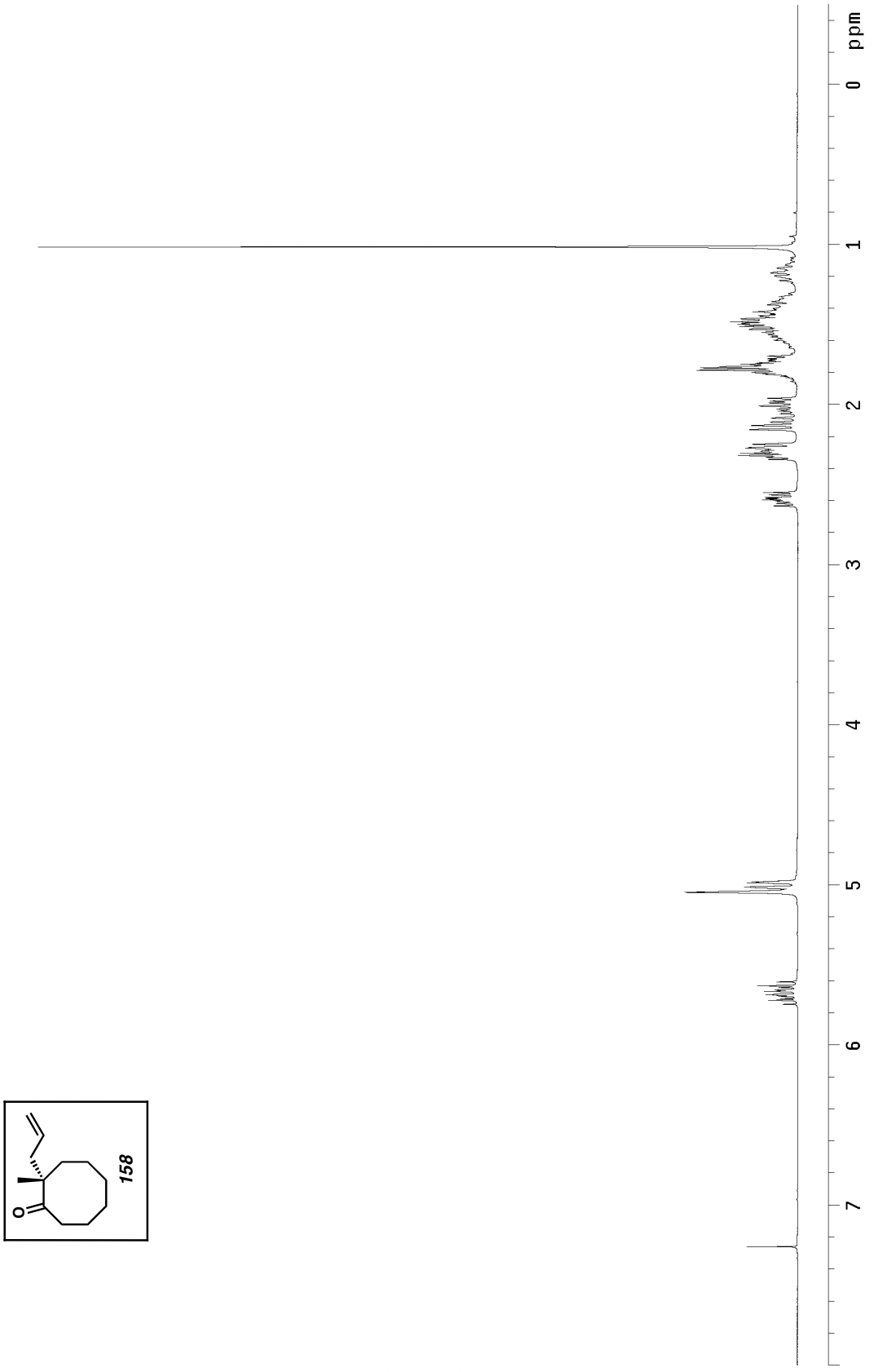


*Figure A1.183 ^{13}C NMR of compound **157** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
158

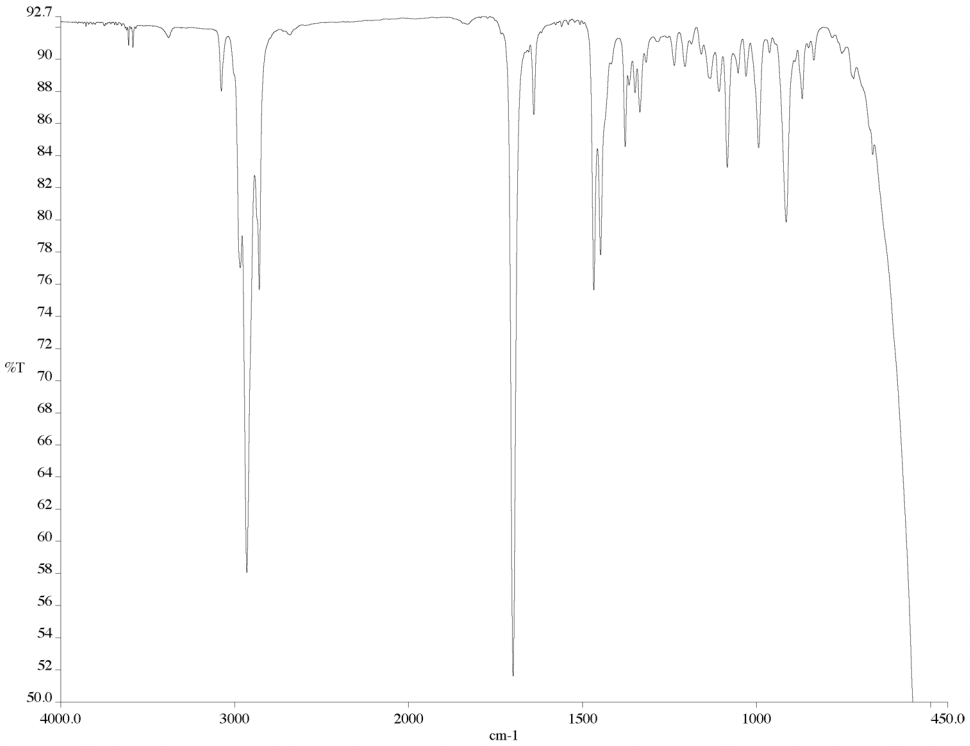


*Figure A1.185 IR of compound **158** (NaCl/film)*

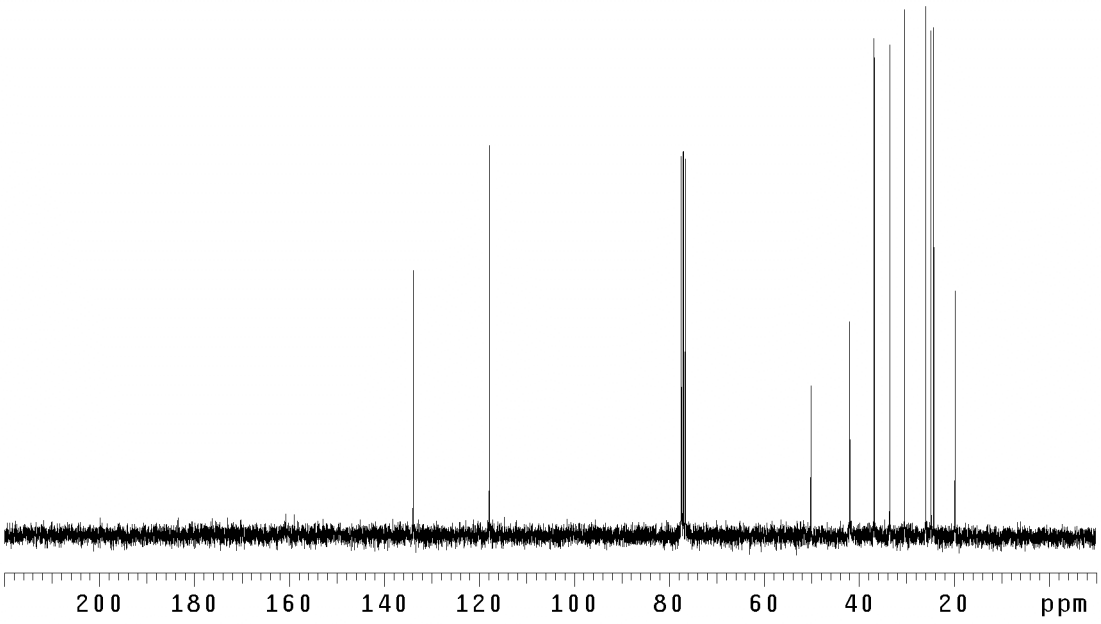
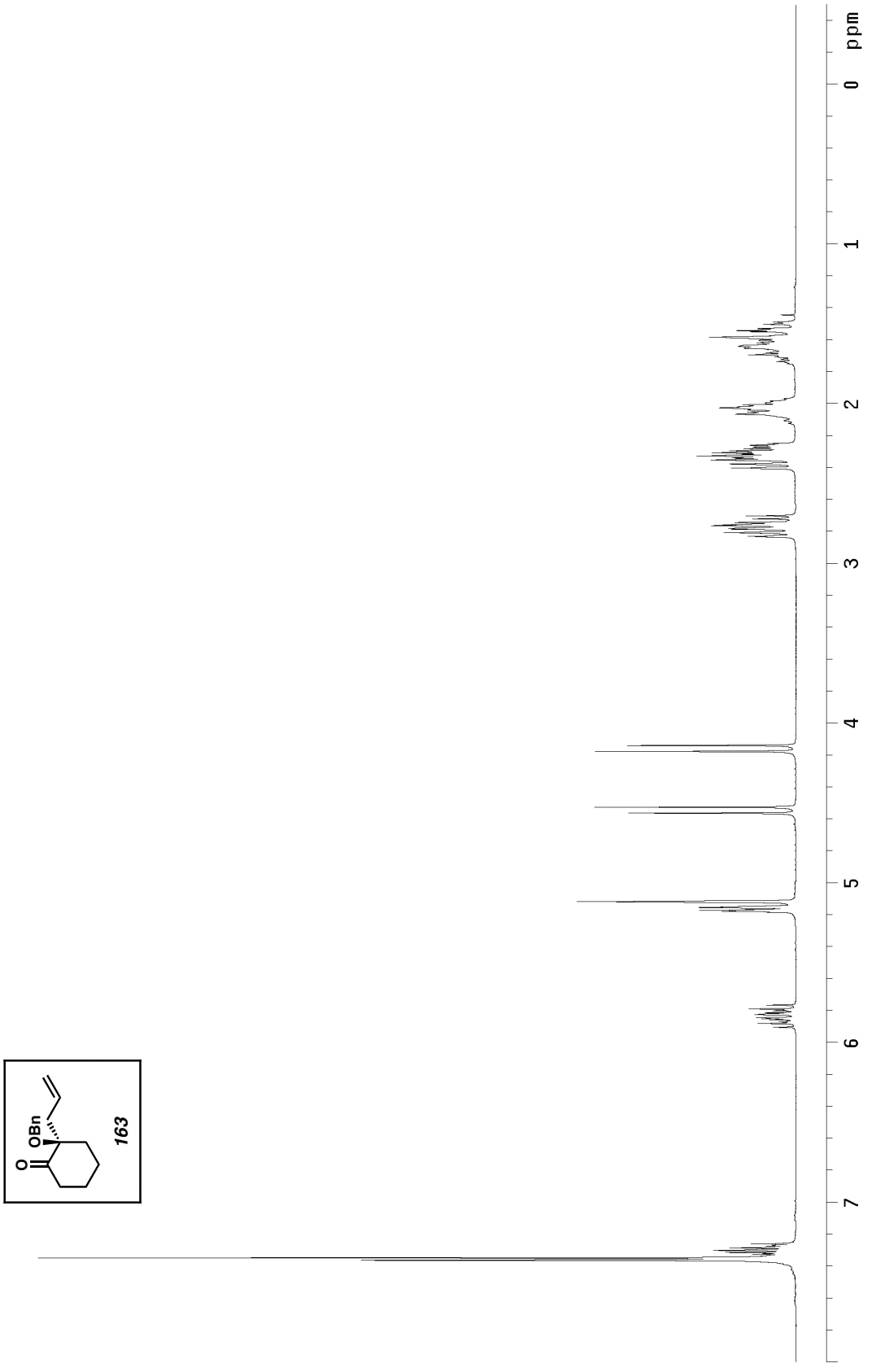


*Figure A1.186 ^{13}C NMR of compound **158** (75 MHz, $CDCl_3$)*


O
OBn
163
7
6
5
4
3
2
1
0
ppm

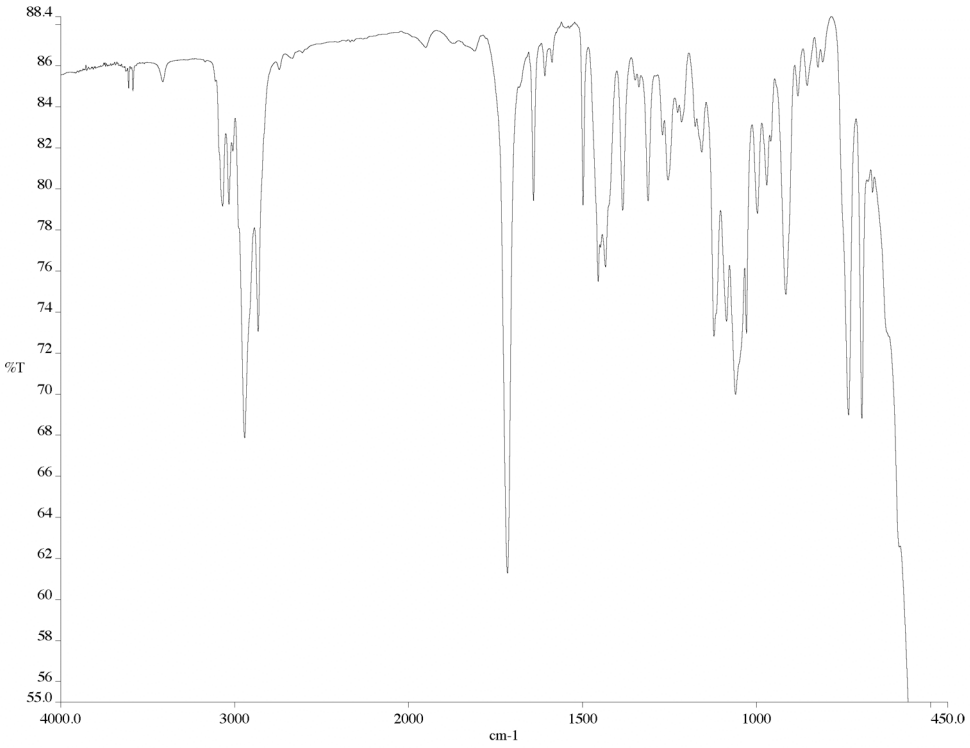


*Figure A1.188 IR of compound **163** (NaCl/film)*

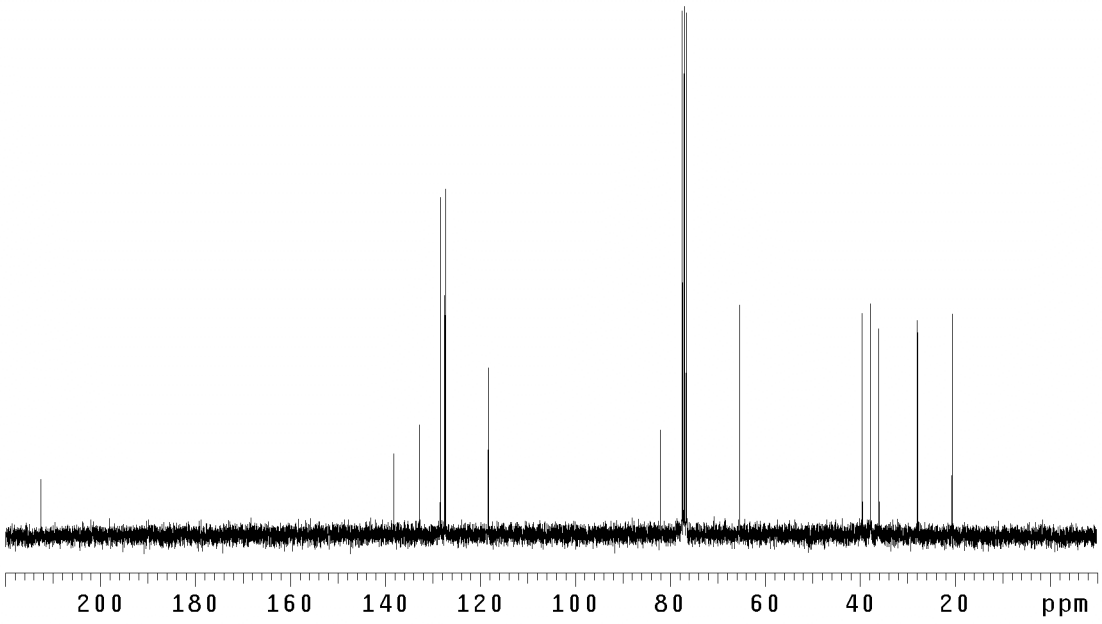
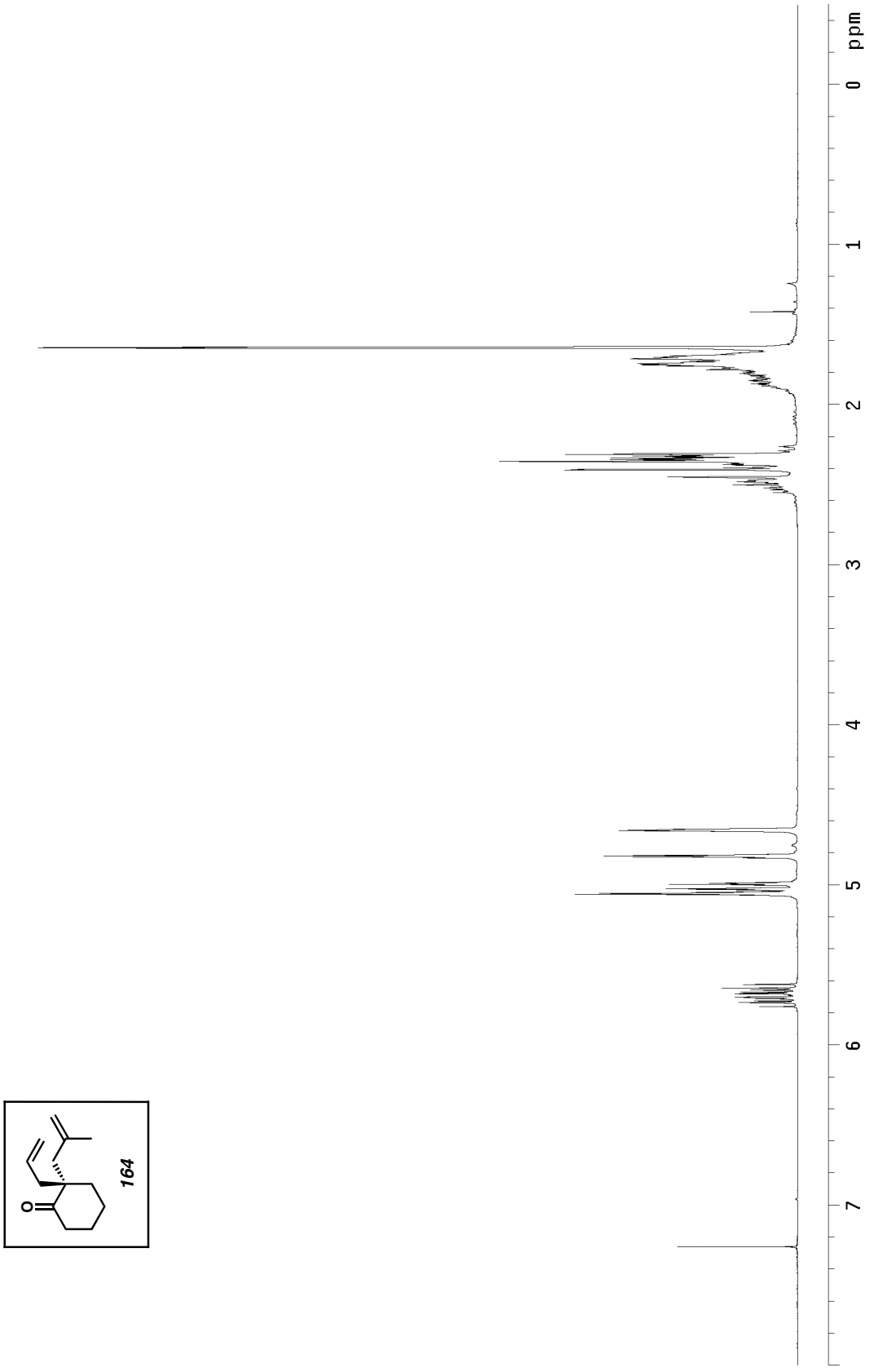


*Figure A1.189 ^{13}C NMR of compound **163** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
164

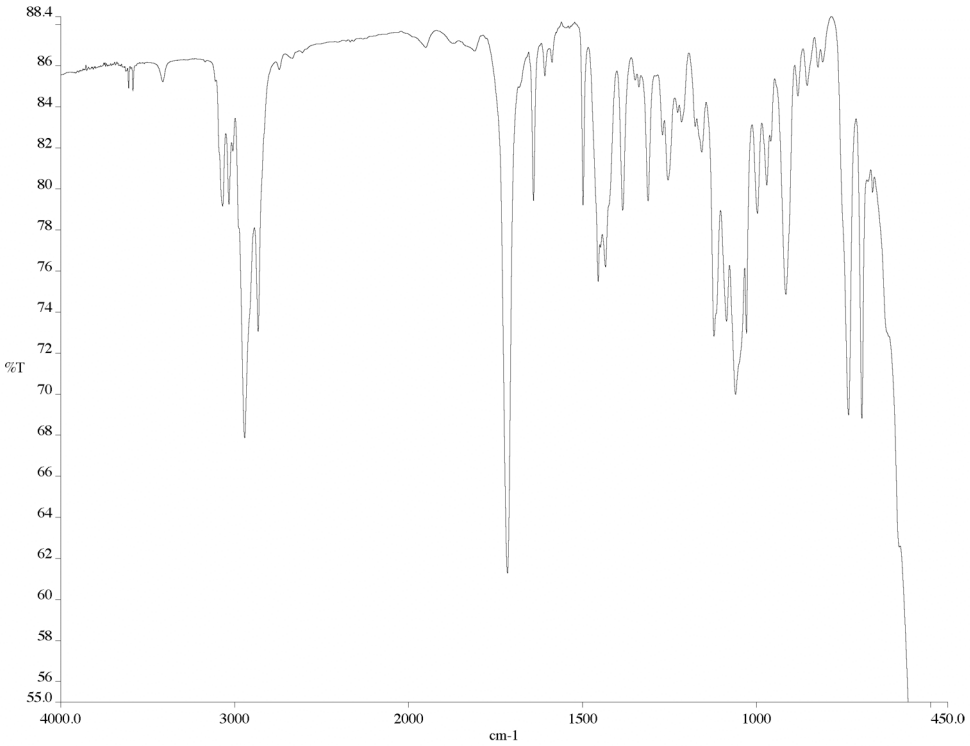


*Figure A1.191 IR of compound **164** (NaCl/film)*

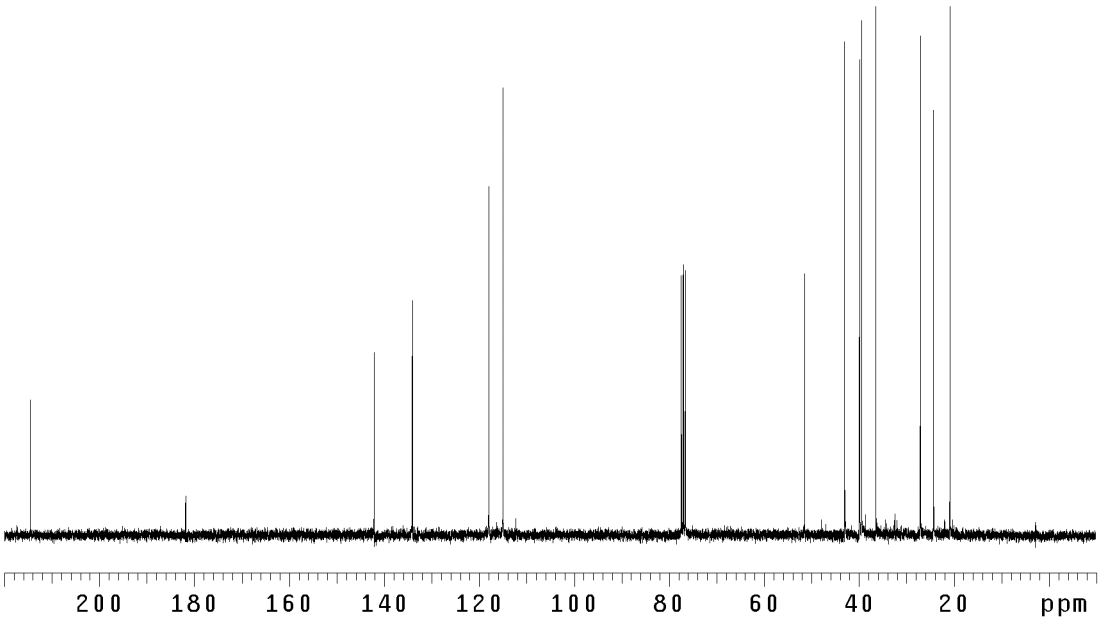
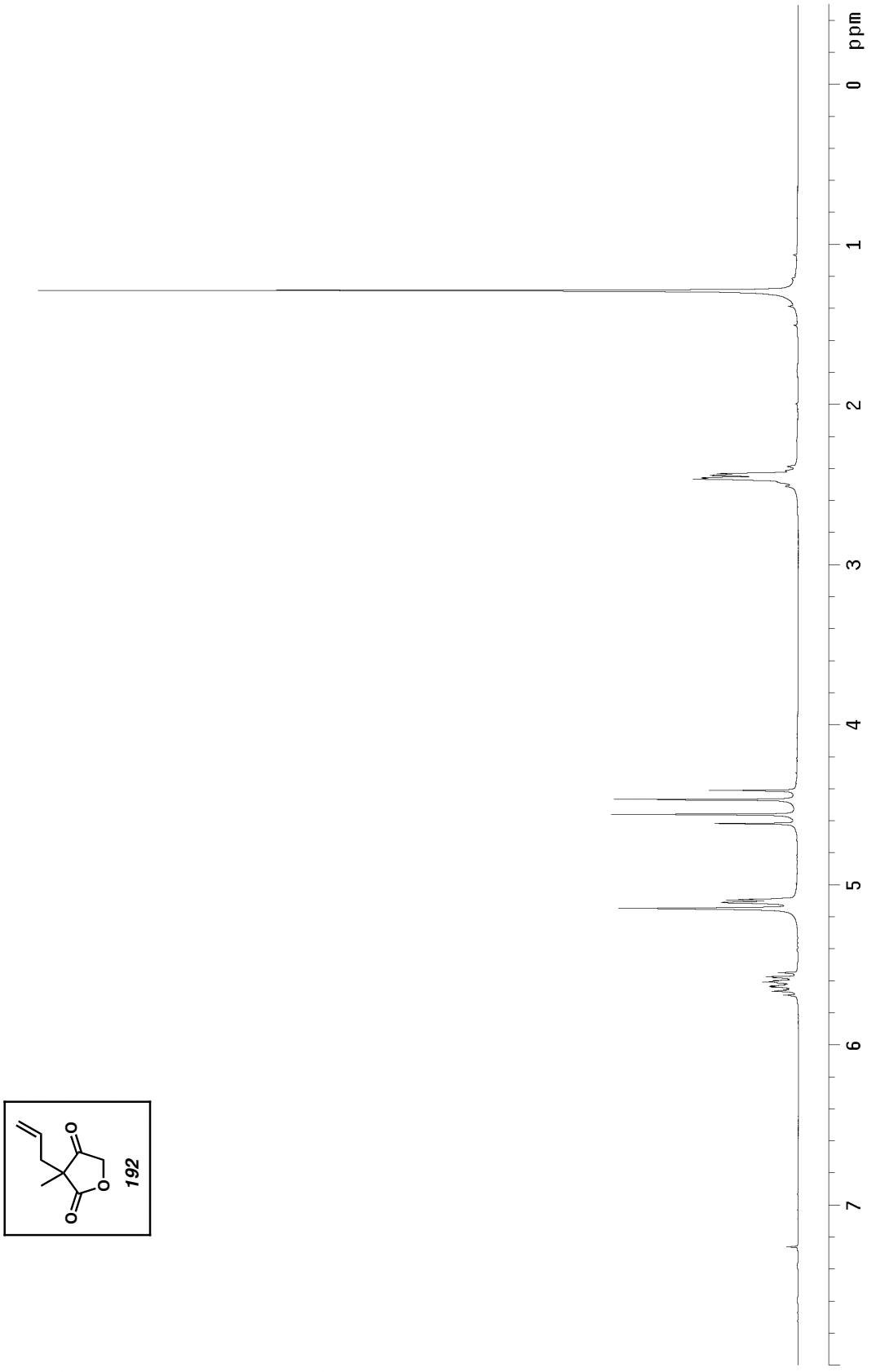


*Figure A1.192 ^{13}C NMR of compound **164** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
O
O
O
192

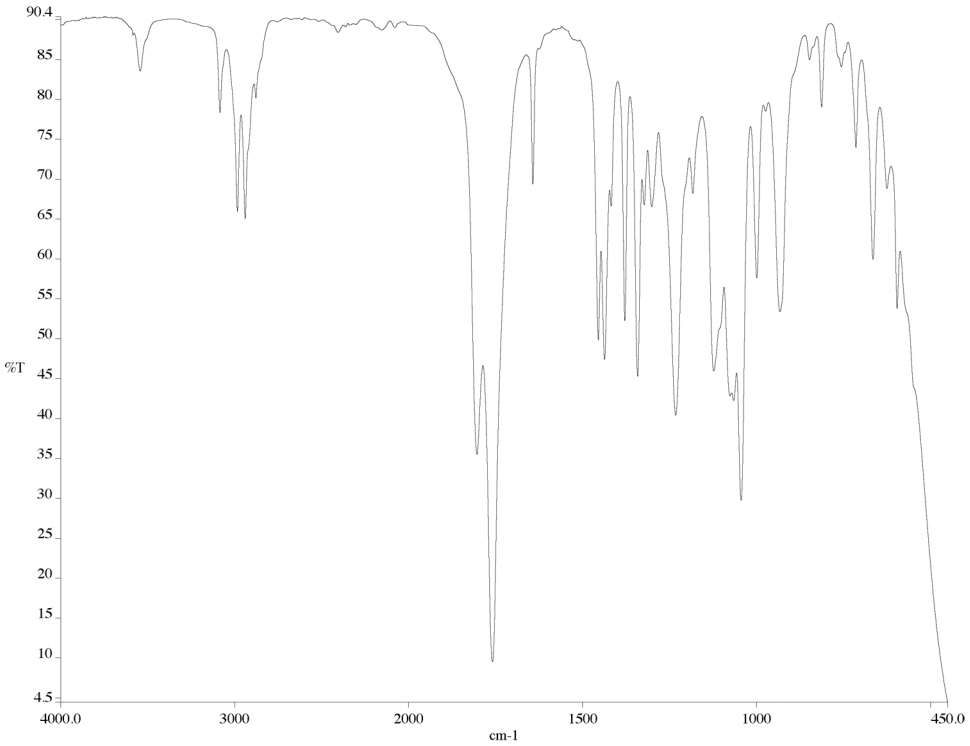


*Figure A1.194 IR of compound **192** (NaCl/film)*

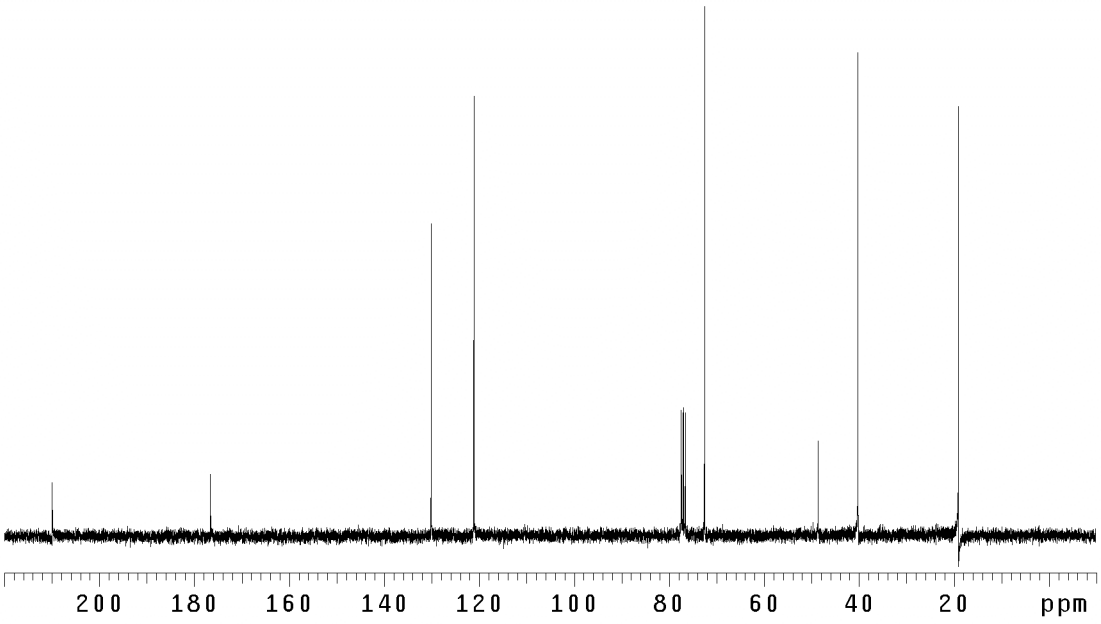
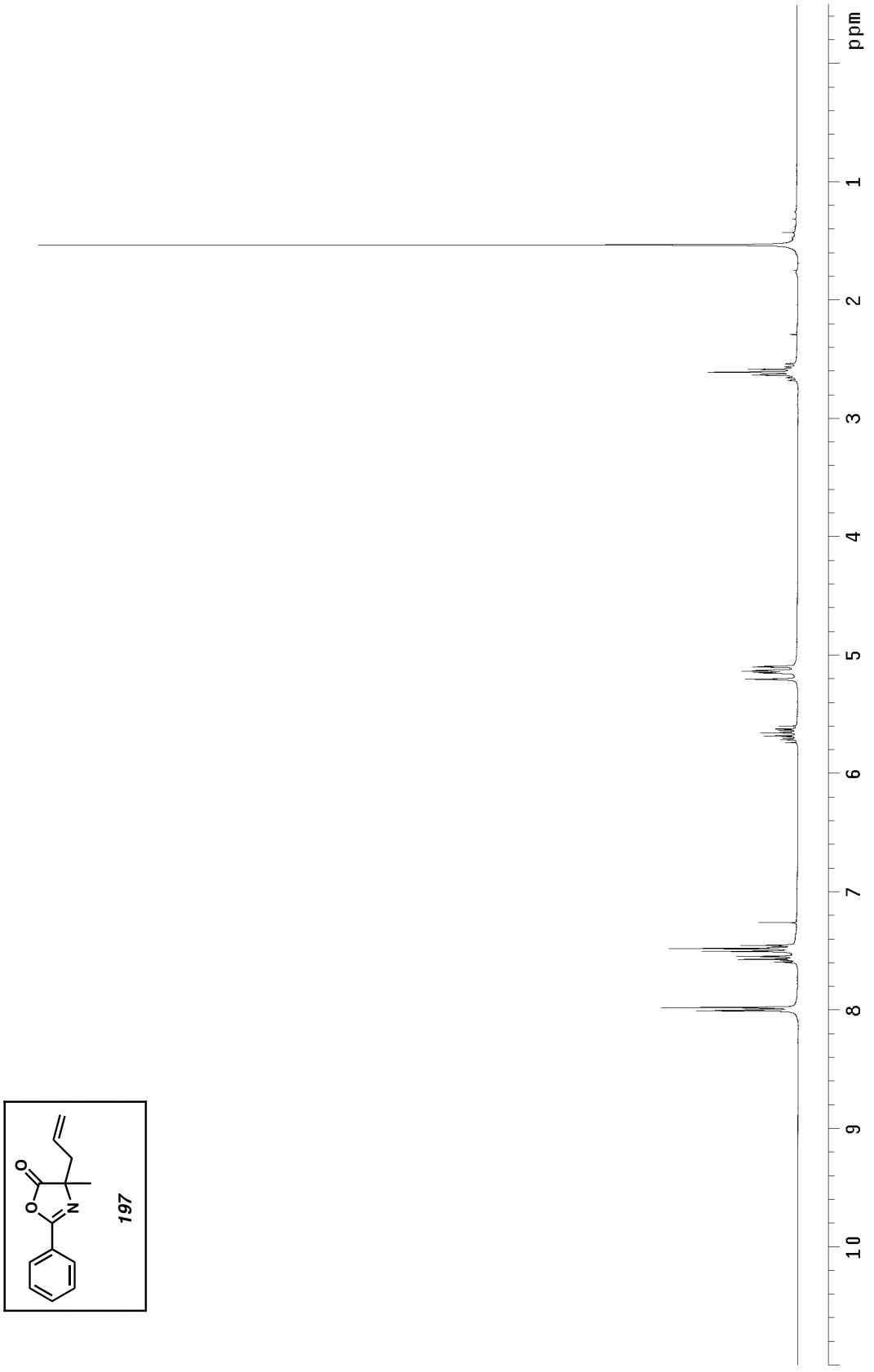


*Figure A1.195 ^{13}C NMR of compound **192** (75 MHz, $CDCl_3$)*


ppm
1
2
3
4
5
6
7
8
9
10

O
O
N
197

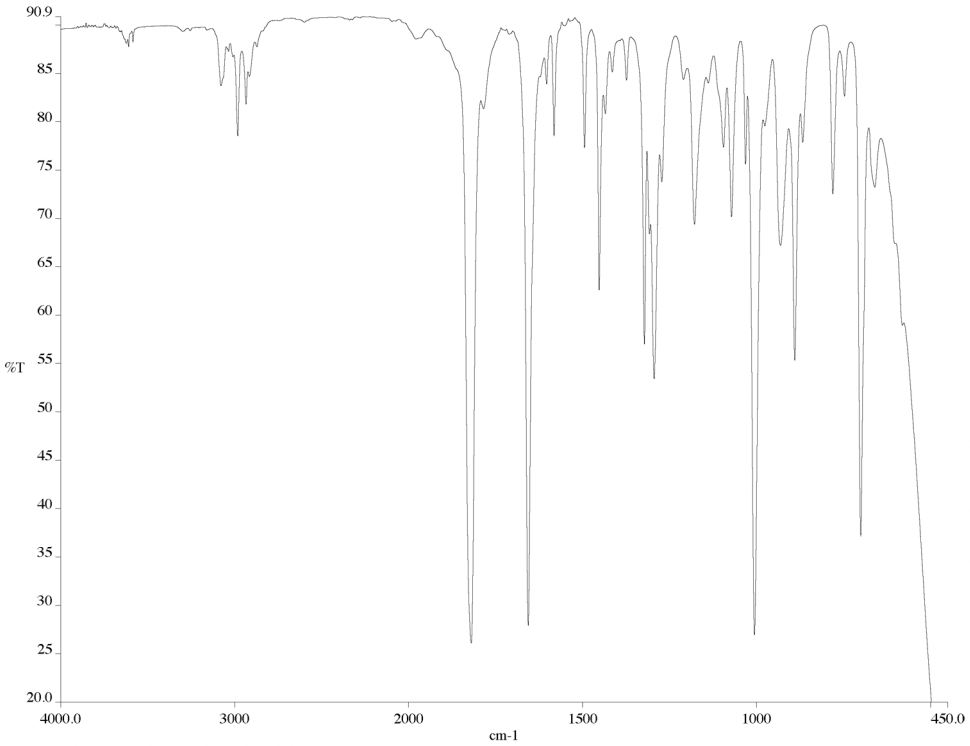


*Figure A1.197 IR of compound **197** (NaCl/film)*

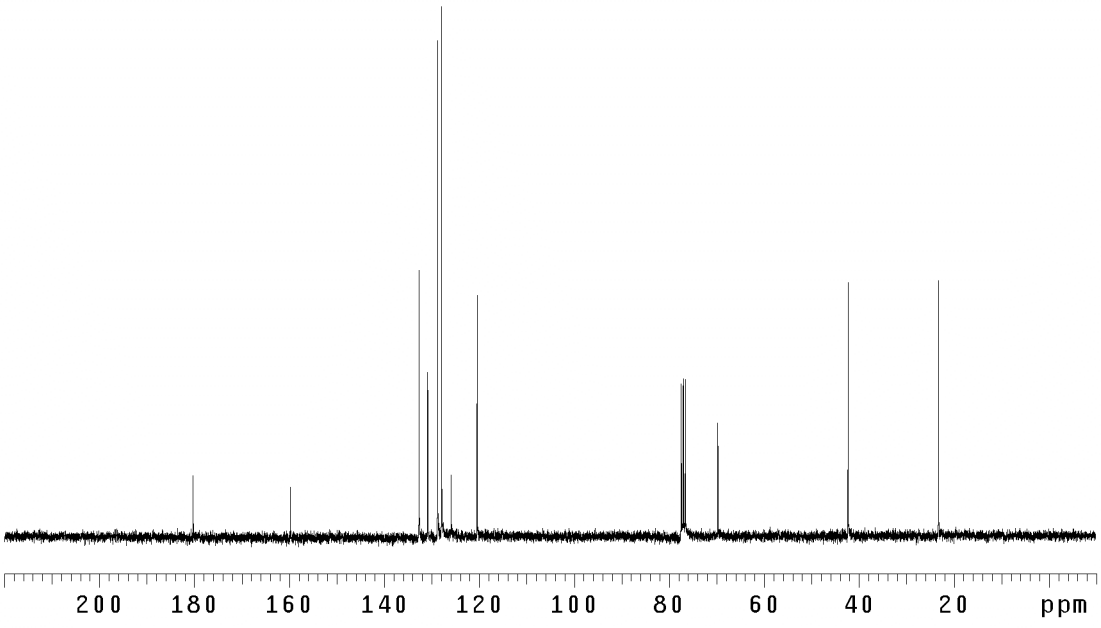
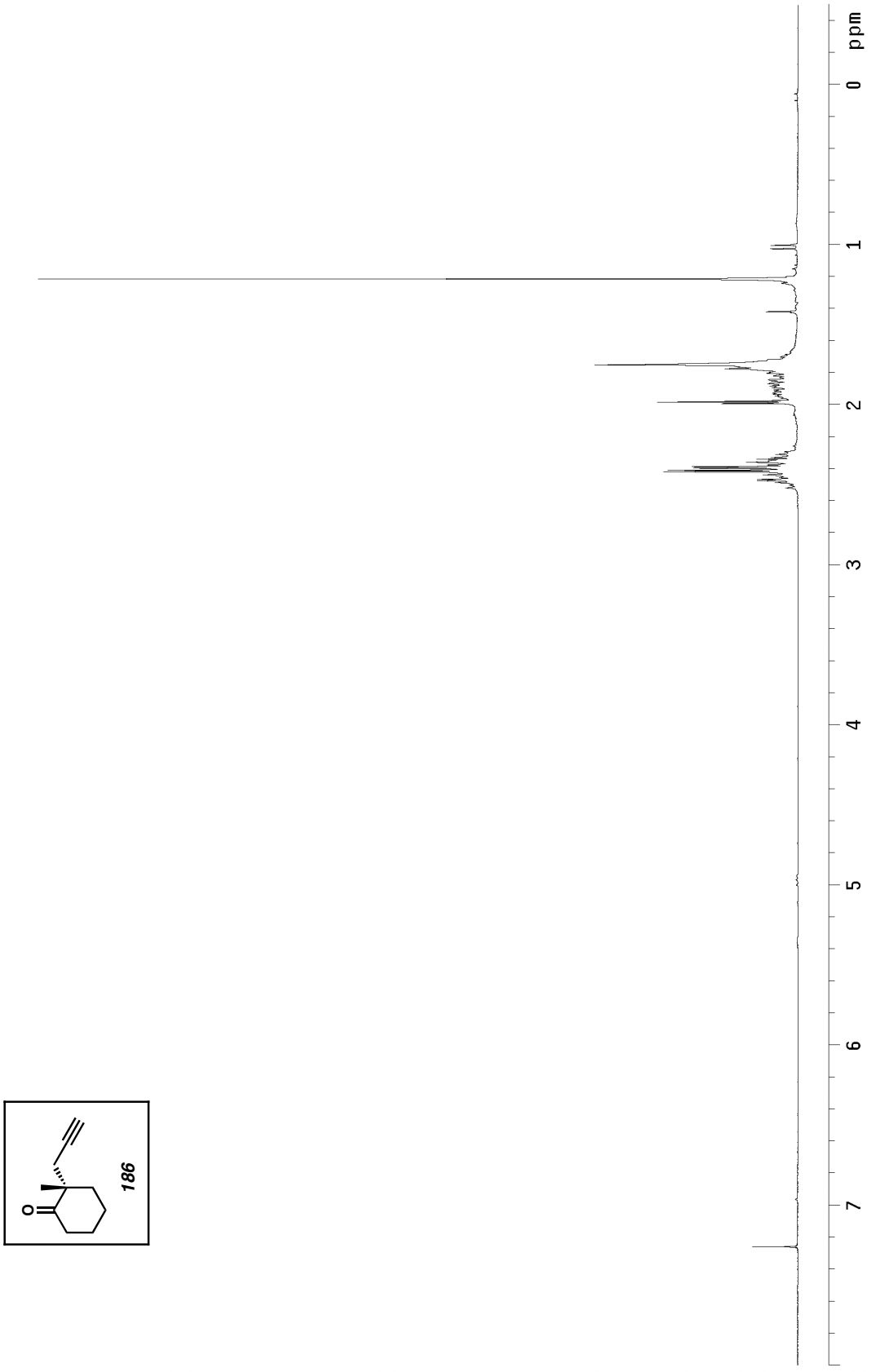


*Figure A1.198 ^{13}C NMR of compound **197** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
186

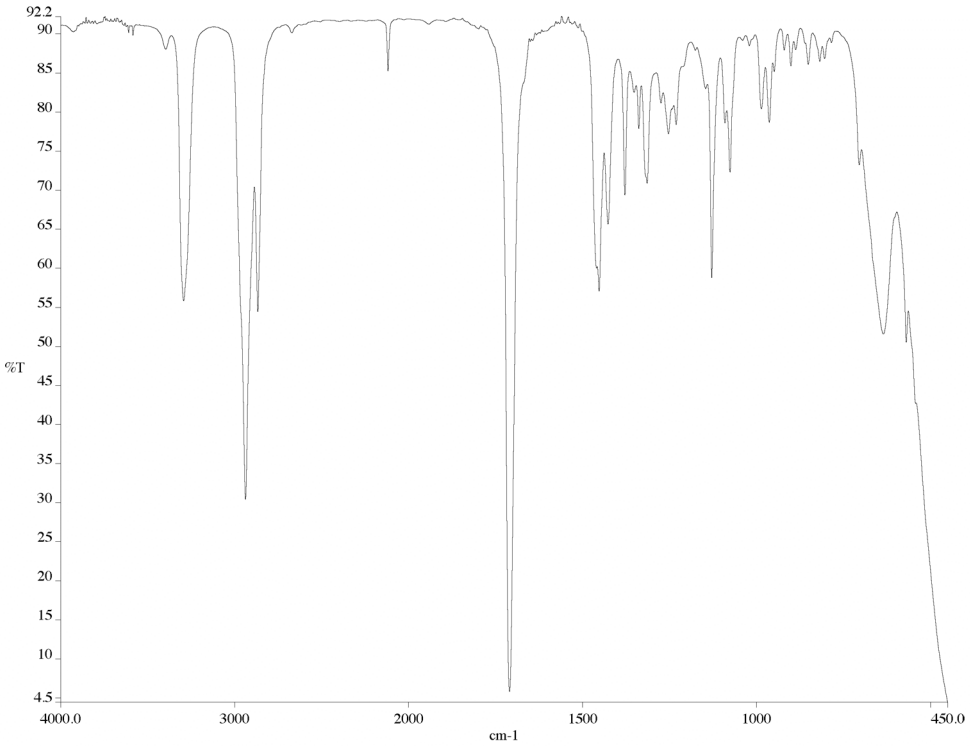


*Figure A1.200 IR of compound **186** (NaCl/film)*

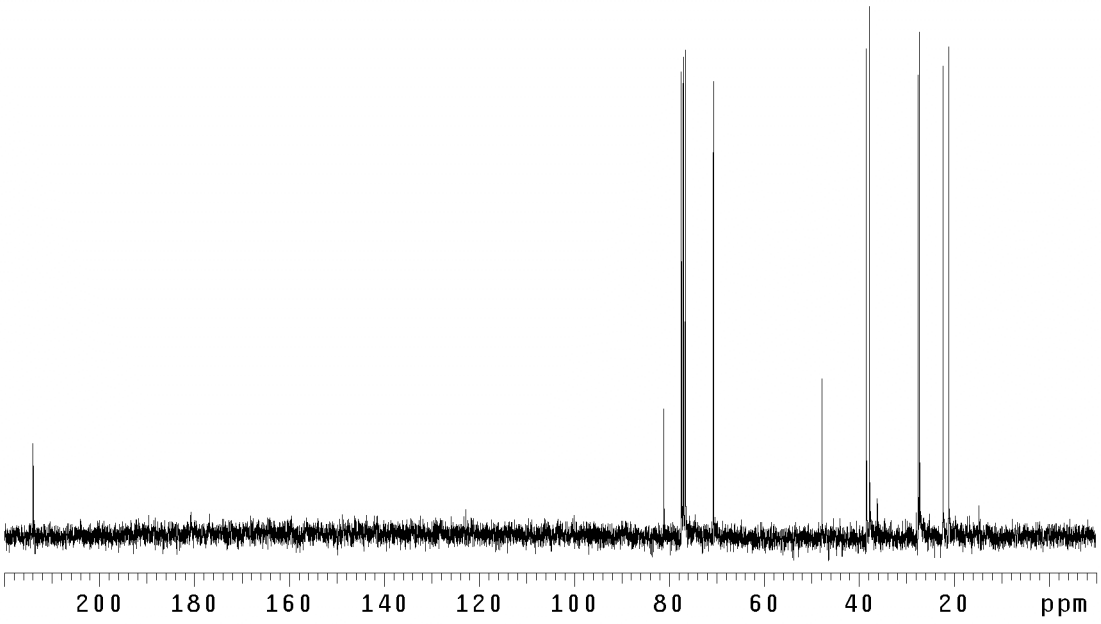
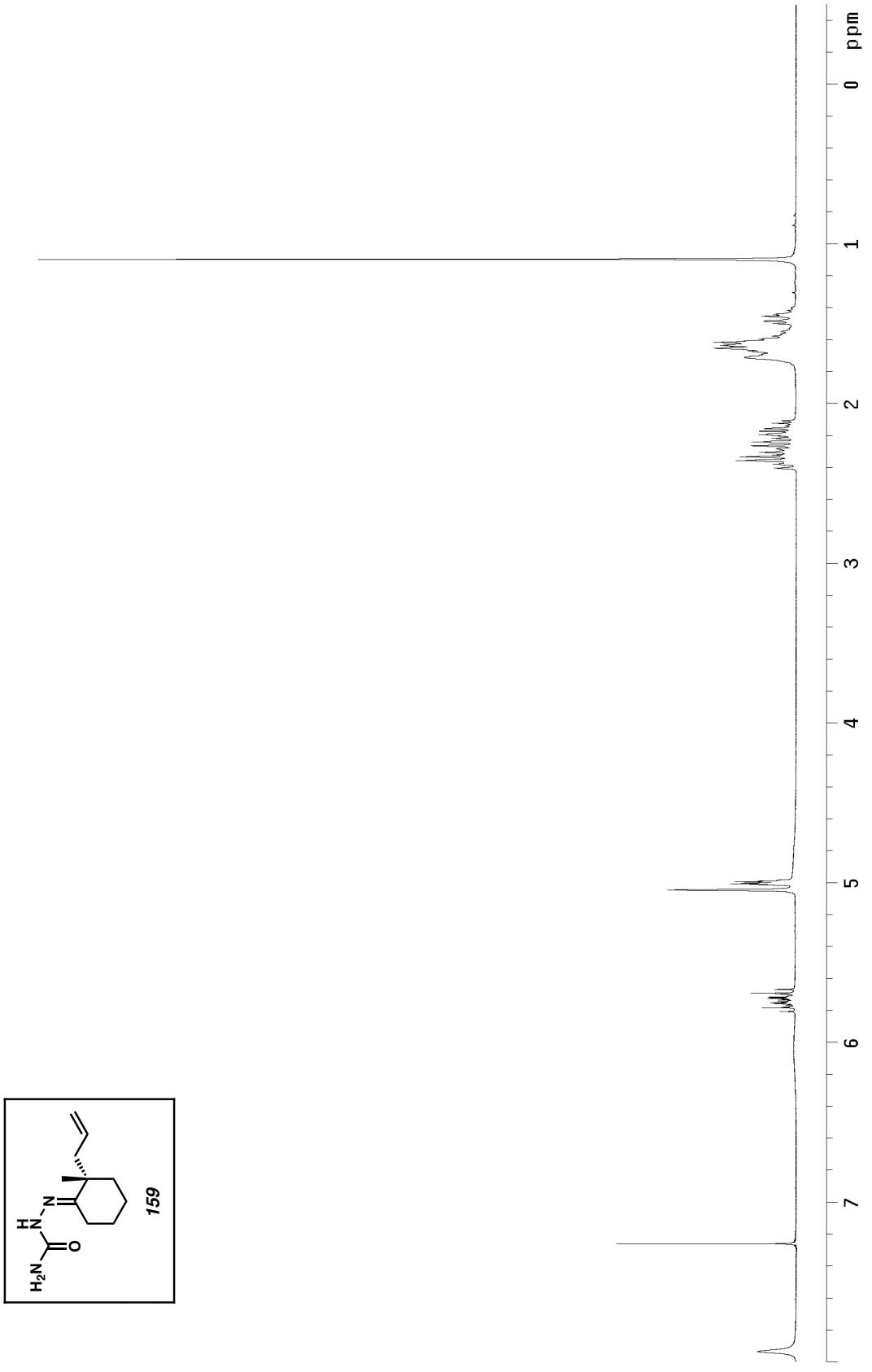


*Figure A1.201 ^{13}C NMR of compound **186** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
H
N
N
O
H_2N
159

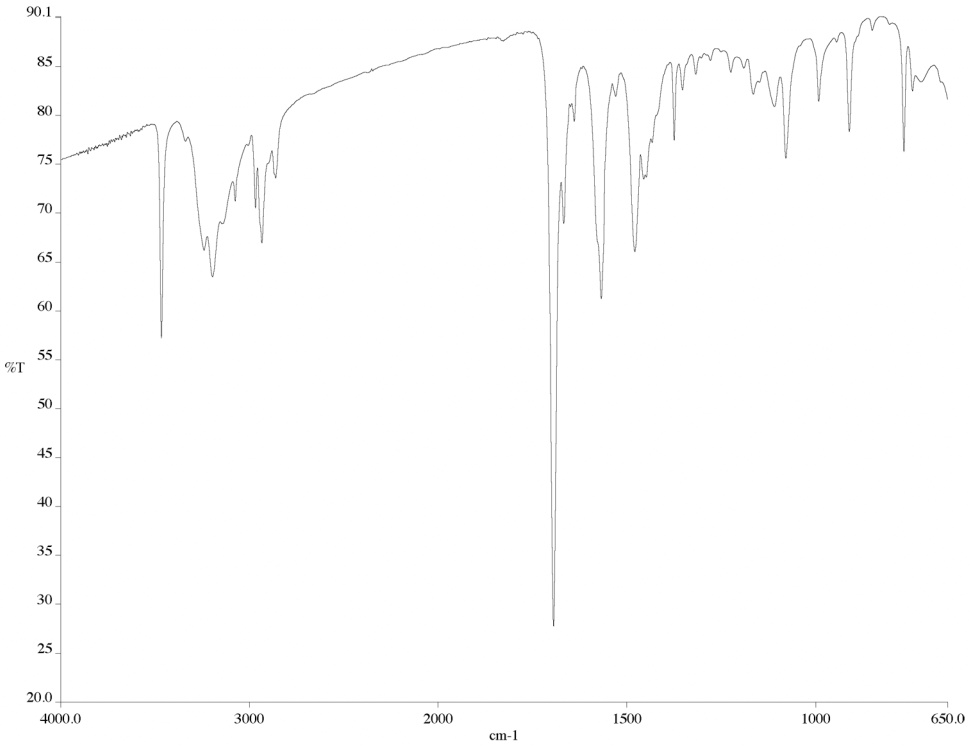


*Figure A1.203 IR of compound **159** (NaCl/film)*

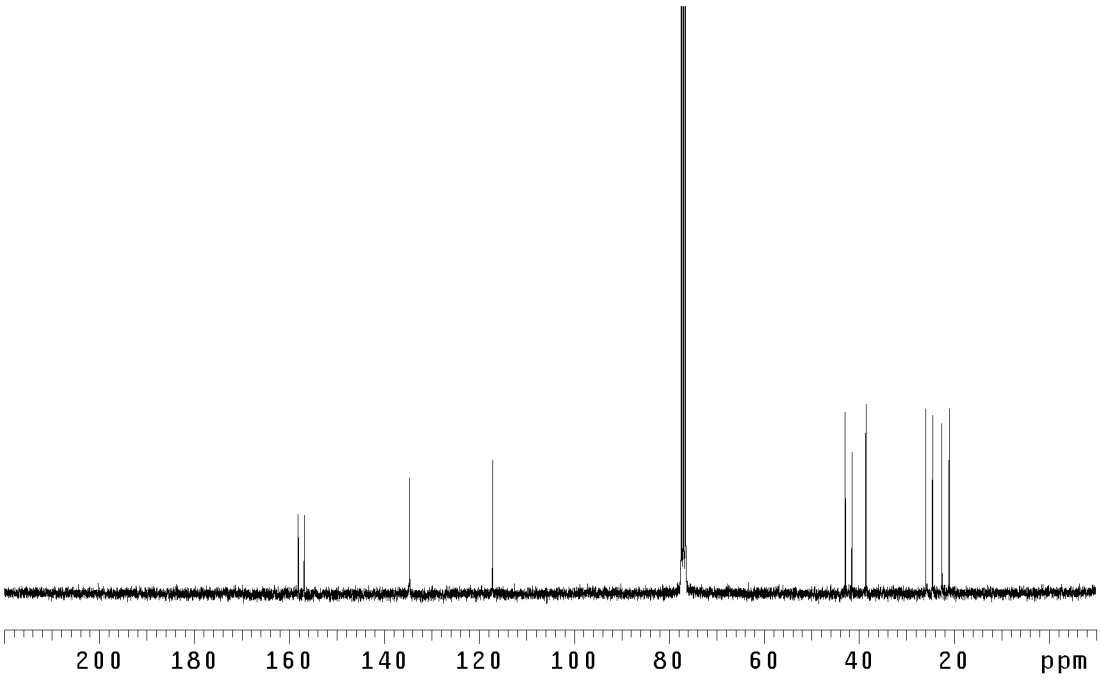
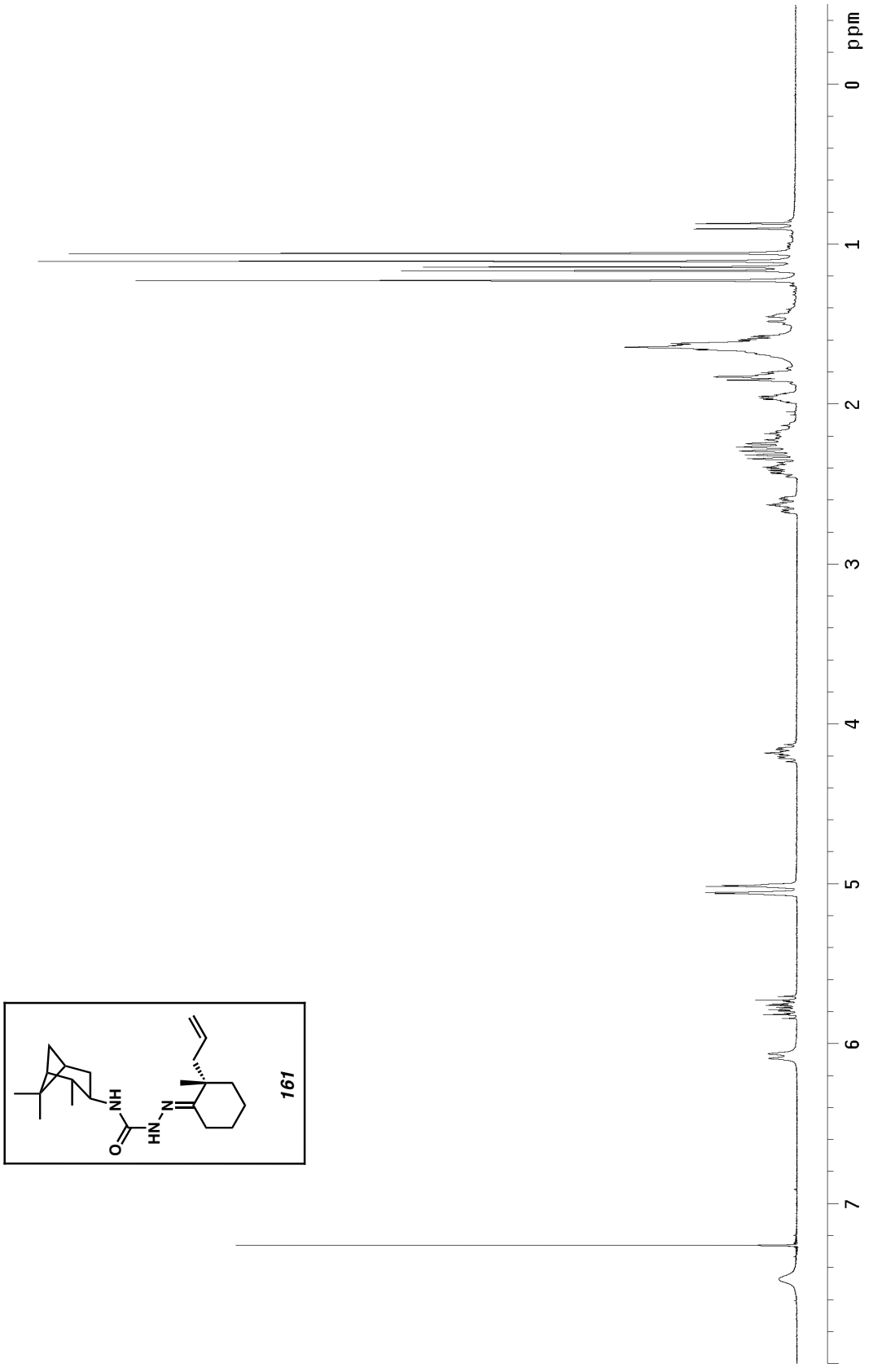


*Figure A1.204 ^{13}C NMR of compound **159** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
NH
HN
O
N
161

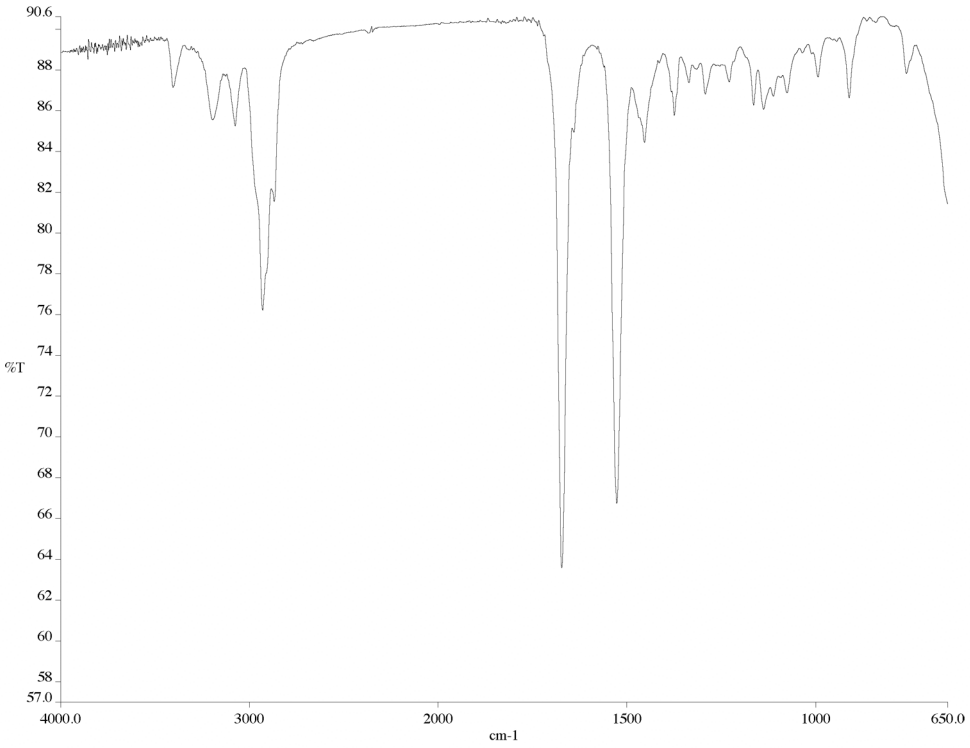


*Figure A1.206 IR of compound **161** (NaCl/film)*

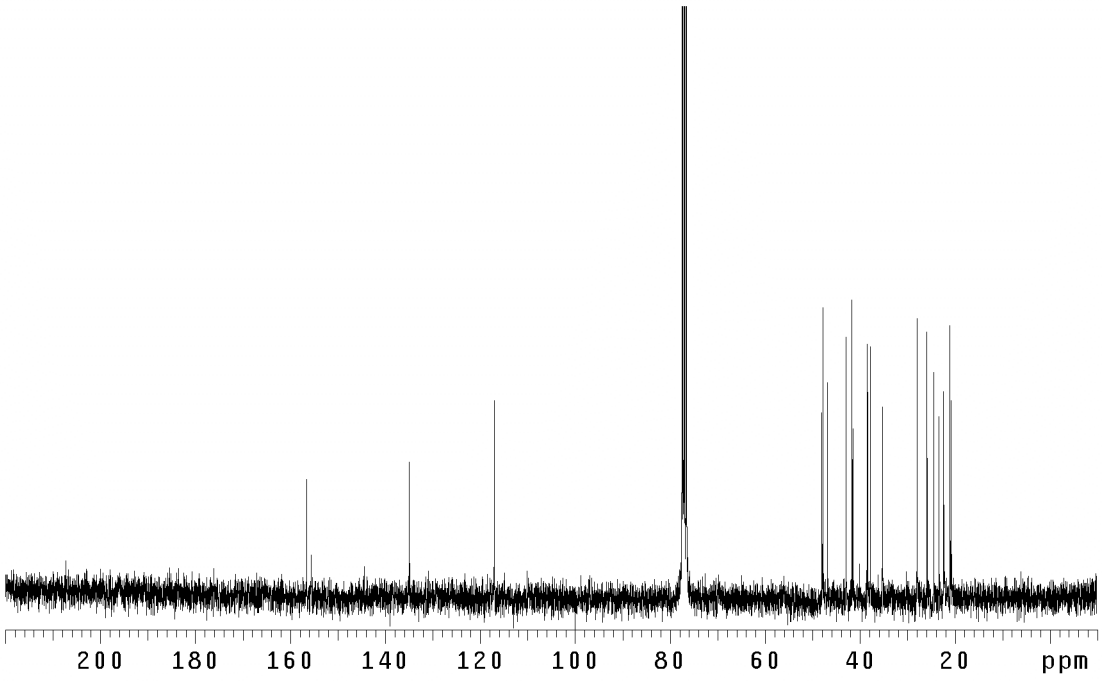
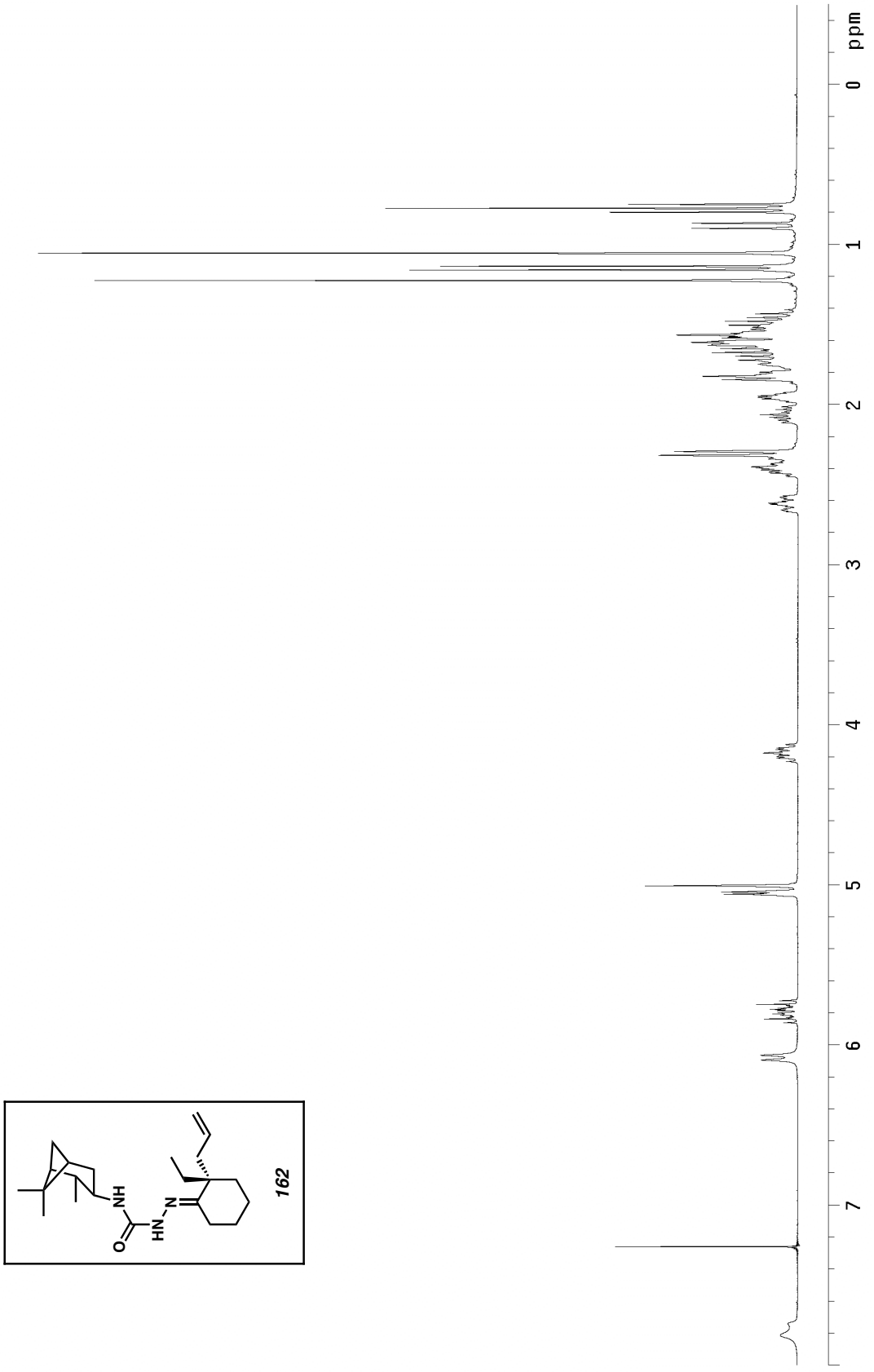


*Figure A1.207 ^{13}C NMR of compound **161** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
NH
HN
O
N
162

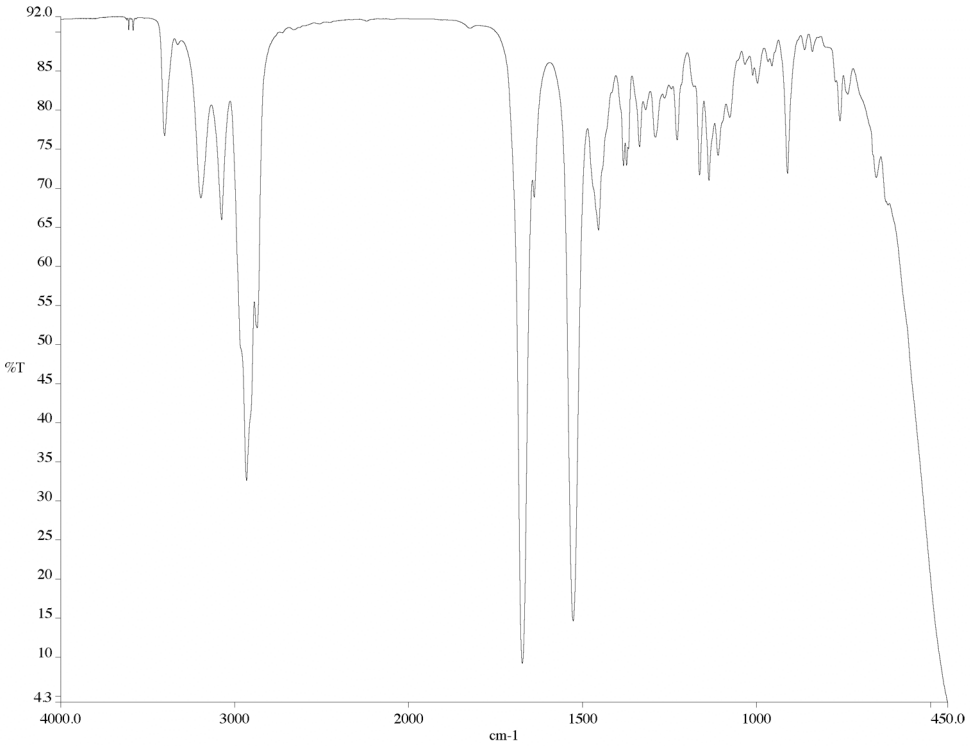


*Figure A1.209 IR of compound **162** (NaCl/film)*

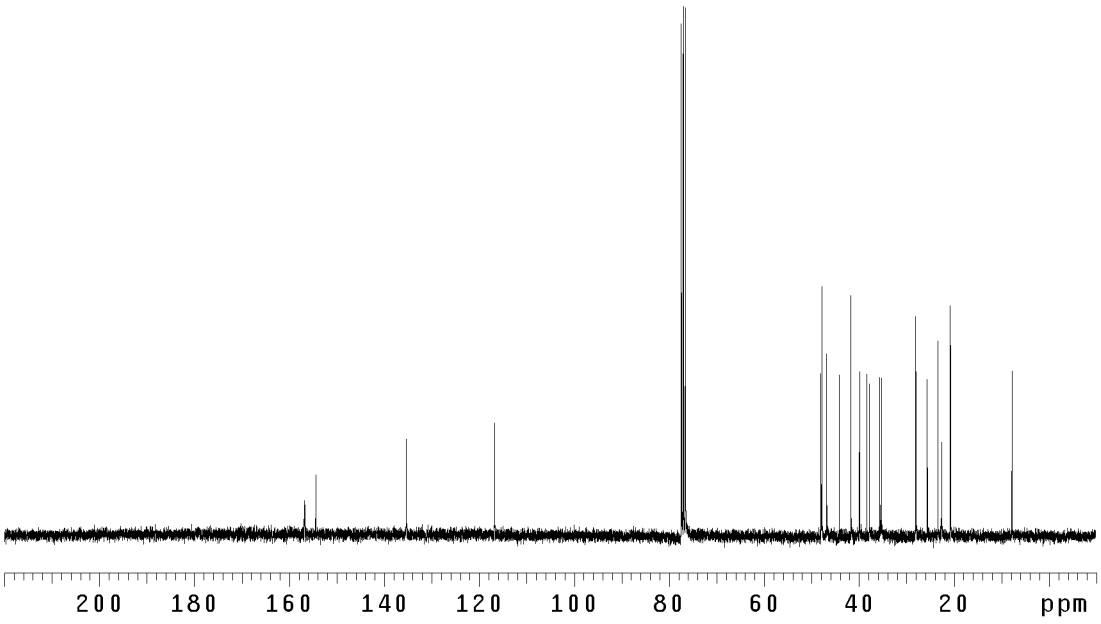
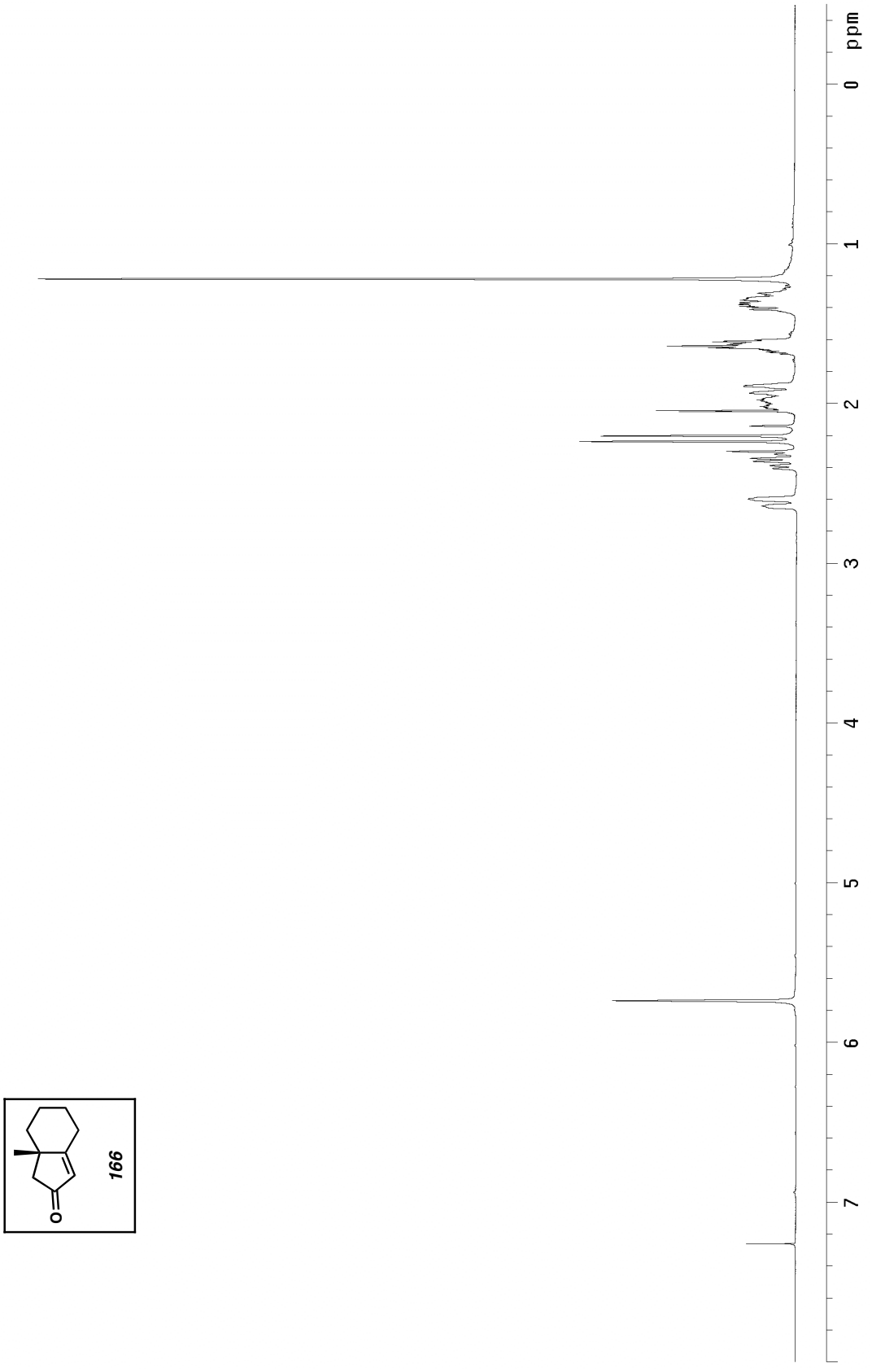


*Figure A1.210 ^{13}C NMR of compound **162** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
166

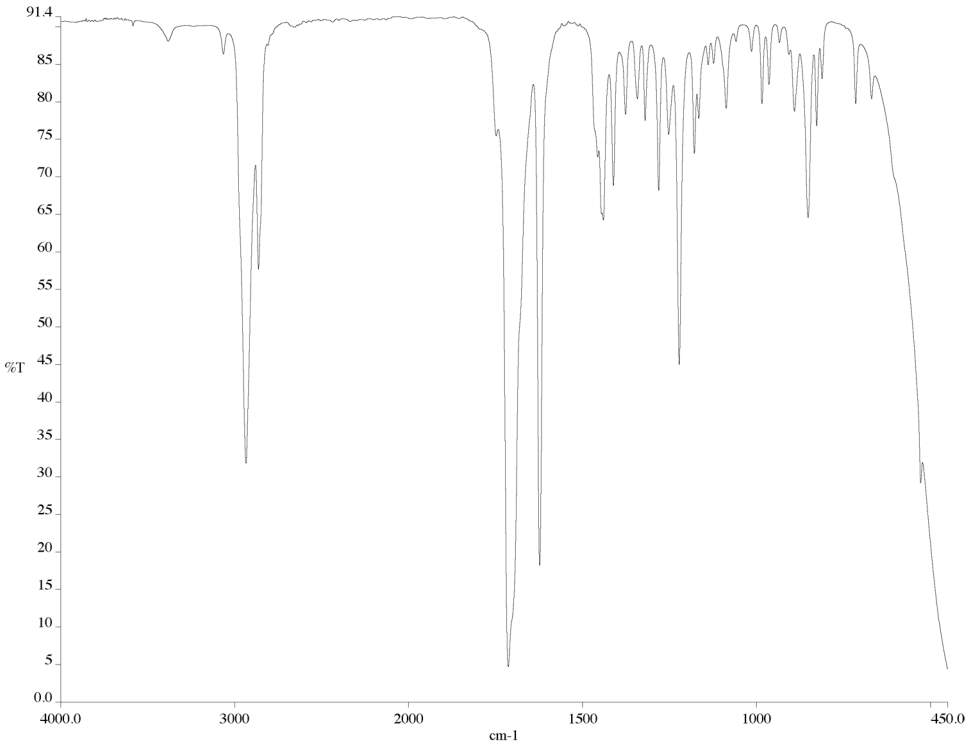


*Figure A1.212 IR of compound **166** (NaCl/film)*

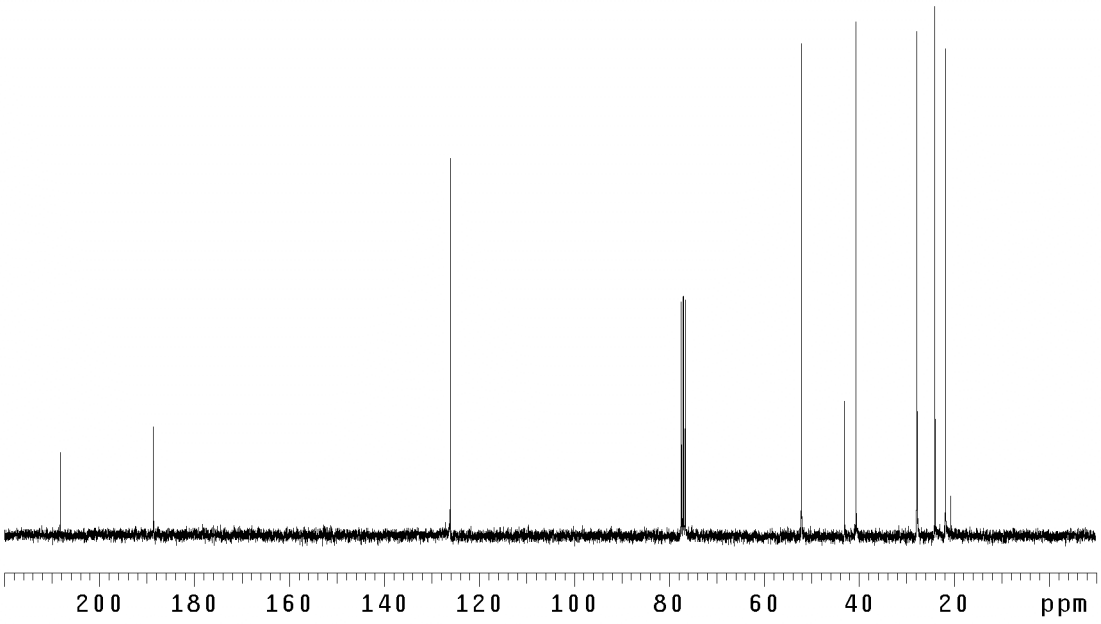
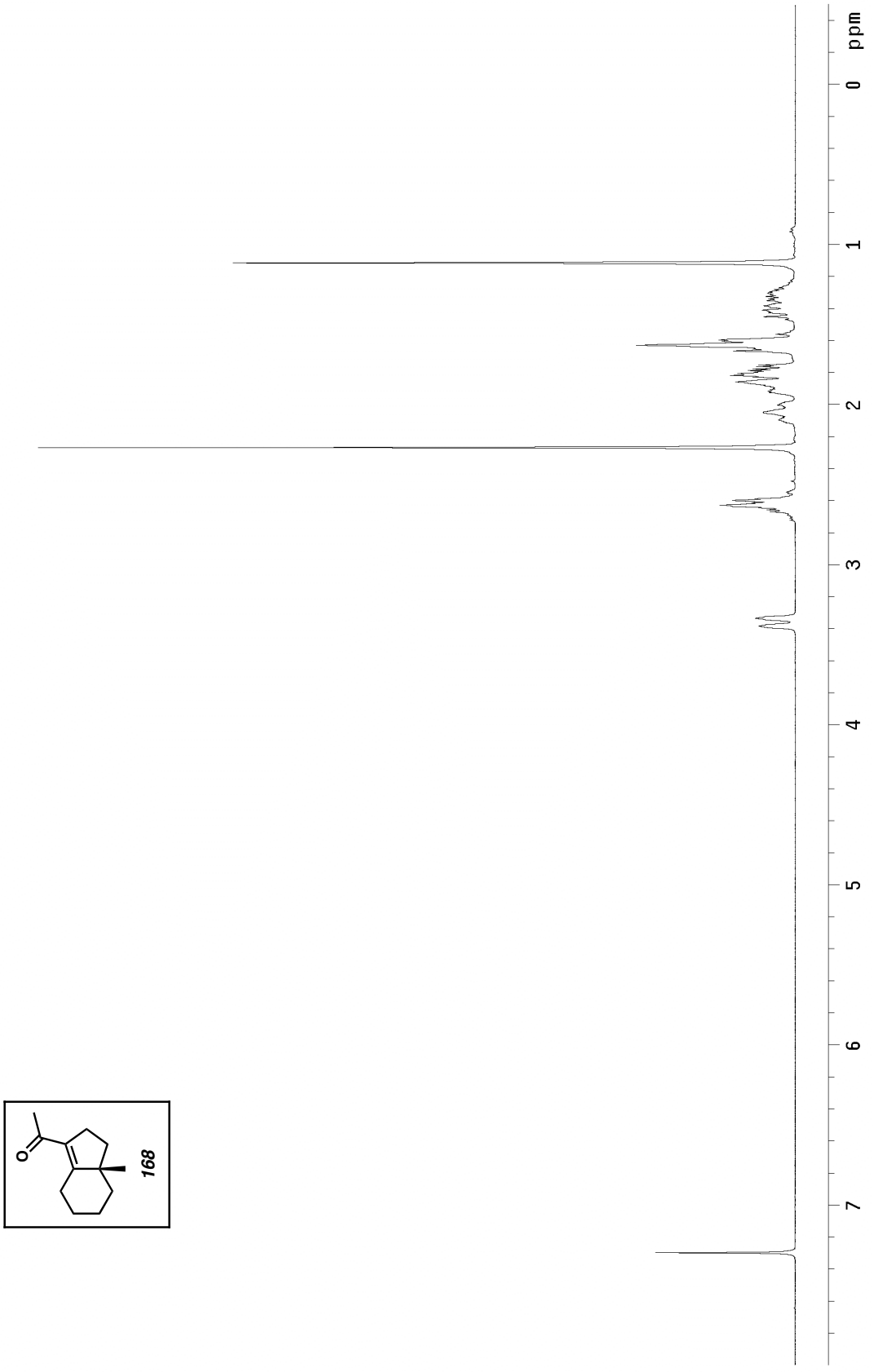


*Figure A1.213 ^{13}C NMR of compound **166** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
168

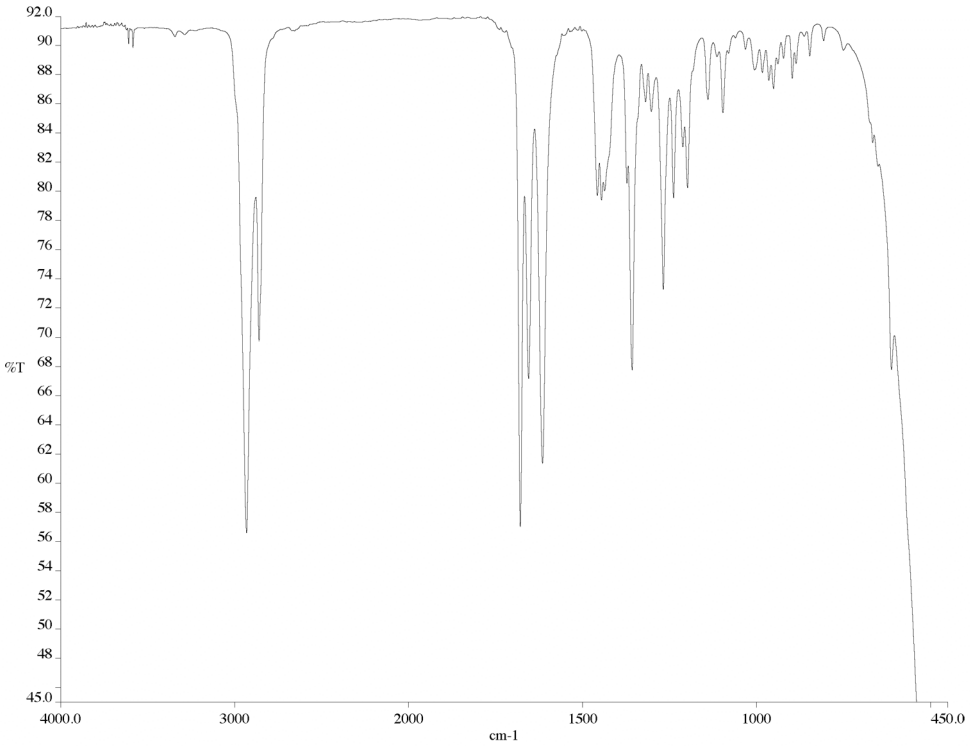


*Figure A1.215 IR of compound **168** (NaCl/film)*

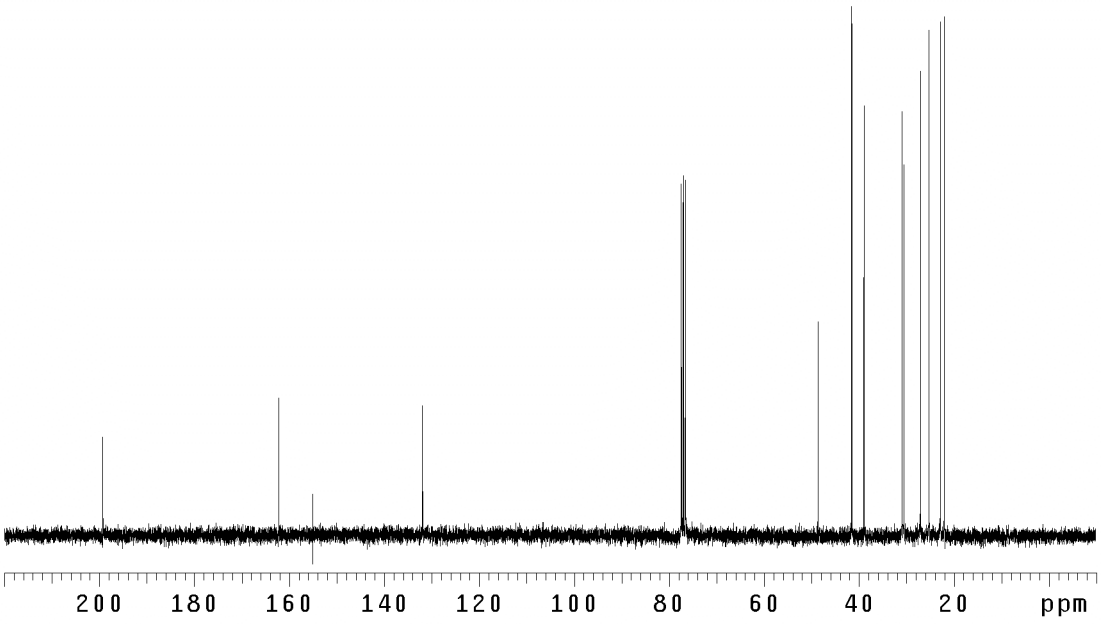
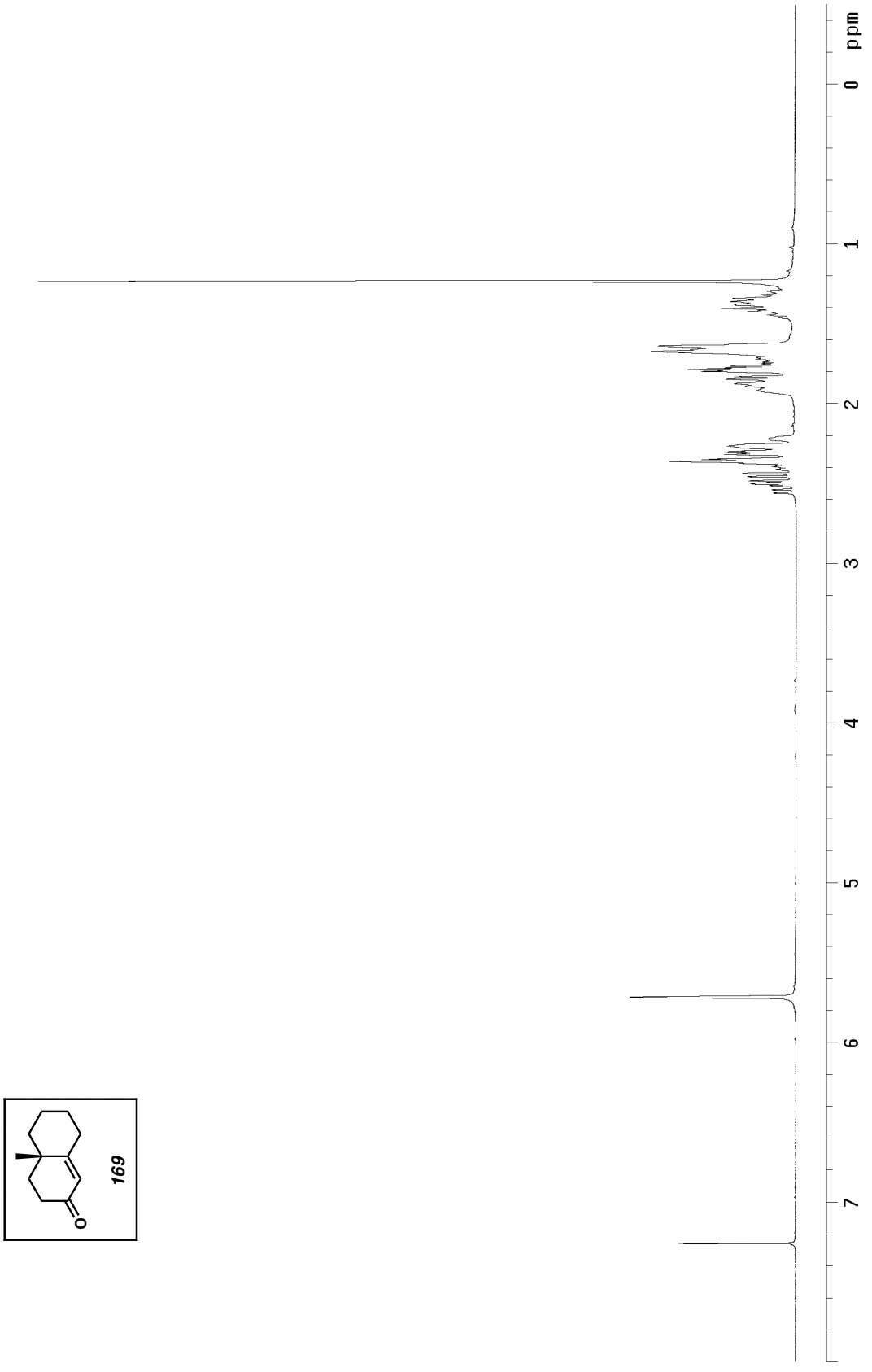


*Figure A1.216 ^{13}C NMR of compound **168** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
169

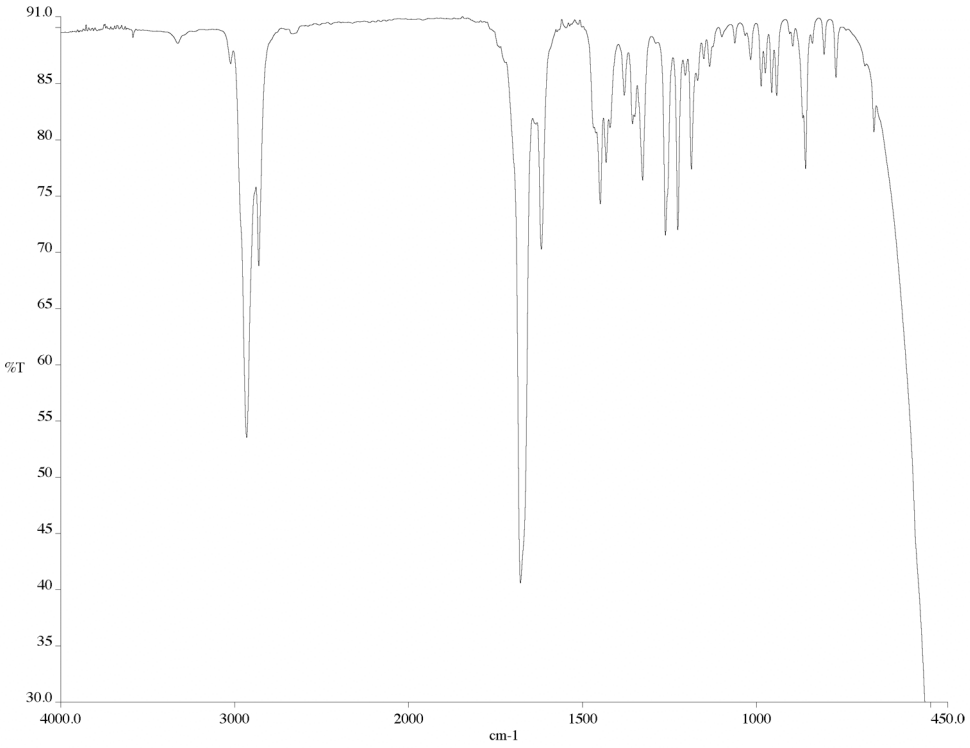


*Figure A1.218 IR of compound **169** (NaCl/film)*

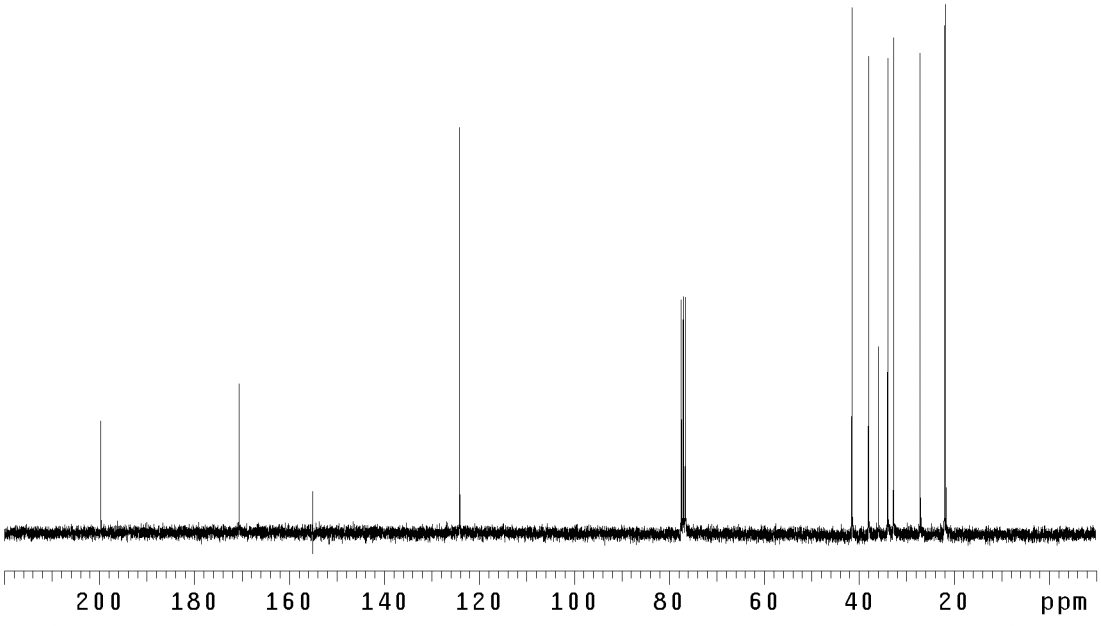
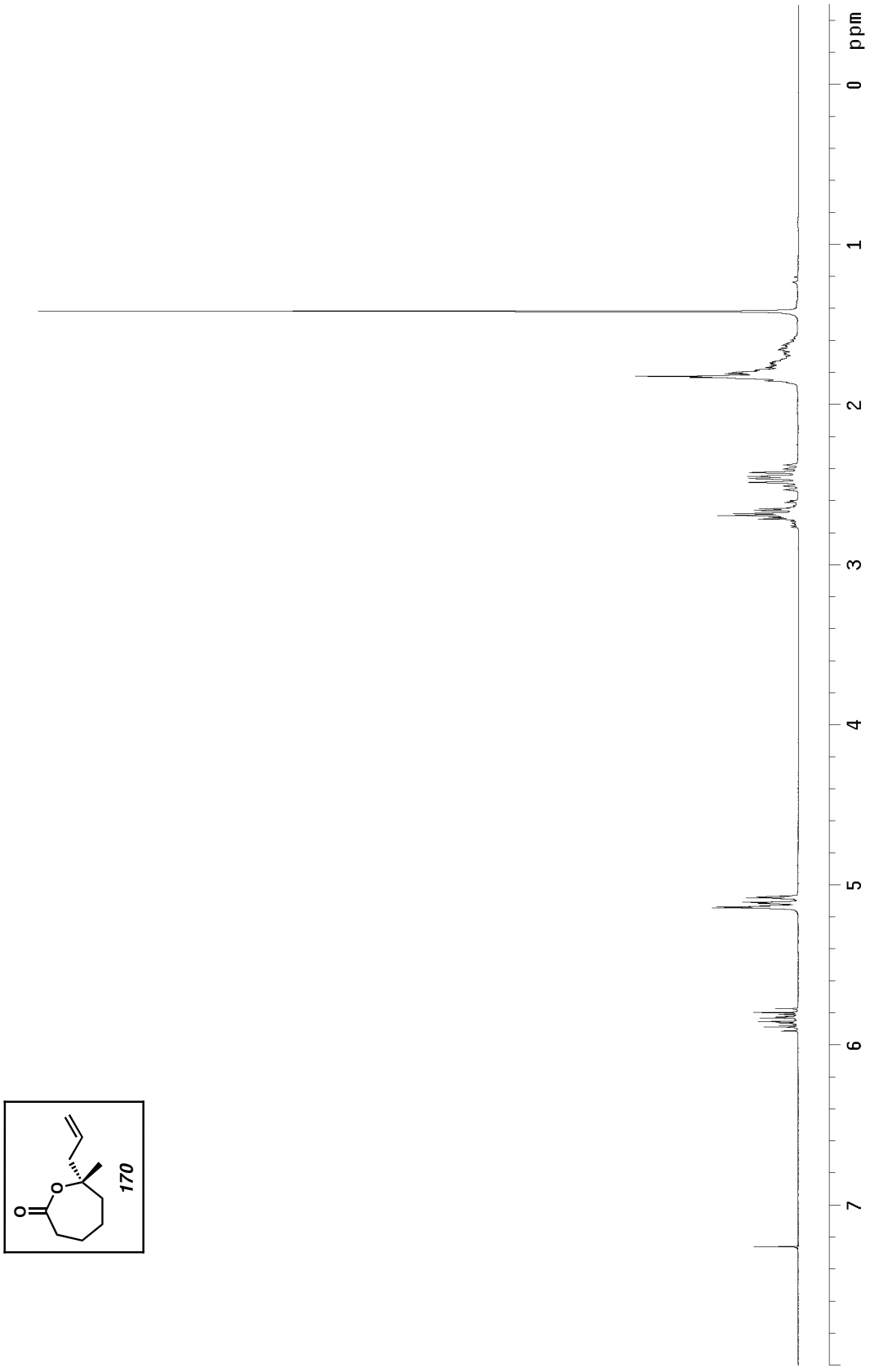


*Figure A1.219 ^{13}C NMR of compound **169** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
O
170

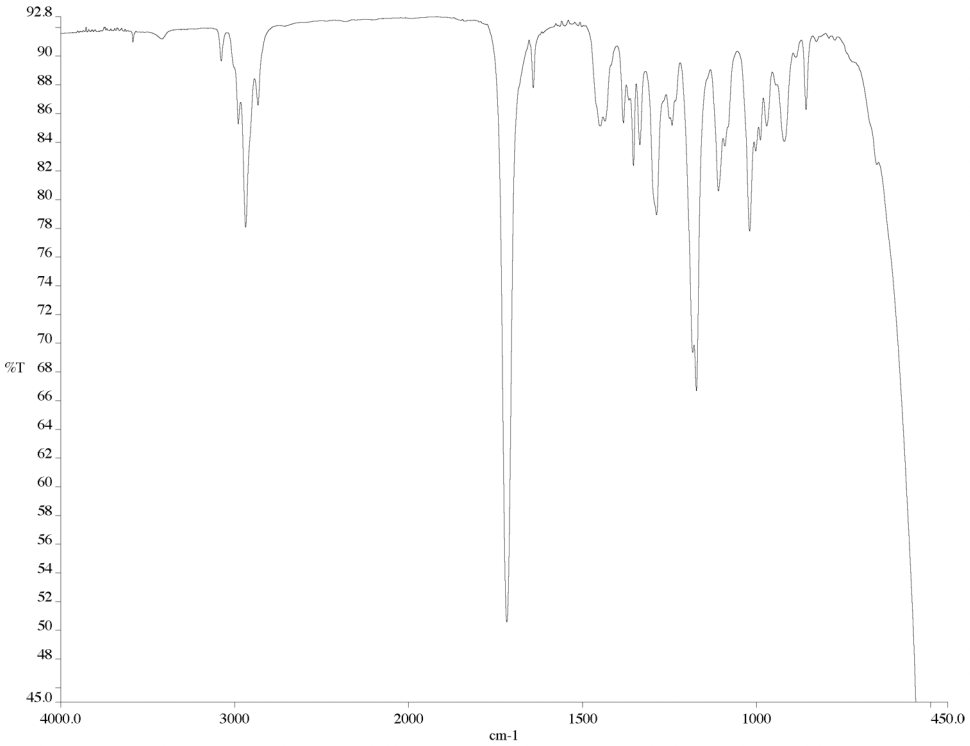


*Figure A1.221 IR of compound **170** (NaCl/film)*

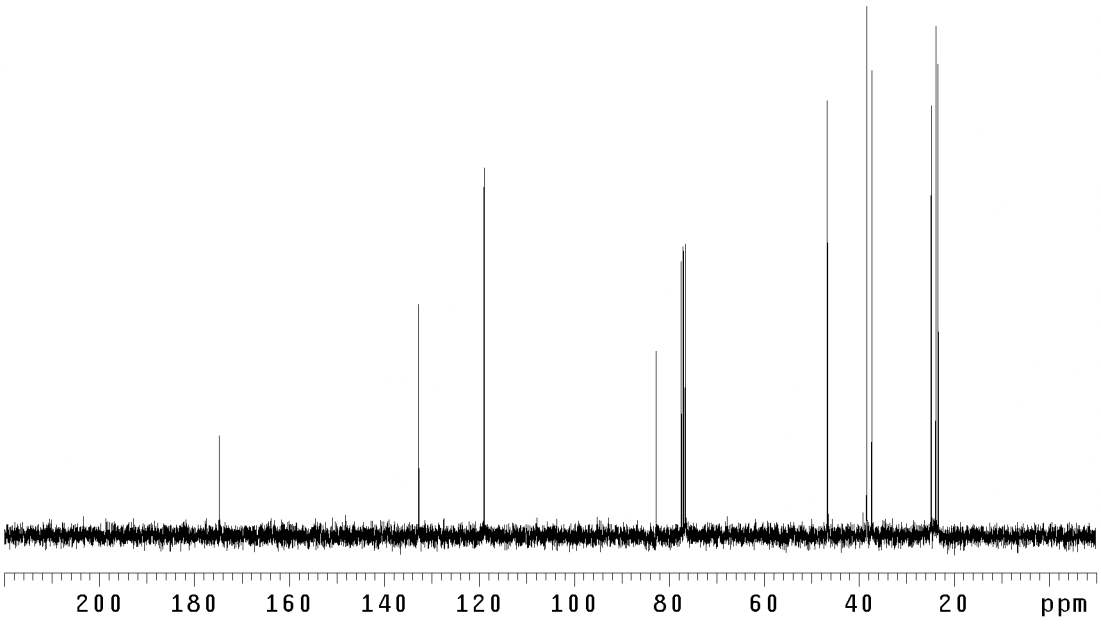
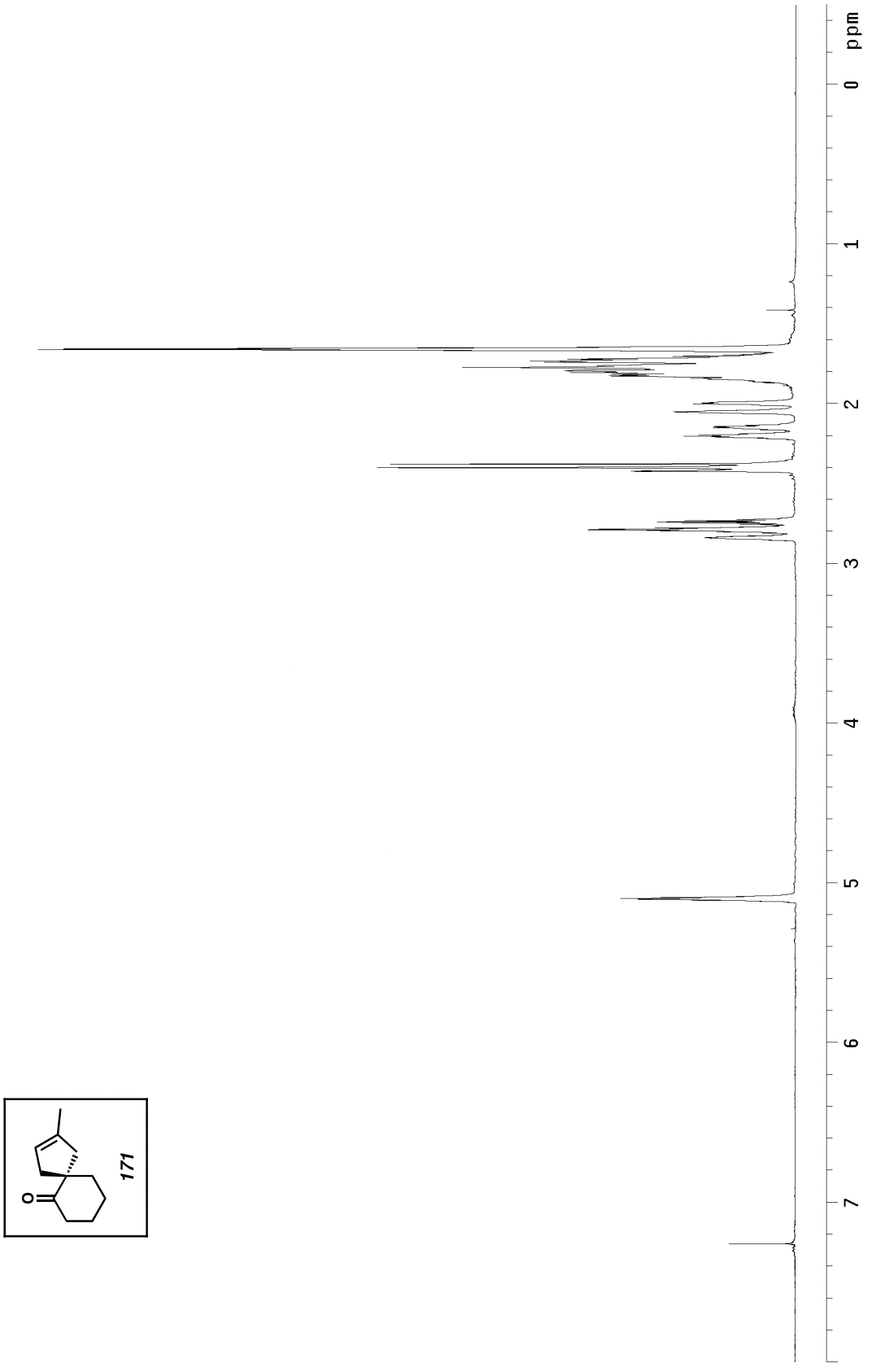


*Figure A1.222 ^{13}C NMR of compound **170** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
171

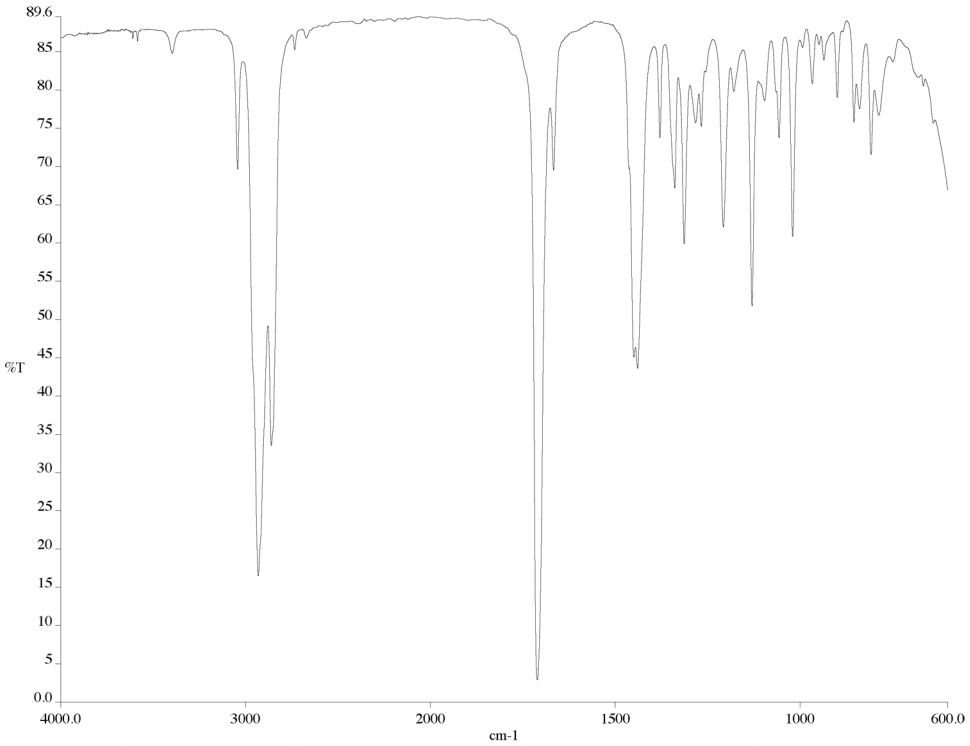


*Figure A1.224 IR of compound **171** (NaCl/film)*

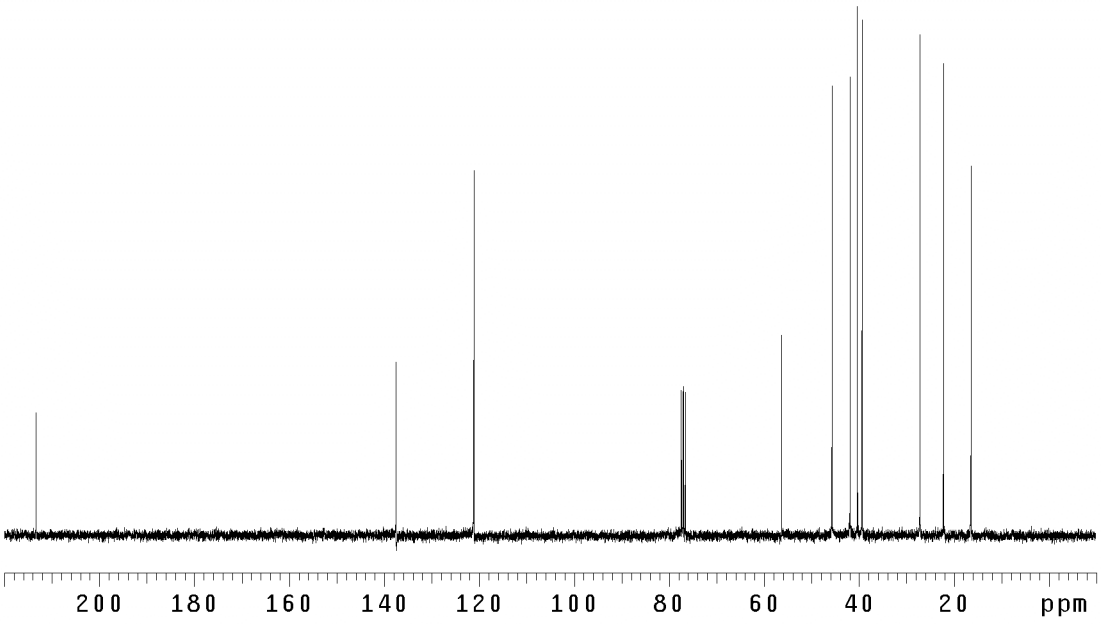
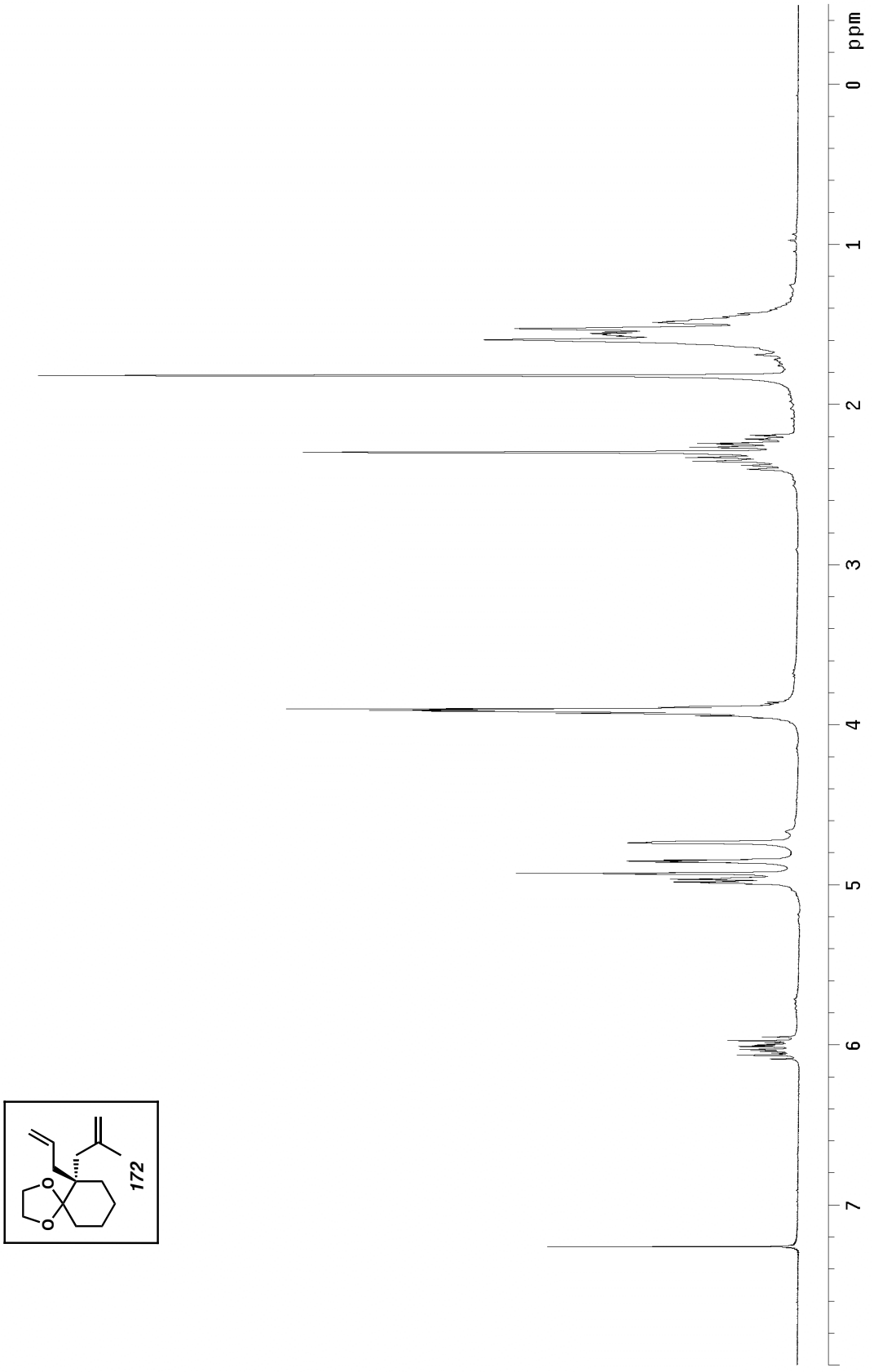


*Figure A1.225 ^{13}C NMR of compound **171** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
172

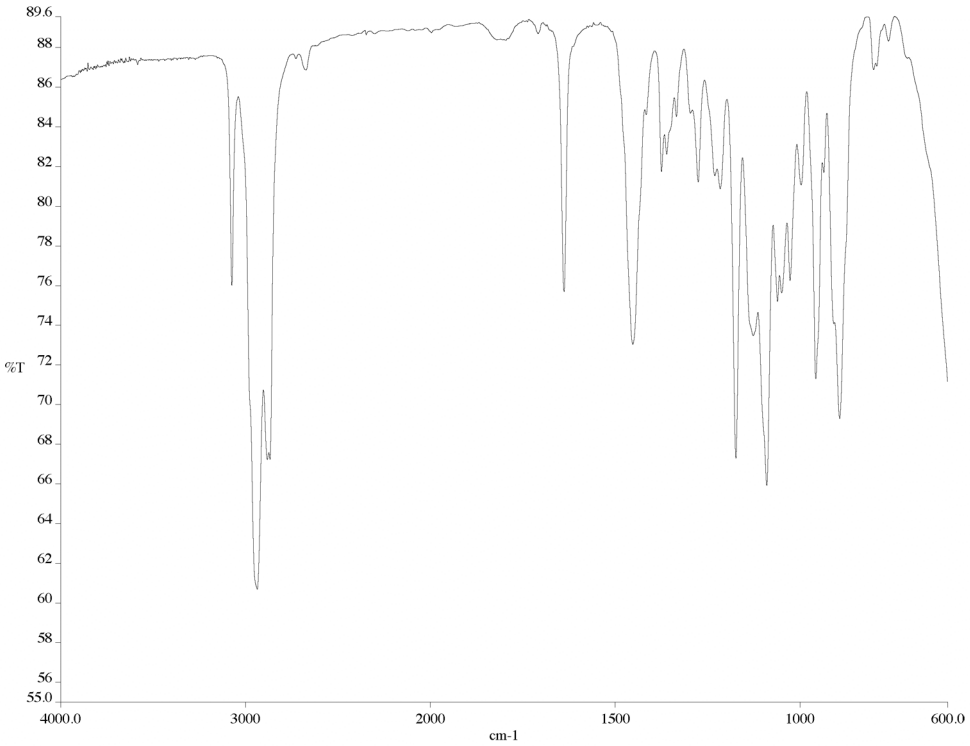


*Figure A1.227 IR of compound **172** (NaCl/film)*

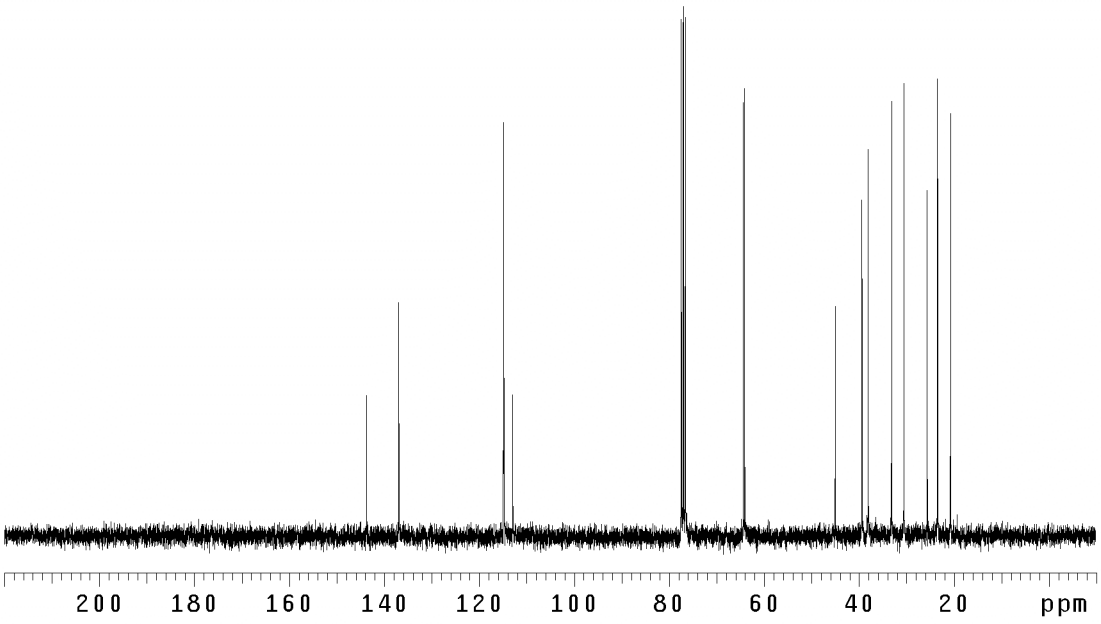
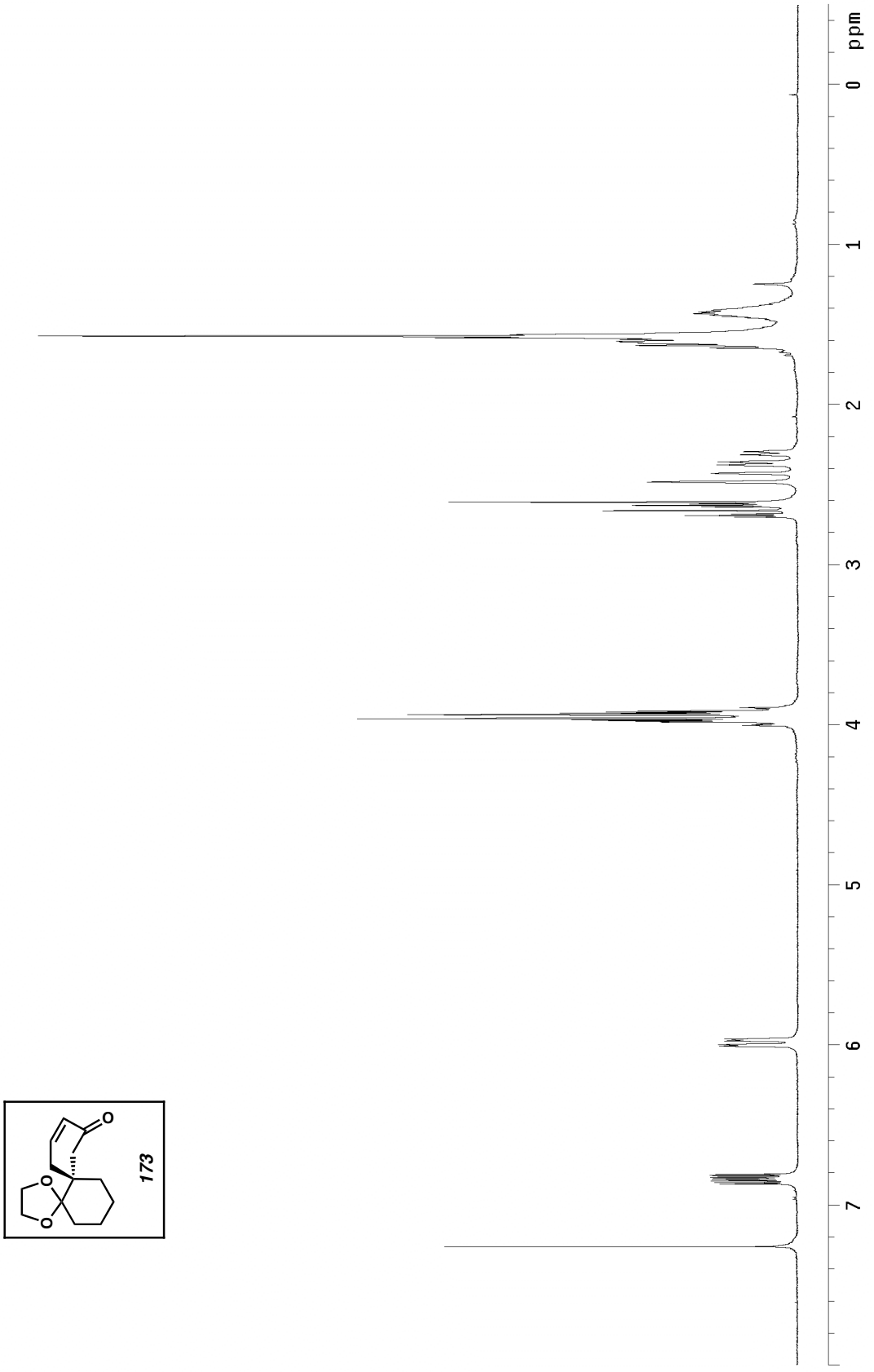


*Figure A1.228 ^{13}C NMR of compound **172** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
O
O
O
173

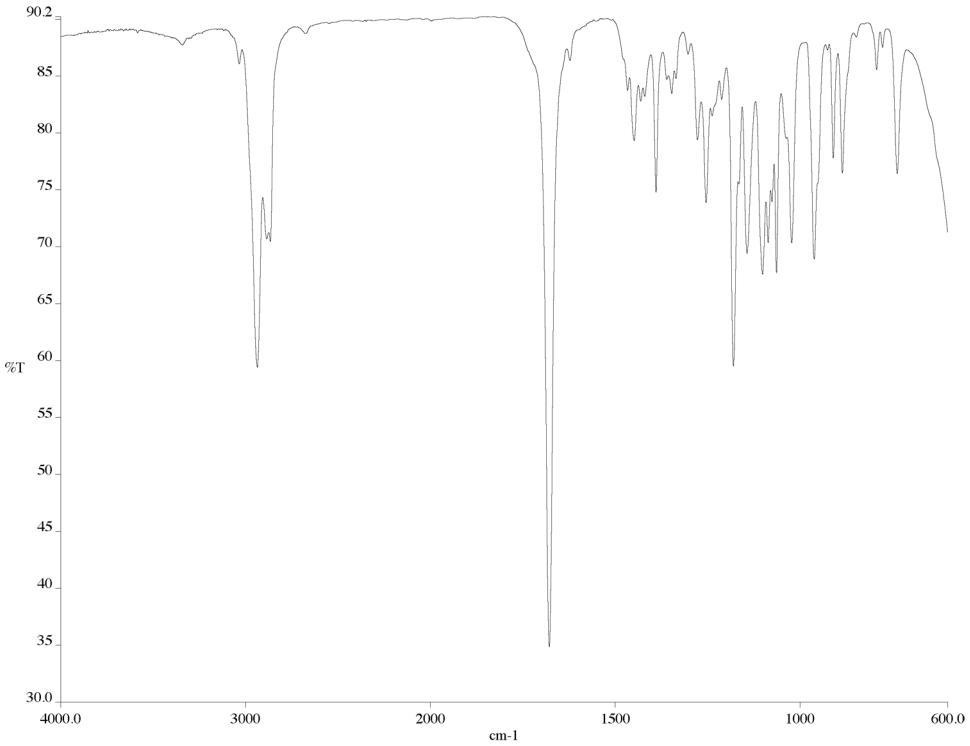


*Figure A1.230 IR of compound **173** (NaCl/film)*

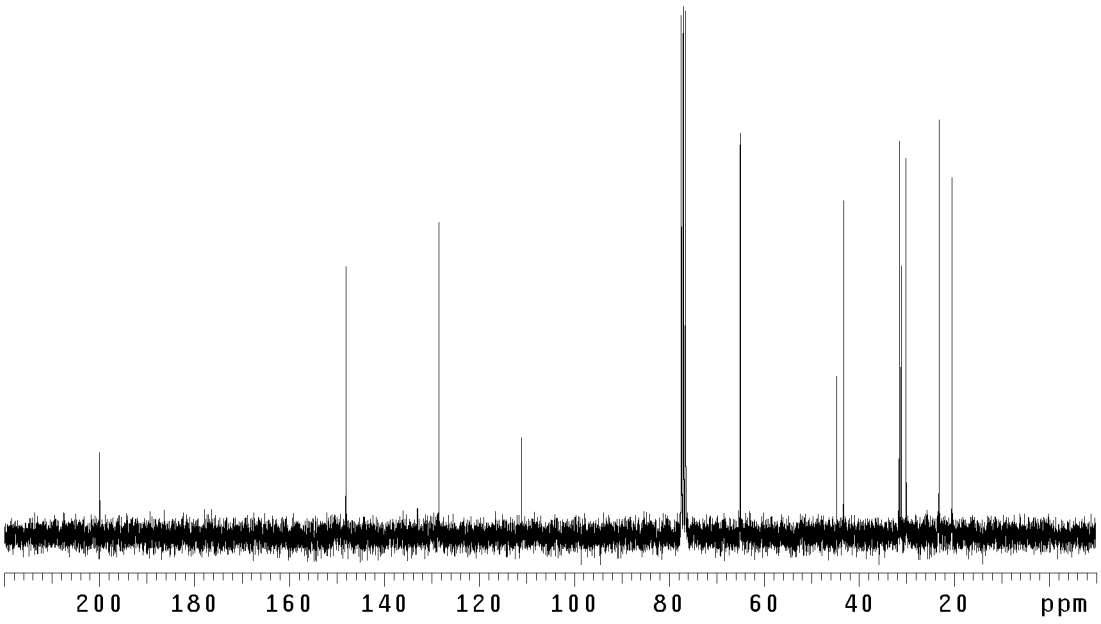
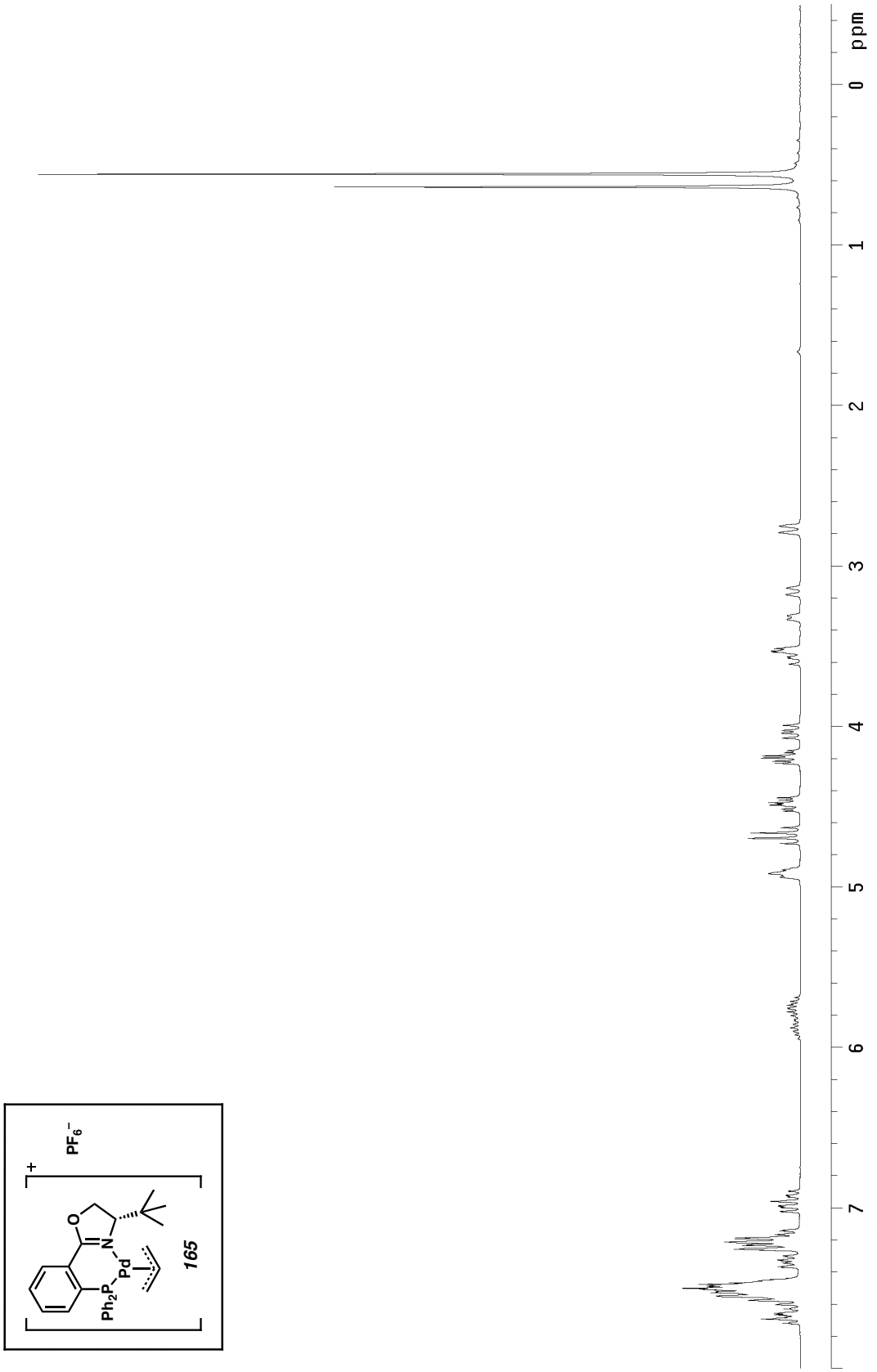


*Figure A1.231 ^{13}C NMR of compound **173** (75 MHz, $CDCl_3$)*


ppm
0
1
2
3
4
5
6
7
PF_6^-
+
O
N
Pd
I
Ph_2P
165

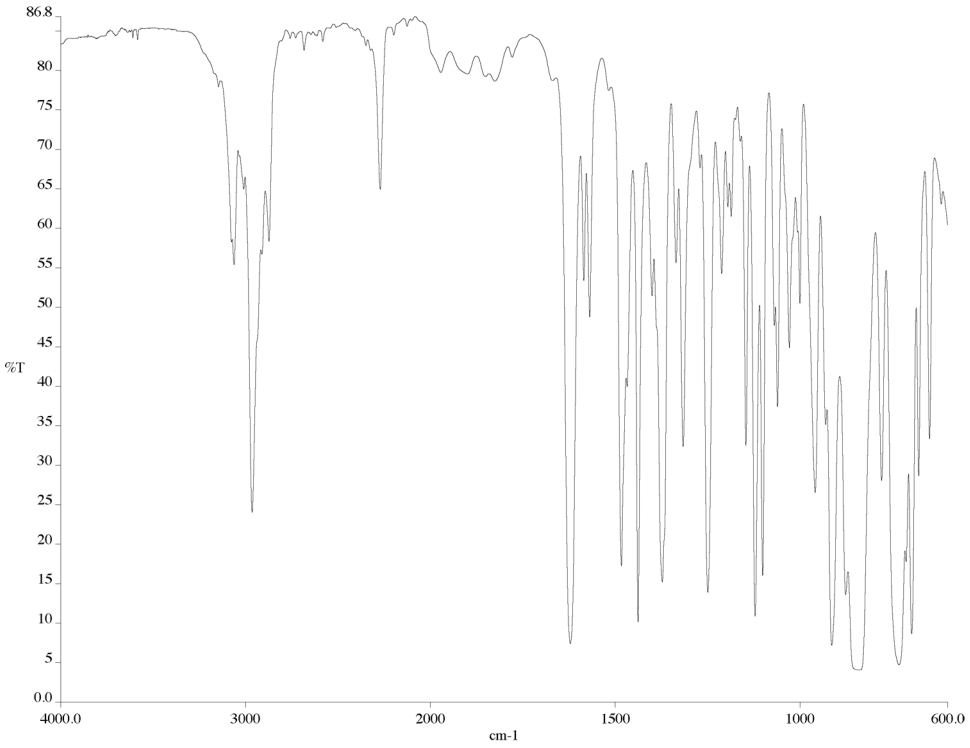


*Figure A1.233 IR of compound **165** (NaCl/film)*

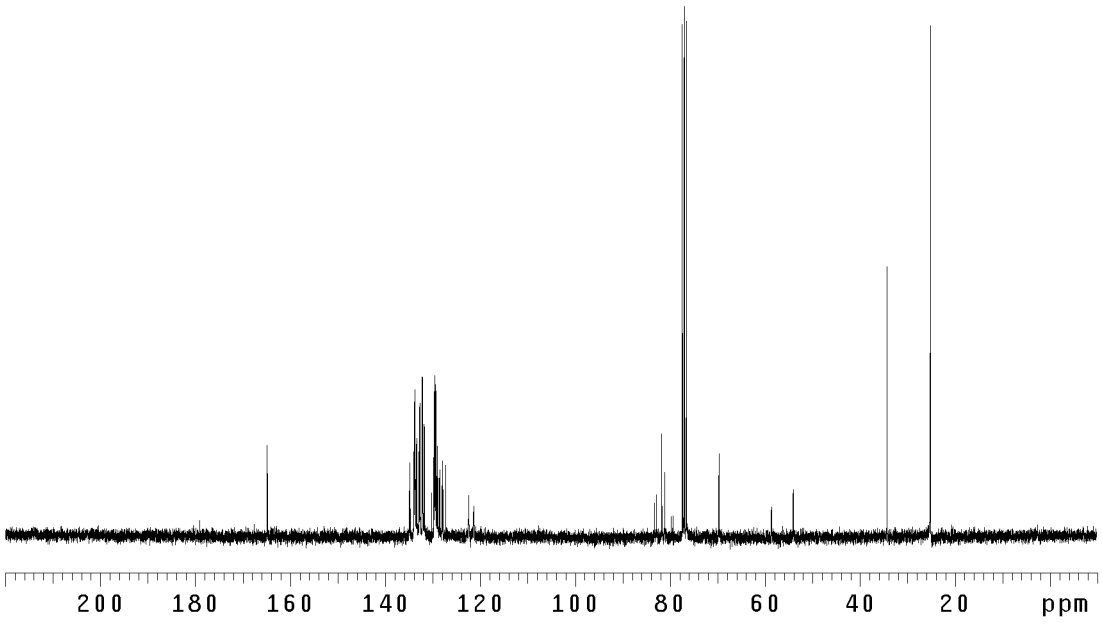


*Figure A1.234 ^{13}C NMR of compound **165** (75 MHz, $CDCl_3$)*

CHAPTER 3

Enantioselective Allylic Alkylations of Ketone Enolates: β-Ketoester Substrates[†]

3.1 INTRODUCTION

In the preceding chapter,[1] we reported the discovery and development of a novel system for the catalytic enantioselective synthesis of all-carbon quaternary stereocenters in order to address this significant challenge in synthetic chemistry.[2,3] Despite the multitude of approaches to the synthesis of these formidable stereocenters,[2] we identified a specific scarcity of methods for the generation of quaternary stereocenters from unstabilized ketone enolates bearing multiple acidic sites.[4,5] We reasoned that the powerful Pd-catalyzed enantioselective allylic alkylation reactions[6] developed by Trost, Helmchen, Pfaltz, and others could provide a valuable solution to this synthetic problem, although few examples had been reported with prochiral nucleophiles prior to our investigations.[7,8] Notably, none of the previous examples demonstrated allylation of an enolate with multiple sites of similar acidity, since this often led to enolate scrambling

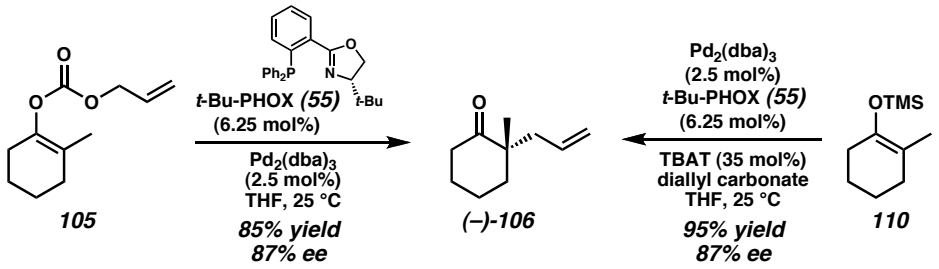
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[†] This work was performed in collaboration with Douglas C. Behenna, John A. Enquist, Jr., Andrew M. Harned, Akihiko Iwashita, Michael R. Krout, Samantha R. Levine, Sandy Ma, Smaranda C. Marinescu, Ryan M. McFadden, Zoltán Novák, Krastina V. Petrova, Jennifer L. Roizen, Masaki Seto, Nathaniel H. Sherden, Kousuke Tani, Scott C. Virgil, and David E. White. Portions of this work have been published as indicated by references in the text.

and allylation at multiple sites.[3e] These limitations prevented direct access to simple α-quaternary ketones, such as 2-allyl-2-methylcyclohexanone (**106**), a cyclohexanone derivative not known as a single enantiomer prior to our work.

We successfully adapted Tsuji's nonenantioselective protocols[9] for enolate alkylation with allyl enol carbonates (e.g., **105**, Scheme 3.1) and silyl enol ethers (e.g., **110**) to asymmetric variants capable of providing many substituted α-quaternary cyclic ketones.[1,10,11,12] We found that high yield and product ee was obtained with the catalyst generated in situ from tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) and the (*S*)-*t*-Bu phosphinooxazoline (PHOX) ligand (**55**).[13,14] Importantly, we demonstrated that the regiochemical fidelity for ketone enolates with multiple acidic sites was maintained in our enantioselective system, and we were pleased to report the first preparation of 2-allyl-2-methylcyclohexanone (**106**) in enantioenriched form.[1,10,15]

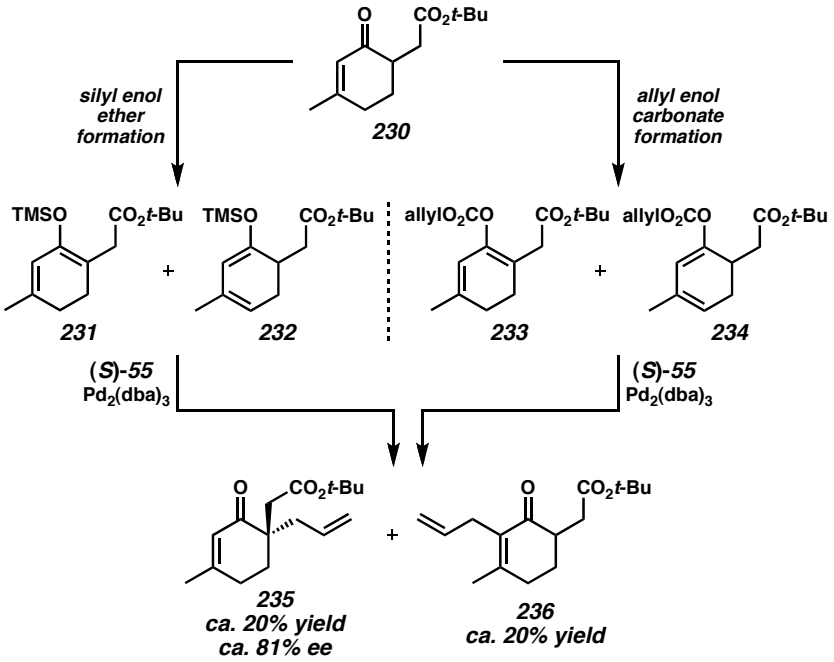
Scheme 3.1. Enantioselective allylation of allyl enol carbonates and silyl enol ethers



Encouraged by our leading results, we sought to exploit this technology for the preparation of a variety of interesting synthetic targets. In one such effort, we encountered difficulty in the preparation of the requisite enol carbonate or silyl enol ether (Scheme 3.2). A variety of conditions for enolate formation and trapping led to inseparable mixtures of enol isomers. As a consequence of the high degree of regiochemical fidelity in the allylation reaction,[9] corresponding mixtures of allylated

products were obtained. To address this problem, we sought a different class of substrates that would afford an alternative method of enolate generation that did not rely on extraneous bases.

Scheme 3.2. Non-selective enolization leads to product mixtures



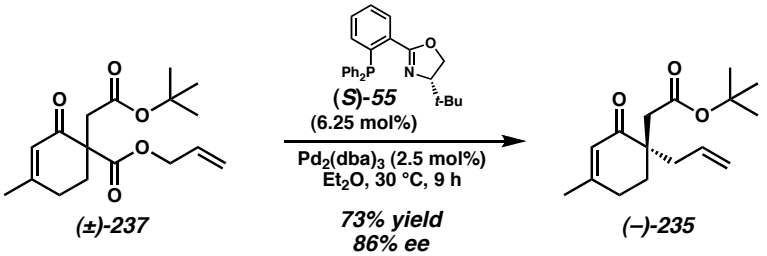
3.2 ASYMMETRIC ALKYLATION WITH RACEMIC ALLYL β-KETOESTERS

3.2.1 INITIAL EXPLORATIONS

β-Ketoesters represent a classical solution to the problem of regioselective ketone alkylation (e.g., the acetoacetic ester synthesis). In 1980, Tsuji and Saegusa reported allyl β-ketoesters as substrates in nonenantioselective Pd-catalyzed enolate alkylations.[16] We reasoned that an allyl β-ketoester might solve the problem of selective enolate

formation in the course of an enantioselective allylation reaction. However, as stereogenic racemic substrates for a catalytic asymmetric reaction, allyl β-ketoesters presented some unique challenges: the catalyst must deallylate the substrate *nonselectively* to avoid kinetic resolution of the substrate, the C–C bond must break at a reasonable temperature in the decarboxylation step to prevent loss of selectivity in the subsequent bond-forming step, and the stereogenic intermediates must not experience diastereomeric transition states that are detrimental to the selectivity of the process.[17] Nonetheless, we prepared the appropriate substrate (**237**, Scheme 3.3) using standard methods (see Scheme 3.5) and exposed racemate (±)-**237** to our standard reaction conditions ($Pd_2(dba)_3$, (*S*)-*t*-Bu-PHOX, THF, 25 °C). Unfortunately, no conversion was observed (by TLC) under these conditions after 24 h. However, we were delighted to find that elevating the temperature to 30 °C and carrying out the reaction in Et_2O restored reactivity, providing enone (–)-**235** in 73% yield and 86% ee after 9 h (Scheme 3.3). This experiment provided a key proof of concept for an enantioconvergent reaction using a racemic allyl β-ketoester.

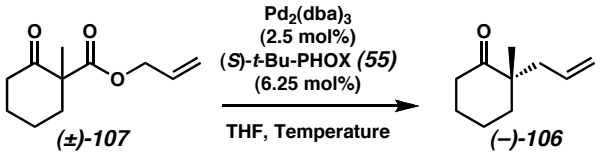
Scheme 3.3. Asymmetric decarboxylative allylation with an allyl β-Ketoester



When further exploring this pivotal reaction, we noted that no significant kinetic resolution of the allyl β-ketoesters was observed.[18] In fact, this facet of the reaction was critical in order to obtain high yield in a reasonable reaction time. The similar levels of

enantioselectivity observed with the allyl β-ketoester substrates and the other substrate classes (compare this work with Scheme 3.1 and Chapter 2) suggest that the enantiodetermining transition state of the reaction remains unchanged. Although the extent to which decarboxylation slowed at ambient temperature varied from substrate to substrate, β-ketoesters were uniformly more sluggish in decarboxylation than allyl enol carbonates.[19] However, the rate of reaction increased greatly at slightly higher temperatures, and thus reasonable reaction times (~2 h) could be achieved by increasing the reaction temperature by ca. 5 °C, which had a negligible effect on enantioselectivity (Table 3.1).

Table 3.1. Temperature effects in decarboxylative allylation of allyl β-ketoesters



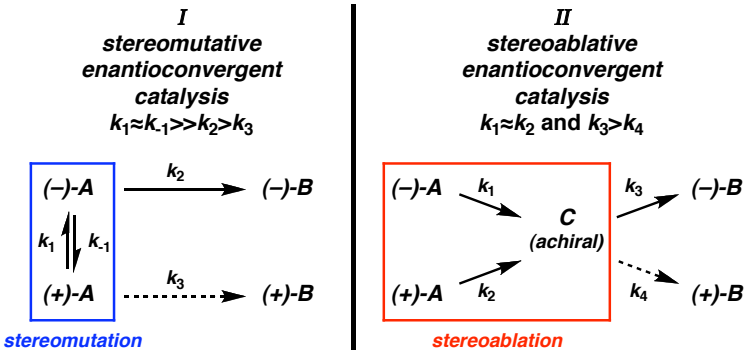
entry	temperature (°C)	time (h)	% yield[a]	% ee[b]
1	18	48	0	ND
2	25	7.5	85	88
3	30	2.25	82	87
4	35	1.25	85	86
5	40	0.67	86	85
6	60	0.15	82	83

[a] Isolated yield from reaction of 1.0 mmol substrate at 0.033 M. [b] Determined by chiral GC.

This enantioconvergent reaction is unusual due to the use of quaternary β-ketoesters (Scheme 3.4). Typical stereomutative enantioconvergent processes (e.g., dynamic kinetic resolution) involve a pre-equilibrium epimerization of the starting material, **A**, followed by enantioselective conversion to product **B** (Pathway I).[20] However, quaternary stereocenters are not typically epimerizable, and we believe that both enantiomers of the starting material, **A**, convert irreversibly to a prochiral intermediate, **C**,[21] which

preferentially forms one enantiomer of the product, **B**, under the influence of the chiral catalyst (Pathway II). We have termed such transformations as *stereoablative* enantioconvergent catalysis.[22,23] As a result of this interesting reaction pathway and the facile synthesis of quaternary β-ketoester substrates, we have been able to expand the substrate scope of the asymmetric alkylation greatly.

Scheme 3.4. Stereoablative enantioconvergent catalysis

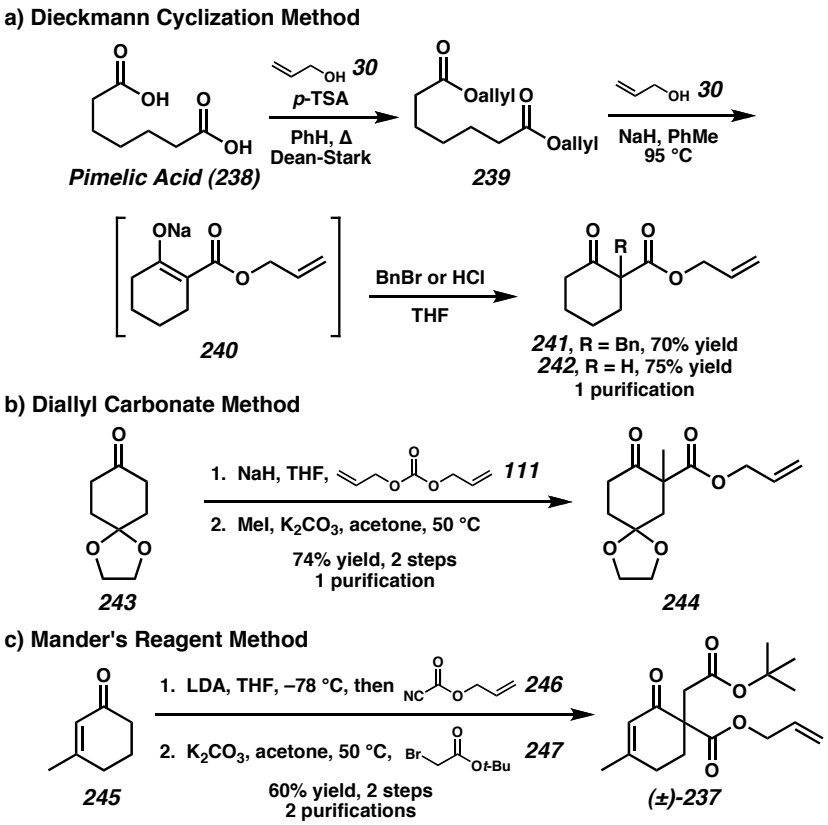


3.2.2 SUBSTRATE SYNTHESES

During the course of our studies, several practical methods for the synthesis of quaternary β-ketoesters have been employed (Scheme 3.5). The Dieckmann cyclization of pimelic acid diallyl ester (**239**) gives an intermediate cyclized sodium salt **240**, that can be alkylated directly in one pot to give quaternary β-ketoesters, such as benzylated compound **241**.[24] Alternatively, sodium salt **240** can be protonated to give 2-carboxyallylcyclohexanone (**242**) and then alkylated in a separate step. Cyclic ketones, such as 1,4-cyclohexanedione monoethylene ketal (**243**), may be treated with base and diallyl carbonate to effect acylation. Mild alkylation conditions (MeI and K_2CO_3 in acetone) lead to the *C*-methylated β-ketoester (**244**) in 74% yield over two steps with a

single chromatographic purification. Both of these methods are inexpensive and can be readily carried out on relatively large scale (e.g., 50 g of pimelic acid (**238**)).[25] In cases where *O*-acylation or multiple sites of *C*-acylation are problematic, such as enone **245**, treatment with LDA under kinetic conditions and then the allyl version of Mander's reagent, allyl cyanoformate (**246**), frequently gives selective *C*-acylation.[26,27]

Scheme 3.5. Methods for the synthesis of racemic quaternary β-ketoesters

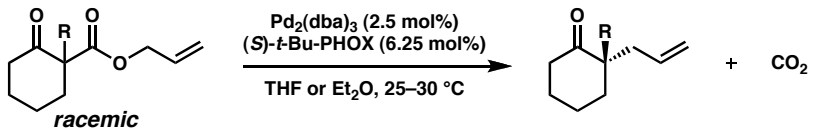


3.2.3 RESULTS OF ENANTIOSELECTIVE KETONE ALKYLATION WITH ALLYL β-KETOESTER SUBSTRATES

A number of α-substituted 2-carboxyallylcyclohexanones were readily prepared by the above methods and successfully underwent enantioconvergent decarboxylative

allylation (Table 3.2). The system was permissive of an array of functionality and substitution, and formed products in excellent yield and high ee. Remarkably, the presumed enolate intermediate tolerated both enolizable (entries 4 and 5) and β-heteroatom (entry 9) substituents without side products corresponding to enolate scrambling or β-elimination.[28] Our conditions also allowed for incorporation of a fluorine atom for the high-yielding synthesis of a stereodefined tertiary fluoride (entry 10). Subsequent to our initial disclosure, others have utilized this chemistry to prepare a range of tertiary fluoride-containing compounds that could be of interest as non-epimerizable pharmaceutical analogues.[15c,15e,15h,15j,29]

Table 3.2. Enantioconvergent decarboxylative allylation of α-Substituted 2-carboxyallylcyclohexanones



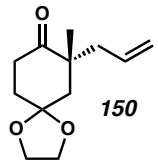
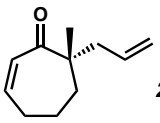
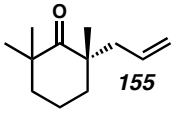
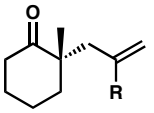
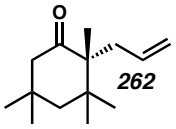
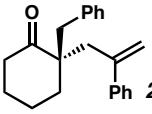
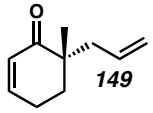
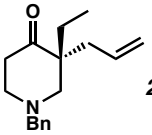
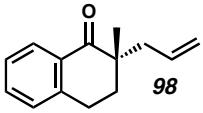
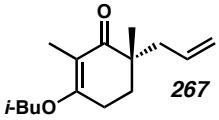
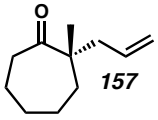
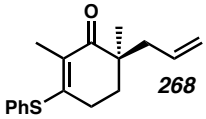
entry	R	substrate	product	time (h)	yield[a]	ee[b]	entry	R	substrate	product	time (h)	yield[a]	ee[b]
1	CH_3	107	106	7.5	85	88	6	$CH_2C_6H_5$	241	153	0.5	99	85
2[c]	CH_3	107	106	4.75	89	88	7	$CH_2(4\text{-}CH_3OC_6H_4)$	254	255	10	80	86
3[c,d]	prenyl	248	249	6	97	91	8	$CH_2(4\text{-}CF_3C_6H_4)$	256	257	0.5	99	82
4[c]	CH_2CH_2CN	250	251	6.5	97	88	9[e]	$CH_2OTBDPS$	258	259	5	86	81
5[c,e]	$CH_2CH_2CO_2Et$	252	253	6	96	90	10[c,d]	F	260	261	3.5	80	91

[a] Isolated yield (%) from reaction of 1.0 mmol substrate with 2.5 mol% $Pd_2(dba)_3$ and 6.25 mol% (*S*)-*t*-Bu-PHOX (**55**) at 0.033 M in THF at 25 °C, unless otherwise noted. [b] Enantiomeric excess (%) determined by chiral GC or HPLC. [c] Performed in Et_2O solvent. [d] Performed at 30 °C. [e] 4 mol% $Pd_2(dba)_3$, 10 mol% (*S*)-**55**, 0.021 M.

In addition to modifications at the α-position of the substrate, the decarboxylative asymmetric allylation of β-ketoesters was also amenable to a wide variety of modification to the carbocycle and allyl fragment (Table 3.3). In particular, the reaction was exceptionally tolerant to the steric demands of substitution at the 3-, 4-, 5-, and 6-positions of the cyclohexane ring: each position can be fully substituted without

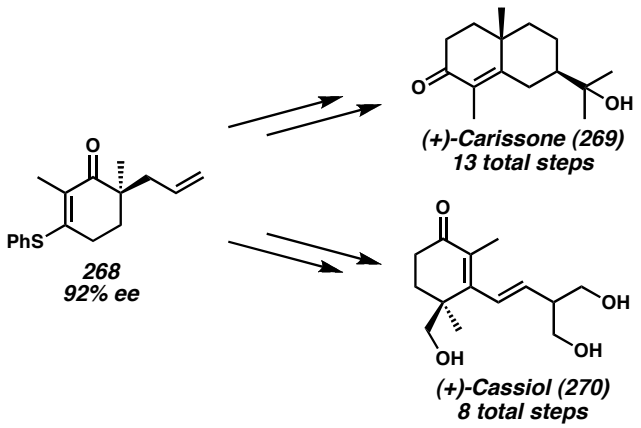
significantly affecting yield or enantioselectivity (entries 1–4). Unsaturated substrates (entries 5 and 6) as well as seven-membered ring containing substrates (entries 7 and 8) performed well in the reaction. As with the previous substrate classes (i.e., allyl enol carbonates and silyl enol ethers),[1] substitution at the central position of the allyl fragment had a beneficial effect on the enantioselectivity of the reaction (entries 9–11). The incorporation of a chlorine atom on the allyl fragment (entry 10) provided both another functional group handle for further manipulation and a higher oxidation state. Inclusion of a phenyl group on the allyl fragment (entry 11) produced the highest ee product we have observed to date. Heterocyclic compounds were also accessible by this method (entry 12). Vinylogous esters were competent in the reaction, but elevated temperatures (up to 80 °C) were required in some cases to achieve high conversion and the ee was somewhat decreased (entry 13). Employing a vinylogous thioester lowered the required temperature and permitted the isolation of highly enantioenriched product (entry 14). This particular vinylogous thioester (**268**, Scheme 3.6) was employed in the enantioselective syntheses of (+)-carissone (**269**)[12e] and (+)-cassiol (**270**).[12f]

Table 3.3. Enantioconvergent decarboxylative allylation of β-ketoesters with substituted carbocycles and allyl fragments

entry	product	% yield[a]	% ee[b]	entry	product	% yield[a]	% ee[b]
1		94	85	8[f]		98	90
2[c]	*150*	94	86		*263*		
3		89	90	9[d,e]	 *148*, R = CH_3	87	92
	155			10[d,e]	*264*, R = Cl	87	91
4		90	85	11[g]		96	94
	262				*265*		
5[d,e]		77	90	12		91	92
	149				*266*		
6[d]		97	92	13[h]		86	75
	98				*267*		
7		83	87	14[i]		85	92
	157				*268*		

[a] Isolated yield from reaction of 1.0 mmol substrate, 2.5 mol% $Pd_2(dba)_3$ and 6.25 mol% (*S*)-*t*-Bu-PHOX (**55**) at 0.033 M in THF at 25–35 °C, unless otherwise noted. Each reaction was complete in 1.5-12 h. [b] Determined by chiral GC or HPLC. [c] 25 mmol substrate, 1.5 mol% $Pd_2(dba)_3$, and 3.75 mol% (*S*)-**55**, 24 h reaction time. [d] Performed in Et_2O. [e] 4 mol% $Pd_2(dba)_3$, and 10 mol% (*S*)-**55** at 0.021 M. [f] Reaction performed with 3.17 mmol substrate, 3 mol% $Pd(dmdba)_2$, and 3.8 mol% (*S*)-**55** at 0.060 M. [g] 2.5 mol% $Pd(dmdba)_2$, 2.5 mol% (*S*)-**55**. [h] Performed with 2.5 mol% $Pd_2(pmdba)_3$ and 6.25 mol% (*S*)-**55** in PhMe at 80 °C. [i] Performed with 2.5 mol% $Pd_2(pmdba)_3$ and 6.25 mol% (*R*)-**55** in PhMe at 50 °C.

*Scheme 3.6. Conversion of ketone **268** to the natural products (+)-carissone (**269**)[12e] and (+)-cassiol (**270**).[12f]*

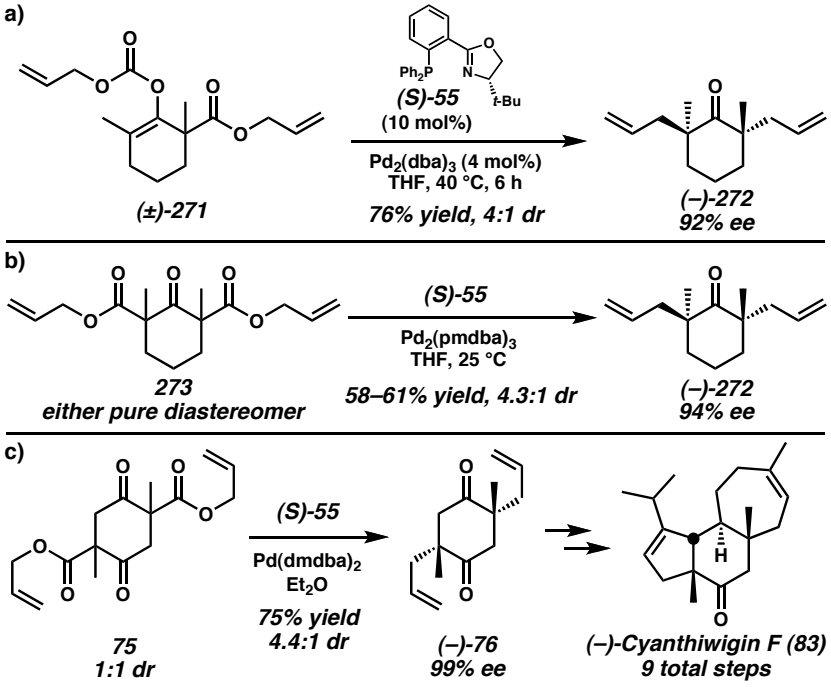


3.2.4 CASCADE REACTIONS GENERATING MULTIPLE QUATERNARY STEREOCENTERS

In an effort to construct more than one quaternary stereocenter in a single transformation, we designed substrate **271** (Scheme 3.7a), which contained a latent allyl β-ketoester moiety to be revealed by the reaction of the allyl enol carbonate portion of the molecule. To our delight, cascade allylation occurred to afford C_2-symmetric ketone **272** as the predominant product in 92% ee with 4:1 dr. Similarly, bis(β-ketoester) substrates may be employed in a stereoconvergent process where each of the three stereoisomeric starting materials are converted to enantioenriched products with excellent stereocontrol (e.g., **273** → **272**, Scheme 3.7b and **75** → **76**, Scheme 3.7c). We have successfully employed the double enantioselective decarboxylative allylation strategy in the total synthesis of the cyathin diterpenoid cyanthiwigin F (**83**, Scheme 3.7c).[30] The further

application of this allylation reaction to the catalytic asymmetric synthesis of natural products is an ongoing topic of research in our laboratories.[12]

Scheme 3.7. Enantioselective cascade allylations generating two quaternary centers

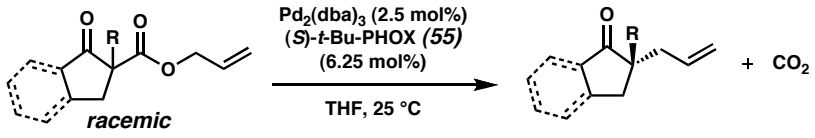


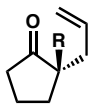
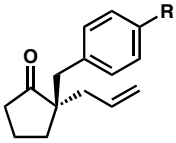
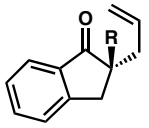
3.2.5 SUBSTRATES CONTAINING FIVE-MEMBERED RINGS

Although enolate precursors contained in six-membered rings composed the bulk of our substrates, we have demonstrated that seven- and eight-membered rings are tolerated with only slight loss in enantioselectivity.[1] Allyl β-ketoesters constructed on five-membered rings provided modest to useful levels of enantioselectivity (Table 3.4). These substrates generally produced α-quaternary ketone products in good yields with enantiomeric excesses about 10% lower than that observed with the cyclohexanone analogue. Ethyl substituted cyclopentenone (**274**) was formed in 86% ee, only 6% lower than observed with the corresponding cyclohexanone (entry 1). Indanones were

produced in good yield and with useful ee (entries 4 and 5). Benzyl appended cyclopentanone substrates gave consistent yields, but electron deficient aromatic rings decreased enantioselectivity more significantly than in the reactions of six-membered β-ketoesters (entries 6–8).

Table 3.4. Enantioconvergent decarboxylative allylation of β-ketoesters containing five-membered rings



entry	product	yield[a]	ee[b]	entry	product	yield[a]	ee[b]
1	 **274**, R = CH_2CH_3	82	86				
2	**275**, R = $CH(CH_3)_2$	77	84	6	 **279**, R = OMe	84	73
3	**276**, R = CH_2NPhth	67	48	7	**280**, R = Me	84	73
4[c]	 **277**, R = Me	82	80	8	**281**, R = CF_3	83	60
5	**278**, R = Bn	93	71				

[a] Isolated yield (%) from reaction of 1.0 mmol of substrate in THF (0.033 M) with 2.5 mol% $Pd_2(dba)_3$ and 6.25 mol% (*S*)-*t*-Bu-PHOX (**55**), unless otherwise noted. Each reaction was complete in 1-3 h. [b] Enantiomeric excess (%) measured by chiral GC or HPLC. [c] Performed on 0.1 mmol scale with 5 mol% $Pd_2(dba)_3$ and 12.5 mol% (*S*)-**55**.

3.3 MECHANISTIC INSIGHTS

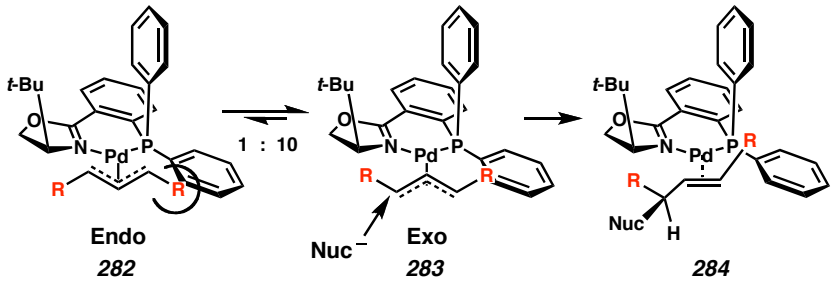
3.3.1 THE OUTER-SPHERE MECHANISM PROPOSED BY HELMCHEN

Although we have not fully elucidated the fine mechanistic details of enantiodiscrimination with the Pd•PHOX catalyst, an intriguing picture of the reaction's general mechanism has emerged from our experimental studies. A number of experimental observations suggest that the mechanism of our allylation of prochiral

nucleophiles differs substantially from that of Pd•PHOX-catalyzed malonate alkylation of prochiral allyl fragments, which has been studied in detail by Helmchen.[31]

Helmchen's model for the asymmetric allylic alkylation of prochiral allyl electrophiles (R ≠ H, Scheme 3.8) with Pd•PHOX catalysts involves attack at one allyl terminus of a (PHOX)Pd-π-allyl complex by an outer-sphere malonate anion. The allyl group isomers **282** and **283** are in rapid equilibrium such that the nucleophile's preferred attack (**283**), from the open quadrant at the allyl terminus *trans* to phosphorus, is the nearly exclusive reaction pathway. The resulting Pd(0)•olefin complexes (e.g., **284)** have been observed at low temperature.[31] Notably, stereoinduction in such alkylation reactions suffered when the steric bulk of the allyl substituents was reduced (e.g., 96% ee when R = *i*-Pr, 71% ee when R = Me).[32] It was difficult to rationalize the high levels of stereoinduction observed in our allylation by this outer-sphere mechanism in that our substrates typically have unsubstituted allyl termini. Additionally, formation of the new stereocenter on the enolate would require the chiral Pd complex to differentiate the prochiral faces of the unassociated enolate, where steric and electronic interactions between the nucleophile and the distant chiral backbone would be minimal. Moreover, a gearing effect through the allyl ligand is unlikely given the lack of sterically large groups (R = H).

Scheme 3.8. Helmchen's outer-sphere mechanism for asymmetric allylation of prochiral allyl electrophiles



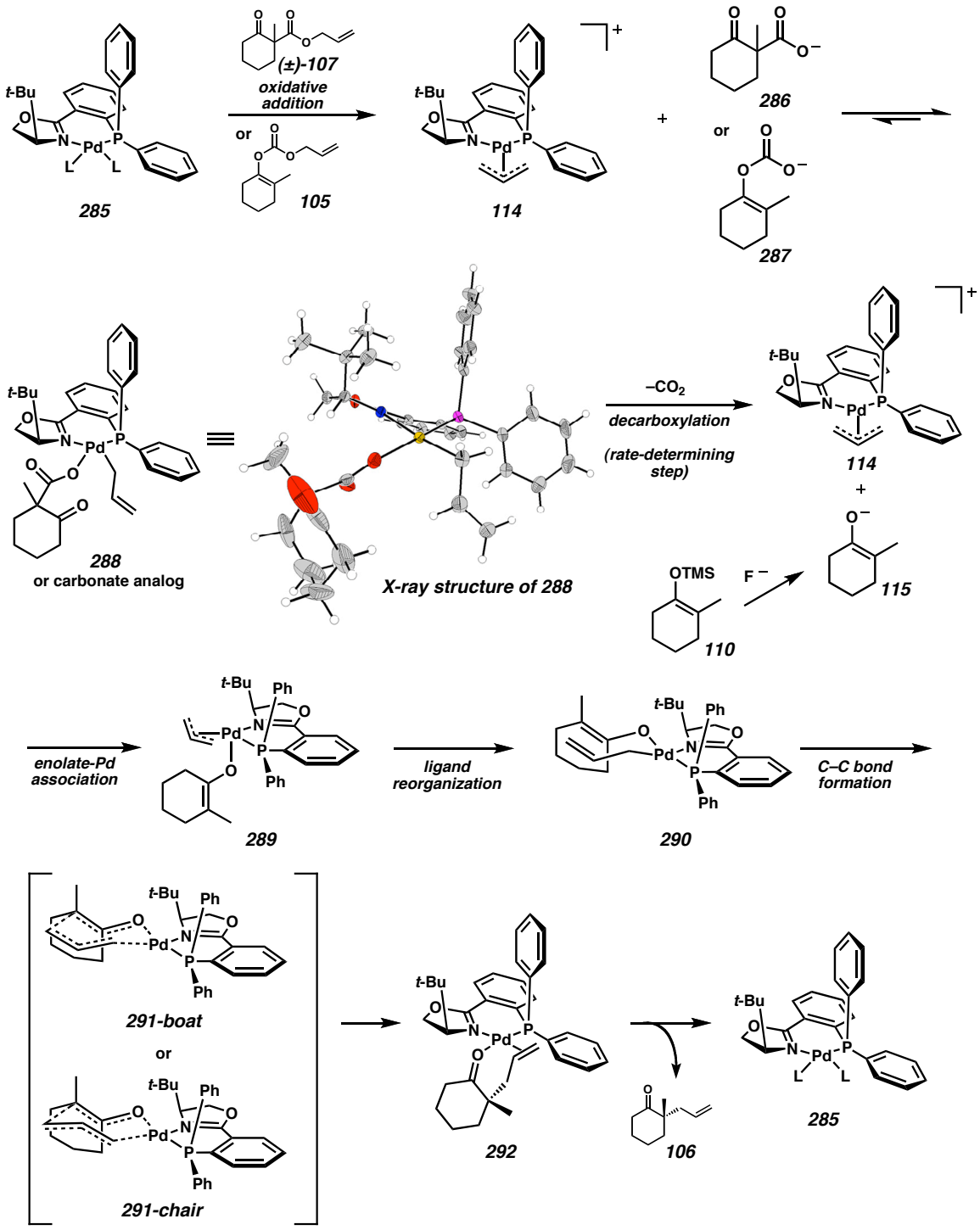
3.3.2 EXPERIMENTAL EVIDENCE CONSISTENT WITH AN INNER-SPHERE MECHANISM

In addition to these hypothetical arguments, we have made several experimental observations that do not correlate well to an outer-sphere enolate attack mechanism. The high enantioselectivity under our conditions appears to correspond with circumstances that would keep ion pairs tightly associated. The range of effective solvents found during our optimization studies demonstrated this trend: ethereal solvents (e.g., THF), aromatic solvents (e.g., benzene), ethyl acetate, and triethylamine share few properties other than having low dielectric constants in the range of 2 to 8, but each provided products in high ee.[1] In such low dielectric media, dissociative solvation of ion pairs is difficult.[33] In conjunction with the lack of other counterions in the reaction, the low dielectric value would tend to enforce an inner-sphere mechanism wherein close contact of the enolate and the chiral environment would facilitate the discrimination between the prochiral enolate faces.[34]

Based on our initial reasoning and empirical observations, we developed a working model for the course of the reaction via an inner-sphere mechanism (Scheme 3.9).

Oxidative addition of Pd(0)•PHOX complex **285** to substrate **107** or **105** leads to [Pd(allyl)PHOX] complex **114** and carboxylate **286** or mixed carbonate **287**. We believe that an equilibrium exists between the charge-separated form and the coordination complex bearing an η^1-allyl group (e.g., **288**). We have isolated and characterized the β-ketocarboxylate analog (**288**) by X-ray crystallography and found that it can be decomposed to deliver enantioenriched ketone **106**, and therefore it appears to be an important intermediate on the reaction pathway.[35] Subsequent loss of CO_2, which may be assisted by Pd(II), leads to enolate **115** and the Pd-complex **114**. Association of these two fragments leads to 5-coordinate intermediate **289**, with the enolate bound to the sterically less-encumbered apical position of the square-planar metal. By slightly different means, allyl enol carbonate and silyl enol ether substrates may intercept the key intermediate **289**. Shifting of the allyl group from an η^3- to an η^1-binding mode allows the enolate fragment to move into the square plane and form intermediate **290** by what is essentially an associative ligand substitution mechanism. From this complex, a standard 3-centered reductive elimination would require a shift from *O*- to *C*-bound Pd-enolate.[36] We reasoned that this isomerization would be unfavorable due to the steric demands of the resulting tertiary palladium species. As an alternative, we postulated an extended reductive elimination pathway proceeding through a cyclic 7-membered pericyclic transition state (**291-boat** or **291-chair**) similar to a sigmatropic rearrangement.[37,38] Importantly, situating the carbocyclic ring of the enolate fragment away from the bulky *t*-Bu group of the oxazoline provides a plausible predictive model for the observed absolute sense of enantiofacial selectivity.[1] Liberation of the product ketone (**106**) from complex **292** regenerates the catalytic Pd(0) species **285**.

Scheme 3.9. Proposed inner-sphere mechanism for asymmetric alkylation of prochiral enolate nucleophiles



Typically, inner- and outer-sphere processes may be differentiated by stereochemically labeling the allyl fragment and evaluating the relative stereochemistry of the products.[39] However, in the present case, these experiments could not be performed since the necessary cyclic carbonates suffered from very poor reactivity and enantioselectivity. In fact, even simple substitution of the termini of acyclic allyl groups (e.g., crotyl carbonates) severely impacted reactivity and perhaps suggests that for such substrates a different mechanism is operative.[40] Given these substrate limitations, we were obliged to seek out other forms of mechanistic evidence to evaluate our proposal.

Since it is conceivable that multiple ion pairs could be involved in the transition state (e.g., an enolate bound to one [Pd(allyl)PHOX] fragment could attack the Pd-bound allyl fragment associated with another enolate), we conducted simple kinetics experiments that support a single metal site pathway (Figure 3.1 through Figure 3.4).[41] Varying the concentration of Pd•PHOX gives a proportional change in reaction rate, suggesting the reaction is first-order in Pd•PHOX (Figure 3.1) and supporting the notion that a single metal center is involved in the mechanism. Additionally, the lack of an observed non-linear effect is also consistent with the action of a single metal center in the enantiodetermining step (Figure 3.2).[42] Interestingly, kinetic studies also found zero-order dependence on substrate concentration in the allyl enol carbonate (Figure 3.3) and β-ketoester (Figure 3.4) cases. Based on these results, we suspect that the rate-limiting step is either loss of CO_2 from a Pd-carboxylate intermediate (e.g., **288** → **114** + **115**, Scheme 3.9), or C–C bond formation (e.g., **290** → **292**, Scheme 3.9). The isolation of the relatively stable Pd-carboxylate complex **288** is indicative of a slow decarboxylation step. The longer reaction times observed with β-ketoester substrates relative to the

corresponding allyl enol carbonates is also more consistent with decarboxylation as the rate determining step, as the rate difference would be attributed to the difference in breaking a C–C bond (β-ketoester) compared to a C–O bond (enol carbonate). However, we cannot rule out the possibility that different substrate classes may have different rate-determining steps.

Figure 3.1. Plot of k_{obs} vs. concentration of Pd(PHOX) complex for allyl enol carbonate

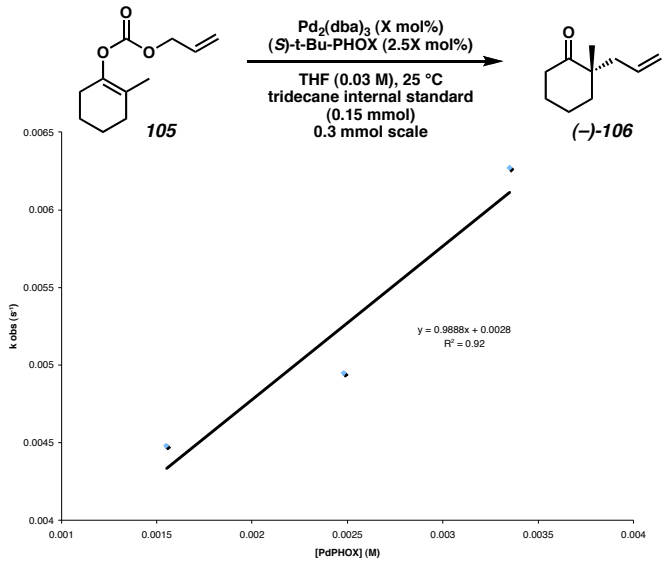


Figure 3.2. Plot of i-Pr-PHOX ee vs. product ee[43]

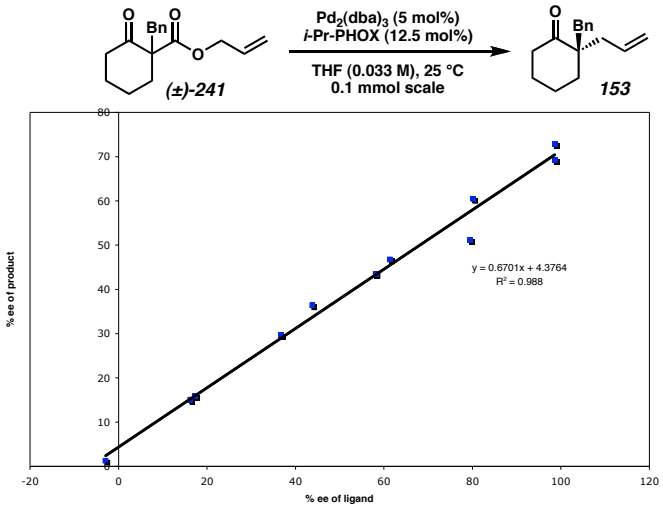


Figure 3.3. Plot of allyl enol carbonate ^{1}H NMR integral vs. time (s)

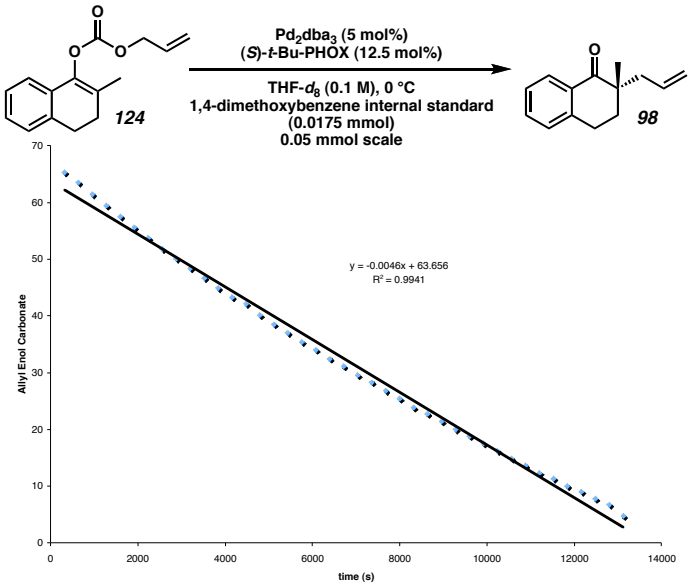
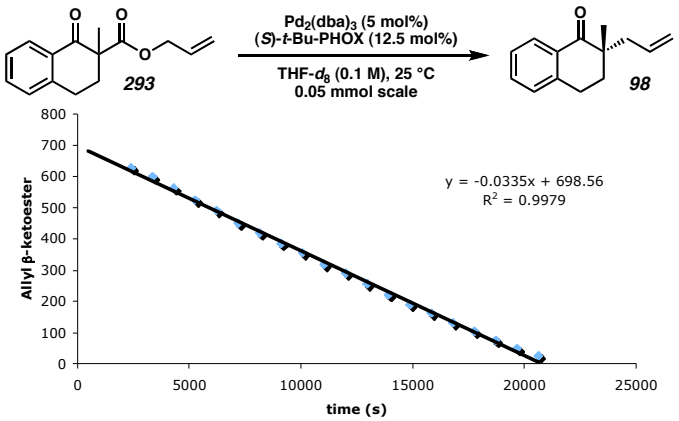


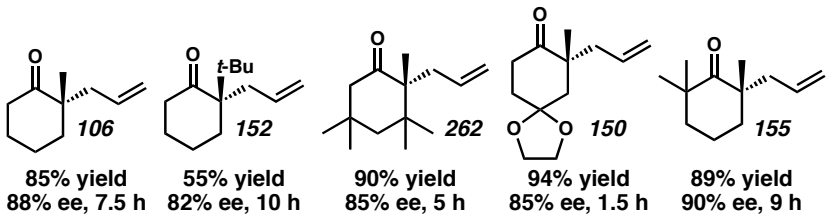
Figure 3.4. Plot of allyl β-ketoester ^{1}H NMR integral vs. time (s)



In addition to these studies, we designed other experiments to differentiate our proposed mechanism from that elucidated by Helmchen.[31] Enolates where charge is delocalized (e.g., those derived from β-ketoesters or α-aryl ketones), and should therefore tend to form weak ion pairs, give high yields but extremely low levels of enantioselectivity.[1,44] This suggests that, in such cases, allylation proceeds primarily via the more conventional, although in this case poorly selective, outer-sphere attack. The

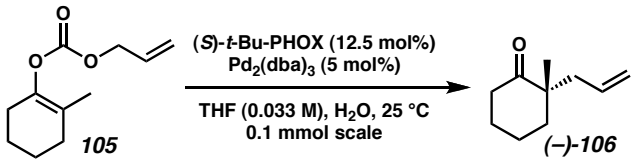
reactivity of sterically demanding substrates in our reaction is also inconsistent with an outer-sphere, intermolecular nucleophilic enolate attack. In a nucleophilic bimolecular reaction, such as the Helmchen allylation mechanism (Scheme 3.8), steric bulk near the site of bond formation typically impedes the rate of the reaction.[45] However, in our case there is little difference in the reaction time, yield, or enantioselectivity when comparing the formation of ketone **106** with more sterically demanding ketones (Figure 3.5). This observation is more consistent with an intramolecular reaction mechanism.

Figure 3.5. Comparison of sterically varied products formed at 25 °C in THF



Another observation at odds with an external attack mechanism is the unusual tolerance to water (Table 3.5). Multiple equivalents of water introduced into the reaction have only a moderate effect on the yield of the reaction. This contrasts typical enolates, which are rapidly quenched by water even at low temperatures, and suggests that the intermediate enolate formed in the reaction is tightly associated with its counterion for most of its lifetime.[46]

Table 3.5. Effect of water on asymmetric alkylation

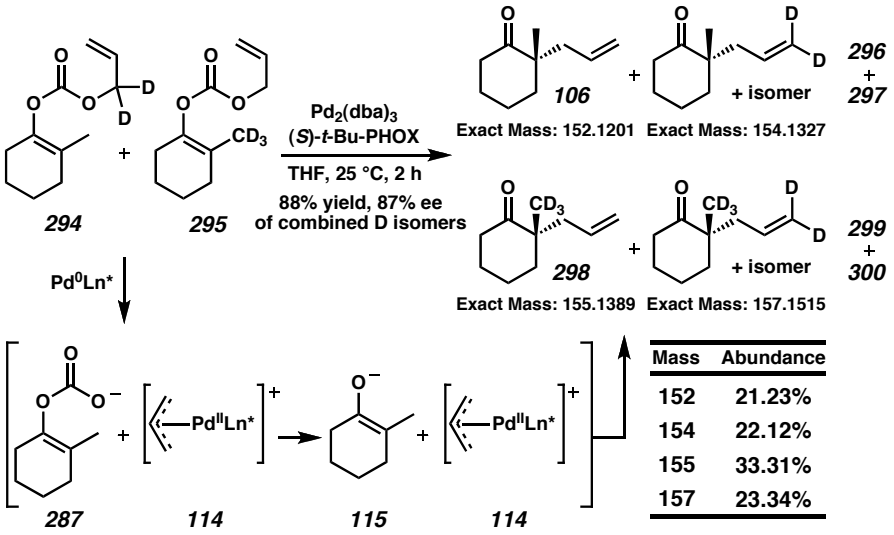


entry[a]	H_2O added (equiv)[b]	% yield[c]	% ee[d]
1	0	95	86
2	0.55	99	87
3	1.64	88	84
4	8.25	70	61
5	16.5	67	49
6	33.3	63	40

[a] Data reported are the average of three trials. [b] H_2O added after Pd/PHOX complexation, but before substrate. [c] GC yield relative to internal standard (tridecane). [d] Enantiomeric excess measured by chiral GC.

In an effort to trace the fate of the allyl and enolate fragments in the course of the reaction, we performed crossover experiments with deuterated allyl enol carbonates **294** and **295** in THF, dioxane, and benzene (Scheme 3.10).[47] Analysis of the products by high-resolution mass spectrometry revealed the presence of all four possible product masses in nearly equal amounts.[48] In conjunction with the water addition experiments, this observation suggests that a palladium enol carbonate species (**114** + **287** or **114•287**) may be a long-lived intermediate. Such an intermediate would not be readily protonated by water,[49] and this delocalized anion may facilitate crossover by dissociation from the metal center. In the case of β-ketoester substrates, a β-ketocarboxylate intermediate may play an analogous role.[50]

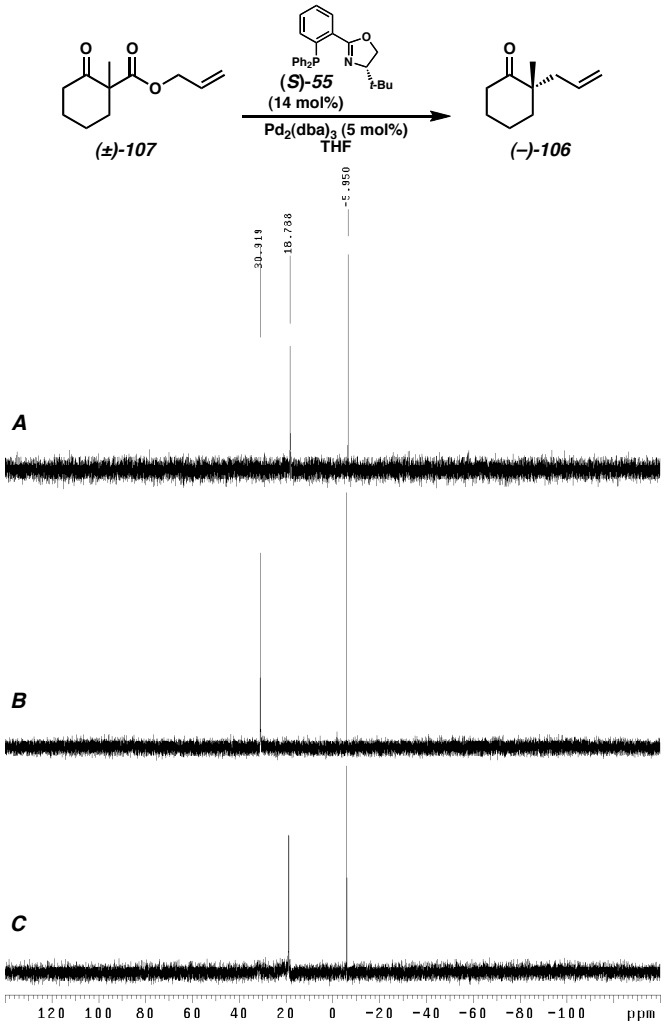
Scheme 3.10. Crossover experiments with deuterated allyl enol carbonates



In order to validate our hypothesis regarding the persistence of an intermediate carboxylate or mono-alkyl carbonate (**286** or **287**, respectively), we collected ^{31}P NMR data during the reaction.[51] Non-ligated *t*-Bu-PHOX (**55**) exhibited a ^{31}P resonance at –5.9 ppm. When $Pd_2(dba)_3$ and *t*-Bu-PHOX were complexed, a new resonance was observed at 18.8 ppm along with excess ligand (Figure 3.6, spectrum A). When substrate (±)-**107** was added, the resonance at 18.8 ppm disappeared immediately and the only observed intermediate was found at 30.9 ppm, which persisted until the end of the reaction (Figure 3.6, spectrum B). When the substrate was completely consumed, the initial Pd•PHOX complex returned at 18.8 ppm (Figure 3.6, spectrum C).[52] Interestingly, similar behavior was observed in reactions with allyl carbonate reactions, although the chemical shift of the intermediate species differed slightly. The separately prepared $[Pd(II)(allyl)(PHOX)]^+[PF_6]^-$ complex exhibited two ^{31}P resonances (other than those due to PF_6^-) at 23.5 and 22.5 ppm in a 2:1 ratio, presumably due to the mixture of *endo*- an *exo*-allyl isomers.[1,31] The different chemical shifts for this Pd(II) complex relative to that observed during the reaction suggest a different ligation environment about the Pd center.

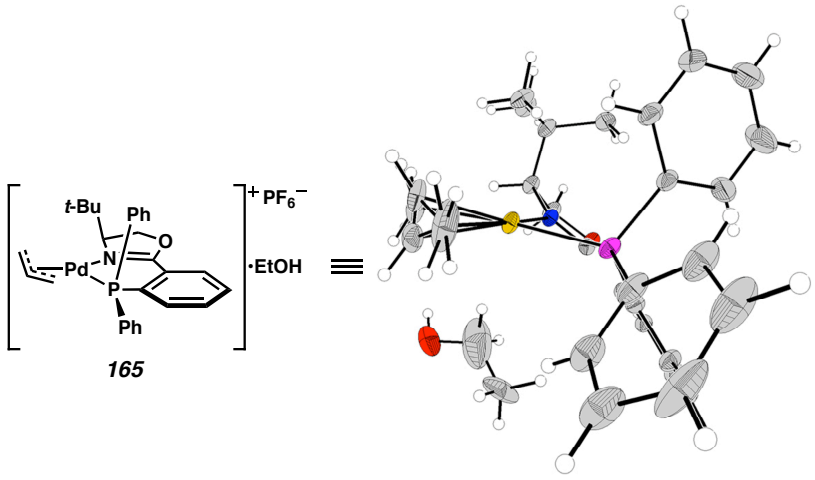
To correlate these two different species, *n*-Bu_4NOAc was added to a solution of [Pd(II)(allyl)(PHOX)]$^+$[PF_6]$^-$, and a new species was observed at 30.9 ppm. Based on these experiments, we believe that the observed catalyst resting state in solution is likely the [Pd(II)(allyl)(PHOX)]$^+$/carboxylate ion pair (**114** + **286**, Scheme 3.9) or the coordination complex **288**. Efforts to fully characterize intermediate structures are ongoing.[35]

*Figure 3.6. ^{31}P NMR collected during the enantioselective allylation reaction: Spectrum A: Pd•PHOX complex (18.8 ppm) and excess PHOX ligand (–5.9 ppm) prior to addition of substrate; Spectrum B: After addition of substrate (±)-**107**, during reaction; Spectrum C: After complete consumption of substrate*



The solid-state structure of independently prepared $[Pd(II)(allyl)PHOX]^+[PF_6]^-$ salt **165** lends credence to the possibility of an apically bound palladium enolate.[1] As shown in Figure 3.7, after recrystallization the complex partially co-crystallizes with a molecule of ethanol in its unoccupied quadrant.[53] We envision this as the likely site of enolate coordination (e.g., apically bound enolate complex **289**, Scheme 3.9).

Figure 3.7. X-Ray structure of [Pd(II)(allyl)PHOX]$^+$[PF_6]$^-$ EtOH adduct



Given the body of evidence accrued in these experimental studies and our inability to probe the mechanism through classical stereochemical labeling experiments,[39] we initiated a collaboration with the Goddard group at Caltech in order to investigate the details of the mechanism via computational modeling (see Chapter 4).[54] The computational studies carried out have corroborated our initial hypothesis regarding the inner-sphere mechanism, the difficult isomerization of *O*- to *C*-bound Pd enolate, and the unusual cyclic 7-membered reductive elimination pathway (Scheme 3.9). Notably, these calculations have found that the traditional outer-sphere mechanism (Scheme 3.8) is significantly higher in energy than the inner-sphere pathway. The simulations have not yet elucidated the fine details of the origin of enantioselectivity. Experiments and computational studies to better characterize the reaction mechanism are under way with the hope of improving the enantioselectivity and scope of the asymmetric alkylation.

3.4 SUMMARY

In order to address a significant problem in asymmetric synthesis, we developed a strategy to prepare enantioenriched cycloalkanones in high yield from either allyl enol carbonates or enol silanes. Difficulties in preparing certain substrates led us to explore allyl β-ketoesters as alternative enolate precursors. Racemic allyl β-ketoesters are competent in the reaction owing to the enantioconvergent mechanism of the transformation, whereby both enantiomers of the starting material are converted to a common achiral intermediate and then proceed to an enantioenriched product. Prompted by several empirical observations, we hypothesize an unusual inner-sphere mechanism for the reaction, which accurately predicts the absolute stereochemistry of the observed products. Kinetics experiments and computational simulations have corroborated our proposed inner-sphere mechanism. Studies directed toward further development of the scope of this reaction and catalyst system, as well as the application of our asymmetric allylation as a key enantiodetermining step in natural product synthesis,[12] are ongoing.

3.5 NOTES AND REFERENCES FOR TEXT

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15. Subsequent to our initial report on asymmetric allylation, several related reports have appeared: (a) For a collected review see ref 10d. (b) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846–2847. (c) Nakamura, M.; Hajra, A.; Endo, K.; Nakamura, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 7248–7251. (d) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180–17181. (e) Burger, E. C.; Barron, B. R.; Tunge, J. A. *Synlett* **2006**, 2824–2826. (f) Trost, B. M.; Bream, R. N.; Xu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3109–3112. (g) Trost, B. M.; Xu, J.; Reichle, M. *J. Am. Chem. Soc.* **2007**, *129*, 282–283. (h) Bélanger, É.; Cantin, K.; Messe, O.; Tremblay, M.; Paquin, J.-F. *J. Am. Chem. Soc.* **2007**, *129*, 1034–1035. (i) Schulz, S. R.; Blechert, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 3966–3970. (j) Bélanger, É.; Houzé, C.; Guimond, N.; Cantin, K.; Paquin, J.-F. *Chem. Commun.* **2008**, 3251–3253. (k) Bélanger, É.; Pouliot, M.-F.; Paquin, J.-F. *Org. Lett.* **2009**, *11*, 2201–2204.

16. (a) Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199–3202. (b) Tsuda, T.; Chujo, Y.; Nishi, S.-i.; Tawara, K; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381–6384. (c) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140–145.

17. For a discussion of double stereodifferentiation, see: Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereochemistry of Organic Compounds*, Wiley: New York, 1994; pp 965–971.

18. Aliquots taken during the reaction with β-ketoester (±)-**107** at 30 °C in THF show the starting material reaches a maximum of 5% ee at 83% conversion for a k_{rel} of 1.1.

19. Presumably, this is the result of the cleavage of a C–C bond during decarboxylation, rather than C–O bond found in carbonates. The exact nature of the rate-determining step of the reaction has not yet been elucidated.

20. For reviews, see: (a) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–56. (b) Stecher, H.; Faber, K. *Synthesis* **1997**, 1–16. (c) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321–331. (d) Pellissier, H. *Tetrahedron* **2003**, *59*, 8291–8327. (e) For representative stereomutative examples, see: Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 2, pp 833–884. (f) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968–5976.

21. This hypothesis has been experimentally supported for non-enantioselective systems, see: (a) Tsuji, J.; Yamada, T.; Minami, I.; Yuhara, M.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1987**, *52*, 2988–2995. (b) Detalle, J.-F.; Riahi, A.; Steinmetz, V.; Hénin, F.; Muzart, J. *J. Org. Chem.* **2004**, *69*, 6528–6532.

22. For a highlight of recent approaches to catalytic enantioselective stereoablative reactions, see: Mohr, J. T.; Ebner, D. C.; Stoltz, B. M. *Org. Biomol. Chem.* **2007**, *5*, 3571–3576.

23. For representative examples of stereoablative enantioconvergent catalysis, see: (a) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261–1268. (b) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420–2423. (c) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594–4595. (d) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404–13405. (e) Nishimura, T.; Katoh, T.; Takatsu, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 14158–14159. (f) Enders, D.; Narine, A. A.; Toulgoat, F.; Bisschops, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5661–5665.

24. This is an adaptation of a procedure by Tsuji and co-workers, see: Tsuji, J.; Nisar, M.; Shimizu, I,; Minami, I. *Synthesis* **1984**, *12*, 1009.

25. For an optimized large-scale procedure, see: Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 194–211.

26. (a) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425–5428. (b) Donnely, D. M. X.; Finet, J.-P.; Rattigan, B. A. *J. Chem. Soc. Perkin Trans. 1* **1993**, 1729–1735.

27. Recently, an alternate, cyanide-free reagent has been developed for the preparation of allyl enol carbonates or allyl β-ketoesters. Selective *O*- or *C*-acylation may achieved by addition of a Lewis acid to the reaction, see: Trost, B. M.; Xu, J. *J. Org. Chem.* **2007**, *72*, 9372–9375.

28. Although only trace β-elimination was observed with this substrate, substrates with better leaving groups (e.g., OAc) predominantly underwent β-elimination to the α,β-unsaturated compounds.

29. Fluorinated compounds have gained frequent use in medicinal chemistry, see: (a) Zoute, L.; Audouard, C.; Plaquevent, J.-C.; Cahard, D. *Org. Biomol. Chem.* **2003**, *1*,

1833–1834. (b) Nagai, K.; Davies, T. A.; Dewasse, B. E.; Jacobs, M. R.; Appelbaum, P. C. *J. Antimicrob. Chemother.* **2001**, *48*, 365–374.

30. Enquist, J. A., Jr.; Stoltz, B. M. *Nature* **2008**, *453*, 1228–1231.

31. (a) Steinhagen, H.; Reggelin, M.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2108–2110. (b) Helmchen, G.; Steinhagen, H.; Reggelin, M.; Kudis, S. In *Selective Reactions of Metal-Activated Molecules*; Werner, H., Schreier, P., Eds.; Vieweg Verlag: Wiesbaden, 1998; pp 205–215. (c) Kollmar, M.; Goldfuss, B.; Reggelin, M.; Rominger, F.; Helmchen, G. *Chem. Eur. J.* **2001**, *7*, 4913–4927. (d) Kollmar, M.; Steinhagen, H.; Janssen, J. P.; Goldfuss, B.; Malinovskaya, S. A.; Vázquez, J.; Rominger, F.; Helmchen, G. *Chem.–Eur. J.* **2002**, *8*, 3103–3114.

32. von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566–568.

33. For Trost's related system, a solvent-caged ion pair has been proposed based on a lack of crossover between enolate and alkyl fragments (ref 15b). However, we observe very different results from crossover experiments (Scheme 3.10), suggesting that the details of the mechanism between these two systems may be substantially different.

34. Unusual patterns in enantioselectivity in a different asymmetric allylation system have led other researchers to consider enolate associated allylation mechanisms as well, see: (a) ref 15b. (b) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590–4591.

35. The crystals are composed of two diastereomeric carboxylate complexes. For clarity, only one of these is shown in Scheme 3.9. See: Sherden, N. H.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6840–6843.

36. For representative examples of *O*- and *C*-bound Pd-enolates, see: (a) Burkhardt, E. R.; Bergman, R. G.; Heathcock, C. H. *Organometallics* **1990**, *9*, 30–44. (b) Balegroune, F.; Grandjean, D.; Lakkisb, D.; Matt, D. *J. Chem. Soc., Chem. Commun.* **1992**, 1084–1085. (c) Byers, P. K.; Canty, A. J.; Skelton, B. W.; Traill, P. R.; Watson, A.

A.; White, A. H. *Organometallics* **1992**, *11*, 3085–3088. (d) Veya, P.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Organometallics* **1993**, *12*, 4899–4901. (e) Sodeoka, M.; Tokunoh, R.; Miyazaki, F.; Hagiwara, E.; Shibasaki, M. *Synlett* **1997**, 463–466. (f) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121,* 1473–1478. (g) Albéniz, A. C.; Catalina, N. M.; Espinet, P.; Redón, R. *Organometallics* **1999**, *18*, 5571–5576. (h) Vicente, J.; Arcas, A.; Fernández-Hernández, J. M.; Bautista, D. *Organometallics* **2001**, *20*, 2767–2774. (i) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 5816–5817. (j) Tian, G.; Boyle, P. D.; Novak, B. M. *Organometallics* **2002**, *21*, 1462–1465. (k) Culkin, D. A.; Hartwig, J. F. *Organometallics* **2004**, *23*, 3398–3416.

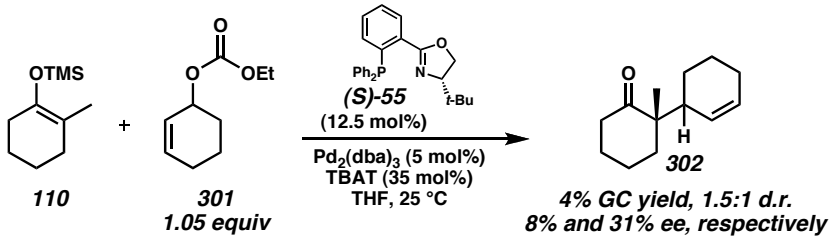
37. Similar transition states have been proposed previously for C–C bond formation, see: (a) Kitching, W.; Sakakiyama, T.; Rappoport, Z.; Sleezer, P. D.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1972**, *94*, 2329–2335. (b) Méndez, M.; Cuerva, J. M.; Gómez-Bengoa, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2002**, *8*, 3620–3628.

38. Similar transition states have been proposed previously for C–O bond formation, see: (a) Bäckvall, J.-E.; Nordberg, R. E.; Björkman, E. E.; Moberg, C. *J. Chem. Soc., Chem. Commun.* **1980**, 943–944. (b) Bäckvall, J.-E.; Nordberg, R. E.; Wilhelm, D. *J. Am. Chem. Soc.* **1985**, *107*, 6892–6898. (c) Grennberg, H.; Langer, V.; Bäckvall, J.-E. *J. Chem. Soc., Chem. Commun.* **1991**, 1190–1192.

39. For representative examples, see: (a) Trost, B. M.; Verhoeven, T. R. *J. Org. Chem.* **1976**, *41*, 3215–3216. (b) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730–4743. (c) Bäckvall, J.-E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1981**, *103*, 4959–4960. (d) Bäckvall, J.-E.; Nordberg, R. E.; Vågberg, J. *Tetrahedron Lett.* **1983**, *24*, 411–412. (e) Keinan, E.; Roth, Z. *J. Org. Chem.* **1983**, *48*, 1769–1772. (f) Sheffy, F. K.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 7173–7175. (g) Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833–4840. (h) Tsuji, Y.; Funato, M.; Ozawa,

M.; Ogiyama, H.; Kajita, S.; Kawamura, T. *J. Org. Chem.* **1996**, *61*, 5779–5787. (i) Rayabarapu, D. K.; Tunge, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13510–13511.

40. A representative experiment with a cyclic carbonate is shown below.



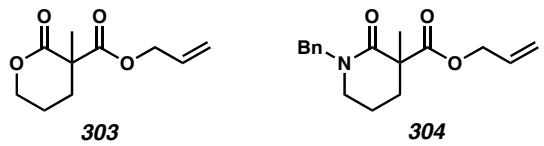
For the preparation of carbonate **301**, see: Genêt, J.-P.; Jugé, S.; Achi, S.; Mallart, S.; Ruiz-Montès, J.; Levif, G. *Tetrahedron* **1988**, *44*, 5263–5275.

41. See the experimental section (section 3.6) for details of the kinetics experiments.

42. For discussions of non-linear effects, see: (a) Guillaneux, D.; Zhao, S.-H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430–9439. (b) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron: Asymmetry* **1997**, *8*, 2997–3017. (c) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922–2959. (d) Kagan, H. B. *Synlett* **2001**, 888–899. (e) Satyanarayana, T.; Abraham, S.; Kagan, H. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 456–494.

43. For these experiments, *i*-Pr-PHOX was used because of the availability of both enantiomers of valine at approximately the same cost.

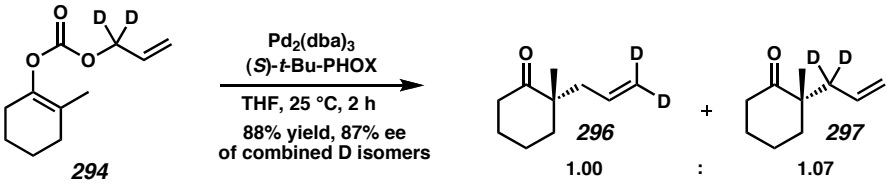
44. Substrates that would lead to highly basic enolate intermediates, such as lactone **303** and lactam **304**, have been problematic, presumably because decarboxylation is slow.



45. For example, replacement of the CH_2 group of the malonate nucleophile with CH(NHAc) increased reaction time from 1 h to 3–4 days. See ref 32.

46. Also consistent with the intermediacy of a Pd-bound enolate, stronger acids (e.g., formic acid) may be employed in order to achieve an enantioselective *protonation* reaction. However, empirical observations indicate that the mechanism of C–H bond formation differs significantly from that of C–C bond formation, see: (a) Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11348–11349. (b) Marinescu, S. C.; Nishimata, T.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2008**, *10*, 1039–1042.

47. A separate reaction with dideuterio allyl enol carbonate **294** confirms that the allyl termini are scrambled during the course of the reaction. See the experimental section (section 3.6) for details.



48. Although the total ion counts are not rigorously quantitative, they are consistent with the presence of all four masses in nearly equal proportions. The slight excess of the 155 *m*/*z* ion is likely due to the natural abundance of ^{13}C present in the dideuterio product.

49. The pK_a of related monomethyl carbonic acid has been estimated at 2.92 (H_2O solvent, 25 °C), see: Guthrie, J. P. *Can. J. Chem.* **1978**, *56*, 2342–2354.

50. Saegusa suggested similar crossover pathways in a related, non-enantioselective system using a $Pd(PPh_3)_4$ catalyst. See ref 16b.

51. For details and other control experiments, see the experimental section (section 3.6).

52. If the reaction mixture is exposed to air, *t*-Bu-PHOX is cleanly converted to the corresponding phosphine oxide. Pd catalyzes this conversion. See the experimental section (section 3.6) for details.

53. PF_6^- counterions removed for clarity. Two out of four of the crystallographically unique [Pd(allyl)PHOX] complexes in the unit cell crystallized with a molecule of ethanol. The *endo*- and *exo*-allyl isomers were present in equal electron density and are modeled as a superposition of the two isomers.

54. For an initial report of our computational studies in collaboration with the W. A. Goddard group at Caltech, see: Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard, W. A., III *J. Am. Chem. Soc.* **2007**, *129*, 11876–11877.

3.6 EXPERIMENTAL SECTION

3.6.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Tetrabutylammonium triphenyldifluorosilicate (TBAT) was purchased from Sigma-Aldrich and azeotropically dried five times from acetonitrile prior to use. Bis(3,5-dimethoxybenzylideneacetone)palladium(0) ($Pd(dmdba)_2$), alkyl halides, diallyl carbonate, Select-fluor®, pimelic acid, and all other ketone starting materials were purchased from Sigma-Aldrich and used as received, unless otherwise noted. Commercial 3-methylcyclohex-2-en-1-one, cyclohex-2-en-1-one, and NaH (60% dispersion in mineral oil) were purchased from Acros and used as received. Dimethallyl carbonate was purchased from Alfa Aesar and used as received. Trimethylsilyl chloride (TMSCl) and triethylamine were distilled from sodium hydride immediately prior to use. Sodium iodide was dried by heating at 90 °C (2 torr) for 12 h. Tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) was purchased from Strem and stored in a glovebox until immediately before use. (*S*)-*tert*-Leucine was purchased from Aldrich or Degussa, used as received, and reduced to the corresponding amino alcohol according to literature precedent.[55] (*R*)-*i*-PrPHOX (**122**) and (*S*)-*t*-BuPHOX (**55**) were prepared according to our previously reported methods.[56] Allyl cyanoformate was prepared by known methods.[57] Ruthenium olefin metathesis catalysts were generously donated by Materia and stored under argon in a dessicator jar at –20 °C until just prior to

use. Preparations of (*S*)-*t*-Bu-PHOX oxide (**125**) and [Pd(allyl)PHOX]•PF_6 salt (**165**) are found in Chapter 2.

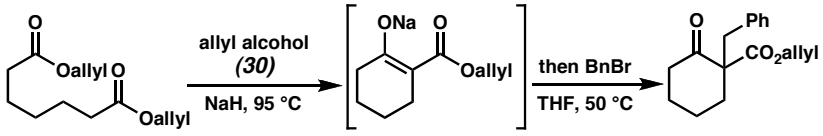
Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, $KMnO_4$ or CAM staining. ICN Silica gel (particle size 0.032–0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralpak AD, Chiracel OD-H, or Chiracel OJ columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries with visualization at 254 nm. Analytical chiral supercritical fluid chromatography was performed with a Berger Analytix SFC (Thar Technologies) utilizing a Chiralpak AD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries with 2 mL/min flow rate at 30 °C and visualization at 244 nm. Analytical chiral GC was performed with an Agilent 6850 GC utilizing a Chiraldex G-TA (30.0 m x 0.25 mm) column (1.0 mL/min He carrier gas flow). Analytical achiral GC was performed with an Agilent 6850 GC utilizing an Agilent DB-WAX (30.0 m x 0.25 mm) column (1.0 mL/min He carrier gas flow). Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz, respectively) or a Varian Inova 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept. = septet, m = multiplet, comp. m = complex multiplet, app. = apparent, br s = broad singlet. Data for ^{13}C NMR spectra are reported in

terms of chemical shift relative to Me_4Si (δ 0.0). ^{19}F NMR spectra were recorded on a Varian Mercury 300 spectrometer at 282 MHz, and are reported relative to the external standard F_3CCO_2H (δ –76.53 ppm) or $CFCl_3$ (δ 0.0 ppm). ^{31}P NMR spectra were recorded on a Varian Mercury 300 spectrometer at 121 MHz, and are reported relative to the external standard H_3PO_4 (δ 0.0 ppm). Temperature controlled ^1H NMR kinetic experiments were performed on a Varian Inova 500 MHz. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility.

3.6.2 SUBSTRATE COMPOUNDS

3.6.2.1 GENERAL PROCEDURES FOR THE SYNTHESIS OF ALLYL β-KETOESTERS

General Procedure 1: Dieckmann Cyclization Method[58,59]

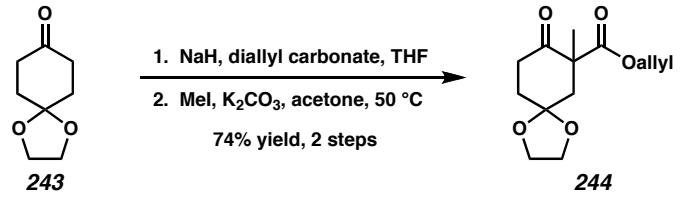


239 *240* *241*

Allyl 1-benzyl-2-oxocyclohexanecarboxylate (241, Table 3.2, Entry 6). To a suspension of NaH (166.4 mg, 4.16 mmol, 1.0 equiv) in toluene (2 mL) was added allyl alcohol (**30**, 79.2 μL, 1.17 mmol, 0.28 equiv). Once gas evolution ceased, pimelic acid diallyl ester (**239**, 1.00 g, 4.16 mmol, 1.0 equiv) was added slowly and the resulting mixture heated to 95 °C for 1 h. Additional toluene (~2 mL) was added during this time

to maintain a fluid reaction mixture. The reaction mixture was cooled to room temperature and the solvent removed by rotary evaporation in vacuo. The resulting solid salt was placed under dry N_2 and dissolved in THF (9 mL). Benzyl bromide (643.2 μL, 5.4 mmol, 1.3 equiv) was then added dropwise. The resulting mixture was warmed to 50 °C for 2.5 h, cooled to ambient temperature, and quenched with saturated aq NH_4Cl (5 mL) followed by H_2O (5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (1 x 10 mL), then dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting oil was purified by flash chromatography (5 x 18 cm SiO_2, 10% Et_2O in pentane) to afford the quaternary compound **241** as a colorless oil (781.4 mg, 70% yield). R_f = 0.30 (10% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.23 (comp. m, 3H), 7.20-7.13 (comp. m, 2H), 5.86 (dddd, J = 17.2, 10.3, 5.9, 5.9 Hz, 1H), 5.29 (m, 2H), 4.57 (m, 2H), 3.38 (d, 1H, J = 13.8 Hz), 2.94 (d, J = 13.8 Hz, 1H), 2.60-2.39 (comp. m, 3H), 2.14-1.97 (m, 1H), 1.83-1.60 (comp. m, 3H), 1.59-1.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8, 170.5, 136.3, 131.2, 130.2, 127.9, 126.5, 119.0, 65.6, 62.1, 41.1, 40.3, 35.7, 27.4, 22.3; IR (Neat Film NaCl) 3029, 2942, 1713, 1452, 1179, 1085 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{20}O_3$ $[M]^+$: 272.1412, found 272.1425.

General Procedure 2: Diallyl Carbonate Method



243 *244*

Allyl 7-methyl-8-oxo-1,4-dioxaspiro[4.5]decane-7-carboxylate (244, Table 3.3, entries 1 and 2):

Part A, Acylation:

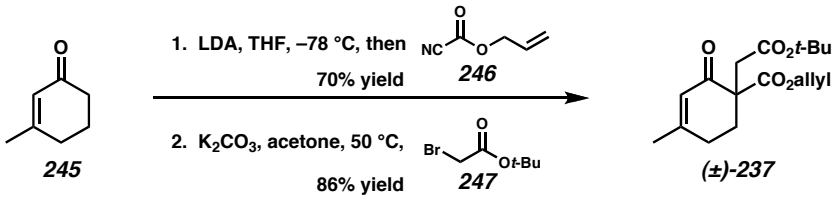
To a cooled (0 °C) suspension of NaH (9.22 g, 240.1 mmol, 2.5 equiv) in THF (125 mL) was added a solution of 1,4-cyclohexanedione monoethylene ketal (**243**, 15.0 g, 96 mmol, 1.0 equiv) in THF (30 mL) dropwise over 15 min. The reaction mixture was warmed to room temperature and diallyl carbonate (**111**, 20.65 mL, 144.0 mmol, 1.5 equiv) was added and the reaction mixture stirred for 16 h. The reaction was quenched with saturated aq NH_4Cl and 1 N aq HCl until a pH of 4 was reached. The phases were separated and the aq phase was extracted with EtOAc (7 x 150 mL). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated, redissolved in CH_2Cl_2, dried ($MgSO_4$), filtered, and concentrated.

Part B, Alkylation:

The resulting oil was added to a suspension of anhydrous K_2CO_3 (26.5 g, 192.0 mmol, 2.0 equiv) in acetone (128 mL). To the reaction mixture was added iodomethane (12.0 mL, 192.0 mmol, 2.0 equiv) and the reaction mixture was then heated to 50 °C for 14 h. The mixture was then cooled, filtered, and the solids washed with acetone. The filtrate was concentrated and the resulting oil purified by flash chromatography (SiO_2, 5 → 40% Et_2O in hexanes) to afford the desired quaternary quaternary β-ketoester **244** as a

colorless oil (18.0 g, 74% yield). R_f = 0.28 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.90 (dddd, *J* = 17.4, 10.5, 5.7, 5.7 Hz, 1H), 5.26 (m, 2H), 4.60 (m, 2H), 3.97 (comp. m, 4H), 3.02 (dt, *J* = 14.8, 10.2 Hz, 1H), 2.68 (dt, *J* = 14.0, 2.0 Hz, 1H), 2.49 (dt, *J* = 14.8, 4.4 Hz, 1H), 2.00 (comp. m, 2H), 1.72 (d, *J* = 14.1 Hz, 1H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.0, 172.9, 131.6, 118.5, 106.5, 65.9, 64.8, 64.3, 54.6, 43.6, 37.4, 35.2, 21.7; IR (Neat Film NaCl) 2939, 2891, 1733, 1717, 1304, 1141 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{13}H_{18}O_5$ $[M]^+$: 254.1154, found 254.1153.

General Procedure 3: Mander's Reagent Method[57]

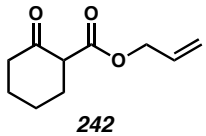


Allyl 1-(2-*tert*-butoxy-2-oxoethyl)-4-methyl-2-oxocyclohex-3-enecarboxylate (237, Scheme 3.3): To a cooled (–78 °C) solution of LDA (18.70 mmol, 1.05 equiv) in THF (90 mL) was added 3-methylcyclohex-2-enone (**245**) (2.02 mL, 17.81 mmol, 1.0 equiv) in a dropwise fashion. The resulting solution was stirred at –78 °C for 30 min and then allyl cyanoformate (**246**)[57] (2.00 g, 18.17 mmol, 1.02 equiv) was added dropwise. The dry ice bath was removed and the reaction mixture slowly warmed to room temperature and stirred for 8 h. The reaction mixture was quenched with saturated aq NH_4Cl (15 mL) followed by H_2O (15 mL). The phases were separated and the aq phase was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (1 x 30 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting oil was purified

by flash chromatography (5 x 24 cm SiO_2, 50% EtOAc in hexanes) to afford the intermediate β-ketoester as a yellow oil (2.4152 g, 70% yield).

A portion of this β-ketoester (500.0 mg, 2.57 mmol, 1.0 equiv) was added to a suspension of anhydrous K_2CO_3 (711.8 mg, 5.15 mmol, 2.0 equiv) in acetone (2.5 mL). To the reaction mixture was added *t*-butyl bromoacetate (**247**, 760.5 μL, 5.15 mmol, 2.0 equiv). The reaction mixture was then warmed to 50 °C and stirred for 48 h. The reaction mixture was then cooled, filtered, and the solids washed with acetone. The filtrate was concentrated and purified by flash chromatography (3 x 20 cm SiO_2, 10→30% EtOAc in hexanes) to afford the desired quaternary β-ketoester **237** as a colorless oil (684.7 mg, 86% yield; 60% overall yield for 2 steps). R_f = 0.28 (30% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (s, 1H), 5.87 (dddd, *J* = 17.3, 10.5, 5.4, 5.4 Hz, 1H), 5.23 (m, 2H), 4.61 (m, 2H), 2.83 (d, *J* = 16.4 Hz, 1H), 2.73 (d, *J* = 16.4 Hz, 1H), 2.58-2.36 (comp. m, 2H), 2.31-2.16 (comp. m, 2H), 1.94 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.2, 169.8, 161.9, 131.7, 125.6, 118.2, 81.1, 65.8, 54.2, 39.8, 30.5, 28.7, 28.0, 24.2; IR (Neat Film NaCl) 2979, 1733, 1677, 1368, 1153 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{24}O_5$ $[M]^+$: 308.1624, found 308.1609.

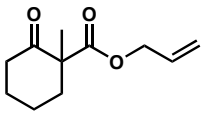
3.6.2.2 CHARACTERIZATION DATA FOR β-KETOESTER SUBSTRATES



242

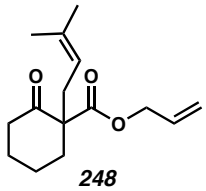
Allyl 2-oxocyclohexanecarboxylate (242, Scheme 3.5): Prepared by general procedure 1. The reaction was quenched with 10% HCl. The product was isolated by

bulb-to-bulb distillation once at 150-155 °C (bath temp, 2 torr), then at 136 °C (bath temp, 2 torr). 75% yield. R_f = 0.53 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of keto and enol tautomers) δ 12.14 (s, 0.7H), 5.99 (dddd, *J* = 5.7, 5.7, 10.8, 17.1 Hz, 0.7H), 5.96 (dddd, *J* = 5.7, 5.7, 10.2, 17.1 Hz, 0.3H), 5.38 (dddd, *J* = 1.5, 1.5, 1.5, 17.1 Hz, 0.3H), 5.37 (dddd, *J* = 1.5, 1.5, 1.5, 17.1 Hz, 0.7H), 5.24 (dddd, *J* = 1.5, 1.5, 1.5, 10.5 Hz, 1H), 4.72-4.55 (m, 2H), 3.41 (ddd, *J* = 1.5, 6.6, 9.6 Hz, 0.3H), 2.52 (dddd, *J* = 1.5, 5.4, 5.4, 14.1 Hz, 0.3H), 2.37 (m, 0.3H), 2.26 (m, 2.7H), 2.22-2.10 (m, 0.6H), 2.04-1.78 (m, 0.9H), 1.75-1.55 (m, 3.3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.9, 172.4, 172.2, 169.6, 132.3, 131.8, 118.4, 117.7, 97.5, 65.6, 64.6, 57.2, 41.5, 29.9, 29.1, 27.0, 23.3, 22.3, 22.3, 21.9; IR (Neat Film NaCl) 3086, 2941, 1746, 1716, 1659, 1617, 1299, 1259, 1217, 1176, 831 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{10}H_{14}O_3$ $[M]^+$: 182.0943, found 182.0941.



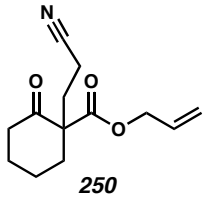
107

Allyl 1-methyl-2-oxocyclohexanecarboxylate (107, Table 3.1; Table 3.2, entries 1 and 2): Prepared by general procedure 1. 62% yield. R_f = 0.38 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (dddd, *J* = 17.1, 10.2, 5.9, 5.9 Hz, 1H), 5.24 (m, 2H), 4.59 (d, *J* = 5.7 Hz, 2H), 2.58-2.34 (comp. m, 3H), 2.08-1.88 (m, 1H), 1.80-1.54 (comp. m, 3H), 1.52-1.37 (m, 1H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9, 172.6, 131.4, 118.7, 65.6, 57.1, 40.5, 38.1, 27.4, 22.5, 21.1; IR (Neat Film NaCl) 3086, 2939, 2867, 1715, 1452, 1259, 1211, 1159, 1084, 976 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{16}O_3$ $[M]^+$: 196.1099, found 196.1096.



248

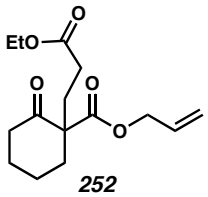
Allyl 1-(3-methylbut-2-enyl)-2-oxocyclohexanecarboxylate (248, Table 3.2, entry 3): Prepared by general procedure 2 part B from ketoester **242** and prenyl bromide. Flash chromatography (SiO_2, 2→12% Et_2O in pentane). 20% yield. R_f = 0.24 (10% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (dddd, J = 17.1, 10.4, 5.8, 5.8 Hz, 1H), 5.31 (d, J = 17.1 Hz, 1H), 5.24 (d, J = 10.1 Hz, 1H), 5.06 (t, J = 7.7 Hz, 1H), 4.59 (d, J = 5.7 Hz, 2H), 2.65-2.27 (comp. m, 5H), 2.07-1.93 (m, 1H), 1.79-1.69 (m, 1H), 1.68 (s, 3H), 1.66-1.59 (m, 1H), 1.58 (s, 3H), 1.54-1.39 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.7, 171.4, 134.8, 131.6, 118.8, 118.5, 65.7, 61.3, 41.2, 35.5, 33.2, 27.5, 26.0, 22.5, 17.8; IR (Neat Film NaCl) 2938, 2863, 1714, 1451, 1438, 1210, 1178, 989 cm^{-1}; HRMS (EI) m/z calc'd for $C_{15}H_{22}O_3$ $[M]^+$: 250.1569, found 250.1574.



250

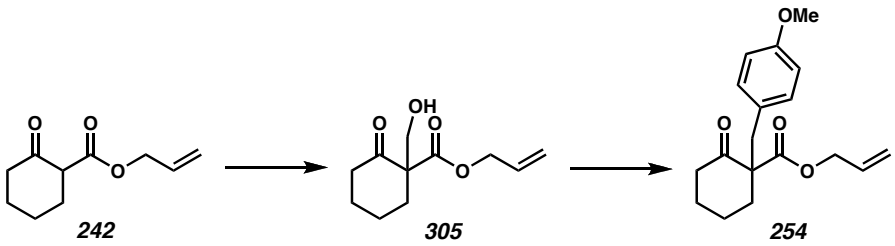
Allyl 1-(cyanomethyl)-2-oxocyclohexanecarboxylate (250, Table 3.2, entry 4): Prepared by general procedure 2 part B from ketoester **242** and acrylonitrile. Flash chromatography (SiO_2, 10% Et_2O in pentane). 55% yield. R_f = 0.27 (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (dddd, J = 17.6, 10.2, 6.0, 6.0 Hz, 1H), 5.41-5.25 (m, 2H), 4.68 (d, J = 6.0 Hz, 2H), 2.64-2.38 (comp. m, 4H), 2.37-2.13 (comp. m, 2H), 2.13-1.86 (comp. m, 2H), 1.85-1.40 (comp. m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.0, 170.6, 130.9,

120.0, 119.3, 66.4, 59.7, 40.9, 36.7, 30.8, 27.4, 22.4, 13.0; IR (Neat Film NaCl) 2945, 2868, 2248, 1713, 1450, 1192, 1136, 941 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{13}H_{17}NO_3$ $[M]^+$: 235.1208, found 235.1218.



252

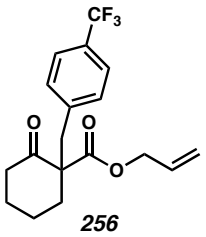
Allyl 1-(3-ethoxy-3-oxopropyl)-2-oxocyclohexanecarboxylate (252, Table 3.2, entry 5): Prepared by general procedure 2 part B from ketoester **242** and ethyl acrylate. Flash chromatography (SiO_2, 10% Et_2O in pentane). 81% yield. R_f = 0.37 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (dddd, *J* = 17.3, 10.3, 5.9, 5.9 Hz, 1H), 5.33 (dd, *J* = 17.3, 1.1 Hz, 1H), 5.26 (dd, *J* = 10.4, 1.3 Hz, 1H), 4.63 (app. t, *J* = 14.9 Hz, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 2.51-2.31 (comp. m, 4H), 2.31-2.11 (comp. m, 2H), 2.08-1.85 (comp. m, 2H), 1.84-1.57 (comp. m, 3H), 1.55-1.40 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.4, 173.0, 171.4, 131.3, 119.3, 65.9, 60.4, 60.1, 41.0, 36.2, 29.6, 29.5, 27.5, 22.5, 14.2; IR (Neat Film NaCl) 2943, 2868, 1734, 1715, 1456, 1181 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{15}H_{22}O_5$ $[M]^+$: 282.1467, found 282.1474.



Allyl 1-(4-methoxybenzyl)-2-oxocyclohexanecarboxylate (254, Table 3.2, entry 7): To a cooled (0 °C) solution of ketoester **242** (4.00 g, 22.0 mmol, 1.0 equiv) in THF (40 ml) was added 35% aqueous formaldehyde (11.3 mL) and $KHCO_3$ (5.93 g, 65.9 mmol, 3.0 equiv). After 30 min at 0 °C the reaction mixture was allowed to warm to ambient temperature. After an additional 90 min, the reaction was quenched with water (100 mL) and CH_2Cl_2 (100 mL). After the layers were separated, the aqueous layer was extracted with CH_2Cl_2 (4 x 50 mL), the combined organics dried (Na_2SO_4) and evaporated. The oil obtained was treated with THF (40 mL) and 3 M aq HCl (4 drops) for 60 min, concentrated, and purified by flash chromatography (SiO_2, 10→45% EtOAc in hexanes) to give **305** (3.75 g, 81% yield).

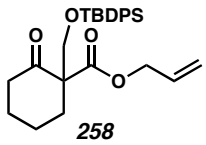
To a cooled (0 °C) suspension of 60% NaH (251 mg, 6.28 mmol, 1.1 equiv) in DMF (20 mL) was added **305** (1.20g, 5.71 mmol, 1.0 equiv) in a dropwise manner over 2 min. Once gas evolution had ceased (10 min), Bu_4NI (527 mg, 1.43 mmol. 0.25 equiv) and PMB-Cl (930 μL, 6.85 mmol, 1.2 equiv) were added, and the reaction mixture slowly allowed to warm to ambient temperature. After 12 h, the reaction mixture was quenched with water (50 mL) and 2:1 CH_2Cl_2:hexanes (50 mL), the aqueous layer extracted with 2:1 CH_2Cl_2:hexanes (3 x 50 mL), dried (Na_2SO_4), evaporated, and purified by flash chromatography (SiO_2, 10→20% Et_2O in hexanes) to give the desired compound **306** (485 mg, 28% yield). R_f = 0.30 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 5.89-5.76 (m, 1H) 5.31-5.21 (m, 2H),

4.59-4.47 (m, 2H), 3.76 (s, 3H), 3.25 (d, J = 14.1 Hz, 1H), 2.84 (d, J = 14.1 Hz, 1H), 2.51-2.35 (m, 3H), 2.04-1.96 (m, 1H), 1.76-1.54 (m, 3H), 1.50-1.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2, 170.8, 158.4, 131.4, 131.3, 128.4, 119.1, 113.4, 65.8, 62.3, 55.1, 41.3, 39.5, 35.8, 27.5, 22.5; IR (Neat Film NaCl) 2943, 1713, 1612, 1513, 1247, 1179 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{18}H_{22}O_4$ [M]$^+$: 302.1518, found 302.1514.



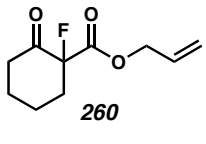
256

Allyl 2-oxo-1-(4-(trifluoromethyl)benzyl)cyclohexanecarboxylate (256, Table 3.2, entry 8): Prepared by general procedure 1 with 4-(trifluoromethyl)benzyl bromide. Flash chromatography (SiO_2, 2→12% Et_2O in pentane). 56% yield. mp 40–41 ºC; R_f = 0.63 (30% Et_2O in pentane); ^{1}H NMR (300 MHz, C_6D_6) δ 7.29 (d, J = 8.1 Hz, 2H), 7.02 (d, J = 8.1 Hz, 2H), 5.45 (dddd, J = 17.3, 10.4, 6.0, 6.0 Hz, 1H), 4.91 (m, 2H), 4.18 (m, 2H), 3.34 (d, J = 13.7 Hz, 1H), 2.78 (d, J = 13.7 Hz, 1H), 2.37-2.15 (comp. m, 3H), 1.57-1.38 (comp. m, 2H), 1.32-1.11 (comp. m, 2H), 1.09-0.94 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.7, 170.4, 140.8 (q, J_{CF} = 1.2 Hz), 131.0, 130.7, 129.0 (q, J_{CF} = 32.3 Hz), 124.9 (q, J_{CF} = 3.9 Hz), 124.2 (q, J_{CF} = 271.7 Hz), 119.4, 65.9, 62.2, 41.2, 40.2, 36.2, 27.5, 22.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.0; IR (Neat Film NaCl) 2945, 1715, 1326, 1164, 1123, 1068 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{18}H_{19}F_3O_3$ [M]$^+$: 340.1286, found 340.1277.



258

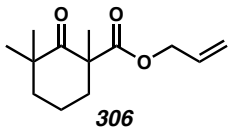
Allyl 1-((*tert*-butyldiphenylsilyloxy)methyl)-2-oxocyclohexanecarboxylate (258, Table 3.2, entry 9): To a solution of **305** (vide supra) (1.20 g, 5.71 mmol. 1.0 equiv), imidazole (583 mg, 8.57 mmol, 1.5 equiv), and DMAP (1.04 g, 8.57 mmol, 1.5 equiv) in DMF (20 mL) was added TBDPS-Cl (1.75 mL, 6.85 mmol, 1.2 equiv). After 24 h at ambient temperature, the reaction mixture was poured into water (75 mL) and 2:1 CH_2Cl_2:hexanes (150 mL), extracted with 2:1 CH_2Cl_2:hexanes (4 x 30 mL), dried (Na_2SO_4), and evaporated. Flash chromatography (SiO_2, 2.5→12% EtOAc in hexanes) gave the desired compound (1.85 g, 72% yield). mp 59-60 °C; R_f = 0.24 (10% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.68 (m, 4H), 7.48-7.37 (m, 6H), 6.00-5.86 (m, 1H), 5.38-5.31 (m, 1H), 5.28-5.23 (m, 1H), 4.74-4.59 (m, 2H), 4.24 (d, *J* = 9.9 Hz, 1H), 3.82 (d, *J* = 9.9 Hz, 1H), 2.78 (dq, *J* = 13.4, 3.3 Hz, 1H), 2.53-2.38 (m, 2H), 2.10-1.99 (m, 1H), 1.88-1.54 (m, 4H) 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.4, 169.8, 135.6, 135.5, 133.1, 132.9, 131.5, 129.6, 127.6 (2C), 118.8, 66.4, 65.8, 62.9, 41.2, 33.6, 27.3, 26.6, 22.1, 19.2; IR (Neat Film NaCl) 3072, 2933, 2858, 1715, 1428, 1200, 1112, 703 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{27}H_{33}O_4Si$ $[M - H]^+$: 449.2148, found 449.2165.



260

Allyl 1-fluoro-2-oxocyclohexanecarboxylate (260, Table 3.2, entry 10): To a solution of ketoester **242** (946.4 mg, 5.19 mmol, 1 equiv) in 50 mL CH_3CN, was added $TiCl_4$ (50 μL, 0.456 mmol, 0.09 equiv). Select-fluor® (2.2224 g, 6.27 mmol, 1.2 equiv)

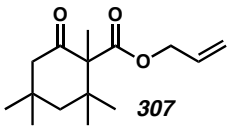
was added after 10 min and the mixture stirred at room temperature for 2 h and 40 min, over which time the orange color disappeared. The mixture was partitioned between H_2O (200 mL) and Et_2O (50 mL). The aqueous layer was separated and washed with Et_2O (30 mL). The combined organic layers were dried ($MgSO_4$), concentrated to about 30 mL, passed through a pad of silica that was washed with Et_2O (5 x 10 mL), and evaporated *in vacuo*. The residue was then bulb-to-bulb distilled at 180–190 °C (bath temp, 2 torr) to afford the title compound as a colorless oil (947.6 mg, 91% yield). R_f = 0.19 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (dddd, J = 5.7, 5.7, 10.5, 17.1 Hz, 1H), 5.37 (dddd, J = 1.5, 1.5, 1.5, 17.4 Hz, 1H), 5.29 (dddd, J = 1.5, 1.5, 1.5, 10.5 Hz, 1H), 4.73 (bd, J = 5.7 Hz, 2H), 2.80-2.67 (m, 1H), 2.66-2.38 (m, 2H), 2.24-2.10 (m, 1H), 1.98-1.80 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5 (d, $J_{C\text{-}F}$ = 19.8 Hz), 166.4 (d, $J_{C\text{-}F}$ = 24.8 Hz), 130.8, 119.2, 96.2 (d, $J_{C\text{-}F}$ = 196.9 Hz), 66.5, 39.4, 35.8 (d, $J_{C\text{-}F}$ = 21.8 Hz), 26.4, 20.7 (d, $J_{C\text{-}F}$ = 6.0 Hz); IR (Neat Film NaCl) 3087, 2952, 1759, 1735, 1650, 1452, 1281, 1223, 1150, 1097, 990 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{10}H_{13}O_3F$ $[M]^+$: 200.0849, found 200.0858.



306

Allyl 1,3,3-trimethyl-2-oxocyclohexanecarboxylate (306, Table 3.3, entry 3): To a cooled (–78 °C) solution of LDA (13.5 mmol, 1.12 equiv) in THF (30 mL) was added 2,2,6-trimethylcyclohexanone (1.6938 g, 12.08 mmol, 1.0 equiv) dropwise. The resulting solution was warmed to 0 °C for 1 h, cooled to –78 °C and HMPA (2.2 mL, 12.6 mmol, 1.04 equiv) was added. After 5 min, allyl cyanoformate (**246**)[57] (1.5014 g, 13.5 mmol,

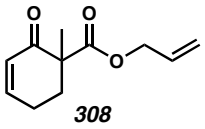
1.12 equiv) was added dropwise. The reaction was warmed to room temperature and allowed to stir overnight. The reaction was then quenched with 50% saturated aq NH_4Cl (40 mL). The aqueous layer was separated and washed with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (SiO_2, 3% Et_2O in hexanes) to afford the β-ketoester as a colorless oil (585.6 mg, 22%), along with the known enol carbonate (vide supra, R_f = 0.53, 10:1 hexane:EtOAc) as a colorless oil (1.3117 g, 48%). R_f = 0.50 (10:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (dddd, *J* = 5.7, 5.7, 10.2, 16.8 Hz, 1H), 5.30 (dddd, *J* = 1.2, 1.2, 1.2, 17.1 Hz, 1H), 5.22 (dddd, *J* = 0.9, 0.9, 0.9, 10.2 Hz, 1H), 4.62 (dddd, *J* = 1.2, 1.2, 5.7, 13.2 Hz, 1H), 4.51 (dddd, *J* = 1.2, 1.2, 5.7, 13.2 Hz, 1H), 2.54 (dddd, *J* = 2.4, 3.9, 3.9, 13.8 Hz, 1H), 1.98 (ddddd, *J* = 3, 4.2, 12, 14.1, 15.6 Hz, 1H), 1.77-1.68 (m, 1H), 1.66-1.52 (m, 2H), 1.42 (ddd, *J* = 4.2, 12.3, 13.8, 1H), 1.32 (s, 3H), 1.09 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.4, 172.4, 131.5, 118.8, 65.7, 55.1, 46.1, 40.6, 36.8, 26.8, 25.5, 23.6, 18.5; IR (Neat Film NaCl) 3089, 2938, 1736, 1707, 1649, 1456, 1377, 1243, 1209, 1174, 1150, 972 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{13}H_{20}O_3$ $[M]^+$: 224.1413, found 224.1413.



307

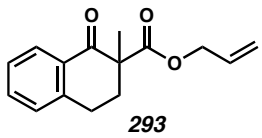
Allyl 1,2,2,4,4-pentamethyl-6-oxocyclohexanecarboxylate (307, Table 3.3, entry 4): Prepared by a modification of general procedure 2. Part A: Reaction of 3,3,5,5-tetramethylcyclohexanone in benzene (1 M) at 80 °C for 40 h using NaH (2 equiv) and diallylcarbonate (3 equiv) gave an ~1:1 mixture of mono- and bis-acylated material after

flash chromatography (SiO_2, 1 → 8% Et_2O in hexanes). Part B: Reaction in acetone (0.42 M) at 75 °C in a sealed flask for 24 h using Cs_2CO_3 (3 equiv) and MeI (4 equiv). Flash chromatography (SiO_2, 1→4% Et_2O in hexanes) gave the desired compound. 25% overall yield. R_f = 0.60 (25% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (dddd, *J* = 17.4, 10.5, 6.0, 6.0 Hz, 1H), 5.29 (d, *J* = 17.1 Hz, 1H), 5.22 (d, *J* = 10.5 Hz, 1H), 4.55 (d, *J* = 6.0 Hz, 2H), 2.78 (d, *J* = 13.5 Hz, 1H), 2.23-2.12 (comp. m, 2H), 1.33 (d, *J* = 14.4 Hz, 1H), 1.26 (s, 3H), 1.11 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9, 171.5, 131.5, 118.8, 65.5, 62.6, 51.7, 49.4, 40.9, 34.8, 34.5, 29.6, 27.7, 26.9, 14.7; IR (Neat Film NaCl) 3087, 2959, 1715, 1456, 1371, 1216, 1101, 979 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{15}H_{24}O_3$ [M]$^+$: 252.1725, found 252.1719.



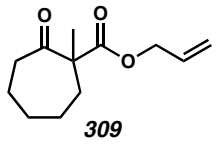
308

Allyl 1-methyl-2-oxocyclohex-3-enecarboxylate (308, Table 3.3, entry 5): Prepared by general procedure 2 from cyclohex-2-en-1-one. Flash chromatography (SiO_2, CH_2Cl_2). 23% yield. R_f = 0.38 (30% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (m, 1H), 6.06 (dt, *J* = 10.1, 2.1 Hz, 1H), 5.86 (dddd, *J* = 17.3, 10.4, 5.6, 5.6 Hz, 1H), 5.24 (m, 2H), 4.61 (m, 2H), 2.57-2.41 (m, 2H), 2.41-2.27 (m, 1H), 1.97-1.82 (m, 1H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 172.3, 149.4, 131.6, 128.9, 118.3, 65.7, 53.4, 33.3, 23.6, 20.3; IR (Neat Film NaCl) 2936, 1733, 1678, 1249, 1192, 1110 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{14}O_3$ [M]$^+$: 194.0943, found 194.0941.



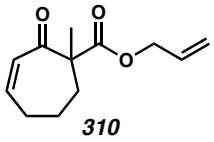
293

Allyl 2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (293, Table 3.3, entry 6): Prepared by general procedure 2 from 1-tetralone. Flash chromatography (SiO_2, 10% Et_2O in pentane). 60% yield. R_f = 0.61 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.8 Hz, 1H), 7.47 (app. t, *J* = 7.5 Hz, 1H), 7.31 (app. t, *J* = 8.1 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 5.79 (dddd, *J* = 17.1, 10.7, 5.4, 5.4 Hz, 1H), 5.19-5.09 (m, 2H), 4.58 (m, 2H), 3.12-2.87 (m, 2H), 2.68-2.57 (m, 1H), 2.13-2.01 (m, 1H), 1.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9, 172.5, 143.1, 133.4, 131.7, 131.5, 128.7, 128.0, 126.8, 118.0, 65.6, 53.9, 33.9, 26.0, 20.6; IR (Neat Film NaCl) 3071, 2982, 2938, 1736, 1690, 1602, 1456, 1377, 1308, 1228, 1189, 1112, 979, 743 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{15}H_{16}O_3$ $[M]^+$: 244.1099, found 244.1094.



309

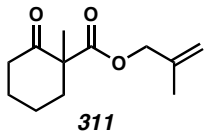
Allyl 1-methyl-2-oxocycloheptanecarboxylate (309, Table 3.3, entry 7): Prepared by general procedure 2 from cycloheptanone. Flash chromatography (SiO_2, 25→100% CH_2Cl_2 in pentane). 30% yield. R_f = 0.60 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (dddd, *J* = 17.3, 10.4, 5.6, 5.6 Hz, 1H), 5.26 (m, 2H), 4.61 (m, 2H), 2.81-2.67 (m, 1H), 2.57-2.45 (m, 1H), 2.25-2.11 (m, 1H), 1.91-1.70 (comp. m, 3H), 1.69-1.49 (comp. m, 4H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 131.6, 118.5, 65.6, 58.8, 42.0, 35.4, 30.1, 25.8, 24.7, 21.5; IR (Neat Film NaCl) 2936, 1740, 1710, 1229, 1151, 1105 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1249.



310

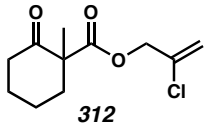
Allyl 1-methyl-2-oxocyclohept-3-enecarboxylate (310, Table 3.3, entry 8): To a cooled (–78 °C) solution of LHMDS (1.0 M soln in THF, 10 mL, 10 mmol, 1.5 equiv) in THF (20 mL) was added cyclohept-2-enone (759 μL, 6.73 mmol, 1.0 equiv). After 30 min, allyl cyanoformate (**246**)[57] (813 mg, 7.32 mmol, 1.1 equiv) was added. The reaction was allowed to stir at –78 °C for 30 min and was then quenched with 50% saturated aq NH_4Cl (40 mL) and allowed to thaw. The aqueous layer was separated and extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting oil was dissolved in 10 mL CH_3CN, then Cs_2CO_3 (3.3271 g, 10.21 mmol, 1.5 equiv) and MeI (2.1 mL, 33.73 mmol, 5.0 equiv) were added. The mixture was then heated to 80 °C for 4 h and then cooled to ambient temperature. The mixture was diluted with ~10 mL EtOAc and filtered through a 3 x 3 cm plug of silica gel which was then washed with 3 x 25 mL EtOAc. Evaportation in vacuo gave an oil that was purified by flash chromatography (3 x 24 cm, 15:1 hexanes:EtOAc) to afford the title compound as a colorless oil (735.2 mg, 52%). R_f = 0.20 (10:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (ddd, J = 4.8, 4.8, 12.6 Hz, 1H), 6.03 (ddd, J = 2.4, 2.4, 12.9 Hz, 1H), 5.86 (dddd, J = 5.4, 5.4, 10.8, 17.1 Hz, 1H), 5.29 (dddd, J = 1.5, 1.5, 1.5, 17.4 Hz, 1H), 5.21 (dddd, J = 1.2, 1.2, 1.2, 10.5 Hz, 1H), 4.65-4.59 (m, 1H), 4.59-4.52 (m, 1H), 2.44-2.30 (m, 3H), 2.10 (m, 1H), 1.82-1.65 (m, 2H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 173.3, 143.2, 131.6, 130.9, 118.2, 65.6, 59.9, 34.2, 31.5, 23.3, 23.1; IR (Neat Film NaCl) 3080, 3018, 2937, 1737,

1686, 1454, 1377, 1232, 1171, 1113, 978, 931, 820 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{16}O_3$ $[M]^+$: 208.1100, found 208.1109.



311

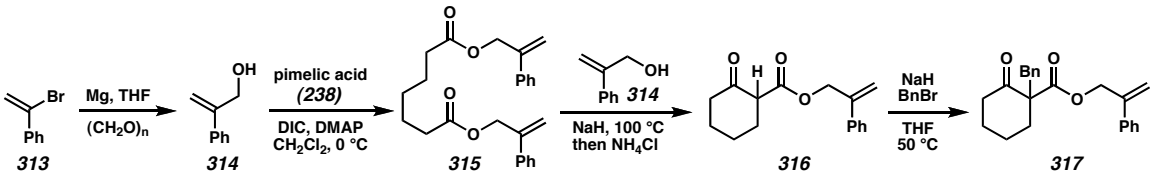
2-Methylallyl 1-methyl-2-oxocyclohexanecarboxylate (311, Table 3.3, entry 9): Prepared by general procedure 2 from cyclohexanone with dimethyallyl carbonate in part A. Flash chromatography (SiO_2, 10% Et_2O in pentane). 46% yield. R_f = 0.24 (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 4.94 (m, 2H), 4.54 (s, 2H), 2.58-2.42 (comp. m, 3H), 2.08-1.93 (m, 1H), 1.80-1.57 (comp. m, 6H), 1.55-1.40 (m, 1H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1, 172.8, 139.4, 113.5, 68.4, 57.2, 40.6, 38.2, 27.5, 22.6, 21.3, 19.5; IR (Neat Film NaCl) 2940, 2867, 1715, 1452, 1260, 1211, 1160, 1086, 907 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1256.



312

2-Chloroallyl 1-methyl-2-oxocyclohexanecarboxylate (312, Table 3.3, entry 10): Prepared by general procedure 2 from cyclohexanone with 1.25 equiv of 2-chloroallyl carbonate[60,61] in part A. Flash chromatography (SiO_2, 10% Et_2O in pentane). 62% yield. R_f = 0.20 (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.45 (m, 2H), 4.71 (m, 2H), 2.62-2.41 (comp. m, 3H), 2.10-1.93 (m, 1H), 1.81-1.62 (comp. m, 3H), 1.57-1.41 (m, 1H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.8, 172.3, 135.4, 115.8, 66.5, 57.2, 40.6, 38.2, 27.4, 22.5, 21.2; IR (Neat Film NaCl) 2942, 2868, 1716, 1640, 1453,

1248, 1221, 1153, 1084, 903 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{15}O_3Cl$ $[M]^+$: 230.0710, found 230.0711.



2-Phenylallyl alcohol (314).[62] A 250 mL two-neck round-bottomed flask equipped with an addition funnel, a condenser, a stir bar, and two septa was charged with Mg turnings (1.71 g, 70.3 mmol), cutting several turnings during addition. The system was then flame dried under vacuum. After refilling with Ar, anhydrous THF (50 mL) and bromoethane (300 μL, 4.02 mmol) were added via syringe. The flask was opened and iodine (110.9 mg, 0.437 mmol) was added under positive Ar pressure. The flask was then sealed and flushed with Ar. After stirring at 23 °C for 15 min, the reaction turned a greenish color. α-Bromostyrene (**313**, 8.4 mL, 64.7 mmol) in anhydrous THF (15 mL) was then added dropwise over 1 h via the addition funnel, during which time a significant exotherm was observed. The reaction was then placed in an oil bath and heated at reflux for 41 min. After cooling to 23 °C, the flask was opened, and paraformaldehyde (3.00 g, 99.9 mmol) was added. The flask was then sealed and flushed with Ar. After stirring at 23 °C for 1.5 h, saturated NH_4Cl (aq) (40 mL) and H_2O (40 mL) were added to quench the reaction and dissolve all solids. The mixture was extracted with Et_2O (3 x 40 mL), and the combined organic layers were washed with H_2O (2 x 50 mL) and brine (50 mL). After drying over $MgSO_4$, solvent was removed under reduced pressure. The crude product was then distilled under high vacuum to provide 2-phenylallyl alcohol (**314**)

(6.542 g, 75%) as a colorless liquid containing minor unidentified impurities by ^{1}H NMR spectroscopy. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.43 (m, 2H), 7.39-7.33 (m, 2H), 7.31-7.28 (m, 1H), 5.48 (dt, *J* = 0.9, 0.7 Hz, 1H), 5.36 (dt, *J* = 1.3, 1.2 Hz, 1H), 4.56 (ddd, *J* = 6.1, 1.3, 0.7 Hz, 2H), 1.58-1.52 (m, 1H).

Bis(ester) 315. A flame-dried 250 mL round-bottomed flask equipped with a stir bar and a septum was charged with 2-phenylallyl alcohol (**314**) (98.6% pure by mass (contained 1.4% CH_2Cl_2 by mass), 5.42 g, 39.8 mmol), pimelic acid (3.35 g, 20.9 mmol), and DMAP (1.95 g, 16.0 mmol). The flask was evacuated under high vacuum and refilled with Ar. Anhydrous CH_2Cl_2 (80 mL) was added via syringe, and the reaction was cooled to 0 °C in an ice bath. *N,N'*-Diisopropylcarbodiimide (6.4 mL, 41.3 mmol) was added in one portion via syringe, and the reaction was stirred for 5 min at 0 °C. The ice bath was removed, and the reaction was allowed to warm to 23 °C as it was stirred for 10.75 h. A white precipitate formed during this time. The reaction was filtered through filter paper and then diluted with CH_2Cl_2 (200 mL). The solution was washed with 0.1 M HCl (aq) (200 mL), saturated $NaHCO_3$ (aq) (100 mL), and brine (100 mL). After drying over $MgSO_4$, solvent was removed under reduced pressure. Flash chromatography over silica gel (10 x 5 cm silica, 20% Et_2O/pentane eluent) then provided bis(ester) **315** (6.251 g, 80%) as a colorless oil containing <1% Et_2O by mass. R_f 0.28 (20% Et_2O/pentane); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.53-7.44 (m, 4H), 7.43-7.27 (m, 6H), 5.60-5.55 (m, 2H), 5.37 (dt, *J* = 1.2, 1.1 Hz, 2H), 5.02-4.98 (m 4H), 2.28 (t, *J* = 7.4 Hz, 4H), 1.59-1.47 (m, 4H), 1.32-1.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 142.6, 138.0, 128.4, 128.0, 126.0, 115.2, 65.5, 34.0, 28.4, 24.5; IR (Neat film, NaCl) ν 3084, 3057, 3031, 2938, 2864, 1736, 1633, 1601, 1575, 1496, 1462, 1445, 1417, 1383, 1320, 1309, 1227, 1167,

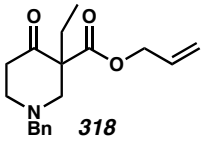
1083, 1027, 1014, 987, 911, 779, 708 cm^{-1}; HRMS (EI+) *m/z* calc'd. for $C_{25}H_{28}O_4$ $[M]^+$: 392.1988, found 392.1998.

β-ketoester 316. A flame-dried 100 mL round-bottomed flask equipped with a stir bar and a septum was charged with NaH (60% dispersion in mineral oil, 679 mg, 17.0 mmol) and evacuated under high vacuum. After refilling with Ar, anhydrous toluene (50 mL) was added via syringe. 2-Phenylallyl alcohol (**314**) (182 mg, 1.36 mmol) in anhydrous toluene (1 mL) was added via syringe, washing the original flask with anhydrous toluene (1 mL). Bis(ester) **315** (6.079 g, 15.5 mmol) in anhydrous toluene (4 mL) was added via syringe, washing the original flask with anhydrous toluene (4 mL). The reaction was then placed in an oil bath and stirred at 100 °C for 15.7 h. After cooling to 23 °C, saturated NH_4Cl (aq) (50 mL) and 1 M HCl (aq) (25 mL) were added to quench the reaction. The mixture was extracted with Et_2O (2 x 50 mL), and the combined organic layers were washed with 50% H_2O/50% brine (150 mL) and brine (150 mL). After drying over $MgSO_4$, solvent was removed under reduced pressure. Flash chromatography over silica gel (10 x 5 cm silica, 10% Et_2O/pentane eluent) then provided β-ketoester **316** (3.172 g, 78%) as a colorless oil containing 2.2% pentane by mass. A 2.7:1 ratio of enol:ketone tautomer was observed by ^1H NMR spectroscopy. R_f 0.19-0.60 (10% Et_2O/pentane, appears as a streak on TLC plate); ^1H NMR (300 MHz, $CDCl_3$) δ 12.1 (s, 0.73 H), 7.48-7.40 (m, 2H), 7.40-7.28 (m, 3H), 5.58-5.55 (m, 1H), 5.41-5.36 (m, 1H), 5.15-5.00 (m 2H), 3.43-3.35 (m, 0.27H), 2.52-1.52 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0, 172.6, 172.2, 169.7, 142.5, 142.2, 138.1, 137.8, 128.47, 128.45, 128.06, 128.03, 126.02, 125.95, 115.7, 114.7, 97.6, 66.3, 65.2, 57.2, 41.4, 29.9, 29.1, 27.0, 23.2, 22.31, 22.28, 21.8; IR (Neat film, NaCl) ν 3084, 3057, 2938, 2859,

1744, 1715, 1655, 1614, 1576, 1496, 1446, 1421, 1396, 1357, 1334, 1294, 1258, 1216, 1175, 1108, 1080, 1059, 1028, 973, 909, 830, 815, 778, 708 cm^{-1}; HRMS (EI+) *m/z* calc'd. for $C_{16}H_{18}O_3$ $[M]^+$: 258.1256, found 258.1250.

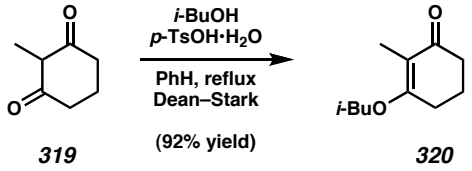
β-ketoester 317 (Table 3.3, entry 11). A flame-dried 1 dram screw-cap vial equipped with a stir bar and a septum-bearing cap was charged with NaH (60% dispersion in mineral oil, 31.7 mg, 0.793 mmol) and evacuated under high vacuum. After refilling with Ar, anhydrous THF (0.4 mL) was added via syringe. β-Ketoester **316** (200 mg, 0.774 mmol) in anhydrous THF (0.5 mL) was added dropwise via syringe, washing the original flask with anhydrous THF (0.5 mL). Benzyl bromide (120 μL, 1.01 mmol) was then added in one portion via syringe. The vial cap was wrapped in Teflon tape, and the Ar inlet was removed. The reaction was then placed in an oil bath and stirred at 55 °C for 5.25 h. After cooling to 23 °C, saturated NH_4Cl (aq) (0.5 mL) and H_2O (0.5 mL) were added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with 50% H_2O/50% brine (15 mL), and brine (15 mL), then dried over $MgSO_4$. Solvent was removed under reduced pressure. Flash chromatography over silica gel (7 x 2 cm silica, 20% Et_2O/pentane eluent) then provided β-ketoester **317** (199 mg, 73%) as a thick yellow syrup containing <1% Et_2O by mass. R_f 0.45 (20% Et_2O/pentane); ^1H NMR (300 MHz, CD_3OD) δ 7.42-7.24 (m, 5H), 7.26-7.11 (m, 3H), 7.08-7.01 (m, 2H), 5.53 (d, *J* = 1.1 Hz, 1H), 5.32 (ddd, *J* = 1.1 Hz, 1H), 5.05 (dd, *J* = 12.8, 1.1 Hz, 1H), 4.90 (dd, *J* = 12.9, 0.9 Hz, 1H), 3.18 (d, *J* = 13.6 Hz, 1H), 2.78 (d, *J* = 13.6 Hz, 1H), 2.34-1.98 (m, 3H), 1.91-1.73 (m, 1H), 1.68-1.34 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD) δ 208.5, 172.0, 144.3, 139.3, 137.8, 131.4, 129.6, 129.2, 129.0, 127.7, 127.3, 117.0, 67.6, 63.4, 42.0,

41.4, 36.8, 28.6, 23.3; IR (Neat film, NaCl) ν 3086, 3060, 3029, 2941, 2866, 1714, 1634, 1603, 1575, 1496, 1453, 1442, 1309, 1264, 1248, 1216, 1175, 1133, 1086, 1053, 1030, 1003, 987, 963, 913, 804, 779, 743, 702 cm^{-1}; HRMS (EI+) *m/z* calcd. for $C_{23}H_{24}O_3$ $[M]^+$: 348.1726, found 348.1712.



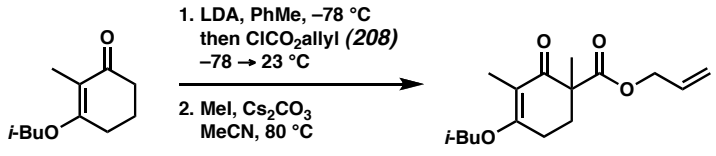
318

Allyl 1-benzyl-3-ethyl-4-oxopiperidine-3-carboxylate (318, Table 3.3, entry 12): Prepared by general procedure 2 from 1-benzylpiperidin-4-one (part A) and iodoethane (part B). Flash chromatography (SiO_2, 2.5→20% EtOAc in hexanes). 55% yield. R_f = 0.50 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.25 (m, 5H), 5.90 (dddd, *J* = 17.4, 10.7, 5.7, 5.7 Hz, 1H), 5.33 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.24 (dq, *J* = 10.4, 1.5 Hz, 1H), 4.70 (ddt, *J* = 13.0, 6.0, 1.4 Hz, 1H), 4.62 (ddt, *J* = 13.0, 6.0, 1.4 Hz, 1H), 3.62 (d, *J* = 13.2 Hz, 1H), 3.56 (d, *J* = 13.2 Hz, 1H), 3.42 (dd, *J* = 11.4, 2.7 Hz, 1H), 3.04-2.80 (m, 2H), 2.45-2.35 (m, 2H), 2.25 (d, *J* = 11.7 Hz, 1H), 1.94-1.82 (m, 1H), 1.65-1.53 (m, 1H), 0.87 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9, 171.3, 137.9, 131.7, 128.8, 128.2, 127.3, 118.7, 65.6, 61.8, 61.5, 61.0, 53.5, 40.6, 25.2, 9.1; IR (Neat Film NaCl) 2966, 2939, 1719, 1224, 1139, 699 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{18}H_{23}O_3$ $[M]^+$: 301.1678, found 301.1691.



319 ***320***

Vinylogous Ester 320.[63] Diketone **319** (3.000 g, 23.78 mmol, 1.0 equiv) was partially dissolved in PhH (42.5 mL, 0.56 M), and *i*-BuOH (12.75 mL, 137.9 mmol, 5.8 equiv) and *p*-TsOH•H_2O (226 mg, 1.19 mmol, 0.05 equiv) were added with vigorous stirring. The flask was affixed with a Dean–Stark adapter and a water-cooled condenser and warmed to reflux in a 104 °C oil bath. Upon consumption of **319** by TLC analysis (ca. 3.5 h), the reaction was cooled to ambient temperature, diluted with Et_2O (50 mL), and poured into saturated aq $NaHCO_3$ (20 mL). The layers were separated and the aqueous was extracted with Et_2O (3 x 15 mL). The organics were combined, washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo to afford a pale brown oil. To this oil was added PhMe (ca. 10 mL) followed by further concentration in vacuo. Purification by bulb-to-bulb distillation yielded vinylogous ester **320** (3.988 g, 21.88 mmol, 92% yield) as a clear, colorless oil. R_f = 0.48 (2:1 EtOAc-hexanes); bp =135–140 °C at 0.8 torr; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76 (d, *J* = 6.5 Hz, 2H), 2.54 (ddd, *J* = 6.1, 1.5, 1.5 Hz, 2H), 2.34 (t, *J* = 7.1 Hz, 2H), 2.08-1.90 (comp m, 3H), 1.72 (app t, *J* = 1.5 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 6H). All other data were consistent with reported values.

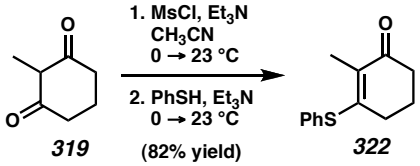


320 (55% yield) *(±)-321*

(±)-β-Ketoester 321 (Table 3.3, entry 13). To a –78 °C solution of *i*-Pr_2NH (425 μL, 3.03 mmol, 1.9 equiv) in PhMe (10 mL) was added dropwise *n*-BuLi (2.55 M in hexanes, 1.16 mL, 2.96 mmol, 1.85 equiv). The reaction vessel was placed in an ice/water bath and allowed to stir for 10 min, and then cooled to –78 °C. A solution of vinylogous ester **320** (291 mg, 1.60 mmol, 1.0 equiv) in PhMe (1.4 mL) was added dropwise via cannula to the reaction vessel, and the resulting solution was allowed to stir for 30 min. Allyl chloroformate (**208**, 173 μL, 1.63 mmol, 1.02 equiv) was added dropwise, and the reaction vessel was allowed to warm to 23 °C over 1 h. After stirring for 4 h, the reaction was slowly quenched with aq $KHSO_4$ (1 N, 4 mL) and the resulting biphasic mixture was allowed to stir for 10 min. The phases were separated, and the aq phase was extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The isolated crude yellow oil was used in the next step without further purification.

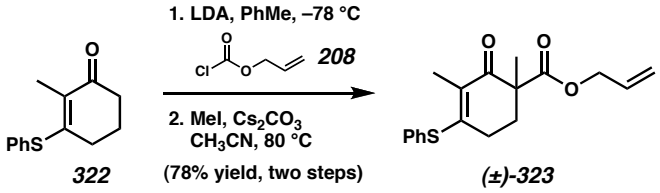
The resulting crude yellow oil was dissolved in MeCN (5.9 mL, 0.27 M), and Cs_2CO_3 (603 mg, 1.85 mmol, 1.16 equiv), and MeI (276 μL, 4.44 mmol, 2.8 equiv) were added. The flask was affixed a water-cooled condenser and resulting suspension was warmed to reflux in an 80 °C oil bath with vigorous stirring. After 10 h, the reaction was cooled to room temperature, diluted with EtOAc (25 mL). The organics were dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. Purification by flash chromatography (15:1 → 9:1 → 4:1 hexanes-EtOAc) afforded β-ketoester (±)-**321** as pale yellow oil (246

mg, 55% yield over two steps). R_f = 0.27 (2:1 hexanes-EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.82 (dddd, *J* = 17.2, 10.7, 5.4, 5.4 Hz, 1H), 5.22 (dddd, *J* = 17.2, 1.6, 1.6, 1.6 Hz, 1H), 5.15 (dddd, *J* = 10.5, 1.2, 1.2, 1.2 Hz, 1H), 4.56 (dddd, *J* = 13.5, 5.4, 1.5, 1.5 Hz, 2H), 3.72 (ddd, *J* = 9.2, 6.6, 3.2 Hz, 2H), 2.69-2.62 (m, 1H), 2.53-2.44 (comp m, 2H), 1.95 (app septuplet, *J* = 6.6 Hz, 1H), 1.85-1.80 (m, 1H), 1.70 (dd, *J* = 1.5, 1.5 Hz, 3H), 1.36 (s, 3H), 0.95 (dd, *J* = 6.7, 0.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 195.8, 172.6, 170.3, 131.9, 117.8, 113.8, 73.9, 65.5, 51.6, 31.2, 28.8, 23.0, 20.8, 19.1, 19.0, 8.0; IR (Neat Film NaCl) 2961, 2935, 2875, 1733, 1649, 1618, 1460, 1382, 1354, 1237, 1176, 1103, 983 cm^{-1}; HRMS (FAB+) *m/z*: calc'd for $C_{16}H_{25}O_4$ $[M + H]^+$: 281.1753, found 281.1740.



Vinylogous Thioester 322.[64] To a solution of diketone **319** (5.00 g, 39.82 mmol, 1.00 equiv) in CH_3CN (44 mL) was added Et_3N (6.2 mL, 44.40 mmol, 1.12 equiv), and the solution was allowed to stir for 5 min, then cooled to 0 °C. Methanesulfonyl chloride (3.26 mL, 42.00 mmol, 1.06 equiv) was added, and the reaction was warmed to 23 °C over 2 h. Stirring was continued for 5 h, and the reaction was cooled to 0 °C. Triethylamine (6.2 mL, 44.40 mmol, 1.12 equiv) was added, followed by benzenethiol (4.2 mL, 40.80 mmol, 1.03 equiv). The reaction was allowed to warm to 23 °C over 2 h and stirring was continued for 9 h. Saturated aq Na_2CO_3 (70 mL) was added, the phases were separated, and the aq phase was extracted with Et_2O (3 x 120 mL). The combined

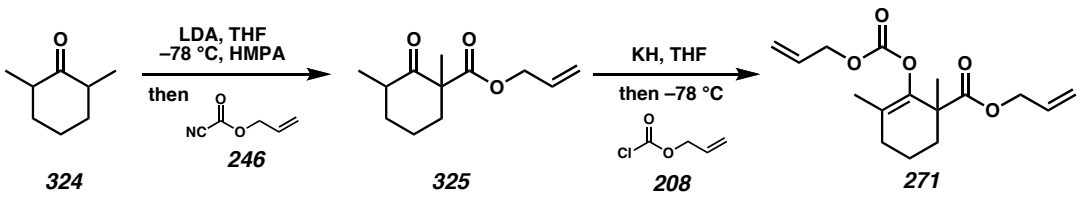
organic extracts were dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. Purification by flash chromatography (18% EtOAc in hexanes) afforded vinylogous thioester **322** (7.15 g, 82% yield) as a white crystalline solid. R_f = 0.33 (20% EtOAc in hexanes); mp 85 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.49 (m, 2H), 7.44-7.37 (comp m, 3H), 2.38 (t, J = 6.5 Hz, 2H), 2.18 (tq, J = 6.5, 2.0 Hz, 2H), 1.97 (t, J = 2.0 Hz, 3H), 1.87 (app pentuplet, J = 6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.6, 157.9, 130.3(2C), 129.6, 129.5, 37.3, 30.5, 22.9, 12.4; IR (Neat Film NaCl) 2944, 1655, 1578, 1339, 1296 cm^{-1}; HRMS (FAB+) *m/z*: calc'd for $C_{13}H_{14}OS$ [M + H]$^+$: 219.0844, found 219.0843.



β-Ketoester 323 (Table 3.3, entry 14).[65] To a –78 °C solution of diisopropylamine (2.63 mL, 18.78 mmol, 2.00 equiv) in toluene (70 mL) was added dropwise *n*-BuLi (2.53 M in hexanes, 7.24 mL, 2.00 equiv). The reaction vessel was warmed to 0 °C, allowed to stir for 10 min, and cooled to –78 °C. A solution of thioester **322** (2.00 g, 9.16 mmol, 1.00 equiv) in toluene (15 mL) was added dropwise via cannula to the reaction vessel, and the resulting solution was allowed to stir for 30 min. Allyl chloroformate (1.02 mL, 9.62 mmol, 1.05 equiv) was added dropwise, and the reaction vessel was allowed to warm to 23 °C over 1 h. Stirring was continued for 4 h, then aq $KHSO_4$ (1 N, 70 ml) was added, and the resulting solution was allowed to stir for 10 min. The phases were separated, and the aq phase was extracted with Et_2O (3 x 30 mL). The combined organic

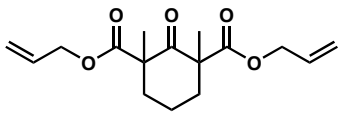
extracts were washed with brine (1 x 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The isolated crude yellow oil was used in the next step without further purification.

To a solution of the crude yellow oil (3.32 g) in CH_3CN (40 mL) was added cesium carbonate (4.48 g, 13.74 mmol, 1.50 equiv), and iodomethane (1.71 mL, 27.48 mmol, 3.00 equiv). The resulting suspension was refluxed at 80 °C for 5 h, and then MeI (1.00 mL, 16.06 mmol, 1.75 equiv) was added. The reaction was refluxed at 80 °C for 2 h, cooled to room temperature, filtered through Celite (EtOAc eluent), dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. Purification by flash chromatography (18% EtOAc in hexanes) afforded β-ketoester (±)-**323** (2.26 g, 78% yield over two steps) as white solid. R_f = 0.35 (30% EtOAc in hexanes); mp 34 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.35 (comp m, 5H), 5.87 (app ddt, *J* = 10.5, 17.1, 5.4 Hz, 1H), 5.27 (app ddt, *J* = 17.1, 1.7, 1.8 Hz, 1H), 5.22 (app ddt, *J* = 9.9, 1.7, 1.2 Hz, 1H), 4.65 (dddd, *J* = 1.5, 1.8, 5.7, 13.5 Hz, 1H), 4.55 (dddd, *J* = 1.5, 1.8, 5.7, 13.5 Hz, 1H), 2.41-2.32 (m, 1H), 2.30-2.21 (m, 1H), 2.16-2.06 (1H), 2.00 (t, *J* = 1.8 Hz, 3H), 1.78 (ddd, *J* = 4.5, 8.1, 13.2 Hz, 1H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0, 172.6, 156.7, 135.6, 131.9, 129.7, 129.5, 128.9, 118.1, 65.7, 52.3, 33.1, 27.4, 20.7, 12.9; IR (Neat Film NaCl) 2936, 1733, 1656, 1580, 1314, 1254, 1238, 1174, 985, 752, 693 cm^{-1}; HRMS (FAB+) *m/z*: calc'd for $C_{18}H_{20}O_3S$ $[M + H]^+$: 317.1211, found 317.1211.



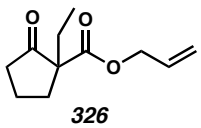
Allyl 1,3-dimethyl-2-oxocyclohexanecarboxylate (325): To a cooled (–78 °C) solution of LDA (8.0 mmol, 1.09 equiv) in THF (24 mL) was added 2,6-dimethylcyclohexanone (**324**, 1 mL, 7.33 mmol, 1.0 equiv) dropwise. The resulting solution was warmed to 0 °C for 1 h, cooled to –78 °C and HMPA (1.3 mL, 7.47 mmol, 1.02 equiv) was added. After 15 min, allyl cyanoformate (**246**)[57] (845.3 mg, 7.61 mmol, 1.04 equiv) was added dropwise. The reaction was warmed to ambient temperature for 30 min and then quenched with 50% saturated aq NH_4Cl. The aq layer was separated and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting oil was purified by flash chromatography (3 x 20 cm, SiO_2, 4% Et_2O in hexanes, then 8% Et_2O in hexanes) to afford β-ketoester **325** as a colorless oil (629.1 mg, 41%), along with the corresponding enol carbonate as a colorless oil (187.1 mg, 12%); R_f = 0.43 (10:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (dddd, J = 6.0, 6.0, 10.5, 17.4 Hz, 1H), 5.28 (dddd, J = 1.5, 1.5, 1.5, 17.1 Hz, 1H), 5.22 (dddd, J = 1.2, 1.2, 1.2, 10.5 Hz, 1H), 4.63 (dddd, J = 1.2, 1.2, 5.4, 13.2 Hz, 1H), 4.56 (dddd, J = 1.5, 1.5, 5.7, 13.2 Hz, 1H), 2.61-2.46 (m, 2H), 2.01 (dddd, J = 3.2, 3.2, 6.3, 16.2 Hz, 1H), 1.85-1.63 (m, 2H), 1.45-1.31 (m, 2H), 1.28 (s, 3H), 1.03 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.1, 172.9, 131.5, 118.7, 65.6, 57.1, 44.3, 38.9, 36.7, 22.8, 21.5, 14.7; IR (Neat Film NaCl) 3087, 2936, 1743, 1715, 1649, 1452, 1377, 1253, 1214, 1161, 976 cm^{-1}; HRMS (EI) m/z calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1249.

Allyl 2-(allyloxycarbonyloxy)-1,3-dimethylcyclohex-2-enecarboxylate (271, Scheme 3.7a): To a suspension of KH (155.9 mg, 3.89 mmol, 1.2 equiv, from a ~30% dispersion in mineral oil, oil removed by washing with hexane) in 10 mL THF was added **325** (680.9 mg, 3.24 mmol, 1 equiv) dropwise. The mixture was stirred at room temperature for 2.5 h, at which time it was cooled to –78 °C. Allyl chloroformate (**208**, 420 μL, 3.95 mmol, 1.2 equiv) was added and the mixture stirred 30 min at –78 °C, then 30 min at room temperature. The reaction was quenched with 50% saturated aq NH_4Cl (10 mL). Et_2O (5 mL) was added and the organic layer separated. The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. Silica gel chromatography (2 x 16 cm, 20:1 hexanes:EtOAc) afforded the title compound **271** as a colorless oil (883 mg, 93% yield). R_f = 0.29 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (dddd, *J* = 5.7, 5.7, 10.2, 17.1 Hz, 1H), 5.90 (dddd, *J* = 5.7, 5.7, 10.5, 17.1 Hz, 1H), 5.37 (dddd, *J* = 1.2, 1.2, 1.2, 17.1 Hz, 1H), 5.31 (dddd, *J* = 1.2, 1.2, 1.2, 17.1 Hz, 1H), 5.27 (dddd, *J* = 1.2, 1.2, 1.2, 10.2 Hz, 1H), 5.20 (dddd, *J* = 1.5, 1.5, 1.5, 10.5 Hz, 1H), 4.66-4.58 (m. 3H), 4.55 (dddd, *J* = 1.2, 1.2, 5.4, 13.5 Hz, 1H), 2.25-2.10 (m, 3H), 1.80-1.52 (m, 3H), 1.58 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 152.9, 142.0, 132.2, 131.5, 124.7, 118.9, 117.7, 68.7, 65.5, 46.7, 35.8, 30.6, 22.4, 19.2, 17.0; IR (Neat Film NaCl) 3087, 2942, 1760, 1732, 1649, 1452, 1366, 1235, 1168, 992 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{16}H_{22}O_5$ $[M]^+$: 294.1467, found 294.1464.



273

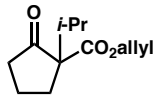
Diallyl 1,3-dimethyl-2-oxocyclohexane-1,3-dicarboxylate (273, Scheme 3.7b): Prepared by general procedure 2 using (±)-**107**. First diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (dddd, *J* = 5.7, 5.7, 10.4, 17.0 Hz, 2H), 5.30 (dddd, *J* = 1.4, 1.4, 3.1, 17.0 Hz, 2H), 5.23 (dddd, *J* = 1.4, 1.4, 2.7, 10.4 Hz, 2H), 4.65 (dddd, *J* = 1.4, 1.4, 5.6, 13.4 Hz, 2H), 4.44 (dddd, *J* = 1.4, 1.4, 5.6, 13.4 Hz, 2H), 2.55-2.50 (m, 2H), 2.23 (dtt, *J* = 4.1, 12.3, 14.5 Hz, 1H), 1.67 (dtt, *J* = 4.4, 4.4, 14.5 Hz, 1H), 1.54–1.47 (m, 2H), 1.39 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.9, 171.7, 131.9, 118.4, 66.1, 57.1, 37.3, 23.6, 19.6; IR (Neat Film NaCl) 3086, 2937, 1726, 1710, 1648, 1456, 1378, 1240, 1183, 1149, 975 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{16}H_{22}O_5$ $[M + H]^+$: 295.1540, found 295.1538. Second diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (dddd, *J* = 6.1, 6.1, 10.4, 17.1 Hz, 2H), 5.32 (dddd, *J* = 1.6, 1.6, 1.6, 17.1 Hz, 2H), 5.24 (dddd, *J* = 1.3, 1.3, 1.3, 10.4 Hz, 2H), 4.63-4.60 (comp. m, 4H), 2.44 (ddd, *J* = 6.0, 6.0, 13.0 Hz, 2H), 1.82 (dtt, *J* = 6.8, 6.8, 0.5 Hz, 2H), 1.85–1.80 (m, 2 H), 1.73–1.67 (m, 2H), 1.36 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.1, 172.4, 131.7, 118.9, 66.1, 56.9, 35.3, 22.3, 17.9; IR (Neat Film NaCl) 2984, 2940, 2877, 1734, 1709, 1647, 1458, 1378, 1234, 1150, 1119, 9780 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{16}H_{22}O_5$ $[M + H]^+$: 295.1540, found 295.1535.



326

Allyl 1-ethyl-2-oxocyclopentanecarboxylate (326, Table 3.4, entry 1): Prepared by general procedure 2 part B from allyl 2-cyclopentanonecarboxylate[66] and using ethyl

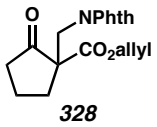
iodide as the electrophile. Flash chromatography (3 x 25 cm SiO_2, 10% Et_2O in hexanes) afforded the title compound as a colorless oil (1.5335 g, 85% yield). R_f = 0.27 (10:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (dddd, *J* = 5.7, 5.7, 10.5, 17.4 Hz, 1H), 5.30 (dddd, *J* = 1.6, 1.6, 1.6, 17.1 Hz, 1H), 5.23 (dddd, *J* = 1.4, 1.4, 1.4, 10.5 Hz, 1H), 4.60 (dddd, *J* = 1.4, 1.4, 1.4, 5.7 Hz, 2H), 2.57-2.36 (m, 2H), 2.31-2.19 (m, 1H), 2.08-1.86 (m, 4H), 1.64 (dddd, *J* = 7.5, 7.5, 7.5, 21 Hz, 1H), 0.89 (dd, *J* = 7.2, 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.6, 170.6, 131.5, 118.1, 65.5, 60.7, 37.9, 32.0, 26.6, 19.4, 9.0; IR (Neat Film NaCl) 3085, 2971, 1752, 1726, 1225, 1142 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{16}O_3$ $[M]^+$: 196.1100, found 196.1099.



327

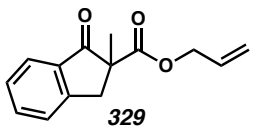
Allyl 1-isopropyl-2-oxocyclopentanecarboxylate (327, Table 3.4, entry 2): Prepared by general procedure 2 part B from allyl 2-cyclopentanonecarboxylate[66] and using 2-iodopropane as the electrophile. Flash chromatography (3 x 25 cm SiO_2, 10%→30% Et_2O in hexane) afforded the title compound as a colorless oil (1.5521 g, 82% yield). R_f = 0.32 (10:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (dddd, *J* = 5.7, 5.7, 10.5, 17.1 Hz, 1H), 5.30 (dddd, *J* = 1.6, 1.6, 1.6, 17.4 Hz, 1H), 5.22 (dddd, *J* = 1.4, 1.4, 1.4, 10.5 Hz, 1H), 4.59 (dddd, *J* = 1.4, 1.4, 1.4, 5.7 Hz, 2H), 2.59 (qq, *J* = 6.9, 6.9 Hz, 1H), 2.51-2.34 (m, 2H), 2.19-2.06 (m, 1H), 1.99-1.83 (m, 3H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.4, 169.8, 131.5, 118.3, 65.6, 65.3, 38.9, 31.9, 27.2, 19.5, 18.3, 17.6; IR (Neat Film NaCl) 3085, 2967,

1752, 1723, 1228, 1130 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1255.



328

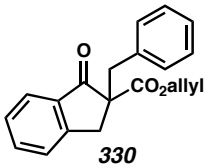
Allyl 1-((1,3-dioxoisoindolin-2-yl)methyl)-2-oxocyclopentanecarboxylate (328, Table 3.4, entry 3): Prepared by general procedure 2 part B from allyl 2-cyclopentanonecarboxylate[66] and using (*N*-chloromethyl)phthalimide as the electrophile. Purified by flash chromatography (SiO_2, 20 → 30% EtOAc in hexanes). 54% yield. mp 56-57 °C; R_f = 0.27 (30% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.73 (dd, *J* = 5.6, 3.2 Hz, 2H), 5.92 (dddd, *J* = 17.0, 10.6, 5.9, 5.9 Hz, 1H), 5.32 (app. ddd, *J* = 17.0, 2.9, 1.6 Hz, 1H), 5.23 (app. ddd, *J* = 10.6, 2.7, 1.3 Hz, 1H), 4.65 (app. ddt, *J* = 5.9, 4.5, 1.3 Hz, 2H), 4.34 (d, *J* = 14.4 Hz, 1H), 3.99 (d, *J* = 14.4 Hz, 1H), 2.59-2.47 (m, 1H), 2.46-2.25 (comp. m, 2H), 2.11-1.84 (comp. m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.0, 169.0, 168.3, 134.3, 131.9, 131.6, 123.7, 118.8, 66.8, 60.5, 41.0, 37.7, 32.1, 19.5; IR (Neat Film NaCl) 2953, 1774, 1752, 1718, 1467, 1457, 1428, 1395, 1359, 1256, 1231, 1170, 991, 722 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{18}H_{17}O_5N$ $[M]^+$: 327.1107, found 327.1106.



329

Allyl 2-methyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (329, Table 3.4, entry 4): Prepared by general procedure 2 from 1-indanone and using methyl iodide as the

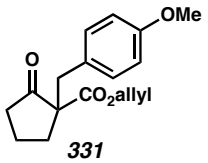
electrophile. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 30% yield. R_f = 0.55 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.7 Hz, 1H), 7.63 (dd, *J* = 7.6, 7.3 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.41 (dd, *J* = 7.6, 7.3 Hz, 1H), 5.83 (dddd, *J* = 17.2, 10.6, 5.6, 5.6 Hz, 1H), 5.21 (dddd, *J* = 17.2, 2.7, 1.6, 1.1 Hz, 1H), 5.16 (dddd, *J* = 10.5, 2.4, 1.3, 1.3 Hz, 1H), 4.58 (ddd, *J* = 5.6, 2.7, 1.1 Hz, 1H), 4.58 (ddd, *J* = 5.6, 2.7, 1.1 Hz, 1H), 3.73 (d, *J* = 17.1 Hz, 1H), 3.01 (d, *J* = 17.1 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.5, 171.8, 152.7, 135.5, 134.9, 131.7, 128.0, 126.6, 125.2, 118.3, 66.0, 56.2, 40.2, 21.2; IR (Neat Film NaCl) 3080, 2982, 2935, 1745, 1715, 1608, 1495, 1282, 1184, 967, 747 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{14}H_{14}O_3$ $[M]^+$: 230.0943, found 230.0936.



330

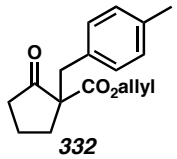
Allyl 2-benzyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (330, Table 3.4, entry 5): Prepared by general procedure 2 from 1-indanone and using benzyl bromide as the electrophile. Purified by flash chromatography (SiO_2, 20% Et_2O in pentane). 78% yield. mp 49-50 °C; R_f = 0.18 (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 1H), 7.53 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.33 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.23-7.06 (comp. m, 5H), 5.84 (dddd, *J* = 17.3, 10.4, 5.6, 5.3 Hz, 1H), 5.22 (app. ddd, *J* = 17.3,, 2.9, 1.6 Hz, 1H), 5.18 (dddd, *J* = 10.4, 2.4, 1.3, 1.1 Hz, 1H), 4.65-4.57 (m, 2H), 3.63 (d, *J* = 17.6 Hz, 1H), 3.50 (d, *J* = 13.8 Hz, 1H), 3.31 (d, *J* = 14.1 Hz, 1H), 3.18 (d, *J* = 17.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 170.6, 153.3, 136.4, 135.5, 135.3, 131.6, 130.2, 128.4, 127.8, 127.0, 126.4, 124.8, 118.5, 66.3, 61.9, 39.8,

35.5; IR (Neat Film NaCl) 3031, 2929, 1744, 1711, 1606, 1589, 1496, 1464, 1454, 1432, 1277, 1244, 1210, 1178, 1051, 1028, 930, 752, 703 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{20}H_{18}O_3$ $[M]^+$: 306.1256, found 306.1259.



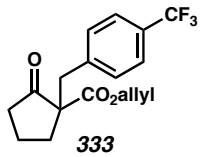
331

Allyl 1-(4-methoxybenzyl)-2-oxocyclopentanecarboxylate (331, Table 3.4, entry 6): Prepared by general procedure 2 part B from allyl 2-cyclopentanonecarboxylate[66] and using 4-methoxybenzyl chloride as the electrophile. Flash chromatography (3 x 25 cm SiO_2, 10:1 hexanes:EtOAc) afforded the title compound as a colorless oil (2.5584 g, 95% yield). R_f = 0.17 (10:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 5.87 (dddd, *J* = 5.7, 5.7, 10.8, 17.1 Hz, 1H), 5.31 (dddd, *J* = 1.5, 1.5, 1.5, 17.1 Hz, 1H), 5.24 (dddd, *J* = 1.2, 1.2, 1.2, 10.5 Hz, 1H), 4.61 (dddd, *J* = 1.4, 1.4, 1.4, 5.7 Hz, 2H), 3.77 (s, 3H), 3.15 (d, *J* = 13.8 Hz, 1H), 3.09 (d, *J* = 13.8 Hz, 1H), 2.45-2.31 (m, 2H), 2.08-1.81 (m, 3H), 1.67-1.53 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.7, 170.5, 158.3, 131.5, 131.0, 128.2, 118.3, 113.6, 65.8, 61.4, 55.0, 38.3, 38.0, 31.5, 19.3; IR (Neat Film NaCl) 2958, 1751, 1726, 1611, 1513, 1249 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{20}O_4$ $[M]^+$: 288.1362, found 288.1369.



332

Allyl 1-(4-methylbenzyl)-2-oxocyclopentanecarboxylate (332, Table 3.4, entry 7): Prepared by general procedure 2 part B from allyl 2-cyclopentanonecarboxylate[66] and using 4-methylbenzyl bromide as the electrophile. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 89% yield. R_f = 0.20 (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.3 Hz, 2H), 5.89 (dddd, *J* = 17.3, 10.5, 5.5, 5.5 Hz, 1H), 5.31 (app. ddd, *J* = 17.3, 3.0, 1.7 Hz, 1H), 5.24 (app. ddd, *J* = 10.5, 2.4, 1.1 Hz, 1H), 4.61 (app. ddd, *J* = 6.9, 2.8, 1.4 Hz, 1H), 4.61 (app. ddd, *J* = 6.9, 2.8, 1.4 Hz, 1H), 3.17 (d, *J* = 13.8 Hz, 1H), 3.10 (d, *J* = 13.8 Hz, 1H), 2.52-2.32 (m, 2H), 2.30 (s, 3H), 2.12-1.81 (comp. m, 3H), 1.68-1.52 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.1, 170.9, 136.6, 133.5, 131.7, 130.2, 129.2, 118.7, 66.1, 61.6, 38.7, 38.6, 31.8, 21.2, 19.6; IR (Neat Film NaCl) 2963, 2925, 1752, 1724, 1652, 1515, 1456, 1404, 1264, 1220, 1184, 1158, 1141, 1116, 992, 924, 813 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{20}O_3$ $[M]^+$: 272.1412, found 272.1412.



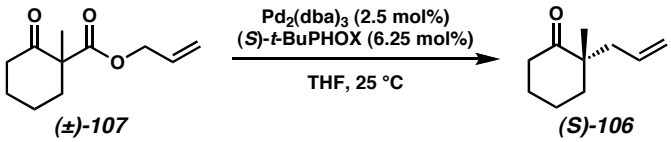
333

Allyl 2-oxo-1-(4-(trifluoromethyl)benzyl)cyclopentanecarboxylate (333, Table 3.4, entry 8): Prepared by general procedure 2 part B from allyl 2-cyclopentanonecarboxylate[66] and using 4-(trifluoromethyl)benzyl bromide as the electrophile. Purified by flash chromatography (SiO_2, 10:1 hexanes:EtOAc) to afford the

title compound as a colorless oil (1.9312 g, 65% yield). R_f = 0.24 (10:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 5.87 (dddd, *J* = 6.0, 6.0, 10.5, 17.4 Hz, 1H), 5.30 (dddd, *J* = 1.7, 1.7, 1.7, 17.4 Hz, 1H), 5.25 (dddd, *J* = 1.1, 1.1, 1.1, 10.5 Hz, 1H), 4.61 (bd, *J* = 6 Hz, 2H), 3.29 (d, *J* = 13.5 Hz, 1H), 3.15 (d, *J* = 13.5 Hz, 1H), 2.50-2.33 (m, 2H), 2.13-1.86 (m, 3H), 1.73-1.62 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.1, 170.3, 140.7, 131.3, 130.6, 142.0, 133.1, 130.6, 129.2 (q, $J_{C\text{-}F}$ = 32.2 Hz), 125.3 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.1 (q, $J_{C\text{-}F}$ = 271.5 Hz), 118.8, 66.2, 61.3, 38.6, 38.1, 31,8, 19.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ –62.54; IR (Neat Film NaCl) 3080, 2966, 1754, 1728, 1619, 1326, 1164, 1116, 1068 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{17}O_3F_3$ $[M]^+$: 326.1130, found 326.1129.

3.6.3 ENANTIOSELECTIVE ALKYLATIONS

3.6.3.1 GENERAL PROCEDURE FOR ENANTIOSELECTIVE DECARBOXYLATIVE ALKYLATION

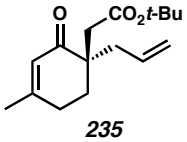


A 100 mL round-bottom flask was equipped with a magnetic stir bar and flame dried under vacuum. After cooling under dry nitrogen, $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol, 0.025 equiv) and (*S*)-*t*-Bu-PHOX (**55**, 24.2 mg, 0.0625 mmol, 0.0625 equiv) were added. The flask containing the solids was evacuated for 15 min and then refilled with dry nitrogen. Dry THF (30 mL) was then added and the resulting solution stirred at 25 ºC for 30 min. At this point, allyl 1-methyl-2-oxocyclohexanecarboxylate ((±)-**107**) was added via

syringe in one portion. When the reaction was complete by TLC (7.5 h), the reaction mixture was evaporated under reduced pressure and the residue purified by column chromatography (SiO_2, 1.5 → 2.5% Et_2O in pentane) to afford ketone (*S*)-**106** (129.6 mg, 85% yield, 88% ee).

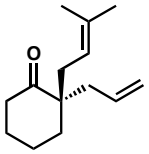
3.6.3.2 CHARACTERIZATION DATA FOR KETONE PRODUCTS

Absolute configuration is noted for product compounds where the configuration has been established (crystallographically or by comparison with literature data, see preceding publication). All other configurations shown are inferred by analogy.



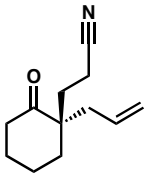
235

***tert*-Butyl 2-(1-allyl-4-methyl-2-oxocyclohex-3-enyl)ethanoate (235, Scheme 3.3):** Reaction time: from β-ketoester, 9 h, performed in Et_2O at 30 ºC. Flash chromatography (SiO_2, 3% Et_2O in pentane). 73% yield. R_f = 0.45 (30% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (s, 1H), 5.70 (dddd, *J* = 16.8, 10.2, 7.3, 7.3 Hz, 1H), 5.12-5.11 (m, 2H), 2.71 (d, *J* = 15.6 Hz, 1H), 2.48-2.13 (comp. m, 6H), 1.93 (s, 3H), 1.91-1.81 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 170.8, 160.3, 133.3, 125.4, 118.7, 80.5, 45.4, 40.5, 39.0, 29.8, 28.1, 27.8, 24.1; IR (Neat Film NaCl) 2978, 1728, 1670, 1367, 1213, 1152 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{16}H_{25}O_3$ $[M + H]^+$: 265.1804, found 265.1803; $[\alpha]_D^{25.4}$ –39.22 (*c* 1.05, CH_2Cl_2, 86% ee).



249

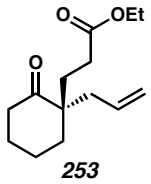
2-Allyl-2-(3-methylbut-2-enyl)cyclohexanone (249, Table 3.2, entry 3): Reaction time: from β-ketoester, 6 h, performed in Et_2O at 30 ºC. Flash chromatography (SiO_2, 1.5 → 2.5% Et_2O in pentane). 97% yield. R_f = 0.38 (10% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67 (dddd, J = 16.5, 10.6, 7.2, 7.2 Hz, 1H), 5.07-4.93 (comp. m, 3H), 2.44-2.24 (comp. m, 5H), 2.16 (dd, J = 14.6, 7.2 Hz, 1H), 1.89-1.64 (comp. m, 9H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.7, 134.2, 134.1, 119.0, 117.7, 52.1, 39.4, 39.3, 35.9, 33.3, 27.1, 26.0, 20.9, 18.0; IR (Neat Film NaCl) 3075, 2934, 2863, 1706, 1446, 1124, 914 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{14}H_{23}O$ [M + H]$^+$: 207.1749, found 207.1744; $[\alpha]_D^{26.0}$ +1.95 (*c* 1.29, CH_2Cl_2, 91% ee).



251

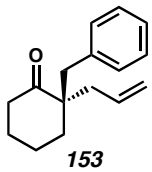
3-(1-Allyl-2-oxocyclohexyl)propanenitrile (251, Table 3.2, entry 4): Reaction time: from β-ketoester, 6.5 h, performed in Et_2O. Flash chromatography (SiO_2, 25% Et_2O in pentane). 97% yield. R_f = 0.32 (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (dddd, J = 16.7, 10.4, 7.4, 7.4 Hz, 1H), 5.17-5.07 (m, 2H), 2.53-2.16 (comp. m, 6H), 2.03-1.62 (comp. m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.2, 131.9, 120.0, 119.3, 50.8, 39.0, 38.9, 35.4, 30.6, 26.9, 20.5, 12.1; IR (Neat Film NaCl) 3081, 2939, 2863, 2246, 1702, 1453,

1126, 921 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{17}NO$ $[M]^+$: 191.1310, found 191.1307; $[\alpha]_D^{25.6}$ –27.00 (*c* 1.56, CH_2Cl_2, 88% ee).



253

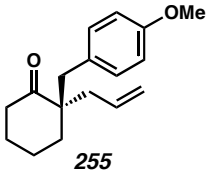
Ethyl 3-(1-allyl-2-oxocyclohexyl)propanoate (253, Table 3.2, entry 5): Reaction time: from β-ketoester, 6 h, performed in Et_2O. Flash chromatography (SiO_2, 5 → 14% Et_2O in pentane). 96% yield. R_f = 0.44 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.66 (dddd, *J* = 16.2, 10.9, 7.7, 7.2 Hz, 1H), 5.11-5.07 (m, 1H), 5.07-5.02 (m, 1H), 4.11 (app. q, *J* = 7.1 Hz, 2H), 2.48-2.18 (comp. m, 5H), 2.16-1.94 (comp. m, 2H), 1.90-1.65 (comp. m, 7H), 1.24 (app. t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.2, 173.5, 133.3, 118.3, 60.4, 50.8, 39.1, 39.0, 36.2, 29.7, 28.8, 27.0, 20.7, 14.2; IR (Neat Film NaCl) 3076, 2937, 2866, 1735, 1704, 1454, 1377, 1309, 1181, 917 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{14}H_{22}O_3$ $[M]^+$: 238.1569, found 238.1574; $[\alpha]_D^{25.8}$ +9.60 (*c* 1.13, CH_2Cl_2, 90% ee).



153

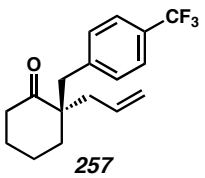
2-Allyl-2-benzylcyclohexanone (153, Table 3.2, entry 6): Reaction time: from allyl enol carbonate, 2 h; from β-ketoester, 0.5 h. ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (comp. m, 3H), 7.12 (comp. m, 2H), 5.74 (ddt, *J* = 17.2, 10.1, 7.2 Hz, 1H), 5.12-5.03 (m, 2H), 2.91 (s, 2H), 2.46 (m, 2H), 2.28 (d, *J* = 7.2 Hz, 2H), 1.86-1.65 (comp. m, 6H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 214.1, 137.5, 133.7, 130.6, 127.9, 126.3, 118.2, 52.5, 40.8, 39.6, 39.2, 35.5, 26.8, 20.8; IR (Neat Film NaCl) 2937, 1704, 1638, 1602 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{16}H_{20}O$ $[M]^+$: 228.1514, found 228.1514; $[\alpha]_D^{28}$ –12.34 (*c* 2.07, hexane, 85% ee).



255

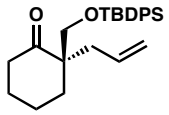
2-Allyl-2-(4-methoxybenzyl)cyclohexanone (255, Table 3.2, entry 7): Reaction time: from β-ketoester, 10 h. Flash chromatography (SiO_2, 3% Et_2O in pentane). 80% yield. R_f = 0.54 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, *J* = 9.0 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 5.72 (dddd, *J* = 17.1, 9.8, 7.0, 7.0 Hz, 1H), 5.12-4.98 (m, 2H), 3.78 (s, 3H), 2.84 (s, 2H), 2.53-2.34 (m, 2H), 2.33-2.17 (m, 2H), 1.91-1.70 (comp. m, 4H), 1.70-1.61 (comp. m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.3, 158.1, 133.9, 131.5, 129.5, 118.1, 113.4, 55.2, 52.6, 40.1, 39.6, 39.3, 35.4, 26.8, 20.8; IR (Neat Film NaCl) 3076, 2935, 2863, 2361, 1702, 1611, 1513, 1456, 1249, 1179, 1036, 834 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{22}O_2$ $[M]^+$: 258.1620, found 258.1627; $[\alpha]_D^{25.9}$ +3.60 (*c* 1.05, CH_2Cl_2, 86% ee).



257

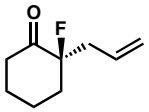
2-Allyl-2-(4-(trifluoromethyl)benzyl)cyclohexanone (257, Table 3.2, entry 8): Reaction time: from β-ketoester, 0.5 h. Flash chromatography (SiO_2, 8 → 14% Et_2O in

pentane). 99% yield. R_f = 0.85 (30% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.7 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.71 (dddd, *J* = 17.0, 10.1, 7.4, 6.9 Hz, 1H), 5.17-5.04 (m, 2H), 3.01 (d, *J* = 13.8 Hz, 1H), 2.88 (d, *J* = 13.8 Hz, 1H), 2.50-2.31 (comp. m, 3H), 2.29-2.17 (m, 1H), 1.97-1.82 (m, 1H), 1.82-1.69 (comp. m, 3H), 1.70-1.59 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.3, 142.0 (q, J_{CF} = 1.2 Hz), 133.0, 130.9, 128.4 (q, J_{CF} = 32.3 Hz), 124.7 (q, J_{CF} = 3.9 Hz), 124.2 (q, J_{CF} = 271.7 Hz), 118.5, 52.5, 40.4, 39.3, 39.3, 35.5, 26.6, 20.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ –62.9; IR (Neat Film NaCl) 3076, 2940, 2867, 1705, 1618, 1418, 1326, 1164, 1123, 1068, 852 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{19}F_3O$ [M]$^+$: 296.1388, found 296.1402; $[\alpha]_D^{26.6}$ –16.31 (*c* 1.17, CH_2Cl_2, 82% ee).



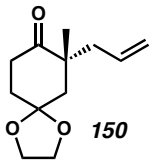
259

2-Allyl-2-((*tert*-butyldiphenylsilyloxy)methyl)cyclohexanone (259, Table 3.2, entry 9): Reaction time: from β-ketoester, 5 h. Flash chromatography (SiO_2, 1 → 2.5% EtOAc in hexanes). 92% yield. R_f = 0.32 (5% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.64 (m, 4H), 7.46-7.36 (m, 6H), 5.69-5.55 (m, 1H), 5.38-5.31 (m, 1H), 5.08-4.99 (m, 2H), 3.84 (d, *J* = 10.2 Hz, 1H), 3.66 (d, *J* = 10.2 Hz, 1H), 2.48 (d, *J* = 7.5 Hz, 2H), 2.40-2.20 (m, 2H), 1.90-1.60 (m, 6H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.4, 135.7, 133.8, 133.3 (2C), 129.7, 129.6, 127.6 (2C), 117.9, 66.4, 53.8, 39.7, 37.3, 34.0, 26.9 (2C), 21.0, 19.3; IR (Neat Film NaCl) 3072, 2933, 2858, 1708, 1428, 1113, 703 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{26}H_{35}O_2Si$ [M + H]$^+$: 407.2406, found 407.2398; $[\alpha]_D^{25}$ –3.96 (*c* 5.00, $CHCl_3$, 81% ee).



261

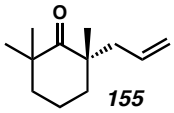
2-Allyl-2-fluorocyclohexanone (261, Table 3.2, entry 10): Reaction time: from β-ketoester, 3.5 h, performed in Et_2O at 30 ºC. Flash chromatography (SiO_2, 2% Et_2O in pentane). 80% yield. R_f = 0.36 (10:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88-5.71 (m, 1H), 5.20-5.10 (m, 2H), 2.76-2.31 (m, 4H), 2.16-2.02 (m, 1H), 1.99-1.78 (m, 4H), 1.75-1.60 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2 (d, $J_{C\text{-}F}$ = 20.0 Hz), 130.7 (d, $J_{C\text{-}F}$ = 3.8 Hz), 119.2, 97.7 (d, $J_{C\text{-}F}$ = 184.3 Hz), 39.4, 38.7 (d, $J_{C\text{-}F}$ = 22.7 Hz), 37.3 (d, $J_{C\text{-}F}$ = 22.2 Hz), 27.2, 21.4 (d, $J_{C\text{-}F}$ = 6.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ –158.15; IR (Neat Film NaCl) 3080, 2946, 1729, 1642, 1453, 1433, 1126, 923 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_9H_{13}OF$ $[M]^+$: 156.0950, found 156.0946; $[\alpha]_D^{24.4}$ –74.65 (*c* 1.05, CH_2Cl_2, 91% ee).



150

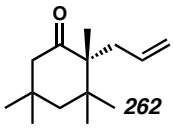
7-Allyl-7-methyl-1,4-dioxaspiro[4.5]decan-8-one (150, Table 3.3, entries 1 and 2): Reaction time: from allyl enol carbonate, 1 h; from silyl enol ether, 2 h; from β-ketoester, 1.5 h (1 mmol scale), 24 h (25 mmol scale) with 1.5 mol% $Pd_2(dba)_3$, 3.75 mol% (*S*)-**5**, in Et_2O. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67 (ddt, *J* = 17.1, 10.5, 7.2 Hz, 1H), 5.07 (br s, 1H), 5.02 (app. d, *J* = 9.3 Hz, 1H), 3.99 (app. d, *J* = 1.5 Hz, 4H), 2.57 (app. t, *J* = 6.3 Hz, 1H), 2.42 (m, 2H), 2.00 (d, *J* = 13.8 Hz, 1H), 1.98 (app. t, *J* = 7.2 Hz, 1H), 1.75 (d, *J* =

14.1 Hz, 1H), 1.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.9, 133.7, 118.4, 107.6, 64.4, 64.3, 47.5, 44.3, 42.7, 35.7, 34.5, 23.9; IR (Neat Film NaCl) 2964, 1710, 1116 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1255; $[\alpha]_D^{29}$ –7.99 (*c* 2.41, hexane, 86% ee).



155

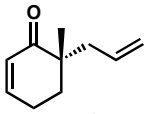
(*S*)-2-Allyl-2,6,6-trimethylcyclohexanone (155, Table 3.3, entry 3): Reaction time: from allyl enol carbonate, 1 h; from β-ketoester, 9 h, performed at 30 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (m, 1H), 5.01 (m, 2H), 2.33 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.18 (dd, *J* = 13.8, 7.8 Hz, 1H), 1.82-1.53 (comp. m, 6H), 1.11 (s, 3H), 1.09 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.8, 134.6, 117.9, 47.6, 44.4, 43.9, 39.7, 36.8, 27.8, 27.2, 25.5, 17.7; IR (Neat Film NaCl) 2933, 1697, 1463 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{20}O$ $[M]^+$: 180.1514, found 180.1521; $[\alpha]_D^{27}$ –35.69 (*c* 2.15, hexane, 92% ee).



262

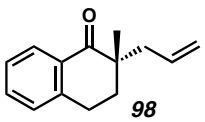
2-Allyl-2,3,3,5,5-pentamethylcyclohexanone (262, Table 3.3, entry 4): Reaction time: from β-ketoester, 5 h. Flash chromatography (SiO_2, 1 → 4% Et_2O in hexanes). 90% yield. R_f = 0.48 (10% Et_2O in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63-5.46 (m, 1H), 5.10-4.94 (m, 2H), 2.61 (d, *J* = 13.5 Hz, 1H), 2.34 (d, *J* = 12.9 Hz, 1H), 2.11 (d, *J* = 12.9 Hz, 1H), 2.02 (d, *J* = 13.8 Hz, 1H), 1.83 (d, *J* = 14.6 Hz, 1H), 1.40 (d, *J* = 14.5 Hz, 1H), 1.02 (s, 3H), 0.99 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 215.5, 134.2, 117.9, 53.8, 51.0, 49.5, 40.5, 39.1, 35.7, 33.7, 29.8, 26.9, 26.3, 15.4; IR (Neat Film NaCl) 3077, 2957, 1708, 1639, 1460, 1392, 1370, 913 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{14}H_{24}O$ $[M]^+$: 208.1827, found 208.1837; $[\alpha]_D^{22.5}$ –4.14 (*c* 2.705, hexane, 85% ee).



149

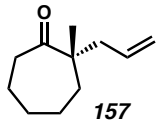
(*S*)-6-Allyl-6-methylcyclohex-2-enone (149, Table 3.3, entry 5): Reaction time: from allyl enol carbonate, 1 h; from β-ketoester, 4 h, performed with 4 mol% $Pd_2(dba)_3$, 10 mol% (*S*)-**5**, in Et_2O. ^1H NMR (300 MHz, $CDCl_3$) δ 6.87 (app. dt, *J* = 10.2, 4.2 Hz, 1H), 5.91 (app. dt, *J* = 10.2, 2.1 Hz, 1H), 5.72 (m, 1H), 5.07 (m, 1H), 5.02 (d, *J* = 9.3 Hz, 1H), 2.35 (m, 3H), 2.16 (dd, *J* = 13.8, 7.5, Hz, 1H), 1.91 (dt, *J* = 13.8, 6.0 Hz, 1H), 1.74 (dt, *J* = 13.8, 6.0 Hz, 1H), 1.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 148.8, 134.0, 128.4, 118.0, 44.4, 40.9, 32.9, 23.1, 21.6; IR (Neat Film NaCl) 2927, 1673 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{10}H_{14}O$ $[M]^+$: 150.1045, found 150.1039; $[\alpha]_D^{26}$ +14.62 (*c* 1.56, hexane, 89% ee).



98

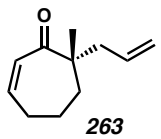
(*S*)-2-Allyl-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (98, Table 3.3, entry 6): Reaction time: from allyl enol carbonate, 2 h, 10 °C; from β-ketoester, 10 h, performed in Et_2O. ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.45 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.29 (app. t, *J* = 7.2 Hz, 1H), 7.21 (app. d, *J* = 7.5 Hz, 1H), 5.85-5.71 (m, 1H),

5.10 (s, 1H), 5.05 (s, 1H), 2.97 (t, J = 6.3 Hz, 2H), 2.46 (dd, J = 13.8, 7.5 Hz, 1H), 2.27 (ddt, J = 14.0, 7.5, 1.2 Hz, 1H), 2.07 (ddd, J = 13.4, 7.2, 6.0 Hz 1H), 1.89 (ddd, J = 14.0, 6.9, 5.7 1H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 143.2, 133.9, 133.0, 131.5, 128.6, 127.9, 126.5, 118.1, 44.5, 41.0, 33.2, 25.3, 21.8; IR (Neat Film NaCl) 3073, 2930, 1682, 1455, 1220, 916, 742 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{14}H_{16}O$ $[M]^+$: 200.1201, found 200.1194; $[\alpha]_D^{27}$ –18.59 (*c* 2.08, hexane, 88% ee).



157

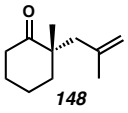
2-Allyl-2-methylcycloheptanone (157, Table 3.3, entry 7): Reaction time: from allyl enol carbonate, 6 h; from silyl enol ether, 2 h; from β-ketoester, 9.5 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (ddt, J = 16.8, 10.2, 7.5, 1H), 5.02 (m, 2H), 2.59 (app. dt, J = 11.1, 2.7 Hz, 1H), 2.42 (app. t, J = 9.0 Hz, 1H), 2.24 (dd, J = 13.8, 7.5 Hz, 1H), 2.16 (dd, J = 13.8, 7.8 Hz, 1H), 1.78-1.30 (comp. m, 8H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.4, 133.8, 117.9, 50.8, 43.6, 40.6, 36.6, 30.6, 26.4, 24.4, 22.3; IR (Neat Film NaCl) 2930, 1702, 1458 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{18}O$ $[M]^+$: 166.1358, found 166.1360; $[\alpha]_D^{28}$ –34.70 (*c* 1.52, hexane, 87% ee).



263

7-Allyl-7-methylcyclohept-2-enone (263, Table 3.3, entry 8): A 100 mL round-bottom flask equipped with a magnetic stir bar was flame dried under vacuum and cycled into a N_2-filled glovebox. $Pd(dmdba)_2$ (78.3 mg, 0.096 mmol, 3 mol%) and (*S*)-*t*-Bu-

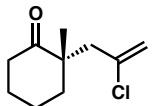
PHOX (46.2 mg, 0.119 mmol, 3.76 mol%) were added, followed by THF (40 mL). The contents were stirred at 25 °C for 30 min, at which time allyl 1-methyl-2-oxocyclohept-3-enecarboxylate (660.1 mg, 3.17 mmol, 1.0 equiv) was added with a total of 10 mL of THF. The reaction was stirred for 3 h at which time TLC indicated complete reaction. The reaction mixture was cycled out of the glovebox, concentrated *in vacuo*, and the residue subjected to flash chromatography (2 x 16 cm, 25:1 hexane:EtOAc) to afford the title compound as a colorless oil (510 mg, 98% yield). R_f = 0.34 (10:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (ddd, *J* = 4.2, 4.2, 12.6 Hz, 1H), 5.91 (ddd, *J* = 2.1, 2.1, 12.6 Hz, 1H), 5.71 (dddd, *J* = 7.5, 7.5, 10.5, 17.1 Hz, 1H), 5.07-5.04 (m, 1H), 5.01 (dddd, *J* = 0.9, 0.9, 2.1, 9.9 Hz, 1H), 2.40-2.32 (m, 2H), 2.30 (m, 1H), 2.21 (dddd, *J* = 0.9, 0.9, 7.2, 13.5 Hz, 1H), 1.88-1.53 (m, 4H), 1.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.2, 141.8, 133.9, 130.3, 117.9, 52.3, 44.4, 35.1, 33.2, 24.1, 22.0; IR (Neat Film NaCl) 3075, 3013, 2929, 1662, 1455, 1419, 1396, 1375, 1199, 995, 915 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{16}O$ $[M]^+$: 164.1201, found 164.1201; $[\alpha]_D^{24.6}$ –63.58 (*c* 1.015, $CHCl_3$, 90% ee).



148

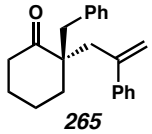
2-Methyl-2-(2-methylallyl)cyclohexanone (148, Table 3.3, entry 9): Reaction time: from allyl enol carbonate, 8 h, performed with 5 mol% $Pd_2(dba)_3$, 12.5 mol% (*S*)-**55**; from silyl enol ether, 4 h, performed with dimethallyl carbonate; from β-ketoester, 6.5 h performed with 5 mol% $Pd_2(dba)_3$, 12.5 mol% (*S*)-**3**, in Et_2O at 35 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.81 (s, 1H), 4.64 (s, 1H), 2.52 (m, 1H), 2.48 (d, *J* = 13.5 Hz, 1H), 2.36

(app. dt, J = 14.7, 6.0 Hz, 1H), 2.25 (d, J = 13.8 Hz, 1H), 1.94-1.53 (comp. m, 6H), 1.65 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.8, 142.2, 114.7, 48.7, 45.4, 40.0, 38.9, 27.6, 24.3, 23.3, 21.1; IR (neat) 2927, 1707 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{18}O$ $[M]^+$: 166.1358, found 166.1358; $[\alpha]_D^{27}$ –26.42 (*c* 1.85, hexane, 90% ee).



264

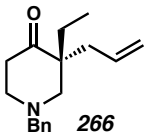
2-(2-Chloroallyl)-2-methylcyclohexanone (264, Table 3.3, entry 10): Reaction time: from β-ketoester, 2.5 h, performed in Et_2O at 35 ºC with 4 mol% $Pd_2(dba)_3$ (45.8 mg, 0.040 mmol), and 10 mol% (*S*)-*t*-BuPHOX (48.4 mg, 0.10 mmol). Flash chromatography (SiO_2, 1 → 2.5% Et_2O in pentane). 87% yield. R_f = 0.63 (30% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.27 (app. d, J = 1.2 Hz, 1H), 5.15-5.09 (m, 1H), 2.80 (d, J = 14.4 Hz, 1H), 2.61 (d, J = 14.4 Hz, 1H), 2.56-2.37 (m, 2H), 1.94-1.61 (comp. m, 6H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.4, 138.7, 116.3, 48.4, 46.5, 39.2, 38.8, 27.4, 22.7, 21.1; IR (Neat Film NaCl) 2936, 2868, 1708, 1630, 1456, 1126, 887 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{10}H_{16}ClO$ $[M + H]^+$: 187.0890, found 187.0884; $[\alpha]_D^{26.6}$ – 5.40 (*c* 3.21, CH_2Cl_2, 91% ee).



265

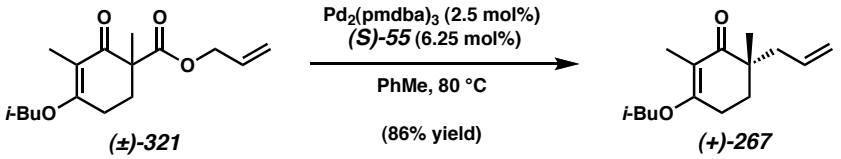
2-Benzyl-2-(2-phenylallyl)cyclohexanone (265, Table 3.3, entry 11): Reaction time: from β-ketoester, 12.25 h, performed at 30 ºC with 2.5 mol% $Pd(dmdba)_2$ (20.4 mg, 0.025 mmol), and 2.5 mol% (*S*)-*t*-BuPHOX (9.6 mg, 0.025 mmol). Flash

chromatography (SiO_2, 15% Et_2O in petroleum ether). 96% yield. R_f = 0.44 (15% Et_2O in petroleum ether); ^{1}H NMR (300 MHz, CD_3OD) δ 7.36-7.10 (m, 8H), 7.07-7.00 (m, 2H), 5.25 (d, *J* = 1.9 Hz, 1H), 5.11-5.08 (m, 1H), 3.04 (d, *J* = 13.8 Hz, 1H), 2.90-2.85 (m, 2H), 2.63 (d, *J* = 13.6 Hz, 1H), 2.42-2.17 (m, 2H), 1.82-1.46 (m, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 216.6, 147.6, 144.6, 139.3, 131.9, 129.3, 128.9, 128.4, 127.9, 127.3, 118.0, 54.8, 42.9, 42.4, 40.8, 36.2, 27.2, 21.8; IR (neat film, NaCl) ν 3082, 3058, 3027, 2938, 2864, 1702, 1624, 1601, 1574, 1494, 1453, 1444, 1315, 1198, 1126, 1080, 1075, 1055, 1030, 968, 905, 778, 754, 744, 702 cm^{-1}; HRMS (EI+) *m/z* calc'd. for $C_{22}H_{24}O$ $[M]^+$: 304.1827, found 304.1841; $[\alpha]_D^{24}$ –13.67 (*c* 1.005, $CHCl_3$, 94% ee).

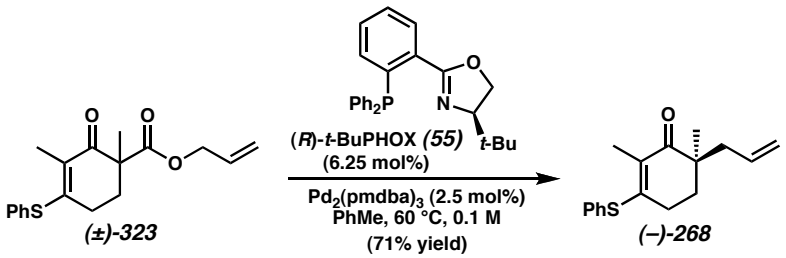


266

3-Allyl-1-benzyl-3-ethylpiperidin-4-one (266, Table 3.3, entry 12): Reaction time: from β-ketoester, 2.5 h. Flash chromatography (SiO_2, 5→7% Et_2O in pentane). 91% yield. R_f = 0.29 (10% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.23 (comp. m, 5H), 5.62 (dddd, *J* = 12.3, 9.6, 7.2, 7.2 Hz, 1H), 5.03 (m, 1H), 4.99 (m, 1H), 3.56 (s, 2H), 2.83-2.69 (m, 1H), 2.65-2.33 (comp. m, 6H), 2.33-2.20 (m, 1H) 1.95 (dq, *J* = 15.3, 7.5 Hz, 1H), 1.51 (dq, *J* = 15.0, 7.5 Hz, 1H), 0.75 (dd, *J* = 7.5, 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.6, 138.6, 133.8, 128.7, 128.3, 127.2, 117.8, 62.2, 61.8, 53.4, 52.2, 39.3, 37.3, 26.7, 7.8; IR (Neat Film NaCl) 3065, 3028, 2965, 2801, 1709, 1454, 1352, 1200, 915, 699 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{23}NO$ $[M]^+$: 257.1780, found 257.1772; $[\alpha]_D^{26.6}$ +31.21 (*c* 1.51, CH_2Cl_2, 92% ee).

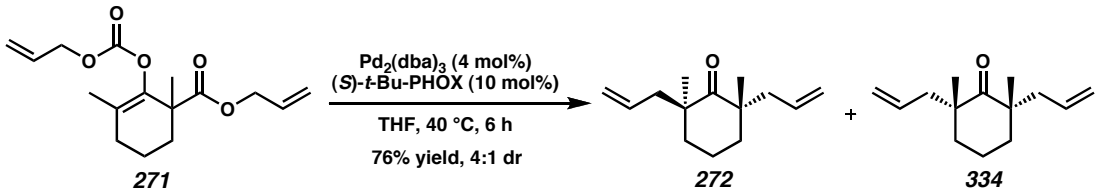


Ketone (+)-267 from β-ketoester (±)-321 (Table 3.3, entry 13). A 2-dram vial containing a stir bar was charged with $Pd_2(pmdba)_3$ (10.6 mg, 0.00968 mmol, 0.025 equiv) and (*S*)-**55** (9.4 mg, 0.0242 mmol, 0.0625 equiv). This was connected to a 1-dram vial containing a stir bar and β-ketoester (±)-**321** (108.6 mg, 0.387 mmol, 1.0 equiv) via a cannula, and PhMe (3.9 mL, 0.1 M) was added to the vial containing the Pd/L and immediately immersed in liquid N_2. The vials were rigorously degassed by three freeze-pump-thaw cycles and warmed to 23 °C. After complexation for 30 min (purple → orange color change), the catalyst solution was transferred to the substrate via cannula and immersed in an 80 °C oil bath. The reaction immediately turned yellow in color. After 23 h the reaction was cooled to ambient temperature, diluted with Et_2O (4 mL), and filtered through a small SiO_2 plug. The filtrate was concentrated and purified by flash chromatography as above to afford ketone (+)-**267** as a colorless oil (78.5 mg, 0.332 mmol, 86% yield, 75% ee). R_f = 0.49 (4:1 hexanes-EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (dddd, *J* = 16.6, 10.6, 7.4, 7.4 Hz, 1H), 5.06-5.04 (m, 1H), 5.04-5.01 (m, 1H), 3.74 (dd, *J* = 9.7, 6.7 Hz, 2H), 2.59-2.47 (comp m, 2H), 2.33 (dd, *J* = 13.7, 7.2 Hz, 1H), 2.16 (dddd, *J* = 13.7, 7.6, 1.0, 1.0 Hz, 1H), 1.98 (app septuplet, *J* = 6.6 Hz, 1H), 1.90 (ddd, *J* = 13.3, 7.2, 5.7 Hz, 1H), 1.72-1.67 (m, 1H), 1.70 (dd, *J* = 1.6, 1.6 Hz, 3H), 1.06 (s, 3H), 0.99 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.7, 169.5, 134.8, 117.8, 113.3, 73.8, 42.5, 41.9, 31.5, 29.0, 22.5, 22.4, 19.2, 8.0; IR (Neat Film NaCl) 3076, 2962, 2931, 1622, 1463, 1381, 1355, 1229, 1113, 1002, 915 cm^{-1}; HRMS (EI+) *m/z*: calc'd for $C_{15}H_{24}O_2$ $[M]^+$: 236.1776, found 236.1771; $[\alpha]_D^{21.2}$ +13.2° (*c* 0.20, CH_2Cl_2, 88% ee).

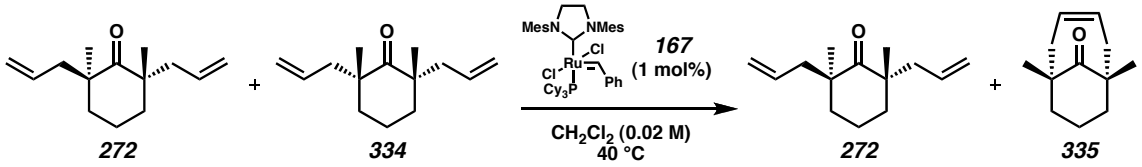


Allyl ketone (–)-268 (Table 3.3, entry 14; Scheme 3.6). A solution of $Pd_2(pmdba)_3$ (0.1306 g, 0.1185 mmol, 0.025 equiv) and (*R*)-*t*-BuPHOX (**55**) (0.1148 g, 0.2964 mmol, 0.0625 equiv) in toluene (30 mL) was prepared in a glovebox under N_2 atmosphere, and allowed to stir at 23 °C for 30 min. A solution of β-ketoester (±)-**323** (1.50 g, 4.741 mmol, 1.00 equiv) in toluene (10 mL) was transferred to the reaction vessel dropwise via glass pipette, washing with toluene (7.5 mL) for quantitative transfer. The reaction vessel was sealed with a rubber septum, removed from the glove box, heated in a 60 °C oil bath, and the solution was allowed to stir for 24 h. The reaction vessel was cooled to room temperature, and the solvent was evaporated in vacuo. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to afford allyl ketone (–)-**268** (0.92 g, 71% yield, 91.6% ee as determined by chiral HPLC using a Chiralpak AD column with 4% EtOH in hexanes as the eluent) as a colorless oil. R_f = 0.45 (30% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.48 (m, 2H), 7.43-7.35 (comp m, 3H), 5.68 (app ddt, *J* = 10.8, 16.8, 7.5 Hz, 1H), 5.03 (dddd, *J* = 9.9, 2.4, 0.9, 0.6 Hz, 1H), 5.01 (dddd, *J* = 17.4, 2.4, 1.5, 1.2 Hz, 1H), 2.32 (app ddt, *J* = 13.8, 7.2, 1.2 Hz), 2.19-2.10 (comp m, 3H), 1.96 (t, *J* = 1.8 Hz, 3H), 1.86-1.75 (m, 1H), 1.66-1.56 (m, 1H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.5, 155.6, 135.6, 134.4 130.3, 129.6, 129.5, 128.8, 118.2, 43.1, 41.7, 33.1, 26.9, 22.3, 12.9; IR (Neat Film NaCl) 3074, 2964, 2929, 1652, 1582, 1440,

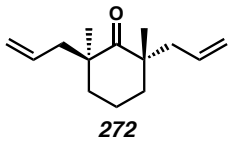
1339, 1287, 1228 cm^{-1}; HRMS (FAB+) *m/z*: calc'd for $C_{17}H_{20}OS$ $[M + H]^+$: 273.1313, found 273.1317; $[\alpha]_D^{25.4}$ –57.4 (*c* 1.00, CH_2Cl_2).



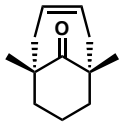
2,6-diallyl-2,6-dimethylcyclohexanone (272, Scheme 3.7a). A 50 mL round-bottom flask equipped with a magnetic stir bar was flame dried under vacuum. After cooling under nitrogen, $Pd_2(dba)_3$ (31.4 mg, 0.0343 mmol, 0.034 equiv) and (*S*)-*t*-Bu-PHOX (**55**) (31.3 mg, 0.0808 mmol, 0.080 equiv) were added. After the flask was evacuated and filled with nitrogen three times, THF (32 mL) was added and the contents were stirred at 25 °C for 30 min, at which time allyl 2-(allyloxycarbonyloxy)-1,3-dimethylcycohex-2-enecarboxylate (**271**) (298 mg, 1.012 mmol, 1.0 equiv) was added by syringe in one portion. The reaction was stirred at 40 °C for 6 h at which time TLC indicated complete reaction. The reaction mixture was allowed to cool and then concentrated to ~1 mL under reduced pressure and the residue chromatographed (100 mL pentane, then 1 → 2% Et_2O in pentane on 2 x 14 cm SiO_2) to afford the title compound as a colorless, volatile oil (157.9 mg, 76% yield). GC analysis indicated the isolated compound was an 80:20 mixture (R_f = 0.51, 10:1 hexane:EtOAc) of C_2-symmetric:*meso* diastereomers (**272**:**334**).



In order to obtain an analytical sample of the C_2-symmetric product (**272**), the following reaction was performed on the mixture of diastereomers: A solution of the diastereomeric ketones (50.4 mg, 0.244 mmol, 1.0 equiv) in 15 mL CH_2Cl_2 was degassed by bubbling Ar through the solution for 15 min. The second generation Grubbs catalyst (**167**)[67] (2 mg, 0.00236 mmol, 0.0097 equiv) was added and the mixture heated to 40 °C. After 90 min, GC analysis indicated none of the minor diastereomer was present. The reaction mixture was allowed to cool and then concentrated to ~1-2 mL under reduced pressure and the residue chromatographed (75 mL pentane, then 2 → 5% Et_2O in pentane on 1.5 x 24 cm SiO_2) to afford the C_2-symmetric **272** (31 mg, 62%), the RCM product **335** (8.3 mg), and 5.8 mg of a mixture of the two compounds.



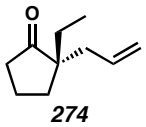
***C_2*-symmetric ketone 272:** R_f = 0.17 (2% Et_2O in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (m, 2H), 5.10-4.95 (m, 4H), 2.33 (dd, *J* = 6.9, 13.8 Hz, 2H), 2.18 (dd, *J* = 7.8, 13.8 Hz, 2H), 1.87-1.68 (m, 4H), 1.59-1.48 (m, 2H), 1.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.6, 134.4, 118.0, 47.6, 43.9, 36.4, 25.0, 17.3; IR (Neat Film NaCl) 3076, 2930, 1694, 1639, 1461, 1374, 992, 914 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{14}H_{22}O$ $[M]^+$: 206.1671, found 206.1675; $[\alpha]_D^{23.6}$ –54.04 (*c* 0.95, hexane, 92% ee).



335

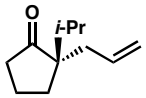
***meso*-Ketone 335:** R_f = 0.13 (2% Et_2O in hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.83-5.72 (m, 2H), 2.53-2.35 (m, 3H), 2.03-1.85 (m, 4H), 1.75-1.62 (m. 2H), 1.48-1.37 (m, 1H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.9, 129.4, 48.5, 41.7, 39.0, 27.2, 20.0; IR (Neat Film NaCl) 2965, 1735, 1699, 1458, 1378, 1239 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{18}O$ $[M]^+$: 178.1358, found 178.1360.

For details of the preparation of bis(β-ketoester) **75** (Scheme 3.7), conversion to diketone **76**, and synthesis of cyanthiwigin F (**83**), see ref 68.



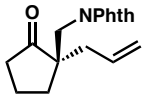
274

2-Allyl-2-ethylcyclopentanone (274, Table 3.4, entry 1): Reaction time: from β-ketoester, 3 h. Flash chromatography (2 x 12 cm SiO_2, 3 → 4% Et_2O in pentane). Colorless oil (125.9 mg, 82% yield). R_f = 0.44 (10:1 Hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.68 (dddd, *J* = 7.2, 7.2, 9.3, 12.3 Hz, 1H), 5.09-5.00 (m, 2H), 2.24-2.14 (m, 4H), 1.90-1.80 (m, 4H), 1.46 (q, *J* = 7.2 Hz, 1H), 1.46 (q, *J* = 7.2 Hz, 1H), 0.83 (dd, *J* = 7.2, 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.4, 169.8, 131.5, 118.3, 65.6, 38.9, 31.9, 27.2, 19.5, 18.3, 17.6; IR (Neat Film NaCl) 3077, 2965, 1735, 1640, 1460, 1406, 1162, 915 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{10}H_{16}O$ $[M]^+$: 152.1201, found 152.1195; $[\alpha]_D^{25.2}$ –18.55 (*c* 1.050, CH_2Cl_2, 86% ee).



275

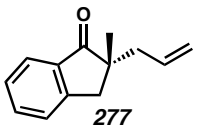
2-Allyl-2-isopropylcyclopentanone (275, Table 3.4, entry 2): Reaction time: from β-ketoester, 3 h. Flash chromatography (2 x 13 cm SiO_2, 3% Et_2O in pentane). Colorless oil (130.4 mg, 77% yield). R_f = 0.44 (10:1 Hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (dddd, *J* = 7.5, 7.5, 9.3, 13.2 Hz, 1H), 5.07-5.00 (m, 2H), 2.30-2.07 (m, 4H), 2.01-1.69 (m, 5H), 0.87 (d, *J* = 7.2 Hz, 3H), 0.80 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 223.6, 134.2, 117.8, 55.1, 39.7, 39.6, 31.8, 29.0, 18.9, 18.2, 17.1; IR (Neat Film NaCl) 3077, 2963, 1734, 1640, 1471, 1406, 1388, 1370, 1190, 914 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{18}O$ $[M]^+$: 166.1358, found 166.1359; $[\alpha]_D^{24.9}$ +43.05 (*c* 1.085, CH_2Cl_2, 84% ee).



276

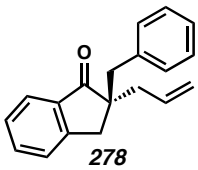
2-((1-Allyl-2-oxocyclopentyl)methyl)isoindoline-1,3-dione (276, Table 3.4, entry 3): Reaction time: from β-ketoester, 2 h. Flash chromatography (SiO_2, 10 → 15% EtOAc in hexanes). 67% yield, 48% ee. R_f = 0.34 (30% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.9, 3.2 Hz, 2H), 7.72 (dd, *J* = 5.9, 3.2 Hz, 2H), 5.73 (dddd, *J* = 16.8, 9.8, 7.7, 6.4 Hz, 1H), 5.18-5.06 (m, 2H), 3.80 (d, *J* = 14.1 Hz, 1H), 3.74 (d, *J* = 14.1 Hz, 1H), 2.56-2.41 (m, 1H), 2.38-2.10 (comp. m, 3H), 2.10-1.86 (comp. m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.1, 168.8, 134.2, 133.3, 132.0, 123.6, 119.4, 53.0, 41.8, 38.7, 38.3, 31.9, 18.9; IR (Neat Film NaCl) 2966, 1773, 1734, 1713, 1429, 1395,

1354, 715, 666 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{17}O_3N$ $[M]^+$: 283.1208, found 283.1209; $[\alpha]_D^{26.5}$ –14.1 (*c* 1.49, CH_2Cl_2, 48% ee).



277

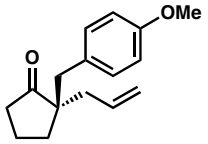
2-Allyl-2-methyl-2,3-dihydro-1*H*-inden-1-one (277, Table 3.4, entry 4): Reaction time: from β-ketoester, 1 h, performed on 0.1 mmol scale. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 82% yield, 80% ee. R_f = 0.37 (10% Et_2O in pentane); $[\alpha]_D^{26.4}$ –38.5 (*c* 0.47, CH_2Cl_2, 80% ee). Spectral data matched those reported in the literature.[69]



278

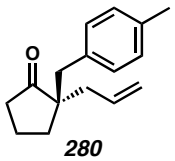
2-Allyl-2-benzyl-2,3-dihydro-1*H*-inden-1-one (278, Table 3.4, entry 5): Reaction time: from β-ketoester, 1 h. Purified by flash chromatography (SiO_2, 2 → 4% Et_2O in pentane). 93% yield, 71% ee. R_f = 0.37 (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.7 Hz, 1H), 7.63 (ddd, *J* = 7.7, 7.7, 1.1 Hz, 1H), 7.49 (comp. m, 2H), 7.36-7.20 (comp. m, 5H), 5.74 (dddd, *J* = 16.7, 10.1, 8.0, 6.6 Hz, 1H), 5.21 (app. d, *J* = 16.8 Hz, 1H), 5.12 (app. d, *J* = 10.1 Hz, 1H), 3.26 (d, *J* = 17.3 Hz, 1H), 3.25 (d, *J* = 13.3 Hz, 1H), 3.10 (d, *J* = 17.3 Hz, 1H), 2.96 (d, *J* = 13.6 Hz, 1H), 2.70 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.46 (dd, *J* = 13.6, 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.3, 153.0, 137.3, 136.8, 134.8, 133.4, 130.2, 128.0, 127.2, 126.4, 126.3, 123.8, 118.7, 53.7, 42.7,

42.5, 35.3; IR (Neat Film NaCl) 3076, 3029, 2917, 1708, 1608, 1496, 1465, 1436, 1296, 1210, 1030, 995, 922, 756, 703 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{19}H_{18}O$ $[M]^+$: 262.1358, found 262.1365; $[\alpha]_D^{26.1}$ +28.4 (*c* 1.42, CH_2Cl_2, 71% ee).



279

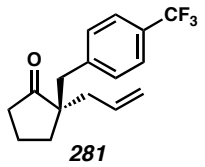
2-Allyl-2-(4-methoxybenzyl)cyclopentanone (279, Table 3.4, entry 6): Reaction time: from β-ketoester, 2 h. Flash chromatography (2 x 14 cm SiO_2, 3% Et_2O in pentane). Colorless oil (207.6 mg, 84% yield). R_f = 0.32 (10:1 Hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 5.71 (dddd, *J* = 7.5, 7.5, 10.2, 14.7 Hz, 1H), 5.14-5.01 (m, 2H), 3.78 (s, 3H), 2.86 (d, *J* = 13.8 Hz, 1H), 2.53 (d, *J* = 13.8 Hz, 1H), 2.26 (dd, *J* = 7.2, 13.5 Hz, 1H), 2.20-2.09 (m, 2H), 1.99 (dd, *J* = 6.6, 8.7 Hz, 1H), 1.95-1.66 (m, 2H), 1.86 (app. dd, *J* = 7.5, 7.5 Hz, 1H), 1.55-1.41 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 223.0, 158.2, 133.7, 131.1, 129.6, 118.5, 113.5, 55.1, 53.2, 40.8, 40.8, 38.9, 30.9, 18.6; IR (Neat Film NaCl) 3075, 2958, 1733, 1611, 1512, 1248, 1178, 1036 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{16}H_{20}O_2$ $[M]^+$: 244.1463, found 156244.1465; $[\alpha]_D^{25.1}$ +7.34 (*c* 1.065, CH_2Cl_2, 73% ee).



280

2-Allyl-2-(4-methylbenzyl)cyclopentanone (280, Table 3.4, entry 7): Reaction time: from β-ketoester, 2 h. Flash chromatography (SiO_2, 5% Et_2O in pentane). 84%

yield, 73% ee. R_f = 0.39 (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, *J* = 7.7 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 5.72 (dddd, *J* = 17.0, 10.4, 8.0, 6.9 Hz, 1H), 5.10 (app. ddd, *J* = 10.1, 2.1, 1.1 Hz, 1H), 5.06 (app. ddd, *J* = 16.7, 2.1, 1.3 Hz, 1H), 2.87 (d, *J* = 13.3 Hz, 1H), 2.55 (d, *J* = 13.3 Hz, 1H), 2.31 (s, 3H), 2.29-2.22 (m, 1H), 2.21-2.07 (comp. m, 2H), 2.05-1.82 (comp. m, 3H), 1.82-1.65 (m, 1H), 1.56-1.41 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 223.2, 136.1, 134.7, 133.9, 130.3, 129.0, 118.8, 53.4, 41.4, 41.0, 39.1, 31.1, 21.2, 18.8; IR (Neat Film NaCl) 3080, 2961, 2915, 1737, 1515, 1441, 1157, 921, 810, 666 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{16}H_{20}O$ $[M]^+$: 228.1514, found 228.1505; $[\alpha]_D^{26.2}$ +9.1 (*c* 2.68, CH_2Cl_2, 73% ee).



281

2-Allyl-2-(4-(trifluoromethyl)benzyl)cyclopentanone (281, Table 3.4, entry 8): Reaction time: from β-ketoester, 2 h. Flash chromatography (2 x 14 cm SiO_2, 2 → 3% Et_2O in pentane). Colorless oil (239.3 mg, 83% yield). R_f = 0.39 (10:1 Hexane:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 5.73 (dddd, *J* = 7.5, 7.5, 10.2, 17.4 Hz, 1H), 5.17-5.05 (m, 2H), 2.97 (d, *J* = 13.2 Hz, 1H), 2.66 (d, *J* = 13.2 Hz, 1H), 2.26 (dd, *J* = 7.2, 13.5 Hz, 1H), 2.24-2.19 (m, 1H), 2.16 (dd, *J* = 7.2, 13.5 Hz, 1H), 2.01-1.70 (m, 3H), 1.59-1.43 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 222.1, 142.0, 133.1, 130.6, 128.7 (q, $J_{C\text{-}F}$ = 32.2 Hz), 125.1 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.2 (q, $J_{C\text{-}F}$ = 269.2 Hz), 119.0, 53.1, 41.0, 40.7, 38.6, 31.0, 18.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ –63.29; IR (Neat Film NaCl) 3078, 2964, 1736, 1618, 1326, 1163, 1123, 1068 cm^{-1};

HRMS (EI) *m/z* calc'd for $C_{16}H_{17}OF_3$ $[M]^+$: 282.1232, found 282.1237; $[\alpha]_D^{24.8}$ +5.65 (*c* 1.085, CH_2Cl_2, 60% ee).

3.6.3.3 METHODS FOR DETERMINATION OF ENANTIOMERIC EXCESS

Table 3.6. Methods used for determining product ee

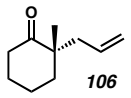
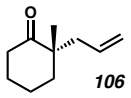
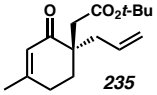
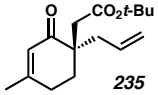
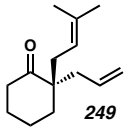
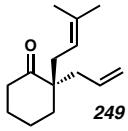
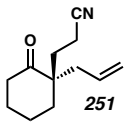
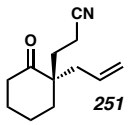
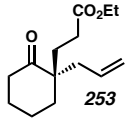
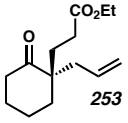
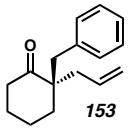
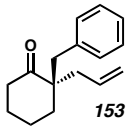
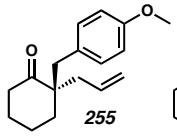
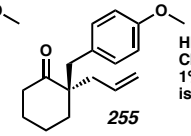
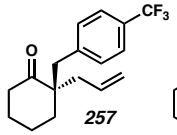
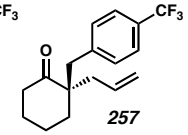
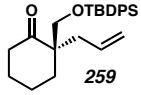
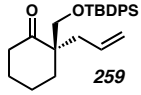
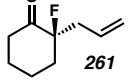
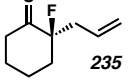
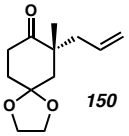
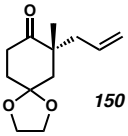
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1	 *106*	 *106*	GC, G-TA 100 °C isotherm	11.13	12.74	88
2	 *235*	 *235*	GC, G-TA 130 °C isotherm	59.36	61.19	86
3	 *249*	 *249*	GC, G-TA 100 °C isotherm	55.511	52.56	91
4	 *251*	 *251*	GC, G-TA 150 °C isotherm	18.75	21.06	88
5	 *253*	 *253*	GC, G-TA 120 °C isotherm	90.98	94.22	90
6	 *153*	 *153*	HPLC Chiracel OJ 2% EtOH in hexane isocratic, 1.0 mL/min	19.81	13.82	85
7	 *255*	 *255*	HPLC Chiralpak AD 1% EtOH in hexane isocratic, 1.0 mL/min	12.87	15.36	86
8	 *257*	 *257*	GC, G-TA 120 °C isotherm for 120 mins, then ramp 3 °C/min	127.74	126.43	82
9	 *259*	 *259*	HPLC Chiracel OD-H 100% hexane isocratic, 1.0 mL/min	16.75	23.91	81
10	 *261*	 *235*	GC, G-TA 110 °C isotherm	6.27	8.02	91
11	 *150*	 *150*	GC, G-TA 120 °C isotherm	26.90	28.64	86

Table 3.6. (continued)

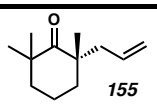
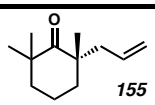
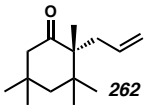
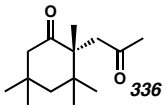
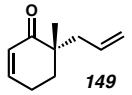
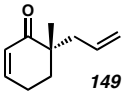
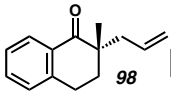
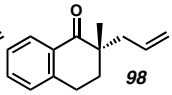
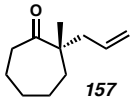
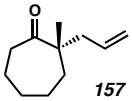
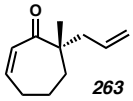
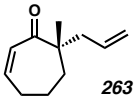
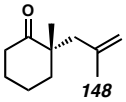
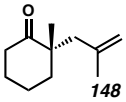
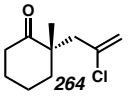
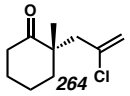
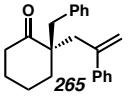
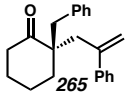
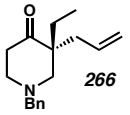
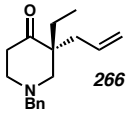
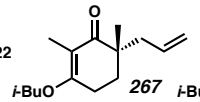
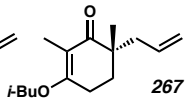
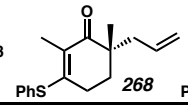
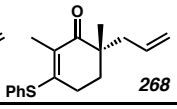
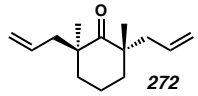
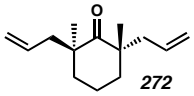
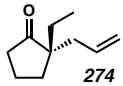
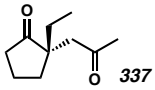
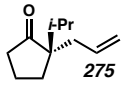
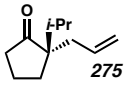
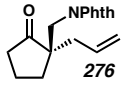
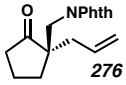
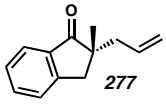
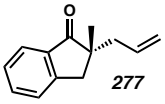
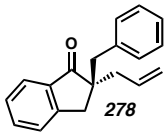
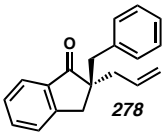
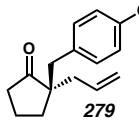
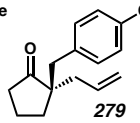
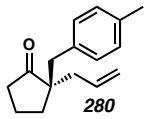
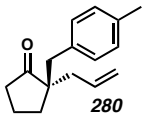
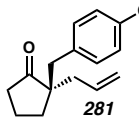
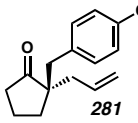
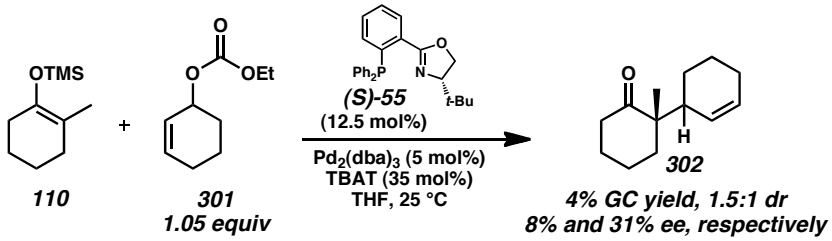
entry	product	compound assayed	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
12	 *155*	 *155*	GC, G-TA 80 °C isotherm	25.48	27.90	92
13	 *262*	 *336*	GC, G-TA 120 °C isotherm	49.12	50.57	85
14	 *149*	 *149*	GC, G-TA 100 °C isotherm	15.31	18.04	90
15	 *98*	 *98*	HPLC Chiracel OD-H 0.1% IPA in heptane isocratic, 0.7 mL/min	19.97	21.48	92
16	 *157*	 *157*	GC, G-TA 110 °C isotherm	9.88	10.68	87
17	 *263*	 *263*	GC, G-TA 125 °C isotherm	10.08	10.61	90
18	 *148*	 *148*	GC, G-TA 100 °C isotherm	15.76	17.65	92
19	 *264* Cl	 *264* Cl	GC, G-TA 100 °C isotherm	44.91	50.06	91
20	 *265* Ph	 *265* Ph	HPLC Chiralpak AD 2.5% EtOH in hexane isocratic, 1.0 mL/min	6.0	6.5	94
21	 *266*	 *266*	HPLC Chiracel OJ 1% EtOH in hexane isocratic, 1.0 mL/min	7.95	8.82	92
22	 *267*	 *267*	SFC, 244 nm Chiralpak AD-H 5% IPA, isocratic 2.0 mL/min, 30 °C	5.175	6.016	75

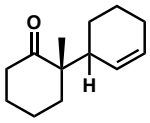
Table 3.6. (continued)

entry	product	compound assayed	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
23	 **268**	 **268**	HPLC Chiralpak AD 4% EtOH in hexane isocratic, 1.0 mL/min	7.243	9.479	92
24	 **272**	 **272**	GC, G-TA 75 °C isotherm	118.51	127.37	92
25	 **274**	 **337**	GC, G-TA 110 °C isotherm	45.22	38.91	86
26	 **275**	 **275**	GC, G-TA 80 °C isotherm	43.95	49.93	84
27	 **276**	 **276**	HPLC Chiracel OD-H 4% IPA in hexane isocratic, 1.0 mL/min	24.13	18.26	48
28	 **277**	 **277**	HPLC Chiracel OD-H 0.1% IPA in hexane isocratic, 0.7 mL/min	21.78	23.74	80
29	 **278**	 **278**	HPLC Chiracel OJ 1% EtOH in hexane isocratic, 1.0 mL/min	28.93	22.38	71
30	 **279**	 **279**	HPLC Chiralpak AD 1% IPA in hexane isocratic, 1.0 mL/min	10.07	11.84	73
31	 **280**	 **280**	HPLC Chiracel OJ 0.3% EtOH in hexane isocratic, 1.0 mL/min	14.88	12.80	73
32	 **281**	 **281**	HPLC Chiralpak AD 1% EtOH in hexane isocratic, 1.0 mL/min	6.42	7.47	60

3.6.3.4 ALLYLATION WITH A SUBSTITUTED ALLYL CARBONATE



In a flame dried 1 dram vial, $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol), (*S*)-*t*-BuPHOX (**55**, 4.7 mg, 0.0625 mmol), and TBAT (18.9 mg, 0.035 mmol) were combined. The vial was evacuated for 10 min prior to addition of THF (3 mL). The mixture was allowed to stir at 25 °C for 30 min prior to addition of tridecane (10 μL, 0.4 mmol), silyl enol ether **110** (18.4 mg, 0.1 mmol), and carbonate **301**[70] (17.9 mg, 0.105 mmol) via syringe. GC yield was determined by a GC assay with tridecane as the internal standard. (Isothermal at 80 °C for 5 min, then ramp from 80 to 115 °C at 10 °C/min, then isothermal at 115°C for 75 min. Silyl enol ether: 5.759 min, tridecane: 7.329 min, minor product diastereomer: 72.223 min, major product diastereomer: 73.434 min). Enantiomeric excess was determined by an Agilent 6850 GC utilizing a G-TA column (30 mm x 0.25 cm) with 1.0 mL/min carrier gas flow. The method utilized for enantiomeric excess determination was isothermal at 110 °C for 60 min (major product diastereomer: 47.504 min and 53.594 min (major enantiomer), minor product diastereomer: 48.282 min (major enantiomer) and 55.842 min). Isolation of products as a mixture of diastereomers was accomplished by flash chromatography (1 cm x 20 cm SiO_2, 2% ether in pentane).

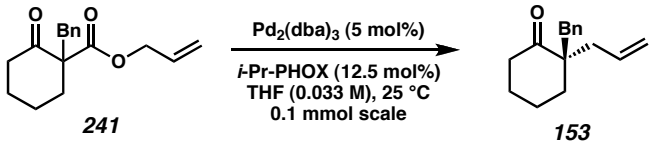


2-(Cyclohex-2-enyl)-2-methylcyclohexanone (302): ^{1}H NMR (300 MHz) δ 5.74 (comp. m, 1H), 5.49 (dddd, 0.7H, *J* = 11.0, 1.9, 1.9, 1.9 Hz), 5.20 (dddd, 0.3H, *J* = 10.1, 2.1, 2.1, 2.1 Hz), 2.84-2.29 (comp. m, 3H), 2.01-1.22 (comp. m, 12H), 0.90 (s, 2.1 H), 0.89 (s, 0.9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.7, 216.1, 129.6, 129.5, 128.0, 127.3, 52.0, 51.7, 39.5, 39.0, 38.6, 37.0, 36.0, 28.0, 27.7, 25.4, 24.0, 23.1, 23.0, 22.9, 21.1, 21.0, 19.4, 18.6; IR (Neat Film, NaCl) 3023, 2934, 2862, 1705, 1452, 1313, 1121 cm^{-1}; HRMS *m/z* calc'd for $C_{13}H_{24}O$ [M_+]: 192.1514, found 192.1519.

3.6.4 MECHANISTIC EXPERIMENTS

3.6.4.1 NONLINEAR EXPERIMENTS

General Procedures for Nonlinear Experiments



241 *153*

THF stock solutions with the desired enantiomeric excess of *i*-Pr-PHOX (**122**) were freshly prepared prior to each experiment. The enantiomeric excess of the *i*-Pr-PHOX delivered was confirmed by subsequent chiral HPLC with a Chiracel OJ column using 1% ethanol in hexanes (1.0 mL/min) as an eluent on the remaining stock solution ((*S*)-*i*-Pr-PHOX (**122**): 13.16 min and (*R*)-*i*-Pr-PHOX: 7.60 min).

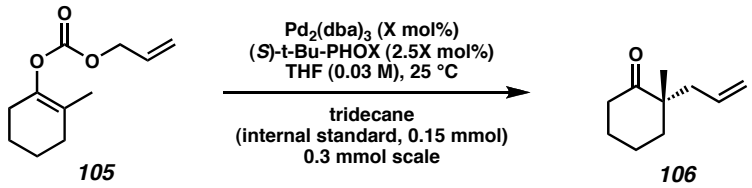
A 1-dram vial equipped with a stir bar was flame dried twice under vacuum. After cooling under nitrogen, $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol) was added. The vial was evacuated for 5 min. THF (3 mL total) was added and then *i*-Pr-PHOX (4.8 mg, 0.0125 mmol) in THF was added via syringe. Contents were allowed to stir for 30 min at 25 °C prior to addition of benzyl β-ketoester **241** (27.2 mg, 0.1 mmol) via syringe. The reaction progress was monitored by TLC. Upon completion, the reaction was concentrated and purified via column chromatography (1 x 11.5 cm SiO_2, 20% Et_2O in pentane). Subsequently, the enantiomeric excess of product was determined by chiral HPLC with a Chiracel OJ column using 1% ethanol in hexanes (1.0 mL/min) as an eluent (**153**: 15.942 min and 24.345 min).

Comparison of the enantiomeric excess of the product vs. the enantiomeric excess of the *i*-Pr-PHOX revealed a linear relationship (Figure 3.2). The absence of a nonlinear effect suggests that the active catalyst in our Tsuji allylation system involves one molecule of *i*-Pr-PHOX, thus one palladium metal center. Furthermore, the absence of a nonlinear effect suggests that the rate-determining step does not involve a bimetallic system, such as a palladium-enolate and a palladium π-allyl complex.

3.6.4.2 KINETICS EXPERIMENTS

General Procedures for Kinetic Experiments

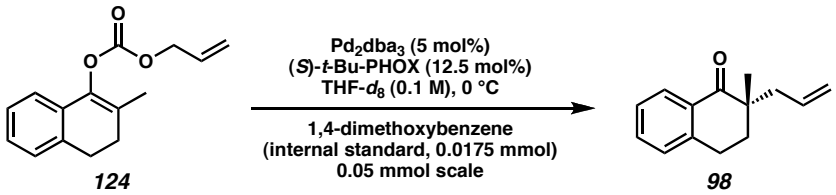
Determination of [Pd(PHOX)] Order



Asymmetric Tsuji allylation of enol carbonate **105** was carried out in an identical manner to general procedure 4, but at different concentrations of the in situ-generated [Pd(PHOX)] complex. Reaction progress was monitored by an achiral GC equipped with a DB-WAX column with tridecane as the internal standard. GC yield was determined by using an acquisition method that ramped the temperature from 70 to 175 °C at a rate of 5 °C/min (tridecane: 6.915 min, cycloalkanone **106**: 12.185 min, and enol carbonate **105**: 17.697 min).

Rate constants (k_{obs}) were determined at 25 °C by GC analysis. The dependence of reaction rate on the concentration of the in situ-generated [Pd(PHOX)] was measured at a constant concentration of **105** (0.03 M) and a constant concentration of tridecane (0.015M). Figure 3.1 shows that the reaction is first-order in [Pd(PHOX)] complex.

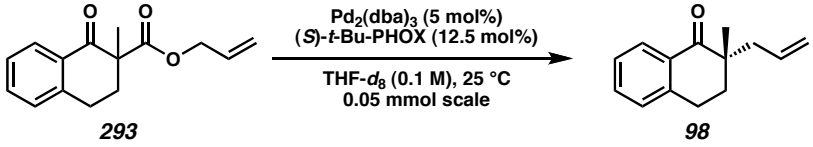
Determination of Substrate Order for Allyl Enol Carbonates



Solid $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol) and (*S*)-*t*-Bu-PHOX (**55**, 2.4 mg, 0.00625 mmol) were placed in a NMR tube equipped with a screw cap and a Teflon septum. The NMR tube was then placed under vacuum and backfilled with argon (3 x 1 min). THF-d_8 (0.2 mL, dried over sodium benzophenone ketyl) was added to the NMR tube via syringe under a positive pressure of argon. The mixture was heated at 40 °C for 30 min. The mixture was then cooled to –78 °C using a CO_2/acetone bath. A THF-d_8 solution (0.3 mL, 0.1 M in substrate total) of allyl enol carbonate **124** (12.2 mg, 0.05 mmol) and 1,4-dimethoxybenzene (2.4 mg, 0.0175 mmol) were added to the reaction mixture under argon. Before recording the ^{1}H NMR spectrum, the sample was allowed to warm for 5–10 s and mixed. Reaction progress was monitored by ^{1}H NMR spectroscopy at 0 ºC, where integral areas of the allylic protons of **124** (δ 4.677 ppm, dt, J = 5.5, 1.0 Hz, 2H) relative to the phenyl protons of the dimethoxybenzene internal standard (δ 6.795 ppm, s, 4H) were obtained at 5 min intervals. The experiment was concluded upon complete conversion of **124**, which was determined by the disappearance of the allylic protons of **124**.

Analysis of consumption of **124** over time is consistent with a zero-order dependence in allyl enol carbonate (Figure 3.3).

Determination of Substrate Order for β-Ketoesters

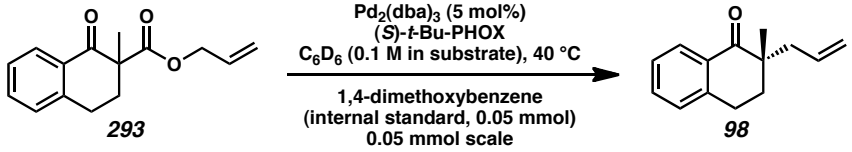


293 ***98***

Solid $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol) and (*S*)-*t*-Bu-PHOX (**55**, 2.4 mg, 0.00625 mmol) were placed in a NMR tube equipped with a screw cap and a Teflon septum. The NMR tube was then placed under vacuum and backfilled with argon (3 x 2 min). THF-d_8 (0.2 mL, dried over sodium benzophenone ketyl) was added to the NMR tube via syringe under a positive pressure of argon. The mixture was heated at 40 °C for 30 min. A THF-d_8 solution (0.3 mL, 0.1 M in substrate total) of allyl β-ketoester **293** (12.2 mg, 0.05 mmol) was added to the reaction mixture under argon. Reaction progress was monitored by ^{1}H NMR spectroscopy at 25 ºC, where integral areas of the allylic protons of **293** (δ 4.494-4.574 ppm, m, 2H) relative to the OCH_2 protons of the THF (δ 3.58 ppm, s, 4H) were obtained at 8 min intervals. The experiment was concluded upon complete conversion of **293**, which was determined by the disappearance of the allylic protons of **293**.

Analysis of consumption of **293** over time is consistent with a zero-order dependence in allyl β-ketoester (Figure 3.4).

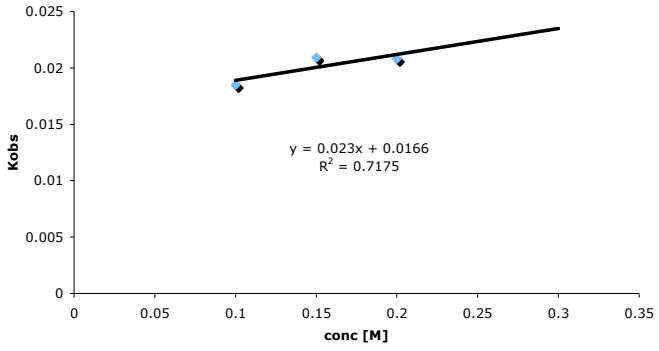
Determination of the Order in (*S*)-*t*-Bu-PHOX



Asymmetric Tsuji allylation of allyl β-ketoester **293** was carried out in C_6D_6 in a similar procedure to the one mentioned above. Reaction progress was monitored by ^{1}H NMR spectroscopy at 40 ºC, where integral areas of the allylic protons of **293** (δ 4.240-4.380 ppm, m, 2H) relative to the CH_3 protons of the internal standard 1,4-dimethoxybenezene (δ 3.338 ppm, s, 6H) were obtained at 4 min intervals.

Rate constants (k_{obs}) were determined at 40 °C by ^{1}H NMR spectroscopy. The dependence of reaction rate on the concentration of the (*S*)-*t*-Bu-PHOX (**55**) was measured at constant concentrations of **293** (0.1 M), $Pd_2(dba)_3$ (0.005 M), and 1,4-dimethoxybenzene (0.01 M). Figure 3.8 shows that the reaction is zero-order in (*S*)-*t*-Bu-PHOX.

Figure 3.8. Plot of k_{obs} vs. concentration of (S)-t-Bu-PHOX.



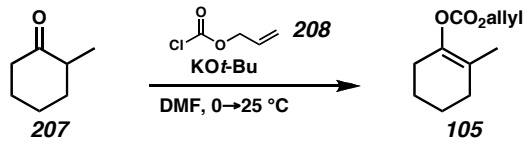
Based on these preliminary kinetic experiments, we believe that our asymmetric Tsuji allylation is zero-order in substrate (for allyl enol carbonate and allyl β-ketoester

substrates), zero-order in PHOX ligand, and first-order in *in situ* palladium(PHOX) complex.

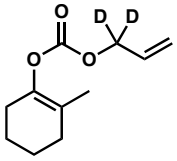
3.6.4.3 DEUTERIUM LABELING EXPERIMENTS

Synthesis of Deuterated Allyl Enol Carbonates

General Procedure:

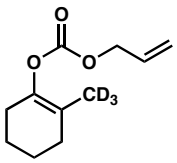


Allyl 2-methylcyclohex-1-enyl carbonate (105):[71] To a solution of potassium *t*-butoxide (5.88 g, 52.5 mmol, 1.05 equiv) in DMF (100 mL) was added 2-methylcyclohexanone (**207**, 6.13 mL, 50 mmol, 1.0 equiv). After 12 h, the reaction mixture was cooled in an ice bath and allyl chloroformate (6.4 mL, 60 mmol, 1.2 equiv) was added in a dropwise fashion. After an additional 30 min in the ice bath and 15 min at 25 °C, the reaction mixture was quenched into water (250 mL), extracted with 2:1 CH_2Cl_2:hexanes (4 x 125 mL), dried ($MgSO_4$), and evaporated. Chromatography (2.5→4% Et_2O in Hexanes on SiO_2) afforded the allyl enol carbonate **105** (4.49 g, 46% yield) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (ddt, *J* = 17.4, 10.5, 5.6 Hz, 1H), 5.36 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.26 (dq, *J* = 10.2, 1.2 Hz, 1H), 4.63 (dt, *J* = 5.7, 1.4 Hz, 2H), 2.13 (m, 2H), 2.02 (m, 2H), 1.70 (m, 2H), 1.59 (m, 2H), 1.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 142.2, 131.5, 120.8, 118.8, 68.5, 30.0, 26.6, 23.1, 22.3, 15.7; IR (Neat Film NaCl) 3936, 1755, 1275, 1239, 1037 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{16}O_3$ $[M]^+$: 196.1100, found 196.1092.



294

Dideuterio allyl enol carbonate 294 (Scheme 3.10): Prepared by general procedure 7 with dideuterioallyl chroroformate, which was synthesized from 1,1-dideuterioallyl alcohol[72] and 20% phosgene in toluene. Flash chromatography (SiO_2, 1 → 2.5% Et_2O in hexanes) gave dideuterio allyl enol carbonate **294** (6% yield) as a colorless oil; R_f = 0.82 (25% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (dd, *J* = 17.0, 10.4 Hz, 1H), 5.38 (d, *J* = 17.1 Hz, 1H), 5.28 (d, *J* = 10.5 Hz, 1H), 2.21-2.09 (comp. m, 2H), 2.08-1.98 (comp. m, 2H), 1.77-1.66 (comp. m, 2H), 1.65-1.53 (comp. m, 2H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 142.2, 131.4, 120.9, 119.0, 30.3, 26.6, 23.1, 22.3, 21.7, 15.8; IR (Neat Film NaCl) 2935, 2862, 1753, 1710, 1280, 1262, 1078 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{14}D_2O_3$ $[M]^+$: 198.1225, found 198.1217.

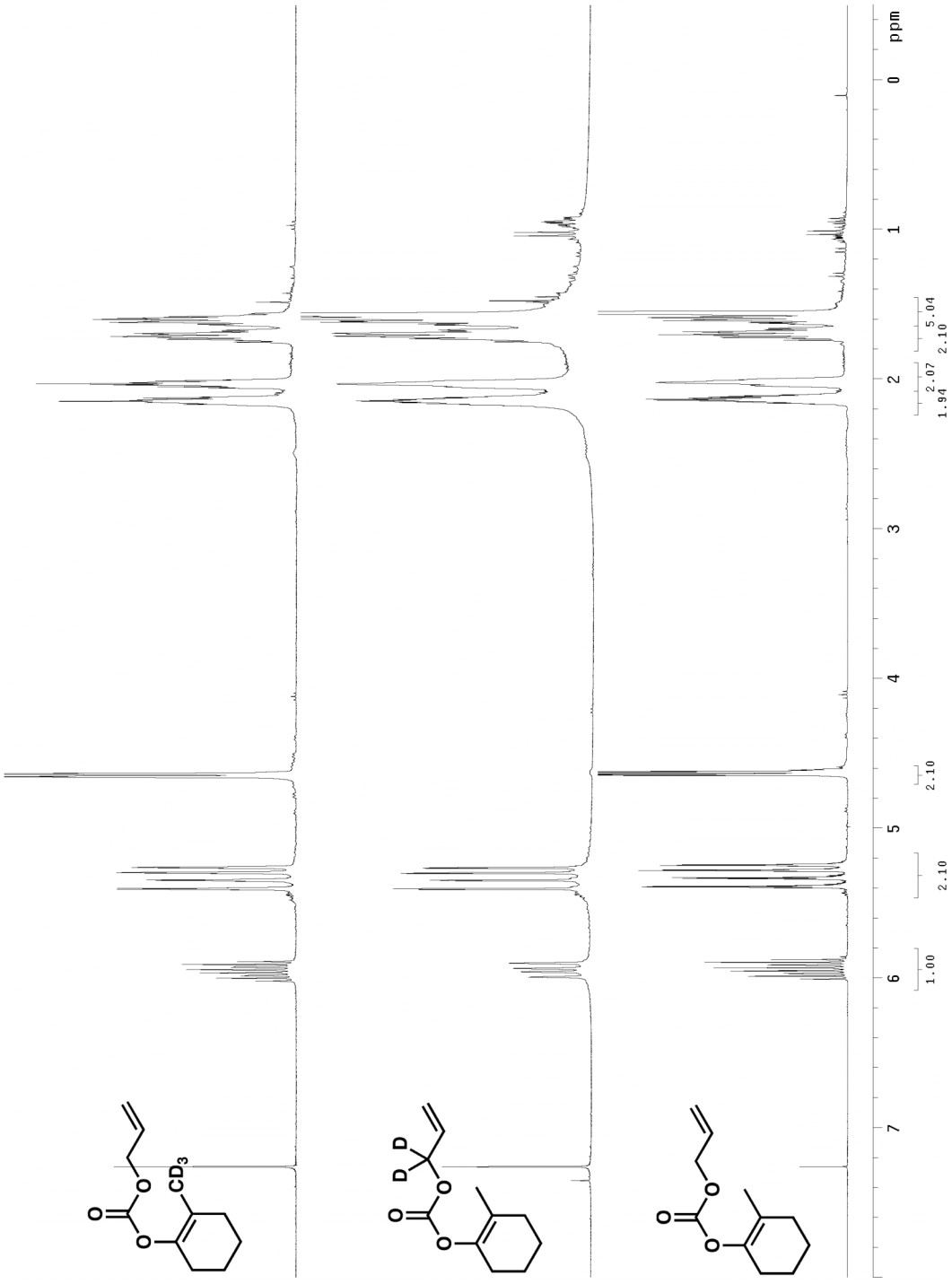


295

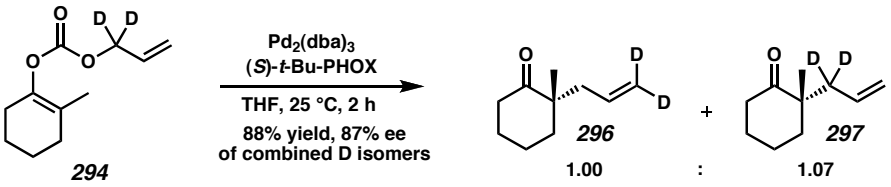
Trideuterio allyl enol carbonate 295 (Scheme 3.10): Prepared by general procedure 7 with 2-trideuteriomethylcyclohexanone.[73.] Flash chromatography (SiO_2, 2 → 2.5% Et_2O in hexanes) gave trideuterio allyl enol carbonate **295** (22% yield) as a colorless oil; R_f = 0.82 (25% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.96 (ddt, *J* = 17.1, 10.8, 6.0 Hz, 1H), 5.38 (d, *J* = 17.3 Hz, 1H), 5.28 (d, *J* = 10.5 Hz, 1H), 4.65 (d, *J*

= 5.7 Hz, 2H), 2.21-2.09 (comp. m, 2H), 2.08-1.98 (comp. m, 2H), 1.77-1.66 (comp. m, 2H), 1.66-1.53 (comp. m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 142.2, 131.5, 120.8, 118.8, 68.5, 30.0, 26.6, 23.1, 22.3; IR (Neat Film NaCl) 2936, 1755, 1705, 1367, 1276, 1247, 1216, 1034, 786 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{13}D_3O_3$ $[M]^+$: 199.1288, found 199.1280.

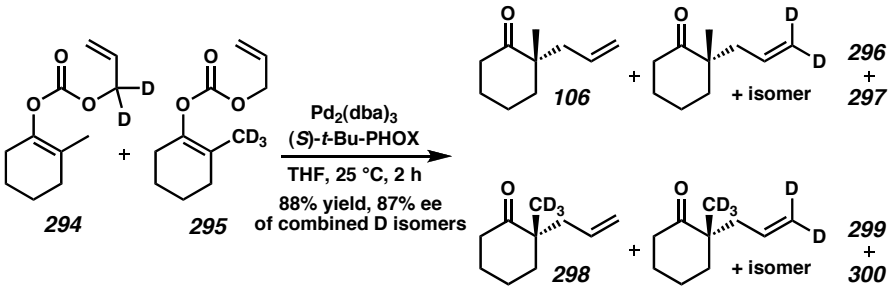
Comparison ^{1}H NMR spectra:



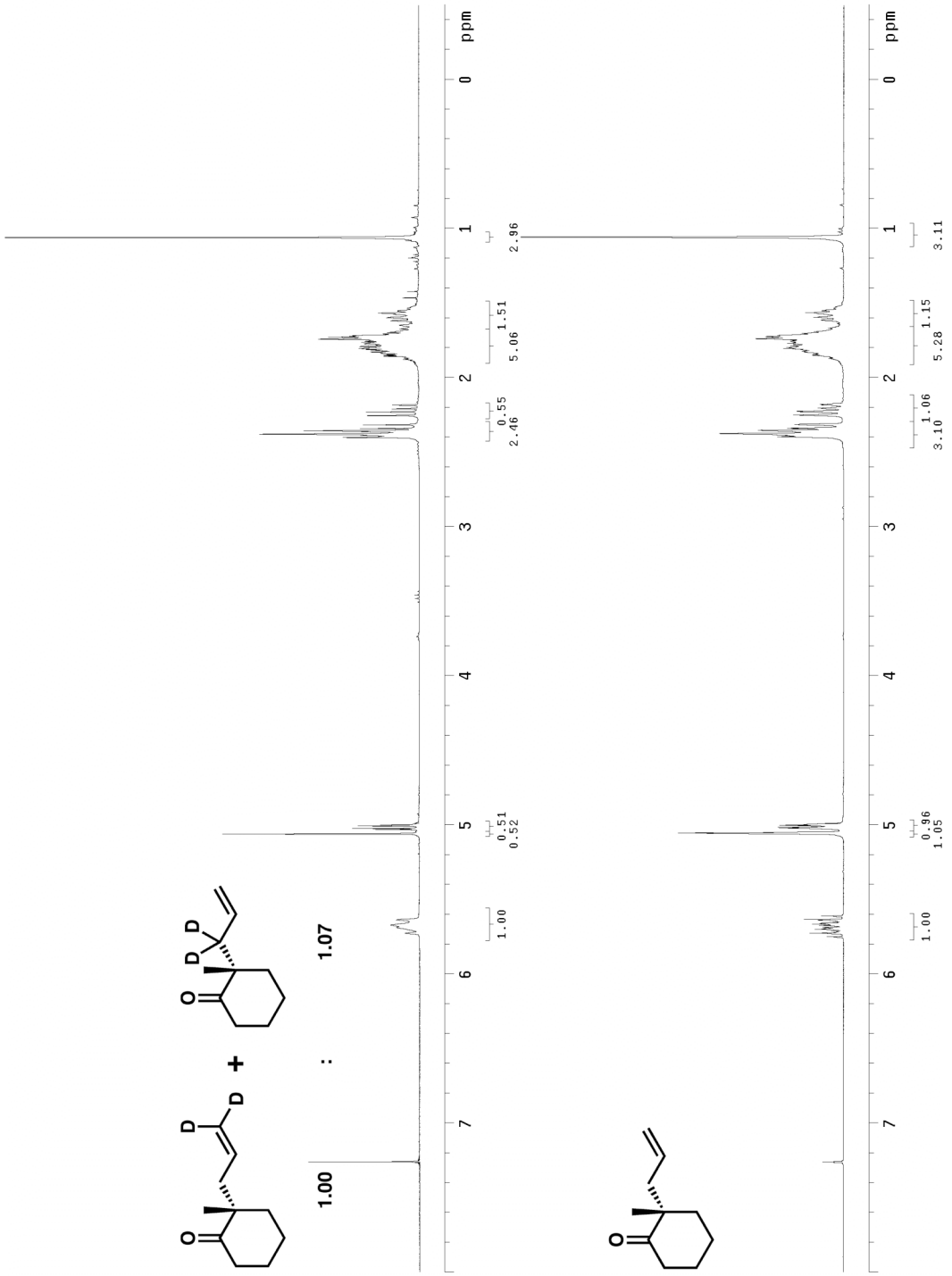
Enantioselective Tsuji Allylation of Deuterated Substrates



Dideuterio allyl enol carbonate **294** (39.7 mg, 0.2 mmol, 1.0 equiv) was exposed under our standard allylation conditions (see Chapter 2). After 2 h, the reaction was complete by TLC. GC analysis showed an 88.1% yield and an 87% ee for the mixture of products. Flash chromatography (SiO_2, 1 → 2.5% Et_2O in pentane) afforded material for NMR analysis, which allowed the ratio of products to be quantified (vide infra).

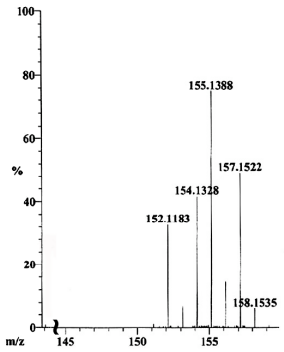


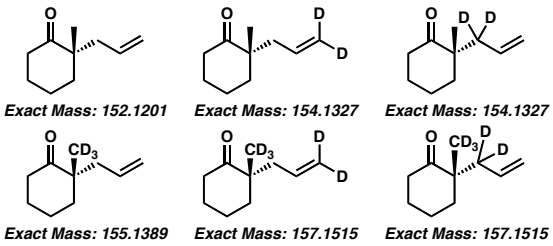
Dideuterio allyl enol carbonate **294** (19.9 mg, 0.1 mmol, 1.0 equiv) and trideuterio allyl enol carbonate **295** (19.8 mg, 0.1 mmol, 1.0 equiv) were simultaneously exposed to our standard conditions (see Chapter 2). After 2 h, the reaction was complete by TLC. GC analysis showed an 88.4% yield and an 87% ee for the mixture of products. Flash chromatography (SiO_2, 1 → 2.5% Et_2O in pentane) afforded material for MS and NMR analysis, which allowed the ratio of products to be quantified (vide infra).


1.00
:
1.07
ppm

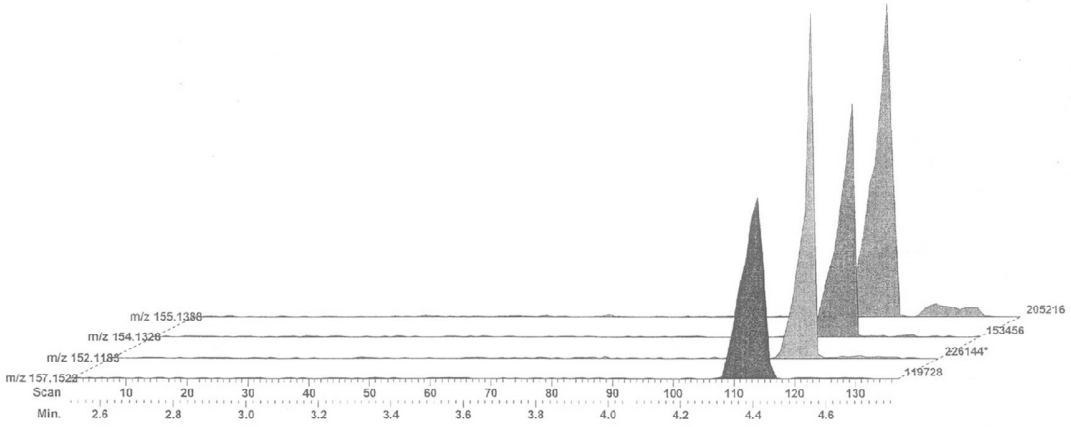
Mass Spectral Analysis of Crossover Experiments

A Representative MS Scan





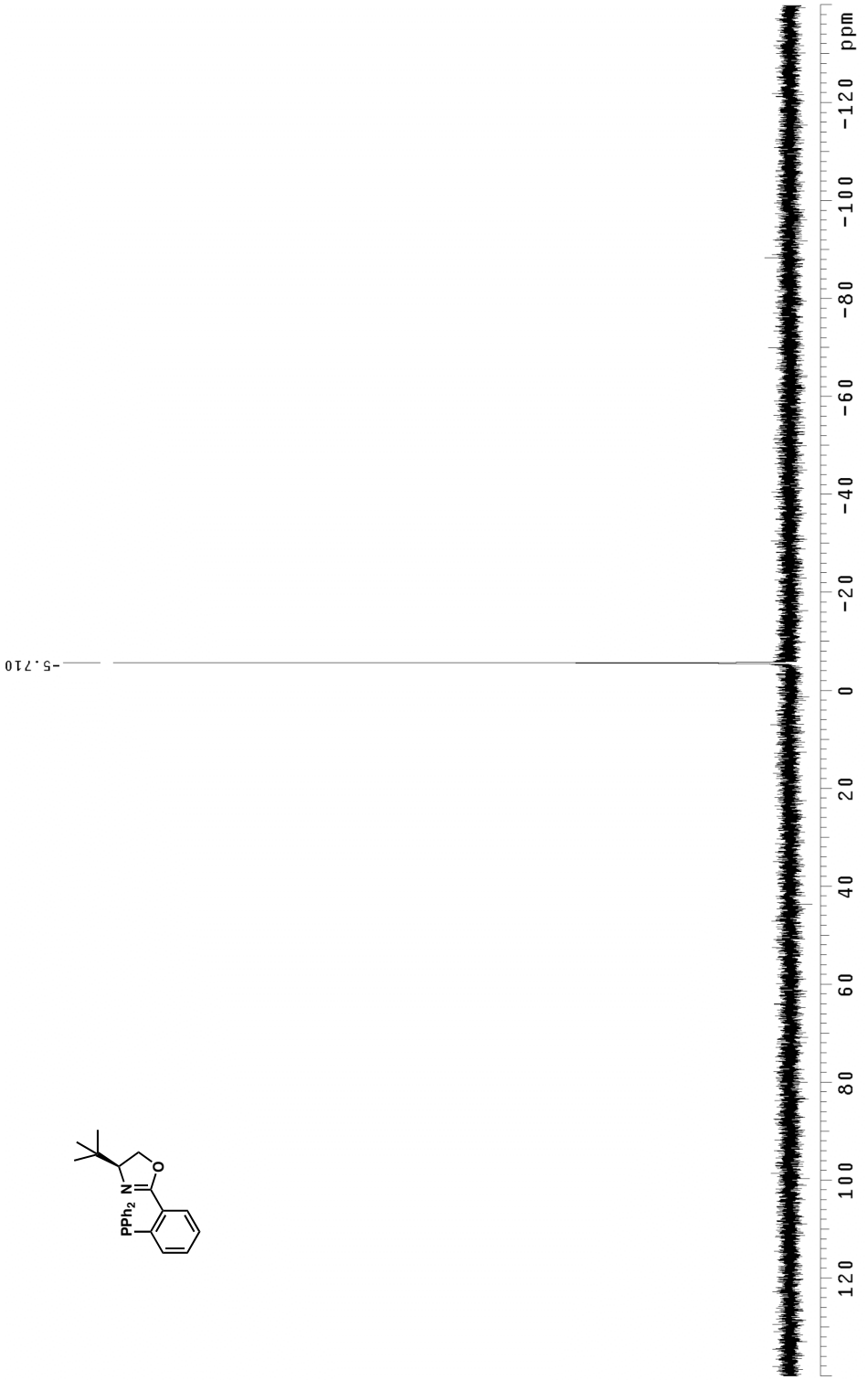
Relative Abundance of Four Product Masses



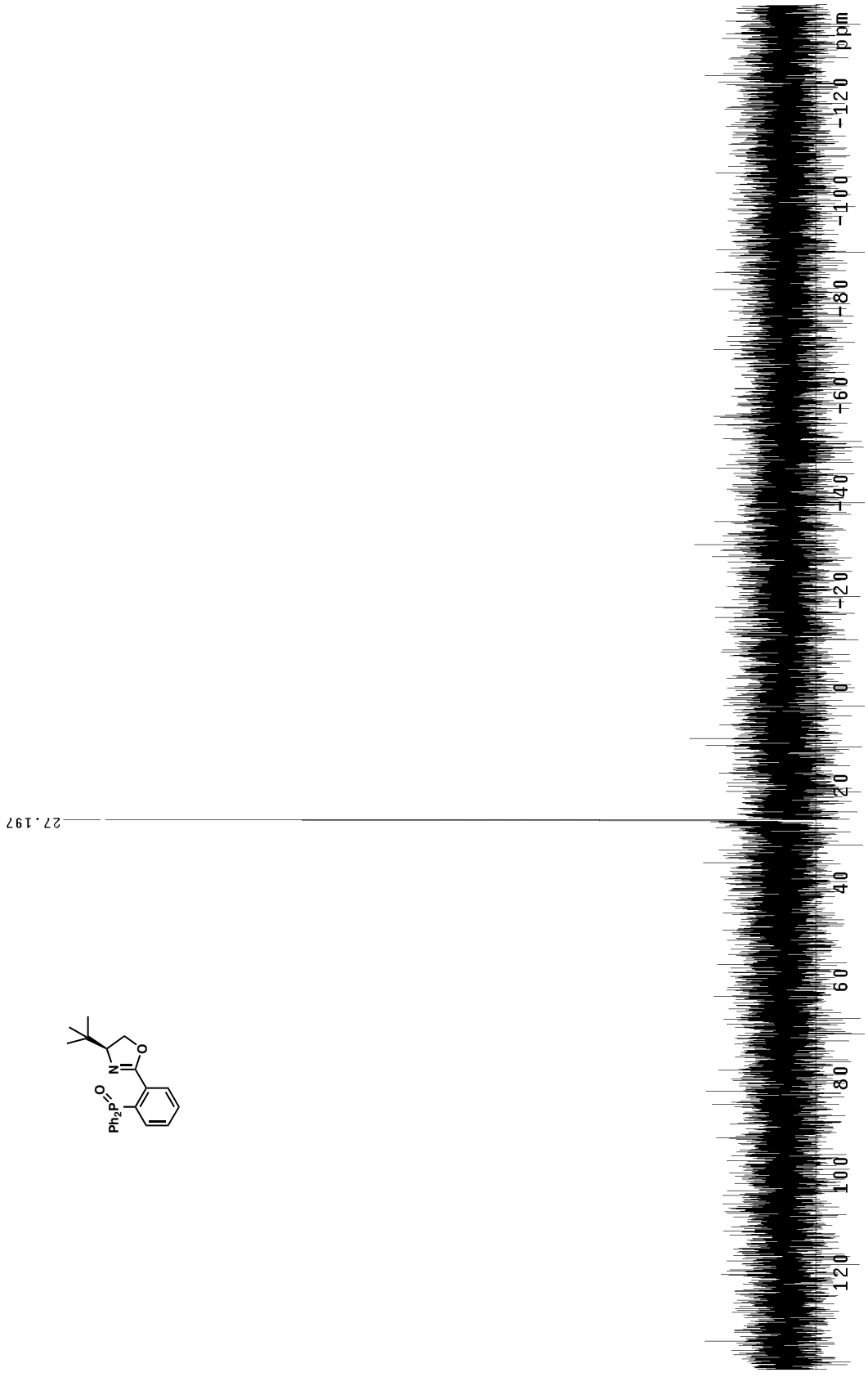
Mass	Scans	Integral	% Abundance
152.1183	110-118	459336	21.23 %
154.1328	110-118	478480	22.12 %
155.1388	108-118	720536	33.31 %
157.1522	107-118	504864	23.34 %
	Total	2163216	100 %

Although the total ion counts are not rigorously quantitative, they clearly suggest that all four masses are present in nearly equal proportions. This was the case whether the reaction was run in THF, dioxane, or benzene.

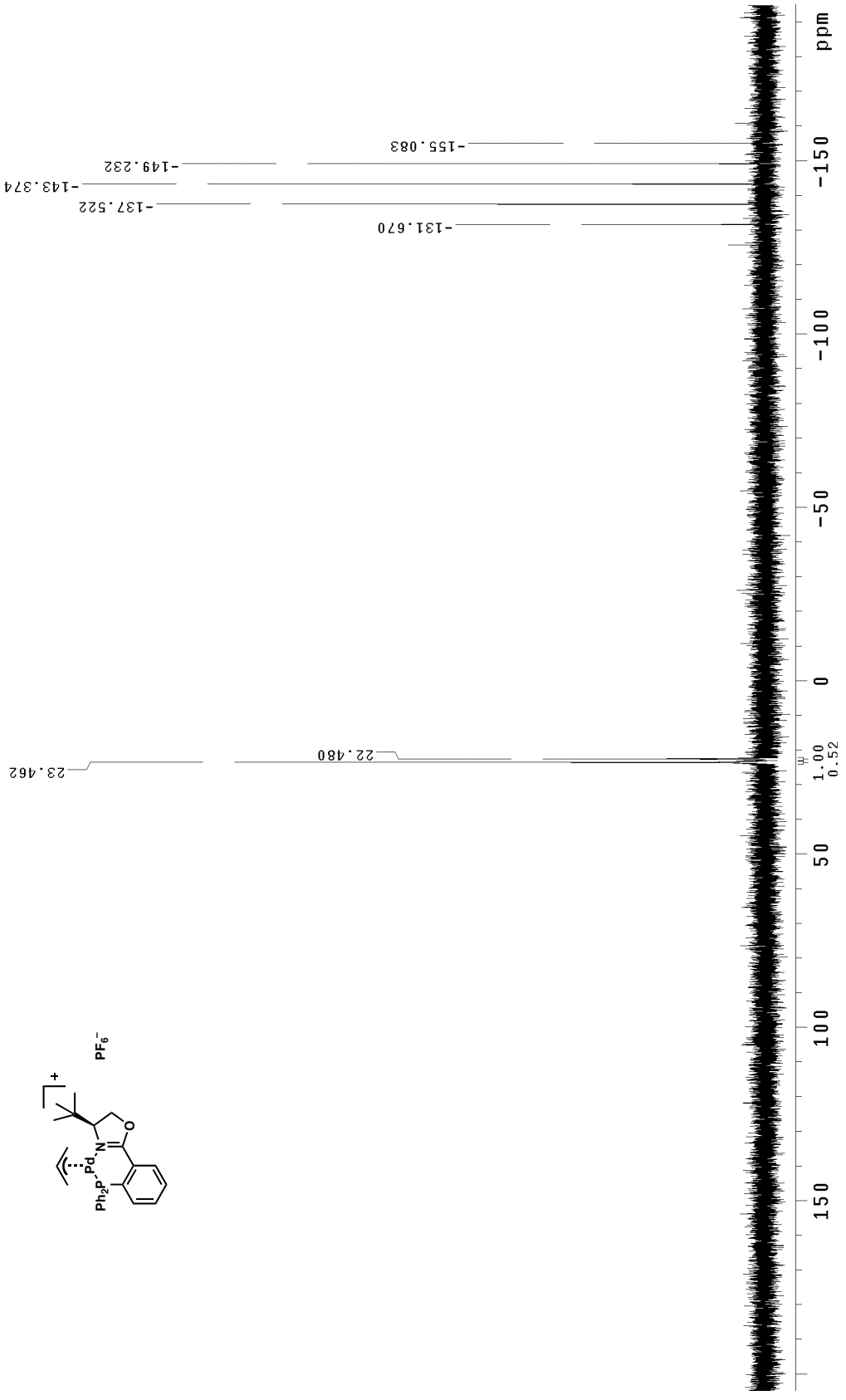
3.6.4.4 ^{31}P NMR STUDIES



^{31}P NMR of (*S*)-*t*-Bu-PHOX (**55**) in THF

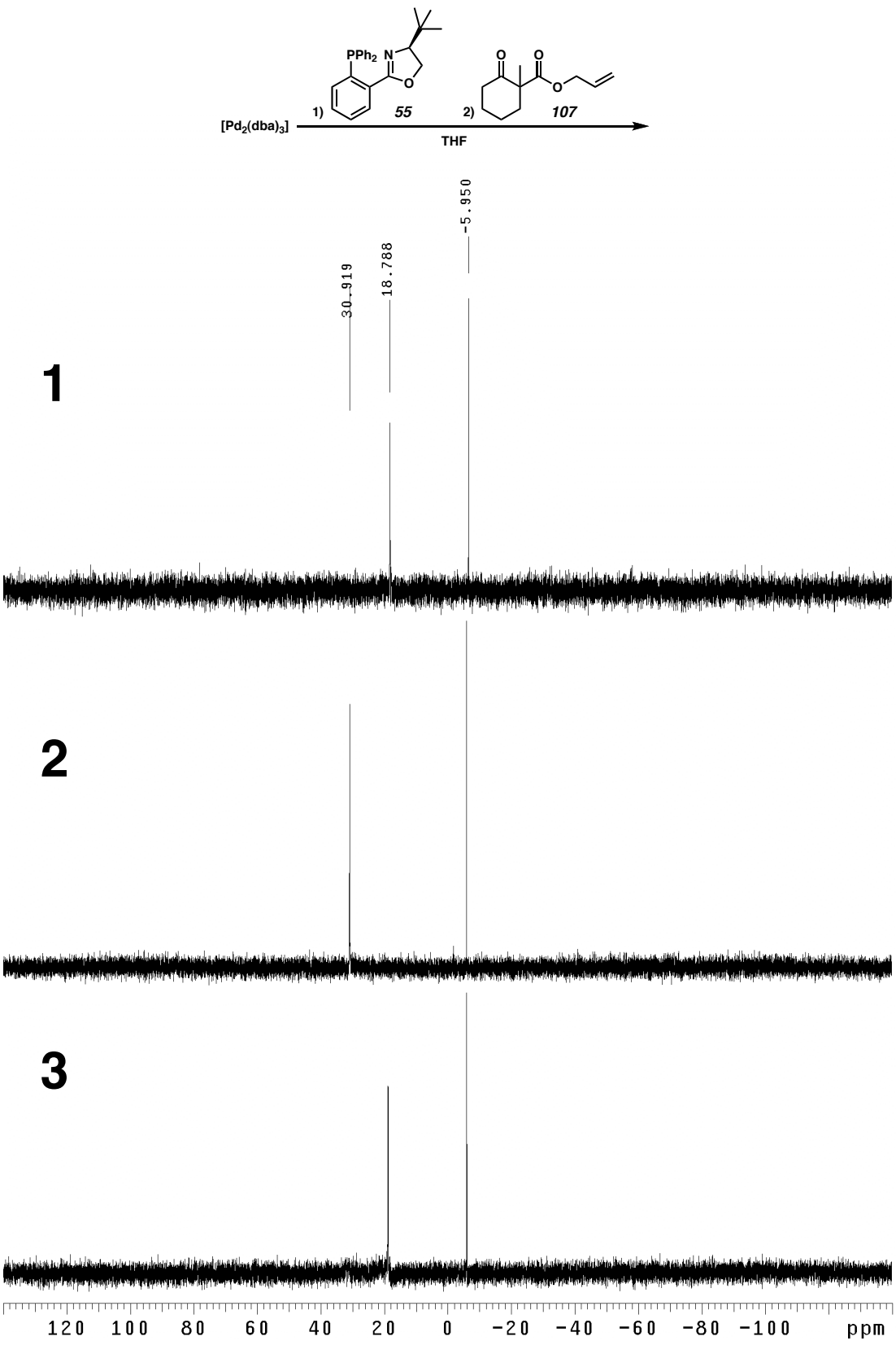


^{31}P NMR of (*S*)-*t*-Bu-PHOX oxide (**125**) in THF

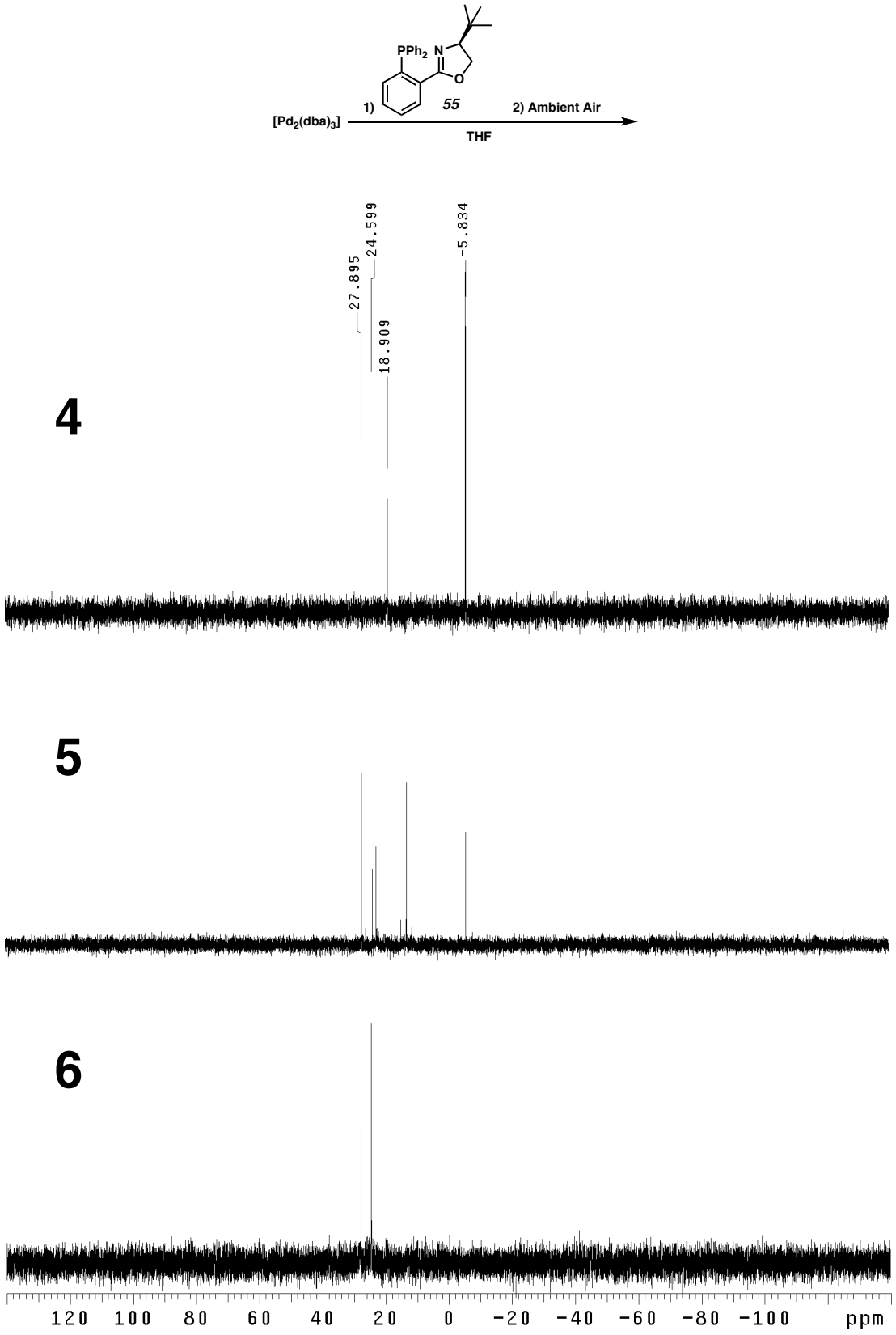


^{31}P NMR of complex **165** in THF

^{31}P NMR study of catalyst resting state. In a nitrogen atmosphere glove box $Pd_2(dba)_3$ (3.0 mg, 3.3 μmol, 1 equiv, dark red-purple powder) was weighed out in a 1 dram vial. Solid (*S*)-*t*-Bu-PHOX ligand (**55**, 3.3 mg, 8.5 μmol, 2.6 equiv, white crystalline solid) was weighed out in a second 1 dram vial. THF (1 mL) that had been dried on an alumina column and then stored over 4Å molecular sieves in the glove box was filtered through a pipette filter constructed with a 2.4 mm GF/A Whatman glass microfiber filter directly into the vial containing the (*S*)-*t*-Bu-PHOX ligand. The solution was mixed manually by pipette until all the material had dissolved forming a clear colorless solution. The solution was then moved by pipette and added to the vial containing $Pd_2(dba)_3$. This solution was mixed manually by pipette for 1 min during which time a dark red-purple solution formed that then lightened to a dark but richly orange color. This solution was then filtered through a pipette filter constructed with a 2.4 mm GF/A Whatman glass microfibre filter directly into an NMR tube separating a bright, richly orange filtrate from a black amorphous precipitate presumed to be colloidal Pd(0) particles. The NMR tube was then sealed with an appropriately sized septum and removed from the glove box. NMR spectrum #1 was taken at this time. Neat 1-methyl-2-oxo-cyclohexanecarboxylic acid allyl ester (**107**) (12.3 mg, 62.8 μmol, 19.1 equiv) was weighed and added to the NMR tube via a 25 μL Hamilton syringe in a single portion. The NMR tube was shaken vigorously for 30 s, and the solution quickly changed color from a rich orange to a lighter yellow-green. NMR spectrum #2 was taken at this time. The NMR tube was then placed in an oil bath regulated at 24 °C and warmed for 3 h, which was 20 min longer than it took for the solution's color to change to a rich orange from a lighter yellow-green. NMR spectrum #3 was taken at this time.


PPh2
N
O
1)
55
2)
O
O
O
107
[Pd2(dba)3]
THF
-5.950
18.788
30.919
1
2
3
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
ppm

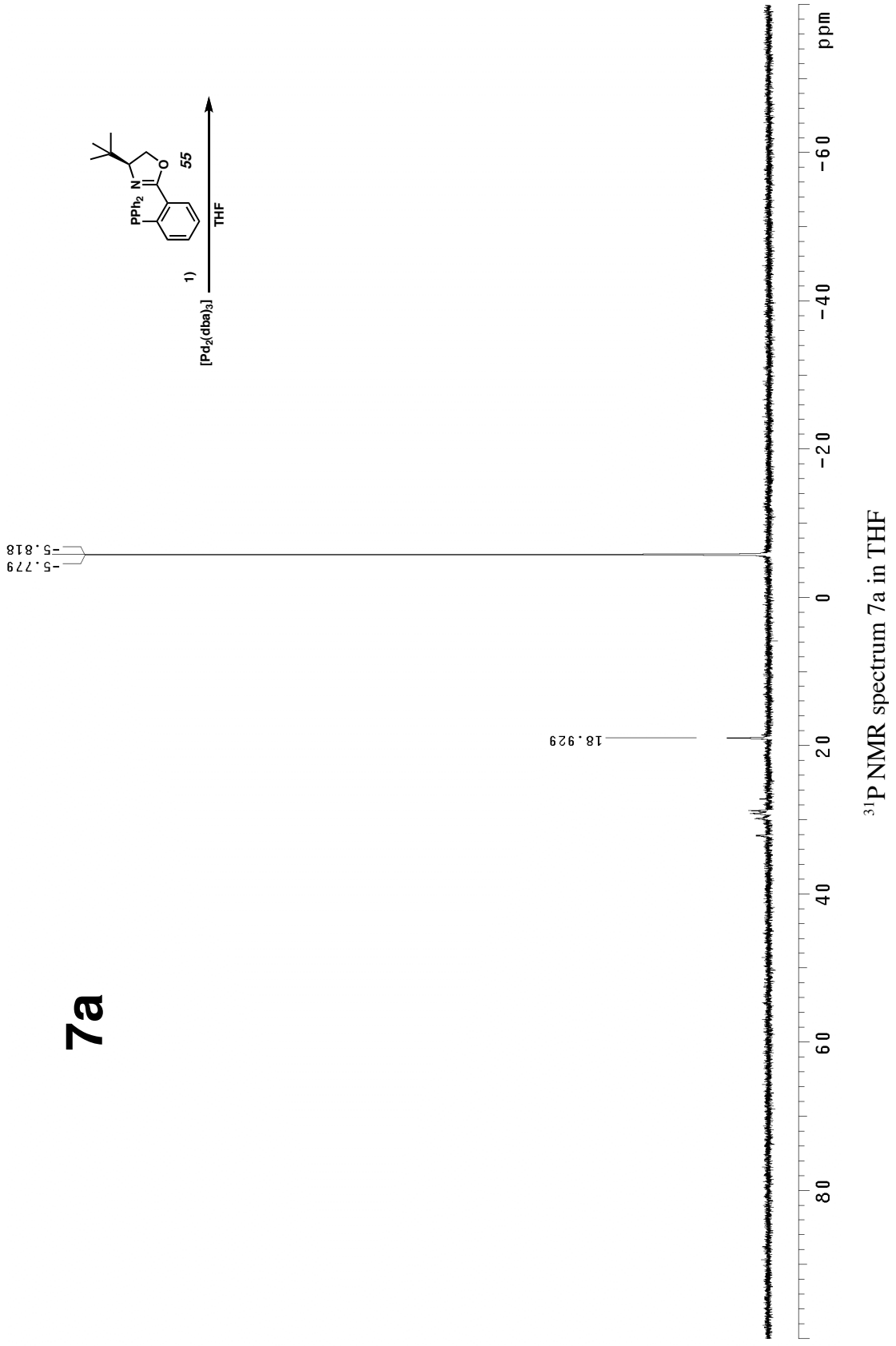
^{31}P NMR study of catalyst decomposition in ambient air. In a nitrogen atmosphere glove box, $Pd_2(dba)_3$ (3.0 mg, 3.3 μmol, 1 equiv, dark red-purple powder) was weighed out in a 1 dram vial. Solid (*S*)-*t*-Bu-PHOX ligand (**55**, 3.3 mg, 8.5 μmols, 2.6 equiv, white crystalline solid) was weighed out in a second 1 dram vial. THF (1 mL) that had been dried on an alumina column and then stored over 4 Å molecular sieves in the glove box was filtered through a pipette filter constructed with a 2.4 mm GF/A Whatman glass microfiber filter directly into the vial containing the (*S*)-*t*-Bu-PHOX ligand (**55**). The solution was mixed manually by pipette until all the material had dissolved forming a clear colorless solution. The solution was then moved by pipette and added to the vial containing $Pd_2(dba)_3$. This solution was mixed manually by pipette for 1 min during which time a dark red-purple solution formed that then lightened to a dark but richly orange solution. This solution was then filtered through a pipette filter constructed with a 2.4 mm GF/A Whatman glass microfibre filter directly into an NMR tube separating a bright, rich orange filtrate from a black amorphous precipitate presumed to be colloidal Pd(0) particles. The NMR tube was then sealed with a standard appropriately sized plastic cap and removed from the glove box. NMR spectrum #4 was taken at this time. The NMR tube was then uncapped on the bench, and quickly flushed with a jet of air to purge the inert atmosphere above the solution in the tube. After 7 h, the solution in the tube had faded from a rich orange to lighter yellow color. NMR spectrum #5 was taken at this time. The tube was left to stand for another 36 h at which point clear crystalline masses had formed. NMR spectrum #6 was taken at this time.


PPh2
N
O
55
1)
2) Ambient Air
[Pd2(dba)3]
THF
27.895
24.599
18.909
-5.834
4
5
6
120 100 80 60 40 20 0 -20 -40 -60 -80 -100 ppm

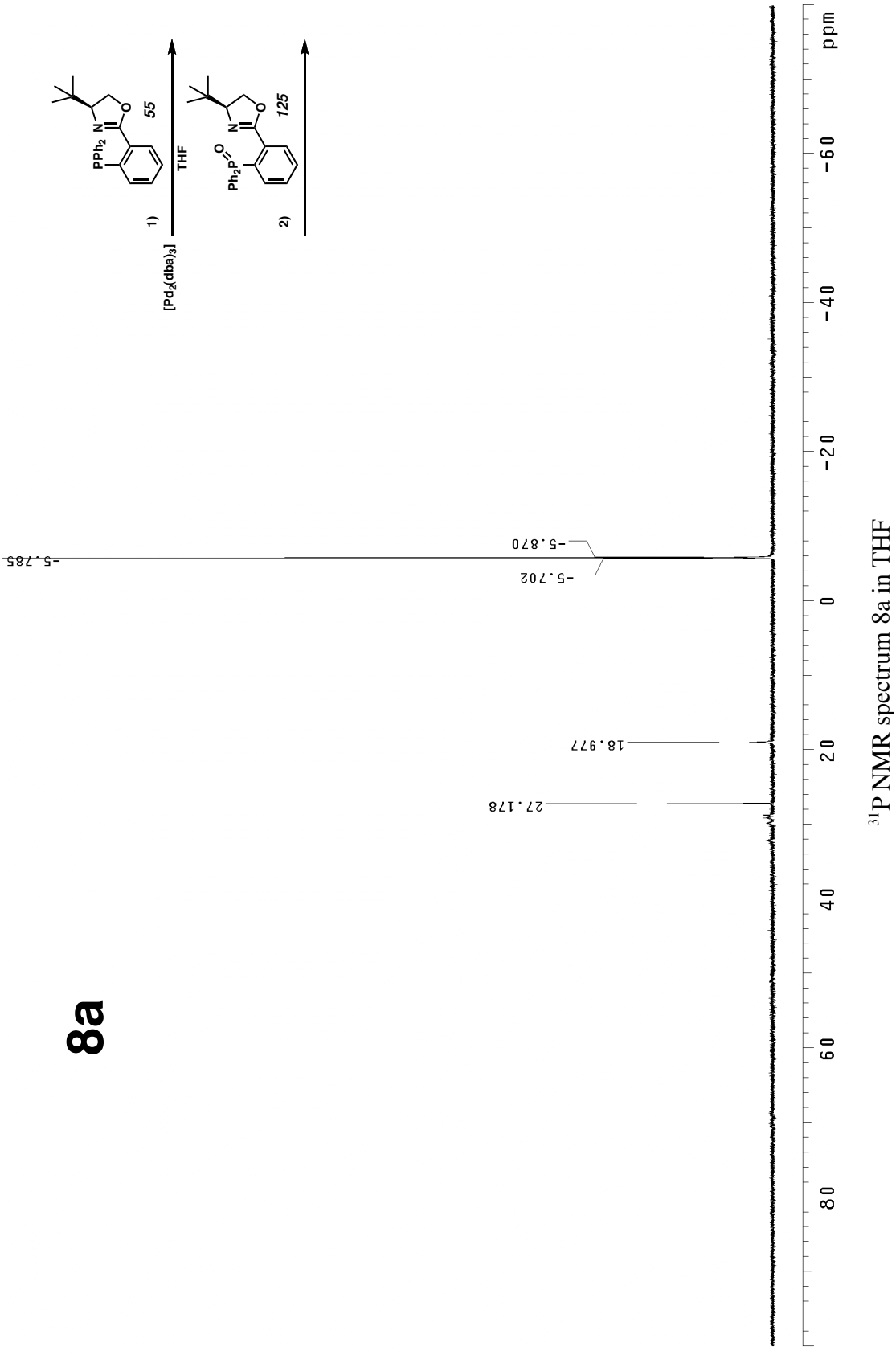
^{31}P NMR study of the Pd-catalyzed conversion of (*S*)-*t*-Bu-PHOX to (*S*)-*t*-Bu-PHOX oxide with ambient air as the oxident. In a nitrogen glove box, (*S*)-*t*-Bu-PHOX ligand (**55**, 18.7 mg, 48.3 μmol, 1 equiv, white crystalline powder) followed by $Pd_2(dba)_3$ (4.8 mg, 5.2 μmol, 0.108 equiv, 10.8 mol%, dark red-purple powder) were weighed directly into a 1 dram vial. THF (1 mL) that had been dried on an alumina column and then stored over 4 Å molecular sieves in the glove box was filtered through a pipette filter constructed with a 2.4 mm GF/A Whatman glass microfiber filter directly into the vial. The solution was mixed manually by pipette for 5 min and then left to mix by diffusion for another 20 min, during which time an initially dark red-purple solution formed that then lightened to a rich orange color. The solution was then filtered through a pipette filter constructed with a 2.4 mm GF/A Whatman glass microfibre filter directly into an NMR tube separating a bright, richly orange filtrate from a black amorphous precipitate presumed to be colloidal Pd(0) particles. The NMR tube was then sealed with an appropriately sized septum and removed from the glove box. NMR spectrum #7a was taken at this time. (*S*)-*t*-Bu-PHOX oxide (**125**, 1.97 mg, 4.9 μmol, 0.101 equiv, 10 mol%, white powder) was weighed out in a 0.5 dram vial. The vial was then sealed with a septum and sparged with argon for 10 s. Anhydrous THF (0.2 mL) was added to the 0.5 dram vial by syringe. The vial was swirled manually until all of its contents dissolved forming a clear solution. The solution in the 0.5 dram vial was then moved by syringe and added as a single portion to the NMR tube. NMR spectrum #8a was taken at this time. The NMR tube was then opened up on the bench and briefly flushed with a jet of ambient air to expel the layer of inert atmosphere above the solution in the tube.

A second NMR tube was flame dried and backfilled with argon. (*S*)-*t*-Bu-PHOX ligand (**55**, 5.0 mg, 12.9 μmol, white crystalline powder) was weighed out and added to the second NMR tube. Anhydrous THF (1 mL) was added to the second NMR tube via a syringe, dissolving the contents of the tube and forming a clear solution. The second NMR tube was then opened on the bench and briefly flushed with a jet of ambient air to expel the layer of inert atmosphere above the solution in the tube.

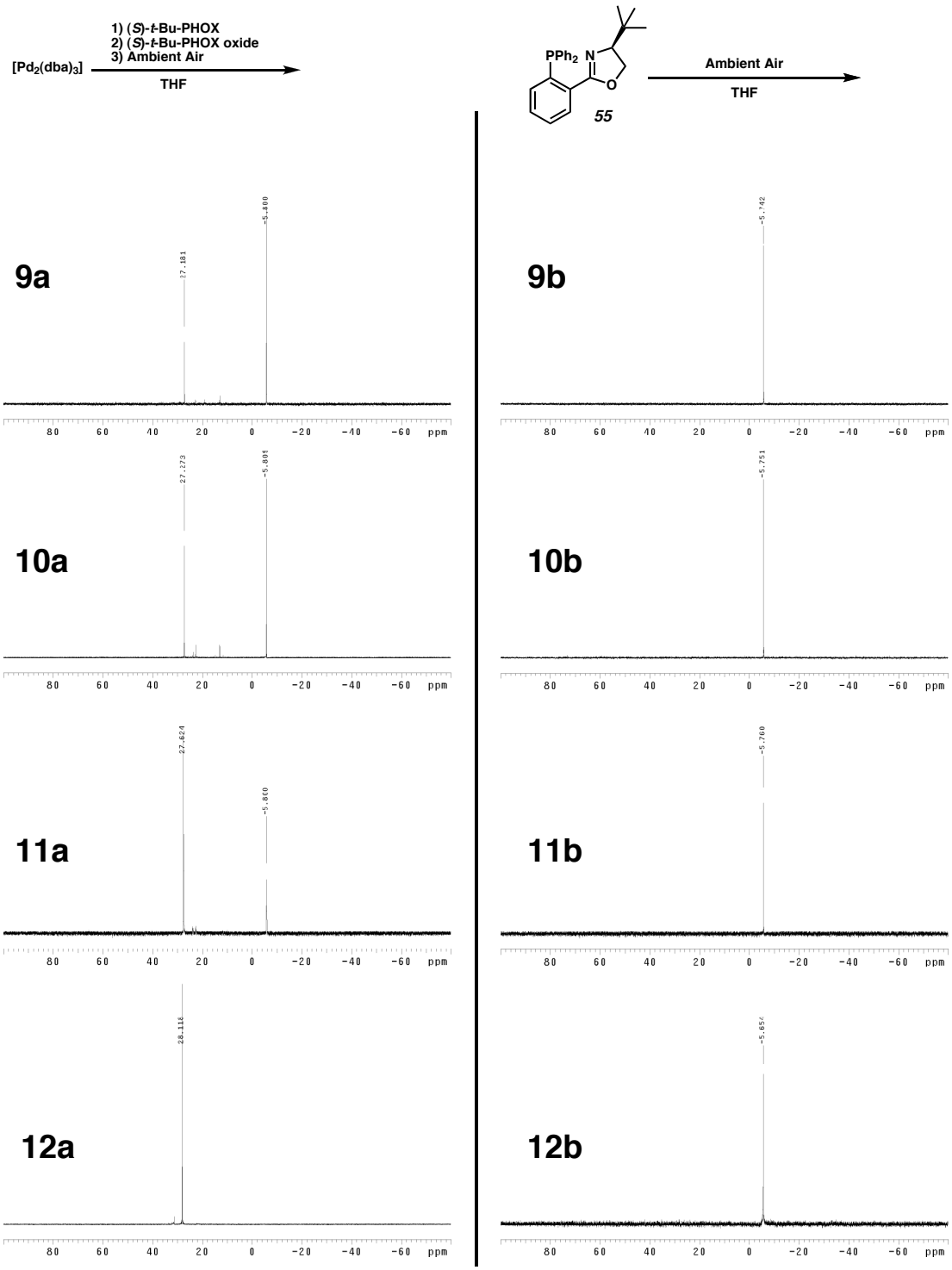
Both NMR tubes were then left opened in an oil bath heated to 25 °C. After 2 h the NMR spectra #9a and #9b were taken of the NMR tube containing the mixture of Pd and ligand, and the NMR tube containing only the ligand, respectively. At 10 h NMR spectra #10a and #10b were taken. At 53 hours NMR spectra #11a and #11b were taken. At 160 hours NMR spectra #12a and #12b were taken.



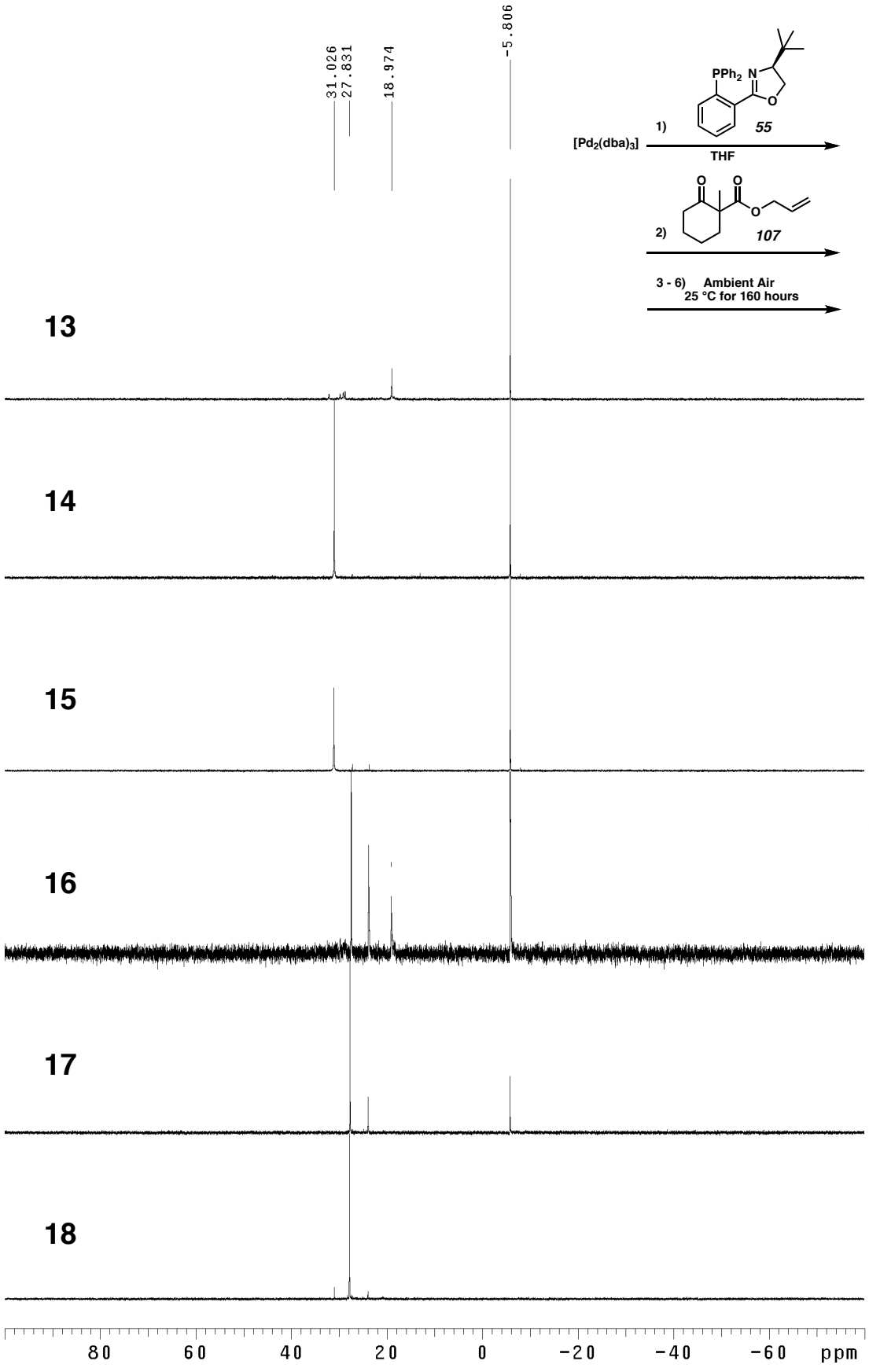
^{31}P NMR spectrum 7a in THF



^{31}P NMR spectrum 8a in THF

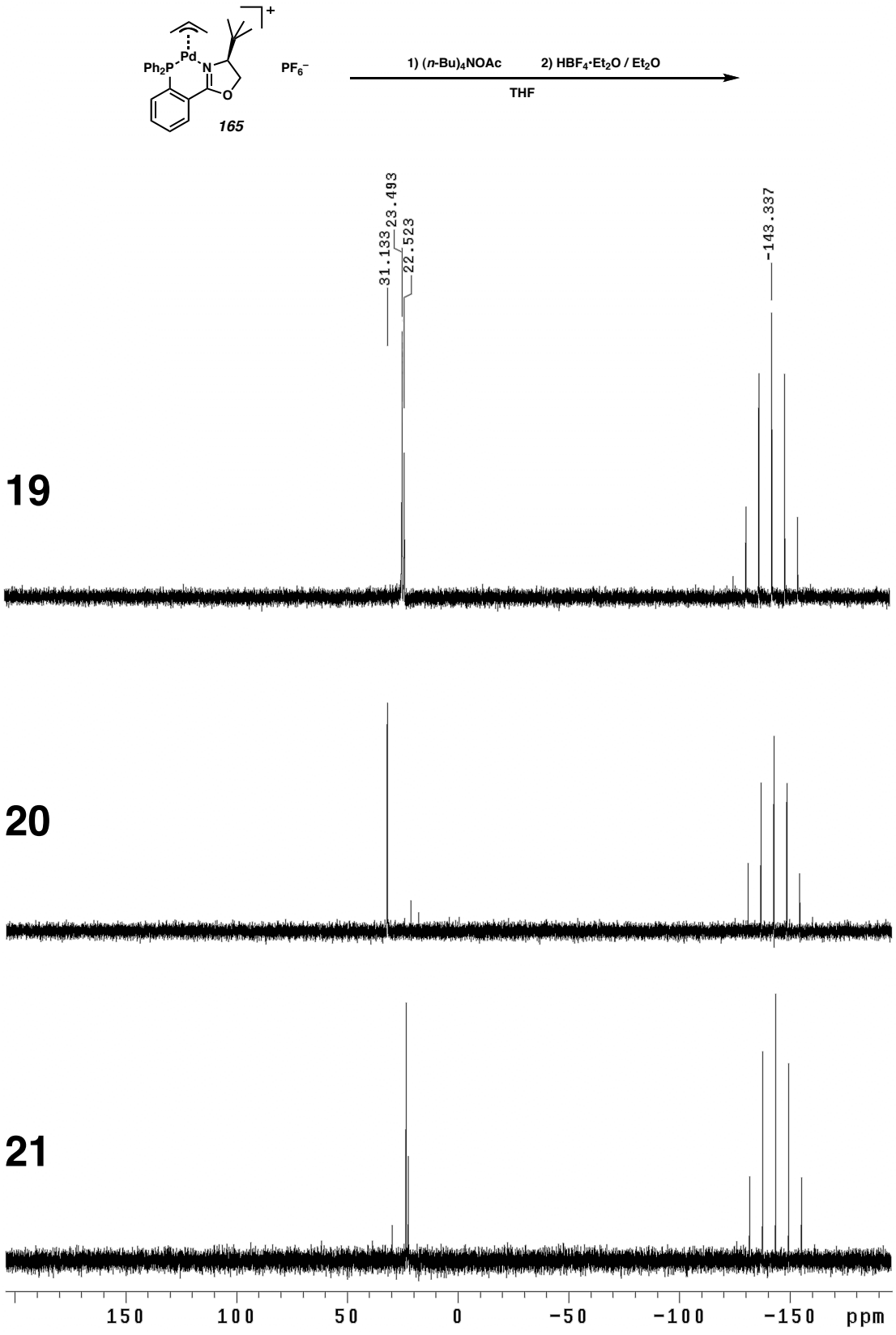

1) (S)-t-Bu-PHOX
2) (S)-t-Bu-PHOX oxide
3) Ambient Air
[Pd2(dba)3]
THF
PPh2
N
O
55
Ambient Air
THF
9a
9b
10a
10b
11a
11b
12a
12b
ppm

^{31}P NMR studies of catalyst decomposition in air from the catalyst's resting state. In a nitrogen glove box $Pd_2(dba)_3$ (8.4 mg, 9.17 μmol, 0.04 equiv, 4.3 mol%, dark red-purple powder) followed by (*S*)-*t*-Bu-PHOX (**55**, 22.0 mg, 56.8 μmol, 26.8 mol%, white crystalline powder) were weighed out neat into a single 1 dram vial. THF (1 mL) that had been dried on an alumina column and then stored over 4 Å molecular sieves in the glove box, was filtered through a pipette filter constructed with a 2.4 mm GF/A Whatman glass microfiber filter directly into the 1 dram vial. The solution was mixed manually by pipette for 5 min and then left to mix by diffusion for another 10 min, during which time an initially dark red-purple solution formed that then lightened to a rich orange color. The solution was then filtered through a pipette filter constructed with a 2.4 mm GF/A Whatman glass microfibre filter directly into an NMR tube separating a bright, rich orange filtrate from a black amorphous precipitate presumed to be colloidal Pd(0) particles. The NMR tube was sealed with an appropriately sized septum and removed from the glove box. NMR spectrum #13 was taken at this time. Neat 1-methyl-2-oxo-cyclohexanecarboxylic acid allyl ester (**107**) (41.5 mg, 211.5 μmol, 1 equiv) was weighed out and added in a single portion via a 100 μL Hamilton syringe. The NMR tube was inverted once, and immediately changed color from a rich orange to a lighter yellow-green. NMR spectrum #14 was taken at this time. The NMR tube was then uncapped on the bench, and quickly flushed with a jet of air to expel the inert atmosphere above the solution in the tube. The NMR tube was left open and then placed in an oil bath regulated to 25 °C. After 2 h, NMR spectrum #15 was taken. After 16 h NMR spectrum #16 was taken. After 48 h NMR spectrum #17 was taken. After 160 h NMR spectrum #18 was taken. The solution had turned a light yellow by this juncture.


31.026
27.831
18.974
-5.806
PPh2 N
O
1)
55
[Pd2(dba)3]
THF
O O
O
2)
107
3 - 6) Ambient Air
25 °C for 160 hours
13
14
15
16
17
18
80
60
40
20
0
-20
-40
-60
ppm

^{31}P NMR study of acetate then acid addition to the palladium π-allyl cation. [Pd(II)(allyl)PHOX]•PF_6 salt (**165**) (12.8 mg, 18.8 μmol, 1 equiv, white powder) was weighed out in a 1 dram vial. Anhydrous THF (0.5 mL) was added to the 1 dram vial via syringe. The vial was sealed, and the solution was mixed manually by swirling until all the solids had dissolved leaving a faintly colored solution. The solution was then transferred via pipette into an NMR tube. NMR spectrum #19 was then collected, showing the endo and exo isomers (23.5 ppm and 22.5 ppm, unknown correspondence) of the [Pd(II)(allyl)PHOX] cation, and the septuplet of the PF_6^- anion. Tetra-*n*-butylammonium acetate (8.8 mg, 30.6 μmol, 1.6 equiv, hygroscopic white nuggets) was weighed into a separate 1 dram vial. Anhydrous THF (0.3 mL) was added to the new vial via syringe. The vial was sealed, and the solution was mixed manually by swirling until all the solids had dissolved, forming a clear colorless solution. The solution was transferred via pipette in a single portion to the NMR tube. Upon addition, the solution instantly became yellow as the two solutions mixed. The NMR tube was sealed and mixed via a single complete inversion turning the entire solution yellow. A ^{31}P NMR spectrum was collected at this time (not depicted) that showed a broad fluxional resonance at 29.9 ppm presumed to be an averaged state of an equilibrium. An additional 7.4 mg of tetra-*n*-butylammonium acetate (25.7 μmol, 1.37 equiv, 3.07 equiv total, hygroscopic white nuggets) was weighed out in a third 1 dram vial. Anhydrous THF (0.2 mL) was added to the third vial via syringe. The vial was sealed, and the solution was mixed manually by swirling until all the solids had dissolved, forming a clear colorless solution. This solution was transferred via pipette in a single portion to the NMR tube. The NMR tube was sealed and mixed via a single complete inversion causing a very

subtle color shift in the solutions appearance. NMR spectrum #20 was collected at this time. Tetrafluoroboric acid diethyl ether adduct (54% weight in diethyl ether, 19.6 mg, 65.4 μmol, 3.47 equiv, light orange viscous solution) was weighed in a 100 μL Hamilton syringe under a blanket of argon, and then added to the NMR tube in a single portion. The NMR tube was sealed and mixed via a single complete inversion, causing the color to rapidly fade from bright yellow to faint beige. NMR spectrum #21 was collected at this time.


Ph2P
Pd
N
O
PF6−
165
1) (n-Bu)4NOAc
2) HBF4·Et2O / Et2O
THF
31.133
23.493
22.523
-143.337
19
20
21
150
100
50
0
-50
-100
-150
ppm

3.6.5 NOTES AND REFERENCES FOR EXPERIMENTAL SECTION

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APPENDIX 2

Spectra of Compound Relevant to Chapter 3

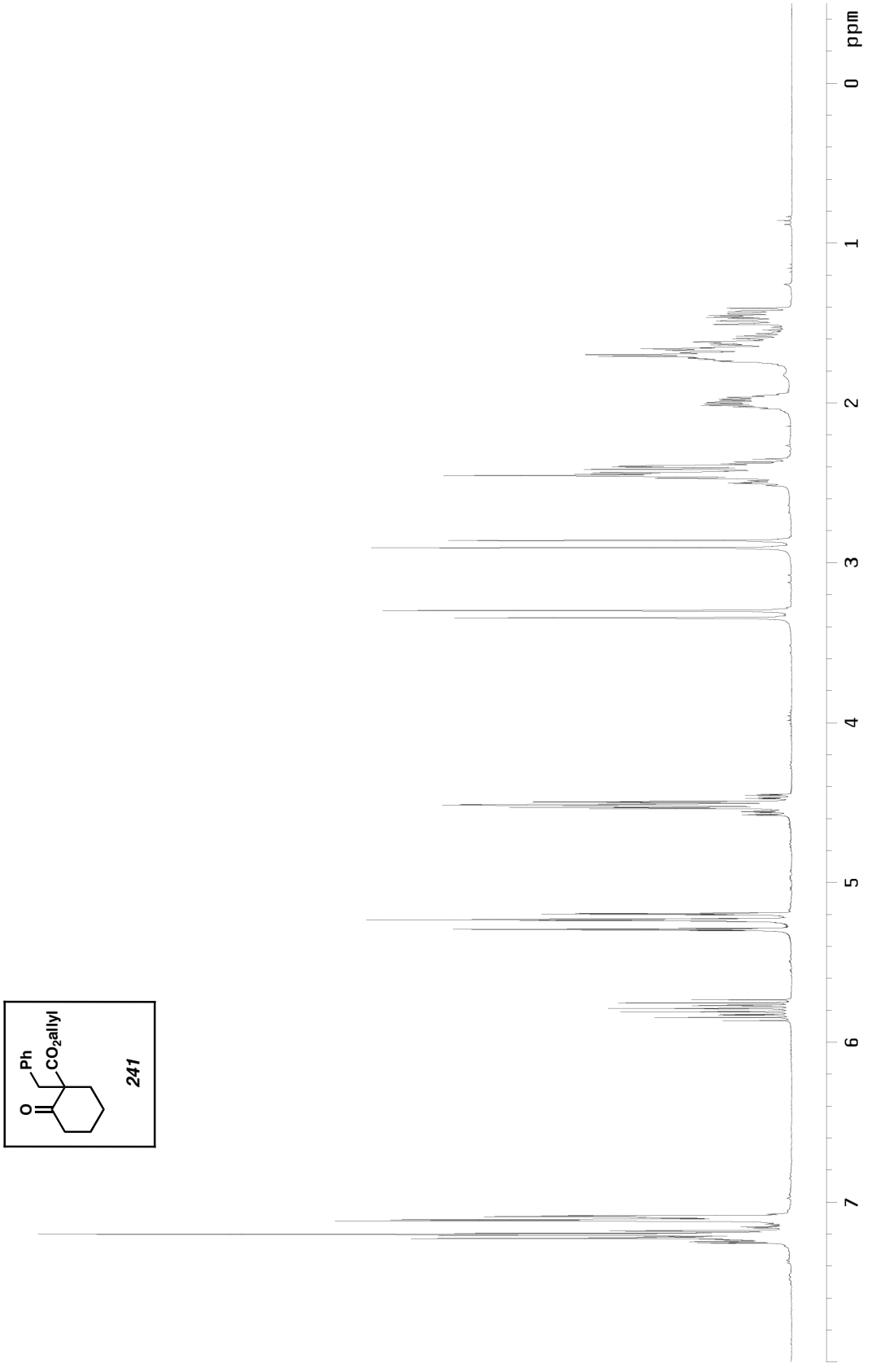


Figure A2.1 ^{1}H *NMR of compound* ***241*** *(300 MHz,* $CDCl_3$*)*

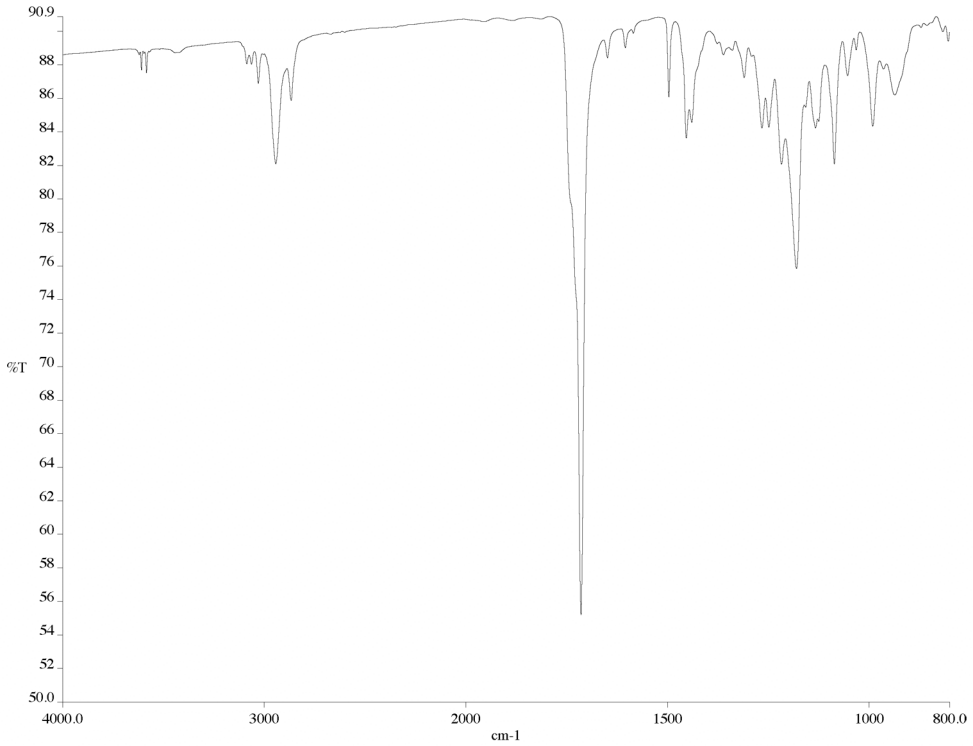


*Figure A2.2 IR of compound **241** (NaCl/film)*

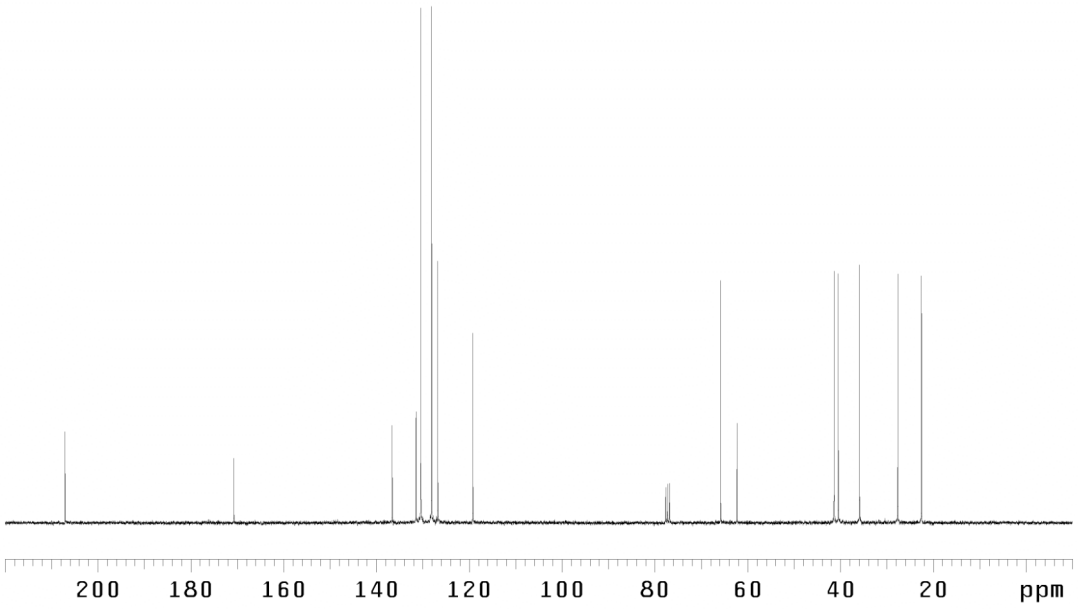


*Figure A2.3 ^{13}C NMR of compound **241** (75 MHz, $CDCl_3$)*

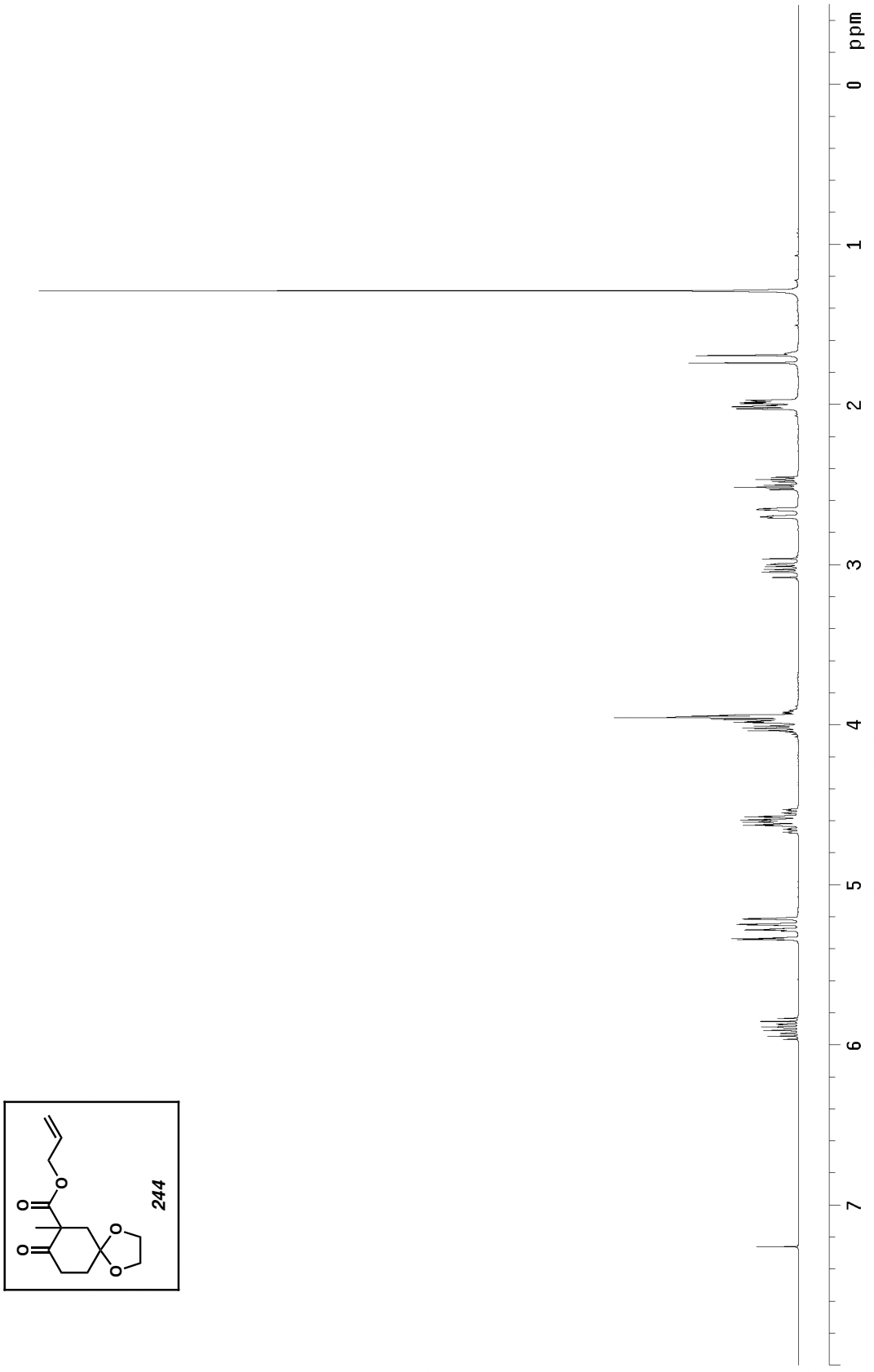


*Figure A2.4 ^1H NMR of compound **244** (300 MHz, $CDCl_3$)*

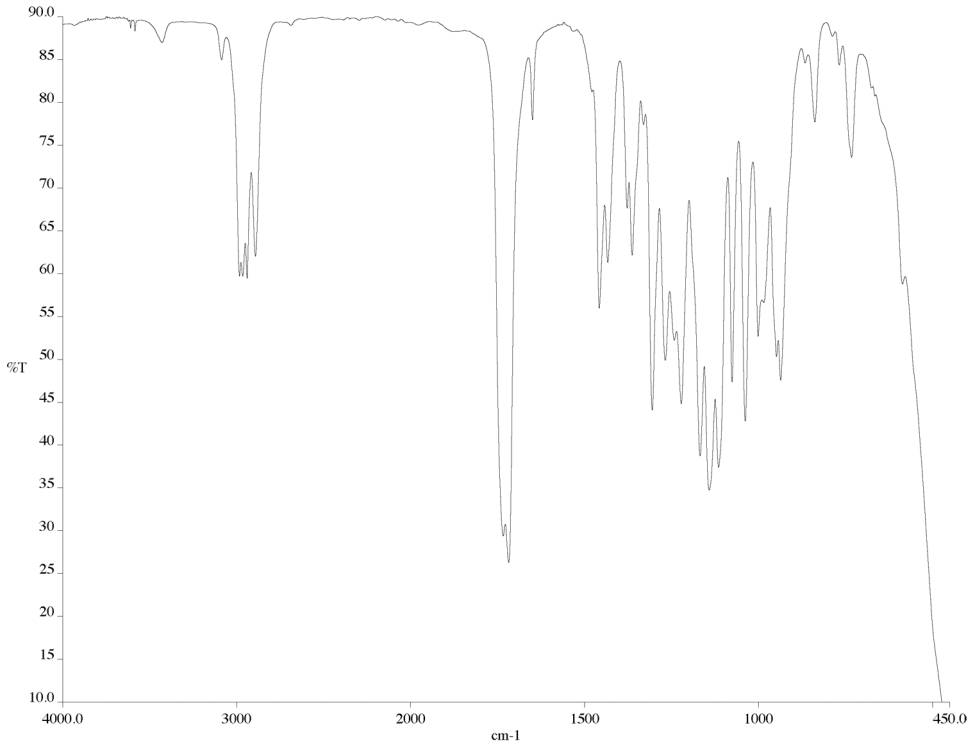


*Figure A2.5 IR of compound **244** (NaCl/film)*

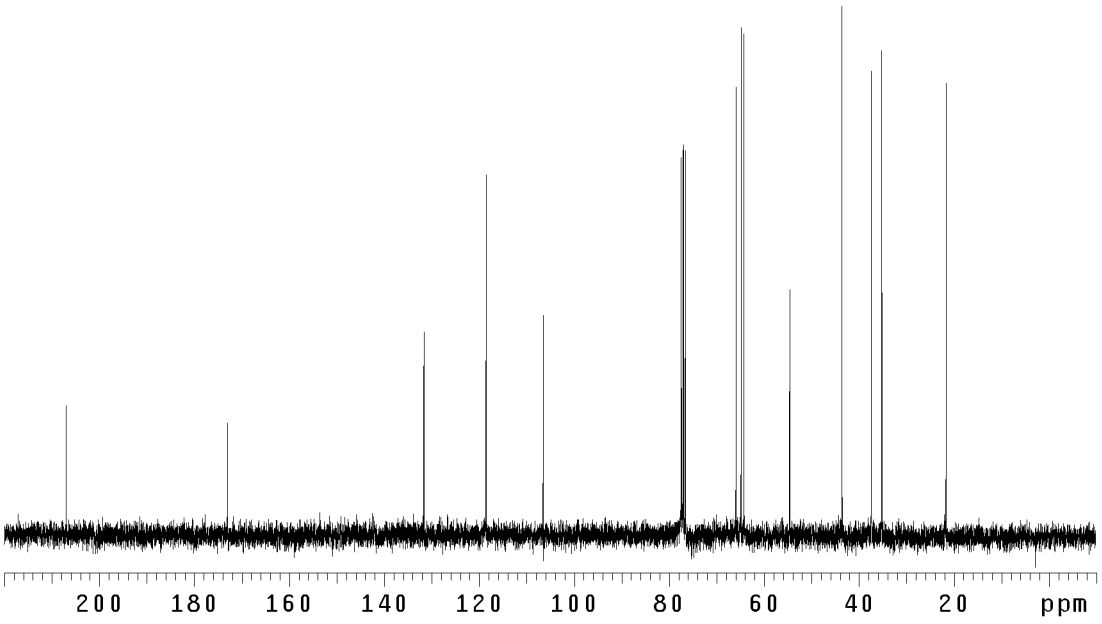


*Figure A2.6 ^{13}C NMR of compound **244** (75 MHz, $CDCl_3$)*

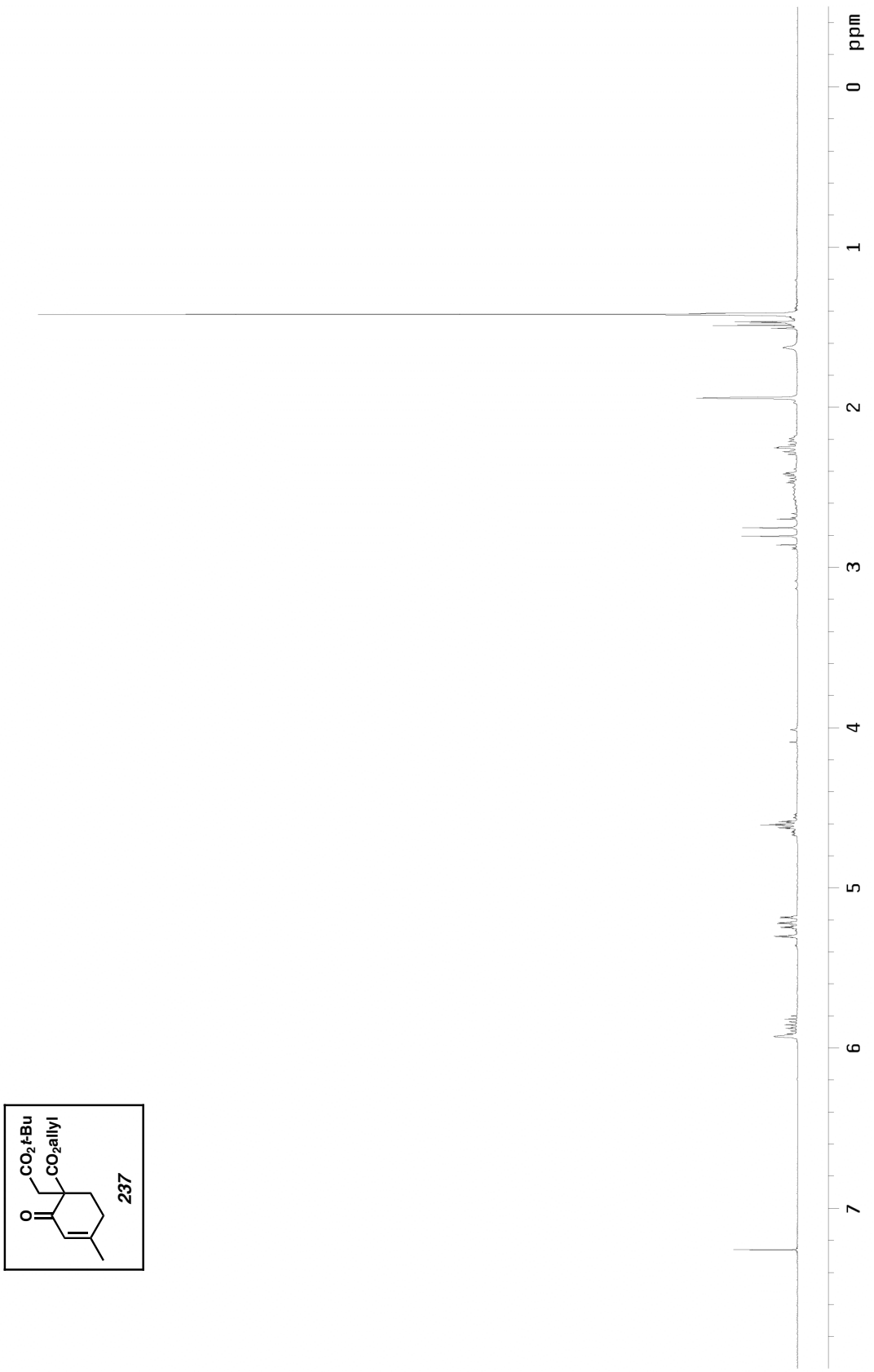


Figure A2.7 ^1H NMR of compound ***237*** *(300 MHz, $CDCl_3$)*

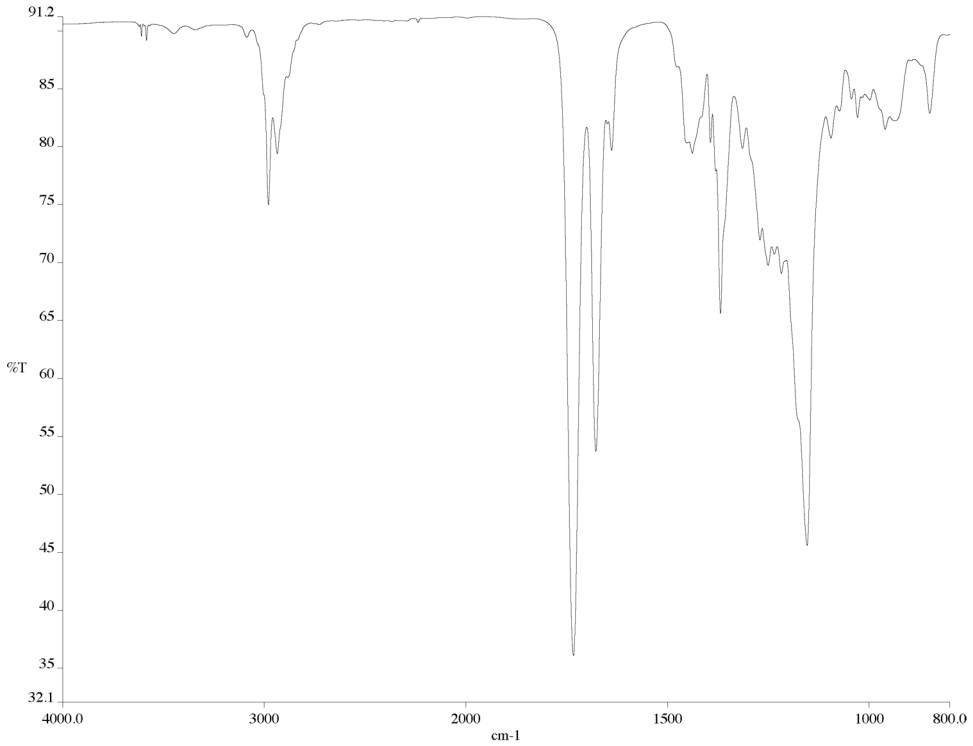


*Figure A2.8 IR of compound **237** (NaCl/film)*

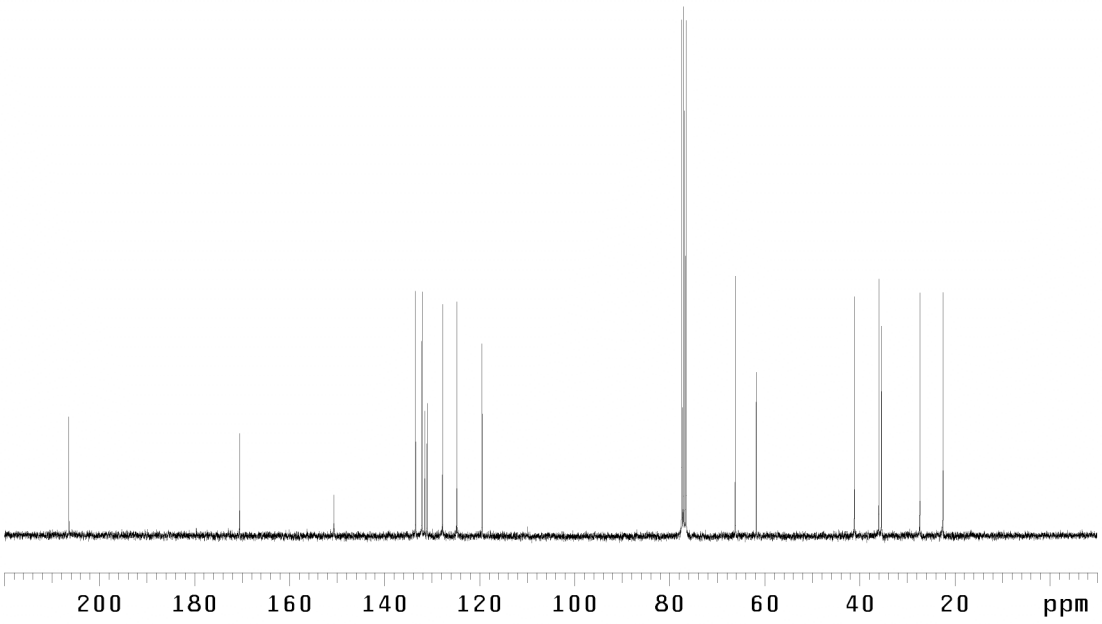


*Figure A2.9 ^{13}C NMR of compound **237** (75 MHz, $CDCl_3$)*

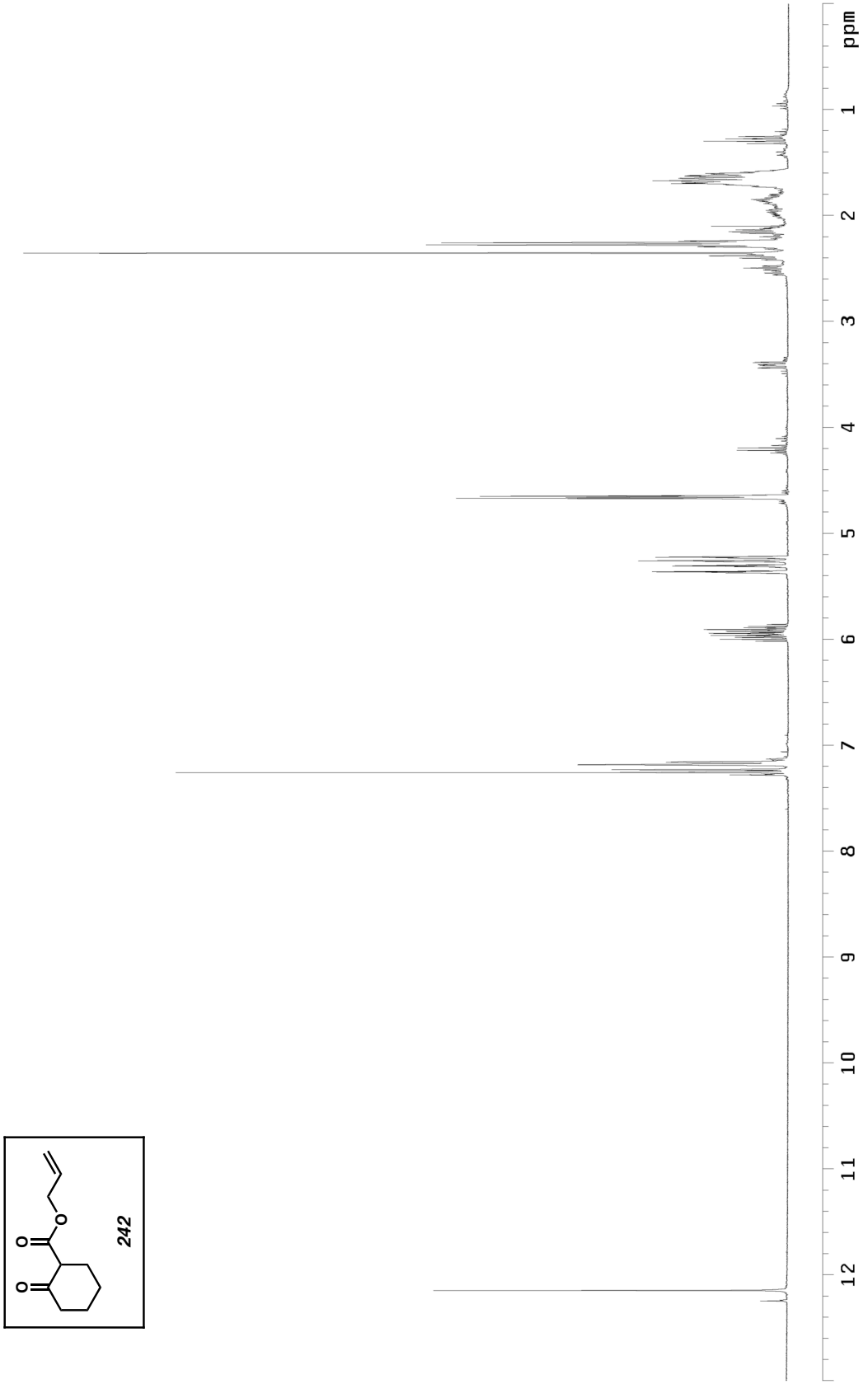
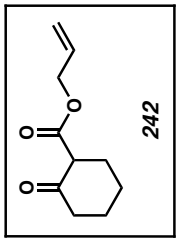


Figure A2.10 ^{1}H NMR of compound **242** *(300 MHz, $CDCl_3$)*



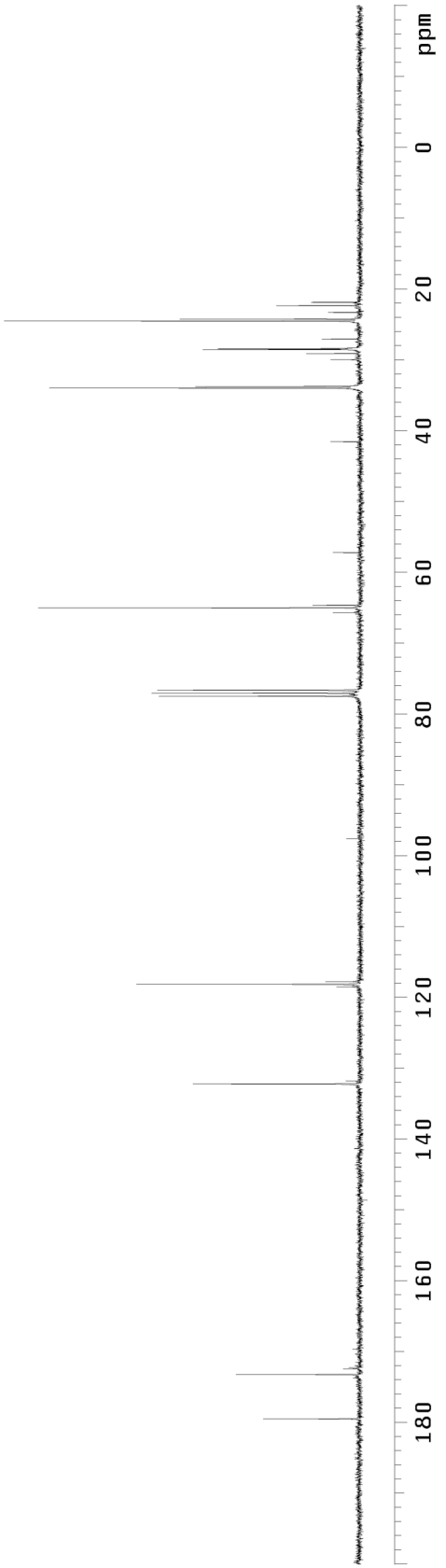


Figure A2.11 ^{13}C *NMR of compound* ***242*** *(75 MHz,* $CDCl_3$*)*

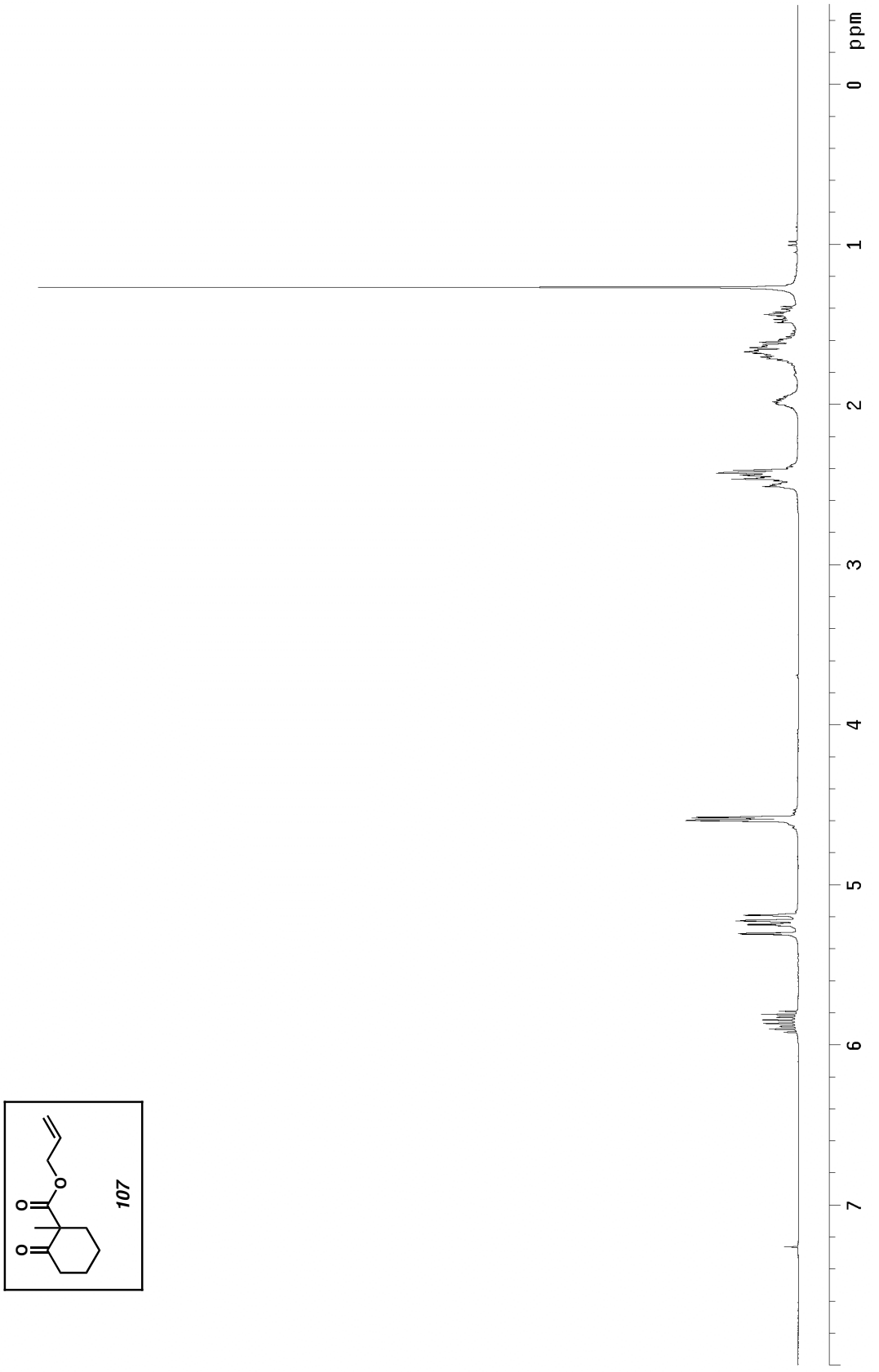


*Figure A2.12 ^{1}H NMR of compound **107** (300 MHz, $CDCl_3$)*

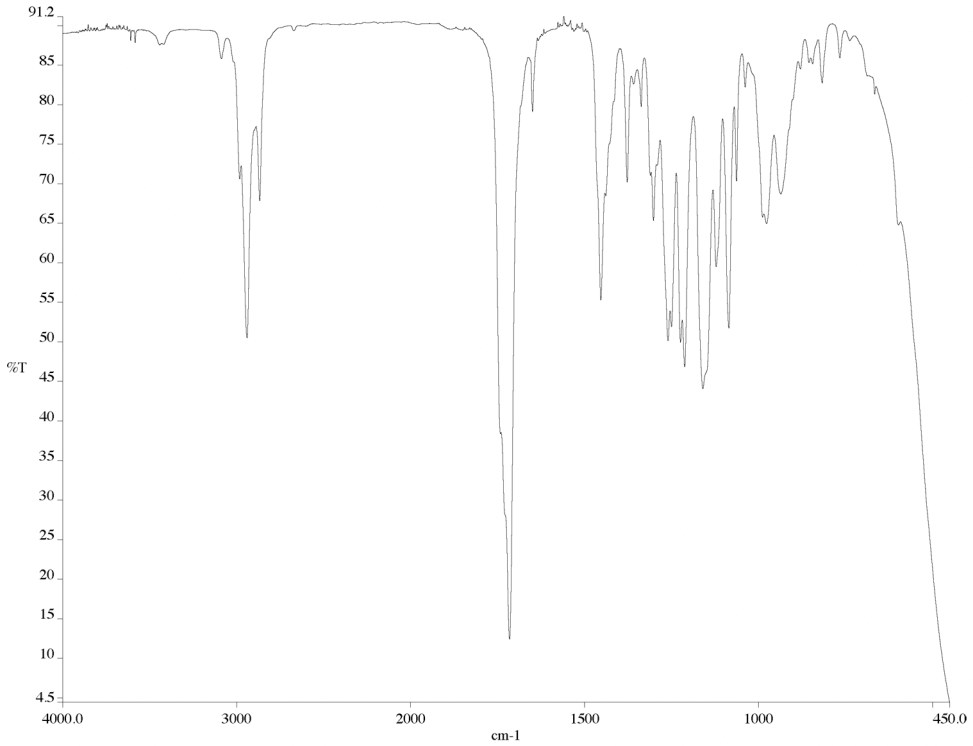


*Figure A2.13 IR of compound **107** (NaCl/film)*

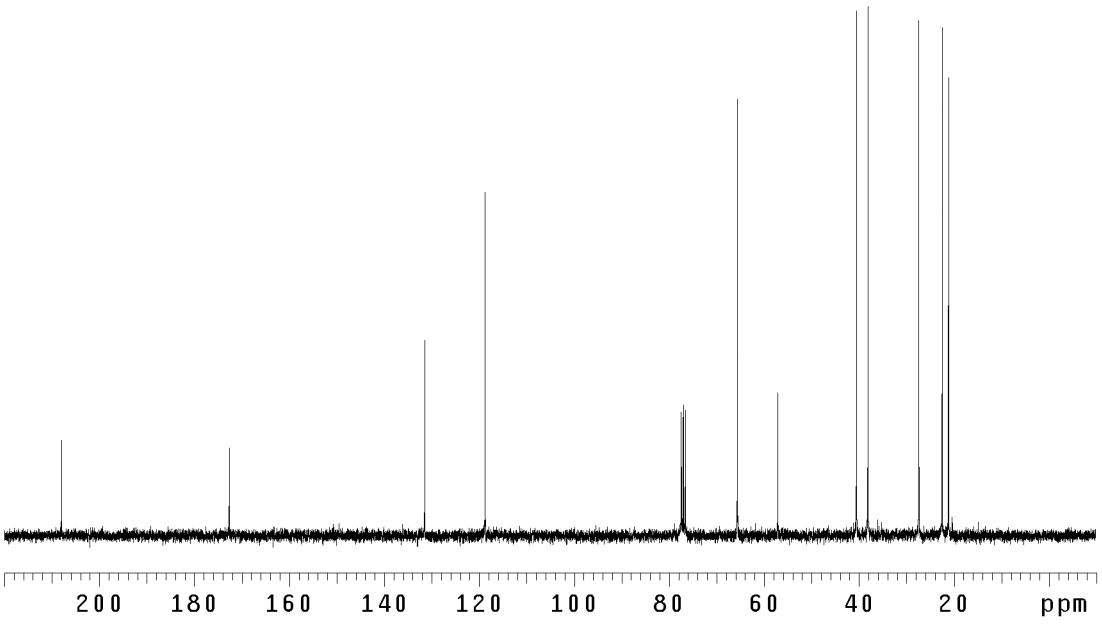


*Figure A2.14 ^{13}C NMR of compound **107** (75 MHz, $CDCl_3$)*

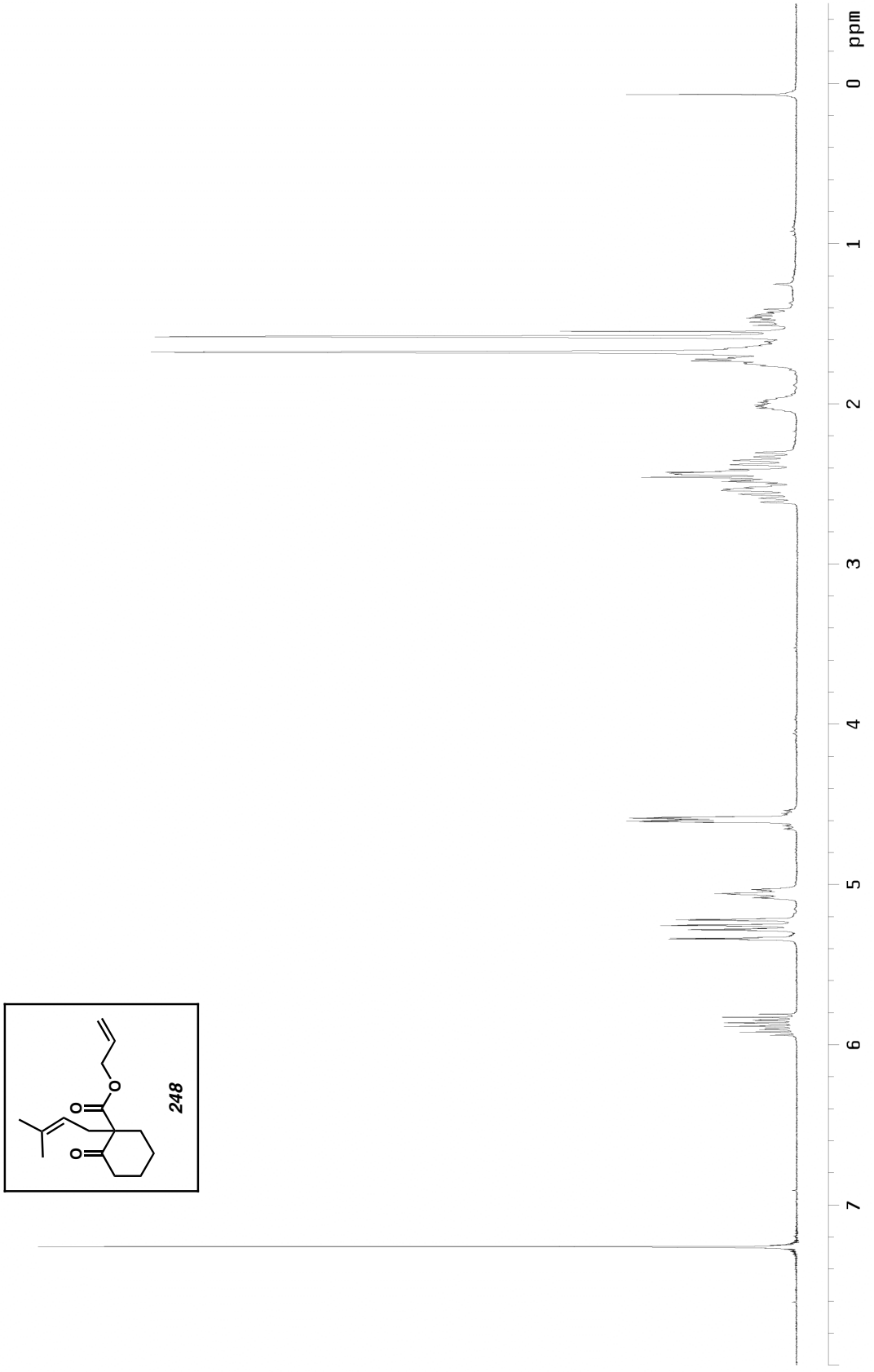


*Figure A2.15 ^1H NMR of compound **248** (300 MHz, $CDCl_3$)*

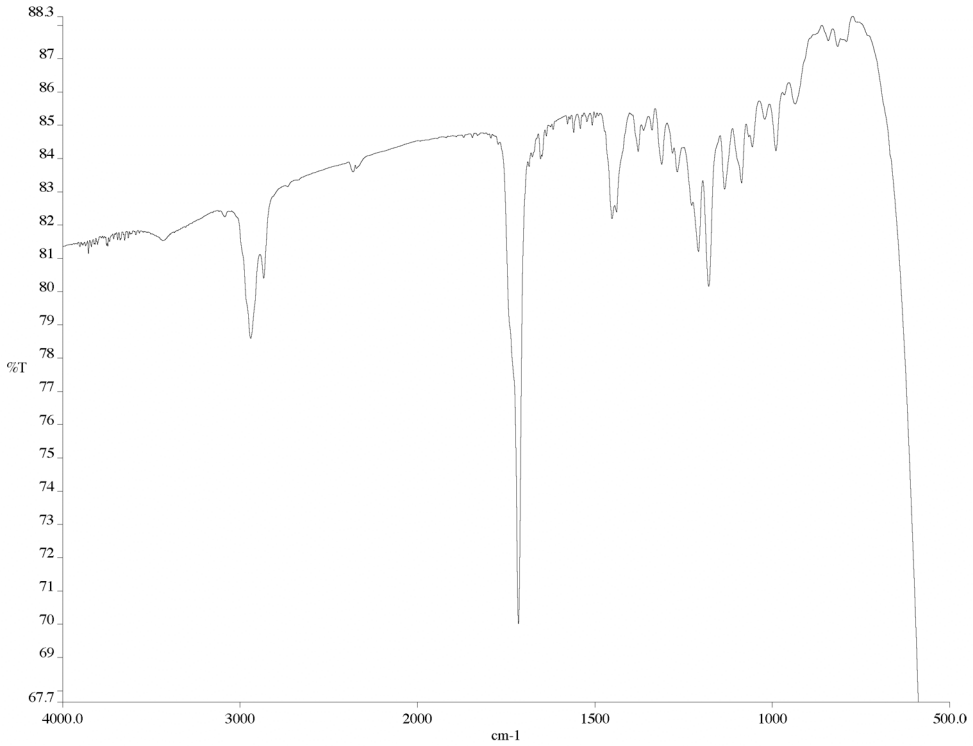


*Figure A2.16 IR of compound **248** (NaCl/film)*

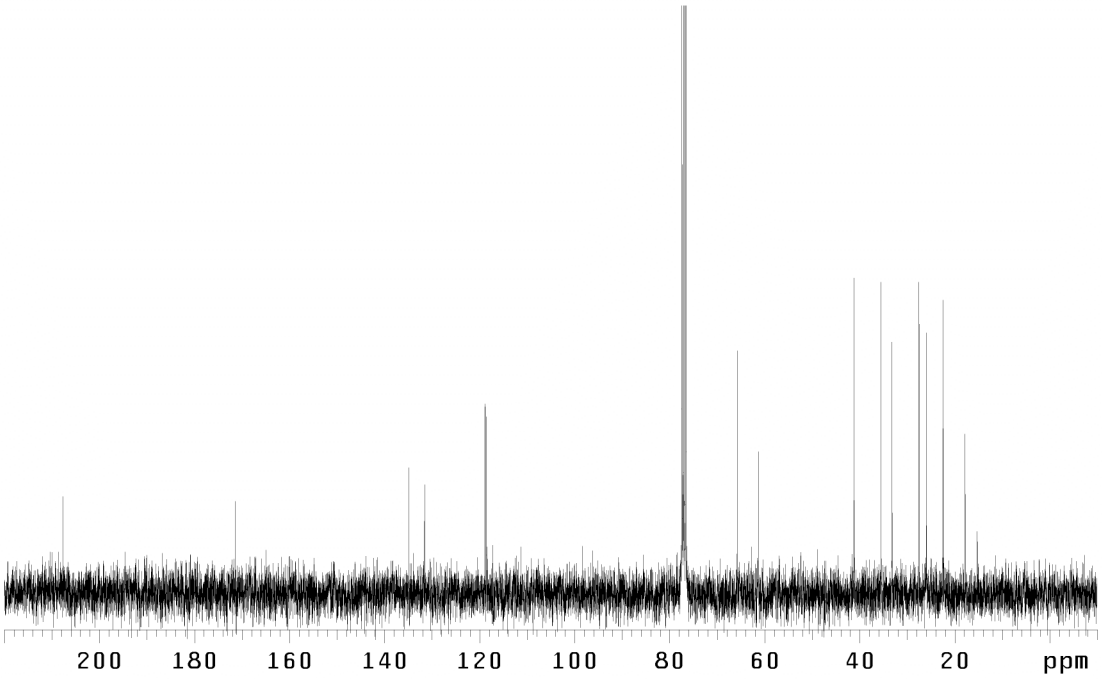


*Figure A2.17 ^{13}C NMR of compound **248** (75 MHz, $CDCl_3$)*

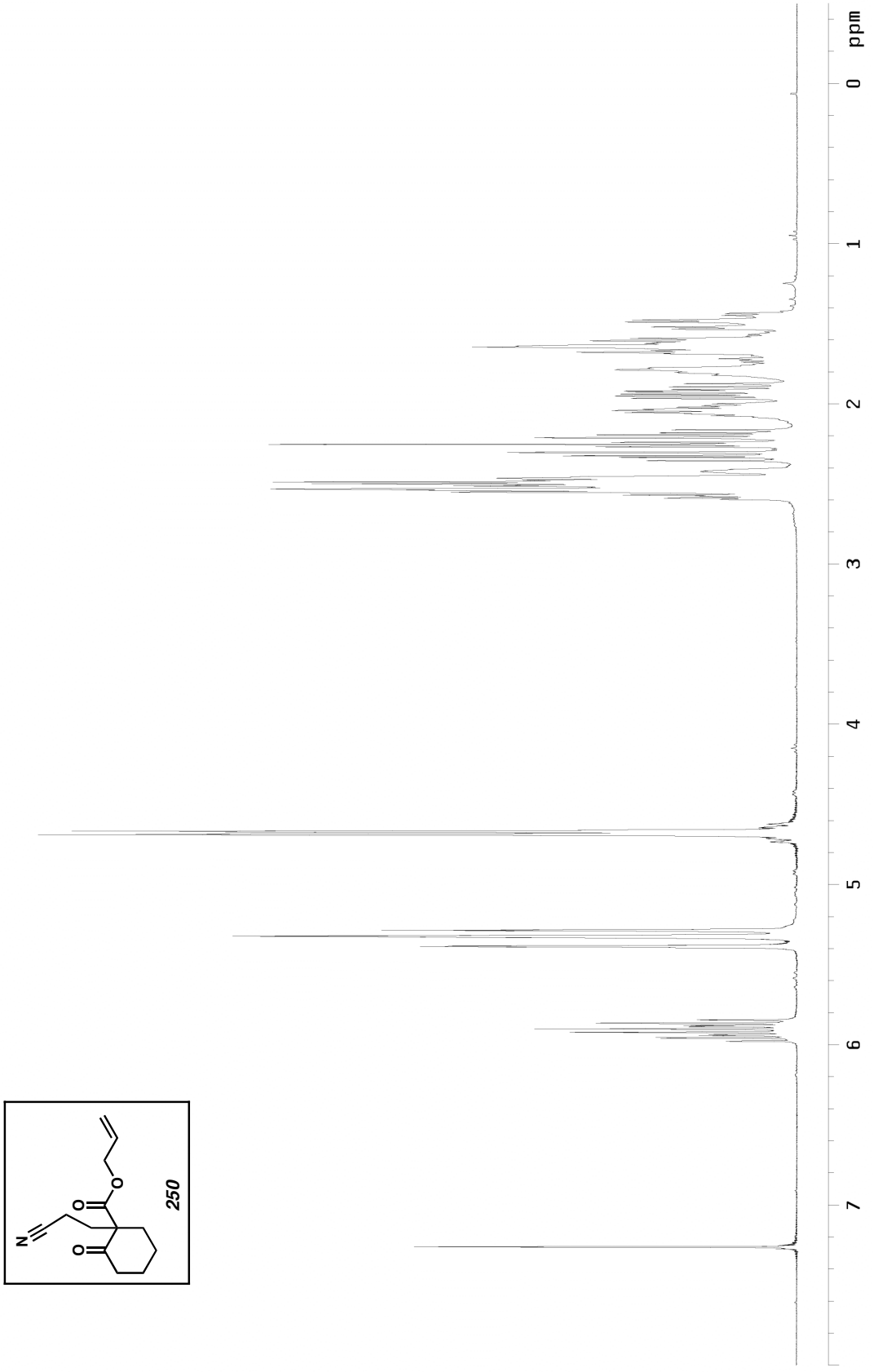


*Figure A2.18 ^{1}H NMR of compound **250** (300 MHz, $CDCl_3$)*

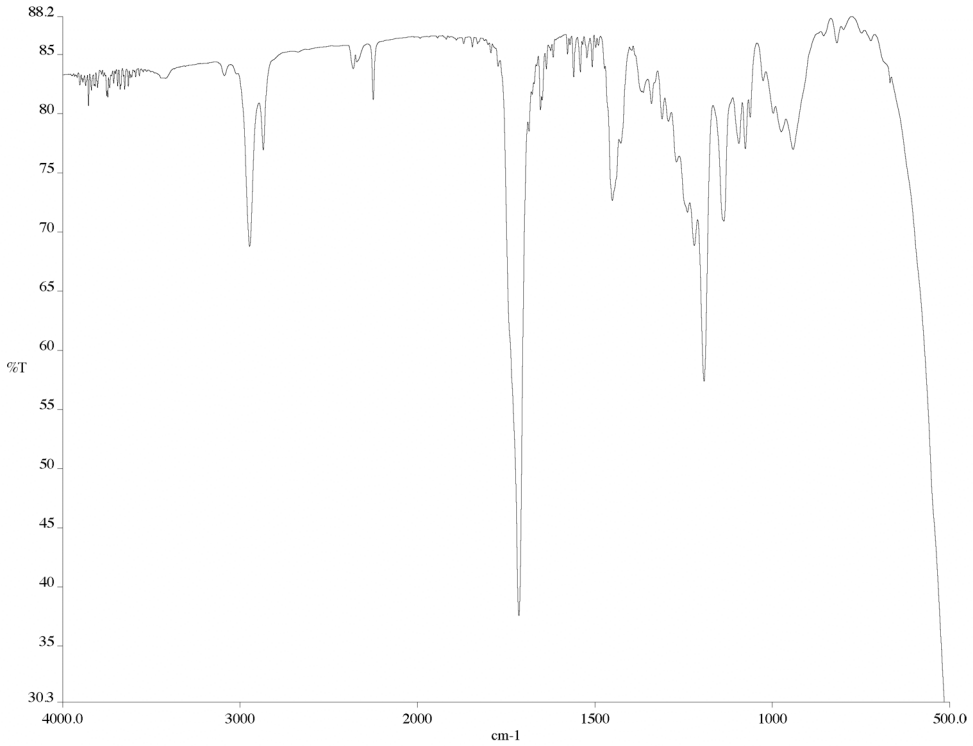


*Figure A2.19 IR of compound **250** (NaCl/film)*

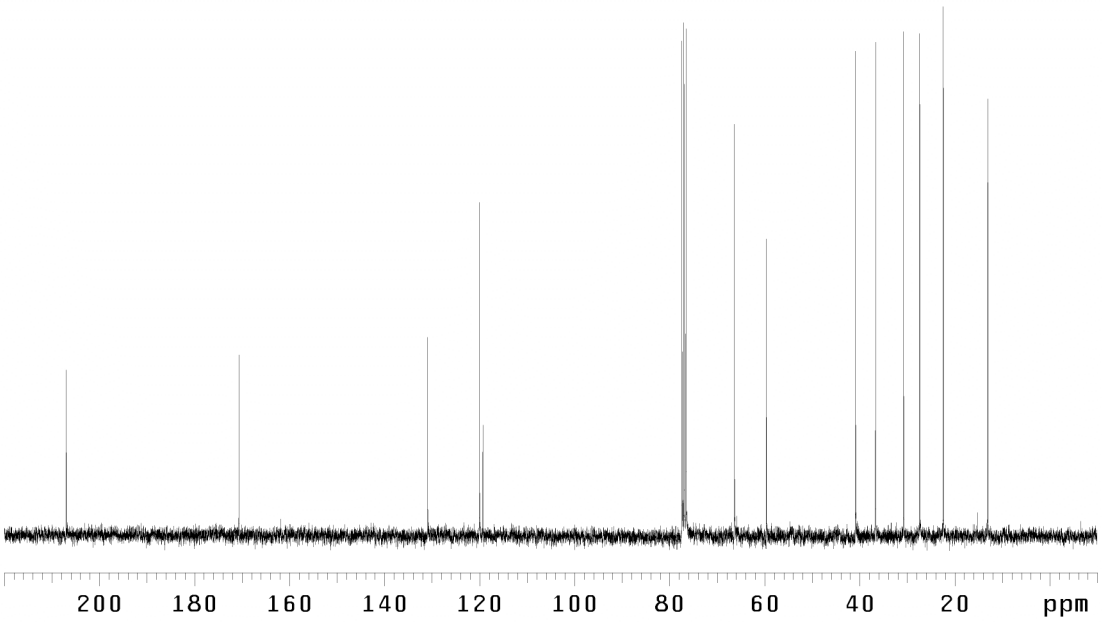


*Figure A2.20 ^{13}C NMR of compound **250** (75 MHz, $CDCl_3$)*

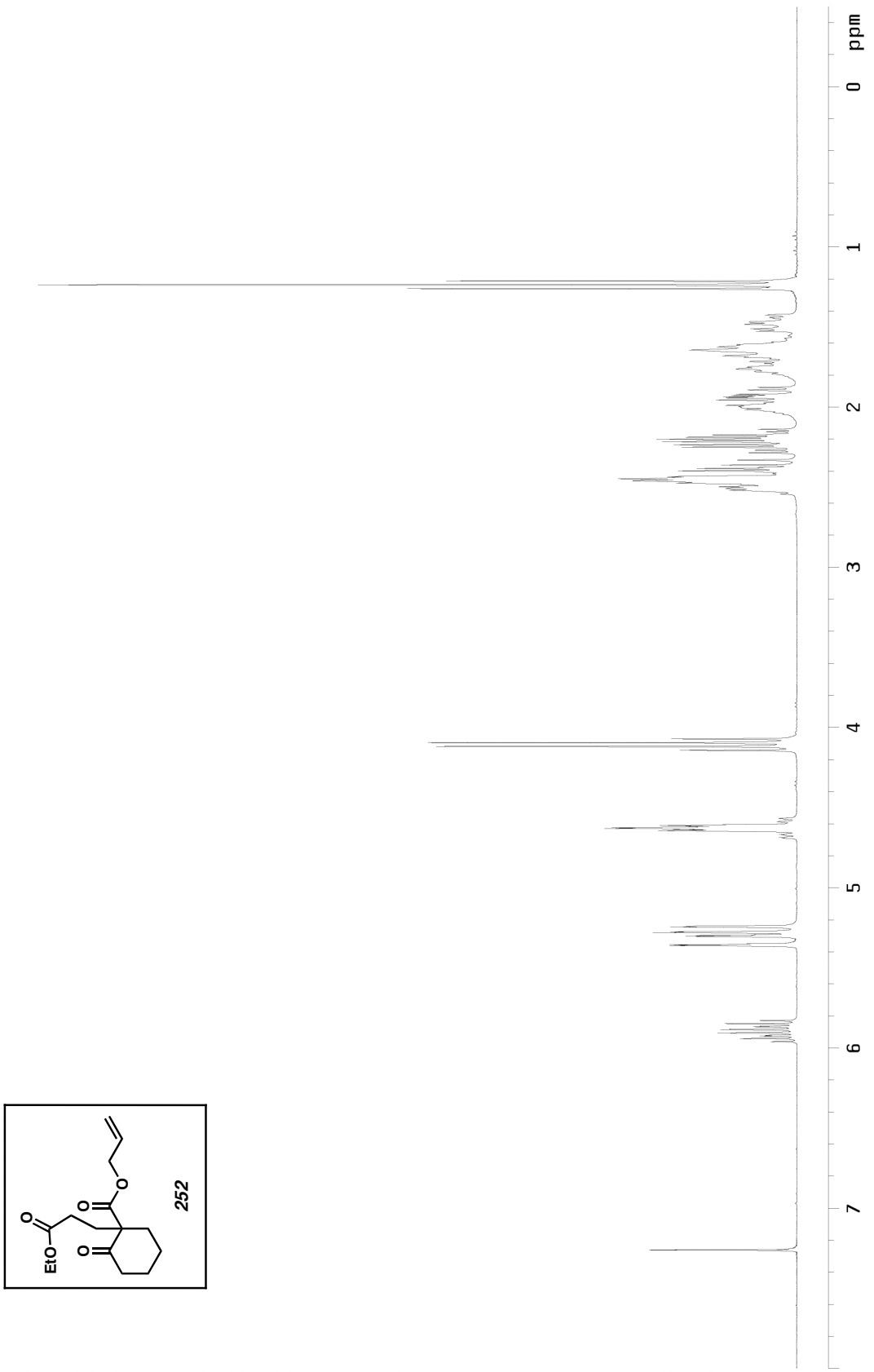


*Figure A2.21 ^1H NMR of compound **252** (300 MHz, $CDCl_3$)*

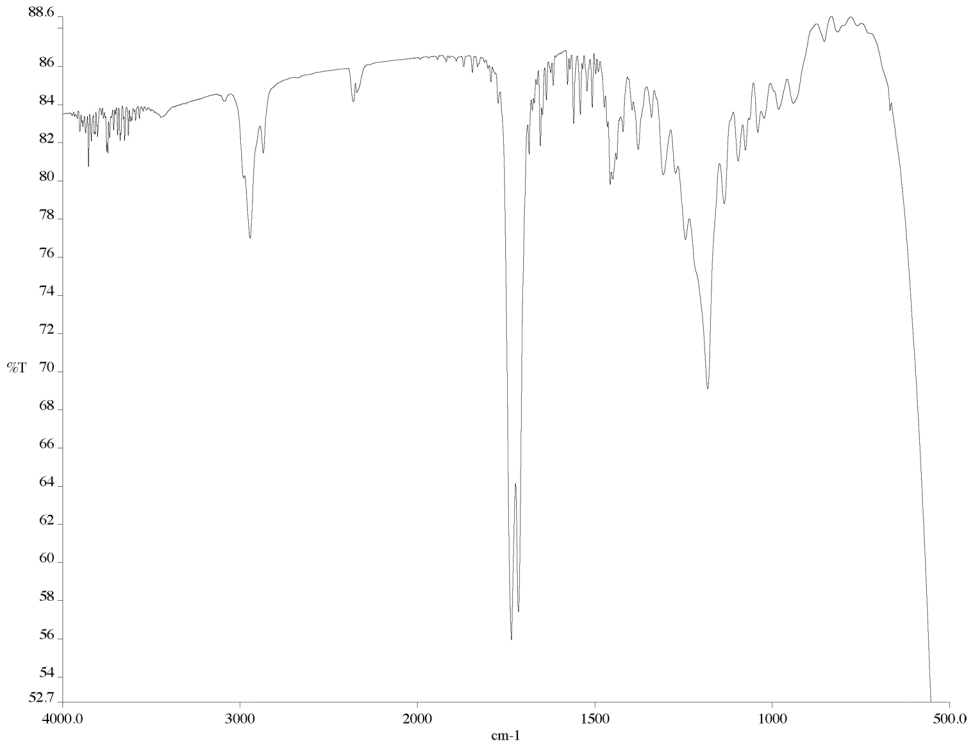


*Figure A2.22 IR of compound **252** (NaCl/film)*

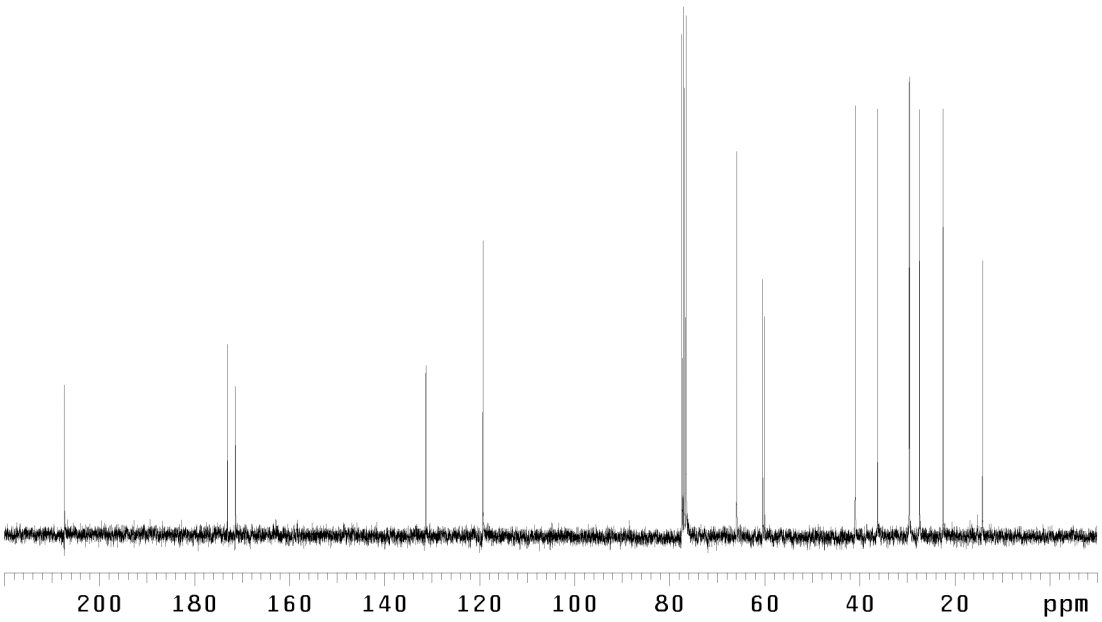


*Figure A2.23 ^{13}C NMR of compound **252** (75 MHz, $CDCl_3$)*

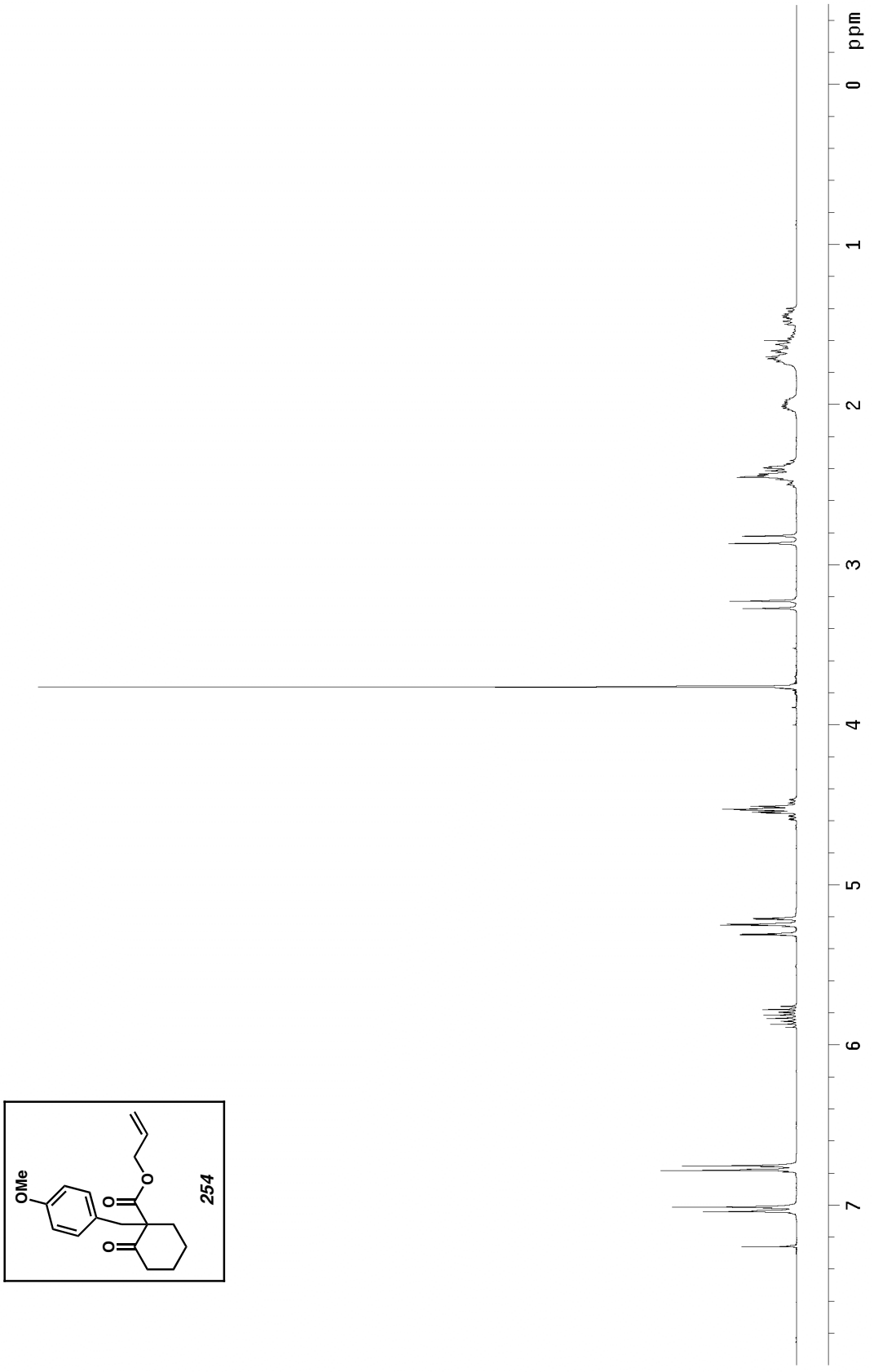


*Figure A2.24 ^1H NMR of compound **254** (300 MHz, $CDCl_3$)*

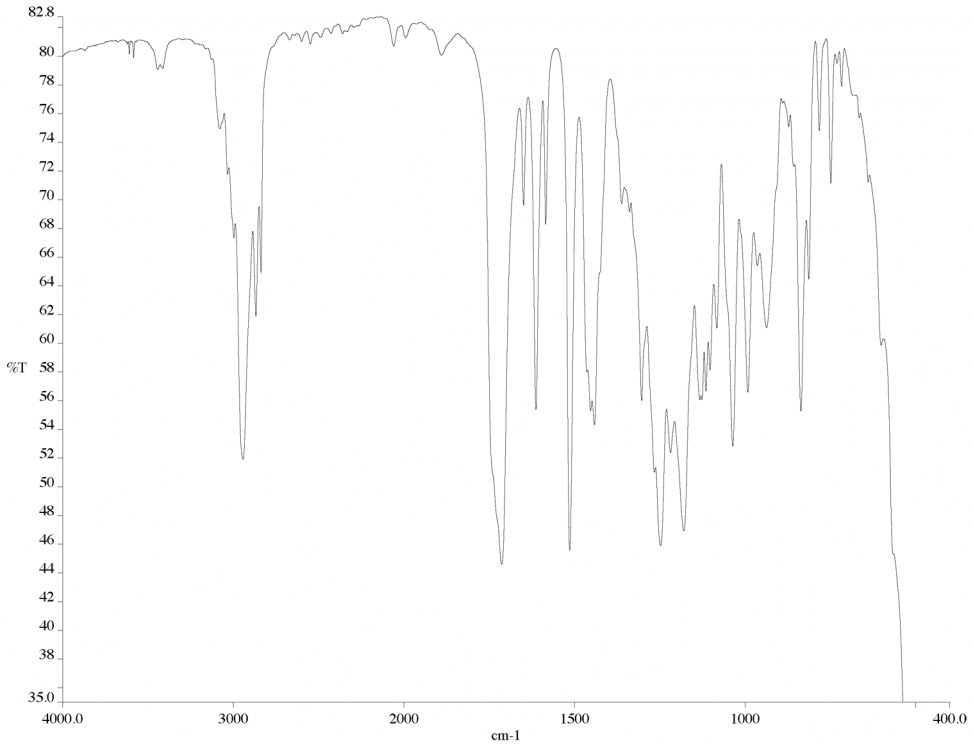


*Figure A2.25 IR of compound **254** (NaCl/film)*

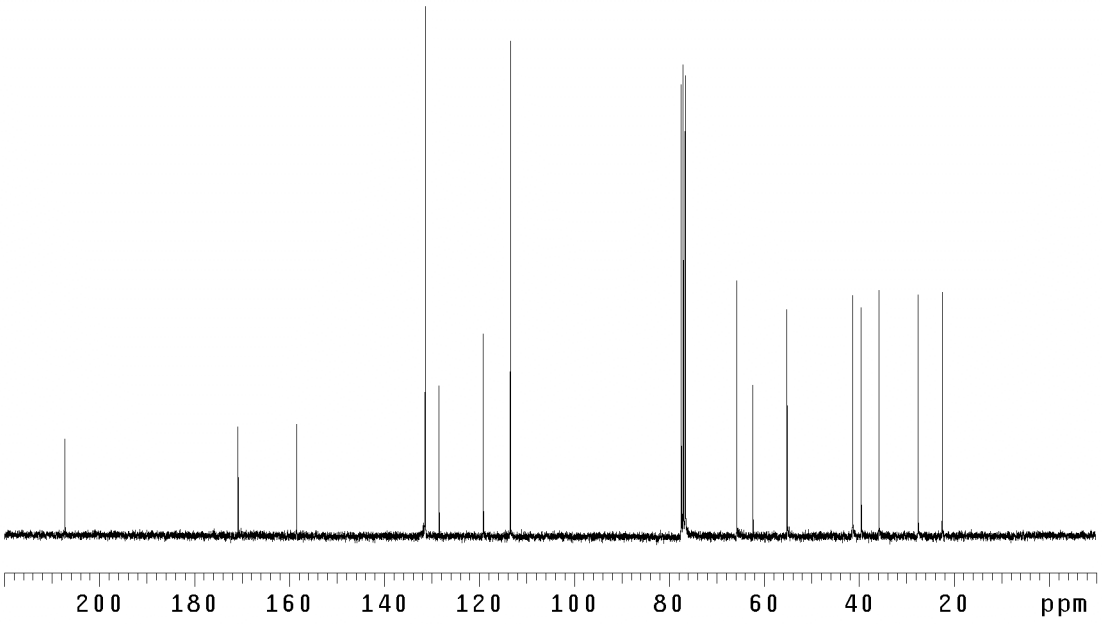


*Figure A2.26 ^{13}C NMR of compound **254** (75 MHz, $CDCl_3$)*

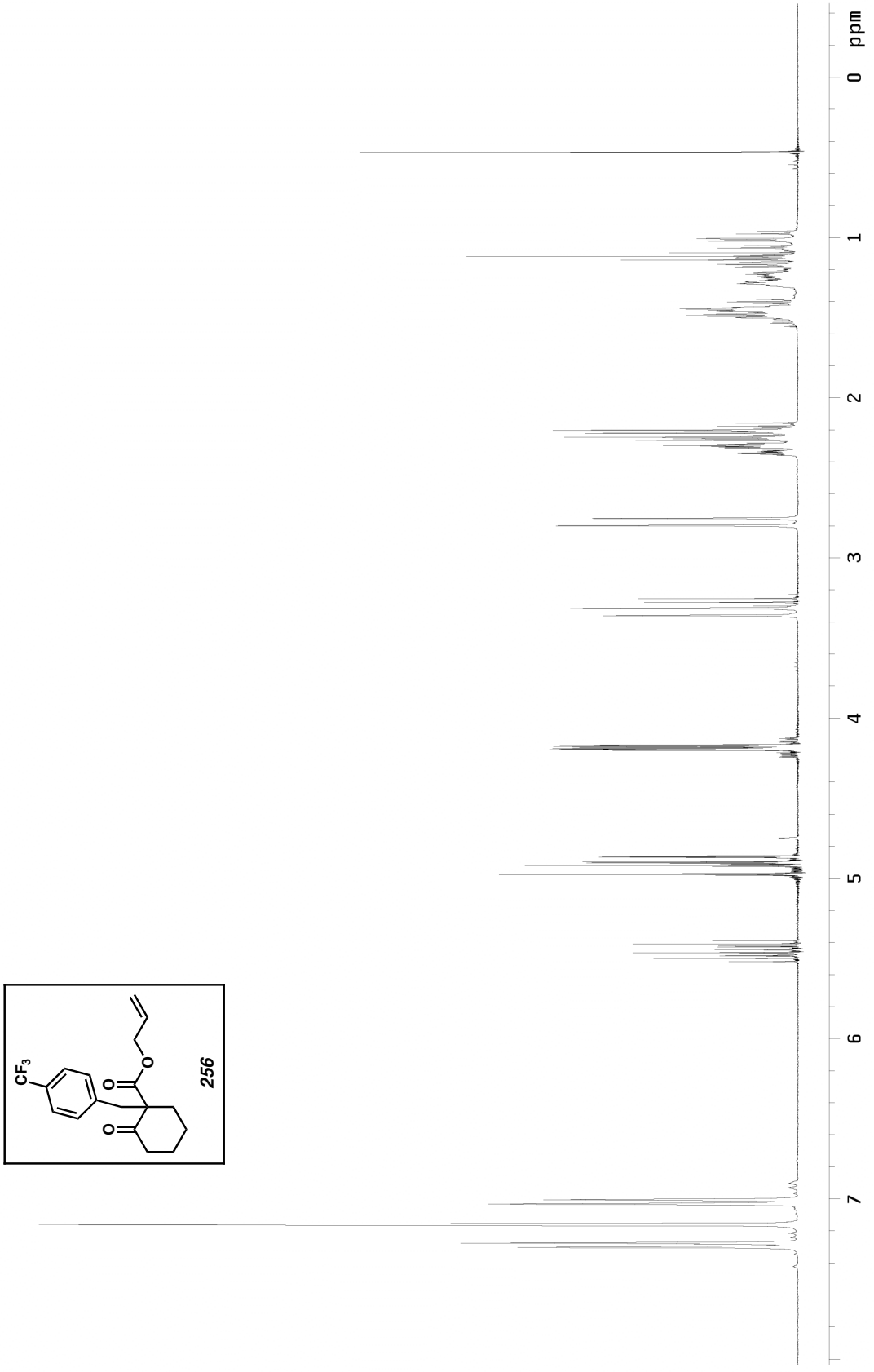


Figure A2.27 ^1H NMR of compound ***256*** *(300 MHz, $CDCl_3$)*

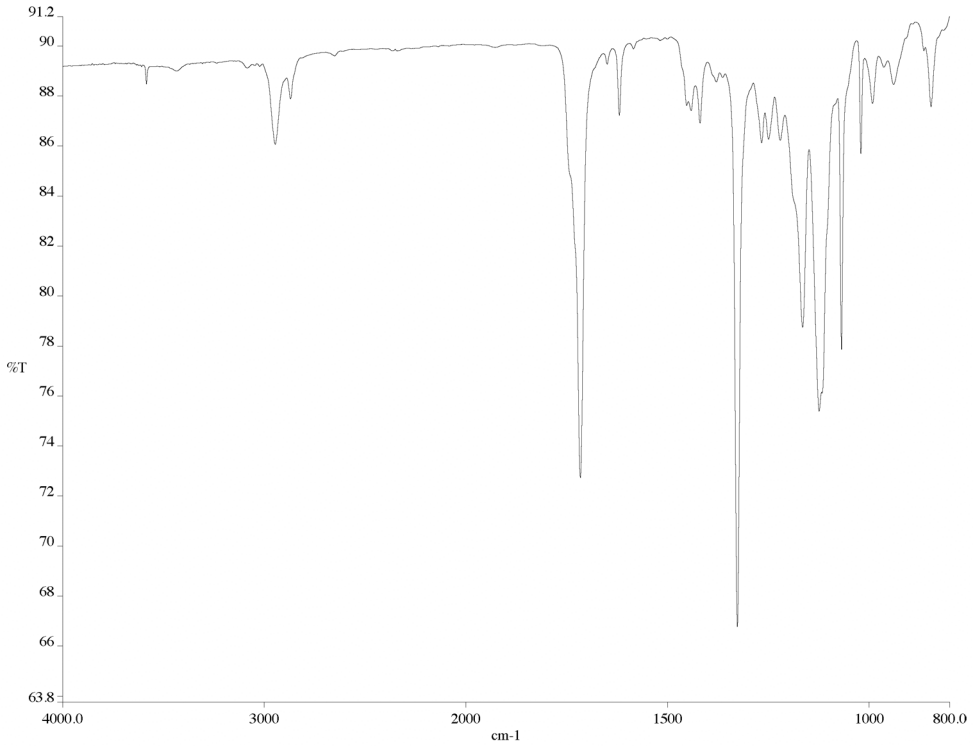


*Figure A2.28 IR of compound **256** (NaCl/film)*

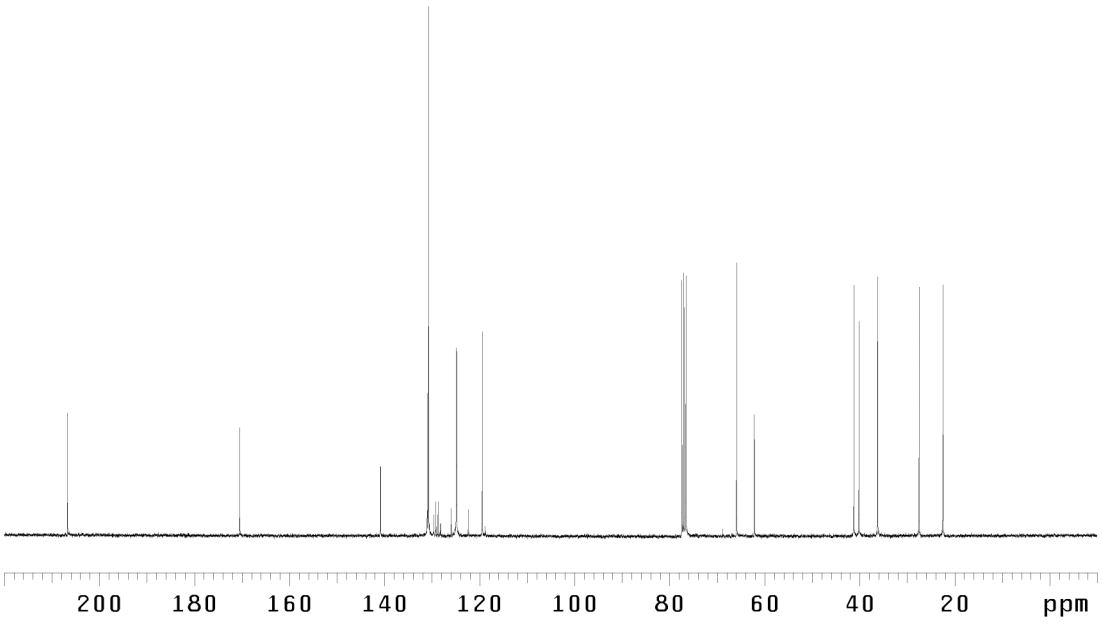


*Figure A2.29 ^{13}C NMR of compound **256** (75 MHz, $CDCl_3$)*

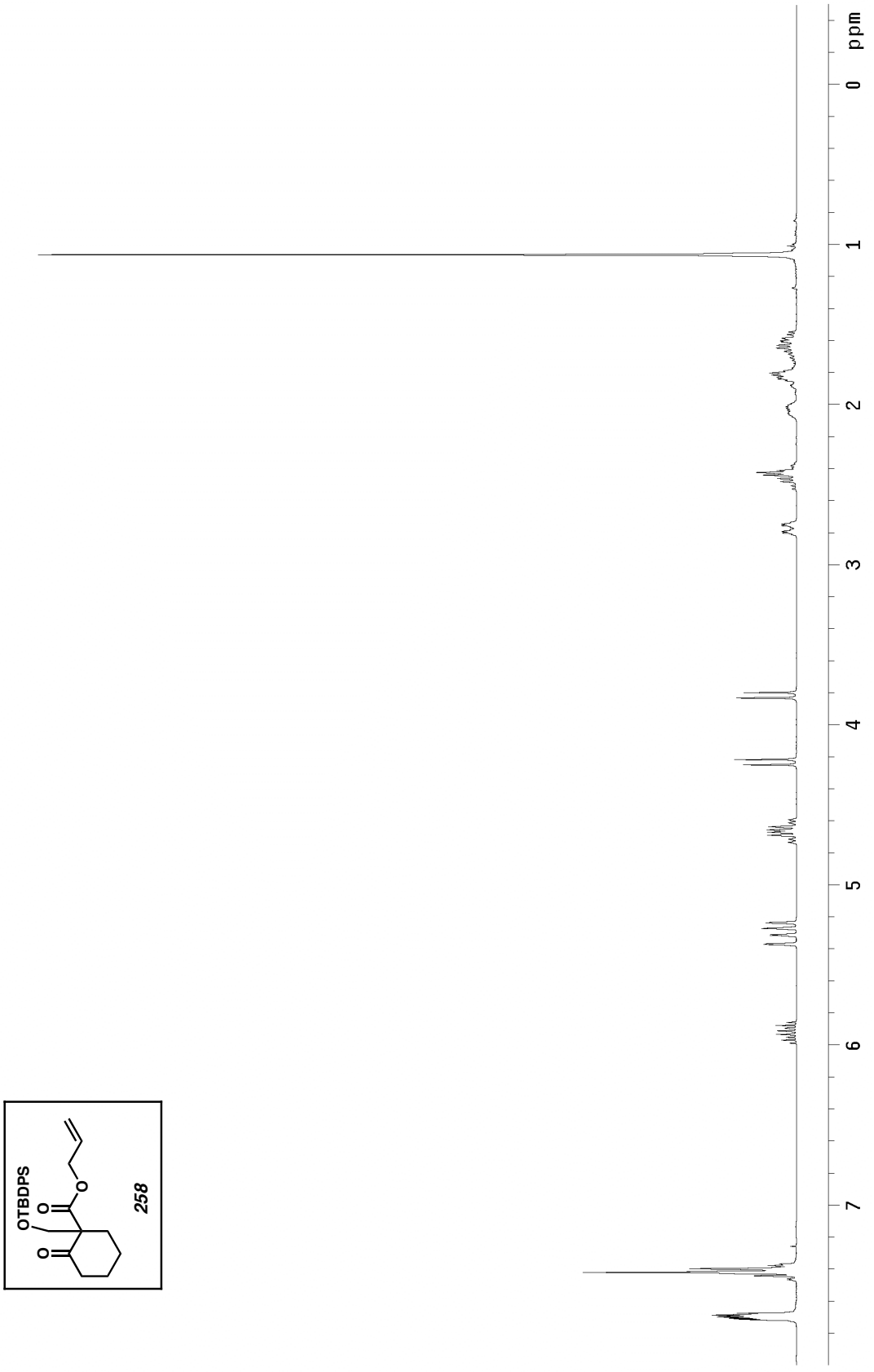


*Figure A2.30 ^{1}H NMR of compound **258** (300 MHz, $CDCl_3$)*

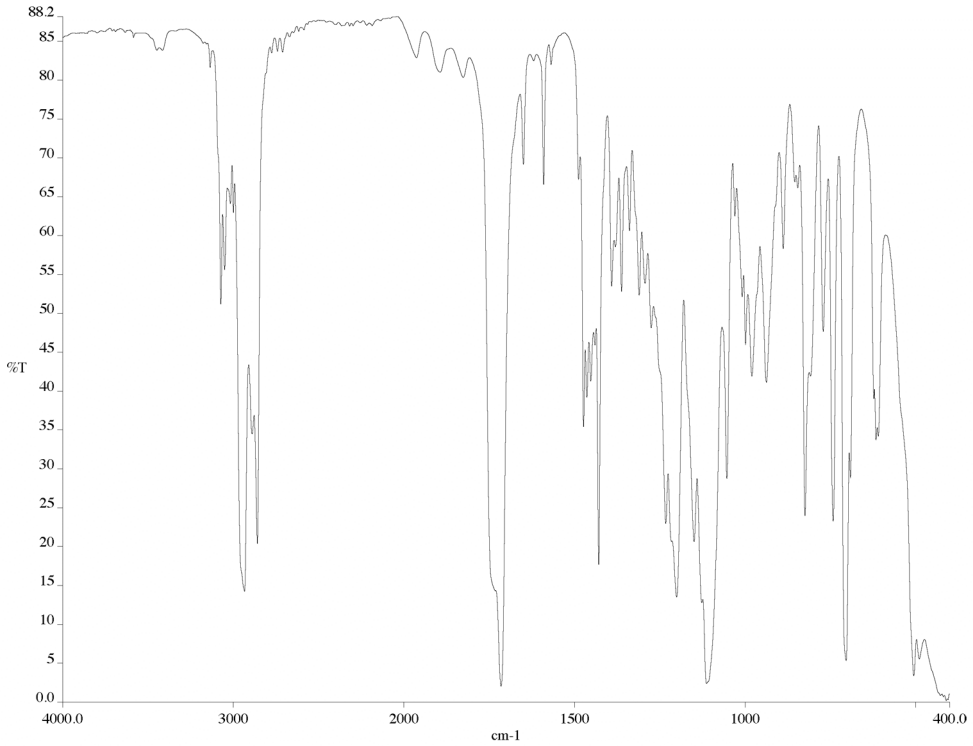


*Figure A2.31 IR of compound **258** (NaCl/film)*

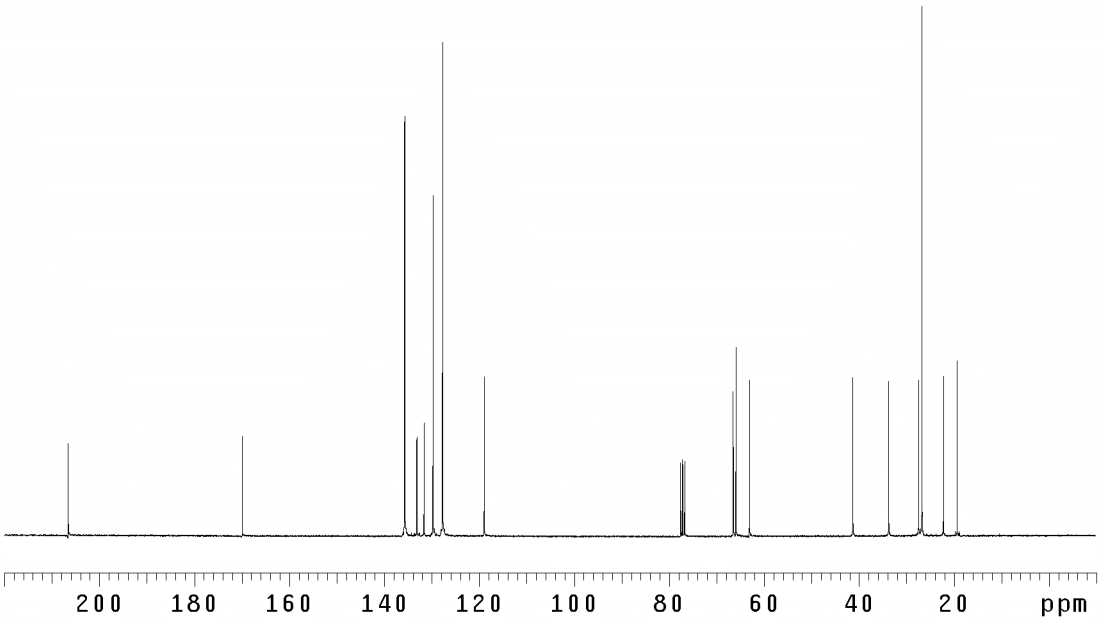


*Figure A2.32 ^{13}C NMR of compound **258** (75 MHz, $CDCl_3$)*

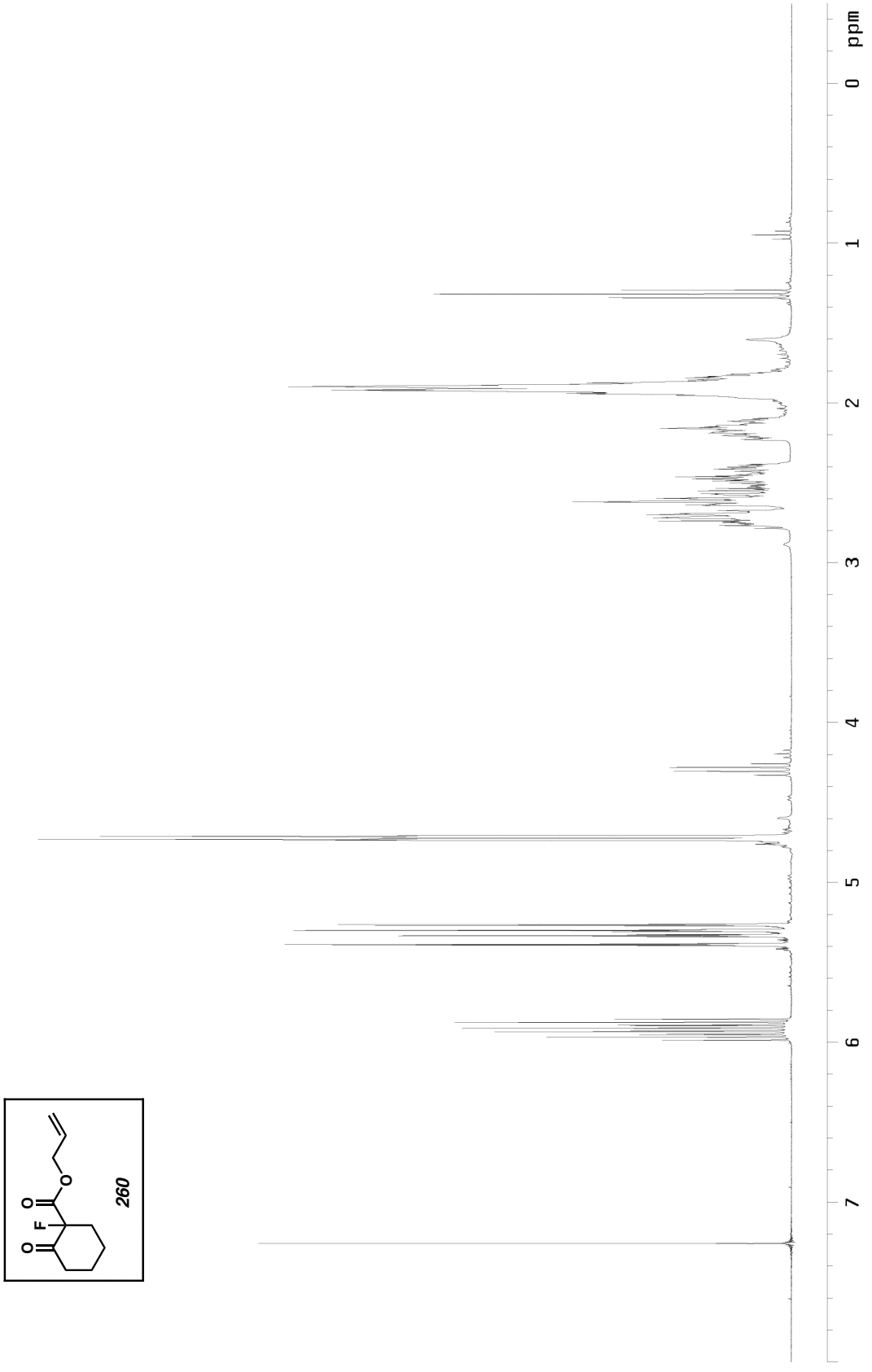


*Figure A2.33 ^1H NMR of compound **260** (300 MHz, $CDCl_3$)*

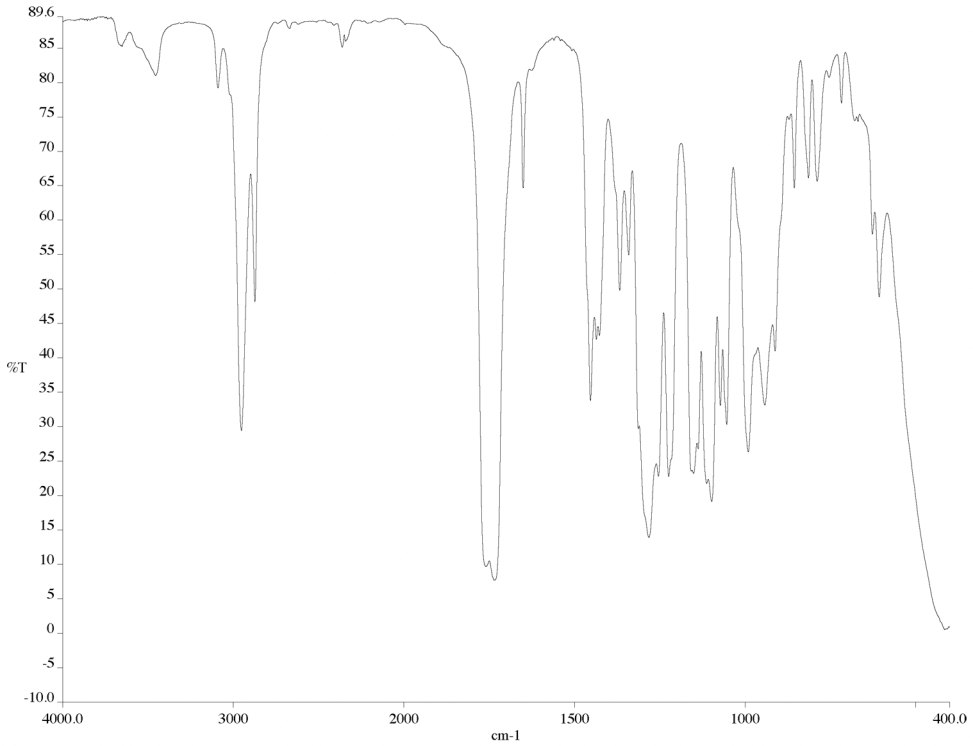


*Figure A2.34 IR of compound **260** (NaCl/film)*

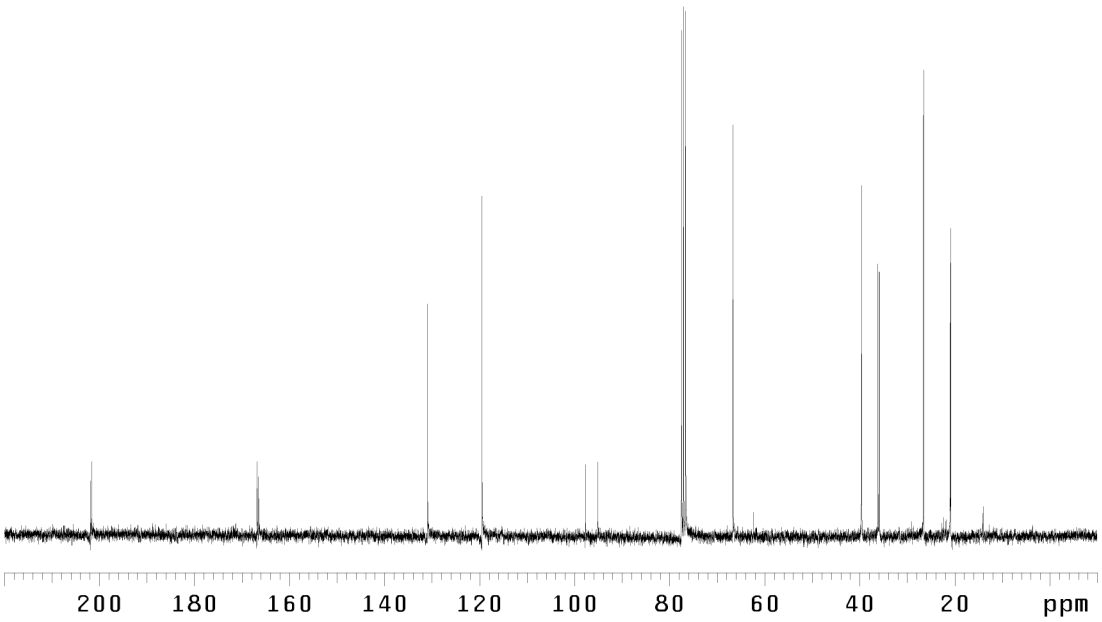


*Figure A2.35 ^{13}C NMR of compound **260** (75 MHz, $CDCl_3$)*

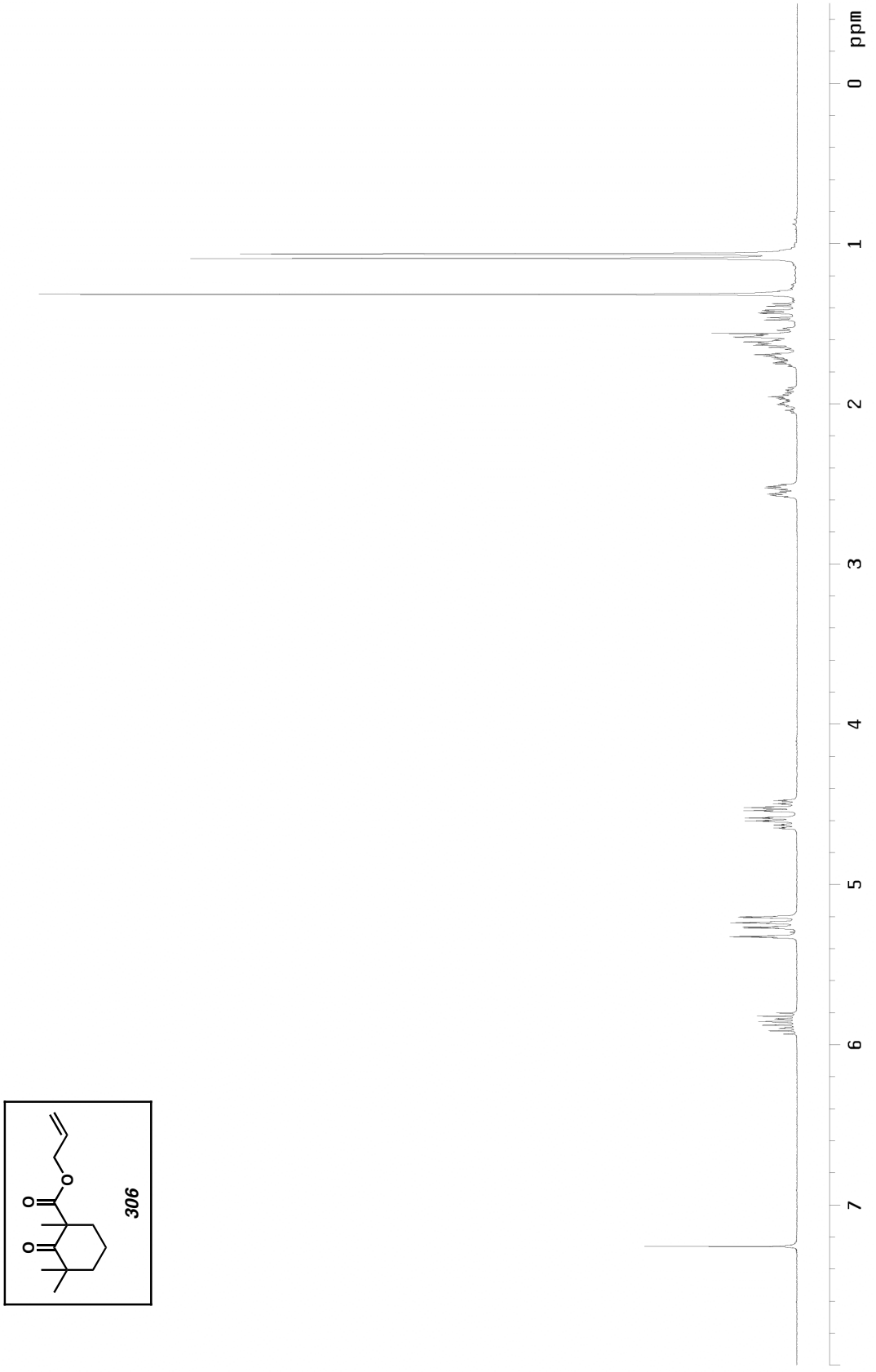


*Figure A2.36 ^1H NMR of compound **306** (300 MHz, $CDCl_3$)*

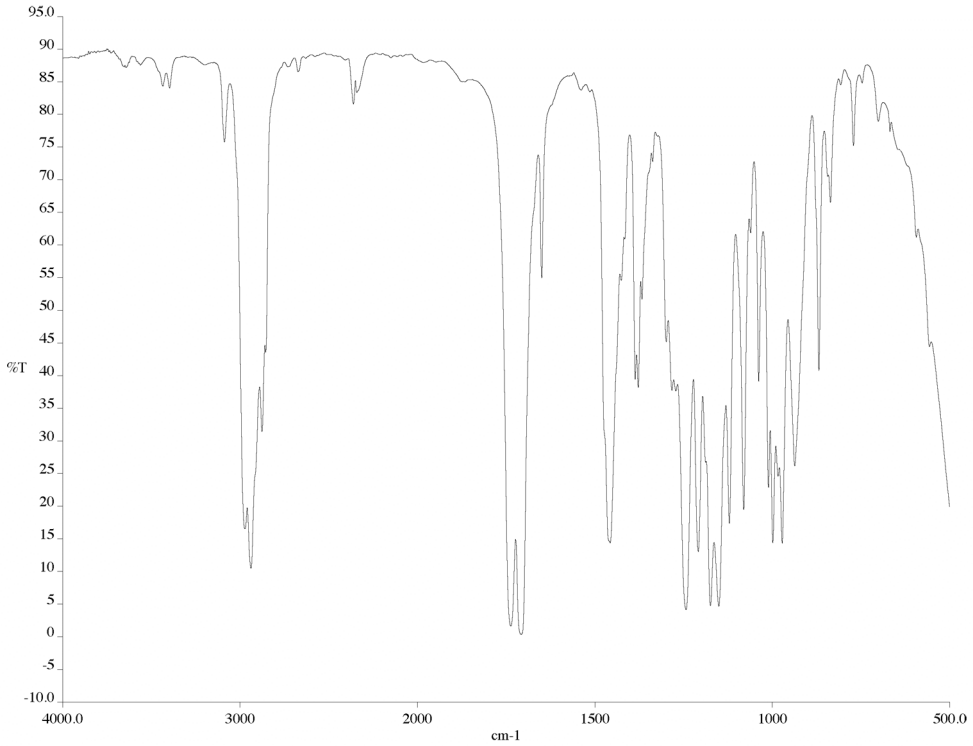


*Figure A2.37 IR of compound **306** (NaCl/film)*

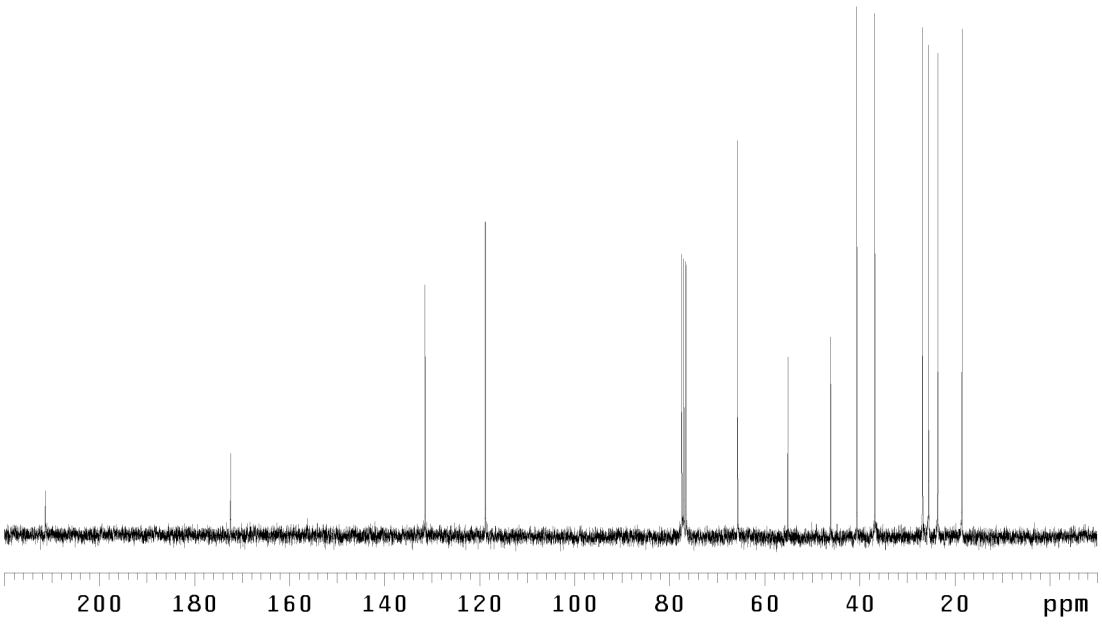


*Figure A2.38 ^{13}C NMR of compound **306** (75 MHz, $CDCl_3$)*

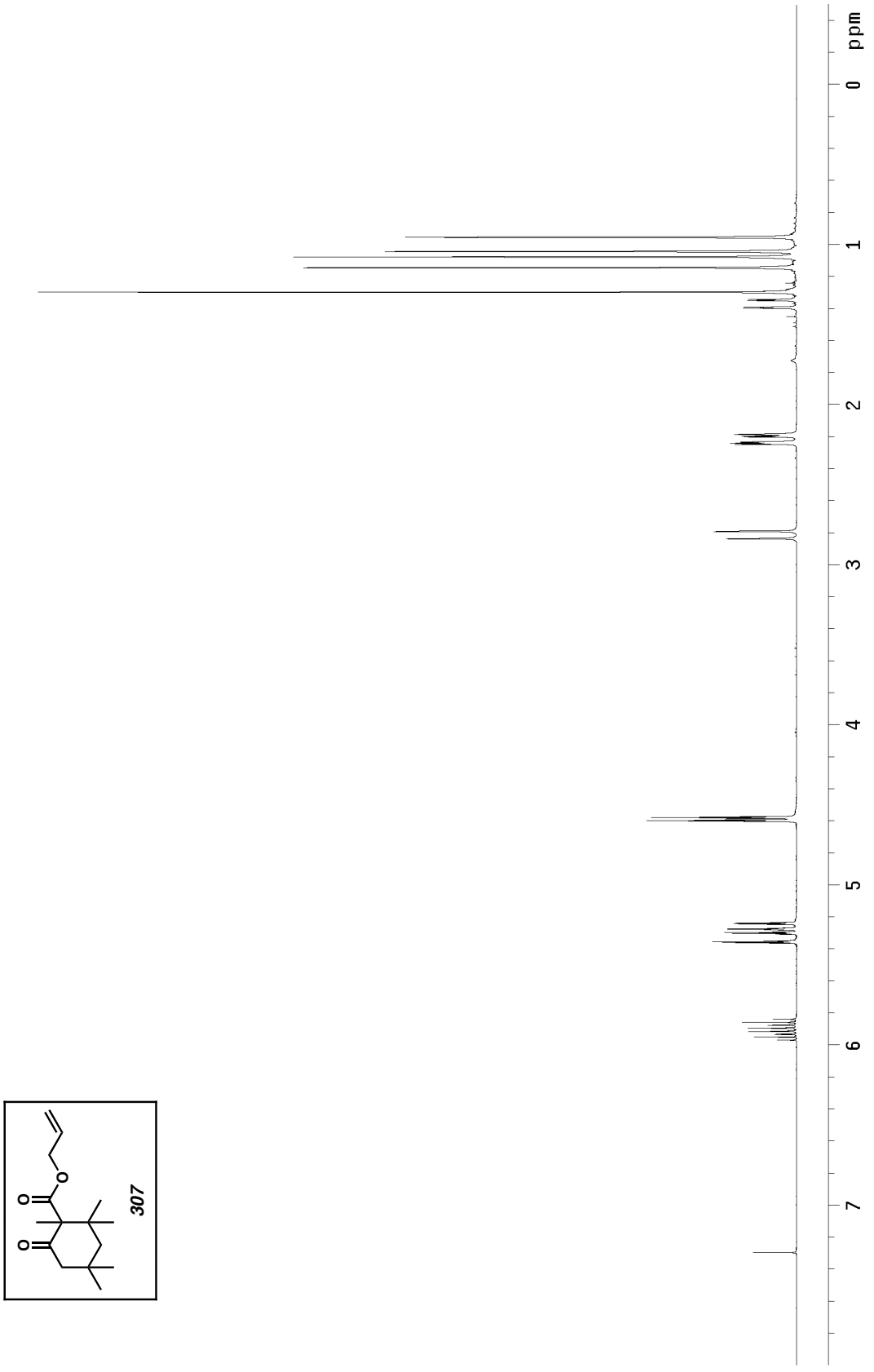


*Figure A2.39 ^1H NMR of compound **307** (300 MHz, $CDCl_3$)*

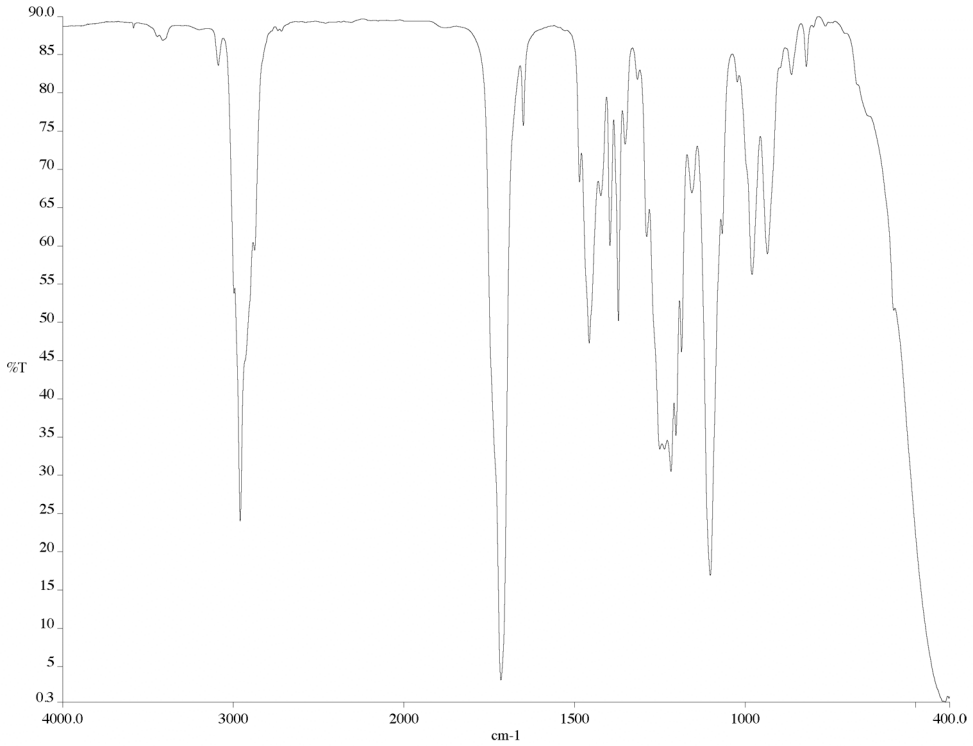


*Figure A2.40 IR of compound **307** (NaCl/film)*

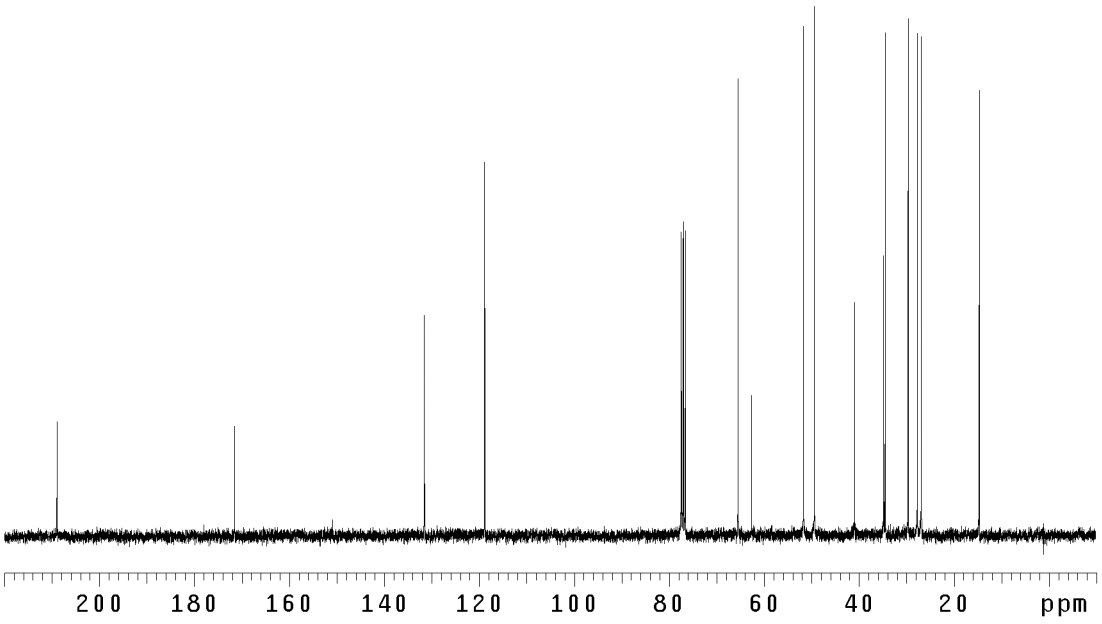


*Figure A2.41 ^{13}C NMR of compound **307** (75 MHz, $CDCl_3$)*

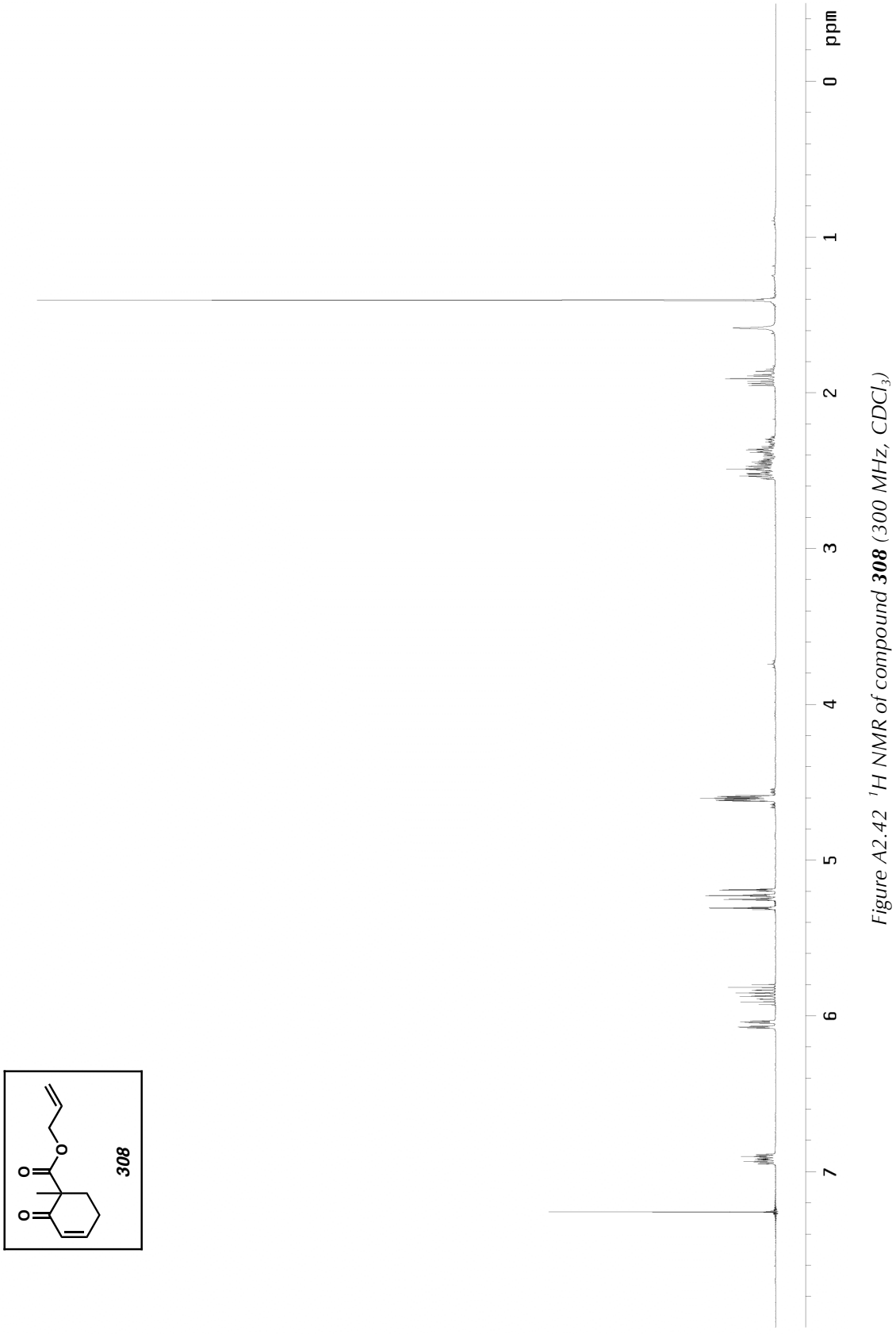


*Figure A2.42 ^1H NMR of compound **308** (300 MHz, $CDCl_3$)*

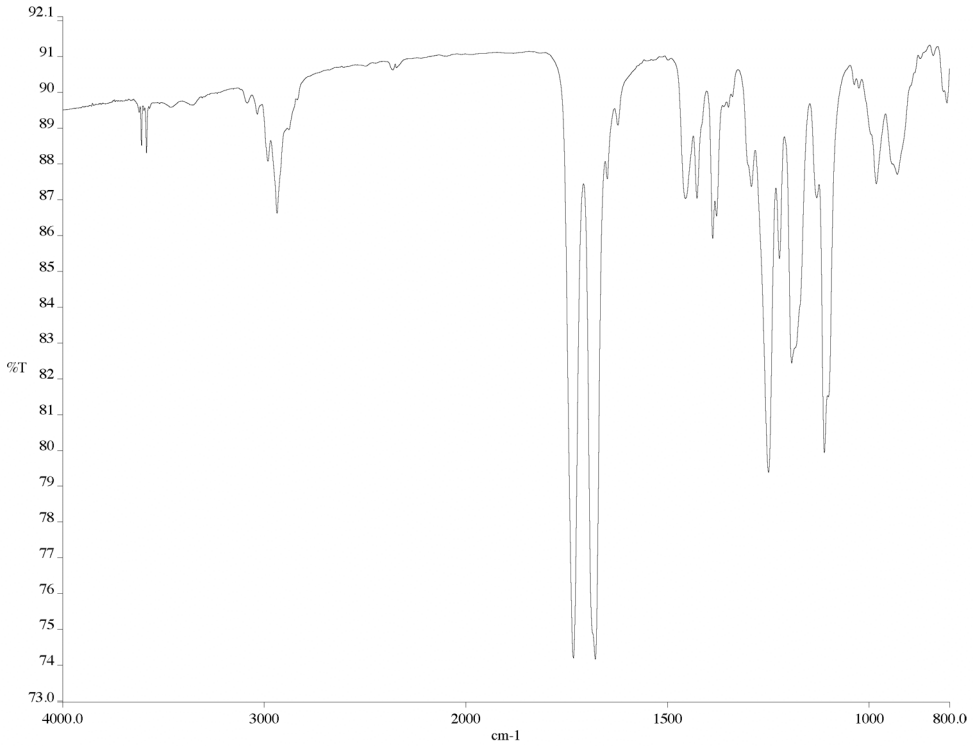


*Figure A2.43 IR of compound **308** (NaCl/film)*

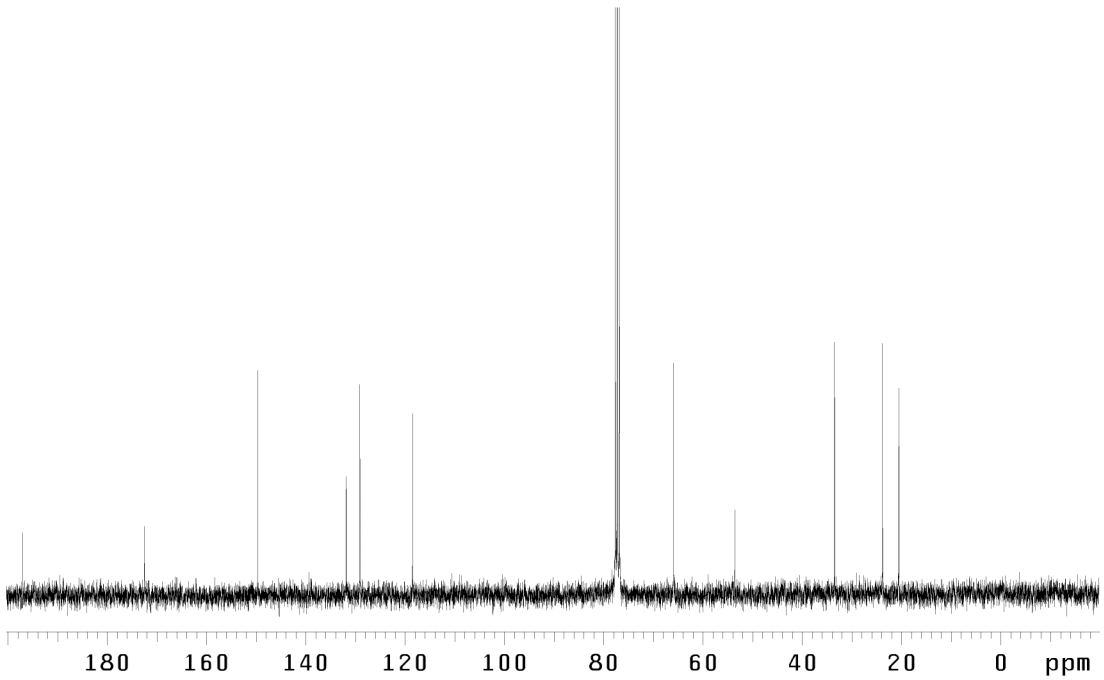


*Figure A2.44 ^{13}C NMR of compound **308** (75 MHz, $CDCl_3$)*

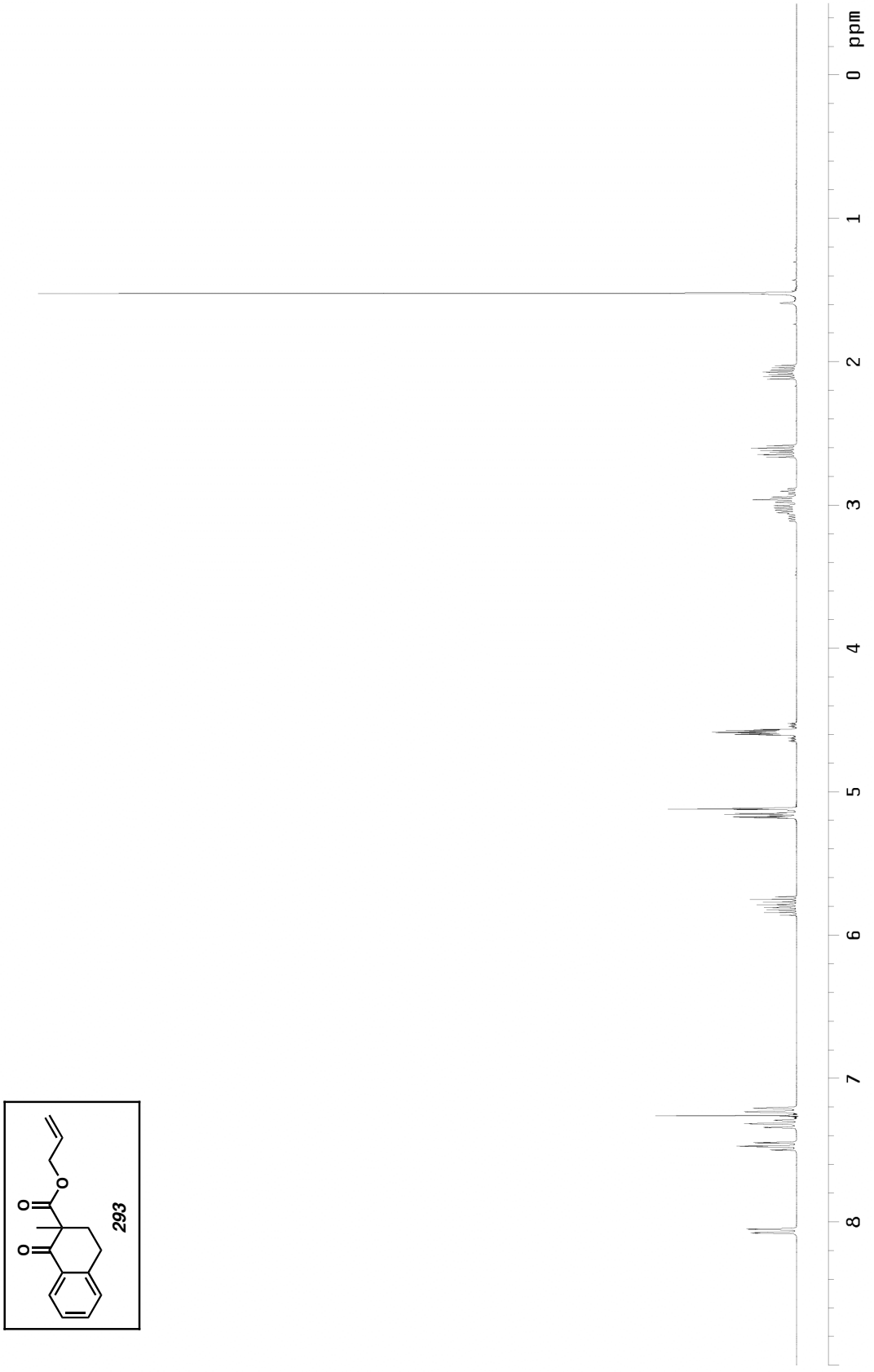


*Figure A2.45 ^1H NMR of compound **293** (300 MHz, $CDCl_3$)*

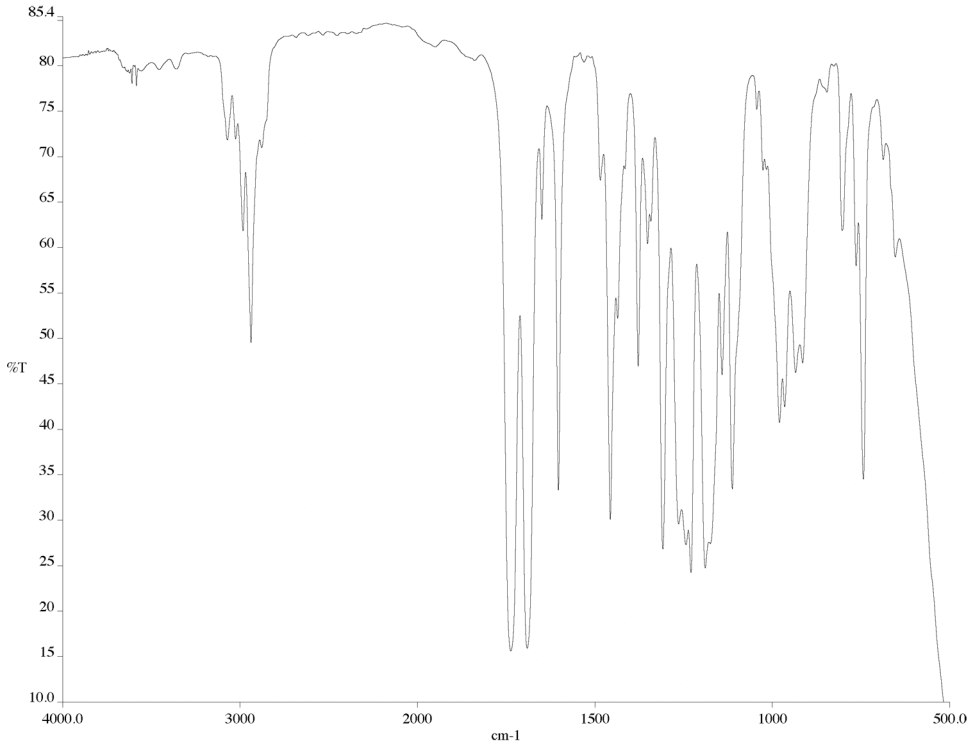


*Figure A2.46 IR of compound **293** (NaCl/film)*

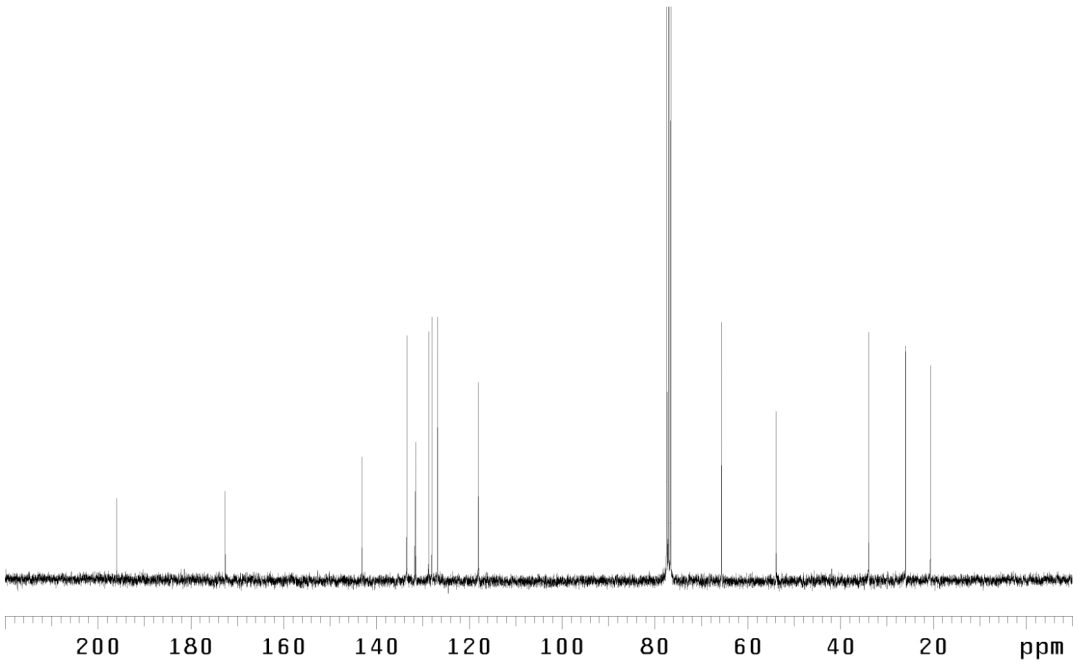


*Figure A2.47 ^{13}C NMR of compound **293** (75 MHz, $CDCl_3$)*

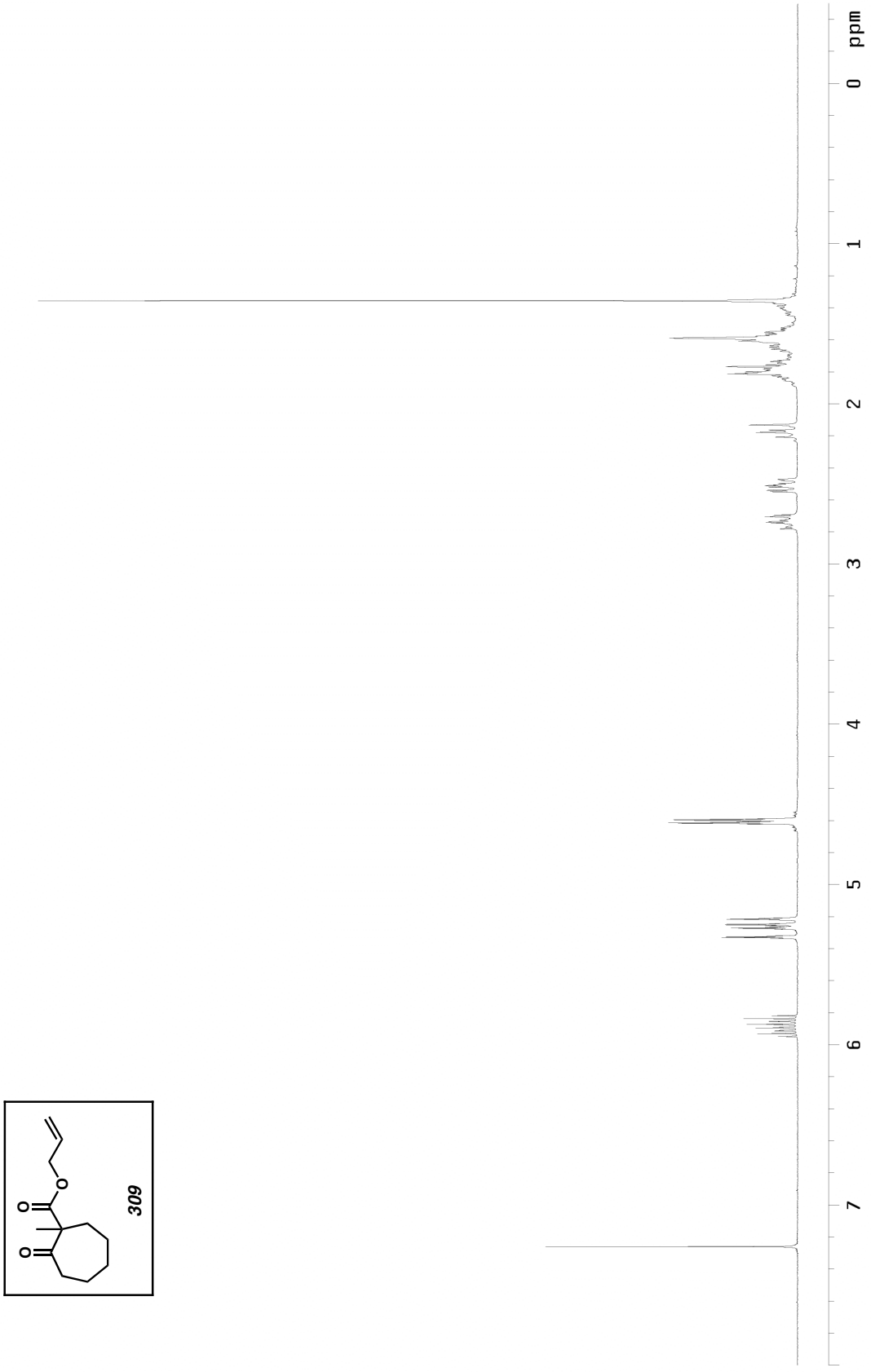


*Figure A2.48 ^1H NMR of compound **309** (300 MHz, $CDCl_3$)*

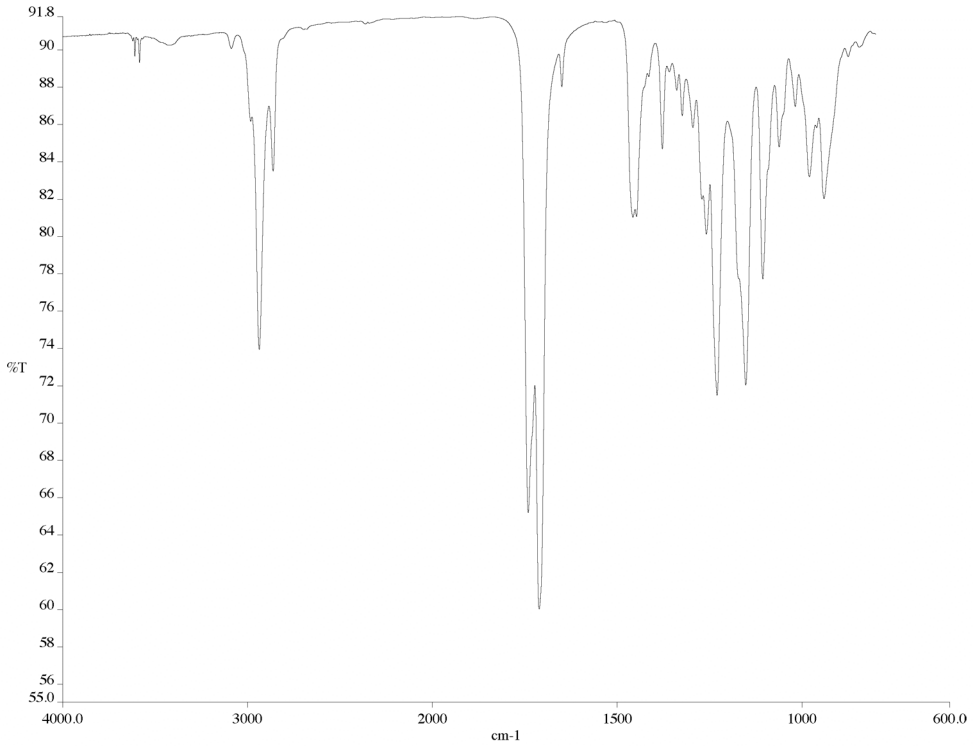


*Figure A2.49 IR of compound **309** (NaCl/film)*

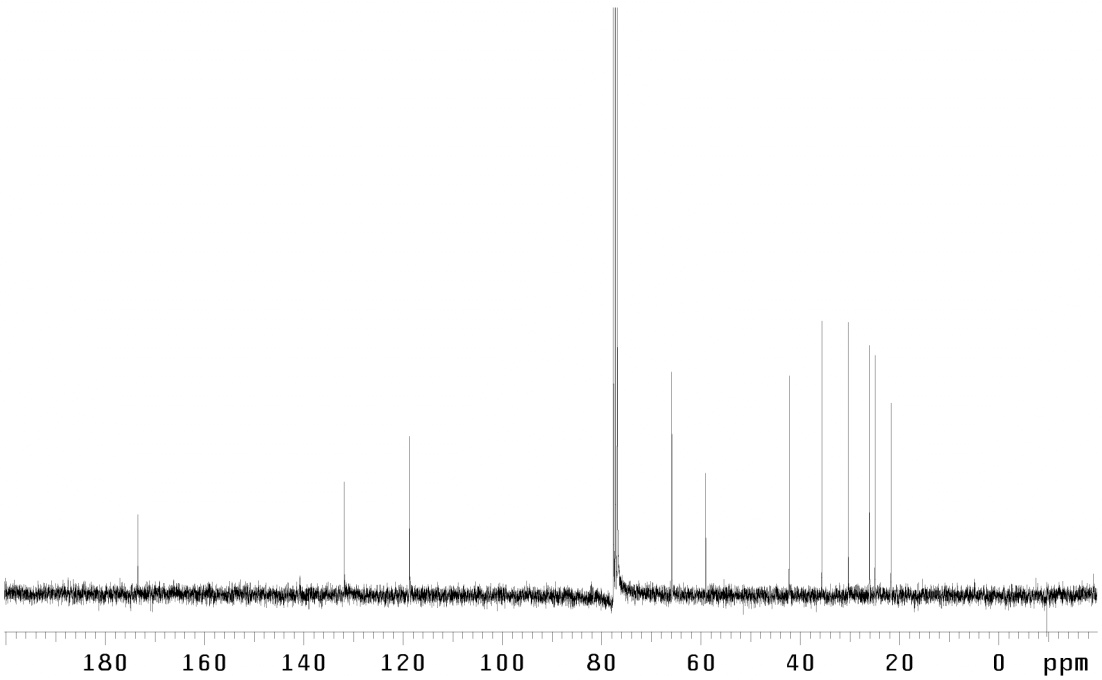


*Figure A2.50 ^{13}C NMR of compound **309** (75 MHz, $CDCl_3$)*

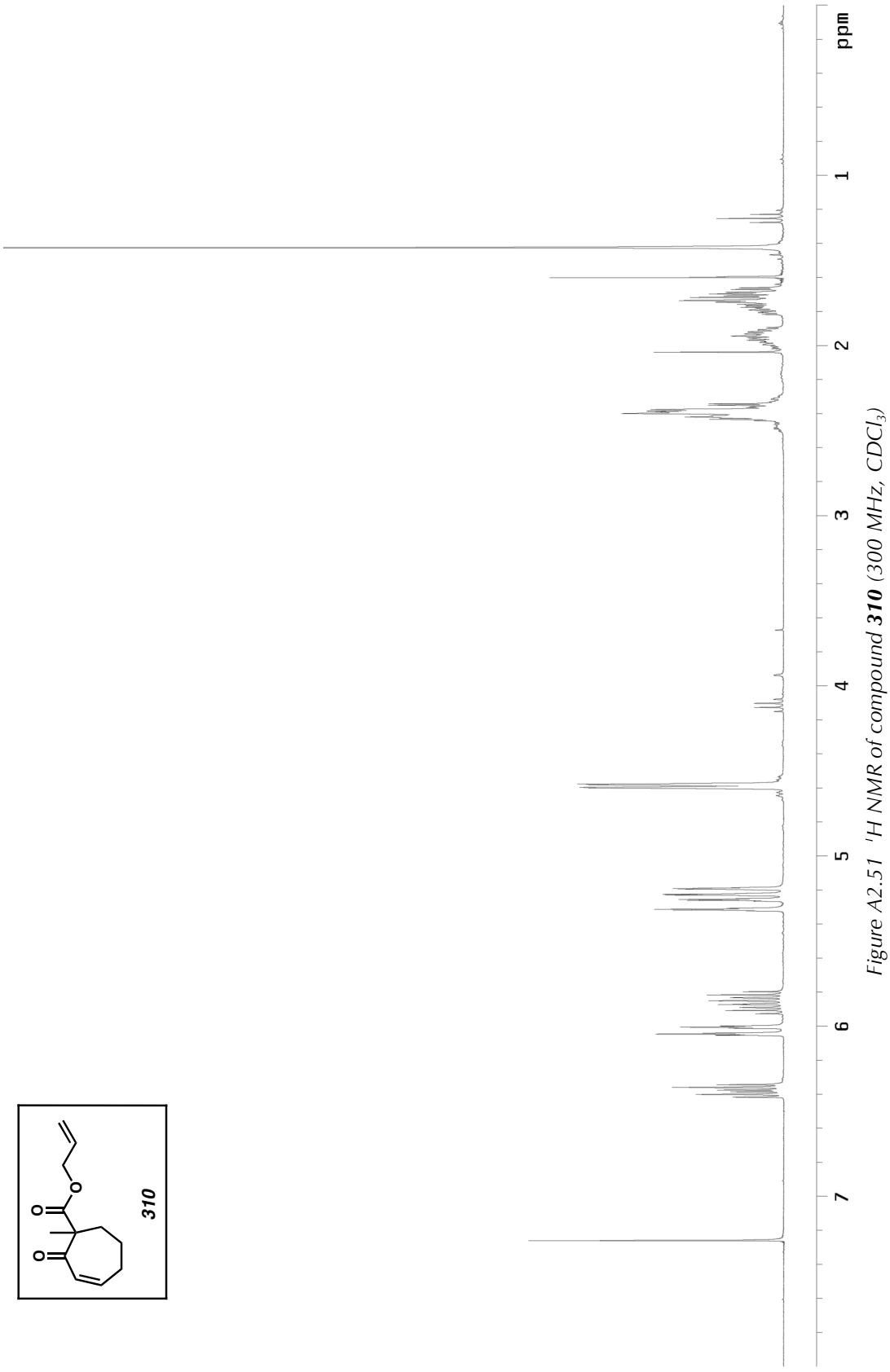


*Figure A2.51 ^1H NMR of compound **310** (300 MHz, $CDCl_3$)*

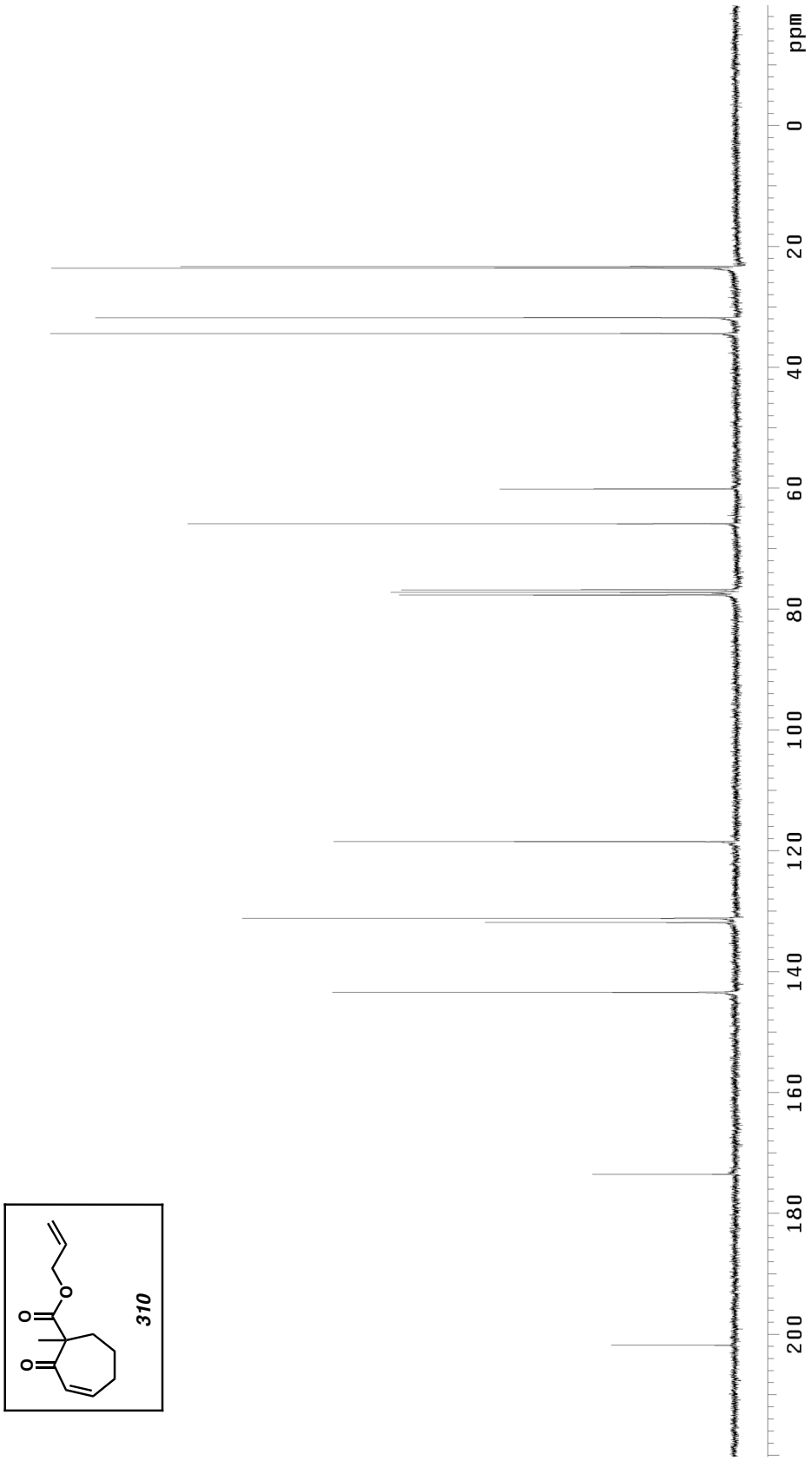


Figure A2.52 ^{13}C *NMR of compound* ***310*** *(75 MHz,* $CDCl_3$*)*

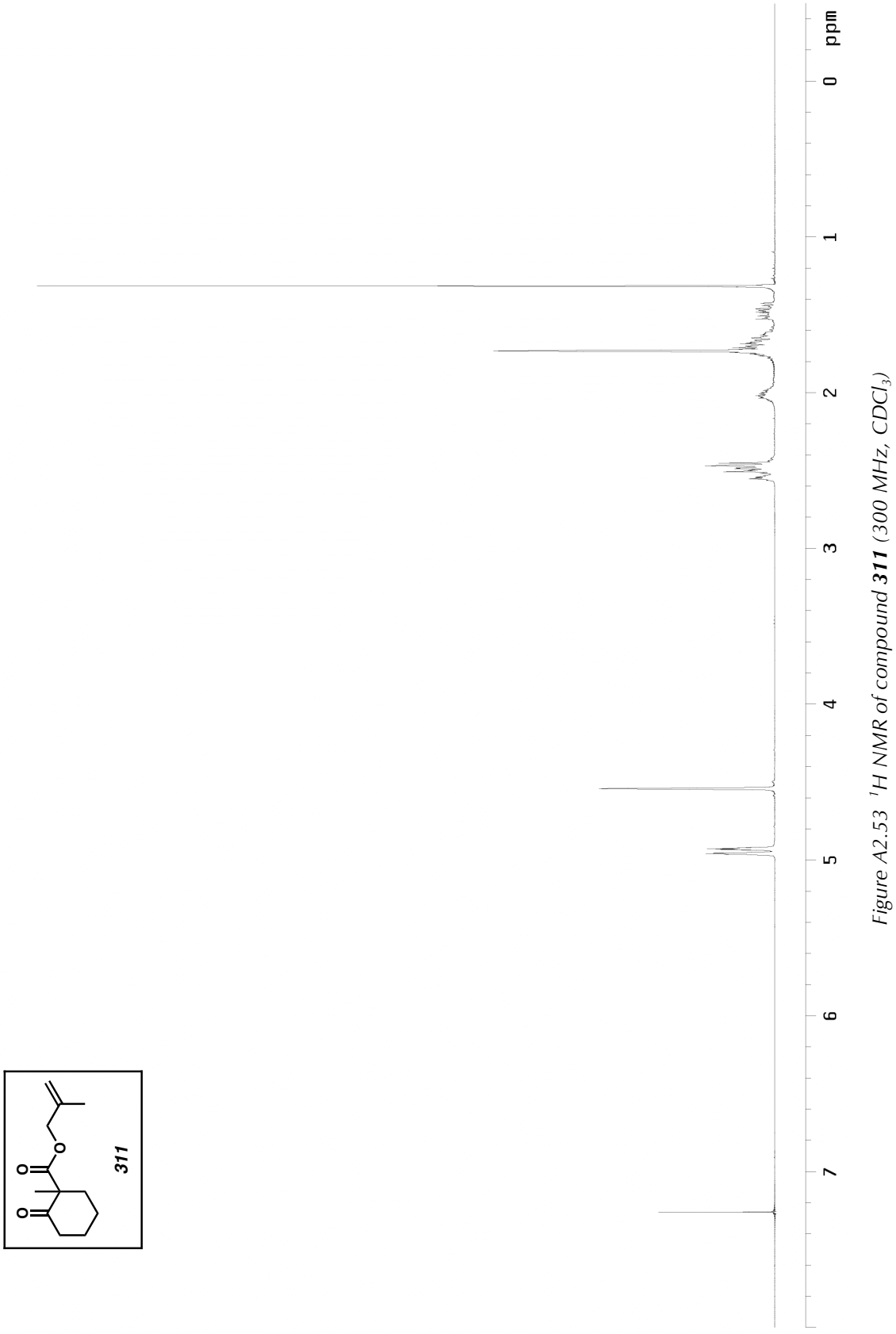


*Figure A2.53 ^1H NMR of compound **311** (300 MHz, $CDCl_3$)*

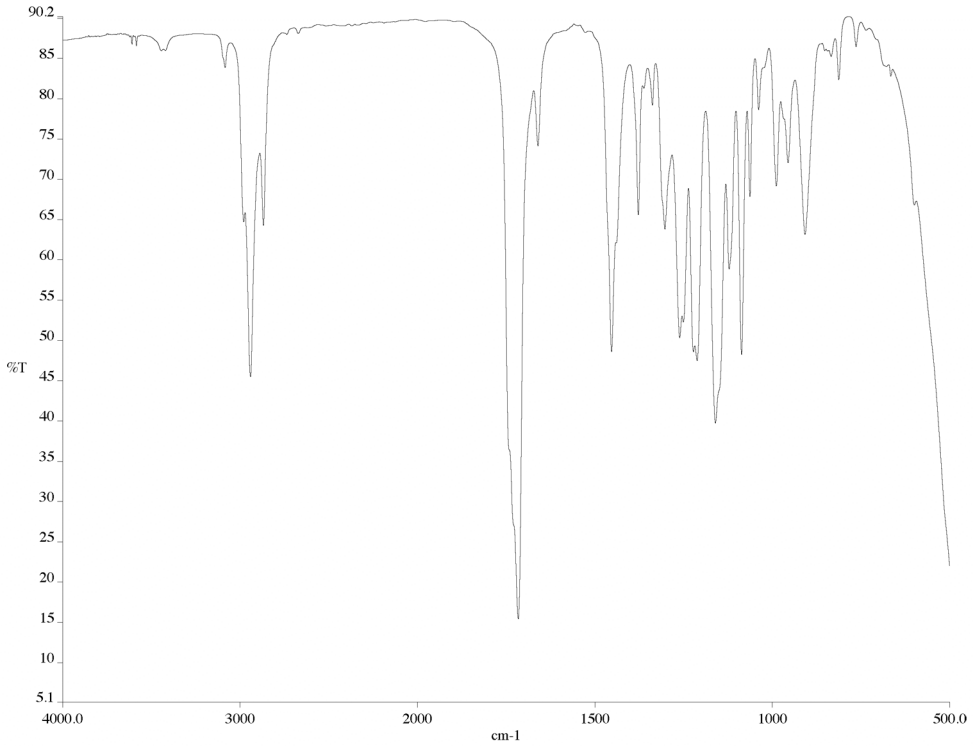


*Figure A2.54 IR of compound **311** (NaCl/film)*

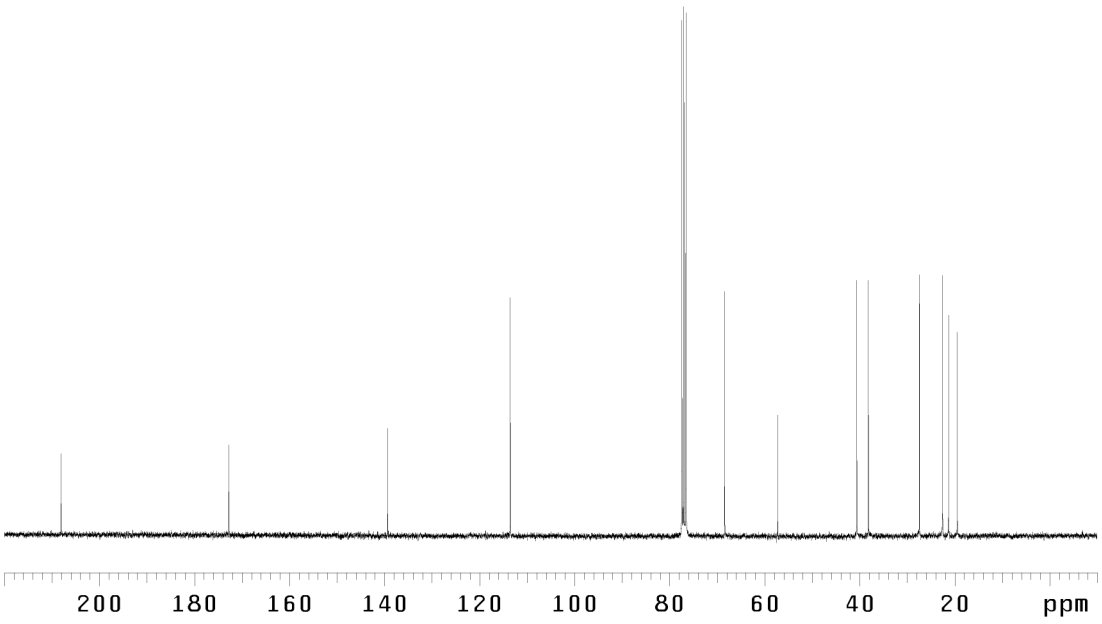


*Figure A2.55 ^{13}C NMR of compound **311** (75 MHz, $CDCl_3$)*

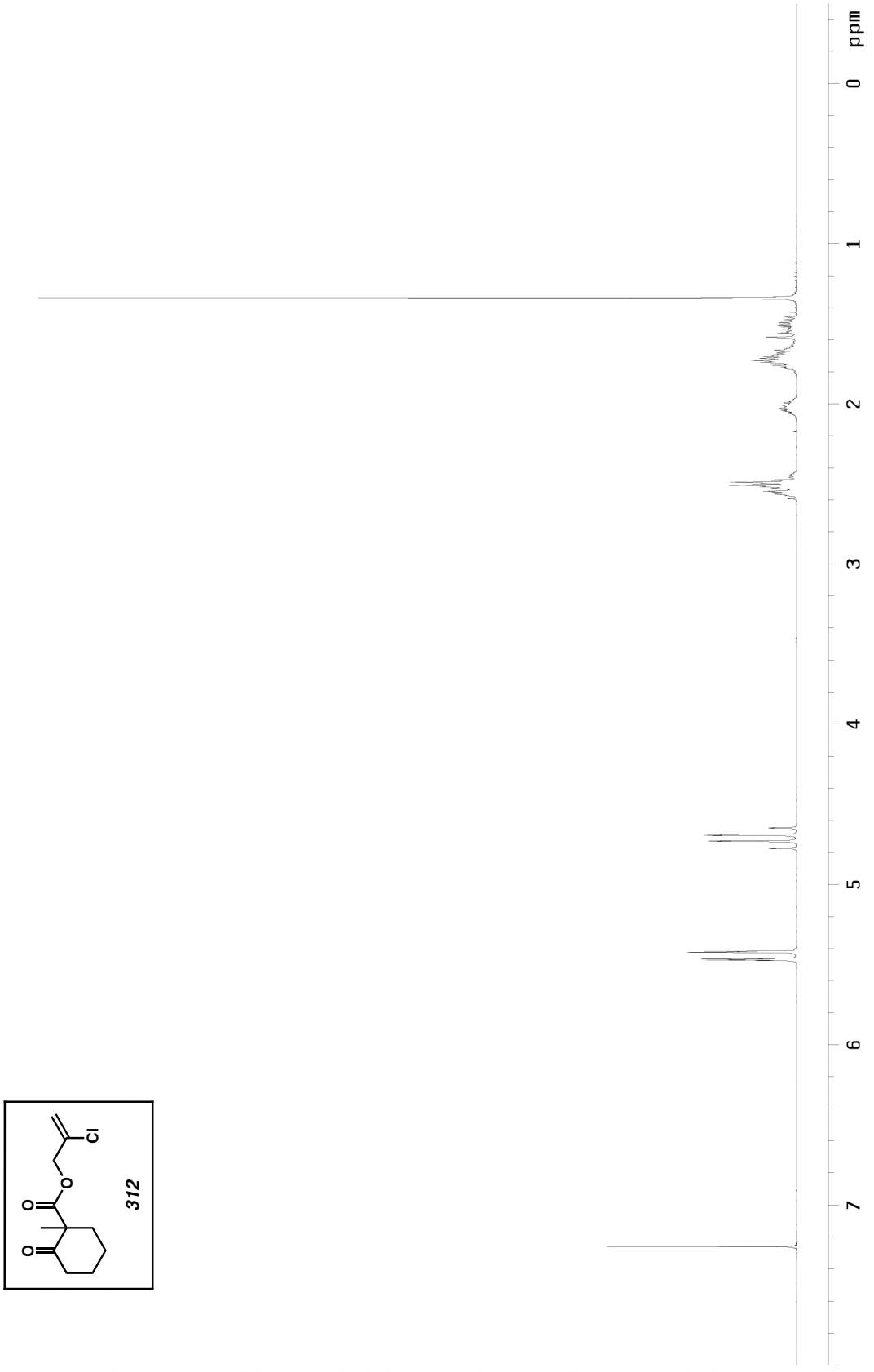


*Figure A2.56 ^1H NMR of compound **312** (300 MHz, $CDCl_3$)*

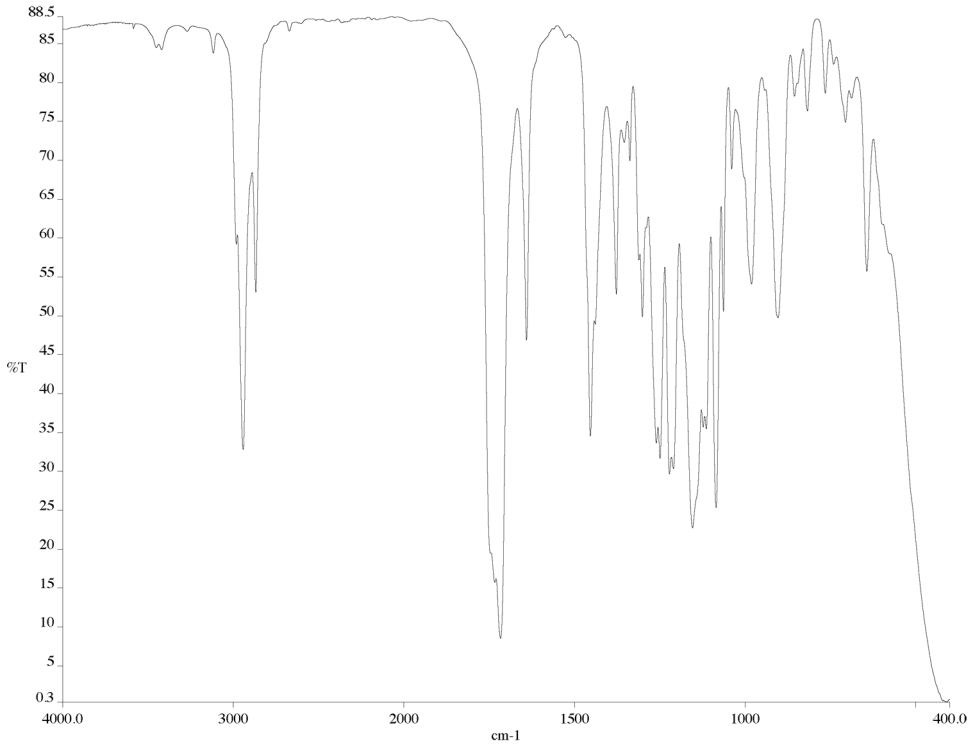


*Figure A2.57 IR of compound **312** (NaCl/film)*

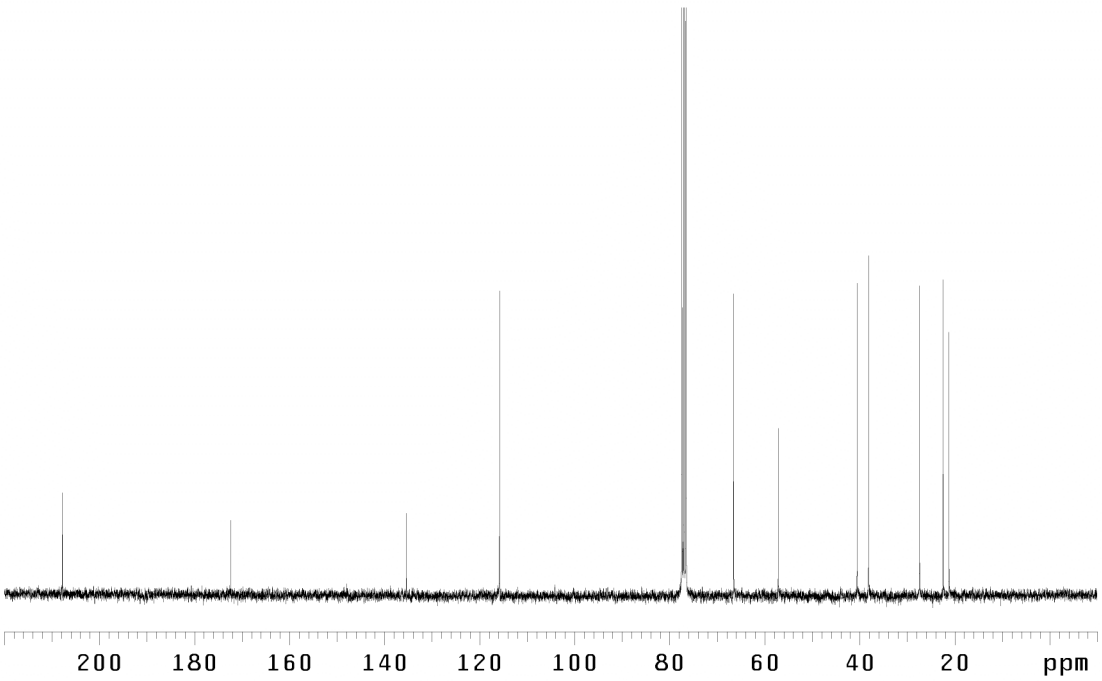


*Figure A2.58 ^{13}C NMR of compound **312** (75 MHz, $CDCl_3$)*

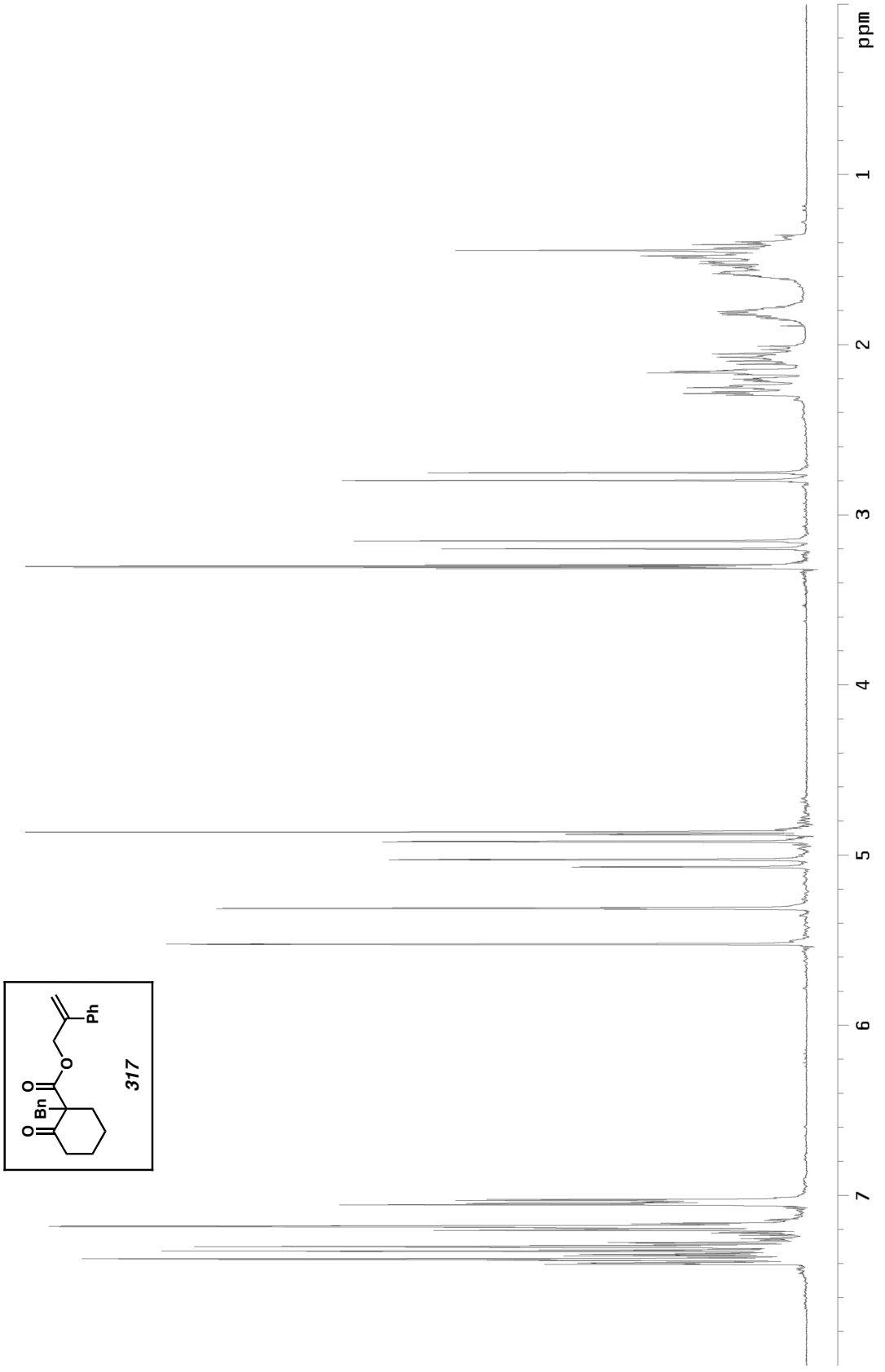


*Figure A2.59 ^1H NMR of compound **317** (300 MHz, $CDCl_3$)*

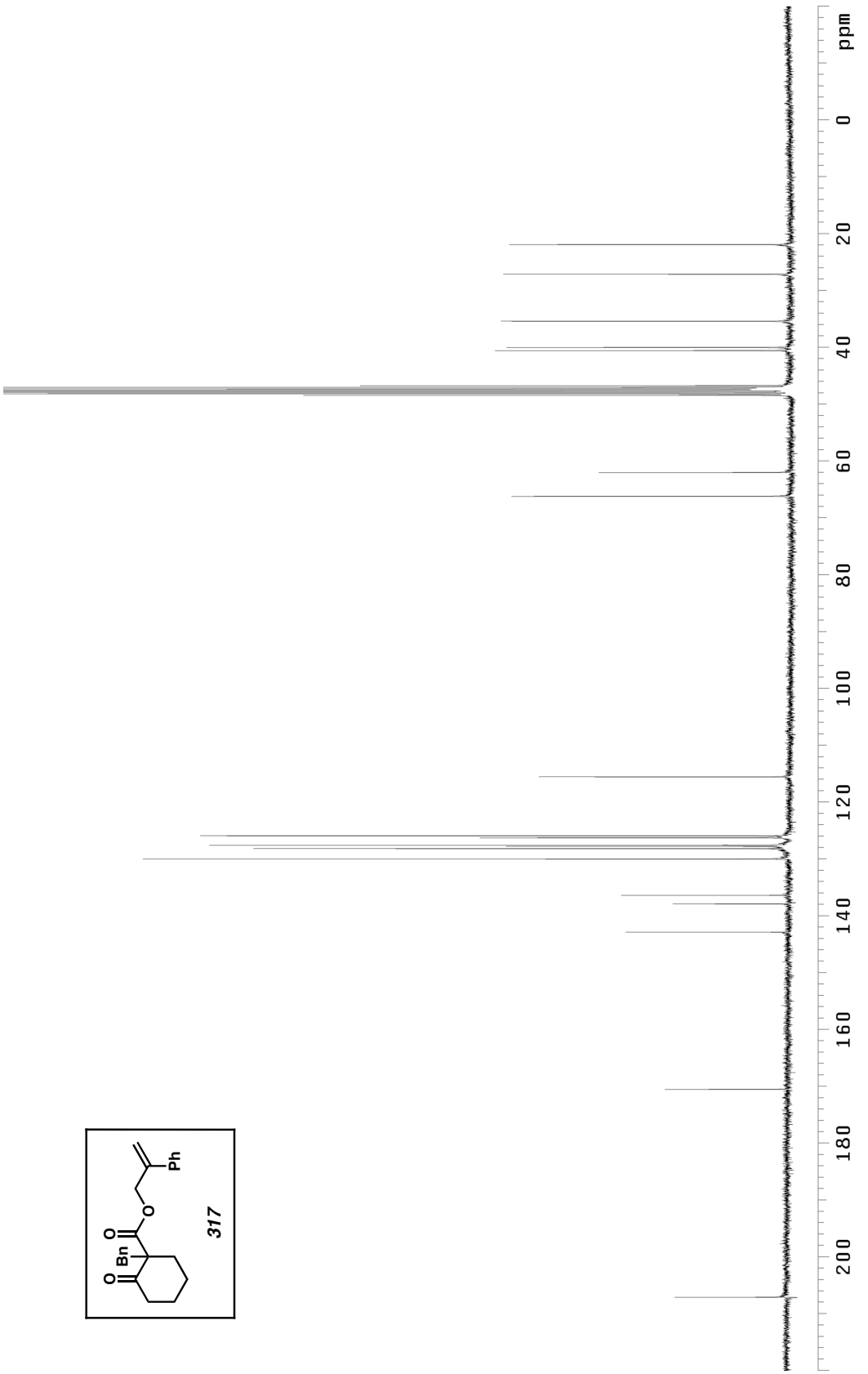


*Figure A2.60 ^{13}C NMR of compound **317** (75 MHz, $CDCl_3$)*

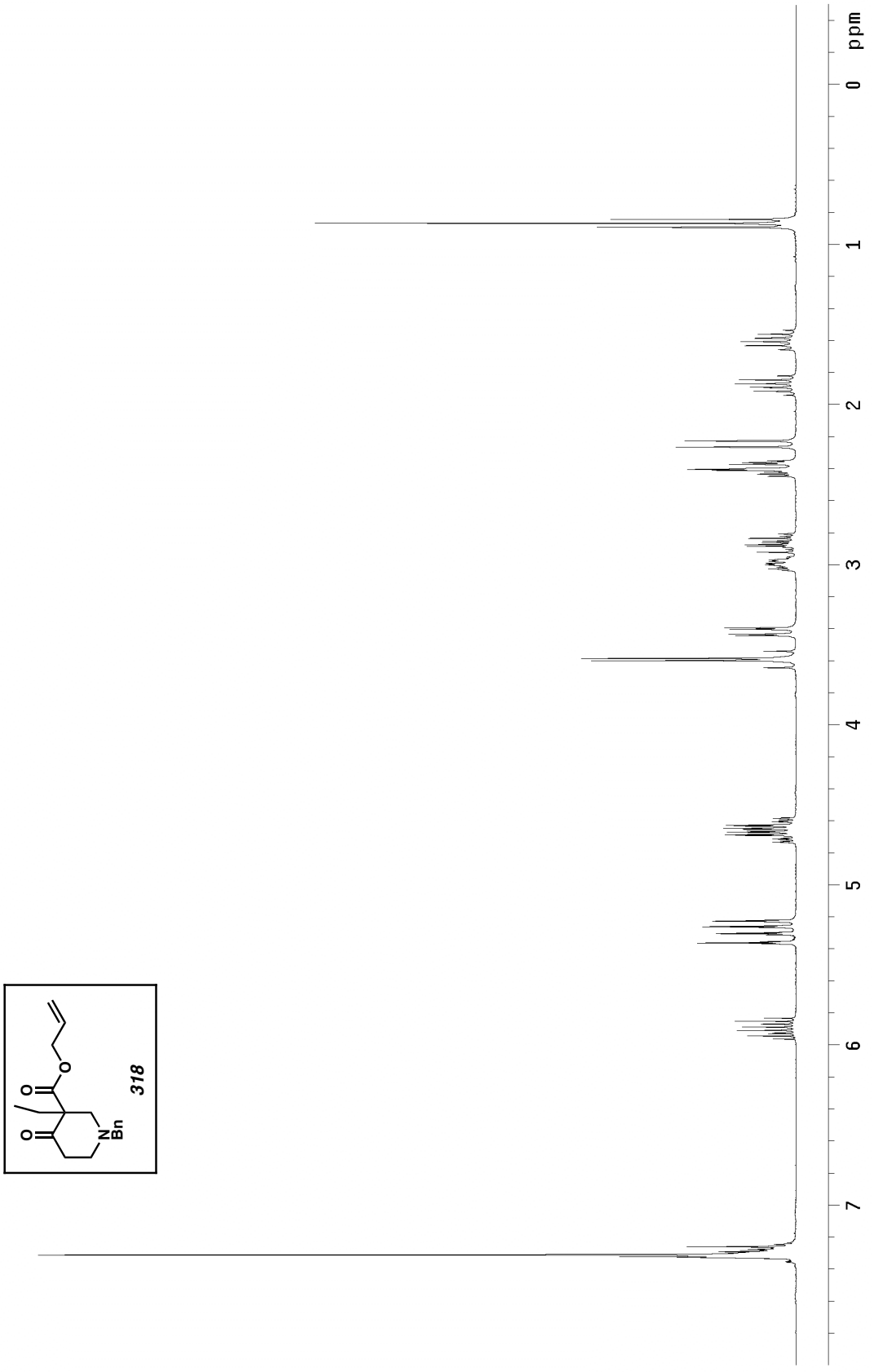


*Figure A2.61 ^1H NMR of compound **318** (300 MHz, $CDCl_3$)*

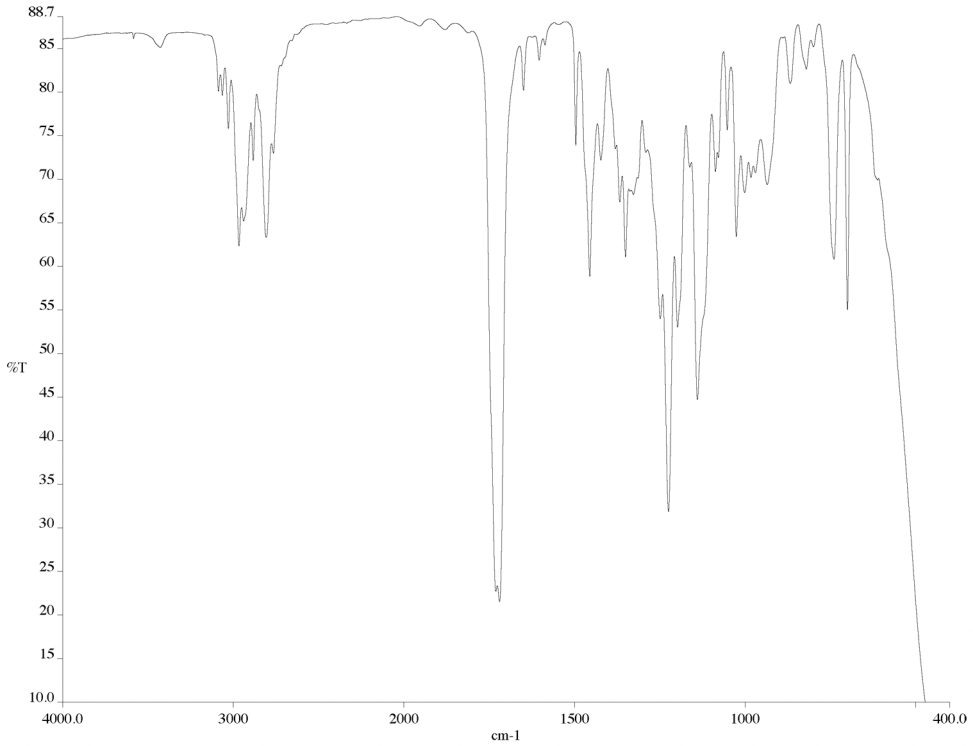


*Figure A2.62 IR of compound **318** (NaCl/film)*

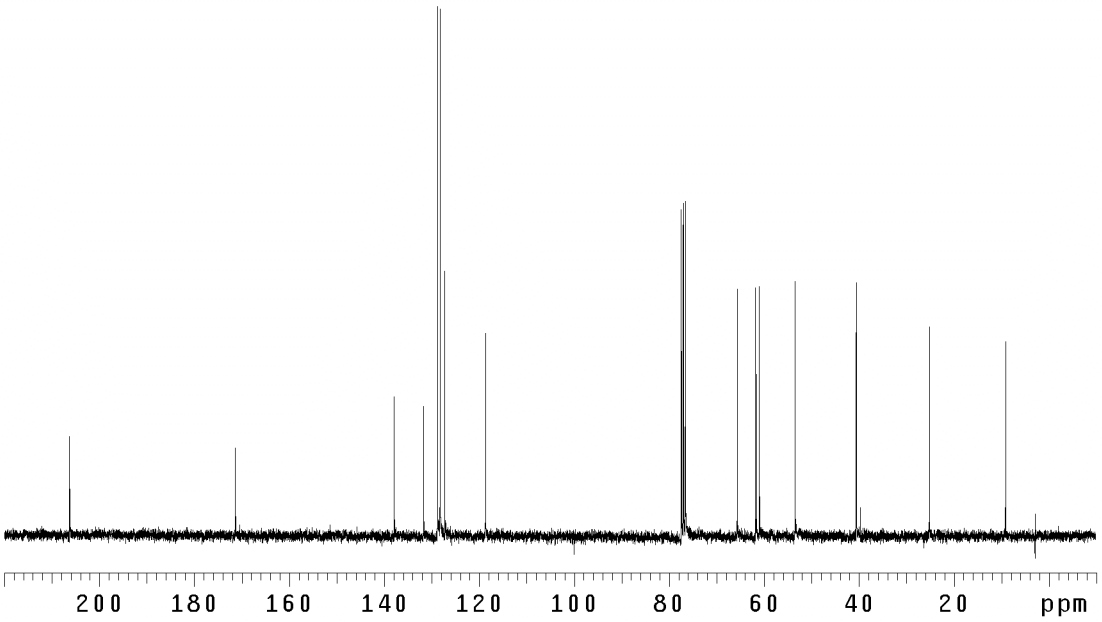


*Figure A2.63 ^{13}C NMR of compound **318** (75 MHz, $CDCl_3$)*



*Figure A2.64 ^1H NMR of compound **321** (500 MHz, $CDCl_3$)*

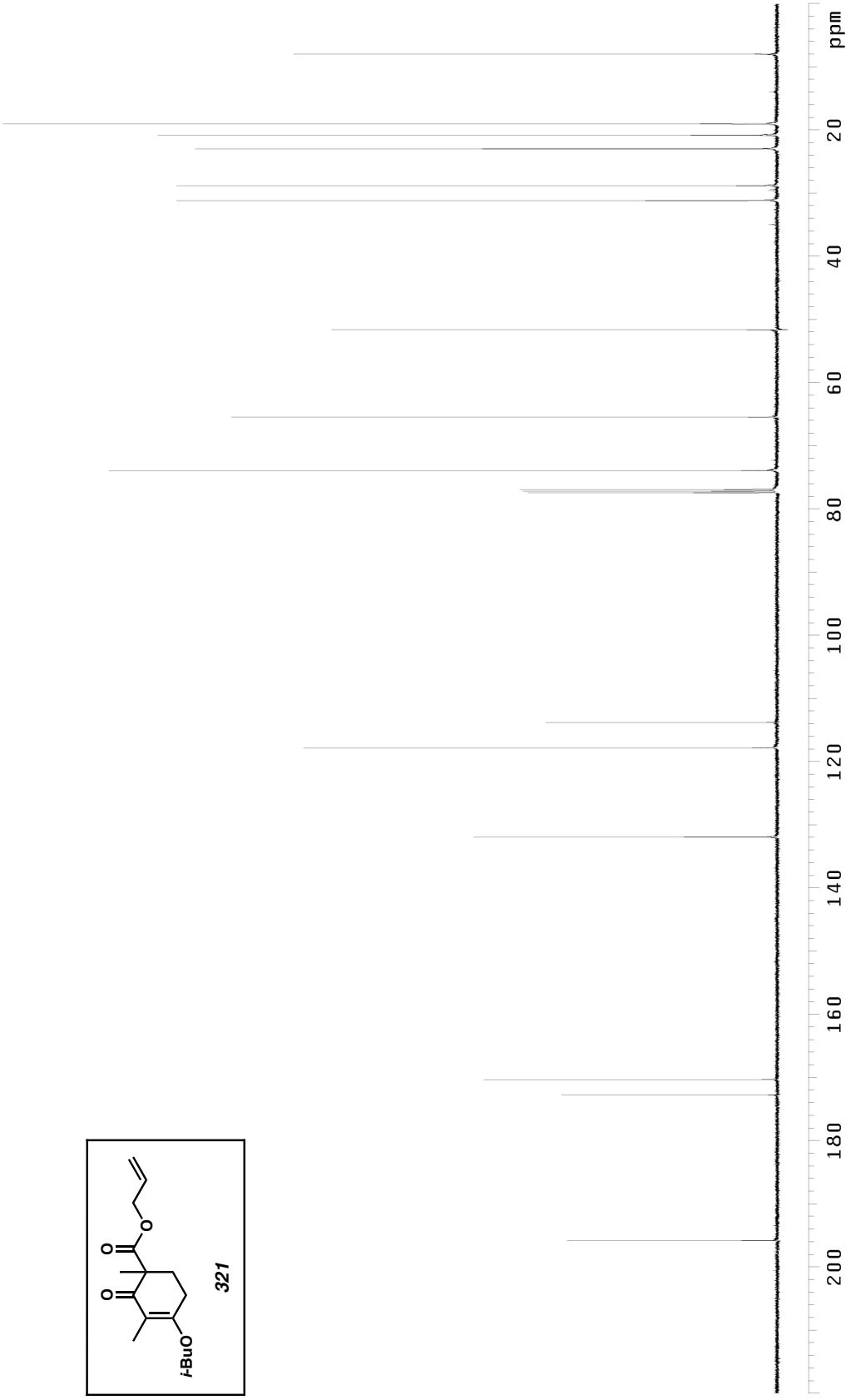


*Figure A2.65 ^{13}C NMR of compound **321** (126 MHz, $CDCl_3$)*

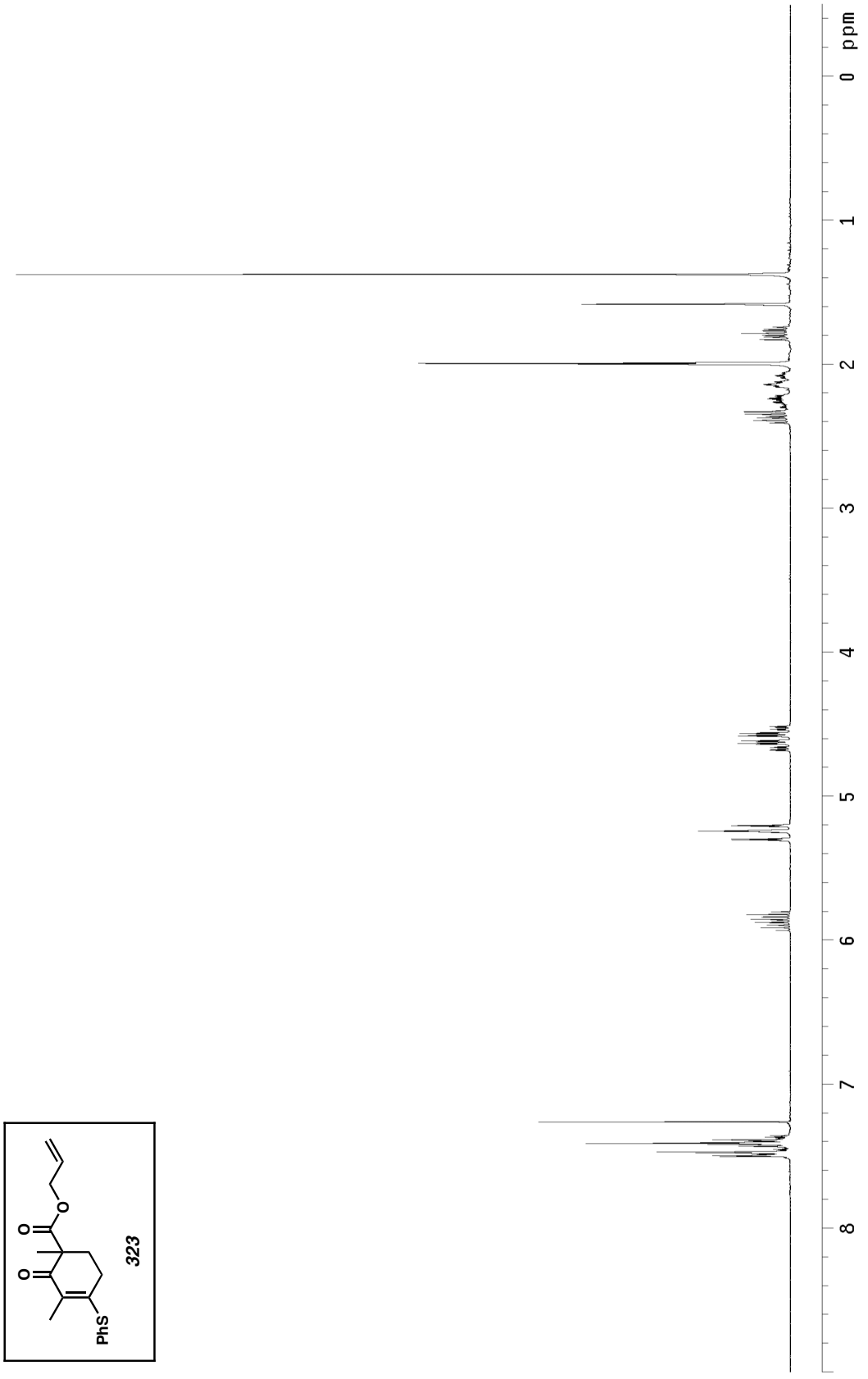


*Figure A2.66 ^1H NMR of compound **323** (300 MHz, $CDCl_3$)*

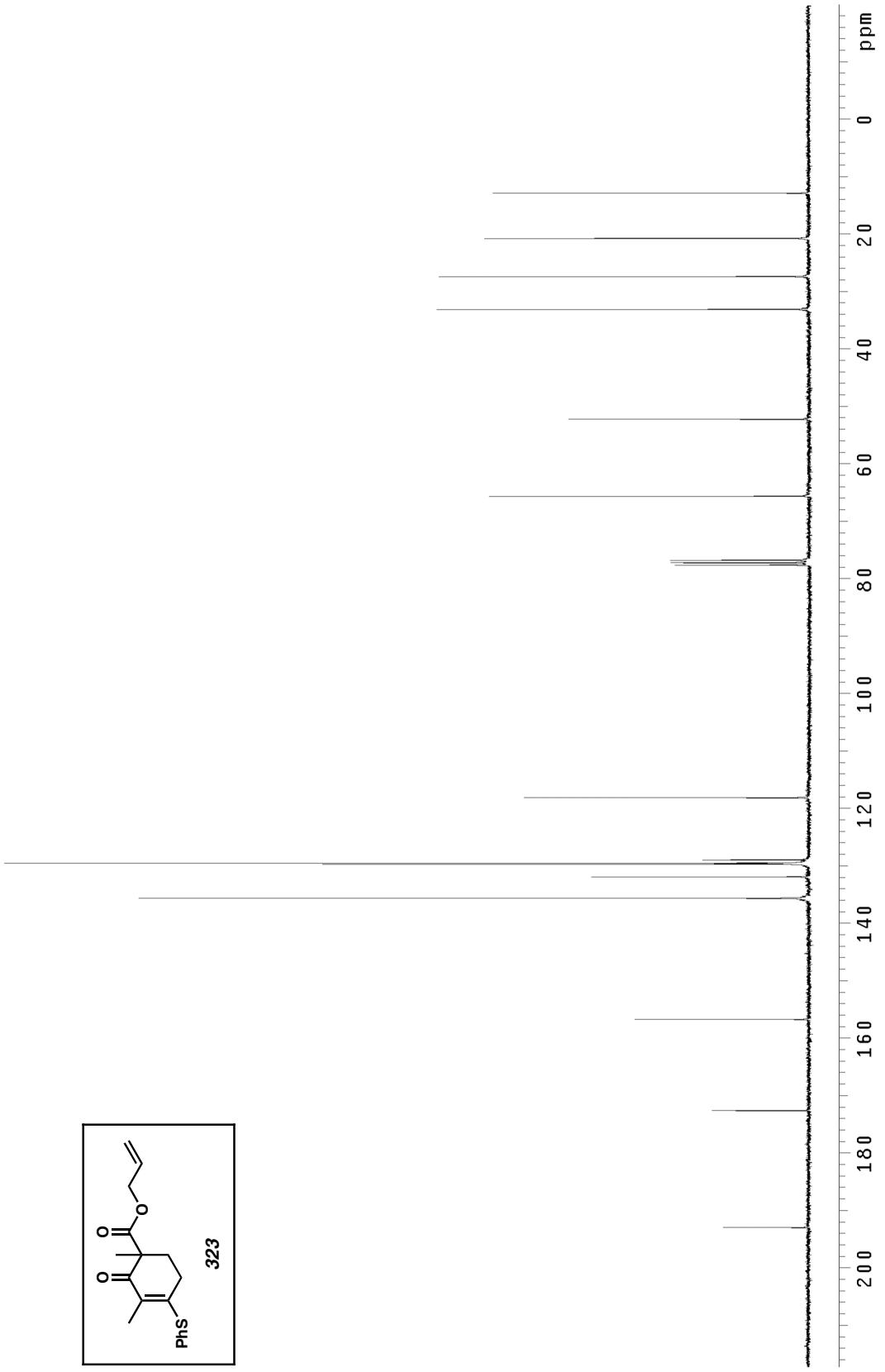


*Figure A2.67 ^{13}C NMR of compound **SI27** (75 MHz, $CDCl_3$)*

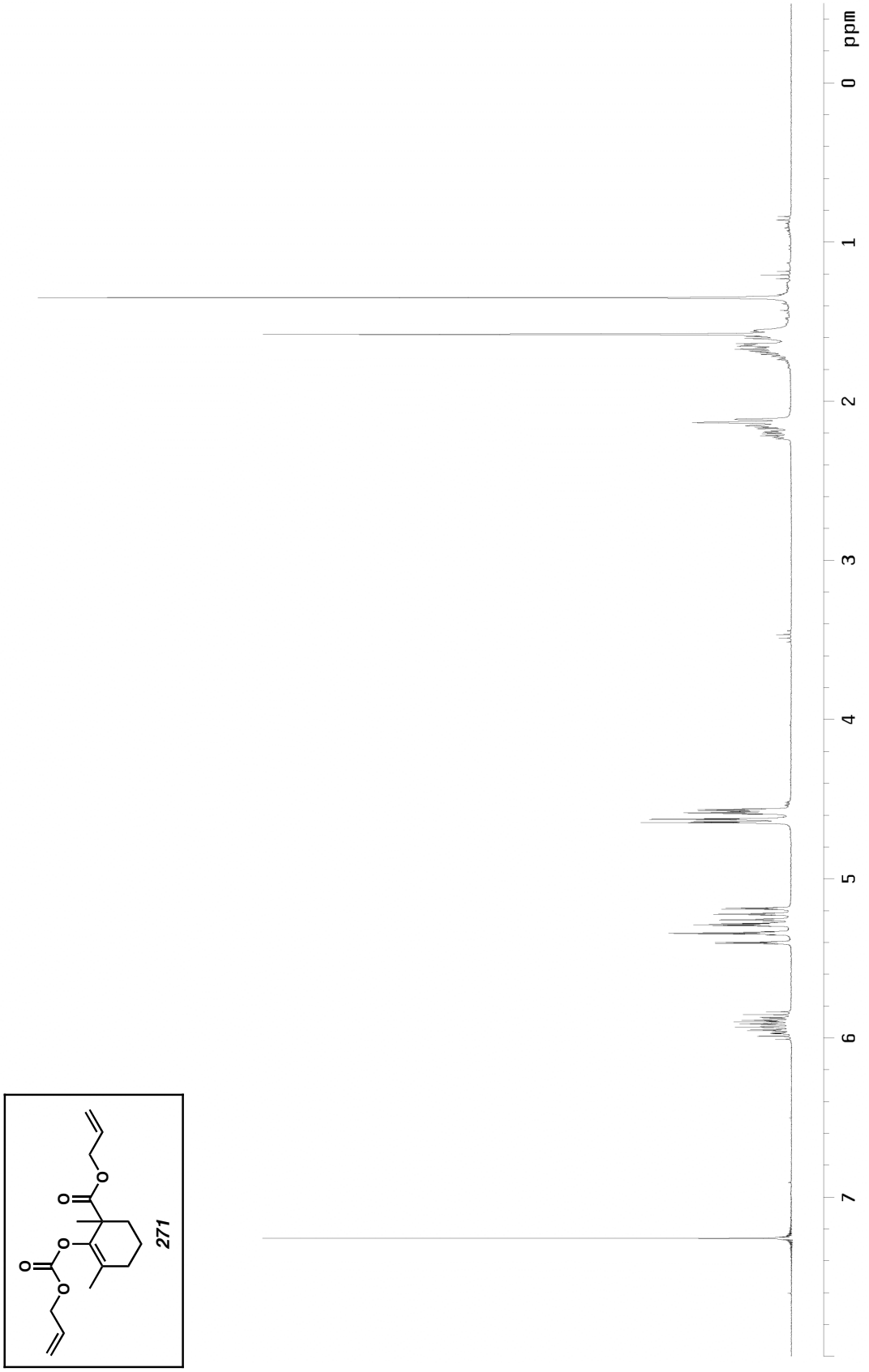


*Figure A2.68 ^{1}H NMR of compound **271** (300 MHz, $CDCl_3$)*

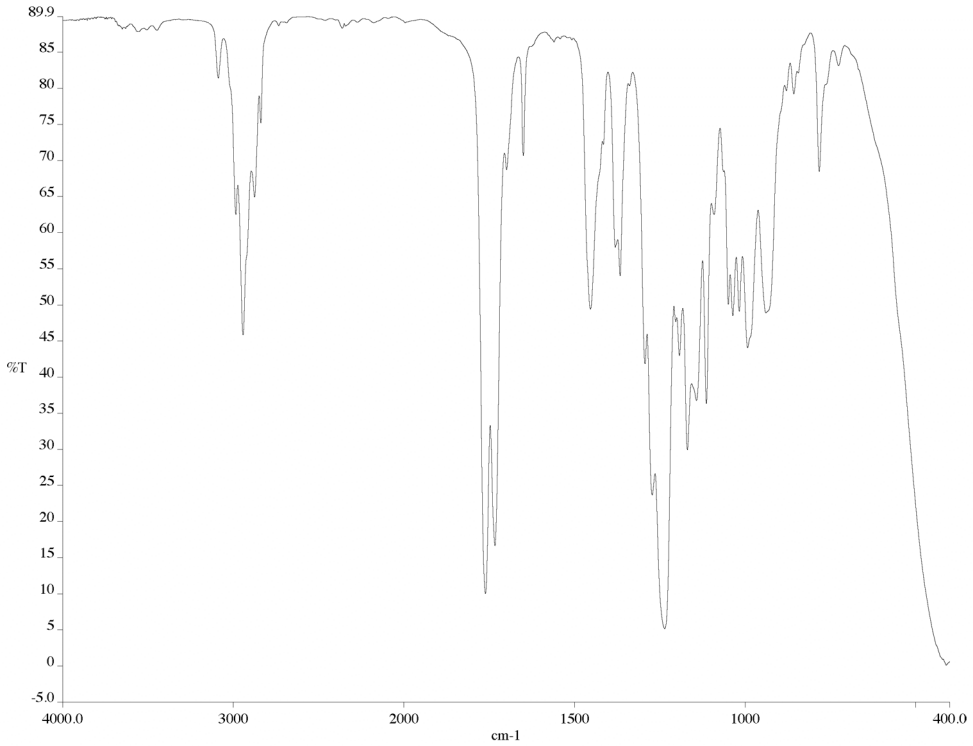


*Figure A2.69 IR of compound **271** (NaCl/film)*

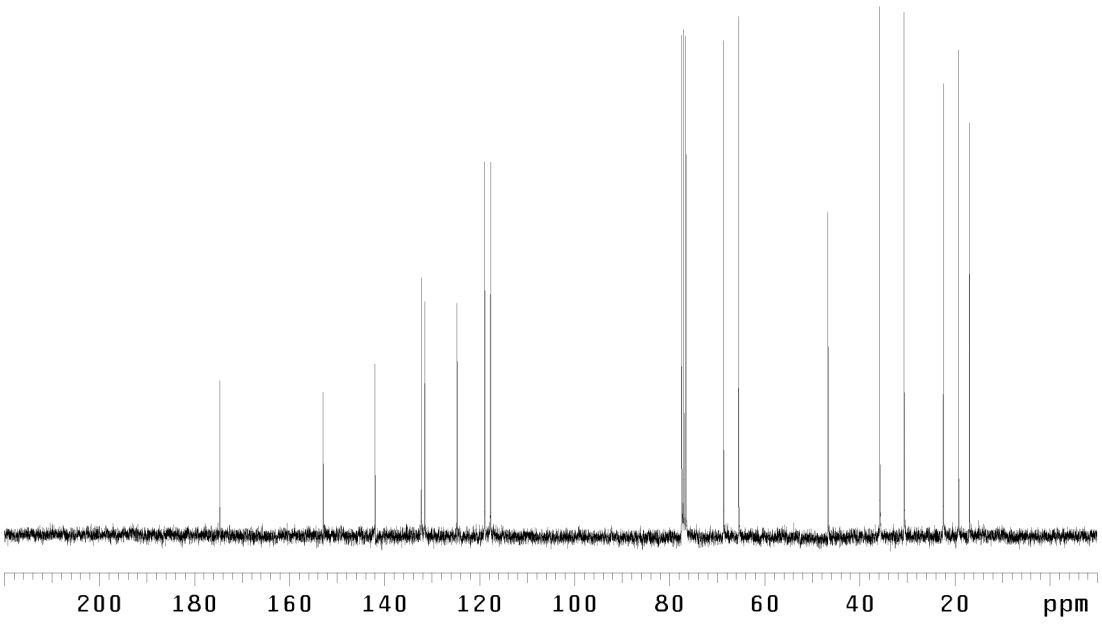


*Figure A2.70 ^{13}C NMR of compound **271** (75 MHz, $CDCl_3$)*

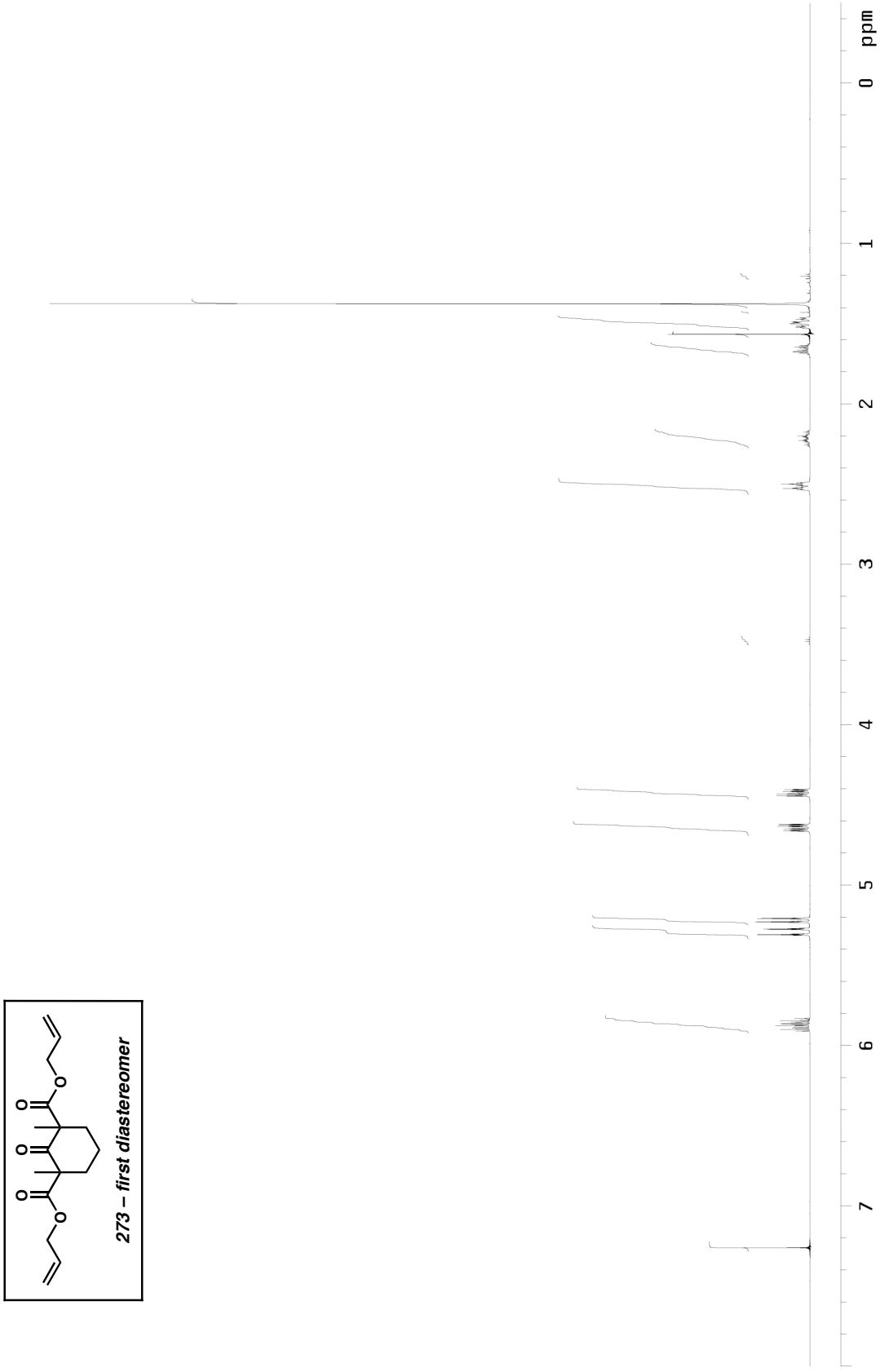


Figure A2.71 ^1H NMR of first diastereomer of compound **273** *(500 MHz, $CDCl_3$)*

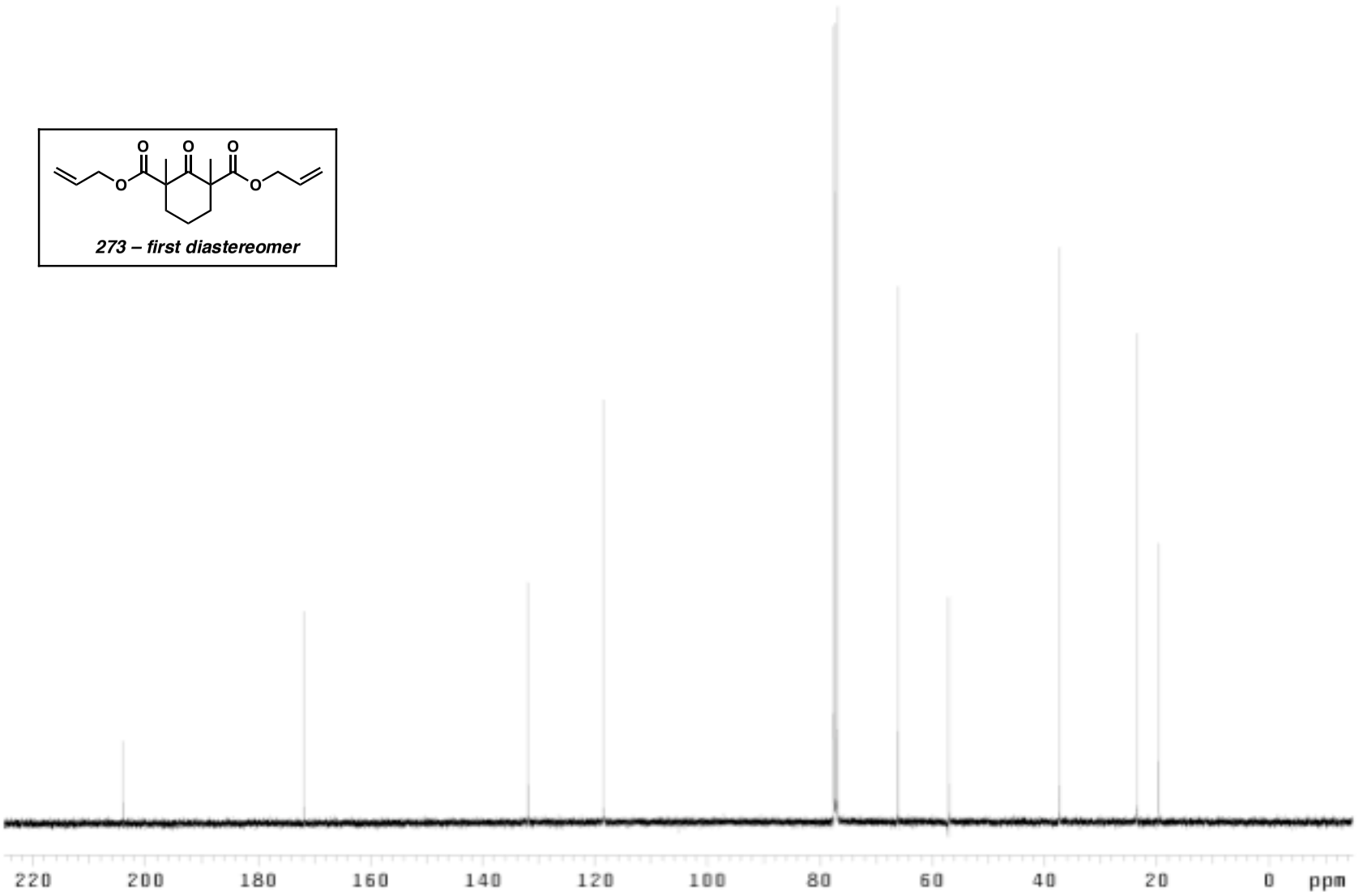
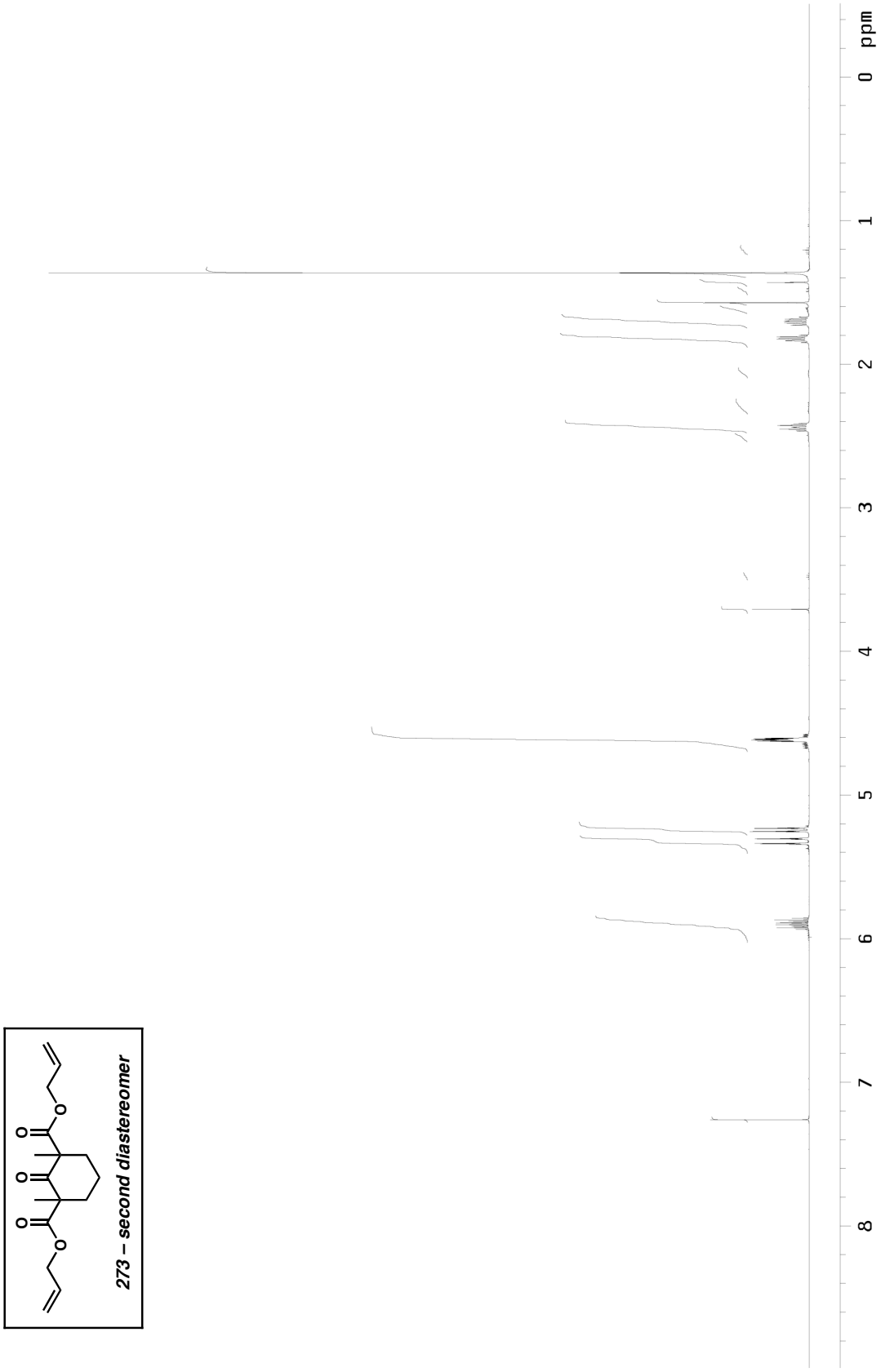


*Figure A2.72 ^{13}C NMR of first diastereomer of compound **273** (125 MHz, $CDCl_3$)*



273 – second diastereomer

Figure A2.73 ^{1}H NMR of second diastereomer of compound ***273*** *(500 MHz, $CDCl_3$)*

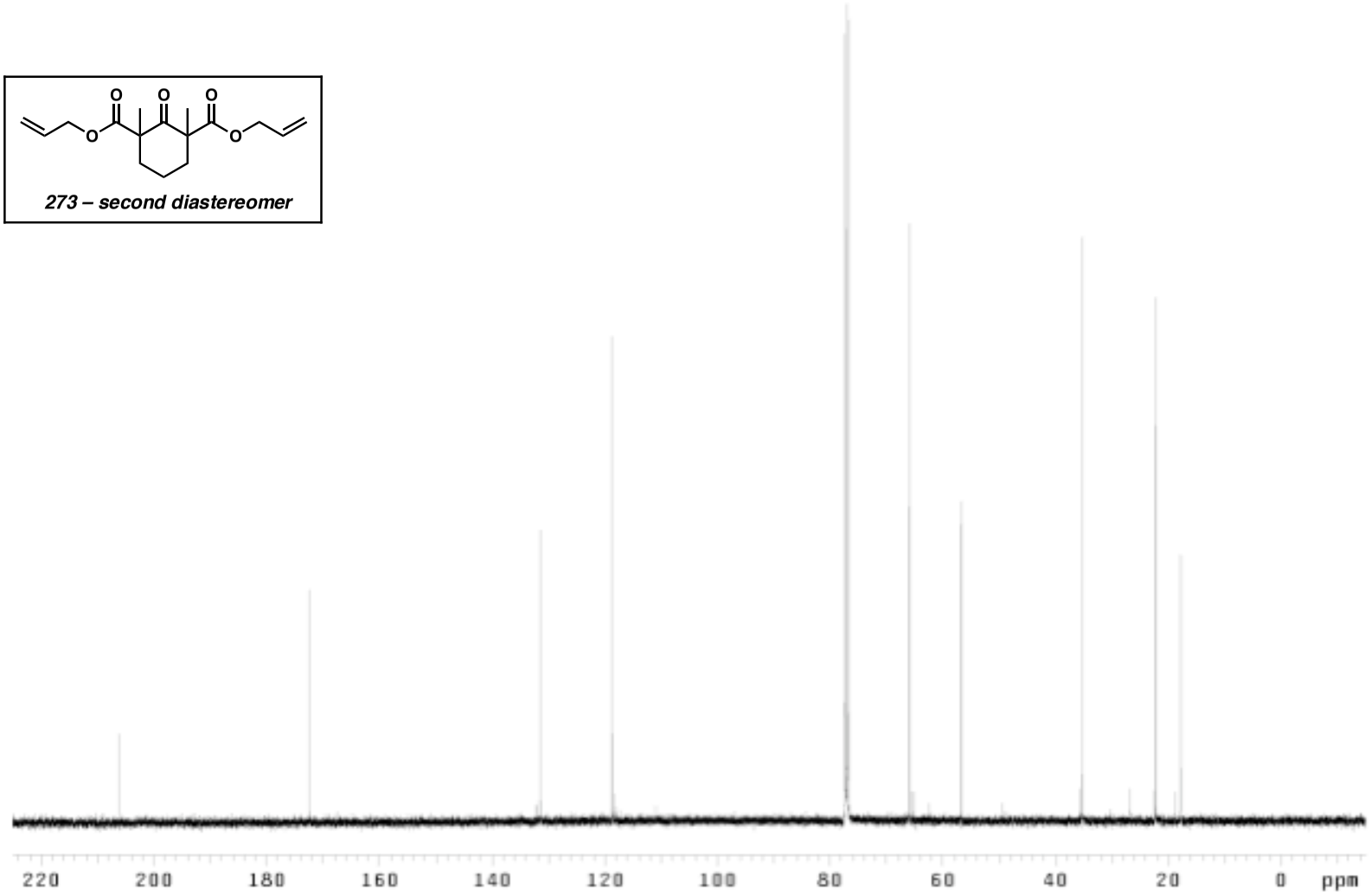


Figure A2.74 ^{13}C *NMR of second diastereomer of compound* ***273*** *(125 MHz,* $CDCl_3$*)*

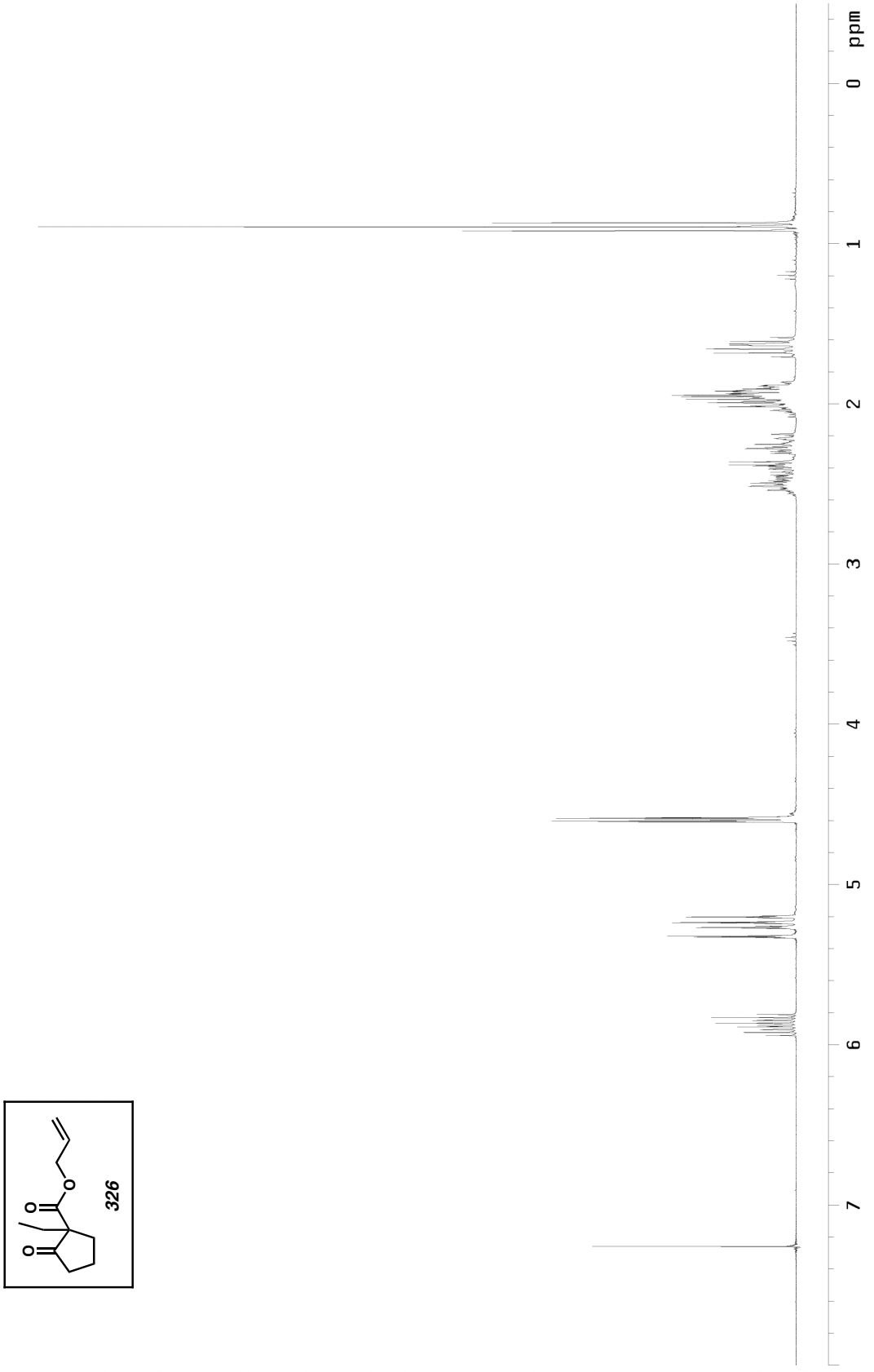


*Figure A2.75 ^1H NMR of compound **326** (300 MHz, $CDCl_3$)*

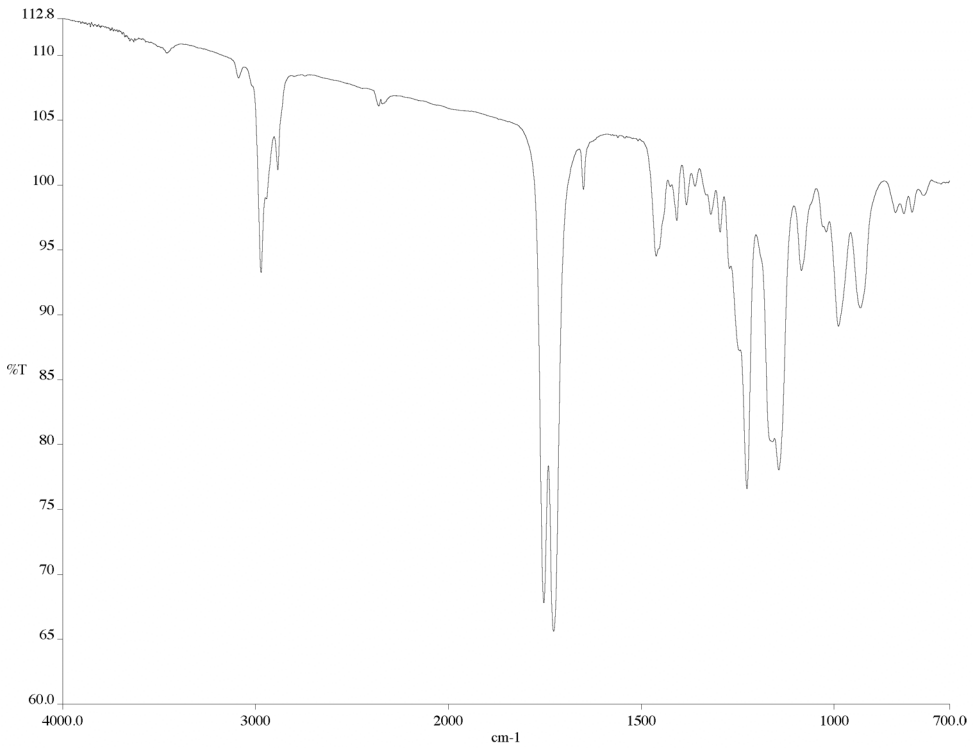


*Figure A2.76 IR of compound **326** (NaCl/film)*

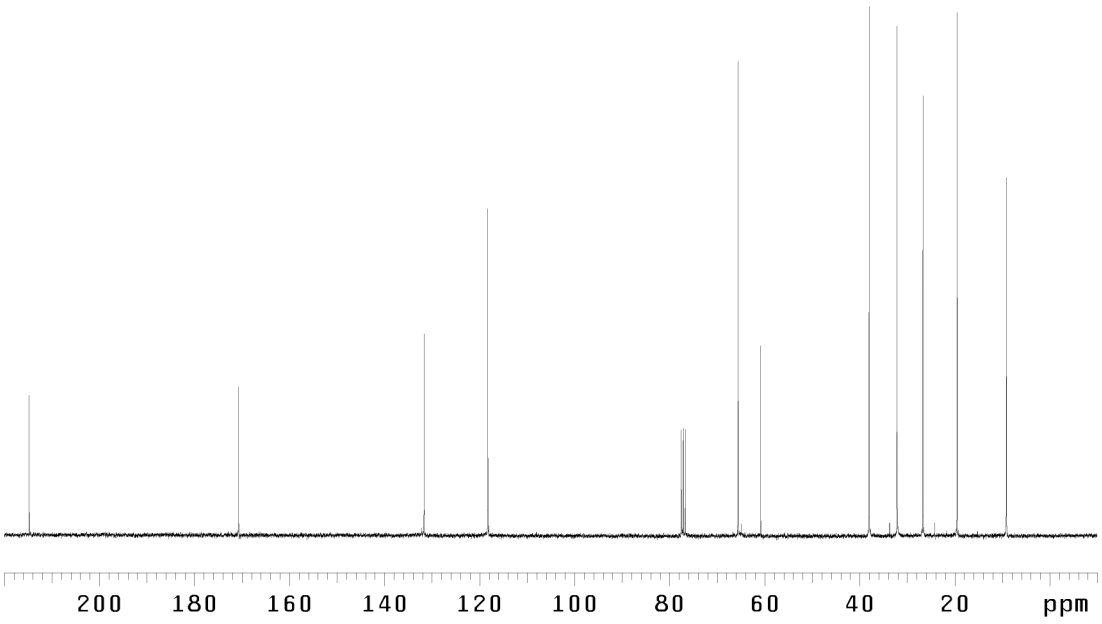


*Figure A2.77 ^{13}C NMR of compound **326** (75 MHz, $CDCl_3$)*

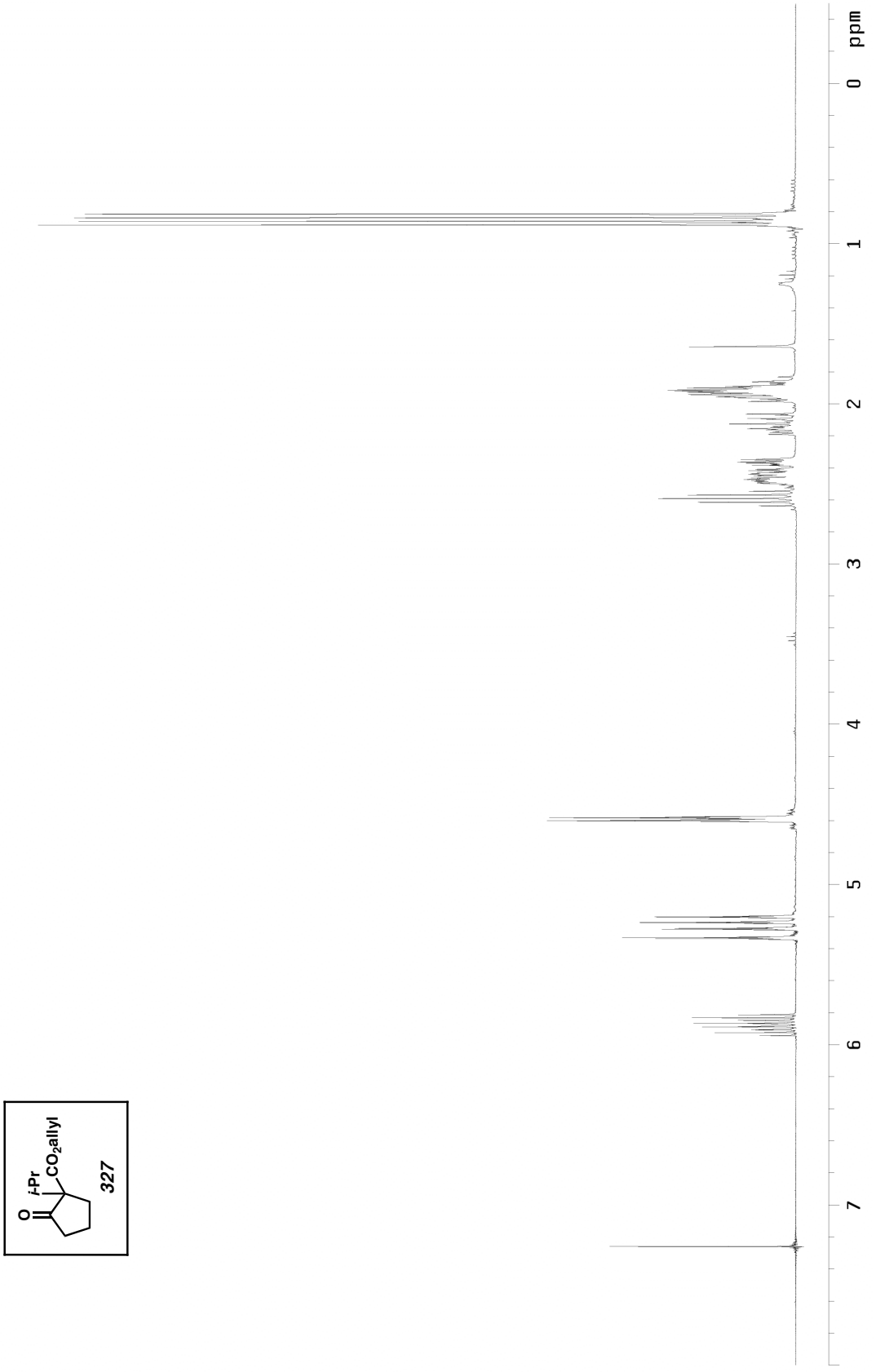


Figure A2.78 ^1H NMR of compound ***327*** *(300 MHz, $CDCl_3$)*

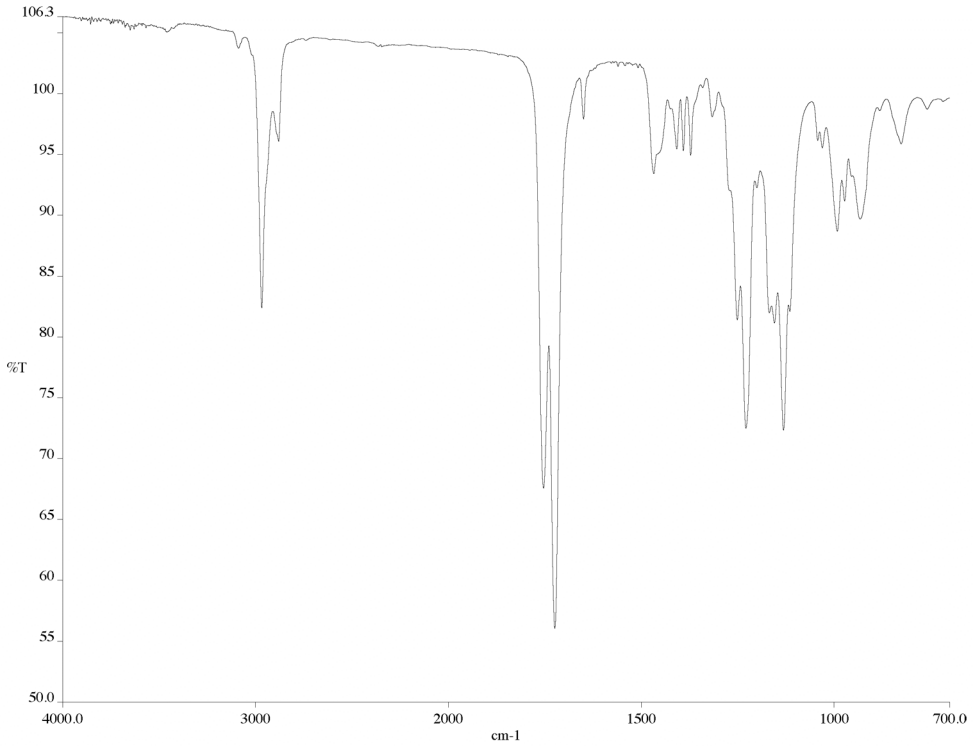


*Figure A2.79 IR of compound **327** (NaCl/film)*

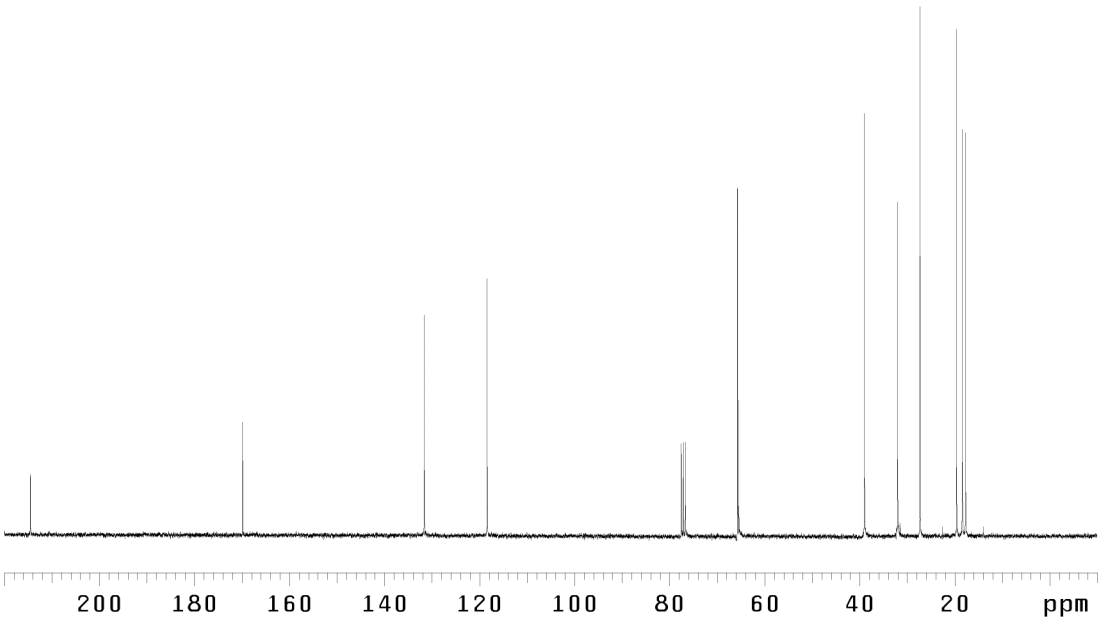


*Figure A2.80 ^{13}C NMR of compound **327** (75 MHz, $CDCl_3$)*

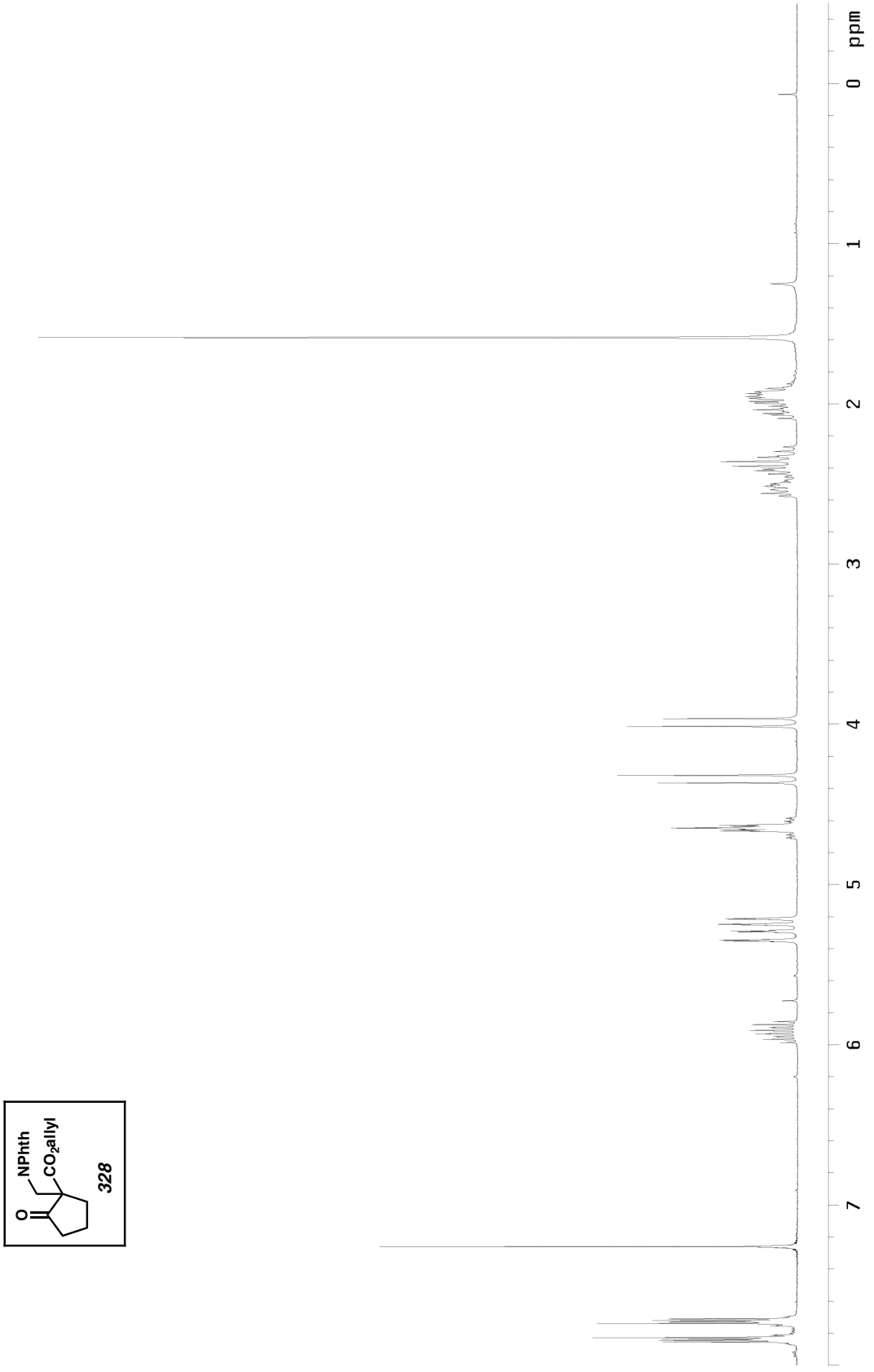


*Figure A2.81 ^1H NMR of compound **328** (300 MHz, $CDCl_3$)*

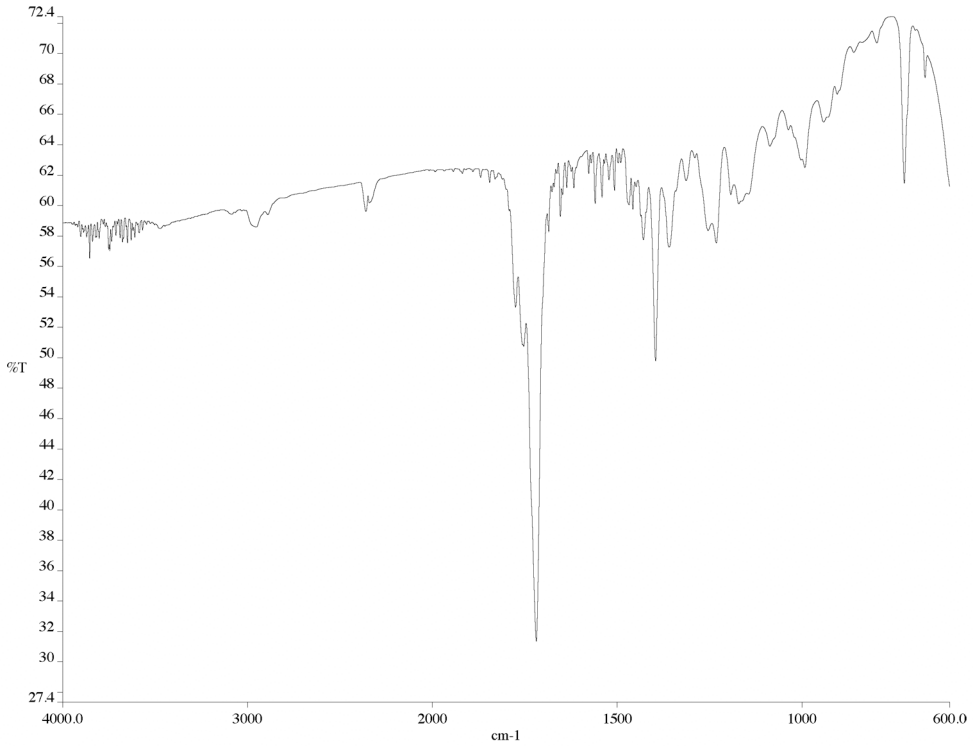


*Figure A2.82 IR of compound **328** (NaCl/film)*

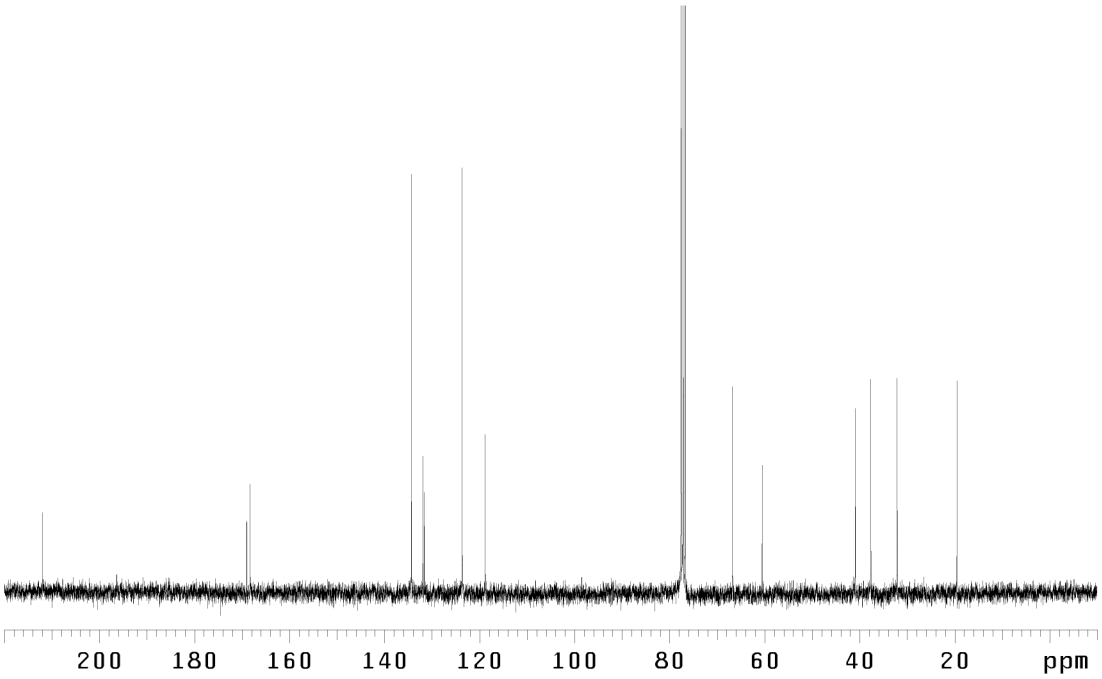
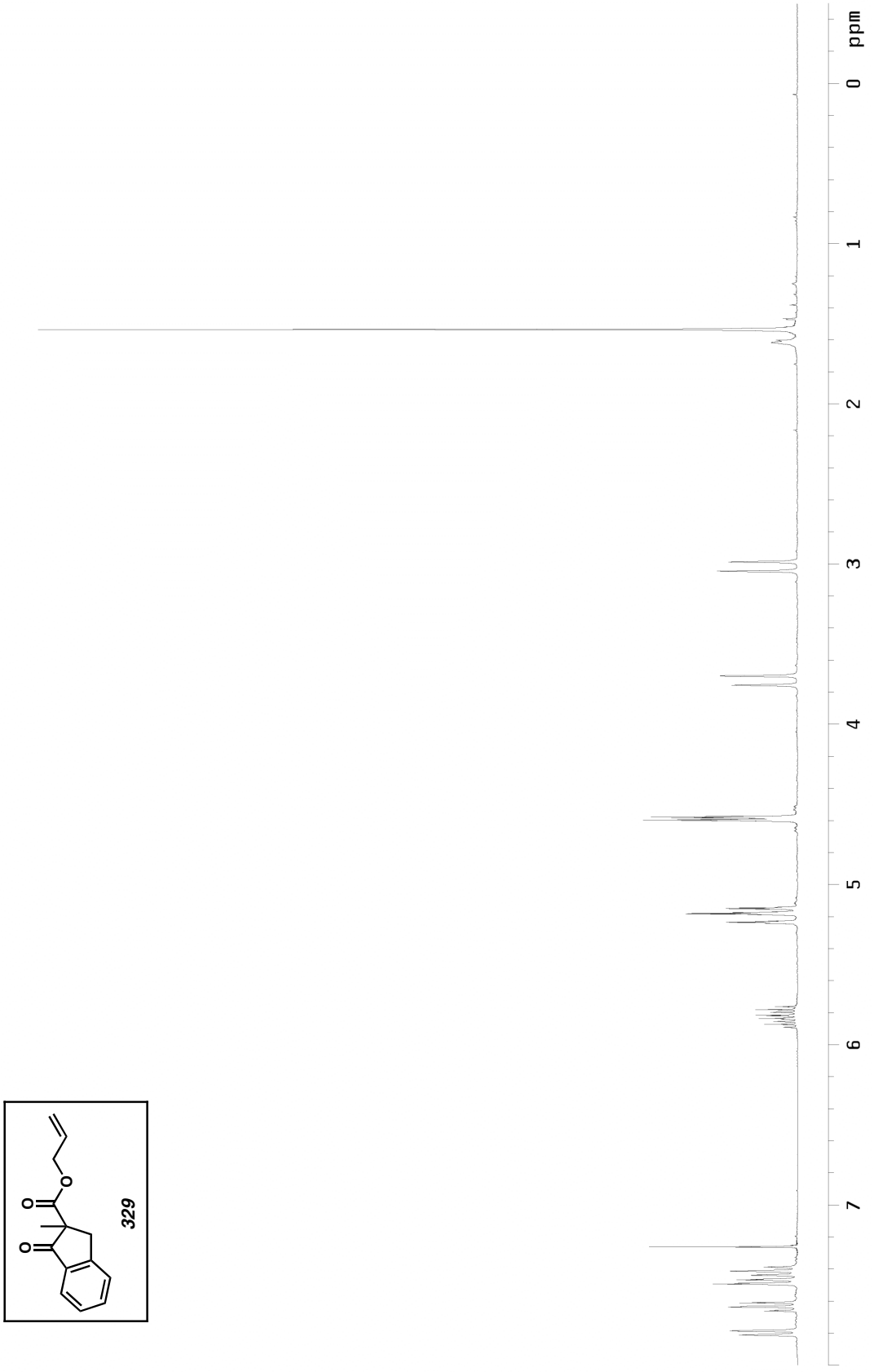


*Figure A2.83 ^{13}C NMR of compound **328** (75 MHz, $CDCl_3$)*



329

*Figure A2.84 ^1H NMR of compound **329** (300 MHz, $CDCl_3$)*

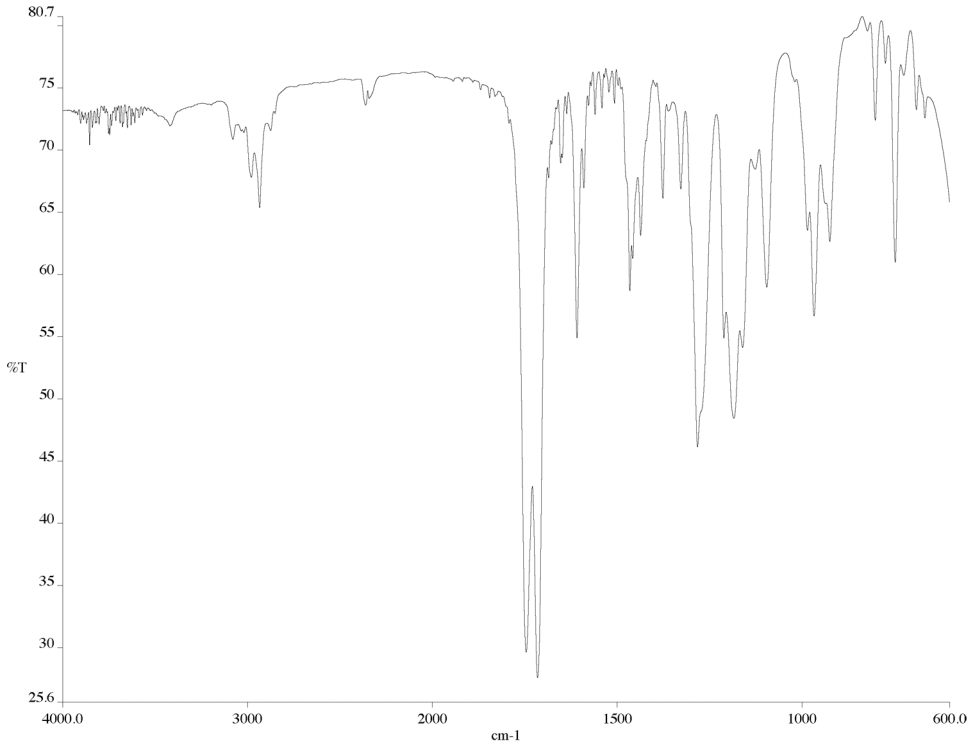


*Figure A2.85 IR of compound **329** (NaCl/film)*

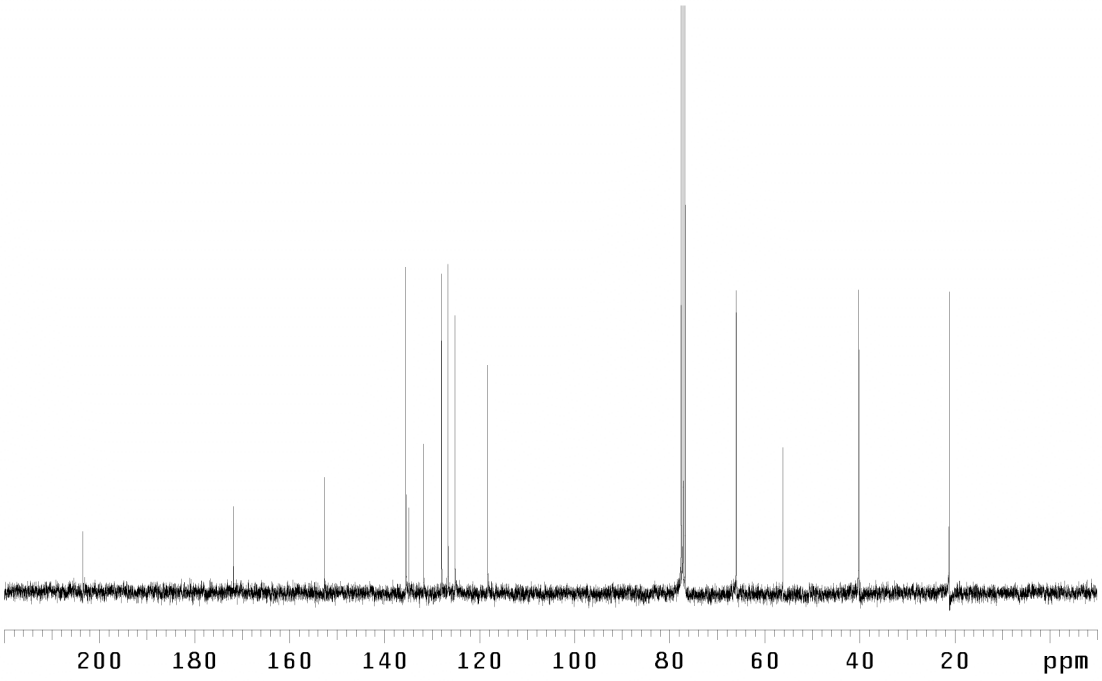


*Figure A2.86 ^{13}C NMR of compound **329** (75 MHz, $CDCl_3$)*

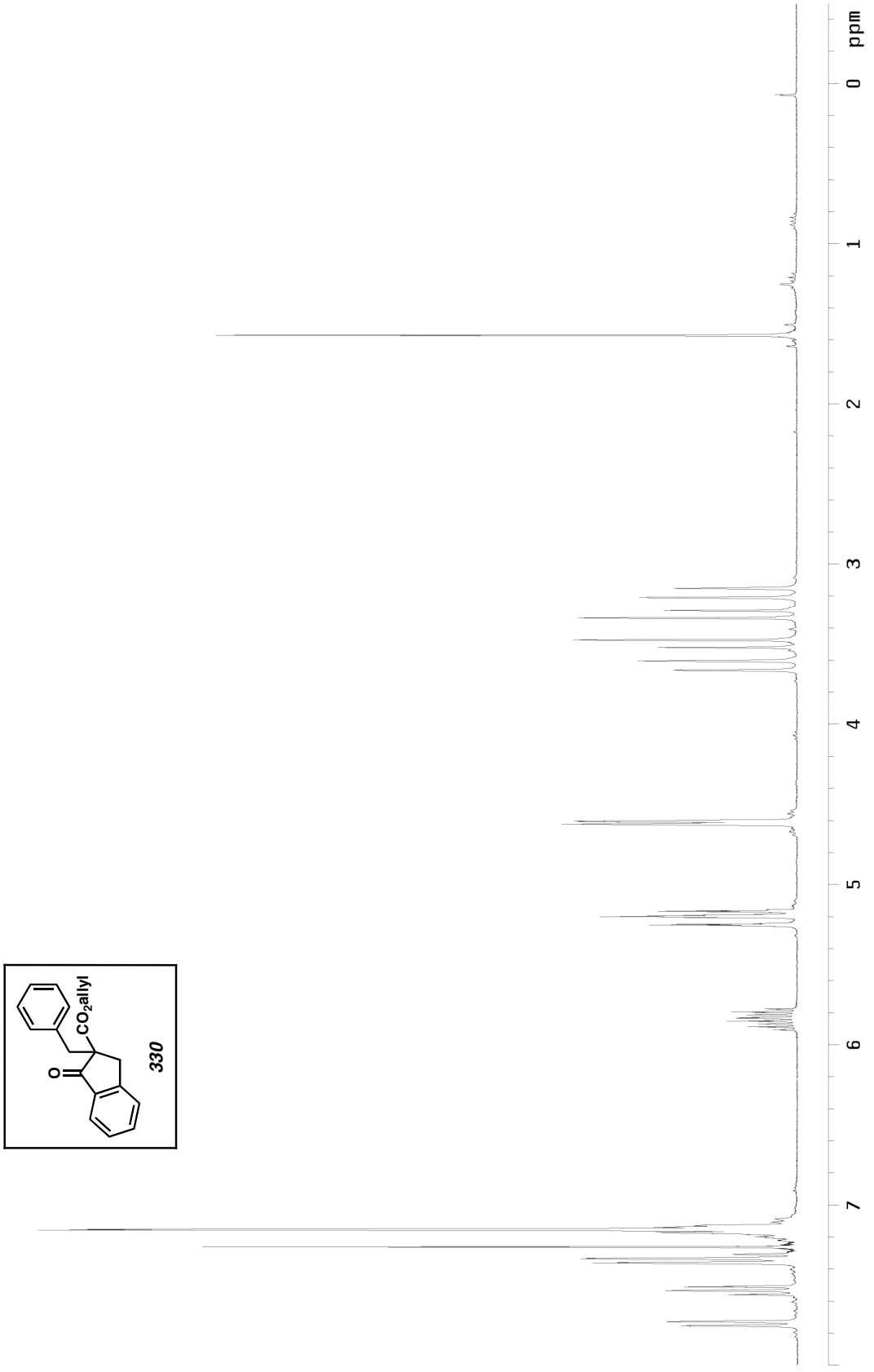


*Figure A2.87 ^{1}H NMR of compound **330** (300 MHz, $CDCl_3$)*

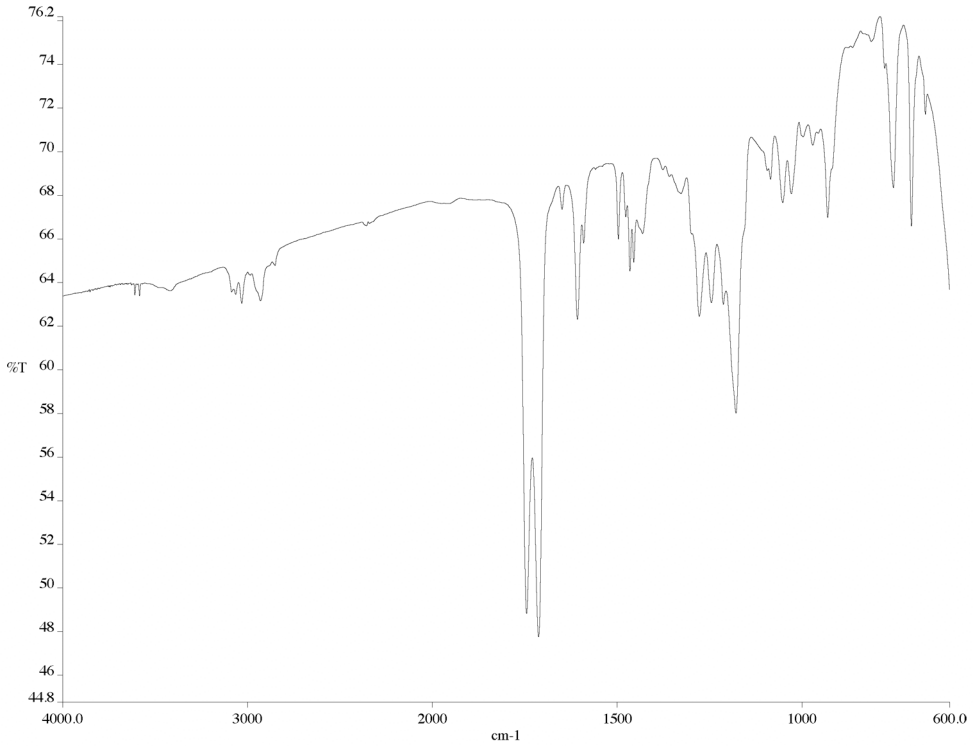


*Figure A2.88 IR of compound **330** (NaCl/film)*

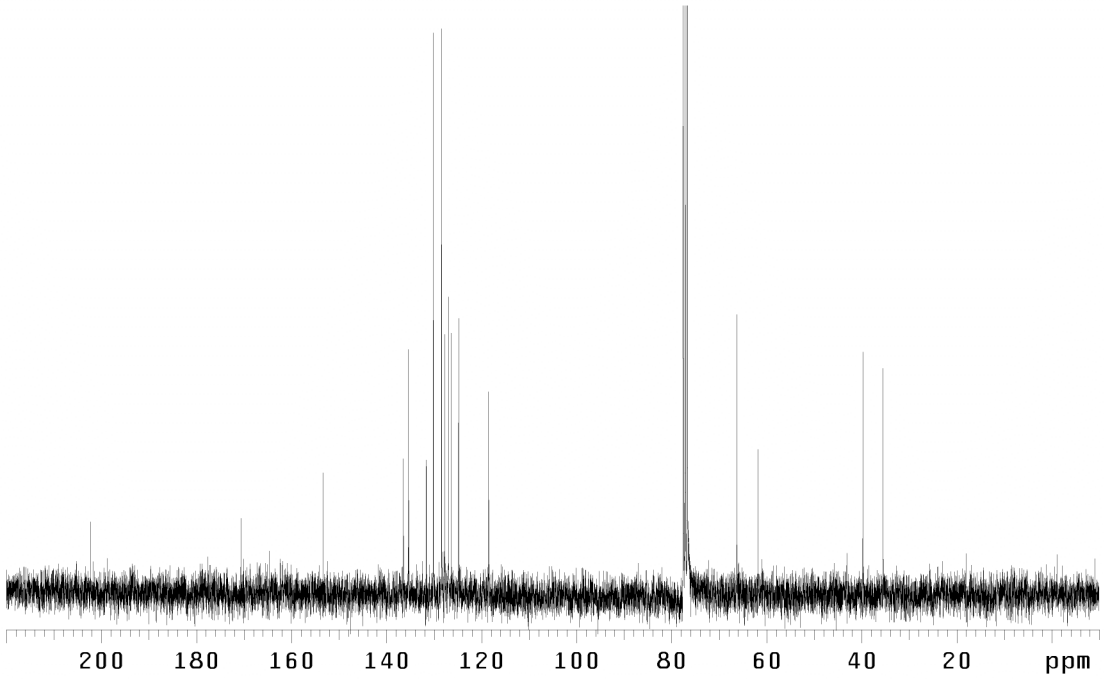


*Figure A2.89 ^{13}C NMR of compound **330** (75 MHz, $CDCl_3$)*

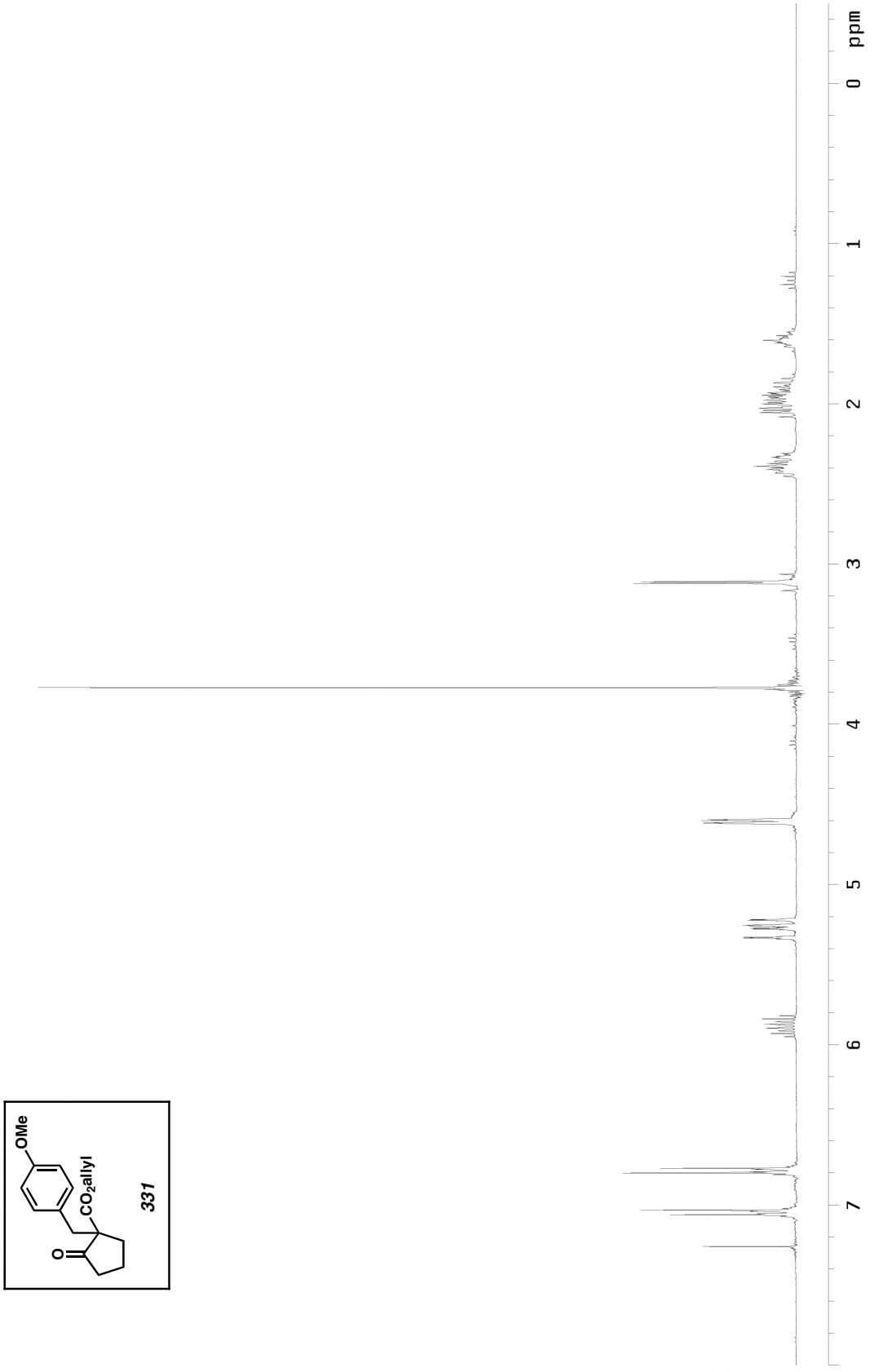


*Figure A2.90 ^1H NMR of compound **331** (300 MHz, $CDCl_3$)*

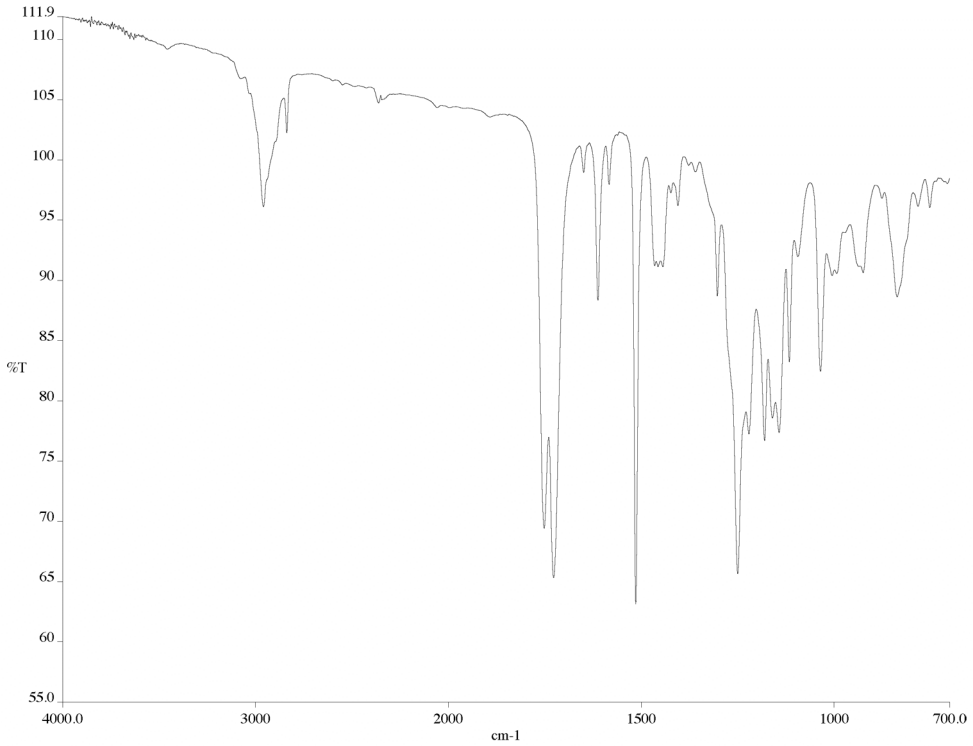


*Figure A2.91 IR of compound **331** (NaCl/film)*

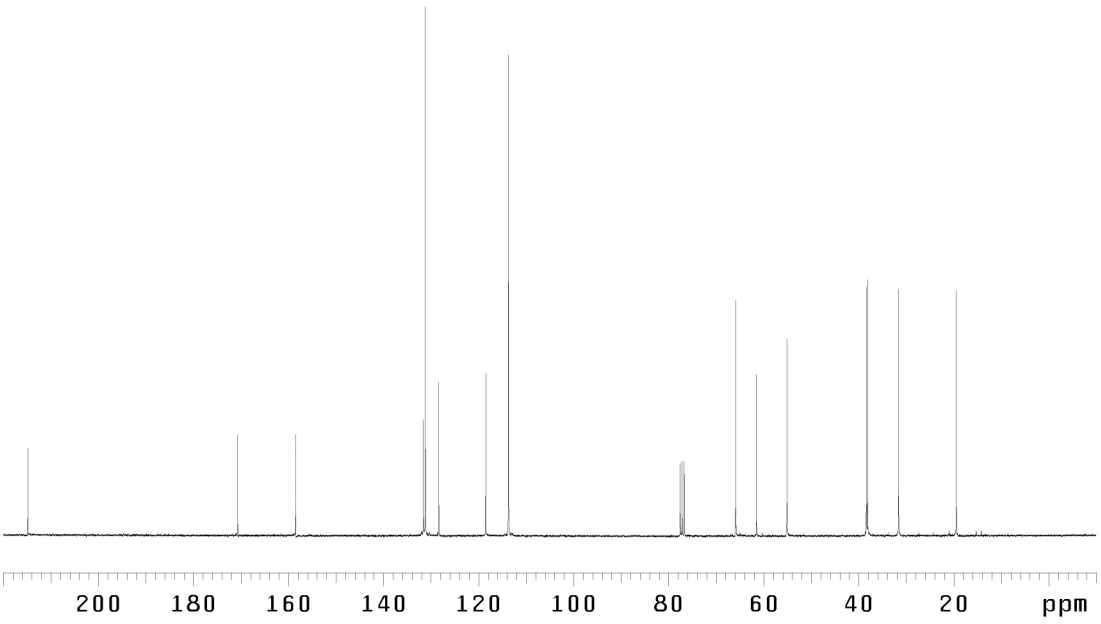


*Figure A2.92 ^{13}C NMR of compound **331** (75 MHz, $CDCl_3$)*

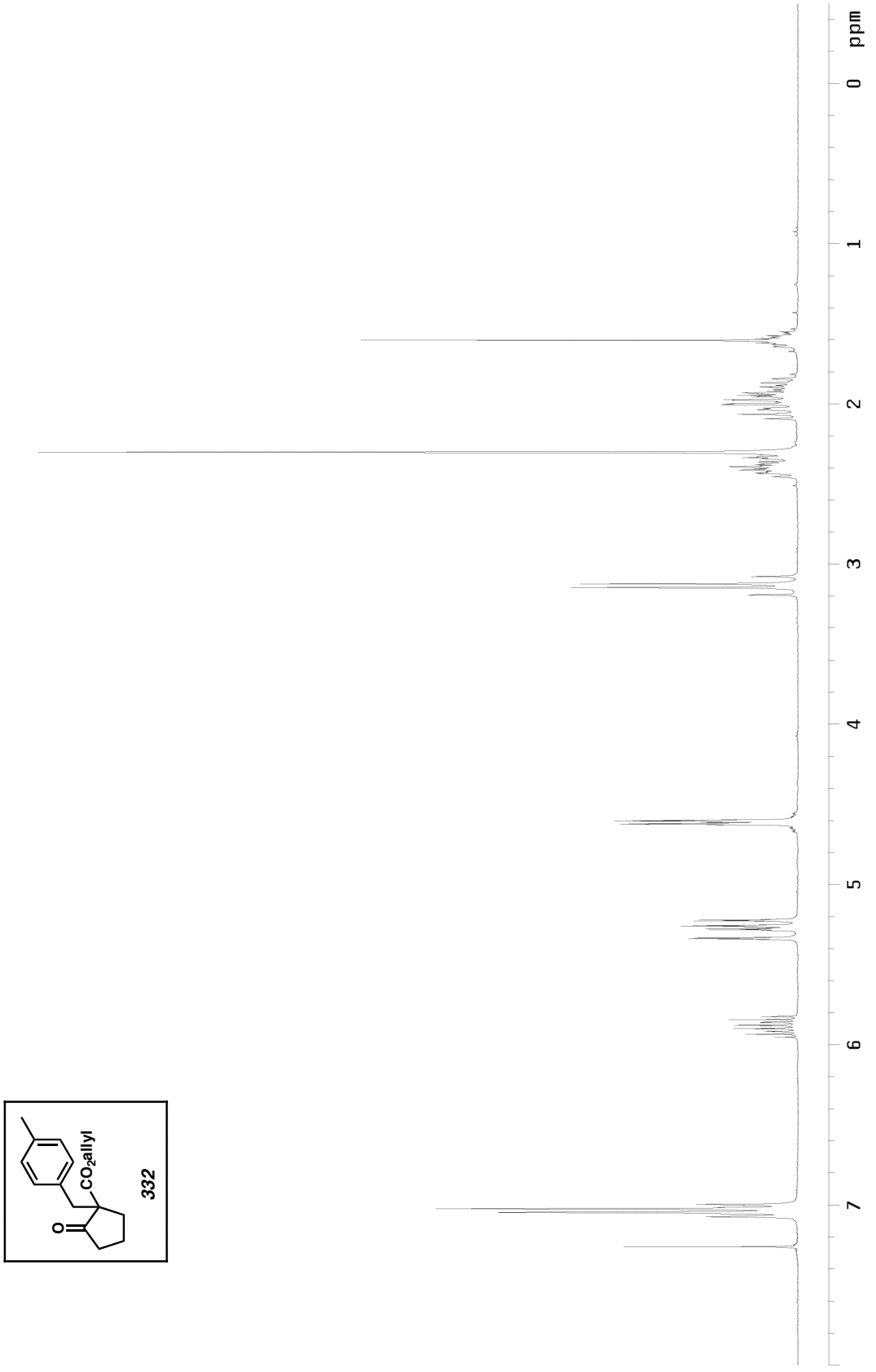


Figure A2.93 ^1H NMR of compound **332** *(300 MHz, $CDCl_3$)*

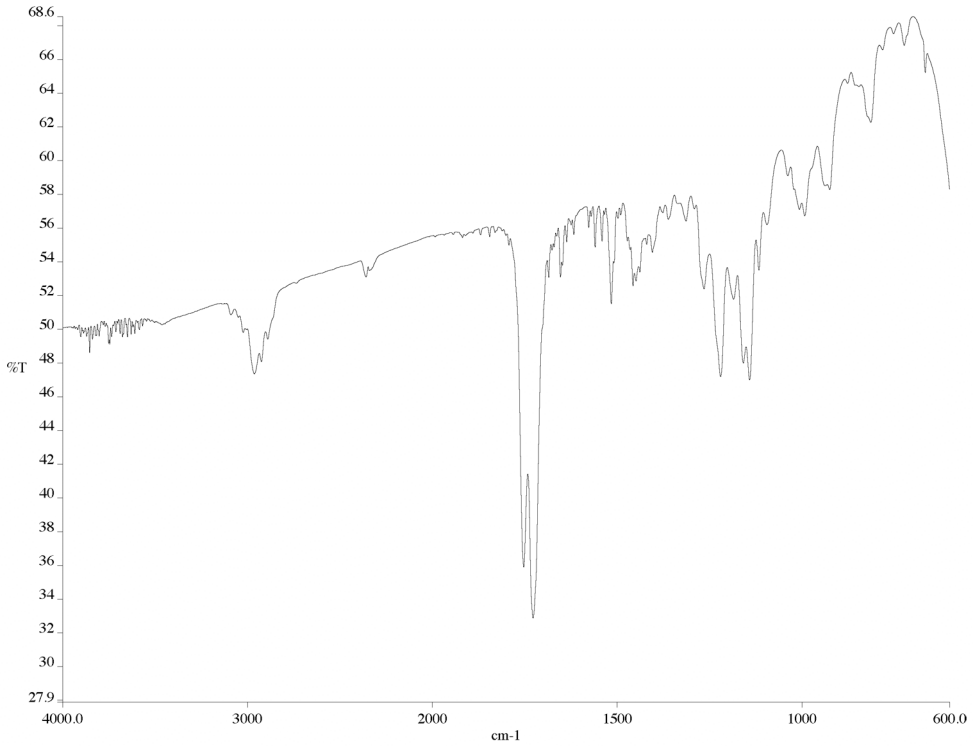


*Figure A2.94 IR of compound **332** (NaCl/film)*

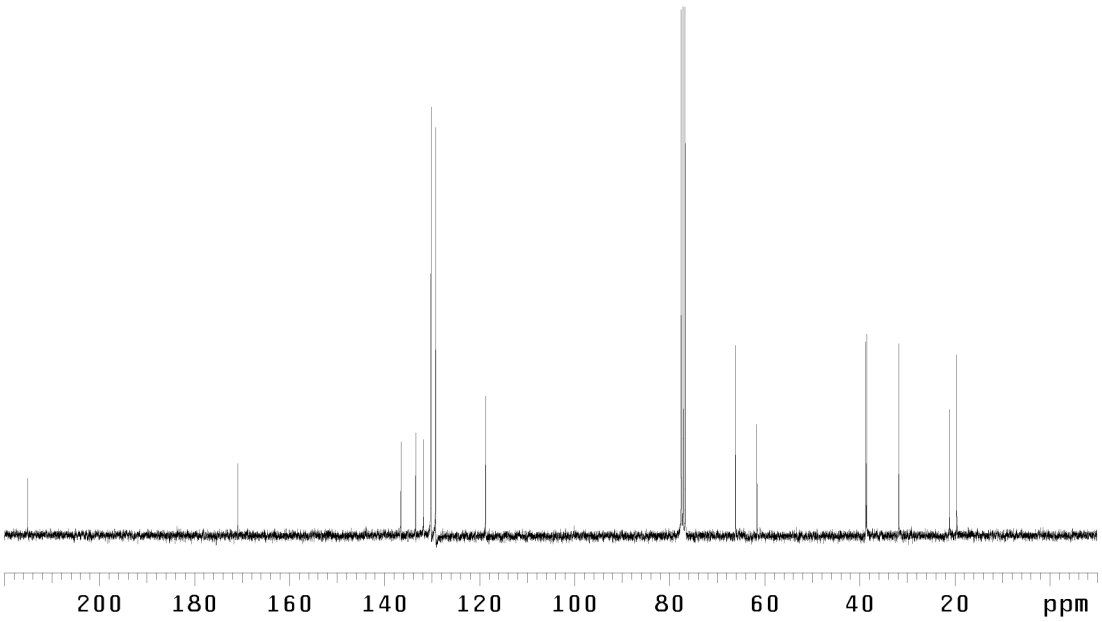


*Figure A2.95 ^{13}C NMR of compound **332** (75 MHz, $CDCl_3$)*

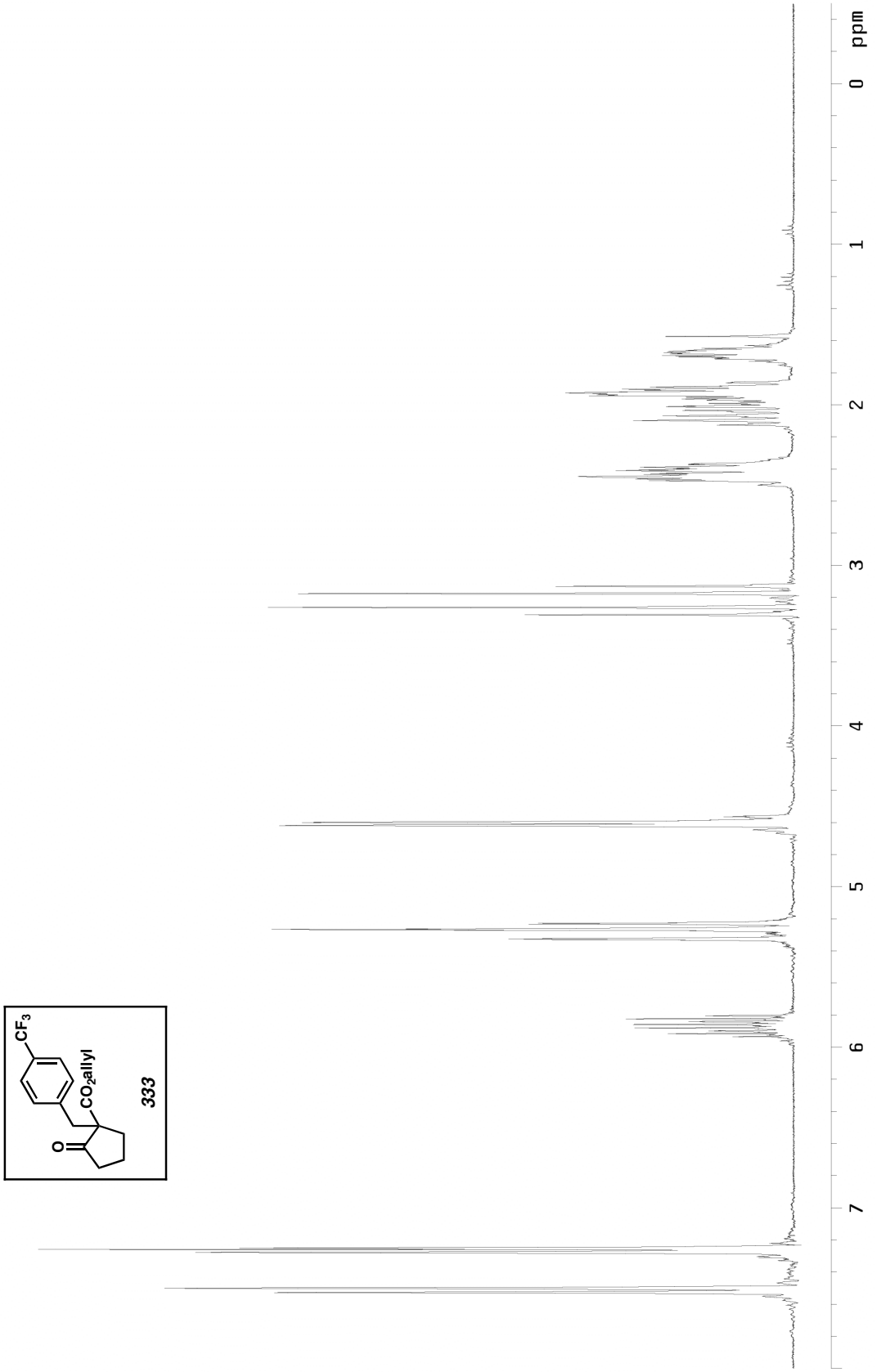


Figure A2.96 ^1H NMR of compound ***333*** *(300 MHz, $CDCl_3$)*

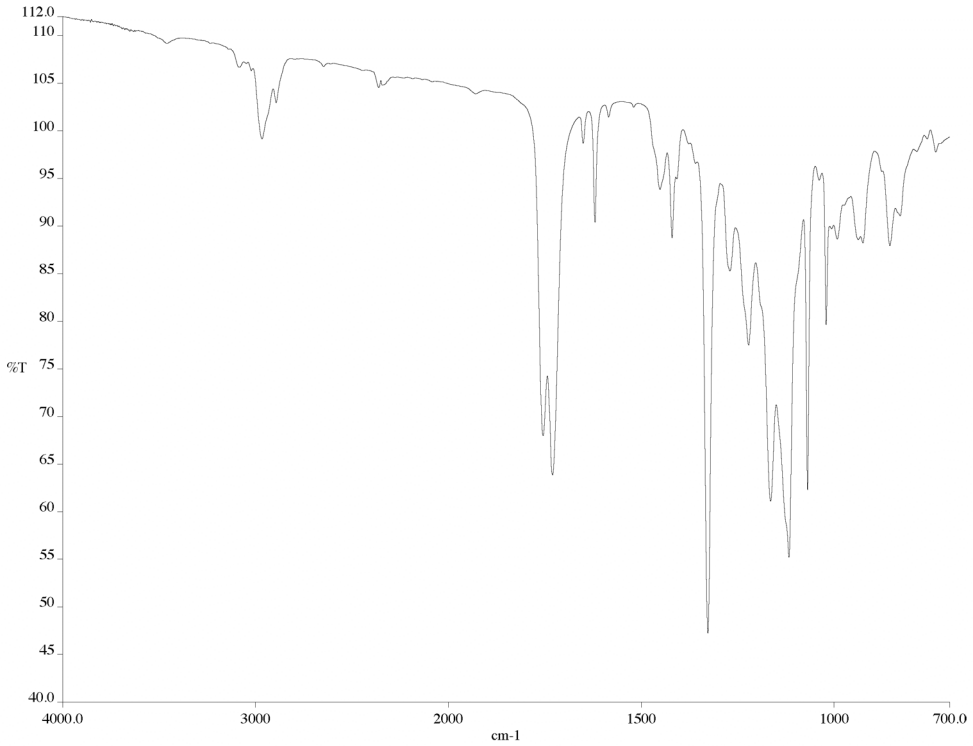


*Figure A2.97 IR of compound **333** (NaCl/film)*

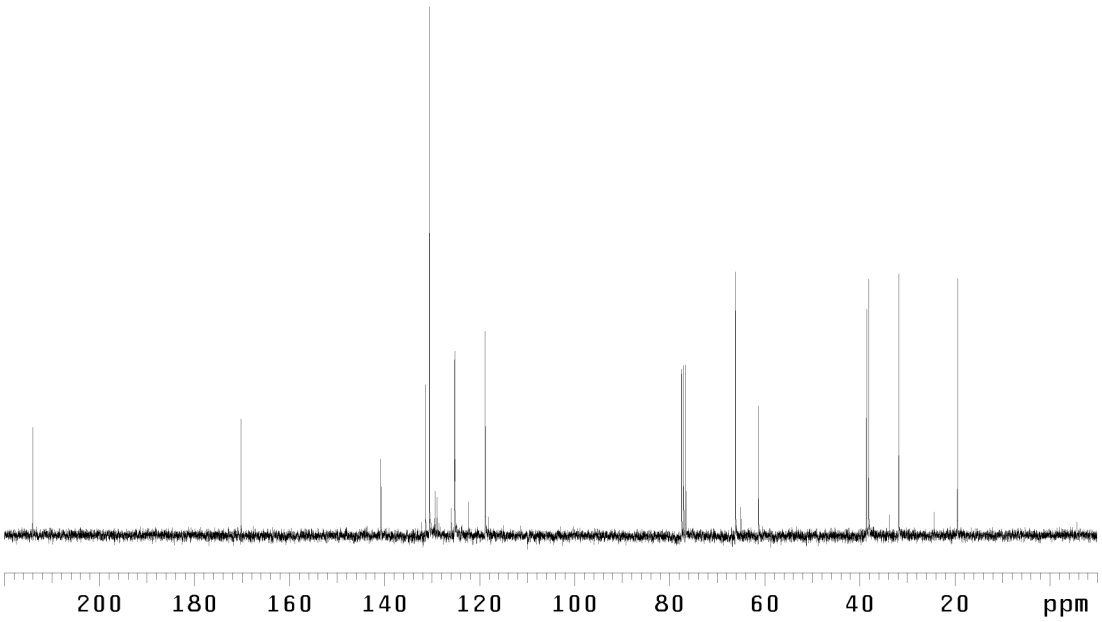


*Figure A2.98 ^{13}C NMR of compound **333** (75 MHz, $CDCl_3$)*

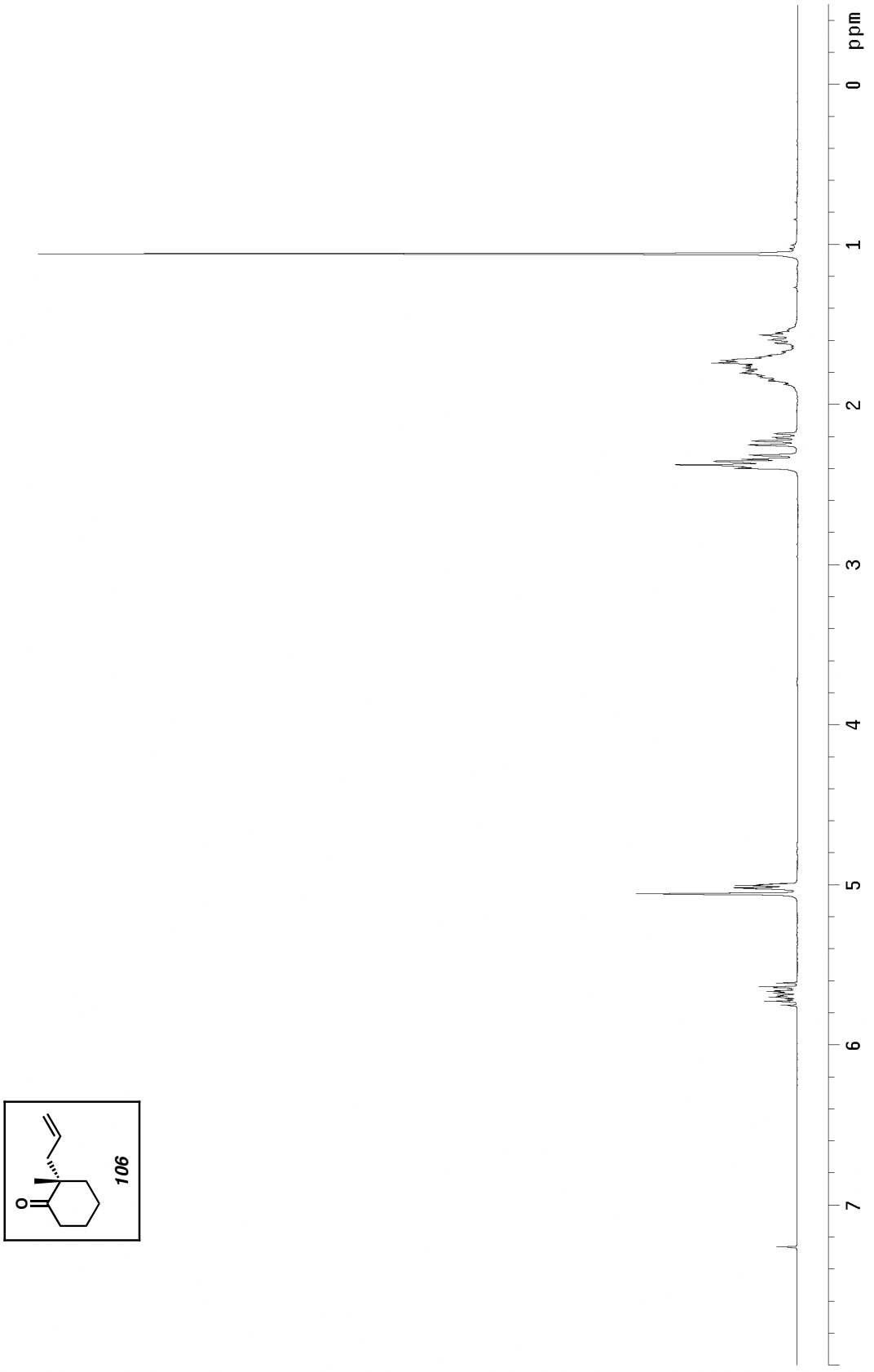


*Figure A2.99 ^1H NMR of compound **106** (300 MHz, $CDCl_3$)*

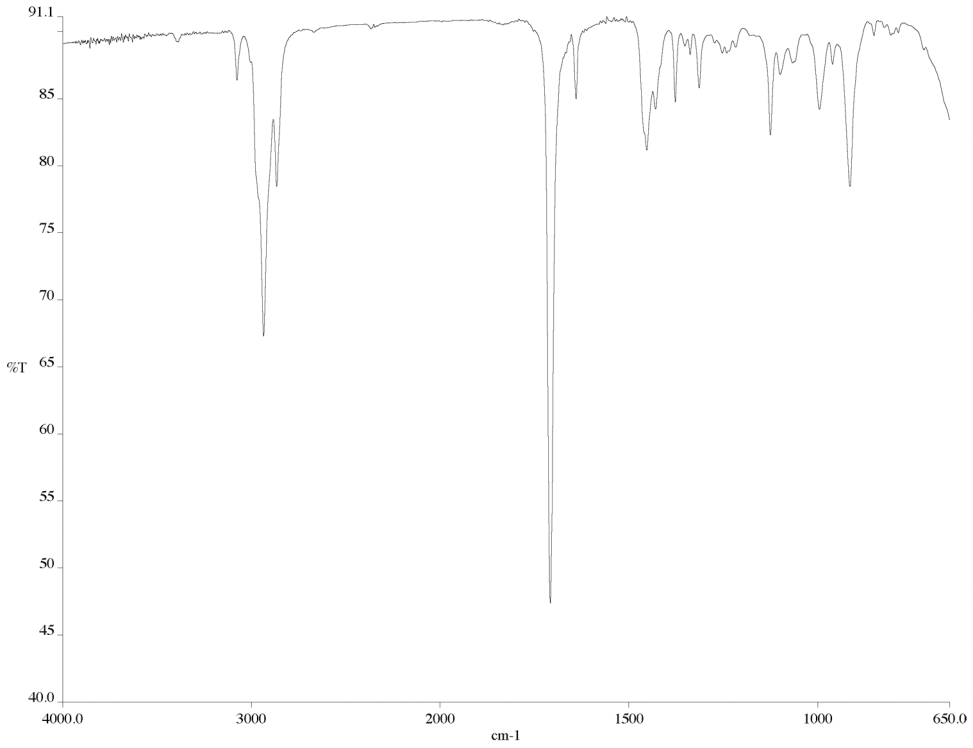


*Figure A2.100 IR of compound **106** (NaCl/film)*

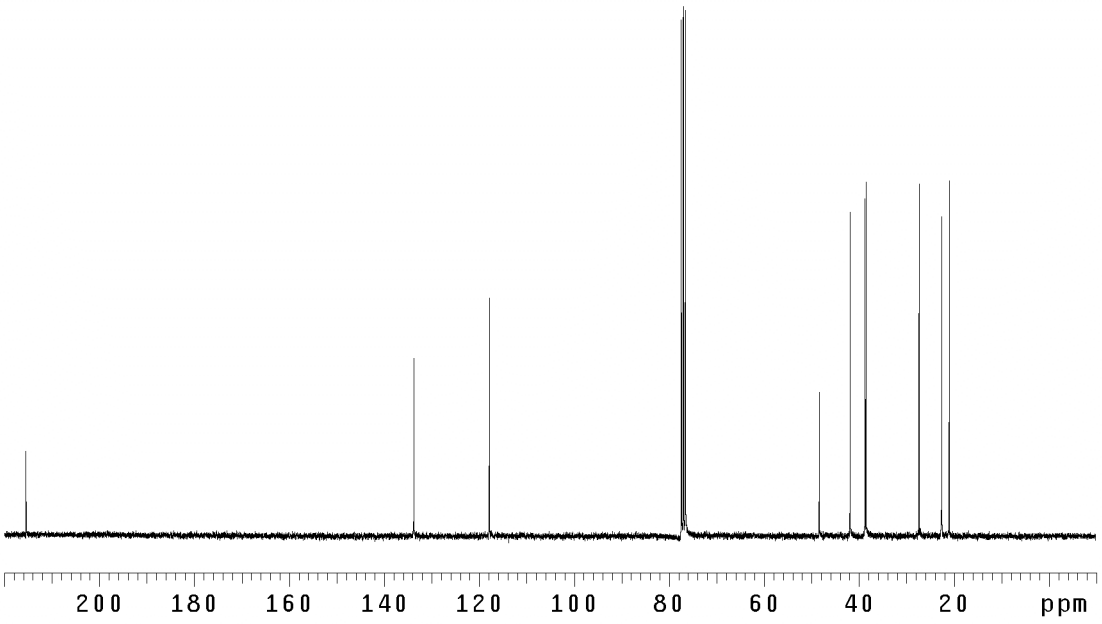


*Figure A2.101 ^{13}C NMR of compound **106** (75 MHz, $CDCl_3$)*

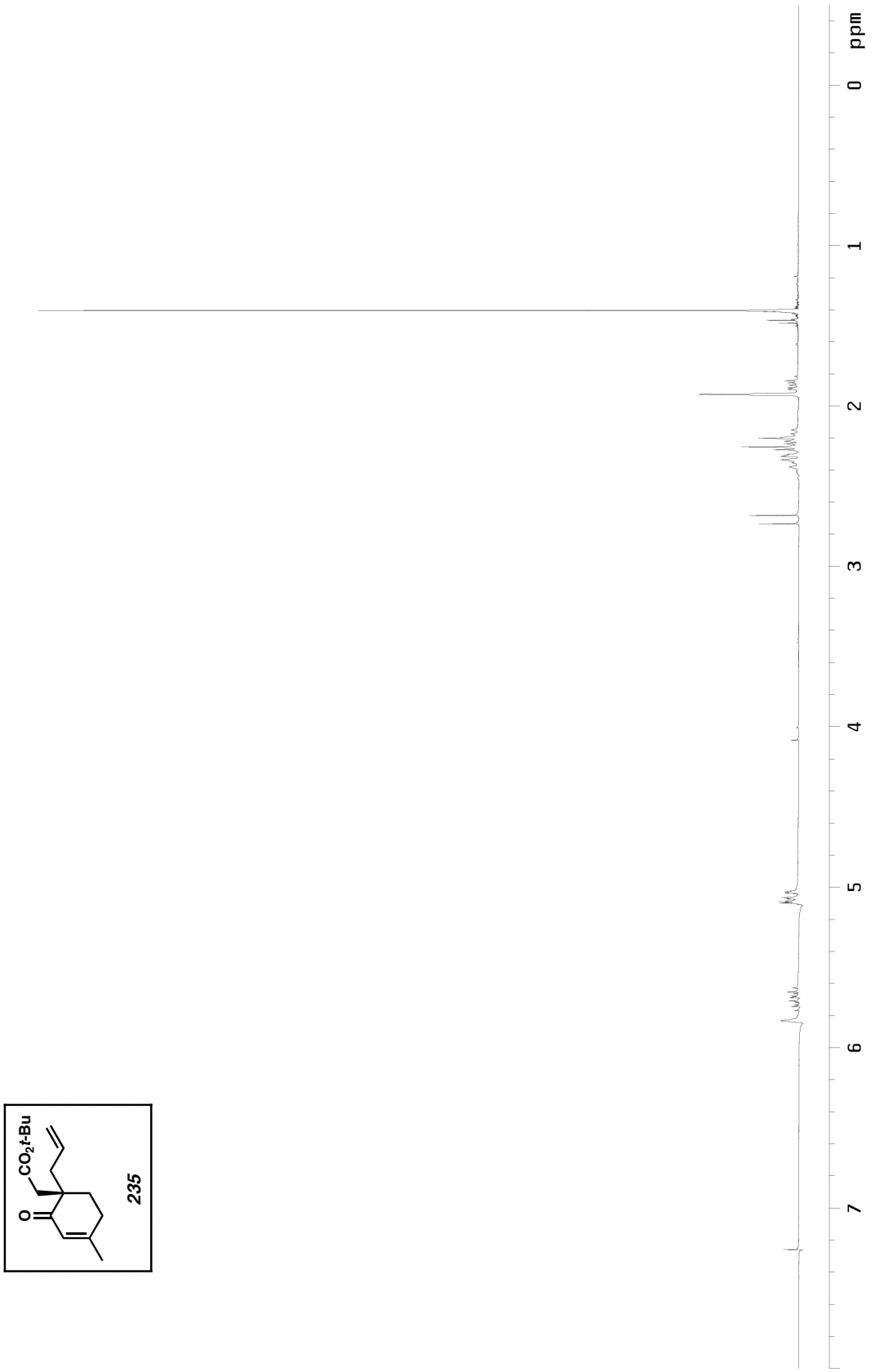


Figure A2.102 ^1H NMR of compound ***235*** *(300 MHz, $CDCl_3$)*

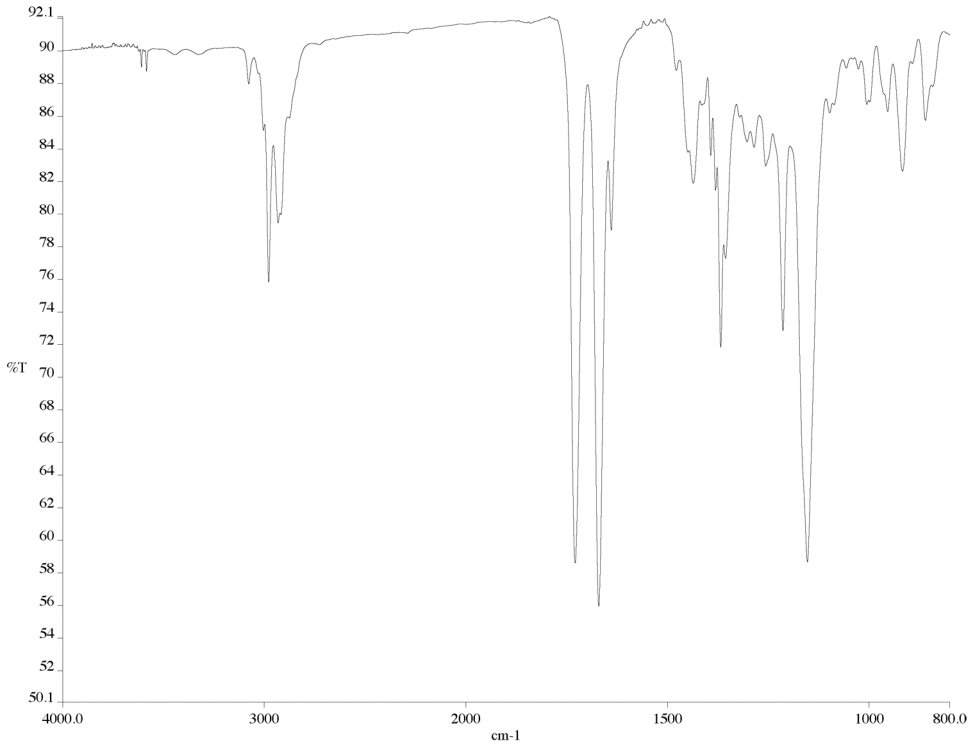


*Figure A2.103 IR of compound **235** (NaCl/film)*

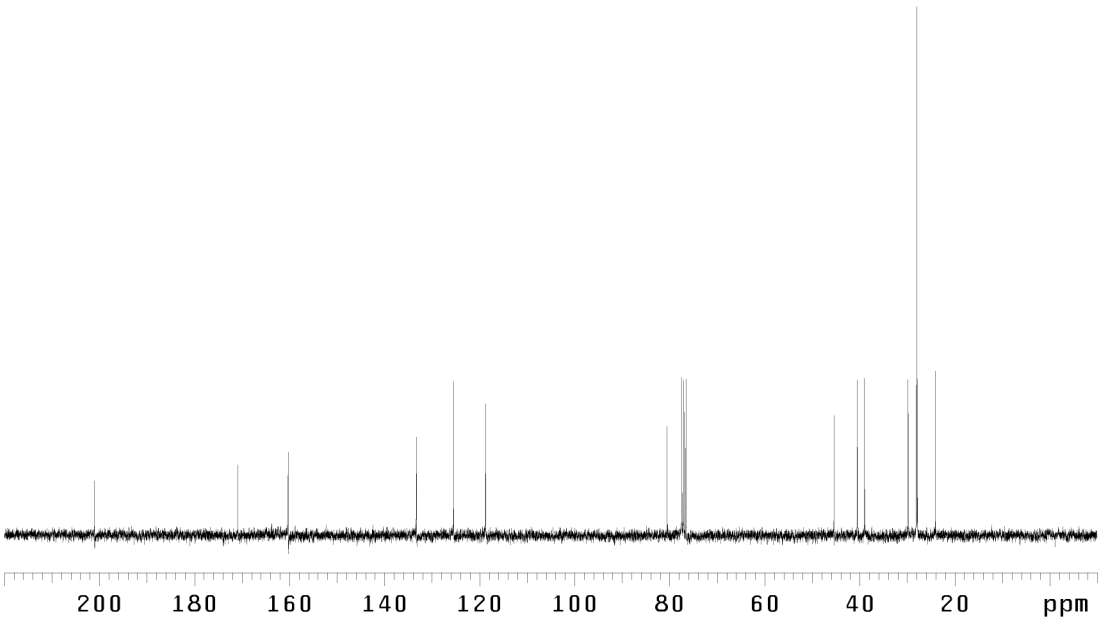


*Figure A2.104 ^{13}C NMR of compound **235** (75 MHz, $CDCl_3$)*

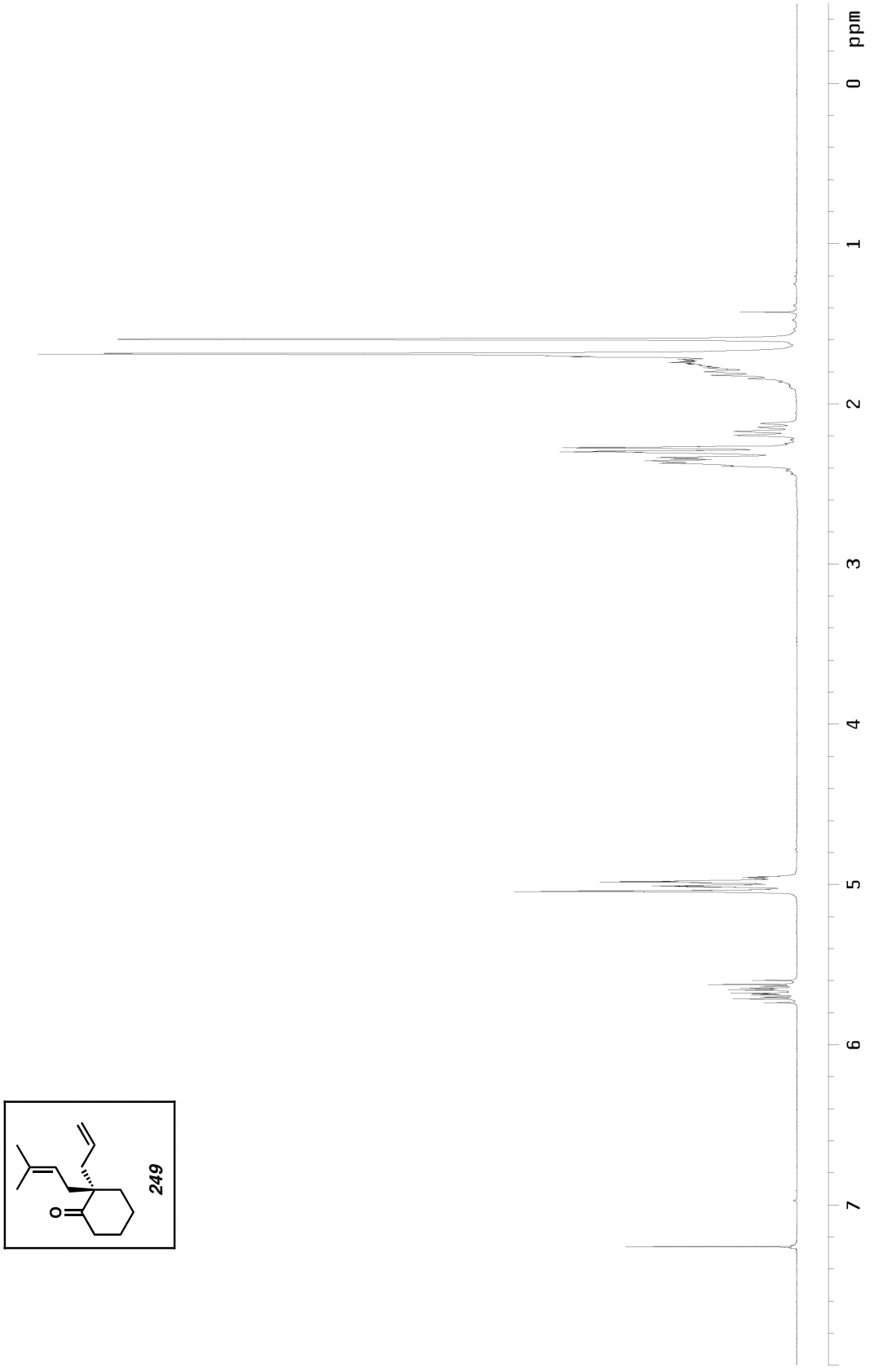


*Figure A2.105 ^1H NMR of compound **249** (300 MHz, $CDCl_3$)*

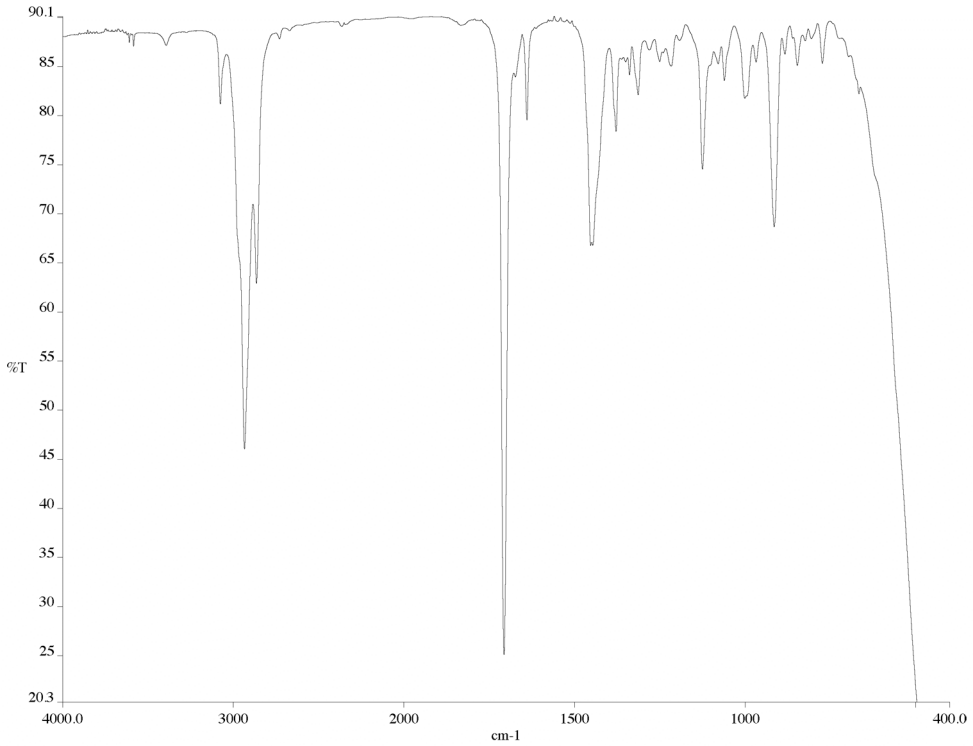


*Figure A2.106 IR of compound **249** (NaCl/film)*

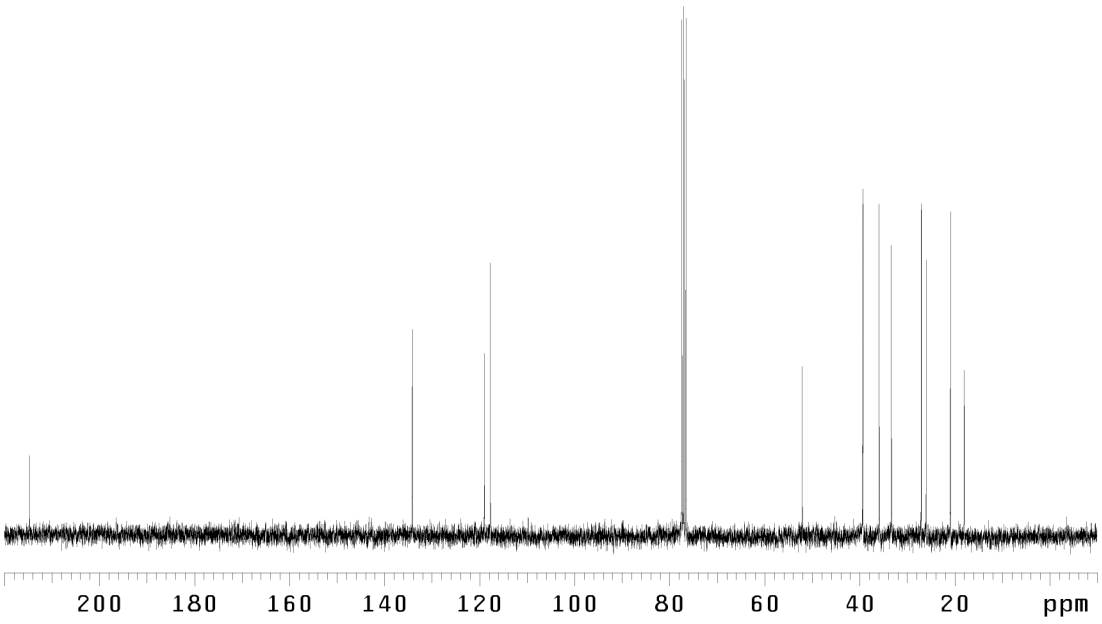


*Figure A2.107 ^{13}C NMR of compound **249** (75 MHz, $CDCl_3$)*

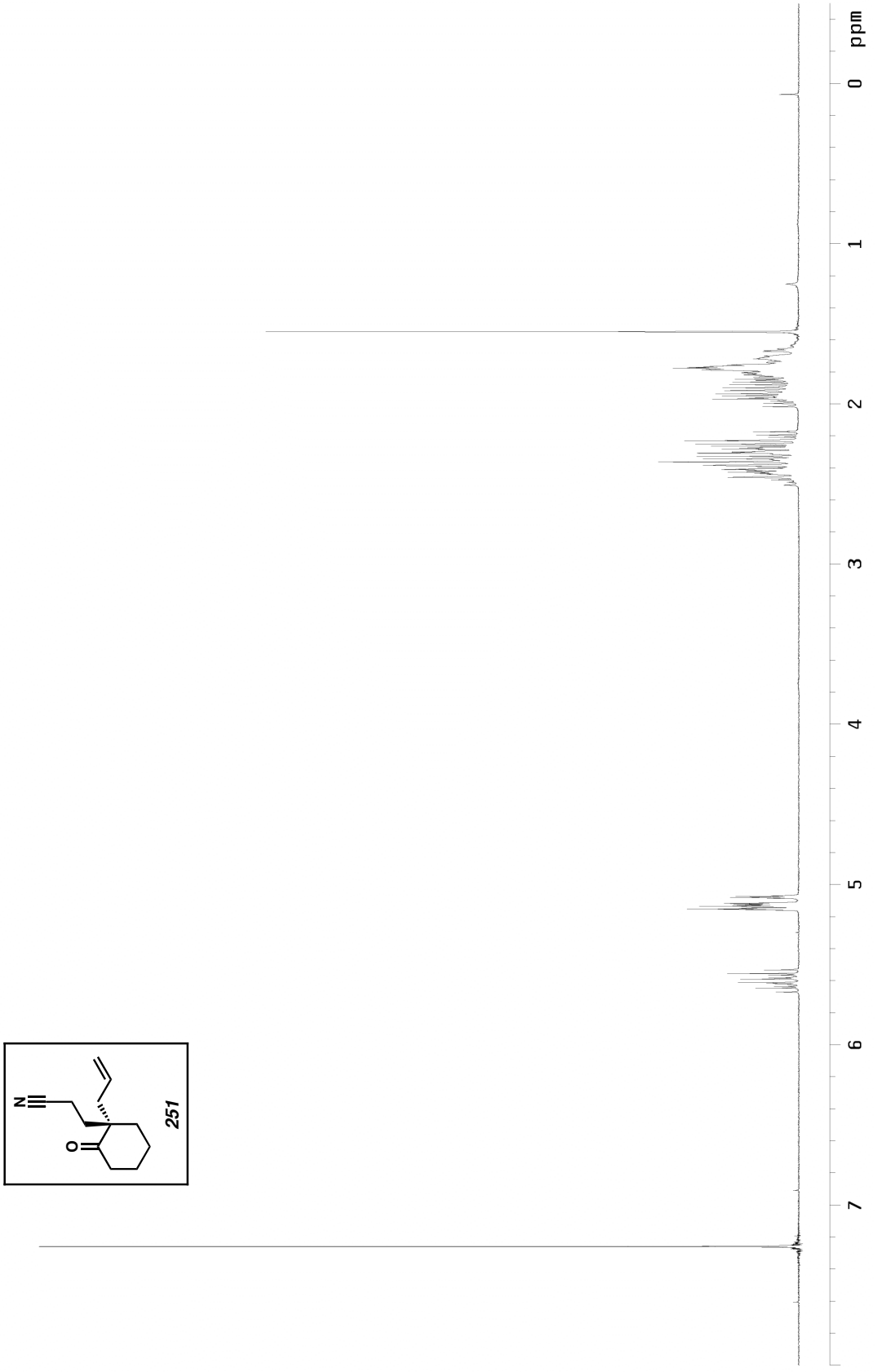


*Figure A2.108 ^1H NMR of compound **251** (300 MHz, $CDCl_3$)*

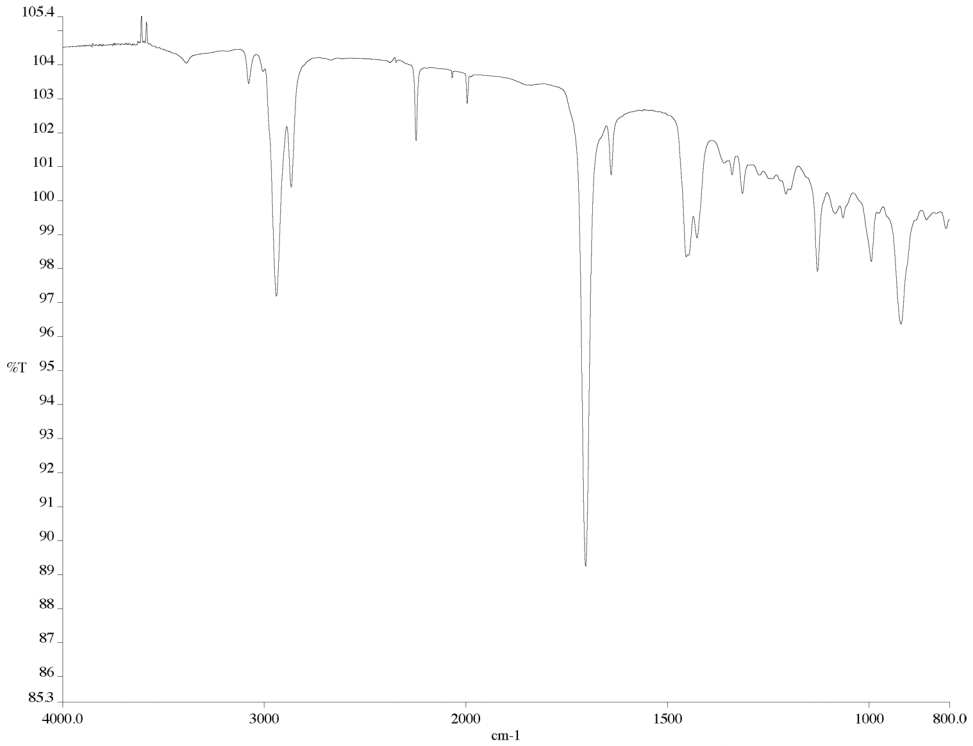


*Figure A2.109 IR of compound **251** (NaCl/film)*

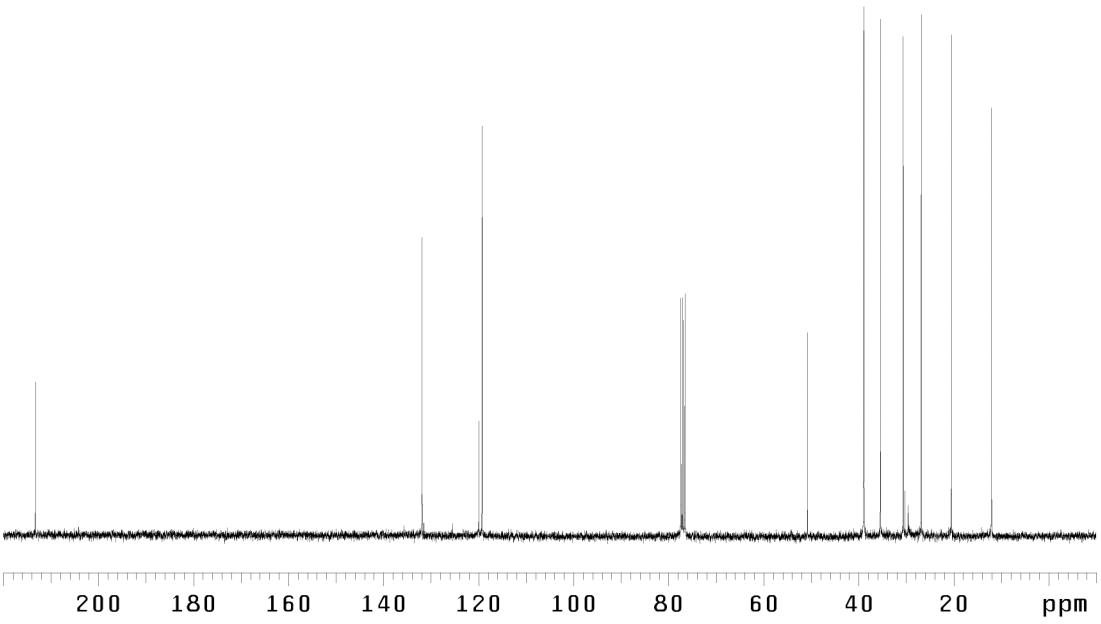


*Figure A2.110 ^{13}C NMR of compound **251** (75 MHz, $CDCl_3$)*

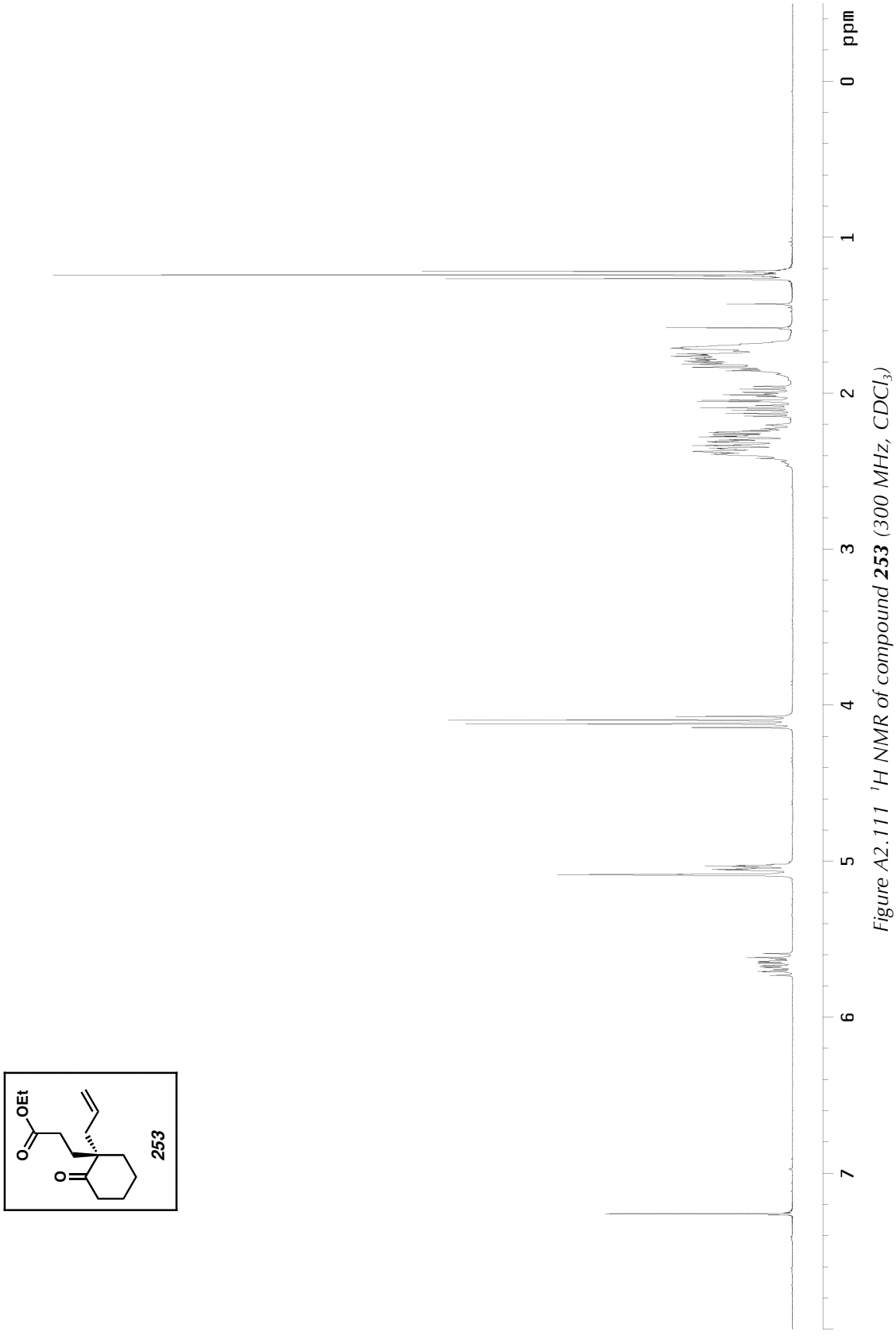


Figure A2.111 ^1H NMR of compound ***253*** *(300 MHz, $CDCl_3$)*

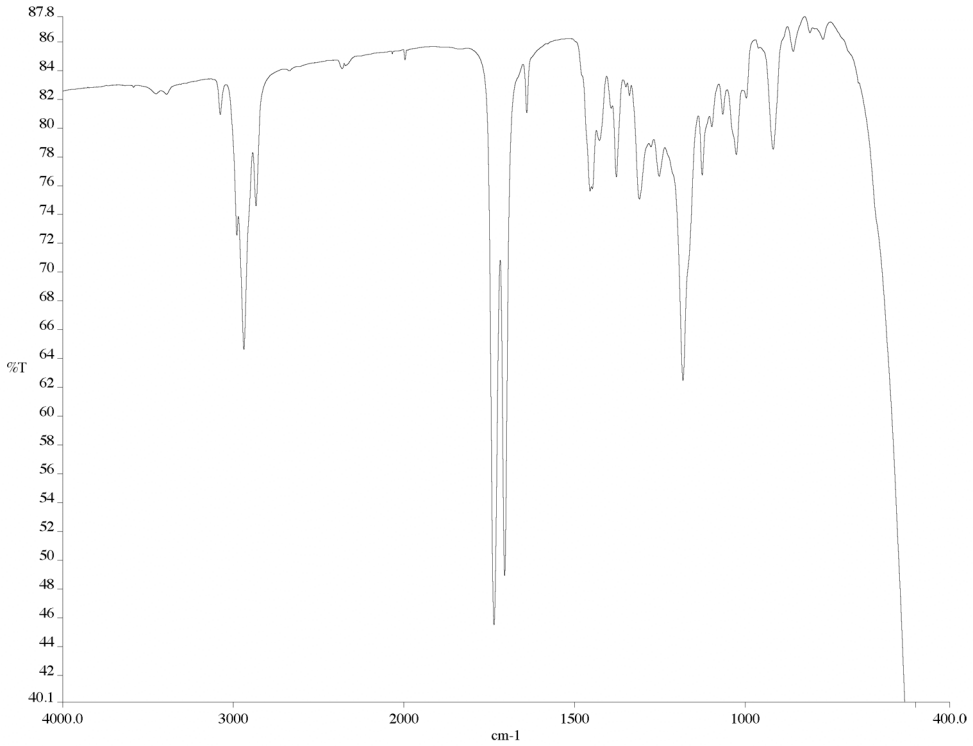


*Figure A2.112 IR of compound **253** (NaCl/film)*

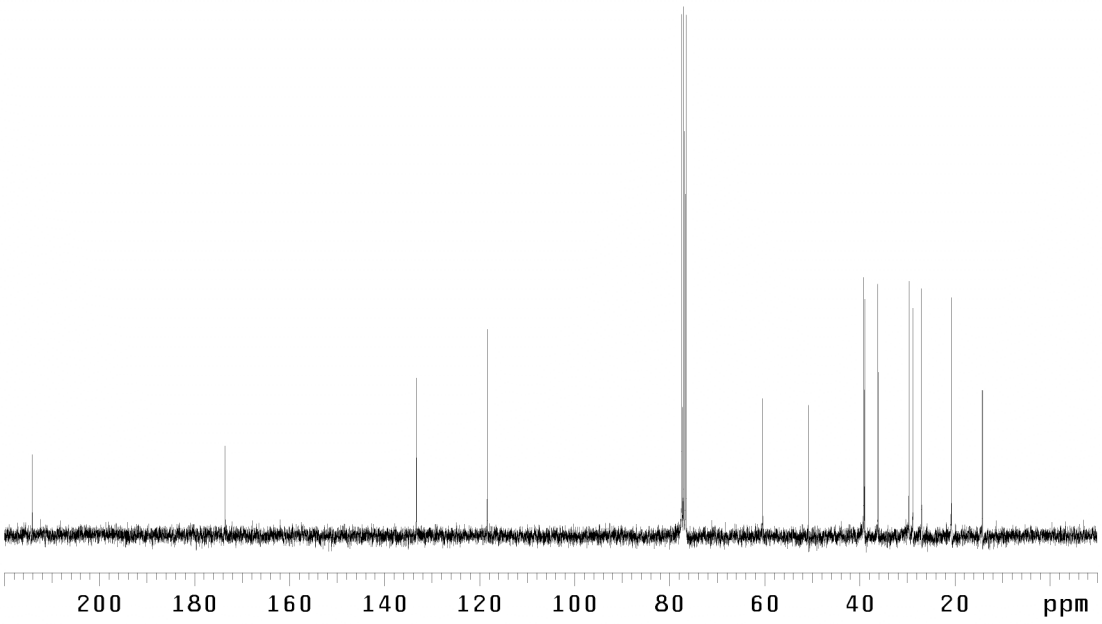


*Figure A2.113 ^{13}C NMR of compound **253** (75 MHz, $CDCl_3$)*

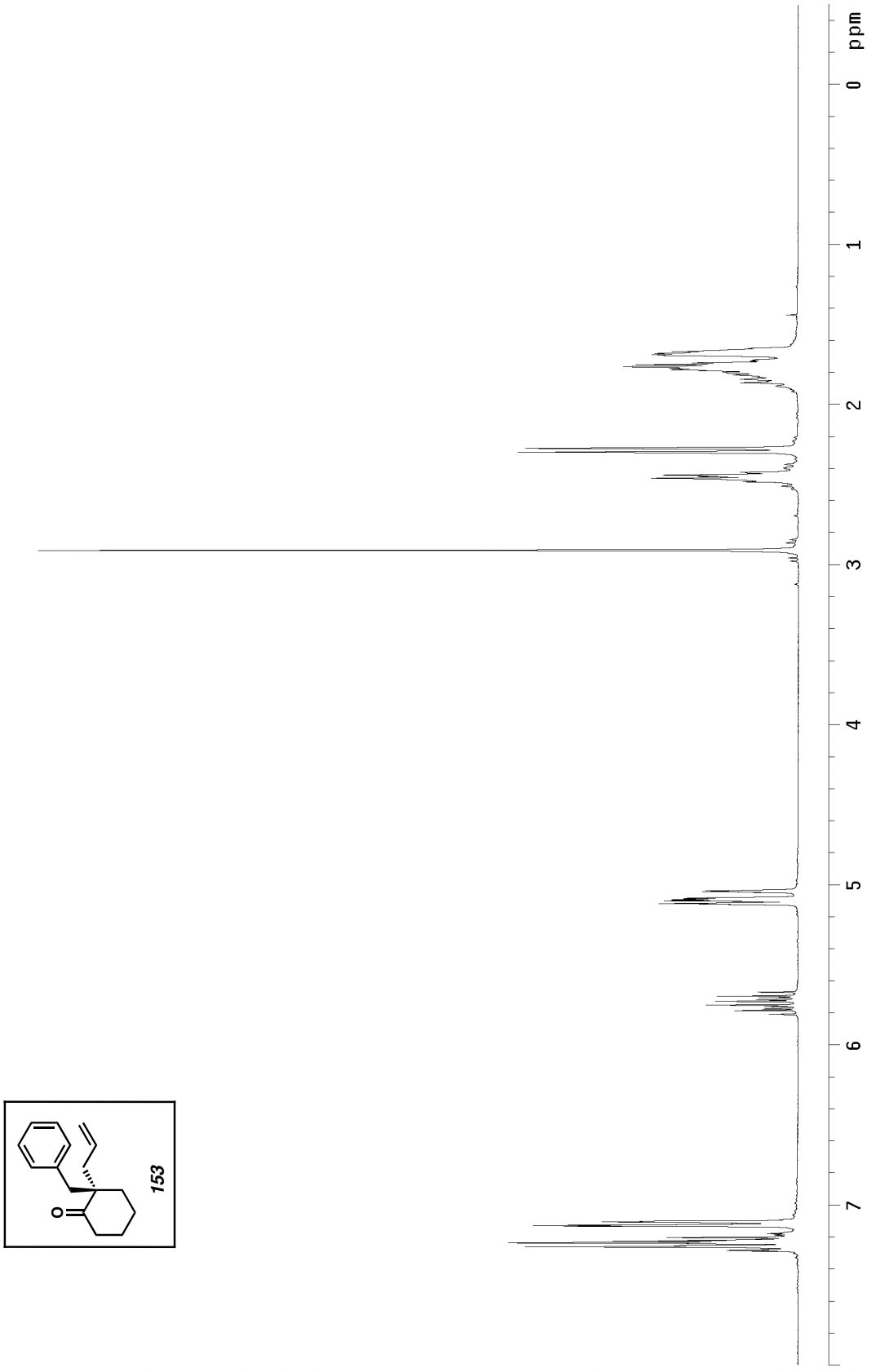


*Figure A2.114 ^1H NMR of compound **153** (300 MHz, $CDCl_3$)*

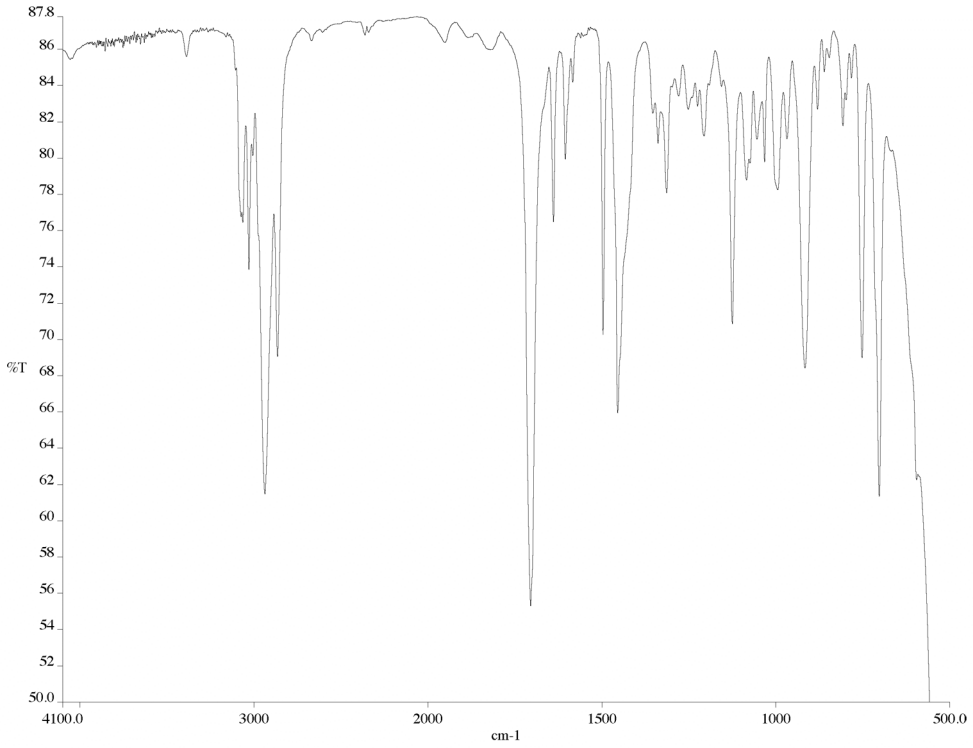


*Figure A2.115 IR of compound **153** (NaCl/film)*

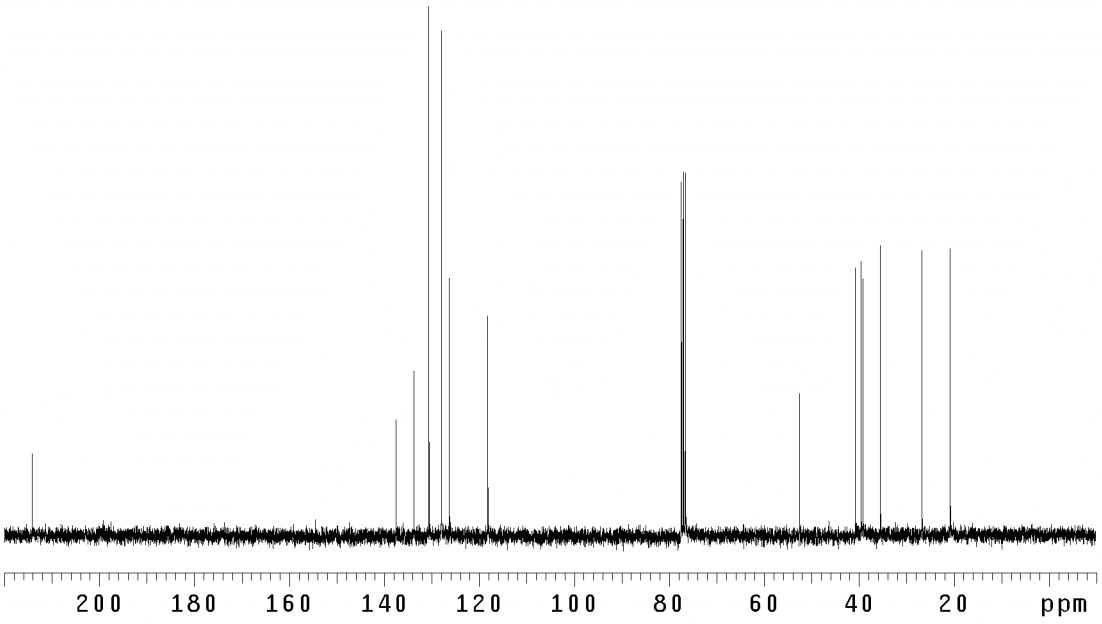


*Figure A2.116 ^{13}C NMR of compound **153** (75 MHz, $CDCl_3$)*

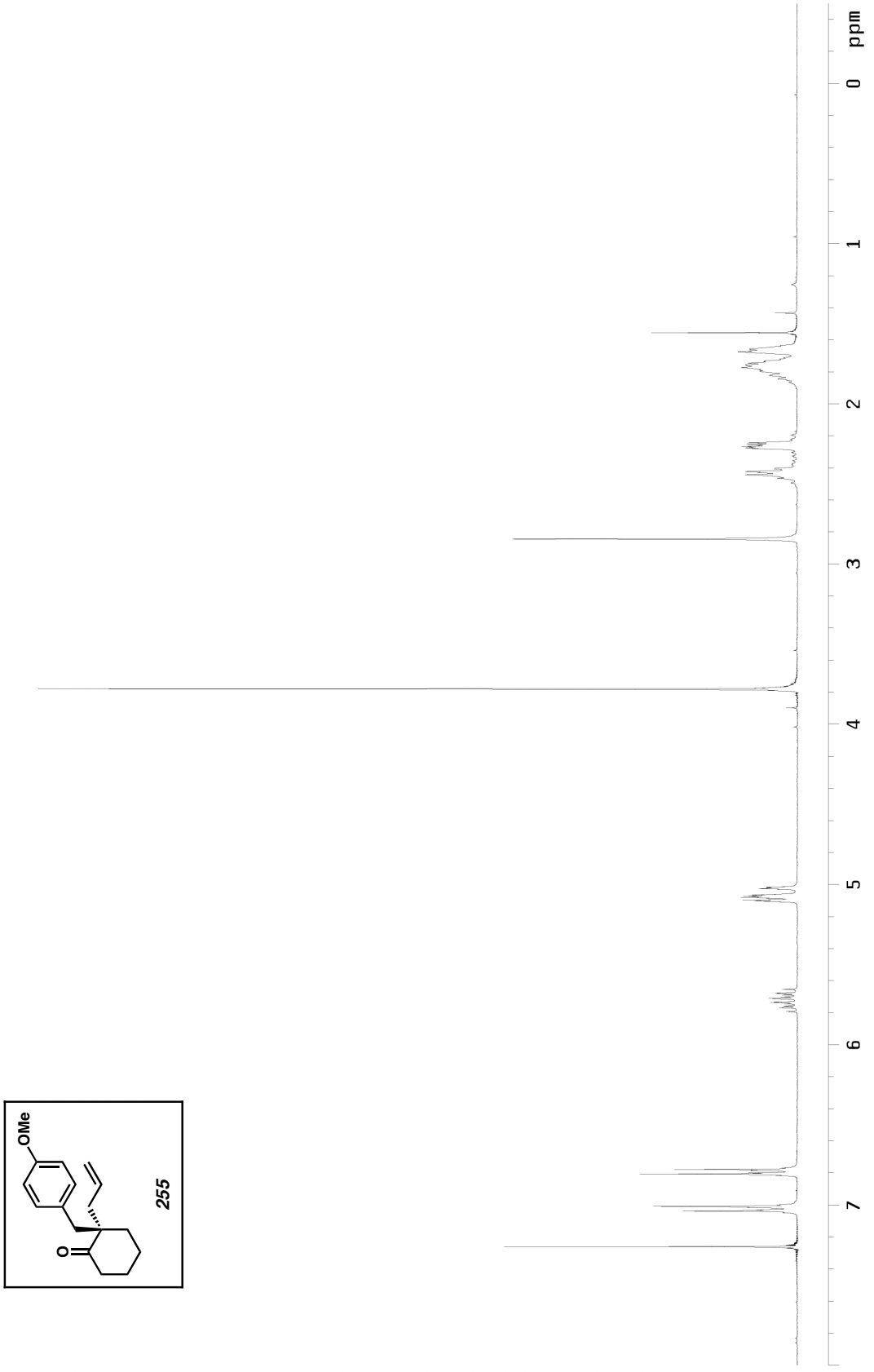


*Figure A2.117 ^1H NMR of compound **255** (300 MHz, $CDCl_3$)*

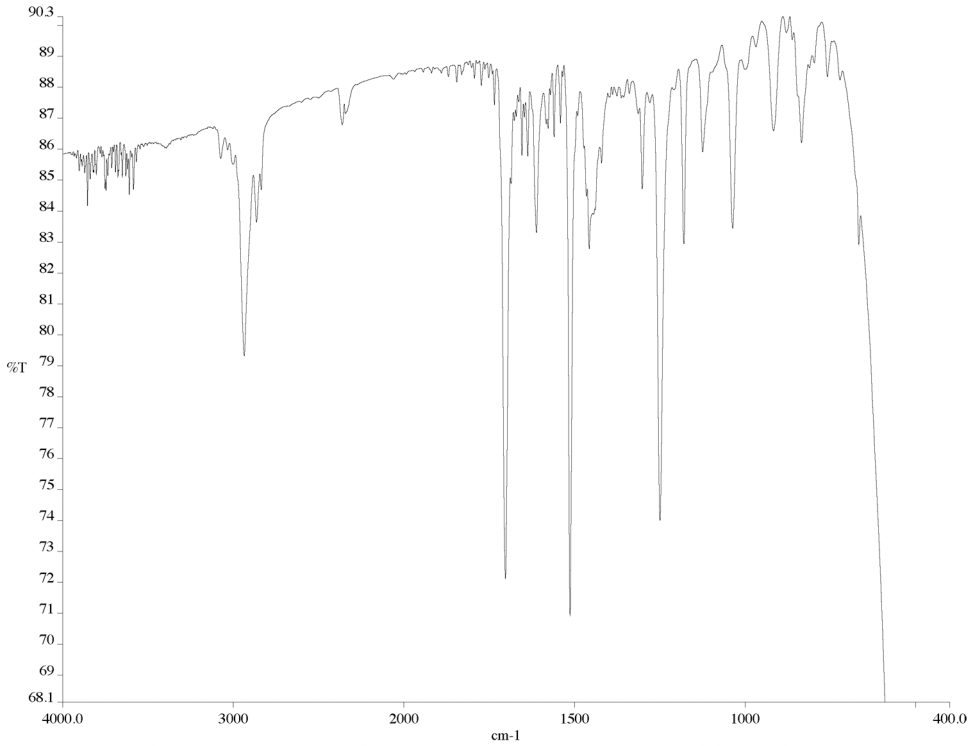


*Figure A2.118 IR of compound **255** (NaCl/film)*

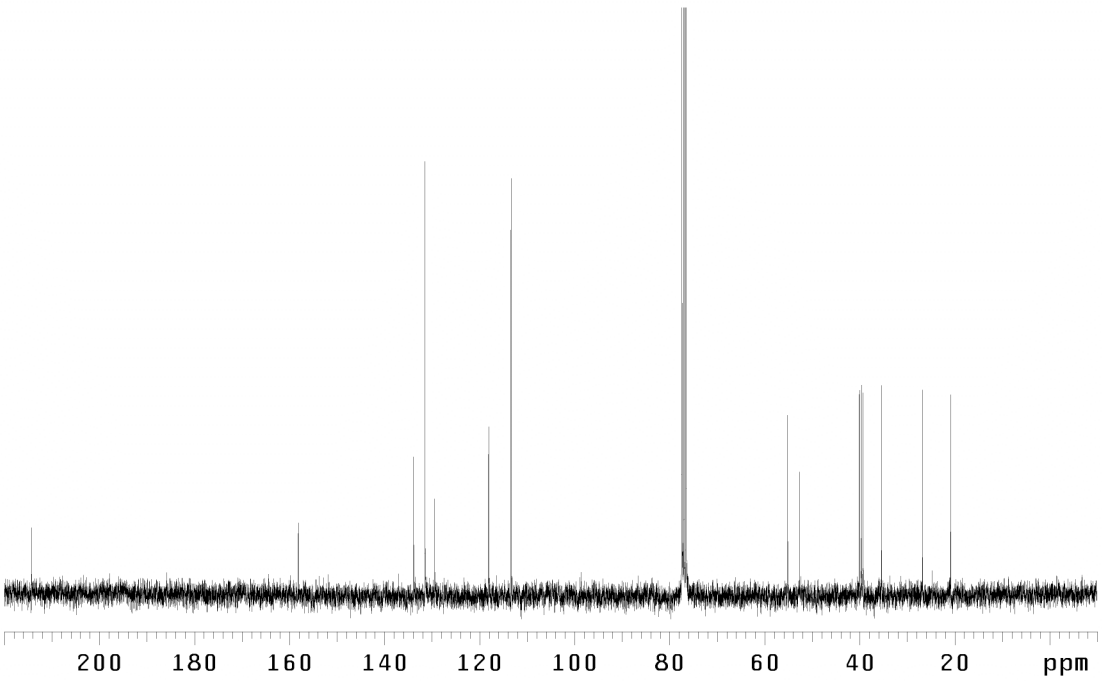


*Figure A2.119 ^{13}C NMR of compound **255** (75 MHz, $CDCl_3$)*

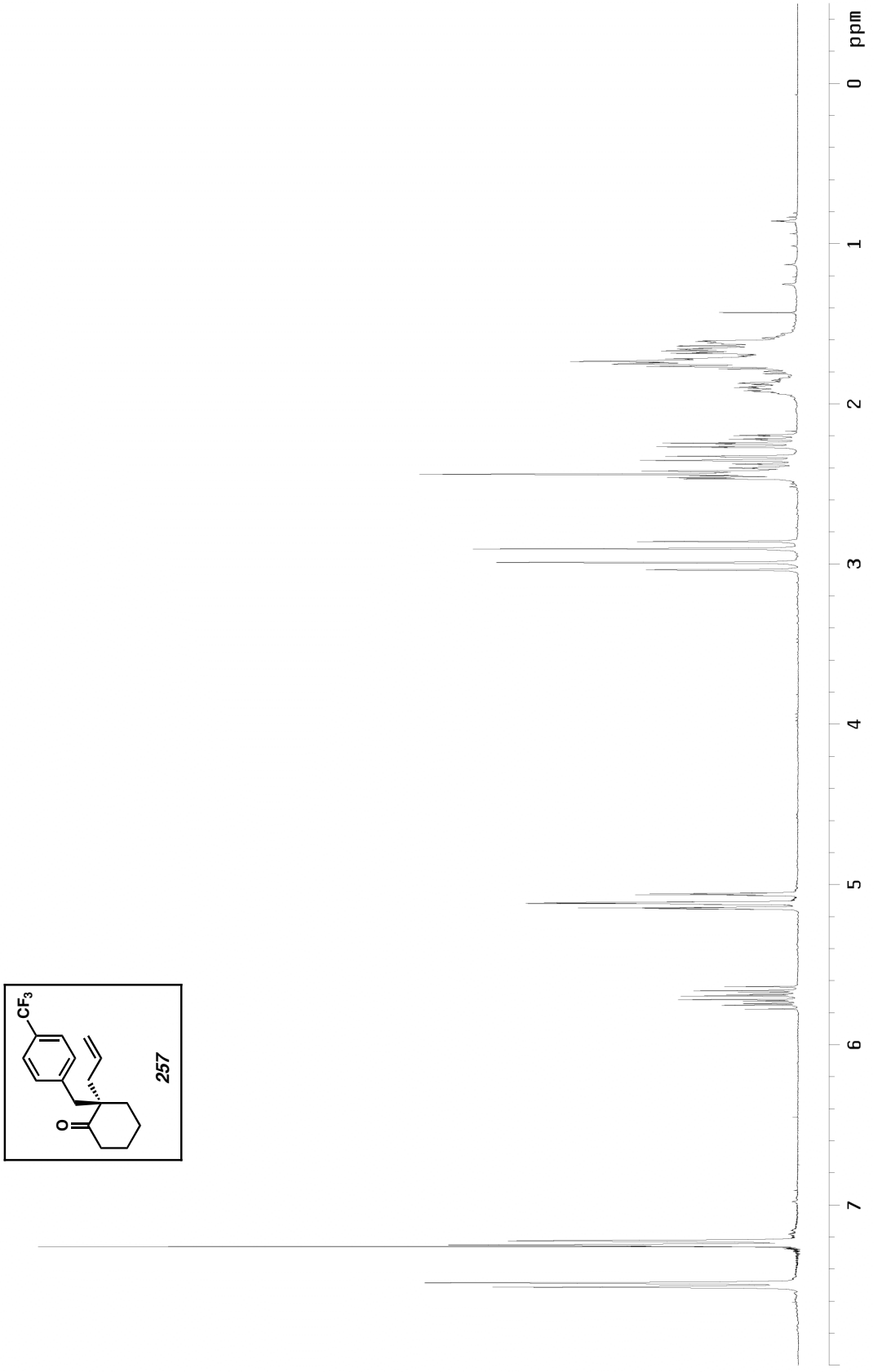


*Figure A2.120 ^1H NMR of compound **257** (300 MHz, $CDCl_3$)*

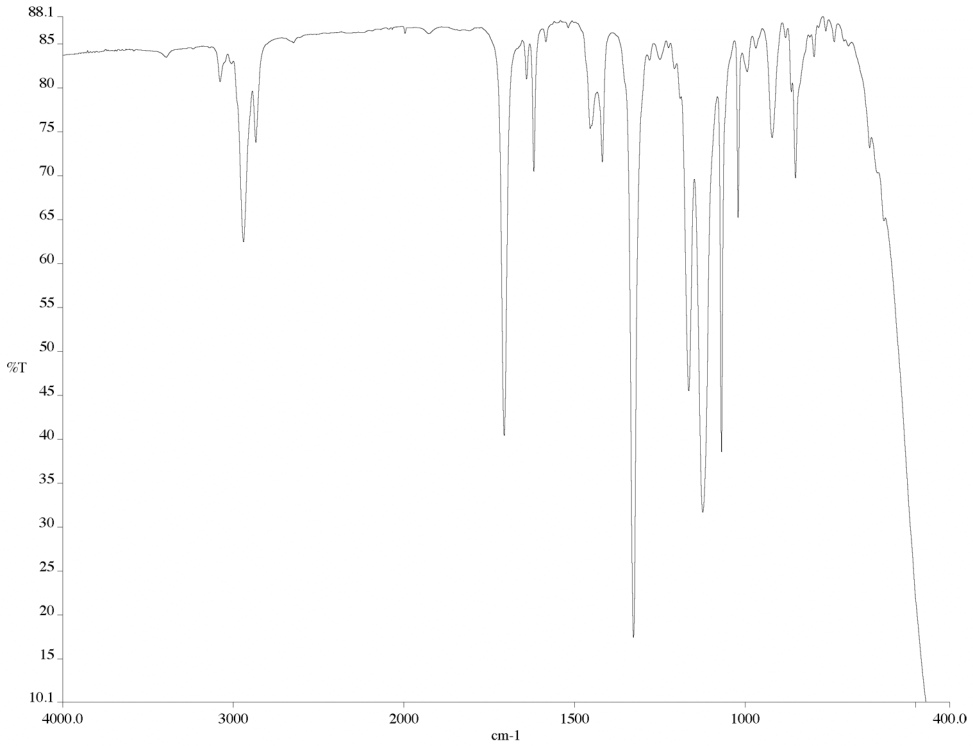


*Figure A2.121 IR of compound **257** (NaCl/film)*

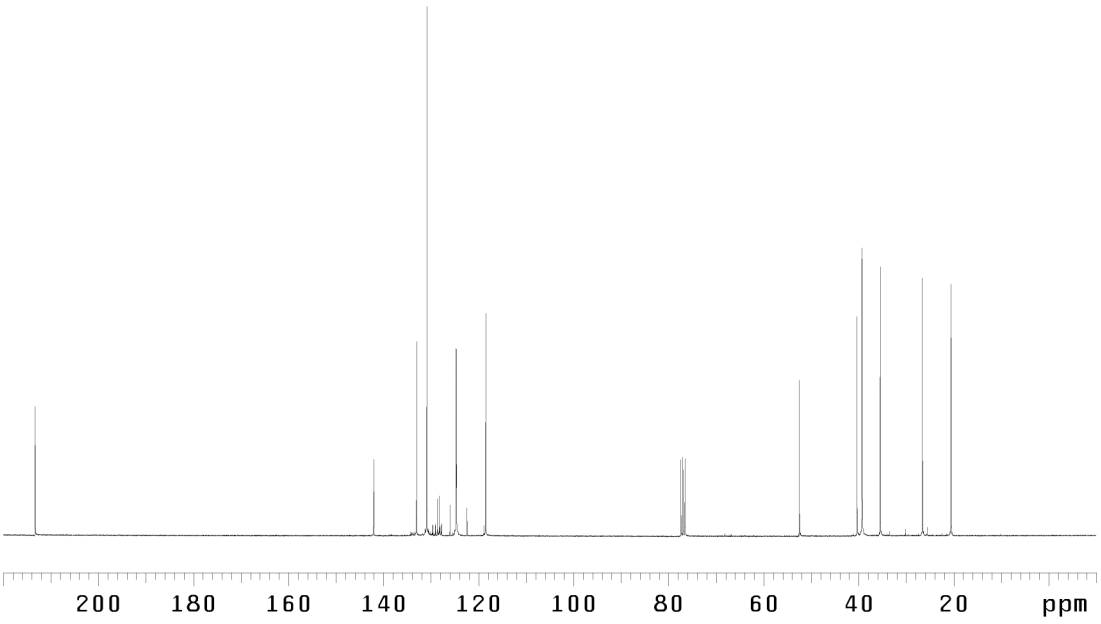


*Figure A2.122 ^{13}C NMR of compound **257** (75 MHz, $CDCl_3$)*

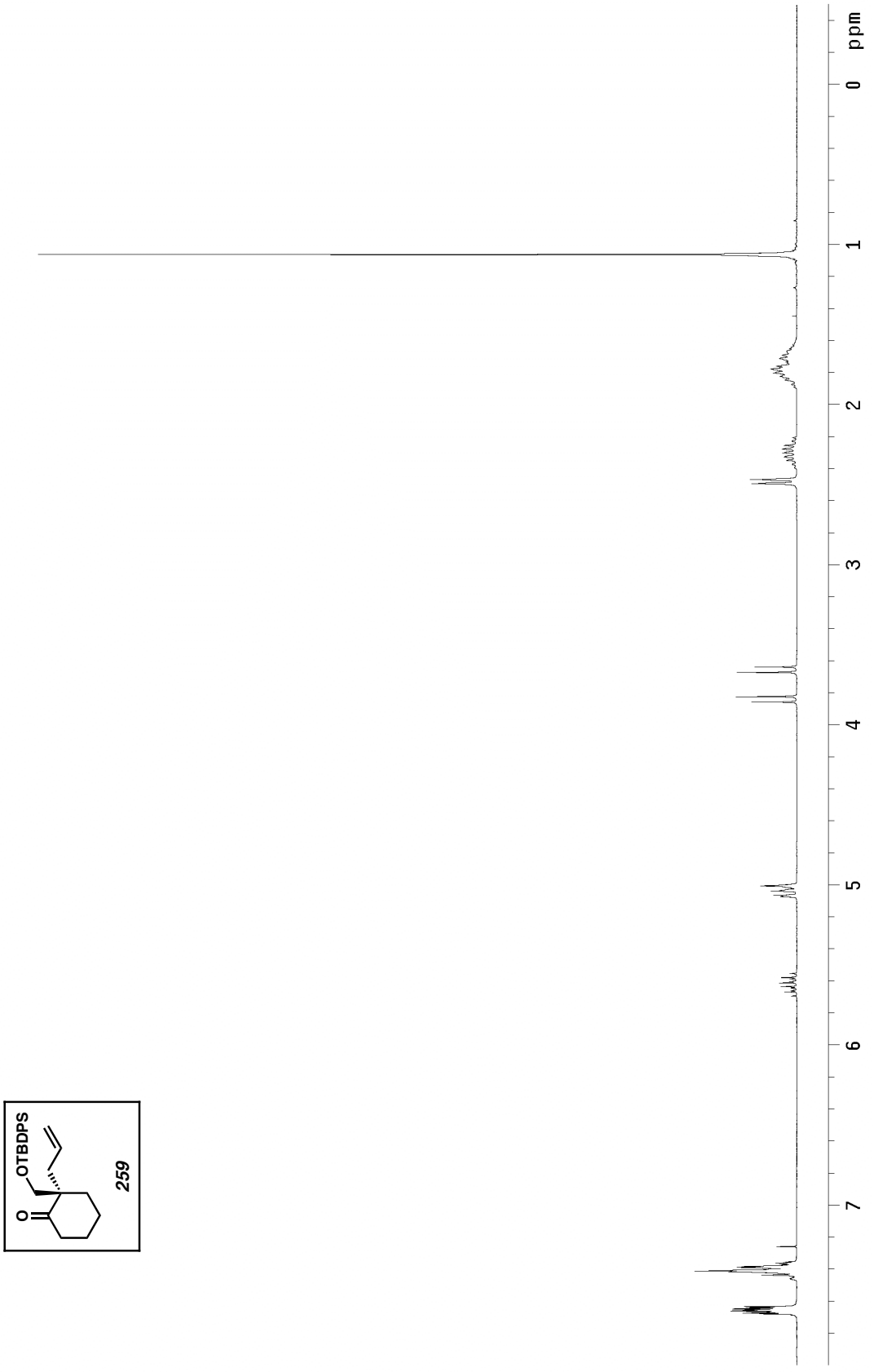


*Figure A2.123 ^1H NMR of compound **259** (300 MHz, $CDCl_3$)*

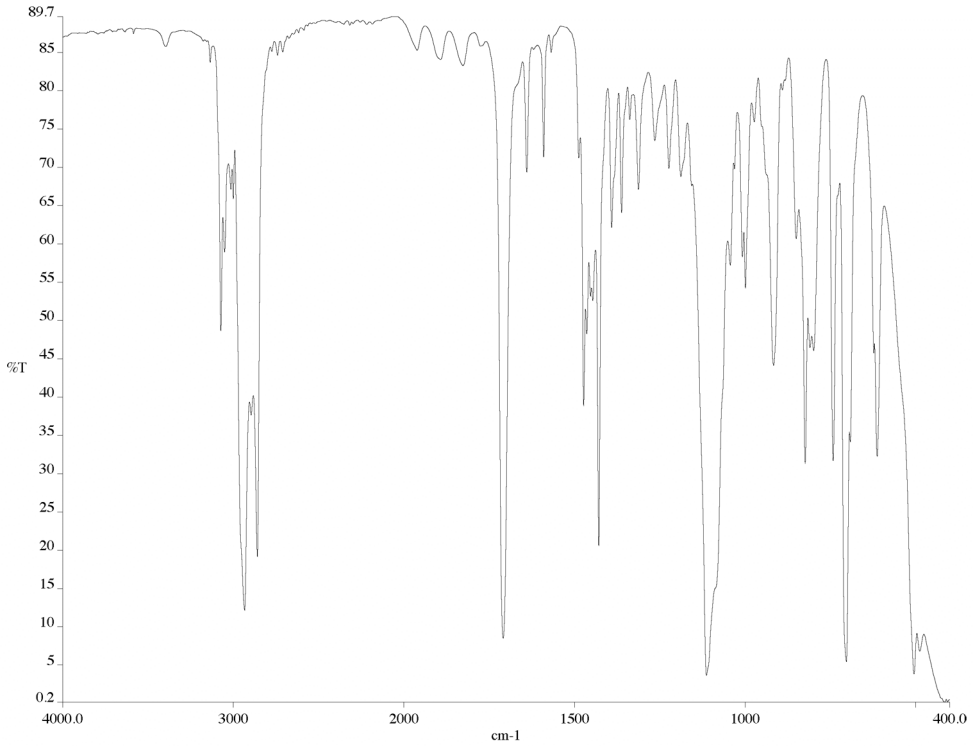


*Figure A2.124 IR of compound **259** (NaCl/film)*

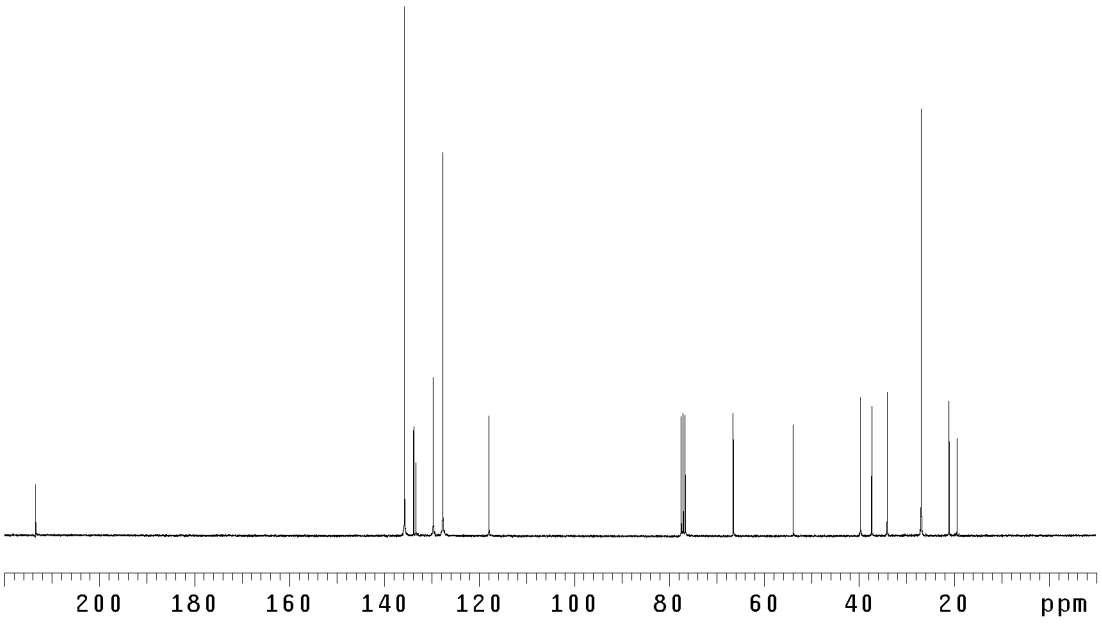


*Figure A2.125 ^{13}C NMR of compound **259** (75 MHz, $CDCl_3$)*

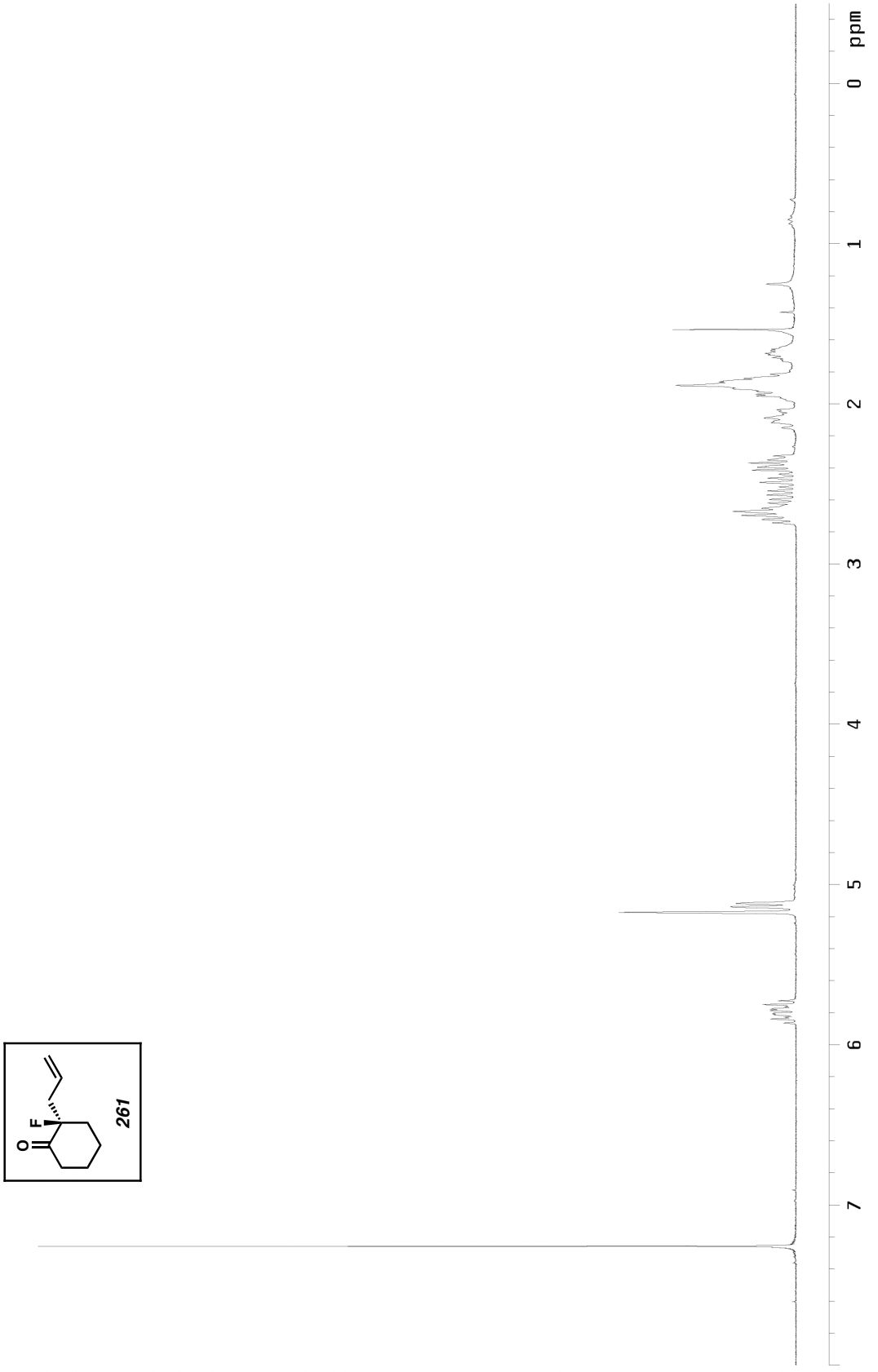


*Figure A2.126 ^1H NMR of compound **261** (300 MHz, $CDCl_3$)*

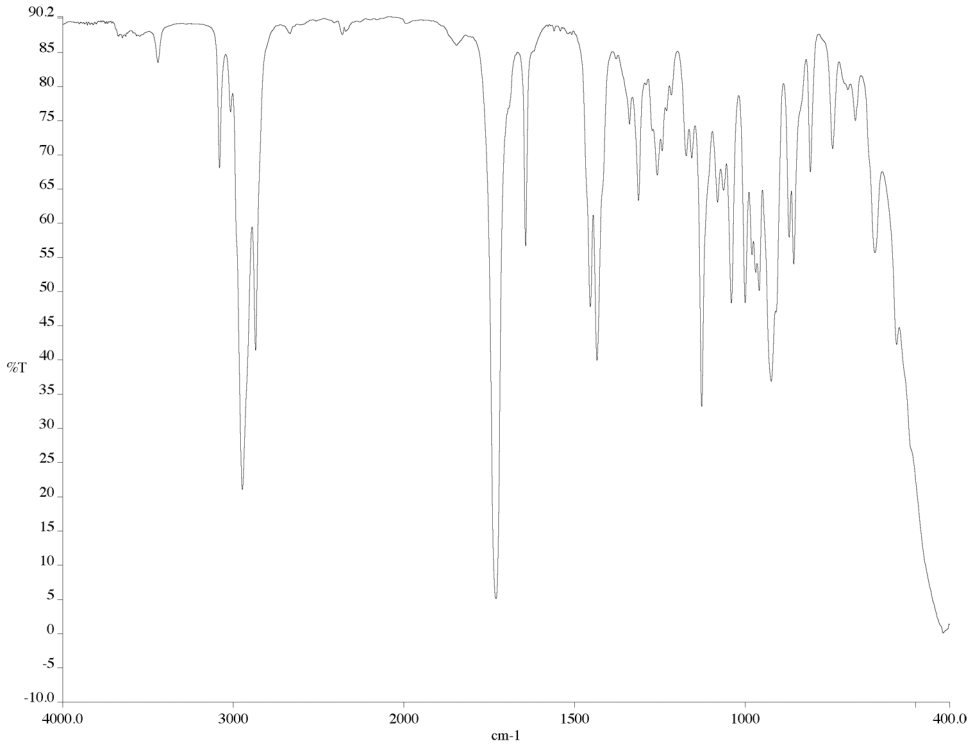


*Figure A2.127 IR of compound **261** (NaCl/film)*

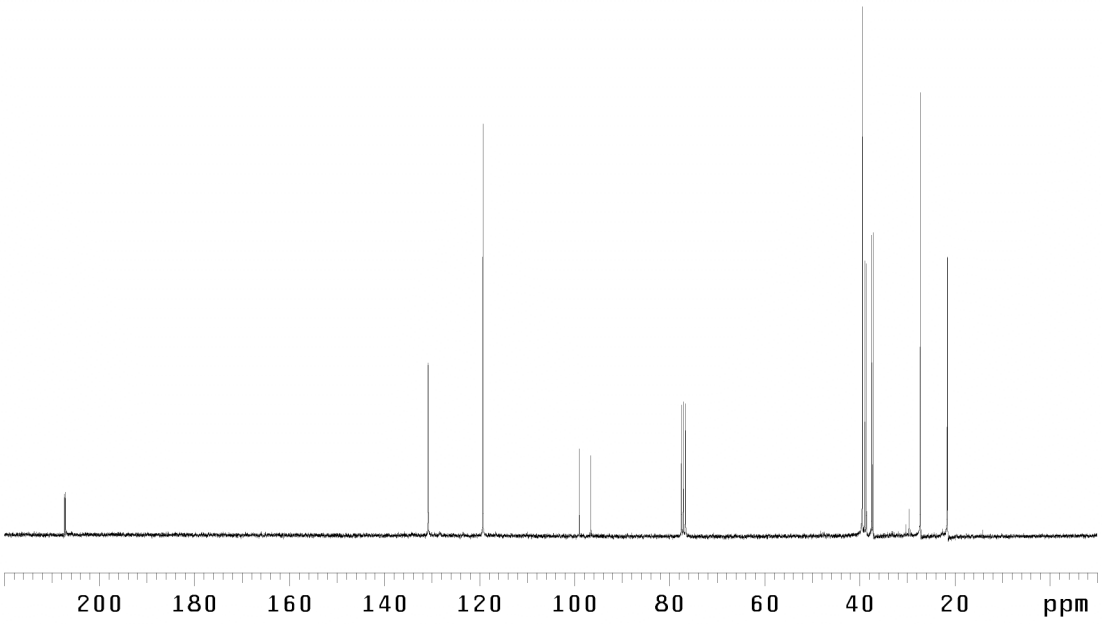


*Figure A2.128 ^{13}C NMR of compound **261** (75 MHz, $CDCl_3$)*

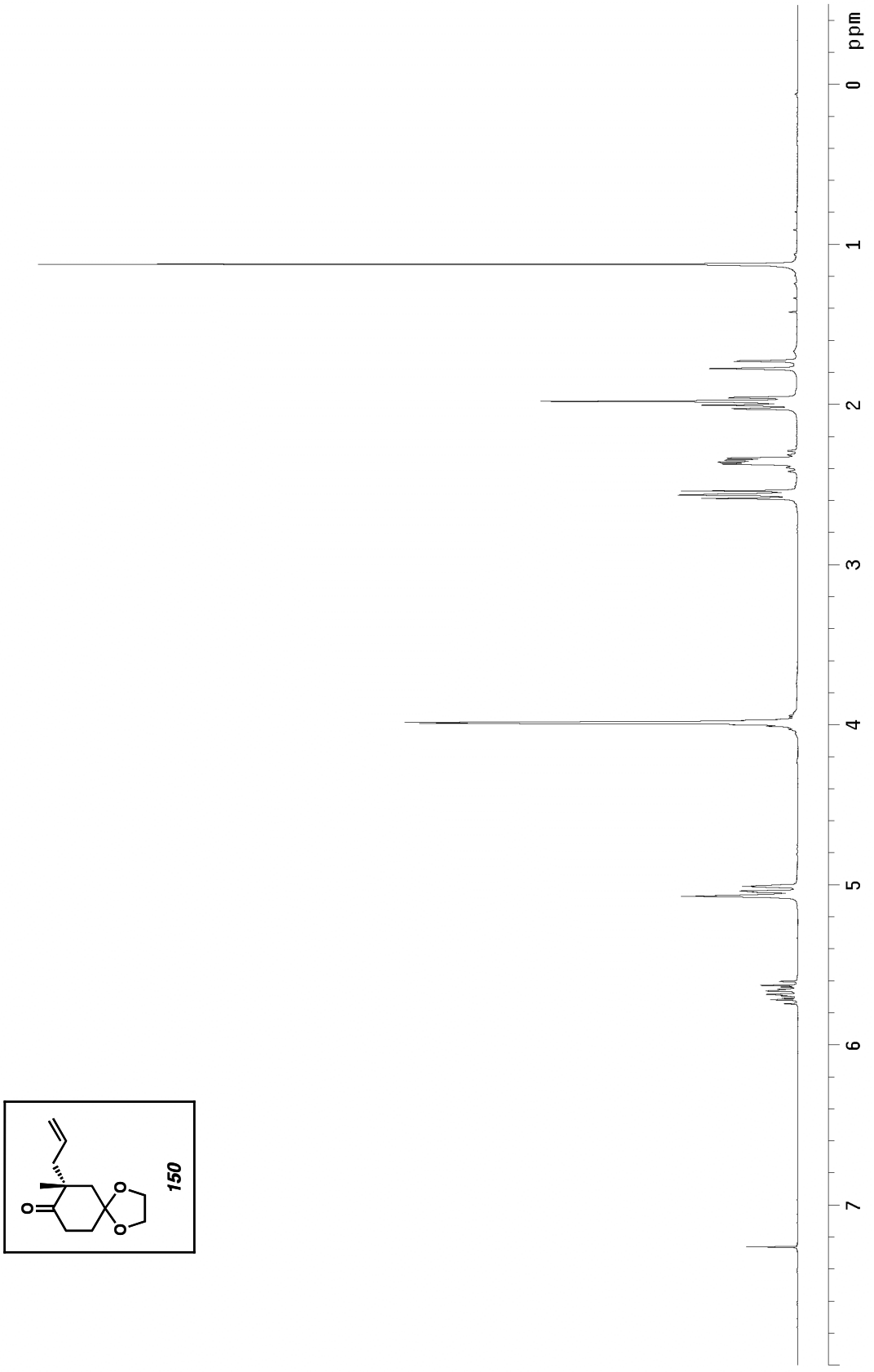


*Figure A2.129 ^1H NMR of compound **150** (300 MHz, $CDCl_3$)*

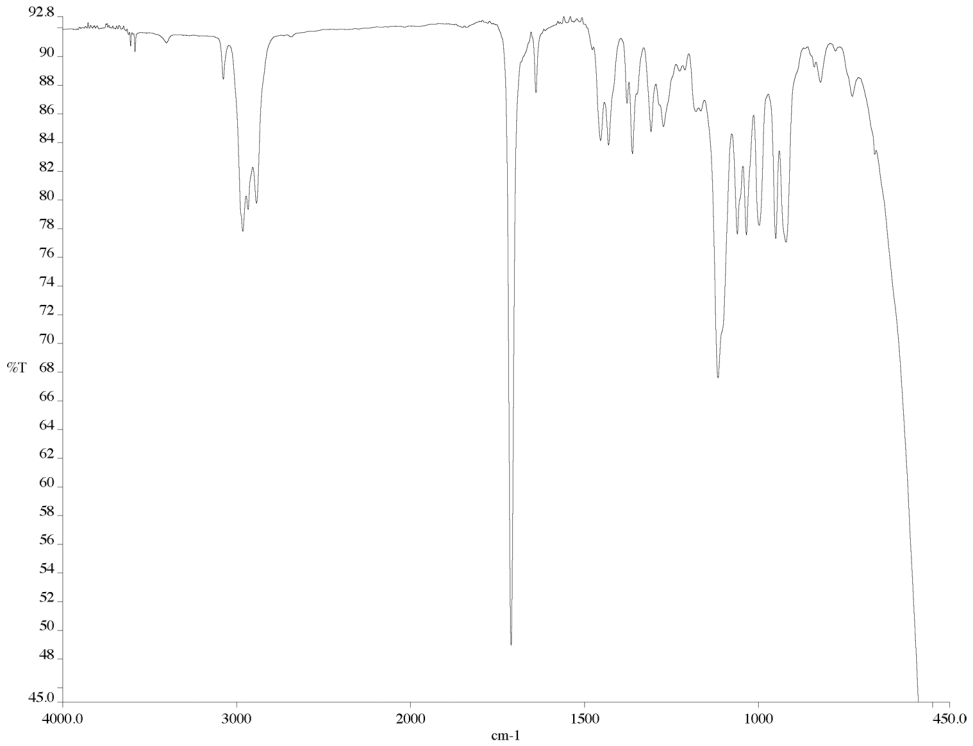


*Figure A2.130 IR of compound **150** (NaCl/film)*

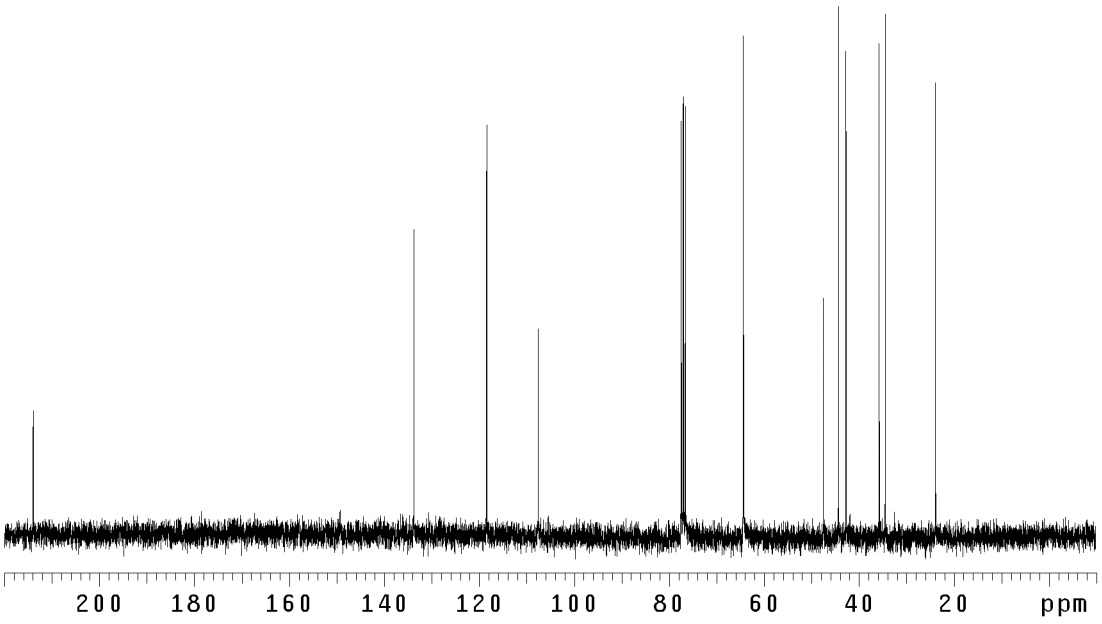


*Figure A2.131 ^{13}C NMR of compound **150** (75 MHz, $CDCl_3$)*

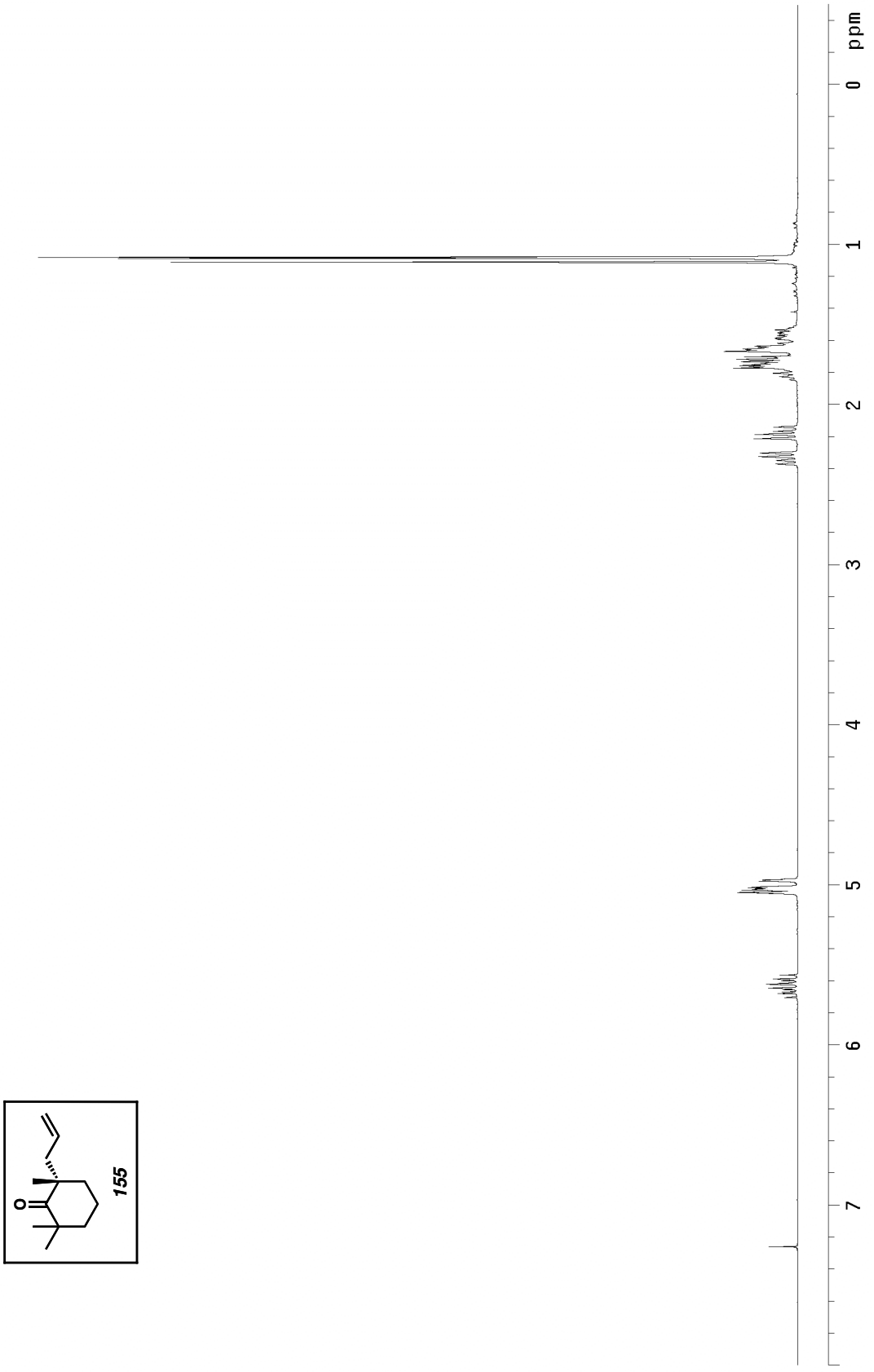


*Figure A2.132 ^1H NMR of compound **155** (300 MHz, $CDCl_3$)*

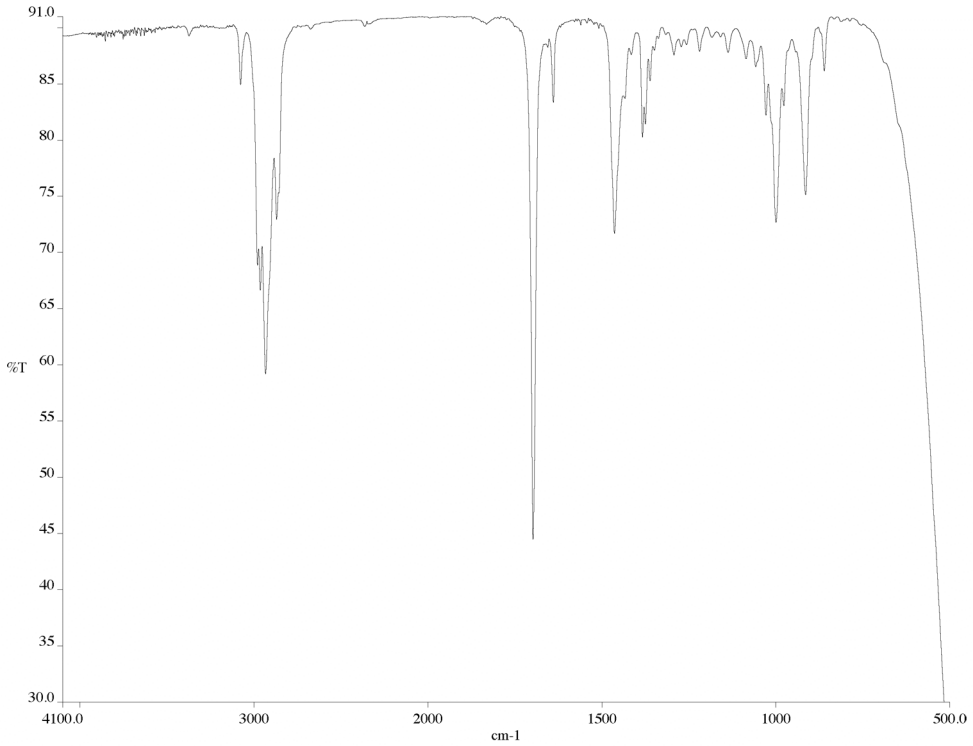


*Figure A2.133 IR of compound **155** (NaCl/film)*

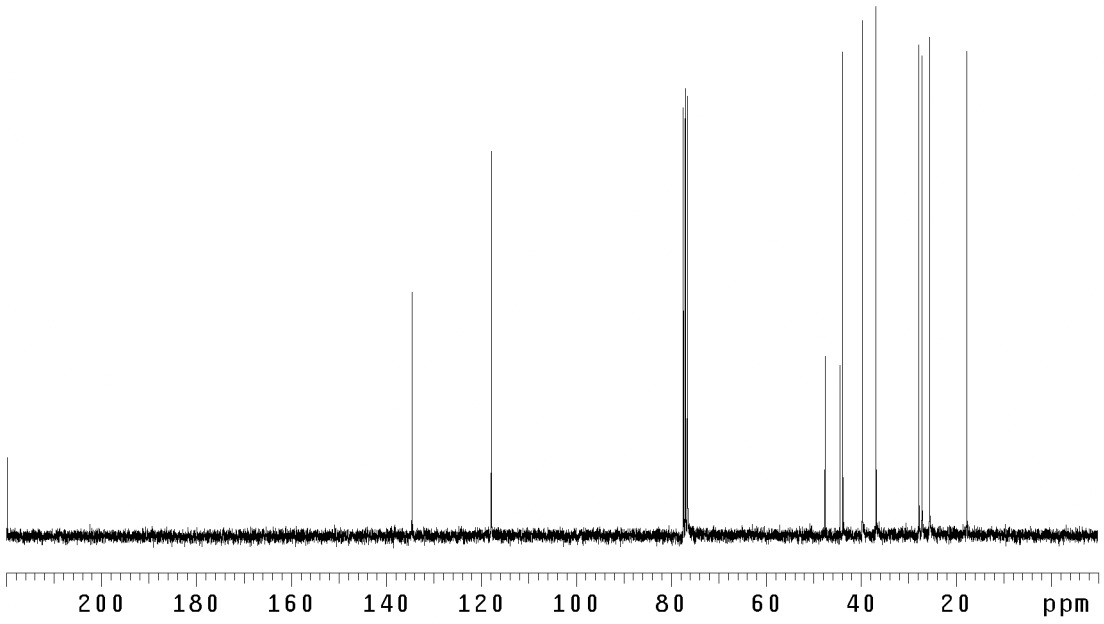


*Figure A2.134 ^{13}C NMR of compound **155** (75 MHz, $CDCl_3$)*

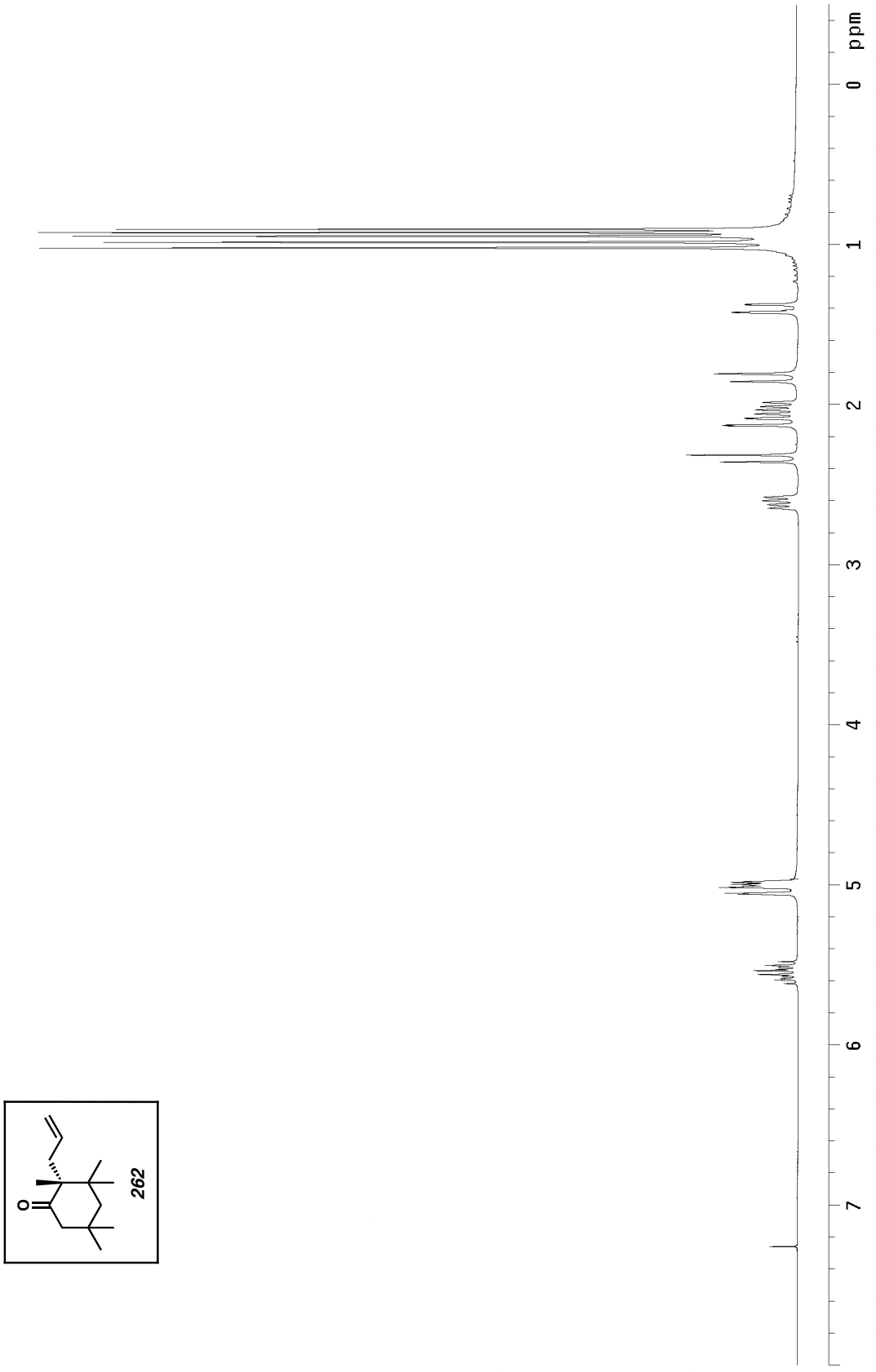


*Figure A2.135 ^1H NMR of compound **262** (300 MHz, $CDCl_3$)*

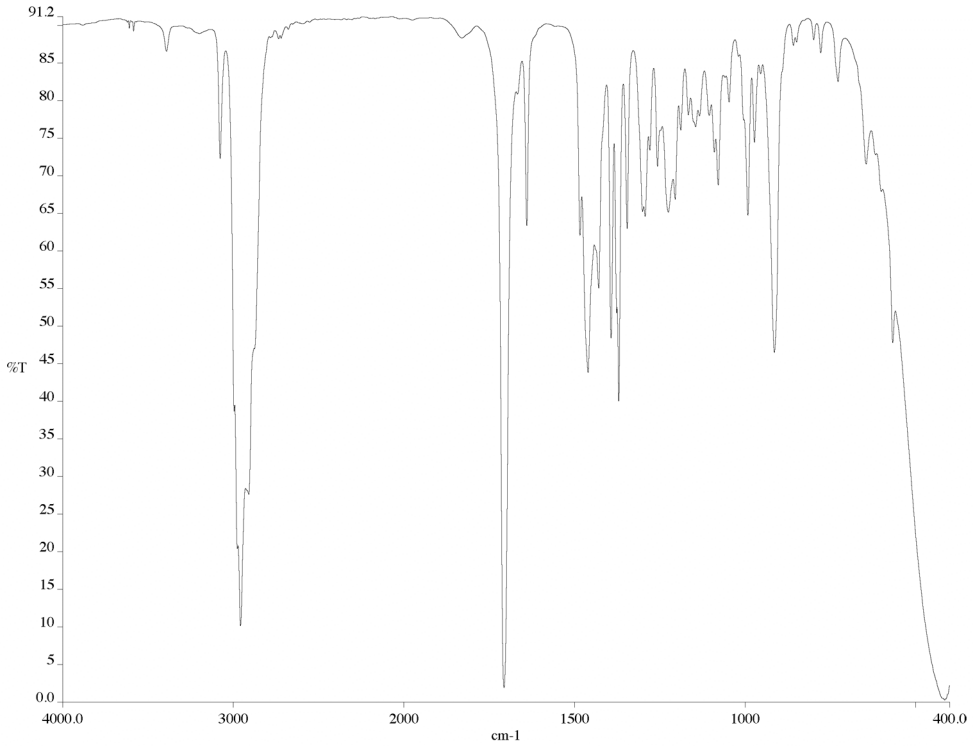


*Figure A2.136 IR of compound **262** (NaCl/film)*

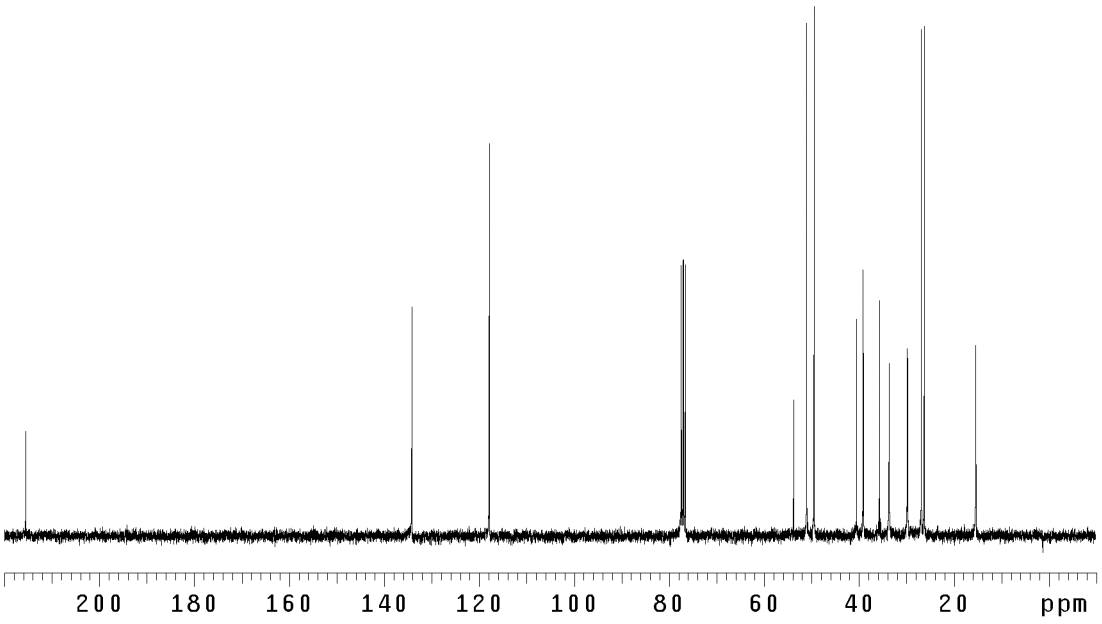
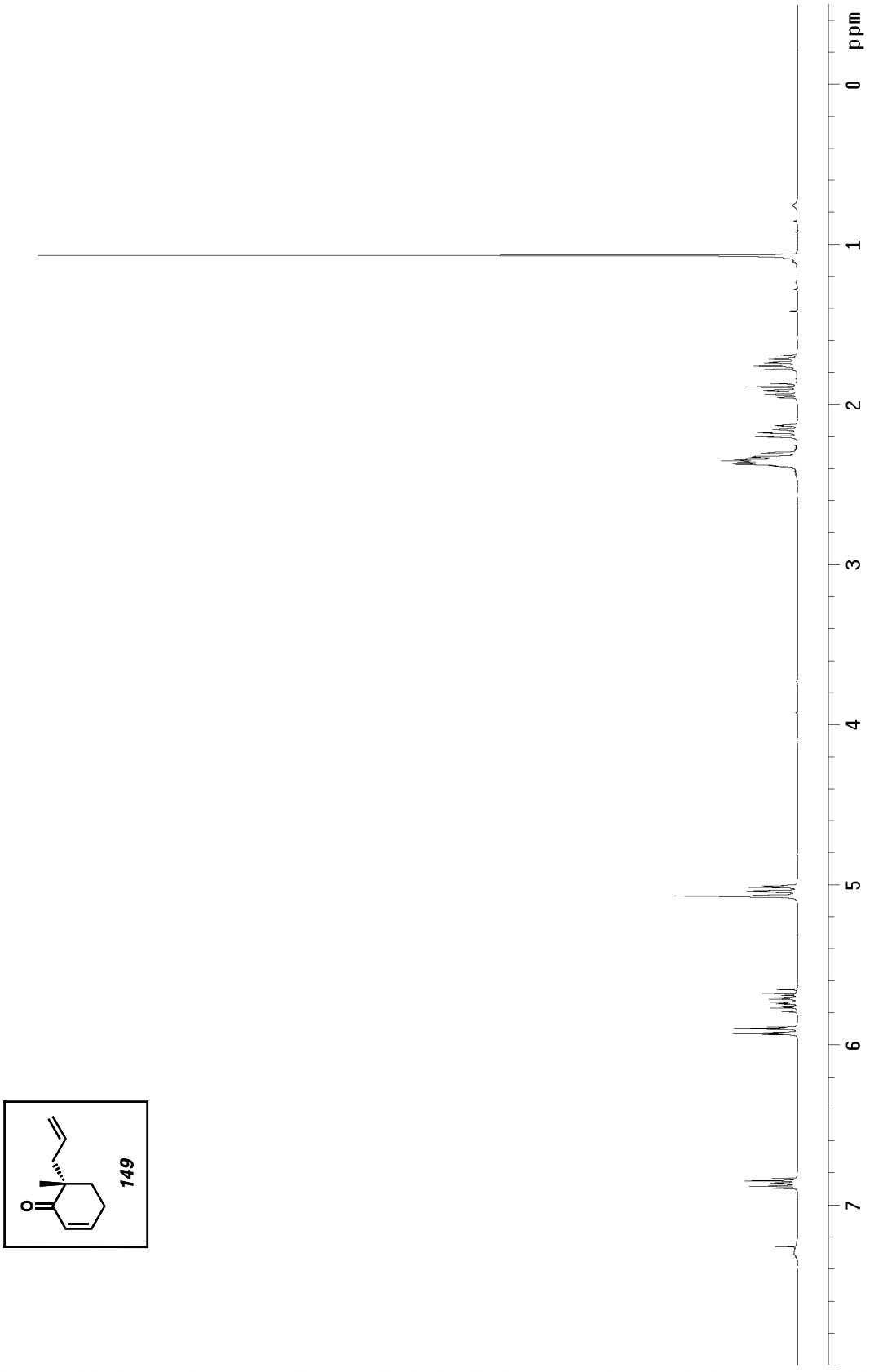


*Figure A2.137 ^{13}C NMR of compound **262** (75 MHz, $CDCl_3$)*



149

*Figure A2.138 ^1H NMR of compound **149** (300 MHz, $CDCl_3$)*

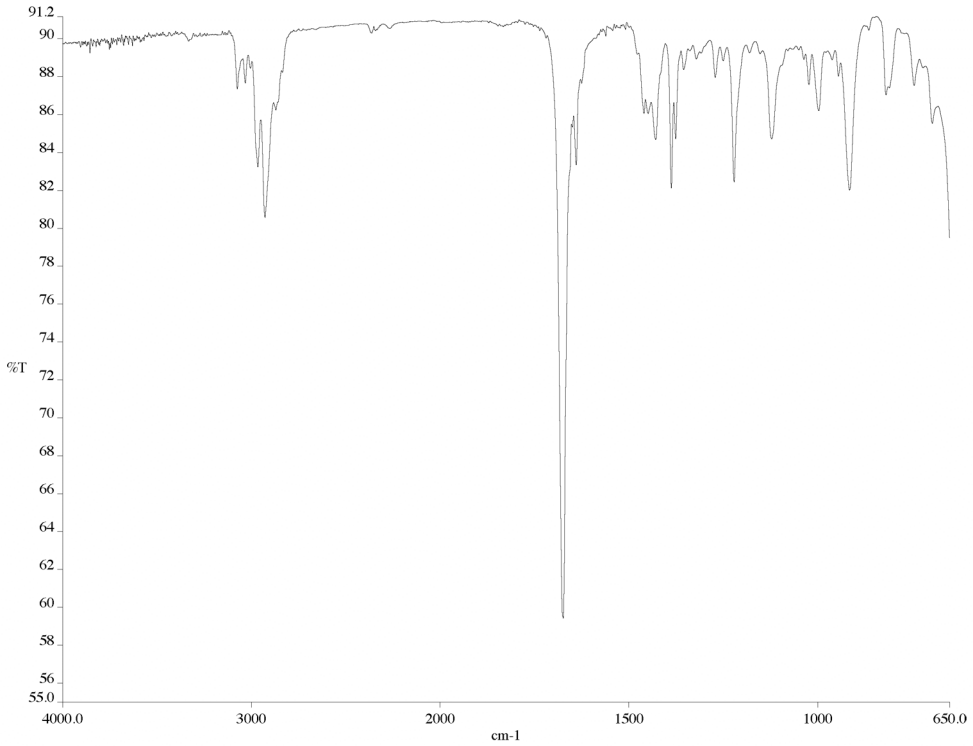


*Figure A2.139 IR of compound **149** (NaCl/film)*

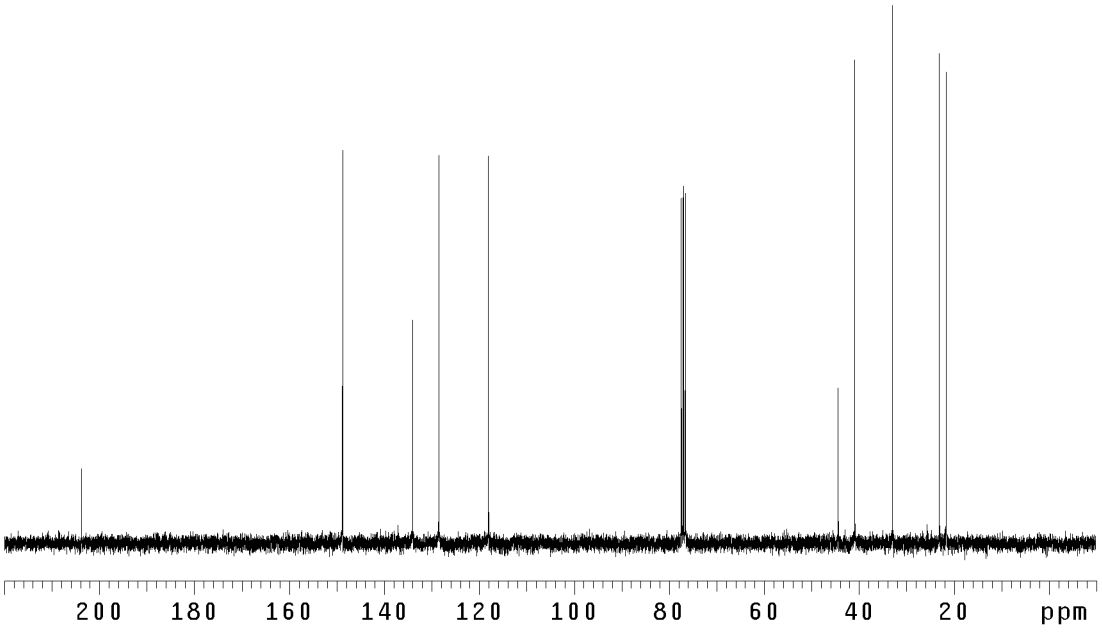


*Figure A2.140 ^{13}C NMR of compound **149** (75 MHz, $CDCl_3$)*

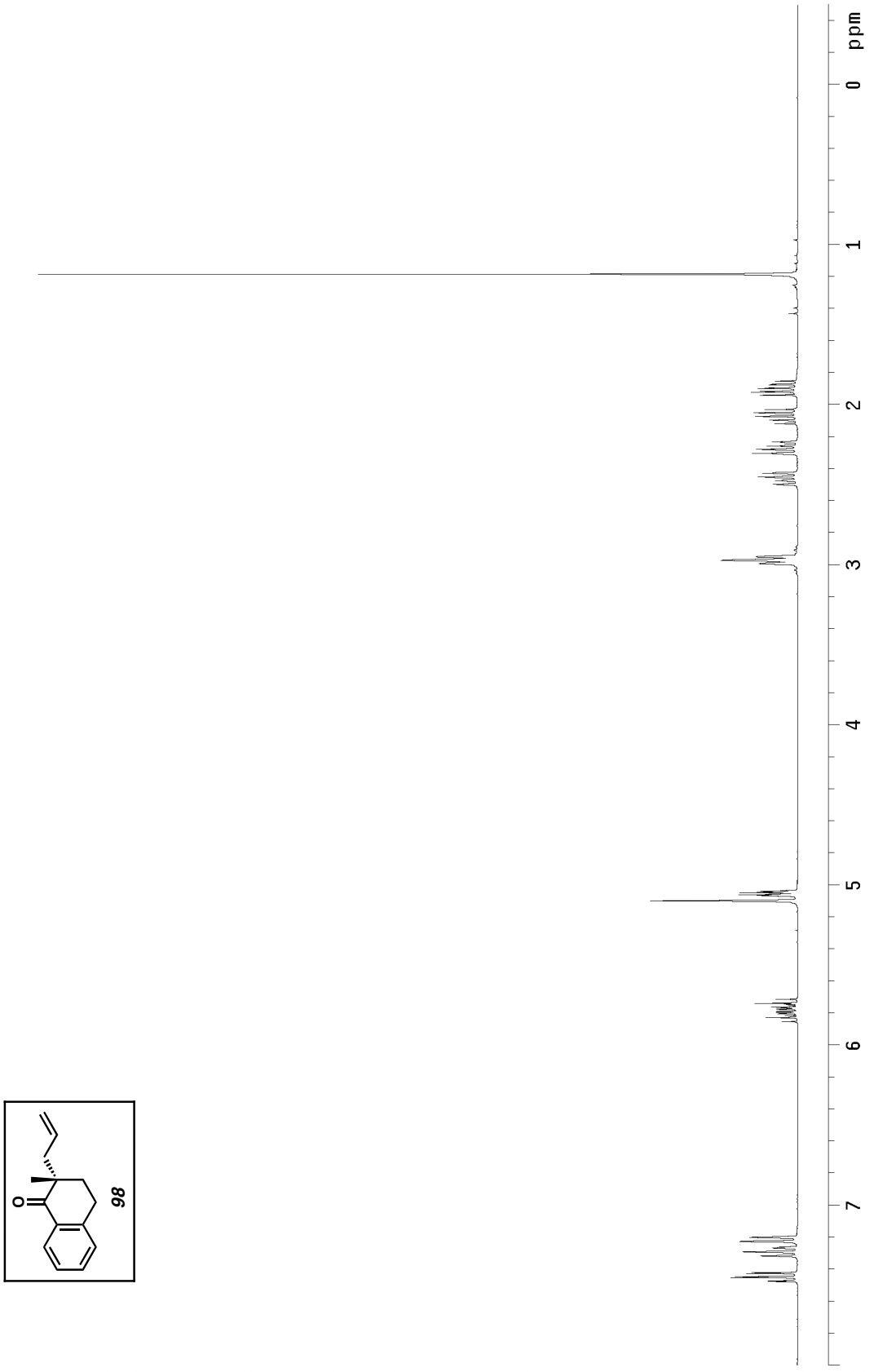


*Figure A2.141 ^1H NMR of compound **98** (300 MHz, $CDCl_3$)*

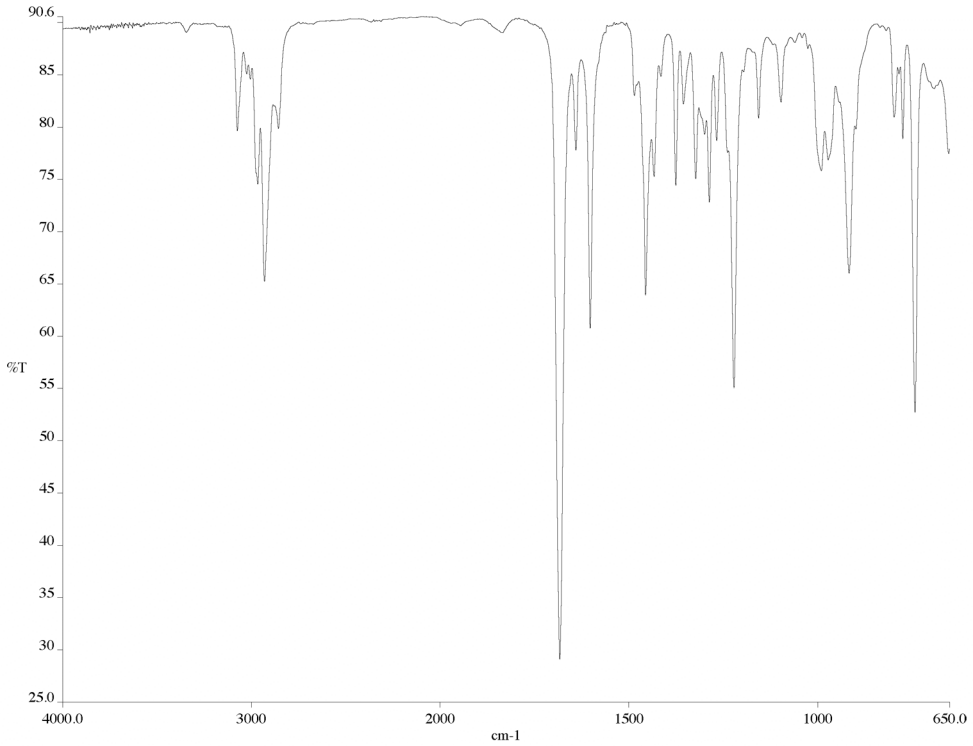


*Figure A2.142 IR of compound **98** (NaCl/film)*

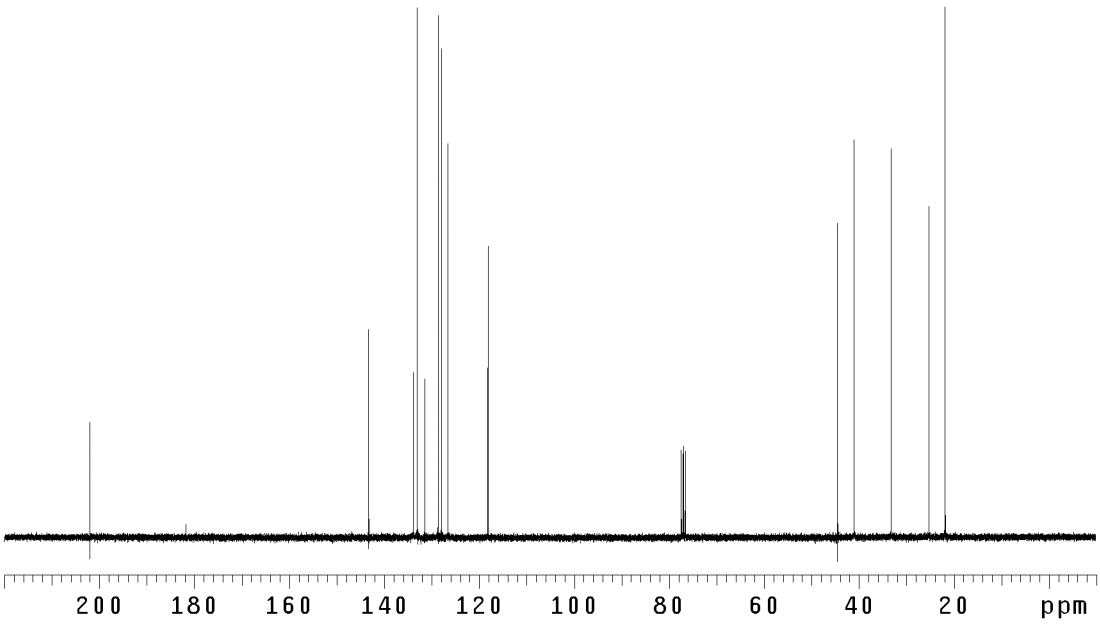


*Figure A2.143 ^{13}C NMR of compound **98** (75 MHz, $CDCl_3$)*

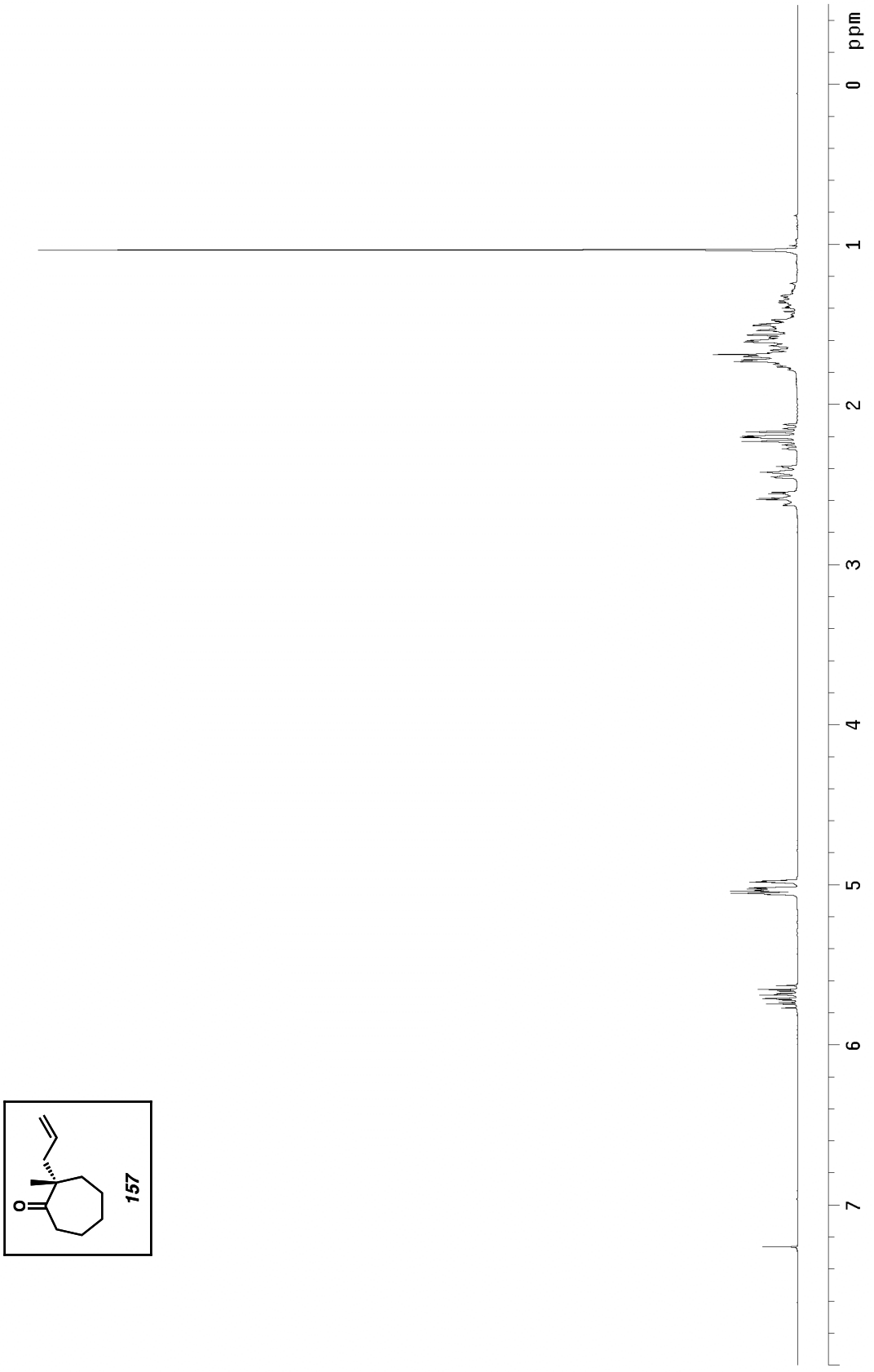


*Figure A2.144 ^1H NMR of compound **157** (300 MHz, $CDCl_3$)*

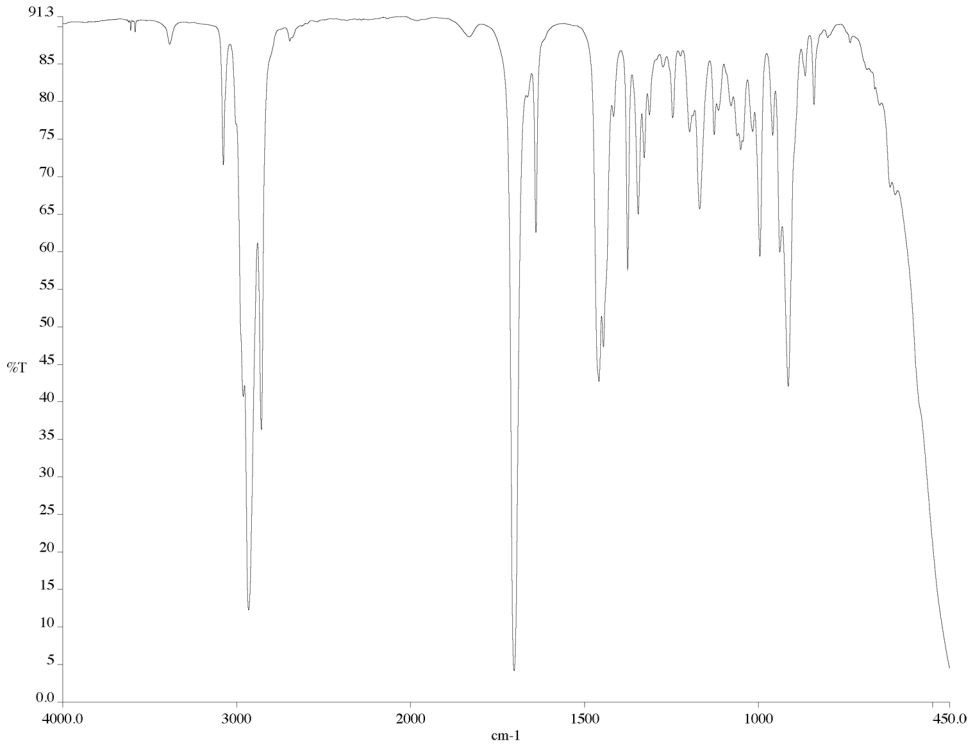


*Figure A2.145 IR of compound **157** (NaCl/film)*

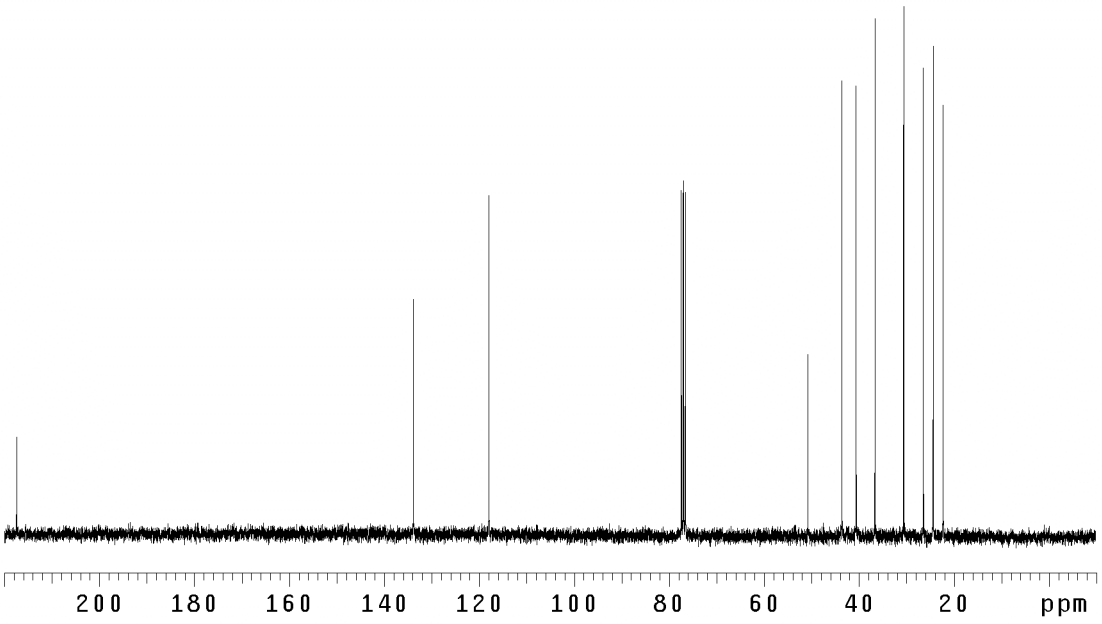


*Figure A2.146 ^{13}C NMR of compound **157** (75 MHz, $CDCl_3$)*

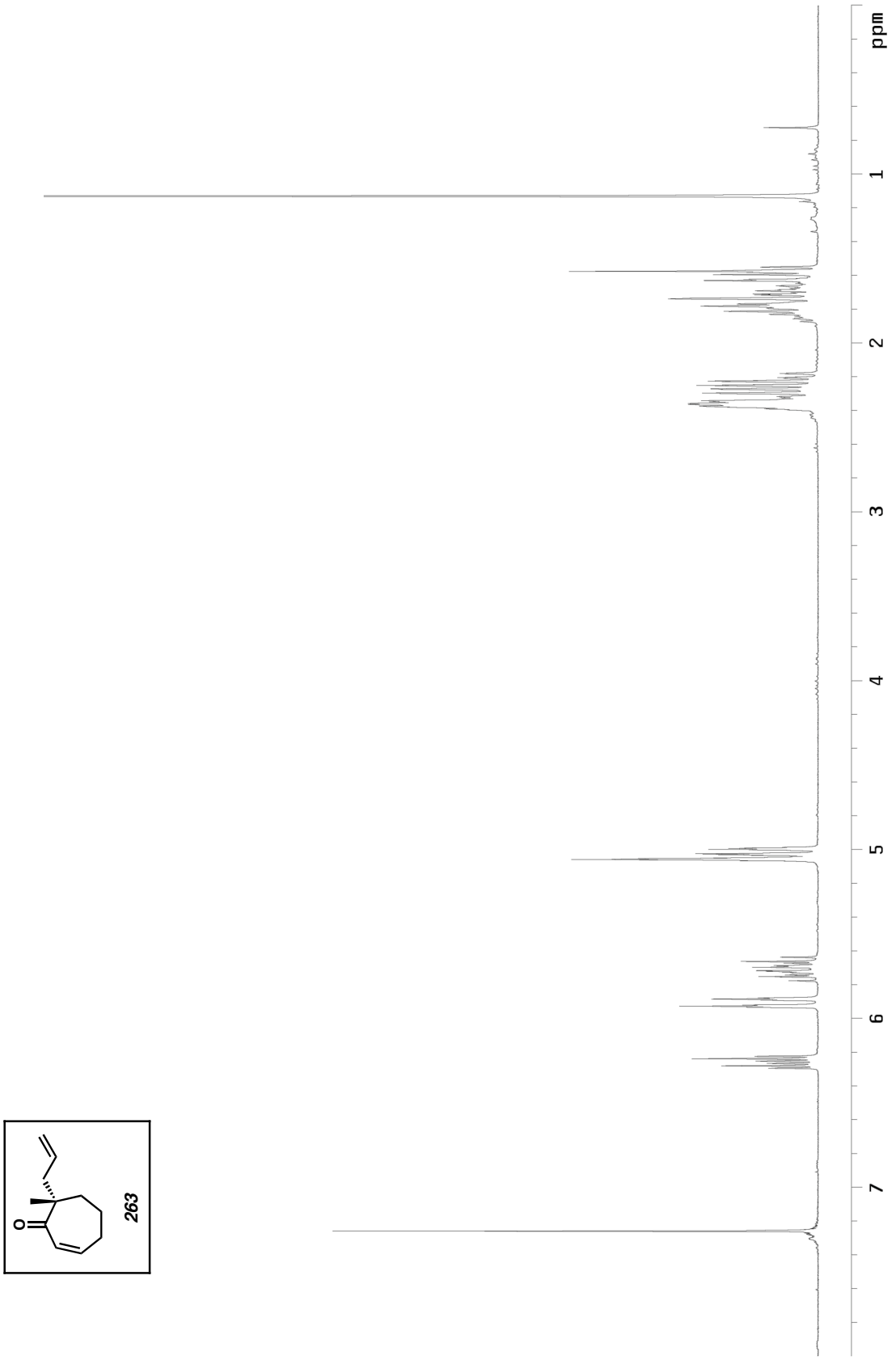


*Figure A2.147 ^1H NMR of compound **263** (300 MHz, $CDCl_3$)*

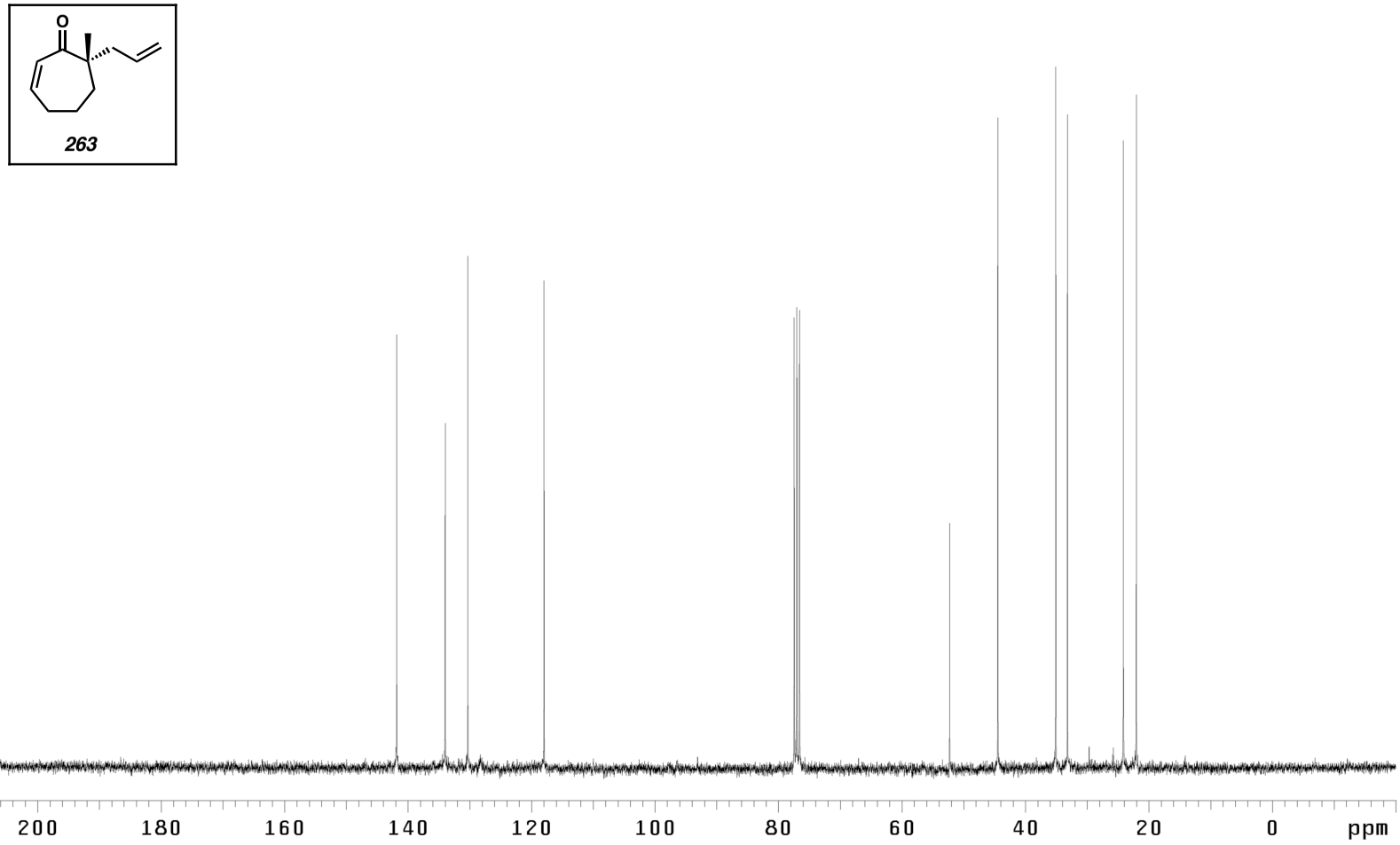


*Figure A2.148 ^{13}C NMR of compound **263** (75 MHz, $CDCl_3$)*

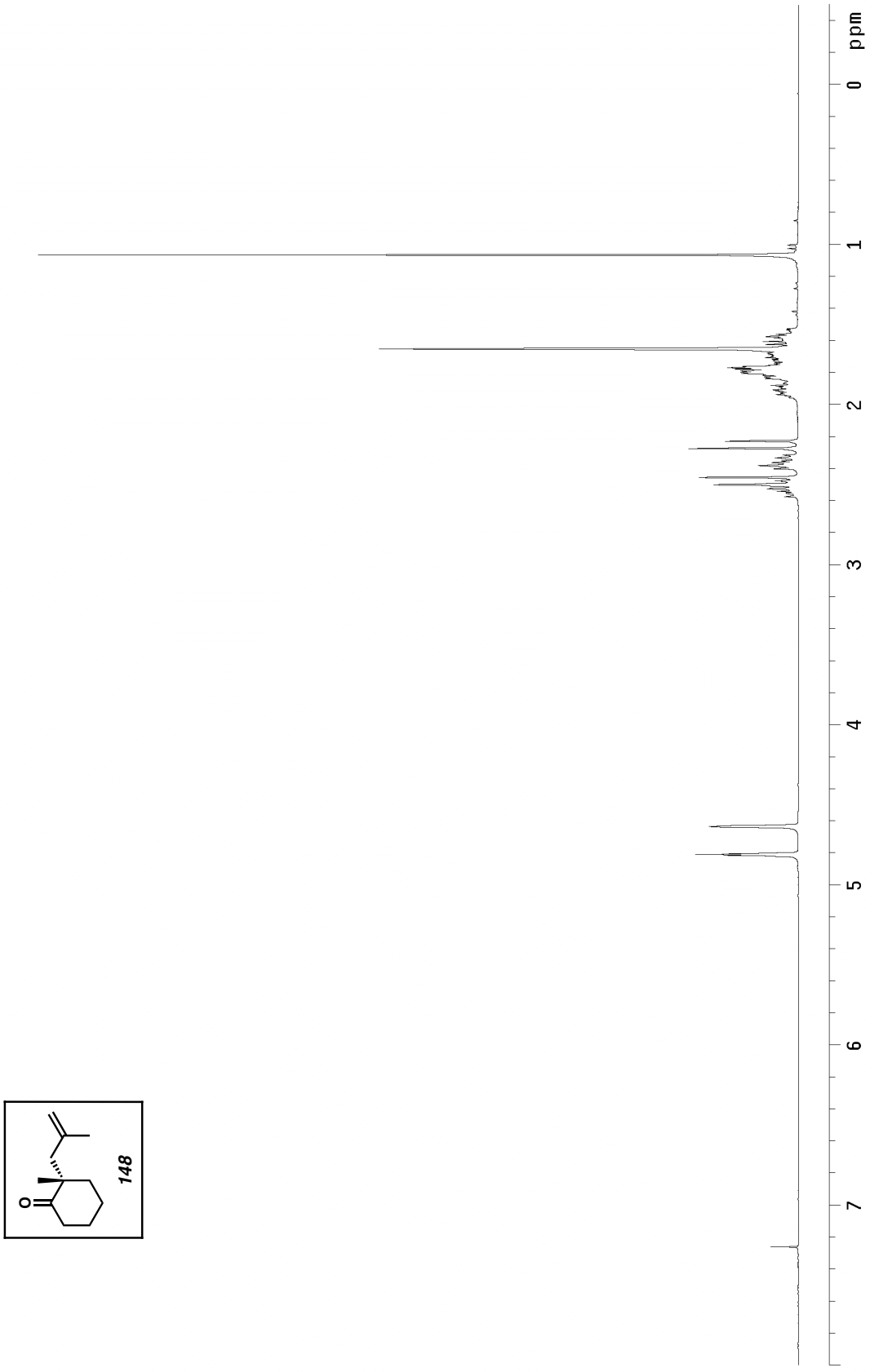


*Figure A2.149 ^1H NMR of compound **148** (300 MHz, $CDCl_3$)*

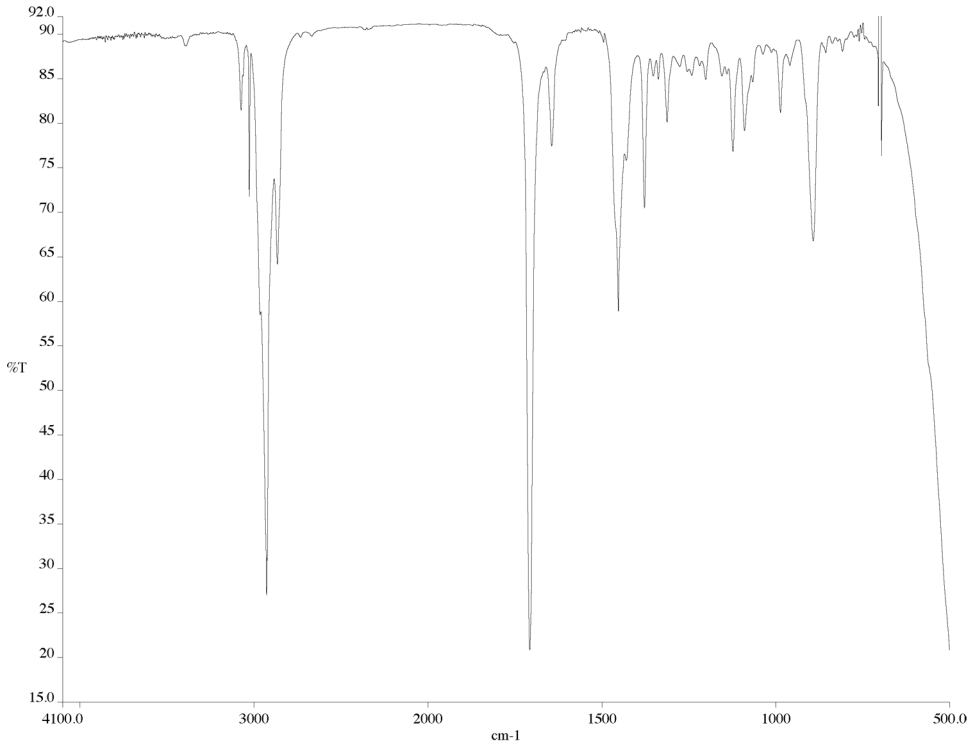


*Figure A2.150 IR of compound **148** (NaCl/film)*

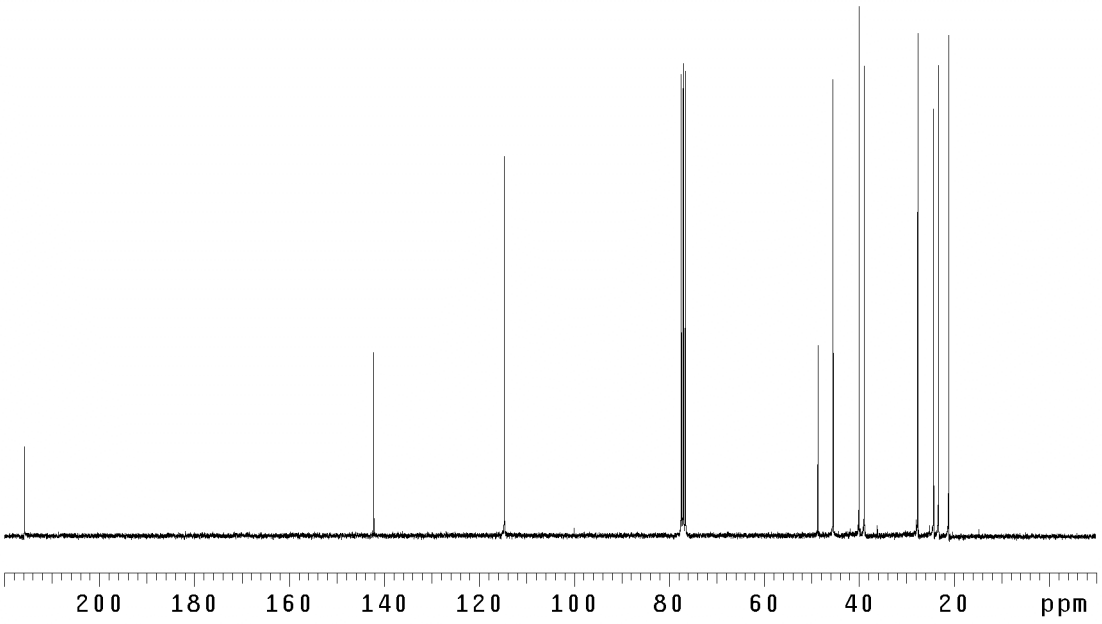


*Figure A2.151 ^{13}C NMR of compound **148** (75 MHz, $CDCl_3$)*

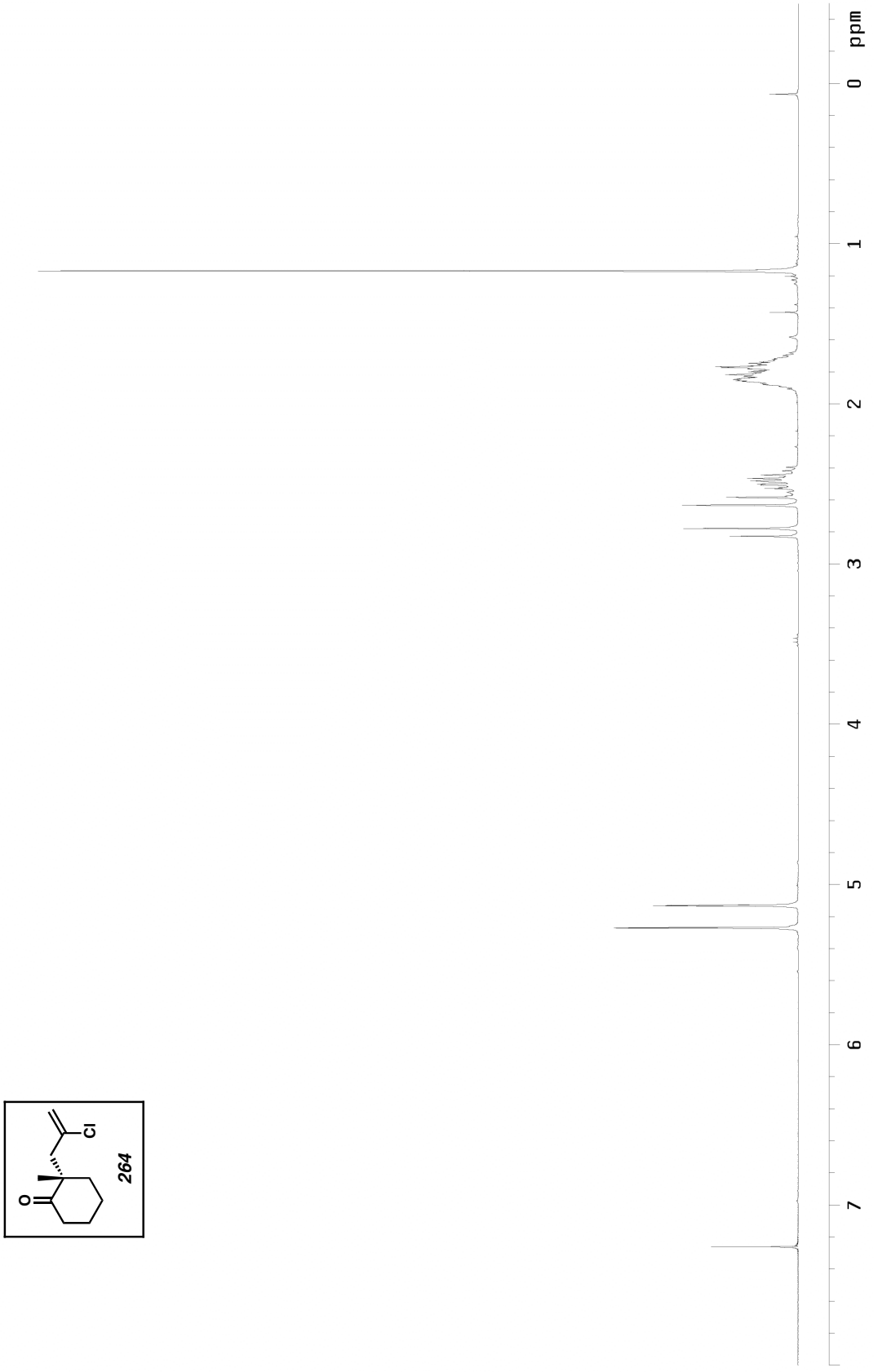


*Figure A2.152 ^1H NMR of compound **264** (300 MHz, $CDCl_3$)*

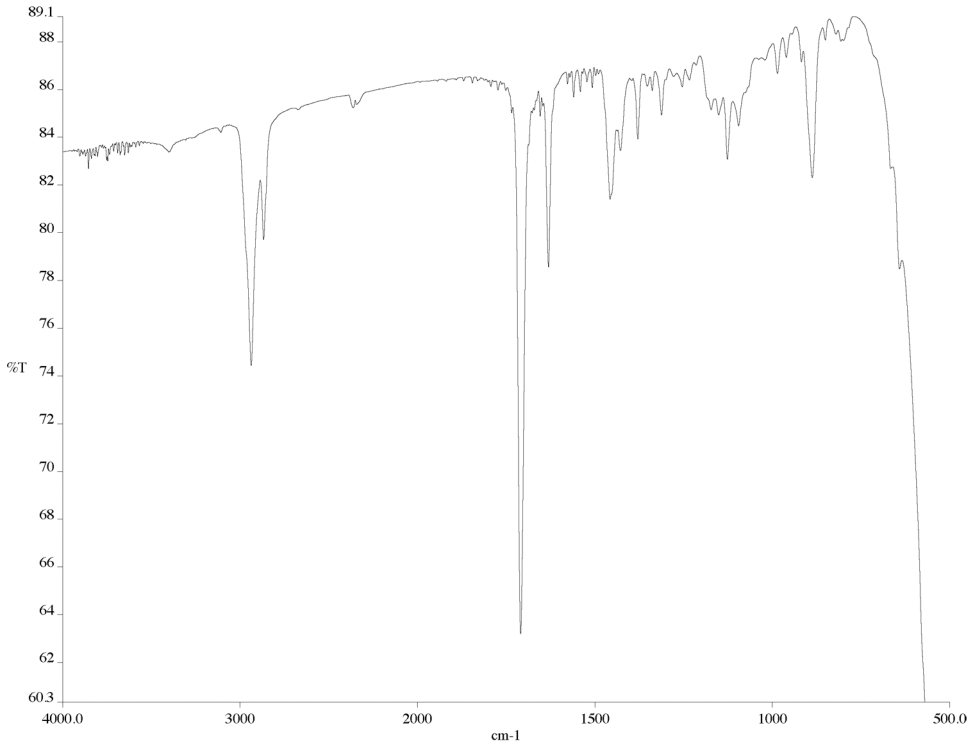


*Figure A2.153 IR of compound **264** (NaCl/film)*

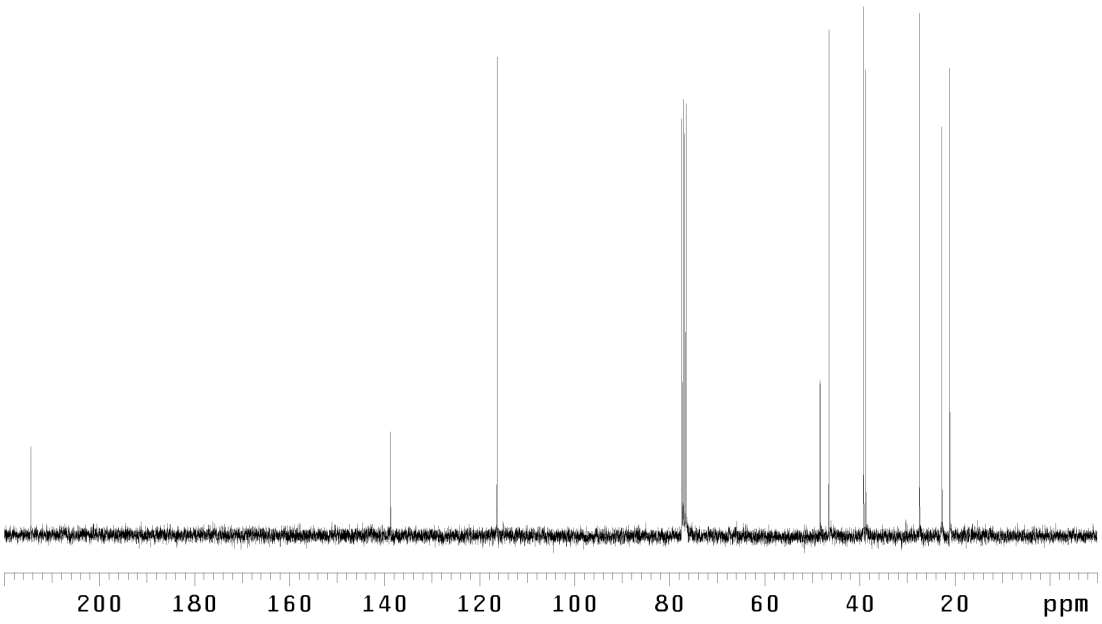


*Figure A2.154 ^{13}C NMR of compound **264** (75 MHz, $CDCl_3$)*

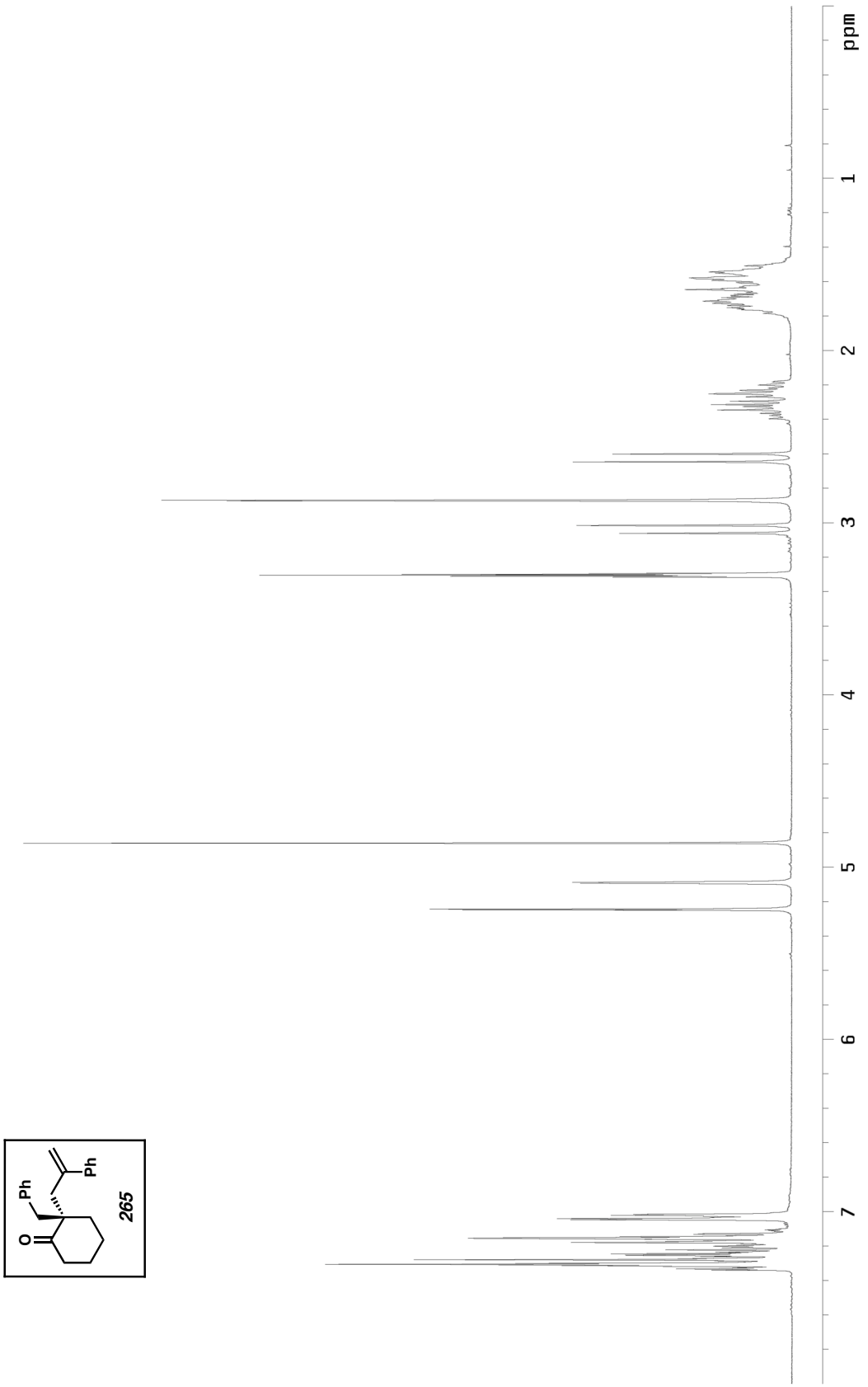


*Figure A2.155 ^1H NMR of compound **265** (300 MHz, $CDCl_3$)*

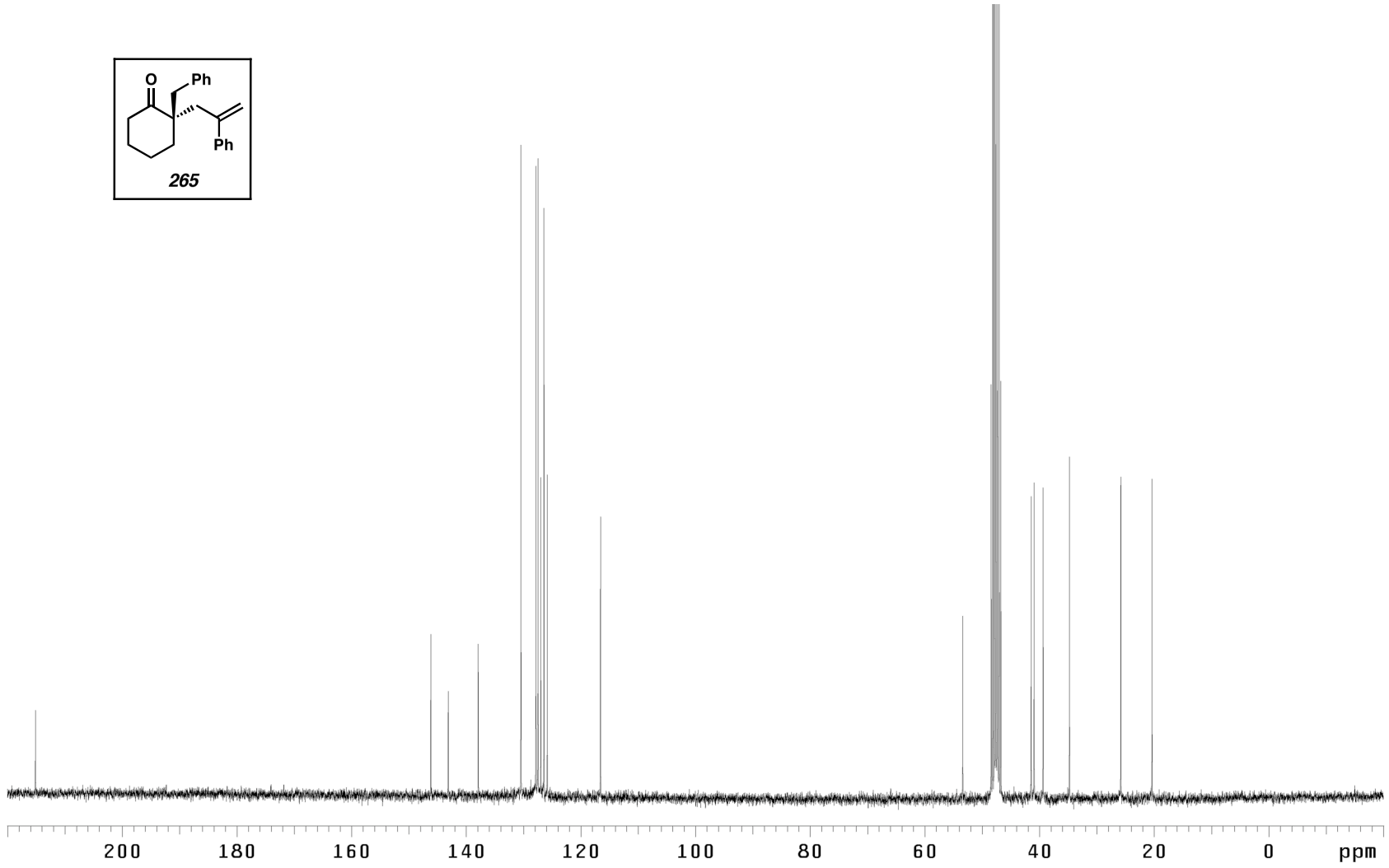


Figure A2.156 ^{13}C *NMR of compound* ***265*** *(75 MHz,* $CDCl_3$*)*

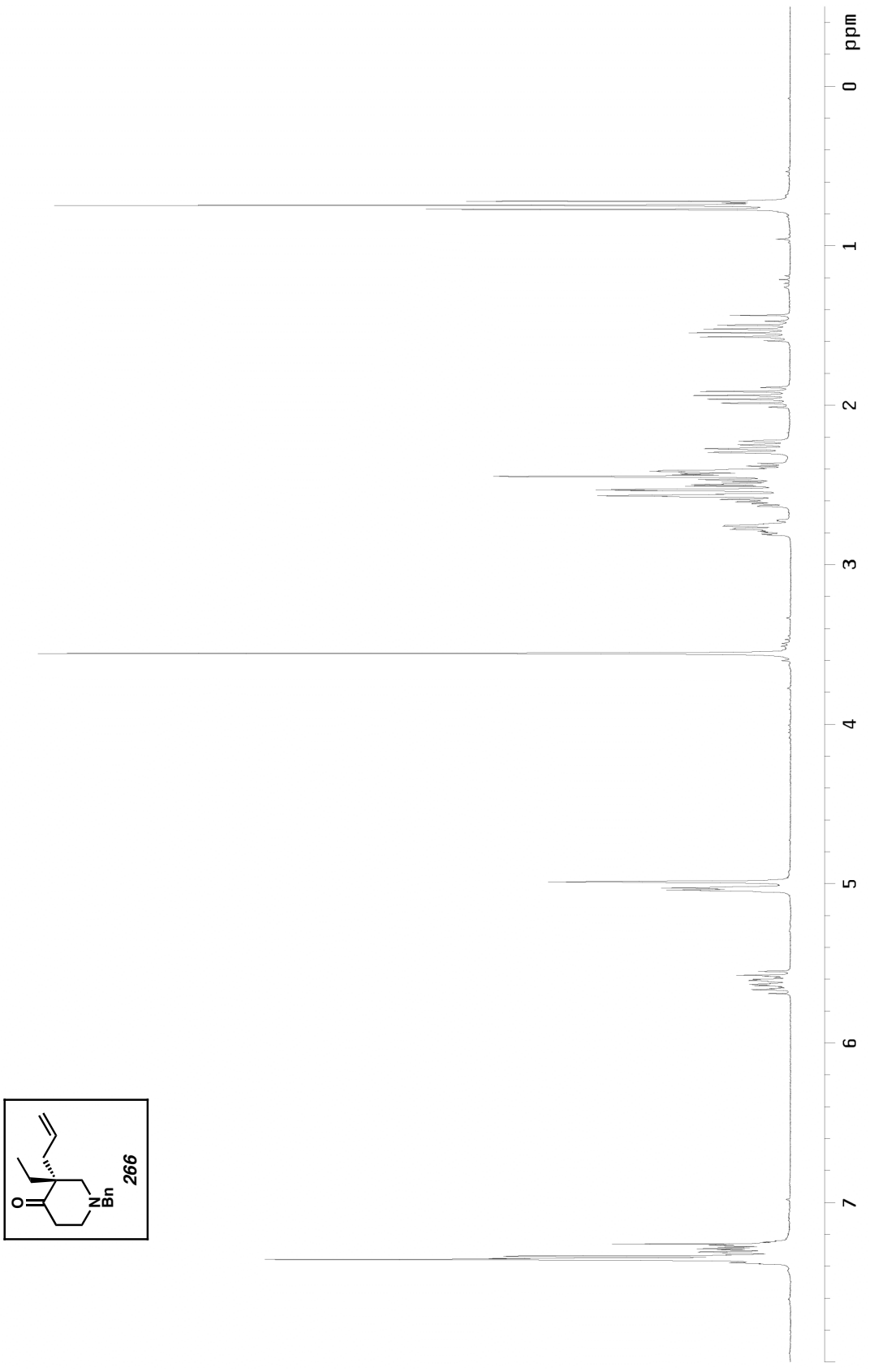


*Figure A2.157 ^1H NMR of compound **266** (300 MHz, $CDCl_3$)*

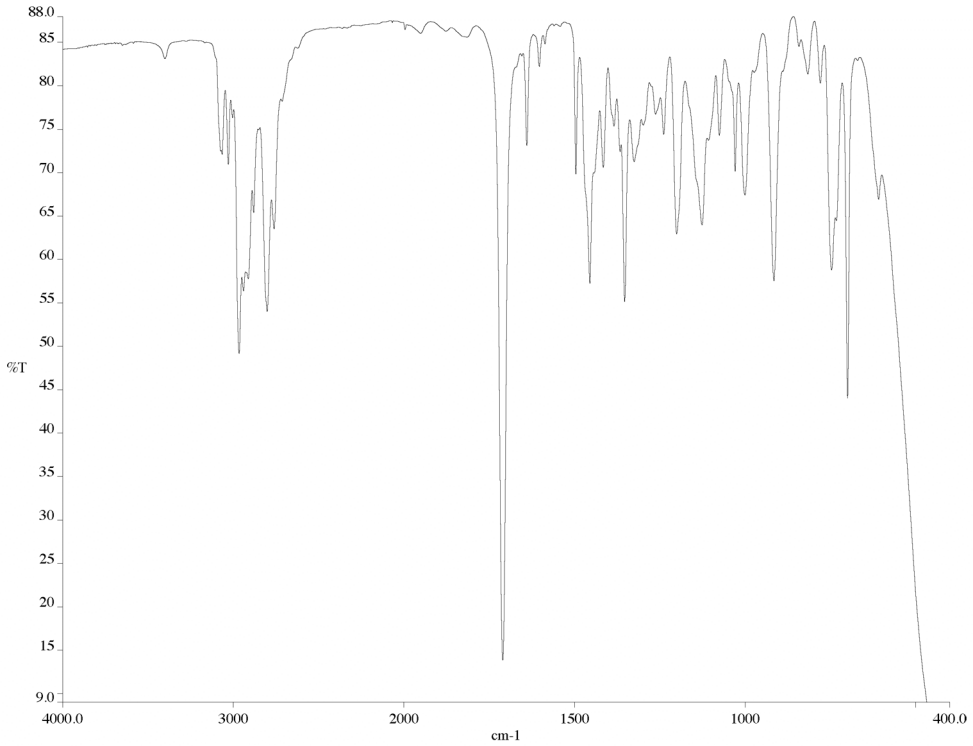


*Figure A2.158 IR of compound **266** (NaCl/film)*

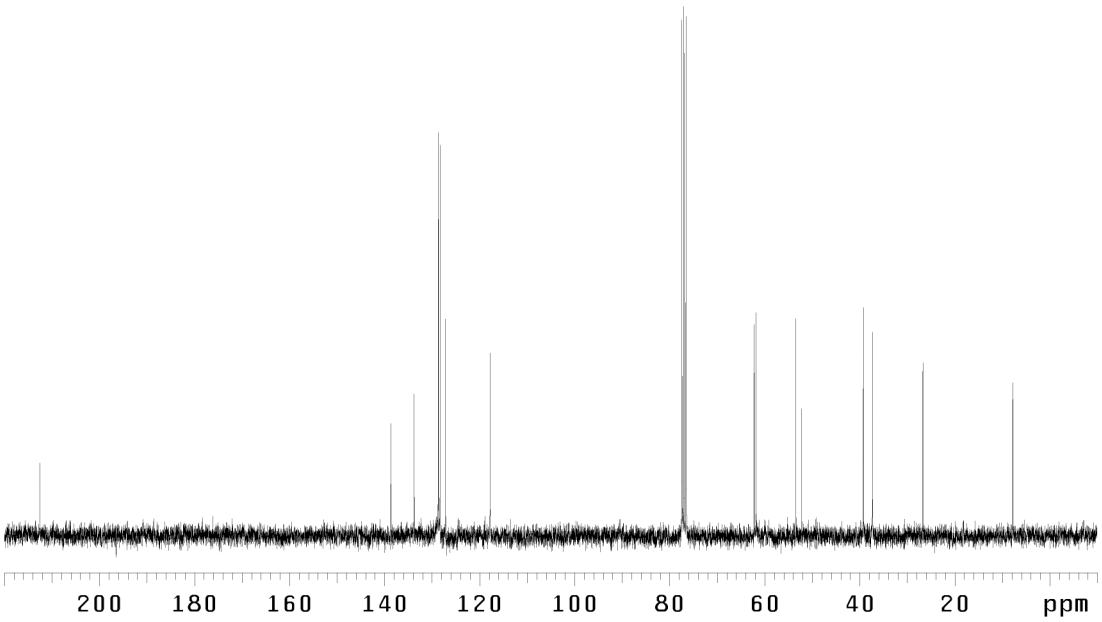


*Figure A2.159 ^{13}C NMR of compound **266** (75 MHz, $CDCl_3$)*



*Figure A2.160 ^1H NMR spectrum of compound **267** (500 MHz, $CDCl_3$)*

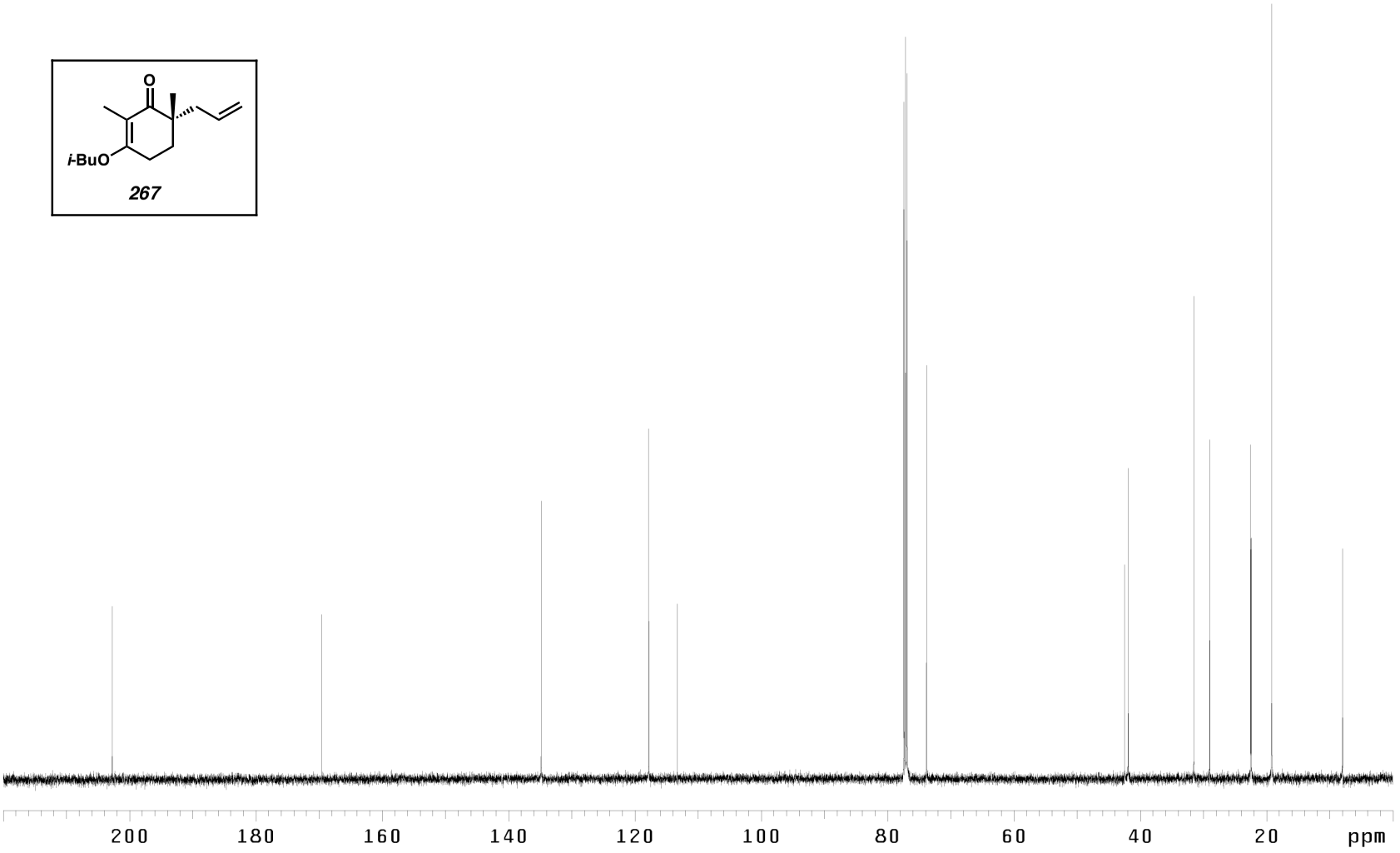


Figure A2.161 ^{13}C *NMR spectrum of compound* ***267*** *(126 MHz,* $CDCl_3$*)*

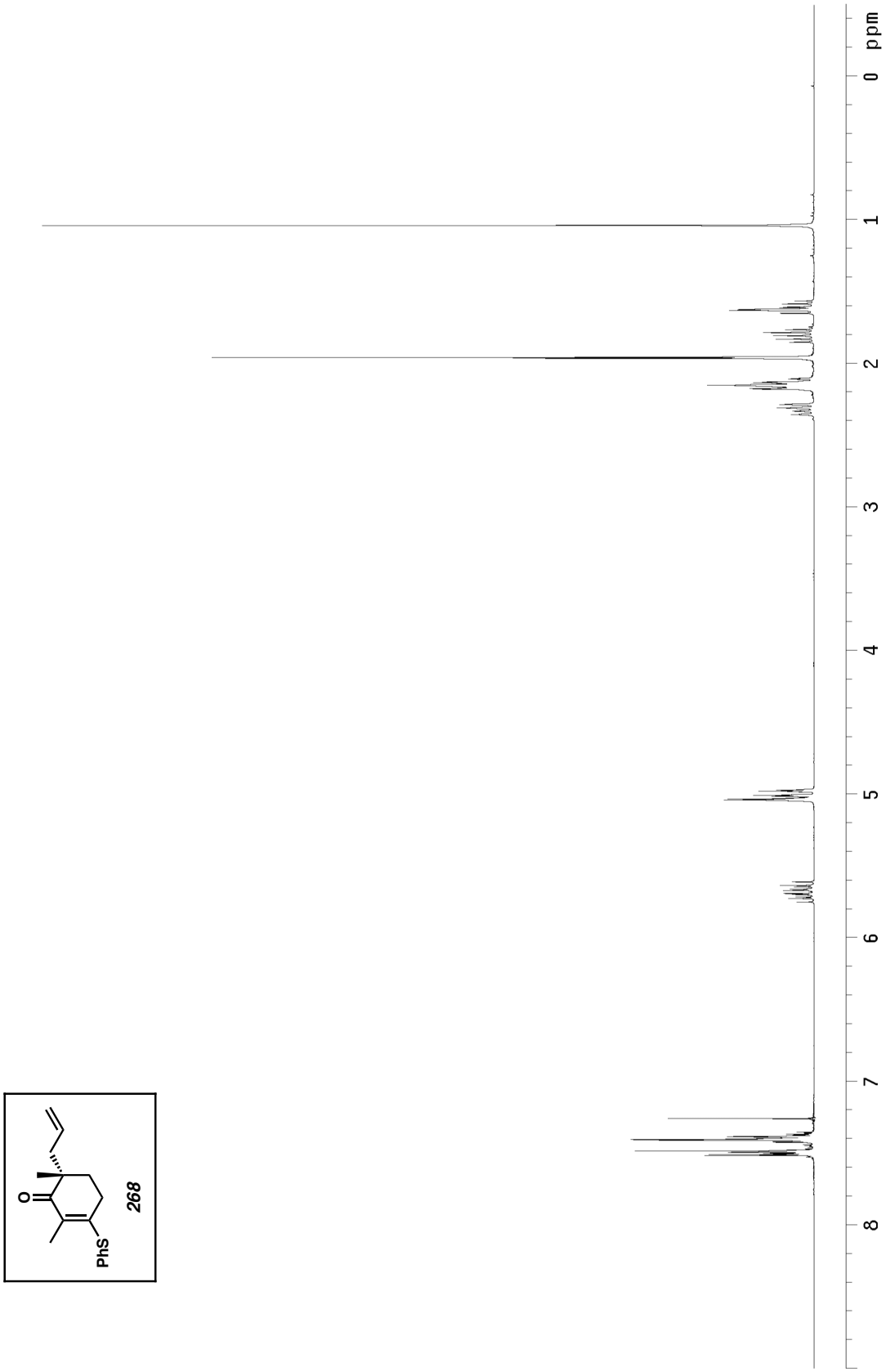


*Figure A2.162 ^{1}H NMR spectrum of compound **268** (300 MHz, $CDCl_3$)*

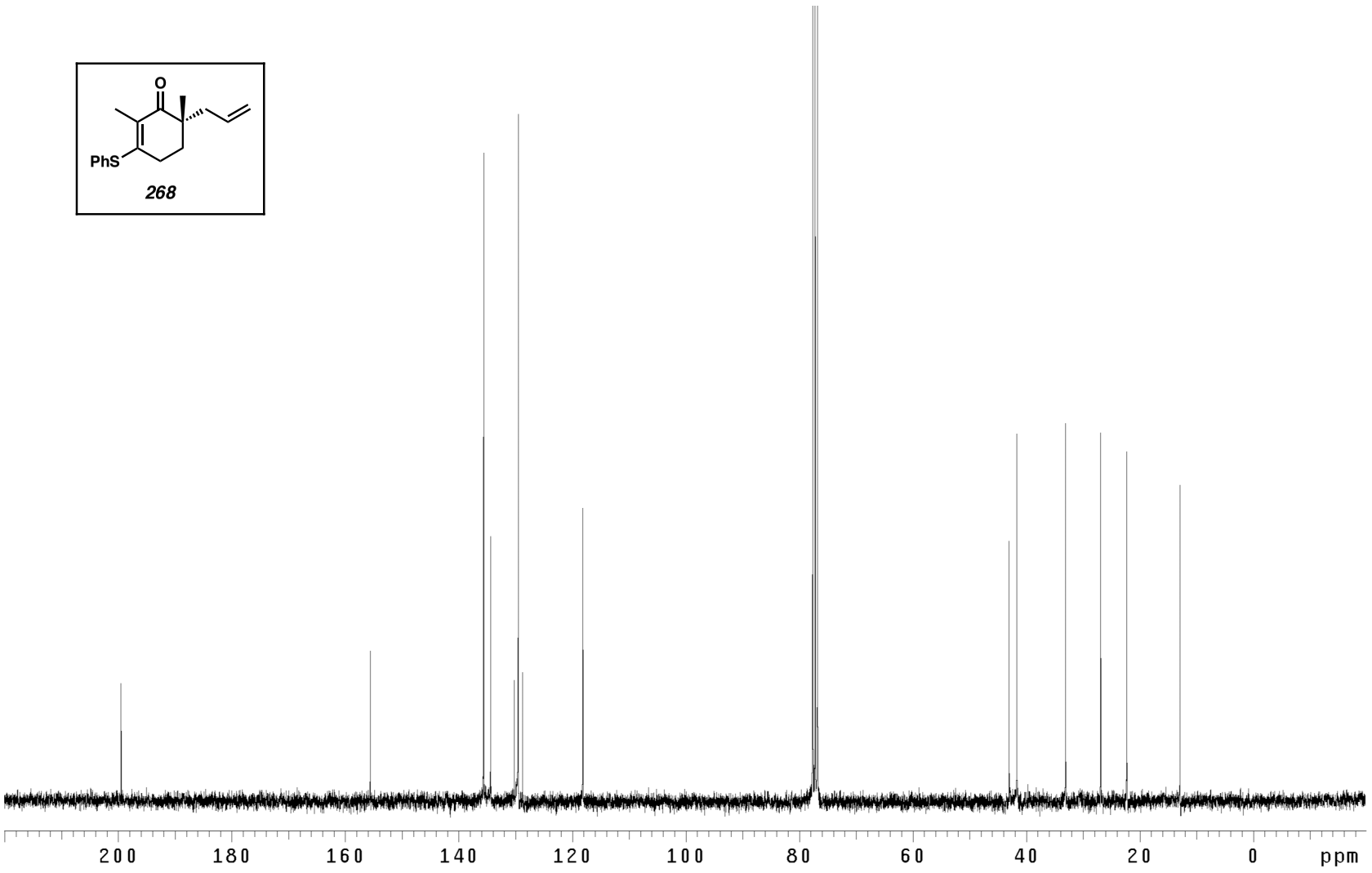


Figure A2.163 ^{13}C *NMR spectrum of compound* ***268*** *(75 MHz,* $CDCl_3$*)*

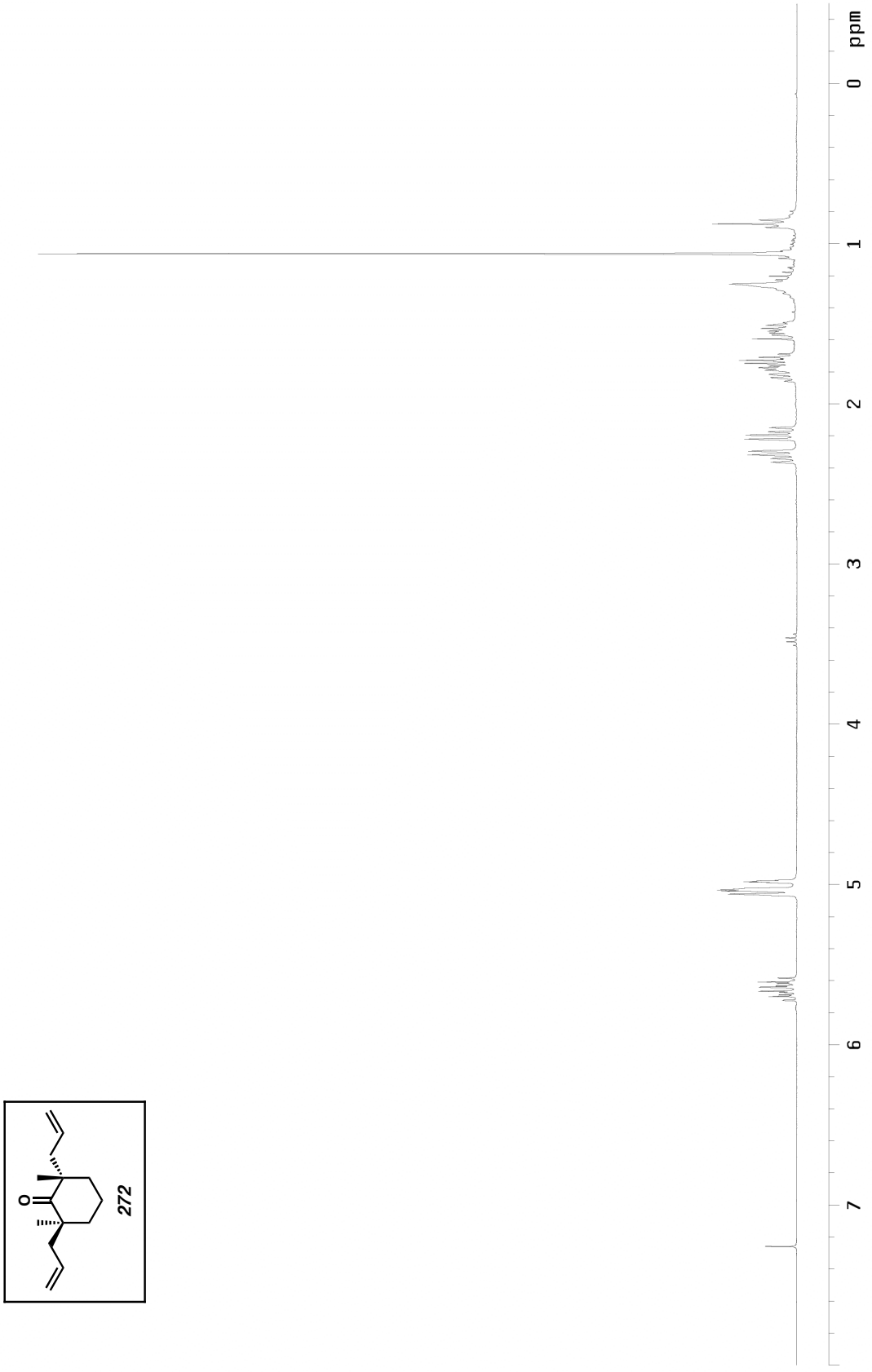


Figure A2.164 ^1H NMR of compound **272** *(300 MHz, $CDCl_3$)*

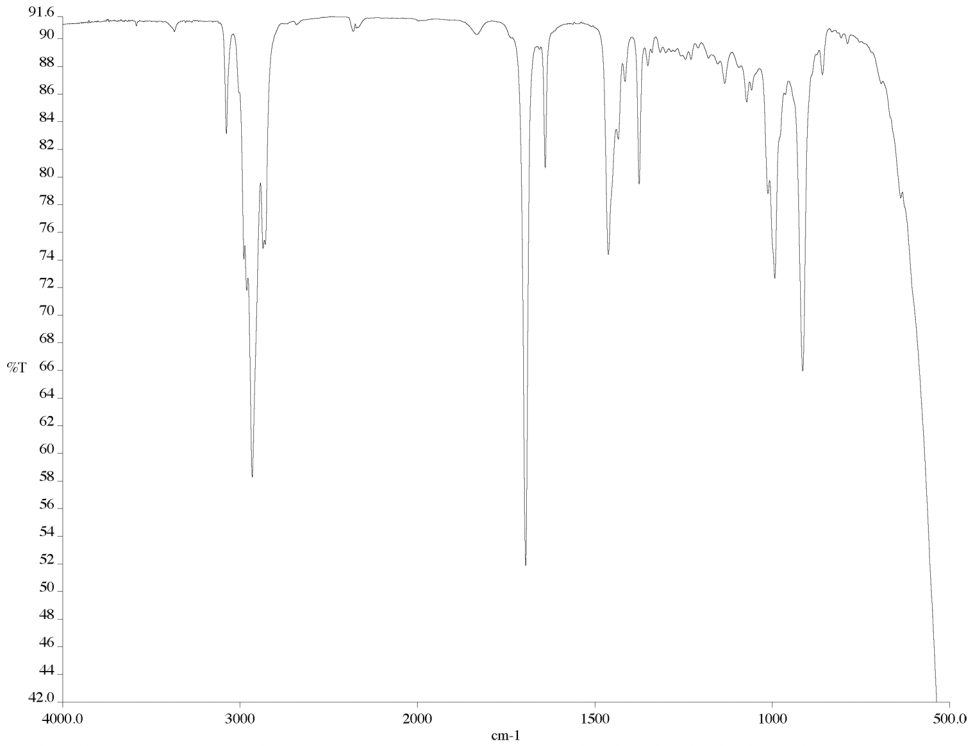


*Figure A2.165 IR of compound **272** (NaCl/film)*

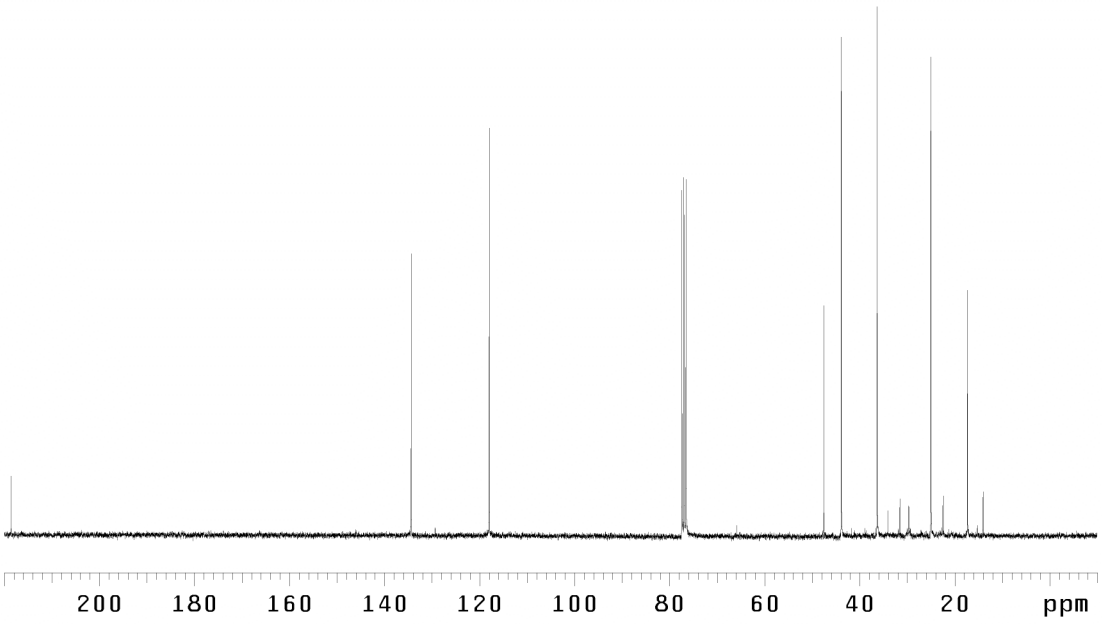


*Figure A2.166 ^{13}C NMR of compound **272** (75 MHz, $CDCl_3$)*

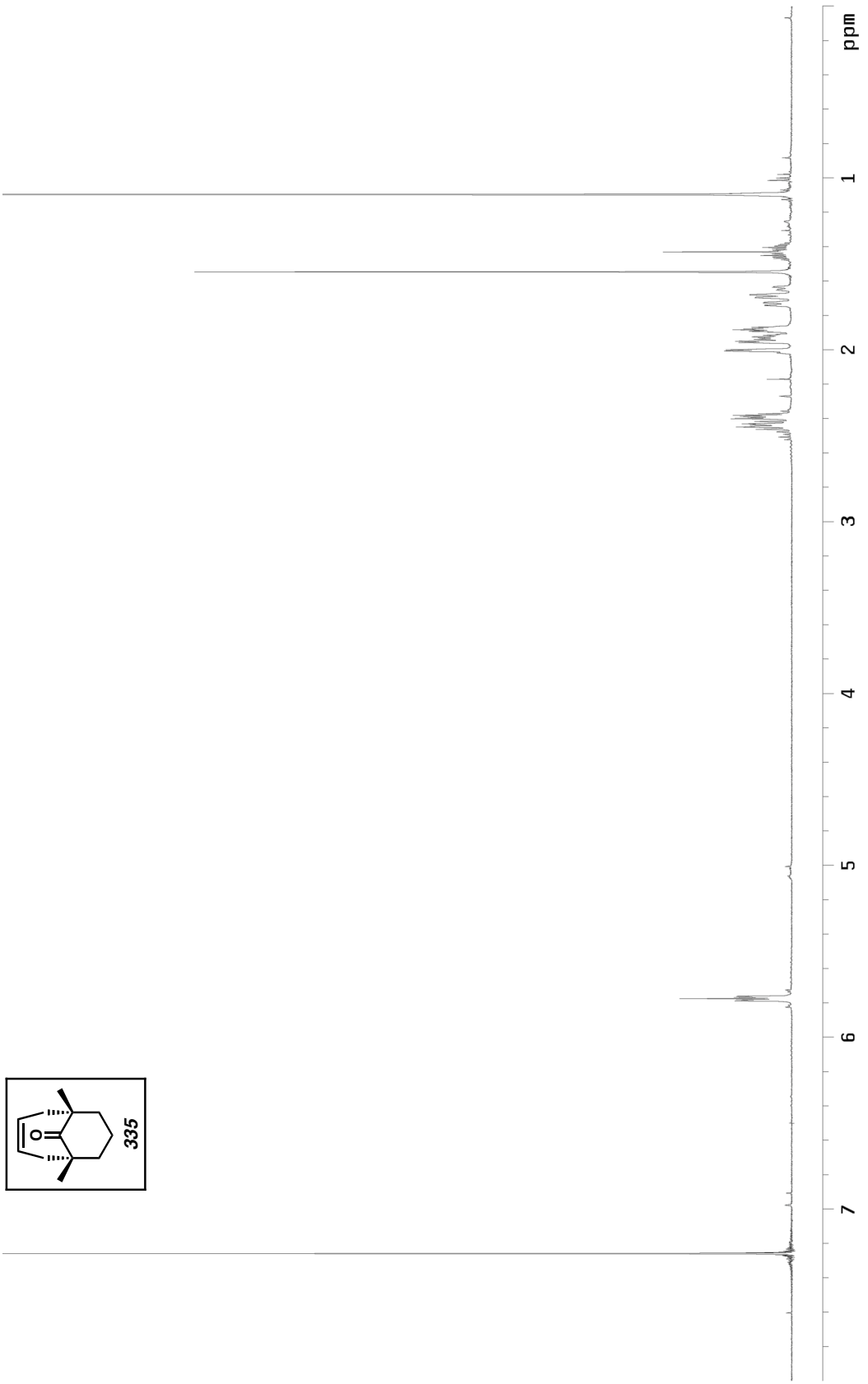


*Figure A2.167 ^{1}H NMR of compound **335** (300 MHz, $CDCl_3$)*

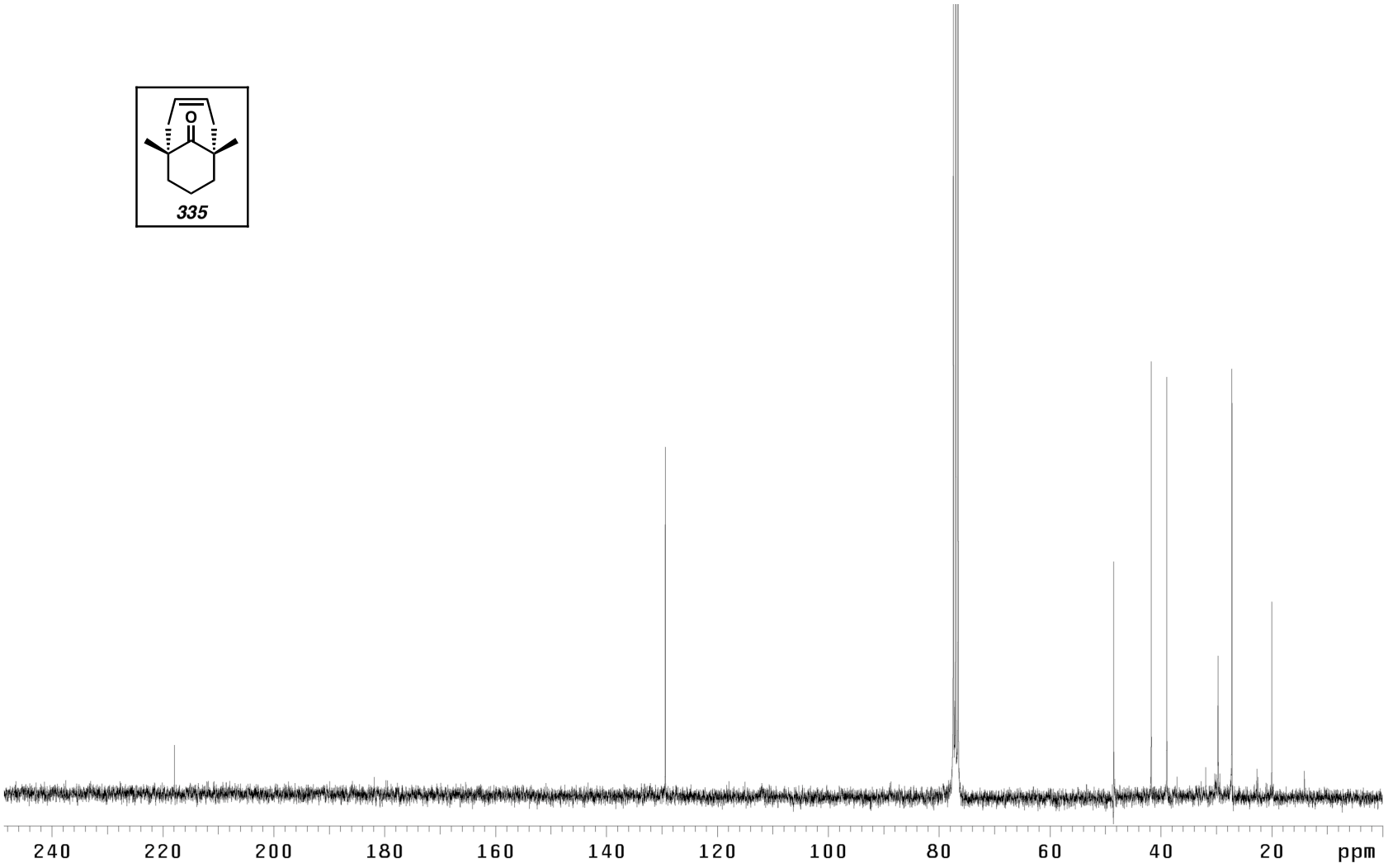


Figure A2.168 ^{13}C *NMR of compound* ***335*** *(75 MHz,* $CDCl_3$*)*

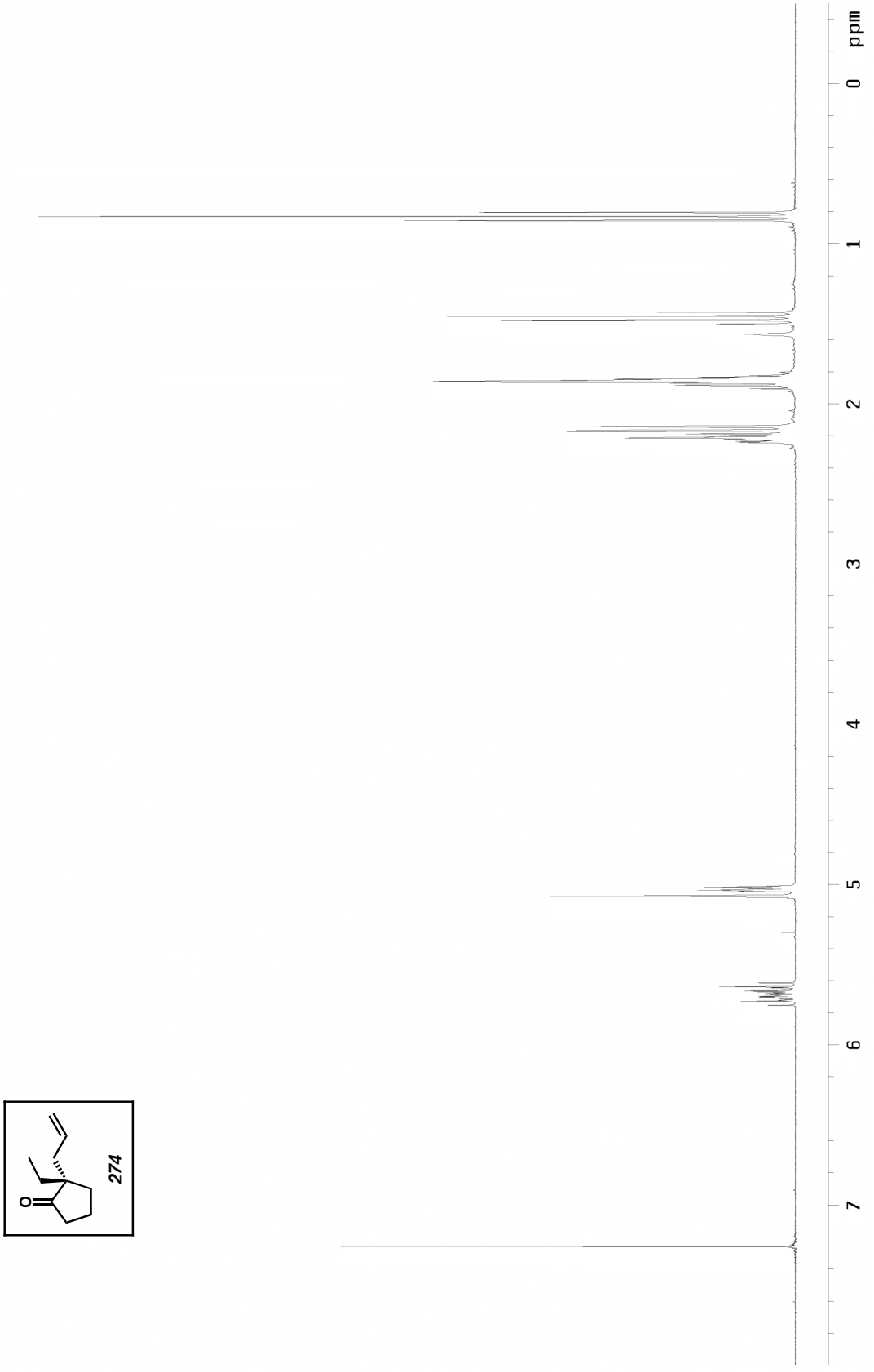


*Figure A2.169 ^1H NMR of compound **274** (300 MHz, $CDCl_3$)*

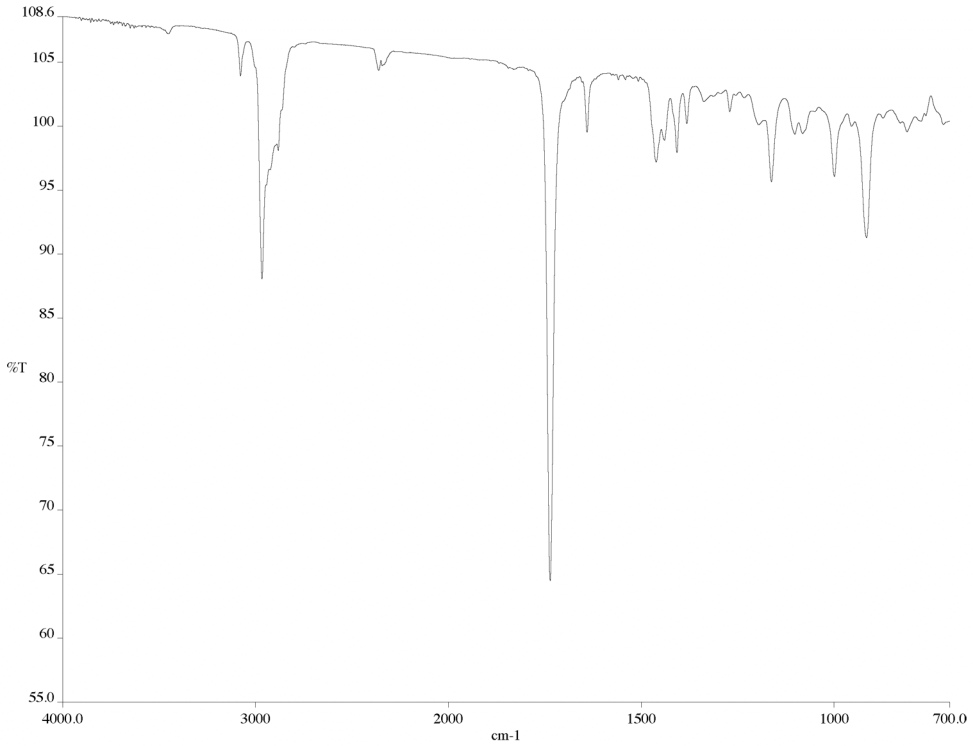


*Figure A2.170 IR of compound **274** (NaCl/film)*

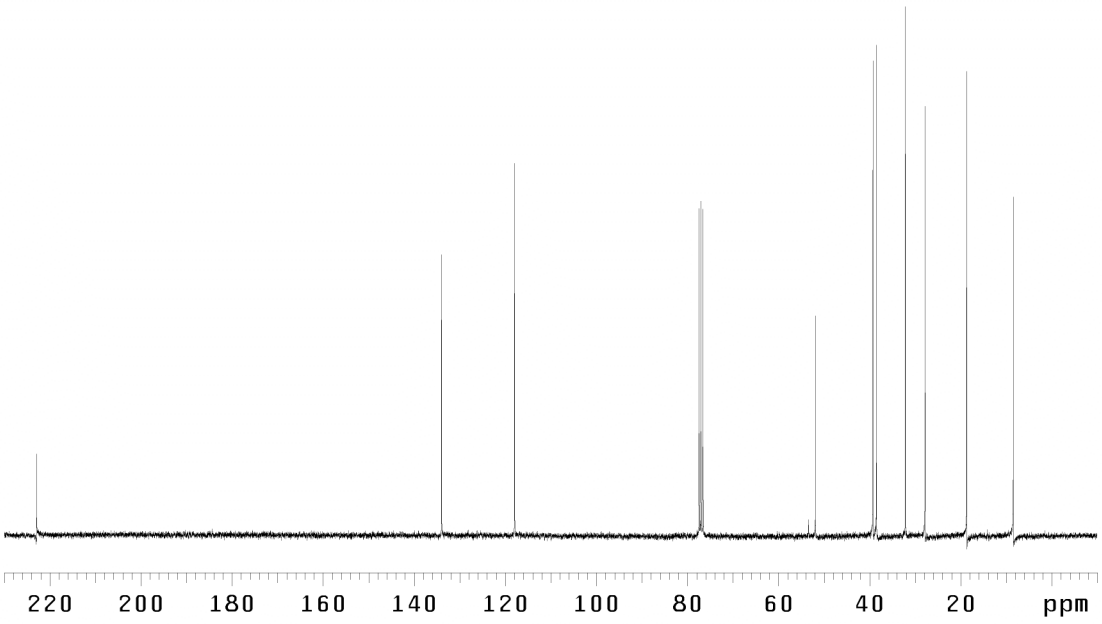


*Figure A2.171 ^{13}C NMR of compound **274** (75 MHz, $CDCl_3$)*

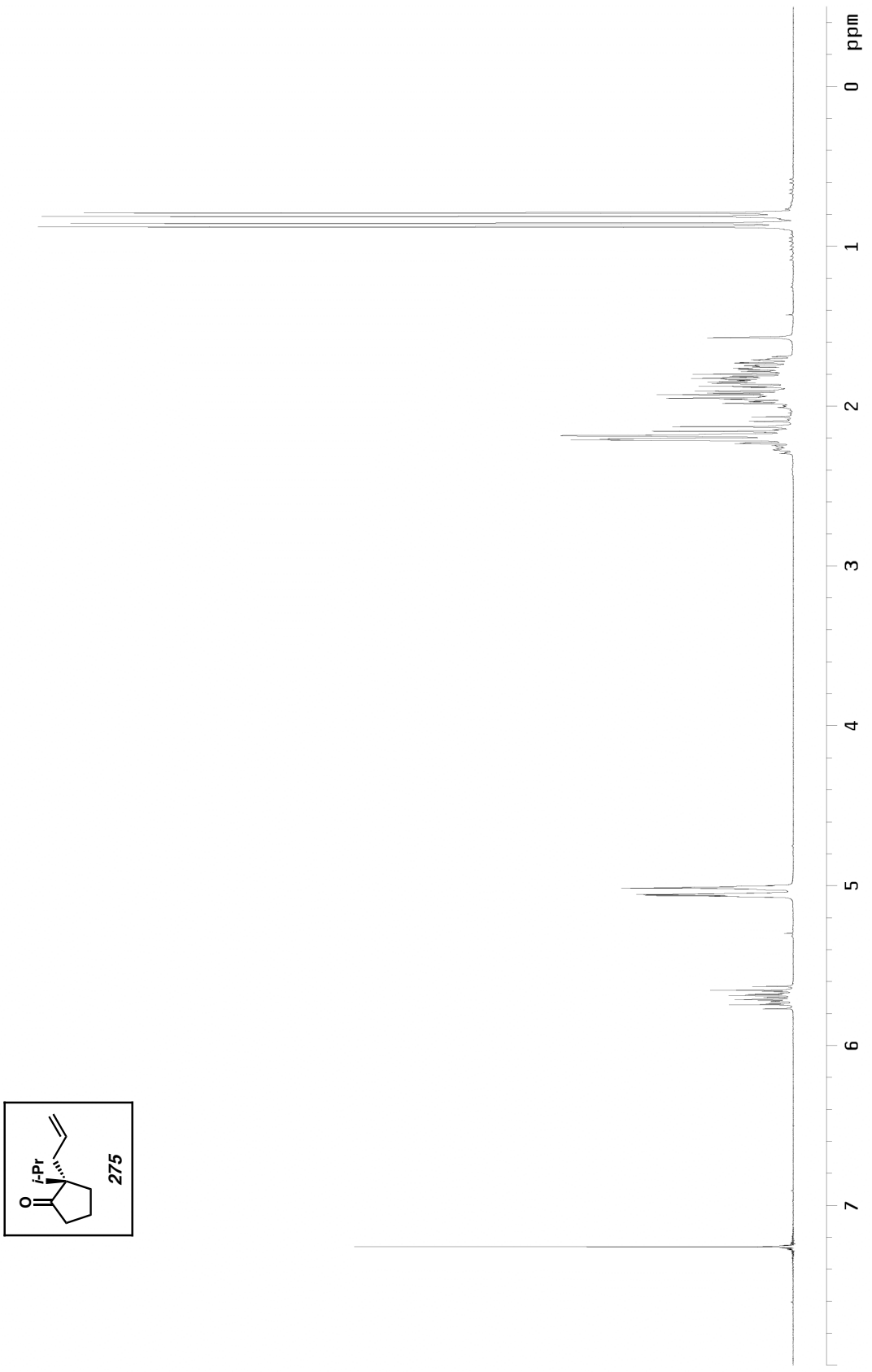


Figure A2.172 ^1H NMR of compound ***275*** *(300 MHz, $CDCl_3$)*

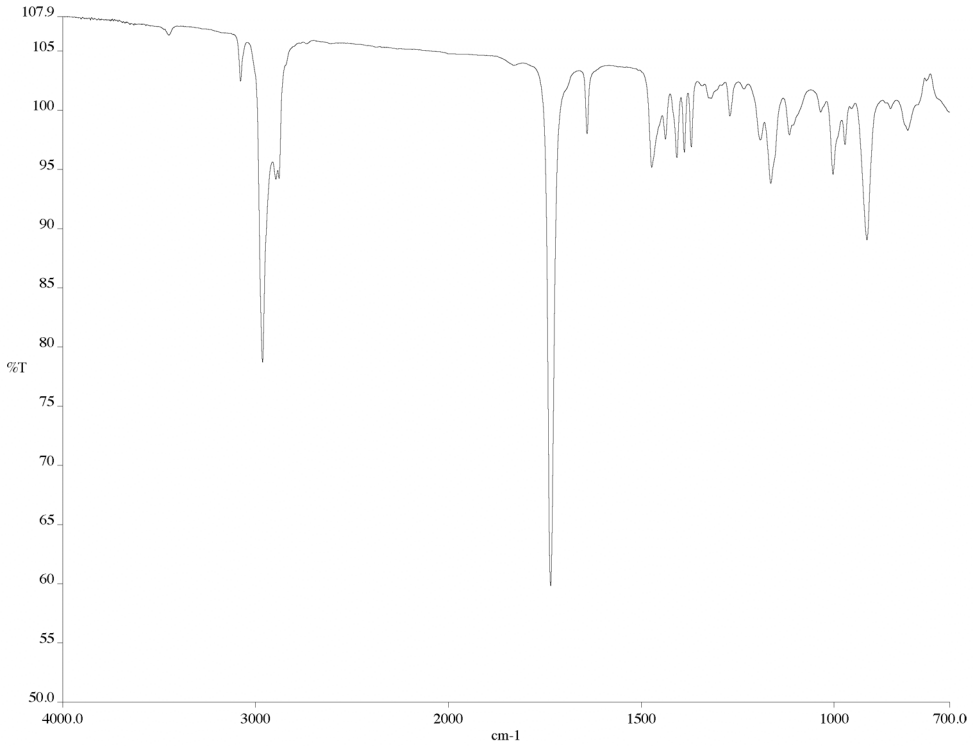


*Figure A2.173 IR of compound **275** (NaCl/film)*

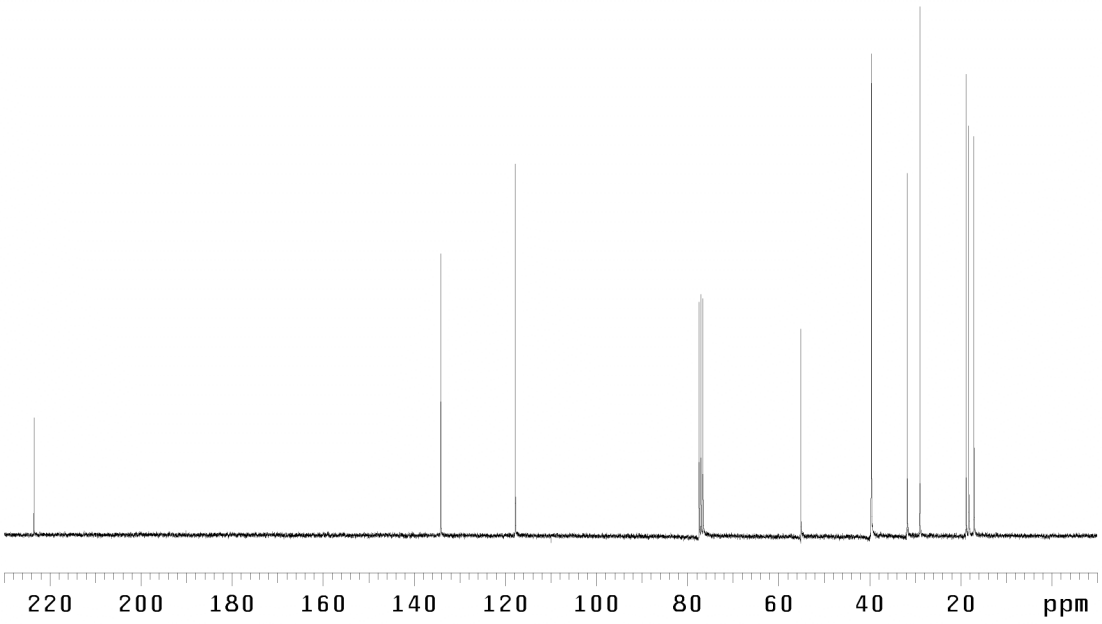


*Figure A2.174 ^{13}C NMR of compound **275** (75 MHz, $CDCl_3$)*

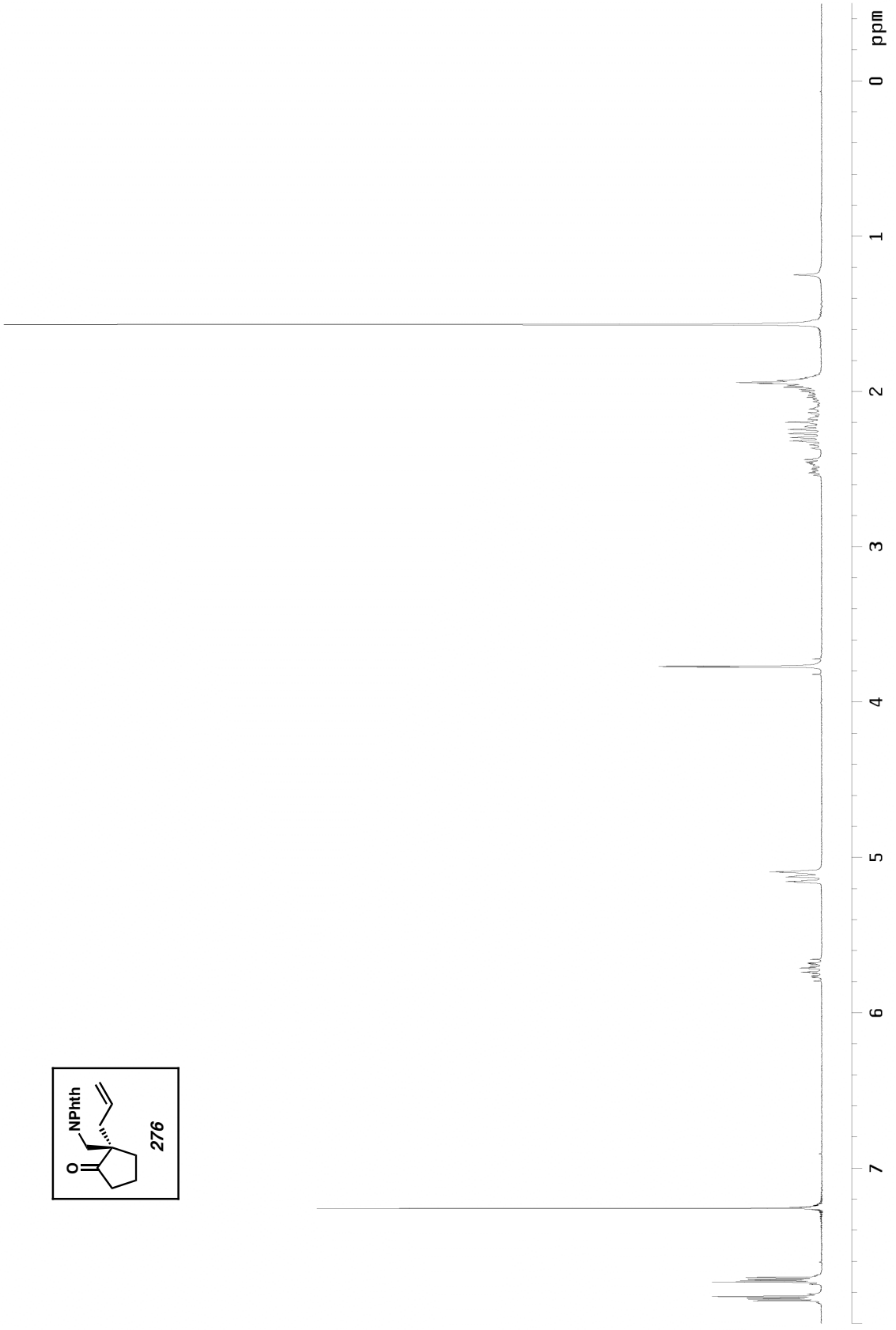


Figure A2.175 ^1H NMR of compound **276** *(300 MHz, $CDCl_3$)*

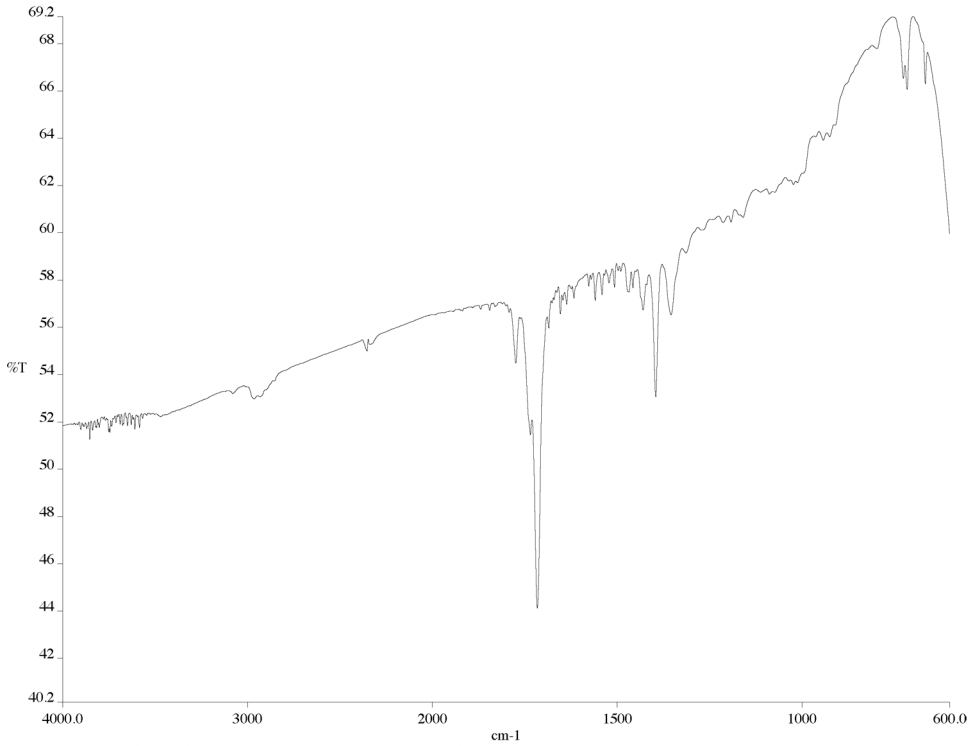


*Figure A2.176 IR of compound **276** (NaCl/film)*

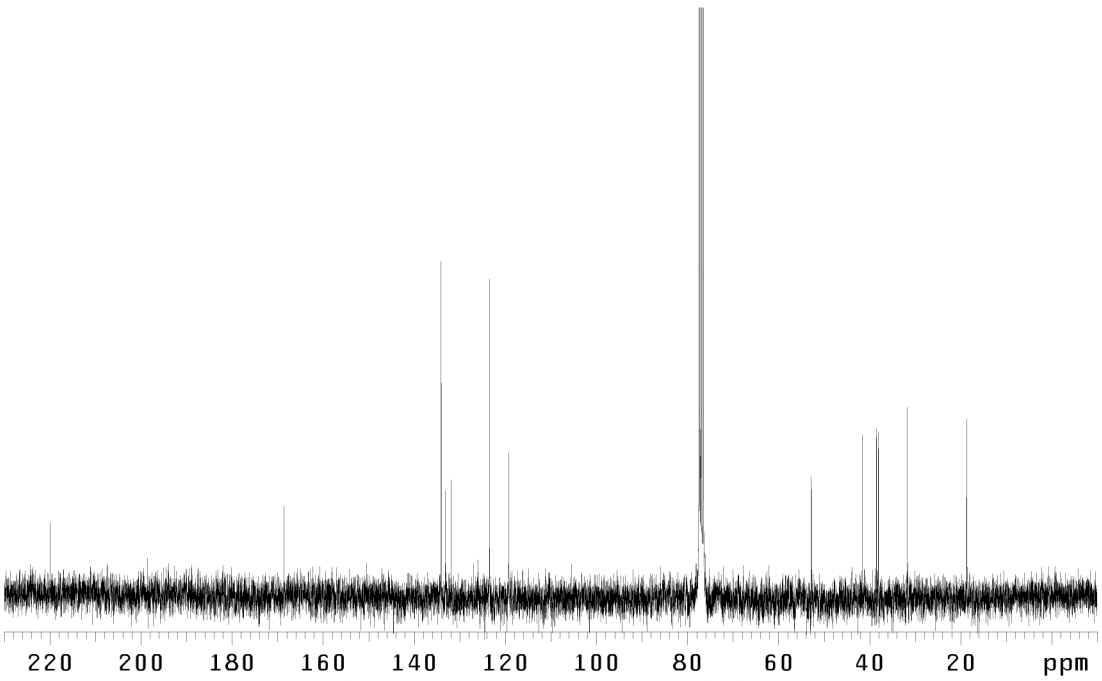


*Figure A2.177 ^{13}C NMR of compound **276** (75 MHz, $CDCl_3$)*

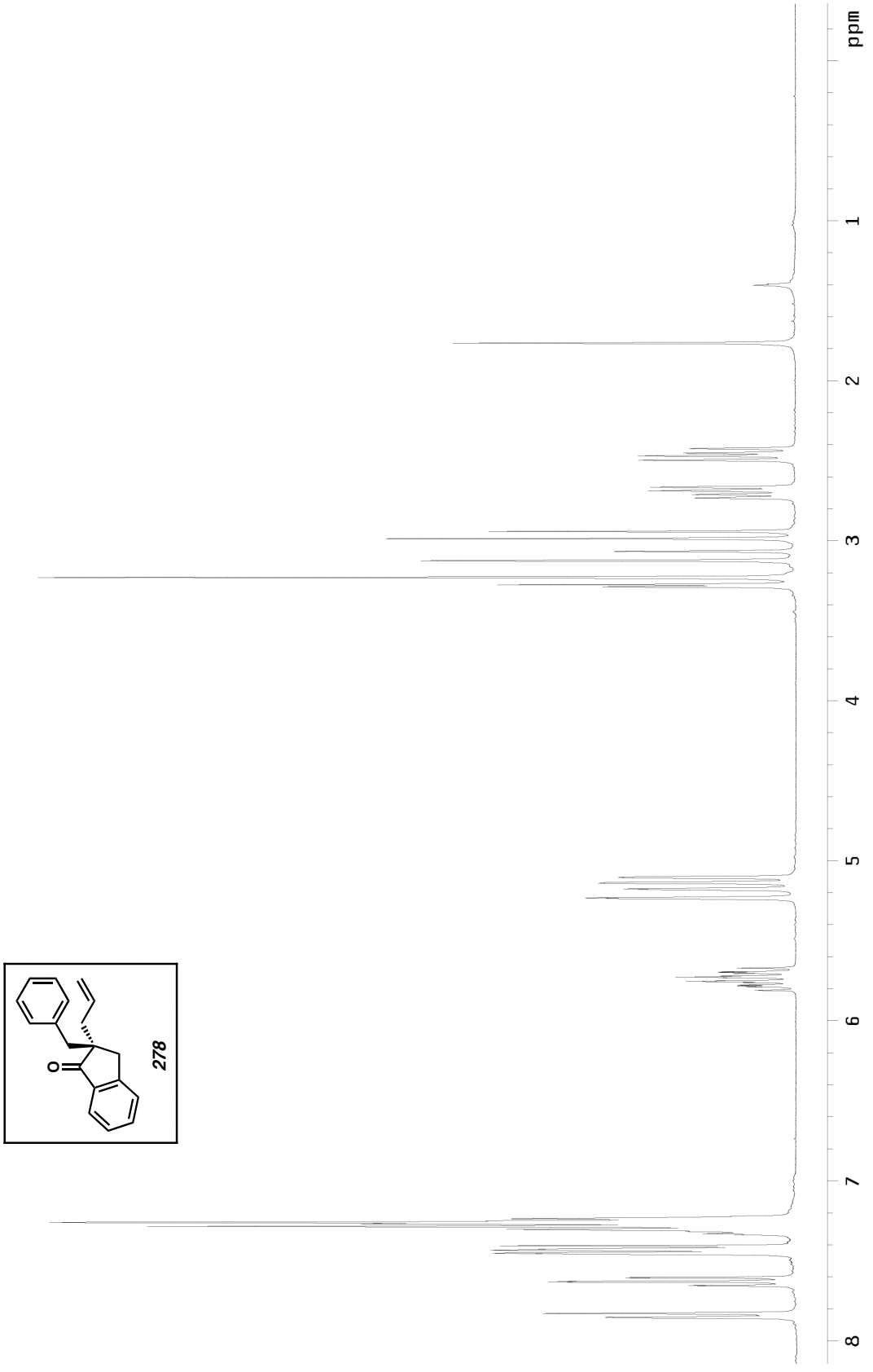


*Figure A2.178 ^{1}H NMR of compound **278** (300 MHz, $CDCl_3$)*

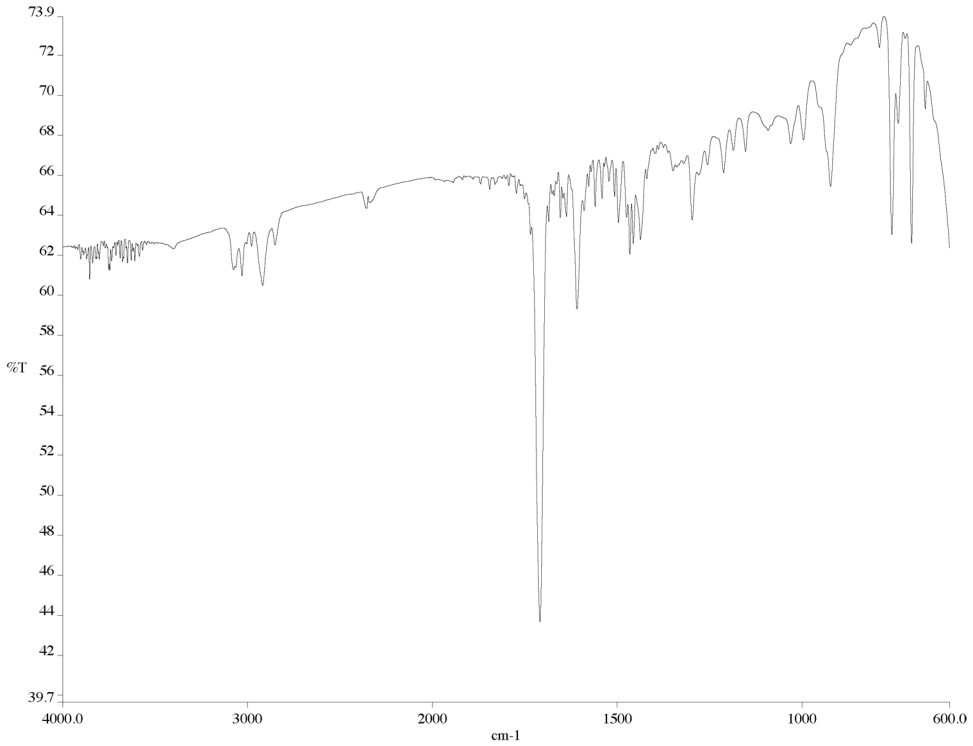


*Figure A2.179 IR of compound **278** (NaCl/film)*

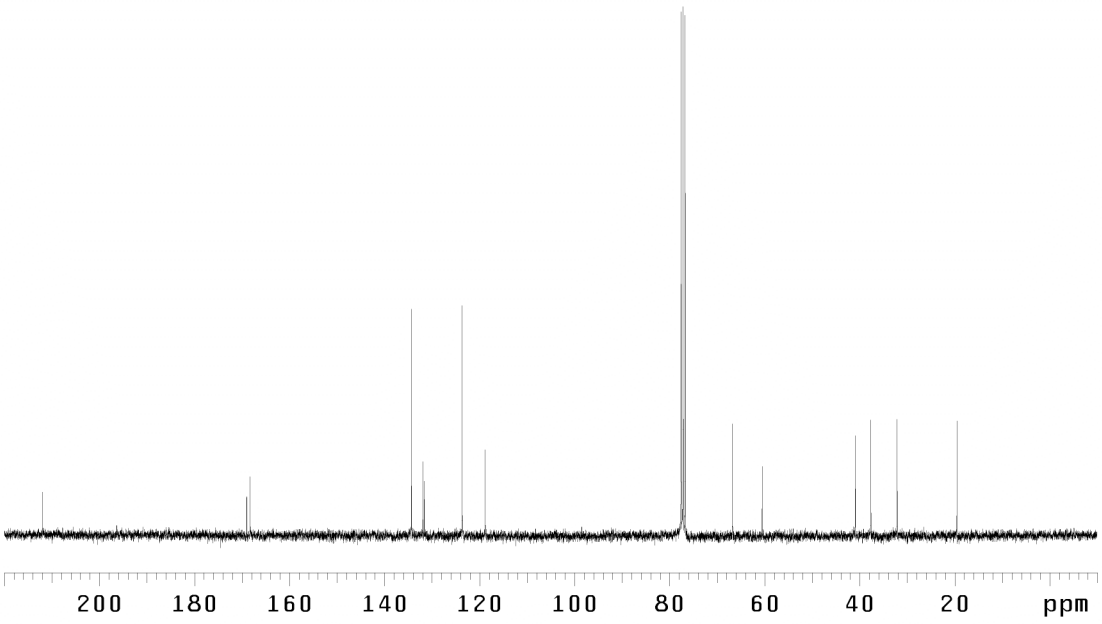


*Figure A2.180 ^{13}C NMR of compound **278** (75 MHz, $CDCl_3$)*

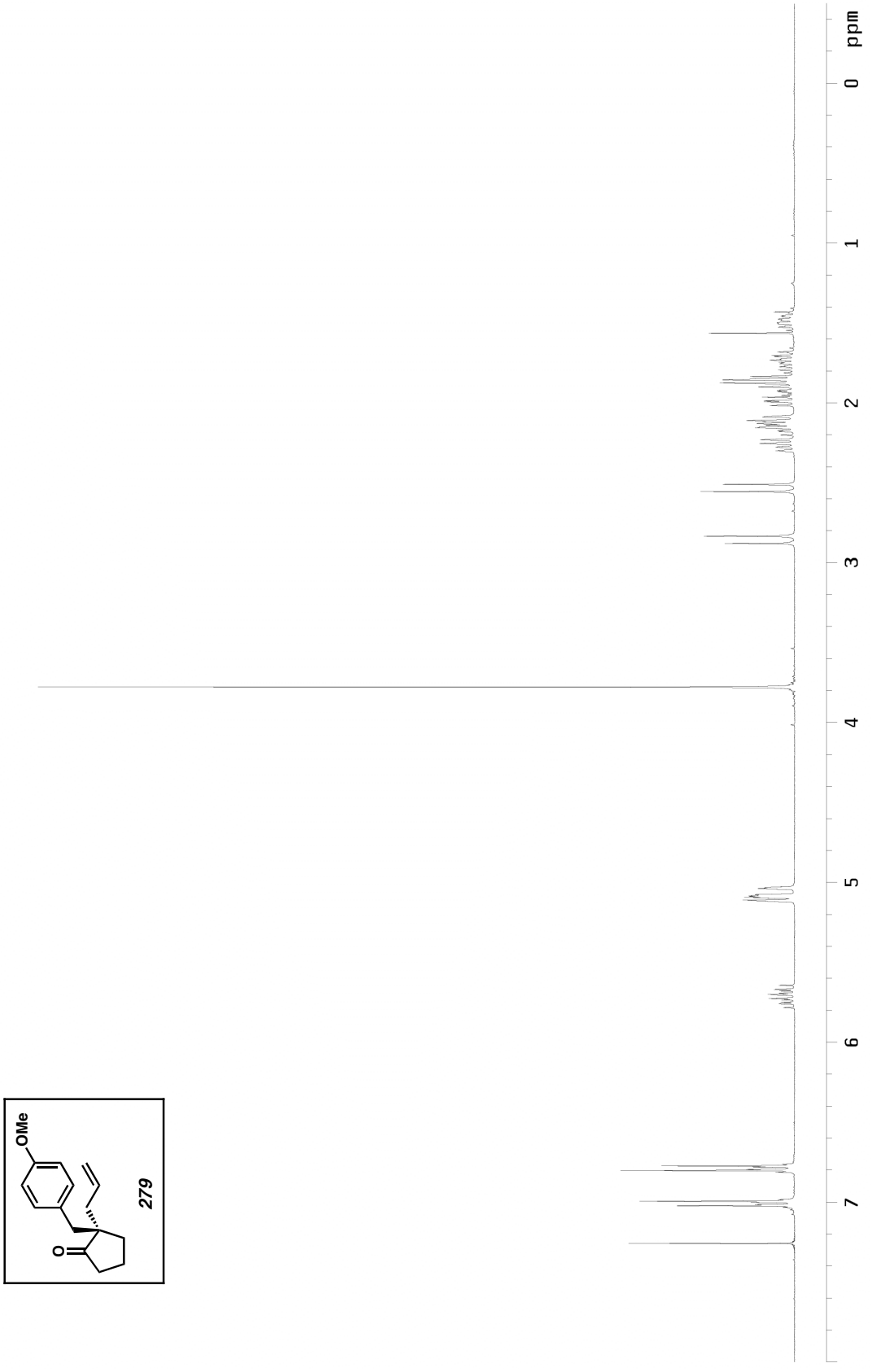


*Figure A2.181 ^1H NMR of compound **279** (300 MHz, $CDCl_3$)*

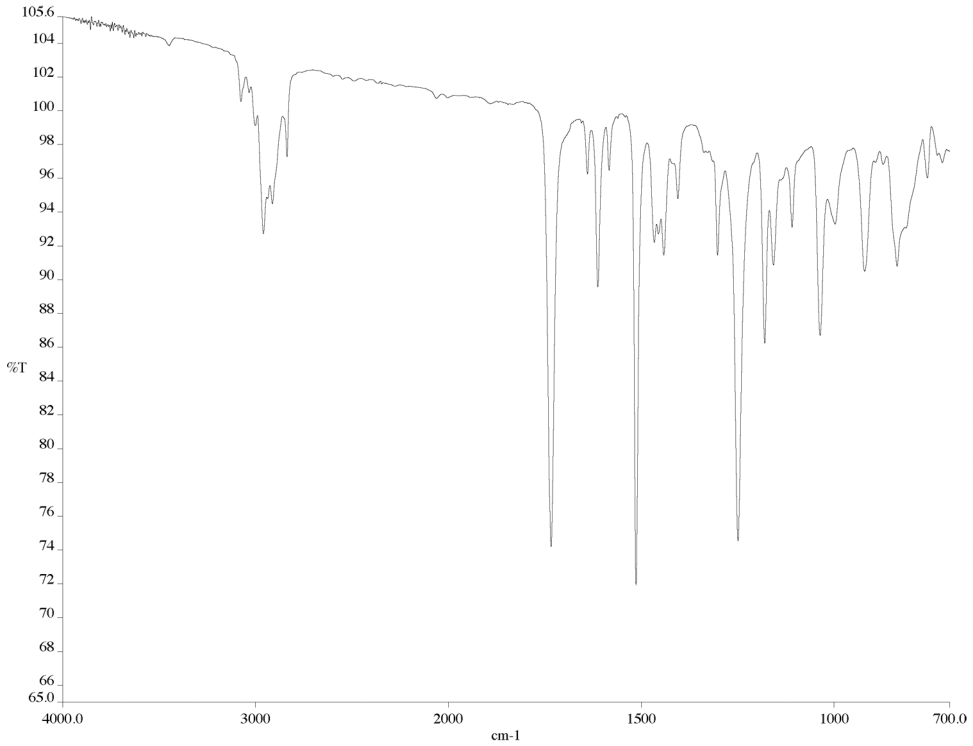


*Figure A2.182 IR of compound **279** (NaCl/film)*

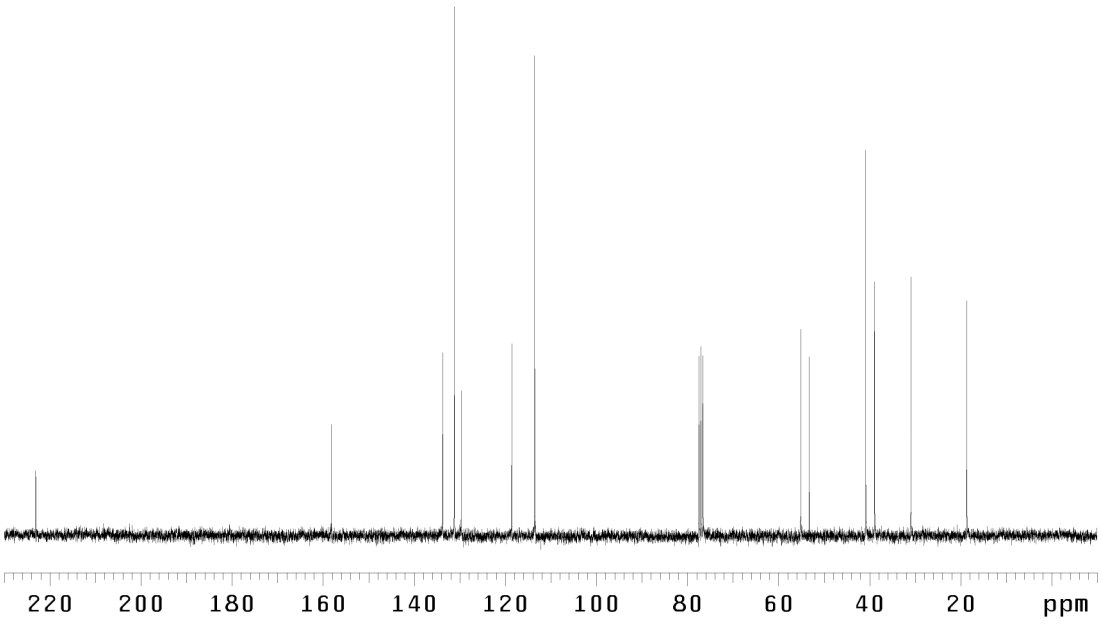


*Figure A2.183 ^{13}C NMR of compound **279** (75 MHz, $CDCl_3$)*

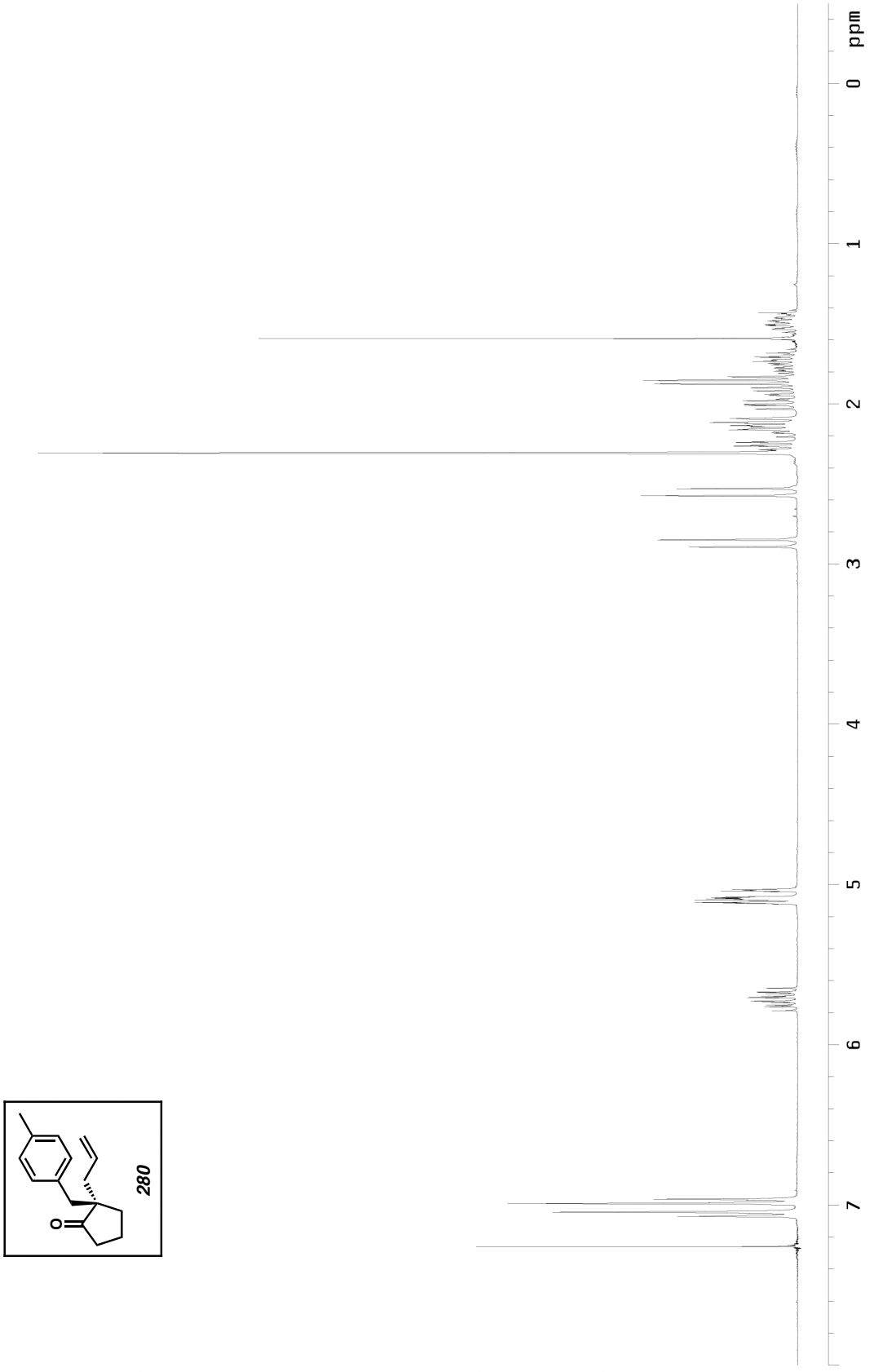


*Figure A2.184 ^1H NMR of compound **280** (300 MHz, $CDCl_3$)*

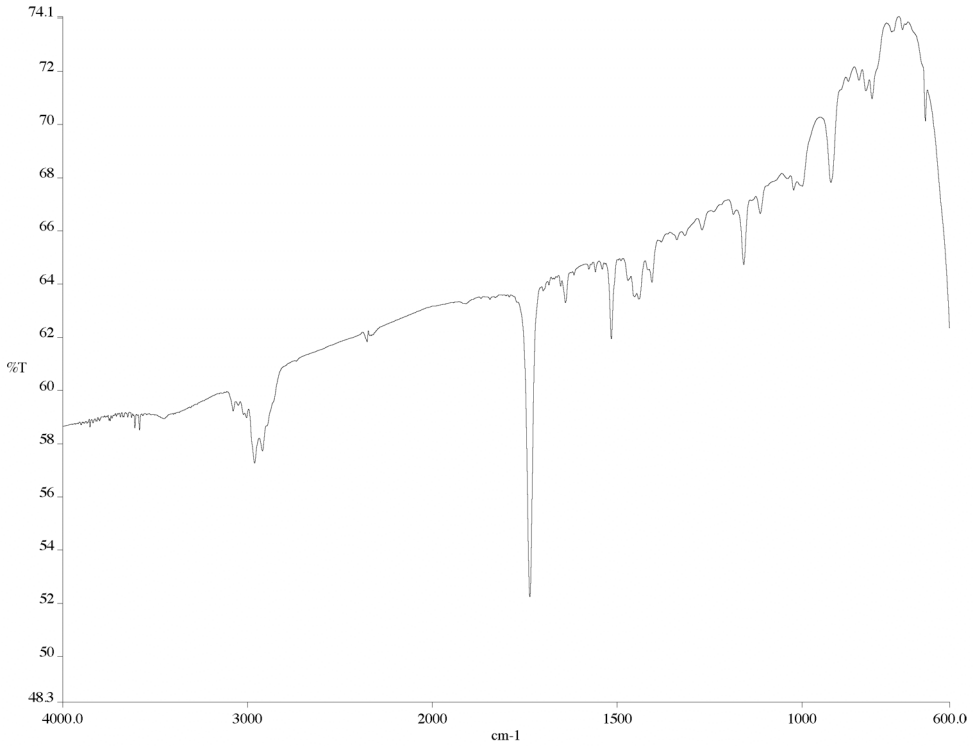


*Figure A2.185 IR of compound **280** (NaCl/film)*

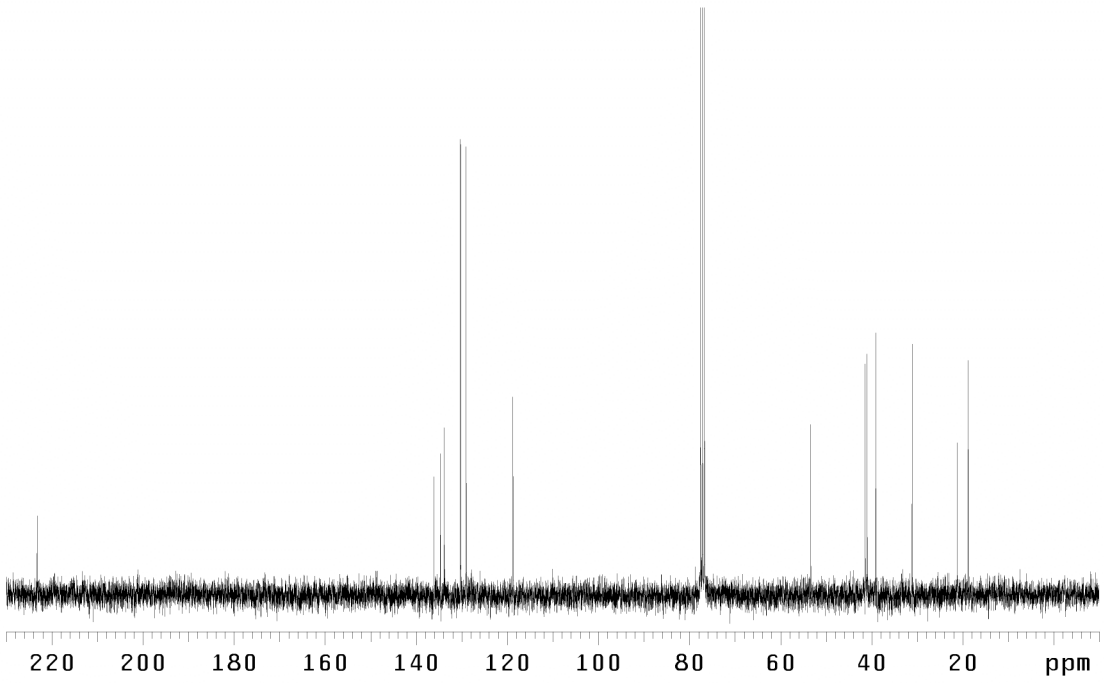


*Figure A2.186 ^{13}C NMR of compound **280** (75 MHz, $CDCl_3$)*

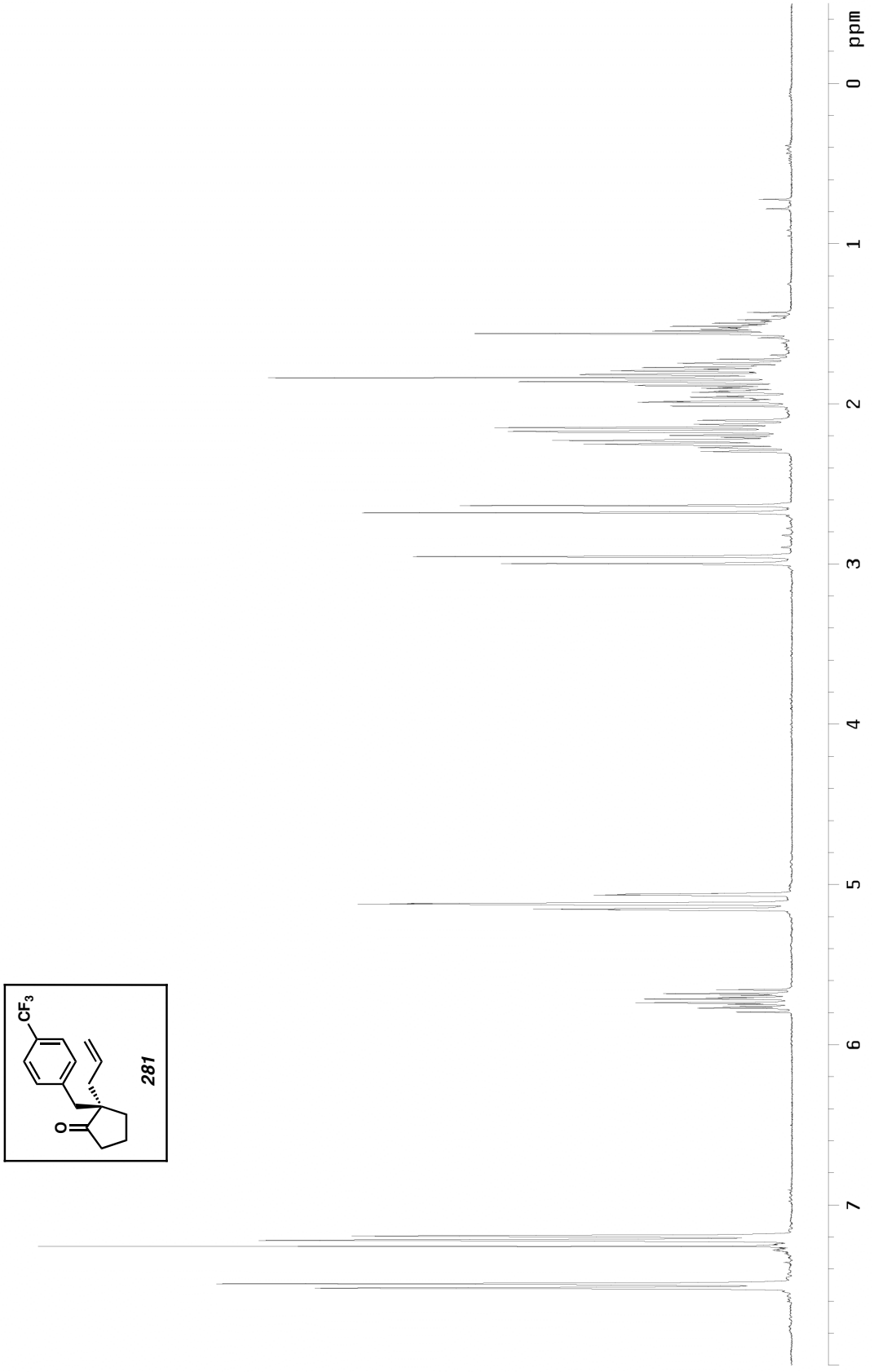


*Figure A2.187 ^1H NMR of compound **281** (300 MHz, $CDCl_3$)*

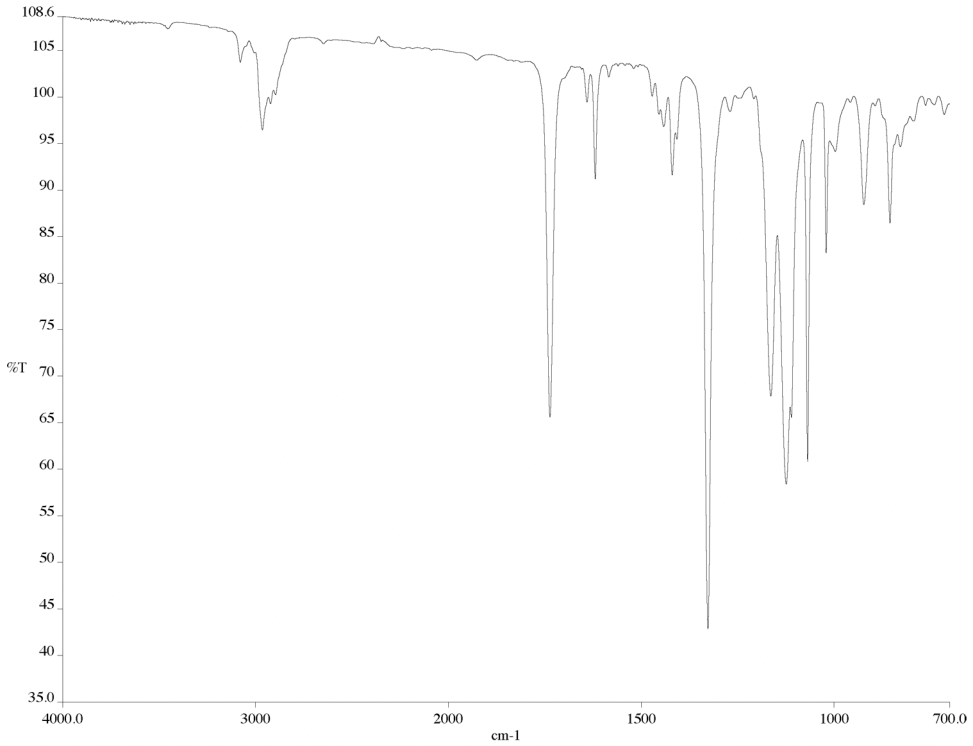


*Figure A2.188 IR of compound **281** (NaCl/film)*

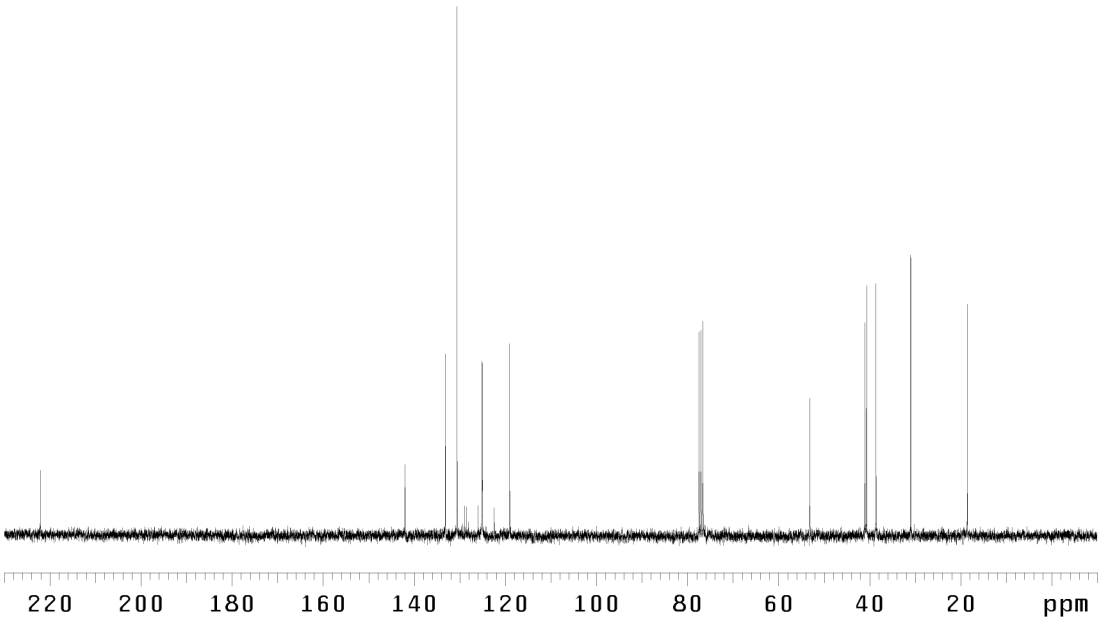


*Figure A2.189 ^{13}C NMR of compound **281** (75 MHz, $CDCl_3$)*

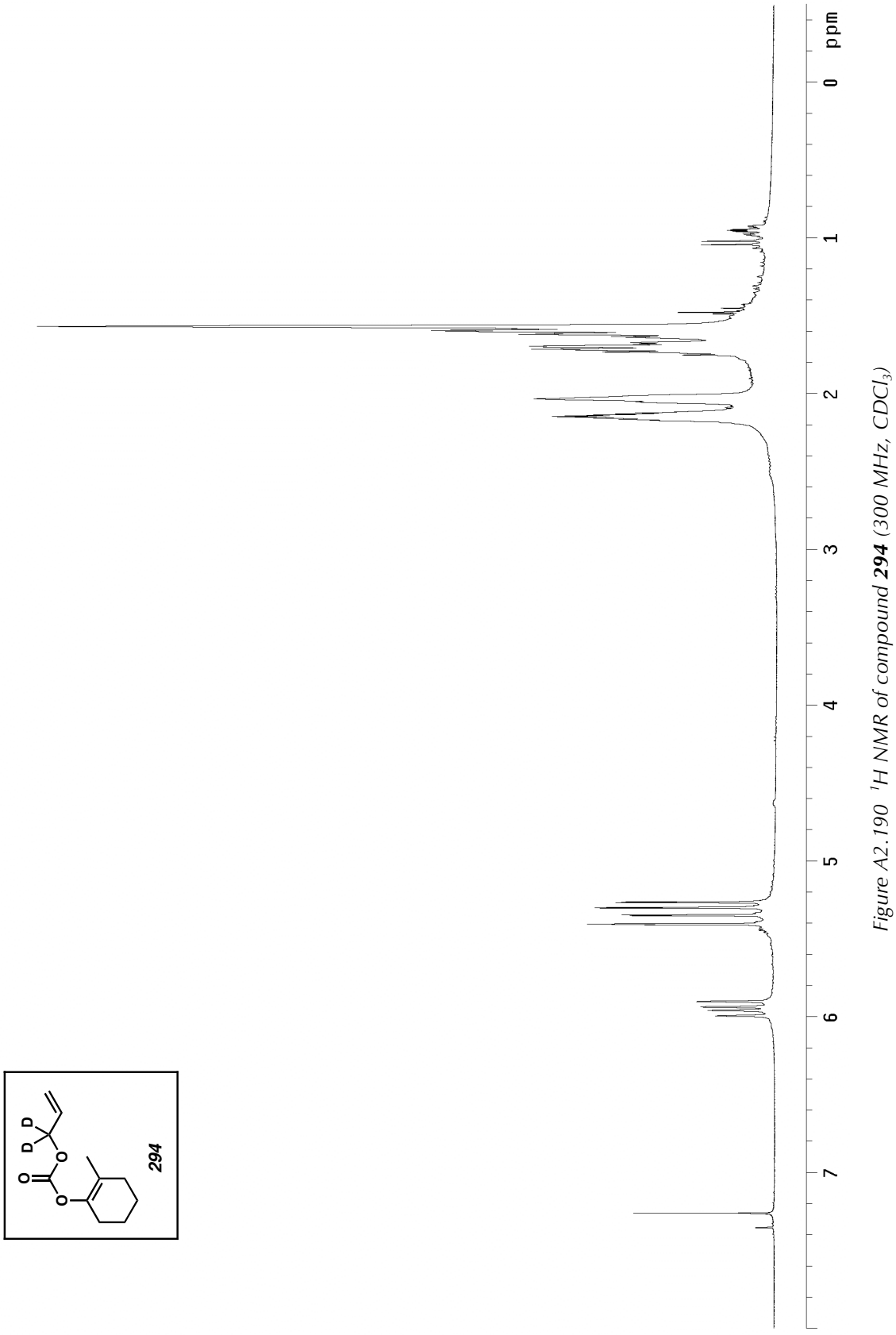


*Figure A2.190 ^1H NMR of compound **294** (300 MHz, $CDCl_3$)*

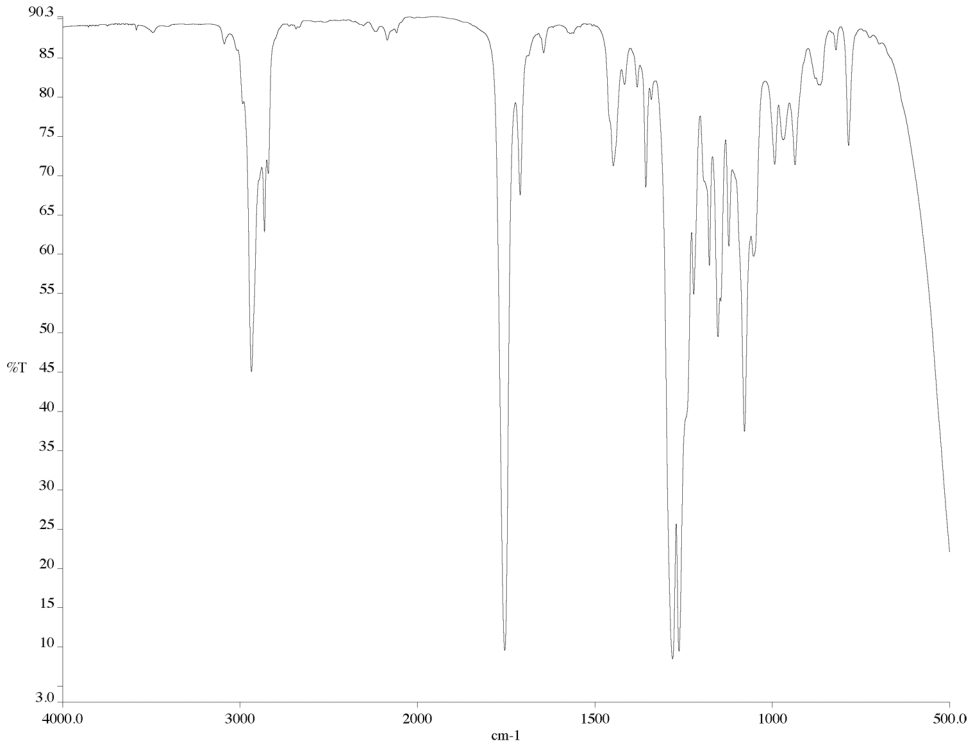


*Figure A2.191 IR of compound **294** (NaCl/film)*

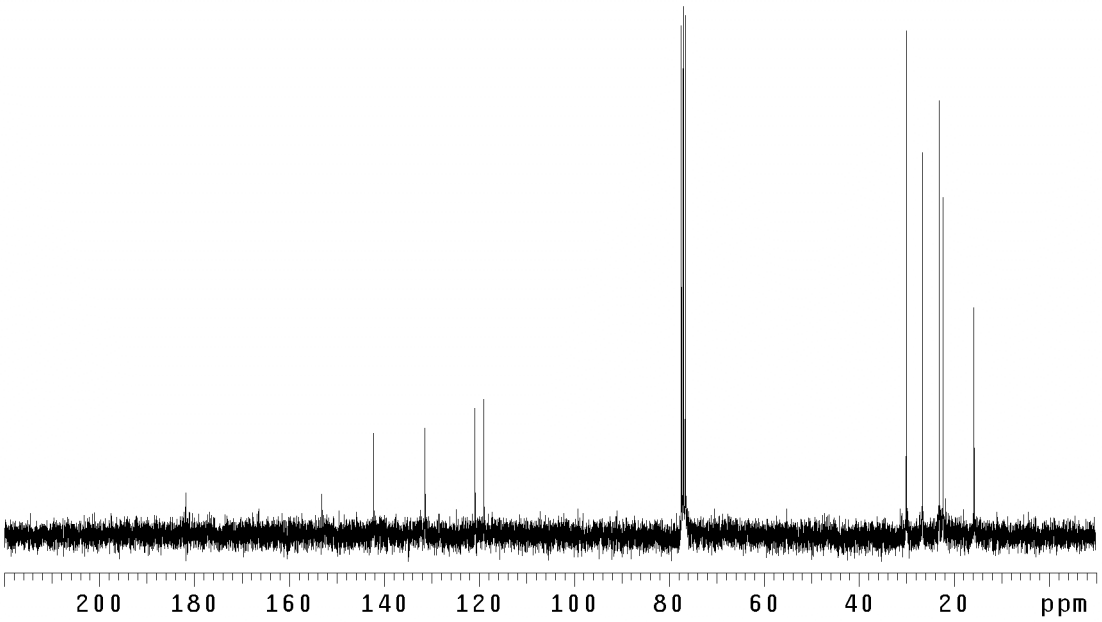


*Figure A2.192 ^{13}C NMR of compound **294** (75 MHz, $CDCl_3$)*

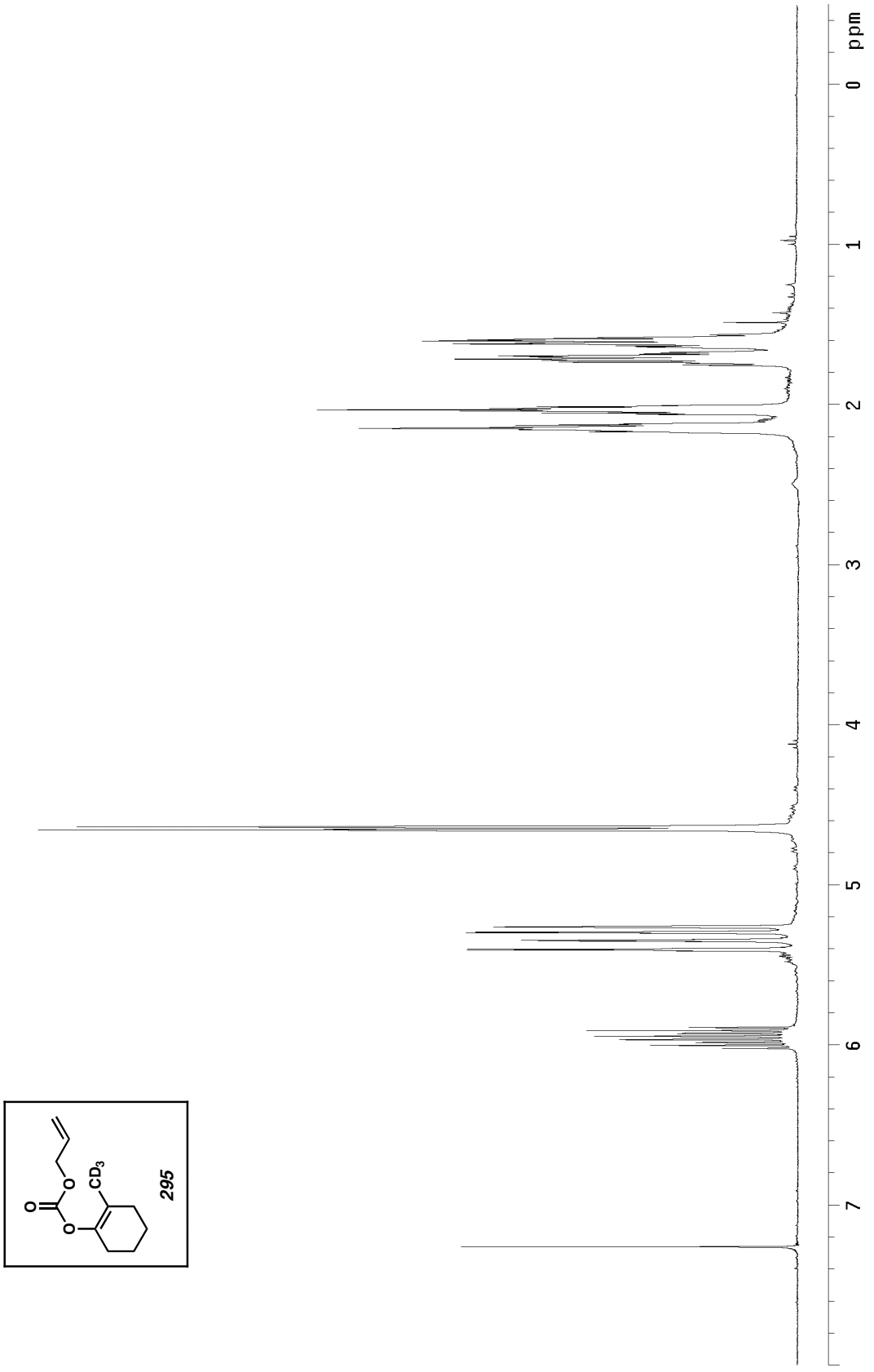


*Figure A2.193 ^1H NMR of compound **295** (300 MHz, $CDCl_3$)*

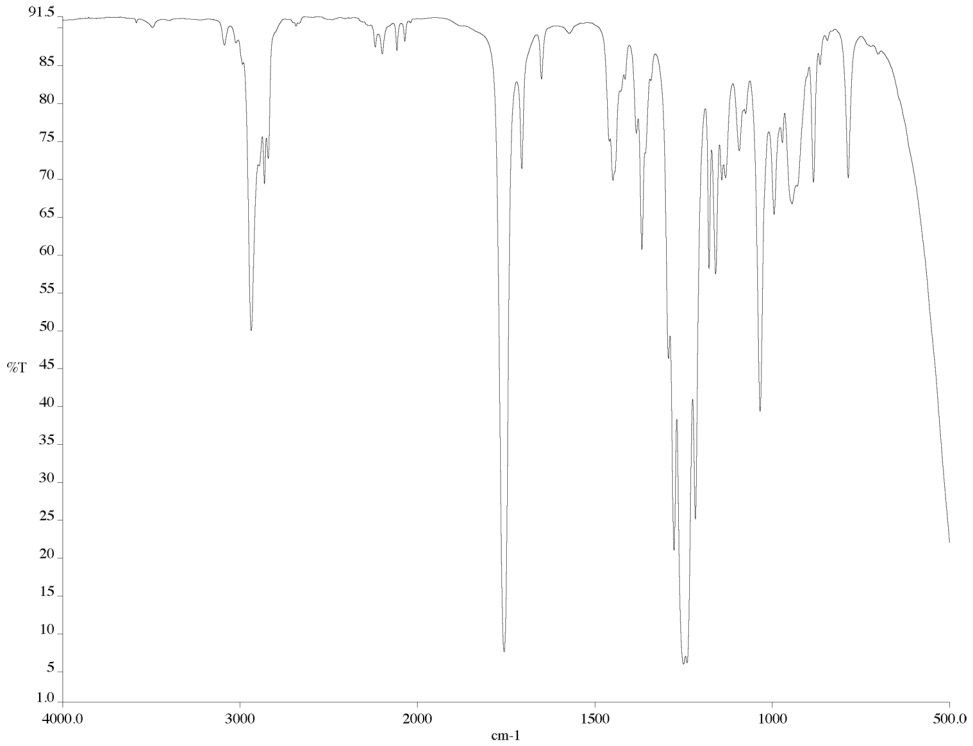


*Figure A2.194 IR of compound **295** (NaCl/film)*

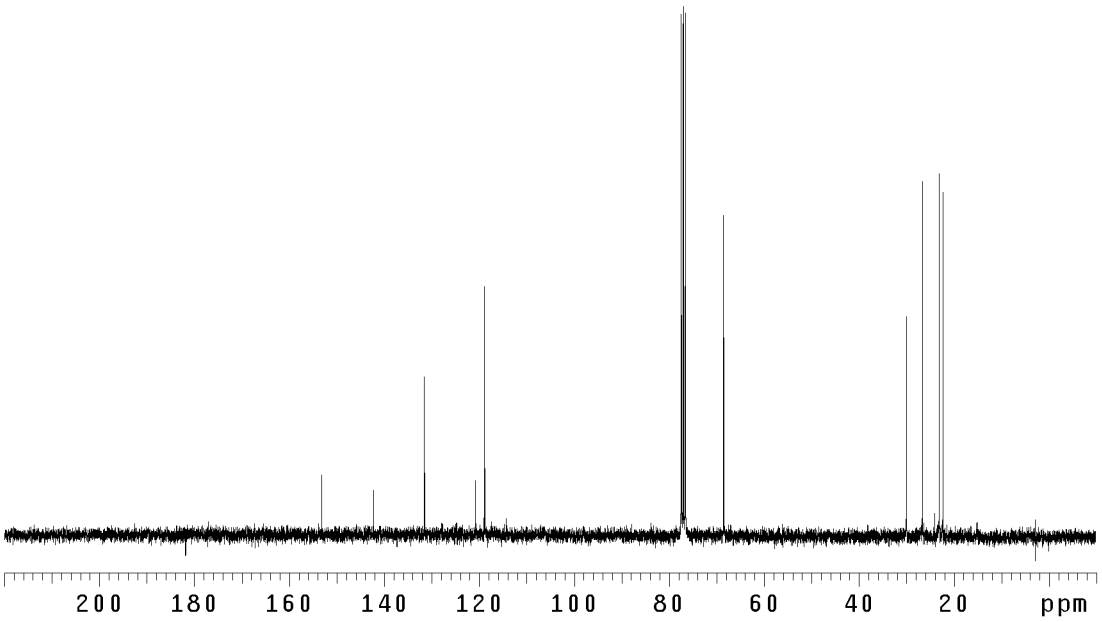


*Figure A2.195 ^{13}C NMR of compound **295** (75 MHz, $CDCl_3$)*

CHAPTER 4

Computational Study of the Mechanism

of the Enantioselective Tsuji Allylation [†]

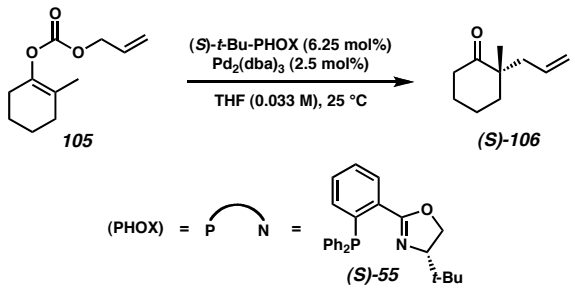
4.1 INTRODUCTION

Challenges in natural product and pharmaceutical synthesis have fueled the development of asymmetric homogeneous catalysis in organometallic chemistry for decades.[1] In particular, the synthesis of enantioenriched quaternary stereocenters without stoichiometric chiral reagents remains an active area of research.

Recently, we described a method for the enantioselective preparation of quaternary stereocenters (Scheme 4.1)[2] based on an enantioselective version of the general Tsuji decarboxylative allylation.[3a] The general allylation process involves oxidative addition to an enol carbonate (e.g., **105**) by a Pd(0) complex. The resulting allylated Pd(II) complex then reacts with ketone enolates with high regiochemical fidelity to form enantioenriched α-quaternary ketones (e.g., **106**).

[†] This work was performed in collaboration with John A. Keith, Douglas C. Behenna, Sandy Ma, Smaranda C. Marinescu, Jonas Oxgaard, and William A. Goddard, III. This study has been published. See: Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard, III, W. A. *J. Am. Chem. Soc.* **2007**, *129*, 11876–11877.

Scheme 4.1. The enantioselective Tsuji allylation



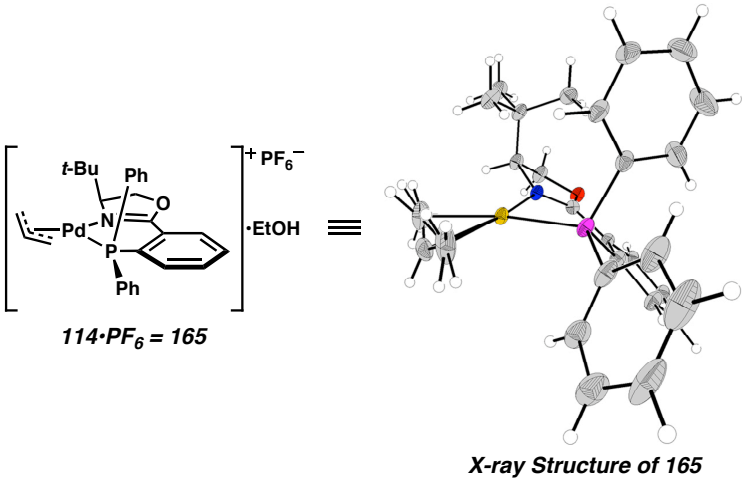
We reported a series of Pd catalysts that perform enantioselective allylation to form quaternary stereocenters from unstabilized prochiral enolates and non-prochiral allyl fragments.[2] In general, these 2-alkyl-2-allylcyclohexanone products are distinct from the majority of asymmetric allylic alkylation products. In contrast to previous works,[1c,3,4] this method has allowed the regiospecific allylic alkylation of hard enolates derived from ketones having two or more α-acidic sites. Furthermore, a variety of enolate precursors can be employed in these reactions (i.e., enol carbonates, silyl enol ethers, and β-ketoesters).

Using the (*S*)-*t*-Bu-phosphinooxazoline (PHOX) ligand (**55**),[5] allylated products form in high yields (80–99%) and enantiomeric excess (79–92%) with a variety of hard enolates. These ees are reduced to negligible levels when soft enolates are utilized. Solvent effects do not seem to play a crucial role in the enantioselectivity of the reaction.[6] Although this level of enantioselectivity is useful for many applications, it would be valuable to achieve ees above 95%. Substantial efforts have not achieved this, prompting us to investigate mechanistic details.[7]

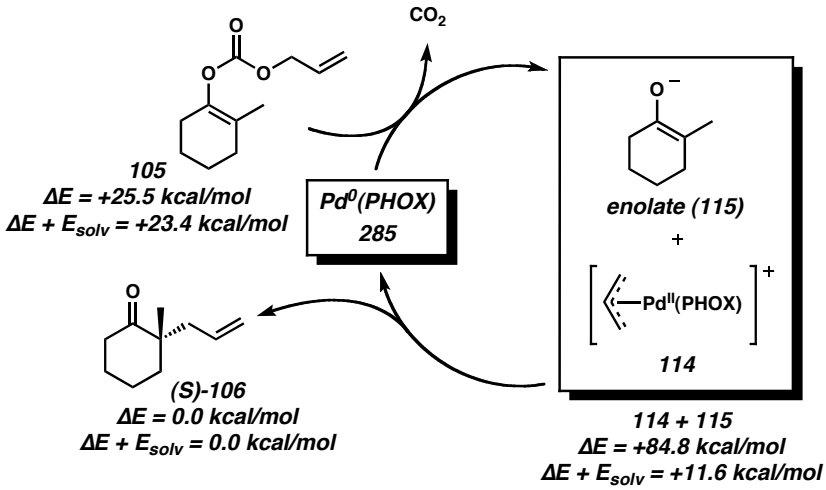
The observation that the reaction gives consistent levels of enantioselectivity regardless of the enolate precursor utilized to generate a particular product[2,8] suggested that these variants share a common intermediate. We obtained an X-ray crystal structure

for a synthetic Pd(II)-allyl complex **114•PF$_6$** (i.e., **165**) and found that it is a viable catalytic precursor to the enantioselective decarboxylative allylation reaction. This suggested to us that the allylated complex (**114**, Figure 4.1) is a likely intermediate in the reaction, and thus **114** + **115** (Scheme 4.2) is an intermediate as well.

*Figure 4.1. X-ray crystal structure for π-allyl complex **114**, with PF_6 as the counter ion (i.e., **165**)*



Scheme 4.2. The enantioselective Tsuji allylation mechanism studied in this work[9]



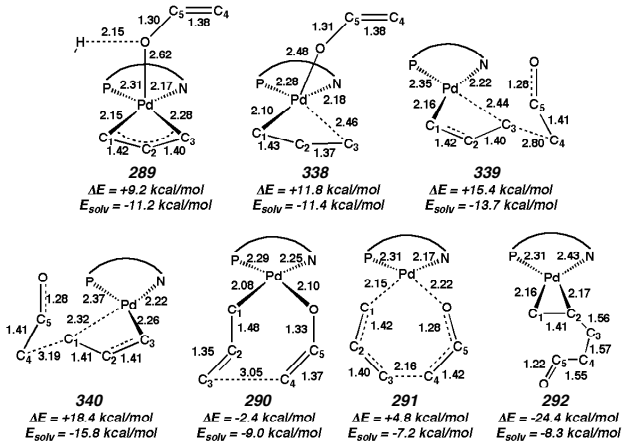
4.2 MECHANISTIC EXPERIMENTS AND COMPUTATIONS

Two unpublished experiments within our group suggested that we consider just one Pd^0(PHOX) complex in our investigation of the mechanism: (1) experiments demonstrated a linear relationship between the ee of the catalyst and the ee of the product; and (2) simple kinetic studies showed that the reaction was first order in Pd^0(PHOX) and zero order in starting material. We used quantum chemistry calculations to investigate possible mechanisms for the reaction presented in Scheme 4.2 starting from intermediate **114** + **115**.

All calculations[10] reported in this study employ the B3LYP hybrid flavor of density functional theory (DFT) that has been established to provide the most accurate energetics of the common methods using Jaguar version 6.5.[11]

The lowest energy conformer for intermediate **114** + **115** is a five-coordinate square pyramidal structure, **289** (Figure 4.2). We found that a multitude of external attack pathways lead to similar energetics, and the two lowest in energy are **339** (*trans*-P attack) and **340** (*trans*-N attack). Neither stereochemistry nor conformation of the allyl fragment (endo or exo) has a significant effect on these barriers.

Figure 4.2. Relevant internal coordinates (Å) and thermodynamic energies of intermediates and transition states in this study (some atoms from the enolate and PHOX ligand are omitted from the figures for clarity)



We also considered an inner-sphere mechanism that converts **289** to the square planar intermediate **290** via a trigonal bipyramidal transition state **338**. We presumed that **290** could then form products through an internal C–C coupling mechanism.

Most interesting is that we find an inner-sphere mechanism that is 2.6 kcal/mol lower than that for the external attack in the gas phase and 1.6 kcal/mol lower in THF solvent (Figure 4.2).

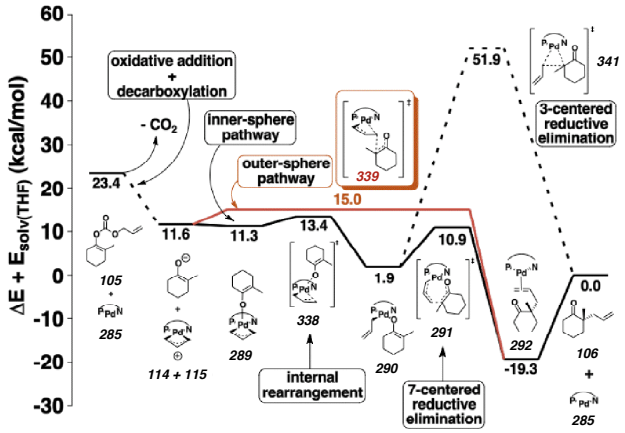
A second interesting result is that reductive elimination can occur from **290** to form the η^2-coordinated product, **292**, through a seven-centered transition state (similar to the thermally facile Claisen rearrangement),[12] **291**, rather than the standard three-centered elimination analogue.[13] Transition state **291** is 7.0 kcal/mol lower than **338** in the gas phase and 2.5 kcal/mol lower in THF (Figure 4.2).

Overall, these results contradict previous asymmetric allylic alkylation results involving soft enolate nucleophiles, prochiral allyl fragments, and Pd(PHOX) complexes that have been determined to proceed through external attack.[3c,i,j] Indeed, this mechanism

explains how high ees can be obtained without prochiral allyl fragments. These computational results constitute strong evidence of an inner-sphere mechanism in the Tsuji allylation reaction and may shed greater light on the details of similar inner-sphere processes already reported in the literature, especially those involving allyl–allyl type couplings.

Thus far, the enantiodetermining step of this reaction has not been identified satisfactorily. The current results suggest that a concerted process forms products directly from **289** to **292**, but have not ruled out stepwise transition states **338** and **291**. Figure 4.3 summarizes the calculated data.

Figure 4.3. Summary of energy pathway □E + E_{solv} for the enantioselective Tsuji Allylation reaction



4.3 NOTES AND REFERENCES FOR TEXT

1. (a) *Applied Homogeneous Catalysis with Organometallic Compounds: A Comprehensive Handbook in Three Volumes*; Cornils, B.; Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, Germany, **2002**. (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: New York, NY, **1999**. (c) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, **1999**; Vol. 2, p. 833–884.

2. Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045.

3. (a) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140–145. (b) Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203–214. (c) Steinhagen, H.; Reggelin, M.; Helmchen, G. *Angew. Chem., Int. Ed.* **1997**, *36*, 2108–2110. (d) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355–364. (e) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1–14. (f) Trost, B. M.; Schroeder, G. M. *Chem.–Eur. J.* **2004**, 11, 174–184. (g) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813–5837. (h) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, **2000**, p. 593–649. (i) Bäckvall, J.-E.; Nordberg, R. E.; Vågberg, J. *Tetrahedron Lett.* **1983**, *24*, 411–412. (j) Helmchen, G.; Steinhagen, H.; Reggelin, M.; Kudis, S. In *Selective Reactions of Metal-Activated Molecules*; Werner, H., Schreier, P., Eds.; Vieweg Verlag: Wiesbaden, **1998**, p. 205–215.

4. For studies utilizing other prochiral nucleophiles, see: (a) Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113–120. (b) Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3236–3237. (c) Kuwano, R.; Uchida, K.; Ito, Y. *Org. Lett.* **2003**, *5*, 2177–2179. (d) Sawamura, M.; Nagata, H.; Sakamoto, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2586–2592.

5. (a) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345. (b) Williams, J. M. J. *Synlett* **1996**, 705–710.

6. See the experimental section (section 4.4). For most substrates the optimal solvent was THF (yield = 96%, ee = 88% for product (*S*)-**106**); however, the reaction also performed surprisingly well in a variety of non-polar solvents including benzene (yield = 99%, ee = 88% for product (*S*)-**106**).

7. We note that substituted allyl fragments typically used as stereochemical probes for asymmetric allylation reactions are unsuitable for our catalyst system. See the experimental section (section 4.4) for details.

8. Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924–6927.

9. Pd^0(PHOX) (**285**) is believed to form allylated complex **114** with the concomitant decarboxylation of **105**. Thermodynamic values are calculated with respect to the uncoordinated products (*S*)-**106** + Pd(PHOX). E_{solv} is the energy associated with placing a gas-phase molecule in a solvent continuum and can be added to ΔE values to obtain solvent-phase results. Other calculation results are in the experimental section (section 4.4).

10. Calculations are on 82-atom systems with B3LYP hybrid DFT and mixed basis set geometries (LACVP** on atoms shown in Figure 4.3 and the MIDI! basis set on all other atoms). Single-point energies are calculated with the LACV3P**++ basis set. In addition to electronic energy and thermodynamic contributions, we considered single-point solvent effects for THF (probe radius = 2.527Å, ε = 7.52) using the Jaguar self-consistent Poisson–Boltzmann solver (ref 10a and 10b) and the LACV3P** basis set. Computational studies by the Goddard group show that this method leads to sufficiently accurate reaction barrier heights for large organometallic complexes including those of

palladium (ref 10c–e). Single point control calculations were carried out at these geometries with the PBE (ref 10f and 10g) pure density functional DFT and the LACV3P**++ basis set, leading to differences between critical barriers with RMS = 1.2 kcal/mol. See: (a) Marten, B.; Kim, K.; Cortis, C.; Friesner, R. A.; Murphy, R. B.; Ringnalda, M. N.; Sitkoff, D.; Honig, B. *J. Phys. Chem.* **1996**, *100*, 11775–11788. (b) Tannor, D. J.; Marten, B.; Murphy, R.; Friesner, R. A.; Sitkoff, D.; Nicholls, A.; Ringnalda, M.; Goddard, W. A., III; Honig, B. *J. Am. Chem. Soc.* **1994**, *116*, 11875–11882. (c) Keith, J. A.; Oxgaard, J.; Goddard, W. A., III. *J. Am. Chem. Soc.* **2006**, *128*, 3132–3133. (d) Keith, J. M.; Nielsen, R. J.; Oxgaard, J.; Goddard, W. A., III. *J. Am. Chem. Soc.* **2005**, *127*, 13172–13179. (e) Nielsen, R. J.; Goddard, W. A., III. *J. Am. Chem. Soc.* **2006**, *128*, 9651–9660. (f) Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* **1996**, *77*, 3865–3868. (g) Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* (Erratum) **1997**, *78*, 1386.

11. Jaguar, version 6.5, Schrödinger, LLC, New York, NY, 2005

12. Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205–247.

13. Calculations on a non-oxy-analog to this unusual mechanism were first presented in ref 13a. The transition state for the 3-membered ring is extremely high, +46.9 in gas phase and +51.9 kcal/mol in solvent. The explanation for high barriers of C–C reductive couplings from Pd(II) is discussed in ref 13b and 13c. See: (a) Mendez, M.; Cuerva, J. M.; Gomez-Bengoa, E.; Cardenas, D. J.; Echavarren, A. M. *Chem.–Eur. J.* **2002**, *8*, 3620–3628. (b) Low, J. J.; Goddard, W. A., III. *J. Am. Chem. Soc.* **1986**, *108*, 6115–6128. (c) Low, J. J.; Goddard, W. A., III. *Organometallics* **1986**, *5*, 609–622.

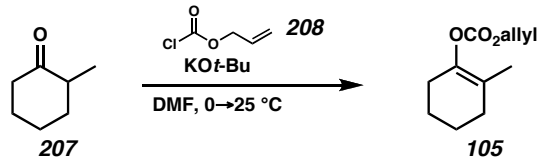
4.4 EXPERIMENTAL SECTION

4.4.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under argon atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) was purchased from Strem and stored in a dessicator under argon atmosphere prior to use. Ligands (*S*)-*t*-Bu-PHOX (**55**), (*S*)-*i*-Pr-PHOX (**122**), (*R*)-*i*-Pr-PHOX (**122**), and all substrates were prepared by our previously reported methods.[14] Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed by using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching or anisaldehyde. ICN silica gel (particle size 0.032–0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC, utilizing a Chiracel OJ column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries with visualization at 254 nm. Analytical achiral GC was performed with an Agilent 6850 GC utilizing a DB-WAX column (30 mm x 0.24 mm with 1.0 mL/min carrier gas flow). Temperature controlled ^{1}H NMR kinetic experiments were performed on a Varian Inova 500 MHz.

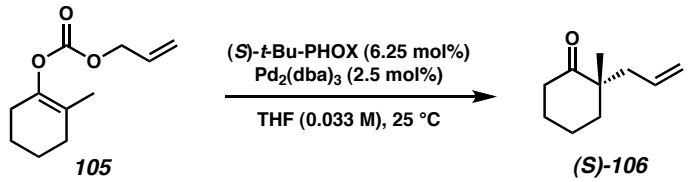
4.4.2 EXPERIMENTAL PROCEDURES FOR ALLYLIC ALKYLATION

General Procedure for the Synthesis of Allyl Enol Carbonates



Allyl 2-methylcyclohex-1-enyl carbonate (105):[15] To a solution of potassium *t*-butoxide (5.88 g, 52.5 mmol, 1.05 equiv) in DMF (100 mL) was added 2-methylcyclohexanone (**207**, 6.13 mL, 50 mmol, 1.0 equiv). After 12 h, the reaction mixture was cooled in an ice bath and allyl chloroformate (**208**, 6.4 mL, 60 mmol, 1.2 equiv) was added in a dropwise fashion. After an additional 30 min in the ice bath and 15 min at 25 °C, the reaction mixture was quenched into water (250 mL), extracted with 2:1 CH_2Cl_2:hexanes (4 x 125 mL), dried ($MgSO_4$), and evaporated. Chromatography (2.5→4% Et_2O in hexanes on SiO_2) afforded the allyl enol carbonate **105** (4.49 g, 46% yield) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (ddt, *J* = 17.4, 10.5, 5.6 Hz, 1H), 5.36 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.26 (dq, *J* = 10.2, 1.2 Hz, 1H), 4.63 (dt, *J* = 5.7, 1.4 Hz, 2H), 2.13 (m, 2H), 2.02 (m, 2H), 1.70 (m, 2H), 1.59 (m, 2H), 1.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 142.2, 131.5, 120.8, 118.8, 68.5, 30.0, 26.6, 23.1, 22.3, 15.7; IR (Neat Film NaCl) 3936, 1755, 1275, 1239, 1037 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{16}O_3$ $[M]^+$: 196.1100, found 196.1092.

General Procedures for Asymmetric Tsuji Allylation

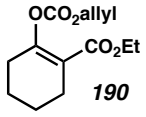
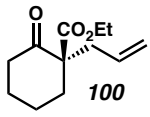
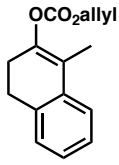
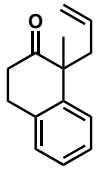
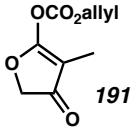
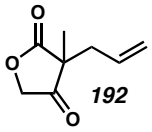
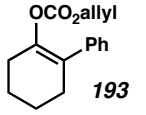
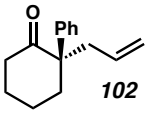
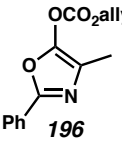
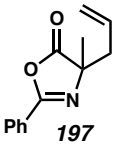


A 50 mL round-bottom flask equipped with a magnetic stir bar was flame dried under vacuum. After cooling under dry argon, $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol, 0.025 equiv) and (*S*)-*t*-Bu-PHOX (**55**, 24.2 mg, 0.0625 mmol, 0.0625 equiv) were added. After the flask was flushed with argon, THF (30 mL) was added, and the contents were stirred at 25 °C for 30 min, at which time allyl enol carbonate **105** (196.2 mg, 1.0 mmol, 1.0 equiv) was added by syringe in one portion. When the reaction was complete by TLC (2 h), the reaction mixture was evaporated under reduced pressure and the residue chromatographed (2→3% Et_2O in pentane on SiO_2) to afford (*S*)-2-allyl-2-methylcyclohexanone ((*S*)-**106**) (129.6 mg, 85.1% yield, 87% ee) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75–5.61 (m, 1H), 5.05 (s, 1H), 5.01 (m, 1H), 2.40–2.31 (comp. m, 3H), 2.21 (dd, J = 13.8, 7.5 Hz, 1H), 1.78 (comp. m, 5H), 1.56 (m, 1H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.4, 133.7, 117.9, 48.4, 41.9, 38.8, 38.5, 27.4, 22.6, 21.0; IR (Neat Film NaCl) 2934, 2865, 1707, 1451, 912 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{10}H_{16}O$ $[M]^+$: 152.1201, found 152.1204; $[\alpha]_D^{21}$ –49.64 (*c* 2.38, hexane, 98% ee).

For results of Tsuji allylations with stabilized enolates (with low pK_a values relative to the typical ketone enolates employed in these reactions), see Table 4.1 (identical to Table 2.11 in Chapter 2). Despite the low levels of enantioselectivity, chemical yield is very high. This may imply that an alternate mechanism is accessible with this low pK_a substrate (e.g.,

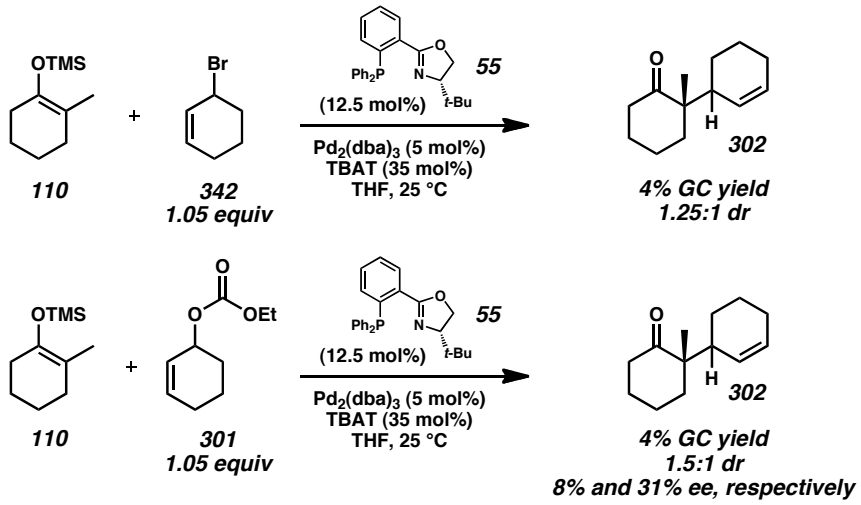
an outer sphere mechanism). Characterization data for new compounds can be found in Chapter 2.

Table 4.1 Asymmetric allylation via stabilized allyl enol carbonates.

entry	substrate	product	% yield[a]	% ee[b]	entry	substrate	product	% yield[a]	% ee[b]
1	 *190*	 *100*	89	24[c]	4	 *194*	 *195*	93	0
2	 *191*	 *192*	87	2					
3	 *193*	 *102*	99	11[c]	5	 *196*	 *197*	89	2

[a] Isolated yield from reactions with 1.0 mmol of substrate in THF (0.033 M) at 25 °C with 2.5 mol% $Pd_2(dba)_3$ and 6.25 mol% (*S*)-*t*-Bu-PHOX (**55**). Each reaction was complete in 2 h. [b] Measured by chiral GC or HPLC. [c] Absolute stereochemistry of products assigned by analogy.

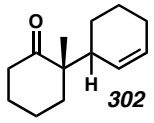
Tsuji Allylation with cyclohexenyl substrates



Sample Procedure

In a flame dried 1-dram vial, $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol), (*S*)-*t*-BuPHOX (**55**, 4.7 mg, 0.0625 mmol), and TBAT (18.9 mg, 0.035 mmol) were combined. The vial was evacuated for 10 min prior to addition of THF (3 mL). The mixture was allowed to stir at

25 °C for 30 min prior to addition of tridecane (10 μL, 0.4 mmol), silyl enol ether (**110**, 18.4 mg, 0.1 mmol), and bromocyclohexene (**342**, 16.1 mg, 0.105 mmol) via syringe. GC yield was determined by a GC assay with tridecane as the internal standard. (Isothermal at 80 °C for 5 min, then ramp from 80 °C to 115 °C at 10 °C/min, then isothermal at 115 °C for 75 min. Silyl enol ether: 5.759 min, tridecane: 7.329 min, bromocyclohexene: 8.426 min, minor product diastereomer: 72.223 min, major product diastereomer: 73.434 min). Enantiomeric excess was determined by an Agilent 6850 GC utilizing a G-TA column (30 mm x 0.25 cm) with 1.0 mL/min carrier gas flow. The method utilized for enantiomeric excess determination was isothermal at 110 °C for 60 min (major product diastereomer: 47.504 min and 53.594 min (major enantiomer), minor product diastereomer: 48.282 min (major enantiomer) and 55.842 min). Isolation of products as a mixture of diastereomers was accomplished by flash chromatography (1 cm x 20 cm SiO_2, 2% ether in pentane).



302

^{1}H NMR (300 MHz) δ 5.74 (complex multiplet, 1H), 5.49 (dddd, 0.7H, *J* = 11.0, 1.9, 1.9, 1.9 Hz), 5.20 (dddd, 0.3H, *J* = 10.1, 2.1, 2.1, 2.1 Hz), 2.84-2.29 (complex multiplet, 3H), 2.01-1.22 (complex multiplet, 12H), 0.90 (s, 2.1 H), 0.89 (s, 0.9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.7, 216.1, 129.6, 129.5, 128.0, 127.3, 52.0, 51.7, 39.5, 39.0, 38.6, 37.0, 36.0, 28.0, 27.7, 25.4, 24.0, 23.1, 23.0, 22.9, 21.1, 21.0, 19.4, 18.6; IR (Neat Film, NaCl) 3023, 2934, 2862, 1705, 1452, 1313, 1121 cm^{-1}; HRMS *m/z* calc'd for $C_{13}H_{24}O$ [M^+]: 192.1514, found 192.1519.

Procedures and results of nonlinear and kinetic experiments can be found in Chapter 3. Procedures and data for the [(PHOX)Pd(allyl][PF_6] salt **165** can be found in Chapter 2. Spectra of the relevant compounds can be found in Appendix 1.

4.4.3 ATOMIC COORDINATES FOR CALCULATED COMPLEXES

Calculation details:

All calculations were run using Jaguar 6.5

Geometry optimization was done with a mixed basis set (MIDI! on all atoms except N, P, Pd, the six atoms from the allyl fragment and enolate component which were treated with LACVP or 6-31G*).

"Gas Phase Energy" was calculated as single point energy calculations from the above geometries with the LACV3P**++ basis set with both B3LYP and PBE.

"Solvent Phase Energy" was calculated with B3LYP and the LACV3P** basis set. Diffuse functions were omitted, as they appear to have adverse effects on Jaguar's solvation model. Solvent = THF (probe radius = 2.527Å, ε = 7.52).

"Zero Point Energy" was calculated from analytic vibrational frequencies.

All transition states were reported were fully optimized and yielded one imaginary frequency.

Contact John Keith for other calculation details (johnk@wag.caltech.edu)

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Complex **105**

(B3LYP)

Gas Phase Energy	= -654.64331885491	= Eh
Solvent Phase Energy	= -0.01095745854	= Eh
Zero Point Energy	= 159.985	= kcal/mol

(PBE)

Gas Phase Energy = -653.82932310282 = Eh

Geometry Coordinates

C1	0.0113083798	0.0124257236	-0.0061783496
C2	-0.0013818048	0.0086824472	1.3267454073
C3	1.2339260089	0.0153211569	2.1717260330
O4	1.1429594509	-1.0908202308	3.1072486300
C5	2.1186404294	-1.1171196145	4.0385647212
O6	3.0180904838	-0.3191945640	4.1324261749
O7	2.0035448532	-2.1647199625	4.8809113190
C8	0.8991992312	-3.0435401244	4.8363028339
C9	1.0771331487	-4.2973061924	4.4017656946
H10	-0.9133147377	0.0566512194	-0.5891741503
H11	0.9476871255	-0.0189251237	-0.5744052870
H12	-0.9534029285	0.0384538672	1.8713083079
H13	2.1474818658	-0.0980871386	1.5652816886
H14	1.3285573872	0.9488691482	2.7535568736
C15	-1.5746866876	-3.4044541922	5.1922740477
C16	-0.3551976806	-2.4877409835	5.4538668734
C17	-0.0529567564	-5.3043896563	4.4860652339
C18	-1.1917306988	-4.8771957822	5.4433840026
H19	-1.9051008295	-3.2856823628	4.1486577507
H20	-2.4102397826	-3.1039696803	5.8392585659
H21	-0.2035478549	-2.3634255284	6.5406674169
H22	-0.5522573151	-1.4841068032	5.0483581460
H23	-0.4659570753	-5.4740200848	3.4748151872
H24	0.3551672995	-6.2753897821	4.8132244080
H25	-0.8589056652	-4.9939727985	6.4867831715
H26	-2.0626868838	-5.5322187705	5.3021157953
C27	2.3661026241	-4.7966479686	3.8064196230
H28	2.7491463200	-5.6575604840	4.3802683709
H29	2.2066227425	-5.1482417926	2.7722771430
H30	3.1442248494	-4.0244807837	3.7932077238

Complex **106**

(B3LYP)

Gas Phase Energy = -466.03738555019 = Eh
Solvent Phase Energy = -0.00763066733 = Eh
Zero Point Energy = 151.022 = kcal/mol

(PBE)

Gas Phase Energy = -465.41294401844 = Eh

Geometry Coordinates

C1	-0.0109108095	-0.0090913358	-0.0039725405
C2	-0.0019377287	0.0036042017	1.3311872844
C3	1.2380737348	-0.0031750635	2.1857876305
C4	1.4287766106	-1.2691160917	3.0695595585
C5	2.7189398847	-1.0964231308	3.9031287517
O6	3.5264703528	-0.2162058183	3.6688334943
C7	0.2197252134	-1.4655974661	4.0267158875
C8	0.4425853342	-2.5256322103	5.1342095225
C9	1.6991627758	-2.1908086263	5.9645485923

C10	2.9434642135	-2.0867930224	5.0391924948
H11	-0.0056320434	-0.5013459258	4.5157686164
H12	-0.6675204448	-1.7358556422	3.4339196855
H13	0.5474941665	-3.5277876176	4.6914167333
H14	-0.4422202193	-2.5569111685	5.7863780637
H15	1.5517832876	-1.2318804997	6.4865076425
H16	1.8737722150	-2.9553599127	6.7343017634
H17	3.8338193270	-1.7655138907	5.5946626836
H18	3.1533849642	-3.0833841603	4.6143920855
C19	1.6086725483	-2.5137696692	2.1667783431
H20	2.4990070331	-2.4061609466	1.5279721473
H21	1.7168858220	-3.4408988269	2.7458276242
H22	0.7345201419	-2.6209798584	1.5084046329
H23	1.2232556197	0.8767106710	2.8575081124
H24	-0.9639896574	0.0470791753	1.8593952008
H25	0.9176493118	-0.0351836527	-0.5858169872
H26	-0.9443975068	0.0188140773	-0.5750236071
H27	2.1318023368	0.1153535642	1.5506968142

Complex CO_2

(B3LYP)

Gas Phase Energy = -188.64660127352 = Eh
Zero Point Energy = 7.282 = kcal/mol

(PBE)

Gas Phase Energy = -188.45726211825 = Eh

Geometry Coordinates

C1	-0.8753363139	0.6870813764	3.6403431163
O2	0.0327656439	1.4194127886	3.5572223432
O3	-1.7834484094	-0.0452538213	3.7234453188

Complex Pd(PHOX) (**285**)

(B3LYP)

Gas Phase Energy = -1566.71636231574 = Eh
Solvent Phase Energy = -0.01365948285 = Eh
Zero Point Energy = 282.286 = kcal/mol

(PBE)

Gas Phase Energy = -1565.11360608546 = Eh

Geometry Coordinates

Pd1	0.1771925079	0.0303972044	-0.4792913529
N2	0.3026055938	-0.1410796128	2.7832384005
P3	2.2198705967	0.1131084513	0.4386177259
C4	-1.0038182842	-0.4993172805	3.3625614198
C5	-1.3695267186	0.7361541683	4.2307918808
O6	-0.3882895714	1.7308207778	3.8622197991
C7	0.5365601358	1.0775218072	3.0867538636
C8	1.7119479275	1.8758559013	2.6970712247
C9	2.5690975521	1.5236726441	1.6174755080
H10	-1.2808860521	0.5535120633	5.3074731832

H11	-2.3613727745	1.1431853758	4.0214715692
H12	-1.7172300412	-0.5928340006	2.5308864595
C13	-0.9841978369	-1.8701715435	4.0945009747
C14	-2.3648552261	-2.1070062927	4.7373306520
H15	-2.5902874904	-1.3712288252	5.5181278530
H16	-3.1649458690	-2.0598774342	3.9887377476
H17	-2.4051576939	-3.0976292088	5.2029555345
C18	0.1177154570	-1.9123891038	5.1697106313
H19	-0.0286262495	-1.1533905905	5.9471385087
H20	0.1230764126	-2.8888419941	5.6667758799
H21	1.1022823775	-1.7536811771	4.7207186916
C22	-0.7141035645	-2.9721399418	3.0521117944
H23	-0.6925443510	-3.9577358762	3.5312475708
H24	-1.4991625169	-2.9905243568	2.2864005629
H25	0.2426939315	-2.8105282874	2.5505088026
C26	3.8406411180	-3.7385110338	2.5048718642
C27	4.1074926647	-2.4953066171	3.0804314492
C28	3.6158390117	-1.3260446596	2.4942467370
C29	2.8405525532	-1.3857520540	1.3280198613
C30	2.5686003340	-2.6405304324	0.7628757974
C31	3.0698671727	-3.8065787580	1.3421728173
H32	4.2263028740	-4.6465171258	2.9601381937
H33	4.7048511534	-2.4314405374	3.9864012030
H34	3.8388033638	-0.3655148675	2.9489214760
H35	1.9555010794	-2.6973239457	-0.1333013057
H36	2.8521177860	-4.7695353786	0.8877957053
C37	5.4861173515	0.6665806808	-2.8578378957
C38	4.2062548075	1.2036606991	-3.0082511302
C39	3.2507099574	1.0247192022	-2.0079837737
C40	3.5613462203	0.3211578322	-0.8338278752
C41	4.8523299578	-0.2141929668	-0.6939888728
C42	5.8049371963	-0.0441991918	-1.7000423116
H43	6.2285709031	0.7952972902	-3.6409822040
H44	3.9476943978	1.7523924171	-3.9099742196
H45	2.2440352795	1.4175481875	-2.1322906313
H46	5.1159062955	-0.7705053528	0.1999946198
H47	6.7974292943	-0.4705309077	-1.5784051954
C48	3.6692839902	2.3615463383	1.3687018727
H49	4.3411402151	2.1287397114	0.5515794144
C50	1.9763230183	3.0296087707	3.4539024330
H51	1.3009806790	3.2790098495	4.2642189791
C52	3.9287604198	3.4947888886	2.1392257713
H53	4.7973722597	4.1073788890	1.9123437951
C54	3.0767496909	3.8370912632	3.1861609677
H55	3.2645320738	4.7206656803	3.7890262267

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Complex **115**

(B3LYP)

Gas Phase Energy = -348.71065236365 = Eh
Solvent Phase Energy = -0.08425259124 = Eh
Zero Point Energy = 102.902 = kcal/mol

(PBE)

Gas Phase Energy = -348.25500040654 = Eh

Geometry Coordinates

O1	-0.0003410345	0.0018492883	-0.0018906891
C2	-0.0012930859	-0.0008335598	1.2724903838
C3	1.1061593054	-0.0010872893	2.1166904574
C4	-1.4104526170	-0.0319872575	1.9233471036
C5	2.4818715361	0.0739164076	1.5196859652
C6	-1.4515514456	0.3591684973	3.4170181569
C7	-0.3527287552	-0.4105932402	4.1753994277
C8	1.0376837131	-0.0101397774	3.6211509483
H9	-1.2650581487	1.4419209104	3.5240176167
H10	-2.4459585505	0.1554018823	3.8553292856
H11	-0.5098798273	-1.4922663929	4.0247324928
H12	-0.4093491028	-0.2110971796	5.2604028648
H13	1.3059029375	0.9803472051	4.0738041013
H14	1.7916277693	-0.7143291969	4.0427607809
H15	-1.8367868734	-1.0464439177	1.7975540590
H16	-2.0494777870	0.6403990799	1.3261341092
H17	2.3821126706	0.0632008815	0.4232794062
H18	3.0422779241	0.9968736269	1.8062482500
H19	3.1410928032	-0.7749511975	1.8204725621

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Complex **114**

(B3LYP)

Gas Phase Energy = -1683.90795339188 = Eh

Solvent Phase Energy = -0.05367430515 = Eh

Zero Point Energy = 330.264 = kcal/mol

(PBE)

Gas Phase Energy = -1682.15272185669 = Eh

Geometry Coordinates

Pd1	0.0179829299	-0.0676708739	-0.0340612533
C2	0.5050195355	-1.1692203769	1.8489587378
C3	-0.8985553714	-1.0206510966	1.6545794544
C4	1.3163391626	-0.0389784858	1.8956242167
H5	-1.5090774567	-1.9019537550	1.4854221069
H6	2.3957602772	-0.1371207332	1.8535746508
H7	-1.4192523527	-0.1889278914	2.1262357489
H8	0.9276249187	0.9130875980	2.2504672281
H9	0.9636611927	-2.1435452811	1.6917623608
N10	1.1511428117	1.0692029511	-1.4617307199
P11	-1.7174002497	-0.1717162380	-1.5812161704
C12	2.6446626690	1.1016133800	-1.4946703082
C13	2.9128829823	2.4582786137	-2.1982793762
O14	1.6458038779	2.7356867692	-2.8905046568
C15	0.7042142647	1.9499153489	-2.3012413409
H16	3.6970106065	2.4401837791	-2.9562777418
C17	-1.0801338212	-3.5570386762	-4.6791348973
C18	-0.9045469272	-3.7929162060	-3.3142014391
C19	-1.0864813043	-2.7594305492	-2.3980923311

C20	-1.4620964696	-1.4768035670	-2.8390164366
C21	-1.6366193894	-1.2479218533	-4.2131459744
C22	-1.4431481568	-2.2866855522	-5.1253184971
H23	-0.9335313877	-4.3634376384	-5.3934074944
H24	-0.6224696672	-4.7828988999	-2.9639494457
H25	-0.9402425784	-2.9505439510	-1.3367592315
H26	-1.9276546004	-0.2655093506	-4.5751408796
H27	-1.5807296881	-2.1020685290	-6.1880005070
C28	-6.0108222495	-0.6827395226	0.0847630174
C29	-5.5822308034	-1.5014328706	-0.9587416830
C30	-4.2929564870	-1.3649872842	-1.4782699849
C31	-3.4198230169	-0.4035262947	-0.9472616242
C32	-3.8571442232	0.4141129064	0.1112558776
C33	-5.1470706008	0.2775924727	0.6174870591
H34	-7.0156694884	-0.7918028681	0.4852892341
H35	-6.2527440211	-2.2501124139	-1.3737276006
H36	-3.9715041448	-2.0086007331	-2.2926869648
H37	-3.1922296286	1.1650736918	0.5348615338
H38	-5.4801222065	0.9178646759	1.4308987877
C39	-2.0917909438	3.8288111183	-3.9397626248
C40	-3.1955760773	3.0087813541	-3.7309847663
C41	-3.0479854883	1.8169764747	-3.0216946696
C42	-1.8029857361	1.4161325566	-2.5147376653
C43	-0.6774653169	2.2487612543	-2.7363715505
C44	-0.8484695501	3.4481733444	-3.4474833487
H45	-2.1943350346	4.7645713961	-4.4827813227
H46	-4.1734051120	3.2929850556	-4.1118290136
H47	-3.9204699432	1.1932225546	-2.8516287667
H48	0.0149971016	4.0830108962	-3.6095204853
H49	3.0945447092	3.2781428195	-1.4921063989
C50	3.2673196683	-0.1322099069	-2.2290481406
C51	4.8097960218	0.0355752320	-2.2321692566
H52	5.1372215469	0.8949872402	-2.8338522574
H53	5.1986577741	0.1574569696	-1.2094740686
H54	5.2753864147	-0.8611778049	-2.6646233451
C55	2.7466860750	-0.2452939683	-3.6796940074
H56	2.9375390805	0.6699273619	-4.2584065984
H57	3.2584862794	-1.0737003009	-4.1902023908
H58	1.6679877242	-0.4548105081	-3.7011281686
C59	2.9295243491	-1.4292044742	-1.4578823501
H60	3.3997035260	-2.2895861753	-1.9559421718
H61	3.3142422646	-1.3859212143	-0.4274744391
H62	1.8451801419	-1.6056103459	-1.4248356794
H63	3.0184804616	1.1146049470	-0.4645288410

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Complex **289**

(B3LYP)

Gas Phase Energy = -2032.73911500101 = Eh
Solvent Phase Energy = -0.01784563176 = Eh
Zero Point Energy = 434.031 = kcal/mol

(PBE)

Gas Phase Energy = -2030.53944632755 = Eh

Geometry Coordinates

Pd1	0.1522421755	-0.1116392671	-0.0014489177
C2	0.3201673009	-0.1796904055	2.2760129712
O3	2.7683828369	-0.1292058406	-0.0509452580
C4	-0.3089759399	1.0020591816	1.8725967702
C5	0.3572462693	1.8198794116	0.9189059555
C6	3.6231836400	-1.0320514691	-0.4454565077
C7	4.5645342779	-0.6017701382	-1.5790101993
C8	3.7319944213	-2.2986969229	0.0963151434
C9	2.9319355116	-2.6638738931	1.3176139803
C10	4.7627721980	-3.3113686164	-0.3585935803
H11	-0.1635796499	2.6681043577	0.4843450687
H12	-0.2222383097	-0.9166488314	2.8606049645
H13	1.4435092171	1.8793455997	0.9323271725
H14	1.4035149507	-0.2611482144	2.2437892374
H15	-1.3662592386	1.1559400314	2.0796270765
N16	-0.0964120286	-2.1721913229	-0.6248671759
P17	0.1746800925	0.4526738241	-2.2431717911
H18	3.9999458625	-0.5790651765	-2.5330843392
H19	4.8626842027	0.4444461070	-1.3794720165
H20	2.9495855916	-3.7566841867	1.4997009411
H21	3.3236753121	-2.1850991038	2.2432746779
H22	1.8783429227	-2.3407749381	1.2329248766
H23	4.3030634936	-4.3222079238	-0.4201911164
H24	5.5694359641	-3.4207278375	0.4055290059
C25	-0.7350831020	-3.2196094825	0.2145874496
C26	0.0253384366	-4.4963013059	-0.2322589823
O27	0.5646050655	-4.1275435673	-1.5433923246
C28	0.5490572057	-2.7557291926	-1.5872860900
H29	-0.5979310895	-5.3814233610	-0.3767989277
C30	1.0751352456	-0.8356551795	-3.2059721504
C31	1.1800742899	-2.1879310773	-2.7905657485
H32	0.8671385414	-4.7299403361	0.4300132078
C33	-2.2861720057	-3.2868486983	0.0078957052
C34	-2.8503553237	-4.4322244334	0.8875736219
H35	-2.4968156257	-5.4213090582	0.5626847308
H36	-2.5704486745	-4.2925639033	1.9434975890
H37	-3.9486254196	-4.4383230060	0.8269120766
C38	-2.6429574335	-3.5374779809	-1.4747726814
H39	-2.1569173063	-4.4433254395	-1.8650556956
H40	-3.7310120313	-3.6646211075	-1.5783460509
H41	-2.3418826533	-2.6849977453	-2.0990721550
C42	-2.9326790960	-1.9607299977	0.4721737948
H43	-4.0245459550	-2.0136723051	0.3421425130
H44	-2.7256056999	-1.7760957874	1.5377230994
H45	-2.5505778966	-1.1091203781	-0.1060660246
H46	-0.5403211568	-2.9996832719	1.2703192523
C47	2.3860184274	4.3928572056	-3.2837949551
C48	1.1849262514	4.1040696560	-3.9307794581
C49	0.4990063076	2.9223334720	-3.6431855483
C50	1.0156992509	2.0222375547	-2.6982728271
C51	2.2242796977	2.3187630128	-2.0406796476
C52	2.9016472517	3.4996854342	-2.3422000820
H53	2.9179077889	5.3148280951	-3.5105141300
H54	0.7783647615	4.7996636351	-4.6623478042
H55	-0.4393082329	2.7098002870	-4.1494234414

H56	2.6195443006	1.6088146650	-1.3055510017
H57	3.8379878854	3.7243131230	-1.8353142604
C58	-4.0140849884	0.8486431113	-4.2294907723
C59	-3.0426757843	0.0654841238	-4.8504161246
C60	-1.7758545288	-0.0722575192	-4.2781553383
C61	-1.4704573260	0.5697076485	-3.0683288784
C62	-2.4649169194	1.3419170502	-2.4406972350
C63	-3.7217207787	1.4881266566	-3.0229061547
H64	-4.9979071726	0.9582920145	-4.6804358217
H65	-3.2670363641	-0.4380494793	-5.7884578786
H66	-1.0232965470	-0.6749349737	-4.7796770291
H67	-2.2502441947	1.8272918150	-1.4903614712
H68	-4.4779273956	2.0969750059	-2.5318640115
C69	1.6776467046	-0.4539878202	-4.4182651942
H70	1.6202426167	0.5839995041	-4.7339037256
C71	1.8801960366	-3.0948204178	-3.6107465389
H72	1.9634346085	-4.1239615571	-3.2816818655
C73	2.3570314890	-1.3677921209	-5.2172415639
H74	2.8120335257	-1.0408065248	-6.1494141375
C75	2.4586284413	-2.6978214199	-4.8070394514
H76	2.9941504587	-3.4227225064	-5.4152182616
C77	5.8108451629	-1.4802030793	-1.7353239197
H78	6.5162215574	-1.2846717852	-0.9091958086
H79	6.3415542060	-1.2405257562	-2.6715555184
C80	5.4125045433	-2.9724497525	-1.7051510232
H81	6.2936522790	-3.6113461306	-1.8783039381
H82	4.7016915621	-3.1642056614	-2.5260393040

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Complex **338**

(B3LYP)

Gas Phase Energy = -2032.73488137273 = Eh
Solvent Phase Energy = -0.01873037575 = Eh
Zero Point Energy = 434.098 = kcal/mol
Frequency = -34.91

(PBE)

Gas Phase Energy = -2030.53248097952 = Eh

Geometry Coordinates

Pd1	0.0000000000	0.0000000000	0.0000000000
O2	0.0000000000	0.0000000000	2.4803720451
C3	2.3476054165	0.0000000000	0.7367316679
P4	-1.8800020861	-0.5618249390	-1.1806220877
N5	-0.7195656370	2.0597627224	0.0137173621
C6	0.9064332782	-1.8840233523	0.2142974169
C7	2.0445691690	-1.0617588596	-0.0915735806
C8	-0.7922314100	0.6676829591	3.2821701313
C9	-2.2509241518	0.1857639555	3.2879022041
C10	-0.4063556970	1.7062882460	4.1018820247
C11	1.0425569704	2.0837572704	4.2713044757
C12	-1.3793764863	2.4634873294	4.9843006402
C13	-3.1383462101	0.7776325158	4.3901106130
C14	-2.8397718715	2.2847274286	4.5576714445
H15	-2.9358046298	0.2743380753	5.3511223962

H16	-4.2047722555	0.6135394931	4.1628775917
H17	-3.5217147132	2.7350407823	5.2969811729
H18	-3.0092349046	2.7942325503	3.5925930708
H19	-2.7000559021	0.3900064897	2.2954888901
H20	-2.2191406357	-0.9177934332	3.3776356079
H21	1.2619118657	3.1338681065	3.9709727183
H22	1.3566809869	2.0156057803	5.3358840075
H23	1.6974826371	1.4175034753	3.6882268715
H24	-1.1277811425	3.5473387431	4.9780721229
H25	-1.2778659160	2.1626772194	6.0543878341
H26	0.6299523797	-2.6735728266	-0.4795275726
H27	3.0728822401	0.7458542597	0.4238115325
H28	0.6660856868	-2.0624677761	1.2615306105
H29	1.9397681570	0.0474465421	1.7466374505
H30	2.5138443074	-1.1399840470	-1.0713262590
C31	0.1812309612	3.1604316961	0.4629063979
C32	-0.7452405288	3.9527408768	1.4154757460
O33	-2.0914874689	3.6008132210	0.9327958474
C34	-1.9379362622	2.4149678241	0.2662991991
H35	-0.6577173350	5.0398267895	1.3699702015
C36	-3.3331200492	0.4700475481	-0.6838786444
C37	-3.2113039348	1.7446025095	-0.0738916922
H38	-0.6625795277	3.5742926563	2.4425828016
C39	0.7450457047	3.9829183995	-0.7415342329
C40	1.6788928218	5.0867728182	-0.1831908470
H41	1.1333993955	5.8178336242	0.4308846595
H42	2.4818338428	4.6497621426	0.4300802510
H43	2.1453981695	5.6346533982	-1.0152001957
C44	-0.3906385962	4.6292424156	-1.5676040534
H45	-1.0344233910	5.2700520102	-0.9488046425
H46	0.0405812648	5.2509039584	-2.3665418098
H47	-1.0170744416	3.8597922931	-2.0401356505
C48	1.5760122526	3.0579503875	-1.6615697933
H49	1.9939656734	3.6413559812	-2.4962698698
H50	2.4117096252	2.6038245279	-1.1088845448
H51	0.9573327549	2.2498820850	-2.0736224508
H52	1.0163878771	2.7227230956	1.0184537406
C53	-3.4086102107	-4.9030843740	-0.5674705694
C54	-3.3279831636	-4.3939449216	-1.8624661290
C55	-2.8845741818	-3.0871164255	-2.0789992967
C56	-2.5132856862	-2.2791085131	-0.9942049296
C57	-2.5818701933	-2.8056336904	0.3091561554
C58	-3.0355866321	-4.1061042413	0.5169557627
H59	-3.7541665409	-5.9212640420	-0.4019386526
H60	-3.6090571493	-5.0145894062	-2.7102397005
H61	-2.8244554032	-2.7014474119	-3.0935496837
H62	-2.2712339676	-2.1974572829	1.1576893747
H63	-3.0889145554	-4.5027041241	1.5287555954
C64	-1.4395461626	0.0044342230	-5.7793216043
C65	-2.6908340590	0.1962592220	-5.1932725625
C66	-2.8553650403	0.0399216749	-3.8163992255
C67	-1.7630296496	-0.3100851497	-3.0062840665
C68	-0.5044470040	-0.4853757023	-3.6055647271
C69	-0.3463340711	-0.3368857458	-4.9827212123
H70	-1.3153088822	0.1284774518	-6.8528320453
H71	-3.5436197597	0.4722026535	-5.8099053953

H72	-3.8341496035	0.2030161266	-3.3744114483
H73	0.3526202106	-0.7246791946	-2.9792211061
H74	0.6334966583	-0.4780263819	-5.4328751065
C75	-4.6206080175	-0.0498147446	-0.9005027928
H76	-4.7270762954	-1.0440822164	-1.3251947583
C77	-4.3817107142	2.4461824658	0.2675069522
H78	-4.2784088137	3.4157065455	0.7403735308
C79	-5.7665363634	0.6634457911	-0.5578048907
H80	-6.7482084736	0.2304573169	-0.7366032364
C81	-5.6440672192	1.9221918765	0.0236956770
H82	-6.5282403983	2.4903939387	0.3019617665

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Complex **339**

(B3LYP)

Gas Phase Energy = -2032.72926163396 = Eh
Solvent Phase Energy = -0.02182969499 = Eh
Zero Point Energy = 434.068 = kcal/mol
Frequency = -30.63

(PBE)

Gas Phase Energy = -2030.52840672257 = Eh

Geometry Coordinates

Pd1	0.0000000000	0.0000000000	0.0000000000
C2	0.0000000000	0.0000000000	2.4380822781
C3	0.6432168078	0.0000000000	5.2288898795
C4	-0.9577996270	0.8242757005	1.8292527455
C5	-1.9333911447	0.3010441896	0.9393466568
C6	1.3920387959	-1.0411775719	4.6521739538
O7	2.4038882128	-0.8626009024	3.8926831343
C8	0.9582318422	-2.4964169892	4.8908529369
C9	1.1490531325	1.4175118987	5.1694290282
C10	-0.5291132928	-0.2378446570	6.1606933875
H11	-2.6383125028	0.9742306191	0.4606679979
H12	-2.2888799627	-0.7201752021	1.0704217078
H13	-0.8301103775	1.9037677609	1.8923316849
H14	0.9290103527	0.3785585874	2.8291907710
H15	-0.1499539666	-1.0723479593	2.4991565056
H16	1.0755042597	-3.0454280781	3.9377318532
H17	1.6900573488	-2.9549284256	5.5873659314
H18	0.3709363831	2.1387011460	4.8407575547
H19	1.4785716180	1.7684365765	6.1722558610
H20	2.0158725557	1.4938857868	4.4933295049
H21	-0.4306748395	0.4183825616	7.0521528150
H22	-1.4820690508	0.0839987822	5.6819176663
N23	2.2012755411	-0.1770214513	-0.2701657118
P24	-0.0746830027	-0.1706195745	-2.3497321554
C25	3.1417415294	-0.7281884090	0.7519737679
C26	4.3768076860	0.1876453930	0.5678148220
O27	4.1972964798	0.7472717266	-0.7857698346
C28	2.8740324098	0.5651857183	-1.0812655715
C29	2.4219869655	1.2718017843	-2.3027869054
C30	1.1917621682	1.0385633280	-2.9727103546
H31	5.3405861920	-0.3246122924	0.5811828515

H32	4.3875997254	1.0240633226	1.2786452064
H33	2.7148545860	-0.6192644112	1.7585164888
C34	3.4375695046	-2.2484693420	0.5347891135
C35	4.3907486126	-2.6996420717	1.6737633360
H36	5.3864747323	-2.2393179696	1.5824731914
H37	3.9597180661	-2.4271499633	2.6491859319
H38	4.5280525539	-3.7907324593	1.6299833012
C39	4.0695216000	-2.5273875995	-0.8464098140
H40	4.9965819577	-1.9542667694	-0.9971420737
H41	4.3206008154	-3.5959200446	-0.9286627601
H42	3.3723668218	-2.2834327564	-1.6610162573
C43	2.1196406902	-3.0445101136	0.6744536143
H44	2.3253943365	-4.1224262846	0.5863410312
H45	1.6726112849	-2.8563674501	1.6605266346
H46	1.4006668427	-2.7668136954	-0.1079690935
C47	-3.9164397725	1.0237571877	-4.6834959146
C48	-3.1101506713	0.0008040066	-5.1816198066
C49	-1.9486547064	-0.3737647815	-4.5042330557
C50	-1.5839113122	0.2712736866	-3.3110678713
C51	-2.4103528689	1.2928404124	-2.8118376405
C52	-3.5634403651	1.6698713517	-3.4973505416
H53	-4.8211297859	1.3126888881	-5.2138114521
H54	-3.3846515179	-0.5092779083	-6.1026847695
H55	-1.3291652504	-1.1724067821	-4.9036477189
H56	-2.1491921337	1.7870732624	-1.8782323947
H57	-4.1931451028	2.4637717511	-3.1015363532
C58	1.0991936356	-4.2519871459	-4.2399010222
C59	1.7062582256	-3.0882490547	-4.7107716932
C60	1.3797715802	-1.8494949096	-4.1550951219
C61	0.4425787059	-1.7645983729	-3.1129760199
C62	-0.1530088040	-2.9457673083	-2.6361437772
C63	0.1677128116	-4.1780335204	-3.2029527657
H64	1.3542028781	-5.2150802439	-4.6763391844
H65	2.4354538428	-3.1416090041	-5.5165096608
H66	1.8537370634	-0.9495705283	-4.5385949304
H67	-0.8712756638	-2.8985923454	-1.8196670867
H68	-0.3040158359	-5.0837941180	-2.8285858033
C69	3.0096058630	2.9563150416	-3.9655288892
C70	3.3081916232	2.2303795607	-2.8181216893
C71	0.9155798386	1.7771799082	-4.1331398154
C72	1.8088181324	2.7271029623	-4.6278451081
H73	3.7131767993	3.6979080775	-4.3358575125
H74	4.2418481011	2.3973850102	-2.2929354265
H75	-0.0206353150	1.6132140828	-4.6575701994
H76	1.5595325253	3.2848774661	-5.5278170572
C77	-0.6739835636	-1.6916908541	6.6302127243
H78	-1.6635797548	-1.8512185521	7.0878784722
H79	0.0799410992	-1.9102276847	7.4059672475
C80	-0.4583710845	-2.6651725868	5.4495242864
H81	-1.2066190791	-2.4485879632	4.6667337224
H82	-0.6270041583	-3.7050178951	5.7739204697

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Complex **340**

(B3LYP)

Gas Phase Energy = -2032.72448663528 = Eh
Solvent Phase Energy = -0.02524726980 = Eh
Zero Point Energy = 433.361 = kcal/mol
Frequency = -15.07

(PBE)
Gas Phase Energy = -2030.52549546915 = Eh

Geometry Coordinates

Pd1	0.0000000000	0.0000000000	0.0000000000
C2	0.0000000000	0.0000000000	2.3211968669
C3	0.8424999870	0.0000000000	5.2512512366
C4	-0.6604120923	-1.9348412135	0.9595233626
C5	2.0348324454	-0.2310662807	4.5376139376
O6	2.6348456752	0.6466958488	3.8354158531
C7	2.6662417406	-1.6330421228	4.5701704904
C8	0.2961210408	1.3961934591	5.3680717406
C9	0.1728499396	-1.0508920472	6.1098325762
H10	0.7948244678	0.5765149642	2.7720940497
H11	-1.0279369486	0.3229104883	2.4686154440
H12	1.2858408351	-1.6542438342	1.8480005605
H13	-0.3944955452	-2.8749897192	0.4852676950
H14	-1.7244022252	-1.7326377282	1.0634760359
H15	3.5597004710	-1.5853182383	5.2270714149
H16	3.0593542203	-1.8489673429	3.5582365913
H17	-0.7921611092	1.4502644686	5.1542871484
H18	0.4156091570	1.7923032950	6.4009815514
H19	0.8276757331	2.0791754177	4.6873643011
H20	-0.1086039186	-0.6061760141	7.0889316396
H21	-0.7975838993	-1.3648843601	5.6603378580
N22	-0.2745441670	-0.2905545527	-2.1920555215
P23	0.8648308863	2.1113477013	-0.6693151461
C24	-1.2509872732	-1.2571523956	-2.7626386475
C25	-0.4420654562	-1.9002773930	-3.9231160958
O26	0.6345547654	-0.9384740923	-4.1632467737
C27	0.6946263401	-0.1464163899	-3.0415768310
C28	1.8728726616	0.7334422716	-2.9853464257
C29	2.0761494729	1.7610679965	-2.0218505857
H30	-0.9906321073	-2.0177097100	-4.8602362182
H31	0.0126772887	-2.8586026226	-3.6381708761
H32	-1.4950380278	-2.0010319604	-1.9954775416
C33	2.4241038645	2.7233170959	1.5561167438
C34	1.7400677103	3.2648340468	0.4560900697
C35	1.7305566879	4.6604610113	0.2713410300
H36	2.4342950681	1.6572310425	1.7657888990
C37	-0.1744459942	3.8005104158	-2.7353763444
C38	-0.3842402897	3.1941069380	-1.4871547730
C39	-1.5873254814	3.4462197271	-0.8046222505
H40	0.7497590375	3.6229391528	-3.2795306915
C41	-2.5829048012	-0.5723812117	-3.2115703309
C42	-3.5226457050	-1.6611799856	-3.7906283054
H43	-3.1206050633	-2.1126142666	-4.7095296194
H44	-3.6984259948	-2.4631779990	-3.0568533627
H45	-4.4954173395	-1.2140115013	-4.0424949399
C46	-2.3236751391	0.5166456810	-4.2766675801
H47	-1.7994590868	0.1136099881	-5.1557923258

H48	-3.2821669514	0.9339498639	-4.6198067842
H49	-1.7273284056	1.3400238101	-3.8615835900
C50	-3.2711894530	0.0620790727	-1.9813446505
H51	-4.2359934795	0.5002592874	-2.2786198113
H52	-3.4654380926	-0.6960811123	-1.2072950761
H53	-2.6515770794	0.8562591986	-1.5472490587
C54	3.0863060738	3.5602725378	2.4558857286
C55	2.4027650897	5.4884113118	1.1684566451
H56	-1.7673404030	2.9824138821	0.1636368688
C57	3.0798840591	4.9403968382	2.2615620909
H58	3.5686606868	3.1019120375	3.3147293051
H59	3.5894325554	5.5940185150	2.9665952082
H60	2.3898130592	6.5665337320	1.0198503902
H61	1.1923191041	5.0998890573	-0.5650727955
C62	3.2639293977	2.5054802833	-2.0831420359
H63	3.4376797169	3.2834967942	-1.3462185188
C64	2.8582121102	0.5133783170	-3.9652365103
H65	2.6930188108	-0.2734663361	-4.6926562066
C66	4.2268004642	2.2702537433	-3.0626286700
H67	5.1353855670	2.8677815670	-3.0804999502
C68	4.0213668206	1.2695081458	-4.0094654907
H69	4.7664559798	1.0728666145	-4.7766134510
C70	-1.1435577183	4.6448497973	-3.2830470551
H71	-0.9667010913	5.1117833019	-4.2499459543
C72	-2.5469733724	4.2973968449	-1.3506503759
H73	-3.4690537648	4.4911595023	-0.8068178154
C74	-2.3280888886	4.8971398964	-2.5920592894
H75	-3.0784118973	5.5595794610	-3.0183503598
C76	1.7313693390	-2.7447299319	5.0553938736
H77	2.2909677741	-3.6804210814	5.2200821173
H78	0.9637938530	-2.9596843707	4.2909866494
C79	1.0289212136	-2.3009106400	6.3589482287
H80	0.4080627879	-3.1172395038	6.7609951908
H81	1.8016646973	-2.0804973041	7.1152871298
C82	0.2694098235	-1.2734770317	1.7771592089

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Complex **290**

(B3LYP)

Gas Phase Energy = -2032.75792237478 = Eh
Solvent Phase Energy = -0.01322731344 = Eh
Zero Point Energy = 434.122 = kcal/mol

(PBE)

Gas Phase Energy = -2030.55097086362 = Eh

Geometry Coordinates

Pd1	0.1915648604	-0.0578528428	-0.0045695048
C2	0.7380779138	0.2487995492	1.9995464524
C3	0.9177841207	-1.0073451258	2.7347292550
C4	2.1009685961	-1.5430077692	3.0837744176
C5	2.4878983867	-3.6194572433	0.6346249865
O6	1.0583871202	-1.9540125174	-0.2257736421
C7	2.2726742622	-2.3890021033	0.0776056574
C8	3.4297966073	-1.4751329042	-0.3067694587

C9	1.3453136245	-4.5030156999	1.0554435136
C10	3.8735081920	-4.2179363732	0.7748355573
H11	1.6597711792	0.8380857605	1.9368195007
H12	-0.0661278683	0.8647676841	2.4088914371
H13	0.0075837368	-1.5471634442	2.9999230666
H14	2.1666842094	-2.4793286188	3.6288899558
H15	3.0398243445	-1.0476341725	2.8491588813
N16	-0.3151411952	-0.2210320715	-2.2673198189
P17	-1.0099909164	1.8893277359	-0.2353169597
H18	1.2026386203	-5.3564874568	0.3580888722
H19	1.5340795723	-4.9528330440	2.0514005731
H20	0.4021506133	-3.9378683602	1.0961707804
H21	3.4558833885	-1.3843806675	-1.4135071228
H22	3.2005713018	-0.4583710791	0.0668447451
H23	4.1612766875	-4.2676650211	1.8487845849
H24	3.8539533942	-5.2762285658	0.4391254461
C25	-0.1707710001	-1.5388970127	-2.9376804206
C26	0.5848833580	-1.1678773667	-4.2428486570
O27	0.3965718734	0.2867028847	-4.3570544158
C28	-0.0234016542	0.6990763044	-3.1184031584
C29	-0.0901801771	2.1649562186	-2.9507016808
C30	-0.5336065898	2.8158246961	-1.7713310450
H31	0.1849787453	-1.6192735173	-5.1539130856
H32	1.6635538895	-1.3603616856	-4.1744656024
H33	0.4335428166	-2.1672215716	-2.2734206758
C34	-1.5507008039	-2.2342628594	-3.1622908909
C35	-1.3000056189	-3.5938690621	-3.8631928080
H36	-0.8746059321	-3.4698997206	-4.8704068576
H37	-0.6150941371	-4.2177932248	-3.2693802954
H38	-2.2505255673	-4.1371046791	-3.9707983782
C39	-2.4955577412	-1.3642139207	-4.0210720513
H40	-2.0550758561	-1.1204001307	-4.9998245432
H41	-3.4376912446	-1.9035547547	-4.2023374903
H42	-2.7378972057	-0.4251752261	-3.5037520189
C43	-2.2033919921	-2.5068433753	-1.7866159330
H44	-3.1236858616	-3.0968506834	-1.9199341474
H45	-1.5148537869	-3.0636939639	-1.1349875996
H46	-2.4641750329	-1.5673286597	-1.2833208377
C47	-0.7351988819	5.1428542117	3.0777342034
C48	-1.9902940587	4.7276393083	2.6361133318
C49	-2.1006118621	3.7627045552	1.6327710106
C50	-0.9499837117	3.1987892116	1.0607850552
C51	0.3118483935	3.6159099203	1.5230068995
C52	0.4159497924	4.5860115161	2.5170725798
H53	-0.6524707600	5.8936163832	3.8605807615
H54	-2.8904676073	5.1553437529	3.0726229093
H55	-3.0854016586	3.4503657429	1.2964933333
H56	1.2147396958	3.1780202374	1.1024854807
H57	1.3977544977	4.9010793435	2.8635438565
C58	-5.5721822676	1.0976674868	-0.6537203254
C59	-4.9793523413	2.0817837082	-1.4447955083
C60	-3.6099851672	2.3339098202	-1.3456845603
C61	-2.8160674451	1.5952320583	-0.4544319317
C62	-3.4200745858	0.5953567211	0.3276738616
C63	-4.7910605004	0.3570153269	0.2342728769
H64	-6.6399550725	0.9052587831	-0.7322854924

H65	-5.5846466717	2.6582142658	-2.1414020266
H66	-3.1622611951	3.1085298952	-1.9630976861
H67	-2.8092648528	0.0016576511	1.0050616425
H68	-5.2473410856	-0.4162861624	0.8481598024
C69	-0.5766164268	4.2191986417	-1.7623943464
H70	-0.9095791948	4.7354282688	-0.8675032058
C71	0.3066134829	2.9389340228	-4.0524075135
H72	0.6546991590	2.4236847708	-4.9406427424
C73	-0.1888534396	4.9709030312	-2.8705946740
H74	-0.2348239360	6.0568682123	-2.8287902764
C75	0.2606249955	4.3274412581	-4.0192348967
H76	0.5763238190	4.9016115004	-4.8869892838
C77	4.9562887125	-3.4610120967	-0.0033264612
H78	4.8661386095	-3.6803287843	-1.0812050486
H79	5.9587135159	-3.7919330880	0.3110557758
C80	4.7963226149	-1.9385504327	0.2112779548
H81	5.6071565314	-1.3895053766	-0.2934912805
H82	4.8835268496	-1.7225425270	1.2893223041

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Complex **291**

(B3LYP)

Gas Phase Energy = -2032.74615186694 = Eh
Solvent Phase Energy = -0.01150958455 = Eh
Zero Point Energy = 434.278 = kcal/mol
Frequency = -310.74

(PBE)

Gas Phase Energy = -2030.54481985386 = Eh

Geometry Coordinates

Pd1	-0.0043666097	0.0634387862	0.0584997996
C2	0.0070301491	0.1093603823	2.2104800572
C3	1.3809836889	0.0923046314	2.5751574707
C4	2.1337719483	1.2231012929	2.9104985345
C5	3.2615043957	2.1293264681	1.3058756248
O6	1.6508404679	1.4960421691	-0.2819578274
C7	2.1093206112	2.3759665974	0.5197675089
C8	1.2867406393	3.6483812887	0.7117120749
C9	4.1528897960	0.9682068027	0.9203252161
C10	3.9828945429	3.2963699640	1.9819053361
H11	-0.5402218720	1.0258575014	2.4494500813
H12	-0.5664594077	-0.7887870614	2.4359080111
H13	1.8911886327	-0.8702890690	2.5576346448
H14	3.0695012544	1.0739744176	3.4420746077
H15	1.5994052343	2.1238049488	3.2026376188
N16	0.0598027013	-0.1507606747	-2.3652811753
P17	-1.8988267118	-1.1875206227	-0.3477454845
H18	4.8116316350	1.2485030675	0.0735001053
H19	4.8134459789	0.6793548089	1.7587925662
H20	3.5634789877	0.0919793950	0.6127374514
H21	1.2084237611	4.1364644156	-0.2796986047
H22	0.2541749651	3.3496393037	0.9756055892
H23	3.9873328709	3.1615714475	3.0835539236
H24	5.0493474817	3.2771056818	1.6831225435

C25	1.3309108023	0.1810614157	-3.0550807095
C26	0.8910225442	1.2580287268	-4.0897827309
O27	-0.5680682715	1.1190895635	-4.1437226055
C28	-0.9058379715	0.3663336690	-3.0417826594
C29	-2.3556196621	0.2503022358	-2.8003711737
C30	-2.9294723790	-0.4275592628	-1.6914924094
H31	1.2716436199	1.1104281738	-5.1038867802
H32	1.1212299331	2.2758671052	-3.7497625271
H33	2.0131888195	0.6092412024	-2.3126094410
C34	1.9944710527	-1.0877589318	-3.6779034594
C35	3.2954968468	-0.6618860827	-4.4036098376
H36	3.0945550658	-0.0098999411	-5.2665946508
H37	3.9712282665	-0.1305765168	-3.7158460289
H38	3.8216624034	-1.5526772970	-4.7781852931
C39	1.0427151133	-1.7914018068	-4.6709814172
H40	0.7079690166	-1.1106221418	-5.4682127999
H41	1.5575815230	-2.6401635697	-5.1462692117
H42	0.1565372175	-2.1790632194	-4.1497984629
C43	2.3663733904	-2.0656736741	-2.5393859493
H44	2.8776872764	-2.9478889243	-2.9550727816
H45	3.0424607685	-1.5817340672	-1.8185428345
H46	1.4711677153	-2.4015219368	-2.0023770477
C47	-4.9857758571	-1.8215422525	3.0822534802
C48	-4.6702699354	-2.8969135612	2.2525319378
C49	-3.7572341243	-2.7377091227	1.2083770539
C50	-3.1437451996	-1.4952556675	0.9828513043
C51	-3.4608629400	-0.4212893720	1.8344622973
C52	-4.3797126106	-0.5822574108	2.8696882541
H53	-5.6966301602	-1.9495905712	3.8958736944
H54	-5.1374082326	-3.8659337610	2.4167936563
H55	-3.5227954964	-3.5838104971	0.5681301190
H56	-2.9803705094	0.5434447887	1.6830382378
H57	-4.6170652447	0.2585608854	3.5180215106
C58	-1.0423446840	-5.5146784482	-1.8369275927
C59	-2.0652162923	-4.7811237959	-2.4378130859
C60	-2.3378093279	-3.4776209438	-2.0172885838
C61	-1.5817596932	-2.8888154214	-0.9916794829
C62	-0.5435110064	-3.6317485021	-0.4041155969
C63	-0.2836971483	-4.9382818293	-0.8171342513
H64	-0.8345014604	-6.5311394994	-2.1646302183
H65	-2.6572510971	-5.2253558197	-3.2355813982
H66	-3.1436769655	-2.9204076742	-2.4882240108
H67	0.0643119259	-3.1770472487	0.3757621197
H68	0.5194360829	-5.5035453497	-0.3491395012
C69	-4.3309567383	-0.4629720977	-1.5913714220
H70	-4.7900339729	-0.9696964429	-0.7484630146
C71	-3.1991766733	0.8608780164	-3.7429400764
H72	-2.7407847681	1.3829060717	-4.5756876027
C73	-5.1507369355	0.1403645374	-2.5425295950
H74	-6.2320589425	0.0880192955	-2.4339354764
C75	-4.5818586235	0.8083042804	-3.6235973487
H76	-5.2103802919	1.2895048275	-4.3693208260
C77	3.3935843916	4.6746888398	1.6482914839
H78	3.6828770373	4.9697891388	0.6253733622
H79	3.8019437690	5.4363281057	2.3301100420
C80	1.8507165035	4.6395234511	1.7395643891

H81	1.4323039335	5.6436565142	1.5706238144
H82	1.5613964410	4.3467043411	2.7621993770

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Complex **292**

(B3LYP)

Gas Phase Energy = -2032.79265164845 = Eh
Solvent Phase Energy = -0.01320247828 = Eh
Zero Point Energy = 436.003 = kcal/mol

(PBE)

Gas Phase Energy = -2030.58452882899 = Eh

Geometry Coordinates

Pd1	0.0720538868	0.0428463229	0.0099922639
C2	0.1823952393	0.0807276368	3.1441744177
C3	0.9868244414	-0.0413482100	4.4706878791
C4	1.0117446381	0.4512350308	1.9246127186
C5	0.8479732080	1.6552857713	1.2186102544
C6	1.9459401444	-1.2505665304	4.3933555328
O7	1.7797394260	-2.1590009219	3.5946976409
C8	3.0834756682	-1.3205780504	5.4113248468
C9	-0.0108204601	-0.3537065252	5.6196570138
C10	1.7656846439	1.2674364822	4.7784009153
H11	1.6760690159	2.0855625627	0.6590397637
H12	0.0702612855	2.3606437920	1.5081520885
H13	1.9744286139	-0.0554575430	1.8517660042
H14	-0.3256968273	-0.8772717915	2.9927053433
H15	-0.6035676672	0.8337681560	3.2886683122
N16	0.0484820169	-2.2853000136	-0.3976119107
P17	-0.7102341132	0.0214395134	-2.2148560190
H18	3.7706645397	-2.1220425249	5.0937819529
H19	2.6427740306	-1.6388325815	6.3782108942
H20	0.4849699728	-0.4715208688	6.5985465661
H21	-0.7381239401	0.4726328396	5.7119503953
H22	-0.5731314347	-1.2806682257	5.4109840625
H23	2.2926459144	1.5902870483	3.8618999508
H24	1.0323602254	2.0635735350	5.0074200204
C25	0.0609439448	-3.2580504675	0.7255767213
C26	1.2631248171	-4.1793755031	0.3705211187
O27	1.5050457660	-3.9039475631	-1.0474204185
C28	0.8256728704	-2.7365105650	-1.3214621184
C29	1.1008358857	-2.1782701010	-2.6615948386
C30	0.4890408738	-1.0109593988	-3.1967527048
H31	1.0716161971	-5.2510148996	0.4680682596
H32	2.1650133576	-3.9099959040	0.9350579742
H33	0.2646088251	-2.7222304050	1.6595664200
C34	-1.3072661327	-3.9997669336	0.8635278086
C35	-1.2098812150	-4.9996551446	2.0435941864
H36	-0.4866097167	-5.8042555496	1.8447936330
H37	-0.9092094092	-4.4848574196	2.9689330704
H38	-2.1899178524	-5.4701321508	2.2140042606
C39	-1.6726280358	-4.7520967625	-0.4362427854
H40	-0.8854136775	-5.4613605143	-0.7329157546
H41	-2.6021536753	-5.3227565150	-0.2879394314

H42	-1.8358339521	-4.0468267949	-1.2624684923
C43	-2.4121125123	-2.9666683809	1.1845480490
H44	-3.3744282653	-3.4814873145	1.3314558084
H45	-2.1726515138	-2.4156799195	2.1068399847
H46	-2.5240247405	-2.2441332382	0.3673154852
C47	-4.8363112980	-2.0144593546	-2.9723984437
C48	-3.7513922214	-2.3705730274	-3.7726248755
C49	-2.5015840574	-1.7803920205	-3.5680641511
C50	-2.3200197983	-0.8286844618	-2.5522219347
C51	-3.4185615847	-0.4875286143	-1.7442527129
C52	-4.6674240007	-1.0694183139	-1.9590789706
H53	-5.8093280350	-2.4731173374	-3.1356856461
H54	-3.8765619927	-3.1077399192	-4.5635379229
H55	-1.6666922446	-2.0622871319	-4.2047590342
H56	-3.2887940948	0.2376267572	-0.9428108291
H57	-5.5094217762	-0.7901086644	-1.3290662510
C58	-1.0241618164	3.9357099438	-4.7255940687
C59	-0.1324344483	3.8237060081	-3.6579522014
C60	-0.0645545666	2.6401959335	-2.9237900966
C61	-0.8753936666	1.5430660785	-3.2587200675
C62	-1.7745918263	1.6692103634	-4.3306614785
C63	-1.8479227101	2.8591134108	-5.0561857332
H64	-1.0842297636	4.8625131638	-5.2926029702
H65	0.5033051520	4.6649184764	-3.3890527821
H66	0.6078759339	2.5615382272	-2.0710561244
H67	-2.4238350807	0.8383667700	-4.5961507454
H68	-2.5518526350	2.9460398511	-5.8818049236
C69	0.8634098162	-0.6036993693	-4.4874960931
H70	0.4144613913	0.2885664182	-4.9115175531
C71	2.0446382301	-2.8727927175	-3.4370646676
H72	2.5050639468	-3.7562853405	-3.0096107953
C73	1.8006810884	-1.3079279906	-5.2410127888
H74	2.0638814782	-0.9595474772	-6.2377039883
C75	2.3948084026	-2.4497335188	-4.7128787974
H76	3.1313153560	-3.0074737718	-5.2868418177
C77	3.8063600601	0.0213914446	5.6105285093
H78	4.5404854526	-0.0664440798	6.4252479976
H79	4.3696318528	0.2801472431	4.6984207991
C80	2.7902258113	1.1494348280	5.9139507169
H81	2.2935087270	0.9442125103	6.8766427542
H82	3.3219781402	2.1059402224	6.0322366545

****

4.4.4 NOTES AND REFERENCES FOR EXPERIMENTAL SECTION

14. (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045. (b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924–6927. (c) Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. *Org. Lett.* **2007**, *9*, 2529–2531. (d) Krout, M. R.; Mohr, J. T.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 181–193.

15. Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1793–1796.

CHAPTER 5

Enantioselective Tsuji Allylations[†]

5.1 INTRODUCTION

Chapters 2–4 have discussed the specific developments of enantioselective enolate alkylation from the Stoltz laboratories. In order to provide a context for these transformations, this chapter provides a review of all of the published works dealing specifically with the enantioselective Tsuji allylation in both the Stoltz labs and others.

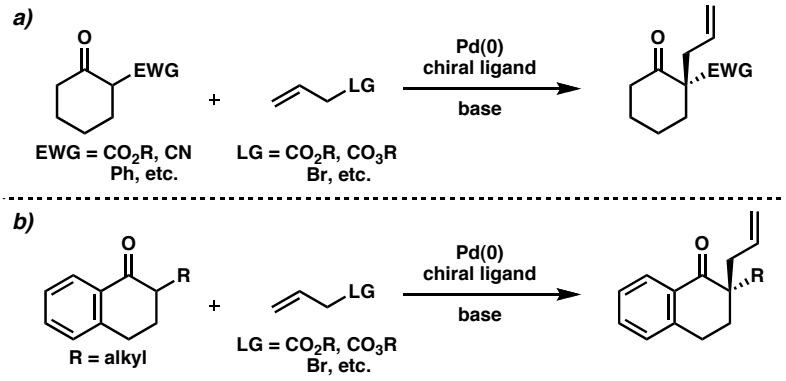
5.1.1 BACKGROUND AND SIGNIFICANCE

The catalytic enantioselective synthesis of quaternary carbon stereocenters is an ongoing challenge to synthetic chemists.[1] Any such reaction must forge a new carbon–carbon bond in the face of significant steric encumbrance to accomplish this goal. As a result, there are relatively few protocols that are both mild and highly enantioselective. Methods for the generation of quaternary stereocenters are extremely desirable given the prevalence of these stereogenic carbon centers in a wide variety of natural products with important structural and biological properties.

[†] An earlier version of this review has been published, see: Mohr, J. T.; Stoltz, B. M. *Chem.–Asian J.* **2007**, *2*, 1476–1491.

One important method for the enantioselective synthesis of quaternary stereocenters is the Pd-catalyzed allylic alkylation of prochiral stabilized enolates developed by Hayashi,[2] Ito,[3] Trost,[4] and Hou and Dai,[5] and their co-workers (Scheme 5.1). These reactions are unusual in the field of asymmetric allylic alkylation because the newly formed stereocenter resides on the nucleophilic partner instead of the electrophilic allyl group.[6] Later, Trost,[7] Hou and Dai,[8] and their co-workers described palladium-catalyzed systems capable of generating quaternary stereocenters with high enantiomeric excess from unstabilized ketone enolates that contain a single acidic position (e.g., tetralones, Scheme 5.1).[9,10] Although these systems have proven useful in a number of applications, one limitation of this methodology is the requirement that there be only a single acidic site or a large pK_a difference between two acidic sites to prevent the formation of mixtures of allylated products from enolate scrambling in situ.[1c] As an example of this deficiency in the literature, the seemingly simple compound 2-allyl-2-methylcyclohexanone (**106**, Scheme 5.2) had not been prepared in highly enantioenriched form prior to the work discussed herein.[11]

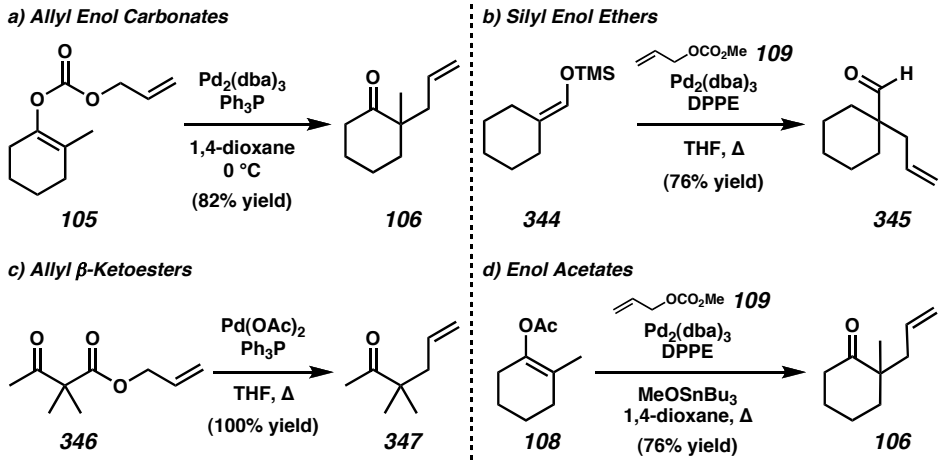
Scheme 5.1. a) Enantioselective allylic alkylation with stabilized enolates b) Enantioselective allylic alkylation with unstabilized enolates



5.1.2 HISTORY

In the 1980s, Professor Jiro Tsuji[12] and his co-workers at the Tokyo Institute of Technology, and later at Okayama University, developed a series of Pd-catalyzed reactions in which unstabilized enolates or enol equivalents were transformed into the corresponding allylated ketones under essentially neutral reaction conditions. Viable substrates for these transformations included allyl enol carbonates,[13] silyl enol ethers,[14] allyl β-ketoesters,[15] and enol acetates[16] (Scheme 5.2). Importantly, each of these Pd-catalyzed decarboxylative reactions is capable of generating a quaternary carbon center.[17] Tsuji published several accounts of his work in the development of this suite of reactions.[18]

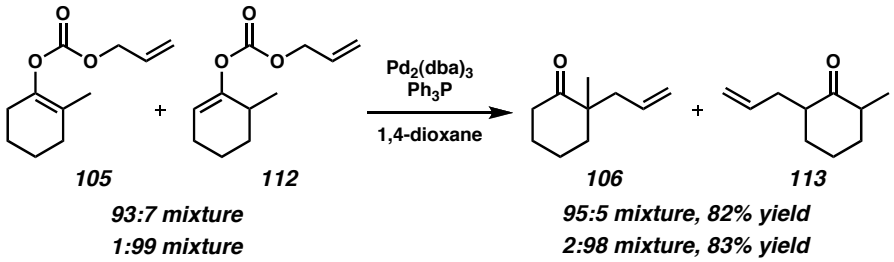
Scheme 5.2. Tsuji allylation reactions



An important observation was the very high levels of regiochemical fidelity observed in these processes (Scheme 5.3). For example, a mixture of allyl enol carbonates enriched in tetrasubstituted enol isomer **105** was converted into α-quaternary ketone **106** with essentially no leakage of material to the isomeric ketone product **113**. Likewise, a mixture enriched in allyl enol carbonate **112** yielded ketone **113** with little trace of the α-

quaternary isomer.[13] Despite this valuable quality, enantioselective variants of these transformations were not disclosed in the 20 years since the initial discoveries.

Scheme 5.3. Regiochemical fidelity in the Tsuji allylation



Over the past three years, significant effort has been underway to develop enantioselective variants of the Tsuji reactions to address the limitations of the asymmetric allylic alkylation protocols. Viable methods for synthesizing all-carbon quaternary stereocenters adjacent to carbonyl groups have been reported from these investigations. In this chapter, the development and utility of these methods for the synthesis of complex molecules will be highlighted.[19] For the purposes herein, the Tsuji allylation is defined as one of the four representative reactions detailed in Scheme 5.2. The enolate intermediate must be revealed in the course of the reaction with CO_2 as a by-product, the enolate must be unstabilized by conjugated electron-withdrawing groups (e.g., esters), and the newly formed stereocenter must reside on the nucleophilic fragment of the product.

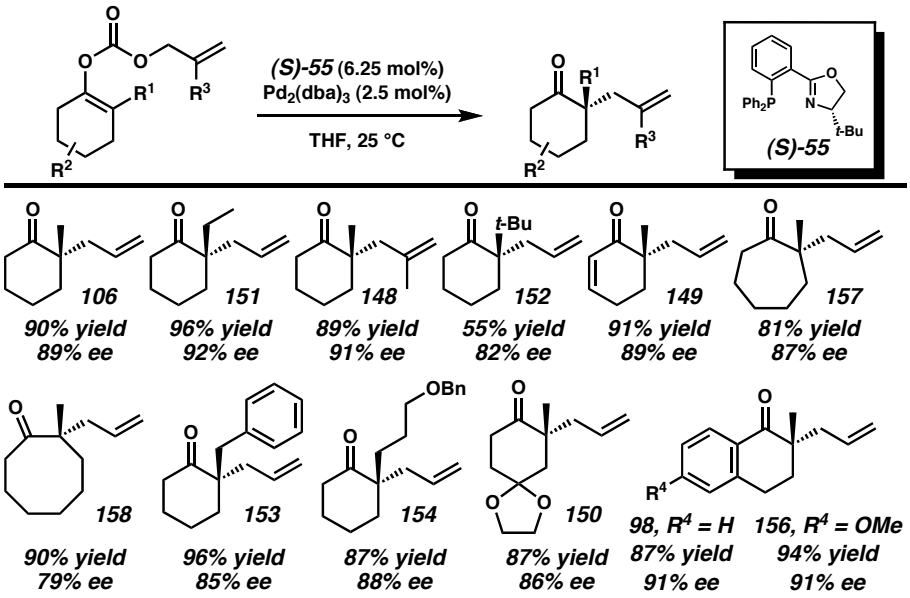
5.2 ALLYL ENOL CARBONATES

5.2.1 SYNTHESIS OF CYCLIC KETONES

In 2004, Behenna and Stoltz reported an enantioselective Tsuji allylation from allyl enol carbonate substrates.[20] An initial screening of chiral ligands quickly identified that chelating P/N ligands were especially effective in terms of yield and enantioselectivity. Specifically, the *tert*-butyl phosphinooxazoline (*t*-BuPHOX; **55**) ligand framework, developed in the 1990s by Pfaltz, Helmchen, and Williams,[21] led to the formation of the elusive 2-allyl-2-methylcyclohexanone (**106**) with up to 89% ee, the first reported synthesis of this simple enantioenriched ketone.

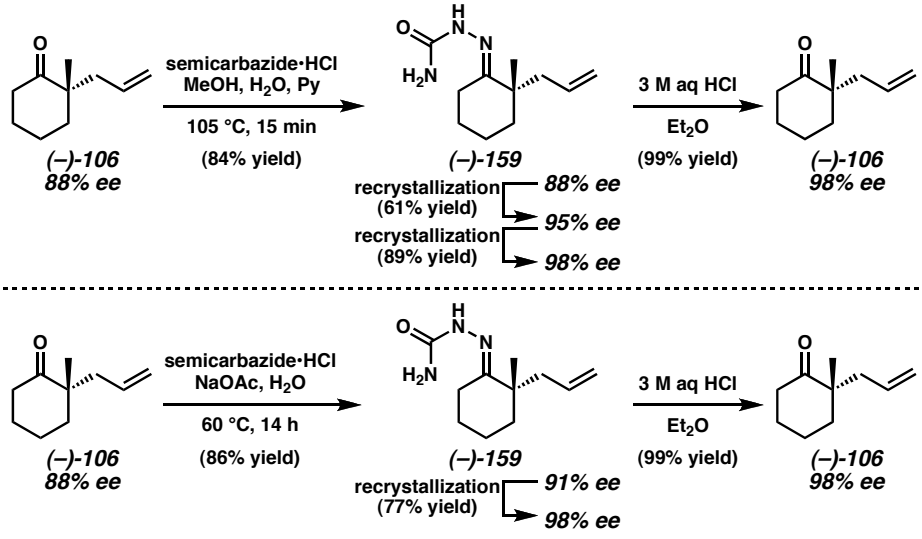
The extension of this result to more complex systems proved rewarding. The mild reaction conditions were tolerant of a variety of substituents and functional groups (Scheme 5.4). Remarkably, these adapted enantioselective Tsuji allylation conditions were capable of generating a quaternary stereocenter adjacent to another quaternary carbon atom in the formation of 2-allyl-2-*tert*-butylcyclohexanone (**152**) with little degradation in enantioselectivity relative to less sterically demanding substrates. The absolute configuration was established for a number of products and, in all cases investigated, the enantiomer shown predominated. An interesting effect observed in this work was that a range of solvents, including ethereal (THF, 1,4-dioxane, Et_2O, *tert*-butyl methyl ether, *i*-Pr_2O), aromatic (benzene, toluene), and carbonyl-containing (EtOAc) solvents, proved to be nearly equally effective for several substrates.

Scheme 5.4. Enantioenriched cycloalkanones produced from allyl enol carbonates



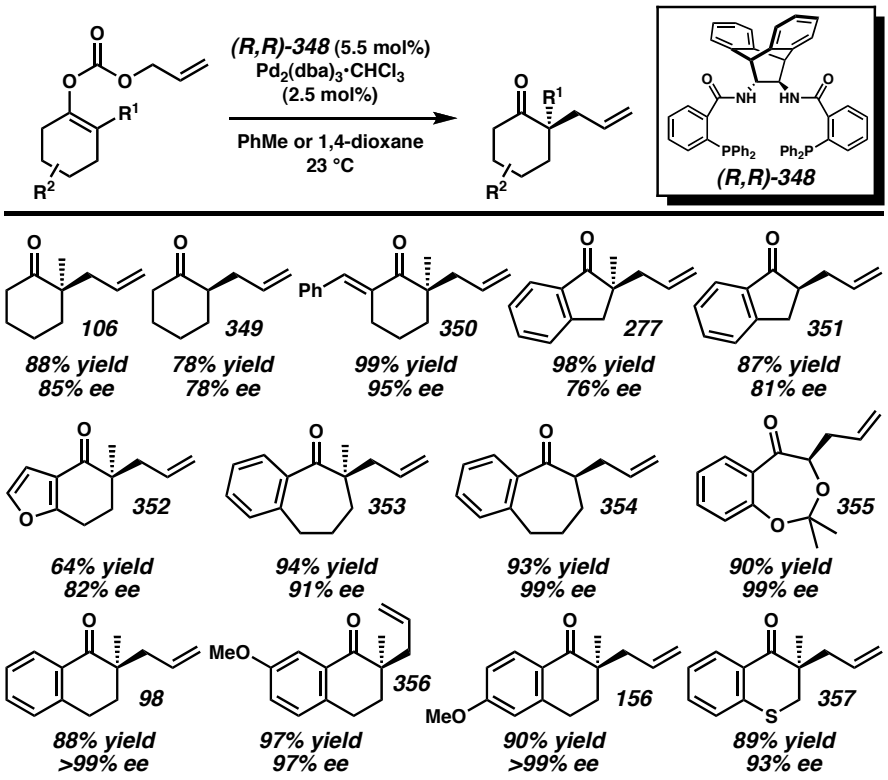
To improve the ee of the cycloalkanone products, straightforward methods of derivitization to the corresponding semicarbazone followed by recrystallization and hydrolysis were developed.[20,22] These protocols allowed the isolation of **106** with 98% ee (Scheme 5.5).

*Scheme 5.5. Enantioenrichment of ketone (–)-**106** via the semicarbazone derivative*



In 2005, Trost disclosed a similar system for enantioselective allylic alkylation from allyl enol carbonate substrates.[23] Although several P/P chelating ligands performed poorly in the work reported by the Stoltz group,[20] Trost found that the uniquely shaped P/P ligand (*R*,*R*)-**348** provided high ee in the allylic alkylation of allyl enol carbonate substrates in toluene (Scheme 5.6). Two examples of substrates with multiple sites of similar acidity were reported. Interestingly, besides the enantioselective formation of quaternary centers, the use of trisubstituted enol precursors led to the formation of highly enantioenriched tertiary stereocenters. Further optimization of the reaction conditions was required in some cases to prevent multiple alkylations at the carbonyl α-position of these trisubstituted enol precursors; use of 1,4-dioxane solvent effectively suppressed overalkylation for some substrates. Also included are the first examples of heterocycles in allylations of this type.[24]

Scheme 5.6. Enantioenriched cycloalkanones produced from allyl enol carbonates

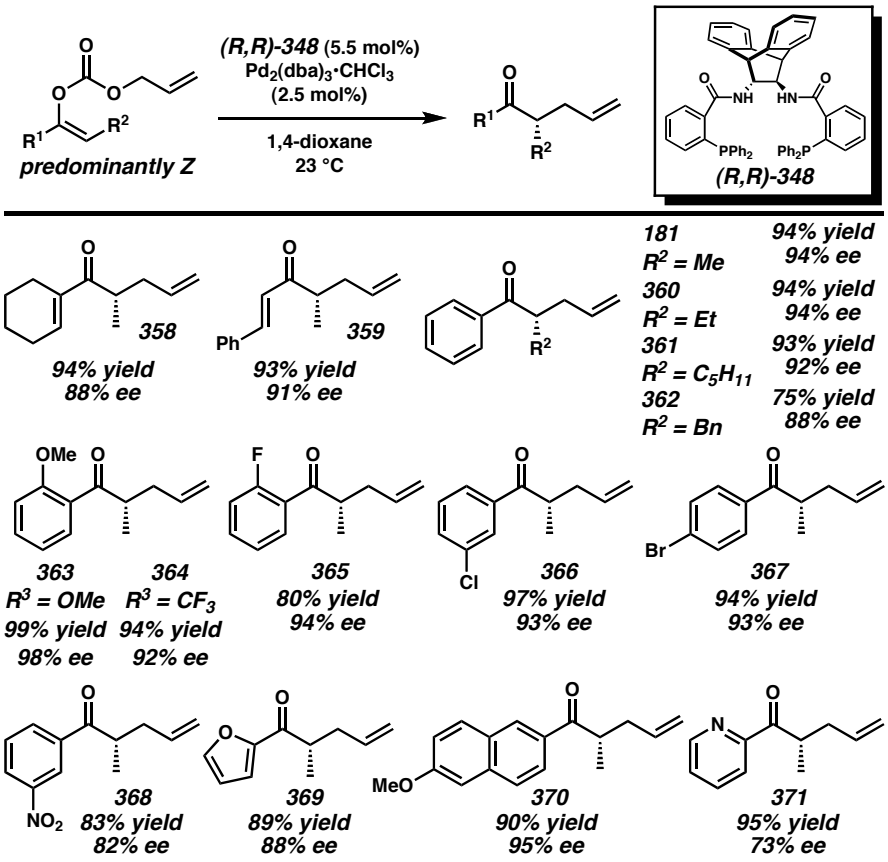


An important facet of this chemistry is the observation that the major enantiomer of the cycloalkanone product is of the opposite sense to that observed in the earlier work of Trost's group with lithium-enolate nucleophiles and a similar ligand in the same enantiomeric series.[7a] This suggests that the mechanism of the reaction with preformed Li-enolate is significantly different from that with Pd-enolate generated in situ.

5.2.2 SYNTHESIS OF ACYCLIC KETONES AND ALDEHYDES

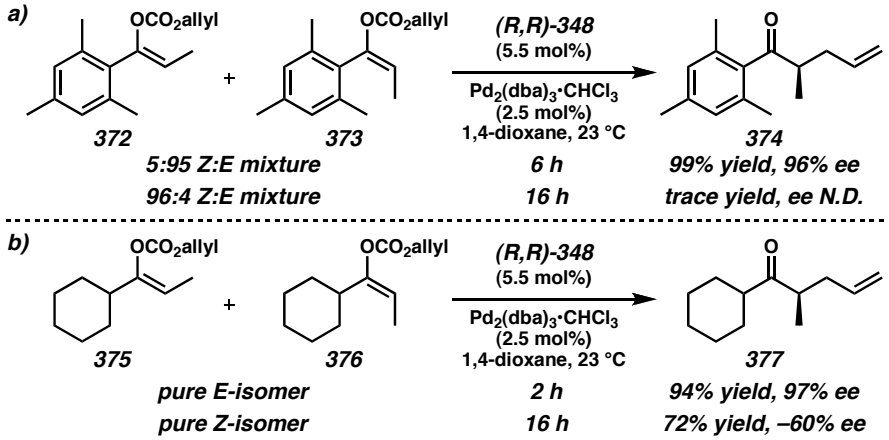
A significant advance in the development of these protocols is the extension to acyclic enolate precursors. Trost's group found that many α-tertiary ketones could be formed with high ee by using the (*R*,*R*)-**348**/Pd(0) catalyst system (Scheme 5.7).[25]

Scheme 5.7. Enantioenriched ketones produced from (Z)-enol carbonates



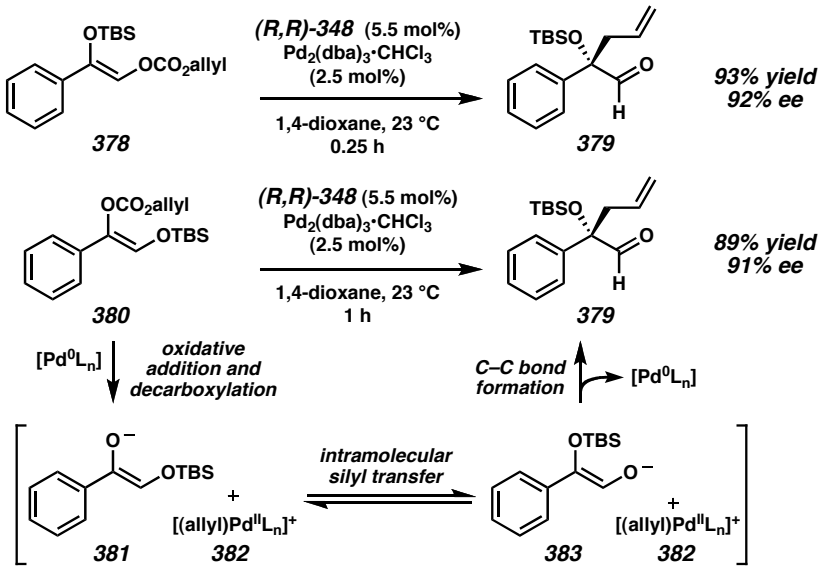
Interestingly, the geometry of the enol precursor affected not only the rate of reaction, but also the absolute configuration of the product (Scheme 5.8). This suggests that neither the enol carbonate nor the putative Pd–enolate complex undergoes significant geometric isomerization. No speculation regarding the origin of the large rate difference between enol isomers was given.

Scheme 5.8. Reactivity differences for (E)- and (Z)-enol carbonates



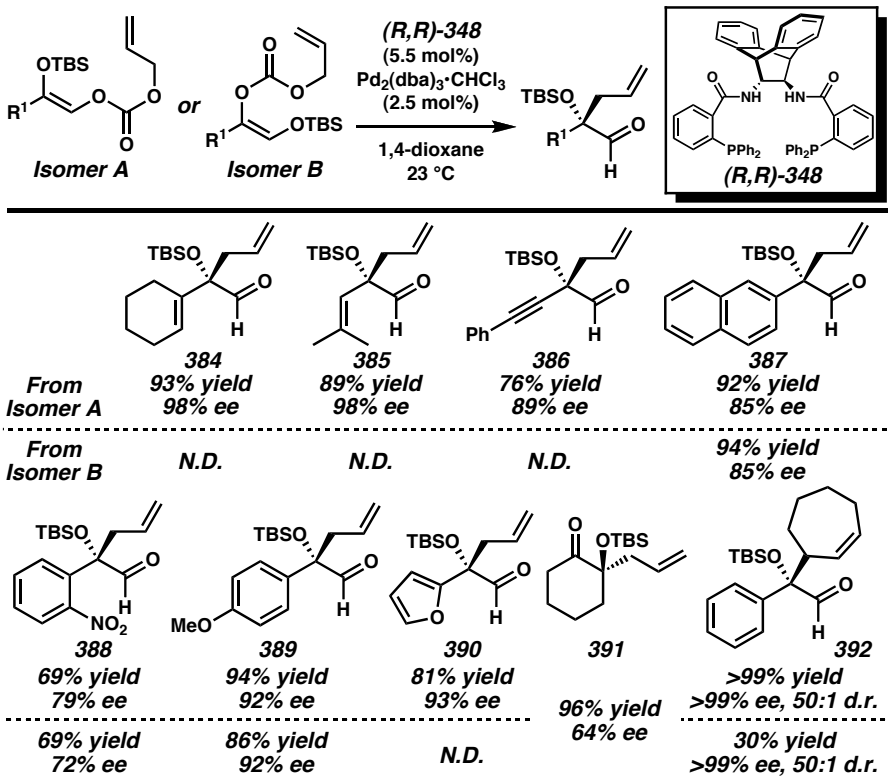
An extension of this chemistry was the incorporation of α-heteroatom-containing substrates. Trost and co-workers found that siloxy-substituted allyl enol carbonates are especially useful in this reaction and are particularly important because of the prevalence of α-hydroxyketones and aldehydes in natural products and pharmaceuticals.[24] Interestingly, isomeric substrates **378** and **380** each led to product **379**, which is derived from a probable aldehyde enolate intermediate (**383**, Scheme 5.9). This most likely occurred by an intramolecular silyl transfer between enolates **381** and **383** followed by subsequent allylation.

Scheme 5.9. Allylic alkylation from isomeric silyloxy substituted allyl enol carbonates



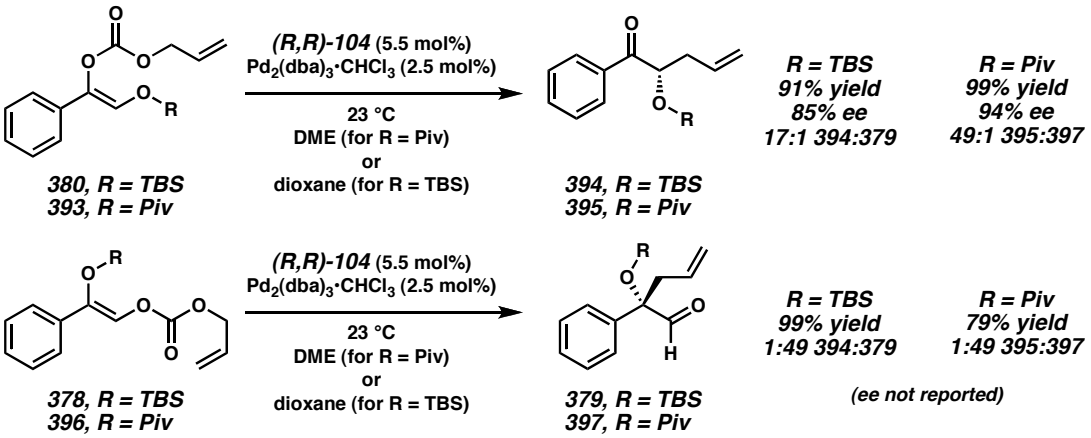
A variety of α-silyloxy aldehydes were prepared in this manner, including one cyclic example of an α□silyloxy ketone (Scheme 5.10). The isomer of the enolate precursor employed affected the rate of reaction and, to a small degree, the level of enantioselectivity. This rate difference was especially noticeable when substituted allyl fragments were employed. The ee of the major diastereomer formed in these cases was uniformly high, and the dr was typically high as well.

Scheme 5.10. Allylic alkylation to form α-silyloxy aldehydes and ketones

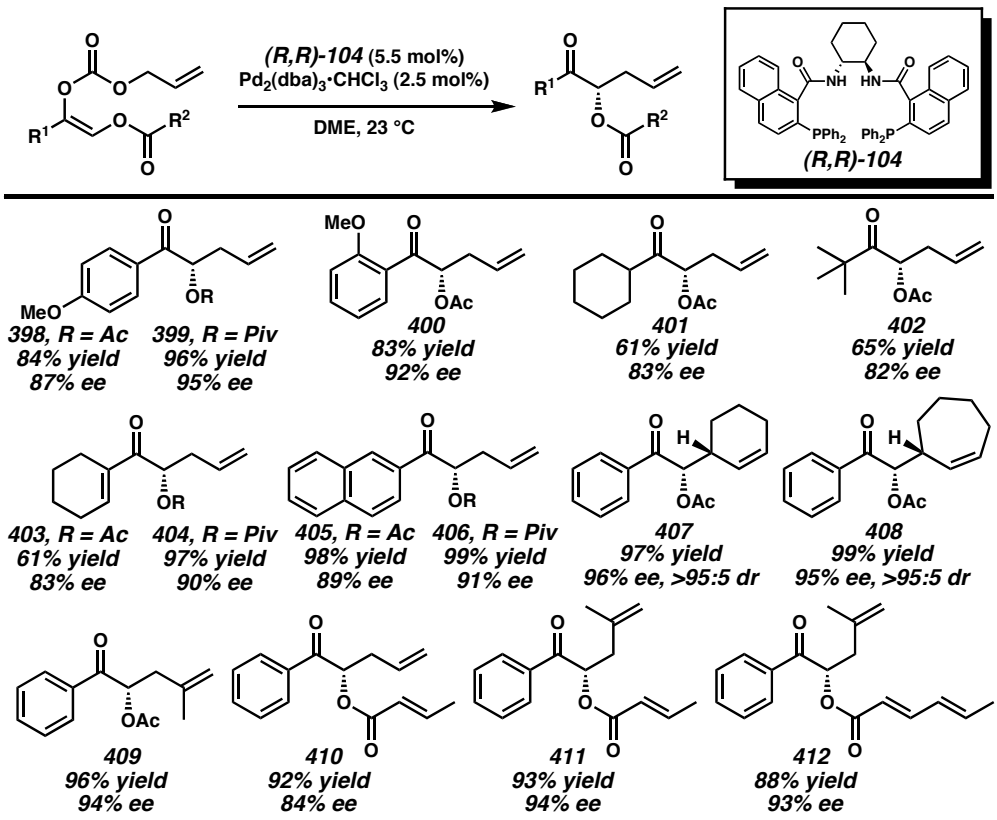


In later work, Trost and co-workers[26] discovered that a change in the nature of the group on oxygen led to a loss of the convergent nature of the reaction. Specifically, acyloxy enol carbonates gave nearly complete regiochemical fidelity depending on the starting material isomer (Scheme 5.11). This result was interpreted as indicating a slow equilibrium between the two isomeric acyloxy enolate intermediates relative to the rate of C–C bond formation. The ratio of product isomers was modulated somewhat by the ligand on Pd, with naphthyl bis(phosphine) ligand **104** ultimately providing the best combination of regioselectivity, yield, and ee for a variety of substrates (Scheme 5.12).

Scheme 5.11. Regiochemical fidelity with acyloxy enol carbonates



Scheme 5.12. Allylic alkylation to form α-acyloxy ketones



Allyl enol carbonate substrates provided the first entries to general allylation of ketone enolates. The importance of this class of enolate precursors is highlighted by their

use in syntheses of natural products and pharmaceutical intermediates. Examples of these applications are discussed in section 5.5.

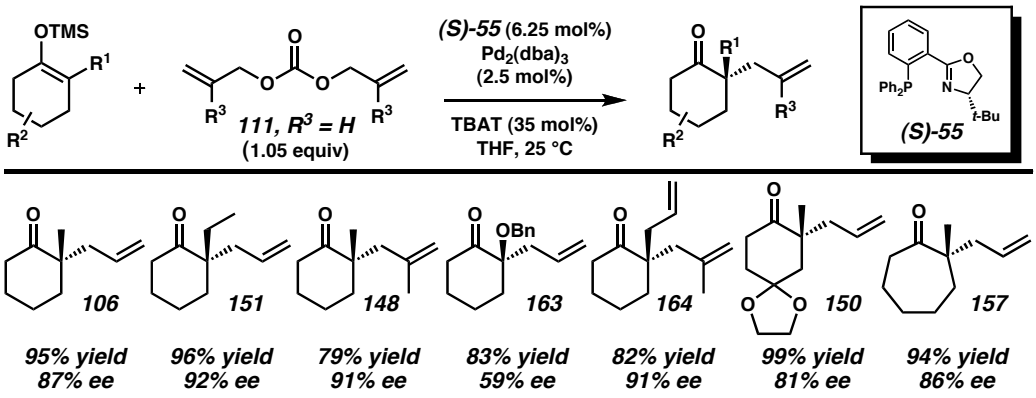
5.3 SILYL ENOL ETHERS

5.3.1 CARBOCYCLIC KETONES

Apart from allyl enol carbonate substrates, Stoltz and co-workers demonstrated the application of the PHOX•Pd(0) catalyst system to a variety of silyl enol ethers.[20,27] These enol silanes are desirable enolate precursors because, in many cases, they are significantly easier to prepare than the corresponding allyl enol carbonates.

The intermolecular nature of this variant of the Tsuji allylation meant that the addition of a diallyl carbonate (e.g., **111**, Scheme 5.13) as a coupling partner was required. Although Tsuji and co-workers reported the allylation of silyl enol ethers without an exogenous activator,[14] it was found that the addition of a substoichiometric amount of the fluoride donor tetrabutylammonium difluorotriphenylsilicate (TBAT) was necessary for the enantioselective reaction at 25 °C. Notably, products obtained from allyl enol carbonate (Scheme 5.4) and silyl enol ether (Scheme 5.13) substrates had nearly identical ee with this catalyst system. This consistent enantioselectivity suggests that the mechanisms of C–C bond formation for both enolate precursors are identical.

Scheme 5.13. Enantioenriched cycloalkanones produced from silyl enol ethers



Although this class of substrate has not been developed to the extent of the allyl enol carbonate variant, the intermolecular reaction could be an important convergent coupling reaction of elaborate fragments toward complex target molecules. Furthermore, this method was recently used in the synthesis of stereodefined tertiary fluorides (see section 5.5.2.1).

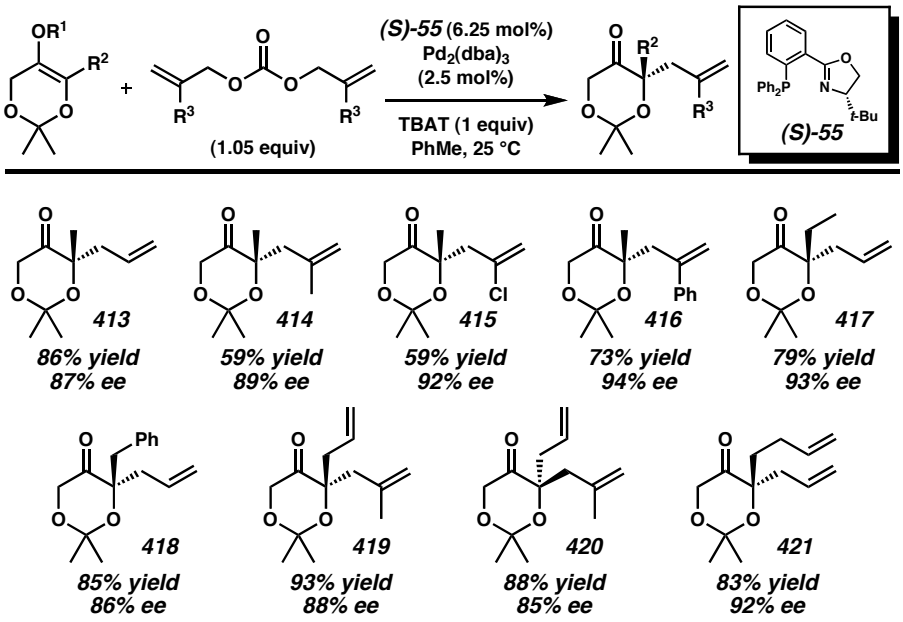
5.3.2 DIOXANONES

Given the success in preparing α-quaternary cycloalkanones, the direct synthesis of enantioenriched α-oxygenated ketones using the Pd•PHOX catalyst was considered as another potentially fruitful avenue of study. Ketones possessing α-oxygenation are particularly challenging and appear in a number of biologically active compounds.[28] Preliminary entries into these systems were through Baeyer–Villiger oxidation of an α-quaternary ketone (see Scheme 5.38a below) or a single example of an oxygenated enol silane that provided a tertiary ether in only moderate ee (**163**, Scheme 5.13). The latter result indicated that an exocyclic heteroatom directly attached to the putative enolate intermediate caused significant disruption to the stereocontrol elements of the catalyst.

Therefore, a class of substrates with the heteroatom contained within the ring were chosen since it would be less likely to interact with the metal center.[29] Dioxanone substrates have been employed in chiral auxiliary-controlled enolate alkylations, and a catalytic enolate alkylation procedure might provide a more efficient entry into these oxygenated products.[30,31]

The solvent had a relatively larger effect on the yield and ee of the product with this class of substrates, and toluene was found to be the preferred solvent. Efficient conversion of the TES enol ethers[32] to product required a full equivalent of TBAT. In the optimal case, exposure of dioxanone-derived enol ethers to the complex derived from [Pd(dmdba)$_2$] and (*S*)-**55** in the presence of diallyl carbonate and TBAT (1 equiv) in toluene at 25 °C led to dioxanone products with high yield and ee (Scheme 5.14). The scope of this transformation was found to include substitutions at the α-position and on the allyl group. These oxygenated products were amenable to a number of subsequent transformations that enabled the enantioselective synthesis of several structural motifs including tertiary oxygenation (see section 5.5.3).

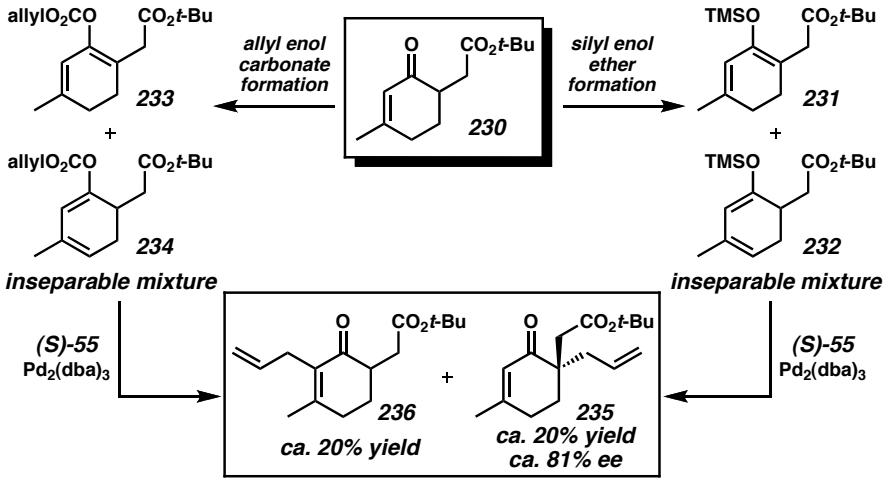
Scheme 5.14. Enantioselective alkylation using dioxanone derived enol silanes



5.4 ALLYL β-KETOESTERS

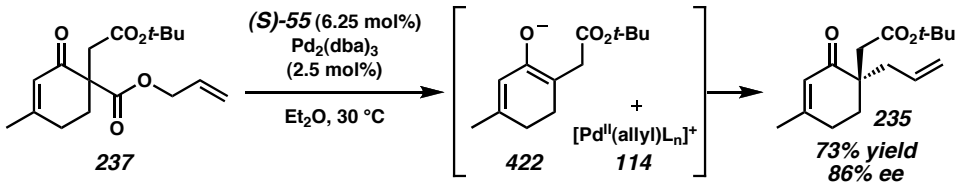
Although the above transformations have proven to be very useful, one particular shortcoming of these protocols is the need to pregenerate the enol equivalent prior to the allylation reaction with an exogenous base (typically an amine or amide base). In some cases, this enolization step provides poor selectivity for the desired enol isomer. Given the high level of regiochemical fidelity demonstrated by Tsuji (Scheme 5.3), these mixtures of enol isomers inevitably lead to mixtures of allylated products and, thus, poor yield. An example is shown in Scheme 5.15.

Scheme 5.15. Non-selective enolization leads to mixtures of allylated products



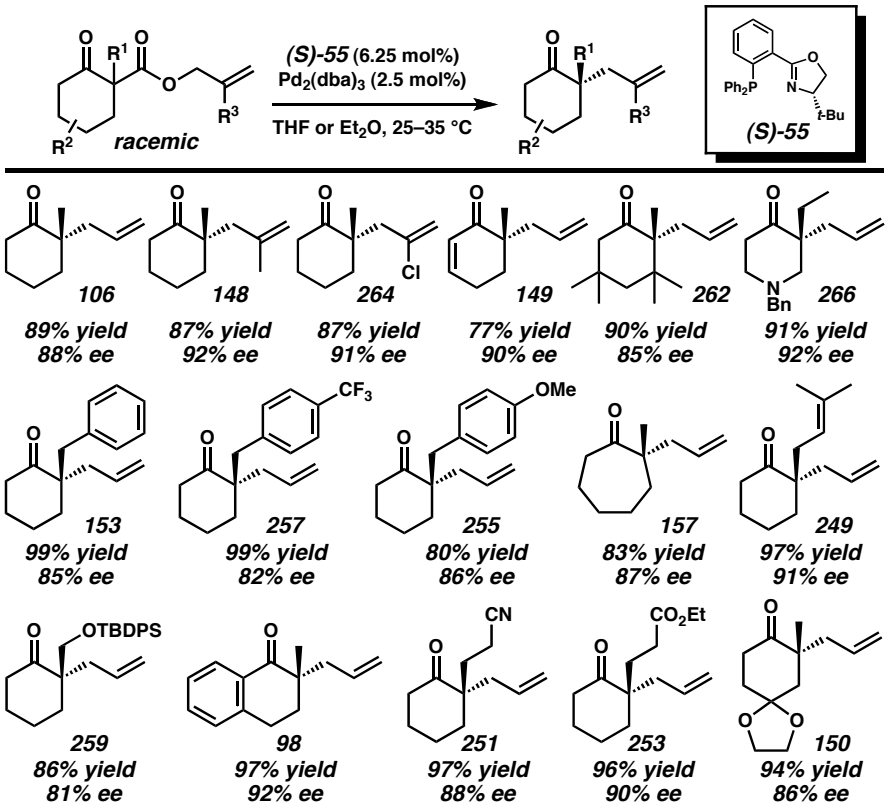
When confronted with this problem, Stoltz and co-workers found a possible solution in the work of Tsuji and Saegusa and their co-workers: allyl β-ketoesters, like the allyl enol carbonate substrates, contain all the necessary components for decarboxylative allylation, and the enolate generation is regiospecific.[15] However, the extension of this substrate class to enantioselective variants was potentially complicated by the intrinsic stereochemistry of the allyl β-ketoester, which could result in kinetic resolution or other problematic effects of double stereodifferentiation.[33] Despite that, substrate kinetic resolution was not observed, and the desired products were formed in excellent yield and with good ee (Scheme 5.16); this transformation of a racemic substrate into an enantioenriched product is an example of an enantioconvergent catalytic reaction.[34] The reaction probably proceeded through Pd-mediated oxidative addition and deallylation of the substrate followed by stereoablative C–C bond cleavage via decarboxylation to form an achiral enolate intermediate, then recombination of the fragments through Pd-mediated stereoselective C–C bond formation.

Scheme 5.16. Enantioselective decarboxylative allylation with an allyl β-ketoester



The substrate scope of the β-ketoester variant of the Tsuji allylation was found to be quite broad. Notably, compounds with high steric demands, such as 2-allyl-2,3,3,5,5-pentamethylcyclohexanone (**262**), were produced in good yield and with high ee (Scheme 5.17). Interestingly, substrates that bear β-leaving groups did not suffer elimination, and substrates that contain other acidic functional groups (e.g., nitrile, ester) did not cause enolate scrambling. Furthermore, allyl groups substituted at the central carbon atom (e.g., methyl, chloro) led to increased ee. The ketones produced from allyl β-ketoesters, allyl enol carbonates, and silyl enol ethers were formed in nearly identical yield and ee with this catalyst system.

Scheme 5.17. Enantioenriched cycloalkanones prepared from allyl β-ketoesters

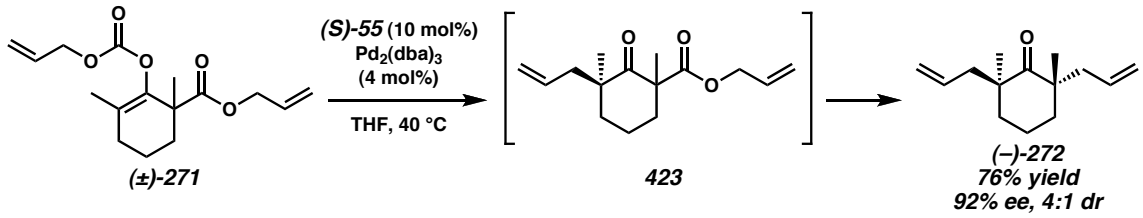


Also demonstrated was the tolerance of a fluorine atom at the α-position of the racemic substrate, a concept that was later developed further by Nakamura and others (see section 5.5.2.1). In the work of Nakamura and co-workers, three examples of the formation of quaternary stereocenters from allyl β-ketoesters were included as well.[35]

Apart from the development of the β-ketoester substrate class, Stoltz and co-workers reported the use of a masked β-ketoester moiety to effect a cascade reaction that generates two quaternary stereocenters in a single reaction (Scheme 5.18).[34] Presumably, the allyl enol carbonate functionality of substrate **14** reacted rapidly, thus generating the first quaternary stereocenter and revealing allyl β-ketoester **15**, which underwent further reaction. Ketone **16** was isolated in 76% yield and with 92% ee as a 4:1 mixture of

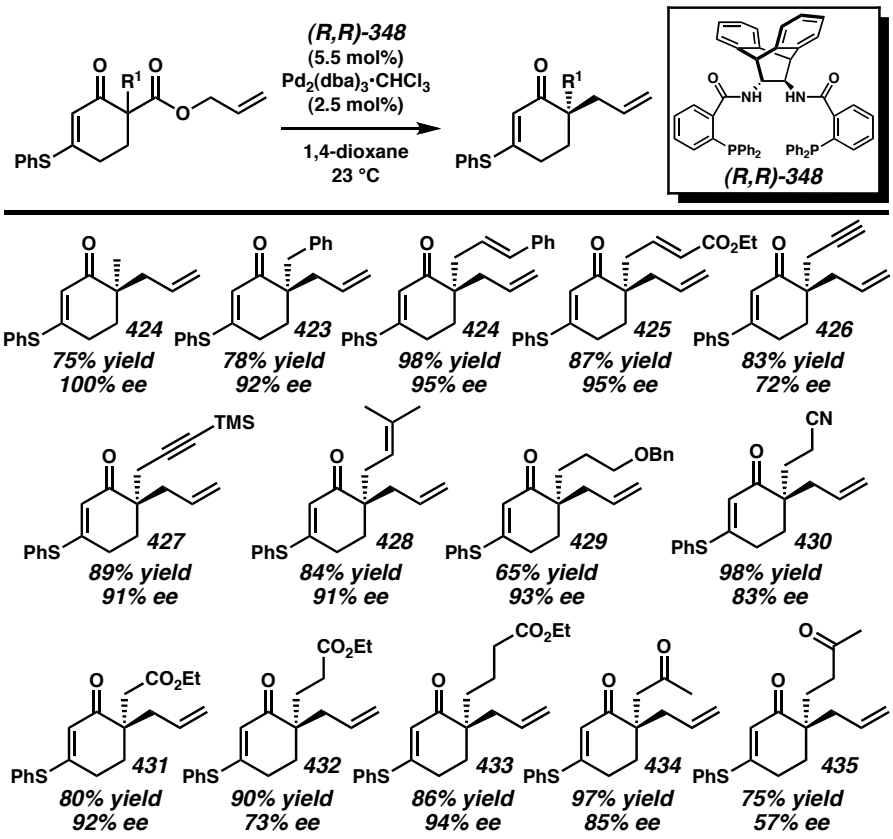
C_2/meso diastereomers. A similar double-alkylation strategy was successfully applied to the total synthesis of cyanthiwigin F (see section 5.5.1.4).

Scheme 5.18. Enantioselective cascade allylation generating two quaternary stereocenters



Subsequent to this initial report, Trost and co-workers described the application of the bis(phosphine)/Pd(0) catalyst to the enantioselective allylic alkylation of vinylogous ester and thioester enolates.[36] When they were confronted with a similar problem of nonselective enolization in enol carbonate formation, the β-ketoester motif was explored. Unlike the PHOX system, some variation in product ee was observed depending on the nature of the enolate precursor (i.e., allyl enol carbonate vs. allyl β-ketoester). Notably, the level of substrate conversion observed was sensitive to the nature of the substituent of the vinylogous ester moiety. To address this problem, vinylogous thioester substrates were examined, and the reactivity was improved. A variety of substitutions were possible, and products with high ee were obtained in many cases (Scheme 5.19). Details of the synthetic utility of these products are shown in section 5.5.3.

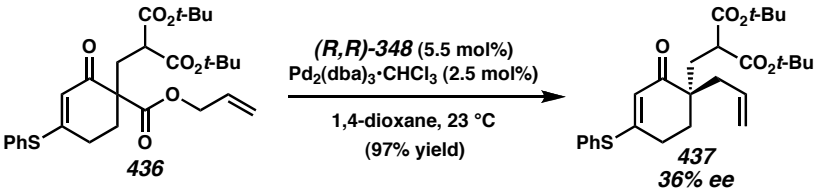
Scheme 5.19. Vinylogous thioesters prepared from allyl β-ketoesters



Trost and co-workers suggested that substrates that bear Lewis basic groups (e.g., alkyne or carbonyl) nearby may cause a decrease in enantioselectivity by chelating to palladium in the course of enantiodetermination, thereby leading to decreased ee in the product. This effect contrasts results in Stoltz' work, whereby neighboring Lewis basic groups had little effect (Scheme 5.17).

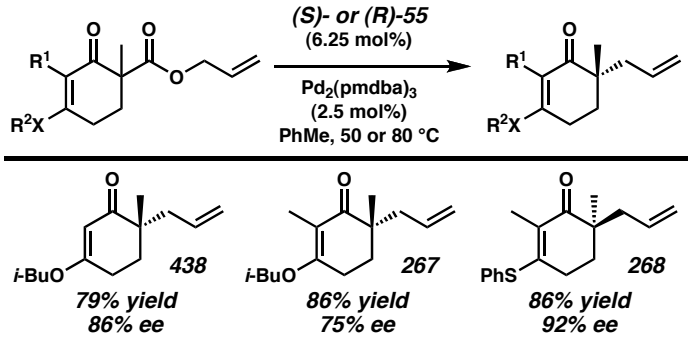
Allylation in the presence of an acidic 1,3-diester moiety highlighted the regiochemical fidelity of the allylation process in an extreme case, although the ee was decreased considerably (Scheme 5.20).

Scheme 5.20. Allylation in the presence of a pendent 1,3-diester



Stoltz and co-workers have reported alkylation of vinylogous esters and thioesters using the Pd•PHOX catalyst system.[37] High yields and enantiomeric excess were obtained under slightly modified reaction conditions. The vinylogous thioester **268** was employed in the total syntheses of carissone (see section 5.5.1.7) and cassiol (see section 5.5.1.8). Enol carbonates could also be used in some cases (see section 5.5.1.5).

Scheme 5.21. Alkylation of vinylogous esters and thioesters with the Pd•PHOX catalyst system



Allyl β-ketoester substrates are very practical because of the simple substrate preparation, the bench-top stability of quaternary β-ketoesters, and the relative ease of purification. These facets have enabled the preparation of ketone products in multi-gram quantities.[22] The enantioconvergent nature of this reaction is conceptually interesting and provides a useful method for the conversion of racemic materials into valuable enantioenriched products.

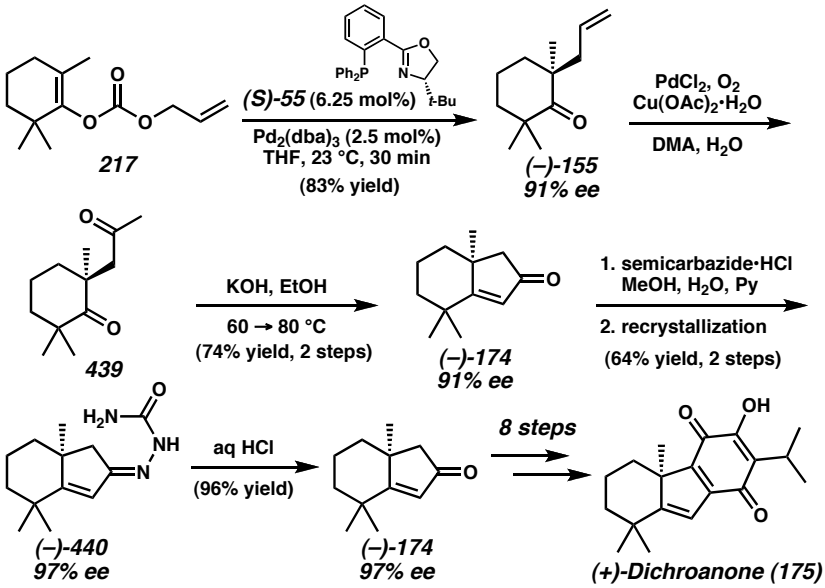
5.5 SYNTHETIC APPLICATIONS OF ENANTIOENRICHED CYCLOALKANONES

5.5.1 APPLICATIONS IN TARGET-DIRECTED SYNTHESIS

5.5.1.1 TOTAL SYNTHESIS OF (+)-DICHROANONE

Although the Tsuji allylation has seen only sparse use in total synthesis to date,[38] the prevalence of quaternary carbon stereocenters in natural products provides an ample proving ground for the utility of the enantioselective Tsuji allylation protocols described above. One class of compounds that bears this structural motif is a group of structurally similar norditerpenoids, which include the tricyclic *p*-quinone dichroanone (**175**, Scheme 5.22).[39] Recently, the enantioselective Tsuji allylation played a key role in the enantioselective total synthesis of (+)-dichroanone (**175**) by McFadden and Stoltz.[40]

Scheme 5.22. Enantioselective Tsuji allylation in the total synthesis of (+)-dichroanone



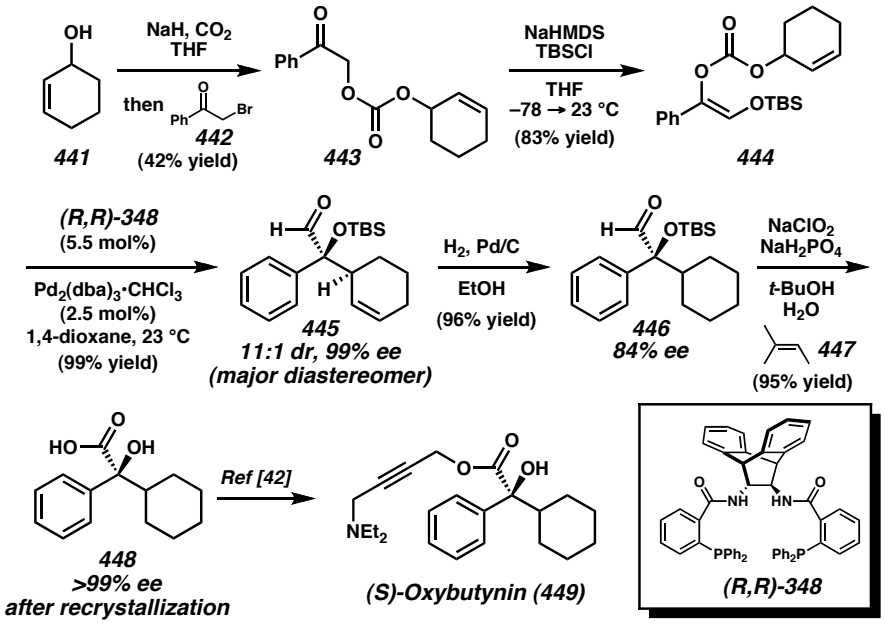
The synthesis commenced from allyl enol carbonate **217**, which underwent enantioselective Tsuji allylation to form ketone (–)-**155** with 91% ee. Attempts to

generate the corresponding semicarbazone derivative to improve the ee of this material (Scheme 5.5) were negated by the presence of two quaternary centers adjacent to the ketone. However, Wacker oxidation and aldol condensation led to bicyclic enone (–)-**174**, which readily formed semicarbazone derivative (–)-**440**. Recrystallization of this material and hydrolysis of the semicarbazone provided enone (–)-**174** with 97% ee. Conversion of bicycle (–)-**174** into **175** was achieved in eight steps. The material produced by this route was enantiomeric to the natural isolate, which was of unknown absolute configuration. Therefore, this total synthesis unambiguously proved the configuration of *nat*-(–)-(*S*)-dichroanone (**175**). Dichroanone was produced in 11 steps from commercially available material in 4% overall yield without the use of protecting groups.

5.5.1.2 FORMAL SYNTHESIS OF OXYBUTYNIN

The reported conversion by Trost's group of allyl enol carbonates into α-hydroxy aldehydes[25] was highlighted by the formal synthesis of (*S*)-oxybutynin (**449**; Scheme 5.23), a pharmaceutical compound used to treat various urinary disorders. Although commercial oxybutynin is sold as a racemic mixture, some studies suggest that enantiopure (*S*)-oxybutynin may offer improved pharmaceutical properties. As a result, asymmetric methods of producing (*S*)-oxybutynin may become valuable.[41]

Scheme 5.23. Enantioselective formal synthesis of (S)-oxybutynin



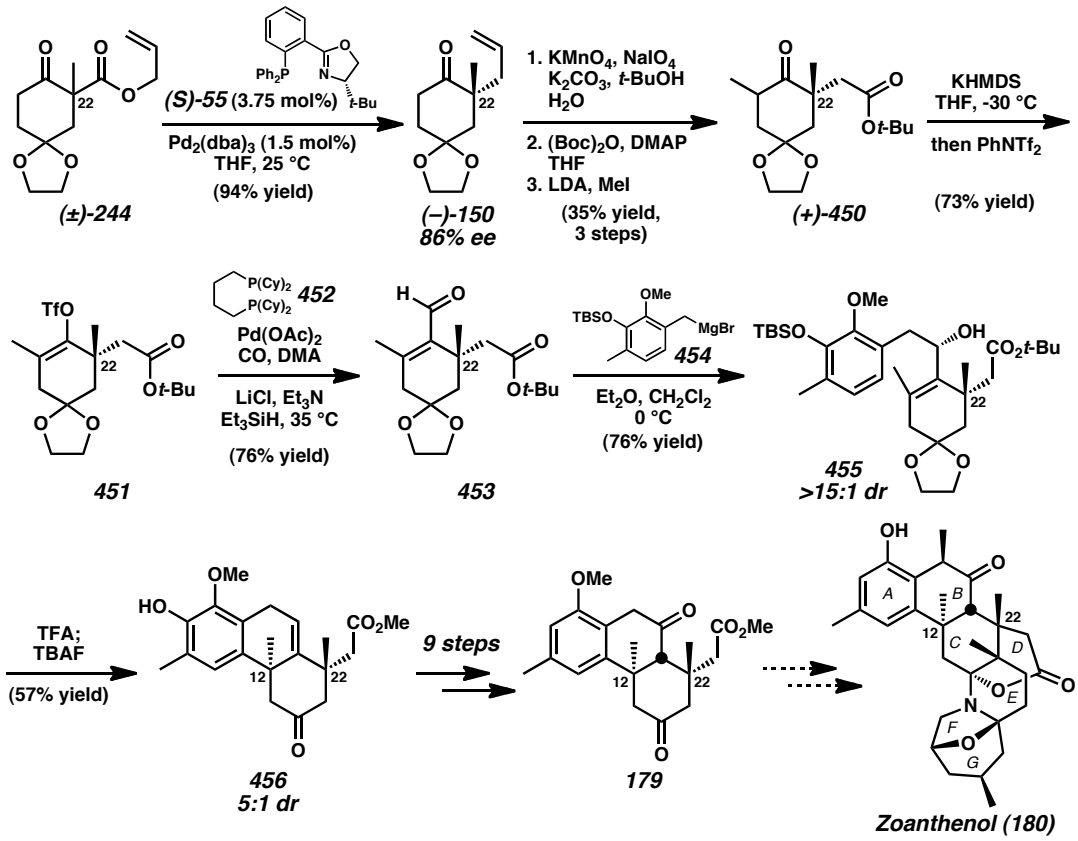
The synthesis began with the one-step formation of mixed carbonate **443** from alcohol **441**, CO_2, and α-bromoacetophenone (**442**). Treatment with base and TBSCl initiated a shift of the carbonate group, and the resulting aldehyde enolate was trapped as the enol silane (**444**). Decarboxylative allylation was effected with Pd(0) supported by bis(phosphine) ligand (*R*,*R*)-**348** to yield α-tertiary aldehyde **445** as an 11:1 mixture of diastereomers. Although the ee of the major diastereomer was 99%, subsequent olefin hydrogenation of the diastereomeric mixture led to aldehyde **446** with 84% ee. Oxidation with concomitant silyl ether cleavage formed (*S*)-**448**, a known intermediate in the synthesis of oxybutynin;[42] recrystallization of (*S*)-**448** increased its ee from 84% to over 99%.

5.5.1.3 PROGRESS TOWARD ZOANTHENOL

The zoanthus alkaloids are a family of polycyclic marine natural products with complex molecular architectures and interesting biological properties. These compounds have attracted significant attention from the synthetic community on the basis of their challenging structural features and their significant biological activity (antiosteoporotic, cytotoxic, antibacterial).[43] Despite the large body of work toward these natural products, only one member of the class, norzoanthamine, has had its total synthesis achieved.[44]

One of the greatest challenges posed by the zoanthus alkaloids is the three quaternary carbon stereocenters about the C ring. The Stoltz group recently reported an approach to the synthesis of one member of this class, zoanthenol (**180**, Scheme 5.24), and addressed these difficult stereocenters by an acid-mediated cyclization reaction to form the B ring.[45] The stereochemistry of the two stereocenters generated in this ring-forming reaction would ultimately be directed by the configuration of the quaternary stereocenter at C22.

Scheme 5.24. Progress toward the total synthesis of zoanthenol



To fully exploit the key diastereoselective steps of this synthetic approach, an enantioselective method to form the C22 quaternary carbon center was required. To this end, readily available allyl β-ketoester **244** was treated with catalytic [$Pd_2(dba)_3$] and (*S*)-tBuPHOX to form ketone (–)-**150** in 94% yield and with 86% ee. Oxidative olefin cleavage followed by esterification and methylation formed ketone (+)-**450**, an immediate precursor to enol triflate **451**.

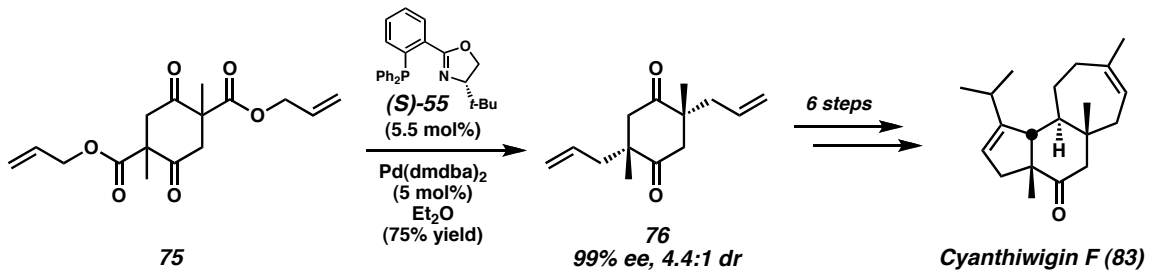
Toward the completion of the tricyclic core, racemic enol triflate **451** was converted into enal **453** through an interesting Pd-catalyzed reductive carbonylation. Highly diastereoselective addition of Grignard reagent **454** yielded cyclization precursor **455**, which, upon exposure to TFA, formed both the B ring and the key C12 quaternary stereocenter with good diastereocontrol. Further elaboration of tricycle **456** over nine

steps led to diketone **179**, which bears the correct stereochemical triad for the natural product (confirmed by X-ray crystallography).

5.5.1.4 TOTAL SYNTHESIS OF CYANTHIWIGIN F

The cytotoxic marine diterpenoid natural product cyanthiwigin F (**83**, Scheme 5.25) possesses a core structure laden with four contiguous stereocenters, two of which are all-carbon quaternary centers. Enquist and Stoltz[46] sought to construct both of these challenging quaternary carbon stereocenters through a double enantioselective Tsuji alkylation reaction. The requisite substrate (**75**) was prepared as mixture of *rac*- and *meso*-diastereomers, but upon exposure to the Pd•PHOX catalyst complex all three substrate stereoisomers were selectively converted to (*R*,*R*)-**76** in 78% yield and a 4.4:1 dr. The major diastereomer was formed with 99% enantiomeric excess, likely through a Horeau-type enhancement of the overall ee.[47] Enantioenriched diketone **76** was elaborated to cyanthiwigin F (**83**) in six additional steps (for a more complete discussion, see section 1.3.7). Owing to the high degree of stereochemical complexity introduced by the double enantioselective alkylation reaction, the completion of cyanthiwigin F required only nine steps from known starting materials.

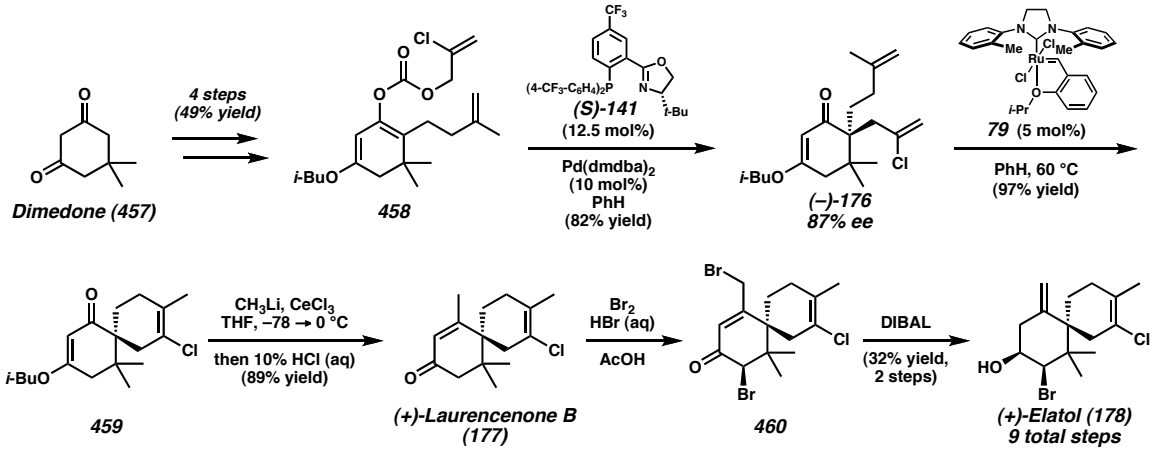
Scheme 5.25. Total synthesis of cyanthiwigin F via double enantioselective alkylation



5.5.1.5 TOTAL SYNTHESIS OF LAURENCENONE B AND ELATOL

Many naturally occurring halogenated compounds have been identified.[48] These metabolites often possess interesting biological activities and their structures pose unusual challenges to synthetic chemistry. One specific example is the cytotoxic and antifungal chamigrene natural product elatol (**178**, Scheme 5.26). From a structural standpoint, the spiro quaternary stereocenter is particularly challenging. Grubbs, Stoltz, and their co-workers[49] envisioned synthesizing the spiro-[6,6] carbocycle via ring-closing metathesis of an α,ω-diene derived from an enantioselective ketone alkylation (i.e., **176**). To this end, enol carbonate substrate **458** was prepared in four steps and 49% yield from dimedone (**457**). The decarboxylative alkylation reaction provided modest results (23% yield, 81% ee) when ligand **55** was used. Installation of electron-withdrawing groups on the ligand provided a substantial increase in reactivity, and permitted alkylation product **176** to be isolated in 82% yield and 87% ee. The challenging ring-closing metathesis reaction to form the tetrasubstituted alkene present in the natural product was achieved using the highly active Ru-catalyst **79**.[50] Addition of methyllithium in the presence of $CeCl_3$ and subsequent acidic workup formed the natural product (+)-laurencenone B (**177**) in 89% yield. Bromination of spirocycle **177** with elemental bromine introduced the necessary secondary bromide with good diastereoselectivity. Reduction of dibromide **460** with DIBAL completed the first total synthesis of (+)-elatol (**178**).

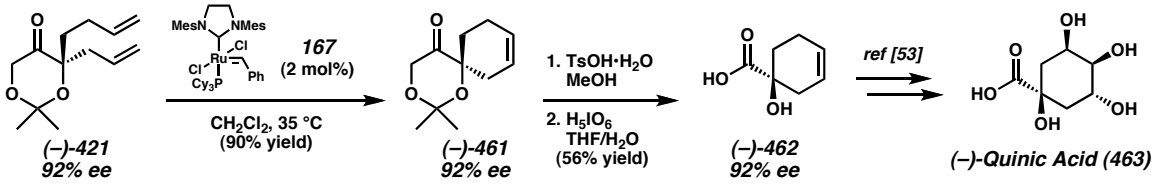
Scheme 5.26. Total syntheses of laurencenone B and elatol



5.5.1.6 FORMAL SYNTHESIS OF QUINIC ACID

Quinic acid (**463**) is a common chiral pool starting material used in many synthetic efforts,[51] including the total synthesis of dragmacidin F reported by Stoltz and co-workers.[52] Dioxanone **421** could be converted to cyclohexene **462** in three steps and 50% yield (Scheme 5.27). Hydroxy acid **462** has previously been employed in the synthesis of quinic acid (**463**).[53]

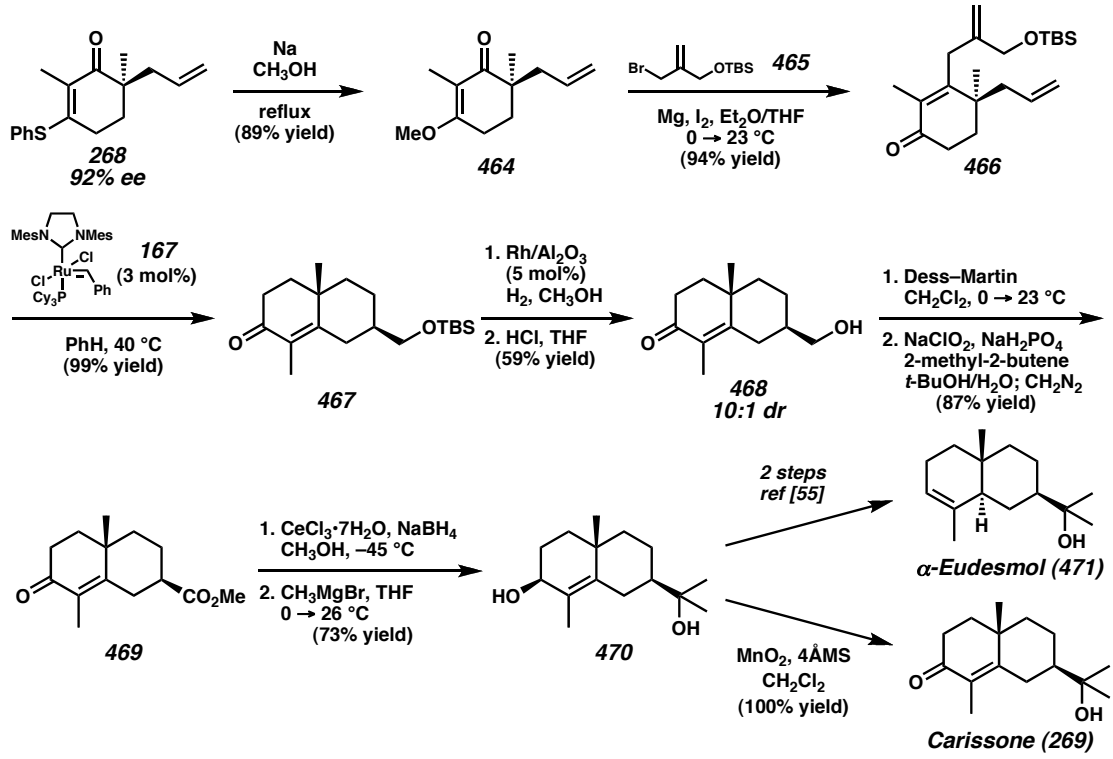
Scheme 5.27. Formal synthesis of quinic acid



5.5.1.7 TOTAL SYNTHESIS OF CARISSONE

The antibiotic carissone (**269**, Scheme 5.28) is representative of the eudsmane class of sesquiterpenoid natural products. Stoltz and co-workers[37a] envisioned a general approach to this group of metabolites through a ring-closing strategy. Toward this goal, enantioenriched vinylogous thioester **268** was converted to the vinylogous ester in order facilitate addition of allyl Grignard reagent derived from bromide **465**. Following acidic workup, substituted cyclohexanone **466** was isolated in excellent yield. Ring-closing metathesis with Grubbs' second-generation catalyst (**167**)[54] was followed by regio- and diastereoselective olefin hydrogenation with heterogeneous Rh. Cleavage of the silyl ether under acidic conditions formed primary alcohol **468**. After oxidation and esterification (**468** → **469**), the enone moiety was reduced diastereoselectively to the allylic alcohol. Addition of methylmagnesium bromide formed diol **470**, which is an intermediate in Aoyama's synthesis of (α)-eudesmol (**471**).[55] Alcohol oxidation by action of manganese dioxide provided (+)-carissone (**269**) quantitatively.

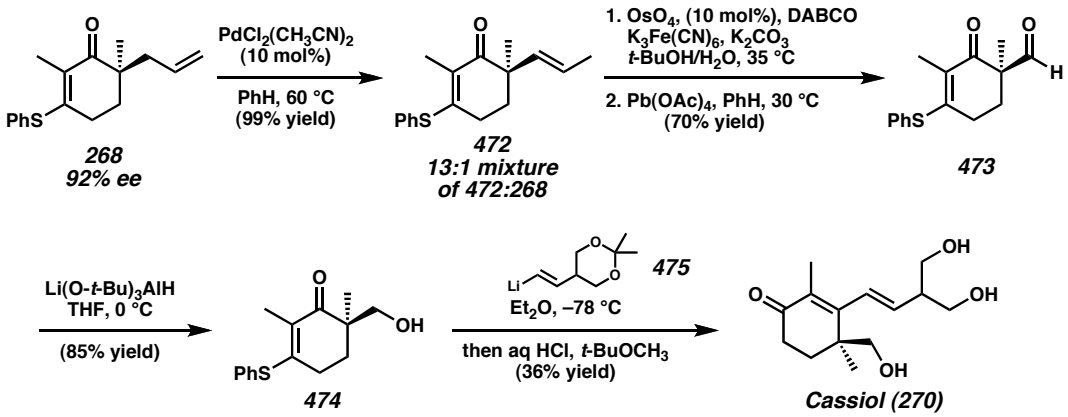
Scheme 5.28. Enantioselective synthesis of carissone



5.5.1.8 TOTAL SYNTHESIS OF CASSIOL

The antiulcerogenic sesquiterpenoid cassiol (**270**, Scheme 5.29) was also targeted by Stoltz and co-workers.[37b] Toward this target molecule, enantioenriched vinylogous thioester **268** was isomerized to (*E*)-alkene **472** with $PdCl_2(CH_3CN)_2$ in refluxing benzene. Oxidative cleavage of the disubstituted alkene was challenging, but ultimately accomplished by olefin dihydroxylation and diol oxidation with lead tetraacetate. The resulting aldehyde (**473**) was chemoselectively reduced with a bulky aluminum hydride reagent to form alcohol **474**. Addition of thioester **474** to a solution of vinyllithium reagent **475** provided (+)-cassiol (**270**) in 12% overall yield after acidic workup. For further details, see Chapter 9.

Scheme 5.29. Enantioselective total synthesis of cassiol



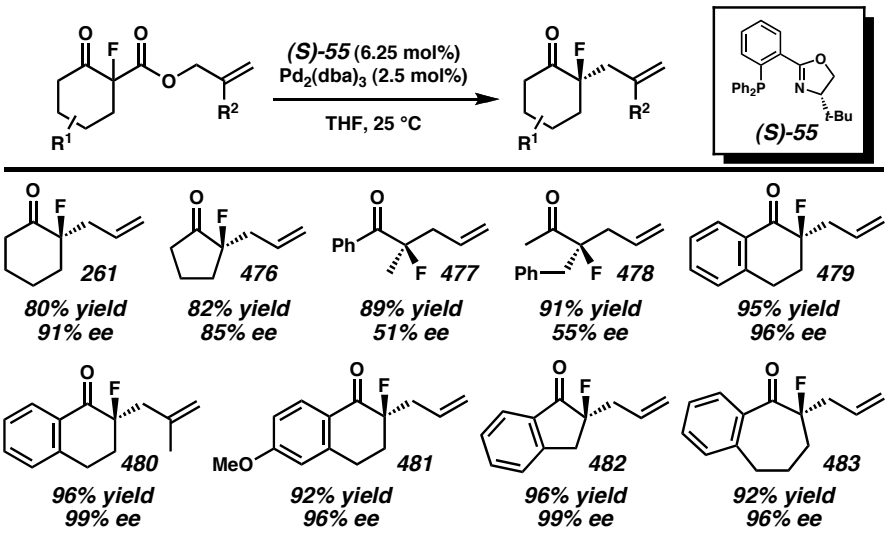
5.5.2 METHODOLOGICAL APPLICATIONS

5.5.2.1 α-FLUORINATED CYCLOALKANONES

Stereodefined α-fluoroketones are intriguing compounds for synthetic and medicinal chemistry. The asymmetric synthesis of such compounds, however, has been quite challenging.[56] The mild reaction conditions and functional-group tolerance of the Tsuji allylation protocol are ideal for the incorporation of fluorine atoms. Moreover, the facile fluorination of β-ketoesters with electrophilic reagents, such as Selectfluor®, allows the straightforward preparation of fluorine-containing substrates.[57]

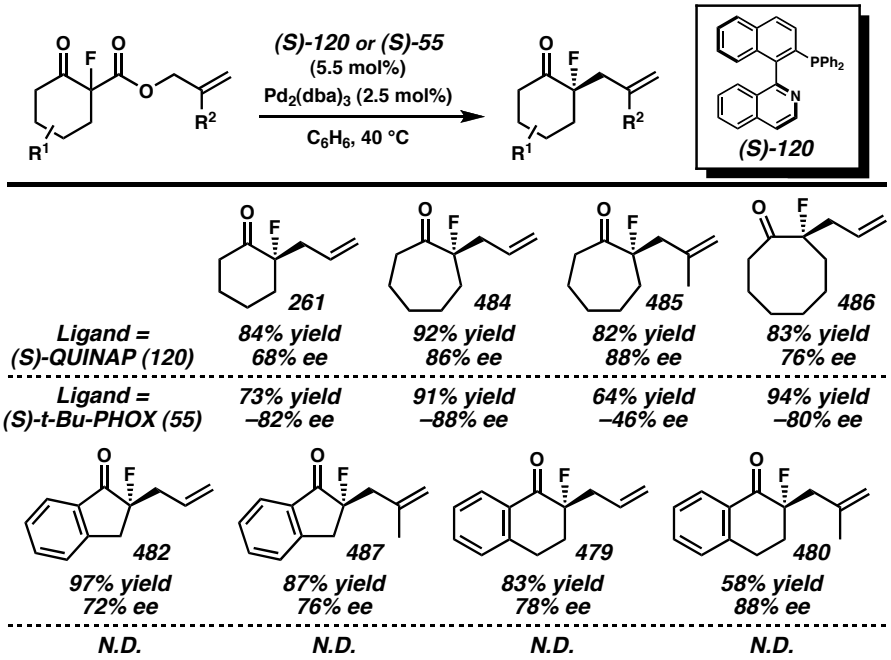
Stoltz and co-workers reported the first use of the enantioselective Tsuji allylation to generate an enantioenriched tertiary fluoride with the preparation of 2-allyl-2-fluorocyclohexanone (**261**) with 91% ee (Scheme 5.30).[34] Soon after, Nakamura and co-workers elaborated this concept with a nearly identical catalyst system.[35] They found high levels of enantioselectivity for a range of cyclic substrates and modest enantioselectivity for acyclic β-ketoester substrates.

Scheme 5.30. Enantioenriched α-fluoroketones derived from allyl β-ketoesters



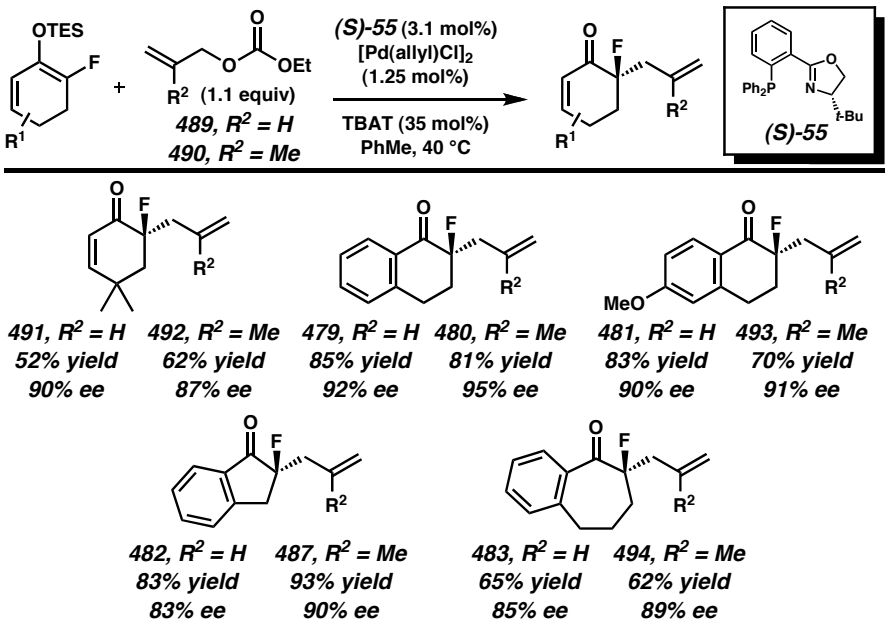
Since the appearance of the nearly simultaneous reports above, other related systems have emerged. Tunge and co-workers also chose allyl β-ketoester substrates and found that the biaryl P/N chelating ligand QUINAP (**120**) provided good levels of enantioselectivity, although *t*-BuPHOX (**55**) was superior in most cases (Scheme 5.31).[58] Notably, (*S*)-QUINAP ((*S*)-**120**) and (*S*)-*t*-BuPHOX ((*S*)-**55**) provided products in the opposite enantiomeric series, an effect also observed by Stoltz for allylation from allyl enol carbonates.[20] This shift in absolute configuration may be advantageous as (*R*)-*t*-BuPHOX, which is derived from (*R*)-*tert*-leucine, is somewhat more expensive than its antipode, whereas both enantiomers of QUINAP are commercially available. In agreement with the findings of Stoltz and co-workers and those of Nakamura and co-workers, P/P and P/O chelating ligands were found to be inferior to P/N ligands in terms of ee.

Scheme 5.31. Enantioenriched α-fluorocycloalkanones prepared from allyl β-ketoesters



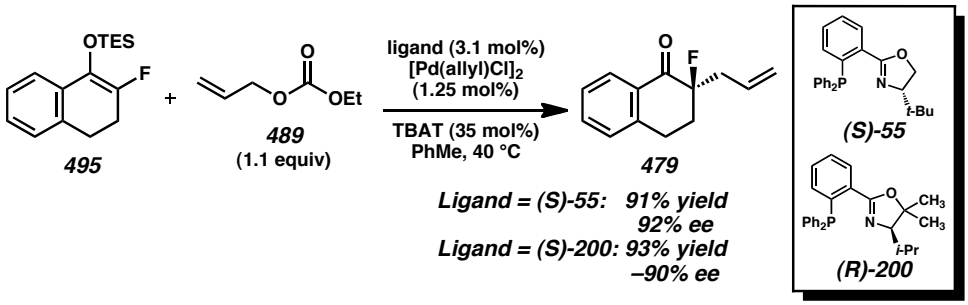
In 2007, Paquin and co-workers reported a system based on the silyl enol ether substrates employed by Stoltz (see section 5.3). The reaction conditions used in Paquin's work were slightly modified: $[Pd(allyl)Cl]_2$, toluene solvent, TES enol ethers in preference to TMS enol ethers, and allyl ethyl carbonates (**489** and **490**) in place of diallyl carbonates (Scheme 5.32).[59] Paquin and co-workers also found that (*S*)-**55** gave α-fluorocycloalkanones with high ee, whereas chelating P/P ligands performed poorly. However, their work has no examples of ketone enolates with multiple acidic sites.

Scheme 5.32. Enantioenriched α-fluorocycloalkanones prepared from silyl enol ethers



The antipode of (*S*)-**55** has been synthesized, although the (*R*)-*tert*-leucine starting material is somewhat more expensive. In order to access the opposite enantiomeric series, Paquin and co-workers prepared 5,5-dimethyl-*i*-PrPHOX (**200**, Scheme 5.33).[60] Reactions using this ligand gave comparable results to reactions with **55**.

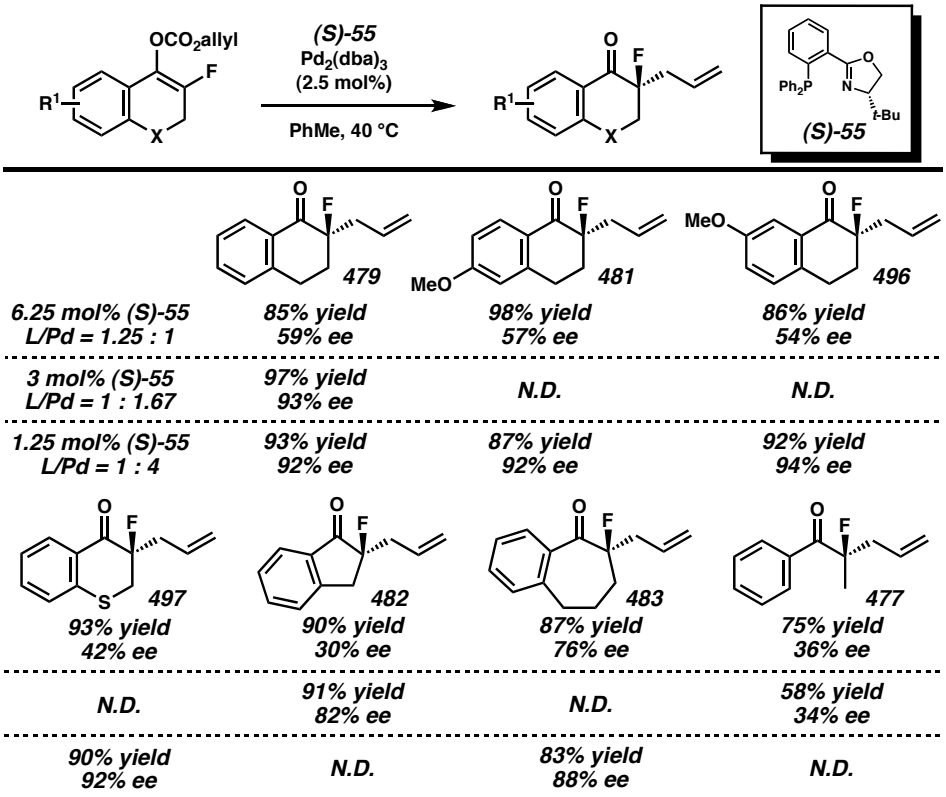
Scheme 5.33. Alkylation with pseudoenantiomeric ligands



Further studies from Paquin and co-workers[61] sought to employ fluorinated enol carbonates as substrates (Scheme 5.34). Initial explorations with standard conditions led to products with moderate ee (ca. 50%). Examination of the ligand-to-metal ratio revealed that using a substoichiometric amount of ligand relative to metal improved the

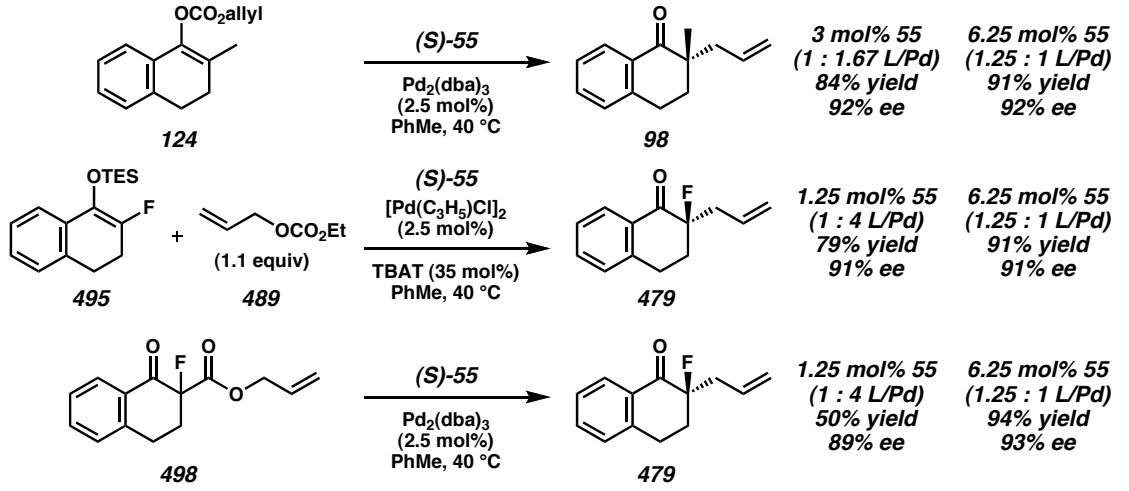
product ee significantly without affecting yields. This effect was observed for a range of fluorinated enol carbonates, although acyclic cases still provided modest ee.

Scheme 5.34. Alkylation using fluorinated enol carbonates



Alkylation using fluorinated enol silanes or β-ketoesters was not improved by lowering the ligand-to-metal ratio (Scheme 5.35). Alkylation forming all-carbon quaternary centers was similarly unaffected.

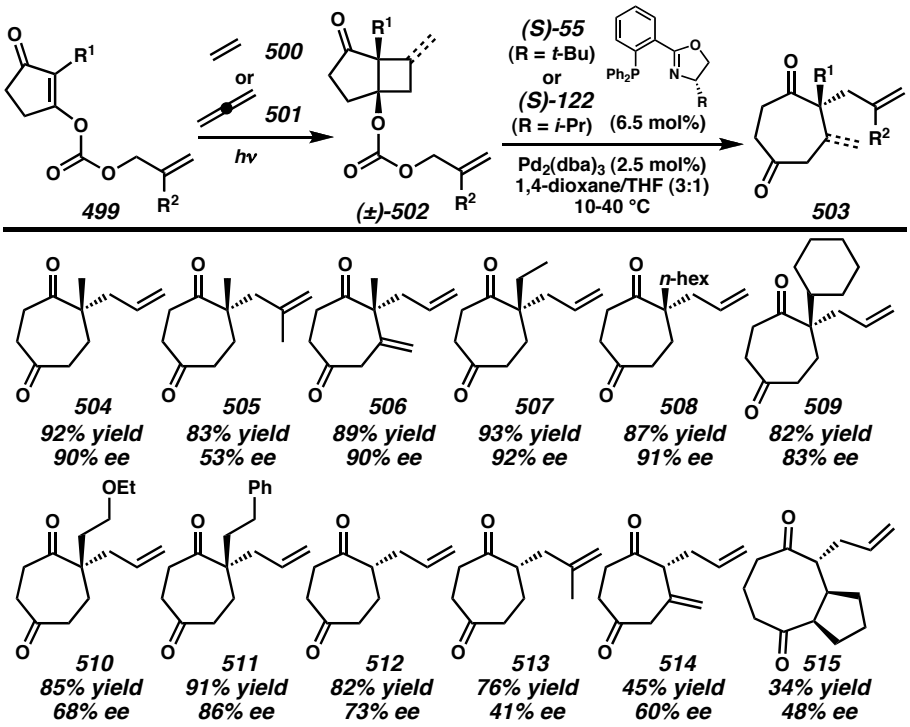
Scheme 5.35. Alkylation reactions relatively unaffected by ligand-to-metal ratio



5.5.2.2 CASCADE REACTIONS TO GENERATE ENOLATES

An ingenious application of the allyl enol carbonate version of the Tsuji allylation was recently reported by Blechert's group (Scheme 5.36).[62] In this work, [3.2.0]bicycles **502** were readily synthesized through photocycloaddition from the corresponding allyl enol carbonates **499**. Subsequently, a retroaldol fragmentation cascade was initiated by decarboxylation of the allyl carbonate, and the resultant enolate underwent enantioselective allylation. As the substrate stereocenters are destroyed in the retroaldol step, racemic starting materials may be used, and the reaction is enantioconvergent. By exploiting this ring-expansion method, a variety of seven-membered-ring diketones **503** were generated with good ee by using the *t*-BuPHOX/Pd(0) catalyst system. Attempts to generate tertiary stereocenters through this reaction were met with moderate ee, and in some cases it was necessary to employ (*S*)-*i*-PrPHOX ((*S*)-**122**) to obtain reasonable yields. The overall sequence represents an enantioselective variant of the de Mayo reaction.[63]

Scheme 5.36. Asymmetric ring-expanding allylation



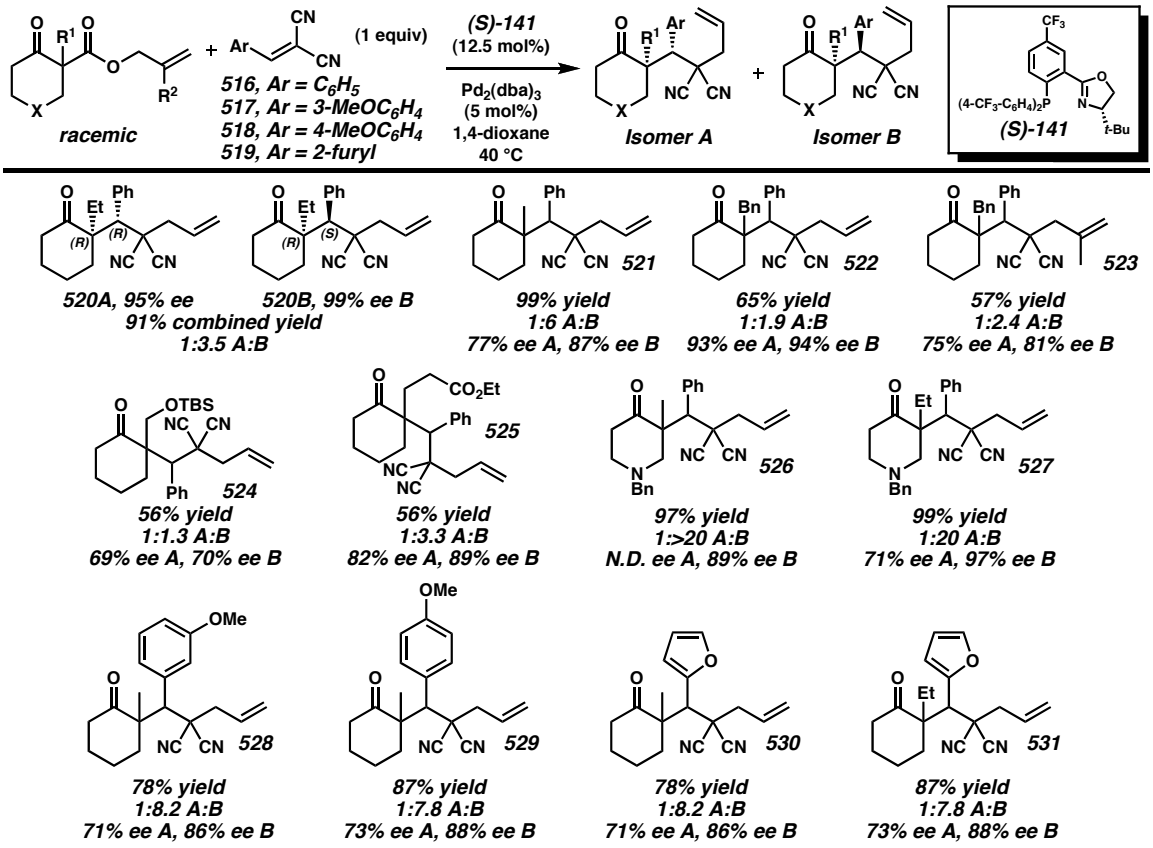
This method allows access to interesting seven-membered ring compounds that may be useful for the synthesis of a variety of natural products. Important to the development of the enantioselective allylation methodology, this work suggests that many distinct methods of accessing a Pd-enolate intermediate may be amenable to enantioselective reactions by using the ligand complexes discussed herein.

5.5.2.3 INTERCEPTED ALKYLATION WITH CONJUGATE ACCEPTORS

Stoltz and co-workers hypothesized that it could be possible to intercept the proposed Pd-enolate intermediate with other electrophiles. Explorations of Brønsted acids led to successful enantioselective protonation protocols (see Chapters 6 and 7).[64] Next, conjugate acceptors were investigated.[65] Inspired by earlier works from other researchers,[66] benzylidenemalononitrile (**516**, Scheme 5.37) was selected as the conjugate

acceptor. Initial screening reactions indicated that electron deficient PHOX ligand **141** was optimal for capturing the presumed enolate intermediate derived from racemic β-ketoester substrates. High yields of the interrupted allylic alkylation products could be obtained. Product dr was somewhat variable with some substrates providing very high dr for unknown reasons. Often both diastereomers of product formed with high ee. Other arenylidenemalononitriles could be used in the reaction as well. The absolute stereochemistry was established via X-ray crystallography and the enantiofacial selectivity differs between trapping with an allyl group and interrupted trapping with a conjugate acceptor (cf. Scheme 5.17 and Scheme 5.37). The facial selectivity for interrupted alkylation did, however, match that of the enantioselective protonation of cyclohexanone-derived enolates.[64] This work represents a significant advance toward a general catalytic system for enantioselective enolate functionalization.

Scheme 5.37. Interrupted allylic alkylation

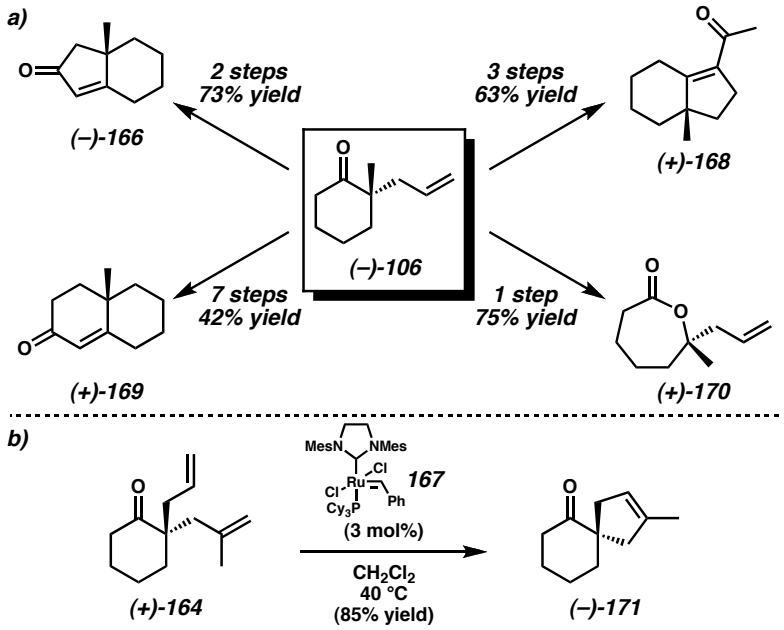


5.5.3 MISCELLANEOUS APPLICATIONS

In the initial report from the Stoltz group, several useful transformations of the α-quaternary cycloalkanone products were carried out (Scheme 5.38a).[20] Among these were functionalizations of the allyl group followed by aldol condensation to generate [6.5] and [6.6] bicycles **166**, **168**, and **169** in good yields. Enone **169** is commonly produced by Robinson annulation[67] and has found many applications in synthesis.[68] Another simple transformation of 2-allyl-2-methylcyclohexanone (**106**) is the conversion into lactone **170** by Baeyer–Villiger oxidation. This transformation provides an entry to enantioenriched tertiary alcohol stereocenters. Spriocyclic systems were accessed with

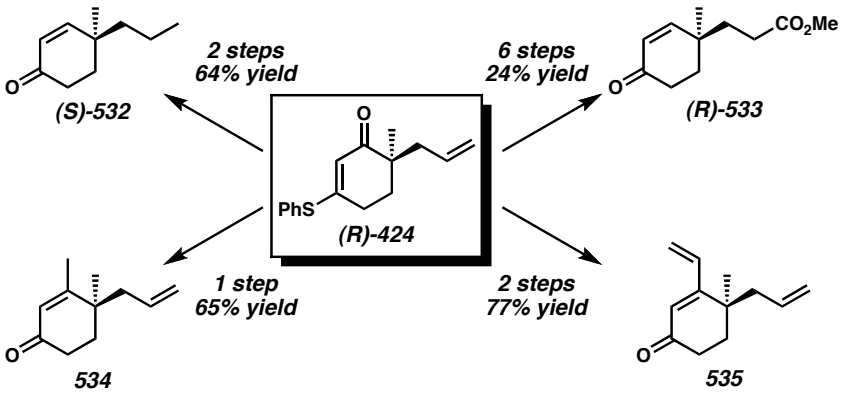
high ee by employing the Grubbs' second-generation olefin metathesis catalyst **167**[54] to transform ketone **164** into **171** (Scheme 5.38b).[27]

*Scheme 5.38. a) Transformations of ketone (–)-**106** b) Ring-closing metathesis to form a spirocycle*



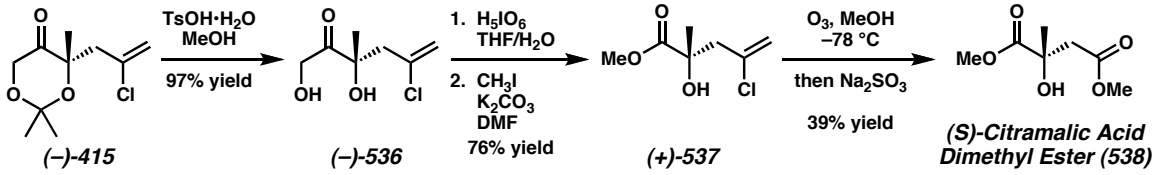
The vinylogous thioesters produced by Trost and co-workers (Scheme 5.19) were amenable to further functionalization by Stork–Danheiser-type manipulations (Scheme 5.39).[69] These transformations provided a valuable route to enantioenriched γ-quaternary stereocenters in enone systems.[70] Two of these derivatives, (*S*)-**532** and (*R*)-**533**, were used to establish the absolute configuration of (*R*)-**424**. Related transformations were used in the total syntheses of carissone (section 5.5.1.7) and cassiol (section 5.5.1.8) by Stoltz and co-workers.

*Scheme 5.39. Stork–Danheiser type transformations of vinylogous thioester (R)-**51***



The dioxanone class of substrates provided entries into other important derivatives (Scheme 5.40). Cleavage of the acetal with *p*-toluenesulfonic acid generated dihydroxy ketones (e.g., **415** → **536**). These dihydroxy ketones underwent selective oxidative cleavage upon exposure to periodic acid and after esterification the corresponding hydroxyesters were isolated (e.g., **537**). Overall yields for the transformation from dioxanone to hydroxyester (**415** → **537**) were 41–81% for three steps. In the case of chlorinated compound **537**, subsequent ozonolysis formed citramalic acid dimethyl ester (**538**) that was correlated to literature data to establish the absolute configuration as *S*.[71]

Scheme 5.40. Useful derivatives of enantioenriched dioxanones

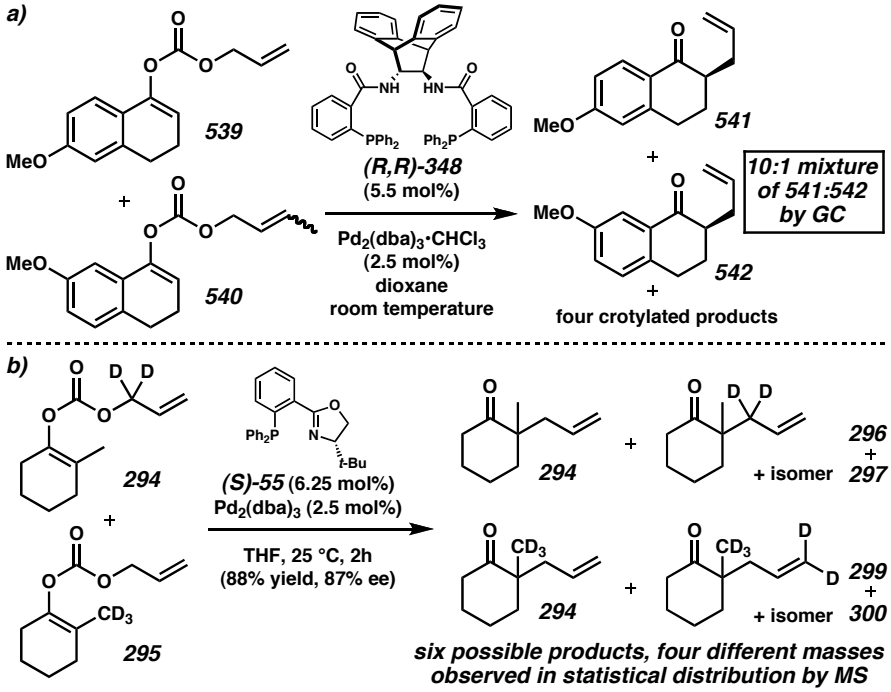


5.6 MECHANISM OF ALLYLATION REACTIONS

To date, there has been relatively little mechanistic evidence presented for these reactions. One important set of experiments that have been reported are crossover

experiments. Both the Trost and Stoltz groups described crossover experiments with enol carbonate substrates and their respective catalyst systems (Scheme 5.41). Trost's group observed minimal crossover between allyl and crotyl carbonates (**539** and **540**, respectively);[23] they attributed the lack of crossover with the bis(phosphine)/Pd(0) catalyst system to a rate of alkylation that exceeds the rate of ion diffusion from solvent-caged ion pairs in dioxane. Further evidence for the importance of these contact ion pairs was the importance of the solvent in suppressing overalkylation and enolate scrambling when forming tertiary stereocenters.[23,25]

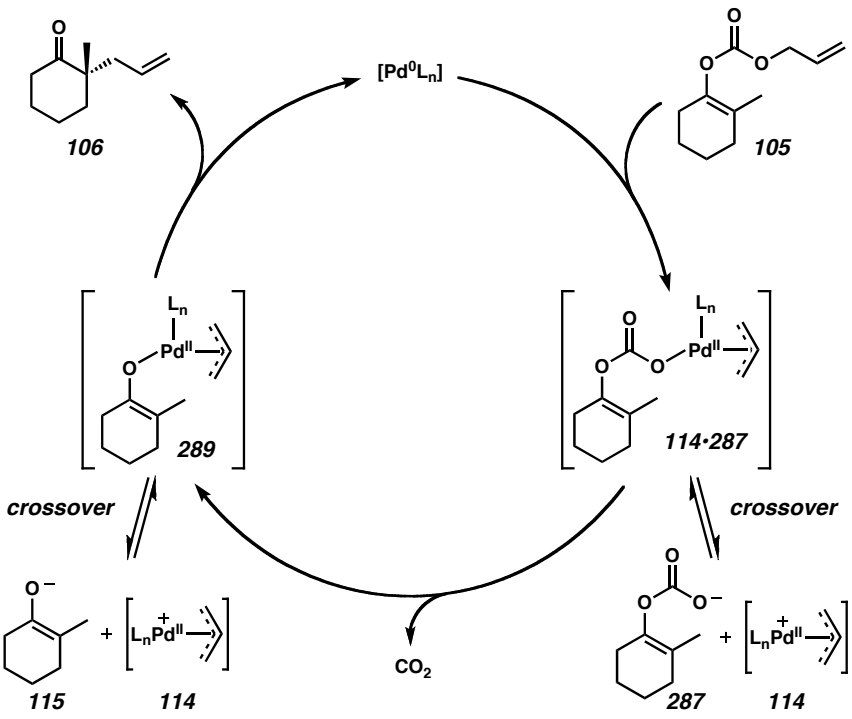
Scheme 5.41. a) Trost's crossover experiment b) Stoltz' crossover experiment



In contrast to the results of Trost's group, Stoltz and co-workers observed scrambling of allyl termini and complete crossover between the two differently deuterated allyl enol carbonates **294** and **295** in THF, dioxane, and benzene (Scheme 5.41b).[34] Saegusa and co-workers also observed crossover in a similar experiment with a non-enantioselective

system and allyl β-ketoester substrates in DMF, although crossover was suppressed in benzene.[15b] At the time, Saegusa and co-workers proposed a catalytic cycle similar to the one shown in Scheme 5.42 that accounted for crossover at two stages in the process. This cycle appears to be consistent with the results obtained by Stoltz and co-workers with the PHOX/Pd(0) catalyst system. Additionally, the recent isolation of a (PHOX)Pd-carboxylate complex[72] is suggestive of a long-lived carboxylate intermediate that may provide an opportunity for crossover. Although Stoltz' crossover results clearly contrast with those of Trost's group, these experiments are not informative as to the mechanism of bond formation or the origin of enantioselectivity in these reactions.

Scheme 5.42. Possible catalytic cycle for decarboxylative allylation



The reversal of enantioselectivity that Trost and co-workers observed between the reaction of pregenerated lithium enolates[7a] and those generated in situ from allyl enol carbonates[23] indicates that these two processes probably have significantly different

mechanisms. However, the details of these differences have not been elucidated experimentally. The possible intermediacy of an inner-sphere Pd enolate[73] rather than the outer-sphere nucleophile typical of other π-allyl alkylations[74] has been suggested and supported by some evidence, although alternates cannot be ruled out at this time. Computational studies of the Pd•PHOX system have found that the inner-sphere mechanism is lower in energy than outer-sphere attack (see Chapter 4).[73] The lack of enolate scrambling observed throughout all the studies presented herein, especially in the presence of an acidic 1,3-diester moiety (Scheme 5.20), would be consistent with the inner-sphere proposal.

5.7 CONCLUSIONS

The important discoveries made by Professor Tsuji and his co-workers laid the groundwork for a multitude of useful processes that will surely find further applications in the coming years. These powerful methods allow for the high-yield synthesis of α-quaternary cycloalkanones from three distinct substrate motifs. Apart from quaternary centers, several examples of the synthesis of tertiary stereocenters have been reported. The versatility of these methods provides valuable inroads toward the ultimate goal of general protocols for the enantioselective functionalization of enolates. The first evidence of the impact of these methods is apparent in the applications to total synthesis and to the synthesis of other important functionalized molecules described in this chapter. The adaptations of other palladium enolate reactions developed by Tsuji to analogous enantioselective variants (e.g., enantioselective protonation[64]) are indicative of the ongoing legacy of these contributions. A multitude of future reports on the utility of

these reactions is anticipated. These will further demonstrate the importance of the pioneering discoveries of Professor Tsuji.

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CHAPTER 6

Enantioselective Protonations[†]

6.1 INTRODUCTION

Enantioselective protonation is a common process in biosynthetic sequences. The decarboxylase and esterase enzymes that effect this valuable transformation are able to control both the steric environment around the proton acceptor (typically an enolate) and the proton donor (typically a thiol). Recently, several chemical methods to achieve enantioselective protonation have been developed by exploiting various means of enantiocontrol in different mechanisms. These laboratory transformations have proven useful for the preparation of a number of valuable organic compounds.

A fundamental method to generate a tertiary carbon stereocenter is to deliver a proton to a carbanion intermediate. However, enantioselective transfer of a proton presents unusual challenges, specifically, manipulating a very small atom and avoiding product racemization at a particularly labile stereocenter. As a result, the conditions for a successful enantioselective protonation protocol may be very specific to a certain substrate class. Tertiary carbon stereocenters are extremely common in valuable

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[†] This review was written in collaboration with Allen Y. Hong and a similar version has been accepted for publication in *Nature: Chemistry*.

biologically active natural products, and thus the need for synthetically useful enantioselective methods to form these stereocenters is vital.[1]

In this chapter, several strategic approaches to enantioselective protonation are presented. Emphasis has been placed on recently developed methods and their accompanying mechanisms in order to update the most recent prior reviews on this topic.[2] Each method relies on particular stereochemical control elements based on the mechanism of the protonation transformation. Appreciation of these controlling elements may lead to improved methods for preparing valuable chiral materials for a variety of synthetic applications.

6.2 IMPORTANT FACTORS IN ACHIEVING ENANTIOSELECTIVE PROTONATION

Several of the most important practical features of enantioselective protonation were enumerated in Fehr's 1996 review.[2] Principal among these is the fact that enantioselective protonations are necessarily kinetic processes since under thermodynamic control racemate would be formed. Accordingly, it is often necessary to match the pK_a of the proton donor and the product to prevent racemization before product isolation. It is unfortunate that the same anion stabilizing groups (e.g., ketones) that make protonations relatively easy to achieve also impart a degree of instability in the product. This has led some researchers to explore hydrogen atom transfer reactions in lieu of Brønsted acid-mediated protonations (see subsection 6.4.4).

In addition to the obvious challenges of product stability under the reaction conditions, the rapid rate of proton exchange in solution often leads to significant levels

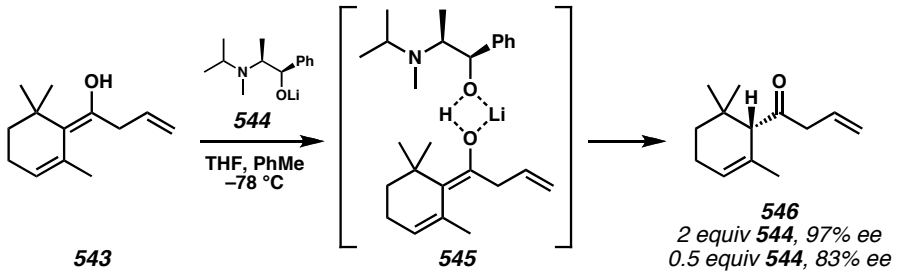
of background reaction without the intercession of the chiral control element. As a result, typical proton donors are relatively weak acids that react with the proton acceptor in a slower and more controlled fashion.

Since substrates for enantioselective protonation generally involve a prochiral sp^2-hybridized atom, the stereochemistry of the substrate is a concern. In some cases, the ability to generate stereodefined proton acceptors (e.g., a pure *E*- or *Z*-enolate) is critical to the success of a protonation method. In other cases, however, the two stereoisomers of enolate may in fact lead to the same enantiomer of product.[2d] To obviate this concern many researchers choose to investigate cyclic substrates; in turn, this may lead to a limited substrate scope for a particular system. The method to access the reactive proton acceptor is among the most important facets of each protonation system, and many strategies have been explored (e.g., conjugate addition, addition to ketenes, and decarboxylation from β-ketoesters).

Finally, the fine mechanistic details of enantioselective protonations are often not well understood. Since typical proton acceptors are stabilized anions, there are multiple Lewis basic sites available for protonation. It is likely that these sites protonate at kinetically different rates dependent on the specific reaction conditions. Potentially, enantioselective protonations may be achieved either by direct protonation to generate the desired stereocenter, or by protonation at a different site followed by enantioselective tautomerization. In an important recent report, Fehr[3] demonstrated that isolated enol **543** (Scheme 6.1) could be transformed enantioselectively into ketone **546** (an immediate precursor to the rose-smelling fragrance compound (*S*)-(α)-damascone) via the proposed aggregate complex **545**, and this mechanistic course seemed to be operative in the

analagous protonation of a lithium enolate with the conjugate acid of alkoxide **544**. Based on these findings, perhaps some protonation protocols are more accurately described as enantioselective *tautomerization* reactions. Although ultimately inconsequential in terms of the products obtained, insights into the specific mechanistic course of the reaction are important in order to improve these systems. However, only rarely have these levels of mechanistic understanding been realized.

Scheme 6.1. Enantioselective tautomerization of an isolated enol



6.3 ENANTIOSELECTIVE PROTONATION IN ENZYMATIC SYSTEMS

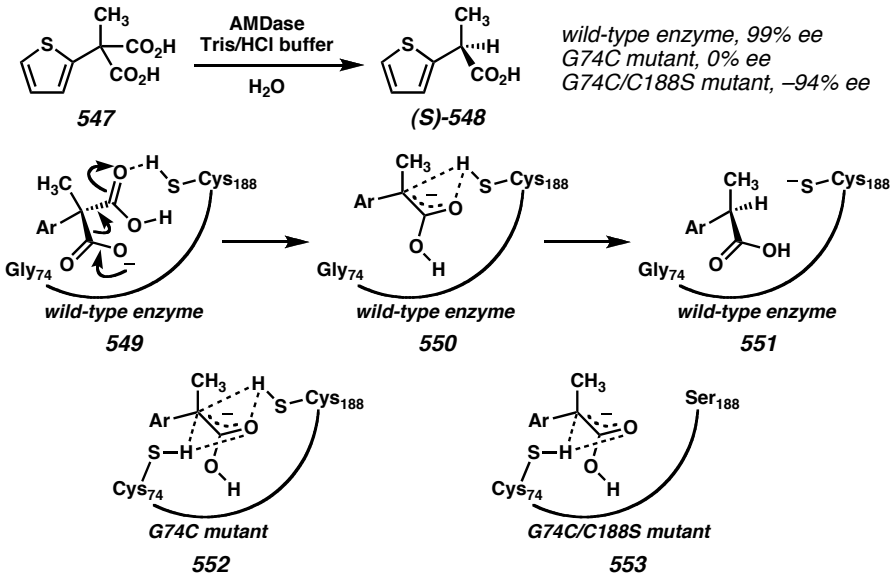
6.3.1 DECARBOXYLASE ENZYMES

Nature has evolved several efficient enzymes that catalyze enantioselective protonation reactions on useful organic building blocks. In recent reports, decarboxylases and esterases have proven to be two popular classes of natural enzymes for the construction of α-stereocenters adjacent to ketones. Esterases release latent enolates from prochiral substrates while decarboxylases generate enolates in situ from malonic acid derivatives (Scheme 6.2 through Scheme 6.4).

Ohta and co-workers[4] isolated arylmalonate decarboxylase (AMDase) from Gram-negative bacterium *Alcaligenes bronchisepticus* and found that it catalyzes the

decarboxylative enantioselective protonation of α-aryl-α-methyl-malonates through the proposed mechanism in Scheme 6.2. Yields and enantiomeric excesses were excellent for substrates with various α-aryl substitutents (up to 99% yield and 99% ee). Experiments have shown that the Cys188 residue is essential for activity, and this site is the putative proton donor that stabilizes the enolate intermediate. A Hammett study[5] of the reaction found a ρ value of +1.19, which is consistent with a negatively charged transition state.[4] Recently, preliminary X-ray diffraction experiments and an X-ray crystal structure of AMDase were reported.[6]

Scheme 6.2. Enzymatic decarboxylative protonation with wild-type and mutant decarboxylases



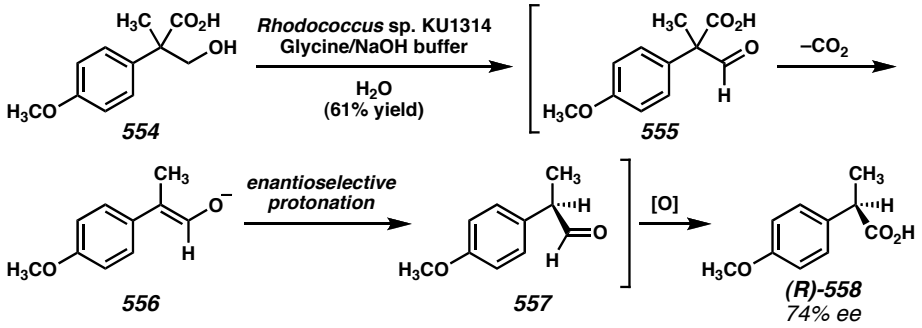
Accessing the opposite enantiomeric series of products required additional investigation.[7] Analysis of the enzyme amino acid sequence was carried out to check for homology with known enzymes. The Cys188 residue is conserved in several racemase enzymes from other microorganisms. Glutamate racemase, found in the bacterium *Lactobacillus fermenti,* contains an active site similar to that of AMDase, but with cysteine residues (Cys188 and Cys74) on both sides of the substrate. Presumably, one of

the cysteine residues acts as a base and generates an enolate intermediate which can then be protonated non-selectively from either cysteine residue to give rise to a racemic mixture. When Ohta and co-workers prepared a G74C mutant of AMDase to mimic these racemase enzymes, they found that racemic α-thienylpropionic acid (**548**, Scheme 6.2) was formed in 37% yield from the malonic acid substrate (**547**). Further explorations based on this homology hypothesis led to the preparation of a double mutant of AMDase (G74C/C188S) that removed the native cysteine residue while maintaining the mutant residue on the opposite face of the substrate. The opposite enantiomer of product was indeed obtained with this new enzyme in 94% enantiomeric excess, although yields decreased to 60% and the activity of this mutant was several orders of magnitude lower than the wild-type. Some activity was rescued by performing random mutagenesis and identifying more active triple mutants.[8]

Decarboxylase-type activity was also observed in the conversion of β-hydroxyacid **554** to optically active α-arylpropionic acid (*R*)-**558** by Gram-positive bacteria *Rhodococcus sp*. KU1314 (Scheme 6.3).[9] In the proposed metabolic pathway, enzymes in the microorganism non-selectively oxidize hydroxyacid substrate **554** to aldehyde **555** and then decarboxylate the corresponding acid to form enolate **556** that undergoes enantioselective protonation to generate aldehyde **557**. Subsequent non-selective oxidation affords enantioenriched α-arylpropionic acid **558**. Mechanistic experiments were consistent with this proposed enantioselective protonation mechanism rather than alternative possibilities such as enantioselective oxidation steps. Enantioselectivity and yield varied considerably depending on the aryl and alkyl groups at the α-position in the substrate, but enantiomeric excesses up to 85% could be achieved. Employing an

electron poor aryl group appeared to give poor enantioselectivity due to increased acidity of the proton in the presumed aldehyde intermediate. When the alkyl group was changed from methyl to ethyl, the reaction yield dropped, suggesting that the enzyme is sensitive to sterics.

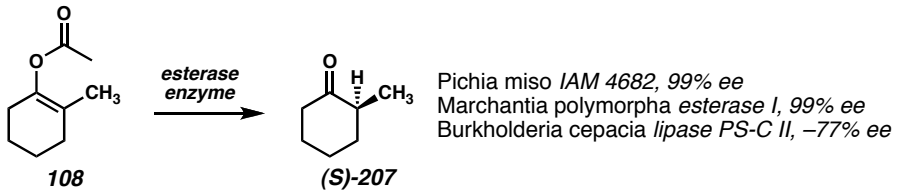
Scheme 6.3. Enzymatic oxidation/decarboxylation/protonation/oxidation cascade



6.3.2 ESTERASE ENZYMES

Several researchers have employed esterases to obtain enantioenriched protonation products. In 1990, Ohta and co-workers[10] reported that live *Pichia miso* IAM 4682 yeast cells catalyze the conversion of enol acetates to enantioenriched ketones (e.g., **108** → **207**, Scheme 6.4). High levels of enantiomeric excess were attained with a variety of enol esters. For larger ring systems, the reaction yield and absolute configuration varied unpredictably with ring size. In an impressive application, this yeast-mediated reaction was used to generate an α-stereocenter in a 12-membered ring with 96% ee.

Scheme 6.4. Enzymatic hydrolysis of enol acetates



108 **(S)-207**

Hirata and co-workers[11] reported that liverwort *Marchantia polymorpha* esterase I also catalyzes the same reaction on a variety of substrates with differing alkyl side chains, but the facial preference for proton delivery varied for different enolate substitutions. For example, the enzyme delivered (*S*)-2-methylcyclohexanone (**207**) and (*R*)-2-*n*-propylcyclohexanone from their respective enol acetates in 99% conversion and 99% ee.

Lipase PS-C II, originating from Gram-negative bacteria *Burkholderia cepacia*, may also be used for the hydrolysis of 1-acetoxy-2-methylcyclohexene (**108**). Sakai and co-workers[12] discovered that the enantiomeric excess of the product ((*R*)-**207**) was largely dependent on the temperature and the proton source. The best results were obtained by running the reaction at 0 °C with solid-supported enzyme PS-C II and ethanol as proton source (82% conversion, 77% ee).

Among these enzymatic approaches, a general problem appears to be the difficulty of enzyme modification to give the unnatural antipode of product. Another limitation is the need for buffers to help stabilize enzymes or cells. Substrate scope is also limited due to the specificity of substrate recognition. For these reasons, enzymatic reactions do not provide a general solution to the synthesis of enantioenriched protonation products. Laboratory means for enantioselective protonation may enable a more universal protocol due to the ability to tune the structural and electronic features of the catalyst. These

natural systems do, however, demonstrate many of the key controlling elements necessary for successful enantioselective protonation.

6.4 STRATEGIC APPROACHES TO NONENZYMATIVE ENANTIOSELECTIVE PROTONATION

6.4.1 GENERAL CONSIDERATIONS

Using enzymatic systems as a guide to the important factors in achieving enantioselective protonation, two distinct factors have been envisioned as opportunities for asymmetric induction: the use of a chiral Brønsted acid (see subsection 6.4.2) and generation of a chiral proton acceptor intermediate (see subsection 6.4.3). Whereas the enzymatic systems exploit both of these control elements, many laboratory methods have sought to use only a single control element not only to minimize the amount of enantiopure material required for the transformation, but also to eliminate complicating diastereomeric interactions possible in systems with multiple chiral additives. In practice, some of these systems seem to involve protonation through an aggregate complex of both proton acceptor and proton donor, typically in a metal complex (e.g., Fehr's tautomerization depicted in Scheme 6.1).

An additional factor important in improving efficiency of enantioselective protonation systems is achieving catalysis. For example, catalytic generation of a chiral metal/enolate complex in situ minimizes the amount of chiral controller required. Alternatively, coupling of a catalytic chiral proton donor to a stoichiometric achiral proton source achieves a similarly efficient use of chiral information. In the latter case,

however, a specific order of *thermodynamic* acidity of the reaction components must be employed (necessarily in this order of decreasing Brønsted acidity: stoichiometric proton source, catalytic chiral protonating agent, and product). An accompanying balance of *kinetic* rates of proton transfer between all of these components must also be achieved to allow a reasonable rate of protonation through the catalyzed pathway while avoiding undesired background reaction between the prochiral proton acceptor and the stoichiometric achiral proton donor. Vedejs and co-workers have disclosed a study of these factors that is representative of these important issues.[13]

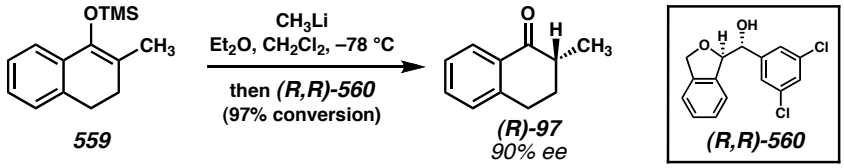
6.4.2 ENANTIOSELECTIVE PROTONATION BY MEANS OF CHIRAL PROTON DONOR

Perhaps the most fundamental means of achieving an enantioselective protonation is to employ a chiral proton donor. The acidic proton often comes from an oxygen, nitrogen, or carbon atom in the proton donor. Indeed, the earliest enantioselective protonation protocols employed this technique.

Among the most popular substrates for enantioselective protonation are lithium enolates, which are often generated from ketones, enol acetates, or silyl enol ethers at low temperatures. This method most closely resembles an esterase approach taken by Nature. Kim and co-workers[14] have synthesized a family of hydroxyethers as chiral proton sources (e.g., **560**, Scheme 6.5) capable of protonating lithium enolates of tetralones and indanones (prepared in situ from silyl enol ethers such as **559**) in up to 97% yield and 90% ee. The acidity of the Brønsted acids had a strong correlation to enantioselectivity and salt-free conditions were important to selectivity. A π–π-stacking interaction

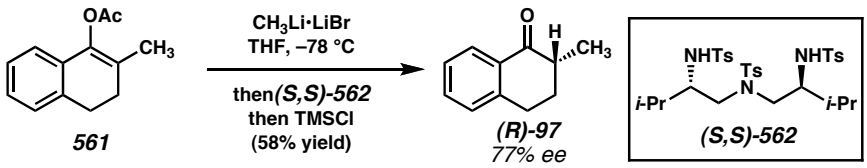
between the substrate and rigid proton source was proposed as the chiral controlling interaction during the protonation event. Since cyclohexanone-derived enolates lack an aryl group to participate in the stacking interaction, poor ee was observed for these substrates.

Scheme 6.5. Kim's enolate protonation



Eames and co-workers[15] have developed several strategies for the asymmetric protonation of prochiral tetralone enolates based on structurally different chiral proton sources. In one example, tris(sulfonamide) protonating agents with chiral backbones (e.g., **562**, Scheme 6.6) provided yields of ketone products (e.g., **97**) up to 70% and enantiomeric excesses of up to 77%.[15c] In these systems, it is believed that the enolates and proton sources can form an organized transition state that is guided by lithium chelation and perhaps more closely resembles a chiral aggregate intermediate than a direct enolate protonation. In some cases it was possible to access the opposite antipode of the product ketone by employing an external quench strategy.[15]

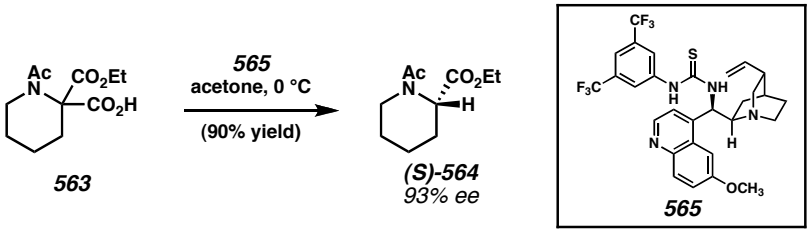
Scheme 6.6. Eames's enolate protonation



Enolate intermediates can also be accessed through decarboxylation. Proton donors derived from Cinchona alkaloids (e.g., **565**, Scheme 6.7) have proven to be especially

useful reagents for this enantioselective protonation strategy. Rouden and co-workers[16] have shown that cyclic and acyclic α-aminomalonate hemiester substrates (e.g., **563**) can be protonated with high levels of enantioselectivity. Enantiomeric excesses of product esters (e.g., **564**) up to 93% could be achieved in cyclic cases and 89% in acyclic cases. Products in the opposite enantiomeric series could be generated in comparable ee using catalysts prepared from naturally occurring diastereomeric alkaloids. The alkaloid derivatives are believed to serve as dual-purpose reagents: they deprotonate malonate hemiester substrates and promote a decarboxylation event. The intermediate enolate can be protonated by the tertiary ammonium salt to give enantioenriched products. This approach is biomimetic and resembles decarboxylase enzymes in Nature.

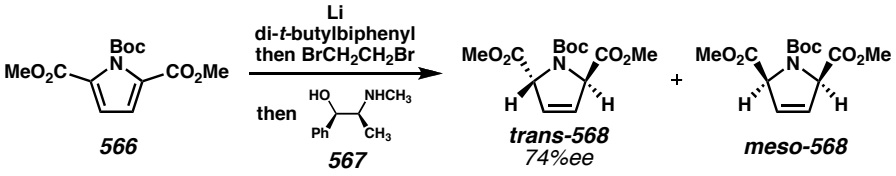
Scheme 6.7. Rouden's decarboxylative protonation



Work done by Donohoe and co-workers[17] has shown that it is possible to perform dissolving metal reductions of pyrrole esters and quench the resulting enolate intermediates with a chiral proton source. Reduction of 2,5-disubstituted pyrroles (e.g., **566**, Scheme 6.8) led to a separable 1:1 mixture of *trans*- and *meso*-diasastereomers of ester **568**, but the asymmetric induction in the chiral *trans*-product was good when (–)-ephedrine (**567**) was used as the chiral proton source. Based on enantioselectivities of reactions with substituted ephedrine derivatives, it was proposed that the hydroxyl group provides the proton and that the ephedrine molecule needs to interact with the lithium

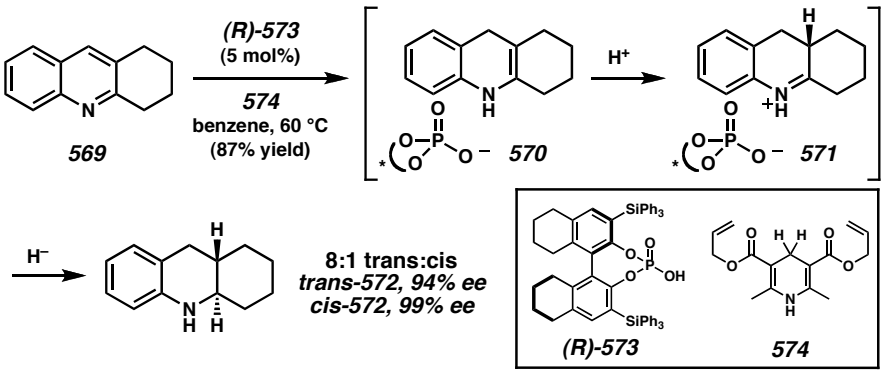
cation in a bidentate fashion for optimal asymmetric induction. Considering this proposal, this transformation may be more accurately described as protonation through a chiral aggregate of Brønsted acid and base. A related transformation of pyrrole mono-esters with oxazolidinone proton donors yielded reduced products in up to 68% ee and 58% yield. These partially reduced pyrroles could be elaborated to form uncommon dihydroxylated amino acids found in the marine mussel *Mytilus edulis*.[17]

Scheme 6.8. Donohoe's partial pyrrole reduction



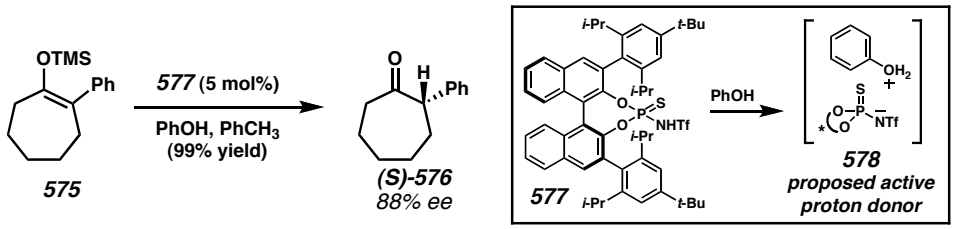
It is often possible to employ catalytic amounts of chiral protonating agents, provided that an appropriate stoichiometric proton source can be identified. For this purpose, a number of chiral organic catalyts have been employed in various transformations. In order to achieve a heterocycle reduction/protonation strategy analogous to that used by Donohoe and co-workers (Scheme 6.8), Rueping and co-workers[18] were able reduce substituted quinolines enantioselectively (Scheme 6.9). Initial hydride reduction of annulated quinoline **569** by a Hantzch dihydropyridine (**574**) to form enamine **570** was followed by enantioselective protonation with a catalytic chiral BINOL-phosphoric acid (**573**). Terminal hydride reduction of iminium ion **571** yielded optically active tetrahydroquinoline **572** as an 8:1 mixture of *trans*- and *cis*-diastereomers with the diastereomers formed in 94% and 99% enantiomeric excess, respectively. Up to 84% yield and 85% enantiomeric excess could be obtained for *mono*-substituted quinolines using the optimal reaction conditions.

Scheme 6.9. Rueping's quinoline reduction/protonation



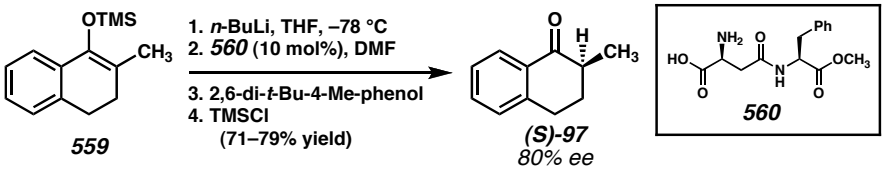
In a mechanistically different approach, Cheon and Yamamoto[19] used a related BINOL *N*-triflyl thiophosphoramide catalyst (**577**) to directly protonate cyclic silyl enol ethers (e.g., ***575*** → ***576***, Scheme 6.10). Regeneration of the chiral proton source was made possible by using phenol as the achiral proton source. With this system, yields up to 99% and enantiomeric excesses up to 90% were achieved. The highest levels of enantioselectivity were obtained with substrates bearing an aryl substituent at the α-position and 7-membered rings performed somewhat better than 6-membered rings. Comparable selectivity and yield could be obtained with catalyst loadings as low as 0.05 mol%. In control experiments, the protonation reaction did not proceed without an achiral proton source, even with stoichiometric chiral Brønsted acid. This observation led to a proposed mechanism that involves pre-association of the chiral and achiral proton sources to form an oxonium ion pair (**578**) that then protonates the silyl enol ether substrate.

Scheme 6.10. Yamamoto's enol silane protonation



A common approach to enantioselective protonation employs a lithium enolate, catalytic chiral proton source, and stoichiometric achiral proton source. These lithium enolates are often prepared from the corresponding enol silanes. Reports of amino acids as catalytic proton sources have appeared in recent literature. Yanagisawa and co-workers[20] employed commercially available dipeptide **560** (Scheme 6.11) for the protonation of lithium enolates of tetralones and cyclohexanones. The catalytic proton source is regenerated through proton transfer from 2,6-di-*t*-butyl-4-methylphenol (BHT). The steric bulk of the phenol is important to suppressing background enolate protonation through a non-selective pathway. The structure of the chiral proton donor is very specific to the success of the reaction because isomeric dipeptide aspartame afforded racemic product. Enolates generated from deprotonation of racemic ketone **97** with lithium diisopropylamide could also be protonated with comparable yield and enantioselectivity using this system.

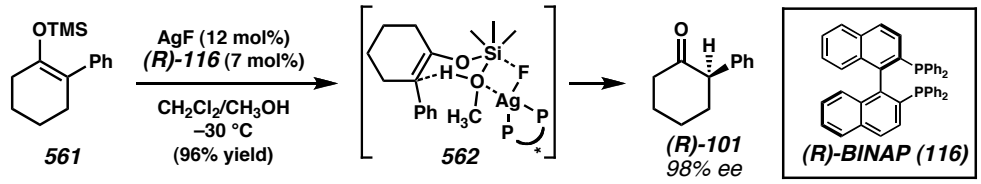
Scheme 6.11. Yanagisawa's lithium enolate protonation



In separate work from Yanagisawa and co-workers,[21] enol silanes were found to react to form ketones in the presence of the complex of AgF and BINAP (**116**, Scheme 6.12)

with methanol as a proton donor. Excellent enantiomeric excesses were reported for a variety of cyclic ketones. Cyclohexanone-derived enol silanes yielded significantly higher ee products than tetralone-derived enol ethers. The highest levels of ee (up to 99%) were found for α-arylcyclohexanones. Although the fine mechanistic details have not been elucidated, one possibility is that the chiral Lewis acidic Ag•BINAP complex binds methanol to generate a potent chiral Brønsted acid capable of protonating the latent enolate. Taking the fluoride activation component into account, aggregate complex **562** was proposed as a potential intermediate leading to the observed enantiomer of product ketone.

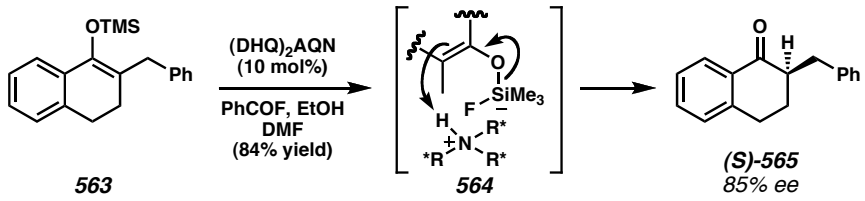
Scheme 6.12. Yanagisawa's enol silane protonation



Levacher and co-workers[22] have reported that catalytic amounts of Cinchona alkaloid derivatives can be coupled to latent hydrogen fluoride sources to achieve enantioselective protonation of silyl enol ethers of 1-indanones and 1-tetralones (e.g., **563** → **565**, Scheme 6.13). The hydrogen fluoride, generated in situ from benzoyl fluoride and ethanol, is presumed to interact with the alkaloid-derived catalyst to form a cinchonium fluoride. The fluoride anion of this active catalyst then activates the silyl group to facilitate proton delivery from the ammonium cation (e.g., **564**) through a proposed transition state reminiscent of the Ag•BINAP protonation protocol described above. The optimal alkaloid catalyt was $(DHQ)_2(AQN)$, a common ligand for Sharpless' enantioselective dihydroxylation reactions.[23] Yields up to 86% and enantiomeric excesses up to 92% were

reported. Protonation of cyclohexanone-derived enol silanes gave moderate enantiomeric excess. Later work revealed that carboxylic acids (e.g., citric acid) could be used directly with the alkaloid-derived catalysts to carry out the enol silane protonation.[24] Enantioselectivity for this variant of the reaction was moderately diminished, however (ee up to 75%). The use of chiral carboxylic acids revealed a moderate, but measureable, influence of both the proton donor and the catalyst on enantioselection, with the catalyst influence apparently dominating.

Scheme 6.13. Levacher's enol silane protonation

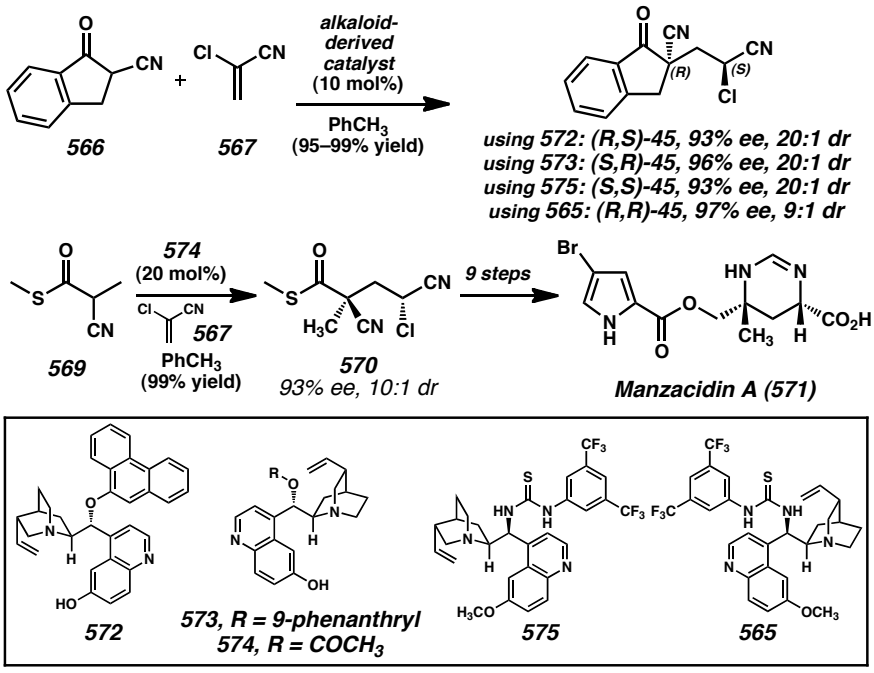


563 ***564*** ***(S)-565*** *85% ee*

In a series of reports by Deng and co-workers,[25] bifunctional Cinchona alkaloid-derivatives (e.g., **565**, **572**–**575**, Scheme 6.14) were reported to catalyze tandem asymmetric conjugate addition/protonation reactions of cyclic and acyclic α-cyanoketone nucleophiles (e.g., **566** and **569**) to 2-chloroacrylonitrile (**567**). The Cinchona alkaloid derivative is proposed to serve two functions: activating the Michael acceptor for addition and serving as the chiral Brønsted acid for the protonation of the nitrile-stabilized carbanion intermediate. The postulated stereochemical model involves a network of hydrogen bonding interactions, and it was found that modification of this network by masking the phenolic hydroxyl group and introducing a thiourea moiety led to preferential formation of the diastereomeric products in excellent ee. By virtue of this discovery, all four stereoisomeric products of **568** could be prepared with high degrees of diastereo- and enantioselectivity. This method was applied to an enantioselective formal

synthesis of (–)-manzacidin A (**571**) via the intermediate thioester **570**, prepared in 93% ee from α-cyanothioester **569** and 2-chloroacrylonitrile (**567**). A very similar transformation was reported by Wu and co-workers[26] for the conjugate addition of thiophenol to an α-substituted acrylamide with subsequent enantioselective protonation in up to 60% ee.

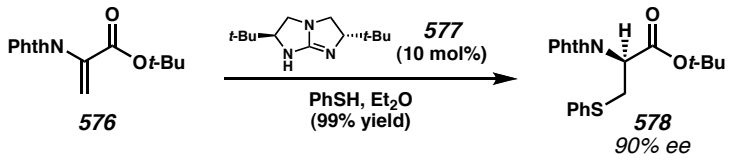
Scheme 6.14. Deng's conjugate addition/protonation



Organic catalysts other than Cinchona alkaloids have shown promise for catalytic asymmetric protonation as well. Tan and co-workers[27] used thiols and phosphine oxides as nucleophiles for 1,4-addition into various phthalimidoacrylates and itaconimides (e.g., **576** → **578**, Scheme 6.15). Subsequent protonation of the intermediate enolates by the conjugate acid of chiral bicyclic guanidine catalyst **577** gave up to 99% yield and 94% enantiomeric excess. Interestingly, the presence of water and relatively acidic thiophenols did not lead to appreciable amounts of non-selective enolate quenching.

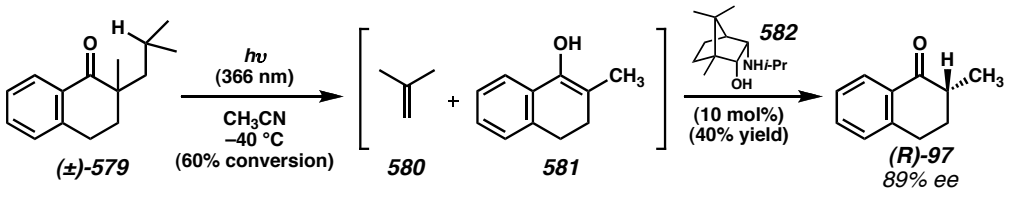
Kinetic isotope effects were explored with D_2O and a primary kinetic isotope effect of 1.5 was found, consistent with cleavage or formation of a bond containing H or D in the rate-determining step.

Scheme 6.15. Tan's conjugate addition/protonation



An unusual technique to generate an enol in situ was reported by Hénin, Muzart and co-workers.[28] In this work, a racemic α-quaternary ketone (e.g., **579**, Scheme 6.16) was exposed to laser photolysis at 366 nm. This irradiation caused a Norrish type II fragmentation (**579** → **581**) to occur with concomitant loss of isobutylene. The enol (**581**) then undergoes enantioselective transformation to the corresponding ketone (**97**) in the presence of amino alcohol **582**. Although high ee was realized for this dealkylative protonation in some cases, yields were low largely due to undesired fragmentation reactions initiated by the photochemical irradiation and decomposition of the resulting radical intermediates. This method represents one of the few enantioselective stereoablative transformations[29] involving destruction of a quaternary stereocenter.

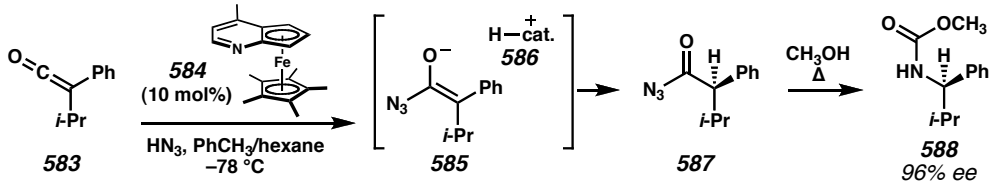
Scheme 6.16. Hénin/Muzart Norrish type II fragmentation/protonation



A variety of transformations catalyzed by planar-chiral heterocycles involve protonation as the enantiodetermining step. In one recent example from Fu and co-

workers,[30] catalyst **584** (Scheme 6.17) was found to promote the addition of HN_3 to ketenes (e.g., **583**). The resulting acyl azides (e.g., **587**) then underwent Curtius rearrangement at elevated temperatures. The carbamate products (e.g., **588**) were isolated with up to 97% ee, presumably from enantioselective protonation of the amide enolate intermediate (**585**). Sterically large ketenes performed best since less encumbered ketenes suffered from rapid uncatalyzed background reaction even at cryogenic temperatures. In control experiments, hydrazoic acid was found to be readily deprotonated by planar-chiral heterocycle catalyst **584**. Since the reaction also proceeded with higher selectivity at low substrate concentration, a mechanism involving an ion pair **585** + **586** was proposed. This behavior of the catalyst as a chiral Brønsted acid (i.e., **586**) rather than the more typical role of these catalysts as Lewis bases[31] is somewhat unusual, but also serves as a testament to the privileged nature of these catalysts.[32]

Scheme 6.17. Fu's addition of hydrazoic acid to ketenes followed by Curtius rearrangement



Although the particular example in Scheme 6.17 is thought to occur through a protonated catalyst molecule as the proton donor, other similar transformations may proceed through a different mechanism (see section 6.4.3), however in both examples the lack of a nonlinear relationship[33] between catalyst ee and product ee suggests that only one catalyst molecule is involved in the enantioselective step and therefore a hybrid mechanism is unlikely. Regardless of which of these two mechanistic hypotheses is operative, the transformation remains an enantioselective protonation process. An

understanding of the mechanistic details, however, is helpful in order to understand the stereochemical control elements important to the success of the transformation.

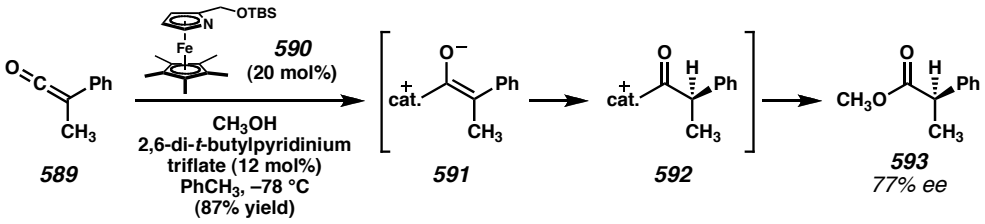
6.4.3 ENANTIOSELECTIVE PROTONATION BY MEANS OF CHIRAL BRØNSTED BASE

The most common form of chiral Brønsted base employed in enantioselective protonations has been chiral metal enolates. To circumvent the challenge of stereoselective generation of acyclic enolates, the majority of methods have focused on cyclic enolate precursors. A variety of techniques for enolate generation have been employed including simple deprotonations, pericyclic reactions, decarboxylations, and dehalogenations. The synthesis of the specific enolate precursor required for a protonation protocol (e.g., enol silane, acrylate, or β-ketoester) may determine how useful the method is for the preparation of specific target molecules. Although several successful chiral Brønsted base protonation protocols have been developed, substrate scope remains a significant problem. Especially lacking are general methods capable of protonation of acyclic enolates with high selectivity.

Planar-chiral heterocycle catalysts have also been employed in the generation of chiral Brønsted base intermediates for enantioselective protonation. Fu and co-workers[34] employed azaferrocene catalyst **590** (Scheme 6.18). In the proposed reaction mechanism the heterocycle catalyst reacts with a ketene (e.g., **589**) to form a zwitterionic chiral enolate intermediate (**591**). Subsequent protonation of the enolate by methanol or an achiral pyridinium cocatalyst then forms an acylferrocenium ion (e.g., **592**) that goes on to form an enantioenriched ester (e.g., **593**). Evidence for this distinct reaction

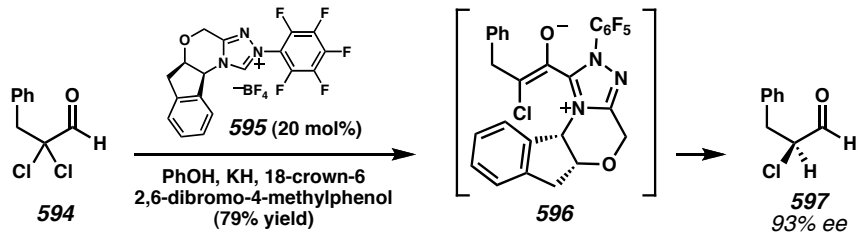
mechanism included the fact that catalyst **590** did not appreciably deprotonate methanol in solution.[35] However, in the case above (Scheme 6.17) the catalyst **584** does readily deprotonate hydrazoic acid. The remarkable ability of these Lewis base catalysts to achieve enantioselective protonation through two different mechanisms highlights the importance of understanding the details of the reaction pathways. The preliminary mechanistic evidence does not always provide sufficient information to determine the operative mechanism, however.[36]

Scheme 6.18. Fu's Addition of alcohols to ketenes



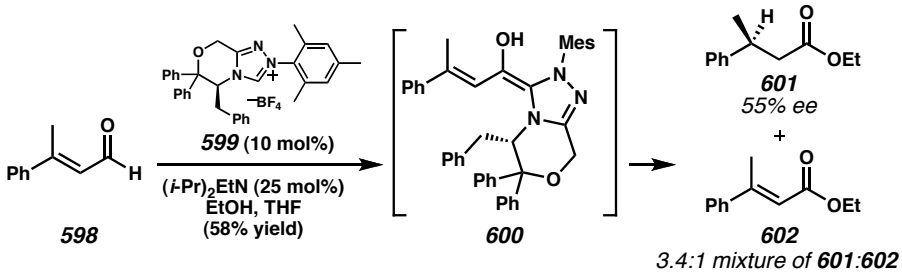
Other organic molecules have been employed for the generation of chiral enolates as well. For example, Rovis and co-workers[37] found that treatment of α,α-dichloroaldehydes such as **594** (Scheme 6.19) with enantiopure triazolium salt catalyst **595** in the presence of a stoichiometric phenoxide base and phenol led to α-chloroaldehydes with high enantiomeric excess. The proposed path of the reaction involves addition of the carbene conjugate base of catalyst **595** to the aldehyde substrate. Subsequent elimination of HCl then generates a zwitterionic enolate intermediate (**596**) that is subject to protonation to form enantioenriched aldehyde **597**. The precise structure of the putative enolate is a matter of conjecture since a number of different strain elements are likely in competition in this intermediate. Nonetheless, this method represents a very valuable technique for the preparation of useful, but synthetically challenging, chiral synthons.

Scheme 6.19. Rovis' protonation of chloroenolates



In a separate application of carbene catalysis, Scheidt and co-workers[38] found that homoenolate equivalents (e.g., **600**, Scheme 6.20), generated in situ from enals such as **598**, could undergo enantioselective protonation when chiral triazolium catalyst **599** was employed. Ester products (e.g., **601**) were obtained in up to 58% yield and up to 59% ee, although competitive formation of overoxidized enoate byproduct **602** complicated the reaction. Although the degree of enantioselectivity observed for this transformation was modest, this represents a significant advance in the type of proton acceptor that can be used for enantioselective protonation reactions since the site of protonation is relatively distant from the chiral control element.

Scheme 6.20. Scheidt's protonation of homoenolate equivalents

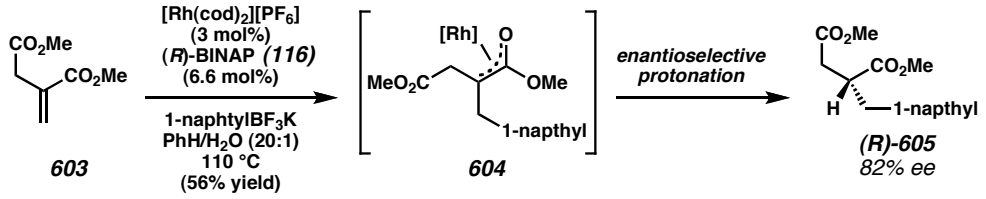


Metal-catalyzed 1,4-additions of organoboranes or organosilanes to enone systems have proven to be a popular strategy for generating chiral enolates for asymmetric protonation. These reactions can employ neutral or cationic rhodium complexes. Arylboron, arylstannane, arylsilicon, or arylzinc (and in some cases, vinylboron) reagents

can be used for coupling, but yields and enantioselectivities can depend on the type of organometallic reagent chosen. Atropisomeric bis(phosphine) ligands such as BINAP (**116**) and its analogues give excellent enantioselectivities for simple β-unsubstituted enone substrates. Diverse proton sources have been used to enable the formation of α-stereocenters. The optimal proton source varies from system to system, but phenols and other low-pK_a proton sources are common. Recent examples have mainly explored simple β-unsubstituted systems, so issues of diastereoselectivity in the generation of multiple stereocenters have not been fully addressed.

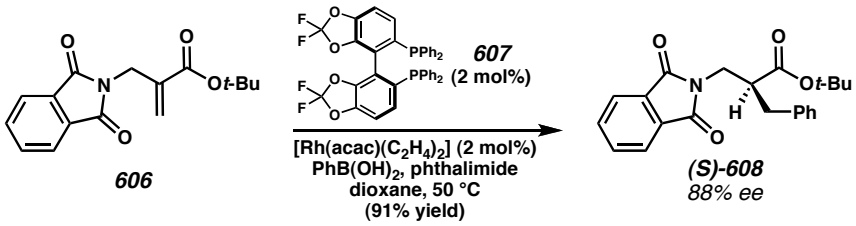
Frost and co-workers[39] explored Rh-catalyzed additions of organotrifluoroborate salts to itaconate substrates with water as the stoichiometric proton donor (e.g., **603** → **604** → **605**, Scheme 6.21). The metal-to-ligand ratio was found to be important in the selectivity of the reaction. Equimolar amounts of metal and ligand gave racemic product in high yield, but 2.2 equivalents of ligand relative to metal gave product in 82% ee and 56% yield. Interestingly, high reaction temperature was found to be an important factor in this reaction; racemic product was obtained when the reaction was carried out at 60 or 80 °C instead of 110 °C. In related work, Frost showed that organosiloxanes are also viable nucleophilic components for 1,4-addition, but such systems give poor yields and low enantioselectivity.[40] In a separate system involving aryl boronic acid organometallic components in microwave reactors, Frost and co-workers[41] examined whether a chiral proton source affected the stereochemical outcome of the reaction. When (*R*)-, (*S*)-, or racemic-BINOL was used with a Rh•BINAP catalyst, the yields and enantioselectivities were comparable in each of the three scenarios. This suggests that the chirality of the bis(phosphine) ligand is the dominant stereodetermining factor.

Scheme 6.21. Frost's Rh-catalyzed conjugate addition/protonation



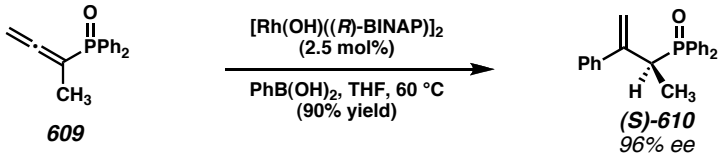
Sibi and co-workers[42] also investigated rhodium-catalyzed conjugate addition-protonation as a method for accessing β^2-amino esters from enoates (e.g., **606** → **608**, Scheme 6.22). Reaction screening revealed that (*S*)-DifluorPhos ligand (**607**) and phthalimide proton donor provided the best enantioselectivity. The best substrate provided 95% yield and 91% ee. Notably, lower temperatures could be used to increase product ee.

Scheme 6.22. Sibi's Rh-catalyzed conjugate addition/protonation



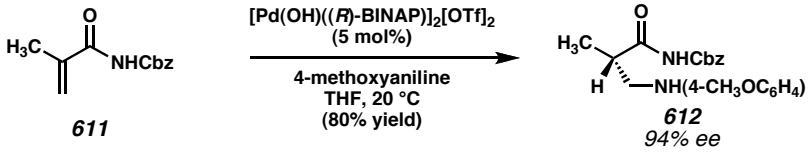
Hayashi and co-workers[43] reported a related conjugate addition/protonation sequence for an analogous diphenylphosphinylallene (e.g., **609**) system with a cationic dimeric rhodium μ_2-hydroxide catalyst (Scheme 6.23). Temperature did not appear to have an effect on enantioselectivities, but the choice of THF as solvent instead of dioxane improved product ee by more than 20%. Minimal isomerization of the β,γ-unsaturated products (e.g., **610**) was observed under the reaction conditions, and excellent yields (up to 97%) and enantiomeric excesses (up to 98%) were obtained. In this case, the arylboronic acid appears to be acting as the proton source based on an NMR experiment.

Scheme 6.23. Hayashi's Rh-catalyzed conjugate addition/protonation



Sodeoka and co-workers[44] found that this conjugate addition/protonation sequence is viable with palladium complexes and heteroatom nucleophiles as well (**611** → **612**, Scheme 6.24). A bimetallic palladium μ_2-hydroxide complex effected the conjugate addition of aniline derivatives to acrylamides. With BINAP ligand (**116**), the enolate intermediate was protonated enantioselectively to give product **612** in 80% yield and 94% ee. Although this is a promising result, the substrate scope has not been fully investigated.

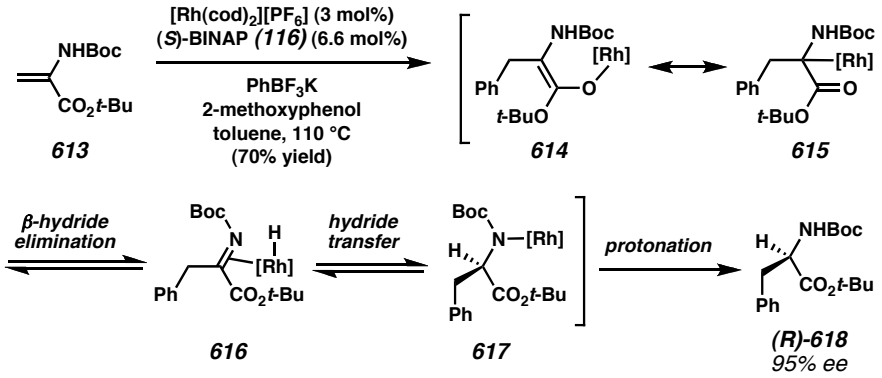
Scheme 6.24. Conjugate addition/protonation with a nitrogen nucleophile catalyzed by palladium



Genet, Darses, and co-workers[45] sought to make α-amino esters using a similar conjugate addition/protonation strategy (e.g., **613** → **618**, Scheme 6.25). In this system, boronic esters, boronic acids, and organosilanes did not provide adequate conversion or enantioselectivity. Organostannanes, however, were reactive under these conditions. In the screening of various proton sources, phenol derivatives appeared to provide the best enantioselectivity. Guaiacol (2-methoxyphenol) was determined to be the best proton donor, giving products with up to 91% yield and 88% ee. Higher temperatures and optimized solvents (such as toluene or dioxane) increased conversion and enantioselectivity. As in Frost's work, the ratio of metal to ligand did have a notable

effect on the enantioselectivity of the reaction, with 2.2 equivalents of chiral ligand relative to metal being optimal. Chiral proton sources were also added to see if the chiral ligand or chiral proton source was the dominant selectivity factor. Studies with (*R*)-BINAP (**116**) and both enantiomers of BINOL provided identical enatiomeric excesses, implying that the chirality of the enolate is dominant, as in the reports by Frost.

Scheme 6.25. Divergent pathway consisting of β-hydride elimination, hydride transfer, and protonation

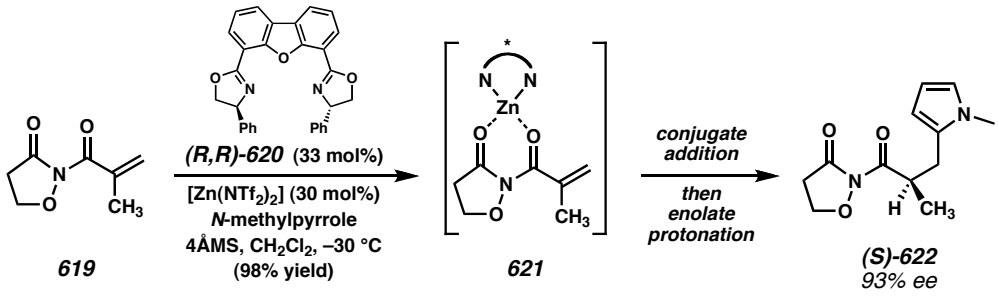


Mechanistic studies showed that the hydrogen on the enamide was essential for reactivity. Deuterium labeling studies showed that the reaction did not proceed via a direct protonation of the rhodium enolate (**614**); in a substrate with a labeled carbamate proton, deuterium incorporation at the α-carbon was high (41%). Based on this observation, a mechanism involving sequential conjugate addition, β-hydride elimination from the carbamate (**615 → 616**), and intramolecular hydride transfer to the α-carbon (**616 → 617**) was proposed. This proposed reaction pathway was supported by DFT calculations with the B3LYP/BII level of theory.[45b] In light of these mechanistic insights, a more electron-poor bis(phophine) ligand was chosen to facilitate the postulated β-

hydride elimination step, and DifluorPhos (**607**) was experimentally shown to give higher enantiomeric excesses.

A related conjugate addition/enantioselective protonation strategy consisted of a Friedel–Crafts-type addition of pyrroles to α-substituted acrylates (e.g., **619** → **622**, Scheme 6.26).[46] Sibi and co-workers employed $Zn(NTf_2)_2$ complexed with chiral dbfox ligand **620** as a Lewis acid catalyst to achieve up to 98% yield and up to 98% ee. The enolate intermediate (**621**) generated from the Friedel–Crafts reaction can be quenched by a proton from the pyrrole fragment to give a chiral product. The isoxazolidinone auxiliary is believed to be critical for improving reactivity and providing greater enolate control during the course of the reaction.

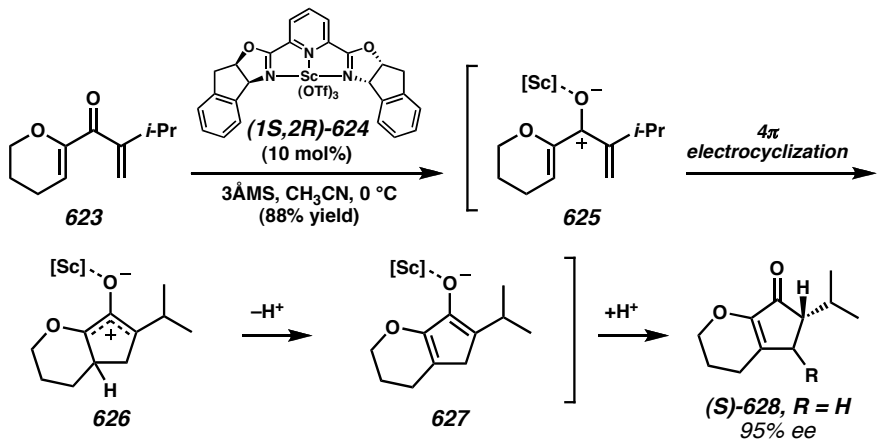
Scheme 6.26. Friedel–Crafts-type conjugate addition followed by enantioselective protonation



A distinct method of accessing a chiral metal enolate is the use of a pericyclic reaction. In the case of the Nazarov cyclization, the enantioselective reaction would not only generate a new stereocenter, but also a new five-membered ring. However, until recently enantioselective variants of this classical reaction were unknown. In studies directed toward the development of a general enantioselective Nazarov cyclization, Trauner and co-workers[47] discovered that high ee cyclopentenone products could be synthesized from electronically activated substrates such as dienone **623** in the presence of Sc•PYBOX complex **624** (Scheme 6.27). Interestingly, this enantioselective

protonation protocol requires no external proton source. Unfortunately, in cases where a second stereocenter would be generated at the β-carbon (i.e., **628** where R ≠ H), low diastereoselectivity was observed. This was interpreted as a result of low stereoselectivity in the electrocyclization step (**625** → **626**) followed by high selectivity in the protonation step (**627** → **628**).

Scheme 6.27. Trauner's Nazarov cyclization/enantioselective protonation

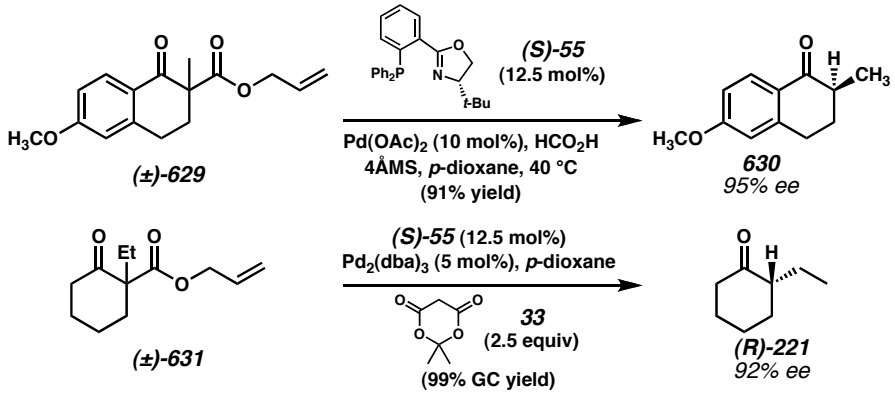


A different strategy for accessing chiral metal enolates is decarboxylation of β-ketoesters. The nature of the ester is typically important to enable enolate formation. In the case of palladium-catalyzed protonation reactions, benzyl and allyl esters have been the most common enolate precursors. The first examples of these reactions, developed extensively by Hénin, Muzart, and co-workers,[48] employed an initiation step such as Pd-mediated hydrogenolysis to generate an achiral enol (or enolate)[49] intermediate that was subsequently protonated with a chiral Brønsted acid (typically an amino alcohol). The results of these studies showed a strong dependence on the specific reaction conditions (e.g., temperature and source of palladium on carbon).

More recently, this strategy has been refined to instead generate a chiral Pd-enolate intermediate from allyl β-ketoester substrates (e.g., **629** and **631**, Scheme 6.28) in the

hopes that chirality at the metal might impart improved stereocontrol in the protonation step and obviate the need for heterogeneous Pd catalysts. Stoltz and co-workers[50] found that the catalyst derived from $Pd(OAc)_2$ and phosphinooxazoline (PHOX) ligand **55** was capable of achieving enantioselective protonation in the presence of formic acid and molecular sieves (MS). High enantiomeric excesses were obtained for a range of cyclic ketone products including tetralone- and cyclohexanone-derived ketones (e.g., **630** and **221**). Attempts to track the source of the proton incorporated in the product with isomeric *mono*-deuterated formic acids (DCO_2H and HCO_2D) led to inconclusive results: with DCO_2H the formyl deuteron was not incorporated into the product, but with HCO_2D only 35% D incorporation was observed in the product, suggesting that another unidentified proton donor is also participating in the reaction.

Scheme 6.28. Stoltz' palladium-catalyzed decarboxylative protonation reactions



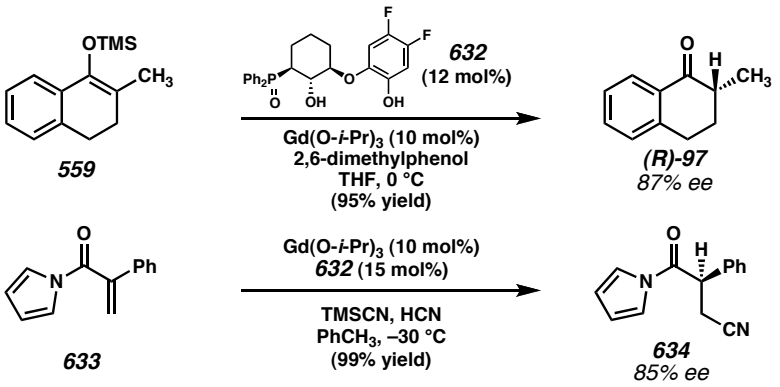
The heterogeneous additive (MS) in the reaction is important to the selectivity for protonation in preference to the competitive allylation reaction also catalyzed by the Pd•PHOX complex,[51] and the specific amount required varied somewhat depending on the substrate. To address this issue, a related *homogeneous* protonation system was developed by Stoltz and co-workers[52] employing Meldrum's acid (**33**, Scheme 6.28) as

the achiral proton donor and a Pd•PHOX catalyst. Similar substrate scope and enantioselectivity was observed with this system, but without the need to optimize the amounts of additives to achieve optimal results. Initial mechanistic studies found zero-order kinetic dependence in substrate, which suggests a fast initial reaction between catalyst and substrate and a slow subsequent step, presumably either decarboxylation or protonation of the putative enolate intermediate common to both the protonation and allylic alkylation reactions with this catalyst system.[53] However, in the protonation reaction opposite enolate facial preference was observed for tetralone- and cyclohexanone-derived enolates, whereas in the alkylation reaction consistent enantiofacial selectivity was observed.[51] This unexpected result suggests a substantial difference in the bond-forming portion of the mechanism.

Kanai, Shibasaki, and co-workers[54] recently reported the use of a chiral gadolinium complex for the enantioselective protonation of Gd-enolates generated in situ (Scheme 6.29). The Gd-enolates were accessed by two means: transmetallation from enol silane (e.g., **559**) or conjugate addition of cyanide to *N*-acryloyl pyrroles (e.g., **633**). Based on optimization studies, a polymetallic enolate intermediate was proposed. The optimal ligand-to-metal ratio is consistent with a 5:6 complex. The lack of reactivity in the absence of ligand **632** was also interpreted as the necessity of polynuclear Gd complexes for the success of the reaction. Kinetic studies also suggested that the reaction proceeds via transmetallation from Si to Gd, and that this step is rate limiting. 2,6-Dimethylphenol was the preferred proton source, providing indanone and tetralone products in up to 99% yield and up to 88% ee. The same Gd•**632** complex was also effective for the conjugate addition/protonation of cyanide to *N*-acryloyl pyrroles (e.g., **633** → **634**). In this case,

hydrogen cyanide was the preferred proton source. This transformation was capable of producing *N*-acyl pyrroles in up to 99% yield and up to 91% ee. In the case of product **634**, recrystallization could be carried out to provide a 74% yield of material with >99% ee. The versatility of this polynuclear Gd catalyst to effect protonation of considerably different enolate intermediates is important to the prospect of a general system for enolate protonation.

Scheme 6.29. Kanai and Shibasaki's gadolinium-catalyzed protonation reactions

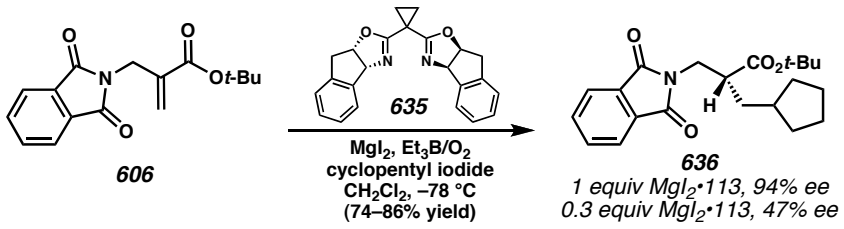


6.4.4 ENANTIOSELECTIVE HYDROGEN ATOM TRANSFER

An analogous strategy for arriving at protonation products is to exploit radical chemistry with a terminal H-atom abstraction step. Although not explicitly an enantioselective protonation reaction, many of the same challenges apply when manipulating a hydrogen atom. A recent example of this tactic by Sibi and co-workers[55,56] has led to new methods for synthesizing β-amino acid derivatives (Scheme 6.30). By employing a Lewis acid complex formed from MgI_2 and bis(oxazoline) ligand **635**, tributyltin hydride, and triethylborane/O_2, alkyl radicals (from alkyl halides) can undergo radical conjugate addition followed by enantioselective hydrogen atom transfer

to afford optically active products (e.g., **636**) in up to 95% yield and up to 98% ee. The reaction is believed to proceed through a bidentate chelate of the substrate to the chiral magnesium complex. The process can be made catalytic in Lewis acid without a significant effect on yield, but product ee suffered greatly in some cases due to a rapid uncatalyzed background reaction. These reactions have the benefit of being essentially neutral as opposed to the acidic or basic conditions required for the transformations described above.

Scheme 6.30. Radical conjugate addition followed by enantioselective H-atom transfer



6.5 CONCLUSION

From the enantioselective enzymatic protonation reactions of nature to the variety of techniques for achieving enantioselective protonation in laboratories, a great deal of energy has been dedicated to understanding this deceptively simple transformation. Despite the many systems reported to date, the search for a highly efficient system with a broad scope continues. Moreover, although many of the key parameters needed to create a successful system have been enumerated here and elsewhere, the current level of mechanistic understanding in nearly all of the enantioselective protonation reactions reported to date remains relatively immature. Nonetheless, these useful transformations allow the synthesis of valuable chiral materials including natural products like α- and β-

amino acids. Given these preliminary successes and improved understanding of the underlying mechanisms, enantioselective protonation reactions should continue to rise to prominence as an important tool for synthetic organic chemistry.

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CHAPTER 7

Catalytic Enantioselective Decarboxylative Protonation[†]

7.1 INTRODUCTION

Enantioselective protonation represents a direct method for generating tertiary carbon stereocenters from an achiral enolate or an enol equivalent. Several distinct approaches toward effecting this process have been reported, including the use of achiral enolates with chiral Brønsted acids, chiral metal enolates with an achiral proton source, and the combination of chiral enolates and chiral Brønsted acids.[1] Of the existing methods, most are limited in scope, few are catalytic, and together they have not provided a general solution to this deceptively simple goal.[1e] This chapter comprises our studies directed toward developing a highly enantioselective general catalytic system for the facile synthesis of tertiary stereocenters by protonation adjacent to ketones.

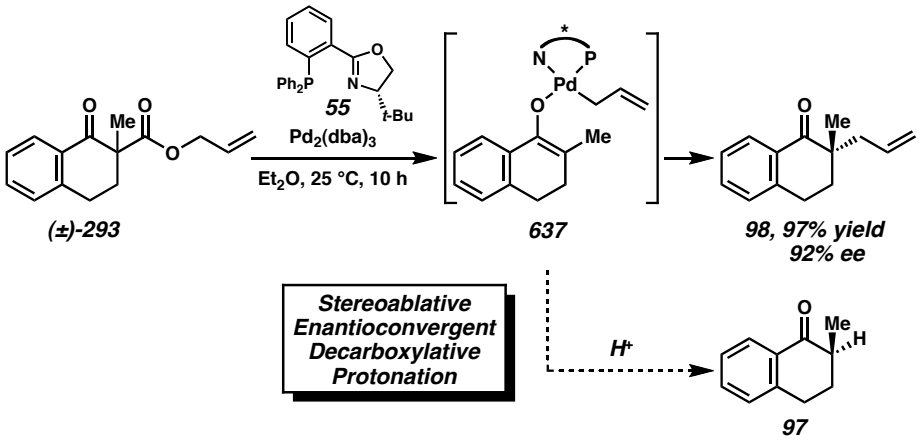
Recently, we disclosed a series of catalytic enantioselective allylation reactions that deliver cyclic ketones bearing all-carbon quaternary stereocenters at the α-position with high efficiency and enantioselectivity.[2] Crucial to the success of these transformations

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[†] This work was performed in collaboration with Toyoki Nishimata, Smaranda C. Marinescu, and Douglas C. Behenna. Portions of this work have been published, see: (a) Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11348–11349. (b) Marinescu, S. C.; Nishimata, T.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2008,** *10*, 1039–1042.

was the use of catalysts derived from Pd(0) and a chiral phosphinooxazoline (PHOX) supporting ligand (e.g., **55**).[3,4] Included in this effort was our exploration of racemic allyl β-ketoesters as substrates for a novel stereoablative enantioconvergent decarboxylative allylic alkylation reaction (e.g., (±)-**293** → **98**, Scheme 7.1).[2b,5] We believe that in the course of this reaction a chiral Pd-enolate (**637**) likely is generated in solution, and that the high degree of organization about the palladium center is responsible for the levels of enolate facial selectivity observed in the alkylation.[6] Interestingly, if this were the case, the catalytic generation and utilization of such chiral enolate complexes by this method would have the potential to be more broadly applicable than we previously recognized. Thus, in an effort to exploit this valuable chiral synthon, we chose to intercept this intermediate with an alternative electrophile, namely, a proton.[7,8]

Scheme 7.1. Interception of the putative Pd-enolate intermediate

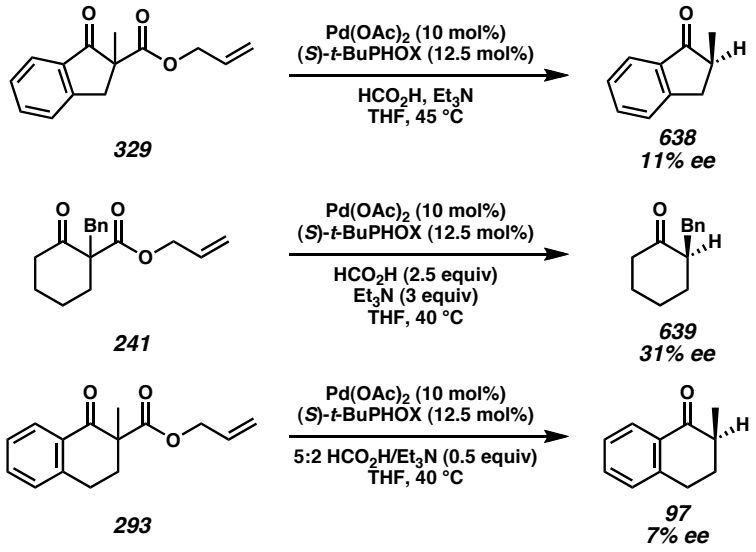


7.2 ENANTIOSELECTIVE PROTONATION WITH FORMIC ACID AS PROTON DONOR

7.2.1 DISCOVERY AND OPTIMIZATION OF REACTION CONDITIONS

Our first attempts to achieve an enantioselective protonation consisted of exposure racemic β-ketoesters **329**, **241**, and **293** to $Pd(OAc)_2$ in the presence of (*S*)-*t*-Bu-PHOX (**55**) with triethylamine and HCO_2H, resulting in smooth conversion to the corresponding ketones (**638**, **639**, and **97**, respectively) with low, but measurable enantiomeric excess (Scheme 7.2).[7]

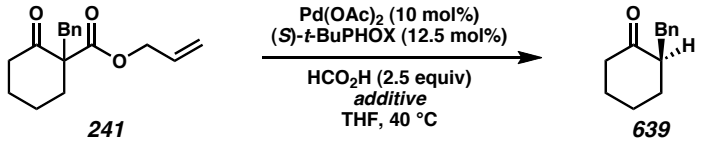
Scheme 7.2. Initial attempts at enantioselective protonation



We suspected that an ammonium species was behaving as the proton donor, and therefore modification of amine base additive would serve to modulate the acidity and perhaps improve enantioselectivity. Examination several basic additives did indeed show a significant influence on product ee (Table 7.1). As a control experiment we also carried

out the reaction in the absence of base and were surprised to find that ketone **639** was formed in 53% ee (entry 9).

Table 7.1. Effect of basic additives on enantioselecitve protonation[a]

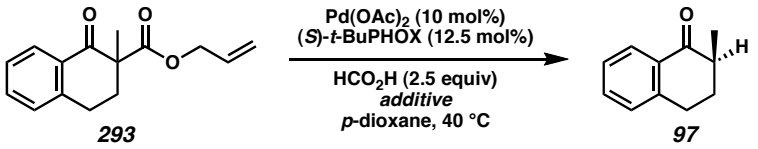


entry	additive	amount (equiv)	%ee of *639*	entry	additive	amount (equiv)	%ee of *639*
1	Et_3N	3	31	6	2,6-lutidine	3	42
2	*i*-Pr_2NEt	3	41	7	K_2CO_3	3	47
3	*i*-Pr_2NH	3	27	8	Na_2SO_4	5	52
4	DABCO	3	1	9	none	–	53
5	pyridine	3	57				

[a] Reactions performed with 0.1 mmol of **241**. Each reaction proceeded to complete conversion.

In order to sequester the small amount of water present in commercially available formic acid, we next examined additives that might remove adventitious moisture (Table 7.2).[9] Whereas many common additives had little effect on the ee of product **97**, oven-dried molecular sieves (MS) dramatically increased enantiopurity (entries 8, 10, and 11).

Table 7.2. Effect of other additives on enantioselective protonation[a]

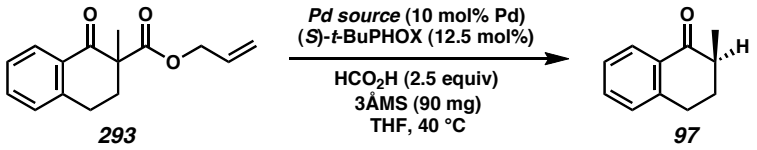


entry	additive	amount	%ee of *97*	entry	additive	amount	%ee of *97*
1	Et_3N	1 equiv	7[b]	7	Celite	90 mg	39
2	none	–	24[b]	8	3ÅMS	90 mg	79
3	activated SiO_2	90 mg	33	9	4ÅMS[c]	90 mg	67
4	activated carbon	90 mg	8	10	4ÅMS	90 mg	88
5	$MgSO_4$	5 equiv	34	11	5ÅMS	90 mg	85
6	$HC(OEt)_3$	5 equiv	30	12	13X MS	90 mg	58

[a] Reactions performed with 0.1 mmol of **293**. Solid additives were oven dried prior to use. Each reaction proceeded to complete conversion. [b] Reaction performed with THF as solvent. [c] Used as received without drying in an oven.

A brief examination of the Pd source indicated that $Pd(OAc)_2$ was preferred and that the metal was required for the reaction to occur (Table 7.3).

Table 7.3. Effect of palladium source on enantioselective protonation

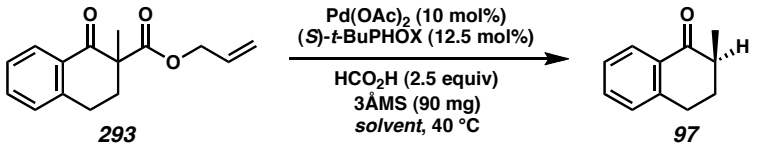


entry	Pd source	%ee of **97**
1	$Pd(OAc)_2$	72
2	$[Pd(allyl)Cl]_2$	41
3	$Pd_2(dba)_3$	49
4	none	–[b]

[a] Reactions performed with 0.1 mmol of **293**. 3ÅMS were oven-dried prior to use. Each reaction proceeded to complete conversion, unless otherwise noted. [b] No conversion was observed.

Solvent was found to influence the enantioselectivity of the protonation reaction significantly (Table 7.4). This contrasts the results for the related alkylation reaction that performed well in a variety of solvents.[2] Ethereal solvents gave mixed results, but *p*-dioxane proved to be superior to all others tested (entry 3).

Table 7.4. Effect of solvent on enantioselective protonation[a]



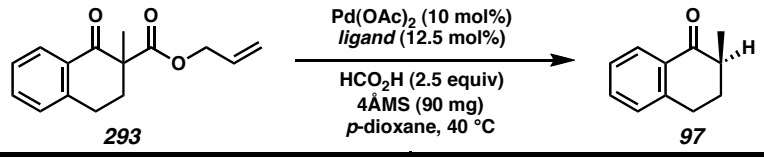
entry	solvent	%ee of **97**	entry	solvent	%ee of **97**
1	tetrahydrofuran	72	7	anisole	21
2	tetrahydropyran	63	8	benzene	39
3	*p*-dioxane	79	9	toluene	53
4	1,2-dimethoxyethane	27	10	ethyl acetate	56
5	*t*-butyl methyl ether	68	11	pinacolone	4
6	diisopropyl ether	58	12	1,2-dichloroethane	–[b]

[a] Reactions performed with 0.1 mmol of **293**. 3ÅMS were oven dried prior to use. Each reaction proceeded to complete conversion, unless otherwise noted. [b] No conversion was observed.

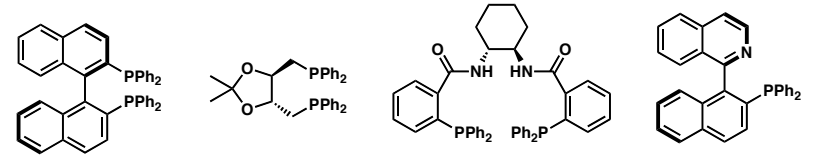
At this point, we also examined the behavior of other chiral ligands in this reaction (Table 7.5). As in our earlier studies,[2] we found chelating P–N ligands to be the most effective, while bis(phosphine)-type ligands (entries 1–3) provided only trace asymmetric induction. Several PHOX-type ligands were tested with good results (entries 5–11), however, none of these was significantly superior to *t*-BuPHOX (**55**). Finally, we found

that when the solvent was freshly distilled and the 4ÅMS were rigorously flame-dried immediately prior to use, the enantiomeric purity was further enhanced, providing **97** in 92% ee (entry 12).

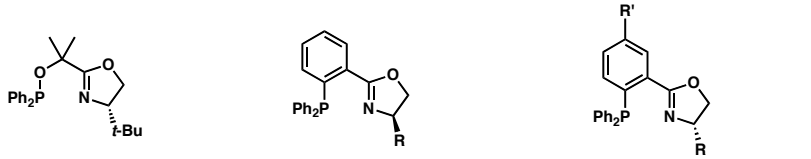
Table 7.5. Ligand screen for enantioselective protonation[a]



entry	ligand	%ee of **97**	entry	ligand	%ee of **97**
1	*(R)-BINAP (116)*	–1	7	*(S)-SimplePHOX (147)*	5
2	*(R,R)-DIOP (118)*	3	8	*(R)-132*	–89
3	*(R,R)-Trost ligand (103)*	3[b]	9	*(S)-187*	86
4	*(S)-QUINAP (120)*	–20	10	*(S)-140*	90
5	*(R)-PhPHOX (121)*	–65	11	*(S)-tBuPHOX (55)*	88
6	*(S)-iPrPHOX (122)*	87	12[c]	*(S)-tBuPHOX (55)*	92



(R)-BINAP (116) *(R,R)-DIOP (118)* *(R,R)-Trost ligand (103)* *(R)-QUINAP (120)*



(S)-SimplePHOX (147)

121, R = Ph, (R)-Ph-PHOX
122, R = i-Pr, (R)-i-Pr-PHOX
132, R = C(Me)$_2$OTBS

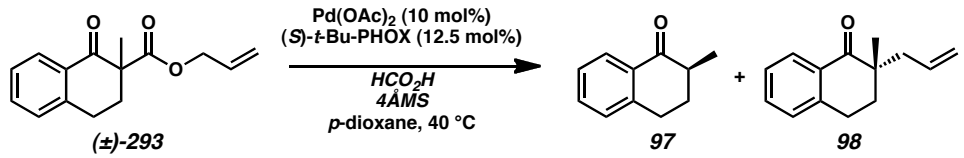
187, R = 2-napthyl, R' = H
140, R = t-Bu, R' = CF$_3$
55, R = t-Bu, R' = H
(S)-t-Bu-PHOX

[a] Reactions performed with 0.1 mmol of **293**. 4ÅMS were oven dried prior to use. Each reaction proceeded to complete conversion, unless otherwise noted. [b] The ee was measured after 72 hours at approximately 60% conversion. [c] MS were flame dried under vacuum and *p*-dioxane was freshly distilled from Na.

Attempts to optimize the amount of HCO_2H and 4ÅMS in the reaction indicated that the balance of these two components was intimately related to both enantio- and chemoselectivity (i.e., the ratio of protonated to allylated products **97**/**98**). In general, an excess of HCO_2H led to decreased enantioselectivity while smaller quantities afforded greater amounts of allylated product **98**. Alternatively, small amounts of 4ÅMS

produced **97** in decreased ee, while large quantities led to increased allylation. Specific results for substrate **293** are shown in Table 7.6. The optimal amount of HCO_2H was found to be 6.0 equiv with a 4ÅMS quantity of 1.80 g/mmol substrate.

Table 7.6. Optimization of relative amounts of HCO_2H and 4ÅMS[a]



amount of HCO_2H (equiv)

amount of 4ÅMS (for 0.1 mmol of **293**)	2.5	3	3.5	4	4.5	5	5.5	6	8	10
90 mg	n.d. 88% ee	82/18 90% ee	96/4 92% ee	100/0 90% ee	100/0 69% ee	100/0 46% ee	–	–	–	–
135 mg	86/14 86% ee	61/39 82% ee	89/11 91% ee	90/10 92% ee	95/5 92% ee	99/1 93% ee	99/1 90% ee	100/0 86% ee	–	–
180 mg	–	–	–	96/4 92% ee	–	95/5 91% ee	–	100/0 93% ee	–	–
225 mg	–	–	–	83/17 92% ee	–	91/9 89% ee	–	96/4 93% ee	99/1 93% ee	100/0 69% ee
270 mg	–	54/46[b] 78% ee	–	–	–	93/7[c] 91% ee	–	91/9 92% ee	100/0 93% ee	100/0 92% ee

Entries report: ratio 97/98 / %ee of 97

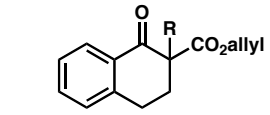
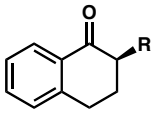
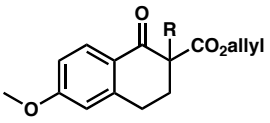
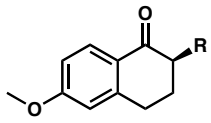
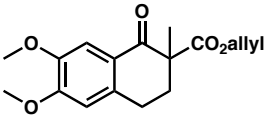
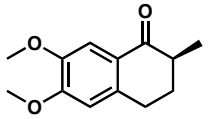
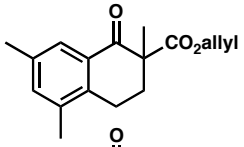
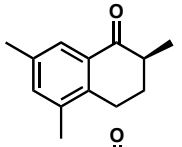
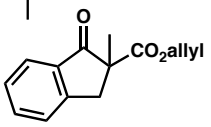
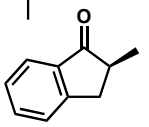
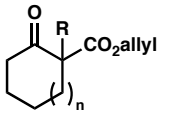
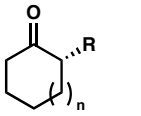
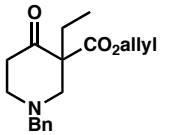
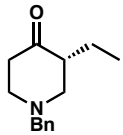
[a] Reactions performed with 0.1 mmol of **293**. 4ÅMS were flame dried under vacuum prior to use. Each reaction proceeded to complete conversion. Data in the table are the ratio of protonation to allylation products (**97**/**98**) and the ee of protonation product **97**. [b] Isolated **98** was found to be 86% ee. [c] Isolated **98** was found to be 87% ee.

7.2.2 RESULTS OF ENANTIOSELECTIVE PROTONATION

We next explored the generality of the reaction. Under the optimized conditions determined in Table 7.6, (*S*)-(–)-2-methyl-1-tetralone (**97**) was produced in 88% yield and 94% ee with no observable allylation (Table 7.7, entry 1). It was necessary to slightly vary the relative amounts of formic acid and MS in order to obtain optimal

results for other substrates. A variety of substitution is tolerated at the ketone α-position (entries 1–3) and various positions about the aromatic ring (entries 4–8) of 1-tetralone derivatives. Enantioenriched (*S*)-(+)-2-methyl-1-indanone (**638**) can also be produced from the corresponding β-ketoester (entry 9). Additionally, monocyclic compounds (entries 10–13) and a heterocycle (entry 14) were easily accessed under similar reaction conditions.

Table 7.7. Enantioconvergent decarboxylative protonations with formic acid

Entry	Substrate		Product			Time (h)	Yield (%)[a]	ee (%)[b]
1		*293*		*97*	R = Me	10	88	94 (*S*)
2		*640*		*641*	R = allyl	4	88	85 (*R*)
3		*498*		*642*	R = F	5	79	88 (*S*)
4		*629*		*630*	R = Me	5	91	95
5		*643*		*541*	R = allyl	6	81	88
6		*644*		*645*	R = Bn	5	95	78
7		*646*		*647*		8.5	62	94
8		*648*		*649*		8	75	92
9[c]		*329*		*638*		22	83	81 (*S*)
10		*650*		*651*	n = 0, R = Bn	4	63	60
11		*107*		*207*	n = 1, R = Me	4.5	99[d]	85 (*R*)
12[e]		*241*		*639*	n = 1, R = Bn	4.5	91	92 (*S*)
13		*652*		*653*	n = 2, R = Bn	5	69	74
14		*318*		*654*		3	81	84

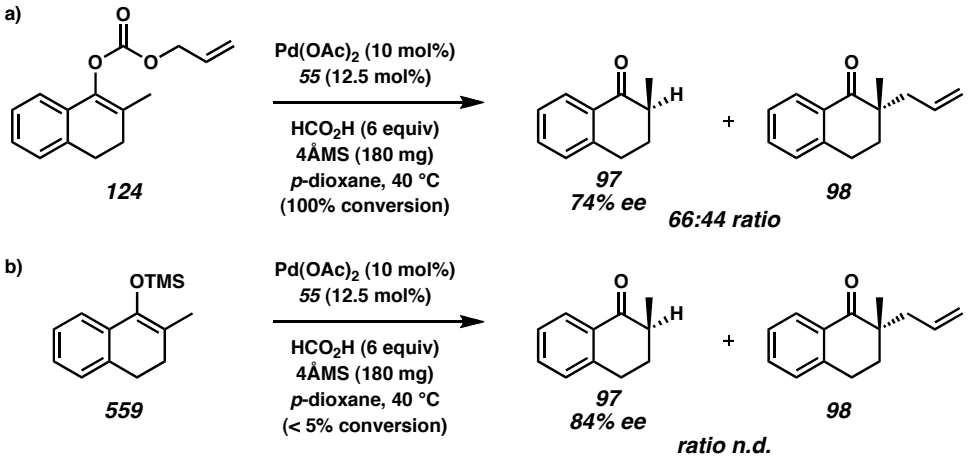
[a] Isolated yield from reaction of 0.3 mmol substrate at 0.033 M in *p*-dioxane with 10 mol% $Pd(OAc)_2$, 12.5 mol% (*S*)-*t*-Bu-PHOX, 5–8 equiv HCO_2H, and 405–810 mg 4ÅMS at 40 °C (ref 10). [b] Determined by chiral HPLC or GC; where noted, the absolute configuration was determined by comparing the sign of optical rotation to literature values (ref 10). [c] Reaction performed with 5 mol% $Pd(OAc)_2$ and 6.25 mol% (*S*)-*t*-Bu-PHOX. [d] GC yield using tridecane as internal standard. [e] Reaction performed at 35 °C.

The absolute configuration of a number of products was established by comparison of the observed sign of optical rotation to literature values (entries 1–3, 9, 11, and 12).[10] Interestingly, fused aromatic substrates (i.e., tetralones and indanones) lead to products in the opposite enantiomeric series compared to the cyclohexanone cases (cf. entries 1–3 and 9 to entries 11–12). These results are in contrast to the consistent enantiofacial selectivity observed across multiple substrate types in our asymmetric allylation chemistry, and suggest stark differences in their corresponding mechanisms.[2,6]

7.2.3 ENANTIOSELECTIVE PROTONATION WITH OTHER ENOLATE PRECURSORS

We were interested in whether the other enolate precursors we have employed for enantioselective allylation chemistry would be competent substrates for the protonation reaction. In order to investigate this possibility, allyl enol carbonate **124** was subjected to our optimized reaction conditions for the formation of **97**. Contrasting the result when (±)-**293** was used (Table 7.2, entry 1), in this case ketone **97** was produced in 74% ee with a 66/44 ratio of **97**/**98** on a 0.1 mmol scale (100% conversion). When enol silane **559** was used, low conversion (<5%) was observed, however, the ee of isolated **97** was 84%. Although these results highlight the advantage of β-ketoester precursors to the reactive enolate intermediate, it is uncertain why the reactivity and selectivity of these substrates is so different.[11]

Scheme 7.3. Enantioselective protonation with allyl enol carbonate and silyl enol ether substrates



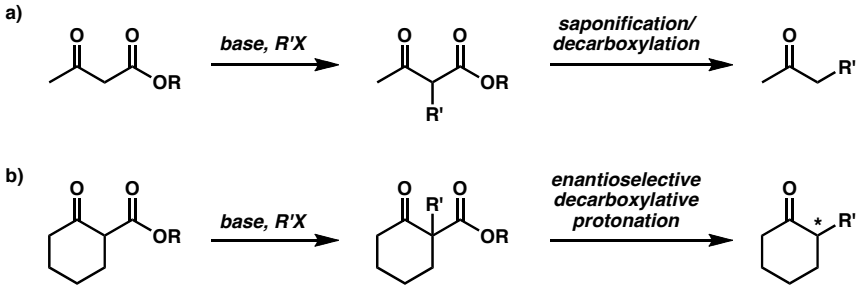
7.2.4 DEUTERIUM LABELING EXPERIMENTS

In order to probe the mechanism of the protonation reaction, we carried out deuterium labeling studies using substrate **293** with *mono*-deuterio-formic acid isomers HCO_2D and DCO_2H.[10] We have maximally observed 35% D-incorporation when using HCO_2D and 4ÅMS dried under vacuum for three days at 320 °C. If the MS were not dried in this way then much lower levels of D-incorporation were observed (ca. 10%). By contrast, under otherwise identical conditions, <1% D-incorporation was observed when DCO_2H was employed. In the absence of MS, 35% D-incorporation was observed when HCO_2D was used, and no detectable D-incorporation was found when DCO_2H was used.[12] The detailed mechanism of proton incorporation (e.g., proton transfer, reductive elimination, or otherwise) remains unclear.

7.2.5 SUMMARY OF ENANTIOSELECTIVE PROTONATION METHODOLOGY USING FORMIC ACID

A novel system for the enantioconvergent decarboxylative protonation of racemic β-ketoesters was developed. The reaction tolerates a variety of substitution and functionality and delivers products of high enantiopurity in excellent yield. The enantioinduction in the observed protonated products is consistent with the intermediacy of an enolate that is intimately associated to the chiral Pd complex. This, in turn, substantiates our initial hypothesis concerning the nature of the reactive intermediate **637** and opens the door to further applications. The process capitalizes on the availability and unique reactivity of racemic α-substituted allyl-β-ketoesters, which are employed directly in the catalytic enantioselective process and deliver valuable tertiary-substituted products in highly enantioenriched form. In general, the overall process (substrate synthesis and use) represents a catalytic enantioselective variant of classic alkylation/decarboxylation sequences (e.g., acetoacetic ester synthesis, cf. Scheme 7.4a and b).[13] Furthermore, the asymmetric protonation described here serves to complement our recently developed asymmetric alkylation methodology that delivers quaternary stereocenters from the same starting materials via catalytic enantioselective allylation.

Scheme 7.4. Acetoacetic ester synthesis vs alkylation/decarboxylation sequence

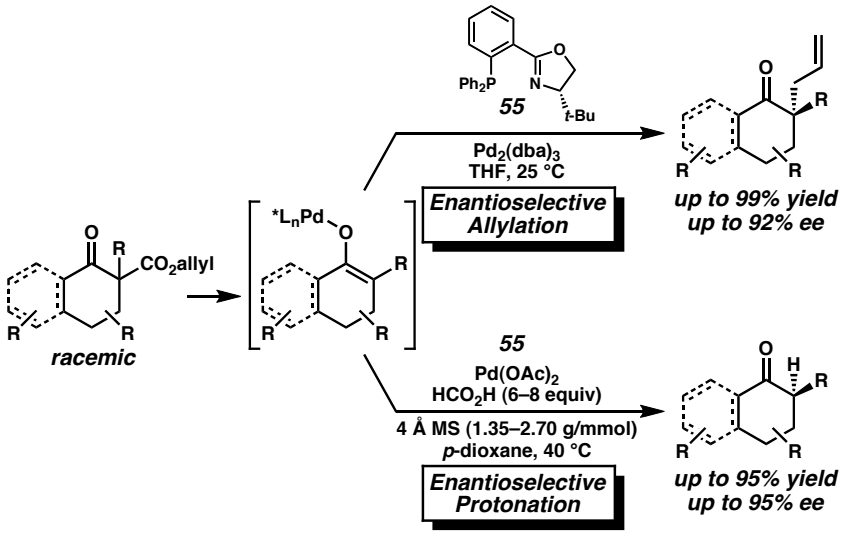


7.3 HOMOGENEOUS ENANTIOSELECTIVE PROTONATION

7.3.1 BACKGROUND

We first reported a highly enantioselective catalytic system for the decarboxylative protonation of racemic allyl β-ketoesters in the presence of $Pd(OAc)_2$, (*S*)-*t*-Bu-PHOX (**55**), 4Å molecular sieves (MS), and HCO_2H (Scheme 7.5).[14] Although this protocol is capable of generating cycloalkanones with excellent ee, each substrate required optimization of the amounts of 4ÅMS and HCO_2H in order to suppress competitive allylation and maximize product ee. Moreover, the heterogeneous nature of the reaction hinders investigation of the mechanism of protonation. In response, we have sought substantially different protonation conditions to allow further development of a practical synthetic process.

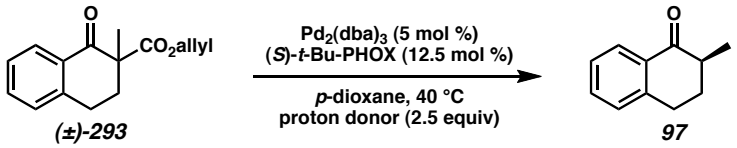
Scheme 7.5. Pd-catalyzed enantioselective decarboxylative allylation and protonation of racemic allyl β-ketoesters



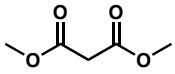
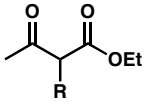
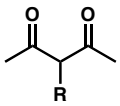
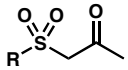
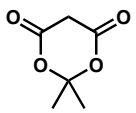
7.3.2 SCREENING OF ALTERNATE PROTON DONORS

To achieve a homogeneous enantioselective protonation, the racemic allyl β-ketoester (±)-**293** was exposed to $Pd_2(dba)_3$, (*S*)-*t*-Bu-PHOX (**55**), and a variety of achiral organic proton donors (Table 7.8). Gratifyingly, the use of dimethyl malonate did indeed lead to protonated product **97**, although the ee was moderate (entry 1). Acetoacetic esters (entries 2 and 3) provided **97** in significantly higher ee than the malonate case, but at the expense of conversion. Acetylacetone derivatives (entries 4–6) were very reactive, with the more acidic analogues providing higher ee products. Noting that the more acidic compounds increased the rate of reaction dramatically, we chose next to explore other highly acidic organic proton donors. Ketosulfones (entries 7–9) led to protonated product **97** in very high ee, though conversion was sometimes slow. However, commercially available Meldrum's acid[15] led to extremely rapid formation of **97** with good enantioselectivity (entry 10). Given the fast reaction at 40 °C, we attempted the transformation at ambient temperature (23 °C) and observed a significant increase in product ee (entry 11). Further lowering the temperature required changing the solvent to THF, and although the ee was excellent, reactivity dropped sharply (entry 12). Notably, addition of MS to the reaction had a severe impact on the ee (entry 13).

Table 7.8. Screening of achiral proton donors[a]



(±)-293 → *97*

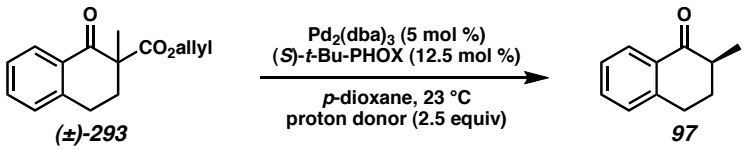
entry	proton donor		time (h)	conversion (%)[b]	ee (%)[c]
1		***655***	24	85	62
2		***656***, R = H	24	50	80
3		***657***, R = F	24	55	89
4		***658***, R = H	24	95	50
5		***659***, R = Ac	2	100	74
6		***660***, R = Ms	3	100	88
7		***661***, R = Me	24	42	89
8		***662***, R = Ph	24	63	90
9		***663***, R = *p*-Tol	5	100	84
10		***33***	0.2	100	85
11[d]			0.5	100	90
12[e]			24	50	95
13[f]			1.5	100	43

[a] Reactions performed with 0.1 mmol of (±)-**293** at 0.033 M in *p*-dioxane. [b] Measured by ^{1}H NMR spectroscopy. [c] Measured by chiral HLPC. [d] Reaction performed at 23 °C. [e] Reaction performed at 0 °C in THF solvent. [f] Reaction performed with 90 mg of 4ÅMS.

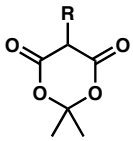
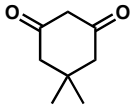
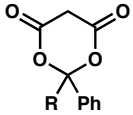
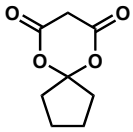
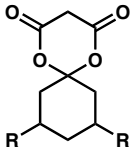
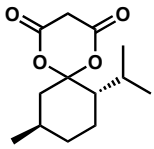
The combination of reactivity, selectivity, and availability prompted us to choose the Meldrum's acid scaffold for our further studies (Table 7.9). It was found that, in general, large substituents between the carbonyls of the proton source decrease the enantiopurity of **97**, although smaller groups (e.g., CH_3) are tolerated (entries 1–5). In contrast to the acyclic case, addition of a third resonance withdrawing group (e.g., acetyl) severely decreased reactivity and product ee (cf. Table 7.8, entry 9 and Table 7.9, entry 5). Electronic perturbation by substituting dimedone (**457**) as the proton source led to only trace product in low ee (entry 6). Variation of the acetal portion with sterically diverse groups had a relatively small effect on ee (entries 7 and 8). Notably, simple spirocyclic derivatives of Meldrum's acid (entries 9 and 10) gave the highest ee, although conversion

to product was sluggish. Larger bicyclic acetals gave mixed results (entries 11–13). Interestingly, the enantiopure menthone derived analogue performed equally well with either antipode of the chiral ligand, indicating that the catalyst directly controls the sense of enantioinduction (entries 12 and 13). None of the slight improvements observed with these various derivatives outweighed the convenience of the commercially available Meldrum's acid (**33**). Additionally, a screen of other chiral PHOX ligands revealed the superiority of the original (*S*)-*t*-Bu-PHOX (**55**).[10]

Table 7.9. Screening of Meldrum's acid derivatives[a]



(±)-293 *97*

entry	proton donor		time (h)	conversion (%)[b]	ee (%)[c]
1		***33***, R = H	0.5	100	90
2		***664***, R = Me	0.2	100	90
3		***665***, R = Ph	24	86	68
4		***666***, R = Allyl	1	100	67
5		***667***, R = Ac	24	1	51
6		***457***	24	8	43
7		***668***, R = H	5	100	85
8		***669***, R = Me	4	100	84
9		***670***	24	25	93
10		***671***, R = H	24	86	91
11		***672***, R = Me	24	100	76
12		***673***	24	100	90
13[d]			24	100	–90

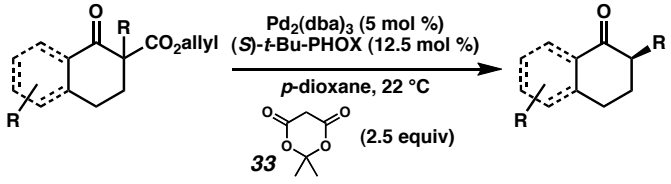
[a] Reactions performed with 0.1 mmol of (±)-**293** at 0.033 M in *p*-dioxane. [b] Measured by ^{1}H NMR spectroscopy. [c] Measured by chiral HLPC. [d] Reaction performed with (*R*)-*t*-Bu-PHOX (12.5 mol%).

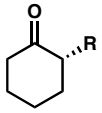
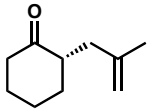
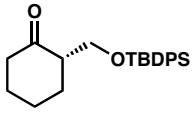
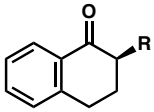
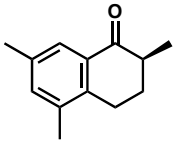
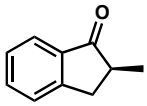
7.3.3 RESULTS OF HOMOGENEOUS ENANTIOSELECTIVE PROTONATION

Encouraged by these results, the scope of this enantioselective protonation was explored (Table 7.10). The general set of reaction conditions employed in these studies

were straightforward: racemic allyl β-ketoester was exposed to $Pd_2(dba)_3$ (5 mol%), (*S*)-*t*-Bu-PHOX (**55**, 12.5 mol%), and Meldrum's acid (**33**, 2.5 equiv) in *p*-dioxane (0.033 M) at room temperature (22 °C). A variety of substituted cyclohexanone derivatives was prepared (entries 1–5). Especially noteworthy is the tolerance of a β-siloxy substituent (entry 5). The near quantitative yield and the absence of β-elimination products (i.e., enone) highlight the mild, neutral reaction conditions. 1-Tetralone derivatives (entries 6–8) were also accessible in high yield and ee. Finally, (*S*)-(+)-2-methyl-1-indanone (**638**, entry 9) was prepared in good yield, although the ee was moderate. When we attempted to carry out the reaction on larger scale, we observed a slight decrease in product ee. The origins of this decrease are unclear at this time.

Table 7.10. Homogeneous enantioconvergent decarboxylative protonations with Meldrum's acid[a]



entry	product		ee A (%)	time (h)	yield (%)	ee B (%)
1		***207***, R = Me	88	0.5	99[b]	86 (***R***)
2		***221***, R = Et	92	0.5	99[b]	89 (***R***)
3		***639***, R = Bn	83	0.5	90	78 (***S***)
4		***674***	91	5	87	89
5		***675***	85	0.5	97	80
6		***97***, R = Me	90	0.5	86	77 (***S***)
7		***641***, R = allyl	82	0.5	83	77 (***R***)
8		***649***	–	0.5	77	77
9		***638***	–	0.5	79	61 (***S***)

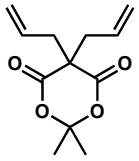
[a] Reactions were performed on two different scales, A: 0.1 mmol of substrate, and B: 0.3 mmol of substrate, each at 0.033 M in *p*-dioxane. Column ee A reflects results for conditions A; time, isolated yield, and ee B are reported for conditions B. Isolated yields from conditions A were comparable to those with conditions B. The major enantiomer was the same under either set of conditions. Enantiomeric excess was measured following chromatography on silica gel; no erosion of ee was observed as a result of purification. [b] GC yield using tridecane as internal standard.

The absolute configuration of a number of products was established by a comparison of the observed sign of optical rotation to literature values (entries 1–3, 6, 7, and 9). Cyclohexanone substrates led to products in the opposite enantiomeric series compared to that of the tetralone and indanone cases (entries 1–3 vs. entries 6, 7, and 9). Identical behavior was observed when the reactions were performed with our heterogeneous

$Pd(OAc)_2/HCO_2H$ conditions,[14] suggesting that the two enantioselective protonations proceed through very similar mechanisms.

Under our optimized reaction conditions, products arising from allylation of our postulated enolate intermediate were not observed. This contrasts with our previous work[14] where it was necessary to supply an excess of acid (up to 8 equiv) to fully suppress competitive allylation. The only by-product isolated under the homogeneous reaction conditions was 5,5-diallyl-2,2-dimethyl-1,3-dioxane-4,6-dione (**676**, Figure 7.1).[16] Interestingly, we did not detect *mono*-allylated Meldrum's acid **666** as a by-product.

Figure 7.1. Diallyl Meldrum's acid by-product of protonation



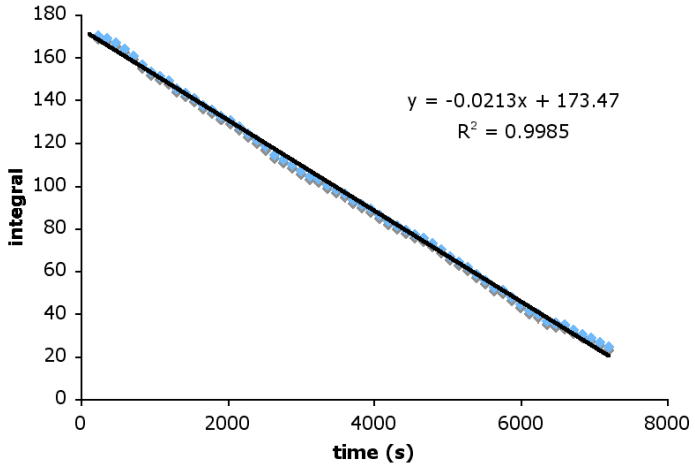
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7.3.4 PRELIMINARY KINETIC STUDIES

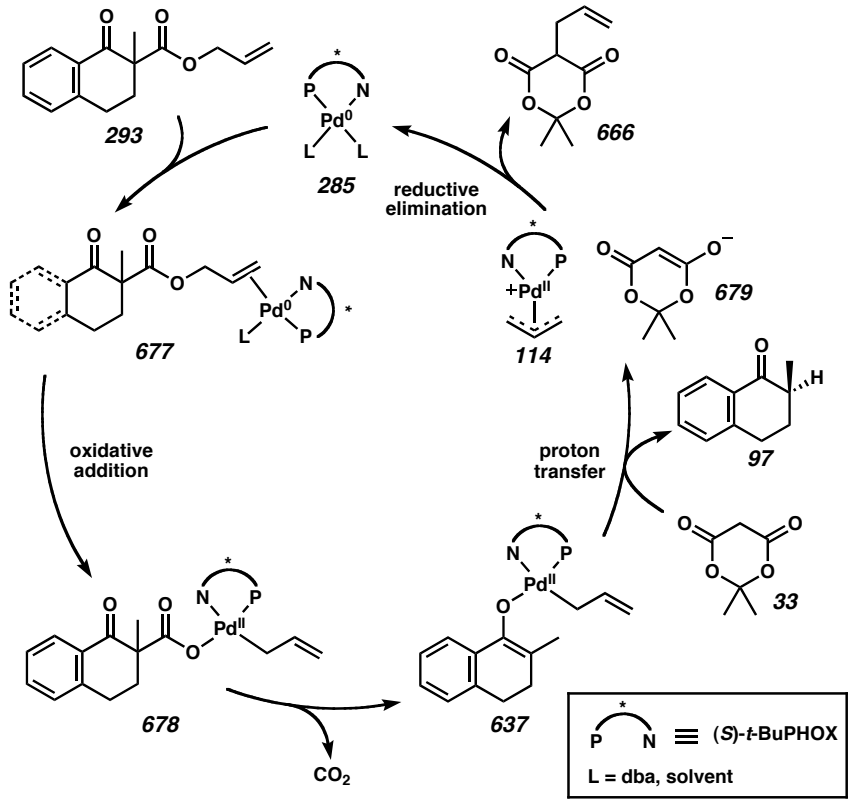
Since we have been unable to perform detailed mechanistic studies with our heterogeneous protonation system, we were eager to examine the mechanism with our new system. Kinetic studies of the homogeneous enantioselective protonation reaction were performed via ^1H NMR spectroscopy in C_6D_6 (Figure 7.2).[10] A plot of amount of allyl β-ketoester substrate **293** over time displayed zero-order decay, suggesting that ketoester **293** reacts very fast and generates an intermediate (possibly a Pd-carboxylate (e.g., **678**) or Pd-enolate(e.g., **637**)) that undergoes further reaction in a slower step

(Scheme 7.6). Similar zero-order dependence in substrate was observed in the case of our related enantioselective allylation reaction,[2,6] implying that the early stages of both processes are similar. Although these results give some information regarding the first portion of the reaction pathway, further studies are required to elucidate the mechanism and origin of enantioselectivity.

Figure 7.2. Plot of substrate ***293*** *^{1}H NMR integral vs time*



Scheme 7.6. Proposed catalytic cycle for enantioselective protonation



7.4 SUMMARY

In conclusion, we have developed two novel palladium-catalyzed system for the enantioconvergent decarboxylative protonation of racemic allyl β-ketoesters. The reaction tolerates a variety of substrate substitution and functionality and generates products with high enantiomeric excess. The method utilizes readily accessible racemic α-substituted allyl β-ketoesters and either formic acid or commercially available Meldrum's acid as the proton donor. Using the former proton source, substrate-specific optimization is required. Using the latter proton donor one standard set of reaction conditions was amenable to the synthesis of a variety of α-tertiary cycloalkanones with

high ee. The homogeneous conditions developed herein enabled preliminary kinetic experiments for investigation of the mechanism of this transformation.

7.5 NOTES AND REFERENCES FOR TEXT

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3. For the development of phosphinooxazoline ligands, see: (a) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345. (b) Williams, J. M. J. *Synlett* **1996**, 705–710, and references therein.

4. We have recently reported a convenient general scaleable synthetic route to PHOX ligands see: (a) Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. *Org. Lett.* **2007**, *9*, 2529–2531. (b) Krout, M. R.; Mohr, J. T.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 181–193.

5. For a review of enantioselective stereoablative reactions, see: Mohr, J. T.; Ebner, D. C.; Stoltz, B. M. *Org. Biomol. Chem.* **2007**, *5*, 3571–3576.

6. For a computation model that supports this hypothesis, see: Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard, III, W. A. *J. Am. Chem. Soc.* **2007**, *129*, 11876–11877.

7. A non-enantioselective decarboxylative protonation has been reported by Tsuji, see: (a) Tsuji, J.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1985**, *50*, 3416–3417. (b) Mandai, T.; Imaji, M.; Takada, H.; Kawata, M.; Nokami, J.; Tsuji, J. *J. Org. Chem.* **1989**, *54*, 5395–5397.

8. To our knowledge, there are three other groups that have reported related Pd-catalyzed systems that produce similar enantioenriched products, see: (a) Hénin, F.; Muzart, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1161–1164. (b) Aboulhoda, S. J.; Hénin, F.; Muzart, J.; Thorey, C.; Behnen, W.; Martens, J.; Mehler, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1321–1326. (c) Aboulhoda, S. J.; Létinois, S.; Wilken, J.; Reiners, I.; Hénin, F.; Martens, J.; Muzart, J. *Tetrahedron: Asymmetry* **1995**, *6*, 1865–1868. (d) Baur, M. A.; Riahi, A.; Hénin, F.; Muzart, J. *Tetrahedron: Asymmetry* **2003**, *14*, 2755–2761. (e) Sugiura, M.; Nakai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2366–2368. (f) Hamashima, Y.; Somei, H.; Shimura, Y.; Tamura, T.; Sodeoka, M. *Org. Lett.* **2004**, *6*, 1861–1864.

9. Substrate **293** was used for most optimization studies due to the ease of product analysis. Protonation with substrate **241** in the presence of 3ÅMS led to product **639** with 81% ee.

10. See the experimental section (section 7.6) for details.

11. Substitution on the allyl group (e.g., methylallyl or crotyl) of β-ketoester substrates had a negligible effect on yield and product ee.

12. In these two experiments, ketone **97** formed in 55% and 48% ee, respectively.

13. Blanchet, J.; Baudoux, J.; Amere, M.; Lasne, M.-C.; Rouden, J. *Eur. J. Org. Chem.* **2008**, 5493–5506.

14. Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11348–11349.

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7.6 EXPERIMENTAL SECTION

7.6.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. *p*-Dioxane was distilled over sodium prior to use unless specifically noted. Other solvents were dried by passage through an activated alumina column under argon. Brine solutions are saturated aqueous sodium chloride solutions. Palladium(II) acetate ($Pd(OAc)_2$) and Tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) were purchased from Strem and used as received. (*S*)-*t*-Bu-PHOX (**55**) was prepared by the method reported in our previous work.[17] Preparations of other PHOX ligands are found in Chapter 2. Ketone starting materials, diallyl carbonate, alkyl halides, L-Selectride®, and Selectfluor™ were purchased from Aldrich and used as received. Sodium hydride (NaH) was purchased as a 60% dispersion in mineral oil from Acros and used as received. Formic acid (98%) was purchased from Fluka and used as received. Deuterated formic acid (HCO_2D and DCO_2H) were purchased from Cambridge Isotope Laboratories and used as received. The HCO_2D (≥98% chemical purity) was from lot #PR-15324/06034FA1 and was assayed by the supplier as containing 99.6% isotopic enrichment and 4% D_2O. The DCO_2H (≥98% chemical purity) was from lot #I1-5333 and was assayed by the supplier as containing >98% isotopic enrichment and 1608 ppm H_2O. Molecular sieves were purchased from Aldrich as activated 5 μm powder and stored in a 120 °C drying oven until immediately prior to use unless otherwise noted; the 4Å molecular sieves (4ÅMS) used in this work were from batch #13128AD. Meldrum's acid (**33**) was recrystallized

from ethyl acetate prior to use. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, $KMnO_4$, or CAM staining. ICN Silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralcel OD-H or Chiralpak AD column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries with visualization at 254 nm, unless otherwise stated. Analytical chiral GC was performed with an Agilent 6850 GC utilizing a G-TA (30 m x 0.25 mm) column (1.0 mL/min carrier gas flow). Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 spectrometer (at 300 and 75 MHz respectively), and are reported relative to Me_4Si (δ 0.0 ppm). ^{19}F NMR spectra were recorded on a Varian Mercury 300 spectrometer at 282 MHz, and are reported relative to the external standard F_3CCO_2H (δ –76.53 ppm). ^{2}H NMR spectra were recorded on a Varian Inova 500 spectrometer at 77 MHz, and are reported relative to Me_4Si (δ 0.0 ppm). Temperature controlled ^{1}H NMR kinetic experiments were performed on a Varian Inova 500 MHz. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Data for ^{13}C, ^{19}F, and ^{2}H NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). Melting points were determined using a Thomas capillary melting point apparatus and the values reported are uncorrected. High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility.

7.6.2 EXPERIMENTAL DATA RELEVANT TO THE FORMIC ACID PROTOCOL

7.6.2.1 OPTIMIZATION OF REACTION CONDITIONS FOR FORMIC ACID PROTOCOL

Optimization reactions were carried out using the following sample procedure with variations as indicated in Table 7.1 through Table 7.5.

Sample Procedure for Optimization Reactions

In a 1 dram glass vial, a solution of $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 0.10 equiv, 10 mol%) and (*S*)-*t*-Bu-PHOX (**55**, 4.8 mg, 0.0125 mmol, 0.125 equiv, 12.5 mol%) in *p*-dioxane (1 mL, purchased from Aldrich and used as received) was stirred at 40 °C for 30 min. To the solution was added oven-dried powdered 3ÅMS (90 mg), followed immediately by a solution of HCO_2H (9.4 μL, 0.25 mmol, 2.5 equiv) in *p*-dioxane (1 mL) and a solution of (±)-**293** (24.4 mg, 0.10 mmol, 1.0 equiv) in *p*-dioxane (1 mL). The vial was then sealed with a teflon-lined cap and stirred at 40 °C until TLC indicated complete consumption of the starting material (about 10 h). The reaction mixture was passed through a small plug of celite and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography on SiO_2 using 10% Et_2O in pentane as the eluent. The ee of the product was determined to be 79% by chiral HPLC using a Chiracel OD-H column with 1% 2-propanol in hexanes as the eluent.

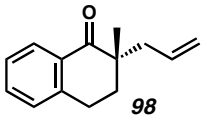
Optimization of Amount of Formic Acid and Molecular Sieves

Optimization of amounts of HCO_2H and 4ÅMS was carried out using the following general procedure with the variations indicated in Table 7.6.

General Procedure

Oven-dried 4Å molecular sieves (4ÅMS) were placed in a 1 dram glass vial equipped with a magnetic stir bar, a screw cap, and a septum. The vial and 4ÅMS were thoroughly flame dried under vacuum and backfilled with dry argon gas. The flame-drying procedure was carried out twice more, and then the vial cooled to ambient temperature (20 °C). To the cooled vial was added $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 0.10 equiv, 10 mol%), (*S*)-*t*-Bu-PHOX (**55**, 4.8 mg, 0.0125 mmol, 0.125 equiv, 12.5 mol%), and freshly distilled *p*-dioxane (1.5 mL). The mixture was heated to 40 °C for 30 mins, at which point neat HCO_2H was added, followed immediately by addition of a solution of (±)-**293** (24.4 mg, 0.10 mmol, 1.0 equiv) in *p*-dioxane (1.5 mL). The reaction mixture was stirred at 40 °C until TLC indicated complete consumption of (±)-**293** (about 10 h). After cooling to ambient temperature, the reaction mixture was filtered through a pad of celite. The filtrate was concentrated by rotary evaporation and the residue purified by flash chromatography on SiO_2 using 10% Et_2O in pentane as eluent. The ee of the product was determined by chiral HPLC with a Chiracel OD-H column using 1% 2-propanol in hexanes as eluent. The ratio of **97**/**98** was determined by ^1H NMR integration.

Compound **98** was formed in comparable enantiomeric excess (and with the same predominant enantiomer) to that from the allylation reaction described in Chapter 3. The alkylated product exhibits the following characteristics:



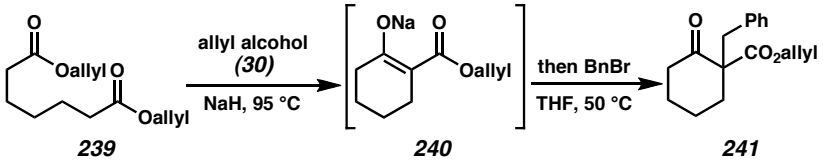
98

(*S*)-2-Allyl-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (98): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.45 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.29 (app. t, *J* = 7.2 Hz, 1H), 7.21 (app. d, *J* = 7.5 Hz, 1H), 5.85-5.71 (m, 1H), 5.10 (s, 1H), 5.05 (s, 1H), 2.97 (t, *J* = 6.3 Hz, 2H), 2.46 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.27 (ddt, *J* = 14.0, 7.5, 1.2 Hz, 1H), 2.07 (ddd, *J* = 13.4, 7.2, 6.0 Hz 1H), 1.89 (ddd, *J* = 14.0, 6.9, 5.7 1H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 143.2, 133.9, 133.0, 131.5, 128.6, 127.9, 126.5, 118.1, 44.5, 41.0, 33.2, 25.3, 21.8; IR (Neat Film NaCl) 3073, 2930, 1682, 1455, 1220, 916, 742 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{14}H_{16}O$ [M]$^{+}$: 200.1201, found 200.1194; $[\alpha]_D^{27}$ –18.59 (*c* 2.08, hexane, 88% ee).

7.6.2.2 SYNTHESES OF SUBSTRATE COMPOUNDS

Substrates were synthesized by the methods reported in our previous work,[18] unless otherwise stated. The following general procedures are representative. Further details and alternate methods may be found in Chapter 3.

General Procedure 1: Dieckmann Cyclization Method[19,20]

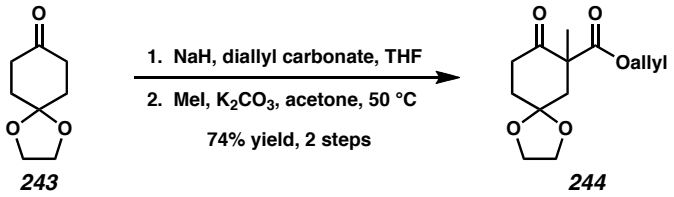


239 ***240*** ***241***

Allyl 1-benzyl-2-oxocyclohexanecarboxylate (241, Scheme 7.2, Table 7.1, Table 7.7, entry 12; Table 7.10, entry 3). To a suspension of NaH (166.4 mg, 4.16 mmol, 1.0

equiv) in toluene (2 mL) was added allyl alcohol (**30**, 79.2 μL, 1.17 mmol, 0.28 equiv). Once gas evolution ceased, pimelic acid diallyl ester (**239**, 1.00 g, 4.16 mmol, 1.0 equiv) was added slowly and the resulting mixture heated to 95 °C for 1 h. Additional toluene (~2 mL) was added during this time to maintain a fluid reaction mixture. The reaction mixture was cooled to room temperature and the solvent removed by rotary evaporation in vacuo. The resulting solid salt was placed under dry N_2 and dissolved in THF (9 mL). Benzyl bromide (643.2 μL, 5.4 mmol, 1.3 equiv) was then added dropwise. The resulting mixture was warmed to 50 °C for 2.5 h, cooled to ambient temperature, and quenched with saturated aq NH_4Cl (5 mL) followed by H_2O (5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (1 x 10 mL), then dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting oil was purified by flash chromatography (5 x 18 cm SiO_2, 10% Et_2O in pentane) to afford the quaternary compound **241** as a colorless oil (781.4 mg, 70% yield). R_f = 0.30 (10% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.23 (comp. m, 3H), 7.20-7.13 (comp. m, 2H), 5.86 (dddd, J = 17.2, 10.3, 5.9, 5.9 Hz, 1H), 5.29 (m, 2H), 4.57 (m, 2H), 3.38 (d, 1H, J = 13.8 Hz), 2.94 (d, J = 13.8 Hz, 1H), 2.60-2.39 (comp. m, 3H), 2.14-1.97 (m, 1H), 1.83-1.60 (comp. m, 3H), 1.59-1.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8, 170.5, 136.3, 131.2, 130.2, 127.9, 126.5, 119.0, 65.6, 62.1, 41.1, 40.3, 35.7, 27.4, 22.3; IR (Neat Film NaCl) 3029, 2942, 1713, 1452, 1179, 1085 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{20}O_3$ $[M]^+$: 272.1412, found 272.1425.

General Procedure 2: Diallyl Carbonate Method



243 *244*

Allyl 7-methyl-8-oxo-1,4-dioxaspiro[4.5]decane-7-carboxylate (244):

Part A, Acylation:

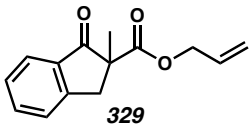
To a cooled (0 °C) suspension of NaH (9.22 g, 240.1 mmol, 2.5 equiv) in THF (125 mL) was added a solution of 1,4-cyclohexanedione monoethylene ketal (**243**, 15.0 g, 96 mmol, 1.0 equiv) in THF (30 mL) dropwise over 15 min. The reaction mixture was warmed to room temperature and diallyl carbonate (**111**, 20.65 mL, 144.0 mmol, 1.5 equiv) was added and the reaction mixture stirred for 16 h. The reaction was quenched with saturated aq NH_4Cl and 1 N aq HCl until a pH of 4 was reached. The phases were separated and the aq phase was extracted with EtOAc (7 x 150 mL). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated, redissolved in CH_2Cl_2, dried ($MgSO_4$), filtered, and concentrated.

Part B, Alkylation:

The resulting oil was added to a suspension of anhydrous K_2CO_3 (26.5 g, 192.0 mmol, 2.0 equiv) in acetone (128 mL). To the reaction mixture was added iodomethane (12.0 mL, 192.0 mmol, 2.0 equiv) and the reaction mixture was then heated to 50 °C for 14 h. The mixture was then cooled, filtered, and the solids washed with acetone. The filtrate was concentrated and the resulting oil purified by flash chromatography (SiO_2, 5 → 40% Et_2O in hexanes) to afford the desired quaternary quaternary β-ketoester **244** as a colorless oil (18.0 g, 74% yield). R_f = 0.28 (30% Et_2O in pentane); ^1H NMR (300 MHz,

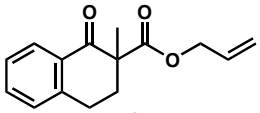
$CDCl_3$) δ 5.90 (dddd, *J* = 17.4, 10.5, 5.7, 5.7 Hz, 1H), 5.26 (m, 2H), 4.60 (m, 2H), 3.97 (comp. m, 4H), 3.02 (dt, *J* = 14.8, 10.2 Hz, 1H), 2.68 (dt, *J* = 14.0, 2.0 Hz, 1H), 2.49 (dt, *J* = 14.8, 4.4 Hz, 1H), 2.00 (comp. m, 2H), 1.72 (d, *J* = 14.1 Hz, 1H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.0, 172.9, 131.6, 118.5, 106.5, 65.9, 64.8, 64.3, 54.6, 43.6, 37.4, 35.2, 21.7; IR (Neat Film NaCl) 2939, 2891, 1733, 1717, 1304, 1141 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{13}H_{18}O_5$ $[M]^+$: 254.1154, found 254.1153. Spectra for this compound may be found in Appendix 2.

7.6.2.3 CHARACTERIZATION DATA FOR SUBSTRATE COMPOUNDS



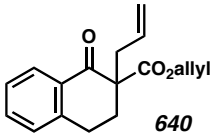
329

Allyl 2-methyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (329, Scheme 7.2, Table 7.7, entry 9; Table 7.10, entry 9): Prepared by the diallyl carbonate method from 1-indanone using methyl iodide as the electrophile. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 30% yield. R_f = 0.55 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.7 Hz, 1H), 7.63 (dd, *J* = 7.6, 7.3 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.41 (dd, *J* = 7.6, 7.3 Hz, 1H), 5.83 (dddd, *J* = 17.2, 10.6, 5.6, 5.6 Hz, 1H), 5.21 (dddd, *J* = 17.2, 2.7, 1.6, 1.1 Hz, 1H), 5.16 (dddd, *J* = 10.5, 2.4, 1.3, 1.3 Hz, 1H), 4.58 (ddd, *J* = 5.6, 2.7, 1.1 Hz, 1H), 4.58 (ddd, *J* = 5.6, 2.7, 1.1 Hz, 1H), 3.73 (d, *J* = 17.1 Hz, 1H), 3.01 (d, *J* = 17.1 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.5, 171.8, 152.7, 135.5, 134.9, 131.7, 128.0, 126.6, 125.2, 118.3, 66.0, 56.2, 40.2, 21.2; IR (Neat Film NaCl) 3080, 2982, 2935, 1745, 1715, 1608, 1495, 1282, 1184, 967, 747 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{14}H_{14}O_3$ $[M]^+$: 230.0943, found 230.0936.



293

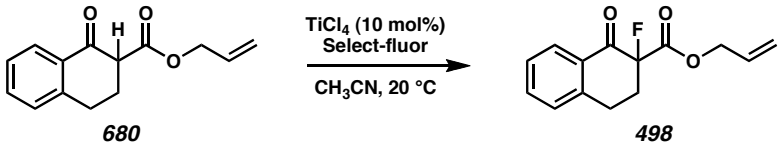
Allyl 2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (293, Scheme 7.2, Table 7.2 through Table 7.10): Prepared by the diallyl carbonate method from 1-tetralone. Flash chromatography (SiO_2, 10% Et_2O in pentane). 60% yield. R_f = 0.61 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 7.8 Hz, 1H), 7.47 (app. t, J = 7.5 Hz, 1H), 7.31 (app. t, J = 8.1 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 5.79 (dddd, J = 17.1, 10.7, 5.4, 5.4 Hz, 1H), 5.19-5.09 (m, 2H), 4.58 (m, 2H), 3.12-2.87 (m, 2H), 2.68-2.57 (m, 1H), 2.13-2.01 (m, 1H), 1.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9, 172.5, 143.1, 133.4, 131.7, 131.5, 128.7, 128.0, 126.8, 118.0, 65.6, 53.9, 33.9, 26.0, 20.6; IR (Neat Film NaCl) 3071, 2982, 2938, 1736, 1690, 1602, 1456, 1377, 1308, 1228, 1189, 1112, 979, 743 cm^{-1}; HRMS (EI) m/z calc'd for $C_{15}H_{16}O_3$ $[M]^+$: 244.1099, found 244.1094.



640

640, Table 7.7, Entry 2: Prepared using the diallyl carbonate method from 1-tetralone and allyl bromide. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 83% yield. R_f = 0.77 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 7.7 Hz, 1H), 7.47 (dd, J = 7.7, 7.4 Hz, 1H), 7.31 (dd, J = 7.7, 7.7 Hz, 1H), 7.21 (d, J = 7.4 Hz, 1H), 5.92-5.71 (comp. m, 2H), 5.21-5.06 (comp. m, 4H), 4.58 (app. d, J = 5.3 Hz, 1H), 4.58 (app. d, J = 5.6 Hz, 1H), 3.08 (ddd, J = 17.3, 10.1, 4.8 Hz, 1H),

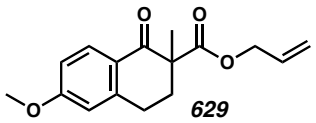
2.93 (ddd, J = 17.3, 5.1, 4.8 Hz, 1H), 2.77 (app. ddd, J = 13.8, 7.2, 1.1 Hz, 1H), 2.70 (app. ddd, J = 13.8, 7.4, 1.1 Hz, 1H), 2.54 (ddd, J = 13.8, 5.1, 4.8 Hz, 1H), 2.16 (ddd, J = 14.1, 10.1, 5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.0, 171.4, 143.3, 133.7, 133.5, 132.1, 131.7, 128.9, 128.2, 126.9, 119.2, 118.4, 65.9, 57.5, 38.7, 30.6, 25.9; IR (Neat Film NaCl) 3077, 2937, 1734, 1689, 1601, 1455, 1236, 1212, 1188, 922, 743 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{18}O_3$ $[M]^+$: 270.1256, found 270.1249.



680 ***498***

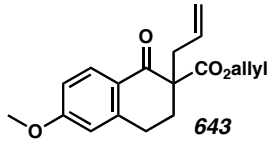
Allyl 2-fluoro-1-tetralone-2-carboxylate (498, Table 7.7, Entry 3): Neat $TiCl_4$ (45.6 μL, 0.42 mmol, 0.10 equiv, 10 mol%) was added to a 20 °C solution of **680**[18] (1.00 g, 4.16 mmol, 1.0 equiv) in acetonitrile (40 mL), resulting in an immediate color change from pale yellow to dark orange-brown. After 5 min, Selectfluor™ (1.77 g, 4.99 mmol, 1.2 equiv) was added in one portion. The mixture was stirred vigorously at 20 °C for 2 h, during which time the dark orange-brown color faded to yellow. The reaction was quenched by addition of H_2O (120 mL). The aqueous phase was extracted with Et_2O (4 x 30 mL). The combined organic extracts were washed with brine (1 x 25 mL), dried over Na_2SO_4, filtered, and the filtrate concentrated in vacuo to a yellow oil. Purification by flash chromatography (SiO_2, 20% Et_2O in pentane) yielded the title compound (**498**) as a colorless oil (879.9 mg, 85% yield). R_f = 0.41 (30% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 8.0 Hz, 1H), 7.56 (dd, J = 7.4, 7.4 Hz, 1H), 7.37 (dd, J = 7.7, 7.4 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 5.88 (dddd, J = 17.3, 10.4, 5.6, 5.1 Hz, 1H), 5.27 (dd, J = 17.3, 1.3 Hz, 1H), 5.24 (dd, J = 10.4, 1.1 Hz, 1H), 4.73 (app. ddd, J = 5.9, 2.1,

1.3 Hz, 1H), 4.73 (app. ddd, J = 5.9, 2.1, 1.3 Hz, 1H), 3.20 (ddd, J = 17.3, 6.4, 6.1 Hz, 1H), 3.08 (ddd, J = 17.3, 7.5, 5.1 Hz, 1H), 2.75 (dddd, $J_{H\text{-}H}$ = 7.4, 7.2, 6.4 Hz, $J_{H\text{-}F}$ = 26.3 Hz, 1H), 2.56 (dddd, $J_{H\text{-}H}$ = 7.2, 6.1, 5.3 Hz, $J_{H\text{-}F}$ = 21.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.6 ($J_{C\text{-}F}$ = 18.6 Hz), 167.2 ($J_{C\text{-}F}$ = 26.3 Hz), 143.2, 132.7, 130.9, 130.7, 128.9, 128.6 ($J_{C\text{-}F}$ = 0.9 Hz), 127.4, 119.4, 93.4 ($J_{C\text{-}F}$ = 194.5 Hz), 66.8, 32.0 ($J_{C\text{-}F}$ = 22.1 Hz), 25.0 ($J_{C\text{-}F}$ = 7.2 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ –165.2 (dd, $J_{F\text{-}H}$ = 24.5, 21.4 Hz, 1F); IR (Neat Film NaCl) 3075, 2945, 1765, 1696, 1602, 1457, 1312, 1277, 1228, 1187, 1138, 1087, 942, 913, 744 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{13}FO_3$ $[M]^+$: 248.0849, found 248.0860.



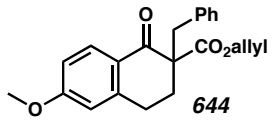
629

629, Table 7.7, Entry 4: Prepared using the diallyl carbonate method from 6-methoxy-1-tetralone and methyl iodide. Purified by flash chromatography (SiO_2, 5% Et_2O in pentane). 82% yield. R_f = 0.34 (30% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 8.8 Hz, 1H), 6.84 (dd, J = 8.8, 2.4 Hz, 1H), 6.66 (d, J = 2.4 Hz, 1H), 5.82 (dddd, J = 17.1, 10.4, 6.0, 5.2 Hz, 1H), 5.23-5.17 (m, 2H), 4.59 (m, 2H), 3.85 (s, 3H), 3.02 (ddd, J = 17.3, 9.6, 4.8 Hz, 1H), 2.89 (ddd, J = 17.0, 5.3, 5.3 Hz, 1H), 2.63 (ddd, J = 13.6, 5.1, 4.8 Hz, 1H), 2.05 (ddd, J = 13.8, 9.6, 5.1 Hz, 1H), 1.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.9, 173.0, 163.8, 145.8, 131.8, 130.7, 125.4, 118.2, 113.6, 112.6, 65.8, 55.6, 53.8, 34.1, 26.5, 20.8; IR (Neat Film NaCl) 2938, 1734, 1676, 1600, 1276, 1262, 1230, 1186, 1172, 1099, 978, 668 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{18}O_4$ $[M]^+$: 274.1205, found 274.1204.



643

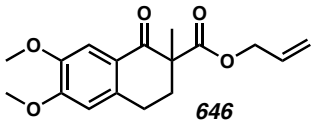
643, Table 7.7, Entry 5: Prepared using the diallyl carbonate method from 6-methoxy-1-tetralone and allyl bromide. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 83% yield. R_f = 0.45 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.7 Hz, 1H), 6.83 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.66 (d, *J* = 2.4 Hz, 1H), 5.91-5.72 (comp. m, 2H), 5.24-5.05 (comp. m, 4H), 4.59 (app. ddd, *J* = 5.3, 1.6, 1.3 Hz, 1H), 4.59 (app. ddd, *J* = 5.3, 1.6, 1.3 Hz, 1H), 3.85 (s, 3H), 3.05 (ddd, *J* = 17.3, 10.1, 4.8 Hz, 1H), 2.88 (ddd, *J* = 17.3, 5.3, 5.1 Hz, 1H), 2.76 (dd, *J* = 13.8, 7.2 Hz, 1H), 2.69 (dd, *J* = 13.8, 7.2 Hz, 1H), 2.52 (ddd, *J* = 13.8, 5.3, 4.8 Hz, 1H), 2.13 (ddd, *J* = 13.8, 10.1, 5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 171.5, 163.8, 145.9, 133.7, 131.8, 130.7, 125.6, 119.0, 118.3, 113.6, 112.5, 65.8, 57.2, 55.6, 38.8, 30.5, 26.3; IR (Neat Film NaCl) 3080, 2942, 1734, 1676, 1600, 1447, 1353, 1272, 1254, 1214, 925 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{18}H_{20}O_4$ $[M]^+$: 300.1362, found 300.1374.



644

644, Table 7.7, Entry 6: Prepared using the diallyl carbonate method from 6-methoxy-1-tetralone and benzyl bromide. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 80% yield. R_f = 0.56 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.8 Hz, 1H), 7.29-7.14 (comp. m, 5H), 6.82 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.60 (d, *J* = 2.2 Hz, 1H), 5.80 (dddd, *J* = 17.3, 10.7, 5.5, 5.5 Hz, 1H), 5.17 (app. ddd,

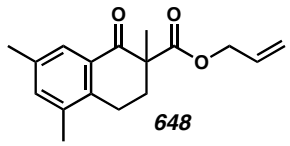
J = 17.6, 3.0, 1.4 Hz, 1H), 5.15 (app. ddd, J = 10.5, 2.5, 1.4 Hz, 1H), 4.57 (app. ddd, J = 5.5, 2.5, 1.4 Hz, 1H), 4.57 (app. ddd, J = 5.5, 2.5, 1.4 Hz, 1H), 3.83 (s, 3H), 3.46 (d, J = 13.8 Hz, 1H), 3.31 (d, J = 13.8 Hz, 1H), 3.06 (ddd, J = 17.3, 11.6, 4.4 Hz, 1H), 2.79 (ddd, J = 17.3, 4.4, 4.4 Hz, 1H), 2.46 (ddd, J = 13.8, 4.4, 4.4 Hz, 1H), 1.97 (ddd, J = 13.5, 11.6, 5.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.1, 171.4, 163.8, 145.9, 136.8, 131.6, 130.9, 130.8, 128.2, 126.8, 125.9, 118.4, 113.6, 112.4, 65.9, 58.6, 55.6, 40.2, 30.5, 26.6; IR (Neat Film NaCl) 2935, 1708, 1688, 1607, 1595, 1497, 1310, 1277, 1244, 1196, 1144, 1080, 1029, 992, 698 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{22}H_{22}O_4$ $[M]^+$: 350.1518, found 350.1503.



646

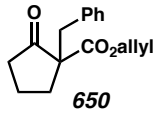
646, Table 7.7, Entry 7: Prepared using the diallyl carbonate method from 6,7-dimethoxy-1-tetralone and methyl iodide. Purified by flash chromatography (SiO_2, 20% EtOAc in hexanes). 18% yield. R_f = 0.14 (30% Et_2O in pentane); mp 78–80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (s, 1H), 6.23 (s, 1H), 5.83 (dddd, J = 17.3, 10.4, 5.6, 5.1 Hz, 1H), 5.19 (dddd, J = 17.3, 3.2, 1.6, 1.6 Hz, 1H), 5.16 (dddd, J = 10.6, 2.7, 1.3, 1.3, 1H), 4.60 (dddd, J = 8.2, 5.3, 2.7, 1.3 Hz, 1H), 4.60 (dddd, J = 8.2, 5.3, 2.7, 1.3 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 2.99 (ddd, J = 17.0, 9.3, 4.8 Hz, 1H), 2.86 (ddd, J = 17.3, 5.6, 5.3 Hz, 1H), 2.61 (ddd, J = 13.3, 5.8, 4.8 Hz, 1H), 2.06 (ddd, J = 13.3, 9.3, 4.8 Hz, 1H), 1.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.0, 172.9, 153.8, 148.2, 138.1, 131.8, 124.9, 118.2, 110.2, 109.3, 65.8, 56.2, 56.1, 53.5, 34.4, 25.9, 20.9; IR (Neat Film NaCl) 3079,

2938, 2836, 1732, 1672, 1600, 1513, 1454, 1368, 1269, 1239, 1183, 1105, 1018, 790 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{20}O_5$ $[M]^+$: 304.1311, found 304.1299.



648

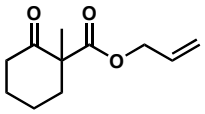
648, Table 7.7, Entry 8: Prepared using the diallyl carbonate method from 5,7-dimethyl-1-tetralone and methyl iodide. Purified by flash chromatography (SiO_2, 10 → 15% Et_2O in pentane). 40% yield. $R_f = 0.67$ (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (br s, 1H), 7.19 (br s, 1H), 5.79 (dddd, *J* = 16.5, 10.1, 5.6, 5.6 Hz, 1H), 5.15 (dd, *J* = 16.5, 1.6 Hz, 1H), 5.14 (dd, *J* = 10.1, 1.6 Hz, 1H), 4.57 (app. ddd, *J* = 5.6, 2.1, 1.3 Hz, 1H), 4.57 (app. ddd, *J* = 5.6, 2.1, 1.3 Hz, 1H), 2.93-2.73 (m, 2H), 2.64 (ddd, *J* = 13.6, 5.3, 5.3 Hz, 1H), 2.33 (s, 3H), 2.25 (s, 3H), 2.03 (ddd, *J* = 13.8, 8.5, 5.9 Hz, 1H), 1.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7, 172.7, 138.6, 136.3, 136.1 (2C), 131.8 (2C), 126.1, 118.1, 65.7, 53.5, 33.3, 23.1, 21.0, 20.7, 19.3; IR (Neat Film NaCl) 2982, 2937, 1736, 1688, 1477, 1453, 1318, 1251, 1197, 1165, 1110, 1051, 984, 928, 874 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{20}O_3$ $[M]^+$: 272.1412, found 272.1413.



650

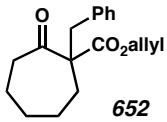
650, Table 7.7, Entry 10: Prepared using the Dieckmann cyclization method from diallyl adipate and benzyl bromide. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 36% yield. $R_f = 0.17$ (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.18 (comp. m, 3H), 7.17-7.09 (comp. m, 2H), 5.89 (dddd, *J* = 17.3, 10.6, 5.6, 4.8

Hz, 1H), 5.31 (dd, *J* = 17.3, 1.3 Hz, 1H), 5.24 (dd, *J* = 10.4, 1.3 Hz, 1H), 4.61 (app. dd, *J* = 5.6, 2.7, 1.6 Hz, 1H), 4.61 (dd, *J* = 5.6, 2.7, 1.6 Hz, 1H), 3.21 (d, *J* = 13.8 Hz, 1H), 3.14 (d, *J* = 13.8 Hz, 1H), 2.51-2.29 (m, 2H), 2.12-1.80 (comp. m, 3H), 1.70-1.51 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.0, 170.8, 136.6, 131.7, 130.4, 128.5, 127.0, 118.8, 66.2, 61.6, 39.2, 38.5, 31.8, 19.6; IR (Neat Film NaCl) 3029, 2963, 1751, 1728, 1496, 1454, 1266, 1220, 1187, 1158, 1141, 1102, 991, 925, 703 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{18}O_3$ $[M]^+$: 258.1256, found 258.1268.



107

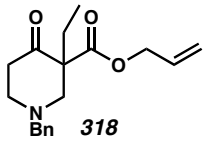
Allyl 1-methyl-2-oxocyclohexanecarboxylate (107, Table 7.7, entry 11; Table 7.10, entry 1): Prepared by the Dieckmann cyclization method. 62% yield. R_f = 0.38 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (dddd, *J* = 17.1, 10.2, 5.9, 5.9 Hz, 1H), 5.24 (m, 2H), 4.59 (d, *J* = 5.7 Hz, 2H), 2.58-2.34 (comp. m, 3H), 2.08-1.88 (m, 1H), 1.80-1.54 (comp. m, 3H), 1.52-1.37 (m, 1H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9, 172.6, 131.4, 118.7, 65.6, 57.1, 40.5, 38.1, 27.4, 22.5, 21.1; IR (Neat Film NaCl) 3086, 2939, 2867, 1715, 1452, 1259, 1211, 1159, 1084, 976 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{16}O_3$ $[M]^+$: 196.1099, found 196.1096.



652

652, Table 7.7, Entry 13: Prepared using the diallyl carbonate method from cycloheptanone and benzyl bromide. Purified by flash chromatography (SiO_2, 20 → 60%

CH_2Cl_2 in hexane). 44% yield. R_f = 0.35 (15% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.19 (comp. m, 3H), 7.19-7.07 (comp. m, 2H), 5.89 (dddd, *J* = 17.3, 10.4, 5.6, 5.6 Hz, 1H), 5.33 (dddd, *J* = 17.3, 2.9, 1.3, 1.3 Hz, 1H), 5.27 (dddd, *J* = 10.4, 2.7, 1.3, 1.3 Hz, 1H), 4.62 (dddd, *J* = 5.6, 5.6, 1.3, 1.3 Hz, 1H), 4.62 (dddd, *J* = 5.6, 5.6, 1.3, 1.3 Hz, 1H), 3.41 (d, *J* = 13.6 Hz, 1H), 3.03 (d, *J* = 13.8 Hz, 1H), 2.65 (ddd, *J* = 12.5, 9.0, 3.7 Hz, 1H), 2.36 (ddd, *J* = 12.8, 8.8, 2.9 Hz, 1H), 2.10 (app. dd, *J* = 13.8, 9.3 Hz, 1H), 1.94-1.62 (comp. m, 5H), 1.62-1.37 (comp. m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.4, 171.7, 136.8, 131.6, 130.6, 128.3, 126.9, 119.0, 66.0, 64.4, 42.5, 40.9, 31.7, 29.9, 25.5, 24.6; IR (Neat Film NaCl) 3028, 2932, 2860, 1734, 1711, 1454, 1195, 1172, 1145, 991, 941, 702 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{18}H_{22}O_3$ $[M]^+$: 286.1569, found 286.1571.



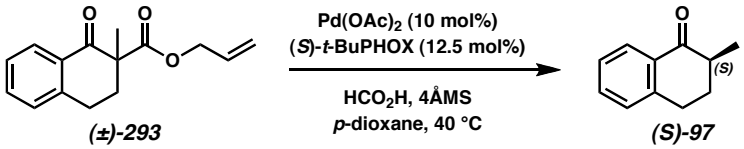
318

Allyl 1-benzyl-3-ethyl-4-oxopiperidine-3-carboxylate (318, Table 7.7, entry 14): Prepared by the diallyl carbonate method from 1-benzylpiperidin-4-one (part A) and iodoethane (part B). Flash chromatography (SiO_2, 2.5→20% EtOAc in hexanes). 55% yield. R_f = 0.50 (30% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.25 (m, 5H), 5.90 (dddd, *J* = 17.4, 10.7, 5.7, 5.7 Hz, 1H), 5.33 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.24 (dq, *J* = 10.4, 1.5 Hz, 1H), 4.70 (ddt, *J* = 13.0, 6.0, 1.4 Hz, 1H), 4.62 (ddt, *J* = 13.0, 6.0, 1.4 Hz, 1H), 3.62 (d, *J* = 13.2 Hz, 1H), 3.56 (d, *J* = 13.2 Hz, 1H), 3.42 (dd, *J* = 11.4, 2.7 Hz, 1H), 3.04-2.80 (m, 2H), 2.45-2.35 (m, 2H), 2.25 (d, *J* = 11.7 Hz, 1H), 1.94-1.82 (m, 1H), 1.65-1.53 (m, 1H), 0.87 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9, 171.3, 137.9, 131.7, 128.8, 128.2, 127.3, 118.7, 65.6, 61.8, 61.5, 61.0, 53.5, 40.6, 25.2, 9.1; IR (Neat

Film NaCl) 2966, 2939, 1719, 1224, 1139, 699 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{18}H_{23}O_3$ $[M]^+$: 301.1678, found 301.1691.

7.6.2.4 ENANTIOCONVERGENT DECARBOXYLATIVE PROTONATION USING FORMIC ACID AS THE PROTON SOURCE

Sample Procedure for Enantioconvergent Protonation



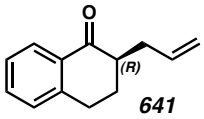
(*S*)-(–)-2-Methyl-1-tetralone (97, Table 7.7, Entry 1):[21] A glass tube (2.5 x 10 cm with a ground glass joint) equipped with a magnetic stir bar was charged with powdered 4Å molecular sieves (540 mg) and then thoroughly flame dried under vacuum (3x, backfill with dry argon). After cooling to ambient temperature under dry argon, $Pd(OAc)_2$ (6.7 mg, 0.030 mmol, 0.10 equiv, 10 mol%), (*S*)-*t*-Bu-PHOX (**55**, 14.5 mg, 0.0375 mmol, 0.125 equiv, 12.5 mol%), and freshly distilled *p*-dioxane (4.5 mL) were added, and the resulting slurry was stirred vigorously at 40 ºC for 30 min. At this point, neat HCO_2H (68 μL, 1.80 mmol, 6.0 equiv) was added to the reaction mixture, followed immediately by addition of a solution of (±)-**293** (73.3 mg, 0.30 mmol, 1.0 equiv) in *p*-dioxane (4.5 mL). When the reaction was complete by TLC, the reaction mixture was cooled to ambient temperature and then filtered through a pad of SiO_2. The filtrate was concentrated under reduced pressure and the residue purified by flash chromatography on SiO_2 using 10% Et_2O in pentane as eluent to afford (*S*)-**97** (42.1 mg, 88% yield). The material was determined to be of 94% ee, measured by chiral HPLC using a Chiracel

OD-H column with 1% 2-propanol in hexanes as the eluent. $[\alpha]_D^{25}$ –44.4 (*c* 1.06, *p*-dioxane, 94% ee).

The absolute configuration was determined by comparison of the observed optical rotation to a literature value for (*S*)-2-methyl-1-tetralone (**97**): $[\alpha]_D^{22}$ –51.2 (*c* 2.5, *p*-dioxane).[22]

Data for product compounds:

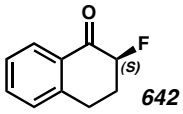
Products were prepared using the above procedure, unless specifically stated otherwise.



641

(*R*)-(–)-2-Allyl-1-tetralone (641, Table 7.7, Entry 2):[23] Reaction performed with 5.0 equiv of HCO_2H (56.6 μL, 1.50 mmol) and 405 mg (1.35 g/mmol of substrate) of powdered 4Å molecular sieves. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 88% yield, 85% ee. $[\alpha]_D^{25}$ –22.2 (*c* 0.63, MeOH, 85% ee).

The absolute configuration was established by comparison of the optical rotation to the literature value for (*R*)-(–)-2-allyl-1-tetralone: $[\alpha]_D^{23}$ –29.7 (*c* 1.21, MeOH, 97% ee).[23]

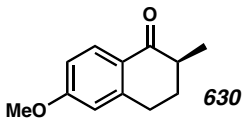


642

(*S*)-(–)-2-Fluoro-1-tetralone (642, Table 7.7, Entry 3):[24] Reaction performed with 8.0 equiv of HCO_2H (90.6 μL, 2.40 mmol) and 810 mg (2.70 g/mmol of substrate) of

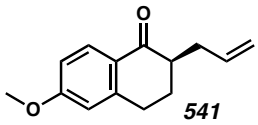
powdered 4Å molecular sieves. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 79% yield, 88% ee. $[\alpha]_D^{25}$ –56.9 (*c* 1.01, *p*-dioxane, 88% ee).

The absolute configuration was established by comparison of the optical rotation to the literature value for (*R*)-(+)-2-fluoro-1-tetralone: $[\alpha]_D$ +64.9 (*c* 0.43, *p*-dioxane, >95% ee).[24]



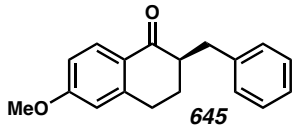
630

(–)-2-Methyl-6-methoxy-1-tetralone (630, Table 7.7, Entry 4):[25] Reaction performed with 6.0 equiv of HCO_2H (67.9 μL, 1.80 mmol) and 540 mg (1.80 g/mmol of substrate) of powdered 4Å molecular sieves. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 91% yield, 95% ee. $[\alpha]_D^{25}$ –62.6 (*c* 1.02, $CHCl_3$, 95% ee).



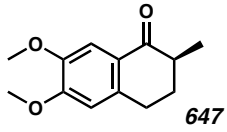
541

(–)-2-Allyl-6-methoxy-1-tetralone (541, Table 7.7, Entry 5):[23] Reaction performed with 5.0 equiv of HCO_2H (56.6 μL, 1.50 mmol) and 405 mg (1.35 g/mmol of substrate) of powdered 4Å molecular sieves. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 81% yield, 88% ee. $[\alpha]_D^{24.9}$ –50.28 (*c* 2.03, CH_2Cl_2, 88% ee).



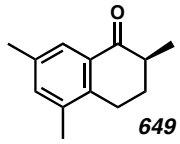
645

(+)-2-Benzyl-6-methoxy-1-tetralone (645, Table 7.7, Entry 6):[26] Reaction performed with 7.0 equiv of HCO_2H (79.2 μL, 2.10 mmol) and 675 mg (2.25 g/mmol of substrate) of powdered 4Å molecular sieves. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 95% yield, 78% ee. $[\alpha]_D^{25}$ +8.6 (*c* 0.79, $CHCl_3$, 78% ee).



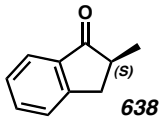
647

(–)-2-Methyl-6,7-dimethoxy-1-tetralone (647, Table 7.7, Entry 7):[27] Reaction performed with 5.0 equiv of HCO_2H (56.6 μL, 1.50 mmol) and 405 mg (1.35 g/mmol of substrate) of powdered 4Å molecular sieves. Purified by flash chromatography (SiO_2, 40% Et_2O in pentane). 62% yield, 94% ee. $[\alpha]_D^{25.9}$ –86.88 (*c* 1.09, CH_2Cl_2, 94% ee).



649

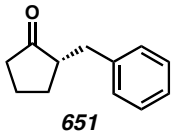
(–)-2,5,7-Trimethyl-1-tetralone (649, Table 7.7, Entry 8):[28] Reaction performed with 5.0 equiv of HCO_2H (56.6 μL, 1.50 mmol) and 405 mg (1.35 g/mmol of substrate) of powdered 4Å molecular sieves. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 75% yield, 92% ee. $[\alpha]_D^{25.8}$ –29.97 (*c* 1.00, CH_2Cl_2, 92% ee).



638

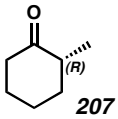
(*S*)-(+)-2-Methyl-1-indanone (638, Table 7.7, Entry 9):[21] Reaction performed with 5 mol% $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 0.050 equiv), 6.25 mol% (*S*)-*t*-Bu-PHOX (7.3 mg, 0.0188 mmol, 0.0625 equiv), 5.0 equiv of HCO_2H (56.6 μL, 1.50 mmol) and 405 mg (1.35 g/mmol of substrate) of powdered 4Å molecular sieves. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 83% yield, 81% ee. $[\alpha]_D^{26.3}$ +35.73 (*c* 1.50, *p*-dioxane, 81% ee).

The absolute configuration was established by comparison of the optical rotation to the literature value for (*R*)-2-methyl-1-indanone: $[\alpha]_D^{22}$ –42 (*c* 1.72, *p*-dioxane).[22]



651

(–)-2-Benzylcyclopentanone (651, Table 7.7, Entry 10):[29] Reaction performed with 6.0 equiv of HCO_2H (67.9 μL, 1.80 mmol) and 675 mg (2.25 g/mmol of substrate) of powdered 4Å molecular sieves. 63% yield, 60% ee. $[\alpha]_D^{27}$ –116.6 (*c* 1.11, $CHCl_3$, 60% ee).

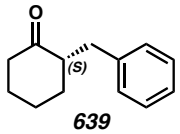


207

(*R*)-(–)-2-Methylcyclohexanone (207, Table 7.7, Entry 11):[21] Reaction performed with 6.0 equiv of HCO_2H (67.9 μL, 1.80 mmol) and 675 mg (2.25 g/mmol of substrate) of powdered 4Å molecular sieves. Yield determined by GC using tridecane (30.0 μL) as

an internal standard. 99% GC yield, 85% ee. Material for optical rotation was obtained by filtering the reaction mixture through a pad of SiO_2, concentrating the filtrate, dissolving the residue in 10% Et_2O in pentane, passing through a short plug of SiO_2, and concentrating the filtrate. $[\alpha]_D^{26.2}$ –6.4 (*c* 0.87, MeOH, 85% ee).

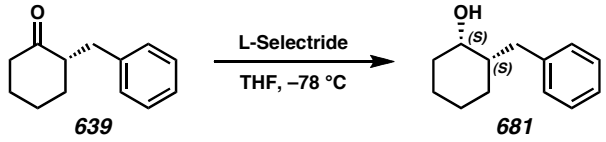
The absolute configuration was established by comparison of the optical rotation to the literature value for (*S*)-(+)-2-methylcyclohexanone: $[\alpha]_D$ +12.2 (*c* 4, MeOH, 87% ee).[30]



639

(*S*)-(–)-2-Benzylcyclohexanone (639, Table 7.7, Entry 12):[21] Reaction performed with 7.0 equiv of HCO_2H (79.2 μL, 2.10 mmol) and 675 mg (2.25 g/mmol of substrate) of powdered 4Å molecular sieves. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 91% yield, 92% ee. $[\alpha]_D^{25.5}$ –42.2 (*c* 1.66, MeOH, 92% ee).

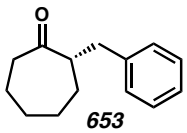
The absolute configuration was established by comparison of the optical rotation to the literature value for (*R*)-(+)-2-benzylcyclohexanone: $[\alpha]_D$ +41.4 (*c* 5, MeOH, 88% ee).[30] This assignment was confirmed by reduction of the ketone to the corresponding *syn* alcohol **681**.



639 681

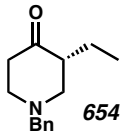
(1*S*,2*S*)-(+)-2-benzylcyclohexanol (681):[31] To a cooled (–78 °C) solution of (–)-2-benzylcyclohexanone (43.9 mg, 0.23 mmol, 1.0 equiv) in THF (2.3 mL) was added a 1.0M solution of L-Selectride® in THF (303.1 μL, 0.30 mmol, 1.3 equiv). After 30 min, the reaction was quenched with H_2O (500 μL) and then warmed to 25 °C. Additional H_2O (3 mL) and EtOAc (5 mL) were added and the phases separated. The aqueous phase was extracted with EtOAc (3 x 4 mL). The combined organics were then washed with brine (1 x 5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to a colorless oil. Flash chromatography (SiO_2, 15% EtOAc in hexanes) provided the title compound as a white crystalline solid that was isolated as one diastereomer (14.1 mg, 32% yield). ^{1}H NMR data matched that previously reported for the *syn* diastereomer.[31] R_f = 0.18 (15% EtOAc in hexanes); mp 66–68 °C (lit.[31] 67–70 °C); $[\alpha]_D^{26.7}$ +30.7 (*c* 0.50, $CHCl_3$).

The absolute configuration was confirmed by comparison of the optical rotation to the literature value for (1*S*,2*S*)-(+)-2-benzylcyclohexanol: $[\alpha]_D^{20}$ +28.2 (*c* 1, $CHCl_3$).[31]



653

(–)-2-Benzylcycloheptanone (653, Table 7.7, Entry 13):[32] Reaction performed with 6.0 equiv of HCO_2H (67.9 μL, 1.80 mmol) and 540 mg (1.80 g/mmol of substrate) of powdered 4Å molecular sieves. Purified by flash chromatography (SiO_2, 30% CH_2Cl_2 in pentane). 69% yield, 74% ee. $[\alpha]_D^{27}$ –43.7 (*c* 1.08, MeOH, 74% ee).



654

(–)-1-Benzyl-3-ethyl-4-piperidone (654, Table 7.7, Entry 14):[33] Reaction performed with 6.0 equiv of HCO_2H (67.9 μL, 1.80 mmol) and 600 mg (2.00 g/mmol of substrate) of powdered 4Å molecular sieves. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 83% yield, 84% ee. $[\alpha]_D^{25}$ –19.6 (*c* 1.03, $CHCl_3$, 84% ee).

Table 7.11. Methods for the determination of enantiomeric excess (formic acid conditions)

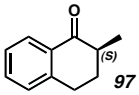
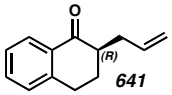
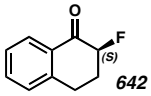
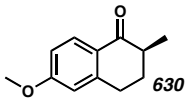
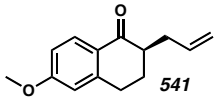
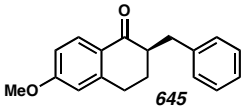
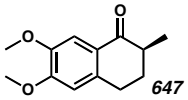
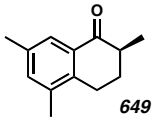
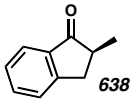
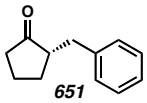
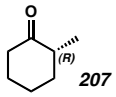
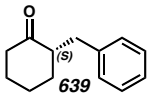
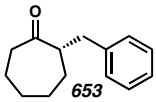
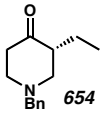
Entry	Product	Assay Conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
1	 **97**	HPLC Chiracel OD-H 1% *i*-PrOH in hexane isocratic, 1.0 mL/min	9.076	8.285	94
2	 **641**	HPLC Chiracel OD-H 0.1% *i*-PrOH in heptane isocratic, 1.0 mL/min	21.732	19.414	85
3	 **642**	HPLC Chiracel OD-H 1% *i*-PrOH in hexane isocratic, 1.0 mL/min	15.860	17.707	88
4	 **630**	HPLC Chiracel OD-H 1% *i*-PrOH in hexane isocratic, 1.0 mL/min	16.768	15.855	95
5	 **541**	HPLC Chiracel OD-H 1% *i*-PrOH in hexane isocratic, 1.0 mL/min	12.796	11.807	88
6	 **645**	HPLC Chiracel OD-H 1% *i*-PrOH in hexane isocratic, 1.0 mL/min	25.940	23.992	78
7	 **647**	HPLC Chiracel AD 1% *i*-PrOH in hexane isocratic, 1.0 mL/min	32.596	36.115	94
8	 **649**	HPLC Chiracel OD-H 1% *i*-PrOH in hexane isocratic, 1.0 mL/min	7.104	7.598	92

Table 7.11. (continued)

Entry	Product	Assay Conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
9	 *638*	HPLC Chiracel OD-H 1% *i*-PrOH in hexane isocratic, 1.0 mL/min	9.381	8.663	81
10	 *651*	HPLC Chiralpak AD 1% EtOH in hexane isocratic, 1.0 mL/min	16.384	13.558	60
11	 *207*	GC G-TA 70 ° isotherm	19.225	17.610	85
12	 *639*	HPLC Chiralpak AD 1% EtOH in hexane isocratic, 1.0 mL/min	9.989	8.453	92
13	 *653*	HPLC Chiralpak AD 1% EtOH in hexane isocratic, 1.0 mL/min UV detection at 210 nm	8.893	8.286	74
14	 *654*	HPLC Chiracel OD-H 1% *i*-PrOH in hexane isocratic, 1.0 mL/min	11.578	10.420	84

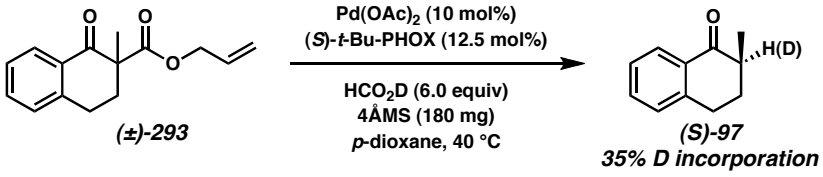
7.6.2.5 DEUTERIUM LABELING EXPERIMENTS

General Procedure for Deuterium Labeling Experiments:

Prior to use, powdered 4ÅMS were dried under vacuum (~1 torr) for 3 days at 320 °C.[34] Subsequently, these 4ÅMS were cooled to 25 °C under dry N_2 and then immediately transferred to a glove box containing an atmosphere of dry N_2. In the labeling experiments below, the powdered 4ÅMS were weighed in the glove box, transferred to a 1 dram glass vial containing a magnetic stir bar and sealed with a screw cap and a septum. The vial was then removed from the glove box and thoroughly flame dried under vacuum, backfilling with dry N_2 (three cycles). The contents were then

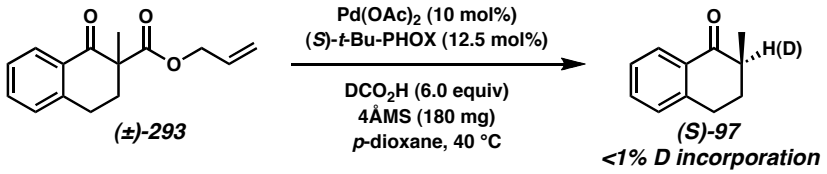
cooled to ambient temperature (25 °C). Once cool, $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 0.10 equiv, 10 mol%), (*S*)-*t*-Bu-PHOX (**55**, 4.8 mg, 0.0125 mmol, 0.125 equiv, 12.5 mol%), and freshly distilled *p*-dioxane (1.5 mL) were added and the resulting suspension stirred at 40 °C for 30 min. At this point, a solution of (±)-**293** (24.4 mg, 0.10 mmol, 1.0 equiv) in *p*-dioxane (1.5 mL) was added, followed immediately by addition of neat formic acid (labeled as shown below). This mixture was stirred at 40 °C until TLC indicated complete consumption of (±)-**293**. After cooling to ambient temperature, the reaction mixture was passed through a pad of SiO_2 and the filtrate concentrated by rotary evaporation. The residue was then purified by flash chromatography on SiO_2 using 5% Et_2O in pentane as eluent. The ee of the isolated material was determined by chiral HPLC with a Chiracel OD-H column using 1% 2-propanol in hexanes as eluent. The amount of deuterium incorporation was determined by ^1H NMR integration and deuteration was confirmed by ^2H NMR.

Deuterium Labeling Experiment 1:



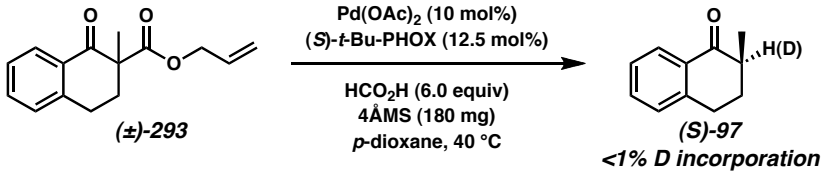
Reaction performed using HCO_2D (23.1 μL, 0.60 mmol, 6.0 equiv). Flash chromatography on SiO_2 with 5% Et_2O in pentane as eluent provided 10.2 mg of product with 89% ee. ^1H NMR integration indicates 35% deuterium incorporation at the 2-position of 2-methyl-1-tetralone (observed at δ 2.06 ppm). ^2H NMR detected deuterium incorporation at only one site. ^2H NMR (77 MHz, C_6H_6) δ 2.05.

Deuterium Labeling Experiment 2:



Reaction performed using DCO_2H (22.6 μL, 0.60 mmol, 6.0 equiv). Flash chromatography on SiO_2 with 5% Et_2O in pentane as eluent provided 13.1 mg of product with 91% ee. ^1H NMR integration indicates <1% deuterium incorporation at the 2-position of 2-methyl-1-tetralone. ^2H NMR detected no deuterium in the product material.

Deuterium Labeling Experiment 3 (Control):



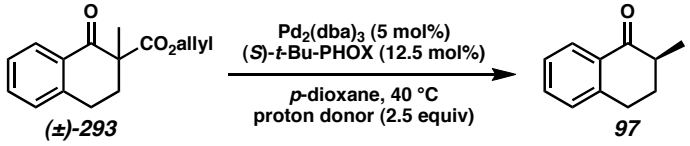
Reaction performed using HCO_2H (22.6 μL, 0.60 mmol, 6.0 equiv). Flash chromatography on SiO_2 with 5% Et_2O in pentane as eluent provided 12.9 mg of product (81% yield) with 93% ee. ^1H NMR integration indicates <1% deuterium incorporation at the 2-position of 2-methyl-1-tetralone. ^2H NMR detected no deuterium in the product material.

7.6.3 EXPERIMENTAL DATA RELEVANT TO THE MELDRUM'S ACID PROTOCOL

7.6.3.1 SCREENING OF ALTERNATE PROTON DONORS

3-(Methylsulfonyl)pentane-2,4-dione (Table 7.8, entry 6) was prepared according to the literature method.[35] Meldrum's acid derivatives in entries 4[36], 8[37], 12, and 13[38] (Table 7.9) were prepared by literature methods.

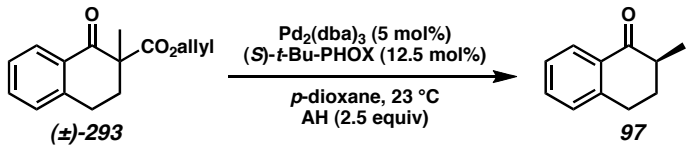
Sample Procedure for Screening of the Achiral Proton Donors (Table 7.8)



(±)-293 *97*

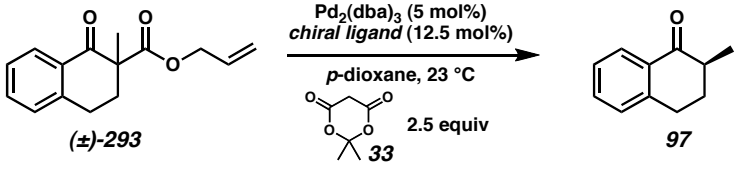
A 10 mL Schlenk tube equipped with a magnetic stir bar and a teflon stopcock was flame dried under vacuum (3x, backfill with dry argon). After cooling to ambient temperature under dry argon, $Pd_2(dba)_3$ (4.5 mg, 0.005 mmol, 0.05 equiv, 5 mol%), (*S*)-*t*-Bu-PHOX (**55**, 4.6 mg, 0.0125 mmol, 0.125 equiv, 12.5 mol%), and freshly distilled *p*-dioxane (1 mL) were added, and the resulting mixture was stirred vigorously at 40 ºC for 30 min. A *p*-dioxane solution (2 mL) of allyl β-ketoester **293** (24.4 mg, 0.1 mmol, 1.0 equiv) and achiral proton donor (0.25 mmol, 2.5 equiv) was added to the reaction mixture at 40 °C. When the reaction was complete by TLC, the reaction mixture was filtered through a pad of SiO_2 and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on SiO_2 using 5% Et_2O in petroleum ether as the eluent. The ee of the product **97** was determined by chiral HPLC using a Chiracel OD-H column with 1% 2-propanol in hexanes as the eluent.

Sample Procedure for Screening of Meldrum's Acid Derivatives (Table 7.9):



A 1 dram glass vial equipped with a magnetic stir bar, a screw cap, and a septum was flame dried under vacuum (3x, backfill with dry argon). After cooling to ambient temperature under dry argon, $Pd_2(dba)_3$ (4.5 mg, 0.005 mmol, 0.05 equiv, 5 mol%), (*S*)-*t*-Bu-PHOX (**55**, 4.6 mg, 0.0125 mmol, 0.125 equiv, 12.5 mol%), and freshly distilled *p*-dioxane (1 mL) were added, and the resulting mixture was stirred vigorously at 40 ºC for 30 min. A *p*-dioxane solution (2 mL) of allyl β-ketoester **239** (24.4 mg, 0.1 mmol, 1.0 equiv) and Meldrum's acid derivative (AH) (0.25 mmol, 2.5 equiv) was added to the reaction mixture at 23 °C. When the reaction was complete by TLC, the reaction mixture was filtered through a pad of SiO_2 and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on SiO_2 using 5% Et_2O in petroleum ether as the eluent. The ee of the product **97** was determined by chiral HPLC using a Chiracel OD-H column with 1% 2-propanol in hexanes as the eluent.

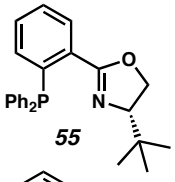
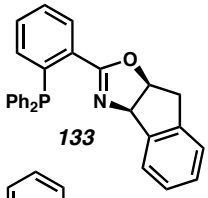
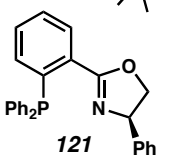
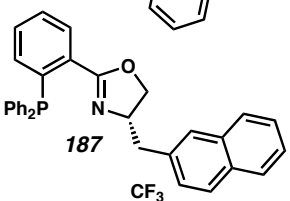
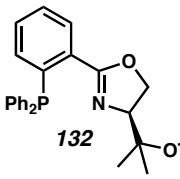
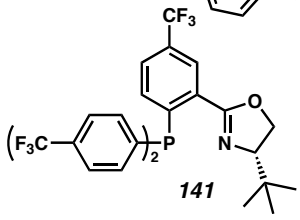
Sample Procedure for Ligand Optimization Reactions (Table 7.12)



A 1 dram glass vial equipped with a magnetic stir bar, a screw cap, and a septum was flame dried under vacuum (3x, backfill with dry argon). After cooling to ambient

temperature under dry argon, $Pd_2(dba)_3$ (4.5 mg, 0.005 mmol, 0.05 equiv, 5 mol%), chiral ligand (0.0125 mmol, 0.125 equiv, 12.5 mol%), and freshly distilled *p*-dioxane (1 mL) were added, and the resulting mixture was stirred vigorously at 40 ºC for 30 min. A *p*-dioxane solution (2 mL) of β-ketoester **239** (24.4 mg, 0.1 mmol, 1.0 equiv) and Meldrum's acid (**33**, 36 mg, 0.25 mmol, 2.5 equiv) was added to the reaction mixture at 23 °C. When the reaction was complete by TLC, the reaction mixture was filtered through a pad of SiO_2 and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on SiO_2 using 5% Et_2O in petroleum ether as the eluent. The ee of the product was determined by chiral HPLC using a Chiracel OD-H column with 1% 2-propanol in hexanes as the eluent.

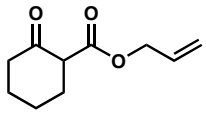
Table 7.12. Optimization of chiral ligand (Meldrum's acid conditions)[a]

entry	chiral ligand	ee (%)[b] of *97*	entry	chiral ligand	ee (%)[b] of *97*
1	 *55*	90	4	 *133*	–82
2	 *121*	–77	5	 *187*	67
3	 *132*	–79	6	 *141*	80

[a]Reactions performed with 0.1 mmol of (±)-**293** at 0.033 M in solvent. [b]Measured by chiral HPLC.

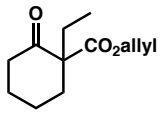
7.6.3.2 ENANTIOCONVERGENT DECARBOXYLATIVE PROTONATION USING MELDRUM'S ACID AS THE PROTON SOURCE

Characterization Data for Substrate Compounds



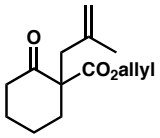
242

Ketoester **242** was prepared using the Dieckmann Cyclization method from our previous work.[18]



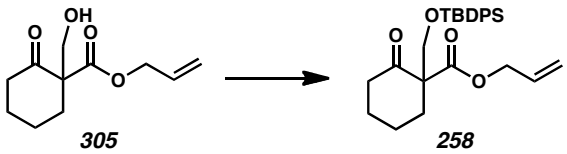
631

631, Table 7.10, Entry 2: Prepared from **242** by general alkylation method (EtI, K_2CO_3, acetone, reflux).[18] Purified by flash chromatography (SiO_2, 2.5 → 5% Et_2O in hexane). 36% yield. R_f = 0.24 (10% Et_2O in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (dddd, *J* = 17.4, 10.8, 6.0, 6.0 Hz, 1H), 5.31 (dddd, *J* = 17.4, 3.0, 1.8, 1.8 Hz, 1H), 5.23 (dddd, *J* = 10.2, 2.4, 0.9, 0.9 Hz, 1H), 4.62 (app. ddd, *J* = 6.0, 1.5, 1.5 Hz, 1H), 4.62 (app. ddd, *J* = 6.0, 1.5, 1.5 Hz, 1H), 2.55-2.37 (comp. m, 3H), 1.96 (app. q, *J* = 7.5 Hz, 1H), 1.92 (app. q, *J* = 7.8 Hz, 1H), 1.80-1.54 (comp. m, 4H), 1.48-1.36 (m, 1H), 0.84 (app. t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9, 171.6, 131.5, 118.9, 65.6, 61.2, 41.1, 35.5, 27.6, 22.5, 8.7; IR (Neat Film NaCl) 3087, 2943, 2867, 1714, 1649, 1452, 1439, 1234, 1203, 1153, 1100, 992, 974, 934 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1258.



682

682, Table 7.10, Entry 4: Prepared from **242** by general alkylation method (3-chloro-2-methyl propene, K_2CO_3, acetone, reflux).[2] Purified by flash chromatography (SiO_2, 5 → 10% Et_2O in pentane). 67% yield. R_f = 0.25 (10% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (dddd, *J* = 17.1, 10.2, 5.7, 5.7 Hz, 1H), 5.32 (dddd, *J* = 17.1, 3.0, 1.5, 1.5 Hz, 1H), 5.25 (dddd, *J* = 10.5, 2.7, 1.2, 1.2 Hz, 1H), 4.82 (app. dd, *J* = 1.8, 1.2 Hz, 1H), 4.66 (app. t, *J* = 0.8 Hz, 1H), 4.64-4.51 (comp. m, 2H), 2.75 (d, *J* = 14.0 Hz, 1H), 2.36 (d, *J* = 14.0 Hz, 1H), 2.62-2.29 (comp. m, 4H), 2.09-1.95 (m, 1H), 1.84-1.72 (m, 2H), 1.66 (s, 3H), 1.52-1.39 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.3, 171.4, 141.4, 131.6, 119.3, 115.6, 66.0, 61.0, 42.4, 41.3, 36.2, 27.8, 24.0, 22.7; IR (Neat Film NaCl) 2946, 1716, 1646, 1452, 1377, 1186, 1086, 989, 898 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{20}O_3$ $[M]^+$: 236.1412, found 236.1401.

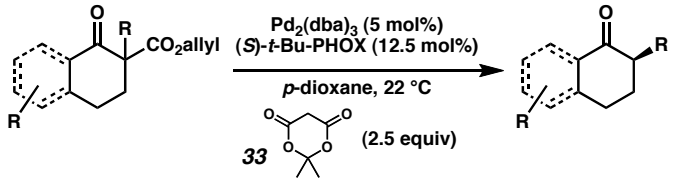


305 ***258***

258, Table 7.10, entry 5): To a solution of **305** (see Chapter 3) (1.20 g, 5.71 mmol. 1.0 equiv), imidazole (583 mg, 8.57 mmol, 1.5 equiv), and DMAP (1.04 g, 8.57 mmol, 1.5 equiv) in DMF (20 mL) was added TBDPS-Cl (1.75 mL, 6.85 mmol, 1.2 equiv). After 24 h at ambient temperature, the reaction mixture was poured into water (75 mL) and 2:1 CH_2Cl_2:hexanes (150 mL), extracted with 2:1 CH_2Cl_2:hexanes (4 x 30 mL), dried (Na_2SO_4), and evaporated. Flash chromatography (SiO_2, 2.5→12% EtOAc in hexanes)

gave the desired compound (1.85 g, 72% yield). mp 59-60 °C; R_f = 0.24 (10% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.68 (m, 4H), 7.48-7.37 (m, 6H), 6.00-5.86 (m, 1H), 5.38-5.31 (m, 1H), 5.28-5.23 (m, 1H), 4.74-4.59 (m, 2H), 4.24 (d, *J* = 9.9 Hz, 1H), 3.82 (d, *J* = 9.9 Hz, 1H), 2.78 (dq, *J* = 13.4, 3.3 Hz, 1H), 2.53-2.38 (m, 2H), 2.10-1.99 (m, 1H), 1.88-1.54 (m, 4H) 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.4, 169.8, 135.6, 135.5, 133.1, 132.9, 131.5, 129.6, 127.6 (2C), 118.8, 66.4, 65.8, 62.9, 41.2, 33.6, 27.3, 26.6, 22.1, 19.2; IR (Neat Film NaCl) 3072, 2933, 2858, 1715, 1428, 1200, 1112, 703 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{27}H_{33}O_4Si$ [M – H]$^+$: 449.2148, found 449.2165.

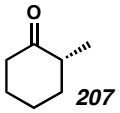
General Procedure for the Enantioconvergent Protonation (Table 7.10)



A 25 mL round-bottom flask equipped with a magnetic stir bar, and a septum was flame dried under vacuum (3x, backfill with dry argon). After cooling to ambient temperature under dry argon, $Pd_2(dba)_3$ (13.7 mg, 0.015 mmol, 0.05 equiv, 5 mol%), (*S*)-*t*-Bu-PHOX (**55**, 14.5 mg, 0.0375 mmol, 0.125 equiv, 12.5 mol%), and freshly distilled *p*-dioxane (4.5 mL) were added, and the resulting mixture was stirred vigorously at 40 ºC for 30 min. A *p*-dioxane solution (4.5 mL) of β-ketoester (0.30 mmol, 1.0 equiv) and Meldrum's acid (**33**, 108.1 mg, 0.75 mmol, 2.5 equiv) was added to the reaction mixture at 22 °C. When the reaction was complete by TLC, the reaction mixture was filtered through a pad of SiO_2 and the filtrate was concentrated under reduced pressure.

Data for product compounds

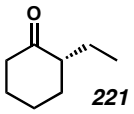
Products were prepared using the above procedure, unless specifically stated otherwise.



207

(*R*)-(–)-2-Methylcyclohexanone (Table 7.10, Entry 1):[21] Yield determined by GC using tridecane (30.0 μL) as an internal standard. 99% GC yield. Purified by flash chromatography (SiO_2, 5% Et_2O in petroleum ether). 86% ee. $[\alpha]_D^{20.8}$ –9.0 (*c* 0.50, MeOH, 86% ee).

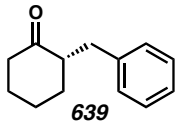
The absolute configuration was established by comparison of the optical rotation to the literature value for (*S*)-(+)-2-methylcyclohexanone: $[\alpha]_D$ +12.2 (*c* 4, MeOH, 87% ee).[30]



221

(*R*)-(–)-2-Ethylcyclohexanone (Table 7.10, Entry 2):[21] Yield determined by GC using tridecane (30.0 μL) as an internal standard. 99% GC yield. Purified by flash chromatography (SiO_2, 5% Et_2O in petroleum ether). 89% ee. $[\alpha]_D^{23.7}$ –22.4 (*c* 0.30, MeOH, 88% ee).

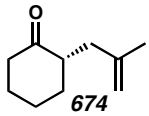
The absolute configuration was established by comparison of the optical rotation to the literature value for (*R*)-(–)-2-ethylcyclohexanone: $[\alpha]_D^{25}$ –23.6 (*c* 4.31, MeOH).[30]



639

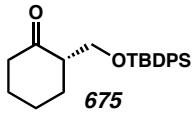
(*S*)-(–)-2-Benzylcyclohexanone (639, Table 7.10, Entry 3):[21] Purified by flash chromatography (SiO_2, 5% Et_2O in petroleum ether). 90% yield, 78% ee. $[\alpha]_D^{23.6}$ –37.6 (*c* 1.36, MeOH, 78% ee).

The absolute configuration was established by comparison of the optical rotation to the literature value for (*R*)-(+)-2-benzylcyclohexanone: $[\alpha]_D$ +41.4 (*c* 5, MeOH, 88% ee),[30] and has been correlated to (1*S,2S)*-(+)-2-benzylcyclohexanol to confirm assignment (see section 0 above).



674

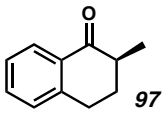
(–)-2-(2-Methylallyl)cyclohexanone (674, Table 7.10, Entry 4):[39] Purified by flash chromatography (SiO_2, 5% Et_2O in petroleum ether). 87% yield, 89% ee. $[\alpha]_D^{21.2}$ –31.1 (*c* 0.25, CH_2Cl_2, 82% ee).



675

(–)-2-((*tert*-butyldiphenylsilyloxy)methyl)cyclohexanone (675, Table 7.10, Entry 5):[40] Purified by flash chromatography (SiO_2, 5% Et_2O in petroleum ether). 97% yield, 80% ee. mp 67–69 °C. R_f = 0.23 (10% Et_2O in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71-7.63 (comp. m, 4H), 7.46-7.34 (comp. m, 6H), 4.01 (dd, *J* = 10.4, 4.8 Hz, 1H), 3.67 (dd, *J* = 10.4, 7.8 Hz, 1H), 2.62-2.48 (m, 1H), 2.43-2.21 (comp. m, 3H), 2.12-

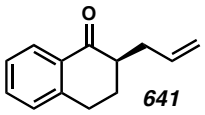
1.97 (m, 1H), 1.96-1.82 (m, 1H), 1.75-1.61 (m, 2H), 1.53-1.40 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.2, 135.8 (2C), 133.9, 133.8, 129.8, 127.8, 63.2, 53.0, 42.3, 31.1, 27.8, 27.1, 24.8, 19.5; IR (Neat Film NaCl) 2932, 2858, 1709, 1472, 1428, 1390, 1113, 1054, 823, 740, 702 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{23}H_{30}SiO_2$ $[M]^+$: 366.2015, found 366.2001. $[\alpha]_D^{23.8}$ –15.2 (*c* 1.05, CH_2Cl_2, 80% ee).



97

(*S*)-(–)-2-Methyl-1-tetralone (97, Table 7.10, Entry 6):[21] Purified by flash chromatography (SiO_2, 5% Et_2O in petroleum ether). 86% yield, 77% ee. $[\alpha]_D^{23.6}$ –38.4 (*c* 0.54, *p*-dioxane, 77% ee).

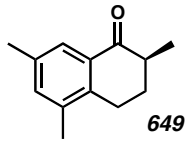
The absolute configuration was determined by comparison of the observed optical rotation to a literature value for (*S*)-2-methyl-1-tetralone: $[\alpha]_D^{22}$ –51.2 (*c* 2.5, *p*-dioxane).[22]



641

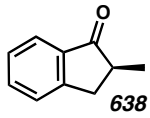
(*R*)-(–)-2-Allyl-1-tetralone (641, Table 7.10, Entry 7):[23] Purified by flash chromatography (SiO_2, 5% Et_2O in petroleum ether). 83% yield, 77% ee. $[\alpha]_D^{23.6}$ –24.1 (*c* 1.02, MeOH, 77% ee).

The absolute configuration was established by comparison of the optical rotation to the literature value for (*R*)-(–)-2-allyl-1-tetralone: $[\alpha]_D^{23}$ –29.7 (*c* 1.21, MeOH, 97% ee).[23]



649

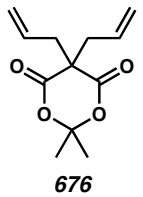
(–)-2,5,7-Trimethyl-1-tetralone (649, Table 7.10, Entry 8):[28] Purified by flash chromatography (SiO_2, 5% Et_2O in petroleum ether). 77% yield, 77% ee. $[\alpha]_D^{23.7}$ –23.2 (*c* 1.05, CH_2Cl_2, 77% ee).



638

(*S*)-(+)-2-Methyl-1-indanone (638, Table 7.10, Entry 9):[21] Purified by flash chromatography (SiO_2, 5% Et_2O in petroleum ether). 79% yield, 61% ee. $[\alpha]_D^{23.6}$ +21.2 (*c* 0.23, *p*-dioxane, 61% ee).

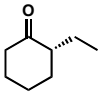
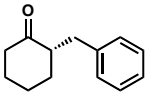
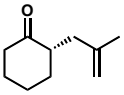
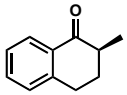
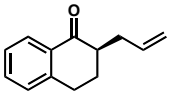
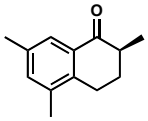
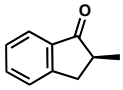
The absolute configuration was established by comparison of the optical rotation to the literature value for (*R*)-2-methyl-1-indanone: $[\alpha]_D^{22}$ –42 (*c* 1.72, *p*-dioxane).[22]



676

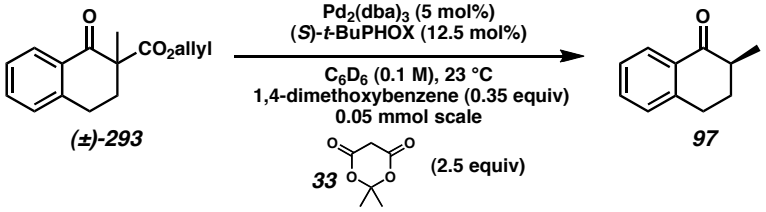
5,5-Diallyl-2,2-dimethyl-1,3-dioxane-4,6-dione[36] **(Figure 7.1):** Purified by flash chromatography (SiO_2, 5% Et_2O in petroleum ether).

Table 7.13. Methods for the determination of enantiomeric excess (Meldrum's acid conditions)

Entry	Product	Assay Conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
1	 ***207***	GC G-TA 70 ° isotherm	19.406	18.306	86
2	 ***221***	GC G-TA 70 ° isotherm	36.643	34.987	89
3	 ***639***	HPLC Chiralpak AD 1% EtOH in hexane isocratic, 1.0 mL/min	11.637	9.885	78
4	 ***674***	GC G-TA 100 ° isotherm	17.133	18.672	89
5	 OTBDPS ***675***	HPLC Chiralpak AD 1% i-PrOH in hexane isocratic, 1.0 mL/min	5.553	6.217	80
6	 ***97***	HPLC Chiracel OD-H 1% i-PrOH in hexane isocratic, 1.0 mL/min	8.723	8.075	77
7	 ***641***	HPLC Chiracel OD-H 0.1% i-PrOH in heptane isocratic, 1.0 mL/min	24.007	20.561	77
8	 ***649***	HPLC Chiracel OD-H 1% i-PrOH in hexane isocratic, 1.0 mL/min	7.283	7.787	77
9	 ***638***	HPLC Chiracel OD-H 1% i-PrOH in hexane isocratic, 1.0 mL/min	10.239	9.446	61

7.6.4 KINETIC STUDIES FOR THE ENANTIOCONVERGENT PROTONATION WITH MELDRUM'S ACID

Determination of Substrate Order (Figure 7.2)



Solid $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol, 0.05 equiv, 5 mol%) and (*S*)-*t*-Bu-PHOX (**55**, 2.4 mg, 0.00625 mmol, 0.125 equiv, 12.5 mol%) were placed in a NMR tube equipped with a screw cap and a Teflon septum. The NMR tube was then placed under vacuum and backfilled with argon (3x). C_6D_6 (0.2 mL, dried over sodium benzophenone ketyl) was added to the NMR tube via syringe under a positive pressure of argon. The mixture was heated at 40 °C for 30 min. A C_6D_6 solution (0.3 mL total) of allyl β-ketoester **293** (0.05 mmol, 1.0 equiv), 1,4-dimethoxybenzene (2.4 mg, 0.0175 mmol, 0.35 equiv), and Meldrum's acid (**33**, 18 mg, 0.125 mmol, 2.5 equiv) was added to the reaction mixture at 23 °C under argon. Reaction progress was monitored by ^{1}H NMR spectroscopy at 23 ºC, where integral areas of the allylic protons of 2 (δ 4.30 ppm, m, 2H) relative to the phenyl protons of the 1,4-dimethoxybenzene internal standard (δ 3.34 ppm, s, 6H) were obtained at 2 minute intervals. The experiment was concluded upon complete conversion of **293**, which was determined by the disappearance of the allylic protons of **293**.

Analysis of consumption of **293** over time is consistent with a zero-order dependence in allyl β-ketoester (Figure 7.2).

7.6.5 NOTES AND REFERENCES FOR EXPERIMENTAL SECTION

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APPENDIX 3

Spectra of Compound Relevant to Chapter 7

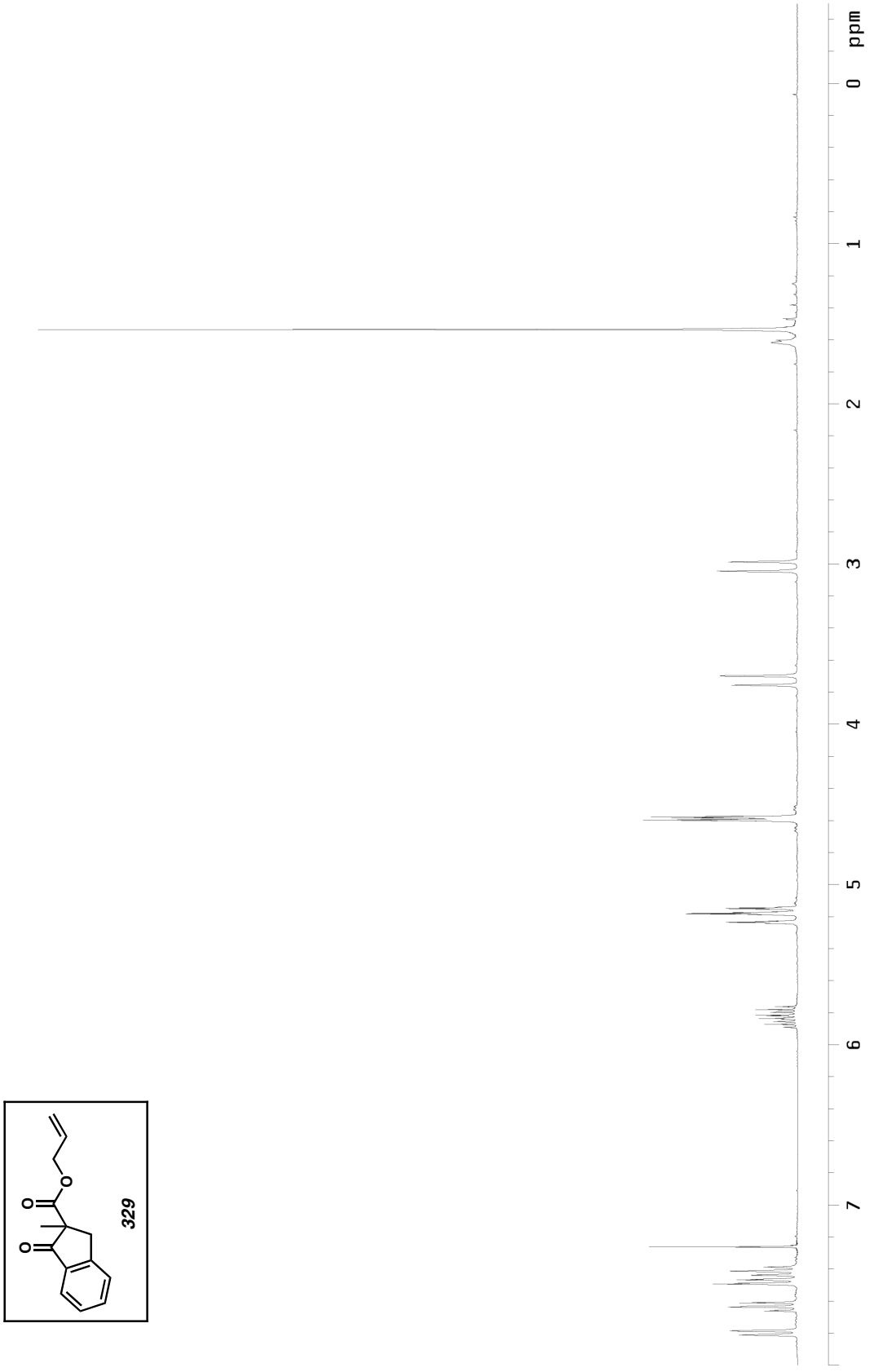


*Figure A3.1 ^{1}H NMR of compound **329** (300 MHz, $CDCl_3$)*

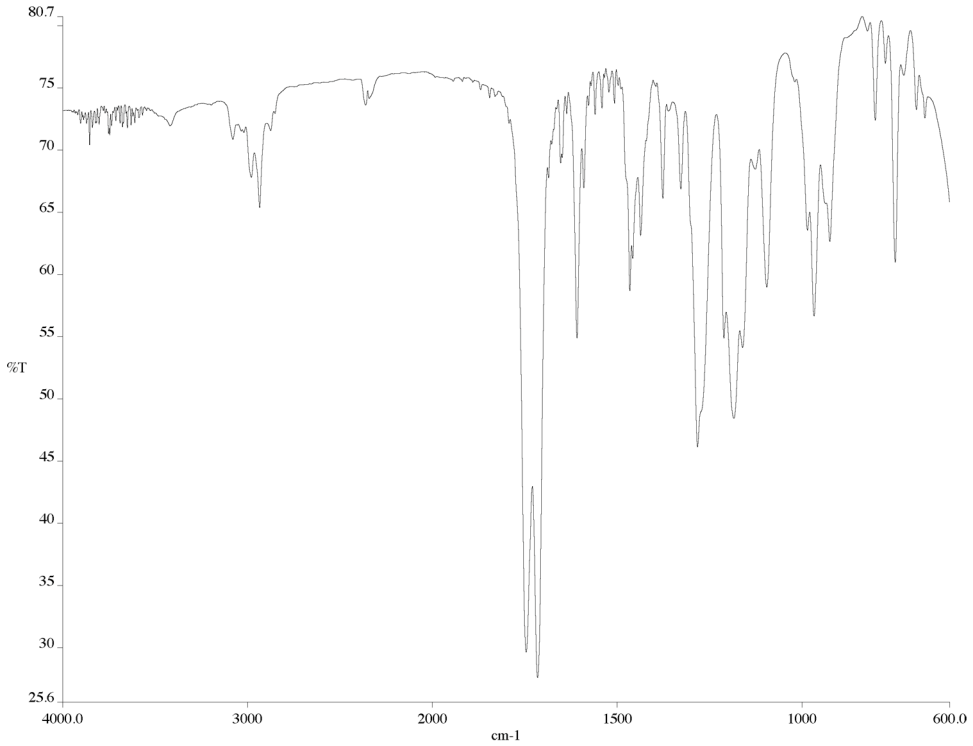


*Figure A3.2 IR of compound **329** (NaCl/film)*

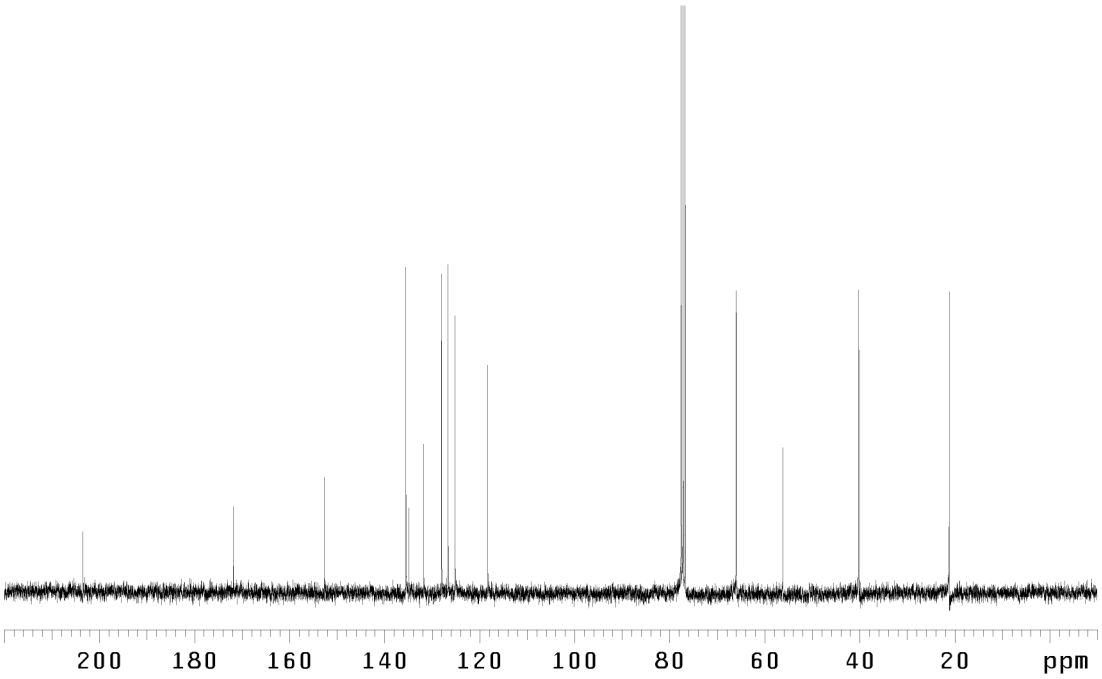


*Figure A3.3 ^{13}C NMR of compound **329** (75 MHz, $CDCl_3$)*

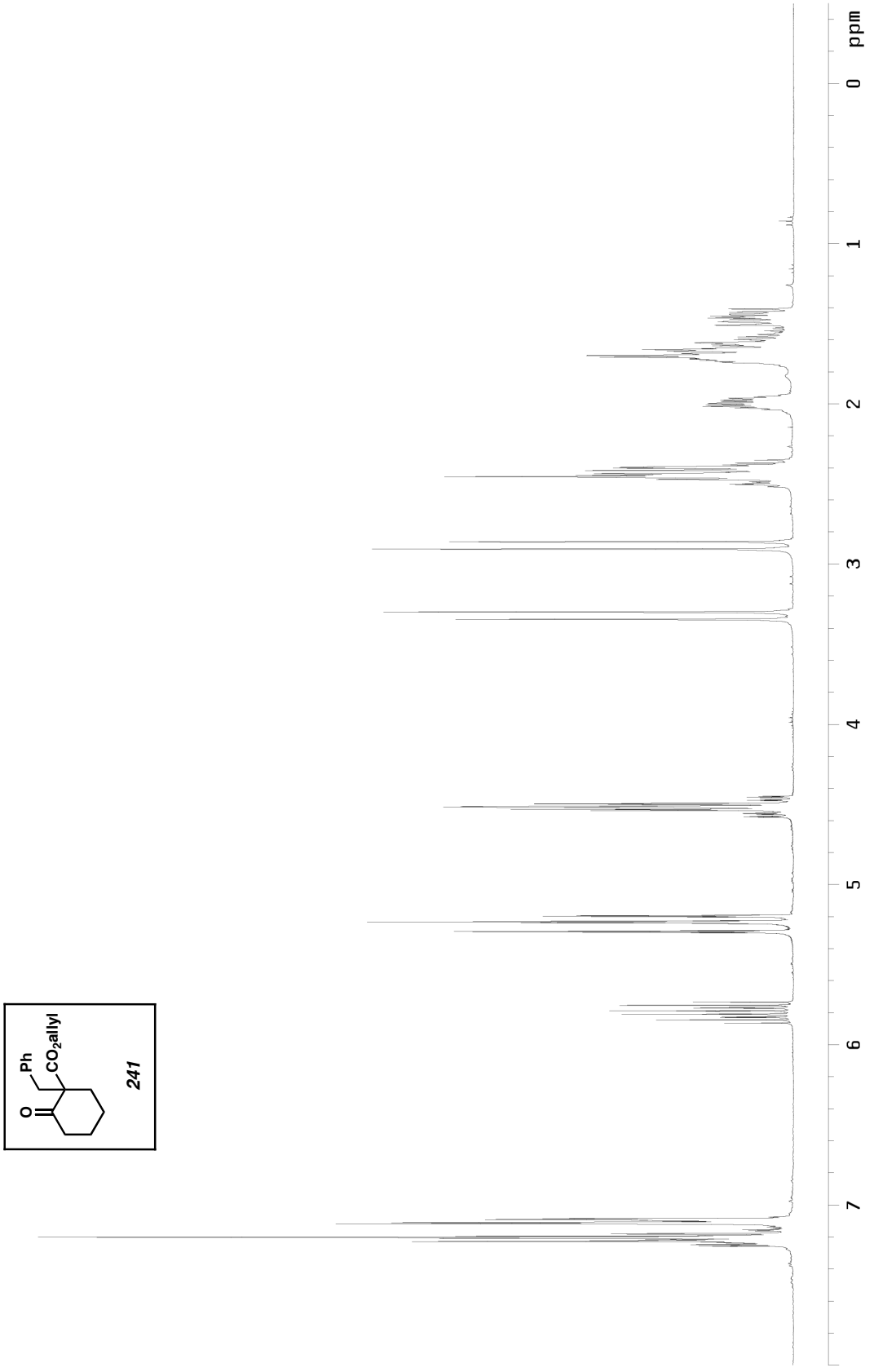


*Figure A3.4 ^1H NMR of compound **241** (300 MHz, $CDCl_3$)*

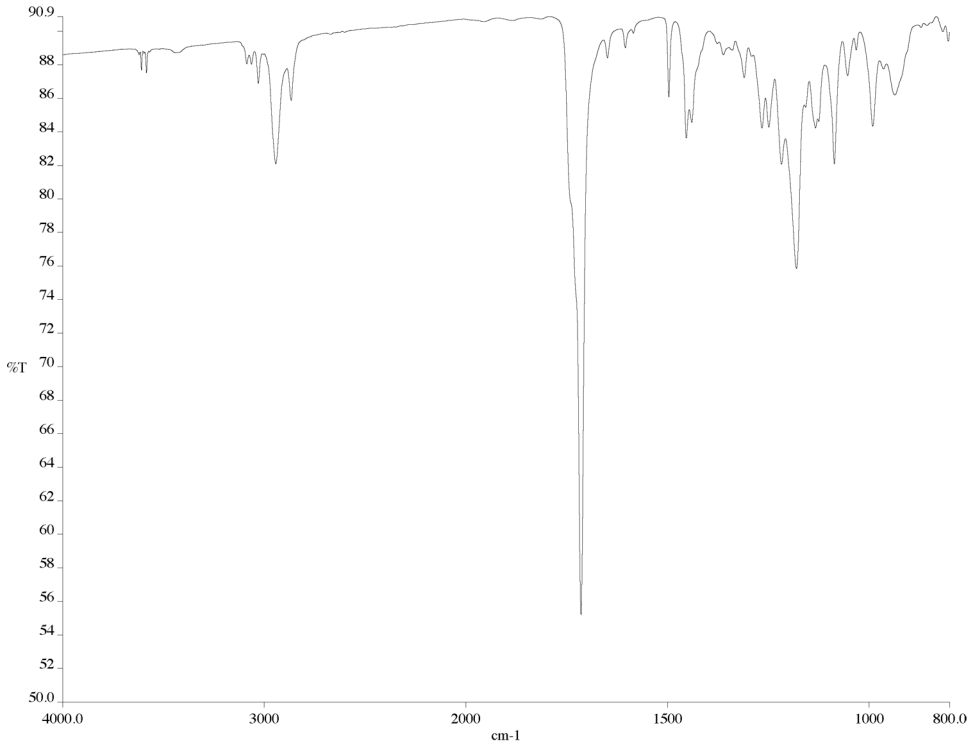


*Figure A3.5 IR of compound **241** (NaCl/film)*

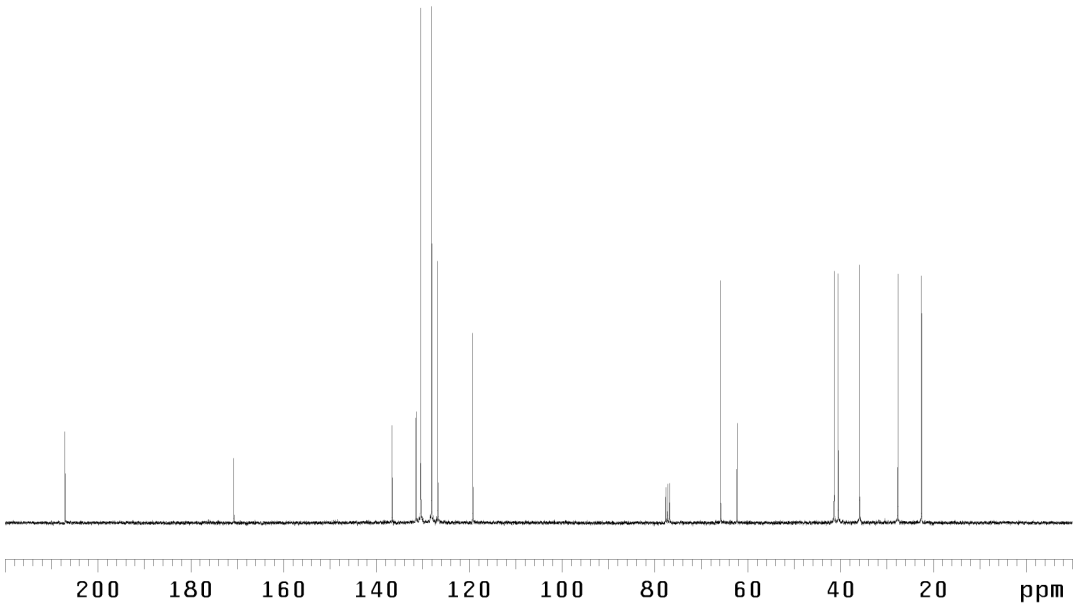


*Figure A3.6 ^{13}C NMR of compound **241** (75 MHz, $CDCl_3$)*

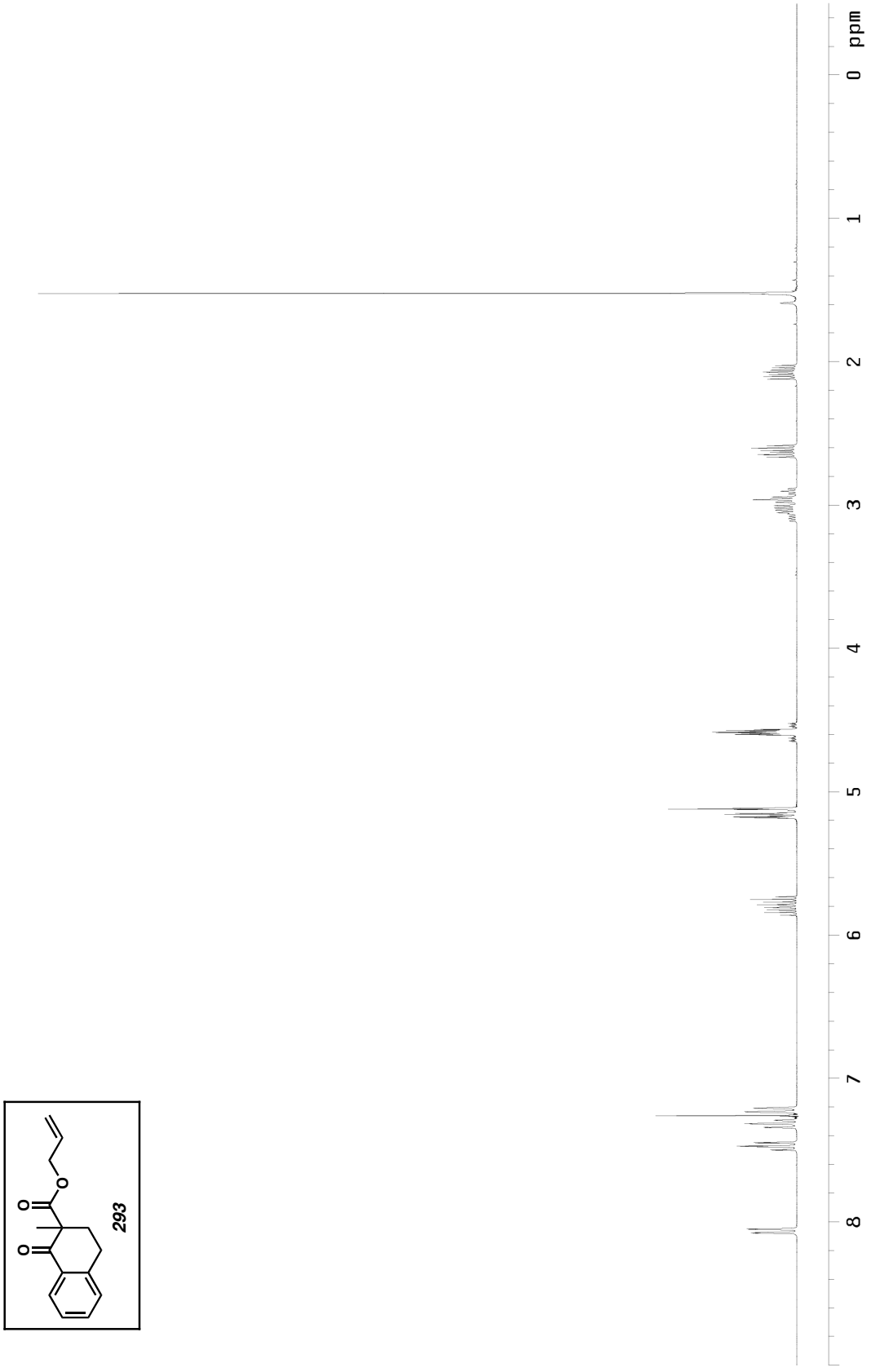


*Figure A3.7 ^{1}H NMR of compound **293** (300 MHz, $CDCl_3$)*

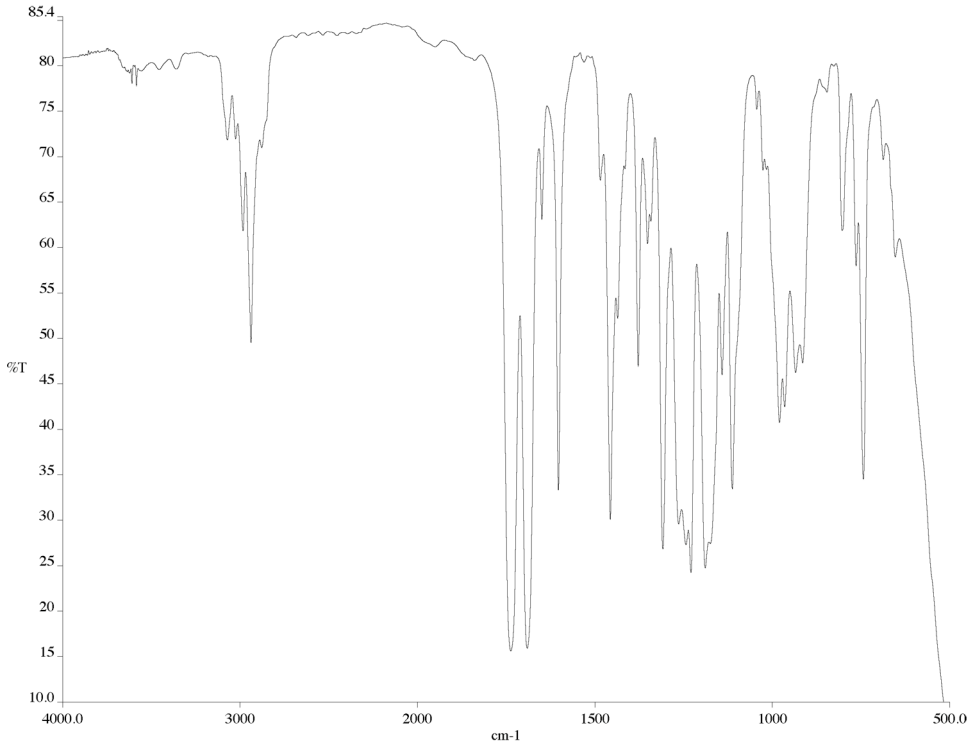


*Figure A3.8 IR of compound **293** (NaCl/film)*

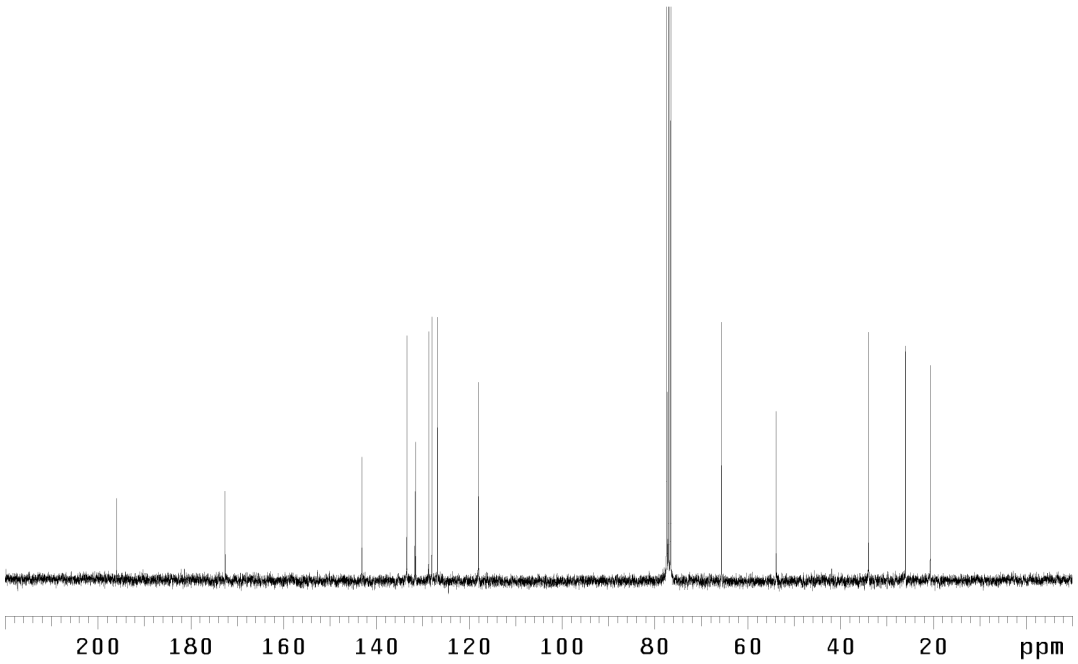


*Figure A3.9 ^{13}C NMR of compound **293** (75 MHz, $CDCl_3$)*

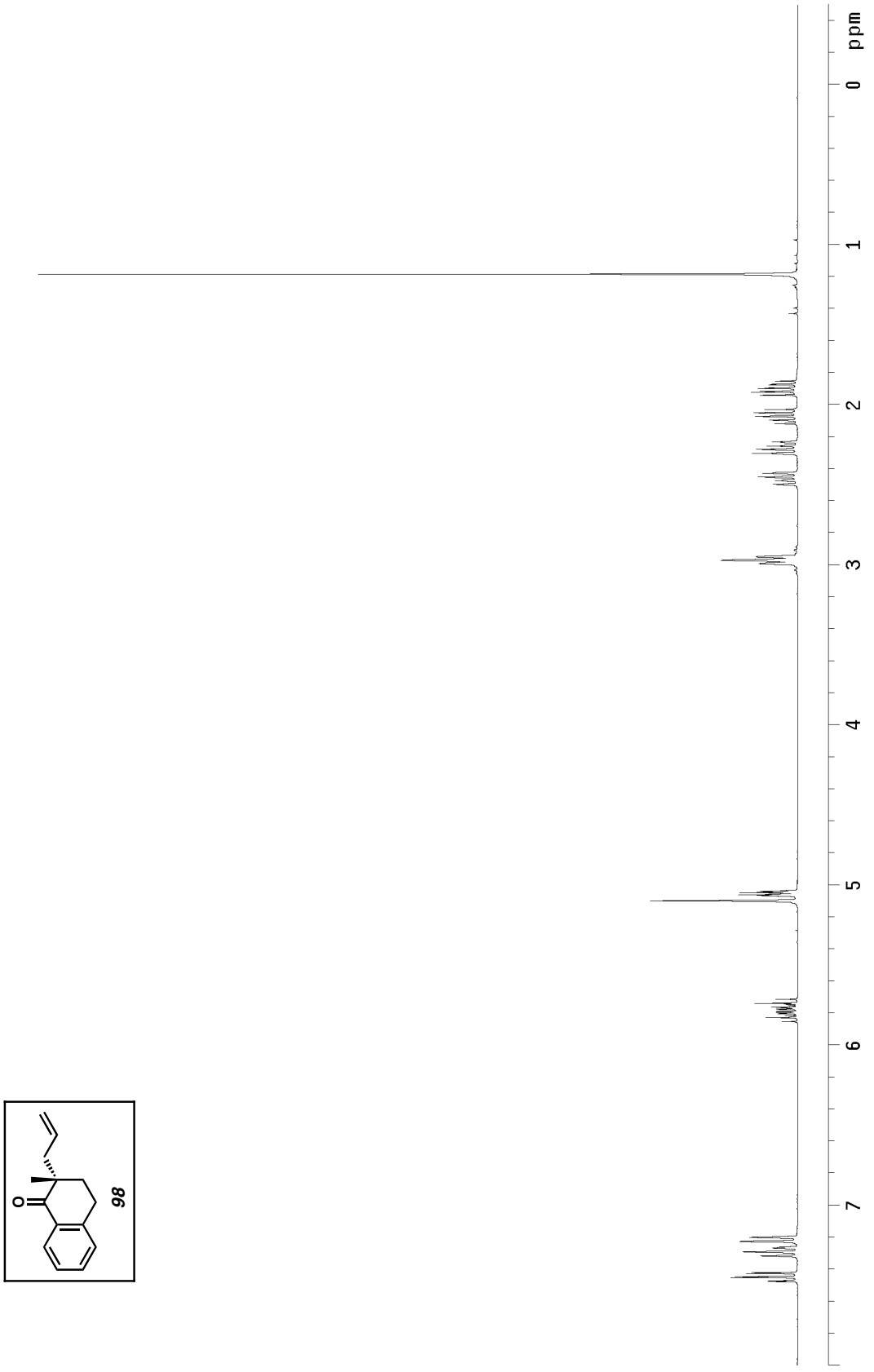


*Figure A3.10 ^{1}H NMR of compound **98** (300 MHz, $CDCl_3$)*

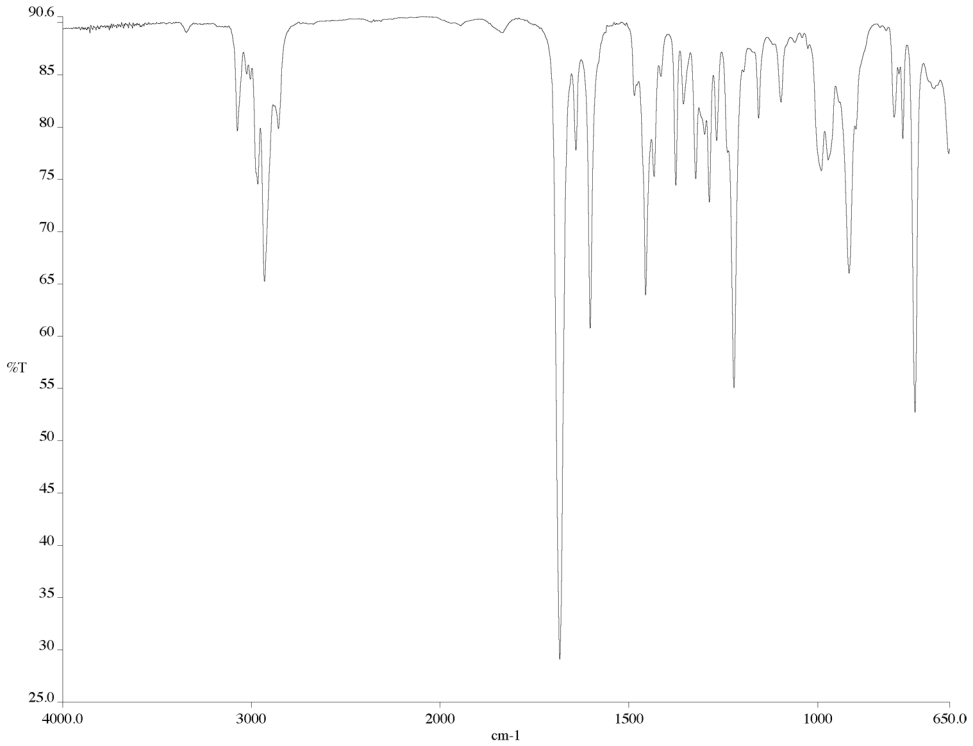


*Figure A3.11 IR of compound **98** (NaCl/film)*

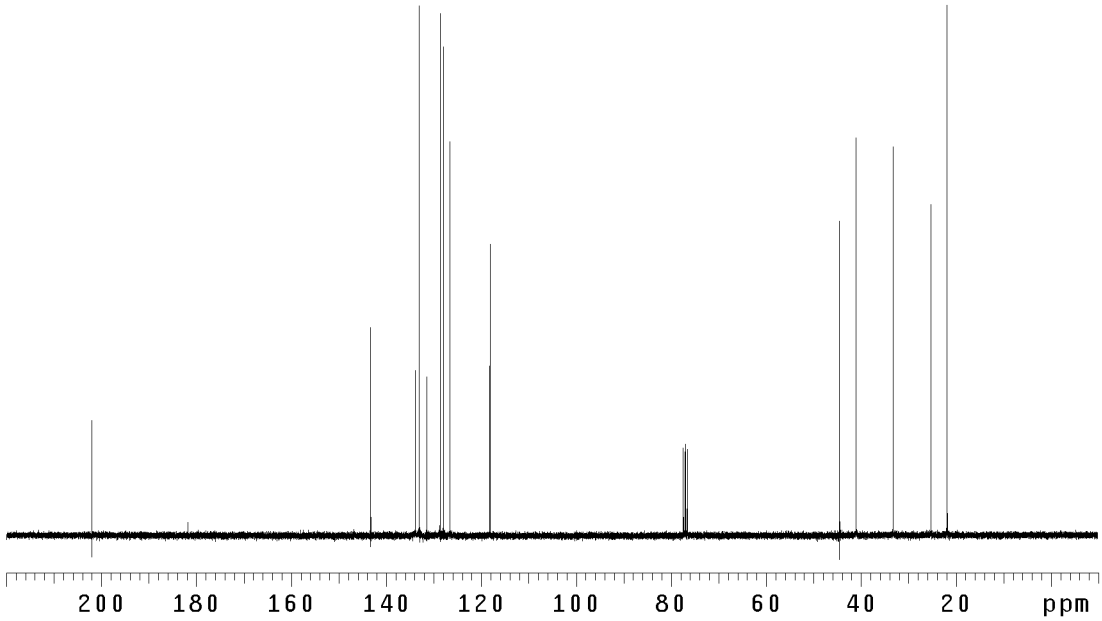


*Figure A3.12 ^{13}C NMR of compound **98** (75 MHz, $CDCl_3$)*

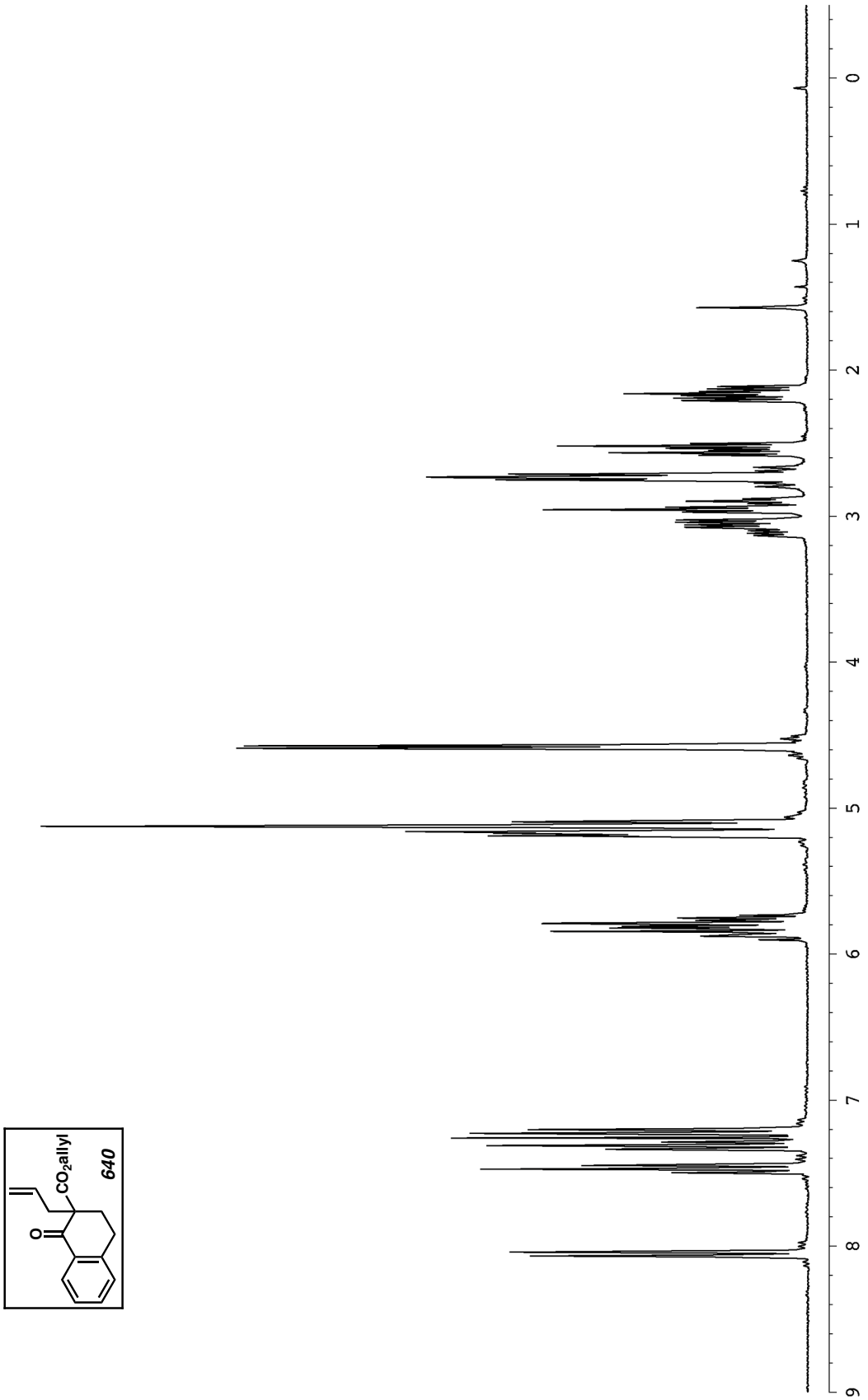


*Figure A3.13 ^1H NMR of compound **640** (300 MHz, $CDCl_3$)*

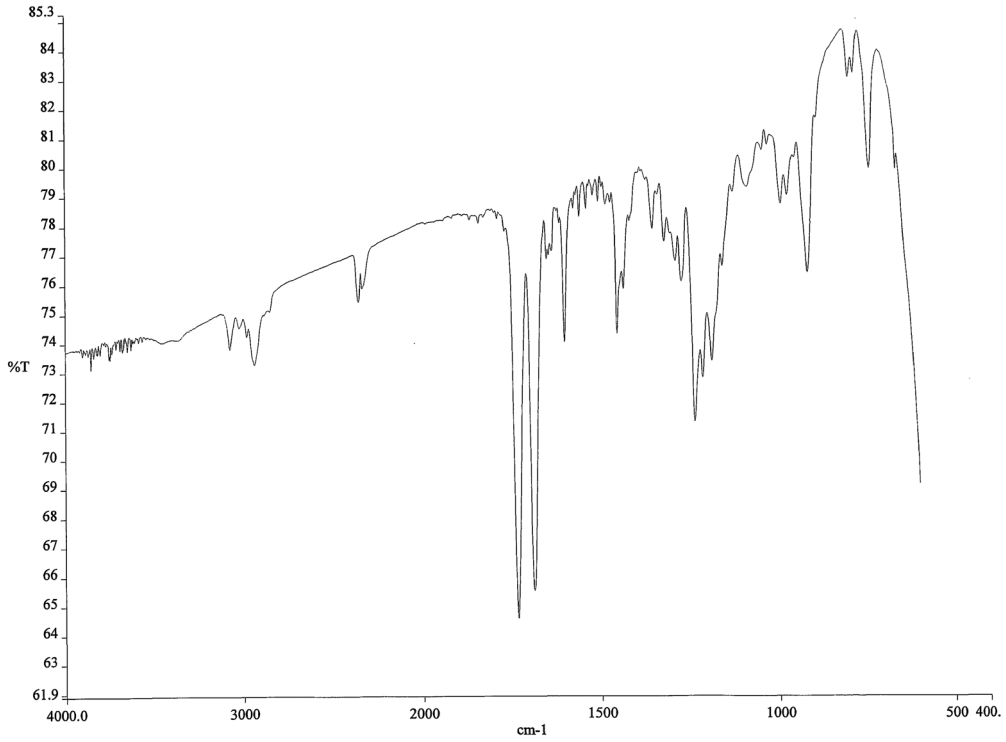


*Figure A3.14 IR of compound **640** (NaCl/film)*

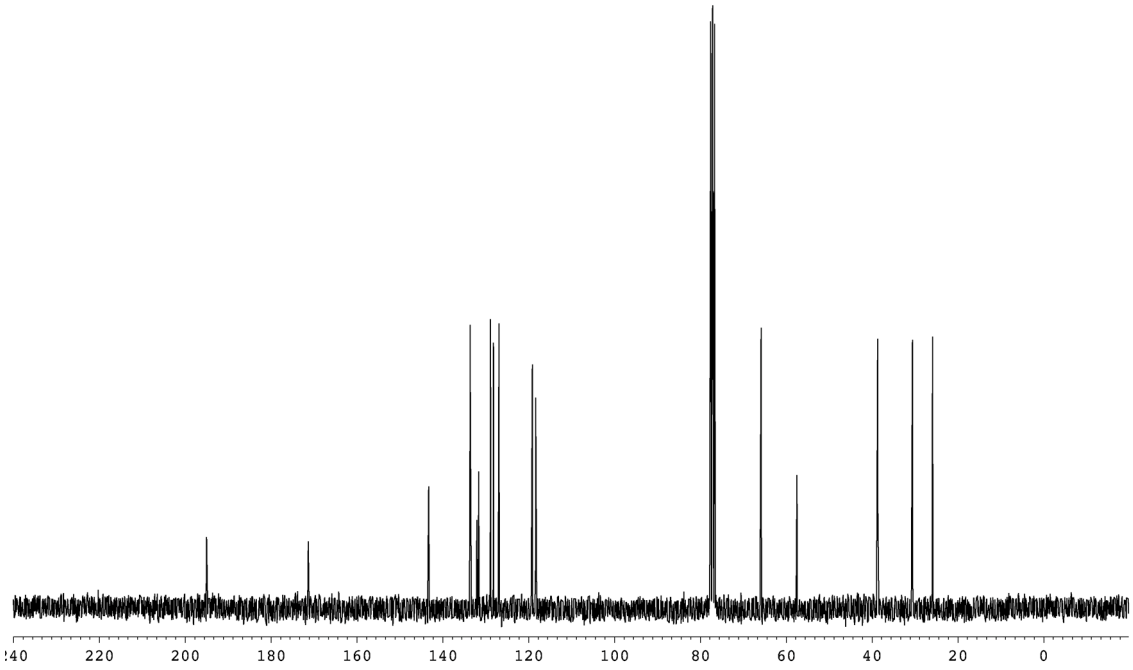


*Figure A3.15 ^{13}C NMR of compound **640** (75 MHz, $CDCl_3$)*

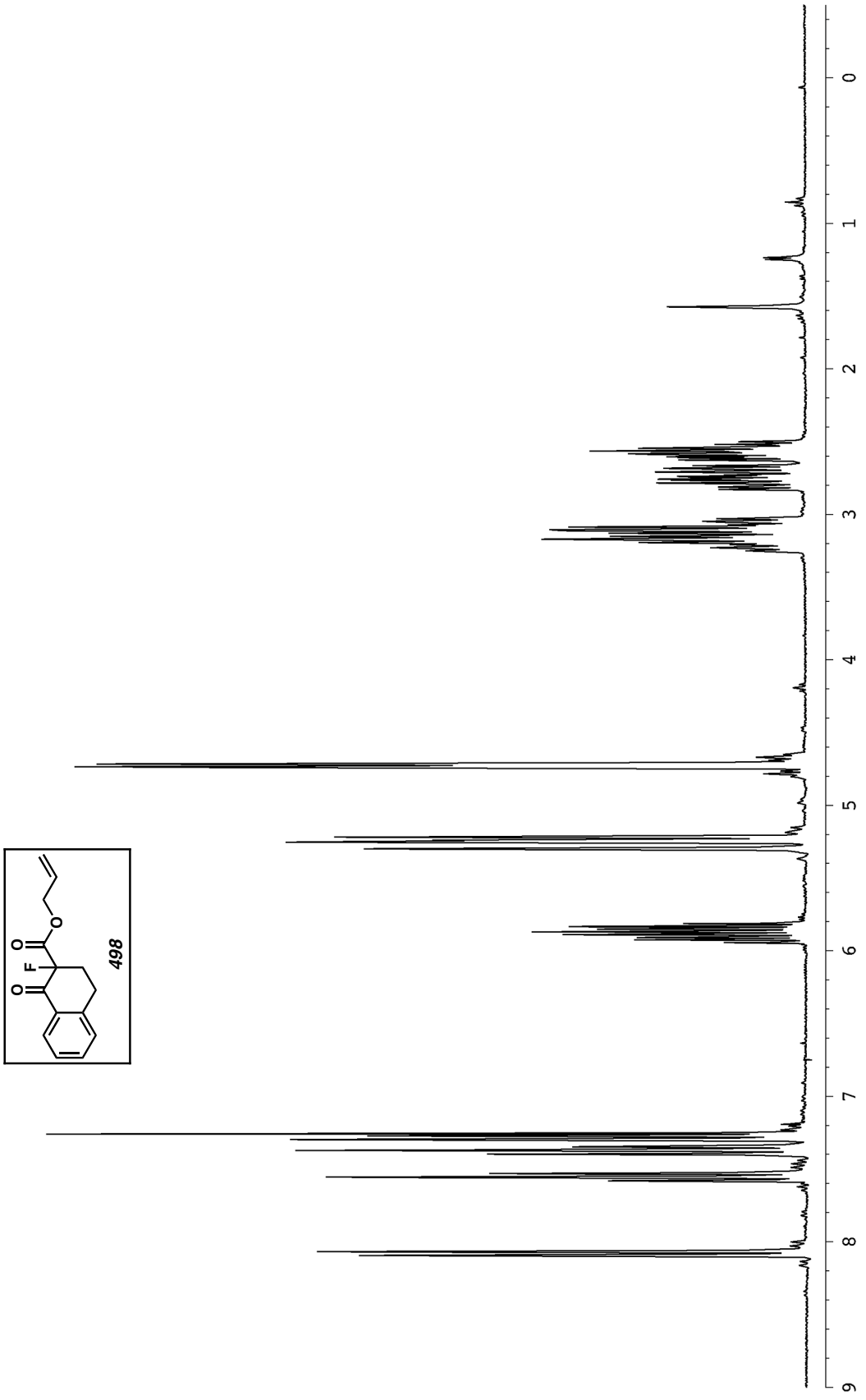


*Figure A3.16 ^1H NMR of compound **498** (300 MHz, $CDCl_3$)*

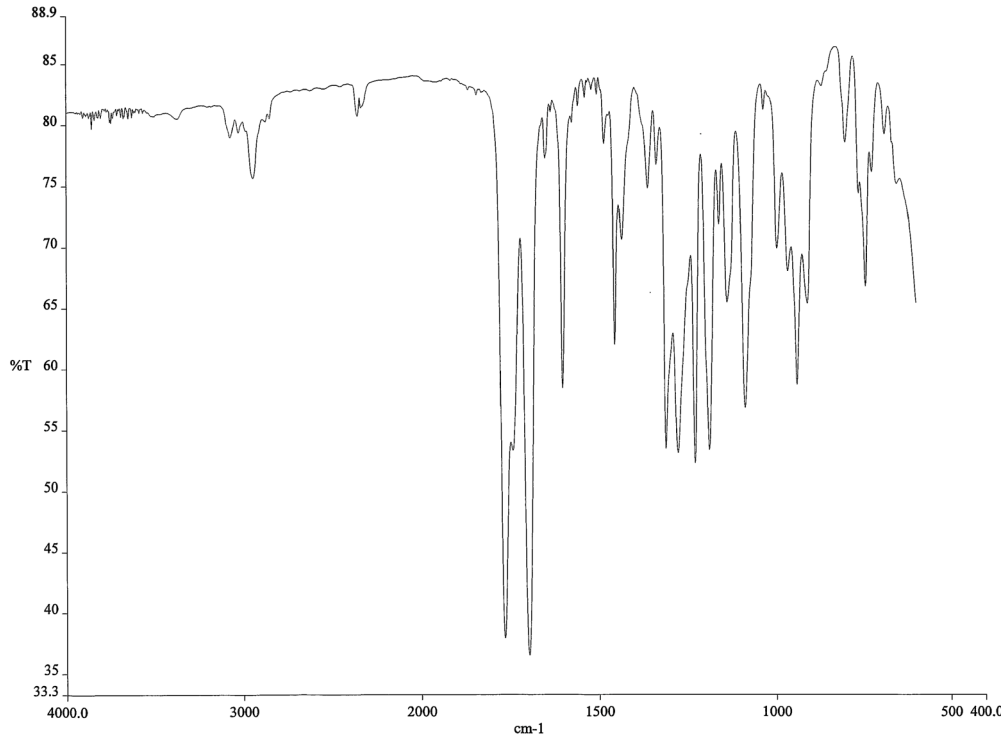


*Figure A3.17 IR of compound **498** (NaCl/film)*

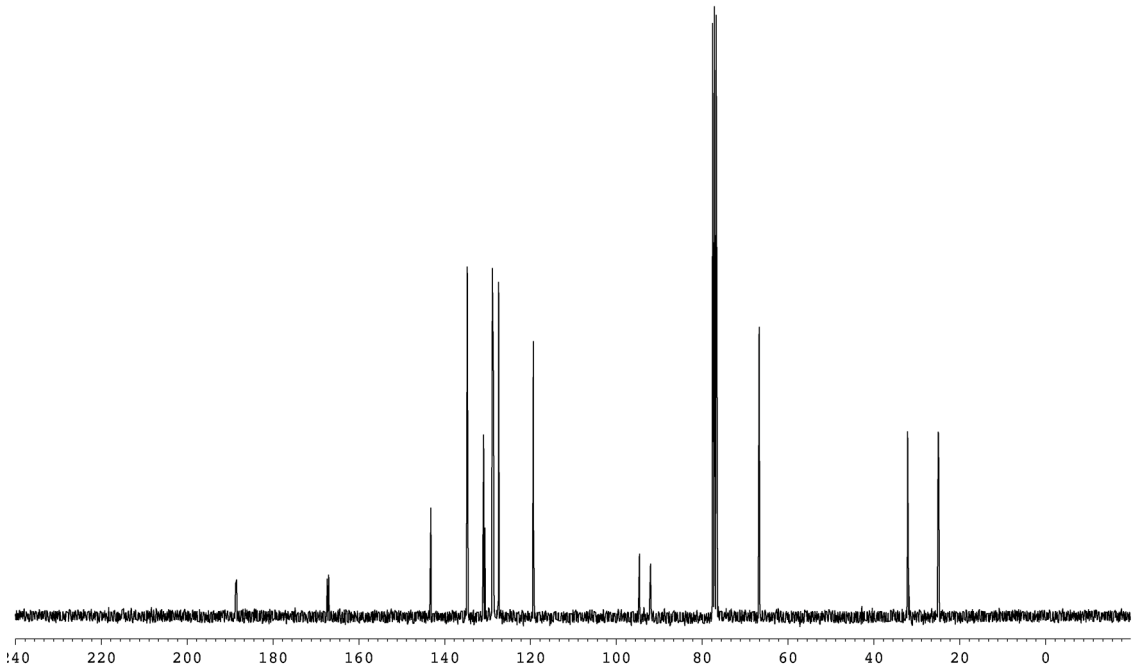


*Figure A3.18 ^{13}C NMR of compound **498** (75 MHz, $CDCl_3$)*

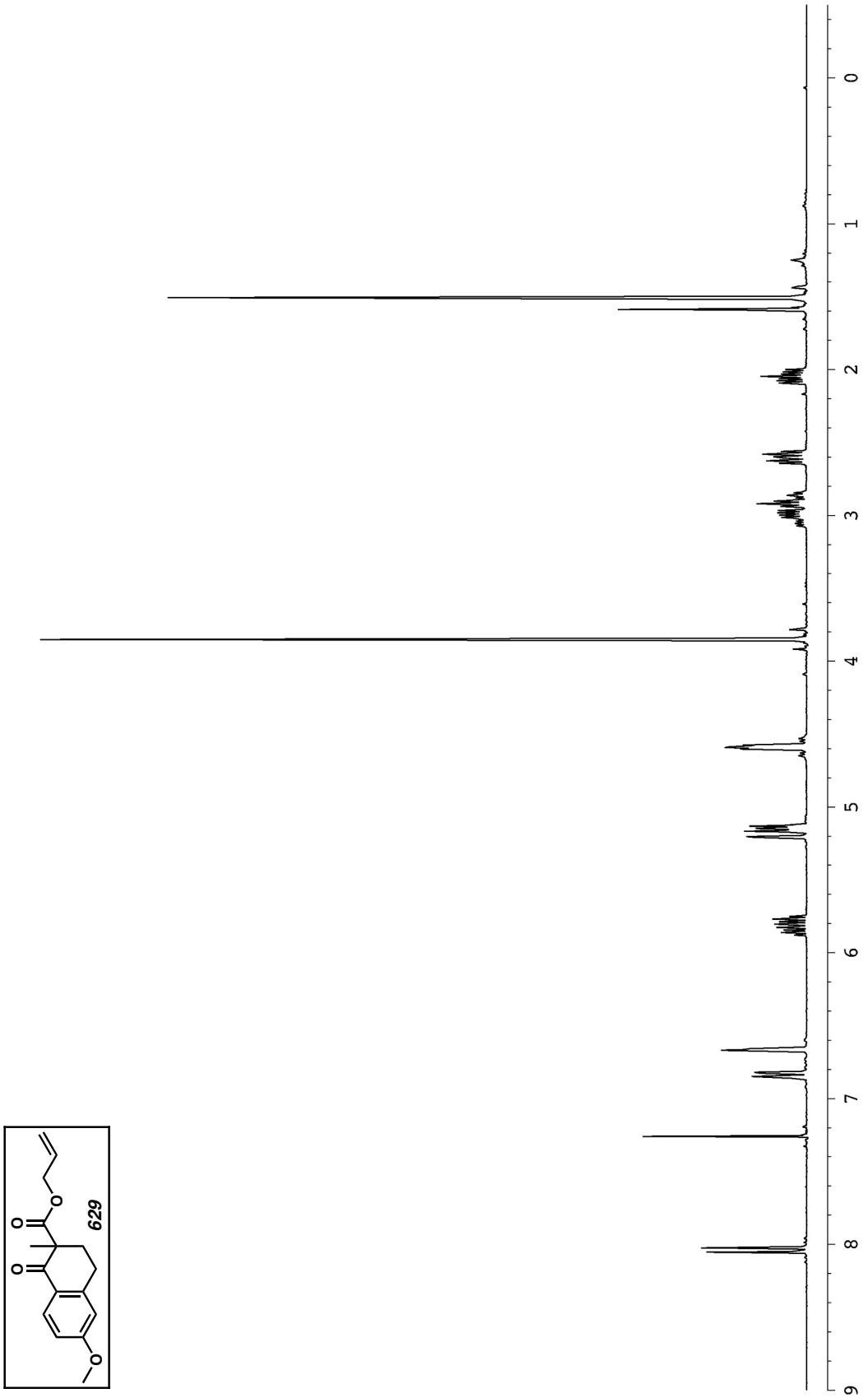


*Figure A3.19 ^{1}H NMR of compound **629** (300 MHz, $CDCl_3$)*

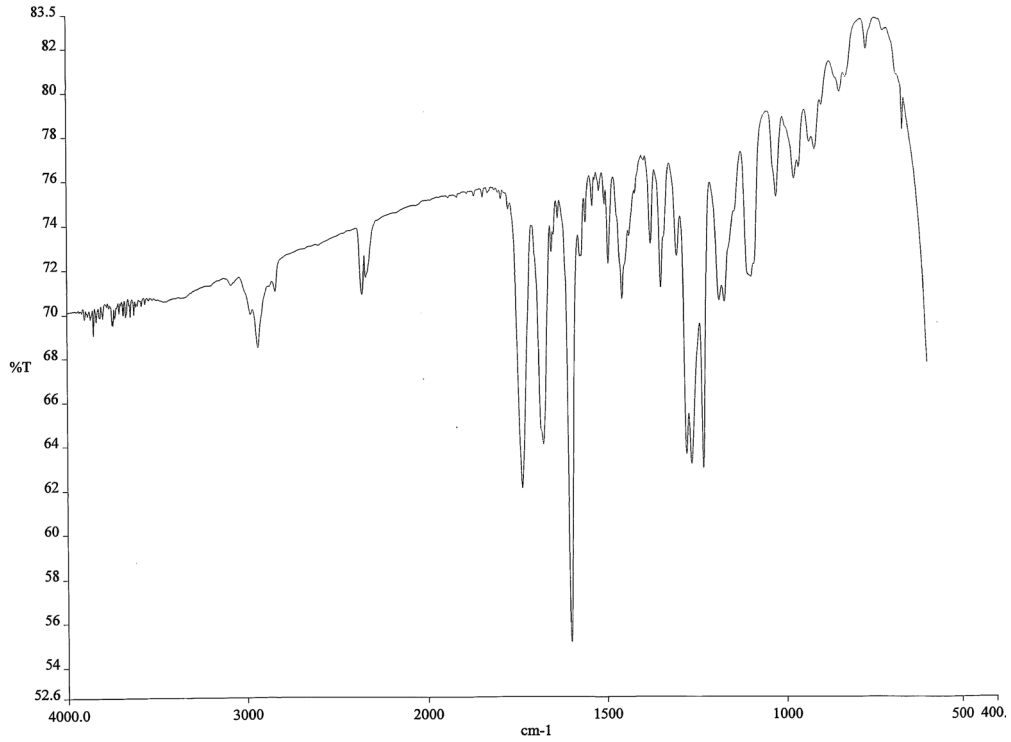


*Figure A3.20 IR of compound **629** (NaCl/film)*

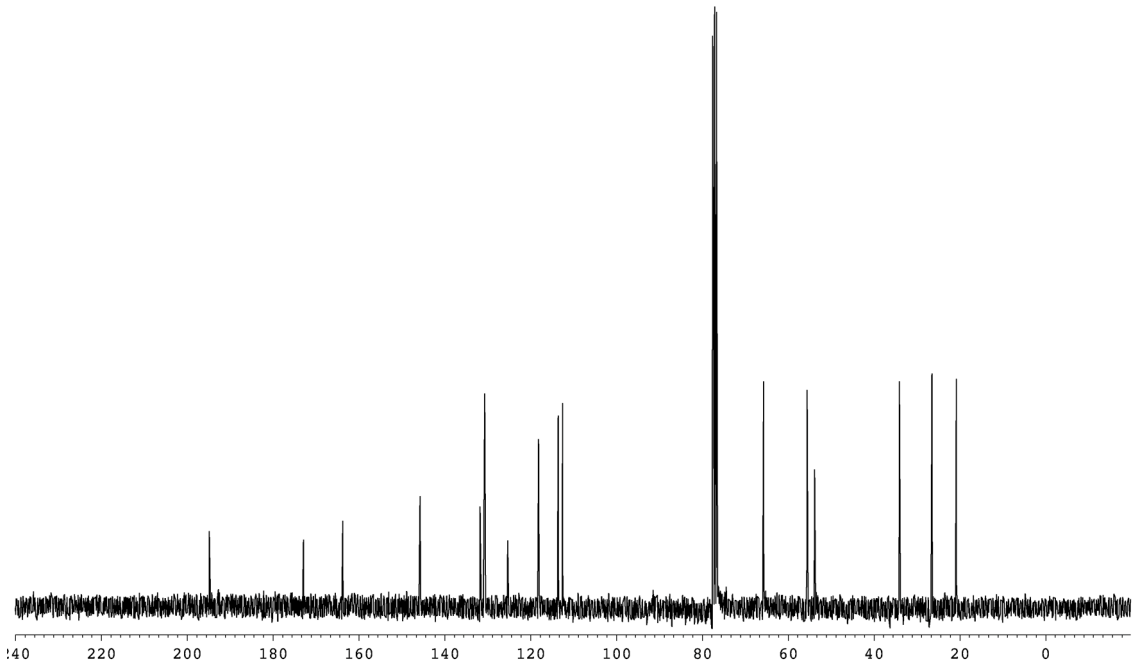


*Figure A3.21 ^{13}C NMR of compound **629** (75 MHz, $CDCl_3$)*

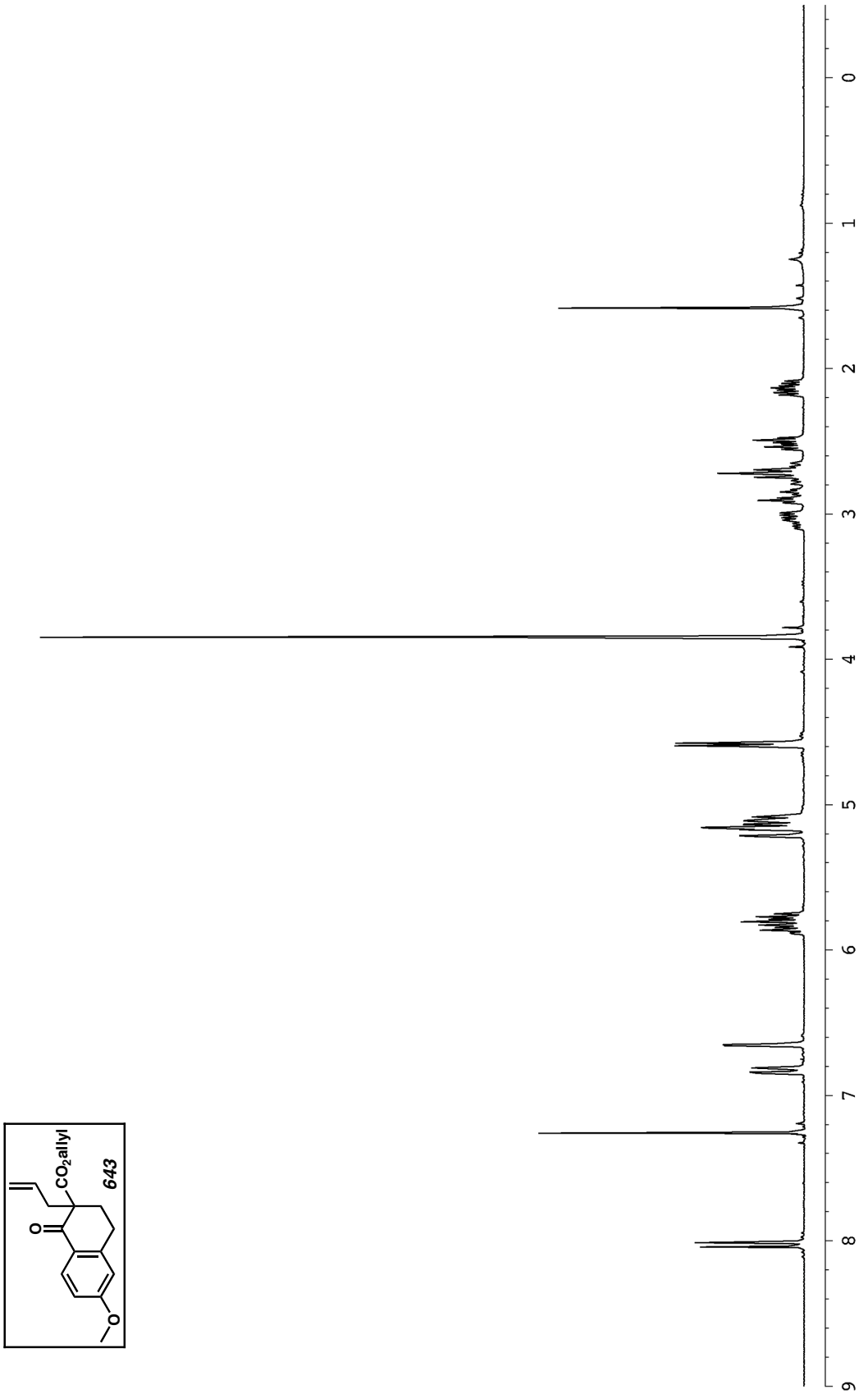


*Figure A3.22 ^1H NMR of compound **643** (300 MHz, $CDCl_3$)*

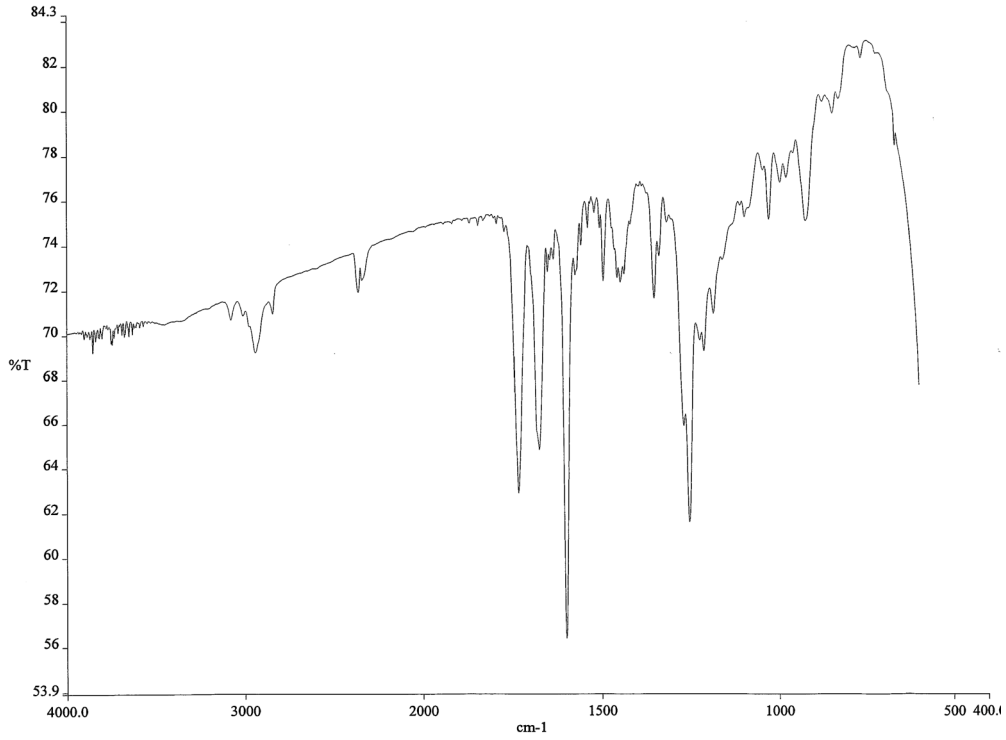


*Figure A3.23 IR of compound **643** (NaCl/film)*

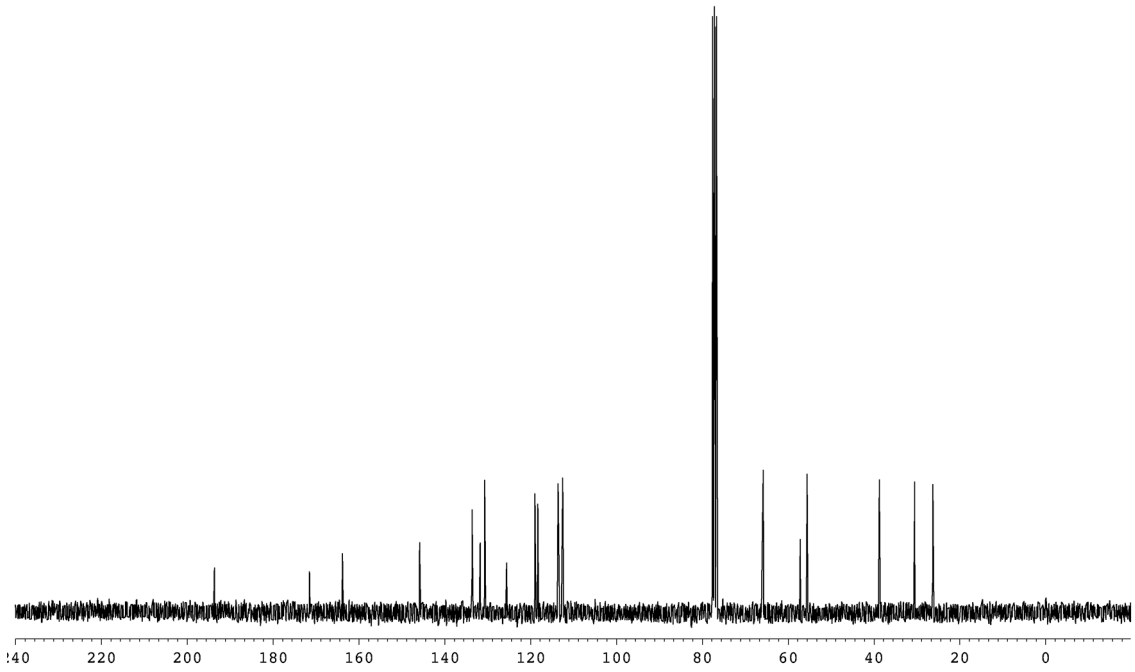


*Figure A3.24 ^{13}C NMR of compound **643** (75 MHz, $CDCl_3$)*

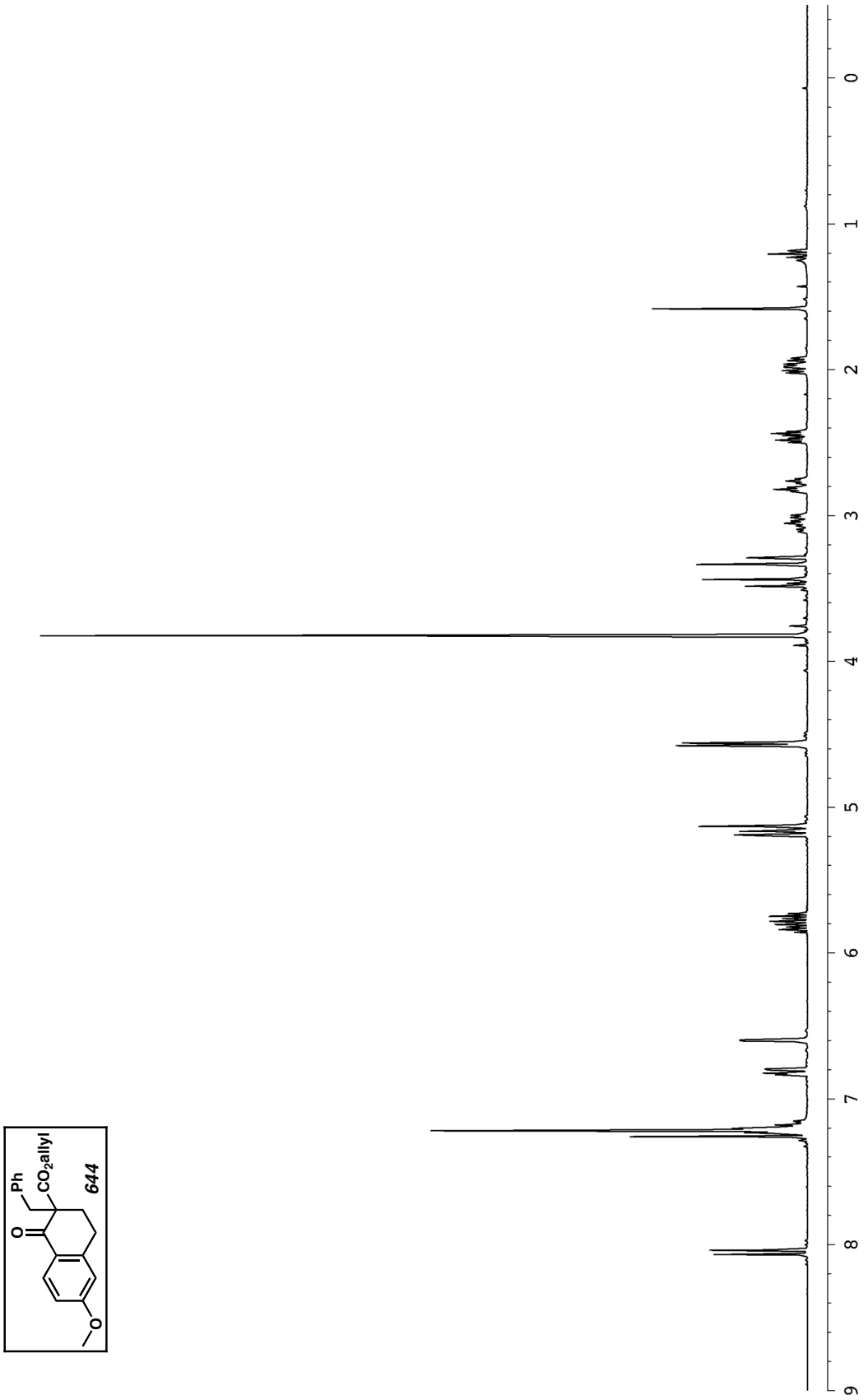


*Figure A3.25 ^1H NMR of compound **644** (300 MHz, $CDCl_3$)*

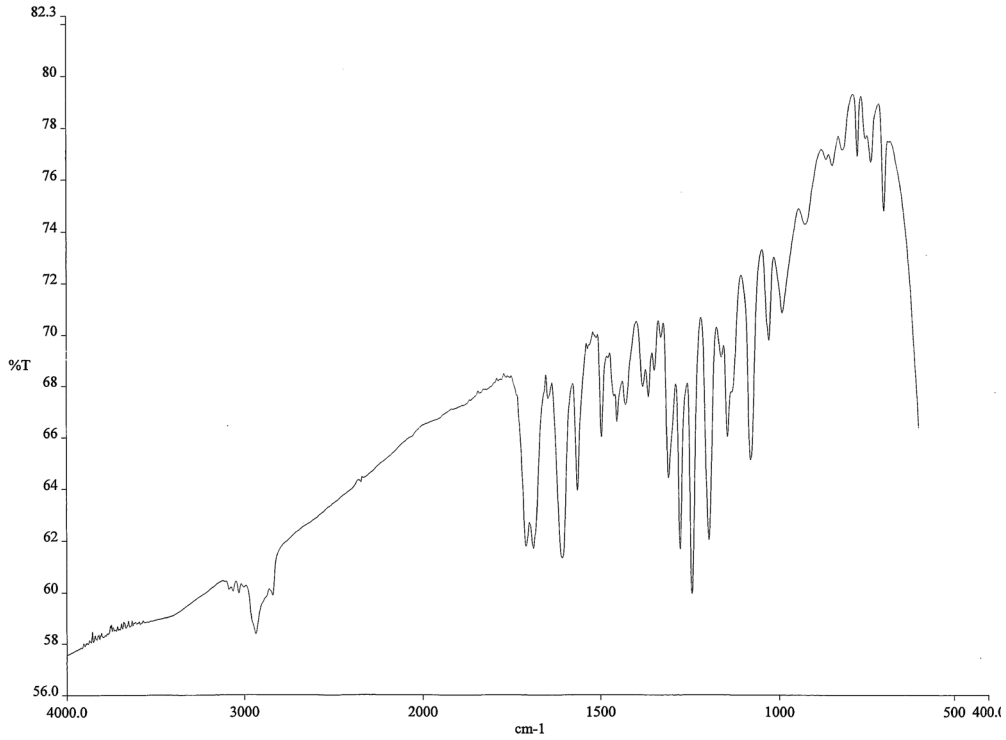


*Figure A3.26 IR of compound **644** (NaCl/film)*

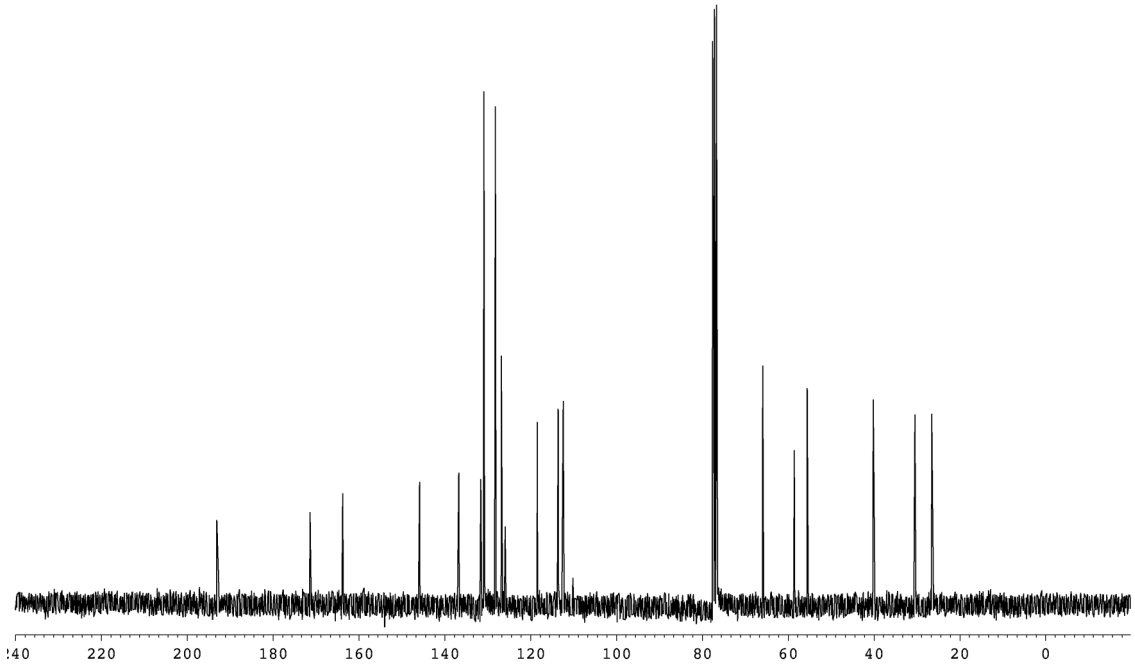


*Figure A3.27 ^{13}C NMR of compound **644** (75 MHz, $CDCl_3$)*

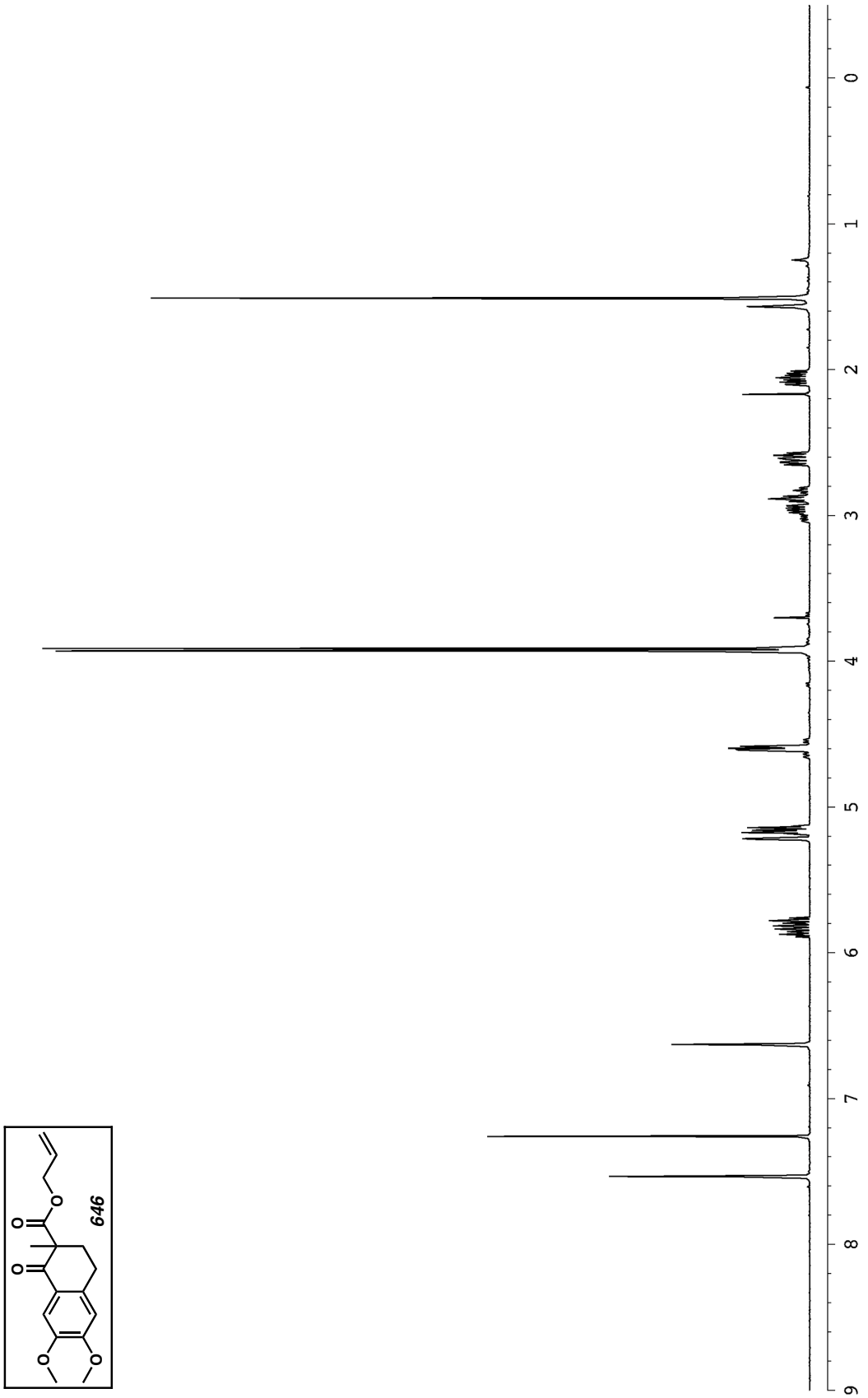


*Figure A3.28 ^{1}H NMR of compound **646** (300 MHz, $CDCl_3$)*

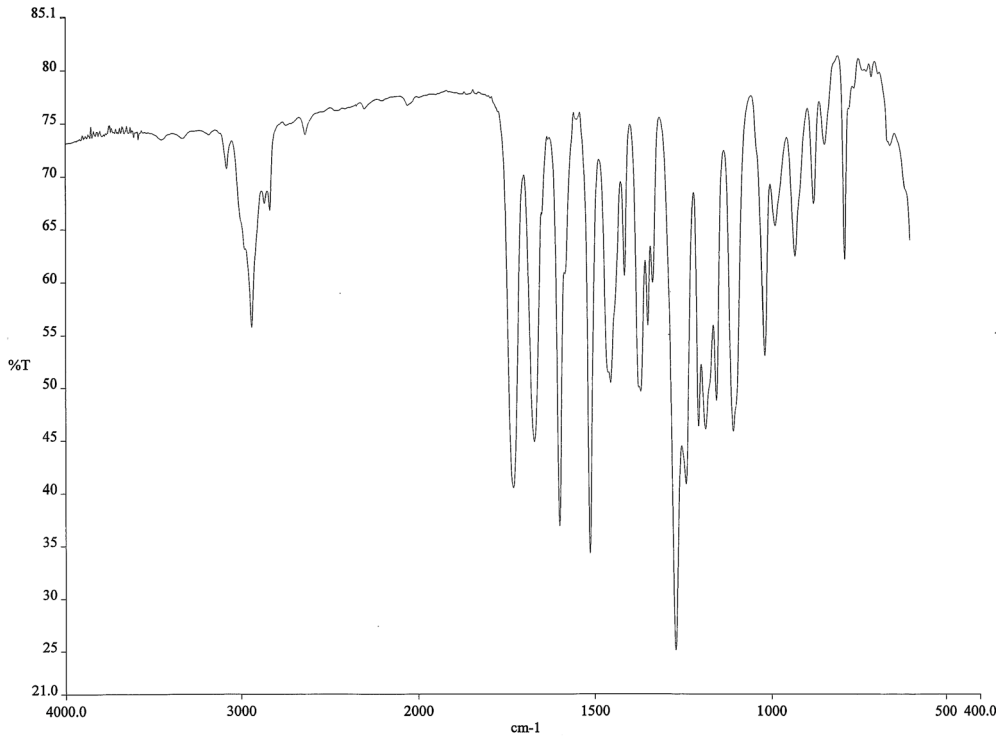


*Figure A3.29 IR of compound **646** (NaCl/film)*

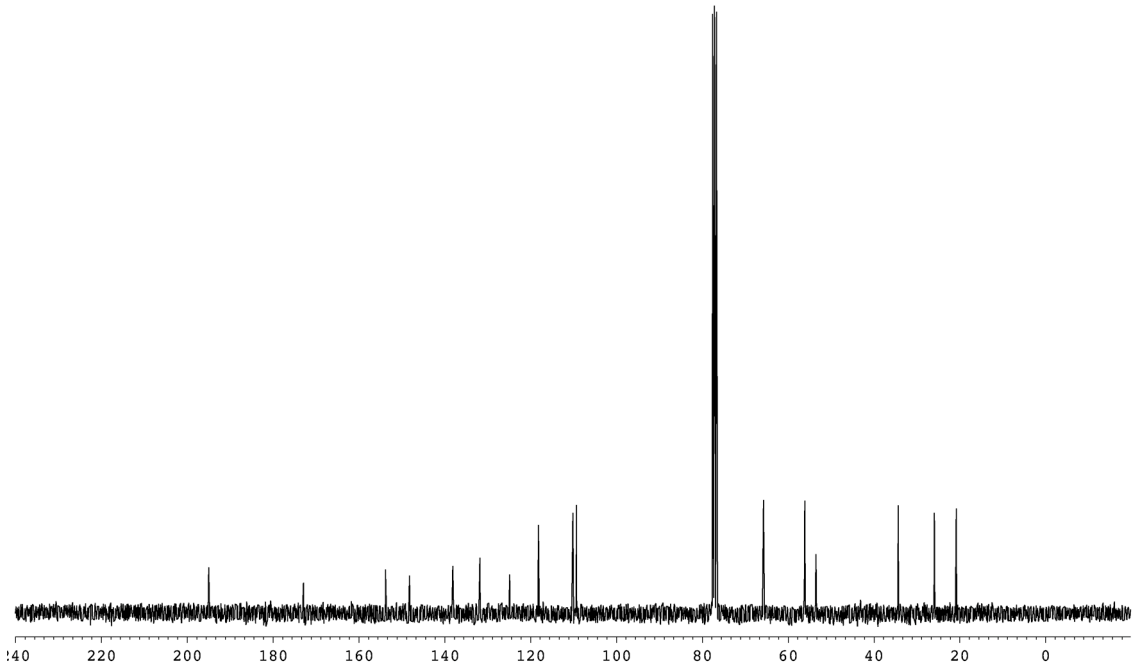


*Figure A3.30 ^{13}C NMR of compound **646** (75 MHz, $CDCl_3$)*

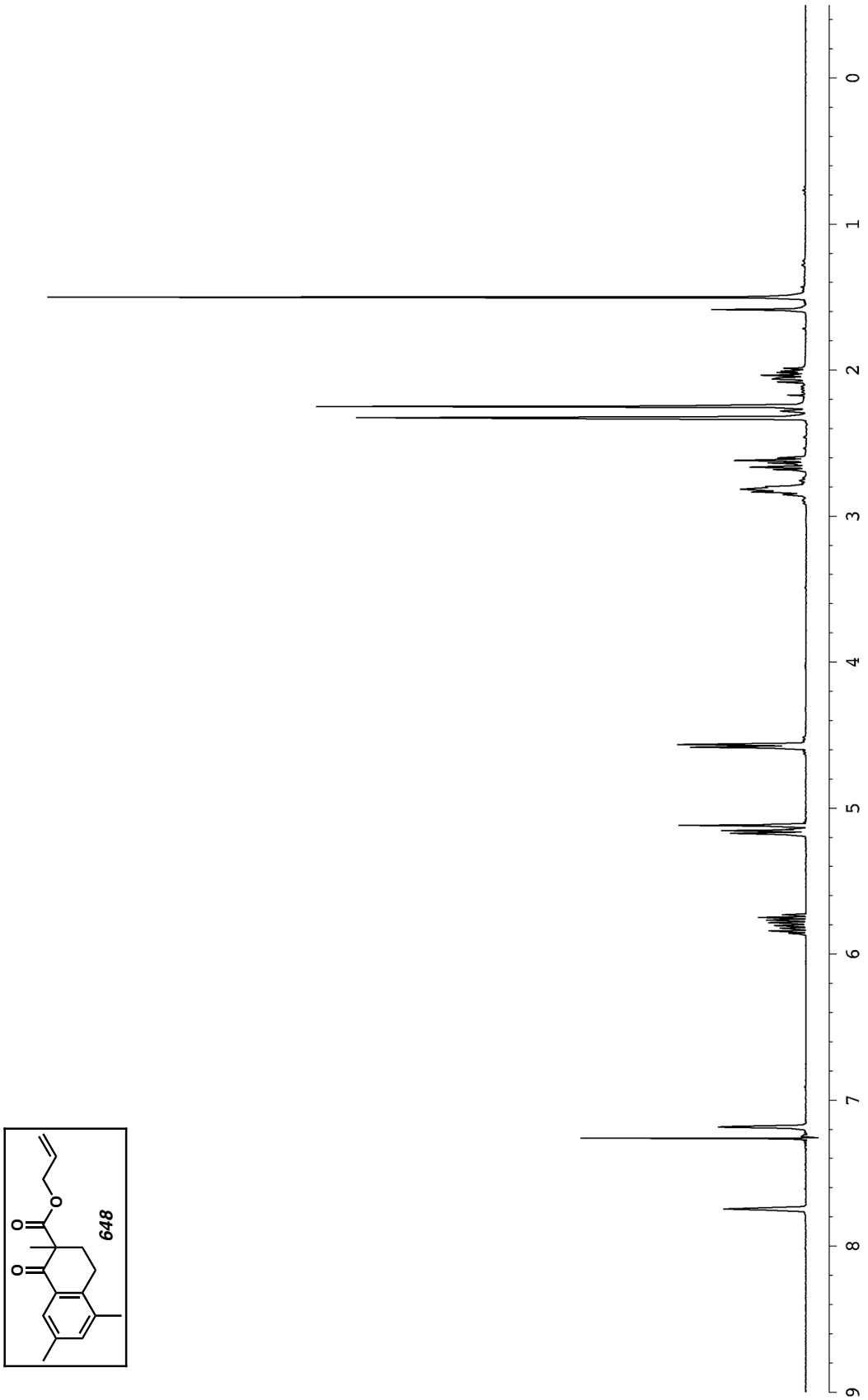


*Figure A3.31 ^{1}H NMR of compound **648** (300 MHz, $CDCl_3$)*

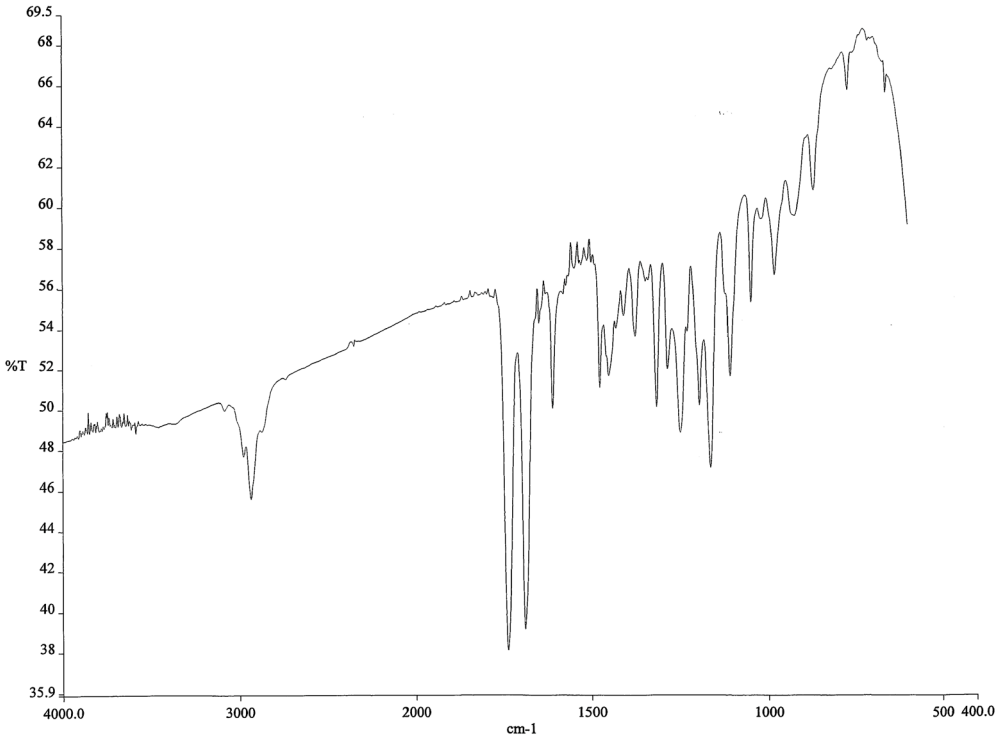


*Figure A3.32 IR of compound **648** (NaCl/film)*

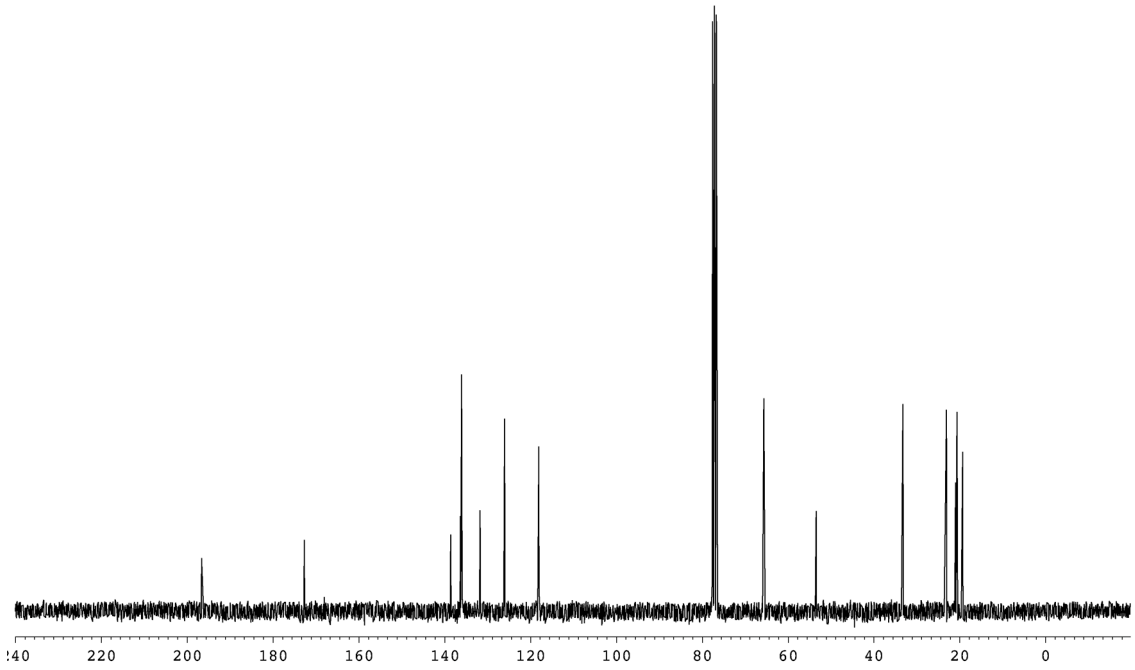


*Figure A3.33 ^{13}C NMR of compound **648** (75 MHz, $CDCl_3$)*

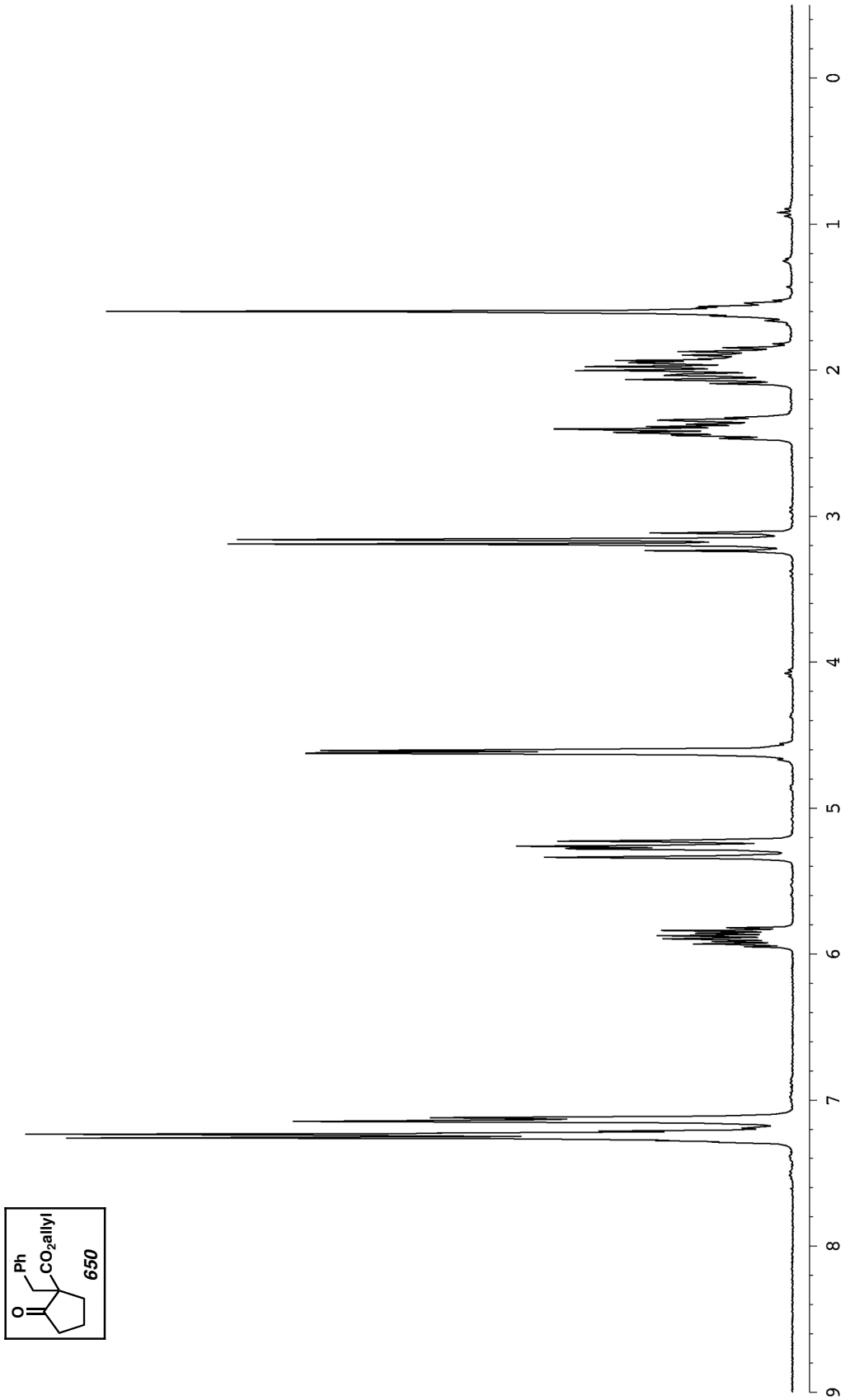


*Figure A3.34 ^{1}H NMR of compound **650** (300 MHz, $CDCl_3$)*

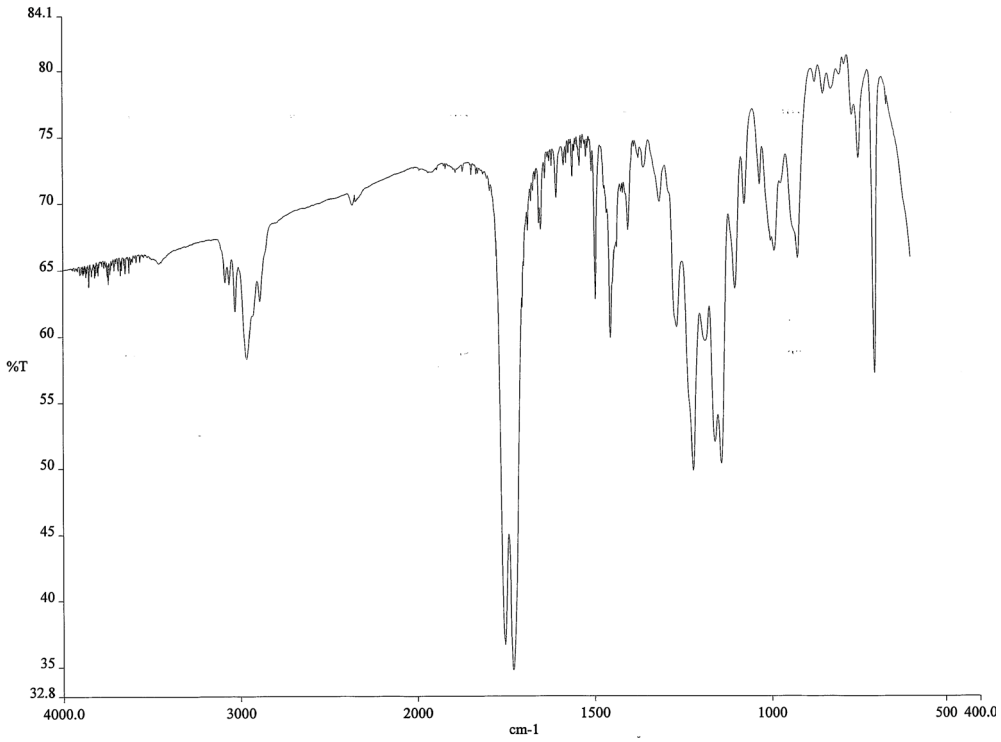


*Figure A3.35 IR of compound **650** (NaCl/film)*

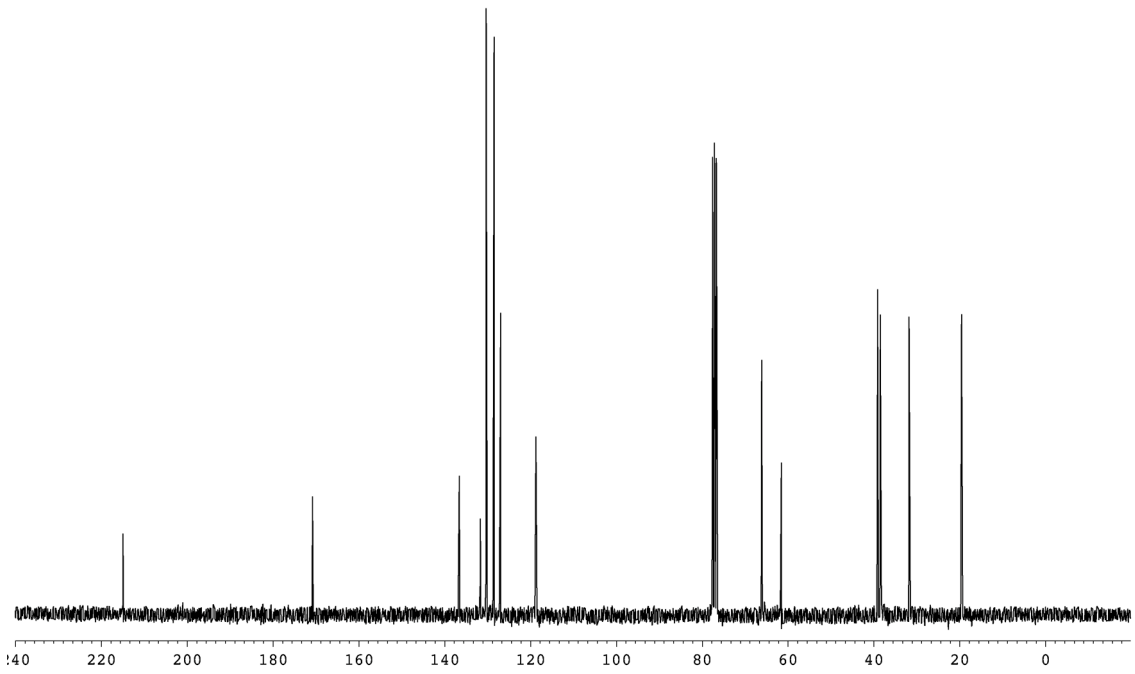


*Figure A3.36 ^{13}C NMR of compound **650** (75 MHz, $CDCl_3$)*

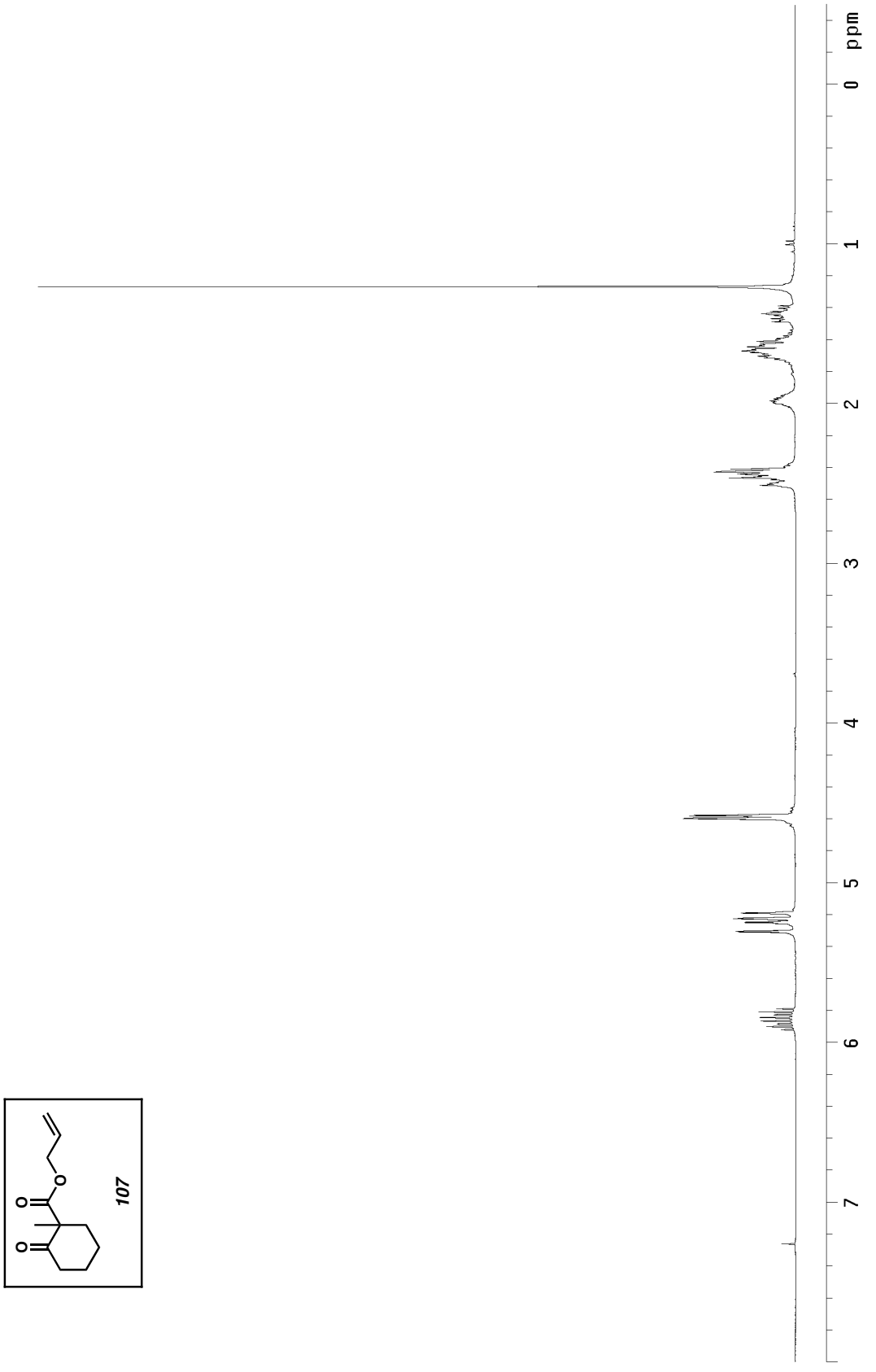


*Figure A3.37 ^{1}H NMR of compound **107** (300 MHz, $CDCl_3$)*

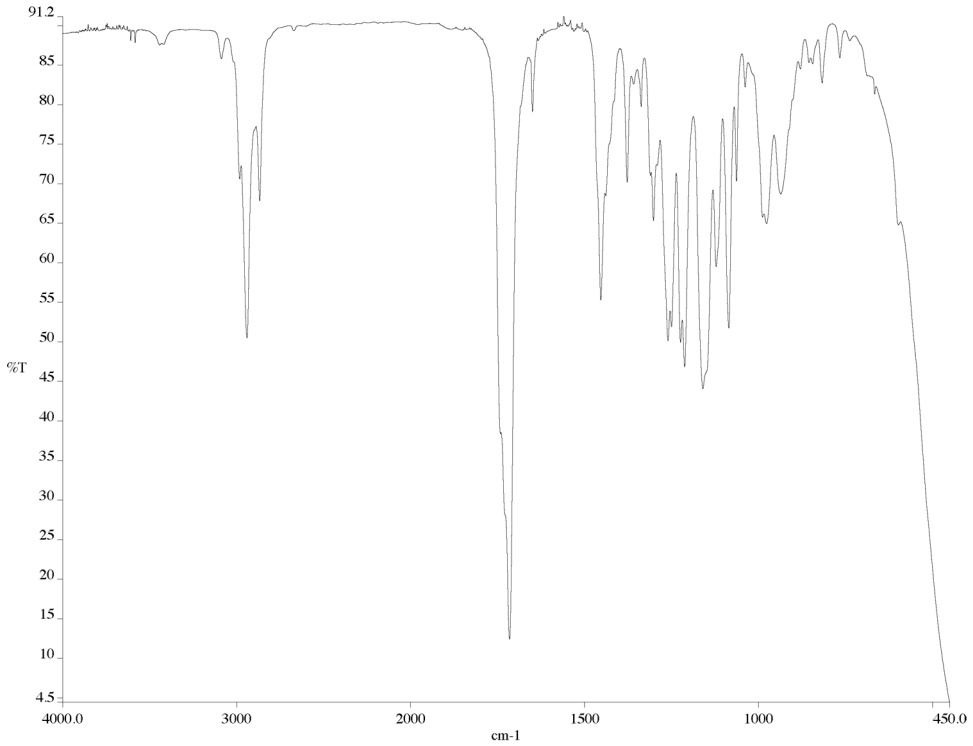


*Figure A3.38 IR of compound **107** (NaCl/film)*

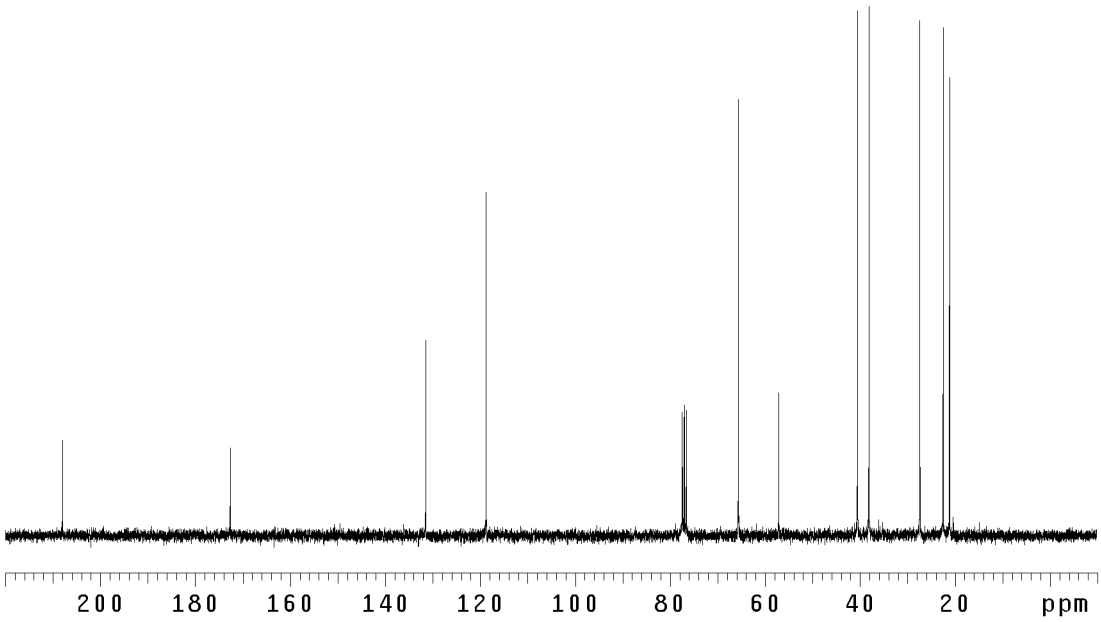


*Figure A3.39 ^{13}C NMR of compound **107** (75 MHz, $CDCl_3$)*

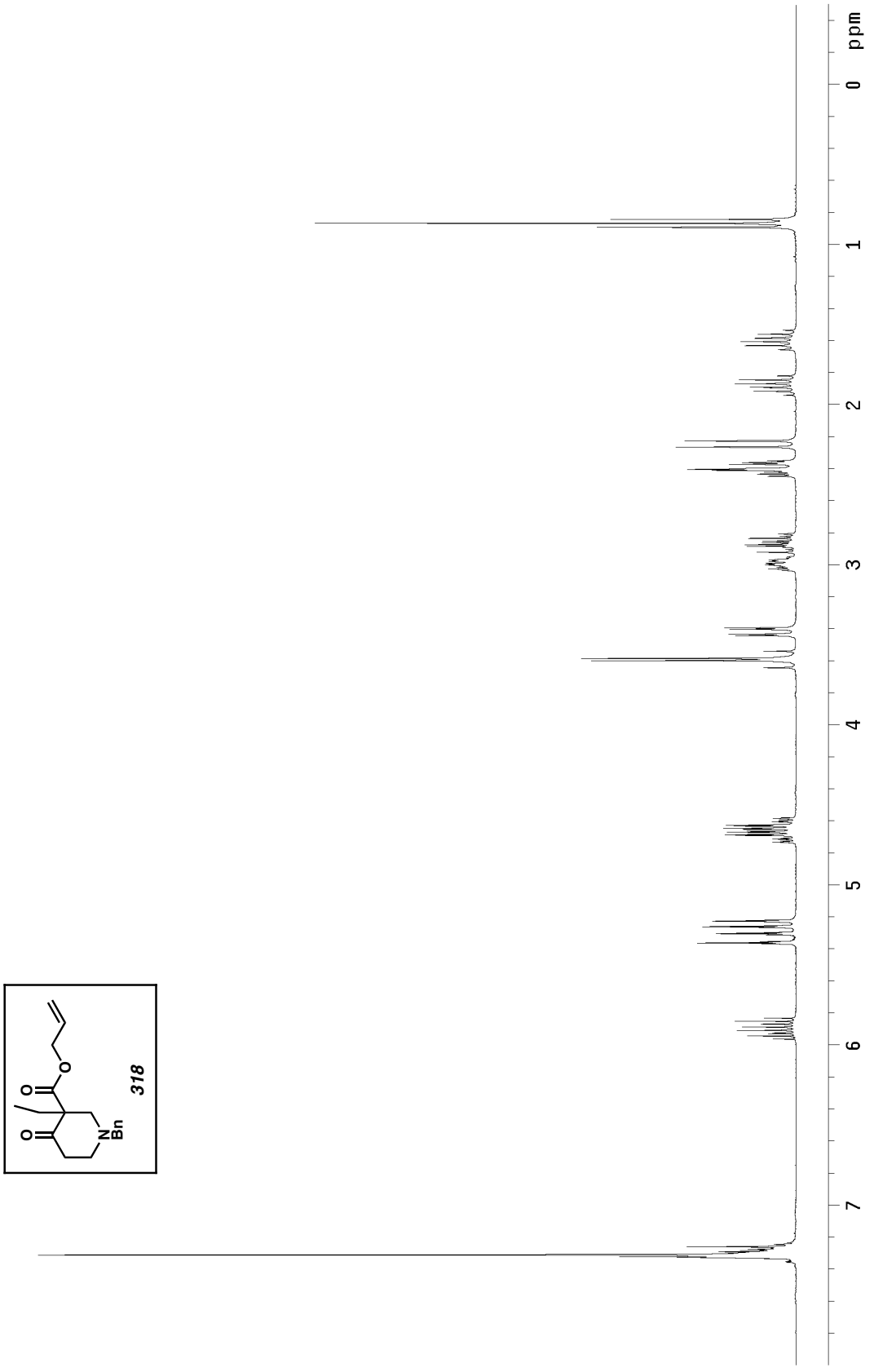


*Figure A3.40 ^1H NMR of compound **318** (300 MHz, $CDCl_3$)*

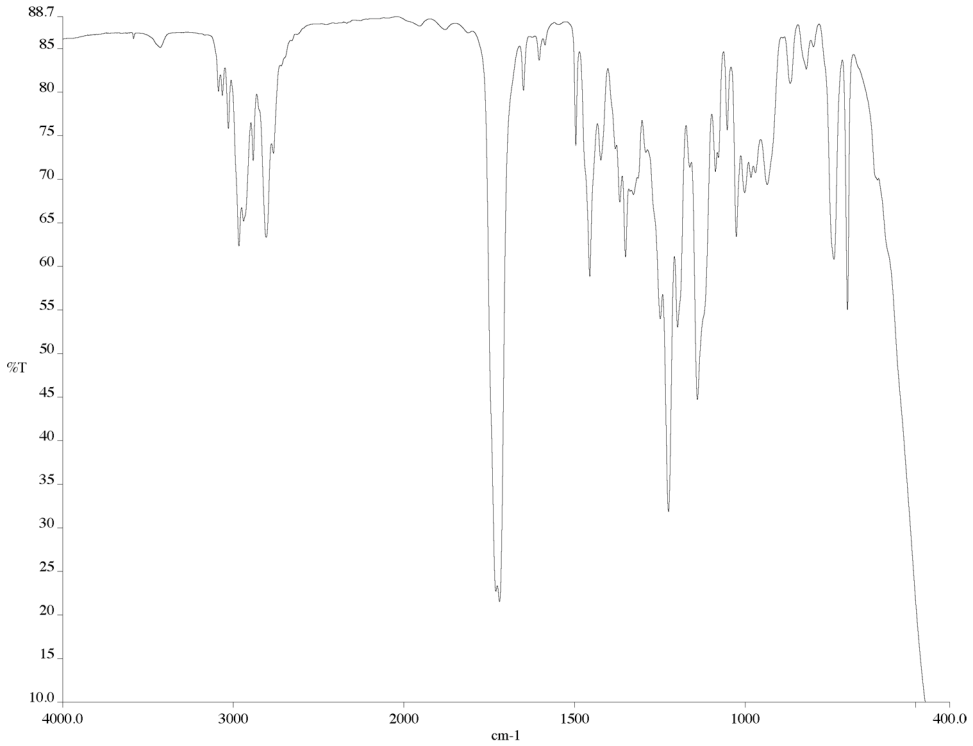


*Figure A3.41 IR of compound **318** (NaCl/film)*

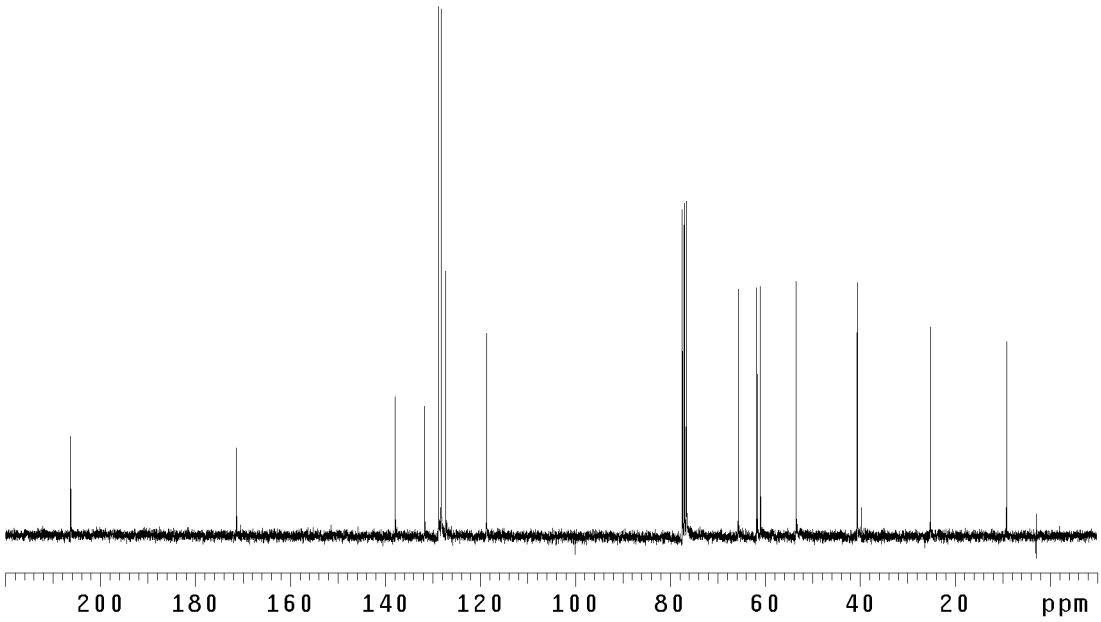


*Figure A3.42 ^{13}C NMR of compound **318** (75 MHz, $CDCl_3$)*

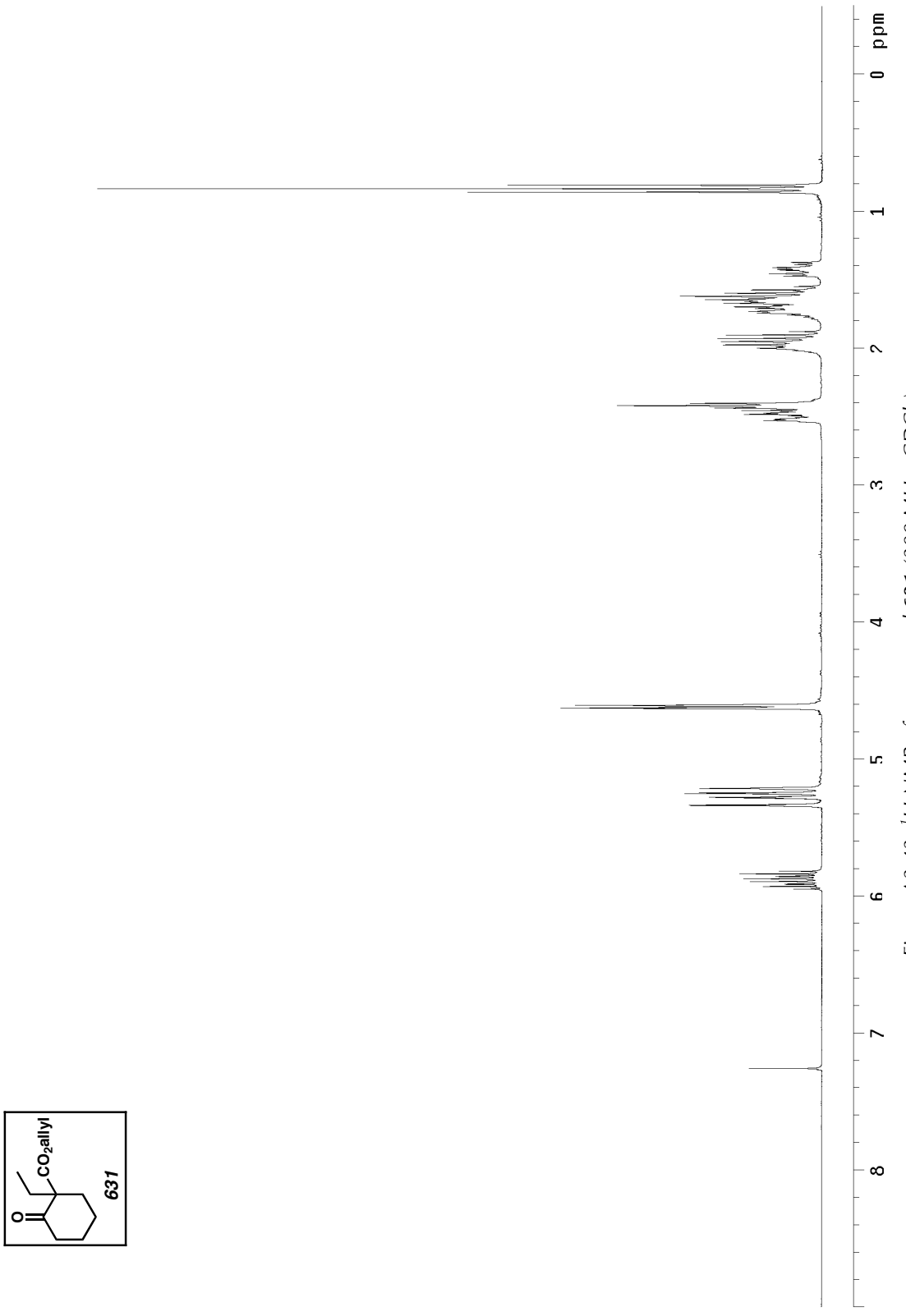


*Figure A3.43 ^{1}H NMR of compound **631** (300 MHz, $CDCl_3$)*

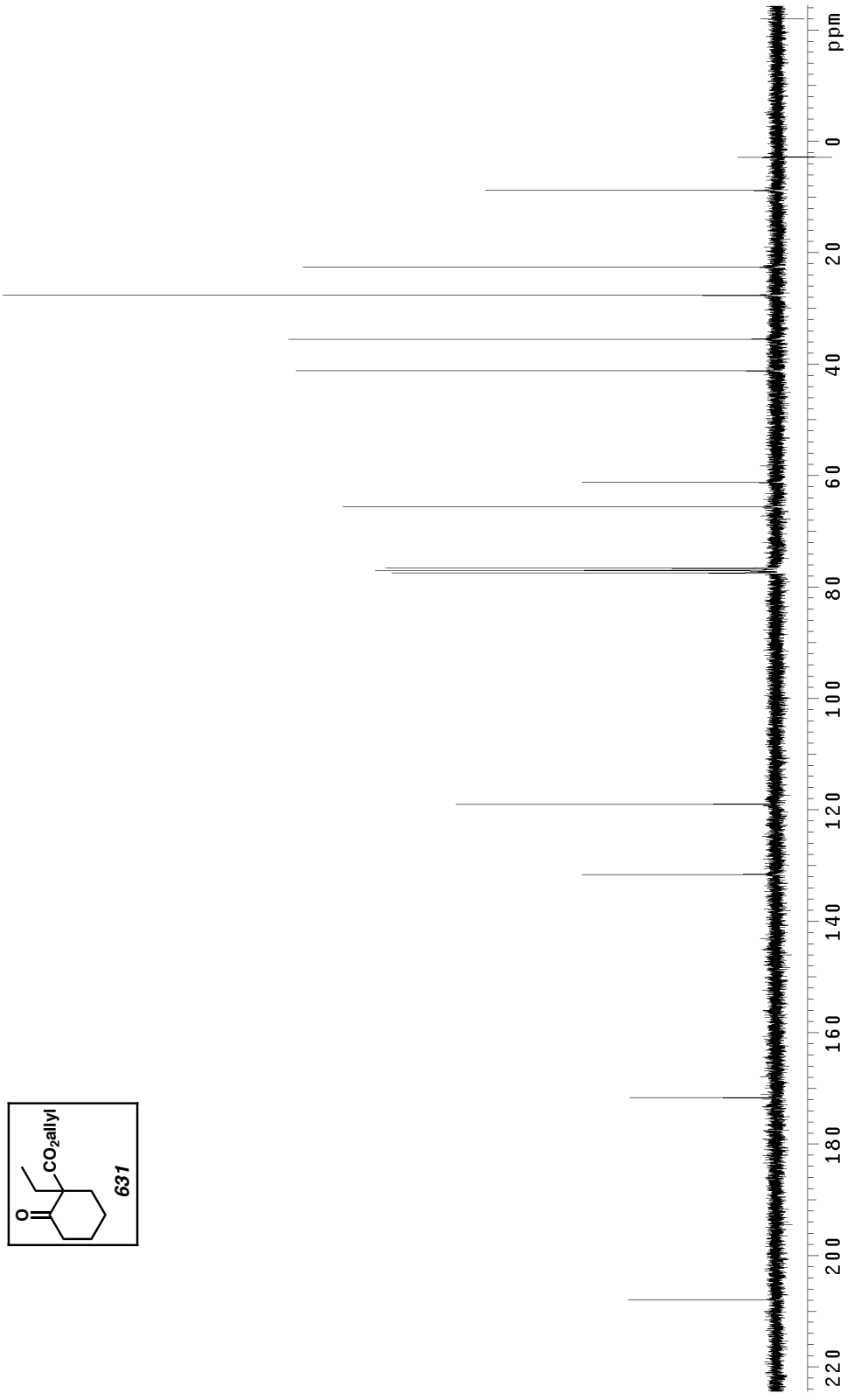


*Figure A3.44 ^{13}C NMR of compound **631** (75 MHz, $CDCl_3$)*

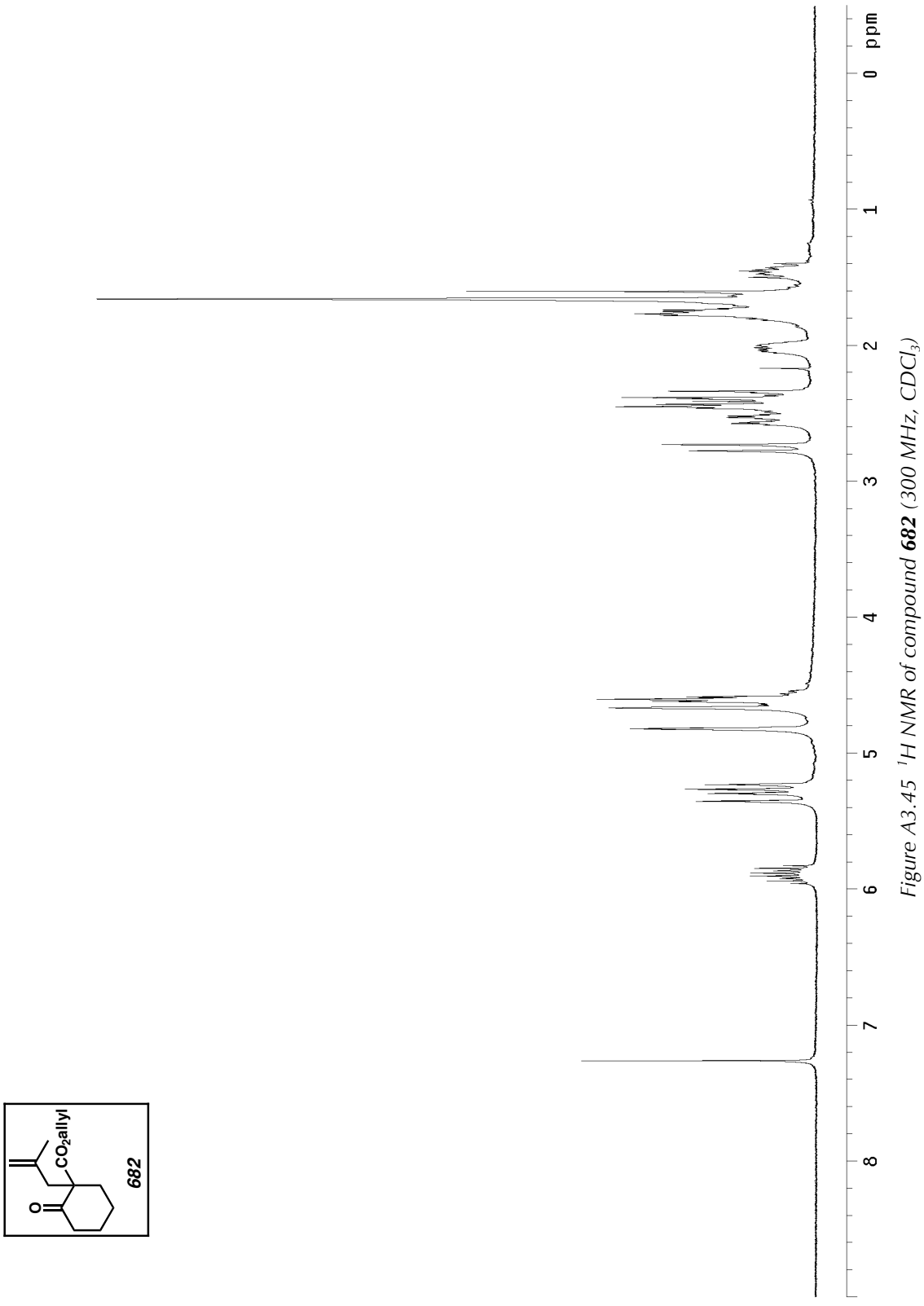


*Figure A3.45 ^1H NMR of compound **682** (300 MHz, $CDCl_3$)*

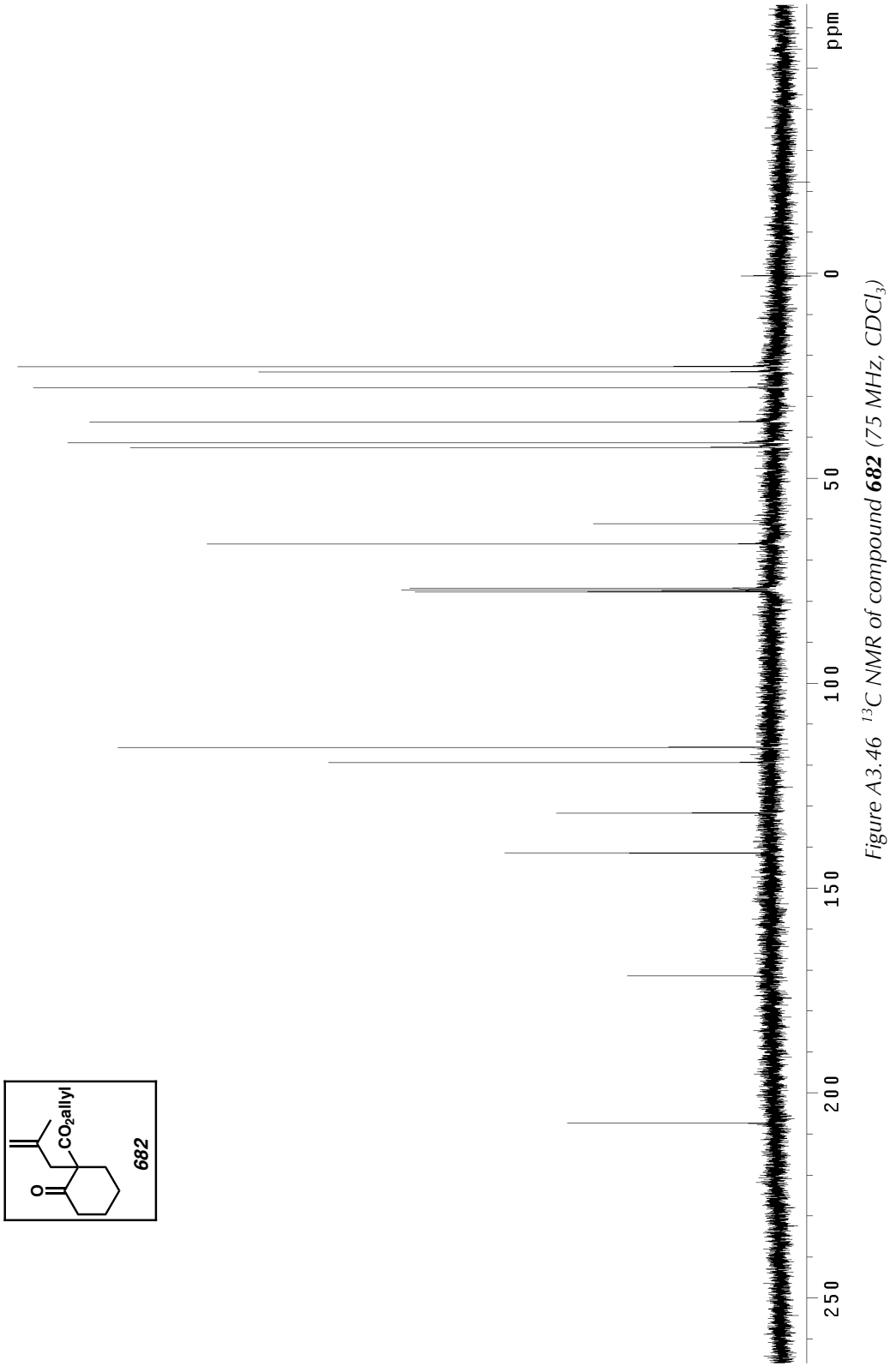


*Figure A3.46 ^{13}C NMR of compound **682** (75 MHz, $CDCl_3$)*

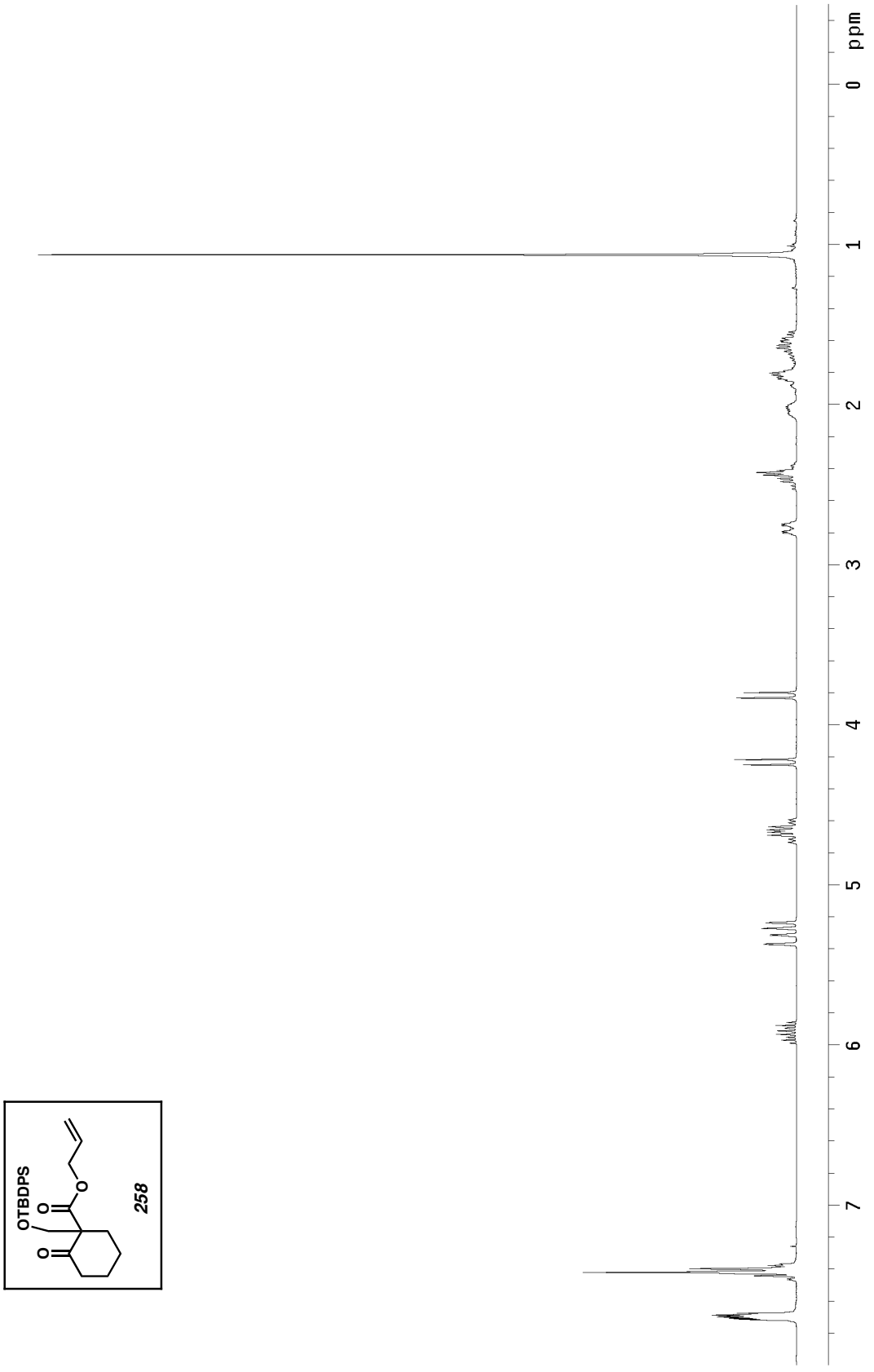


*Figure A3.47 ^{1}H NMR of compound **258** (300 MHz, $CDCl_3$)*

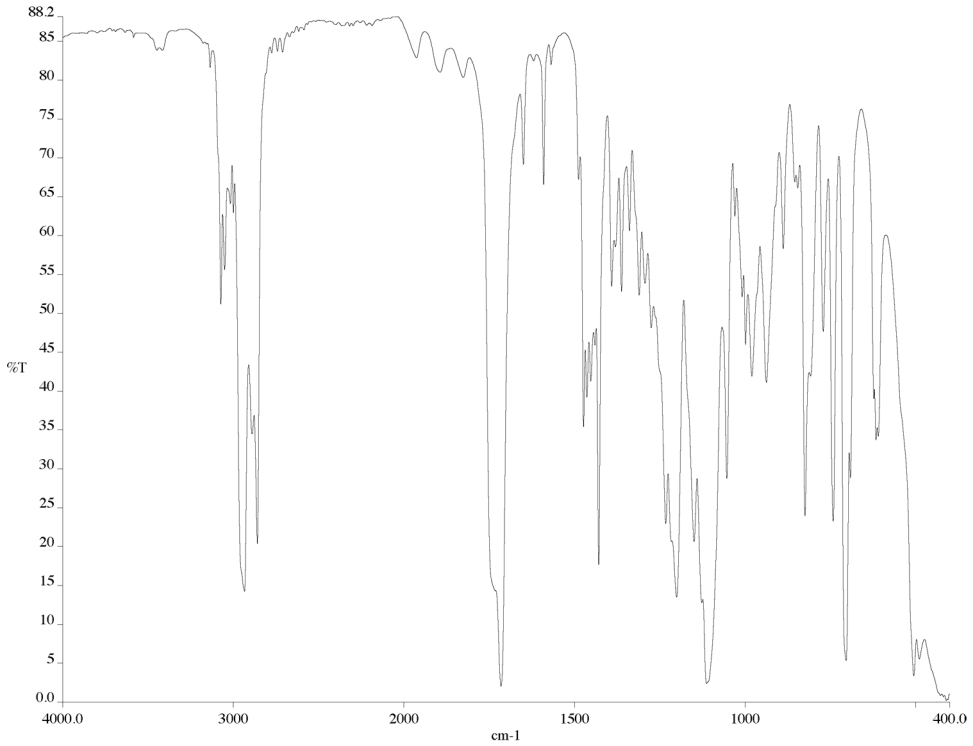


*Figure A3.48 IR of compound **258** (NaCl/film)*

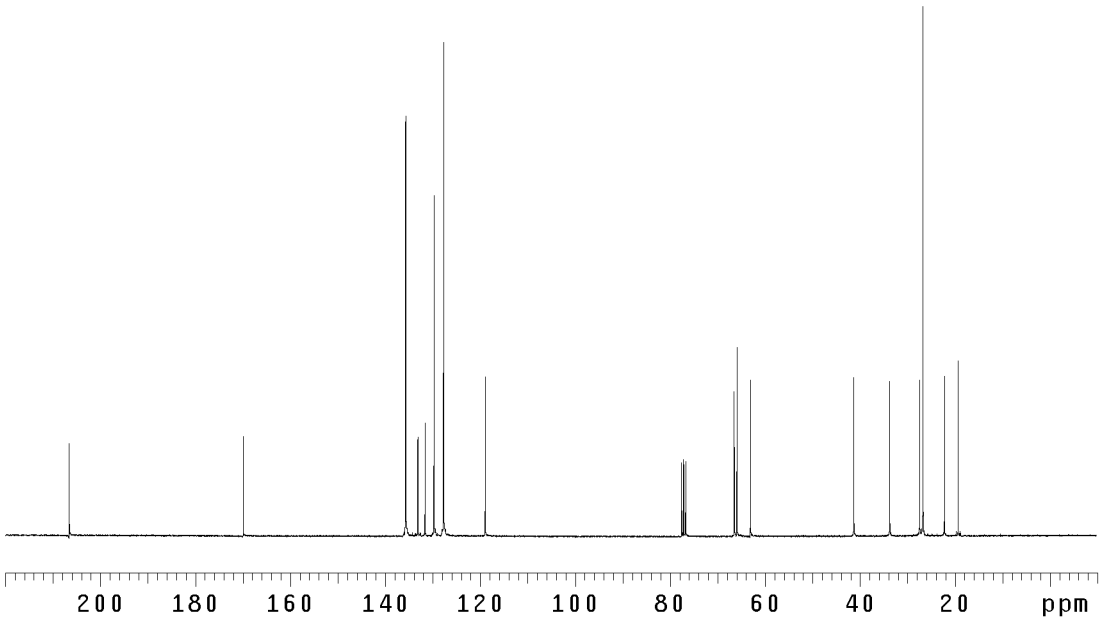


*Figure A3.49 ^{13}C NMR of compound **258** (75 MHz, $CDCl_3$)*

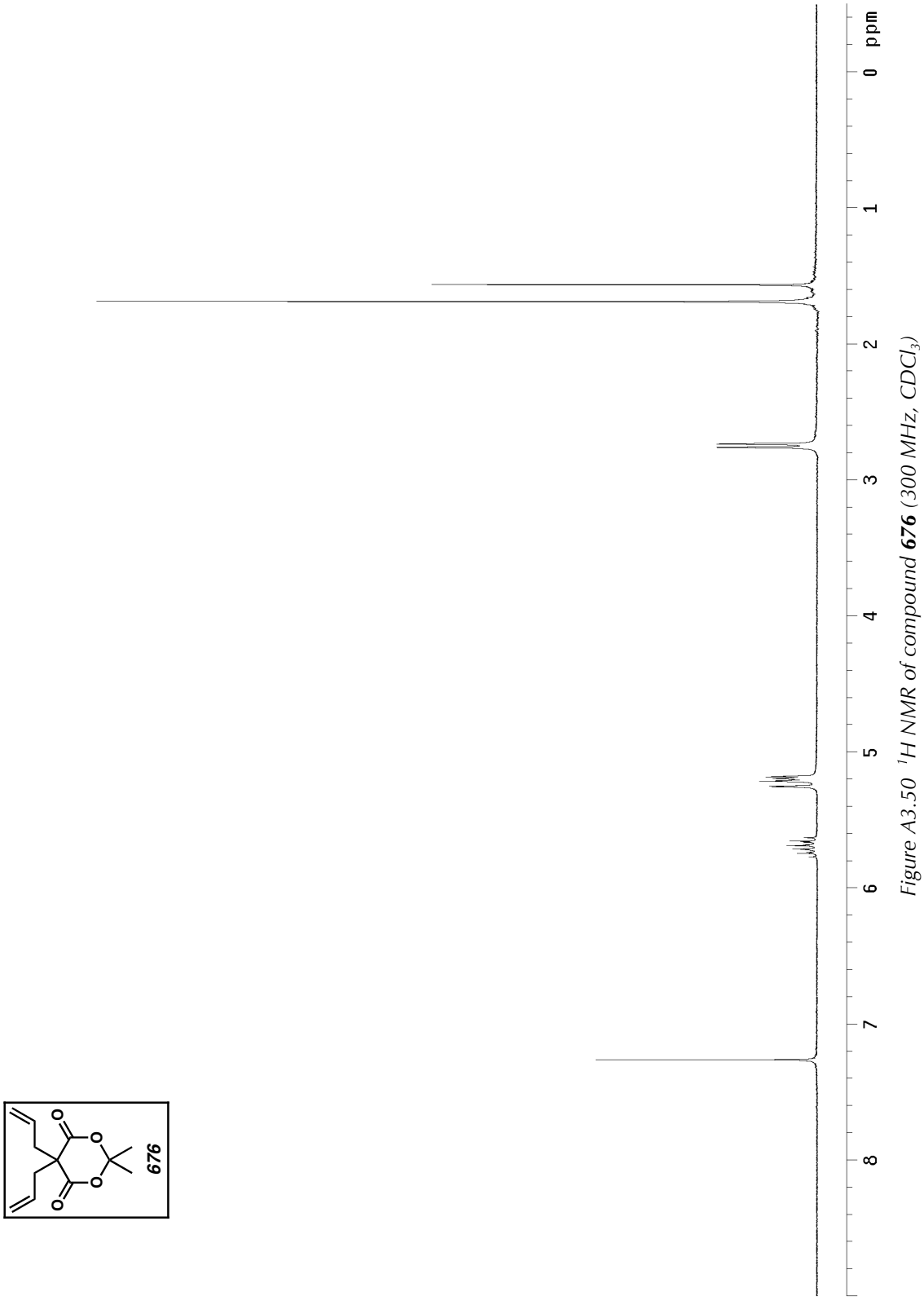


*Figure A3.50 ^1H NMR of compound **676** (300 MHz, $CDCl_3$)*

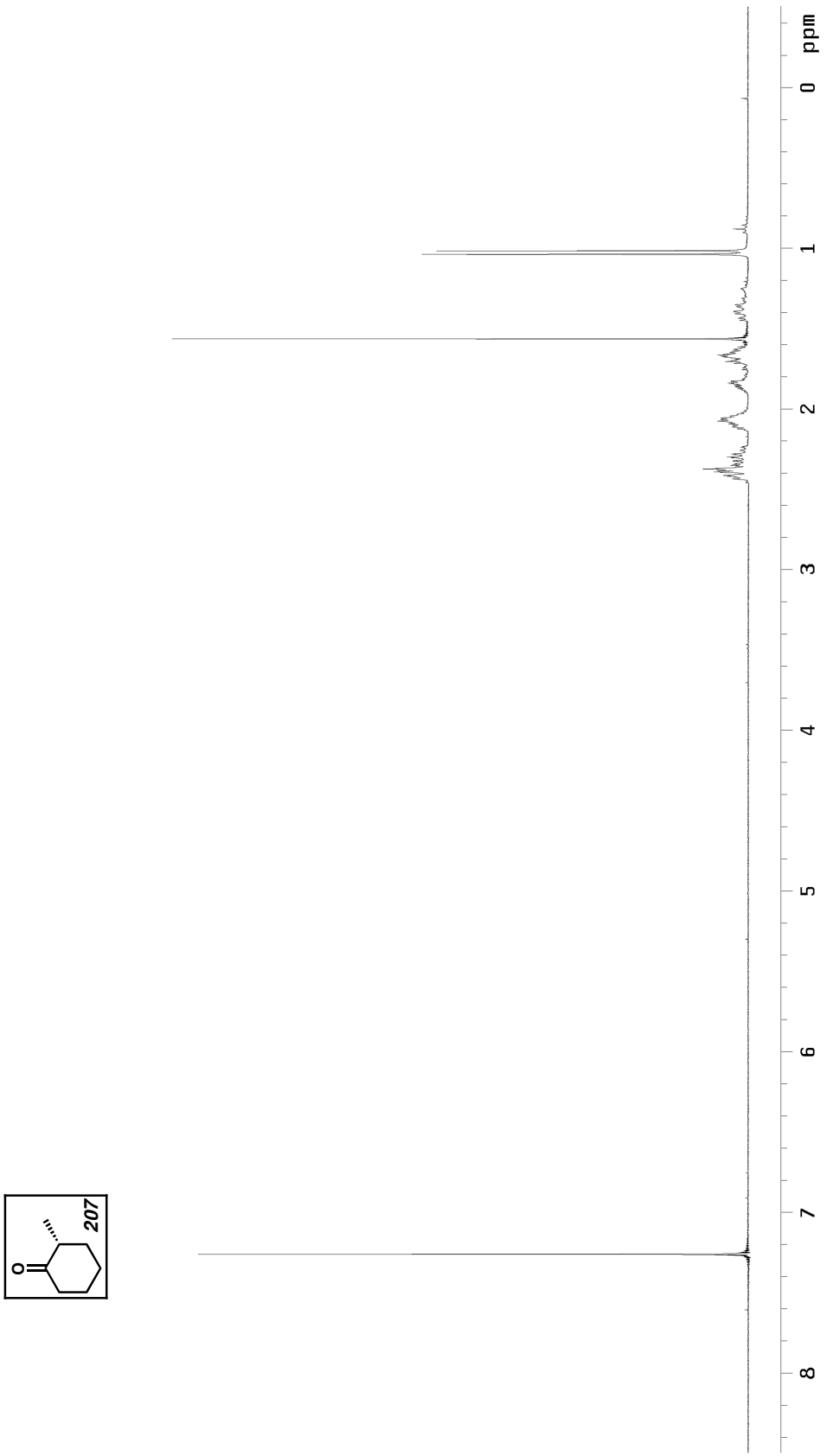


*Figure A3.51 ^1H NMR of compound **207** (300 MHz, $CDCl_3$)*

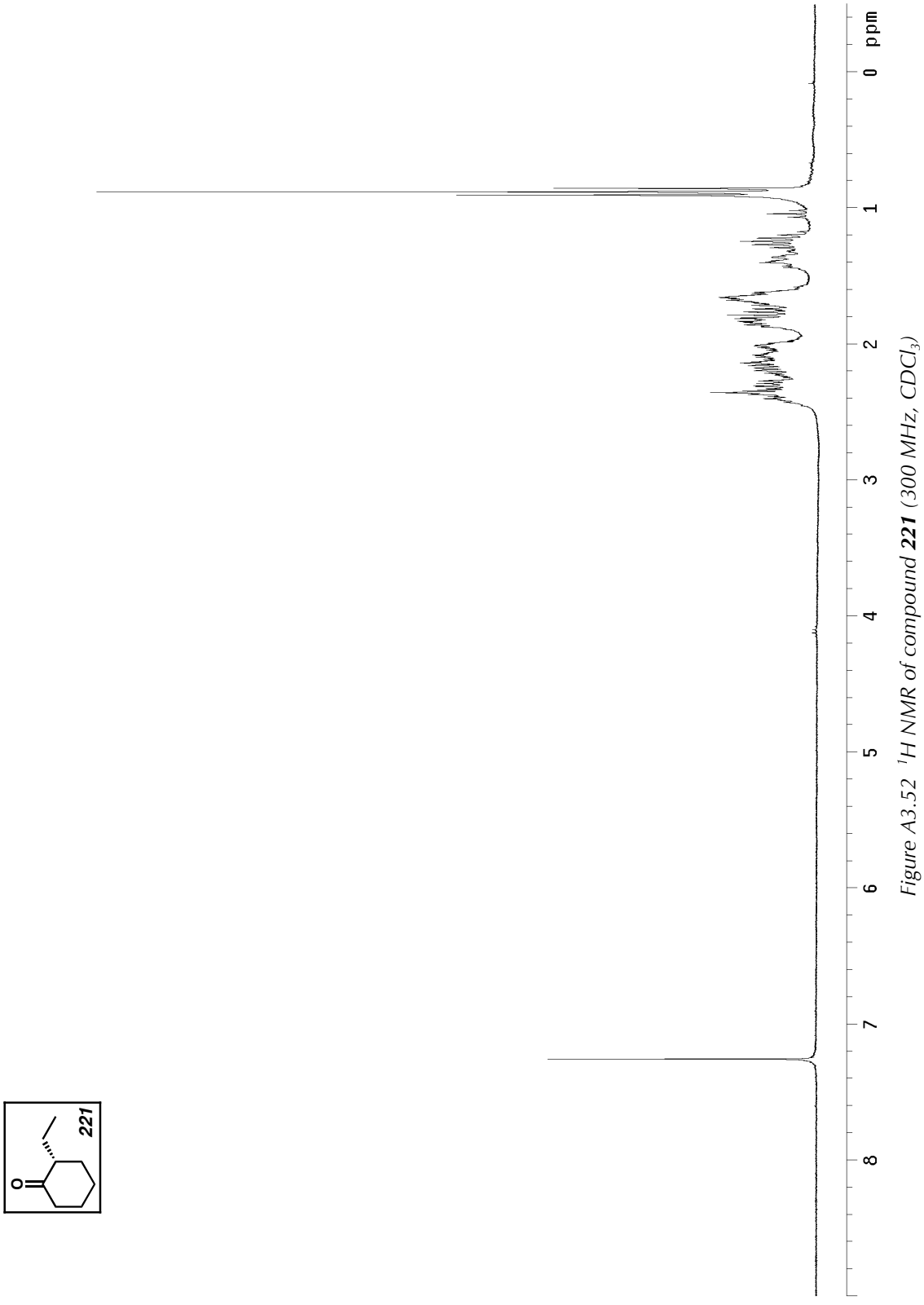


*Figure A3.52 ^1H NMR of compound **221** (300 MHz, $CDCl_3$)*

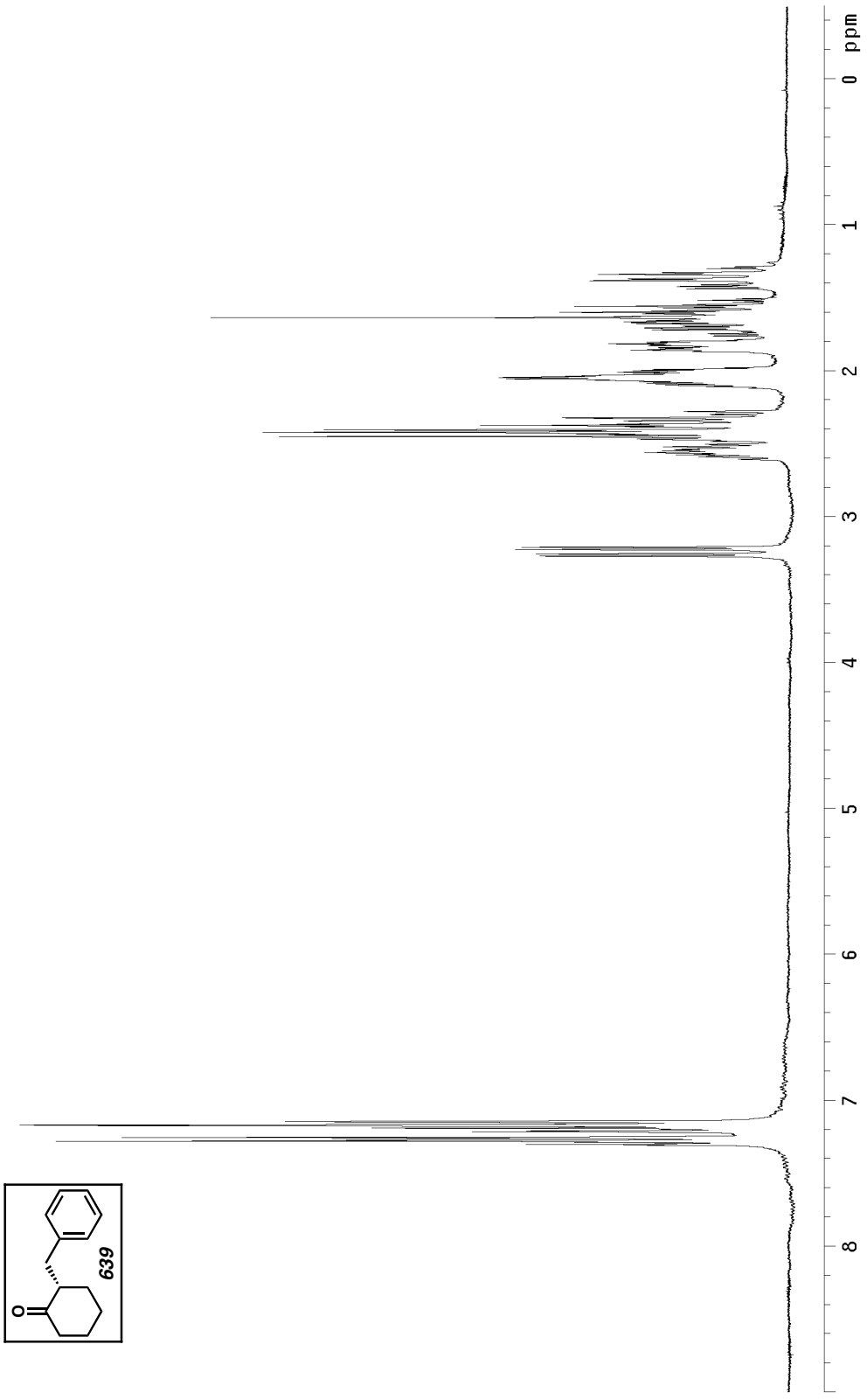


*Figure A3.53 ^1H NMR of compound **639** (300 MHz, $CDCl_3$)*

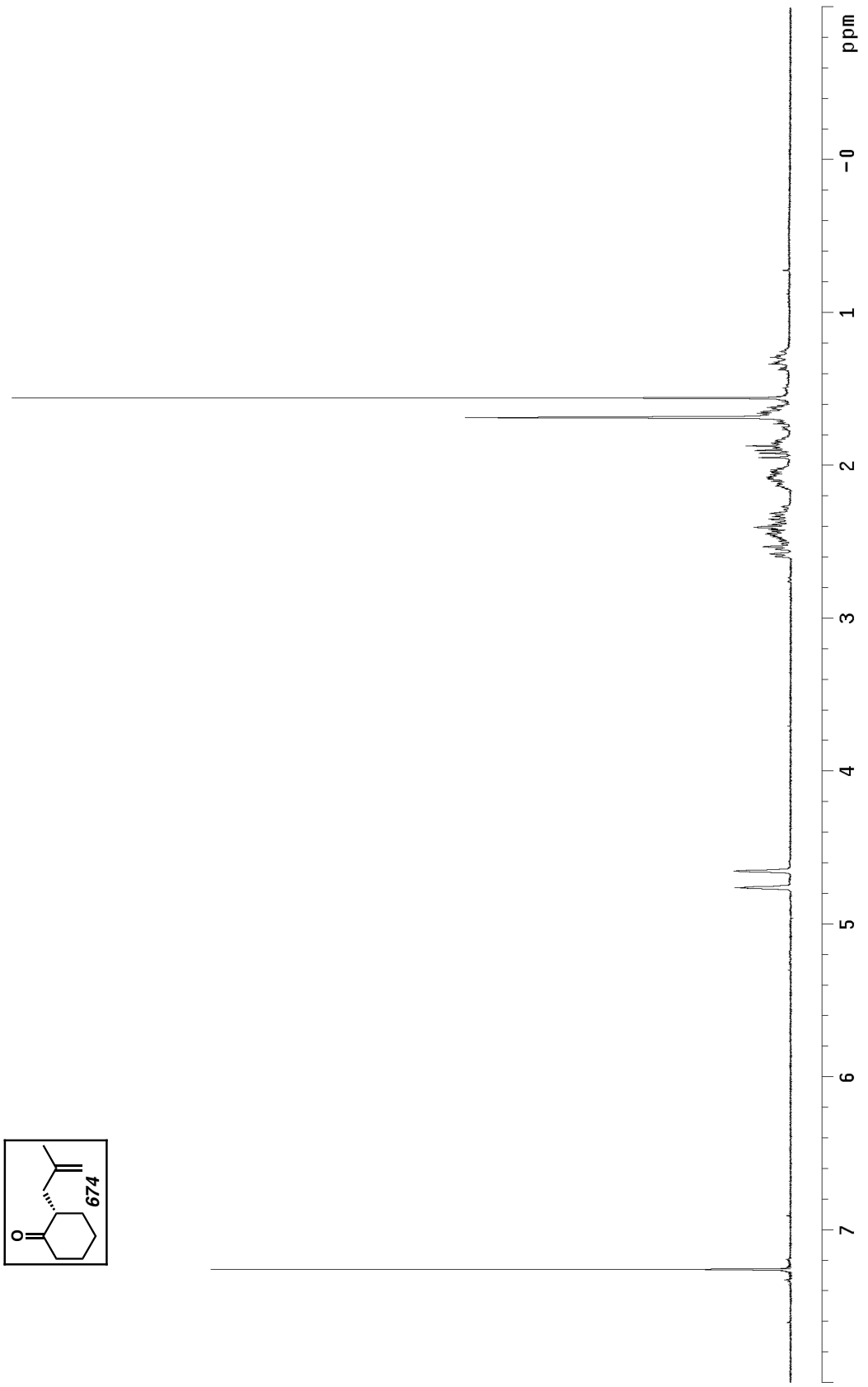


*Figure A3.54 ^{1}H NMR of compound **674** (300 MHz, $CDCl_3$)*

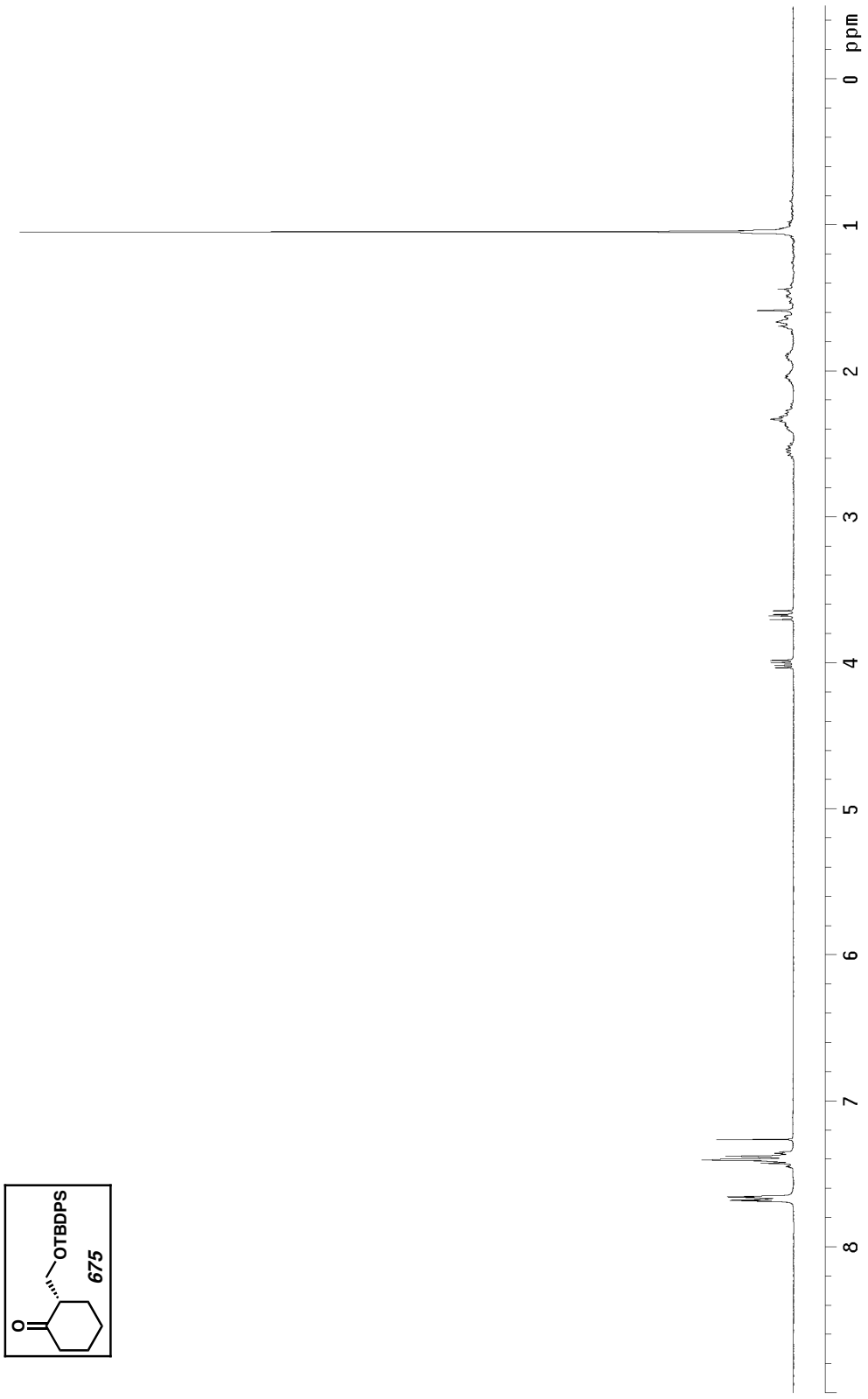


*Figure A3.55 ^1H NMR of compound **675** (300 MHz, $CDCl_3$)*

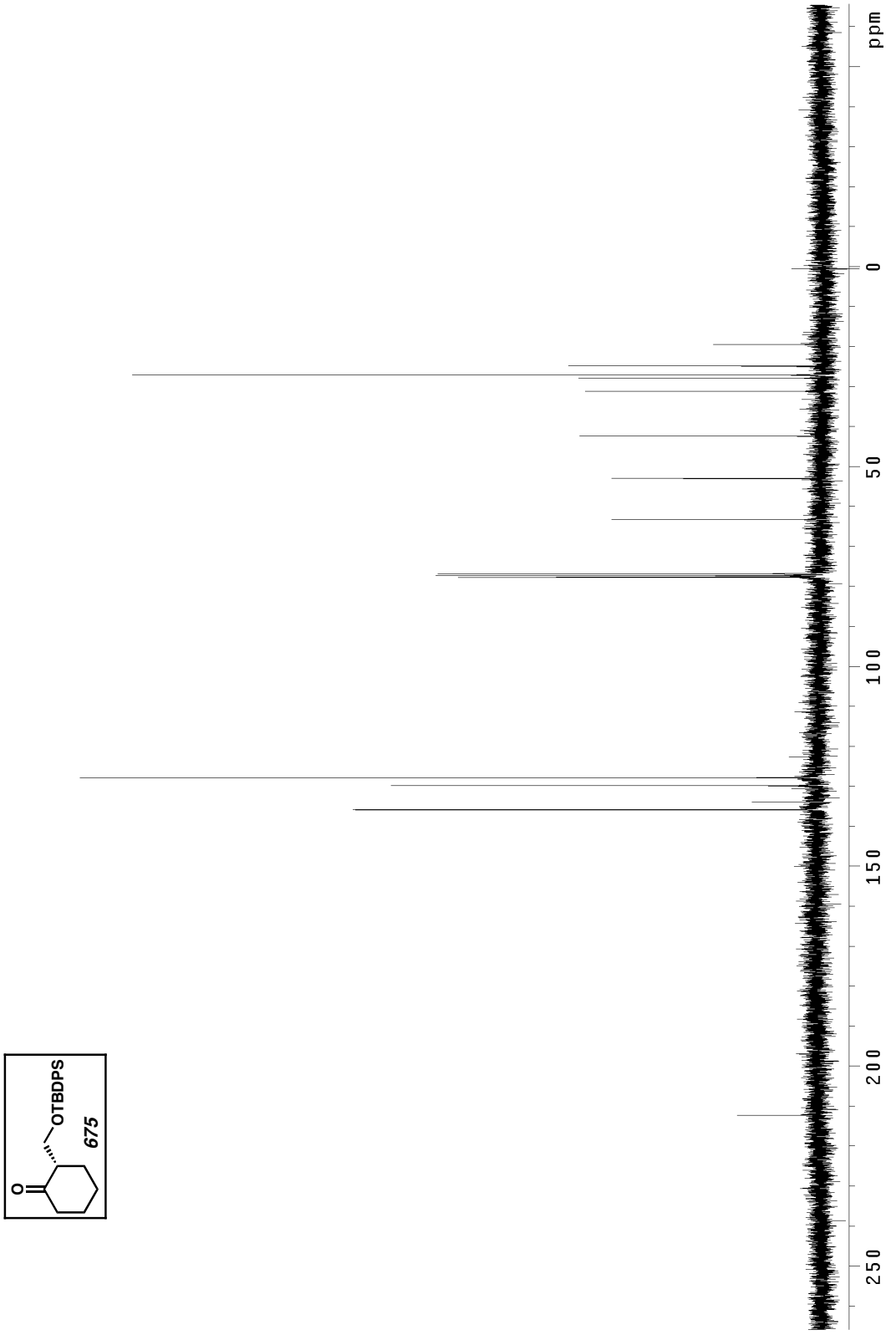


*Figure A3.56 ^{13}C NMR of compound **675** (75 MHz, $CDCl_3$)*

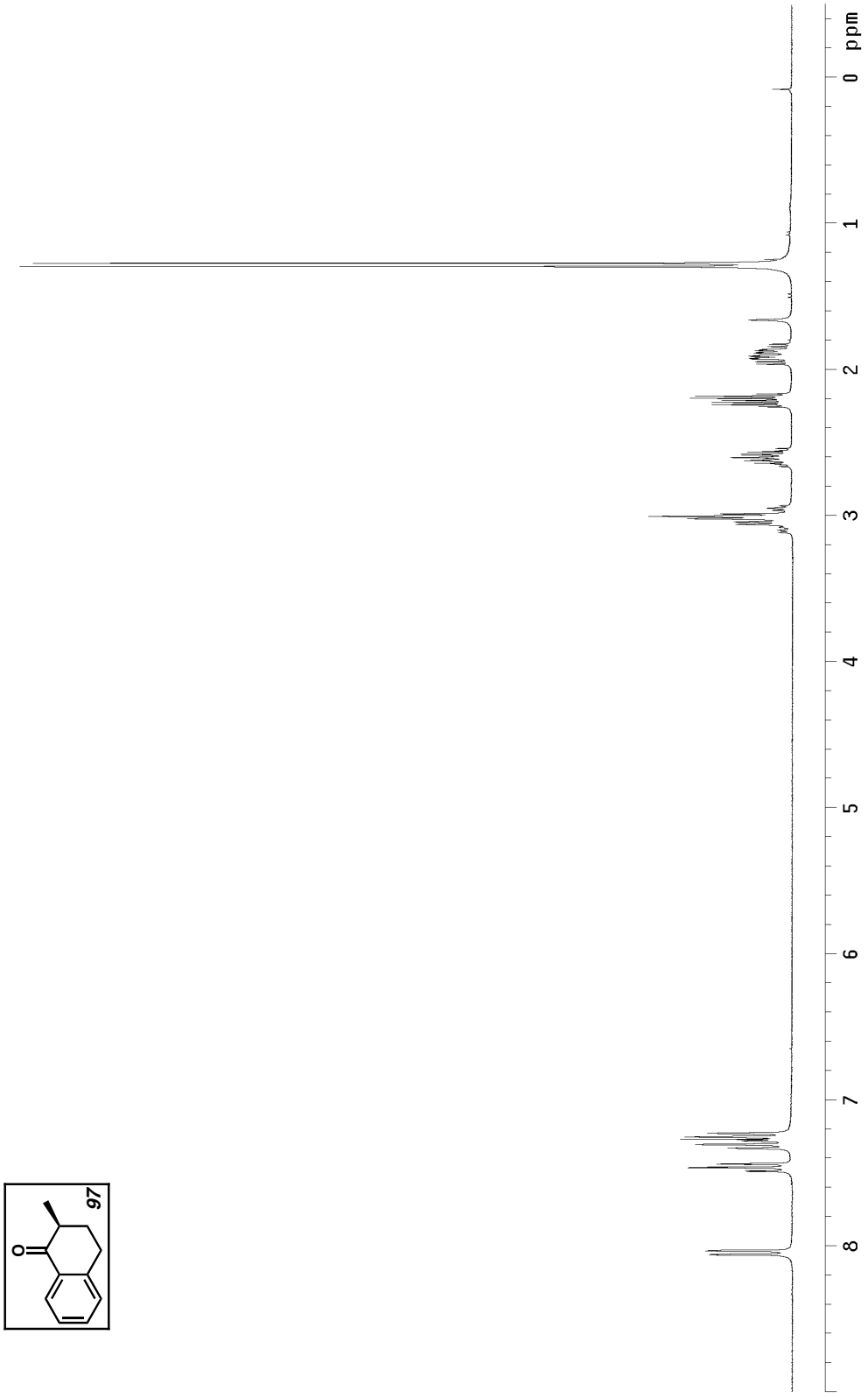


*Figure A3.57 ^1H NMR of compound **97** (300 MHz, $CDCl_3$)*

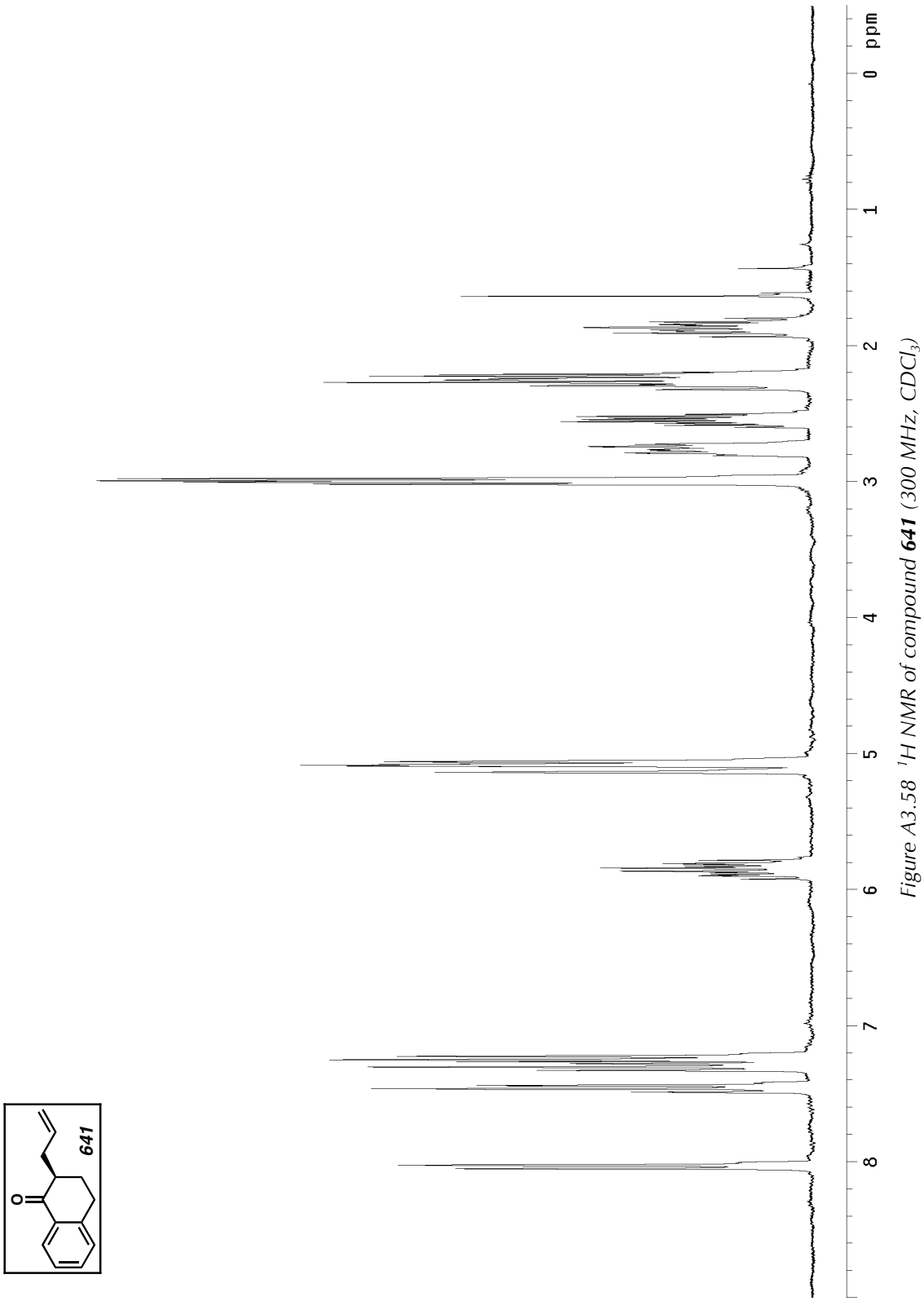


*Figure A3.58 ^1H NMR of compound **641** (300 MHz, $CDCl_3$)*

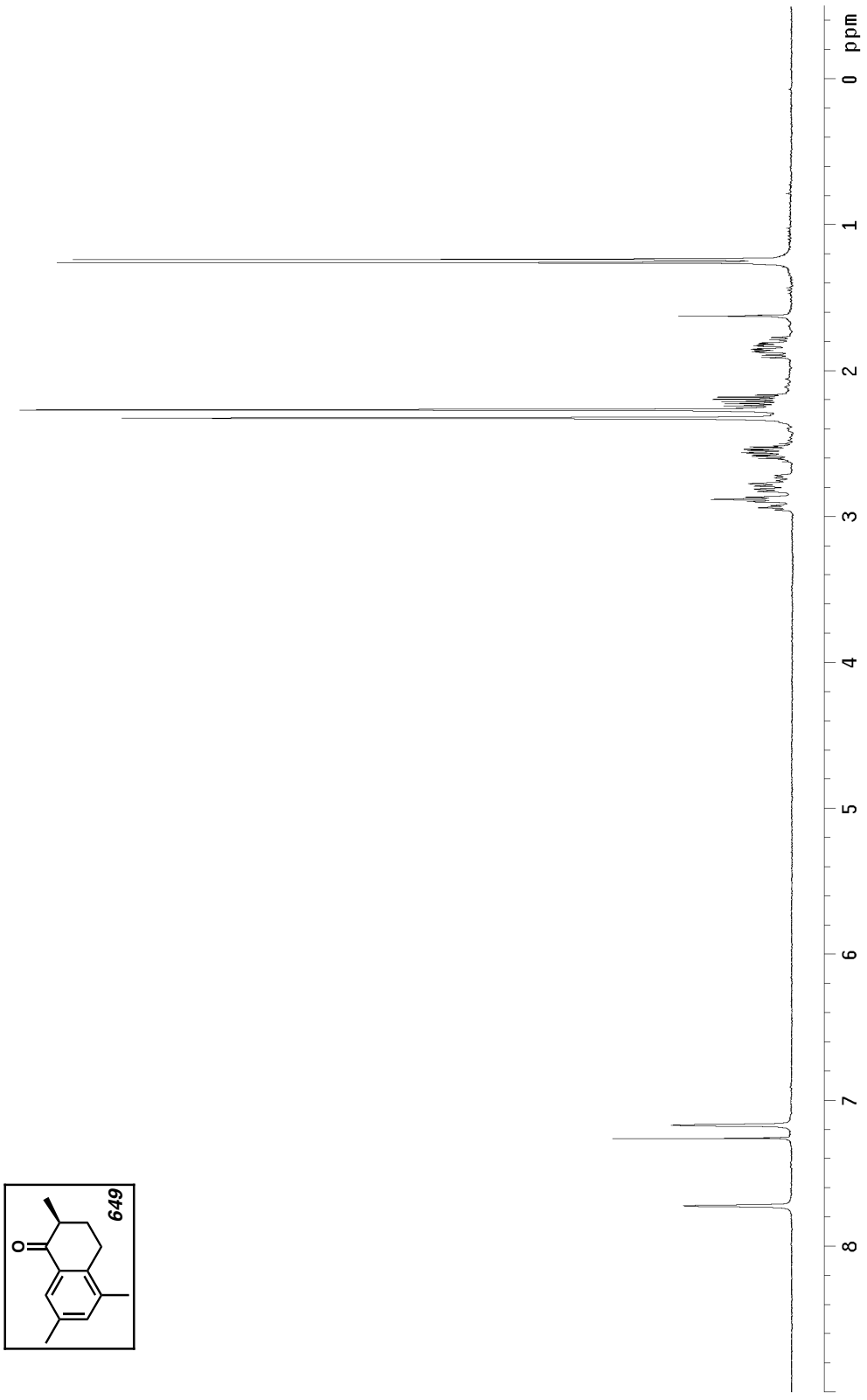


*Figure A3.59 ^1H NMR of compound **649** (300 MHz, $CDCl_3$)*

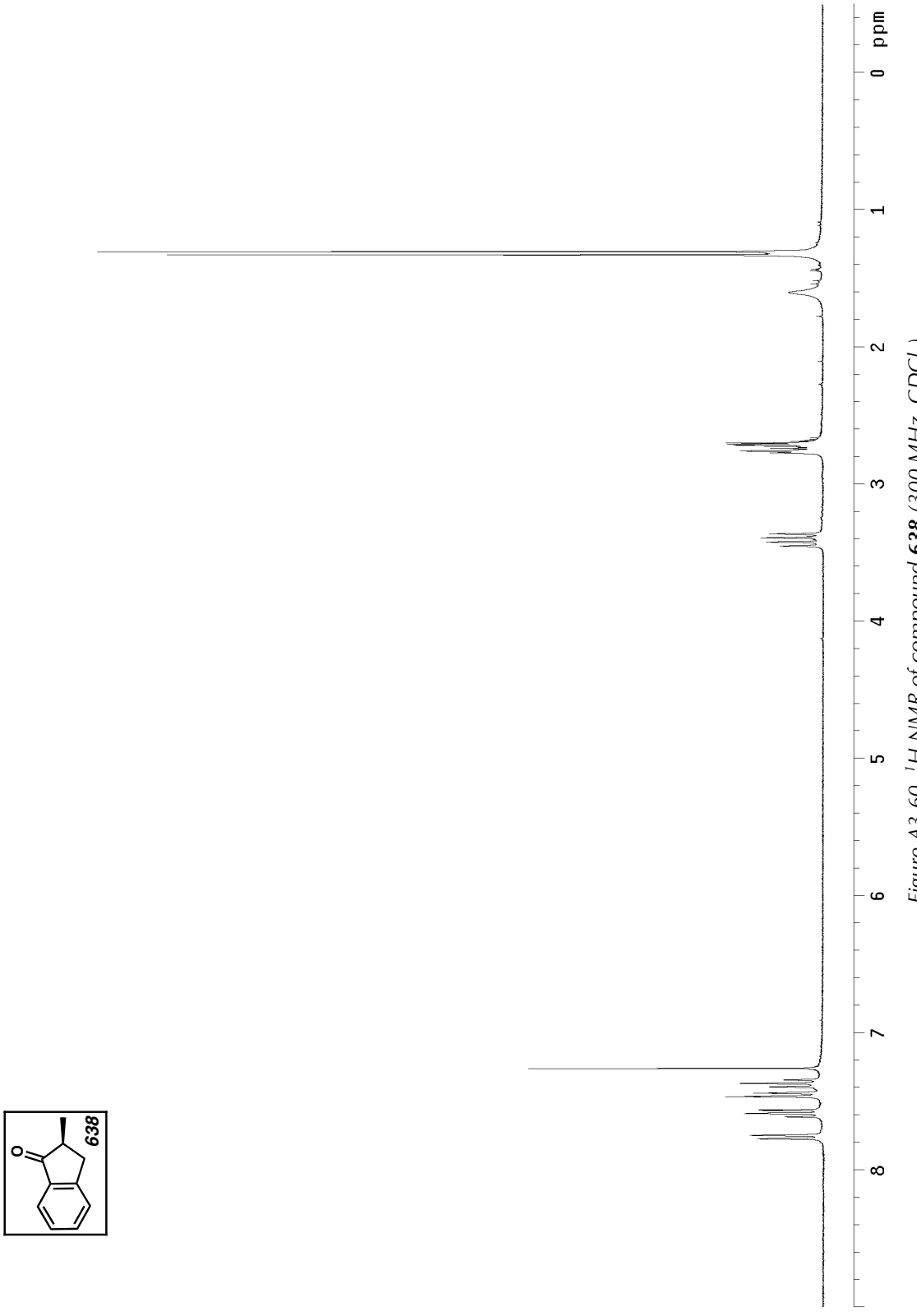


*Figure A3.60 ^1H NMR of compound **638** (300 MHz, $CDCl_3$)*

CHAPTER 8

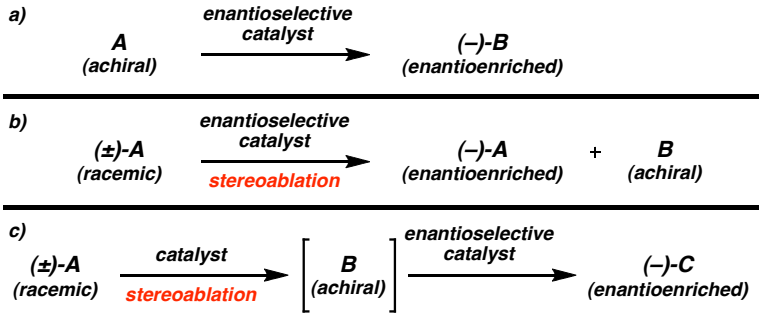
Catalytic Enantioselective Stereoablative Reactions[†]

8.1 INTRODUCTION

Since the inception of enantioselective catalytic methodology, the prevailing strategic approach has relied on inducing chirality into a prochiral atom by the generation of new asymmetric centers or axes (Scheme 8.1). Although this tactic has proven extremely effective, the number of viable prochiral functional groups is relatively limited. An alternative approach to the production of enantioenriched materials is to begin with a racemic mixture and subsequently eliminate the intrinsic stereochemistry from a portion or all of this mixture. The scope of this approach to enantioselective catalysis is as wide as the number of chiral molecules in existence. Although inherently a complexity minimizing process, this approach has proven to be valuable in the synthesis of chiral building blocks and more complex synthetic targets.

[†] This review was written in collaboration with David C. Ebner and a similar version has been published. See: Mohr, J. T.; Ebner, D. C.; Stoltz, B. M. *Org. Biomol. Chem.* **2007**, *5*, 3571–3576.

Scheme 8.1. Strategies for enantioselective catalysis



In 2005, the term "stereoablation" was defined in the context of an enantioconvergent reaction.[1] Our initial definition was "the conversion of a chiral molecule to an achiral molecule," based on the Oxford English Dictionary definition for ablation: "the action or process of carrying away or removing; removal."[2] Upon further consideration of the importance of such methods in enantioselective chemical transformations, we have seen fit to expand the scope of this definition to include reactions where an existing stereocenter in a molecule is destroyed, but the intermediate molecule need not be wholly achiral.[3] This revised definition thereby includes many other important advances. To date, few stereoablative strategies have been exploited for enantioselective catalysis, although notable exceptions include metal π-allyl alkylations[4] and many dynamic kinetic resolutions.[5] In this chapter, recent examples of novel approaches to asymmetric catalytic methods for stereoablation will be discussed. These chemistries will demonstrate that this is an important, though underutilized, method of asymmetric synthesis.[6]

When considering catalytic enantioselective stereoablative reactions, two possible regimes arise: one in which the stereoablative step is the enantioselective step (Scheme 8.1b), and one in which stereoablation precedes the enantioselective step (Scheme 8.1c). In the first case, a catalyst must selectively react with one enantiomer or enantiotopic

group of the substrate to provide enantioenrichment. In the second case, a nonselective stereoablation is required before the enantioselective step.

8.2 EXAMPLES OF STEREOABLATIVE ENANTIOSELECTIVE REACTIONS

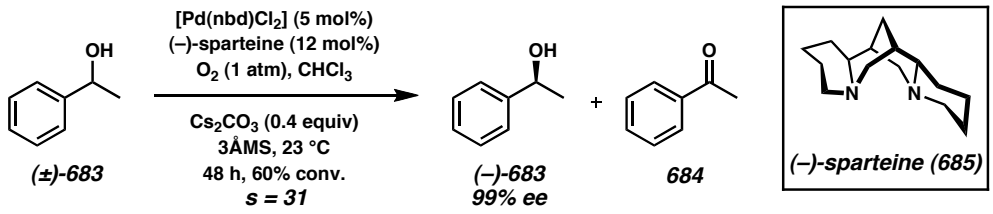
8.2.1 KINETIC RESOLUTIONS

8.2.1.1 OXIDATION OF RACEMIC ALCOHOLS

Kinetic resolution is of the former type, selectively transforming one enantiomer of a racemic mixture to product (cf. Scheme 8.1b). In addition to making enantiomer isolation a trivial process, stereoablative approaches often have the added capability of converting the achiral product back into a racemic starting material mixture by a relatively straightforward procedure. Recycling this material minimizes the waste common to many kinetic resolutions due to discard of the undesired enantiomer.

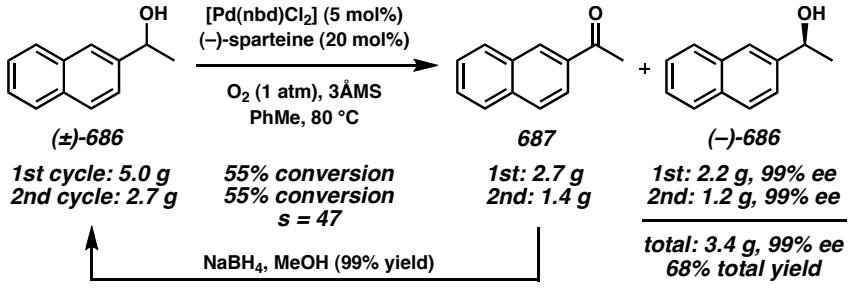
Recently, the Stoltz laboratory has reported an oxidative kinetic resolution (OKR) of secondary alcohols (Scheme 8.2).[7,8,9,10] Utilizing molecular oxygen as the terminal oxidant, [Pd(nbd)Cl_2] and (–)-sparteine (**685**) catalyze the oxidation of alcohol (±)-**683** to achiral ketone **684**, leaving unreacted alcohol (–)-**683** of high ee. Selective stereoablation by β-hydride elimination of a Pd-alkoxide to form product ketone has been shown to be enantiodetermining by extensive mechanistic[7d,8] and computational[7f] studies. To date, a wide variety of secondary alcohols have been successfully resolved with this catalyst system.

Scheme 8.2. Stoltz' oxidative kinetic resolution of secondary alcohols



Additionally, ketone **687**, obtained in the resolution of alcohol (±)-**686**, can be recycled by reduction to racemic (±)-**686** in quantitative yield, allowing greater than 50% overall yield of the enantioenriched alcohol after a second resolution (Scheme 8.3).

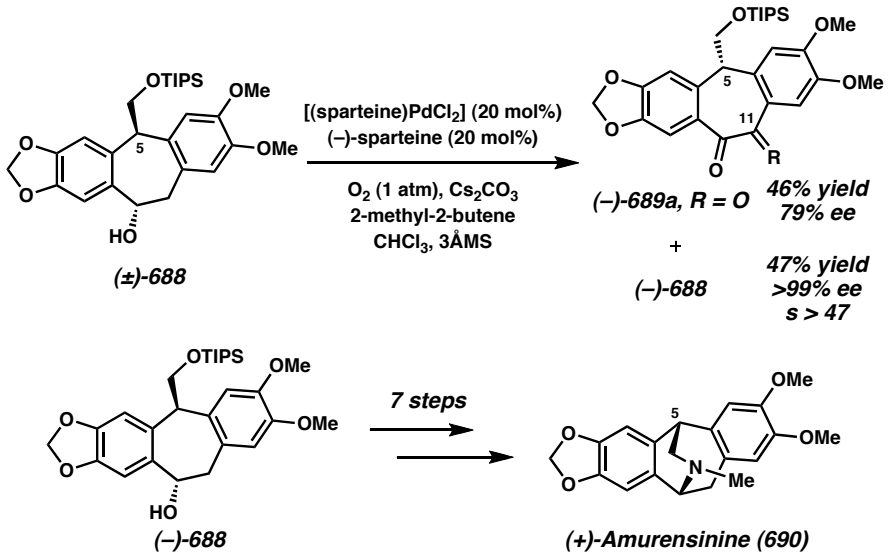
Scheme 8.3. Stoltz' stereoablative kinetic resolution with recycle



When other stereocenters are present in the alcohol, enantioenriched ketones can be obtained. In the Stoltz synthesis of (+)-amurensinine (**690**), racemic alcohol (±)-**688** was resolved successfully using the [(sparteine)$PdCl_2$] catalyst system (Scheme 8.4).[11] In addition to highly enantioenriched alcohol (–)-**688**, diketone (–)-**689a** was obtained in 79% ee. This diketone presumably arises from overoxidation of the initial ketone product ((+)-**689b**, R = H_2) in the presence of O_2. In fact, the monoketone (+)-**689b** could be isolated with 77% ee at shorter reaction times, albeit with lower ee of alcohol (–)-**688**. Importantly, the products (–)-**689a** and (+)-**689b** have the opposite configuration at C5, potentially providing access to (–)-amurensinine (**690**). In general, OKR of alcohols with

multiple stereocenters can provide enantioenriched product ketones as well as alcohols, opening the door to enantiodivergent synthetic strategies.[12]

Scheme 8.4. OKR in the Stoltz synthesis of (+)-amurensinine

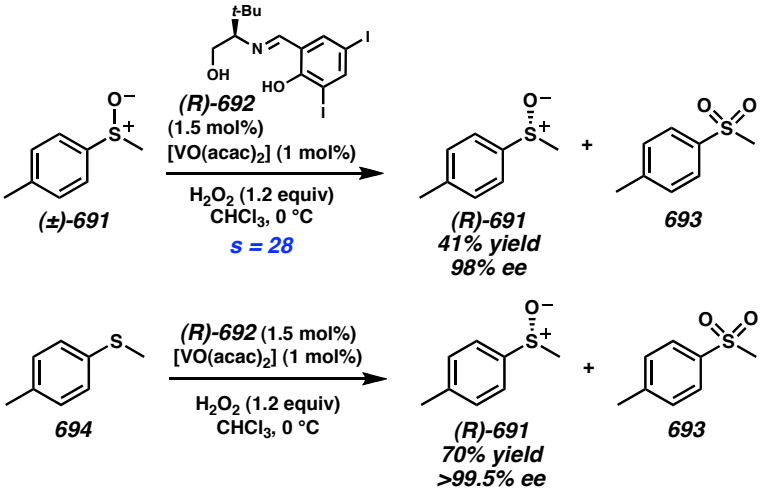


8.2.1.2 OXIDATION OF SULFOXIDES AND SULFIDES

Oxidative resolution of sulfoxides has also been demonstrated. Unlike alcohol oxidation, in which C–H bond *cleavage* is stereoablative, in sulfoxide oxidation S–O bond *formation* leads to stereoablation. Of particular note is an example by Jackson and co-workers. It was found that a racemic mixture of sulfoxides was effectively resolved with a vanadium catalyst and diiodide ligand (*R*)-**692** (Scheme 8.5).[13] The high selectivity in sulfoxide oxidative kinetic resolution led them to investigate a tandem enantioselective sulfide oxidation followed by sulfoxide resolution. Treatment of sulfide **694** with their oxidative conditions provided sulfoxide (*R*)-**691** in 70% yield and >99.5% ee, along with achiral sulfone **693**. The combined effect of the two processes allows the synthesis of highly enantioenriched sulfoxides with higher yields than a typical kinetic

resolution. Additionally, coupling two enantioselective reactions has the potential to bring poorly selective methods into the synthetically useful range because of the enhanced yield and product enantiopurity relative to the individual steps.

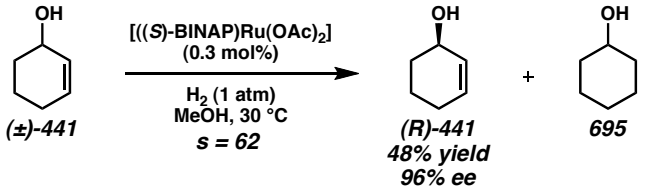
Scheme 8.5. Jackson's oxidation of sulfoxides and sulfides



8.2.1.3 HYDROGENATION OF ALKENES

An unusual example of stereoablative kinetic resolution has been reported by Noyori and co-workers.[14] Hydrogenation of allylic alcohols with chiral catalyst [((*S*)-BINAP)Ru(OAc)$_2$] results in kinetic resolution by symmetrizing one enantiomer of substrate (Scheme 8.6). This reductive kinetic resolution (RKR) is capable of resolving racemic alcohols such as (±)-**441** with exceptionally high selectivity factors, providing achiral alcohol **695** as the by-product. Although (*R*)-**441** is obtained in high ee, there is currently no simple, direct method for recycling **695** back to (±)-**441**. Nonetheless, this RKR process provides a complementary method to the previously described OKR, using a reductive gas instead of an oxidative gas.

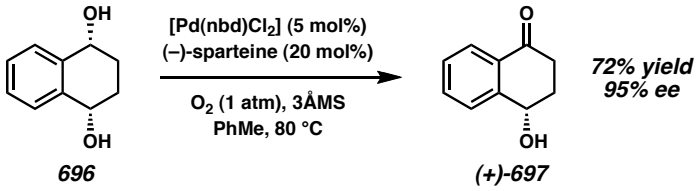
Scheme 8.6. Noyori's reductive kinetic resolution



8.2.2 DESYMMETRIZATIONS

In addition to by-product recycling, greater than 50% yield in a stereoablative process can be achieved by performing a desymmetrization. Such reactions utilize substrates that contain two enantiotopic functional groups, one of which selectively reacts with a chiral catalyst. Stoltz and Ferreira have reported a desymmetrization of meso diol **696** using their Pd-catalyzed oxidation conditions to obtain ketoalcohol (+)-**697** in 72% yield with 95% ee (Scheme 8.7).[7a] A similar desymmetrization strategy has been employed in the synthesis of lobeline.[7i]

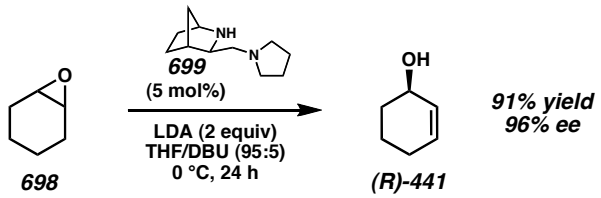
*Scheme 8.7. Stoltz' desymmetrization of meso diol **696***



Catalytic enantioselective processes have also been employed in the desymmetrization of epoxides. Andersson and Södergren have reported the use of chiral diamine **699** in the rearrangement of epoxides to allylic alcohols.[15] Treatment of cyclohexene oxide (**698**) with 5 mol% **699** in the presence of LDA as the stoichiometric base provided (*R*)-2-cyclohexenol (**441**) in 96% ee (Scheme 8.8). Selective removal of

one of the enantiotopic protons in the starting material accompanies destruction of one of the stereocenters of the epoxide in the elimination step. Although there have been several other examples of catalytic asymmetric epoxide desymmetrization, this system has the largest reported substrate scope, with five allylic alcohols formed with good to excellent ee.

Scheme 8.8. Andersson's epoxide desymmetrization



8.2.3 ENANTIOCONVERGENT REACTIONS

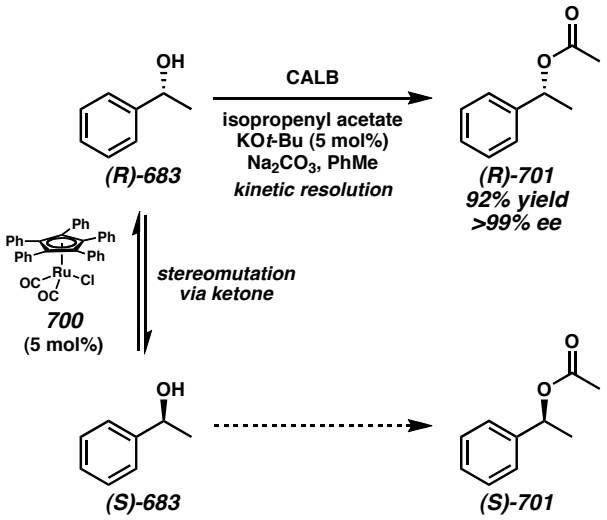
A second type of stereoablative enantioselective catalysis consists of stereoablation followed by enantioselective bond formation. In these enantioconvergent processes, both enantiomers of a racemic mixture are converted to an achiral intermediate, which is converted subsequently to an enantioenriched product in a separate process (Scheme 8.1c). It is critical to avoid kinetic resolution in the stereoablative step in order to ensure good yield in a reasonable time.

8.2.3.1 DYNAMIC KINETIC RESOLUTION

A prominent type of enantioconvergent catalysis is dynamic kinetic resolution (DKR) of racemic alcohols. A particularly elegant system was developed by Bäckvall and co-workers, wherein an achiral metal catalyst (**700**) capable of rapid stereomutation via the

corresponding ketone was coupled with selective acylating enzyme CALB (Scheme 8.9).[16] The rates of these two simultaneous reactions are critical to the success of the process. The rate of stereomutation must be considerably greater than the rate of acylation in order to maintain an optimal 1:1 mixture of alcohol enantiomers for the enzymatic resolution. Although kinetic resolution by acylation is a common approach to obtaining enantioenriched alcohols, the pairing of the stereoablative Ru catalyst and the acylation enzyme increases the overall efficiency of the reaction, as it allows yields greater than 50%. However, systems such as this are rare because the two concurrent catalytic reactions must tolerate one another.

Scheme 8.9. Bäckvall's dynamic kinetic resolution of alcohols

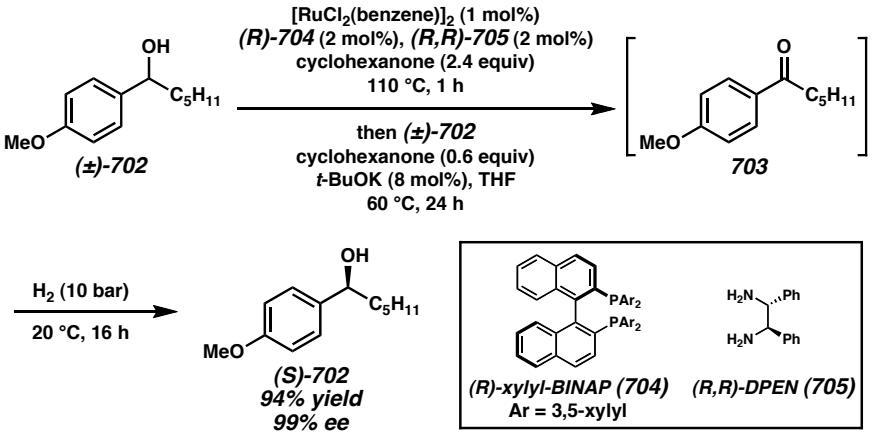


8.2.3.2 DERACEMIZATION

To avoid catalyst incompatibility, it is desirable to identify a single catalyst system capable of both the stereoablative step and enantioselective bond-forming step. In the realm of alcohol oxidation, Williams and Adair recently reported a deracemization of

secondary alcohols utilizing a bifunctional Ru catalyst (Scheme 8.10).[17] This system uses a single catalyst to perform a nonselective stereoablative oxidation followed by an enantioselective reduction. Exposure of racemic alcohol mixture (±)-**702** to a catalyst formed in situ from $[RuCl_2(benzene)]_2$, phosphine **704**, and (*R*,*R*)-DPEN (**705**) with cyclohexanone as a hydrogen acceptor produces achiral ketone **703**. Pressurization of the reaction with H_2 promotes enantioselective hydrogenation to the enantioenriched alcohol (*S*)-**702**. Although the demonstrated substrate scope of this reaction is still limited, the system overcomes the shortcoming of low yields of kinetic resolution processes, providing benzylic alcohols in 82–97% yield. The unique ability of the Ru catalyst to operate via two distinct mechanisms is critical to the success of this method. According to the principle of microscopic reversibility, the nonselective transfer dehydrogenation must also be nonselective in the reverse reaction, and therefore cannot complete the deracemization. However, introduction of an atmosphere of H2 opens a different, highly selective mechanistic pathway leading to alcohols of high ee.

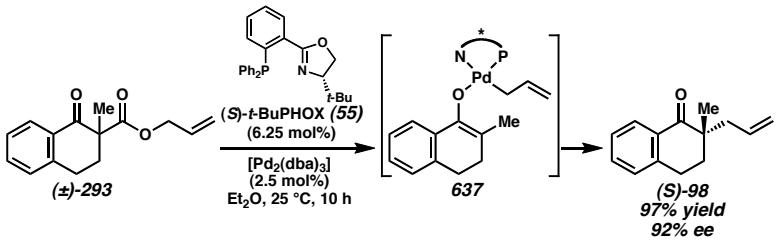
Scheme 8.10. Williams' deracemization of benzylic alcohols



8.2.3.3 DESTRUCTION/CONSTRUCTION SEQUENCES

Recently, Stoltz and co-workers established that racemic mixtures of allyl β-ketoesters are efficiently converted to enantioenriched α-quaternary cycloalkanones in an enantioconvergent process mediated by Pd and phosphinooxazoline (PHOX) ligands (Scheme 8.11).[1] The mechanism is presumed to proceed through a Pd-enolate (**637**) formed by deallylation and stereoablative loss of CO_2 from (±)-**293**. No significant kinetic resolution of the racemic starting materials was observed, and, coupled with the high chemical yield and enantioselectivity, these reactions represent an efficient method for the generation of enantioenriched building blocks for synthesis.[18]

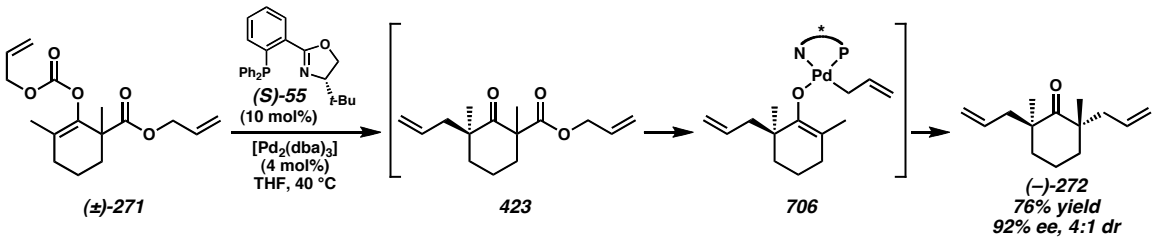
Scheme 8.11. Stoltz' stereoablative enantioconvergent ketone alkylation



An interesting extension of this enantioconvergent method is the combination of a reactive allyl enol carbonate moiety with a latent allyl β-ketoester (**271**, Scheme 8.12). In the course of this reaction, a new stereocenter is first generated via decomposition of the allyl enol carbonate to reveal a Pd-enolate that undergoes enantioselective allylation. It is important that the catalyst be able to effectively overcome the inherent stereochemical preference of the substrate since the starting material is a racemic mixture. If the catalyst is unable to overcome the substrate preference, then a poor product dr will result. Notably, in this reaction, a 7:3 dr was obtained with Ph_3P as ligand, while an enhanced dr of 4:1 was observed with (*S*)-*t*-BuPHOX (**55**) as ligand. In the second step of this

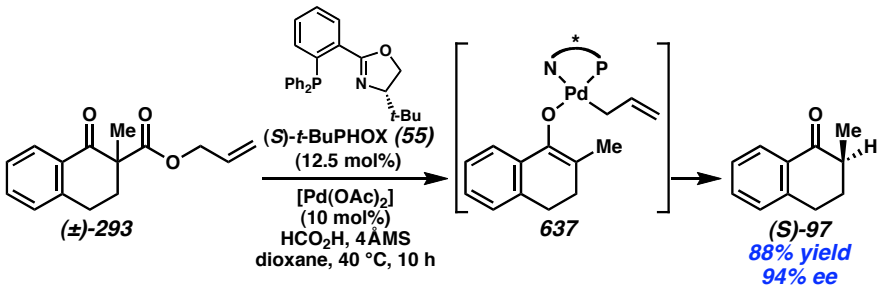
double-alkylation reaction, the newly revealed ketone in **423** activates the allyl ester toward decarboxylation and formation of Pd-enolate **706**. Catalyst control over the configuration of the second stereocenter leads to a Horeau-type enhancement[19] of the overall ee of the product. In this case, product (–)-**272** forms in 92% ee. A similar double-alkylation technique was applied to the total synthesis of cyanthiwigin F.[20]

Scheme 8.12. Stoltz' cascade asymmetric allylation generating two quaternary stereocenters



A second stereoablative reaction has been reported with the Pd•PHOX catalyst system. In this case, the putative Pd-enolate (**637**) is trapped with an alternate electrophile: a proton (Scheme 8.13).[21] Again, the enantiopure catalyst is involved in both the bond-breaking and bond-forming steps, although the exact mechanistic course of the reaction remains unclear.[22] The divergent reactivity of the enolate intermediate toward different electrophiles highlights the effectiveness and convenience of these stereoablative reactions. Although the stereoablative step in both reactions is likely identical, two different structural motifs (α-quaternary and α-tertiary ketones) are both available from a common starting material.[23] Recently, conjugate acceptors were also found to intercept the putative enolate intermediate providing different α-quaternary cycloalkanones in high ee (see section 5.5.2.3).[24]

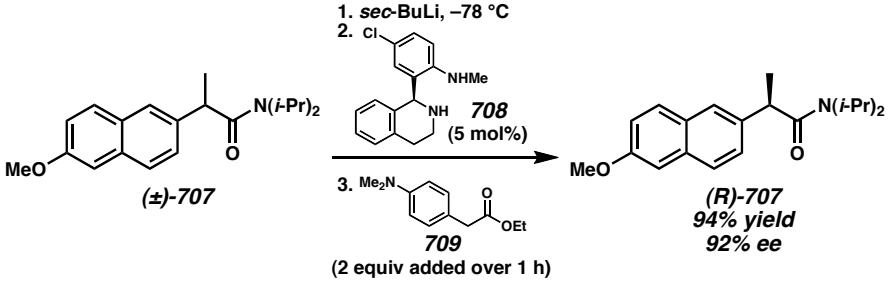
Scheme 8.13. Stoltz' stereoablative enantioconvergent protonation



Catalyst design in catalytic enantioconvergent processes is especially important in cases such as the enantioselective decarboxylative allylation and protonation reactions described above. Since the catalyst is intimately involved in both the stereoablative (C–C bond-breaking) and enantioselective (C–C or C–H bond-forming) steps, it is critical that the first step be insensitive to substrate stereochemistry.

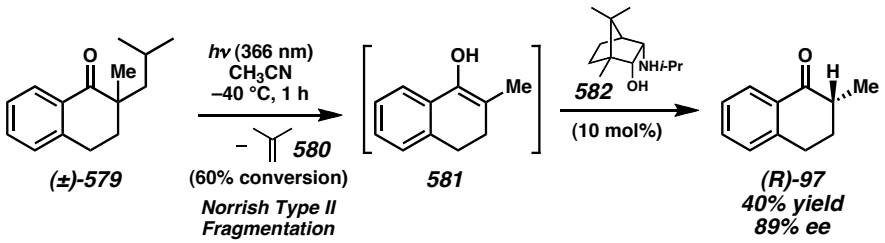
Analogous enolate methods are known in which stoichiometric reagents are used in the stereoablative step.[25] Importantly, kinetic resolution of the starting material is avoided by employing an achiral reagent (e.g., *sec*-BuLi) for this process. Among these is the enantioselective Li-enolate protonation method of Vedejs and Kruger, wherein a catalytic amount of a chiral amine (**708**) coupled with slow addition of stoichiometric phenylacetic acid derivative **709** leads to amide (*R*)-**707** in high ee (Scheme 8.14).[26]

Scheme 8.14. Vedejs' enantioselective enolate protonation



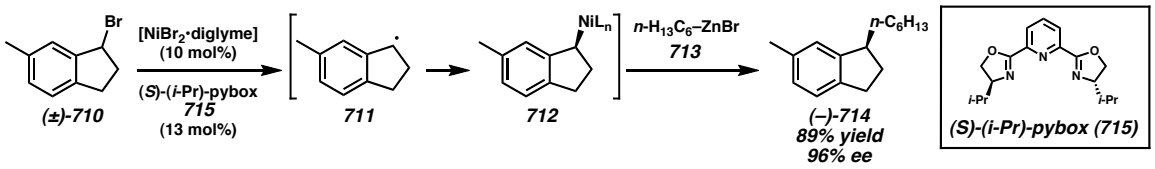
A unique, metal-free approach to stereoablation was developed by Hénin, Muzart, and co-workers.[27] In this work, a light initiated Norrish Type II fragmentation is employed to eliminate the stereocenter present in tetralone **579** and access intermediate enol **581** (Scheme 8.15). Subsequently, amino alcohol **582** mediates tautomerization to the enantioenriched product (*R*)-**97**. Other amino alcohols provide higher levels of conversion and yield at the cost of enantioselectivity.

Scheme 8.15. Hénin and Muzart's photolytic stereoablative process



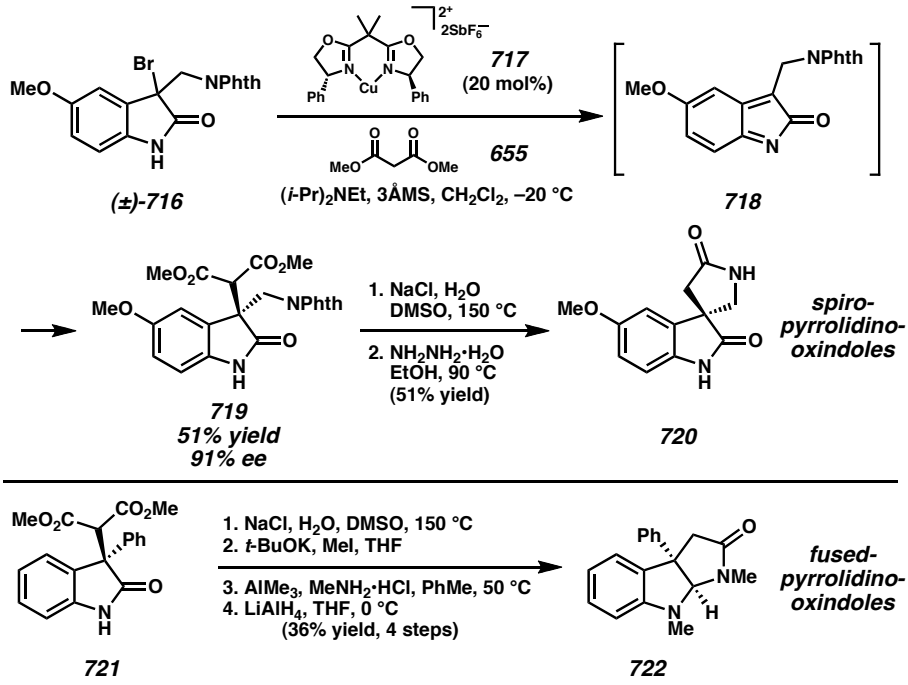
A recent report of a stereoablative enantioconvergent process for cross-coupling was detailed by Fu and co-workers in 2005. In the reaction, a racemic α-bromo amide or benzylic bromide is treated with catalytic Ni, enantiopure (*i*-Pr)-pybox ligand, and an alkylzinc reagent to create an enantioenriched tertiary stereocenter (Scheme 8.16).[28] Although the mechanistic details have not been fully elucidated, it has been hypothesized that the racemic bromide (**710**) initially decomposes to a radical intermediate (**711**), negating the stereochemistry of the starting material. Subsequent combination of the carbon-centered radical with the Ni catalyst and Negishi-type coupling provides (–)-**714** and completes the catalytic cycle.

Scheme 8.16. Fu's enantioconvergent Negishi coupling



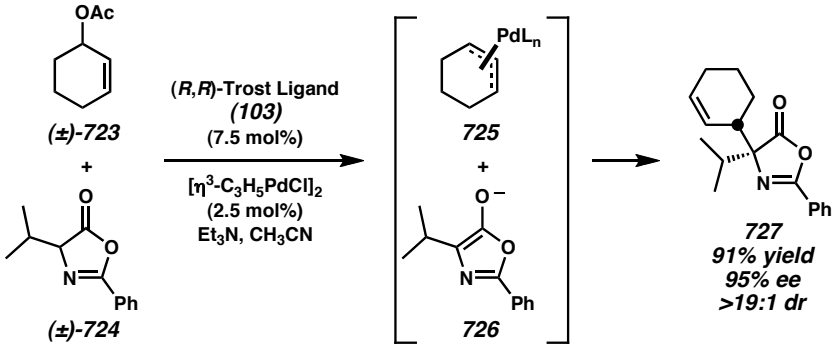
Stoltz and co-workers also used a halide leaving group to develop an enantioconvergent reaction, albeit through a considerably different mechanism (Scheme 8.17).[29] As a strategy to access oxindoles bearing all-carbon quaternary centers at the 3-position, racemic halooxindoles were envisioned as synthons for an electrophilic *o*-azaxylylene intermediate (e.g., **718**) that could be trapped by action of a nucleophile such as a malonate (e.g., **655**). The overall transformation is unusual since oxindoles are typically nucleophiles, but in this case the stereoablative step of the mechanism leads to an electrophilic intermediate. The technique was first demonstrated in a non-enantioselective version of the reaction, but later studies found that optimization of the stoichiometric base enabled enantioselective catalysis with a Cu(box) complex (i.e., **717**). Highly enantioenriched C3-quaternary oxindoles (up to 94% ee) were prepared, and the products were shown to be useful for synthesizing spiro- and fused-pyrrolidinoxindole architectures found in several families of natural products (e.g., **720** and **722**).

Scheme 8.17. Stoltz' stereoablative oxindole functionalization



As a final example, Trost and Ariza have reported an intermolecular system where both the electrophilic and nucleophilic partners are racemic (**723** and **724**, Scheme 8.18).[30] It is proposed that (±)-**723** is converted to an achiral γ^3-allyl ligand bound to Pd (**725**), which is subsequently attacked by deprotonated azlactone **726**, forming product **727** with excellent enantio- and diastereocontrol. The remarkable stereochemical control in this work is made possible by two separate stereoablative steps.

Scheme 8.18. Trost's doubly-stereoconvergent allylic alkylation



8.3 CONCLUSIONS

Although to date the primary focus during the development of enantioselective catalysis has been the creation of new stereocenters on prochiral substrates, asymmetric catalysis is not limited to the selective construction of new stereocenters. The selective destruction of stereogenic elements is also a viable, and increasingly important, technique that is beginning to show its utility in synthetic applications. This approach has several advantages including easily recycled by-products, easily accessible racemic or meso starting materials, entries into enantioconvergent catalytic processes, and opportunities for enantiodivergent synthesis. As these new methods become more prominent and are further developed by the synthetic community they will surely play a pivotal role in the construction of enantiopure materials.

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3. We suggest the following as a concise, inclusive definition for stereoablation: A chemical process where an existing stereogenic element in a molecule is eliminated.

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9. The selectivity factor s was determined using the equation: $s = k_{fast}/k_{slow} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where C = conversion, see: Kagan, H. B.; Fiaud, J. C. in *Topics in Stereochemistry*, Vol. 18 (Eliel, E. L., ed.), Wiley & Sons, New York, 1988, pp 249–330.

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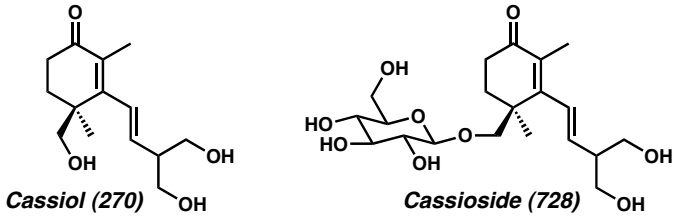
CHAPTER 9

Enantioselective Total Synthesis of (+)-Cassiol[†]

9.1 INTRODUCTION

In 1988, Fukaya reported the isolation of (–)-cassioside (**728**) (Figure 9.1) from the stem bark of *Cinnamonum cassia* Blume.[1] This glycosylated sesquiterpenoid exhibited potent antiulcerogenic activity in rats. The aglycon of (–)-cassioside, (+)-cassiol (**270**), demonstrated even stronger antiulcerogenic activity than observed with the glycosylated precursor. Given this useful biological property, (+)-cassiol (**270**) has attracted a great deal of attention from synthetic laboratories.[2] Herein, we report an expedient enantioselective synthesis of (+)-cassiol with a longest linear sequence of eight steps.

Figure 9.1. Structures of (+)-cassiol and (–)-cassioside



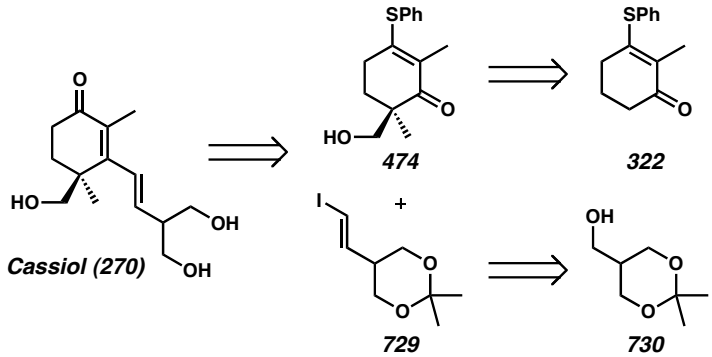
[†] This work was performed primarily by Krastina V. Petrova as a Amgen Summer Undergraduate Research Fellow. Portions we also perfomed in collaboration with Samantha R. Levine and Michael R. Krout. These works have been published. See: (a) Petrova, K. V.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 293–295. (b) Levine, S. R.; Krout, M. R.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 289–292.

A principal challenge to the synthesis of (+)-cassiol (**270**) is the presence of an all-carbon quaternary stereocenter.[3] Several total syntheses of cassiol have been reported; however, most have relied on chiral pool starting materials, or chiral auxiliaries.[4,5] Few of these syntheses addressed the challenge of catalytic enantioselective quaternary carbon stereocenter generation. For example, successful catalytic enantioselective approaches have utilized Diels–Alder,[6] intramolecular alkylidine insertion,[7] and enzymatic[8] reactions to form the quaternary carbon.

9.2 RETROSYNTHETIC ANALYSIS

We envisioned a different strategy[9] wherein the key quaternary stereocenter would be installed through an enantioselective Pd-catalyzed allylic alkylation method recently developed in our laboratories.[10] Our plan consisted of coupling two complex pieces (**474** and **729**, Scheme 9.1) in the final step of the synthesis through a Stork–Danheiser-type addition/rearrangement reaction.[11] Precursors **474** and **729** would in turn be available from known vinylogous thioester **322**[12] and primary alcohol **730**,[13] respectively.

*Scheme 9.1. Retrosynthetic analysis of (+)-cassiol (**270**)*

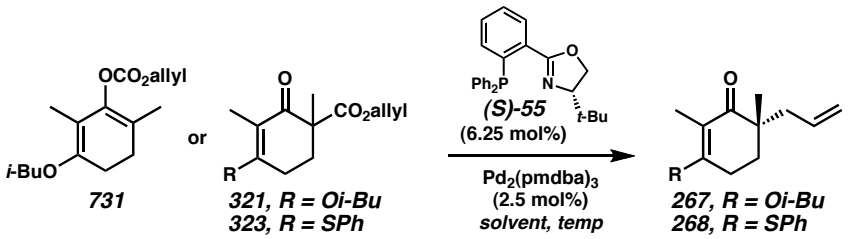


9.3 TOTAL SYNTHESIS OF (+)-CASSIOL

9.3.1 ENANTIOSELECTIVE ALKYLATION WITH VINYLOGOUS ESTERS

Given the success with enol carbonate substrates derived from vinylogous esters both in our laboratory[14] and others,[12] we first pursued enantioselective alkylation with substrate **731** (Table 9.1). Upon exposure to the catalyst complex derived from $Pd_2(dba)_3$ and phosphinooxazoline (PHOX) ligand (*S*)-**55**,[15] desired product **267** was isolable, but the yield and ee were variable (entry 1). A further complication was the instability of the enol carbonate.[16] To circumvent this complication, the corresponding β-ketoester substrate **321** was chosen with the hope of improving stability.[12b] Although the substrate proved stable, reactivity with our catalyst was quite low at 50 °C in toluene (entry 2).[17] Increasing the reaction temperature led to complete conversion, but the ee of product ketone **267** was moderate (entry 3). In order to increase the reactivity of the ester substrate, vinylogous thioester analog **323** was prepared. With substrate **323**, both high yield and product ee were obtained with a range of solvents (entries 4–7). With a suitable synthesis of **268** in hand, we moved on to the synthesis of (+)-cassiol.[18]

Table 9.1. Enantioselective alkylation of vinylogous esters



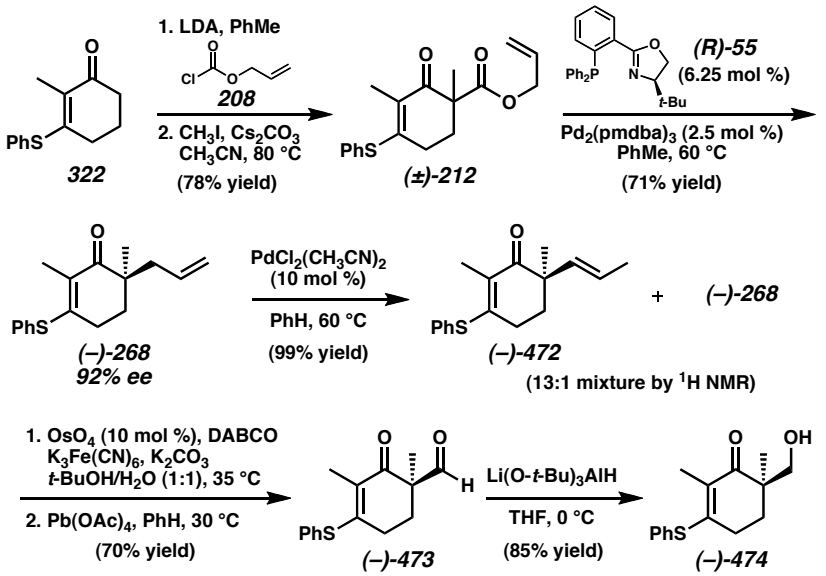
entry	substrate	solvent	T (°C)	product	isolated yield (%)	ee[a] (%)
1	*731*	toluene	25	*267*	22–61	84–88
2	*321*	toluene	50	*267*	19[b]	79
3	*321*	toluene	80	*267*	86	75
4	*323*	toluene	50	*268*	86	92
5	*323*	benzene	50	*268*	61[c]	92
6	*323*	THF	50	*268*	88	92
7	*323*	1,4-dioxane	50	*268*	90	91

[a] Enantiomeric excess determined by chiral HPLC or SFC. [b] β-ketoester (±)-**10** was recovered in 69% yield. [c] β-ketoester (±)-**11** was recovered in 26% yield.

9.3.2 PREPARATION OF THE CYCLOHEXENONE CORE

Our synthesis commenced with the deprotonation of vinylogous thioester **322** with LDA and acylation of the resulting enolate with allyl chloroformate (Scheme 9.2). Subsequent position-selective alkylation with iodomethane provided racemic β-ketoester **323** in 78% overall yield from **322**. In the presence of the catalyst complex derived from $Pd_2(pmdba)_3$ and (*R*)-*t*-BuPHOX (**55**), β-ketoester (±)-**323** was readily transformed into allyl ketone (–)-**268** in good yield and excellent enantiomeric excess.[12a] Isomerization of the terminal alkene occurred upon exposure to catalytic $PdCl_2(CH_3CN)_2$ in hot benzene, resulting in quantitative recovery of an inseparable 13:1 mixture of *E*-alkene **472** and starting material **268**.

*Scheme 9.2. Enantioselective synthesis of alcohol (–)-**474***



In order to convert the propenyl sidechain of **472** into a hydroxymethylene unit, we sought to carry out an oxidative olefin cleavage reaction. This transformation, however, proved challenging. Competing oxidative reactions of the thioester moiety appeared to occur rapidly under ozonolysis conditions. Modified Lemieux–Johnson conditions (OsO_4, $NaIO_4$, 2,6-lutidine, dioxane/water)[19] were also investigated, but led to a complex mixture of products lacking the desired compound. Both Upjohn dihydroxylation (OsO_4, NMO, acetone)[20] and Sharpless asymmetric dihydroxylation conditions (AD-mix-α or AD-mix-β, *t*-BuOH/H_2O)[21] resulted in slow and only partial conversion to the desired diol product.

Confronted by these difficulties, we considered possible opportunities to improve reactivity for our system. We wished to take advantage of the well-precedented rate acceleration of amine additives in osmium-catalyzed dihydroxylation reactions,[22] but we reasoned that the bulky chiral ligands employed in the Sharpless protocol might hamper reactivity toward our sterically encumbered, enantiomerically enriched olefin. Warren,

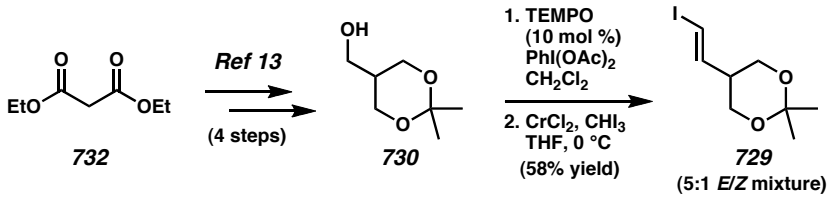
Wyatt, and co-workers had found DABCO to be a convenient achiral ligand for non-enantioselective dihydroxylations,[23] and we suspected that the smaller steric size of this ligand might improve the rate of oxidation in our system. This proved to be the case, and dihydroxylation proceeded smoothly with no evidence of undesired vinylogous thioester oxidation.[24] Immediate exposure of the crude diol to $Pb(OAc)_4$ furnished pure aldehyde (–)-**473** in 70% overall yield for the two oxidative transformations.

Treatment of aldehyde (–)-**473** with $NaBH_4$ or $NaBH(OAc)_3$ resulted in rapid reduction of both carbonyl groups present in the substrate. Fortunately, use of the bulkier reducing agent $Li(O\text{-}t\text{-}Bu)_3AlH$ circumvented the problem of overreduction and provided the desired alcohol (–)-**474** in good yield. Chiral HPLC analysis of (–)-**474** indicated that no significant erosion of enantiomeric purity had occured over the course of these steps.

9.3.3 PREPARATION OF THE SIDECHAIN SYNTHON

Turning our attention to the synthesis of vinyl iodide **729**, we prepared alcohol **730** in four known steps from diethyl malonate (**732**).[13,25] Catalytic oxidation of alcohol **730** to the corresponding aldehyde was accomplished with TEMPO and $PhI(OAc)_2$ as the stoichiometric co-oxidant (Scheme 9.3).[26] Takai olefination[27] of the crude aldehyde to stereoselectively introduce the alkene functionality yielded vinyl iodide **729** in a 5:1 *E*/*Z* ratio.

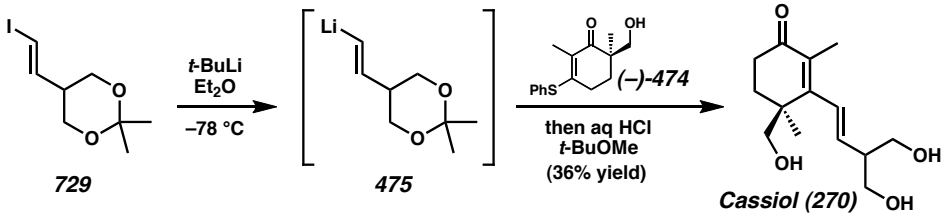
*Scheme 9.3. Synthesis of vinyl iodide **729***



9.3.4 FRAGMENT COUPLING

In the final step of the synthesis, lithium–halogen exchange of vinyl iodide **729** (2 equiv) through exposure to *t*-BuLi (4.25 equiv) in diethyl ether furnished vinyllithium **475**. Addition of a solution of alcohol (–)-**474** (1 equiv) to the solution of organolithium **475** and subsequent acid-catalyzed rearrangement and hydrolysis yielded (+)-cassiol (**270**).[7] The spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, HRMS, optical rotation) were identical to the reported data for natural **270**.

*Scheme 9.4. Preparation of (+)-cassiol (**270**)*



9.4 SUMMARY

In summary, we report a brief and convergent total synthesis of the antiulcerogenic natural product (+)-cassiol. Our route requires eight linear steps from vinylogous ester **322** and proceeds in 12% overall yield. Employing our recently developed enolate

alkylation technology, the key quaternary carbon stereocenter was generated at an early stage in high ee. The versatile reactivity of the allyl group enabled installation of the hydroxymethylene unit present in the natural product through chemoselective oxidation and reduction reactions. Late-stage installation of the diol sidechain via Stork–Danheiser-type addition/rearrangement completed the synthesis. Other synthetic efforts featuring enantioselective enolate functionalization reactions are underway.[28]

9.5 NOTES AND REFERENCES FOR TEXT

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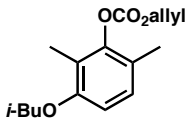
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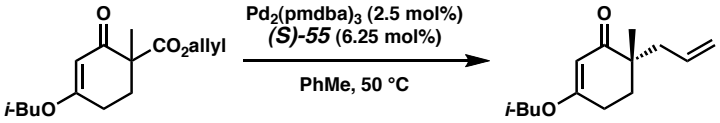
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16. Enol carbonate **731** was unstable to air, forming complex reaction mixtures that substantially affected yields and selectivities for the alkylation. Aromatic carbonate **733** was identified from this mixture. See the experimental section (section 9.6) for details.



733

17. The reactivity of β-ketoester (±)-**321** contrasts significantly with that of related derivative (±)-**734**, which generates **438** in 79% yield and 86% ee under identical conditions.



(±)-734 ***438, 86% ee***

18. Enantioenriched thioester **268** has also been used in the enantioselective synthesis of carissone (details are shown in section 5.5.1.7). See: Levine, S. R.; Krout, M. R.; Stoltz, B. M. *Org. Lett.* **2008**, *11*, 289–292.

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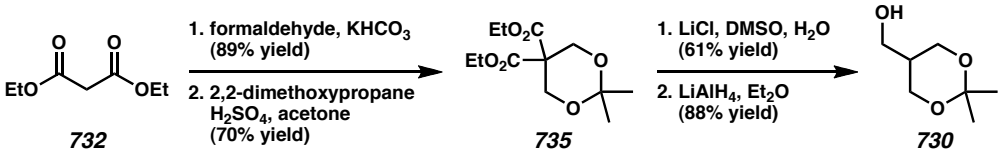
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This sequence is based on ref 13.

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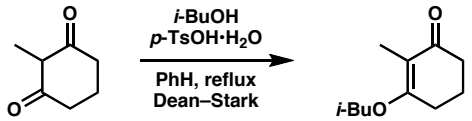
9.6 EXPERIMENTAL SECTION

9.6.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Brine solutions are saturated aqueous sodium chloride solutions. Liquids and solutions were transferred via syringe or cannula. All the starting materials were purchased from Sigma-Aldrich or Alfa Aesar, and used as received, unless otherwise stated. Benzenethiol was distilled under nitrogen prior to use. Previously reported methods were used to prepare (*R*)-*t*-BuPHOX (**55**),[29] $Pd_2(pmdba)_3$,[30] and $PdCl_2(CH_3CN)_2$.[31] Osmium tetroxide and $Pb(OAc)_4$ were purchased from Sigma-Aldrich, and the $Pb(OAc)_4$ was stored under a glovebox atmosphere prior to use. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, or $KMnO_4$ staining. SiliCycle® SiliaFlash® P60 Academic Silica Gel (particle size 40–63 μm; pore diameter 60 Å), or Florisil® (100–200 mesh) were used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak AD column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries with visualization at 254 nm. Analytical chiral supercritical fluid chromatography was performed with a Berger Analytix SFC (Thar Technologies) utilizing a Chiralpak AD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with 2 mL/min flow rate at 30 °C and visualization at 244 nm. Optical

rotations were measured with a Jasco P-1010 polarimeter at 589 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 and 75 MHz respectively) or a Varian Inova 500 (at 500 and 125 MHz respectively), and are reported relative to Me_4Si (δ 0.0 ppm). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility.

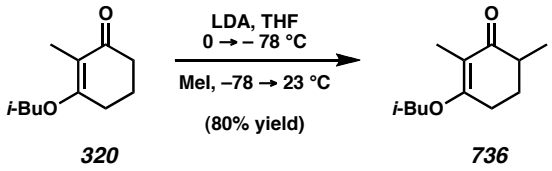
9.6.2 EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA



319 *320*

Vinylogous Ester 320.[32] Diketone **319** (3.000 g, 23.78 mmol, 1.0 equiv) was partially dissolved in PhH (42.5 mL, 0.56 M), and *i*-BuOH (12.75 mL, 137.9 mmol, 5.8 equiv) and *p*-TsOH•H_2O (226 mg, 1.19 mmol, 0.05 equiv) were added with vigorous stirring. The flask was affixed with a Dean–Stark adapter and a water-cooled condenser and warmed to reflux in a 104 °C oil bath. Upon consumption of **319** by TLC analysis (ca. 3.5 h), the reaction was cooled to ambient temperature, diluted with Et_2O (50 mL), and poured into saturated aq $NaHCO_3$ (20 mL). The layers were separated and the aqueous was extracted with Et_2O (3 x 15 mL). The organics were combined, washed

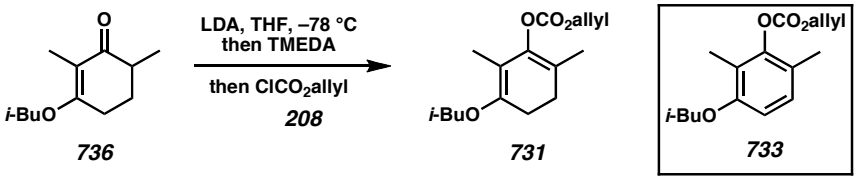
with brine, dried with Na_2SO_4, filtered, and concentrated *in vacuo* to afford a pale brown oil. To this oil was added PhMe (ca. 10 mL) followed by further concentration *in vacuo*. Purification by bulb-to-bulb distillation yielded vinylogous ester **320** (3.988 g, 21.88 mmol, 92% yield) as a clear, colorless oil. R_f = 0.48 (2:1 EtOAc-hexanes); bp = 135–140 °C at 0.8 torr; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76 (d, *J* = 6.5 Hz, 2H), 2.54 (ddd, *J* = 6.1, 1.5, 1.5 Hz, 2H), 2.34 (t, *J* = 7.1 Hz, 2H), 2.08-1.90 (comp m, 3H), 1.72 (app t, *J* = 1.5 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 6H). All other data were consistent with reported values.



320 *736*

Methyl Vinylogous Ester 736.[32] To a solution of *i*-Pr_2NH (1.12 mL, 7.99 mmol, 1.9 equiv) in THF (26 mL, 0.15 M) at 0 ˚C was added dropwise a solution of *n*-BuLi (2.55 M in hexanes, 3.06 mL, 7.80 mmol, 1.85 equiv). After 15 min, a solution of vinylogous ester **320** (765.2 mg, 4.198 mmol, 1.0 equiv) in THF (2.0 mL) was added dropwise via cannula transfer. The resulting solution was cooled to –78 ˚C and stirred for 45 min, to which a solution of MeI (485 μL, 7.80 mmol, 1.85 equiv) in THF (5.0 mL) was added over 30 min via positive-pressure cannula transfer. The cooling bath was allowed to expire over ca. 4 h and the reaction was quenched with brine (15 mL). The phases were separated and the aqueous phase was extracted with hexanes (3 x 25 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to a yellow oil. Purification by flash chromatography (4:1 → 2:1 hexanes-Et_2O)

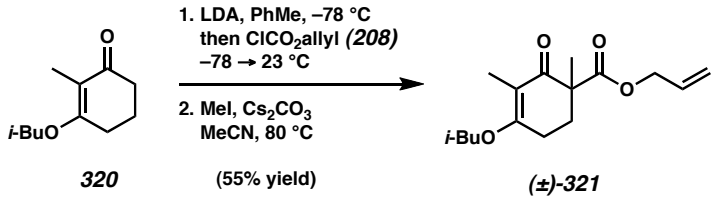
afforded methyl vinylogous ester **736** (659 mg, 3.36 mmol, 80% yield) as a pale yellow oil. R_f = 0.48 (2:1 hexanes-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.73 (ddd, *J* = 15.6, 9.2, 6.5 Hz, 2H), 2.61 (ddd, *J* = 17.3, 5.3, 1.2 Hz, 1H), 2.55-2.44 (m, 1H), 2.35-2.19 (m, 1H), 2.06 (app dq, *J* = 8.3, 4.8 Hz, 1H), 1.98 (app septet, *J* = 6.6 Hz, 1H), 1.71 (dd, *J* = 1.6, 1.6 Hz, 3H), 1.73-1.60 (m, 1H), 1.14 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 6H). All other data are consistent with reported values.



Enol Carbonate 731. To a solution of *i*-Pr_2NH (1.56 mL, 11.15 mmol, 1.2 equiv) in THF (85 mL, 0.11 M) at 0 ˚C was added a solution of *n*-BuLi (2.55 M in hexanes, 4.0 mL, 10.22 mmol, 1.1 equiv) dropwise. The reaction mixture was allowed to stir for 30 min and then cooled to –78 ˚C. A solution of ketone **736** (1.824 g, 9.29 mmol, 1.0 equiv) in THF (10 mL) was added dropwise via cannula and stirred for 1 h. TMEDA (1.67 mL, 11.15 mmol, 1.2 equiv) was then added via syringe and the resulting solution stirred for 75 min. To this solution allyl chloroformate (**208**, 1.08 mL, 10.13 mmol, 1.09 equiv) was added via syringe and the reaction mixture was stirred at –78 ˚C for an additional hour. The reaction was quenched with saturated aq $NaHCO_3$ (40 mL) and H_2O (40 mL), and the flask was transferred to a 23 ˚C water bath and allowed to equilibrate. The phases were separated and the aqueous was extracted with Et_2O (2 x 200 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford enol carbonate **731** as a yellow oil (2.472 g); ^{1}H NMR analysis shows **731** is the major

product with other impurities present. R_f = *unstable to* SiO_2; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.97 (dddd, *J* = 16.4, 10.8, 5.8, 5.8 Hz, 1H), 5.42 (app d, *J* = 17.2 Hz, 1H), 5.33 (app d, *J* = 10.4 Hz, 1H), 4.72 (dd, *J* = 5.7, 0.8 Hz, 2H), 3.86 (d, *J* = 6.7 Hz, 2H), 2.85 (app t, *J* = 7.9 Hz, 2H), 2.52 (app t, *J* = 7.9 Hz, 2H), 2.19 (s, 3H), 1.92 (app septuplet, *J* = 6.7 Hz, 1H), 1.82 (s, 3H), 0.93 (d, *J* = 6.7 Hz, 6H); IR (Neat Film NaCl) 2963, 1760, 1736, 1699, 1361, 1248, 1170, 990 cm^{-1}; HRMS (FAB+) *m/z*: calc'd for $C_{13}H_{19}O_4$ $[M - C_3H_5]^+$: 239.1283, found 239.1273.

This material was unstable to various purification attempts (distillation or flash chromatography using silica gel or Florisil) and storage. Aromatic carbonate **733** was identified as a colorless oil from this complex mixture. R_f = 0.51 (4:1 hexanes-EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 (d, *J* = 8.4 Hz, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 6.00 (dddd, *J* = 17.1, 10.5, 5.7, 5.7 Hz, 1H), 5.43 (dddd, *J* = 17.2, 1.4, 1.4, 1.4 Hz, 1H), 5.33 (dddd, *J* = 10.5, 1.2, 1.2, 1.2 Hz, 1H), 4.75 (app dt, *J* = 5.8, 1.3 Hz, 2H), 3.70 (d, *J* = 6.4 Hz, 2H), 2.14 (s, 3H), 2.09 (s, 3H), 2.09 (app septuplet, *J* = 6.6 Hz, 1H), 1.03 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.3, 153.0, 148.7, 131.4, 127.7, 121.8, 119.5, 119.4, 109.1, 74.9, 69.2, 28.6, 19.5, 15.7, 9.2; IR (Neat Film NaCl) 2960, 2874, 1762, 1620, 1494, 1470, 1365, 1244, 1202, 1172, 1115, 1048, 799 cm^{-1}; HRMS (FAB+) *m/z*: calc'd for $C_{16}H_{22}O_4$ $[M]^+$: 278.1518, found 278.1517.

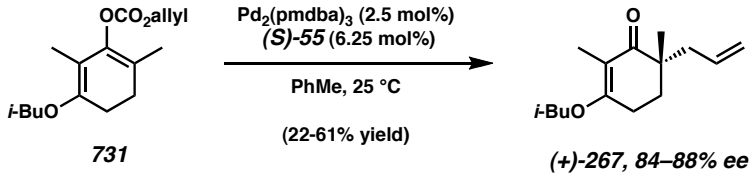


(±)-β-Ketoester 321. To a –78 °C solution of *i*-Pr_2NH (425 μL, 3.03 mmol, 1.9

equiv) in PhMe (10 mL) was added dropwise *n*-BuLi (2.55 M in hexanes, 1.16 mL, 2.96 mmol, 1.85 equiv). The reaction vessel was placed in an ice/water bath and allowed to stir for 10 min, and then cooled to –78 °C. A solution of vinylogous ester **320** (291 mg, 1.60 mmol, 1.0 equiv) in PhMe (1.4 mL) was added dropwise via cannula to the reaction vessel, and the resulting solution was allowed to stir for 30 min. Allyl chloroformate (**208**, 173 μL, 1.63 mmol, 1.02 equiv) was added dropwise, and the reaction vessel was allowed to warm to 23 °C over 1 h. After stirring for 4 h, the reaction was slowly quenched with aq $KHSO_4$ (1 N, 4 mL) and the resulting biphasic mixture was allowed to stir for 10 min. The phases were separated, and the aq phase was extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The isolated crude yellow oil was used in the next step without further purification.

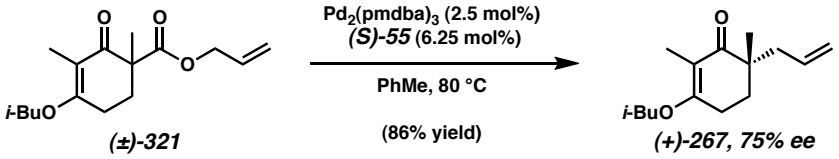
The resulting crude yellow oil was dissolved in MeCN (5.9 mL, 0.27 M), and Cs_2CO_3 (603 mg, 1.85 mmol, 1.16 equiv), and MeI (276 μL, 4.44 mmol, 2.8 equiv) were added. The flask was affixed a water-cooled condenser and resulting suspension was warmed to reflux in an 80 °C oil bath with vigorous stirring. After 10 h, the reaction was cooled to room temperature, diluted with EtOAc (25 mL). The organics were dried with $MgSO_4$, filtered, and the solvent was evaporated *in vacuo*. Purification by flash chromatography (15:1 → 9:1 → 4:1 hexanes-EtOAc) afforded β-ketoester (±)-**321** as pale yellow oil (246 mg, 55% yield over two steps). R_f = 0.27 (2:1 hexanes-EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.82 (dddd, *J* = 17.2, 10.7, 5.4, 5.4 Hz, 1H), 5.22 (dddd, *J* = 17.2, 1.6, 1.6, 1.6 Hz, 1H), 5.15 (dddd, *J* = 10.5, 1.2, 1.2, 1.2 Hz, 1H), 4.56 (dddd, *J* = 13.5, 5.4, 1.5, 1.5 Hz, 2H), 3.72 (ddd, *J* = 9.2, 6.6, 3.2 Hz, 2H), 2.69-2.62 (m, 1H), 2.53-2.44 (comp m,

2H), 1.95 (app septuplet, J = 6.6 Hz, 1H), 1.85-1.80 (m, 1H), 1.70 (dd, J = 1.5, 1.5 Hz, 3H), 1.36 (s, 3H), 0.95 (dd, J = 6.7, 0.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 195.8, 172.6, 170.3, 131.9, 117.8, 113.8, 73.9, 65.5, 51.6, 31.2, 28.8, 23.0, 20.8, 19.1, 19.0, 8.0; IR (Neat Film NaCl) 2961, 2935, 2875, 1733, 1649, 1618, 1460, 1382, 1354, 1237, 1176, 1103, 983 cm^{-1}; HRMS (FAB+) *m/z*: calc'd for $C_{16}H_{25}O_4$ $[M + H]^+$: 281.1753, found 281.1740.

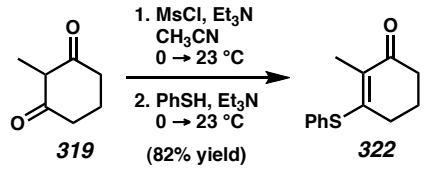


Ketone (+)-267 from enol carbonate 731. A 1-dram vial containing a stir bar was charged with $Pd_2(pmdba)_3$ (4.9 mg, 0.0045 mmol, 0.025 equiv) and (*S*)-**55** (4.4 mg, 0.0112 mmol, 0.0625 equiv), sealed with a septum, and the atmosphere was purged by three evacuate/purge cycles. To this was added PhMe (0.9 mL) and the complexation was stirred for 30 min in a 25 °C oil bath, upon which time a solution of enol carbonate **731** (50.2 mg, 0.179 mmol, 1.0 equiv) in PhMe (0.9 mL, 0.1 M total) was added via cannula. After 21.5 h at 25 °C, the reaction was diluted with Et_2O (2 mL), filtered through a SiO_2 plug, and concentrated in vacuo. The filtrate was purified by flash chromatography on SiO_2 (15:1 → 4:1 hexanes-EtOAc) to afford ketone (+)-**267** as a pale yellow oil (22-61% yield, 84–88% ee). R_f = 0.49 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (dddd, J = 16.6, 10.6, 7.4, 7.4 Hz, 1H), 5.06-5.04 (m, 1H), 5.04-5.01 (m, 1H), 3.74 (dd, J = 9.7, 6.7 Hz, 2H), 2.59-2.47 (comp m, 2H), 2.33 (dd, J = 13.7, 7.2 Hz, 1H), 2.16 (dddd, J = 13.7, 7.6, 1.0, 1.0 Hz, 1H), 1.98 (app septuplet, J = 6.6 Hz, 1H),

1.90 (ddd, J = 13.3, 7.2, 5.7 Hz, 1H), 1.72-1.67 (m, 1H), 1.70 (dd, J = 1.6, 1.6 Hz, 3H), 1.06 (s, 3H), 0.99 (d, J = 6.7 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.7, 169.5, 134.8, 117.8, 113.3, 73.8, 42.5, 41.9, 31.5, 29.0, 22.5, 22.4, 19.2, 8.0; IR (Neat Film NaCl) 3076, 2962, 2931, 1622, 1463, 1381, 1355, 1229, 1113, 1002, 915 cm^{-1}; HRMS (EI+) *m/z*: calc'd for $C_{15}H_{24}O_2$ $[M]^+$: 236.1776, found 236.1771; $[\alpha]_D^{21.2}$ +13.2° (*c* 0.20, CH_2Cl_2, 88% ee). SFC conditions: 5% IPA, AD-H column, t_R (min): major = 5.18, minor = 6.02.

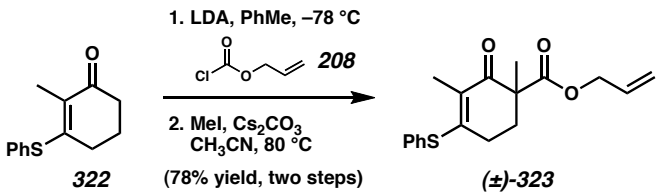


Ketone (+)-267 from β-ketoester (±)-321. A 2-dram vial containing a stir bar was charged with $Pd_2(pmdba)_3$ (10.6 mg, 0.00968 mmol, 0.025 equiv) and (*S*)-**55** (9.4 mg, 0.0242 mmol, 0.0625 equiv). This was connected to a 1-dram vial containing a stirbar and β-ketoester (±)-**321** (108.6 mg, 0.387 mmol, 1.0 equiv) via a cannula, and PhMe (3.9 mL, 0.1 M) was added to the vial containing the Pd/L and immediately immersed in liquid N_2. The vials were rigorously degassed by three freeze-pump-thaw cycles and warmed to 23 °C. After complexation for 30 min (purple → orange color change), the catalyst solution was transferred to the substrate via cannula and immersed in an 80 °C oil bath. The reaction immediately turned yellow in color. After 23 h the reaction was cooled to ambient temperature, diluted with Et_2O (4 mL), and filtered through a small SiO_2 plug. The filtrate was concentrated and purified by flash chromatography as above to afford ketone (+)-**267** as a colorless oil (78.5 mg, 0.332 mmol, 86% yield, 75% ee).



319 *322*

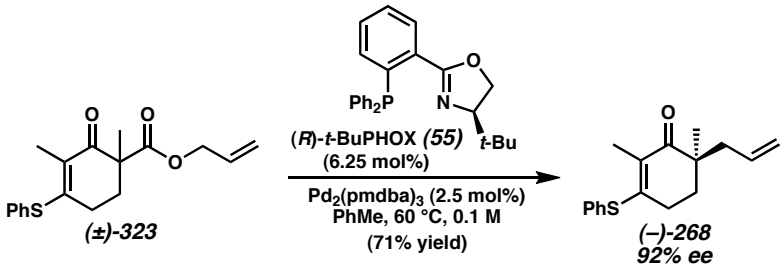
Vinylogous Thioester 322.[33] To a solution of diketone **319** (5.00 g, 39.82 mmol, 1.00 equiv) in CH_3CN (44 mL) was added Et_3N (6.2 mL, 44.40 mmol, 1.12 equiv), and the solution was allowed to stir for 5 min, then cooled to 0 °C. Methanesulfonyl chloride (3.26 mL, 42.00 mmol, 1.06 equiv) was added, and the reaction was warmed to 23 °C over 2 h. Stirring was continued for 5 h, and the reaction was cooled to 0 °C. Triethylamine (6.2 mL, 44.40 mmol, 1.12 equiv) was added, followed by benzenethiol (4.2 mL, 40.80 mmol, 1.03 equiv). The reaction was allowed to warm to 23 °C over 2 h and stirring was continued for 9 h. Saturated aq Na_2CO_3 (70 mL) was added, the phases were separated, and the aq phase was extracted with Et_2O (3 x 120 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. Purification by flash chromatography (18% EtOAc in hexanes) afforded vinylogous thioester **322** (7.15 g, 82% yield) as a white crystalline solid. $R_f = 0.33$ (20% EtOAc in hexanes); mp 85 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.49 (m, 2H), 7.44-7.37 (comp m, 3H), 2.38 (t, J = 6.5 Hz, 2H), 2.18 (tq, J = 6.5, 2.0 Hz, 2H), 1.97 (t, J = 2.0 Hz, 3H), 1.87 (app pentuplet, J = 6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.6, 157.9, 130.3(2C), 129.6, 129.5, 37.3, 30.5, 22.9, 12.4; IR (Neat Film NaCl) 2944, 1655, 1578, 1339, 1296 cm^{-1}; HRMS (FAB+) *m/z*: calc'd for $C_{13}H_{14}OS$ $[M + H]^+$: 219.0844, found 219.0843.



β-Ketoester 323.[34] To a –78 °C solution of diisopropylamine (2.63 mL, 18.78 mmol, 2.00 equiv) in toluene (70 mL) was added dropwise *n*-BuLi (2.53 M in hexanes, 7.24 mL, 2.00 equiv). The reaction vessel was warmed to 0 °C, allowed to stir for 10 min, and cooled to –78 °C. A solution of thioester **322** (2.00 g, 9.16 mmol, 1.00 equiv) in toluene (15 mL) was added dropwise via cannula to the reaction vessel, and the resulting solution was allowed to stir for 30 min. Allyl chloroformate (1.02 mL, 9.62 mmol, 1.05 equiv) was added dropwise, and the reaction vessel was allowed to warm to 23 °C over 1 h. Stirring was continued for 4 h, then aq $KHSO_4$ (1 N, 70 ml) was added, and the resulting solution was allowed to stir for 10 min. The phases were separated, and the aq phase was extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine (1 x 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The isolated crude yellow oil was used in the next step without further purification.

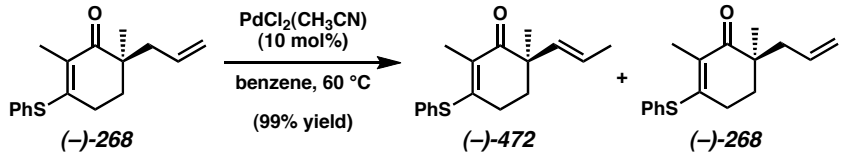
To a solution of the crude yellow oil (3.32 g) in CH_3CN (40 mL) was added cesium carbonate (4.48 g, 13.74 mmol, 1.50 equiv), and iodomethane (1.71 mL, 27.48 mmol, 3.00 equiv). The resulting suspension was refluxed at 80 °C for 5 h, and then MeI (1.00 mL, 16.06 mmol, 1.75 equiv) was added. The reaction was refluxed at 80 °C for 2 h, cooled to room temperature, filtered through Celite (EtOAc eluent), dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. Purification by flash chromatography (18% EtOAc in hexanes) afforded β-ketoester (±)-**323** (2.26 g, 78% yield over two steps) as white solid. R_f = 0.35 (30% EtOAc in hexanes); mp 34 °C; ^{1}H NMR (300 MHz,

$CDCl_3$) δ 7.51-7.35 (comp m, 5H), 5.87 (app ddt, *J* = 10.5, 17.1, 5.4 Hz, 1H), 5.27 (app ddt, *J* = 17.1, 1.7, 1.8 Hz, 1H), 5.22 (app ddt, *J* = 9.9, 1.7, 1.2 Hz, 1H), 4.65 (dddd, *J* = 1.5, 1.8, 5.7, 13.5 Hz, 1H), 4.55 (dddd, *J* = 1.5, 1.8, 5.7, 13.5 Hz, 1H), 2.41-2.32 (m, 1H), 2.30-2.21 (m, 1H), 2.16-2.06 (1H), 2.00 (t, *J* = 1.8 Hz, 3H), 1.78 (ddd, *J* = 4.5, 8.1, 13.2 Hz, 1H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0, 172.6, 156.7, 135.6, 131.9, 129.7, 129.5, 128.9, 118.1, 65.7, 52.3, 33.1, 27.4, 20.7, 12.9; IR (Neat Film NaCl) 2936, 1733, 1656, 1580, 1314, 1254, 1238, 1174, 985, 752, 693 cm^{-1}; HRMS (FAB+) *m/z*: calc'd for $C_{18}H_{20}O_3S$ $[M + H]^+$: 317.1211, found 317.1211.



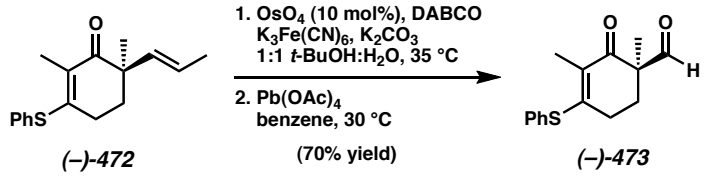
Allyl ketone (–)-268. A solution of $Pd_2(pmdba)_3$ (0.1306 g, 0.1185 mmol, 0.025 equiv) and (*R*)-*t*-BuPHOX (**55**) (0.1148 g, 0.2964 mmol, 0.0625 equiv) in toluene (30 mL) was prepared in a glovebox under N_2 atmosphere, and allowed to stir at 23 °C for 30 min. A solution of β-ketoester (±)-**323** (1.50 g, 4.741 mmol, 1.00 equiv) in toluene (10 mL) was transferred to the reaction vessel dropwise via glass pipette, washing with toluene (7.5 mL) for quantitative transfer. The reaction vessel was sealed with a rubber septum, removed from the glove box, heated in a 60 °C oil bath, and the solution was allowed to stir for 24 h. The reaction vessel was cooled to room temperature, and the solvent was evaporated in vacuo. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to afford allyl ketone (–)-**268** (0.92 g, 71%

yield, 91.6% ee as determined by chiral HPLC using a Chiralpak AD column with 4% EtOH in hexanes as the eluent) as a colorless oil. R_f = 0.45 (30% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.48 (m, 2H), 7.43-7.35 (comp m, 3H), 5.68 (app ddt, *J* = 10.8, 16.8, 7.5 Hz, 1H), 5.03 (dddd, *J* = 9.9, 2.4, 0.9, 0.6 Hz, 1H), 5.01 (dddd, *J* = 17.4, 2.4, 1.5, 1.2 Hz, 1H), 2.32 (app ddt, *J* = 13.8, 7.2, 1.2 Hz), 2.19-2.10 (comp m, 3H), 1.96 (t, *J* = 1.8 Hz, 3H), 1.86-1.75 (m, 1H), 1.66-1.56 (m, 1H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.5, 155.6, 135.6, 134.4 130.3, 129.6, 129.5, 128.8, 118.2, 43.1, 41.7, 33.1, 26.9, 22.3, 12.9; IR (Neat Film NaCl) 3074, 2964, 2929, 1652, 1582, 1440, 1339, 1287, 1228 cm^{-1}; HRMS (FAB+) *m/z*: calc'd for $C_{17}H_{20}OS$ [M + H]$^+$: 273.1313, found 273.1317; $[\alpha]_D^{25.4}$ –57.4 (*c* 1.00, CH_2Cl_2).



Isomerized alkene (–)-472. A solution of allyl ketone (–)-**268** (0.80 g, 2.94 mmol, 1.00 equiv) and $PdCl_2(CH_3CN)_2$ (76.3 mg, 0.29 mmol, 0.10 equiv) in benzene (5.8 mL) was sparged with Ar for 10 min. The flask was sealed, and heated to 60 °C for 12 h. The reaction was cooled to room temperature, the solvent was evaporated in vacuo, and the resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to afford an inseparable mixture of isomerized alkene (–)-**472** and starting material (–)-**268** (0.7951 g, 99% overall yield, ratio of 13:1 of **472**:**268** by NMR). R_f = 0.45 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ (additional peaks correspond to compound **268**) 7.52-7.47 (m, 2H), 7.36-7.42 (comp m, 3H), 5.45 (dq, *J* = 1.5, 15.5 Hz, 1H), 5.33 (dq, *J* =

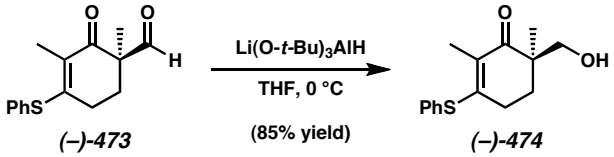
6.0, 15.5 Hz, 1H), 2.26-2.04 (m, 2H), 1.98 (t, J = 1.5 Hz, 3H), 1.83-1.72 (m, 2H), 1.66 (dd, J = 2.0, 6.5 Hz, 3H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 155.9, 135.5, 133.7, 130.4, 129.5, 129.4, 129.3, 124.9, 46.2, 35.3, 27.4, 24.3, 18.5, 12.9; IR (Neat Film NaCl) 2923, 1651, 1588, 1440, 1372, 1339 1287, 1230 cm^{-1}; HRMS (FAB+) *m/z*: calc'd for $C_{17}H_{20}OS$ [M + H]$^+$: 273.1313, found 273.1314; $[\alpha]_D^{26.0}$ –34.8 (*c* 1.00, CH_2Cl_2).



Aldehyde (–)-473. To a solution of $K_3Fe(CN)_6$ (2.18 g, 6.61 mmol, 3.00 equiv), K_2CO_3 (0.91 g, 6.61 mmol, 3.00 equiv), 1,4-diazabicyclo[2.2.2]octane (DABCO) (0.124 g, 1.01 mmol, 0.50 equiv), and 13:1 isomeric mixture of α-vinyl ketone (–)-**472** and α-allyl ketone (–)-**268** (0.60 g, 2.20 mmol, 1.00 equiv) was added solid OsO_4 (56.0 mg, 0.22 mmol, 0.10 equiv), and the solution was allowed to stir at 35 °C for 12 h. Saturated aq Na_2SO_3 (20 mL) was added, and the solution was allowed to stir for 1 h. The phases were separated, and the aq phase was extracted with Et_2O (3 x 30 mL), dried over Na_2SO_3, filtered, and concentrated. The isolated white solid was used in the next step without further purification.

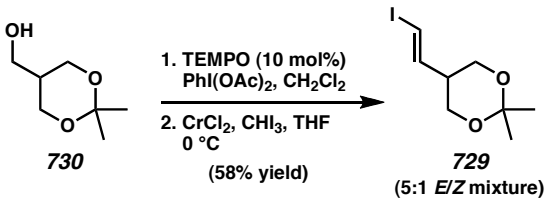
To a solution of the crude white solid (0.64 g) in benzene (17 mL) was added $Pb(OAc)_4$ (1.02 g, 2.31 mmol, 1.10 equiv), and the solution was allowed to stir at 30 °C for 1 h. The solution was concentrated in vacuo, and the resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to afford aldehyde (–)-**473** (0.40 g, 70% yield over two steps) as a white solid. R_f = 0.60 (30% EtOAc in hexanes); mp 41

°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.52-7.36 (comp m, 5H), 2.35-2.10 (m, 3H), 1.98 (t, *J* = 1.5 Hz, 3H), 1.76-1.67 (m, 1H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 193.7, 159.2, 135.9, 130.0, 129.7, 129.4, 128.9, 56.4, 29.0, 26.7, 18.9, 12.5; IR (Neat Film NaCl) 2931, 1725, 1642, 1578, 1440, 1339, 1312, 1239, 1025 cm^{-1}; HRMS (FAB+) *m/z*: calc'd for $C_{15}H_{16}O_2S$ $[M + H]^+$: 261.0949, found 261.0944; $[\alpha]_D^{25.6}$ –30.4 (*c* 1.00, CH_2Cl_2).



Alcohol (–)-474. A solution of lithium tri-*tert*-butoxy aluminium hydride (1.34 mL, 1.00 M solution in THF, 1.41 mmol, 1.05 equiv) in THF (7 mL) was cooled to 0 °C. This solution was then added to a 0 °C solution of aldehyde (–)-**473** (0.35 g, 1.35 mmol, 1.00 equiv) in THF (20 mL) in seven equal portions over 2 h. The reaction was allowed to stir for an additional 30 min, then H_2O (0.3 mL) was added, followed by 15% aq NaOH (0.3 mL), and then H_2O (0.9 mL). The reaction was warmed to 23 °C, and allowed to stir for 30 min. The solution was filtered through Celite (washing with EtOAc), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford alcohol (–)-**474** (0.30 g, 85% yield) as a white solid (90.3% ee as determined by chiral HPLC using a Chiralpak AD column with 80% EtOH in hexanes as the eluent). R_f = 0.22 (30% EtOAc in hexanes); mp 49 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54-7.49 (m, 2H), 7.46-7.40 (comp m, 3H), 3.51 (dd, *J* =11.1, 8.1 Hz, 2H), 2.88 (dd, *J* = 5.1, 7.8 Hz, 1H), 2.38-2.10 (comp m, 2H), 1.98-1.88 (comp m, 4H), 1.46 (ddd, *J* = 3.3, 4.8, 13.2 Hz, 1H), 1.11 (s, 3H); ^{13}C NMR (75 MHz,

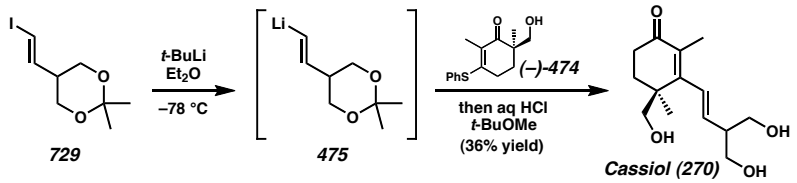
$CDCl_3$) δ 201.2, 157.8, 135.8, 129.8, 129.6, 128.4, 69.5, 44.5, 31.1, 26.7, 18.8, 12.5; IR (Neat Film NaCl) 3433 (br.), 2927, 1642, 1578, 1440, 1339, 1025, 750 cm^{-1}; HRMS (FAB+) *m/z*: calc'd for $C_{15}H_{18}O_2S$ $[M + H]^+$: 263.1106, found 263.1115; $[\alpha]_D^{26.1}$ –13.3 (*c* 1.00, CH_2Cl_2).



Vinyl iodide 729. 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO, 0.0424 g, 0.27 mmol, 0.10 equiv) was added to a solution of alcohol **730**[35] (0.40 g, 2.74 mmol, 1.00 equiv) in CH_2Cl_2 (8 mL), and the reaction was allowed to stir for 5 min. To the reaction vessel was added solid bis(acetoxy)iodobenzene (0.97 g, 3.01 mmol, 1.10 equiv) was added, and the reaction was allowed to stir for 12 h at 23 °C. The reaction was diluted with CH_2Cl_2 (8 mL), washed with saturated aq $Na_2S_2O_3$ (1 x 15 mL), and the aq phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were washed with saturated aq $NaHCO_3$ (1 x 15 mL) and brine (1 x 15 mL), dried over Na_2SO_4, filtered through Celite, and concentrated in vacuo to yield a white oil. The crude product was used without further purification in the following step.

The crude oil was added to a solution of iodoform (2.15 g, 5.47 mmol, 2.00 equiv) in THF (7 mL), and then cooled to 0 °C. The resulting solution was transferred via cannula to a 0 °C suspension of chromium(II) chloride (2.00 g, 16.27 mmol, 5.95 equiv) in THF (30 mL), washing with THF (2 mL) to effect quantitative transfer. The reaction was allowed to stir for 4 h, and then H_2O (40 mL) was added, the phases were separated, and

the aq phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with H_2O (1 x 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography (gradient elution of 3% to 10% EtOAc in hexanes) yielded vinyl iodide **729** (0.42 g, 58% yield, 5:1 *E*/*Z* by ^{1}H NMR) as a thick yellow oil. R_f = 0.29 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ (trans isomer) 6.02 (dd, *J* = 8.5, 15.0 Hz, 1H), 5.62 (d, *J* = 15.0 Hz, 1H), 3.45 (dd, *J* = 5.0, 12.0 Hz, 2H), 3.25 (dd, *J* = 9.0, 12.0 Hz, 2H), 2.04 (dtt, *J* = 9.0, 8.5, 5.0 Hz, 1H), 1.38 (s, 3H), 1.20 (s, 3H); (cis isomer): 5.89 (d, *J* = 7.5 Hz, 1H), 5.79 (dd, *J* = 7.5, 8.5 Hz, 1H), 3.67 (dd, *J* = 4.0, 11.5 Hz, 2H), 3.41 (dd, *J* = 7.0, 11.5 Hz, 2H), 3.25 (dd, *J* = 9.0, 11.5 Hz, 2H), 2.66 (dtt, *J* = 7.0, 8.5, 4.0 Hz, 1H), 1.36 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ (trans isomer) 143.6, 98.0, 78.5, 63.2, 42.2, 27.6, 21.2; IR (Neat Film NaCl) 2992, 2940, 2863, 1604, 1478, 1453, 1386, 1371, 1262, 1205, 1153, 1131, 1076, 1036, 949, 830 cm^{-1}; HRMS (FAB+) *m*/*z*: calc'd for $C_8H_{13}O_2I$ $[M + H]^+$: 269.0039, found 269.0040.



(+)-Cassiol (270).[36] To a solution of vinyl iodide **729** (0.204 g, 0.76 mmol, 2.00 equiv) in diethyl ether (5 mL) at –78 °C was added dropwise *t*-BuLi (1.37 M soln in pentane, 1.18 mL, 1.62 mmol, 4.25 equiv). The solution was allowed to stir for 1 h, and then warmed to 0 °C. A solution of alcohol (–)-**474** (0.10 g, 0.38 mmol, 1 equiv) in diethyl ether (2.5 mL) was cooled to 0 °C, and added to the reaction vessel dropwise via

cannula, washing with ether (2.5 mL) for quantitative transfer. The resulting solution was warmed to 24 °C, and allowed to stir for 72 h. To the reaction vessel was added saturated aq $NaHCO_3$ buffered to pH 8 with saturated aq NH_4Cl (7 mL). The phases were separated, the aq phase was extracted with EtOAc (3 x 10 mL), and the combined organic extracts were concentrated in vacuo. The residue was dissolved in *t*-butyl methyl ether (8 mL), and 10% aq HCl solution (10 mL) was added to the reaction vessel. The solution was allowed to stir for 2 h, and solid $NaHCO_3$ (4.0 g) was added in small portions. The phases were separated, and the aq phase was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (10% MeOH in EtOAc), followed by purification by column chromatography on Florisil (100% EtOAc) afforded (+)-cassiol (**270**, 35.0 mg, 36%) as a thick colorless oil. R_f = 0.10 (10% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, D_2O) δ 6.27 (d, *J* = 16.5 Hz, 1H), 5.66 (dd, *J* = 8.5, 16.5 Hz, 1 H), 3.77 (d, *J* = 11.5 Hz, 1H), 3.74 (ddd, *J* = 3.0, 6.0, 11.0 Hz, 2H), 3.66 (ddd, *J* = 2.0, 7.0, 11.0 Hz, 2H), 3.43 (d, *J* =11.5, 1H), 2.68-2.52 (comp m, 3H), 2.17 (ddd, *J* = 5.5, 11.0, 14.0 Hz, 1H), 1.80 (s, 3H), 1.75 (app dt, *J* = 13.5, 6.0 Hz, 1H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, D_2O, uncorrected) δ 204.8, 162.4, 136.7, 132.0, 129.0, 68.0, 62.1, 48.0, 40.8, 33.5, 30.8, 20.5, 13.2; IR (Neat Film NaCl) 3369, 2930, 2868, 1643, 1591, 1455, 1358, 1038 cm^{-1}; HRMS (FAB+) *m/z*: calc'd for $C_{14}H_{22}O_4$ $[M + H]^+$: 255.1596, found 255.1604; $[\alpha]_D^{26.8}$ +8.2 (*c* 1.00, MeOH).

NMR data for (+)-cassiol was also collected in $CDCl_3$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23 (d, *J* = 16.5 Hz, 1H), 5.59 (dd, *J* = 8.0, 16.5 Hz, 1H), 3.73-3.86 (comp m, 4H), 3.67 (d, *J* = 11.5 Hz, 1H), 3.38 (d, *J* = 11.5 Hz, 1H), 2.78-2.58 (comp. m, 3H), 2.58-2.51

(comp m, 2H), 2.41 (br. s, 1H), 2.21 (ddd, J = 6.5, 10.5, 14.0 Hz, 1H), 1.82 (s, 3H), 1.64 (dt, J = 13.5, 5.5 Hz, 1H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6, 158.4, 135.2, 132.1, 129.6, 69.7, 64.139, 64.131, 47.7, 41.0, 34.0, 32.1, 21.1, 13.7.

9.6.3 COMPARISON TABLES FOR PROPERTIES OF SYNTHETIC AND NATURAL CASSIOL

Table 9.2. Comparison of ^{1}H NMR data for synthetic, literature, and natural (+)-cassiol

Synthetic[a] (ppm)	Multiplicity	Literature[b] (ppm)	Multiplicity	Natural sample[c] (ppm)	Multiplicity
6.27	d (1H)	6.28	d (1H)	6.28	dt (1H)
5.66	dd (1H)	5.67	dd (1H)	5.67	dd (1H)
3.76	d (1H)	3.76	d (1H)	3.76	d (1H)
3.75	ddd (2H)	3.75	dd (2H)	3.75	dd (2H)
3.66	ddd (2H)	3.66	dd (2H)	3.66	dd (2H)
3.43	d (1H)	3.43	d (1H)	3.43	d (1H)
2.68–2.52	comp m (3H)	2.71–2.55	m (3H)	2.69–2.51	ddd (3H)
2.17	ddd	2.17	ddd (1H)	2.17	ddd (1H)
1.80	br s	1.81	d (3H)	1.81	d (3H)
1.75	app dt	1.74	dt (1H)	1.75	ddd (1H)
1.11	s (3H)	1.12	s (3H)	1.12	s (3H)

[a] ^{1}H NMR data measured at 500 MHz in D_2O (this work).
[b] ^{1}H NMR data measured at 250 MHz in D_2O.[37]
[c] ^{1}H NMR data measured at 250 MHz in D_2O.[38]

Table 9.3. Comparison of ^{13}C NMR data for synthetic, literature, and natural (+)-cassiol

Synthetic[a]	Literature[b]	Natural sample[c]
204.8	207.12	207.1
162.4	164.87	164.7
136.7	139.17	139.0
132.0	134.35	134.2
129.0	131.37	131.3
68.0	70.44	70.4
62.1	64.55	64.5
48.0	50.30	50.1
40.8	43.18	43.1
33.5	35.89	35.8
30.8	33.28	33.2
20.5	23.02	22.9
13.2	15.63	15.5

[a] ^{13}C NMR data measure at 125 MHz in D_2O (this work).
[b] ^{13}C NMR data measure at 50 MHz in D_2O.[37]
[c] ^{13}C NMR data measure at 50.3 MHz in 1:1 $CDCl_3$/methanol-d_4.[38]

Table 9.4. Comparison of IR data for synthetic, literature, and natural (+)-cassiol

Synthetic[a]	Literature[b]	Natural sample[c]
3369	3368	3400
2930	2930	
2868	2876	
1643	1644	1650
1591	1594	1600
1455	1456	
1358		1340
1038	1044	1040
975		980

[a] Thin film (this work).
[b] Neat.[37]
[c] Thin film.[38]

Table 9.5. Comparison of HRMS data for synthetic, literature, and natural (+)-cassiol

Synthetic calculated	Synthetic found[a]	Literature calculated	Literature found[b]	Natural sample found[c]
255.1596	255.1604	254.1518	254.1519	254

[a] FAB+, measured $[M + H]^+$ (this work).
[b] EI-MS, measured $[M]^+$.[39]
[c] EI-MS, measured $[M]^+$.[38]

Table 9.6. Comparison of optical rotation data for synthetic, literature, and natural (+)-cassiol

Synthetic[a]	Literature[b]	Natural sample[c]
$[\alpha]_D^{26.8}$ +8.2	$[\alpha]_D^{30}$ +8.3	$[\alpha]_D^{28.5}$ +8.6

[a] $c = 1.00$ in MeOH (this work).
[b] $c = 0.35$ in MeOH.[37]
[c] $c = 0.25$ in MeOH.[38]

9.6.4 NOTES AND REFERENCES FOR EXPERIMENTAL SECTION

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APPENDIX 4

Spectra of Compound Relevant to Chapter 9



*Figure A4.1 ^1H NMR spectrum of compound **731** (500 MHz, $CDCl_3$)*

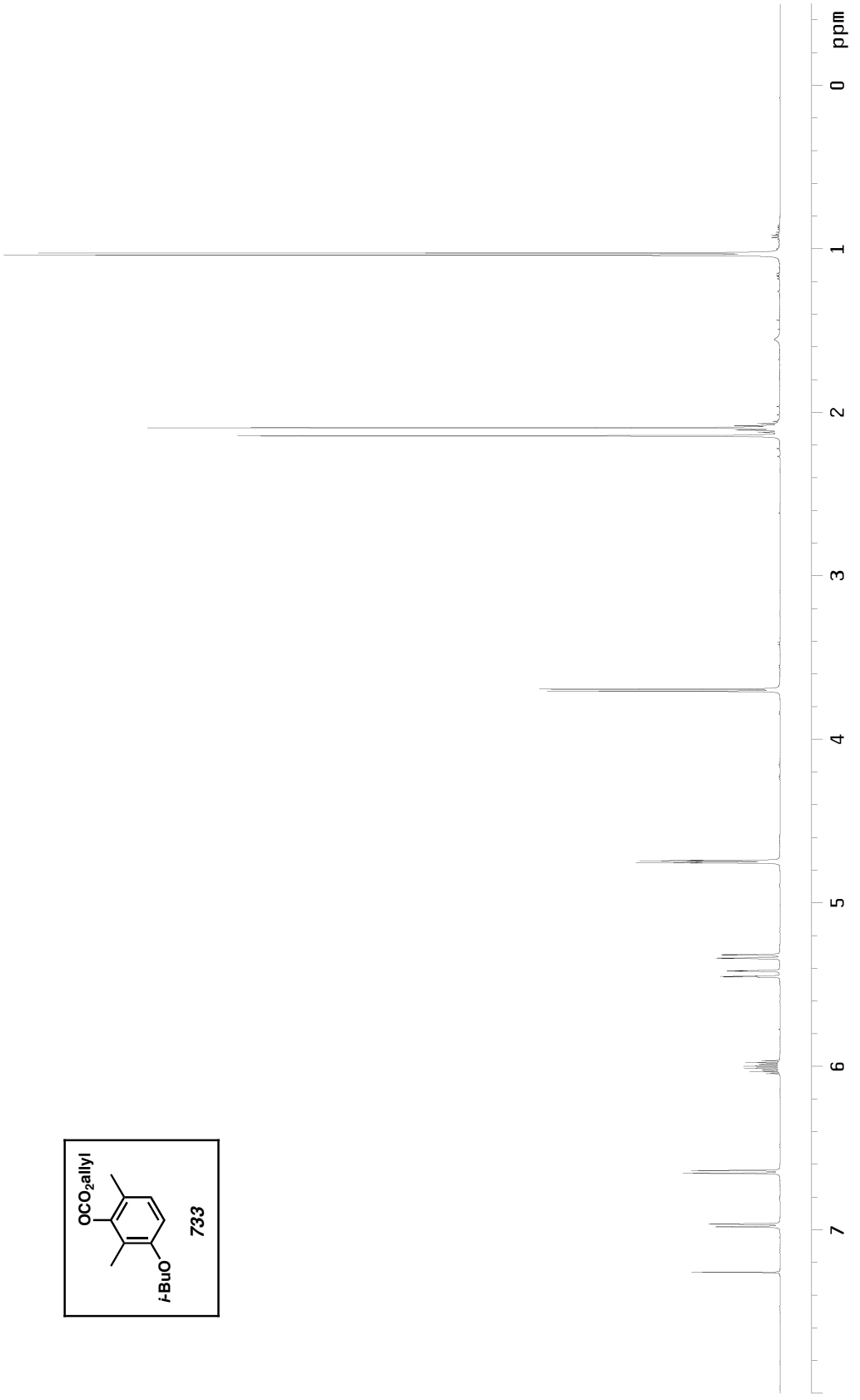


*Figure A4.2 ^1H NMR spectrum of compound **733** (500 MHz, $CDCl_3$)*

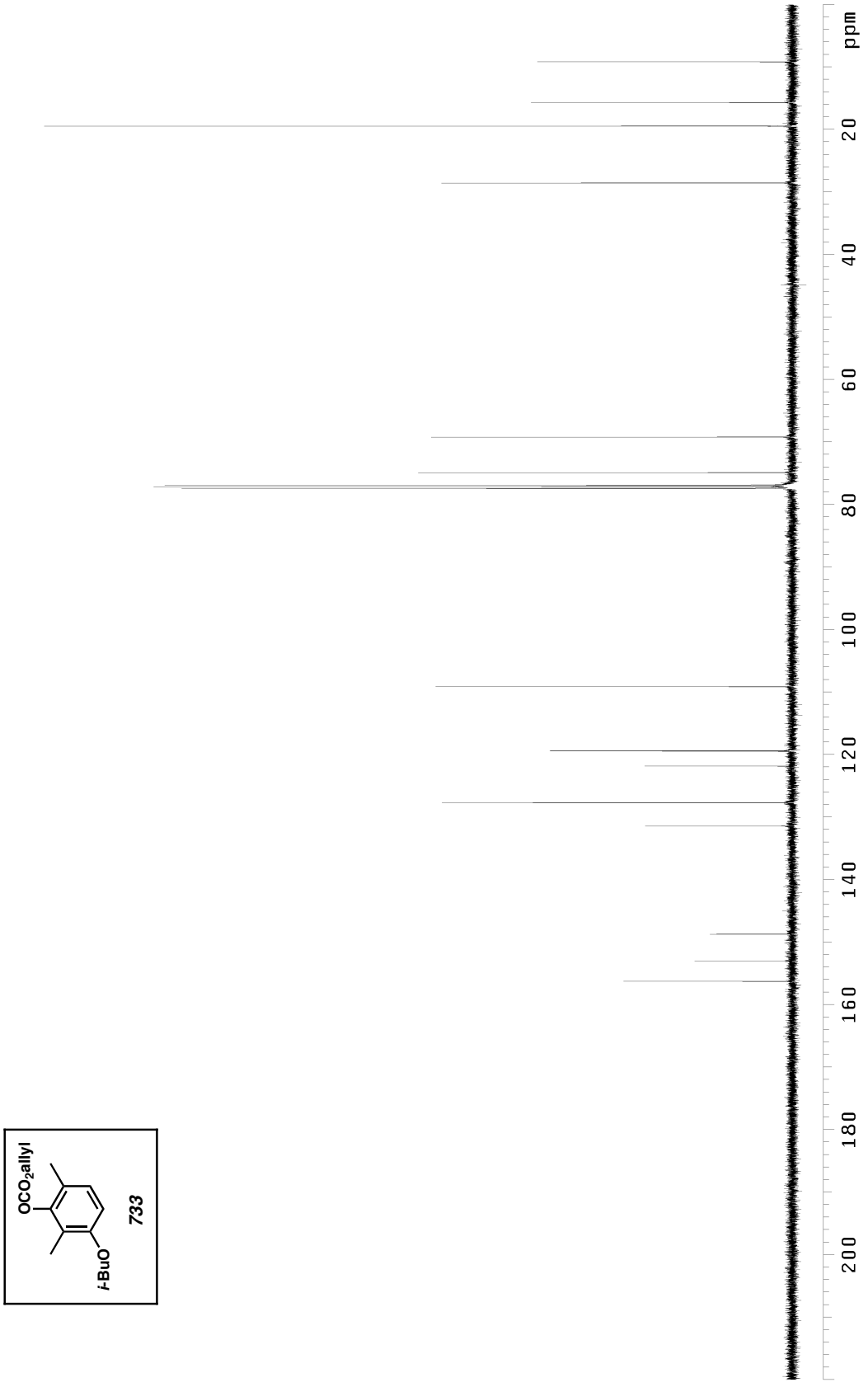


*Figure A4.3 ^{13}C NMR spectrum of compound **733** (126 MHz, $CDCl_3$)*

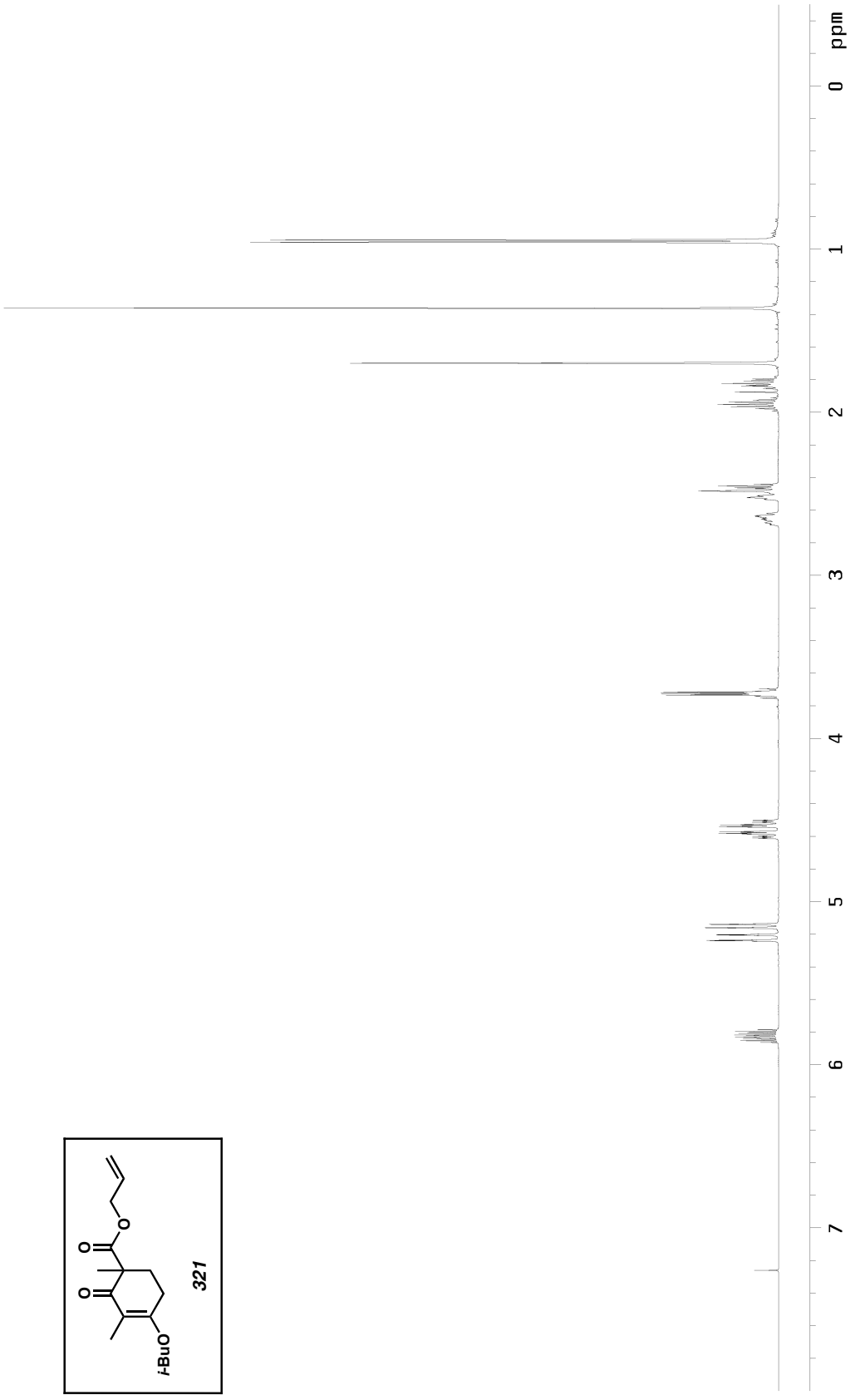


*Figure A4.4 ^1H NMR spectrum of compound **321** (500 MHz, $CDCl_3$)*

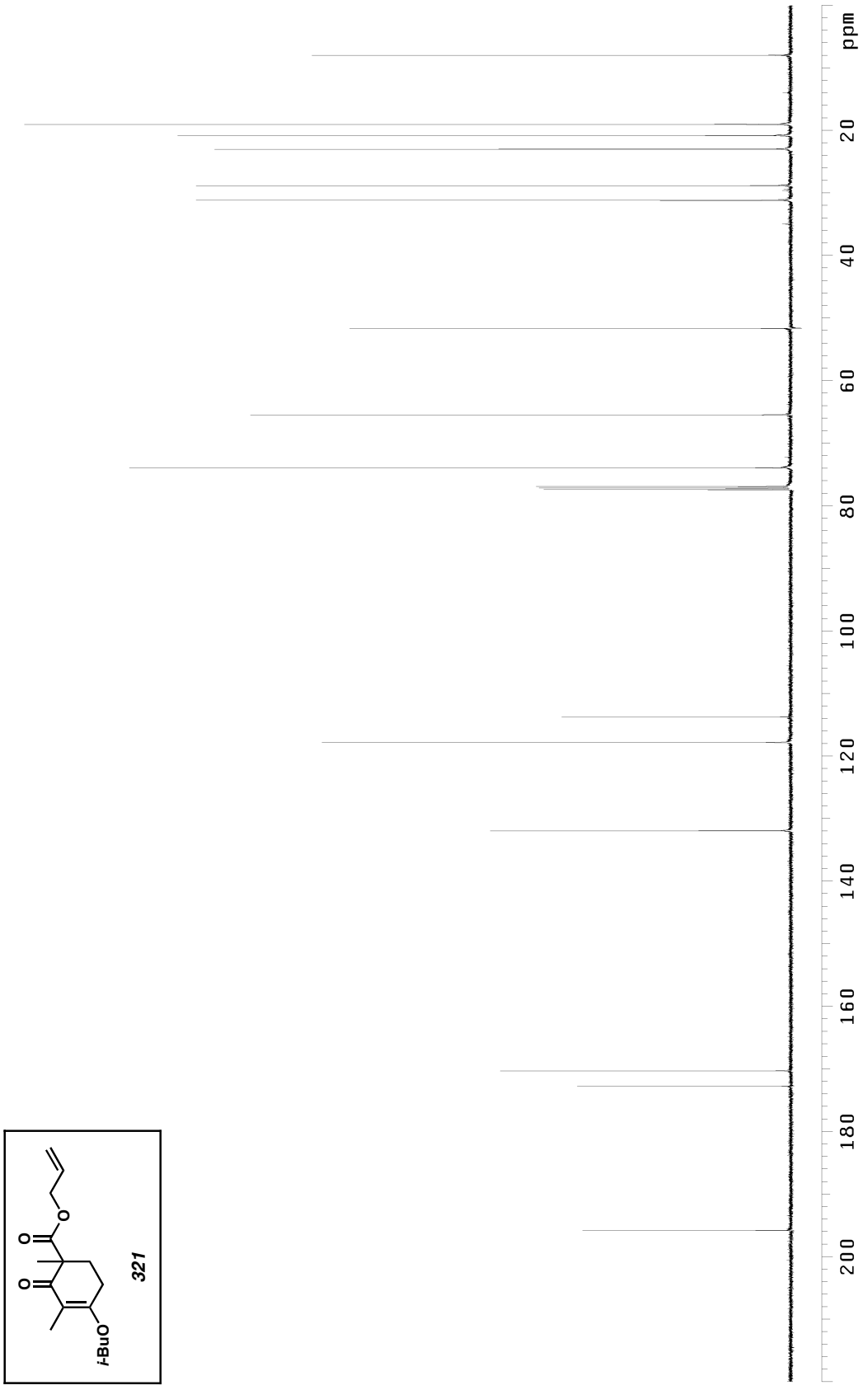


*Figure A4.5 ^{13}C NMR spectrum of **321** (126 MHz, $CDCl_3$)*

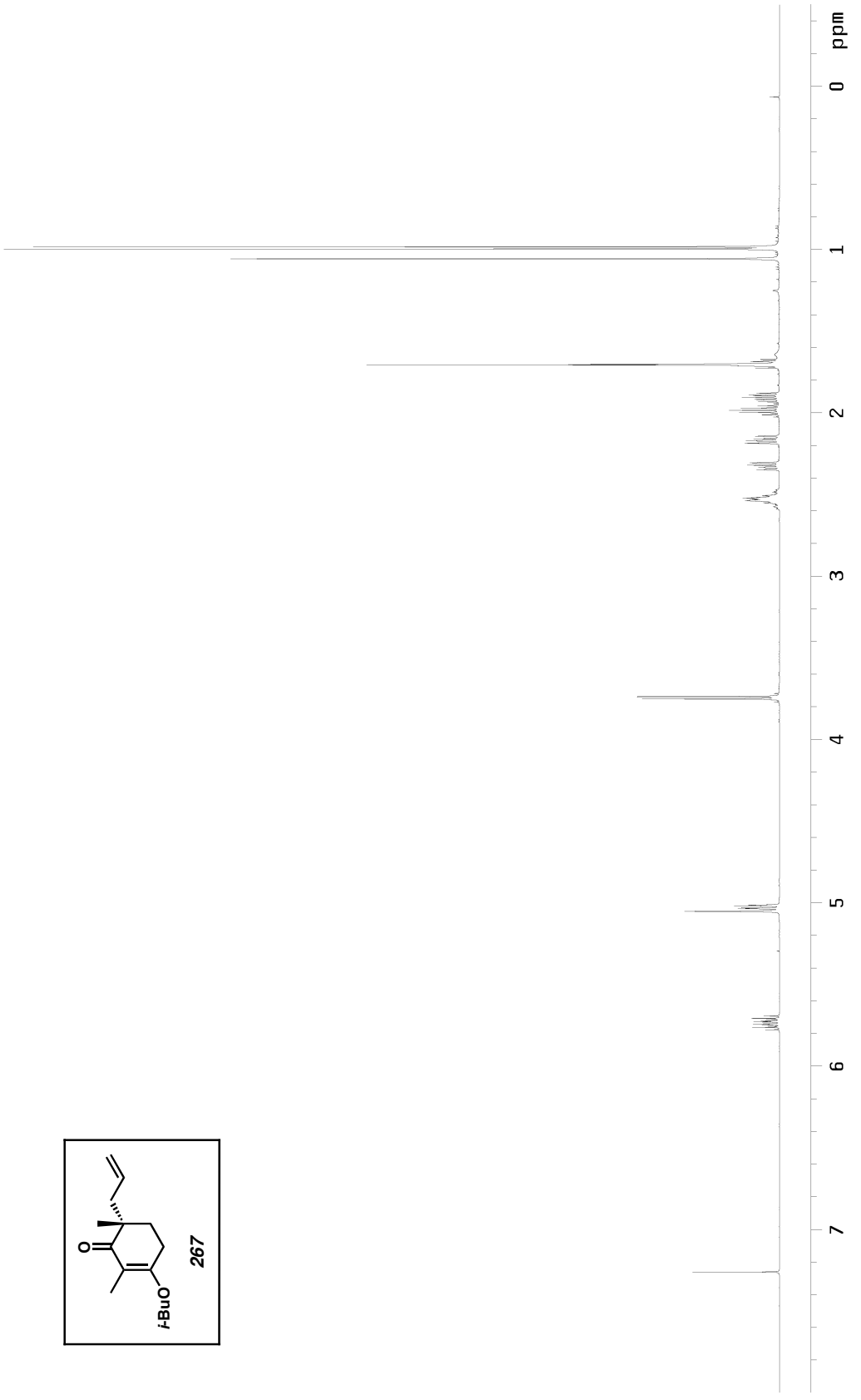


*Figure A4.6 ^1H NMR spectrum of compound **267** (500 MHz, $CDCl_3$)*

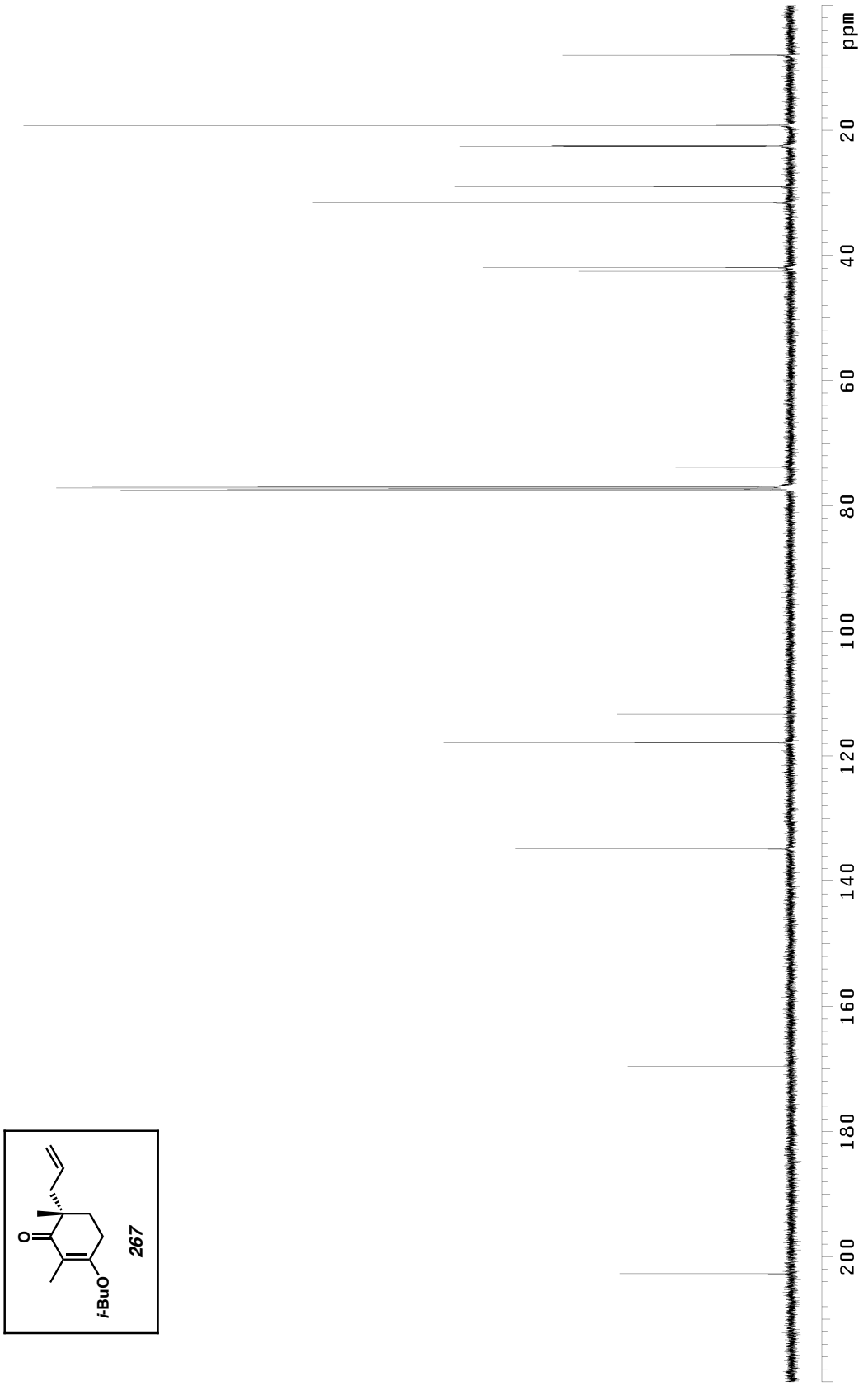


*Figure A4.7 ^{13}C NMR spectrum of compound **267** (126 MHz, $CDCl_3$)*

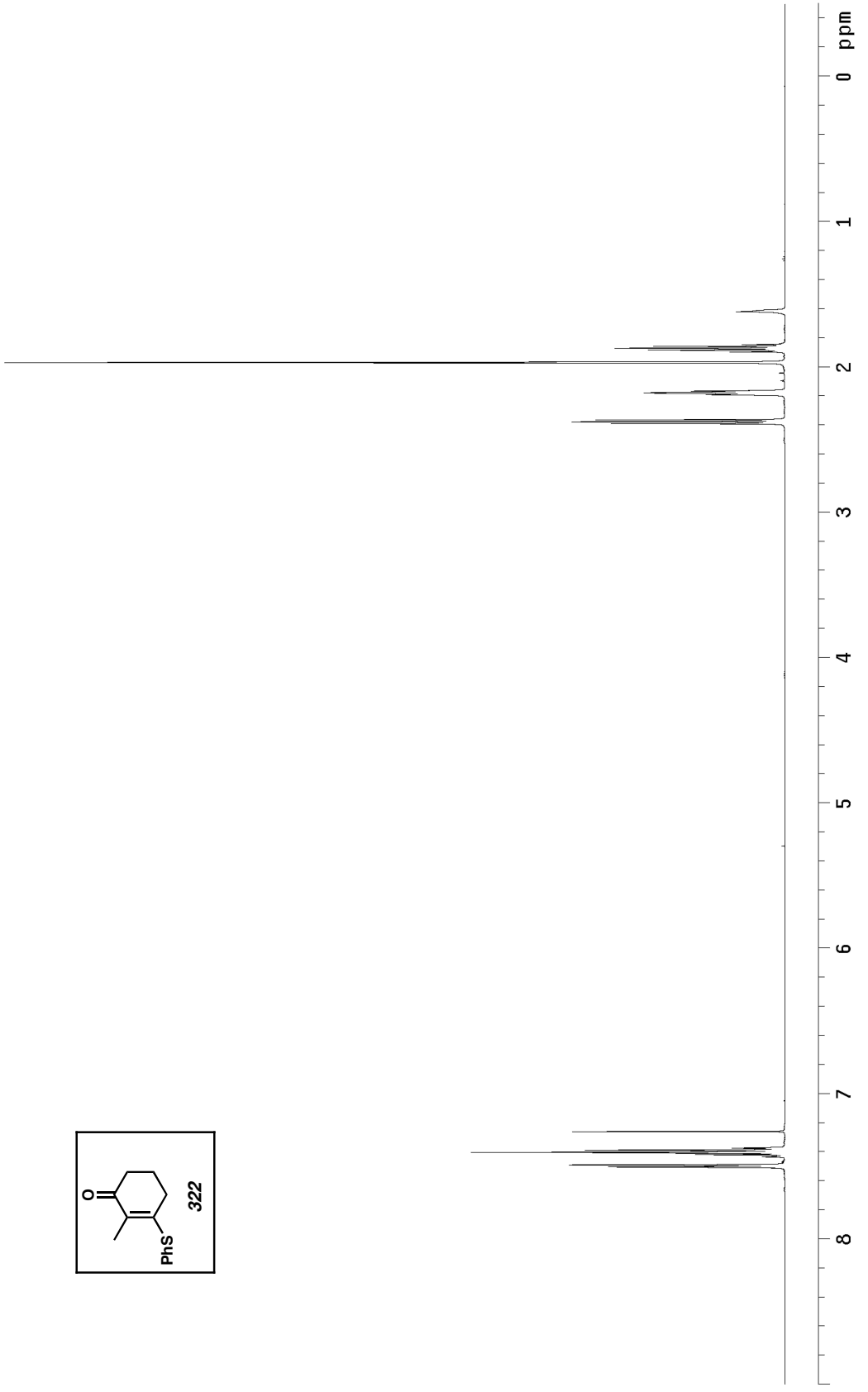


Figure A4.8 ^1H NMR spectrum of compound ***322*** *(500 MHz, $CDCl_3$)*

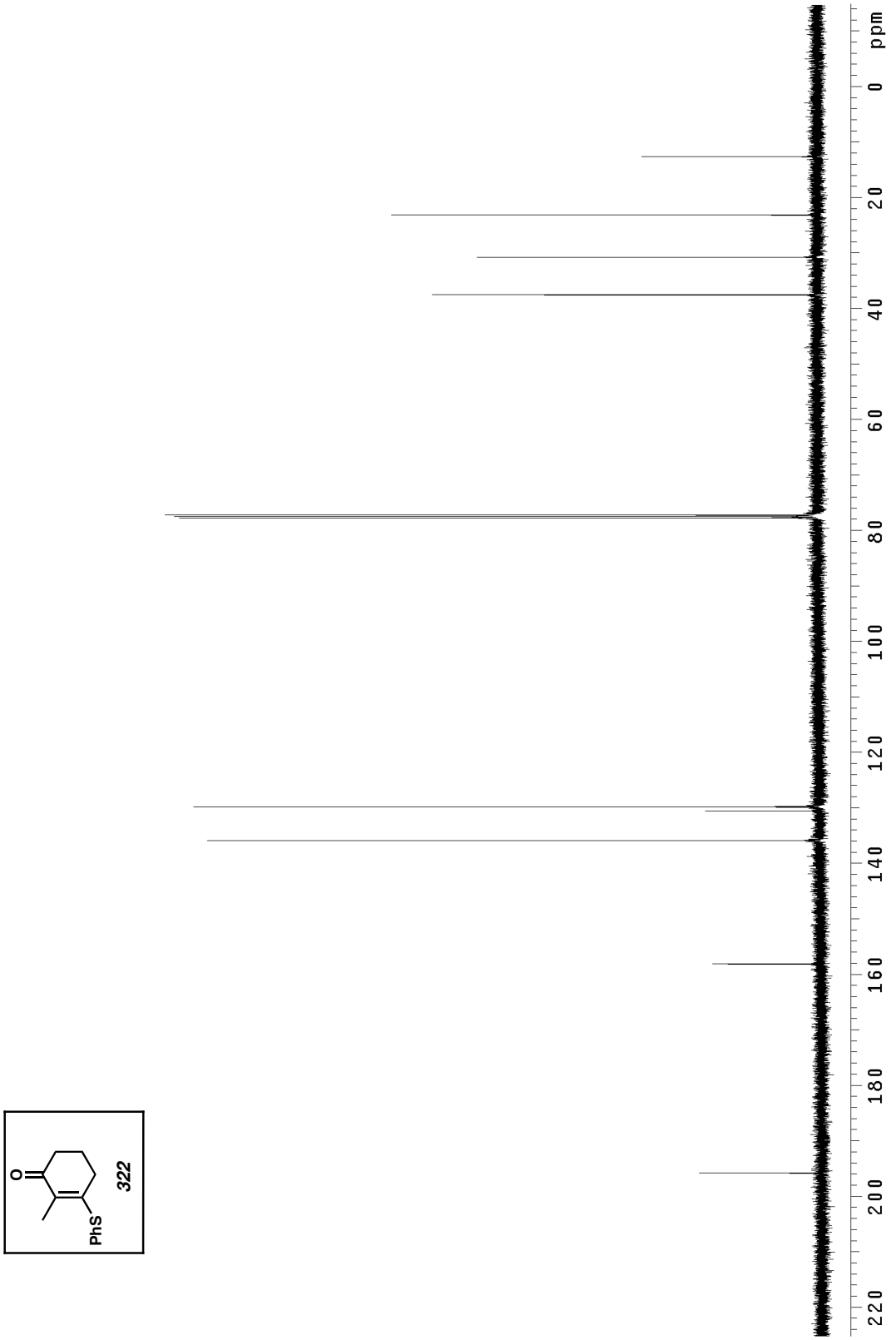


Figure A4.9 ^{13}C NMR spectrum of compound **322** *(126 MHz, $CDCl_3$)*

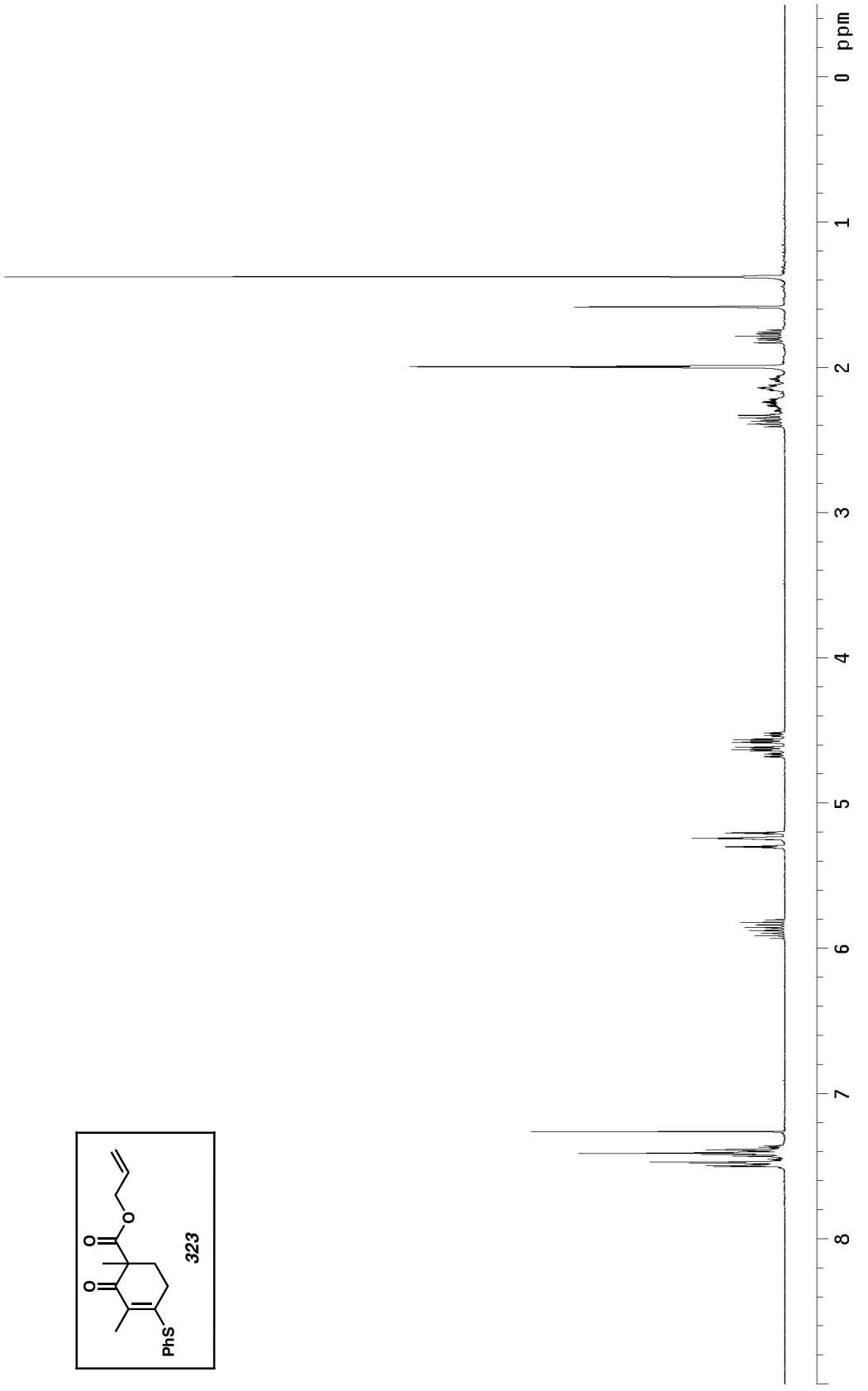


Figure A4.10 ^{1}H *NMR spectrum of compound* ***323*** *(300 MHz,* $CDCl_3$*)*

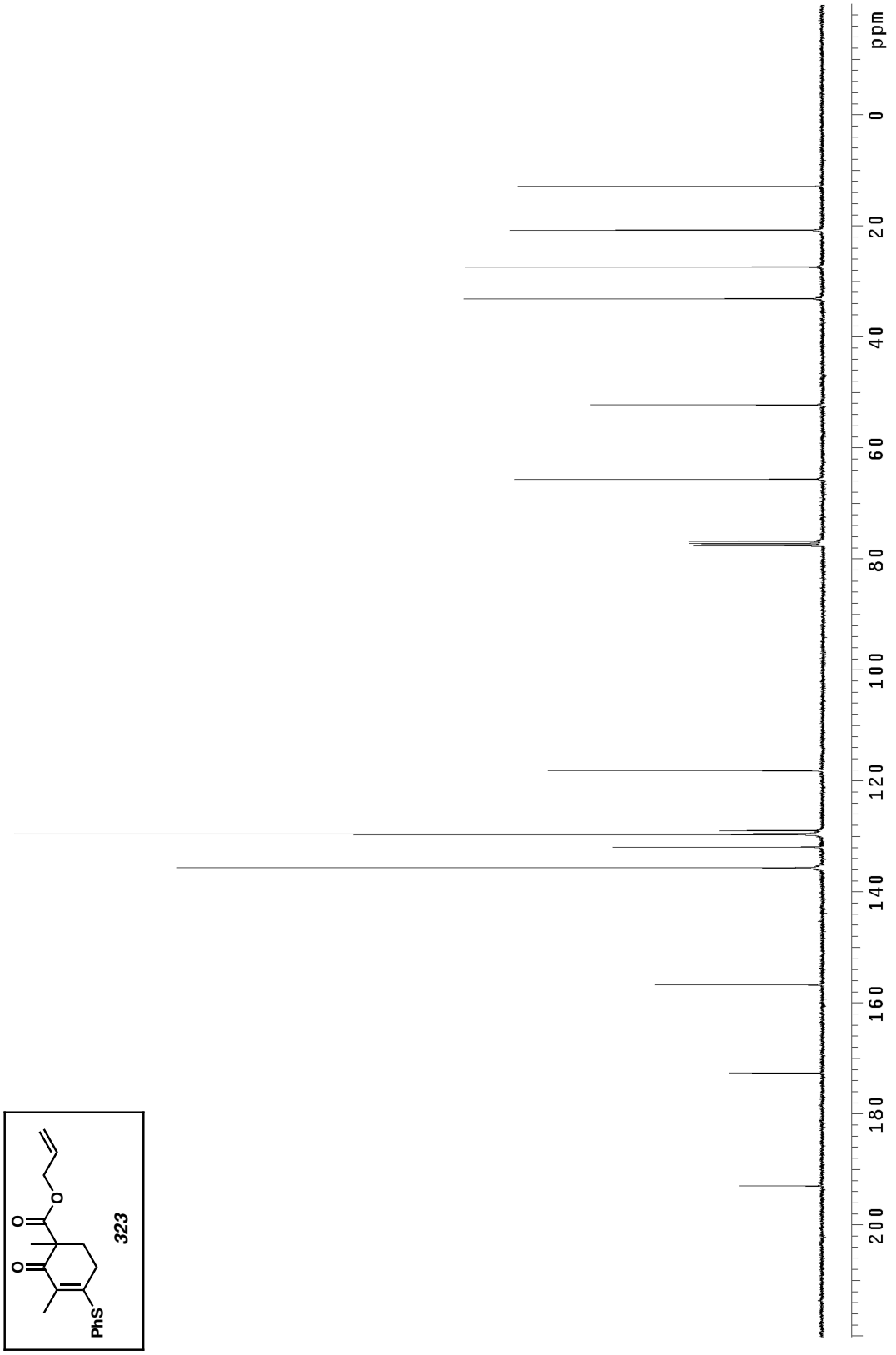


Figure A4.11 ^{13}C *NMR spectrum of compound* ***323*** *(75 MHz,* $CDCl_3$*)*

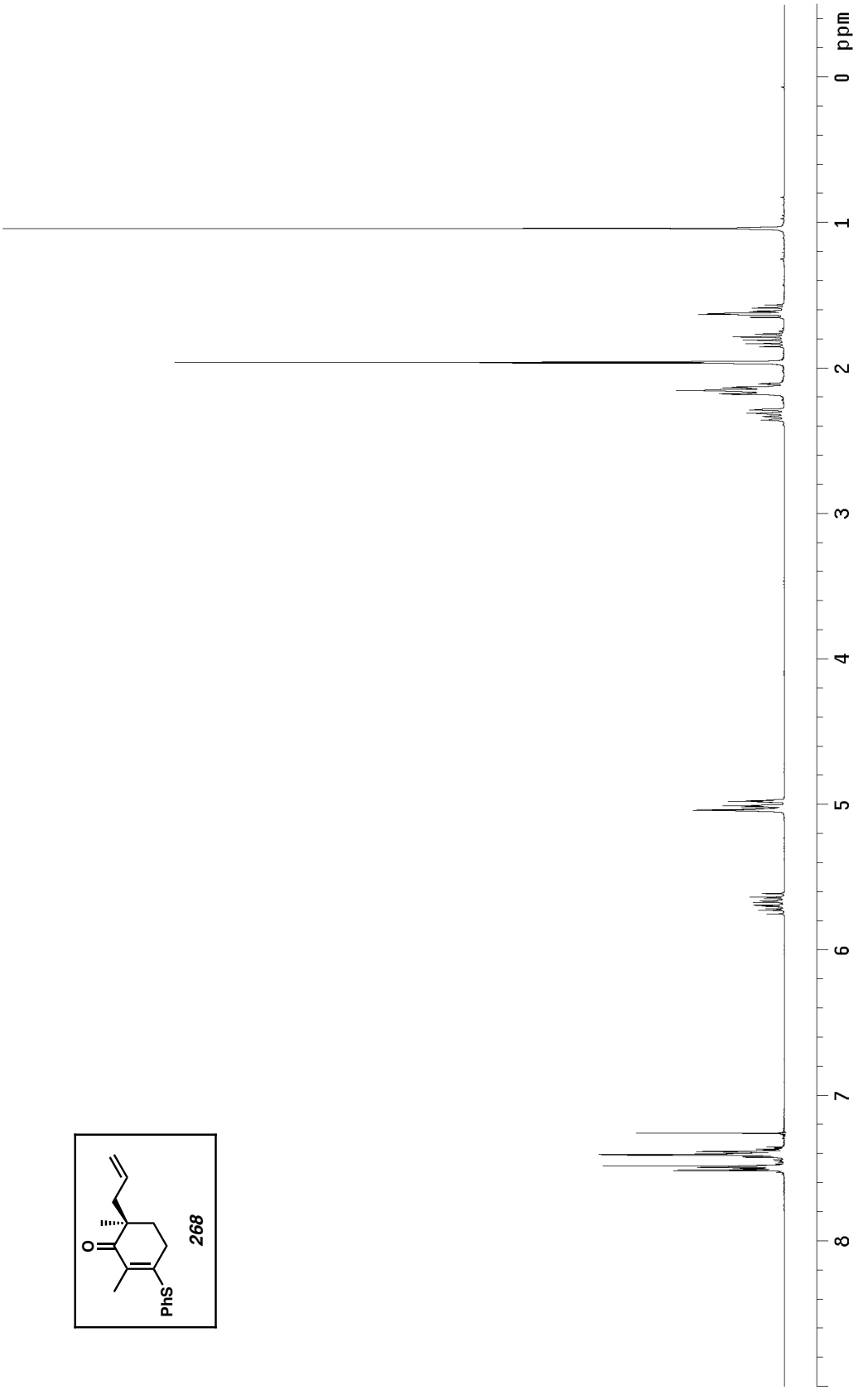


Figure A4.12 ^{1}H *NMR spectrum of compound* ***268*** *(300 MHz,* $CDCl_3$*)*

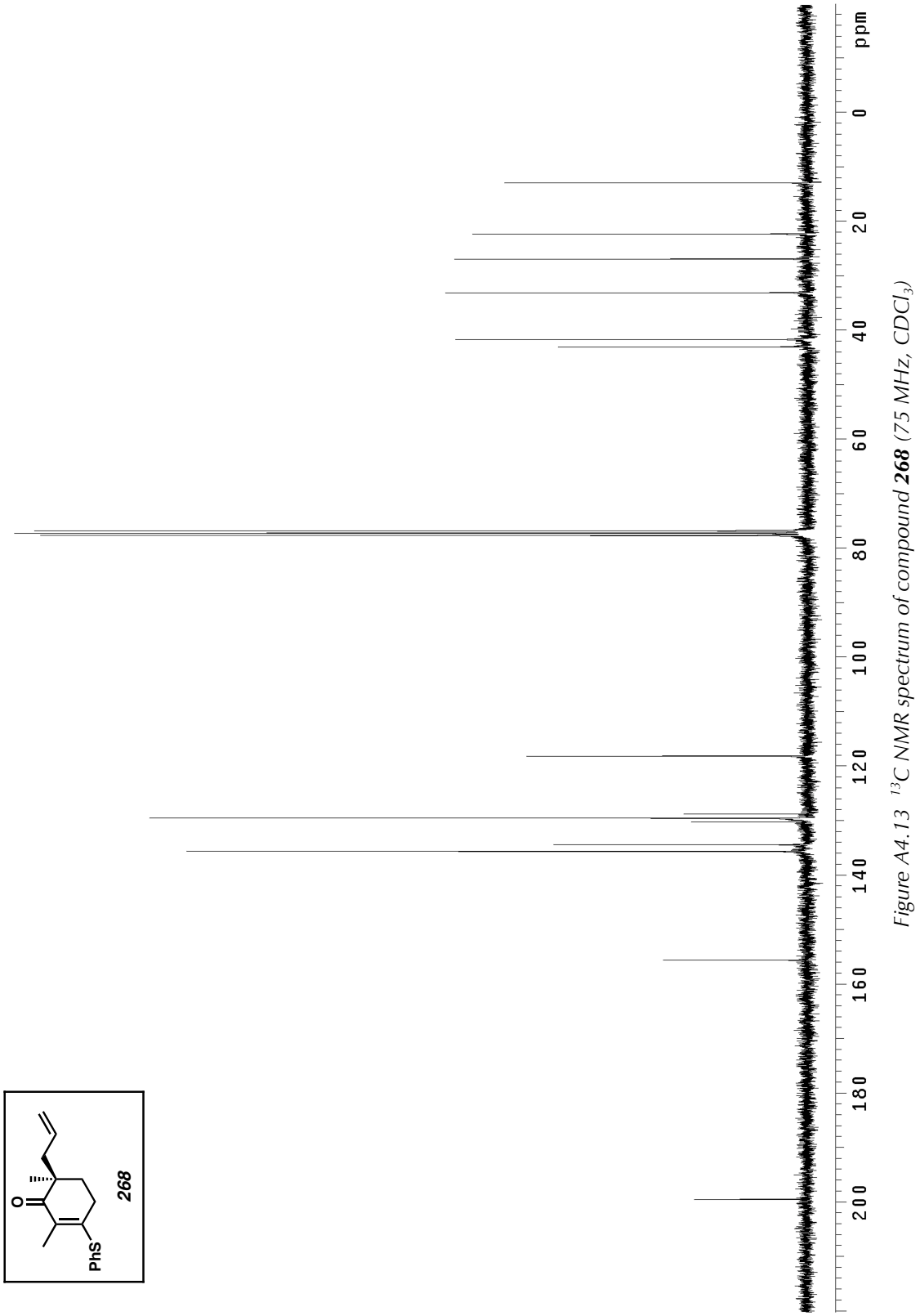


*Figure A4.13 ^{13}C NMR spectrum of compound **268** (75 MHz, $CDCl_3$)*

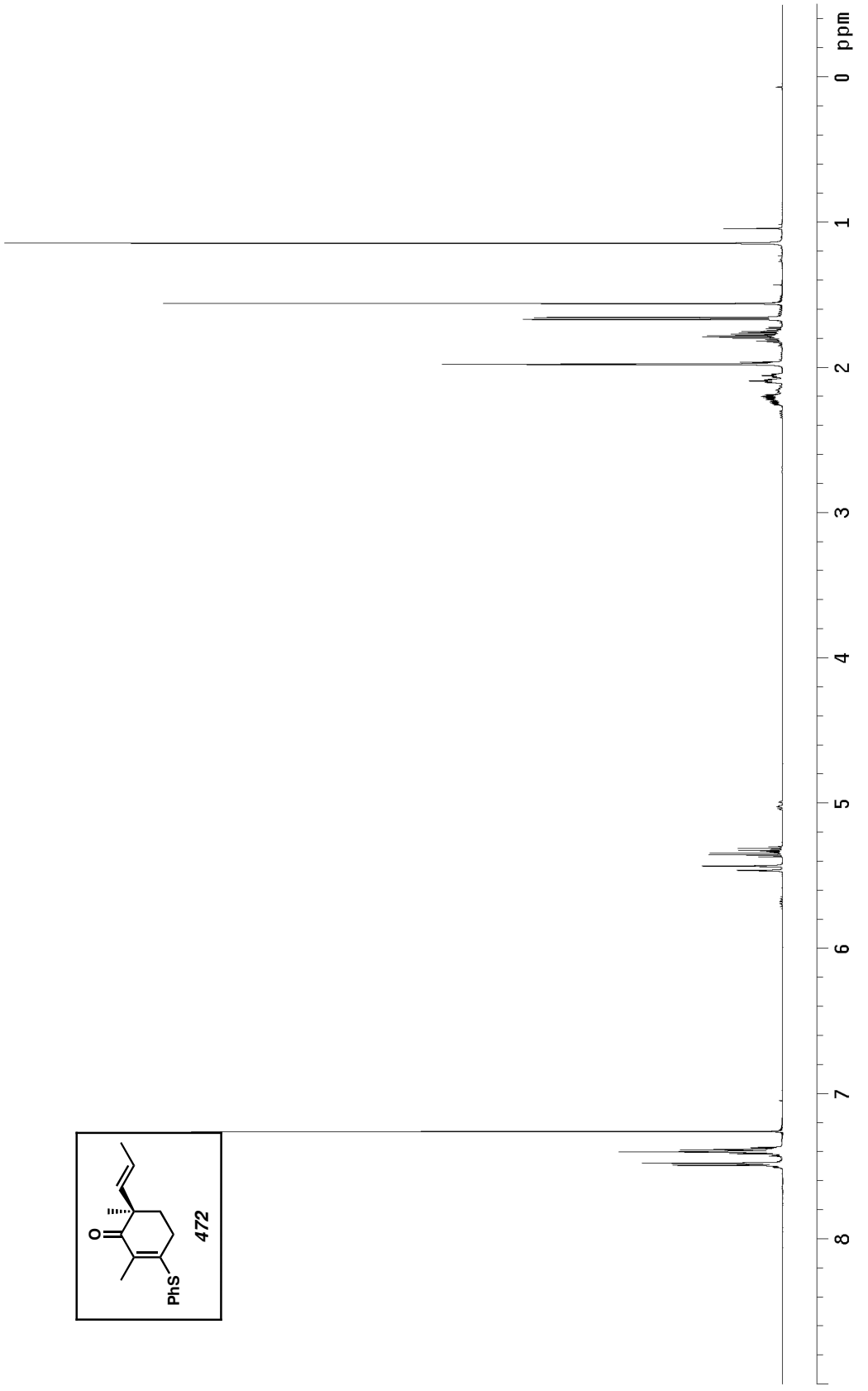


Figure A4.14 ^{1}H NMR spectrum of compound ***472*** *(500 MHz, $CDCl_3$)*

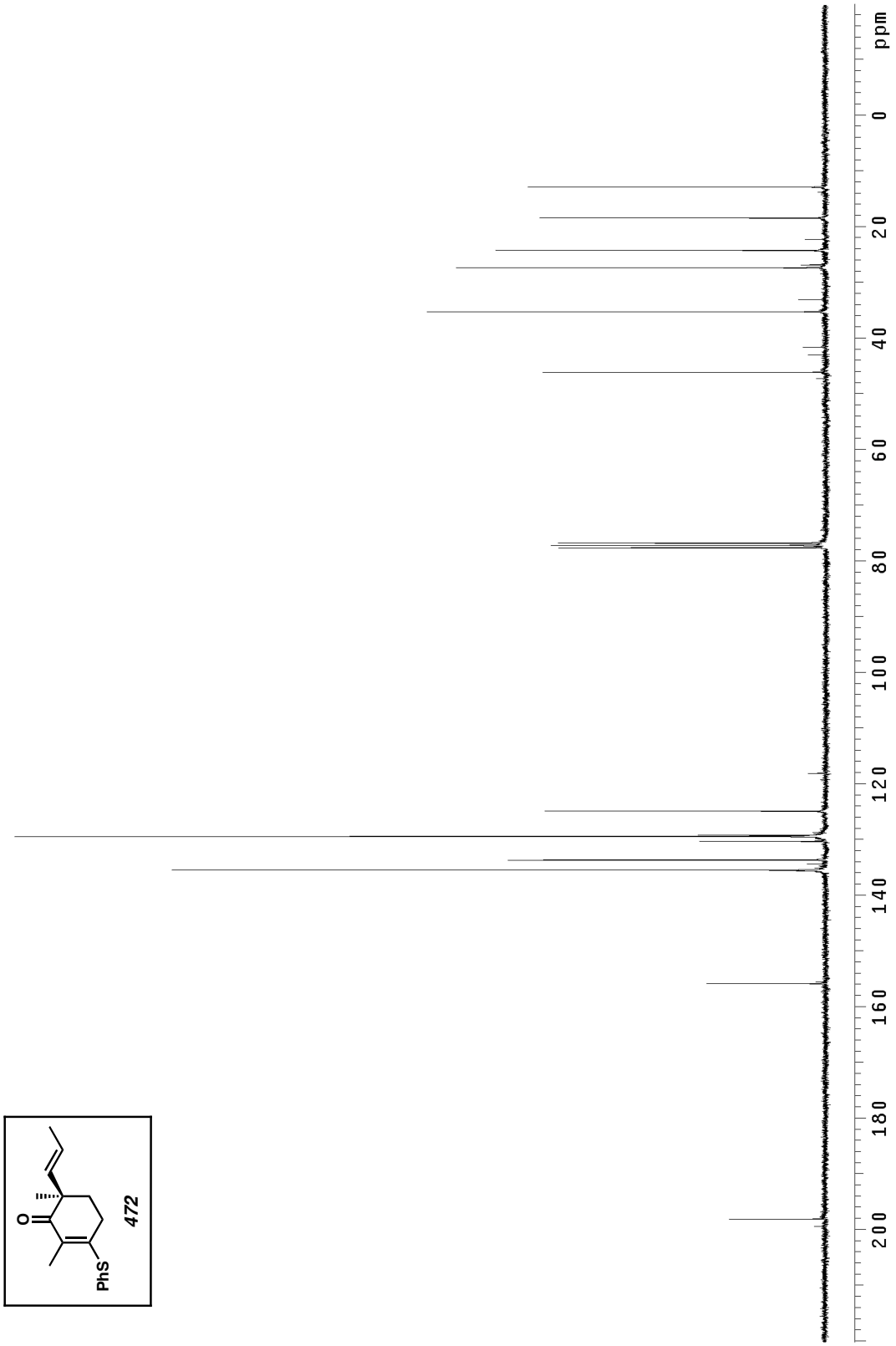


Figure A4.15 ^{13}C NMR spectrum of compound ***472*** *(75 MHz, $CDCl_3$)*

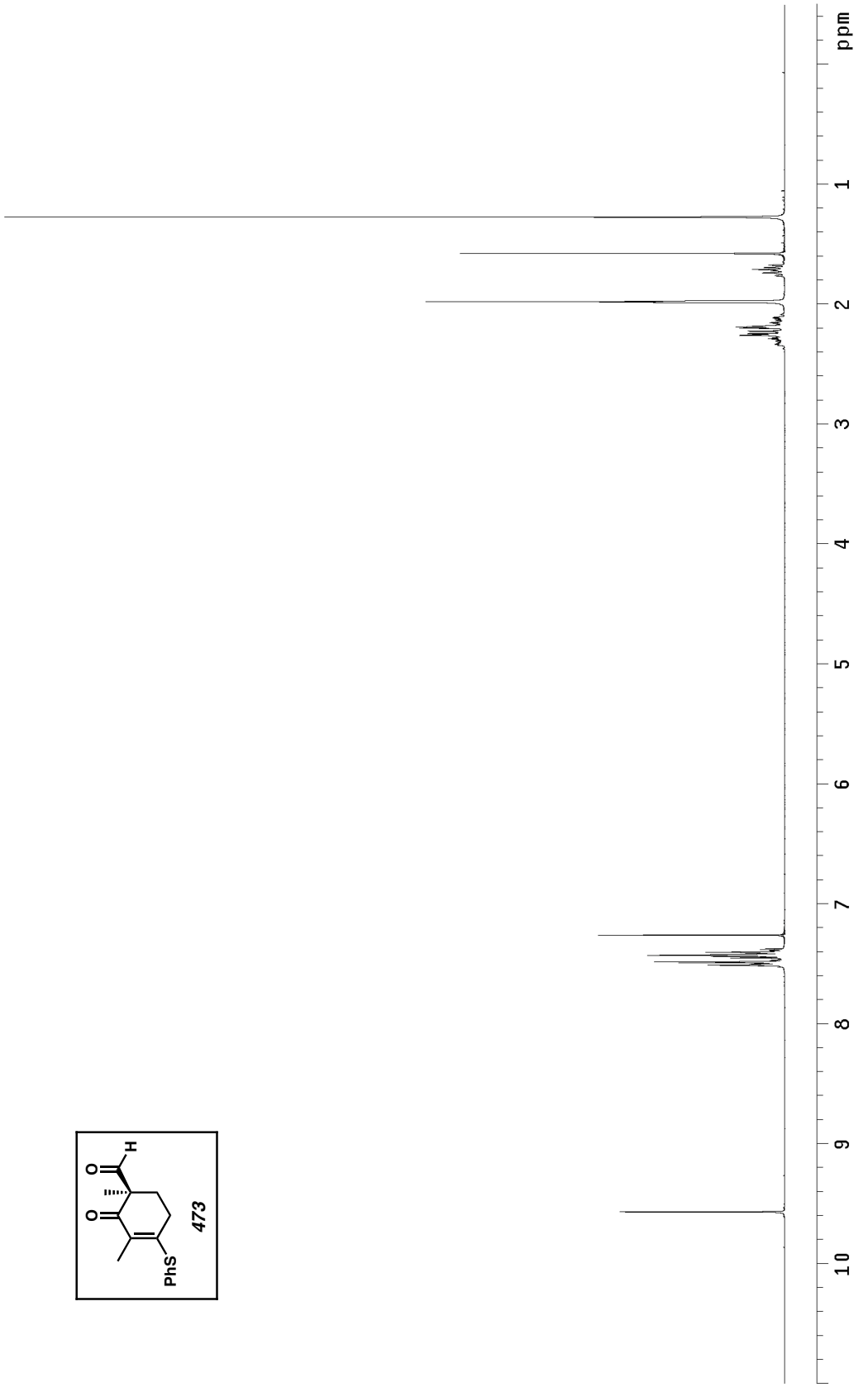


*Figure A4.16 ^1H NMR spectrum of compound **473** (300 MHz, $CDCl_3$)*

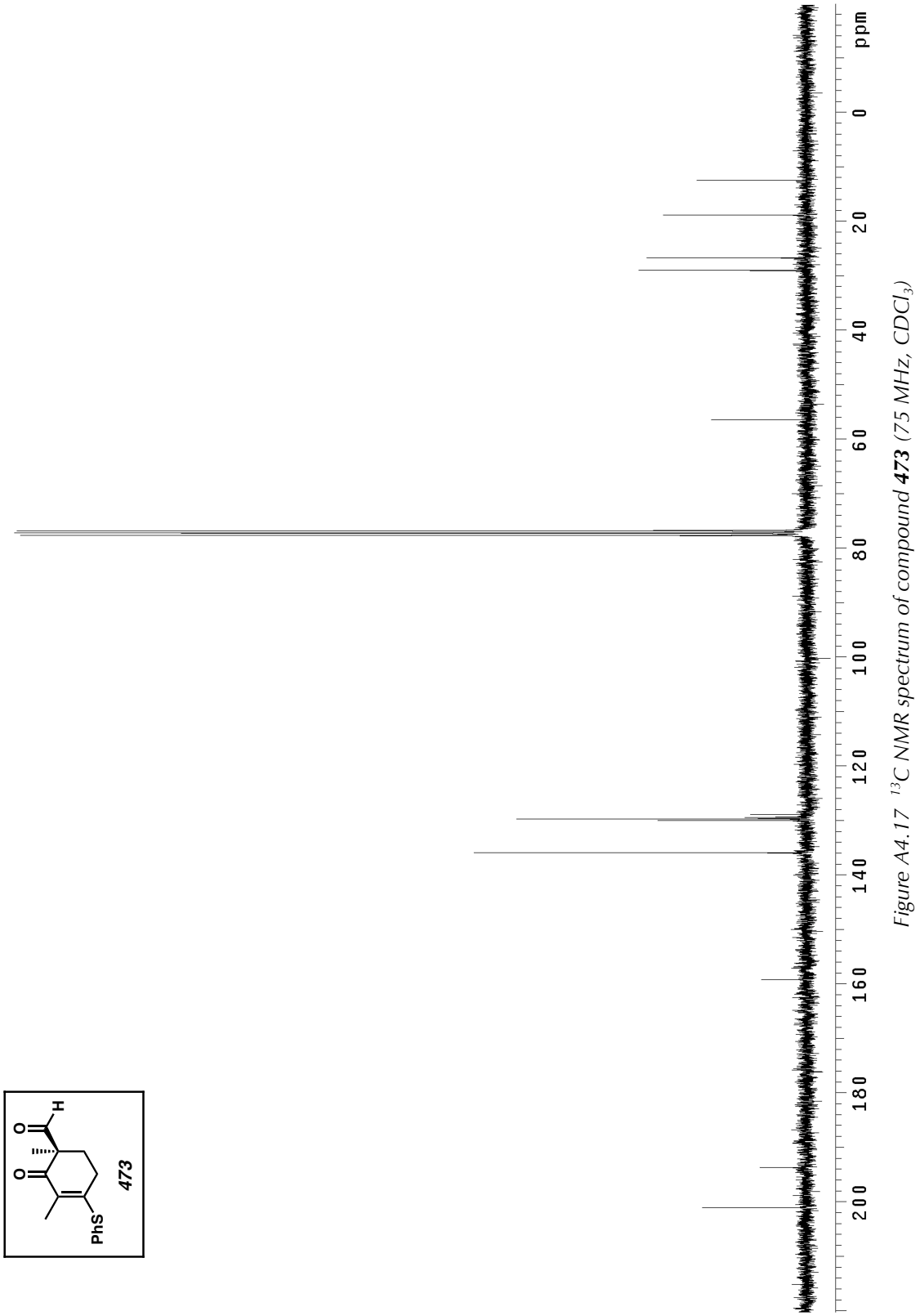


*Figure A4.17 ^{13}C NMR spectrum of compound **473** (75 MHz, $CDCl_3$)*

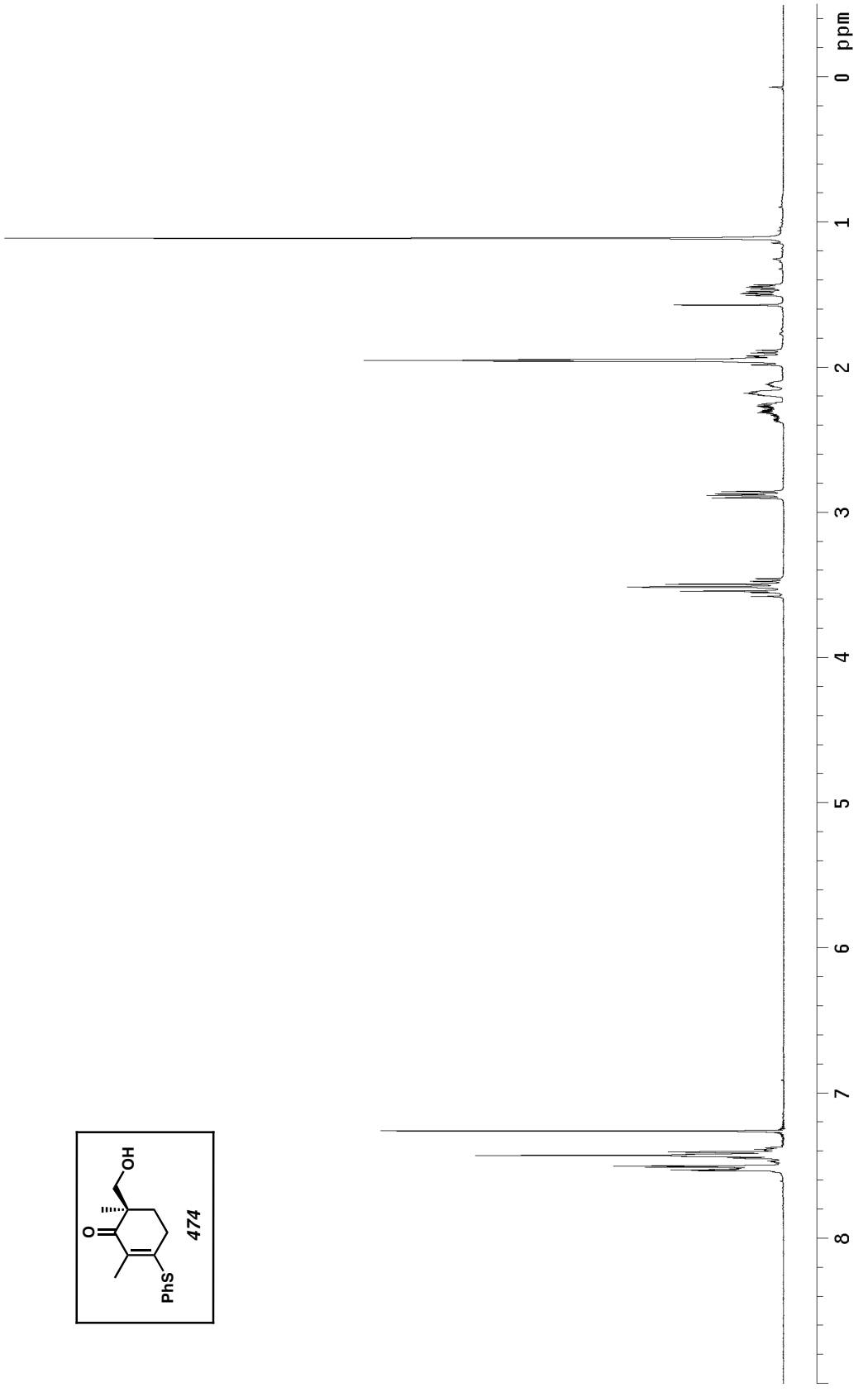


*Figure A4.18 ^1H NMR spectrum of compound **474** (500 MHz, $CDCl_3$)*

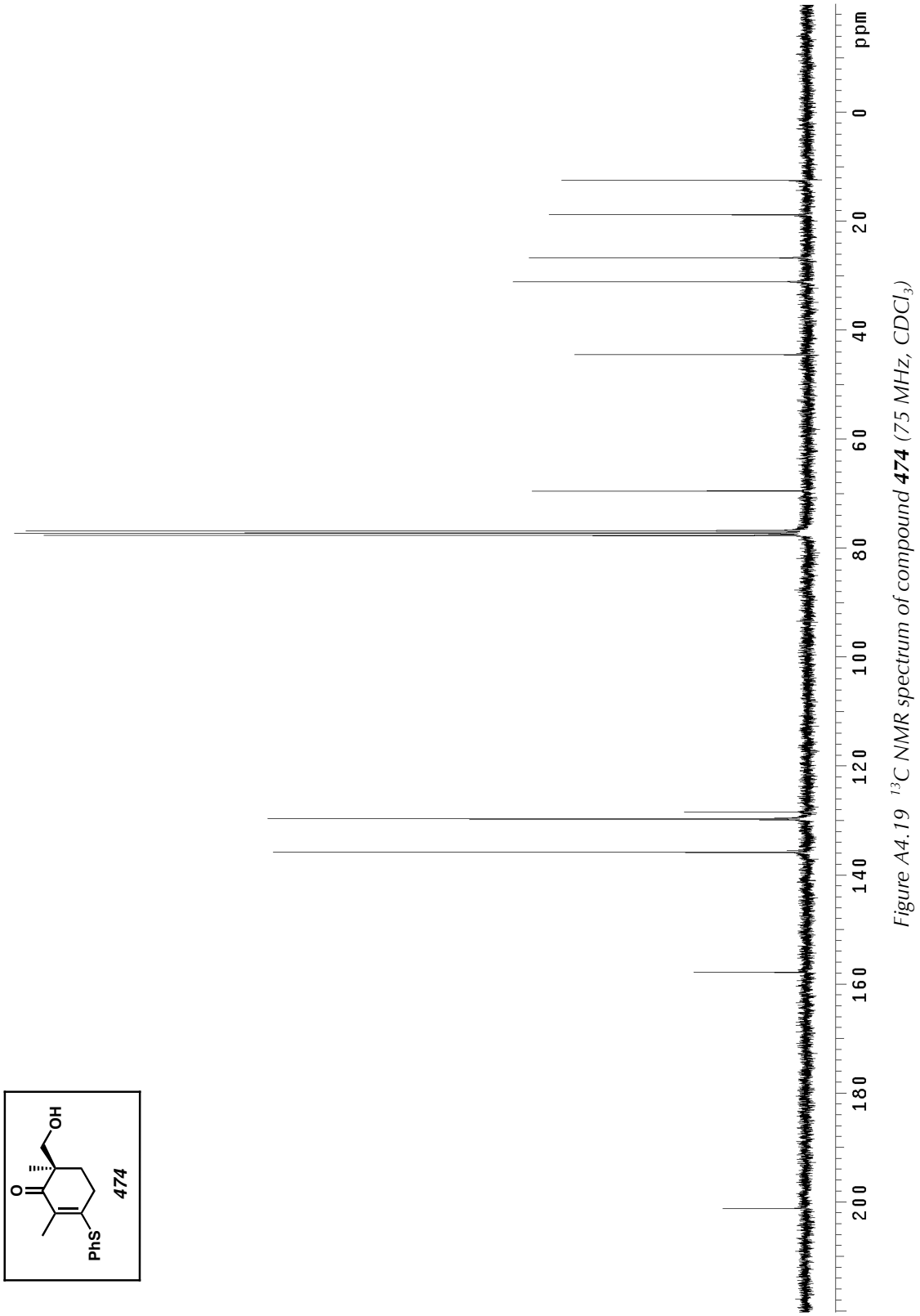


*Figure A4.19 ^{13}C NMR spectrum of compound **474** (75 MHz, $CDCl_3$)*

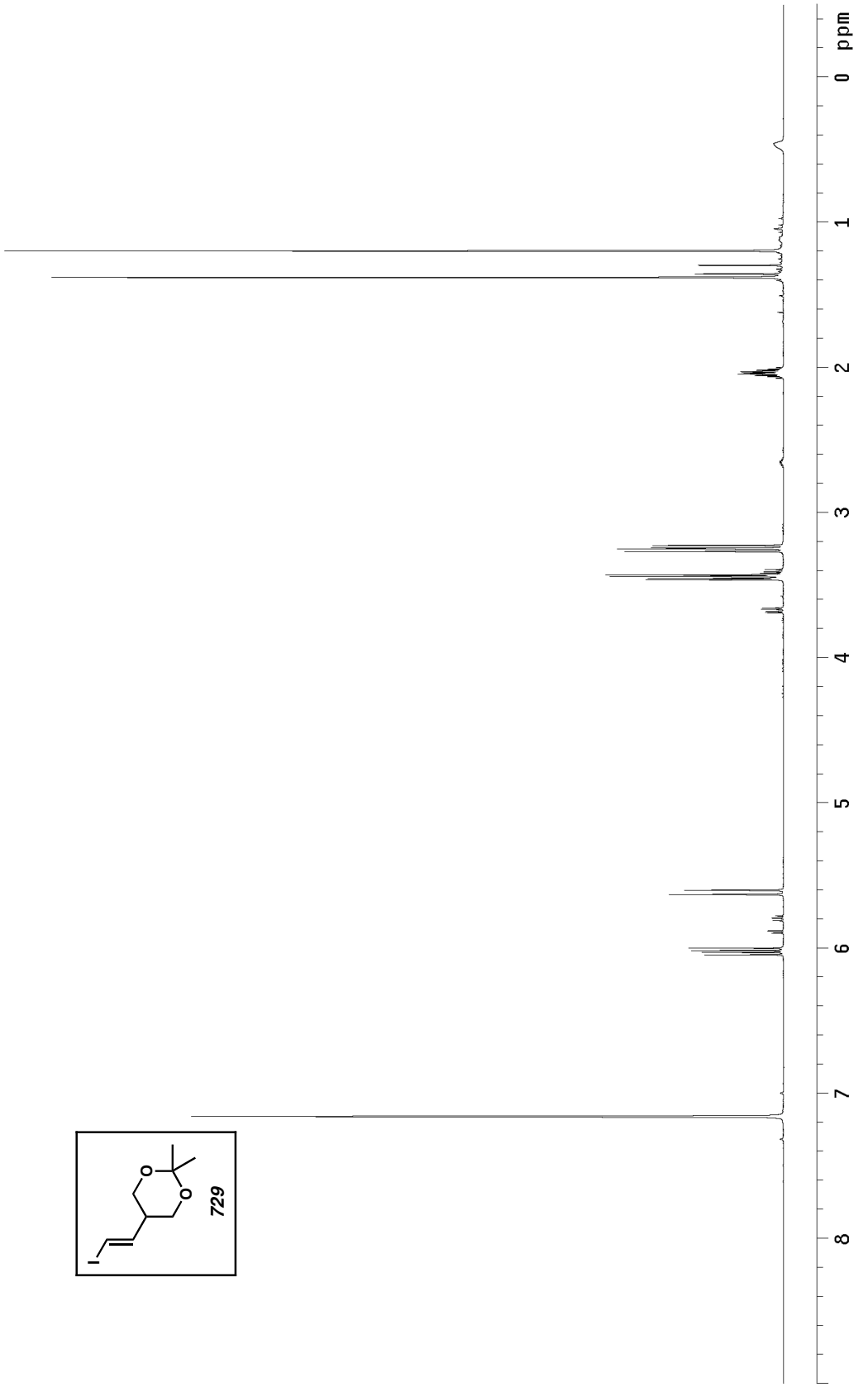


Figure A4.20 ^1H NMR spectrum of compound ***729*** *(500 MHz, C_6D_6)*

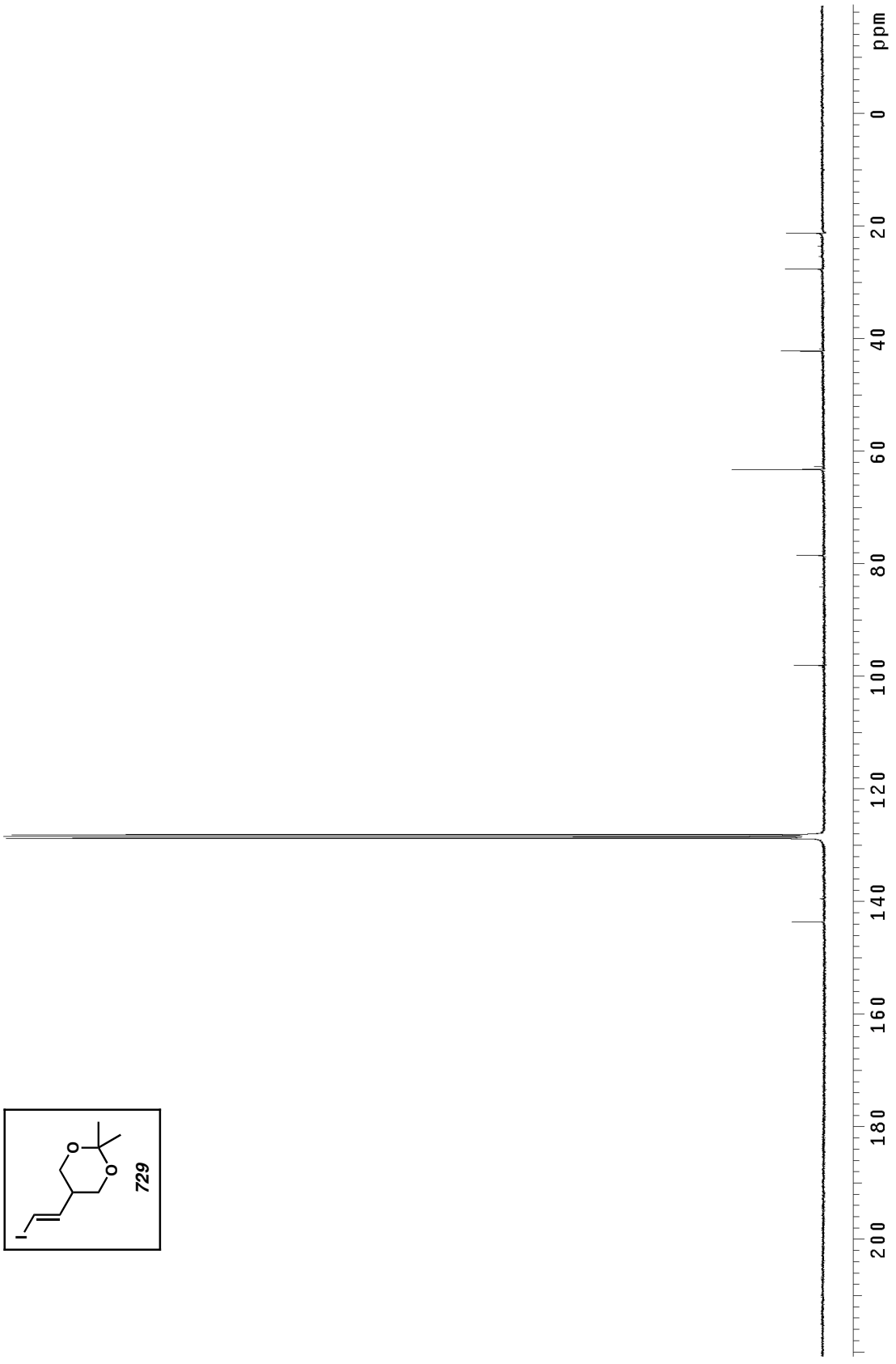


*Figure A4.21 ^{13}C NMR spectrum of compound **729** (75 MHz, C_6D_6)*

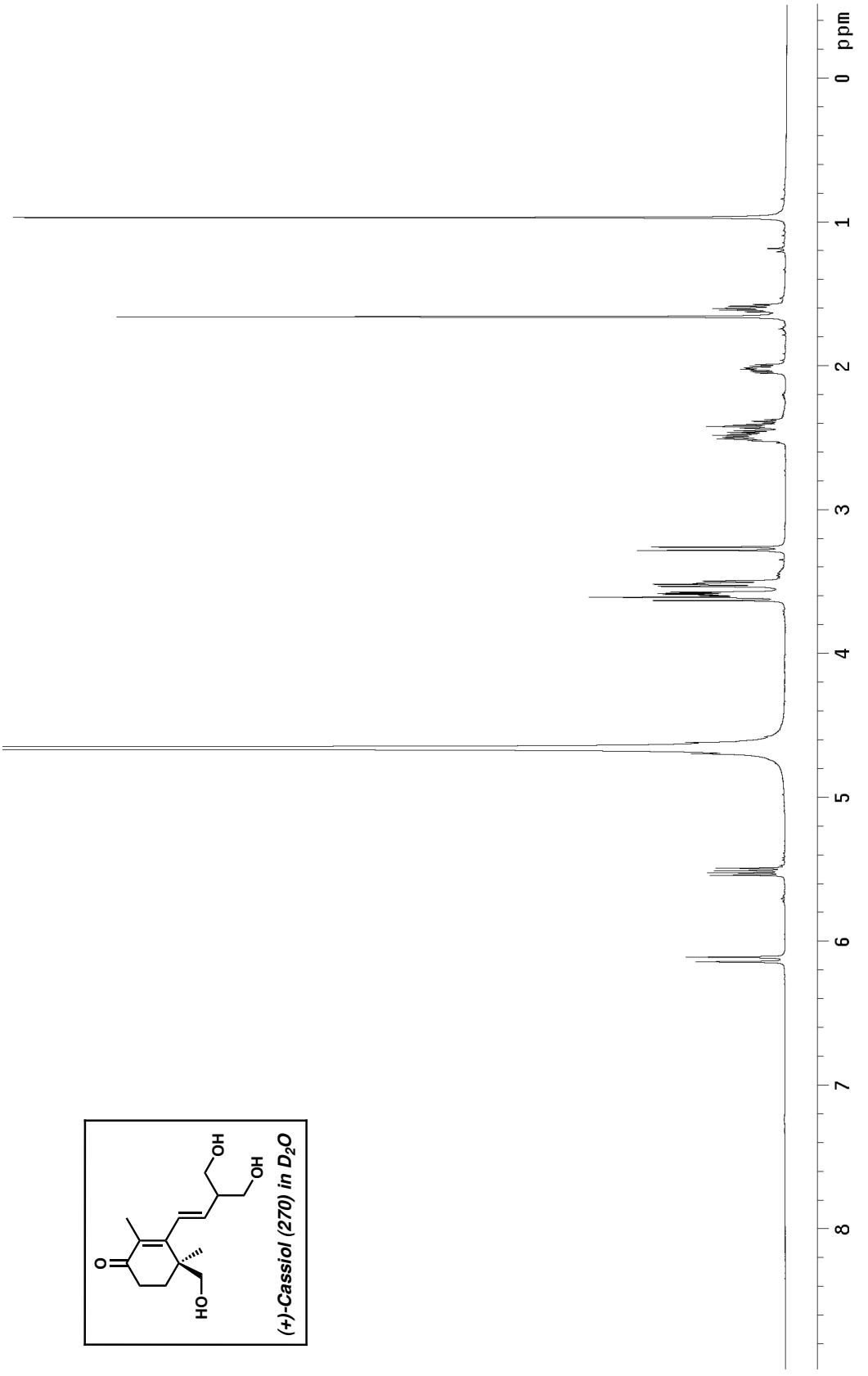


Figure A4.22 ^{1}H *NMR spectrum of compound* ***270*** *(500 MHz,* D_2O*)*

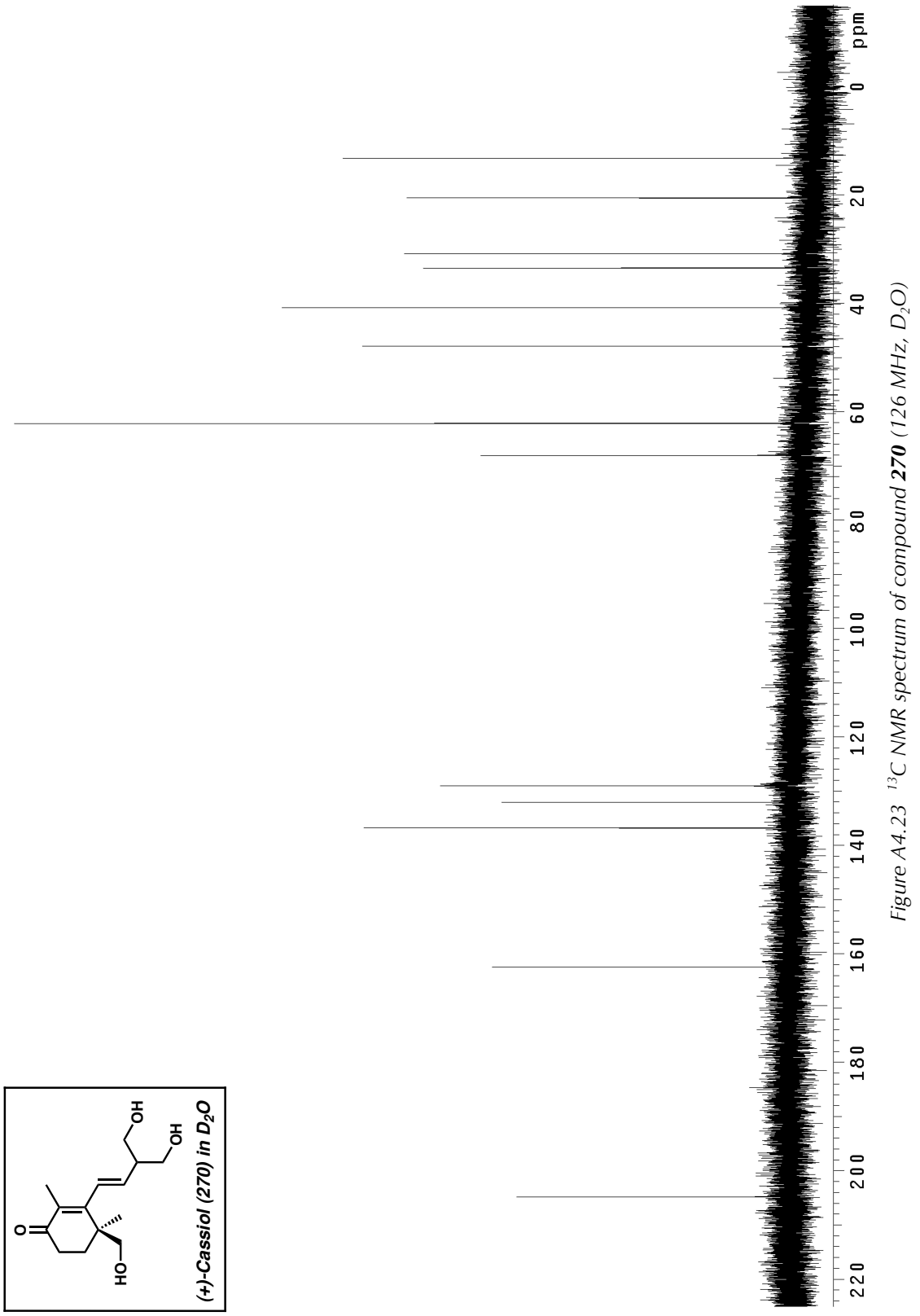


*Figure A4.23 ^{13}C NMR spectrum of compound **270** (126 MHz, D_2O)*

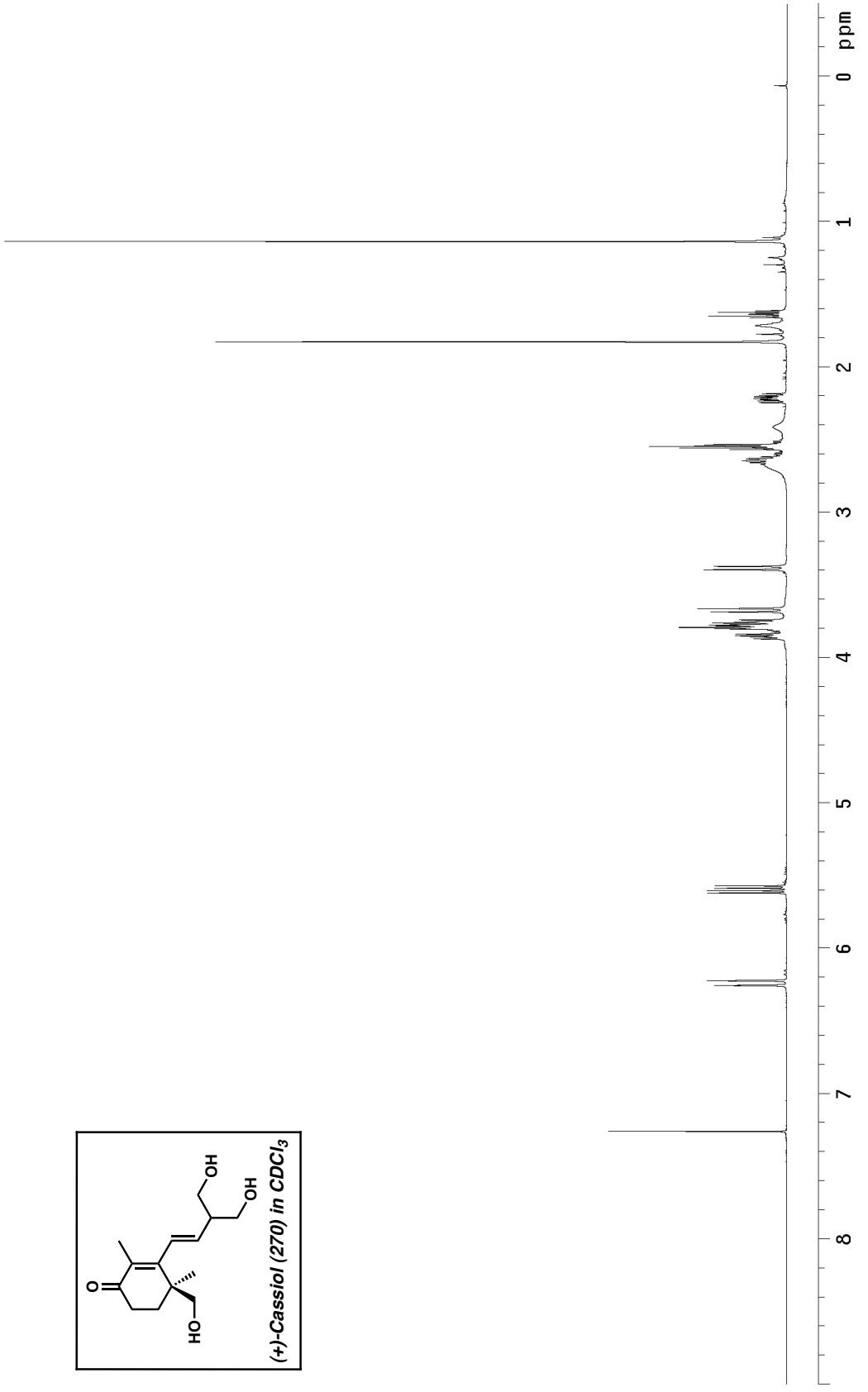


Figure A4.24 ^{1}H NMR spectrum of compound **270** *(500 MHz, $CDCl_3$)*

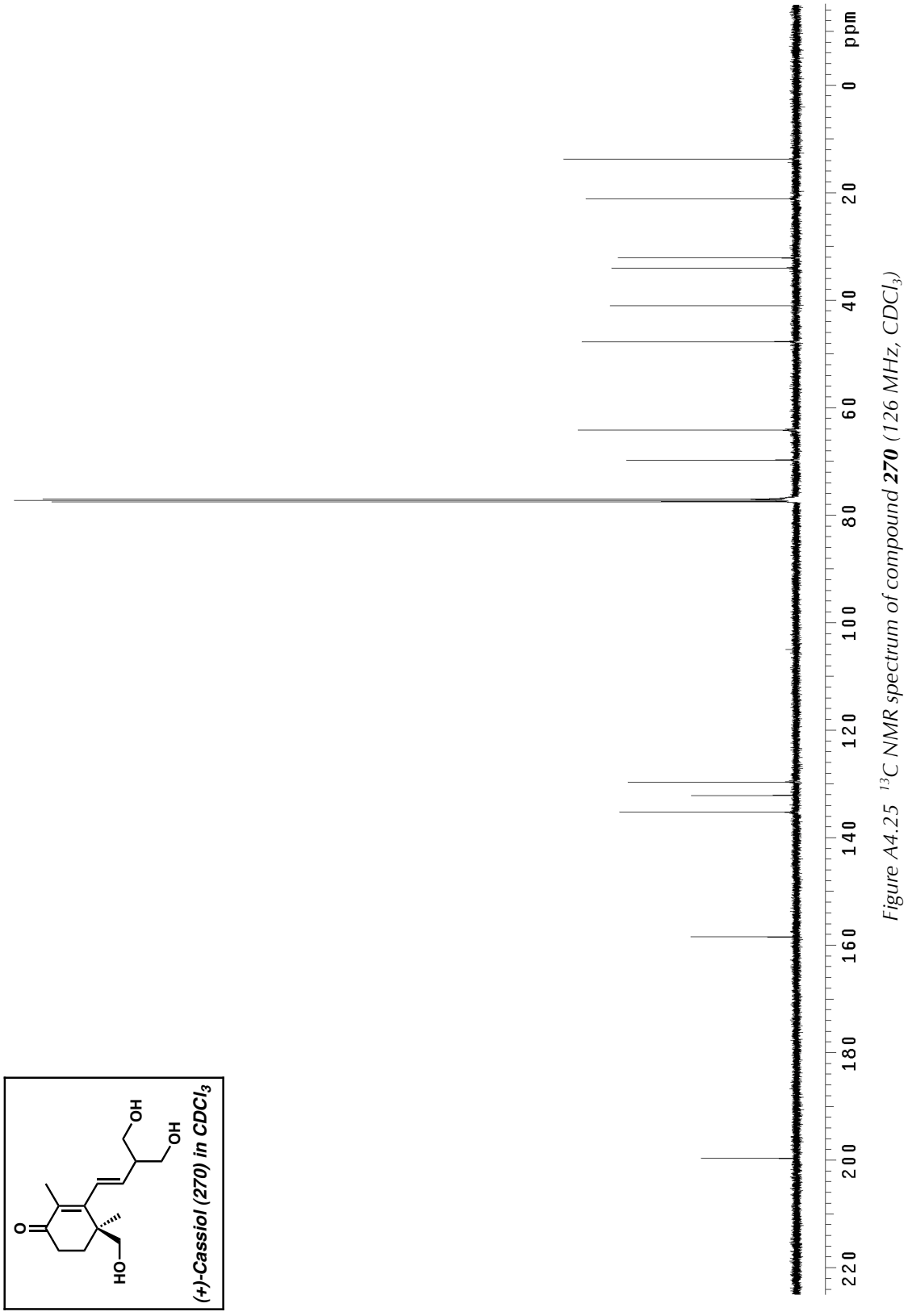


*Figure A4.25 ^{13}C NMR spectrum of compound **270** (126 MHz, $CDCl_3$)*

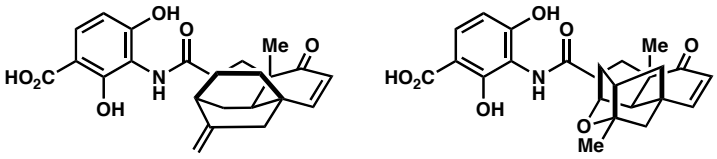
CHAPTER 10

Enantioselective Formal Synthesis of Platencin[†]

10.1 INTRODUCTION

The growing resistance of several pathogenic bacterial strains against commercially available antibiotics necessitates the rapid and efficient development of novel active ingredients. In this quest natural products serve as valuable lead structures.[1] Recently, platencin (**737**, Figure 10.1)[2] and platensimycin (**738**)[3] were isolated by Merck scientists as highly active in vitro and in vivo antibiotics possessing a novel mode of action. These natural products attracted tremendous interest from the synthetic community, and a number of different approaches to each natural product have been reported.[4,5] Herein, we disclose a short and efficient enantioselective formal synthesis of platencin (**737**) making use of enantioconvergent allylation methodology developed in our group.[6]

*Figure 10.1. Structures of the antibiotics platencin (**737**) and platensimycin (**738**)*



Platencin (737) ***Platensimycin (738)***

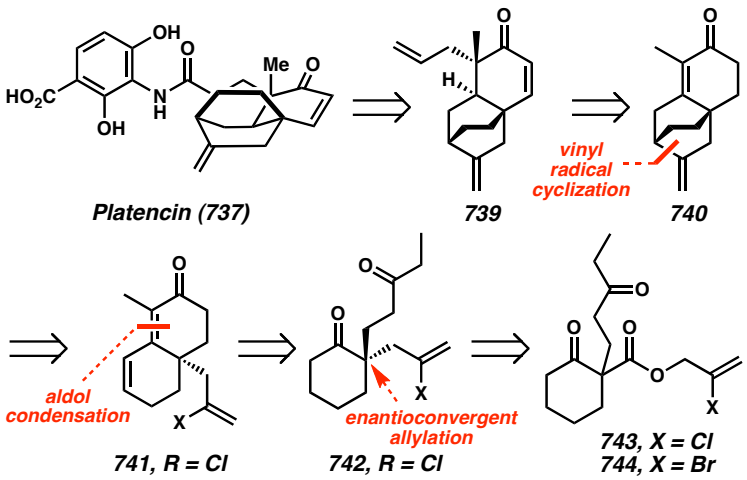
[†] This work was performed in collaboration with Christian Defieber.

10.2 RETROSYNTHETIC ANALYSIS

We have pursued a research strategy that consists of identifying particular structural challenges of natural products to guide the development of novel methods in enantioselective catalysis.[7] In accord with this tactic, we have developed a series of Pd-catalyzed enolate alkylation reactions for the enantioselective synthesis of quaternary stereocenters and applied these transformations in synthetic studies toward several target molecules.[8,9] The presence of two all-carbon quaternary stereocenters in both platencin (**737**) and platensimycin (**738**) entreated us to explore the synthesis of these molecules using our method. We first chose to explore the synthesis of platencin (**737**) because of the interesting dual-mode of action in inhibiting bacterial fatty-acid biosynthesis exhibited by platencin but not platensimycin. Moreover, we have an ongoing interest in strained [2.2.2]bicyclic compounds due to their special structural and chemical properties.[10] Since Nicolaou[4a] and Rawal[4b] have each reported procedures to introduce the aromatic portion of the natural product, we targeted tricyclic intermediate **739** (Scheme 10.1) for our synthetic studies.

Initially, our retrosynthetic plan included the assembly of the [2.2.2]bicyclic structure **739** by employing an intramolecular vinyl radical cyclization[11] of precursor **740** (Scheme 10.1). We envisioned constructing dienone **741** through an intramolecular aldol condensation with cyclohexanone **742**. The absolute stereochemistry of diketone **742** would be controlled via Pd-catalyzed enantioconvergent alkylation using racemic β-ketoester **743** or **744**.

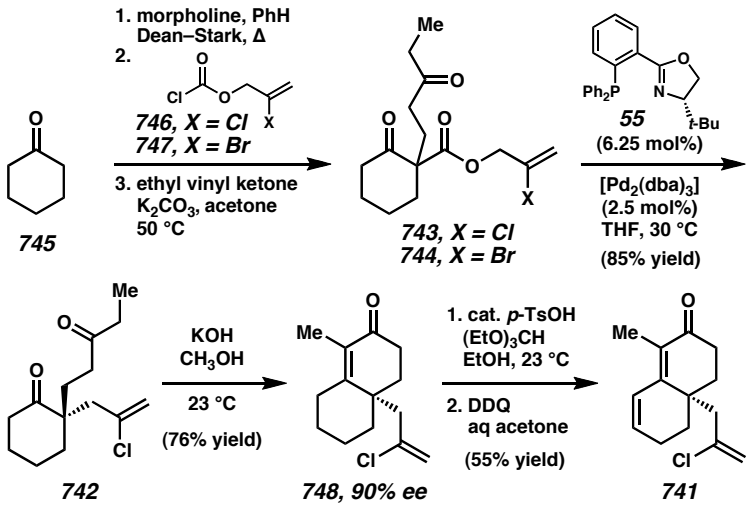
*Scheme 10.1. Retrosynthetic analysis of platencin (**737**)*



10.3 INITIAL STUDIES TOWARD PLATENCIN

The necessary precursor for the projected Tsuji allylation was readily assembled through a three-step protocol (Scheme 10.2). Cyclohexanone (**745**) was converted to its corresponding morpholine enamine that then reacted with 2-haloallyl chloroformates (**746** or **747**) to afford the allyl β-ketoesters.[12] Subsequent alkylation with ethyl vinyl ketone yielded racemic allylation precursors **743** and **744**. With these substrates in hand, we next explored enantioconvergent decarboxylative alkylation reactions in the presence of the complex derived from $[Pd_2(dba)_3]$ and phosphinooxazoline (PHOX) ligand **55**.[13,14] Whereas chloro-substituted β-ketoester underwent a clean conversion to provide cyclohexanone **742** in 85% yield, the corresponding bromo derivative **744** remained unreactive under identical reaction conditions. Subsequent experimentation led us to conclude that the palladium complex inserts oxidatively in the C–Br bond and is precluded from participation in the allylation chemistry.[15]

Scheme 10.2. Investigations of the Tsuji allylation



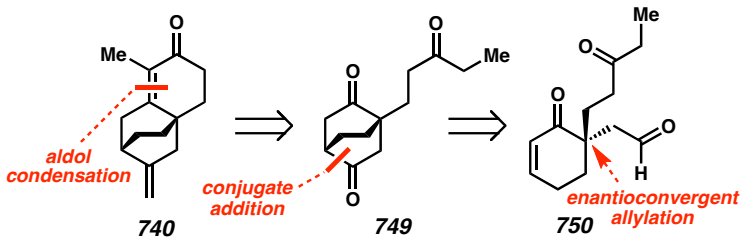
Further synthetic manipulations toward our target intermediate (**739**) involved annulation by means of aldol cyclization with Tsuji product **742**, followed by dehydrogenation[16] to afford dienone **741** (Scheme 10.2). Several reaction conditions to effect the key cyclization to the bicyclo[2.2.2]octane **740** were examined, albeit to no avail. Application of radical conditions (Bu_3SnH, AIBN, benzene, 80 °C)[17] only led to recovery of starting material; anionic conditions (*t*-BuLi, CuCN, THF, –78 °C)[18] resulted in the formation of a complex mixture of unidentified products.

10.4 REVISED RETROSYNTHESIS

In order to tackle the challenging synthesis of the chiral bicyclo[2.2.2]octane scaffold, we reconsidered our retrosynthetic plan and decided to reverse the order of ring assembly (Scheme 10.3). Postponing the aldol condensation to a later stage in the synthesis, our focus shifted entirely toward construction of the chiral bicyclo[2.2.2]octadione **749**. We envisioned an umpolung strategy in which aldehyde **750** would undergo an

intramolecular conjugate addition (Stetter cyclization).[19] The aldehyde itself would again be the result of an enantioselective decarboxylative alkylation.

Scheme 10.3. Revised retrosynthesis of the platencin core

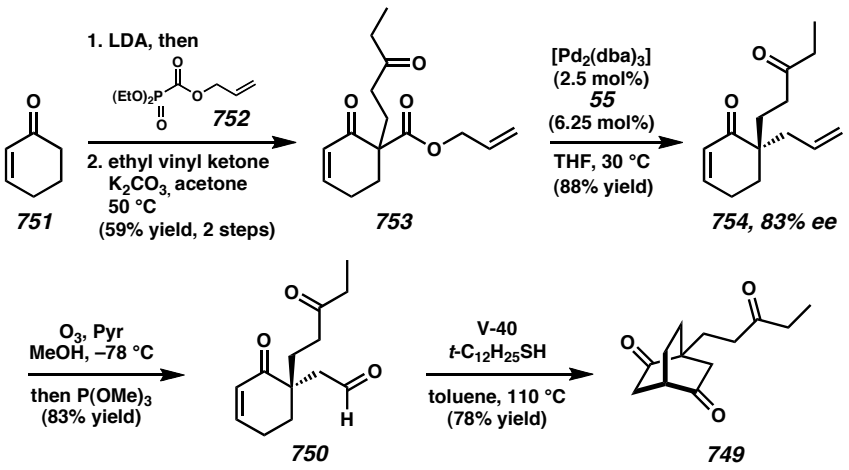


10.5 IMPLEMENTATION OF THE REVISED STRATEGY—FORMAL SYNTHESIS OF PLATENCIN

Following our revised strategy, the lithium enolate of cyclohex-2-en-1-one (**751**) was treated with allyl diethylphosphonoformate **752**,[20] an inexpensive alternative to Mander's reagent[21] (Scheme 10.4). The intermediate β-ketoester was alkylated with ethyl vinyl ketone to afford racemic substrate **753**. The subsequent enantioselective decarboxylative alkylation reaction proceeded smoothly to provide cyclohexenone **754** in good yield (88%) and enantiomeric excess (83%). Selective oxidative cleavage of the more electron-rich double bond in enone **754** was effected by ozone in the presence of pyridine.[22] However, when aldehyde **750** was subjected to Stetter cyclization conditions promoted by thiazolium- or triazolium-based catalysts,[23] only a benzoin-type condensation product was isolated.[24] Given our recent success with an aldehyde/olefin radical cyclization in another synthetic effort,[9c] we exposed tricarbonyl compound **750** to the radical initiator V-40 and *t*-dodecanethiol in refluxing toluene. We were pleased to

find that the radical cyclization conditions provided the desired chiral bicyclo[2.2.2]octadione **749** in 78% yield.[25]

Scheme 10.4. Assembly of the bicyclo[2.2.2]octadione scaffold



The key bridged bicycle **749** was then subjected to basic conditions (KOH, MeOH, 23 °C, Scheme 10.5). These conditions promoted an intramolecular aldol cyclization that appeared to be completely regioselective for formation of the desired tricyclic compound (**751**). Dione **751** was highly crystalline and a single recrystallization from hexanes allowed us to increase the enantiomeric excess to 99%. The structure of tricycle **751** was confirmed by single-crystal X-ray diffraction analysis (Figure 10.2).[26]

Scheme 10.5. Formal synthesis of platencin

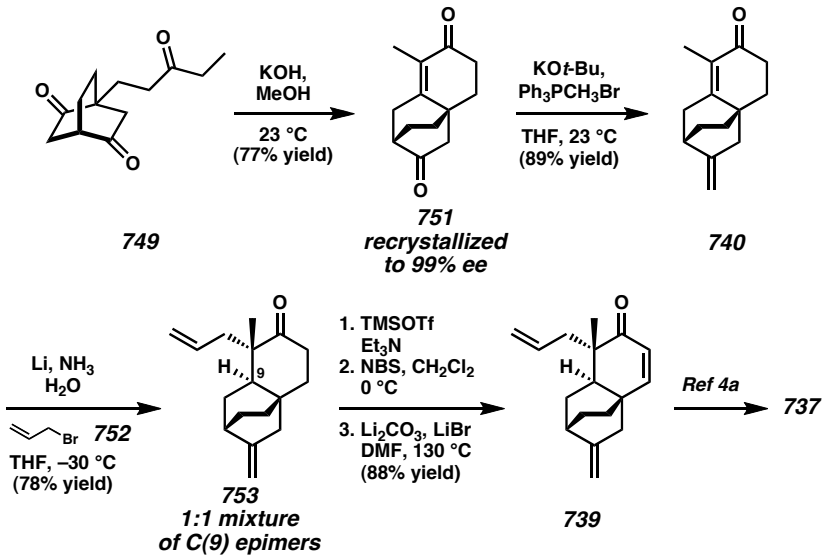
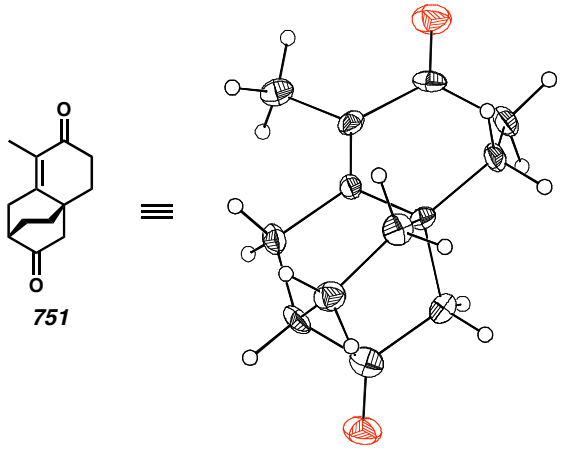


*Figure 10.2. ORTEP plot of dione **751** derived from X-ray crystallographic analysis (nonhydrogen atoms are shown with ellipsoids at 50% probability)*



Chemoselective methylenation of the ketone moiety of **751** was achieved in 89% yield by action of a Wittig reagent (Scheme 10.5). Exposure of the resulting alkene (**740**) to Li metal led to enone reduction with concomitant formation of a lithium enolate that was trapped with allyl bromide (**752**) to provide ketone **753** in 78% yield as a 1:1 mixture of epimers at C(9). A three-step protocol was employed to introduce the enone

functionality present in the target structure (**739**) in 88% yield. This compound was an intermediate in Nicolaou's total synthesis of platencin (**737**),[4a] and therefore this work constitutes a formal synthesis of the natural product.

10.6 SUMMARY

In conclusion, we have developed a short enantioselective formal synthesis of the antibiotic platencin (**737**). Key features include the enantioconvergent catalytic alkylation to set the absolute stereochemistry as well as a radical-mediated cyclization to assemble the core bicyclo[2.2.2]octane structure. The synthesis and biological evaluation of platencin analogues is underway and will be reported in due course.

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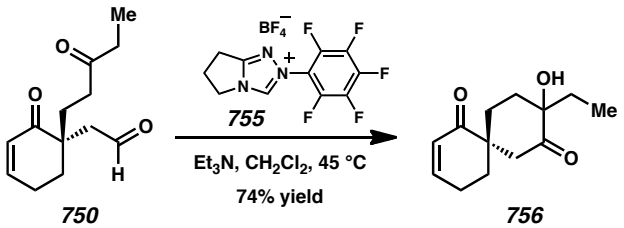
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10.8 EXPERIMENTAL SECTION

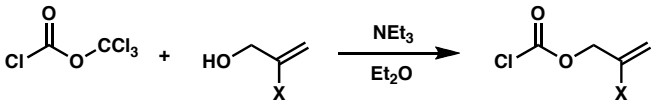
10.8.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Brine solutions are saturated aqueous sodium chloride solutions. Tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$],[27] (*S*)-*t*-BuPHOX (**55**),[28] and trizaolium salt **755**[29] were synthesized according to standard procedures and stored in a desiccator until immediately before use. Trimethylsilyl chloride (TMSCl) and triethyl amine (TEA) were distilled from sodium hydride immediately prior to use. Cyclohex-2-enone and ethyl vinyl ketone were distilled immediately prior to use. All other commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 pre coated plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. ICN Silica gel (particle size 0.032-0.063 mm) was used for flash column chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralpak AD or Chiralcel OD-H columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 254 nm. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. ^{1}H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) or a Varian Inova 500 (at 500 MHz) and are reported relative to residual solvent peaks ($CDCl_3$, δ 7.26; DMSO-d_6, δ 2.49). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm)

(multiplicity, coupling constant (Hz), integration). ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz) or a Varian Inova 500 (at 125 MHz) and are reported relative to residual solvent peaks ($CDCl_3$, δ 77.3; DMSO-d_6, δ 39.5). Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility.

10.8.2 EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

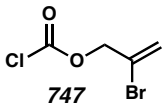
Procedure for the Synthesis of the 2-Haloallyl chloroformates[30]



757 *758, X = Cl* *759, X = Br* *746, X = Cl* *747, X = Br*

2-Chloroallyl chloroformate 746: A 50 mL three-neck round-bottom flask equipped with a 25 mL addition funnel, a stir bar, and three septa was flame dried under vacuum. After refilling with argon, anhydrous Et_2O (6 mL) was added via syringe, and the system was cooled to ca. –10 °C. Diphosgene (**757**, 1.0 mL, 8.46 mmol, 1.21 equiv) was added dropwise via syringe, and the solution was cooled to approx. –20 °C. 2-chloroallyl alcohol (**758**, 0.56 mL, 7.0 mmol, 1.0 equiv) in anhydrous Et_2O (6 mL) was added dropwise via the addition funnel, and the solution was stirred at approx. –20 °C for an additional 15 min. The reaction was cooled to approx. –30 °C, and triethylamine (1.17 mL, 8.37 mmol, 1.20 equiv) in anhydrous Et_2O (6 mL) was added dropwise via the addition funnel, generating a white precipitate. The reaction was then cooled to approx.

–30 °C and stirred for 3 h, at which time it was allowed to warm to 23 °C. During this time, the reaction mixture became very thick, anhydrous Et_2O (10 mL) was added to obtain a stirable suspension. Argon was bubbled through the suspension for 2 h to remove excess phosgene. The reaction mixture was filtered via vacuum filtration through a fritted funnel, and the filtrate was concentrated by rotary evaporation under reduced pressure. The title compound **746** (553 mg, 3.57 mmol, 51%) was obtained as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.58 (dt, *J* = 2.0, 1.0 Hz, 1H), 5.53 (d, *J* = 2.2 Hz, 1H), 4.84 (d, *J* = 0.7 Hz, 2H). The other spectroscopic data are in agreement with the literature data.[30b]

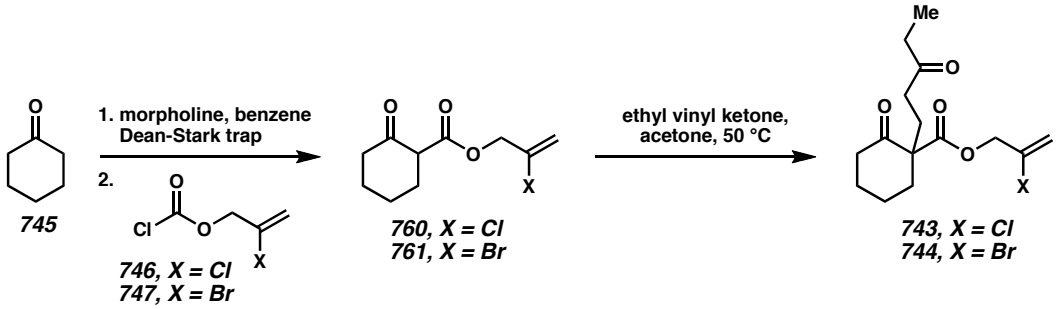


747

2-Bromoallyl chloroformate 747: A solution of 2-bromoallyl alcohol[31] (**759**. 1.00 g, 7.30 mmol, 1.0 equiv) in Et_2O (6 mL) was added to a –30 °C solution of diphosgene (**757**, 898.8 μL, 7.44 mmol, 1.02 equiv) in Et_2O (6 mL). After 15 min, neat Et_3N (1.03 mL, 7.37 mmol, 1.01 equiv) was added, causing the immediate formation of a white precipitate. After 3.5 h at –30 °C, the mixture was removed from the cooling bath and then quickly passed through a sintered glass filter. The filtrate was concentrated carefully by rotary evaporation. Distillation of the residue through a short path apparatus into an receiving flask cooled in an ice/water bath provided the title compound **747** as a clear, colorless liquid (582.3 mg, 40% yield). bp 69–71 °C/22 torr; ^{1}H NMR (300 MHz, C_6D_6) δ 5.26 (dt, *J* = 2.5, 1.1 Hz, 1H), 5.17 (dt, *J* = 2.5, 0.6 Hz, 1H), 4.13 (dd, *J* = 1.1, 0.6 Hz,

2H); ^{13}C NMR (75 MHz, C_6D_6) δ 150.3, 124.0, 121.7, 73.8; IR (Neat Film NaCl) 2954, 1786, 1634, 1439, 1413, 1268, 1148, 1128, 918, 839, 811, 686 cm^{-1}.

Procedure for the Preparation of the β-Ketoesters 743 and 744[32]

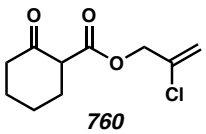


Cyclohexanone (**745**, 3.8 mL, 40.8 mmol, 1.0 equiv) and morpholine (6.4 mL, 73.4 mmol, 1.8 equiv) were diluted in dry benzene (12 mL) in a 50 mL round-bottom flask equipped with a Dean–Stark trap and a reflux condenser. The resulting reaction mixture was heated to reflux until no further separation of water was observed. The volatiles were removed by rotary evaporation under reduced pressure. The resulting oily orange residue is distilled to remove excess morpholine to afford 5.0 g (29.9 mmol, 73%) morpholine enamine of cyclohexanone as a colorless liquid.

A portion of this intermediate (971 mg, 5.8 mmol, 1.8 equiv) was diluted in benzene (5 mL). Under a nitrogen atmosphere, 2-chloroallyl chloroformate (**746**, 500 mg, 3.23 mmol, 1.0 equiv) was slowly added via syringe while the enamine solution was stirred rapidly. After refluxing for about 10 h, the solution was cooled to 23 °C and filtered, the precipitate of enamine hydrochloride being washed with dry ether. The combined filtrate and washings were returned to the reaction flask, ca. 7 mL of 10% aqueous hydrochloride acid was added, and the mixture was stirred vigorously for 15-30 minutes. The layers were separated, the aqueous layer was extracted three times with diethyl ether (20 mL x

3) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude 2-chloroallyl 2-oxocyclohexanecarboxylate (638 mg, 2.94 mmol, 91%) was analyzed by ^1H NMR. The sample possessed sufficient quality to be used immediately in the next reaction obviating the need for further purification.

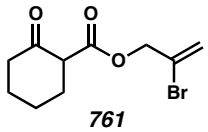
The crude β-ketoester (**760**, 638 mg, 2.94 mmol, 1.0 equiv) was added to a suspension of potassium carbonate (814 mg, 5.89 mmol, 2.0 equiv) in acetone (4 mL). At 23 °C, ethyl vinyl ketone (586 μL, 5.89 mmol, 2.0 equiv) was added slowly via syringe. The resulting heterogeneous mixture was stirred for 7 h at 50 °C, then cooled to 23 °C, filtered and the filtrate concentrated by rotary evaporation under reduced pressure. The residue was purified by flash column chromatography (silica, hexanes-EtOAc 15:1 to 3:1) to afford 2-chloroallyl 2-oxo-1-(3-oxopentyl)cyclohexanecarboxylate (676 mg, 2.24 mmol, 76%) **743** as a colorless liquid.



760

2-Chloroallyl 2-oxocyclohexanecarboxylate (760): Neat 2-chloroallyl chloroformate[33] (**746**, 257.4 mg, 1.66 mmol, 1.0 equiv) was added to a solution of 1-morpholinocyclohexene[34] (500.0 mg, 2.99 mmol, 1.8 equiv) in dry benzene (2.5 mL). The mixture was heated to reflux for 9 h, during which time some solids precipitated and the solution became orange in color. The mixture was cooled and then filtered through cotton, rinsing with diethyl ether. The combined filtrate and washings were treated with 2 N aq hydrochloric acid (2 mL) and the resulting biphasic mixture was stirred vigorously for 1 h. The phases were separated and then the aq phase was extracted with diethyl ether

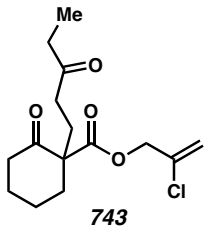
(3 x 2 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated to an orange-brown oil. Flash chromatography (silica gel, 2 cm diameter x 10 cm height, 15% EtOAc in hexanes eluent) yielded a colorless liquid (199.3 mg, 55% yield). Characterized as a 3.5:1 mixture of enol:keto tautomers in C_6D_6: ^{1}H NMR (500 MHz, C_6D_6) δ 12.50 (s, 0.8H), 5.21 (app. dt, *J* = 1.7, 1.2 Hz, 0.2H), 5.10 (app. dt, *J* = 1.7, 0.7 Hz, 0.2H), 5.06 (dt, *J* = 1.7, 0.7 Hz, 0.8H), 5.03 (dt, *J* = 1.7, 1.2 Hz, 0.8H), 4.54 (ddd, *J* = 13.7, 1.0, 0.5 Hz, 0.2H), 4.50 (ddd, *J* = 13.7, 1.0, 0.5 Hz, 0.2H), 4.44 (dd, *J* = 1.2, 0.7 Hz, 1.6H), 3.00 (ddd, *J* = 11.0, 5.6, 1.0 Hz, 0.2H), 2.18–2.11 (comp. m, 1.8H), 2.05–2.02 (m, 1.6H), 1.88 (dddd, *J* = 13.7, 11.2, 11.0, 3.7 Hz, 0.2H), 1.70 (dddd, *J* = 13.7, 11.2, 5.4 1.0 Hz, 0.2H), 1.67–1.59 (m, 0.2H), 1.31–1.18 (comp. m, 3.6H), 1.18–1.07 (m, 0.2H), 0.96–0.86 (m, 0.2H); ^{13}C NMR (125 MHz, C_6D_6) δ 204.1, 173.9, 171.8, 169.1, 136.6, 136.2, 115.4, 114.8, 97.3, 66.3, 65.6, 57.2, 41.5, 29.9, 29.4, 26.9, 23.4, 22.6, 22.4, 21.9; IR (Neat Film NaCl) 2941, 2861, 1755, 1717, 1659, 1642, 1614, 1450, 1422, 1396, 1363, 1297, 1259, 1217, 1174, 1082, 1062, 894, 829, 811, 708, 644 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{10}H_{14}O_3Cl$ $[M + H]^+$: 217.0632, found 217.0627.



761

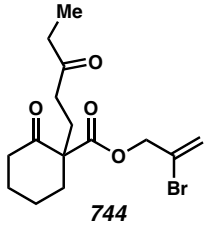
2-Bromoallyl 2-oxocyclohexanecarboxylate (761): Neat 2-bromoallyl chloroformate (**747**, 250.0 mg, 1.25 mmol, 1.0 equiv) was added to a solution of 1-morpholinocyclohexene[34] (377.4 mg, 2.26 mmol, 1.8 equiv) in dry benzene (2 mL). The mixture was heated to reflux for 9 h, during which time some solids precipitated and the solution became slightly yellow in color. The mixture was cooled and then filtered

through cotton, rinsing with diethyl ether. The combined filtrate and washings were treated with 2 N aq hydrochloric acid (1 mL) and the resulting biphasic mixture was stirred vigorously for 1 h. The phases were separated and then the aq phase was extracted with diethyl ether (3 x 2 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated to a yellow oil. Flash chromatography (silica gel, 2 cm diameter x 8 cm height, 10% EtOAc in hexanes eluent) yielded a colorless liquid (**761**, 184.1 mg, 56% yield). Characterized as a 3.7:1 mixture of enol:keto tautomers in C_6D_6: R_f = 0.16 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 12.50 (s, 0.8H), 5.65 (app. dt, *J* = 1.5, 0.7 Hz, 0.2H), 5.44 (dt, *J* = 1.2, 0.7 Hz, 0.8H), 5.33 (app. dt, *J* = 1.2, 0.7 Hz, 0.2H), 5.29 (dt, *J* = 1.2, 0.7 Hz, 0.8H), 4.60 (ddd, *J* = 13.9, 0.7, 0.7 Hz, 0.2H), 4.56 (ddd, *J* = 13.9, 0.7, 0.7 Hz, 0.2H), 4.49 (app. s, 1.6H), 3.00 (dd, *J* = 10.7, 5.4 Hz, 0.2H), 2.18–2.11 (comp. m, 1.8H), 2.02 (app. t, *J* = 5.1 Hz, 1.6H), 1.89 (dddd, *J* = 13.9, 11.0, 11.0, 3.2 Hz, 0.2H), 1.71 (ddd, *J* = 13.9, 11.5, 5.4 Hz, 0.2H), 1.67–1.60 (m, 0.2H), 1.31–1.18 (comp. m, 3.6H), 1.18–1.06 (m, 0.2H), 0.97–0.87 (m, 0.2H); ^{13}C NMR (125 MHz, C_6D_6) δ 204.1, 173.9, 171.7, 168.9, 127.1, 126.6, 119.6, 118.9, 97.3, 67.9, 67.1, 57.2, 41.5, 29.9, 29.4, 26.9, 23.4, 22.6, 22.4, 21.9; IR (Neat Film NaCl) 2940, 2860, 1753, 1716, 1659, 1613, 1449, 1429, 1394, 1361, 1296, 1258, 1216, 1174, 1143, 1080, 1061, 894, 829, 810, 647 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{10}H_{14}O_3Br$ $[M + H]^+$: 261.0126, found 261.0118.



743

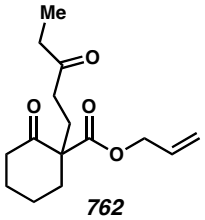
2-chloroallyl 2-oxo-1-(3-oxopentyl)cyclohexanecarboxylate 743: Prepared according to the representative procedure on a 3.23 mmol scale. The title compound **743** (676 mg, 2.24 mmol, 69% over 2 steps) was obtained as a colorless liquid. R_f 0.56 (silica, hexanes/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.50 (s, 1H), 5.44 (s, 1H), 4.73 (d, *J* = 13.3 Hz, 1H), 4.68 (d, *J* = 13.3 Hz, 1H), 2.58–2.37 (m, 7H), 2.16 (m, 2H), 2.02–1.98 (m, 1H), 1.91 (m, 2H), 1.79–1.77 (m, 1H), 1.67 (m, 2H), 1.52 (m, 1H), 1.03 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.4, 207.5, 171.4, 135.3, 116.5, 66.8, 60.1, 40.9, 37.3, 36.5, 35.9, 28.3, 27.4, 22.4, 7.8; IR (neat Film, NaCl): ν 2941, 2868, 1715, 1451, 1239, 1212, 1177, 1134, 1086, 906 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{22}O_4Cl$ $[M + H]^+$: 301.1207, found 301.1205.



744

2-bromoallyl 2-oxo-1-(3-oxopentyl)cyclohexanecarboxylate 744: Prepared according to the representative procedure on a 3.46 mmol scale. The title compound **744** (651 mg, 1.89 mmol, 55% over 2 steps) was obtained as a colorless liquid. R_f 0.61 (silica, hexanes/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.94 (s, 1H), 5.44 (s, 1H), 4.79 (d, *J* = 13.4 Hz, 1H), 4.73 (d, *J* = 13.4 Hz, 1H), 2.58–2.34 (m, 7H), 2.16 (m, 2H), 2.01–1.99

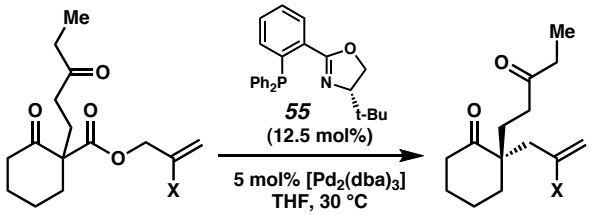
(m, 1H), 1.92 (m, 2H), 1.80–1.77 (m, 1H), 1.72–1.65 (m, 2H), 1.52 (m, 1H), 1.03 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.3, 207.5, 171.3, 125.6, 120.7, 68.4, 60.2, 40.9, 37.3, 36.5, 35.9, 28.3, 27.4, 22.4, 7.8; IR (neat Film, NaCl): ν 2940, 2867, 1714, 1450, 1310, 1177, 1133, 1085, 980, 908 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{15}H_{22}O_4Br$ $[M+H]^+$: 345.0701, found 345.0712.



762

Allyl 2-oxo-1-(3-oxopentyl)cyclohexanecarboxylate 762: Prepared according to the representative procedure on a 56.6 mmol scale. The title compound **762** (4.04 g, 15.1 mmol, 27% over 2 steps) was obtained as a colorless liquid. R_f 0.39 (silica, hexanes/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.08 (m, 1H), 5.33 (dd, J = 1.2, 16.6 Hz, 1H), 5.26 (dd, J = 1.0, 10.6 Hz, 1H), 4.63–4.61 (m, 2H), 2.56–2.30 (m, 6H), 2.12 (dddd, J = 5.1, 5.1, 5.1, 14.3 Hz, 1H), 2.01–1.97 (m, 1H), 1.88 (dddd, J = 5.4, 5.4, 5.4, 14.2 Hz, 1H), 1.77–1.74 (m, 1H), 1.67–1.61 (m, 2H), 1.15–1.50 (m, 1H), 1.03 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.4, 207.8, 171.4, 131.4, 119.3, 65.9, 60.1, 41.0, 37.4, 36.6, 35.9, 28.4, 27.5, 22.5, 7.8; IR (neat Film, NaCl): ν 3087, 2941, 2868, 1714, 1649, 1452, 1376, 1292, 1240, 1211, 1182, 1136, 1115, 1086, 993, 938, 814 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{15}H_{23}O_4$ $[M + H]^+$: 267.1596, found 267.1604.

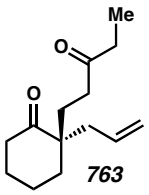
Representative Procedure for the Enantioconvergent Allylation[35]



743, X = Cl ***762, X = H*** ***742, X = Cl*** ***763, X = H***

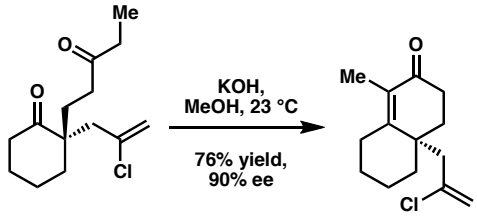
A 25 mL Schlenk flask was equipped with a magnetic stir bar and flame dried under vacuum. After cooling to 23 °C under dry argon, $Pd_2(dba)_3$ (4.6 mg, 5 μmol, 5 mol%) and (*S*)-*t*-BuPHOX (**55**, 4.8 mg, 12.5 μmol, 12.5 mol%) were added. The flask containing the solids was evacuated for 15 min and then refilled with dry argon. Dry THF (3 mL) was then added and the resulting solution stirred at 23 °C for 30 min. At this point, 2-chloroallyl 2-oxo-1-(3-oxopentyl)cyclohexanecarboxylate **743** (30 mg, 0.1 mmol, 1.0 equiv) was added via syringe in one portion. The reaction was warmed to 30–35 °C. When the reaction was complete as judged by TLC, the reaction mixture was evaporated under reduced pressure and the residue purified by flash column chromatography (silica, hexanes/EtOAc 10:1) to afford (*R*)-2-(2-chloroallyl)-2-(3-oxopentyl)cyclohexanone **742** (21.7 mg, 85 μmol, 85%) as a colorless liquid. The enantiomeric excess was determined after the aldol cyclization on compound **748**. R_f 0.42 (silica, hexanes/EtOAc 3:1); $[\alpha]_D^{22.5}$ +20.4° (*c* 1.04, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.28 (app. d, *J* = 1.2 Hz, 1H), 5.13 (s, 1H), 2.70 (d, *J* = 14.9 Hz, 1H), 2.63 (d, *J* = 14.9 Hz, 1H), 2.51–2.42 (m, 3H), 2.40 (q, *J* = 7.3 Hz, 2H), 2.18–2.09 (m, 2H), 1.95–1.70 (m, 7H), 1.03 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.7, 210.7, 138.5, 116.8, 50.7, 43.4, 39.1, 36.7, 36.7, 36.1, 28.2, 26.9, 20.7, 7.8; IR (neat Film,

NaCl): ν 2939, 2867, 1706, 1628, 1455, 1374, 1113, 889 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{22}O_2Cl$ $[M+H]^+$: 257.1308, found 257.1317.



763

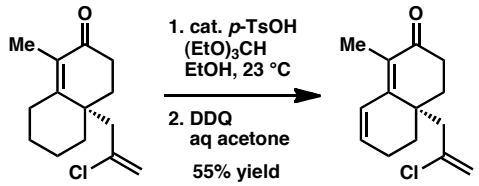
2-Allyl-2-(3-oxopentyl)cyclohexanone 763: Prepared according to the representative procedure on a 0.1 mmol scale. The title compound **763** (20.0 mg, 90 μmol, 90%) was obtained as a colorless liquid. R_f 0.40 (silica, hexanes/EtOAc 3:1); $[\alpha]_D^{22.5}$ +16.4° (*c* 1.28, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.69–5.61 (m, 1H), 5.07–5.02 (m, 2H), 2.43–2.14 (m, 8H), 1.99 (ddd, *J* = 4.9, 10.7, 15.9 Hz, 1H), 1.88–1.67 (m, 7H), 1.03 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 214.6, 211.1, 133.4, 118.3, 50.7, 39.2, 39.2, 36.6, 36.3, 36.0, 28.4, 27.0, 20.7, 7.8; IR (neat Film, NaCl): ν 2937, 2866, 1703, 1639, 1455, 1375, 1113, 916 cm^{-1}.



742 ***748***

(*R*)-4a-(2-Chloroallyl)-1-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one 748: The 1,5-diketone **742** (210 mg, 0.82 mmol, 1.0 equiv) was added to 1.85 mL 1 M KOH (1.85 mmol, 3 equiv) in methanol. The reaction mixture was stirred at 23 °C for 7 h during which time color gradually changes from yellow to orange. After the reaction

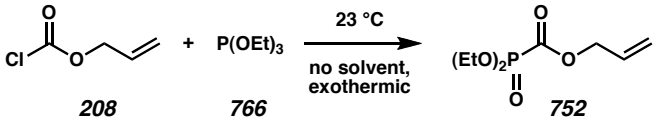
was complete as judged by TLC, ca. 4 mL Et_2O and ca. 4 mL H_2O were added. The organic phase was separated and the aqueous phase acidified by addition of 10% aq HCl (ca. 2 mL) before it was extracted three times with Et_2O (10 mL x 3). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (silica, hexanes/EtOAc 10:1) to afford 142 mg (0.59 mmol, 73%) of the title compound **748** as a colorless liquid. The enantiomeric excess was determined to be 88% ee. It was measured with HPLC using chiral stationary phase columns (Chiralcel OD-H, 1% isopropanol in hexanes, flow rate 1 mL/min, 254 nm, 10.9 min (major), 13.2 min (minor)). R_f 0.39 (silica, hexanes/EtOAc 3:1); $[\alpha]_D^{21.0}$ –70.7° (*c* 0.99, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.36 (d, *J* = 1.0 Hz, 1H), 5.17 (s, 1H), 2.78 (d, *J* = 14.6 Hz, 1H), 2.77–2.73 (m, 1H), 2.62 (d, *J* = 14.1 Hz, 1H), 2.62–2.54 (m, 1H), 2.40 (ddd, *J* = 3.9, 4.6, 17.3 Hz, 1H), 2.18 (ddd, *J* = 3.9, 5.0, 13.9 Hz, 1H), 2.15–2.07 (m, 1H), 2.02 (ddd, *J* = 3.2, 5.4, 13.9 Hz, 1H), 1.97–1.92 (m, 1H), 1.78 (s, 3H), 1.73–1.60 (m, 3H), 1.44–1.34 (m, 1H), 1.28 (ddd, *J* = 4.2, 13.5, 13.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.8, 161.2, 138.7, 129.9, 116.7, 42.1, 39.7, 38.1, 33.9, 33.1, 27.7, 26.7, 21.2, 11.1; IR (neat Film, NaCl): ν 2932, 2862, 1665, 1627, 1608, 1456, 1362, 1304, 1163, 1076, 882 cm^{-1}; HRMS (EI+) *m*/*z* calc'd for $C_{14}H_{20}ClO$ $[M+H]^+$: 239.1203, found 239.1209.



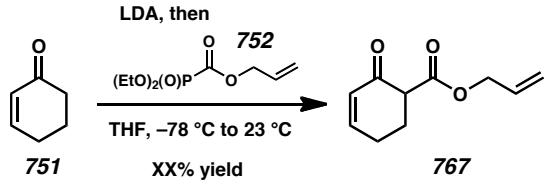
748 ***741***

(*R*)-4a-(2-Chloroallyl)-1-methyl-4,4a,5,6-tetrahydronaphthalen-2(3*H*)-one 741:[36]

The enone **748** (170 mg, 0.71 mmol, 1.0 equiv), triethyl orthoformate (535 μL, 2.85 mmol, 4.0 equiv) and a catalytic amount of *p*-toluenesulfonic acid monohydrate were diluted in dry ethanol (4 mL). The yellow reaction mixture was stirred at 23 °C for 24 h during which time its color turned dark brown. The reaction mixture was then poured into saturated sodium bicarbonate (10 mL) and extracted with hexanes (15 mL x 3). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude ethyl dienol ether (173 mg, 0.65 mmol, 92%) is unstable and therefore it was immediately dissolved in 95% aqueous acetone (4 mL). A solution of 2,6-dichloro-5,6-dicyano-*p*-benzoquinone (188 mg, 0.68 mmol, 1.05 equiv) in acetone (1 mL) was slowly added to the reaction mixture via syringe. The mixture turned black immediately, stirring was continued for 3 h at 23 °C before the solids were removed by filtration, and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography (silica, hexanes/EtOAc 10:1) to afford dienone **741** (92 mg, 0.39 mmol, 55% over 2 steps) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.54–6.41 (m, 1H), 6.21–6.15 (m, 1H), 5.33 (d, *J* = 1.5 Hz, 1H), 5.14 (d, *J* = 1.0 Hz, 1H); 2.67–2.57 (m, 1H), 2.52–2.36 (m, 4H), 2.24–2.15 (m, 2H), 2.15–2.10 (m, 1H), 2.03–1.96 (m, 1H), 1.76 (s, 3H), 1.72–1.60 (m, 1H), 1.46–1.30 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.9, 153.6, 138.6, 136, 8, 128.7, 124.5, 116.8, 40.9, 36.9, 33.9, 32.3, 32.2, 23.2, 10.3; HRMS (EI+) *m*/*z* calc'd for $C_{14}H_{18}OCl$ $[M+H]^+$: 237.1046, found 237.1045.

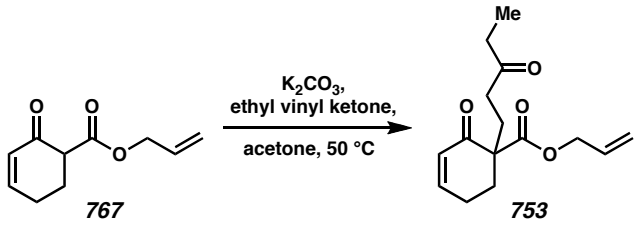


Allyl diethylphosphonoformate 752:[37] Allyl chloroformate (**208**, 7.7 mL (72 mmol, 1 equiv) was slowly added to triethyl phosphite (**766**, 12.4 mL, 72 mmol, 1 equiv) in a 250 mL round-bottom flask. The reaction was very rapid at 23 °C, creating heat and emitting bubbles of chloroethane. After stirring was continued for 20 min at 23 °C, the progress of the reaction was monitored by ^{31}P NMR (δ –4.2). When no more starting material was present, the reaction mixture was diluted with 20 mL THF and used without further purification.



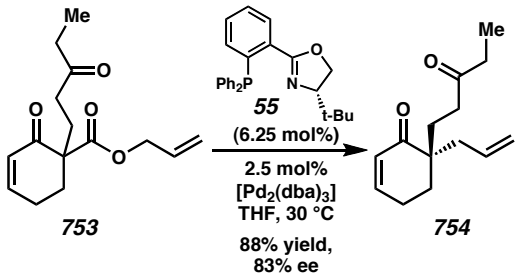
Allyl 2-oxocyclohex-3-enecarboxylate 767:[38] Lithium diisopropylamide was prepared by slow addition of *n*-butyllithium (2.5 M solution in hexanes, 26.4 mL, 66 mmol, 1.1 equiv) to a solution of diisopropylamine (10 mL, 72 mmol, 1.2 equiv) in THF (120 mL) at –78 °C. The resulting colorless solution was stirred for 1 h at –78 °C before a solution of freshly distilled cyclohex-2-enone (5.8 mL, 60 mmol, 1.0 equiv) in THF (20 mL) was slowly added via canula. The resulting yellow reaction mixture was stirred for 1 h at –78 °C. A freshly prepared solution of allyl diethylphosphonoformate **752** (16 g, 72 mmol, 1.2 equiv) in THF (20 mL) was added to the reaction mixture via canula at such a rate that the reaction temperature did not exceed –70 °C. The resulting yellow reaction

mixture was stirred for an additional hour at –78 °C before it was allowed to warm to 23 °C over a period of 4 h. When the reaction was complete as judged by TLC, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (50 mL) at 23 °C. Most of the organic layer was evaporated by rotary evaporation under reduced pressure. The mixture was diluted with ca. 70 mL Et_2O and the layers were separated. The aqueous phase was extracted three times with Et_2O (ca. 50 mL x 3). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (silica, hexanes/EtOAc (3:1) to afford the title compound **767** (7.8 g, 43 mmol, 72%) as a colorless liquid. R_f 0.21 (silica, hexanes/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.01 (ddd, *J* = 3.7, 3.7, 10.3 Hz, 1H), 6.07 (ddd, *J* = 1.7, 1.7, 10.0 Hz, 1H), 5.92 (dddd, *J* = 5.6, 5.6, 11.2, 16.1 Hz, 1H), 5.34 (1.5, 1.5, 1.5, 17.3 Hz, 1H), 5.24 (dd, *J* = 1.2, 10.5 Hz, 1H), 4.70–4.62 (m, 2H), 3.46–3.43 (m, 1H), 2.54–2.36 (m, 3H), 2.26–2.21 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.7, 169.6, 150.6, 131.7, 129.1, 118.5, 65.7, 53.4, 25.6, 24.3; IR (neat Film, NaCl): ν 3624, 3084, 3034, 2941, 2878, 1740, , 1681, 1650, 1455, 1426, 1373, 1388, 1307, 1232, 1166, 1124, 1078, 1040, 1023, 994, 937, 892 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{10}H_{12}O_3$ $[M]^+$: 180.0786, found 180.0786.



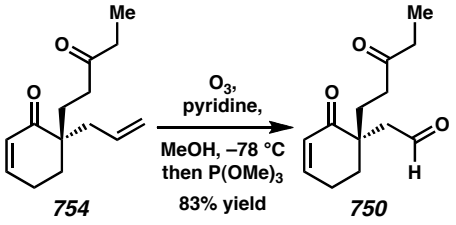
Allyl 2-oxo-1-(3-oxopentyl)cyclohex-3-enecarboxylate 753: Allyl 2-oxocyclohex-3-enecarboxylate **767** (4.00 g, 22.2 mmol, 1.0 equiv) was added to a suspension of

potassium carbonate (6.14 g, 44.4 mmol, 2.0 equiv) in acetone (30 mL). At 23 °C, ethyl vinyl ketone (4.42 mL, 44.4 mmol, 2.0 equiv) was added slowly via syringe. The resulting heterogeneous mixture was stirred for 2.5 h at 50 °C, then cooled to 23 °C, filtered and the filtrate concentrated by rotary evaporation under reduced pressure. The residue was purified by flash column chromatography (silica, hexanes/EtOAc 5:1 to 3:1) to afford allyl 2-oxo-1-(3-o42xopentyl)cyclohex-3-enecarboxylate (4.77 g, 18.0 mmol, 82%) **753** as a colorless liquid. R_f 0.19 (silica, hexanes/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.92–6.88 (m, 1H), 6.03 (ddd, J = 1.9, 1.9, 10.0 Hz, 1H), 5.90–5.82 (m, 1H), 5.31–5.27 (m, 1H), 4.64–4.57 (m, 2H), 2.61–2.50 (m, 1H), 2.49–2.37 (m, 6H), 2.20–2.14 (m, 1H), 2.07–2.01 (m, 1H), 1.97–1.92 (m, 1H), 1.04 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.5, 196.1, 171.3, 149.2, 131.5, 129.1, 118.6, 65.8, 56.2, 37.6, 35.9, 31.0, 27.3, 23.5, 7.8; IR (neat Film, NaCl): ν 3085, 3035, 2975, 2939, 1731, 1716, 1682, 1449, 1452, 1387, 1376, 1354, 1237, 1221, 1188, 1116, 1094, 993, 974, 943 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{15}H_{20}O_4$ $[M]^+$: 264.1362, found 264.1347.



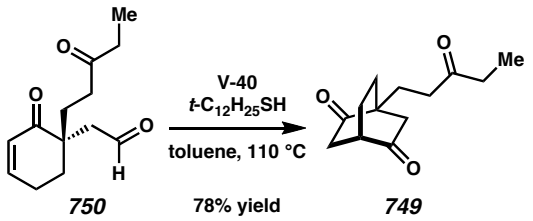
(*R*)-6-allyl-6-(3-oxopentyl)cyclohex-2-enone 754: A 500 mL round-bottom flask was equipped with a magnetic stir bar and flame-dried under vacuum. After cooling to 23 °C under dry argon, $Pd_2(dba)_3$ (260 mg, 0.28 mmol, 2.5 mol%) and (*S*)-*t*-BuPHOX (**55**, 275 mg, 0.71 mmol, 6.25 mol%) were added. The flask containing the solids was

evacuated for 15 min and then refilled with dry argon. Dry THF (3 mL) was then added and the resulting solution stirred at 23 °C for 30 min. At this point, allyl 2-oxo-1-(3-oxopentyl)cyclohex-3-enecarboxylate **753** (3.00 g, 11.4 mmol, 1.0 equiv) was added via syringe in one portion. The reaction was warmed to 30-35 °C. When the reaction was complete as judged by TLC, the reaction mixture was evaporated under reduced pressure and the residue purified by flash column chromatography (silica, hexanes/EtOAc 10:1) to afford (*R*)-6-allyl-6-(3-oxopentyl)cyclohex-2-enone **754** (2.19 g, 10.0 mmol, 88%) as a colorless liquid. The enantiomeric excess was determined to be 83% ee. It was measured with SFC using chiral stationary phase columns (Chiralcel OD-H, 5% isopropanol in hexanes, flow rate 1 mL/min, 244 nm, 5.5 min (minor), 5.8 min (major)). R_f 0.25 (silica, hexanes/EtOAc 3:1); $[\alpha]_D^{20.9}$ +13.9° (*c* 1.09, $CHCl_3$, 83% ee); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.87 (ddd, *J* = 3.9, 3.9, 10.0 Hz, 1H), 5.90 (ddd, *J* = 2.0, 2.0, 10.0 Hz, 1H), 5.73–5.65 (m, 1H), 5.09-5.05 (m, 2H), 2.46–2.27 (m, 7H), 2.20 (dd, *J* = 7.8, 13.9 Hz, 1H), 1.93–1.75 (m, 4H), 1.03 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.2, 202.6, 148.9, 133.5, 128.7, 118.4, 46.8, 38.8, 36.7, 36.0, 31.1, 27.6, 22.9, 7.8; IR (neat Film, NaCl): ν 3075, 3033, 2976, 2935, 1714, 1670, 1449, 1430, 1387, 1221, 1115, 997, 916 cm^{-1}; HRMS (EI+) *m*/*z* calc'd for $C_{14}H_{20}O_2$ $[M]^+$: 220.1463, found 220.1487.



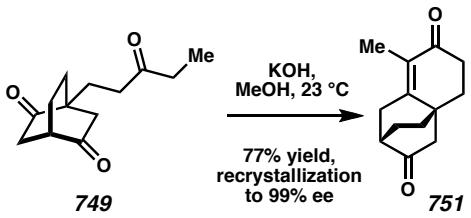
(*R*)-2-(2-oxo-1-(3-oxopentyl)cyclohex-3-enyl)acetaldehyde 750:[39] A 500 mL round-bottom flask equipped with a stir bar was charged with the enone **754** (2.19 g, 10.0 mmol,

1.0 equiv), pyridine (899 μL, 11.1 mmol, 1.12 equiv) and methanol (331 mL). Some Sudan Red 7B (tip of a spatula) was added as an indicator to determine the end point of the ozonolysis. A flow of ozone (125 mL/min oxygen flow, 302 mg/h) was passed through the solution until there was no starting material left by TLC analysis. The reaction flask was purged with nitrogen. Trimethyl phosphite (7.3 mL, 49.6 mmol, 5.0 equiv) was added via syringe, and the flask was allowed to slowly warm to 23 °C. After an additional hour stirring at 23 °C, the reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography (silica, hexanes/EtOAc, 5:1) to afford the title compound **750** (1.83 g, 8.25 mmol, 83%) as a colorless liquid. R_f 0.18 (silica, hexanes/EtOAc 3:1); $[\alpha]_D^{20.9}$ +36.6° (*c* 1.04, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.73 (m, 1H), 6.94–6.91 (m, 1H), 5.97 (ddd, *J* = 1.5, 2.4, 10.1 Hz, 1H), 2.83 (dd, *J* = 1,5, 16.2 Hz, 1H), 2.56–2.49 (m, 1H), 2.45–2.31 (m, 6H), 2.18 (dq, *J* = 5.4, 13.8 Hz, 1H), 2.00 (dq, *J* = 5.4, 15.1 Hz, 1H), 1.91–1.81 (m, 2H), 1.03 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.2, 201.2, 200.9, 149.4, 128.1, 48.1, 46.1, 36.5, 36.1, 31.7, 27.5, 22.8, 7.8; IR (neat Film, NaCl): ν 2975, 2938, 2737, 1714, 1668, 1455, 1389, 1223, 1112, 940, 807 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{18}O_3$ $[M]^+$: 222.1256, found 222.1233.



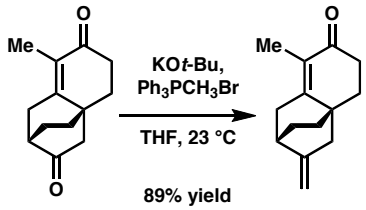
(1*R*, 4*S*)-1-(3-oxopentyl)bicyclo[2.2.2]octane-2,5-dione 749:[40] 1,1'-Azobis(cyclohexanecarbonitrile) (V-40) (2.47 g, 10.1 mmol, 1.5 equiv) was added to a

solution of the alkenal **750** (1.50 g, 6.75 mmol, 1.0 equiv) and *t*-dodecanethiol (4.76 mL, 20.2 mmol, 3.0 equiv) in dry toluene (68 mL). The solution was degassed three times by the freeze-thaw procedure. The reaction mixture was then refluxed under argon atmosphere for 24 h. After cooling to 23 °C, the solvents were evaporated under reduced pressure. The residue was purified by flash column chromatography (silica, hexanes/EtOAc 3:1 to 1:1) to afford bicyclo[2.2.2]octadione **749** (1.17 g, 5.26 mmol, 78%) as a white solid. R_f 0.10 (silica, hexanes/EtOAc 3:1); mp 73 °C; $[\alpha]_D^{19.7}$ +29.3° (*c* 0.99, $CHCl_3$, 83% ee); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.74 (quint, *J* = 2.9 Hz, 1H), 2.53–2.33 (m, 8H), 2.09–2.03 (m, 1H), 1.98–1.91 (m, 1H), 1.86–1.69 (m, 4H), 1.05 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.7, 211.0, 210.6, 48.7, 44.8, 44.3, 40.7, 37.0, 35.9, 28.0, 26.8, 22.6, 7.8; IR (neat Film, NaCl): ν 2940, 2879, 1720, 1450, 1399, 1115, 1086, 952 cm^{-1}; HRMS (EI+) *m*/*z* calc'd for $C_{13}H_{18}O_3$ $[M]^+$: 222.1256, found 222.1254.



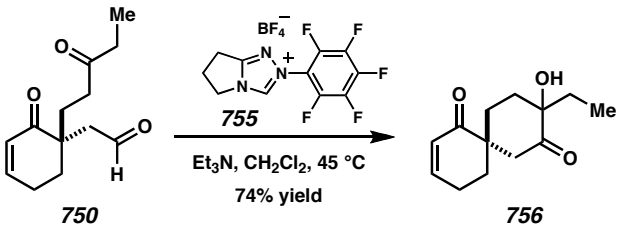
Dione 751: The 1,5-diketone **749** (1.75 g, 7.87 mmol, 1.0 equiv) was added to 11.8 mL 1 M KOH (11.8 mmol, 1.5 equiv) in methanol (33 mL). The reaction mixture was stirred at 23 °C for 7 h during which time color gradually changes to orange. After the reaction was complete as judged by TLC, the reaction mixture was concentrated in vacuo. Subsequently, the residue was redissolved in ca. 30 mL Et_2O and ca. 30 mL H_2O. The organic phase was separated and the aqueous phase acidified by addition of 10% aq

HCl (ca. 12 mL) before it was extracted three times with Et_2O (30 mL x 3). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (silica, hexanes/EtOAc 3:1). The colorless solid material was recrystallized from hexanes to afford 1.31 g **751** (6.41 mmol, 81%) as colorless crystals suitable for X-ray analysis. The enantiomeric excess was determined to be 99% ee (measured by HPLC using a Chiralpak AD column and 10% isopropanol in hexanes as eluent at a flow rate of 1 mL/min and detection at 254 nm; retention times: 13.3 min (major), 14.7 min (minor)). R_f 0.13 (silica, hexanes/EtOAc 3:1); mp = 110 °C; $[\alpha]_D^{20.0}$ +30.5° (*c* 1.00, $CHCl_3$, >99% ee); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.65 (s, 2H), 2.62 (t, *J* = 2.7 Hz, 1H), 2.46–2.42 (m, 2H), 2.37 (dd, *J* = 2.7, 18.7 Hz, 1H), 2.23 (d, *J* = 18.5 Hz, 1H), 2.01–1.96 (m, 2H), 1.90–1.84 (m, 3H), 1.72 (s, 3H), 1.64–1.59 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.5, 197.3, 157.2, 130.3, 48.4, 43.7, 38.2, 33.5, 32.4, 31.7, 29.9, 23.1, 10.6; IR (neat Film, NaCl): ν 2966, 2952, 2915, 1720, 1660, 1631, 1472, 1402, 1310, 1295, 1124, 889, 867, 709 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{16}O_2$ $[M]^+$: 204.1150, found 204.1114.



Enone 740: A 25 mL round-bottom flask was charged with methyltriphenylphosphonium bromide (879 mg, 2.46 mmol, 1.5 equiv) and THF (8 mL). The solution was cooled to 0 °C and a solution of potassium *t*-butoxide (221 mg, 1.97 mmol, 1.2 equiv) in THF (2 mL) was slowly added via syringe. The solution was stirred

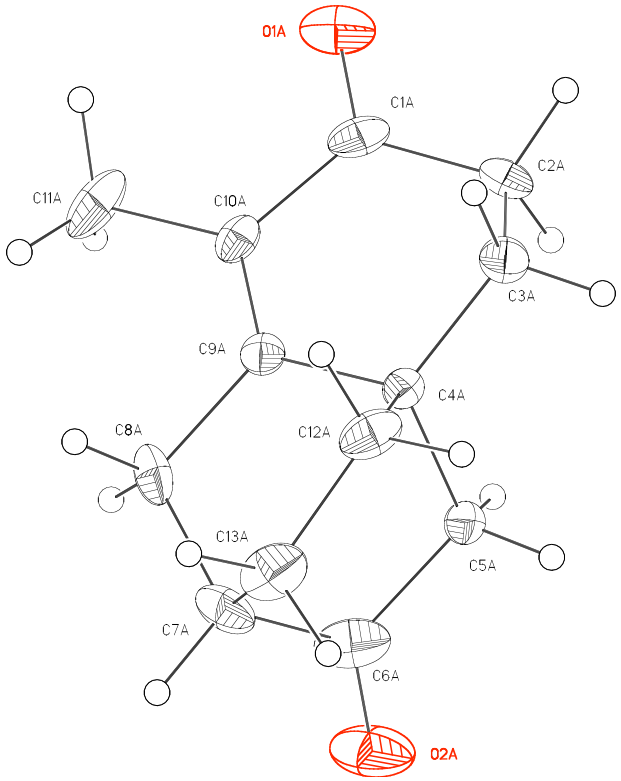
at 0 °C for 15 min before a solution of the dione **751** (335 mg, 1.64 mmol, 1.0 equiv) in THF (2 mL) was added via syringe. Upon addition the color of the reaction mixture changed from yellow to red/brown. Stirring was continued, first at 0 °C for 30 min, then at 23 °C for another 30 min. The reaction was quenched by addition of saturated aqueous NH_4Cl (7 mL) and Et_2O (7 mL). The layers were separated and the aqueous layer was extracted with Et_2O (10 mL x3). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (silica, hexanes/EtOAc 7:1) to afford the enone **740** (295 mg, 1.45 mmol, 89%) as a colorless liquid. R_f 0.24 (silica, hexanes/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.85 (dd, J = 2.2, 4.0 Hz, 1H), 4.67 (dd, J = 2.2, 3.8 Hz, 1H), 2.55 (quintet, J = 2.9 Hz, 1H), 2.45 (s, 2H). 2.41–2.38 (m, 3H), 2.24 (dd, J = 2.0, 17.8 Hz, 1H), 1.81–1.74 (m, 4H), 1.67 (s, 3H), 1.66–1.63 (m, 1H), 1.52–1.49 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.2, 182.2, 149.2, 129.0, 106.4, 40.2, 37.0, 36.4, 35.7, 33.8, 32.2, 30.7, 26.4, 10.3; IR (neat Film, NaCl): ν 3069, 2928, 2870, 2823, 1666, 1630, 1449, 1308, 1198, 1082, 881, 754 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{14}H_{18}O$ $[M]^+$: 202.1358, found 202.1351.



(6*R*)-9-Ethyl-9-hydroxyspiro[5.5]undec-2-ene-1,8-dione 756: A 25 mL round-bottom flask was charged with a stir bar and CH_2Cl_2 (5 mL). The aldehyde **750** (100 mg, 0.45 mmol, 1.0 equiv), triazolium salt (**755**. 124 mg, 0.45 mmol, 1.0 equiv) and

triethylamine (63 μL, 0.45 mmol, 1.0 equiv) were added consecutively. The resulting yellow mixture was stirred at 45 °C for 2 h. After cooling to 23 °C, the reaction mixture was concentrated in vacuo and the residue purified by flash column chromatography (silica, hexanes/EtOAc 2:1) to afford the title compound **756** (74 mg, 0.33 mmol, 74%) as a colorless liquid. R_f 0.18 (silica, hexanes/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.96–6.92 (m, 1H), 6.01 (ddd, *J* = 2.0, 2.0, 10.3 Hz, 1H), 3.89 (s, 1H), 3.15 (d, *J* = 13.9, 1H), 2.39–2.36 (m, 2H), 2.23–2.16 (m, 2H), 2.03–1.76 (m, 6H), 1.71 (dddd, *J* = 7.3, 7.3, 7.3, 14.3 Hz, 1H), 0.81 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.8, 199.7, 149.5, 128.1, 78.6, 50.0, 43.6, 35.6, 30.2, 29.3, 27.1, 22.6, 7.0; IR (neat Film, NaCl): ν 3477, 2956, 2938, 2922, 2877, 1710, 1672, 1463, 1386, 1259, 1218, 1155, 1132, 1023, 803 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{19}O_3$ $[M + H]^+$: 223.1334, found 223.1336.

10.8.3 X-RAY STRUCTURE OF DIKETONE 751



Diketone **751**

Note: The crystallographic data have been deposited in the Cambridge Database (CCDC) and has been placed on hold pending further instructions from me. The deposition number is 686706. Ideally the CCDC would like the publication to contain a footnote of the type: "Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 686706."

*Table 10.1 Crystal data and structure refinement for diektone **751** (CCDC 686706).*

Empirical formula	$C_{13}H_{16}O_2$
Formula weight	204.26
Crystallization solvent	hexanes
Crystal habit	prism
Crystal size	0.42 x 0.15 x 0.11 mm^3
Crystal color	colorless

Data Collection

Type of diffractometer	Bruker KAPPA APEX II
Wavelength	0.71073 Å MoKα
Data Collection Temperature	100(2) K
θ range for 2641 reflections used in lattice determination	2.33 to 34.42°
Unit cell dimensions	a = 12.0658(7) Å b = 7.1991(4) Å β= 92.724(5)° c = 12.0987(10) Å
Volume	1049.74(12) $Å^3$
Z	4
Crystal system	Monoclinic
Space group	$P2_1$
Density (calculated)	1.292 Mg/m^3
F(000)	440
Data collection program	Bruker APEX2 v2.1-0
θ range for data collection	2.44 to 34.55°
Completeness to θ = 34.55°	78.3 %
Index ranges	$-17 \le h \le 17, 0 \le k \le 11, 0 \le l \le 17$
Data collection scan type	ω scans; 12 settings
Data reduction program	Bruker SAINT-Plus v7.34A
Reflections collected	3732
Independent reflections	3732 [R_{int}= 0.0000]
Absorption coefficient	0.086 mm^{-1}
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7468 and 0.6368

Table 10.1 (cont.)

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 2008)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 2008)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	3732 / 1 / 274
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	2.574
Final R indices [I>2σ(I), 3246 reflections]	R1 = 0.0659, *w*R2 = 0.0929
R indices (all data)	R1 = 0.0805, *w*R2 = 0.0943
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.002
Average shift/error	0.000
Absolute structure determination	Unable to determine reliably
Absolute structure parameter	–1.8(16)
Largest diff. peak and hole	0.387 and –0.359 e.$Å^{-3}$

Special Refinement Details

The structure was refined as a twin with two orientations, BASF=0.452, using an HKLF 5 format reflection file prepared with TWINABS (see below). The two orientations were separated using CELL_NOW as follows.

Rotated from first domain by 179.7 degrees about reciprocal axis 0.000 0.000 1.000 and real axis 0.042 0.003 1.000. Twin law to convert hkl from first to this domain (SHELXL TWIN matrix):

-1.000	0.007	-0.001
-0.003	-1.000	0.000
0.085	0.005	1.000

Saint refined twin law; Twin Law, Sample 1 of 1 transforms h1.1(1)->h1.2(2)

-1.00019 0.00027 -0.00402

-0.00010 -1.00014 -0.00007

0.09148 -0.00022 1.00008

Twinabs;

PART 1 - Refinement of parameters to model systematic errors

2121 data (819 unique) involve domain 1 only, mean I/sigma 18.8

2180 data (823 unique) involve domain 2 only, mean I/sigma 16.4

12491 data (3743 unique) involve 2 domains, mean I/sigma 13.2

HKLF 5 dataset constructed from all observations involving domain 1

7697 Corrected reflections written to file twin5.hkl

Reflections merged according to point-group 2/m

Single reflections that also occur in composites omitted

Minimum and maximum apparent transmission: 0.636799 0.746793

Additional spherical absorption correction applied with mu*r = 0.2000

Crystals were mounted on a glass fiber using Paratone oil then placed on the diffractometer under a nitrogen stream at 100K.

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Figure 10.3 Representations of diketone ***751***

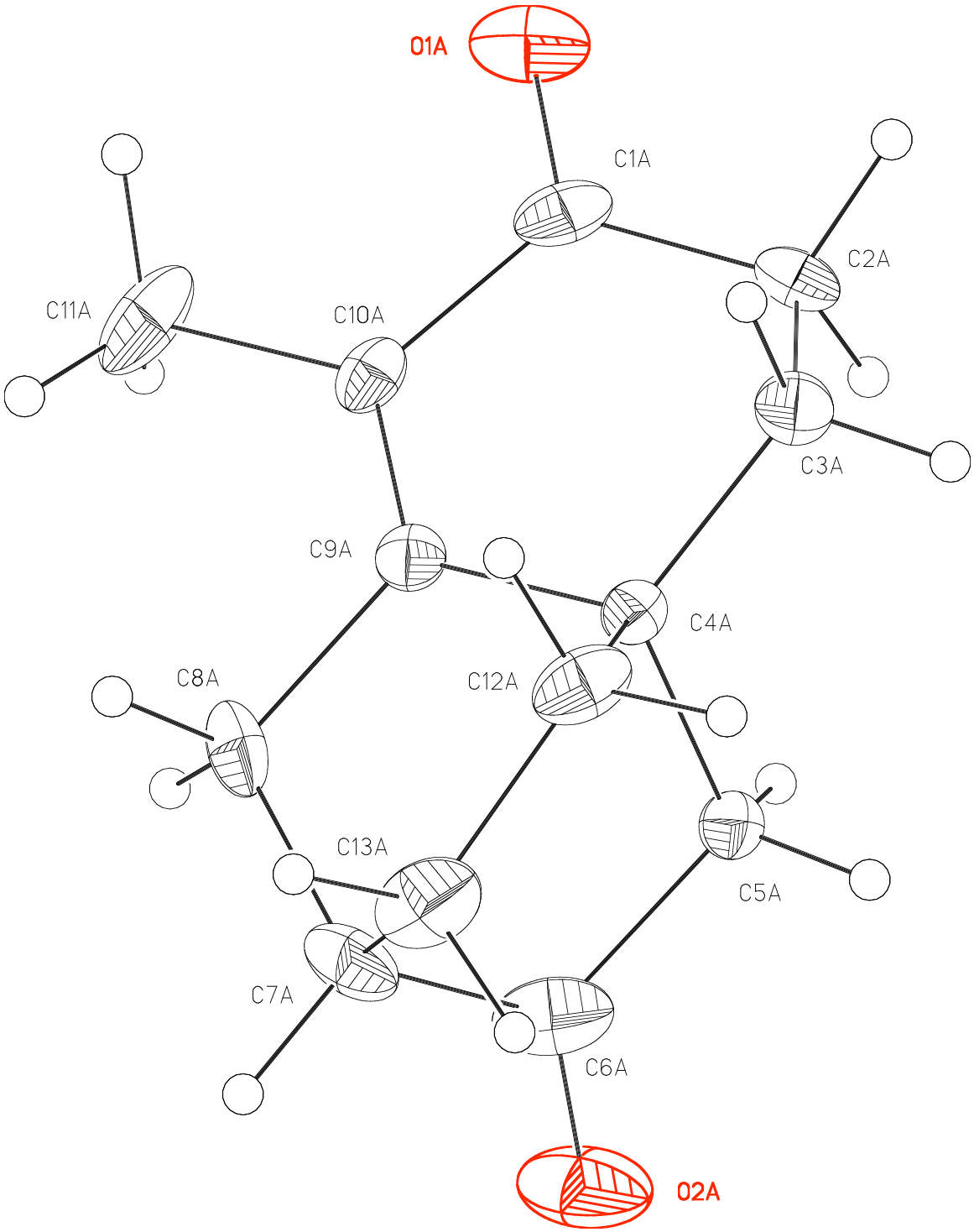


Figure 10.3 (continued)

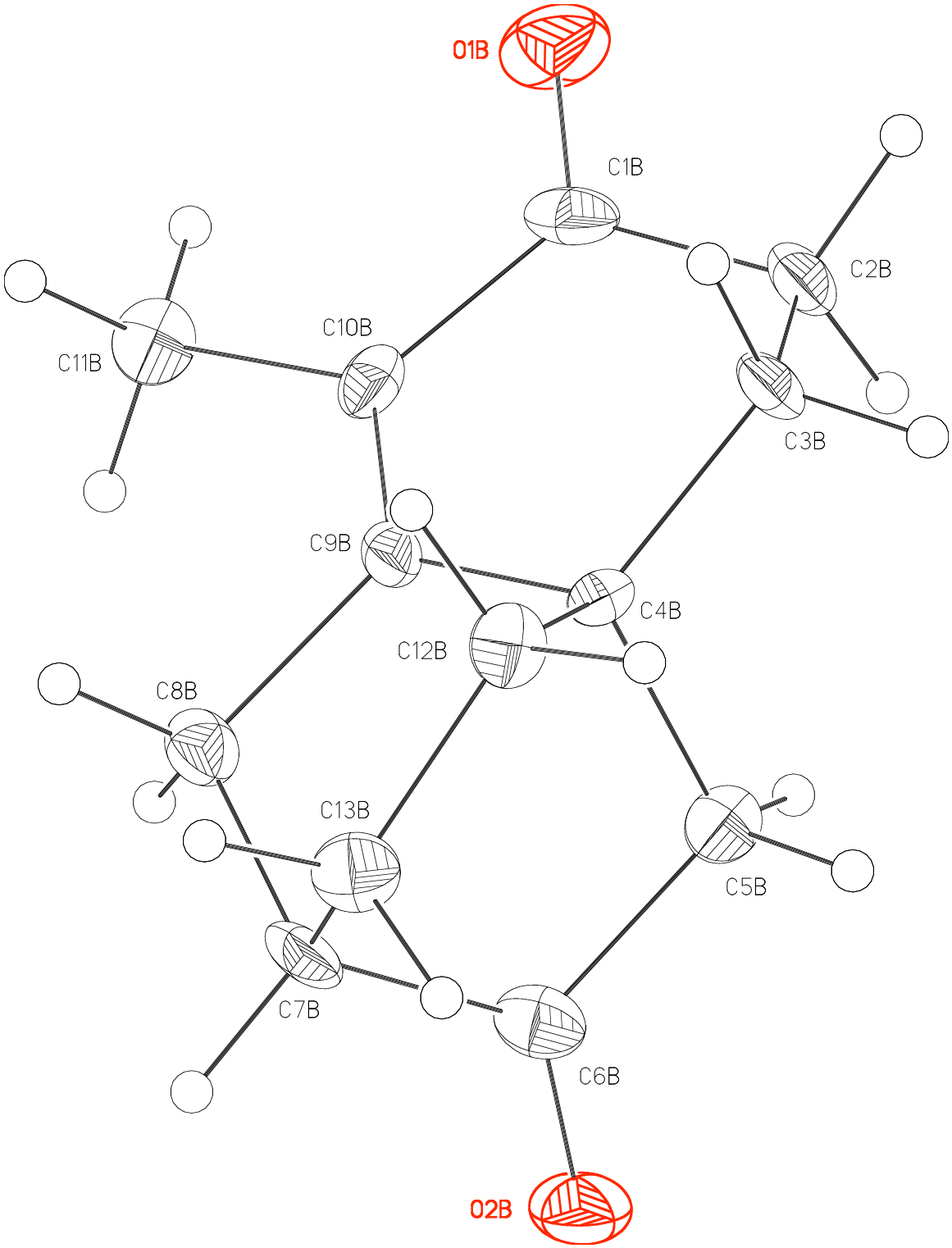


*Table 10.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **751** (CCDC 686706). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U_{eq}
O(1A)	8680(2)	193(3)	8344(2)	34(1)
O(2A)	6770(3)	4232(3)	3573(3)	44(1)
C(1A)	8512(3)	250(4)	7345(3)	24(1)
C(2A)	9440(3)	503(5)	6585(3)	27(1)
C(3A)	9187(3)	-422(4)	5456(3)	24(1)
C(4A)	8084(3)	196(4)	4923(3)	17(1)
C(5A)	8115(3)	2139(4)	4372(3)	18(1)
C(6A)	6953(4)	2683(4)	3920(3)	32(1)
C(7A)	6156(3)	1123(4)	3966(3)	27(1)
C(8A)	6042(3)	637(4)	5198(3)	24(1)
C(9A)	7182(3)	315(4)	5760(3)	16(1)
C(10A)	7346(3)	262(4)	6850(3)	18(1)
C(11A)	6440(3)	272(5)	7646(3)	32(1)
C(12A)	7718(3)	-1199(4)	4011(3)	26(1)
C(13A)	6617(3)	-572(4)	3390(3)	32(1)
O(1B)	779(2)	360(3)	3326(2)	34(1)
O(2B)	3569(2)	-3383(3)	-872(2)	32(1)
C(1B)	1121(3)	274(4)	2398(3)	21(1)
C(2B)	358(3)	-75(4)	1415(3)	22(1)
C(3B)	714(3)	901(4)	388(3)	20(1)
C(4B)	1919(3)	450(4)	129(3)	16(1)
C(5B)	2022(3)	-1471(4)	-433(3)	20(1)
C(6B)	3247(3)	-1894(4)	-580(3)	23(1)
C(7B)	3990(3)	-237(4)	-312(3)	20(1)
C(8B)	3889(3)	213(4)	922(3)	20(1)
C(9B)	2657(3)	388(4)	1167(3)	16(1)
C(10B)	2324(2)	336(4)	2205(3)	17(1)
C(11B)	3100(3)	345(5)	3213(3)	22(1)
C(12B)	2369(3)	1934(4)	-650(3)	20(1)
C(13B)	3541(3)	1410(4)	-1012(3)	23(1)

Table 10.3 Bond lengths [Å] and angles [°] for ***751*** *(CCDC 686706).*

O(1A)-C(1A)	1.217(4)	C(12A)-C(4A)-C(5A)	107.0(3)
O(2A)-C(6A)	1.208(4)	C(6A)-C(5A)-C(4A)	110.1(3)
C(1A)-C(2A)	1.493(5)	O(2A)-C(6A)-C(7A)	127.2(4)
C(1A)-C(10A)	1.502(4)	O(2A)-C(6A)-C(5A)	120.6(4)
C(2A)-C(3A)	1.537(5)	C(7A)-C(6A)-C(5A)	112.2(3)
C(3A)-C(4A)	1.518(5)	C(6A)-C(7A)-C(13A)	109.7(3)
C(4A)-C(9A)	1.523(4)	C(6A)-C(7A)-C(8A)	107.2(3)
C(4A)-C(12A)	1.541(5)	C(13A)-C(7A)-C(8A)	108.1(3)
C(4A)-C(5A)	1.550(4)	C(9A)-C(8A)-C(7A)	110.3(3)
C(5A)-C(6A)	1.531(5)	C(10A)-C(9A)-C(8A)	122.5(3)
C(6A)-C(7A)	1.482(5)	C(10A)-C(9A)-C(4A)	125.7(3)
C(7A)-C(13A)	1.524(5)	C(8A)-C(9A)-C(4A)	111.7(3)
C(7A)-C(8A)	1.543(6)	C(9A)-C(10A)-C(11A)	124.3(3)
C(8A)-C(9A)	1.523(4)	C(9A)-C(10A)-C(1A)	119.3(3)
C(9A)-C(10A)	1.325(4)	C(11A)-C(10A)-C(1A)	116.4(3)
C(10A)-C(11A)	1.491(4)	C(4A)-C(12A)-C(13A)	111.3(3)
C(12A)-C(13A)	1.561(5)	C(7A)-C(13A)-C(12A)	109.4(3)
O(1B)-C(1B)	1.215(4)	O(1B)-C(1B)-C(10B)	121.4(3)
O(2B)-C(6B)	1.199(4)	O(1B)-C(1B)-C(2B)	121.5(3)
C(1B)-C(10B)	1.482(4)	C(10B)-C(1B)-C(2B)	116.8(3)
C(1B)-C(2B)	1.491(5)	C(1B)-C(2B)-C(3B)	112.9(3)
C(2B)-C(3B)	1.508(5)	C(2B)-C(3B)-C(4B)	112.3(3)
C(3B)-C(4B)	1.537(4)	C(9B)-C(4B)-C(3B)	111.3(3)
C(4B)-C(9B)	1.505(4)	C(9B)-C(4B)-C(12B)	108.7(3)
C(4B)-C(12B)	1.540(4)	C(3B)-C(4B)-C(12B)	110.0(3)
C(4B)-C(5B)	1.548(4)	C(9B)-C(4B)-C(5B)	106.4(2)
C(5B)-C(6B)	1.527(4)	C(3B)-C(4B)-C(5B)	112.0(2)
C(6B)-C(7B)	1.518(4)	C(12B)-C(4B)-C(5B)	108.2(3)
C(7B)-C(8B)	1.539(5)	C(6B)-C(5B)-C(4B)	109.1(3)
C(7B)-C(13B)	1.540(4)	O(2B)-C(6B)-C(7B)	124.6(3)
C(8B)-C(9B)	1.535(4)	O(2B)-C(6B)-C(5B)	122.8(3)
C(9B)-C(10B)	1.337(5)	C(7B)-C(6B)-C(5B)	112.5(3)
C(10B)-C(11B)	1.502(4)	C(6B)-C(7B)-C(8B)	107.4(3)
C(12B)-C(13B)	1.546(5)	C(6B)-C(7B)-C(13B)	107.4(3)
		C(8B)-C(7B)-C(13B)	109.2(3)
O(1A)-C(1A)-C(2A)	121.4(3)	C(9B)-C(8B)-C(7B)	109.0(3)
O(1A)-C(1A)-C(10A)	120.3(3)	C(10B)-C(9B)-C(4B)	126.4(3)
C(2A)-C(1A)-C(10A)	118.0(3)	C(10B)-C(9B)-C(8B)	121.0(3)
C(1A)-C(2A)-C(3A)	111.8(3)	C(4B)-C(9B)-C(8B)	112.4(3)
C(4A)-C(3A)-C(2A)	112.6(3)	C(9B)-C(10B)-C(1B)	119.3(3)
C(3A)-C(4A)-C(9A)	111.9(3)	C(9B)-C(10B)-C(11B)	124.0(3)
C(3A)-C(4A)-C(12A)	109.2(3)	C(1B)-C(10B)-C(11B)	116.7(3)
C(9A)-C(4A)-C(12A)	108.9(3)	C(4B)-C(12B)-C(13B)	110.9(3)
C(3A)-C(4A)-C(5A)	114.1(3)	C(7B)-C(13B)-C(12B)	109.6(3)
C(9A)-C(4A)-C(5A)	105.5(2)		

*Figure 10.4 Anisotropic displacement parameters ($Å^2$ x 10^4) for **751** (CCDC 686706). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1A)	469(17)	284(11)	261(15)	12(13)	-90(14)	47(14)
O(2A)	573(19)	210(11)	500(19)	80(11)	-201(18)	-1(13)
C(1A)	380(20)	126(11)	227(19)	59(15)	17(18)	38(16)
C(2A)	200(18)	295(16)	310(20)	100(16)	-34(18)	90(16)
C(3A)	210(20)	208(14)	300(20)	64(13)	16(19)	34(13)
C(4A)	169(17)	169(12)	169(16)	25(13)	6(14)	-13(15)
C(5A)	163(19)	185(13)	188(19)	24(12)	-3(16)	-28(12)
C(6A)	520(30)	213(14)	210(20)	-26(13)	-60(20)	27(16)
C(7A)	230(20)	294(16)	280(20)	-21(15)	-131(19)	0(16)
C(8A)	130(17)	251(16)	340(20)	-42(14)	14(17)	-39(13)
C(9A)	183(16)	110(11)	200(17)	10(13)	16(15)	13(15)
C(10A)	230(18)	103(12)	204(18)	5(13)	61(16)	-15(15)
C(11A)	500(20)	240(14)	250(20)	-25(17)	230(20)	-40(20)
C(12A)	410(20)	225(14)	157(18)	-5(12)	63(19)	22(16)
C(13A)	450(30)	304(16)	200(20)	-25(14)	-60(20)	-135(18)
O(1B)	416(16)	360(12)	255(15)	-63(12)	157(14)	-73(15)
O(2B)	294(14)	213(10)	450(18)	-94(11)	112(14)	24(11)
C(1B)	248(19)	130(12)	250(20)	-12(15)	108(17)	33(16)
C(2B)	99(16)	167(14)	410(20)	-48(13)	28(17)	11(12)
C(3B)	91(17)	216(14)	300(20)	-37(13)	24(17)	26(12)
C(4B)	165(16)	154(12)	161(16)	-60(12)	22(15)	-5(13)
C(5B)	220(18)	172(13)	190(20)	2(12)	-19(17)	14(13)
C(6B)	230(20)	235(14)	230(20)	18(13)	72(18)	20(14)
C(7B)	108(16)	236(14)	270(20)	3(13)	87(17)	4(12)
C(8B)	161(16)	177(12)	264(19)	5(14)	-4(15)	20(14)
C(9B)	119(15)	115(12)	255(19)	-33(13)	14(15)	-14(13)
C(10B)	203(17)	118(11)	177(17)	-24(13)	-35(15)	-9(14)
C(11B)	252(18)	184(12)	227(18)	30(14)	-21(16)	12(17)
C(12B)	216(19)	204(14)	160(20)	46(12)	-35(17)	11(14)
C(13B)	255(19)	228(15)	210(20)	13(13)	37(18)	3(15)

10.8.4 NOTES AND REFERENCES FOR EXPERIMENTAL SECTION

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APPENDIX 5

Spectra of Compound Relevant to Chapter 10

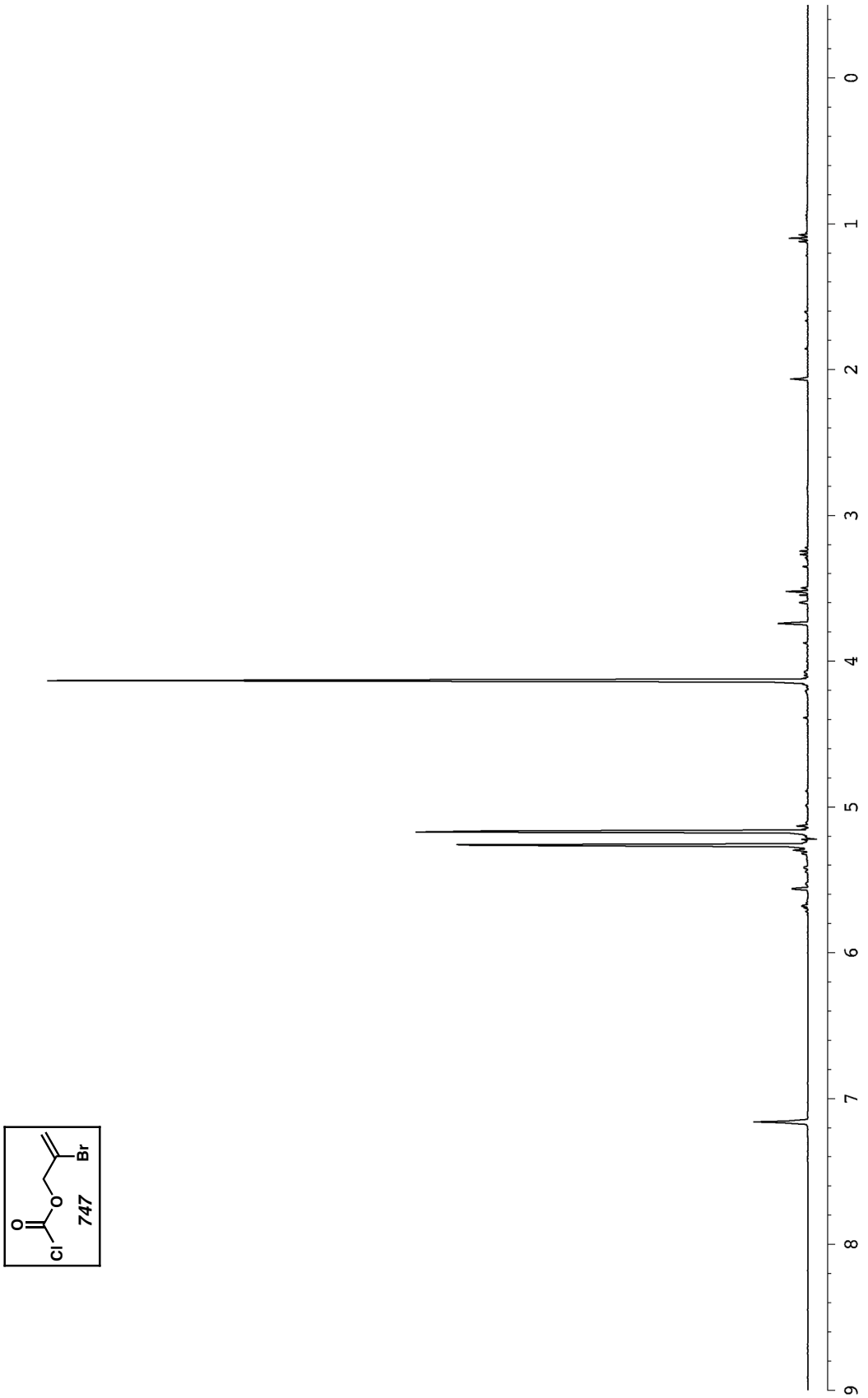


*Figure A5.1 ^1H NMR of compound **747** (300 MHz, C_6D_6)*

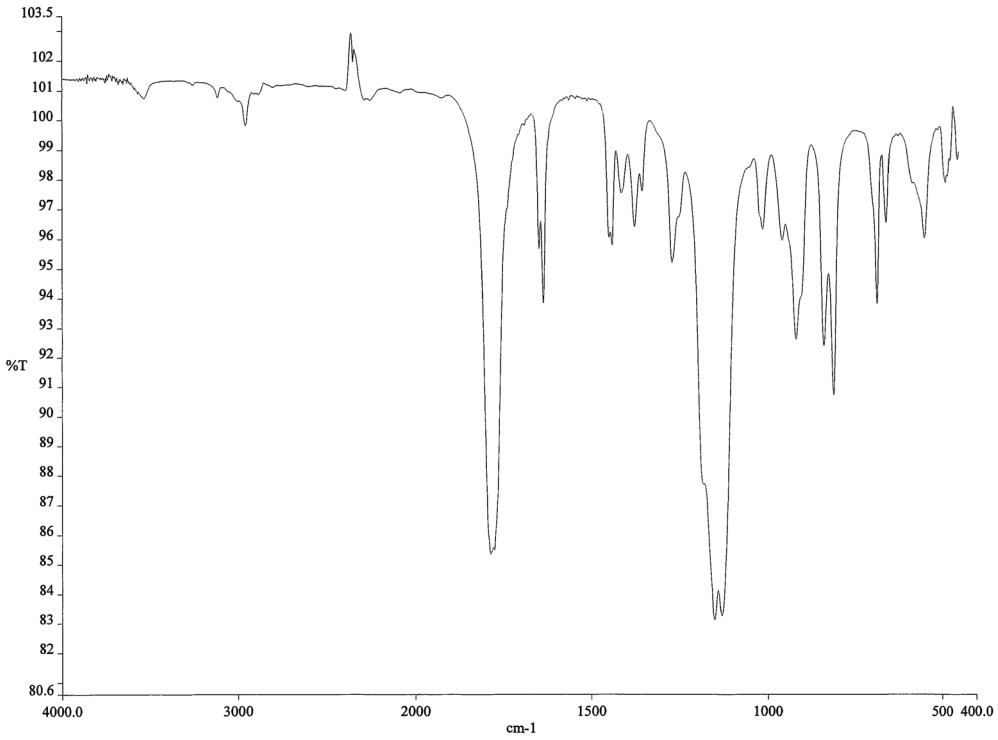


*Figure A5.2 IR of compound **747** (NaCl/film)*

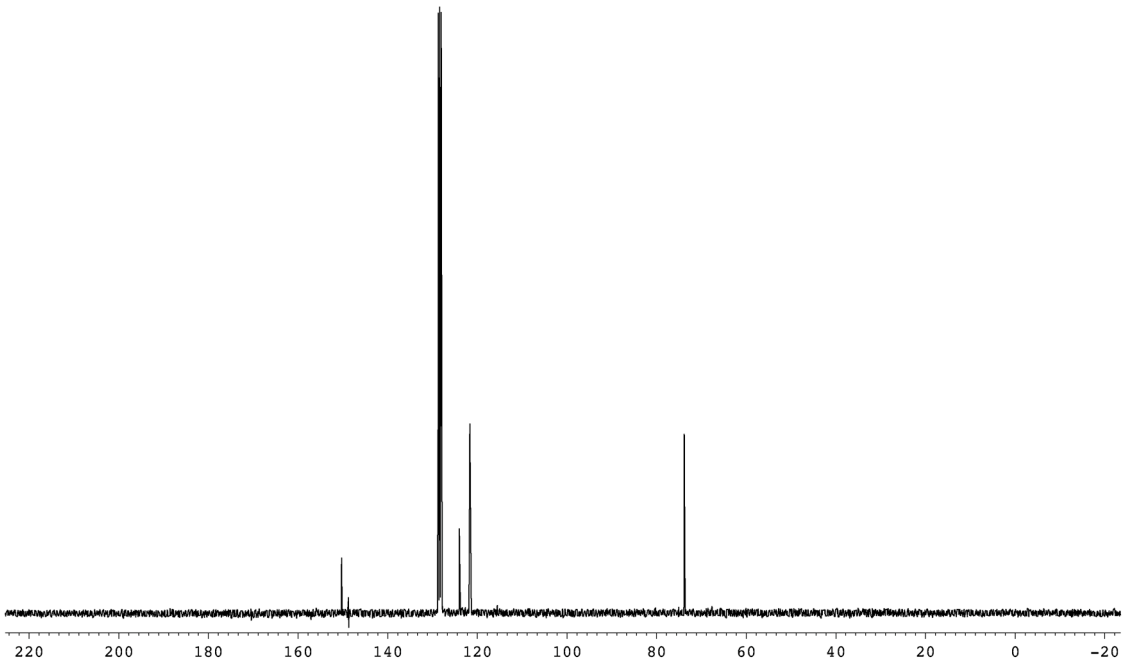


*Figure A5.3 ^{13}C NMR of compound **747** (75 MHz, C_6D_6)*

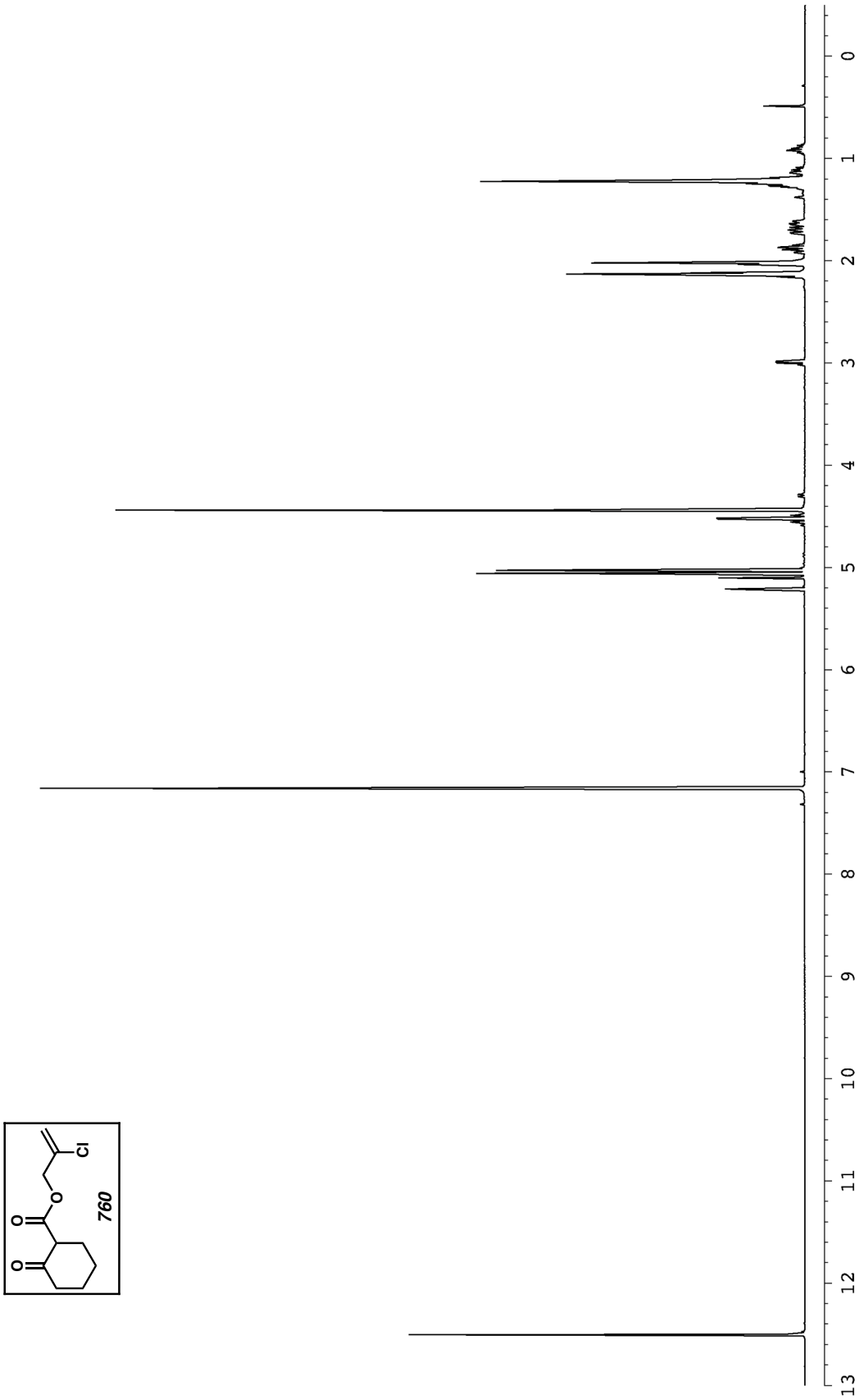


*Figure A5.4 ^1H NMR of compound **760** (500 MHz, C_6D_6)*

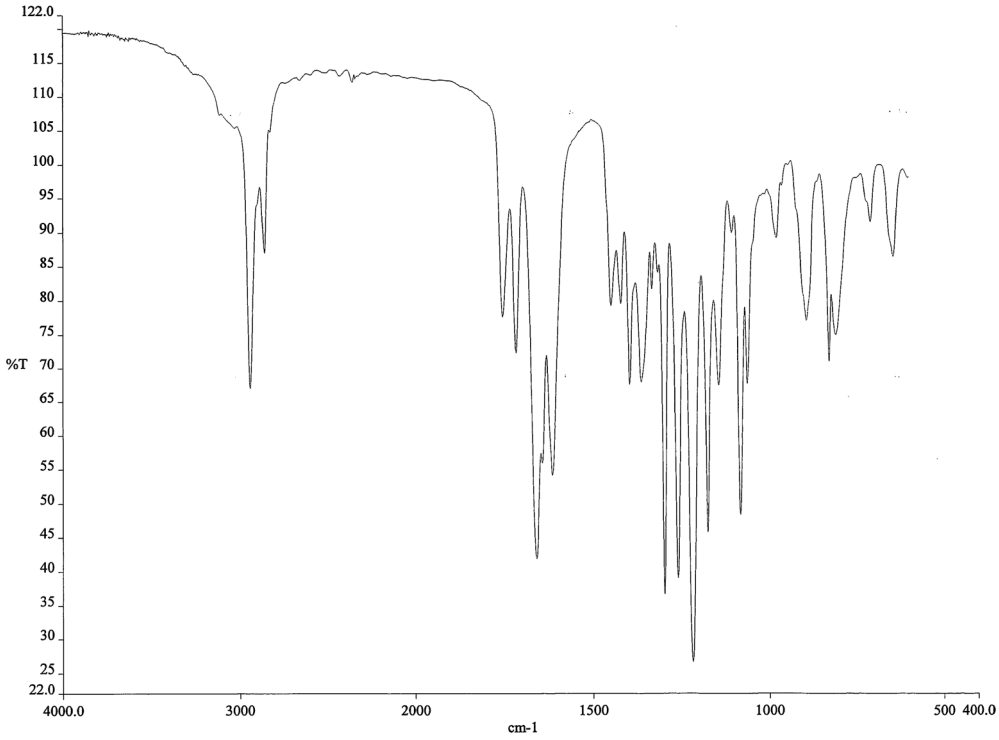


*Figure A5.5 IR of compound **760** (NaCl/film)*

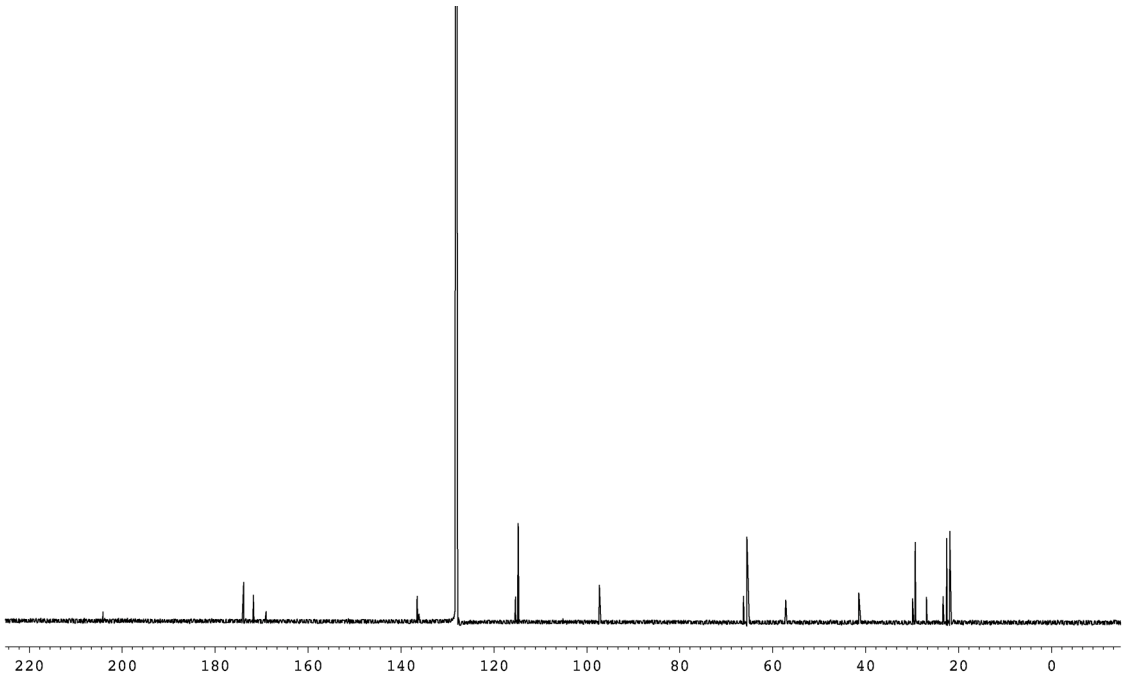


*Figure A5.6 ^{13}C NMR of compound **760** (125 MHz, C_6D_6)*

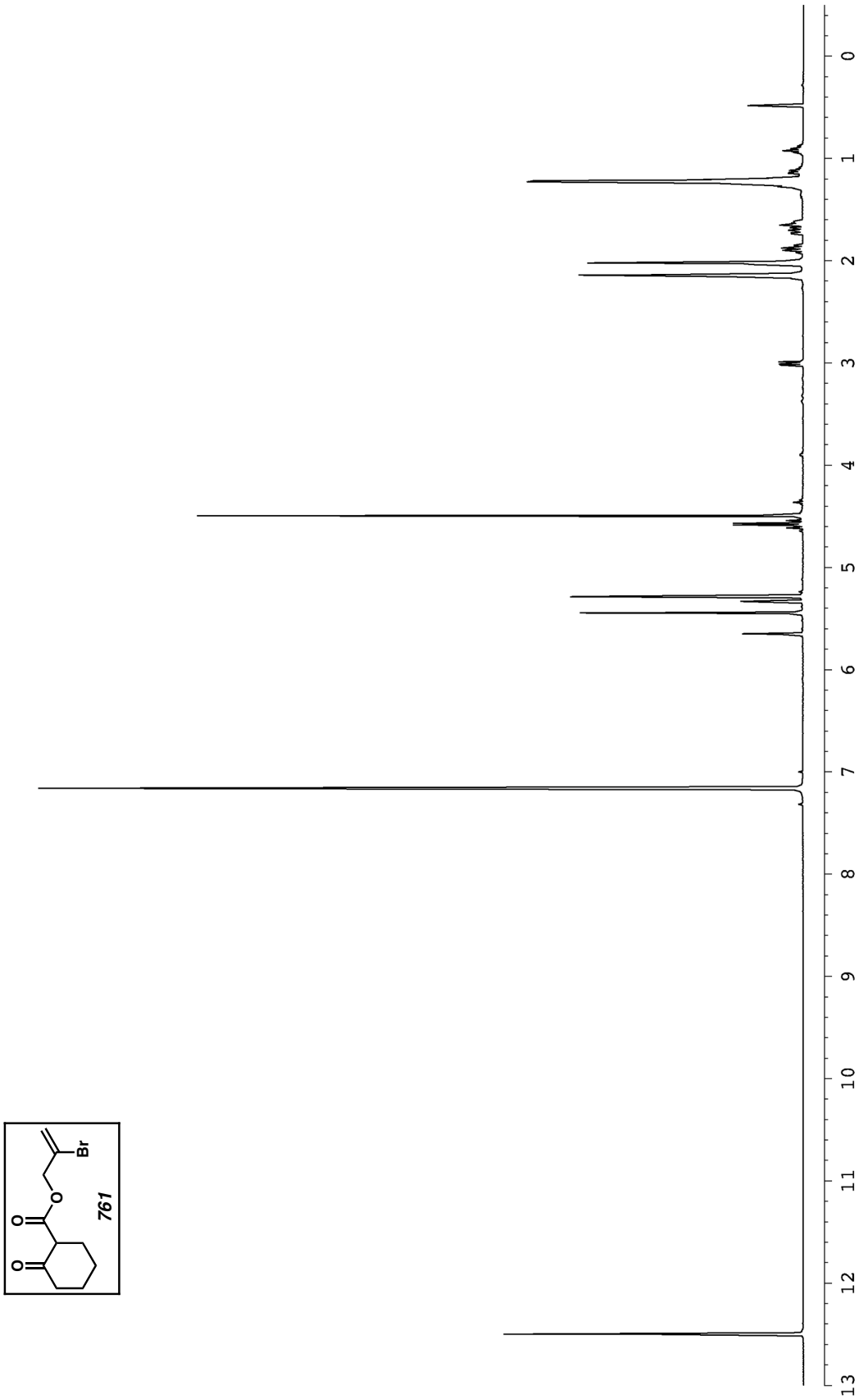


*Figure A5.7 ^{1}H NMR of compound **761** (500 MHz, C_6D_6)*

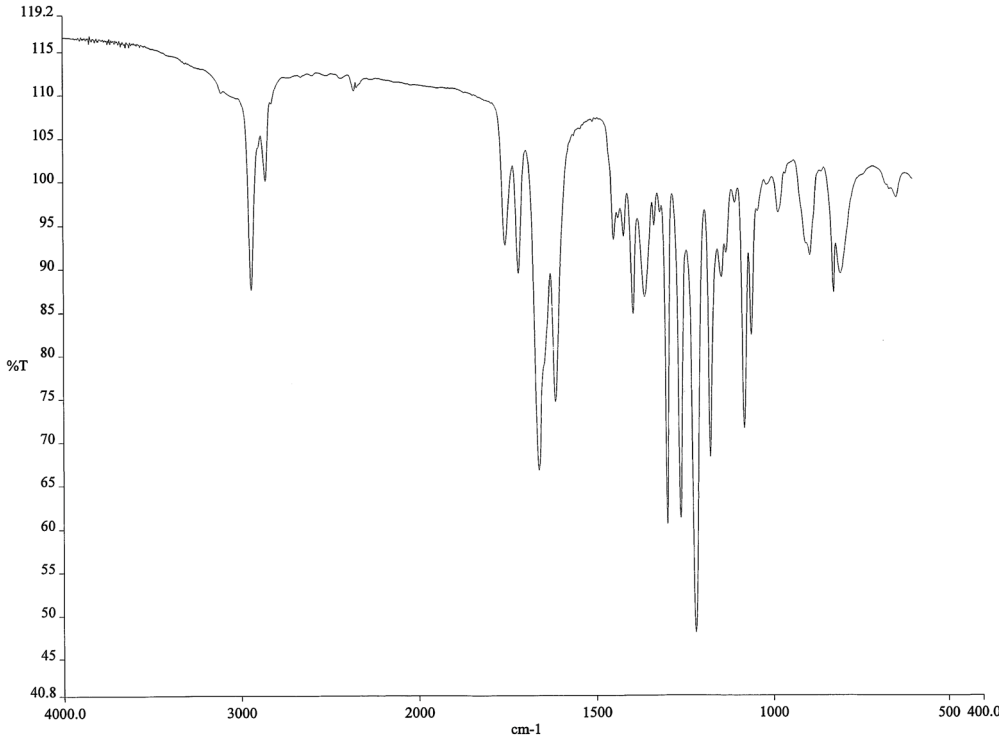


*Figure A5.8 IR of compound **761** (NaCl/film)*

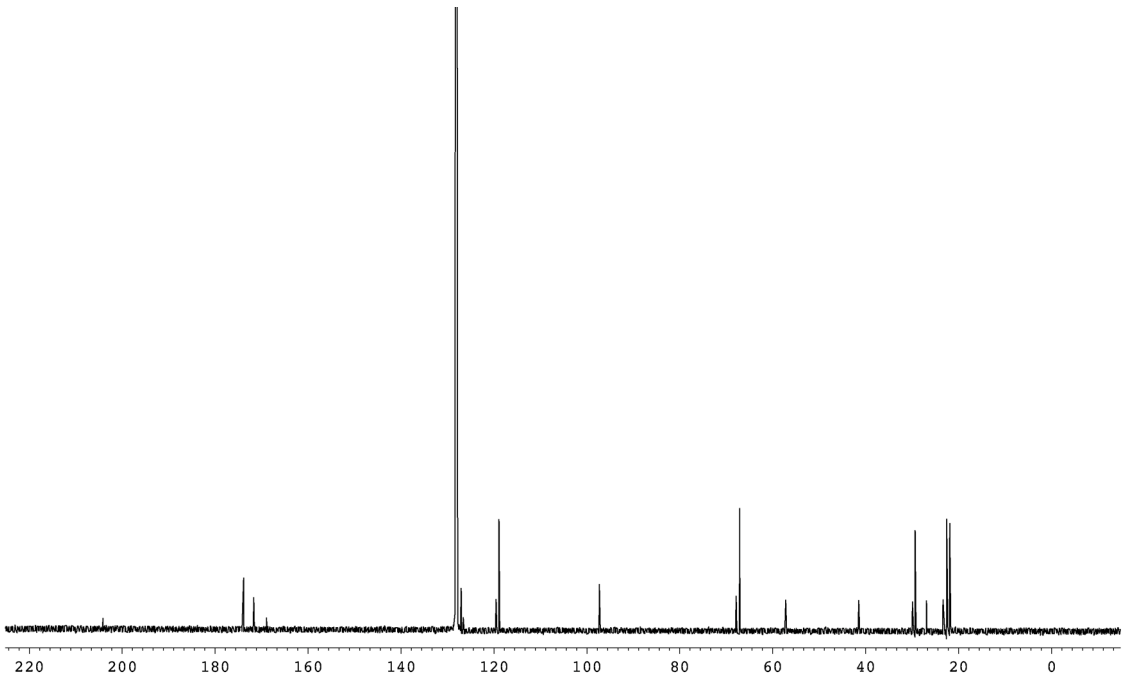


*Figure A5.9 ^{13}C NMR of compound **761** (125 MHz, C_6D_6)*

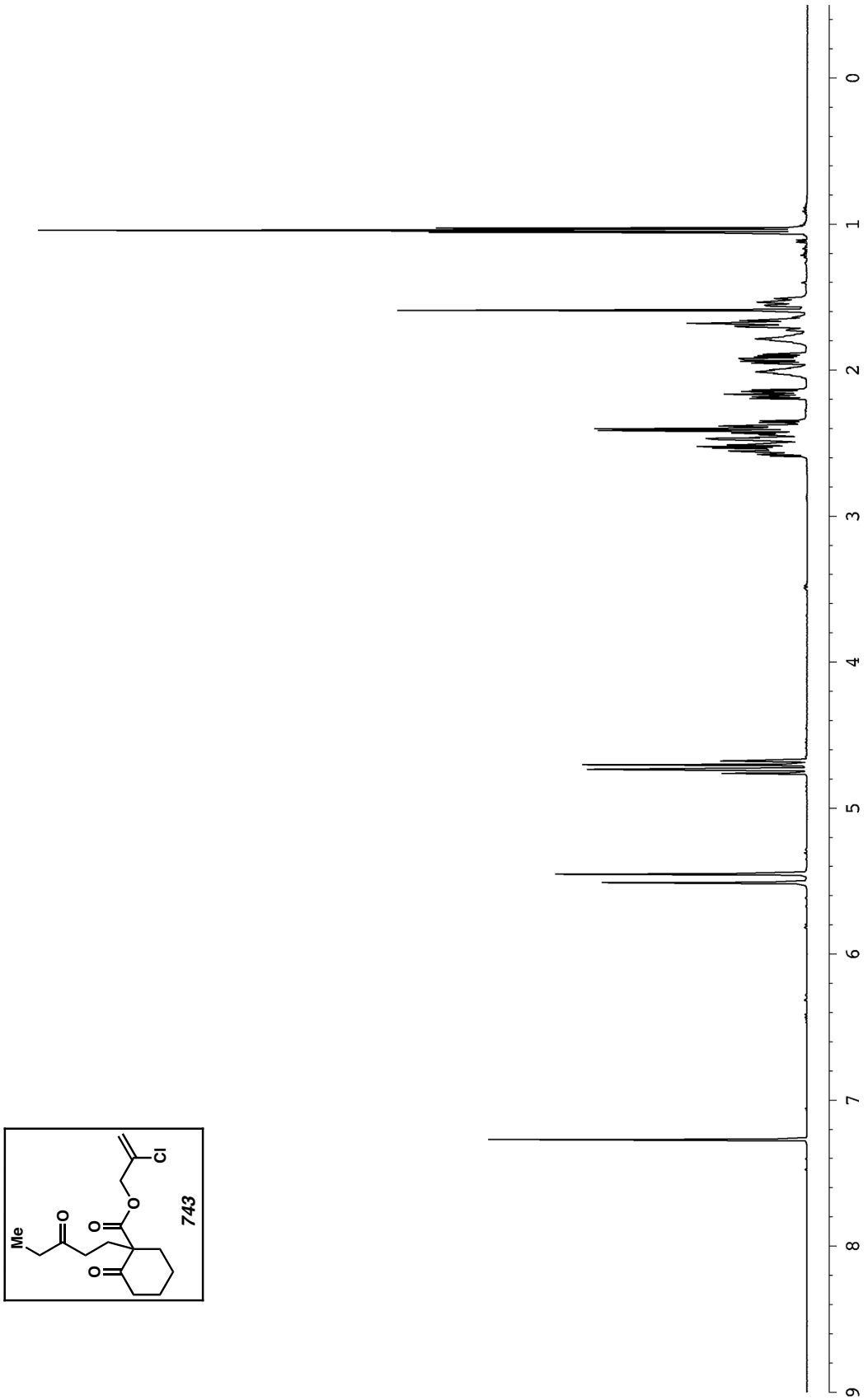


*Figure A5.10 ^{1}H NMR of compound **743** (500 MHz, $CDCl_3$)*

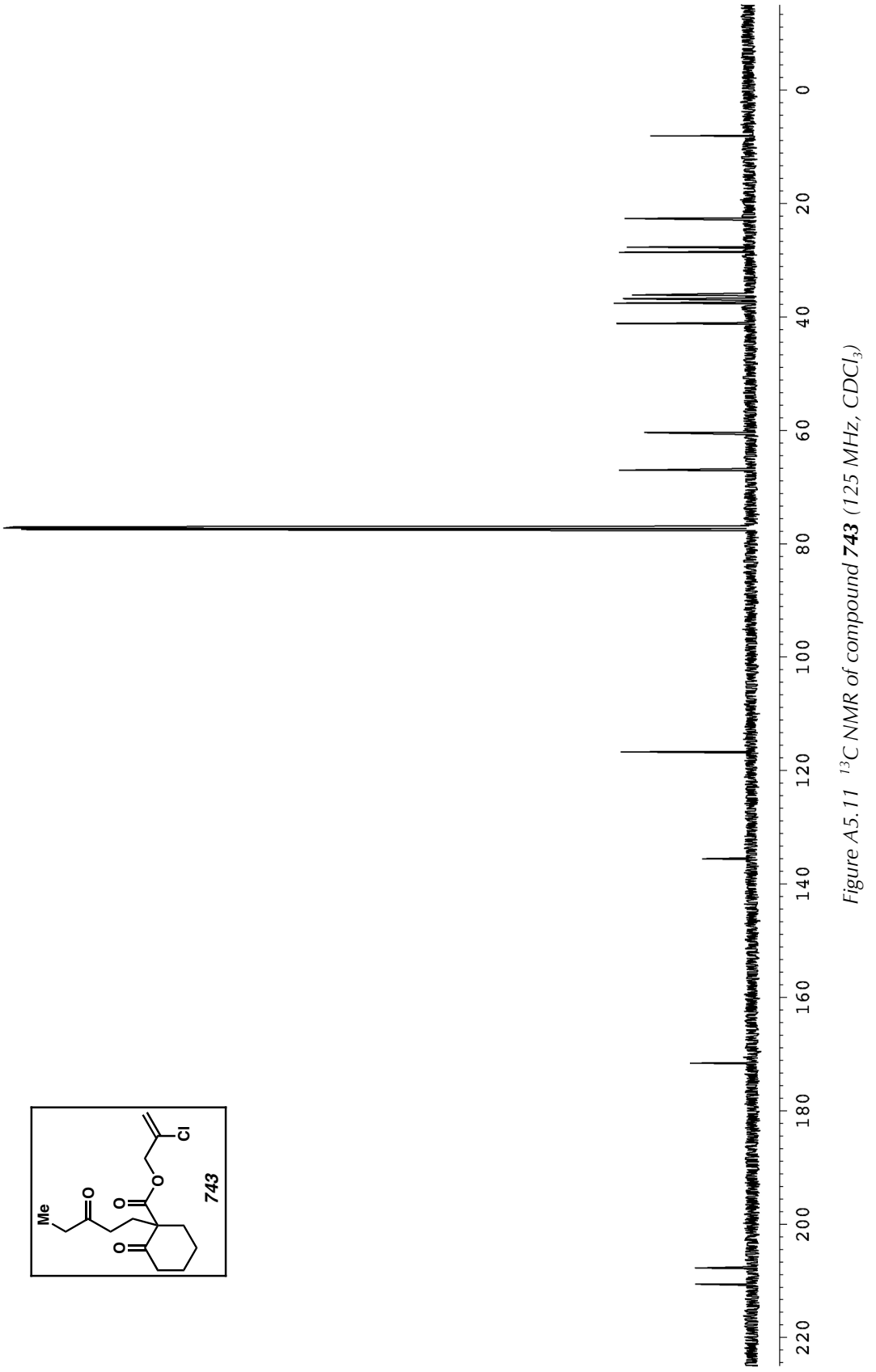


Figure A5.11 ^{13}C *NMR of compound* ***743*** *(125 MHz,* $CDCl_3$*)*

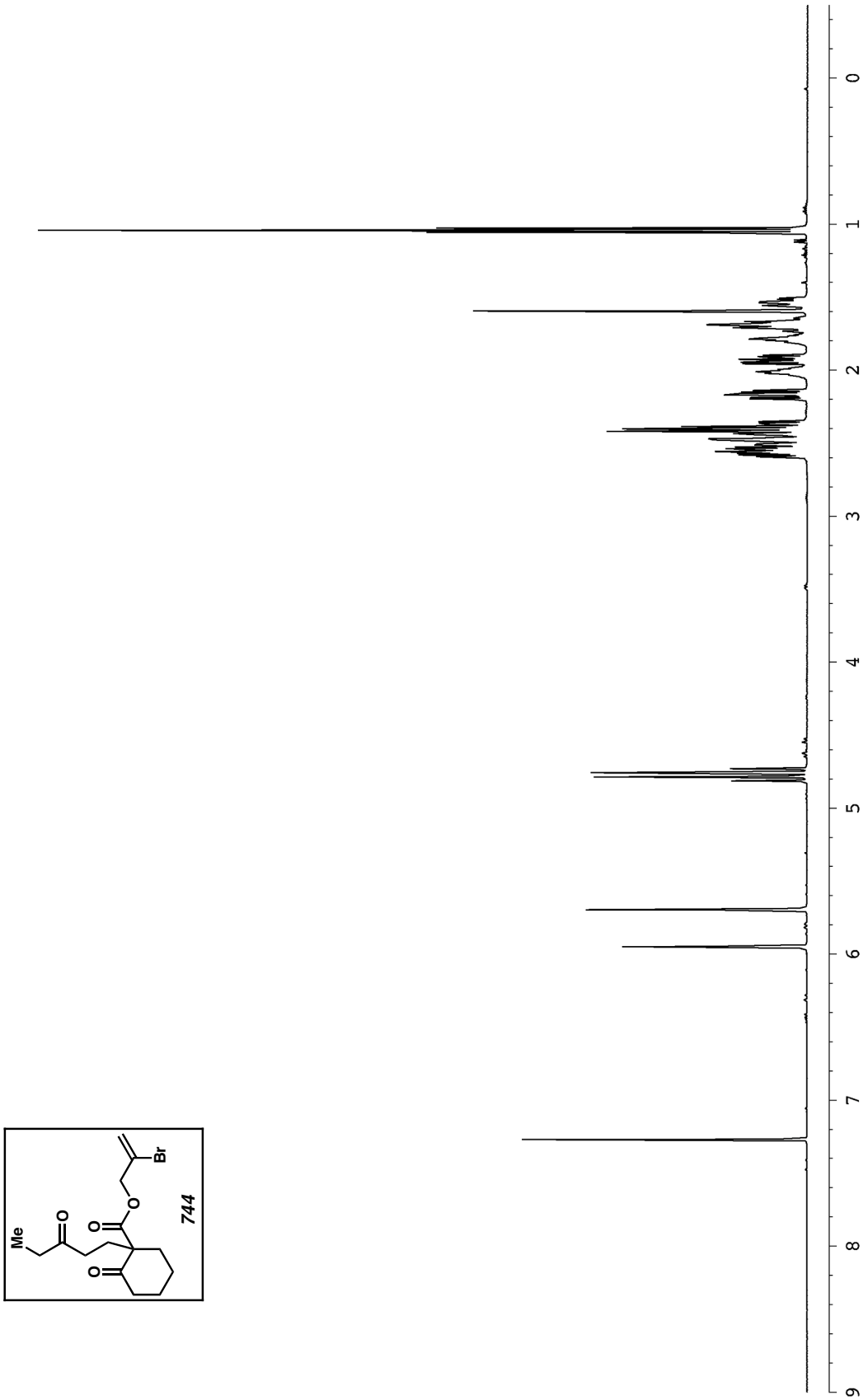


*Figure A5.12 ^1H NMR of compound **744** (500 MHz, $CDCl_3$)*

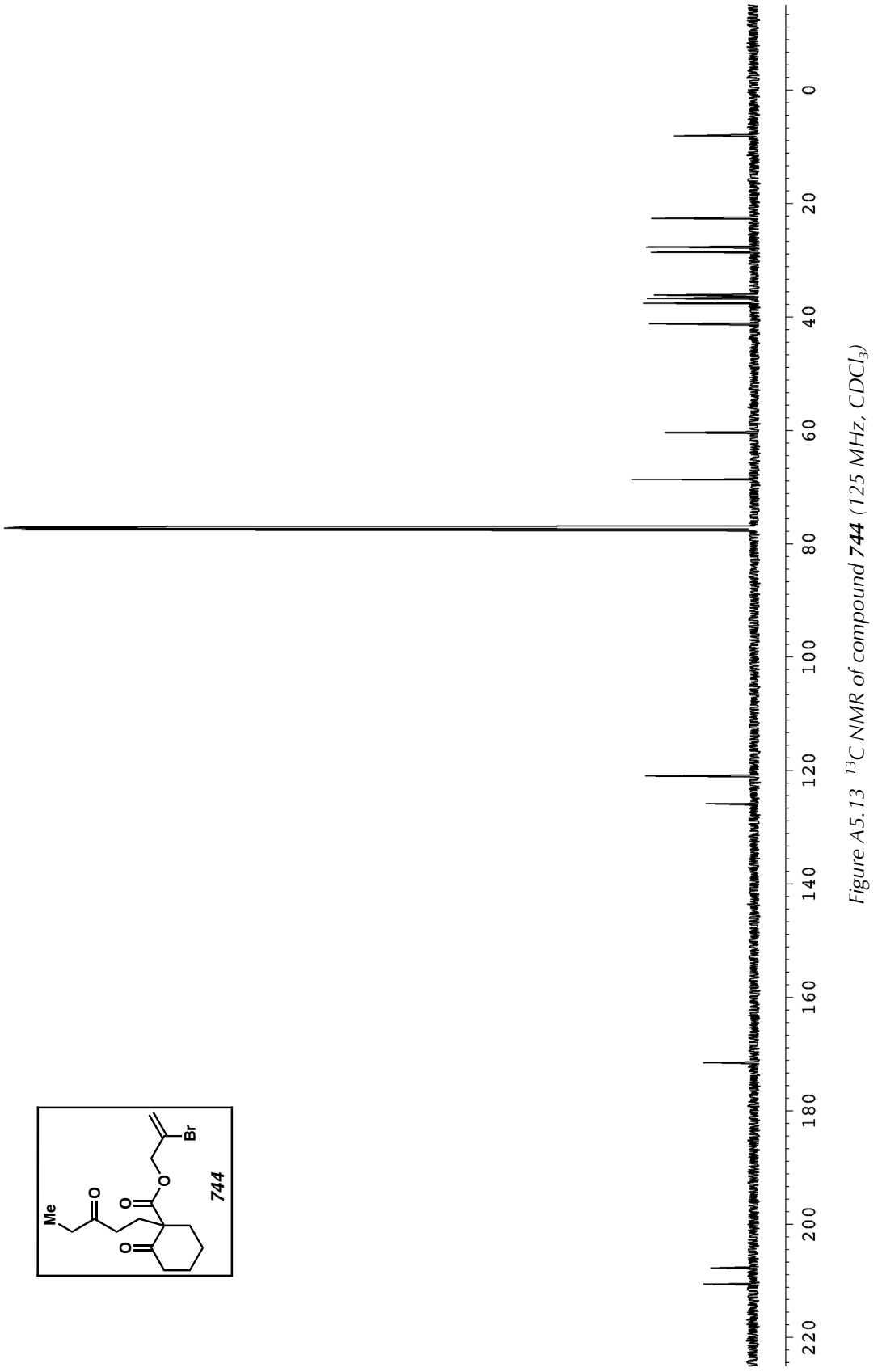


*Figure A5.13 ^{13}C NMR of compound **744** (125 MHz, $CDCl_3$)*

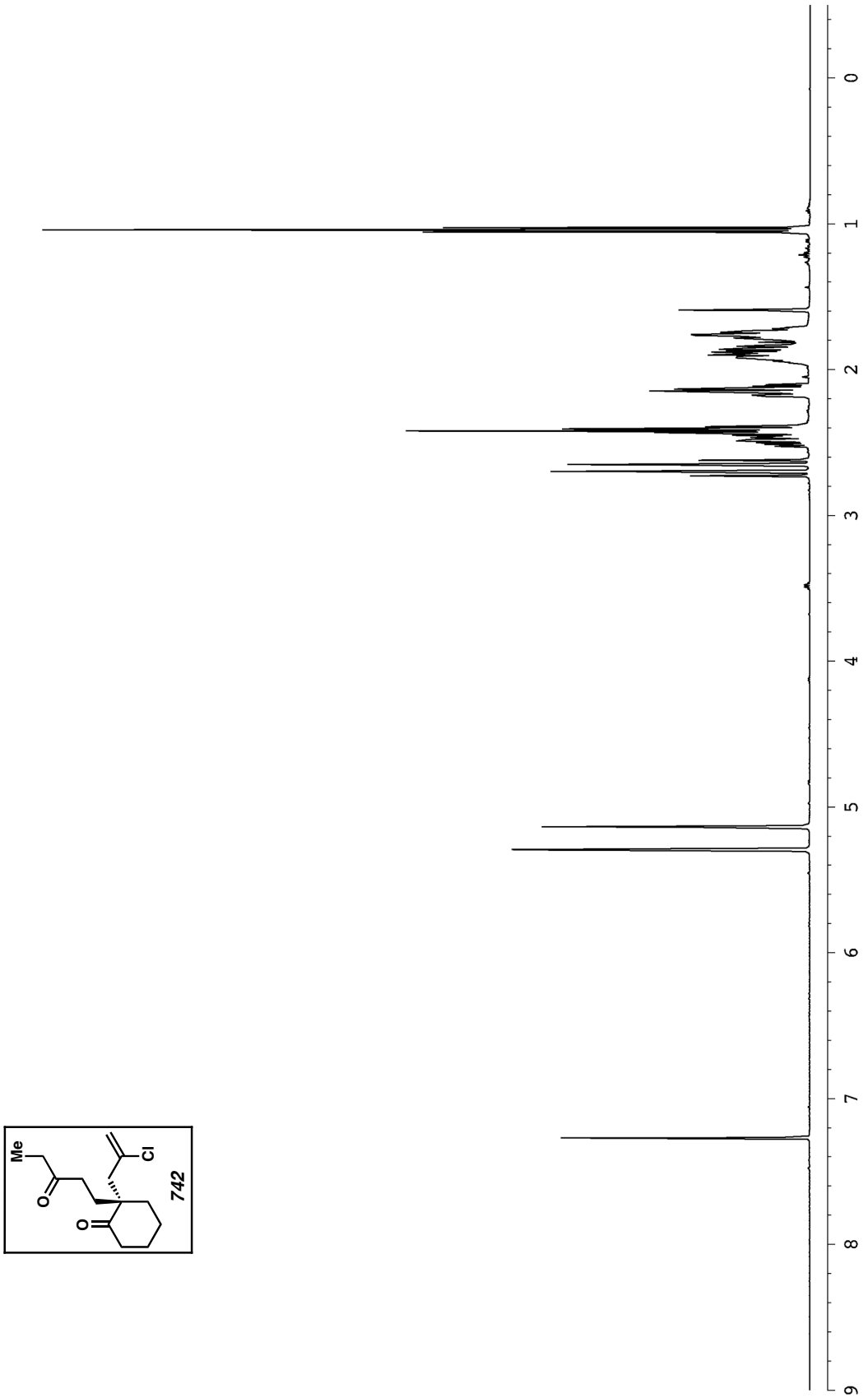


*Figure A5.14 ^{1}H NMR of compound **742** (500 MHz, $CDCl_3$)*

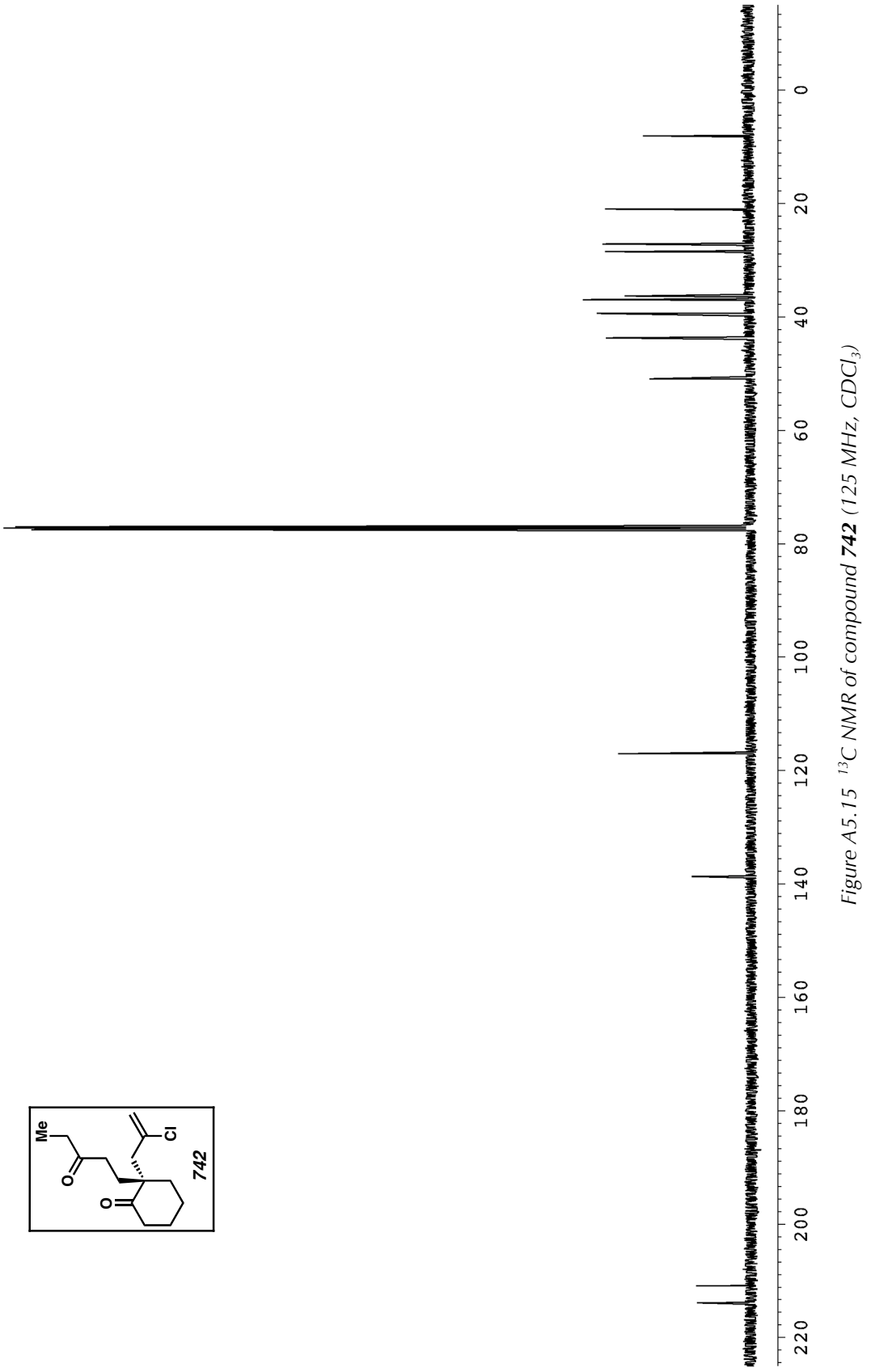


*Figure A5.15 ^{13}C NMR of compound **742** (125 MHz, $CDCl_3$)*

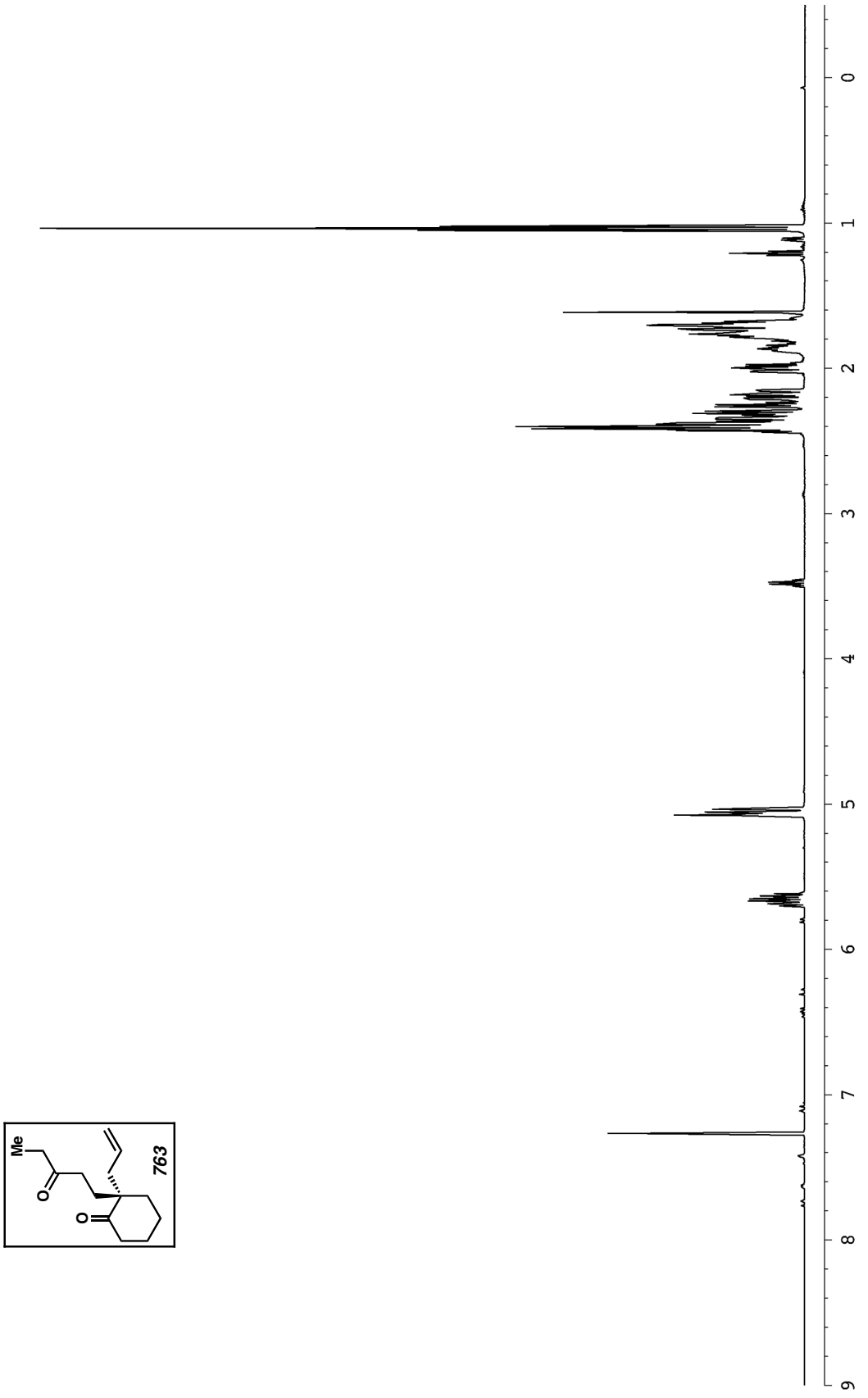


*Figure A5.16 ^1H NMR of compound **763** (500 MHz, $CDCl_3$)*

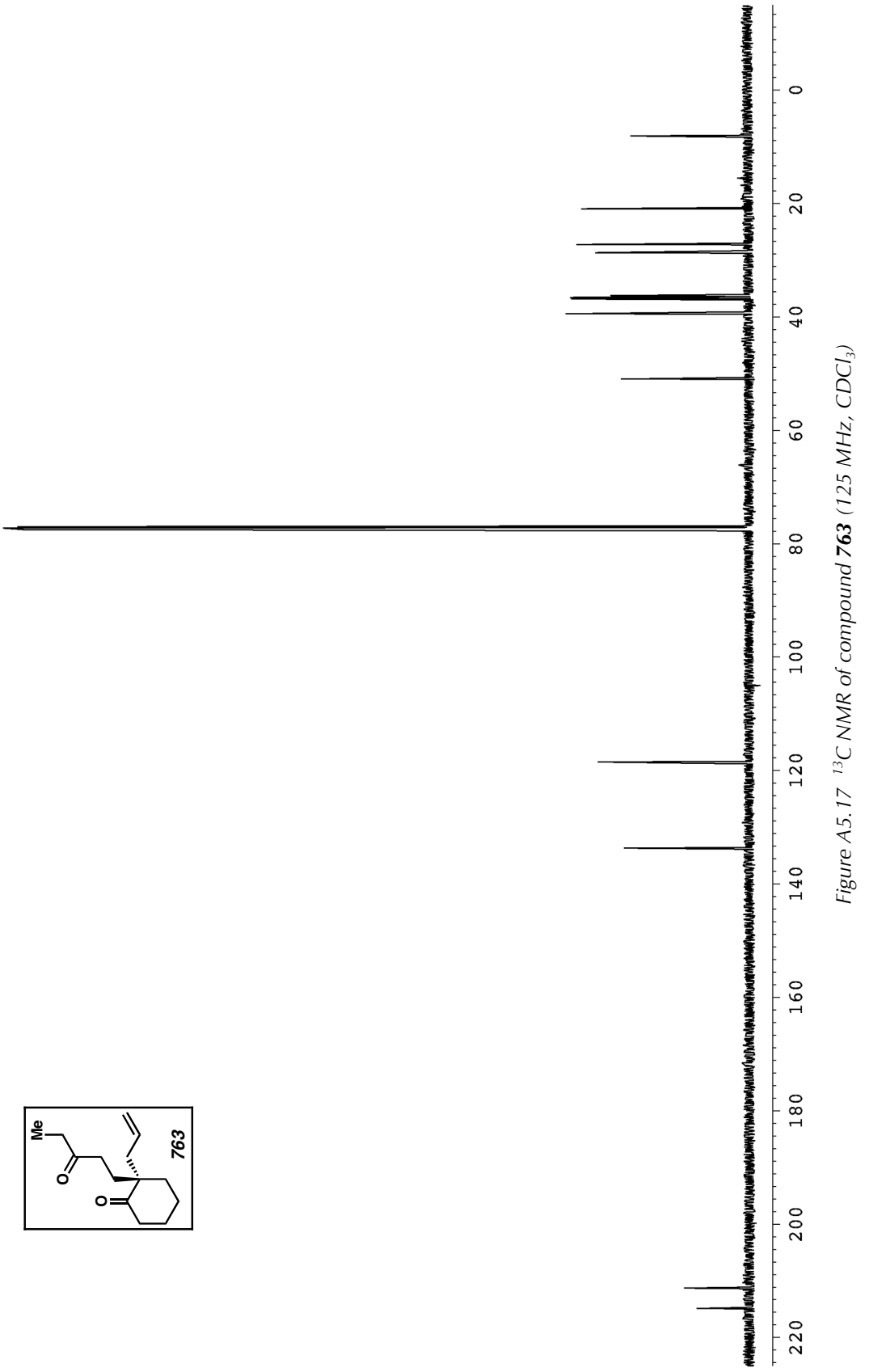


Figure A5.17 ^{13}C *NMR of compound* ***763*** *(125 MHz,* $CDCl_3$*)*

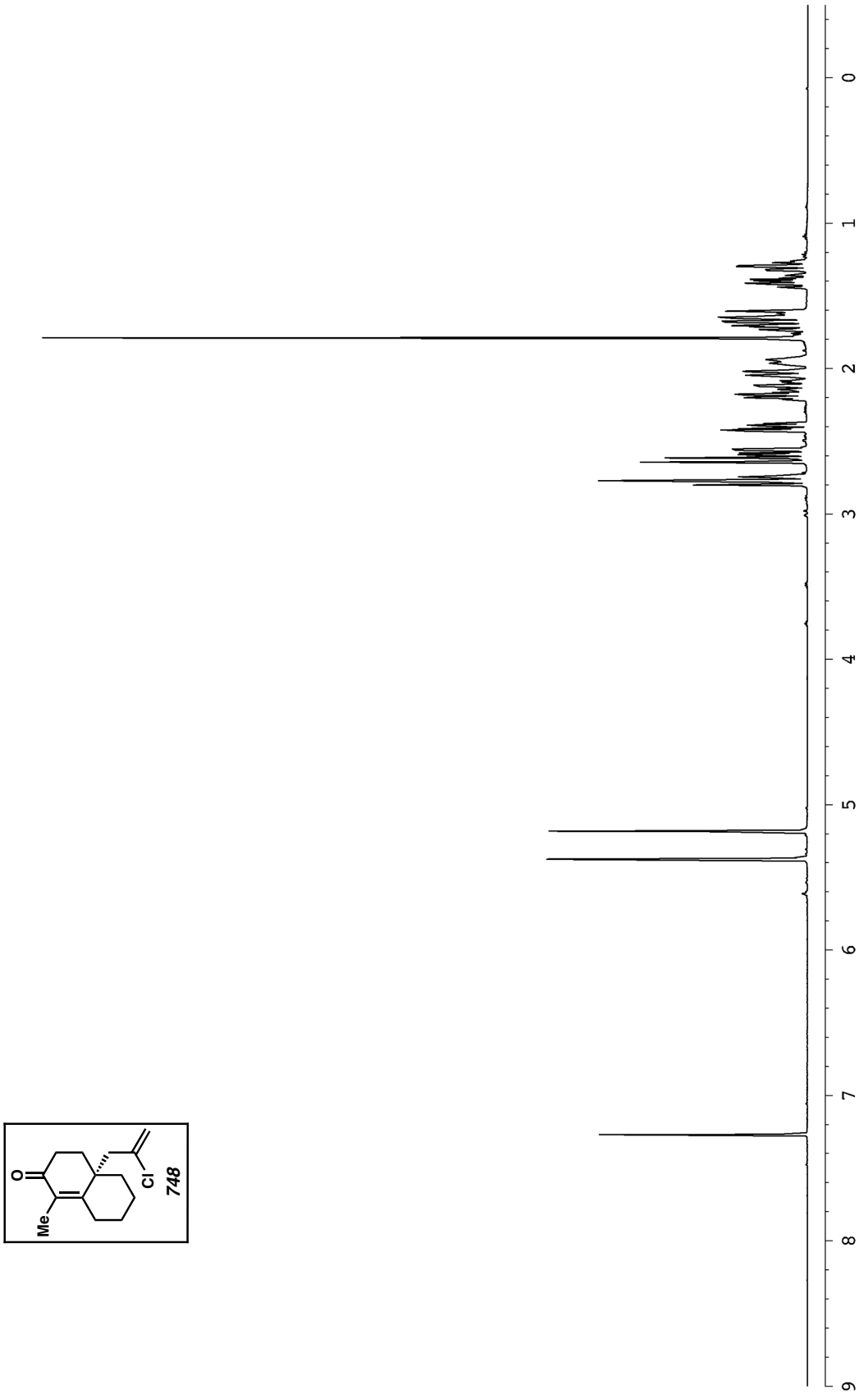


*Figure A5.18 ^1H NMR of compound **748** (500 MHz, $CDCl_3$)*

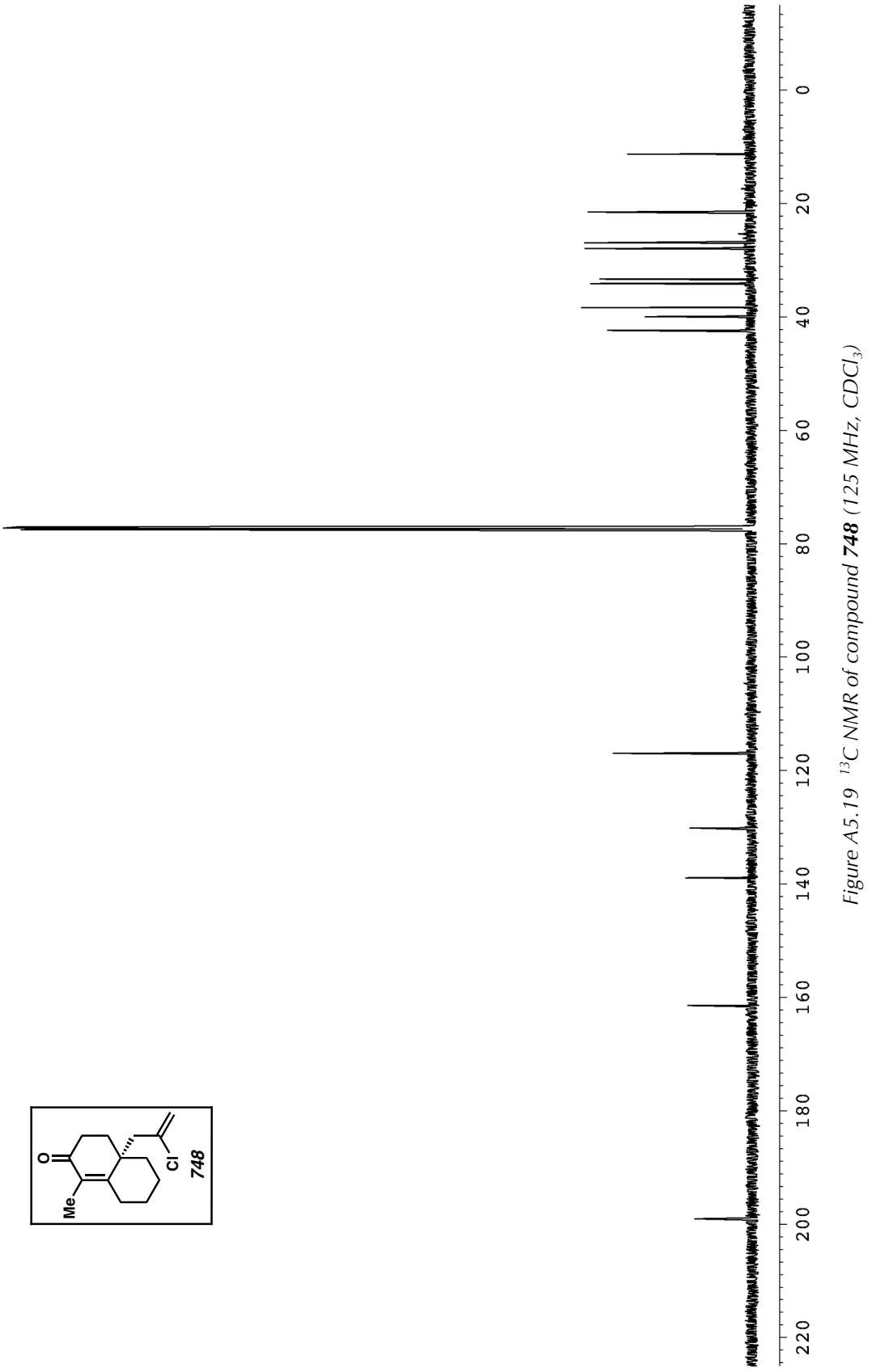


*Figure A5.19 ^{13}C NMR of compound **748** (125 MHz, $CDCl_3$)*

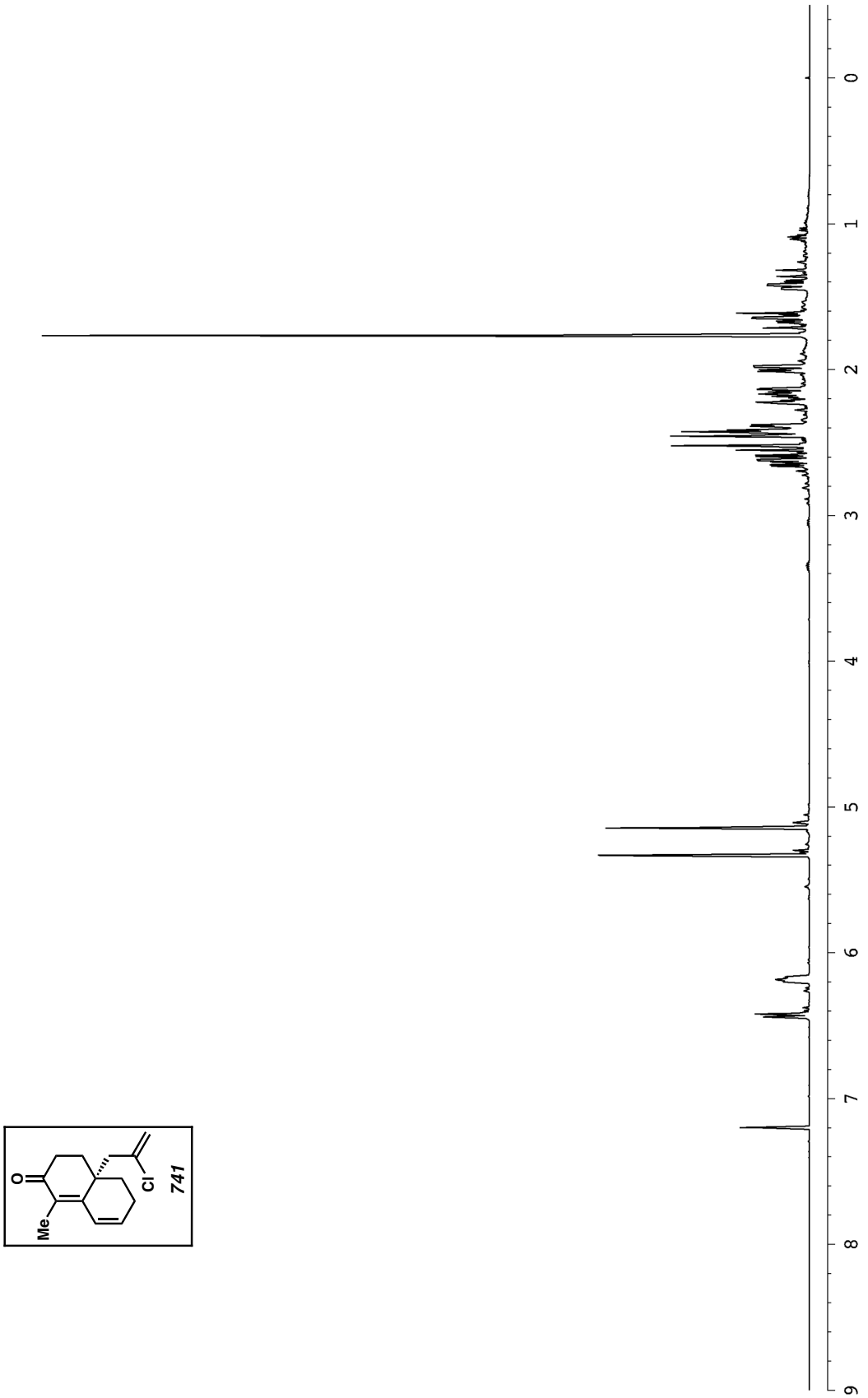


*Figure A5.20 ^1H NMR of compound **741** (500 MHz, $CDCl_3$)*

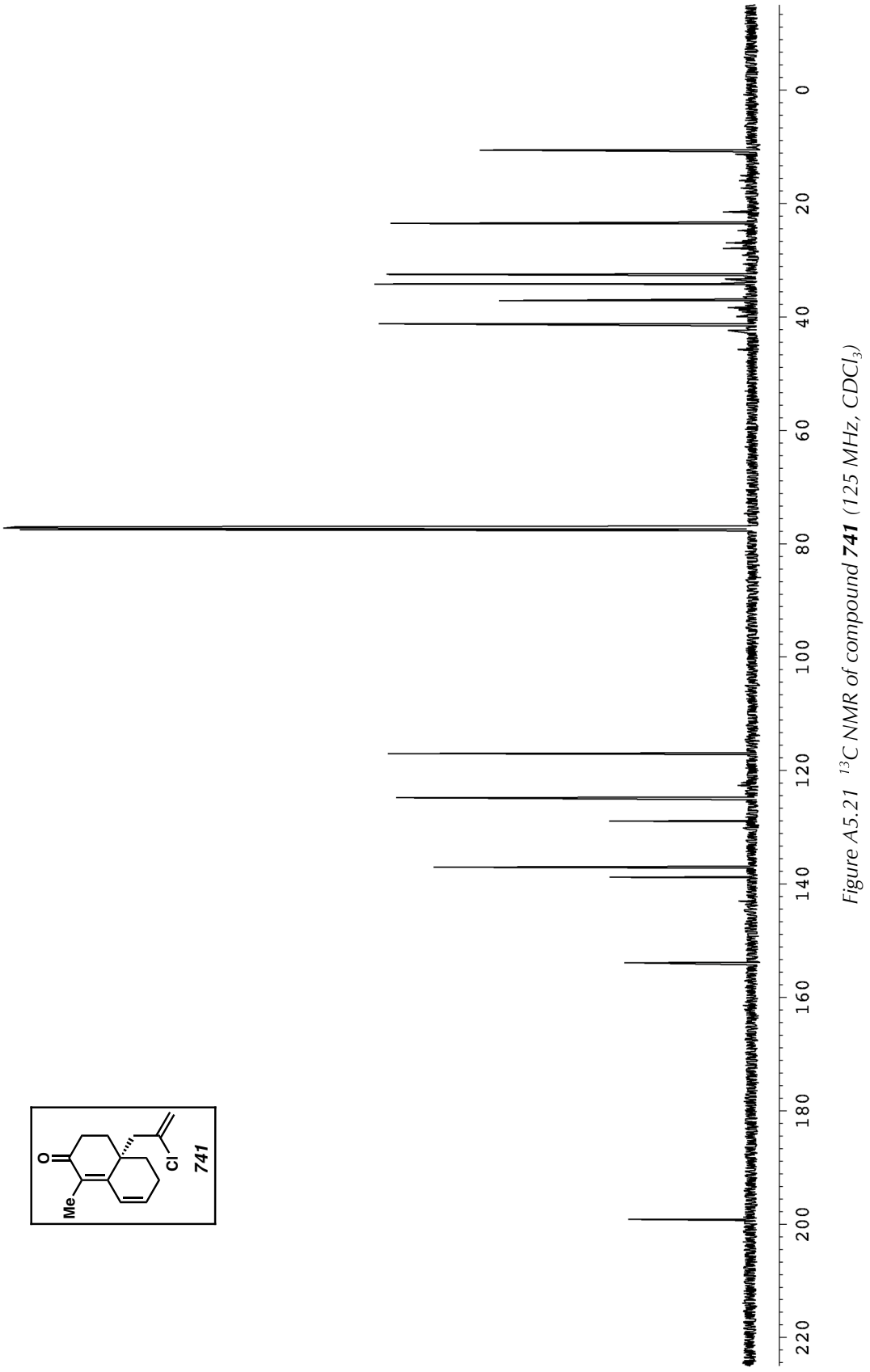


*Figure A5.21 ^{13}C NMR of compound **741** (125 MHz, $CDCl_3$)*

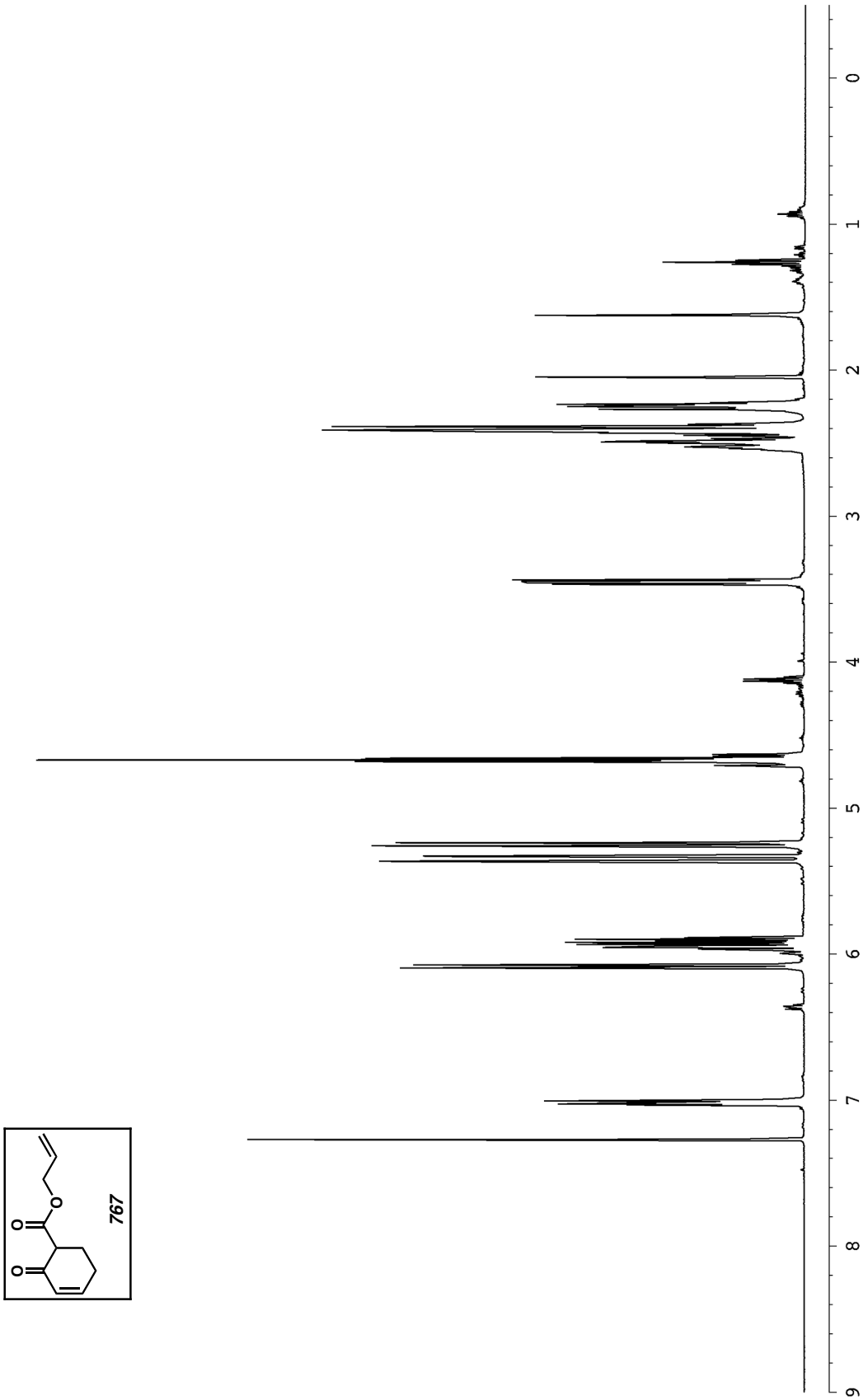


*Figure A5.22 ^1H NMR of compound **767** (500 MHz, $CDCl_3$)*

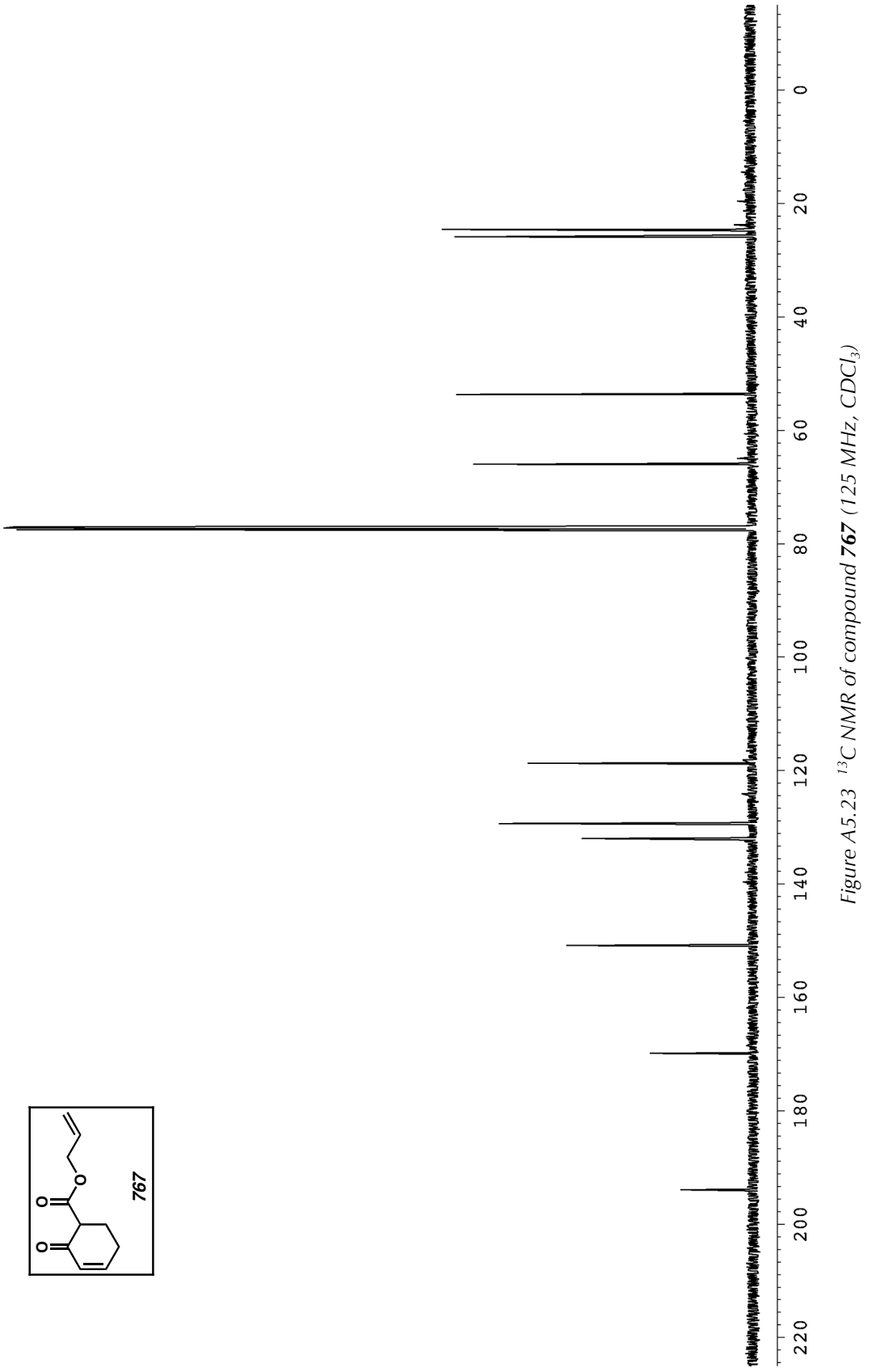


*Figure A5.23 ^{13}C NMR of compound **767** (125 MHz, $CDCl_3$)*

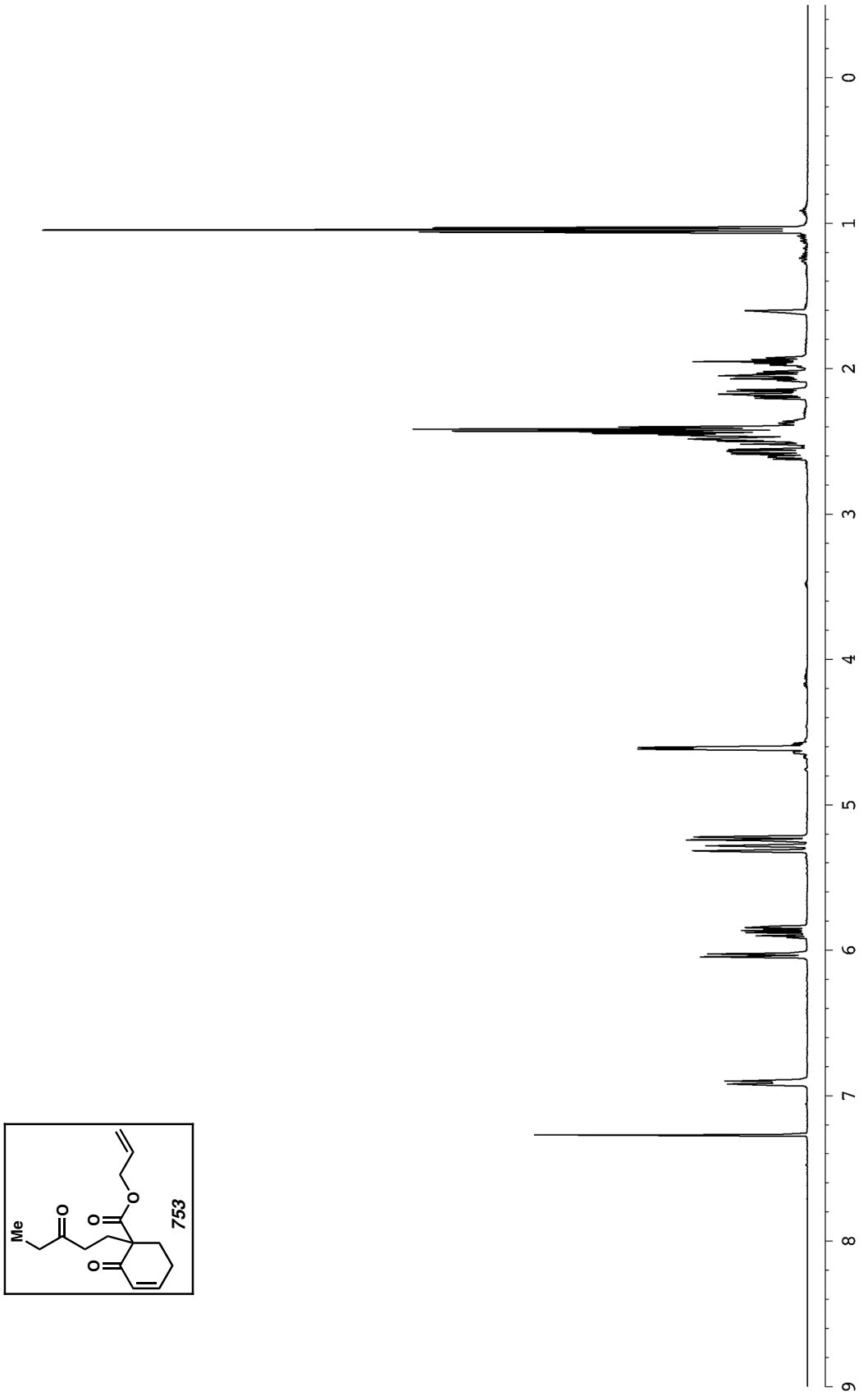


*Figure A5.24 ^{1}H NMR of compound **753** (500 MHz, $CDCl_3$)*

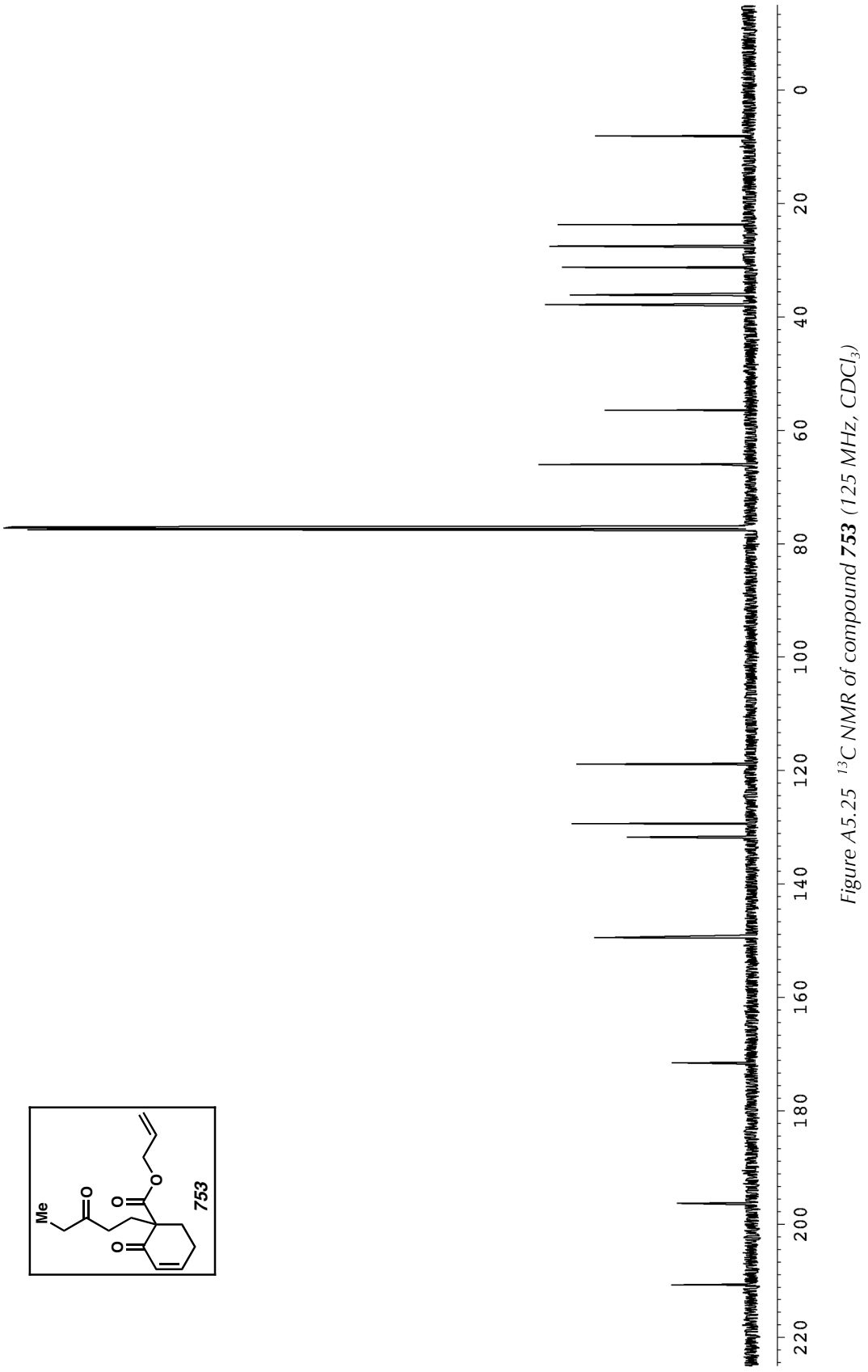


*Figure A5.25 ^{13}C NMR of compound **753** (125 MHz, $CDCl_3$)*

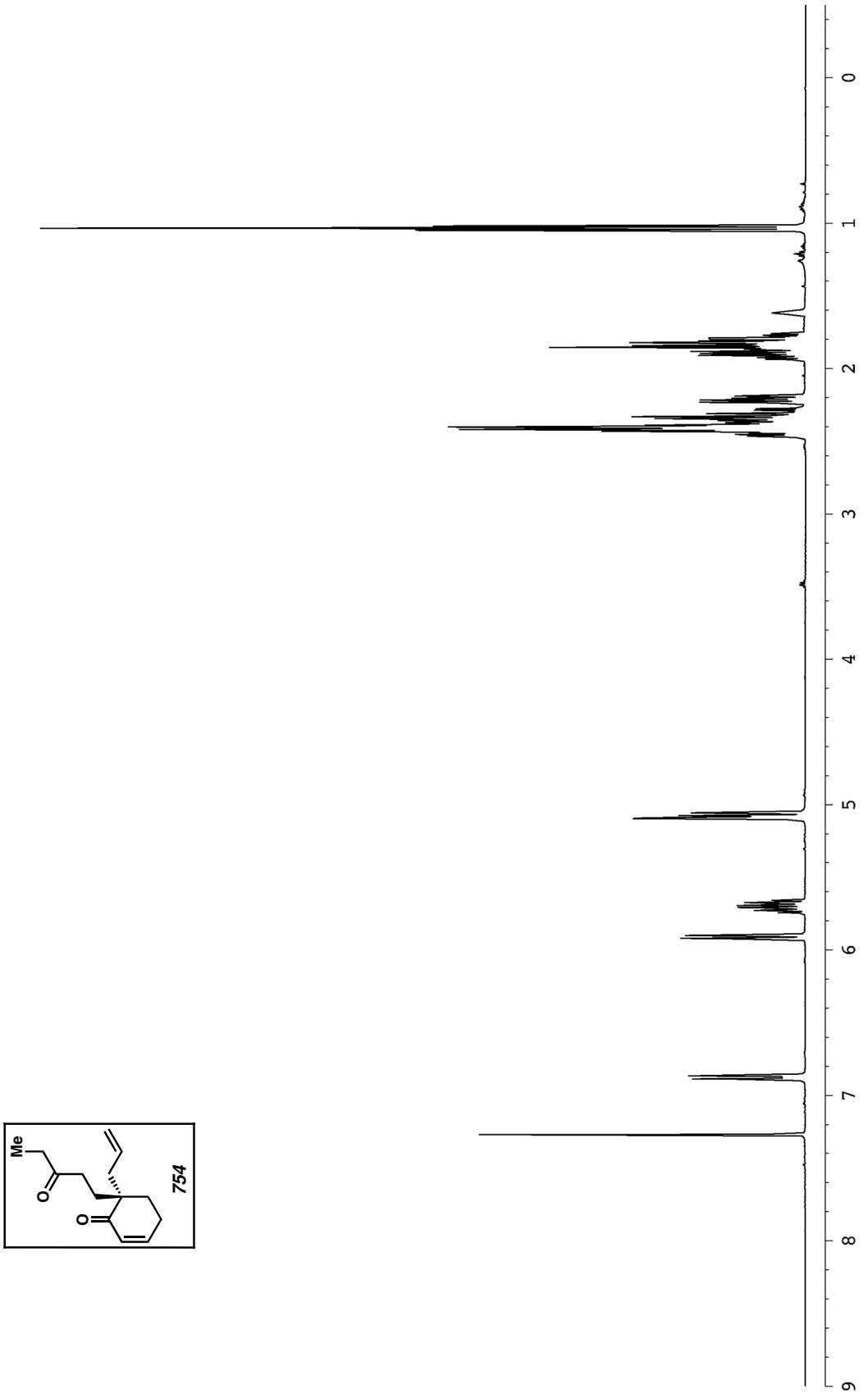


*Figure A5.26 ^1H NMR of compound **754** (500 MHz, $CDCl_3$)*

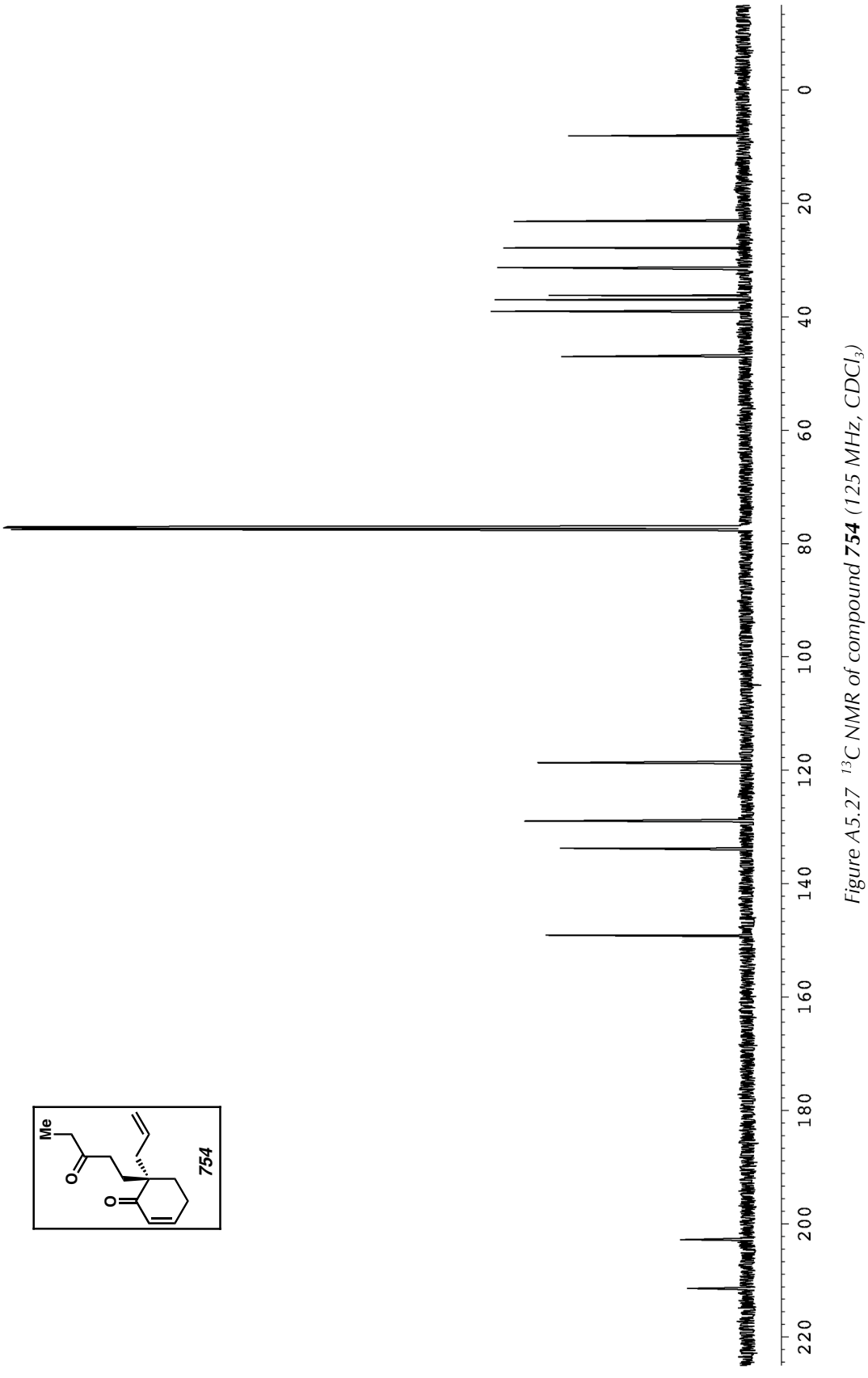


*Figure A5.27 ^{13}C NMR of compound **754** (125 MHz, $CDCl_3$)*

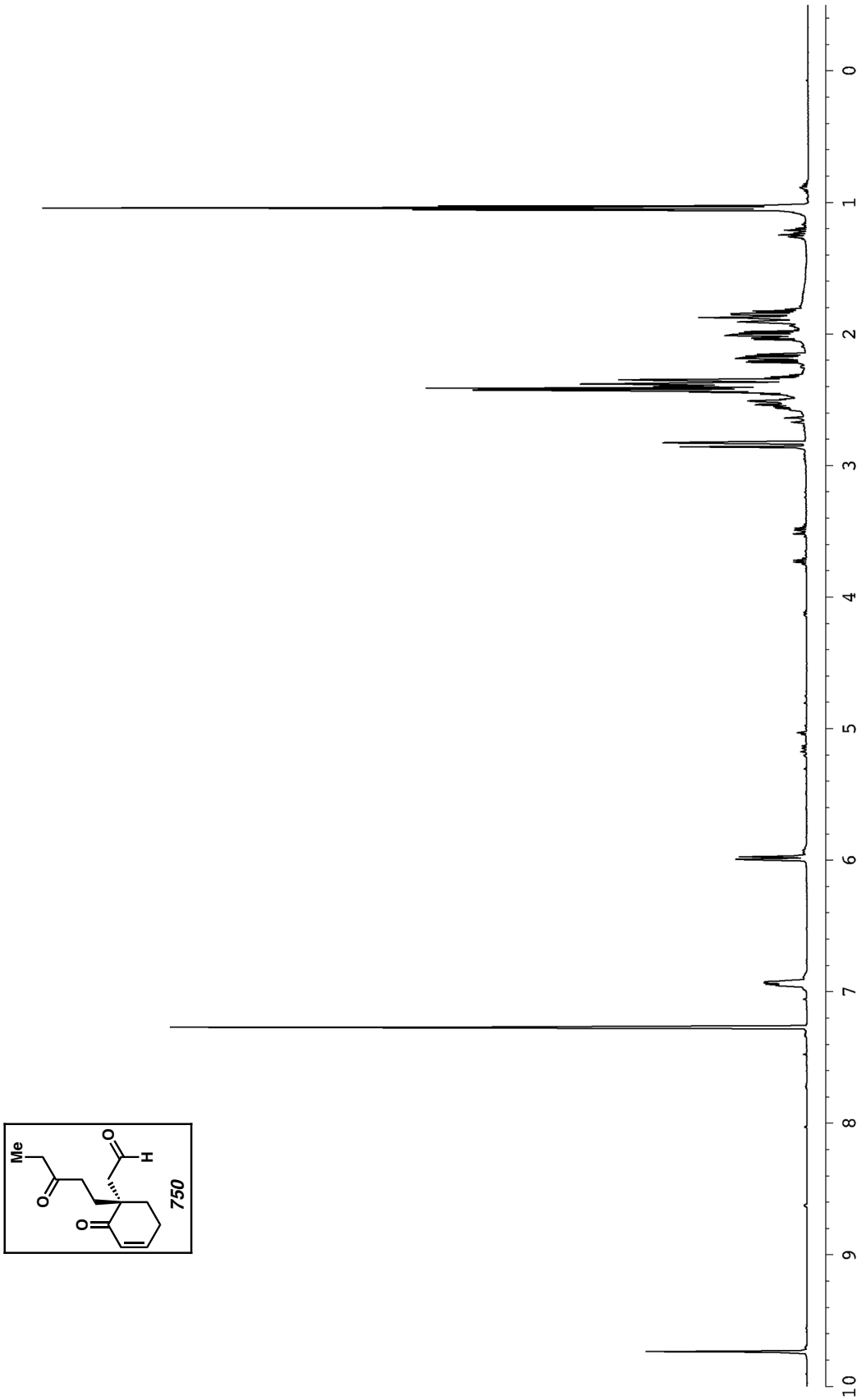


*Figure A5.28 ^{1}H NMR of compound **750** (500 MHz, $CDCl_3$)*

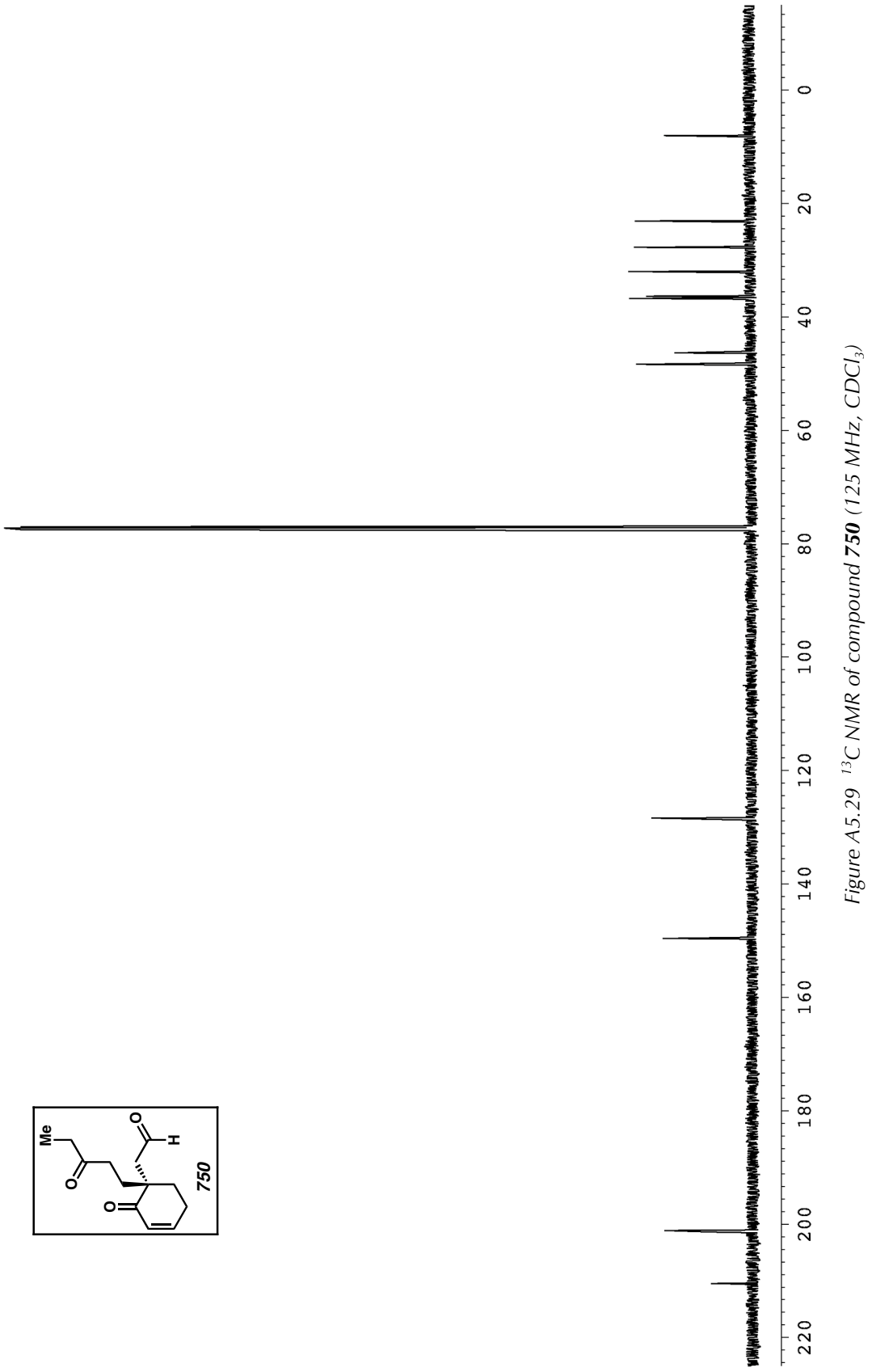


*Figure A5.29 ^{13}C NMR of compound **750** (125 MHz, $CDCl_3$)*

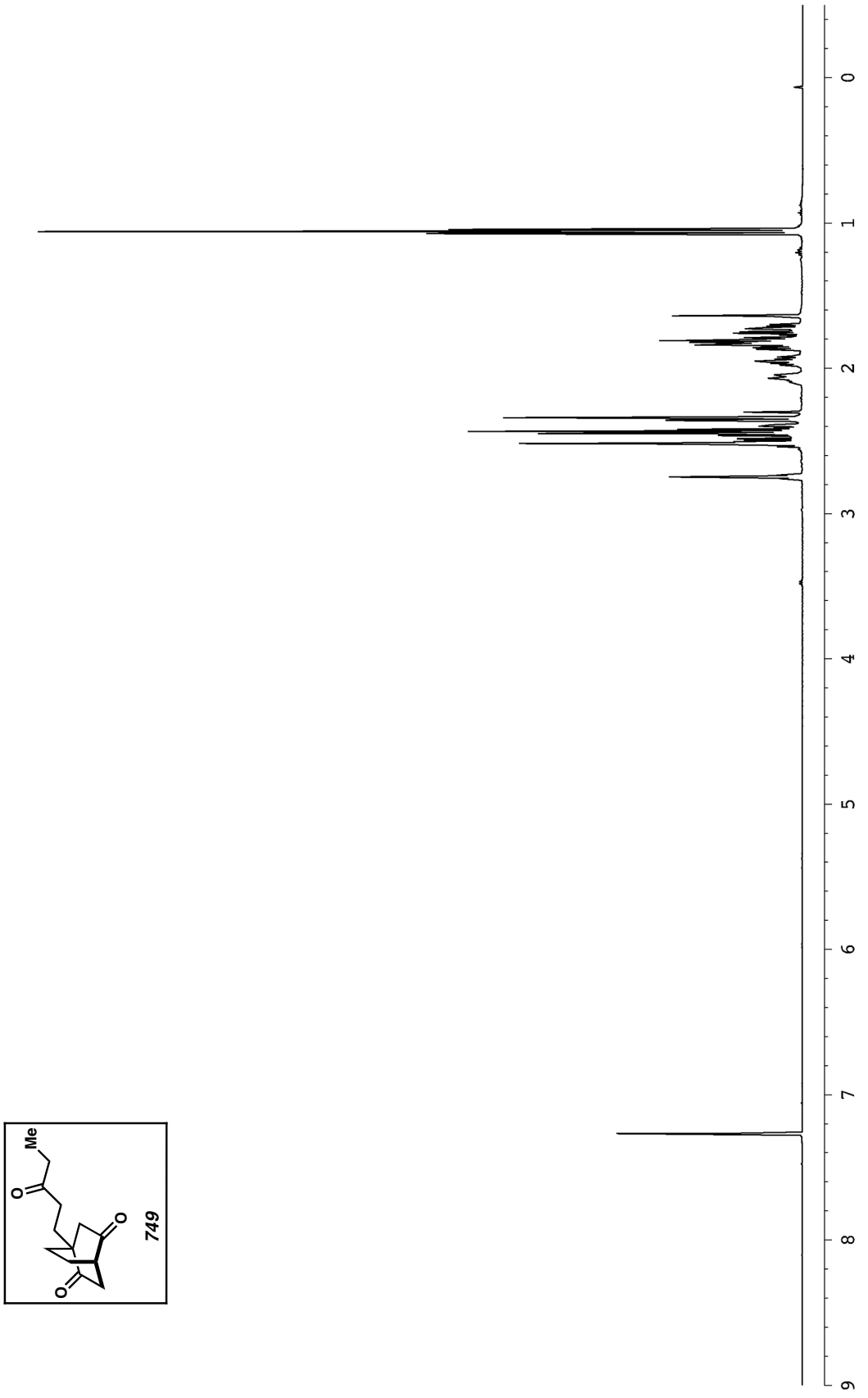


*Figure A5.30 ^1H NMR of compound **749** (500 MHz, $CDCl_3$)*

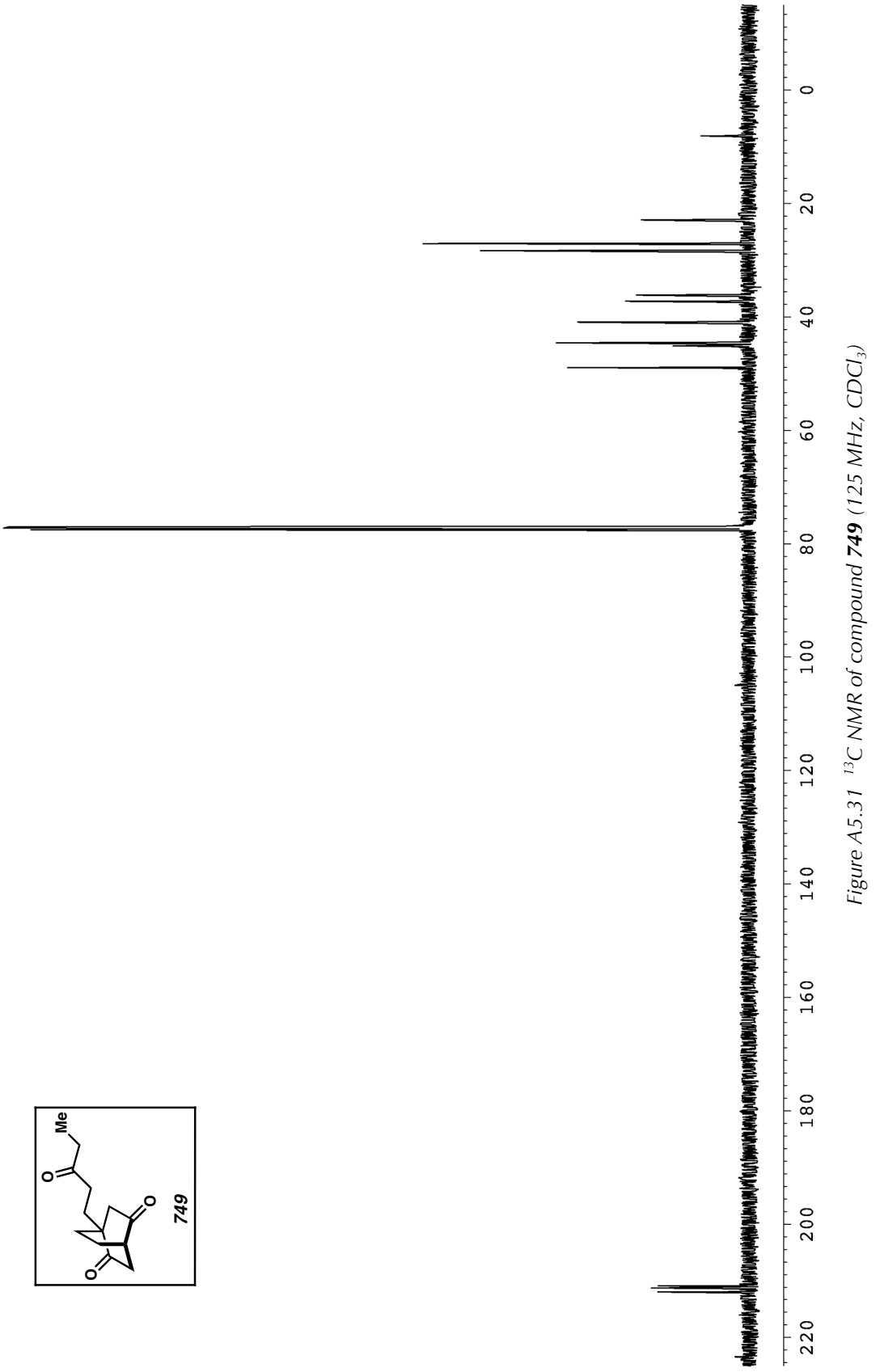


Figure A5.31 ^{13}C *NMR of compound* ***749*** *(125 MHz,* $CDCl_3$*)*

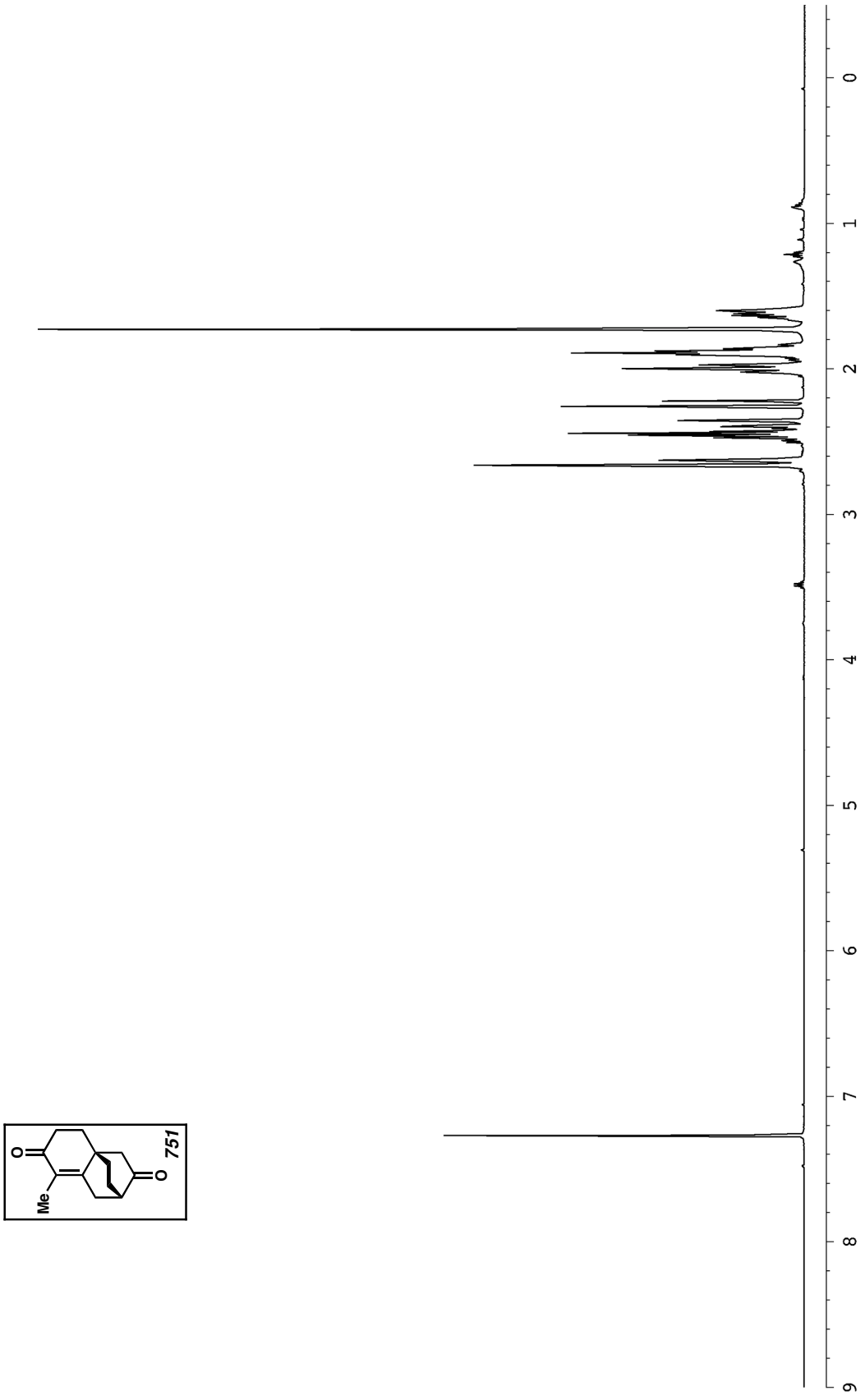


*Figure A5.32 ^1H NMR of compound **751** (500 MHz, $CDCl_3$)*

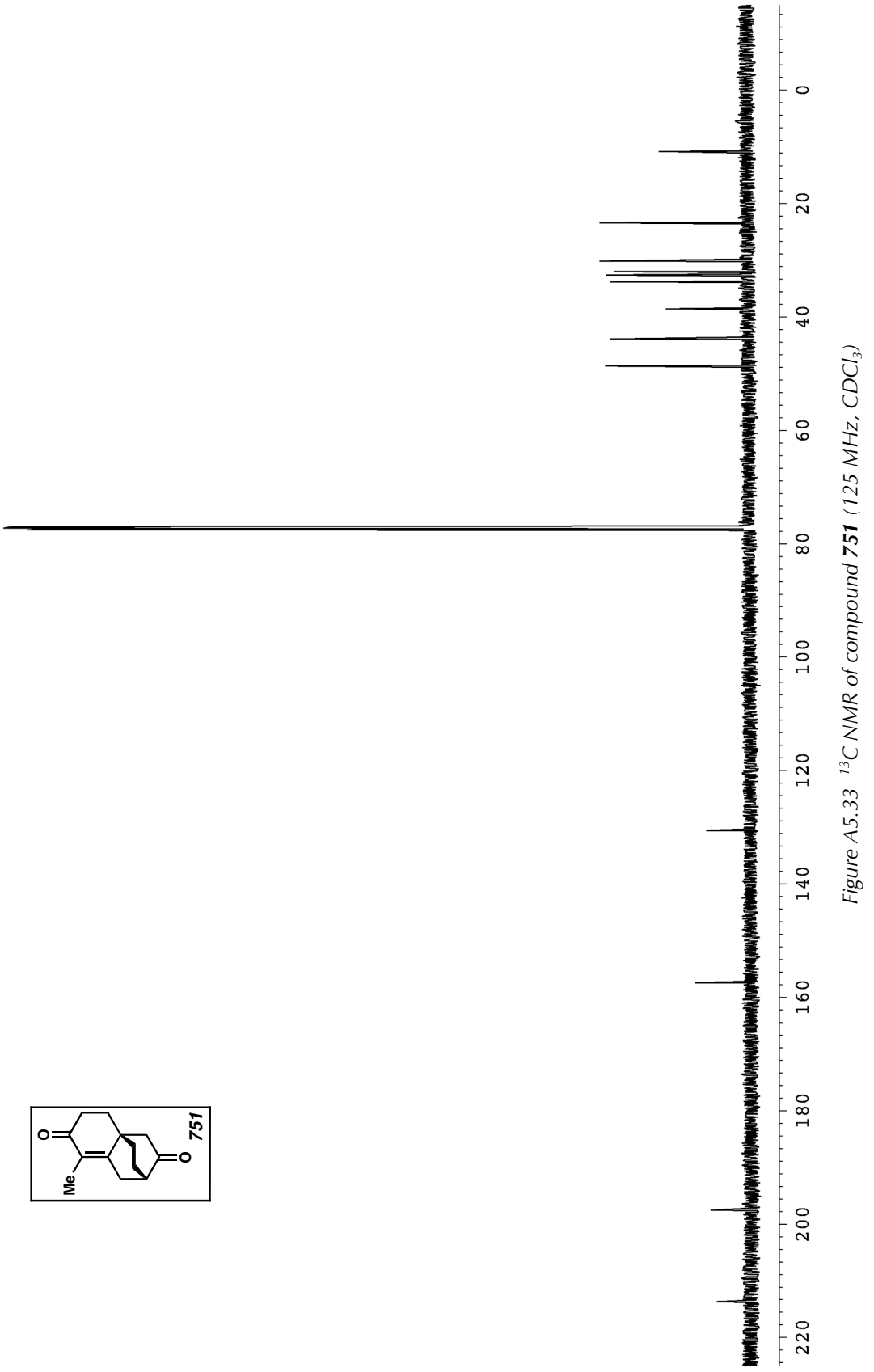


*Figure A5.33 ^{13}C NMR of compound **751** (125 MHz, $CDCl_3$)*

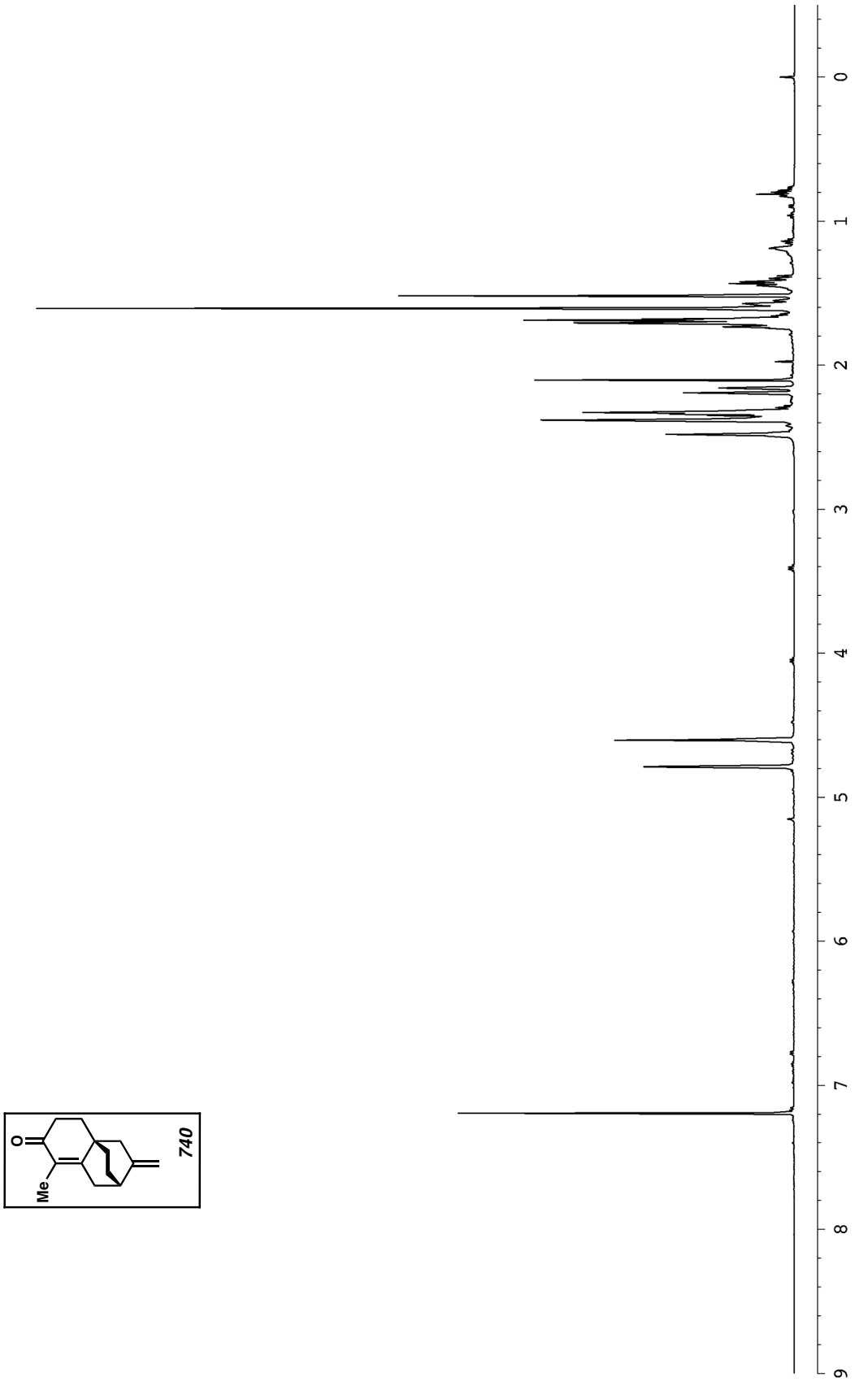


*Figure A5.34 ^1H NMR of compound **740** (500 MHz, $CDCl_3$)*

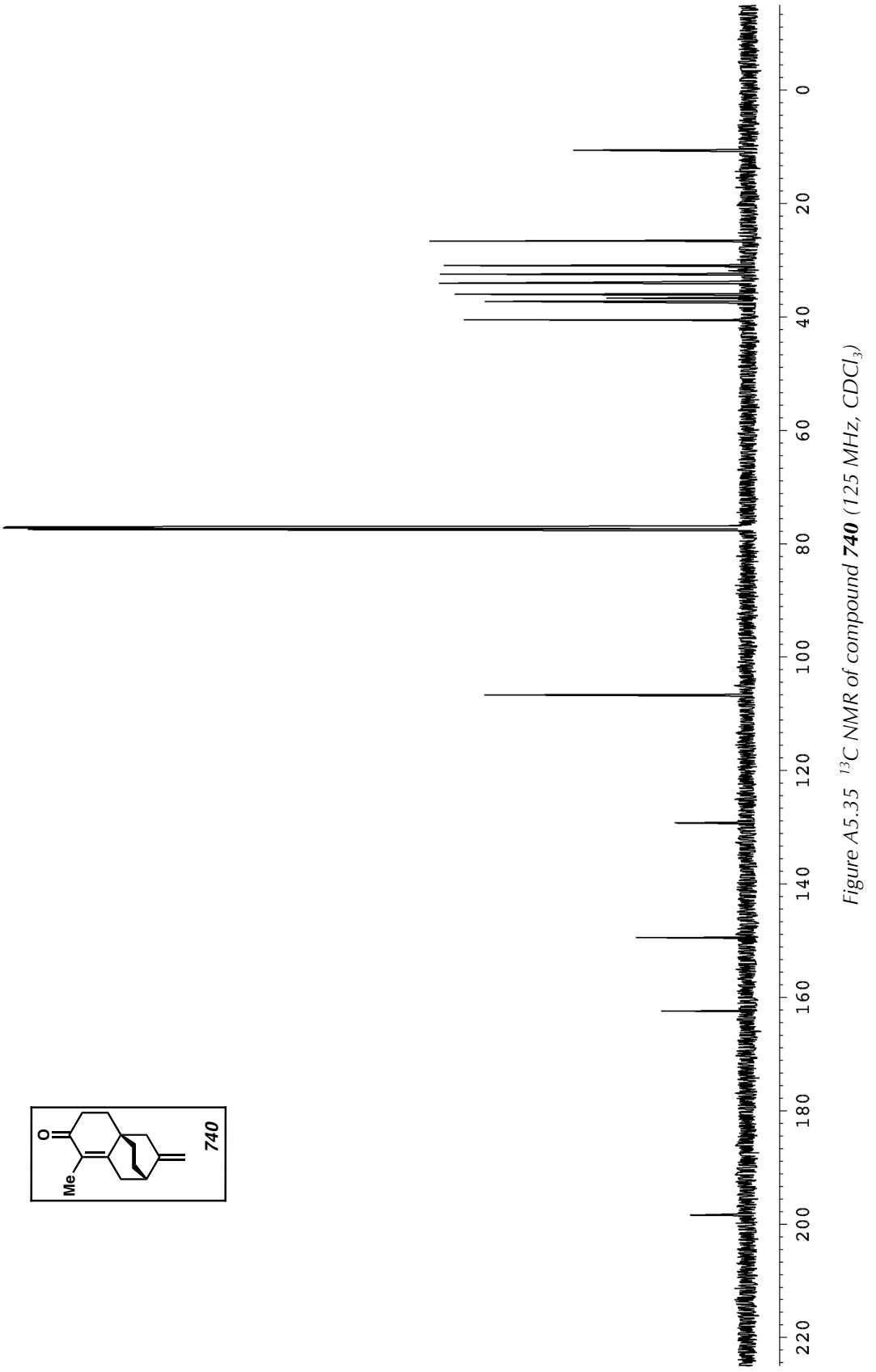


*Figure A5.35 ^{13}C NMR of compound **740** (125 MHz, $CDCl_3$)*

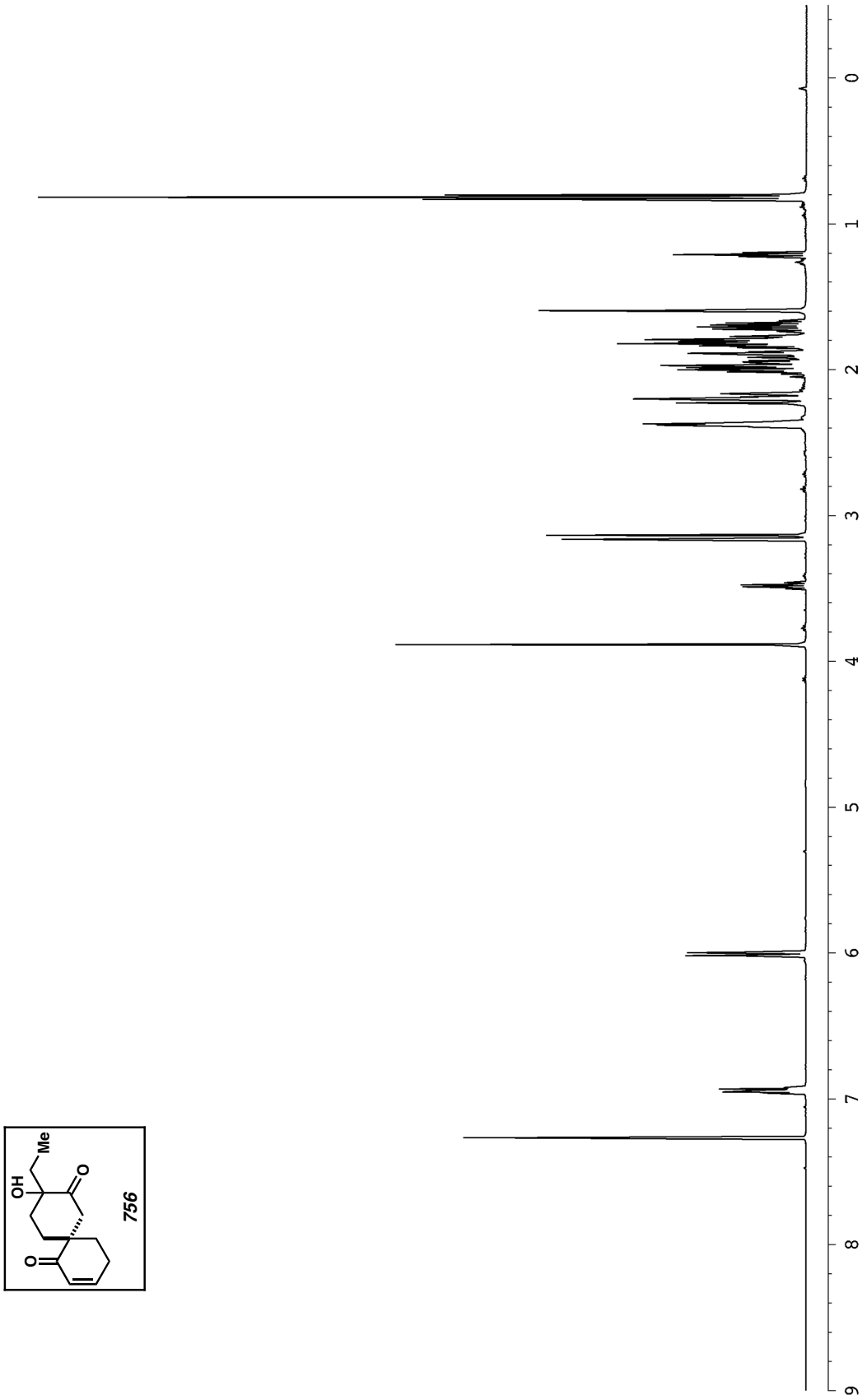


*Figure A5.36 ^1H NMR of compound **756** (500 MHz, $CDCl_3$)*

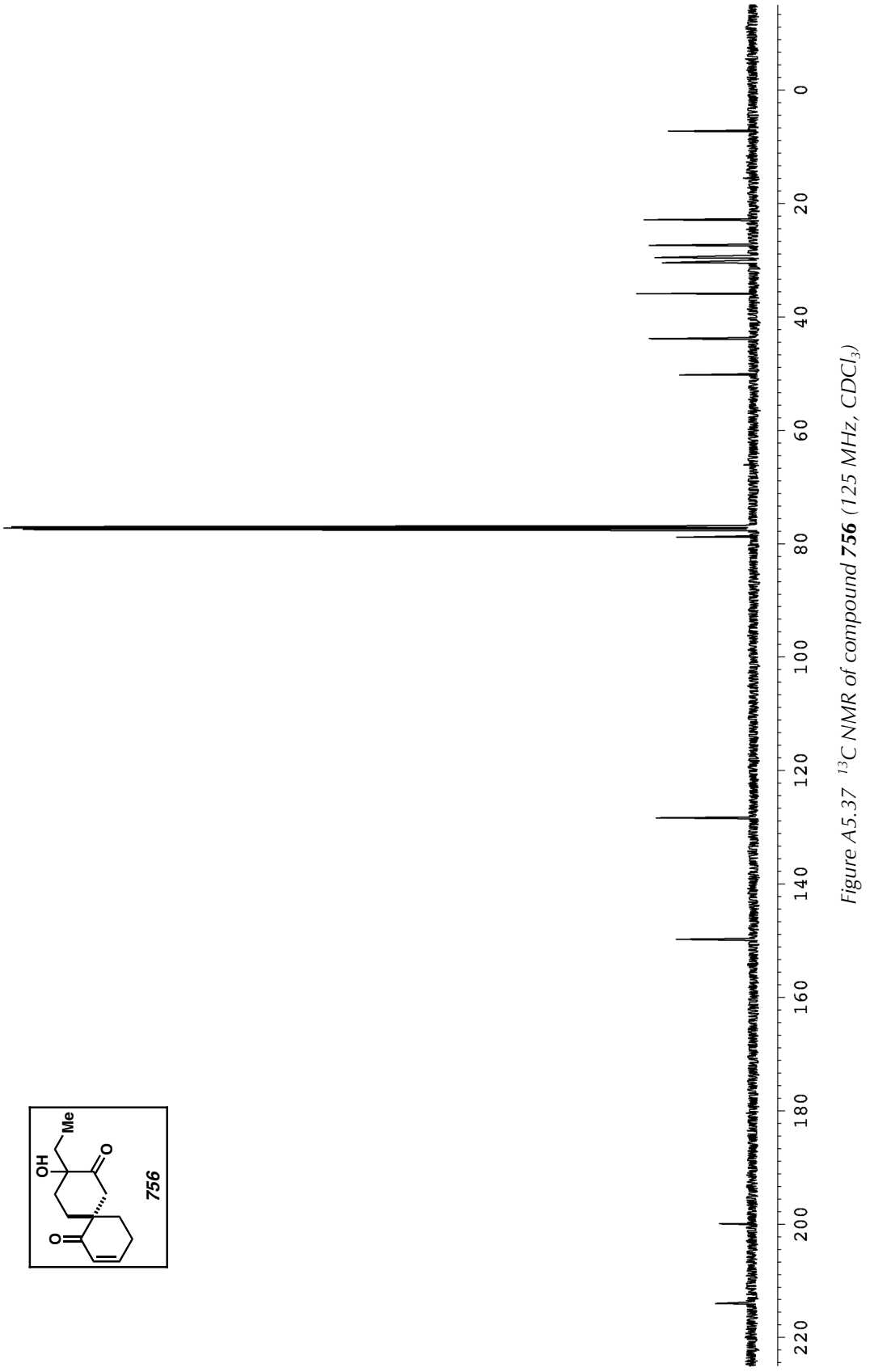


*Figure A5.37 ^{13}C NMR of compound **756** (125 MHz, $CDCl_3$)*

APPENDIX 6

Optimized Large-Scale Procedure for

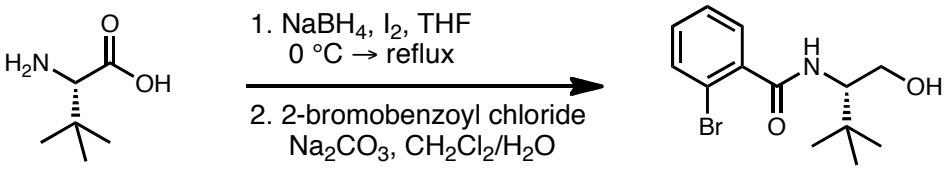
Preparation of t-Bu-PHOX[†]

A6.1 PROCEDURE

A6.1.1 2-BROMO-*N*-[(1*S*)-1-(HYDROXYMETHYL)-2,2-DIMETHYLPROPYL]-BENZAMIDE

Caution! This procedure should be carried out in an efficient fume hood due to the evolution of hydrogen gas during the reaction.

Scheme A6.1 Amino acid reduction and amide bond formation



An oven-dried 500 mL 3-neck flask equipped with a 3.0 cm x 1.4 cm, egg-shaped, Teflon-coated magnetic stirring bar, pressure-equalizing addition funnel, an internal

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[†] This work was carried out in collaboration with Michael R. Krout and the procedures herein have been published in *Org. Synth.* Some of the data contained in this procedure were collected by the *Org. Synth.* checkers (A. Schumacher and A. Pfaltz, University of Basel) during the normal *Org. Synth.* review process. See: Krout, M. R.; Mohr, J. T.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 181–193.

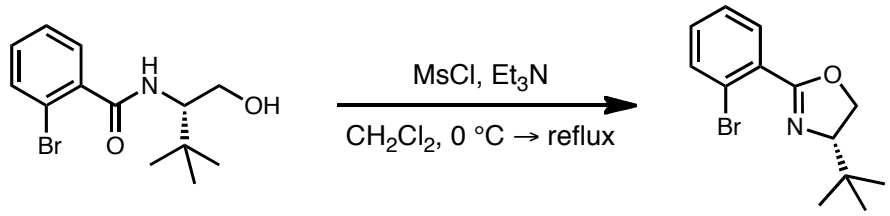
thermometer, and a reflux condenser (central neck) equipped with a two-tap Schlenk adapter connected to a bubbler and an argon/vacuum manifold (Note 1) is assembled hot and cooled under a stream of argon. The flask is charged with (L)-tert-leucine (5.00 g, 38.1 mmol, 1.00 equiv, 99% ee) (Note 2) and tetrahydrofuran (100 mL, 0.38 M) (Note 3) under a positive pressure of argon. The resulting suspension is cooled to approximately 4 °C in an ice-water bath and sodium borohydride (3.46 g, 91.5 mmol, 2.40 equiv) (Note 2) is added in one portion (Note 4). The addition funnel is charged with a solution of iodine (9.67 g, 38.1 mmol, 1.00 equiv) (Note 2) in tetrahydrofuran (25 mL) (Note 3) via syringe and added dropwise to the suspension over 30 min. After complete addition, the bath is removed, the addition funnel and the thermometer are removed and replaced by glass stoppers and the reaction is warmed to reflux (80 °C oil bath temperature). After 18 h the reaction is allowed to cool to ambient temperature and methanol (50 mL) (Note 3) is added slowly resulting in an almost clear solution (Note 5). After stirring for 30 min the solution is quantitatively transferred to a 500 mL 1-necked flask with methanol (ca. 50 mL) and concentrated on a rotary evaporator under reduced pressure (40 °C, ca. 53 torr) to a white semi-solid. The resulting material is dissolved in 20% aqueous potassium hydroxide (75 mL) and stirred for 5 h at ambient temperature with a 3.0 cm x 1.4 cm egg-shaped Teflon-coated magnetic stirring bar. The aqueous phase is extracted with dichloromethane (6 x 60 mL) and the combined organic extracts are dried over sodium sulfate (ca. 7 g), filtered, and concentrated on a rotary evaporator under reduced pressure (40 °C, 38 torr) and dried under vacuum (0.13 mmHg) to yield 4.42–4.45 g (37.7–37.9 mmol, 99% yield) of crude (*S*)-tert-leucinol as a colorless oil (Note 6). This material is used in the following step without purification.

A 500 mL flask containing a 3.0 cm x 1.4 cm egg-shaped Teflon-coated magnetic stirring bar is charged with crude (*S*)-tert-leucinol (4.42 g, 37.7 mmol, 1.00 equiv), dichloromethane (125 mL, 0.30 M) (Note 3) and then a solution of sodium carbonate (11.98 g, 113.1 mmol, 3.00 equiv) (Note 2) in distilled water (95 mL) (Note 3) is added at ambient temperature. The biphasic mixture is stirred vigorously to emulsify and neat 2-bromobenzoyl chloride (5.67 mL, 43.3 mmol, 1.15 equiv) (Note 2) is added dropwise via syringe over approximately 15 min. The reaction flask is capped with a two-tap Schlenk adapter connected to a bubbler (Note 1) and stirred for 10 h, after which time the layers are partitioned in a 500 mL separatory funnel and the aqueous phase is extracted with dichloromethane (4 x 50 mL). The combined organic extracts are stirred with 1 N potassium hydroxide solution in methanol (19 mL) in a 500 mL Erlenmeyer flask with a 3.0 cm x 1.4 cm egg-shaped Teflon-coated magnetic stirring bar for 30 min at ambient temperature and then acidified to neutral pH with 1 N hydrochloric acid (ca. 16 mL). Water (25 mL) is added, the phases are partitioned in a 1 L separatory funnel, and the aqueous phase is extracted with dichloromethane (4 x 35 mL). The combined organic extracts are washed with saturated brine (75 mL), dried over sodium sulfate (3.00 g), filtered, and concentrated on a rotary evaporator under reduced pressure (40 °C, ca. 11 torr) to an off-white solid. The crude white solid is dissolved in a minimal amount of hot acetone (ca. 10 mL) (Note 3) and hexanes (Note 3) are added until a cloudy solution is obtained (ca. 45 mL). The crystals formed upon cooling and aging for 3 hours at 0 °C are collected, washed with hexanes, and dried under vacuum to afford 2-bromo-*N*-[(1*S*)-1-(hydroxymethyl)-2,2-dimethylpropyl]-benzamide (9.23–9.61 g, 30.8–32.0 mmol) as white blocks (Note 7). The filtrate is concentrated and recrystallized in a similar manner

(with acetone (ca. 2 mL) and hexanes (10 mL)) to provide additional product (0.62–1.13 g, 2.1–3.76 mmol) as white blocks (Note 8), for a combined yield of 9.85–10.74 g (32.8–35.77 mmol, 86–94 % yield over two steps).

A6.1.2 2-(2-BROMOPHENYL)-4-(1,1-DIMETHYLETHYL)-4,5-DIHYDRO-(4*S*)-OXAZOLE

Scheme A6.2 Oxazoline formation

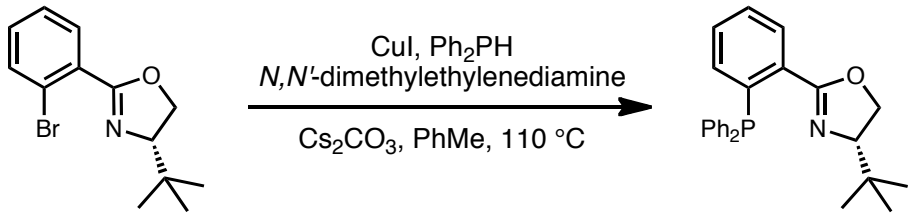


An oven-dried 500 mL 3-necked flask equipped with a 3.0 cm x 1.4 cm egg-shaped Teflon-coated magnetic stirring bar, an internal thermometer, a glass stopper and a reflux condenser (central neck) equipped with a two-tap Schlenk adapter connected to a bubbler and an argon/vacuum manifold (Note 1) is assembled hot and cooled under a stream of argon. The flask is charged with 2-bromo-*N*-[(1*S*)-1-(hydroxymethyl)-2,2-dimethylpropyl]-benzamide (9.85 g, 32.8 mmol, 1.00 equiv), dichloromethane (170 mL, 0.19 M) (Note 3), and triethylamine (11.0 mL, 78.6 mmol, 2.40 equiv) (Note 2) under a positive pressure of argon. The resulting colorless solution is cooled to approximately 4 °C in an ice-water bath and neat methanesulfonyl chloride (2.92 mL, 37.7 mmol, 1.15 equiv) (Note 2) is added dropwise via syringe over 3 min, at which point the solution turns slightly yellow. The reaction is warmed to reflux (50 °C oil bath temperature) while monitoring conversion by TLC (Note 9). Upon completed cyclization, the reaction

is allowed to cool to ambient temperature and 60 mL of saturated aqueous sodium bicarbonate is added with vigorous stirring for 5 min. The layers are partitioned in a 1 L separatory funnel, the aqueous phase is extracted with dichloromethane (2 x 35 mL), the combined organic phases are washed with saturated brine (75 mL), dried over anhydrous magnesium sulfate (1.50 g), filtered, and concentrated on a rotary evaporator under reduced pressure (40 °C, 23 mmHg) to afford a red-brown semi-solid. The residue is dissolved in a minimal amount of dichloromethane (ca. 35 mL), dry-loaded onto silica gel (8 g), and purified by silica gel chromatography (Note 10) to afford 8.85–8.86 g (31.4 mmol, 96% yield) of 2-(2-bromophenyl)-4-(1,1-dimethyl-ethyl)-4,5-dihydro-(4*S*)-oxazole as a pale yellow oil. This material solidifies when placed in a –20 °C freezer and is preferred in this state for the subsequent reaction (Note 11).

A6.1.3 4-(1,1-DIMETHYLETHYL)-2-[2-(DIPHENYLPHOSPHINO)PHENYL]-4,5-DIHYDRO-(4*S*)-OXAZOLE ((*S*)-TERT-BUTYLPHOX)

Scheme A6.3 C–P cross-coupling



A 150 mL Schlenk flask equipped with a glass valve, a glass stopper, and a 1.7 cm x 0.7 cm egg-shaped teflon-coated magnetic stirring bar is dried with a heat gun under vacuum and cooled under argon atmosphere. The glass stopper is removed under a positive pressure of argon and the flask is charged with copper(I) iodide (19.0 mg, 0.10

mmol, 0.005 equiv) (Note 2), diphenylphosphine (4.35 mL, 25.0 mmol, 1.25 equiv) (Note 2), *N*,*N*'-dimethylethylenediamine (53 μL, 0.50 mmol, 0.025 equiv) (Note 2) and toluene (20 mL) (Note 3). The flask is sealed with the glass stopper and the colorless contents are stirred at ambient temperature for 20 min. The glass stopper is then removed under a positive pressure of argon and the flask is charged with 2-(2-bromophenyl)-4-(1,1-dimethylethyl)-4,5-dihydro-(4*S*)-oxazole (5.64 g, 20.0 mmol, 1.00 equiv), cesium carbonate (9.78 g, 30.0 mmol, 1.50 equiv) (Note 2), and toluene (20 mL, 0.50 M total) to wash the neck and walls of the flask. The flask is equipped with a reflux condenser with a two-tap Schlenk adapter connected to a bubbler and an argon/vacuum manifold (Note 1). The now yellow heterogeneous reaction is placed in a 110 °C oil bath and vigorously stirred under argon atmosphere (Note 12). Following consumption of starting material (Note 13), the reaction is allowed to cool to ambient temperature, filtered through a pad of Celite, and the filter cake is washed with dichloromethane (2 x 40 mL) (Note 14). The filtrate is concentrated on a rotary evaporator under reduced pressure (40 °C, 15 torr) to a pale yellow semi-solid. The residue is dissolved in a minimal amount of dichloromethane (ca. 40 mL) (Note 15), dry-loaded onto silica gel (10 g), and purified by silica gel chromatography eluting with 24:1 hexanes/diethyl ether until excess Ph_2PH elutes, then with a 9:1 dichloromethane/diethyl ether mixture until the desired product elutes (Note 16). The combined fractions are concentrated on a rotary evaporator under reduced pressure (40 °C, 14 torr) to a viscous pale yellow oil and layered with acetonitrile (ca. 5 mL) to facilitate crystallization (Notes 3 and 17). The flask is swirled while crystals form within seconds (Note 18). After approximately 15 min, the flask is placed

under high vacuum to remove volatiles to afford 6.81 g (17.6 mmol, 88% yield) of (*S*)-tert-ButylPHOX as white blocks (Note 19).

A6.2 NOTES

1. A two-tap Schlenk adapter connected to a bubbler and an argon/vacuum manifold is illustrated in Yu, J.; Truc, V.; Riebel, P.; Hierl, E. and Mudryk, B. *Org. Synth.* **2008**, *85*, 64–71.

2. Submitters and checkers purchased (L)-*tert*-leucine (99%, 99% ee), sodium borohydride (98%), cesium carbonate (99%), and *N,N'*-dimethylethylenediamine (99%) from Aldrich and used as received. (2)-Bromobenzoyl chloride (98%) and methanesulfonyl chloride (99.5%) were purchased from Acros and used as received. Copper iodide (98%) was purchased from Strem and used as received. Submitters and checkers purchased triethylamine (99.5%) from Aldrich and distilled it from calcium hydride prior to use. Submitters and checkers purchased diphenylphosphine (99%) from Strem and transferred it through a cannula to a dry Schlenk tube under nitrogen to prolong reagent life. The submitters purchased iodine (≥99%) and sodium carbonate (99%) from Aldrich and used as received. The checkers purchased iodine (puriss. p. a.) and potassium hydroxide (puriss. p. a.) from Riedel-de-Haën (puriss. p. a.) and sodium carbonate (99.5%) from Merck and used as received.

3. Submitters distilled tetrahydrofuran from sodium 9-fluorenone ketyl[1] prior to use. Submitters and checkers used methylene chloride, toluene, and acetonitrile purified by passage through an activated alumina column under argon.[2] The submitters purchased reagent grade acetone from EMD, and hexanes and methanol (both ACS grade) were

purchased from Fisher and used as received. The submitters used distilled water purified with a Barnstead NANOpure Infinity UV/UF system. The checkers used tetrahydrofuran (VWR, HPLC-grade) dried using a Pure-Solve™ system. Reagent grade acetone was purchased from VWR, methanol (Baker analyzed) was purchased from J.T. Baker and hexanes were distilled.

4. The evolution of hydrogen gas during the addition of sodium borohydride is minor due to the adequate size of the reaction flask and the surface area of cooling. This is readily vented through the oil bubbler.

5. The initial reaction quench with methanol proceeds with vigorous gas evolution. Methanol should be added dropwise until the intensity of gas evolution abates.

6. The reduction product, (*S*)-*tert*-leucinol, can be purified by distillation,[3] but this was not necessary for this application. The material showed the following characterization data: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (s, 9 H), 2.49 (dd, *J* = 10.2, 3.9 Hz, 1 H), 3.19 (t, *J* = 10.2 Hz, 1 H), 3.70 (dd, *J* = 10.2, 3.9 Hz, 1 H). This material may also be purchased from commercial sources, but is less expensive in the amino acid form. Similar amino acid reductions have appeared in *Organic Syntheses*.[4]

7. 2-Bromo-*N*-[(1*S*)-1-(hydroxymethyl)-2,2-dimethylpropyl]-benzamide showed the following characterization data: mp 117–118 °C from acetone/hexanes; R_f = 0.14 (2:1 hexanes/acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.03 (s, 9 H), 2.40 (br dd, *J* = 5.0 Hz, 1 H), 3.64–3.70 (m, 1 H), 3.91-3.97 (m, 1 H), 4.04–4.08 (m, 1 H), 6.20 (br d, *J* = 8.4 Hz, 1 H), 7.27 (ddd, *J* = 7.9, 7.9, 1.6 Hz, 1 H), 7.35 (dd, *J* = 7.5, 7.5 Hz, 1 H), 7.55 (dd, *J* = 7.6, 1.5 Hz, 1 H), 7.59 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 27.1, 33.8, 60.3, 63.0, 119.0, 127.6, 129.7, 131.3, 133.3, 137.9, 168.6; IR (ATR) 3223, 3065, 2961, 1627,

1544 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{13}H_{19}NO_2Br$ $[M + H]^+$: 300.0599, found 300.0590; MS (FAB) *m/z* (relative intensity): 300 (100%), 185 (49%), 77 (21%); $[\alpha]_D^{20}$ +17.3 (*c* 2.38, methanol); Anal. calc'd. for $C_{13}H_{18}NO_2Br$: C, 52.01; H, 6.04; N, 4.67. Found: C, 52.01; H, 5.95; N, 4.51.

8. In some cases the resulting filtrate was purified by silica gel flash chromatography, eluting with a 3:1 → 2:1 hexanes/acetone gradient to afford an additional 2–6% of an off-white amorphous solid that is spectroscopically identical to the crystalline material.

9. Reaction progress can be monitored by TLC analysis (the checkers used Polygram®SIL/UV_{254}-TLC-plates from Macherey-Nagel) using 2:1 ethyl acetate/hexanes as the eluent with UV visualization (R_f amide = 0.28, R_f mesylate = 0.43, R_f bromooxazoline = 0.64). Mesylate formation is typically complete upon final addition of methanesulfonyl chloride, whereas cyclization to the bromooxazoline typically requires ca. 5 h at 50 °C to complete.

10. Flash chromatography column dimensions: 3 cm diameter x 20 cm height of silica gel (checkers used "Silica Gel 60" (0.040–0.063 mm) from Merck), eluting with 200 mL of 9:1 hexanes/ethyl acetate, then 450 mL of 6:1 hexanes/ethyl acetate, collecting ca. 20–25 mL fractions. Fraction purity can be assayed by TLC (the checkers used Polygram®SIL/UV_{254}-TLC-plates from Macherey-Nagel) analysis using 4:1 hexanes/ethyl acetate with UV visualization. This method of purification removes color from the crude material and a minor impurity at $R_f = 0.33$.

11. 2-(2-Bromophenyl)-4-(1,1-dimethylethyl)-4,5-dihydro-(4*S*)-oxazole showed the following characterization data: mp 47–48 °C; $R_f = 0.27$ (4:1 hexanes/ethyl acetate); ^1H

NMR (500 MHz, $CDCl_3$) δ: 1.00 (s, 9 H), 4.11 (dd, *J* = 10.2, 8.0 Hz, 1 H), 4.26 (dd, *J* = 8.3, 8.3 Hz, 1 H), 4.38 (dd, *J* = 10.2, 8.7 Hz, 1 H), 7.27 (ddd, *J* = 7.7, 7.6, 1.9 Hz, 1 H), 7.33 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1 H), 7.63 (dd, *J* = 8.0, 0.9 Hz, 1 H), 7.66 (dd, *J* = 7.6, 1.3 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 26.0, 34.1, 69.0, 76.8, 121.9, 127.1, 130.3, 131.3, 131.5, 133.7, 162.8; IR (ATR) 2958, 1660, 1476, 1358, 1095, 1022, 959 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{13}H_{17}NOBr$ $[M + H]^+$: 282.0493, found 282.0488; MS (FAB) *m/z* (relative intensity): 282 (100%), 224 (10%), 183 (17%), 77 (12%); $[\alpha]_D^{20}$ –48.9 (c 3.77, hexane); Anal. calc'd. for $C_{13}H_{16}NOBr$: C, 55.33; H, 5.72; N, 4.96. Found: C, 55.37; H, 5.70; N, 4.84.

12. Submitters sealed the Teflon valve and placed the sealed flask in a 110 °C oil bath protected with a blast shield. Reactions performed with minimal stirring or that cease to stir result in incomplete conversion. The preferred stirring rate of the coupling reaction is ca. 700 setting (ca. 700 rpm) on an IKAmag RET basic stir/hot plate (a range between 500–800 rpm is sufficient). Additionally, the color of the reaction becomes an intense yellow within 5–10 minutes of heating. The color of the inorganic base then dominates as it turns to light gray, and finally to a dark maroon/purple color after several hours.

13. The reaction typically requires 21 h to reach complete conversion. Reaction progress can be monitored by TLC analysis (the checkers used Polygram®SIL/UV_{254}-TLC-plates from Macherey-Nagel) using 4:1 hexanes/diethyl ether as the eluent (developed twice) with UV visualization (R_f bromooxazoline = 0.17, R_f reduced oxazoline = 0.27, R_f *tert*-ButylPHOX = 0.33, R_f Ph_2PH = 0.51).

14. Fritted glass funnel (Por. 3, pore size 15–40 μm), 4 cm diameter x 5 cm height) filled with 16 g of Celite.

15. Submitters dissolved the pale yellow semi-solid in a minimal amount of dichloromethane (ca. 40 mL) and diethyl ether (ca. 50 mL).

16. Flash chromatography column dimensions: 5 cm diameter x 16 cm height of silica gel, (checkers used "Silica Gel 60" (0.040-0.063 mm) from Merck). Checkers eluted with 500 mL of 24:1 hexanes/diethyl ether, then 400 mL of 9:1 dichloromethane/diethyl ether, collecting ca. 50 mL fractions. Fraction purity can be assayed by TLC (the checkers used Polygram®SIL/UV_{254}-TLC-plates from Macherey-Nagel) analysis using 4:1 hexanes/diethyl ether with UV visualization. The mixture of products may contain reduced arene, starting bromooxazoline, and desired (*S*)-*tert*-ButylPHOX, depending on the extent of reaction (Note 12).

17. As the percentage of desired (*S*)-*tert*-ButylPHOX in the crude mixture increases, the oil readily solidifies upon concentration under reduced pressure. To decrease the time required to induce crystallization, this oil can then be dissolved in diethyl ether and further concentrated. Additionally, acetonitrile efficiently promotes crystallization of (*S*)-*tert*-ButylPHOX in concentrated solutions.

18. If the reaction is pushed to completion, the material obtained from this simple purification is typically quite pure (no impurities were detected by ^{1}H NMR analysis of the crude oil). If the purity is unsatisfactory, this crystalline material can be recrystallized with hot acetonitrile. A typical recrystallization is performed as follows: in an experiment run on 20.0 mmol scale, 7.033 g (18.15 mmol) of crude product was dissolved in a minimal amount (ca. 8–10 mL) of boiling acetonitrile and allowed to cool

slowly to ambient temperature. The crystals are then filtered and washed with ca. 15–25 mL of hexanes, then dried under high vacuum to yield 6.613 g (17.07 mmol, 85.3% yield) of white blocks. This material is analytically pure by ^{1}H NMR and all other spectroscopic data (see Note 19).

19. In a run carried out on half-scale, 3.49 g of (*S*)-*tert*-ButylPHOX was obtained (90% yield). (*S*)-*tert*-ButylPHOX showed the following characterization data; mp 113–114 °C from acetonitrile; R_f = 0.33 (4:1 hexanes/diethyl ether); ^{31}P NMR (162 MHz, $CDCl_3$) δ: –5.49 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.73 (s, 9 H), 3.88 (dd, *J* = 10.2, 8.2 Hz, 1 H), 4.01 (dd, *J* = 8.3 Hz, 8.3 Hz, 1 H), 4.08 (dd, *J* = 10.2, 8.5 Hz, 1 H), 6.87 (ddd, *J* = 7.7, 4.0, 0.8 Hz, 1 H), 7.33–7.21 (m, 11 H), 7.36 (apparent dt, *J* = 7.6, 1.3 Hz, 1 H), 7.94 (ddd, *J* = 7.7, 3.7, 0.9 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 25.8, 33.6, 68.3, 76.7 (overlaps with $CHCl_3$-rest-signal, detected in DEPT135-experiment), 128.0, 128.3 (d, J_{CP} = 5.9 Hz), 128.2 (2 lines), 128.5 (d, J_{CP} = 9.7 Hz), 129.8 (d, J_{CP} = 3.1 Hz), 130.3, 132.0 (d, J_{CP} = 19.7 Hz), 133.6 (d, J_{CP} = 20.2 Hz), 134.1, 134.3 (d, J_{CP} = 21.0 Hz), 138.3 (d, J_{CP} = 9.7 Hz), 138.5 (d, J_{CP} = 12.6 Hz), 138.8 (d, J_{CP} = 25.5 Hz), 162.7 (d, J_{CP} = 2.7 Hz); IR (ATR) 3069, 2955, 2897, 2866, 1653, 1583, 1475, 1433, 1354, 1090, 1024, 955, 742, 669, 580, 511 cm^{-1}; HRMS (FAB+) *m*/*z* calc'd for $C_{25}H_{27}NOP$ $[M + H]^+$: 388.1830, found 388.1831; MS (EI) *m*/*z* (relative intensity): 388 (1%), 372 (9%), 330 (55%), 302 (100), 228 (6), 183 (12); $[\alpha]_D^{20}$ –75.2 (c 0.925, $CHCl_3$); Anal. calc'd. for $C_{25}H_{26}NOP$: C, 77.50; H, 6.76; N, 3.62. Found: C, 77.22; H, 6.82; N, 3.57. The enantiomeric excess of (*S*)-*tert*-ButylPHOX can be determined by analytical supercritical fluid chromatography; this was performed using a Berger Analytix SFC (Thar Technologies) equipped with a Chiralcel® OJ-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries,

Ltd. and a diode array detector. The assay conditions are 10% ethanol, 35 °C, 2 mL/min flow rate, with visualization at 210 nm (optimal), retention times: (*R*) enantiomer = 4.67 min, (*S*) enantiomer = 5.17 min. The minor (*R*) enantiomer can not be detected from SFC analyses of ligand prepared from the reported procedure, and is therefore >99% ee. This crystalline material is stable indefinitely at ambient temperatures in a closed container under an atmosphere of nitrogen or argon.

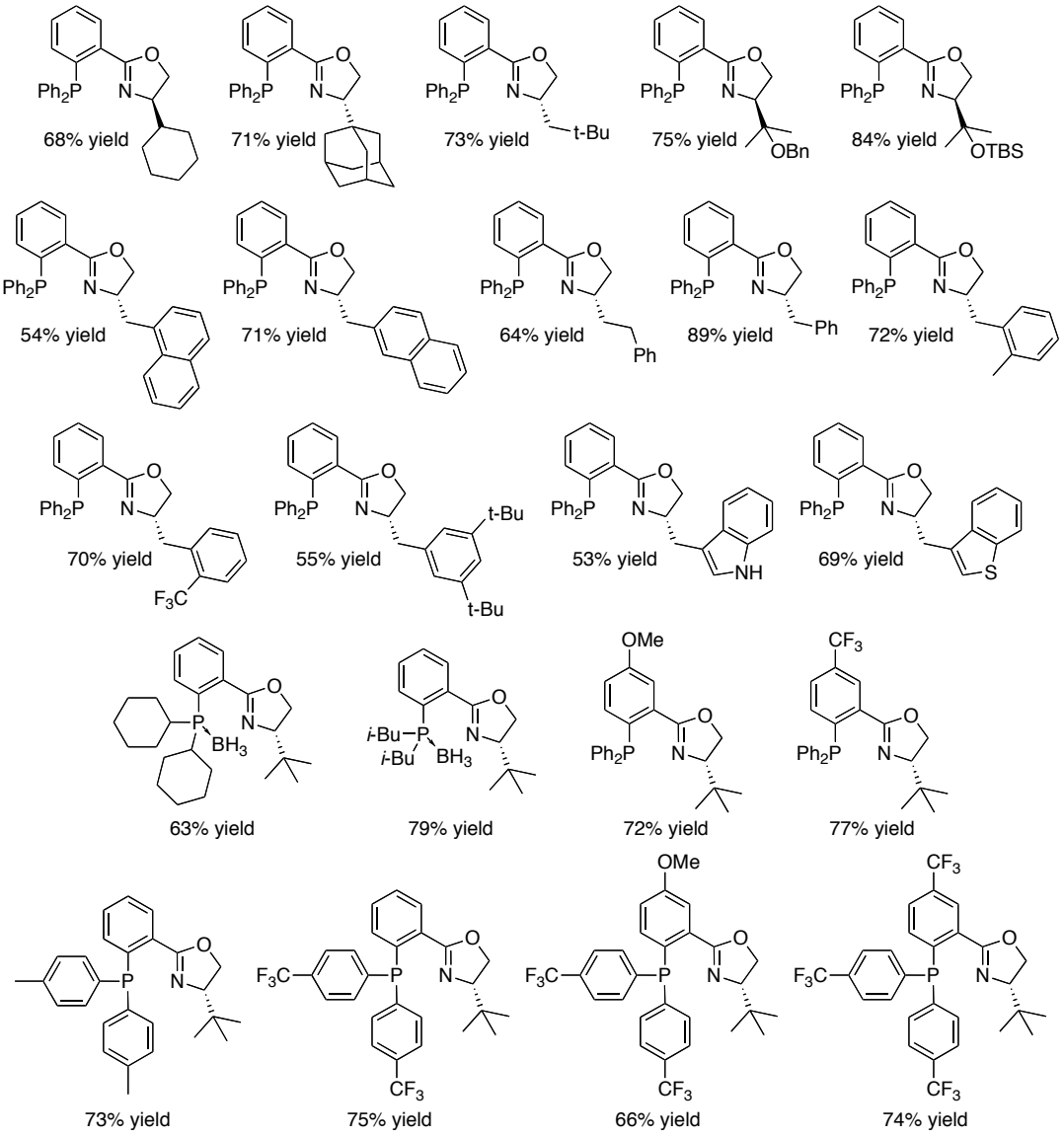
A6.3 DISCUSSION

This synthesis of (*S*)-*tert*-ButylPHOX (4-(1,1-dimethylethyl)-2-[2-(diphenylphosphino)phenyl]-4,5-dihydro-(4*S*)-oxazole) is a modification of our previously reported procedure.[5] Several improvements have been implemented that facilitate large-scale preparation of this ligand. Recrystallization of 2-bromo-*N*-[(1*S*)-1-(hydroxymethyl)-2,2-dimethylpropyl]-benzamide obviates the previous need for flash column chromatography. Subsequent oxazoline formation is now accomplished via mesylate displacement with improved efficiency and yield. The use of methanesulfonyl chloride enables rapid mesylate formation at milder temperatures, and aqueous reaction workup is favored over the previous method, where incomplete hydrolysis of *p*-toluenesulfonyl chloride complicated purification. The copper(I) iodide-catalyzed phosphine coupling[6] has been optimized to maximize the efficiency of the reaction by minimizing the use of catalyst and diamine ligand, as well as reducing the quantities of phosphine, cesium carbonate, and solvent. Finally, a procedure to purify (*S*)-*tert*-ButylPHOX is described, using a simple silica gel plug, followed by crystallization with

acetonitrile (or recrystallization when necessary), to afford the ligand as a white crystalline solid in four steps from (L)-*tert*-leucine in excellent overall yield (71.9–80.4% over four steps).

The phosphinooxazoline[7] (*S*)-*tert*-ButylPHOX is a chiral P/N-ligand useful for an array of organometallic transformations, including alkylations,[7,8] desymmetrizations of *meso*-anhydrides,[9] Heck reactions,[10] hetero-Diels–Alder cycloadditions,[11] Meerwein–Eschenmoser Claisen rearrangements,[12] and hydrogenations.[13] Our laboratory has recently described its use as a uniquely effective ligand for the palladium-catalyzed asymmetric decarboxylative allylation[5,14] and protonation[15] of prochiral ketone enolates. This synthesis of (*S*)-*tert*-ButylPHOX highlights improvements of a general and efficient strategy to access PHOX ligands of varied structure and electronics in substantial quantities (Figure A6.1).[5b]

Figure A6.1 PHOX derivatives prepared via this protocol



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APPENDIX 7

Optimized Large-Scale Procedure for

Enantioselective Tsuji Allylation[†]

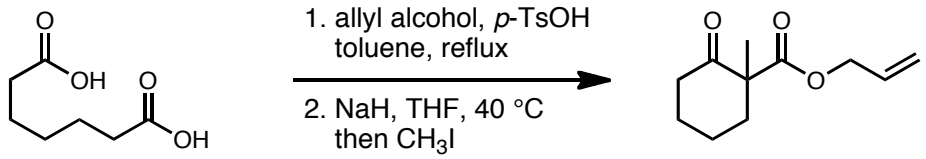
A7.1 PROCEDURE

A7.1.1 1-METHYL-2-OXO-CYCLOHEXANECARBOXYLIC ACID 2-PROPENYL ESTER

Caution! This procedure should be carried out in an efficient fume hood due to the evolution of hydrogen gas during the reaction. Appropriate precautions should be taken to avoid inhalation or direct contact with iodomethane or allyl alcohol. The former is a known carcinogen, and the latter is a potent toxin due to its in vivo metabolism to acrolein, a known carcinogen.

[†] This work was carried out in collaboration with Michael R. Krout and the procedures herein have been published in *Org. Synth.* Some of the data contained in this procedure were collected by the *Org. Synth.* checkers (C. Ebner, and A. Pfaltz, University of Basel) during the normal *Org. Synth.* review process. See: Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 194–211.

Scheme A7.1 Substrate synthesis



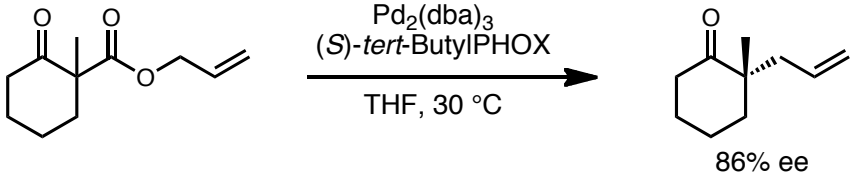
A 500-mL, single-necked, round-bottomed flask equipped with a large magnetic stir bar (38 x 8 mm) is charged with 50.0 g of pimelic acid (313 mmol, 1.00 equiv), 156 mL of toluene, and 63.9 mL of allyl alcohol (939 mmol, 3.00 equiv) (Note 1). The mixture is stirred vigorously to create a uniform suspension, and 297 mg of *p*-toluenesulfonic acid monohydrate (1.57 mmol, 0.005 equiv) is added. A Dean–Stark trap and a water-cooled condenser with a two-tap Schlenk adapter connected to a bubbler and an argon/vacuum manifold (Note 2) are affixed to the flask, and the resulting suspension is heated to reflux (120 °C oil bath temperature). The mixture in the flask soon became homogeneous. After 16 h at reflux, approximately 11 mL of water had accrued in the Dean–Stark trap. The vessel is cooled to ambient temperature and the solution is transferred to a separatory funnel (500 mL). The organic solution is washed successively with saturated aqueous sodium bicarbonate (3 x 15 mL) and brine (2 x 15 mL) and then dried over anhydrous magnesium sulfate (6 g). After filtration through cotton, the organic solution is concentrated by rotary evaporation under vacuum (60 °C, 15 torr) and then the last traces of solvent are removed under high vacuum (0.15 torr) to yield 72.3–74.6 g of diallyl pimelate (301–311 mmol, 96–99% yield) as a slightly yellow-colored, free-flowing liquid. GC analysis indicated >99% purity (Note 3).

A flame-dried, three-necked, 1-L flask equipped with a glass stopper, a water-cooled reflux condenser with a two-tap Schlenk adapter connected to a bubbler and an

argon/vacuum manifold (Note 2), a rubber septum, and a magnetic stir bar is charged with 13.2 g of 60% sodium hydride (331 mmol, 1.10 equiv) and tetrahydrofuran (250 mL) (Note 1). The flask is immersed in a water bath (22 °C) and a solution of 72.2 g of crude diallyl pimelate (301 mmol, 1.00 equiv) in 50 mL of tetrahydrofuran is added in a steady stream via cannula during the course of 5 min. Some moderate bubbling (hydrogen evolution) of the reaction mixture is observed during the addition. Following the addition, the suspension is heated to 40 °C and then stirred for 10 h (Note 4) whereupon the reaction mixture turned to a clear, yellowish solution. Once the starting material is consumed (based on TLC, Note 5), 24.3 mL of neat iodomethane (391 mmol, 1.30 equiv) (Note 1) is added to the mixture, which became a white suspension. After an additional 15 h at 40 °C, the mixture is cooled to ambient temperature (22 °C) and water (60 mL) is added carefully via syringe over the course of 9 min to obtain a clear, yellowish solution. The mixture is transferred to a 1-L, single-necked, round-bottomed flask, the THF is removed by rotary evaporation under vacuum (40 °C, 150 torr) (Note 6), and the remaining solution is transferred to a separatory funnel (500 mL) and diluted with ethyl acetate (100 mL). The phases are separated and the aqueous phase is extracted with ethyl acetate (3 x 75 mL). The combined organic extracts are washed with brine (1 x 50 mL) and dried over anhydrous magnesium sulfate (5 g). After filtration through cotton, the organic solution is concentrated by rotary evaporation under vacuum (40 °C, 75 torr) to yield a yellow liquid. The material is purified by short-path distillation until the first drop of the distillate turned yellow to give 52.9–53.0 g (270 mmol, 90% yield) (Note 7) of a clear, colorless liquid boiling from 69–72 °C/0.08 torr. GC analysis found >99% product purity (Note 8).

A7.1.2 (2*S*)-2-METHYL-2-(2-PROPEN-1-YL)-CYCLOHEXANONE

Scheme A7.2 Enantioselective decarboxylative allylation

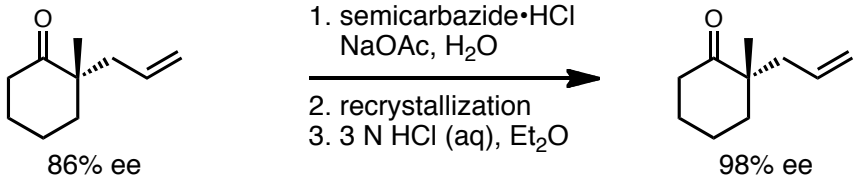


A flame-dried, 50-mL, conical flask equipped with a rubber septum is charged with a portion of 1-methyl-2-oxo-cyclohexanecarboxylic acid 2-propenyl ester, placed under vacuum (0.06 torr) for 60 min to remove any dissolved gases, and then backfilled with argon. A 1-L, three-necked, round-bottomed flask is equipped with a stir bar, two rubber septa, and a two-tap Schlenk adapter connected to a bubbler and an argon/vacuum manifold (Note 2). The apparatus is flame-dried under vacuum and backfilled with dry argon (three cycles). After cooling the flask to ambient temperature, 435 mL of anhydrous tetrahydrofuran (Notes 1 and 9) is added and the flask is immersed in a 30 °C water bath. A twelve-inch needle is inserted through one of the septa and used to bubble dry argon gas through the liquid for 30 min. The needle is removed and then 1.02 g of tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$, 1.11 mmol, 0.0125 equiv) and 1.03 g of (*S*)-*tert*-ButylPHOX (2.67 mmol, 0.030 equiv) (Note 1) are added. The mixture immediately became opaque and took on a golden brown color. This mixture is stirred at 30 °C for 30 min (Note 10). Subsequently, neat 1-methyl-2-oxo-cyclohexanecarboxylic acid 2-propenyl ester (17.5 g, 89.03 mmol, 1.00 equiv) from the conical flask is added via syringe in a dropwise fashion to the catalyst mixture over the course of 10 min.

When the transfer is complete, the syringe is rinsed successively with two 5 mL portions of anhydrous tetrahydrofuran into the reaction mixture. Upon addition of the substrate to the catalyst mixture, the color changed to olive green. The mixture is maintained at 30–32 °C for 22–23 h (Note 11), when TLC indicated complete consumption of the starting material (Note 12). The olive green-colored mixture is then passed through a pad of silica gel (5 cm diameter x 5 cm height) and rinsed with diethyl ether (200 mL). The bright yellow filtrate is concentrated by rotary evaporation under vacuum (150 torr, 40 °C) (Note 13). The liquid is then transferred to a 50-mL round-bottomed flask and distilled through a short path apparatus into a receiving flask immersed in an ice water bath to provide 11.5–12.8 g (75.7–84.2 mmol, 85–95% yield) of (*S*)-2-allyl-2-methylcyclohexanone as a clear, colorless liquid boiling from 91–93 °C/16 torr that is analytically pure based on standard techniques (Note 14). Analysis of this material by GC on a chiral stationary phase found 86–87% enantiomeric excess (Note 15). In a reaction that gave 85% yield after distillation, additional product was obtained by subjecting the material remaining in the distillation pot to flash chromatography on silica gel (Notes 16 and 17), which provided an additional 1.14 g of product (7.50 mmol, 8% yield), also of 86% ee, for a combined yield of 12.64 g (83.2 mmol, 93% yield) (Note 18).

A7.1.3 ENRICHMENT OF (2*S*)-2-METHYL-2-(2-PROPEN-1-YL)-CYCLOHEXANONE VIA (2*E*)-2-[(2*S*)-2-METHYL-2-(2-PROPENYL)CYCLOHEXYLIDENE]-HYDRAZINECARBOXAMIDE

Scheme A7.3 Increase of ee by means of semicarbazone derivative



Into a 250-mL, pear-shaped flask is added 5.58 g of sodium acetate (68.0 mmol, 1.00 equiv), 8.38 g of semicarbazide hydrochloride (74.8 mmol, 1.10 equiv), 75 mL of purified water (Note 1), and a large magnetic stir bar. The solution is stirred until all of the solids dissolved. At this point, 10.34 g of neat 2-allyl-2-methylcyclohexanone (68.0 mmol, 1.00 equiv) is added via syringe. When the addition is complete, a two-tap Schlenk adapter connected to a bubbler and an argon/vacuum manifold (Note 2) is attached and the mixture is heated to 60 °C for 14 h (Note 19). The thick slurry is vacuum filtered (water aspirator) directly through filter paper on a porcelain Büchner funnel and rinsed with water (2 x 20 mL). The white solid is dried for 30 min on the funnel, transferred to a 250-mL round-bottomed flask, which then is immersed in a 50 °C water bath. The white solid is dried under vacuum (0.3 torr) until a constant mass of 12.2 g (58.3 mmol, 86% yield) is achieved (about 8 h). At this point, the semicarbazone is found to have 90–91% ee (measured by reverting to the ketone, Note 20).

A stir bar is added to the flask and the solids are suspended in 150 mL of toluene with mixing at approximately 400 rpm. After a water-cooled reflux condenser is attached to the flask, the mixture is then heated to 110 °C (bath temperature) in an oil bath. After a

few minutes at this temperature, the solids dissolve completely to afford a clear colorless solution (Note 21). Heating is discontinued and the stirred mixture is allowed to cool to ambient temperature (20 °C) overnight while still immersed in the oil bath (Note 22). The cooled heterogeneous mixture is vacuum filtered (water aspirator) through filter paper on a porcelain Büchner funnel. The solids are rinsed with toluene (2 x 10 mL) and then dried on the filter for 15 min (Note 23). The solids are transferred to a 250-mL pear-shaped flask and dried under vacuum (0.3 torr) until a constant mass of 10.8–10.9 g (51.7–52.2 mmol, 76–77% yield, 89–90% recovery) is observed. This material is found to have 98–99% enantiomeric excess (measured by reverting to the ketone, Note 20).

A 250-mL pear-shaped flask containing a magnetic stir bar and 10.5 g of semicarbazone (50.2 mmol) and 40 mL of diethyl ether is stirred to suspend the solids. To the suspension is added 20 mL of 3 N aqueous hydrochloric acid (Note 1). No appreciable heat evolution is observed. The mixture is stirred vigorously for 3 h at ambient temperature (20 °C), at which time all of the solids had disappeared and two clear colorless phases are observed. The biphasic mixture is transferred to a 100-mL separatory funnel and the phases are separated. The aqueous phase is extracted with diethyl ether (3 x 10 mL). The combined organic layers are then washed successively with saturated sodium bicarbonate (2 x 5 mL), water (1 x 5 mL), and brine (2 x 5 mL). The organic phase is dried over anhydrous magnesium sulfate (1 g) and then filtered through cotton and concentrated by rotary evaporation under vacuum (150 torr, first at 20 °C, then at 40 °C to remove the last traces of solvent) to provide 7.62–7.63 g (50.1–50.2 mmol, >99% yield) of (*S*)-2-allyl-2-methylcyclohexanone of 98% ee (Notes 14 and 15). GC analysis demonstrates the product is formed in >99% product purity (Note 24).

A7.2 NOTES

1. Pimelic acid (≥99%, Fluka), allyl alcohol (≥99%, Sigma-Aldrich), *p*-toluenesulfonic acid monohydrate (ACS reagent, ≥98.5%, Sigma-Aldrich), toluene (Baker ultra resi-analyzed, J.T. Baker), solid sodium bicarbonate (tech grade, Brenntag Schweizerhall AG), magnesium sulfate (tech. grade, Brenntag Schweizerhall AG), sodium hydride (60% dispersion in mineral oil, Acros), iodomethane (Reagent Plus, 99%, Sigma-Aldrich), tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$, Strem), sodium acetate (puriss. p.a., ACS reagent, anhydrous, ≥99.0% (NT), Fluka), semicarbazide hydrochloride (99%, Alfa Aesar), and hydrochloric acid (36–38 wt%, J.T.Baker), were purchased and used as received. Checkers purchased purified water (for HPLC, Fluka), submitters used water purified with a Barnstead NANOpure Infinity UV/UF system. Ethyl acetate (tech. grade, Brenntag Schweizerhall AG) was distilled prior to use, diethyl ether (tech. grade, Brenntag Schweizerhall AG) was distilled and passed through an activated alumina column under nitrogen prior to use,[1] tetrahydrofuran (HPLC grade, Fisher) was distilled from sodium 9-fluorenone ketyl[2] or passed through an activated alumina column under argon prior to use. The ligand (*S*)-*tert*-ButylPHOX was prepared using our accompanying procedure in *Organic Syntheses*.[3,4]

2. A two-tap Schlenk adapter connected to a bubbler and an argon/vacuum manifold is illustrated in Yu, J.; Truc, V.; Riebel, P.; Hierl, E.; Mudryk, B. *Org. Synth.* **2008**, *85*, 64–71.

3. The esterification product, diallyl pimelate, may be distilled (bp 134–135 °C/0.2 torr), but this is not necessary for this application. Distillation of a separate sample of diallyl pimelate led to significant loss of material to unidentified polymeric byproducts formed in the distillation flask, and distillation is therefore not recommended. Product purity was measured by GC using a CE Instruments GC 8000 Top equipped with a Restek Rtx-1701 column (30.0 m x 0.25 mm) and a flame ionization detector using a method of 100 °C isothermal for 5 min, then ramp 13 °C/min to 240 °C, then 240 °C isothermal for 5 min with 60 kPa He carrier gas flow. The retention time for the product was 17.85 min. No further signals were observed by the checkers, and therefore a product purity of 98% was assigned with >99% yield. Submitters reported observation of a predominant but unidentified impurity with slightly shorter retention time than the product. The product exhibited the following characteristics: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33–1.40 (m, 2 H), 1.66 (apparent quintet, J = 7.7 Hz, 4 H), 2.34 (t, J = 7.6 Hz, 4 H), 4.57 (apparent dt, J = 5.7, 1.4 Hz, 4 H), 5.23 (apparent dq, J = 10.4, 1.3 Hz, 2 H), 5.30 (apparent dq, J = 17.2, 1.5 Hz, 2 H), 5.91 (ddt, J = 17.2, 10.4, 5.7 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 24.7, 28.7, 34.1, 65.1, 118.3, 132.4, 173.3; IR (neat film, NaCl) 3086, 3025, 2942, 2866, 1733, 1648, 1456, 1421, 1378, 1272, 1173, 1086, 991, 932, 734 cm^{-1}; MS (FAB, NBA) *m/z* (%) 242 (11), 241 (100, $[M+H]^+$), 183 (85), 137 (31), 136 (14), 125 (53), 77 (10), 69 (12), 41 (59), 39 (12); HRMS (EI) *m/z* calc'd for $C_{13}H_{20}O_4$ $[M]^+$: 240.1362, found 240.1355; TLC (Hex/EtOAc = 4:1) R_f = 0.46. Anal calcd for $C_{13}H_{20}O_4$: C 64.98, H 8.39, found C 65.28, H 8.38.

4. Submitters reported 7 h at 22 °C and an additional 4 h at 40 °C until all starting material was consumed. After this time the checkers did not observe full conversion by TLC analysis using the TLC method described in Note 5.

5. The progression of the cyclization may be monitored by TLC analysis using 20% ethyl acetate in hexanes as eluent with $KMnO_4$ staining (submitters used *p*-anisaldehyde staining): R_f diallyl pimelate = 0.46, R_f cyclized intermediate = 0.58–0.77 (broad, also UV active), R_f alkylation product = 0.56. The detection of diallyl pimelate is often obscured by the cyclized intermediate.

6. Following the submitters' procedure, THF was not removed before diluting with ethyl acetate. In the checkers' hands no phase separation took place under these conditions.

7. Submitters reported 67% yield and 92% purity.

8. Using the GC method described in Note 3, 1-methyl-2-oxo-cyclohexanecarboxylic acid 2-propenyl ester has a retention time of 14.77 min. The distilled material contains a small amount (<1% by GC) of uncyclized pimelate and <1% of an unidentified byproduct (retention time of 14.61 min). Submitters report observation of 6% of uncyclized diallyl pimelate and 2% of unidentified byproduct, which does not significantly affect the subsequent step. Out of this mixture analytically pure material may be obtained by flash chromatography on silica gel using a gradient of 1.5 → 4% diethyl ether in hexanes as eluent. GC response factors between 1-methyl-2-oxo-cyclohexanecarboxylic acid 2-propenyl ester and diallyl pimelate were determined with purified products to confirm these ratios, however assuming a 1:1 response factor gave the same ratios. The product showed the following characterization data: ^{1}H NMR (400

MHz, $CDCl_3$) δ: 1.30 (s, 3 H), 1.43–1.50 (m, 1 H), 1.59–1.78 (m, 3 H), 1.98–2.05 (m, 1 H), 2.42–2.54 (m, 3 H), 4.58–4.66 (m, 2 H), 5.24 (dd, *J* = 10.4, 0.8 Hz, 1 H), 5.31 (dd, *J* = 17.2, 1.4 Hz, 1 H), 5.83–5.93 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 21.4, 22.7, 27.6, 38.3, 40.8, 57.3, 65.9, 119.0, 131.6, 172.9, 208.2; IR (neat film, NaCl) 3442, 3082, 2939, 2866, 1719, 1648, 1452, 1377, 1336, 1301, 1259, 1212, 1160, 1121, 1084, 1062, 1038, 977, 936, 854, 816, 767, 668, 599 cm^{-1}; MS (EI, 70 eV) *m/z* (%) 196 (26, $[M]^+$), 168 (18), 139 (12), 138 (23), 137 (26), 127 (44), 111 (27), 110 (14), 109 (48), 83 (30), 82 (23), 81 (100), 69 (34), 67 (16), 55 (56), 43 (22), 41 (85), 39 (24); HRMS (EI) *m/z* calc'd for $C_{11}H_{16}O_3$ $[M]^+$: 196.1099, found 196.1096; TLC (Hex/EtOAc = 4:1) R_f = 0.56. Anal calcd for $C_{11}H_{16}O_3$: C 67.32, H 8.22, found C 67.17, H 8.15.

9. The substrate concentration (0.2 M) described herein yields product of slightly lower enantiomeric excess (about 1% lower) than the previously reported, optimized conditions (0.033 M in substrate). For smaller scale where overall quantity of solvent is less important, the lower substrate concentration is recommended.

10. The complexation time prior to adding substrate is important to the overall reaction. Shorter or longer complexation times led to lower product yield and incomplete substrate conversion.

11. Submitters reported 26 h reaction time.

12. Although the reaction produces an equivalent of carbon dioxide, the evolution of this byproduct is not visually apparent during the reaction. The reaction is readily evaluated by TLC analysis using 10% diethyl ether in pentane as eluent with $KMnO_4$ staining (submitters used *p*-anisaldehyde staining): R_f dibenzylideneacetone = 0.24 (also UV active), R_f β-ketoester = 0.33, R_f product = 0.46.

13. Care should be taken to ensure that the moderately volatile product is not lost during concentration of the filtrate. However, if a substantial amount of solvent remains, distillation of the product does not occur smoothly. At 150 torr and 40 °C, tetrahydrofuran and diethyl ether are easily removed and product is not lost.

14. The distilled material showed the following analytical data: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.06 (s, 3 H), 1.54–1.61 (m, 1 H), 1.65–1.90 (m, 5 H), 2.23 (apparent ddt, J = 13.9, 7.3, 0.9 Hz, 1 H), 2.33–2.40 (m, 3 H), 5.01–5.06 (m, 2 H), 5.69 (apparent ddt, J = 16.6, 11.1, 7.4 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 21.2, 22.8, 27.5, 38.7, 38.9, 42.1, 48.6, 118.0, 133.9, 215.5; IR (neat film, NaCl) 3393, 3076, 2933, 2864, 1706, 1451, 1124, 995, 913 cm^{-1}; MS (EI, 70 eV) *m/z* (%) 152 (31, $[M]^+$), 137 (36), 123 (29), 109 (60), 108 (27), 95 (33), 94 (21), 93 (69), 83 (49), 82 (16), 81 (31), 79 (21), 69 (14), 68 (17), 67 (66), 55 (100), 53 (13), 41 (50), 39 (25); HRMS (EI) *m/z* calc'd for $C_{10}H_{16}O$ $[M]^+$: 152.1201, found 152.1204; TLC (Pentane/Et_2O = 9:1) R_f = 0.46. Anal calcd for $C_{10}H_{16}O$: C 78.90, H 10.59, found C 78.86, H 10.48; optical rotation following enrichment (Part C): $[\alpha]_D^{21.0}$ –47.0 (*c* 2.30, dichloromethane, 98% ee).

15. GC analyses were performed with a Fisons Instruments HRGC Mega2 series equipped with a Chiraldex G-TA column (30.0 m x 0.25 mm) and a flame ionization detector. The assay conditions for 2-allyl-2-methylcyclohexanone are 100 °C isothermal, 60 kPa H_2 carrier gas flow, retention times: major (*S*) enantiomer = 14.15 min, minor (*R*) enantiomer = 17.09 min. The absolute configuration was established by X-ray crystallographic analysis of a semicarbazone derivative bearing a substituent with known absolute configuration.[5]

16. Column chromatography: 5 cm diameter x 10 cm height, eluting with 10% diethyl ether in pentane, 100 mL forerun, collecting 30 mL fractions. Product appeared in fractions 9–20. See Note 12 for TLC conditions. For smaller scale preparations, it is often convenient to perform chromatography directly rather than distilling the product.

17. In the reaction that gave 95% yield after distillation, TLC (see Note 12) of the distillation residue showed only traces of product. Therefore no flash chromatography was performed.

18. Submitters reported 76% yield after distillation and an additional 11% from flash chromatography for an overall yield of 87%.

19. Semicarbazone formation begins before the addition of ketone is complete, although conversion at room temperature is sluggish.

20. To ensure an accurate ee value, the powder was mixed thoroughly prior to measurement. The enantiomeric excess was determined by suspending a small amount of semicarbazone (approximately 10 mg) in a biphasic mixture of diethyl ether (1 mL) and 2 N aqueous hydrochloric acid (1 mL) at ambient temperature. After 30 min of stirring, all of the solids had dissolved and the organic layer was separated, dried briefly over anhydrous magnesium sulfate, filtered through cotton, and the filtrate concentrated by rotary evaporation. The residue was then dissolved in *tert*-butyl methyl ether and analyzed by GC (see Note 15 for separation conditions). The semicarbazone was homogeneous according to the proton and carbon NMR spectra, and appears to be a single geometric isomer. However a correct elemental analysis could not be achieved. The following properties were observed: mp 190–191 °C (toluene, 98% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.09 (s, 3 H), 1.41–1.48 (m, 1 H), 1.53–1.71 (m, 5 H), 2.14–2.25

(m, 2 H), 2.32–2.39 (m, 2 H), 5.00 (apparent d, J = 3.5 Hz, 1 H), 5.03 (s, 1 H), 5.68–5.9 (m, 1 H), 8.29 (s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 21.2, 22.9, 24.7, 26.1, 38.7, 41.6, 43.1, 117.3, 134.9, 157.3, 158.7; IR (neat film, NaCl) 3465, 3243, 3198, 3074, 2967, 2860, 1695, 1665, 1567, 1477, 1374, 1111, 1078, 991, 909 cm^{-1}; MS (EI, 70 eV) *m/z* (%) 209 (35, $[M]^+$), 194 (44), 168 (15), 165 (100), 151 (33), 150 (70), 149 (23), 148 (10), 135 (48), 134 (28), 125 (95), 108 (36), 107 (15), 98 (35), 96 (21), 95 (18), 93 (33), 91 (18), 82 (12), 81 (63), 80 (14), 79 (30), 77 (12), 67 (42), 55 (30), 53 (17), 44 (11), 41 (48), 39 (14); HRMS (CI, CH_4) *m/z* calc'd for $C_{11}H_{20}N_3O$ $[M + H]^+$: 210.1606, found 210.1599; $[\alpha]_D^{21.0}$ –50.5 (*c* 1.91, methanol, 98% ee).

21. At the reported concentration, the hot toluene solution is not saturated. The additional solvent helps maintain efficient stirring as the crystallization progresses and the viscosity of the mixture increases. The additional solvent does not significantly affect the efficiency of product recovery.

22. Stirring during the crystallization process is very important to the efficiency of the ee improvement. For example, two separate 300 mg portions of semicarbazone with 89% ee were recrystallized from hot toluene (about 3 mL) with and without stirring. Although product recovery was comparable for either procedure (81% and 80%, respectively), the unstirred crystallization provided semicarbazone of 93% ee while the stirred crystallization provided semicarbazone of 96% ee. Either procedure yields the product as very fine needles.

23. Concentration of the filtrate by rotary evaporation provided an additional 1.24–1.32 g (10–11% recovery) of semicarbazone. GC analysis of the corresponding ketone found 20–26% ee for this material (see Note 20).

24. Using the GC method described in Note 3, 2-allyl-2-methylcyclohexanone has a retention time of 11.43 min.

A7.3 DISCUSSION

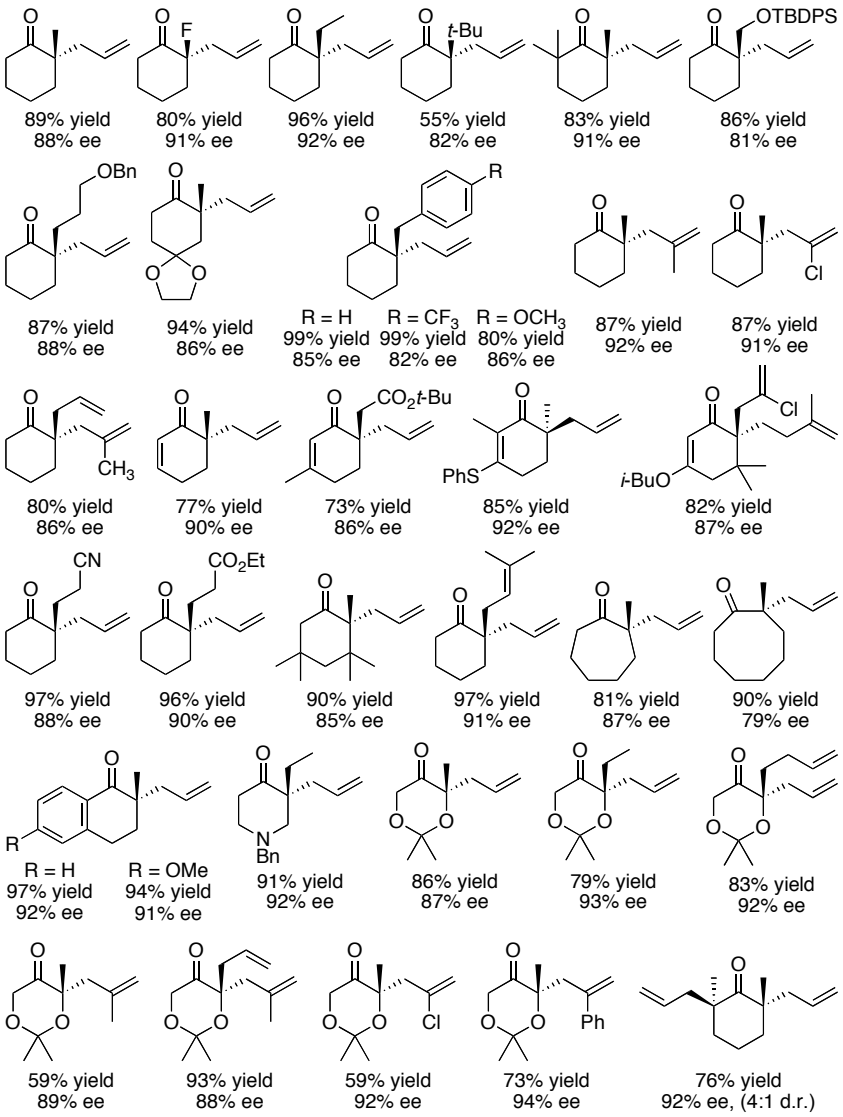
The Dieckmann cyclization protocol employed here is a modification of a similar procedures developed by Tsuji and coworkers[6] and Fuchs and coworkers.[7] This improved procedure allows preparation of racemic allyl β-keto ester substrates in two steps with a single purification. Importantly, the single-pot cyclization/alkylation is an improvement over our previously reported method that required solvent exchange.[8] The Dieckmann protocol is useful for the preparation of a number of substituted allyl β-keto esters by varying the electrophile. Possible substituents include alkyl, benzyl, substituted benzyl, and alkenyl.[9] Other more sensitive substituents may be introduced by quenching the intermediate β-keto ester enolate with aqueous acid and then alkylating the resulting β-keto ester under more mild conditions (e.g., K_2CO_3, acetone, 50 °C).[8] In this manner, the β-keto ester enolate may undergo conjugate addition, aldol, or fluorination reactions with appropriate electrophilic components.[8] The β-keto ester substrates are useful not only for enantioselective decarboxylative allylation, but also for enantioselective decarboxylative protonation reactions generating α-tertiary cycloalkanones.[9] Alternative methods for synthesis of β-keto ester substrates include acylation of ketones with diallyl carbonates,[8] allyl cyanoformates,[8,10] allyl chloroformates,[11] or allyl 1*H*-imidazole-1-carboxylates.[12]

The enantioselective decarboxylative allylation method from allyl β-keto esters,[8,13] based on non-enantioselective transformations pioneered by Tsuji and Saegusa,[14] represents a substantial advance in asymmetric allylation since prior methods[15] required that the putative prochiral enolate intermediate[16] be stabilized by an electron-withdrawing group (e.g., esters or aryl groups) or contain only a single acidic site.[17,18] To highlight the previous deficiency in the literature, 2-allyl-2-methylcyclohexanone had not been prepared in high enantiomeric excess prior to our work since few alternative synthetic methods are available.[19] Related enantioselective transformations for the conversion of allyl enol carbonates and silyl enol ethers to α-quaternary cycloalkanones, also based on earlier work by Tsuji,[20] have been developed by our group[5,21] and others.[22] However, β-keto ester substrates are often preferable due to the straightforward synthesis and ease of substrate handling. The procedure reported herein has been optimized for large-scale preparation and features lower catalyst loading and higher substrate concentration than our previously reported work. These changes have minimal impact on the efficiency and selectivity observed in the reaction. Improvements to purification include conditions for distillation of the product and an improved protocol for conversion to the corresponding semicarbazone derivative. Conditions for recrystallization of the semicarbazone derivative are also reported, and provide access to highly enantioenriched 2-allyl-2-methylcyclohexanone.

The scope of this transformation[8] and the related transformation of allyl enol carbonates and enol silanes[5,21] has been demonstrated to include alkyl, alkenyl, aryl, ethereal, siloxy, halogen,[23] ketone, ester, and nitrile substituents. Additionally, the ring may be appended, unsaturated, enlarged, or substituted with heteroatoms. The delivered

allyl group may be substituted at the internal position. Cascade allylation has also been performed to generate two quaternary stereocenters. Good levels of enantioselectivity are observed throughout these variations and products may be obtained in 55–99% yield and 80–94% ee (Figure A7.1).[5,8,21]

Figure A7.1 Ketones prepared via enantioselective decarboxylative allylation[5,8,21]



The non-enantioselective Tsuji allylation reaction has been used sparingly in total synthesis efforts.[24] Since the development of asymmetric variants, however,

enantioselective decarboxylative allylation has functioned as a key asymmetric step in the synthesis of the natural products (+)-dichroanone,[25] (+)-elatol,[26] (+)-laurencenone B,[26] (–)-cyanthiwigin F,[27] (+)-carissone,[28] and (+)-cassiol[29] as well as in an approach to the natural product zoanthenol[30] (Figure A7.2). Other useful transformations of the product (*S*)-2-allyl-2-methyl cyclohexanone include elaboration to various [6.5]- and [6.6]-fused bicycles and oxidation to a caprolactone derivative (Figure A7.3a).[5] Spirocyclic systems are accessible by employing Grubbs' olefin metathesis catalysts[31] with α,ω-dienes[17,21,26] (Figure A7.3b). Dioxanone products may be cleaved to access acyclic keto diols and α-hydroxy esters (Figure A7.3c).

Figure A7.2 Synthetic targets accessed via enantioselective decarboxylative allylation

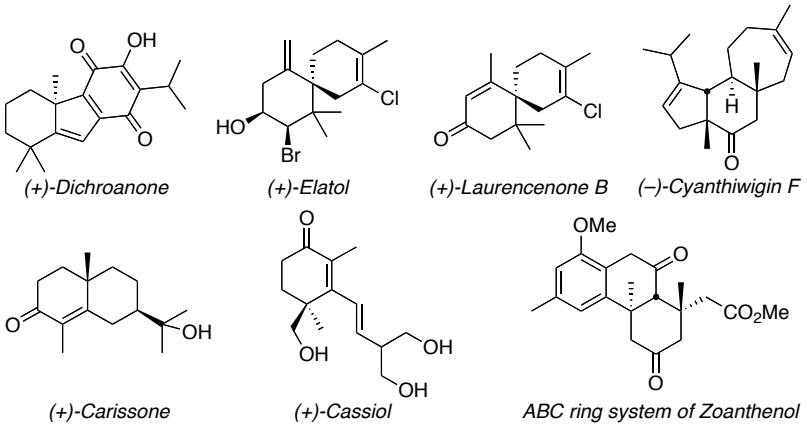
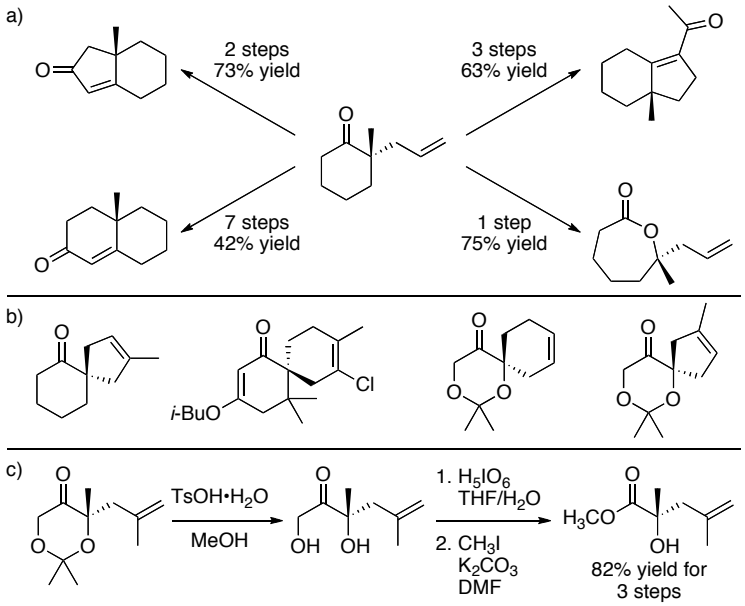


Figure A7.3 (a) Derivatives of 2-allyl-2-methylcyclohexanone.[6] (b) Spirocycles accessible via ring-closing metathesis.[18,22,27] (c) Cleavage of dioxanones to access acyclic products.[22]



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Notebook Cross-Reference

The following notebook cross-reference is included to facilitate access to the original data obtained for the compounds presented in this thesis. All notebooks and spectroscopic data are stored in the Stoltz group archives.

Compound	Notebook ID
98	DCBXXII_71
105	DCBXXII_51
106	DCBXXII_061
107	DCBXXIII_265
110	DCBXXII_MeSi
124	DCBXVI_241
125	DCBXVI_195
126	KTIII033
127	KTIII_021
128	KTI_261
129	RMM-CYPHOX
130	KTII_225
131	KTIII_023
132	KTIII_025
135	KTIII_223
136	DCBXIV_107
137	KTIII_221
138	DCBXVIII_299
139	KTIII_213
140	KTIII_215
141	KTIII_231
142	DCBXV_99
143	DCBXIV_165
145	DCBXIV_233
146	DCBXV_45
148	DCBXXII_201
149	DCBXXII_109
150	DCBXXIII_97
151	DCBXXII_133
153	DCBXXII_135
154	DCBXXII_229
155	DCBXXII_115
156	DCBXXII_105
157	DCBXXIII_51

Compound	Notebook ID
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159	DCBXVI_227
161	DCBXXII_079
162	DCBXXIII_49
163	DCBXXIII_287
164	DCBXXIII_297
165	DCBXXVIII_295
166	DCBXXIII_223
168	DCBXXIII_209
169	DCBXXIII_219
170	DCBXXIII_159
171	DCBXXVIII_301
172	DCBXXVIII_299
173	DCBXXVIII_303
182	DCBXV_259
185	DCBXXII_183
186	DCBXXIII_263
187	KTI_265
188	KTII_075
189	KTIII_191
190	DCBXV_283
191	DCBXVI_153
192	DCBXXIII_301
193	ECKI_61
194	DCBXXIII_251
196	DCBXV_285
197	DCBXXIII_259
209	DCBXXII_247
210	DCBXXII_123
211	DCBXXII_193
212	DCBXXII_91
213	DCBXXIII_93
214	DCBXXII_199
215	DCBXVII_047

Compound	Notebook ID
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222	DCBXXIII_273
223	DCBXXIII_073
224	DCBXXIII_81
225	DCBXXII_295
226	DCBXXIII_79
227	DCBXXIII_33
235	JTMVI-161B
237	JTMVI-151B
241	JTMVI-85C
242	AMH-I-159
244	DCBXXIV_101
248	JTMVII-35C
249	JTMVII-63B
250	JTMVII-39E
251	JTMVII-89B
252	JTMVII-37D
253	JTMVII-73B
254	DCBXXIV_297
255	JTMVII-57B
256	JTMVI-121D
257	JTMVI-177B
258	DCBXXIV_295
259	DCBXXV_59
260	AMH-I-225
261	AMH-I-229
262	DCBXXIV_151
263	AMH-XI-233
264	JTMVII-31C
265	DEW-III-281
266	JTMVII-81B
271	AMH-II-159
272	AMH-III-061-C2
274	AMH-V-075
275	AMH-V-073
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278	JTMVII-287B
279	AMHV-127
280	JTMVII-291B
281	AMHV-133

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309	JTMVI-99B
310	AMH-XI-227
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312	JTMVI-215B
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326	AMH-II-035
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328	JTMVII-273B
329	JTMVII-189B
330	JTMVII-245B
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332	JTMVII-275B
333	AMH-V-065A
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498	JTMIX-163B
629	JTMIX-105B
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643	JTMIX-107B
644	JTMIX-109C
646	JTMIX-209B
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739	CD-III-127
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Compound	Notebook ID
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762	CD-II-149
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767	CD-III-103

Subject Index

Cassiol,

320–322, 640, 650–651, 660, 849–856

Catalytic cycle,

55–57, 663, 734, 841

Cross-over,

333–334, 345, 348, 426, 661–663

Decarboxylation,

55, 315–316, 328–330, 343, 347, 592, 628, 635, 656, 677, 681, 685–686, 695, 703, 705, 724, 839

Decarboxylative,

25, 62, 74, 315–316, 318–324, 387, 585–587, 620, 635–636, 643, 647, 663, 668, 679, 686, 704, 714–715, 724, 840, 910, 912

Desymmetrization,

38, 834–835

Diastereomer,

14, 24, 26–28, 315, 323, 345, 628, 638, 643, 646, 658, 683, 686–687, 691–692,

Diastereoselective,

5, 15, 18, 20, 645, 649,

Deuterium labelling,

11, 420–426, 701, 723, 764–766, 780, 333–334

Dynamic kinetic resolution,

316, 829, 835–836

Enantioconvergent,

315–317, 344, 635, 640, 656, 715, 724, 829, 835–843, 908

Enolate,

21–25, 39–42, 55–56, 62–65, 312–314, 319, 325–333, 585–589, 618–621, 625–629, 635–638, 656–659, 662–664, 677–682, 684–686, 689–690, 694–697, 703–706, 715, 724, 838–840,

Kinetic resolution,

315, 635, 829–834

Mechanism,

11, 25, 21, 56, 65, 324–337, 585–590, 625, 631, 661–664, 679–680, 688, 694–696, 701, 705, 722–724, 732–734, 837–838, 842

Meso,

24, 638, 646, 686, 834

Olefin metathesis,

24, 59, 61, 647, 649, 660,

Oxidation,

59, 320, 632, 642–643, 649–650, 659, 680–681, 830–834, 836–837, 854

Oxidative addition,

12, 41, 55–56, 327–328, 585, 628, 635, 734

Pharmaceutical,

4, 8, 319, 642

Platencin,

908–913

Prochiral,

39–40, 312, 316–317, 324–328, 586, 589–590, 619, 678, 684–685, 828, 844

Quaternary stereocenters,

8, 15–16, 18, 21, 23, 26, 28–29, 38–40, 48, 52–54, 59–60, 312, 316, 322, 585–586, 618–622, 637–638, 644, 647, 660, 693, 714, 724, 839, 850, 909

Racemic,

13–14, 24, 51, 314–317, 635, 637, 640, 642, 645, 656, 680, 689, 693, 698, 715–716, 724–726, 828, 830–844, 909

Rate-determining,

328, 330, 415

Reduction,

3–4, 9, 24, 648, 686–688, 760, 831, 837, 854, 914,

Reductive elimination,

327, 337, 589, 723, 734

Retrosynthesis,

1, 12–13, 24, 850, 909–912

Stereoablation,

25, 317, 635, 693, 715, 828–844

Stereoisomer,

24–25, 322, 646, 677, 691

Stereomutation,

316–317, 343, 835–836

Stoichiometric,

4, 56, 585, 631, 655, 683–684, 687–689, 696, 698, 834, 840, 842, 854

Total synthesis,

2, 8, 13, 16, 26, 28, 322, 638, 641, 644, 646–651, 839, 849–856,

Transition state,

22, 315, 327, 329, 346, 589–590, 593, 679, 685, 690

X-ray,

54, 58, 134, 327, 328, 337, 587, 646, 658, 679, 913–914, 943

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About the Author

Justin Thomas Mohr was born in Anchorage, Alaska in 1980. He was educated through the Anchorage public school system, first at Inlet View Elementary School and later at Romig Junior High School and West Anchorage High School. His interest in the physical sciences was piqued early in his education. The author participated in the band and theater programs in addition to competing with the school's riflery and soccer teams. The author graduated from the Anchorage School District *summa cum laude* in 1999.

In 1999, the author matriculated at Dartmouth College in Hanover. NH. The author focused his scientific interests on chemistry largely due to the guidance of Professor Robert S. Cantor. The author began performing laboratory research in 2001 under the supervision of Professor Gordon W. Gribble. These studies, in collaboration with Professor Cantor, sought to develop synthetic strategies for the synthesis of long-chain *n*-polyols and their use as anesthetics. The author was the recipient of a Beckman Fellowship from 2002–2003 to fund this research. While at Dartmouth, the author was also involved in the management of the student-run commercial radio stations WFRD and WDCR. In 2003, the author received his A. B. degree *cum laude* (with honors in chemistry) with a major in chemistry and a minor in theater.

In July of 2003, the author joined Professor Brian M. Stoltz' group at the California Institute of Technology. The author explored the utility of chiral palladium enolates for enantioselective reactions pertinent to target-directed synthesis. His time at Caltech was highlighted by the birth of his daughter, Marie Elise, in 2008. The author defended his PhD thesis in June of 2009 and will pursue postdoctoral research with Professor Gregory C. Fu at the Massachusetts Institute of Technology.