

TOTAL SYNTHESIS OF HYPERSAMPSONE M AND STUDIES OF RELATED
POLYCYCLIC POLYPRENYLATED ACYLPHLOROGLUCINOL SYSTEMS

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To my partner, parents, and brother

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ABSTRACT

Research in the Stoltz group is primarily focused on the total synthesis of complex, bioactive natural products and on the development of reaction methodologies to enable these synthetic endeavors. This thesis focuses on the homoadamantane polycyclic polyprenylated acylphloroglucinol (PPAP) class of natural products, our efforts toward their synthesis, and discoveries made along the way. Chapter 1 describes the completed synthesis of hypersampson M, while Chapter 2 describes ongoing efforts toward wilsonglucinol G and hypersampson A. Appendix 5 presents the culmination of optimization studies and unsuccessful routes toward these natural products. Chapter 3 describes selective fragmentations of α -bromocaranones, reactions that were tailored to the synthesis of PPAPs. Chapter 4 discloses the synthesis and characterization of an unexpected, caged side product isolated during an unsuccessful route to the homoadamantane PPAPs. Chapter 5 discusses the development and scope of the key cyclopentene annulation methodology that enabled the installation of the challenging, hindered 5-membered ring on the homoadamantane PPAPs.

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TABLE OF CONTENTS

Dedication	iii
Acknowledgements	iv
Abstract	x
Published Content and Contributions	xi
Table of Contents	xii
List of Figures	xvi
List of Schemes	xxv
List of Tables	xxviii
List of Abbreviations	xxx
 CHAPTER 1	 1
<i>Total Synthesis of Hypersampson M</i>	
1.1 Introduction	1
1.2 Retrosynthetic Analysis	2
1.3 Unsuccessful Chiral Pool Route	3
1.4 Total Synthesis of Hypersampson M	4
1.5 Conclusion	10
1.6 Experimental Section	10
1.6.1 Materials and Methods	10
1.6.2 Experimental Procedures	12
1.7 References and Notes	37
 APPENDIX 1	 48
<i>Synthetic Summary for Chapter 1</i>	
 APPENDIX 2	 50
<i>Spectra Relevant to Chapter 1</i>	
 CHAPTER 2	 89
<i>Toward the Total Synthesis of Hypersonin A and Wilsonglucinol G</i>	
2.1 Introduction	89
2.2 Retrosynthetic Analysis	91
2.3 Development of a 3-component Cyclopentene Annulation	92

2.4	Current Progress Toward Wilsonglucinol G.....	94
2.5	Conclusion.....	98
2.6	Experimental Section.....	98
2.6.1	Materials and Methods.....	98
2.6.2	Experimental Procedures.....	100
2.7	References and Notes.....	122
APPENDIX 3		126
<i>Synthetic Summary for Chapter 2</i>		
APPENDIX 4		128
<i>Spectra Relevant to Chapter 2</i>		
APPENDIX 5		164
<i>Early Strategies Toward the Synthesis of Homoadamantane PPAPs</i>		
A5.1	Introduction	164
A5.2	Chiral Pool Efforts Starting from Limonene	164
A5.3	Chiral Pool Efforts Starting from (+)-Carene	168
A5.4	Eastern Ring-First Strategy	173
A5.5	Cyclohexenone Strategy: Hydroindene Formation.....	176
A5.6	Cyclohexenone Strategy: Hydroindene Ring Expansion.....	179
A5.7	Cyclohexenone Strategy: Forming the C5–C9 Bond.....	183
A5.8	Cyclohexenone Strategy: Opening the Caged Lactone.....	186
A5.9	Experimental Section.....	192
A5.9.1	Materials and Methods.....	192
A5.9.2	Experimental Procedures.....	193
A5.10	References and Notes	233
CHAPTER 3		238
<i>Some Unusual Transformations of a Highly Reactive α-Bromocaranone</i>		
3.1	Introduction	238
3.2	Cationic Fragmentations of the Bromocaranone	240
3.3	Radical Fragmentations of the Bromocaranone.....	241
3.4	Conclusion.....	244
3.5	Experimental Section.....	244
3.5.1	Materials and Methods.....	244

3.5.2	Experimental Procedures.....	246
3.5.3	Computational Details	258
3.6	References and Notes.....	260
APPENDIX 6		264
<i>Spectra Relevant to Chapter 3</i>		
CHAPTER 4		288
<i>On the Unexpected Formation of [2.2.1]- and [2.1.1]Homotriblattanes</i>		
4.1	Introduction	288
4.2	Synthesis of the Homotriblattanes	289
4.3	Conclusion.....	293
4.4	Experimental Section.....	293
4.4.1	Materials and Methods.....	293
4.4.2	Experimental Procedures.....	295
4.4.3	Computational Details	307
4.5	References and Notes.....	308
APPENDIX 7		312
<i>Spectra Relevant to Chapter 4</i>		
APPENDIX 8		349
<i>X-Ray Crystallography Reports Relevant to Chapter 4</i>		
A8.1	General Experimental Information.....	350
A8.2	X-Ray Structure Analysis of 236	351
A8.3	X-Ray Structure Analysis of 255	365
A8.4	References and Notes.....	375
CHAPTER 5		376
<i>A Modular Cyclopentene Annulation</i>		
5.1	Introduction	377
5.2	Reaction Optimization	378
5.3	Scope and Limitations	379
5.4	Product Derivatization	382
5.5	Conclusion.....	383
5.6	Experimental Section.....	384

5.6.1	Materials and Methods.....	384
5.6.2	Experimental Procedures.....	386
5.7	References and Notes.....	410
APPENDIX 9		413
<i>Spectra Relevant to Chapter 5</i>		
APPENDIX 10		474
<i>Notebook Cross-Reference for New Compounds</i>		
	About the Author.....	480

LIST OF FIGURES

CHAPTER 1

Total Synthesis of Hypersampsonone M

Figure 1.1.1.	Hypersampsonone M and representative PPAP classes.	2
Figure 1.6.3.1.	Synthetic and natural ^1H NMR of Hypersampsonone M (1), CDCl_3	35
Figure 1.6.3.2.	Synthetic and natural ^{13}C NMR of Hypersampsonone M (1), CDCl_3	35

APPENDIX 2

Spectra Relevant to Chapter 1

Figure A2.1.	^1H NMR (400 MHz, C_6D_6) of compound 26	51
Figure A2.2.	Infrared spectrum (Thin Film, NaCl) of compound 26	52
Figure A2.3.	^{13}C NMR (100 MHz, C_6D_6) of compound 26	52
Figure A2.4.	^1H NMR (500 MHz, CDCl_3) of compound 7	53
Figure A2.5.	^1H NMR (400 MHz, C_6D_6) of compound 10	54
Figure A2.6.	Infrared spectrum (Thin Film, NaCl) of compound 10	55
Figure A2.7.	^{13}C NMR (100 MHz, C_6D_6) of compound 10	55
Figure A2.8.	COSY NMR (400 MHz, C_6D_6) of compound 10	56
Figure A2.9.	HSQC NMR (400 MHz, C_6D_6) of compound 10	57
Figure A2.10.	NOESY NMR (400 MHz, C_6D_6) of compound 10	58
Figure A2.11.	^1H NMR (400 MHz, C_6D_6) of compound 12	59
Figure A2.12.	Infrared spectrum (Thin Film, NaCl) of compound 12	60
Figure A2.13.	^{13}C NMR (100 MHz, C_6D_6) of compound 12	60
Figure A2.14.	^1H NMR (400 MHz, CDCl_3) of compound 28	61
Figure A2.15.	Infrared spectrum (Thin Film, NaCl) of compound 28	62
Figure A2.16.	^{13}C NMR (100 MHz, CDCl_3) of compound 28	62
Figure A2.17.	^1H NMR (400 MHz, CDCl_3) of compound 13	63
Figure A2.18.	^1H NMR (400 MHz, CDCl_3) of compound 14	64
Figure A2.19.	Infrared spectrum (Thin Film, NaCl) of compound 14	65
Figure A2.20.	^{13}C NMR (100 MHz, CDCl_3) of compound 14	65
Figure A2.21.	^1H NMR (400 MHz, C_6D_6) of compound 29	66
Figure A2.22.	Infrared spectrum (Thin Film, NaCl) of compound 29	67
Figure A2.23.	^{13}C NMR (100 MHz, C_6D_6) of compound 29	67

Figure A2.24.	¹ H NMR (400 MHz, C ₆ D ₆) of compound 16	68
Figure A2.25.	Infrared spectrum (Thin Film, NaCl) of compound 16	69
Figure A2.26.	¹³ C NMR (100 MHz, C ₆ D ₆) of compound 16	69
Figure A2.27.	¹ H NMR (400 MHz, C ₆ D ₆) of compound 17	70
Figure A2.28.	¹ H NMR (400 MHz, C ₆ D ₆) of compound 18	71
Figure A2.29.	Infrared spectrum (Thin Film, NaCl) of compound 18	72
Figure A2.30.	¹³ C NMR (100 MHz, C ₆ D ₆) of compound 18	72
Figure A2.31.	¹ H NMR (400 MHz, C ₆ D ₆) of compound 30	73
Figure A2.32.	Infrared spectrum (Thin Film, NaCl) of compound 30	74
Figure A2.33.	¹³ C NMR (100 MHz, C ₆ D ₆) of compound 30	74
Figure A2.34.	¹ H NMR (400 MHz, C ₆ D ₆) of compound 19	75
Figure A2.35.	Infrared spectrum (Thin Film, NaCl) of compound 19	76
Figure A2.36.	¹³ C NMR (100 MHz, C ₆ D ₆) of compound 19	76
Figure A2.37.	¹ H NMR (400 MHz, C ₆ D ₆) of compound 21	77
Figure A2.38.	Infrared spectrum (Thin Film, NaCl) of compound 21	78
Figure A2.39.	¹³ C NMR (100 MHz, C ₆ D ₆) of compound 21	78
Figure A2.40.	¹ H NMR (400 MHz, C ₆ D ₆) of compound 25	79
Figure A2.41.	Infrared spectrum (Thin Film, NaCl) of compound 25	80
Figure A2.42.	¹³ C NMR (100 MHz, C ₆ D ₆) of compound 25	80
Figure A2.43.	¹ H NMR (400 MHz, C ₆ D ₆) of compound 31	81
Figure A2.44.	Infrared spectrum (Thin Film, NaCl) of compound 31	82
Figure A2.45.	¹³ C NMR (100 MHz, C ₆ D ₆) of compound 31	82
Figure A2.46.	¹ H NMR (400 MHz, C ₆ D ₆) of compound 22	83
Figure A2.47.	Infrared spectrum (Thin Film, NaCl) of compound 22	84
Figure A2.48.	¹³ C NMR (100 MHz, C ₆ D ₆) of compound 22	84
Figure A2.49.	¹ H NMR (400 MHz, C ₆ D ₆) of compound 2	85
Figure A2.50.	Infrared spectrum (Thin Film, NaCl) of compound 2	86
Figure A2.51.	¹³ C NMR (100 MHz, C ₆ D ₆) of compound 2	86
Figure A2.52.	¹ H NMR (400 MHz, CDCl ₃) of compound 1	87
Figure A2.53.	Infrared spectrum (Thin Film, NaCl) of compound 1	88
Figure A2.54.	¹³ C NMR (100 MHz, CDCl ₃) of compound 1	88

CHAPTER 2

Toward the Total Synthesis of Hypersonin A and Wilsonglucinol G

Figure 2.1.1.	Hypersonin A, wilsonglucinol G and representative PPAP classes	90
---------------	--	----

APPENDIX 4

Spectra Relevant to Chapter 2

Figure A4.1.	^1H NMR (600 MHz, CDCl_3) of compound 62	129
Figure A4.2.	Infrared spectrum (Thin Film, NaCl) of compound 62	130
Figure A4.3.	^{13}C NMR (100 MHz, CDCl_3) of compound 62	130
Figure A4.4.	^1H NMR (400 MHz, C_6D_6) of compound 64	131
Figure A4.5.	Infrared spectrum (Thin Film, NaCl) of compound 64	132
Figure A4.6.	^{13}C NMR (100 MHz, C_6D_6) of compound 64	132
Figure A4.7.	^1H NMR (400 MHz, C_6D_6) of compound 51	133
Figure A4.8.	Infrared spectrum (Thin Film, NaCl) of compound 51	134
Figure A4.9.	^{13}C NMR (100 MHz, C_6D_6) of compound 51	134
Figure A4.10.	^1H NMR (400 MHz, C_6D_6) of compound 65	135
Figure A4.11.	Infrared spectrum (Thin Film, NaCl) of compound 65	136
Figure A4.12.	^{13}C NMR (100 MHz, C_6D_6) of compound 65	136
Figure A4.13.	^1H NMR (400 MHz, C_6D_6) of compound 66	137
Figure A4.14.	Infrared spectrum (Thin Film, NaCl) of compound 66	138
Figure A4.15.	^{13}C NMR (100 MHz, C_6D_6) of compound 66	138
Figure A4.16.	^1H NMR (400 MHz, C_6D_6) of compound 52	139
Figure A4.17.	Infrared spectrum (Thin Film, NaCl) of compound 52	140
Figure A4.18.	^{13}C NMR (100 MHz, C_6D_6) of compound 52	140
Figure A4.19.	^1H NMR (400 MHz, C_6D_6) of compound 54	141
Figure A4.20.	Infrared spectrum (Thin Film, NaCl) of compound 54	142
Figure A4.21.	^{13}C NMR (100 MHz, C_6D_6) of compound 54	142
Figure A4.22.	^1H NMR (400 MHz, C_6D_6) of compound 56	143
Figure A4.23.	Infrared spectrum (Thin Film, NaCl) of compound 56	144
Figure A4.24.	^{13}C NMR (100 MHz, C_6D_6) of compound 56	144
Figure A4.25.	^1H NMR (400 MHz, C_6D_6) of compound 57	145
Figure A4.26.	Infrared spectrum (Thin Film, NaCl) of compound 57	146
Figure A4.27.	^{13}C NMR (100 MHz, C_6D_6) of compound 57	146
Figure A4.28.	^1H NMR (400 MHz, C_6D_6) of compound 67	147
Figure A4.29.	Infrared spectrum (Thin Film, NaCl) of compound 67	148
Figure A4.30.	^{13}C NMR (100 MHz, C_6D_6) of compound 67	148
Figure A4.31.	^1H NMR (400 MHz, C_6D_6) of compound 58	149

Figure A4.32.	Infrared spectrum (Thin Film, NaCl) of compound 58	150
Figure A4.33.	¹³ C NMR (100 MHz, C ₆ D ₆) of compound 58	150
Figure A4.34.	¹ H NMR (400 MHz, C ₆ D ₆) of compound 68	151
Figure A4.35.	Infrared spectrum (Thin Film, NaCl) of compound 68	152
Figure A4.36.	¹³ C NMR (100 MHz, C ₆ D ₆) of compound 68	152
Figure A4.37.	¹ H NMR (400 MHz, C ₆ D ₆) of compound 59	153
Figure A4.38.	¹ H NMR (400 MHz, C ₆ D ₆) of compound 60	154
Figure A4.39.	Infrared spectrum (Thin Film, NaCl) of compound 60	155
Figure A4.40.	¹³ C NMR (100 MHz, C ₆ D ₆) of compound 60	155
Figure A4.41.	¹ H NMR (400 MHz, C ₆ D ₆) of compound 69	156
Figure A4.42.	Infrared spectrum (Thin Film, NaCl) of compound 69	157
Figure A4.43.	¹³ C NMR (100 MHz, C ₆ D ₆) of compound 69	157
Figure A4.44.	¹ H NMR (400 MHz, C ₆ D ₆) of compound 61	158
Figure A4.45.	Infrared spectrum (Thin Film, NaCl) of compound 61	159
Figure A4.46.	¹³ C NMR (100 MHz, C ₆ D ₆) of compound 61	159
Figure A4.47.	¹ H NMR (400 MHz, C ₆ D ₆) of compound 38	160
Figure A4.48.	Infrared spectrum (Thin Film, NaCl) of compound 38	161
Figure A4.49.	¹³ C NMR (100 MHz, C ₆ D ₆) of compound 38	161
Figure A4.50.	¹ H NMR (400 MHz, C ₆ D ₆) of compound 37	162
Figure A4.51.	Infrared spectrum (Thin Film, NaCl) of compound 37	163
Figure A4.52.	¹³ C NMR (100 MHz, C ₆ D ₆) of compound 37	163

CHAPTER 3

Some Unusual Transformations of a Highly Reactive α -Bromocaranone

Figure 3.5.3.1.	Minimum free energy pathway from 226 toward 224 and 235	259
-----------------	--	-----

APPENDIX 6

Spectra Relevant to Chapter 3

Figure A6.1.	¹ H NMR (400 MHz, CDCl ₃) of compound 223	265
Figure A6.2.	¹ H NMR (400 MHz, CDCl ₃) of compound 204	266
Figure A6.3.	¹ H NMR (400 MHz, CDCl ₃) of compound 207	267
Figure A6.4.	Infrared spectrum (Thin Film, NaCl) of compound 207	268
Figure A6.5.	¹³ C NMR (100 MHz, CDCl ₃) of compound 207	268
Figure A6.6.	¹ H NMR (400 MHz, CDCl ₃) of compound 208	269
Figure A6.7.	¹ H NMR (400 MHz, CDCl ₃) of compound 210	270

Figure A6.8.	Infrared spectrum (Thin Film, NaCl) of compound 210	271
Figure A6.9.	¹³ C NMR (100 MHz, CDCl ₃) of compound 210	271
Figure A6.10.	¹ H NMR (400 MHz, CDCl ₃) of compound 205	272
Figure A6.11.	Infrared spectrum (Thin Film, NaCl) of compound 205	273
Figure A6.12.	¹³ C NMR (100 MHz, CDCl ₃) of compound 205	273
Figure A6.13.	¹ H NMR (400 MHz, CDCl ₃) of compound 211	274
Figure A6.14.	Infrared spectrum (Thin Film, NaCl) of compound 211	275
Figure A6.15.	¹³ C NMR (100 MHz, CDCl ₃) of compound 211	275
Figure A6.16.	¹ H NMR (400 MHz, CDCl ₃) of compound 212	276
Figure A6.17.	Infrared spectrum (Thin Film, NaCl) of compound 212	277
Figure A6.18.	¹³ C NMR (100 MHz, CDCl ₃) of compound 212	277
Figure A6.19.	¹ H NMR (400 MHz, CDCl ₃) of compound 213	278
Figure A6.20.	Infrared spectrum (Thin Film, NaCl) of compound 213	279
Figure A6.21.	¹³ C NMR (100 MHz, CDCl ₃) of compound 213	279
Figure A6.22.	¹ H NMR (400 MHz, CDCl ₃) of compound 214	280
Figure A6.23.	Infrared spectrum (Thin Film, NaCl) of compound 214	281
Figure A6.24.	¹³ C NMR (100 MHz, CDCl ₃) of compound 214	281
Figure A6.25.	¹ H NMR (400 MHz, CDCl ₃) of compound 215	282
Figure A6.26.	Infrared spectrum (Thin Film, NaCl) of compound 215	283
Figure A6.27.	¹³ C NMR (100 MHz, CDCl ₃) of compound 215	283
Figure A6.28.	¹ H NMR (400 MHz, CDCl ₃) of compound 220	284
Figure A6.29.	Infrared spectrum (Thin Film, NaCl) of compound 220	285
Figure A6.30.	¹³ C NMR (100 MHz, CDCl ₃) of compound 220	285
Figure A6.31.	¹ H NMR (400 MHz, CDCl ₃) of compound 221	286
Figure A6.32.	Infrared spectrum (Thin Film, NaCl) of compound 221	287
Figure A6.33.	¹³ C NMR (100 MHz, CDCl ₃) of compound 221	287

APPENDIX 7

Spectra Relevant to Chapter 4

Figure A7.1.	¹ H NMR (400 MHz, CDCl ₃) of compound 130	313
Figure A7.2.	Infrared spectrum (Thin Film, NaCl) of compound 130	314
Figure A7.3.	¹³ C NMR (100 MHz, CDCl ₃) of compound 130	314
Figure A7.4.	¹ H NMR (400 MHz, CDCl ₃) of compound 131	315
Figure A7.5.	COSY NMR (400 MHz, CDCl ₃) of compound 131	316
Figure A7.6.	NOESY NMR (400 MHz, CDCl ₃) of compound 131	317

Figure A7.7.	Infrared spectrum (Thin Film, NaCl) of compound 131	318
Figure A7.8.	¹³ C NMR (100 MHz, CDCl ₃) of compound 131	318
Figure A7.9.	¹ H NMR (400 MHz, CDCl ₃) of compound 245	319
Figure A7.10.	COSY NMR (400 MHz, CDCl ₃) of compound 245	320
Figure A7.11.	HSQC NMR (400 MHz, CDCl ₃) of compound 245	321
Figure A7.12.	Infrared spectrum (Thin Film, NaCl) of compound 245	322
Figure A7.13.	¹³ C NMR (100 MHz, CDCl ₃) of compound 245	322
Figure A7.14.	¹ H NMR (400 MHz, CDCl ₃) of compound 246	323
Figure A7.15.	Infrared spectrum (Thin Film, NaCl) of compound 246	324
Figure A7.16.	¹³ C NMR (100 MHz, CDCl ₃) of compound 246	324
Figure A7.17.	¹ H NMR (400 MHz, CDCl ₃) of compound 133	325
Figure A7.18.	Infrared spectrum (Thin Film, NaCl) of compound 133	326
Figure A7.19.	¹³ C NMR (100 MHz, CDCl ₃) of compound 133	326
Figure A7.20.	¹ H NMR (400 MHz, CDCl ₃) of compound 236	327
Figure A7.21.	Infrared spectrum (Thin Film, NaCl) of compound 236	328
Figure A7.22.	¹³ C NMR (100 MHz, CDCl ₃) of compound 236	328
Figure A7.23.	¹ H NMR (400 MHz, CDCl ₃) of compound 242	329
Figure A7.24.	Infrared spectrum (Thin Film, NaCl) of compound 242	330
Figure A7.25.	¹³ C NMR (100 MHz, CDCl ₃) of compound 242	330
Figure A7.26.	¹ H NMR (400 MHz, CDCl ₃) of compound 244	331
Figure A7.27.	COSY NMR (400 MHz, CDCl ₃) of compound 244	332
Figure A7.28.	HSQC NMR (400 MHz, CDCl ₃) of compound 244	333
Figure A7.29.	NOESY NMR (400 MHz, CDCl ₃) of compound 244	334
Figure A7.30.	Infrared spectrum (Thin Film, NaCl) of compound 244	335
Figure A7.31.	¹³ C NMR (100 MHz, CDCl ₃) of compound 244	335
Figure A7.32.	¹ H NMR (400 MHz, CDCl ₃) of compound 255	336
Figure A7.33.	COSY NMR (400 MHz, CDCl ₃) of compound 255	337
Figure A7.34.	HSQC NMR (400 MHz, CDCl ₃) of compound 255	338
Figure A7.35.	Infrared spectrum (Thin Film, NaCl) of compound 255	339
Figure A7.36.	¹³ C NMR (100 MHz, CDCl ₃) of compound 255	339
Figure A7.37.	¹ H NMR (400 MHz, CDCl ₃) of compound 256	340
Figure A7.38.	Infrared spectrum (Thin Film, NaCl) of compound 256	341
Figure A7.39.	¹³ C NMR (100 MHz, CDCl ₃) of compound 256	341
Figure A7.40.	¹ H NMR (400 MHz, CDCl ₃) of compound 241	342
Figure A7.41.	Infrared spectrum (Thin Film, NaCl) of compound 241	343

Figure A7.42.	^{13}C NMR (100 MHz, CDCl_3) of compound 241	343
Figure A7.43.	^1H NMR (400 MHz, CDCl_3) of compound 243	344
Figure A7.44.	COSY NMR (400 MHz, CDCl_3) of compound 243	345
Figure A7.45.	HSQC NMR (400 MHz, CDCl_3) of compound 243	346
Figure A7.46.	NOESY NMR (400 MHz, CDCl_3) of compound 243	347
Figure A7.47.	Infrared spectrum (Thin Film, NaCl) of compound 243	348
Figure A7.48.	^{13}C NMR (100 MHz, CDCl_3) of compound 243	348

APPENDIX 8

X-Ray Crystallography Reports Relevant to Chapter 4

Figure A8.2.1.	X-ray crystal structure of 236	351
Figure A8.3.1.	X-ray crystal structure of 255	365

APPENDIX 9

Spectra Relevant to Chapter 5

Figure A9.1.	^1H NMR (600 MHz, CDCl_3) of compound 269	414
Figure A9.2.	HMBC NMR (600 MHz, CDCl_3) of compound 269	415
Figure A9.3.	Infrared spectrum (Thin Film, NaCl) of compound 269	416
Figure A9.4.	^{13}C NMR (100 MHz, CDCl_3) of compound 269	416
Figure A9.5.	^1H NMR (500 MHz, CDCl_3) of compound 270	417
Figure A9.6.	Infrared spectrum (Thin Film, NaCl) of compound 270	418
Figure A9.7.	^{13}C NMR (100 MHz, CDCl_3) of compound 270	418
Figure A9.8.	^1H NMR (400 MHz, CDCl_3) of compound 275	419
Figure A9.9.	Infrared spectrum (Thin Film, NaCl) of compound 275	420
Figure A9.10.	^{13}C NMR (100 MHz, CDCl_3) of compound 275	420
Figure A9.11.	^1H NMR (400 MHz, CDCl_3) of compound 276	421
Figure A9.12.	Infrared spectrum (Thin Film, NaCl) of compound 276	422
Figure A9.13.	^{13}C NMR (100 MHz, CDCl_3) of compound 276	422
Figure A9.14.	^1H NMR (400 MHz, CDCl_3) of compound 89	423
Figure A9.15.	COSY NMR (400 MHz, CDCl_3) of compound 89	424
Figure A9.16.	NOESY NMR (400 MHz, CDCl_3) of compound 89	425
Figure A9.17.	Infrared spectrum (Thin Film, NaCl) of compound 89	426
Figure A9.18.	^{13}C NMR (100 MHz, CDCl_3) of compound 89	426
Figure A9.19.	^1H NMR (400 MHz, CDCl_3) of compound 277	427

Figure A9.20.	Infrared spectrum (Thin Film, NaCl) of compound 277	428
Figure A9.21.	^{13}C NMR (100 MHz, CDCl_3) of compound 277	428
Figure A9.22.	^1H NMR (400 MHz, CDCl_3) of compound 278	429
Figure A9.23.	Infrared spectrum (Thin Film, NaCl) of compound 278	430
Figure A9.24.	^{13}C NMR (100 MHz, CDCl_3) of compound 278	430
Figure A9.25.	^1H NMR (400 MHz, CDCl_3) of compound 279	431
Figure A9.26.	Infrared spectrum (Thin Film, NaCl) of compound 279	432
Figure A9.27.	^{13}C NMR (100 MHz, CDCl_3) of compound 279	432
Figure A9.28.	^1H NMR (400 MHz, CDCl_3) of compound 280	433
Figure A9.29.	Infrared spectrum (Thin Film, NaCl) of compound 280	434
Figure A9.30.	^{13}C NMR (100 MHz, CDCl_3) of compound 280	434
Figure A9.31.	^1H NMR (500 MHz, CDCl_3) of compound 281	435
Figure A9.32.	Infrared spectrum (Thin Film, NaCl) of compound 281	436
Figure A9.33.	^{13}C NMR (100 MHz, CDCl_3) of compound 281	436
Figure A9.34.	^1H NMR (400 MHz, CDCl_3) of compound 282	437
Figure A9.35.	Infrared spectrum (Thin Film, NaCl) of compound 282	438
Figure A9.36.	^{13}C NMR (100 MHz, CDCl_3) of compound 282	438
Figure A9.37.	^1H NMR (400 MHz, CDCl_3) of compound 283	439
Figure A9.38.	Infrared spectrum (Thin Film, NaCl) of compound 283	440
Figure A9.39.	^{13}C NMR (100 MHz, CDCl_3) of compound 283	440
Figure A9.40.	^1H NMR (400 MHz, CDCl_3) of compound 271	441
Figure A9.41.	Infrared spectrum (Thin Film, NaCl) of compound 271	442
Figure A9.42.	^{13}C NMR (100 MHz, CDCl_3) of compound 271	442
Figure A9.43.	^1H NMR (400 MHz, CDCl_3) of compound 288	443
Figure A9.44.	Infrared spectrum (Thin Film, NaCl) of compound 288	444
Figure A9.45.	^{13}C NMR (100 MHz, CDCl_3) of compound 288	444
Figure A9.46.	^1H NMR (400 MHz, CDCl_3) of compound 289	445
Figure A9.47.	Infrared spectrum (Thin Film, NaCl) of compound 289	446
Figure A9.48.	^{13}C NMR (100 MHz, CDCl_3) of compound 289	446
Figure A9.49.	^1H NMR (400 MHz, CDCl_3) of compound 290	447
Figure A9.50.	Infrared spectrum (Thin Film, NaCl) of compound 290	448
Figure A9.51.	^{13}C NMR (100 MHz, CDCl_3) of compound 290	448
Figure A9.52.	^1H NMR (400 MHz, CDCl_3) of compound 291	449
Figure A9.53.	Infrared spectrum (Thin Film, NaCl) of compound 291	450
Figure A9.54.	^{13}C NMR (100 MHz, CDCl_3) of compound 291	450

Figure A9.55.	^1H NMR (400 MHz, CDCl_3) of compound 292	451
Figure A9.56.	Infrared spectrum (Thin Film, NaCl) of compound 292	452
Figure A9.57.	^{13}C NMR (100 MHz, CDCl_3) of compound 292	452
Figure A9.58.	^1H NMR (400 MHz, CDCl_3) of compound 293	453
Figure A9.59.	Infrared spectrum (Thin Film, NaCl) of compound 293	454
Figure A9.60.	^{13}C NMR (100 MHz, CDCl_3) of compound 293	454
Figure A9.61.	^1H NMR (400 MHz, CDCl_3) of compound 294	455
Figure A9.62.	COSY NMR (400 MHz, CDCl_3) of compound 294	456
Figure A9.63.	HSQC NMR (400 MHz, CDCl_3) of compound 294	457
Figure A9.64.	NOESY NMR (400 MHz, CDCl_3) of compound 294	458
Figure A9.65.	Infrared spectrum (Thin Film, NaCl) of compound 294	459
Figure A9.66.	^{13}C NMR (100 MHz, CDCl_3) of compound 294	459
Figure A9.67.	^1H NMR (400 MHz, CDCl_3) of compound 295	460
Figure A9.68.	COSY NMR (400 MHz, CDCl_3) of compound 295	461
Figure A9.69.	HSQC NMR (400 MHz, CDCl_3) of compound 295	462
Figure A9.70.	NOESY NMR (400 MHz, CDCl_3) of compound 295	463
Figure A9.71.	Infrared spectrum (Thin Film, NaCl) of compound 295	464
Figure A9.72.	^{13}C NMR (100 MHz, CDCl_3) of compound 295	464
Figure A9.73.	^1H NMR (400 MHz, CDCl_3) of compound 296	465
Figure A9.74.	COSY NMR (400 MHz, CDCl_3) of compound 296	466
Figure A9.75.	HSQC NMR (400 MHz, CDCl_3) of compound 296	467
Figure A9.76.	NOESY NMR (400 MHz, CDCl_3) of compound 296	468
Figure A9.77.	Infrared spectrum (Thin Film, NaCl) of compound 296	469
Figure A9.78.	^{13}C NMR (100 MHz, CDCl_3) of compound 296	469
Figure A9.79.	^1H NMR (400 MHz, CDCl_3) of compound 297	470
Figure A9.80.	Infrared spectrum (Thin Film, NaCl) of compound 297	471
Figure A9.81.	^{13}C NMR (100 MHz, CDCl_3) of compound 297	471
Figure A9.82.	^1H NMR (400 MHz, CDCl_3) of compound 298	472
Figure A9.83.	Infrared spectrum (Thin Film, NaCl) of compound 298	473
Figure A9.84.	^{13}C NMR (100 MHz, CDCl_3) of compound 298	473

LIST OF SCHEMES

CHAPTER 1

Total Synthesis of Hypersampson M

Scheme 1.2.1.	Retrosynthetic strategy toward hypersampson M	3
Scheme 1.3.1.	Cyclopentene annulation of enone 7	4
Scheme 1.4.1.	Cyclopentene annulation of enone 13	5
Scheme 1.4.2.	Synthesis of aldehyde 19	6
Scheme 1.4.3.	Cyclization of aldehyde 19 to lactone 21	7
Scheme 1.4.4.	Attempts to functionalize Weinreb amide 25	8
Scheme 1.4.5.	Completion of hypersampson M (1)	9

APPENDIX 1

Synthetic Summary for Chapter 1

Scheme A1.1.	Total synthesis of hypersampson M	49
--------------	---	----

CHAPTER 2

Toward the Total Synthesis of Hypersonin A and Wilsonglucinol G

Scheme 2.2.1.	Retrosynthetic strategy toward wilsonglucinol G	91
Scheme 2.3.1.	Toward a functionalized cyclopentene annulation	92
Scheme 2.4.1.	Scalable preparation of ketone 12	94
Scheme 2.4.2.	Installing the hydroindene core	95
Scheme 2.4.3.	Synthetic sequence advancing ketone 56 to lactone 38	96
Scheme 2.4.4.	Proposed completion of wilsonglucinol G (36) and hypersonin A (32)	97

APPENDIX 3

Synthetic Summary for Chapter 2

Scheme A3.1.	Synthesis of intermediate 37 en route to Wilsonglucinol G (36)	127
--------------	--	-----

APPENDIX 5

Early Strategies Toward the Synthesis of Homoadamantane PPAPs

Scheme A5.2.1.	Limonene-based approach toward the homoadamantane PPAPs	164
----------------	---	-----

Scheme A5.2.2.	Synthesis of isopropenyl-flanked cycloheptenone 7	165
Scheme A5.2.3.	Unsuccessful cyclopentene annulation of ester 7	166
Scheme A5.2.4.	Selective reduction of the enone in hydrazulene 10	168
Scheme A5.3.1.	Yang's anti-addition into ester 75	169
Scheme A5.3.2.	Cyclopentene annulation and other nucleophilic additions to 75	170
Scheme A5.3.3.	Additions involving cycloheptenone 95 and 75	171
Scheme A5.3.4.	Danheiser annulation of cycloheptenone 75	172
Scheme A5.4.1.	Eastern ring first approach to the homoadamantane PPAPs	173
Scheme A5.4.2.	Unexpected formation of rearranged allylketone 118	174
Scheme A5.4.3.	Attempts to destabilize captodative radical 121	175
Scheme A5.4.4.	Cyclopentadiene protected enone radical fragmentation.....	176
Scheme A5.5.1.	Unsuccessful tertiary conjugate additions to 11	177
Scheme A5.5.2.	Unsuccessful strategies toward the key hydroindene	178
Scheme A5.6.1.	Early unsuccessful ring expansion strategies	180
Scheme A5.6.2.	Successful diazo-mediated ring expansion of 149	181
Scheme A5.6.3.	Diazoacetate-mediated ring expansion of 58	182
Scheme A5.7.1.	Lactonization of aldehyde 61	183
Scheme A5.7.2.	Synthesis and deployment of Claisen substrates.....	185
Scheme A5.7.3.	Synthesis and deployment of des-prenyl ester 178	186
Scheme A5.8.1.	Proposed future steps for lactone 38	186
Scheme A5.8.2.	Weinreb amide opening of lactone 38	188
Scheme A5.8.3.	Studies carried out on model Weinreb amide 186	189

CHAPTER 3

Some Unusual Transformations of a Highly Reactive α -Bromocaranone

Scheme 3.1.1.	Synthesis of an α -bromocaranone (207) from (+)-3-carene (73).....	239
Scheme 3.3.1.	Radical mediated cyclopropane fragmentation of 207	241
Scheme 3.3.2.	Proposed mechanism and control study for the formation of 215	242

CHAPTER 4

On the Unexpected Formation of [2.2.1]- and [2.1.1]Homotriblattanes

Scheme 4.1.1.	Unexpected cyclization of bromide 131 to cage 133	289
Scheme 4.2.1.	Synthesis of α -brominated cycloheptanones.....	290
Scheme 4.2.2.	Proposed mechanism and minimum free energy pathway to 240	291

Scheme 4.2.3.	Synthesis of other homotriblattanes	292
---------------	---	-----

CHAPTER 5

A Modular Cyclopentene Annulation

Scheme 5.1.1.	Cyclopentane-Containing Natural Products and a Previous Propargyl Zinc Cyclopentene Annulation	377
Scheme 5.3.1.	Enone and Propargyl Bromide Scope.....	380
Scheme 5.3.2.	Electrophile Scope	382
Scheme 5.4.1.	Product Derivatizations	383

LIST OF TABLES

CHAPTER 1

Total Synthesis of Hypersampson M

Table 1.4.1.	Attempts to open lactone 21	7
Table 1.6.3.1.	Comparison of ^1H and ^{13}C NMR shifts of Hypersampson M (1), CDCl_3	36

CHAPTER 2

Toward the Total Synthesis of Hypersonin A and Wilsonglucinol G

Table 2.3.1.	Optimization of the intercepted cyclopentene annulation	93
--------------	---	----

APPENDIX 5

Early Strategies Toward the Synthesis of Homoadamantane PPAPs

Table A5.5.1.	Attempts to reduce the enone olefin in hydrazulene 10	167
Table A5.7.1.	Unsuccessful aldol reaction of aldehyde 61	184
Table A5.8.1.	Attempts to open lactone 38 to tricycle 180	187
Table A5.8.2.	Other amines used to open the caged lactones 171 and 38	191

CHAPTER 3

Some Unusual Transformations of a Highly Reactive α -Bromocaranone

Table 3.2.1.	Ag^{I} -mediated reactions of 207	240
--------------	--	-----

APPENDIX 8

X-Ray Crystallography Reports Relevant to Chapter 4

Table A8.2.1.	Crystal data and structure refinement for 236 (CCDC# 2430670).....	351
Table A8.2.2.	Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for 236 . $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.	352
Table A8.2.3.	Bond lengths [$\text{\AA}$] and angles [$^\circ$] for 236	353
Table A8.2.4.	Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for 236 . The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + \dots + 2 h k a^* b^* U^{12}]$	359
Table A8.2.5.	Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for 236	360

Table A8.2.6.	Torsion angles [°] for 236	361
Table A8.2.7.	Hydrogen bonds for 236 [Å and °].....	364
Table A8.3.1.	Crystal data and structure refinement for 255 (CCDC# 2430671).....	365
Table A8.3.2.	Atomic coordinates (x 10 ⁴) and equivalent isotropic displacement parameters (Å ² x 10 ³) for 255 . U(eq) is defined as one third of the trace of the orthogonalized U ^{ij} tensor	366
Table A8.3.3.	Bond lengths [Å] and angles [°] for 255	367
Table A8.3.4.	Anisotropic displacement parameters (Å ² x 10 ³) for 255 . The anisotropic displacement factor exponent takes the form: -2p ² [h ² a ^{*2} U ¹¹ + ... + 2 h k a [*] b [*] U ¹²]	371
Table A8.3.5.	Hydrogen coordinates (x 10 ⁴) and isotropic displacement parameters (Å ² x 10 ³) for 255	372
Table A8.3.6.	Torsion angles [°] for 255	373

CHAPTER 5

A Modular Cyclopentene Annulation

Table 5.2.1.	Optimization of Reaction Conditions	379
--------------	---	-----

APPENDIX 10

Notebook Cross-Reference for New Compounds

Table A10.1.	Notebook cross-reference for Chapter 1	475
Table A10.2.	Notebook cross-reference for Chapter 2	476
Table A10.3.	Notebook cross-reference for Appendix 5	477
Table A10.4.	Notebook cross-reference for Chapter 3	478
Table A10.5.	Notebook cross-reference for Chapter 4	478
Table A10.6.	Notebook cross-reference for Chapter 5	479

LIST OF ABBREVIATIONS

Å	Ångstrom
λ	wavelength
μ	micro
μ wave	microwave
$[\alpha]_D$	specific rotation at wavelength of sodium D line
[H]	reduction
[O]	oxidation
°C	degrees Celsius
Ac	acetyl
AcOH	acetic acid
An	<i>para</i> -anisoyl
APCI	atmospheric pressure chemical ionization
aq	aqueous
Ar	aryl
atm	atmosphere
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
bp	boiling point
br	broad
Bu	butyl
Bz	benzoyl
c	concentration for specific rotation measurements (g/100 mL)
calc'd	calculated

CAN	ceric ammonium nitrate
cat	catalytic
cm ⁻¹	wavenumber(s)
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl
CPME	cyclopentyl methyl ether
CuTC	copper(I) thiophene-2-carboxylate
Cy	cyclohexyl
d	doublet
D	deuterium
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano- <i>p</i> -benzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMA	<i>N,N</i> -dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
DPPF	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
e.g.	for example (Latin <i>exempli gratia</i>)
ee	enantiomeric excess
equiv	equivalent(s)

ESI	electrospray ionization
esp	$\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionic acid
Et	ethyl
EtOAc	ethyl acetate
FAB	fast atom bombardment
FD	field desorption
g	gram(s)
G4	fourth-generation Buchwald precatalyst
GC	gas chromatography
h	hour(s)
HFIP	1,1,1,3,3,3-hexafluoropropan-2-ol
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
Hz	hertz
<i>i</i> -Bu	isobutyl
i.e.	that is (Latin id est)
IBX	2-iodoxybenzoic acid
IPA	isopropanol, 2-propanol
<i>i</i> -Pr	isopropyl
IR	infrared (spectroscopy)
<i>J</i>	coupling constant
K	Kelvin(s) (absolute temperature)
kcal	kilocalorie
L	liter; neutral ligand
LC–MS	liquid chromatography–mass spectrometry

LDA	lithium diisopropylamide
m	multiplet; milli
<i>m</i>	meta
M	metal; molar; molecular ion
<i>m/z</i>	mass to charge ratio
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
MM	mixed method
mol	mole(s)
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
MTBE	methyl <i>tert</i> -butyl ether
n	nano
N	normal
NBS	<i>N</i> -bromosuccinimide
<i>n</i> -Bu	butyl
NCS	<i>N</i> -chlorosuccinimide
ND	not determined
NHK	Nozaki–Hiyama–Kishi
NMP	<i>N</i> -methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NR	no reaction detected
Nu [−]	nucleophile

<i>o</i>	ortho
<i>p</i>	para
Pd/C	palladium on carbon
PEG	polyethylene glycol
PG	protecting group
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PHOX	phosphinooxazoline ligand
Phth	phthaloyl
PIFA	(bis(trifluoroacetoxy)iodo)benzene
Piv	pivaloyl
pmdba	bis(4-methoxybenzylidene)acetone
PPA	polyphosphoric acid
PPAP	polycyclic polyprenylated acylphloroglucinol
ppm	parts per million
Pr	propyl
PTSA	<i>para</i> -toluenesulfonic acid
Py	pyridine
q	quartet
R	generic for any atom or functional group
Ref.	reference
s	singlet
SFC	supercritical fluid chromatography
t	triplet
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBHP	<i>tert</i> -butyl hydroperoxide

TBS	<i>tert</i> -butyldimethylsilyl
<i>t</i> -Bu	<i>tert</i> -butyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMG	1,1,3,3-tetramethylguanidine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TOF	time-of-flight
TosMIC	<i>para</i> -toluenesulfonylmethyl isocyanide
t_R	retention time
Ts	<i>p</i> -toluenesulfonyl (tosyl)
TTMSS	tris(trimethylsilyl)silane
UV	ultraviolet
v/v	volume to volume
w	weak
w/v	weight to volume
w/w	weight to weight
X	anionic ligand or electronegative element

CHAPTER 1

Total Synthesis of Hypersampsonone M[†]

1.1 INTRODUCTION

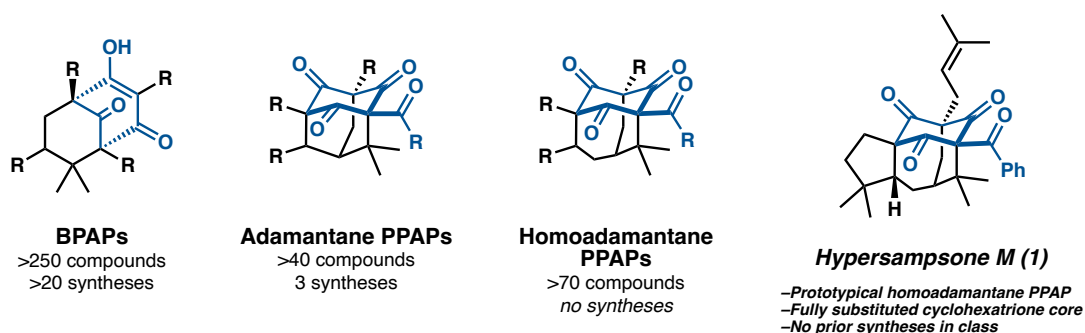
Since their discovery, the polycyclic polyprenylated acylphloroglucinols (PPAPs) have provided scientists a continuous reservoir of diverse natural products with a broad spectrum of bioactivities and structural architectures.¹ A large part of why the PPAP class of compounds has attracted continued interest from synthetic chemists is that a viable structure–activity relationship (SAR) has not yet been established for them, and in many cases, small structural changes lead to unexpected “turn on” or “turn off” effects on biological activity.² With over 400 isolated compounds as of 2018, it becomes useful to further subdivide the PPAP class of compounds into the bicyclic polyprenylated acylphloroglucinols (BPAPs), the caged adamantane and homoadamantane PPAPs, and other spirocyclic or otherwise rearranged PPAPs (Figure 1.1.1).^{1c}

This interest has led dozens of researchers to develop synthetic approaches to PPAPs, with many having completed sophisticated total syntheses. The bicyclo[3.3.1]nonane subclass (BPAPs) in particular has enjoyed significant attention in the realm of natural product synthesis, reflecting their overall prevalence within the PPAP family, well-established structural diversity, and medicinal potential.³ Despite these

[†]This research was conducted in collaboration with Dr. Scott Virgil. Portions of this chapter have been reproduced with permission from Samkian, A. E.; Virgil, S. C.; Stoltz, B. M. J. *Am. Chem. Soc.* **2024**, *146*, 18886–18891. © 2024 American Chemical Society.

extensive efforts, to date there exist only three syntheses of adamantane PPAP natural products.⁴ Moreover, there are no homoadamantane PPAP syntheses, which is surprising in relation to the subclasses' substantial scope of at least 70 members.^{1e,5}

Figure 1.1.1. *Hypersampsonone M* and representative PPAP classes.



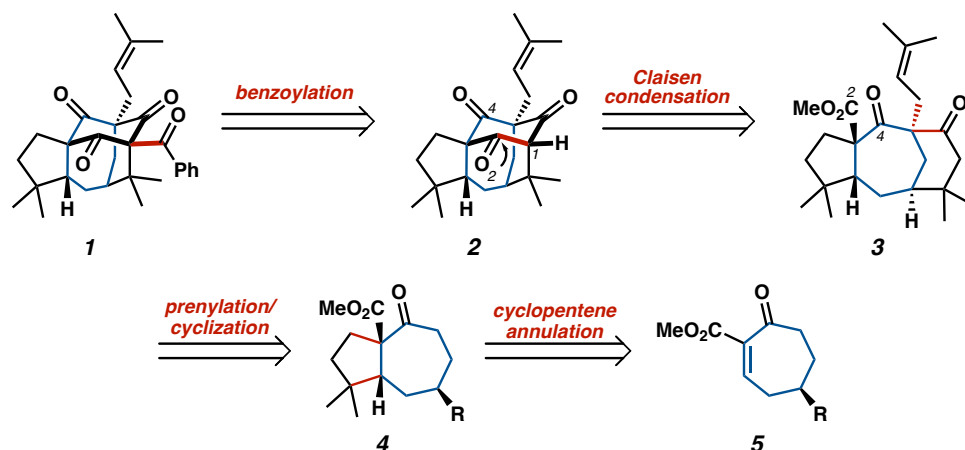
We identified hypersampsonone M (**1**), isolated from *Hypericum sampsonii* in 2014, to be a prototypical representative of this subclass, making it an excellent target for our initial investigations into this family of PPAPs.⁶ Many homoadamantane PPAPs have been known for decades⁷ and many more have provided glimpses into the promising bioactivity of this class, with several being implicated to have antitumor,^{7c} anti-inflammatory/immunosuppressive,^{5i,8} hepatoprotective,^{5c} and antiadipogenesis⁹ properties. Like other homoadamantane PPAPs, the phloroglucinol moiety in hypersampsonone M (**1**) is clearly conserved (Figure 1.1.1, highlighted in blue), yet the unsymmetrical homoadamantane core and fused cyclopentane make it difficult to utilize an alkylative dearomatization strategy such as was cleverly applied to an adamantane PPAP by Porco and co-workers.^{4b}

1.2 RETROSYNTHETIC ANALYSIS

We devised a retrosynthetic strategy that centers on the C4-cycloheptanone ring (Scheme 1.2.1, highlighted in blue), electing to employ a late stage Claisen condensation

and bridgehead benzoylation on C1 from tricycle **3**. Utilizing the C4 ketone as a handle, prenylation and cyclization would allow access to tricycle **3** from simplified hydrazulene **4**, which could finally be traced back to cycloheptenone **5** through a key cyclopentene annulation.

Scheme 1.2.1. Retrosynthetic strategy toward hypersampson M.

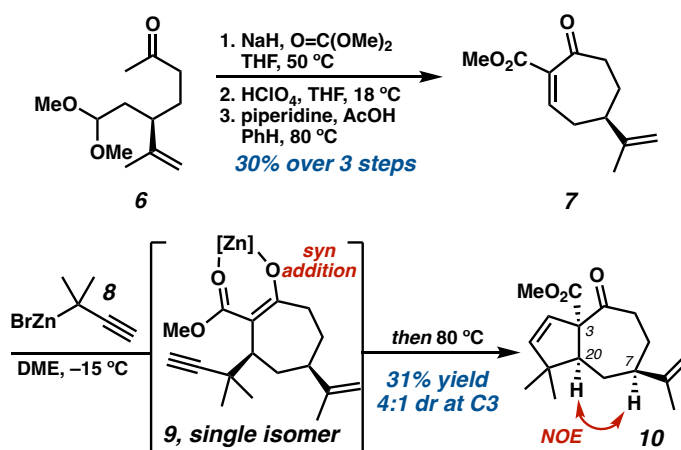


1.3 UNSUCCESSFUL CHIRAL POOL ROUTE

We began by targeting cycloheptenone **7** (Scheme 1.3.1). Acylation of known ketone **6**¹⁰ with NaH and dimethyl carbonate provides access to the required β -ketoester. Cleavage of the acetal, followed by a Knoevenagel condensation, delivers cycloheptenone **7**. While several cyclopentene annulation reactions were considered, the demanding *gem*-dimethyl moiety excluded most obvious options.¹¹ After significant optimization, our observations indicated that 1,1-dimethylpropargylzinc bromide **8** undergoes facile 1,4-addition to enone **7**, providing zinc enolate **9** as a single isomer.¹² Subsequent heating of zinc enolate **9** following conjugate addition was sufficient to effect cyclization, affording the hydrazulene product (**10**) in a single step.¹³ To our surprise,¹⁴ NOESY studies indicated that the undesired *syn*-isomer (i.e., C20 and C7) was

exclusively isolated as a 4:1 mixture of diastereomers at C3 (i.e., *cis* and *trans* ring junctures). Attempts to control the addition temperature or alter solvents did not invert the stereochemical outcome, and we propose that the bulky nature of the nucleophile was likely responsible for the undesired initial *syn* conjugate addition stereochemistry, perhaps through torsional steering effects. Further investigation of this reaction and other attempts with chiral starting materials are discussed in Appendix 3.

Scheme 1.3.1. Cyclopentene annulation of enone **7**.

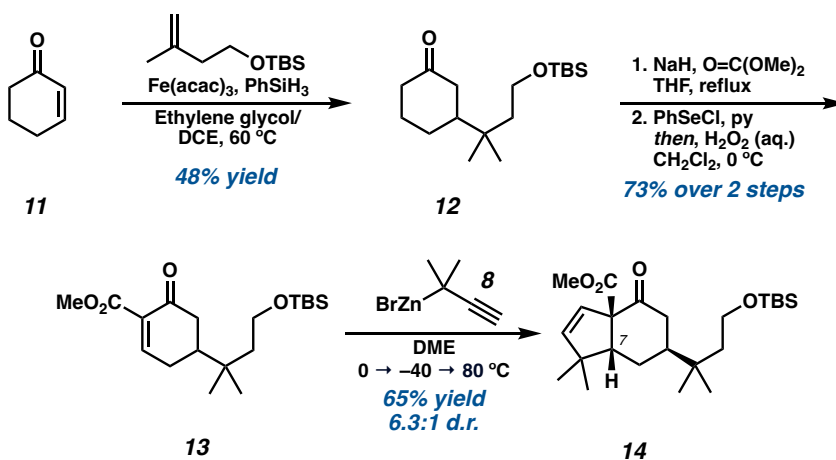


1.4 TOTAL SYNTHESIS OF HYPERSAMPSON M

We rationalized that a cyclohexenone substrate would provide a more predictable stereochemical outcome in the cyclopentene annulation and a successive ring expansion would intercept the original retrosynthesis at hydrazulene **4**. We began by targeting the annulation substrate (**13**, Scheme 1.4.1). We were able to access ketone **12** from cyclohexenone (**11**) in a single step using a radical HAT coupling.¹⁵ Acylation and selenoxide elimination provided activated enone **13** in 73% yield over 2 steps. Proceeding to the key cyclopentene annulation, we were surprised to still observe the presence of the *syn* addition product at C7. Fortunately, further lowering the temperature to -40 °C

during the propargylzinc (**8**) addition resulted in the formation of the desired *anti*-isomer **14** (6.3:1) with exclusively *cis* ring fusion.

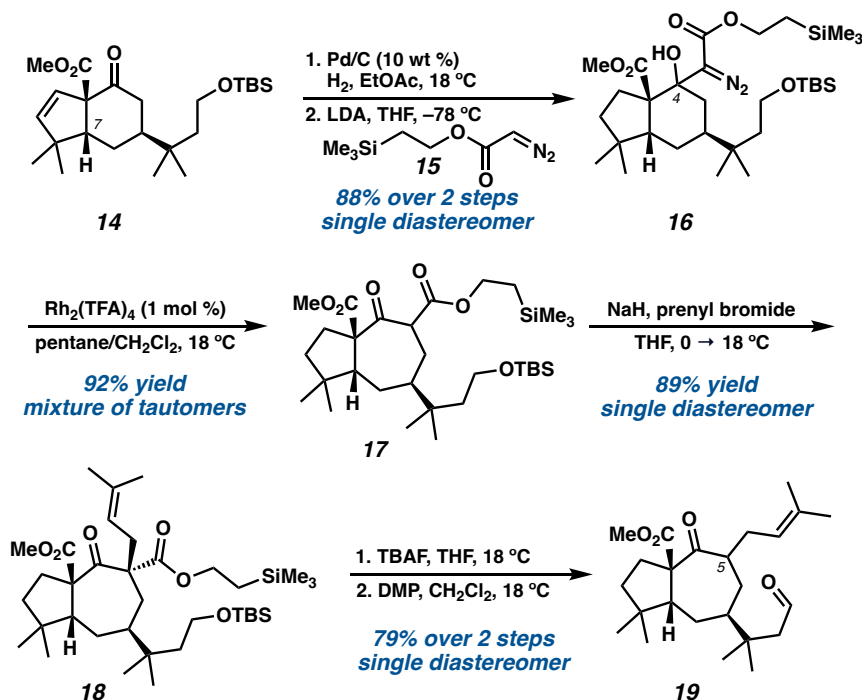
Scheme 1.4.1. Cyclopentene annulation of enone **13**.



Following hydrogenation of the cyclopentene, we shifted our focus to ring-expansion of the hydroindene system to access the required hydrazulene (**4**). Significant effort was made on this front, and it was found necessary to use a designer diazoacetate (**15**, Scheme 1.4.2).¹⁶ Deprotonation of **15** with LDA enabled nucleophilic addition to the neopentyl ketone furnished alcohol **16**.¹⁷ Catalytic $\text{Rh}_2(\text{TFA})_4$ was found to be uniquely effective in initiating the ring-expansion rearrangement, resulting in β -ketoester **17** as a mixture of three inseparable isomers, which were putatively assigned to the enol and two ketone diastereomers. Commercially available ethyl diazoacetate and *tert*-butyl diazoacetate undergo similar rearrangements but ultimately proved to be synthetic impasses, as selective decarboxylation of the newly installed esters could not be accomplished in the presence of the neighboring, preexistent methyl ester. The trimethylsilylethyl ester thus proved vital, as following prenylation to form bicycle **18**, treatment with TBAF resulted in the selective decarboxylation of the trimethylsilylethyl

ester. Concomitant TBS cleavage produces the desired primary alcohol as a single diastereomer, which upon DMP oxidation results in aldehyde **19** in excellent yield (79%, 2 steps).¹⁷

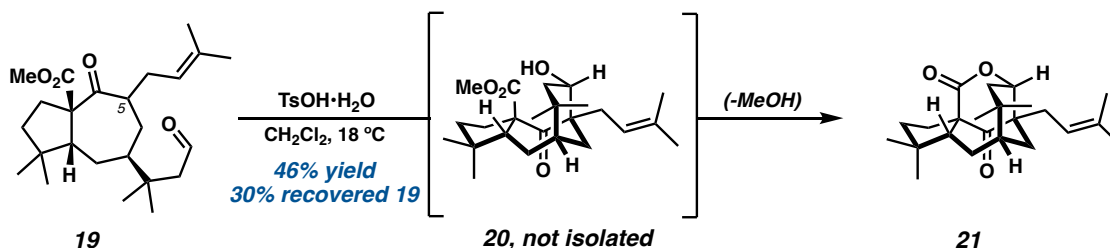
Scheme 1.4.2. Synthesis of aldehyde 19.



With a scalable route to aldehyde **19** established, we were optimistic about the aldol reaction proposed to provide tricycle **20** (Scheme 1.4.3). Unfortunately, classic aldol conditions lead to decomposition or, in most cases, return the starting aldehyde without any trace of desired tricycle **20**. In fact, TsOH·H₂O in CH₂Cl₂ was the only set of conditions evaluated that resulted in a product of interest, forging caged lactone **21** slowly in moderate yield. We hypothesized that the aldol reaction to form tricycle **20** is likely highly reversible under most conditions, and perhaps even favors aldehyde **19** due to strain induced upon cyclization. Further lactonization of the aldol product (**20**) provides a

powerful thermodynamic driving force for cyclization and highlights the opportune placement of the methyl ester.

Scheme 1.4.3. Cyclization of aldehyde **19** to lactone **21**.



Formation of the lactone (**21**) seemed so favorable that attempts to reopen or saponify it (Table 1.4.1, **21** $\rightarrow$ **24**) with any number of acidic or basic conditions resulted in no reaction or decomposition (entries 1–4). We concluded that the lactone would need to be opened in an irreversible fashion and hypothesized that an amide would be suitably stable. While this approach seemed promising, it introduced the eventual synthetic challenge of needing to activate an extremely hindered amide in order to progress with our plans.

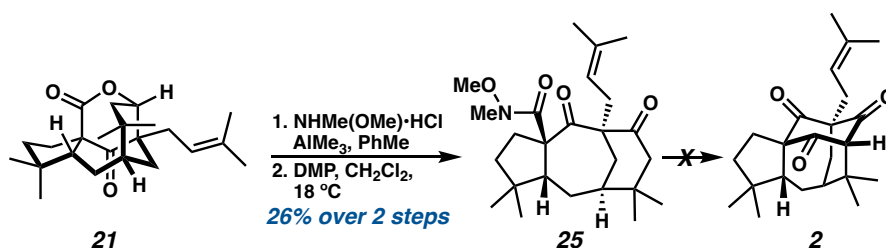
Table 1.4.1. Attempts to open lactone **21**.

entry	conditions	R	result ^a
1	NaOMe/MeOH	$-\text{OMe}$	decomp.
2	Bu_3SnOMe	$-\text{OMe}$	0%
3	$\text{Al}(\text{O}i\text{-Pr})_3/\text{MeOH}$	$-\text{OMe}$	0%
4	$\text{KOH}/\text{H}_2\text{O}$	$-\text{OH}$	decomp.
5	$\text{NHMe}(\text{OMe}) \cdot \text{HCl}/\text{AlMe}_3$	$-\text{NMe}(\text{OMe})$	85%
6	$\text{NH}_4\text{Cl}/\text{AlMe}_3$	$-\text{NH}_2$	73%
7	$\text{NHMe}_2 \cdot \text{HCl}/\text{AlMe}_3$	$-\text{NMe}_2$	0%
8	$\text{PhNH}_2 \cdot \text{HCl}/\text{AlMe}_3$	$-\text{NHPh}$	84% ^b

^aDetermined by ^1H NMR analysis. ^bIsolated yield.

For example, opening the lactone with AlMe_3 /*N,O*-dimethylhydroxylamine to afford the Weinreb amide proceeded smoothly (entry 5), but following oxidation, we were unable to further transform amide **25** (Scheme 1.4.4) in a useful fashion (**25** $\rightarrow$ **2**). Some amides, such as the unsubstituted ammonia-derived amide, were also formed successfully (entry 6), but subsequent oxidation resulted in decomposition. Many disubstituted amides simply failed

Scheme 1.4.4. Attempts to functionalize Weinreb amide **25**.

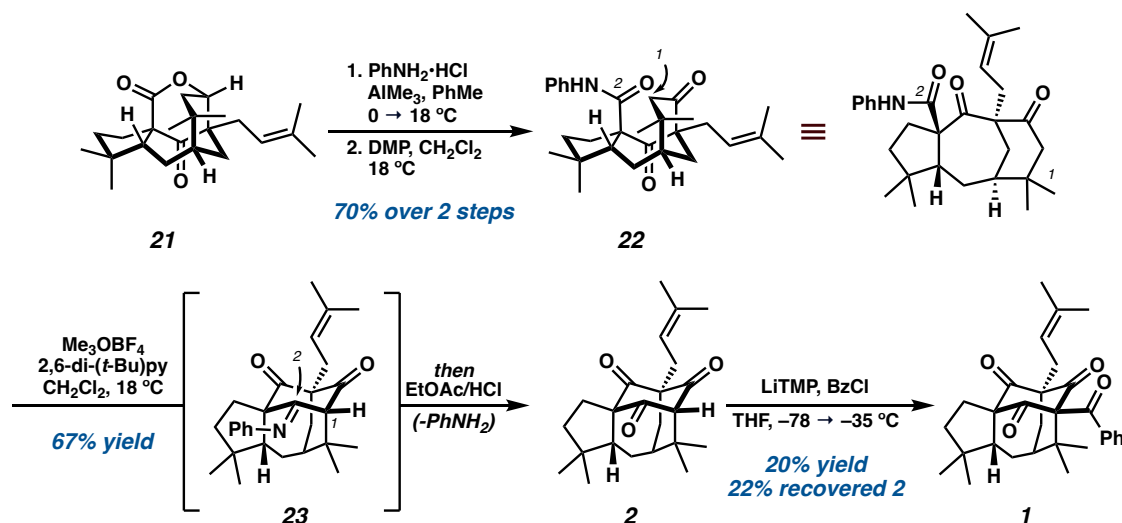


to form, as was the case with dimethylamide (entry 7). Fortunately, we were able to install aniline (entry 8) and oxidize the revealed alcohol, providing anilide **22** (Scheme 1.4.5) in good yield (70%, 2 steps).

We next aimed to methanolyze the anilide (**22**) to the methyl ester, targeting homoadamantane **2** via Dieckmann cyclization. The direct installation of a methyl ester with MeOH/H^+ was not successful; however, we believed that treatment with Me_3OBF_4 (methyl-Meerwein's salt) would form the methyl imidate, which could then be hydrolyzed to the methyl ester.¹⁸ Excitingly, we observed direct cyclization to the homoadamantane cage instead, isolating imine **23**. Mechanistically, we propose that methyl imidate formation likely occurs first. We then envision that one of two scenarios is likely for bond construction. In one case, enol addition would occur directly to the imidate to form a particularly sterically hindered tetrahedral intermediate. Alternatively,

elimination of MeOH or Me₂O could form a nitrilium that can cyclize to the observed imine (**23**). Following optimization, 2,6-di-*tert*-butylpyridine (DTBP) was added to suppress decomposition of the prenyl group, and an acidic workup was performed to hydrolyze the imine product and provide access to trione **2** in a single step.

Scheme 1.4.5. Completion of hypersampsonone M (**1**).



To install the final benzoyl group, we attempted variations of the Danishefsky protocol involving an intermediate bridgehead iodide,^{3b} as well as Shair's direct bridgehead acylation protocol.^{3p} Deuterium incorporation experiments with LiTMP showed that no deprotonation occurs at -78 °C, whereas complete decomposition is observed at 0 °C. A screen of several intermediary temperatures established that 40% deuterium incorporation could be achieved at -35 °C. It has been shown that deprotonation of bridgehead homoadamantane protons is challenging compared to those on bicyclo[3.3.1]nonane systems.¹⁹ Interestingly, the challenge associated with bridgehead acylations in the sister BPAP systems seems to stem from lack of anion reactivity, rather than generation of the stabilized anion itself.^{3h} This was found to be in stark contrast with homoadamantane **2**, as despite the difficulty in generating the required anion, treatment

with BzCl directly affords hypersampson M (**1**) in moderate yield with an equivalent amount of isolated starting trione (**2**).

1.5 CONCLUSION

To conclude, we have completed the synthesis of hypersampson M (**1**) in 15 steps starting from cyclohexenone, thus achieving the first total synthesis of a homoadamantane PPAP natural product. Additionally, the enabling cyclopentene annulation provides an orthogonal method for installing highly substituted five-membered rings using simple reagents and techniques. This strategy is likely of sufficient generality to allow access to other homoadamantane PPAPs. Biological studies and further development of this route to synthesize additional PPAPs are in progress.

1.6 EXPERIMENTAL SECTION

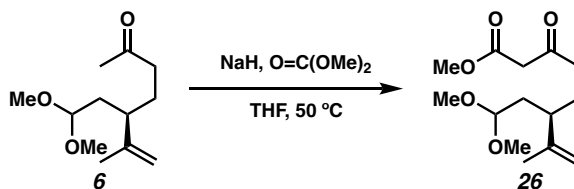
1.6.1 MATERIALS AND METHODS

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.²⁰ Cyclohexenone was distilled prior to use. Pyridine and 2,2,6,6-Tetramethylpiperidine were distilled from CaH₂ prior to use. Freshly purchased TsOH•H₂O was stored in a desiccator and dried under high vacuum for several hours prior to use. Activated zinc dust was prepared according to a previously reported procedure.²¹ All other reagents were purchased from commercial sources and used as received unless otherwise stated. Reaction progress was monitored by thin-layer chromatography (TLC), or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F₂₅₄ precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, CAM stain, or KMnO₄ staining. Silicycle SiliaFlash® P60 Academic Silica gel

(particle size 40–63 μm) was used for flash chromatography. Teledyne ISCO CombiFlashRf⁺, Teledyne ISCO CombiFlashRf⁺ LumenTM, or Teledyne ISCO CombiFlashRfNEXTGEN⁺ systems were used for automated flash chromatography using Luknova SuperSepTM silica columns or RediSepRf GOLD C₁₈ columns. Agilent 1100 or 1200 preparatory HPLC systems were used for high-performance reverse phase separations. ¹H NMR spectra were recorded on Varian Inova 500 MHz and Bruker 400 MHz spectrometers and are reported relative to residual non-deuterated solvent CHCl₃ (δ 7.26 ppm) or C₆H₆ (δ 7.16 ppm). ¹³C NMR spectra were recorded on a Bruker 400 MHz spectrometers (100 MHz) and are reported relative to residual non-deuterated solvent CHCl₃ (δ 77.16 ppm) or C₆H₆ (δ 128.06). Data for ¹H NMR 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, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet. Data for ¹³C NMR are reported in terms of chemical shifts (δ ppm). Diastereomeric ratios were calculated based on ratios of integrals from crude ¹H NMR spectra. Some spectra contain minor solvent impurities of water, ethyl acetate, dichloromethane, diethyl ether, acetone, grease, and/or silicone grease, which do not impact product assignments. IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm⁻¹). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-T2000GC AccuTOFTM GC-Alpha High Resolution

Mass Spectrometer in field ionization (FI⁺) or field desorption (FD⁺) mode, or an Agilent 6230 Series TOF with and Agilent Jet Stream ion source in electrospray ionization (ESI⁺).

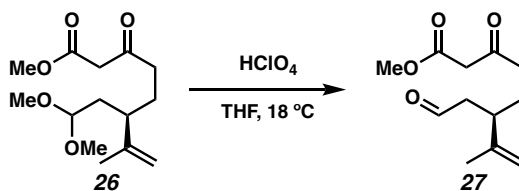
1.6.2 EXPERIMENTAL PROCEDURES



methyl (R)-6-(2,2-dimethoxyethyl)-7-methyl-3-oxooct-7-enoate **26.**

A 100 mL flask with reflux condenser under Ar was charged with NaH (1.4 g, 58.3 mmol, 2.5 equiv), THF (25 mL), (OMe)₂CO (5.25 g, 58.3 mmol, 2.5 equiv) and a drop of MeOH. The reaction was heated to 50 °C and ketone **6** (prepared according to a previously reported procedure¹⁰)(5 g, 23.3 mmol, 1.0 equiv) was added dropwise, neat, over 1 min and the reaction was allowed to stir at this temperature for 1 h. The apparatus was allowed to cool slightly, and the entire contents of the flask were poured into a cold saturated aqueous NH₄Cl solution with stirring. The mixture was extracted 3x with ether, and the combined organics were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified via flash column chromatography (20% acetone/hexanes) to afford **26** (4.64 g, 74% yield) as a colorless oil. Note: **26** was isolated as a 6.7:1 mixture of keto/enol tautomers. Keto tautomer: ¹H NMR (400 MHz, C₆D₆) δ = 4.75 – 4.73 (m, 1H), 4.73 – 4.72 (m, 1H), 4.40 – 4.34 (m, 1H), 3.28 (s, 3H), 3.17 (s, 3H), 3.13 (s, 3H), 2.95 (s, 2H), 2.25 – 2.17 (m, 1H), 2.09 – 2.01 (m, 2H), 1.69 – 1.56 (m, 3H), 1.51 – 1.44 (m, 1H), 1.44 (s, 3H); ¹³C{¹H} NMR (101 MHz, C₆D₆) δ = 201.31, 167.44, 146.74, 112.84, 103.08, 52.58, 52.08, 51.63, 48.97, 42.86, 40.66, 36.62, 26.86, 17.87. Enol tautomer: ¹H NMR (400 MHz, C₆D₆) δ = 12.72 (s, 1H), 5.02 (s, 1H), 4.80 – 4.76 (m, 1H),

4.76 – 4.74 (m, 1H), 4.40 – 4.34 (m, 1H), 3.34 (s, 3H), 3.15 (s, 3H), 3.12 (s, 3H), 2.29 – 2.18 (m, 1H), 2.13 – 1.98 (m, 2H), 1.70 – 1.55 (m, 3H), 1.52 – 1.45 (m, 1H), 1.44 – 1.43 (m, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, C_6D_6) δ = 179.57, 146.36, 113.67, 113.08, 89.12, 52.57, 52.03, 50.79, 43.05, 36.81, 36.58, 33.18, 29.90; IR (Neat Film, NaCl) 2951, 1747, 1716, 1438, 1126, 1062, 894 cm^{-1} ; HRMS (ESI+): m/z calc'd for $\text{C}_{14}\text{H}_{24}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$: 295.1516, found 295.1520; $[\alpha]_{\text{D}}^{23.20}$ 13.44 (c 1.0, CHCl_3).

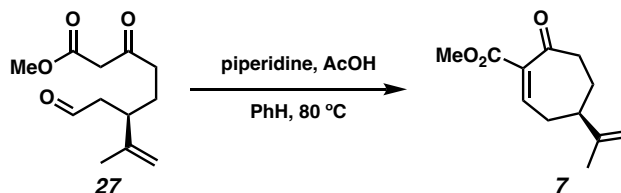


methyl (*R*)-7-methyl-3-oxo-6-(2-oxoethyl)oct-7-enoate **27.**

A solution of acetal **26** (3 g, 11 mmol, 1.0 equiv) in THF (30 mL) was added to HClO_4 (3% aq., 30 mL) at $0\text{ }^\circ\text{C}$ under air. The solution was stirred vigorously and allowed to warm to $18\text{ }^\circ\text{C}$, after which it was further stirred for 2 h. The solution was then poured into brine (10 mL) and extracted 2x with ether. The combined organics were washed with brine, dried over Na_2SO_4 , and concentrated gently under reduced pressure, leaving 20 mL of solvent remaining.

Note: This material was directly carried forward to the next step as a solution in THF/ Et_2O .

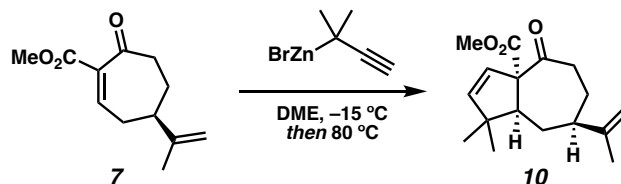
27 degrades rapidly upon concentration or on silica/alumina and cannot be easily purified.



methyl (*R*)-7-oxo-4-(prop-1-en-2-yl)cyclohept-1-ene-1-carboxylate **7.**

A 500 mL flask equipped with a Dean-Stark apparatus was charged with PhH (210 mL) and the solution of aldehyde (**27**, theoretical: 11 mmol in 20 mL THF/Et₂O). A solution of piperidine (375 mg, 4.4 mmol, 0.4 equiv) and AcOH (1.59 g, 26.4 mmol, 2.4 equiv) in PhH (20 mL) was added rapidly and the flask was heated to reflux for 30 min and then cooled to 18 °C. The solution was concentrated under reduced pressure, saturated aqueous NaHCO₃ was added, and the mixture then extracted 3x with ether. The combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography (5→10% acetone/hexanes) to furnish **7** as a yellow oil (730 mg, 40% yield, two steps).

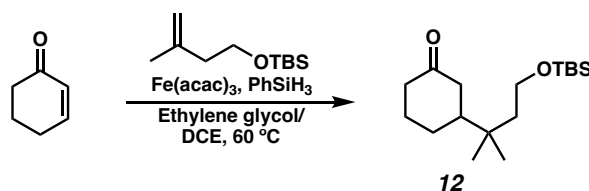
Note: This material was directly carried forward to the next step. Additionally, **7** is not stable for extended periods of time, even when stored at −15 °C. ¹H NMR spectral data and HRMS data is provided as a courtesy. HRMS (ESI⁺): *m/z* calc'd for C₁₂H₁₆O₃Na [M+Na]⁺; 231.0992, found 231.0998.



methyl (3*aS*,7*R*,8*aS*)-1,1-dimethyl-4-oxo-7-(prop-1-en-2-yl)-4,5,6,7,8,8a-hexahydroazulene-3*a*(1*H*)-carboxylate 10.

To a dry 2 dram vial under N₂ was added activated Zn dust (94 mg, 1.44 mmol, 2.5 equiv) and DME (1.2 mL). The mixture was cooled to 0 °C and 3-bromo-3-methylbut-1-yne (prepared according to a previously reported procedure²²)(212 mg, 1.44 mmol, 2.5 equiv) was added in one portion. After 1 h most of the Zn has dissolved and the mixture was cooled to −15 °C at which point enone **7** (120 mg, 0.58 mmol, 1.0 equiv) in DME (1.2 mL) was added dropwise over 10 min. The cloudy solution was then stirred at −15 °C for 12 h. The reaction was then allowed to warm to 18 °C and filtered into a fresh flask via a Teflon syringe filter to yield a perfectly homogeneous, yellow solution. The solution was heated to 80 °C for 4 h *without stirring* and then cooled to 0 °C and quenched with saturated, aqueous NH₄Cl. The mixture was extracted with EtOAc, and the combined organic extracts were washed with brine, dried with Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→10% EtOAc/hexanes) to furnish **10** (50 mg, 31% yield) as a 4:1 mixture of diastereomers. Characterization data for the major diastereomer is given. ¹H NMR (400 MHz, C₆D₆) δ = 5.83 (d, *J* = 5.7 Hz, 1H), 5.51 (d, *J* = 5.6 Hz, 1H), 4.70 – 4.68 (m, 1H), 4.66 (p, *J* = 1.5 Hz, 1H), 3.24 (s, 3H), 3.14 (dd, *J* = 13.2, 3.5 Hz, 1H), 2.47 – 2.33 (m, 2H), 2.33 – 2.27 (m, 1H), 1.78 (dt, *J* = 14.5, 3.0 Hz, 1H), 1.71 – 1.62 (m, 1H), 1.53 (d, *J* = 1.9 Hz, 3H), 1.51 – 1.39 (m, 1H), 1.38 – 1.25 (m, 1H), 1.06 (s, 3H), 0.80 (s, 3H); ¹³C{¹H}

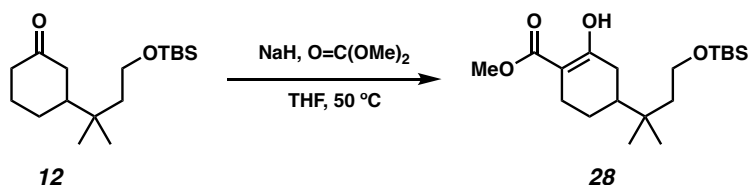
NMR (101 MHz, C₆D₆) δ = 205.53, 172.92, 150.40, 145.03, 126.20, 109.39, 77.77, 52.32, 50.51, 49.20, 45.85, 40.18, 33.72, 30.68, 29.93, 24.53, 20.69; IR (Neat Film, NaCl) 2953, 1743, 1711, 1445, 1247, 1213, 1018, 886, 799 cm⁻¹; HRMS (ESI⁺): m/z calc'd for C₁₇H₂₅O₃ [M+H]⁺: 277.1798, found 277.1787; $[\alpha]_D^{23.23}$ 66.63 (c 0.4, CHCl₃).



3-(4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)cyclohexan-1-one **12**.

A procedure from the literature²³ was modified as follows: a flask with stir bar under N₂ was charged with Fe(acac)₃ (7.3 g, 20.8 mmol, 1.0 equiv), DCE (58 mL) and ethylene glycol (11 mL). Cyclohexenone (2.0 g, 20.8 mmol, 1.0 equiv) and *tert*-butyldimethyl((3-methylbut-3-en-1-yl)oxy)silane²⁴ (7.5 g, 37.5 mmol, 1.8 equiv) were added sequentially, followed by PhSiH₃ (4.0 g, 37.5 mmol, 1.8 equiv). The solution was stirred at 60 °C for 20 h, cooled to 18 °C, and additional Fe(acac)₃ (3.1 g, 8.8 mmol, 0.4 equiv) was added. The mixture was then heated to 60 °C for 20 h and the DCE was removed under reduced pressure. Water (100 mL) was added to the red residue, and this mixture was extracted with hexanes (5 x 50 mL). The combined organic extracts were dried with Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→10% EtOAc/hexanes) to furnish **12** (2.9 g, 48% yield) as a colorless oil. A small sample was further purified via silica gel chromatography to obtain an analytical sample. ¹H NMR (400 MHz, C₆D₆) δ = 3.56 (t, J = 7.2 Hz, 2H), 2.39 – 2.31 (m, 1H), 2.21 (ddq, J = 13.9, 4.1, 2.1 Hz, 1H), 1.76 (tdd, J = 13.9,

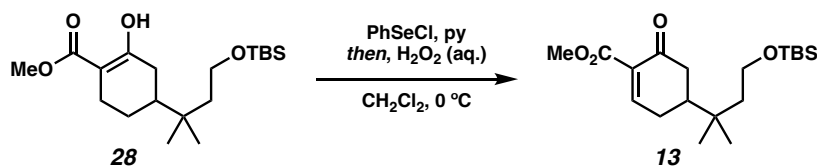
6.4, 1.0 Hz, 1H), 1.67 (td, $J = 13.4, 1.0$ Hz, 1H), 1.57 (dddd, $J = 13.1, 6.1, 3.3, 2.4$ Hz, 1H), 1.54 – 1.46 (m, 1H), 1.39 (td, $J = 7.0, 3.4$ Hz, 2H), 1.28 (ddt, $J = 13.3, 11.9, 3.3$ Hz, 1H), 1.22 – 1.08 (m, 1H), 0.98 (s, 9H), 0.90 – 0.78 (m, 1H), 0.67 (s, 3H), 0.66 (s, 3H), 0.07 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, C_6D_6) $\delta = 209.32, 59.86, 47.75, 43.20, 42.59, 41.29, 34.49, 26.19, 25.86, 25.64, 24.85, 24.65, 18.46, -5.13$; IR (Neat Film, NaCl) 2955, 2930, 2858, 1714, 1471, 1388, 1253, 1092, 835, 777 cm^{-1} ; HRMS (ESI⁺): m/z calc'd for $\text{C}_{17}\text{H}_{35}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$: 299.2401, found 299.2396.



methyl 4-(4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)-2-hydroxycyclohex-1-ene-1-carboxylate 28.

To a 100 mL flask fitted with a reflux condenser under N_2 was added NaH (60% dispersion in mineral oil, 1.3 g, 24 mmol, 5.0 equiv), THF (30 mL), and $\text{CO}(\text{OMe})_2$ (2.4 g, 26.8 mmol, 4.0 equiv). The vigorously stirred solution was brought to a reflux at which point a solution of ketone **12** (2.0 g, 6.7 mmol, 1.0 equiv) in THF (15 mL) was added dropwise over 2 h with a syringe pump. After a further 2 h at reflux the solution was cooled to 0 °C and saturated aqueous NH_4Cl (10 mL) was added slowly (Warning – H_2 evolution!). Once gas evolution ceased, H_2O (50 mL) and ether (20 mL) were added and the organic layer was separated, washed with brine, dried with Na_2SO_4 , and concentrated under reduced pressure. The crude oil was purified by automated silica gel flash chromatography (5→7.5% EtOAc/hexanes) to furnish **28** as a yellow oil (1.78 g, 75% yield). ^1H NMR (400 MHz,

CDCl_3) δ = 12.08 (s, 1H), 3.75 (s, 3H), 3.66 (t, J = 7.5 Hz, 2H), 2.41 (ddt, J = 15.9, 5.1, 1.8 Hz, 1H), 2.27 (ddt, J = 17.7, 5.2, 1.4 Hz, 1H), 2.16 – 2.01 (m, 2H), 1.84 (ddt, J = 14.6, 4.3, 2.0 Hz, 1H), 1.52 (td, J = 7.3, 2.6 Hz, 2H), 1.44 (tdd, J = 11.9, 5.3, 2.1 Hz, 1H), 1.10 (qd, J = 12.2, 5.1 Hz, 1H), 0.89 – 0.88 (m, 15H), 0.05 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 173.04, 172.53, 97.59, 59.95, 51.50, 42.52, 42.42, 34.09, 30.71, 26.12, 24.78, 24.47, 23.64, 23.27, 18.45, -5.13; IR (Neat Film, NaCl) 2954, 2856, 1660, 1620, 1441, 1360, 1282, 1220, 1093, 833, 774 cm^{-1} ; HRMS (ESI⁺): m/z calc'd for $\text{C}_{19}\text{H}_{37}\text{O}_4\text{Si}$ $[\text{M}+\text{H}]^+$: 357.2456, found 357.2465.

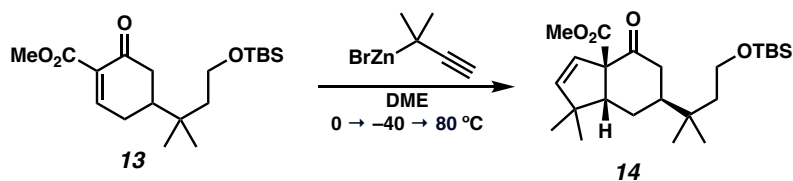


methyl 4-(4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)-6-oxocyclohex-1-ene-1-carboxylate 13.

Pyridine (1.32 g, 16.8 mmol, 1.5 equiv) was added dropwise to a solution of PhSeCl (5.9 g, 30.8 mmol, 1.1 equiv) in CH_2Cl_2 (40 mL) at 0 $^\circ\text{C}$ in a 250 mL flask under N_2 . A solution of ester **28** (4.0 g, 11.2 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added dropwise over 30 min and the resulting solution was stirred at 0 $^\circ\text{C}$ for a further 2 h. Saturated aqueous NH_4Cl (80 mL) was added, and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (20 mL x 2), and the combined organic extracts were concentrated under reduced pressure into a 250 mL flask. CH_2Cl_2 (140 mL) was added to the residue and the solution was cooled to 0 $^\circ\text{C}$ followed by addition of 35% H_2O_2 (5 mL). The mixture was stirred vigorously for 2.5 h, then H_2O (20 mL) was added, and the organic layer separated. The

aqueous layer was further extracted with CH₂Cl₂ (20 mL), and the combined organic extracts were washed with saturated aqueous NaHCO₃ and dried with Na₂SO₄. The solution was concentrated under reduced pressure to yield a yellow residue that was agitated with pentane (40 mL), filtered to remove solids, and concentrated to yield the title compound (**13**) as a yellow oil (3.9 g, 97% yield).

Note: This material was directly carried forward to the next step. While this material is sufficiently pure for most purposes, **13** degrades rapidly on silica or alumina and cannot be easily purified. Additionally, **13** is not stable for extended periods of time, even when stored at –15 °C. ¹H NMR and HRMS data is provided as a courtesy. ¹H NMR (600 MHz, CDCl₃) δ = 7.73 (dd, *J* = 6.3, 2.3 Hz, 1H), 3.79 (s, 3H), 3.65 (t, *J* = 7.1 Hz, 2H), 2.63 – 2.56 (m, 2H), 2.27 (ddd, *J* = 19.8, 11.4, 2.2 Hz, 1H), 2.24 – 2.18 (m, 1H), 1.99 (ddt, *J* = 14.9, 11.5, 3.9 Hz, 1H), 1.53 – 1.43 (m, 2H), 0.90 (s, 6H), 0.86 (s, 9H), 0.02 (s, 6H); HRMS (ESI⁺): *m/z* calc'd for C₁₉H₃₅O₄Si [M+H]⁺: 355.2313, found 355.2299.

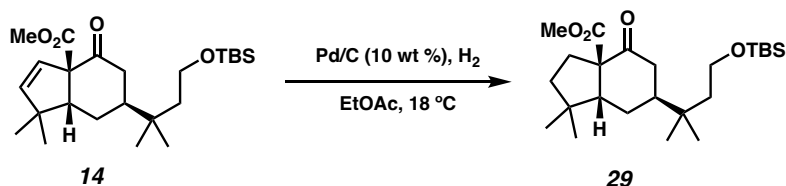


methyl 6-(((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)-1,1-dimethyl-4-oxo-1,4,5,6,7,7a-hexahydro-3aH-indene-3a-carboxylate 14.

To a dry flask under N₂ was added activated Zn dust (2.12 g, 32.43 mmol, 2.5 equiv) and DME (46 mL). The mixture was cooled to 0 °C and 3-bromo-3-methylbut-1-yne (prepared according to a previously reported procedure²²)(4.77 g, 32.43 mmol, 2.5 equiv) was added in one portion. After 1 h most of the Zn had dissolved and the mixture was cooled to –40

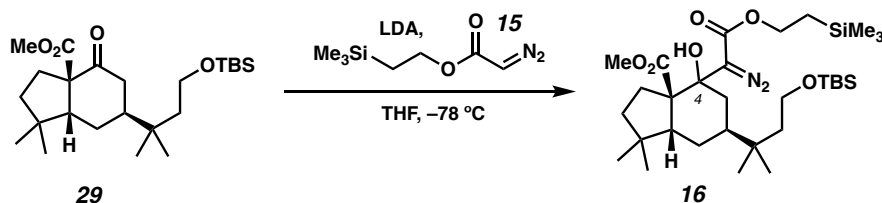
°C at which point enone **13** (4.6 g, 12.97 mmol, 1.0 equiv) in DME (46 mL) was added dropwise over 1 h. The cloudy solution was then gradually allowed to warm to –15 °C and stirred at that temperature for 16 h. The reaction was then allowed to warm to 18 °C and filtered into a fresh flask via a glass fritted cannula filter to yield a perfectly homogeneous, yellow solution. The solution was heated to 80 °C for 5 h *without stirring* and then cooled to 0 °C and quenched with saturated, aqueous NH₄Cl. The mixture was extracted with EtOAc (75 mL x 3), and the combined organic extracts were washed with brine, dried with Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→15% EtOAc/hexanes) to furnish **14** (3.54 g, 65% yield) as a 6.3:1 mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ = 5.82 (d, *J* = 5.7 Hz, 1H), 5.80 (d, *J* = 5.8 Hz, 1H), 3.74 (s, 3H), 3.65 (t, *J* = 7.5 Hz, 2H), 2.84 (dd, *J* = 6.8, 1.7 Hz, 1H), 2.41 (ddd, *J* = 12.8, 3.8, 1.9 Hz, 1H), 2.32 (t, *J* = 12.4 Hz, 1H), 1.95 – 1.74 (m, 3H), 1.52 (tt, *J* = 13.4, 6.7 Hz, 2H), 1.10 (s, 3H), 0.91 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 210.02, 171.52, 144.92, 126.45, 71.21, 59.76, 52.91, 52.61, 48.28, 45.41, 41.95, 41.34, 35.11, 28.63, 25.99, 24.72, 24.55, 24.36, 22.59, 18.34, -5.25; IR (Neat Film, NaCl) 2954, 2858, 1740, 1715, 1471, 1254, 1092, 836, 775 cm⁻¹; HRMS (ESI⁺): *m/z* calc'd for C₂₄H₄₃O₄Si [M+H]⁺: 423.2925, found 423.2929.

Note: The presence of the minor diastereomer does not impede future steps, but an analytical sample was prepared through reverse phase chromatography (Teledyne ISCO, MeCN/water).



methyl 6-(4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)-1,1-dimethyl-4-oxooctahydro-3aH-indene-3a-carboxylate 29.

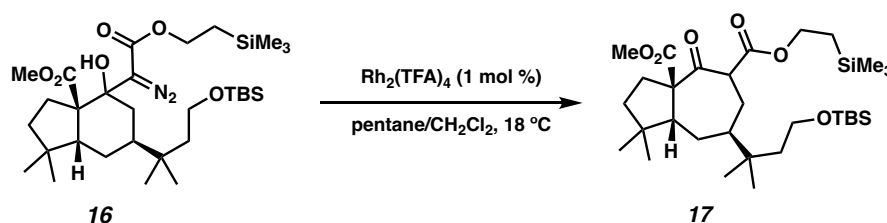
A 50 mL flask under N₂ was charged with Pd/C (30 mg, 10%w loading) and a solution of compound **14** (310 mg, 0.73 mmol, 1 equiv) in EtOAc (10 mL) was added. A H₂ filled balloon was used to purge the solution for 10 min, at which point a fresh H₂ balloon was installed, and the mixture was stirred vigorously for 3 h. The mixture was filtered through celite and concentrated under reduced pressure to furnish **29** as a colorless oil (310 mg, >98% yield). ¹H NMR (400 MHz, C₆D₆) δ = 3.62 (t, *J* = 7.2 Hz, 2H), 3.24 (s, 3H), 3.04 (ddd, *J* = 14.2, 10.9, 8.2 Hz, 1H), 2.74 (dd, *J* = 5.4, 3.6 Hz, 1H), 2.61 – 2.54 (m, 1H), 2.28 (dd, *J* = 13.1, 12.1 Hz, 1H), 1.95 (ddd, *J* = 14.2, 8.7, 2.8 Hz, 1H), 1.85 – 1.73 (m, 1H), 1.69 (tdd, *J* = 5.7, 3.3, 1.7 Hz, 2H), 1.56 – 1.31 (m, 4H), 0.99 (s, 9H), 0.89 (s, 3H), 0.74 (s, 3H), 0.71 (s, 3H), 0.68 (s, 3H), 0.09 (s, 6H); ¹³C {¹H} NMR (101 MHz, C₆D₆) δ = 207.29, 173.64, 65.12, 59.90, 54.55, 52.22, 45.62, 43.08, 42.53, 41.88, 40.79, 35.02, 29.06, 29.04, 26.20, 24.64, 24.33, 23.77, 23.06, 18.48, -5.11; IR (Neat Film, NaCl) 2952, 2860, 1739, 1714, 1469, 1250, 1206, 1092, 837, 774 cm⁻¹; HRMS (ESI+): *m/z* calc'd for C₂₄H₄₅O₄Si [M+H]⁺: 425.3082, found 425.3070.



methyl 6-(4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)-4-(1-diazo-2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)-4-hydroxy-1,1-dimethyloctahydro-3aH-indene-3a-carboxylate 16.

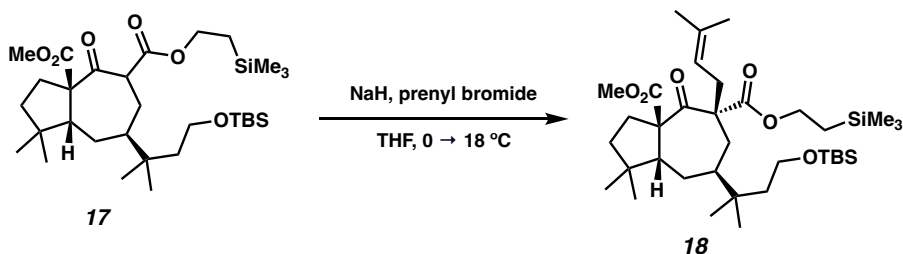
To a 100 mL Schlenk flask under N₂ was added NH(*i*-Pr)₂ (1.37 g, 13.5 mmol, 4.5 equiv) and THF (7 mL). The flask was cooled to –78 °C in a dry ice/acetone bath. *n*-BuLi (2.5M in hexanes, 4.2 mL, 10.5 mmol, 3.5 equiv) was added dropwise over 15 min and the solution was left to stir at –78 °C for 15 min. A solution of diazoacetate **15** (prepared according to a previously reported procedure²⁵) (2.23 g, 12 mmol, 4.0 equiv) in THF (7 mL) was added dropwise over 15 min and the blood-red solution was stirred for a further 30 min. A solution of ketone **29** (1.26 g, 3.0 mmol, 1.0 equiv) in THF (24 mL) was then added dropwise over 30 min and the reaction was left to stir for an additional 45 min. A solution of AcOH (810 mg) in Et₂O (4 mL) was added slowly and the reaction was removed from the cold bath. Water (80 mL) was added, and the mixture was extracted with EtOAc (20 mL x 3). The combined organic extracts were dried with Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→15% EtOAc/hexanes) to furnish a yellow oil. The oil was dried *in vacuo* overnight to remove residual diazoacetate (**15**), furnishing **16** (1.63 g, 89% yield) as a yellow oil. We have been unable to unambiguously determine the stereochemistry at C4 to date. ¹H NMR (400 MHz, C₆D₆) δ = 5.88 (br s, 1H), 4.12 (qdd, *J* = 10.9, 9.0, 7.5 Hz, 2H), 3.91 – 3.75 (m, 2H), 3.39 (s, 3H), 2.74 (ddd, *J* = 13.8, 7.8, 3.6 Hz,

1H), 2.52 (ddd, $J = 13.7, 10.3, 7.7$ Hz, 1H), 2.25 – 2.04 (m, 4H), 1.80 – 1.66 (m, 3H), 1.61 (ddt, $J = 11.3, 7.6, 4.3$ Hz, 2H), 1.49 (ddd, $J = 12.3, 10.4, 7.8$ Hz, 1H), 1.07 (s, 3H), 1.01 (s, 9H), 0.98 (s, 3H), 0.94 (s, 6H), 0.76 (ddd, $J = 9.2, 7.2, 1.5$ Hz, 2H), 0.13 (d, $J = 2.1$ Hz, 6H), -0.14 (s, 9H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, C_6D_6) $\delta = 176.51, 168.61, 72.10, 63.71, 63.58, 60.10, 53.42, 51.65, 43.26, 42.57, 41.21, 35.73, 35.55, 34.81, 34.27, 30.78, 28.83, 26.24, 25.19, 24.83, 23.44, 22.34, 18.51, 17.51, -1.64, -5.03$; IR (Neat Film, NaCl) 3419, 2952, 2089, 1667, 1386, 1305, 1090, 840, 775 cm^{-1} ; HRMS (ESI⁺): m/z calc'd for $\text{C}_{31}\text{H}_{58}\text{N}_2\text{O}_6\text{Si}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 633.3726, found 633.3719.



3a-methyl 5-(2-(trimethylsilyl)ethyl)-7-(4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)-1,1-dimethyl-4-oxooctahydroazulene-3a,5(1H)-dicarboxylate 17

To a solution of diazoacetate **16** (97 mg, 0.16 mmol, 1 equiv) in pentane/ CH_2Cl_2 (4:1, 5 mL) under Ar was added $\text{Rh}_2(\text{TFA})_4$ (1 mg, 0.0016 mmol, 0.01 equiv). The reaction was stirred at 18 °C for 24 h, concentrated under reduced pressure and purified by automated silica gel flash chromatography (Teledyne ISCO, 0→10% EtOAc/hexanes) to furnish **17** (85 mg, 92% yield) as a colorless oil. **Note:** Title compound **17** was isolated as a mixture of dynamically interconverting tautomers and was used directly in the next step. ^1H NMR spectral data (See page S36) and HRMS data is provided as a courtesy. HRMS (ESI⁺): m/z calc'd for $\text{C}_{31}\text{H}_{58}\text{O}_6\text{Si}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 605.3664, found 605.3656.

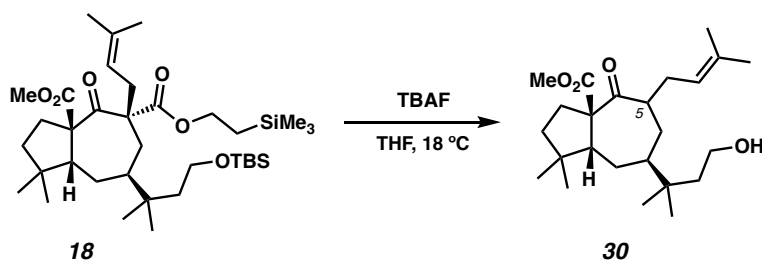


3a-methyl 5-(2-(trimethylsilyl)ethyl)-7-(4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)-1,1-dimethyl-5-(3-methylbut-2-en-1-yl)-4-oxooctahydroazulene-3a,5(1H)-dicarboxylate **18.**

A 25 mL flask under N_2 was charged with ester **17** (85 mg, 0.14 mmol, 1.0 equiv) and THF (4.5 mL). The solution was cooled to 0°C and NaH (60% dispersion in mineral oil, 16 mg, 0.41 mmol, 4 equiv) was added in one portion and the cold bath was removed. After stirring at 18°C for 1 h, the solution was cooled to 0°C and prenol bromide (101 mg, 0.68 mmol, 5 equiv) was added dropwise. The reaction was allowed to warm to 18°C and stirred at this temperature for 2.5 h after which it was cooled to 0°C and quenched slowly with saturated aqueous NH_4Cl (1 mL). The mixture was extracted with EtOAc (1 mL x 3), and the combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure.^a The crude residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→10% Et_2O /hexanes) to furnish **18** (79 mg, 89% yield) as colorless oil.

Note: ^aCare should be taken to completely remove excess prenol bromide before loading onto silica as prenol bromide may decompose to HBr with significant exotherm resulting in a drastically decreased yield. ^1H NMR (400 MHz, C_6D_6) δ = 5.62 (dddd, J = 6.9, 5.5, 2.8, 1.4 Hz, 1H), 4.34 – 4.20 (m, 2H), 3.78 (ddt, J = 10.9, 7.2, 3.6 Hz, 2H), 3.27 (s, 3H), 3.26 – 3.21 (m, 1H), 3.11 (td, J = 13.9, 6.2 Hz, 1H), 3.03 (dd, J = 14.9, 8.2 Hz, 1H), 2.46 (ddt, J = 14.9, 4.8, 1.5 Hz, 1H), 2.26 – 2.11 (m, 2H), 2.01 – 1.94 (m, 1H), 1.94 – 1.70 (m,

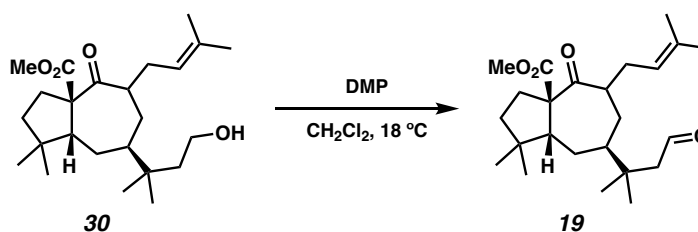
5H), 1.69 (d, $J = 1.5$ Hz, 3H), 1.67 (s, 3H), 1.39 (ddd, $J = 13.8, 12.0, 6.2$ Hz, 1H), 1.27 (ddd, $J = 12.1, 6.2, 1.6$ Hz, 1H), 1.08 (d, $J = 1.2$ Hz, 6H), 1.06 (s, 3H), 1.02 (s, 11H), 0.78 (s, 3H), 0.15 (s, 3H), 0.15 (s, 3H), -0.10 (s, 9H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, C_6D_6) $\delta = 201.68, 174.33, 171.83, 133.43, 120.43, 70.21, 63.35, 63.20, 59.84, 51.90, 48.32, 44.69, 43.70, 40.81, 39.08, 38.84, 36.31, 34.55, 33.95, 28.68, 26.74, 26.59, 26.23, 26.23, 24.05, 22.77, 18.50, 18.31, 17.83, -1.71, -4.95, -4.99$; IR (Neat Film, NaCl) 2953, 2860, 1731, 1703, 1458, 1386, 1367, 1304, 1250, 1093, 838, 776, 671; HRMS (ESI⁺): m/z calc'd for $\text{C}_{36}\text{H}_{66}\text{O}_6\text{Si}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 673.4298, found 673.4301.



methyl 7-(4-hydroxy-2-methylbutan-2-yl)-1,1-dimethyl-5-(3-methylbut-2-en-1-yl)-4-oxooctahydroazulene-3a(1H)-carboxylate 30.

To a solution of compound **18** (73 mg, 0.11 mmol, 1 equiv) in THF (1.1 mL) at 0 °C under N_2 was slowly added TBAF (1M in THF, 0.39 mL, 0.39 mmol, 3.5 equiv). The solution warmed to 18 °C and stirred at this temperature for 18 h. Saturated aqueous NH_4Cl (1 mL) was added, and the mixture extracted with EtOAc (1 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→50% EtOAc/hexanes) to furnish **30** (43 mg, 98% yield) as colorless oil. We have been unable to unambiguously determine the stereochemistry at C5 to date. ^1H NMR (400 MHz,

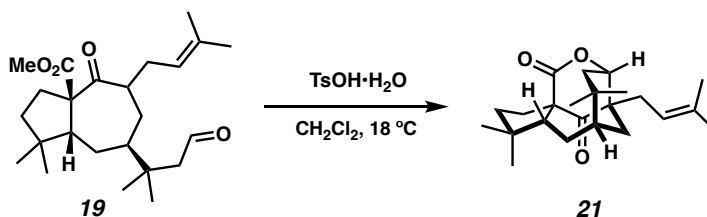
C_6D_6) δ = 5.09 (ddq, J = 8.7, 5.8, 1.5 Hz, 1H), 3.43 (t, J = 7.5 Hz, 2H), 3.28 (s, 3H), 3.21 (td, J = 13.5, 6.4 Hz, 1H), 3.07 – 2.98 (m, 1H), 2.96 (dd, J = 12.4, 2.9 Hz, 1H), 2.77 (dq, J = 9.6, 4.7 Hz, 1H), 2.17 (dt, J = 14.9, 9.5 Hz, 1H), 1.74 – 1.66 (m, 3H), 1.65 (d, J = 1.8 Hz, 3H), 1.64 – 1.57 (m, 2H), 1.55 (d, J = 1.2 Hz, 3H), 1.54 – 1.43 (m, 3H), 1.37 – 1.32 (m, 1H), 1.21 (ddd, J = 15.7, 7.9, 4.5 Hz, 1H), 1.04 (s, 3H), 0.89 (s, 3H), 0.86 (s, 3H), 0.73 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, C_6D_6) δ = 207.27, 175.50, 132.68, 123.42, 68.22, 59.19, 52.10, 48.69, 48.20, 43.79, 43.74, 40.14, 38.62, 36.05, 32.18, 28.26, 27.24, 26.08, 25.99, 25.86, 25.68, 24.77, 22.17, 17.97; IR (Neat Film, NaCl) 3392, 2957, 1703, 1462, 1366, 1251, 1199, 1120, 1051, 1018; HRMS (ESI⁺): m/z calc'd for $\text{C}_{24}\text{H}_{41}\text{O}_4$ $[\text{M}+\text{H}]^+$: 393.2999, found 393.3008.



methyl 1,1-dimethyl-7-(2-methyl-4-oxobutan-2-yl)-5-(3-methylbut-2-en-1-yl)-4-oxooctahydroazulene-3a(1H)-carboxylate 19.

To an 8 mL vial was added alcohol **30** (43 mg, 0.11 mmol, 1.0 equiv) and CH_2Cl_2 (4 mL). DMP (116 mg, 0.28 mmol, 2.5 equiv) was added, and the vial was stirred under Ar for 3 h. The reaction was concentrated under reduced pressure and hexanes (1 mL) was added. The heterogeneous mixture was agitated and concentrated under reduced pressure. Hexanes (4 mL) was added, and the mixture was sonicated for 2 min. The mixture was filtered over celite, and the filter cake rinsed with hexanes (4 mL). The combined organic fractions were concentrated under reduced pressure to and purified by flash silica gel

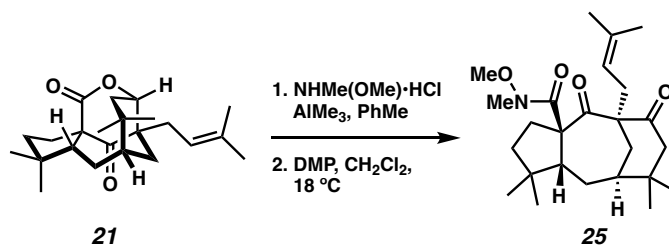
chromatography (0→20% EtOAc/hexanes) to provide aldehyde **19** (35 mg, 81% yield) as a colorless oil. ^1H NMR (400 MHz, C_6D_6) δ = 9.51 (t, J = 2.9 Hz, 1H), 5.07 (ddq, J = 8.8, 5.8, 1.5 Hz, 1H), 3.27 (s, 3H), 3.19 (td, J = 13.7, 6.4 Hz, 1H), 3.05 – 2.94 (m, 1H), 2.86 (dd, J = 12.5, 2.7 Hz, 1H), 2.73 (dq, J = 9.5, 4.6 Hz, 1H), 2.10 (dt, J = 14.9, 9.4 Hz, 1H), 2.02 (dd, J = 14.6, 2.9 Hz, 1H), 1.90 (dd, J = 14.6, 2.9 Hz, 1H), 1.66 (d, J = 1.6 Hz, 3H), 1.65 – 1.55 (m, 4H), 1.55 (d, J = 1.2 Hz, 3H), 1.54 – 1.49 (m, 2H), 1.36 – 1.28 (m, 1H), 1.14 (ddd, J = 16.3, 12.6, 6.6 Hz, 1H), 0.98 (s, 3H), 0.90 (s, 3H), 0.86 (s, 3H), 0.69 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, C_6D_6) δ = 206.82, 201.24, 175.38, 132.94, 123.08, 68.15, 53.91, 52.12, 48.52, 48.08, 43.69, 40.06, 39.22, 37.19, 32.15, 28.18, 27.16, 25.97, 25.96, 25.82, 25.70, 24.68, 22.06, 17.92; IR (Neat Film, NaCl) 2957, 1703, 1460, 1255, 1196, 1120; HRMS (ESI⁺): m/z calc'd for $\text{C}_{24}\text{H}_{39}\text{O}_4$ $[\text{M}+\text{H}]^+$: 391.2843, found 391.2841.



1,1,8,8-tetramethyl-5-(3-methylbut-2-en-1-yl)decahydro-4H-6,3a-(epoxymethano)-5,9-methanocyclopenta[9]annulene-4,13-dione **2.**

A 250 mL flask was charged with aldehyde **19** (57 mg, 0.15 mmol, 1.0 equiv), p -TsOH $\cdot$ H $_2$ O (111 mg, 0.58 mmol, 4.0 equiv) and CH_2Cl_2 (15 mL). The vial was sealed under Ar and stirred at 18 °C for 36 h. The solution was concentrated under reduced pressure, hexanes (20 mL) was added, and the solution was filtered to remove p -TsOH $\cdot$ H $_2$ O. The crude residue was purified by flash silica gel chromatography (0→30% Et $_2$ O/hexanes) to furnish **21** (24 mg, 46% yield) as a colorless oil. Starting aldehyde **19** (17

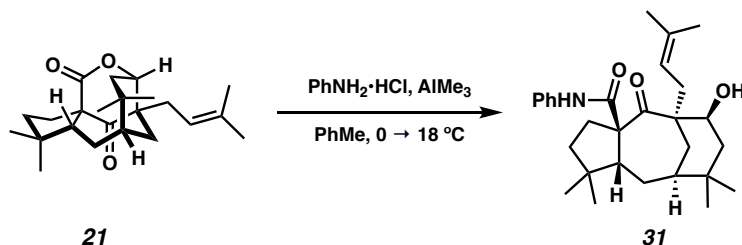
mg, 30%) could also be recovered. ^1H NMR (400 MHz, C_6D_6) δ = 5.15 (ddp, J = 8.4, 7.0, 1.5 Hz, 1H), 4.57 (dd, J = 10.4, 7.8 Hz, 1H), 2.84 (td, J = 12.8, 6.1 Hz, 1H), 2.64 (dd, J = 14.4, 8.3 Hz, 1H), 2.31 (tdd, J = 11.6, 7.6, 4.5 Hz, 2H), 2.21 (dd, J = 13.4, 4.0 Hz, 1H), 2.14 (td, J = 12.3, 6.2 Hz, 1H), 1.90 (ddd, J = 15.9, 10.4, 1.4 Hz, 1H), 1.78 (ddd, J = 14.2, 3.1, 1.8 Hz, 1H), 1.65 (dddd, J = 15.2, 6.1, 3.8, 1.8 Hz, 1H), 1.58 (d, J = 1.2 Hz, 3H), 1.58 – 1.53 (m, 2H), 1.53 (d, J = 1.4 Hz, 3H), 1.40 (dd, J = 14.1, 3.6 Hz, 1H), 1.13 – 1.00 (m, 2H), 0.86 (s, 3H), 0.69 (s, 3H), 0.66 (s, 3H), 0.59 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, C_6D_6) δ = 207.83, 175.98, 136.30, 118.95, 74.24, 67.24, 51.49, 49.52, 44.59, 43.79, 42.76, 40.22, 37.41, 36.99, 32.62, 31.49, 30.62, 30.55, 28.83, 28.30, 26.09, 23.34, 17.96; IR (Neat Film, NaCl) 2957, 1748, 1708, 1458, 1366, 1247; HRMS (ESI+): m/z calc'd for $\text{C}_{23}\text{H}_{35}\text{O}_3$ $[\text{M}+\text{H}]^+$: 359.2581, found 359.2571.



N-methoxy-N,1,1,8,8-pentamethyl-5-(3-methylbut-2-en-1-yl)-4,6-dioxodecahydro-5,9-methanocyclopenta[9]annulene-3a(1H)-carboxamide 25.

A small test tube equipped with a septum under N_2 was charged with *N,O*-dimethylhydroxylamine hydrochloride (27 mg, 0.28 mmol, 10 equiv) and PhMe (0.3 mL). The reaction was cooled to 0 °C and AlMe_3 (0.14 mL, 2M in PhMe, 0.28 mmol, 10 equiv) was added dropwise. The homogenous solution was stirred at 0 °C for 45 min, at which point lactone **21** (10 mg, 28 μmol , 1.0 equiv) in PhMe (0.3 mL) was added dropwise and the reaction was left to warm naturally over 20 h. The reaction was quenched by

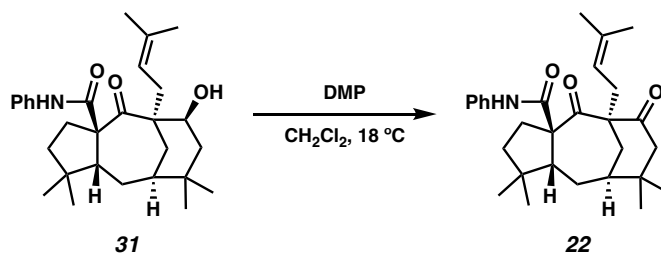
sequentially adding a saturated solution of potassium sodium tartrate (1 mL), water (0.2 mL), CH₂Cl₂ (1 mL), and stirring for 3 h. The organic layer was separated, and the aqueous layer extracted further with CH₂Cl₂ (2x2 mL). The combined organic extracts were dried with Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by preparatory TLC (18% EtOAc in hexanes) and directly used in the next step. The crude residue was transferred to a 4 mL vial, and CH₂Cl₂ (1 mL) was added. DMP (30 mg, 0.07 mmol, 2.5 equiv) was added, and the solution was stirred under Ar for 2 h. The reaction was concentrated under reduced pressure and hexanes (1 mL) was added. The mixture was agitated and filtered over celite, and the filter cake rinsed with hexanes (1 mL). The combined organic fractions were concentrated under reduced pressure to and purified by preparatory TLC (10% EtOAc in hexanes) to provide amide **25** (3 mg, 26% yield) as a colorless oil. ¹H NMR (400 MHz, C₆D₆) δ = 5.35 (ddp, *J* = 9.6, 5.4, 1.4 Hz, 1H), 3.28 – 3.03 (m, 5H), 2.94 (s, 3H), 2.88 (s, 3H), 2.43 (ddd, *J* = 14.0, 3.6, 1.7 Hz, 1H), 2.29 (dd, *J* = 19.2, 1.8 Hz, 1H), 1.89 (dddd, *J* = 15.1, 6.0, 4.0, 1.7 Hz, 1H), 1.73 (dd, *J* = 12.5, 5.6 Hz, 1H), 1.68 (t, *J* = 1.4 Hz, 3H), 1.64 (d, *J* = 3.2 Hz, 1H), 1.64 – 1.62 (m, 3H), 1.55 (ddd, *J* = 13.0, 5.7, 2.3 Hz, 1H), 1.43 – 1.36 (m, 2H), 1.29 (td, *J* = 14.6, 2.1 Hz, 1H), 1.23 (s, 3H), 0.89 (s, 3H), 0.84 (s, 3H), 0.76 (s, 3H); ¹³C{¹H} NMR (101 MHz, C₆D₆) δ = 210.01, 201.59, 176.51, 134.80, 121.66, 70.70, 67.17, 59.18, 53.04, 46.09, 43.64, 40.76, 39.72, 38.83, 35.31, 34.73, 34.41, 33.41, 31.96, 31.62, 29.15, 27.05, 26.08, 24.40, 18.27; IR (Neat Film, NaCl) 2960, 2868, 1684, 1654, 1458, 1364, 1185, 1005, 983, 941, 844; HRMS (ESI⁺): *m/z* calc'd for C₂₅H₄₀NO₄ [M+H]⁺: 418.2952, found 418.2968.



6-hydroxy-1,1,8,8-tetramethyl-5-(3-methylbut-2-en-1-yl)-4-oxo-N-phenyldecahydro-5,9-methanocyclopenta[9]annulene-3a(1H)-carboxamide 31.

A small test tube equipped with a septum under N_2 was charged with aniline hydrochloride (86 mg, 0.66 mmol, 10 equiv) and PhMe (1.2 mL). The reaction was cooled to 0 °C and AlMe_3 (0.33 mL, 2M in PhMe, 0.66 mmol, 10 equiv) was added dropwise. The homogenous solution was stirred at 0 °C for 45 min, at which point lactone **21** (24 mg, 66 μmol , 1.0 equiv) in PhMe (1.2 mL) was added dropwise and the reaction was left to warm naturally over 20 h. The reaction was quenched by sequentially adding a saturated solution of potassium sodium tartrate (8 mL), water (5 mL), CH_2Cl_2 (10 mL), and stirring for 1 h. The entire mixture was filtered over celite, the organic layer separated, and the aqueous layer extracted further with CH_2Cl_2 (2x5 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography (0→15% EtOAc/hexanes) to furnish **31** (25 mg, 84% yield) as a colorless oil. ^1H NMR (400 MHz, C_6D_6) δ = 7.55 – 7.49 (m, 2H), 7.35 (s, 1H), 7.10 – 7.04 (m, 2H), 6.91 – 6.79 (m, 1H), 5.49 (ddt, J = 7.7, 6.1, 1.5 Hz, 1H), 3.71 (dt, J = 11.6, 5.6 Hz, 1H), 3.63 (dd, J = 11.7, 4.3 Hz, 1H), 2.76 (dd, J = 14.3, 7.9 Hz, 1H), 2.47 (dd, J = 14.3, 7.5 Hz, 1H), 2.43 – 2.28 (m, 3H), 1.98 (d, J = 5.2 Hz, 1H), 1.87 – 1.79 (m, 1H), 1.73 (ddd, J = 14.8, 4.4, 1.4 Hz, 1H), 1.63 (d, J = 1.4 Hz, 3H), 1.60 – 1.50 (m, 4H), 1.39 (dd, J = 14.8, 2.5 Hz, 1H), 1.35 – 1.21 (m, 7H), 0.97 (s, 3H), 0.86 (s, 3H), 0.81 (s, 3H); ^{13}C { ^1H }

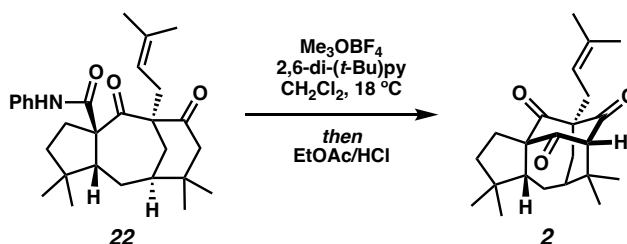
NMR (101 MHz, C_6D_6) δ = 215.13, 169.34, 139.31, 134.79, 129.06, 123.98, 121.95, 120.12, 76.36, 72.63, 58.83, 44.76, 42.93, 40.57, 40.08, 39.48, 38.00, 37.78, 35.51, 34.46, 32.11, 31.17, 29.68, 27.84, 26.27, 25.97, 18.06; IR (Neat Film, NaCl) 3338; 2934, 1660, 1598, 1529, 1439, 1311, 1246, 1030, 752; HRMS (ESI⁺): m/z calc'd for $C_{29}H_{42}NO_3$ $[M+H]^+$: 452.3159, found 452.3163.



1,1,8,8-tetramethyl-5-(3-methylbut-2-en-1-yl)-4,6-dioxo-N-phenyldecahydro-5,9-methanocyclopenta[9]annulene-3a(1H)-carboxamide **22.**

To a 4 mL vial was added alcohol **31** (25 mg, 0.055 mmol, 1.0 equiv) and CH_2Cl_2 (1.1 mL). DMP (52 mg, 0.12 mmol, 2.2 equiv) was added, and the solution was stirred under Ar for 2 h. The reaction was concentrated under reduced pressure and hexanes (0.5 mL) was added. The heterogeneous mixture was agitated and concentrated under reduced pressure. Hexanes (2 mL) was added, and the mixture was sonicated for 2 min. The mixture was filtered over celite, and the filter cake rinsed with hexanes (2 mL). The combined organic fractions were concentrated under reduced pressure and the crude residue purified by silica gel plug (10% EtOAc/hexanes) to provide dione **22** (20 mg, 80% yield) as a white foam. 1H NMR (400 MHz, C_6D_6) δ = 7.38 – 7.34 (m, 2H), 7.07 – 7.02 (m, 2H), 6.88 – 6.81 (m, 1H), 6.70 (s, 1H), 5.36 (ddp, J = 8.0, 6.4, 1.5 Hz, 1H), 3.42 – 3.32 (m, 2H), 2.97 (dd, J = 14.0, 6.5 Hz, 1H), 2.80 (dd, J = 13.9, 8.6 Hz, 1H), 2.64 (td, J = 13.6, 5.8 Hz, 1H), 2.32 –

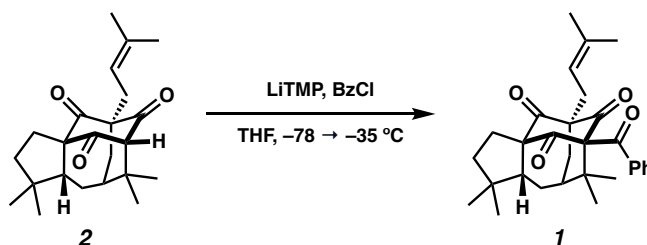
2.22 (m, 2H), 1.94 (dtd, $J = 13.4, 5.7, 2.6$ Hz, 2H), 1.64 (d, $J = 1.4$ Hz, 3H), 1.59 (d, $J = 1.4$ Hz, 3H), 1.58 – 1.51 (m, 1H), 1.41 – 1.33 (m, 2H), 1.28 – 1.22 (m, 4H), 1.21 – 1.12 (m, 1H), 0.89 (s, 3H), 0.79 (s, 3H), 0.72 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, C_6D_6) $\delta = 208.86, 206.64, 168.81, 138.12, 135.52, 128.99, 124.87, 121.20, 121.17, 75.03, 67.36, 52.31, 44.06, 43.56, 40.40, 39.10, 38.64, 35.69, 35.18, 32.27, 31.85, 29.88, 29.67, 27.13, 26.14, 24.86, 18.25$; IR (Neat Film, NaCl) 3363, 2960, 1694, 1671, 1599, 1524, 1438, 1312, 1236, 1170, 1117, 748; HRMS (ESI⁺): m/z calc'd for $\text{C}_{29}\text{H}_{40}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 450.3003, found 450.3016.



1,1,8,8-tetramethyl-5-(3-methylbut-2-en-1-yl)octahydro-4H-3a,7:5,9-dimethanocyclopenta[9]annulene-4,6,12(5H)-trione **2.**

In a glovebox, an 8 mL vial was charged with finely ground Me_3OBF_4 (132 mg, 0.89 mmol, 10 equiv) and a solution of amide **22** (40 mg, 89 μmol , 1.0 equiv) and 2,6-di-*tert*-butylpyridine (187 mg, 0.98 mmol, 11 equiv) in CH_2Cl_2 (4 mL) was added in one portion. The reaction was sealed with a Teflon cap and electrical tape, brought out of the glovebox, sonicated for 3 min, and then vigorously stirred at 18 °C for 45 h. Saturated NaHCO_3 (10 mL) was added, and the organic layer was separated and further extracted with CH_2Cl_2 (3x3 mL). The combined organic fractions were concentrated under reduced pressure, EtOAc (4 mL) and 1M aq. HCl (4 mL) were added, and the mixture stirred at 35 °C for 18

h. The reaction was cooled to 18 °C and saturated NaHCO₃ was added dropwise until effervescence stopped at which point the reaction was extracted with EtOAc (3x2 mL), dried with Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→15% EtOAc/hexanes) to furnish **2** (24 mg, 67% yield) as a colorless oil. ¹H NMR (400 MHz, C₆D₆) δ = 5.51 (tp, *J* = 7.4, 1.5 Hz, 1H), 3.36 (s, 1H), 2.68 (d, *J* = 7.4 Hz, 2H), 2.56 (ddd, *J* = 13.6, 10.6, 8.3 Hz, 1H), 2.44 (ddd, *J* = 13.5, 9.5, 2.6 Hz, 1H), 2.21 (ddd, *J* = 14.1, 5.9, 1.3 Hz, 1H), 1.76 (dd, *J* = 11.6, 8.4 Hz, 1H), 1.72 – 1.64 (m, 5H), 1.63 (d, *J* = 1.4 Hz, 3H), 1.56 (dt, *J* = 12.2, 10.0 Hz, 1H), 1.41 (ddd, *J* = 7.4, 5.7, 1.6 Hz, 1H), 1.34 – 1.30 (m, 1H), 1.10 (ddd, *J* = 14.4, 11.6, 1.5 Hz, 1H), 0.83 (s, 3H), 0.82 (s, 3H), 0.73 (s, 3H), 0.70 (s, 3H); ¹³C {¹H} NMR (101 MHz, C₆D₆) δ = 204.42, 203.37, 200.98, 133.78, 120.30, 77.99, 75.21, 66.65, 54.69, 44.24, 44.03, 42.74, 41.66, 38.40, 30.04, 29.34, 29.02, 28.71, 26.55, 25.81, 24.78, 20.06, 17.75; IR (Neat Film, NaCl) 2953, 1739, 1702, 1690, 1460, 1223, 1205; HRMS (ESI⁺): *m/z* calc'd for C₂₃H₃₃O₃ [M+H]⁺: 357.2424, found 357.2429.



Hypersampsonone M 1.

To a freshly prepared solution of LiTMP²⁶ (0.5M, 225 μL, 0.112 mM, 4.0 equiv) at –78 °C in a test tube was added triketone **2** (10 mg, 28 μM, 1.0 equiv) in THF (350 uL) dropwise over 5 min. The reaction was warmed to –35 °C over 10 min, and this temperature was

maintained for 1 h. The reaction was then cooled to -78°C and BzCl (0.4 M in THF, 295 μL , 0.118 mmol, 4.2 equiv) was added dropwise. The brown solution was warmed to -25°C over 10 min, and this temperature was maintained for 15 min. The reaction was quenched cold with sat. aq. NaHCO_3 and extracted 3x with EtOAc. The crude residue was purified by preparatory TLC (10% Et_2O in hexanes) followed by preparatory HPLC (9.4x250mm XDB-C18 column, 70 – 100% MeCN/water over 5 min, then held at 100% MeCN for 3 min. The title compound eluted at 6.49 min and was observed at 254 nm. **1** (2.5 mg, 20% yield) was isolated as a crystalline solid and unreacted **2** was also recovered (2.2 mg, 22% rsm). ^1H NMR (400 MHz, CDCl_3) δ = 7.39 (ddt, J = 7.9, 6.7, 1.2 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.14 – 7.06 (m, 2H), 5.04 – 4.96 (m, 1H), 2.60 – 2.46 (m, 4H), 2.36 (ddd, J = 13.5, 10.2, 5.1 Hz, 1H), 2.32 – 2.24 (m, 1H), 2.15 – 2.10 (m, 1H), 2.06 (dd, J = 11.0, 9.6 Hz, 1H), 2.02 – 1.95 (m, 1H), 1.87 – 1.75 (m, 2H), 1.66 (s, 3H), 1.65 (d, J = 1.0 Hz, 3H), 1.49 (s, 3H), 1.44 (s, 3H), 1.01 (s, 3H), 0.89 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 205.94, 205.38, 205.21, 193.04, 135.23, 134.93, 132.10, 129.26, 128.03, 119.27, 81.35, 76.32, 68.64, 57.71, 51.51, 44.75, 44.19, 43.64, 41.64, 30.32, 30.02, 29.07, 28.81, 26.20, 25.91, 22.91, 22.02, 18.25; IR (Neat Film, NaCl) 2954, 2930, 1732, 1694, 1446, 1393, 1370, 1243, 1223, 1123, 684; HRMS (ESI⁺): m/z calc'd for $\text{C}_{30}\text{H}_{37}\text{O}_4$ $[\text{M}+\text{H}]^+$: 461.2686, found 461.2690.

Analytical data are in agreement with those reported in the literature.⁶

1.6.3 COMPARISON OF NATURAL AND SYNTHETIC HYPERSAMPSONONE M

Figure 1.6.3.1. Synthetic and natural ^1H NMR of Hypersampsonone M (**1**), CDCl_3 .

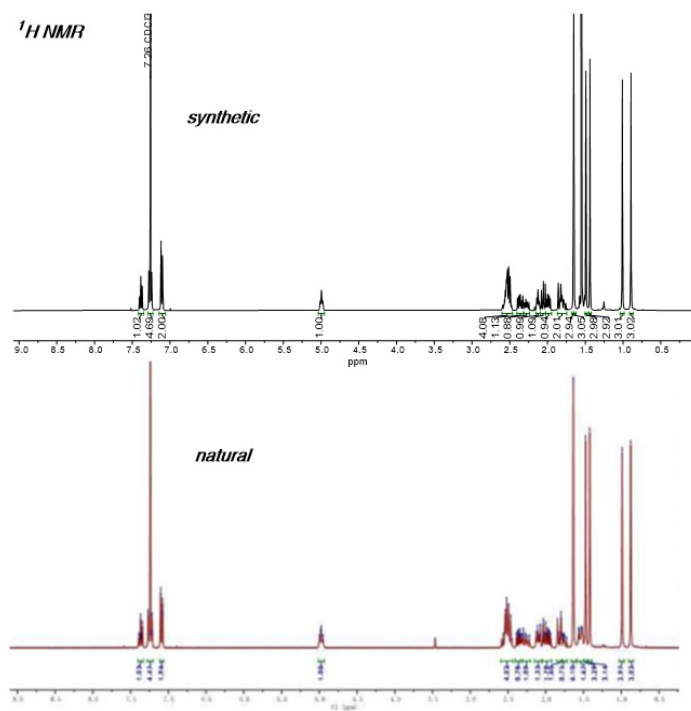


Figure 1.6.3.2. Synthetic and natural ^{13}C NMR of Hypersampsonone M (**1**), CDCl_3 .

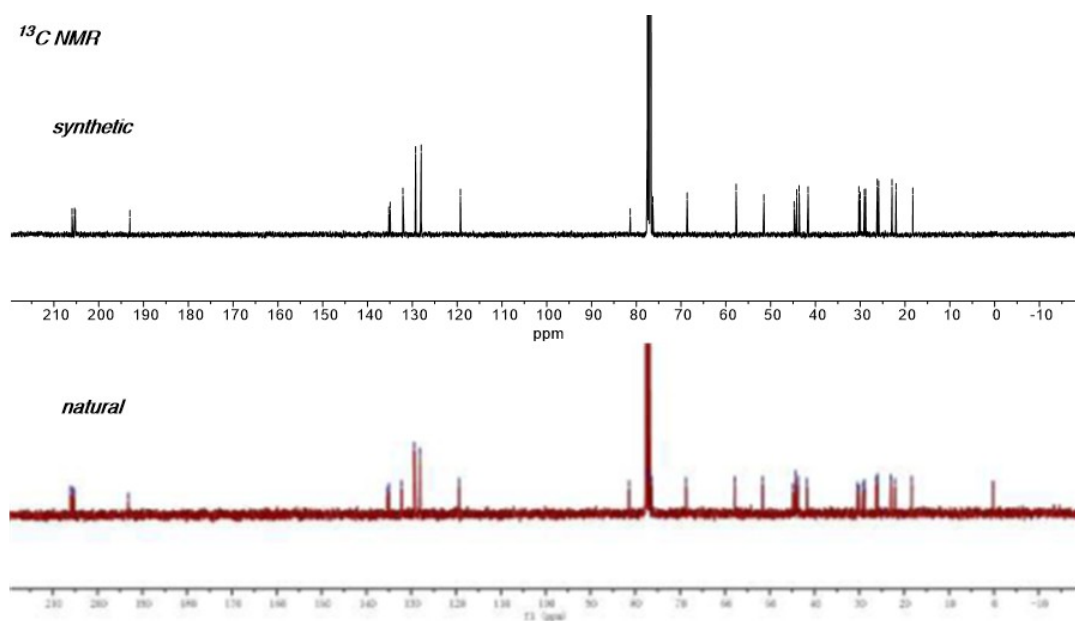
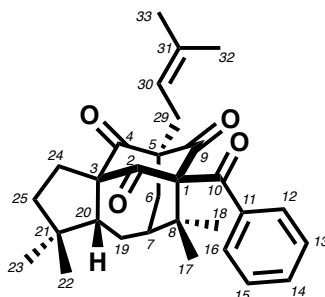


Table 1.6.3.1. Comparison of ^1H and ^{13}C NMR shifts of Hypersampsonone M (1), CDCl_3 .

C no.	δ_{H} (ppm)		δ_{C} (ppm)	
	natural	synthetic	natural	synthetic
1			81.4	81.4
2			206.0	205.9
3			76.4	76.3
4			205.3	205.2
5			68.7	68.6
6 α	2.50 (m)	2.50 (m)	44.8	44.8
6 β	1.83 (m)	1.84 (d, 13.7)	44.8	44.8
7	2.10 (m)	2.13 (t, 6.5)	43.7	43.6
8			51.6	51.5
9			205.6	205.4
10			193.1	193.0
11			135.3	135.2
12,16	7.09 (br.d, 7.5)	7.11 (br.d, 7.7)	129.3	129.3
13,15	7.24 (br.t, 7.5)	7.26 (br.t 7.9)	128.1	128.0
14	7.37 (br.t, 7.5)	7.39 (br.t, 7.6)	132.2	132.1
17	1.47 (s)	1.50 (s)	23.0	22.9
18	1.41 (s)	1.44 (s)	26.0	25.9
19	2.26 (m), 1.54 (m)	2.29 (dt, 15.7, 8.4); 1.54 (m)	29.1	29.1
20	2.01 (m)	2.06 (dd, 10.9, 9.6)	57.8	57.7
21			44.3	44.2
22	0.99 (s)	1.01 (s)	30.4	30.3
23	0.88 (s)	0.90 (s)	22.1	22.1
24	2.34 (m), (Not provided*)	2.36 (ddd, 13.4, 10.2, 5.1); 2.50 (m)	28.9	28.8
25	1.98 (m), 1.78 (m)	2.00 (ddd, 13.6, 8.7, 5.1); 1.80 (ddd, 12.5, 10.1, 7.5)	41.7	41.6
29	2.50 (m)	2.50 (m)	30.1	30.0
30	4.98 (br.t, 6.9)	5.00 (br.t, 6.9)	119.3	119.3
31			135.0	134.9
32	1.63 (s)	1.65 (s)	18.3	18.3
33	1.64 (s)	1.66 (s)	26.3	26.2

*A shift for the second vicinal proton on carbon #24 was not provided in the original isolation report.⁶ The proton was found to be in an overlapping multiplet centered at 2.50 ppm. The integration value supporting this can be seen in both the natural and synthetic spectra.

1.7 REFERENCES AND NOTES

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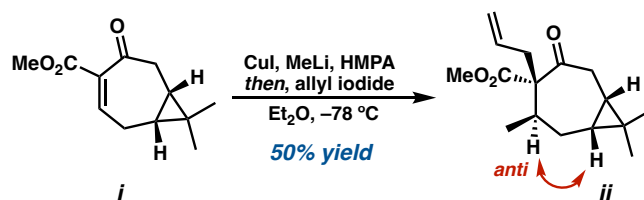
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APPENDIX 1

Synthetic Summary for Chapter 1:

Total Synthesis of Hypersampsonone M

[illegible]

APPENDIX 2

Spectra Relevant to Chapter 1:

Total Synthesis of Hypersampsonone M

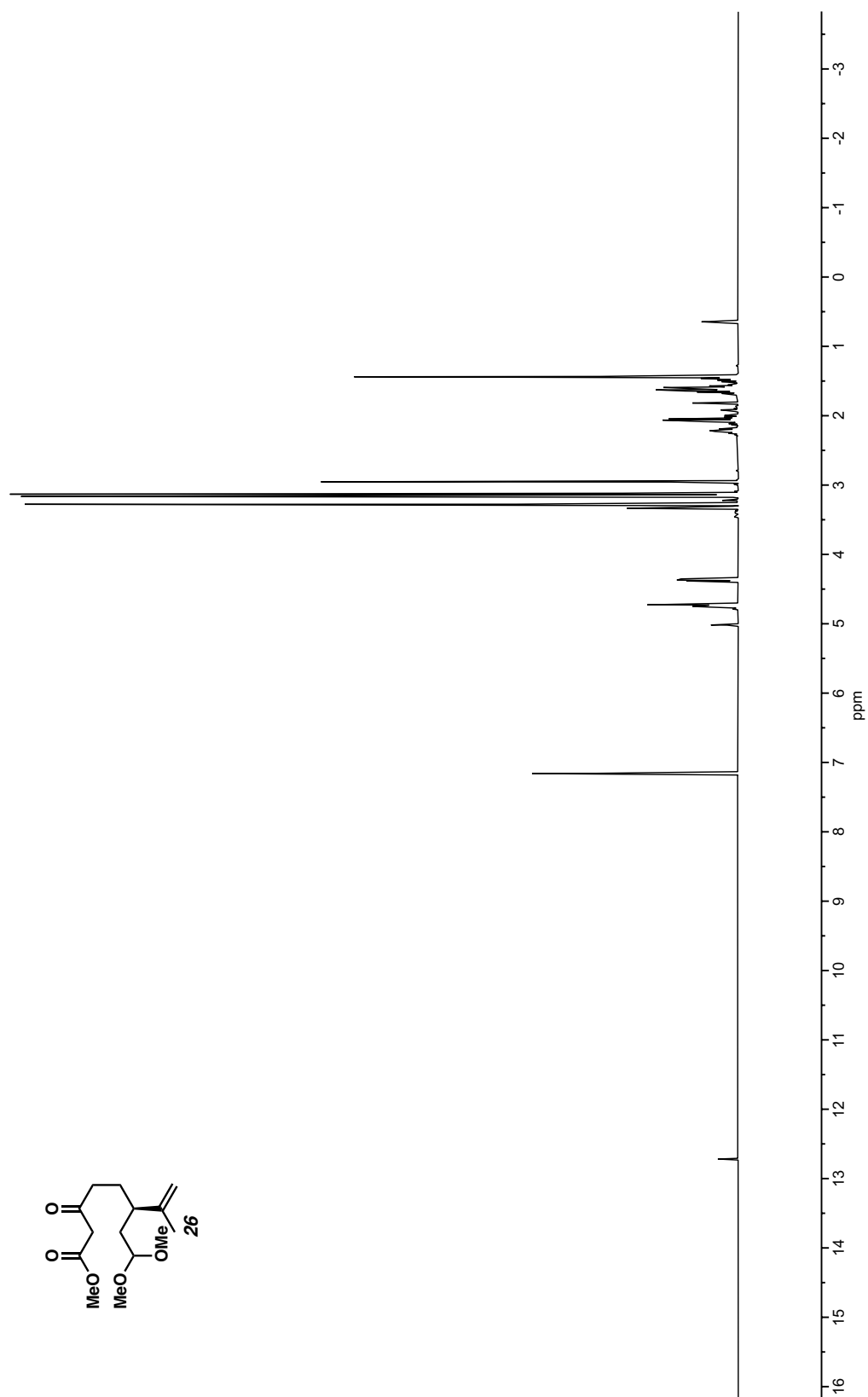


Figure A2.1 ¹H NMR (400 MHz, CDCl₃) of compound 26.

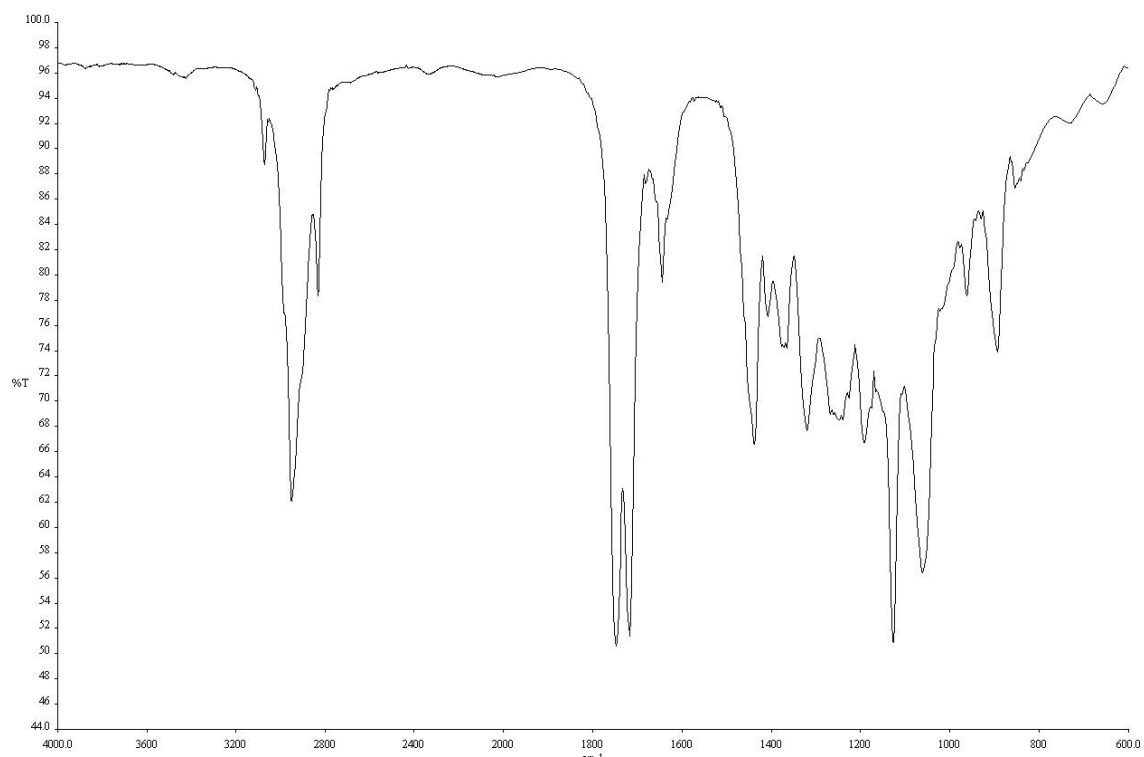


Figure A2.2 Infrared spectrum (Thin Film, NaCl) of compound 26.

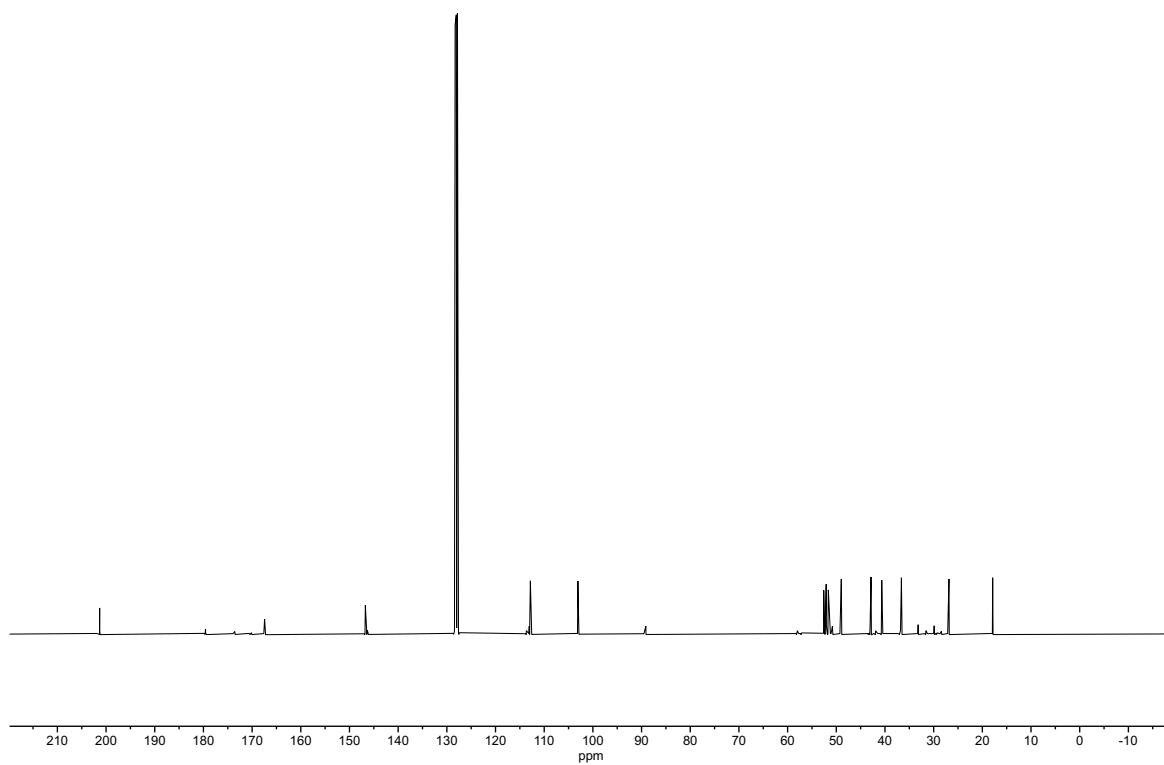


Figure A2.3 ¹³C NMR (100 MHz, C₆D₆) of compound 26.



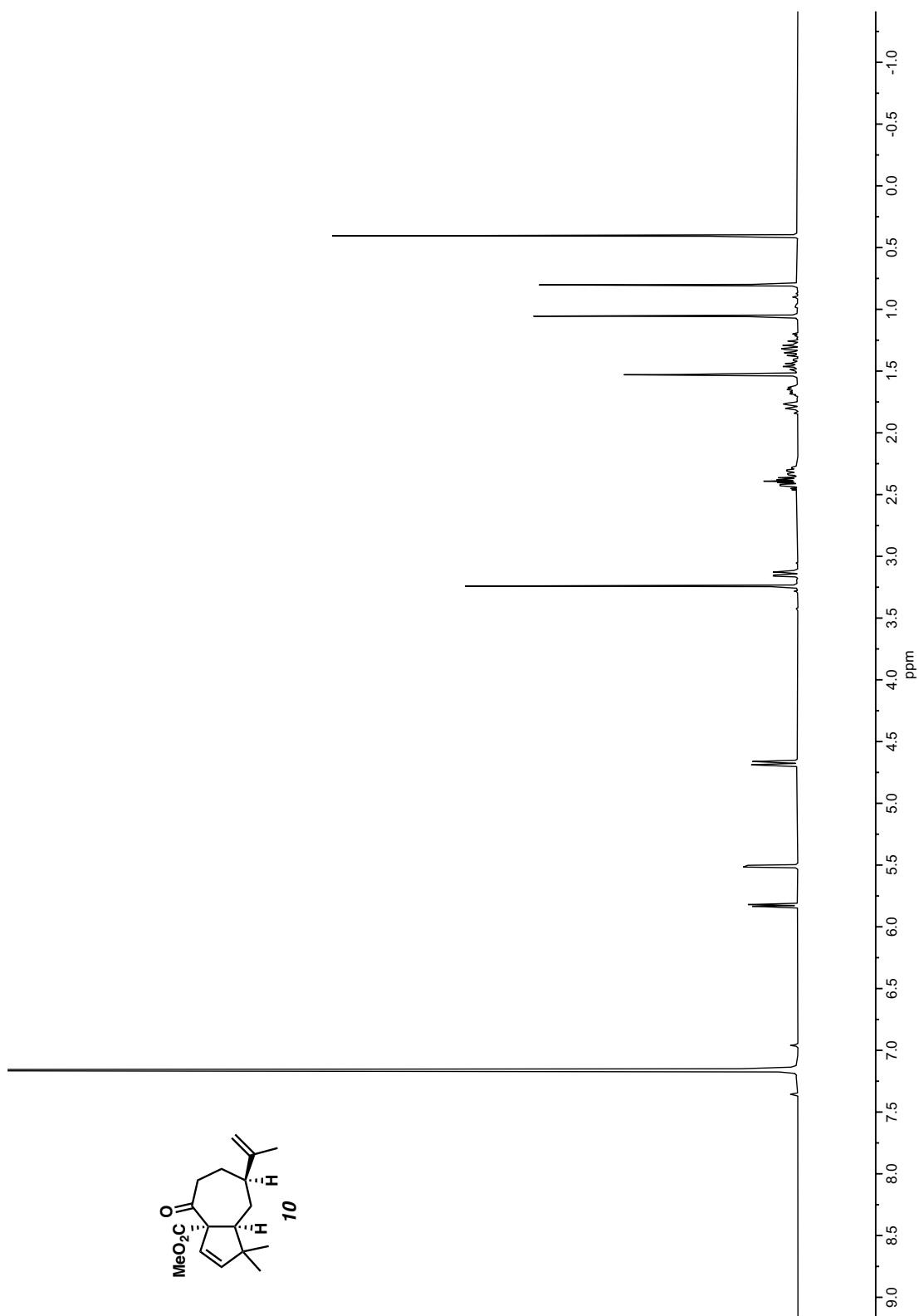


Figure A2.5 ¹H NMR (400 MHz, C₆D₆) of compound **10**.

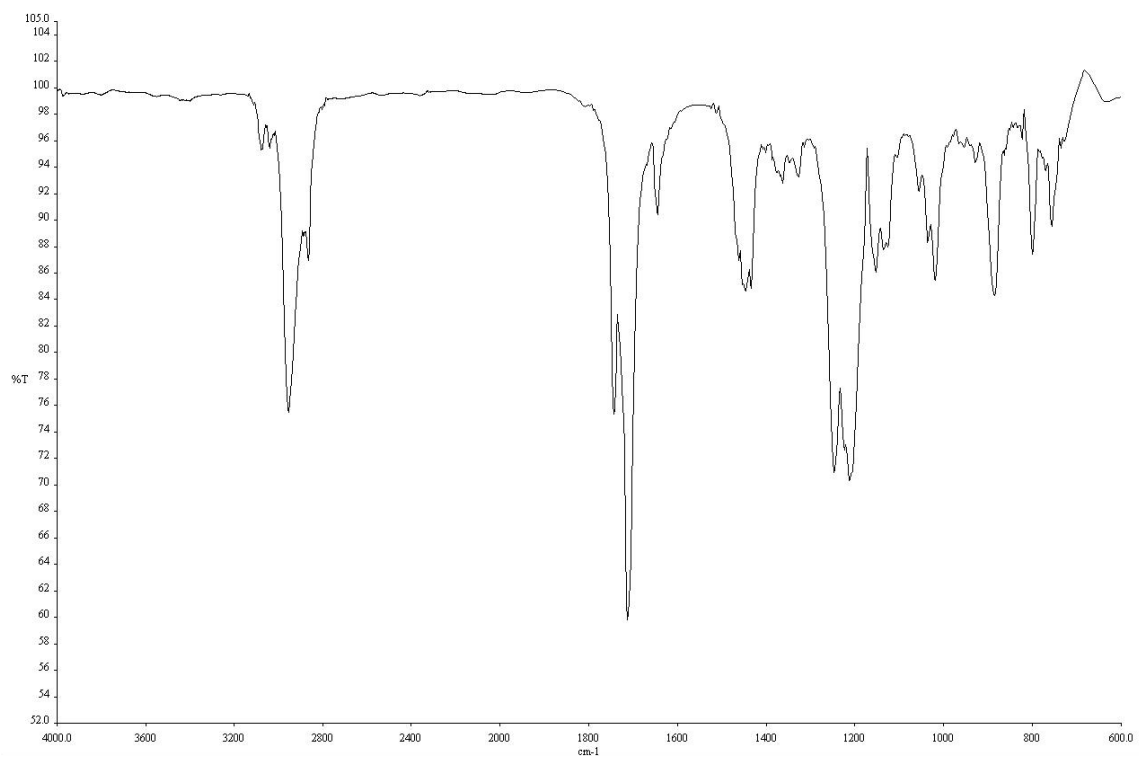


Figure A2.6 Infrared spectrum (Thin Film, NaCl) of compound **10**.

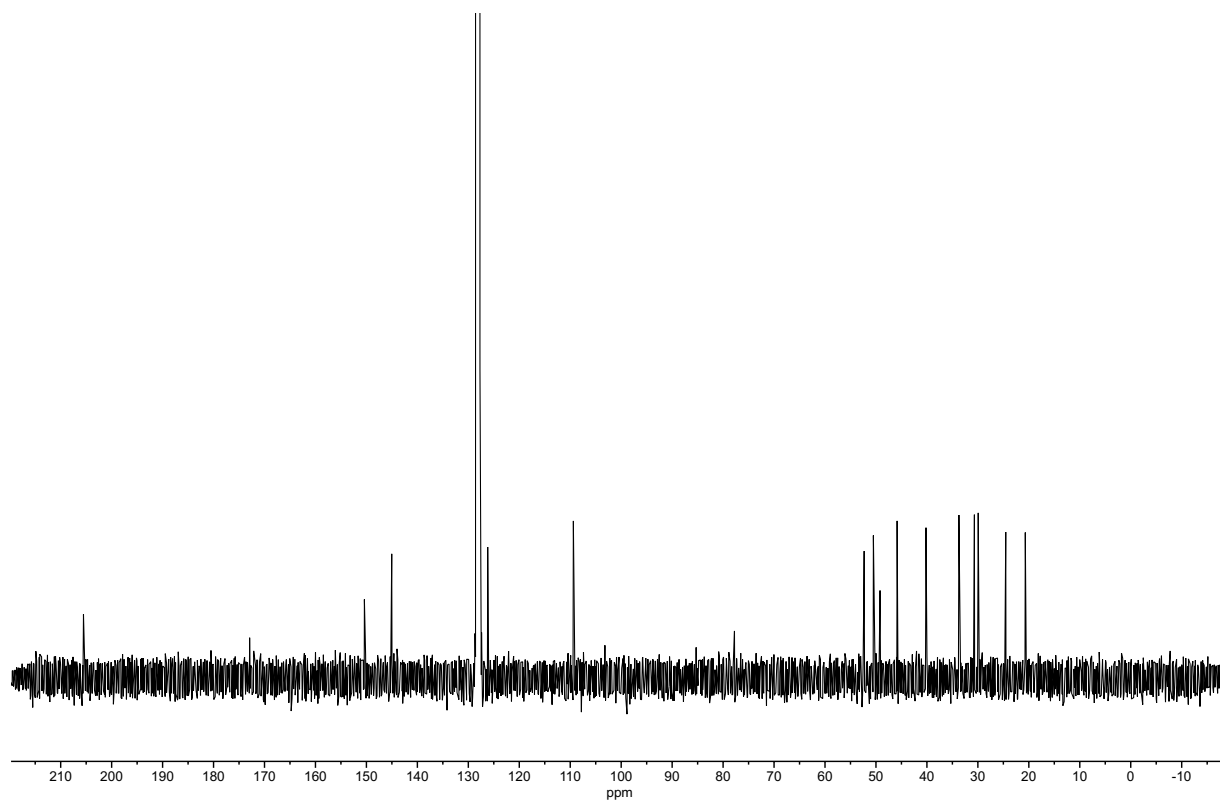
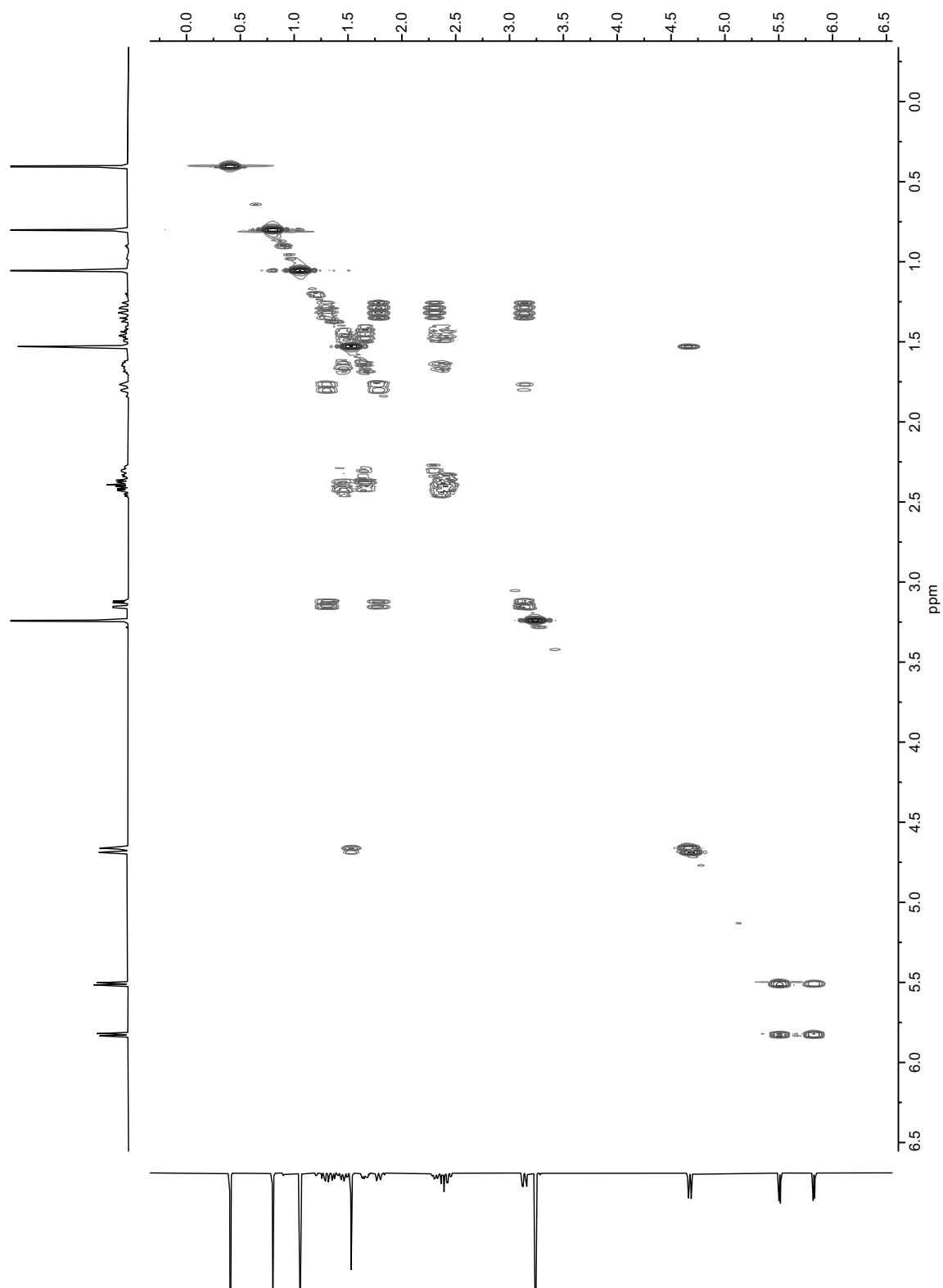


Figure A2.7 ¹³C NMR (100 MHz, C₆D₆) of compound **10**.



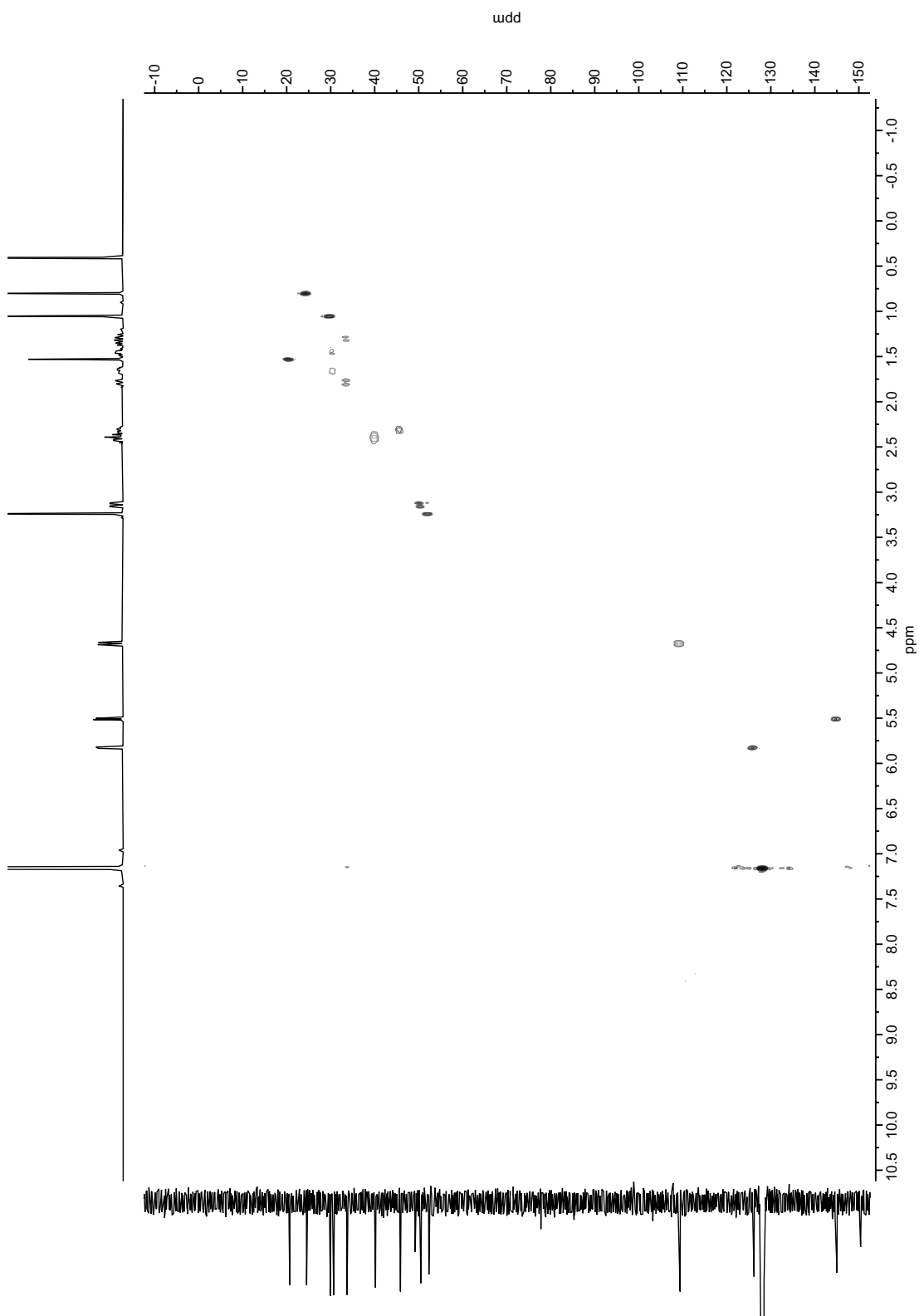


Figure A2.9 HSQC NMR (400, 100 MHz, C_6D_6) of compound **10**.

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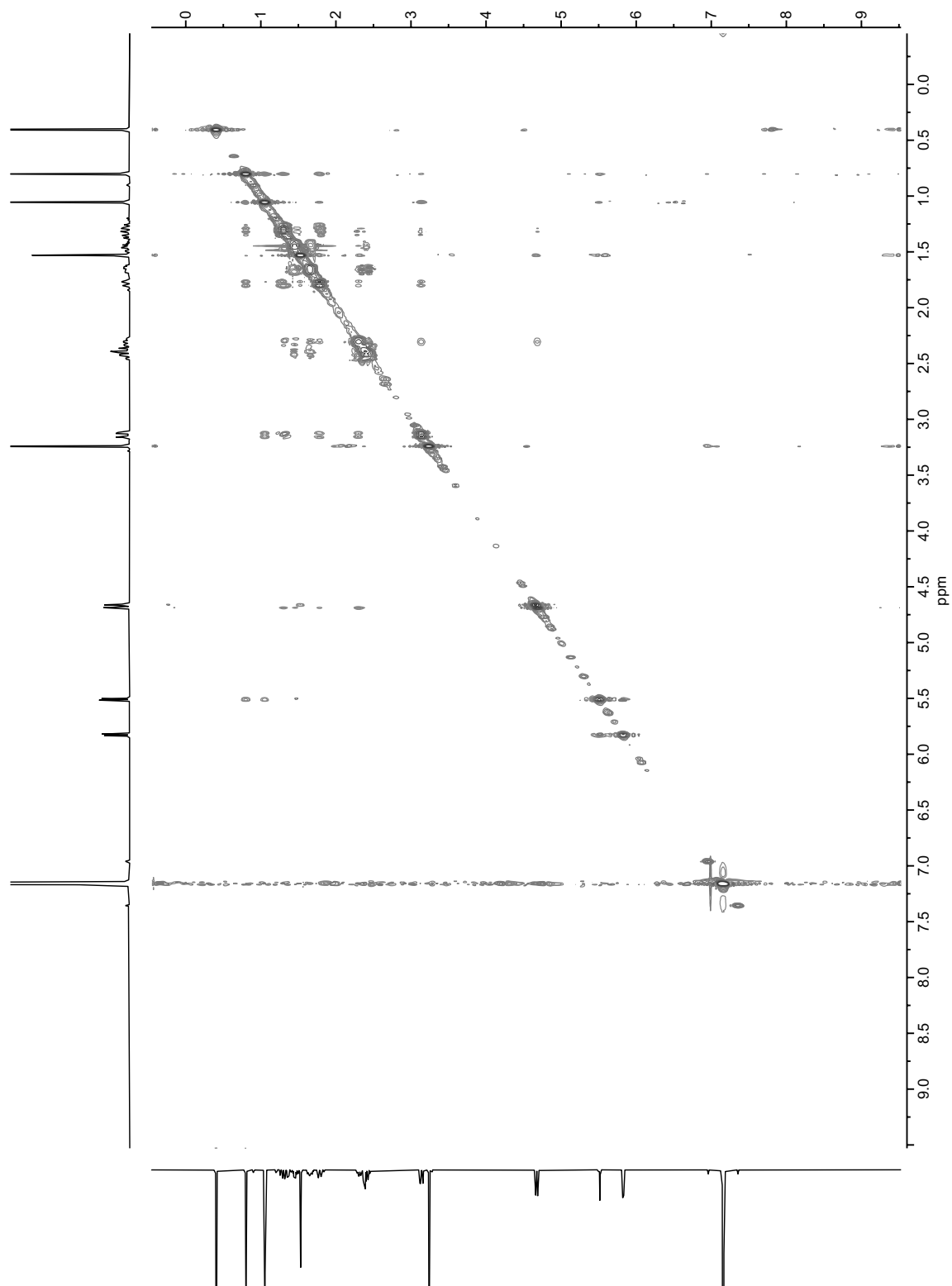


Figure A2.10 NOESY NMR (400 MHz, C₆D₆) of compound **10**.

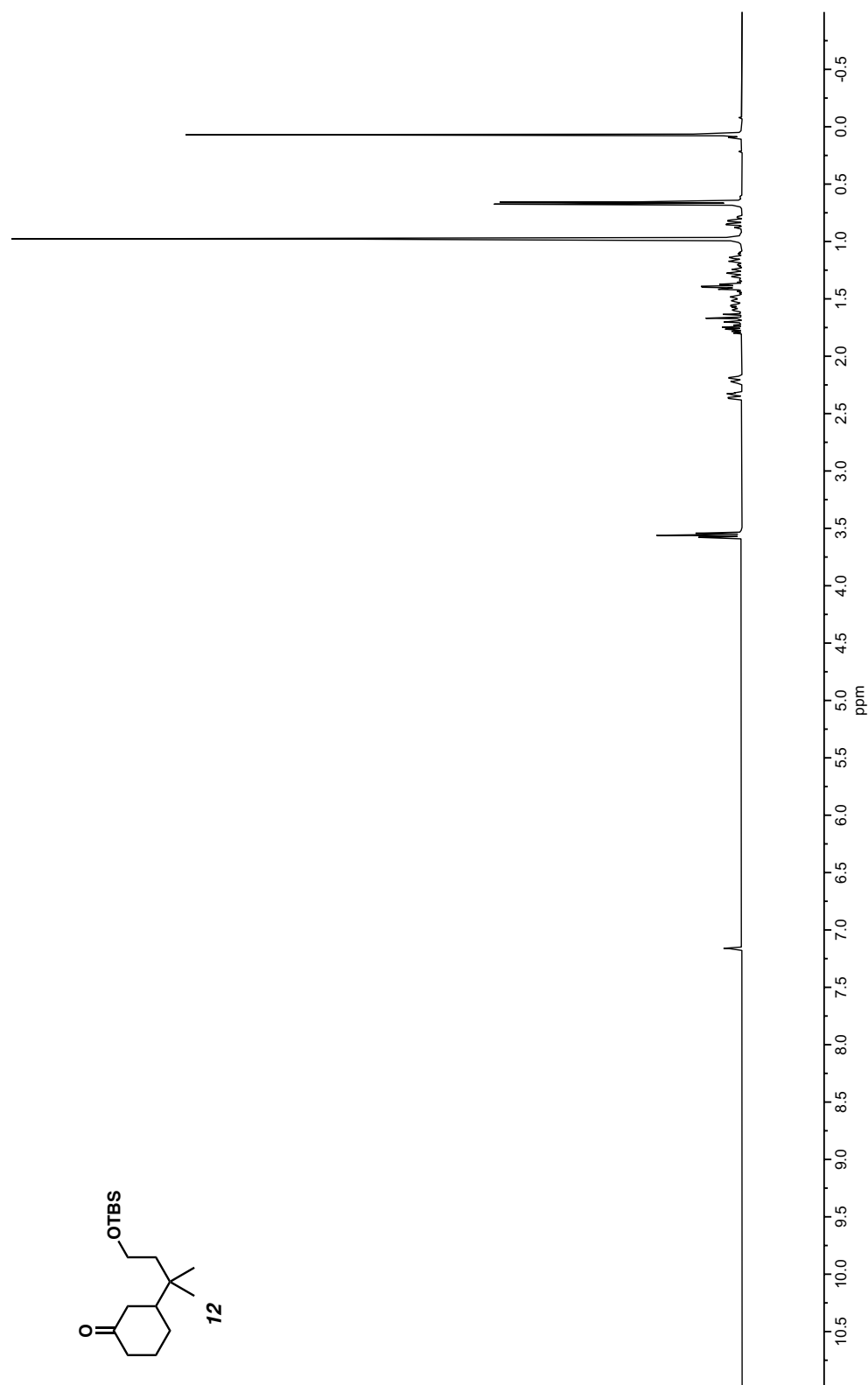


Figure A2.11 ¹H NMR (400 MHz, CDCl₃) of compound 12.

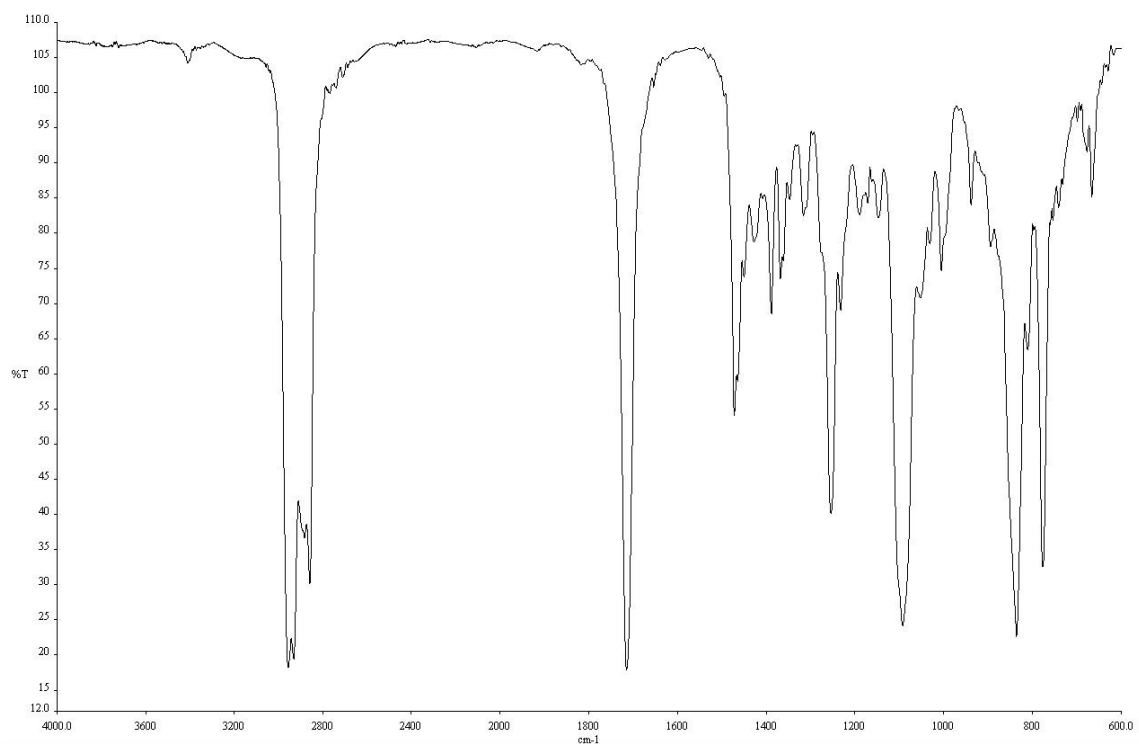


Figure A2.12 Infrared spectrum (Thin Film, NaCl) of compound 12.

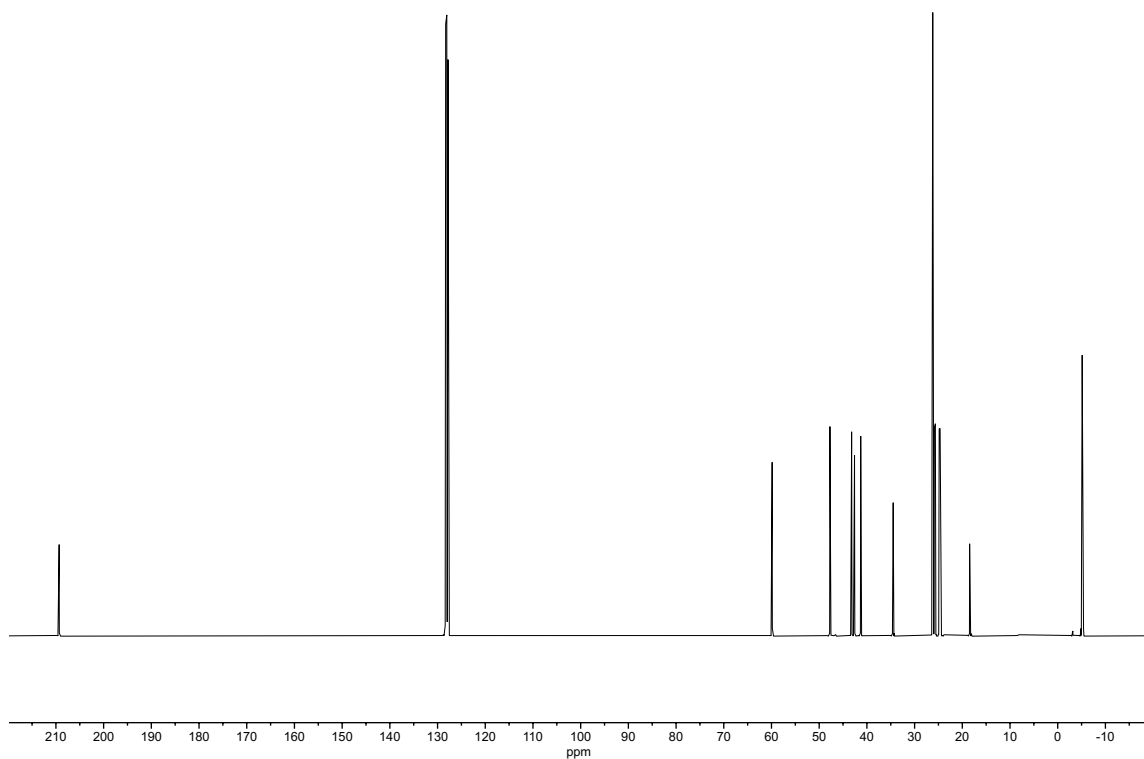


Figure A2.13 ¹³C NMR (100 MHz, C₆D₆) of compound 12.

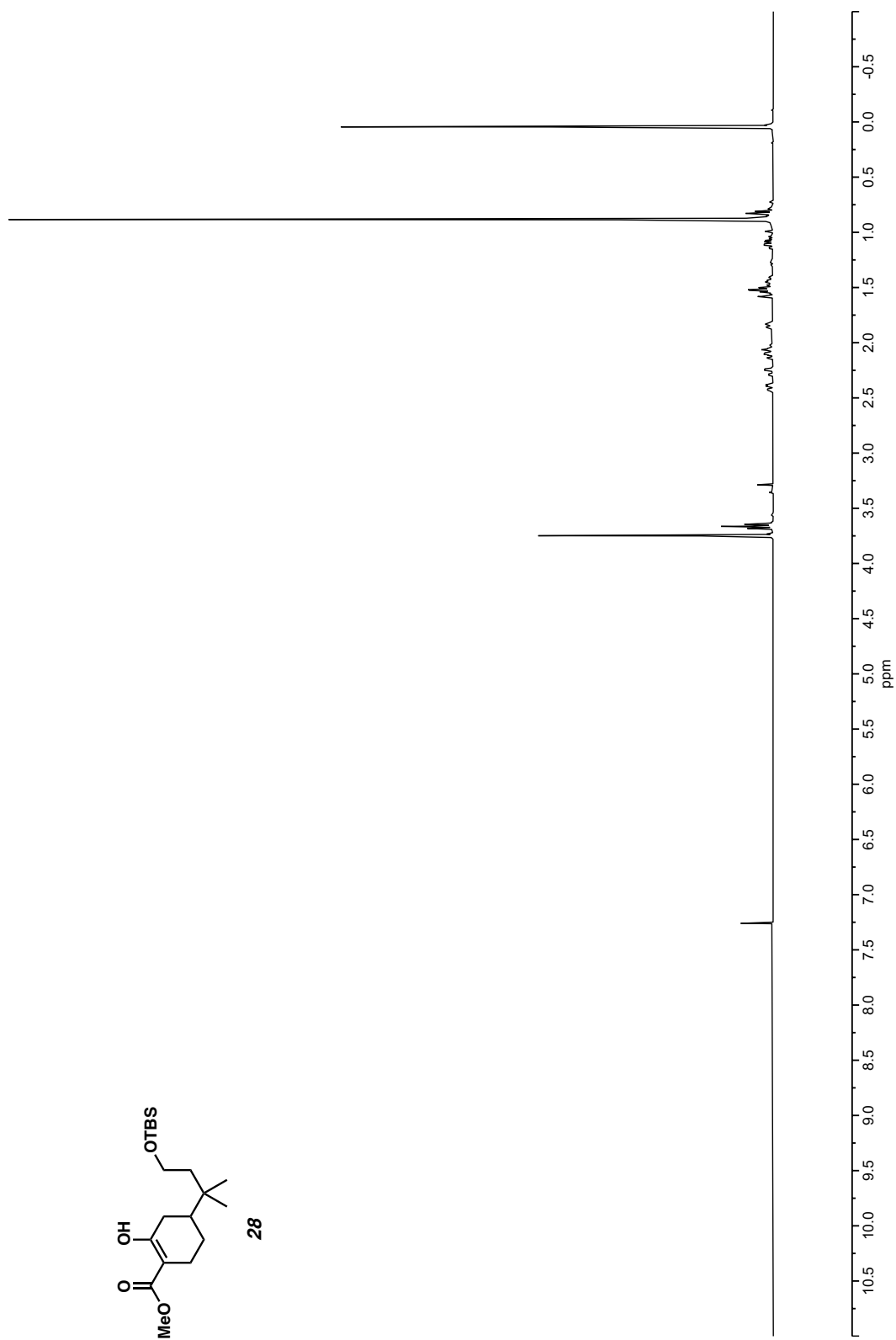


Figure A2.14 ^1H NMR (400 MHz, CDCl_3) of compound **28**.

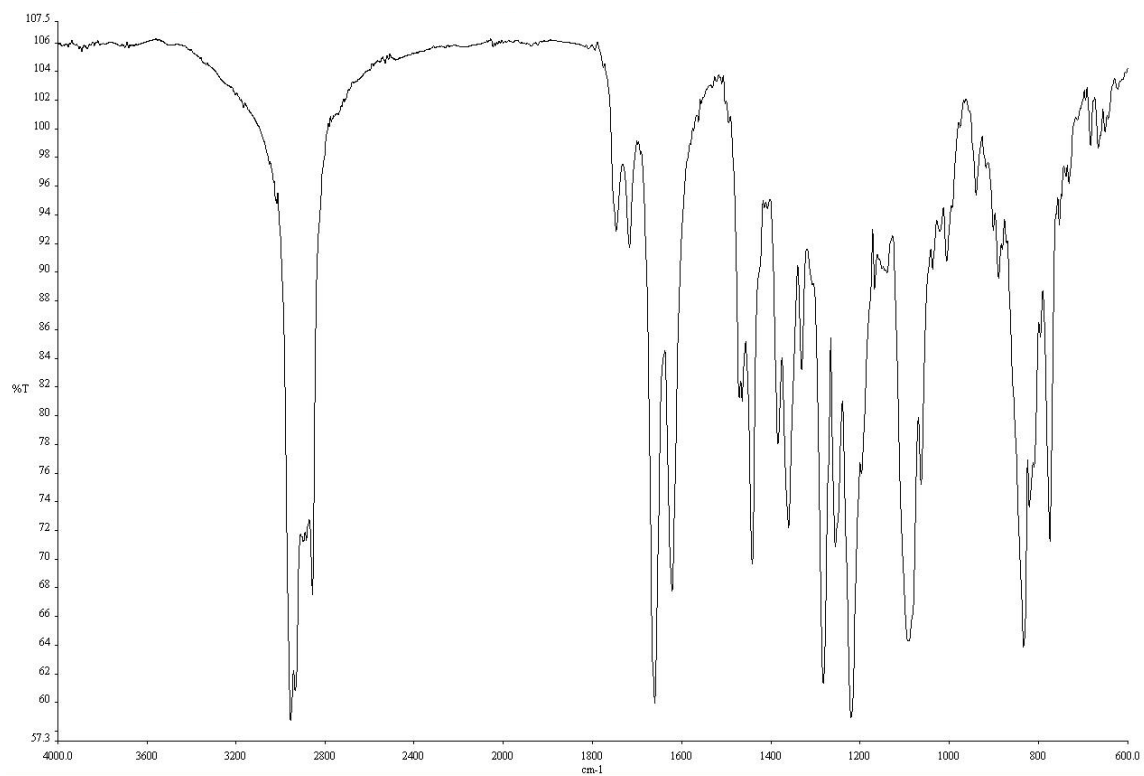


Figure A2.15 Infrared spectrum (Thin Film, NaCl) of compound **28**.

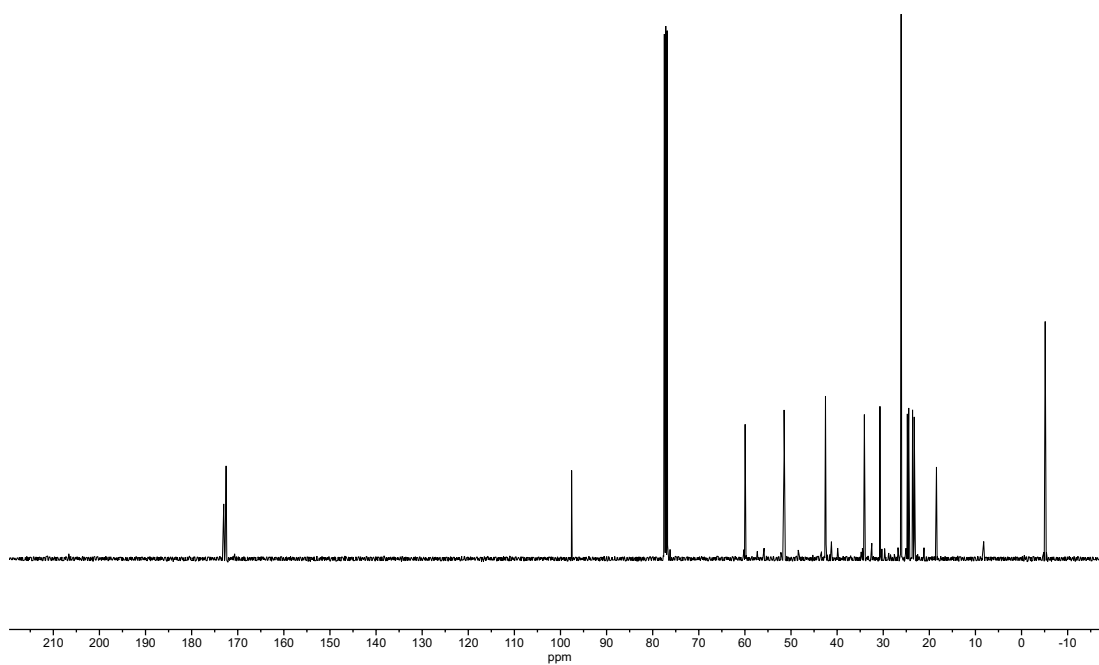


Figure A2.16 ¹³C NMR (100 MHz, CDCl₃) of compound **28**.

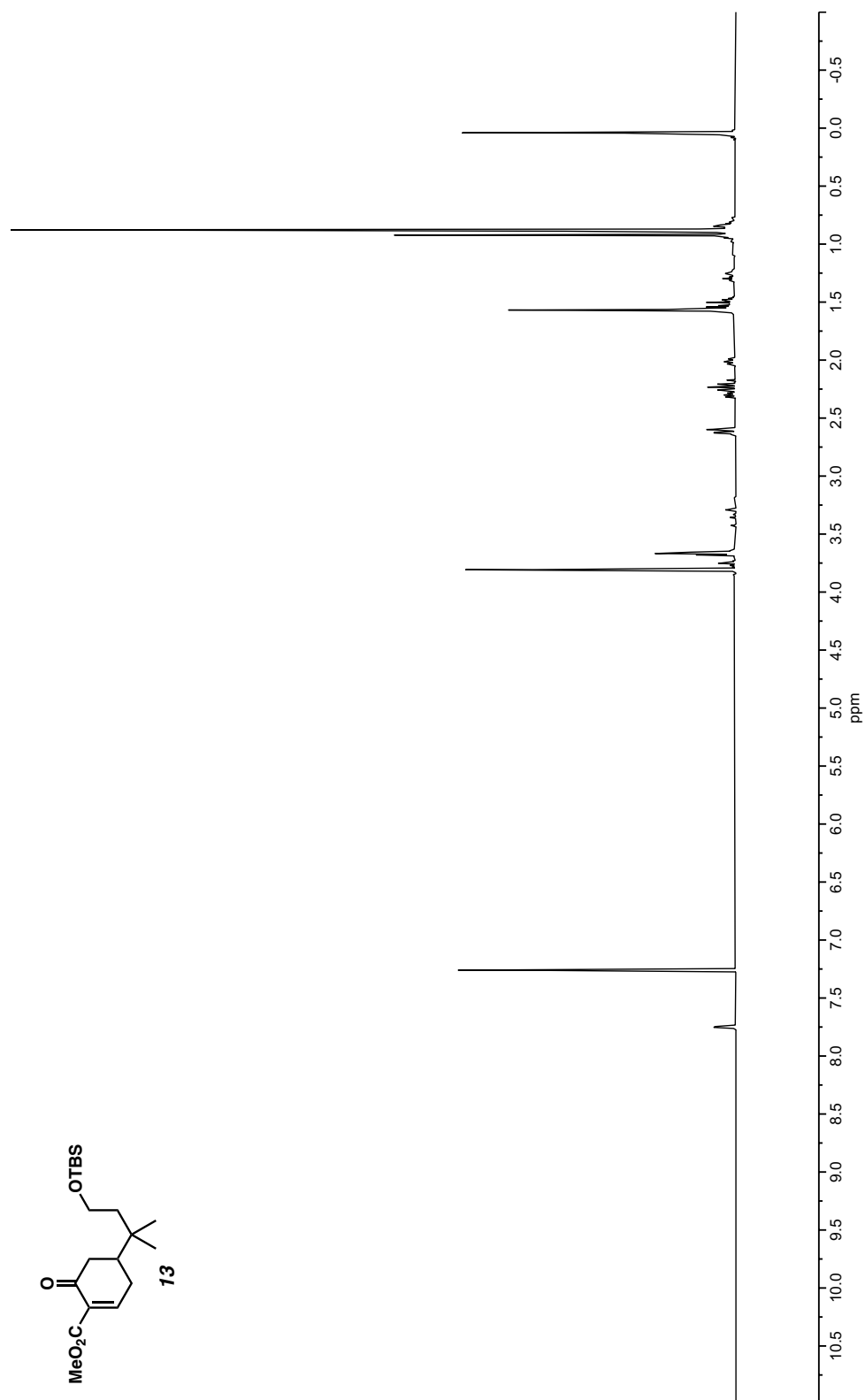
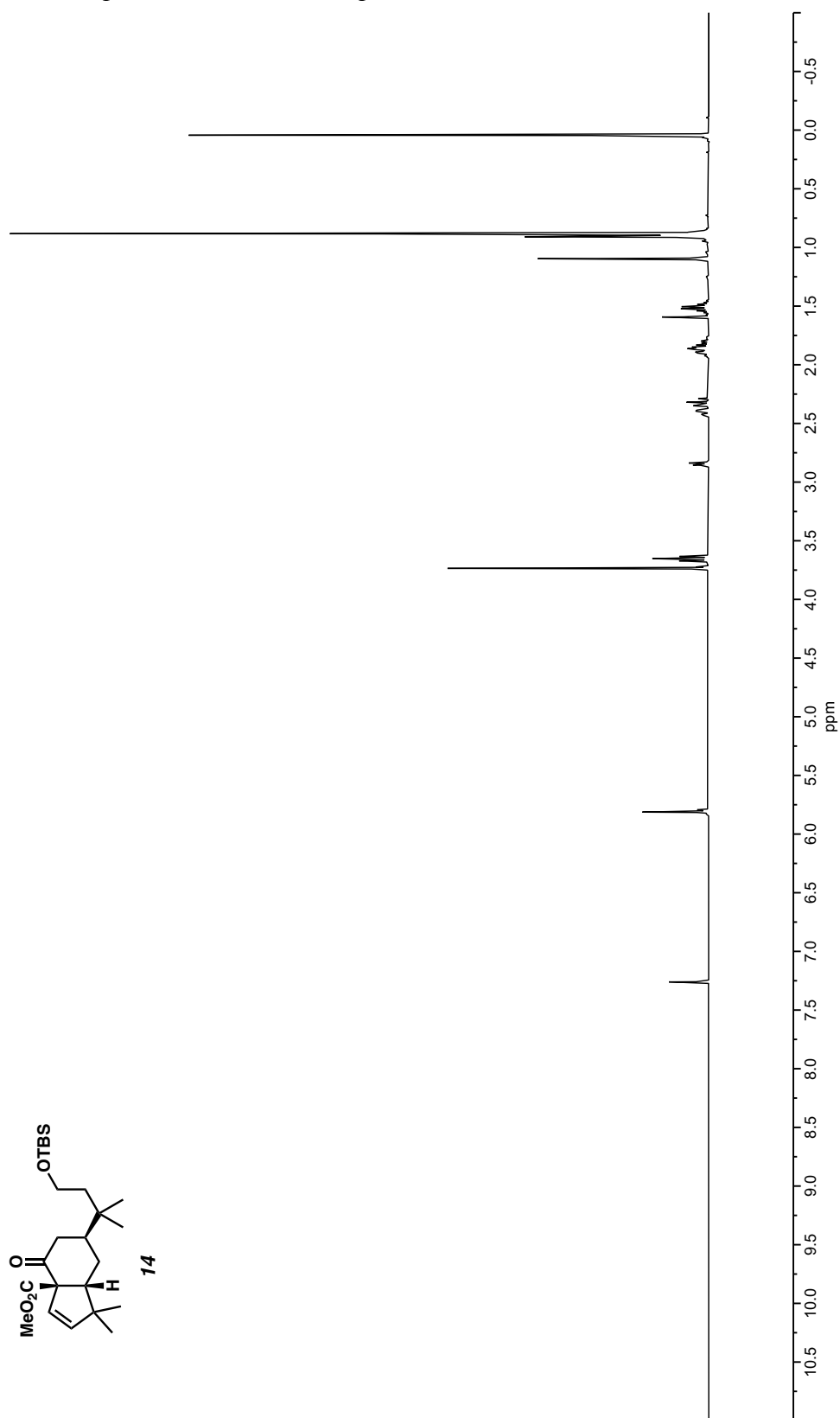


Figure A2.17 ^1H NMR (400 MHz, CDCl_3) of compound **13**.



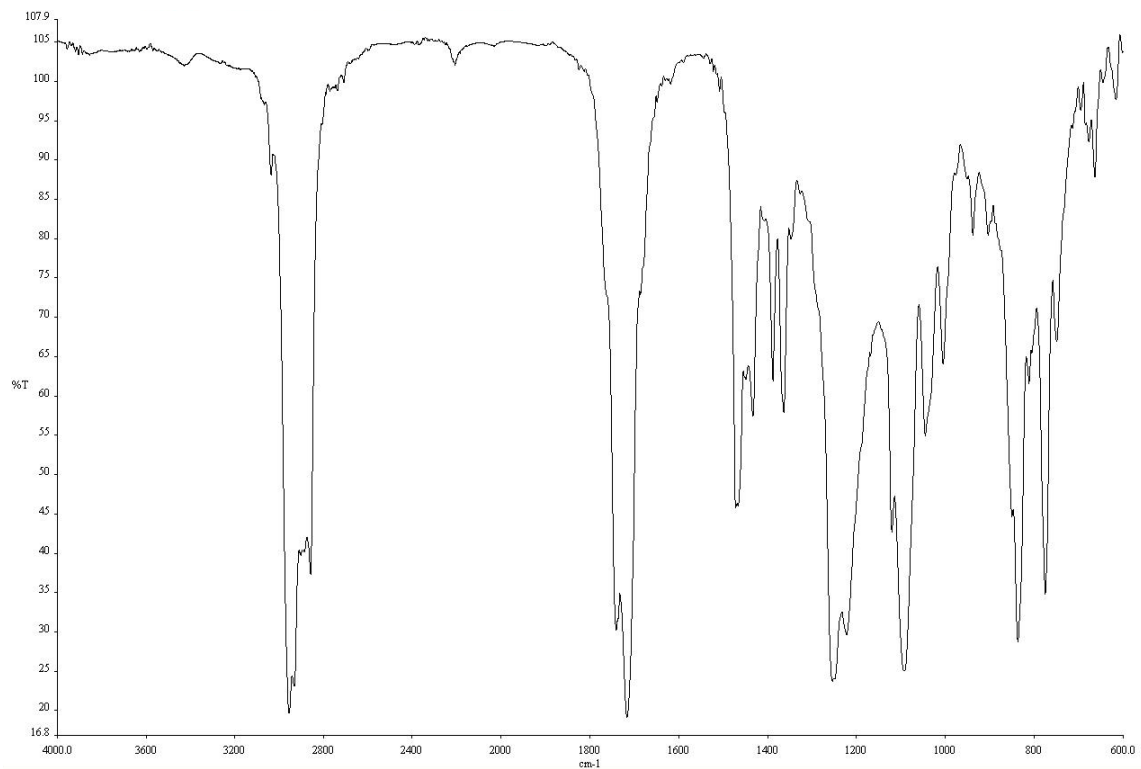


Figure A2.19 Infrared spectrum (Thin Film, NaCl) of compound 14.

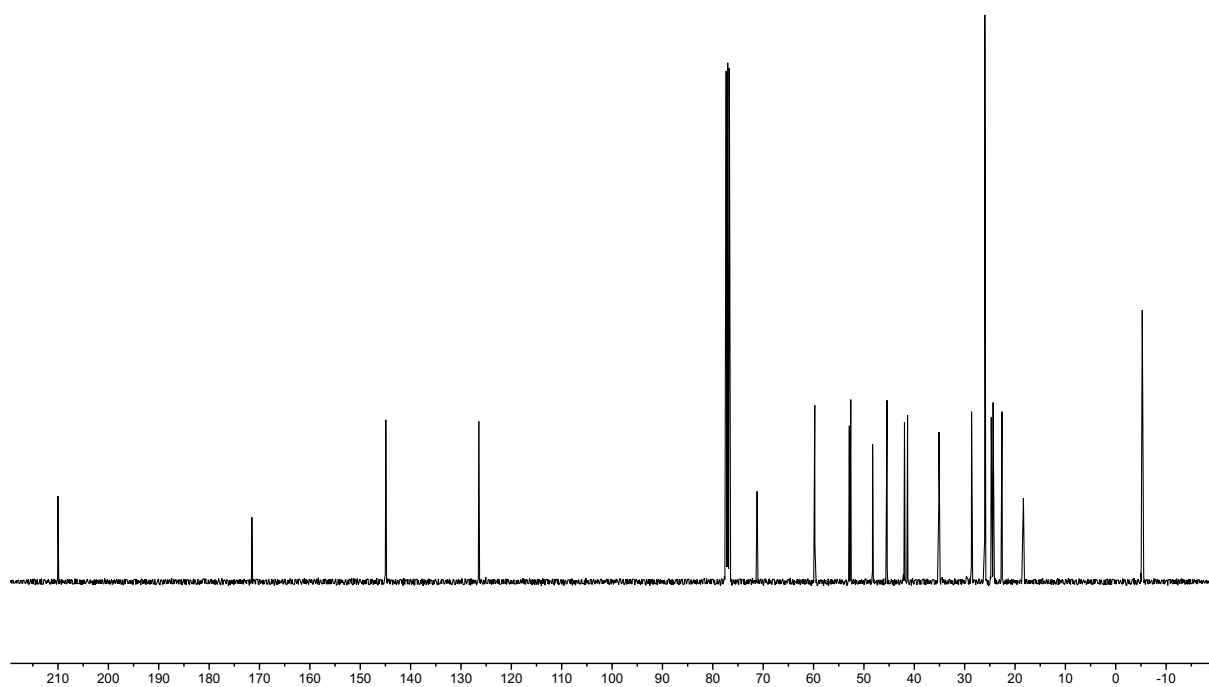


Figure A2.20 ¹³C NMR (100 MHz, CDCl₃) of compound 14.

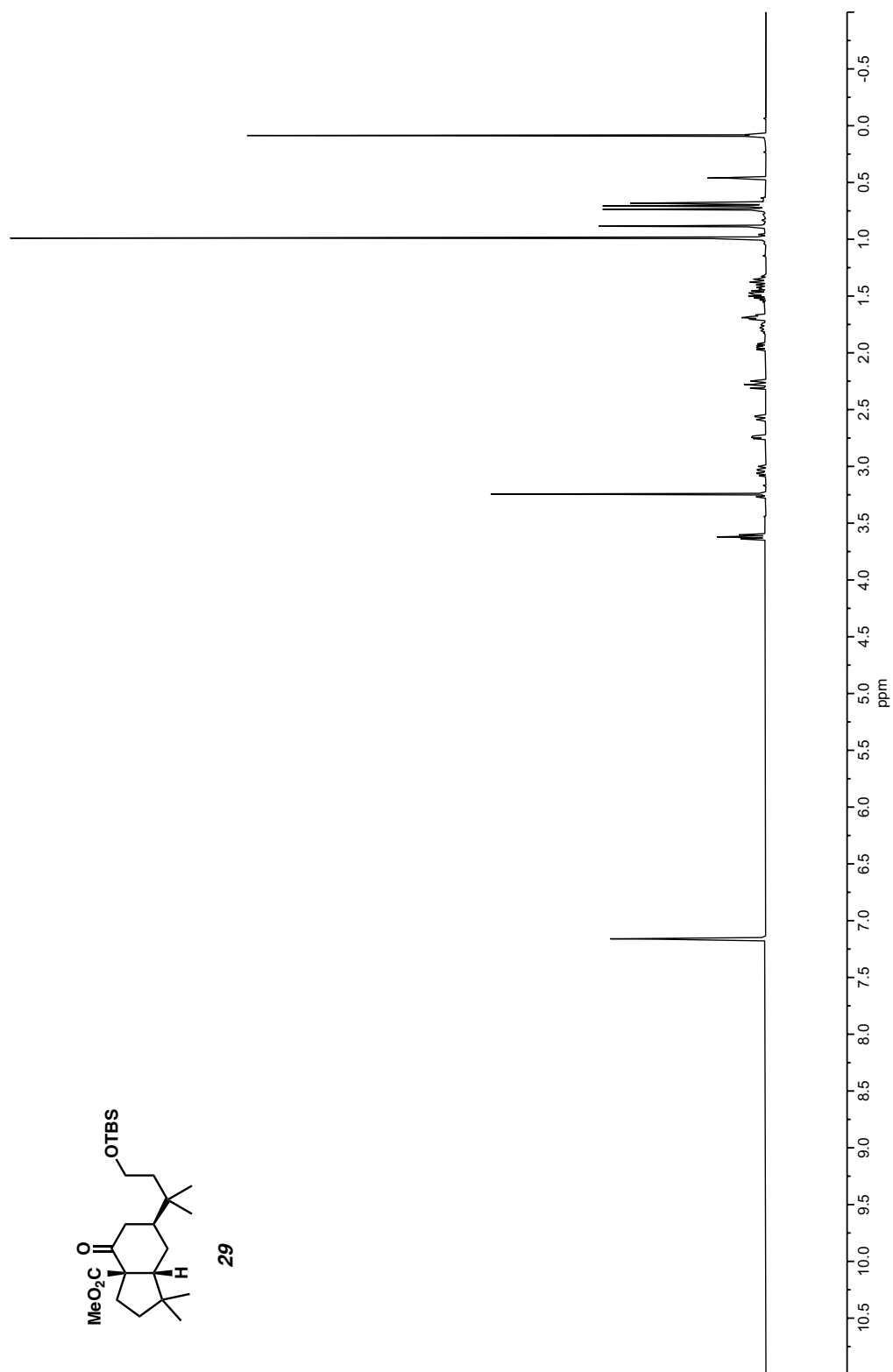


Figure A2.21 ^1H NMR (400 MHz, C_6D_6) of compound **29**.

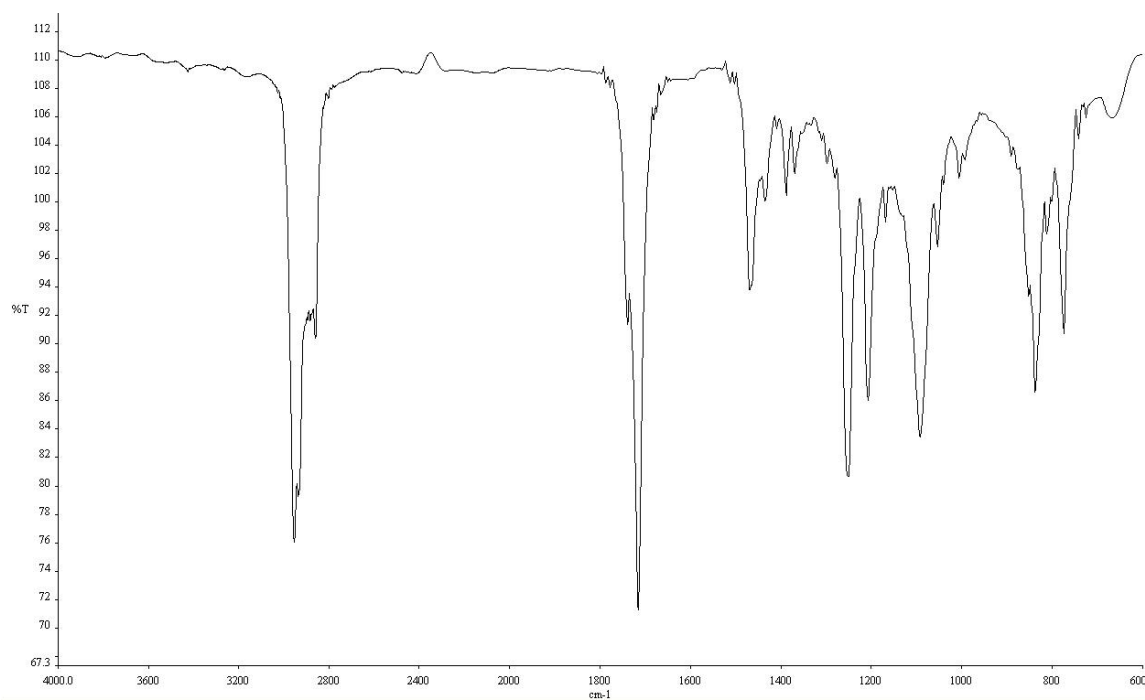


Figure A2.22 Infrared spectrum (Thin Film, NaCl) of compound **29**.

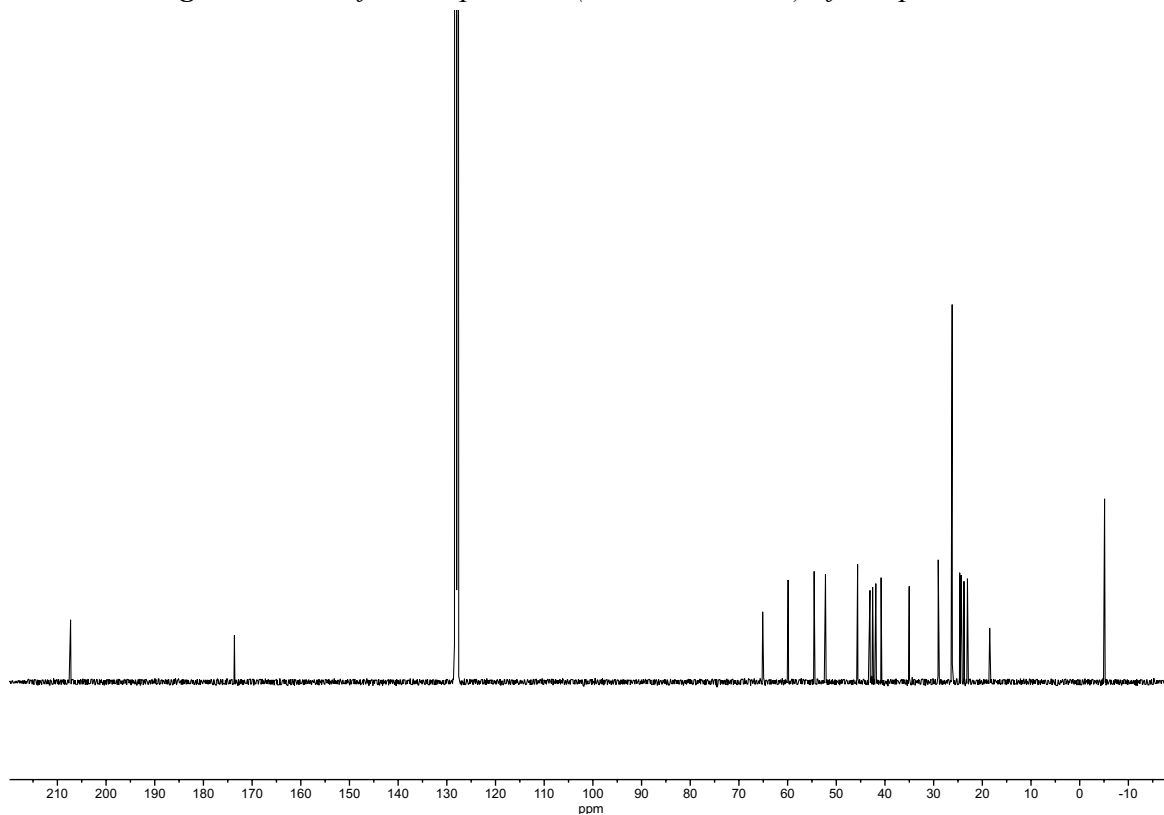


Figure A2.23 ¹³C NMR (100 MHz, C₆D₆) of compound **29**.

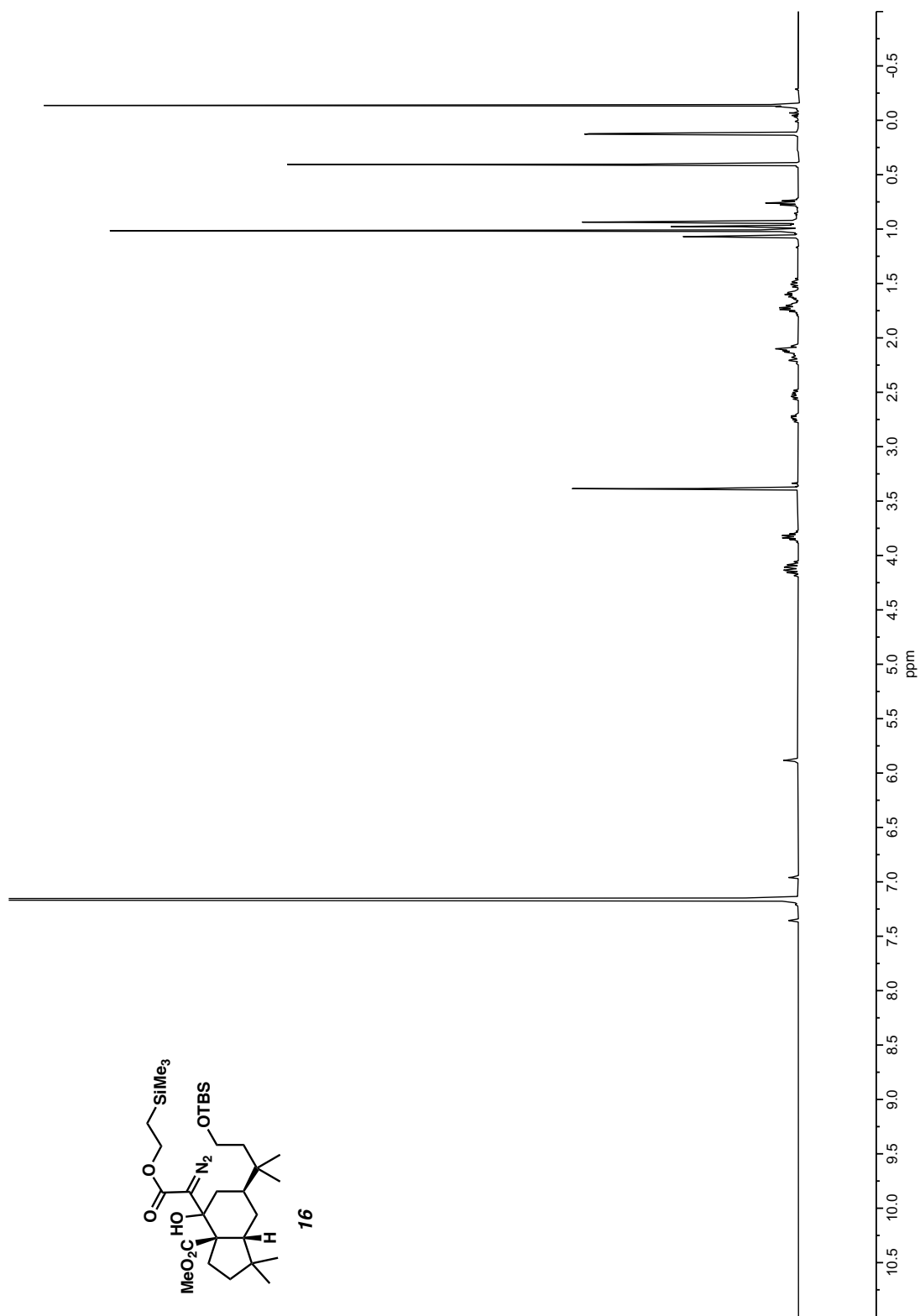


Figure A2.24 ¹H NMR (400 MHz, C₆D₆) of compound **16**.

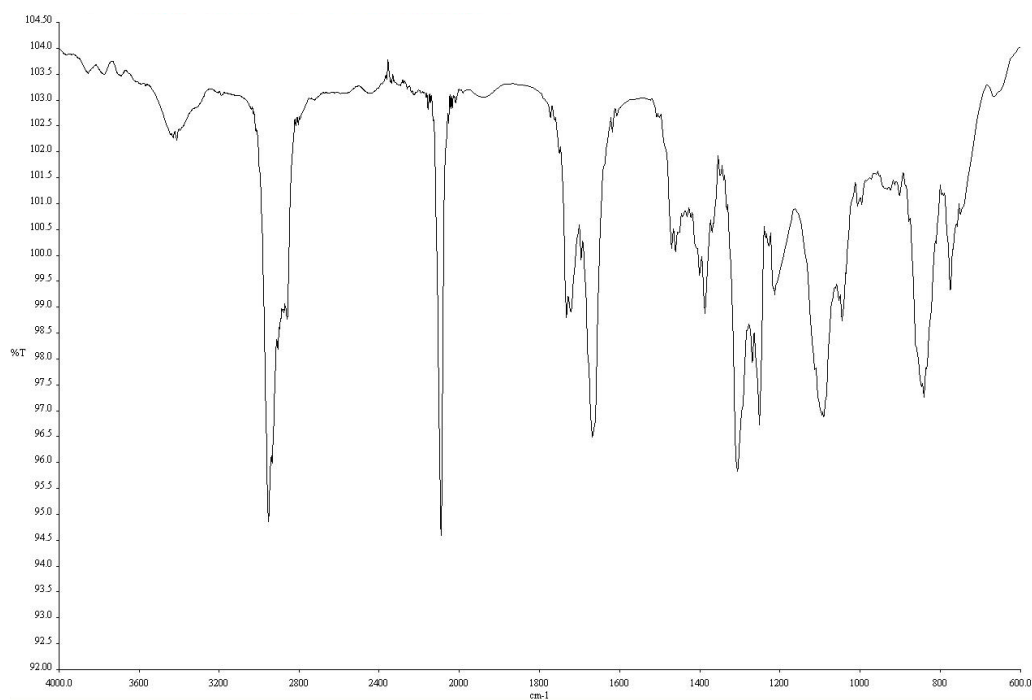


Figure A2.25 Infrared spectrum (Thin Film, NaCl) of compound 16.

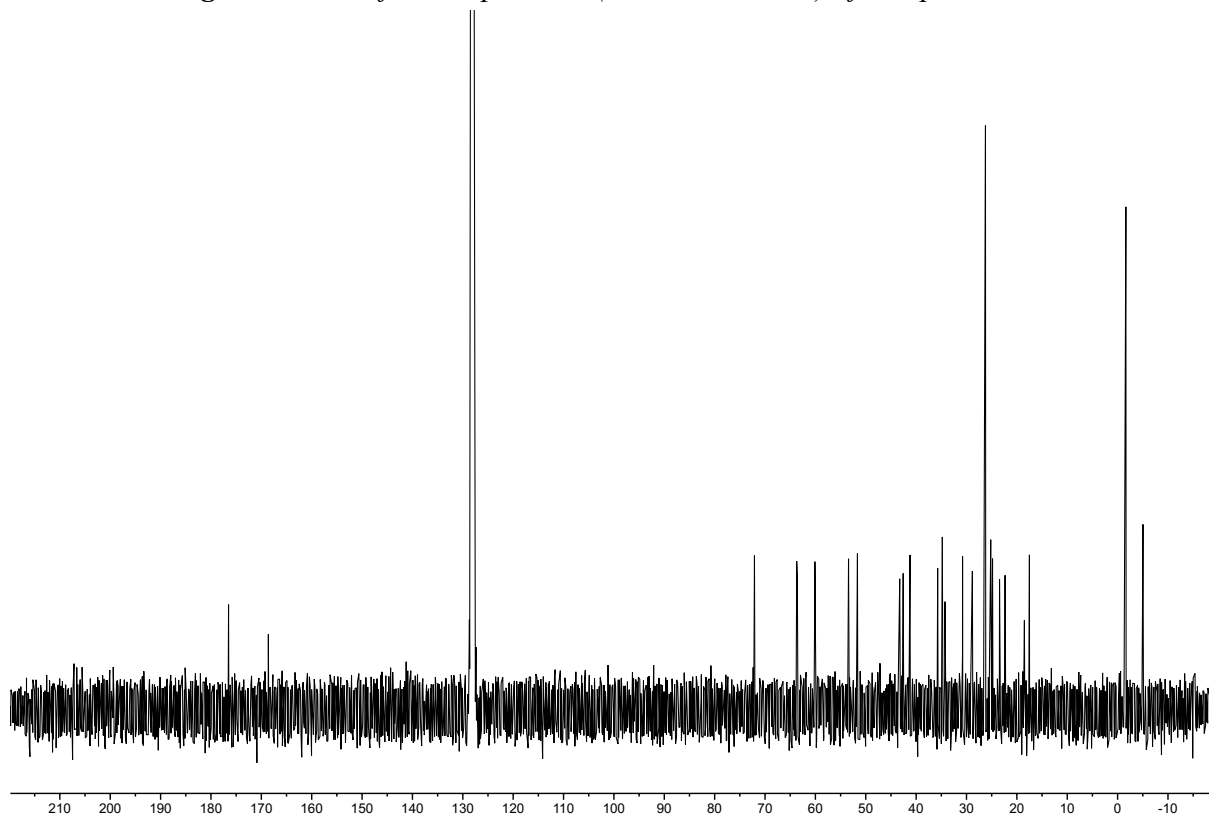


Figure A2.26 ¹³C NMR (100 MHz, C₆D₆) of compound 16.

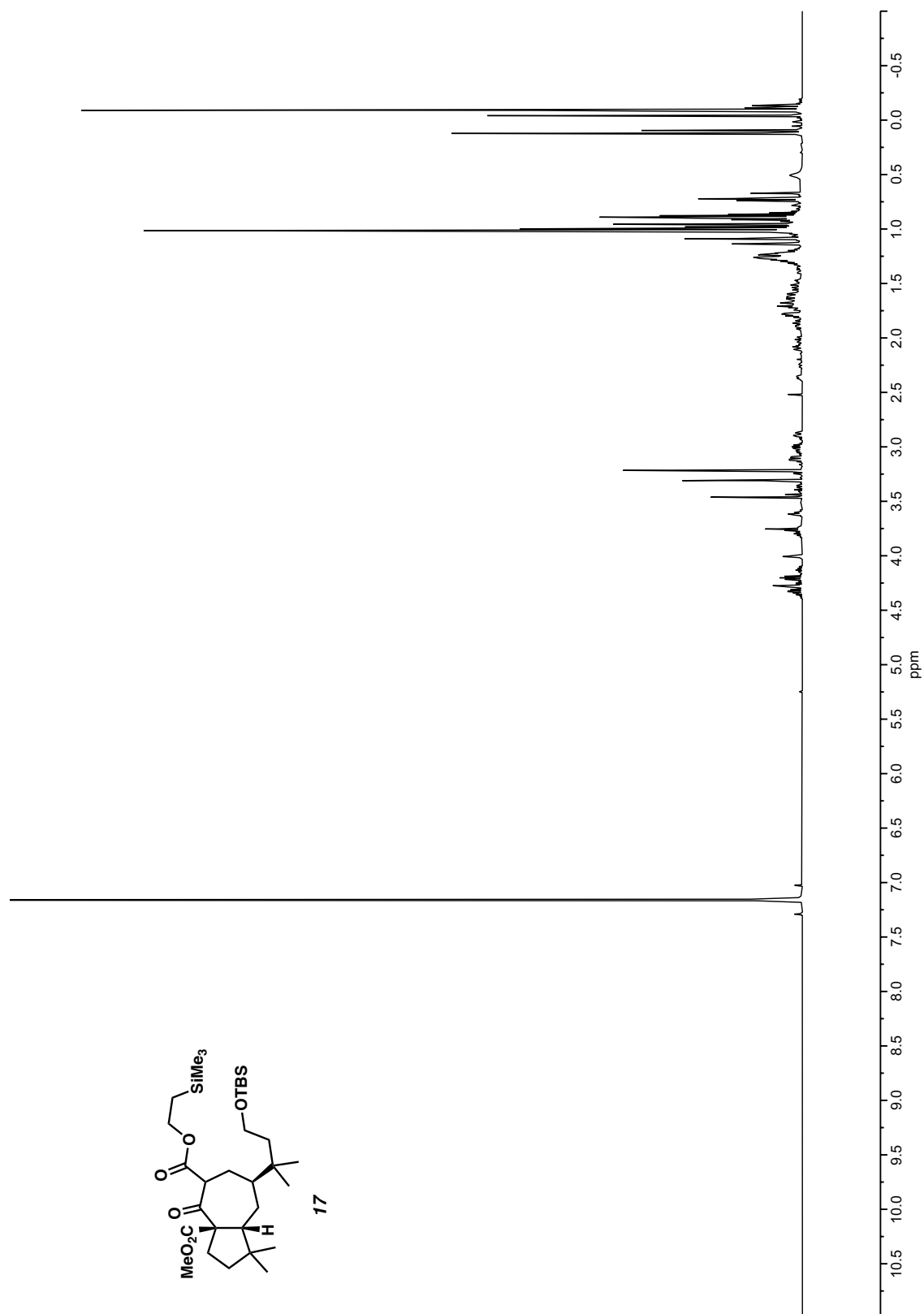


Figure A2.27 ^1H NMR (400 MHz, C_6D_6) of compound **17**.

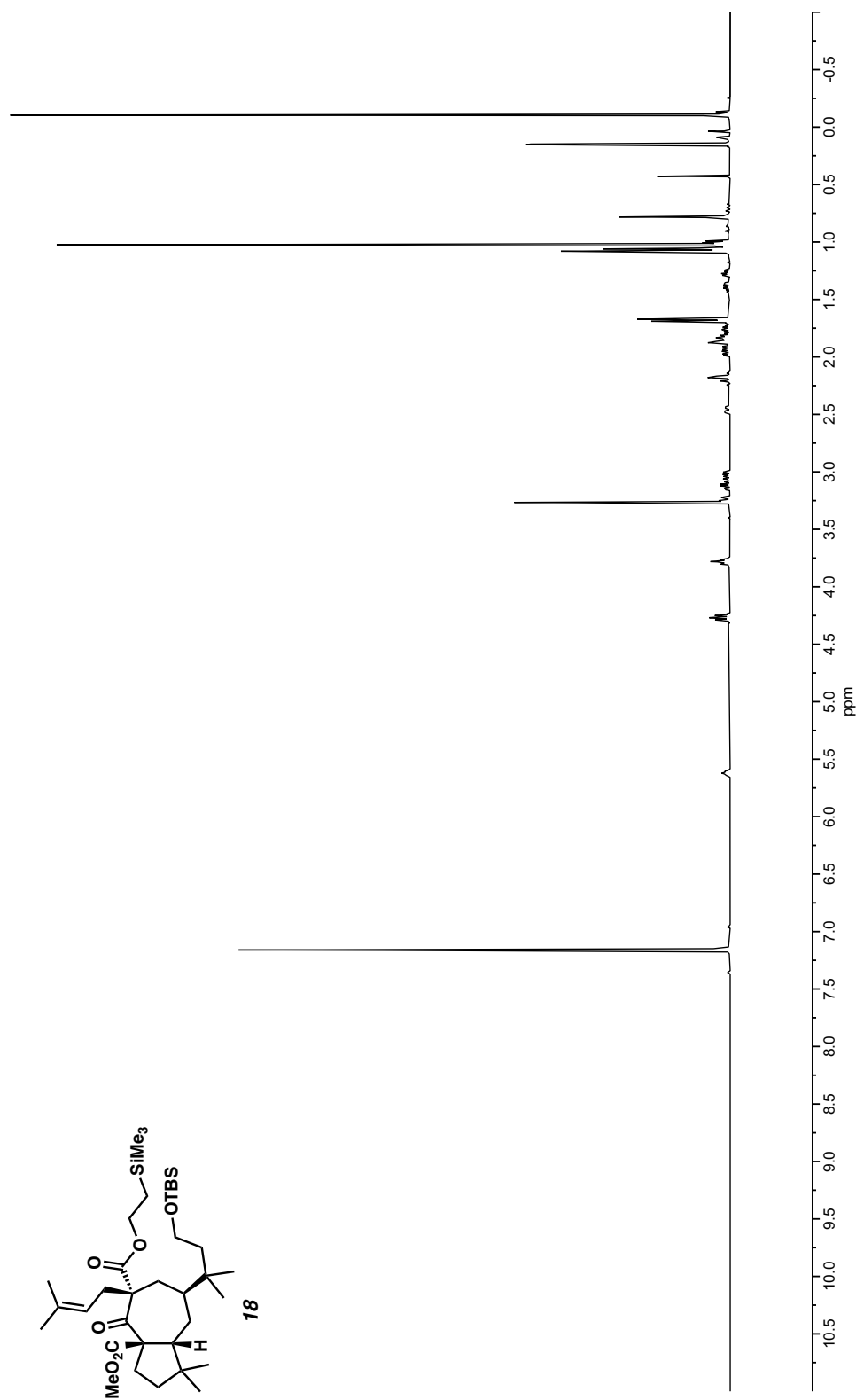


Figure A2.28 ^1H NMR (400 MHz, C_6D_6) of compound **18**.

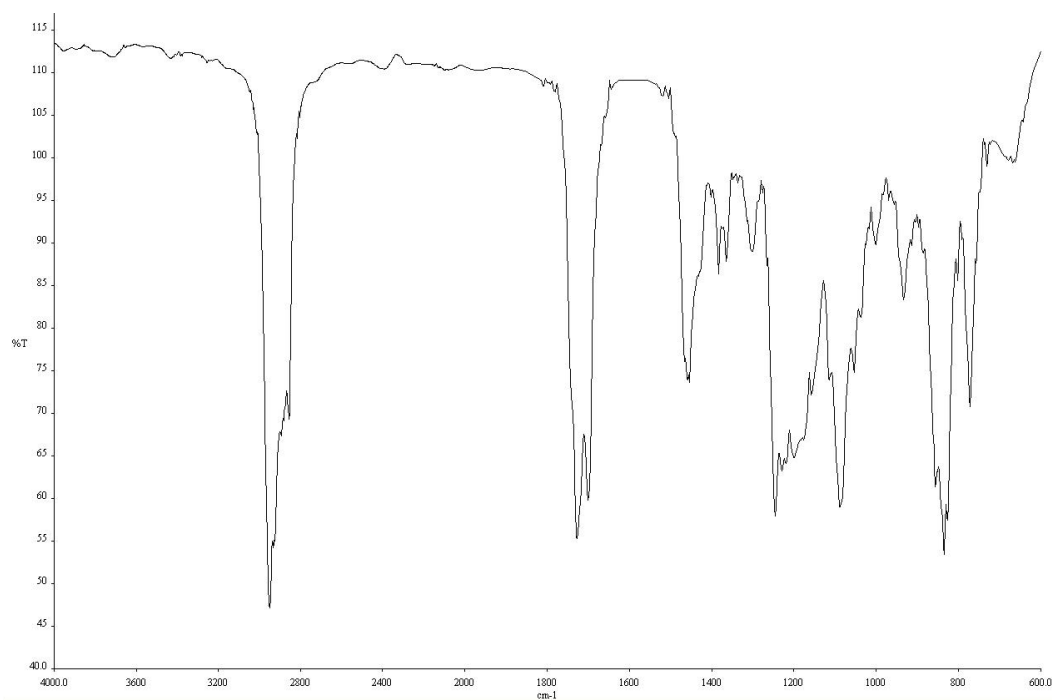


Figure A2.29 Infrared spectrum (Thin Film, NaCl) of compound 18.

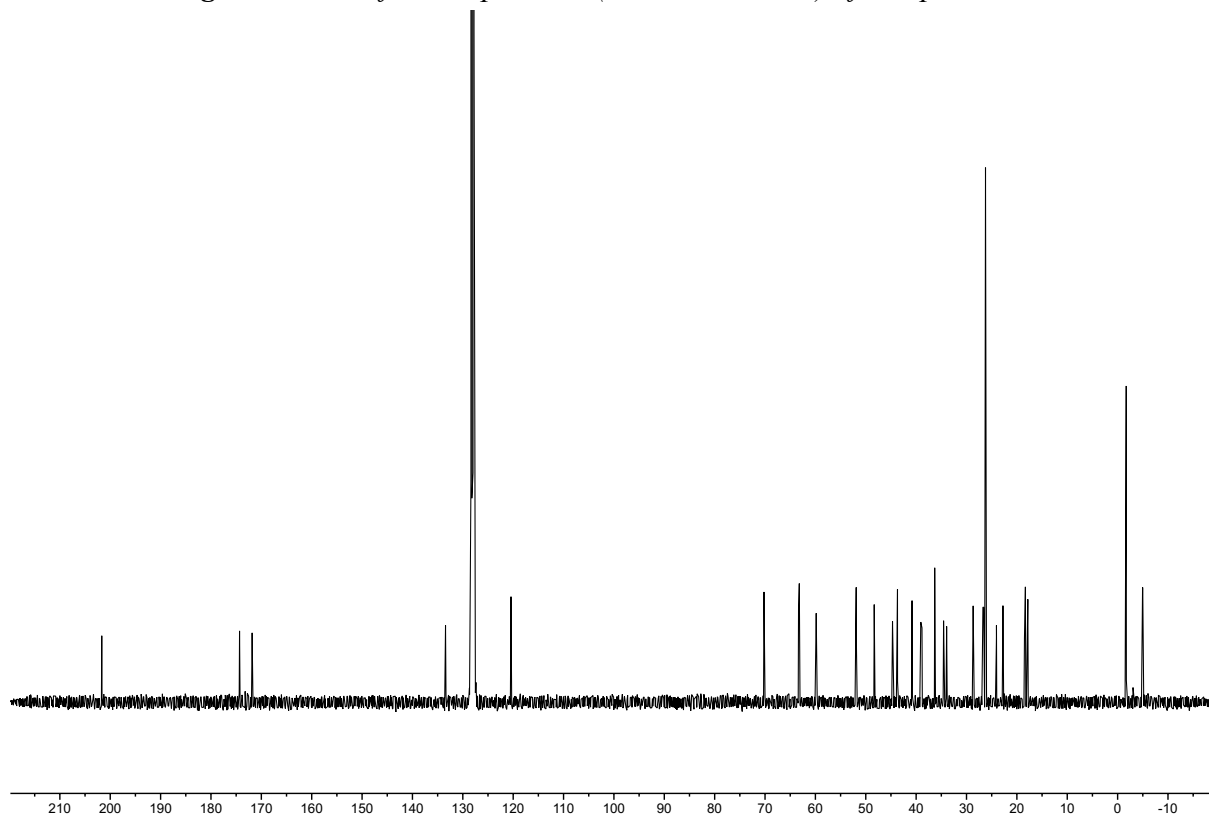


Figure A2.30 ¹³C NMR (100 MHz, C₆D₆) of compound 18.

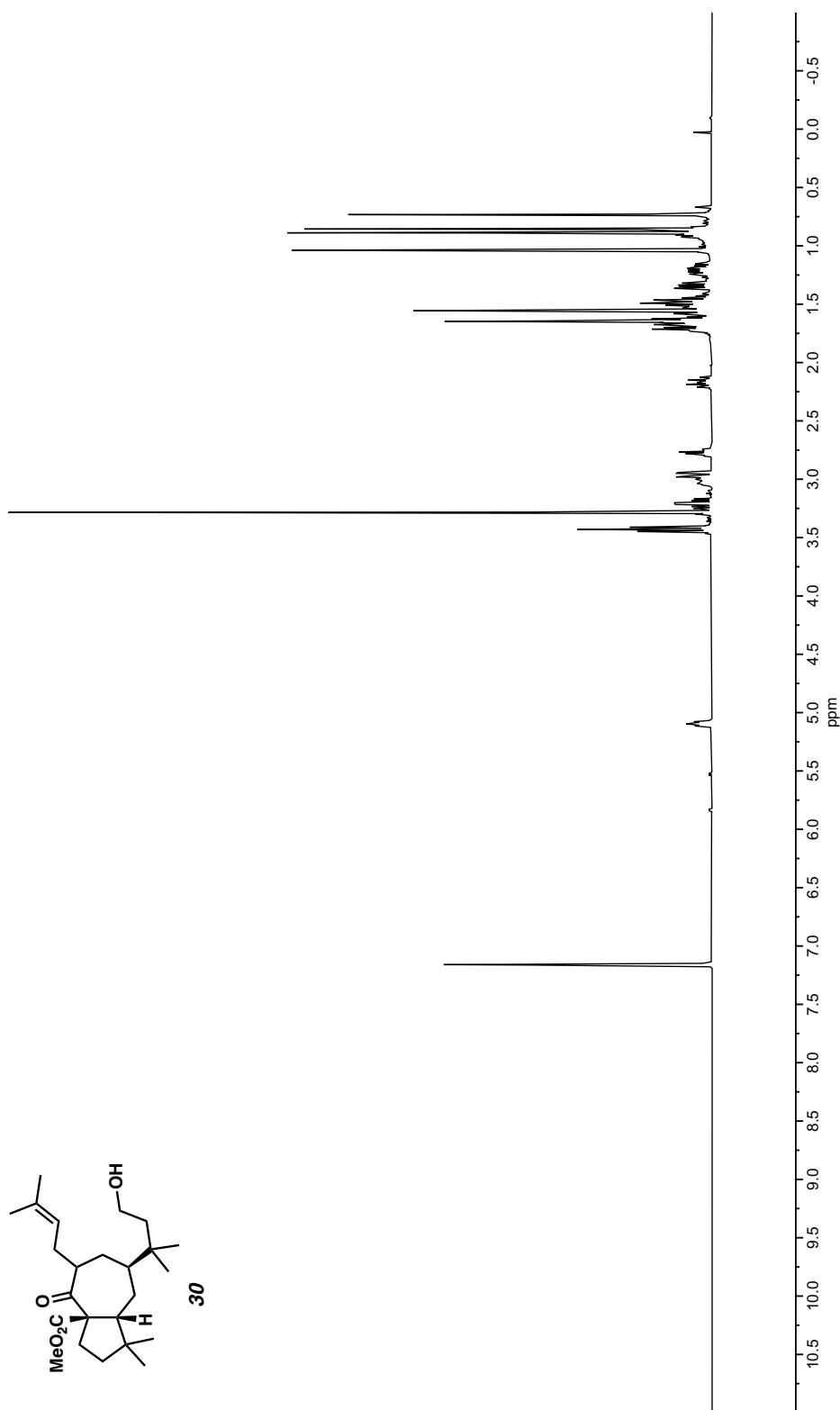


Figure A2.31 ¹H NMR (400 MHz, C₆D₆) of compound **30**.

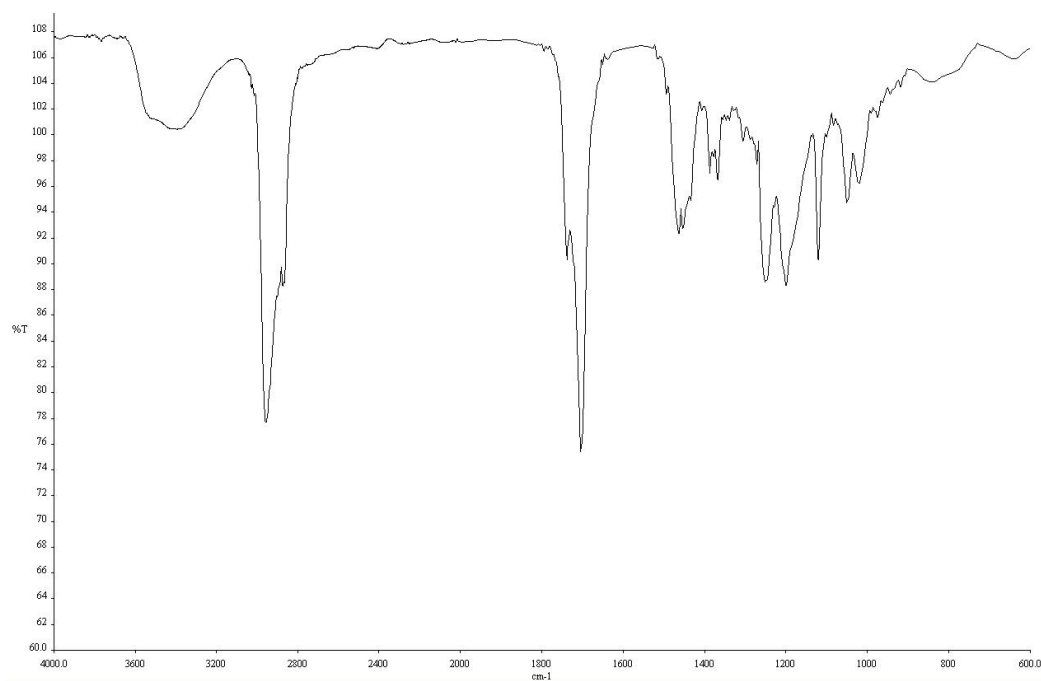


Figure A2.32 Infrared spectrum (Thin Film, NaCl) of compound **30**.

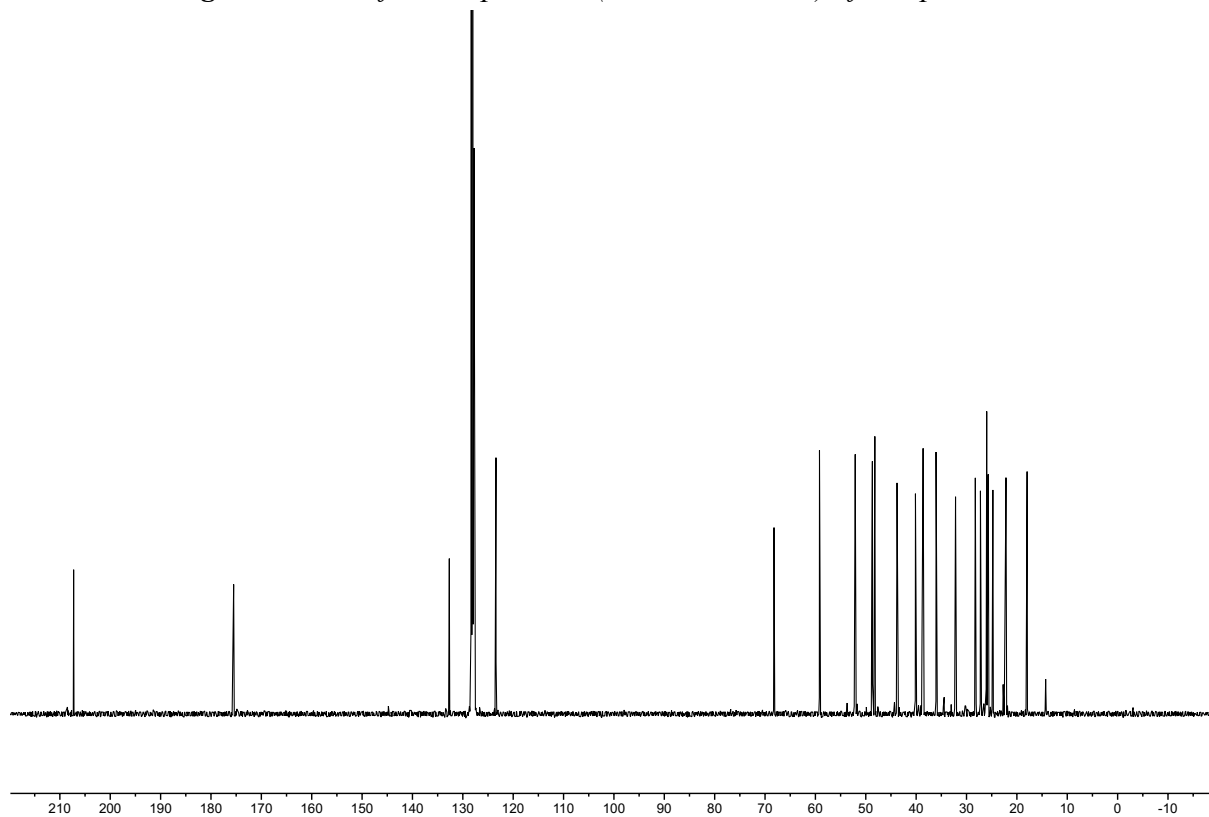


Figure A2.33 ¹³C NMR (100 MHz, C₆D₆) of compound **30**.

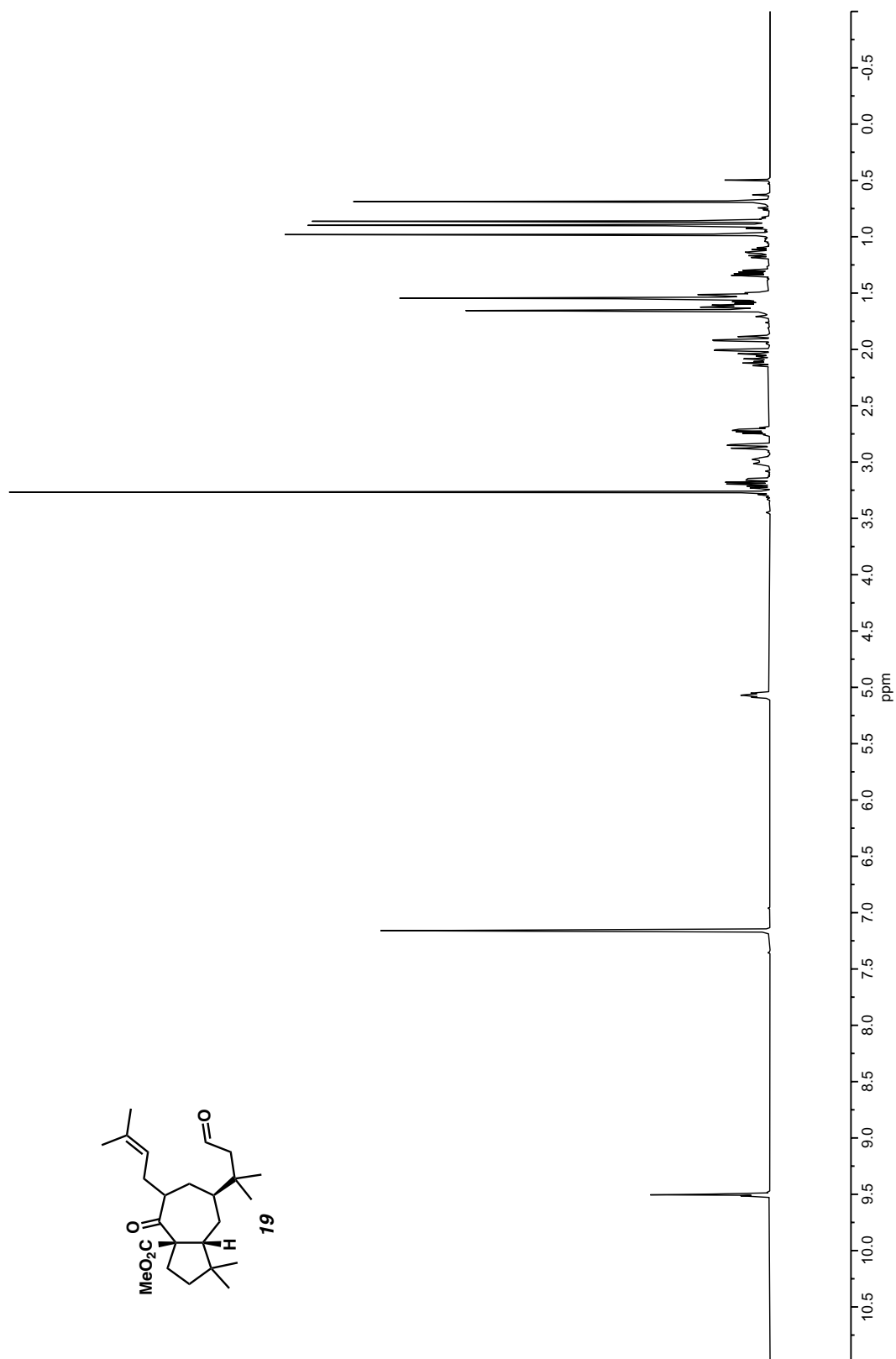


Figure A2.34 ¹H NMR (400 MHz, C₆D₆) of compound **19**.

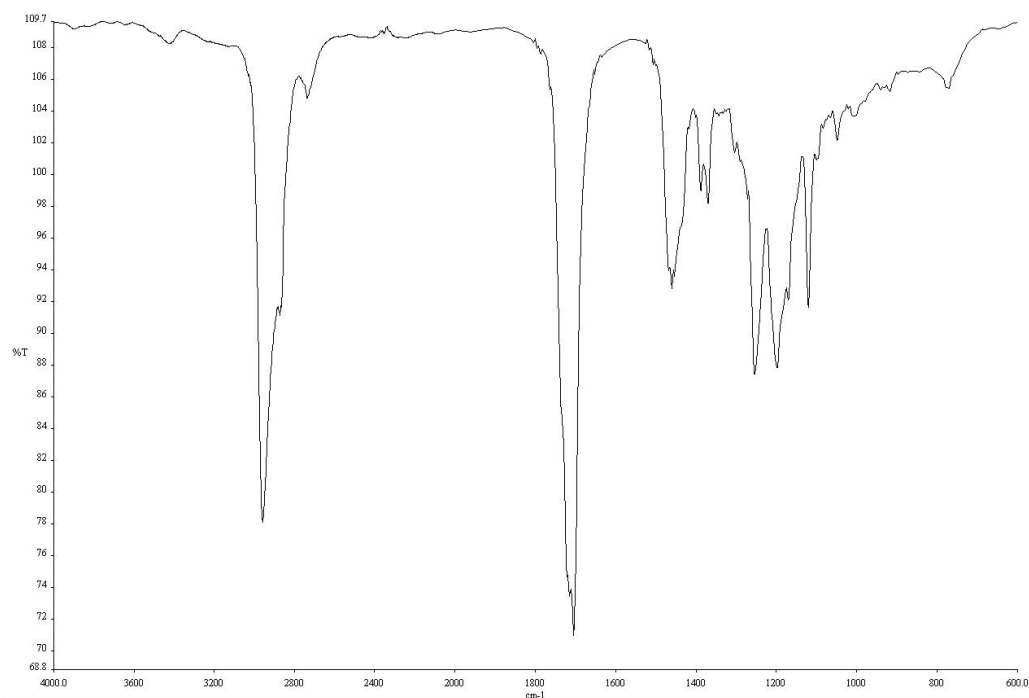


Figure A2.35 Infrared spectrum (Thin Film, NaCl) of compound 19.

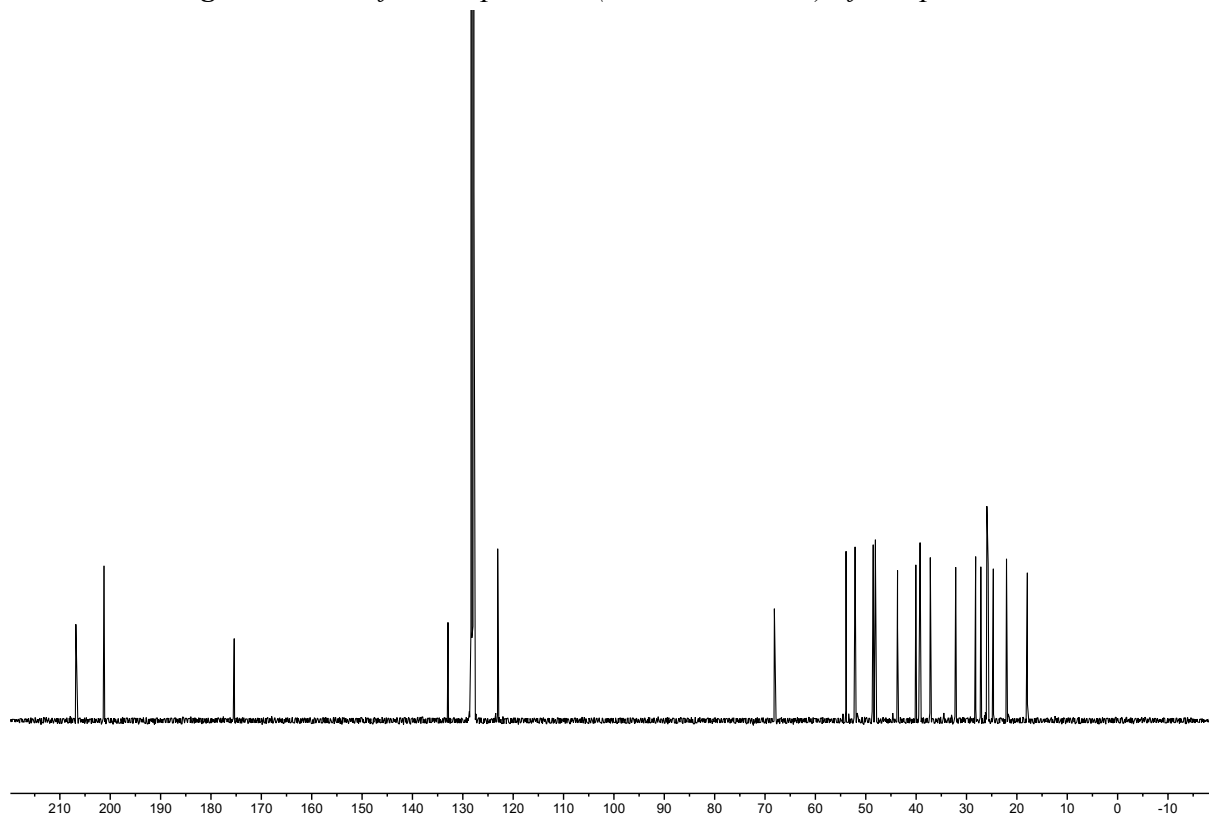


Figure A2.36 ¹³C NMR (100 MHz, C₆D₆) of compound 19.

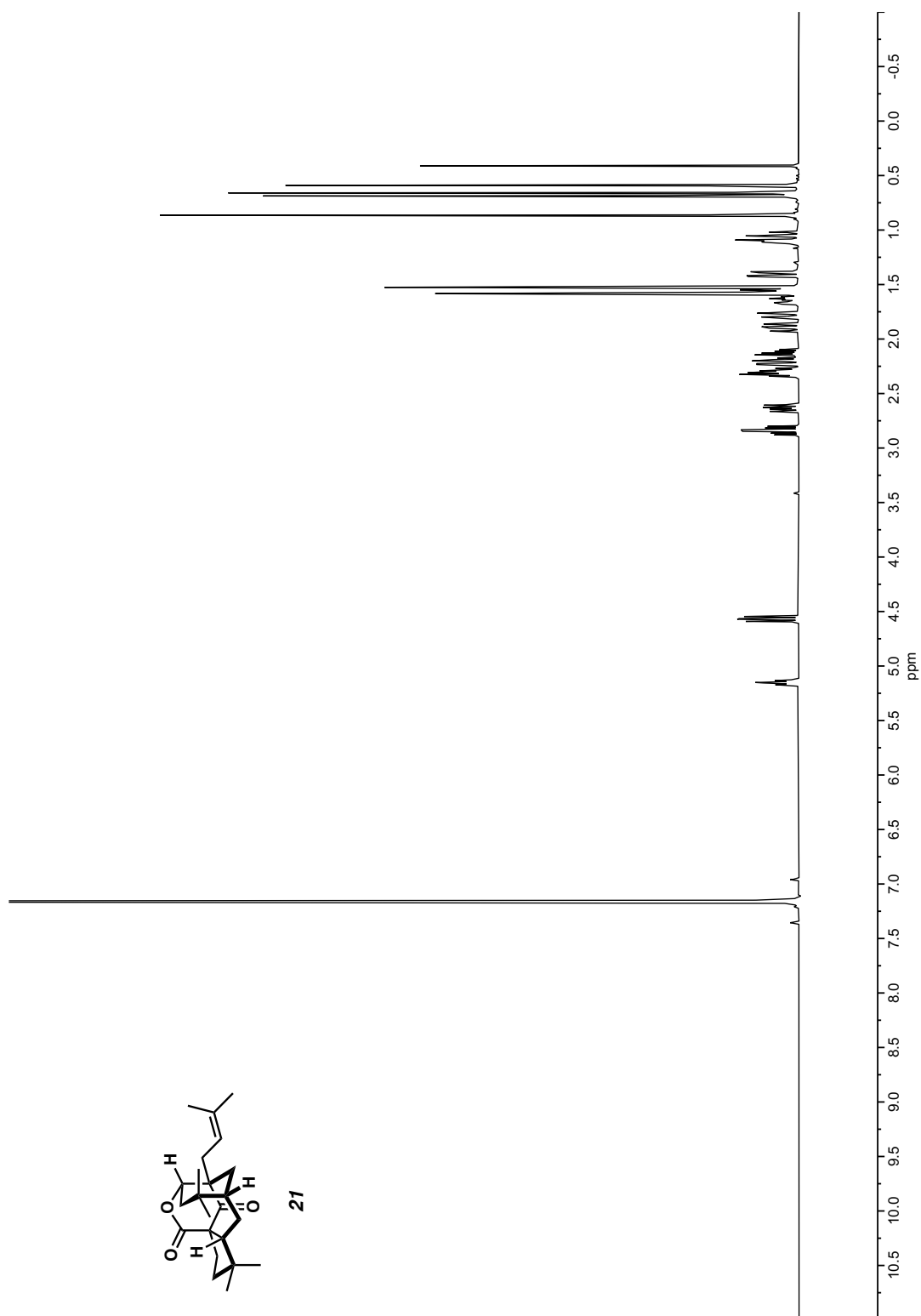


Figure A2.37 ^1H NMR (400 MHz, C_6D_6) of compound **21**.

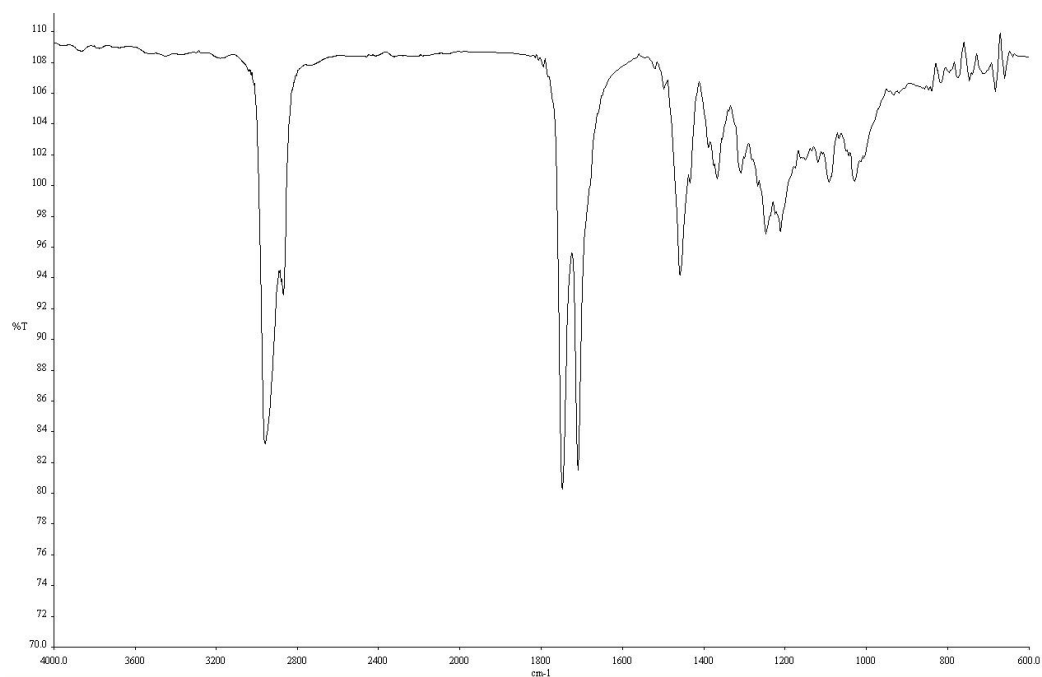


Figure A2.38 Infrared spectrum (Thin Film, NaCl) of compound 21.

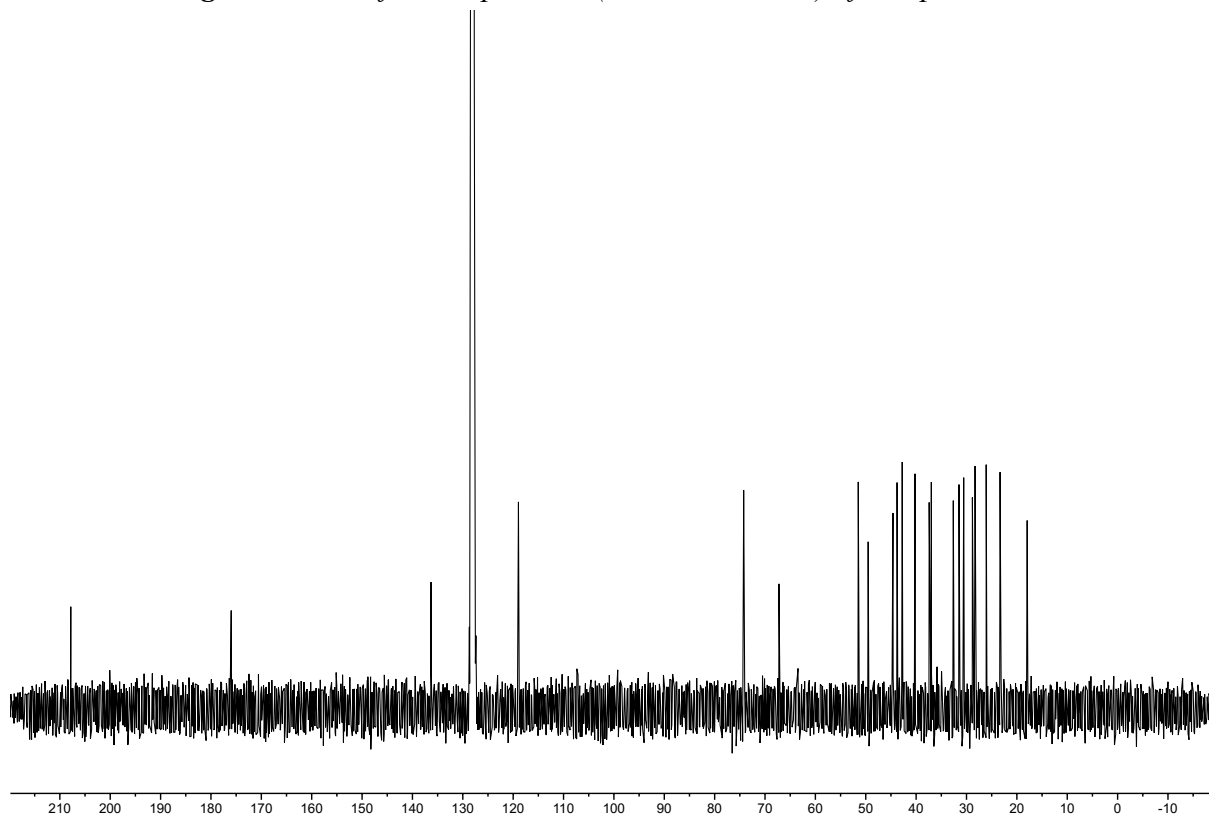


Figure A2.39 ¹³C NMR (100 MHz, C₆D₆) of compound 21.

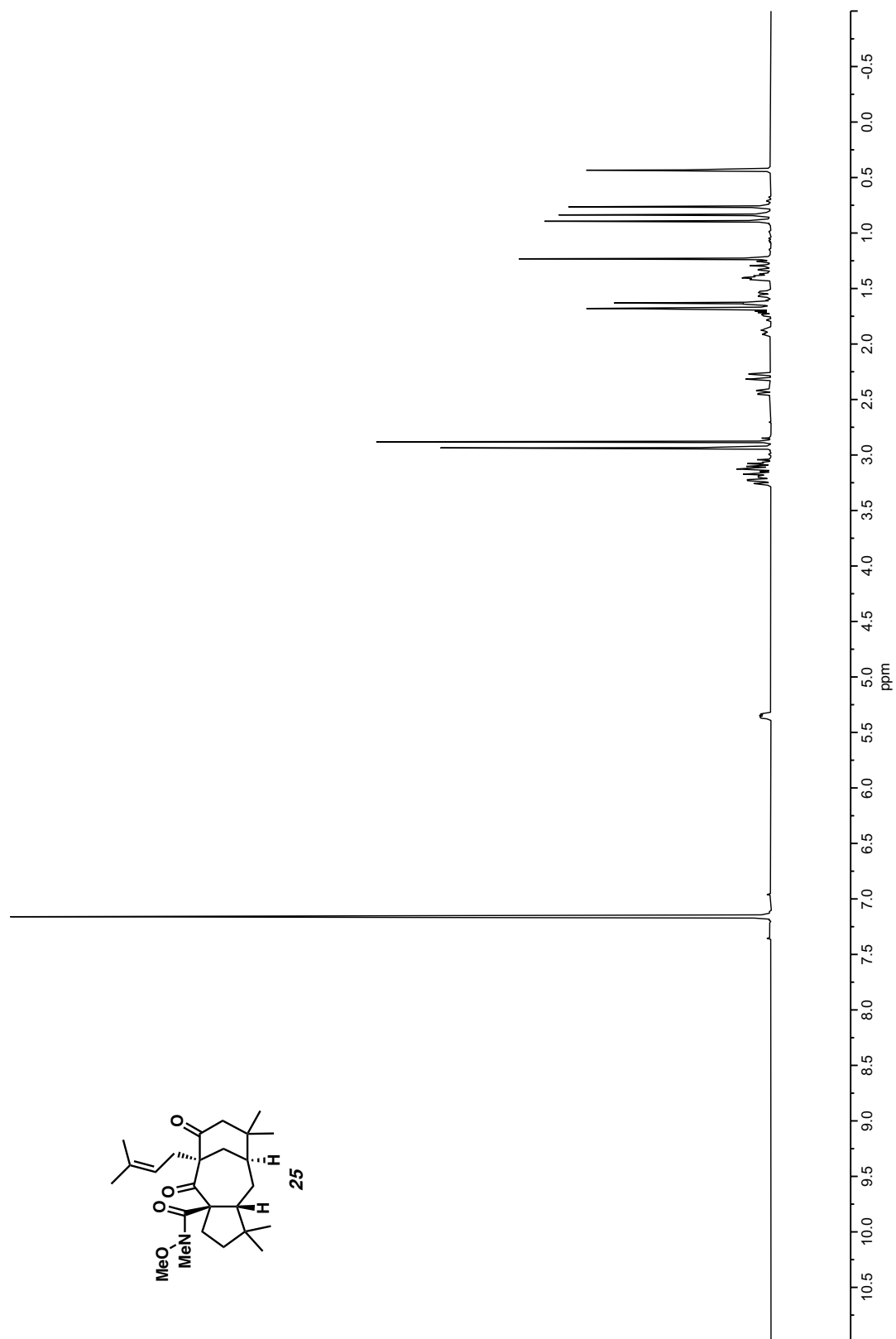


Figure A2.40 ^1H NMR (400 MHz, CDCl_3) of compound 25.

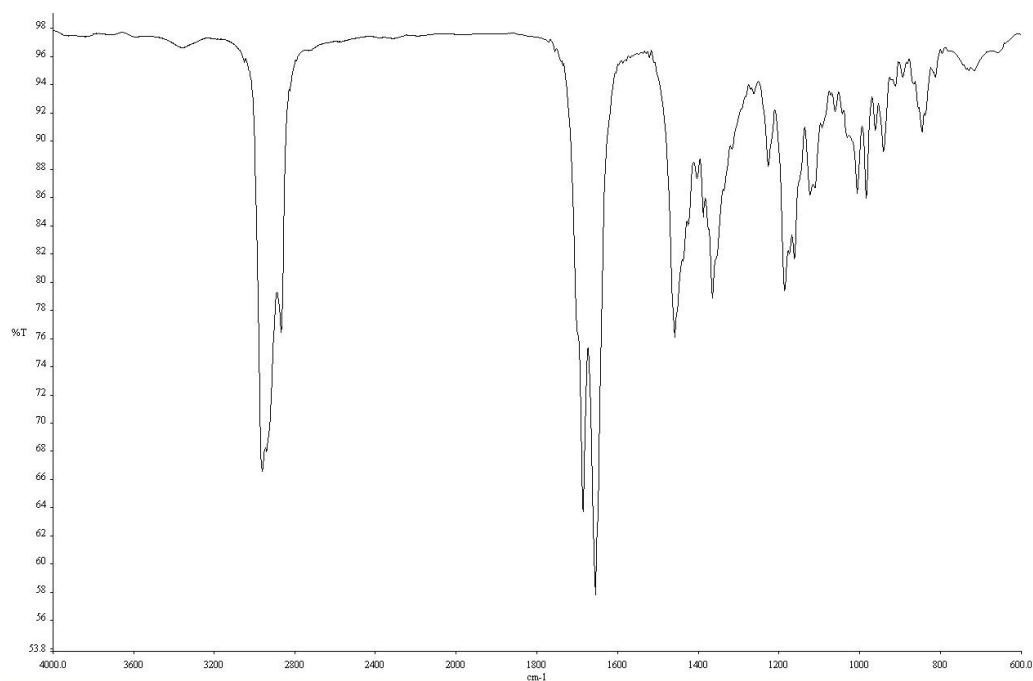


Figure A2.41 Infrared spectrum (Thin Film, NaCl) of compound 25.

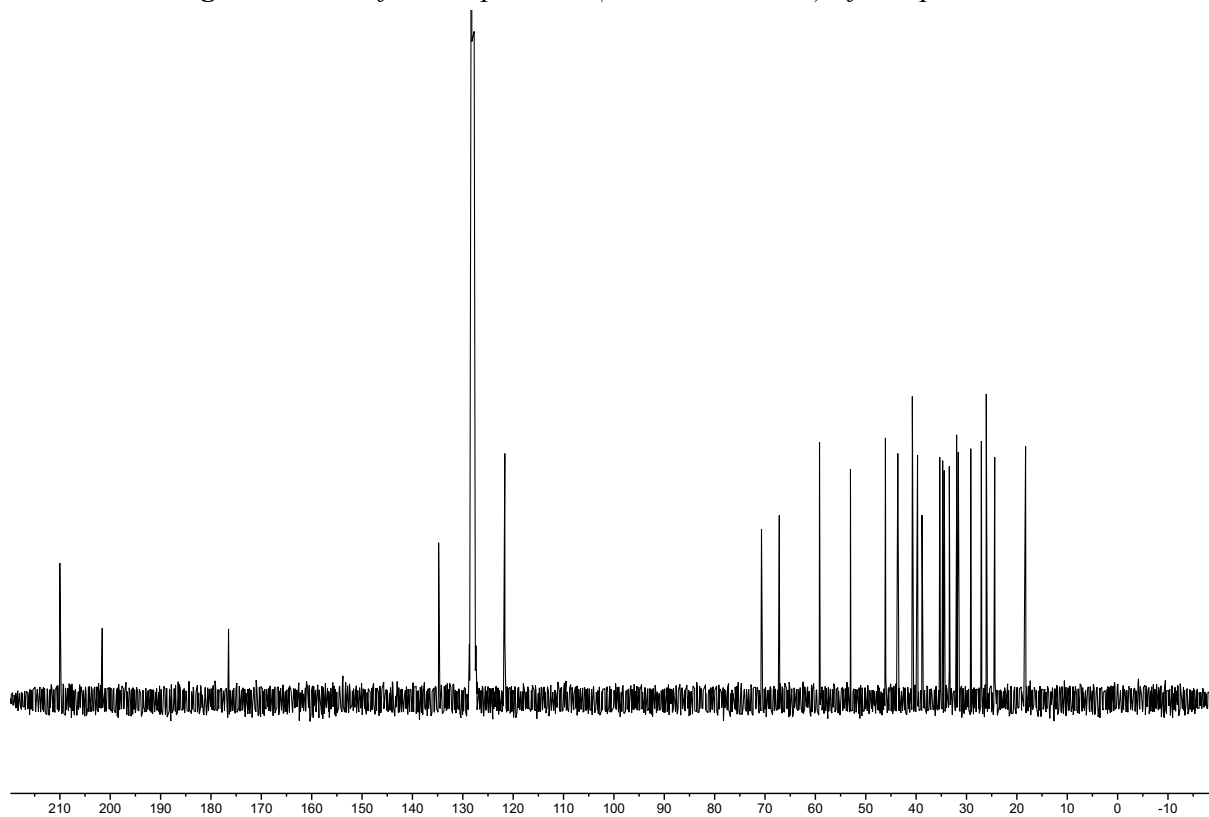


Figure A2.42 ^{13}C NMR (100 MHz, C_6D_6) of compound 25.

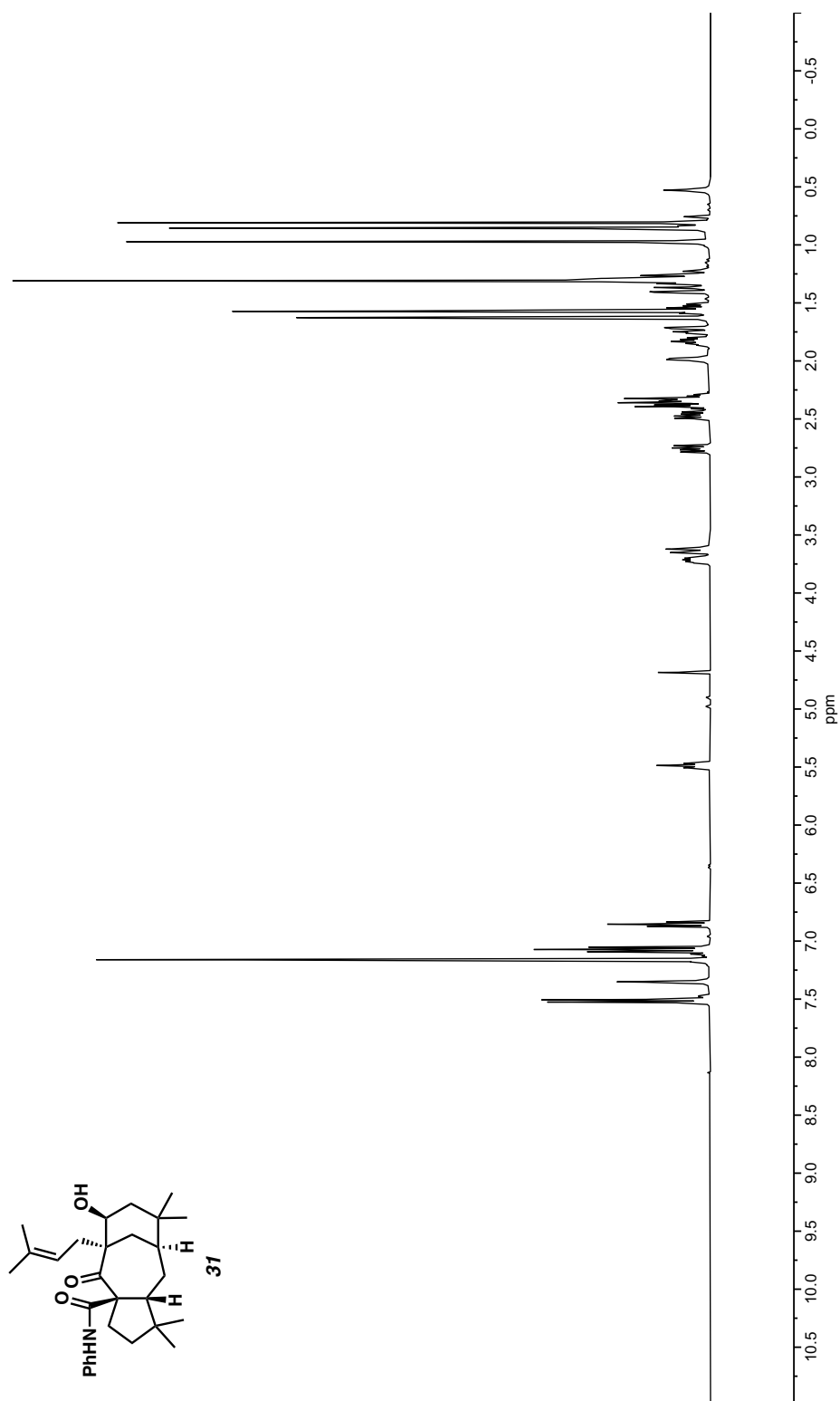


Figure A2.43 ^1H NMR (400 MHz, CDCl_3) of compound **31**.

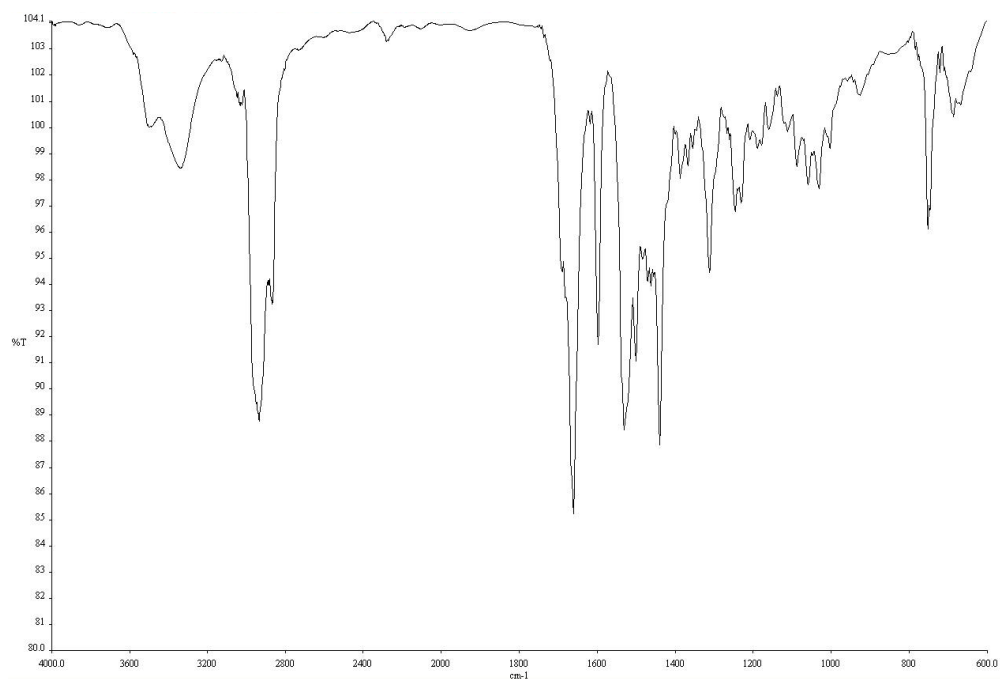


Figure A2.44 Infrared spectrum (Thin Film, NaCl) of compound **31**.

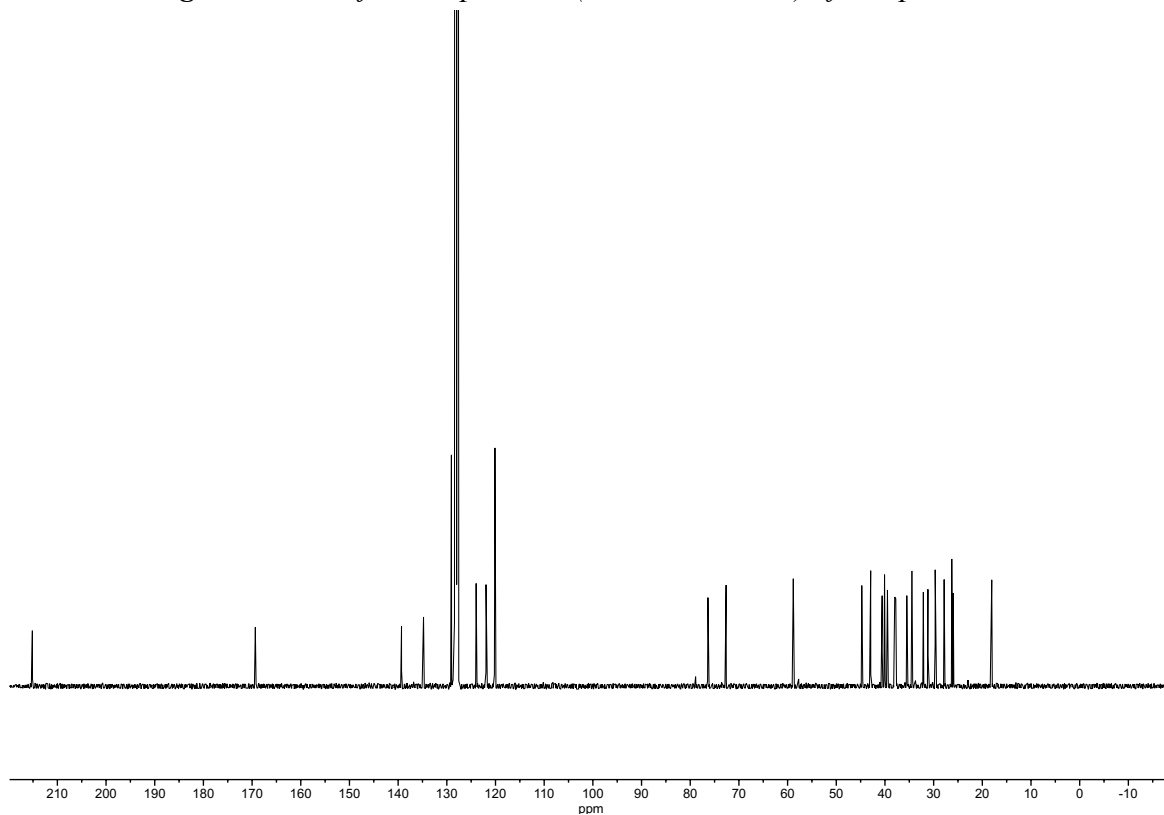


Figure A2.45 ¹³C NMR (100 MHz, C₆D₆) of compound **31**.

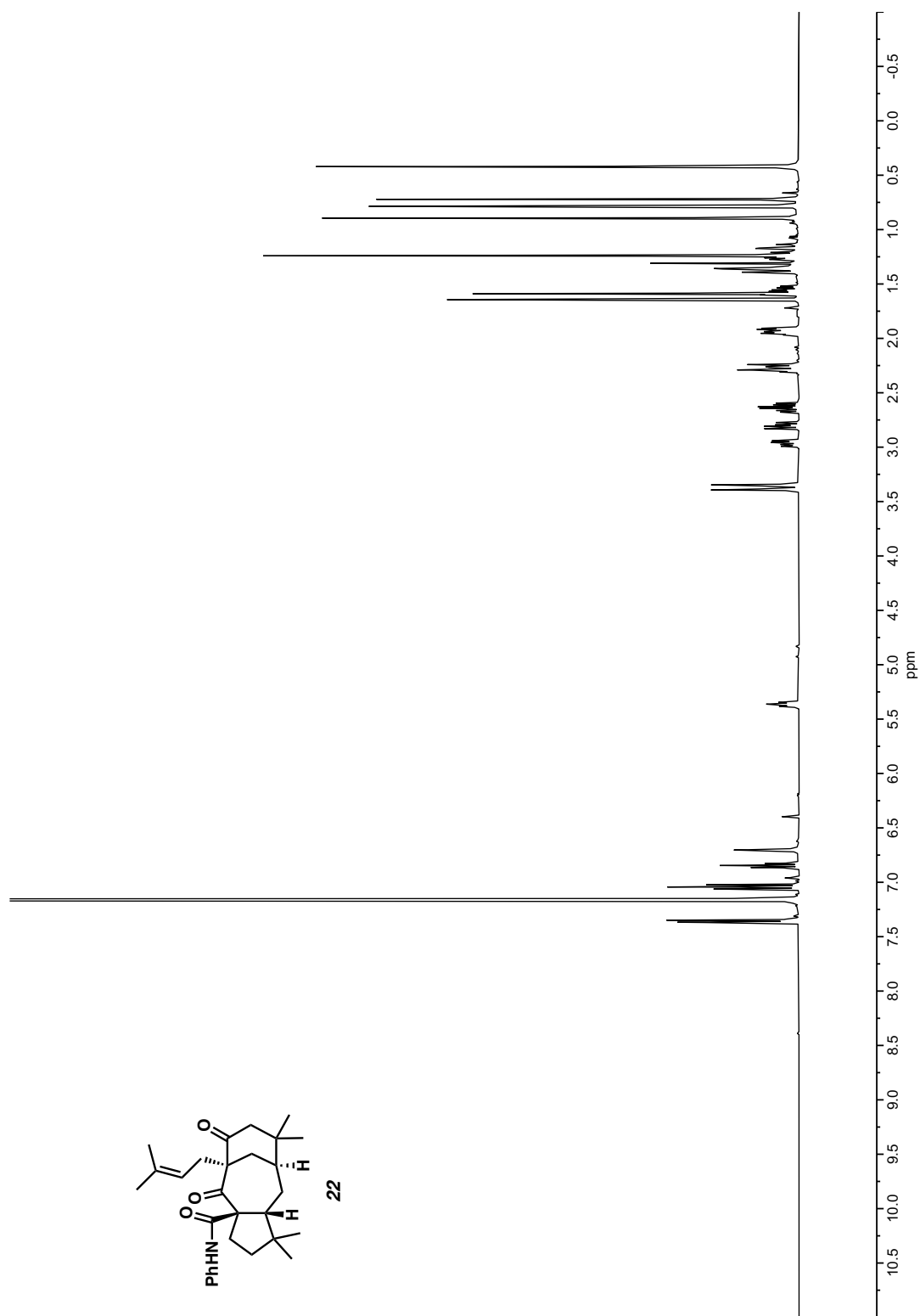


Figure A2.46 ¹H NMR (400 MHz, CDCl₃) of compound 22.

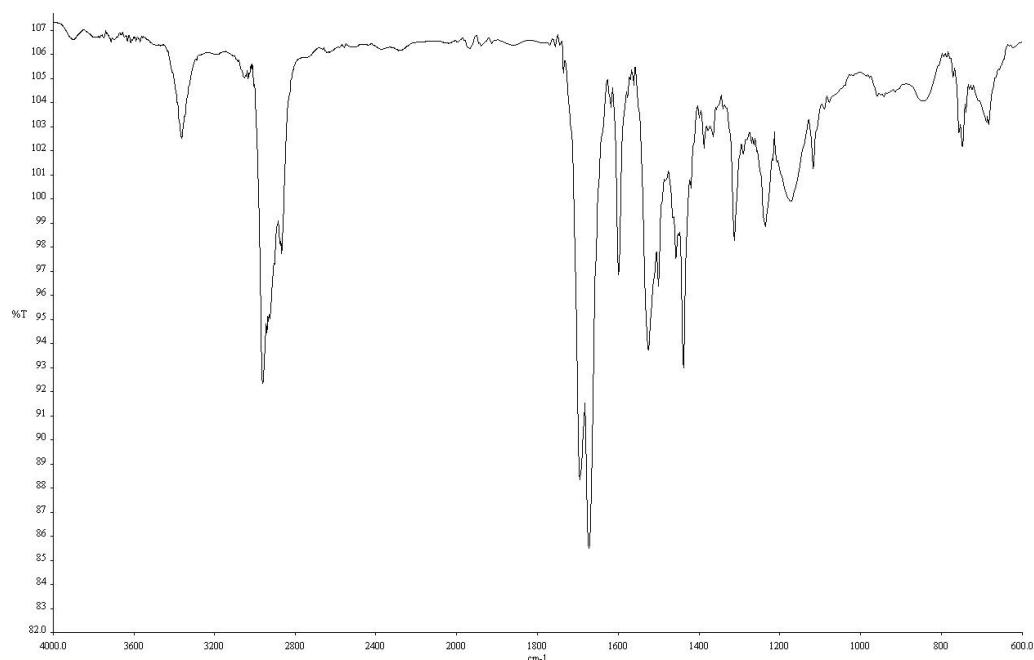


Figure A2.47 Infrared spectrum (Thin Film, NaCl) of compound 22.

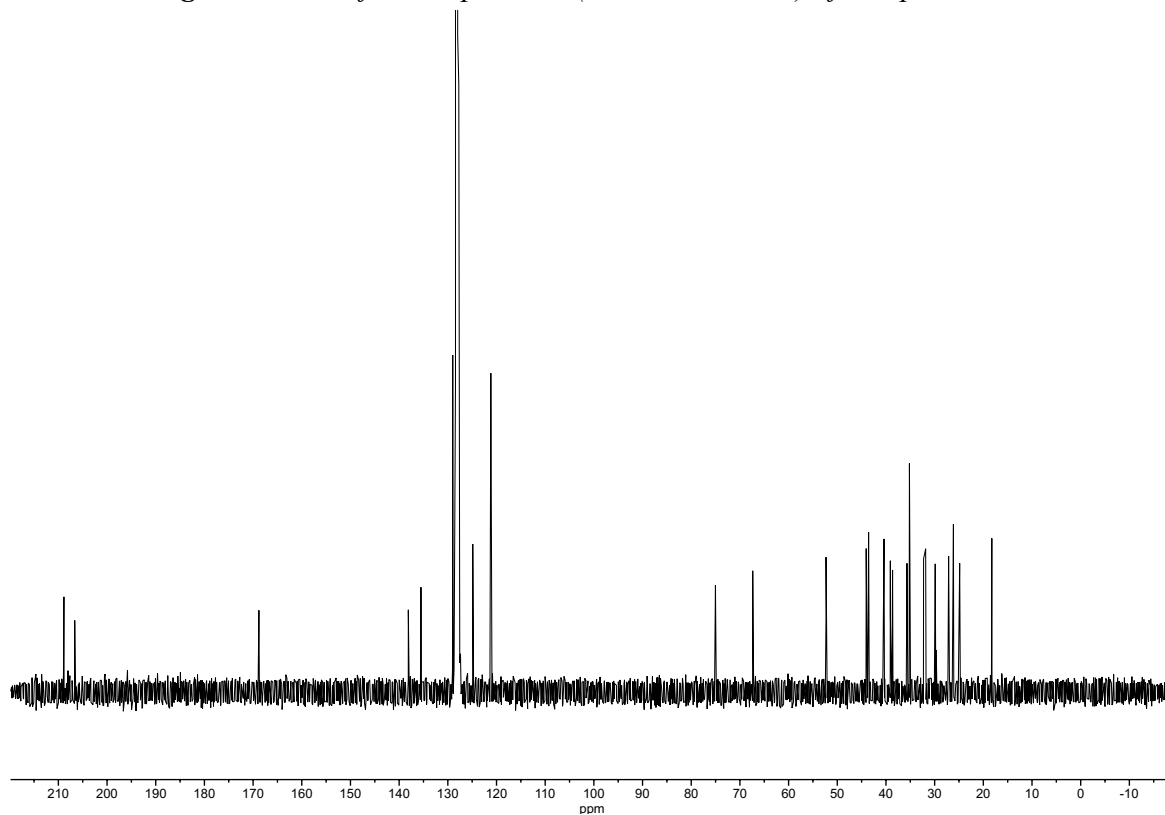


Figure A2.48 ¹³C NMR (100 MHz, CDCl₃) of compound 22.

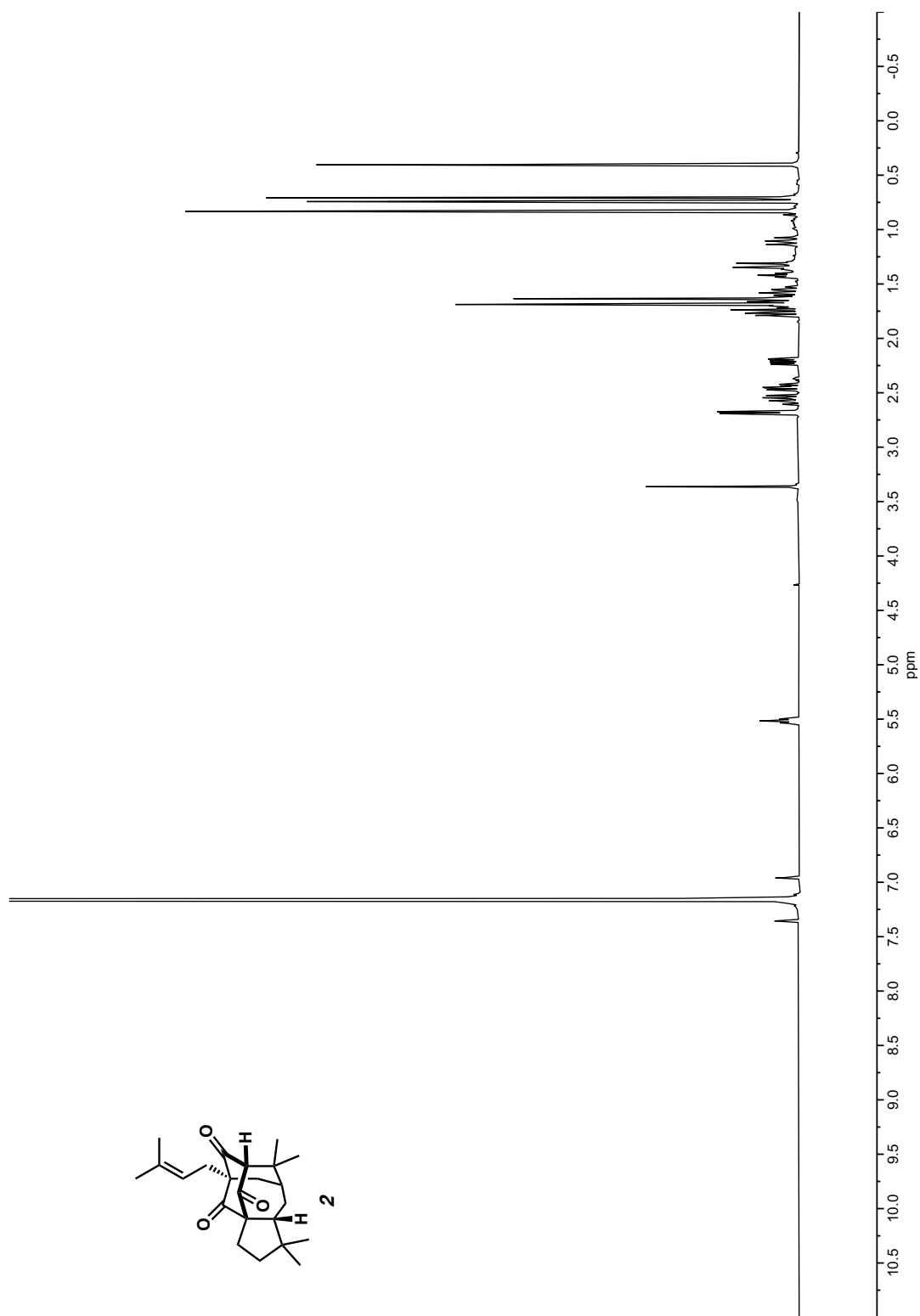


Figure A2.49 ^1H NMR (400 MHz, C_6D_6) of compound **2**.

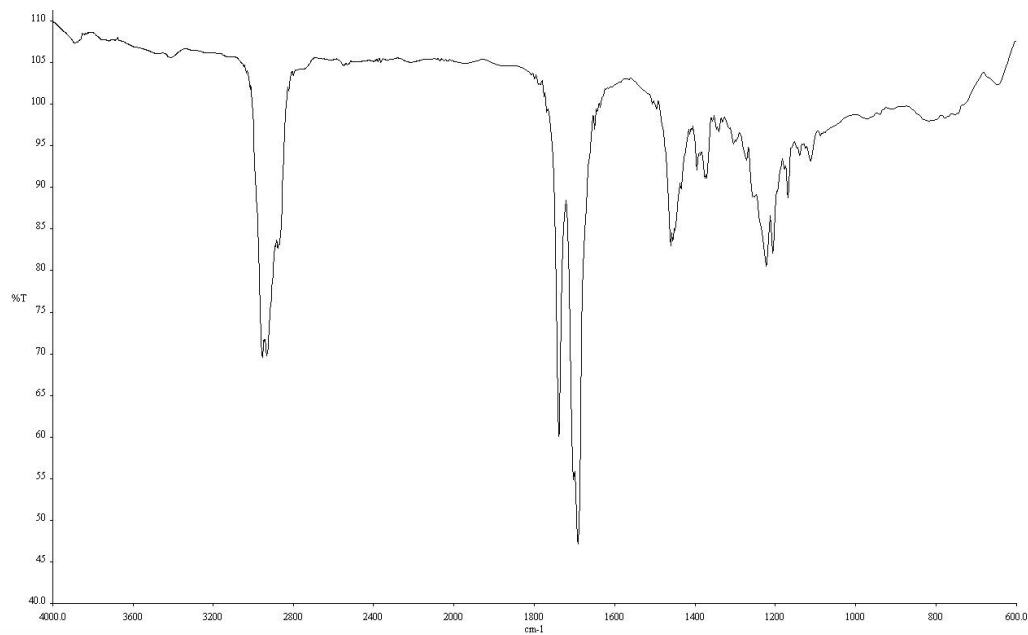


Figure A2.50 Infrared spectrum (Thin Film, NaCl) of compound 2.

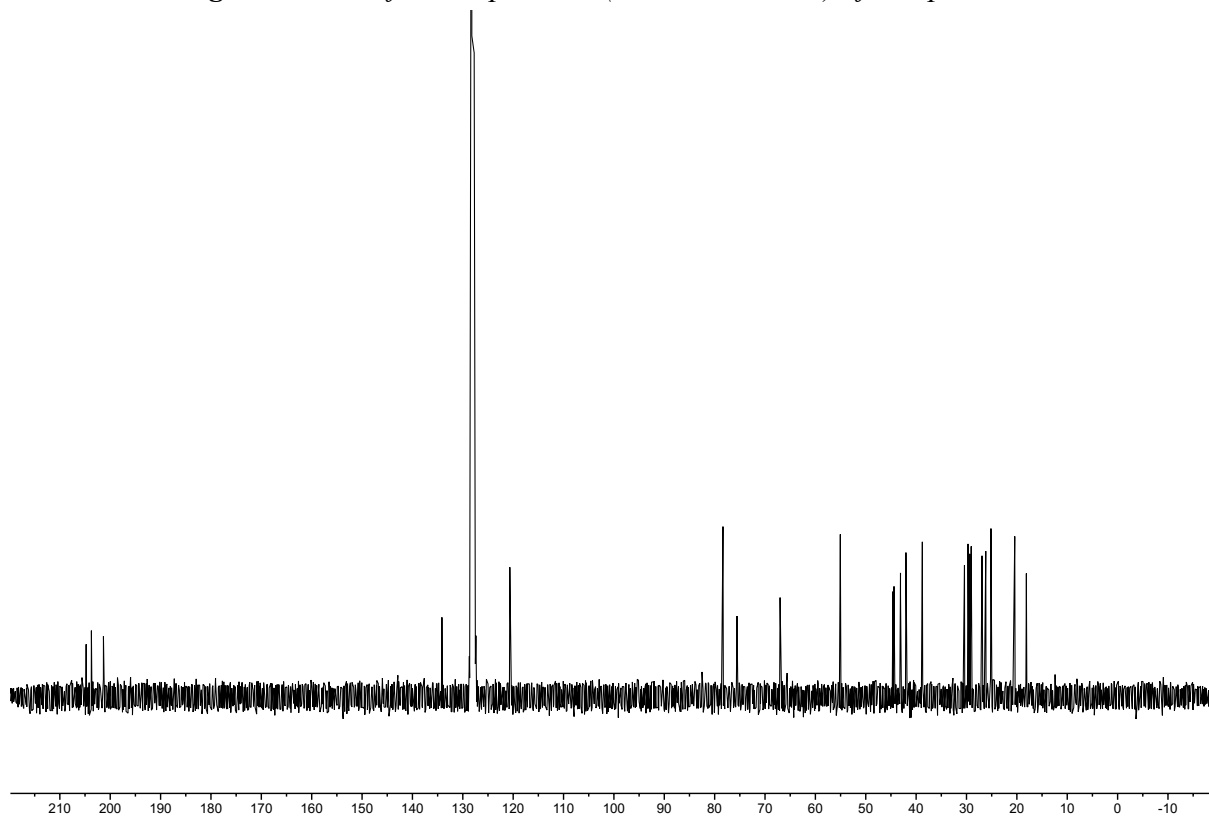


Figure A2.51 ¹³C NMR (100 MHz, C₆D₆) of compound 2.

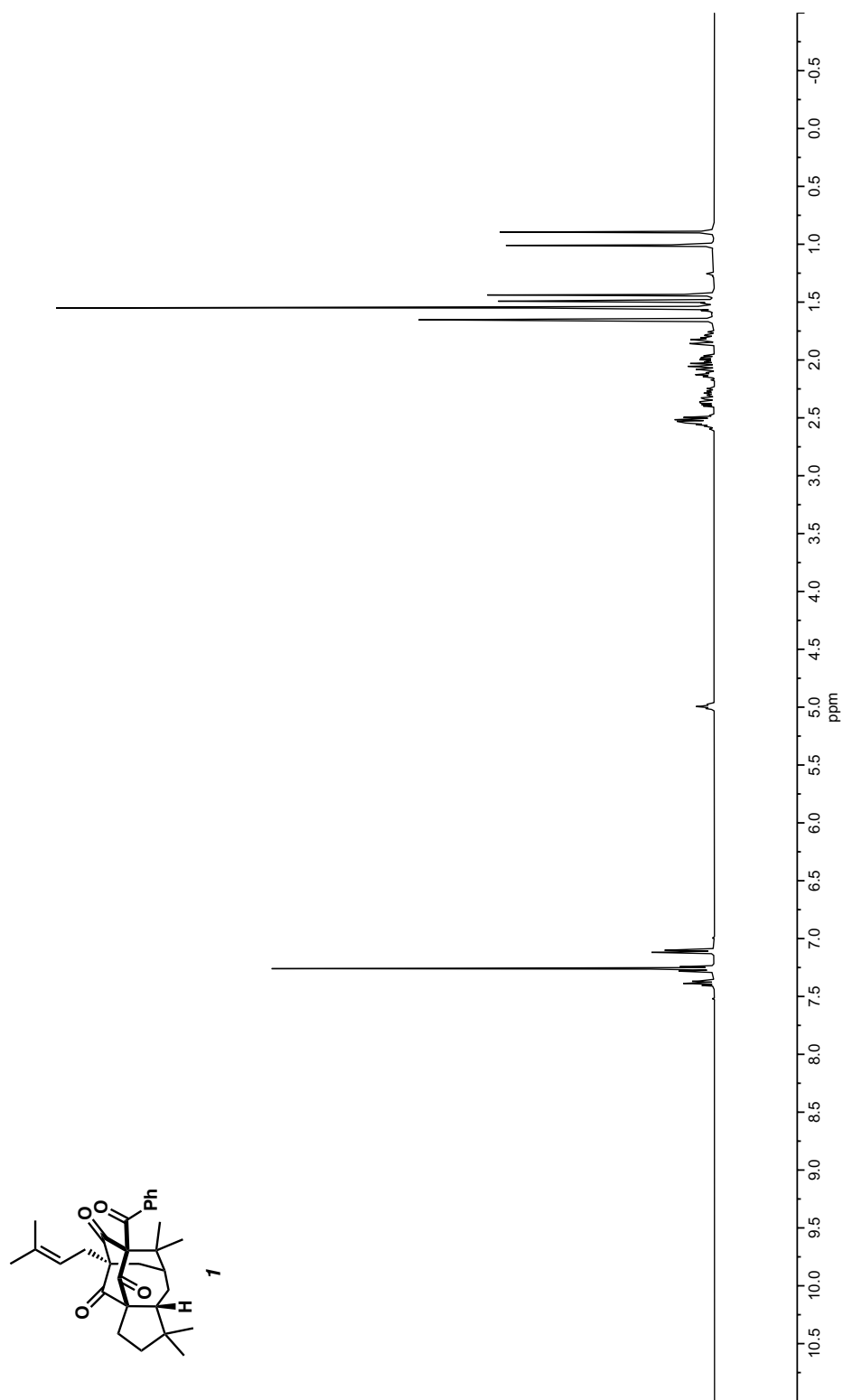


Figure A2.52 ^1H NMR (400 MHz, CDCl_3) of compound **1**.

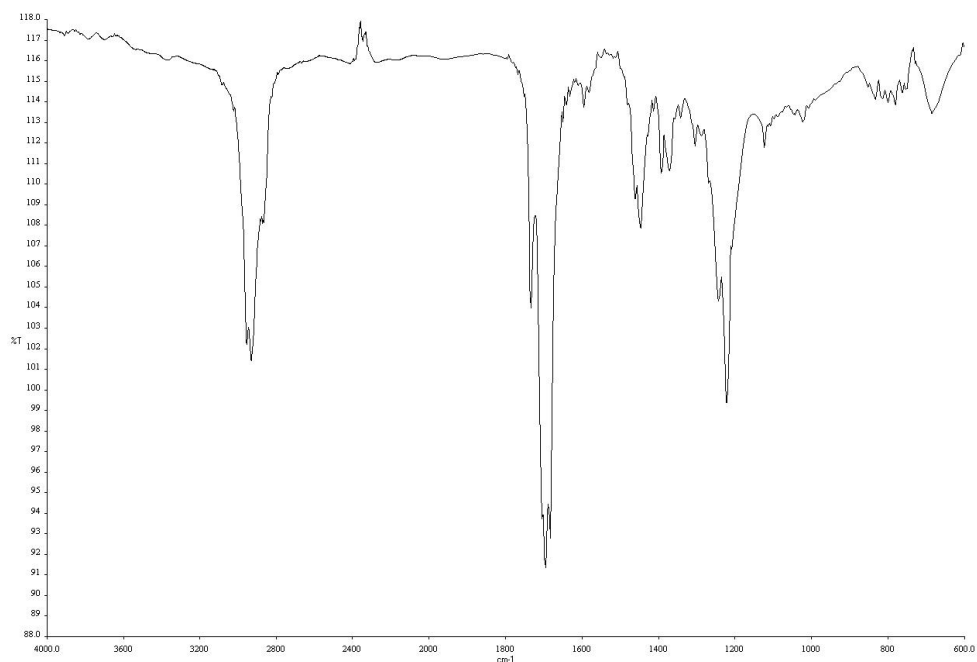


Figure A2.53 Infrared spectrum (Thin Film, NaCl) of compound **1**.

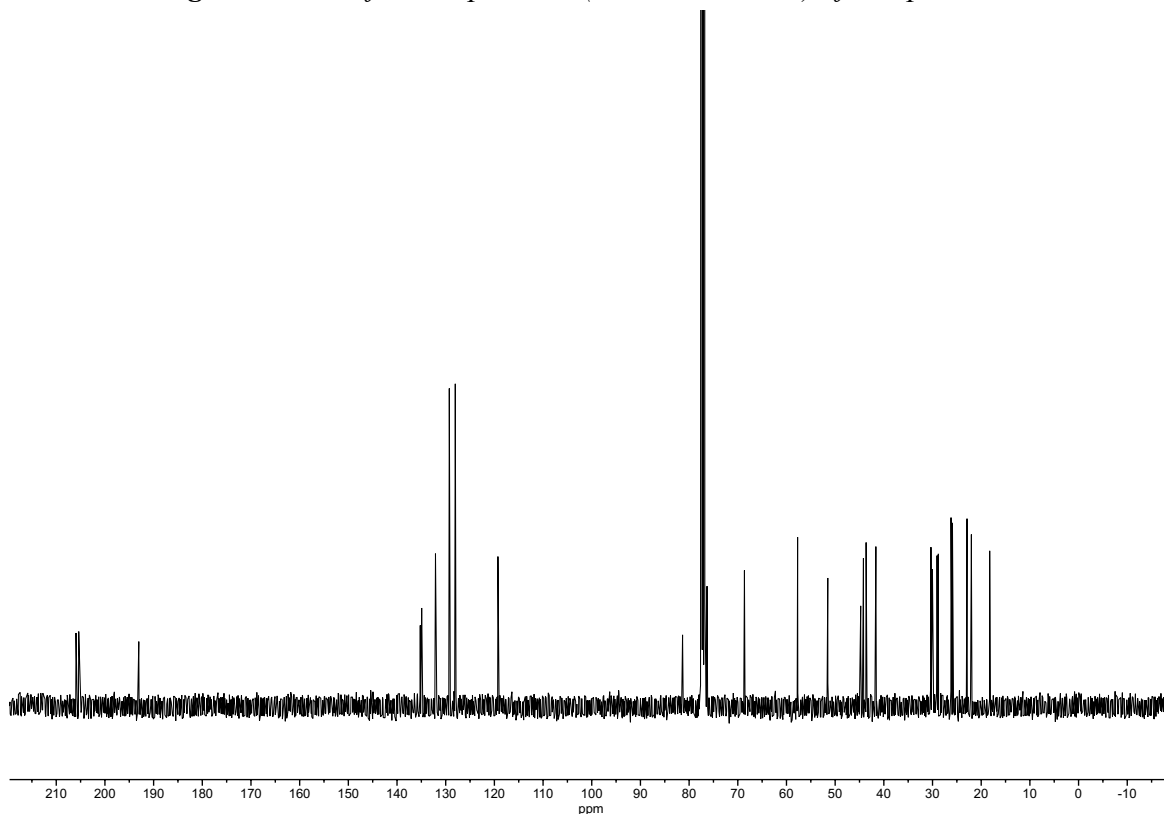


Figure A2.54 ^{13}C NMR (100 MHz, CDCl_3) of compound **1**.

CHAPTER 2

Toward the Total Synthesis of Hypersonin A and Wilsonglucinol G[†]

2.1 INTRODUCTION

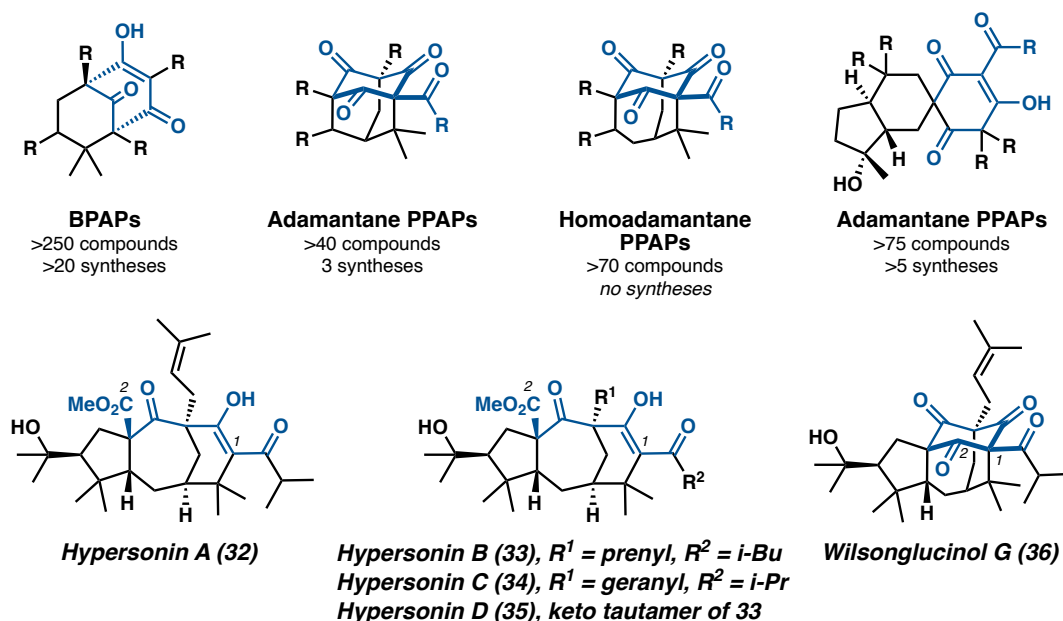
The polycyclic polyprenylated acylphloroglucinols (PPAPs) are a vast and diverse class of natural products comprised of over 400 members.¹ The notable bioactivity and range of fundamentally different structures have fueled the attention PPAPs have received, both in synthetic chemistry and chemical biology communities. The sheer number and complexity of these natural products necessitates a further subdivision—namely into the bicyclic polyprenylated acylphloroglucinols (BPAPs), the adamantane and homoadamantane PPAPs, and the spirocyclic or otherwise rearranged PPAPs (Figure 2.1.1).^{1e} While the BPAPs, homoadamantane, and rearranged PPAPs have all received significant attention in the context of total synthesis, a homoadamantane PPAP (hypersampson M, **1**, Figure 1.1.1) was only recently synthesized by our lab in 2024.^{2,3}

During our studies of the homoadamantane PPAPs we became interested in hypersonin A (**32**), isolated from *Hypericum wilsonii* in 2020 alongside three other closely related natural products (**33–35**).⁴ Hypersonin A displays moderate immunosuppressive bioactivity in preliminary murine studies (IC₅₀ = 8.3 μM), but we found the most striking feature to be its 5-7-6 tricyclic core: a rare example of a *seco*-homoadamantane PPAP.

[†]This research was conducted in collaboration with Kasem Poonswat.

Indeed, of over 70 homoadamantane PPAPs isolated to date,^{1e,5} the hypersonins are the only compounds featuring a disconnection between the C1 and C2 positions. Interestingly, the cyclized, homoadamantane version of hypersonin A, wilsonglucinol G (**36**), is also a natural product isolated from the same flowering plant *Hypericum wilsonii* in 2019.⁶

Figure 2.1.1. Hypersonin A, wilsonglucinol G and representative PPAP classes.



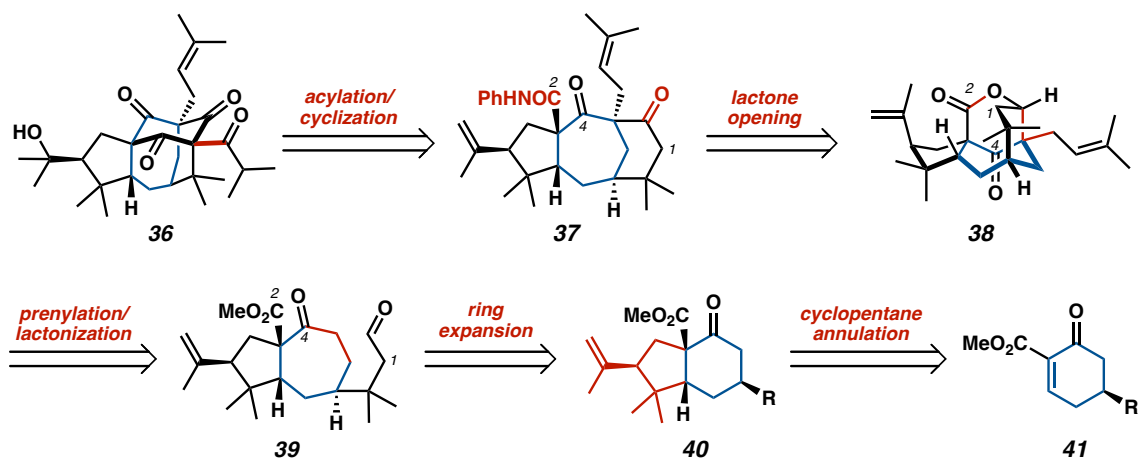
Furthermore, both compounds are implicated to have similar immunosuppressive bioactivity (albeit the IC_{50} is $> 40 \mu\text{M}$ for **36**), and the hypersonins are isolated via methanol chromatography. These points seemed coincidental and led us to hypothesize that the hypersonins are potentially isolation artifacts arising during extraction or chromatography of the wilsonglucinols. The hypersonins are significantly more potent immunosuppressants than their ring-closed counterparts, likely due to increased conformational flexibility and enhanced polar interactions at the biological target. This suggests that subtle structural changes in the PPAP scaffold can have a profound impact on bioactivity. Hoping to showcase the applicability of our previous 15-step route,

potentially address this isolation puzzle, and shed light on the biochemistry of this class of PPAPs we set out to synthesize wilsonglucinol G, hoping to access hypersonin A (**32**) via subsequent ring opening.

2.2 RETROSYNTHETIC ANALYSIS

The retrosynthetic strategy for wilsonglucinol G (**36**, Scheme 2.2.1) is analogous to that of hypersampson M (**1**). Wilsonglucinol G (**36**) features an exocyclic 3° alcohol on the 5-membered ring. To avoid elimination of this alcohol throughout the synthesis, this alcohol will be masked as an isopropenyl group. A late-stage bridgehead acylation and olefin hydration follows cyclization of amide **37** after amidation of lactone **38**. Lactone **38** will be formed through prenylation and cyclization of aldehyde **39**, which can arise from ring-expansion of cyclohexanone **40**. The key challenge in this synthesis will be installation of the exocyclic functionality on this 5-membered ring, which ultimately should be accessible from enone **41**.

Scheme 2.2.1. Retrosynthetic strategy toward wilsonglucinol G.

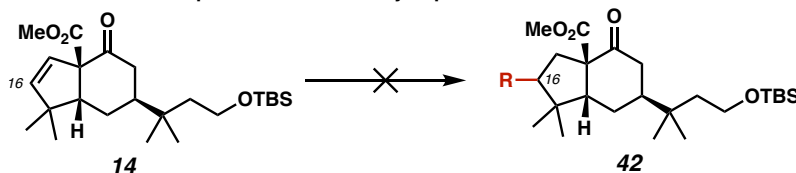


2.3 DEVELOPMENT OF A 3-COMPONENT CYCLOPENTENE ANNULATION

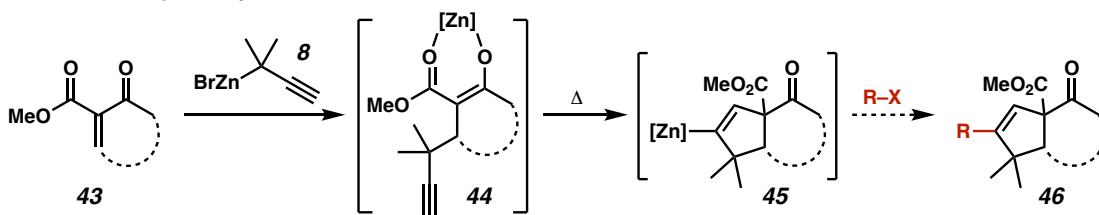
Significant efforts were made to install functionality that could later be advanced to the requisite, exocyclic 3° alcohol. Disappointingly, installation of any functionality following construction of the cyclopentene (**14**→**42**, Scheme 2.3.1A) proved difficult. These attempts, as well as other unsuccessful cyclopentane installation attempts are discussed in more detail in Appendix 5. The conclusion we made in those efforts was that installation of functionality at the C16 position needs to occur during the construction of the cyclopentene.

Scheme 2.3.1. Toward a functionalized cyclopentene annulation.

A) Unsuccessful attempts to functionalize cyclopentene 14.



B) Potential intercepted vinyl zinc functionalization.



To this end we revisited the cyclopentene annulation developed by Bellassoued and coworkers,⁷ and that we previously used in the synthesis of hypersampson M.² Mechanistically, addition of propargyl zinc **8** (Scheme 2.3.1B) to enone **43** results in zinc enolate **44**. Heating of this enolate results in cyclization resulting in the olefin product, presumably via vinyl zinc intermediate **45**. We hypothesized that interception of this vinyl zinc moiety, for example with an electrophile, could lead to a functionalized product (**46**).

Investigations commenced into the tandem annulation using ketoester **47** as a model (Table 2.3.1). Propargyl zinc bromide **8** underwent clean 1,4-addition to ketoester **47** (determined via complete consumption of starting material), and further heating of the solution resulted in partial conversion to vinyl zinc intermediate **48**, identified by a protic quench (entry 1). Direct addition into electrophiles (e.g., acetone, entry 2) was unsuccessful due to the low reactivity of vinyl zinc **48**. Instead, coupling with AcCl was explored, resulting in desired hydrazulene **49** (E = Ac, entries 3,4). Several solvents were next evaluated, and it was found that 1,2-dimethoxyethane (DME) improves the thermal cyclization significantly, although the subsequent acetylation still proceeds in low yield (entry 5). After further investigation, it was discovered that excess AcCl slowly decomposes vinyl zinc **48** and changing the order of addition (i.e. adding **48** dropwise into Pd(PPh₃)₄/AcCl, entry 6) led to greatly improved yield (65%).

Table 2.3.1. Optimization of the intercepted cyclopentene annulation.

entry	conditions	E	yield XX ^{a,b}
1	THF/H ⁺ /H ₂ O	H	44%
2	THF/acetone		0%
3	Pd(PPh ₃) ₄ (5 mol%) THF/AcCl	Ac	15%
4	CuBr (1 equiv) THF/AcCl	Ac	11%
5	Pd(PPh ₃) ₄ (5 mol%) DME/AcCl	Ac	27%
6	Pd(PPh ₃) ₄ (5 mol%) DME/AcCl inverse addition	Ac	65%

^a yield determined by ¹H NMR;

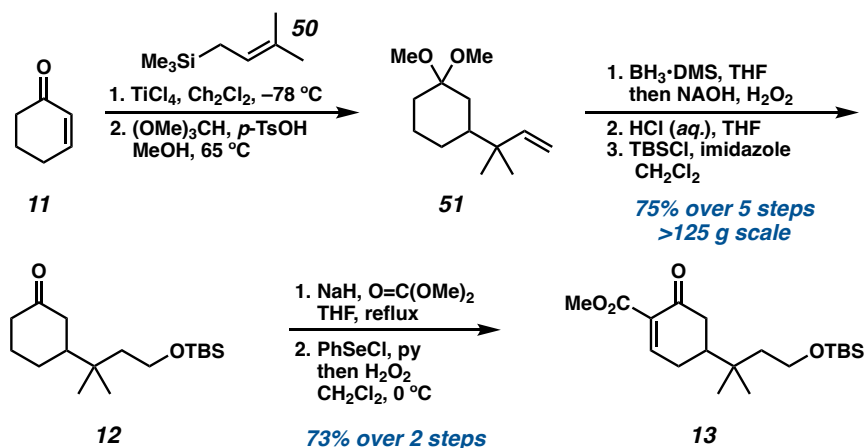
^b yields represent a 6:1 ratio of *cis* to *trans* fused hydrazulenes.

This reaction stands as an enabling step on route to wilsonglucinol G (**36**). It forges three C–C bonds (all of which are neopentylic) and forms two stereocenters and a tetrasubstituted center. Further discussion of this reaction is presented in Chapter 5. With these promising results on model substrate **47**, we turned our attention to the substituted cyclohexenone on route to wilsonglucinol G.

2.4 CURRENT PROGRESS TOWARD WILSONGLUCINOL G

Enone **13** was previously synthesized via acylation and desaturation of cyclohexanone **12**, which itself was accessible through an Fe-mediated HAT coupling from cyclohexenone (**11**, see Scheme 1.4.1). Though concise, this route suffers from poor material throughput due to the low yield and difficult isolation of the HAT coupling. To address this, a longer, more scalable route was developed.

Scheme 2.4.1. Scalable preparation of ketone 12.



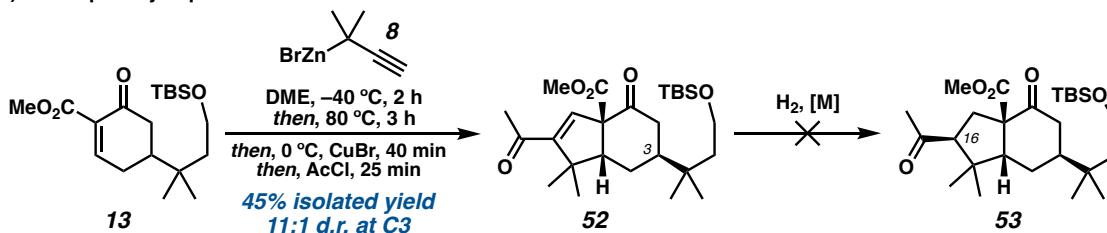
Starting again from cyclohexenone (**11**, Scheme 2.4.1), a Sakurai allylation with prenyl silane **50** followed by protection of the ketone afforded acetal **51**. Hydroboration/oxidation, ketone deprotection, and TBS protection of the alcohol afforded

cyclohexanone **12** in 75% over 5 steps with no intermediate chromatography. This route allowed for >125 g of ketone **12** to be prepared in a single pass.

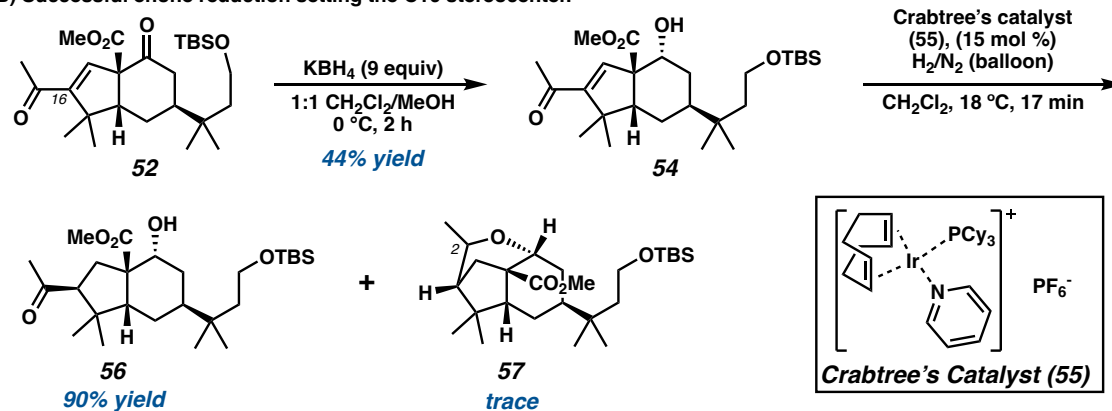
With a scalable route to **13** secured we proceeded on to the intercepted cyclopentene annulation. Starting with the optimized conditions from Table 2.3.1 (entry 6), using Pd(PPh₃)₄, unfortunately resulted in irreproducible yields and very difficult purification sequences. Further optimization led to the conclusion that using stoichiometric Cu led to simpler reaction protocols avoiding dropwise additions and producing reproducible yields. This enabled the synthesis of hydroindene **52** in up to 45% isolated yield (Scheme 2.4.2A).

Scheme 2.4.2. Installing the hydroindene core.

A) Intercepted cyclopentene annulation of enone 13.



B) Successful enone reduction setting the C16 stereocenter.

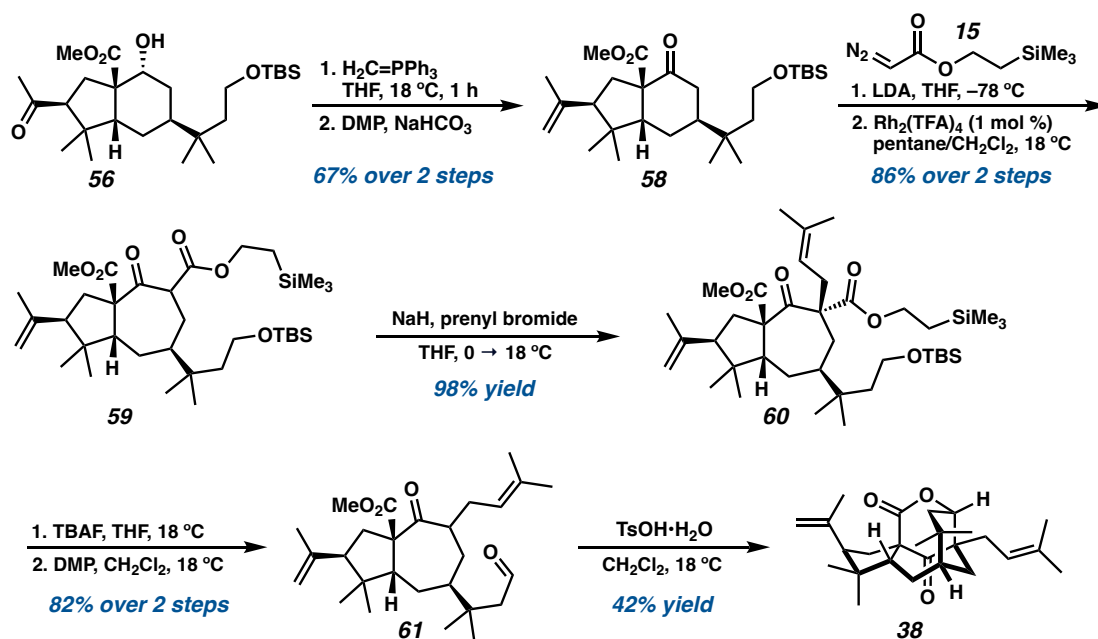


Our efforts to set the C16 stereocenter via hydrogenation of **52** unfortunately did not provide the desired diketone **53**. Instead, NOE experiments pointed to a structure tentatively assigned as the incorrect C16 epimer (not shown). Efforts to epimerize this site

were not fruitful, and eventual DFT calculations indicated that the desired epimer **53** is neither the kinetic, nor the thermodynamic product, forcing us to adjust our strategy.

Attempting to execute a directed hydrogenation, a thorough screen of ketone reductions allowed isolation of ketoalcohol **54** (Scheme 2.4.2B) in 44% yield using KBH_4 . As the newly installed 2° alcohol was positioned inside the concave portion of the bowl-like structure of **54**, we were confident that a directed hydrogenation would provide the correct stereochemistry at C16. Gratifyingly, reduction with 15 mol % Crabtree's catalyst (**55**) under rigorously anhydrous conditions in a carefully controlled H_2/N_2 atmosphere allowed for an excellent 90% yield of the desired enone reduction product **56**. This reaction is unfortunately very sensitive to setup and execution.

Scheme 2.4.3. Synthetic sequence advancing ketone **56** to lactone **38**.

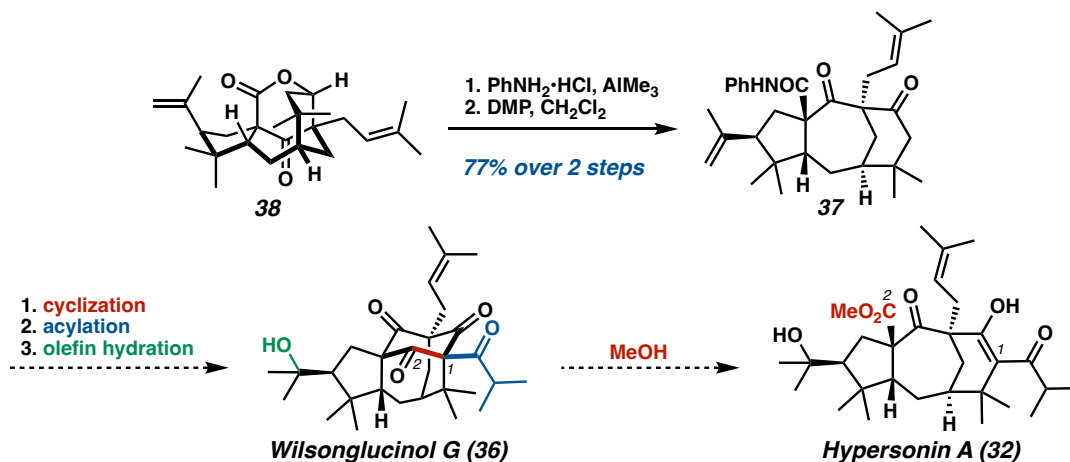


Ketone **56** is unstable and will epimerize during the reaction resulting in a hemiacetal (not shown) as the 2° alcohol engages the nearby ketone. The hemiacetal can be further reduced to side-product **57** with liberation of water. The extra water causes decomposition of

Crabtree's catalyst and further epimerization of ketone **56**, a situation that must be carefully avoided. Thus, wet solvent, performing the reaction for even a few minutes too long or too short (unreacted **54** is not separable from **56**), and high H₂ concentrations (cutting the H₂ with N₂ results in a slower and more controllable reaction rate) are deleterious, resulting in almost exclusive formation of ether **57**.

With ketoalcohol **56** in hand, we proceeded to olefinate the exocyclic ketone using salt-free Wittig conditions and oxidized the 2° alcohol to afford ketone **58** (Scheme 2.4.3). Ketone **58** is analogous to ketone **29** en route to hypersampson M (**1**) and was advanced in a similar fashion. Addition of diazoacetate **15** followed by Rh-catalyzed ring-expansion resulted in β -ketoester **59**, isolated as a mixture of tautomers. Then, prenylation (**60**), deprotection, and oxidation resulted in desired aldehyde **61**. As with hypersampson M (**1**), aldol/lactonization with TsOH resulted in caged lactone **38** in moderate yield.

Scheme 2.4.4. Proposed completion of wilsonglucinol G (**36**) and hypersonin A (**32**).



Currently, we have been successful in advancing lactone **38** to amide **37** (Scheme 2.4.4). From amide **37**, we anticipate cyclization with Me-Meerwine salt, bridgehead

acylation, and olefin hydration directly providing wilsonglucinol G (**36**) and hypersonin A (**32**).

2.5 CONCLUSION

To conclude, we have developed an enabling 3-component cyclopentene annulation that incorporates two stereocenters and forms three C–C bonds in a single step. Additionally, a late-stage intermediate (**37**) just three steps away from wilsonglucinol G has been accessed. Current efforts are focused on completion of wilsonglucinol G, with the anticipation that the retro-Claisen ring-opening to hypersonin A will provide invaluable insight into the biosynthesis of this class of PPAPs.

2.6 EXPERIMENTAL SECTION

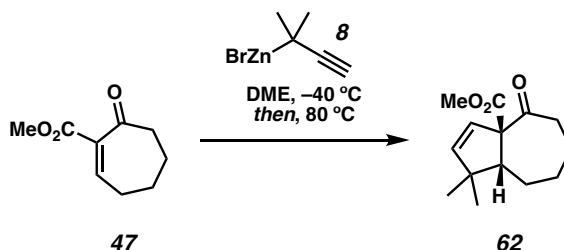
2.6.1 MATERIALS AND METHODS

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.⁸ Cyclohexenone was distilled prior to use. Pyridine and 2,2,6,6-Tetramethylpiperidine were distilled from CaH₂ prior to use. Freshly purchased TsOH•H₂O was stored in a desiccator and dried under high vacuum for several hours prior to use. Activated zinc dust was prepared according to a previously reported procedure.⁹ 3-bromo-3-methylbut-1-yne was prepared according to a previously reported procedure.¹⁰ All other reagents were purchased from commercial sources and used as received unless otherwise stated. Reaction progress was monitored by thin-layer chromatography (TLC), or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F₂₅₄ precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, CAM stain, or KMnO₄ staining. Silicycle SiliaFlash® P60 Academic Silica gel

(particle size 40–63 μm) was used for flash chromatography. Teledyne ISCO CombiFlashRf⁺, Teledyne ISCO CombiFlashRf⁺ LumenTM, or Teledyne ISCO CombiFlashRfNEXTGEN⁺ systems were used for automated flash chromatography using Luknova SuperSepTM silica columns or RediSepRf GOLD C₁₈ columns. Agilent 1100 or 1200 preparatory HPLC systems were used for high-performance reverse phase separations. ¹H NMR spectra were recorded on Varian Inova 500 MHz and Bruker 400 MHz spectrometers and are reported relative to residual non-deuterated solvent CHCl₃ (δ 7.26 ppm) or C₆H₆ (δ 7.16 ppm). ¹³C NMR spectra were recorded on a Bruker 400 MHz spectrometers (100 MHz) and are reported relative to residual non-deuterated solvent CHCl₃ (δ 77.16 ppm) or C₆H₆ (δ 128.06). Data for ¹H NMR 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, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet. Data for ¹³C NMR are reported in terms of chemical shifts (δ ppm). Diastereomeric ratios were calculated based on ratios of integrals from crude ¹H NMR spectra. Some spectra contain minor solvent impurities of water, ethyl acetate, dichloromethane, diethyl ether, acetone, grease, and/or silicone grease, which do not impact product assignments. IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm⁻¹). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-T2000GC AccuTOFTM GC-Alpha High Resolution

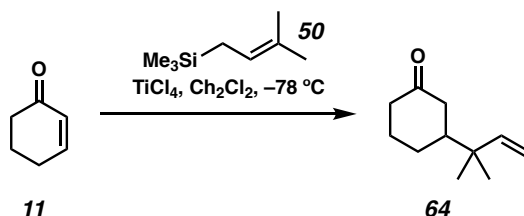
Mass Spectrometer in field ionization (FI⁺) or field desorption (FD⁺) mode, or an Agilent 6230 Series TOF with an Agilent Jet Stream ion source in electrospray ionization (ESI⁺).

2.6.2 EXPERIMENTAL PROCEDURES



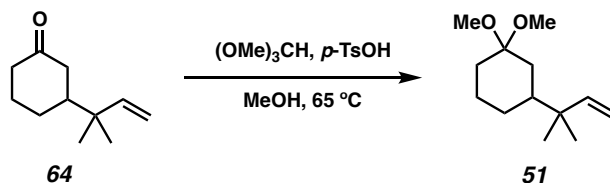
methyl 1,1-dimethyl-4-oxo-4,5,6,7,8,8a-hexahydroazulene-3a(1H)-carboxylate 62.

A 4 mL vial was charged with Zn (65 mg, 1.0 mmol, 5 equiv) and DME (1 mL) and cooled to $-15\text{ }^{\circ}\text{C}$. 3-bromo-3-methylbut-1-yne (147 mg, 1.0 mmol, 5 equiv) was added in one portion. After 1 h, a solution of enone **47** (prepared according to a previously reported procedure¹¹)(33 mg, 0.2 mmol, 1.0 equiv) was added dropwise and the solution was stirred at $-15\text{ }^{\circ}\text{C}$. After 2 days, the mixture was filtered into a fresh vial and heated to $65\text{ }^{\circ}\text{C}$ without stirring. After 3 days, the solution was cooled to $20\text{ }^{\circ}\text{C}$, then quenched with saturated aqueous NH_4Cl , and extracted with CH_2Cl_2 (3x). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (10–20% EtOAc/hexanes) to furnish ketone **62** as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ = 5.73 (d, J = 5.6 Hz, 1H), 5.51 (d, J = 5.6 Hz, 1H), 3.75 (s, 3H), 2.82 (dd, J = 13.4, 3.3 Hz, 1H), 2.53 (ddd, J = 13.7, 9.3, 4.3 Hz, 1H), 2.44 – 2.32 (m, 1H), 1.92 – 1.73 (m, 3H), 1.56 (s, 3H), 1.14 (s, 3H), 0.90 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 208.4, 173.0, 145.9, 125.3, 77.2, 53.0, 50.0, 49.2, 41.4, 30.0, 26.9, 26.3, 24.6, 24.3; IR (Neat Film, NaCl) 2949, 1742, 1706, 1454, 1241, 1225, 799 cm^{-1} ; HRMS (EI⁺): m/z calc'd for $\text{C}_{14}\text{H}_{20}\text{O}_3$ $[\text{M}]^+$: 236.1407, found 236.1411.

**3-(2-methylbut-3-en-2-yl)cyclohexan-1-one **64**.**

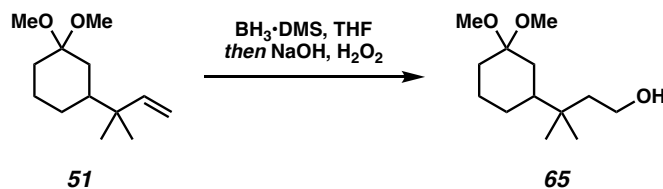
To a dry 5 L flask under N_2 was added CH_2Cl_2 (2.23 L) and cyclohexenone (**11**) (42.8 g, 0.445 mol, 1.0 equiv). The reaction flask was cooled to $-78\text{ }^\circ\text{C}$ in a dry ice/acetone bath and prenyltrimethylsilane **50** (prepared according to a previously reported procedure¹²) (76 g, 0.534 mol, 1.2 equiv) was added in one portion. TiCl_4 (92.9 g, 0.490 mol, 1.1 equiv) was then added slowly over 15 min, resulting in a deep-red solution. After an additional 15 min, H_2O (250 mL) was slowly added, and the flask was removed from the cold bath. Additional H_2O (1.5 L) was added, and the flask was allowed to warm to $23\text{ }^\circ\text{C}$. The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (300 mL x 2). The combined organic layers were concentrated under reduced pressure to a volume of 1.5 L, washed with brine, dried with Na_2SO_4 , and then further concentrated under reduced pressure to yield **64** as yellow oil (97 g). The crude oil was used directly in the next step, but an analytical sample was obtained via basic alumina chromatography (CH_2Cl_2). ^1H NMR (400 MHz, C_6D_6) δ = 5.49 (ddt, J = 17.4, 10.8, 1.7 Hz, 1H), 4.90 (dt, J = 10.8, 1.3 Hz, 1H), 4.80 (dt, J = 17.4, 1.4 Hz, 1H), 2.42 – 2.31 (m, 1H), 2.21 (dddt, J = 13.9, 3.4, 2.3, 1.3 Hz, 1H), 1.78 – 1.68 (m, 1H), 1.64 (tt, J = 13.5, 1.2 Hz, 1H), 1.55 (dddd, J = 10.7, 9.7, 5.1, 2.3 Hz, 1H), 1.47 (dtd, J = 11.1, 3.5, 1.6 Hz, 1H), 1.22 – 1.06 (m, 2H), 0.84 – 0.76 (m, 1H), 0.74 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, C_6D_6) δ = 209.23, 146.58, 111.85, 48.12, 43.53, 41.25, 38.91, 26.23, 25.49, 24.16, 23.74; IR (Neat Film, NaCl) 2964, 2865, 1713,

1229, 1004, 912, 682 cm^{-1} ; HRMS (FI⁺): m/z calc'd for $\text{C}_{11}\text{H}_{18}\text{O}$ $[\text{M}]^+$: 166.1358 found, 166.1363.

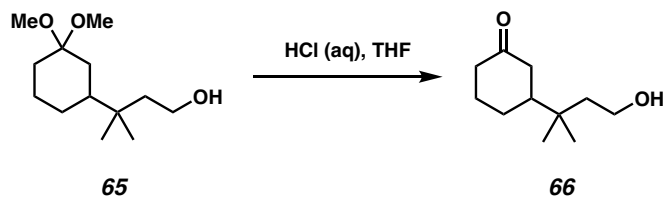


1,1-dimethoxy-3-(2-methylbut-3-en-2-yl)cyclohexane **51**.

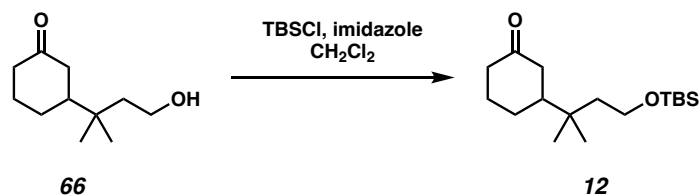
To a 1 L flask under N_2 was added ketone **64** (97 g), MeOH (450 mL), $p\text{-TsOH}\cdot\text{H}_2\text{O}$ (1.7 g, 8.9 mmol, 0.02 equiv), and $\text{CH}(\text{OMe})_3$ (94 g, 0.89 mol, 2 equiv). The flask was heated in an Al heating block at $75\text{ }^{\circ}\text{C}$ until complete conversion was observed by TLC (usually 2 h). The reaction was allowed to cool to $23\text{ }^{\circ}\text{C}$ and NaOMe was added until a litmus test returned an alkaline result. The solution was concentrated under reduced pressure and the residue was dissolved in hexanes and filtered to remove salts. The hexanes solution was concentrated to yield **51** as a colorless oil. The crude oil was used directly in the next step, but an analytical sample was obtained via silica gel chromatography. ^1H NMR (400 MHz, C_6D_6) δ = 5.72 (dd, J = 17.5, 10.8 Hz, 1H), 4.95 (dd, J = 10.9, 1.5 Hz, 1H), 4.91 (dd, J = 17.5, 1.5 Hz, 1H), 3.13 (s, 3H), 3.04 (s, 3H), 2.16 (dq, J = 13.1, 2.8 Hz, 1H), 2.05 – 1.98 (m, 1H), 1.64 (ddd, J = 12.5, 4.4, 2.3 Hz, 1H), 1.58 – 1.51 (m, 1H), 1.46 (dt, J = 13.5, 3.9 Hz, 1H), 1.39 (dt, J = 12.5, 3.2 Hz, 1H), 1.14 (td, J = 13.2, 4.9 Hz, 1H), 1.04 (t, J = 12.9 Hz, 1H), 0.91 (s, 3H), 0.90 (s, 3H), 0.78 (qd, J = 12.5, 4.4 Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, C_6D_6) δ = 147.91, 111.15, 101.06, 47.22, 47.09, 43.66, 38.79, 34.37, 33.15, 27.01, 24.57, 23.86, 23.01; IR (Neat Film, NaCl) 2948, 2867, 1458, 1365, 1139, 1089, 1054, 910, 843 cm^{-1} ; HRMS (FI⁺): m/z calc'd for $\text{C}_{13}\text{H}_{24}\text{O}_2$ $[\text{M}]^+$: 212.1776 found, 212.1777.

**3-(3,3-dimethoxycyclohexyl)-3-methylbutan-1-ol 65.**

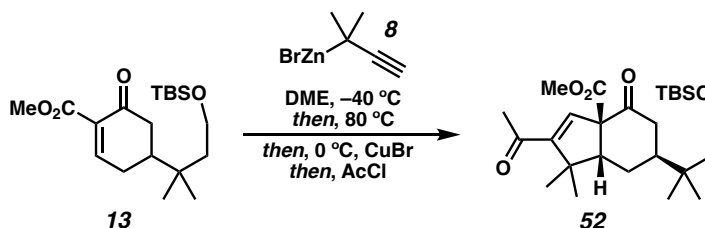
To a 12 L flask equipped with an overhead stirrer and under N₂ was added olefin **51** and THF (3 L). The solution was cooled to 0 °C and BH₃•SMe₂ (135 g, 1.78 mol, 4 equiv) was added slowly. The solution was then warmed to 23 °C and stirred for 4 h. After cooling to 0 °C, aqueous 3M NaOH (770 mL) was added slowly (Warning – violent H₂ evolution!) followed by 30% H₂O₂ (770 mL). The solution was allowed to warm to 23 °C overnight and hexanes (2 L) and H₂O (2L) was added. The combined organic/aqueous mixture is filtered through a coarse filter to remove solids. The organic layer was separated, and the aqueous layer was stirred with ether (1 L) overnight. The combined organic layers were dried with Na₂SO₄ and concentrated under reduced pressure to yield **65** as colorless oil. The crude oil was used directly in the next step, but an analytical sample was obtained via silica gel chromatography. ¹H NMR (400 MHz, C₆D₆) δ = 3.53 – 3.41 (m, 2H), 3.13 (s, 3H), 3.04 (s, 3H), 2.12 (dq, *J* = 13.0, 2.7 Hz, 1H), 2.06 – 1.98 (m, 1H), 1.63 – 1.50 (m, 2H), 1.49 – 1.31 (m, 4H), 1.15 (td, *J* = 13.3, 4.6 Hz, 1H), 1.03 (t, *J* = 12.9 Hz, 1H), 0.79 – 0.74 (m, 1H), 0.76 (s, 3H), 0.76 (s, 3H); ¹³C {¹H} NMR (101 MHz, C₆D₆) δ = 101.12, 59.33, 47.22, 47.14, 43.07, 34.07, 33.92, 33.08, 26.58, 25.17, 25.04, 23.03; IR (Neat Film, NaCl) 3408, 2947, 1469, 1367, 1089, 1049, 923 cm⁻¹; HRMS (ESI⁺): *m/z* calc'd for C₁₃H₂₆O₃K [M+K]⁺: 269.1514, found 269.1516.

**3-(4-hydroxy-2-methylbutan-2-yl)cyclohexan-1-one 66.**

To a 2 L flask was added alcohol **65** and THF (1 L). 1M aq. HCl (112 mL) was added, and the solution was stirred at 23 °C for 2 h. The THF was removed under reduced pressure and the residue was extracted with CH₂Cl₂ (200 mL x 3). The combined organic extracts were washed with brine, dried with Na₂SO₄, and concentrated under reduced pressure to yield **66** as colorless oil. The crude oil was used directly in the next step, but an analytical sample was obtained via silica gel chromatography. ¹H NMR (400 MHz, C₆D₆) δ = 3.44 (t, *J* = 7.9 Hz, 2H), 2.36 (ddt, *J* = 13.4, 3.7, 2.2 Hz, 1H), 2.22 (ddq, *J* = 14.0, 4.2, 2.0 Hz, 1H), 1.76 (tdd, *J* = 13.9, 6.5, 1.0 Hz, 1H), 1.67 (td, *J* = 13.4, 1.0 Hz, 2H), 1.61 – 1.52 (m, 1H), 1.51 – 1.43 (m, 1H), 1.40 – 1.29 (m, 2H), 1.29 – 1.21 (m, 1H), 1.21 – 1.08 (m, 1H), 0.87 – 0.77 (m, 1H), 0.65 (s, 3H), 0.63 (s, 3H); ¹³C {¹H} NMR (101 MHz, C₆D₆) δ = 210.45, 58.98, 47.66, 43.21, 42.64, 41.29, 34.38, 25.79, 25.63, 24.73, 24.69; IR (Neat Film, NaCl) 3428, 2958, 2868, 1708, 1448, 1267, 1233, 1041, 1029 cm⁻¹; HRMS (FI⁺): *m/z* calc'd for C₁₁H₂₀O₂ [M]⁺: 184.1463, found 184.1466.

**3-(4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)cyclohexan-1-one 12.**

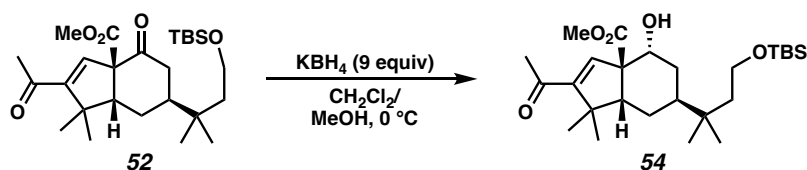
To a 1 L flask under N₂ was added ketone **66**, CH₂Cl₂ (760 mL), and imidazole (75.6 g, 1.11 mol, 2.4 equiv). The solution was cooled to 0 °C and TBSCl (84 g, 0.556 mol, 1.25 equiv) was added in one portion. The solution was allowed to warm to 23 °C and stirred at this temperature for 3 h. H₂O (800 mL) was added, and the organic layer was separated. The aqueous layer was further extracted with CH₂Cl₂ (200 mL), and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure to yield **12** as colorless oil (125 g). This material is sufficiently pure for the next step, having only various silyl impurities. The purity was determined to be 54–57% by weight using ¹H NMR and 1,3,5-trimethoxybenzene as an internal standard. A small sample was further purified via silica gel chromatography to obtain an analytical sample. Characterization data were consistent with previously reported data (see Chapter 1).



methyl 2-acetyl-6-(4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)-1,1-dimethyl-4-oxo-1,4,5,6,7,7a-hexahydro-3aH-indene-3a-carboxylate 52.

To a dry 500 mL flask under N₂ was added activated Zn dust (4.6 g, 70.5 mmol, 2.5 equiv) and DME (140 mL). The mixture was cooled to 0 °C and 3-bromo-3-methylbut-1-yne (10.36 g, 70.5 mmol, 2.5 equiv) was added in one portion. After 1.5 h most of the Zn has dissolved and the mixture was cooled to –40 °C at which point enone **13** (10 g, 28.2 mmol, 1.0 equiv) in DME (140 mL) was added dropwise over 15 min. The cloudy solution was then gradually allowed to warm to –15 °C and stirred at that temperature for 16 h. The reaction was then allowed to warm to 23 °C and filtered into a fresh 500 mL flask via a glass fritted cannula filter to yield a perfectly homogeneous, yellow solution. The solution was then heated to 80 °C for 4 h and cooled to 0 °C, followed by addition of CuBr (17.9 g, 70.5 mmol, 2.5 equiv). The mixture was stirred at 0 °C for 1.5 h, and AcCl (5.53 g, 70.5 mmol, 2.5 equiv) was added slowly. The reaction flask was rapidly warmed in a 23 °C water bath and stirred at this temperature for 30 min before being cooled to 0 °C and quenched with saturated, aqueous NH₄Cl. The mixture was extracted with EtOAc (75 mL x 3) and the combined organic extracts were washed with brine, dried with Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→15% EtOAc/hexanes) to furnish **52** as a colorless oil (3.9 g, 30% yield). ¹H NMR (400 MHz, CDCl₃) δ = 6.77 (s, 1H), 3.79 (s, 3H), 3.65 (t, *J* = 7.4 Hz, 2H), 2.87 (t, *J* = 4.2 Hz, 1H), 2.41 – 2.38 (m, 1H), 2.34 – 2.33f (m,

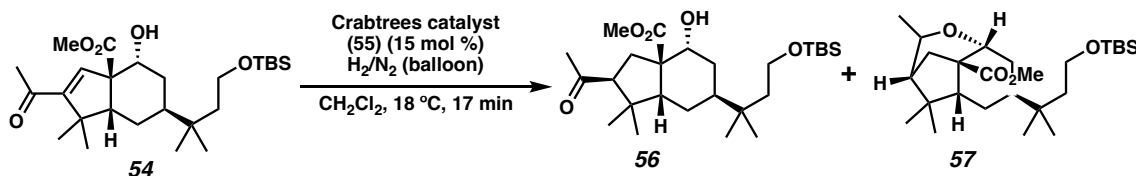
4H), 1.97 – 1.84 (m, 3H), 1.61 – 1.43 (m, 3H), 1.38 (s, 3H), 1.04 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 208.53, 196.41, 170.07, 152.69, 140.07, 59.70, 53.88, 53.31, 49.07, 45.71, 41.94, 35.19, 32.91, 28.09, 26.71, 25.99, 24.90, 24.53, 24.39, 23.69, 21.78, 18.34, -5.26; IR (Neat Film, NaCl) 2954, 2857, 1743, 1713, 1677, 1364, 1252, 1223, 1090, 837, 778 cm^{-1} ; HRMS (ESI⁺): m/z calc'd for $\text{C}_{26}\text{H}_{45}\text{O}_5\text{Si}$ $[\text{M}+\text{H}]^+$: 465.3031, found 465.3027.



methyl 2-acetyl-6-(4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)-4-hydroxy-1,1-dimethyl-1,4,5,6,7,7a-hexahydro-3aH-indene-3a-carboxylate 54.

To a dry 100 mL flask under N_2 was added CH_2Cl_2 (19 mL), MeOH (23 mL), and KBH_4 (523 mg, 9.7 mmol, 12 equiv). The solution was cooled to 0 °C, and a solution of enone **52** (500 mg, 75% purity, 0.81 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added over 5 min. The solution was stirred at 0 °C for 2.5 h before adding saturated aqueous NH_4Cl (10 mL) followed by H_2O (50 mL). The mixture was stirred for an hour to ensure complete deborylation and the organic phase separated. The aqueous phase was extracted with CH_2Cl_2 (30 mL x 2), and the combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→30% EtOAc/hexanes) to furnish **54** as a colorless oil (164 mg, 44%) that solidified into a waxy solid. ^1H NMR (400 MHz, CDCl_3) δ = 6.65 (s, 1H), 4.31 (dt, J = 6.4, 3.4 Hz, 1H), 3.74 (s, 3H), 3.65 (t, J = 7.5 Hz, 2H), 2.50

(dd, $J = 7.4, 1.4$ Hz, 1H), 2.34 (s, 3H), 1.71 – 1.55 (m, 5H), 1.53 – 1.45 (m, 4H), 1.28 (s, 3H), 1.20 (s, 3H), 0.88 (s, 9H), 0.87 (s, 3H), 0.84 (s, 3H), 0.04 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) $\delta = 196.79, 175.41, 154.12, 141.42, 69.91, 62.08, 60.11, 52.67, 49.78, 48.99, 42.37, 35.24, 34.65, 30.03, 29.45, 28.46, 26.16, 24.81, 24.39, 22.11, 21.56, 18.52, -5.06, -5.07$; IR (Neat Film, NaCl) 3466, 2952, 2858, 1732, 1673, 1366, 1248, 1228, 1084, 835, 773 cm^{-1} ; HRMS (ESI $^{+}$): m/z calc'd for $\text{C}_{26}\text{H}_{47}\text{O}_5\text{Si}$ $[\text{M}+\text{H}]^{+}$: 467.3187, found 467.3195.



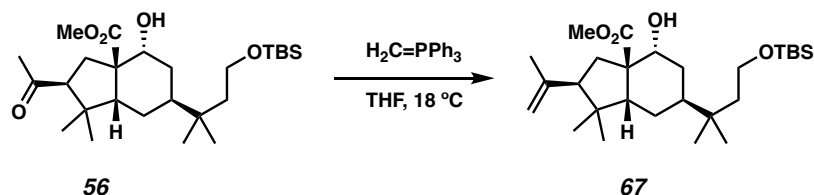
Ketoalcohol **56** and ether **57**.

To a dry 500 mL flask was added a large football-shaped stir bar, alcohol **54** (1.13 g, 2.4 mmol, 1.0 equiv), and Crabtree's catalyst (**55**) (480 mg, 0.6 mmol, 0.25 equiv) in a N_2 glovebox. The flask was sealed with a white, silicone septum and the joint wrapped in electrical tape. The flask was removed from the glovebox (do not connect to Schlenk line or inert gas balloon), CH_2Cl_2 (96 mL) was added, and the stirring adjusted to 500 rpm. Two concentric balloons fitted with a 1.5 in x 21G needle are filled with H_2 and inserted into the septum, resulting in a pressure release from the flask into the balloons. A 60 mL syringe fitted with a 26G needle was used to remove 240 mL of headspace from inside the flask.^a The reaction was left to stir at 23 °C for 19 min during which time the bright orange color fades to a yellow or colorless, followed by the return of a muted brown orange. After this time the solution is concentrated under reduced pressure as quickly as possible, and the crude residue was purified by automated silica gel flash chromatography (Teledyne ISCO,

0→35% EtOAc/hexanes) to separate **57** (54 mg, 5% yield) from **56^b** (990 mg, 88% yield) as a colorless oil.^c

Notes: ^aA headspace of pure H₂ was found to decompose Crabtree's catalyst rapidly, resulting in excessive formation of **57**. ^b**56** is not stable in long term storage, especially neat. The material should be used right away or stored as a frozen solution in benzene. ^cThe reaction is highly reproducible when run in this fashion, however, small changes in reaction time, water contamination, and H₂/N₂ ratio can either lead to incomplete conversion or loss in yield due to decomposition to ether **57**. Characterization data for ketoalcohol **56**: ¹H NMR (400 MHz, C₆D₆) δ = 4.15 (dd, J = 6.9, 3.4 Hz, 1H), 3.77 – 3.69 (m, 2H), 3.34 (s, 3H), 2.91 – 2.74 (m, 2H), 2.55 (t, J = 5.0 Hz, 1H), 2.16 (dd, J = 12.3, 6.0 Hz, 1H), 1.80 (s, 3H), 1.70 – 1.62 (m, 1H), 1.63 – 1.54 (m, 2H), 1.52 – 1.41 (m, 3H), 1.38 – 1.31 (m, 1H), 1.18 (s, 3H), 1.02 – 1.00 (m, 1H), 1.01 (s, 9H), 0.90 (s, 3H), 0.86 (s, 3H), 0.83 (s, 3H), 0.12 (s, 6H); ¹³C{¹H} NMR (101 MHz, C₆D₆) δ = 207.97, 177.44, 70.81, 61.43, 60.23, 55.78, 51.90, 50.86, 45.10, 42.80, 36.26, 35.08, 33.02, 31.47, 30.13, 27.48, 26.23, 25.83, 24.78, 24.46, 22.37, 18.53, -5.02, -5.05; IR (Neat Film, NaCl) 3503, 2954, 2857, 1728, 1707, 1467, 1364, 1250, 1087, 835, 773 cm⁻¹; HRMS (ESI⁺): m/z calc'd for C₂₆H₄₉O₅Si [M+H]⁺: 469.3344, found 469.3349. Characterization data for ether **57**: ¹H NMR (400 MHz, C₆D₆) δ = 4.34 (dd, J = 3.7, 2.1 Hz, 1H), 3.86 – 3.73 (m, 2H), 3.57 (q, J = 6.9 Hz, 1H), 3.34 (s, 3H), 2.37 (dt, J = 6.3, 1.7 Hz, 1H), 2.09 (td, J = 11.2, 5.4 Hz, 2H), 2.00 – 1.90 (m, 1H), 1.75 – 1.57 (m, 5H), 1.34 (s, 3H), 1.27 – 1.19 (m, 4H), 1.15 (d, J = 5.1 Hz, 1H), 1.02 (s, 9H), 0.96 (s, 3H), 0.88 (s, 3H), 0.87 (s, 3H), 0.12 (d, J = 3.2 Hz, 6H); ¹³C{¹H} NMR (101 MHz, C₆D₆) δ = 174.33, 77.75, 75.29, 59.81, 53.11, 50.91, 49.48, 47.77, 43.08, 41.62, 41.43, 35.62, 35.29, 34.03, 29.04, 25.89, 24.85, 24.59, 22.38, 21.57, 18.15, -5.36; IR (Neat

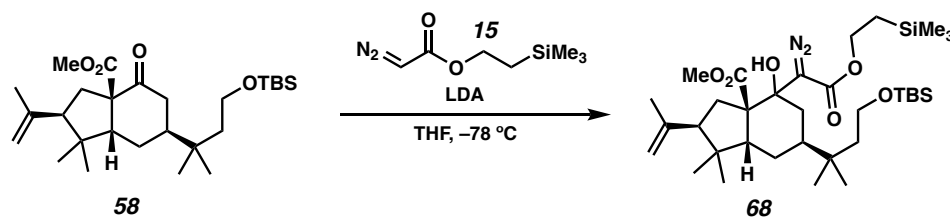
Film, NaCl) 2954, 1732, 1471, 1255, 1088, 1066, 835, 774 cm^{-1} ; HRMS (ESI⁺): m/z calc'd for $\text{C}_{26}\text{H}_{49}\text{O}_4\text{Si}$ $[\text{M}+\text{H}]^+$: 453.3395, found 453.3401.



methyl 6-(4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)-4-hydroxy-1,1-dimethyl-2-(prop-1-en-2-yl)octahydro-3aH-indene-3a-carboxylate 67.

A conical flask was charged with NaNH_2 (2.18 g, 56 mmol), MePPh_3Br (8.0 g, 22 mmol), PhMe (75 mL), and heated to reflux for 2 h. The heating and stirring were then turned off, and the heterogeneous mixture was left overnight, allowing the solids to settle. To a 250 mL flask at 0 °C under N_2 was added alcohol **56** (990 mg, 2.11 mmol, 1.0 equiv) and PhMe (75 mL). The prepared solution of $\text{CH}_2=\text{PPh}_3$ (0.3M, 48 mL, 14.4 mmol, 6.8 equiv) was added dropwise over 5 min, and the solution was left to stir at 0 °C for 5 h. Silica gel (16 g) was added slowly, and the solution was further stirred for 20 min at 0 °C. The heterogeneous mixture was filtered, and the silica cake was rinsed (30% EtOAc in hexanes, 200 mL). The combined organic fractions were concentrated under reduced pressure and purified by automated silica gel flash chromatography (Teledyne ISCO, 0→25% EtOAc/hexanes) to furnish **67** (460 mg, 47% yield) as a colorless oil. ^1H NMR (400 MHz, C_6D_6) δ = 4.96 (t, J = 1.7 Hz, 1H), 4.89 – 4.86 (m, 1H), 4.23 (dt, J = 8.0, 5.4 Hz, 1H), 3.72 (t, J = 7.2 Hz, 2H), 3.38 (s, 3H), 2.60 (d, J = 7.7 Hz, 2H), 2.49 (dd, J = 6.2, 3.9 Hz, 1H), 2.28 – 2.16 (m, 1H), 1.74 (d, J = 1.3 Hz, 3H), 1.73 – 1.64 (m, 1H), 1.59 (q, J = 7.0 Hz, 2H), 1.55 – 1.47 (m, 2H), 1.43 (dd, J = 7.7, 5.6 Hz, 2H), 1.30 (d, J = 4.8 Hz, 1H), 1.07 (s,

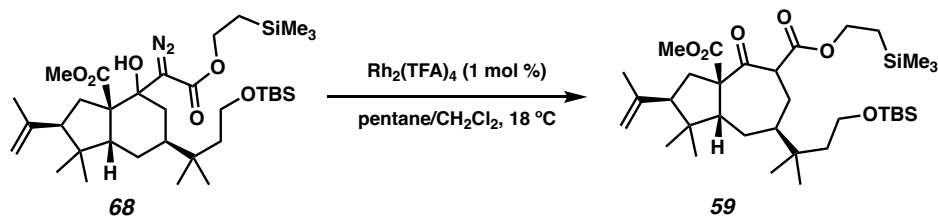
= 14.4, 12.5, 6.9 Hz, 1H), 1.67 (ddt, J = 14.5, 4.2, 2.2 Hz, 1H), 1.65 – 1.59 (m, 3H), 1.49 (td, J = 7.0, 3.0 Hz, 2H), 1.00 (s, 9H), 0.90 (s, 3H), 0.83 (s, 3H), 0.78 (s, 3H), 0.74 (s, 3H), 0.10 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, C_6D_6) δ = 206.82, 172.92, 145.92, 112.65, 64.67, 59.93, 56.00, 54.06, 52.25, 46.03, 44.45, 42.40, 41.51, 35.21, 34.72, 27.25, 27.19, 26.20, 24.54, 24.38, 23.96, 23.95, 18.49, -5.11; IR (Neat Film, NaCl) 2952, 2857, 1740, 1715, 1470, 1388, 1367, 1248, 1093, 890, 835, 775 cm^{-1} ; HRMS (ESI $^{+}$): m/z calc'd for $\text{C}_{27}\text{H}_{49}\text{O}_4\text{Si}$ $[\text{M}+\text{H}]^{+}$: 465.3395, found 465.3395.



methyl 6-(4-((*tert*-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)-4-(1-diazo-2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)-4-hydroxy-1,1-dimethyl-2-(prop-1-en-2-yl)octahydro-3a*H*-indene-3a-carboxylate 68.

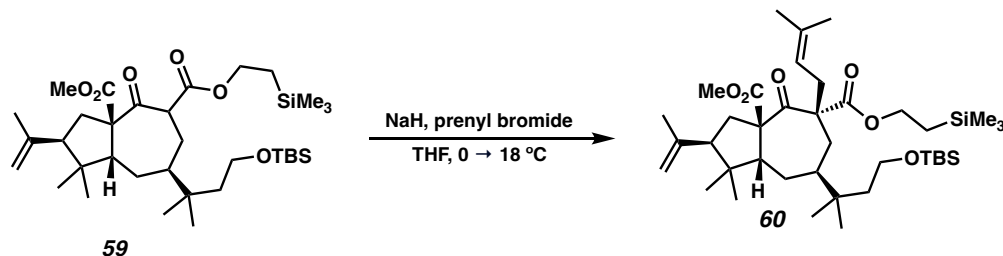
To a 100 mL Schlenk flask under N_2 was added $\text{NH}(\textit{i}\text{-Pr})_2$ (480 mg, 4.73 mmol, 5 equiv) and THF (1.2 mL). The flask was cooled to $-78\text{ }^{\circ}\text{C}$ in a dry ice/acetone bath. $n\text{-BuLi}$ (2.5M in hexanes, 1.5 mL, 3.79 mmol, 4 equiv) was added dropwise over 5 min and the solution was left to stir at $-78\text{ }^{\circ}\text{C}$ for 15 min. A solution of diazoacetate **15** (prepared according to a previously reported procedure¹³)(792 mg, 4.26 mmol, 4.5 equiv) in THF (1.2 mL) was added dropwise over 15 min and the blood-red solution was stirred for a further 10 min. A solution of ketone **58** (440 mg, 0.95 mmol, 1.0 equiv) in THF (5 mL) was then added dropwise over 20 min and the reaction was left to stir an additional 20 min. A solution of AcOH (270 mg) in Et_2O (4.5 mL) was added slowly and the reaction was removed from

the cold bath. Water (10 mL) was added, and the mixture was extracted with EtOAc (5 mL x 3). The combined organic extracts were dried with Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→20% EtOAc/hexanes) to furnish a yellow oil. The oil was dried *in vacuo* overnight to remove residual diazoacetate **15**, furnishing **68** (547 mg, 88% yield) as a yellow oil. ¹H NMR (600 MHz, C₆D₆) δ = 5.95 (s, 1H), 4.94 (t, *J* = 1.7 Hz, 1H), 4.91 (s, 1H), 4.11 (t, *J* = 8.4 Hz, 2H), 3.84 – 3.78 (m, 2H), 3.43 (s, 3H), 2.97 (dd, *J* = 13.4, 11.5 Hz, 1H), 2.90 – 2.78 (m, 2H), 2.51 (dd, *J* = 9.7, 6.1 Hz, 1H), 2.28 (pd, *J* = 11.8, 4.0 Hz, 2H), 2.02 (dd, *J* = 10.6, 4.2 Hz, 1H), 1.85 (ddd, *J* = 14.0, 9.7, 6.8 Hz, 1H), 1.81 – 1.67 (m, 6H), 1.10 (s, 3H), 1.02 (s, 9H), 1.01 (s, 3H), 0.98 (s, 3H), 0.83 (s, 3H), 0.75 (tt, *J* = 8.4, 4.3 Hz, 2H), 0.13 (s, 6H), -0.15 (s, 9H); ¹³C{¹H} NMR (151 MHz, C₆D₆) δ = 177.06, 168.82, 145.12, 128.35, 112.52, 73.50, 63.69, 62.16, 60.19, 54.37, 53.95, 52.11, 44.45, 43.10, 36.19, 35.64, 34.02, 32.63, 26.49, 26.23, 25.51, 24.96, 24.95, 24.07, 22.26, 18.50, 17.52, -1.65, -5.02; IR (Neat Film, NaCl) 3420, 2955, 2088, 1719, 1667, 1305, 1250, 1095, 837 cm⁻¹; HRMS (ESI⁺): *m/z* calc'd for C₃₄H₆₂N₂O₆Si₂Na [M+Na]⁺: 673.4039, found 673.4038.



3a-methyl 5-(2-(trimethylsilyl)ethyl) 7-(4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)-1,1-dimethyl-4-oxo-2-(prop-1-en-2-yl)octahydroazulene-3a,5(1H)-dicarboxylate 59.

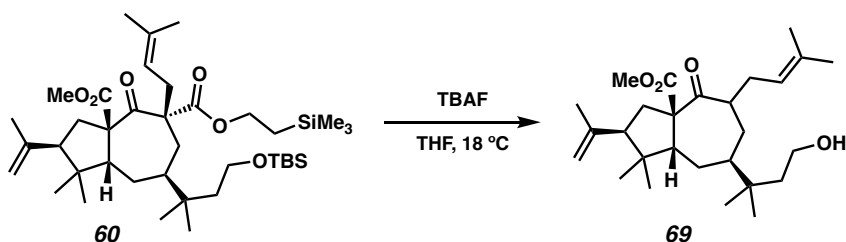
To a solution of diazoacetate **68** (547 mg, 0.84 mmol, 1 equiv) in pentane/CH₂Cl₂ (4:1, 100 mL) under Ar was added Rh₂(TFA)₄ (6 mg, 0.009 mmol, 0.01 equiv). The reaction was stirred at 23 °C for 24 h, concentrated under reduced pressure and purified by automated silica gel flash chromatography (Teledyne ISCO, 0→15% EtOAc/hexanes) to furnish **59** (502 mg, 96% yield) as a colorless oil. **Note:** Title compound **59** was isolated as a mixture of dynamically interconverting tautomers and was used directly in the next step. ¹H NMR and HRMS data is provided as a courtesy. HRMS (ESI⁺): *m/z* calc'd for C₃₄H₆₂O₆Si₂Na [M+Na]⁺: 645.3977, found 645.3996.



3a-methyl 5-(2-(trimethylsilyl)ethyl) 7-(4-(((tert-butyl)dimethylsilyl)oxy)-2-methylbutan-2-yl)-1,1-dimethyl-5-(3-methylbut-2-en-1-yl)-4-oxo-2-(prop-1-en-2-yl)octahydroazulene-3a,5(1H)-dicarboxylate 60.

An 8 mL vial under N₂ was charged with ester **59** (19 mg, 0.03 mmol, 1.0 equiv) and THF (1.1 mL). The solution was cooled to 0 °C and NaH (60% dispersion in mineral oil, 6 mg, 0.15 mmol, 5 equiv) was added in one portion and the cold bath was removed. After stirring at 23 °C for 1 h, the solution was cooled to 0 °C and prenyl bromide (27 mg, 0.18 mmol, 6 equiv) was added dropwise. The reaction was allowed to warm to 23 °C and stirred at this temperature for 2 h after which it was cooled to 0 °C and quenched slowly with saturated aqueous NH₄Cl (1 mL). The mixture was extracted with EtOAc (1 mL x 3), and the combined organic extracts were dried with Na₂SO₄ and concentrated under reduced pressure.^a The crude residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→20% EtOAc/hexanes) to furnish **60** (20 mg, 98% yield) as colorless oil. **Note:** ^aCare should be taken to completely remove excess prenyl bromide before loading onto silica as prenyl bromide may exothermically decompose to HBr. ¹H NMR (400 MHz, C₆D₆) δ = 5.46 (tt, *J* = 6.4, 1.6 Hz, 1H), 4.90 (t, *J* = 1.7 Hz, 1H), 4.72 – 4.68 (m, 1H), 4.37 – 4.22 (m, 2H), 3.79 (dd, *J* = 8.3, 6.8 Hz, 2H), 3.61 (dd, *J* = 13.5, 6.5 Hz, 1H), 3.38 (dd, *J* = 13.2, 1.7 Hz, 1H), 3.29 (s, 3H), 2.98 (dd, *J* = 15.0, 8.6 Hz, 1H), 2.55 (dd, *J* = 14.3, 12.8 Hz, 1H), 2.38 (dd, *J* = 13.3, 6.5 Hz, 1H), 2.29 – 2.20 (m, 1H), 2.20 – 2.07

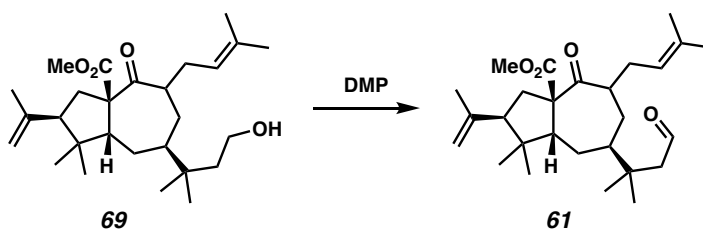
(m, 3H), 2.07 – 1.99 (m, 1H), 1.92 – 1.72 (m, 3H), 1.67 (d, $J = 2.0$ Hz, 6H), 1.57 (s, 3H), 1.11 – 1.02 (m, 17H), 1.00 (s, 3H), 0.96 (s, 3H), 0.16 (d, $J = 1.9$ Hz, 6H), -0.11 (s, 9H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, C_6D_6) $\delta = 200.73, 173.88, 171.92, 143.49, 133.95, 119.94, 113.25, 68.34, 64.41, 63.39, 59.81, 52.32, 51.90, 50.68, 46.62, 44.63, 40.81, 37.55, 37.45, 36.51, 33.41, 26.71, 26.60, 26.23, 26.20, 26.19, 25.38, 24.99, 24.06, 18.50, 18.42, 17.87, -1.70, -4.94, -4.98$; IR (Neat Film, NaCl) 2954, 1730, 1704, 1470, 1454, 1250, 1223, 1088, 838, 777 cm^{-1} ; HRMS (ESI $^{+}$): m/z calc'd for $\text{C}_{39}\text{H}_{70}\text{O}_6\text{Si}_2\text{Na}$ $[\text{M}+\text{Na}]^{+}$: 713.4603, found 713.4630.



methyl 7-(4-hydroxy-2-methylbutan-2-yl)-1,1-dimethyl-5-(3-methylbut-2-en-1-yl)-4-oxo-2-(prop-1-en-2-yl)octahydroazulene-3a(1H)-carboxylate 69.

To a solution of compound **60** (56 mg, 82 μmol , 1 equiv) in THF (0.8 mL) at 0 $^{\circ}\text{C}$ under N_2 was slowly added TBAF (1M in THF, 0.29 mL, 0.29 mmol, 3.5 equiv). The solution warmed to 23 $^{\circ}\text{C}$ and stirred at this temperature for 18 h. Saturated aqueous NH_4Cl (1 mL) was added, and the mixture extracted with EtOAc (1 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0 $\rightarrow$ 50% EtOAc/hexanes) to furnish **69** (31 mg, 89% yield) as colorless oil. ^1H NMR (600 MHz, C_6D_6) $\delta = 5.10$ (t, $J = 7.4$ Hz, 1H), 4.95 (t, $J = 1.7$ Hz, 1H), 4.75 (s, 1H), 3.40 (t, $J =$

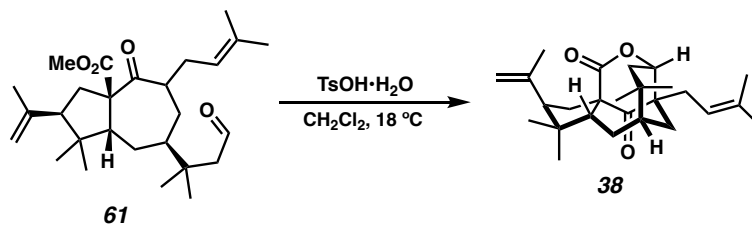
7.5 Hz, 2H), 3.32 – 3.27 (m, 4H), 3.12 (dd, $J = 13.1, 2.5$ Hz, 1H), 2.96 (d, $J = 15.0$ Hz, 1H), 2.68 (dq, $J = 9.4, 4.7$ Hz, 1H), 2.43 (dd, $J = 12.5, 6.5$ Hz, 1H), 2.21 (dt, $J = 15.2, 9.2$ Hz, 1H), 2.09 – 2.00 (m, 2H), 1.82 (d, $J = 15.8$ Hz, 1H), 1.66 (s, 3H), 1.65 (s, 3H), 1.58 (s, 3H), 1.49 (q, $J = 7.2$ Hz, 1H), 1.46 – 1.43 (m, 2H), 1.22 – 1.15 (m, 2H), 1.03 (s, 3H), 0.93 (s, 3H), 0.86 (s, 3H), 0.84 (s, 3H), 0.45 (br s, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, C_6D_6) $\delta = 206.39, 175.03, 143.99, 132.80, 123.28, 113.38, 66.61, 59.21, 53.63, 52.11, 50.12, 48.64, 46.45, 43.58, 39.19, 36.95, 36.42, 27.31, 26.11, 26.07, 25.98, 25.86, 25.71, 25.69, 25.67, 24.10, 18.03$; IR (Neat Film, NaCl) 3385, 2963, 1740, 1705, 1453, 1235, 1023, 889 cm^{-1} ; HRMS (ESI⁺): m/z calc'd for $\text{C}_{27}\text{H}_{45}\text{O}_4$ $[\text{M}+\text{H}]^+$: 433.3312, found 433.3316.



methyl 1,1-dimethyl-7-(2-methyl-4-oxobutan-2-yl)-5-(3-methylbut-2-en-1-yl)-4-oxo-2-(prop-1-en-2-yl)octahydroazulene-3a(1H)-carboxylate 61.

To a 4 mL vial was added alcohol **69** (6.8 mg, 16 μmol , 1.0 equiv) and CH_2Cl_2 (1.5 mL). DMP (17 mg, 39 μmol , 2.5 equiv) was added, and the flask was stirred under Ar for 3 h. The reaction was concentrated under reduced pressure and hexanes (1 mL) was added. The heterogeneous mixture was agitated and concentrated under reduced pressure. Hexanes (2 mL) was added, and the mixture was sonicated for 2 min. The mixture was filtered over celite, and the filter cake rinsed with hexanes (2 mL). The combined organic fractions were concentrated under reduced pressure to and purified by flash silica gel chromatography (0→10% EtOAc/hexanes) to provide aldehyde **61** (6 mg, 88% yield) as a colorless oil. ^1H

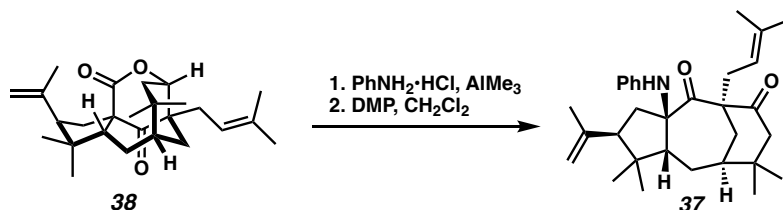
NMR (400 MHz, C₆D₆) δ = 9.51 (t, J = 2.9 Hz, 1H), 5.06 (dddt, J = 7.3, 5.8, 2.8, 1.4 Hz, 1H), 4.94 (h, J = 1.7 Hz, 1H), 4.74 (dt, J = 2.0, 0.9 Hz, 1H), 3.30 – 3.23 (m, 4H), 3.01 (dd, J = 13.0, 2.6 Hz, 1H), 2.91 (dd, J = 13.6, 6.6 Hz, 1H), 2.63 (tt, J = 9.3, 4.2 Hz, 1H), 2.38 (dd, J = 12.5, 6.5 Hz, 1H), 2.14 (dt, J = 14.9, 9.2 Hz, 1H), 2.04 – 1.99 (m, 1H), 1.99 – 1.86 (m, 3H), 1.73 – 1.66 (m, 1H), 1.64 (dt, J = 5.5, 1.4 Hz, 6H), 1.59 – 1.53 (m, 4H), 1.53 – 1.47 (m, 1H), 1.11 (ddd, J = 15.9, 13.0, 7.4 Hz, 1H), 0.99 (s, 3H), 0.87 (s, 6H), 0.85 (s, 3H); ¹³C{¹H} NMR (101 MHz, C₆D₆) δ = 206.03, 201.21, 174.92, 143.88, 133.03, 122.98, 113.45, 66.55, 53.74, 53.57, 52.16, 49.89, 48.47, 46.38, 39.75, 37.52, 36.90, 27.25, 26.06, 25.96, 25.80, 25.78, 25.77, 25.72, 25.64, 24.08, 18.00; IR (Neat Film, NaCl) 2963, 1706, 1455, 1374, 1234, 890 cm⁻¹; HRMS (ESI⁺): m/z calc'd for C₂₇H₄₃O₄ [M+H]⁺: 431.3156, found 431.3150.



1,1,8,8-tetramethyl-5-(3-methylbut-2-en-1-yl)-2-(prop-1-en-2-yl)decahydro-4H-6,3a-(epoxymethano)-5,9-methanocyclopenta[9]annulene-4,13-dione 38.

A 100 mL flask was charged with aldehyde **61** (180 mg, 0.42 mmol, 1.0 equiv), *p*-TsOH·H₂O (400 mg, 2.1 mmol, 5.0 equiv) and CH₂Cl₂ (60 mL). The flask was sealed under Ar and stirred at 23 °C for 4 d. The solution was concentrated under reduced pressure, hexanes (20 mL) was added, and the solution was filtered to remove *p*-TsOH·H₂O. The crude residue was purified by flash silica gel chromatography (0→10% EtOAc/hexanes). Impure **38** was further purified by preparatory SFC (silica gel, 1% *i*-PrOH/CO₂, 25

mL/min) to furnish **38** (45 mg, 25% yield) as a colorless, crystalline solid. ^1H NMR (400 MHz, C_6D_6) δ = 5.14 (dddt, J = 6.8, 5.8, 2.9, 1.5 Hz, 1H), 4.99 (p, J = 1.5 Hz, 1H), 4.87 (dt, J = 2.0, 0.9 Hz, 1H), 4.59 (dd, J = 10.9, 7.2 Hz, 1H), 3.22 (dd, J = 13.9, 13.0 Hz, 1H), 2.78 (dd, J = 12.9, 6.4 Hz, 1H), 2.62 (dd, J = 14.2, 8.6 Hz, 1H), 2.44 (dd, J = 13.9, 6.3 Hz, 1H), 2.38 (dd, J = 13.9, 3.5 Hz, 1H), 2.27 – 2.24 (m, 1H), 1.93 – 1.82 (m, 2H), 1.77 (ddd, J = 14.1, 2.9, 1.5 Hz, 1H), 1.71 (s, 3H), 1.64 – 1.57 (m, 4H), 1.53 (d, J = 1.3 Hz, 3H), 1.44 (dd, J = 14.0, 3.9 Hz, 1H), 1.14 (d, J = 4.6 Hz, 1H), 1.10 (s, 3H), 0.96 (ddd, J = 15.5, 13.9, 1.9 Hz, 1H), 0.76 (s, 3H), 0.67 (s, 3H), 0.60 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, C_6D_6) δ = 207.66, 174.34, 143.42, 136.30, 118.85, 114.10, 74.33, 64.30, 52.68, 52.22, 50.34, 47.81, 43.59, 40.58, 37.63, 36.78, 34.05, 32.91, 32.82, 31.40, 28.22, 26.29, 26.09, 24.87, 23.93, 17.96; IR (Neat Film, NaCl) 2961, 1745, 1708, 1457, 1244, 1162, 1087, 1027, 889 cm^{-1} ; HRMS (ESI $^{+}$): m/z calc'd for $\text{C}_{26}\text{H}_{39}\text{O}_3$ $[\text{M}+\text{H}]^{+}$: 399.2894, found 399.2902.



1,1,8,8-tetramethyl-5-(3-methylbut-2-en-1-yl)-4,6-dioxo-N-phenyl-2-(prop-1-en-2-yl)decahydro-5,9-methanocyclopenta[9]annulene-3a(1H)-carboxamide 37. A small test tube equipped with a septum under N_2 was charged with aniline hydrochloride (18 mg, 0.13 mmol, 10 equiv) and PhMe (0.6 mL). The reaction was cooled to 0 $^{\circ}\text{C}$ and AlMe_3 (63 mL, 2M in PhMe, 0.13 mmol, 10 equiv) was added dropwise. The homogenous solution was stirred at 0 $^{\circ}\text{C}$ for 1 h, at which point lactone **38** (5 mg, 12.6 μmol , 1.0 equiv) in PhMe (0.6 mL) was added dropwise and the reaction was left to warm naturally over 20 h. The

reaction was quenched by sequentially adding a saturated solution of potassium sodium tartrate (8 mL), water (5 mL), CH_2Cl_2 (10 mL), and stirring for 1 h. The entire mixture was filtered over celite, the organic layer separated, and the aqueous layer extracted further with CH_2Cl_2 (2x5 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography (0→15% EtOAc/hexanes) and the resulting oil directly subjected to the next step. To a 4 mL vial charged with the alcohol was added CH_2Cl_2 (0.4 mL) and DMP (9 mg, 21 mmol, 2.0 equiv). The vial was stirred under Ar for 2 h. The reaction was concentrated under reduced pressure and hexanes (0.5 mL) was added. The heterogeneous mixture was agitated and concentrated under reduced pressure. EtOAc (2 mL) was added, and the mixture was sonicated for 2 min. The mixture was filtered over celite, and the filter cake rinsed with EtOAc (2 mL). The combined organic fractions were concentrated under reduced pressure to and purified by flash silica gel chromatography (10% EtOAc/hexanes) to provide dione **37** (4.8 mg, 77% over 2 steps) as a white foam. ^1H NMR (400 MHz, C_6D_6) δ = 7.40 – 7.35 (m, 2H), 7.09 – 7.02 (m, 2H), 6.89 – 6.81 (m, 1H), 6.47 (s, 1H), 5.44 (ddq, J = 9.0, 7.4, 1.5 Hz, 1H), 4.95 (p, J = 1.5 Hz, 1H), 4.73 – 4.67 (m, 1H), 3.55 (d, J = 19.0 Hz, 1H), 3.42 – 3.28 (m, 2H), 2.92 (dd, J = 13.8, 7.2 Hz, 1H), 2.75 (dd, J = 13.8, 7.9 Hz, 1H), 2.40 – 2.30 (m, 2H), 2.28 – 2.15 (m, 2H), 2.09 (t, J = 13.1 Hz, 1H), 1.69 (d, J = 1.4 Hz, 3H), 1.62 (s, 3H), 1.58 (d, J = 1.4 Hz, 3H), 1.52 (dd, J = 14.0, 3.4 Hz, 1H), 1.40 (s, 1H), 1.13 (ddd, J = 15.1, 14.0, 2.5 Hz, 1H), 1.06 (s, 3H), 0.90 (d, J = 1.9 Hz, 6H), 0.73 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, C_6D_6) δ = 208.99, 205.08, 169.19, 143.07, 138.06, 135.32, 129.02, 124.95, 121.54, 121.35, 113.73, 70.77, 68.23, 52.58, 52.53, 47.73, 47.33, 41.00, 39.94, 38.59, 35.85, 35.48, 33.16, 31.73, 27.22, 26.22, 25.70, 25.50, 23.93, 18.23; IR (Neat

Film, NaCl) 3366, 2964, 1694, 1674, 1522, 1438, 1311, 750 cm^{-1} ; HRMS (ESI⁺): m/z calc'd for $\text{C}_{32}\text{H}_{44}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 490.3316, found 490.3313.

2.7 REFERENCES AND NOTES

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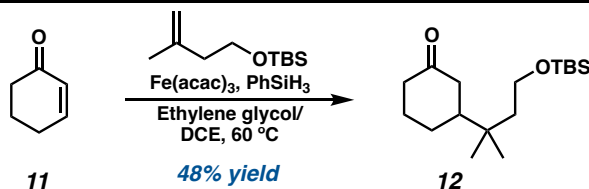
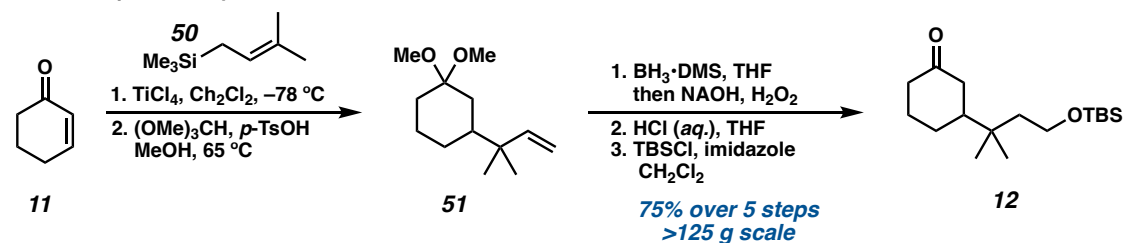
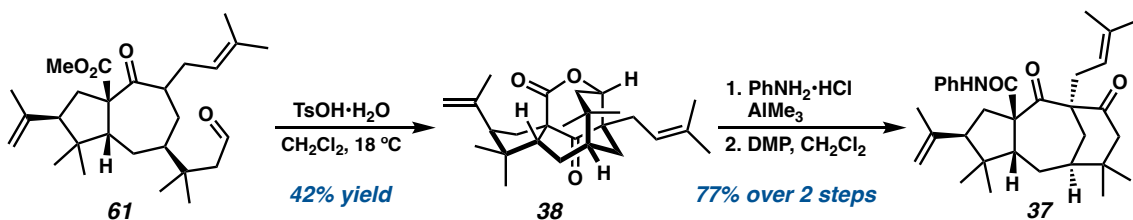
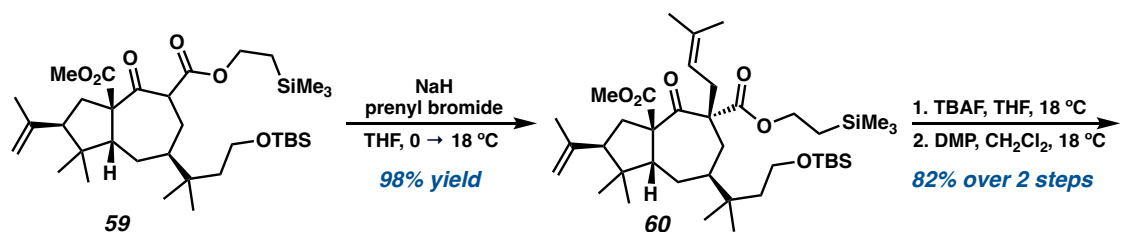
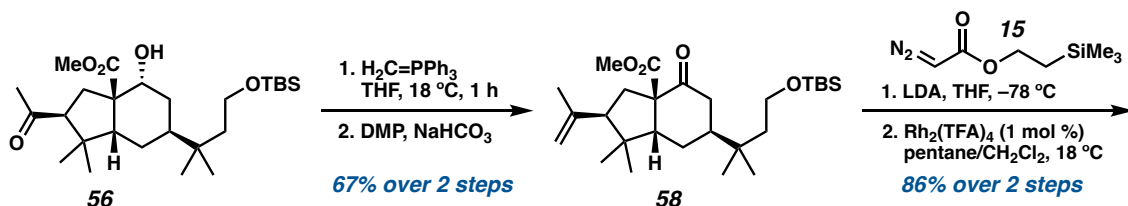
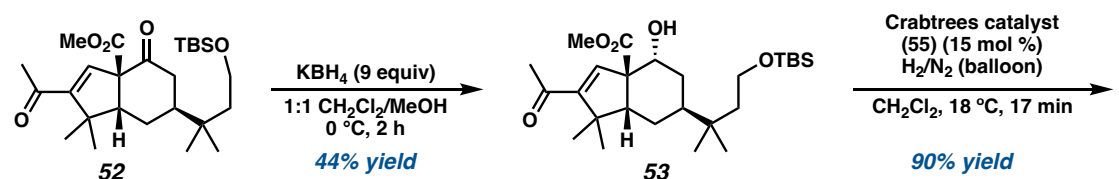
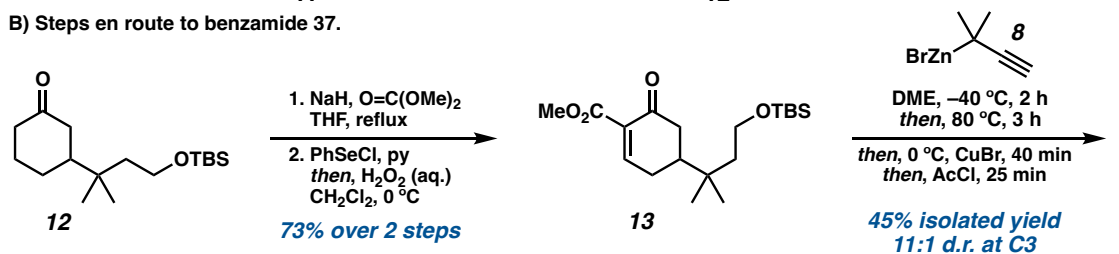
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APPENDIX 3

Synthetic Summary for Chapter 2:

Toward the Total Synthesis of Hypersonin A and Wilsonglucinol G

Scheme 3.1 Synthesis of intermediate **37** en route to Wilsonglucinol **G** (**36**).A) Both sequences to protected ketoalcohol **12**.B) Steps en route to benzamide **37**.

APPENDIX 4

Spectra Relevant to Chapter 2:

Toward the Total Synthesis of Hypersonin A and Wilsonglucinol G

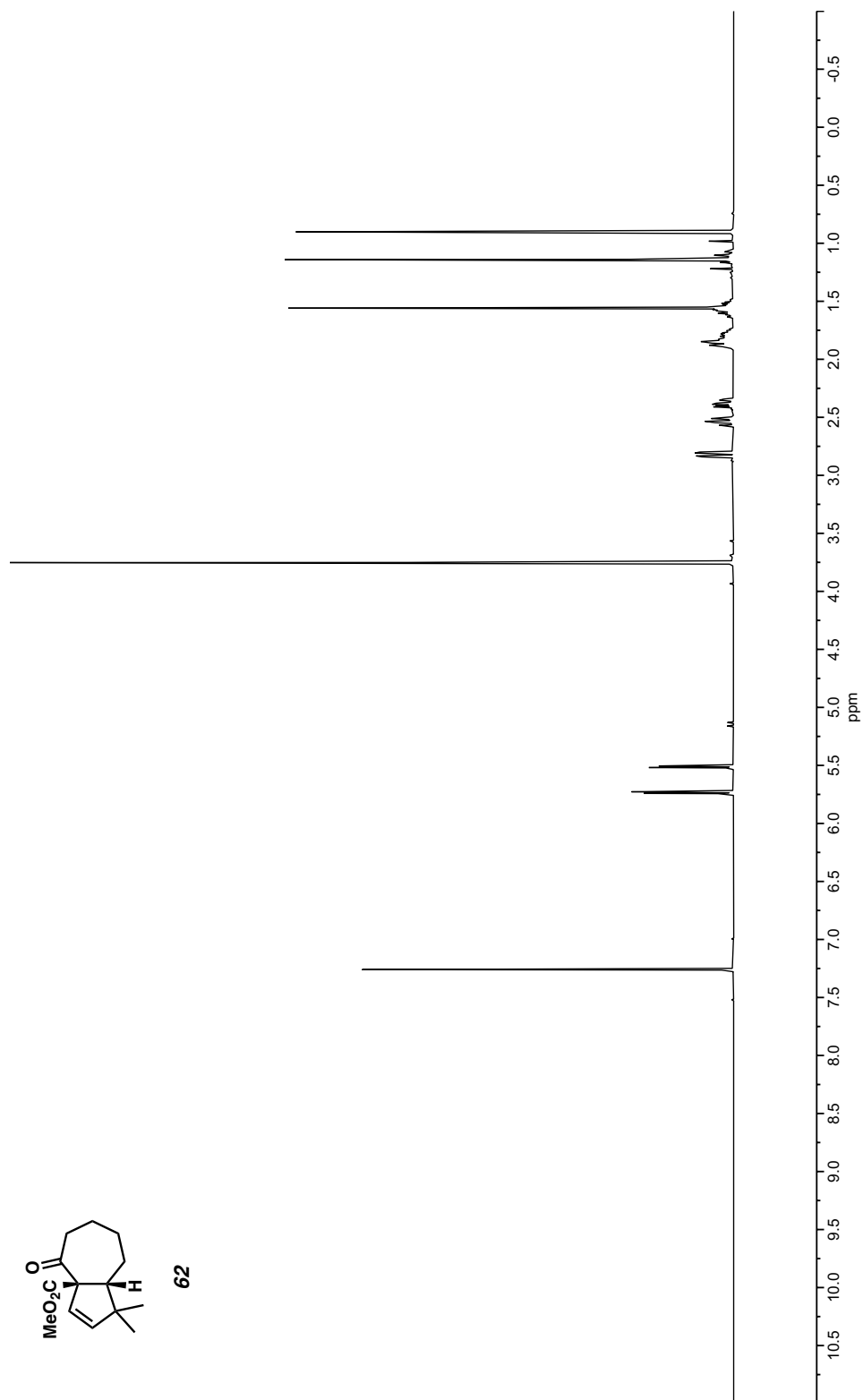


Figure A4.1 ^1H NMR (600 MHz, CDCl_3) of compound **62**.

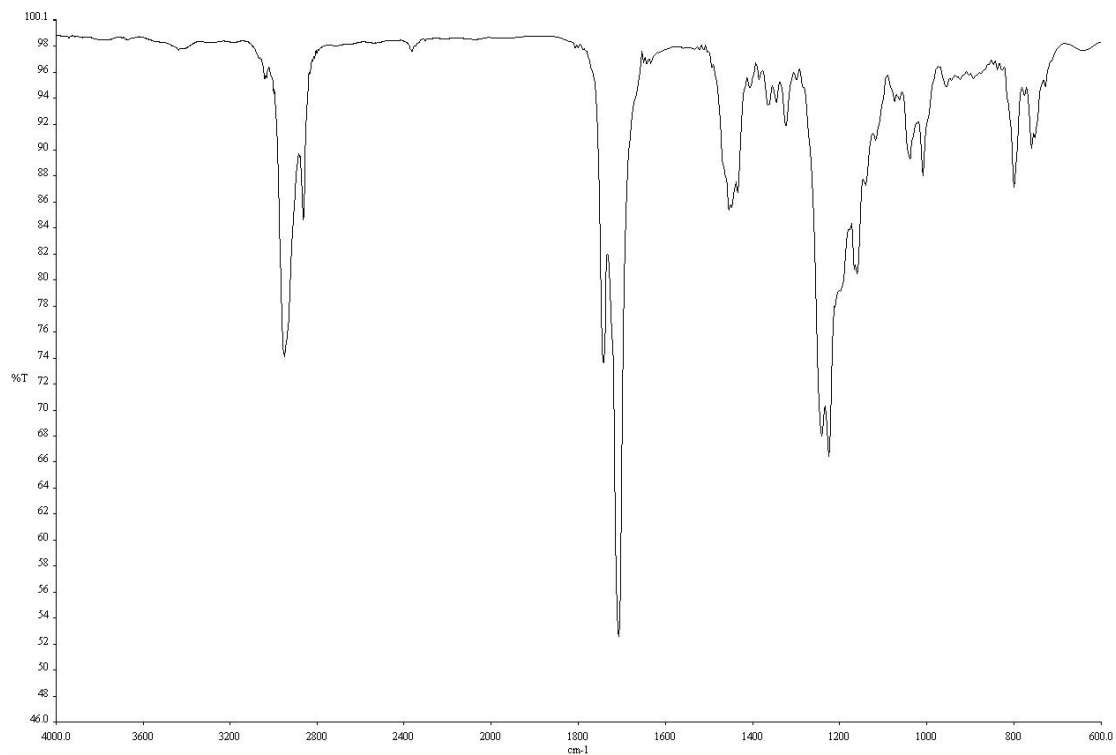


Figure A4.2 Infrared spectrum (Thin Film, NaCl) of compound **62**.

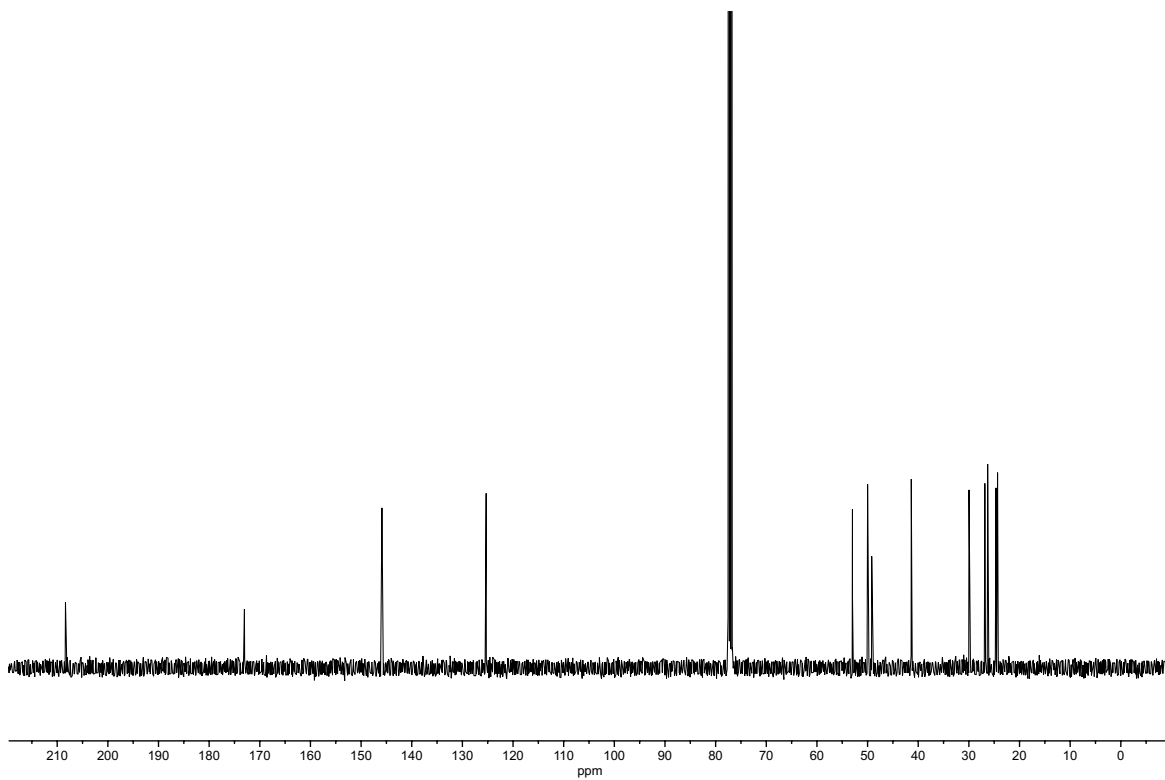


Figure A4.3 ¹³C NMR (100 MHz, CDCl₃) of compound **62**.

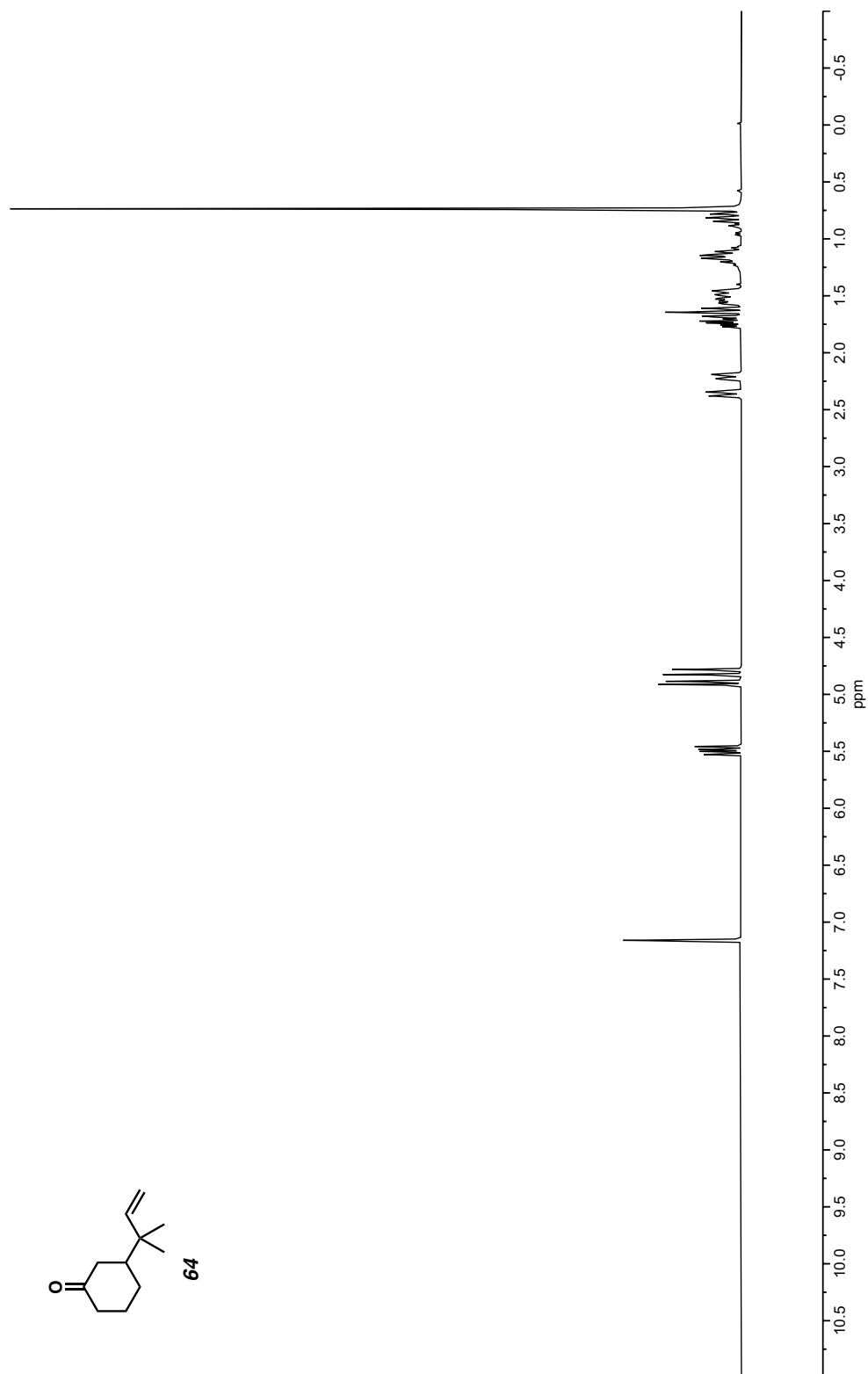


Figure A4.4 ¹H NMR (400 MHz, CDCl₃) of compound **64**.

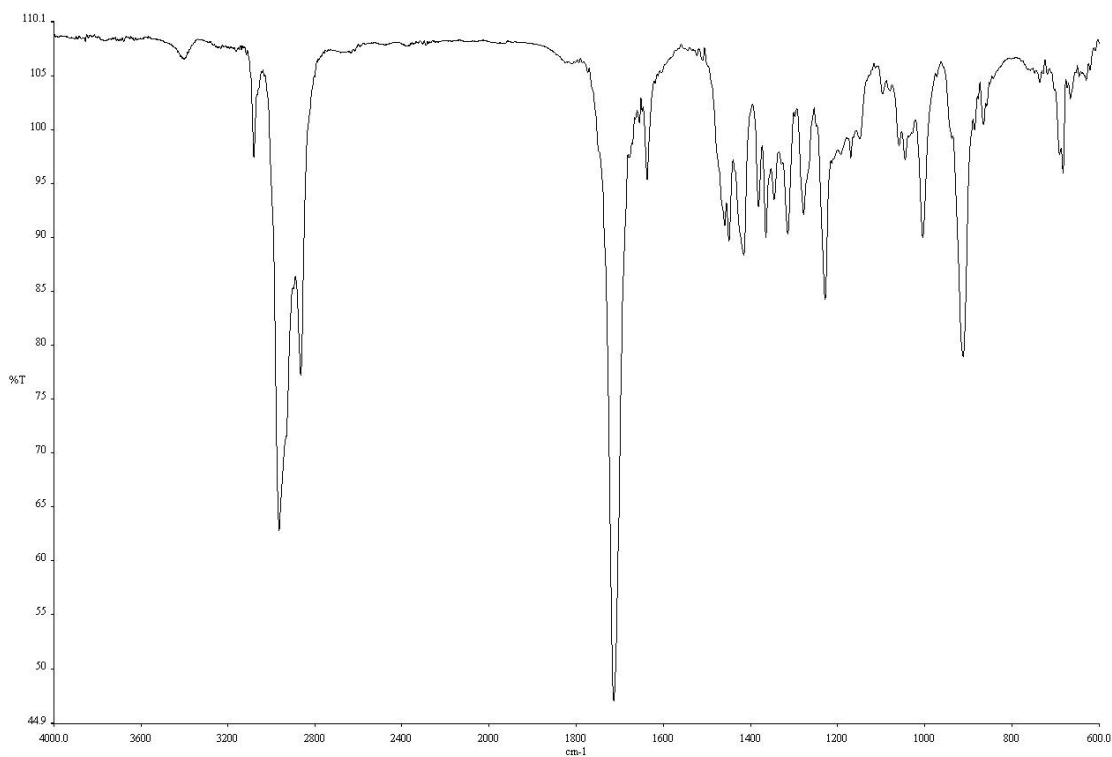


Figure A4.5 Infrared spectrum (Thin Film, NaCl) of compound **64**.

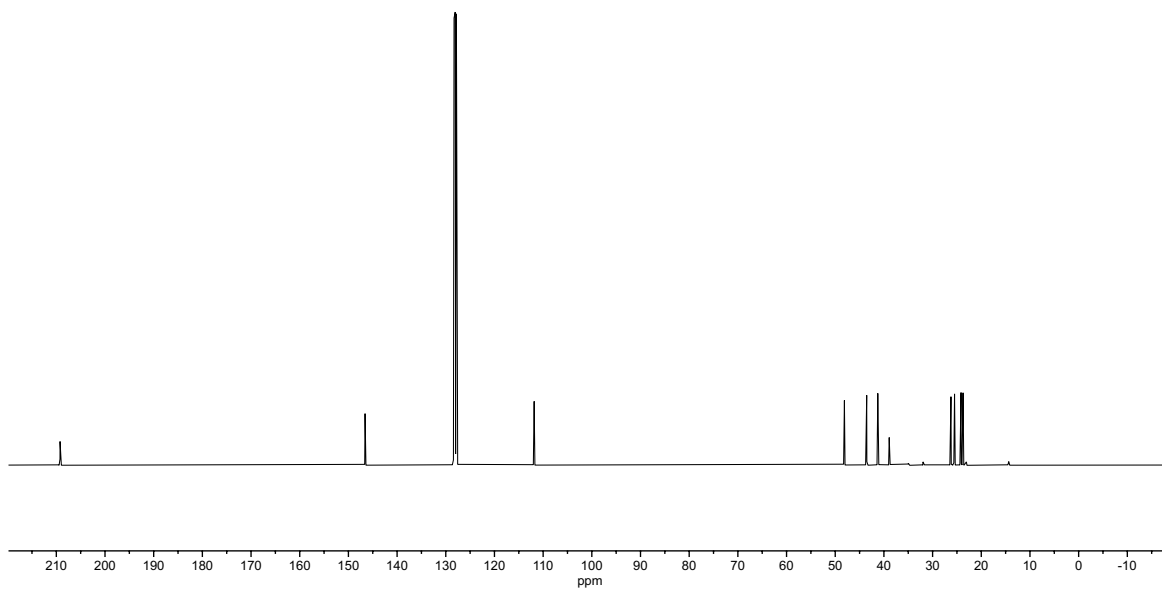


Figure A4.6 ¹³C NMR (100 MHz, C₆D₆) of compound **64**.

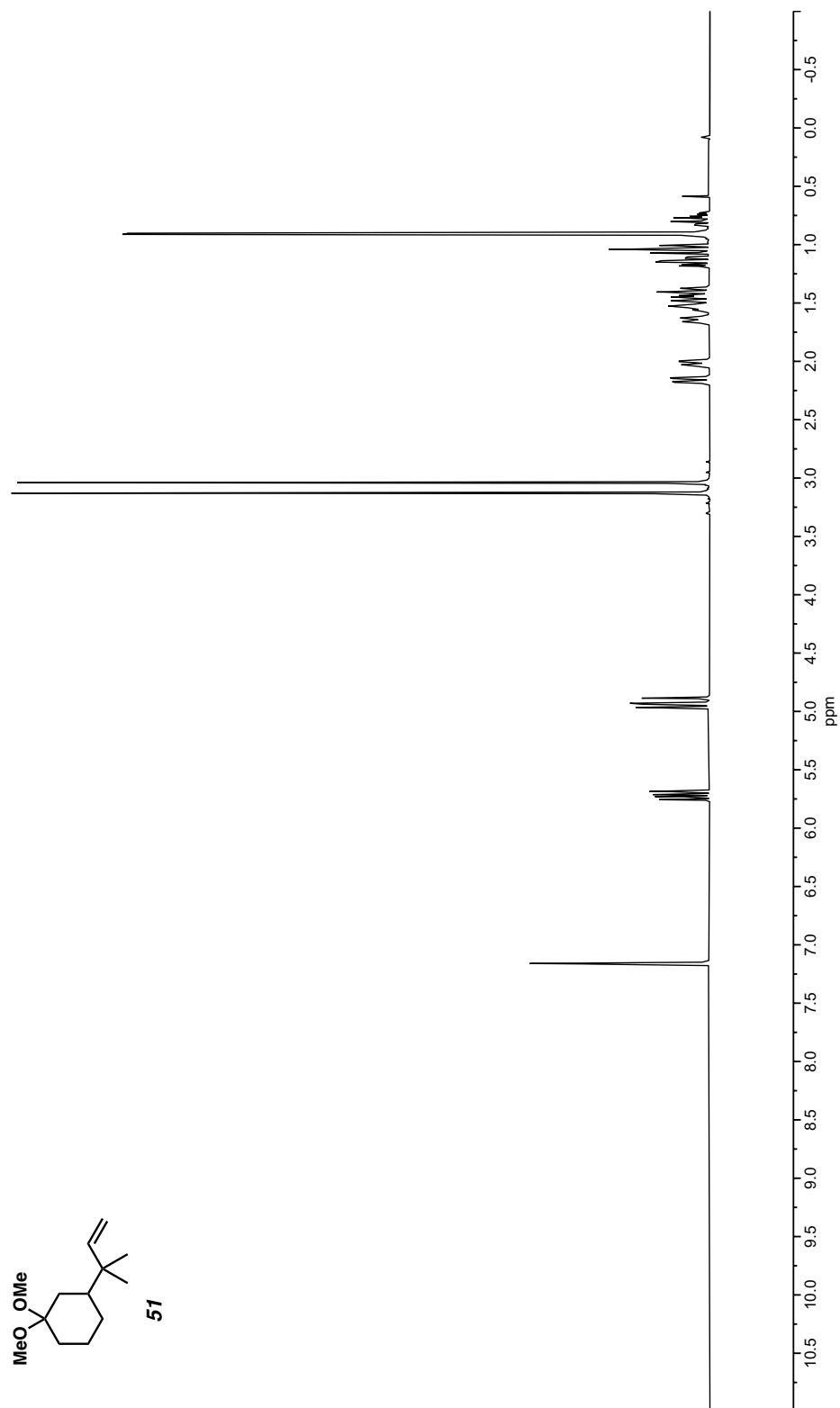


Figure A4.7 ¹H NMR (400 MHz, CDCl₃) of compound **51**.

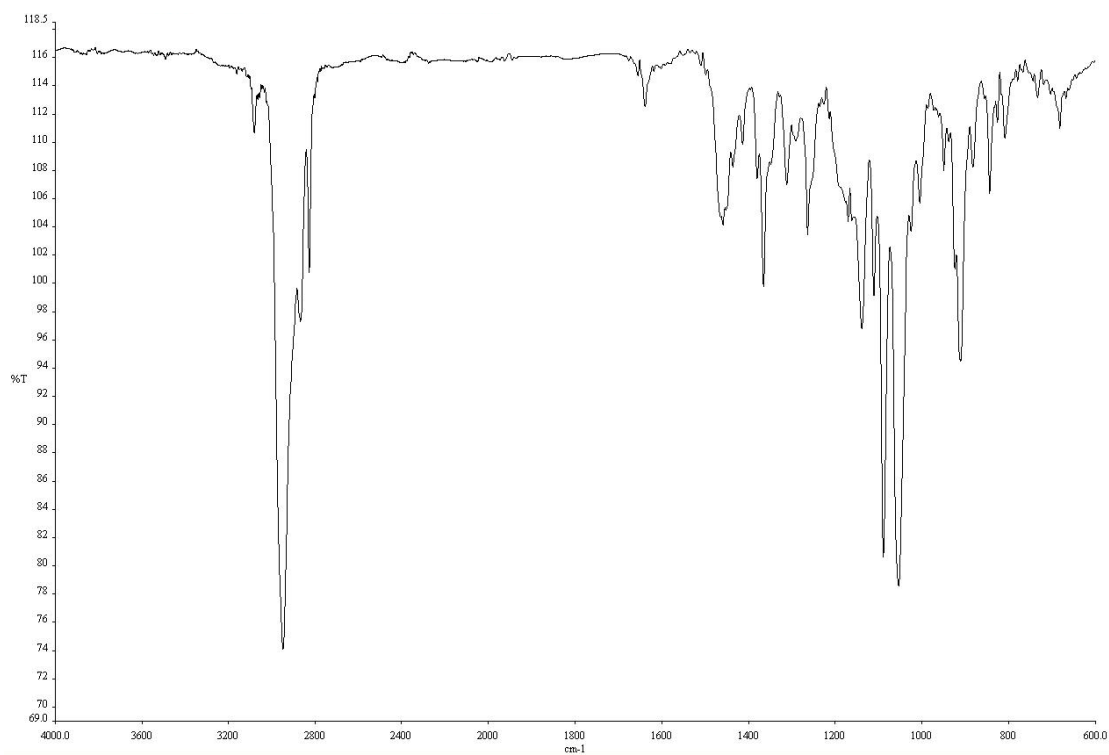


Figure A4.8 Infrared spectrum (Thin Film, NaCl) of compound **51**.

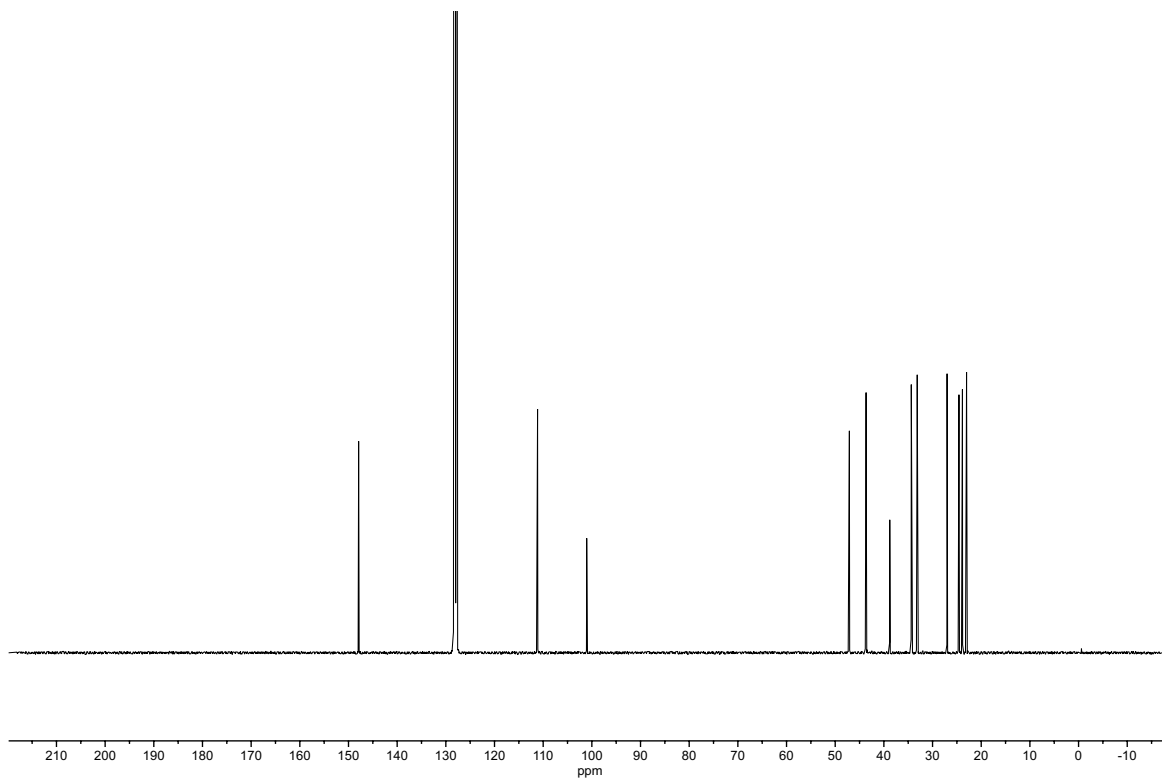


Figure A4.9 ¹³C NMR (100 MHz, C₆D₆) of compound **51**.

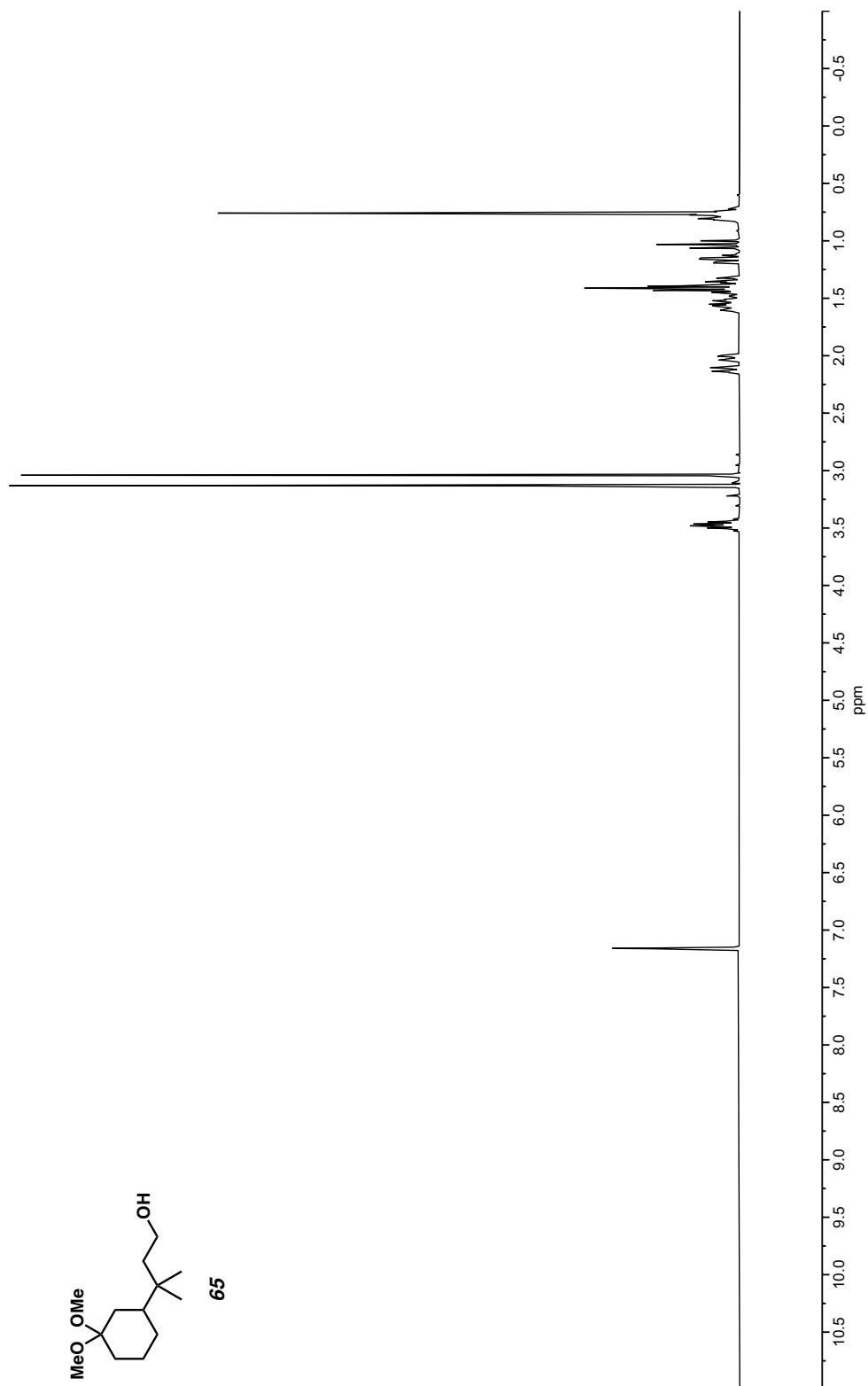


Figure A4.10 ¹H NMR (400 MHz, CDCl₃) of compound **65**.

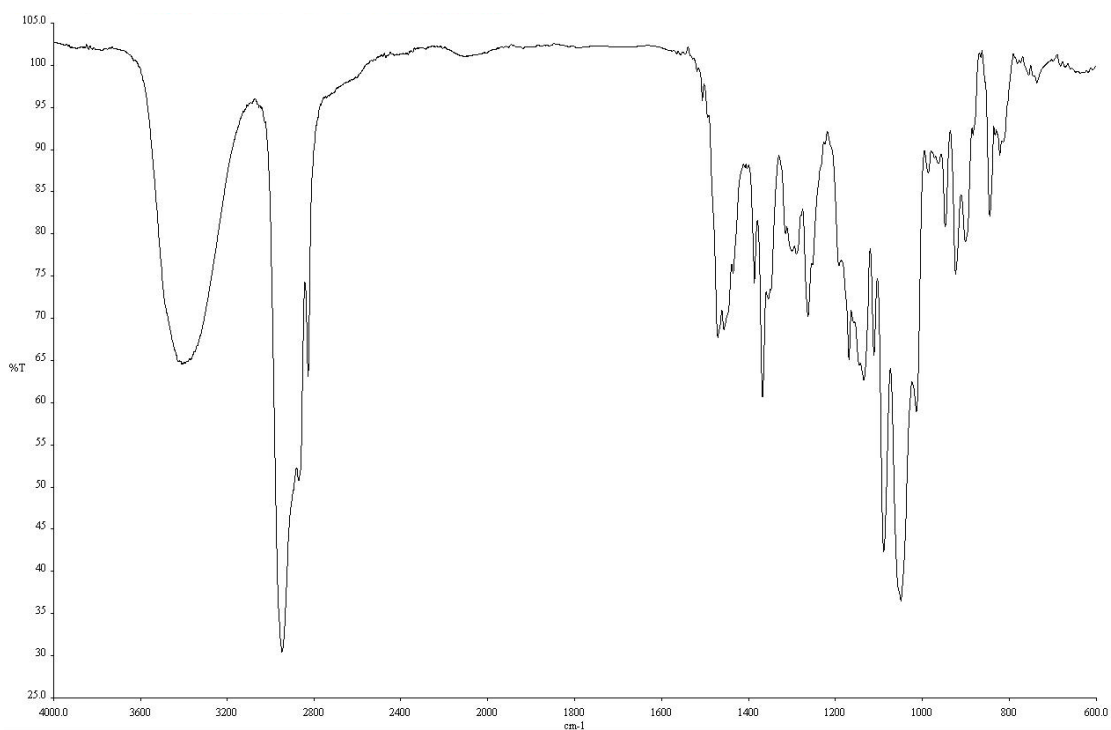


Figure A4.11 Infrared spectrum (Thin Film, NaCl) of compound **65**.

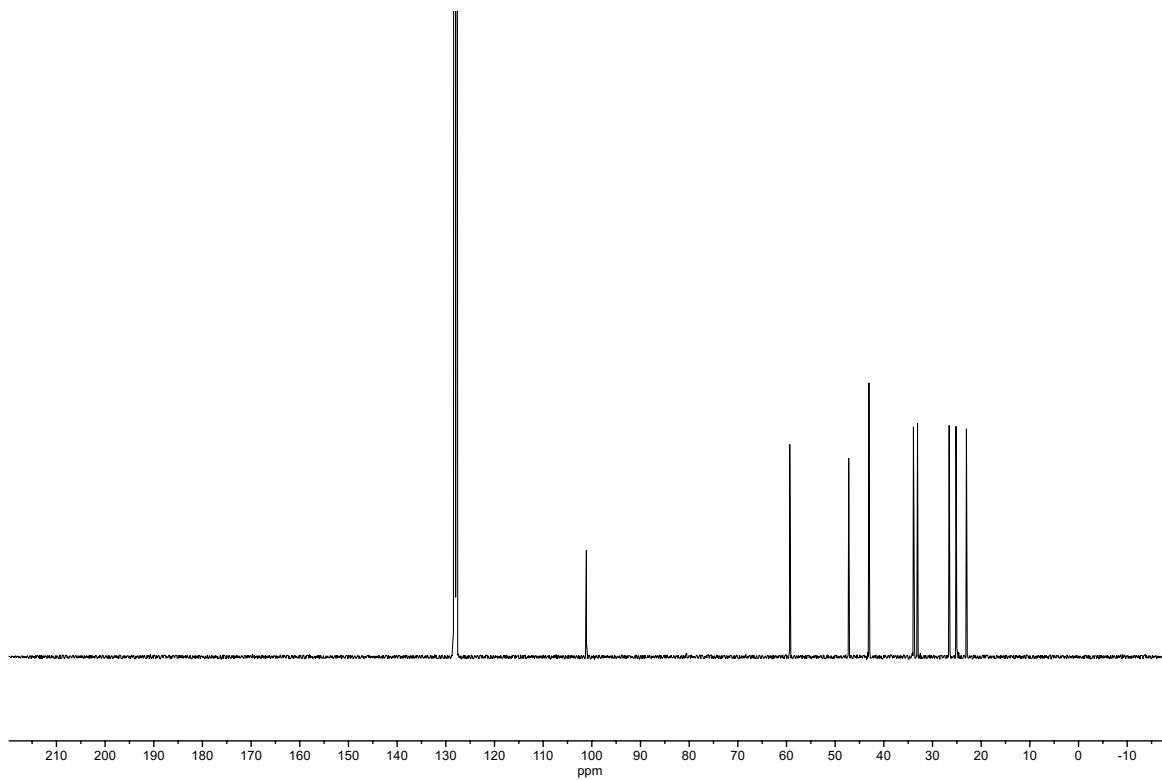


Figure A4.12 ¹³C NMR (100 MHz, C₆D₆) of compound **65**.

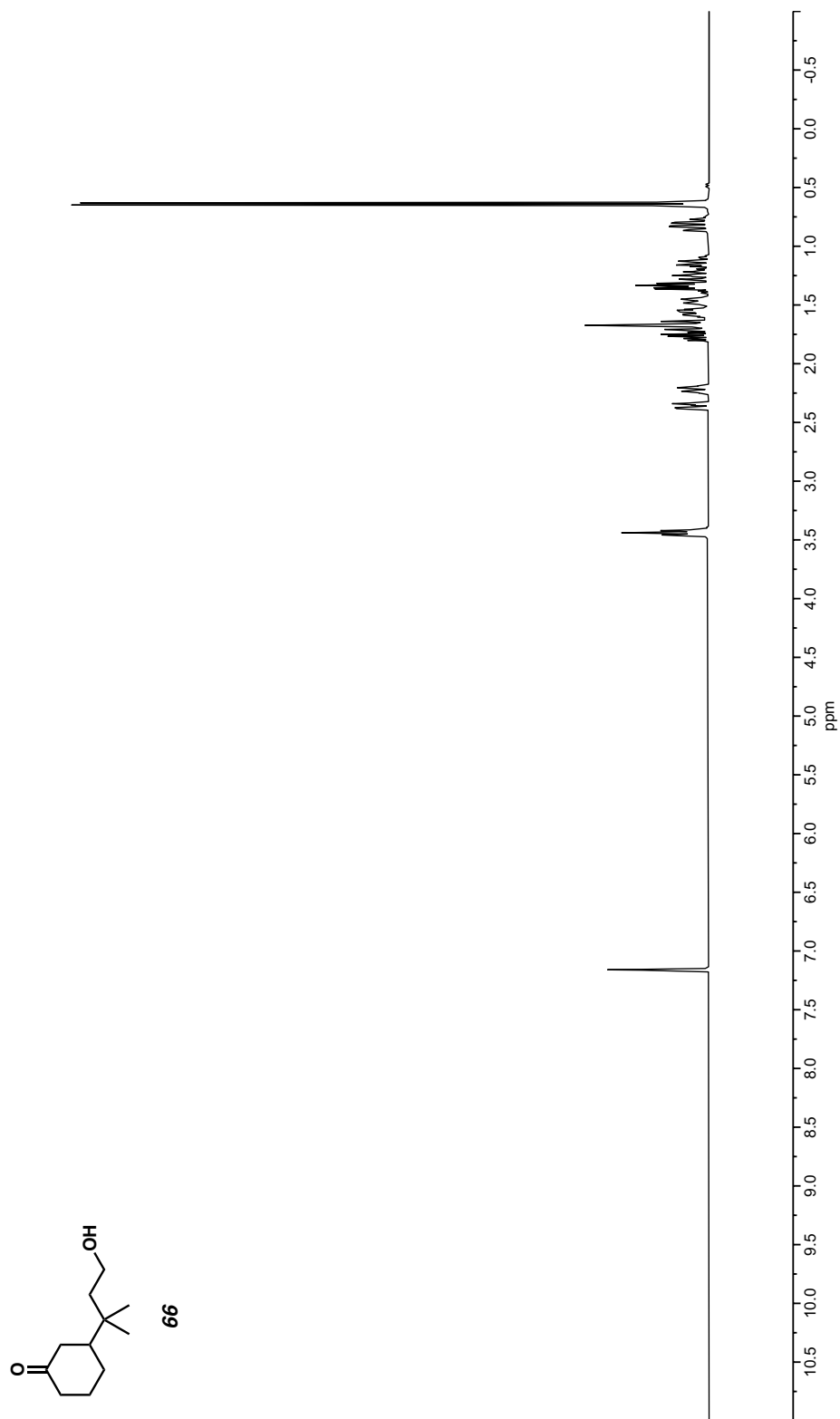


Figure A4.13 ¹H NMR (400 MHz, CDCl₃) of compound **66**.

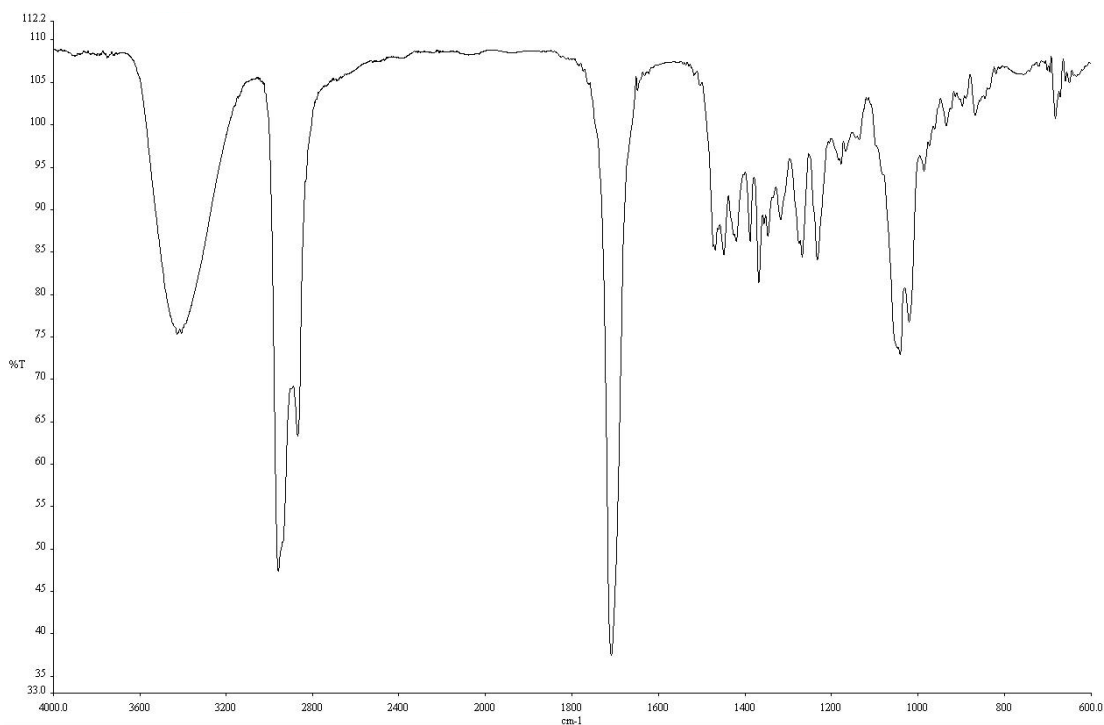


Figure A4.14 Infrared spectrum (Thin Film, NaCl) of compound **66**.

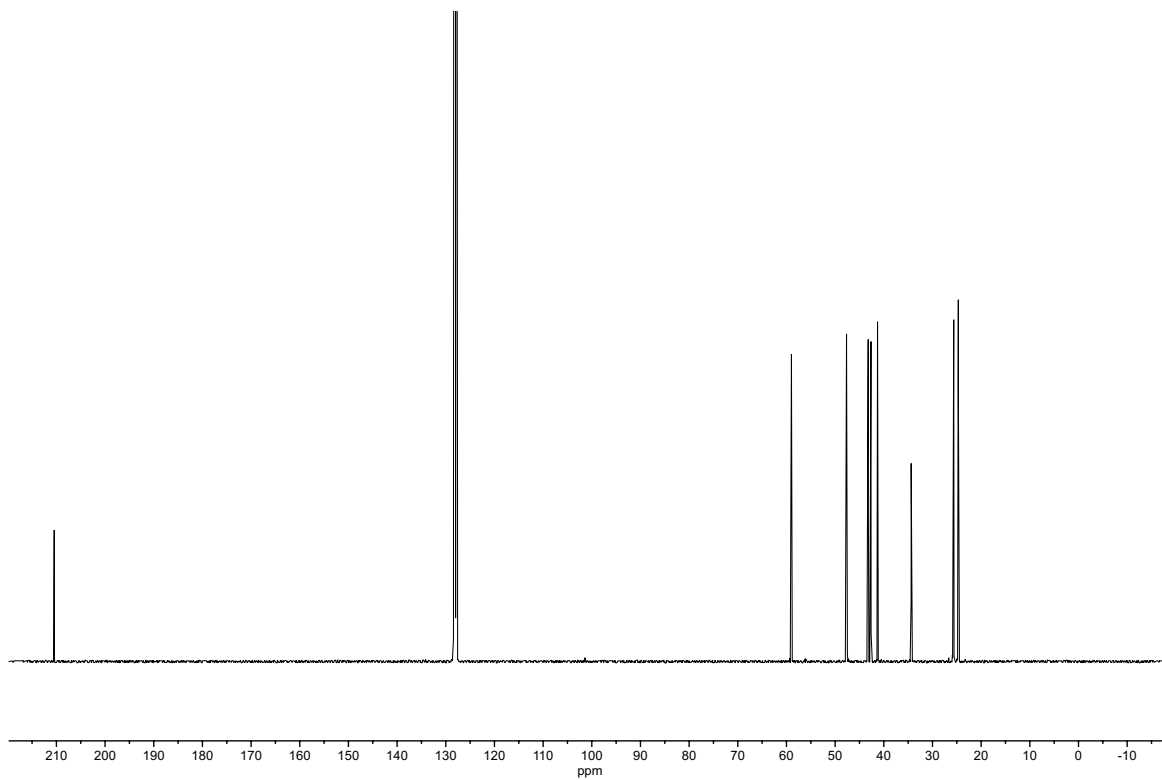


Figure A4.15 ¹³C NMR (100 MHz, C₆D₆) of compound **66**.

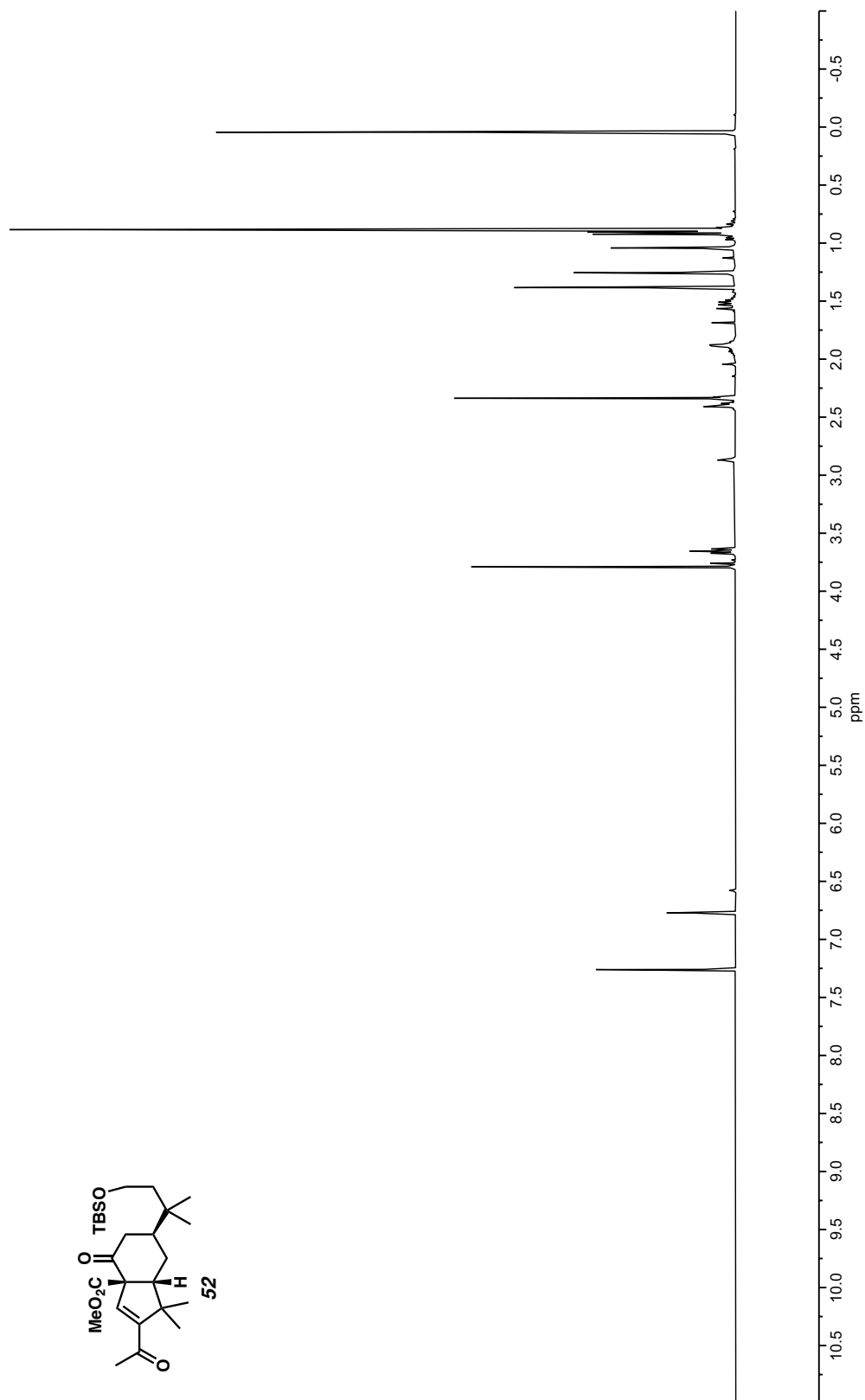
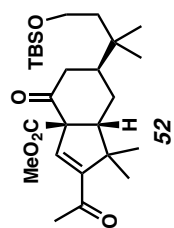


Figure A4.16 ¹H NMR (400 MHz, C₆D₆) of compound 52.

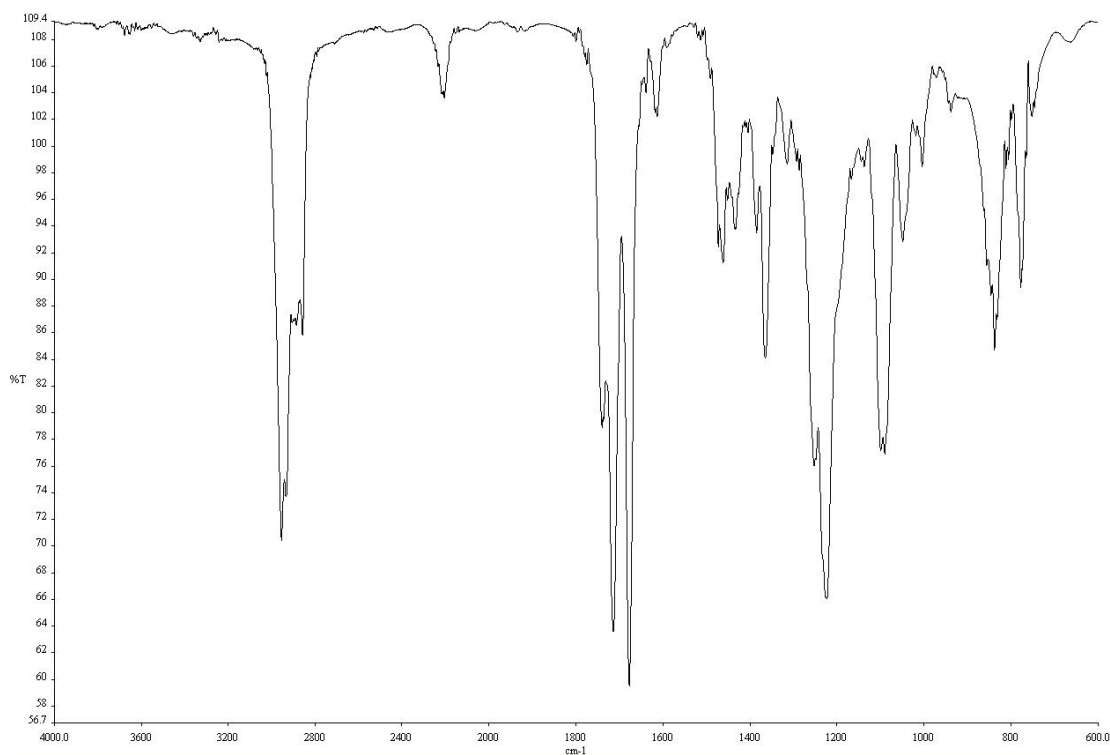


Figure A4.17 Infrared spectrum (Thin Film, NaCl) of compound 52.

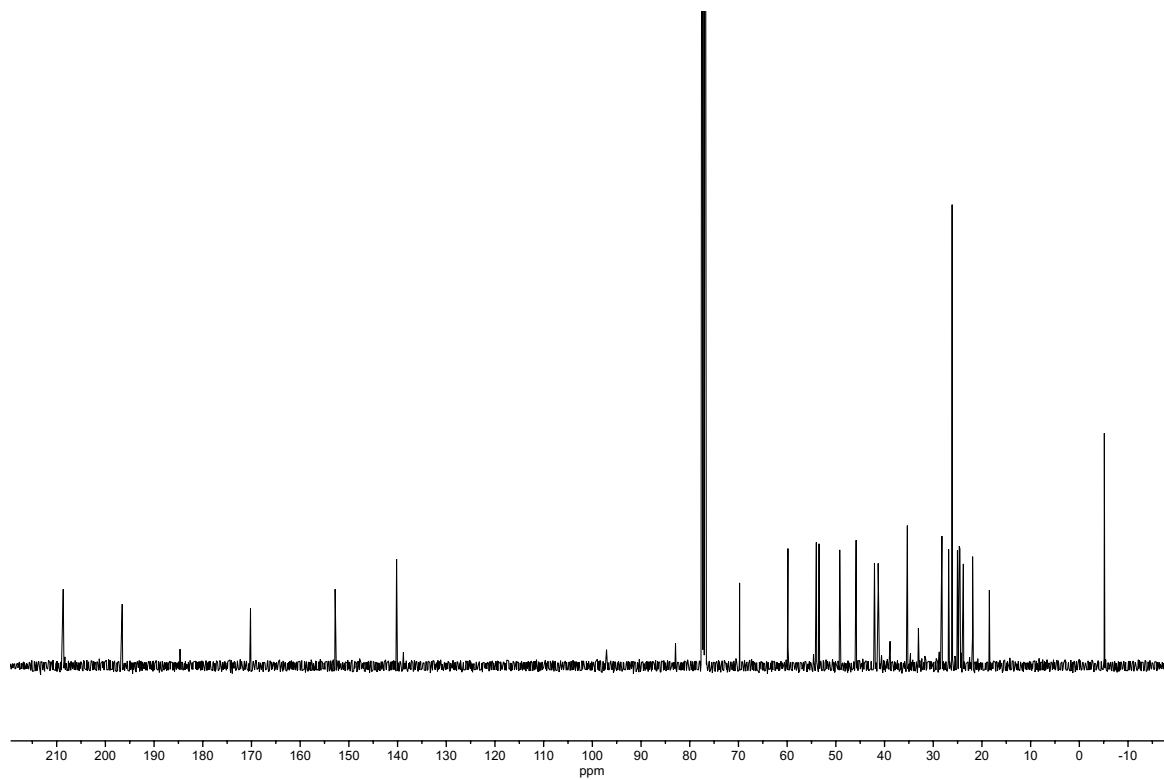


Figure A4.18 ¹³C NMR (100 MHz, C₆D₆) of compound 52.

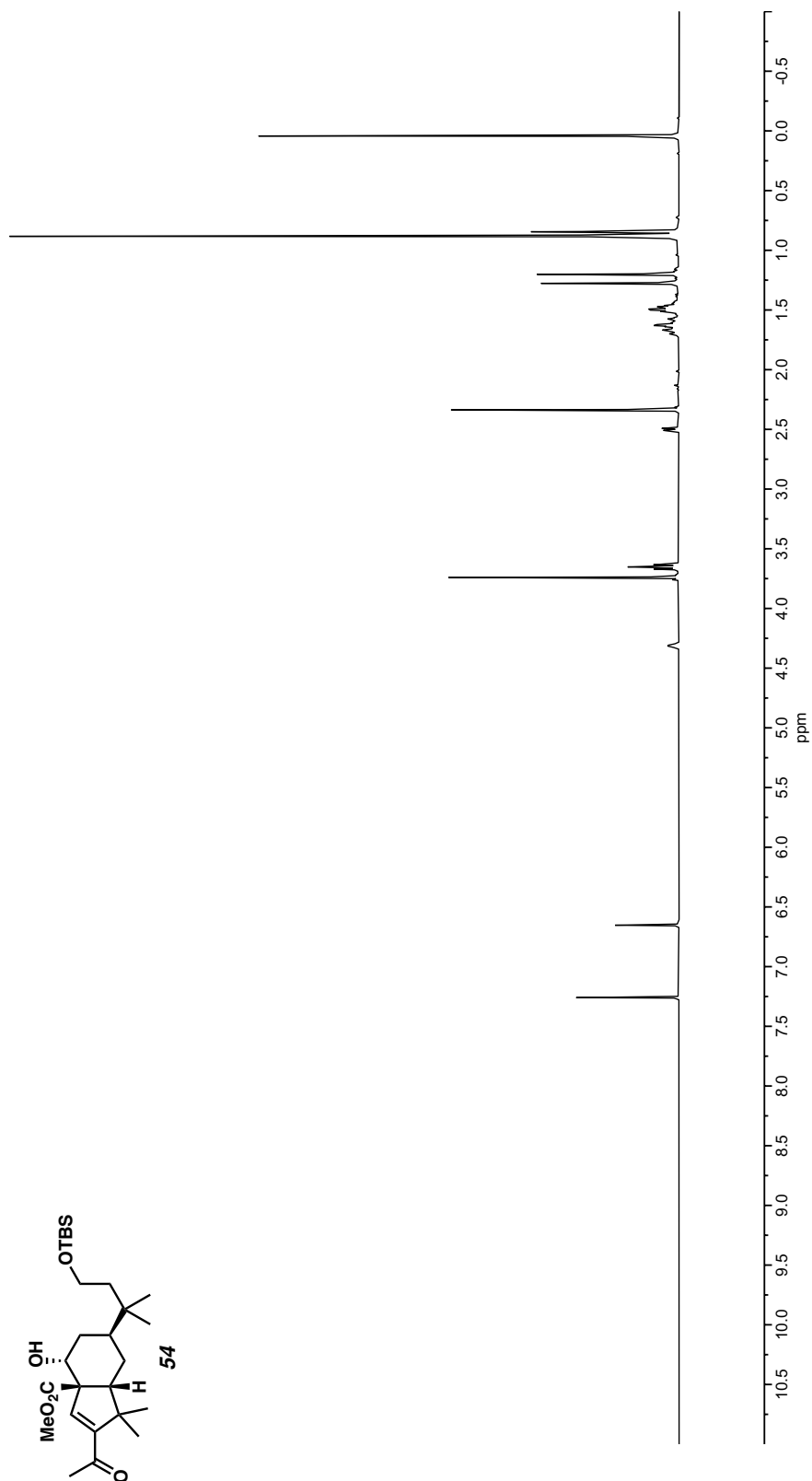


Figure A4.19 ^1H NMR (400 MHz, C_6D_6) of compound **54**.

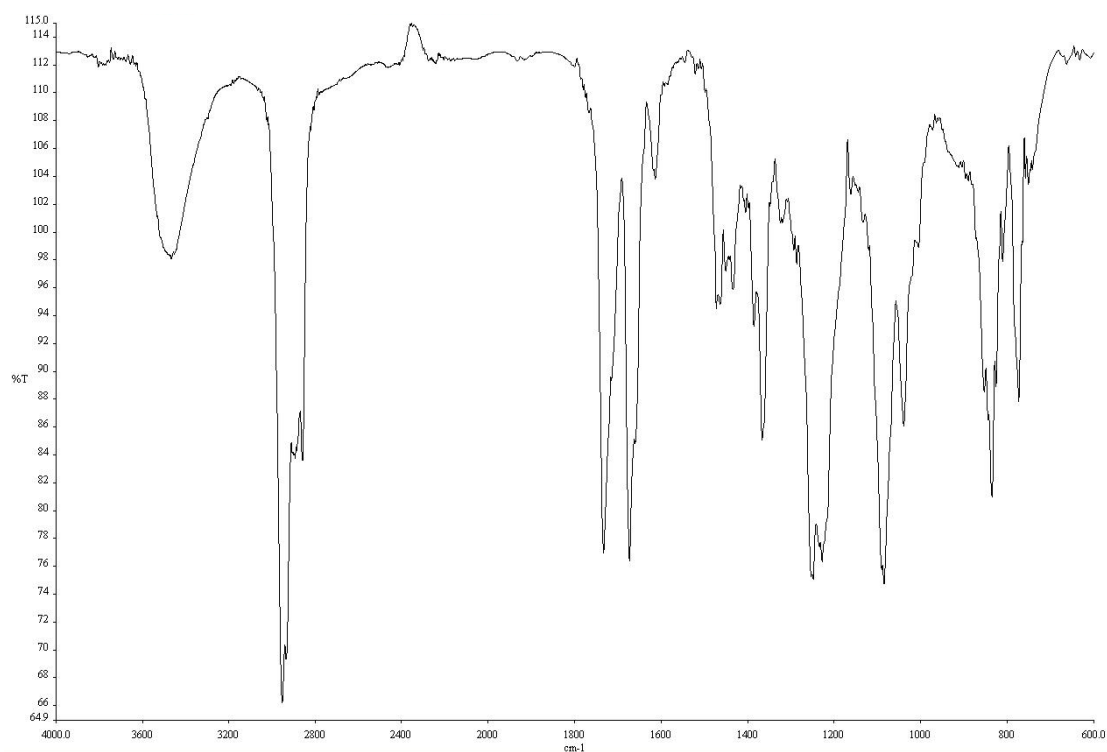


Figure A4.20 Infrared spectrum (Thin Film, NaCl) of compound 54.

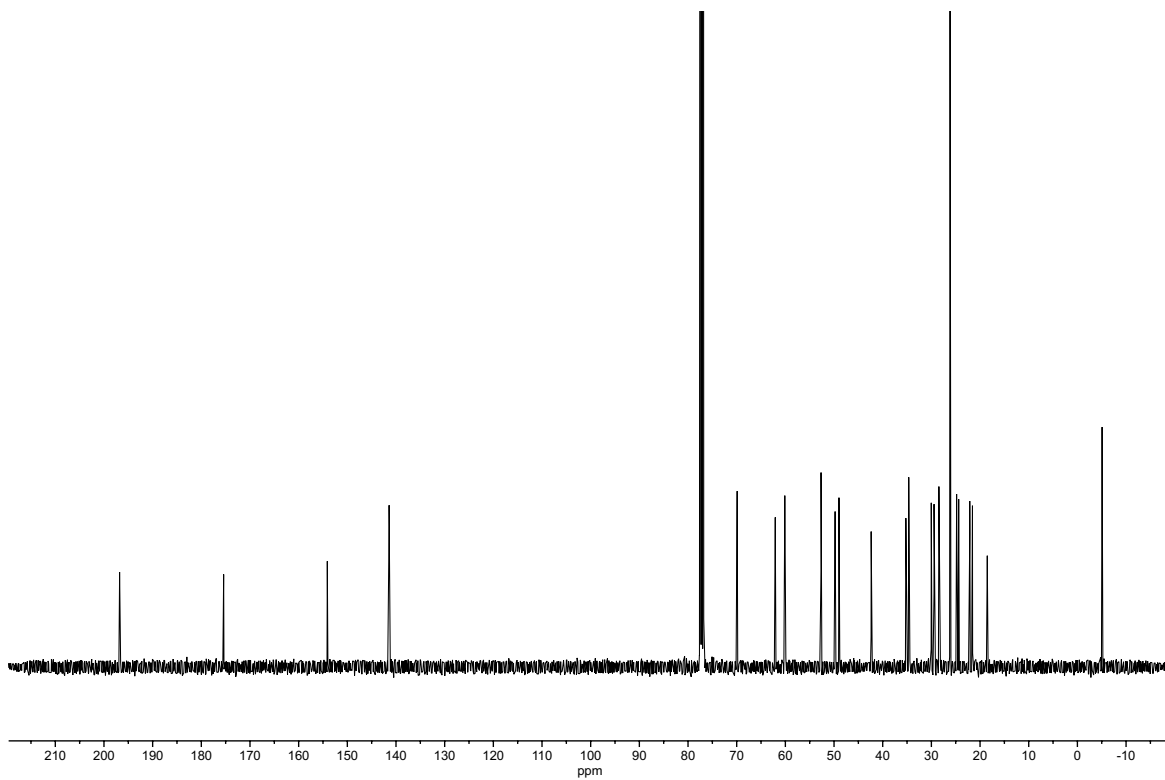


Figure A4.21 ¹³C NMR (100 MHz, C₆D₆) of compound 54.

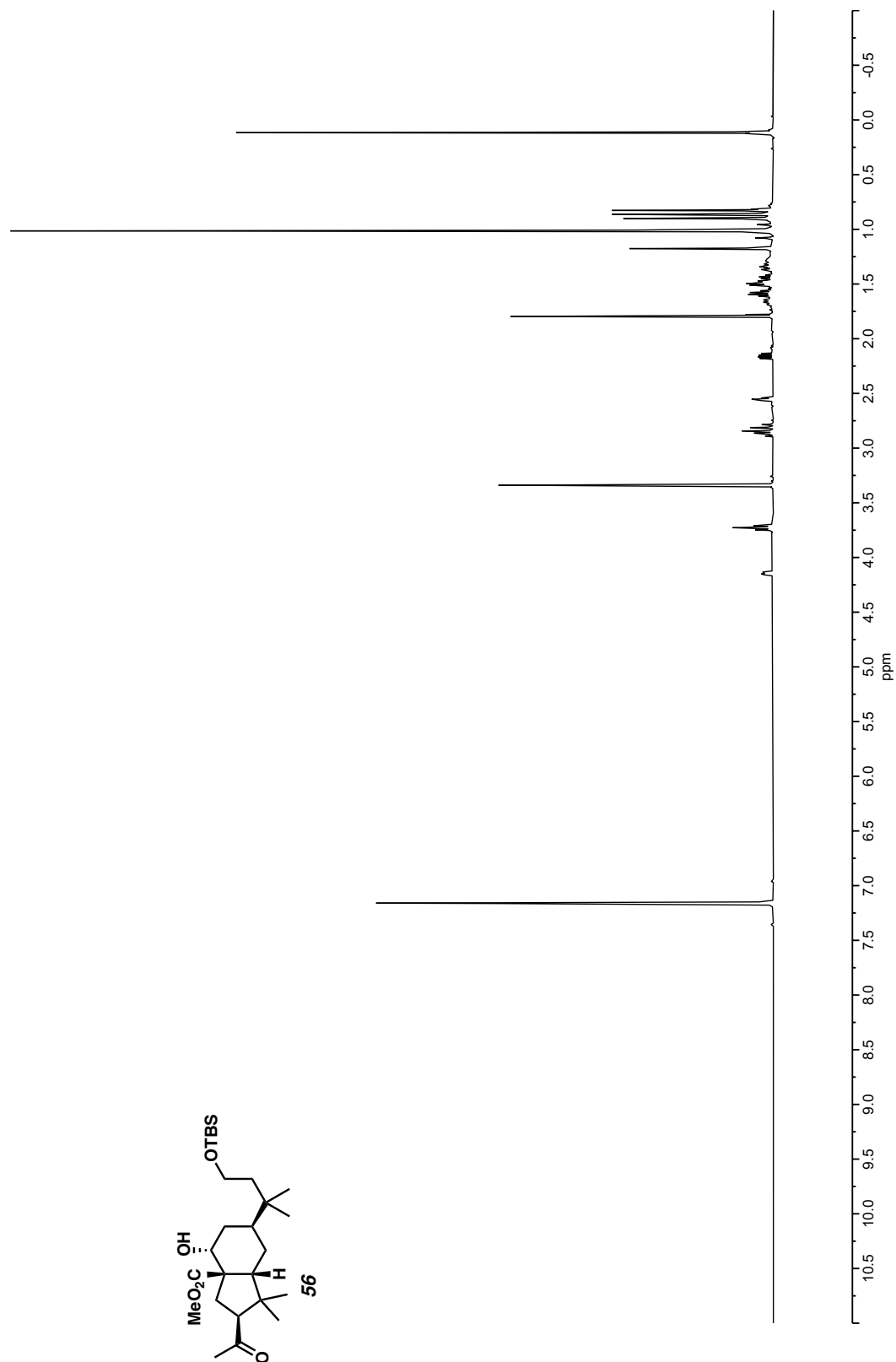


Figure A4.22 ¹H NMR (400 MHz, C₆D₆) of compound **56**.

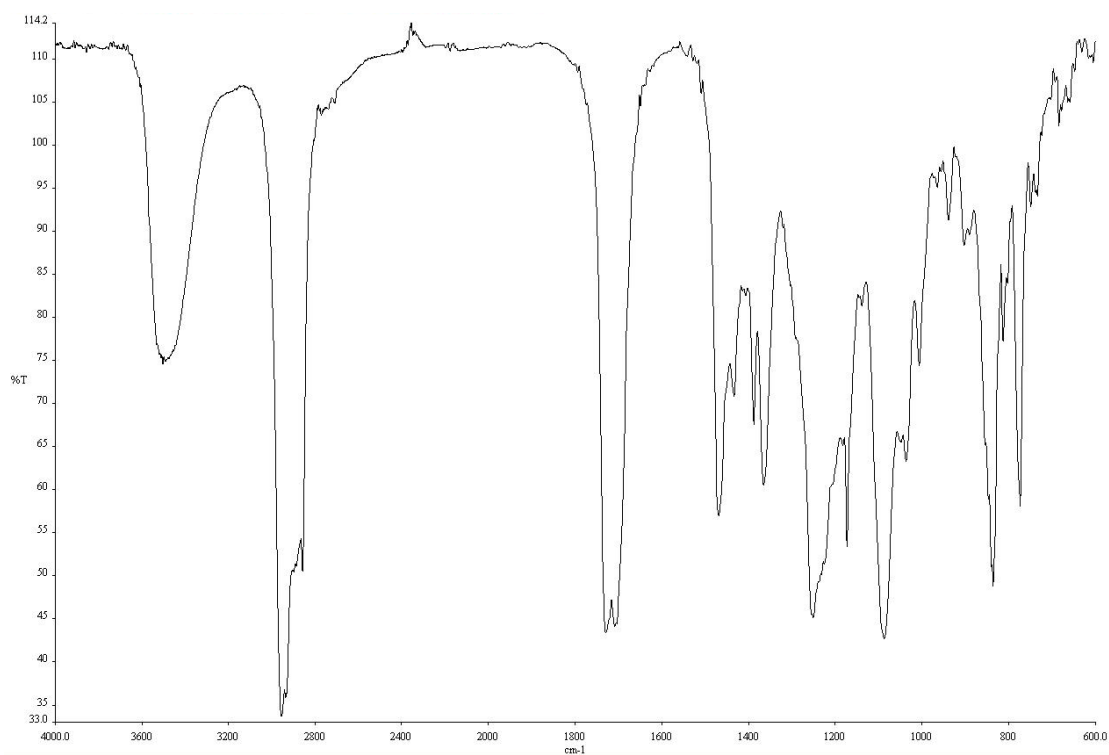


Figure A4.23 Infrared spectrum (Thin Film, NaCl) of compound **56**.

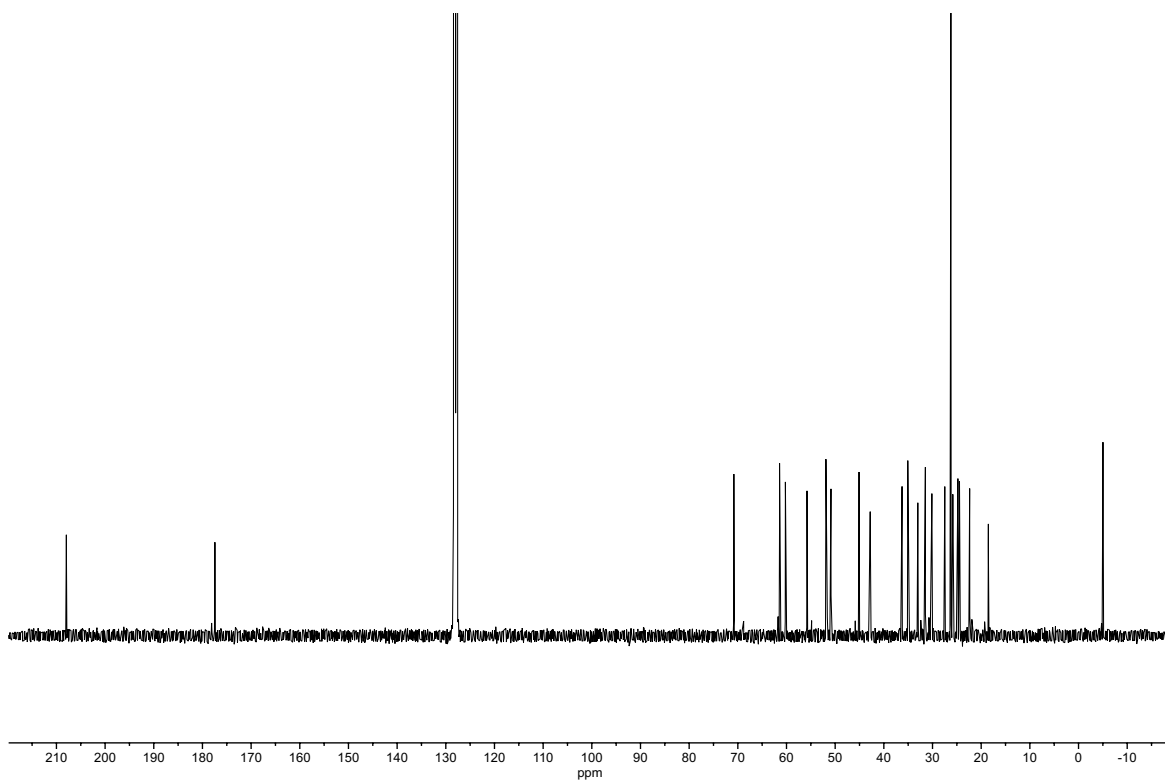


Figure A4.24 ¹³C NMR (100 MHz, C₆D₆) of compound **56**.

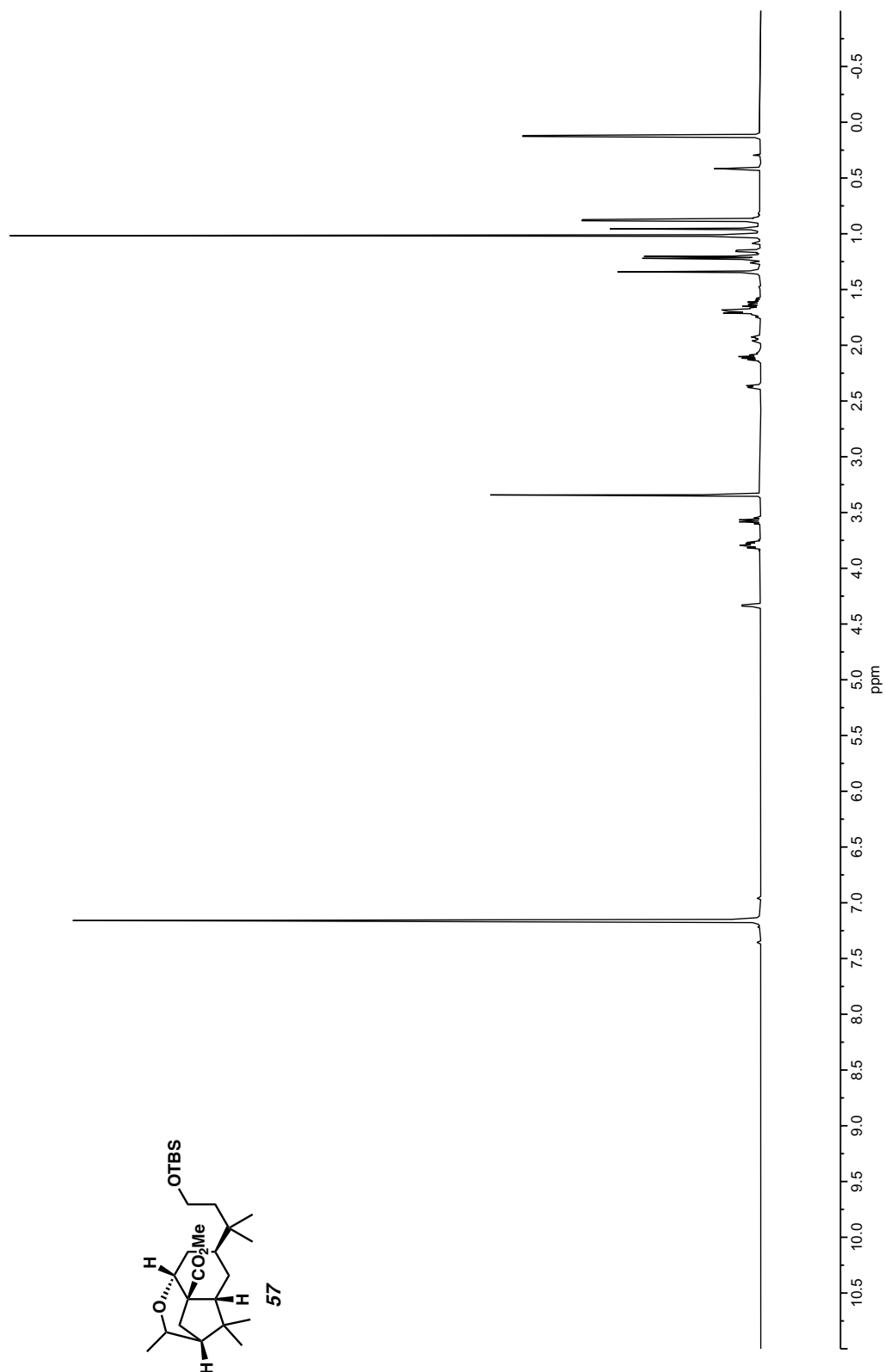


Figure A4.25 ¹H NMR (400 MHz, C₆D₆) of compound 57.

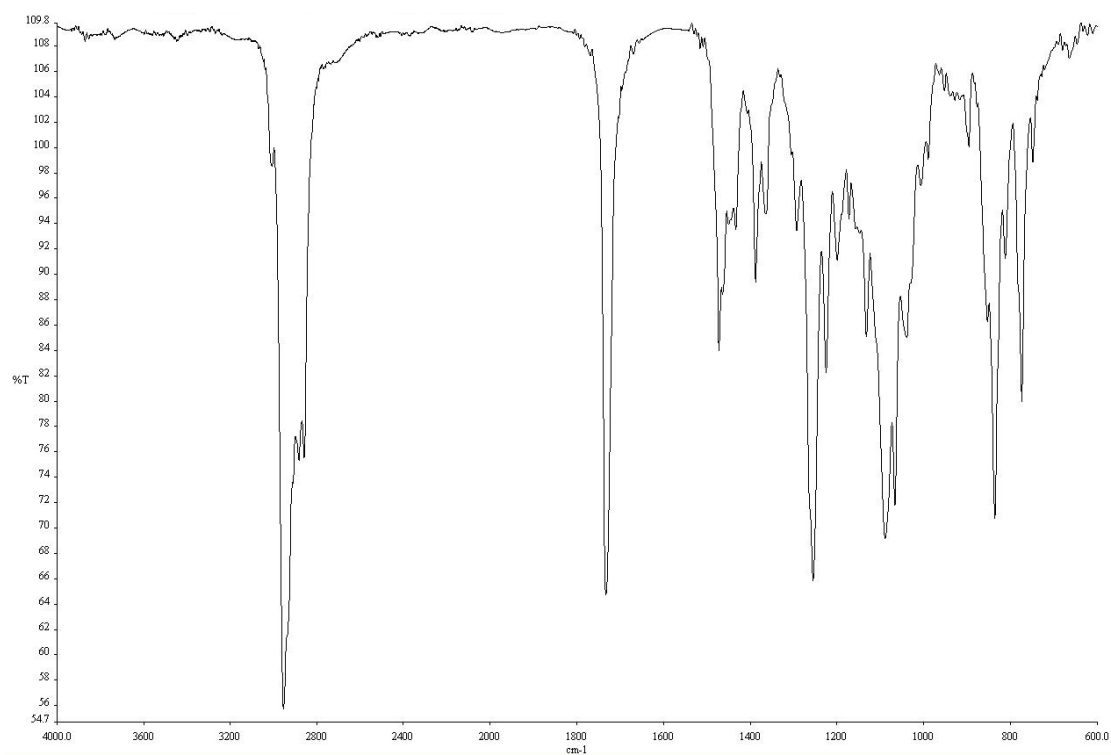


Figure A4.26 Infrared spectrum (Thin Film, NaCl) of compound 57.

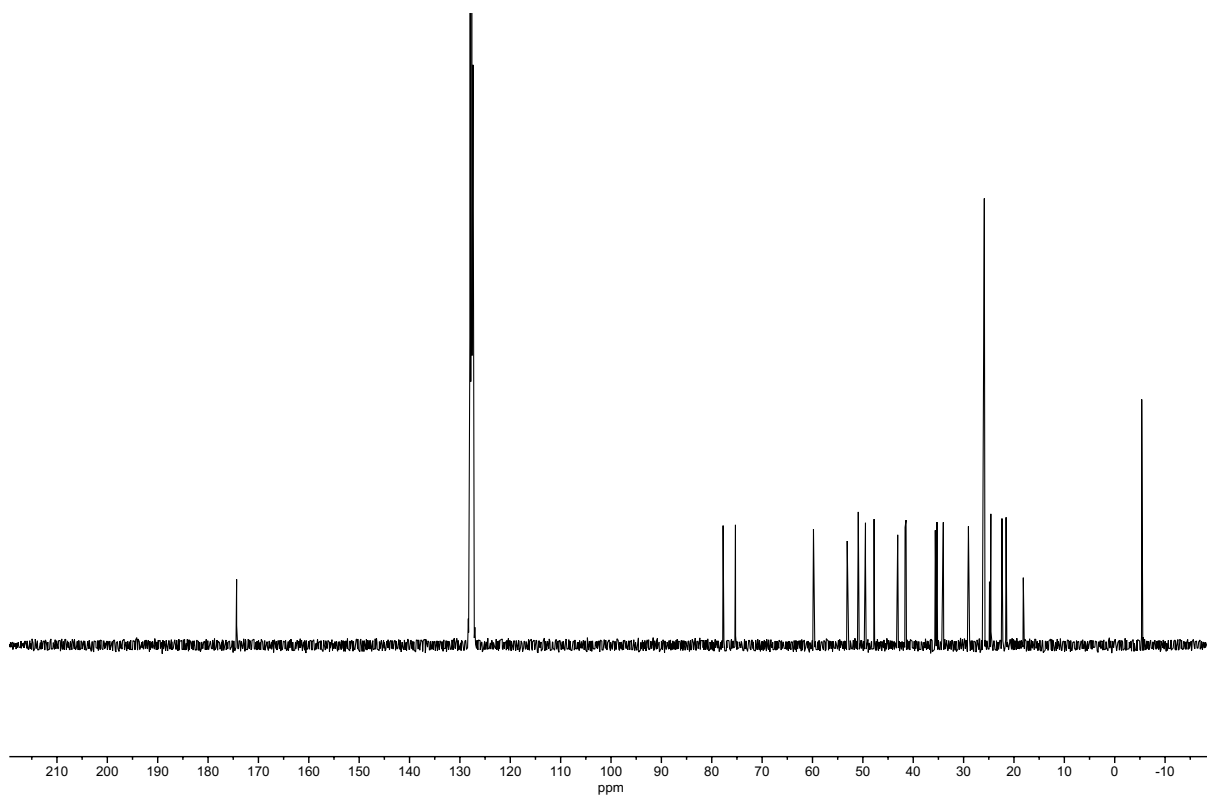


Figure A4.27 ¹³C NMR (100 MHz, C₆D₆) of compound 57.

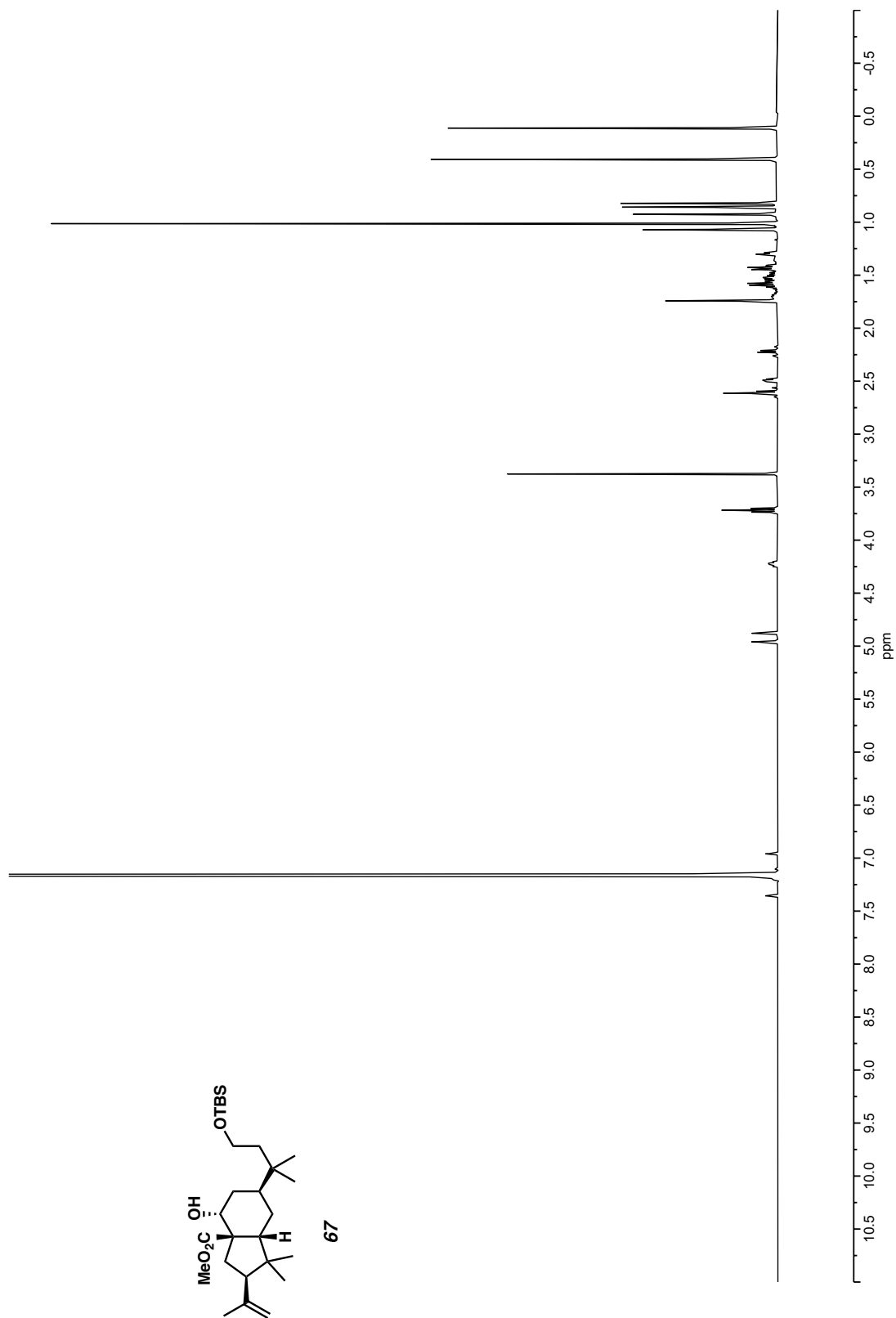


Figure A4.28 ^1H NMR (400 MHz, C_6D_6) of compound **67**.

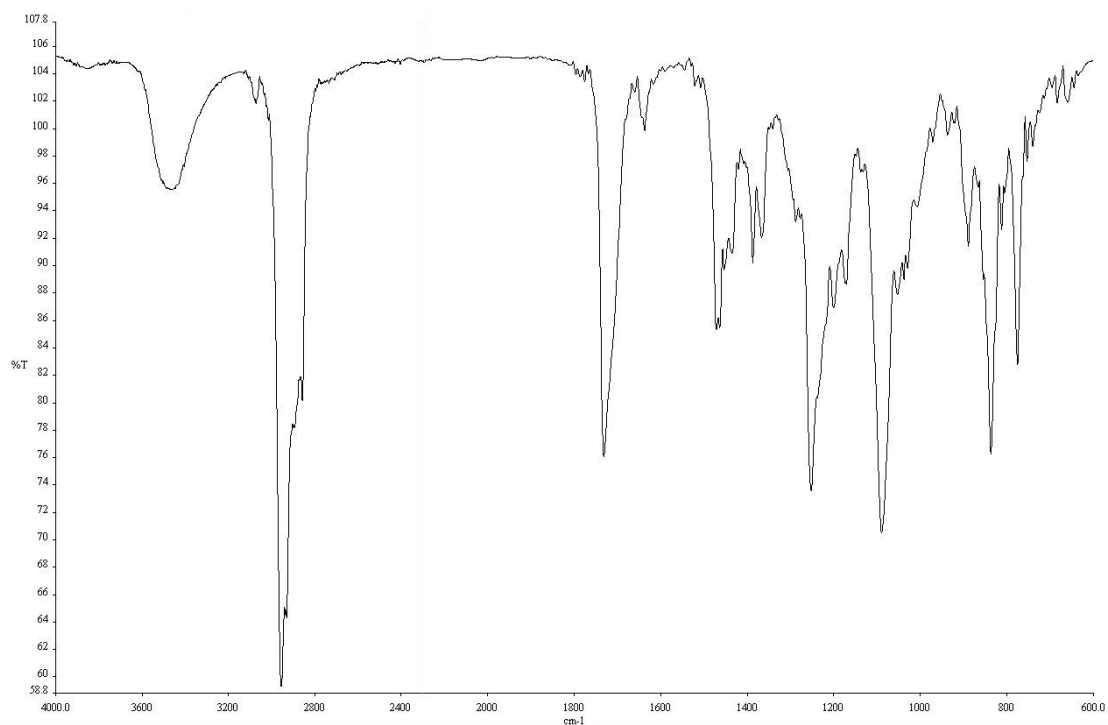


Figure A4.29 Infrared spectrum (Thin Film, NaCl) of compound **67**.

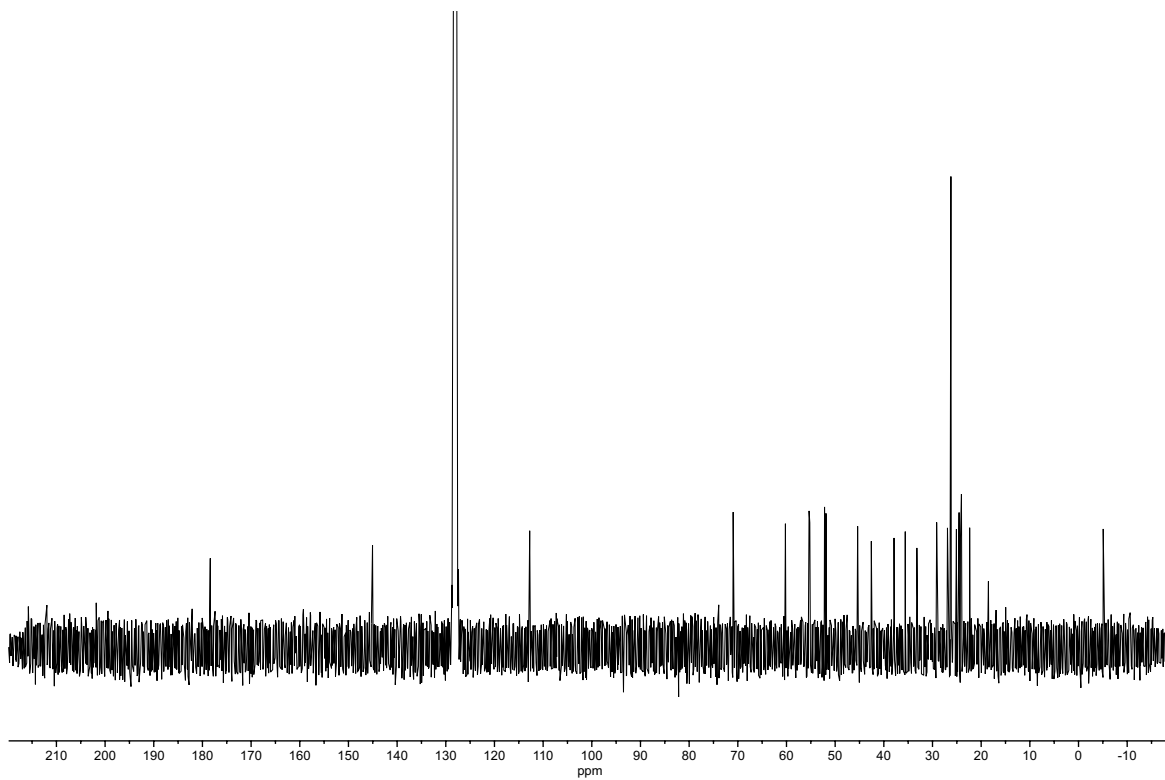


Figure A4.30 ¹³C NMR (100 MHz, C₆D₆) of compound **67**.

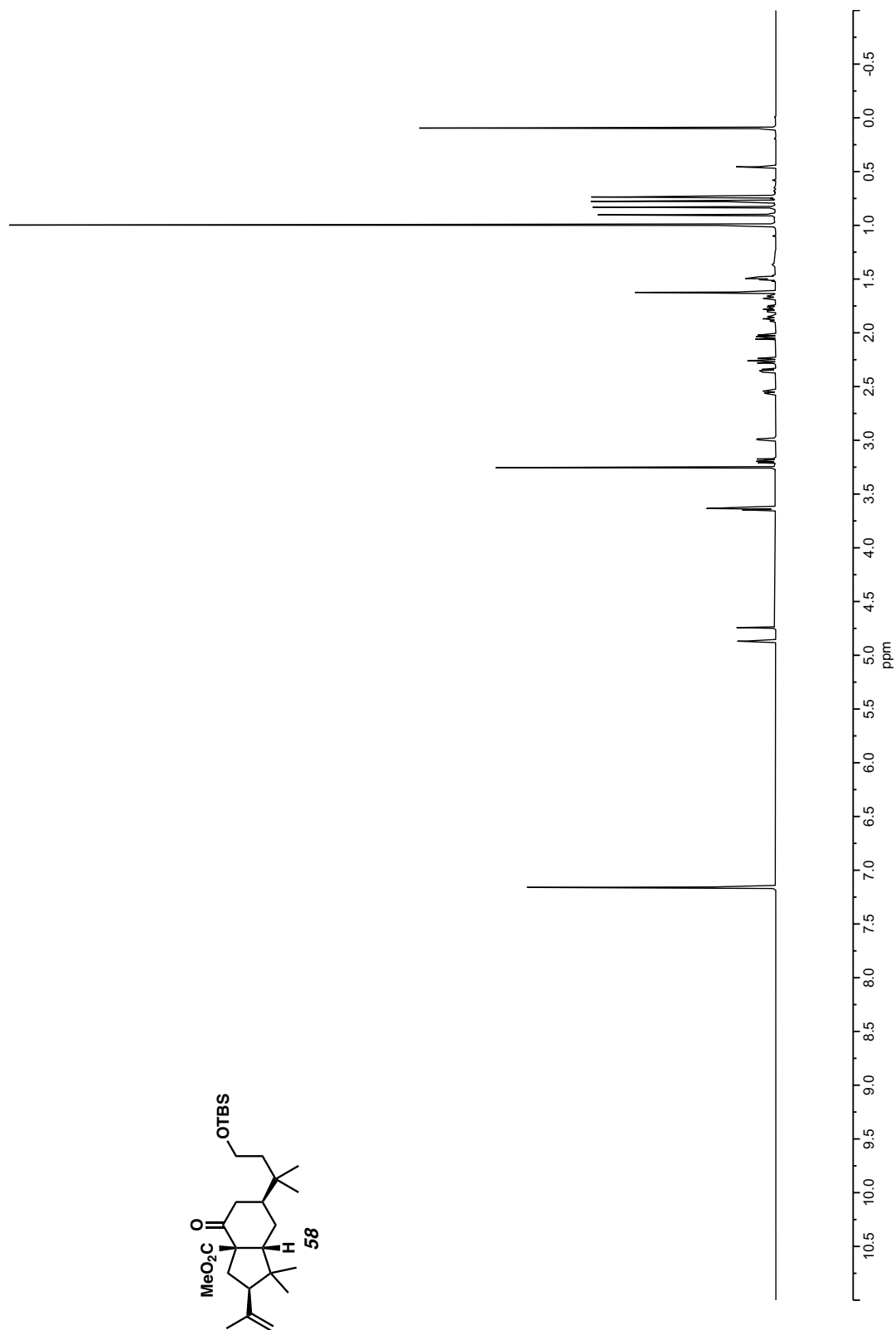


Figure A4.31 ^1H NMR (400 MHz, C_6D_6) of compound **58**.

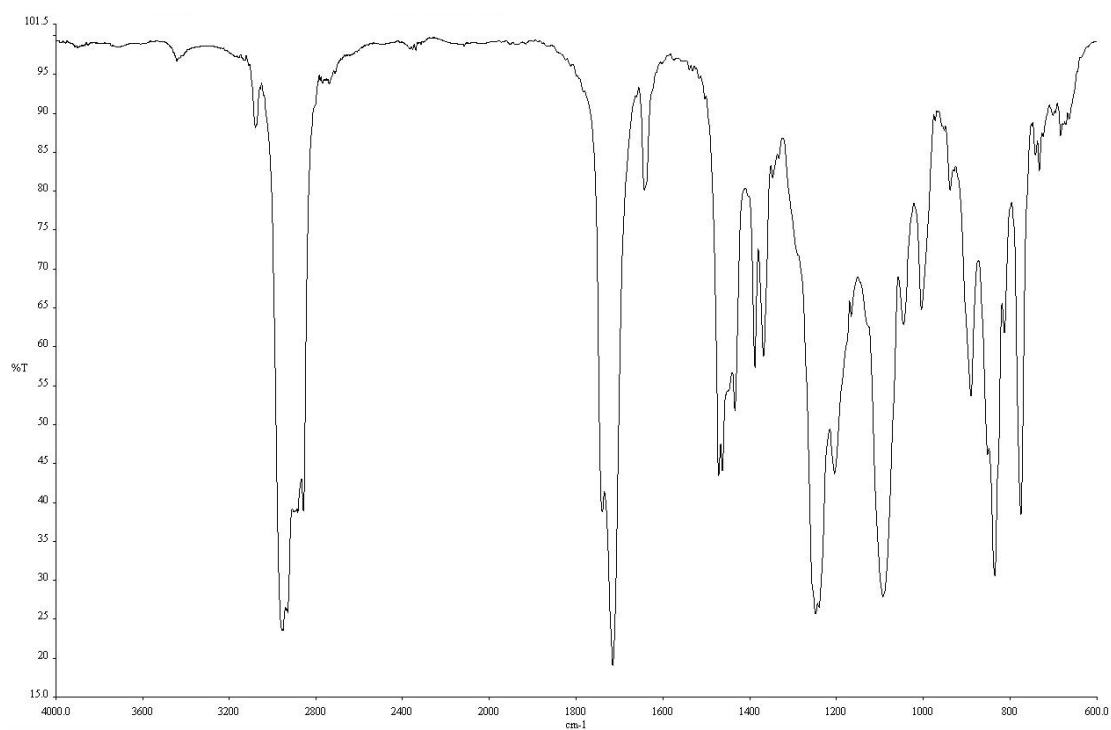


Figure A4.32 Infrared spectrum (Thin Film, NaCl) of compound **58**.

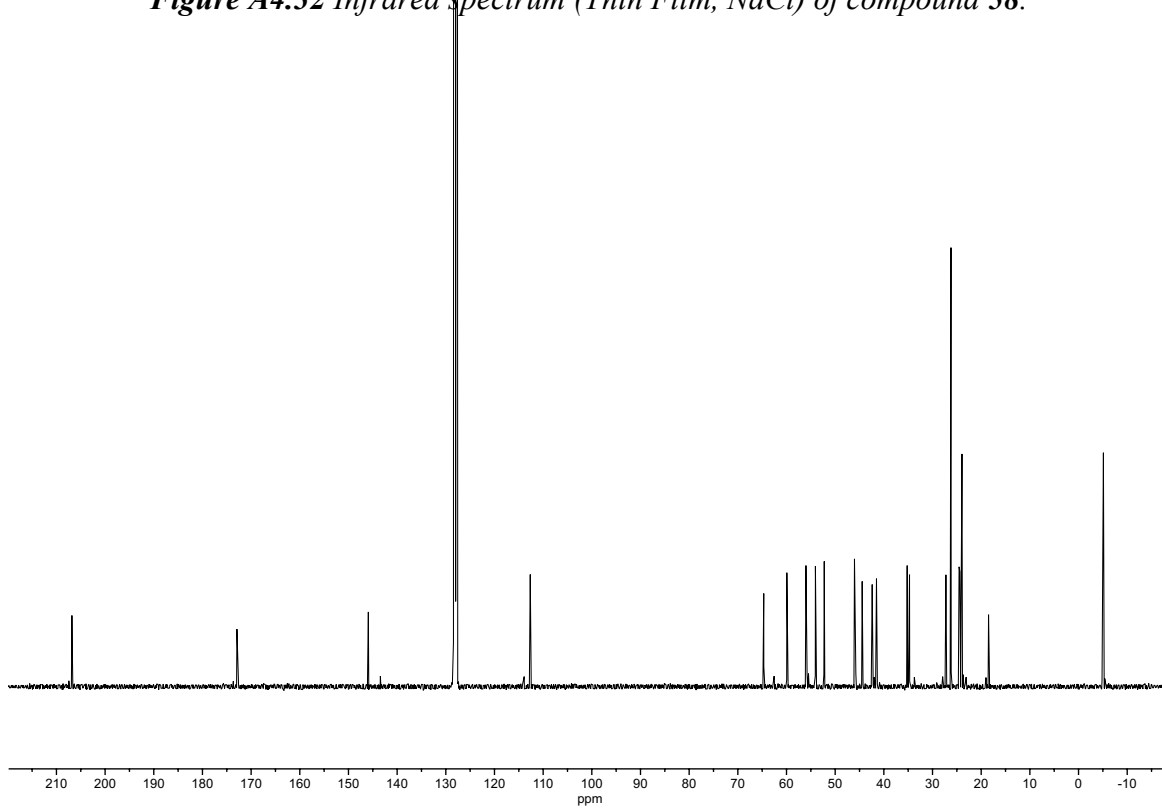


Figure A4.33 ¹³C NMR (100 MHz, C₆D₆) of compound **58**.

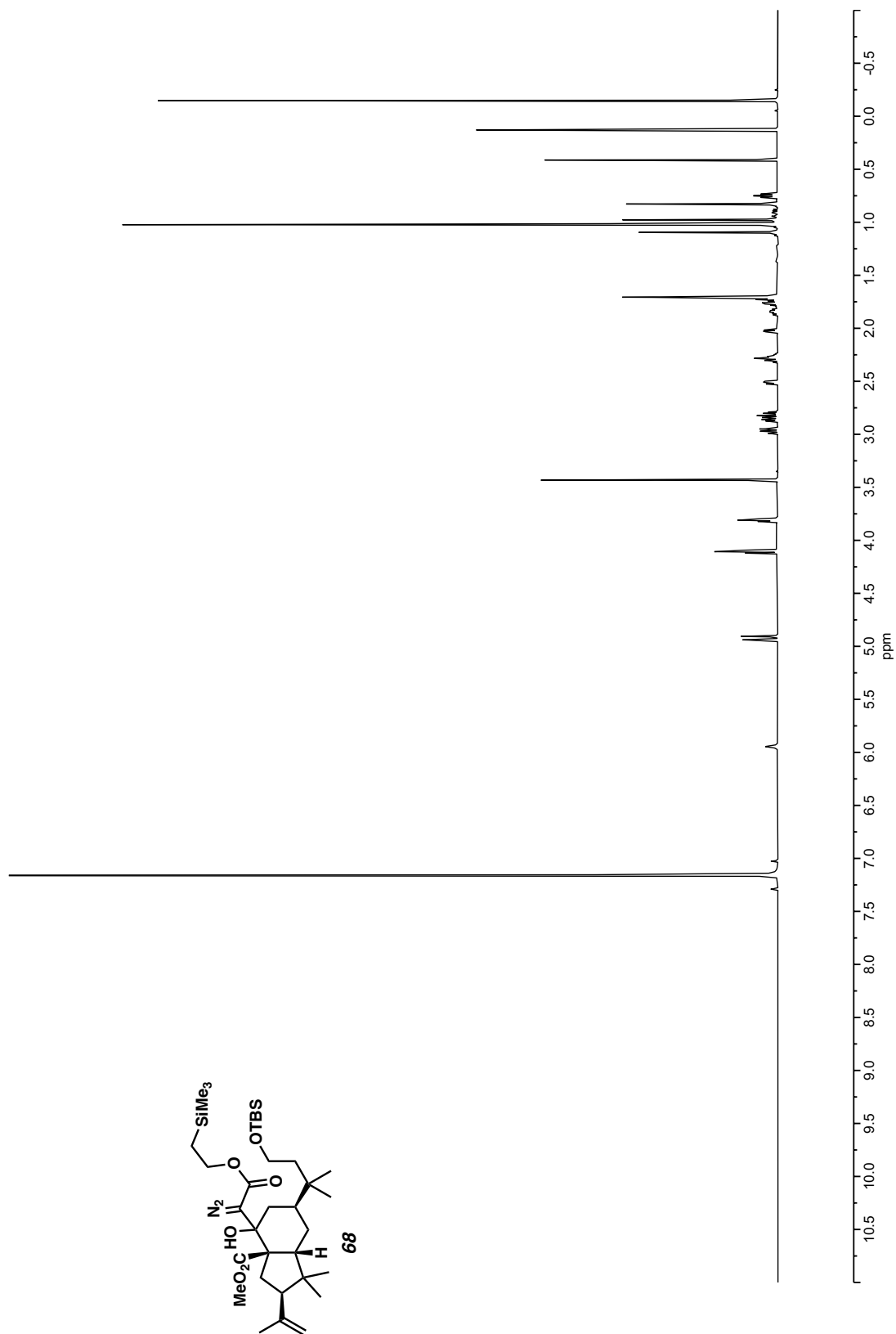


Figure A4.34 ¹H NMR (400 MHz, C₆D₆) of compound **68**.

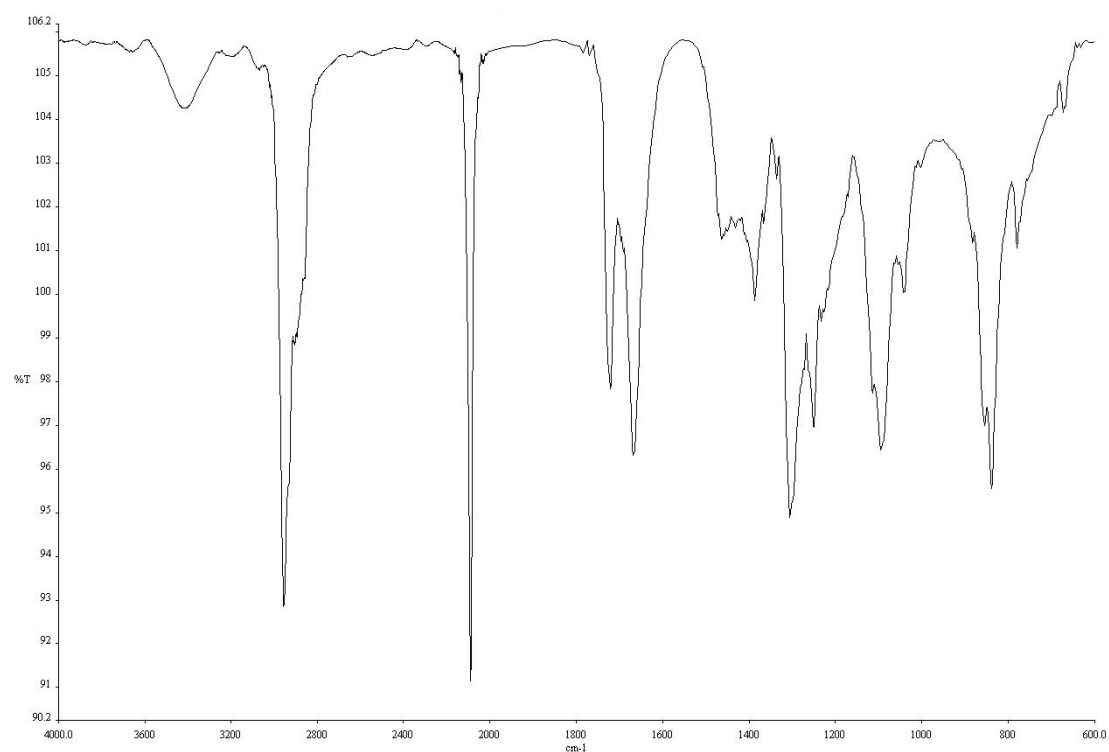


Figure A4.35 Infrared spectrum (Thin Film, NaCl) of compound **68**.

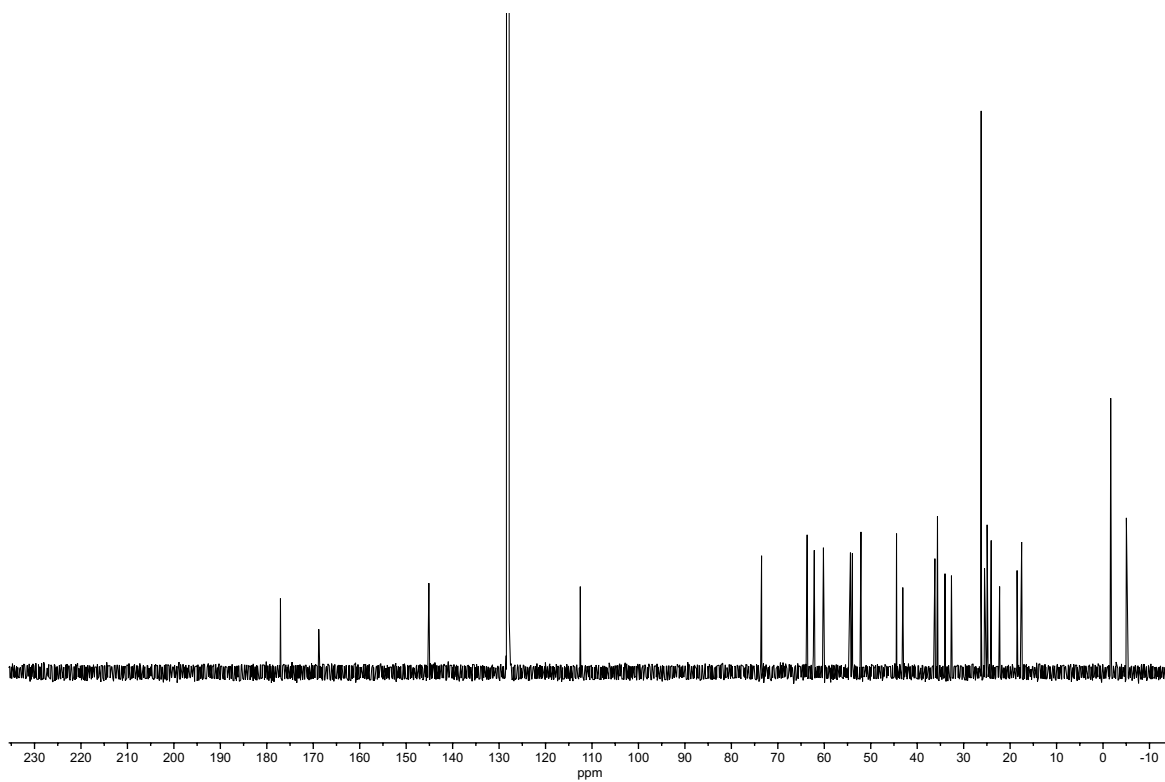


Figure A4.36 ¹³C NMR (100 MHz, C₆D₆) of compound **68**.

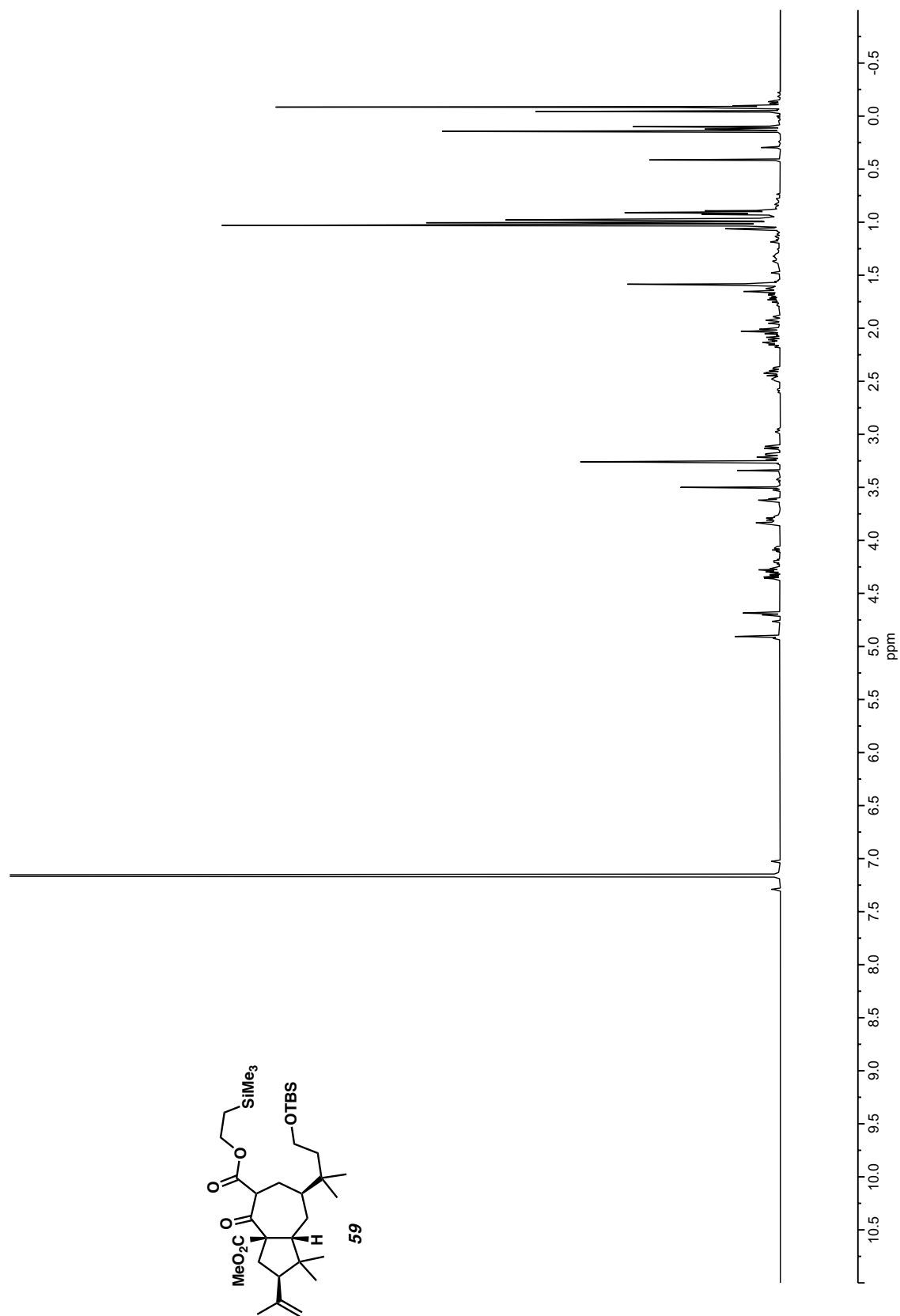


Figure A4.37 ^1H NMR (400 MHz, CDCl_3) of compound **59**.

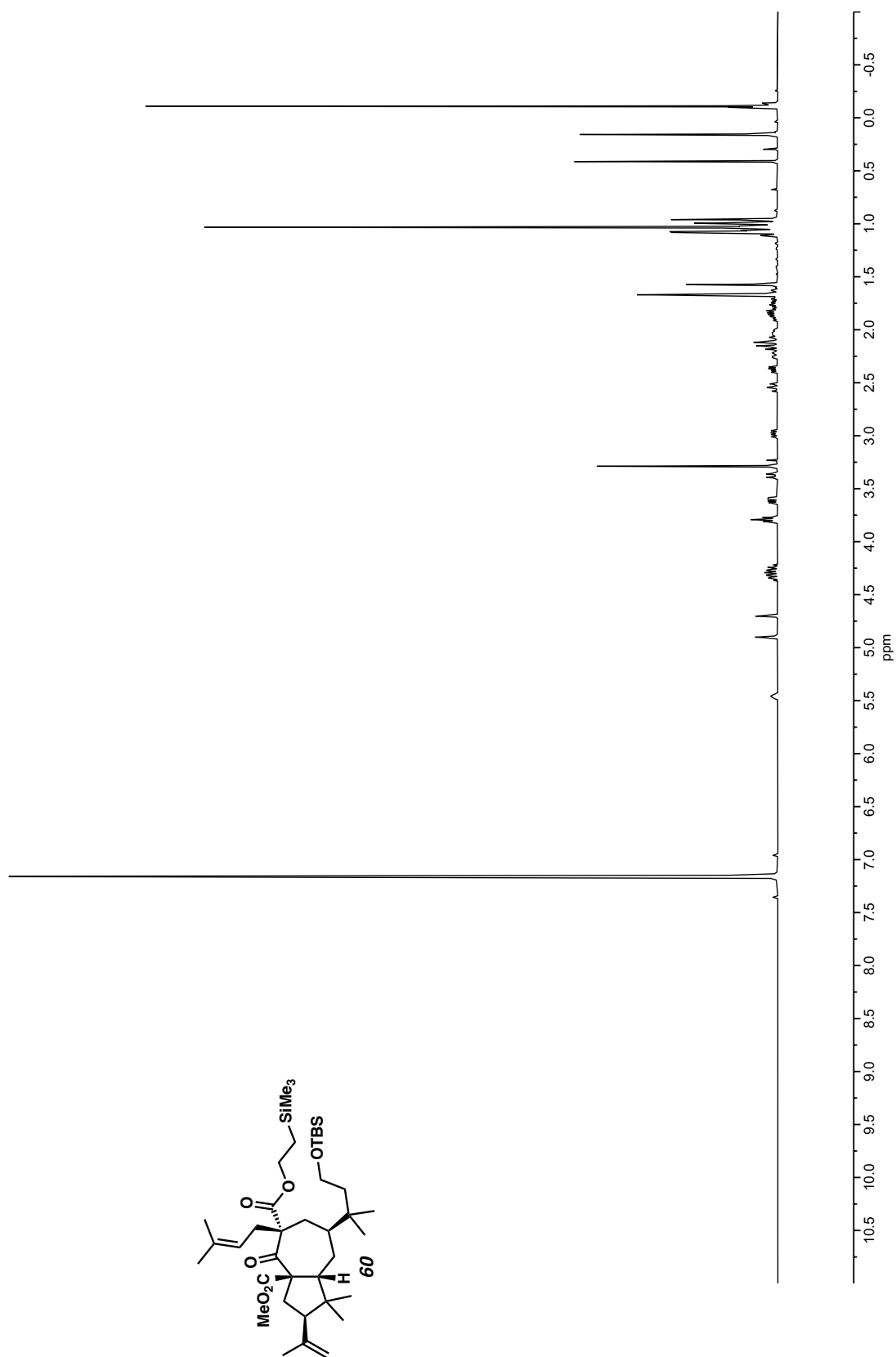


Figure A4.38 ¹H NMR (400 MHz, C₆D₆) of compound **60**.

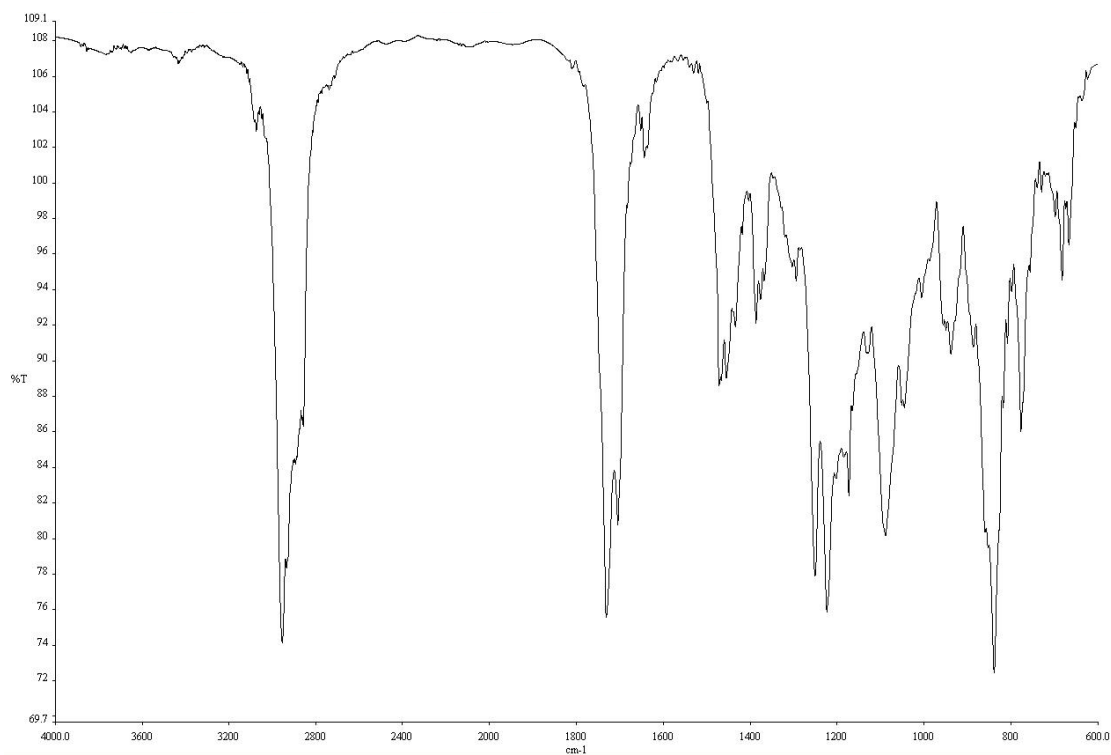


Figure A4.39 Infrared spectrum (Thin Film, NaCl) of compound **60**.

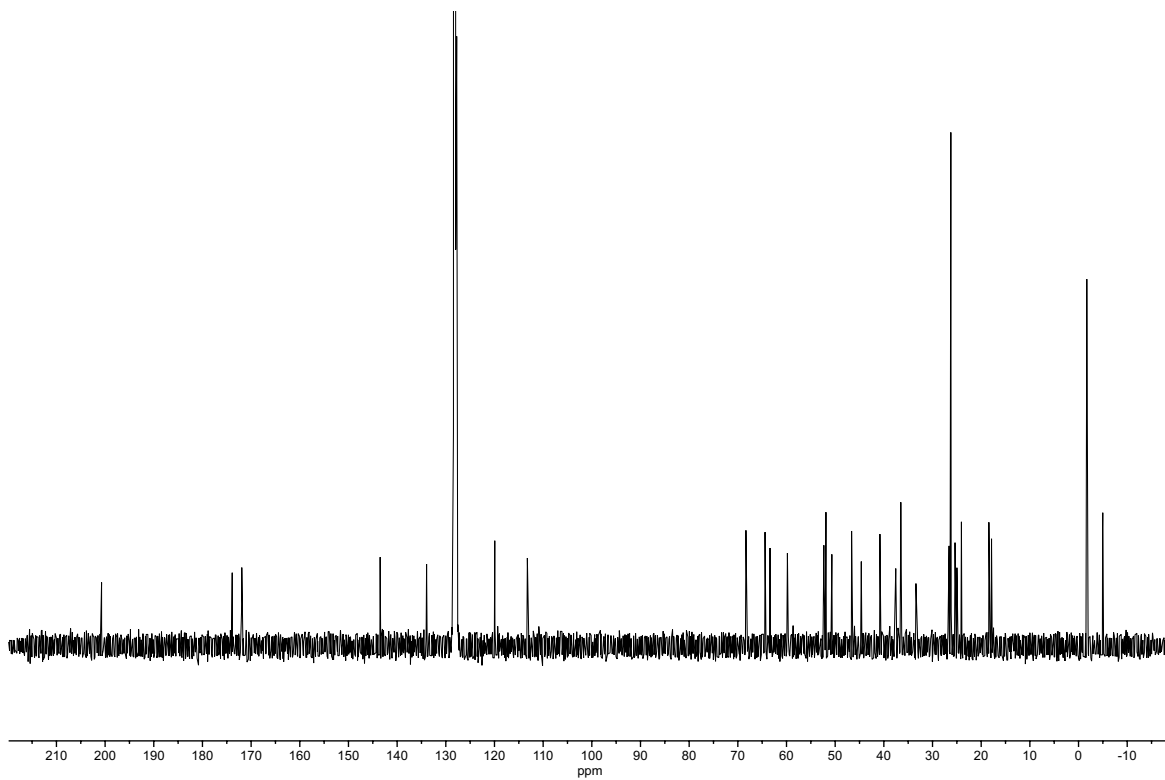


Figure A4.40 ¹³C NMR (100 MHz, C₆D₆) of compound **60**.

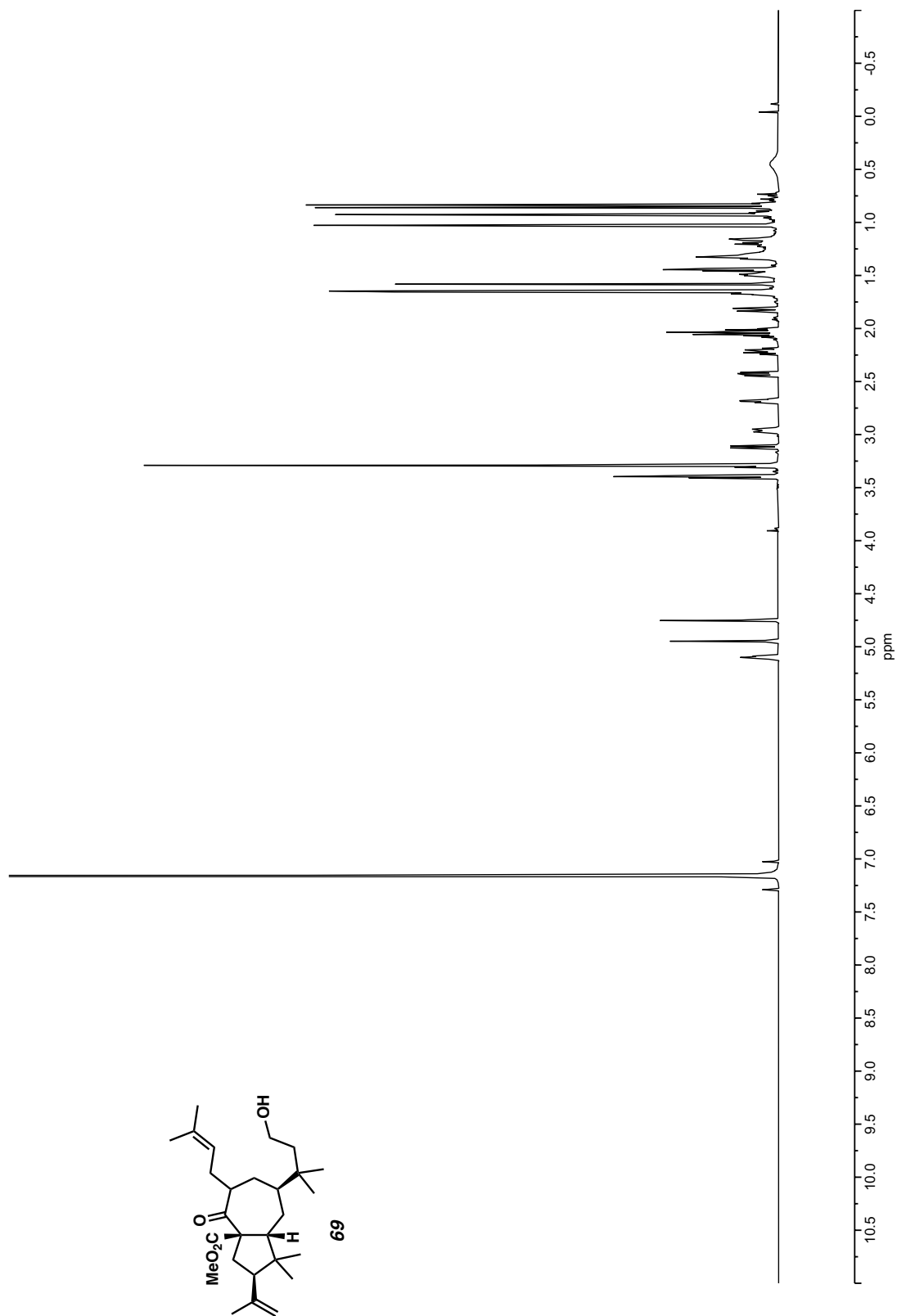


Figure A4.41 ^1H NMR (400 MHz, C_6D_6) of compound **69**.

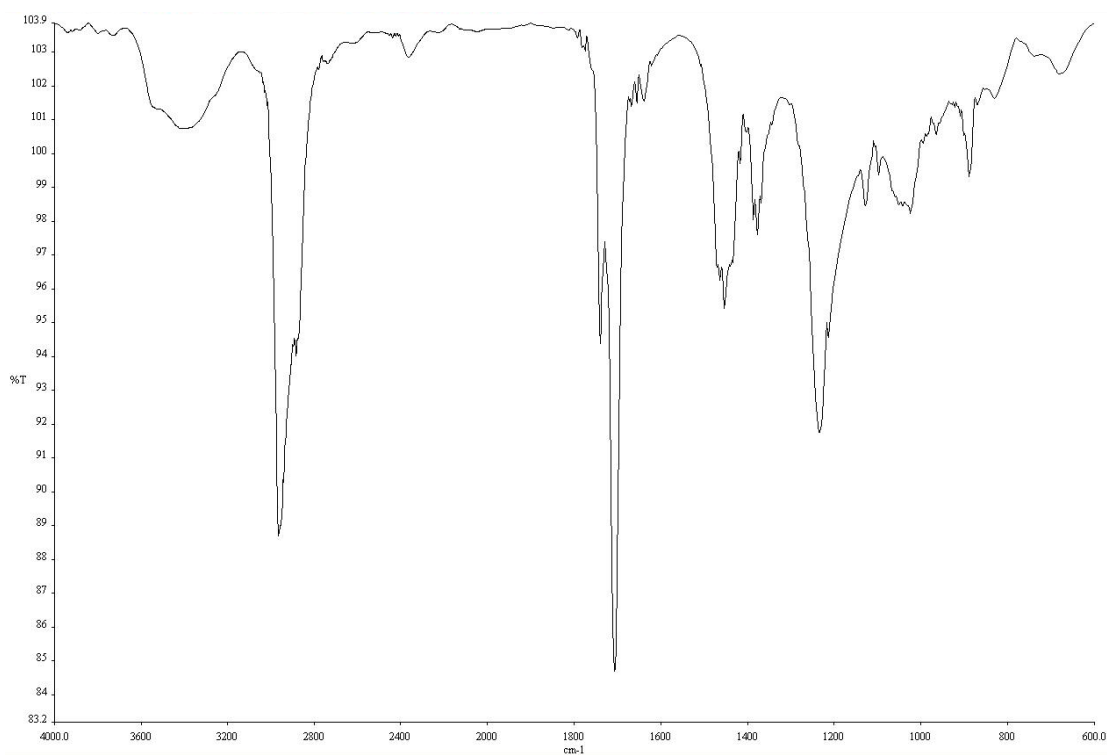


Figure A4.42 Infrared spectrum (Thin Film, NaCl) of compound **69**.

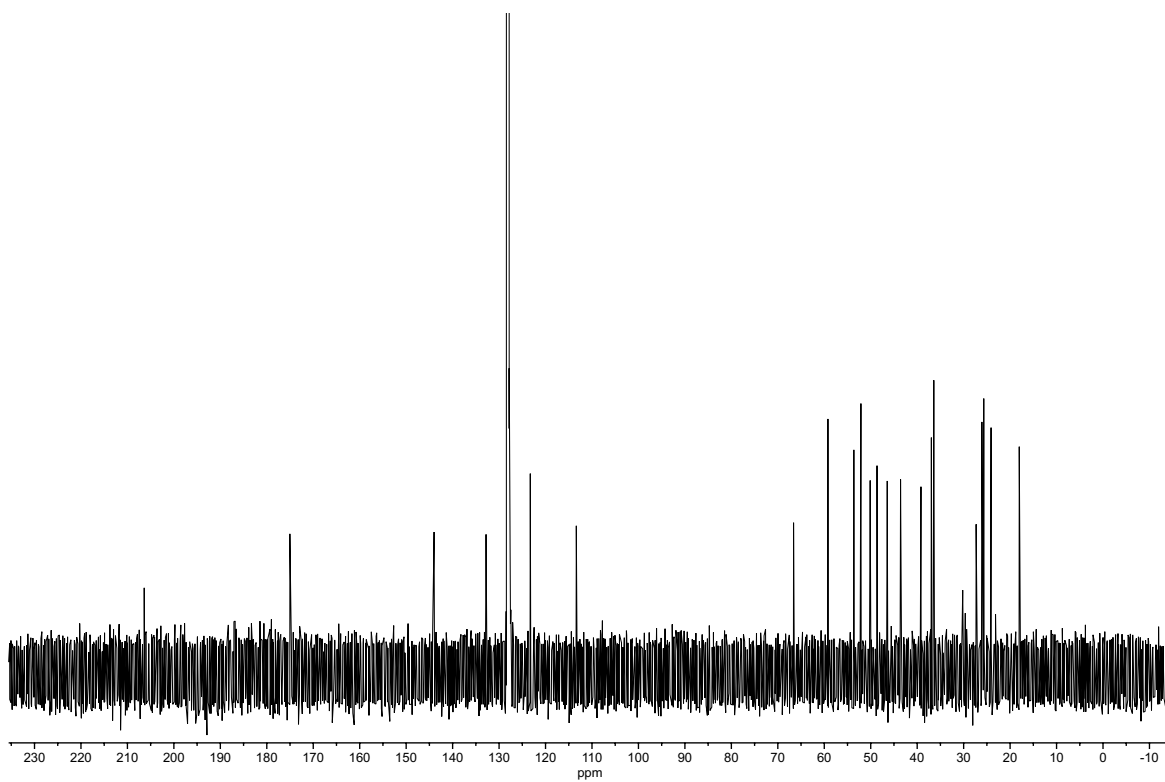


Figure A4.43 ¹³C NMR (100 MHz, C₆D₆) of compound **69**.

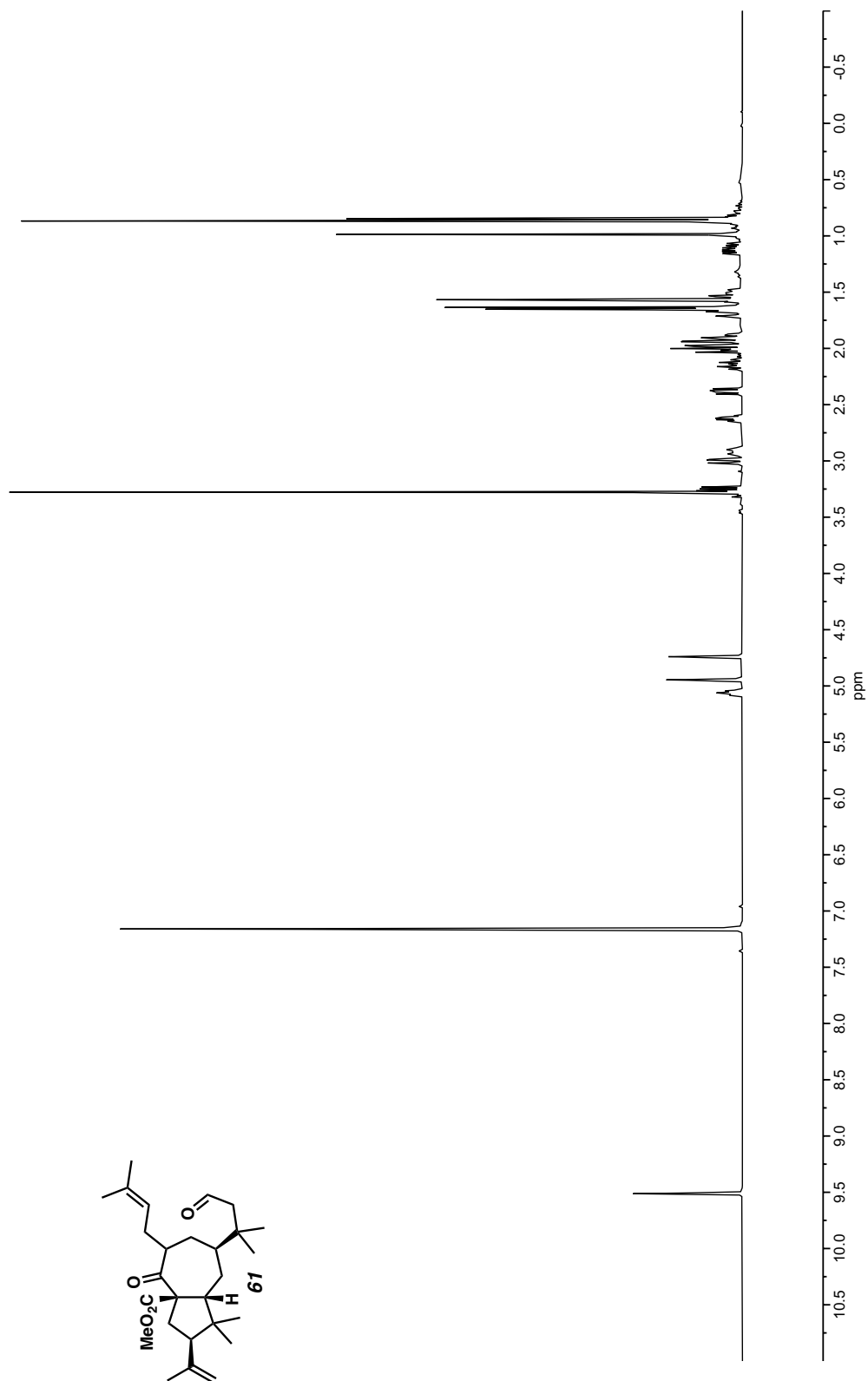


Figure A4.44 ¹H NMR (400 MHz, C₆D₆) of compound **61**.

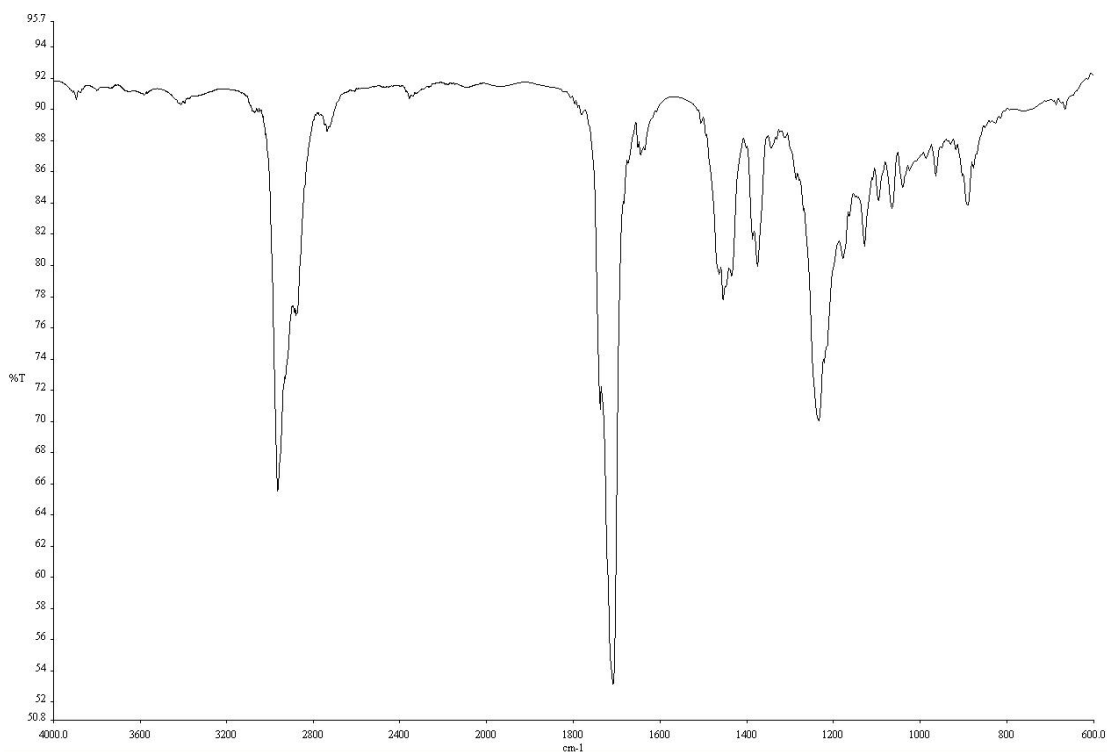


Figure A4.45 Infrared spectrum (Thin Film, NaCl) of compound **61**.

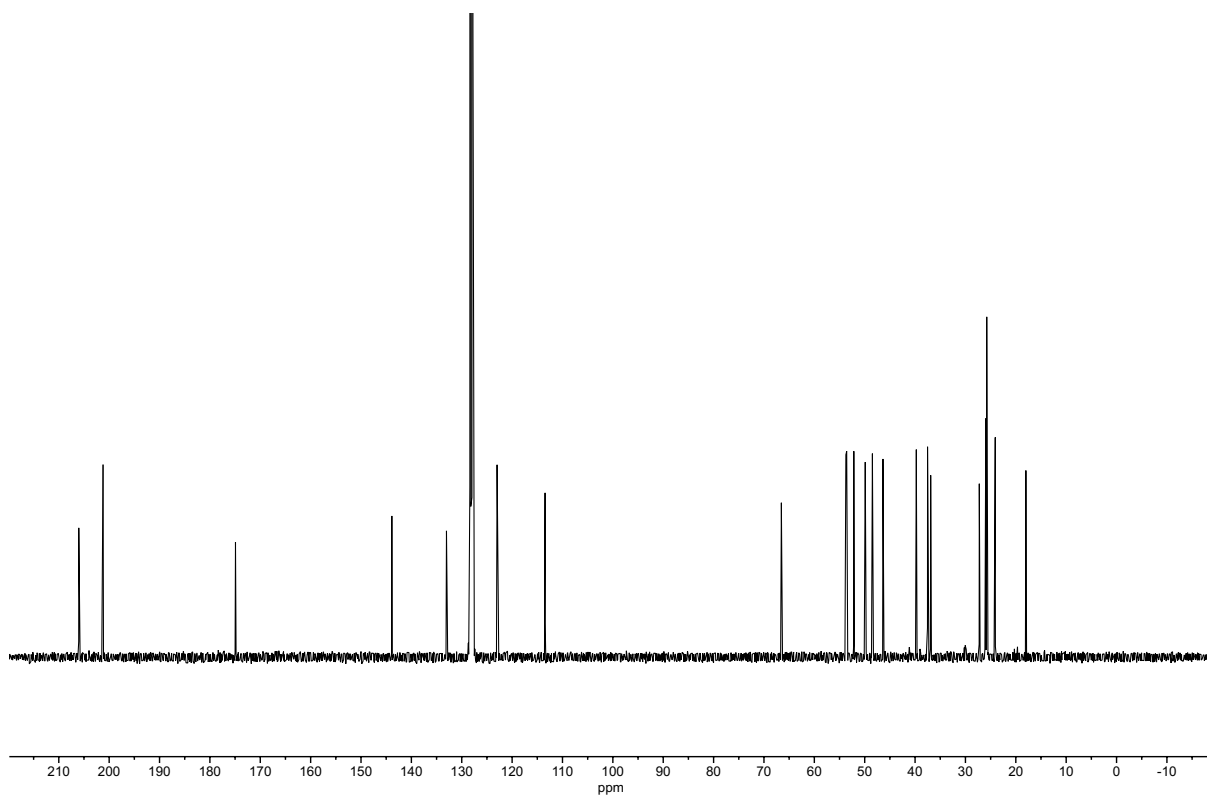


Figure A4.46 ¹³C NMR (100 MHz, C₆D₆) of compound **61**.

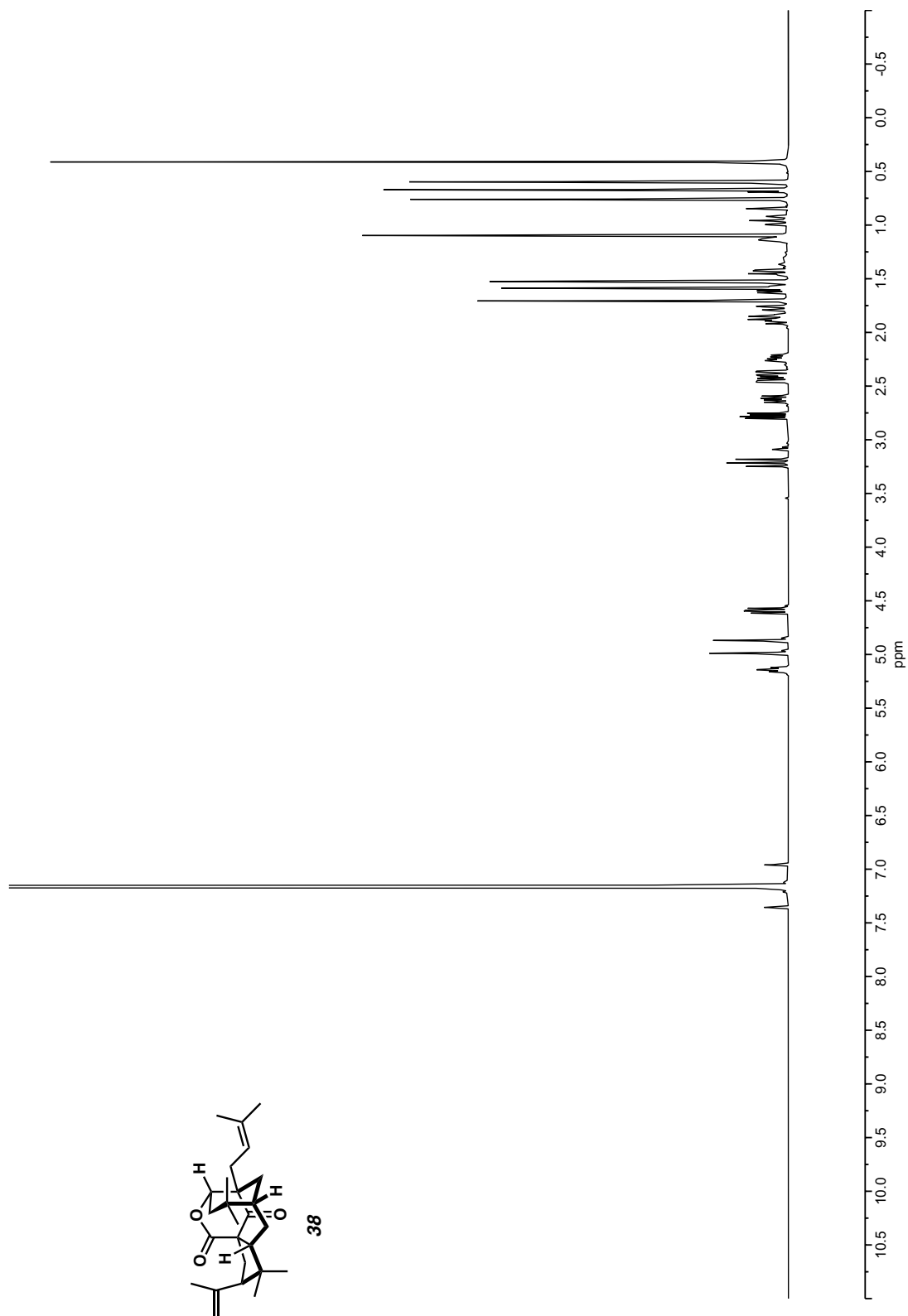


Figure A4.47 ^1H NMR (400 MHz, CDCl_3) of compound **38**.

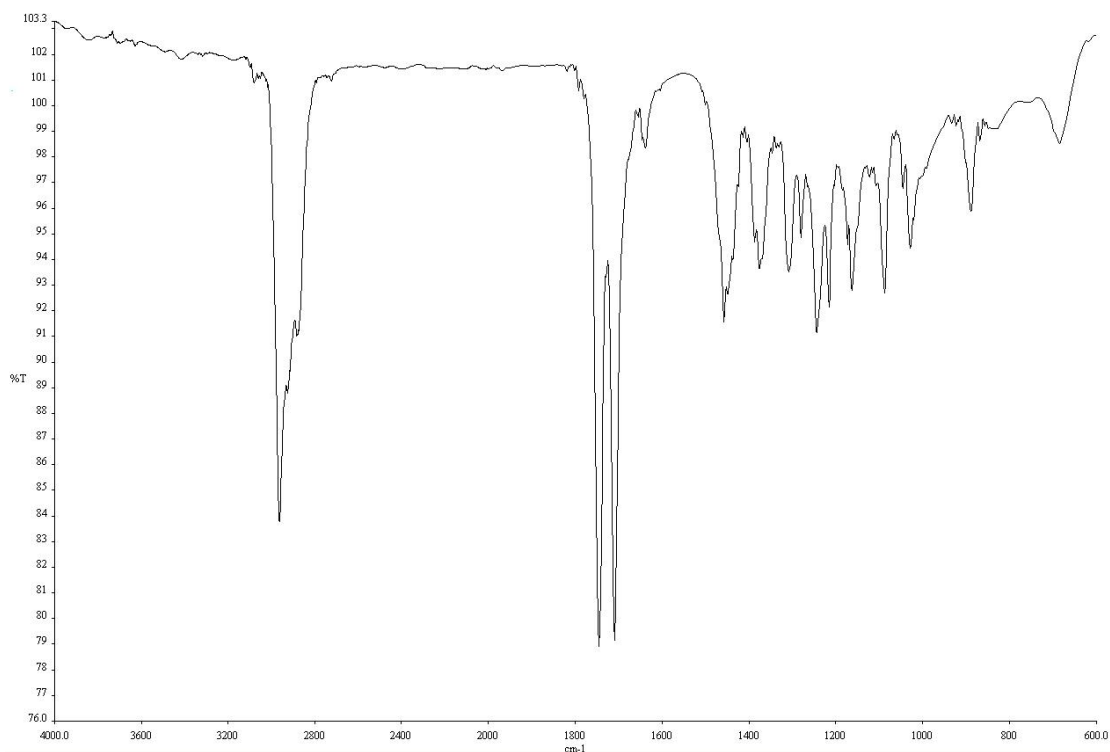


Figure A4.48 Infrared spectrum (Thin Film, NaCl) of compound **38**.

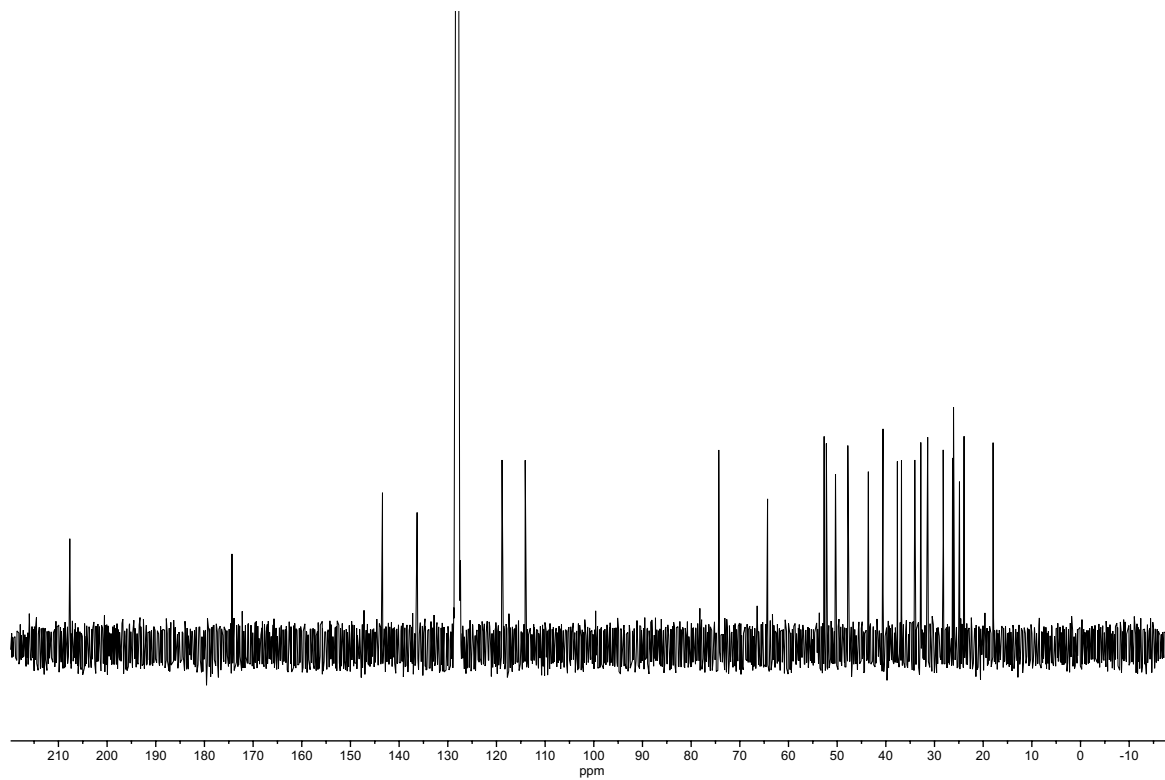


Figure A4.49 ¹³C NMR (100 MHz, C₆D₆) of compound **38**.

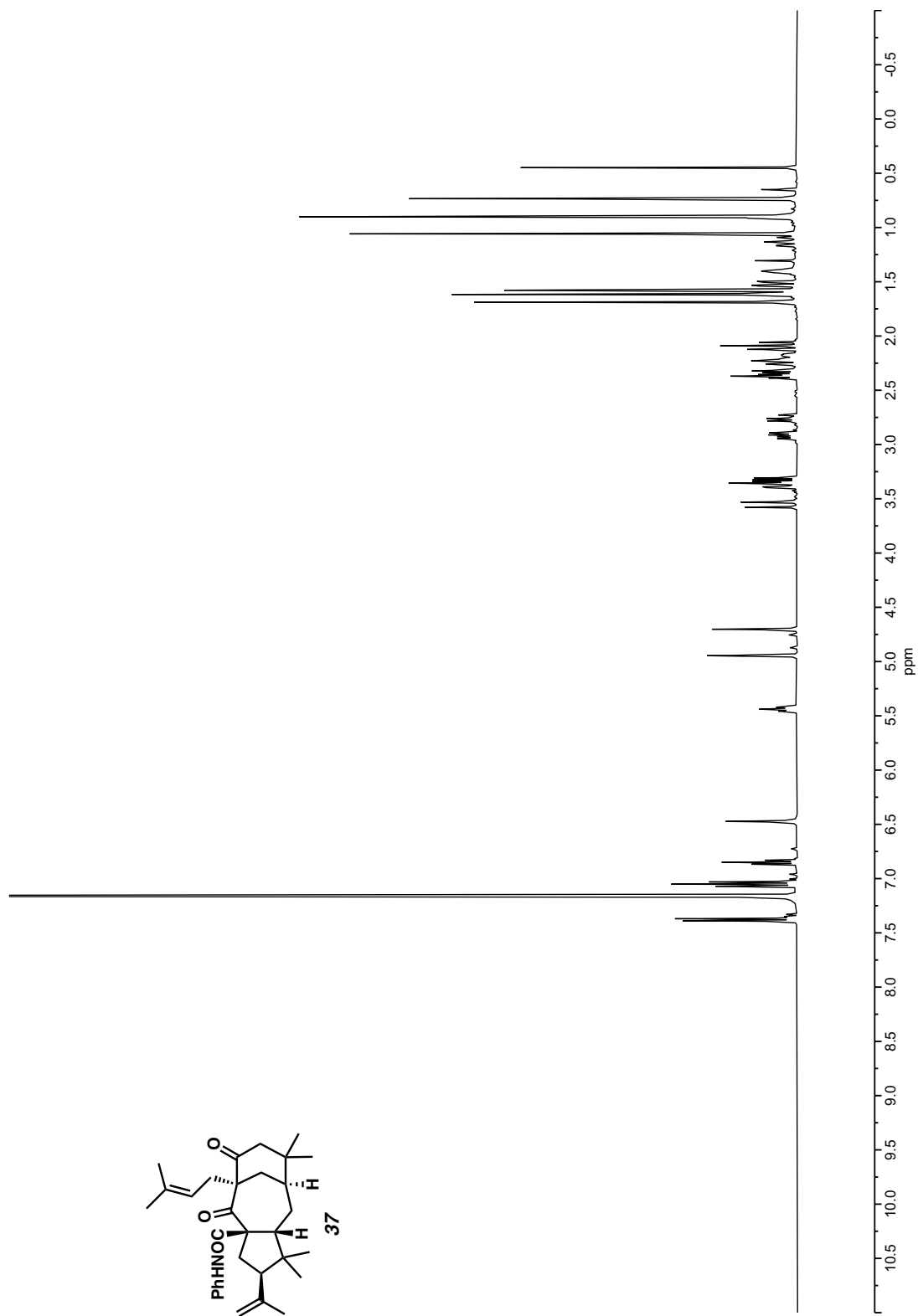


Figure A4.50 ¹H NMR (400 MHz, C₆D₆) of compound **37**.

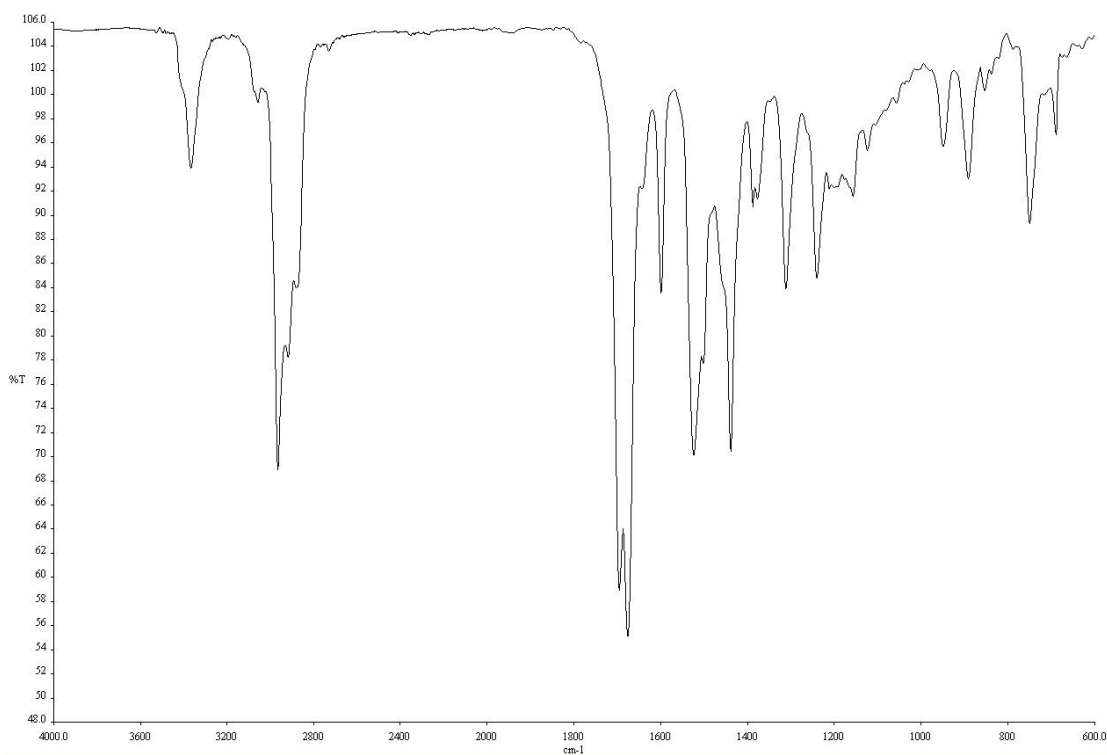


Figure A4.51 Infrared spectrum (Thin Film, NaCl) of compound 37.

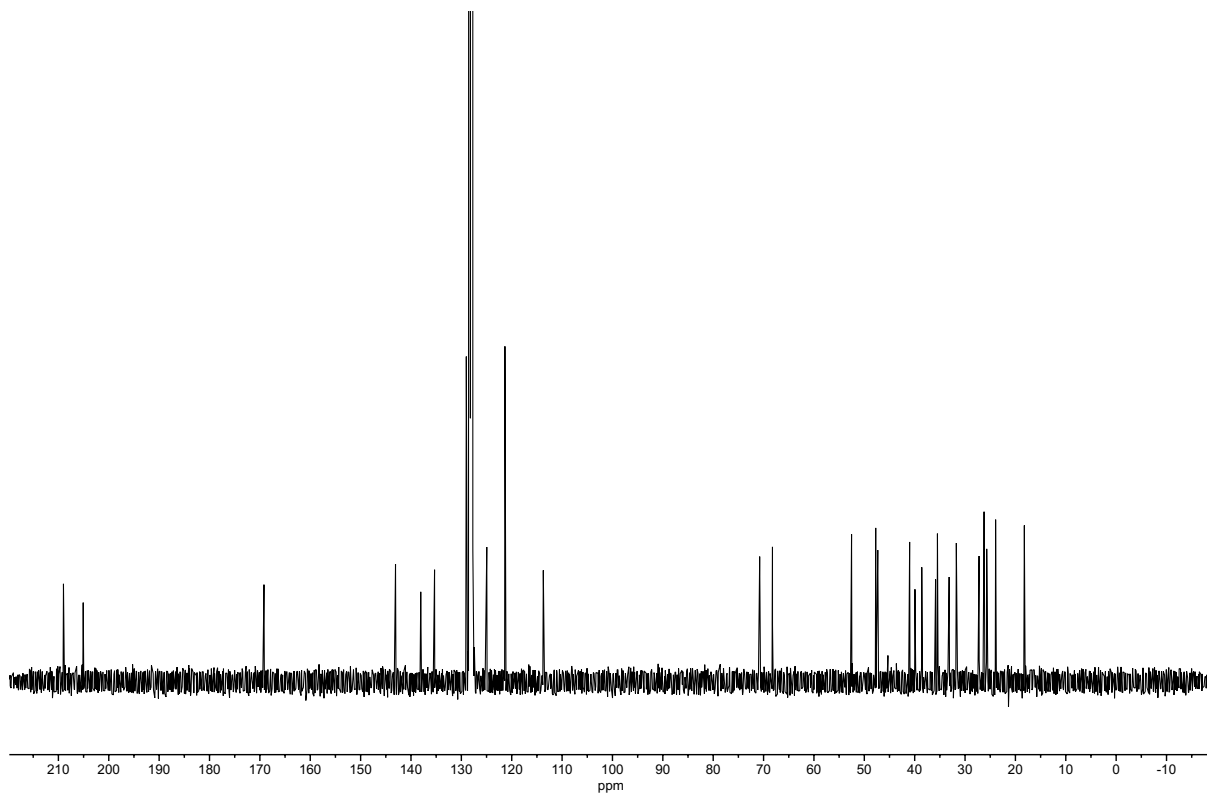


Figure A4.52 ¹³C NMR (100 MHz, C₆D₆) of compound 37.

APPENDIX 5

Early Strategies Toward the Synthesis of Homoadamantane PPAPs

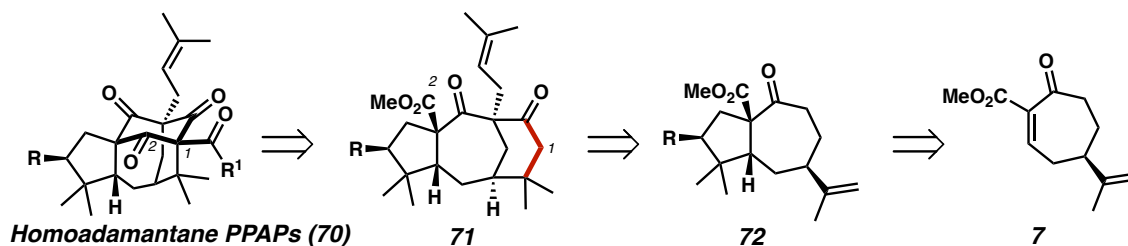
A5.1 INTRODUCTION

Over the course of our synthetic studies toward hypersampson M, wilsonglucinol G, and hypersonin A, several strategies were pursued and abandoned as new data came to light. These early strategies, as well as the model studies and optimizations that eventually led to the route in Chapters 1 and 2, are reported in this appendix.

A5.2 CHIRAL POOL EFFORTS STARTING FROM LIMONENE

Our initial approach to the homoadamantane PPAPs (**70**, Scheme A5.2.1) involved the same early disconnections to tricycle **71**. From there, we imagined opening the eastern 6-membered ring and removing the prenyl group in a fashion analogous to that in Chapters 1 and 2, resulting in hydrazulene **72**.

Scheme A5.2.1. Limonene-based approach toward the homoadamantane PPAPs.

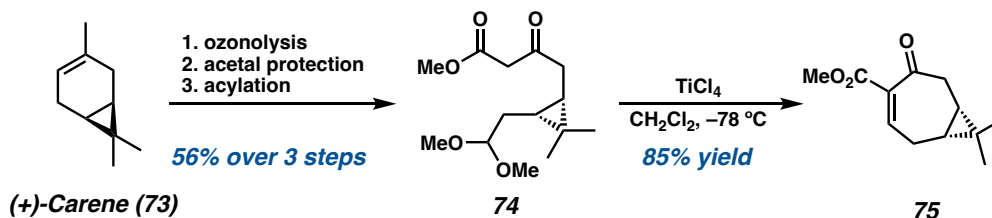


The key distinction is that hydrazulene **72** would be accessed via cyclopentene annulation of cycloheptenone **7**, derived from the chiral pool (limonene). This also means that the two carbons in the eastern ring (**71**, highlighted in red) would be installed after the cyclopentene annulation, through functionalization of the isopropenyl group in hydrazulene **72**.

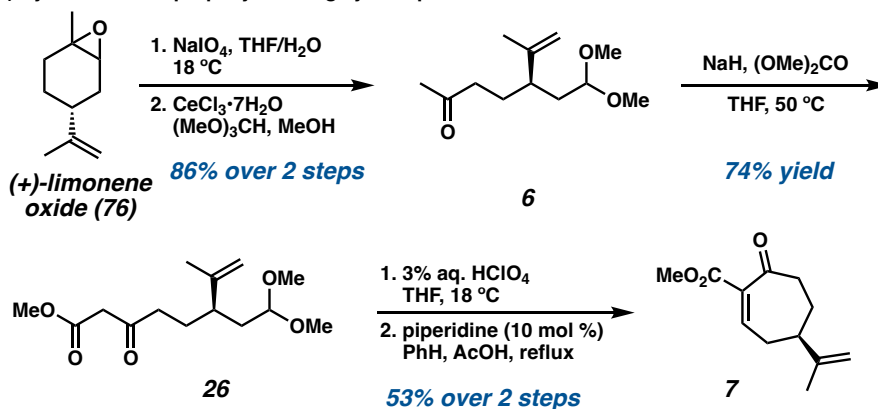
We started by developing a route toward cycloheptenone **7**, taking inspiration from Yang's approach to ester **75** (Scheme A5.2.2A),¹ involving oxidative cleavage of (+)-Carene (**73**), followed by acetal protection and acylation to afford β -ketoester **74**. They report that a Lewis acid-mediated cyclization of **74** directly resulted in cycloheptenone **75**. Starting from (+)-limonene oxide (**76**, Scheme A5.2.2B), we followed a procedure by Renaud and coworkers who demonstrated its oxidative cleavage and protection to form acetal **6**.²

Scheme A5.2.2. Synthesis of isopropenyl-flanked cycloheptenone 7.

A) Previously reported route to cyclopropyl-bearing 75. (Yang, 2020)



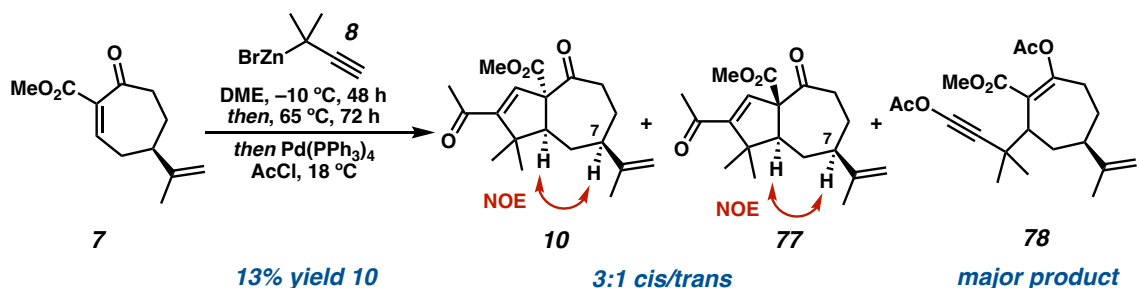
B) Synthesis of isopropenyl-bearing cycloheptenone 7.



This was followed by acetylation to afford β -ketoester **26**. Unfortunately, direct cyclization with TiCl_4 did not result in the formation of the desired ester **7**. Instead, a two-step procedure involving deprotection of acetal **26** followed by a Knoevenagel condensation successfully provided ester **7**.

We subjected this substrate (**7**) to an early version of our cyclopentene annulation conditions but were met with multiple complications (Scheme A5.2.3). First, a significantly decreased yield was observed, with diacetylated **78** being the major product. We believe that the introduction of the isopropenyl group may have congested the system, resulting in a decreased aptitude for cyclization. Second, a diminished 3:1 *cis* to *trans* ratio (**10** and **77**) was isolated, a noticeable reduction from the 6:1 ratio isolated in the model system (See Table 2.3.1). Finally, both diastereomers were isolated as the undesired *syn*-addition product in relation to the isopropenyl group. This surprising outcome prevented us from advancing through our intended route. After some consideration, we reasoned that oxidative cleavage of the isopropenyl group in hydrazulene **10** would provide an epimerizable site at C7 that could be used to attain the correct diastereomer required for the synthesis.

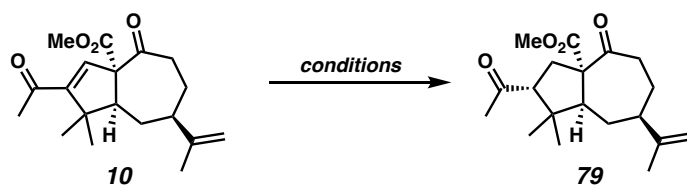
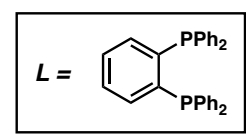
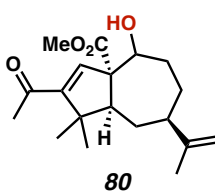
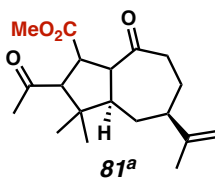
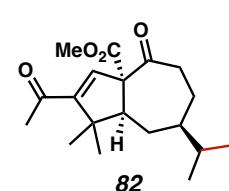
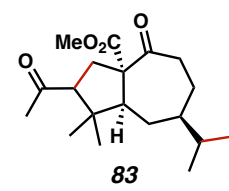
Scheme A5.2.3. Unsuccessful cyclopentene annulation of ester **7**.



Before oxidative cleavage, we needed to reduce and methylate the enone olefin (**10**) and realized this may be a good opportunity to investigate the conjugate reduction and

selective methylation. We were dismayed to see that a variety of 1,4-selective reduction conditions were unsuccessful on our system: L-selectride resulted in a complex mixture while Cu-hydride reductants instead reduced the cycloheptanone carbonyl to give alcohol **80** (Table A5.2.1).^{3,4,5} Interestingly using Birch conditions did result in the reduction of the enone olefin, however this was accompanied by migration of the methyl ester to afford hydrazulene **81**. More exotic reducing conditions involving Si⁶

Table A5.2.1. Attempts to reduce the enone olefin in hydrazulene **10**.

			
conditions	outcome	conditions	outcome
L-selectride THF, -78 °C, 1 h	complex mixture	PPh ₃ O, SiCl ₃ H CH ₂ Cl ₂ , 18 °C, 2h – OR – ZnCl ₂ , Pd(PPh ₃) ₄ Bu ₃ SnH, THF, 18 °C, 1 h	no reaction
Cu(OAc) ₂ , PMHS, L PhMe, <i>t</i> -BuOH, 18 °C, 12 h – OR – CuI, MeLi, HMPA, DIBAL THF, -45 °C, 3h		Pd/C or Rh/C or Pt/C EtOAc, H ₂ (10 bar), 48 h	complex mixture
Li ⁰ , <i>t</i> -BuOH, NH ₃ Et ₂ O, -78 °C, 30 min		Raney Ni THF, 18 °C, 5 h	
		Rh/alumina, EtOAc H ₂ (10 bar), 48 h	

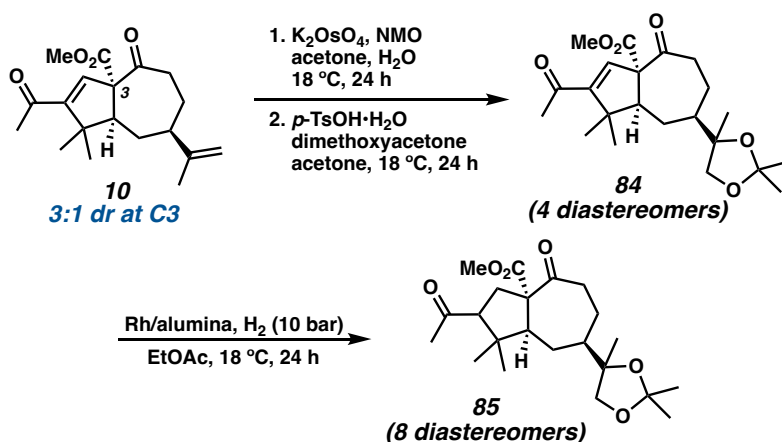
^a isolated as a mixture of diastereomers

or Sn⁷ did not have any effect on our system. This string of failures led us to focus on heterogenous hydrogenation catalysts. We found that Pd, Pt, or Rh on C gave complex mixtures, and Raney Nickel⁸ selectively reduced the isopropenyl group to afford enone **82**.

We were happy to see that Rh/alumina resulted in smooth reduction of the enone and isopropenyl group, allowing us to isolate dione **83**.

Since we intended to oxidatively cleave the isopropenyl group eventually, it was decided to preemptively dihydroxylate and protect this olefin as the acetonide (**84**, Scheme A5.2.4). This allowed us to selectively reduce the enone olefin using Rh/alumina to afford dione **85**. These steps were high yielding, however, what was two diastereomers after the cyclopentene annulation became eight following reduction. Some of these diastereomers are inconsequential, however due to the challenges involved in trying to isolate and characterize anything at this stage, it was decided to reevaluate the current route.

Scheme A5.2.4. Selective reduction of the enone in hydrazulene **10**.

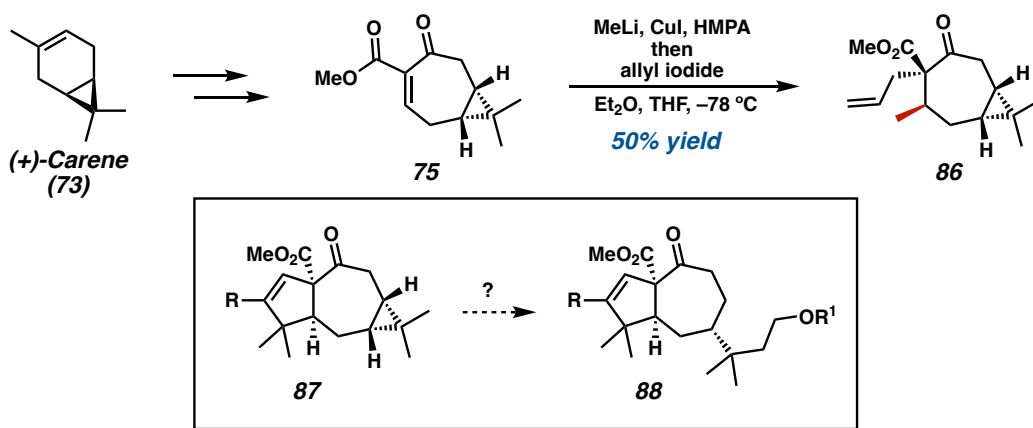


A5.3 CHIRAL POOL EFFORTS STARTING FROM (+)-CARENE

Initially, we had made the assumption that the cyclopentene annulation would occur *anti* to the isopropenyl group, both based on our intuition of analogous 6-membered systems, as well as a recent report by Yang and coworkers.¹ In their report, unsaturated β -ketoester **75** (Scheme A5.3.1) was treated with cuprate reagents which resulted in isolation of the *anti*-addition product **86**. While it is true that the dimethylcyclopropyl group is

significantly more rigid than an isopropenyl group, we were initially hesitant to use the cyclopropyl appended ester **75** for two reasons. First, it is derived from (+)-carene (**73**) which exists naturally only as a single enantiomer, meaning we would need to target the *ent*-PPAPs. Second, even if we could get the cyclopentene annulation to proceed as desired and isolate hydrazulene **87**, we would have no way of functionalizing the cyclopropane in a useful fashion. There are a multitude of cyclopropane fragmentation conditions in the literature,^{9,10} but many rely on strong acids, or simply do not provide us with a handle (**88**) that we could advance to the PPAPs. It was thus decided to invest time in studying this type of β,γ -cyclopropyl ketone fragmentation so that we could use the bulkier ketoester **75** in our synthesis. The results of this fragmentation study are presented in Chapter 3.

Scheme A5.3.1. Yang's anti-addition into ester **75**.

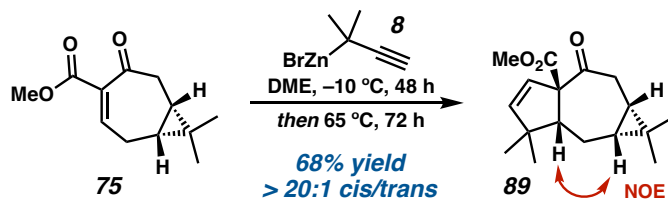


Ester **75** was prepared as outlined previously by Yang and coworkers, providing access to several grams of material.¹ Ester **75** was subjected to the first two steps of the cyclopentene annulation resulting in the formation of a single diastereomer of hydrazulene **89** (Scheme A5.3.2A). Unfortunately, this diastereomer (**89**) was the undesired *syn*-addition product (*cis*-fused) once again, indicating that a more rigid backbone does not seem to affect the stereochemical outcome in this case. We reasoned that the Yang group's

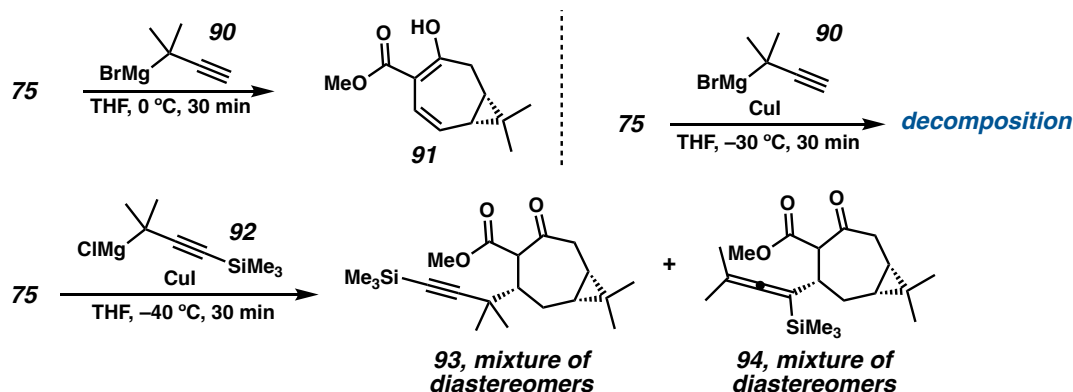
use of Cu nucleophiles may instead have been the deciding factor, prompting us to test different propargylic nucleophiles. Using a propargyl Mg nucleophile (**90**, Scheme A5.3.2B) resulted in quantitative, irreversible deprotonation of ester **75** to the enol tautomer (**91**)—this is not entirely surprising given the basicity of Mg reagents. Attempting to make a propargyl cuprate delivered a complex mixture, likely due to the interaction of the Cu with the terminal alkyne.¹¹ A protected alkyne (**92**) was used instead, delivering the expected conjugate addition products. We isolated a mixture of four isomers, two propargylic (**93**) and two allene (**94**) products, each as two diastereomers at the methyl ester. However, all four compounds were isolated as the *syn*-addition products with respect to the cyclopropyl ring.

Scheme A5.3.2. Cyclopentene annulation and other nucleophilic additions to **75**.

A) Cyclopentene annulation of ester **75**.



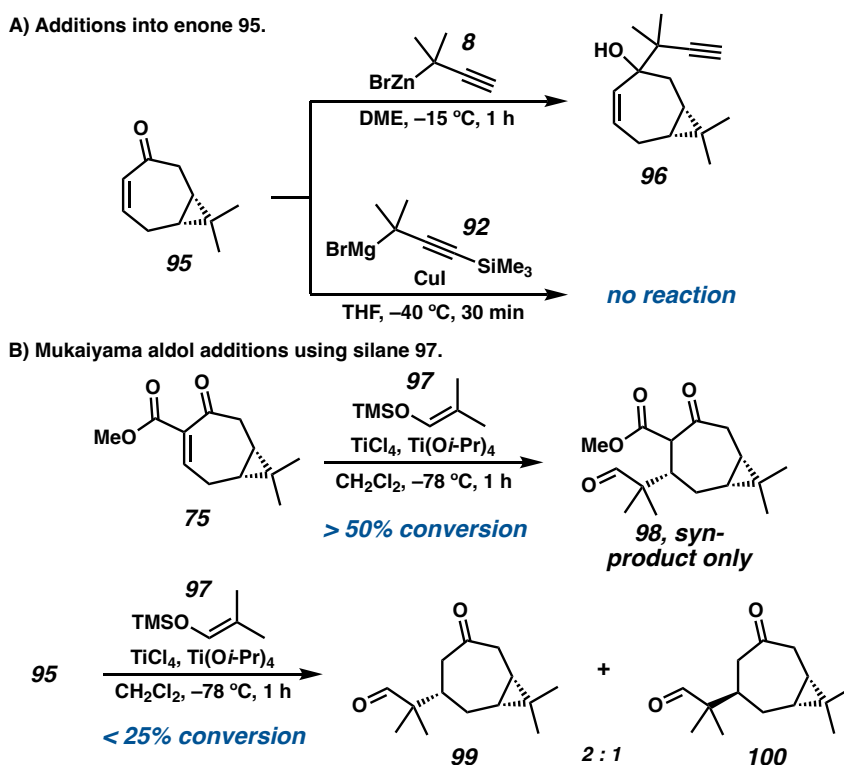
B) Alternative dimethyl-propargyl nucleophiles.



In an attempt to drastically change the substrate, we elected to use cycloheptenone **95** (Scheme A5.3.3A), previously reported by Wood and coworkers.¹² The lack of the

methyl ester prevents chelation via a bidentate interaction, possibly affecting the transition state during addition, and thus, the subsequent stereochemical outcome. However, without the highly activated dicarbonyl, propargyl zinc **8** undergoes the undesired 1,2-addition affording tertiary alcohol **96** cleanly. Using the Cu reagent **92** instead led to no reaction.

Scheme A5.3.3. Additions involving cycloheptenone **95** and **75**.

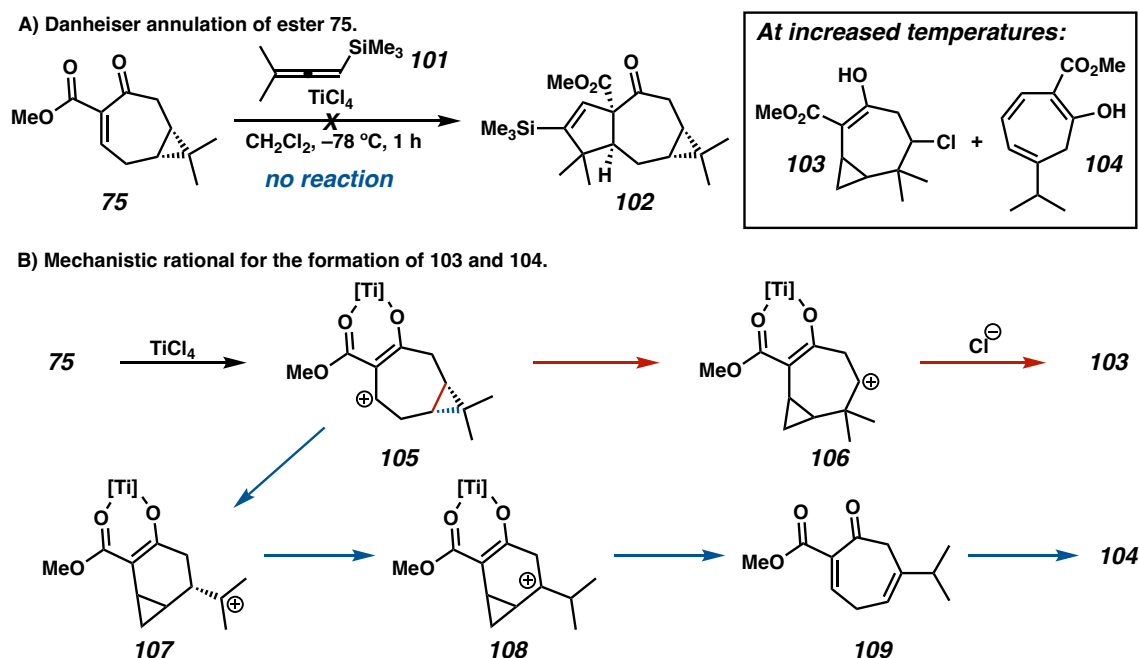


Several Mukaiyama Michael additions were attempted next (Scheme A5.3.3B).¹³ Using vinyloxysilane **97**, we were able to effect the desired transformation with ester **75** to afford aldol product **98**, isolated exclusively as the *syn*-product. Using heptanone **95** instead led to a mixture of the undesired *syn*-aldehyde (**99**) and the desired *anti*-aldehyde (**100**). This reaction has been the only example thus far that has provided any *anti*-addition product from these 7-membered systems with bulky carbo-nucleophiles. However, due to

the low yield and poor selectivity, we did not see this result as particularly promising and pressed forward.

A Danheiser annulation¹⁴ was attempted next using ester **75** and allenylsilane **101** (Scheme A5.3.4A), to access hydrazulene **102**. Although the substitution pattern on hydrazulene **102** is not ideal, we nonetheless believed that it would be worth attempting. However, we observed no reaction at decreased temperatures, and a mixture of chloride **103** and cycloheptatriene **104** at elevated temperatures. Mechanistically, we propose that coordination of ester **75** to TiCl_4 could generate a strong positive charge at the beta position (**105**, Scheme A5.3.4B). This could then fragment the neighboring cyclopropane *internally* (red) resulting in cation **106**, which is trapped, or *externally* (blue), leading to tertiary cation **107**. A 1,2-hydride shift to **108** followed by fragmentation of the cyclopropane and tautomerization could result in ester **109**.

Scheme A5.3.4. Danheiser annulation of cycloheptenone **75.**

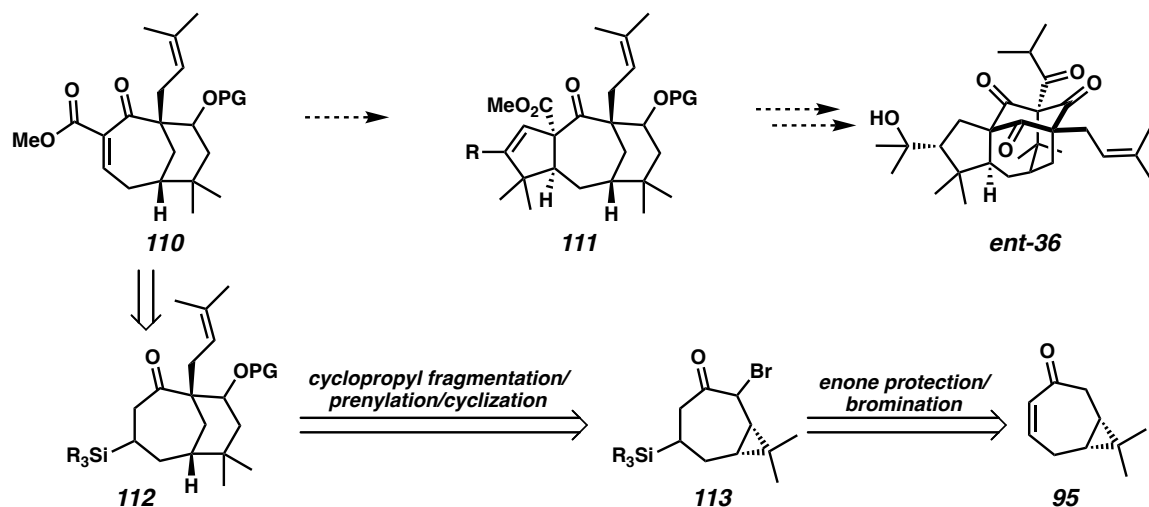


A5.4 EASTERN RING-FIRST STRATEGY

It became clear at this point that the intrinsic bias for bulky nucleophiles on esters **75** or **95** was not to give the desired *anti*-addition products, and our continued efforts to force this were not productive. We instead imagined an alternate approach where we would first construct the eastern 6-membered ring (**110**, Scheme A5.4.1), thereby rigidifying and increasing the steric bulk to a point where it could be reasonably assumed that nucleophiles would attack on the *anti*-face, providing **111**. The remaining steps to **ent-36** would be mostly unchanged.

Retrosynthetically, the unsaturated β -ketoester moiety is very reactive and must be installed directly before use. We elected to use a silane as a temporary placeholder and blocking group in ketone **112**. Ketone **112** could be accessed from bromoketone **113** via a cyclopropyl fragmentation, prenylation, and cyclization. Finally, enone protection and bromination of **95** would afford bromoketone **113**.

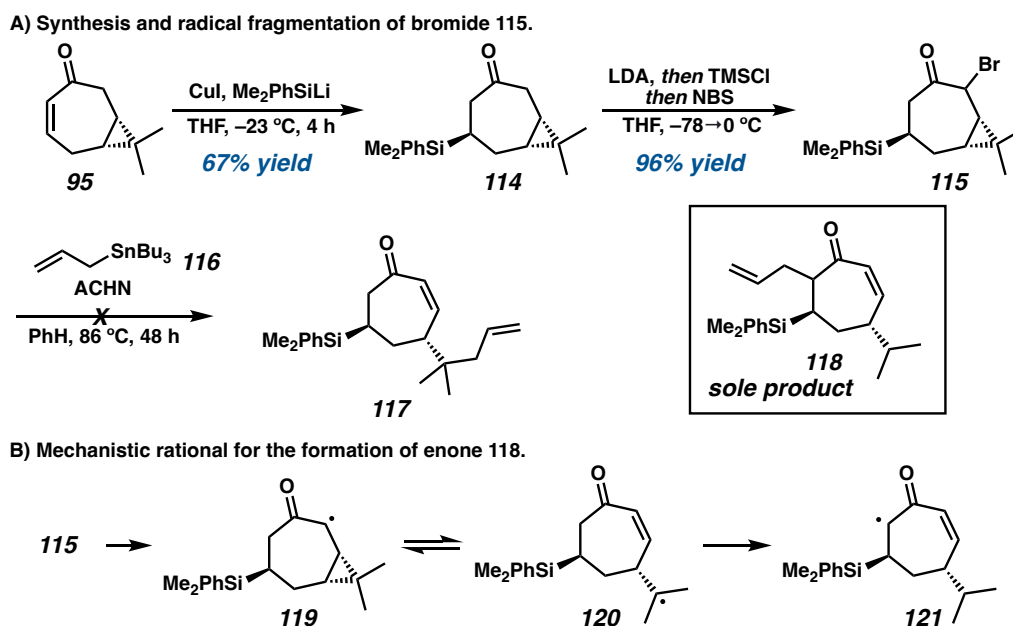
Scheme A5.4.1. Eastern ring first approach to the homoadamantane PPAPs.



Starting from enone **95** (Scheme A5.4.2A), we were able to protect the enone as a β -silylketone (**114**) by addition of a silylcuprate, following a procedure by Patel and

coworkers.¹⁵ Curiously, in this case we isolated the *anti*-addition product. Bromination afforded bromide **115** in excellent yield, however our radical fragmentation conditions with stannane **116** did not result in desired allyl enone **117**. Instead, undesired enone **118** was isolated. Mechanistically, we reasoned that generation of secondary radical **119** (Scheme A5.4.2B) would be followed by fragmentation to form tertiary radical **120**. This radical is nucleophilic in nature and would thus be slow to engage with the kinetically mismatched stannane (**116**), which would also provide a nucleophilic radical. Instead, a facile 1,5-HAT could occur: this would not only be kinetically matched but would also generate a highly stabilized push-pull radical (**121**).¹⁶

Scheme A5.4.2. Unexpected formation of rearranged allylketone 118.

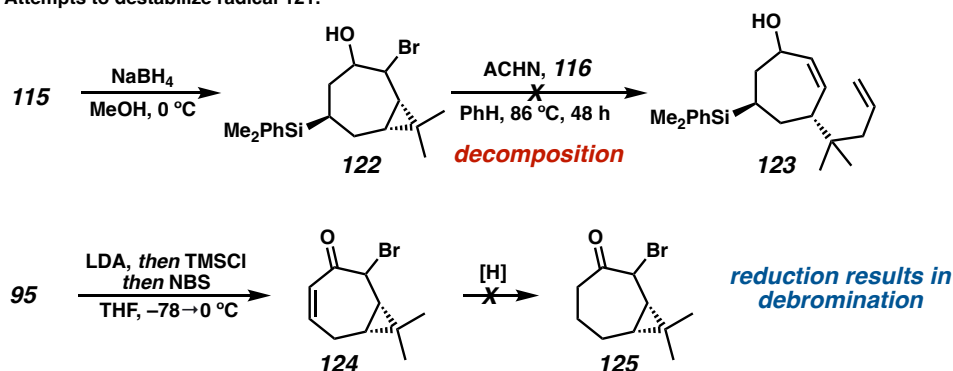


We reasoned that in order to destabilize this push-pull, “captodative” radical, and thus shut down this side reaction, we need to either remove the pulling group (carbonyl) or the pushing group (β -Si effect). We were able to reduce bromide **115** to the corresponding secondary alcohol (**122**, Scheme A5.4.3A), however this only resulted in decomposition

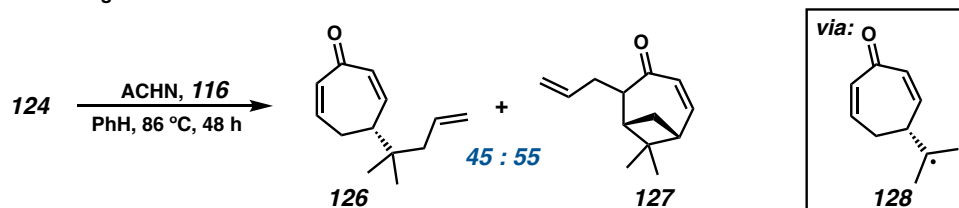
products upon treatment with our radical fragmentation conditions (**123** was not observed). We next tried to make the desilylated version of bromide **115**. Starting from enone **95**, we were able to selectively brominate alpha to the carbonyl, yielding bromide **124**. Unfortunately, all reductive conditions that were tried in order to reduce the enone olefin resulted in concomitant reduction of the bromide as well. Next, we tried to subject bromide **124** to the radical fragmentation conditions directly (Scheme A5.4.3B). We isolated a mixture of two isomers, the desired allyldieneone **126** as well as a curious dimethylcyclobutane (**127**) byproduct. It was not entirely surprising to observe this undesired isomer, as following fragmentation, the resulting tertiary radical **128** has three viable pathways to termination. It could directly engage an allyl group forming allyl dienone **126**, it could engage the neighboring olefin regenerating the initial enone (these two species are likely in equilibrium), or it could engage the second enone, resulting in cyclobutane **127** after termination with allyl stannane **116**.

Scheme A5.4.3. Attempts to destabilize captodative radical 121.

A) Attempts to destabilize radical 121.

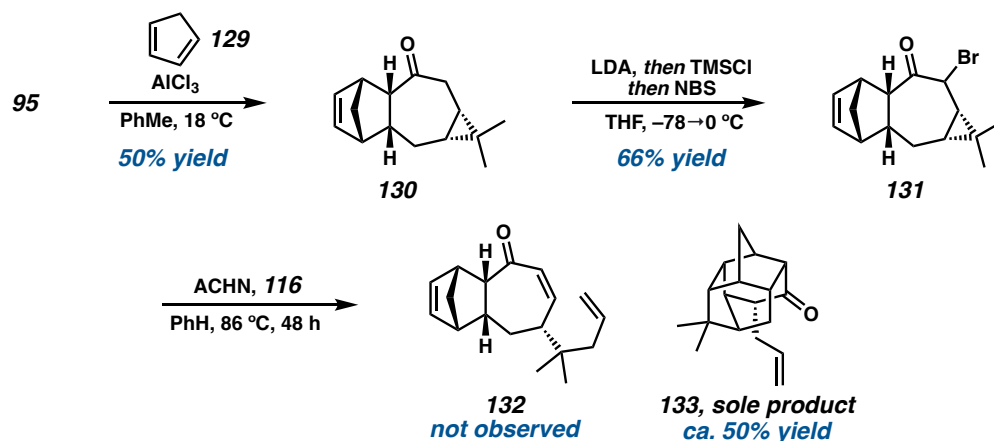


B) Radical fragmentation of bromide 124.



At this point we elected to try cyclopentadiene (cp, **120**, Scheme A5.4.4) as an enone protecting group, hoping to avoid the issues we observed with the silyl group.¹⁷ We were pleased to find that simple Diels-Alder conditions with enone **95** and cp (**129**) resulted in the desired adduct **130**. This could then be brominated to afford bromide **131** which we subjected to the radical fragmentation conditions. Unfortunately, we did not isolate the desired allyl enone **132** and instead found the major product to be an unusual cage (**133**). Further studies of this reaction, **133**, and its relevance, is explored in Chapter 4.

Scheme A5.4.4. Cyclopentadiene protected enone radical fragmentation.



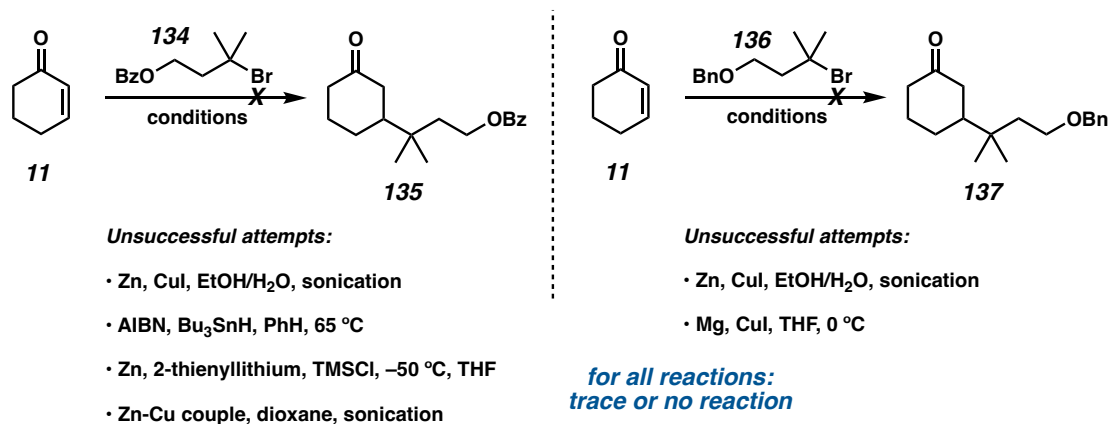
A5.5 CYCLOHEXENONE STRATEGY: HYDROINDENE FORMATION

Due to the challenges faced in both the first and second approaches, a third route was targeted, focusing specifically on omitting the seven membered ring until necessary. Ultimately, this strategy proved successful, with the key outcomes presented in Chapters 1 and 2. Additional efforts, including unsuccessful attempts, are discussed in these sections (A5.5–A5.9).

Initial attempts to synthesize a 6-membered substrate for the cyclopentene annulation were met with limited success (Scheme A5.5.1). Starting from 3° alkyl bromides **134** and **136**, various radical and organometallic additions were attempted with

only trace product being observed in most cases. Only two routes, a Sakurai allylation and Fe-mediated HAT addition ultimately proved successful (see. Scheme 1.4.1 and Scheme 2.4.1).

Scheme A5.5.1. *Unsuccessful tertiary conjugate additions to 11.*

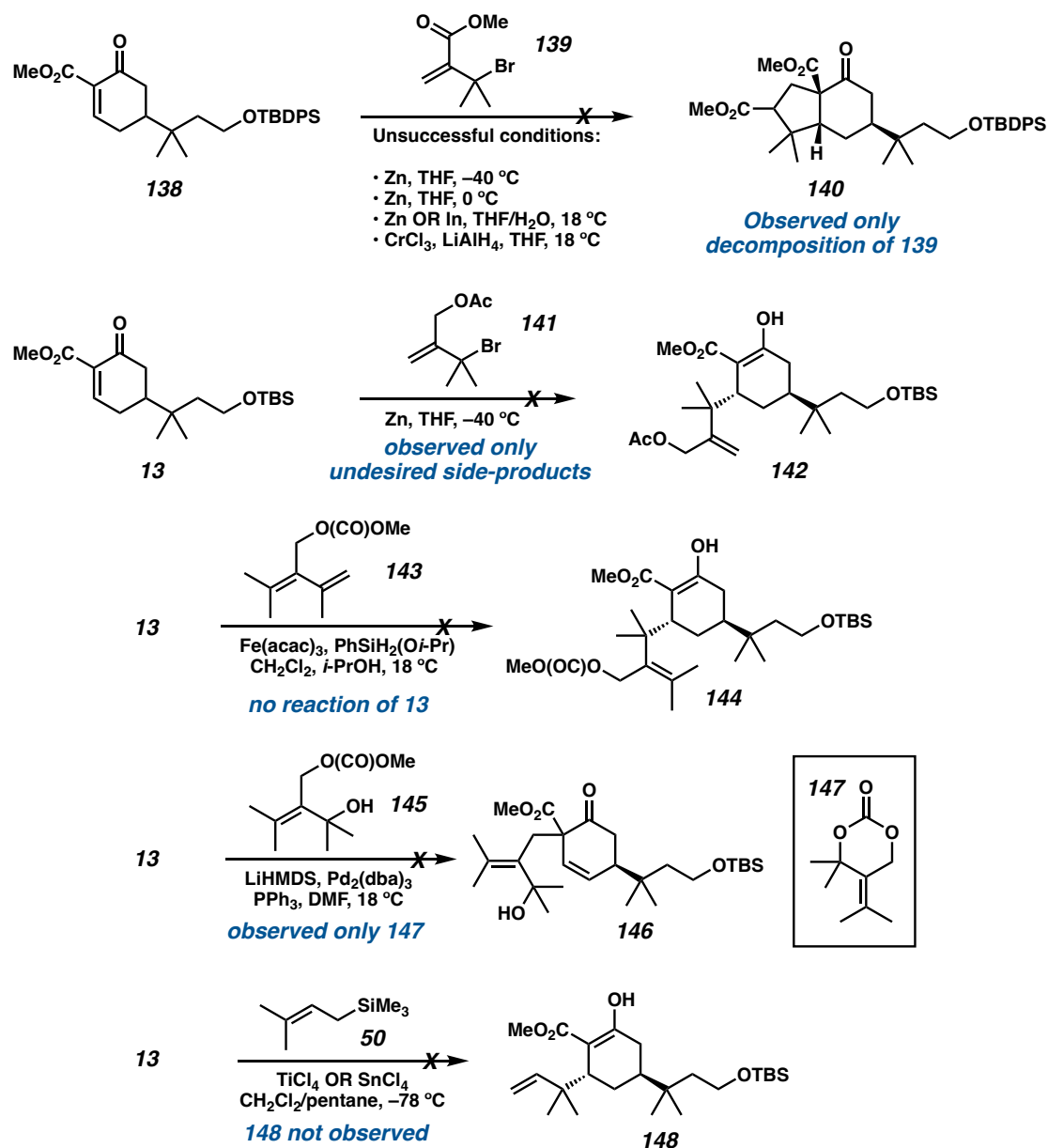


Having access to cyclohexanones **13** and **138**, multiple strategies to install the cyclopentane ring were attempted (Scheme A5.5.2). Despite having developed a cyclopentene annulation for this purpose, the challenging reaction protocols and moderate yields led us to question whether more suitable methodologies exist.

Allylic bromide **139** was initially selected with the expectation that Zn-mediated metalation would enable branched addition into enone **138**, followed by a formally forbidden 5-endo-trig cyclization to form hydroindene **140**.¹⁸ While the cyclization was anticipated to be challenging, we were disappointed to see that metalation of bromide **139** resulted in decomposition, leaving enone **138** unreacted. Attempts to run this reaction under aqueous (Reformatsky) conditions or with Cr^{II} were also unsuccessful. Hypothesizing that the acrylate was leading to premature decomposition we attempted this reaction using bromide **141**, now bearing an isolated acetate. Several new compounds were

observed by TLC; however, these were formed in trace quantities and were not stable to isolation.

Scheme A5.5.2. Unsuccessful strategies toward the key hydroindene.



Carbonate **143** was synthesized with the aim of using an iron catalyzed HAT coupling to generate β -ketoester **144**.¹⁹ Ideally, the nucleophilic ketoester could then displace the carbonate in an S_N2 reaction to generate the cyclopentane. However, this HAT

coupling provided mainly unreacted starting material (**13**). It is possible the symmetric allylic radical formed is too stable and hindered to engage in a Giese type addition to ester **13**. Deprotonation of enone **13** at the γ -position using LHMDs, followed by treatment with a mixture of Pd and allylic carbonate **145**, was expected to result in allylation to form diene **146**.²⁰ Unfortunately, carbonate **145** is not stable to base and cyclic carbonate **147** was isolated. A final attempt was made to extend the previously successful Sakurai allylation to the synthesis of β -ketoester **148**, using either a Ti or Sn Lewis acid. Surprisingly, Ti resulted in no reaction while Sn produced non-specific decomposition.

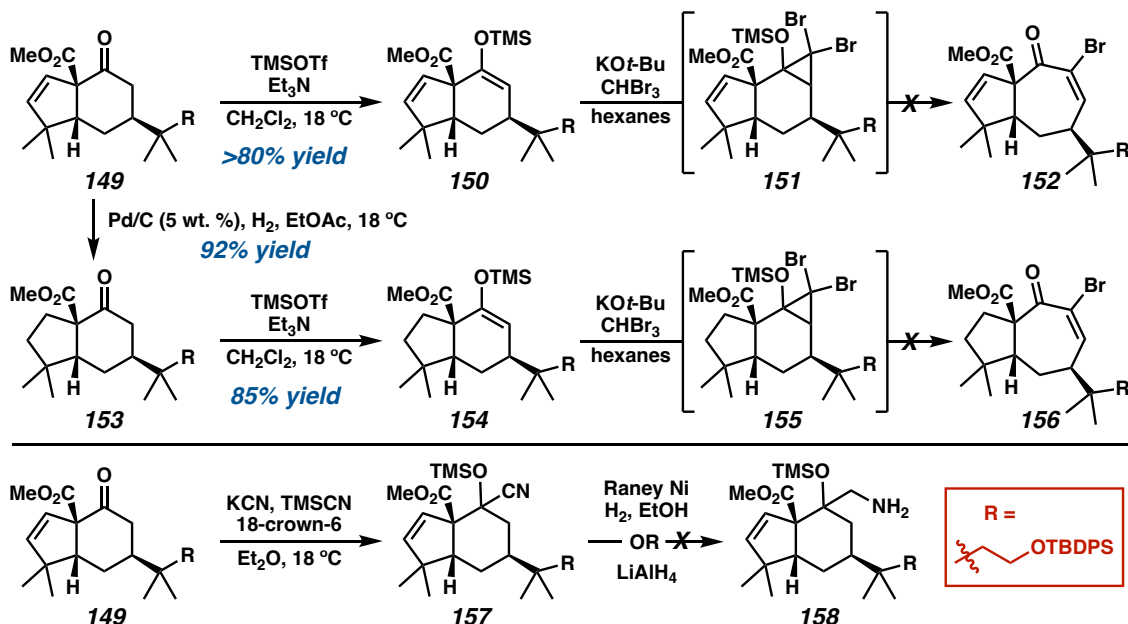
The combined outcome of these efforts underscored the challenges associated with constructing this hindered cyclopentane ring and reinforced the notion that our previously developed 3-component cyclopentane annulation (see Chapter 5) remains among the most effective ways to construct this motif.

A5.6 CYCLOHEXENONE STRATEGY: HYDROINDENE RING EXPANSION

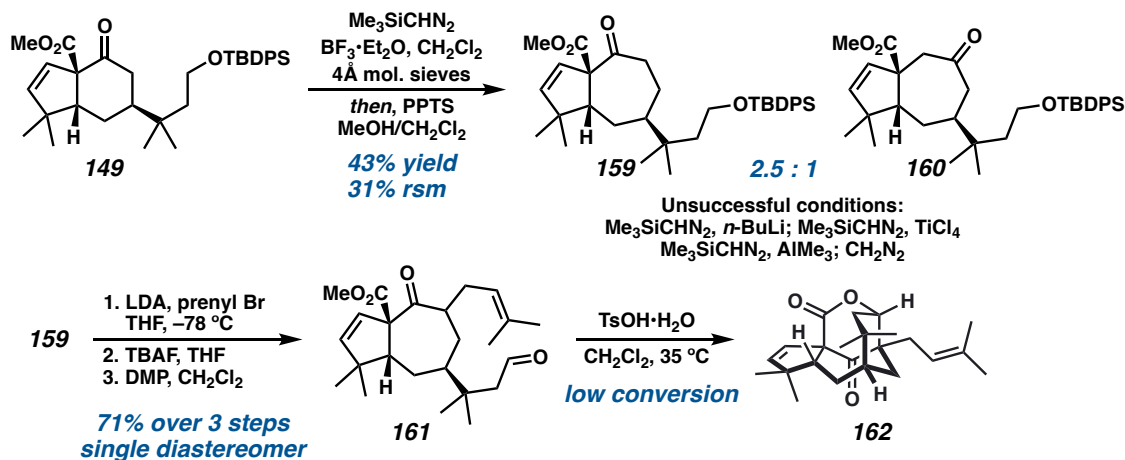
Following preparation of hydroindenes **149** and **14** (bearing an OTBS group), it became necessary to perform a ring expansion to access the respective hydrazulenes (Scheme A5.6.1). Several reactions were investigated to this end. After successful preparation of silyl enol ether **150**, a cyclopropanation using dibromocarbene was attempted in order to access dibromide **151**, which is anticipated to undergo spontaneous rearrangement to hydrazulene **152**.²¹ This reaction resulted in a complex mixture with several unidentified species. To mitigate potential interference from the cyclopentyl olefin, cyclopentene **149** was hydrogenated to form the saturated hydroindene (**153**), followed by silylation to form enol ether **154**. Subjection to dibromocarbene resulted in no reaction, likely due to the steric congestion near the silyl enol ether. We also attempted a Tiffeneau-

Demjanov ring expansion which requires primary amine **158**.²² While cyanohydrin **157** was formed successfully, we were unable to reduce the cyanide in the presence of the neighboring ester (**158**). Hydrogenation resulted in no reaction, while LiAlH_4 resulted in decomposition. This strategy would likely also have been plagued by undesired lactam cyclization of the primary amine.

Scheme A5.6.1. Early unsuccessful ring expansion strategies.



We next investigated diazo-mediated ring expansion strategies. Although various conditions were unsuccessful (see Scheme A5.6.2), the reaction of **149** with trimethylsilyldiazomethane, BF_3 , and molecular sieves resulted in desired hydrazulene **159** in a modest 31% yield with smaller amounts of the undesired ketone isomer (**160**).²³ Separation of isomers **159** and **160** was possible with reverse phase preparatory HPLC enabling **159** to be advanced to aldehyde **161** via prenylation, deprotection, and oxidation. Treatment of aldehyde **161** with acidic conditions then allowed isolation of lactone **162** in small quantities.

Scheme A5.6.2. Successful diazo-mediated ring expansion of **149**.

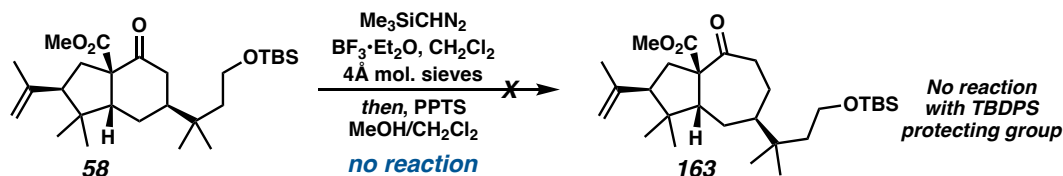
The success of trimethylsilyldiazomethane ring expansion and subsequent advancement to lactone **162** gave us confidence in this overall strategy, however, we decided to invest more time into developing a more practical ring expansion. This set of conditions resulted in low yields and reproducibility due to the heterogenous nature of the reaction. Additionally, separation of isomers **159** and **160** via HPLC was only feasible on a small scale (<100 mg), and finally, this set of conditions was unsuccessful on substituted cyclopentane rings, such as ketone **58** (Scheme A5.6.3A).

Effecting a ring expansion of substituted hydroindene **58** became a necessity as we set out to target wilsonglucinol G (**36**) and hypersonin A (**32**). The isopropenyl group, although oriented away from the concave face, is currently believed to further compress the bowl-like topology of **58** and hinder the ability of the neutral diazomethane nucleophile to engage the ketone. To address this, neutral diazoacetate nucleophiles were employed in conjunction with Lewis acids, while anionic diazoacetates were generated under basic conditions with LDA (Scheme A5.6.3B). Unsurprisingly, the neutral nucleophiles were similarly ineffective, however both anionic ethyl and *t*-butyl diazoacetate reacted smoothly

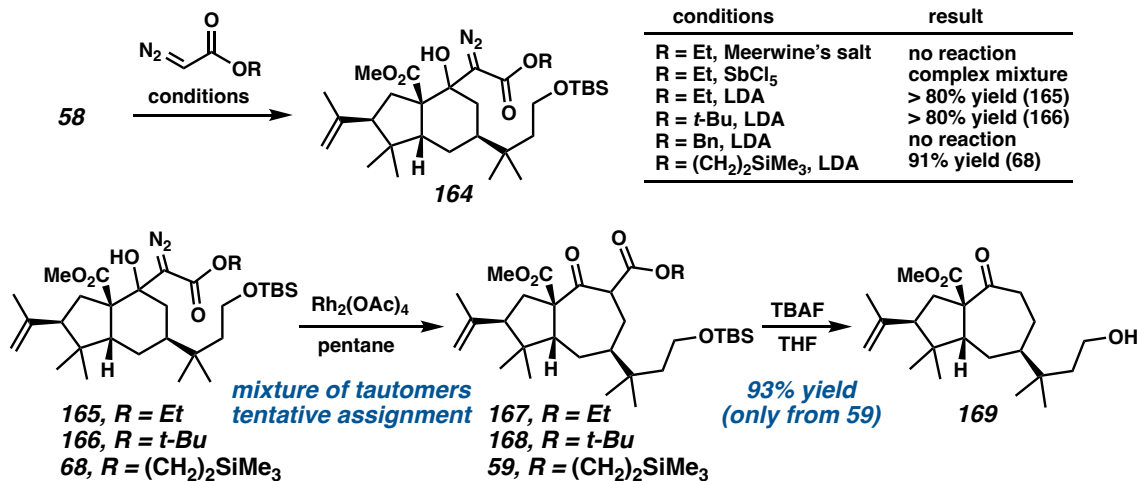
with **58**, resulting in 3° alcohols **165** and **166**, respectively. Both alcohols underwent tentative ring expansion with $\text{Rh}_2(\text{OAc})_4$ to afford β -ketoesters **167** and **168**. Unfortunately, **167** and **168** both exist as a mixture of dynamically interconverting isomers, preventing characterization.

Scheme A5.6.3. Diazoacetate-mediated ring expansion of 58.

A) Unsuccessful ring expansion of hydroindene **58** using trimethylsilyldiazomethane.



B) Ring expansion attempts using diazoacetates.



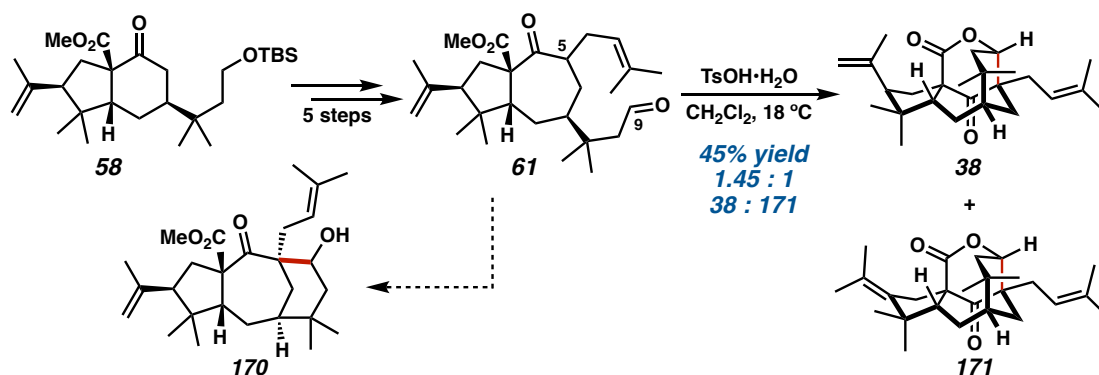
Attempts to selectively decarboxylate either **167** or **168** to hydrazulene **163** proved exceedingly challenging in the presence of the neighboring methyl ester. Custom diazoacetates bearing benzyl and trimethylsilyl ethyl esters were synthesized to facilitate the selective decarboxylation step. Deprotonation of benzyl diazoacetate resulted in decomposition and alcohol **164** bearing a benzyl group was never observed. Ultimately, trimethylsilyl ethyl diazoacetate added cleanly to hydroindene **58** forming **68**, and following ring expansion with Rh, the resulting tautomeric mixture (**59**) could be

selectively decarboxylated with TBAF, providing a high-yielding and scalable route to hydrazulene **169**.

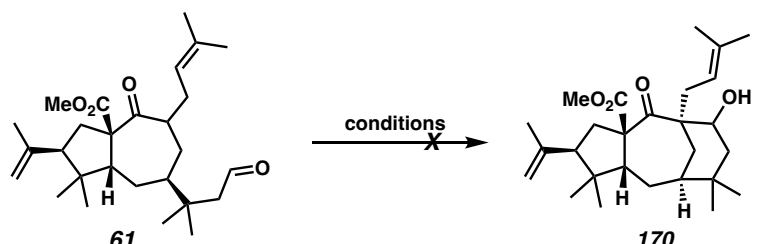
A5.7 CYCLOHEXENONE STRATEGY: FORMING THE C5–C9 BOND

Hydroindene **58** was advanced to aldehyde **61** (Scheme A5.7.1) in five steps, outlined in Chapter 2. Previous model studies with **161** to form **162** (Scheme A5.6.2) led us to believe that a similar set of conditions could be used to access lactone **38** from aldehyde **61**. Indeed, lactone **38** could be isolated, albeit in low yield and with significant amounts of isomerized **171**, which proved inseparable without preparatory HPLC. Significant efforts were made to forge the C5–C9 bond (**61**) without lactonization, to yield **170**. These efforts are described in this section.

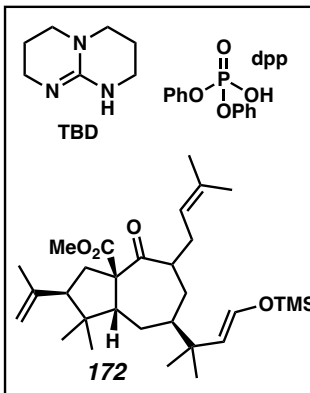
Scheme A5.7.1. Lactonization of aldehyde **61**.



A variety of aldol conditions (at multiple temperatures) were employed in an attempt to isolate aldol product **170** from aldehyde **61** (Table A5.7.1). Unfortunately, essentially all of conditions resulted in no reaction. Various bases (entries 1–5), including TBD, and acids (entries 7–11), including dpp, returned starting material. Interestingly Mukaiyama aldol conditions (entry 6) resulted in formation of silyl enol ether **172**, but not condensation products.

Table A5.7.1. Unsuccessful aldol reaction of aldehyde **61**.


entry	conditions ^a	result	entry	conditions ^a	result
1	TBD, THF	no reaction	7	TsOH·H ₂ O Et ₂ O OR PhH	no reaction
2	DBU, CH ₂ Cl ₂	no reaction	8	CSA, CH ₂ Cl ₂ OR Et ₂ O OR PhH	no reaction
3	pyrrolidine, DMF	no reaction	9	BF ₃ ·Et ₂ O OR TFA, CH ₂ Cl ₂	no reaction
4	NaOMe, MeOH	no reaction	10	PPTS, CH ₂ Cl ₂	no reaction
5	CsCO ₃ , PhH	no reaction	11	dpp, PhMe, 65 °C	no reaction
6	TMSOTf, EtN(<i>i</i> -Pr) ₂	isolated 172			



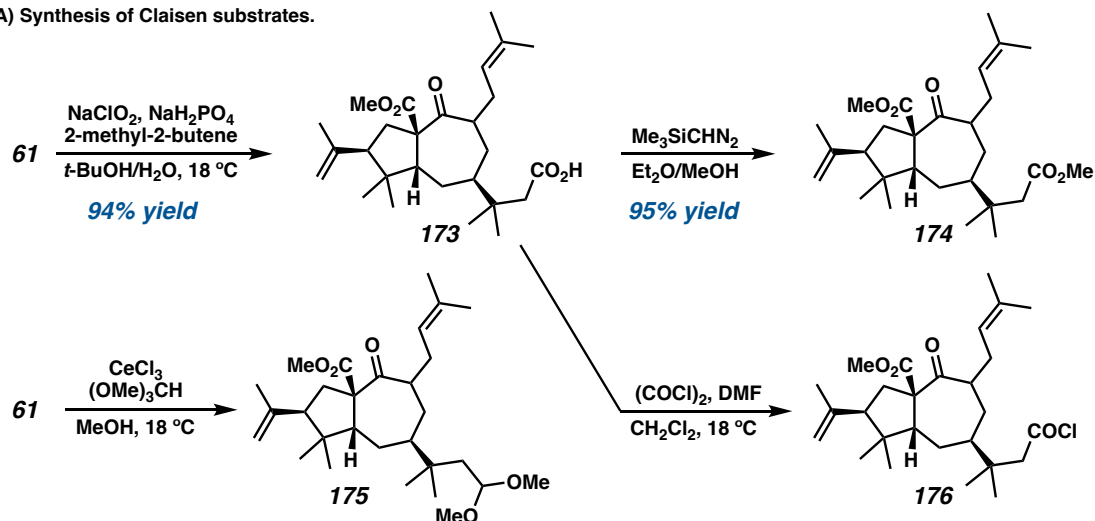
^aAll reactions performed at 18 °C and heated until reflux unless otherwise stated.

Anticipating that perhaps this aldol reaction is reversible, acid (**173**), ester (**174**), and acid chloride (**176**) substrates were prepared (Scheme 5.7.2A). Literature precedent suggested it may be possible to directly cyclize the carboxylic acid (**173**) using forcing acidic conditions.^{24,25} Targeting Claisen product **177**, we treated acid **173** with Amberlyst 15 in PhMe, which unfortunately resulted in decomposition of the isoproprenyl group (Scheme A5.7.2B). Polyphosphoric acid in AcOH resulted in nonspecific decomposition. All attempts to utilize ester **174** under basic or Lewis acidic conditions resulted in no reaction.²⁶ Next, acid chloride **176** was treated with AlCl₃ to generate the highly electrophilic oxocarbenium/ketene. Unfortunately, this also resulted in a complex mixture. Finally, dimethyl acetal **175** was prepared and treated with Lewis acids, resulting in elimination to the methyl enol ether (not shown) with TMSOTf/Hunig's base, and hydrolysis to the aldehyde (**61**) with SnCl₄. Elimination of **175** to the methyl enol ether

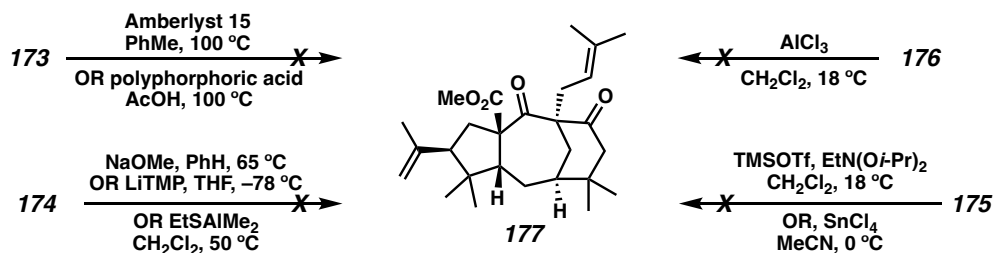
suggests that the oxocarbenium electrophile was formed, but cyclization was unfavorable, possibly due to an insurmountable steric interaction.

Scheme A5.7.2. *Synthesis and deployment of Claisen substrates.*

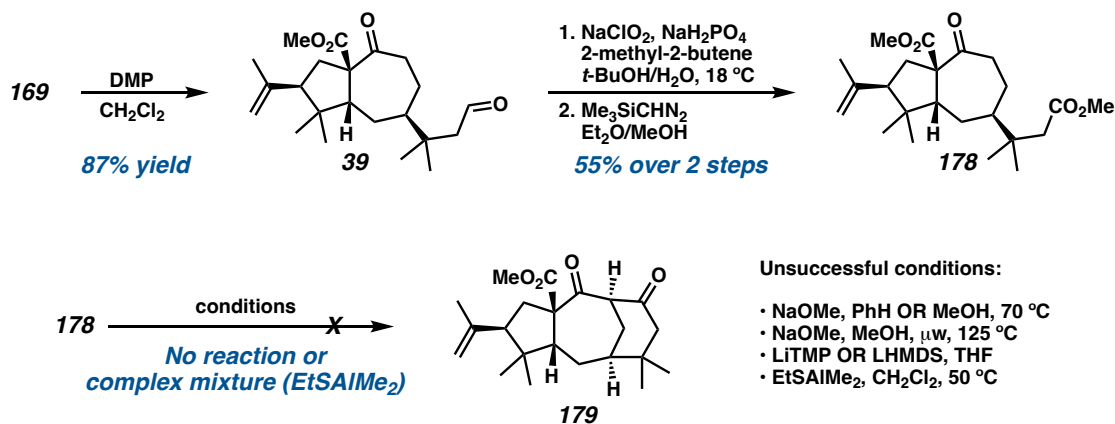
A) Synthesis of Claisen substrates.



B) Attempts to close the C5–C9 bond irreversibly.



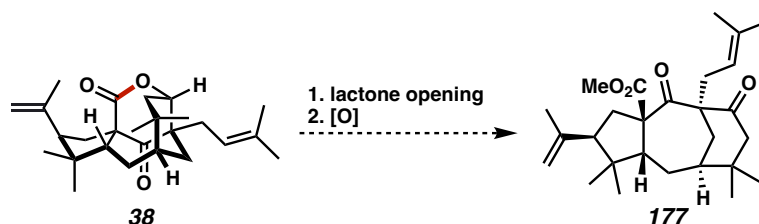
At this stage we hypothesized that perhaps the prenyl group was responsible for a deleterious steric interaction and elected to synthesis ester **178** (Scheme A5.7.3). Ester **178** was prepared via sequential oxidation and methylation of alcohol **169** (Scheme A5.6.3). Cyclization of **178** to dione **179** was anticipated to proceed more readily, with the acidic 1,3-diketone serving as a handle for subsequent installation of the prenyl group. However, a range of basic conditions resulted in no reaction, while EtSAIme₂ resulted in decomposition.

Scheme A5.7.3. Synthesis and deployment of des-prenyl ester **178**.

The accumulated results from attempts to forge the C5–C9 bond led to the conclusion that cyclization was unlikely to be favorable thermodynamically due to the strain induced in the tricyclic system. The isolation of lactone **38** was recognized as a fortunate outcome, arising from the serendipitous lactonization of the aldol product, which acted as a thermodynamic sink. At this point, rather than continuing to pursue cyclization of these systems to the aldol/Claisen products, efforts were redirected toward utilizing lactone **38** as a synthetic intermediate.

A5.8 CYCLOHEXENONE STRATEGY: OPENING THE CAGED LACTONE

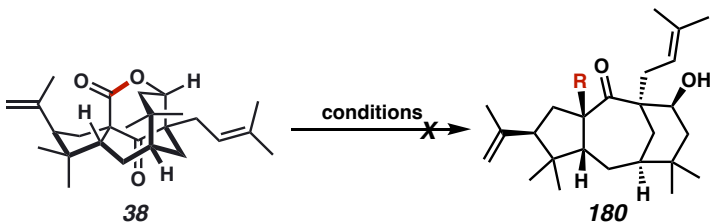
Proceeding with lactone **38** (Scheme A5.8.1), a lactone opening followed by oxidation was anticipated to provide tricycle **177**, intercepting the original retrosynthesis for the homoadamantane PPAPs.

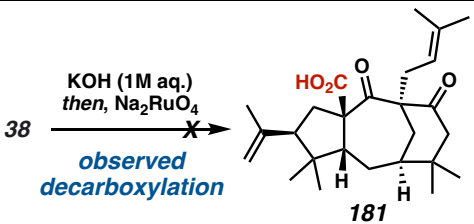
Scheme A5.8.1. Proposed future steps for lactone **38**.

Targeting alcohol **180** (Table A5.8.1), where R = ester, a variety of lactone opening conditions were attempted (entries 1–5).^{27,28} In all cases, even at greatly elevated temperatures, no reaction was observed. Our current hypothesis is that lactone opening is not prohibitively challenging, rather, the rigid backbone of alcohol **180** provides a strong driving force for cyclization back to lactone **38**.

It was determined that to proceed with lactone **38**, ester opening must lead to a thermodynamically favorable product, making the process effectively irreversible. A set of unique conditions using Na₂RuO₄ published by Corey could potentially saponify the ester to the potassium salt using KOH, followed by basic oxidation of the 2° alcohol to afford ketone **181**.²⁹

Table A5.8.1. Attempts to open lactone **38** to tricycle **180**.

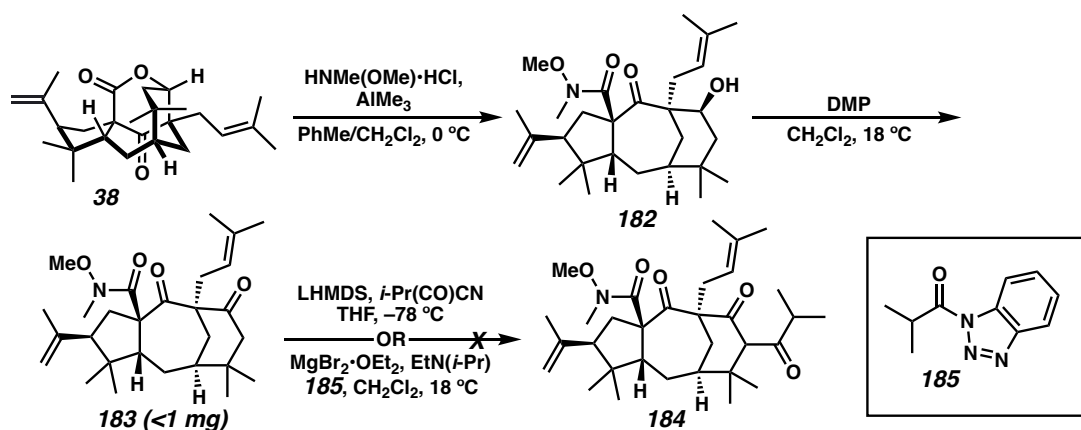
			
entry	conditions	R	result
1	NaOMe, MeOH	-CO ₂ Me	no reaction
2	Al(O ^{<i>i</i>} -Pr) ₃ , MeOH	-CO ₂ Me	no reaction
3	AlMe ₃ , MeOH, PhMe	-CO ₂ Me	no reaction
4	Bu ₃ SnOMe	-CO ₂ Me	no reaction
5	Mg(OEt) ₂ , EtOH	-CO ₂ Et	no reaction
6	LiAlH ₄ , THF	-CH ₂ OH	complex mixture

	
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Unfortunately, the only product identified by mass spectrometry was the decarboxylated species, suggesting a potentially favorable pathway for relieving strain in this compound.

Moving beyond esters, it was decided to try opening lactone **38** using an AlMe_3 -mediated Weinreb amine amidation, a reaction that has significant precedent for opening stubborn lactones.³⁰ We were happy to see that indeed, a small sample could be progressed to ketone **183** via amide **182** following oxidation (Scheme A5.8.2). This material was then subjected to both hard and soft enolization conditions with the hopes of accessing 1,3-diketone **184**, however this dione was never observed.^{31,32}

Scheme A5.8.2. Weinreb amide opening of lactone **38**.

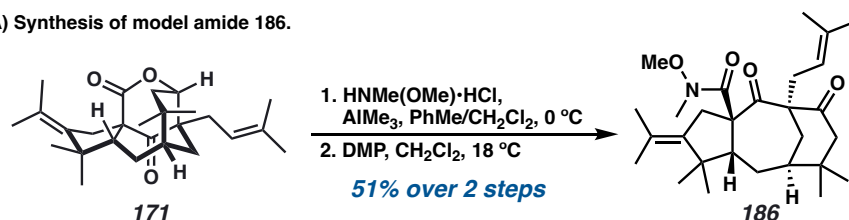


The challenges associated with these late-stage intermediates were exasperated by difficulties in scalability and material throughput. To alleviate these challenges, isomer **171** was deemed a viable model system for investigating future steps following amidation and oxidation to dione **186** (Scheme A5.8.3A). Functionalization of both the amide and the eastern ketone was attempted. The Weinreb amide had sufficient thermodynamic drive to open lactone **171**, however this stability also proved problematic for further functionalization. Both esterification of the amide to ester **187** or cyclization to homoadamantane **188** were unsuccessful, with the amide remaining unaffected (Scheme

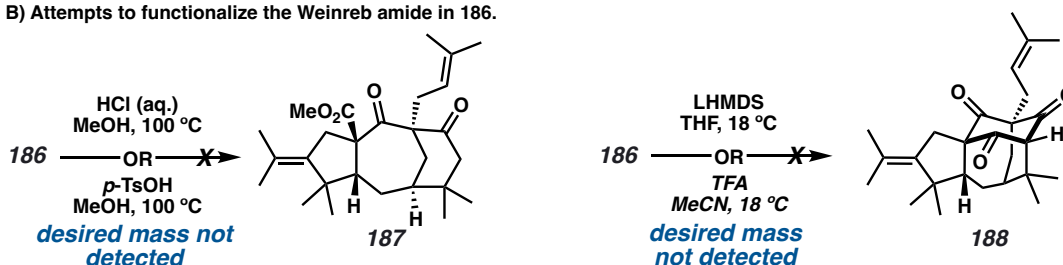
A5.8.3B). We also attempted to acylate dione **186** to install the final four carbons required in the natural product (Scheme A.5.8.4C).

Scheme A5.8.3. Studies carried out on model Weinreb amide **186**.

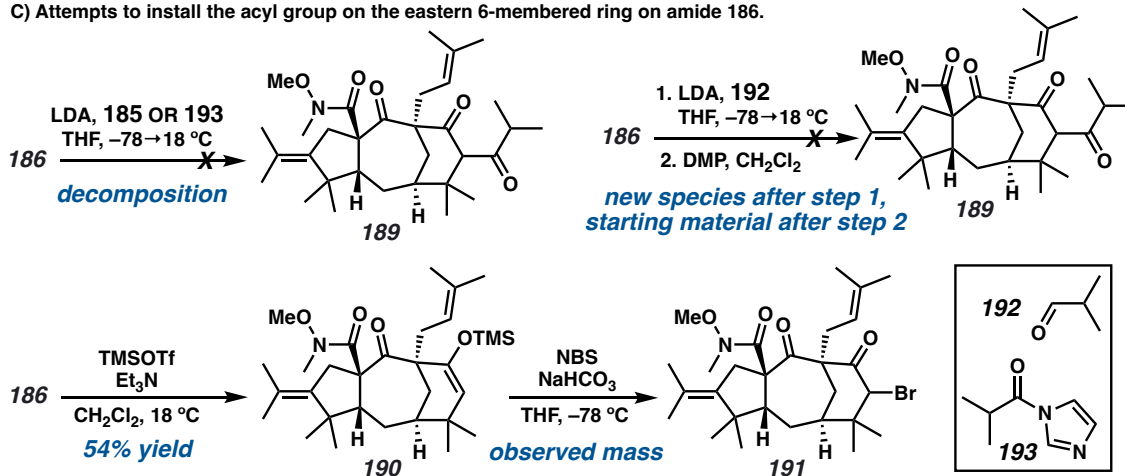
A) Synthesis of model amide **186**.



B) Attempts to functionalize the Weinreb amide in **186**.



C) Attempts to install the acyl group on the eastern 6-membered ring on amide **186**.

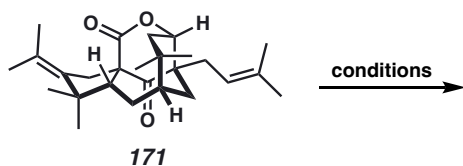


Using acyl imidazole (**193**) with LDA resulted in no reaction, however using benzotriazole **185** resulted in a new species with the desired mass. Although the newly formed species could not be fully assigned upon isolation, it was clear that it was not the desired trione (**189**). It was also attempted to access trione **189** through an aldol reaction with aldehyde **192** followed by oxidation. Following the aldol step, several new species were observed, however, these reverted to dione **186** upon oxidation. Finally, silyl enol

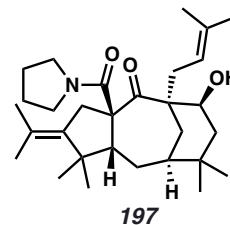
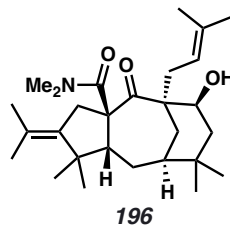
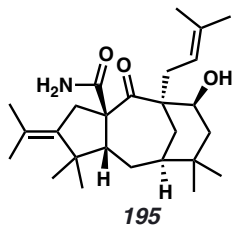
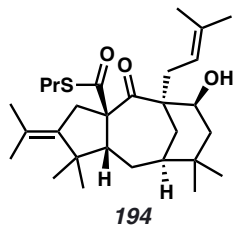
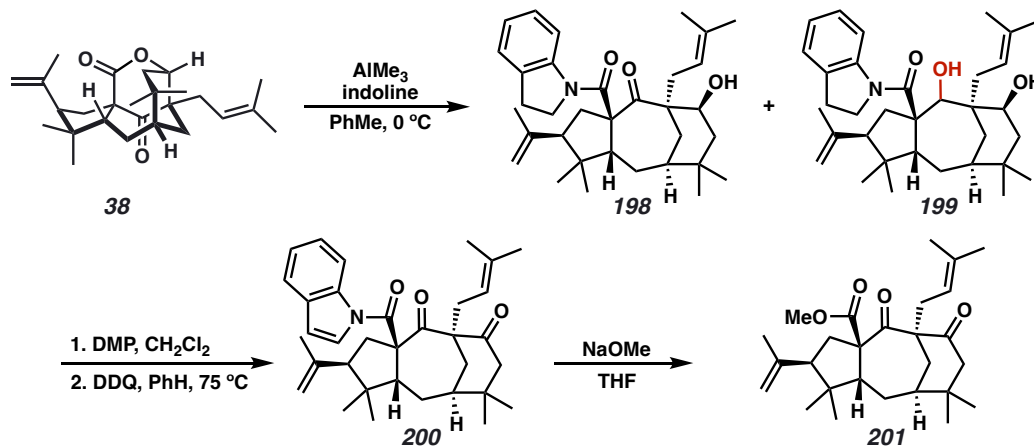
ether **190** was prepared to access bromide **191**. Although bromination of **190** appeared promising, this pathway was ultimately abandoned due to the challenges associated with the Weinreb amide.

Several other nucleophiles were tried in the hope that some of these compounds (**194–197**) would be more labile and amenable to further transformation (Table A5.8.2A). Treatment with propanethiol to access thioester **194** proved unfruitful, resulting in only starting material (entry 1).³³ Using a combination of NH₄Cl/AlMe₃ resulted in isolation of acetamide **195** (entry 2), however subsequent oxidation of the 2° alcohol resulted in decomposition. Dimethylamine and pyrrolidine led to unidentified side-products and no reaction, respectively (entries 3,4).

An interesting report by Barrett and Barton outlines the use of indoline as a nucleophilic 2° amine whose amides are stable, but become labile indoles following oxidation with DDQ.³⁴ To our delight, indoline successfully afforded a mixture of desired amide **198** and over reduced diol **199**, indicating an unusual ketone reduction in which indoline may be acting as a reducing agent (Table 5.8.2B). This mixture could be oxidized with DMP to yield the dione (not shown), followed by DDQ oxidation to yield acyl indole **200**. With a tricyclic ring system bearing a labile leaving group in hand, dione **200** was subjected to basic methanolysis. Excitingly, this allowed us to observe ester **201** by mass spectrometry. Despite the indoline strategy showing promise, concomitant studies done with aniline proved far more fruitful, leading to the final route presented in Chapters 1 and 2.

Table A5.8.2. Other amines used to open the caged lactones **171** and **38**.A) Opening of lactone **171** with selected amines.

entry	conditions	product	result
1	AlMe ₃ , PrSH, CH ₂ Cl ₂	194	no reaction
2	AlMe ₃ , NH ₄ Cl, PhMe	195	decomposition following oxidation
3	AlMe ₃ , HNMe ₂ ·HCl, PhMe	196	two unidentified side products
4	AlMe ₃ , pyrrolidine, PhMe	197	no reaction

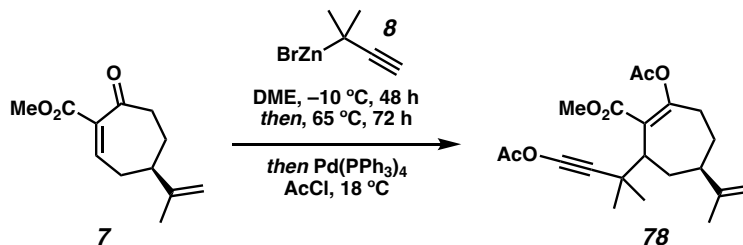
B) Opening lactone **38** using indoline.

A5.9 EXPERIMENTAL SECTION

A5.9.1 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.³⁵ NBS was recrystallized from boiling water prior to use and amines were distilled under nitrogen prior to use. 3-bromo-3-methylbut-1-yne was prepared according to a previously reported procedure.³⁶ Activated zinc dust was prepared according to a previously reported procedure.³⁷ Allene **101**³⁸ was prepared according to a previously reported procedure. All other reagents were purchased from commercial sources and used as received unless otherwise indicated. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching or KMnO₄ staining. Silicycle SiliaFlash® P60 Academic Silica gel (particle size 40–63 nm) was used for flash chromatography. ¹H NMR spectra were recorded on Varian Inova 500 MHz, 600MHz, and Bruker 400 MHz spectrometers and are reported relative to residual CHCl₃ (δ 7.26 ppm). Data for ¹H NMR 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, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet.

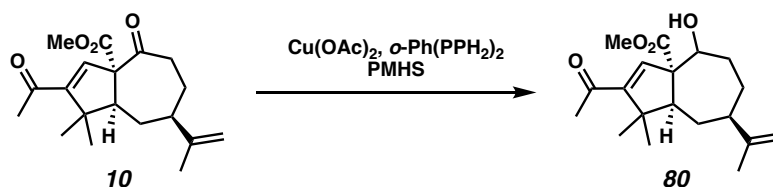
A5.9.2 EXPERIMENTAL PROCEDURES



methyl (5*R*)-2-acetoxy-7-(4-acetoxy-2-methylbut-3-yn-2-yl)-5-(prop-1-en-2-yl)cyclohept-1-ene-1-carboxylate 78.

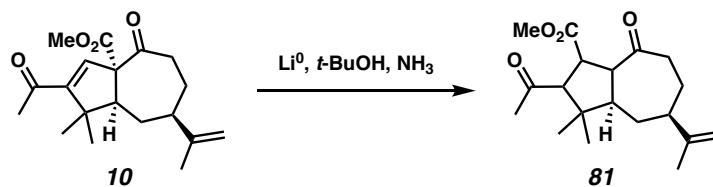
A 500 mL Teflon-stoppered flask under Ar was charged with Zn (1.56 g, 24 mmol, 2.5 equiv) and DME (50 mL). The reaction was cooled to $-10\text{ }^{\circ}\text{C}$ and 3-bromo-3-methylbut-1-yne (3.5 g, 24 mmol, 2.5 equiv) was added in one portion. The solution was stirred at this temperature for 2 days, after which the mixture was brought into a glovebox and filtered. A solution of **7** (2.0 g, 9.6 mmol, 1 equiv) in DME (50 mL) was added dropwise and the reaction was stirred at $76\text{ }^{\circ}\text{C}$ for 2 d. A separate solution of $\text{Pd}(\text{PPh}_3)_4$ (665 mg, 0.576 mmol, 0.06 equiv) and AcCl (11 g, 144 mmol, 15 equiv) in DME (50 mL) was prepared, and the zinc reagent solution was added dropwise over several minutes. The reaction was stirred for 15 min and quenched with ice-cold saturated aqueous NH_4Cl . The mixture was neutralized with potassium phosphate and water, extracted with EtOAc ($3 \times 50\text{ mL}$), and the combined organic layers were washed with water and brine, dried over Na_2SO_4 , and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (5 $\rightarrow$ 15% EtOAc/hexanes) to furnish **78** as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ = 4.75 – 4.67 (m, 2H), 3.73 (s, 3H), 3.16 – 3.07 (m, 2H), 2.34 (s, 3H), 2.25 (td, J = 10.8, 6.8 Hz, 1H), 2.15 (s, 3H), 2.02 (ddd, J = 14.6, 5.8, 1.9 Hz, 1H), 1.95 (dd, J = 13.8, 8.7 Hz, 1H), 1.87 (tt, J = 13.0, 6.3 Hz, 1H), 1.73 (s, 3H), 1.71 – 1.63

(m, 1H), 1.54 – 1.46 (m, 1H), 1.30 (s, 3H), 1.27 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 185.1, 168.9, 168.9, 155.2, 149.7, 120.2, 109.7, 98.7, 82.3, 52.1, 47.2, 40.8, 37.4, 32.9, 30.0, 29.4, 28.3, 26.7, 26.6, 20.9, 20.4.



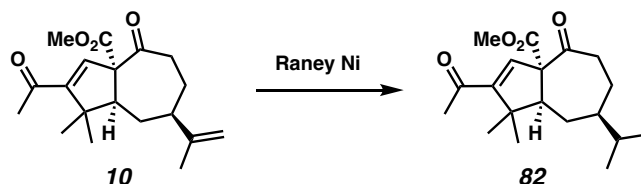
methyl methyl (3a*S*,7*R*,8a*S*)-2-acetyl-4-hydroxy-1,1-dimethyl-7-(prop-1-en-2-yl)-4,5,6,7,8,8a-hexahydroazulene-3a(1*H*)-carboxylate 80.

A vial was charged with $\text{Cu}(\text{OAc})_2$ (6 mg, 0.03 mmol, 1.0 equiv) and *o*-Ph(PPh_2)₂ (1.3 mg, 0.003 mmol, 0.1 equiv), purged with N_2 , and then PhMe/*t*-BuOH (4:1, 2.6 mL) was added. After the solids dissolved, PMHS (400 μL , 6 mmol, 200 equiv) was added and the reaction was stirred for 1 h. Enone **10** (10 mg, 0.031 mmol, 1.0 equiv) in PhH (0.2 mL) was then added. After 2 days, the reaction was quenched with water and hexanes, extracted with EtOAc, and the solvent was removed under reduced pressure. The crude residue was purified by preparative thin-layer chromatography (25% EtOAc in hexanes) to furnish **80**. ^1H NMR (400 MHz, CDCl_3) δ = 6.46 (s, 1H), 4.67 (s, 1H), 4.61 (dq, J = 2.9, 1.4 Hz, 1H), 4.47 – 4.41 (m, 1H), 3.76 (s, 3H), 3.04 (dd, J = 12.8, 6.3 Hz, 1H), 2.31 (s, 3H), 2.25 – 2.17 (m, 1H), 2.03 (ddt, J = 14.9, 6.0, 3.7 Hz, 1H), 1.87 – 1.76 (m, 1H), 1.74 (dd, J = 1.5, 0.8 Hz, 3H), 1.73 – 1.64 (m, 2H), 1.42 (dddd, J = 14.8, 13.4, 4.6, 1.4 Hz, 1H), 1.27 (s, 4H), 1.17 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 196.5, 174.5, 153.3, 152.7, 143.7, 107.8, 73.3, 68.7, 52.9, 51.4, 49.3, 44.1, 33.9, 31.9, 30.6, 28.8, 28.5, 23.2, 20.4.



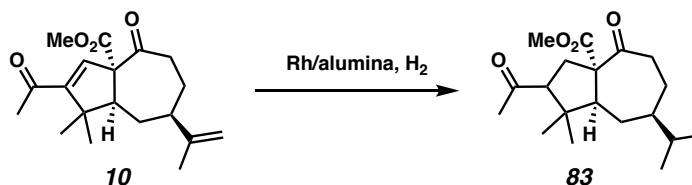
methyl (3a*R*,5*R*)-2-acetyl-8-hydroxy-3,3-dimethyl-5-(prop-1-en-2-yl)decahydroazulene-1-carboxylate **81.**

A solution of enone **10** (100 mg, 0.31 mmol, 1.0 equiv), *t*-BuOH (23.3 mg, 0.31 mmol, 1.0 equiv), and Et₂O (0.4 mL) was prepared under Ar. Separately, Li (4.79 mg, 0.69 mmol, 2.2 equiv) was added to NH₃ (4 mL, 0.25 M) at –78 °C. The ether solution was added dropwise to the stirred ammonia solution at –78 °C and stirred for 30 min. The reaction was quenched with saturated aqueous NH₄Cl and allowed to warm to 23 °C. The mixture was extracted with EtOAc and filtered, and the solvent was removed under reduced pressure. Purification by preparative thin-layer chromatography (30% EtOAc in hexanes) furnished **81**. ¹H NMR (400 MHz, CDCl₃) δ = 4.70 (dq, *J* = 10.7, 1.3 Hz, 2H), 3.93 (dd, *J* = 9.6, 6.5 Hz, 1H), 3.65 – 3.59 (m, 4H), 2.80 (d, *J* = 9.6 Hz, 1H), 2.69 (dt, *J* = 18.7, 3.9 Hz, 1H), 2.55 – 2.43 (m, 1H), 2.19 (s, 3H), 1.94 – 1.84 (m, 3H), 1.79 – 1.71 (m, 4H), 1.51 – 1.42 (m, 1H), 1.34 (s, 1H), 1.11 (s, 3H), 0.89 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 211.1, 207.4, 174.2, 150.9, 109.2, 63.0, 57.5, 53.9, 52.2, 48.2, 45.7, 44.4, 42.6, 35.9, 32.2, 29.0, 28.1, 20.5, 17.5.



methyl (3a*S*,7*R*,8a*S*)-2-acetyl-7-isopropyl-1,1-dimethyl-4-oxo-4,5,6,7,8,8a-hexahydroazulene-3a(1*H*)-carboxylate 82.

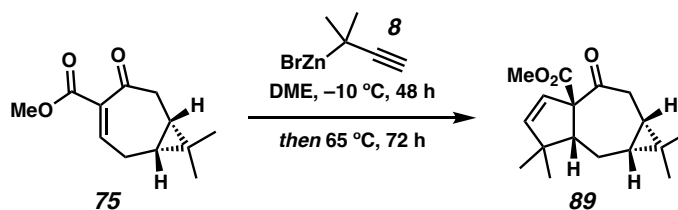
A vial was charged with enone **10** (15 mg, 0.047 mmol, 1.0 equiv) and THF (1.5 mL). Raney-Ni (0.25 g) was added and the reaction was stirred. After 1 h, an additional portion of Raney-Ni (0.25 g) was added and stirring was continued. After 3 h, the reaction was removed from the glovebox and the solvent was removed under reduced pressure to yield **82**. ¹H NMR (400 MHz, CDCl₃) δ = 6.50 (s, 1H), 4.12 (q, J = 7.1 Hz, 1H), 3.80 (s, 3H), 2.89 (dd, J = 13.2, 3.7 Hz, 1H), 2.60 – 2.51 (m, 1H), 2.45 (td, J = 6.6, 4.1 Hz, 1H), 2.33 (s, 3H), 2.04 (s, 1H), 1.93 – 1.82 (m, 2H), 0.96 (d, J = 6.6 Hz, 6H). Note: only key peaks are provided, indicating the absence of the isopropenyl protons, but not the enone resonance.



methyl (3a*S*,7*R*,8a*S*)-2-acetyl-7-isopropyl-1,1-dimethyl-4-oxooctahydroazulene-3a(1*H*)-carboxylate 84.

A vial was charged with enone **10** (10 mg, 0.031 mmol, 1.0 equiv), 5% Rh/Alumina (6 mg), and EtOAc (1 mL). The reaction was placed in a Parr bomb and pressurized to 10 atm with hydrogen and stirred for 2 days. The pressure was released and the reaction mixture was filtered and concentrated under reduced pressure. The crude residue was passed

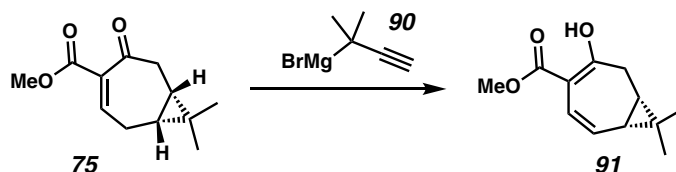
through a short silica plug (15% EtOAc/hexanes) to yield **83**. Major diastereomer: ^1H NMR (400 MHz, CDCl_3) δ = 3.74 (s, 3H), 3.20 (t, J = 14.0 Hz, 1H), 2.67 (ddd, J = 13.7, 8.7, 4.5 Hz, 2H), 2.47 – 2.42 (m, 2H), 2.16 (s, 3H), 1.75 – 1.67 (m, 1H), 0.87 (d, J = 1.6 Hz, 3H), 0.85 (d, J = 1.6 Hz, 3H); Minor diastereomer: ^1H NMR (400 MHz, CDCl_3) δ = 3.69 (s, 3H), 2.87 (dd, J = 13.8, 7.6 Hz, 1H), 2.81 – 2.72 (m, 1H), 2.57 (dd, J = 12.1, 7.5 Hz, 1H), 2.17 (s, 3H), 1.75 – 1.67 (m, 1H), 0.89 (d, J = 1.5 Hz, 3H), 0.88 (d, J = 3.3 Hz, 3H). Note: only key peaks are provided, indicating the absence of all olefinic resonances.



methyl (1aR,2aR,5aR,7aS)-1,1,3,3-tetramethyl-6-oxo-1,1a,2,2a,3,6,7,7a-octahydro-5aH-cyclopropa[f]azulene-5a-carboxylate 89.

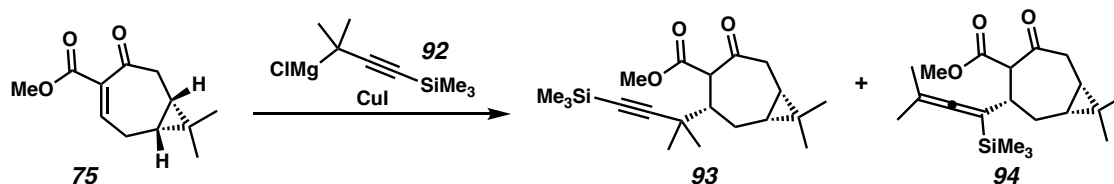
A 4 mL vial was charged with zinc powder (39 mg, 0.60 mmol, 2.5 equiv) and DME (1 mL) and cooled to $-15\text{ }^{\circ}\text{C}$. 3-bromo-3-methylbut-1-yne (80 μL , 88.2 mg, 0.60 mmol, 2.5 equiv) was added and the mixture was stirred. After 1 hour, most of the zinc had dissolved and ester **75** (50 mg, 0.24 mmol, 1.0 equiv) was added. The mixture was stirred at $-15\text{ }^{\circ}\text{C}$ overnight, then warmed to $60\text{ }^{\circ}\text{C}$ the following day. After stirring at this temperature for 2 days, the reaction was quenched with saturated aqueous NH_4Cl . The mixture was extracted, and the organic layer was concentrated. Purification by silica gel flash chromatography (5 $\rightarrow$ 10% EtOAc/hexanes) yielded **89**. ^1H NMR (400 MHz, CDCl_3) δ = 5.90 (d, J = 5.7 Hz, 1H), 5.44 (dd, J = 5.7, 0.7 Hz, 1H), 3.78 (s, 3H), 3.08 (dd, J = 13.5, 4.4 Hz, 1H), 2.98 (dd, J = 19.9, 8.8 Hz, 1H), 2.15 (dd, J = 19.9, 8.1 Hz, 1H), 1.90 (dt, J = 14.1, 4.0 Hz, 1H), 1.12

(s, 3H), 1.06 (s, 3H), 0.98 (s, 3H), 0.90 (ddd, $J = 12.1, 8.5, 3.6$ Hz, 1H), 0.84 – 0.76 (m, 1H), 0.75 (s, 3H), 0.49 (q, $J = 8.5$ Hz, 1H).



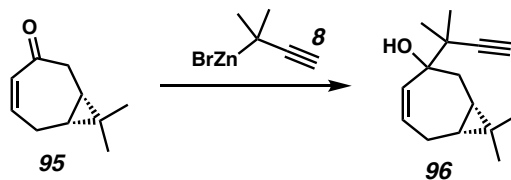
methyl (1R,7S)-5-hydroxy-8,8-dimethylbicyclo[5.1.0]octa-2,4-diene-4-carboxylate **91.**

A 1 M solution of propargylmagnesium bromide (**90**) in THF was prepared by charging a flame-dried Schlenk flask with magnesium turnings (97 mg, 4.0 mmol, 2.0 equiv) under vacuum. Anhydrous THF (1.7 mL) was added, followed by 3-bromo-3-methylbut-1-yne (294 mg, 2.00 mmol, 1.0 equiv) at room temperature. The reaction mixture was stirred and gently warmed to 38 °C, at which point it turned yellow and began to evolve gas. A white precipitate formed, and the mixture was heated to 50 °C for 1 hour, then allowed to cool. The resulting 1 M solution of the Grignard reagent was used directly in the next step without further purification. To a solution of the enone **75** (25 mg, 0.12 mmol, 1.0 equiv) in THF (1 mL) under argon at 0 °C was added the freshly prepared propargylmagnesium bromide (0.144 mL, 0.144 mmol, 1.2 equiv) in one portion. The reaction mixture turned slightly yellow and was stirred for 30 minutes, after which TLC analysis showed complete consumption of the starting material. The reaction was quenched by concentration under reduced pressure to afford **91**. ^1H NMR (500 MHz, CDCl_3) $\delta = 12.93$ (s, 1H), 6.08 (dd, $J = 11.1, 2.4$ Hz, 1H), 5.84 (ddd, $J = 11.1, 2.1, 0.7$ Hz, 1H), 3.78 (s, 3H), 2.49 – 2.36 (m, 2H), 1.36 – 1.32 (m, 1H), 1.11 (s, 3H), 1.08 (dt, $J = 8.2, 2.3$ Hz, 1H), 1.05 (s, 3H).



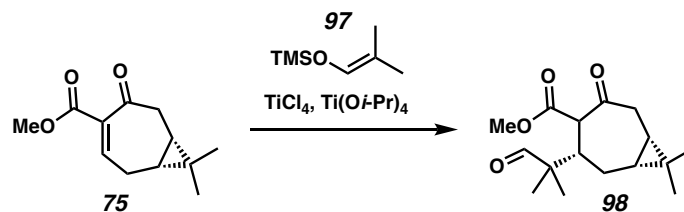
β-ketoesters 93 and 94.

To a test tube charged with magnesium turnings (42 mg, 1.7 mmol, 1.5 equiv) under nitrogen was added anhydrous THF (1 mL), followed by (3-Chloro-3-methyl-1-butyne-1-yl)trimethylsilane (250 mg, 1.1 mmol, 1.0 equiv). The mixture was heated to 60 °C, initiating the Grignard reaction, which proceeded rapidly to give a homogenous yellow solution with excess Mg settling at the bottom. After stirring at 60 °C for 20–30 minutes, the reaction was cooled to room temperature, resulting in the precipitation of a solid. The mixture was cooled to 0 °C, and CuI (130 mg, 0.68 mmol, 0.6 equiv) was added in one portion. In a separate vessel, a solution of enone **75** (40 mg, 0.21 mmol, 0.15 equiv) was prepared in THF (0.25 mL). The Gilman reagent was transferred to the enone solution. After stirring for 30 minutes at 0 °C, the reaction was quenched with saturated aqueous NH₄Cl and extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (2→5% EtOAc in hexanes) to afford **93** and **94**. Clean NMR spectra were not attained for **93** and **94**.



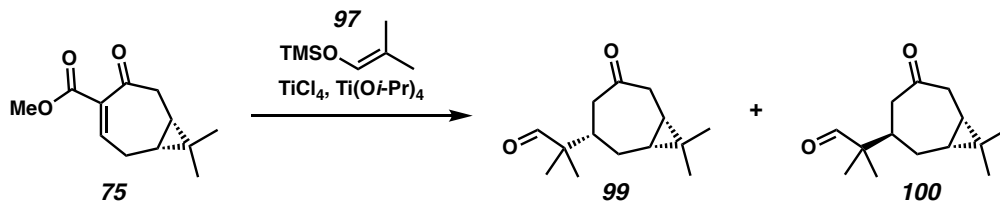
(1*S*,7*R*)-8,8-dimethyl-3-(2-methylbut-3-yn-2-yl)bicyclo[5.1.0]oct-4-en-3-ol **96.**

To a test tube charged with zinc dust (27 mg, 0.415 mmol, 2.5 equiv) and anhydrous DME (1.6 mL) was added 3-bromo-3-methylbut-1-yne (61 mg, 0.415 mmol, 2.5 equiv) at $-15\text{ }^{\circ}\text{C}$ under inert atmosphere. The mixture was stirred for 1 hour, after which a solution of enone **95** (25 mg, 0.166 mmol, 1.0 equiv) in Et₂O (0.4 mL) was added dropwise. The reaction was allowed to stir at $-15\text{ }^{\circ}\text{C}$ for an additional 1 hour and monitored by TLC, showing full consumption of starting material and formation of a clean new product spot. The reaction was quenched with saturated aqueous NH₄Cl and extracted with hexanes. The organic layer was dried over Na₂SO₄, filtered, and concentrated to yield **96**. ¹H NMR (500 MHz, CDCl₃) δ = 5.95 (ddd, J = 11.8, 8.6, 4.1 Hz, 1H), 5.61 (dt, J = 11.8, 2.8 Hz, 1H), 2.23 (s, 1H), 2.16 – 2.12 (m, 1H), 2.02 (s, 1H), 1.86 (dddd, J = 15.6, 11.1, 4.1, 2.9 Hz, 1H), 1.64 – 1.56 (m, 2H), 1.26 (d, J = 1.3 Hz, 6H), 1.11 (s, 3H), 1.04 (s, 3H), 1.02 – 0.97 (m, 1H), 0.85 – 0.79 (m, 1H).



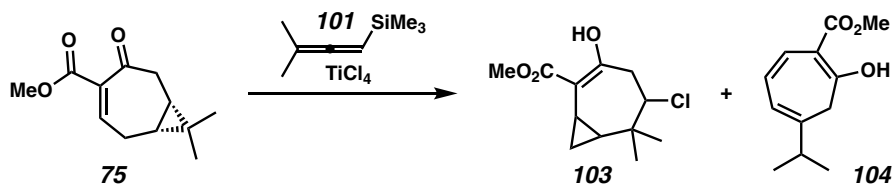
methyl (1*R*,3*S*,7*S*)-8,8-dimethyl-3-(2-methyl-1-oxopropan-2-yl)-5-oxobicyclo[5.1.0]octane-4-carboxylate 98.

A test tube under N₂ was charged with CH₂Cl₂ (3.0 mL) and cooled to −78 °C. TiCl₄ (143 mg, 0.75 mmol, 1.9 equiv) was added, followed by Ti(O*i*-Pr)₄ (142.1 mg, 0.50 mmol, 1.3 equiv). After 5 min, a solution of enone **75** (83 mg, 0.4 mmol, 1.0 equiv) in CH₂Cl₂ (0.8 mL) was added dropwise, and the mixture was stirred for 30 min before a solution of **97** (86 mg, 0.6 mmol, 1.4 equiv) in CH₂Cl₂ (0.8 mL) was added over 1 min. The reaction was stirred at −78 °C for 30 min before removing the cold bath and allowing the mixture to warm to 18 °C. The reaction was quenched with saturated aqueous NaHCO₃ (1 mL) and extracted with Et₂O (3 x 1 mL). The combined organic extracts were dried with Na₂SO₄ and concentrated under reduced pressure to yield **98**. ¹H NMR (400 MHz, C₆D₆) δ = 9.41 (s, 1H), 3.72 (p, *J* = 1.7 Hz, 1H), 3.66 (s, 3H), 2.87 (dd, *J* = 11.9, 10.7 Hz, 1H), 2.40 (ddd, *J* = 11.9, 6.5, 1.7 Hz, 1H), 2.19 – 2.10 (m, 2H), 1.69 (s, 1H), 1.13 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H), 0.98 (s, 3H), 0.73 – 0.66 (m, 1H), 0.62 (ddd, *J* = 10.8, 8.9, 6.5 Hz, 1H).



Ketones **99** and **100**.

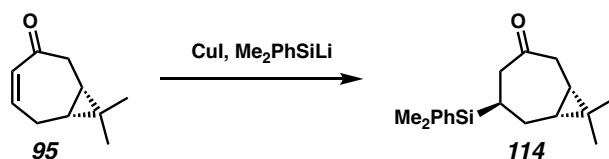
A test tube under N₂ was charged with CH₂Cl₂ (3.0 mL) and cooled to –78 °C. TiCl₄ (143 mg, 0.75 mmol, 1.9 equiv) was added, followed by Ti(Oi-Pr)₄ (142.1 mg, 0.50 mmol, 1.3 equiv). After 5 min, a solution of enone **75** (60 mg, 0.4 mmol, 1.0 equiv) in CH₂Cl₂ (0.8 mL) was added dropwise, and the mixture was stirred for 30 min before a solution of **97** (86 mg, 0.6 mmol, 1.4 equiv) in CH₂Cl₂ (0.8 mL) was added over 1 min. The reaction was stirred at –78 °C for 30 min before removing the cold bath and allowing the mixture to warm to 18 °C. The reaction was quenched with saturated aqueous NaHCO₃ (1 mL) and extracted with Et₂O (3 x 1 mL). The combined organic extracts were dried with Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (0→15% EtOAc in hexanes) to afford a mixture of **99** and **100**. Clean NMR spectra were not attained for **99** and **100**.



Chloride **103** and Enol **104**.

A 4 mL vial under N₂ was charged with allene **101** (20 mg, 0.14 mmol, 1.0 equiv) and CH₂Cl₂ (0.75 mL). Ester **75** (30 mg, 0.14 mmol, 1.0 equiv) was then added, and the solution was cooled to –78 °C. TiCl₄ (41 mg, 0.22 mmol, 1.5 equiv) was added dropwise. The

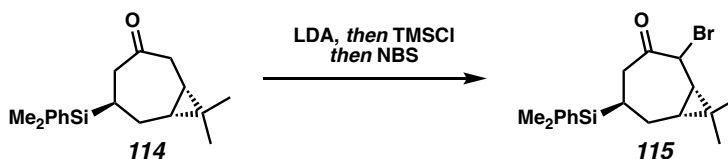
reaction was stirred as it gradually warmed to 18 °C over 2 h. Upon completion by TLC, the reaction was quenched with water and extracted with CH₂Cl₂, and the organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (5% EtOAc/hexanes) to furnish **103** and **104** as colorless oils. Characterization data for chloride **103**: ¹H NMR (400 MHz, CDCl₃) δ = 11.92 (s, 1H), 3.81 (s, 3H), 2.44 (ddd, *J* = 17.1, 5.7, 1.9 Hz, 1H), 2.38 – 2.28 (m, 1H), 2.01 (dd, *J* = 17.0, 12.3 Hz, 1H), 1.78 (td, *J* = 8.5, 4.6 Hz, 1H), 1.68 (s, 3H), 1.67 (s, 3H), 1.49 – 1.38 (m, 1H), 0.89 (td, *J* = 8.3, 5.1 Hz, 1H), 0.45 (dtd, *J* = 5.9, 4.9, 0.8 Hz, 1H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 172.6, 169.1, 99.0, 73.8, 51.8, 43.2, 30.9, 30.3, 27.5, 13.3, 10.3, 7.3. Characterization data for enol **104**: ¹H NMR (400 MHz, CDCl₃) δ = 12.50 (d, *J* = 1.0 Hz, 1H), 6.71 (d, *J* = 11.3 Hz, 1H), 6.24 (ddd, *J* = 11.4, 5.5, 0.6 Hz, 1H), 5.95 (dd, *J* = 5.5, 1.1 Hz, 1H), 3.81 (d, *J* = 1.0 Hz, 3H), 2.66 (s, 2H), 2.55 – 2.45 (m, 1H), 1.12 (s, 3H), 1.10 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 172.4, 166.6, 140.9, 124.7, 124.1, 120.4, 101.1, 51.9, 36.6, 35.9, 21.1.



(1*S*,5*R*,7*R*)-5-(dimethyl(phenyl)silyl)-8,8-dimethylbicyclo[5.1.0]octan-3-one 114.

A 25 mL Schlenk flask under N₂ was charged with CuI (757 mg, 3.4 mmol, 1.3 equiv) and THF (3 mL) and cooled to –23 °C. Dimethyl(phenyl)silyllithium (0.86 M in THF, 9.23 mL, 7.9 mmol, 2.7 equiv) was added slowly over 5 min and the mixture was stirred at –23 °C for 4 h. Enone **95** (448 mg, 2.99 mmol, 1.0 equiv) in THF (3 mL) was then added, and the reaction was stirred for an additional 30 min. The reaction was poured into 25 g crushed

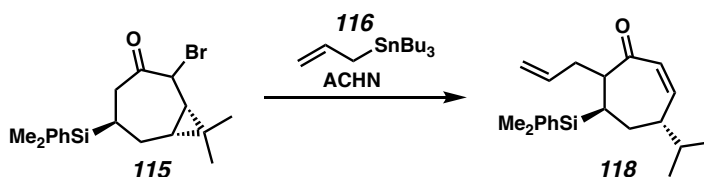
ice with concentrated aq. HCl (5 mL) and extracted with CH₂Cl₂ (3x). The combined organic extracts were washed with aq. 3M HCl, saturated NaHCO₃, water, and dried over Na₂SO₄. After concentration under reduced pressure the crude residue was purified by silica gel chromatography (3→7.5% EtOAc/hexanes) to furnish **114** as an oil. ¹H NMR (500 MHz, CDCl₃) δ = 7.52 – 7.49 (m, 2H), 7.38 – 7.36 (m, 3H), 2.91 (t, *J* = 11.8 Hz, 1H), 2.62 (dd, *J* = 17.6, 8.0 Hz, 1H), 2.19 (dd, *J* = 12.0, 4.9 Hz, 1H), 2.13 (dd, *J* = 17.6, 9.4 Hz, 1H), 1.94 (ddd, *J* = 14.9, 5.4, 2.7 Hz, 1H), 1.45 – 1.38 (m, 1H), 1.37 – 1.30 (m, 1H), 1.04 (s, 3H), 0.96 (s, 3H), 0.77 – 0.71 (m, 1H), 0.60 (ddd, *J* = 11.2, 8.9, 5.3 Hz, 1H), 0.37 (s, 3H), 0.35 (s, 3H). Note: a minor diastereomer was also observed (1 : 0.3) but is inseparable from the major diastereomer.



(1*S*,5*R*,7*R*)-2-bromo-5-(dimethyl(phenyl)silyl)-8,8-dimethylbicyclo[5.1.0]octan-3-one
115.

A test tube under N₂ was charged with *i*-Pr₂NH (85 mg, 0.84 mmol, 1.2 equiv) and THF (1.7 mL) and cooled to –78 °C. *n*-BuLi (2.5 M in hexanes, 0.3 mL, 0.735 mmol, 1.05 equiv) was added dropwise. After 30 min, ketone **114** (200 mg, 0.70 mmol, 1.0 equiv) in THF (0.6 mL) was added slowly. After another 30 min, TMSCl (114 mg, 1.05 mmol, 1.5 equiv, 0.133 mL) was added slowly and the reaction was allowed to warm to 18 °C. After 1 h, *n*-bromosuccinimide (187 mg, 1.05 mmol, 1.5 equiv) was added in one portion and the reaction was stirred at 18 °C for 20 minutes. The reaction was quenched with saturated aqueous NaHCO₃ and poured into Et₂O, and the aqueous phase was extracted once more

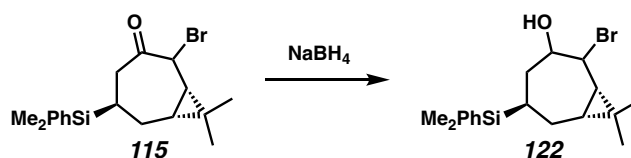
with Et₂O. The combined organic layers were washed with water and brine, dried over Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (0→5% EtOAc/hexanes) to furnish **115** as an oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.52 – 7.49 (m, 2H), 7.40 – 7.36 (m, 3H), 4.30 (d, *J* = 10.1 Hz, 1H), 2.82 (dd, *J* = 13.7, 9.1 Hz, 1H), 2.41 (dd, *J* = 13.7, 5.0 Hz, 1H), 2.06 – 2.00 (m, 1H), 1.53 – 1.44 (m, 2H), 1.10 (s, 3H), 1.08 (s, 3H), 1.07 – 1.01 (m, 1H), 0.84 – 0.73 (m, 1H), 0.35 (d, *J* = 6.0 Hz, 6H).



(4*S*,6*R*)-7-allyl-6-(dimethyl(phenyl)silyl)-4-isopropylcyclohept-2-en-1-one **118.**

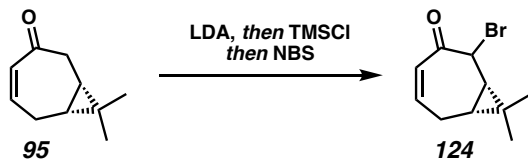
A Teflon-stoppered flask was charged with bromide **115** (74 mg, 0.20 mmol, 1.0 equiv), ACHN (9.8 mg, 0.04 mmol, 0.2 equiv), allylstannane **116** (265 mg, 0.80 mmol, 4.0 equiv), and PhH (2.8 mL) and heated to 76 °C in an oil bath. After 48 h, an additional portion of ACHN (10 mg) was added and the reaction was heated at 76 °C overnight. The flask was removed from the oil bath and allowed to cool before the solvent was removed under reduced pressure. The crude residue was purified by silica gel chromatography (2→6% EtOAc/hexanes) to furnish **118** as an oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.53 – 7.49 (m, 2H), 7.38 – 7.34 (m, 3H), 6.31 (ddd, *J* = 12.4, 3.2, 0.8 Hz, 1H), 5.91 (dd, *J* = 12.4, 2.5 Hz, 1H), 5.64 – 5.51 (m, 1H), 4.95 – 4.86 (m, 2H), 2.79 (ddd, *J* = 9.1, 6.9, 5.1 Hz, 1H), 2.43 (dddt, *J* = 14.1, 9.1, 6.5, 1.3 Hz, 1H), 2.23 (ddt, *J* = 11.6, 5.7, 2.9 Hz, 1H), 2.14 (dddt, *J* = 13.8, 7.4, 5.1, 1.1 Hz, 1H), 1.83 – 1.75 (m, 1H), 1.74 – 1.67 (m, 2H), 1.33 – 1.29 (m, 1H),

0.83 (dd, $J = 6.9, 5.6$ Hz, 6H), 0.36 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) $\delta = ^{13}\text{C}$ NMR (101 MHz, CDCl_3) $\delta = 206.8, 147.3, 138.1, 136.2, 134.0, 131.5, 129.4, 128.1, 116.5, 54.2, 46.9, 37.2, 32.8, 29.3, 25.2, 20.1, 19.4, -2.7, -2.9$.



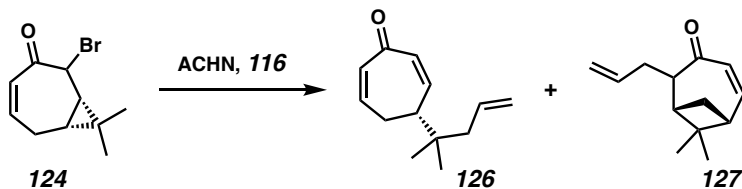
(1*S*,5*R*,7*R*)-2-bromo-5-(dimethyl(phenyl)silyl)-8,8-dimethylbicyclo[5.1.0]octan-3-ol
122.

A 4 mL vial under N_2 was charged with bromide **115** (23 mg, 0.063 mmol, 1.0 equiv) and MeOH (0.4 mL) and cooled to 0 °C. NaBH_4 (29 mg, 0.78 mmol, 12 equiv) was added in one portion and the cold bath was removed after 20 min. After an additional 20 min, the reaction was quenched with saturated aqueous NH_4Cl . The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 , filtered again, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (2→10% EtOAc/hexanes) to furnish **122** as a single diastereomer. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.51$ (dddd, $J = 6.9, 4.7, 3.2, 1.5$ Hz, 2H), 7.39 – 7.34 (m, 3H), 4.05 (dddd, $J = 9.6, 5.9, 4.0, 2.2$ Hz, 1H), 3.80 (dd, $J = 11.3, 9.4$ Hz, 1H), 2.27 (dd, $J = 2.2, 1.1$ Hz, 1H), 2.20 (dddd, $J = 13.4, 8.1, 3.5, 1.1$ Hz, 1H), 1.94 – 1.86 (m, 1H), 1.62 (ddd, $J = 14.5, 5.5, 3.4$ Hz, 1H), 1.42 (ddt, $J = 9.0, 7.4, 3.8$ Hz, 1H), 1.32 (dt, $J = 11.3, 3.7$ Hz, 1H), 1.11 – 1.07 (m, 1H), 1.06 (d, $J = 4.7$ Hz, 6H), 0.69 – 0.60 (m, 1H), 0.33 (d, $J = 2.3$ Hz, 6H).



(1*S*,7*R*)-2-bromo-8,8-dimethylbicyclo[5.1.0]oct-4-en-3-one (124).

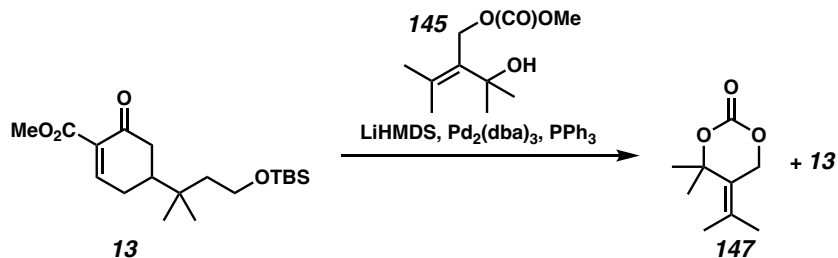
A test tube under N₂ was charged with *i*-Pr₂NH (76 mg, 0.75 mmol, 1.2 equiv) and THF (1.5 mL) and cooled to −78 °C. *n*-BuLi (2.5M in hexanes 0.27 mL, 0.66 mmol, 1.05 equiv) was added slowly. After 30 min, enone **95** (101 mg, 0.63 mmol, 1.0 equiv) was added slowly. After an additional 1.5 h, TMSCl (103 mg, 0.95 mmol, 1.5 equiv) was added and the reaction was allowed to warm to 18 °C. *n*-Bromosuccinimide (168 mg, 0.95 mmol, 1.5 equiv) was added and the mixture was stirred for 40 min. The reaction was quenched with saturated aqueous NaHCO₃, extracted with Et₂O (2x), washed with water and brine, and dried over Na₂SO₄ before concentration under reduced pressure. The crude residue was purified by silica gel chromatography (5→10% EtOAc/hexanes) to furnish **124** as an oil. ¹H NMR (400 MHz, CDCl₃) δ = 6.86 (ddd, *J* = 12.0, 8.7, 3.5 Hz, 1H), 6.20 (dd, *J* = 11.7, 3.2 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 2.69 (ddd, *J* = 17.0, 8.7, 6.4 Hz, 1H), 2.10 (ddt, *J* = 17.3, 10.9, 3.4 Hz, 1H), 1.32 – 1.27 (m, 4H), 1.20 – 1.12 (m, 4H).



Trienone 126 and cyclobutane 127.

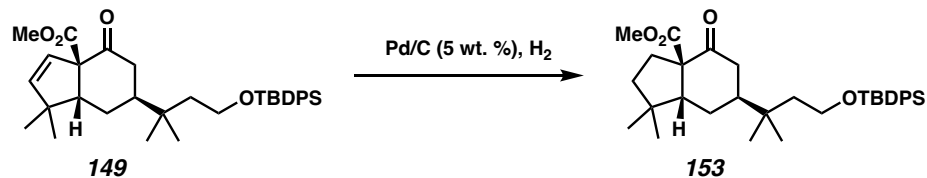
A flame-dried 8 mL vial was charged with bromide **124** (65 mg, 0.28 mmol, 1.0 equiv), PhH (3.75 mL), and ACHN (14 mg, 0.057 mmol, 0.2 equiv) under N₂. Allylstannane **116**

(370 mg, 1.1 mmol, 4.0 equiv) was added, and the mixture was heated to 84 °C. After 48 hours, the reaction mixture was concentrated, and the crude residue was purified by silica gel chromatography (5→12% EtOAc/hexanes). The pure fractions consisted of a mixture of **126** and **127** which were further separated by preparatory HPLC (65→75 MeCN/H₂O, 12 mL/min, C18 column). Characterization data for trienone **126**: ¹H NMR (400 MHz, CDCl₃) δ = 6.78 – 6.70 (m, 1H), 6.70 – 6.64 (m, 1H), 6.13 (ddt, *J* = 12.9, 9.7, 2.2 Hz, 2H), 5.77 (ddt, *J* = 16.9, 10.2, 7.5 Hz, 1H), 5.11 – 5.01 (m, 2H), 2.56 – 2.45 (m, 2H), 2.31 (dddd, *J* = 16.5, 12.8, 4.9, 2.3 Hz, 1H), 2.10 (ddt, *J* = 7.5, 6.4, 1.2 Hz, 2H), 0.96 (d, *J* = 1.7 Hz, 6H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 146.3, 145.2, 134.4, 133.5, 133.0, 118.2, 46.1, 44.7, 36.1, 28.6, 24.9, 24.8. Note: the ketone carbon resonance for **126** is not visible due to low sample concentration. Characterization data for cyclobutane **127**: ¹H NMR (400 MHz, CDCl₃) δ = 7.01 (dd, *J* = 9.7, 6.8 Hz, 1H), 5.89 (dd, *J* = 9.7, 1.7 Hz, 1H), 5.74 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.08 – 4.98 (m, 2H), 2.47 – 2.29 (m, 3H), 2.25 (q, *J* = 1.5 Hz, 1H), 2.04 – 1.90 (m, 2H), 1.79 (dd, *J* = 12.6, 8.4 Hz, 1H), 1.11 (s, 3H), 1.04 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 203.7, 153.1, 137.3, 127.6, 116.1, 65.0, 48.6, 48.3, 39.9, 38.9, 34.1, 27.5, 22.4.



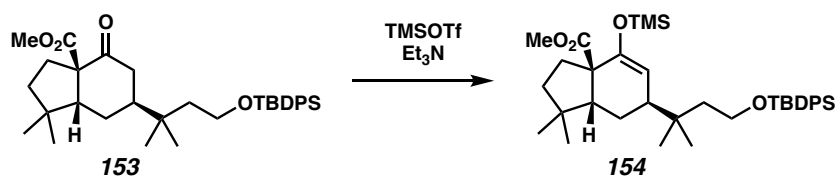
4,4-dimethyl-5-(propan-2-ylidene)-1,3-dioxan-2-one **147.**

A 4 mL vial under N₂ was charged with enone **13** (50 mg, 0.141 mmol, 1.0 equiv) and DMF (0.22 mL), then cooled to 0 °C. LiHMDS (1.0 M in THF, 0.18 mL, 0.183 mmol, 1.3 equiv) was added dropwise to the solution. In a separate 4 mL vial, Pd₂(dba)₃ (3.2 mg, 0.0035 mmol, 0.025 equiv) and PPh₃ (3.7 mg, 0.014 mmol, 0.1 equiv) were dissolved in DMF (1.2 mL) and stirred at 18 °C to form a homogeneous solution. Carbonate **145** (35 mg, 0.17 mmol, 1.2 equiv) was added neat to the Pd solution, after which the enolate solution was added slowly. The reaction was stirred 20 h after which the reaction mixture was cooled to 0 °C and quenched with saturated aqueous NH₄Cl (1 mL). EtOAc and water were added, and the layers were separated. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (10% EtOAc/hexanes) to furnish **147** and a mixture of enol and keto tautomers of **13**. ¹H NMR (500 MHz, CDCl₃) δ = 4.73 (dt, *J* = 2.4, 1.3 Hz, 2H), 1.82 (t, *J* = 1.3 Hz, 3H), 1.74 (d, *J* = 0.8 Hz, 3H), 1.65 (s, 6H).



methyl 6-(4-((*tert*-butyldiphenylsilyl)oxy)-2-methylbutan-2-yl)-1,1-dimethyl-4-oxooctahydro-3a*H*-indene-3a-carboxylate 153.

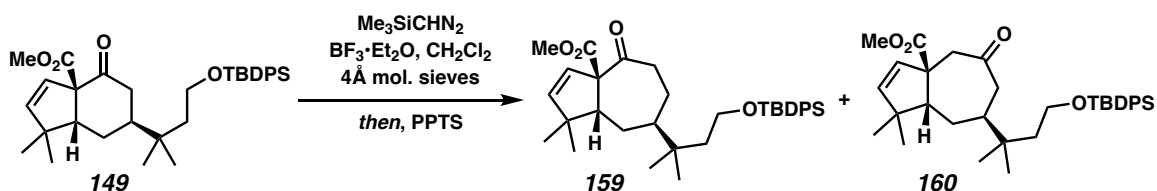
A 25 mL round-bottom flask was charged with ketone **149** (81 mg, 0.15 mmol, 1.0 equiv) and EtOAc (1 mL), then purged with N₂. Pd/C (16 mg) was added, and the flask was purged with H₂ and stirred at 18 °C for 20 h. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure to furnish **153** as an oil. ¹H NMR (500 MHz, C₆D₆) δ = 7.81 – 7.77 (m, 4H), 7.28 – 7.23 (m, 6H), 3.73 (ddt, *J* = 10.1, 6.1, 3.1 Hz, 2H), 3.24 (s, 3H), 3.01 (ddd, *J* = 14.2, 10.9, 8.1 Hz, 1H), 2.71 (dd, *J* = 5.7, 2.6 Hz, 1H), 2.54 – 2.48 (m, 1H), 2.23 (t, *J* = 12.3 Hz, 1H), 1.94 (ddd, *J* = 14.1, 8.9, 2.7 Hz, 1H), 1.73 – 1.57 (m, 4H), 1.51 (ddd, *J* = 13.8, 8.1, 6.3 Hz, 1H), 1.44 – 1.37 (m, 1H), 1.34 (ddd, *J* = 12.3, 8.1, 2.6 Hz, 1H), 1.19 (s, 9H), 0.83 (s, 3H), 0.67 (s, 3H), 0.63 (s, 3H), 0.59 (s, 3H).



methyl 6-(4-((*tert*-butyldiphenylsilyl)oxy)-2-methylbutan-2-yl)-1,1-dimethyl-4-((trimethylsilyl)oxy)-1,2,3,6,7,7a-hexahydro-3a*H*-indene-3a-carboxylate 154.

A 25 mL flask under N₂ was charged with ketone **153** (75 mg, 0.14 mmol, 1.0 equiv) and CH₂Cl₂ (0.85 mL) and cooled to 0 °C. Et₃N (139 mg, 1.37 mmol, 10.0 equiv) was added, followed by slow addition of TMSOTf (122 mg, 0.55 mmol, 4.0 equiv). After 5 minutes,

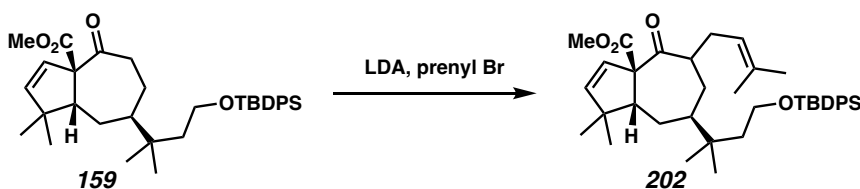
the cold bath was removed and the reaction was stirred at 18 °C for 24 h. The reaction mixture was cooled to 0 °C and quenched with saturated aqueous NaHCO₃. The mixture was extracted with Et₂O (3 × 1 mL), the combined organic layers were dried over Na₂SO₄, and the solvent was removed under reduced pressure. The crude residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 5–7.5% EtOAc/hexanes) to furnish **154** as an oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.73 – 7.65 (m, 4H), 7.46 – 7.34 (m, 6), 4.80 (d, *J* = 2.3 Hz, 1H), 3.79 – 3.69 (m, 2H), 3.63 (d, *J* = 0.8 Hz, 3H), 2.46 – 2.37 (m, 1H), 2.05 (ddd, *J* = 9.4, 6.7, 2.3 Hz, 1H), 1.92 – 1.82 (m, 2H), 1.67 – 1.58 (m, 2H), 1.56 – 1.43 (m, 4H), 1.05 (d, *J* = 1.0 Hz, 9H), 0.96 (s, 3H), 0.88 (s, 3H), 0.83 (s, 3H), 0.82 (s, 3H), 0.16 (d, *J* = 0.8 Hz, 9H).



Ketones **159** and **160**.

A vial was charged with 4Å molecular sieves (450 mg) in a glovebox, followed by a solution of ketone **149** (100 mg, 0.27 mmol, 1.0 equiv) in CH₂Cl₂ (3 mL), and the mixture was cooled to –78 °C. BF₃·OEt₂ (43 mg, 0.30 mmol, 1.1 equiv) was added, followed by slow addition of Me₃SiCHN₂ (2 M in CH₂Cl₂, 0.41 mL, 0.82 mmol, 3.0 equiv). After 2 h the cold bath was removed and the reaction was stirred at 18 °C for 10 min. The reaction was quenched with saturated aqueous NaHCO₃ and extracted with EtOAc (3 × 1 mL), and the combined organic extracts were centrifuged. The resulting solution was dried over Na₂SO₄ and concentrated under reduced pressure. The crude residue was dissolved in 1:1

MeOH/CH₂Cl₂ (3 mL) containing PPTS (15 mg, 0.06 mmol, 0.22 equiv), and the mixture was stirred at 18 °C for 18 h. A drop of dimethylethylamine was added, and the solvent was removed under reduced pressure. The residue was purified by a short silica gel plug followed by preparative HPLC (C18, 100% MeCN, 14 mL/min, eluted at 2–4 min) to furnish ketones **159** and **160**. Characterization data for **159**: ¹H NMR (400 MHz, C₆D₆) δ = 7.84 – 7.79 (m, 4H), 7.25 (ddt, *J* = 6.3, 3.3, 1.1 Hz, 6H), 5.77 (d, *J* = 5.6 Hz, 1H), 5.49 (d, *J* = 5.6 Hz, 1H), 3.74 (dddd, *J* = 26.0, 10.1, 8.2, 6.6 Hz, 2H), 3.26 – 3.21 (m, 4H), 2.59 (ddd, *J* = 17.8, 4.5, 3.4 Hz, 1H), 2.07 (ddd, *J* = 17.6, 13.8, 3.5 Hz, 1H), 1.78 – 1.59 (m, 4H), 1.34 – 1.27 (m, 1H), 1.26 – 1.22 (m, 1H), 1.21 – 1.78 (m, 10H), 1.14 (s, 3H), 0.83 (s, 3H), 0.82 (s, 3H), 0.80 (s, 3H). Characterization data for **160**: ¹H NMR (400 MHz, C₆D₆) δ = 7.83 (ddd, *J* = 7.0, 5.2, 2.1 Hz, 4H), 7.27 – 7.23 (m, 6H), 5.65 (d, *J* = 5.8 Hz, 1H), 5.43 (d, *J* = 5.8 Hz, 1H), 3.87 (t, *J* = 7.5 Hz, 2H), 3.29 (s, 3H), 2.73 (d, *J* = 5.0 Hz, 1H), 2.72 – 2.69 (m, 1H), 2.30 (d, *J* = 4.9 Hz, 1H), 1.86 – 1.62 (m, 6H), 1.20 (s, 9H), 1.16 (s, 3H), 1.08 – 1.03 (m, 1H), 0.99 (s, 3H), 0.81 (s, 3H), 0.77 (s, 3H).



methyl 7-(4-((*tert*-butyldiphenylsilyl)oxy)-2-methylbutan-2-yl)-1,1-dimethyl-5-(3-methylbut-2-en-1-yl)-4-oxo-4,5,6,7,8,8a-hexahydroazulene-3a(1*H*)-carboxylate 202.

A test tube under N₂ was charged with *i*-Pr₂NH (11 mg, 0.108 mmol, 12 equiv), THF (0.2 mL), and the mixture was cooled to –78 °C. *n*-BuLi (2.5 M in hexanes, 36 μL, 0.09 mmol, 10 equiv) was added slowly. After 15 min, ketone **159** (5 mg, 0.009 mmol, 1.0 equiv) in

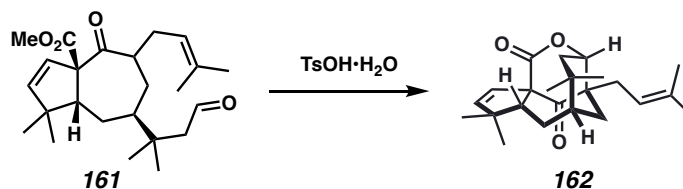
THF (0.05 mL) was added dropwise. After 1.5 h, prenyl bromide (27 mg, 0.18 mmol, 20 equiv) was added dropwise. After 5 min, the reaction was transferred to an ice bath at 0 °C. After 45 min, the reaction was quenched with saturated aqueous NH₄Cl (1 mL), extracted with EtOAc (1 mL × 3), dried over Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by passing through a short silica gel plug (20% EtOAc/hexanes) to furnish **202** as an oil. ¹H NMR (500 MHz, C₆D₆) δ = 7.82 (dp, *J* = 6.2, 2.2 Hz, 4H), 7.26 (ddd, *J* = 9.8, 4.9, 2.9 Hz, 6H), 5.93 (d, *J* = 5.6 Hz, 1H), 5.47 (d, *J* = 5.6 Hz, 1H), 5.23 (dddd, *J* = 7.8, 6.2, 2.8, 1.4 Hz, 1H), 3.79 (ddd, *J* = 8.3, 6.6, 1.7 Hz, 2H), 3.41 – 3.36 (m, 1H), 3.30 (s, 3H), 2.63 – 2.54 (m, 1H), 2.32 (tt, *J* = 9.6, 5.0 Hz, 1H), 2.18 (dt, *J* = 14.2, 8.9 Hz, 1H), 1.80 – 1.68 (m, 3H), 1.66 (d, *J* = 1.4 Hz, 3H), 1.57 (s, 3H), 1.52 – 1.46 (m, 1H), 1.35 (t, *J* = 6.3 Hz, 1H), 1.30 (dd, *J* = 9.3, 3.1 Hz, 1H), 1.21 (s, 9H), 1.19 (d, *J* = 3.3 Hz, 1H), 1.14 (s, 3H), 0.89 (d, *J* = 1.2 Hz, 6H), 0.86 (s, 3H).



methyl 7-(4-hydroxy-2-methylbutan-2-yl)-1,1-dimethyl-5-(3-methylbut-2-en-1-yl)-4-oxo-4,5,6,7,8,8a-hexahydroazulene-3a(1*H*)-carboxylate 161.

A 4 mL vial under N₂ was charged with ketone **202** (5.5 mg, 0.009 mmol, 1.0 equiv) and THF (0.5 mL), and the solution was cooled to 0 °C. TBAF (1 M in THF, 30 μL, 0.027 mmol, 3.0 equiv) was added dropwise. The ice bath was removed and the reaction was allowed to warm to 18 °C. After 24 h, the reaction was quenched with saturated aqueous NH₄Cl (1 mL), extracted with EtOAc (1 mL × 3), dried over Na₂SO₄, and concentrated

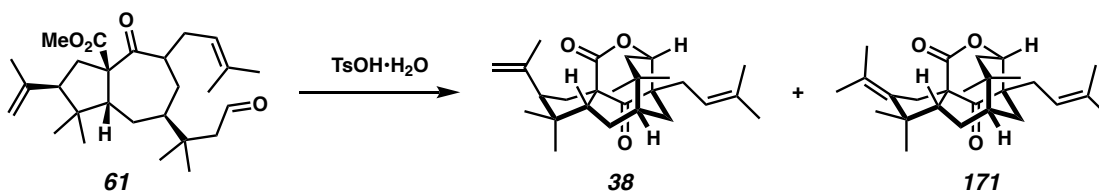
under reduced pressure to furnish the alcohol as a colorless oil that was directly used in the next step. A 4 mL vial was charged with DMP (11 mg, 0.023 mmol, 2.5 equiv), followed by a solution of crude alcohol (0.009 mmol, 1.0 equiv) in CH₂Cl₂ (0.4 mL). The mixture was stirred at 18 °C for 1 h. The crude reaction mixture was purified by passing through a short silica gel plug (20% EtOAc/hexanes) followed by preparative thin-layer chromatography (20% EtOAc/hexanes) to furnish **161** as an oil. ¹H NMR (400 MHz, C₆D₆) δ = 9.51 – 9.46 (m, 1H), 5.88 (d, J = 5.6 Hz, 1H), 5.46 (d, J = 5.6 Hz, 1H), 5.22 (ddp, J = 7.7, 6.0, 1.5 Hz, 1H), 3.29 (s, 3H), 3.29 – 3.25 (m, 1H), 2.64 – 2.54 (m, 1H), 2.32 (dddd, J = 12.4, 9.5, 5.1, 2.9 Hz, 1H), 2.21 – 2.12 (m, 1H), 2.02 (dd, J = 14.6, 3.1 Hz, 1H), 1.90 (dd, J = 14.6, 2.9 Hz, 1H), 1.68 (d, J = 1.2 Hz, 3H), 1.66 – 1.58 (m, 3H), 1.57 (d, J = 1.1 Hz, 3H), 1.34 – 1.27 (m, 2H), 1.08 (s, 3H), 0.89 (s, 3H), 0.86 (s, 3H), 0.84 (s, 3H).



1,1,8,8-tetramethyl-5-(3-methylbut-2-en-1-yl)-1,5,6,7,8,9,10,10a-octahydro-4H-6,3a-(epoxymethano)-5,9-methanocyclopenta[9]annulene-4,13-dione **162.**

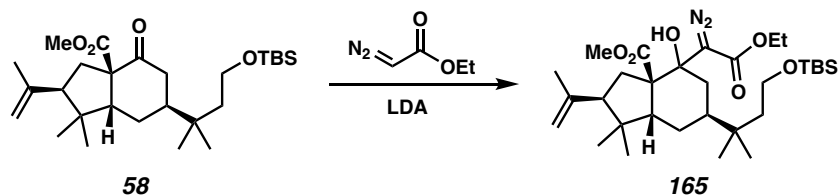
A 4 mL vial under N₂ was charged with TsOH·H₂O (1.7 mg, 0.009 mmol, 1.0 equiv), dissolved in CH₂Cl₂ (0.1 mL). Aldehyde **161** (2.5 mg, 0.009 mmol, 1.0 equiv) in CH₂Cl₂ (0.2 mL) was added. The mixture was heated to 35 °C for 24 h, after which the crude mixture was passed through a short silica gel plug. The residue was purified by preparative thin-layer chromatography to furnish an impure sample of **162**. ¹H NMR (400 MHz, C₆D₆) δ = 5.90 – 5.87 (m, 1H) 5.38 (d, J = 5.6 Hz, 1H), 4.77 (d, J = 12.9 Hz, 3H), 4.35 – 4.26 (m,

1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.00 (s, 3H), 0.99 (d, $J = 1.9$ Hz, 3H), 0.80 (s, 3H), 0.78 (s, 3H). Note: only key peaks are provided, indicating the presence of 6 methyl groups, the 3 olefin resonances, the notable the α -hydroxy proton at 4.26 ppm, and the absence of the methyl ester peak.



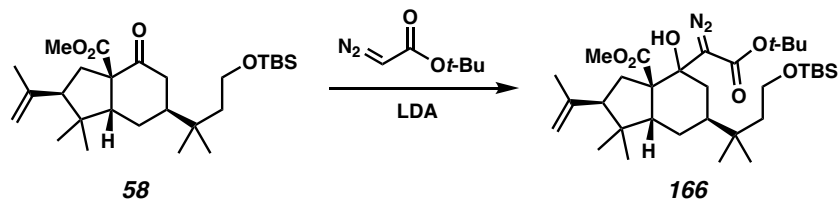
Lactones **38** and **171**.

A 100 mL flask was charged with aldehyde **61** (180 mg, 0.42 mmol, 1.0 equiv), *p*-TsOH·H₂O (400 mg, 2.1 mmol, 5.0 equiv) and CH₂Cl₂ (60 mL). The flask was sealed under Ar and stirred at 23 °C for 4 d. The solution was concentrated under reduced pressure, hexanes (20 mL) was added, and the solution was filtered to remove *p*-TsOH·H₂O. The crude residue was purified by flash silica gel chromatography (0→10% EtOAc/hexanes) to provide a 3:2 mixture of olefin isomers **38** and **171**, respectively. This mixture was further purified by preparatory SFC (silica gel, 1% *i*-PrOH/CO₂, 25 mL/min) to furnish **38** (45 mg, 25% yield) and **171** (31 mg, 17% yield) as a colorless, crystalline solid. Characterization data for **38** is provided in Chapter 2. Characterization data for **171**: ¹H NMR (600 MHz, C₆D₆) δ = 5.22 – 5.14 (m, 1H), 4.59 (dd, $J = 10.5, 7.4$ Hz, 1H), 3.58 (d, $J = 15.8$ Hz, 1H), 3.16 (d, $J = 15.7$ Hz, 1H), 2.69 (dd, $J = 14.4, 8.3$ Hz, 1H), 2.43 (dd, $J = 13.4, 3.6$ Hz, 1H), 2.28 (dd, $J = 14.4, 6.9$ Hz, 1H), 1.90 (dd, $J = 16.1, 10.6$ Hz, 1H), 1.82 – 1.77 (m, 4H), 1.73 – 1.67 (m, 4H), 1.62 – 1.57 (m, 4H), 1.55 (s, 3H), 1.44 (dd, $J = 14.2, 3.7$ Hz, 1H), 1.21 (s, 3H), 1.17 – 1.08 (m, 2H), 0.90 (s, 3H), 0.68 (s, 3H), 0.61 (s, 3H).



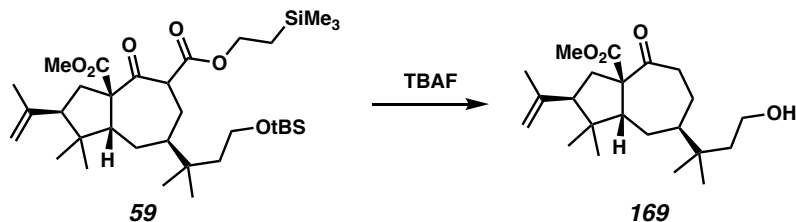
methyl 6-(4-((*tert*-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)-4-(1-diazo-2-ethoxy-2-oxoethyl)-4-hydroxy-1,1-dimethyl-2-(prop-1-en-2-yl)octahydro-3a*H*-indene-3a-carboxylate **165.**

A small test tube under N₂ was charged with *i*-Pr₂NH (24 mg, 0.234 mmol, 20 equiv) and THF (50 μ L), and the mixture was cooled to -78 $^{\circ}$ C. *n*-BuLi (2.5 M in hexanes, 75 μ L, 0.187 mmol, 16 equiv) was added slowly. After 15 min, ethyl diazoacetate (23.5 mg, 0.176 mmol, 15 equiv) in THF (50 μ L) was added slowly. After 20 min, ketone **58** (4 mg, 0.012 mmol, 1.0 equiv) in THF (0.1 mL) was added dropwise. After 20 min, AcOH (50 μ L) in THF (0.1 mL) was added. The reaction mixture was extracted with water (1 mL) and EtOAc, dried over Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0 $\rightarrow$ 20% EtOAc/hexanes) to furnish **165** as a yellow oil. ¹H NMR (400 MHz, C₆D₆) δ = 5.79 (s, 1H), 4.95 (t, *J* = 1.7 Hz, 1H), 4.90 (d, *J* = 2.0 Hz, 1H), 3.90 – 3.76 (m, 4H), 3.37 (s, 3H), 2.94 (dd, *J* = 12.8, 11.1 Hz, 1H), 2.87 – 2.71 (m, 2H), 2.50 (dd, *J* = 9.8, 6.1 Hz, 1H), 2.30 – 2.20 (m, 2H), 1.96 (d, *J* = 6.5 Hz, 1H), 1.87 – 1.77 (m, 1H), 1.76 – 1.64 (m, 6H), 1.08 (s, 3H), 1.02 (s, 9H), 1.01 – 0.99 (m, 3H), 0.96 (s, 3H), 0.83 – 0.77 (m, 6H), 0.12 (s, 6H).



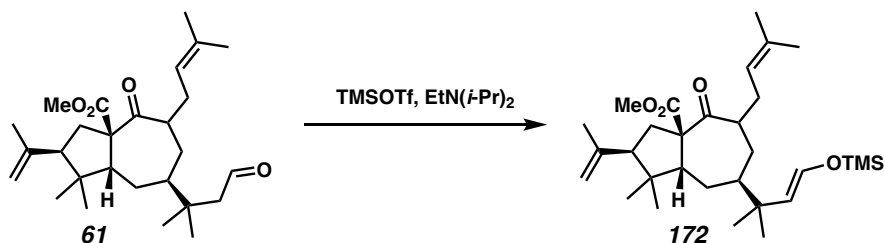
methyl 4-(2-(*tert*-butoxy)-1-diazo-2-oxoethyl)-6-(4-((*tert*-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)-4-hydroxy-1,1-dimethyl-2-(prop-1-en-2-yl)octahydro-3a*H*-indene-3a-carboxylate **166.**

A small test tube under N₂ was charged with *i*-Pr₂NH (47 mg, 0.47 mmol, 20 equiv) and THF (0.1 mL), and the mixture was cooled to −78 °C. *n*-BuLi (2.5 M in hexanes, 0.15 mL, 0.37 mmol, 16 equiv) was added slowly. After 15 min, *t*-butyl diazoacetate (60 mg, 0.42 mmol, 18 equiv) in THF (0.1 mL) was added slowly. After 20 min, ketone **58** (8 mg, 0.023 mmol, 1.0 equiv) in THF (0.2 mL) was added dropwise. After 20 min, AcOH (0.1 mL) in THF (0.2 mL) was added. The reaction mixture was extracted with water (1 mL) and EtOAc, dried over Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→20% EtOAc/hexanes) to furnish **166** as a yellow oil. ¹H NMR (600 MHz, C₆D₆) δ = 5.82 (s, 1H), 4.95 (t, *J* = 1.7 Hz, 1H), 4.91 (s, 1H), 3.79 (t, *J* = 7.2 Hz, 2H), 3.40 (s, 3H), 2.93 (dd, *J* = 13.5, 11.4 Hz, 1H), 2.86 – 2.74 (m, 2H), 2.50 (dd, *J* = 9.8, 6.0 Hz, 1H), 2.23 (td, *J* = 8.0, 3.8 Hz, 2H), 1.97 (d, *J* = 6.3 Hz, 1H), 1.82 (ddd, *J* = 15.8, 9.6, 6.4 Hz, 1H), 1.77 – 1.64 (m, 6H), 1.27 (s, 9H), 1.09 (s, 3H), 1.02 (s, 9H), 0.99 (s, 3H), 0.96 (s, 3H), 0.83 (s, 3H), 0.12 (s, 6H).



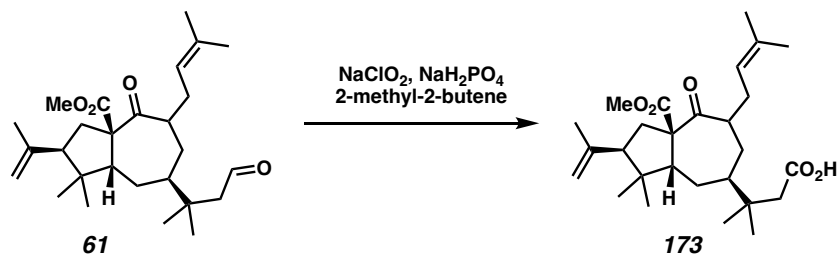
methyl 7-(4-hydroxy-2-methylbutan-2-yl)-1,1-dimethyl-4-oxo-2-(prop-1-en-2-yl)octahydroazulene-3a(1*H*)-carboxylate 169.

A small test tube under N₂ was charged with ketoester **59** (1 mg, 1.6 μmol, 1.0 equiv) and THF (16 μL). TBAF (1 M in THF, 5 μL, 4.8 μmol, 3.0 equiv) was added and the reaction mixture was stirred at 18 °C for 20 h. The reaction was quenched with saturated aqueous NH₄Cl (0.2 mL) and extracted with EtOAc. The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by pipette column chromatography (10→30% EtOAc/hexanes) to furnish **169** as a colorless oil. ¹H NMR (600 MHz, C₆D₆) δ = 4.94 (t, *J* = 1.7 Hz, 1H), 4.73 (s, 1H), 3.35 (dt, *J* = 8.6, 6.5 Hz, 2H), 3.26 (s, 3H), 3.22 (dd, *J* = 12.8, 6.4 Hz, 1H), 3.06 (dd, *J* = 13.2, 2.4 Hz, 1H), 2.59 (dt, *J* = 17.2, 3.9 Hz, 1H), 2.39 (dd, *J* = 13.1, 6.4 Hz, 1H), 2.27 (ddd, *J* = 17.5, 13.9, 3.9 Hz, 1H), 1.98 (t, *J* = 12.9 Hz, 1H), 1.85 – 1.80 (m, 1H), 1.76 (qd, *J* = 14.1, 3.8 Hz, 1H), 1.63 (s, 3H), 1.46 – 1.34 (m, 6H), 1.02 (s, 3H), 0.90 (s, 3H), 0.83 (s, 3H), 0.80 (s, 3H).



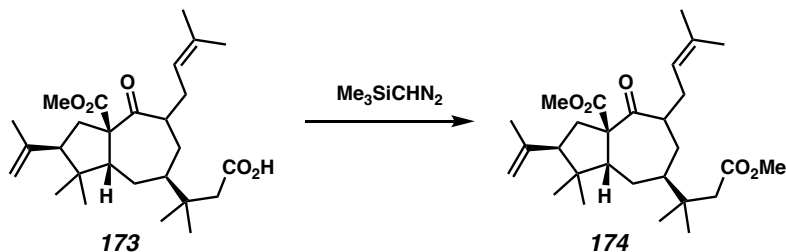
1,1-dimethyl-7-((*E*)-2-methyl-4-((trimethylsilyl)oxy)but-3-en-2-yl)-5-(3-methylbut-2-en-1-yl)-4-oxo-2-(prop-1-en-2-yl)octahydroazulene-3a(1*H*)-carboxylate
172.

A small vial under N₂ was charged with aldehyde **61** (0.5 mg, 0.0012 mmol, 1.0 equiv) and CH₂Cl₂ (24 μL). EtNi-Pr₂ (0.23 mg, 0.0018 mmol, 1.5 equiv) and TMSOTf (0.4 mg, 0.0018 mmol, 1.5 equiv) were added sequentially and the reaction mixture was stirred at 18 °C for 20 h. The solvent was removed under reduced pressure and the crude residue was purified by preparative TLC to furnish **172** as an oil. ¹H NMR (600 MHz, C₆D₆) δ = 6.02 (d, *J* = 6.7 Hz, 1H), 5.20 (s, 1H), 4.95 (q, *J* = 1.7 Hz, 2H), 4.76 (d, *J* = 1.9 Hz, 1H), 4.27 (d, *J* = 6.6 Hz, 1H), 3.30 (s, 3H), 3.05 – 2.99 (m, 2H), 2.79 – 2.73 (m, 1H), 2.50 (dd, *J* = 12.4, 6.5 Hz, 1H), 2.31 – 2.25 (m, 1H), 0.07 (s, 9H). Note: only key peaks are provided, indicating the presence of a silyl enol ether and the absence of an aldehyde resonance



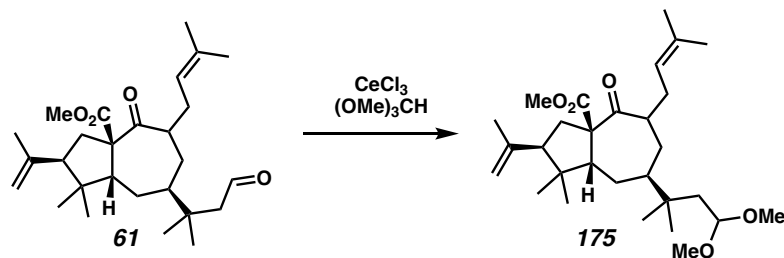
3-(8a-(methoxycarbonyl)-3,3-dimethyl-7-(3-methylbut-2-en-1-yl)-8-oxo-2-(prop-1-en-2-yl)decahydroazulen-5-yl)-3-methylbutanoic acid **173.**

A 4 mL vial open to air was charged with aldehyde **61** (8 mg, 0.0186 mmol, 1.0 equiv) and *t*-BuOH/H₂O 5:1 (0.6 mL), followed by NaH₂PO₄ (9 mg, 0.074 mmol, 4.0 equiv) and methyl butene (80 mg, 1.12 mmol, 60 equiv). NaClO₂ (80%, 5 mg, 0.056 mmol, 3.0 equiv) was then added and the reaction was stirred at 18 °C for 1.5 h. The reaction was quenched with brine and extracted with EtOAc. The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by pipette column chromatography (20→50% EtOAc/hexanes) to furnish **173** (7.8 mg, 97% yield). ¹H NMR (600 MHz, C₆D₆) δ = 5.15 – 5.10 (m, 1H), 4.94 (t, *J* = 1.8 Hz, 1H), 4.74 (s, 1H), 3.29 – 3.24 (m, 4H), 3.07 (dd, *J* = 13.0, 2.4 Hz, 1H), 2.96 (d, *J* = 14.8 Hz, 1H), 2.66 (dq, *J* = 9.4, 4.7 Hz, 1H), 2.40 (dd, *J* = 12.4, 6.6 Hz, 1H), 2.22 (dt, *J* = 14.6, 9.1 Hz, 2H), 2.17 (s, 2H), 2.05 – 1.95 (m, 2H). Note: only key peaks are provided; note the presence of the broad singlet at 2.22 ppm corresponding to the methylene α to the carboxylic acid and the absence of an aldehyde resonance



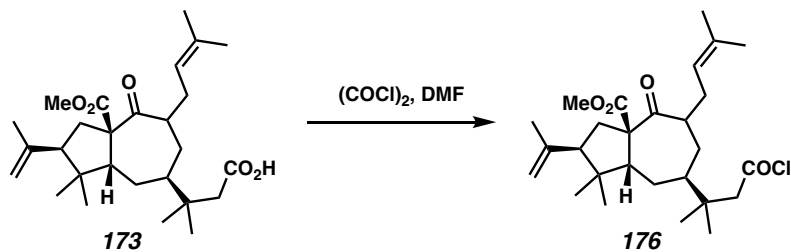
methyl 7-(4-methoxy-2-methyl-4-oxobutan-2-yl)-1,1-dimethyl-5-(3-methylbut-2-en-1-yl)-4-oxo-2-(prop-1-en-2-yl)octahydroazulene-3a(1*H*)-carboxylate 174.

A 4 mL vial was charged with carboxylic acid **173** (4 mg, 0.0089 mmol, 1.0 equiv) and Et₂O/MeOH 1:1 (0.4 mL) and cooled to 0 °C. Me₃SiCHN₂ (2 M in hexanes, 70 μL, 0.14 mmol, 16 equiv) was added slowly and the reaction was stirred for 10 min at 0 °C, then allowed to warm to 18 °C. AcOH (1 equiv) was added and the solvent was removed under reduced pressure. The crude residue was purified by pipette column chromatography (0→10% EtOAc/hexanes) to furnish **174** as an oil. ¹H NMR (600 MHz, C₆D₆) δ = 5.12 (dt, *J* = 14.7, 1.5 Hz, 1H), 4.94 (t, *J* = 1.7 Hz, 1H), 4.74 (d, *J* = 1.9 Hz, 1H), 3.34 (s, 3H), 3.31 – 3.23 (m, 4H), 3.08 (dd, *J* = 12.9, 2.6 Hz, 1H), 2.97 (d, *J* = 15.0 Hz, 1H), 2.67 (dq, *J* = 9.3, 4.7 Hz, 1H), 2.41 (dd, *J* = 12.4, 6.6 Hz, 1H), 2.23 (dd, *J* = 14.9, 8.7 Hz, 1H), 2.20 (s, 2H), 2.05 – 1.97 (m, 2H), 1.83 (dt, *J* = 16.0, 2.6 Hz, 1H), 1.79 – 1.73 (m, 1H), 1.69 (dt, *J* = 14.3, 4.0 Hz, 1H), 1.64 (s, 3H), 1.63 (s, 3H), 1.60 (s, 3H), 1.28 – 1.20 (m, 1H), 1.06 (s, 3H), 1.03 (s, 3H), 1.00 (s, 3H), 0.91 (s, 3H).

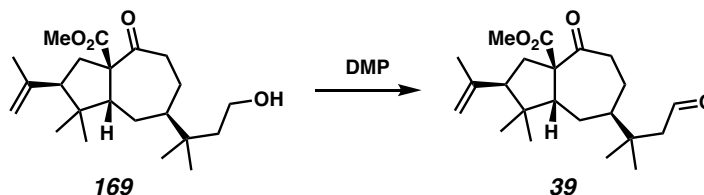


methyl 7-(4,4-dimethoxy-2-methylbutan-2-yl)-1,1-dimethyl-5-(3-methylbut-2-en-1-yl)-4-oxo-2-(prop-1-en-2-yl)octahydroazulene-3a(1*H*)-carboxylate 175.

A 2 mL vial was charged with aldehyde **61** (2 mg, 0.0046 mmol, 1.0 equiv) and MeOH (0.1 mL), followed by trimethyl orthoformate (24 mg, 0.23 mmol, 50 equiv). CeCl₃ (1.7 mg, 0.0046 mmol, 1.0 equiv) was then added and the reaction was stirred at 18 °C for 20 h. The reaction was quenched with saturated aqueous NH₄Cl and extracted with EtOAc. The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure to furnish **175**. ¹H NMR (600 MHz, C₆D₆) δ = 5.16 – 5.11 (m, 1H), 4.94 (dt, *J* = 5.3, 1.7 Hz, 1H), 4.75 (s, 1H), 4.49 (t, *J* = 5.0 Hz, 1H), 3.32 – 3.28 (m, 4H), 3.17 (s, 3H), 3.16 (s, 3H), 3.03 – 2.95 (m, 1H), 2.70 (dq, *J* = 9.3, 4.7 Hz, 1H), 2.44 (dd, *J* = 12.5, 6.6 Hz, 1H), 2.24 (dt, *J* = 14.9, 9.1 Hz, 1H). Note: only key peaks are provided; note the presence of the triplet at 4.49 ppm, the two additional methyl ester peaks corresponding to the dimethyl acetal and the absence of the aldehyde resonance.

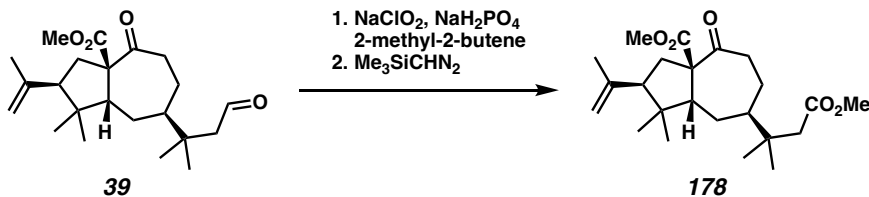


methyl 7-(4-chloro-2-methyl-4-oxobutan-2-yl)-1,1-dimethyl-5-(3-methylbut-2-en-1-yl)-4-oxo-2-(prop-1-en-2-yl)octahydroazulene-3a(1H)-carboxylate 176. A 2 mL vial was charged with carboxylic acid **173** (2 mg, 0.0045 mmol, 1.0 equiv) and CH_2Cl_2 (225 μL), followed by DMF (2 μL). Oxalyl chloride (7 mg, 0.054 mmol, 12 equiv) was added dropwise and the reaction was stirred at 18 °C for 1.5 h. The solvent was removed under reduced pressure followed by high vacuum to afford **176** as an oil. ^1H NMR (600 MHz, C_6D_6) δ = 5.04 (tdd, J = 5.7, 2.8, 1.4 Hz, 1H), 4.95 (q, J = 1.6 Hz, 1H), 4.74 (d, J = 1.9 Hz, 1H), 3.28 (s, 3H), 3.27 – 3.22 (m, 1H), 2.98 – 2.90 (m, 2H), 2.61 (dq, J = 9.5, 4.7 Hz, 1H), 2.52 (d, J = 17.0 Hz, 1H), 2.46 (d, J = 17.0 Hz, 1H), 2.39 – 2.34 (m, 1H), 2.20 – 2.16 (m, 1H), 1.99 (t, J = 12.8 Hz, 1H), 1.89 – 1.82 (m, 1H), 1.69 (d, J = 1.8 Hz, 4H), 1.65 – 1.62 (m, 3H), 1.61 (d, J = 1.3 Hz, 3H), 1.60 – 1.56 (m, 1H), 1.45 (dt, J = 14.1, 3.9 Hz, 1H), 1.09 (ddd, J = 16.0, 13.1, 7.6 Hz, 1H), 0.97 (s, 3H), 0.86 (s, 3H), 0.84 (s, 3H), 0.80 (s, 3H).



methyl 1,1-dimethyl-7-(2-methyl-4-oxobutan-2-yl)-4-oxo-2-(prop-1-en-2-yl)octahydroazulene-3a(1*H*)-carboxylate **39.**

A 4 mL vial was charged with alcohol **169** (30 mg, 0.082 mmol, 1.0 equiv) and CH₂Cl₂ (0.2 mL), and the solution was cooled to 0 °C. A separate solution of DMP (56 mg, 0.13 mmol, 1.6 equiv) in CH₂Cl₂ (0.6 mL) was prepared and added to the reaction mixture. After 2 h, additional DMP (33 mg, 0.0823 mmol, 1.0 equiv) was added. After stirring, pentane was added and the mixture was filtered, the solvent was removed, additional pentane was added, and the mixture was filtered again. The combined organic layers were concentrated under reduced pressure. The crude residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→60% EtOAc/hexanes) to furnish **39** (26 mg, 87% yield) as a colorless oil. ¹H NMR (600 MHz, C₆D₆) δ = 9.41 (t, *J* = 2.9 Hz, 1H), 4.87 (h, *J* = 1.8 Hz, 1H), 4.67 – 4.64 (m, 1H), 3.19 (s, 3H), 3.16 – 3.09 (m, 1H), 2.89 (dd, *J* = 13.6, 2.4 Hz, 1H), 2.46 (dt, *J* = 17.3, 3.9 Hz, 1H), 2.28 (dd, *J* = 13.1, 6.4 Hz, 1H), 2.14 (ddd, *J* = 17.5, 13.9, 3.9 Hz, 1H), 1.92 – 1.80 (m, 3H), 1.64 – 1.54 (m, 5H), 1.23 – 1.13 (m, 2H), 1.04 (ddd, *J* = 16.0, 13.5, 7.7 Hz, 1H), 0.92 (s, 3H), 0.78 (s, 3H), 0.78 (s, 3H), 0.74 (s, 3H).



methyl 7-(4-methoxy-2-methyl-4-oxobutan-2-yl)-1,1-dimethyl-4-oxo-2-(prop-1-en-2-yl)octahydroazulene-3a(1*H*)-carboxylate 178.

A 4 mL vial was charged with aldehyde **39** (20 mg, 0.055 mmol, 1.0 equiv), *t*-BuOH/H₂O 5:1 (0.6 mL), NaH₂PO₄ (25 mg, 0.22 mmol, 4.0 equiv), and methyl butene (232 mg, 3.31 mmol, 60 equiv). NaClO₂ (80%, 15 mg, 0.17 mmol, 3.0 equiv) was then added and the reaction mixture was stirred at room temperature. After 2.5 h, the reaction was quenched with brine and extracted with EtOAc. The combined organic layers were dried with Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→70% EtOAc/hexanes) to furnish the acid. The acid was dissolved in Et₂O/MeOH 1:1 (0.5 mL) and cooled to 0 °C. TMSCHN₂ (2M in hexanes, 0.1 mL, 0.2 mmol, 16 equiv) was added slowly. After 15 min, the cold bath was removed and the mixture was stirred at room temperature. After 1.5 h, AcOH (0.2 mmol) was added followed by EtOAc and water. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried with Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by pipette column chromatography (10→20% EtOAc/hexanes) to furnish ester **178** as an oil.

¹H NMR (600 MHz, C₆D₆) δ = 4.93 (p, *J* = 1.6 Hz, 1H), 4.73 – 4.69 (m, 1H), 3.34 (s, 3H), 3.25 (s, 3H), 3.22 – 3.18 (m, 1H), 3.02 (dd, *J* = 13.4, 2.4 Hz, 1H), 2.57 (dt, *J* = 17.3, 3.9 Hz, 1H), 2.37 (dd, *J* = 13.0, 6.4 Hz, 1H), 2.29 (ddd, *J* = 17.5, 13.8, 3.9 Hz, 1H), 2.20 (d, *J* = 13.7 Hz, 1H), 2.13 (d, *J* = 13.7 Hz, 1H), 1.96 (t, *J* = 12.9 Hz, 1H), 1.81 (dd, *J* = 16.0, 2.5

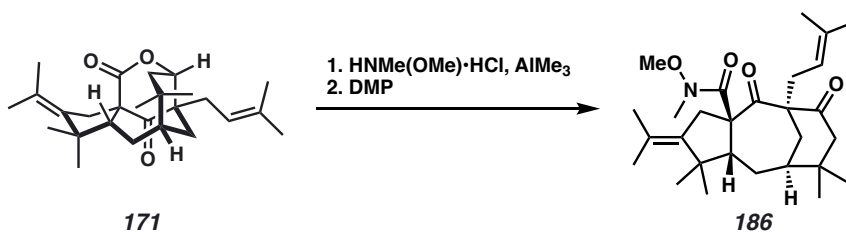
Hz, 1H), 1.73 (tdd, $J = 13.9, 12.3, 3.8$ Hz, 1H), 1.61 (t, $J = 1.0$ Hz, 3H), 1.51 (dddd, $J = 12.1, 7.6, 3.8, 1.9$ Hz, 1H), 1.45 (dq, $J = 13.9, 4.0$ Hz, 1H), 1.26 – 1.18 (m, 1H), 1.03 (s, 3H), 0.99 (s, 6H), 0.88 (s, 3H).



***N*-methoxy-*N*,1,1,8,8-pentamethyl-5-(3-methylbut-2-en-1-yl)-4,6-dioxo-2-(prop-1-en-2-yl)decahydro-5,9-methanocyclopenta[9]annulene-3a(1*H*)-carboxamide 183.**

An 8 mL vial under N_2 was charged with (OMe)NMeH·HCl (17 mg, 0.18 mmol, 20 equiv) and PhMe (240 μL), and the solution was cooled to 0 °C. Me_3Al (2M in PhMe, 86 μL , 0.17 mmol, 19.6 equiv) was added dropwise. After 10 min, a solution of lactone **38** (2 mg, 0.0088 mmol, 1.0 equiv) in CH_2Cl_2 (0.4 mL) was added dropwise, and the reaction mixture was removed from the ice bath. After 24 h, the mixture was cooled to 0 °C, and saturated aqueous potassium sodium tartrate and CH_2Cl_2 were added. The mixture was allowed to warm to 18 °C and stirred vigorously for 3 h. The mixture was extracted with CH_2Cl_2 (2x) and Et_2O (2x). The combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by pipette column chromatography (10→20% EtOAc/hexanes) to furnish the alcohol which was directly used in the next step. A 4 mL vial was charged with the alcohol (1.3 mg, 0.0028 mmol, 1.0 equiv) and CH_2Cl_2 (0.3 mL). The vial was brought into the glovebox and DMP (2.5 mg, 0.006 mmol, 2.0 equiv) was added. The reaction mixture was stirred at room temperature with an additional

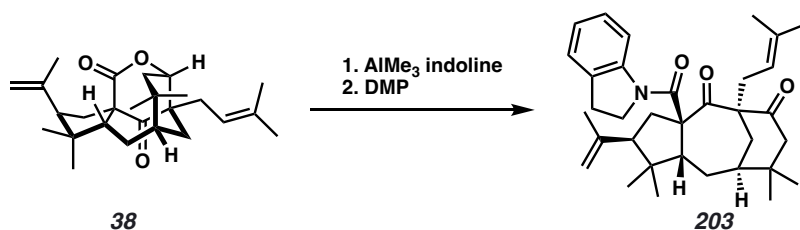
portion of DMP (2.5 mg, 0.006 mmol, 2.0 equiv) being added after 1 h. After 3.5 h, the solvent was removed under reduced pressure. Hexanes/EtOAc was added, the mixture was filtered, and the solution was concentrated under reduced pressure. The crude residue was purified by preparative TLC (20% EtOAc/hexanes) to furnish **183**. ^1H NMR (600 MHz, C_6D_6) δ = 5.37 – 5.31 (m, 1H), 4.99 (t, J = 1.7 Hz, 1H), 4.78 (d, J = 1.9 Hz, 1H), 3.37 – 3.29 (m, 2H), 3.23 (dd, J = 12.4, 6.5 Hz, 1H), 3.05 (dd, J = 14.0, 10.1 Hz, 1H), 2.94 (s, 3H), 2.92 (s, 3H), 2.55 (dd, J = 13.3, 6.5 Hz, 1H), 2.48 – 2.42 (m, 1H), 2.33 (dd, J = 19.5, 1.7 Hz, 1H), 2.22 – 2.14 (m, 1H), 1.93 (t, J = 12.8 Hz, 1H), 1.75 (dd, J = 13.9, 3.5 Hz, 1H), 1.69 (d, J = 5.6 Hz, 7H), 1.64 (s, 3H), 1.46 (s, 1H), 1.24 (td, J = 13.7, 2.5 Hz, 1H), 1.17 (s, 3H), 0.92 (d, J = 8.0 Hz, 6H), 0.78 (s, 3H).



***N*-methoxy-*N*,1,1,8,8-pentamethyl-5-(3-methylbut-2-en-1-yl)-4,6-dioxo-2-(propan-2-ylidene)decahydro-5,9-methanocyclopenta[9]annulene-3a(1*H*)-carboxamide **186**.**

A 25 mL flask under N_2 was charged with $(\text{OMe})\text{NMeH}\cdot\text{HCl}$ (152 mg, 1.56 mmol, 20 equiv) and PhMe (3.6 mL), and the solution was cooled to 0 °C. Me_3Al (2 M in PhMe, 765 μL , 1.53 mmol, 19.6 equiv) was added dropwise. After completion of addition, the mixture was cooled to 0 °C and lactone **171** (31 mg, 0.078 mmol, 1.0 equiv) was added in CH_2Cl_2 (6 mL) dropwise over 5 min. The mixture was allowed to gradually warm to room temperature and stirred for 20 h. The reaction was cooled to 0 °C and quenched with

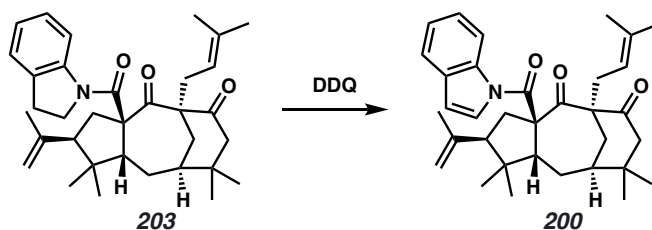
TMSOTf (16 μ L, 0.090 mmol, 16 equiv) was added. The reaction mixture was allowed to warm gradually to 18 °C and stirred. After 2 d, the mixture was cooled to 0 °C, quenched with saturated NaHCO₃ and EtOAc, and extracted. The combined organic extracts were dried with Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by pipette column chromatography on alumina (10% EtOAc/hexanes) to furnish **190** as an oil. ¹H NMR (600 MHz, C₆D₆) δ = 5.23 (d, J = 7.5 Hz, 1H), 4.80 (s, 1H), 3.54 (d, J = 13.9 Hz, 1H), 3.38 (d, J = 15.4 Hz, 1H), 3.25 (s, 3H), 3.06 – 2.96 (m, 2H), 2.90 (s, 3H), 2.76 (d, J = 15.6 Hz, 1H), 2.37 (d, J = 13.8 Hz, 1H), 1.93 (dd, J = 14.6, 5.9 Hz, 1H), 1.72 (d, J = 2.9 Hz, 6H), 1.70 (dd, J = 5.5, 2.1 Hz, 6H), 1.66 (s, 3H), 1.54 (dd, J = 13.4, 3.5 Hz, 1H), 1.44 (s, 1H), 1.23 (t, J = 14.6 Hz, 1H), 1.17 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H), 0.29 (s, 9H).



3a-(indoline-1-carbonyl)-1,1,8,8-tetramethyl-5-(3-methylbut-2-en-1-yl)-2-(prop-1-en-2-yl)octahydro-5,9-methanocyclopenta[9]annulene-4,6(1*H*,5*H*)-dione 203.

A small test tube under N₂ was charged with indoline (36 mg, 0.3 mmol, 40 equiv) and PhMe (0.4 mL), and the solution was cooled to 0 °C. Me₃Al (1 M in hexanes, 0.3 mL, 0.3 mmol, 40 equiv) was added dropwise, and the ice bath was removed. After 1 h, a solution of lactone **38** (3 mg, 0.0075 mmol, 1.0 equiv) in PhMe (0.4 mL) was added dropwise at 0 °C, and the reaction was allowed to warm 18 °C. After 20 h, the mixture was cooled to 0

°C and quenched with saturated aqueous potassium sodium tartrate. The mixture was stirred, extracted with EtOAc, dried with Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by preparative TLC (20% EtOAc/hexanes) to furnish the product which was directly used in the next step. A 20 mL vial was charged with the crude alcohol (0.0075 mmol, 1.0 equiv) and CH₂Cl₂ (1 mL). The vial was brought into the glovebox and DMP (5 mg, 0.019 mmol, 2.5 equiv) was added. The reaction was stirred for 2 h, then diluted with CH₂Cl₂/hexanes, filtered, and concentrated under reduced pressure to furnish **203** as an oil. ¹H NMR (600 MHz, C₆D₆) δ = 8.71 (d, *J* = 8.1 Hz, 1H), 7.10 (s, 1H), 6.87 (d, *J* = 6.0 Hz, 2H), 5.16 (s, 1H), 4.97 (s, 1H), 4.73 (s, 1H), 3.74 – 3.67 (m, 2H), 3.61 (d, *J* = 6.8 Hz, 1H), 3.52 – 3.44 (m, 1H), 3.34 (dd, *J* = 12.5, 6.9 Hz, 1H), 3.06 (d, *J* = 9.9 Hz, 1H), 3.00 (s, 1H), 2.58 (d, *J* = 6.6 Hz, 1H), 2.49 – 2.42 (m, 2H), 2.38 (s, 1H), 1.64 (s, 3H), 1.63 (s, 3H), 1.57 (s, 3H), 1.13 (s, 3H), 0.97 (s, 3H), 0.94 (s, 3H), 0.76 (s, 3H). Note: only key peaks are provided; note the presence of the four aromatic resonances and the four resonances between 3.75 – 3.40 ppm corresponding to the incorporated indoline.



3a-(1*H*-indole-1-carbonyl)-1,1,8,8-tetramethyl-5-(3-methylbut-2-en-1-yl)-2-(prop-1-en-2-yl)octahydro-5,9-methanocyclopenta[9]annulene-4,6(1*H*,5*H*)-dione 200.

A 2 mL vial was charged with dione **203** (0.0013 mmol, 1.0 equiv) and PhH (0.1 mL). DDQ (3 mg, 0.0132 mmol, 10 equiv) was added and the reaction mixture was stirred at 18

°C for 3 days. The solvent was then removed under reduced pressure. The crude residue was purified by preparative TLC (20% Et₂O/hexanes) to furnish **200**. ¹H NMR (600 MHz, C₆D₆) δ = 8.95 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 3.9 Hz, 1H), 7.11 (s, 1H), 6.28 (d, *J* = 3.9 Hz, 1H), 4.87 (s, 1H), 4.57 (s, 1H). Note: this sample was very dilute, and only key peaks are provided. Note the presence of the six aromatic protons corresponding to the oxidized indole.

A5.10 REFERENCES AND NOTES

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CHAPTER 3

Some Unusual Transformations of a Highly Reactive α -Bromocaranone[†]

3.1 INTRODUCTION

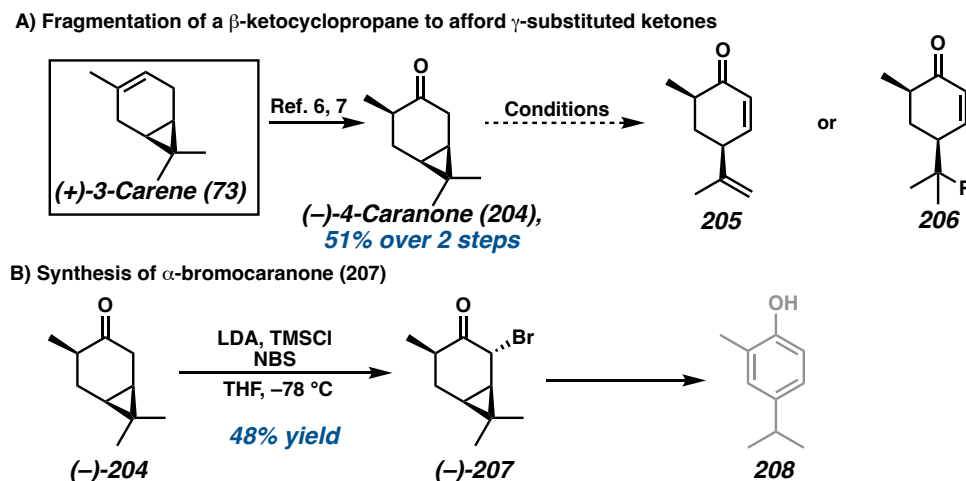
The advent of asymmetric catalysis has greatly increased the number and variety of synthetically accessible chiral building blocks.¹ Nevertheless, the syntheses of many natural products and consumer commodities continue to rely on starting materials from the readily available chiral pool and derivatives thereof.^{2,3} As such, strategies for the derivatization of chiral building blocks remain vital in organic synthesis. (+)-3-Carene (**73**, Scheme 3.1.1A) is one such building block: the defining dimethylcyclopropane moiety of this molecule coupled with its widespread availability and conveniently rigid structure have made it a popular chiral feedstock.^{2,4} However, among the numerous syntheses beginning from **73**, most feature the presence of the intact dimethylcyclopropane moiety in the target. This is due in part to the lack of mild and selective methods for the fragmentation of the strained ring. Although such fragmentations have been performed on carene (**73**) and related dimethylcyclopropane-containing compounds, the vast majority rely on strongly acidic conditions.⁵

In the course of a total synthesis effort, we identified the fragmentation of α,β -ketodimethylcyclopropane (**204**) as a valuable transformation for revealing a reactive γ -

[†]This research was conducted in collaboration with Zachary P. Sercel and Dr. Scott Virgil. Portions of this chapter have been reproduced with permission from Samkian, A. E.; Sercel, Z. P.; Virgil, S. C.; Stoltz, B. M. *Tetrahedron Lett.* **2022**, 89, 153496. © 2021 Elsevier.

isopropenyl group (**205**) from the relatively unreactive, “protected” cyclopropane. Furthermore, we aimed to develop a method to trap the species immediately after ring fragmentation to access the challenging γ -gem-dimethyl synthon (**206**). We realized that in order to affect this transformation in a mild and efficient fashion, a synthetic handle would be necessary at the α -position. α -Bromocaranone **207** was selected as a promising model system to study the feasibility of this synthetic transformation due to its straightforward synthesis from carene (**73**) (Scheme 3.1.1B).

Scheme 3.1.1. Synthesis of an α -bromocaranone (**207**) from (+)-3-carene (**73**).



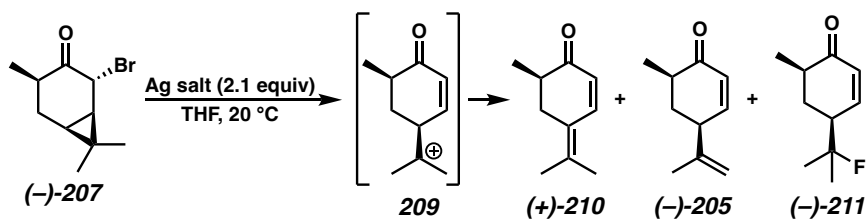
Hydroboration of commercially available (+)-3-carene (**73**) followed by oxidation afforded (–)-4-caranone (**204**) in modest yields on a >10 g scale.^{6,7} Enolization of (–)-**204** with LiHMDS and direct bromination with NBS led to the production of several inseparable side products,⁸ however, formation of the silyl enol ether with LDA and TMSCl followed by quenching with NBS led to diminished side product formation, affording (–)-**207**.⁹ Although bromide (–)-**207** decomposes rapidly on silica, purification was possible *via* chromatography on neutral alumina. While this compound can be stored for at least several weeks at –15 °C as a solution in benzene, neat samples of bromide (–)-

207 stored at ambient temperature undergo spontaneous, exothermic decomposition to isocarvacrol (**208**), with the release of HBr, after several hours. Despite the unstable nature of bromide (–)-**207**, it was possible to manipulate neat samples of this intermediate for short periods of time.

3.2 CATIONIC FRAGMENTATIONS OF THE BROMOCARANONE

We began by treating bromide (–)-**207** with Ag^{I} reagents in order to effect a carbocation-mediated fragmentation. Treatment of (–)-**207** with AgClO_4 or AgOTf in THF afforded dienone (+)-**210** (Table 3.2.1, entries 1 and 2) in modest yields. Trace quantities of the desired compound featuring an isopropenyl group (**205**) were also observed. Attempts to favor the formation of (–)-**205** by performing the reaction in the presence of a bulky base were not successful. The rapid elimination of tertiary carbocation **209** toward (+)-**210** would appear to impede formation of (–)-**205** or trapping with nucleophiles. Despite this, we were surprised to observe tertiary fluoride (–)-**211** as the major product when AgBF_4 was used as a Ag^{I} source (entry 3).

Table 3.2.1. Ag^{I} -mediated reactions of **207**.

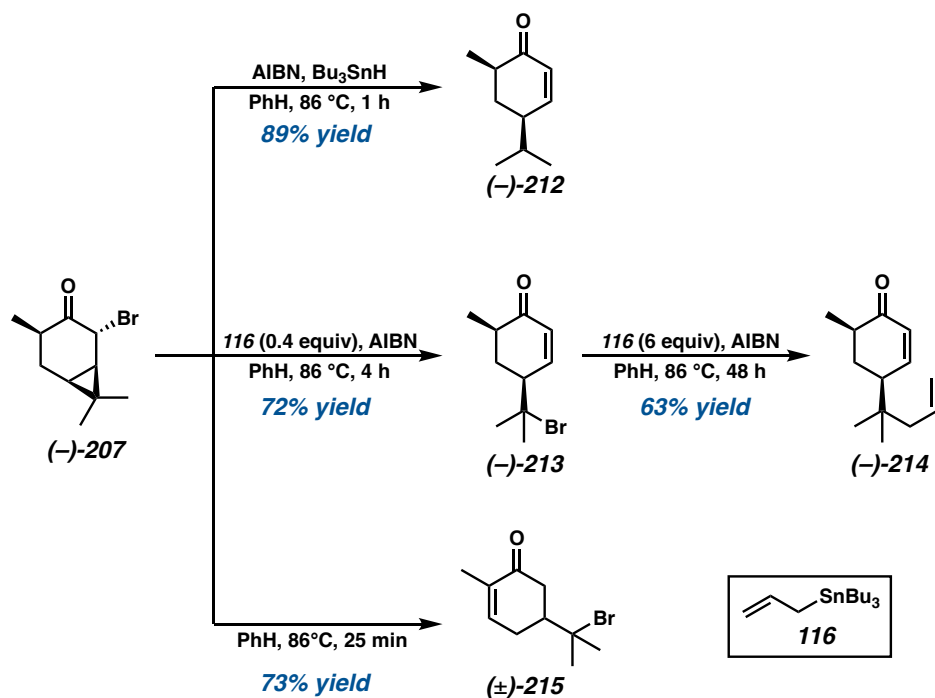


entry	Ag salt	Yield 209	Yield 210	Yield 211
1	AgOTf	55%	<5%	—
2	AgClO_4	67%	<5%	—
3	AgBF_4	10%	5%	35%

3.3 RADICAL FRAGMENTATIONS OF THE BROMOCARANONE

The lack of control observed in carbocation-mediated reactions led us to study radical-mediated fragmentations next. Treatment of (–)-**207** with AIBN and Bu_3SnH afforded isopropyl enone (–)-**212** (Scheme 3.3.1) in excellent yield. Allyltributylstannane (**116**) was used in place of Bu_3SnH , in an attempt to prepare the allylated product (–)-**214**.¹⁰ Pleasingly, (–)-**214** was observed, though in moderate yields (<40%), with the tertiary bromide (–)-**213** instead being the major product. Using catalytic amounts of **116** led to high yields of (–)-**213**, which could then be isolated and subjected to similar conditions, albeit with an excess of **116**, to afford the desired allylated species (–)-**214**.

Scheme 3.3.1. Radical mediated cyclopropane fragmentation of 207.

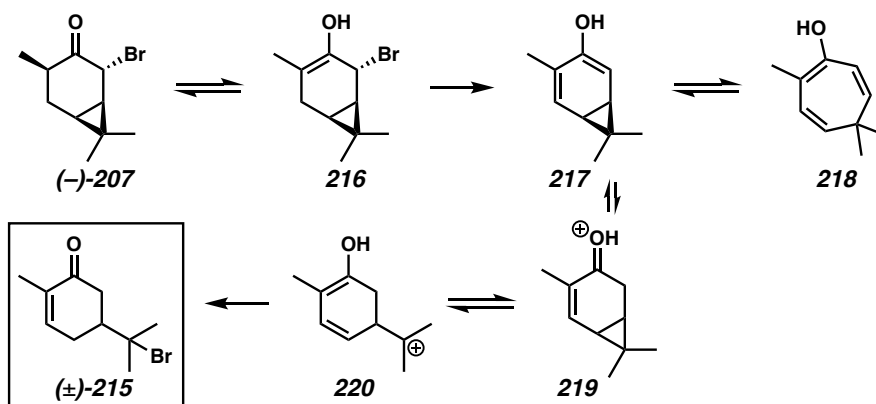


It is noteworthy that treatment of dienone (+)-**210** with **116** and AIBN did not afford (–)-**214**, suggesting (+)-**210** is not an intermediate on route to (–)-**214**. The presence of catalytic stannane radicals proved vital for the production of (–)-**213**. Indeed, a control experiment

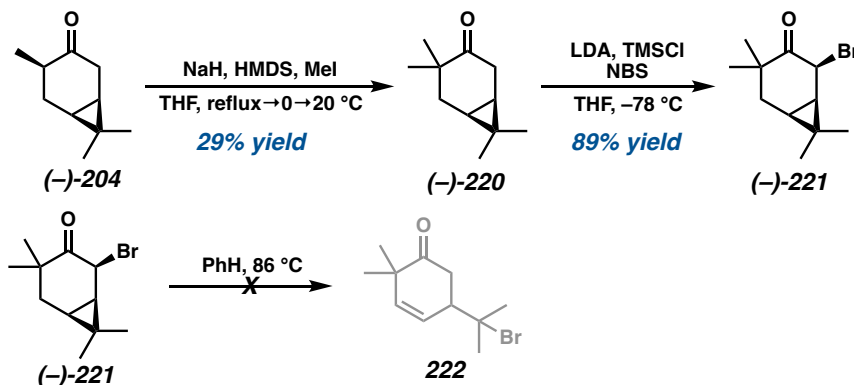
performed by simply heating a solution of (–)-**207** in benzene provided racemic carvone derivative ($\pm$)-**215** in high yields, with phenol **208** being observed as a minor product. To explain this surprising divergence in reactivity between (–)-**213** and ($\pm$)-**215**, further mechanistic studies were performed.

Scheme 3.3.2. Proposed mechanism and control study for the formation of **215**.

A) Proposed mechanism for the formation of racemic **215** from **207**



A) Synthesis of bromide **221** and control reaction in benzene



We initially suspected that the mechanism to form ($\pm$)-**215** may be radical mediated, perhaps through the homolysis of the carbon-bromine bond followed by 1,4-HAT. However, such a mechanism would not explain a racemic product. Furthermore, DFT calculations^{11,12,13} (see Section 3.5.3 for details) suggested that the barriers for such a transformation are kinetically inaccessible (>31 kcal/mol). Instead, we propose a polar mechanism (Scheme 3.3.2A) that, through elimination of the bromide through enol **216**,

could afford diene **217**. Such a system is preceded to rapidly racemize through an electrocyclic reaction *via* cycloheptatriene **218**.¹⁴ Ultimately, **217** may be protonated in its keto form (**219**), eventually leading to tertiary cation **220**, which is trapped by bromide, affording ($\pm$)-**215**.

The conversion of (–)-**207** to ($\pm$)-**215** is likely catalyzed by HBr formed *via* the decomposition of (–)-**207** to **208**. Interestingly, despite the formation of (–)-**213** requiring longer reaction times (4 h vs. 25 min), carvone derivative ($\pm$)-**215** is not observed. Indeed, heating bromide (–)-**207** in PhH in the presence of allylstannane **116** with no radical initiator entirely suppressed the formation of ($\pm$)-**215**. We propose that this observation is due to the quenching of HBr by **116**. Another reaction performed with (–)-**207** and bis(tributylstannane), which exists in equilibrium with two tributyltin radicals,¹⁵ also suppressed the formation of ($\pm$)-**215** whilst producing (–)-**213**, albeit in lower yields. No reaction was observed when (–)-**207** was heated in hexanes, but ($\pm$)-**215** was produced rapidly in dioxane or 1,2-dichloroethane with greater quantities of phenol **208**, further implicating a polar mechanism. Finally, control compound (–)-**221** (Scheme 3.3.2B), featuring an additional *gem*-dimethyl group, was prepared in two steps from (–)-**204**. This compound was found to be significantly more stable than (–)-**207**, decomposing neither on silica nor spontaneously as a solid compound. Importantly, only clean starting material was observed when (–)-**204** was heated in benzene for extended periods of time, providing further evidence that the reaction leading to ($\pm$)-**215** proceeds *via* the mechanism proposed in Scheme 3.3.2A.

3.4 CONCLUSION

Over the course of this study, readily available (+)-3-carene was derivatized into an array of useful chiral building blocks through a highly reactive α -bromocaranone as a synthetic branching point. These chiral products are expected to be useful in future synthetic efforts, and we believe that the convenient fragmentation of β -cyclopropyl ketones will also find applications outside of carene-derived systems.

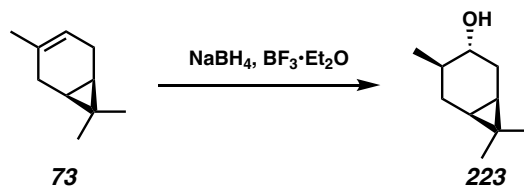
3.5 EXPERIMENTAL SECTION

3.5.1 MATERIALS AND METHODS

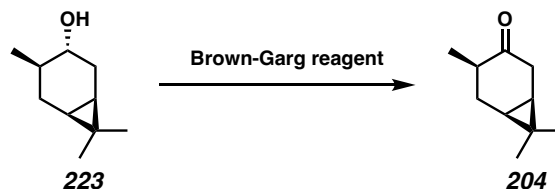
Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.¹⁶ (+)-3-Carene was purchased from TCI and used as received, *N*-bromosuccinimide (NBS) was recrystallized from boiling water prior to use, trimethylsilyl chloride (TMSCl) was distilled under argon prior to use, all other reagents and solvents were purchased from various commercial suppliers and used as received. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching or *p*-anisaldehyde staining. Silicycle SiliaFlash® P60 Academic Silica gel (particle size 40–63 μ m) or Sigma-Aldrich aluminum oxide (activated, neutral, Brockmann Activity I) were used for flash chromatography. Preparatory HPLC was performed on an Agilent 1200 preparatory HPLC system using a 9.4 x 250 mm Eclipse XDB-C18 column. A water/MeCN gradient was used as the mobile phase and the compounds were detected at 230.8 nm and 254.4 nm. Analytical SFC was performed with a Mettler SFC supercritical

CO₂ analytical chromatography system utilizing a Chiralpak AD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. ¹H NMR spectra were recorded on Varian Inova 500 MHz, Varian 400 MHz, and Bruker 400 MHz spectrometers and are reported relative to residual CHCl₃ (δ 7.26 ppm). ¹³C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125 MHz), a Varian 400 MHz spectrometer (100 MHz), and Bruker 400 MHz spectrometers (100 MHz) and are reported relative to CHCl₃ (δ 77.16 ppm). Data for ¹H NMR 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, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet. Data for ¹³C NMR are reported in terms of chemical shifts (δ ppm) Some reported spectra include minor solvent impurities of water (δ 1.56ppm), ethyl acetate (δ 4.12, 2.05, 1.26 ppm), methylene chloride (δ 5.30 ppm), acetone (δ 2.17 ppm), grease (δ 1.26, 0.86 ppm), and/or silicon grease (δ 0.07 ppm), which do not impact product assignments. IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm⁻¹). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell. High-resolution mass spectrometry was performed by the Multi User Mass Spectrometry Laboratory at the California Institute of Technology using a JMS-T200 GC AccuTOF GC-Alpha mass spectrometer.

3.5.2 EXPERIMENTAL PROCEDURES

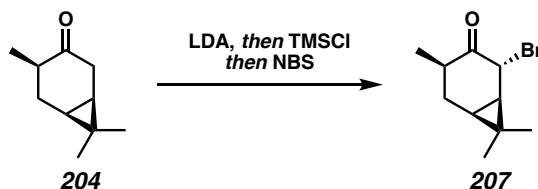
**(1R,3R,4R,6S)-4,7,7-trimethylbicyclo[4.1.0]heptan-3-ol 223.**

The procedure was adapted from the literature:⁶ To a dried 500 mL round bottom flask was added NaBH₄ (6.94 g, 183 mmol, 1.0 equiv), THF (60 mL), and (+)-3-carene (**73**) (25 g, 180 mmol, 1.0 equiv). The reaction flask was cooled to 0 °C in an ice bath, and BF₃·OEt₂ (26 g, 160 mmol, 1.0 equiv) was added dropwise over 30 min. The reaction was stirred at this temperature for 4 h, after which the reaction was cooled to –10 °C and aq. NaOH (3M, 60 mL) was added dropwise over 40 min. H₂O₂ (30 wt %, 100 mL) was then added dropwise over 1 h, and the reaction allowed to warm to 20 °C. The solution was concentrated under reduced pressure to remove THF, and the aqueous layer was extracted with CH₂Cl₂ (3 x 40 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over Na₂SO₄, and filtered. Concentration under reduced pressure afforded an oil that was distilled under vacuum (0.5 mmHg, 150 °C) to afford **223** (22 g, 78%) as a colorless oil that solidified upon cooling. ¹H NMR (chloroform-*d*, 400 MHz): δ = 3.07 (ddd, *J* = 10.3, 9.3, 6.6 Hz, 1H), 2.10 (ddd, *J* = 14.1, 6.6, 0.9 Hz, 1H), 2.01 – 1.92 (m, 1H), 1.61 – 1.51 (m, 1H), 1.29 – 1.17 (m, 1H), 0.97 (s, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.90 (s, 3H), 0.86 – 0.77 (m, 1H), 0.75 – 0.67 (m, 2H). Spectral data are in agreement with previously reported values.¹⁷



(1R,4R,6S)-4,7,7-trimethylbicyclo[4.1.0]heptan-3-one 204.

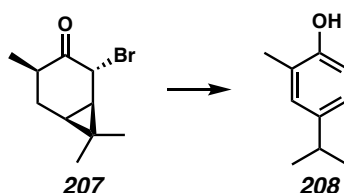
A procedure from the literature⁷ was modified as follows: To a 1 L round bottom flask was added alcohol **223** (20 g, 130 mmol, 1.0 equiv) and Et₂O (280 mL). The solution was cooled in an ice bath, and Brown–Garg (BG) reagent^{18,19} (70 mL) was added dropwise over 20 min with vigorous stirring, maintaining the reaction temperature below 20 °C. The ice bath was then removed, and the solution stirred for 1 h. Additional BG reagent (70 mL) was added slowly, and the reaction was left to stir for 18 h. The organic layer was then separated, and the aqueous layer was extracted with Et₂O (2 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residual oil was distilled under vacuum (0.5 mmHg, 130 °C) to yield **204** (12.8 g, 65%) as fragrant, yellow oil. ¹H NMR (chloroform-*d*, 400 MHz): δ = 2.52 (ddd, *J* = 18.0, 8.4, 0.9 Hz, 1H), 2.41 – 2.32 (m, 1H), 2.32 – 2.25 (m, 2H), 1.31 – 1.19 (m, 1H), 1.07 (m, 1H), 1.04 (s, 3H), 1.02 – 0.97 (m, 1H), 0.95 (d, *J* = 6.4 Hz, 3H), 0.84 (s, 3H). Spectral data are in agreement with previously reported values.⁷



(1R,2R,4R,6S)-2-bromo-4,7,7-trimethylbicyclo[4.1.0]heptan-3-one 207.

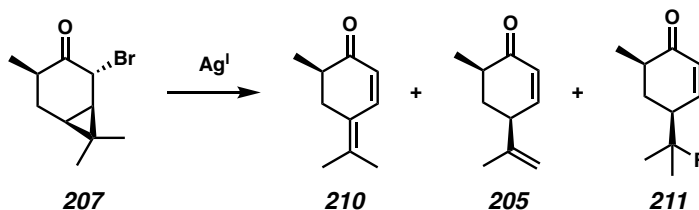
To a flame-dried 250 mL Schlenk flask was added THF (29 mL) and diisopropylamine (1.59 g, 15.8 mmol, 1.2 equiv). The solution was cooled to $-78\text{ }^{\circ}\text{C}$ and *n*-butyllithium (2.5 M in hexanes, 5.5 mL, 13.8 mmol, 1.05 equiv) was added dropwise over 8 min. After stirring for 30 min, a solution of ketone **204** (2 g, 13.1 mmol, 1.0 equiv) in THF (2 mL) was added dropwise over 5 min and the reaction mixture allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 1.5 h. TMSCl (2.14 g, 19.7 mmol, 1.5 equiv) was added and the reaction was allowed to warm to $0\text{ }^{\circ}\text{C}$ in an ice bath, and further stirred at $0\text{ }^{\circ}\text{C}$ for 1 h. The reaction flask was then wrapped in Al foil to exclude light and NBS (3.5 g, 19.7 mmol, 1.5 equiv) was added in a single portion. After stirring for a further 30 min in the dark, the reaction was quenched* with saturated aq. NaHCO_3 (50 mL) and extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with water (2 x 40 mL) and brine (40 mL), dried over Na_2SO_4 , and filtered. The solution was concentrated under reduced pressure to yield 2.1 g of residue. A small amount of this residue (255 mg) was purified *via* flash chromatography on neutral alumina (hexanes) to yield **207** (173 mg, extrapolated to 48% overall yield) as an unstable straw-colored oil which crystallized when pure. **207** was used immediately or stored as a frozen solution in benzene. ^1H NMR (chloroform-*d*, 400 MHz): δ = 4.37 (d, J = 1.2 Hz, 1H), 3.22 (ddq, J = 13.0, 7.7, 6.5 Hz, 1H), 2.45 (ddd, J = 14.7, 9.7, 7.6 Hz, 1H), 1.52 (dd, J = 8.6, 1.3 Hz, 1H), 1.40 (ddd, J = 14.8, 13.0, 4.3 Hz, 1H), 1.18 (td, J = 8.9, 4.2 Hz, 1H), 1.07 (s, 3H), 1.00 (d, J = 6.5 Hz, 3H), 0.84 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (chloroform-*d*, 100

MHz): δ = 209.7, 48.2, 36.2, 33.7, 30.7, 28.2, 22.2, 20.5, 14.7, 14.1; IR (Neat Film, NaCl) 2933, 1719, 1455, 1378, 1162, 848, 776, 622 cm^{-1} ; HRMS (FI+): m/z calc'd for $\text{C}_{10}\text{H}_{15}\text{OBr}$ $[\text{M}]^+$: 230.0301 found, 230.0308; $[\alpha]_{\text{D}}^{22.16}$ -278.99 (c 1.0, CHCl_3). *Due to the light-sensitivity of the product, it is recommended to perform the work-up in the dark.



4-isopropyl-2-methylphenol **208**.

207 (39 mg, 0.17 mmol) was left in a sealed 4 mL vial under ambient conditions for 24 h. During this time, the oil was found to spontaneously decompose with notable exotherm* and change in consistency. The blackened tar was purified *via* flash chromatography on silica (5% EtOAc in hexanes) to afford **208** (8 mg, 32%) as a colorless oil. ^1H NMR (chloroform- d , 400 MHz): δ = 6.99 (d, J = 2.3 Hz, 1H), 6.94 (dd, J = 8.1, 2.2 Hz, 1H), 6.71 (d, J = 8.1 Hz, 1H), 4.62 (s, 1H), 2.83 (hept, J = 7.0 Hz, 1H), 2.26 (s, 3H), 1.23 (d, J = 6.9 Hz, 6H). Spectral data are in agreement with previously reported values.²⁰ *On large scales (>200 mg) the exotherm and release of HBr can lead to dangerous pressure build up; this can be avoided by leaving the vial open to atmosphere.



Enones **210**, **205**, and **211**.

To a solution of the indicated silver salt (0.182 mmol, 2.1 equiv) in THF (0.6 mL) was added a solution of bromoketone **207** (20 mg, 0.0865 mmol, 1.0 equiv) in THF (0.3 mL, 0.1 M total concentration) dropwise over 1 min with stirring at 20 °C. In all cases, a thick precipitate immediately formed. Stirring was continued for an additional 20 min, after which the reaction mixture was quenched with saturated aq. NaHCO₃ (1 mL) and filtered through a plug of celite with EtOAc. The layers were separated and the organic layer was dried with Na₂SO₄, filtered, and concentrated under reduced pressure to provide a crude product that was purified by silica gel flash chromatography (5% EtOAc in hexanes).

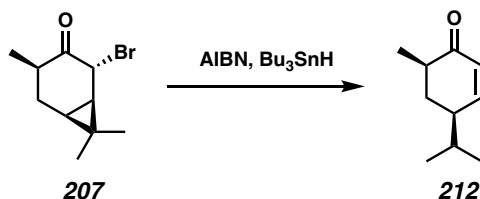
Characterization data for **(R)-6-methyl-4-(propan-2-ylidene)cyclohex-2-en-1-one (210)**.

8.7 mg (67%) yield with AgClO₄; 7.1 mg (55%) yield with AgOTf; ¹H NMR (chloroform-d, 400 MHz): δ = 7.42 (dd, J = 10.1, 0.9 Hz, 1H), 5.80 (d, J = 10.0 Hz, 1H), 2.84 (dd, J = 14.6, 5.4 Hz, 1H), 2.48 (dq, J = 10.9, 6.8, 5.4 Hz, 1H), 2.39 – 2.27 (m, 1H), 1.93 (dd, J = 1.6, 0.8 Hz, 3H), 1.90 (s, 3H), 1.14 (d, J = 6.8 Hz, 3H); ¹³C{¹H} NMR (chloroform-d, 100 MHz): δ = 203.0, 143.1, 139.4, 126.7, 124.0, 40.9, 34.1, 21.9, 20.8, 15.9; IR (Neat Film, NaCl) 2927, 1672, 1623, 1453, 1216, 812 cm⁻¹; HRMS (FI⁺): m/z calc'd for C₁₀H₁₄O [M]⁺: 150.1039, found 150.1039; [α]_D^{21.95} +137.36 (c 0.5, CHCl₃).

Characterization data for **(4S,6R)-6-methyl-4-(prop-1-en-2-yl)cyclohex-2-en-1-one (205)**. Isopropenyl enone **205** was observed in trace quantities in the Ag^I-mediated fragmentation of bromide **207**. 0.7 mg (5% yield) with AgBF₄. A sample suitable for

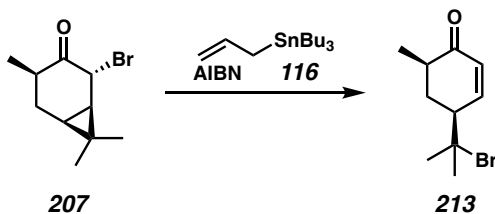
characterization, albeit containing a minor impurity, could be obtained by automated silica gel flash chromatography (Teledyne ISCO, 0→10% EtOAc in hexanes) on a 100 mg scale. ^1H NMR (chloroform- d , 400 MHz): δ = 6.81 (dt, J = 10.1, 2.0 Hz, 1H), 6.03 (dd, J = 10.1, 3.0 Hz, 1H), 4.86 (p, J = 1.5 Hz, 1H), 4.81 (dq, J = 1.6, 0.8 Hz, 1H), 3.21 – 3.12 (m, 1H), 2.42 (dq, J = 13.5, 6.7, 4.5 Hz, 1H), 2.13 (dtd, J = 13.0, 4.5, 2.0 Hz, 1H), 1.77 (dd, J = 1.4, 0.9 Hz, 3H), 1.72 – 1.61 (m, 1H), 1.15 (d, J = 6.6 Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (chloroform- d , 100 MHz): δ = 202.0, 152.5, 146.9, 129.6, 112.0, 45.2, 41.8, 37.7, 20.8, 15.1; IR (Neat Film, NaCl) 2964, 2934, 2862, 1683, 1649, 1454, 1376, 1215, 1188, 1118, 895, 804 cm^{-1} ; HRMS (FI+): m/z calc'd for $\text{C}_{10}\text{H}_{14}\text{O}$ $[\text{M}]^+$: 150.1039, found 150.1030; $[\alpha]_{\text{D}}^{21.23}$ –92.59 (c 0.33, CHCl_3).

Characterization data for **(4S,6R)-4-(2-fluoropropan-2-yl)-6-methylcyclohex-2-en-1-one (211)**. 6.6 mg of a 3.4:1 (w/w) mixture of fluoride **211** and dienone **210** was isolated with AgBF_4 , corresponding to a 35% yield of fluoride **211**. While this mixture was inseparable by silica gel flash chromatography, an analytical sample of **211** was isolated by reverse-phase preparative HPLC (50–70% MeCN in H_2O over 3.5 min at 10 mL/min); ^1H NMR (chloroform- d , 400 MHz): δ = 6.96 (dt, J = 10.3, 2.0 Hz, 1H), 6.09 (dd, J = 10.3, 3.0 Hz, 1H), 2.88 – 2.75 (m, 1H), 2.41 (dq, J = 13.5, 6.7, 4.6 Hz, 1H), 2.08 (dtdd, J = 12.8, 4.5, 2.1, 0.9 Hz, 1H), 1.53 – 1.45 (m, 1H), 1.42 (d, J = 22.0 Hz, 3H), 1.32 (d, J = 22.0 Hz, 3H), 1.16 (d, J = 6.7 Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (chloroform- d , 100 MHz): δ = 201.6, 148.9, 148.8, 130.5, 97.3, 95.6, 47.4, 47.2, 41.3, 33.4, 33.4, 25.6, 25.4, 23.7, 23.4, 15.1; IR (Neat Film, NaCl) 2930, 1682, 1453, 1376, 1219, 878, 812, 522 cm^{-1} ; HRMS (FI+): m/z calc'd for $\text{C}_{10}\text{H}_{15}\text{FO}$ $[\text{M}]^+$: 170.1101, found 170.1099; $[\alpha]_{\text{D}}^{21.82}$ –37.10 (c 0.167, CHCl_3).



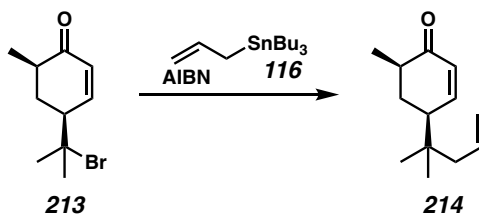
(4R,6R)-4-isopropyl-6-methylcyclohex-2-en-1-one 212.

AIBN (20 mg, 0.121 mmol, 0.2 equiv) was loaded into a 20 mL vial with septum cap. A solution of bromide **207** (140 mg, 0.606 mmol, 1.0 equiv) and Bu_3SnH (353 mg, 1.21 mmol, 2.0 equiv) in anhydrous benzene (6 mL) was added. The reaction mixture was stirred at 86 °C for 1 h, after which the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica (0–10% EtOAc in hexanes) to afford **212** (82 mg, 89%) as a colorless oil. The resulting product is pure enough for most purposes, but a sample of higher purity for analysis was obtained by distillation. ^1H NMR (chloroform-*d*, 400 MHz): δ = 6.82 (dt, J = 10.2, 2.2 Hz, 1H), 6.01 (dd, J = 10.2, 3.0 Hz, 1H), 2.39 (m, 2H), 1.96 (dtd, J = 13.0, 4.5, 2.0 Hz, 1H), 1.80 (pd, J = 6.9, 4.8 Hz, 1H), 1.54 – 1.49 (ddd, J = 13.9, 13.0, 11.4 Hz, 1H), 1.15 (d, J = 6.6, 3H), 0.96 (d, J = 7.1, 3H), 0.94 (d, J = 6.9, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (chloroform-*d*, 100 MHz): δ = 202.7, 153.5, 129.7, 43.5, 41.7, 34.2, 31.8, 19.6, 19.3, 15.2; IR (Neat Film, NaCl) 2959, 2872, 1684, 1458, 1386, 1219, 803 cm^{-1} ; HRMS (FI+): m/z calc'd for $\text{C}_{10}\text{H}_{16}\text{O}$ $[\text{M}]^+$: 152.1196 found, 152.1198; $[\alpha]_{\text{D}}^{22.31}$ –35.30 (c 1.0, CHCl_3).



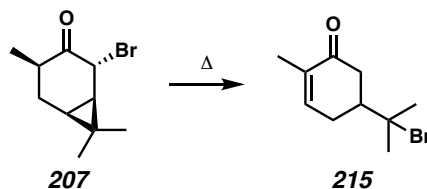
(4S,6R)-4-(2-bromopropan-2-yl)-6-methylcyclohex-2-en-1-one **213.**

To a 4 mL vial was added bromide **207** (36 mg, 0.156 mmol, 1.0 equiv) in anhydrous benzene (1.5 mL). To this solution was added allyltributyltin **116** (21 mg, 0.062 mmol, 0.4 equiv) and AIBN (5 mg, 0.03 mmol, 0.2 equiv). The vial was sealed, and the reaction mixture stirred at 86 °C for 4 h. The reaction was then allowed to cool to 20 °C and concentrated under reduced pressure. The residue was purified *via* flash chromatography on silica (5–10% EtOAc in hexanes) to afford **213** (26 mg, 72%) as a colorless oil. ^1H NMR (chloroform-*d*, 400 MHz): δ = 7.09 (dt, J = 10.3, 2.1 Hz, 1H), 6.09 (dd, J = 10.3, 2.8 Hz, 1H), 2.85 (dddd, J = 11.4, 4.6, 2.9, 2.0 Hz, 1H), 2.41 (dq, J = 13.4, 6.7, 4.5 Hz, 1H), 2.24 (dtd, J = 12.7, 4.4, 2.2 Hz, 1H), 1.89 (s, 3H), 1.74 (s, 3H), 1.67 – 1.58 (m, 1H), 1.17 (d, J = 6.7 Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (chloroform-*d*, 100 MHz): δ = 201.3, 150.1, 130.2, 68.3, 50.5, 41.0, 34.2, 32.9, 30.9, 15.1; IR (Neat Film, NaCl) 2967, 1682, 1455, 1372, 1213, 1125, 803, 644, 601 cm^{-1} ; HRMS (FI⁺): m/z calc'd for $\text{C}_{10}\text{H}_{15}\text{OBr}$ $[\text{M}]^+$: 230.0301, found 230.0300; $[\alpha]_{\text{D}}^{22.13}$ –62.67 (c 1.0, CHCl_3).



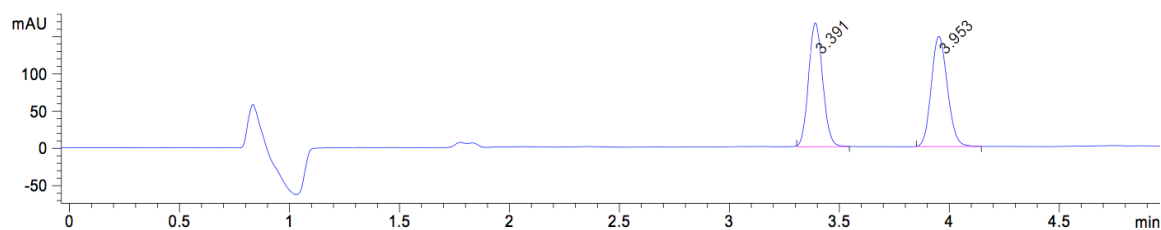
(4S,6R)-6-methyl-4-(2-methylpent-4-en-2-yl)cyclohex-2-en-1-one **214.**

To a 20 mL vial was added bromide **213** (45 mg, 0.195 mmol, 1.0 equiv) in anhydrous benzene (4 mL). To this was added allyltributyltin **116** (390 mg, 1.17 mmol, 6.0 equiv) and AIBN (6.4 mg, 0.039 mmol, 0.2 equiv). The vial was sealed, and the reaction mixture stirred at 86 °C for 48 h. The solution was concentrated under reduced pressure and the residue purified *via* flash chromatography on silica (5% EtOAc in hexanes) to afford **214** (24 mg, 63%) as a colorless oil. The compound is pure enough for most purposes, but a sample of higher purity for analysis was obtained by preparatory HPLC (60–80% MeCN in H₂O over 5 min at 12 mL/min). ¹H NMR (chloroform-*d*, 400 MHz): δ = 6.96 (dt, J = 10.3, 2.1 Hz, 1H), 6.03 (dd, J = 10.3, 3.0 Hz, 1H), 5.83 (ddt, J = 16.8, 10.2, 7.4 Hz, 1H), 5.13 – 5.02 (m, 2H), 2.36 (m, 2H), 2.11 – 2.06 (m, 2H), 2.03 (ddq, J = 11.0, 4.4, 2.2 Hz, 1H), 1.55 – 1.46 (m, 1H), 1.15 (d, J = 6.7 Hz, 3H), 0.95 (s, 3H), 0.92 (s, 3H); ¹³C{¹H} NMR (chloroform-*d*, 100 MHz): δ = 202.4, 151.7, 134.7, 130.0, 118.0, 45.7, 44.5, 41.8, 35.7, 33.1, 24.9, 24.6, 15.3; IR (Neat Film, NaCl) 2961, 1683, 1385, 1222, 914, 802 cm⁻¹; HRMS (FI⁺): m/z calc'd for C₁₃H₂₀O [M]⁺: 192.1509, found 192.1509; [α]_D^{22.49} –25.44 (c 0.25, CHCl₃).



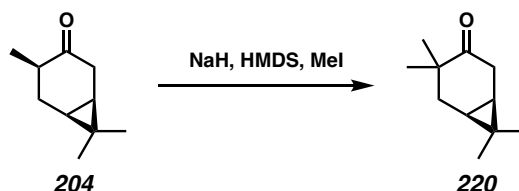
5-(2-bromopropan-2-yl)-2-methylcyclohex-2-en-1-one 215.

To a 4 mL vial was added bromide **207** (86 mg, 0.372 mmol, 1.0 equiv) in anhydrous benzene (1.6 mL). The vial was sealed, and the reaction mixture stirred at 86 °C for 25 min. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography on neutral alumina (5% EtOAc in hexanes) to afford **215** (63 mg, 73%) as a colorless oil. ^1H NMR (chloroform-*d*, 400 MHz): δ = 6.75 (ddq, J = 5.4, 2.8, 1.4 Hz, 1H), 2.74 (ddd, J = 16.0, 3.7, 1.8 Hz, 1H), 2.59 (dddt, J = 18.2, 6.2, 4.6, 1.5 Hz, 1H), 2.41 (m, 2H), 2.05 (dddd, J = 13.5, 11.1, 4.6, 3.7 Hz, 1H), 1.79 (m, 3H), 1.79 (s, 3H), 1.77 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (chloroform-*d*, 100 MHz): δ = 199.2, 144.3, 135.4, 70.1, 48.3, 41.2, 32.5, 32.2, 29.2, 15.7; IR (Neat Film, NaCl) 2972, 1674, 1451, 1370, 1254, 1103, 1062, 904, 690 cm^{-1} ; HRMS (FI⁺): m/z calc'd for $\text{C}_{10}\text{H}_{15}\text{OBr}$ $[\text{M}]^+$: 230.0301, found 230.0302. **215** was determined to be racemic by chiral SFC analysis (AD-H, EtOH/ CO_2 = 5/95, flow rate = 3.5 mL/min, λ = 210 nm) t_{R} = 3.39, 3.95.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.391	BB	0.0683	742.96808	165.59497	49.6580
2	3.953	BB	0.0839	753.20081	146.78207	50.3420

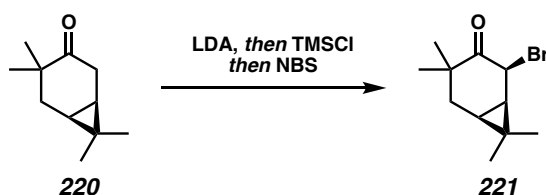
Totals : 1496.16888 312.37704



(1R,6S)-4,4,7,7-tetramethylbicyclo[4.1.0]heptan-3-one 220.

To a rapidly stirred suspension of NaH (60% dispersion in mineral oil, 289 mg, 7.23 mmol, 1.1 equiv) in THF (5.6 mL, 1 M final substrate concentration) in a 50 mL 2-neck flask equipped with a reflux condenser was added ketone **204** (1.00 g, 6.57 mmol, 1.0 equiv) through the top of the condenser. Additional THF (1 mL) was used to rinse the ketone into the reaction mixture. The suspension was then heated to reflux in an oil bath and stirred for 1.5 h. Then, HMDS (0.21 mL, 0.986 mmol, 0.15 equiv) was added through the top of the condenser and the reaction mixture was stirred under reflux for an additional 25 min. The flask was then cooled to 0 °C in an ice bath, and the reflux condenser was replaced with a septum. MeI (0.45 mL, 7.23 mmol, 1.1 equiv) was added dropwise, after which the ice bath was removed. After stirring at 20 °C for 17 h, the reaction mixture was quenched with H₂O (20 mL), the layers were separated, and the aqueous layer was extracted with Et₂O (4x10 mL). The combined organic layers were dried over MgSO₄, concentrated under reduced pressure, and purified *via* silica gel flash chromatography (10% Et₂O in hexanes). The resulting oil was purified again by automated silica gel flash chromatography (Teledyne ISCO, 0→10% EtOAc in hexanes) to provide dimethyl ketone **220** (361 mg, 29% yield desired isomer) as a fragrant, colorless oil containing 11% of an inseparable isomeric impurity; ¹H NMR (chloroform-*d*, 400 MHz): δ = 2.65 – 2.52 (m, 1H), 2.19 – 2.07 (m, 1H), 1.94 (ddt, *J* = 14.9, 9.3, 1.4 Hz, 1H), 1.39 (ddt, *J* = 14.9, 6.2, 0.9 Hz, 1H), 1.22 (s,

3H), 1.11 – 1.06 (m, 1H), 1.04 (s, 3H), 0.94 (s, 3H), 0.90 – 0.80 (m, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (chloroform- d , 100 MHz): δ = 218.9, 42.4, 35.1, 34.6, 28.0, 24.8, 24.3, 22.4, 19.5, 18.2, 14.9; IR (Neat Film, NaCl) 2930, 2867, 1709, 1460, 1412, 1379, 1111, 1051, 986, 808 cm^{-1} ; m/z calc'd for $\text{C}_{11}\text{H}_{18}\text{O}$ $[\text{M}]^+$: 166.1352, found 166.1358; $[\alpha]_{\text{D}}^{21.48}$ –68.91 (c 1.0, CHCl_3).



(1R,2S,6S)-2-bromo-4,4,7,7-tetramethylbicyclo[4.1.0]heptan-3-one 221.

To a solution of diisopropylamine (0.10 mL, 0.722 mmol, 1.2 equiv) in THF (1.3 mL, 0.45 M substrate concentration) was added *n*-butyllithium (2.5 M in hexanes, 0.25 mL, 0.632 mmol, 1.05 equiv) dropwise at $-78\text{ }^{\circ}\text{C}$. The solution was allowed to warm to $0\text{ }^{\circ}\text{C}$ and immediately cooled back to $-78\text{ }^{\circ}\text{C}$, whereafter ketone **220** (100 mg, 0.602 mmol, 1.0 equiv) was added dropwise and the solution stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h. TMSCl (0.11 mL, 0.903 mmol, 1.5 equiv) was added and the reaction was allowed to warm to $0\text{ }^{\circ}\text{C}$ in an ice bath and stirred for an additional 45 min. The reaction was then protected from light and NBS (161 mg, 0.903 mmol, 1.5 equiv) was added in one portion. After stirring for a further 30 min in the dark, the reaction was quenched with saturated aq. NaHCO_3 (1 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (1 mL). The combined organic layers were washed with water (1 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. The crude product was purified *via* silica gel flash chromatography to afford α -bromoketone **221** (126 mg, 89% yield desired isomer) as a white crystalline solid containing 8% of an inseparable isomeric impurity; ^1H NMR

(chloroform-*d*, 400 MHz): δ = 4.23 (dd, J = 6.0, 0.8 Hz, 1H), 1.91 (ddd, J = 15.1, 8.3, 0.9 Hz, 1H), 1.44 (ddd, J = 15.0, 8.4, 0.8 Hz, 1H), 1.40 – 1.35 (m, 4H), 1.13 (s, 3H), 1.11 – 1.05 (m, 4H), 1.03 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (chloroform-*d*, 100 MHz): δ = 209.2, 49.2, 44.4, 33.7, 30.4, 27.7, 26.6, 26.0, 21.8, 21.5, 14.2; IR (Neat Film, NaCl) 2954, 2869, 1721, 1462, 1376, 1244, 1054, 911, 742 cm^{-1} ; m/z calc'd for $\text{C}_{11}\text{H}_{17}\text{OBr}$ $[\text{M}]^+$: 244.0457, found 244.0459; $[\alpha]_{\text{D}}^{21.55}$ –148.50 (c 1.0, CHCl_3).

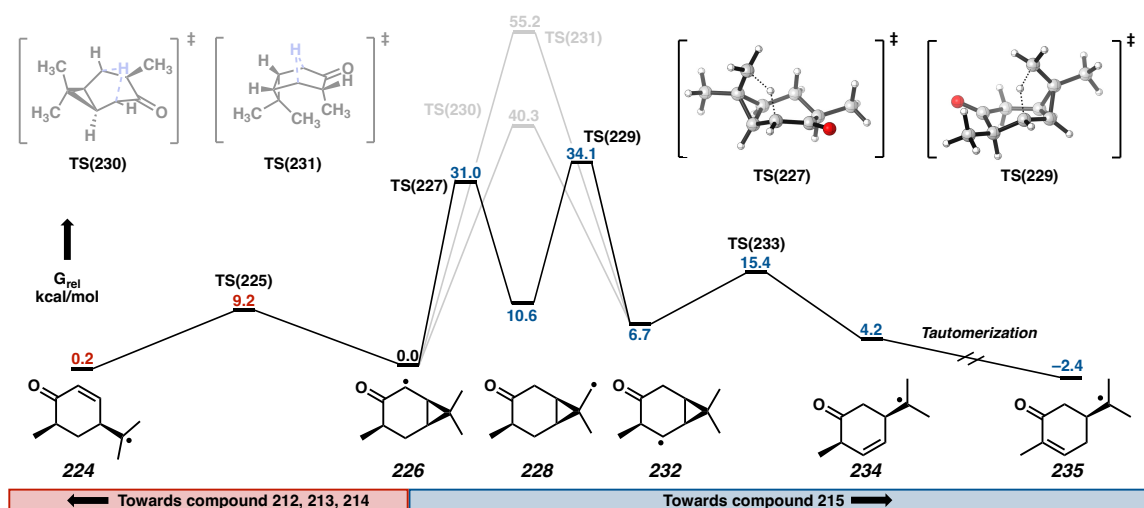
3.5.3 COMPUTATIONAL DETAILS

All quantum mechanical calculations were carried out with the ORCA program.^{12,13} DFT geometry optimizations and harmonic frequency calculations were carried out in the gas phase with the M06-2X functional²¹ and def2-TZVP basis set²² on all atoms. Thermodynamic corrections from harmonic frequency calculations employ the quasi-rigid rotor harmonic oscillator approach to correct for the breakdown of the harmonic oscillator approximation at low vibrational frequencies.²³ Stationary points are characterized by the correct number of imaginary vibrational modes (zero for minima and one for saddle points). Intrinsic reaction coordinate (IRC) analysis²⁴ confirms the nature of transition states. Electronic energies are further refined with single point calculations at the M06-2X/def2-TZVPP level of theory employing the SMD implicit solvation model for benzene.²⁵ Final Gibbs free energies were obtained by applying thermodynamic corrections obtained at the optimization level of theory to these refined solvated electronic energies.

The resolution of identity (RI) and Chain-of-Spheres (COS) approximations are employed for efficient evaluation of Coulomb and exchange integrals, respectively.²⁶ The

def2/J auxiliary basis²⁷ and very fine grid settings are employed in all calculations (keyword: DefGrid3). Calculations on open-shell systems employ unrestricted Kohn–Sham orbitals (UKS). Spin contamination is generally minor.

Figure 3.5.3.1. Minimum free energy pathway from 226 toward 224 and 235.^a



^aRelative free energies (in blue) provided in kcal/mol obtained at the M06-2X/def2-TZVPP/SMD(Benzene)//M06-2X/def2-TZVP level of theory. Note that 224 and 226 exist in a rapid equilibrium. Direct 1,4-HAT over (TS(230)) or under (TS(231)) the ring, as well as indirect HAT through primary radical 228, involve barriers that are kinetically inaccessible at the temperatures at which these reactions were performed.

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mL was attained. The mixture was stirred until homogeneous and used immediately.

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APPENDIX 6

Spectra Relevant to Chapter 3:

Some Unusual Transformations of a Highly Reactive α -Bromocaranone

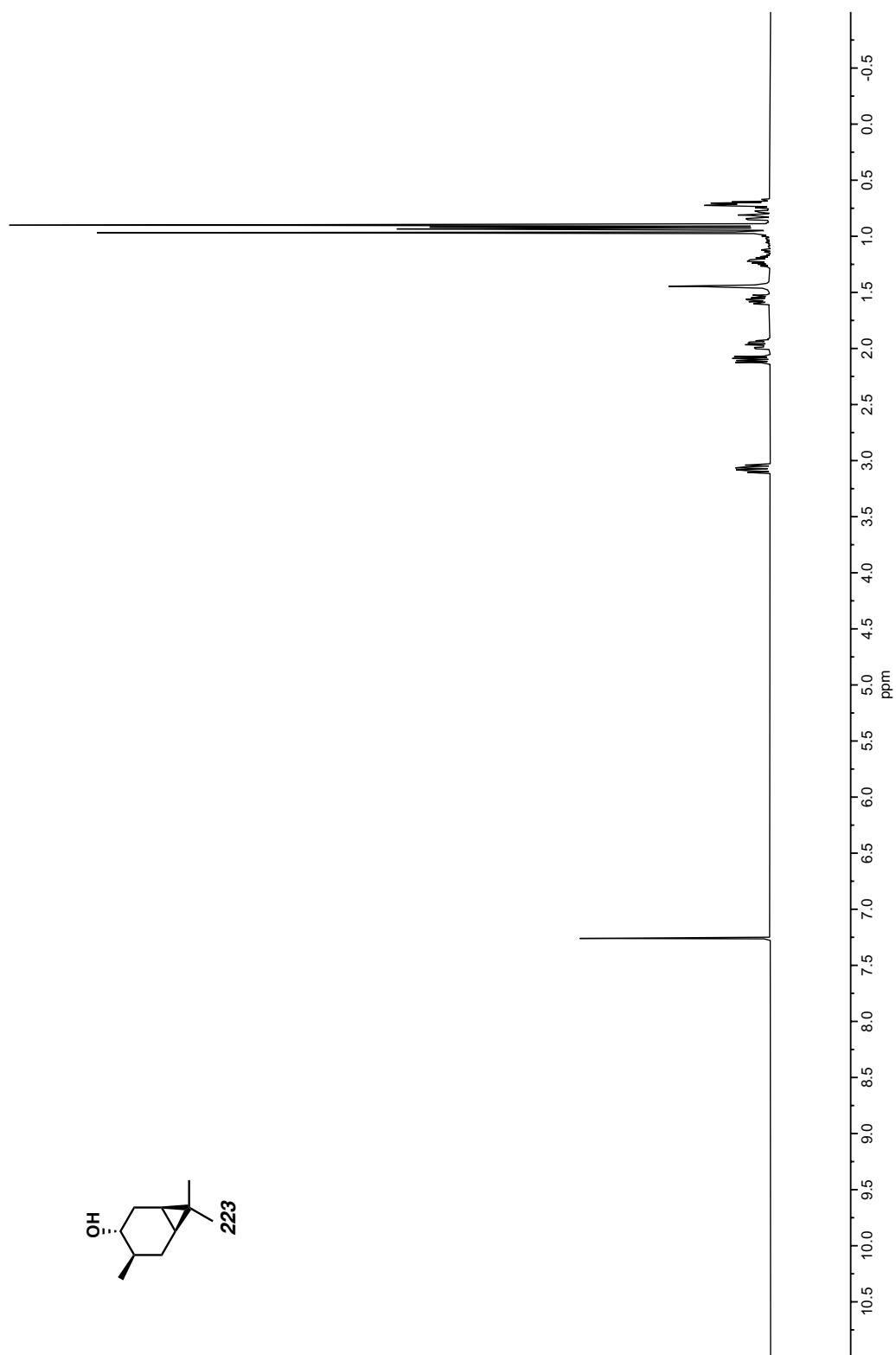


Figure A6.1 ^1H NMR (400 MHz, CDCl_3) of compound 223.

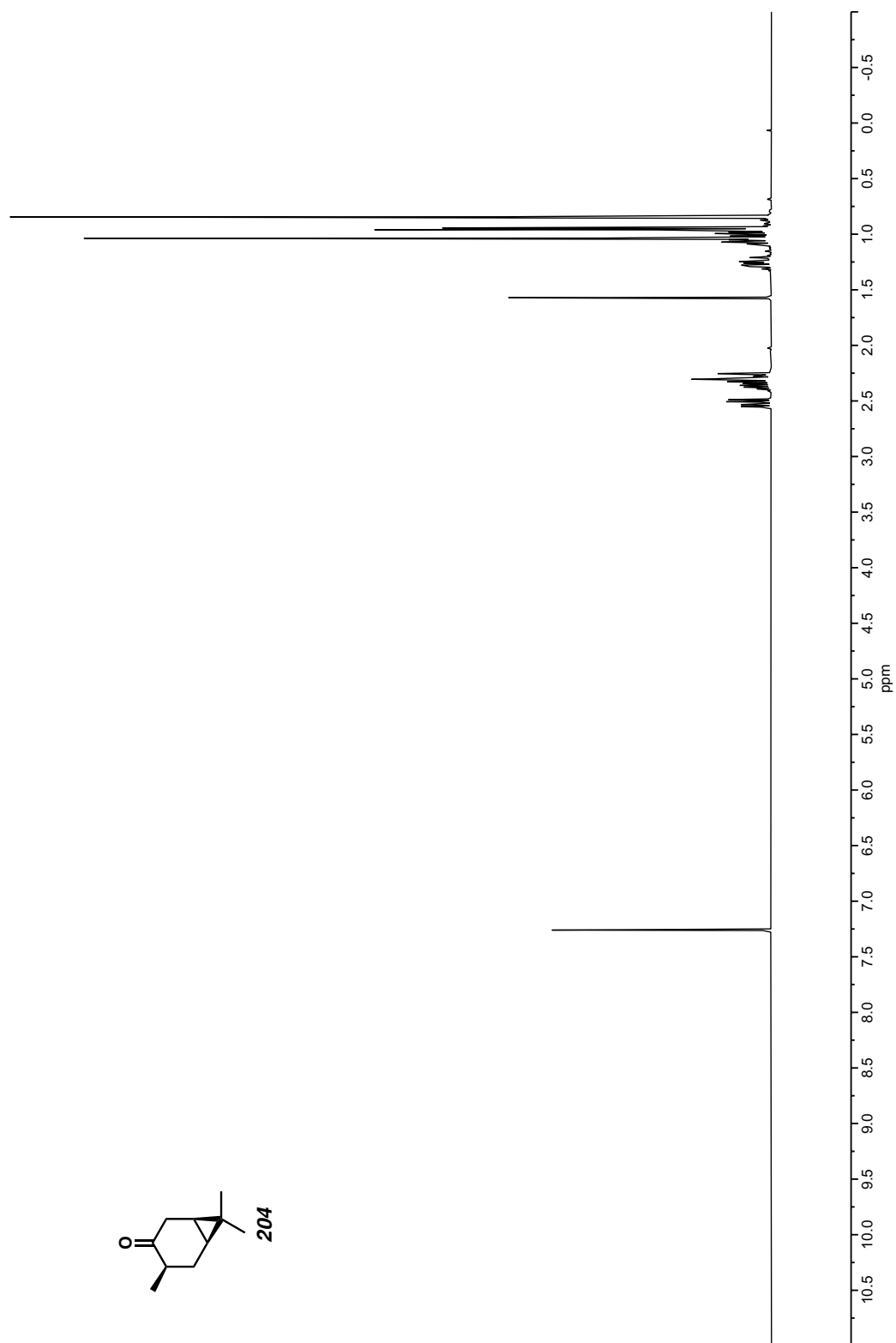


Figure A6.2 ^1H NMR (400 MHz, CDCl_3) of compound **204**.

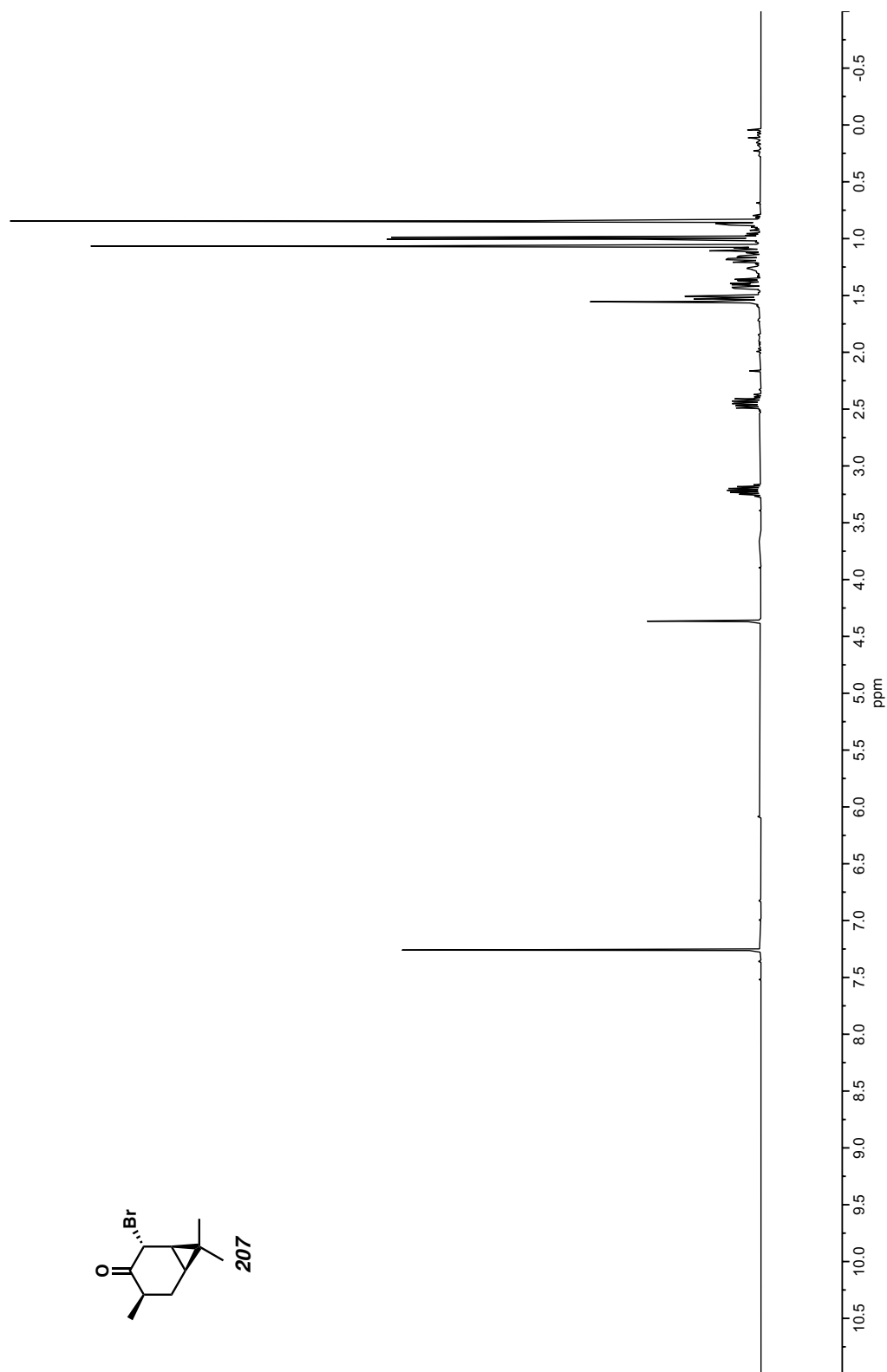


Figure A6.3 ^1H NMR (400 MHz, CDCl_3) of compound **207**.

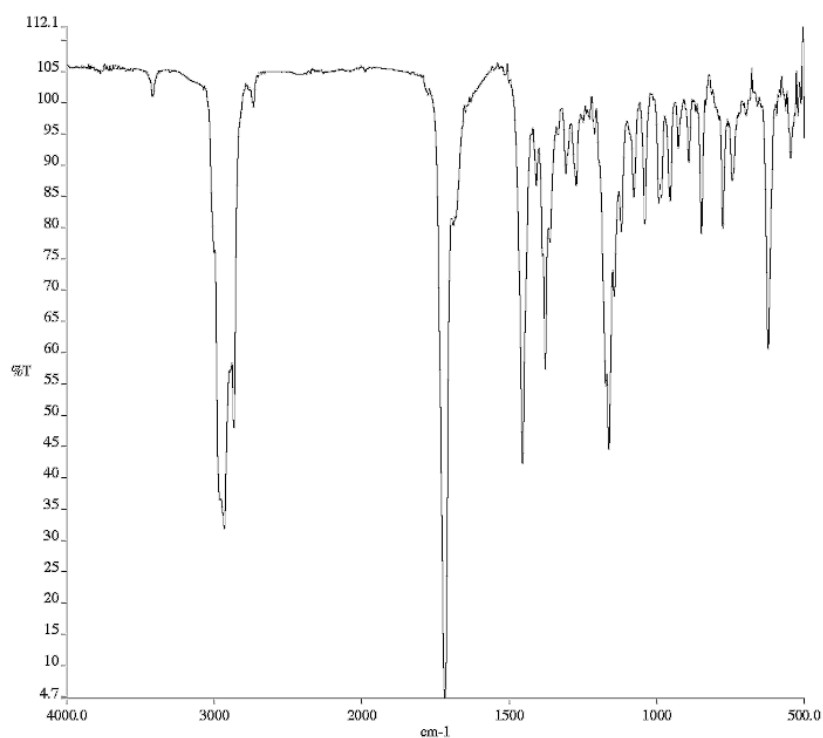


Figure A6.4 Infrared spectrum (Thin Film, NaCl) of compound **207**.

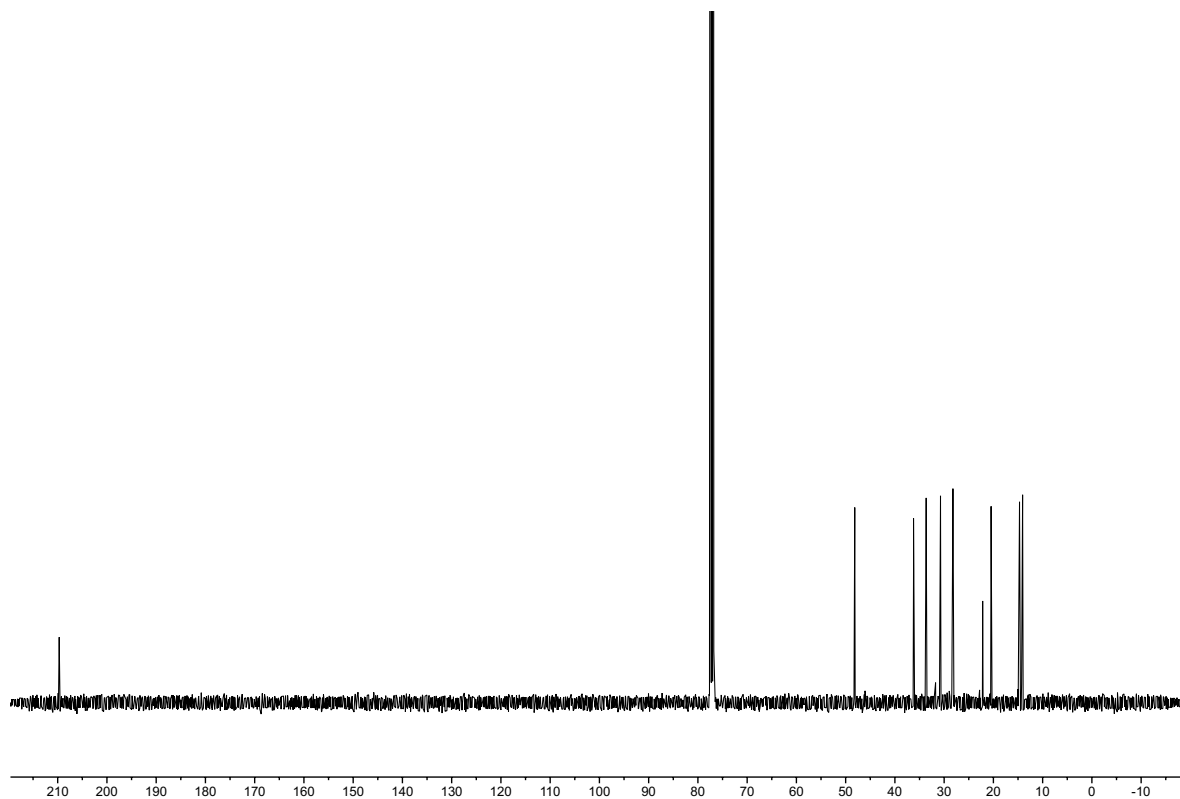


Figure A6.5 ¹³C NMR (100 MHz, CDCl₃) of compound **207**.

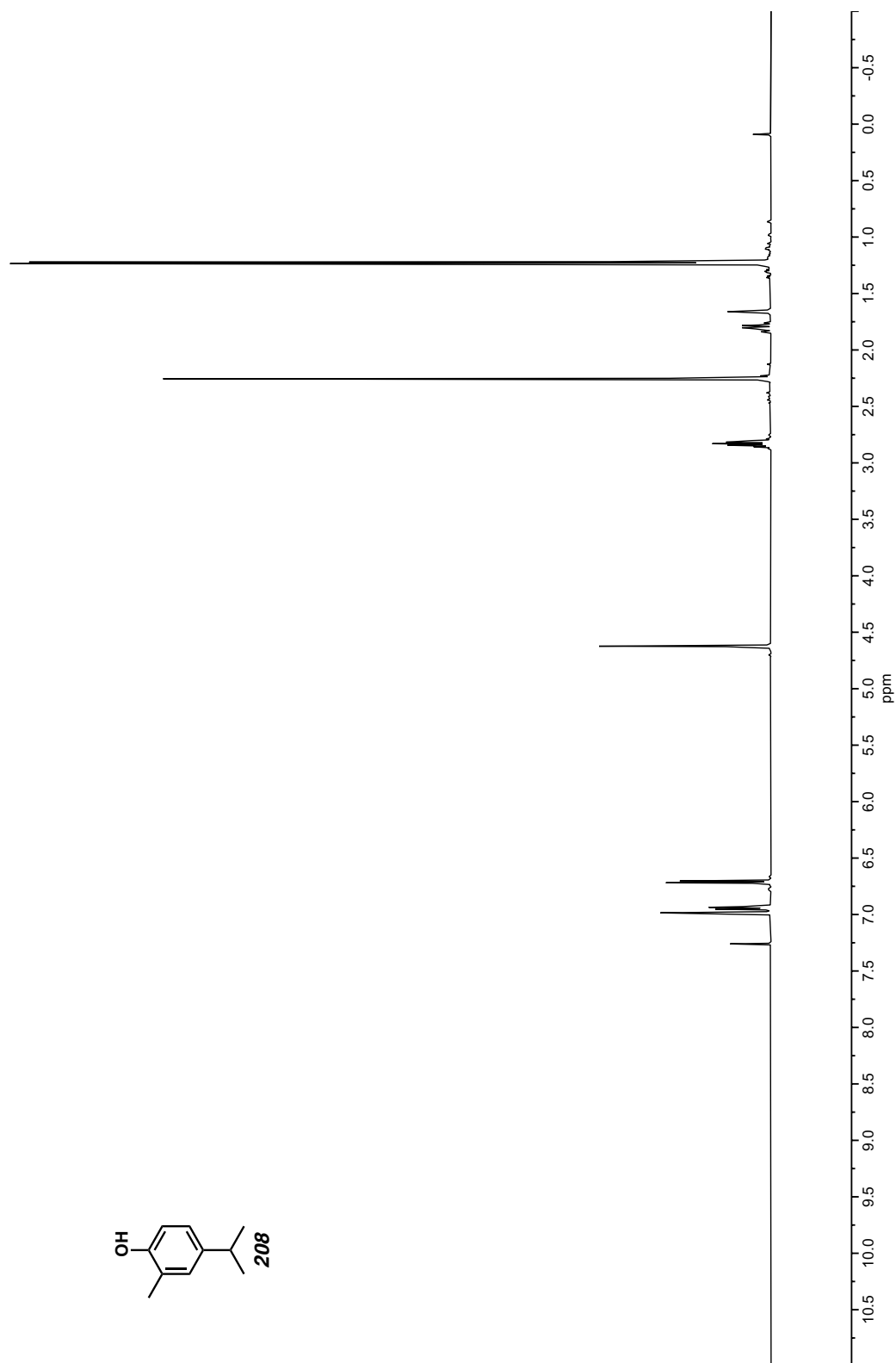


Figure A6.6 ^1H NMR (400 MHz, CDCl_3) of compound 208.

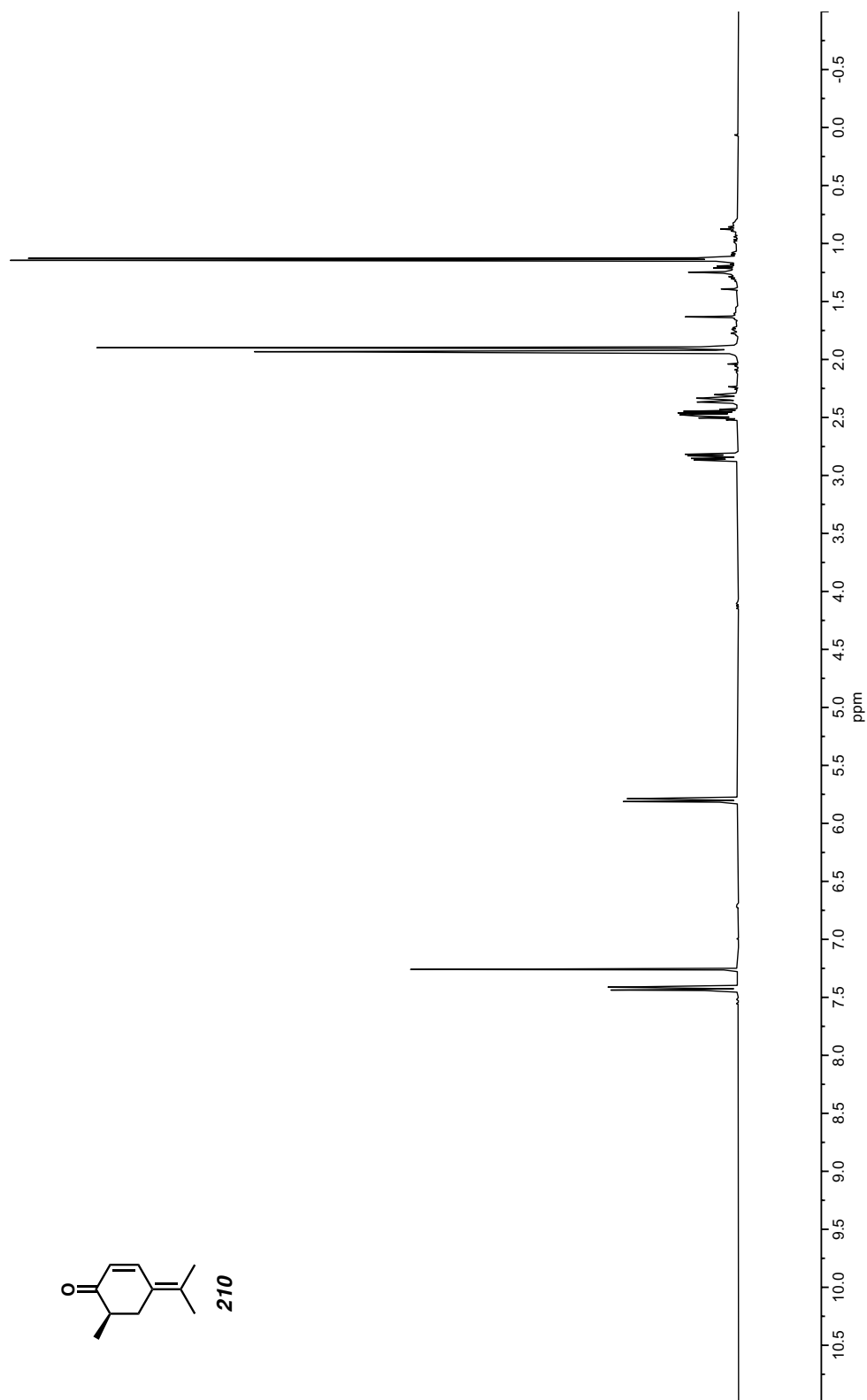


Figure A6.7 ¹H NMR (400 MHz, CDCl₃) of compound **210**.

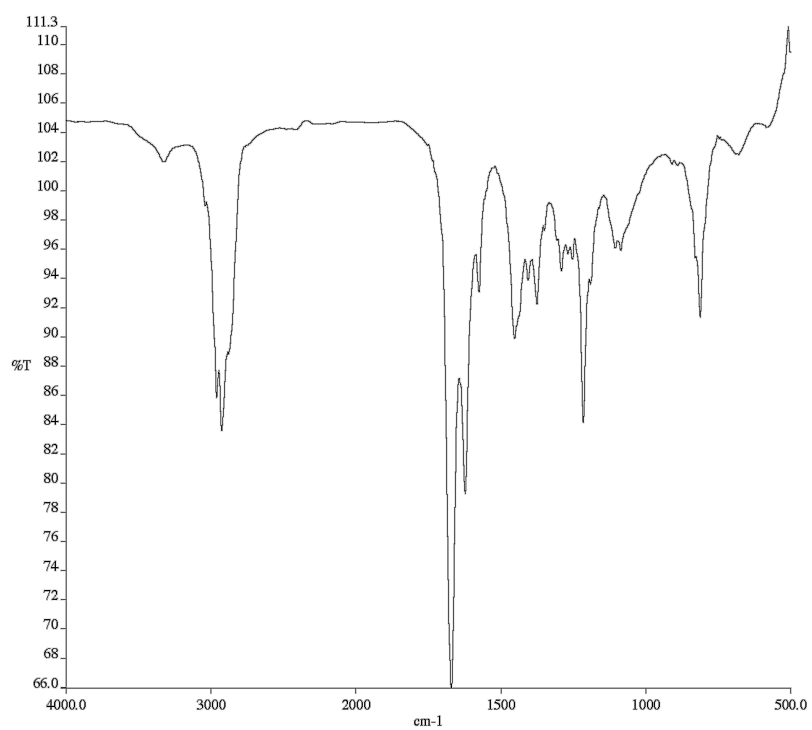


Figure A6.8 Infrared spectrum (Thin Film, NaCl) of compound **210**.

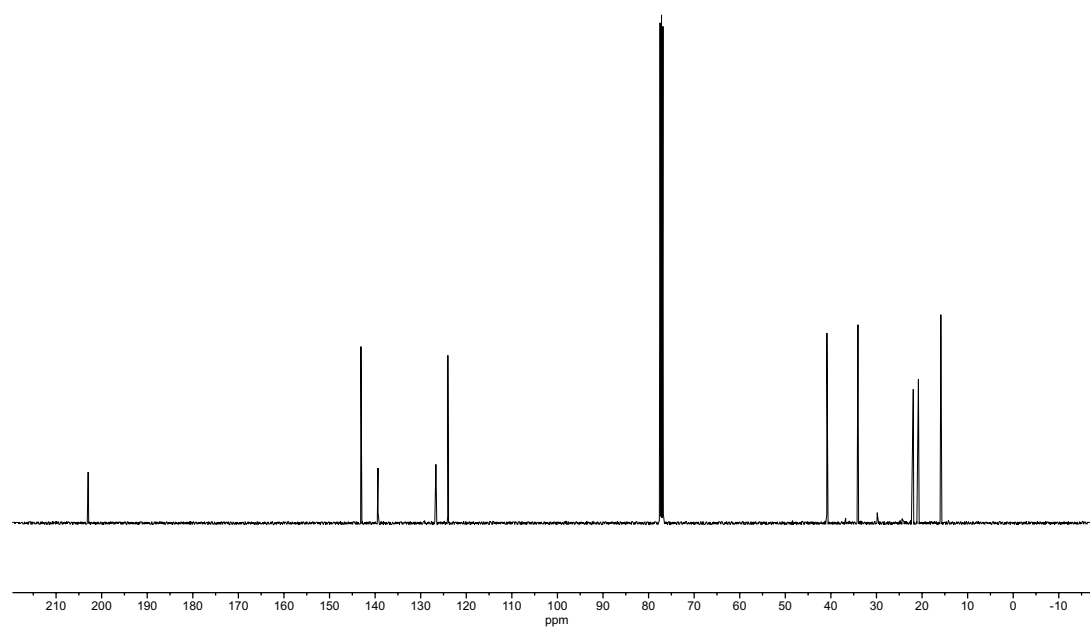
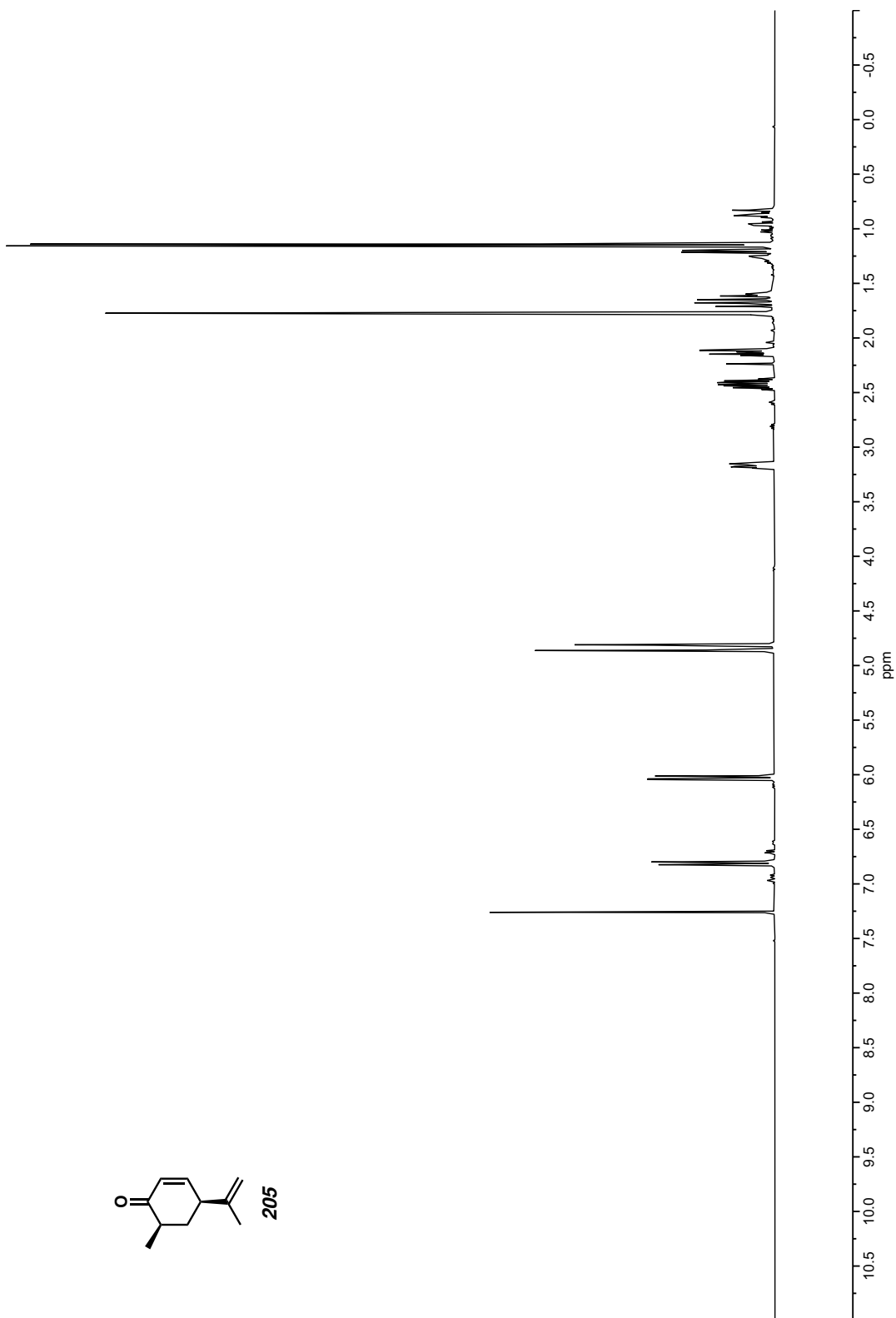


Figure A6.9 ¹³C NMR (100 MHz, CDCl₃) of compound **210**.



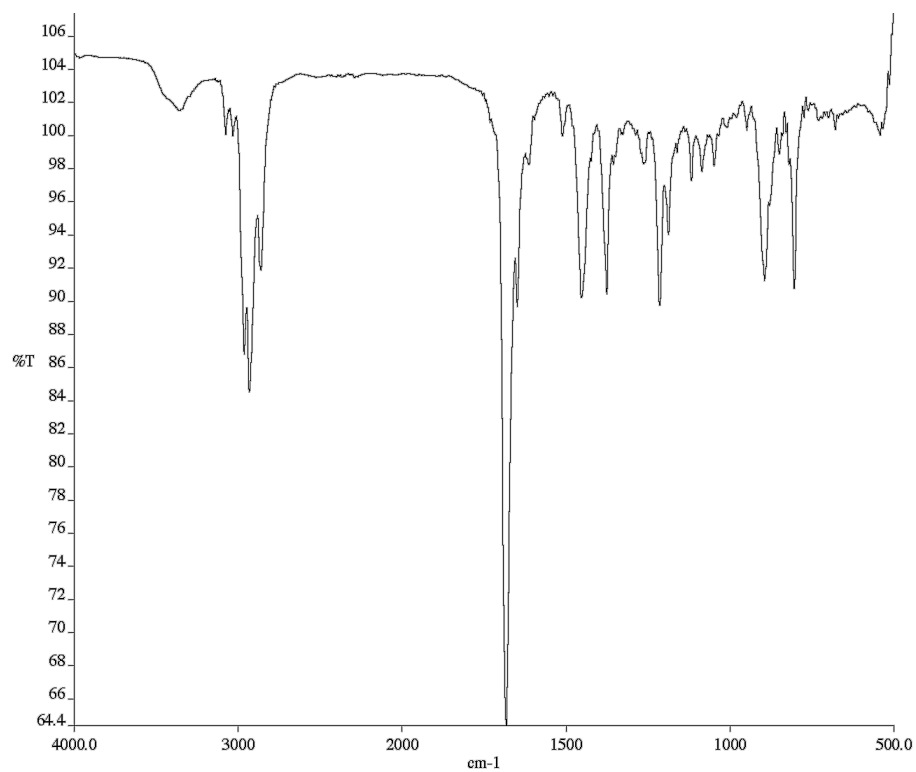


Figure A6.11 Infrared spectrum (Thin Film, NaCl) of compound **205**.

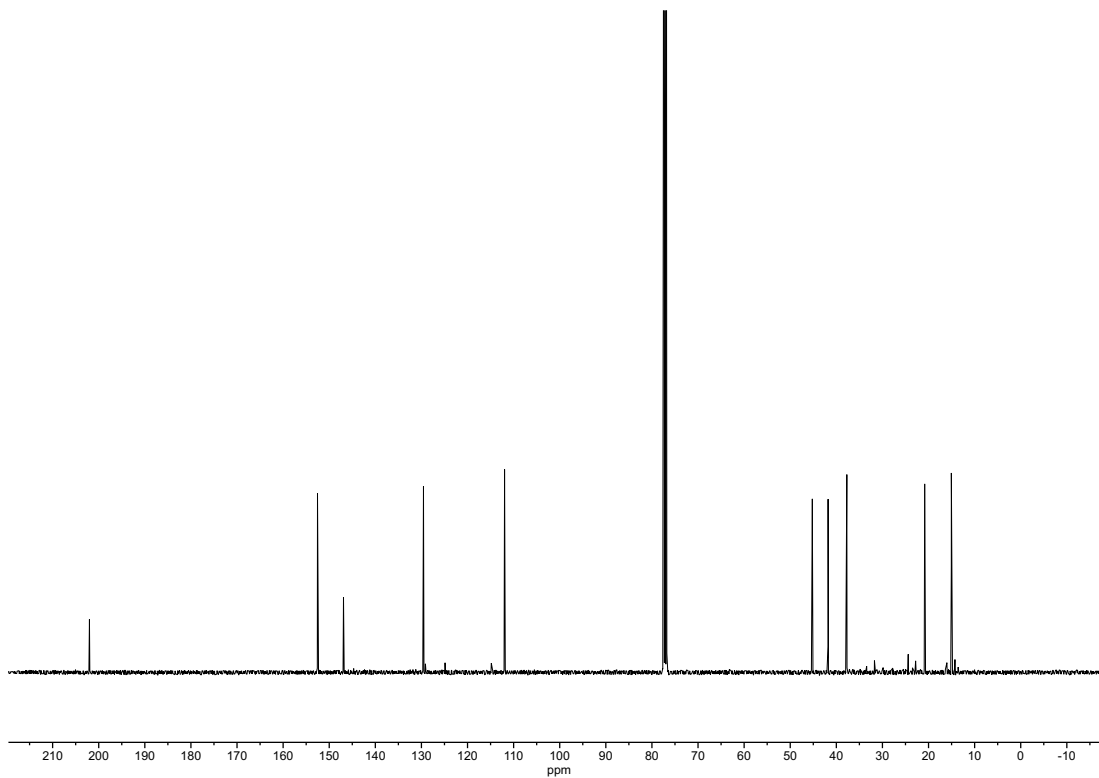


Figure A6.12 ¹³C NMR (100 MHz, CDCl₃) of compound **205**.

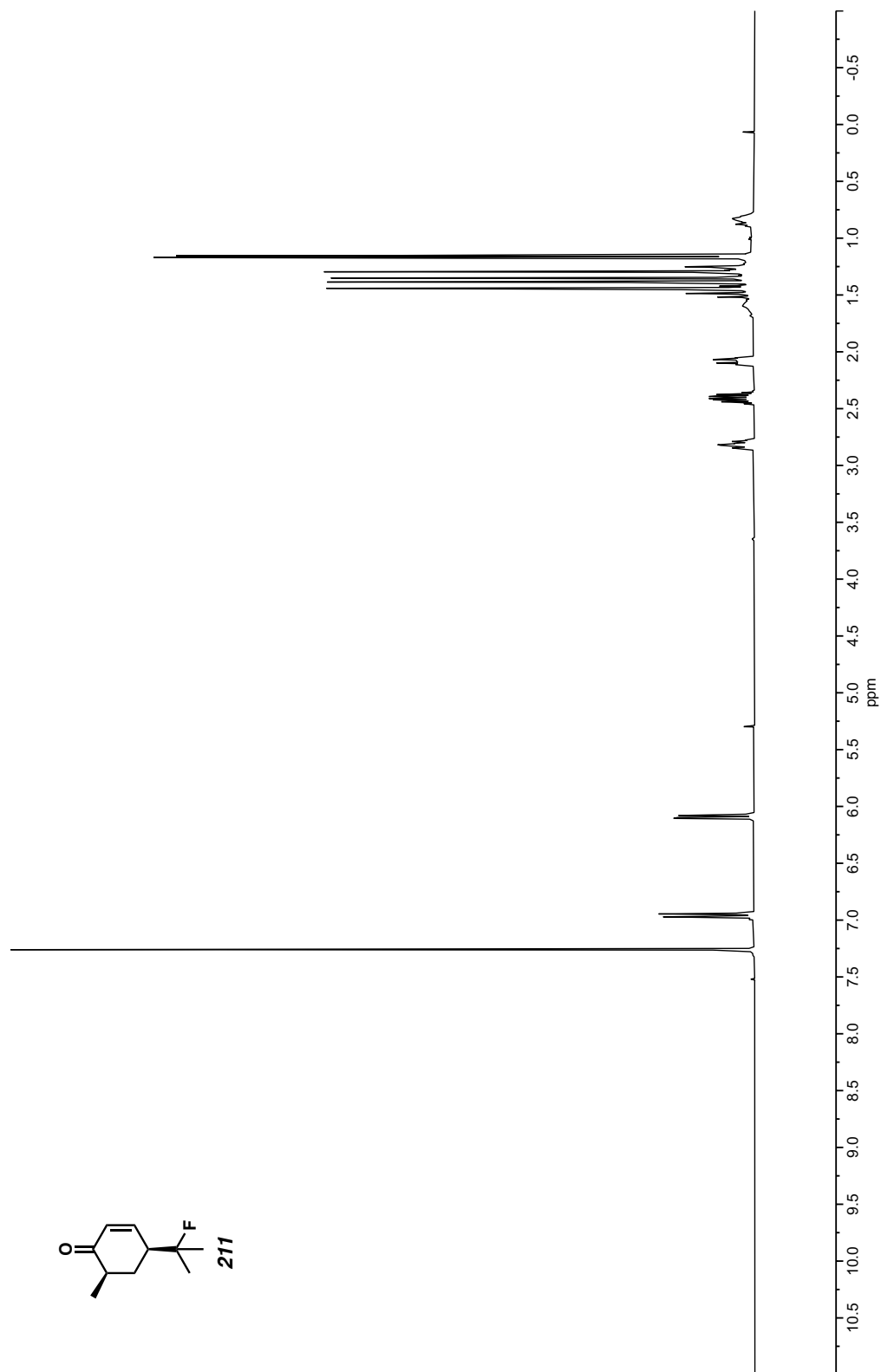


Figure A6.13 ^1H NMR (400 MHz, CDCl_3) of compound **211**.

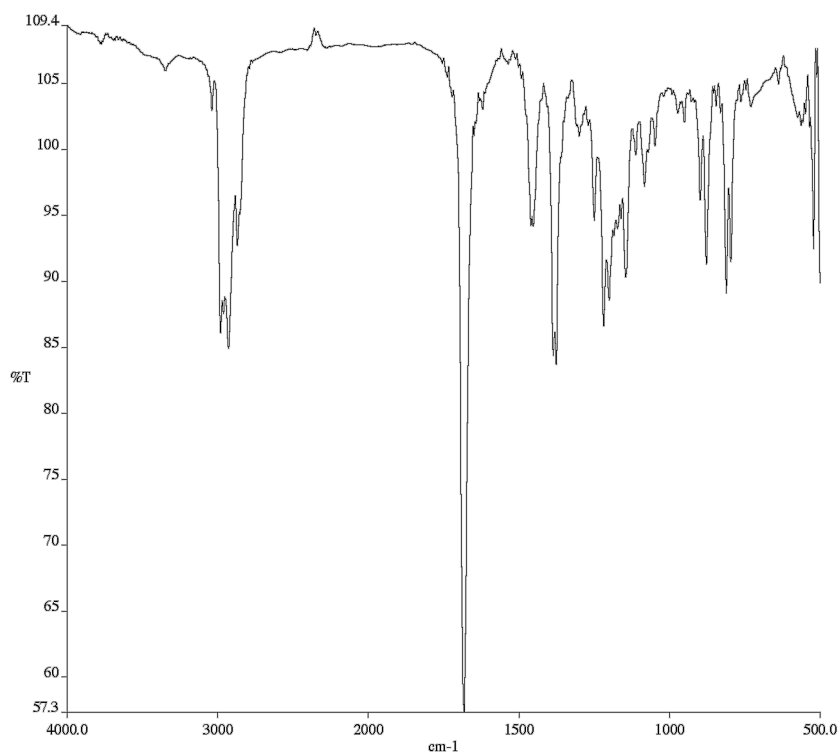


Figure A6.14 Infrared spectrum (Thin Film, NaCl) of compound **211**.

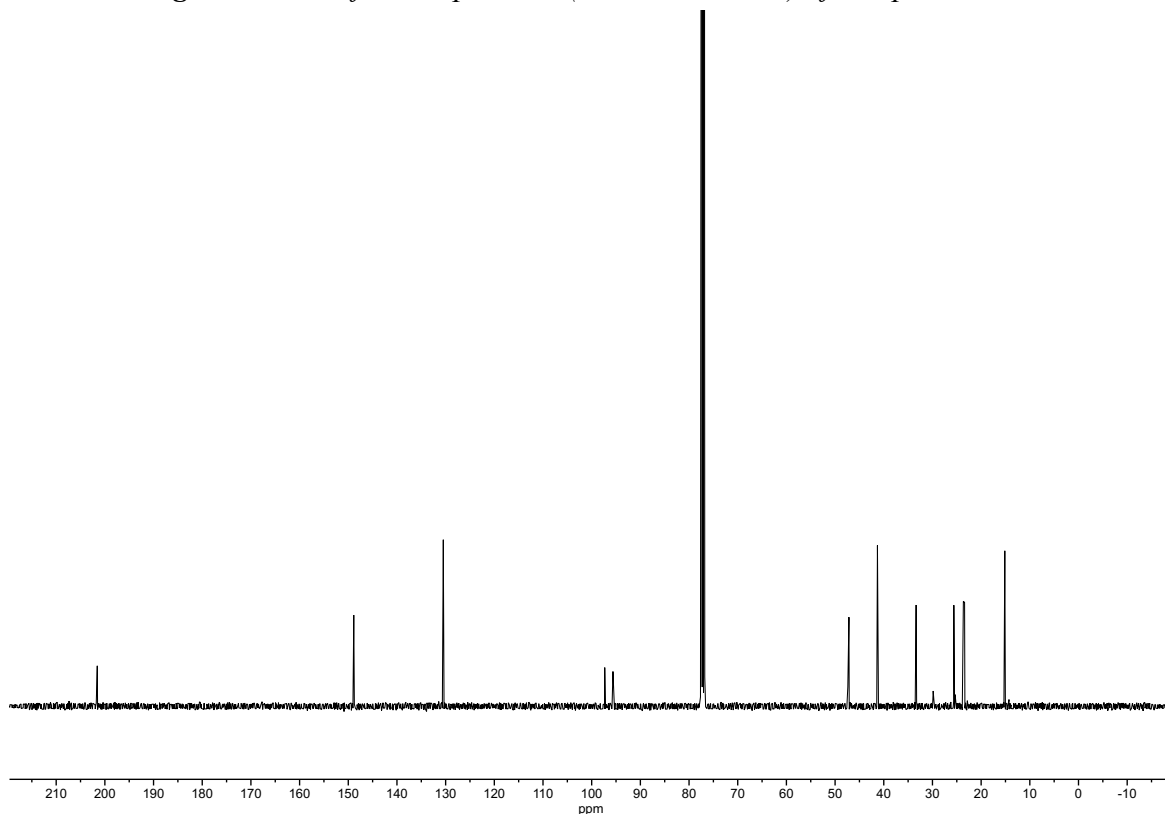


Figure A6.15 ¹³C NMR (100 MHz, CDCl₃) of compound **211**.

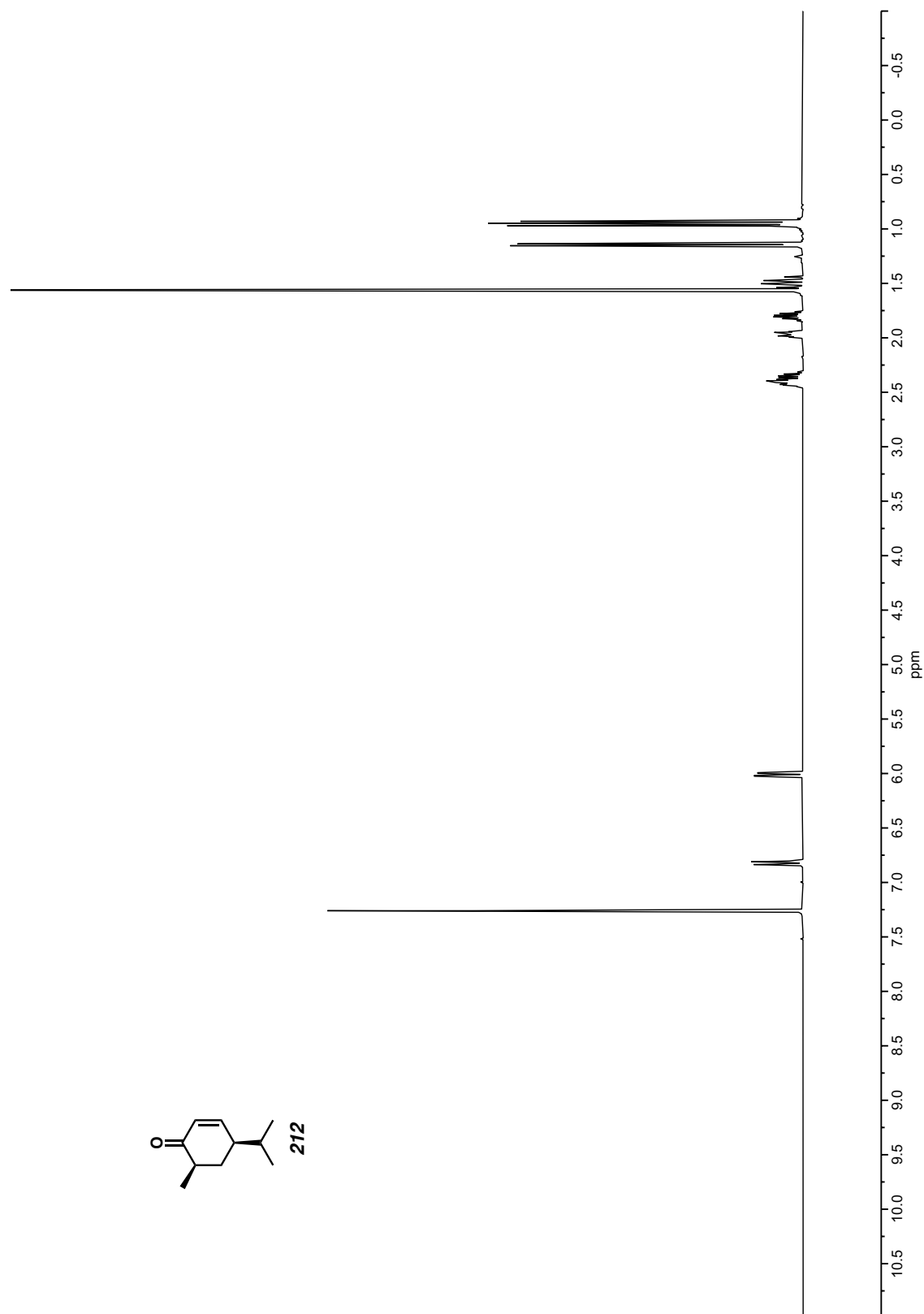


Figure A6.16 ¹H NMR (400 MHz, CDCl₃) of compound 212.

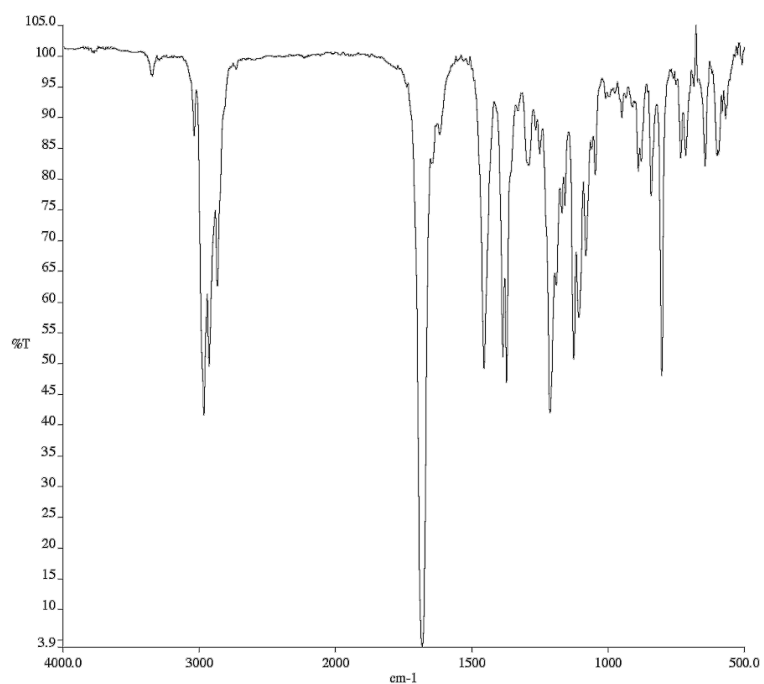


Figure A6.17 Infrared spectrum (Thin Film, NaCl) of compound **212**.

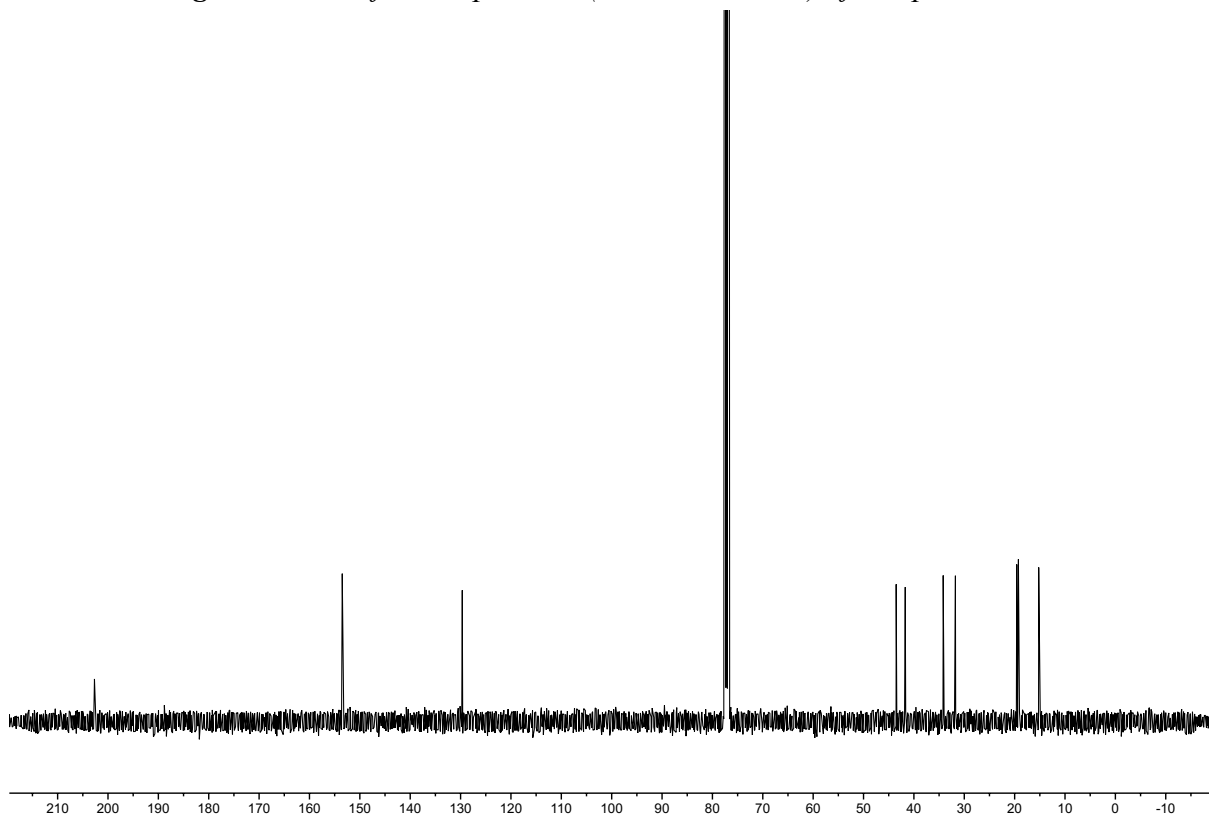


Figure A6.18 ¹³C NMR (100 MHz, CDCl₃) of compound **212**.

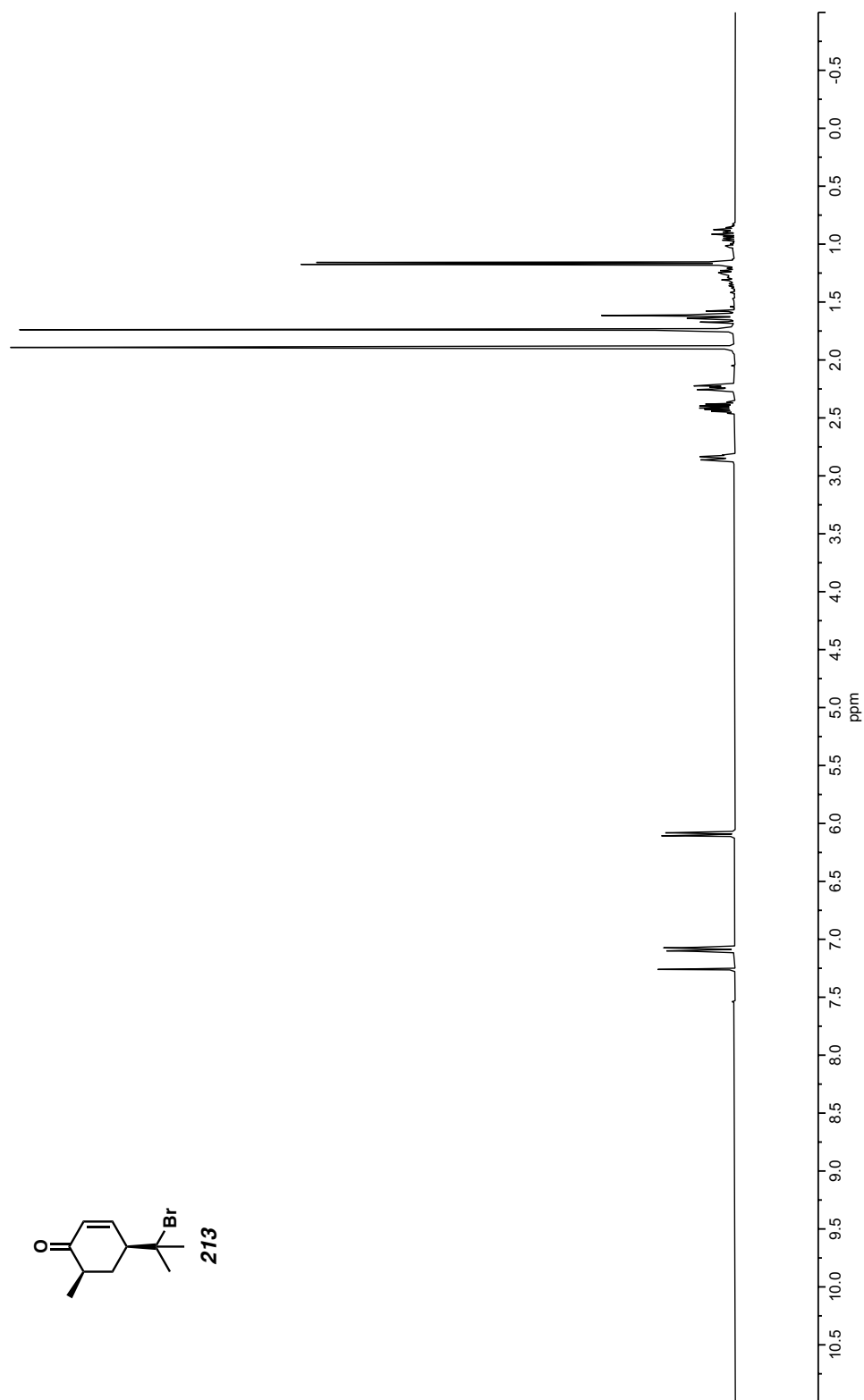


Figure A6.19 ¹H NMR (400 MHz, CDCl₃) of compound 213.

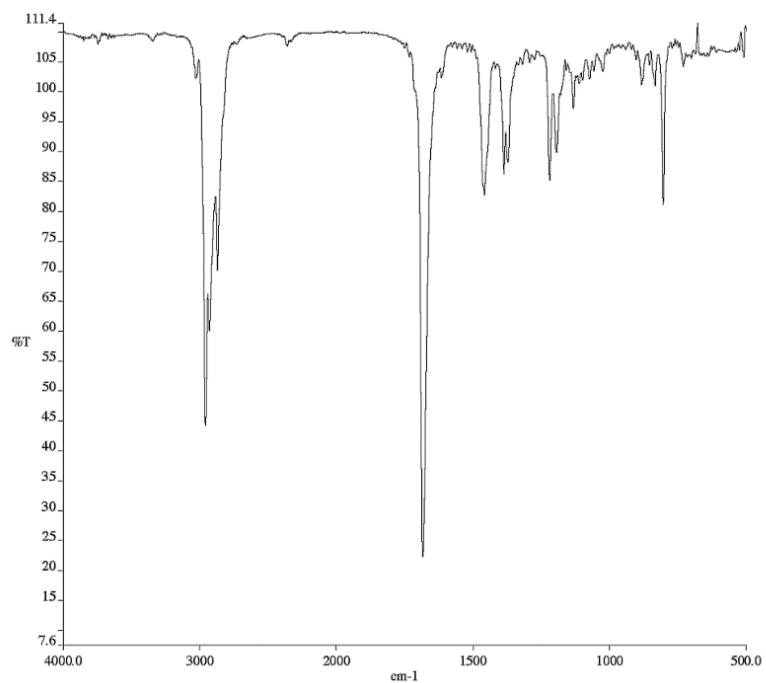


Figure A6.20 Infrared spectrum (Thin Film, NaCl) of compound **213**.

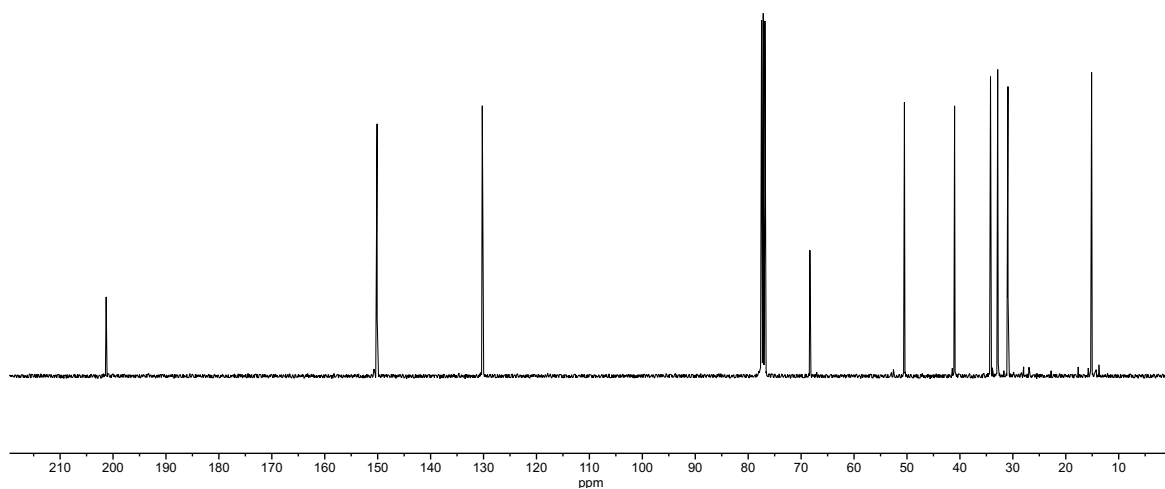


Figure A6.21 ¹³C NMR (100 MHz, CDCl₃) of compound **213**.

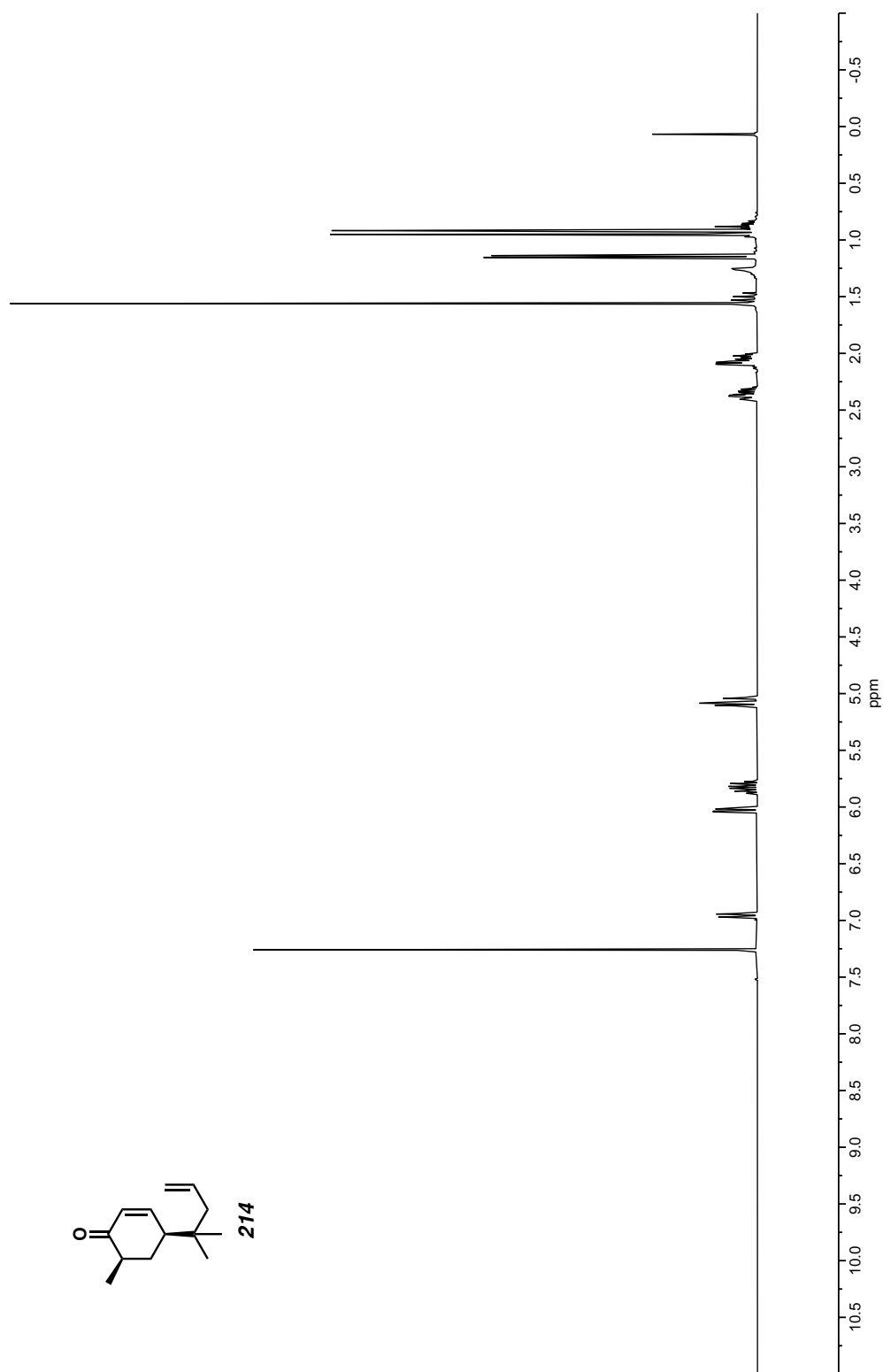


Figure A6.22 ¹H NMR (400 MHz, CDCl₃) of compound 214.

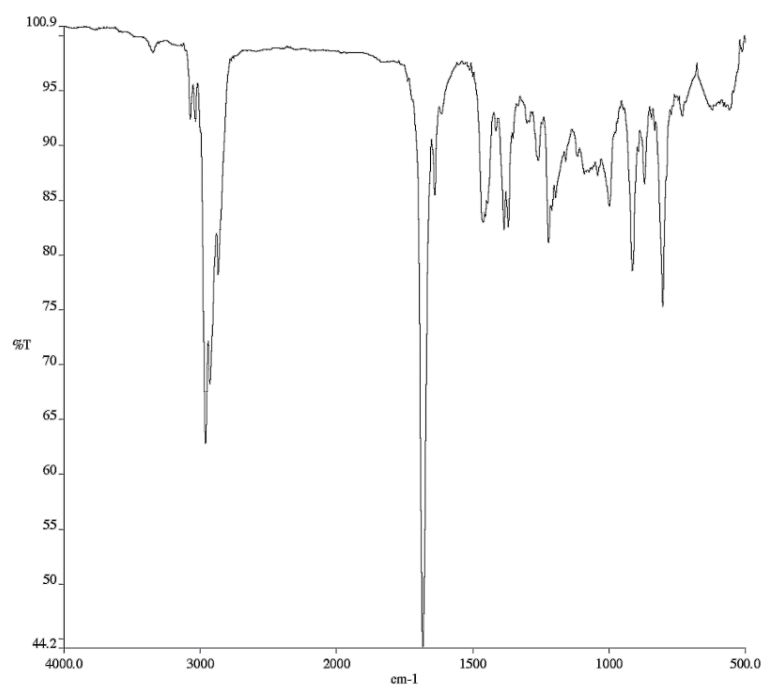


Figure A6.23 Infrared spectrum (Thin Film, NaCl) of compound **214**.

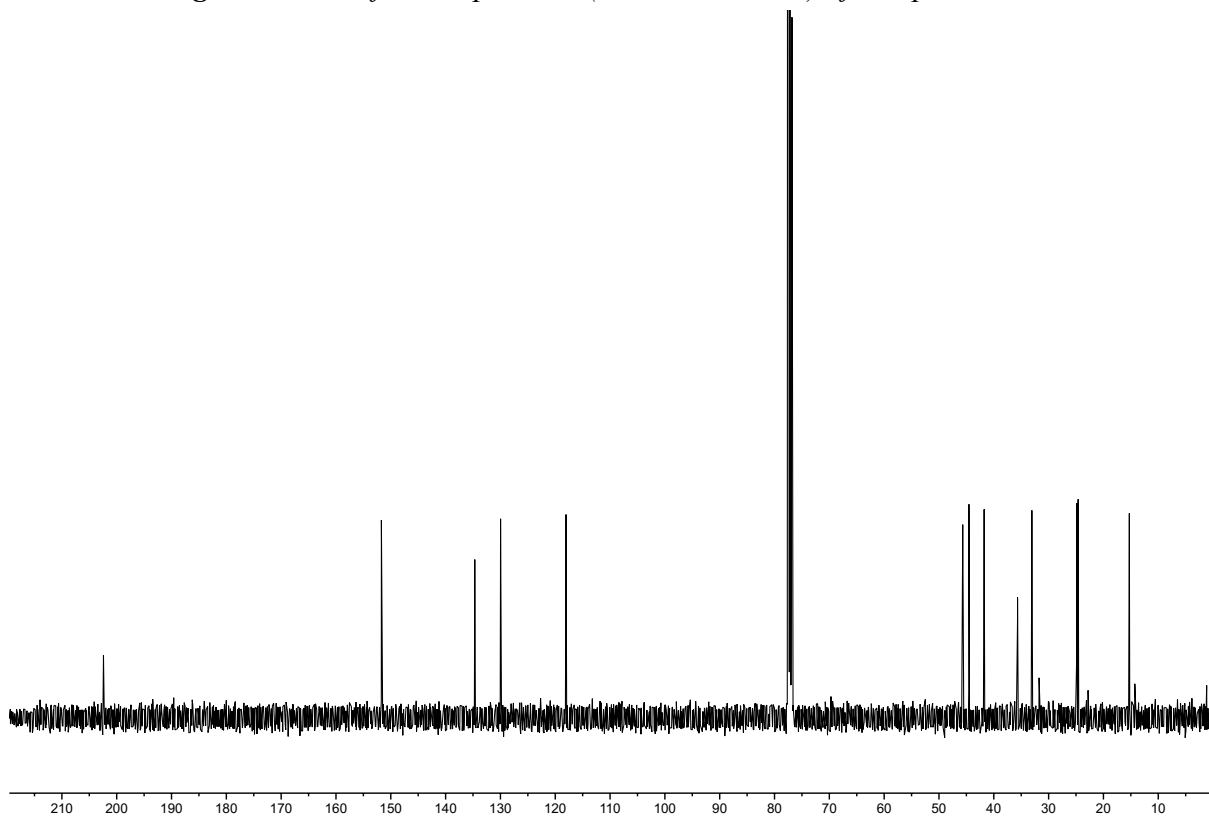


Figure A6.24 ¹³C NMR (100 MHz, CDCl₃) of compound **214**.

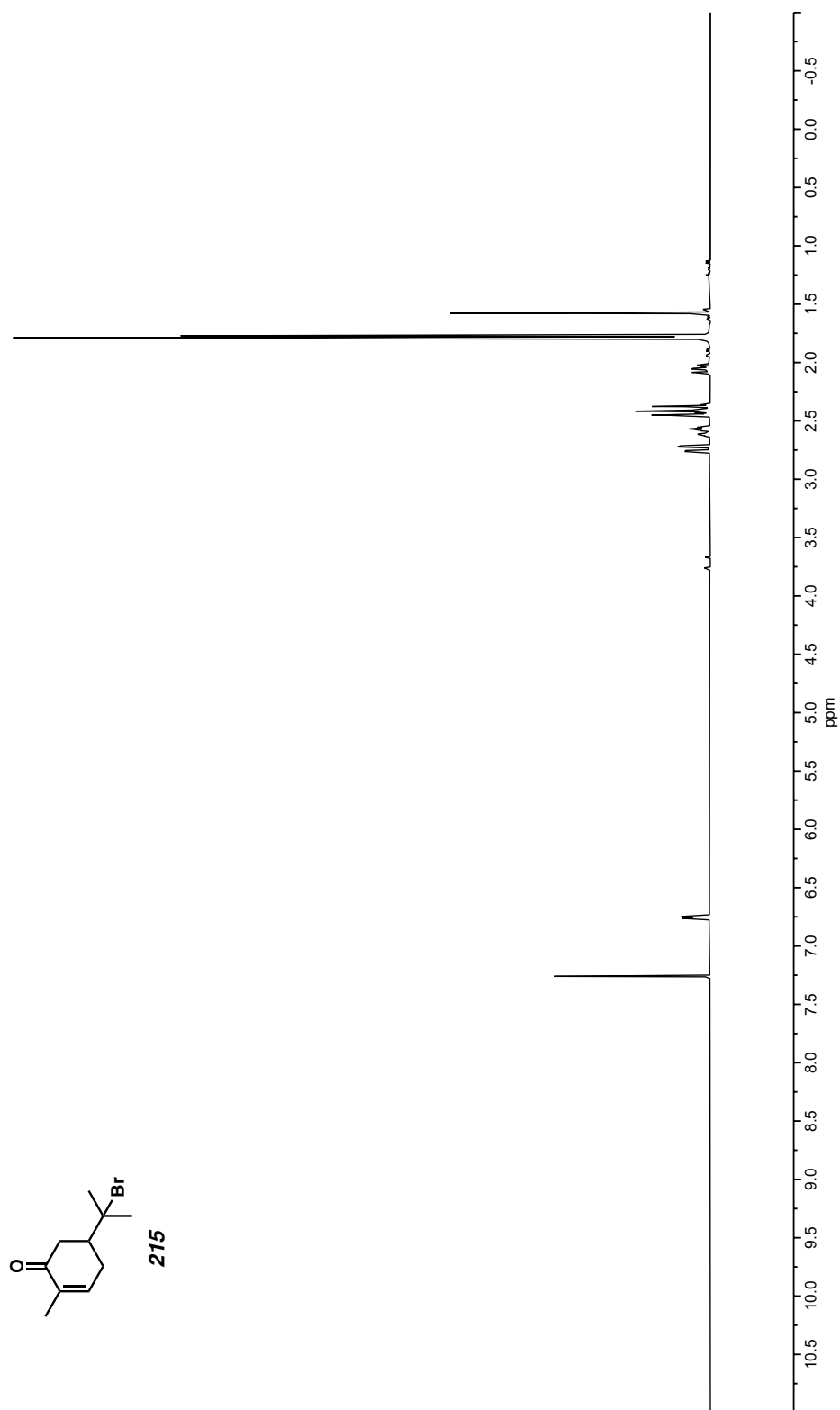


Figure A6.25 ^1H NMR (400 MHz, CDCl_3) of compound 215.

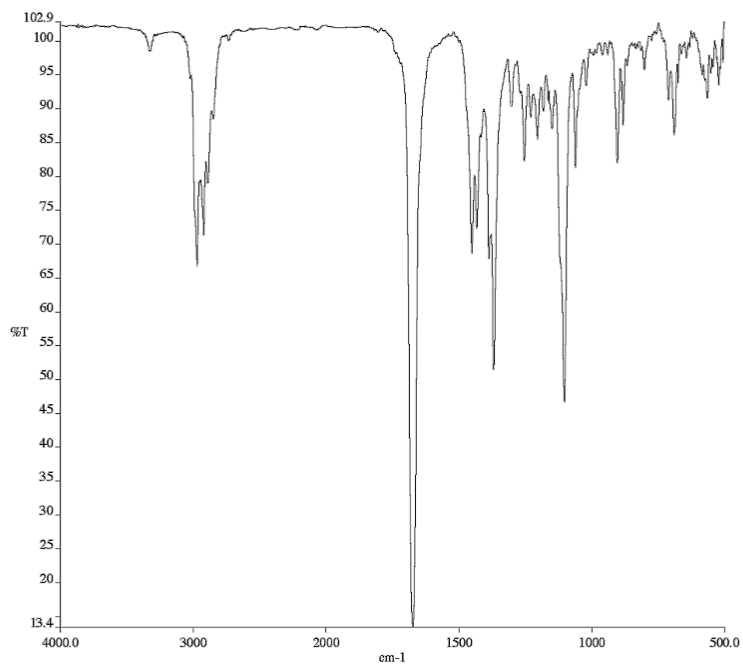


Figure A6.26 Infrared spectrum (Thin Film, NaCl) of compound **215**.

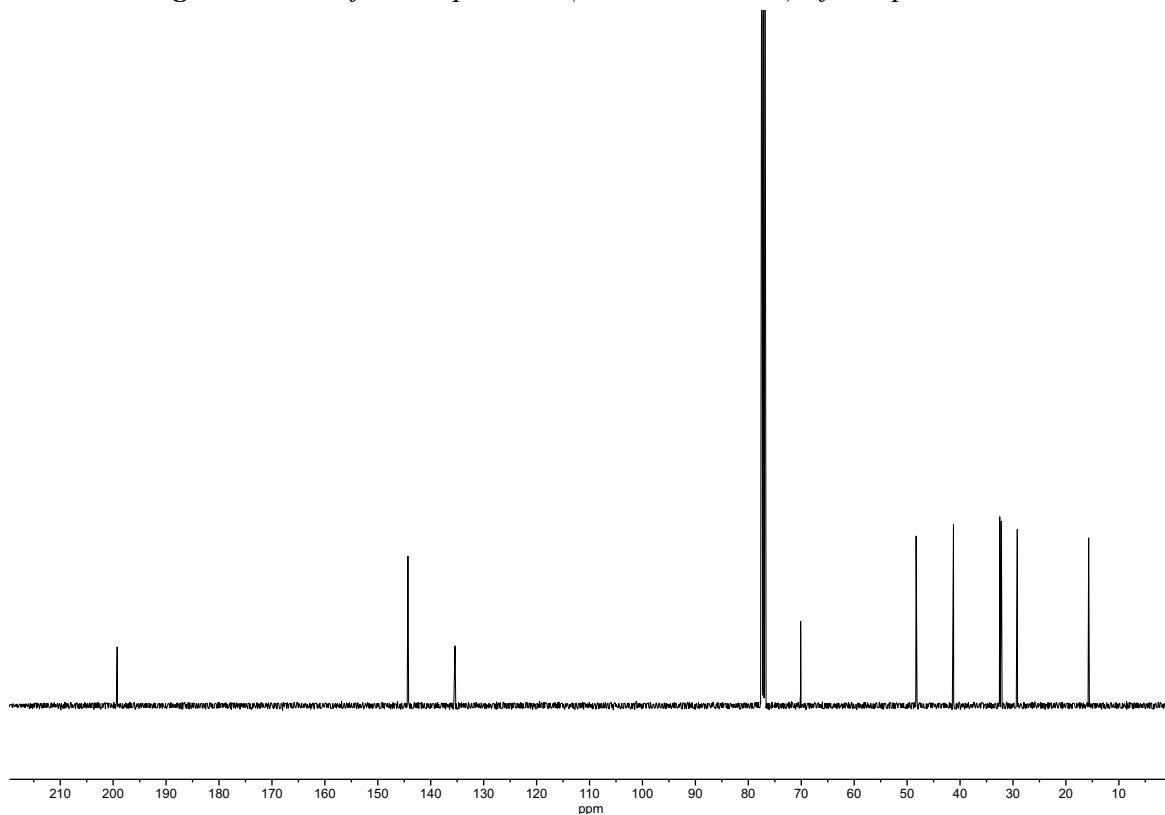


Figure A6.27 ¹³C NMR (100 MHz, CDCl₃) of compound **215**.

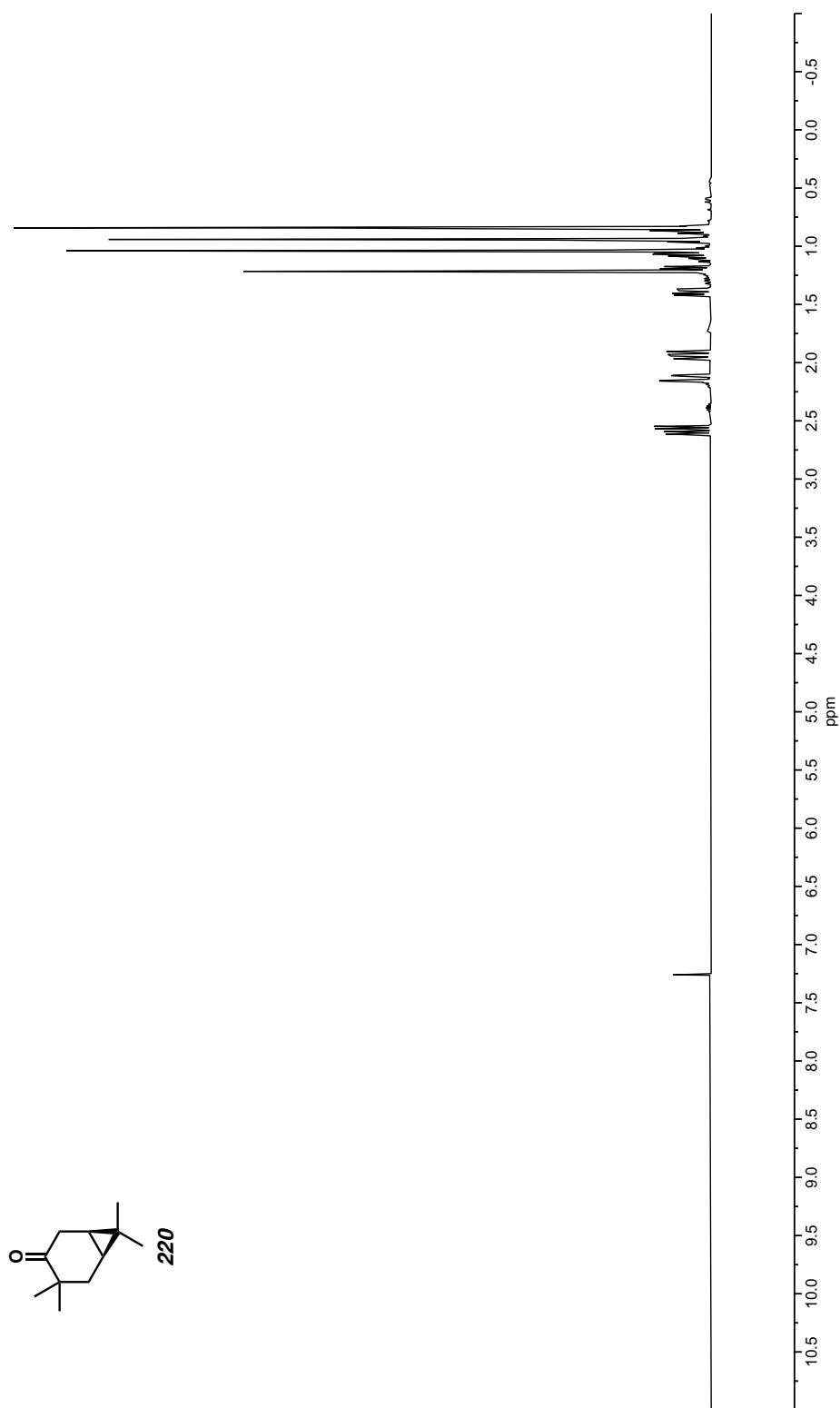


Figure A6.28 ^1H NMR (400 MHz, CDCl_3) of compound 220.

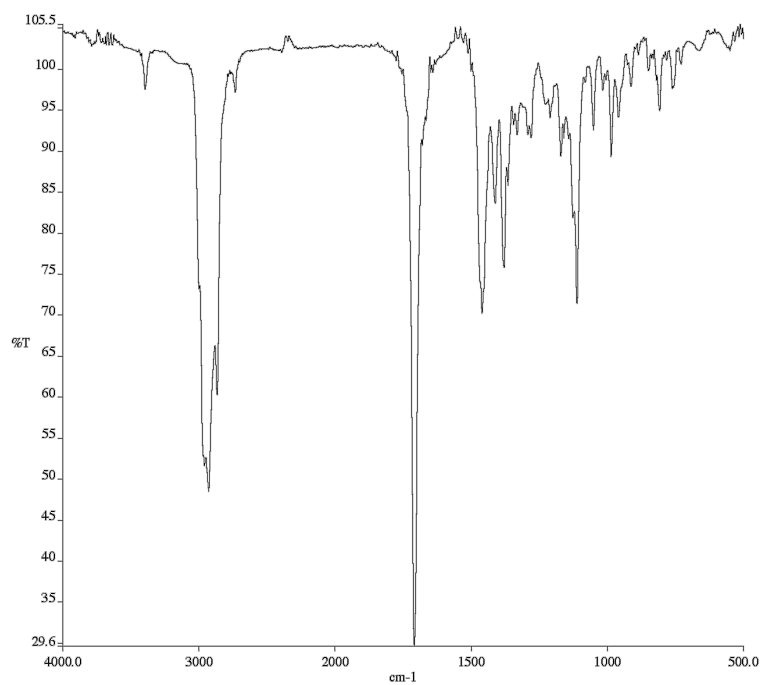


Figure A6.29 Infrared spectrum (Thin Film, NaCl) of compound **220**.

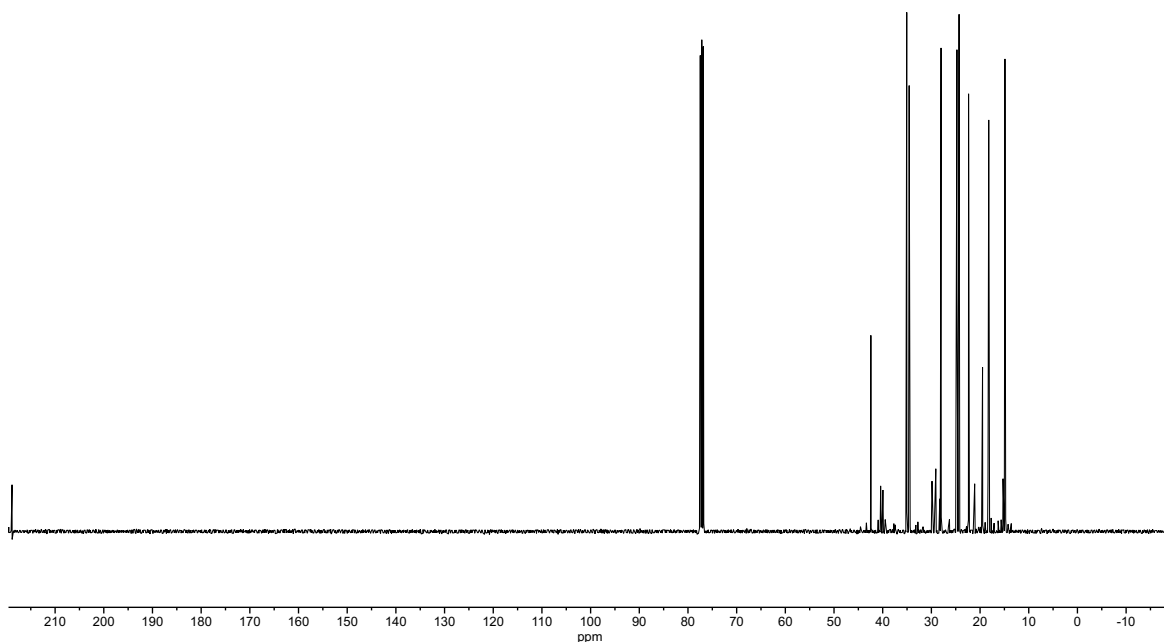


Figure A6.30 ¹³C NMR (100 MHz, CDCl₃) of compound **220**.

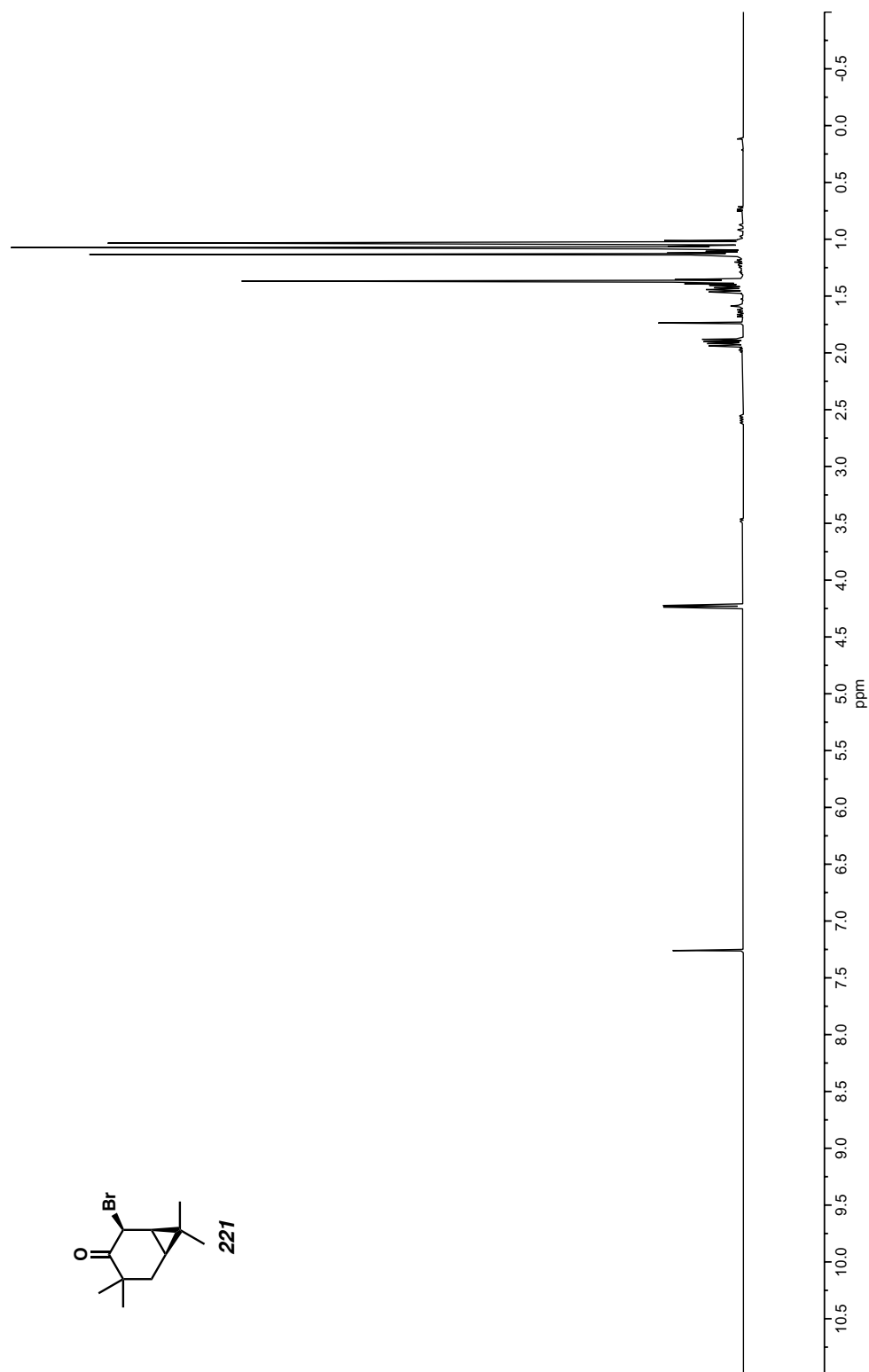


Figure A6.31 ¹H NMR (400 MHz, CDCl₃) of compound 221.

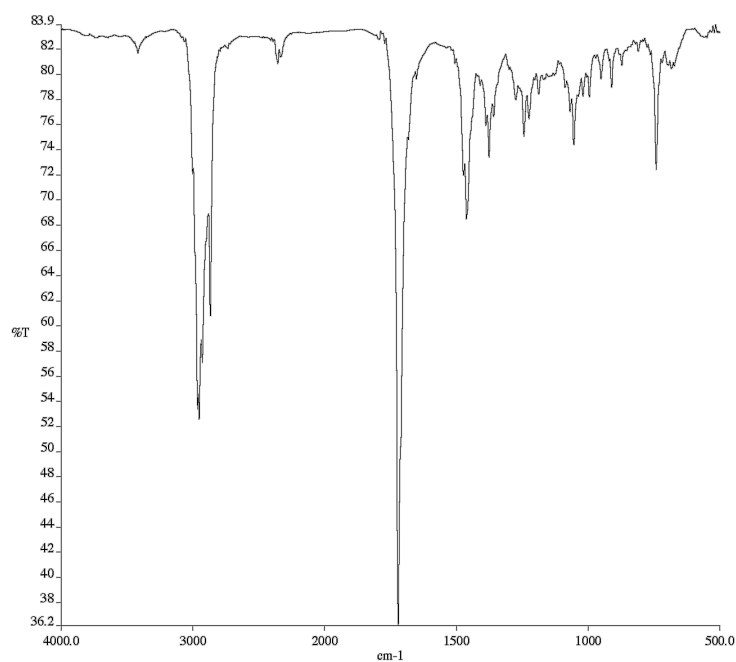


Figure A6.32 Infrared spectrum (Thin Film, NaCl) of compound **221**.

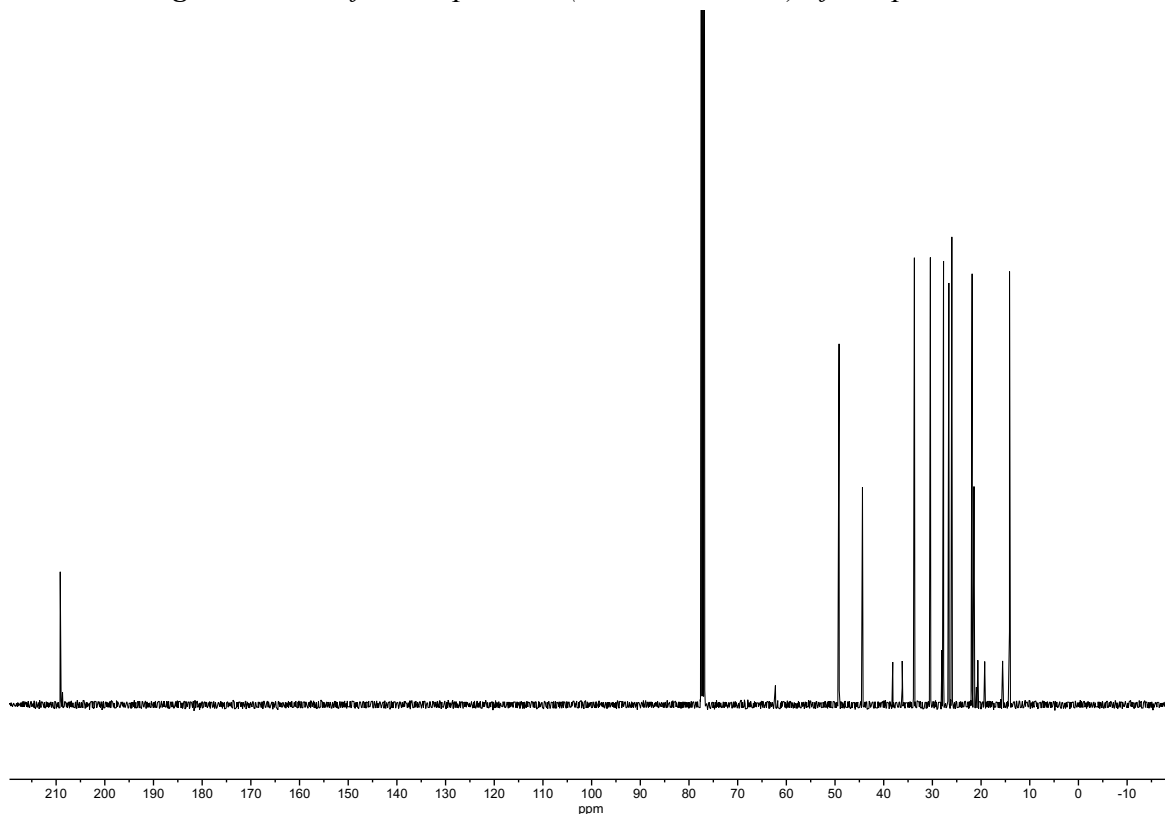


Figure A6.33 ¹³C NMR (100 MHz, CDCl₃) of compound **221**.

CHAPTER 4

On the Unexpected Formation of [2.2.1]- and [2.1.1]Homotriblattanes[†]

4.1 INTRODUCTION

Polycyclic caged structures have interested chemists since the advent of organic chemistry. Several such systems have played a crucial role in elucidating phenomena like fluxionality,^{1,2} nonclassical carbocations,^{3,4} and the reactivity of strained, conformationally restricted systems.⁵ More recently, polycyclic caged compounds have attracted interest in medicinal chemistry with many derivatives finding themselves utilized as bioisosteres or alternate scaffolds for drug molecules.^{6,7,8,9}

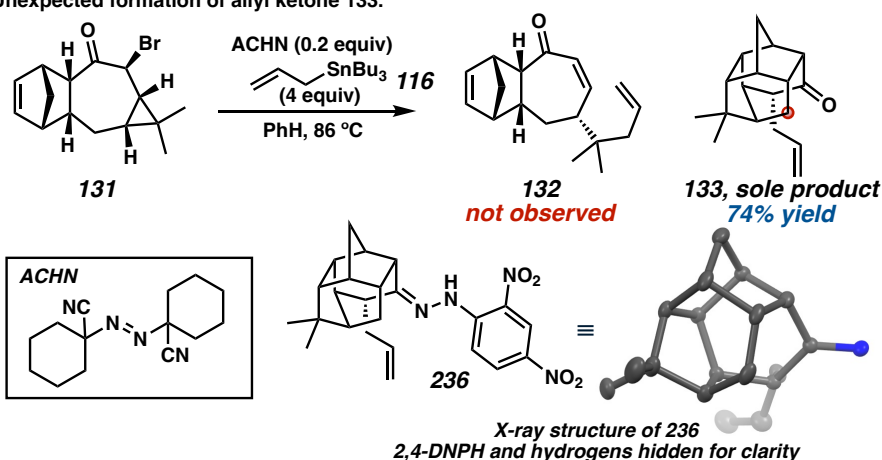
In our investigations toward a polycyclic polyprenylated acylphloroglucinol (PPAP) natural product, we sought to generate allyl cycloheptenone **132** (Scheme 4.1.1A) from a protected bromocycloheptenone (**131**). We previously developed a radical cyclopropane fragmentation/allylation using allyltributylstannane that we believed could be applied to this system.¹⁰ Surprisingly, upon treatment of **131** with a radical initiator (ACHN) and allyl tributylstannane (**116**), **132** was not observed, and instead caged compound **133** was isolated in excellent yield (confirmed via X-ray structure of compound **236**).¹¹ Cage **133** is a homotriblattane featuring an additional carbon (red) compared to the previously known [2.1.1]triblattane (**239**, Scheme 4.1.1B).¹² To our knowledge, this represents the first

[†]This research was conducted in collaboration with Hanh T. Nguyen and Christopher D. Vanderwal. Portions of this chapter have been reproduced with permission from Samkian, A. E.; Nguyen, H. T.; Vanderwal, C. D.; Stoltz, B. M. *Tetrahedron Lett.* **2025**, *164*, 155591. © 2025 Elsevier.

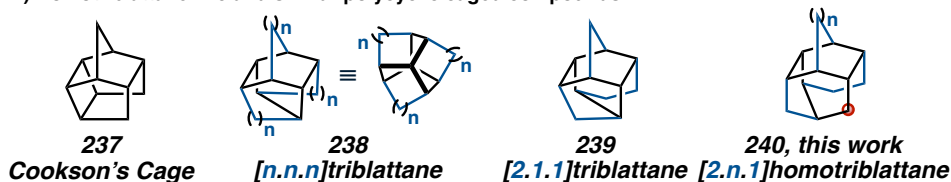
isolation of a homotriblattane (**240**), a framework that expands on the chemical space of the known triblattanes (**238**), which are defined as [2.2.2]-bicycles with three helically arranged carbon bridges (in blue). Given that derivatives of Cookson's cage (**237**) have been shown to exhibit notable neuroprotective bioactivity,^{13,14} we were intrigued by the similarity of cage **133** and elected to synthesize several derivatives.

Scheme 4.1.1. Unexpected cyclization of bromide **131** to cage **133**.

A) Unexpected formation of allyl ketone 133.

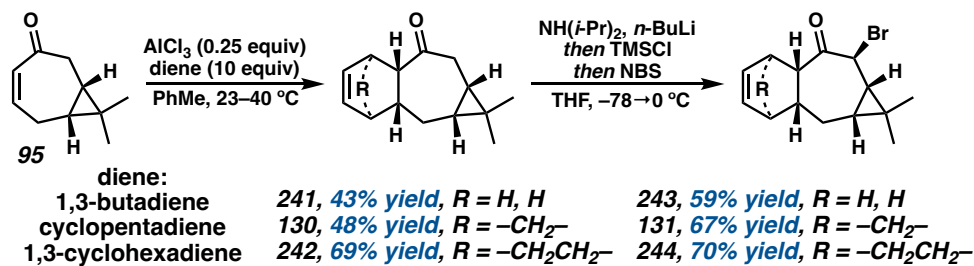


B) Homotriblattane 240 and similar polycyclic caged compounds.



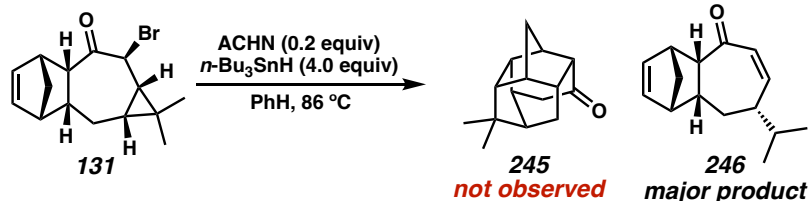
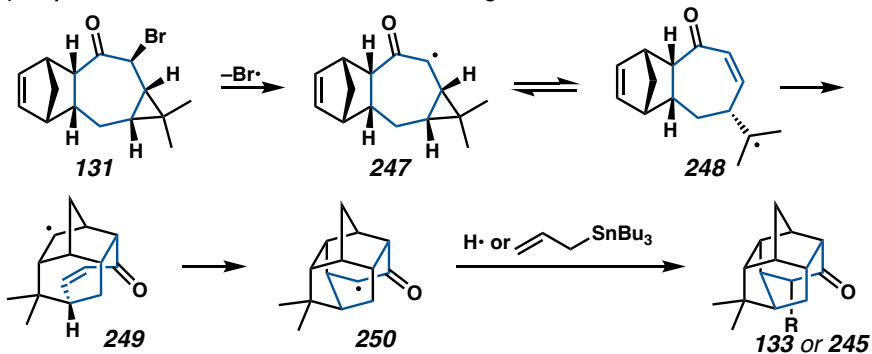
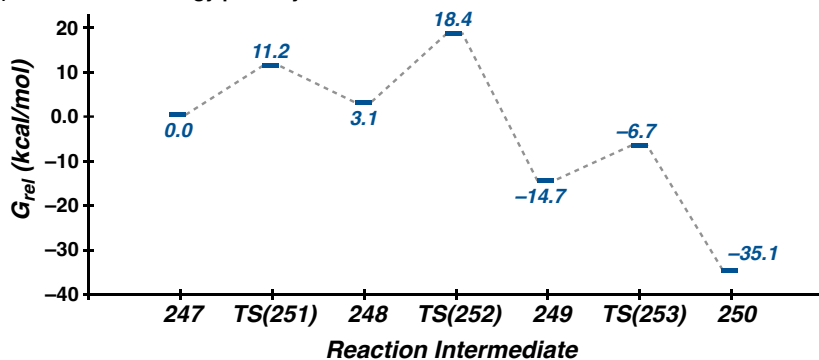
4.2 SYNTHESIS OF THE HOMOTRIBLATTANES

Bromide **131** (Scheme 4.2.1) was prepared via an AlCl_3 -catalyzed Diels–Alder reaction of cyclopentadiene with known enone **95** (prepared from (+)-carene, (**73**)).¹⁵ Bromination of the respective silyl enol ether, generated in situ, provided bromide **131** in good yield. The stereochemical assignment of bromide **131** was accomplished via NOE analysis (see Appendix 7). Two other closely related bromides, **243** and **244**, were synthesized in a similar fashion, utilizing 1,3-butadiene or 1,3-cyclohexadiene as the diene.

Scheme 4.2.1. Synthesis of α -brominated cycloheptanones.

We began by attempting to access *des*-allyl cage **245** (Scheme 4.2.2A) using a hydrogen atom donor. Initial radical cyclization experiments with *n*-Bu₃SnH did not deliver the desired cage, instead providing enone **246**. To form the desired cage **245**, we hypothesized that bromine abstraction leads to α -keto radical **247** (Scheme 4.2.2B) which undergoes cyclopropyl fragmentation to afford tertiary radical **248**. Addition of this radical into the proximal olefin affords secondary radical **249**, which can cyclize with the enone to generate the observed polycyclic ring system (**250**), followed by radical termination through either H• abstraction or trapping with an allyl group.

Given the unexpected formation of cage **133** and the competing pathway leading to enone **246**, we proceeded to investigate this sequence via DFT analysis to better understand the radical intermediates involved (Scheme 4.2.2C, see Section 4.4.3 for more details). As we have found in previous studies involving a similar bromocarene system,¹⁰ α -keto radical **247** and 3° radical **248** are close in energy and separated by a shallow barrier, indicating equilibrium behavior. Presumably, the 6-*exo* cyclization of **248** is slow due to the formation of a strained intermediate (**249**), but subsequent 5-*exo* (or 6-*endo*) ring closure to cage **250** is rapid and thermodynamically favored, driven by geometric constraints and an electronically matched Giese addition.

Scheme 4.2.2. Proposed mechanism and minimum free energy pathway to **240**.**A) Attempts to access homotriblattane 245.****B) Proposed mechanism for the formation of the caged ketone.****C) Minimum free energy pathway from 247 toward 250.^a**

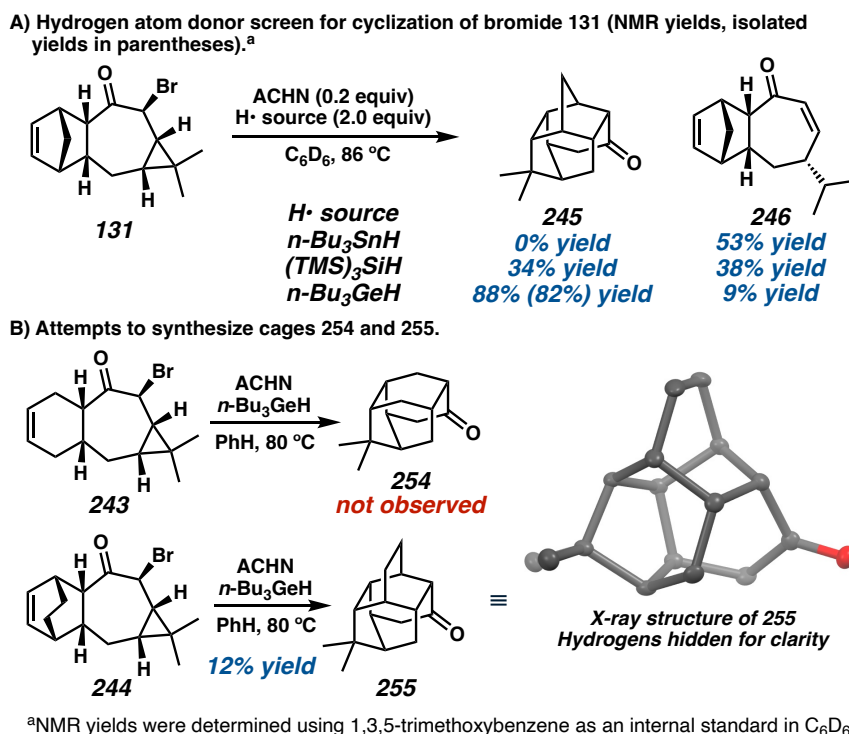
^aRelative Gibbs free energies in kcal/mol at the M06-2X/def2-TZVPP/SMD(Benzene)//M06-2X/def2-TZVP level of theory.

The proposed mechanism is consistent with the observed formation of enone **246**, which arises from premature hydrogen atom transfer (HAT) quenching of the equilibrium mixture of intermediates **247** and **248**. Although this outcome was initially desired with allyltributylstannane, allylated enone **132** was never observed, likely due to the significantly lower rate of radical addition to an allyl group.¹⁶ To mitigate premature HAT, we utilized triethylborane as the initiator at much lower reaction temperatures,¹⁷ as well as n -

Bu₃SnCl/sodium cyanoborohydride mixtures to minimize the concentration of available *n*-Bu₃SnH.¹⁸ Unfortunately, both strategies resulted in enone **246** or complex mixtures.

We next attempted to attenuate the reactivity of the hydrogen atom donor by employing super silane ((Me₃Si)₃SiH) or *n*-Bu₃GeH, which have hydrogen abstraction rates that are approximately 5- and 10-fold slower than *n*-Bu₃SnH, respectively.¹⁹ We anticipated that the decreased rate of H• abstraction would reduce premature quenching of intermediate **248**, allowing the subsequent cyclization to **249** to occur. Gratifyingly, in both cases cage **245** was observed, with *n*-Bu₃GeH providing an excellent 82% isolated yield of **245** with only minimal enone **246** observed (Scheme 4.2.3A).

Scheme 4.2.3. *Synthesis of other homotriblattanes.*



Interestingly, while these conditions with bromide **243** resulted in a complex mixture, bromide **244** provided [2.2.1]homotriblattane **255** (Scheme 4.2.3B), albeit in decreased yield.

It is possible that the rigid nature of the bicycles in bromides **131** and **244** is necessary to facilitate cyclization.

4.3 CONCLUSION

In conclusion, we have developed a facile sequence to access a new class of enantiomerically pure polycyclic cages from readily available chiral pool starting materials. Given the similarity of the trihomoblattane scaffolds to bioactive caged systems such as Cookson's cage (**237**), we believe these structures, and derivatives thereof, warrant further exploration.

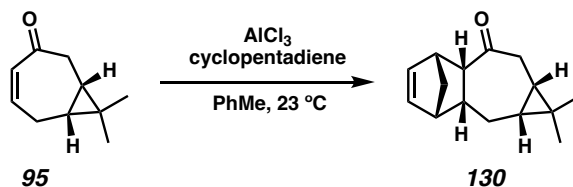
4.4 EXPERIMENTAL SECTION

4.4.1 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.²⁰ Enone **95** was prepared according to a previously reported procedure.¹⁵ All other reagents were purchased from commercial sources and used as received unless otherwise stated. Reaction progress was monitored by thin-layer chromatography (TLC). TLC was performed using E. Merck silica gel 60 F₂₅₄ precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, CAM stain, or KMnO₄ staining. Silicycle SiliaFlash® P60 Academic Silica gel (particle size 40–63 µm) was used for flash chromatography. Teledyne ISCO CombiFlashRf+, Teledyne ISCO CombiFlashRf+ Lumen™, or Teledyne ISCO CombiFlashRf NEXTGEN+ systems were used for automated flash chromatography using Luknova SuperSep™ silica columns. ¹H NMR spectra were recorded on Varian Inova 600 MHz and Bruker 400 MHz spectrometers and are reported relative to residual non-deuterated solvent

CHCl_3 (δ 7.26 ppm). ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometers (100 MHz) and are reported relative to residual non-deuterated solvent CDCl_3 (δ 77.16 ppm). Data for ^1H NMR 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, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). Diastereomeric ratios were calculated based on ratios of integrals from crude ^1H NMR spectra. Some spectra contain minor solvent impurities of water, ethyl acetate, dichloromethane, diethyl ether, acetone, grease, and/or silicone grease, which do not impact product assignments. IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-T2000GC AccuTOFTM GC-Alpha High Resolution Mass Spectrometer in field ionization (FI+) or field desorption (FD+) mode, or an Agilent 6230 Series TOF with and Agilent Jet Stream ion source in electrospray ionization (ESI+).

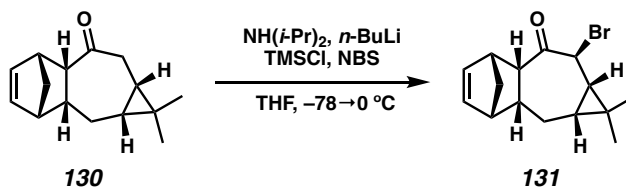
4.4.2 EXPERIMENTAL PROCEDURES



(1*aR*,2*aR*,3*S*,6*R*,6*aS*,8*aS*)-1,1-dimethyl-1*a*,2,2*a*,3,6,6*a*,8,8*a*-octahydro-3,6-methanobenzo[*a*]cyclopropa[*d*][7]annulen-7(1*H*)-one 130.

A 100 mL flask under N₂ was charged with enone **95** (450 mg, 3.0 mmol, 1.0 equiv) and PhMe (12 mL). With good stirring, a suspension of anhydrous AlCl₃ (100 mg, 0.75 mmol, 0.25 equiv) in PhMe (12 mL) was slowly added at 23 °C, and the orange suspension stirred for 45 min. Freshly cracked cyclopentadiene (1.94 g, 29.4 mmol, 9.8 equiv) in PhMe (6 mL) was then added and the reaction monitored by TLC until the disappearance of enone **95** was observed (1.5 h). The reaction was rapidly poured into 100 mL of ice cold 1% NaHCO₃ solution, and the layers vigorously mixed. The mixture was extracted with Et₂O (2 x 25 mL), and the combined organic extracts washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→100% PhMe/hexanes) to furnish **130** (312 mg, 48% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ = 6.26 (dd, *J* = 6.0, 2.5 Hz, 1H), 5.98 (dd, *J* = 5.7, 3.0 Hz, 1H), 3.17 – 3.11 (m, 2H), 2.74 (s, 1H), 2.70 – 2.59 (m, 2H), 2.11 (dd, *J* = 16.4, 7.3 Hz, 1H), 1.90 (ddd, *J* = 14.2, 5.3, 3.0 Hz, 1H), 1.40 (dt, *J* = 8.3, 1.8 Hz, 1H), 1.30 (d, *J* = 8.3 Hz, 1H), 1.02 (s, 3H), 0.92 – 0.84 (m, 4H), 0.66 – 0.51 (m, 2H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 213.6, 137.6, 133.2, 56.0, 48.7, 47.6, 47.1, 43.4, 41.2, 28.6, 27.5, 27.3, 19.6, 18.5, 15.3; IR (Neat Film, NaCl) 2927, 2863, 1688, 1454, 1124,

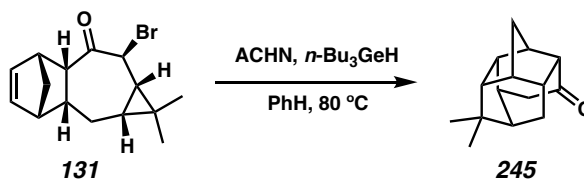
711 cm^{-1} ; HRMS (ESI⁺): m/z calc'd for $\text{C}_{15}\text{H}_{21}\text{O}$ $[\text{M}+\text{H}]^+$: 217.1587, found 217.1580; $[\alpha]_{\text{D}}^{22.75} +70.5$ ($c = 0.1$, CHCl_3).



(1a*R*,2a*R*,3*S*,6*R*,6a*S*,8*S*,8a*S*)-8-bromo-1,1-dimethyl-1a,2,2a,3,6,6a,8,8a-octahydro-3,6-methanobenzo[*a*]cyclopropa[*d*][7]annulen-7(1*H*)-one 131.

To a solution of diisopropylamine (112 mg, 1.11 mmol, 1.2 equiv) in THF (2 mL) at -78°C , *n*-BuLi (2.5M, 0.39 mL, 0.97 mmol, 1.05 equiv) was added dropwise and the solution stirred at this temperature for 20 min. A solution of ketone **130** (200 mg, 0.925 mmol, 1.0 equiv) in THF (1.5 mL) was added dropwise over 10 minutes and the resulting solution stirred for 1.5 h. Trimethylsilyl chloride (151 mg, 1.39 mmol, 1.5 equiv) was added dropwise and the reaction was warmed to 0°C in an ice bath and stirred for 1 h. Solid *N*-bromosuccinimide (248 mg, 1.39 mmol, 1.5 equiv) was added in one portion and the reaction was stirred at 0°C for 30 min in the dark. The reaction was quenched with sat. aq. NaHCO_3 (5 mL) and extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with water (2 x 5 mL) and brine (10 mL), then dried of Na_2SO_4 and concentrated under reduced pressure. The residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→5% EtOAc/hexanes) to furnish **131** (272 mg, 67% yield) as a colorless oil. Frozen solutions of **131** in PhH could be stored at -15°C for months without degradation. However, **131** is sensitive to light and will discolor in its presence. ^1H NMR (400 MHz, CDCl_3) δ = 6.20 (dd, J = 5.7, 2.8 Hz, 1H), 6.15 (dd, J = 5.8,

2.9 Hz, 1H), 4.06 (d, $J = 9.5$ Hz, 1H), 3.42 (dd, $J = 9.5, 3.6$ Hz, 1H), 3.28 – 3.22 (m, 1H), 2.84 (tp, $J = 3.0, 1.5$ Hz, 1H), 2.66 (ddt, $J = 13.2, 9.5, 3.9$ Hz, 1H), 2.08 – 1.98 (m, 1H), 1.47 (dt, $J = 8.4, 1.9$ Hz, 1H), 1.40 (dt, $J = 8.4, 1.5$ Hz, 1H), 1.09 (s, 3H), 1.08 – 1.01 (m, 4H), 0.97 (t, $J = 9.2$ Hz, 1H), 0.73 (ddd, $J = 14.6, 13.2, 11.9$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) $\delta = 204.3, 136.2, 135.7, 56.6, 53.0, 49.5, 49.5, 48.0, 44.0, 29.3, 28.7, 28.1, 27.6, 22.1, 14.3$; IR (Neat Film, NaCl) 2924, 1703, 1456, 1254, 1137, 743 cm^{-1} ; HRMS (ESI⁺): m/z calc'd for $\text{C}_{15}\text{H}_{20}\text{OBr}$ $[\text{M}+\text{H}]^+$: 295.0692, found 295.0683; $[\alpha]_{\text{D}}^{22.95} +92.7$ ($c = 0.2, \text{CHCl}_3$).

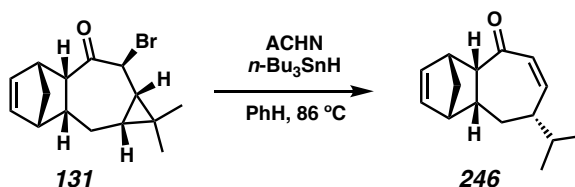


3,3-dimethyldecahydro-6*H*-2,7,4-(epiethane[1,1,2]triy)cyclopenta[*cd*]inden-6-one

245.

In a glovebox, a solution of bromide **131** (5 mg, 17.0 μmol , 1.0 equiv) in PhH (0.5 mL) was added to 1,1'-azobis(cyclohexanecarbonitrile) (0.8 mg, 3.4 μmol , 0.2 equiv) in a 1-dram vial with a stir bar. $n\text{-Bu}_3\text{GeH}$ (8.3 mg, 34.0 μmol , 2.0 equiv) was added, and the vial was carefully sealed with a Teflon lined cap. The vial was taken out of the glovebox and heated to 80 $^{\circ}\text{C}$ for 24 h with stirring. After cooling to 23 $^{\circ}\text{C}$, the solution was concentrated under reduced pressure and the residue was purified by preparative TLC (25% Et_2O /hexanes) to furnish **245** (3.0 mg, 82% yield) as a waxy solid. ^1H NMR (400 MHz, CDCl_3) $\delta = 2.77 - 2.70$ (m, 1H), 2.56 (tdd, $J = 9.7, 6.8, 1.8$ Hz, 1H), 2.47 (dt, $J = 10.7, 2.3$ Hz, 1H), 2.38 – 2.31 (m, 3H), 2.31 – 2.21 (m, 2H), 1.93 – 1.85 (m, 2H), 1.56 – 1.44 (m,

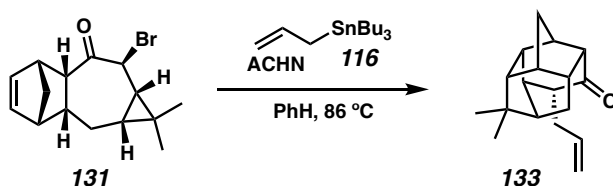
3H), 1.37 – 1.28 (m, 1H), 1.05 (s, 3H), 0.95 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 217.2, 58.6, 58.1, 47.4, 42.6, 40.3, 40.2, 39.1, 38.7, 38.1, 35.5, 33.8, 27.7, 24.5, 22.6; IR (Neat Film, NaCl) 2930, 1711, 1465, 1231 cm^{-1} ; HRMS (ESI⁺): m/z calc'd for $\text{C}_{15}\text{H}_{21}\text{O}$ $[\text{M}+\text{H}]^+$: 217.1587, found 217.1585; $[\alpha]_{\text{D}}^{22.92} +11.3$ ($c = 0.3$, CHCl_3).



(1*S*,4*R*,4*aS*,8*S*,9*aR*)-8-isopropyl-1,4,4*a*,8,9,9*a*-hexahydro-5*H*-1,4-methanobenzo[7]annulen-5-one **246.**

In a glovebox, a solution of bromide **131** (100 mg, 0.169 mmol, 1.0 equiv) in PhH (4.5 mL) was added to 1,1'-azobis(cyclohexanecarbonitrile) (16 mg, 0.068 mmol, 0.2 equiv) in a 2-dram vial with a stir bar. $n\text{-Bu}_3\text{SnH}$ (394 mg, 1.36 mmol, 4.0 equiv) was added, and the vial was carefully sealed with a Teflon lined cap. The vial was taken out of the glovebox and heated to 86 °C for 48 h with stirring. After cooling to 23 °C, the solution was concentrated under reduced pressure and the residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→10% Et_2O /hexanes) to furnish **246** (8.3 mg, 23% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ = 6.35 (dd, $J = 5.9, 2.6$ Hz, 1H), 6.23 (dt, $J = 12.5, 2.1$ Hz, 1H), 6.01 (dd, $J = 5.7, 3.0$ Hz, 1H), 5.94 (dd, $J = 12.5, 3.3$ Hz, 1H), 3.20 – 3.11 (m, 2H), 2.77 (tq, $J = 3.3, 1.4$ Hz, 1H), 2.48 (dddd, $J = 13.7, 9.8, 3.5, 1.7$ Hz, 1H), 2.32 – 2.23 (m, 1H), 1.84 – 1.71 (m, 2H), 1.45 (dt, $J = 8.3, 1.8$ Hz, 1H), 1.33 (dt, $J = 8.0, 1.5$ Hz, 1H), 0.95 – 0.87 (m, 1H), 0.85 (dd, $J = 7.0, 5.3$ Hz, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 204.1, 147.5, 137.9, 132.7, 131.3, 59.9, 48.8, 48.4, 48.3, 45.5, 43.0,

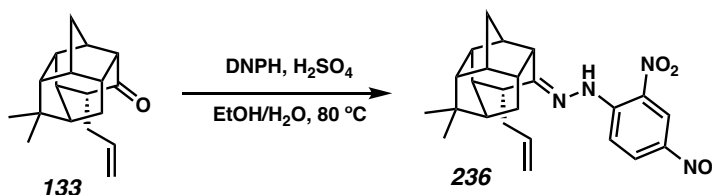
34.0, 33.7, 19.3, 19.1; IR (Neat Film, NaCl) 2957, 1665, 1458, 1335, 728 cm^{-1} ; HRMS (ESI⁺): m/z calc'd for $\text{C}_{15}\text{H}_{21}\text{O}$ $[\text{M}+\text{H}]^+$: 217.1587, found 217.1580; $[\alpha]_{\text{D}}^{22.72} -16.9$ ($c = 0.9$, CHCl_3).



5-allyl-3,3-dimethyldecahydro-6*H*-2,7,4-(epiethane[1,1,2]triyl)cyclopenta[*cd*]inden-6-one **133.**

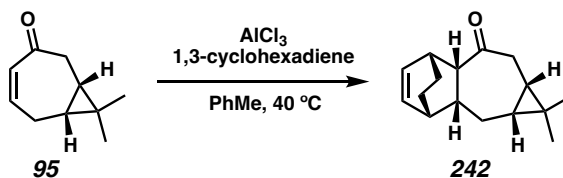
In a glovebox, a solution of bromide **131** (50 mg, 0.169 mmol, 1.0 equiv) in PhH (2.25 mL) was added to 1,1'-azobis(cyclohexanecarbonitrile) (8.2 mg, 0.034 mmol, 0.2 equiv) in a 1-dram vial with a stir bar. Allyltributylstannane **116** (224 mg, 0.676 mmol, 4.0 equiv) was added, and the vial was carefully sealed with a Teflon lined cap. The vial was taken out of the glovebox and heated to 86°C for 48 h with stirring. After cooling to 23°C , the solution was concentrated under reduced pressure and the residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→15% Et_2O /hexanes) to furnish **133** (32 mg, 74% yield) as a colorless oil. The stereochemistry of the allyl group was assigned based on the X-ray crystal structure of compound **236**. However, we acknowledge the possibility of epimerization during the hydrazine condensation step. ^1H NMR (600 MHz, CDCl_3) δ = 5.79 (dddd, J = 16.4, 10.3, 8.4, 5.8 Hz, 1H), 5.09 – 5.05 (m, 1H), 5.04 (t, J = 1.2 Hz, 1H), 2.68 – 2.63 (m, 1H), 2.51 (tdd, J = 9.9, 6.8, 1.9 Hz, 1H), 2.45 (dt, J = 10.6, 2.4 Hz, 1H), 2.39 – 2.34 (m, 2H), 2.29 – 2.19 (m, 3H), 2.15 – 2.08 (m, 1H), 1.91 – 1.86 (m, 2H), 1.55 – 1.49 (m, 2H), 1.46 (dt, J = 9.9, 1.5 Hz, 1H), 1.31 (dd, J = 15.0,

4.2 Hz, 1H), 1.04 (s, 3H), 0.94 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 218.8, 136.4, 116.9, 58.4, 57.9, 48.5, 47.2, 42.8, 40.5, 40.2, 38.8, 38.4, 37.5, 35.9, 34.3, 27.7, 24.6, 22.6; IR (Neat Film, NaCl) 2946, 1701, 1463, 910 cm^{-1} ; HRMS (ESI⁺): m/z calc'd for $\text{C}_{18}\text{H}_{25}\text{O}$ $[\text{M}+\text{H}]^+$: 257.1900, found 257.1896; $[\alpha]_{\text{D}}^{22.74}$ -24.6 (c = 1.1, CHCl_3).



(Z)-1-((5R)-5-allyl-3,3-dimethyldecahydro-6H-2,7,4-(epiethane[1,1,2]triy)cyclopenta[cd]inden-6-ylidene)-2-(2,4-dinitrophenyl)hydrazine 236.

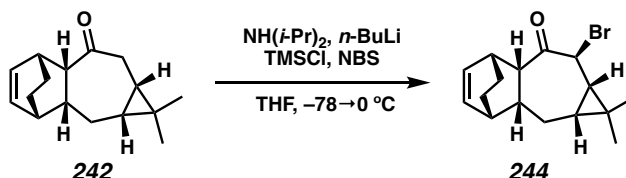
A solution of 2,4-dinitrophenylhydrazine (140 mg) and H_2SO_4 (0.5 mL) was prepared in EtOH/ H_2O (5:1, 6 mL). Ketone **133** (16 mg, 0.06 mmol, 1 equiv) was dissolved in this solution in a 20 mL vial. The reaction was heated to 80 °C for 3 h, cooled to 23 °C, quenched with sat. aq. NaHCO_3 (16 mL) and extracted with CH_2Cl_2 (20 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (5→10% EtOAc/hexanes) to afford **236** (26 mg, 96% yield) as an orange solid. Compound **236** was isolated as a 1.1:1 mixture of inseparable isomers, ^1H , ^{13}C , IR, HRMS, and polarimetry data is provided for this mixture. IR (Neat Film, NaCl) 3315, 2926, 1616, 1590, 1517, 1334, 1133, 1073, 918 cm^{-1} ; HRMS (ESI⁺): m/z calc'd for $\text{C}_{24}\text{H}_{29}\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$: 437.2183, found 437.2202; $[\alpha]_{\text{D}}^{22.68}$ -64.4 (c 0.9, CHCl_3).



(1aR,2aR,3S,6R,6aS,8aS)-1,1-dimethyl-1a,2,2a,3,6,6a,8,8a-octahydro-3,6-ethanobenzo[a]cyclopropa[d][7]annulen-7(1H)-one **242.**

In a glovebox, a 20 mL vial was charged with enone **95** (200 mg, 1.3 mmol, 1.0 equiv) and PhMe (7 mL). With good stirring, a suspension of anhydrous AlCl₃ (89 mg, 0.67 mmol, 0.50 equiv) in PhMe (3 mL) was slowly added at 20 °C, and the suspension was stirred rigorously for 1.5 h. 1,3-cyclohexadiene (1.09 g, 13.6 mmol, 10 equiv), dried over neutral alumina, diluted in PhMe (3 mL), and then added to the reaction vial. The reaction was heated to 40 °C and monitored by TLC until the disappearance of enone **95** was observed (18 h). The reaction was rapidly poured into 50 mL of ice cold 5% NaHCO₃ solution, and the layers vigorously mixed. The mixture was extracted with Et₂O (2 x 25 mL), and the combined organic extracts washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (10→50% PhMe/hexanes) to furnish **242** (210 mg, 69% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ = 6.42 – 6.34 (m, 1H), 6.07 – 5.98 (m, 1H), 3.08 (dd, *J* = 10.5, 2.2 Hz, 1H), 2.83 – 2.67 (m, 2H), 2.49 – 2.31 (m, 3H), 1.70 (ddd, *J* = 14.4, 5.8, 1.9 Hz, 1H), 1.60 – 1.53 (m, 1H), 1.46 – 1.37 (m, 1H), 1.23 (m, *J* = 9.7, 3.0 Hz, 2H), 1.00 (s, 3H), 0.92 (ddd, *J* = 11.4, 9.1, 5.8 Hz, 1H), 0.85 (s, 3H), 0.78 – 0.63 (m, 2H); ¹³C {¹H} NMR (101 MHz, CDCl₃) δ = 212.5, 135.1, 129.8, 57.0, 43.2, 42.5, 37.0, 32.4, 29.8, 29.2, 28.5, 26.6, 23.5, 19.5, 17.8, 15.4; IR (Neat Film, NaCl) 2941, 2864, 1698, 1451, 1313, 1127, 680 cm⁻¹; HRMS (ESI⁺):

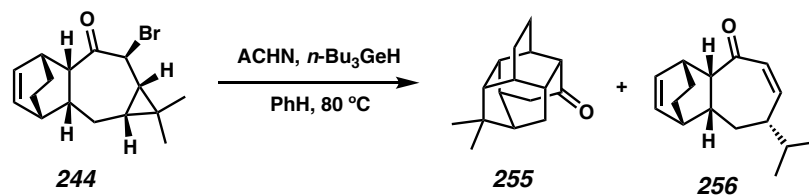
m/z calc'd for $C_{16}H_{23}O$ $[M+H]^+$: 231.1743, found 231.1742; $[\alpha]_D^{23.83}$ -35.2 ($c = 1.0$, $CHCl_3$).



(1*aR*,2*aR*,3*S*,6*R*,6*aS*,8*S*,8*aS*)-8-bromo-1,1-dimethyl-1*a*,2,2*a*,3,6,6*a*,8,8*a*-octahydro-3,6-ethanobenzo[*a*]cyclopropa[*d*][7]annulen-7(1*H*)-one 244.

To a solution of diisopropylamine (79 mg, 0.78 mmol, 1.2 equiv) in THF (3 mL) at -78 °C, titrated $nBuLi$ (0.36 mL, 0.72 mmol, 1.1 equiv) was added dropwise and the solution stirred at this temperature for 30 min. A solution of ketone **242** (150 mg, 0.65 mmol, 1.0 equiv) in THF (1.5 mL) was added dropwise over 10 minutes and the resulting solution stirred for 1.5h. Trimethylsilyl chloride (106 mg, 0.98 mmol, 1.5 equiv) was added dropwise and the reaction was warmed to 0 °C in an ice bath and stirred for 1 h. N -bromosuccinimide (174 mg, 0.98 mmol, 1.5 equiv) in THF (1.5 mL) was added slowly and the reaction was stirred at 0 °C for 30 min in the dark. The reaction was quenched with sat. aq. $NaHCO_3$ (5 mL) and extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with water (2 x 5 mL) and brine (10 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (10→20% PhMe/hexanes) to furnish **244** (140 mg, 70% yield) as a colorless oil. Frozen solutions of in PhH could be stored at -15 °C for several days without degradation. 1H NMR (400 MHz, $CDCl_3$) δ = 6.38 (m, $J = 8.3, 6.2, 0.9$ Hz, 1H), 6.10 (m, $J = 8.3, 6.3, 1.1$ Hz, 1H), 4.26 – 4.20 (m, 1H), 3.67 (dd, $J = 10.4, 2.1$ Hz, 1H), 2.75 (dd, J

= 6.4, 3.5, 1.8 Hz, 1H), 2.45 – 2.34 (m, 2H), 1.77 (dq, J = 15.3, 2.6 Hz, 1H), 1.63 – 1.52 (m, 2H), 1.33 – 1.20 (m, 2H), 1.08 (m, 5H), 0.92 (s, 3H), 0.87 – 0.74 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 205.5, 134.6, 130.9, 53.6, 51.9, 43.9, 37.0, 33.4, 29.7, 29.4, 28.3, 27.9, 25.9, 24.3, 21.8, 15.0; IR (Neat Film, NaCl) 2941, 2866, 1700, 1458, 1311, 1165, 705 cm^{-1} ; HRMS (ESI $^{+}$): m/z calc'd for $\text{C}_{16}\text{H}_{22}\text{BrO}$ $[\text{M}+\text{H}]^{+}$: 309.0849, found 309.0846; $[\alpha]_{\text{D}}^{23.97} +40.0$ (c = 1.0, CHCl_3).



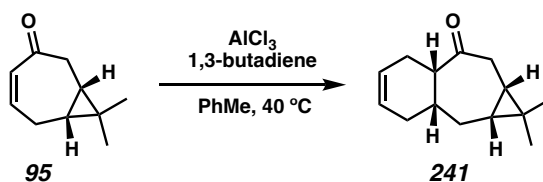
2,2-dimethyldecahydro-3,6,1-(epiethane[1,1,2]triyl)acenaphthylen-7(2a1*H*)-one 255.

In a glovebox, a solution of bromide **244** (30 mg, 97 μmol , 1.0 equiv) in PhH (1.3 mL) was added to 1,1'-azobis(cyclohexanecarbonitrile) (6.3 mg, 26 μmol , 0.27 equiv) in a 1-dram vial with a stir bar. $n\text{-Bu}_3\text{GeH}$ (47 mg, 50 μL , 0.26 mmol, 2.0 equiv) was added, and the vial was carefully sealed with a Teflon lined cap. The vial was taken out of the glovebox and heated to 80 °C for 24 h with stirring. After cooling to 23 °C, the solution was concentrated under reduced pressure and the residue was purified by preparatory TLC (20% Et_2O /hexanes) to furnish cage **255** (2.6 mg, 12% yield) as a colorless crystalline solid. Characterization data for **255**: ^1H NMR (400 MHz, CDCl_3) δ = 2.83 – 2.74 (m, 1H), 2.54 – 2.39 (m, 3H), 2.33 – 2.23 (m, 1H), 1.97 (m, 1H), 1.93 – 1.76 (m, 3H), 1.57 – 1.38 (m, 6H), 1.34 (ddd, J = 15.0, 4.1, 1.8 Hz, 1H), 1.06 (s, 3H), 0.99 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 216.3, 52.1, 48.2, 47.4, 41.5, 39.3, 37.5, 36.5, 31.7, 28.5, 27.9, 27.8, 26.8, 24.3, 22.2, 21.0; IR (Neat Film, NaCl) 2922, 2888, 1710, 1466, 1403, 1381, 1196

cm^{-1} ; HRMS (ESI⁺): m/z calc'd for $\text{C}_{16}\text{H}_{23}\text{O}$ $[\text{M}+\text{H}]^+$: 231.1743, found 231.1742; $[\alpha]_{\text{D}}^{23.56}$ -40.3 ($c = 0.05$, CHCl_3).

(1*S*,4*R*,4*aS*,8*S*,9*aR*)-8-isopropyl-1,4,4*a*,8,9,9*a*-hexahydro-5*H*-1,4-ethanobenzo[7]annulen-5-one **256.**

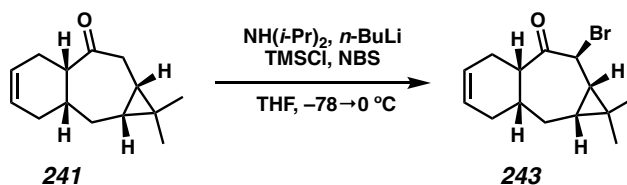
Further purification of the crude residue yielded enone **256** (8.6 mg, 38% yield) as a colorless oil. Characterization data for **256**: ^1H NMR (400 MHz, CDCl_3) $\delta = 6.44 - 6.32$ (m, 1H), 6.17 – 6.07 (m, 2H), 5.94 (dd, $J = 12.3, 3.2$ Hz, 1H), 3.01 – 2.91 (m, 2H), 2.47 – 2.39 (m, 1H), 2.27 (dp, $J = 11.2, 2.9$ Hz, 1H), 2.18 (ddt, $J = 12.2, 10.4, 2.0$ Hz, 1H), 1.76 (dtq, $J = 10.5, 7.0, 3.5$ Hz, 1H), 1.62 – 1.50 (m, 2H), 1.48 – 1.38 (m, 1H), 1.27 (m, $J = 11.8, 9.1, 3.2$ Hz, 2H), 1.13 (ddd, $J = 13.9, 11.9, 10.8$ Hz, 1H), 0.85 (s, 3H), 0.83 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) $\delta = 204.6, 144.7, 134.7, 131.5, 131.1, 60.0, 50.1, 43.2, 38.5, 36.3, 33.8, 31.3, 26.0, 23.6, 19.3, 19.3$; IR (Neat Film, NaCl) 2953, 2931, 2867, 1674, 1461, 1371, 704 cm^{-1} ; HRMS (ESI⁺): m/z calc'd for $\text{C}_{16}\text{H}_{23}\text{O}$ $[\text{M}+\text{H}]^+$: 231.1743, found 231.1742; $[\alpha]_{\text{D}}^{23.35} -11.7$ ($c = 0.5$, CHCl_3).



(1*aR*,2*aS*,6*aS*,8*aS*)-1,1-dimethyl-1*a*,2,2*a*,3,6,6*a*,8,8*a*-octahydrobenzo[*a*]cyclopropa[*d*][7]annulen-7(1*H*)-one **241.**

A 2-dram vial was charged with AlCl_3 (33.3 mg, 0.025 mmol, 0.25 equiv) and PhMe (3.6 mL) under a N_2 atmosphere. A solution of enone **95** (150 mg, 1.0 mmol, 1.0 equiv) in PhMe (3 mL) was added dropwise with good stirring resulting in a cloudy, orange solution

that was stirred for 40 min further. Butadiene (80 wt% in PhMe, 3.38 mL, 10 mmol, 10 equiv) is then added and the reaction was heated to 40 °C and stirred at this temperature for 24 h. The reaction was rapidly poured into 40 mL of ice cold 2.5% NaHCO₃ solution, a sat. aq. solution of Rochelle salt (10 mL) was added, and the layers vigorously mixed. The mixture was extracted with Et₂O (2 x 20 mL), and the combined organic extracts washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→10% EtOAc/hexanes) to furnish **241** (89 mg, 43% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ = 5.72 – 5.65 (m, 1H), 5.65 – 5.58 (m, 1H), 3.53 (td, *J* = 6.2, 4.1 Hz, 1H), 2.59 – 2.51 (m, 1H), 2.34 (dt, *J* = 18.2, 3.9, 1.7 Hz, 1H), 2.24 (dddd, *J* = 10.9, 8.6, 5.1, 1.1 Hz, 1H), 2.18 – 2.02 (m, 3H), 2.02 – 1.94 (m, 1H), 1.66 – 1.56 (m, 1H), 1.09 (s, 3H), 1.03 (s, 3H), 1.00 – 0.77 (m, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 214.6, 125.2, 125.1, 46.9, 37.9, 34.4, 31.2, 28.8, 28.7, 25.1, 25.0, 21.9, 20.4, 15.3; IR (Neat Film, NaCl) 2917, 1703, 1458, 1138, 655 cm⁻¹; HRMS (ESI⁺): *m/z* calc'd for C₁₄H₂₁O [M+H]⁺: 205.1587, found 205.1580; [α]_D^{22.81} +83.3 (*c* = 1.0, CHCl₃).



(1*aR*,2*aS*,6*aS*,8*S*,8*aS*)-8-bromo-1,1-dimethyl-1*a*,2,2*a*,3,6,6*a*,8,8*a*-octahydrobenzo[*a*]cyclopropa[*d*][7]annulen-7(1*H*)-one 243.

To a solution of diisopropylamine (39 mg, 0.38 mmol, 1.2 equiv) in THF (0.7 mL) at –78 °C, *n*BuLi (2.5M, 0.13 mL, 0.34 mmol, 1.05 equiv) was added dropwise and the solution

stirred at this temperature for 20 min. A solution of ketone **241** (69 mg, 0.32 mmol, 1.0 equiv) in THF (0.5 mL) was added dropwise over 10 minutes and the resulting solution stirred for 2 h. Trimethylsilyl chloride (52 mg, 0.48 mmol, 1.5 equiv) was added dropwise and the reaction was warmed to 0 °C in an ice bath and stirred for 1 h. Solid N-bromosuccinimide (85 mg, 0.48 mmol, 1.5 equiv) was added in one portion and the reaction was stirred at 0 °C for 30 min in the dark. The reaction was quenched with 5% aq. NaHCO₃ (2 mL) and extracted with Et₂O (2 x 5 mL). The combined organic extracts were washed with water (2 x 2 mL) and brine (2 mL), then dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→15% EtOAc/hexanes) to furnish **243** (53 mg, 59% yield) as a colorless oil. Frozen solutions of **243** in PhH could be stored at –15 °C for several days without degradation. However, **243** is sensitive to light and will discolor in its presence. ¹H NMR (400 MHz, CDCl₃) δ = 5.71 – 5.58 (m, 2H), 4.34 (d, *J* = 10.5 Hz, 1H), 3.32 (td, *J* = 6.7, 4.4 Hz, 1H), 2.37 – 2.22 (m, 3H), 2.17 (dddd, *J* = 15.7, 6.1, 3.6, 1.4 Hz, 1H), 1.88 (ddd, *J* = 15.0, 5.8, 3.6 Hz, 1H), 1.77 (dddd, *J* = 17.5, 7.0, 4.8, 2.2 Hz, 1H), 1.29 – 1.20 (m, 1H), 1.19 – 1.12 (m, 7H), 1.07 – 0.95 (m, 1H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 204.8, 125.1, 124.3, 51.1, 47.9, 34.8, 32.0, 31.4, 29.5, 28.1, 27.8, 24.9, 22.8, 14.3; IR (Neat Film, NaCl) 2920, 1715, 1456, 1135, 680 cm⁻¹; HRMS (ESI+): *m/z* calc'd for C₁₄H₂₀BrO [M+H]⁺: 283.0692, found 283.0693; [α]_D^{24.00} +54.3 (c = 0.5, CHCl₃).

4.4.3 COMPUTATIONAL DETAILS

All quantum mechanical calculations were carried out with the ORCA program.^{21,22} DFT geometry optimizations and harmonic frequency calculations were carried out in the gas phase with the M06-2X functional²³ and def2-TZVP basis set²⁴ on all atoms. Thermodynamic corrections from harmonic frequency calculations employ the quasi-rigid rotor harmonic oscillator approach to correct for the breakdown of the harmonic oscillator approximation at low vibrational frequencies.²⁵ Stationary points are characterized by the correct number of imaginary vibrational modes (zero for minima and one for saddle points). Intrinsic reaction coordinate (IRC) analysis²⁶ confirms the nature of transition states. Electronic energies are further refined with single point calculations at the M06-2X/def2-TZVPP level of theory employing the SMD implicit solvation model for benzene.²⁷ Final Gibbs free energies were obtained by applying thermodynamic corrections obtained at the optimization level of theory to these refined solvated electronic energies.

The resolution of identity (RI) and Chain-of-Spheres (COS) approximations are employed for efficient evaluation of Coulomb and exchange integrals, respectively.²⁸ The def2/J auxiliary basis²⁹ and very fine grid settings are employed in all calculations (keyword: DefGrid3). Calculations on open-shell systems employ unrestricted Kohn–Sham orbitals (UKS). Spin contamination is generally minor.

4.5 REFERENCES AND NOTES

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APPENDIX 7

Spectra Relevant to Chapter 4:

On the Unexpected Formation of [2.2.1]- and [2.1.1]Homotriblattanes

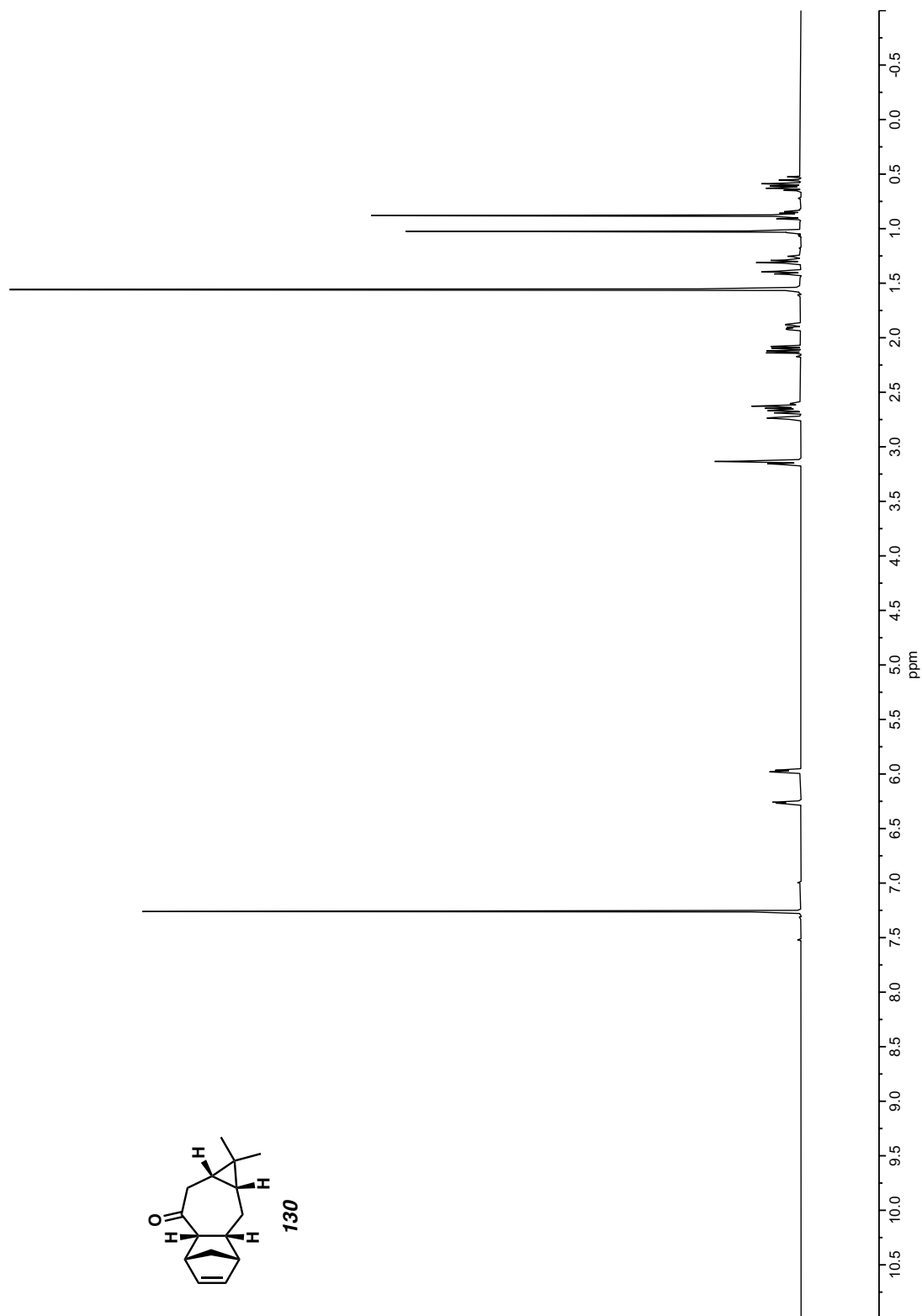


Figure A7.1 ^1H NMR (400 MHz, CDCl_3) of compound **130**.

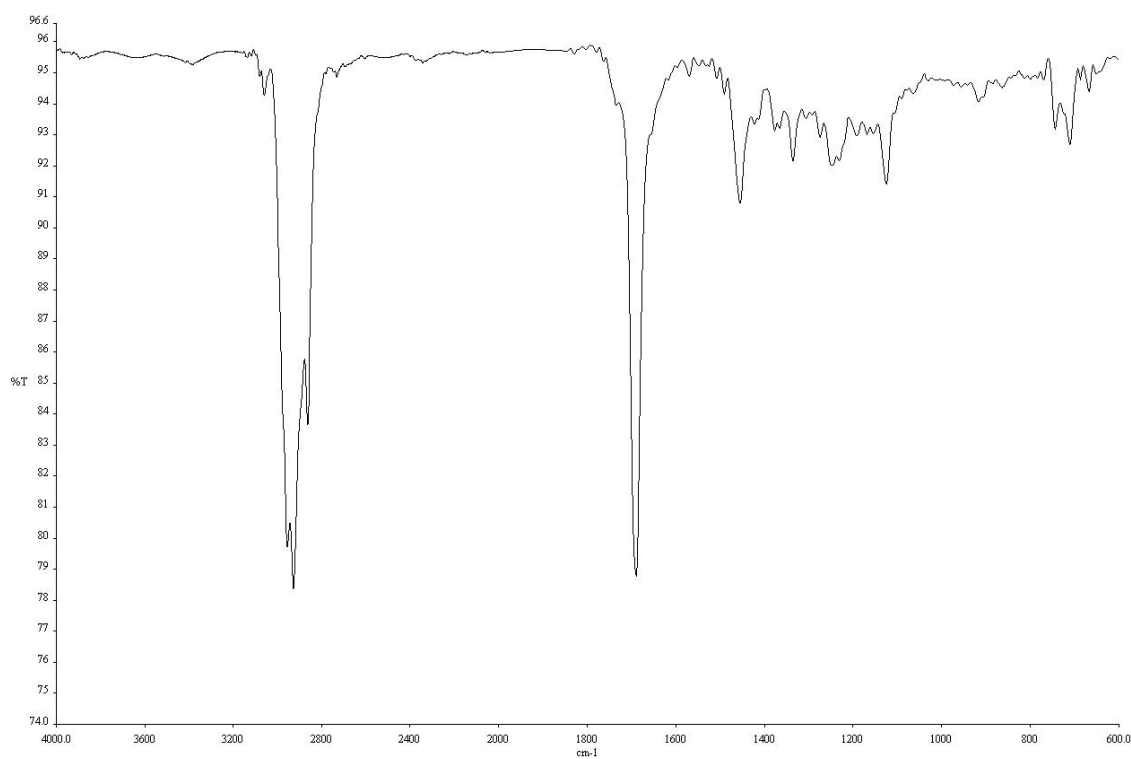


Figure A7.2 Infrared spectrum (Thin Film, NaCl) of compound **130**.

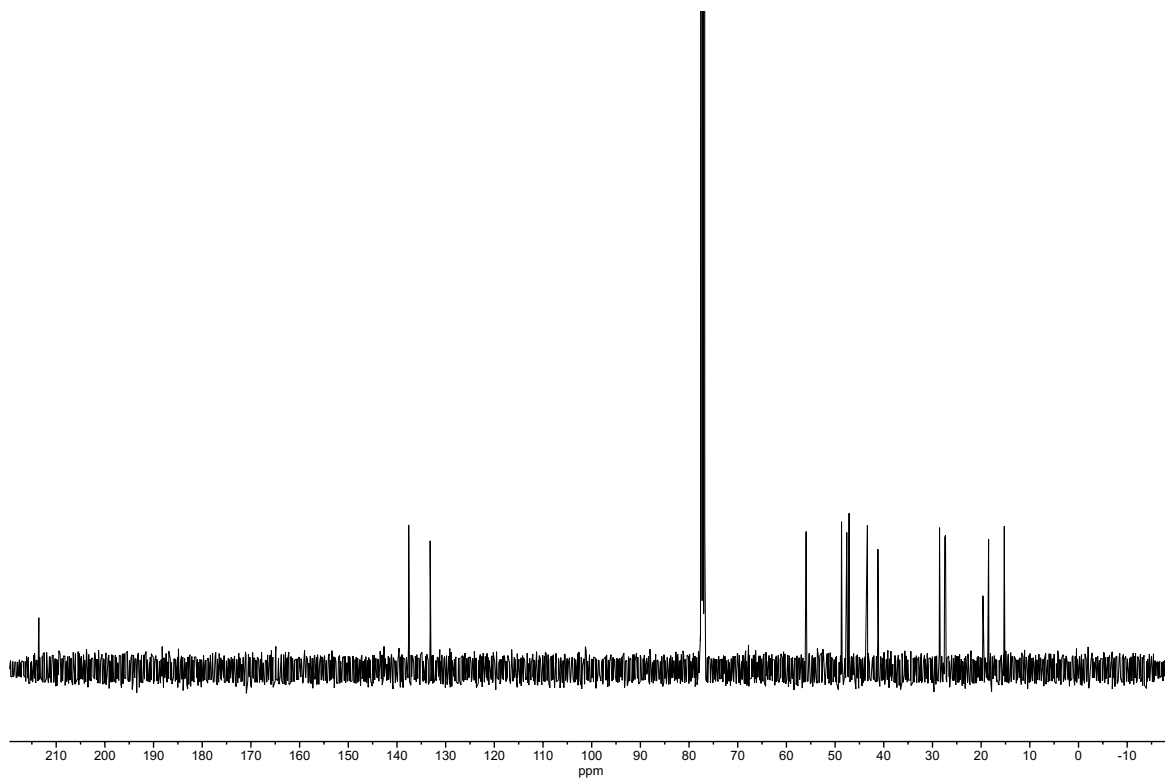


Figure A7.3 ¹³C NMR (100 MHz, CDCl₃) of compound **130**.

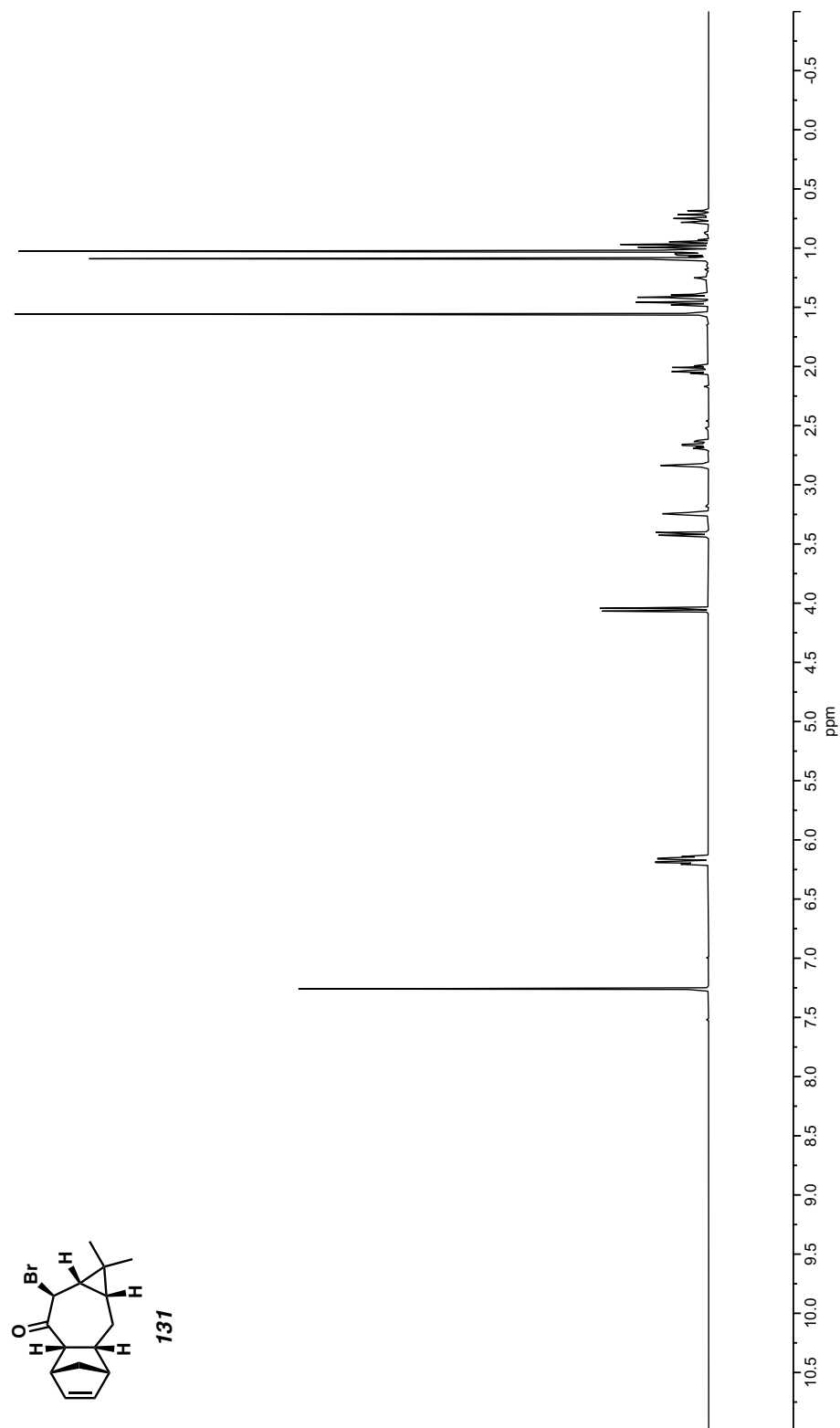


Figure A7.4 ¹H NMR (400 MHz, CDCl₃) of compound 131.

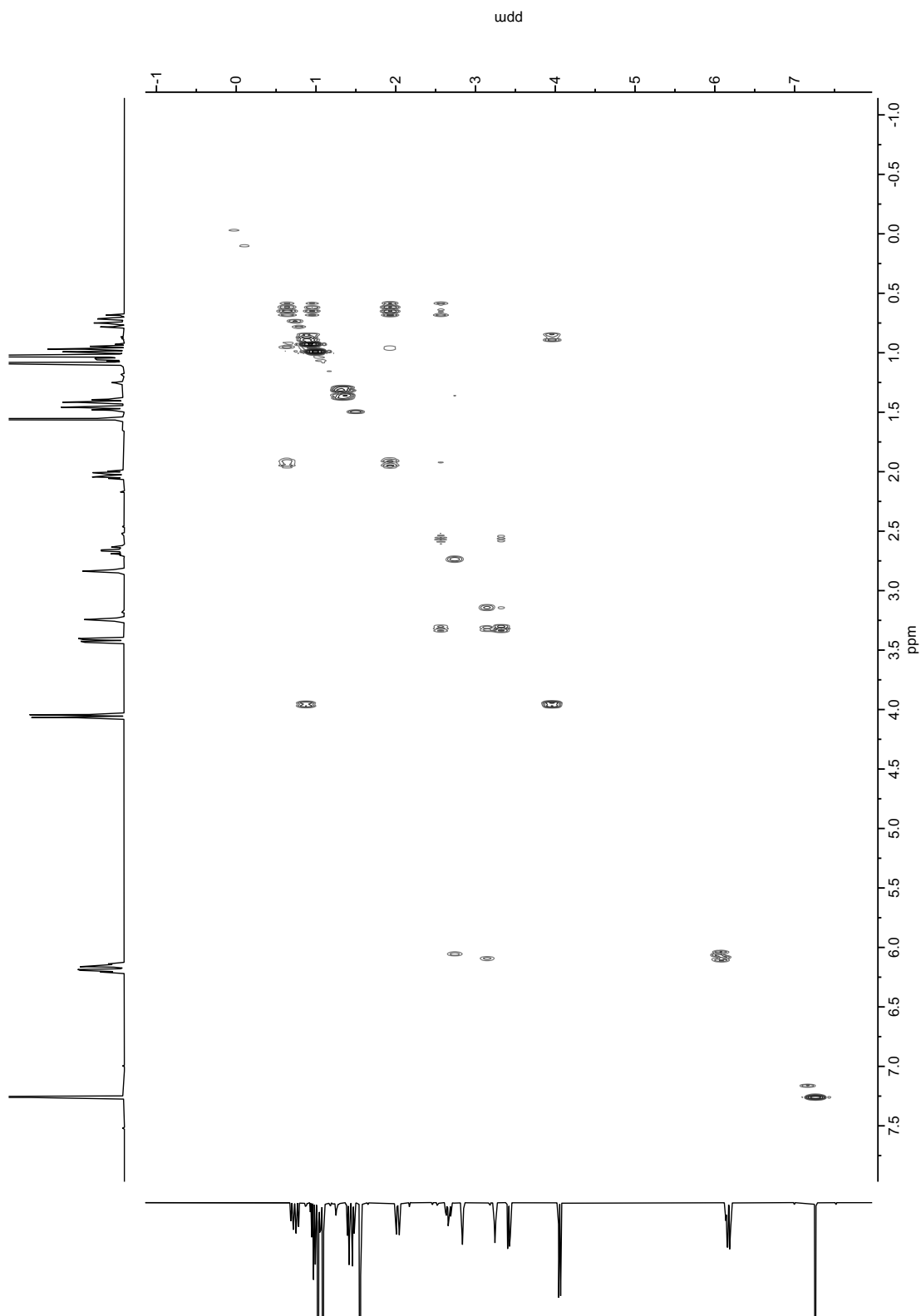


Figure A7.5 COSY NMR (400 MHz, CDCl_3) of compound **131**.

udd

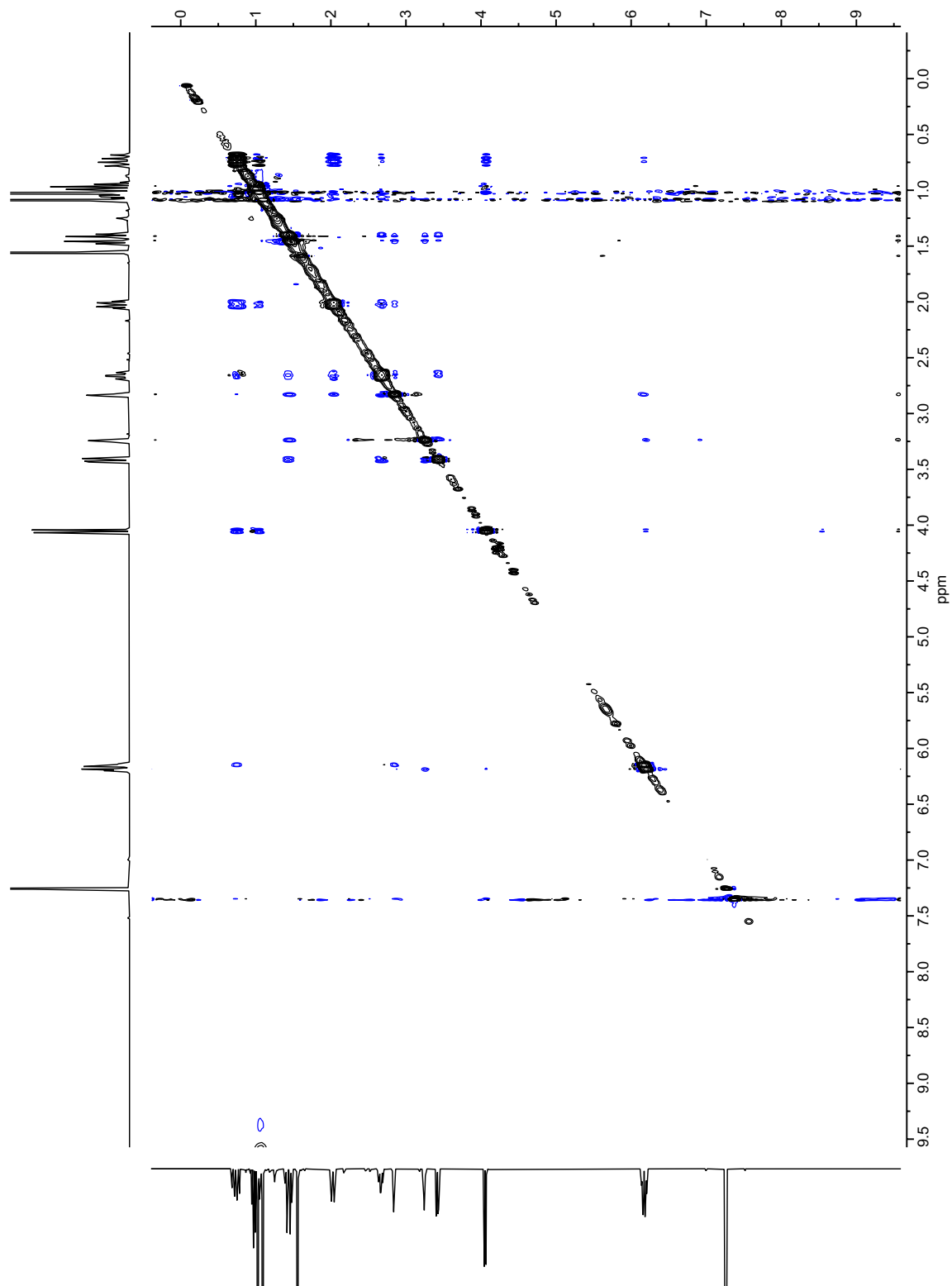


Figure A7.6 NOESY NMR (400 MHz, CDCl₃) of compound **131**.

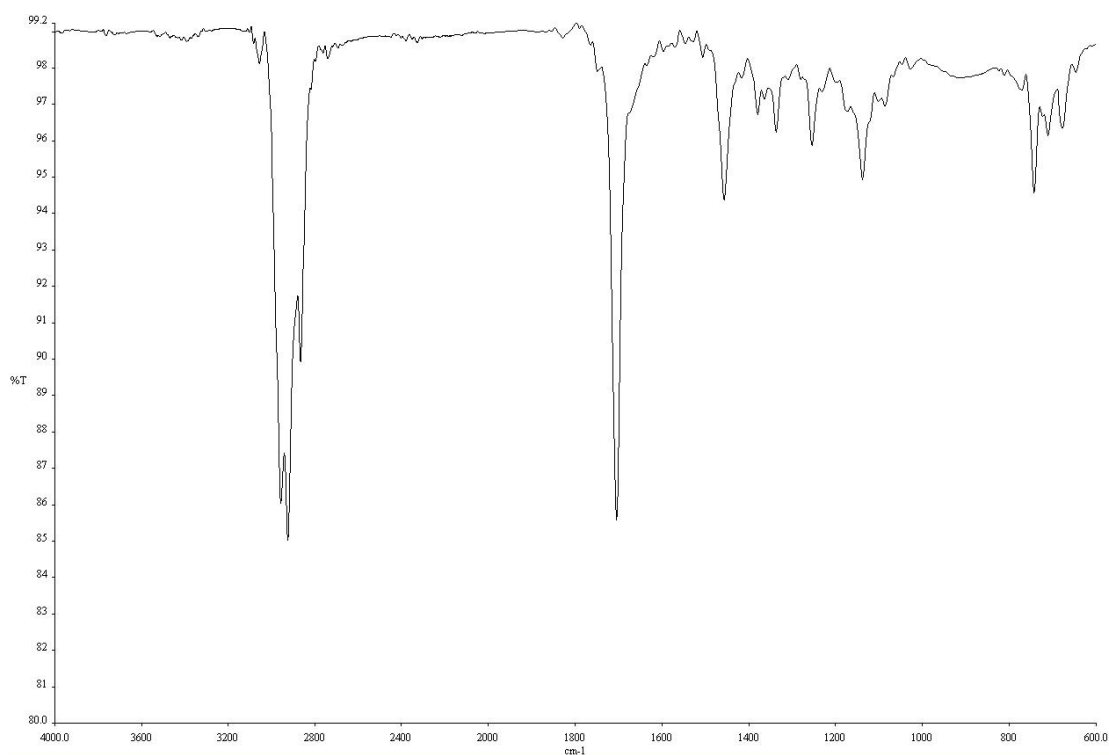


Figure A7.7 Infrared spectrum (Thin Film, NaCl) of compound **131**.

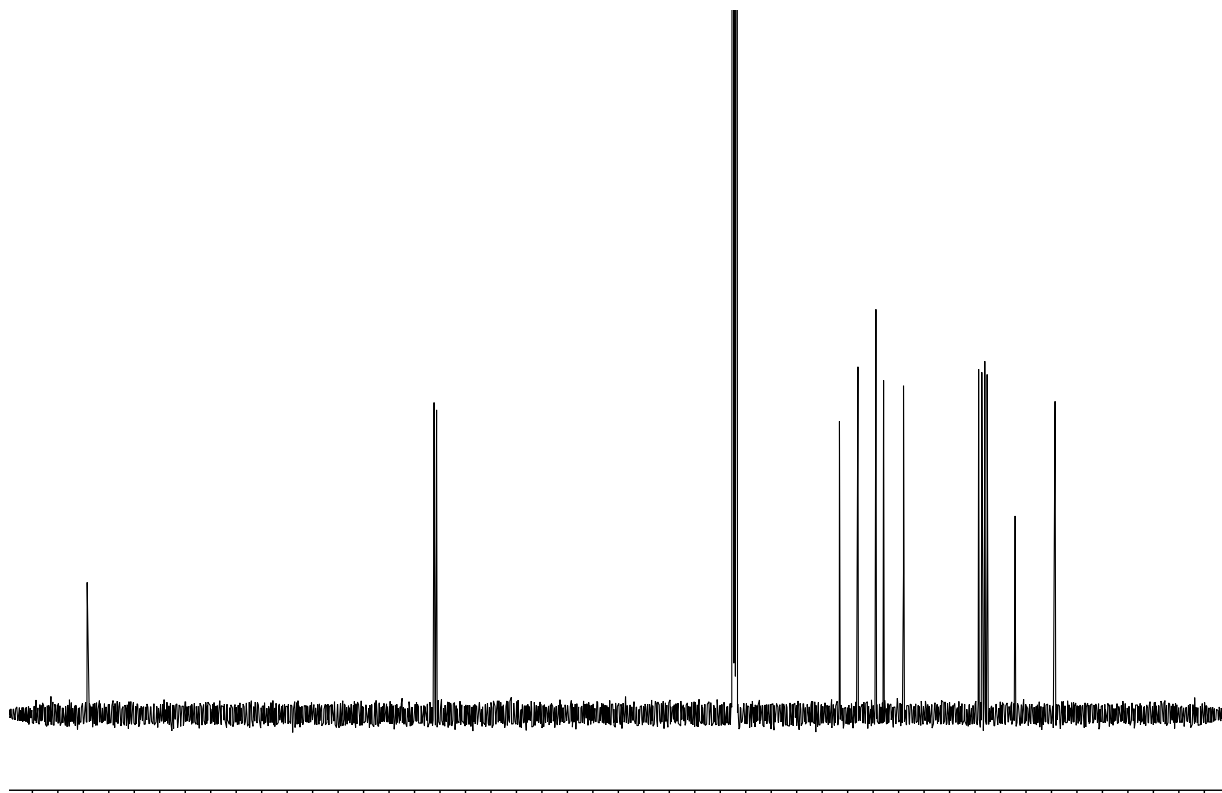


Figure A7.8 ¹³C NMR (100 MHz, CDCl₃) of compound **131**.

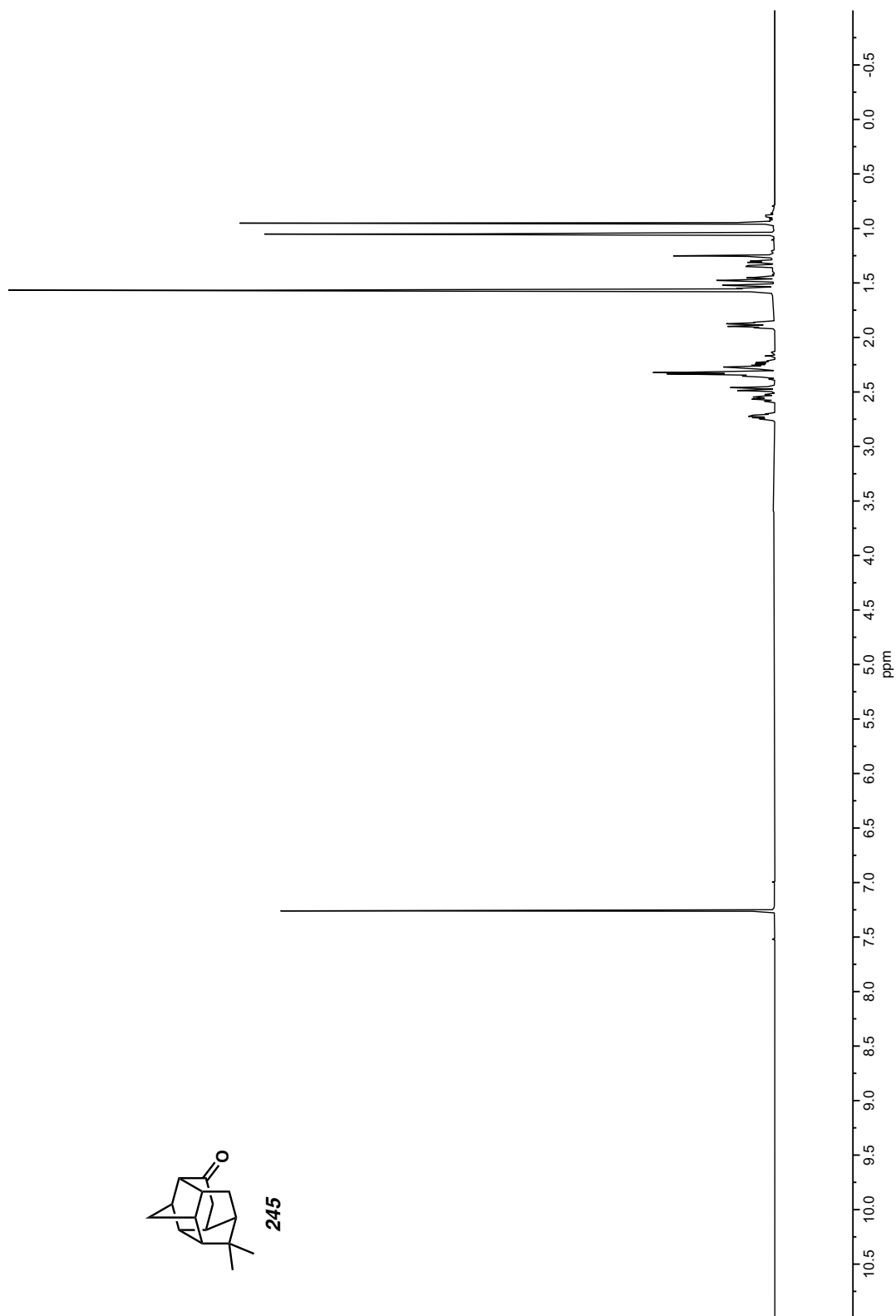


Figure A7.9 ^1H NMR (400 MHz, CDCl_3) of compound 245.

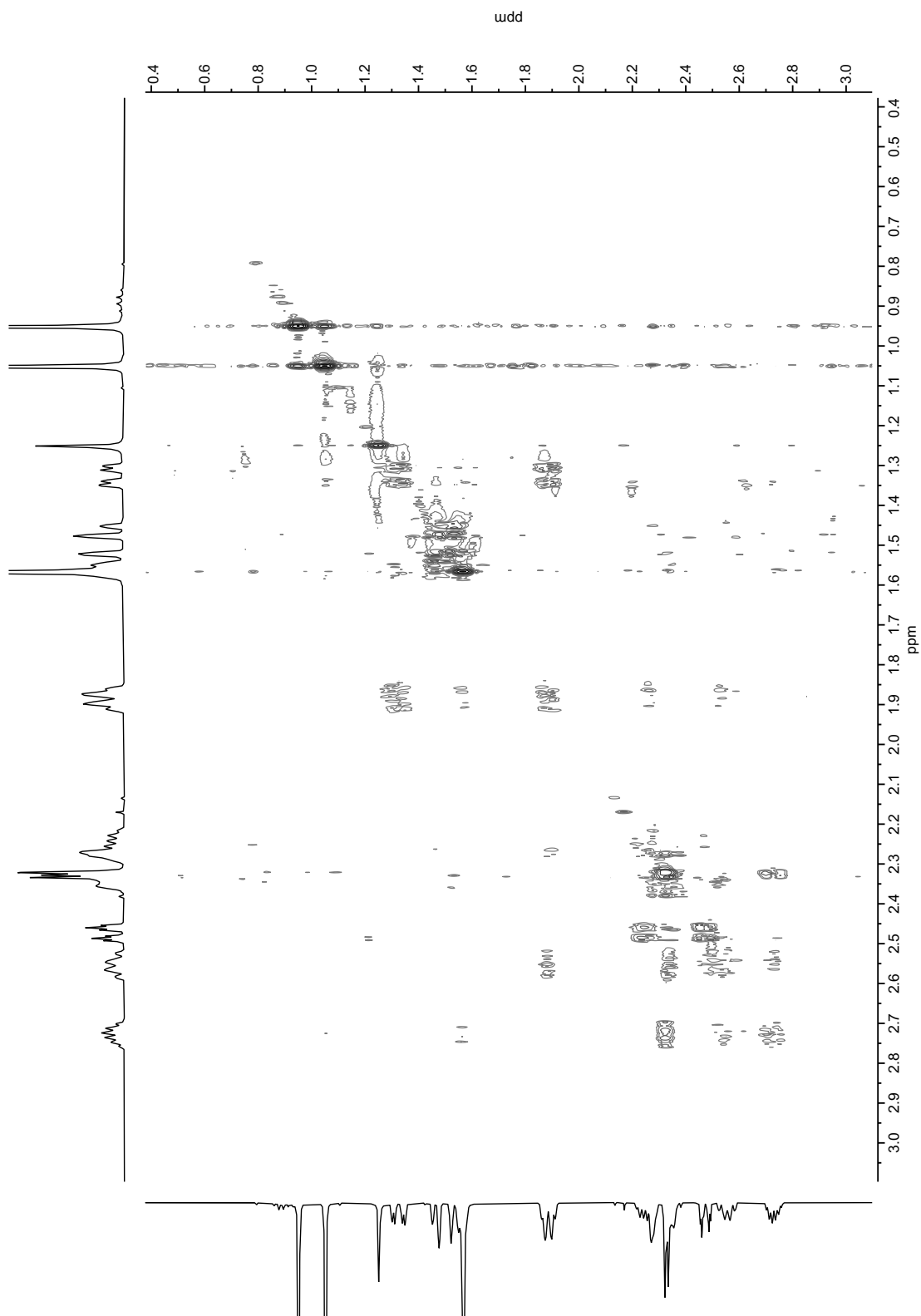


Figure A7.10 COSY NMR (400 MHz, CDCl₃) of compound **245**.

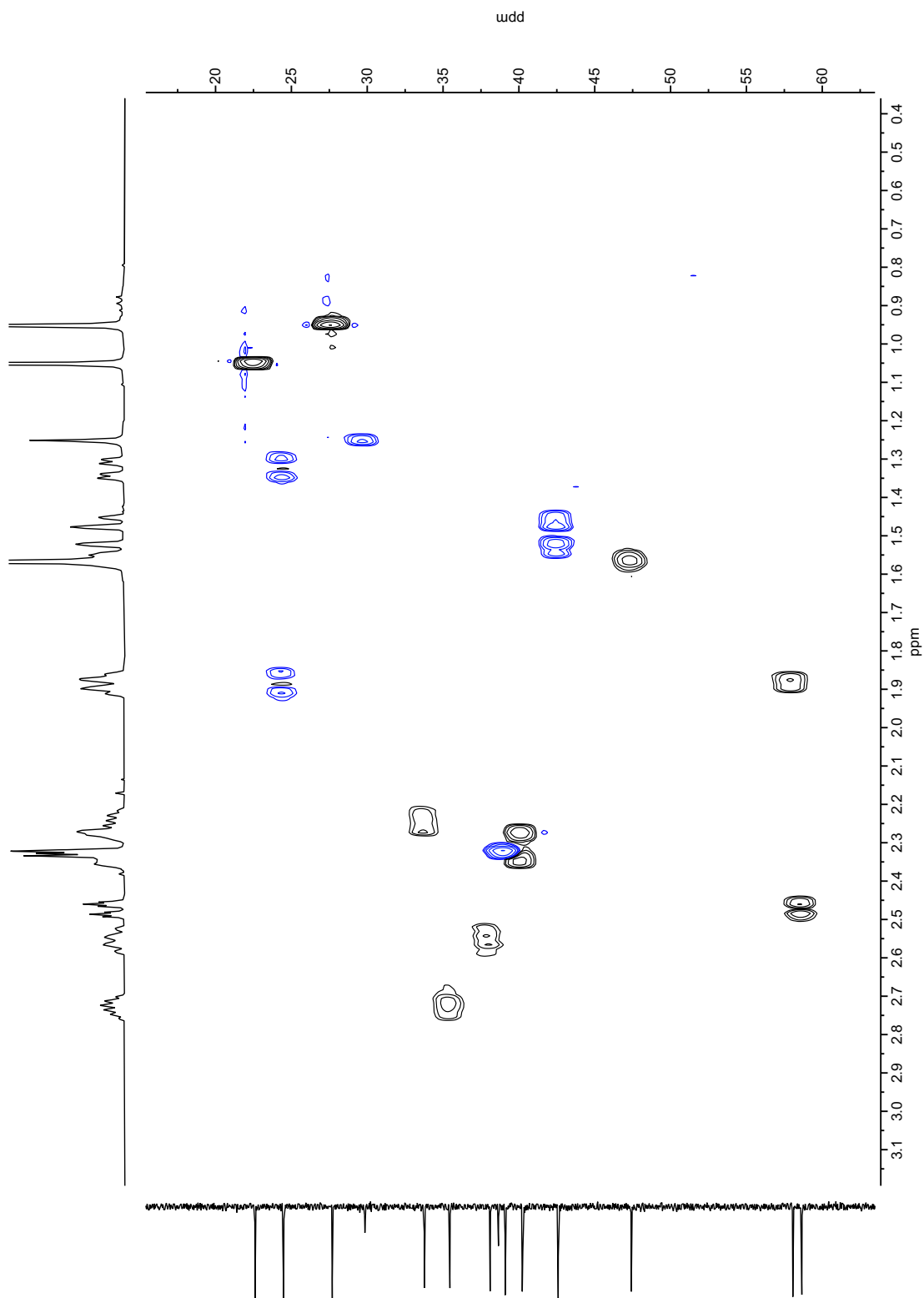


Figure A7.11 HSQC NMR (400 MHz, CDCl_3) of compound 245.

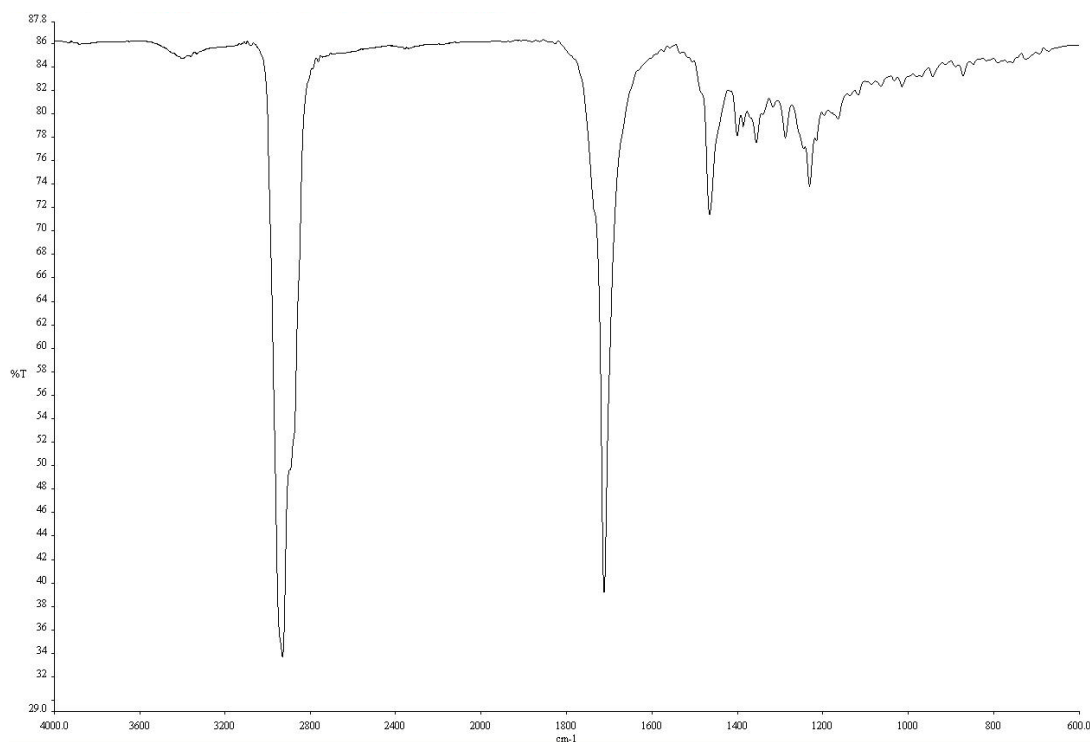


Figure A7.12 Infrared spectrum (Thin Film, NaCl) of compound **245**.

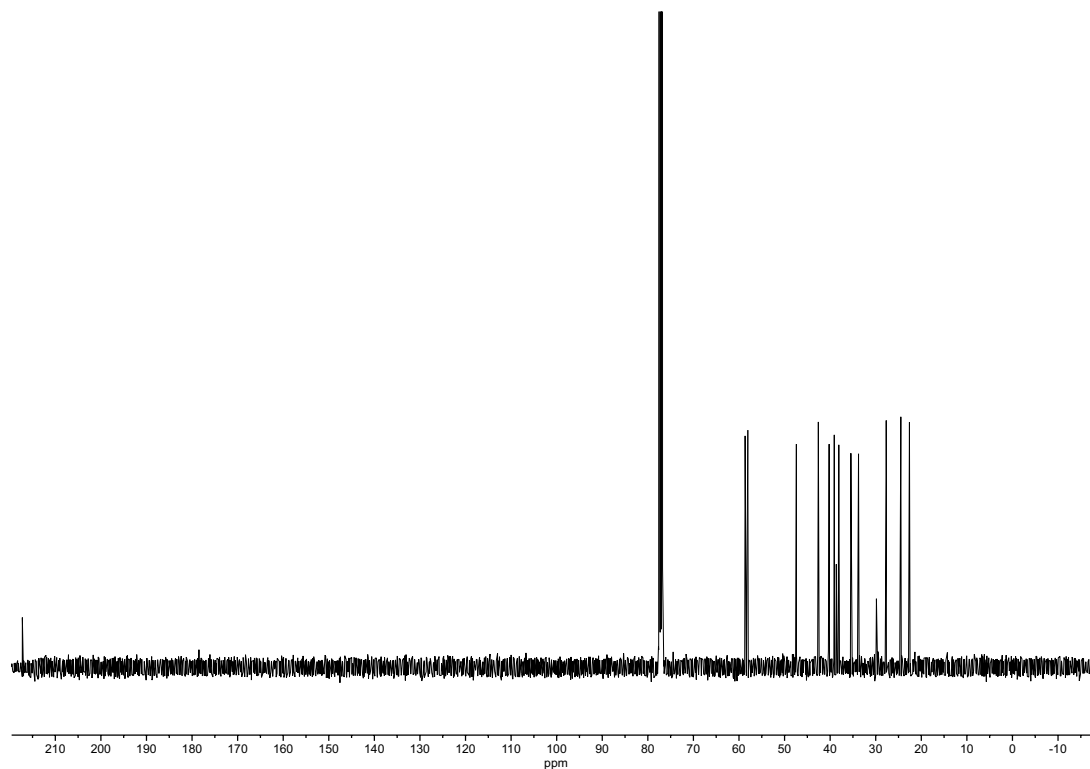


Figure A7.13 ¹³C NMR (100 MHz, C₆D₆) of compound **245**.

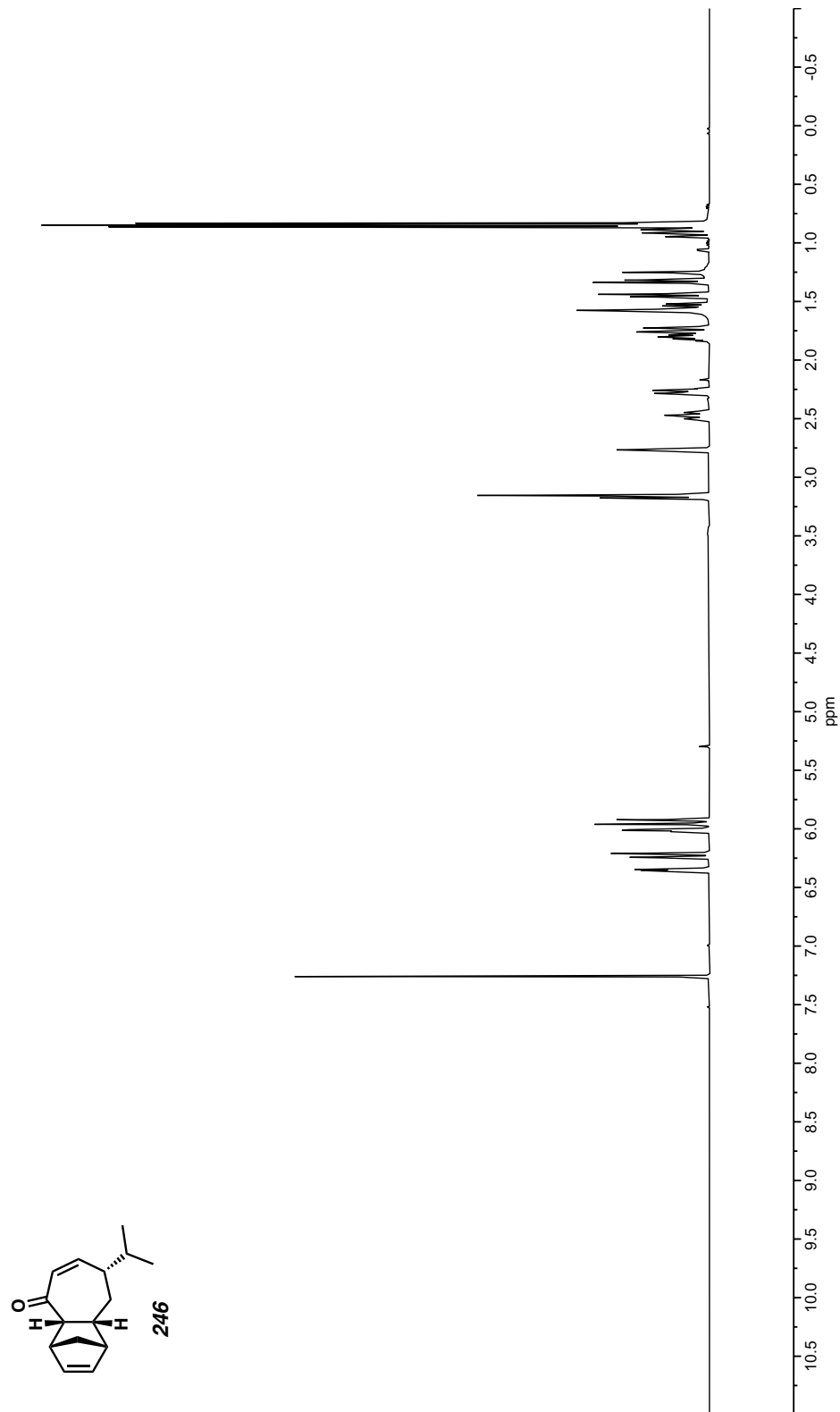


Figure A7.14 ¹H NMR (400 MHz, CDCl₃) of compound 246.

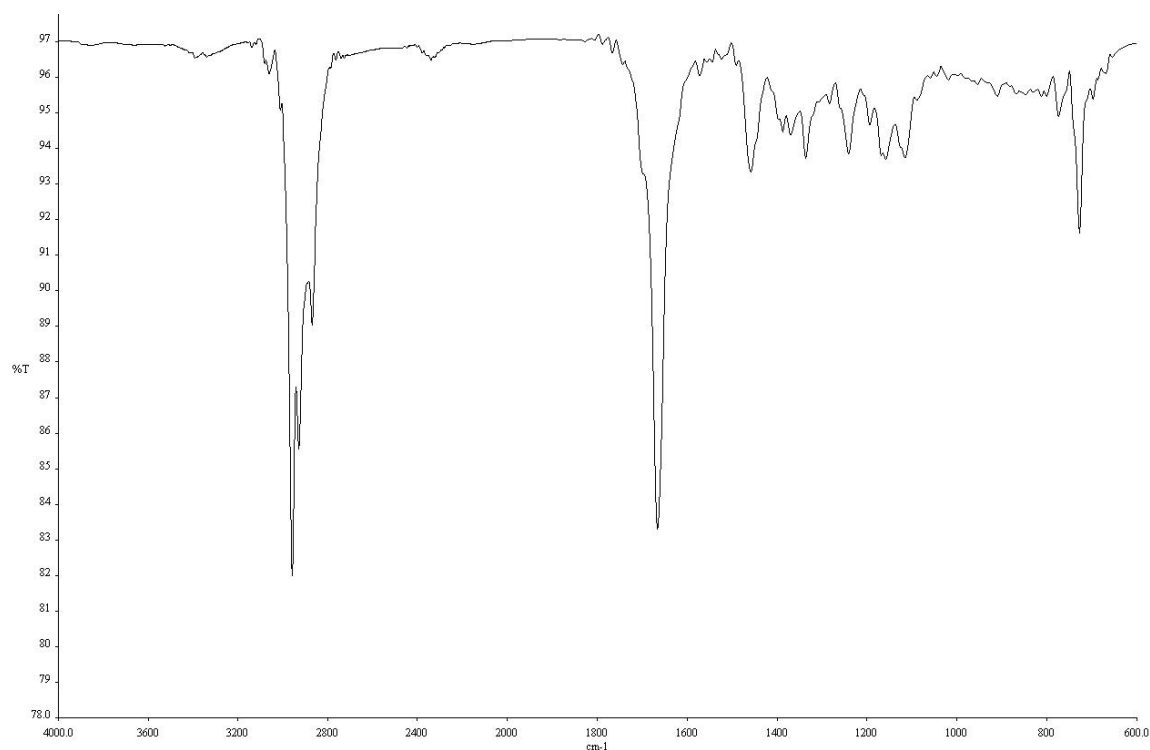


Figure A7.15 Infrared spectrum (Thin Film, NaCl) of compound **246**.

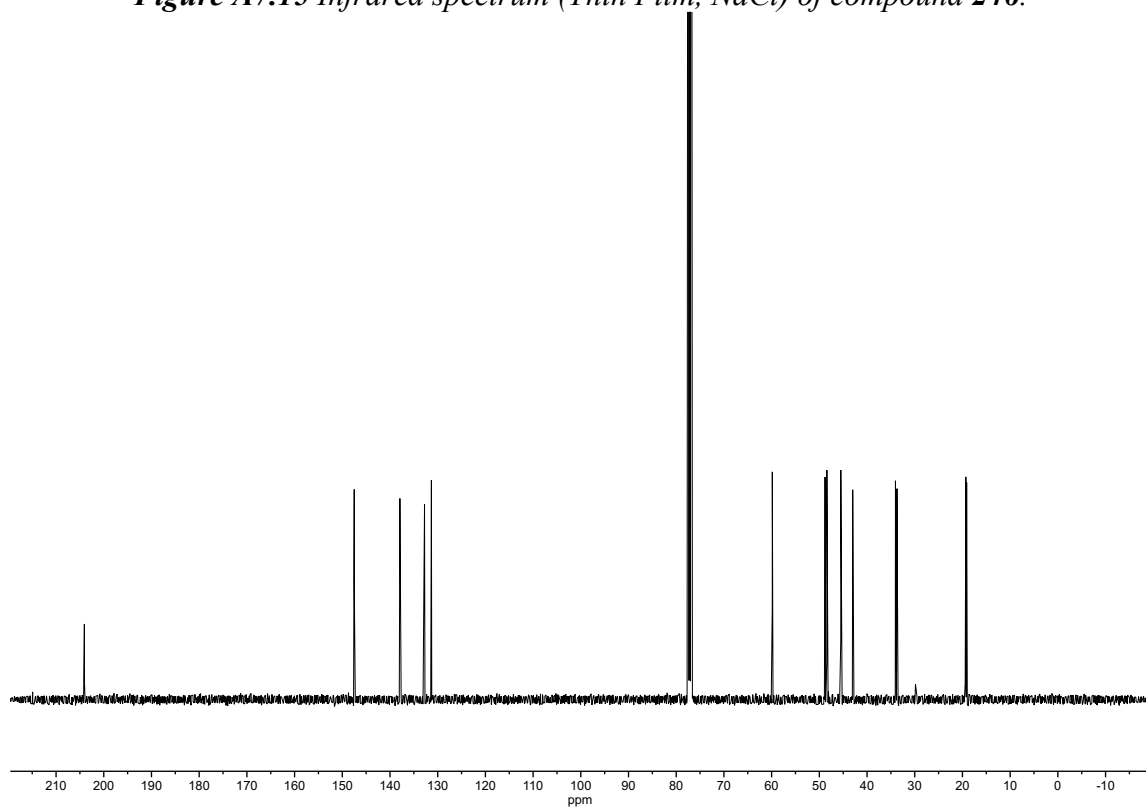


Figure A7.16 ¹³C NMR (100 MHz, CDCl₃) of compound **246**.

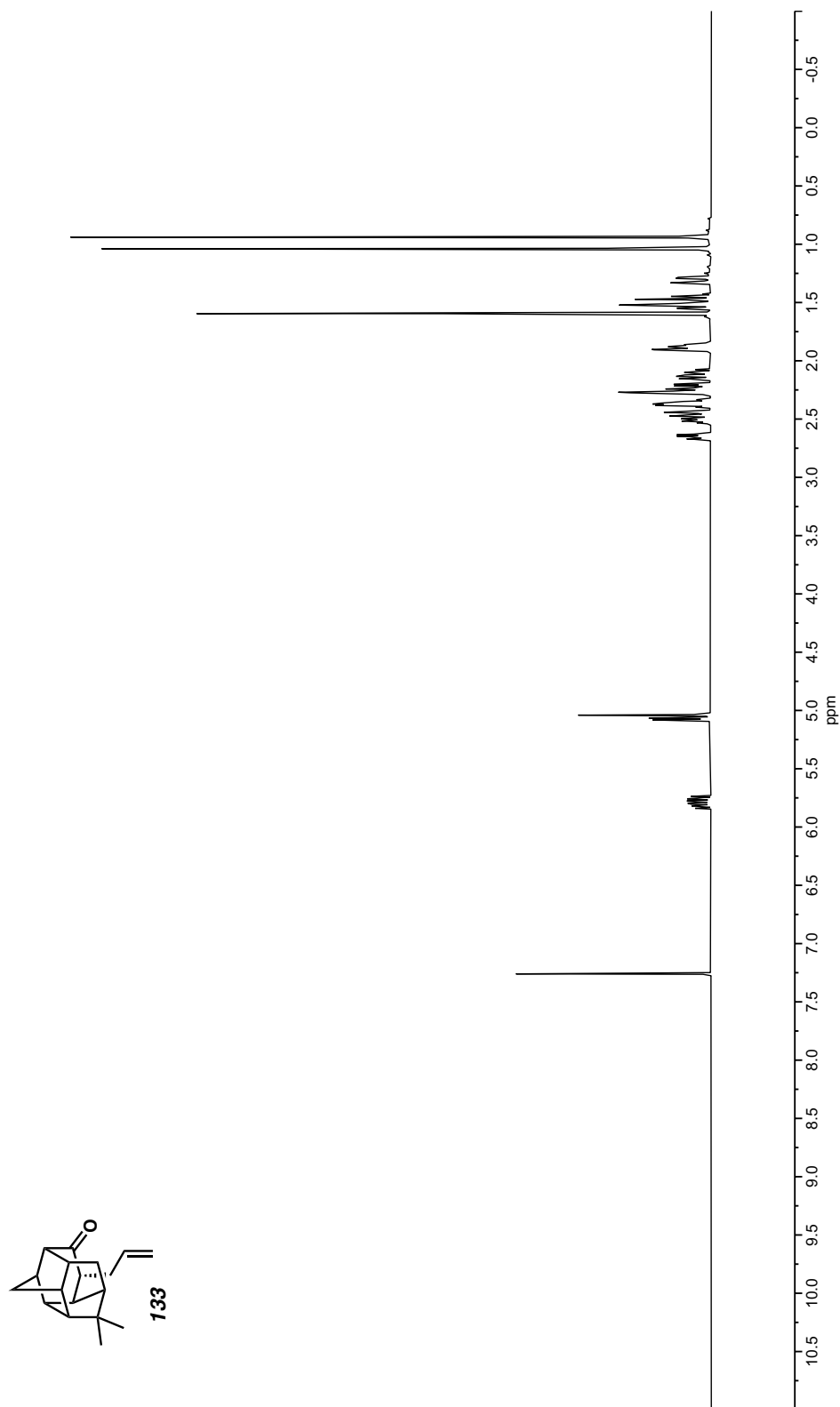


Figure A7.17 ¹H NMR (400 MHz, CDCl₃) of compound **133**.

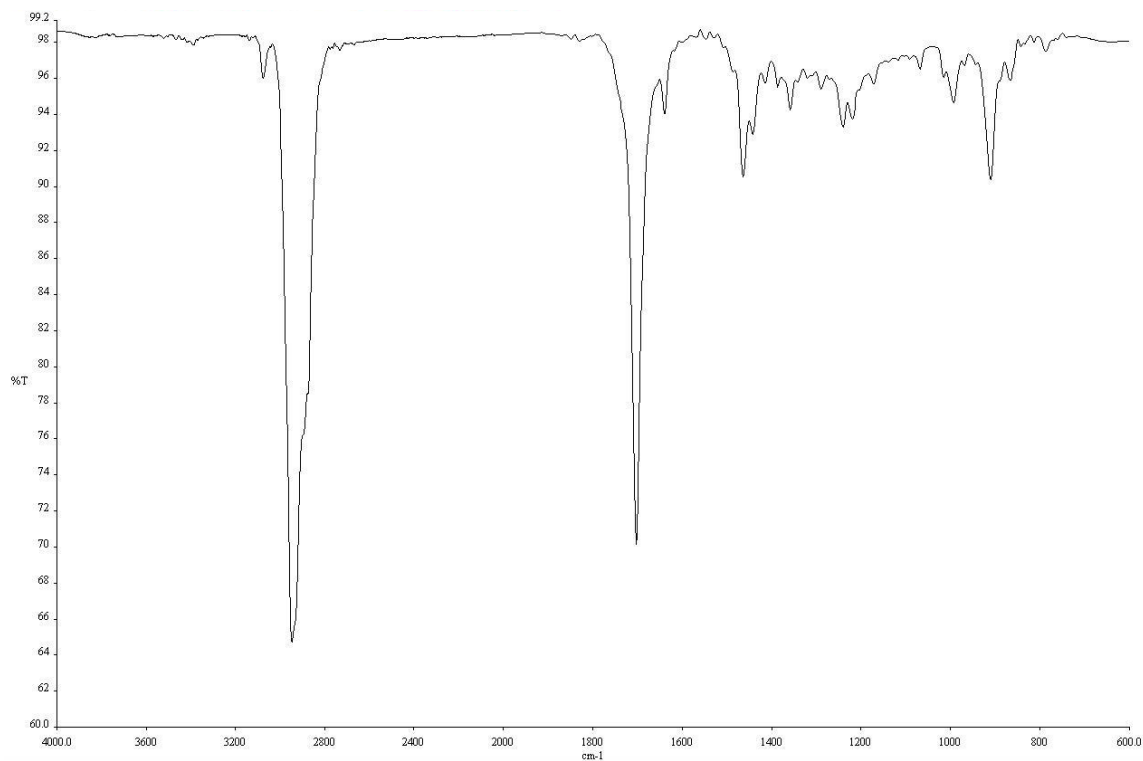


Figure A7.18 Infrared spectrum (Thin Film, NaCl) of compound **133**.

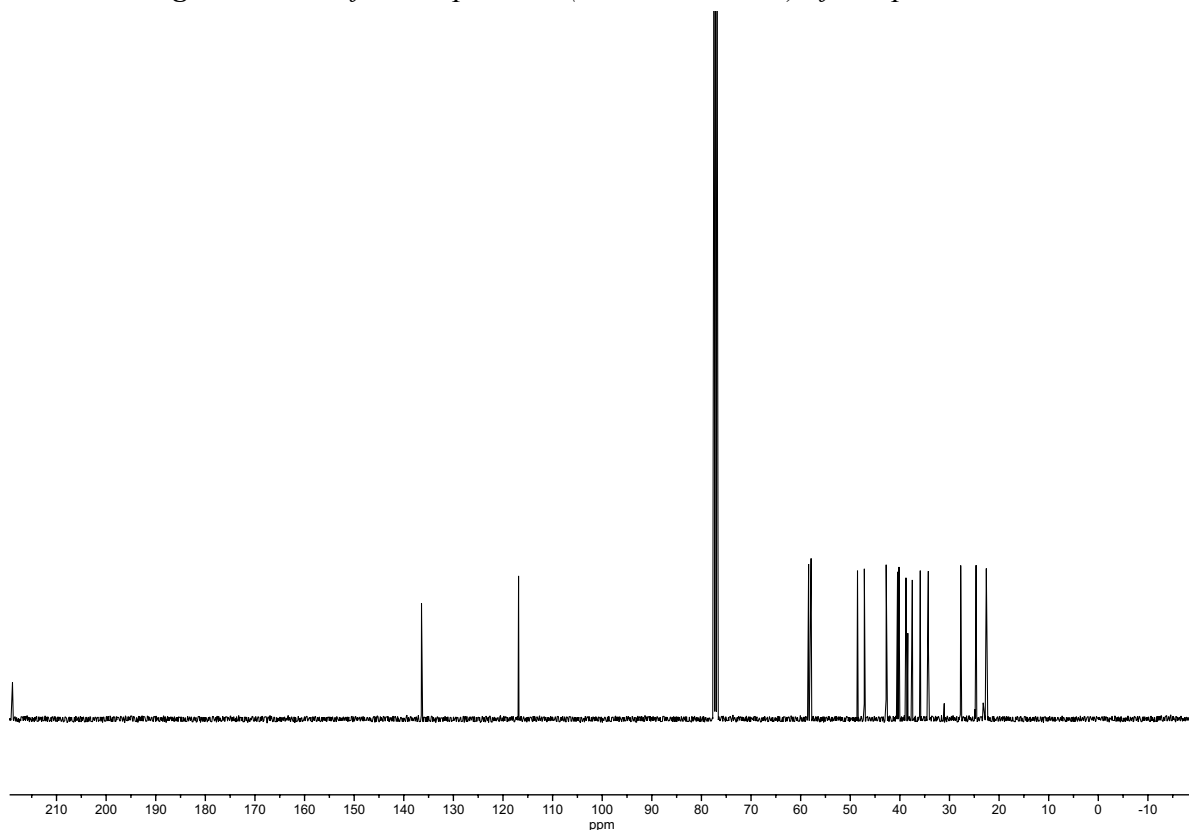


Figure A7.19 ¹³C NMR (100 MHz, CDCl₃) of compound **133**.

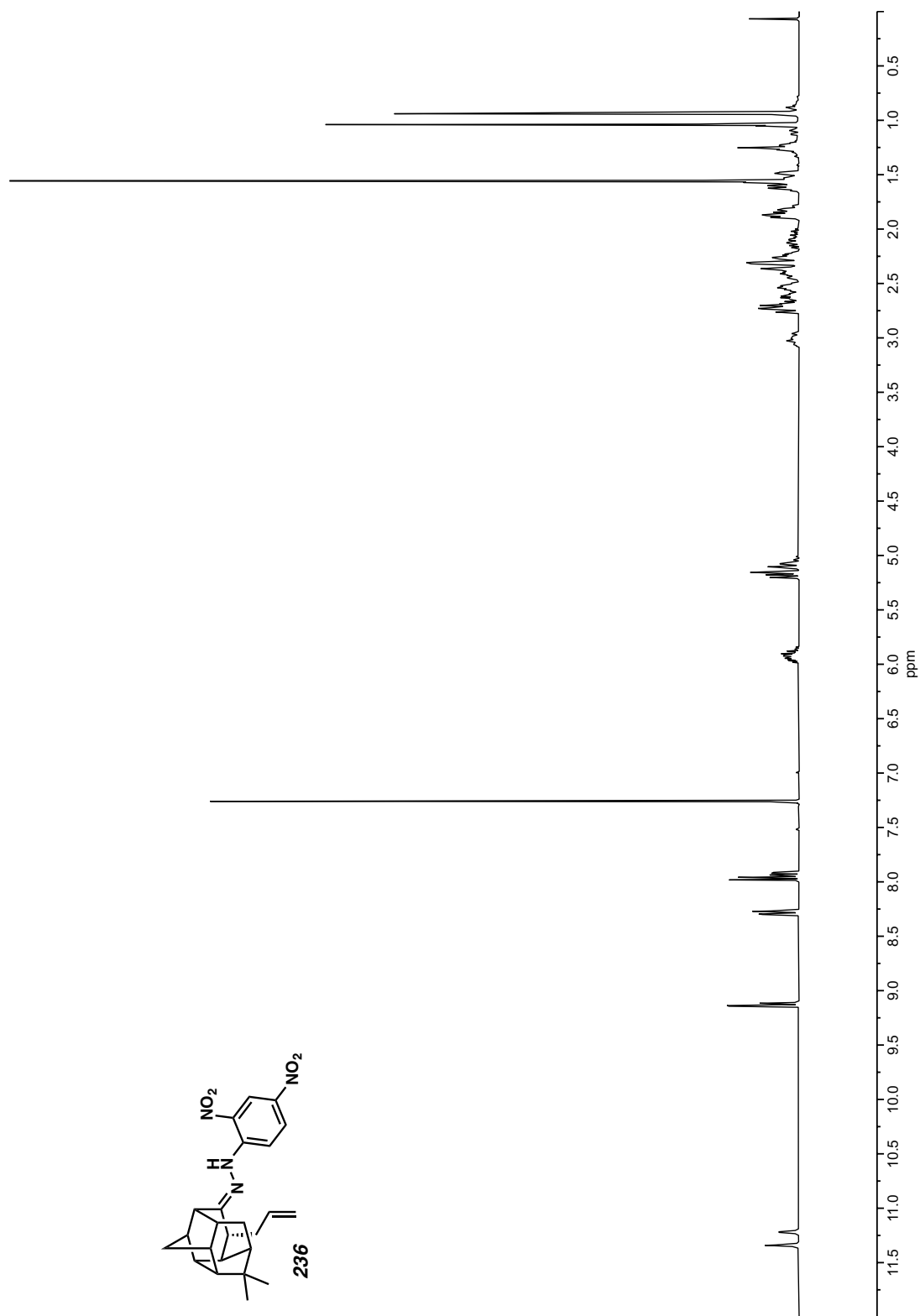


Figure A7.20 ^1H NMR (400 MHz, CDCl_3) of compound **236**.

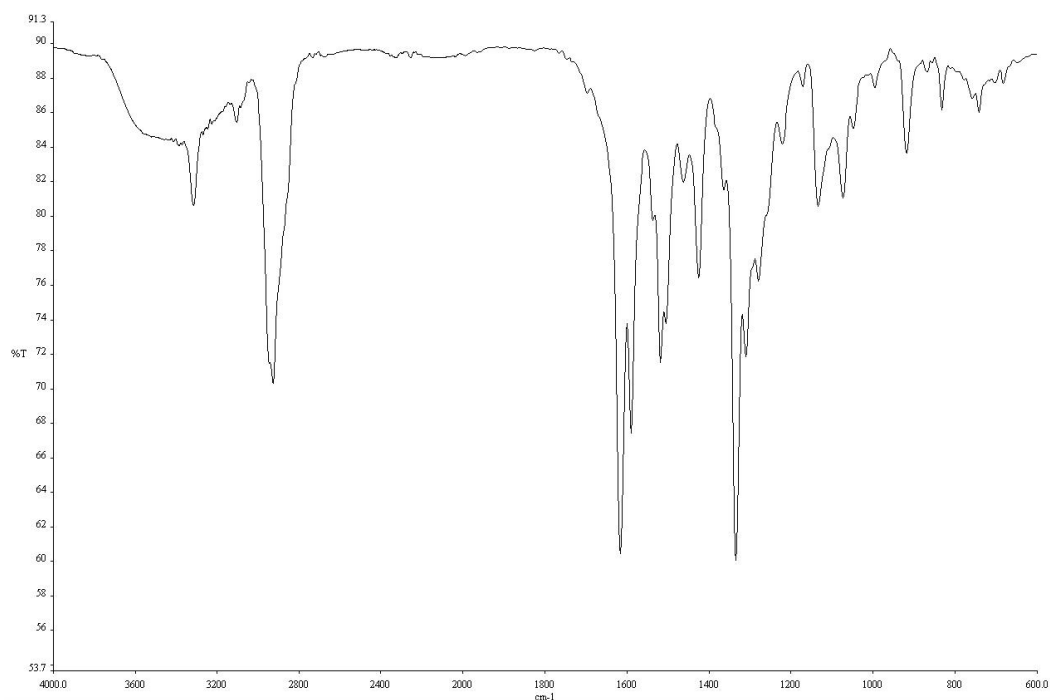


Figure A7.21 Infrared spectrum (Thin Film, NaCl) of compound **236**.

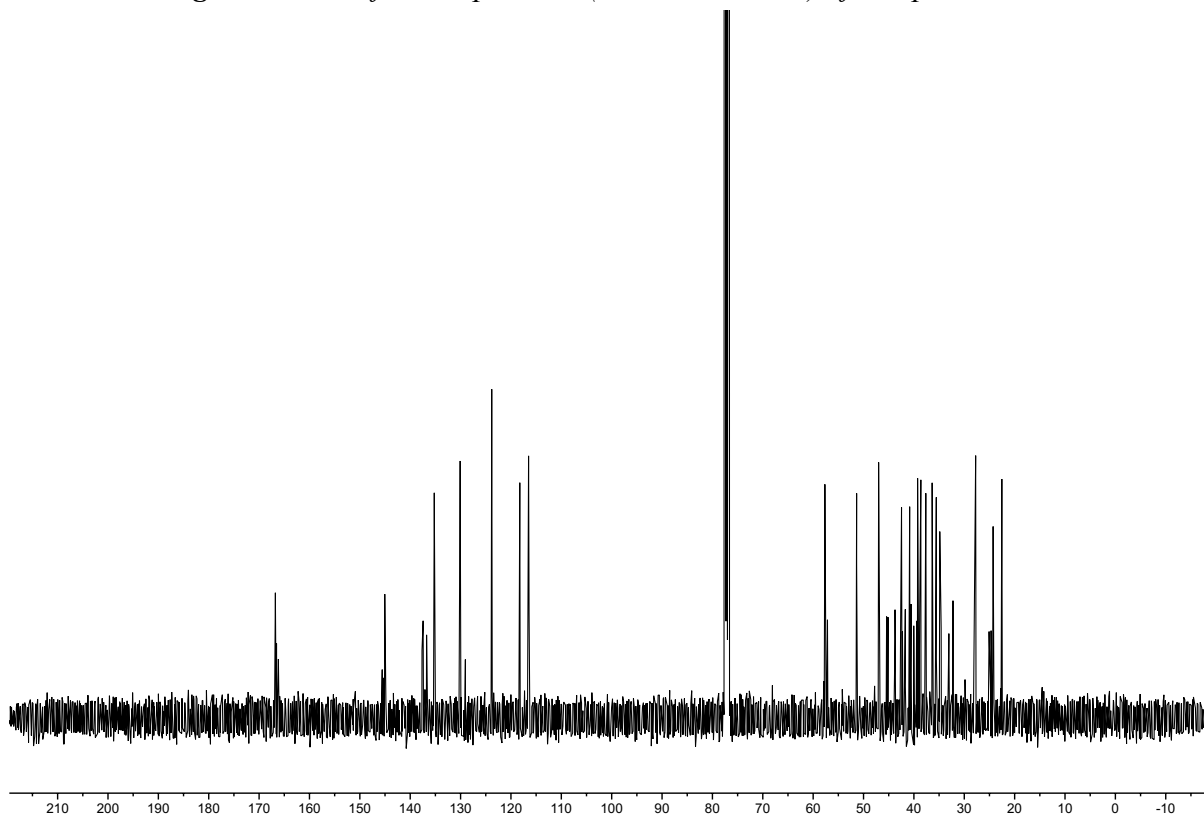


Figure A7.22 ¹³C NMR (100 MHz, CDCl₃) of compound **236**.

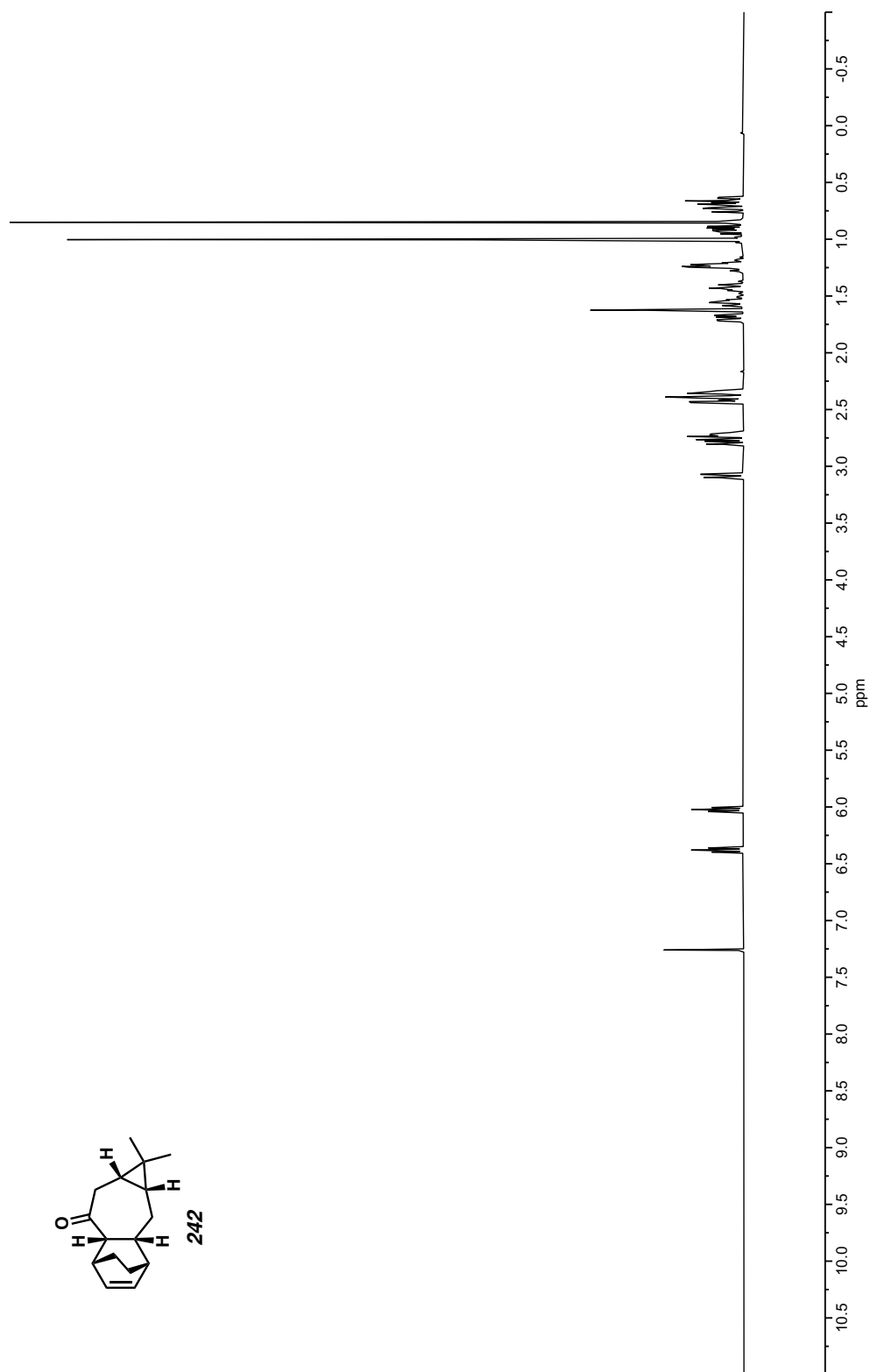


Figure A7.23 ^1H NMR (400 MHz, CDCl_3) of compound 242.

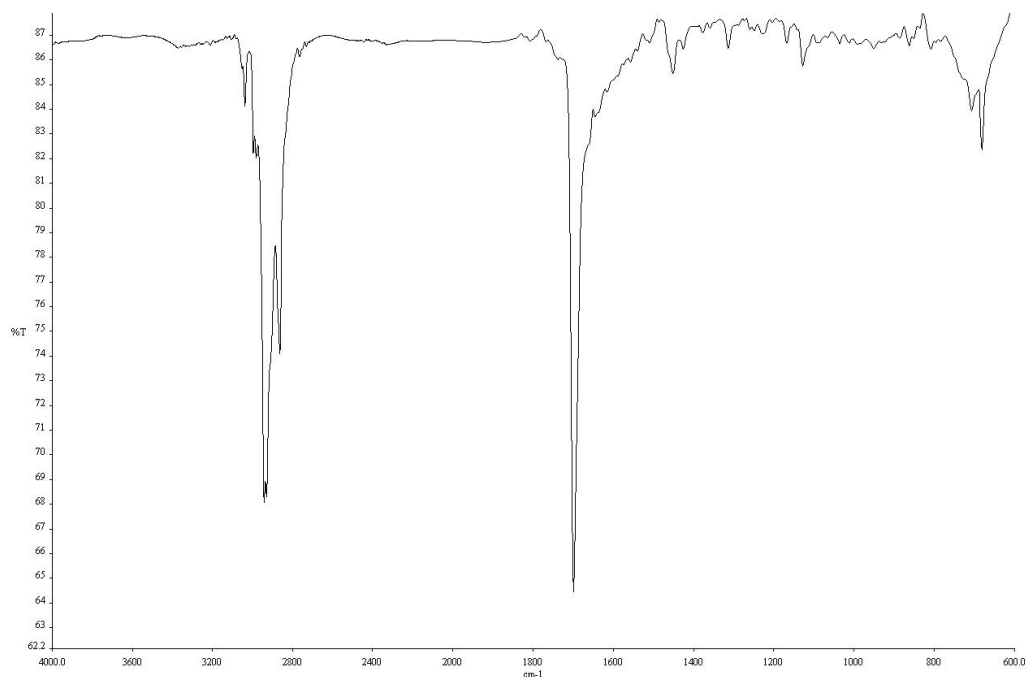


Figure A7.24 Infrared spectrum (Thin Film, NaCl) of compound **242**.

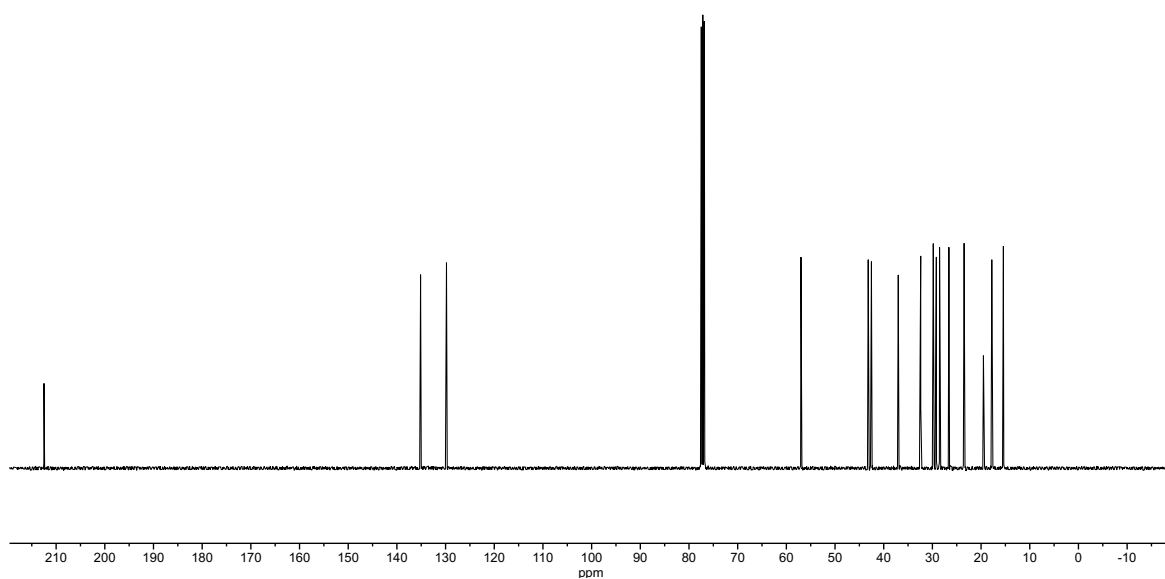


Figure A7.25 ¹³C NMR (100 MHz, CDCl₃) of compound **242**.

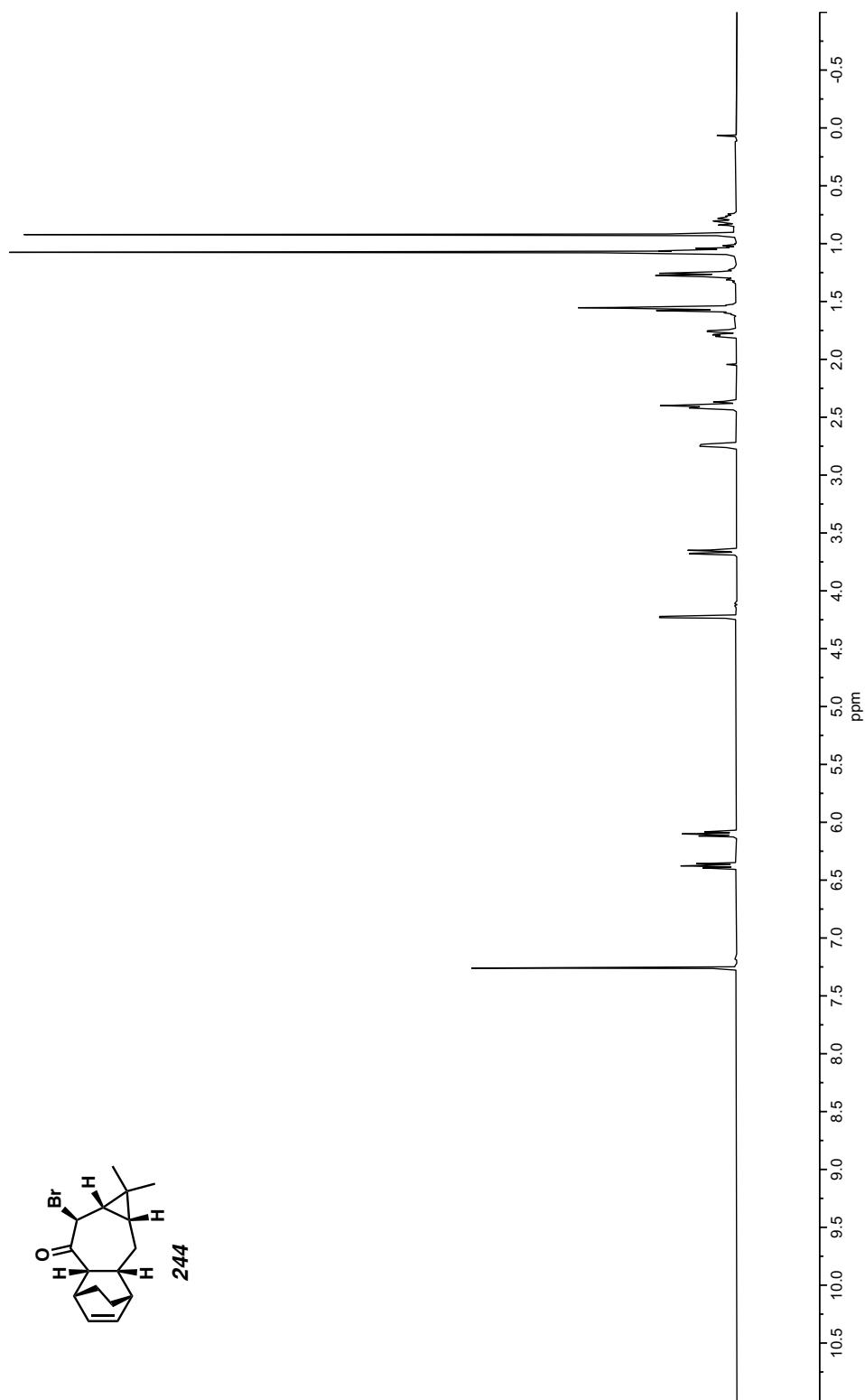


Figure A7.26 ^1H NMR (400 MHz, CDCl_3) of compound 244.

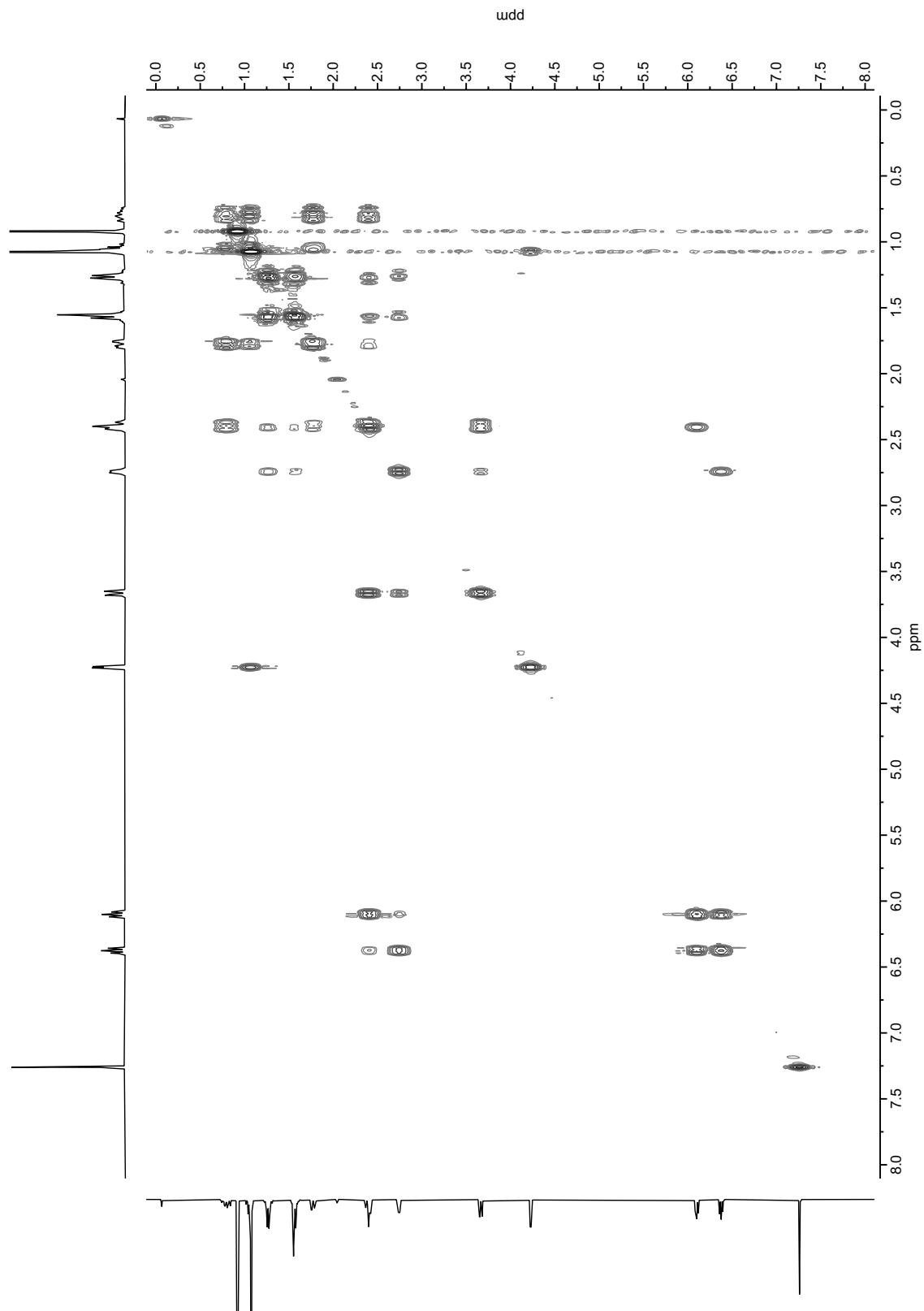


Figure A7.27 COSY NMR (400 MHz, CDCl_3) of compound **244**.

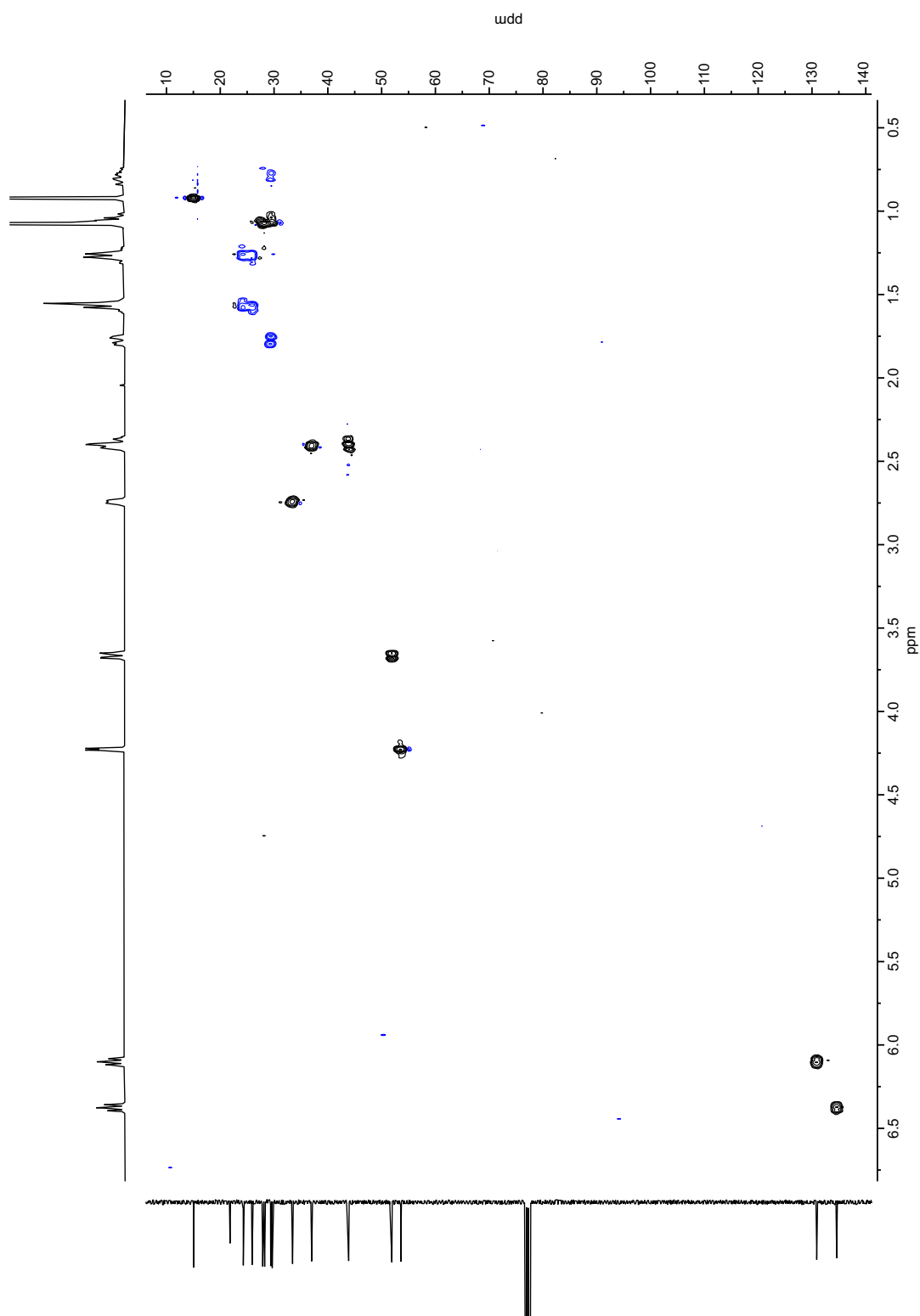


Figure A7.28 HSQC NMR (400 MHz, CDCl_3) of compound **244**.

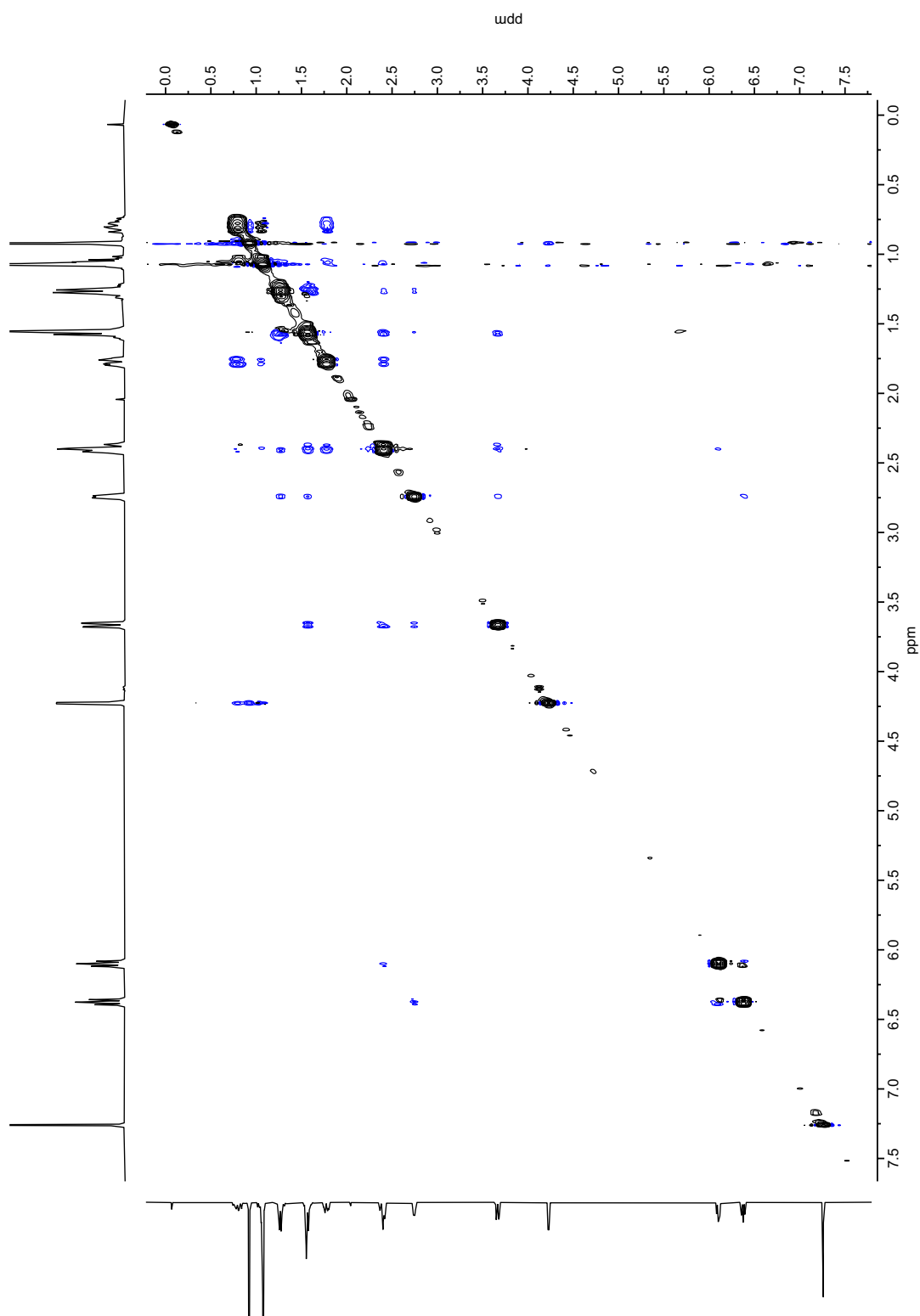


Figure A7.29 NOESY NMR (400 MHz, CDCl_3) of compound 244.

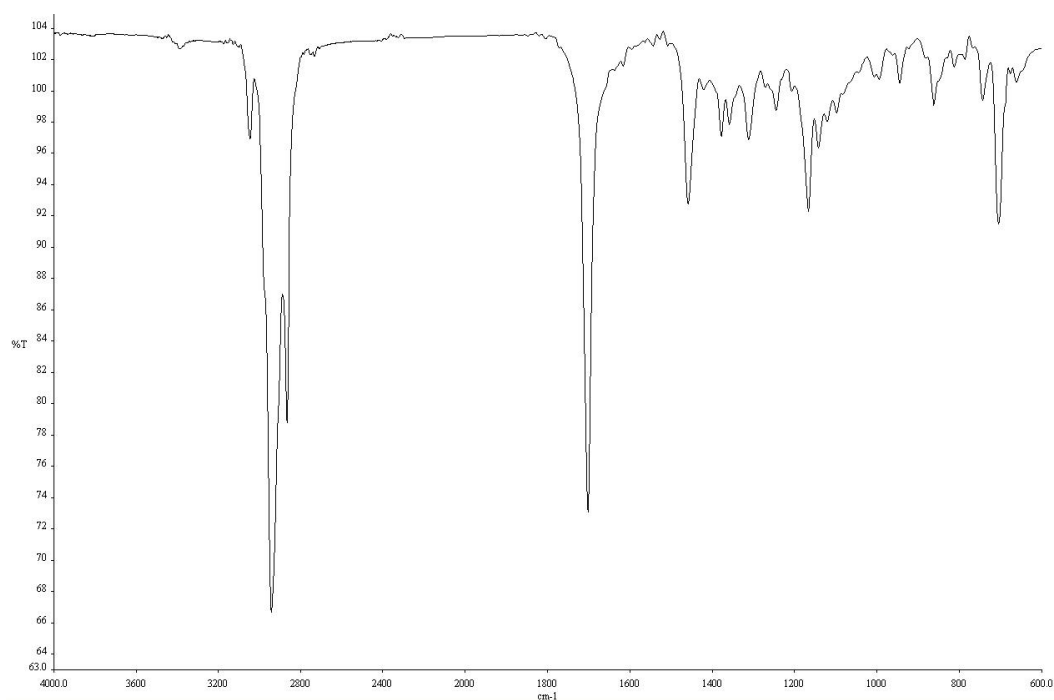


Figure A7.30 Infrared spectrum (Thin Film, NaCl) of compound **244**.

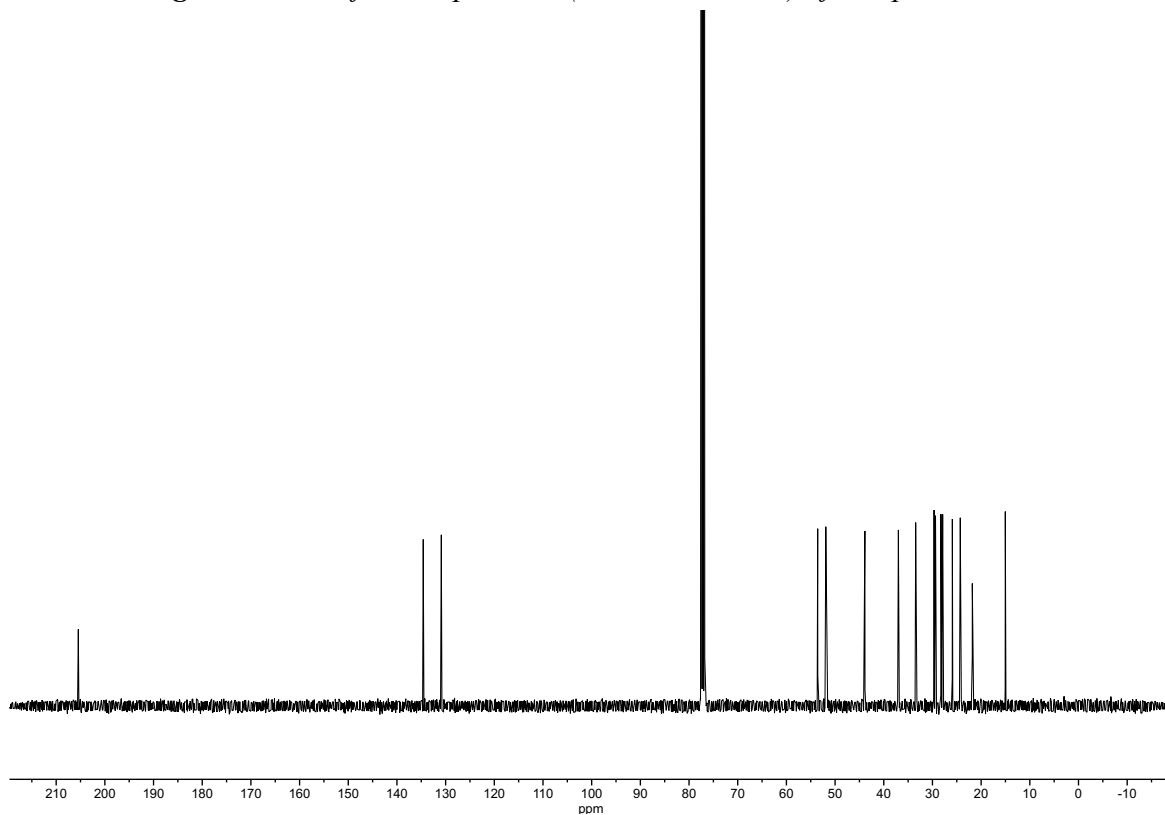


Figure A7.31 ¹³C NMR (100 MHz, C₆D₆) of compound **244**.

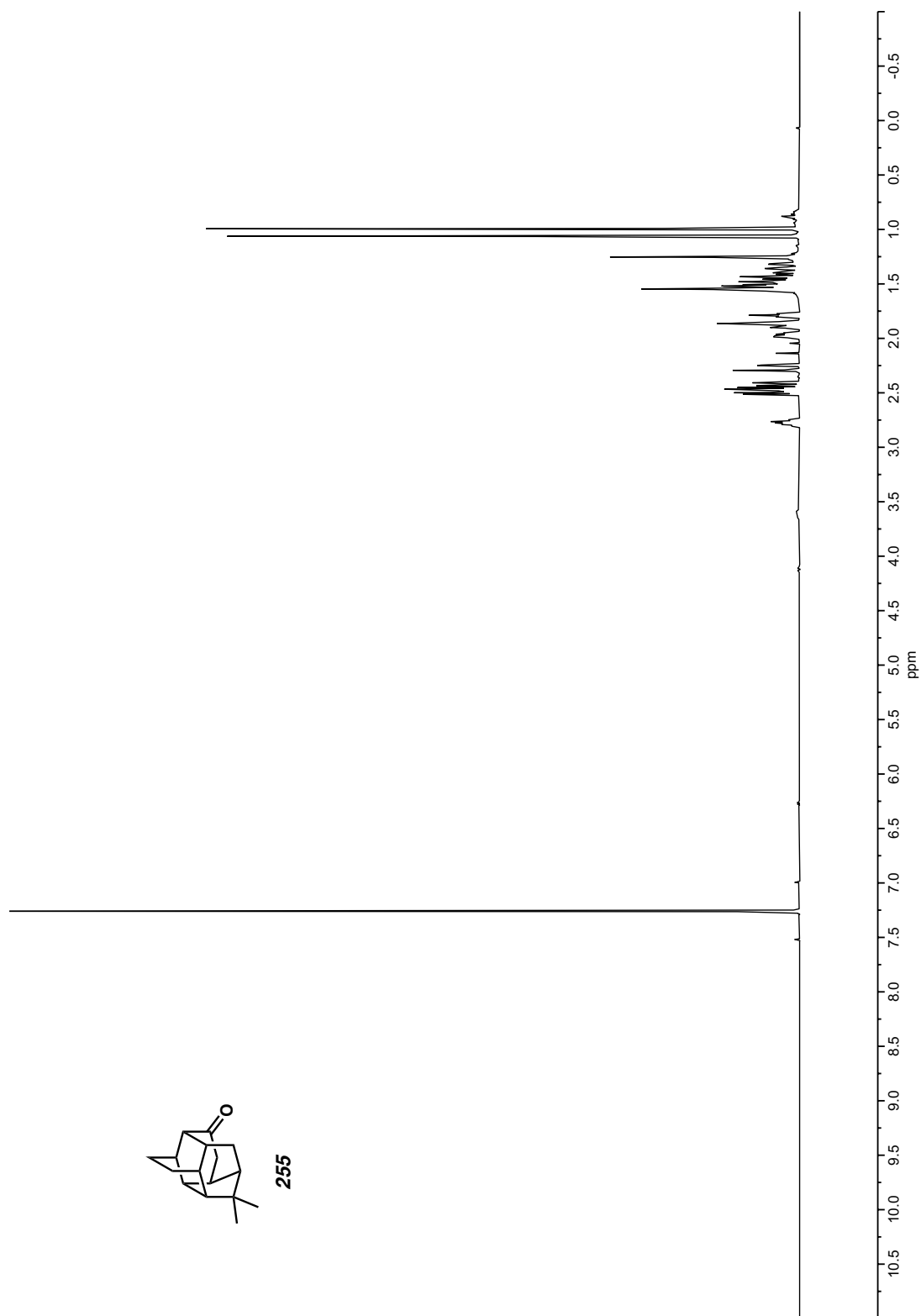


Figure A7.32 ^1H NMR (400 MHz, CDCl_3) of compound 255.

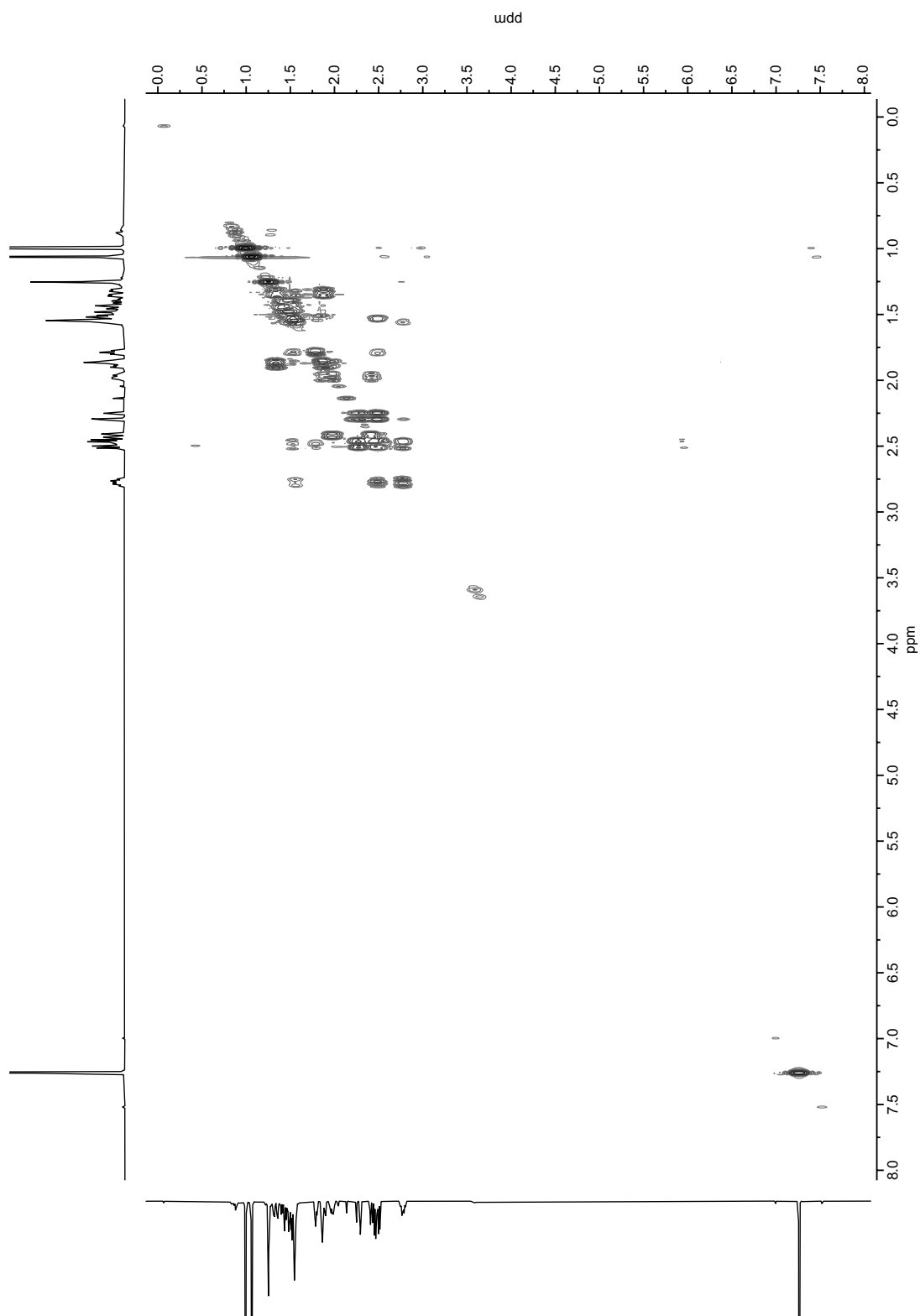


Figure A7.33 COSY NMR (400 MHz, CDCl₃) of compound 255.

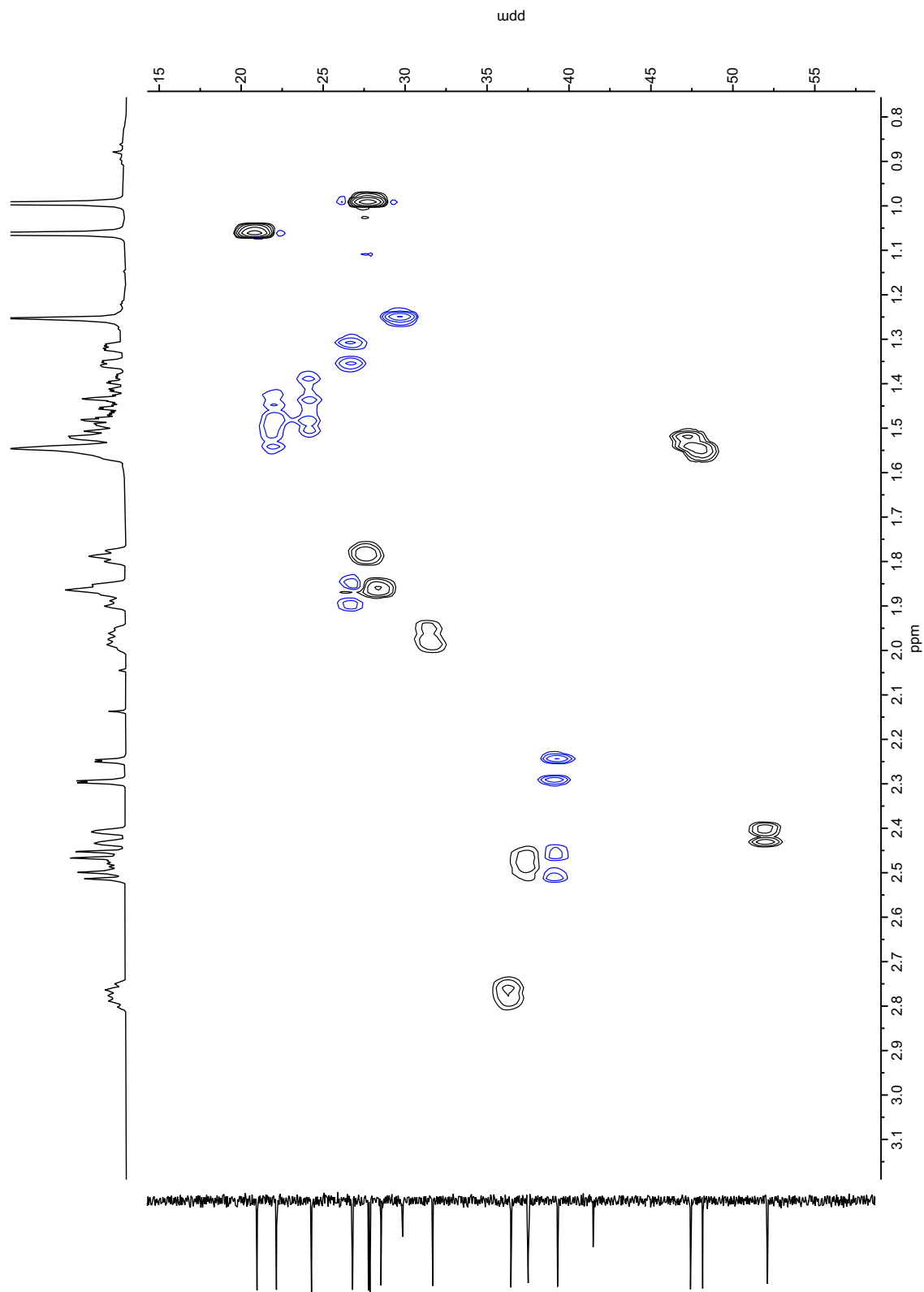


Figure A7.34 HSQC NMR (400 MHz, CDCl_3) of compound **255**.

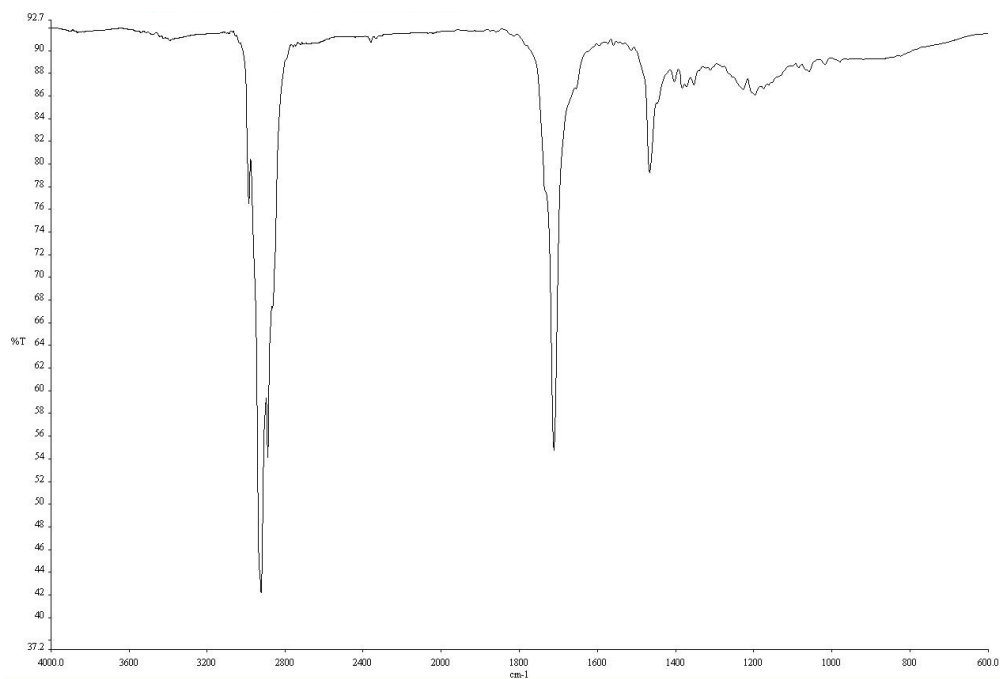


Figure A7.35 Infrared spectrum (Thin Film, NaCl) of compound 255.

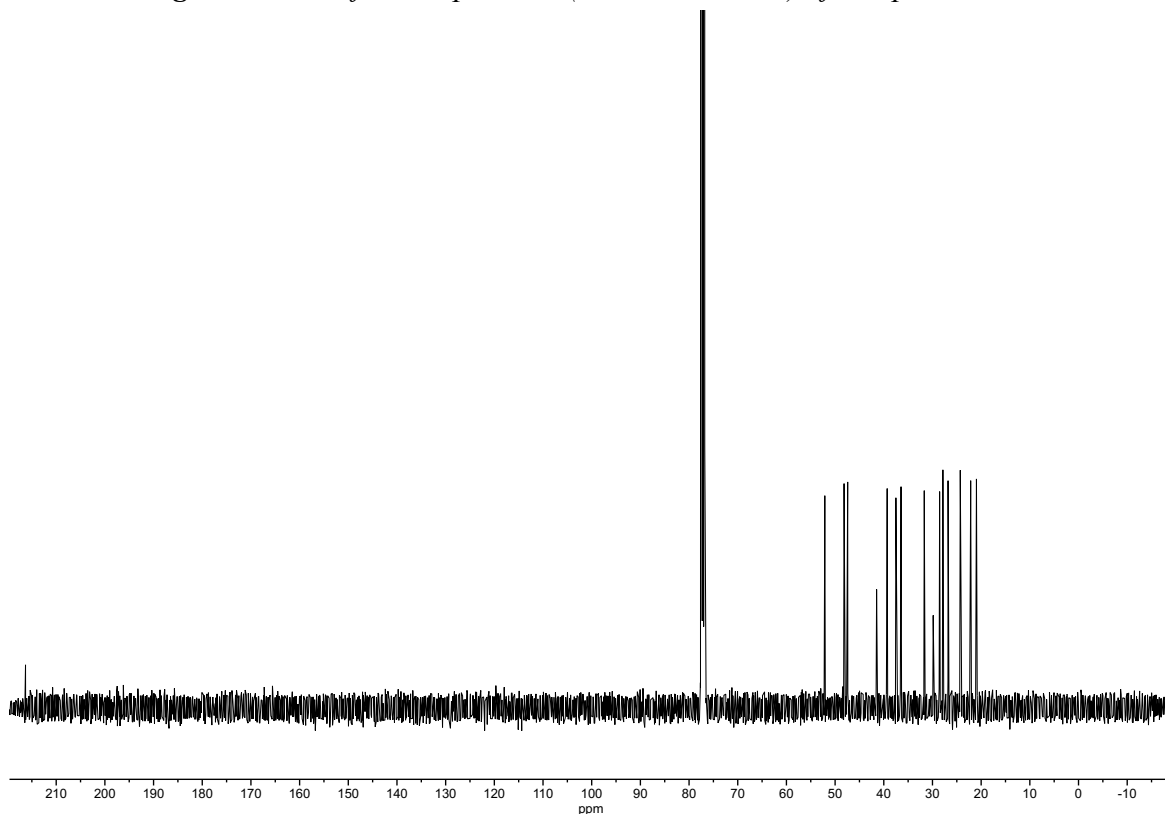


Figure A7.36 ¹³C NMR (100 MHz, CDCl₃) of compound 255.

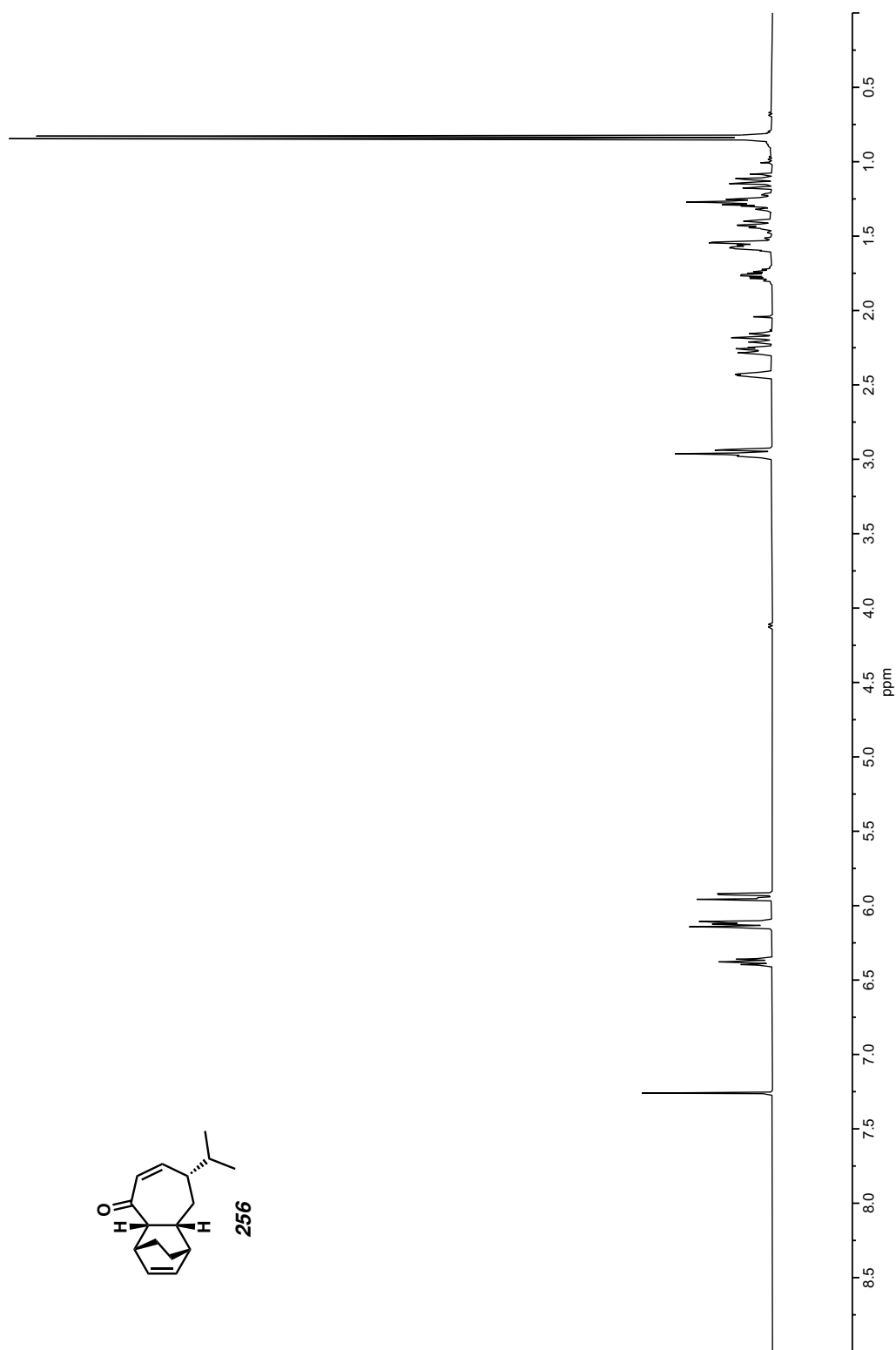


Figure A7.37 ^1H NMR (400 MHz, CDCl_3) of compound **256**.

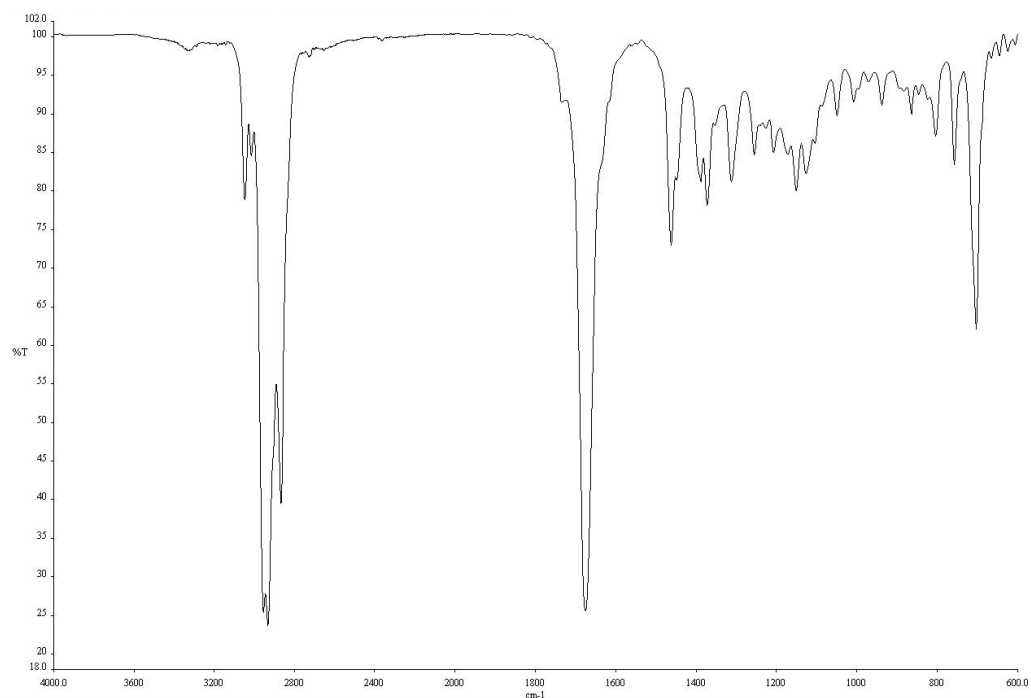


Figure A7.38 Infrared spectrum (Thin Film, NaCl) of compound **256**.

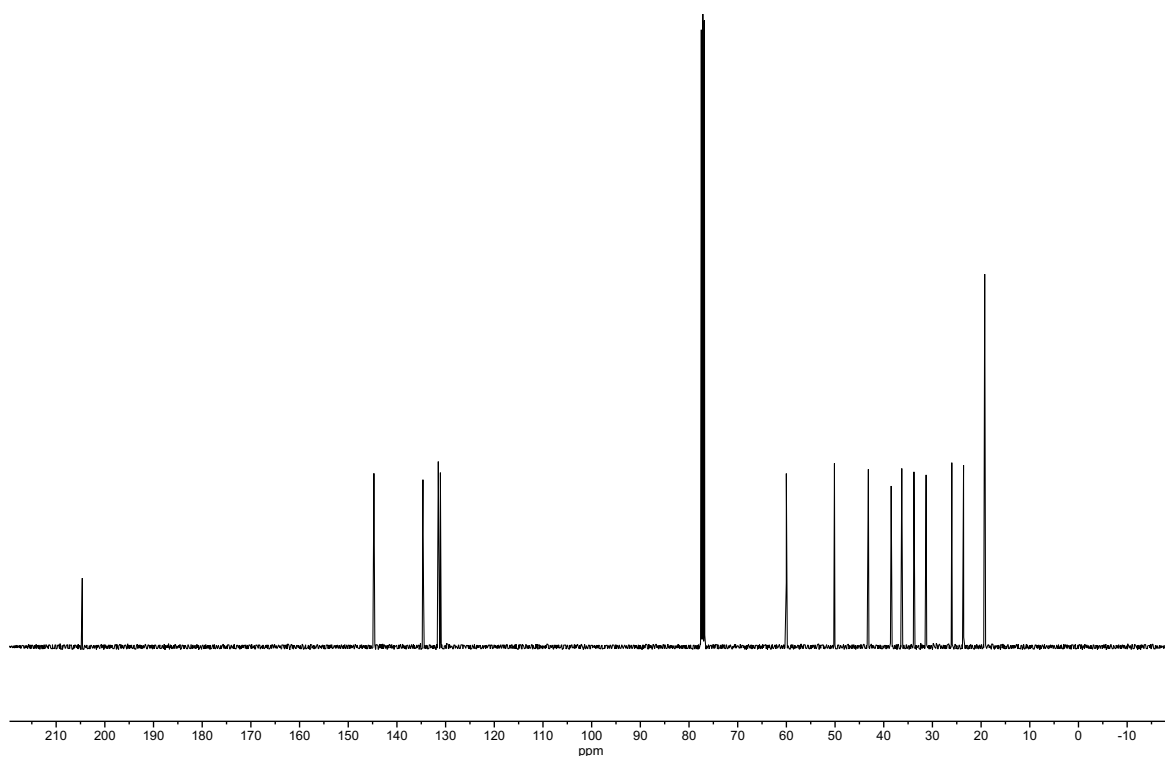


Figure A7.39 ¹³C NMR (100 MHz, CDCl₃) of compound **256**.

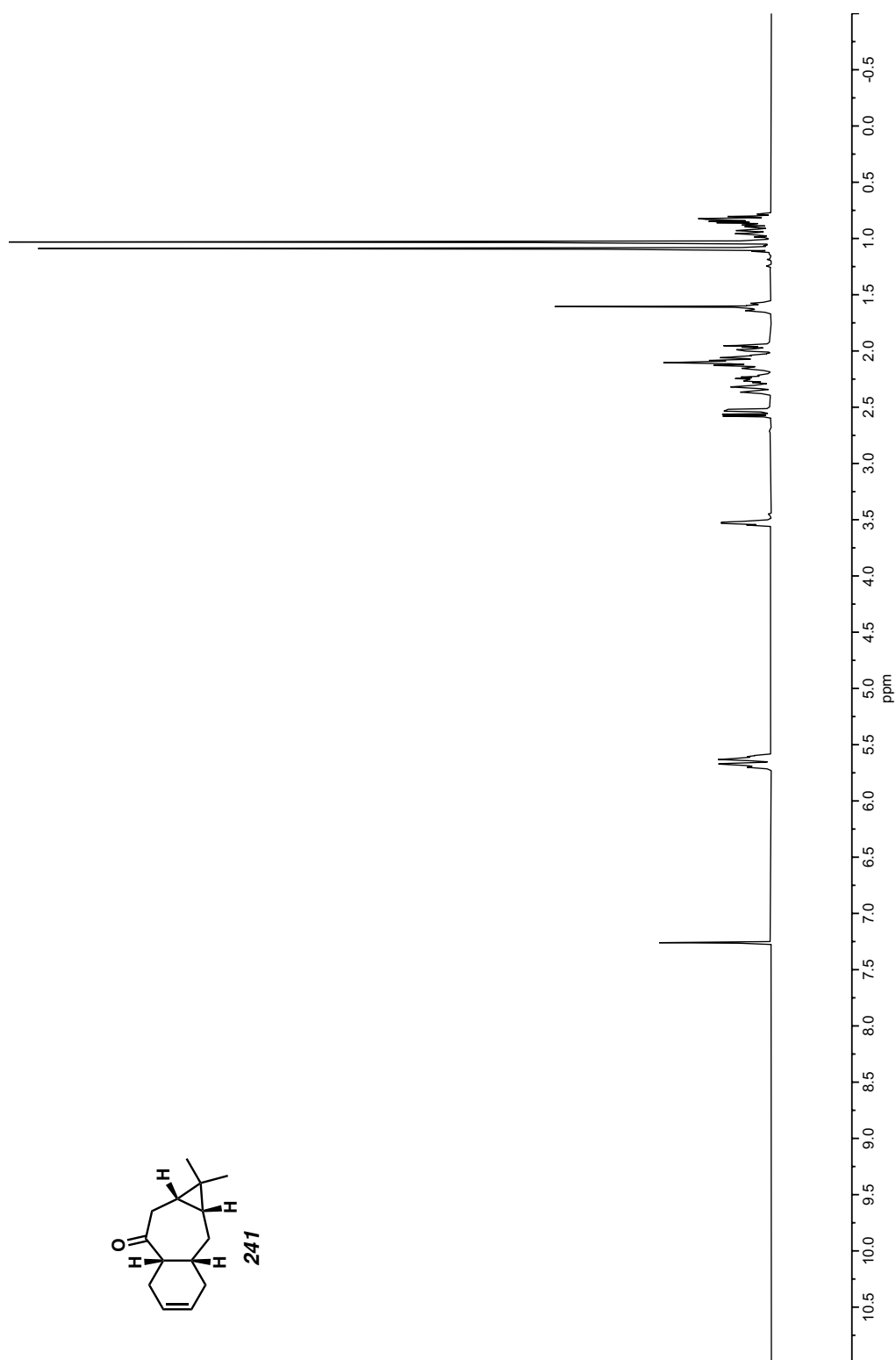


Figure A7.40 ^1H NMR (400 MHz, CDCl_3) of compound 241.

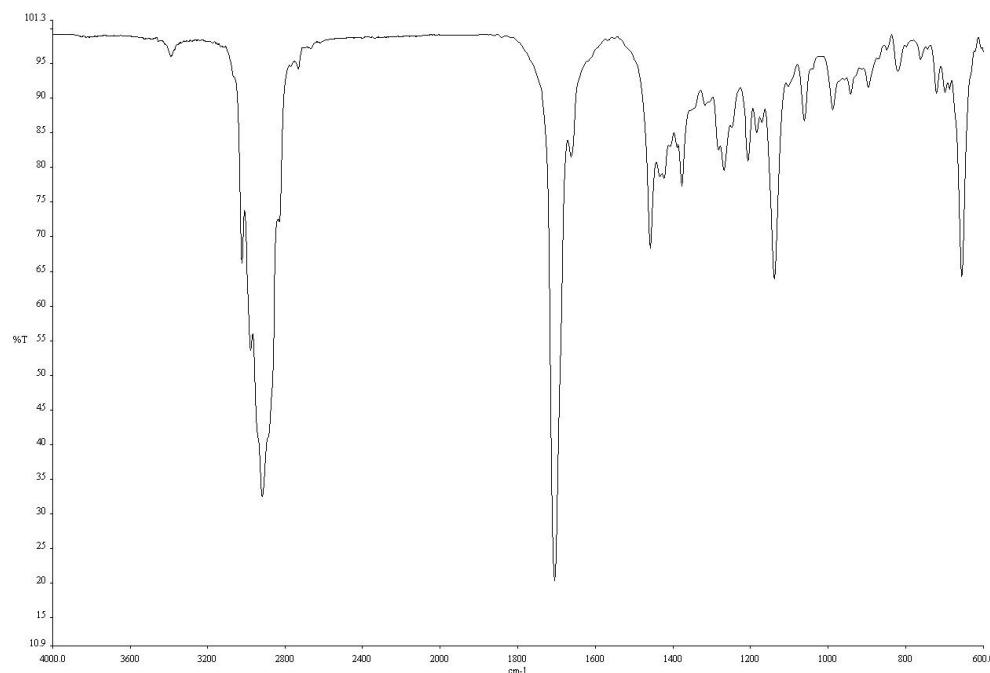


Figure A7.41 Infrared spectrum (Thin Film, NaCl) of compound **241**.

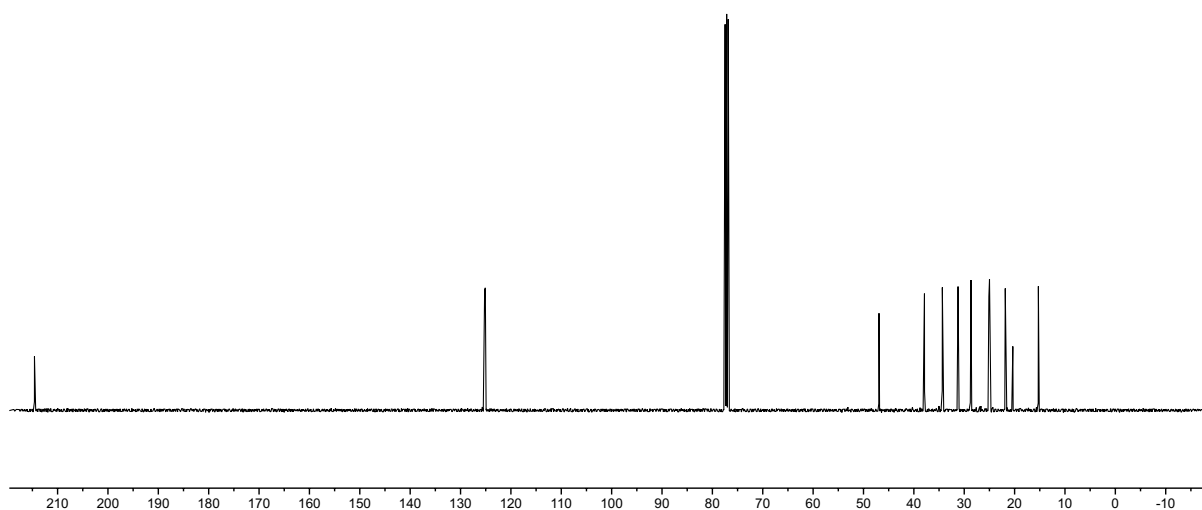


Figure A7.42 ¹³C NMR (100 MHz, CDCl₃) of compound **241**.

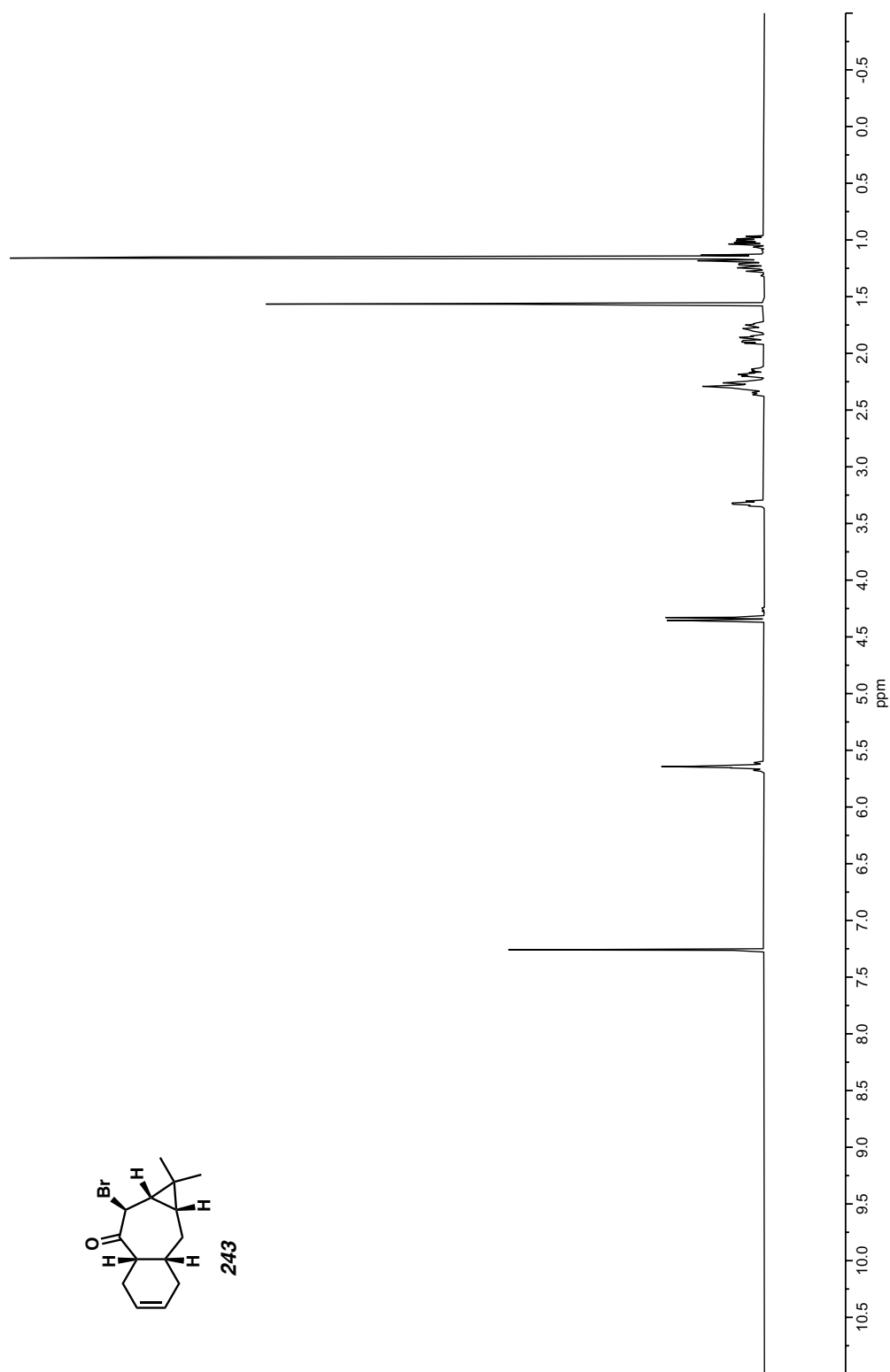


Figure A7.43 ^1H NMR (400 MHz, CDCl_3) of compound 243.

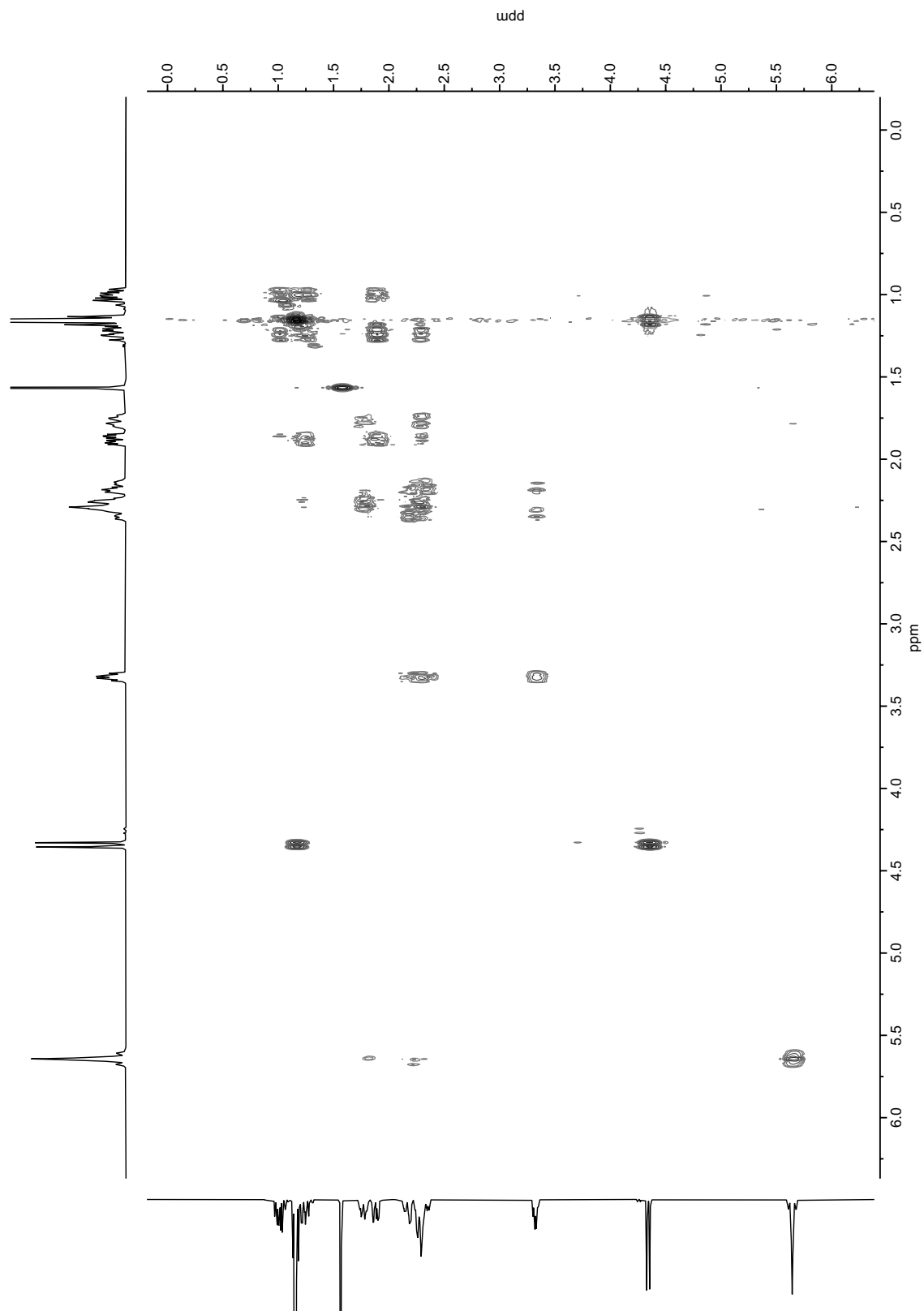


Figure A7.44 COSY NMR (400 MHz, CDCl_3) of compound 243.

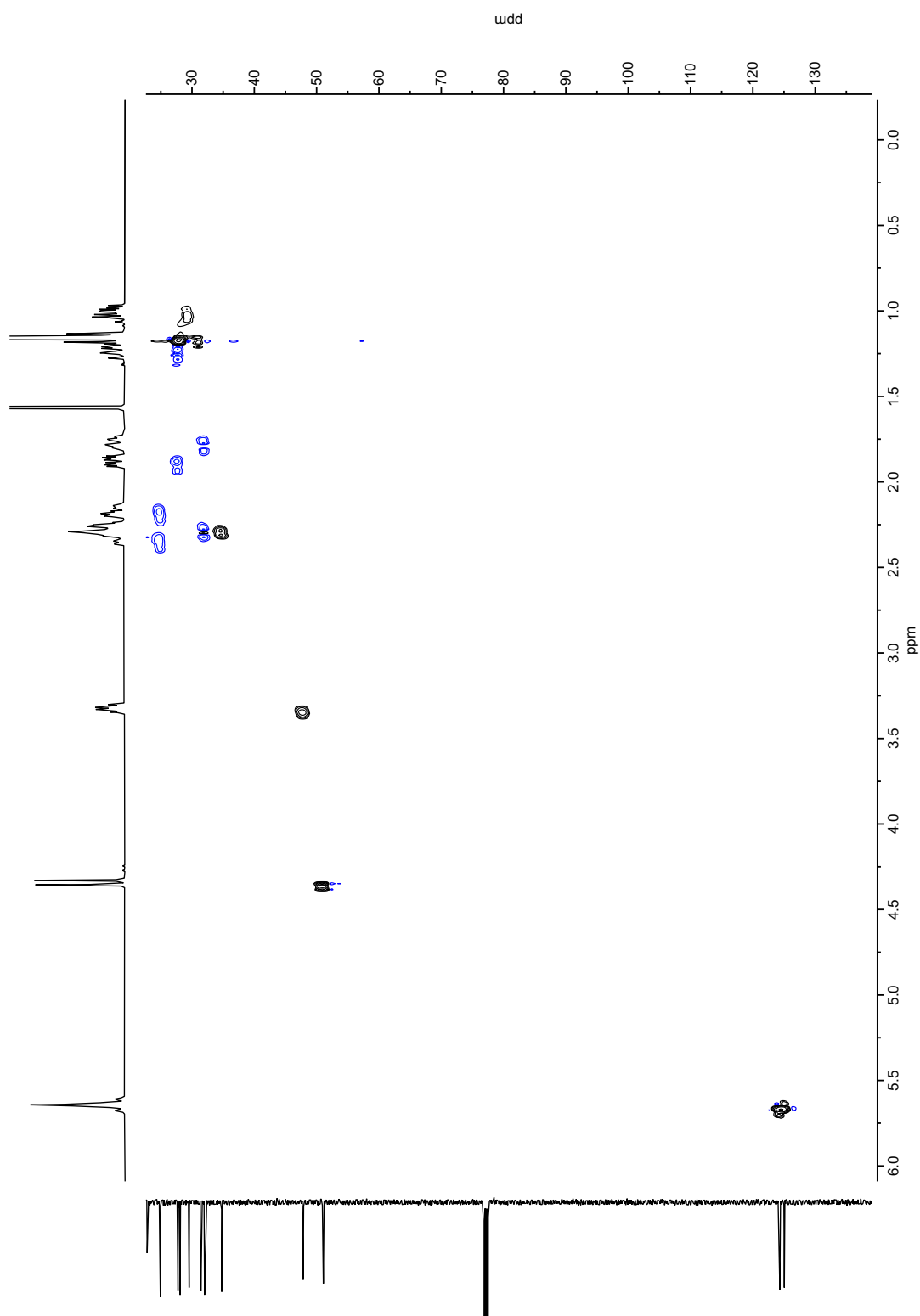


Figure A7.45 HSQC NMR (400 MHz, CDCl₃) of compound 243.

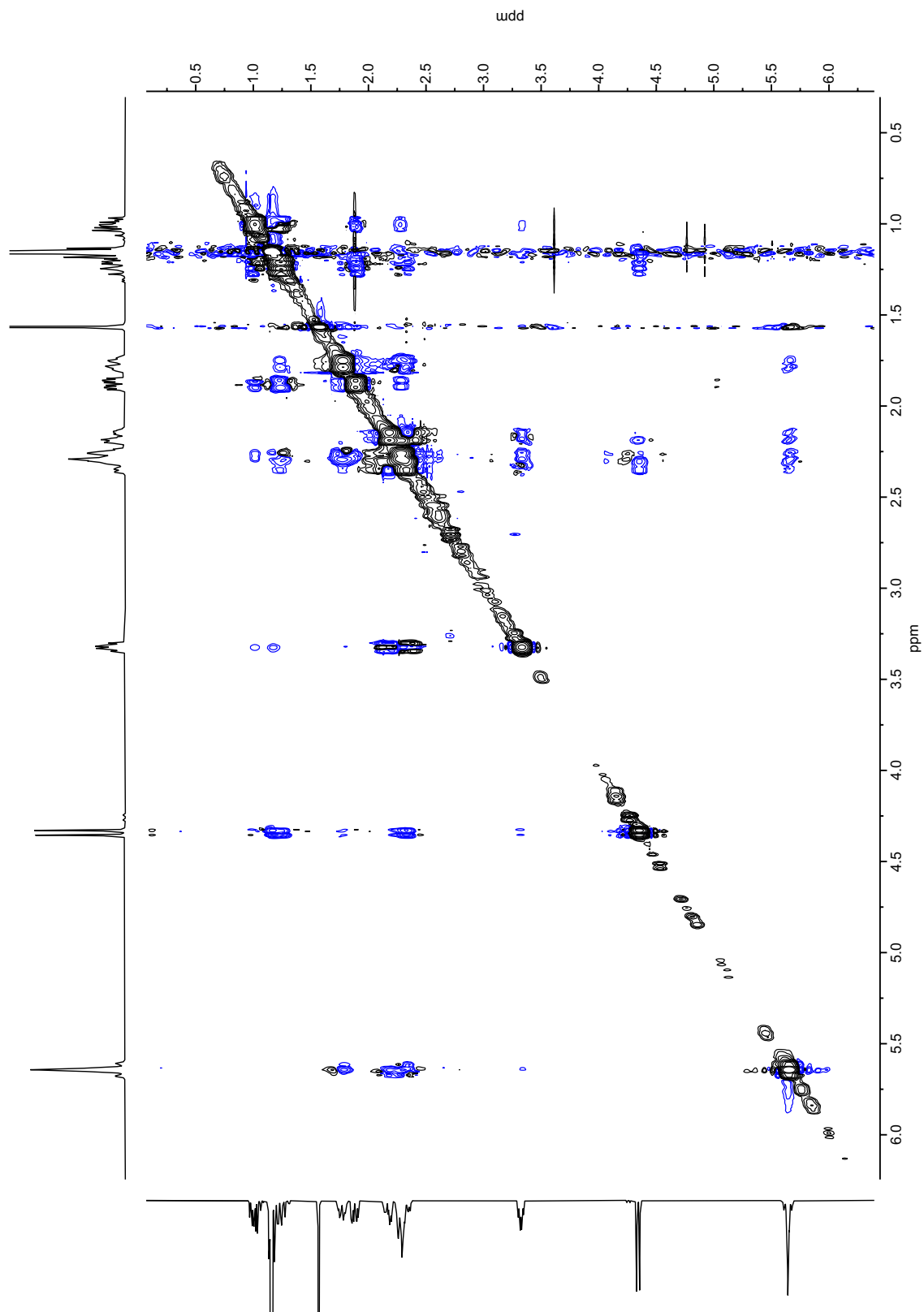


Figure A7.46 NOESY NMR (400 MHz, CDCl_3) of compound 243.

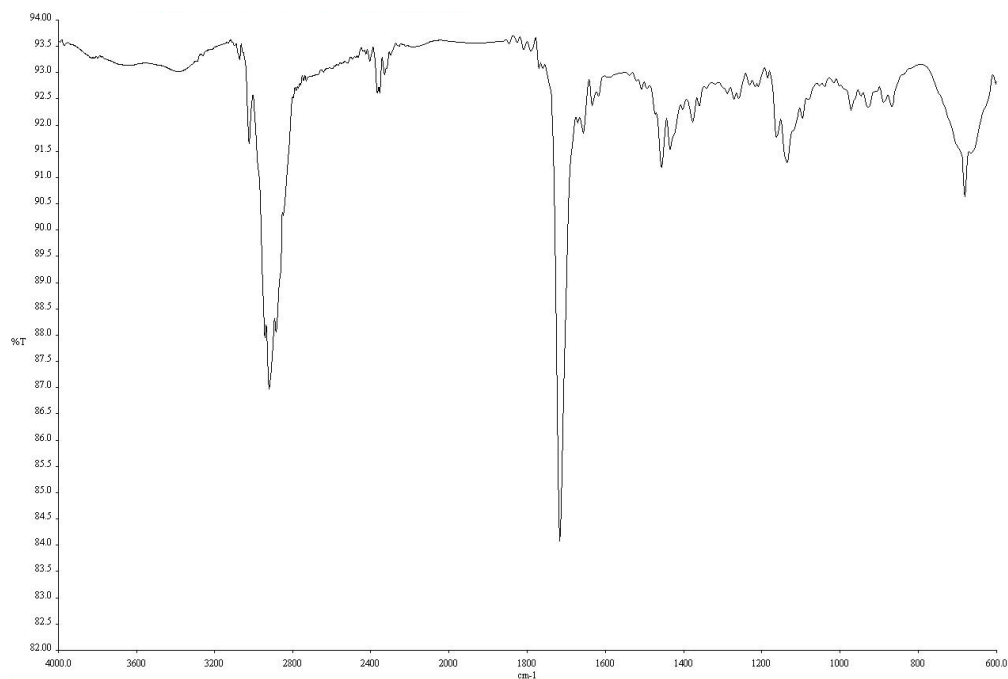


Figure A7.47 Infrared spectrum (Thin Film, NaCl) of compound **243**.

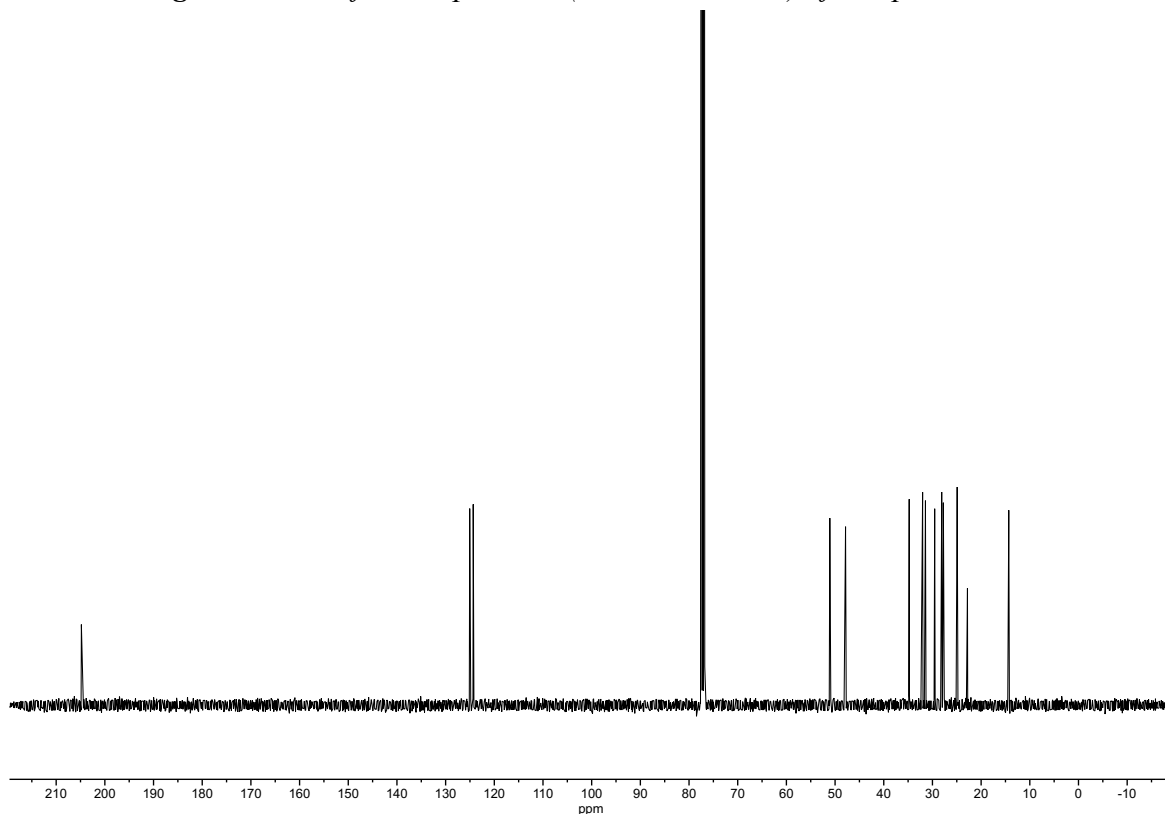


Figure A7.48 ¹³C NMR (100 MHz, CDCl₃) of compound **243**.

APPENDIX 8

X-Ray Crystallography Reports Relevant to Chapter 4:

On the Unexpected Formation of [2.2.1]- and [2.1.1]Homotriblattanes

A8.1 GENERAL EXPERIMENTAL INFORMATION

Low-temperature diffraction data (ϕ - and ω -scans) were collected on a Bruker AXS D8 VENTURE KAPPA diffractometer coupled to a PHOTON II CPAD detector with Cu K_α radiation ($\lambda = 1.54178 \text{ \AA}$) from an I μ S micro-source for the structure of compounds **236** and **255**. The structure was solved by direct methods using SHELXS¹ and refined against F^2 on all data by full-matrix least squares with SHELXL-2017² (for **236**) or SHELXL-2019² (for **255**) using established refinement techniques.³ All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms they are linked to (1.5 times for methyl groups). Software used for molecular graphics: Mercury 4.1.0.⁴

Compound **236** crystallizes in the orthorhombic space group $P2_12_12_1$ with one molecule in the asymmetric unit. The coordinates for the hydrogen atom bound to N1 were located in the difference Fourier synthesis and refined semi-freely with the help of a restraint on the N-H distance (0.91(4) $\text{\AA}$).

Compound **255** crystallizes in the orthorhombic space group $P2_12_12_1$ with one molecule in the asymmetric unit.

A8.2 X-RAY CRYSTAL STRUCTURE ANALYSIS OF 236

Hydrazine **236** was recrystallized by slow evaporation at 23 °C to provide suitable crystals for X-ray analysis.

Figure A8.2.1. X-ray crystal structure of **236**.

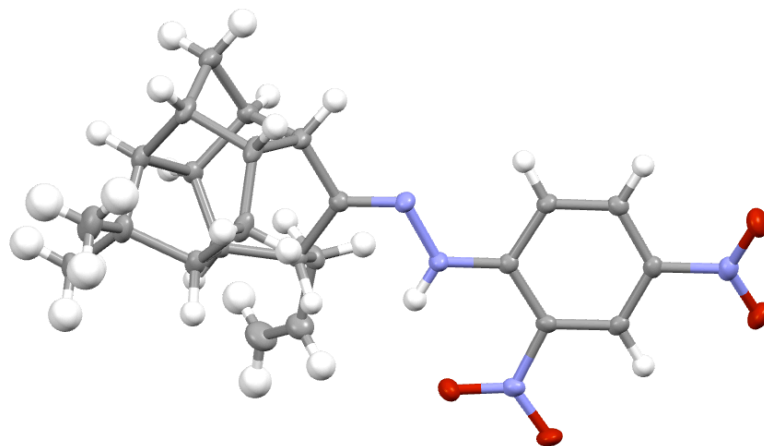


Table A8.2.1. Crystal data and structure refinement for **236** (CCDC# 2430670).

Identification code	V21331	
Empirical formula	C ₂₄ H ₂₈ N ₄ O ₄	
Formula weight	436.50	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2 ₁ 2 ₁ 2 ₁	
Unit cell dimensions	a = 7.6098(6) Å	a = 90°.
	b = 16.6020(16) Å	b = 90°.
	c = 17.229(2) Å	g = 90°.
Volume	2176.6(4) Å ³	
Z	4	
Density (calculated)	1.332 Mg/m ³	
Absorption coefficient	0.751 mm ⁻¹	
F(000)	928	
Crystal size	0.250 x 0.150 x 0.150 mm ³	
Theta range for data collection	3.697 to 74.373°.	

Index ranges	-9<=h<=9, -20<=k<=20, -20<=l<=21
Reflections collected	37438
Independent reflections	4456 [R(int) = 0.0459]
Completeness to theta = 67.679°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7538 and 0.6621
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	4456 / 1 / 294
Goodness-of-fit on F ²	1.037
Final R indices [I>2sigma(I)]	R1 = 0.0294, wR2 = 0.0763
R indices (all data)	R1 = 0.0305, wR2 = 0.0769
Absolute structure parameter	0.03(4)
Extinction coefficient	n/a
Largest diff. peak and hole	0.343 and -0.188 e.Å ⁻³

Table A8.2.2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **236**. $U(eq)$ is defined as one-third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
N(1)	3840(2)	6403(1)	6198(1)	18(1)
C(1)	4045(2)	7178(1)	5986(1)	15(1)
C(2)	2618(2)	7733(1)	5954(1)	16(1)
N(3)	844(2)	7506(1)	6155(1)	19(1)
O(1)	544(2)	6802(1)	6364(1)	25(1)
O(2)	-322(2)	8014(1)	6112(1)	29(1)
C(3)	2850(2)	8525(1)	5710(1)	17(1)
C(4)	4498(2)	8770(1)	5494(1)	17(1)
N(4)	4741(2)	9592(1)	5226(1)	20(1)
O(3)	3574(2)	10084(1)	5360(1)	31(1)
O(4)	6109(2)	9757(1)	4876(1)	30(1)
C(5)	5952(2)	8256(1)	5539(1)	16(1)

C(6)	5737(2)	7481(1)	5794(1)	16(1)
N(2)	5278(2)	5885(1)	6176(1)	18(1)
C(7)	5023(2)	5188(1)	6478(1)	17(1)
C(8)	3357(2)	4906(1)	6876(1)	16(1)
C(20)	3138(2)	5349(1)	7665(1)	21(1)
C(21)	1251(3)	5384(1)	7927(1)	29(1)
C(22)	667(3)	5148(1)	8603(1)	36(1)
C(9)	3376(2)	3989(1)	6985(1)	17(1)
C(10)	5086(2)	3656(1)	7371(1)	18(1)
C(11)	6767(2)	4176(1)	7241(1)	20(1)
C(12)	6533(2)	4615(1)	6464(1)	20(1)
C(13)	6312(2)	3882(1)	5888(1)	23(1)
C(14)	4419(3)	3798(1)	5594(1)	24(1)
C(15)	3176(2)	3489(1)	6230(1)	21(1)
C(16)	3762(3)	2638(1)	6496(1)	24(1)
C(23)	2453(3)	2266(1)	7073(1)	31(1)
C(24)	4023(3)	2030(1)	5833(1)	38(1)
C(17)	5476(2)	2862(1)	6909(1)	21(1)
C(18)	6980(3)	3152(1)	6384(1)	24(1)
C(19)	8159(2)	3553(1)	6994(1)	27(1)

Table A8.2.3. Bond lengths [$\text{\AA}$] and angles [$^\circ$] for **236**.

N(1)-C(1)	1.346(2)
N(1)-N(2)	1.3920(19)
N(1)-H(1N)	0.888(19)
C(1)-C(6)	1.421(2)
C(1)-C(2)	1.426(2)
C(2)-C(3)	1.391(2)
C(2)-N(3)	1.443(2)
N(3)-O(2)	1.2267(19)
N(3)-O(1)	1.244(2)
C(3)-C(4)	1.370(2)
C(3)-H(3)	0.9500

C(4)-C(5)	1.400(2)
C(4)-N(4)	1.454(2)
N(4)-O(3)	1.228(2)
N(4)-O(4)	1.234(2)
C(5)-C(6)	1.369(2)
C(5)-H(5)	0.9500
C(6)-H(6)	0.9500
N(2)-C(7)	1.284(2)
C(7)-C(12)	1.492(2)
C(7)-C(8)	1.516(2)
C(8)-C(9)	1.533(2)
C(8)-C(20)	1.555(2)
C(8)-H(8)	1.0000
C(20)-C(21)	1.506(3)
C(20)-H(20A)	0.9900
C(20)-H(20B)	0.9900
C(21)-C(22)	1.307(3)
C(21)-H(21)	0.9500
C(22)-H(22A)	0.9500
C(22)-H(22B)	0.9500
C(9)-C(15)	1.551(2)
C(9)-C(10)	1.563(2)
C(9)-H(9)	1.0000
C(10)-C(11)	1.559(2)
C(10)-C(17)	1.567(2)
C(10)-H(10)	1.0000
C(11)-C(12)	1.535(2)
C(11)-C(19)	1.540(3)
C(11)-H(11)	1.0000
C(12)-C(13)	1.579(2)
C(12)-H(12)	1.0000
C(13)-C(14)	1.533(3)
C(13)-C(18)	1.567(2)
C(13)-H(13)	1.0000
C(14)-C(15)	1.536(3)

C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900
C(15)-C(16)	1.550(2)
C(15)-H(15)	1.0000
C(16)-C(17)	1.532(3)
C(16)-C(24)	1.537(3)
C(16)-C(23)	1.537(3)
C(23)-H(23A)	0.9800
C(23)-H(23B)	0.9800
C(23)-H(23C)	0.9800
C(24)-H(24A)	0.9800
C(24)-H(24B)	0.9800
C(24)-H(24C)	0.9800
C(17)-C(18)	1.536(3)
C(17)-H(17)	1.0000
C(18)-C(19)	1.534(3)
C(18)-H(18)	1.0000
C(19)-H(19A)	0.9900
C(19)-H(19B)	0.9900

C(1)-N(1)-N(2)	119.45(14)
C(1)-N(1)-H(1N)	119.8(15)
N(2)-N(1)-H(1N)	120.6(15)
N(1)-C(1)-C(6)	120.43(14)
N(1)-C(1)-C(2)	122.70(15)
C(6)-C(1)-C(2)	116.86(14)
C(3)-C(2)-C(1)	121.72(15)
C(3)-C(2)-N(3)	115.96(14)
C(1)-C(2)-N(3)	122.30(14)
O(2)-N(3)-O(1)	122.03(14)
O(2)-N(3)-C(2)	118.87(14)
O(1)-N(3)-C(2)	119.10(13)
C(4)-C(3)-C(2)	118.62(15)
C(4)-C(3)-H(3)	120.7
C(2)-C(3)-H(3)	120.7

C(3)-C(4)-C(5)	121.86(15)
C(3)-C(4)-N(4)	118.81(15)
C(5)-C(4)-N(4)	119.32(15)
O(3)-N(4)-O(4)	123.76(15)
O(3)-N(4)-C(4)	118.15(15)
O(4)-N(4)-C(4)	118.09(14)
C(6)-C(5)-C(4)	119.71(15)
C(6)-C(5)-H(5)	120.1
C(4)-C(5)-H(5)	120.1
C(5)-C(6)-C(1)	121.07(15)
C(5)-C(6)-H(6)	119.5
C(1)-C(6)-H(6)	119.5
C(7)-N(2)-N(1)	115.29(14)
N(2)-C(7)-C(12)	116.88(14)
N(2)-C(7)-C(8)	126.04(14)
C(12)-C(7)-C(8)	117.03(14)
C(7)-C(8)-C(9)	110.76(13)
C(7)-C(8)-C(20)	109.82(13)
C(9)-C(8)-C(20)	111.27(14)
C(7)-C(8)-H(8)	108.3
C(9)-C(8)-H(8)	108.3
C(20)-C(8)-H(8)	108.3
C(21)-C(20)-C(8)	112.54(15)
C(21)-C(20)-H(20A)	109.1
C(8)-C(20)-H(20A)	109.1
C(21)-C(20)-H(20B)	109.1
C(8)-C(20)-H(20B)	109.1
H(20A)-C(20)-H(20B)	107.8
C(22)-C(21)-C(20)	125.4(2)
C(22)-C(21)-H(21)	117.3
C(20)-C(21)-H(21)	117.3
C(21)-C(22)-H(22A)	120.0
C(21)-C(22)-H(22B)	120.0
H(22A)-C(22)-H(22B)	120.0
C(8)-C(9)-C(15)	115.33(14)

C(8)-C(9)-C(10)	114.30(13)
C(15)-C(9)-C(10)	104.39(13)
C(8)-C(9)-H(9)	107.5
C(15)-C(9)-H(9)	107.5
C(10)-C(9)-H(9)	107.5
C(11)-C(10)-C(9)	115.25(13)
C(11)-C(10)-C(17)	103.74(13)
C(9)-C(10)-C(17)	103.87(13)
C(11)-C(10)-H(10)	111.2
C(9)-C(10)-H(10)	111.2
C(17)-C(10)-H(10)	111.2
C(12)-C(11)-C(19)	99.03(14)
C(12)-C(11)-C(10)	107.00(13)
C(19)-C(11)-C(10)	103.43(14)
C(12)-C(11)-H(11)	115.2
C(19)-C(11)-H(11)	115.2
C(10)-C(11)-H(11)	115.2
C(7)-C(12)-C(11)	112.20(14)
C(7)-C(12)-C(13)	114.81(15)
C(11)-C(12)-C(13)	101.22(13)
C(7)-C(12)-H(12)	109.4
C(11)-C(12)-H(12)	109.4
C(13)-C(12)-H(12)	109.4
C(14)-C(13)-C(18)	114.49(15)
C(14)-C(13)-C(12)	112.19(14)
C(18)-C(13)-C(12)	102.64(14)
C(14)-C(13)-H(13)	109.1
C(18)-C(13)-H(13)	109.1
C(12)-C(13)-H(13)	109.1
C(13)-C(14)-C(15)	111.92(14)
C(13)-C(14)-H(14A)	109.2
C(15)-C(14)-H(14A)	109.2
C(13)-C(14)-H(14B)	109.2
C(15)-C(14)-H(14B)	109.2
H(14A)-C(14)-H(14B)	107.9

C(14)-C(15)-C(16)	109.74(15)
C(14)-C(15)-C(9)	111.02(14)
C(16)-C(15)-C(9)	102.27(13)
C(14)-C(15)-H(15)	111.2
C(16)-C(15)-H(15)	111.2
C(9)-C(15)-H(15)	111.2
C(17)-C(16)-C(24)	113.30(17)
C(17)-C(16)-C(23)	110.38(15)
C(24)-C(16)-C(23)	107.49(16)
C(17)-C(16)-C(15)	99.26(13)
C(24)-C(16)-C(15)	114.59(15)
C(23)-C(16)-C(15)	111.74(16)
C(16)-C(23)-H(23A)	109.5
C(16)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
C(16)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
C(16)-C(24)-H(24A)	109.5
C(16)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
C(16)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
C(16)-C(17)-C(18)	115.84(15)
C(16)-C(17)-C(10)	106.22(14)
C(18)-C(17)-C(10)	100.19(14)
C(16)-C(17)-H(17)	111.3
C(18)-C(17)-H(17)	111.3
C(10)-C(17)-H(17)	111.3
C(19)-C(18)-C(17)	99.69(15)
C(19)-C(18)-C(13)	103.13(15)
C(17)-C(18)-C(13)	108.76(15)
C(19)-C(18)-H(18)	114.6
C(17)-C(18)-H(18)	114.6

C(13)-C(18)-H(18)	114.6
C(18)-C(19)-C(11)	94.51(14)
C(18)-C(19)-H(19A)	112.8
C(11)-C(19)-H(19A)	112.8
C(18)-C(19)-H(19B)	112.8
C(11)-C(19)-H(19B)	112.8
H(19A)-C(19)-H(19B)	110.3

Symmetry transformations used to generate equivalent atoms:

Table 8.2.4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **236**. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$.

Atom	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
N(1)	15(1)	16(1)	25(1)	1(1)	3(1)	1(1)
C(1)	17(1)	16(1)	13(1)	-2(1)	-1(1)	1(1)
C(2)	14(1)	19(1)	17(1)	-2(1)	-2(1)	0(1)
N(3)	15(1)	21(1)	21(1)	-2(1)	-2(1)	1(1)
O(1)	19(1)	21(1)	36(1)	2(1)	4(1)	-2(1)
O(2)	14(1)	28(1)	45(1)	5(1)	-2(1)	5(1)
C(3)	18(1)	17(1)	16(1)	-3(1)	-5(1)	3(1)
C(4)	21(1)	16(1)	14(1)	0(1)	-2(1)	-1(1)
N(4)	25(1)	17(1)	19(1)	0(1)	-3(1)	0(1)
O(3)	31(1)	18(1)	43(1)	4(1)	-2(1)	6(1)
O(4)	32(1)	25(1)	33(1)	7(1)	6(1)	-4(1)
C(5)	16(1)	20(1)	14(1)	-2(1)	0(1)	-1(1)
C(6)	16(1)	17(1)	16(1)	-2(1)	0(1)	3(1)
N(2)	17(1)	17(1)	22(1)	0(1)	2(1)	4(1)
C(7)	17(1)	17(1)	16(1)	-1(1)	1(1)	0(1)
C(8)	16(1)	17(1)	17(1)	-1(1)	0(1)	0(1)
C(20)	23(1)	21(1)	21(1)	-4(1)	4(1)	-4(1)

C(21)	26(1)	31(1)	28(1)	-4(1)	6(1)	1(1)
C(22)	31(1)	43(1)	33(1)	-3(1)	11(1)	-3(1)
C(9)	18(1)	18(1)	15(1)	0(1)	-1(1)	-2(1)
C(10)	20(1)	19(1)	15(1)	2(1)	-1(1)	-1(1)
C(11)	18(1)	21(1)	21(1)	4(1)	-2(1)	0(1)
C(12)	18(1)	19(1)	24(1)	3(1)	5(1)	3(1)
C(13)	31(1)	18(1)	20(1)	4(1)	8(1)	7(1)
C(14)	40(1)	18(1)	14(1)	0(1)	-2(1)	7(1)
C(15)	27(1)	17(1)	19(1)	-2(1)	-6(1)	0(1)
C(16)	34(1)	16(1)	23(1)	0(1)	-4(1)	0(1)
C(23)	35(1)	18(1)	39(1)	4(1)	-4(1)	-6(1)
C(24)	58(1)	20(1)	35(1)	-6(1)	-10(1)	4(1)
C(17)	27(1)	16(1)	19(1)	4(1)	-1(1)	2(1)
C(18)	30(1)	18(1)	24(1)	4(1)	6(1)	9(1)
C(19)	21(1)	26(1)	34(1)	10(1)	1(1)	5(1)

Table A8.2.5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **236**.

Atom	x	y	z	U(eq)
H(1N)	2780(30)	6219(13)	6318(13)	22
H(3)	1886	8888	5693	20
H(5)	7084	8443	5393	20
H(6)	6734	7141	5844	20
H(8)	2335	5048	6538	20
H(20A)	3844	5067	8064	26
H(20B)	3599	5904	7616	26
H(21)	417	5597	7572	34
H(22A)	1458	4931	8976	43
H(22B)	-548	5192	8722	43

H(9)	2369	3847	7332	20
H(10)	4899	3542	7934	22
H(11)	7109	4527	7688	24
H(12)	7635	4914	6334	24
H(13)	7114	3959	5434	27
H(14A)	4396	3420	5150	29
H(14B)	3999	4328	5408	29
H(15)	1929	3485	6047	25
H(23A)	2895	1742	7247	46
H(23B)	1312	2194	6818	46
H(23C)	2318	2624	7521	46
H(24A)	4936	2228	5480	57
H(24B)	2918	1966	5547	57
H(24C)	4382	1510	6049	57
H(17)	5874	2422	7264	25
H(18)	7564	2716	6078	29
H(19A)	9220	3805	6766	33
H(19B)	8493	3183	7420	33

Table A8.2.6. Torsion angles [$^{\circ}$] for **236**.

N(2)-N(1)-C(1)-C(6)	-4.5(2)
N(2)-N(1)-C(1)-C(2)	176.63(14)
N(1)-C(1)-C(2)-C(3)	-177.89(16)
C(6)-C(1)-C(2)-C(3)	3.2(2)
N(1)-C(1)-C(2)-N(3)	0.5(2)
C(6)-C(1)-C(2)-N(3)	-178.37(15)
C(3)-C(2)-N(3)-O(2)	-1.3(2)
C(1)-C(2)-N(3)-O(2)	-179.76(15)
C(3)-C(2)-N(3)-O(1)	178.66(15)
C(1)-C(2)-N(3)-O(1)	0.2(2)
C(1)-C(2)-C(3)-C(4)	0.1(2)
N(3)-C(2)-C(3)-C(4)	-178.44(15)
C(2)-C(3)-C(4)-C(5)	-2.3(2)

C(2)-C(3)-C(4)-N(4)	179.03(14)
C(3)-C(4)-N(4)-O(3)	15.7(2)
C(5)-C(4)-N(4)-O(3)	-163.03(16)
C(3)-C(4)-N(4)-O(4)	-164.25(15)
C(5)-C(4)-N(4)-O(4)	17.0(2)
C(3)-C(4)-C(5)-C(6)	1.0(2)
N(4)-C(4)-C(5)-C(6)	179.68(14)
C(4)-C(5)-C(6)-C(1)	2.6(2)
N(1)-C(1)-C(6)-C(5)	176.57(15)
C(2)-C(1)-C(6)-C(5)	-4.5(2)
C(1)-N(1)-N(2)-C(7)	171.66(15)
N(1)-N(2)-C(7)-C(12)	179.88(14)
N(1)-N(2)-C(7)-C(8)	-2.8(2)
N(2)-C(7)-C(8)-C(9)	166.32(16)
C(12)-C(7)-C(8)-C(9)	-16.3(2)
N(2)-C(7)-C(8)-C(20)	-70.4(2)
C(12)-C(7)-C(8)-C(20)	106.94(17)
C(7)-C(8)-C(20)-C(21)	155.54(15)
C(9)-C(8)-C(20)-C(21)	-81.47(19)
C(8)-C(20)-C(21)-C(22)	126.8(2)
C(7)-C(8)-C(9)-C(15)	-70.42(18)
C(20)-C(8)-C(9)-C(15)	167.13(14)
C(7)-C(8)-C(9)-C(10)	50.59(18)
C(20)-C(8)-C(9)-C(10)	-71.85(18)
C(8)-C(9)-C(10)-C(11)	-27.0(2)
C(15)-C(9)-C(10)-C(11)	99.93(16)
C(8)-C(9)-C(10)-C(17)	-139.73(14)
C(15)-C(9)-C(10)-C(17)	-12.84(16)
C(9)-C(10)-C(11)-C(12)	-28.46(19)
C(17)-C(10)-C(11)-C(12)	84.38(15)
C(9)-C(10)-C(11)-C(19)	-132.46(15)
C(17)-C(10)-C(11)-C(19)	-19.61(16)
N(2)-C(7)-C(12)-C(11)	135.89(16)
C(8)-C(7)-C(12)-C(11)	-41.7(2)
N(2)-C(7)-C(12)-C(13)	-109.26(18)

C(8)-C(7)-C(12)-C(13)	73.16(19)
C(19)-C(11)-C(12)-C(7)	170.89(14)
C(10)-C(11)-C(12)-C(7)	63.76(18)
C(19)-C(11)-C(12)-C(13)	48.00(16)
C(10)-C(11)-C(12)-C(13)	-59.13(16)
C(7)-C(12)-C(13)-C(14)	-13.1(2)
C(11)-C(12)-C(13)-C(14)	108.00(15)
C(7)-C(12)-C(13)-C(18)	-136.46(15)
C(11)-C(12)-C(13)-C(18)	-15.39(17)
C(18)-C(13)-C(14)-C(15)	44.5(2)
C(12)-C(13)-C(14)-C(15)	-71.99(18)
C(13)-C(14)-C(15)-C(16)	-61.89(18)
C(13)-C(14)-C(15)-C(9)	50.43(19)
C(8)-C(9)-C(15)-C(14)	47.8(2)
C(10)-C(9)-C(15)-C(14)	-78.49(16)
C(8)-C(9)-C(15)-C(16)	164.76(15)
C(10)-C(9)-C(15)-C(16)	38.51(17)
C(14)-C(15)-C(16)-C(17)	69.34(16)
C(9)-C(15)-C(16)-C(17)	-48.57(16)
C(14)-C(15)-C(16)-C(24)	-51.7(2)
C(9)-C(15)-C(16)-C(24)	-169.59(17)
C(14)-C(15)-C(16)-C(23)	-174.24(15)
C(9)-C(15)-C(16)-C(23)	67.85(18)
C(24)-C(16)-C(17)-C(18)	52.7(2)
C(23)-C(16)-C(17)-C(18)	173.29(15)
C(15)-C(16)-C(17)-C(18)	-69.27(18)
C(24)-C(16)-C(17)-C(10)	162.90(15)
C(23)-C(16)-C(17)-C(10)	-76.50(17)
C(15)-C(16)-C(17)-C(10)	40.95(16)
C(11)-C(10)-C(17)-C(16)	-138.62(14)
C(9)-C(10)-C(17)-C(16)	-17.78(16)
C(11)-C(10)-C(17)-C(18)	-17.72(16)
C(9)-C(10)-C(17)-C(18)	103.12(15)
C(16)-C(17)-C(18)-C(19)	163.10(15)
C(10)-C(17)-C(18)-C(19)	49.38(15)

C(16)-C(17)-C(18)-C(13)	55.6(2)
C(10)-C(17)-C(18)-C(13)	-58.16(17)
C(14)-C(13)-C(18)-C(19)	-144.46(15)
C(12)-C(13)-C(18)-C(19)	-22.62(17)
C(14)-C(13)-C(18)-C(17)	-39.3(2)
C(12)-C(13)-C(18)-C(17)	82.55(17)
C(17)-C(18)-C(19)-C(11)	-60.85(15)
C(13)-C(18)-C(19)-C(11)	51.16(16)
C(12)-C(11)-C(19)-C(18)	-61.39(15)
C(10)-C(11)-C(19)-C(18)	48.63(15)

Symmetry transformations used to generate equivalent atoms:

Table A8.2.7. *Hydrogen bonds for 236 [$\text{\AA}$ and $^\circ$].*

D-H...A	d(D-H)	d(H...A)	d(D...A)	$\angle(\text{DHA})$
N(1)-H(1N)...O(1)	0.888(19)	1.96(2)	2.6098(19)	129.0(19)
C(5)-H(5)...O(2)#1	0.95	2.44	3.029(2)	120.3
C(8)-H(8)...O(4)#2	1.00	2.63	3.513(2)	147.7

Symmetry transformations used to generate equivalent atoms:

#1 $x+1, y, z$ #2 $x-1/2, -y+3/2, -z+1$

A8.3 X-RAY CRYSTAL STRUCTURE ANALYSIS OF 255

Ketone **255** was recrystallized by slow evaporation from CH₂Cl₂ at 4 °C to provide suitable crystals for X-ray analysis.

Figure A8.3.1. X-ray crystal structure of **255**.

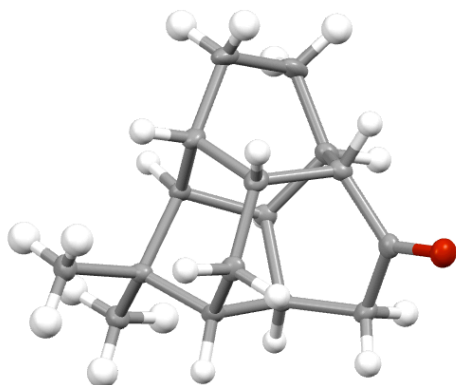


Table A8.3.1. Crystal data and structure refinement for **255** (CCDC# 2430671).

Identification code	V25098	
Empirical formula	C ₁₆ H ₂₂ O	
Formula weight	230.33	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2 ₁ 2 ₁ 2 ₁	
Unit cell dimensions	a = 8.0806(8) Å	a = 90°.
	b = 11.9089(11) Å	b = 90°.
	c = 12.6284(10) Å	c = 90°.

Volume	1215.24(19) Å ³
Z	4
Density (calculated)	1.259 Mg/m ³
Absorption coefficient	0.578 mm ⁻¹
F(000)	504
Crystal size	0.300 x 0.300 x 0.200 mm ³
Theta range for data collection	5.105 to 74.416°.
Index ranges	-10<=h<=9, -14<=k<=14, -15<=l<=14
Reflections collected	16253
Independent reflections	2480 [R(int) = 0.0621]
Completeness to theta = 67.679°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7538 and 0.5044
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	2480 / 0 / 156
Goodness-of-fit on F ²	1.045
Final R indices [I>2sigma(I)]	R1 = 0.0454, wR2 = 0.1193
R indices (all data)	R1 = 0.0464, wR2 = 0.1199
Absolute structure parameter	-0.1(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.271 and -0.301 e.Å ⁻³

Table A8.3.2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **255**. $U(eq)$ is defined as one-third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
C(1)	6329(3)	7818(2)	3103(2)	16(1)
C(2)	8056(3)	7279(2)	3196(2)	17(1)
C(3)	8157(3)	6332(2)	4063(2)	16(1)

C(4)	6735(3)	6440(2)	4829(2)	16(1)
O(1)	6878(2)	6827(1)	5712(1)	23(1)
C(5)	5112(3)	5989(2)	4407(2)	17(1)
C(6)	5062(3)	5884(2)	3194(2)	14(1)
C(7)	5039(3)	7024(2)	2614(2)	15(1)
C(8)	5570(3)	6693(2)	1478(2)	15(1)
C(15)	4283(3)	5933(2)	942(2)	18(1)
C(16)	5833(3)	7688(2)	728(2)	21(1)
C(9)	7136(2)	6009(2)	1743(2)	14(1)
C(10)	8575(3)	6753(2)	2126(2)	17(1)
C(11)	10119(3)	6019(2)	2270(2)	23(1)
C(12)	9658(3)	4960(2)	2905(2)	23(1)
C(13)	8038(3)	5184(2)	3498(2)	17(1)
C(14)	6599(3)	5262(2)	2706(2)	14(1)

Table A8.3.3. Bond lengths [$\text{\AA}$] and angles [$^\circ$] for **255**.

C(1)-C(7)	1.537(3)
C(1)-C(2)	1.540(3)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(2)-C(10)	1.547(3)
C(2)-C(3)	1.574(3)
C(2)-H(2)	1.0000
C(3)-C(4)	1.507(3)
C(3)-C(13)	1.546(3)
C(3)-H(3)	1.0000
C(4)-O(1)	1.212(3)
C(4)-C(5)	1.514(3)
C(5)-C(6)	1.538(3)

C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-C(7)	1.542(3)
C(6)-C(14)	1.573(3)
C(6)-H(6)	1.0000
C(7)-C(8)	1.548(3)
C(7)-H(7)	1.0000
C(8)-C(16)	1.532(3)
C(8)-C(15)	1.536(3)
C(8)-C(9)	1.541(3)
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
C(9)-C(10)	1.539(3)
C(9)-C(14)	1.568(3)
C(9)-H(9)	1.0000
C(10)-C(11)	1.534(3)
C(10)-H(10)	1.0000
C(11)-C(12)	1.541(4)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(13)	1.532(3)
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-C(14)	1.536(3)
C(13)-H(13)	1.0000
C(14)-H(14)	1.0000
C(7)-C(1)-C(2)	112.89(17)
C(7)-C(1)-H(1A)	109.0
C(2)-C(1)-H(1A)	109.0
C(7)-C(1)-H(1B)	109.0

C(2)-C(1)-H(1B)	109.0
H(1A)-C(1)-H(1B)	107.8
C(1)-C(2)-C(10)	110.32(17)
C(1)-C(2)-C(3)	113.51(17)
C(10)-C(2)-C(3)	107.68(17)
C(1)-C(2)-H(2)	108.4
C(10)-C(2)-H(2)	108.4
C(3)-C(2)-H(2)	108.4
C(4)-C(3)-C(13)	108.95(18)
C(4)-C(3)-C(2)	110.23(17)
C(13)-C(3)-C(2)	108.00(16)
C(4)-C(3)-H(3)	109.9
C(13)-C(3)-H(3)	109.9
C(2)-C(3)-H(3)	109.9
O(1)-C(4)-C(3)	123.4(2)
O(1)-C(4)-C(5)	122.8(2)
C(3)-C(4)-C(5)	113.83(18)
C(4)-C(5)-C(6)	113.72(18)
C(4)-C(5)-H(5A)	108.8
C(6)-C(5)-H(5A)	108.8
C(4)-C(5)-H(5B)	108.8
C(6)-C(5)-H(5B)	108.8
H(5A)-C(5)-H(5B)	107.7
C(5)-C(6)-C(7)	113.74(17)
C(5)-C(6)-C(14)	114.07(18)
C(7)-C(6)-C(14)	103.77(16)
C(5)-C(6)-H(6)	108.3
C(7)-C(6)-H(6)	108.3
C(14)-C(6)-H(6)	108.3
C(1)-C(7)-C(6)	110.02(17)
C(1)-C(7)-C(8)	109.91(17)
C(6)-C(7)-C(8)	102.29(16)
C(1)-C(7)-H(7)	111.4
C(6)-C(7)-H(7)	111.4
C(8)-C(7)-H(7)	111.4

C(16)-C(8)-C(15)	106.06(17)
C(16)-C(8)-C(9)	115.42(18)
C(15)-C(8)-C(9)	109.91(18)
C(16)-C(8)-C(7)	114.48(18)
C(15)-C(8)-C(7)	111.75(17)
C(9)-C(8)-C(7)	99.28(16)
C(8)-C(15)-H(15A)	109.5
C(8)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
C(8)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
C(8)-C(16)-H(16A)	109.5
C(8)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
C(8)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
C(10)-C(9)-C(8)	112.59(17)
C(10)-C(9)-C(14)	106.97(17)
C(8)-C(9)-C(14)	103.94(16)
C(10)-C(9)-H(9)	111.0
C(8)-C(9)-H(9)	111.0
C(14)-C(9)-H(9)	111.0
C(11)-C(10)-C(9)	108.90(19)
C(11)-C(10)-C(2)	110.33(17)
C(9)-C(10)-C(2)	107.61(17)
C(11)-C(10)-H(10)	110.0
C(9)-C(10)-H(10)	110.0
C(2)-C(10)-H(10)	110.0
C(10)-C(11)-C(12)	109.37(18)
C(10)-C(11)-H(11A)	109.8
C(12)-C(11)-H(11A)	109.8
C(10)-C(11)-H(11B)	109.8
C(12)-C(11)-H(11B)	109.8

H(11A)-C(11)-H(11B)	108.2
C(13)-C(12)-C(11)	108.56(18)
C(13)-C(12)-H(12A)	110.0
C(11)-C(12)-H(12A)	110.0
C(13)-C(12)-H(12B)	110.0
C(11)-C(12)-H(12B)	110.0
H(12A)-C(12)-H(12B)	108.4
C(12)-C(13)-C(14)	109.84(17)
C(12)-C(13)-C(3)	109.07(18)
C(14)-C(13)-C(3)	107.11(17)
C(12)-C(13)-H(13)	110.3
C(14)-C(13)-H(13)	110.3
C(3)-C(13)-H(13)	110.3
C(13)-C(14)-C(9)	109.24(17)
C(13)-C(14)-C(6)	111.80(17)
C(9)-C(14)-C(6)	104.77(16)
C(13)-C(14)-H(14)	110.3
C(9)-C(14)-H(14)	110.3
C(6)-C(14)-H(14)	110.3

Symmetry transformations used to generate equivalent atoms:

Table A8.3.4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **255**. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + \dots + 2 h k a^* b^* U^{12}]$.

Atom	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
C(1)	20(1)	10(1)	19(1)	0(1)	2(1)	1(1)
C(2)	16(1)	16(1)	19(1)	-1(1)	1(1)	-5(1)
C(3)	14(1)	18(1)	17(1)	-1(1)	-2(1)	1(1)
C(4)	19(1)	12(1)	16(1)	3(1)	0(1)	1(1)
O(1)	26(1)	25(1)	18(1)	-4(1)	0(1)	0(1)

C(5)	16(1)	17(1)	19(1)	2(1)	4(1)	-1(1)
C(6)	12(1)	13(1)	18(1)	1(1)	1(1)	-1(1)
C(7)	14(1)	12(1)	18(1)	2(1)	3(1)	2(1)
C(8)	12(1)	16(1)	18(1)	2(1)	1(1)	1(1)
C(15)	16(1)	21(1)	18(1)	1(1)	-1(1)	-1(1)
C(16)	22(1)	20(1)	20(1)	5(1)	1(1)	0(1)
C(9)	12(1)	16(1)	14(1)	-1(1)	1(1)	2(1)
C(10)	13(1)	21(1)	17(1)	1(1)	2(1)	-3(1)
C(11)	12(1)	38(1)	20(1)	-4(1)	2(1)	3(1)
C(12)	17(1)	30(1)	21(1)	-4(1)	-2(1)	11(1)
C(13)	17(1)	15(1)	18(1)	-1(1)	-2(1)	3(1)
C(14)	15(1)	11(1)	18(1)	-1(1)	0(1)	1(1)

Table A8.3.5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **255**.

	x	y	z	U(eq)
H(1A)	5950	8048	3816	20
H(1B)	6412	8502	2661	20
H(2)	8870	7880	3382	20
H(3)	9231	6387	4453	19
H(5A)	4206	6492	4638	21
H(5B)	4908	5240	4722	21
H(6)	4041	5460	2994	17
H(7)	3909	7366	2621	18
H(15A)	3223	6330	896	28
H(15B)	4142	5246	1359	28
H(15C)	4662	5738	228	28
H(16A)	6245	7414	45	31
H(16B)	6641	8206	1037	31

H(16C)	4780	8080	622	31
H(9)	7481	5535	1128	17
H(10)	8800	7358	1596	20
H(11A)	10984	6447	2652	28
H(11B)	10565	5802	1569	28
H(12A)	9520	4314	2420	28
H(12B)	10549	4778	3415	28
H(13)	7824	4573	4024	20
H(14)	6276	4495	2458	17

Table A8.3.6. Torsion angles [$^{\circ}$] for **255**.

C(7)-C(1)-C(2)-C(10)	50.4(2)
C(7)-C(1)-C(2)-C(3)	-70.6(2)
C(1)-C(2)-C(3)-C(4)	-18.8(2)
C(10)-C(2)-C(3)-C(4)	-141.19(18)
C(1)-C(2)-C(3)-C(13)	100.1(2)
C(10)-C(2)-C(3)-C(13)	-22.3(2)
C(13)-C(3)-C(4)-O(1)	138.2(2)
C(2)-C(3)-C(4)-O(1)	-103.4(2)
C(13)-C(3)-C(4)-C(5)	-40.1(2)
C(2)-C(3)-C(4)-C(5)	78.2(2)
O(1)-C(4)-C(5)-C(6)	162.0(2)
C(3)-C(4)-C(5)-C(6)	-19.7(3)
C(4)-C(5)-C(6)-C(7)	-69.3(2)
C(4)-C(5)-C(6)-C(14)	49.5(2)
C(2)-C(1)-C(7)-C(6)	50.8(2)
C(2)-C(1)-C(7)-C(8)	-61.1(2)
C(5)-C(6)-C(7)-C(1)	45.2(2)
C(14)-C(6)-C(7)-C(1)	-79.27(19)
C(5)-C(6)-C(7)-C(8)	162.00(18)
C(14)-C(6)-C(7)-C(8)	37.5(2)
C(1)-C(7)-C(8)-C(16)	-57.3(2)
C(6)-C(7)-C(8)-C(16)	-174.13(17)
C(1)-C(7)-C(8)-C(15)	-177.88(17)

C(6)-C(7)-C(8)-C(15)	65.3(2)
C(1)-C(7)-C(8)-C(9)	66.23(19)
C(6)-C(7)-C(8)-C(9)	-50.61(18)
C(16)-C(8)-C(9)-C(10)	51.4(2)
C(15)-C(8)-C(9)-C(10)	171.27(17)
C(7)-C(8)-C(9)-C(10)	-71.4(2)
C(16)-C(8)-C(9)-C(14)	166.82(18)
C(15)-C(8)-C(9)-C(14)	-73.33(19)
C(7)-C(8)-C(9)-C(14)	43.97(18)
C(8)-C(9)-C(10)-C(11)	-174.77(16)
C(14)-C(9)-C(10)-C(11)	71.7(2)
C(8)-C(9)-C(10)-C(2)	65.6(2)
C(14)-C(9)-C(10)-C(2)	-47.9(2)
C(1)-C(2)-C(10)-C(11)	-168.78(18)
C(3)-C(2)-C(10)-C(11)	-44.4(2)
C(1)-C(2)-C(10)-C(9)	-50.1(2)
C(3)-C(2)-C(10)-C(9)	74.3(2)
C(9)-C(10)-C(11)-C(12)	-48.0(2)
C(2)-C(10)-C(11)-C(12)	69.9(2)
C(10)-C(11)-C(12)-C(13)	-19.7(2)
C(11)-C(12)-C(13)-C(14)	69.4(2)
C(11)-C(12)-C(13)-C(3)	-47.7(2)
C(4)-C(3)-C(13)-C(12)	-167.89(17)
C(2)-C(3)-C(13)-C(12)	72.4(2)
C(4)-C(3)-C(13)-C(14)	73.3(2)
C(2)-C(3)-C(13)-C(14)	-46.4(2)
C(12)-C(13)-C(14)-C(9)	-44.9(2)
C(3)-C(13)-C(14)-C(9)	73.4(2)
C(12)-C(13)-C(14)-C(6)	-160.43(18)
C(3)-C(13)-C(14)-C(6)	-42.1(2)
C(10)-C(9)-C(14)-C(13)	-22.0(2)
C(8)-C(9)-C(14)-C(13)	-141.30(17)
C(10)-C(9)-C(14)-C(6)	97.94(19)
C(8)-C(9)-C(14)-C(6)	-21.4(2)
C(5)-C(6)-C(14)-C(13)	-16.0(2)

C(7)-C(6)-C(14)-C(13)	108.30(18)
C(5)-C(6)-C(14)-C(9)	-134.19(18)
C(7)-C(6)-C(14)-C(9)	-9.9(2)

Symmetry transformations used to generate equivalent atoms:

A8.4 REFERENCES AND NOTES

- (1) Sheldrick, G. M. Phase Annealing in SHELX-90: Direct Methods for Larger Structures. *Acta Cryst.* **1990**, *A46*, 467-473.
- (2) Sheldrick, G. M. Crystal structure refinement with SHELXL. *Acta Cryst.* **2015**, *C71*, 3–8.
- (3) Müller, P. Practical suggestions for better crystal structures. *Crystallography Reviews* **2009**, *15*, 57-83.
- (4) Mercury Software from CCDC: <http://www.ccdc.cam.ac.uk/Solutions/CSDSystem/Pages/Mercury.aspx>.

CHAPTER 5

A Modular Cyclopentene Annulation[†]

5.1 INTRODUCTION

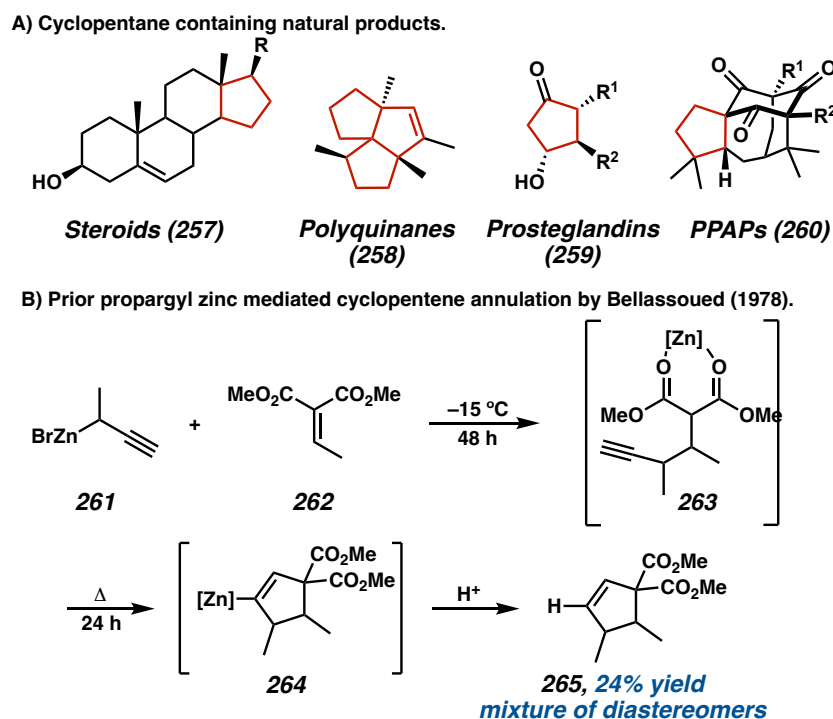
Reactions that construct complex, substituted carbocyclic ring systems sit at the heart of natural product synthesis, often leveraged as key transformations. Among these, the construction of 5-membered rings has been particularly important in the synthesis of countless natural products including steroids,¹ prostaglandins,² triquinanes,³ and more recently, the polycyclic polyprenylated acylphloroglucinols (PPAPs) (**257–260**, Scheme 5.1.1A).⁴ Several reactions for the construction of 5-membered rings have been employed successfully toward the synthesis of these challenging natural products.^{5,6} Notable examples include the Danheiser annulation,⁷ the Pauson–Khand reaction,⁸ and trimethylenemethane chemistry.⁹

Despite their success, these methods often yield products with highly specific oxidation patterns, which can render them unsuitable for many synthetic applications. In our efforts toward a homoadamantane PPAP natural product, we were unable to construct the sterically demanding cyclopentane (e.g., in **260**) using conventional approaches.¹⁰ Our attention was drawn to the work of Bellassoued and coworkers, who reported that propargyl zinc nucleophiles (**261**, Scheme 5.1.1B) react with unsaturated 1,3-diester (**262**) to afford substituted cyclopentenenes (**265**).¹¹ Despite the long reaction times and modest yields, we

[†]This research was conducted in collaboration with Kasam Poonswat and Scott C. Virgil. Portions of this chapter have been reproduced with permission from Samkian, A. E.; Poonswat, K.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2025**, 27, 5876–5879. © 2025 American Chemical Society.

recognized the potential of this transformation to construct diverse cyclopentenenes, including those bearing the substitution pattern required for the PPAPs, and thus embarked on a study to improve the yield, increase the operational simplicity, and examine its generality.

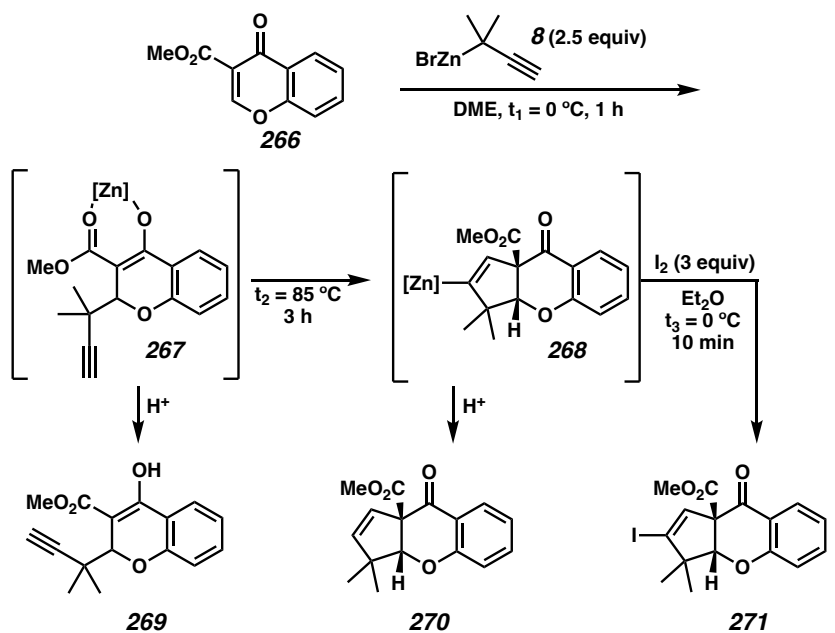
Scheme 5.1.1. *Cyclopentane-Containing Natural Products and a Previous Propargyl Zinc Cyclopentene Annulation.*



The mechanism proposed by Bellassoued involves a conjugate addition of the propargyl zinc nucleophile (**261**) into the activated enone (**262**) to form zinc enolate **263**. Upon heating, this enolate is proposed to cyclize to form vinyl zinc intermediate **264**. While all iterations of this reaction in Bellassoued's work involve a protic quench, we hypothesized that the vinyl zinc intermediate (**264**) is persistent and could potentially be intercepted by various electrophiles.

5.2 REACTION OPTIMIZATION

To probe this, we initiated an optimization campaign targeting vinyl iodide **271** (Table 5.2.1). We selected chromone **266** as an optimization substrate due to its stability and favorable isolation properties. We found that performing this reaction in 1,2-dimethoxyethane (DME) with 2.5 equivalents of propargyl zinc **8** at 0.1 M provided the optimal yield at 0.1 mmol scale. (entry 1). The reaction sequence involves dropwise addition of enone **266** into a solution of propargyl zinc **8** at 0 °C followed by heating to affect cyclization at 85 °C, and finally quenching with a solution of I₂ in Et₂O at 0 °C. Tracking the reaction led us to identifying enol **269** and cyclopentene **270** as byproducts, likely formed via protic quench of intermediates **267** and **268**. Under the optimal conditions, cyclization of the zinc enolate is highly efficient, with the major side reaction being protodemetalation. Both iodide **271** and cyclopentene **270** were isolated exclusively as the *cis* fused isomer. Unsurprisingly, a protic quench with NH₄Cl provided cyclopentene **270** in excellent yield (entry 2). Changing either the solvent or running the reaction at higher concentration significantly reduces the yield (entries 4 and 5). Interestingly, using only 1.5 equivalents of **8** resulted in no iodide **271** being observed, suggesting that significant protodemetalation occurred, and that propargyl zinc **8** possibly plays a role beyond a simple nucleophile. Performing the cyclization at lower temperature (60 °C) results in incomplete cyclization (entry 6), while increasing the temperature (105 °C) results in significant protodemetalation and non-specific decomposition (entry 7). Excitingly, the yield of iodide **271** increased significantly at 1 mmol scale, resulting in a 62% isolated yield for this 3-component coupling.

Table 5.2.1. Optimization of Reaction Conditions.

entry	variation from standard conditions ^a	yield 269 ^b	yield 270 ^b	yield 271 ^b
1	none	< 5%	39%	43%
2	NH_4Cl quench	< 5%	87%	0%
3	THF	< 5%	7%	15%
4	0.3 M	0%	39%	27%
5	1.5 equiv 8	0%	40%	0%
6	$t_2 = 60\text{ }^{\circ}\text{C}$	36%	16%	18%
7	$t_2 = 105\text{ }^{\circ}\text{C}$	0%	55%	12%
8	1 mmol scale	0%	15%	68% (62%) ^c

^aConditions: 0.1 mmol **266** in 1.0 mL solvent (0.1M). ^bYields determined by ^1H NMR with respect to 1,3,5-trimethoxybenzene or $\text{Si}(\text{SiMe}_3)_4$ (entry 8) as internal standard. ^cIsolated yield.

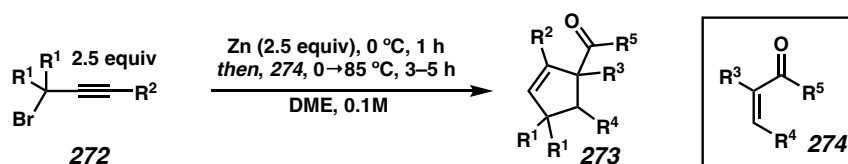
5.3 SCOPE AND LIMITATIONS

With optimal conditions in hand (Scheme 5.3.1A), we set about exploring the scope of this reaction using a protic quench (NH_4Cl) for simplicity (Scheme 5.3.1B). In addition to chromone **270** coumarin **275** and nitrile bearing chromone **276** were both accessible,

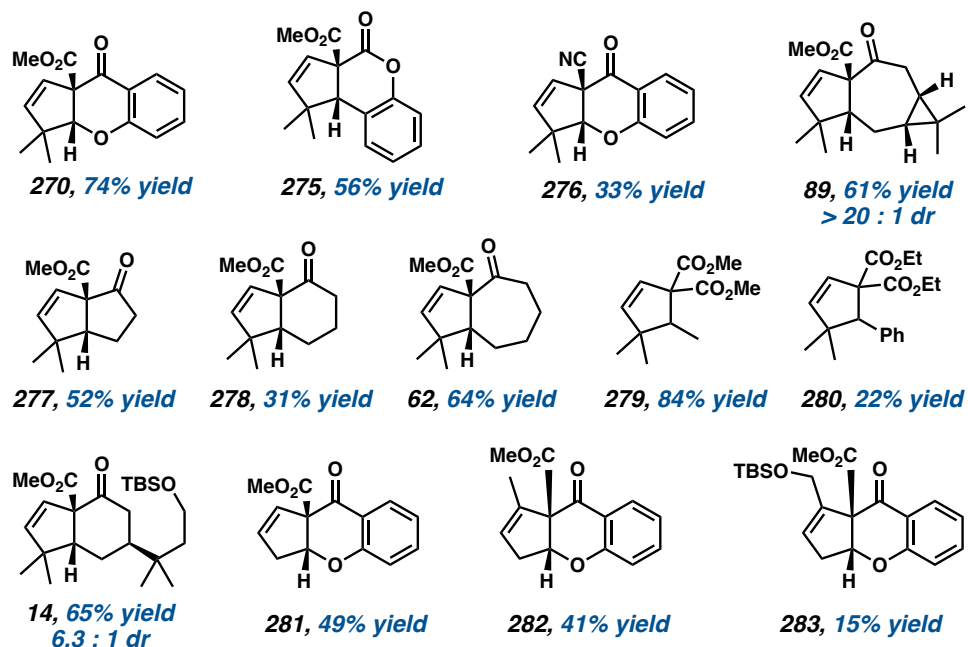
though in decreased yield. Several cycloalkyl β -ketoesters were competent, and hydropentalene **277**, hydroindene **278**, and hydrazulenes **62** and **89** could all be formed in moderate yields. The lower yields in some cases (e.g. **278**) were partially due to the poor stability of the starting enones, which have a propensity to tautomerize to the unproductive enol tautomer (See Section 5.6.2).

Scheme 5.3.1. Enone and Propargyl Bromide Scope.^a

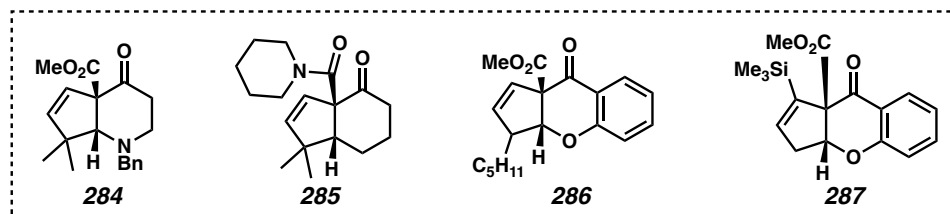
A) Optimized reaction conditions.



B) Scope of enones and propargyl bromides.



C) Challenging substrates.



^aIsolated yield reported. See section 5.6.2 for more details.

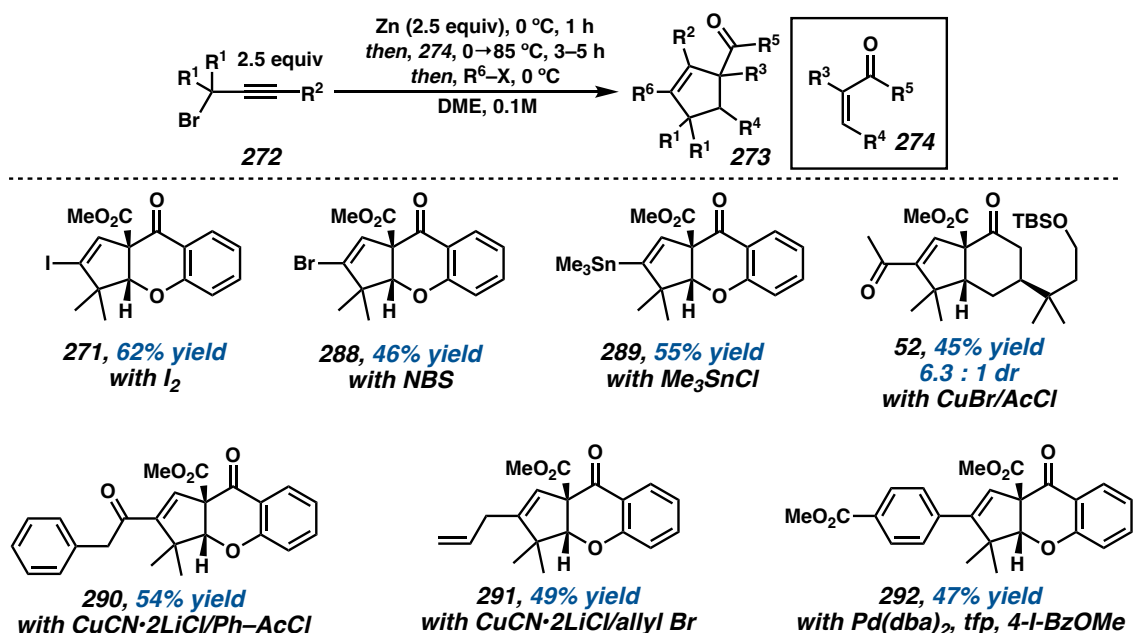
Substitution can fortuitously attenuate this decomposition, as seen for the enone used to prepare hydroindene **14**. Both hydroindene **14** and hydrazulene **89** indicate that the initial conjugate addition is diastereoselective, affording the *anti* and *syn cis*-cyclized products, respectively. We also attempted to use acyclic diester **262** (Scheme 5.1.1B), resulting in cyclopentene **279** in excellent yield. Interestingly, the phenyl substituted substrate resulted in a drastically decreased yield (**280**). Attempts to use vinylogous amides or ketoamides (**284**, **285**) unfortunately resulted in no reaction and allenyl addition, respectively (Scheme 5.3.1C).

Next exploring the propargyl bromide scope, we were pleased to find that unsubstituted propargyl bromide was competent (**281**), albeit in moderate yield. During isolation several allenyl products were observed: a decomposition pathway not seen with dimethylpropargyl nucleophiles. Monosubstituted propargyl bromides did result in cyclopentene product (**286**), however this resulted in an inseparable mixture of diastereomers, limiting synthetic utility. Additionally, terminally substituted alkynes were also successful (**282** and **283**). Hindered alkynes inhibit cyclization, an effect that was obvious with trimethylsilylpropargyl bromide, resulting in conjugate addition (not shown), but not cyclization (**287**).

Finally, we attempted to expand the electrophile scope (Scheme 5.3.2), finding that in addition to iodine, NBS and Me_3SnCl could be used to access vinyl bromide **288** and vinyl stannane **289** in good yield.¹² We were pleased to find that a variety of reactions generally compatible with organozinc reagents worked well for this system. For example, transmetalation with CuBr enabled access to acetylated cyclopentene **52**, and using $\text{CuCN}\cdot 2\text{LiCl}$ to generate the “mixed cuprate” also enabled acylation (**290**) and allylation

(291).¹³ We were also excited to find that the vinylzinc reagents were competent nucleophiles in Negishi couplings, and a combination of Pd(dba)₂ and tri(2-furyl)phosphine (tfp) generated styrene 292.¹⁴ Unfortunately, treatment with TsCN did not afford the desired acrylonitrile, despite previous precedent for vinylzinc cyanation using this reagent.¹⁴

Scheme 5.3.2. Electrophile Scope.^a



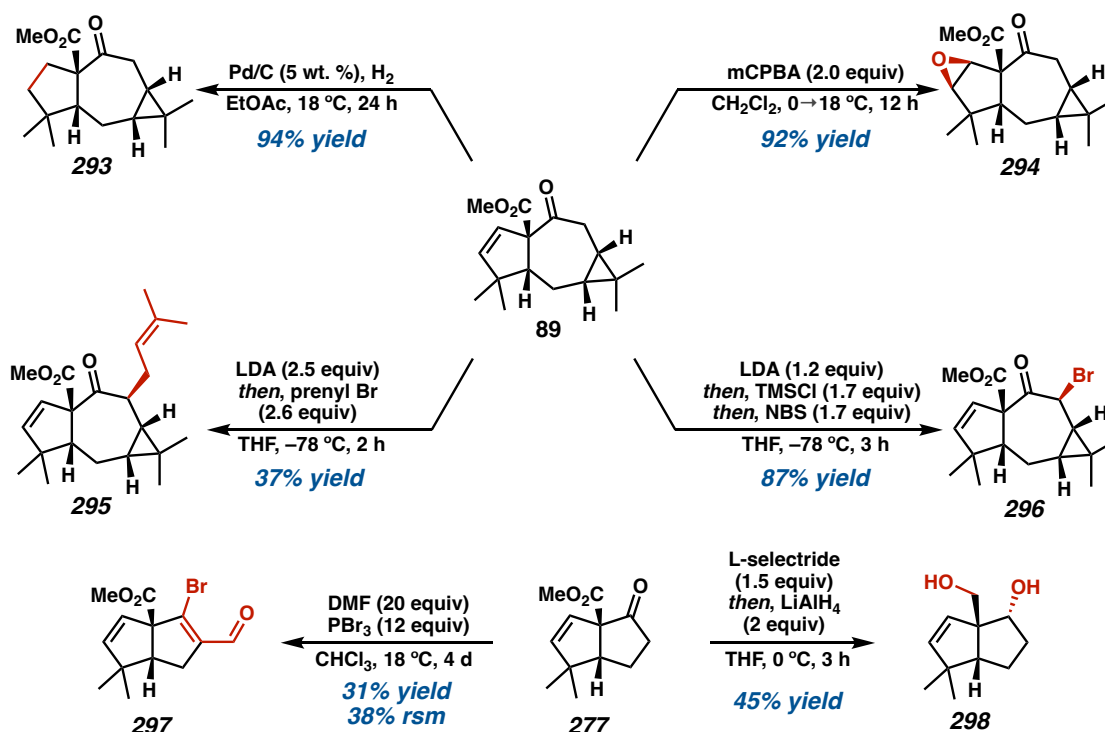
^aIsolated yield reported. See section 5.6.2 for more details.

5.4 PRODUCT DERIVATIZATION

Having demonstrated the scope of this 3-component cyclopentene annulation, we aimed to evaluate the potential synthetic applications of these scaffolds (Scheme 5.4.1). Starting from hydrazulene **89**, a range of transformations on the olefin and ketone functional groups resulted in the expected products. Hydrogenation (**293**) and epoxidation (**294**) of the olefin proceeded smoothly, as did prenylation (**295**) and α -bromination of the ketone (**296**). Using hydropentalene **277** as the starting material, exhaustive reduction

resulted in diol **298**, albeit in only modest yield due to undesired ring-opening side reactions. Subjecting **277** to the Vilsmeier reagent provided β -bromo enone **297**, a highly substituted hydropentalene accessed from an activated cyclopentenone in only two steps.

Scheme 5.4.1. Product Derivatizations.



5.5 CONCLUSION

To conclude, a new 3-component cyclopentene annulation is presented herein. The components are commercially available or readily synthesized, providing access to a wide array of substituted cyclopentenones. While several substrates afford only moderate yields, we provide these results as a foundation, noting that reaction times and temperatures can often be adjusted to improve outcomes for specific substrate combinations. We anticipate this reaction will prove valuable in natural product synthesis, and current efforts are focused toward development of an asymmetric variant.

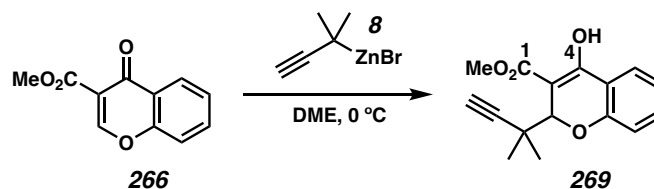
5.6 EXPERIMENTAL SECTION

5.6.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. 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.¹⁵ Activated Zn was prepared according to a previously reported procedure.¹⁶ 3-bromo-3-methylbut-1-yne¹⁷ and propargyl bromide **304**¹⁸ were prepared according to previously reported procedures. Enones **13**¹⁰, **47**,¹⁹ **75**,²⁰ **266**,²¹ **299**,²² **301**,²³ and **302**²⁴ were prepared according to previously reported procedures. Procedures for compounds **14** and **52** were previously presented in Chapters 1, and 2, respectively, and are therefore not reproduced here. Anhydrous 1,2-dimethoxyethane (DME) was purchased from Chem-Impex, used as received, and stored in a glovebox. All other reagents were purchased from commercial sources and used as received unless otherwise stated. Reaction progress was monitored by thin-layer chromatography (TLC). TLC was performed using E. Merck silica gel 60 F₂₅₄ precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, CAM stain, or KMnO₄ staining. Silicycle SiliaFlash® P60 Academic Silica gel (particle size 40–63 µm) was used for flash chromatography. Teledyne ISCO CombiFlashRf+, Teledyne ISCO CombiFlashRf+ Lumen™, or Teledyne ISCO CombiFlashRf NEXTGEN+ systems were used for automated flash chromatography using Luknova SuperSep™ silica columns. ¹H NMR spectra were recorded on Varian Inova 600 MHz, Varian Inova 500 MHz, and Bruker 400 MHz spectrometers and are reported relative to residual non-deuterated solvent CHCl₃ (δ

7.26 ppm). ^{13}C NMR spectra were recorded on Bruker 400 MHz and Varian Inova 600 MHz spectrometers (100 MHz) and are reported relative to residual non-deuterated solvent CDCl_3 (δ 77.16 ppm). Data for ^1H NMR 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, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). Diastereomeric ratios were calculated based on ratios of integrals from crude ^1H NMR spectra. Some spectra contain minor solvent impurities of water, ethyl acetate, dichloromethane, diethyl ether, acetone, grease, and/or silicone grease, which do not impact product assignments. IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-T2000GC AccuTOFTM GC-Alpha High Resolution Mass Spectrometer in field ionization (FI+), electron impact (EI+), or field desorption (FD+) mode, or an Agilent 6230 Series TOF with an Agilent Jet Stream ion source in electrospray ionization (ESI+).

5.6.2 EXPERIMENTAL PROCEDURES

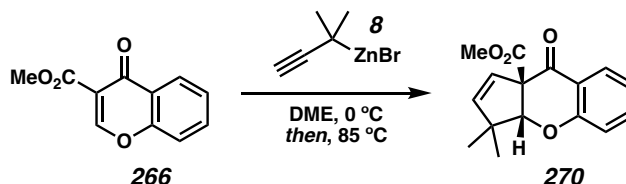
**methyl 4-hydroxy-2-(2-methylbut-3-yn-2-yl)-2H-chromene-3-carboxylate 269.**

In a glovebox, a 1-dram vial was charged with activated Zn (16.4 mg, 0.25 mmol, 2.5 equiv) and DME (0.5 mL) and sealed with a septum cap. The vial was brought out of the glovebox, put under N₂, and cooled to 0 °C in an ice bath. 3-bromo-3-methylbut-1-yne (37 mg, 0.25 mmol, 2.5 equiv) was added in one portion and the resulting suspension was stirred vigorously for 2 h. A solution of **266** (20 mg, 0.1 mmol, 1 equiv) in DME (0.5 mL) was added dropwise over 5 min, and the solution was stirred for 1 h at 0 °C and 2 h at 18 °C. The reaction was quenched with sat. aq. NH₄Cl, extracted with EtOAc (3x). The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→10% EtOAc/hexanes) to furnish **269** as a colorless oil. This compound was characterized to be used as a standard in the optimization studies and a yield was thus not recorded. ¹H NMR (600 MHz, CDCl₃) δ = 12.40 (s, 1H), 7.61 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.31 (ddd, *J* = 8.2, 7.3, 1.7 Hz, 1H), 6.95 (td, *J* = 7.5, 1.0 Hz, 1H), 6.88 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.14 (s, 1H), 3.81 (s, 3H), 1.87 (s, 1H), 1.26 (s, 3H), 1.17 (s, 3H); NMR (101 MHz, CDCl₃) δ = 171.3, 164.1, 157.4, 133.5, 124.3, 121.1, 118.7, 116.2, 88.5, 78.9, 70.9, 51.5, 39.8, 25.9, 25.8; IR (Neat Film, NaCl) 3292, 2976, 1652, 1626, 1441, 1351, 1268, 761 cm⁻¹; HRMS (ESI⁺): *m/z* calc'd for C₁₆H₁₇O₄ [M+H]⁺: 273.1121, found 273.1125. Note: the carbon peaks at 171.3 ppm and 164.1 ppm corresponding to C1 and C4 are not

visible in the ^{13}C spectrum, possibly due to tautomer effects. However, the presence of these peaks can easily be observed on the HMBC spectrum.

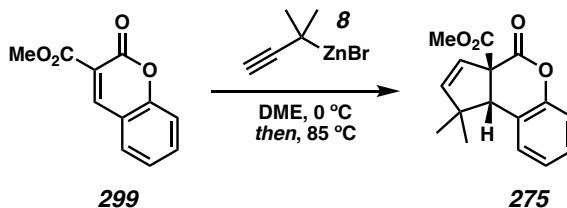
General Procedure A: Zn-mediated Cyclopentene Annulation (Protic Quench).

The requisite propargyl bromide (2.5 equiv) was added to a suspension of activated Zn (2.5 equiv) in DME (0.5 M with respect to propargyl bromide) at 0 °C under N_2 . After 1 h of stirring at 0 °C, a solution of the requisite α,β -unsaturated carbonyl compound (1.0 equiv) in DME (0.2 M with respect to dicarbonyl) was added dropwise. The suspension was stirred at this temperature for 1 h, and then at 18 °C for 2 h before being heated to 85 °C for 4 h *without stirring*.^{*} After cooling to 0 °C, the reaction was quenched with sat. aq. NH_4Cl and extracted with EtOAc (3x). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to yield a crude residue which was purified according to the listed conditions (vide infra). ^{*}Stirring during the heating step was found to significantly increase the rate of protodemetalation of the vinyl zinc intermediate. While this is less important for reactions that are to eventually be quenched with H^+ , we found it was beneficial to eliminate stirring at this stage altogether.



methyl 3,3-dimethyl-9-oxo-3,3a-dihydrocyclopenta[b]chromene-9a(9H)-carboxylate
270.

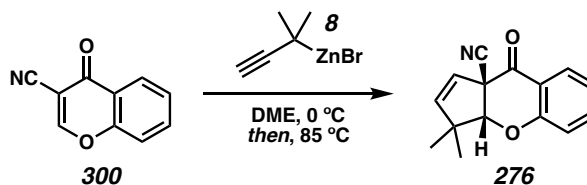
Prepared according to General Procedure A using enone **266** (50 mg, 0.24 mmol) and 3-bromo-3-methylbut-1-yne (90 mg, 0.61 mmol). Purified by automated silica gel flash chromatography (Teledyne ISCO, 0→10% EtOAc/hexanes) to yield **270** (48 mg, 74% yield) as a yellow oil. ^1H NMR (500 MHz, CDCl_3) δ = 7.85 (dd, J = 7.9, 1.7 Hz, 1H), 7.51 (ddd, J = 8.7, 7.1, 1.8 Hz, 1H), 7.03 – 6.94 (m, 2H), 6.04 (d, J = 6.0 Hz, 1H), 5.88 (d, J = 6.0 Hz, 1H), 4.95 (s, 1H), 3.73 (s, 3H), 1.29 (s, 3H), 0.87 (s, 3H); ^{13}C { ^1H } NMR (101 MHz, CDCl_3) δ = 188.13, 170.82, 161.14, 142.59, 136.97, 127.35, 126.19, 121.08, 119.41, 117.93, 88.82, 64.92, 53.38, 50.17, 27.23, 23.68; IR (Neat Film, NaCl) cm^{-1} ; HRMS (ESI $^+$): m/z calc'd for $\text{C}_{16}\text{H}_{17}\text{O}_4$ [$\text{M}+\text{H}$] $^+$: 273.1121, found 273.1125.



methyl 1,1-dimethyl-4-oxo-1,9b-dihydrocyclopenta[c]chromene-3a(4H)-carboxylate
275.

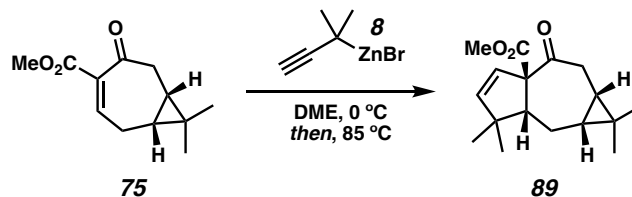
Prepared according to General Procedure A using enone **299** (50 mg, 0.24 mmol) and 3-bromo-3-methylbut-1-yne (90 mg, 0.61 mmol). Purified by automated silica gel flash chromatography (Teledyne ISCO, 0→10% EtOAc/hexanes) to yield **275** (37 mg, 56%

yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ = 7.32 (ddd, J = 8.2, 6.8, 2.3 Hz, 1H), 7.21 – 7.14 (m, 2H), 7.14 – 7.10 (m, 1H), 6.05 (d, J = 5.5 Hz, 1H), 6.02 (d, J = 5.6 Hz, 1H), 3.68 (s, 3H), 3.45 (s, 1H), 1.33 (s, 3H), 0.63 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 170.6, 166.5, 151.4, 145.8, 129.0, 128.8, 126.6, 124.9, 120.2, 117.2, 62.5, 55.4, 53.6, 50.5, 27.5, 23.3; IR (Neat Film, NaCl) 2958, 1764, 1739, 1456, 1254, 1233, 1164, 760 cm^{-1} ; HRMS (FD $^+$): m/z calc'd for $\text{C}_{16}\text{H}_{16}\text{O}_4$ $[\text{M}]^+$: 272.1043, found 272.1036.



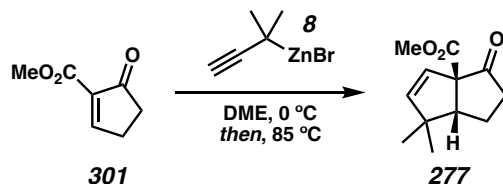
3,3-dimethyl-9-oxo-3,3a-dihydrocyclopenta[b]chromene-9a(9H)-carbonitrile 276.

Prepared according to General Procedure A using enone **300** (51 mg, 0.3 mmol) and 3-bromo-3-methylbut-1-yne (110 mg, 0.75 mmol). Purified by automated silica gel flash chromatography (Teledyne ISCO, 0→10% EtOAc/hexanes) to yield **276** (24 mg, 33% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ = 7.92 – 7.84 (m, 1H), 7.57 (ddd, J = 8.5, 7.2, 1.8 Hz, 1H), 7.09 – 6.99 (m, 2H), 6.03 (d, J = 5.8 Hz, 1H), 5.88 (d, J = 5.9 Hz, 1H), 5.01 (s, 1H), 1.36 (s, 3H), 0.96 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 183.1, 160.8, 145.3, 137.9, 128.0, 123.6, 122.1, 118.3, 118.3, 118.2, 89.3, 52.7, 50.8, 27.0, 23.2; IR (Neat Film, NaCl) 2922, 1687, 1604, 1459, 1296, 751 cm^{-1} ; HRMS (FD $^+$): m/z calc'd for $\text{C}_{15}\text{H}_{13}\text{NO}_2$ $[\text{M}]^+$: 239.0941, found 239.0929.



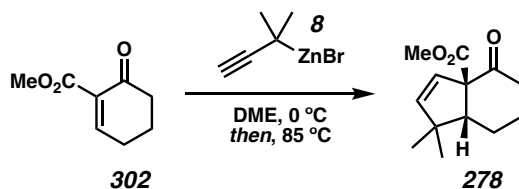
methyl (1aR,2aR,5aR,7aS)-1,1,3,3-tetramethyl-6-oxo-1,1a,2,2a,3,6,7,7a-octahydro-5aH-cyclopropa[f]azulene-5a-carboxylate **89.**

Prepared according to General Procedure A using enone **75** (42 mg, 0.2 mmol) and 3-bromo-3-methylbut-1-yne (74 mg, 0.5 mmol). Purified by automated silica gel flash chromatography (Teledyne ISCO, 0→10% Et₂O/hexanes) to yield **22** (34 mg, 61% yield) as a colorless oil. The stereochemistry of **89** was assigned based on diagnostic NOESY correlations. ¹H NMR (400 MHz, CDCl₃) δ = 5.91 (d, *J* = 5.6 Hz, 1H), 5.45 (d, *J* = 5.7 Hz, 1H), 3.79 (s, 3H), 3.08 (dd, *J* = 13.5, 4.3 Hz, 1H), 2.99 (dd, *J* = 19.9, 8.8 Hz, 1H), 2.16 (dd, *J* = 19.9, 8.1 Hz, 1H), 1.90 (dt, *J* = 14.0, 4.0 Hz, 1H), 1.13 (s, 3H), 1.06 (s, 3H), 0.99 (s, 3H), 0.96 – 0.87 (m, 1H), 0.85 – 0.77 (m, 1H), 0.75 (s, 3H), 0.50 (q, *J* = 8.5 Hz, 1H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 210.2, 172.1, 146.7, 126.3, 73.7, 52.9, 52.6, 46.9, 38.4, 28.5, 28.0, 27.1, 23.5, 21.5, 20.8, 18.7, 15.0; IR (Neat Film, NaCl) 2952, 1744, 1701, 1241, 1227, 796 cm⁻¹; HRMS (FD⁺): *m/z* calc'd for C₁₇H₂₄O₃ [M]⁺: 276.1720, found 276.1712; [α]_D^{22.90} –72.5 (c = 0.2, CHCl₃).



methyl 6,6-dimethyl-3-oxo-2,3,6,6a-tetrahydropentalene-3a(1H)-carboxylate 277.

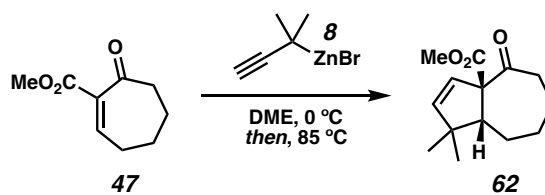
Prepared according to General Procedure A using enone **301** (42 mg, 0.3 mmol) and 3-bromo-3-methylbut-1-yne (110 mg, 0.75 mmol). Purified by automated silica gel flash chromatography (Teledyne ISCO, 0→10% EtOAc/hexanes) to yield **277** (33 mg, 52% yield) as a colorless solid. ^1H NMR (400 MHz, CDCl_3) δ = 5.68 (d, J = 5.4 Hz, 1H), 5.58 (d, J = 5.4 Hz, 1H), 3.72 (s, 3H), 2.89 (t, J = 8.4 Hz, 1H), 2.54 – 2.33 (m, 2H), 2.06 (dddd, J = 12.5, 8.7, 7.9, 3.7 Hz, 1H), 1.75 – 1.64 (m, 1H), 1.10 (s, 3H), 1.06 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 212.2, 172.1, 144.8, 124.3, 73.5, 55.7, 52.8, 48.1, 39.8, 30.41, 22.9, 21.9; IR (Neat Film, NaCl) 2955, 1750, 1732, 1258, 1162, 792, 750 cm^{-1} ; HRMS (ESI $^{+}$): m/z calc'd for $\text{C}_{12}\text{H}_{17}\text{O}_3$ $[\text{M}+\text{H}]^{+}$: 209.1172, found 209.1165.



methyl 1,1-dimethyl-4-oxo-1,4,5,6,7,7a-hexahydro-3aH-indene-3a-carboxylate 278.

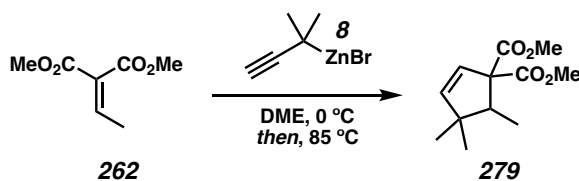
Prepared according to General Procedure A using enone **302** (50 mg, 0.32 mmol) and 3-bromo-3-methylbut-1-yne (120 mg, 0.81 mmol). Purified by automated silica gel flash chromatography (Teledyne ISCO, 0→10% EtOAc/hexanes) to yield **278** (22 mg, 31% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ = 5.79 (d, J = 5.7 Hz, 1H), 5.77 – 5.74 (m, 1H), 3.74 (d, J = 0.7 Hz, 3H), 2.83 (t, J = 6.9 Hz, 1H), 2.62 (dtd, J = 15.7, 7.1, 0.9

Hz, 1H), 2.30 (dt, $J = 15.6, 6.1$ Hz, 1H), 2.06 – 1.89 (m, 3H), 1.61 – 1.51 (m, 1H), 1.10 (s, 3H), 0.93 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) $\delta = 209.6, 172.3, 145.1, 126.3, 72.0, 53.8, 53.1, 48.2, 39.4, 28.9, 24.5, 23.5, 22.8$; IR (Neat Film, NaCl) 2953, 1714, 1246, 1223 cm^{-1} ; HRMS (FD $^+$): m/z calc'd for $\text{C}_{13}\text{H}_{18}\text{O}_3$ $[\text{M}]^+$: 222.1251, found 222.1246. Note that **302** is prone to tautomerization to the enol form, at which point it is inactive toward this chemistry. **302** should be prepared immediately before use to ensure reproducible yield.



methyl 1,1-dimethyl-4-oxo-4,5,6,7,8,8a-hexahydroazulene-3a(1H)-carboxylate 62.

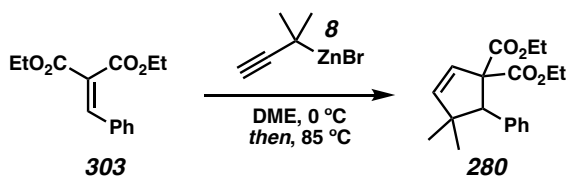
Prepared according to General Procedure A using enone **47** (50 mg, 0.30 mmol) and 3-bromo-3-methylbut-1-yne (110 mg, 0.74 mmol). Purified by automated silica gel flash chromatography (Teledyne ISCO, 0→10% Et_2O /hexanes) to yield **62** (45 mg, 64% yield) as a colorless oil. Characterization data for compound **62** is presented in Chapter 2.



dimethyl 4,4,5-trimethylcyclopent-2-ene-1,1-dicarboxylate 279.

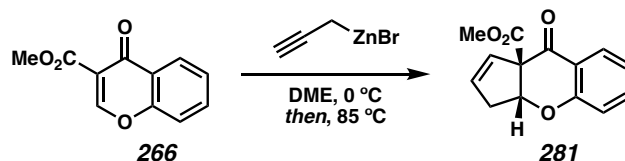
Prepared according to General Procedure A using enone **262** (48 mg, 0.3 mmol) and 3-bromo-3-methylbut-1-yne (110 mg, 0.75 mmol). Purified by automated silica gel flash chromatography (Teledyne ISCO, 0→10% EtOAc /hexanes) to yield **279** (57 mg, 84%

yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ = 5.87 (d, J = 5.7 Hz, 1H), 5.66 (d, J = 5.7 Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 2.62 (q, J = 7.4 Hz, 1H), 1.08 (s, 3H), 1.02 (d, J = 7.4 Hz, 3H), 0.93 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 171.8, 171.3, 146.9, 125.9, 77.4, 70.4, 52.7, 52.3, 48.3, 47.5, 28.4, 23.1, 10.8; IR (Neat Film, NaCl) 2955, 1731, 1434, 1261, 798 cm^{-1} ; HRMS (ESI⁺): m/z calc'd for $\text{C}_{12}\text{H}_{18}\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 249.1097, found 249.1090.



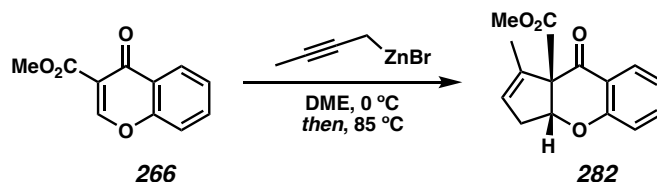
diethyl 4,4-dimethyl-5-phenylcyclopent-2-ene-1,1-dicarboxylate 280.

Prepared according to General Procedure A using enone **303** (74 mg, 0.3 mmol) and 3-bromo-3-methylbut-1-yne (110 mg, 0.75 mmol). Purified by automated silica gel flash chromatography (Teledyne ISCO, 0→10% EtOAc/hexanes) to yield **280** (21 mg, 22% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ = 7.22 – 7.14 (m, 5H), 5.92 (d, J = 5.6 Hz, 1H), 5.89 (d, J = 5.6 Hz, 1H), 4.27 – 4.10 (m, 2H), 3.99 (s, 1H), 3.80 (dq, J = 10.7, 7.1 Hz, 1H), 3.64 (dq, J = 10.7, 7.1 Hz, 1H), 1.22 (t, J = 7.1 Hz, 3H), 1.19 (s, 3H), 0.82 (s, 3H), 0.77 (t, J = 7.1 Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 170.7, 170.2, 145.8, 139.3, 130.1, 127.6, 126.9, 126.5, 72.5, 61.8, 61.2, 60.0, 49.6, 30.6, 25.7, 14.1, 13.5; IR (Neat Film, NaCl) 2958, 1731, 1253, 1191, 1091 cm^{-1} ; HRMS (ESI⁺): m/z calc'd for $\text{C}_{19}\text{H}_{25}\text{O}_4$ $[\text{M}+\text{H}]^+$: 317.1747, found 317.1748.



methyl 9-oxo-3,3a-dihydrocyclopenta[b]chromene-9a(9H)-carboxylate 281.

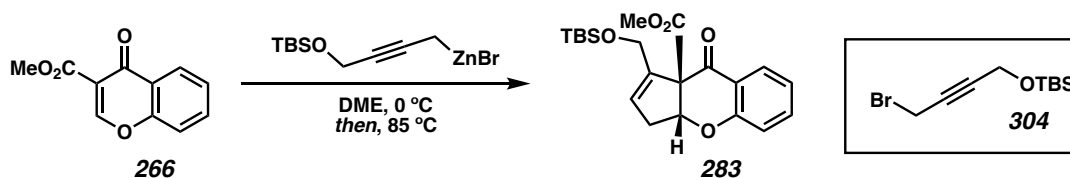
Prepared according to General Procedure A using enone **266** (100 mg, 0.49 mmol) and 3-bromoprop-1-yne (147 mg, 1.22 mmol). Purified by automated silica gel flash chromatography (Teledyne ISCO, 0→20% EtOAc/hexanes) to yield **281** (59 mg, 49% yield) as a yellow oil. ^1H NMR (500 MHz, CDCl_3) δ = 7.92 (dd, J = 7.9, 1.8 Hz, 1H), 7.52 (ddd, J = 8.7, 7.1, 1.8 Hz, 1H), 7.03 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H), 6.98 (dd, J = 8.4, 1.2 Hz, 1H), 6.06 (dt, J = 5.9, 2.3 Hz, 1H), 5.99 (dt, J = 6.0, 2.0 Hz, 1H), 5.39 (dd, J = 7.2, 6.1 Hz, 1H), 3.76 (s, 3H), 2.86 (dddd, J = 16.8, 7.2, 2.6, 1.8 Hz, 1H), 2.66 (ddt, J = 16.8, 6.1, 2.2 Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 187.1, 170.6, 159.8, 136.9, 132.8, 130.0, 127.9, 121.8, 121.0, 118.9, 82.7, 66.9, 53.3, 38.2; IR (Neat Film, NaCl) 2953, 1745, 1681, 1606, 1462, 1311, 1248, 945, 769 cm^{-1} ; HRMS (ESI $^{+}$): m/z calc'd for $\text{C}_{14}\text{H}_{12}\text{NaO}_4$ $[\text{M}+\text{Na}]^{+}$: 267.0628, found 267.0621.



methyl 1-methyl-9-oxo-3,3a-dihydrocyclopenta[b]chromene-9a(9H)-carboxylate 282.

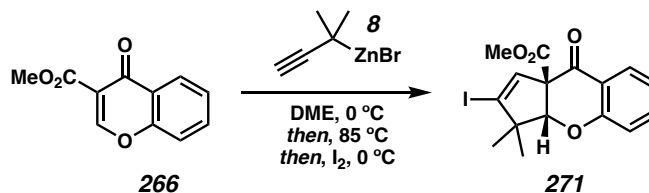
Prepared according to General Procedure A using enone **266** (50 mg, 0.24 mmol) and 1-bromobut-2-yne (81 mg, 0.61 mmol). Purified by automated silica gel flash chromatography (Teledyne ISCO, 0→10% EtOAc/hexanes) to yield **282** (26 mg, 41% yield) as a yellow oil.

yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ = 7.91 – 7.86 (m, 1H), 7.52 (ddd, J = 8.1, 7.3, 1.8 Hz, 1H), 7.06 – 6.98 (m, 2H), 5.66 – 5.58 (m, 2H), 3.72 (s, 3H), 3.21 – 3.10 (m, 1H), 3.07 – 2.94 (m, 1H), 1.66 (dd, J = 2.8, 1.4 Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 190.0, 170.8, 158.6, 137.6, 136.8, 127.7, 127.4, 121.7, 120.7, 118.5, 88.4, 62.5, 53.2, 38.6, 13.6; IR (Neat Film, NaCl) 2953, 1742, 1681, 1606, 1463, 1311, 1247, 768 cm^{-1} ; HRMS (FD $^+$): m/z calc'd for $\text{C}_{15}\text{H}_{14}\text{O}_4$ $[\text{M}]^+$: 258.0887, found 258.0890.



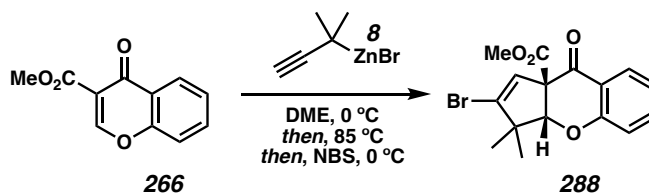
methyl 1-(((tert-butyldimethylsilyl)oxy)methyl)-9-oxo-3,3a-dihydrocyclopenta[b]chromene-9a(9H)-carboxylate 283.

Prepared according to General Procedure A using enone **266** (61 mg, 0.3 mmol) and propargyl bromide **304** (198 mg, 0.75 mmol). Purified by preparatory thin layer chromatography (10% EtOAc/hexanes) to yield **283** (17 mg, 15% yield) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ = 7.92 (dd, J = 7.9, 1.8 Hz, 1H), 7.51 (ddd, J = 8.7, 7.1, 1.8 Hz, 1H), 7.04 – 7.00 (m, 1H), 6.99 – 6.94 (m, 1H), 6.02 (p, J = 2.2 Hz, 1H), 5.42 (t, J = 6.3 Hz, 1H), 4.52 – 4.37 (m, 2H), 3.74 (s, 3H), 2.82 – 2.67 (m, 1H), 2.67 – 2.53 (m, 1H), 0.89 (s, 9H), 0.06 (d, J = 4.0 Hz, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 186.7, 170.3, 159.9, 142.0, 136.8, 127.8, 126.5, 121.7, 121.4, 118.8, 84.2, 67.0, 60.9, 53.2, 36.1, 26.0, 18.5, -5.3; IR (Neat Film, NaCl) 2953, 2854, 1742, 1681, 1606, 1462, 1249, 837 cm^{-1} ; HRMS (ESI $^+$): m/z calc'd for $\text{C}_{21}\text{H}_{29}\text{O}_5\text{Si}$ $[\text{M}+\text{H}]^+$: 389.1779, found 389.1789.



methyl 2-iodo-3,3-dimethyl-9-oxo-3,3a-dihydrocyclopenta[*b*]chromene-9a(9*H*)-carboxylate 271.

Activated Zn (164 mg, 2.5 mmol, 2.5 equiv) and DME (5 mL) were added to a 40 mL vial in a glovebox. The vial was fitted with a septum cap and cooled to 0 °C under N₂. 3-bromo-3-methylbut-1-yne (368 mg, 2.5 mmol, 2.5 equiv) was added in one portion and the suspension was left to stir at the same temperature. After 1 h, a solution of enone **266** (204 mg, 1.0 mmol, 1.0 equiv) in DME (5 mL) was added dropwise over 10 min. The suspension was stirred at 0 °C for 1 h, and then at 18 °C for 2 h before being heated to 85 °C for 3 h *without stirring*. After cooling to 0 °C, a solution of I₂ (761 mg, 3.0 mmol, 3.0 equiv) in Et₂O (3 mL) was added slowly and the brown solution allowed to stir for a further 10 min. The reaction was quenched with sat. aq. Na₂S₂O₃ and extracted with EtOAc (3x). The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→10% EtOAc/hexanes) to furnish **271** (285 mg, 72% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.89 – 7.82 (m, 1H), 7.52 (ddd, *J* = 8.4, 7.2, 1.8 Hz, 1H), 7.06 – 6.95 (m, 2H), 6.50 (s, 1H), 5.03 (s, 1H), 3.74 (s, 3H), 1.23 (s, 3H), 0.81 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 186.2, 169.4, 160.8, 137.3, 133.6, 127.4, 121.5, 119.1, 117.9, 113.7, 85.4, 65.7, 54.7, 53.6, 27.8, 23.0; IR (Neat Film, NaCl) 2962, 1736, 1679, 1607, 1460, 1301, 1249, 764 cm⁻¹; HRMS (FD⁺): *m/z* calc'd for C₁₆H₁₅IO₄ [M]⁺: 398.0010, found 397.9990.

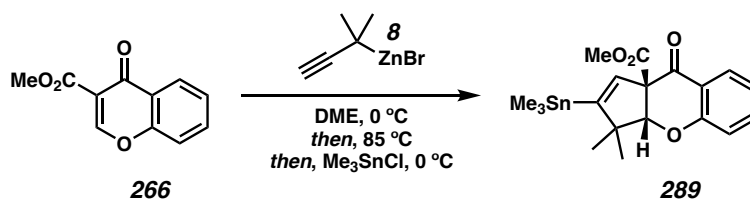


methyl 2-bromo-3,3-dimethyl-9-oxo-3,3a-dihydrocyclopenta[*b*]chromene-9a(9*H*)-carboxylate **288.**

Activated Zn (50 mg, 0.75 mmol, 2.5 equiv) and DME (1.5 mL) were added to a test tube in a glovebox. The test tube was fitted with a septum and cooled to 0 °C under N₂. 3-bromo-3-methylbut-1-yne (110 mg, 0.75 mmol, 2.5 equiv) was added in one portion and the suspension was left to stir at –15 °C for 18 h.* The solution was warmed to 0 °C and a solution of enone **266** (61 mg, 0.3 mmol, 1.0 equiv) in DME (1.5 mL) was added dropwise over 10 min. The suspension was stirred at 0 °C for 1 h, and then at 18 °C for 2 h before being heated to 85 °C for 3 h *without stirring*. After cooling to 0 °C, NBS (160 mg, 0.9 mmol, 3.0 equiv) was added as a solid in one portion and the reaction was allowed to stir for a further 10 min at the same temperature. The reaction was quenched with sat. aq. NH₄Cl and extracted with EtOAc (3x). The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→10% EtOAc/hexanes) to furnish **288** (48 mg, 46% yield) as a colorless solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.85 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.53 (ddd, *J* = 8.4, 7.2, 1.8 Hz, 1H), 7.04 – 6.96 (m, 2H), 6.24 (s, 1H), 5.03 (s, 1H), 3.74 (s, 3H), 1.29 (s, 3H), 0.90 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 186.6, 169.7, 160.8, 137.3, 136.2, 127.4, 125.9, 121.5, 119.2, 117.9, 87.0, 63.7, 53.6, 53.1, 26.2, 22.3; IR (Neat Film, NaCl) 2968, 1741, 1681, 1607, 1460, 1302, 1252, 1213, 761

cm⁻¹; HRMS (ESI⁺): *m/z* calc'd for C₁₆H₁₆BrO₄ [M+H]⁺: 351.0226, found 351.0219.

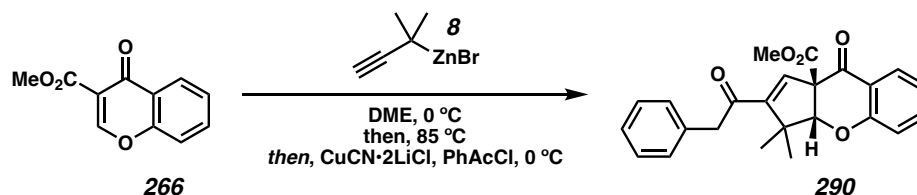
*Metalation of the propargyl bromide is generally complete after 1 h. However, solutions of the propargyl zinc bromide are stable at -15 °C for at least 24 h allowing operators to pause the reaction if required.



methyl 3,3-dimethyl-9-oxo-2-(trimethylstannyl)-3,3a-dihydrocyclopenta[*b*]chromene-9a(9*H*)-carboxylate **289.**

Activated Zn (50 mg, 0.75 mmol, 2.5 equiv) and DME (1.5 mL) were added to a test tube in a glovebox. The test tube was fitted with a septum and cooled to 0 °C under N₂. 3-bromo-3-methylbut-1-yne (110 mg, 0.75 mmol, 2.5 equiv) was added in one portion and the suspension left to stir at the same temperature. After 1 h, a solution of enone **266** (61 mg, 0.3 mmol, 1.0 equiv) in DME (1.5 mL) was added dropwise over 10 min. The suspension was stirred at 0 °C for 1 h, and then at 18 °C for 2 h before being heated to 85 °C for 3 h *without stirring*. After cooling to 18 °C, Me₃SnCl (179 mg, 0.9 mmol, 3.0 equiv) was added as a solution in THF (0.3 mL) and the reaction was allowed to stir for a further 18 h. The reaction was quenched with sat. aq. NH₄Cl and extracted with EtOAc (3x). The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→10% EtOAc/hexanes) to furnish **289** (71 mg, 55% yield) as a colorless solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.86 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.50 (ddd, *J* = 8.7, 7.1, 1.8 Hz, 1H),

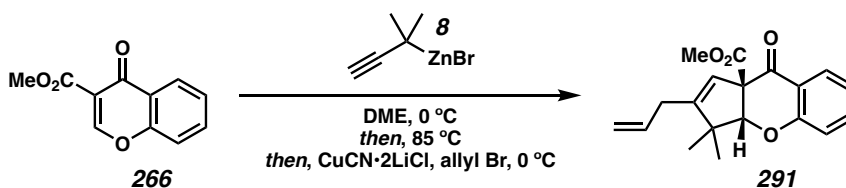
7.03 – 6.93 (m, 2H), 6.11 (s, 1H), 4.95 (s, 1H), 3.72 (s, 3H), 1.29 (s, 3H), 0.81 (s, 3H), 0.21 (s, 9H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 187.7, 170.7, 161.2, 158.2, 136.8, 134.5, 127.4, 120.9, 119.6, 117.9, 89.1, 66.0, 56.0, 53.4, 28.4, 24.4, -8.6; IR (Neat Film, NaCl) 2958, 1739, 1678, 1605, 1461, 1245, 766 cm^{-1} ; HRMS (ESI⁺): m/z calc'd for $\text{C}_{19}\text{H}_{25}\text{O}_4\text{Sn}$ $[\text{M}+\text{H}]^+$: 437.0769, found 437.0778.



methyl 3,3-dimethyl-9-oxo-2-(2-phenylacetyl)-3,3a-dihydrocyclopenta[b]chromene-9a(9H)-carboxylate 290.

Activated Zn (50 mg, 0.75 mmol, 2.5 equiv) and DME (1.5 mL) were added to a 2 dram vial in a glovebox. The vial was fitted with a septum cap and cooled to 0 °C under N_2 . 3-bromo-3-methylbut-1-yne (110 mg, 0.75 mmol, 2.5 equiv) was added in one portion and the suspension left to stir at the same temperature. After 1 h, a solution of enone **266** (61 mg, 0.3 mmol, 1.0 equiv) in DME (1.5 mL) was added dropwise over 10 min. The suspension was stirred at 0 °C for 1 h, and then at 18 °C for 2 h before being heated to 85 °C for 3 h *without stirring*. After cooling to 0 °C, $\text{CuCN}\cdot 2\text{LiCl}$ (1M in THF, 0.3 mL, 0.3 mmol, 1.0 equiv) and phenylacetyl chloride (139 mg, 0.9 mmol, 3.0 equiv) were added sequentially and the reaction was allowed to stir for a further 18 h at 18 °C. The reaction was quenched with sat. aq. NH_4Cl and extracted with CH_2Cl_2 (3x). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→20%

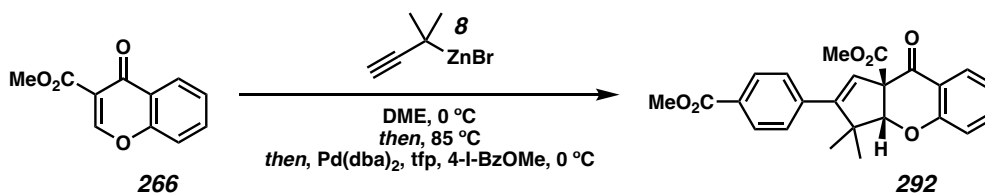
EtOAc/hexanes) to furnish **290** (63 mg, 54% yield) as an off-white solid. ^1H NMR (400 MHz, CDCl_3) δ = 7.84 (dd, J = 7.9, 1.8 Hz, 1H), 7.54 (ddd, J = 8.7, 7.1, 1.8 Hz, 1H), 7.32 (td, J = 7.4, 1.5 Hz, 3H), 7.21 – 7.16 (m, 2H), 7.04 – 6.97 (m, 3H), 4.92 (s, 1H), 4.02 (d, J = 2.0 Hz, 2H), 3.77 (s, 3H), 1.37 (s, 3H), 0.99 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 195.7, 186.5, 169.5, 161.2, 150.0, 137.5, 137.3, 133.9, 129.7, 129.5, 128.8, 128.8, 127.3, 127.1, 121.4, 119.3, 118.1, 88.7, 63.9, 53.7, 51.2, 46.7, 25.7, 22.4; IR (Neat Film, NaCl) 2956, 1738, 1678, 1605, 1460, 1304, 1217, 767 cm^{-1} ; HRMS (ESI $^{+}$): m/z calc'd for $\text{C}_{24}\text{H}_{23}\text{O}_5$ $[\text{M}+\text{H}]^{+}$: 391.1540, found 391.1551.



methyl 2-allyl-3,3-dimethyl-9-oxo-3,3a-dihydrocyclopenta[b]chromene-9a(9H)-carboxylate 291.

Activated Zn (50 mg, 0.75 mmol, 2.5 equiv) and DME (1.5 mL) were added to a 2 dram vial in a glovebox. The vial was fitted with a septum cap and cooled to 0 °C under N_2 . 3-bromo-3-methylbut-1-yne (110 mg, 0.75 mmol, 2.5 equiv) was added in one portion and the suspension left to stir at the same temperature. After 1 h, a solution of enone **266** (61 mg, 0.3 mmol, 1.0 equiv) in DME (1.5 mL) was added dropwise over 10 min. The suspension was stirred at 0 °C for 1 h, and then at 18 °C for 2 h before being heated to 85 °C for 3 h *without stirring*. After cooling to 0 °C, $\text{CuCN}\cdot 2\text{LiCl}$ (1M in THF, 0.3 mL, 0.3 mmol, 1.0 equiv) and allyl bromide (109 mg, 0.9 mmol, 3.0 equiv) were added sequentially and the reaction was allowed to stir for a further 18 h at 18 °C. The reaction was quenched

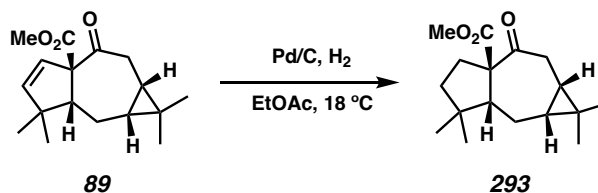
with sat. aq. NH_4Cl and extracted with CH_2Cl_2 (3x). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparatory HPLC (60→76% $\text{MeCN}/\text{H}_2\text{O}$, 10 mL/min, 254 nm) to furnish **291** (46 mg, 49% yield) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ = 7.85 (dd, J = 7.9, 1.8 Hz, 1H), 7.50 (ddd, J = 8.7, 7.1, 1.8 Hz, 1H), 7.03 – 6.94 (m, 2H), 5.86 (ddt, J = 18.0, 9.4, 6.9 Hz, 1H), 5.73 (t, J = 1.7 Hz, 1H), 5.13 (dq, J = 6.1, 1.6 Hz, 1H), 5.09 (t, J = 1.3 Hz, 1H), 4.95 (s, 1H), 3.71 (s, 3H), 2.84 – 2.67 (m, 2H), 1.24 (s, 3H), 0.84 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 188.6, 171.0, 161.3, 152.0, 136.9, 134.5, 127.3, 121.0, 120.7, 119.7, 117.9, 117.5, 89.1, 63.1, 53.3, 51.3, 31.8, 25.5, 22.7; IR (Neat Film, NaCl) 1960, 1739, 1679, 1605, 1460, 1300, 1213, 765 cm^{-1} ; HRMS (ESI $^{+}$): m/z calc'd for $\text{C}_{19}\text{H}_{21}\text{O}_4$ $[\text{M}+\text{H}]^{+}$: 313.1434, found 313.1443.



methyl 2-(4-(methoxycarbonyl)phenyl)-3,3-dimethyl-9-oxo-3,4-dihydrocyclopenta[b]chromene-9a(9H)-carboxylate 292.

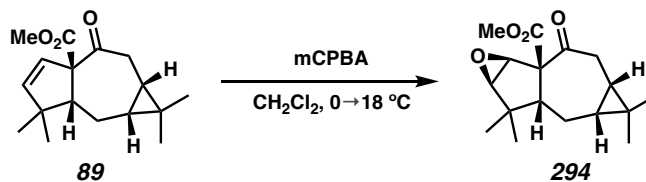
Activated Zn (50 mg, 0.75 mmol, 2.5 equiv) and DME (1.5 mL) were added to a 2-dram vial in a glovebox. The vial was fitted with a septum cap and cooled to 0 °C under N_2 . 3-bromo-3-methylbut-1-yne (110 mg, 0.75 mmol, 2.5 equiv) was added in one portion and the suspension left to stir at the same temperature. After 1 h, a solution of enone **266** (61 mg, 0.3 mmol, 1.0 equiv) in DME (1.5 mL) was added dropwise over 10 min. The suspension was stirred at 0 °C for 1 h, and then at 18 °C for 2 h before being heated to 85

°C for 3 h *without stirring*. A separate 1-dram vial in a glovebox was charged with Pd(dba)₂ (5.2 mg, 0.009 mmol, 3 mol %), tri(2-furyl)phosphine (tfp, 4.2 mg, 0.018 mmol, 6 mol %), and THF (0.8 mL). This suspension was stirred in the glovebox at 18 °C for 5 min and methyl 4-iodobenzoate (157 mg, 0.6 mmol, 2.0 equiv) was added to the catalyst solution and stirred until complete dissolution (20 min). The catalyst solution was then added to the vinyl zinc solution and the reaction was allowed to stir for 20 h. The reaction was quenched with sat. aq. NH₄Cl and extracted with CH₂Cl₂ (3x). The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 10→20% EtOAc/hexanes) to furnish **292** (57 mg, 47% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 8.02 – 7.97 (m, 2H), 7.88 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.54 (ddd, *J* = 8.7, 7.1, 1.8 Hz, 1H), 7.42 – 7.37 (m, 2H), 7.08 – 6.98 (m, 2H), 6.23 (s, 1H), 5.08 (s, 1H), 3.92 (s, 3H), 3.76 (s, 3H), 1.33 (s, 3H), 1.07 (s, 3H); ¹³C {¹H} NMR (101 MHz, CDCl₃) δ = 188.1, 170.5, 166.9, 161.2, 152.0, 140.1, 137.1, 129.8, 129.7, 127.3, 125.2, 121.3, 119.7, 117.9, 89.2, 63.2, 53.5, 52.3, 51.9, 26.1, 23.5; IR (Neat Film, NaCl) 2954, 1722, 1680, 1606, 1461, 1280, 1240, 1105, 771 cm⁻¹; HRMS (ESI⁺): *m/z* calc'd for C₂₄H₂₃O₆ [M+H]⁺: 407.1489, found 407.1492.



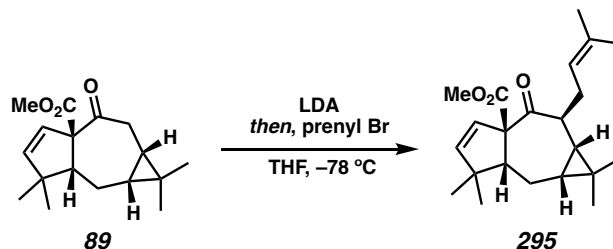
methyl (1aR,2aR,5aR,7aS)-1,1,3,3-tetramethyl-6-oxodecahydro-5aH-cyclopropa[f]azulene-5a-carboxylate **293.**

A 1-dram vial was charged with cyclopentene **89** (53 mg, 0.19 mmol, 1.0 equiv), Pd/C (10 wt. % loading on C, 5 mg, 10 wt. %), and cycled under N₂. EtOAc (1 mL) was added, and the vial was purged with H₂ (balloon) and stirred vigorously for 24 h. The suspension was filtered over celite and the filtrate was concentrated under reduced pressure. The residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→10% EtOAc/hexanes) to furnish **293** (50 mg, 94% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ = 3.74 (s, 3H), 3.04 – 2.88 (m, 2H), 2.82 (dd, *J* = 13.5, 3.8 Hz, 1H), 2.18 (dd, *J* = 19.8, 8.0 Hz, 1H), 1.79 (dt, *J* = 14.2, 3.8 Hz, 1H), 1.59 – 1.44 (m, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 0.96 (s, 3H), 0.84 (ddd, *J* = 12.4, 8.7, 3.9 Hz, 1H), 0.66 – 0.54 (m, 4H), 0.44 (q, *J* = 8.5 Hz, 1H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 208.7, 175.0, 66.3, 55.7, 52.5, 42.0, 40.6, 38.7, 30.5, 28.6, 28.2, 27.3, 21.6, 20.8, 20.6, 18.4, 15.2; IR (Neat Film, NaCl) 2948, 1700, 1460, 1212 cm⁻¹; HRMS (ESI⁺): *m/z* calc'd for C₁₇H₂₇O₃ [M+H]⁺: 279.1955, found 279.1942; [α]_D^{22.81} –29.4 (c = 0.9, CHCl₃).



methyl (1a*S*,1b*S*,3a*S*,4a*R*,5a*R*,6a*R*)-4,4,6,6-tetramethyl-2-oxodecahydro-1b*H*-cyclopropa[5,6]azuleno[1,2-*b*]oxirene-1b-carboxylate **294.**

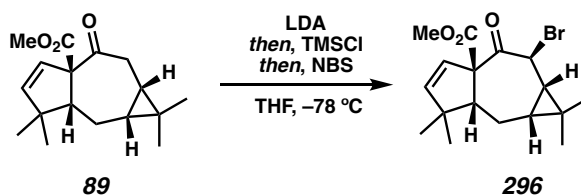
A 2-dram vial under N₂ was charged with cyclopentene **89** (24 mg, 88 μmol, 1.0 equiv), CH₂Cl₂ (1.75 mL), and cooled to 0 °C. Solid mCPBA (45 mg, 0.27 mmol, 3.0 equiv) was added in one portion and the reaction was allowed to warm to 18 °C and stirred at this temperature for 18 h. The crude reaction was quenched with saturated aq. Na₂S₂O₃ solution and extracted with CH₂Cl₂. The combined organic extracts were washed with saturated aq. NaHCO₃, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified via a silica plug to yield epoxide **294** (24 mg, 92 % yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ = 3.82 (s, 3H), 3.76 (d, *J* = 2.6 Hz, 1H), 3.25 (d, *J* = 2.6 Hz, 1H), 2.94 (dd, *J* = 20.1, 8.7 Hz, 1H), 2.67 (dd, *J* = 13.8, 4.8 Hz, 1H), 2.13 (dd, *J* = 20.1, 8.3 Hz, 1H), 1.79 (dt, *J* = 14.2, 4.3 Hz, 1H), 1.12 (s, 3H), 1.04 (s, 3H), 0.97 (s, 3H), 0.88 (ddd, *J* = 12.3, 8.6, 3.8 Hz, 1H), 0.73 (s, 3H), 0.67 (td, *J* = 14.0, 12.3 Hz, 1H), 0.43 (q, *J* = 8.5 Hz, 1H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 209.9, 169.9, 66.6, 65.9, 60.3, 52.9, 48.8, 40.8, 38.7, 28.6, 27.2, 23.9, 21.4, 21.3, 19.6, 18.8, 15.0; IR (Neat Film, NaCl) 2952, 1752, 1698, 1227, 1164 cm⁻¹; HRMS (ESI⁺): *m/z* calc'd for C₁₇H₂₅O₄ [M+H]⁺: 293.1747, found 293.1743; [α]_D^{22.80} -42.7 (c = 0.9, CHCl₃).



methyl (1aR,2aR,5aR,7S,7aR)-1,1,3,3-tetramethyl-7-(3-methylbut-2-en-1-yl)-6-oxo-1,1a,2,2a,3,6,7,7a-octahydro-5aH-cyclopropa[f]azulene-5a-carboxylate **295.**

A small test tube fitted with a septum under N₂ was charged with *i*-Pr₂NH (29 mg, 0.28 mmol, 3.0 equiv), THF (0.15 mL), and cooled to −78 °C. *n*-BuLi (2.5 M in hexanes, 95 μL, 0.24 mmol, 2.5 equiv) was added dropwise and the solution was stirred at this temperature for a further 20 min. A solution of cyclopentene **89** (26 mg, 95 μmol, 1.0 equiv) in THF (0.20 mL) was added dropwise and the reaction was stirred at this temperature for 1 h. Prenyl bromide (37 mg, 0.25 mmol, 2.6 equiv) was added in one portion and the reaction was stirred at −78 °C for 30 min, then quenched with saturated aq. NH₄Cl, and extracted with EtOAc (3x). The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0→10% EtOAc/hexanes) to furnish **295** (12 mg, 37% yield) as a colorless oil. The stereochemistry of **295** was assigned based on diagnostic NOESY correlations. ¹H NMR (400 MHz, CDCl₃) δ = 5.88 (d, *J* = 5.7 Hz, 1H), 5.51 (d, *J* = 5.7 Hz, 1H), 5.09 (ddt, *J* = 8.4, 7.0, 1.4 Hz, 1H), 3.77 (s, 3H), 3.11 (dd, *J* = 13.0, 4.8 Hz, 1H), 2.76 – 2.65 (m, 1H), 2.20 (dt, *J* = 13.9, 9.3 Hz, 1H), 1.99 – 1.85 (m, 2H), 1.72 (d, *J* = 1.5 Hz, 3H), 1.64 – 1.61 (m, 3H), 1.12 (s, 3H), 1.02 (s, 3H), 0.93 (s, 3H), 0.90 – 0.76 (m, 2H), 0.72 (s, 3H), 0.13 (dd, *J* = 9.7, 8.3 Hz, 1H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 212.0, 172.2, 146.1, 132.8, 127.2, 122.2, 73.8, 54.0, 52.4, 49.8, 46.6, 33.0, 28.7, 27.7, 27.2,

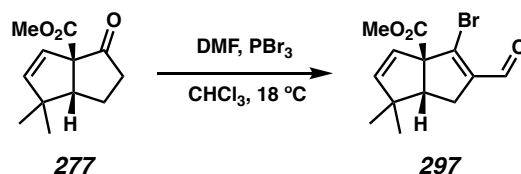
26.1, 25.6, 23.6, 21.6, 21.0, 18.0, 15.4; IR (Neat Film, NaCl) 2953, 2925, 1745, 1697, 1456, 1223, 1146, 800 cm^{-1} ; HRMS (ESI⁺): m/z calc'd for $\text{C}_{22}\text{H}_{33}\text{O}_3$ $[\text{M}+\text{H}]^+$: 345.2424, found 345.2423; $[\alpha]_{\text{D}}^{22.87} -60.3$ ($c = 0.8$, CHCl_3).



methyl (1aR,2aR,5aR,7S,7aS)-7-bromo-1,1,3,3-tetramethyl-6-oxo-1,1a,2,2a,3,6,7,7a-octahydro-5aH-cyclopropa[f]azulene-5a-carboxylate 296.

A small test tube fitted with a septum under N_2 was charged with $i\text{-Pr}_2\text{NH}$ (18 mg, 0.18 mmol, 1.4 equiv), THF (0.35 mL), and cooled to $-78\text{ }^\circ\text{C}$. $n\text{-BuLi}$ (2.5 M in hexanes, 63 μL , 0.16 mmol, 1.2 equiv) was added dropwise and the solution was stirred at this temperature for a further 20 min. A solution of cyclopentene **89** (37 mg, 0.13 μmol , 1.0 equiv) in THF (0.25 mL) was added dropwise and the reaction was stirred at this temperature for 1.5 h. TMSCl (24 mg, 0.23 mmol, 1.7 equiv) was added dropwise and the reaction was warmed to $0\text{ }^\circ\text{C}$ in an ice bath and stirred at this temperature for 1 h. NBS (40 mg, 0.23 mmol, 1.7 equiv) was added as a solid in one portion and the reaction was stirred at $0\text{ }^\circ\text{C}$ for 30 min.* The reaction was quenched with saturated aq. NaHCO_3 , extracted with EtOAc (3x), and the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (0 $\rightarrow$ 10% EtOAc /hexanes) to afford bromide **296** (40 mg, 87 % yield) as a colorless oil. The stereochemistry of **296** was assigned based on diagnostic NOESY correlations. ^1H NMR (400 MHz, CDCl_3) $\delta = 5.91$ (d, $J = 5.6$ Hz, 1H), 5.57 (d, $J = 5.7$ Hz, 1H), 4.03 (d, $J = 10.1$

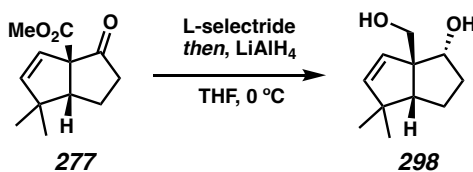
Hz, 1H), 3.82 (s, 3H), 3.18 (dd, $J = 13.5, 5.0$ Hz, 1H), 1.94 (dt, $J = 14.3, 4.5$ Hz, 1H), 1.17 – 1.12 (m, 9H), 1.09 (ddd, $J = 12.8, 9.0, 4.0$ Hz, 1H), 1.00 – 0.78 (m, 2H), 0.72 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) $\delta = 203.8, 171.2, 146.6, 126.6, 73.8, 54.5, 52.8, 48.9, 46.6, 30.2, 29.5, 28.3, 27.4, 23.7, 22.5, 21.4, 14.2$; IR (Neat Film, NaCl) 2923, 1739, 1706, 1221, 1150, 786 cm^{-1} ; HRMS (ESI⁺): m/z calc'd for $\text{C}_{17}\text{H}_{27}\text{BrNO}_3$ $[\text{M}+\text{NH}_4]^+$: 372.1169, found 372.1166; $[\alpha]_{\text{D}}^{22.51} -119.7$ ($c = 0.1, \text{CHCl}_3$). * α -bromoketones can be light sensitive, so this step, including purification, was performed in the dark.



methyl 4-bromo-5-formyl-1,1-dimethyl-6,6a-dihydropentalene-3a(1H)-carboxylate **297.**

A 1-dram vial under N_2 was charged with DMF (56 mg, 0.76 mmol, 20 equiv), CHCl_3 (1.2 mL) and cooled to 0 °C. PBr_3 (123 mg, 0.46 mmol, 12 equiv) was added and the reaction was allowed to stir at 18 °C for 30 min. A solution of ketone **277** (8 mg, 38 μmol , 1.0 equiv) in CHCl_3 (1.2) mL was added dropwise and the resulting solution was allowed to stir for 4 d. The reaction was then quenched with ice cold saturated aq. NaHCO_3 and extracted with CH_2Cl_2 (3x). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparatory thin-layer chromatography (10% EtOAc/hexanes) to afford starting ketone **277** (3.0 mg, 38% yield) and bromide **297** (3.5 mg, 31% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) $\delta = 9.86$ (s, 1H), 5.81 (d, $J = 5.6$ Hz, 1H), 5.79 (d, $J = 5.6$ Hz, 1H), 3.77 (s, 3H), 2.85 (dd, $J =$

8.6, 3.4 Hz, 1H), 2.72 (dd, $J = 16.8, 8.6$ Hz, 1H), 2.64 (dd, $J = 16.8, 3.4$ Hz, 1H), 1.12 (s, 3H), 0.97 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) $\delta = 189.5, 172.8, 146.7, 140.9, 139.3, 124.7, 78.7, 54.1, 53.0, 48.5, 30.6, 30.6, 23.9$; IR (Neat Film, NaCl) 2955, 1735, 1677, 1239, 795 cm^{-1} ; HRMS (ESI $^{+}$): m/z calc'd for $\text{C}_{13}\text{H}_{16}\text{BrO}_3$ $[\text{M}+\text{H}]^{+}$: 299.0277, found 299.0273.



6a-(hydroxymethyl)-4,4-dimethyl-1,2,3,3a,4,6a-hexahydropentalen-1-ol 298. A 1-dram vial under N_2 was charged with ketone **277** (8.4 mg, 40 μmol , 1.0 equiv), THF (0.2 mL), and cooled to 0 $^{\circ}\text{C}$. L-Selectride (1 M in THF, 60 μL , 60 μmol , 1.5 equiv) was added dropwise and the reaction was allowed to stir at 0 $^{\circ}\text{C}$ for 45 min. Solid LiAlH_4 (3.0 mg, 80 mmol, 2.0 equiv) was added in one portion and the reaction was stirred for another 2 h. The reaction was quenched by adding H_2O (10 μL), aq. NaOH (2 M, 30 μL), and H_2O (10 μL), sequentially and then filtered over celite. The filtrate was extracted with EtOAc (3x) and the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparatory thin-layer chromatography (33% EtOAc /hexanes) to afford diol **298** (3.3 mg, 45% yield) as a colorless solid. ^1H NMR (400 MHz, CDCl_3) $\delta = 5.73$ (d, $J = 5.6$ Hz, 1H), 5.51 (d, $J = 5.7$ Hz, 1H), 4.00 (t, $J = 6.5$ Hz, 1H), 3.71 (d, $J = 10.1$ Hz, 1H), 3.62 (d, $J = 10.2$ Hz, 1H), 1.94 – 1.88 (m, 1H), 1.83 – 1.69 (m, 2H), 1.68 – 1.58 (m, 2H), 1.54 – 1.46 (m, 2H), 1.08 (s, 3H), 1.04 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) $\delta = 147.1, 125.9, 78.3, 70.1, 67.5, 53.2, 47.7, 34.4, 32.6, 24.3,$

23.8; IR (Neat Film, NaCl) 3233, 2923, 1359, 1008 cm^{-1} ; HRMS (FI+): m/z calc'd for $\text{C}_{11}\text{H}_{18}\text{O}_2$ $[\text{M}]^+$: 182.1301, found 182.1307.

5.7 REFERENCES AND NOTES

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APPENDIX 9

*Spectra Relevant to Chapter 5:
A Modular Cyclopentene Annulation*

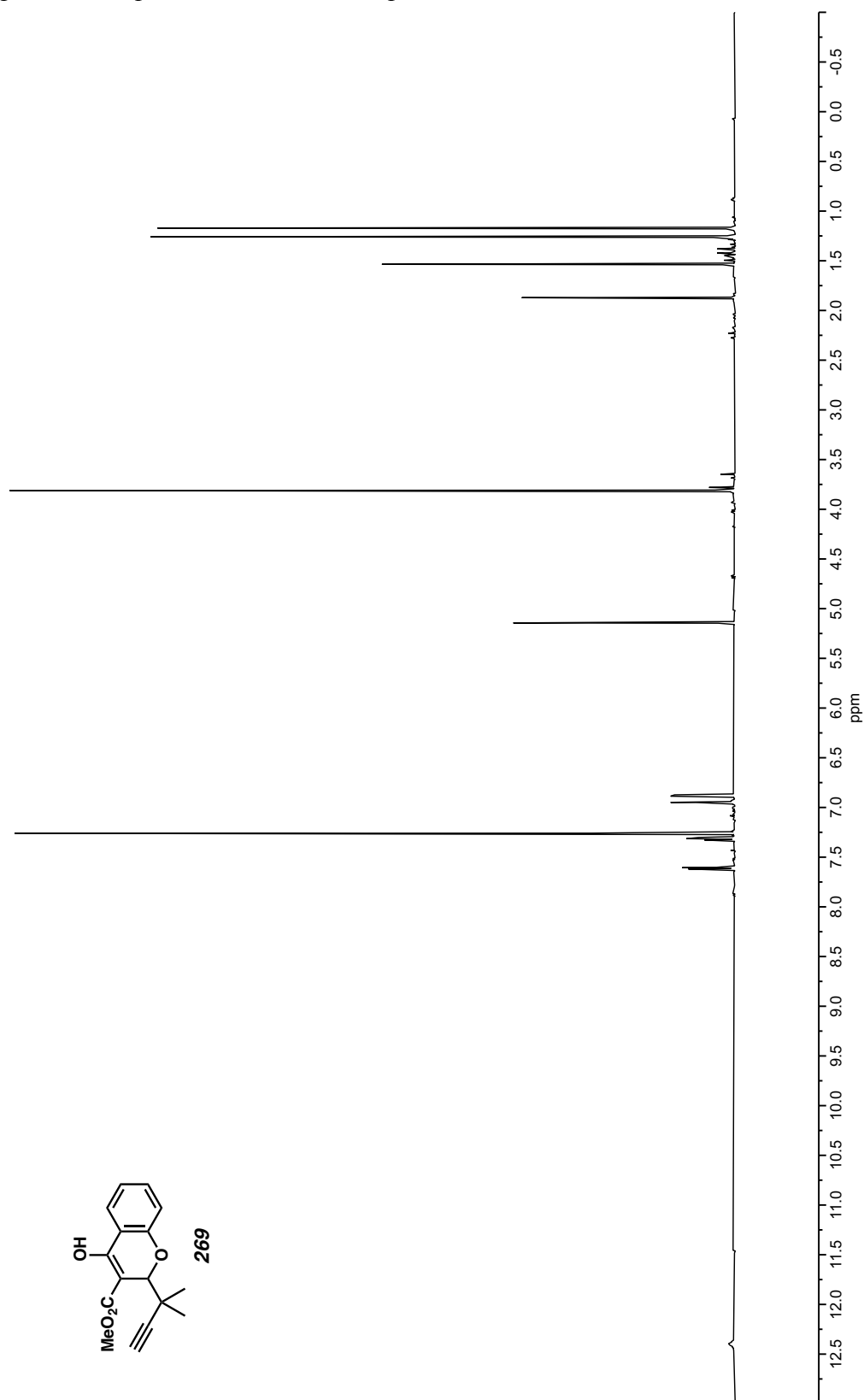


Figure A9.1 ¹H NMR (600 MHz, CDCl₃) of compound **269**.

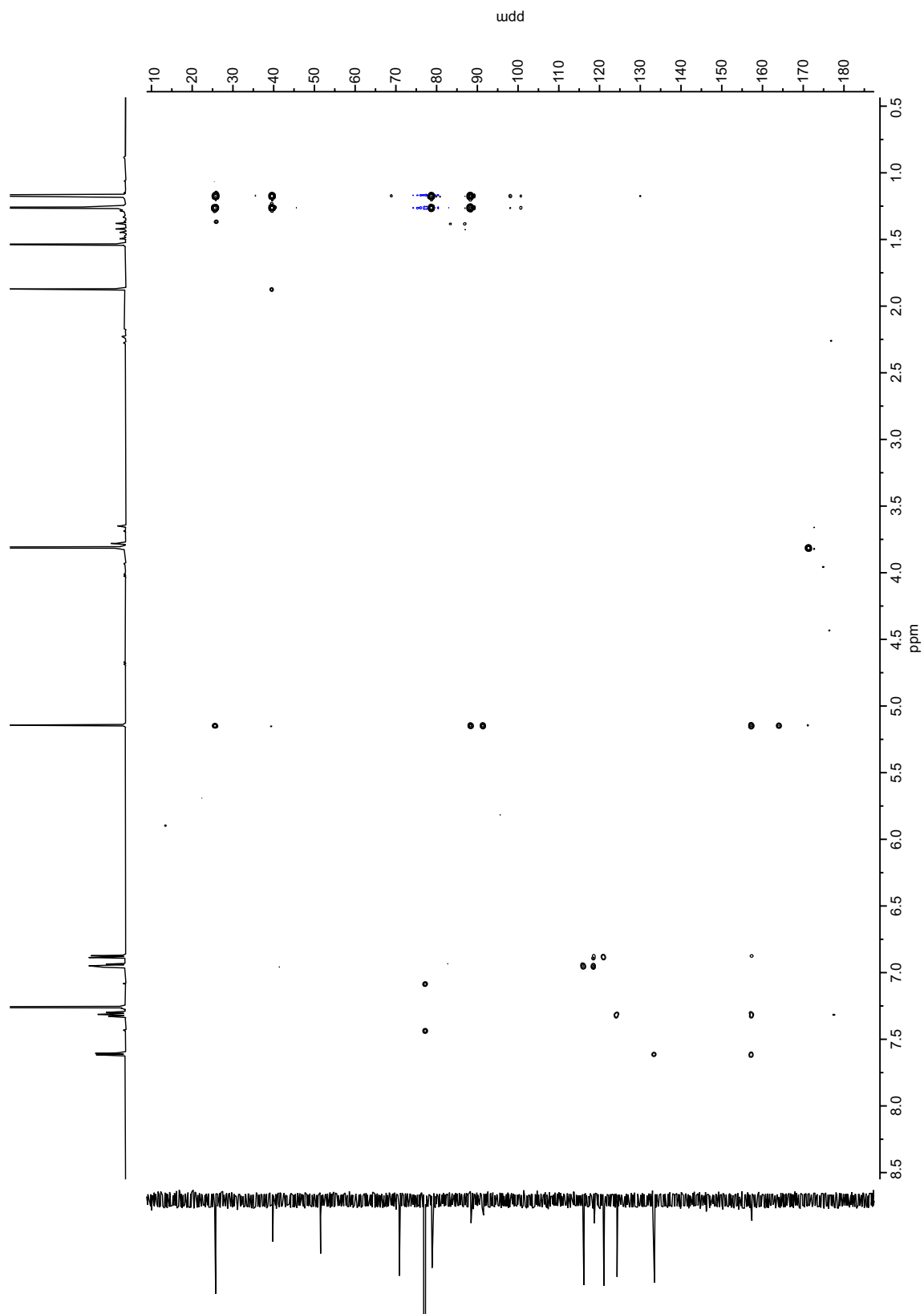


Figure A9.2 HMBC NMR (600 MHz, CDCl_3) of compound **269**.

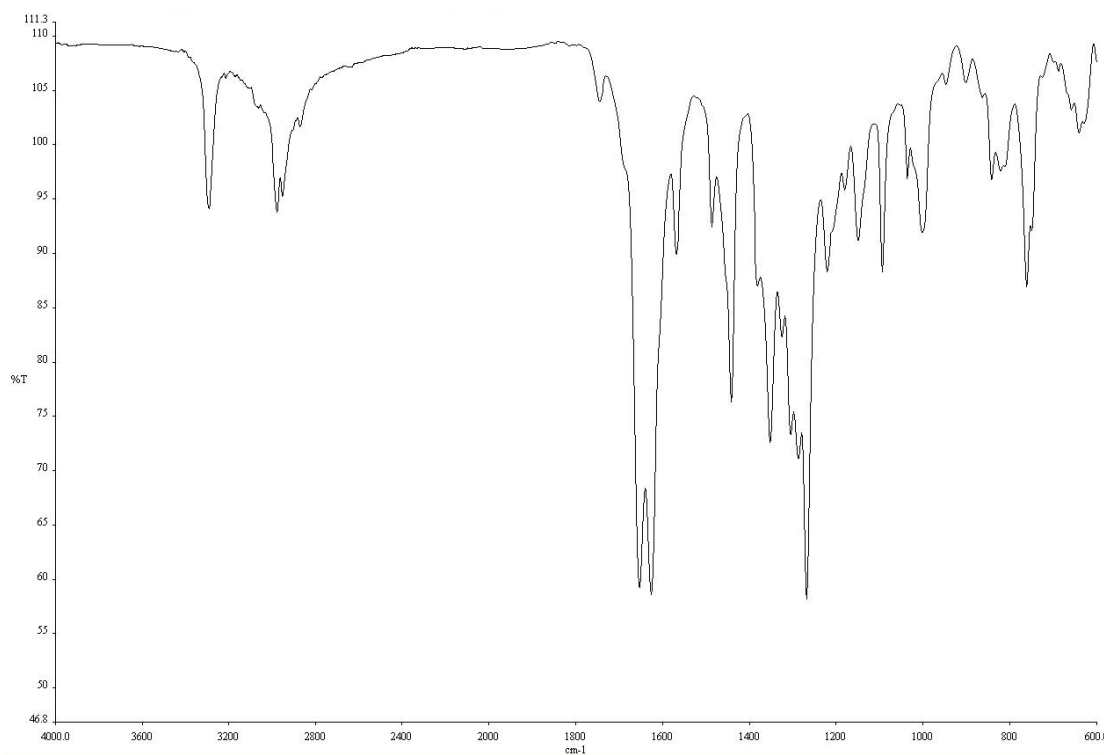


Figure A9.3 Infrared spectrum (Thin Film, NaCl) of compound **269**.

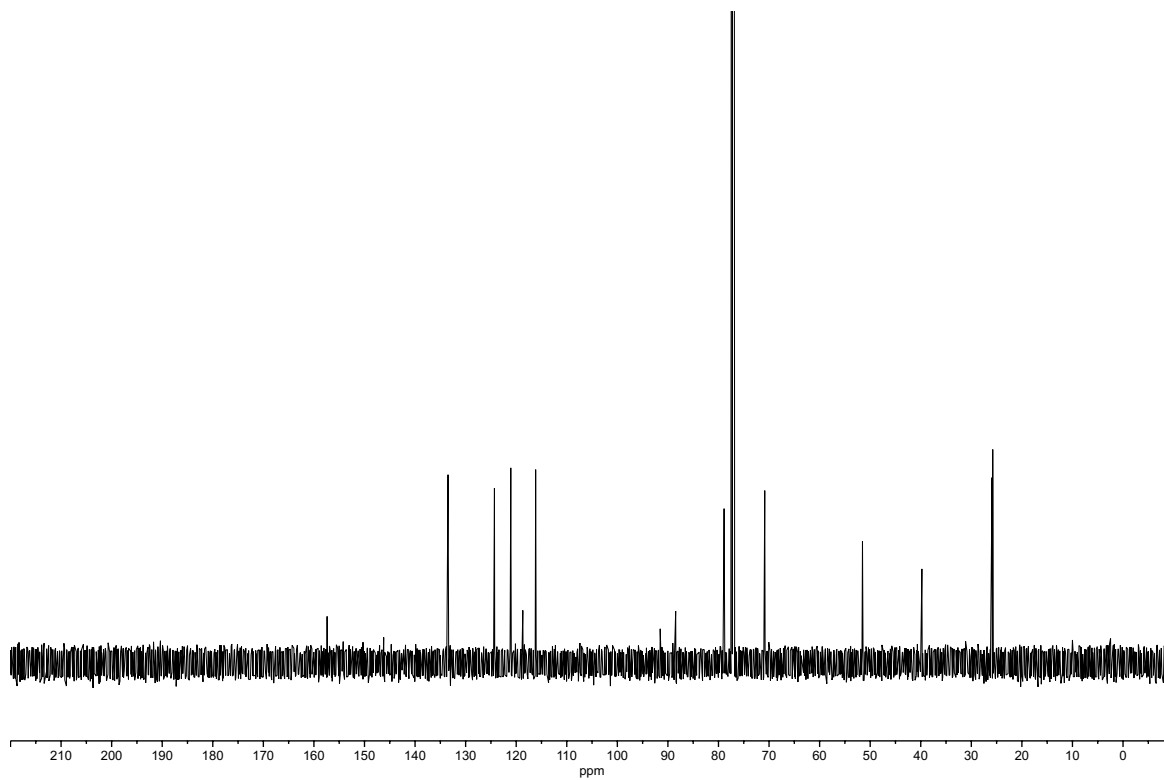


Figure A9.4 ¹³C NMR (100 MHz, CDCl₃) of compound **269**.

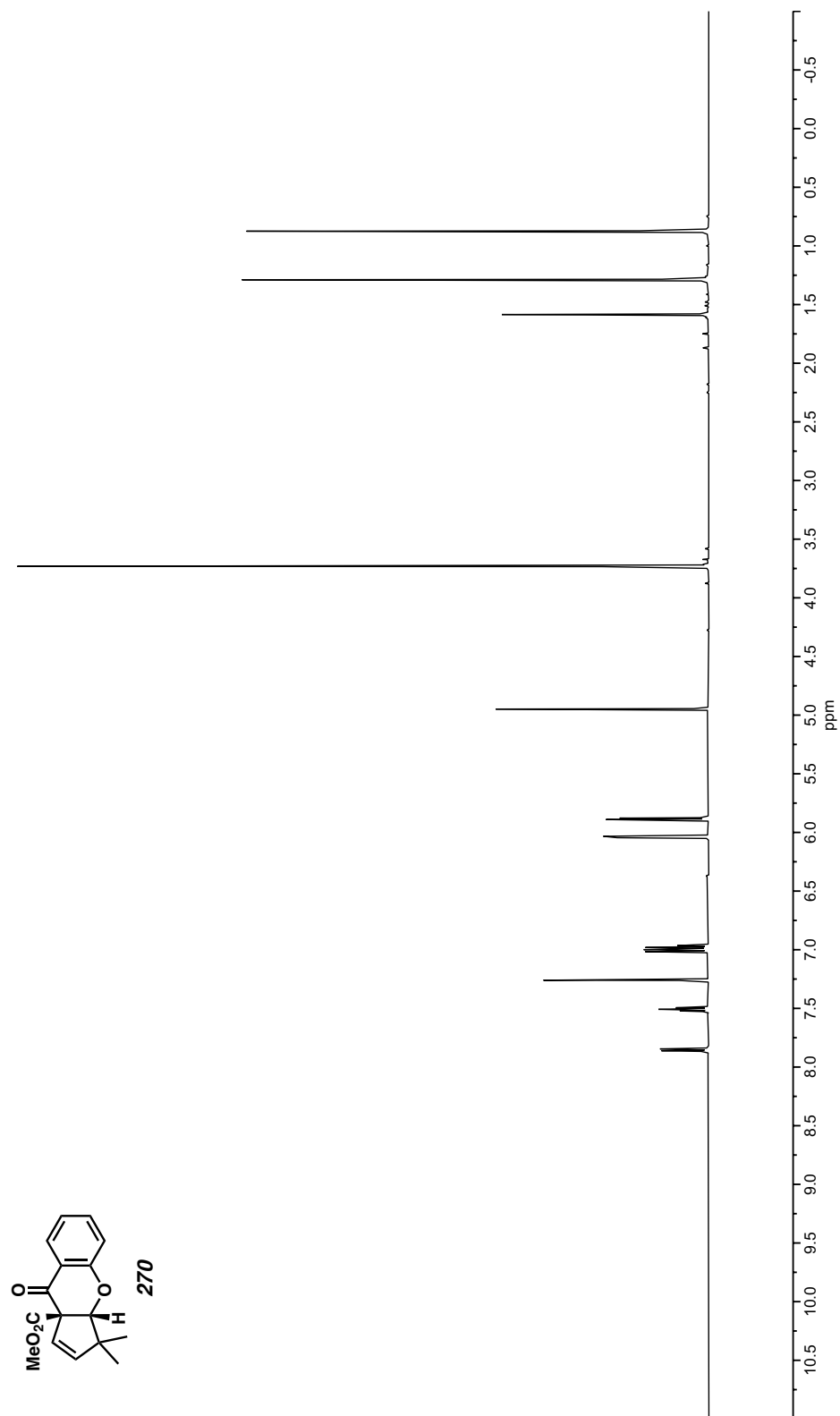


Figure A9.5 ¹H NMR (500 MHz, CDCl₃) of compound 270.

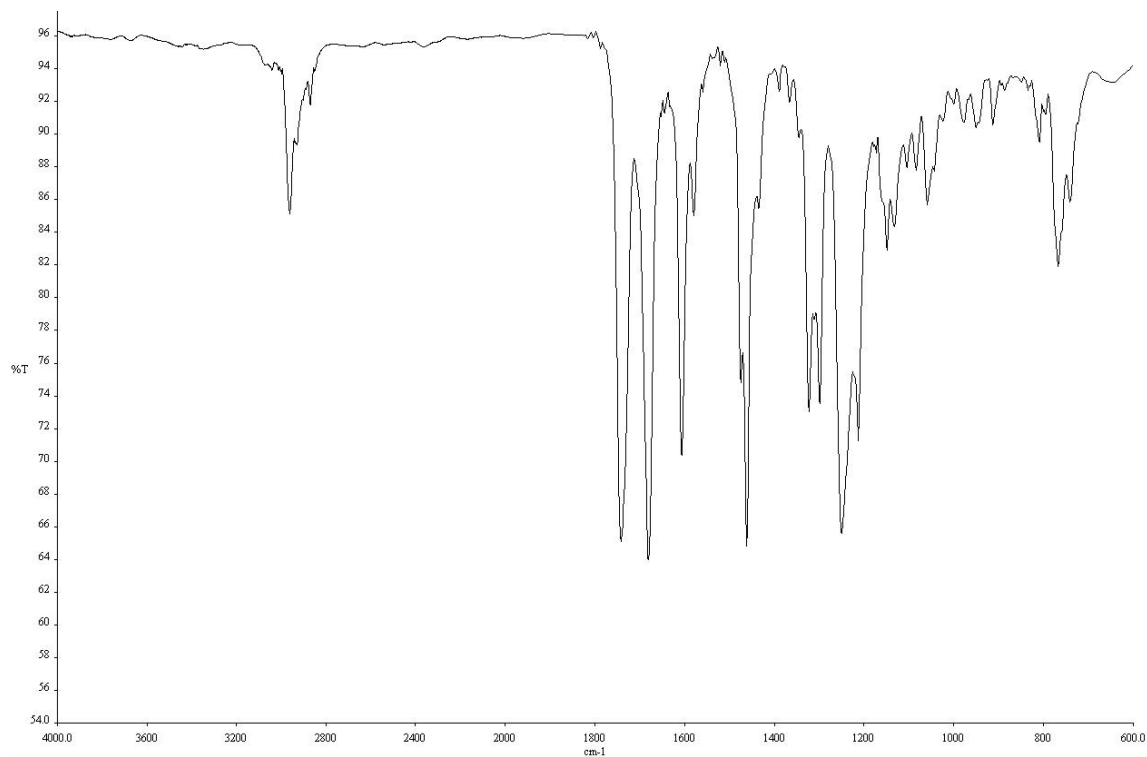


Figure A9.6 Infrared spectrum (Thin Film, NaCl) of compound 270.

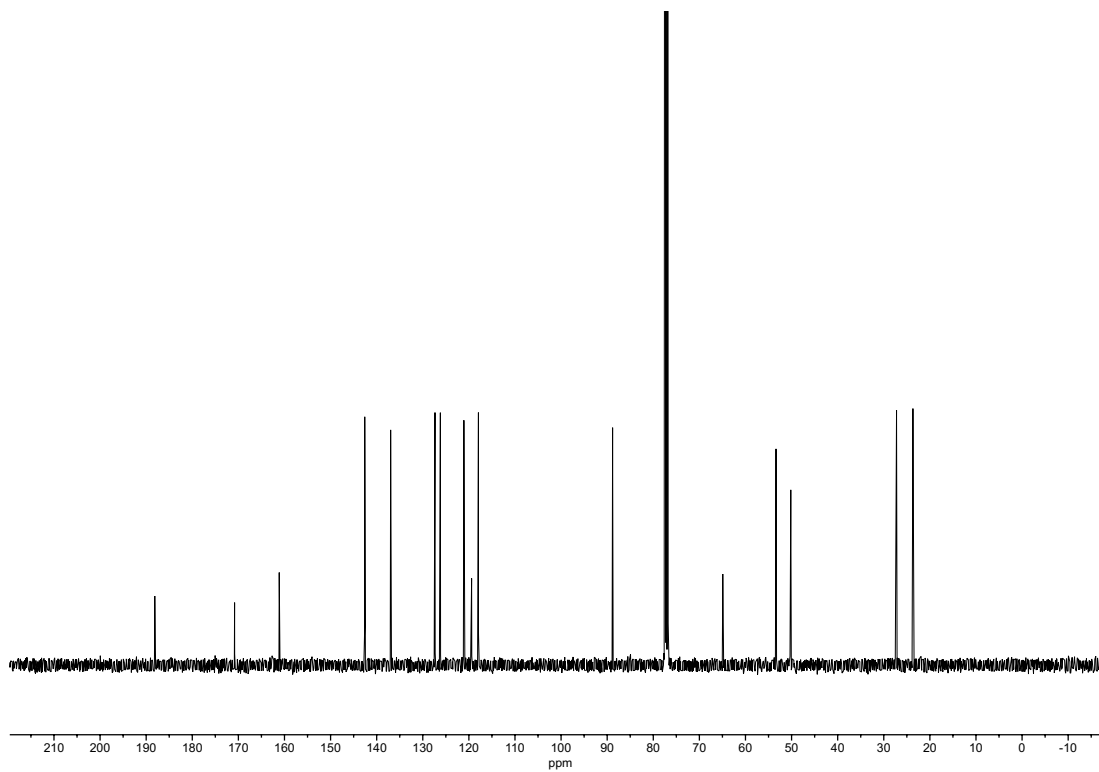


Figure A9.7 ¹³C NMR (100 MHz, CDCl₃) of compound 270.

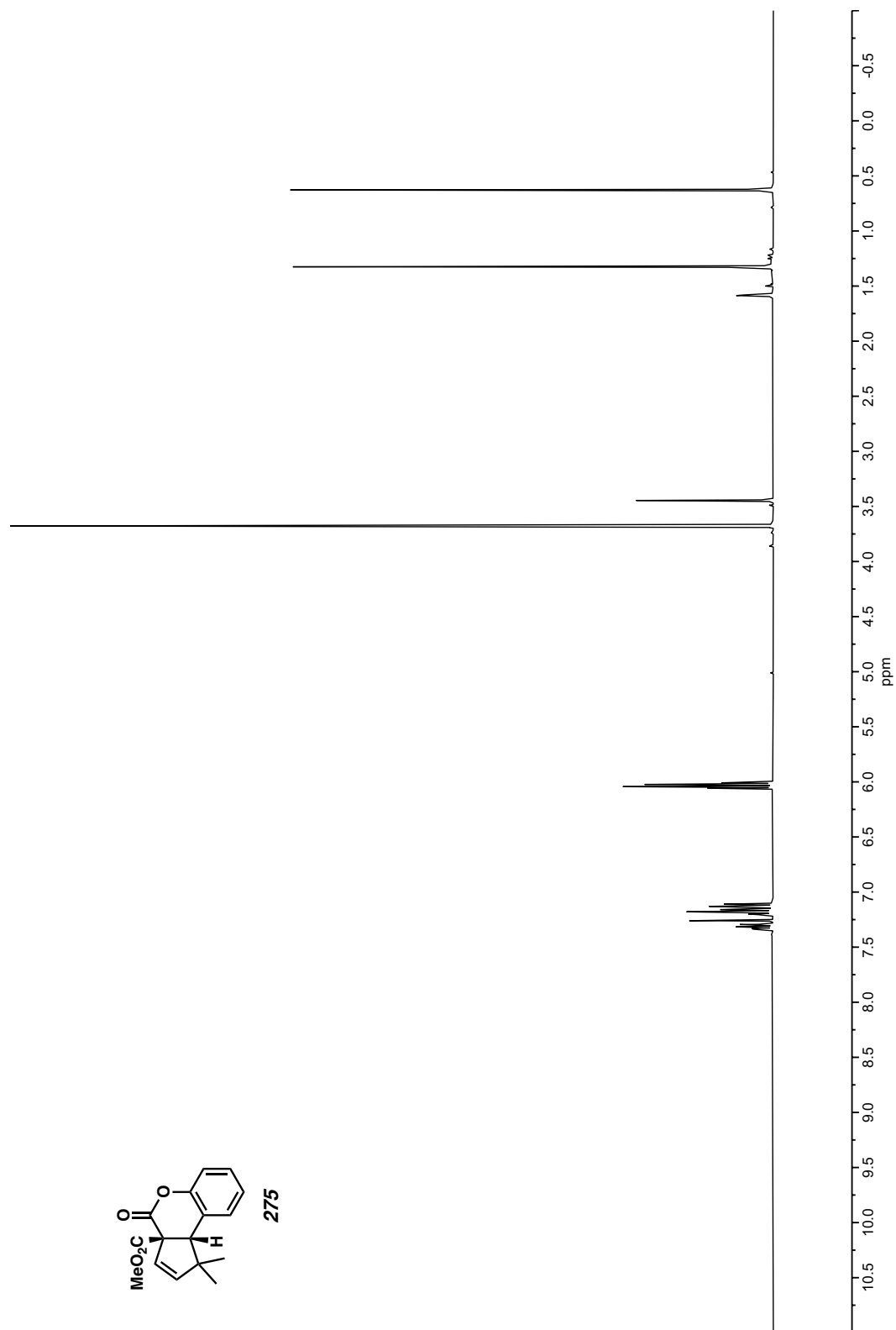


Figure A9.8 ¹H NMR (400 MHz, CDCl₃) of compound 275.

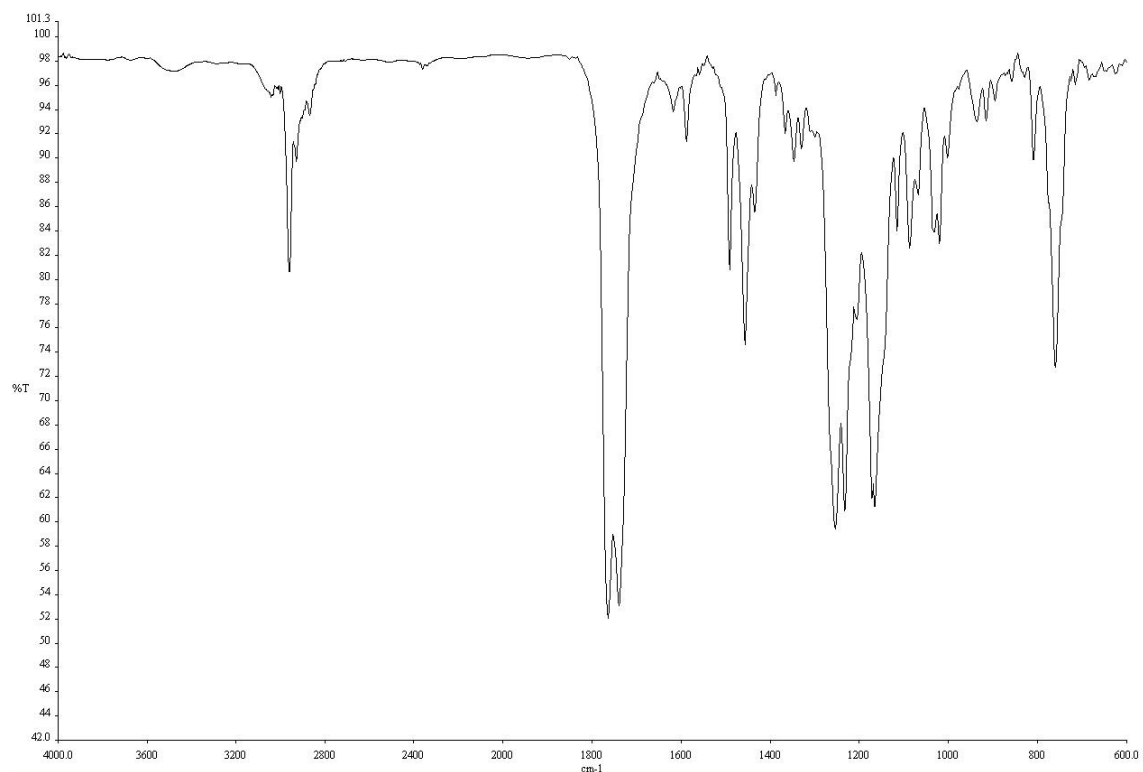


Figure A9.9 Infrared spectrum (Thin Film, NaCl) of compound 275.

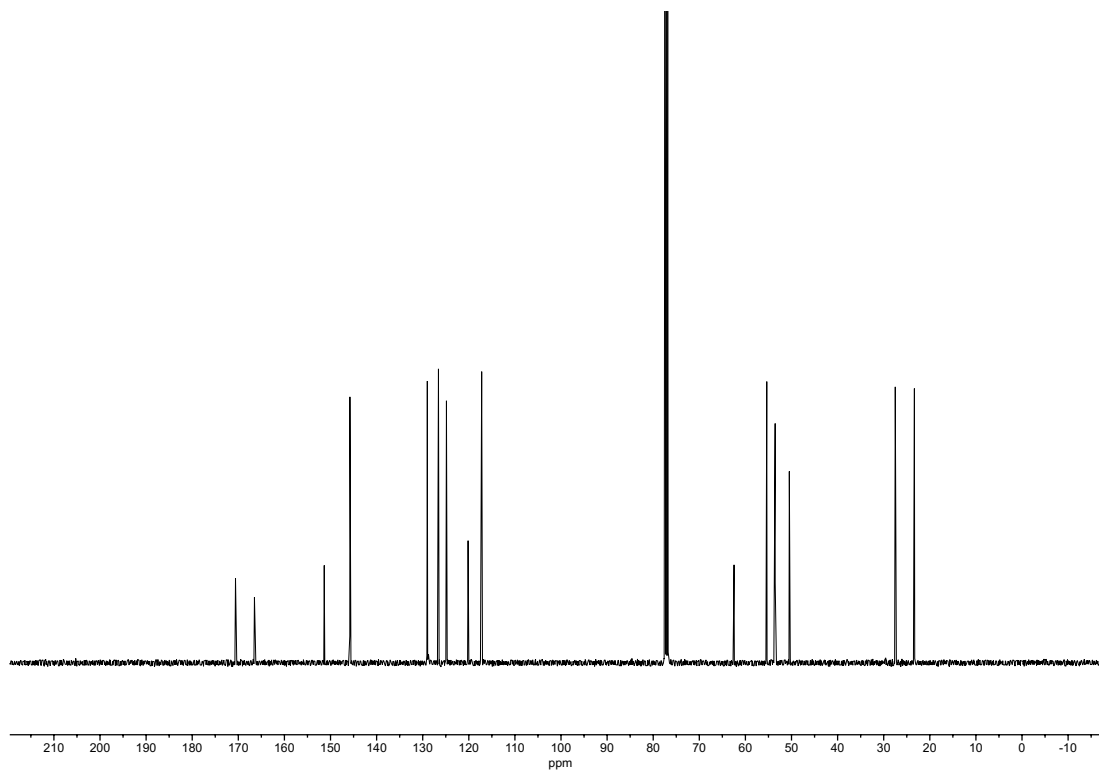


Figure A9.10 ¹³C NMR (100 MHz, CDCl₃) of compound 275.

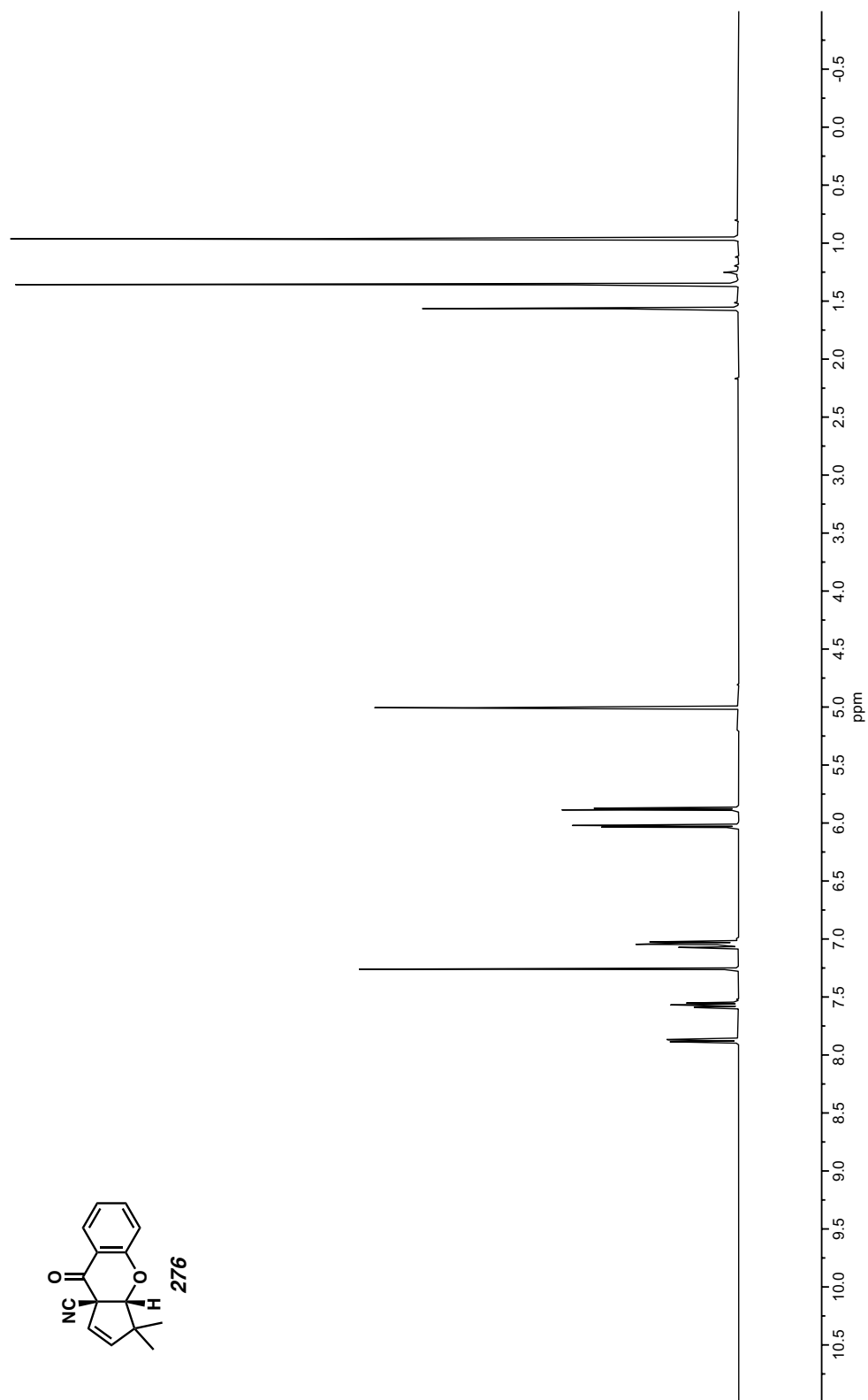


Figure A9.11 ¹H NMR (400 MHz, CDCl₃) of compound **276**.

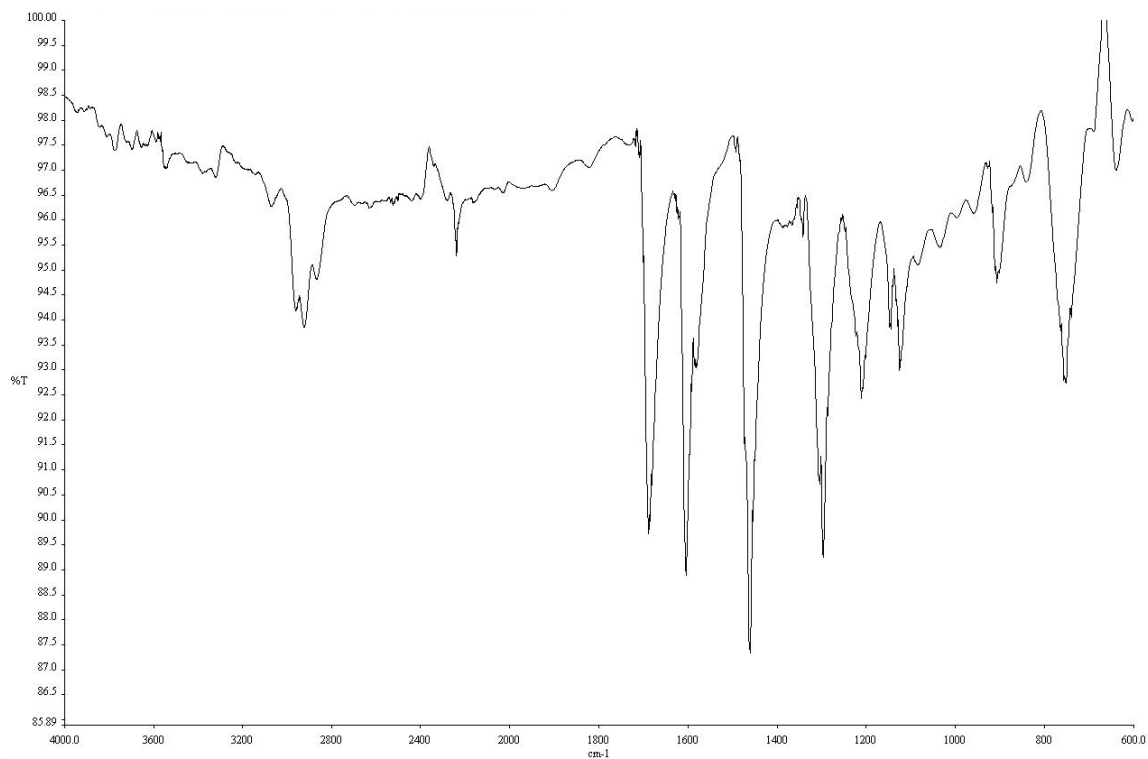


Figure A9.12 Infrared spectrum (Thin Film, NaCl) of compound 276.

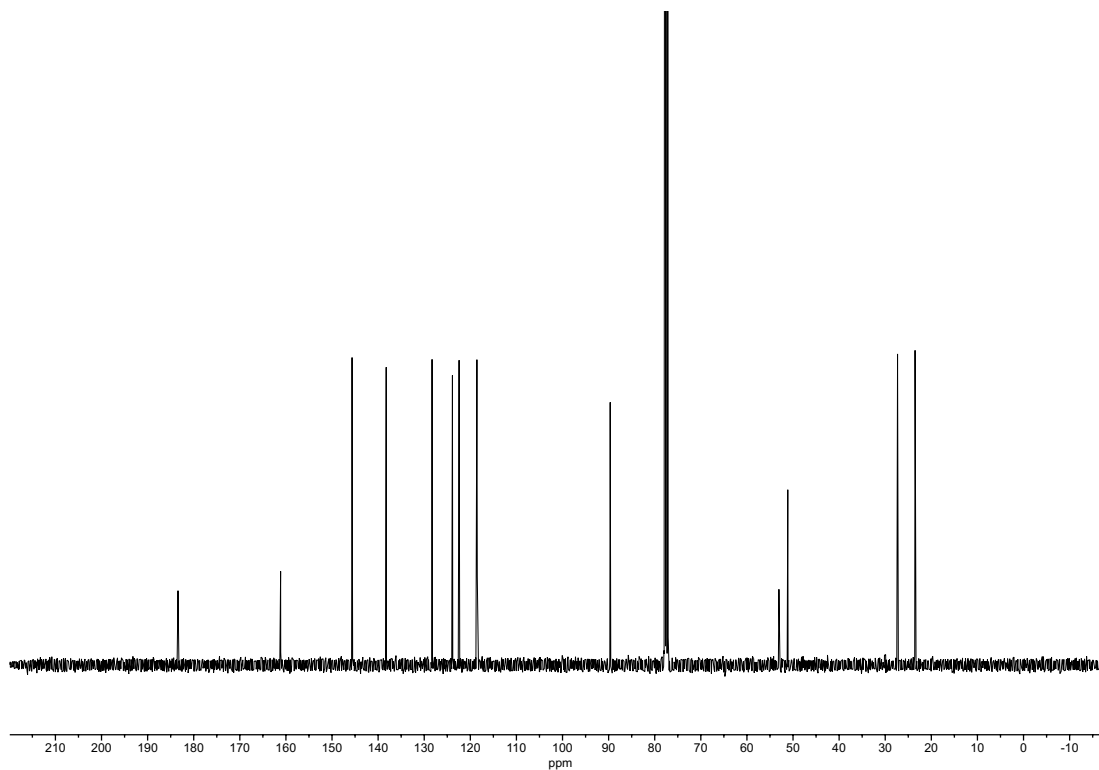


Figure A9.13 ¹³C NMR (100 MHz, CDCl₃) of compound 276.

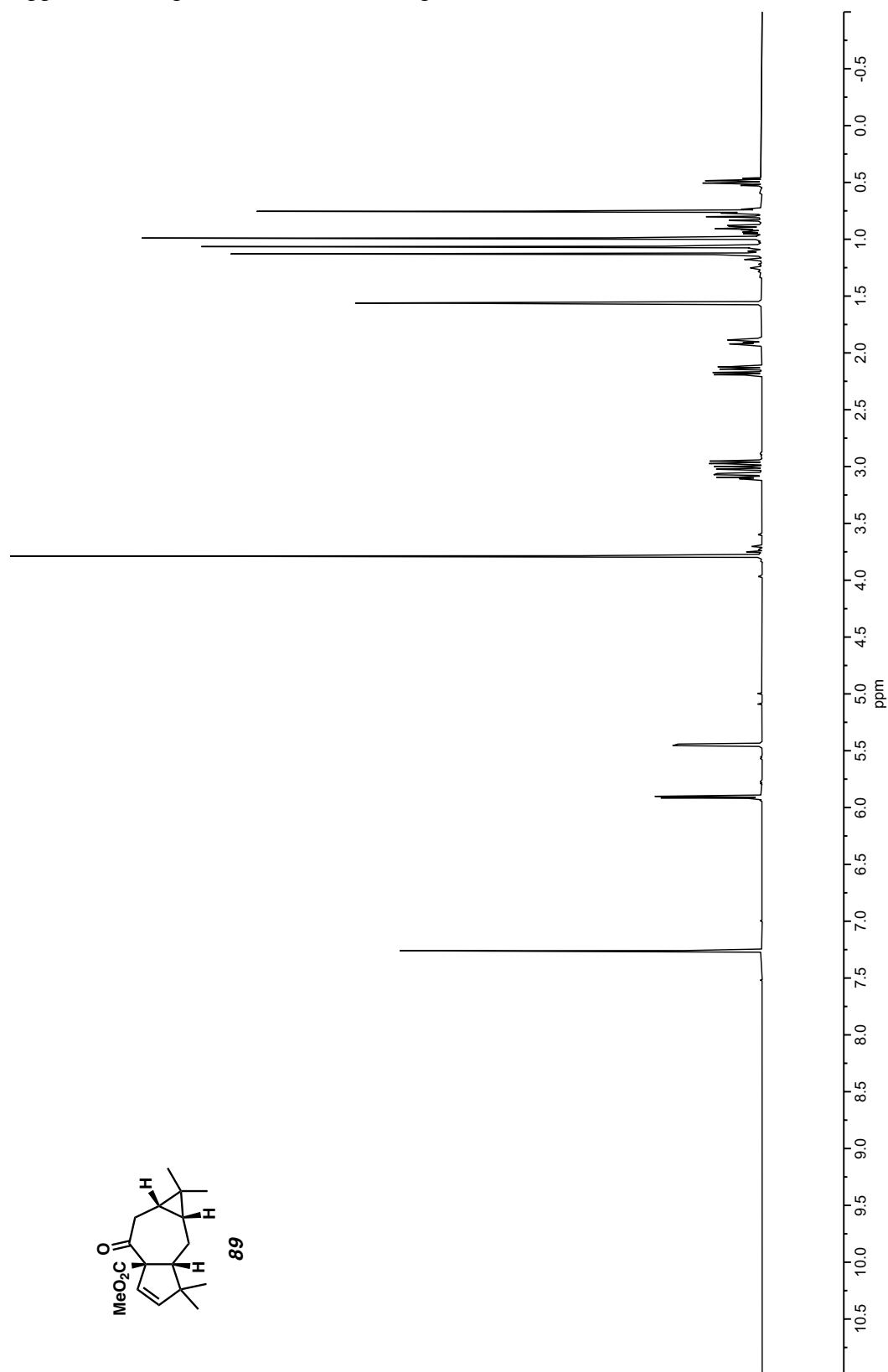


Figure A9.14 ¹H NMR (400 MHz, CDCl₃) of compound **89**.

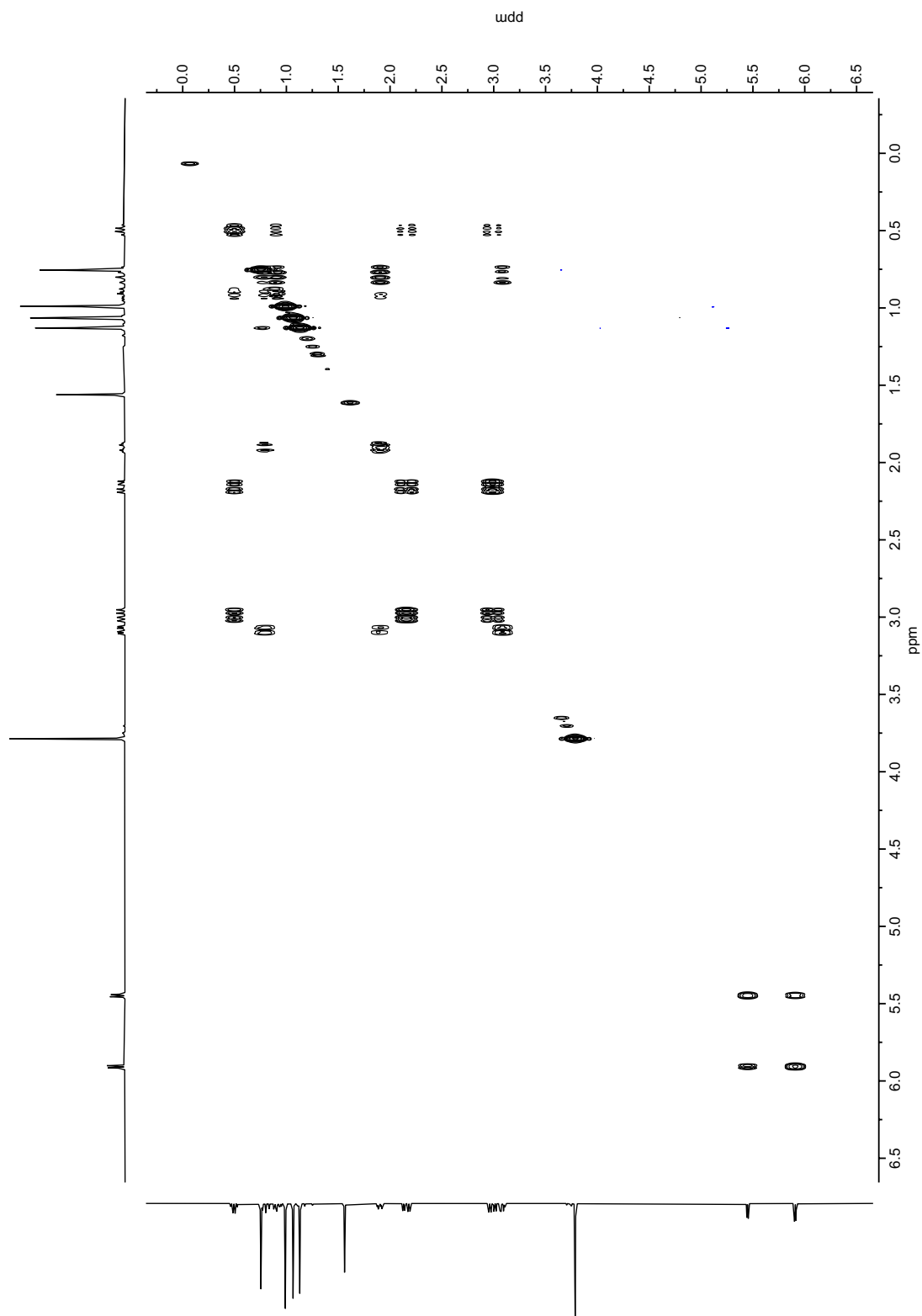


Figure A9.15 COSY NMR (400 MHz, CDCl_3) of compound **89**.

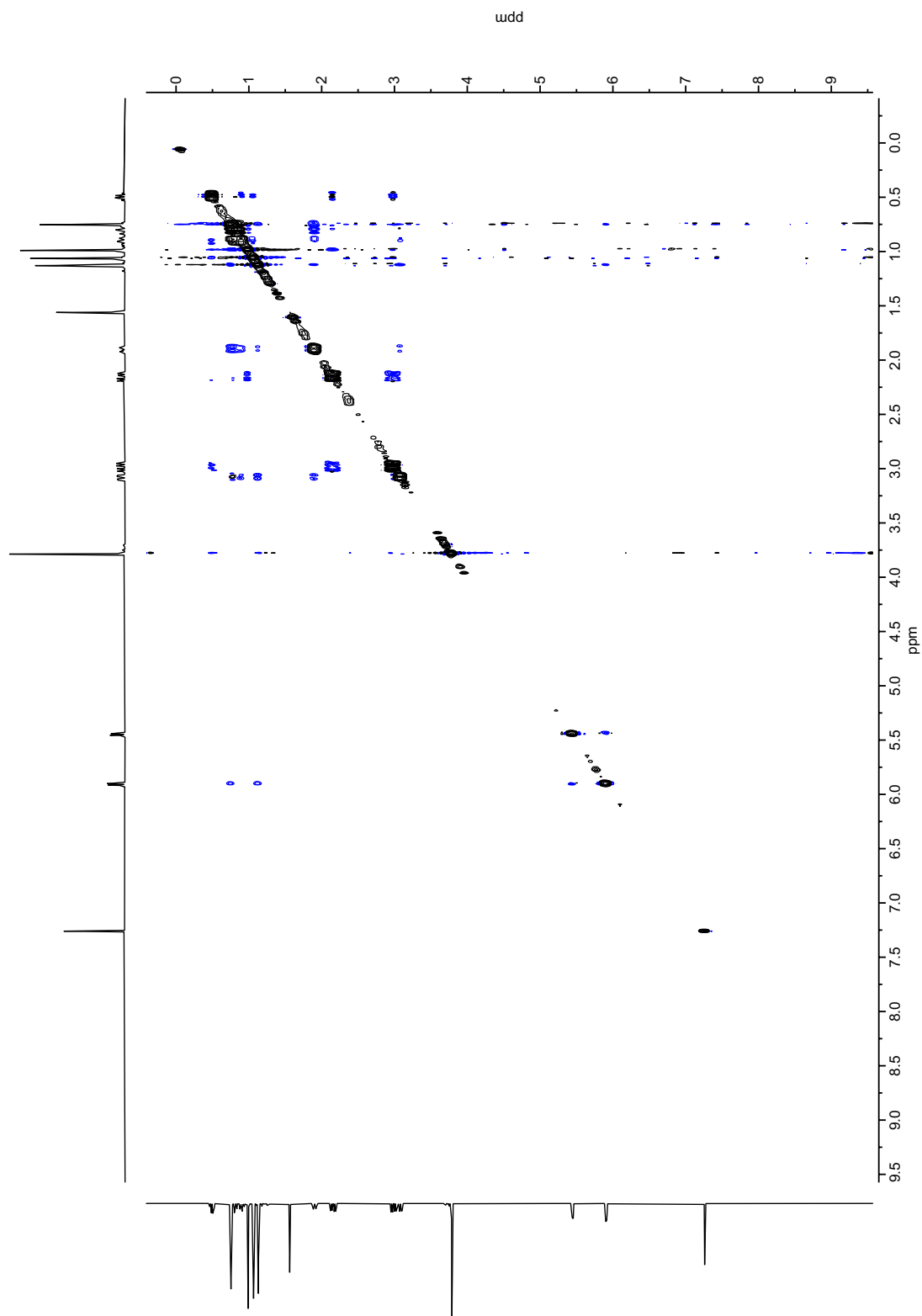


Figure A9.16 NOESY NMR (400 MHz, CDCl_3) of compound **89**.

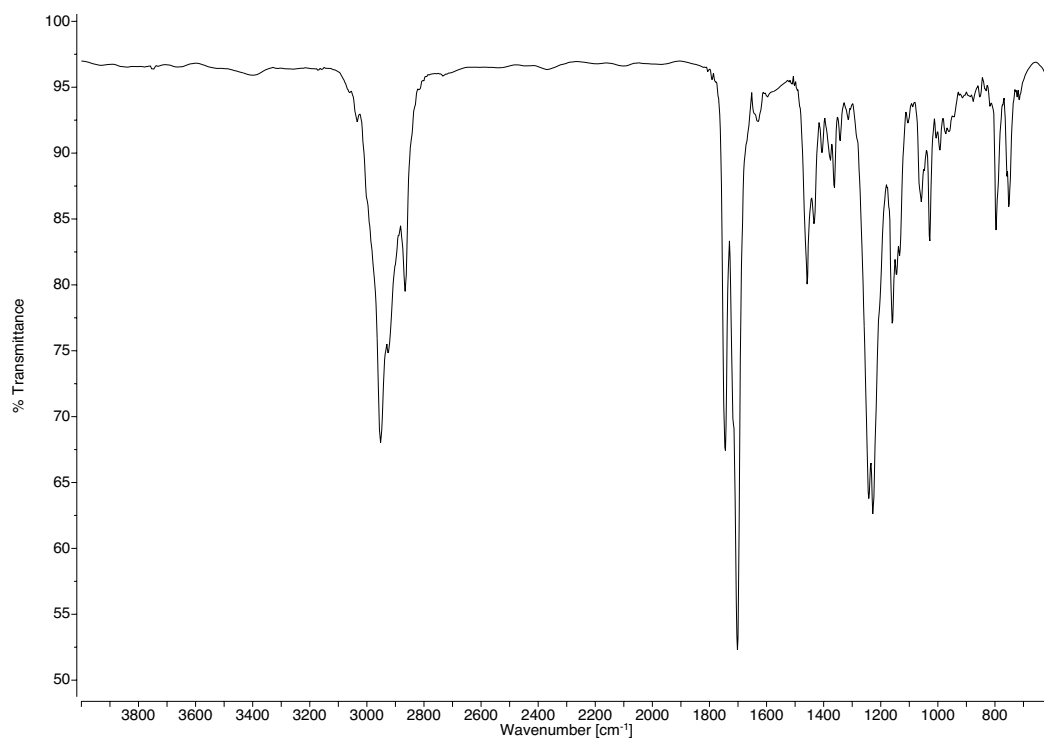


Figure A9.17 Infrared spectrum (Thin Film, NaCl) of compound **89**.

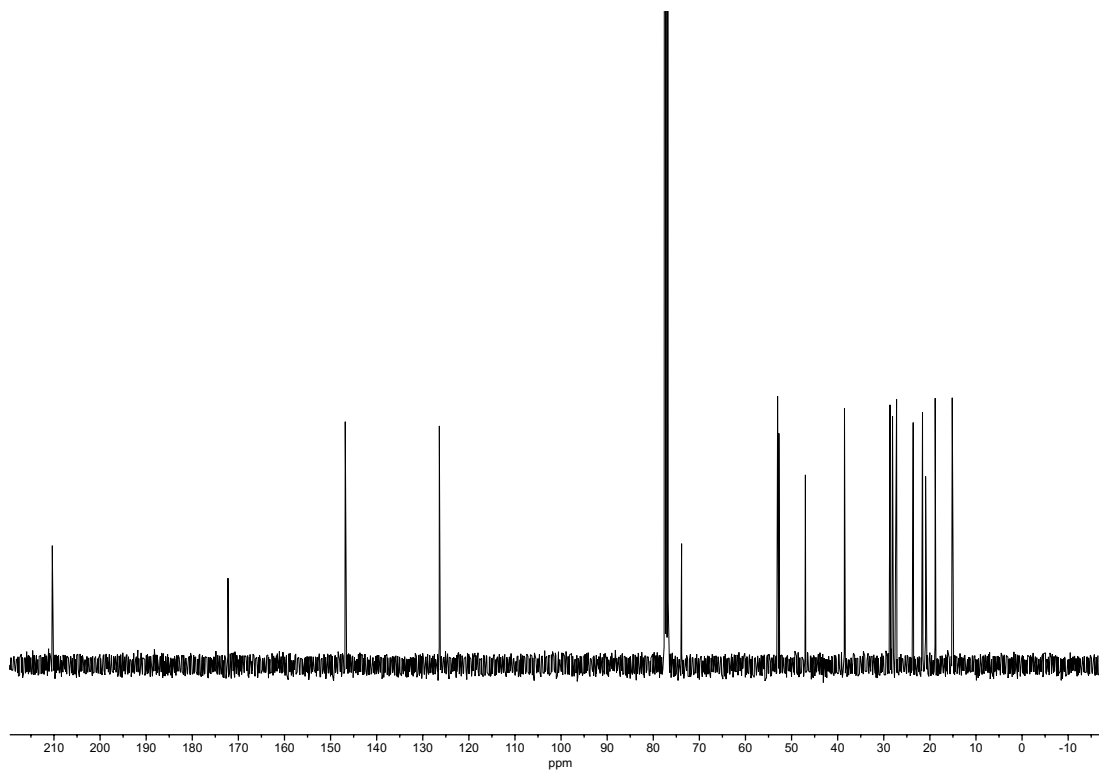


Figure A9.18 ¹³C NMR (100 MHz, CDCl₃) of compound **89**.

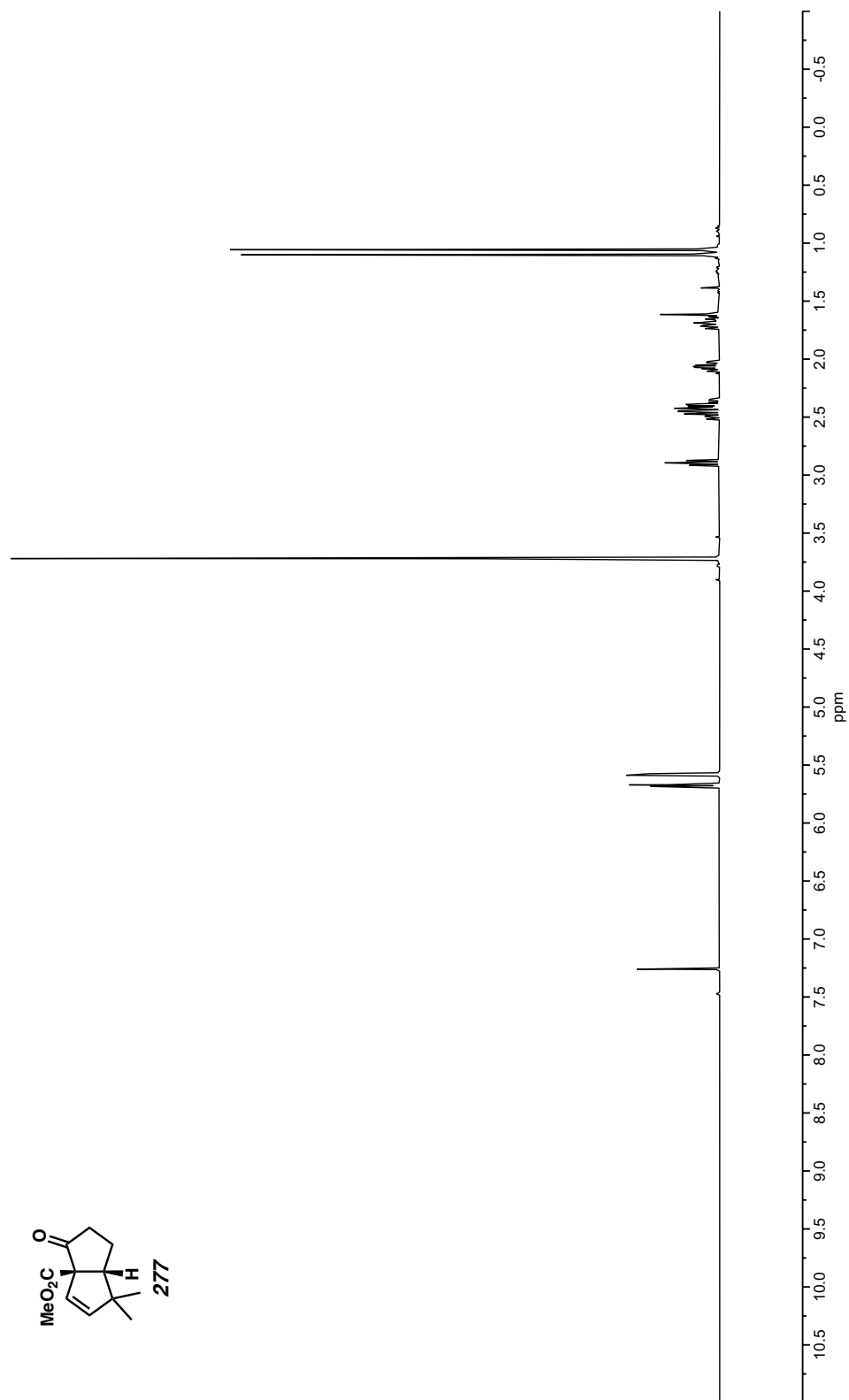


Figure A9.19 ¹H NMR (400 MHz, CDCl₃) of compound 277.

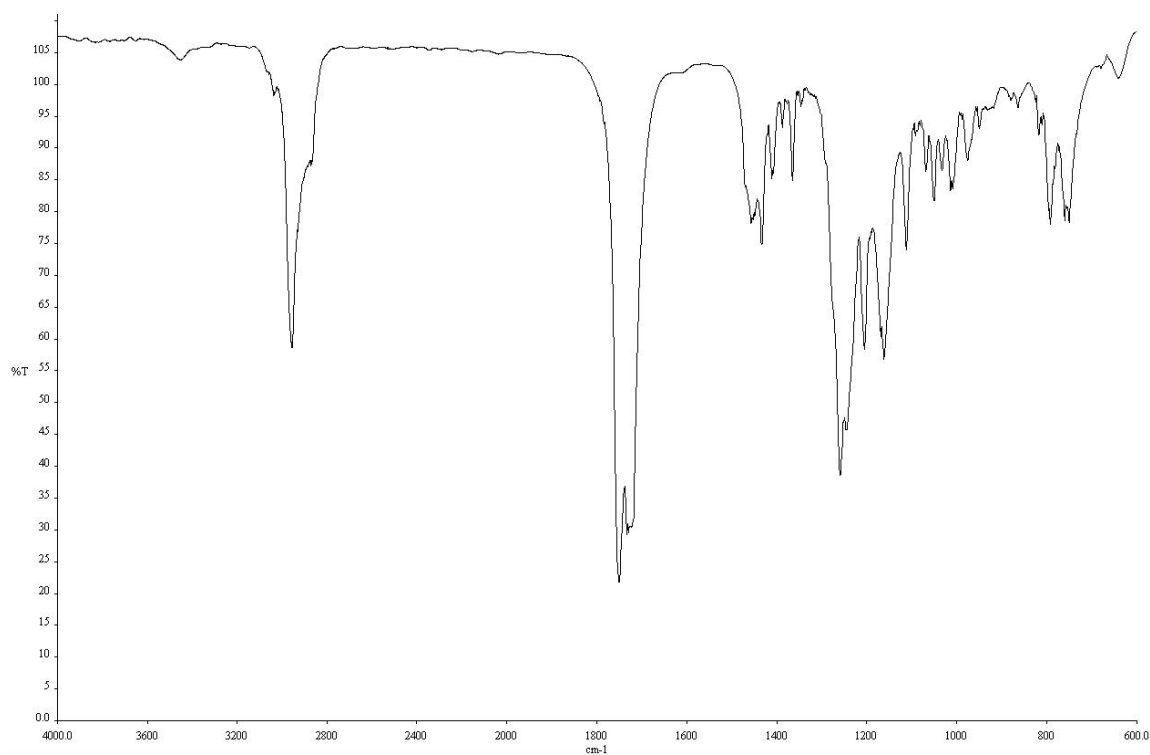


Figure A9.20 Infrared spectrum (Thin Film, NaCl) of compound 277.

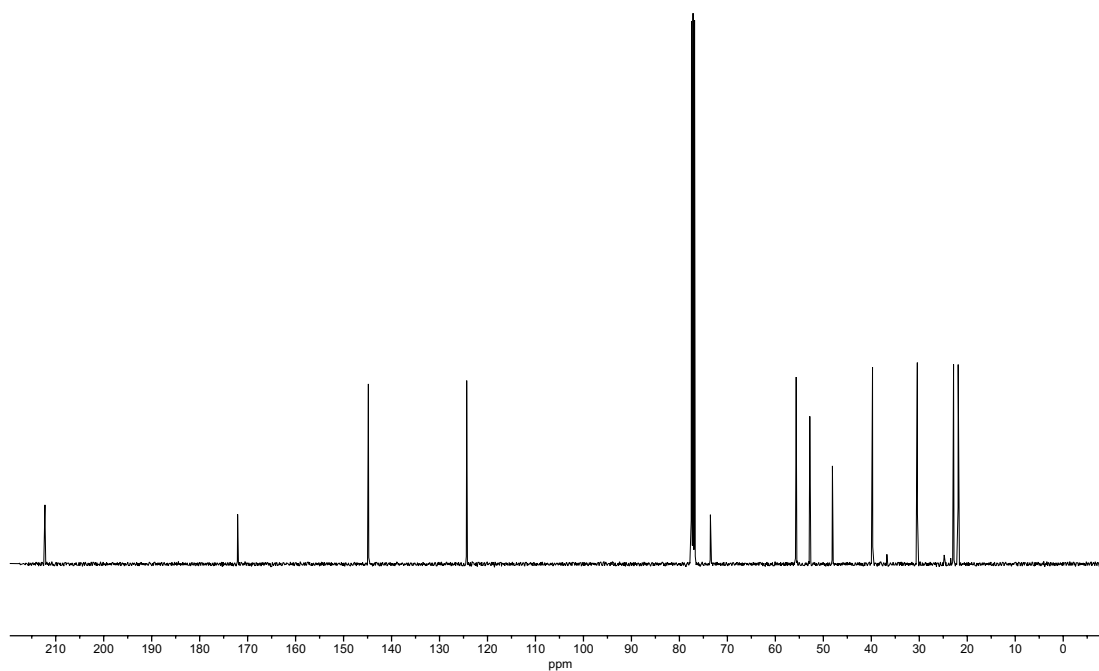


Figure A9.21 ¹³C NMR (100 MHz, CDCl₃) of compound 277.

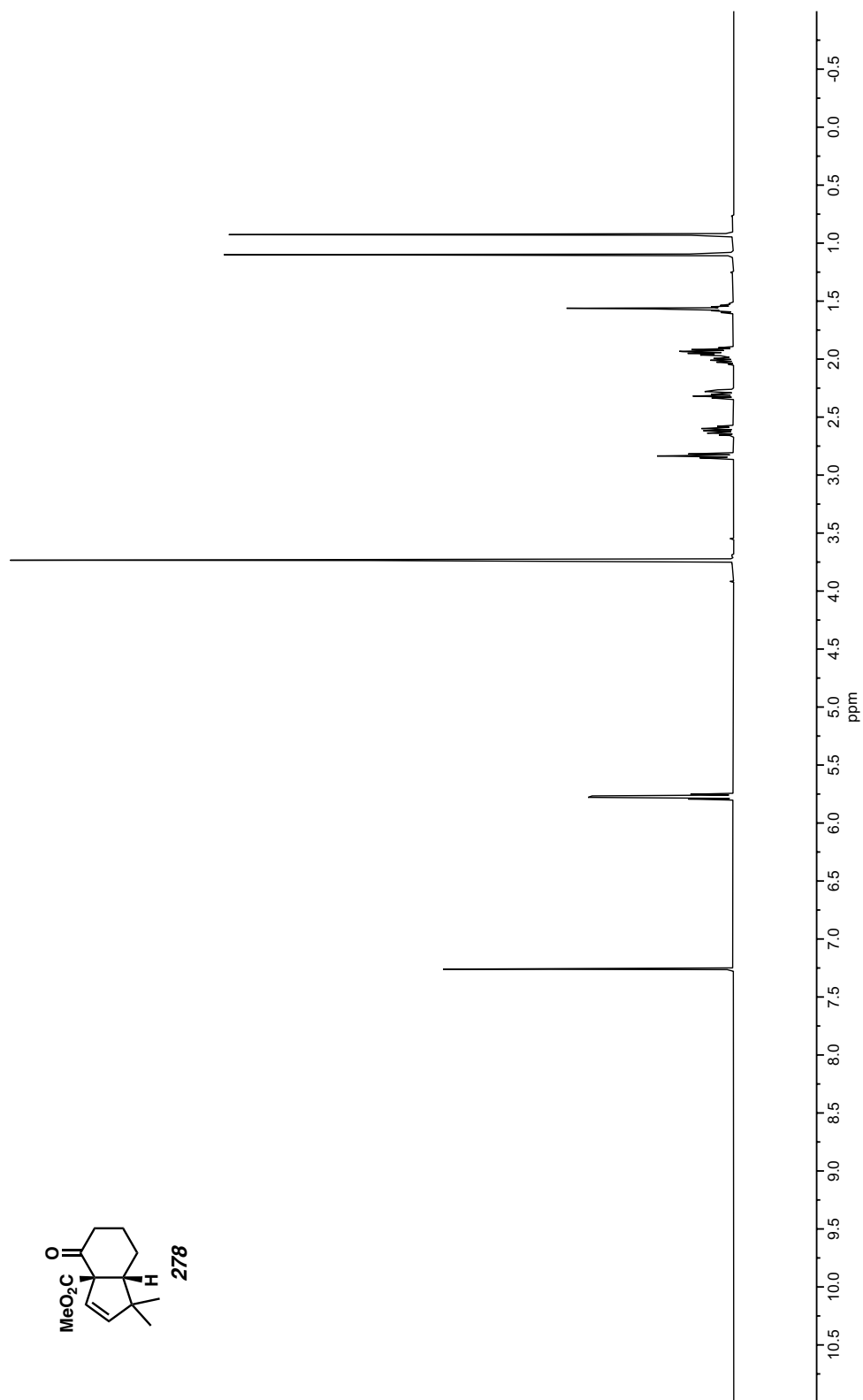


Figure A9.22 ^1H NMR (400 MHz, CDCl_3) of compound 278.

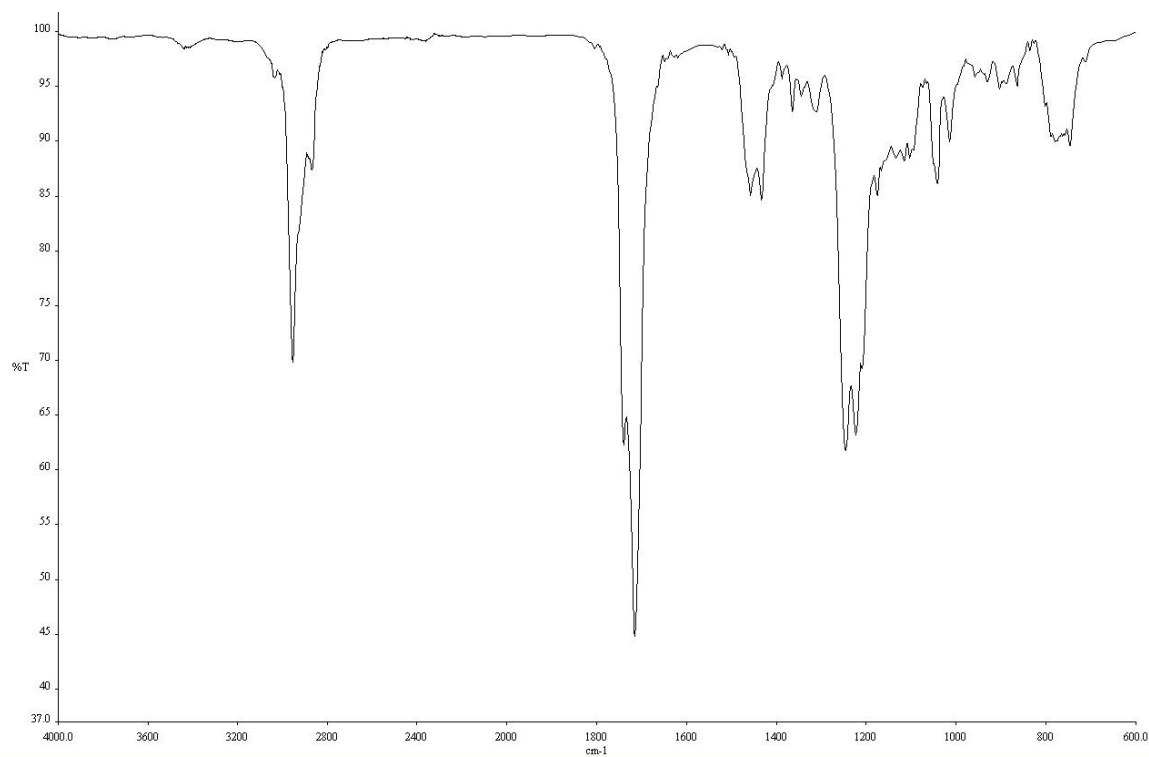


Figure A9.23 Infrared spectrum (Thin Film, NaCl) of compound 278.

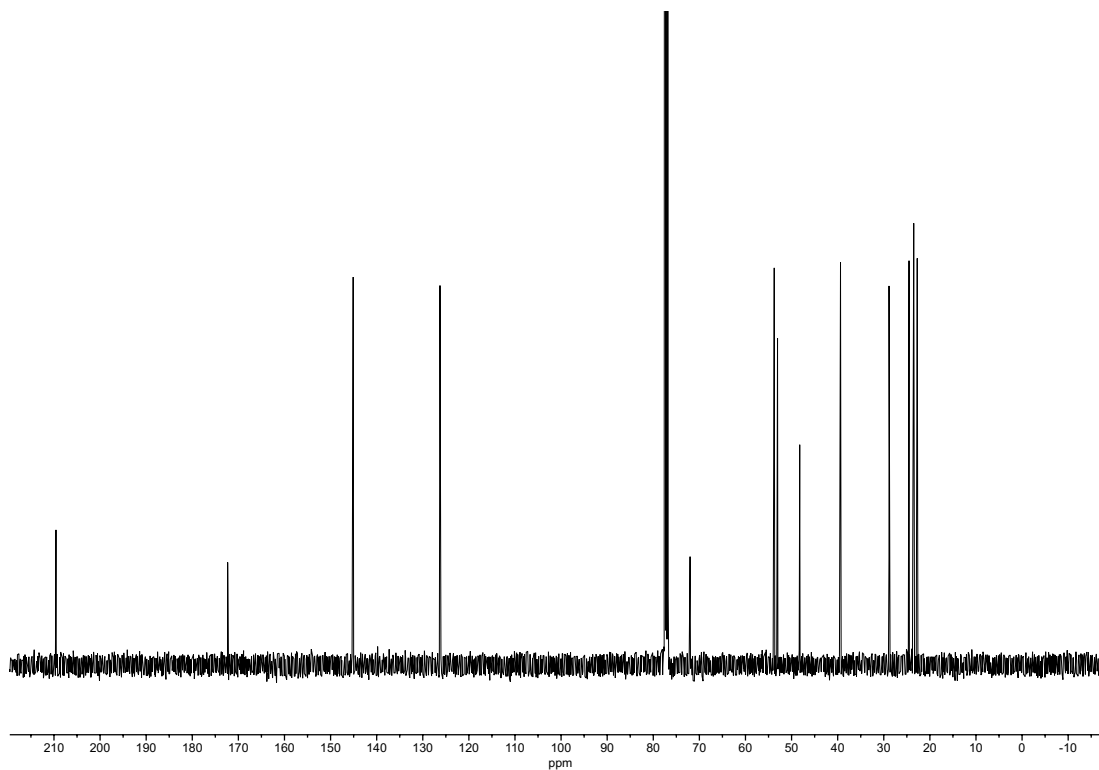


Figure A9.24 ¹³C NMR (100 MHz, CDCl₃) of compound 278.

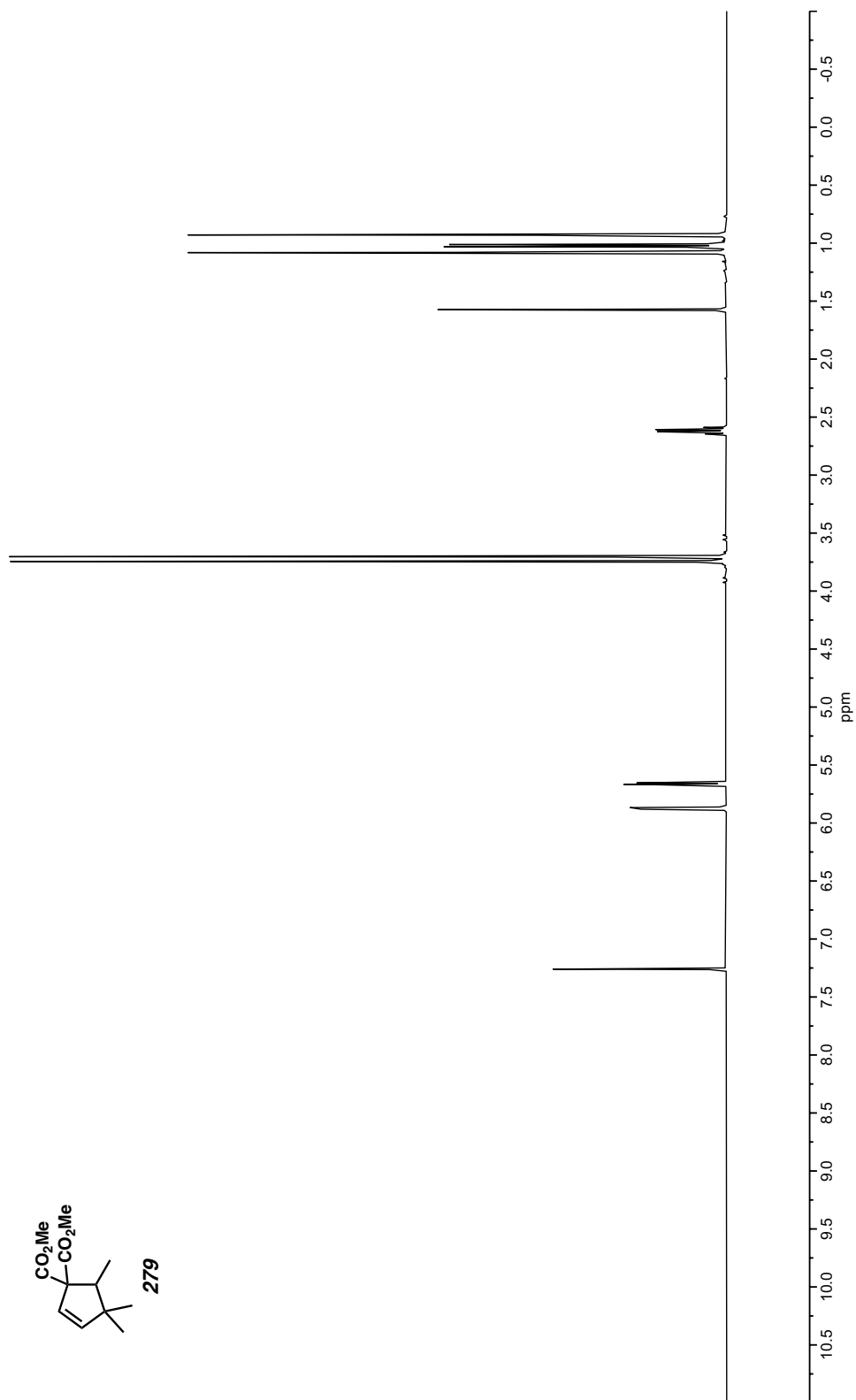


Figure A9.25 ^1H NMR (400 MHz, CDCl_3) of compound **279**.

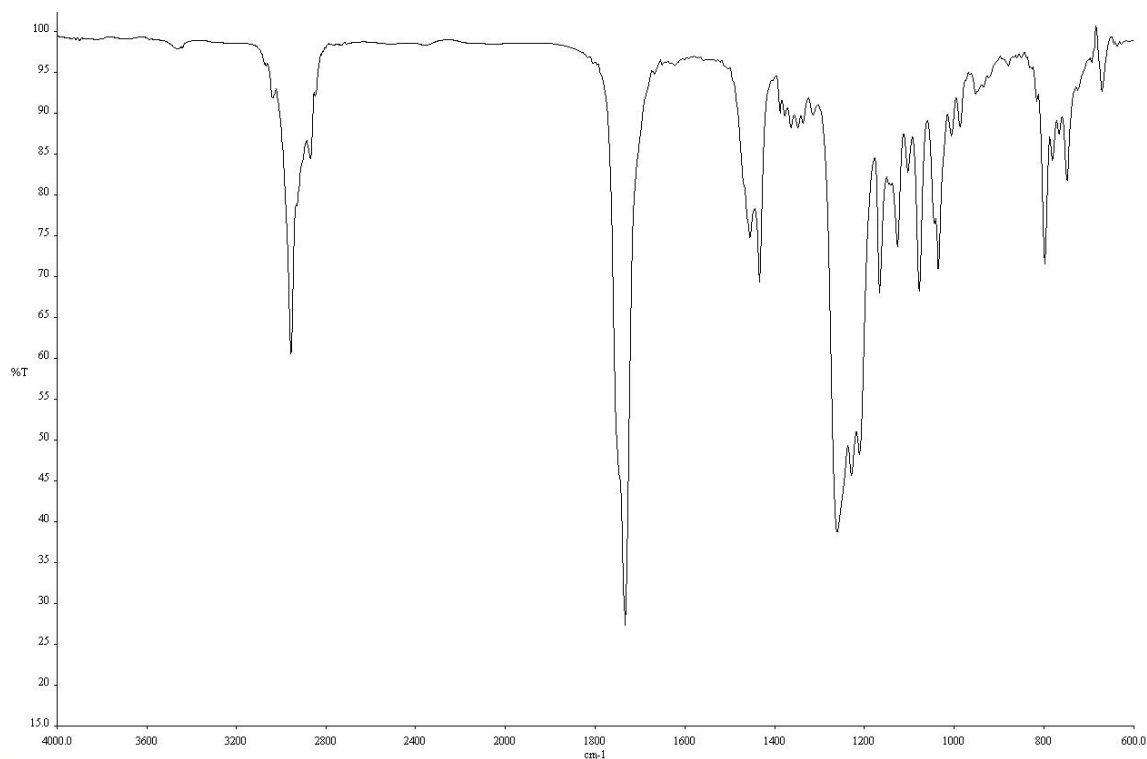


Figure A9.26 Infrared spectrum (Thin Film, NaCl) of compound **279**.

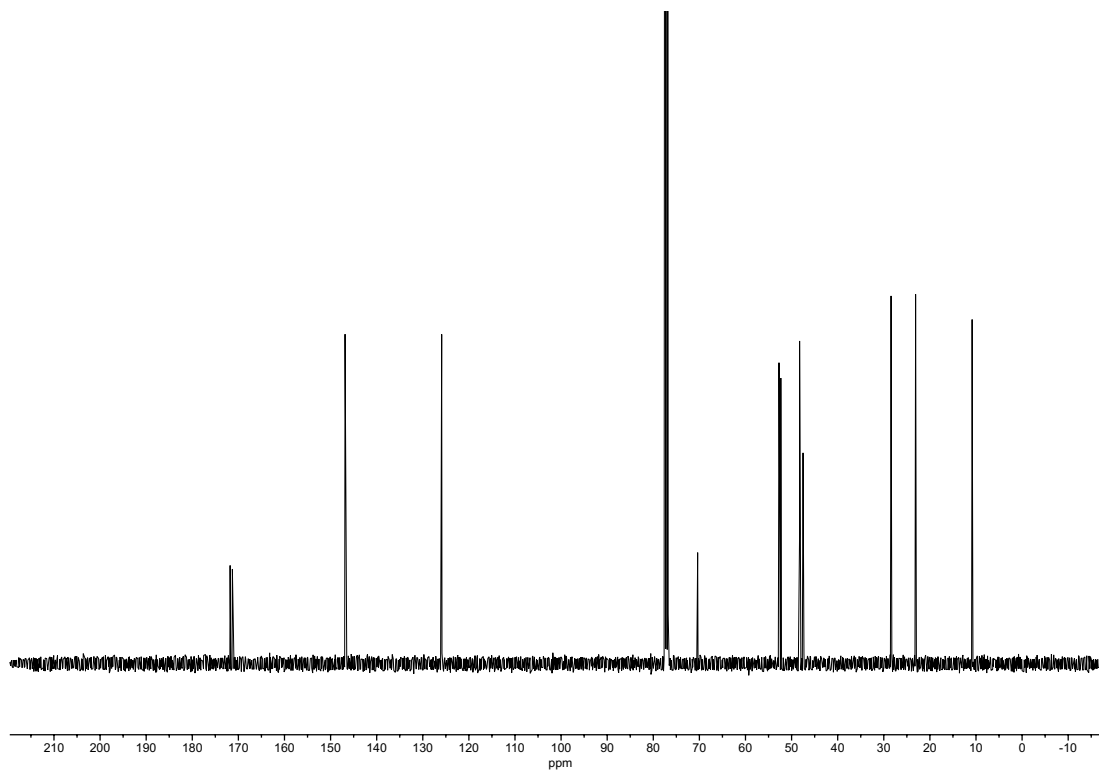


Figure A9.27 ¹³C NMR (100 MHz, CDCl₃) of compound **279**.

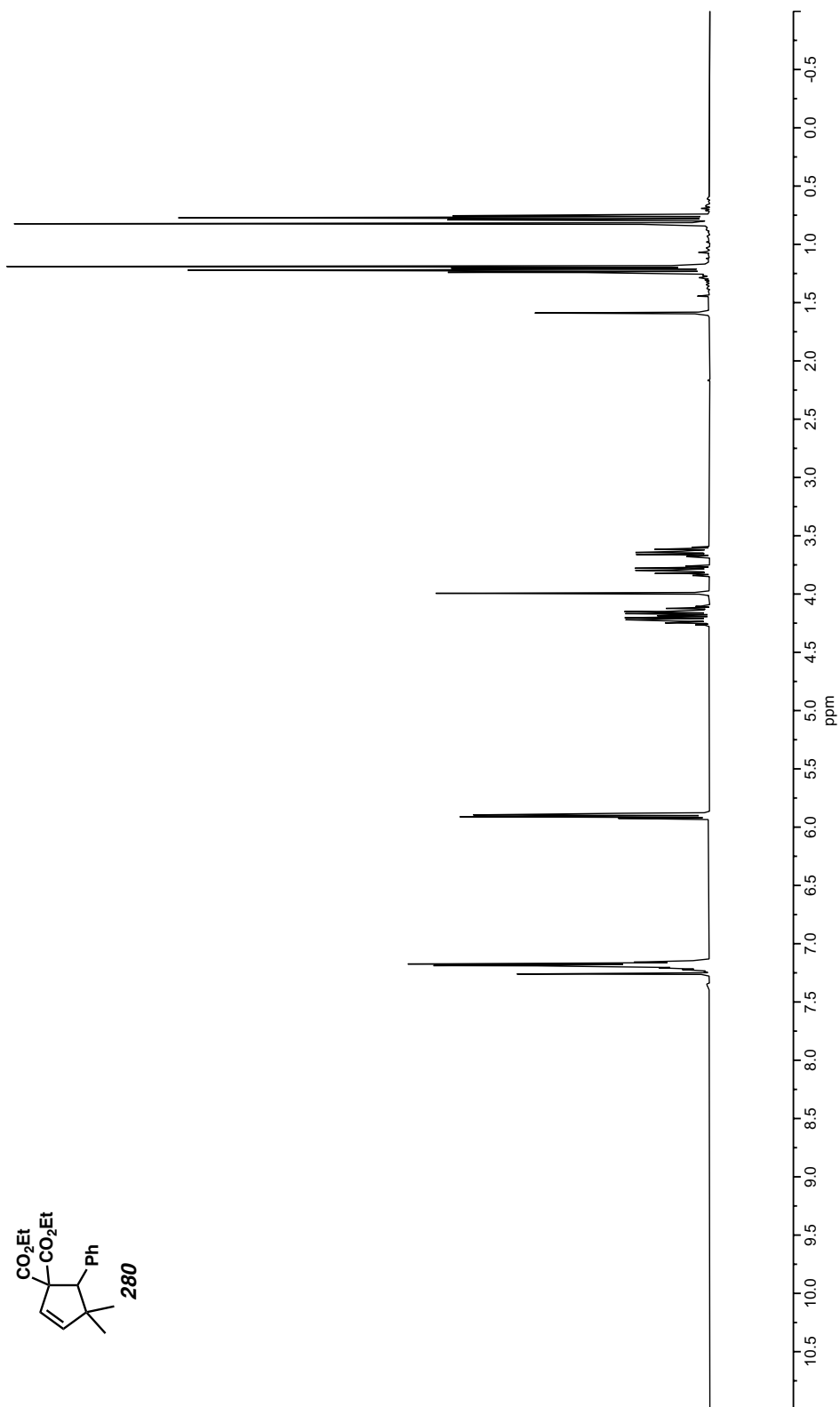


Figure A9.28 ^1H NMR (400 MHz, CDCl_3) of compound 280.

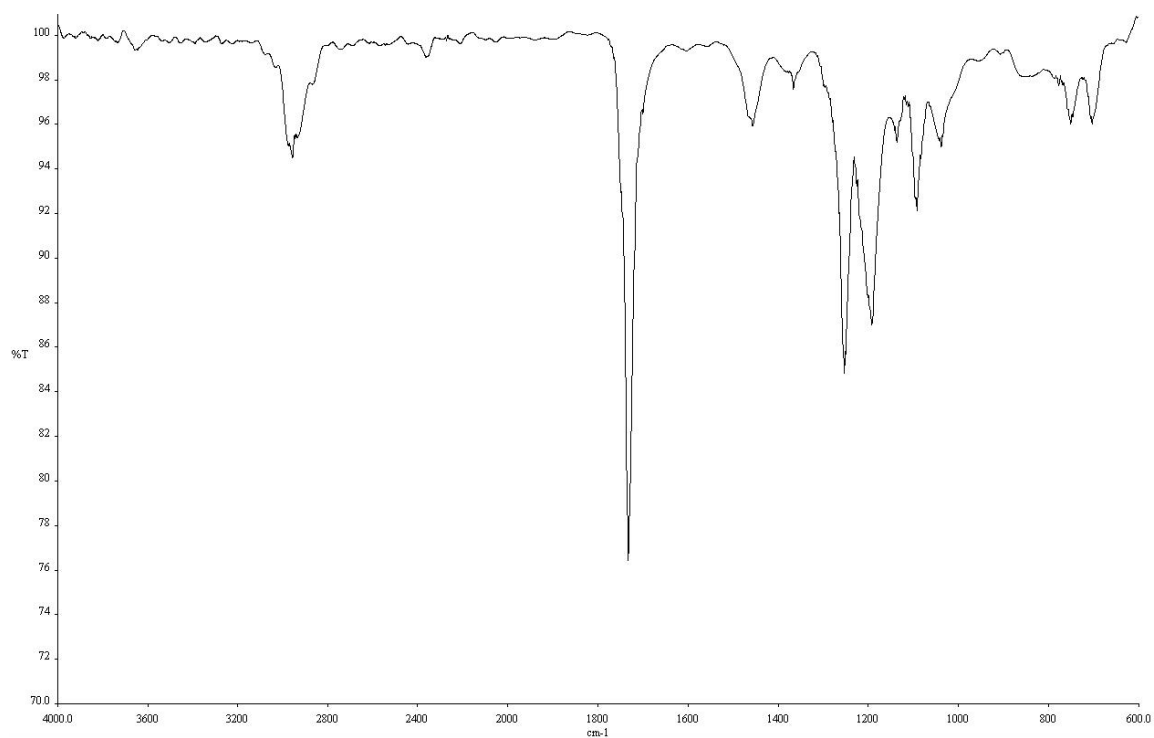


Figure A9.29 Infrared spectrum (Thin Film, NaCl) of compound **280**.

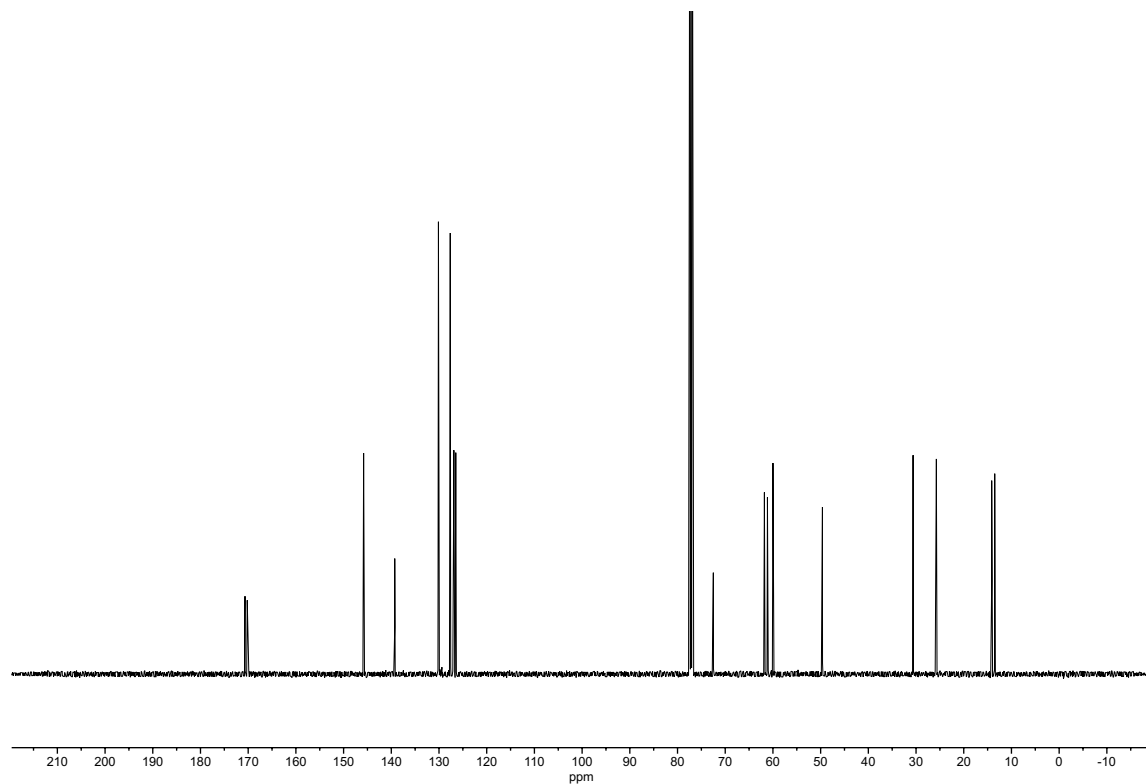


Figure A9.30 ¹³C NMR (100 MHz, CDCl₃) of compound **280**.

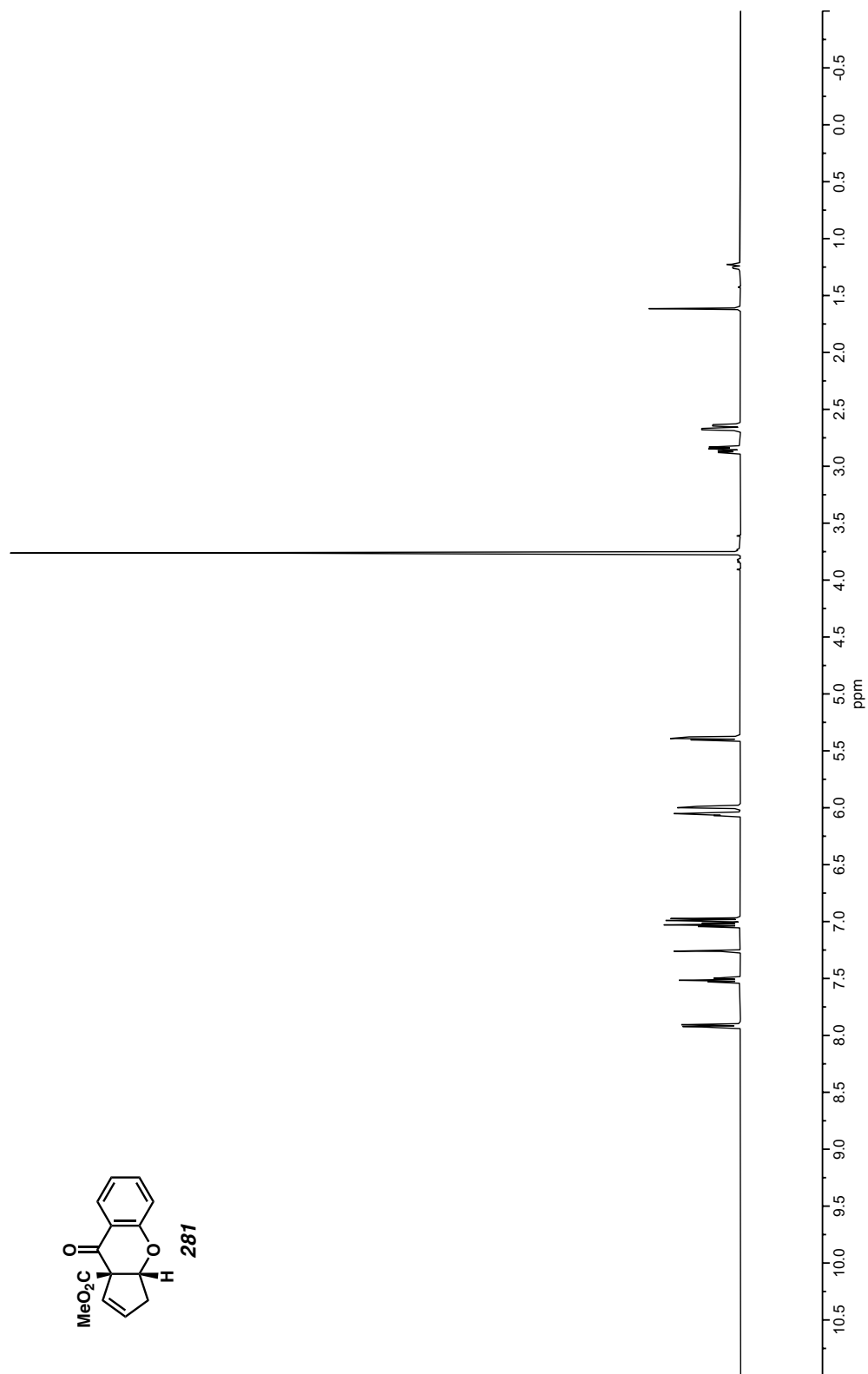


Figure A9.31 ¹H NMR (500 MHz, CDCl₃) of compound 281.

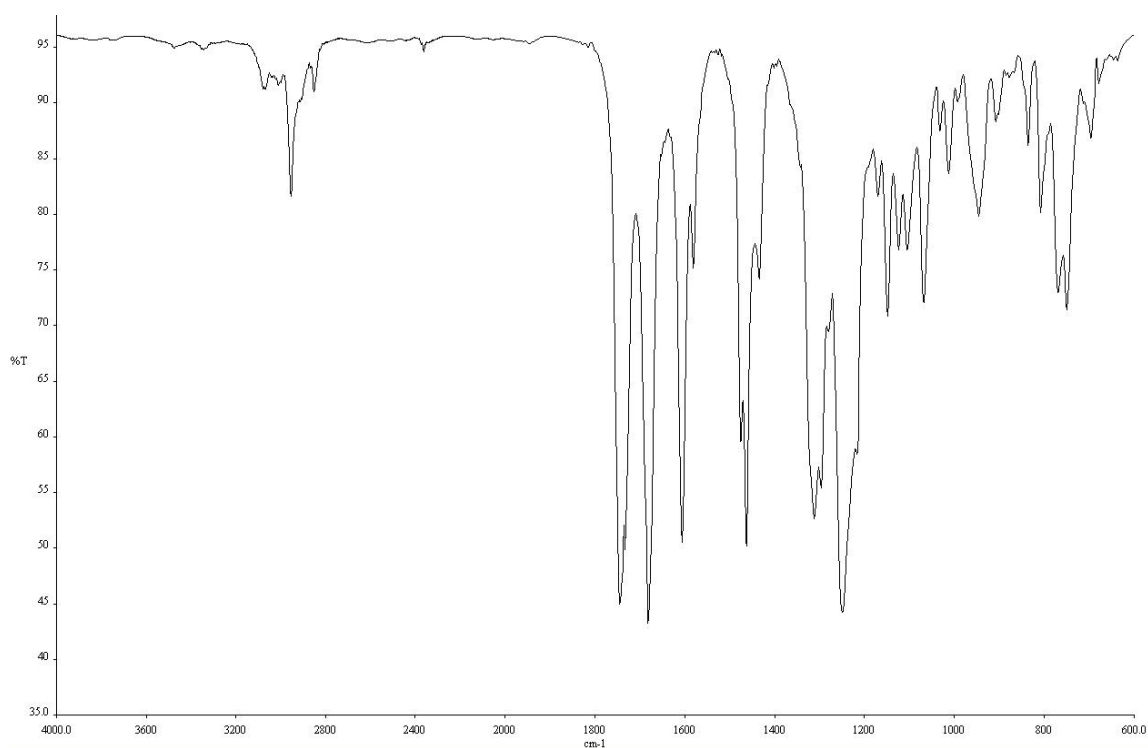


Figure A9.32 Infrared spectrum (Thin Film, NaCl) of compound **281**.

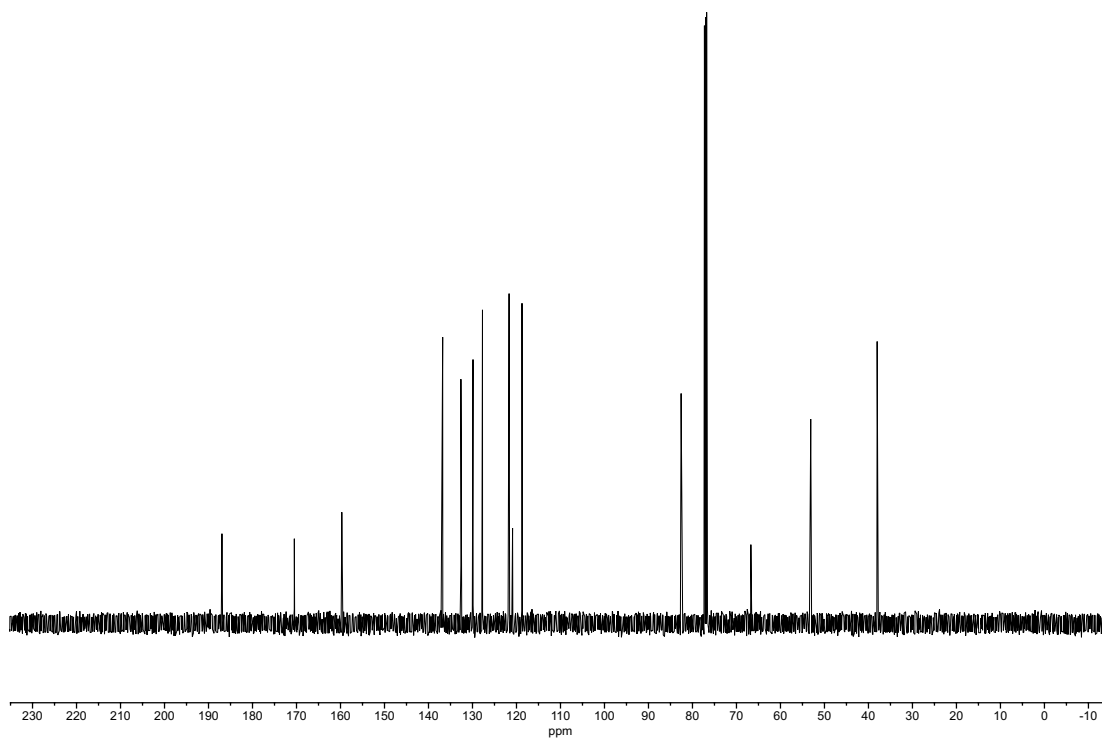


Figure A9.33 ¹³C NMR (100 MHz, CDCl₃) of compound **281**.

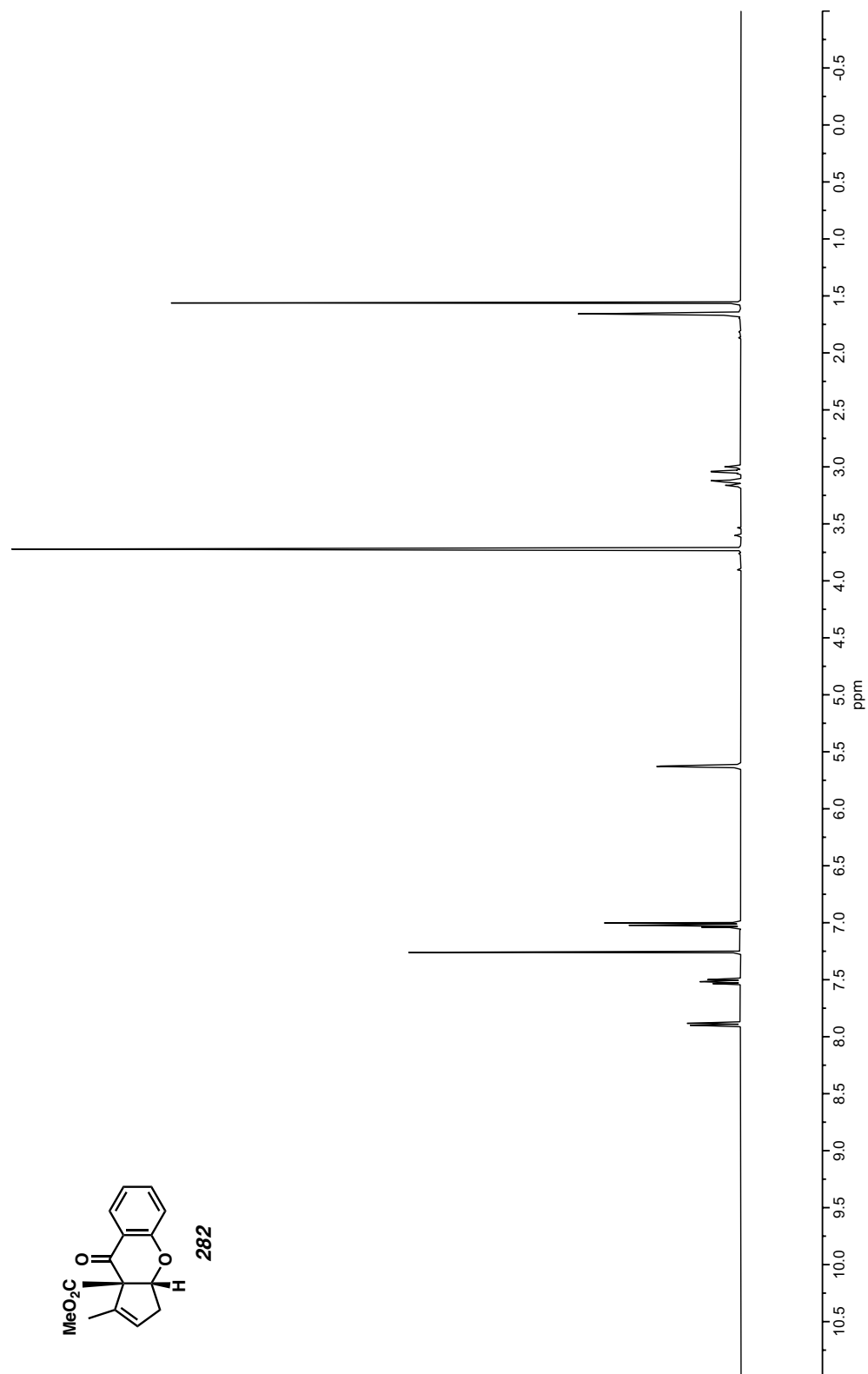


Figure A9.34 ^1H NMR (400 MHz, CDCl_3) of compound 282.

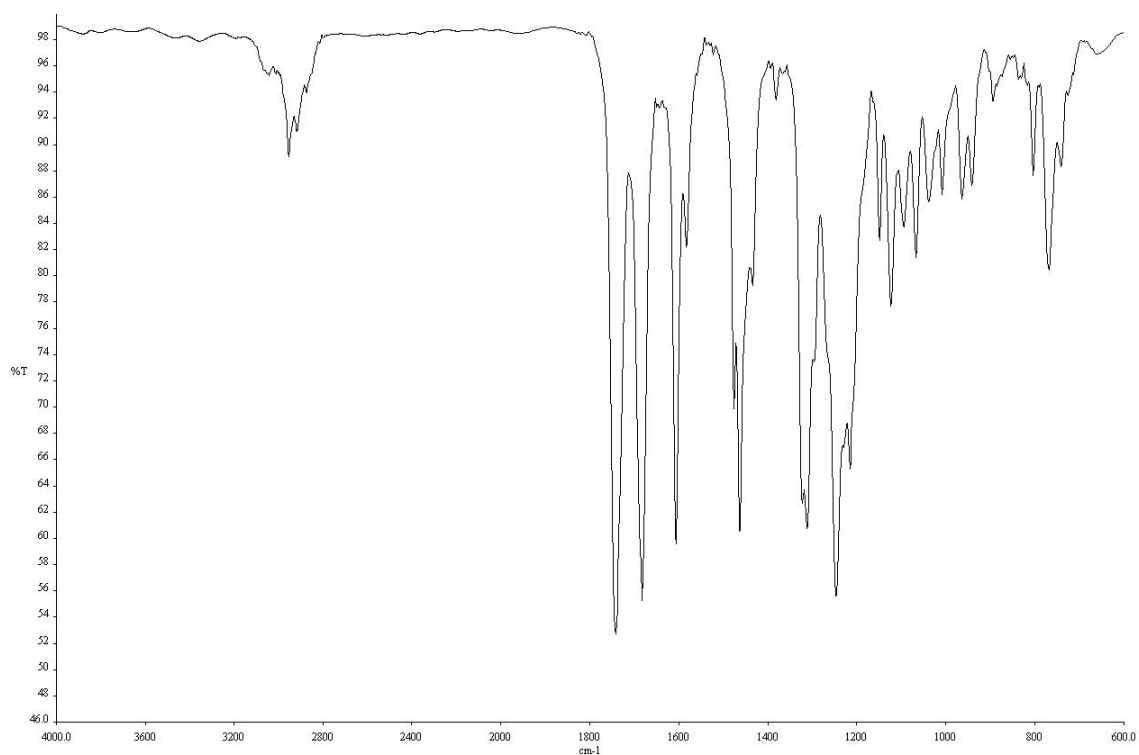


Figure A9.35 Infrared spectrum (Thin Film, NaCl) of compound **282**.

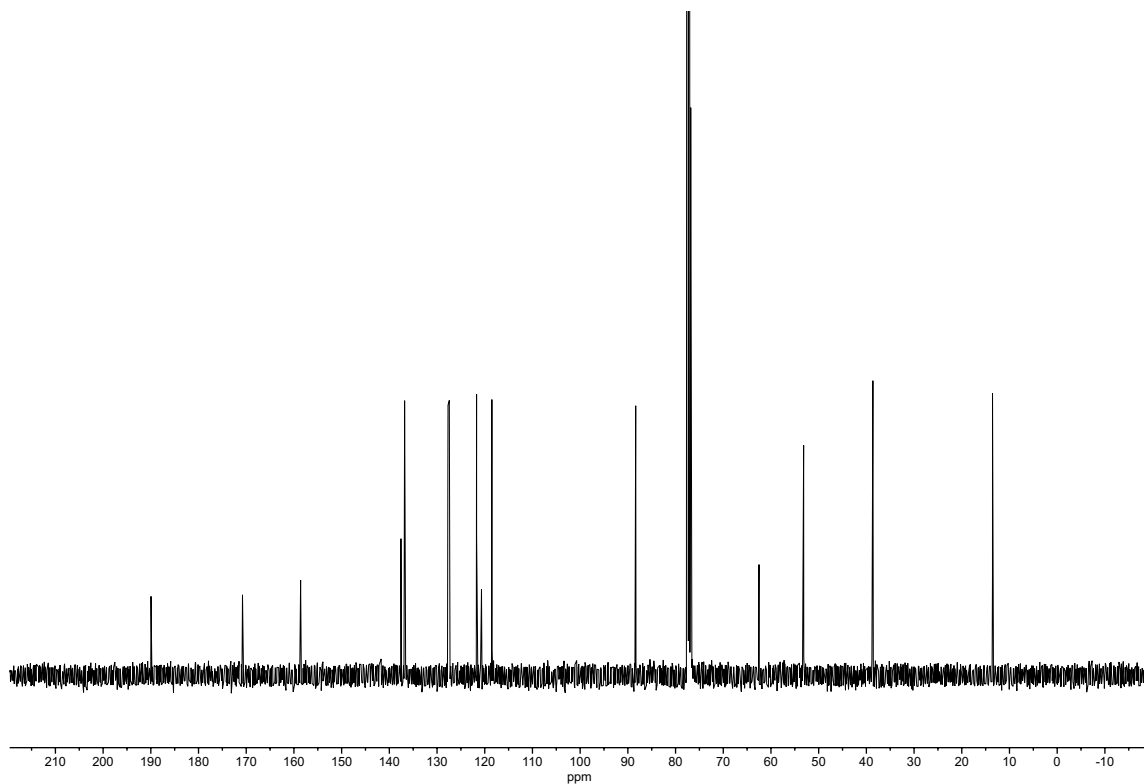


Figure A9.36 ¹³C NMR (100 MHz, CDCl₃) of compound **282**.

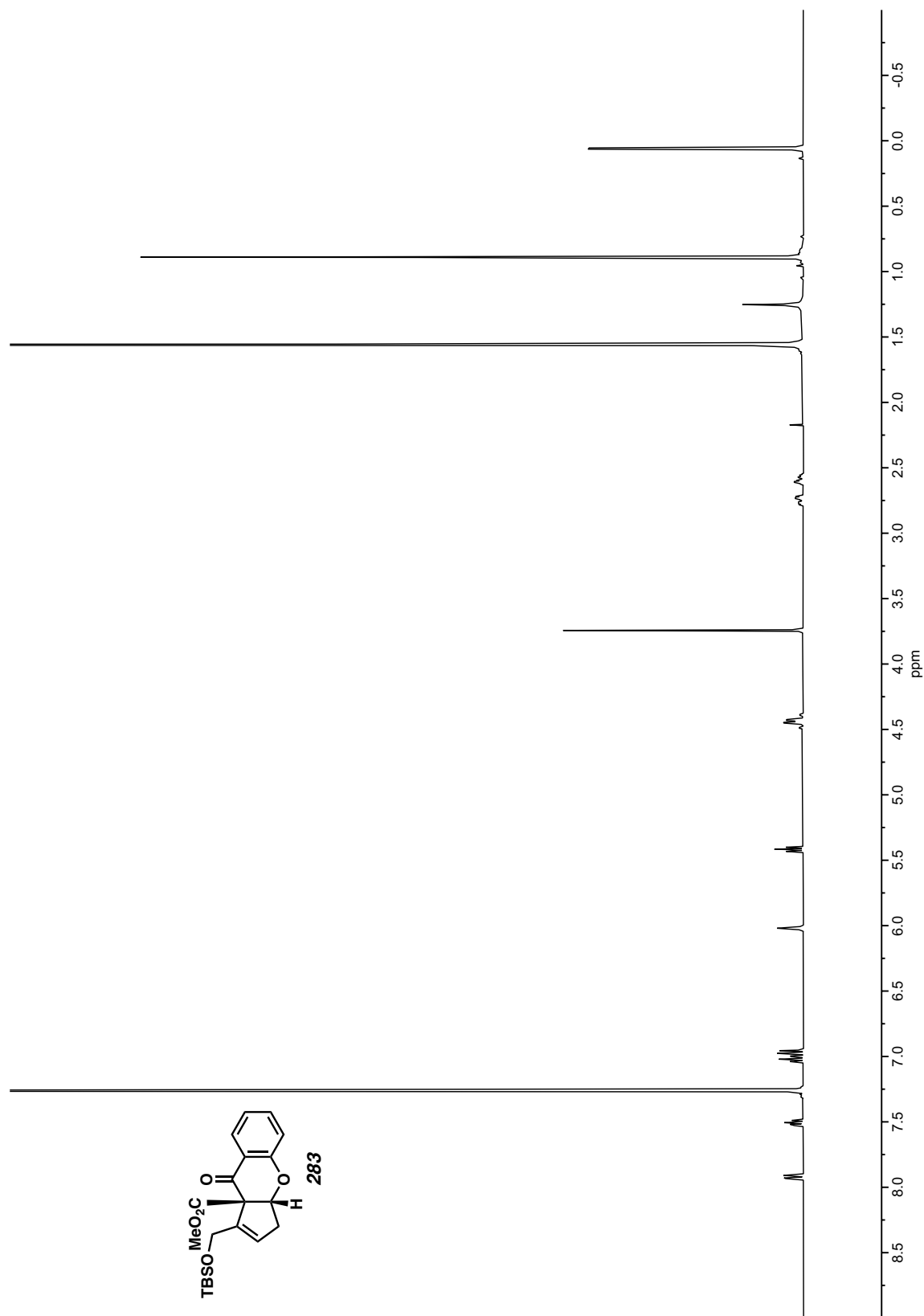


Figure A9.37 ^1H NMR (400 MHz, CDCl_3) of compound 283.

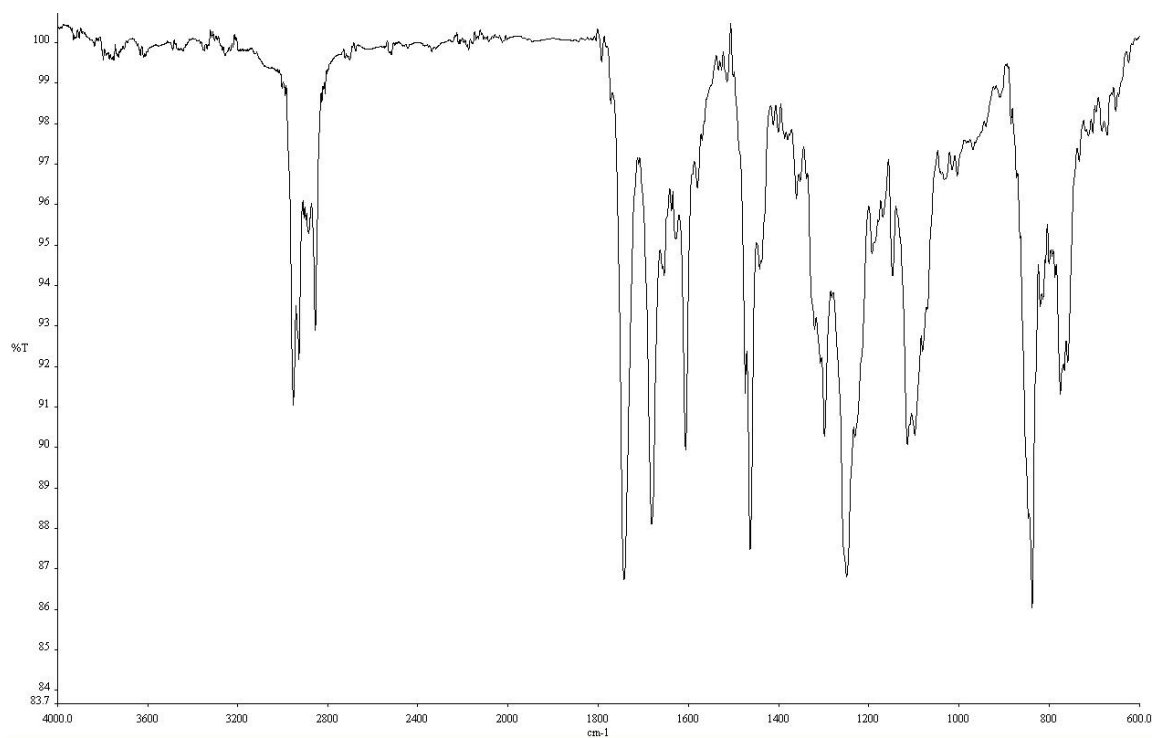


Figure A9.38 Infrared spectrum (Thin Film, NaCl) of compound **283**.

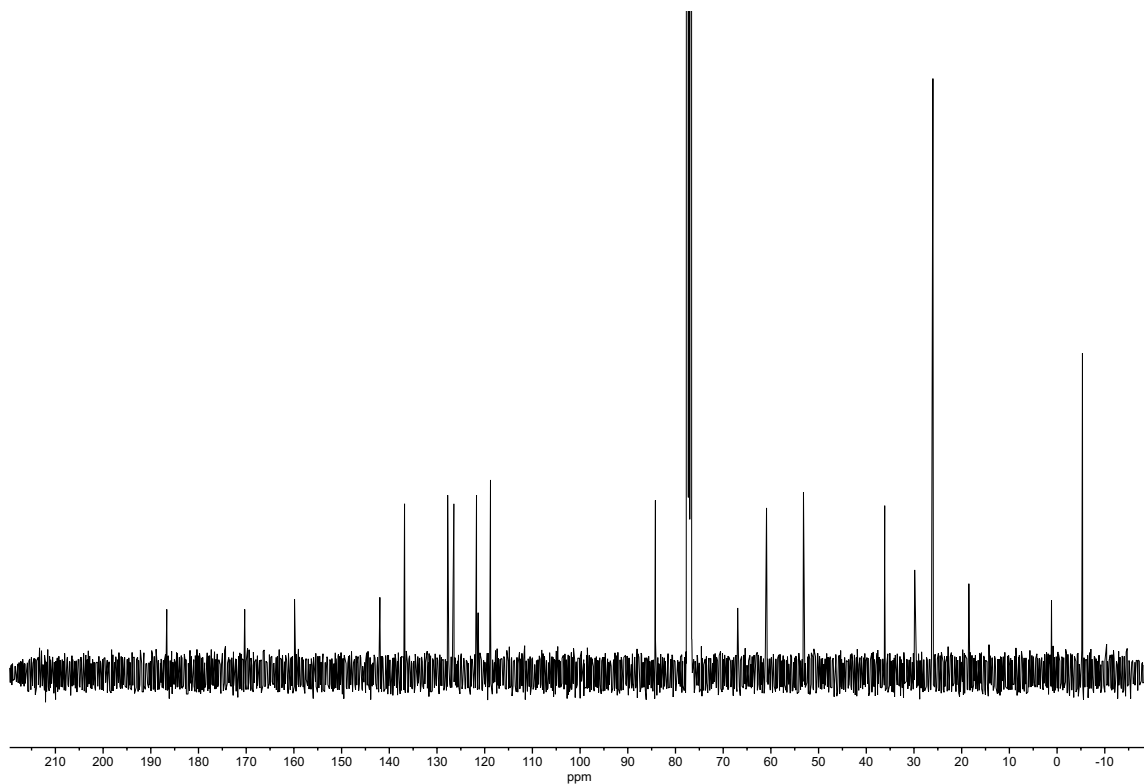


Figure A9.39 ¹³C NMR (100 MHz, CDCl₃) of compound **283**.

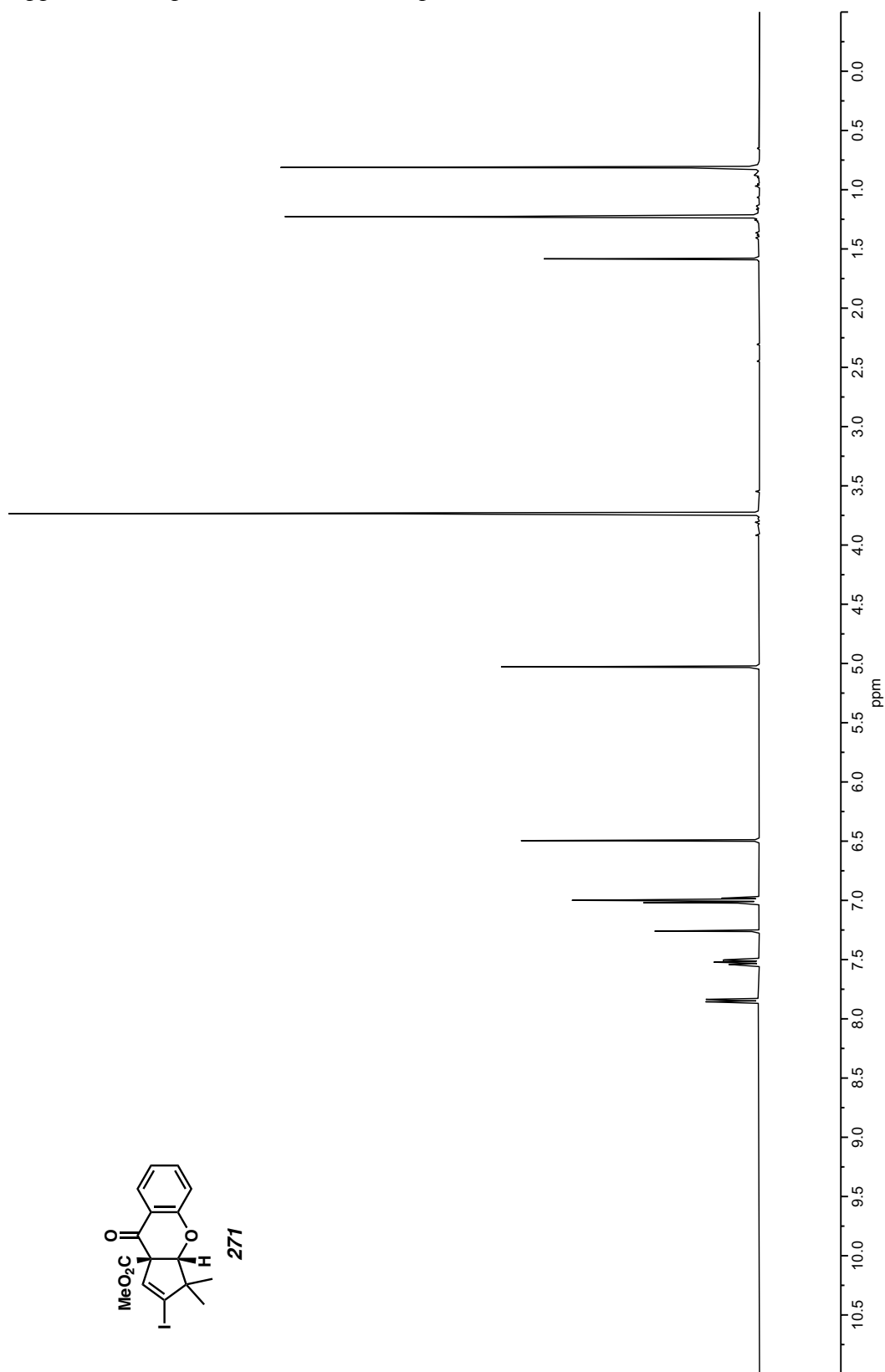


Figure A9.40 ¹H NMR (400 MHz, CDCl₃) of compound 271.

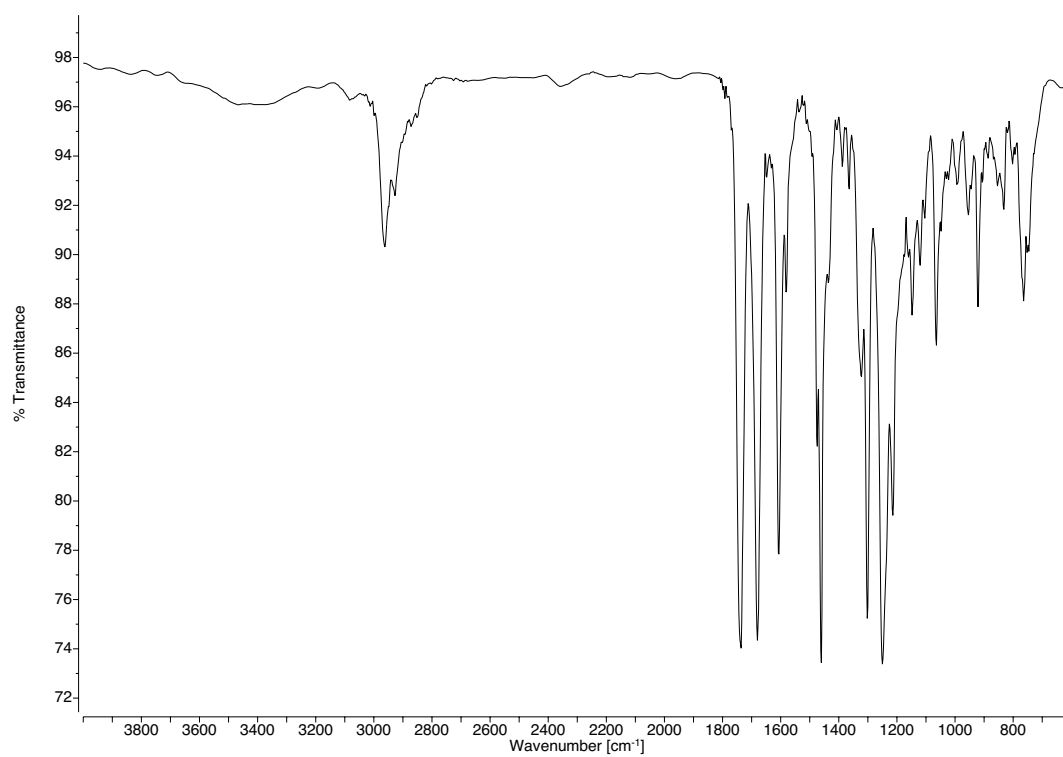


Figure A9.41 Infrared spectrum (Thin Film, NaCl) of compound **271**.

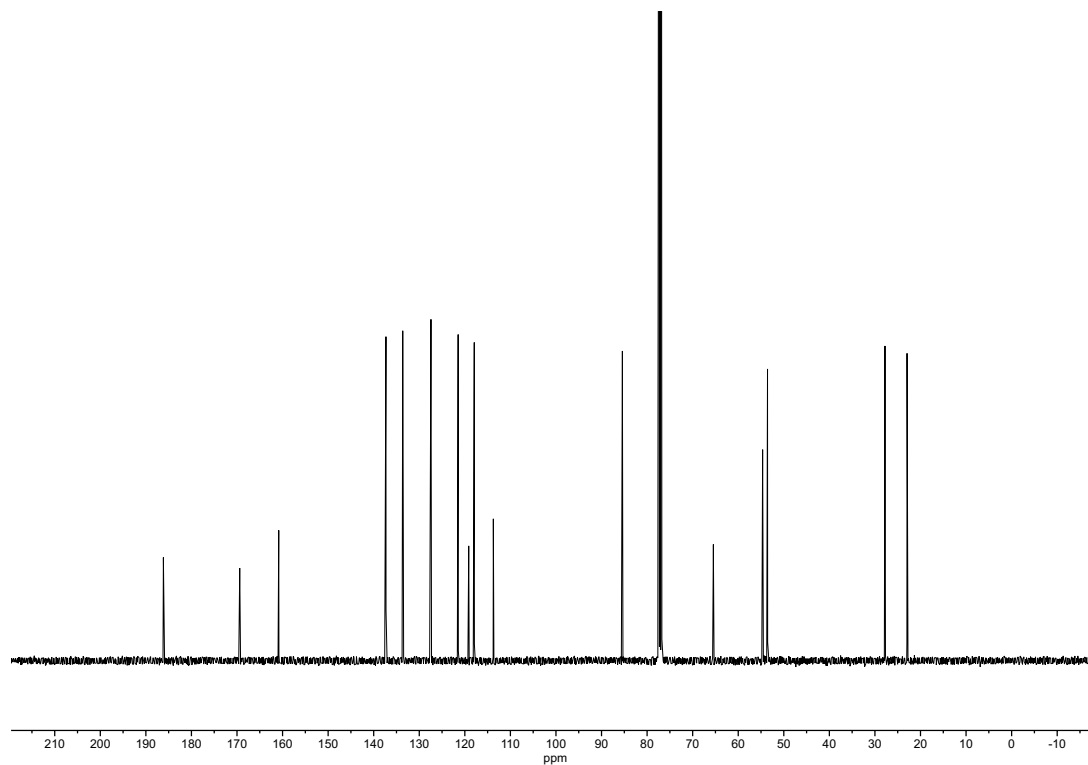


Figure A9.42 ^{13}C NMR (100 MHz, CDCl_3) of compound **271**.

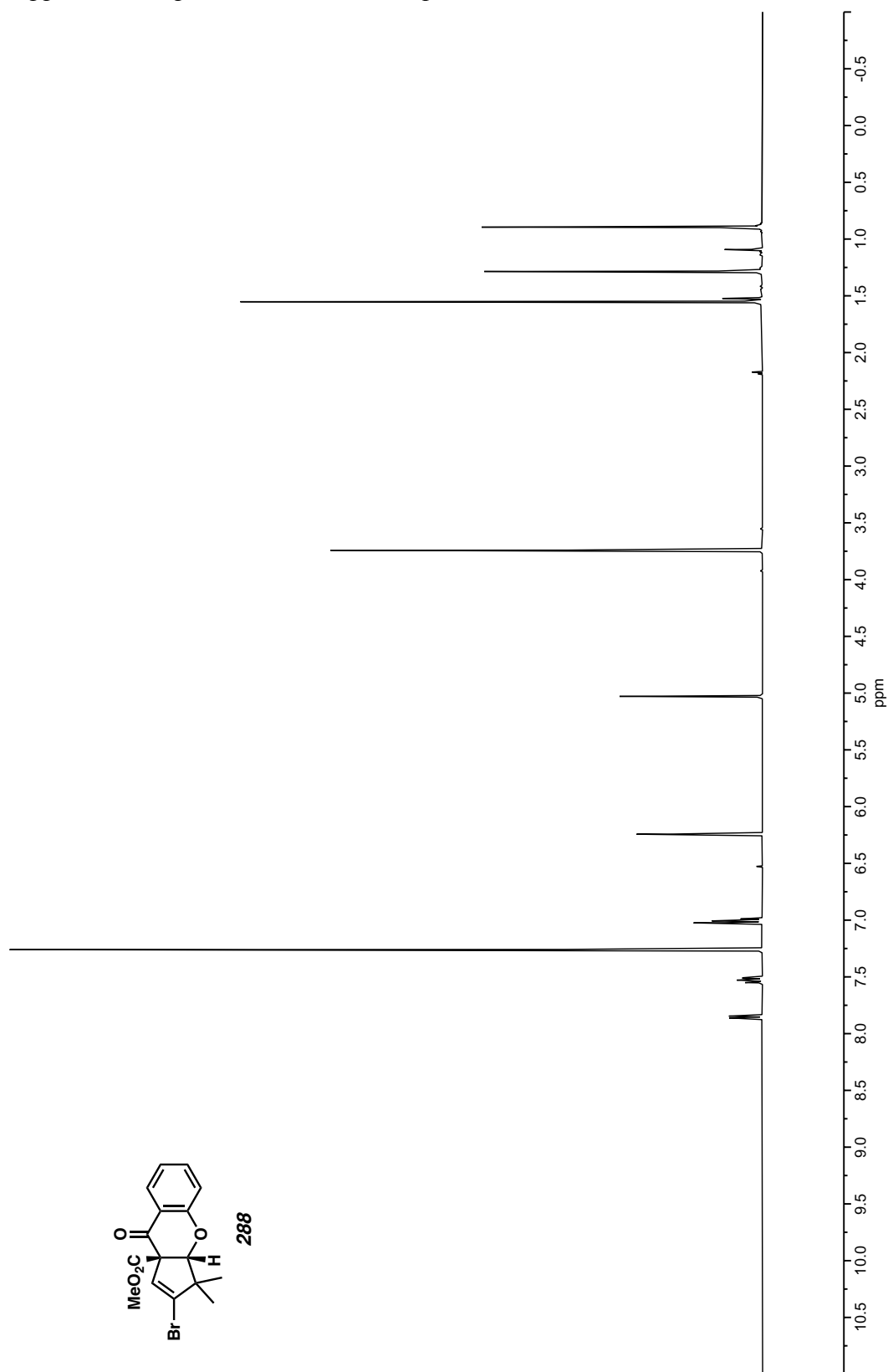


Figure A9.43 ¹H NMR (400 MHz, CDCl₃) of compound 288.

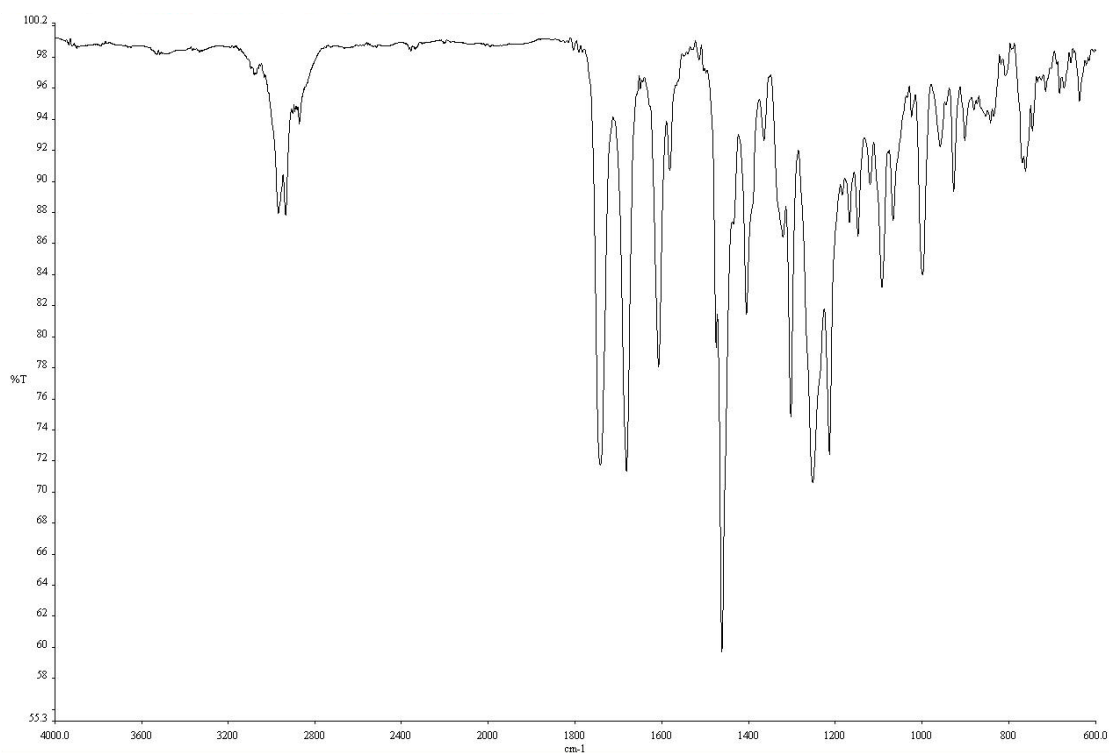


Figure A9.44 Infrared spectrum (Thin Film, NaCl) of compound **288**.

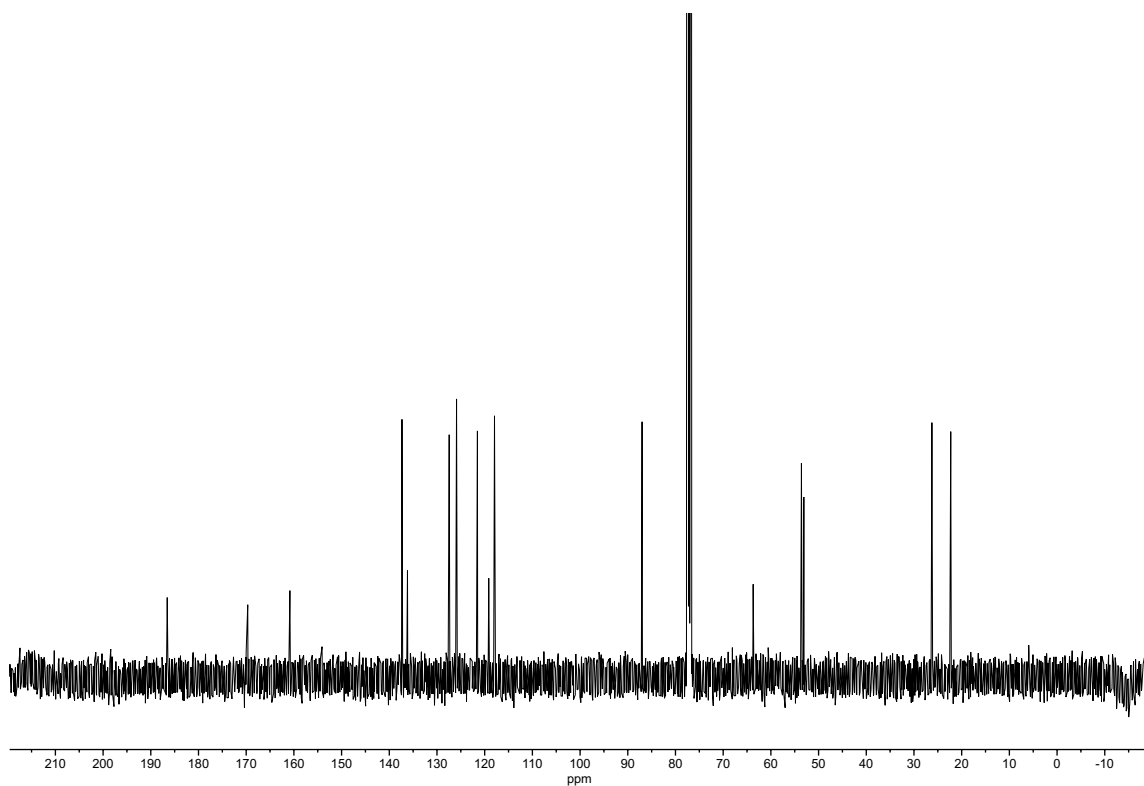


Figure A9.45 ¹³C NMR (100 MHz, CDCl₃) of compound **288**.

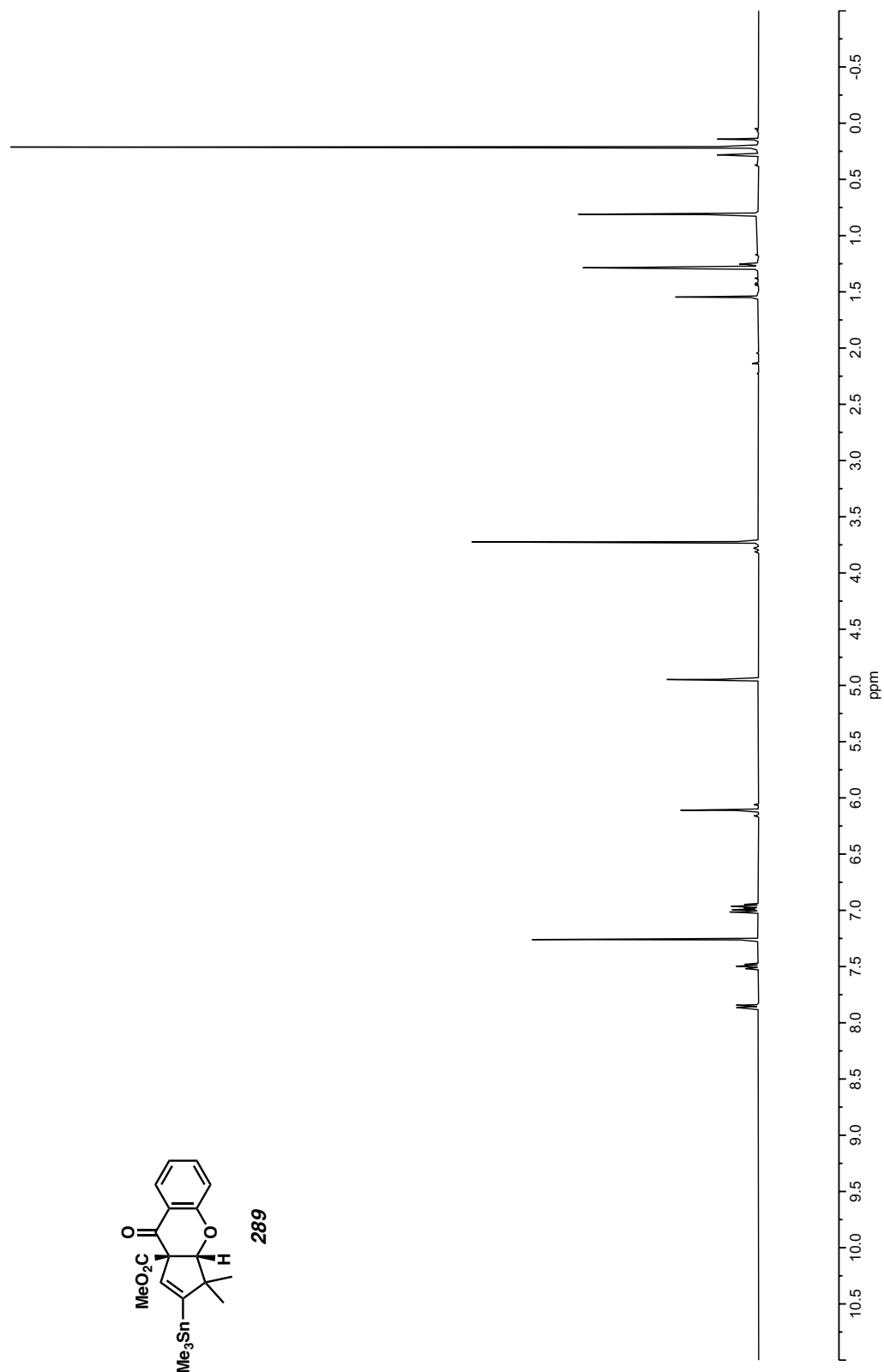


Figure A9.46 ^1H NMR (400 MHz, CDCl_3) of compound 289.

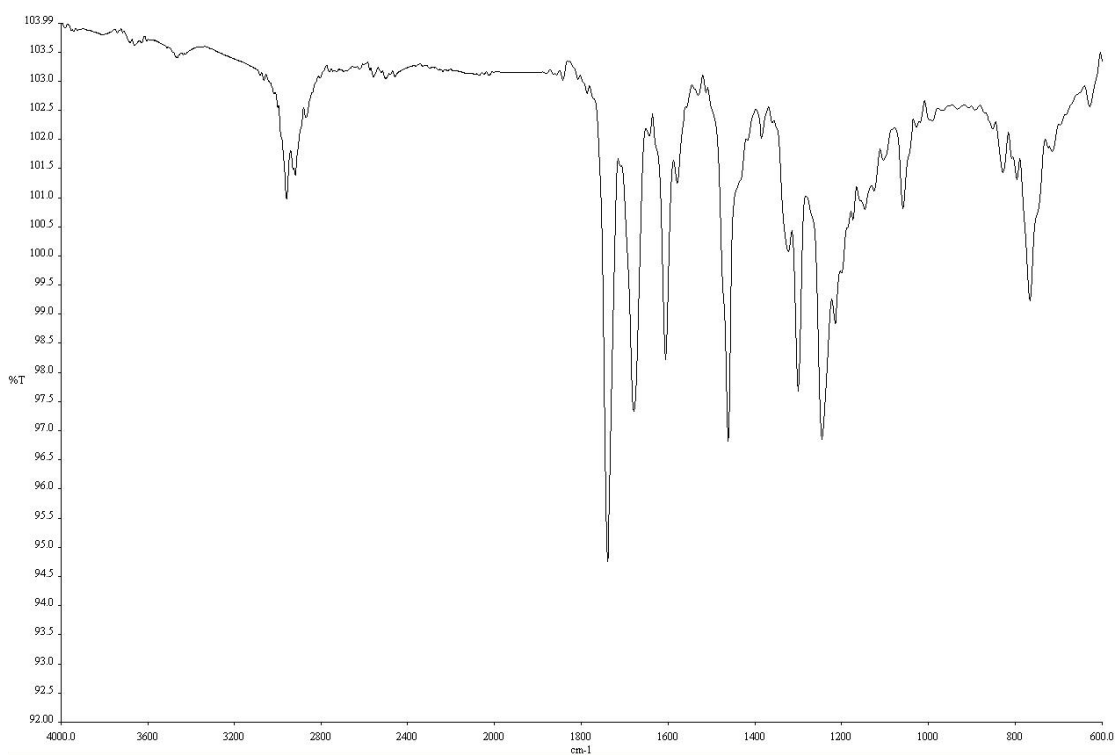


Figure A9.47 Infrared spectrum (Thin Film, NaCl) of compound **289**.

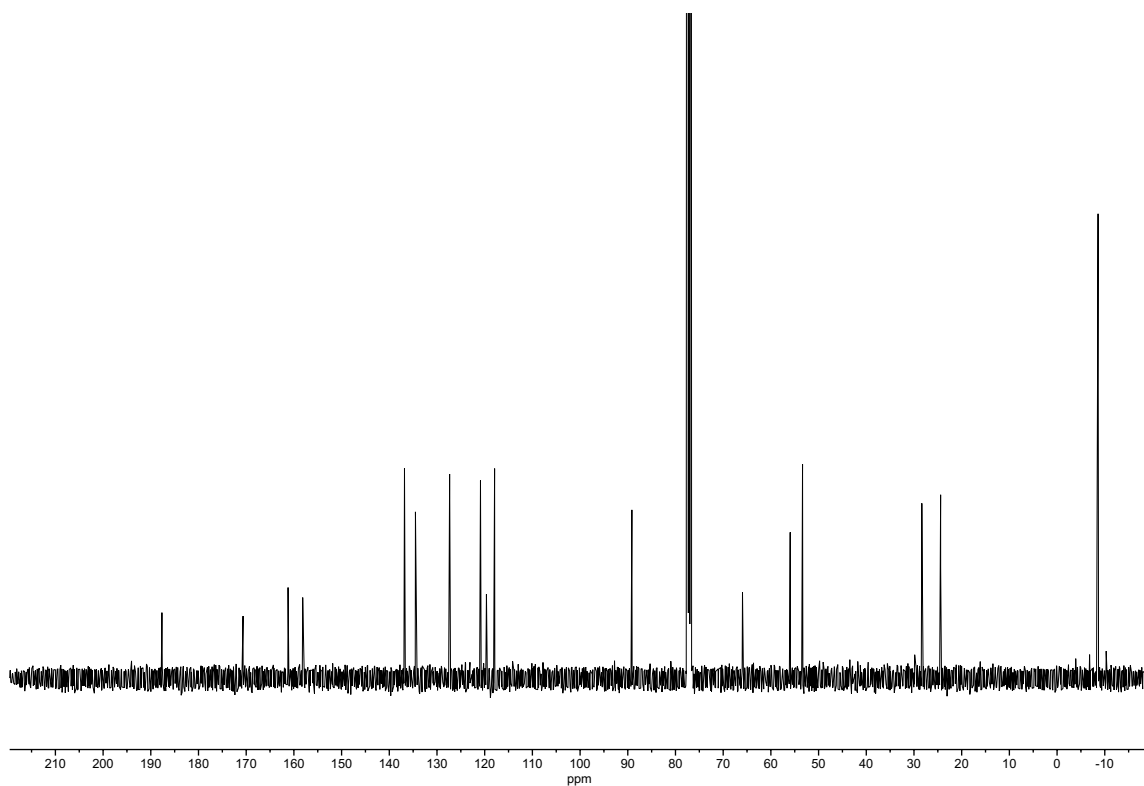


Figure A9.48 ¹³C NMR (100 MHz, CDCl₃) of compound **289**.

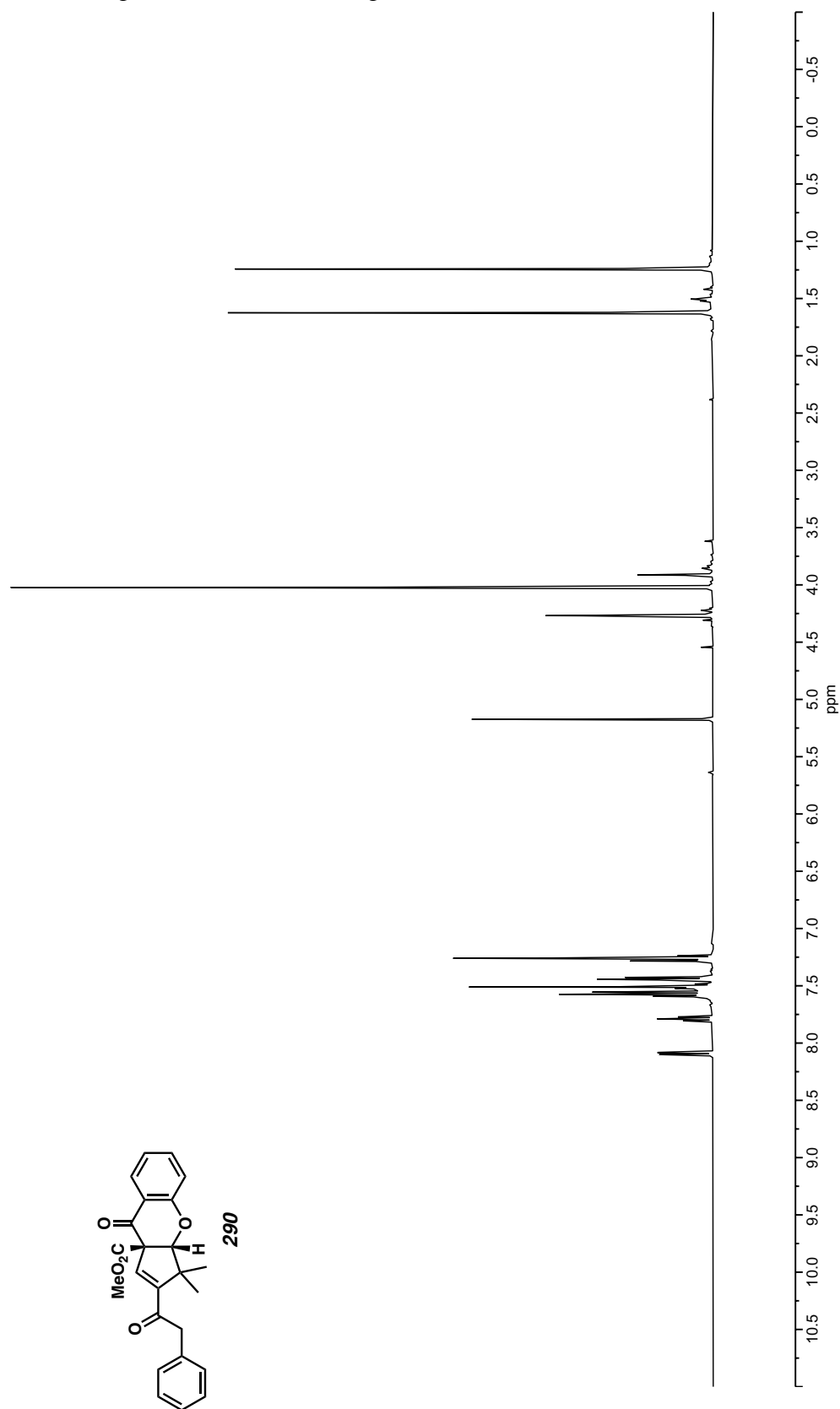


Figure A9.49 ^1H NMR (400 MHz, CDCl_3) of compound 290.

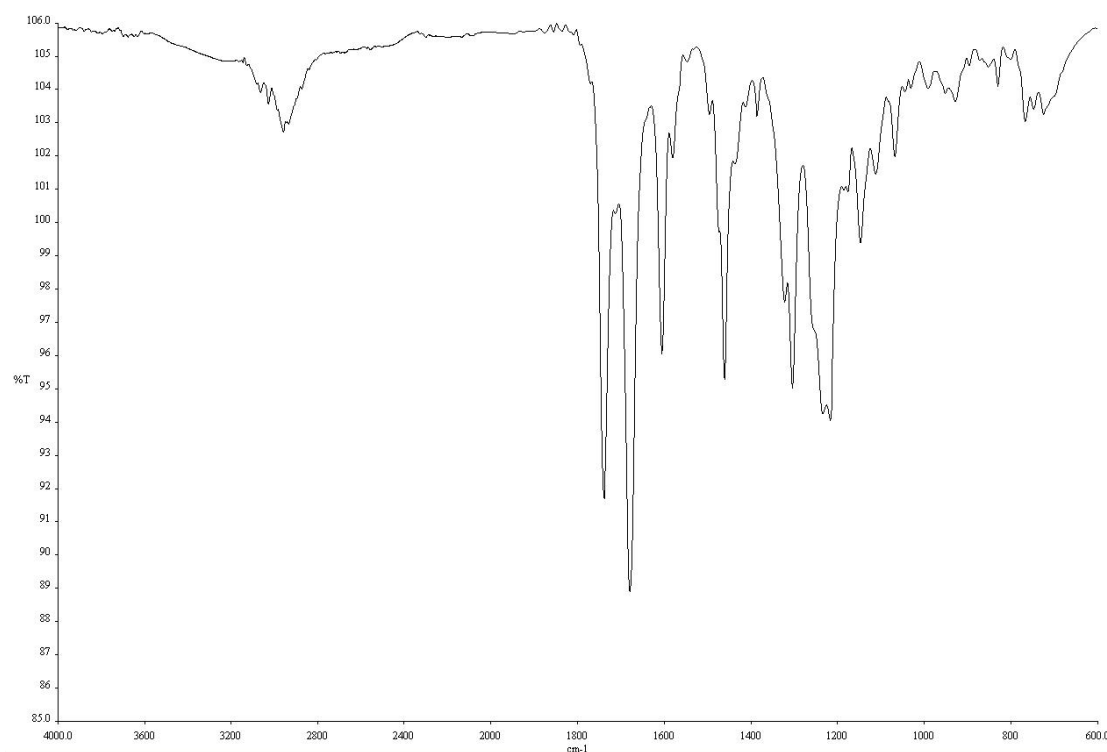


Figure A9.50 Infrared spectrum (Thin Film, NaCl) of compound **290**.

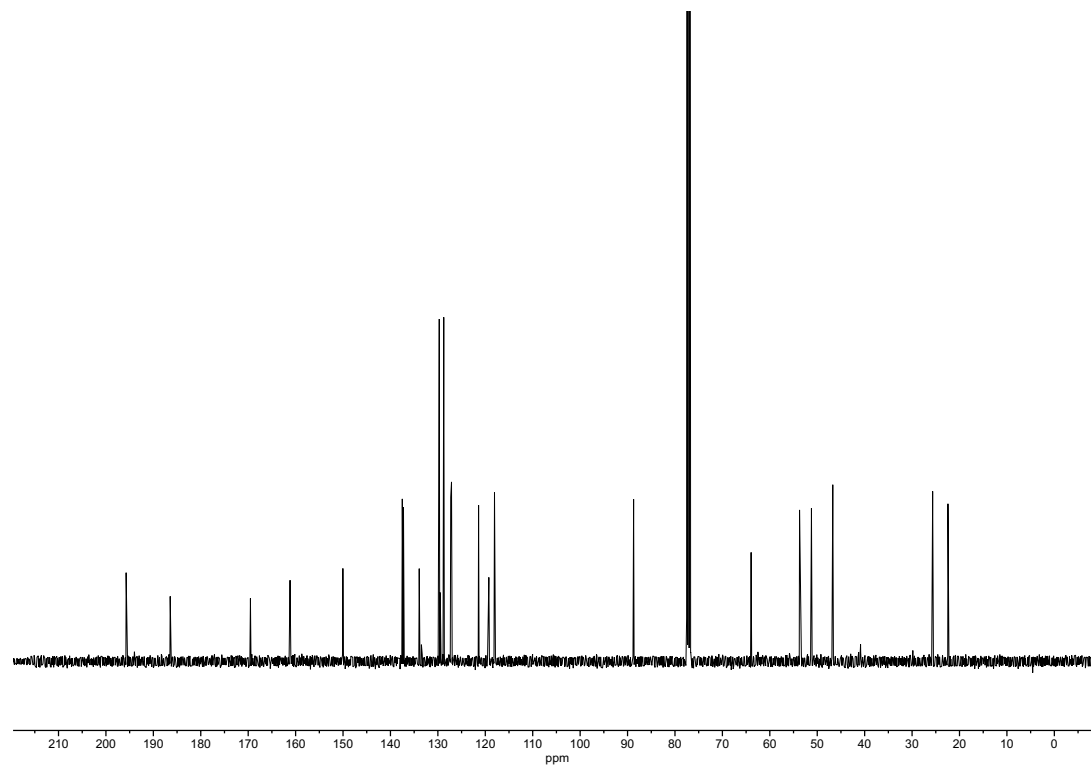


Figure A9.51 ¹³C NMR (100 MHz, CDCl₃) of compound **290**.

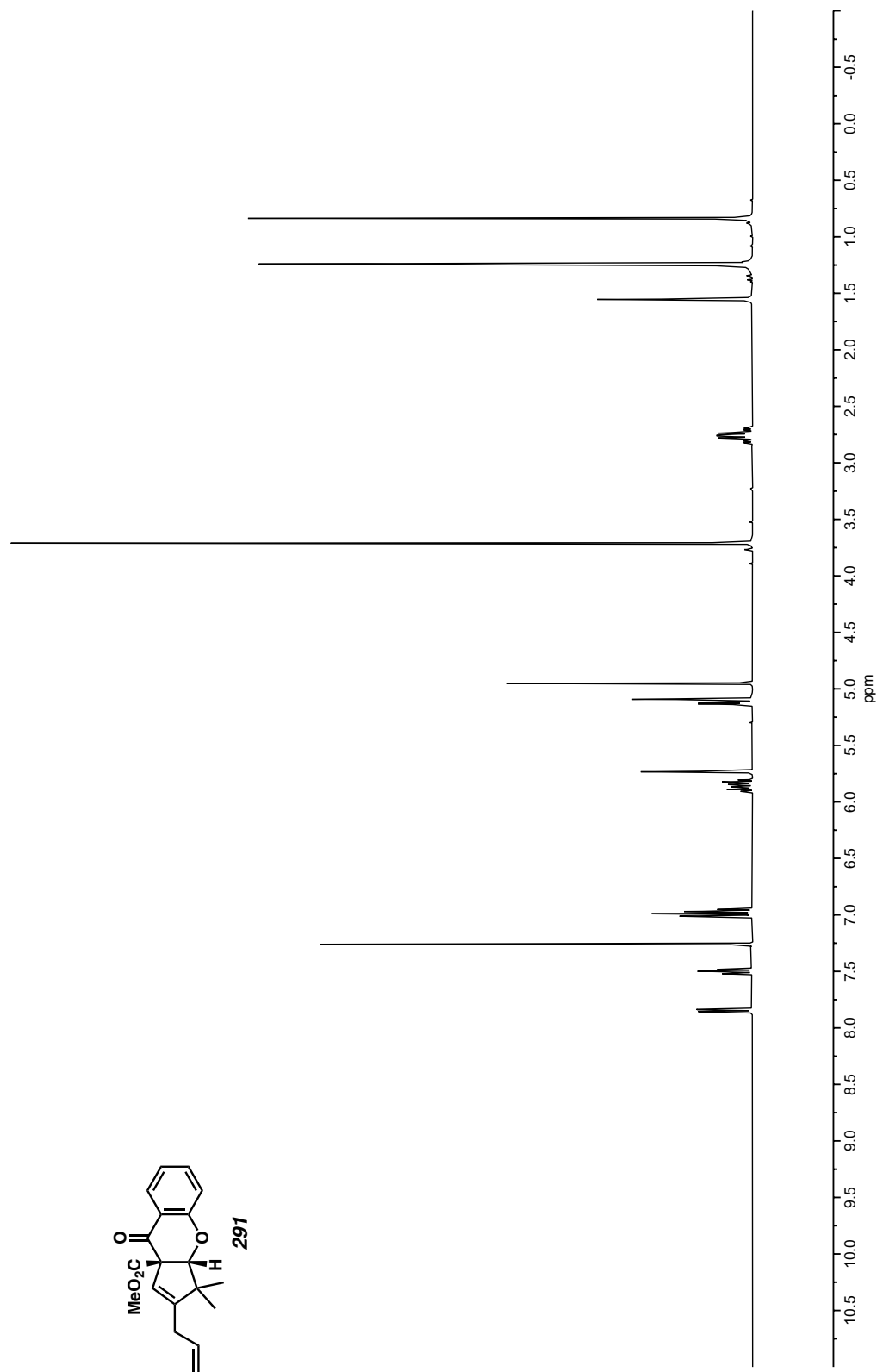


Figure A9.52 ¹H NMR (400 MHz, CDCl₃) of compound 291.

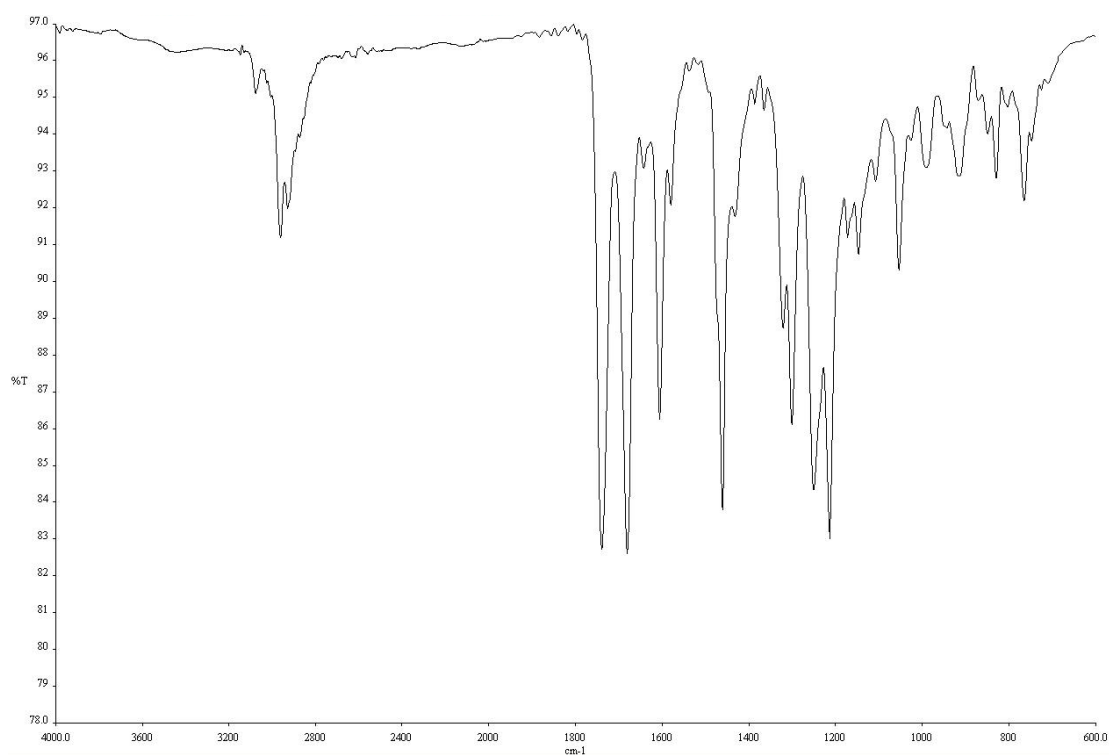


Figure A9.53 Infrared spectrum (Thin Film, NaCl) of compound **291**.

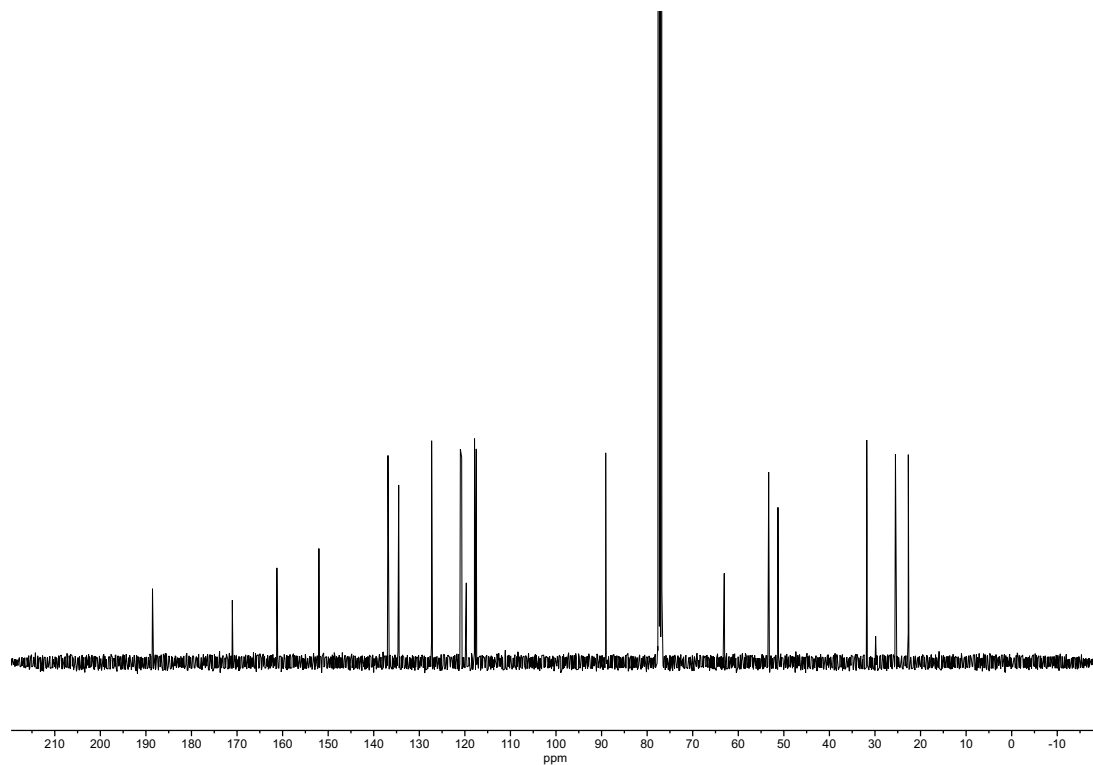


Figure A9.54 ¹³C NMR (100 MHz, CDCl₃) of compound **291**.

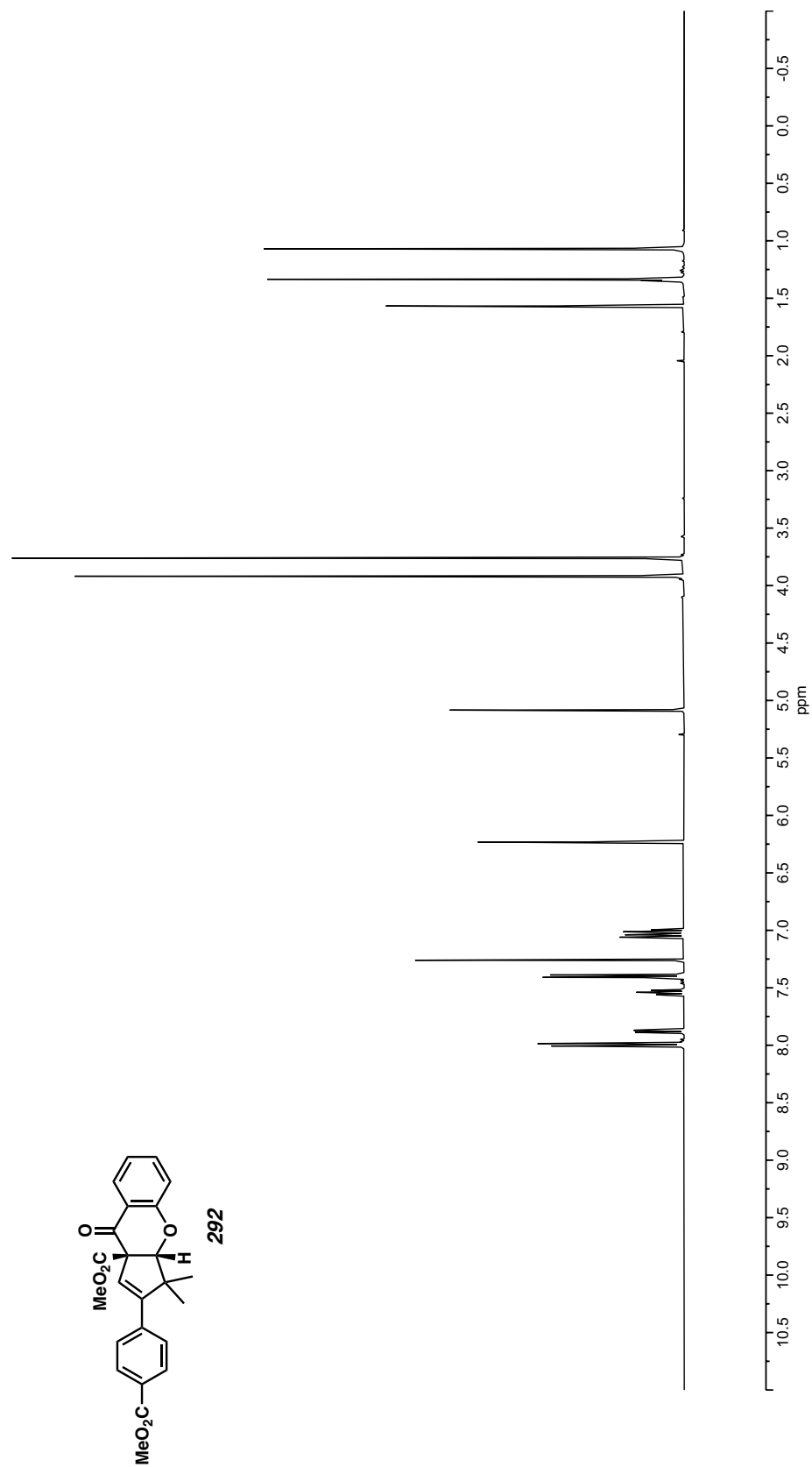


Figure A9.55 ¹H NMR (400 MHz, CDCl₃) of compound 292.

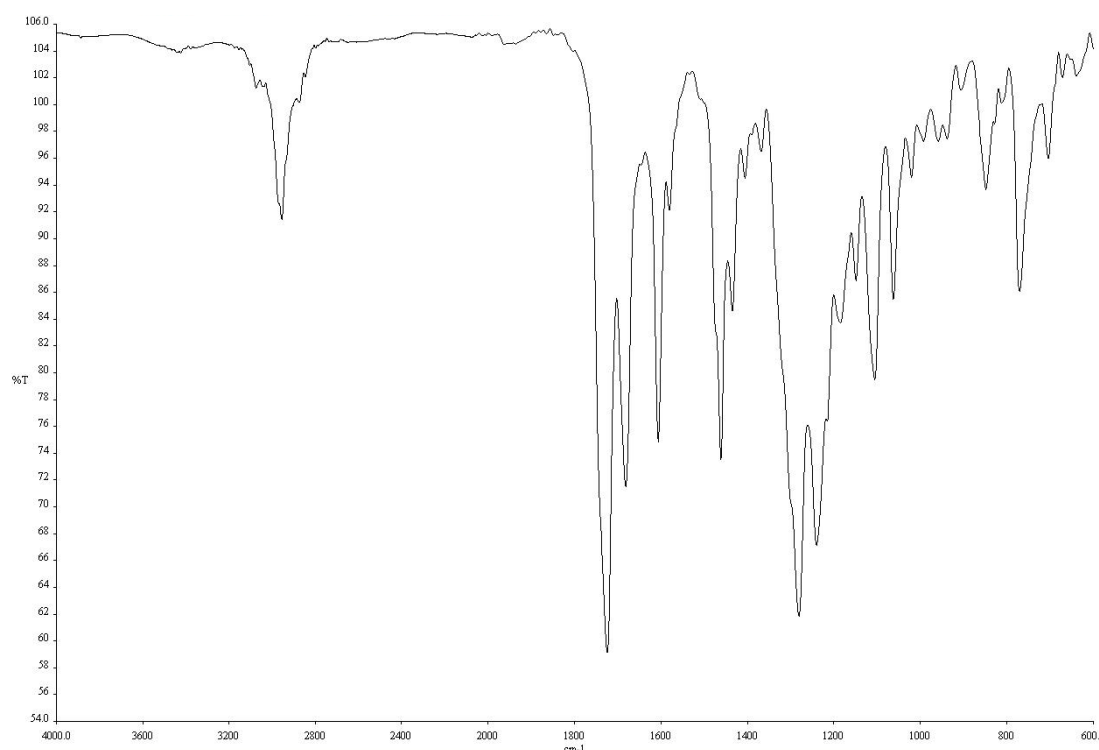


Figure A9.56 Infrared spectrum (Thin Film, NaCl) of compound **292**.

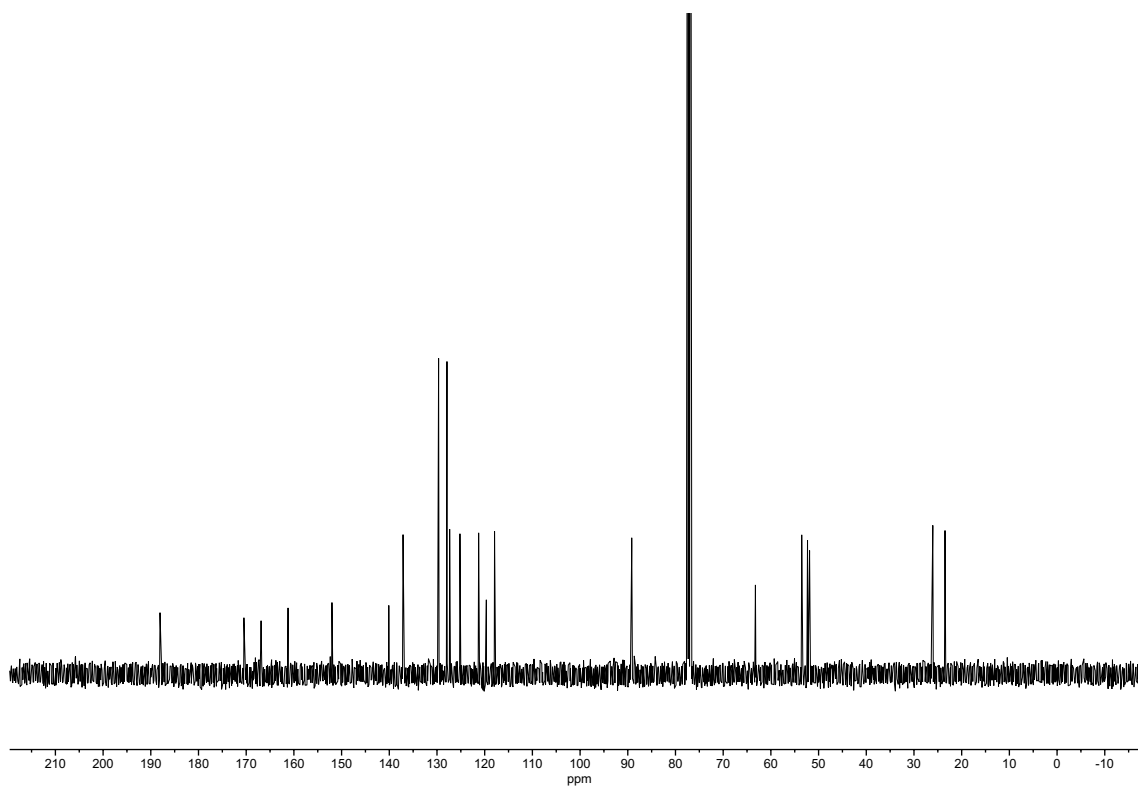


Figure A9.57 ¹³C NMR (100 MHz, CDCl₃) of compound **292**.

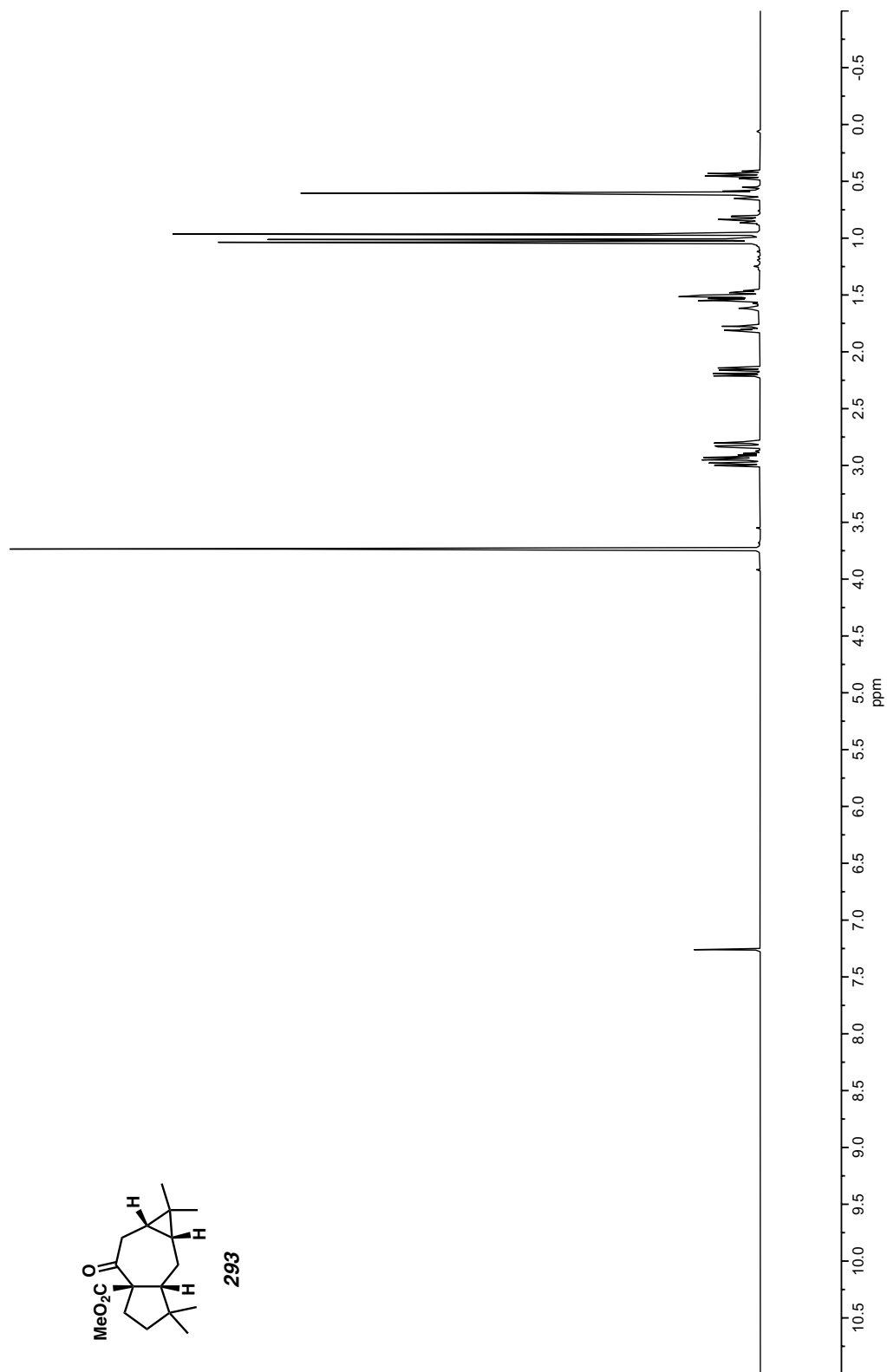


Figure A9.58 ¹H NMR (400 MHz, CDCl₃) of compound 293.

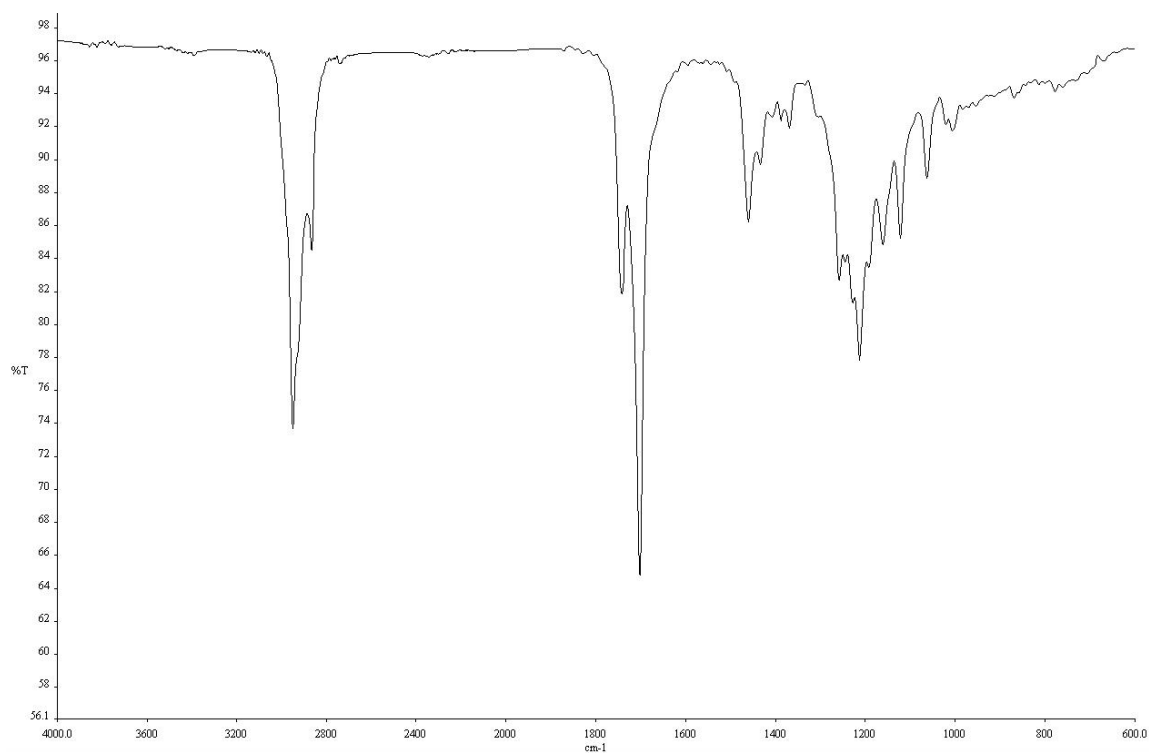


Figure A9.59 Infrared spectrum (Thin Film, NaCl) of compound **293**.

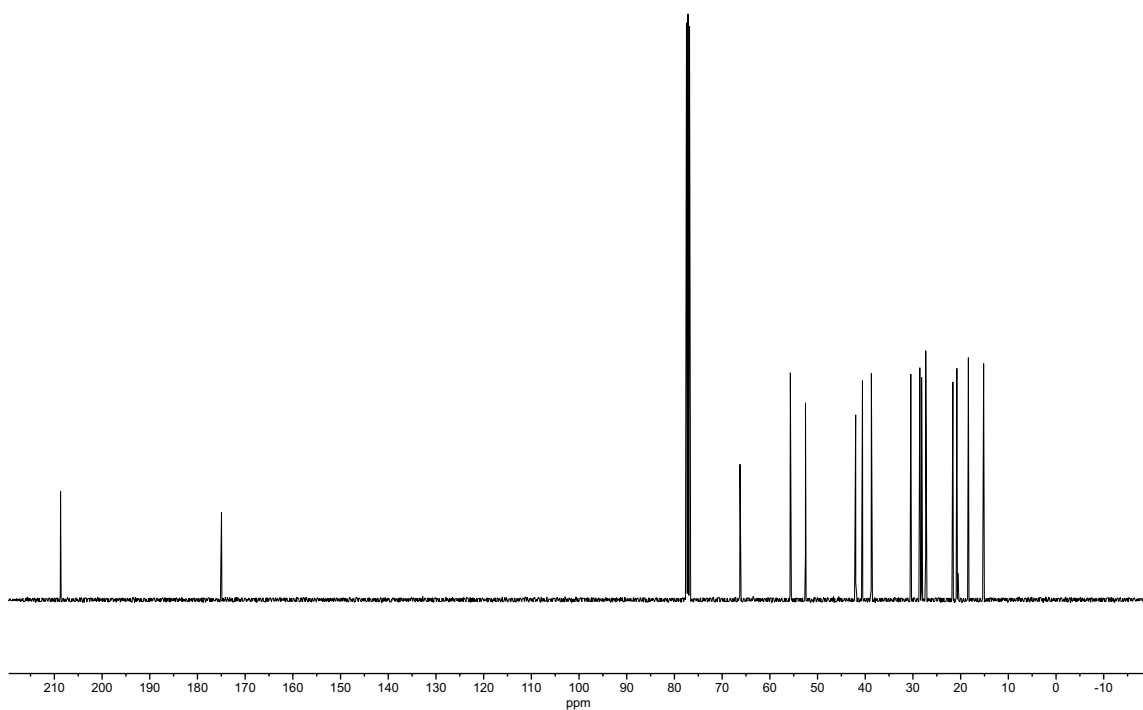


Figure A9.60 ¹³C NMR (100 MHz, CDCl₃) of compound **293**.

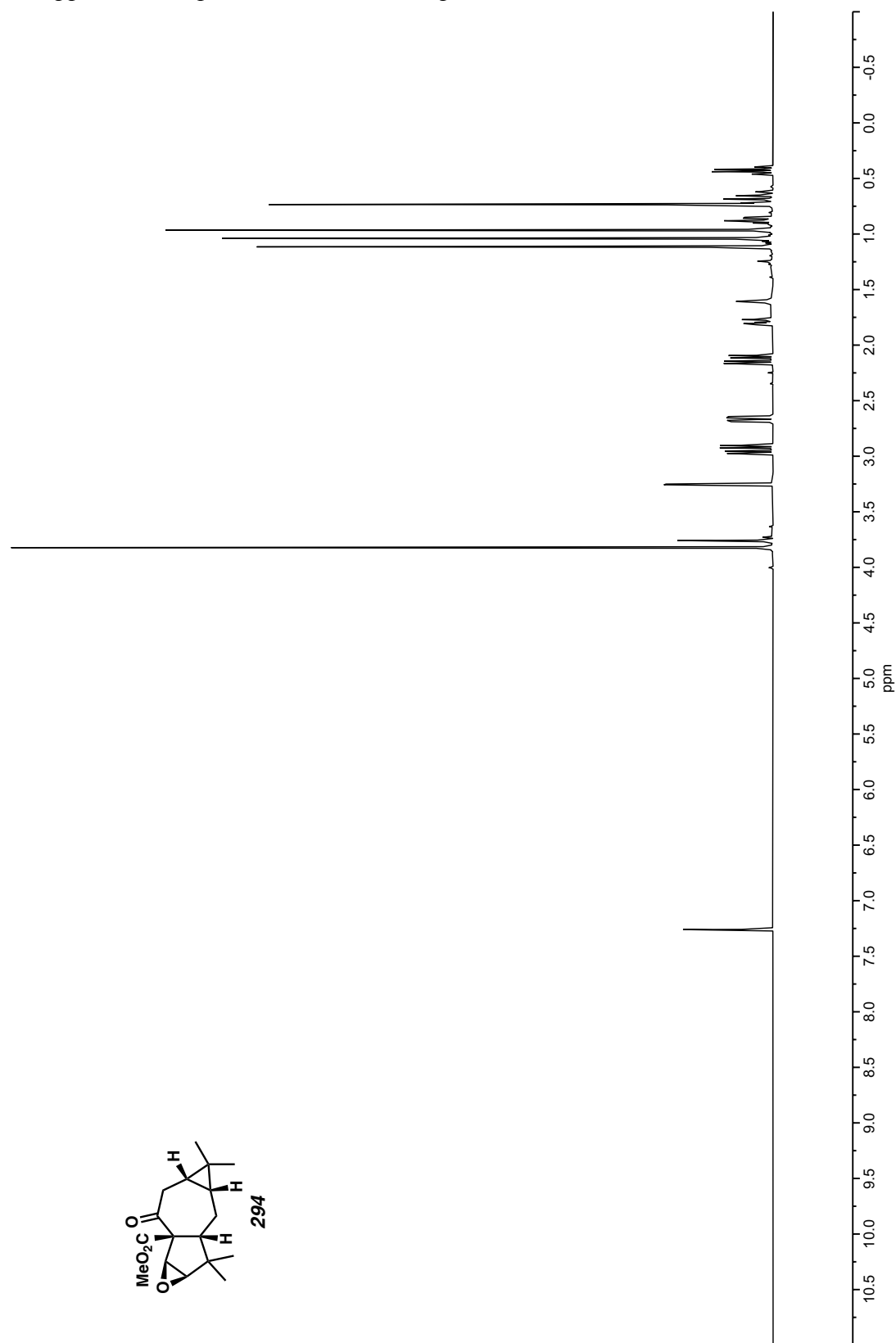
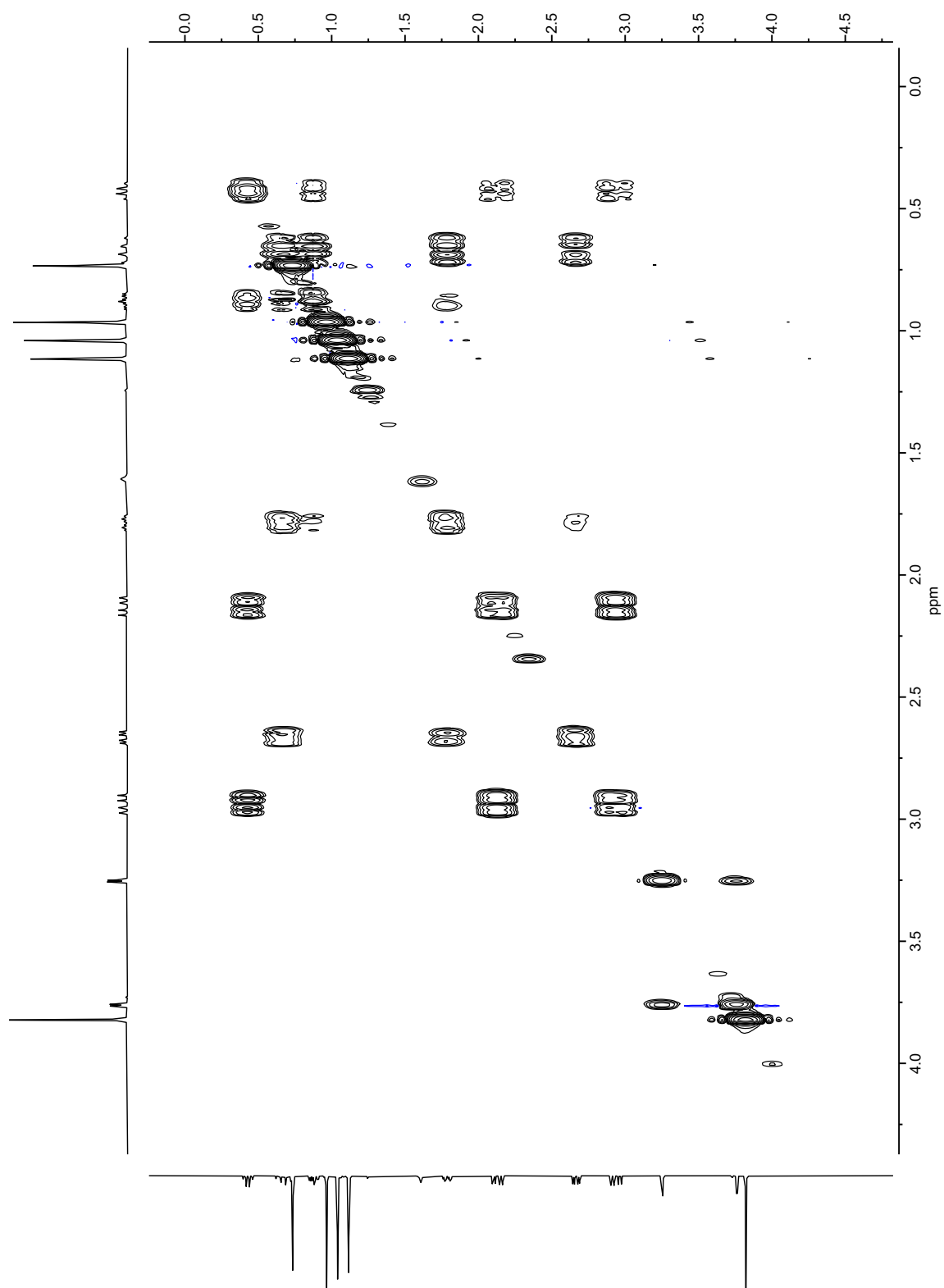


Figure A9.61 ¹H NMR (400 MHz, CDCl₃) of compound 294.



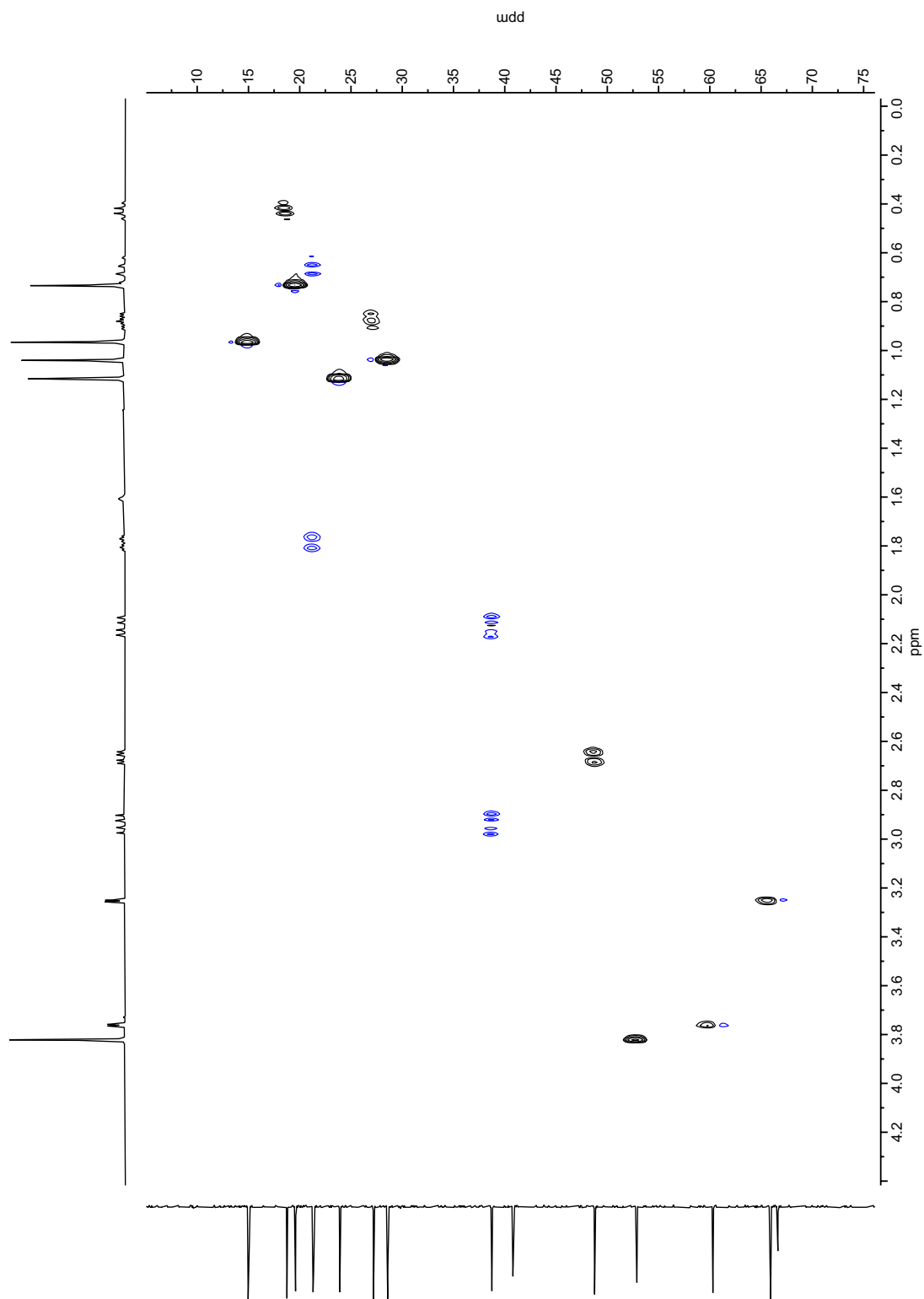


Figure A9.63 HSQC NMR (400 MHz, CDCl₃) of compound **294**.

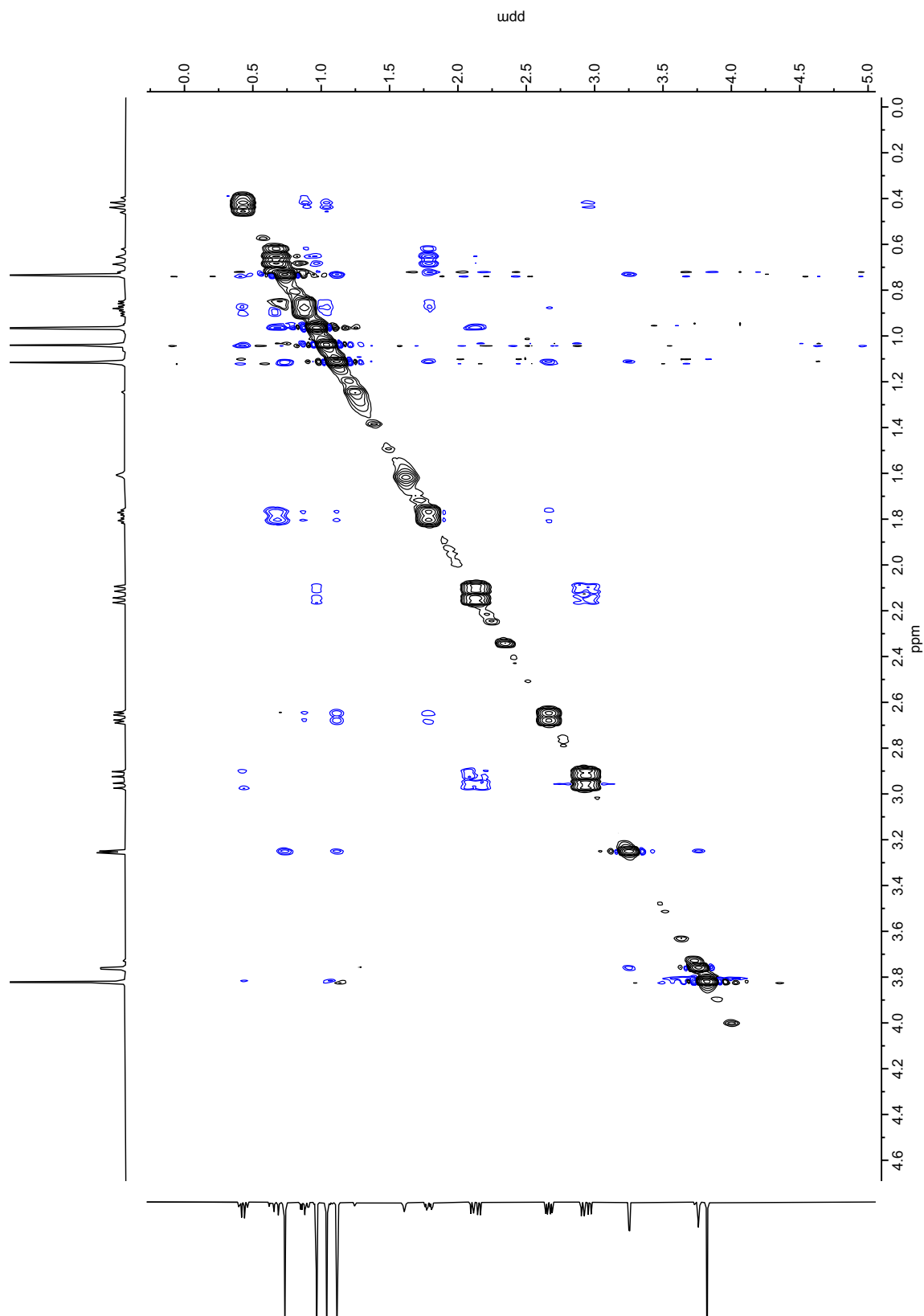


Figure A9.64 NOESY NMR (400 MHz, CDCl_3) of compound **294**.

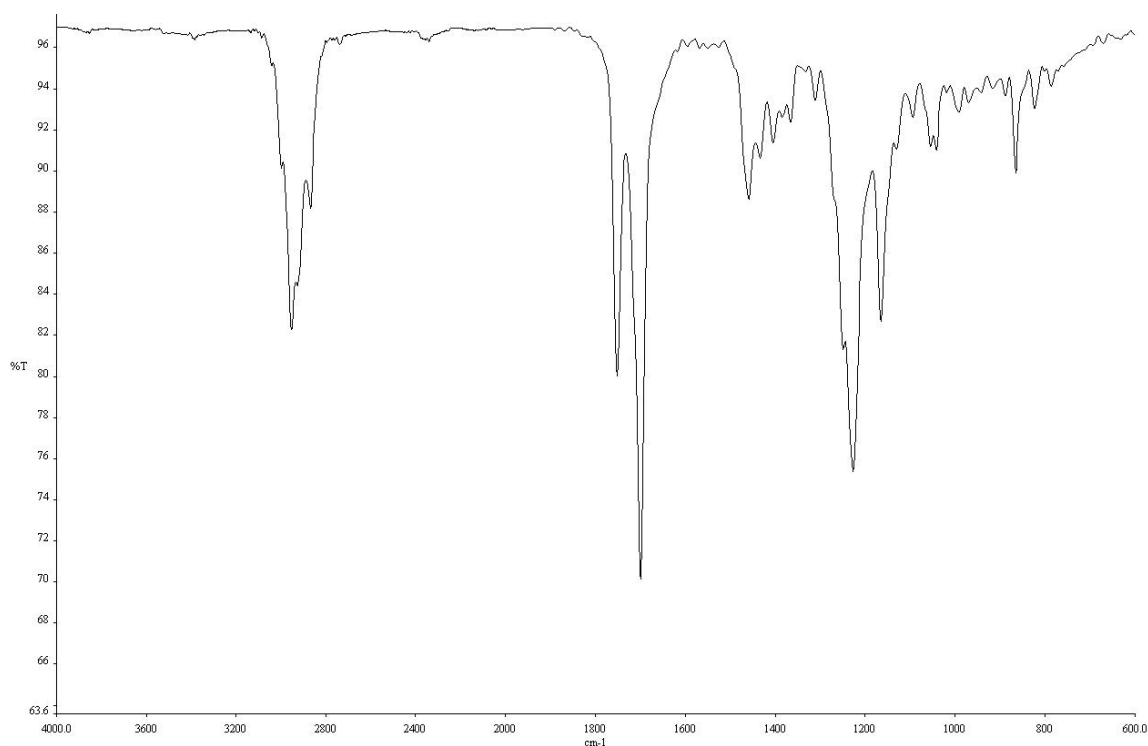


Figure A9.65 Infrared spectrum (Thin Film, NaCl) of compound **294**.

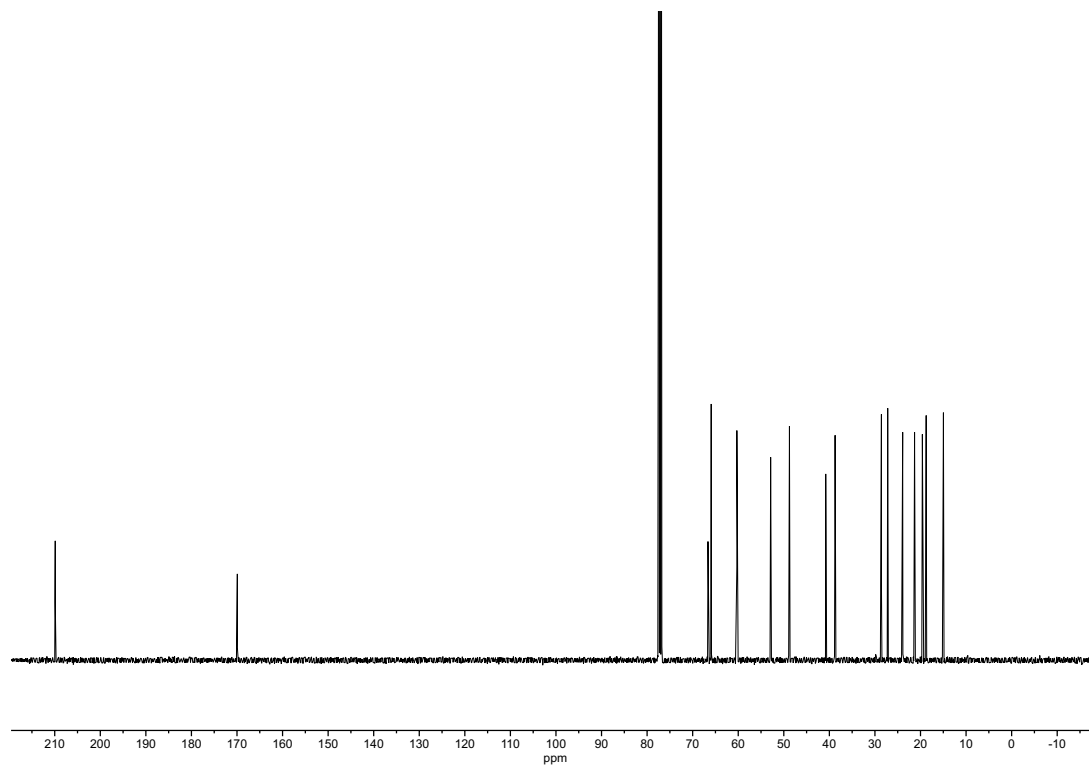


Figure A9.66 ¹³C NMR (100 MHz, CDCl₃) of compound **294**.

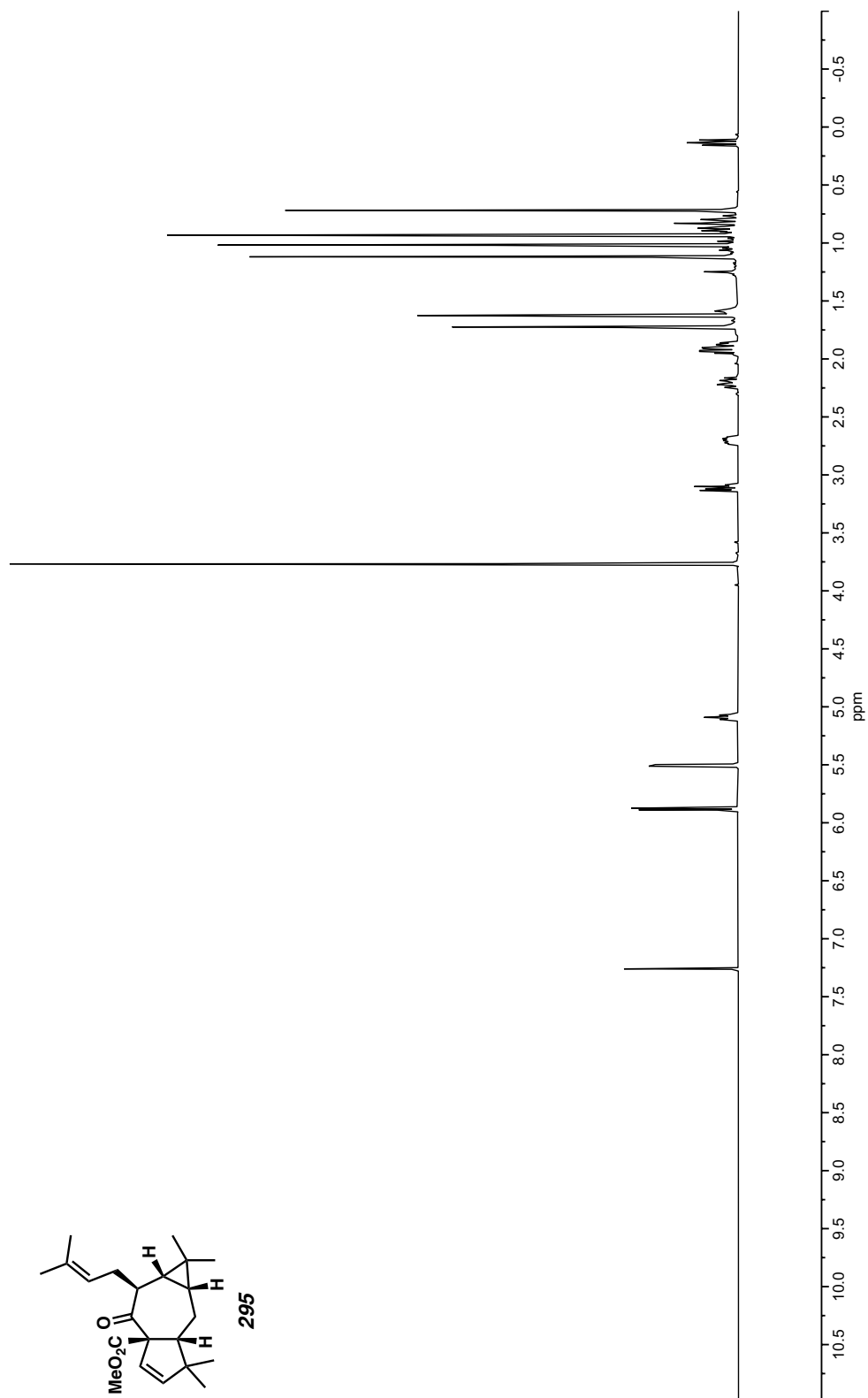


Figure A9.67 ¹H NMR (400 MHz, CDCl₃) of compound 295.

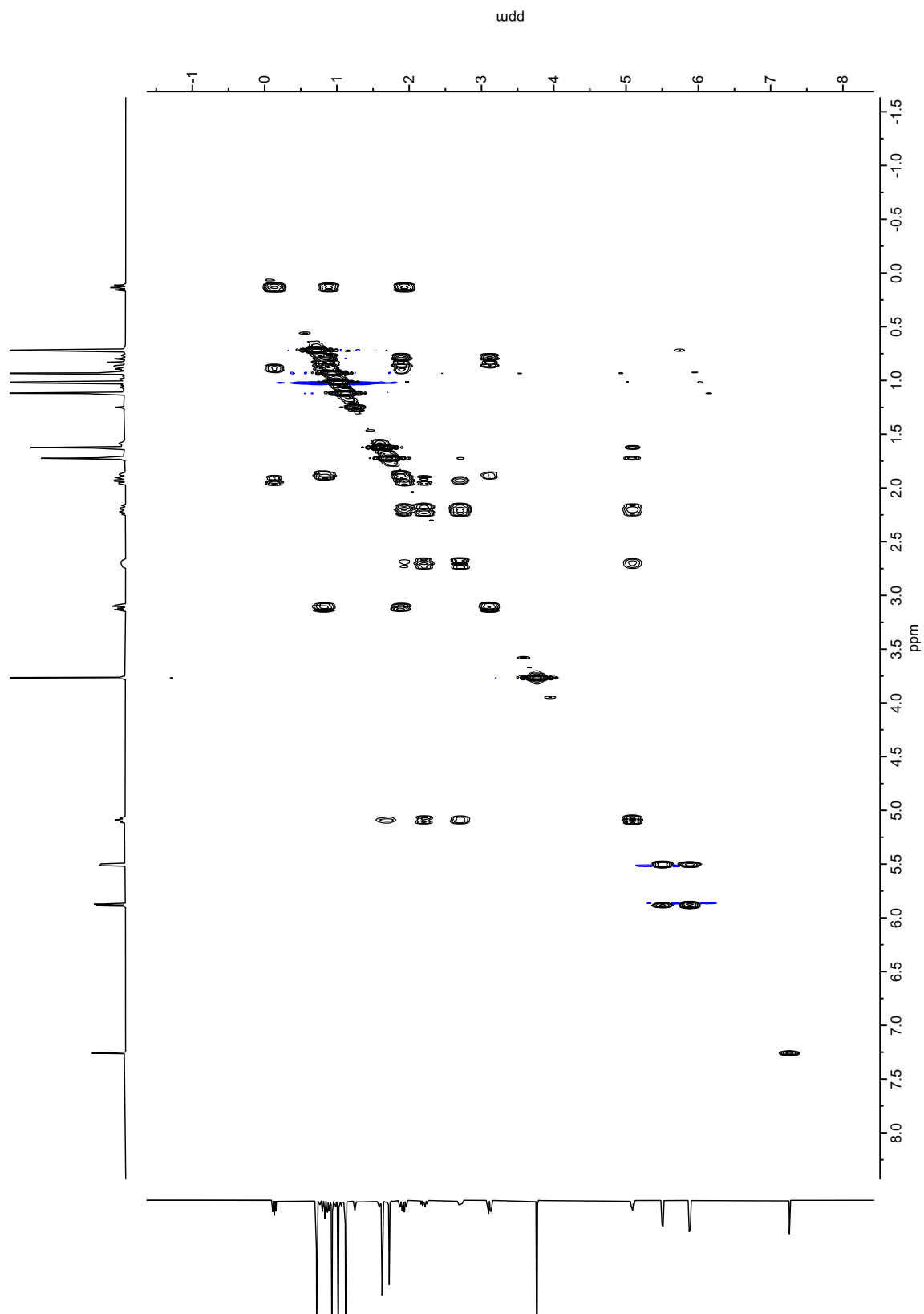
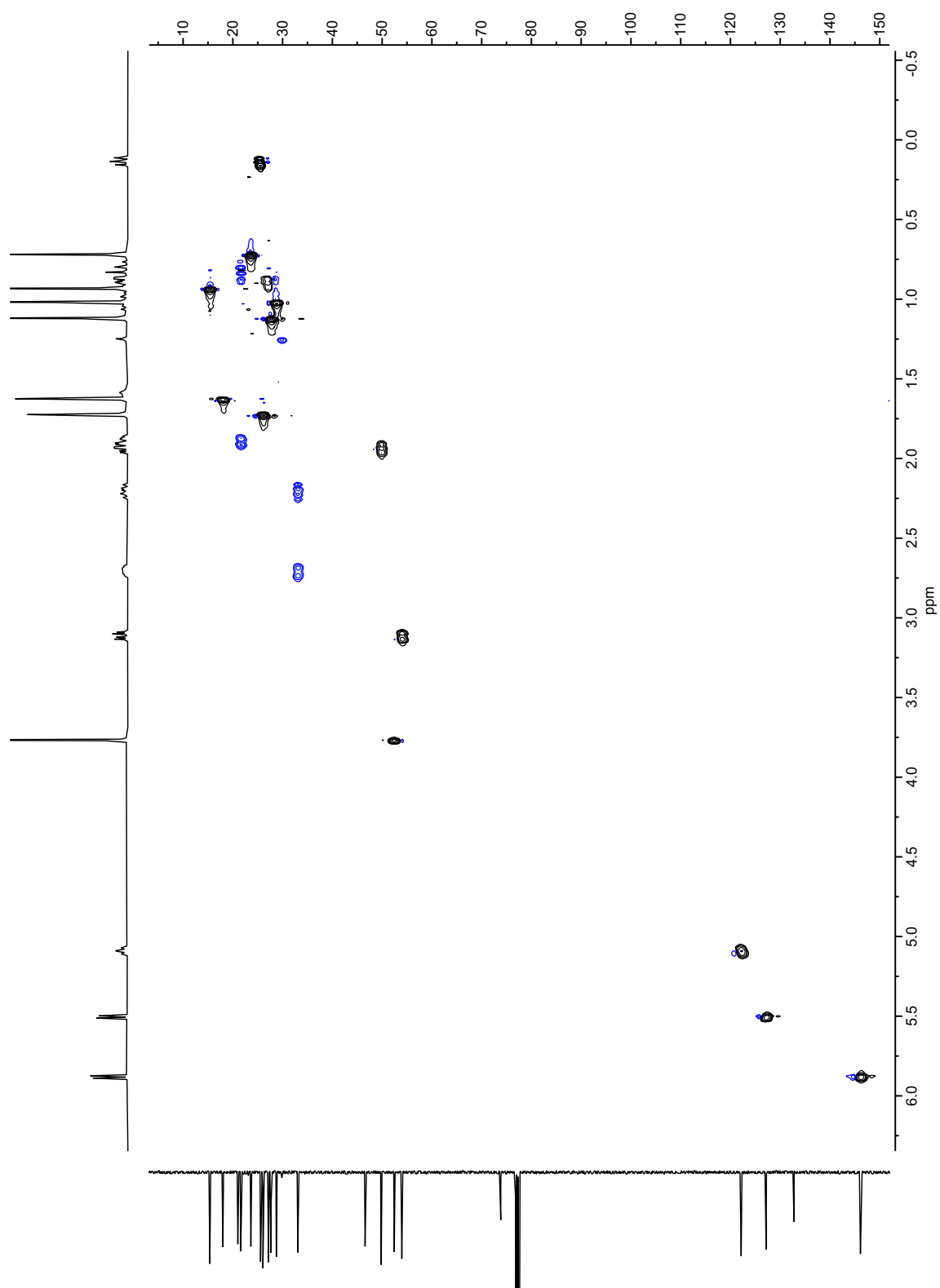


Figure A9.68 COSY NMR (400 MHz, CDCl_3) of compound **295**.



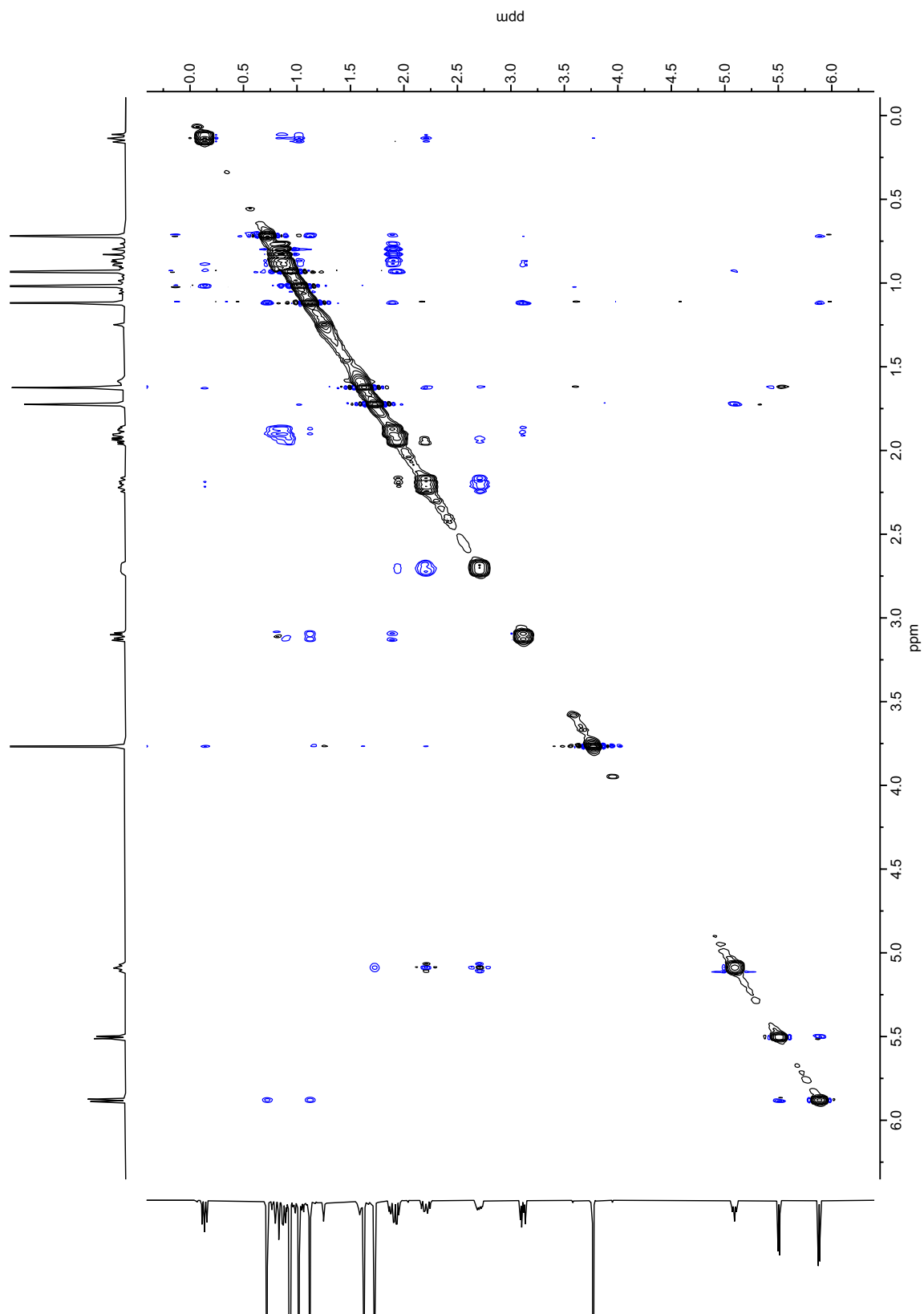


Figure A9.70 NOESY NMR (400 MHz, CDCl₃) of compound 295.

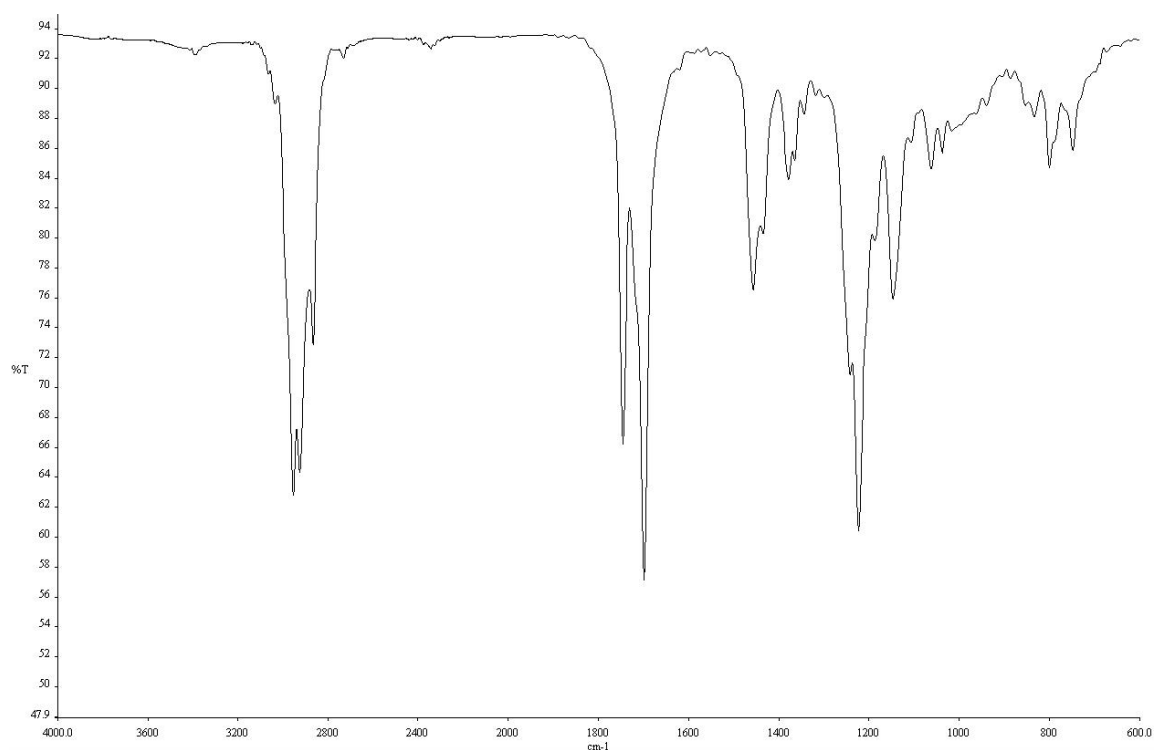


Figure A9.71 Infrared spectrum (Thin Film, NaCl) of compound **295**.

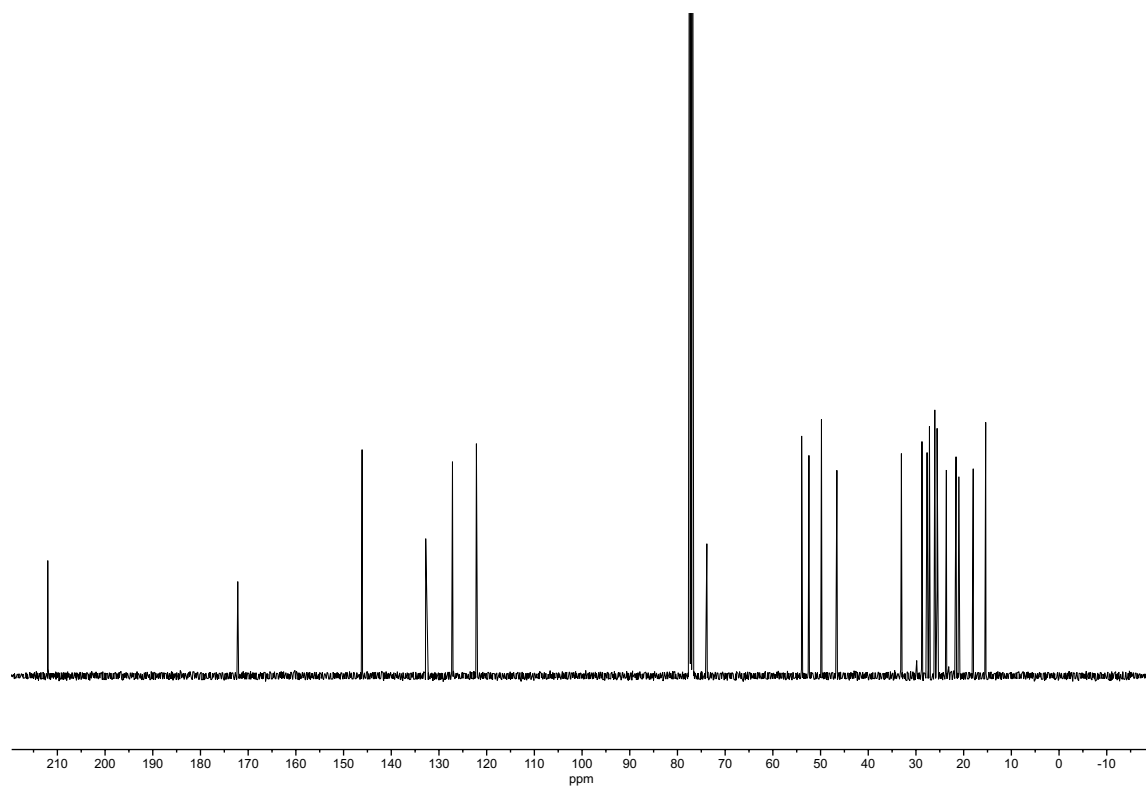


Figure A9.72 ¹³C NMR (100 MHz, CDCl₃) of compound **295**.

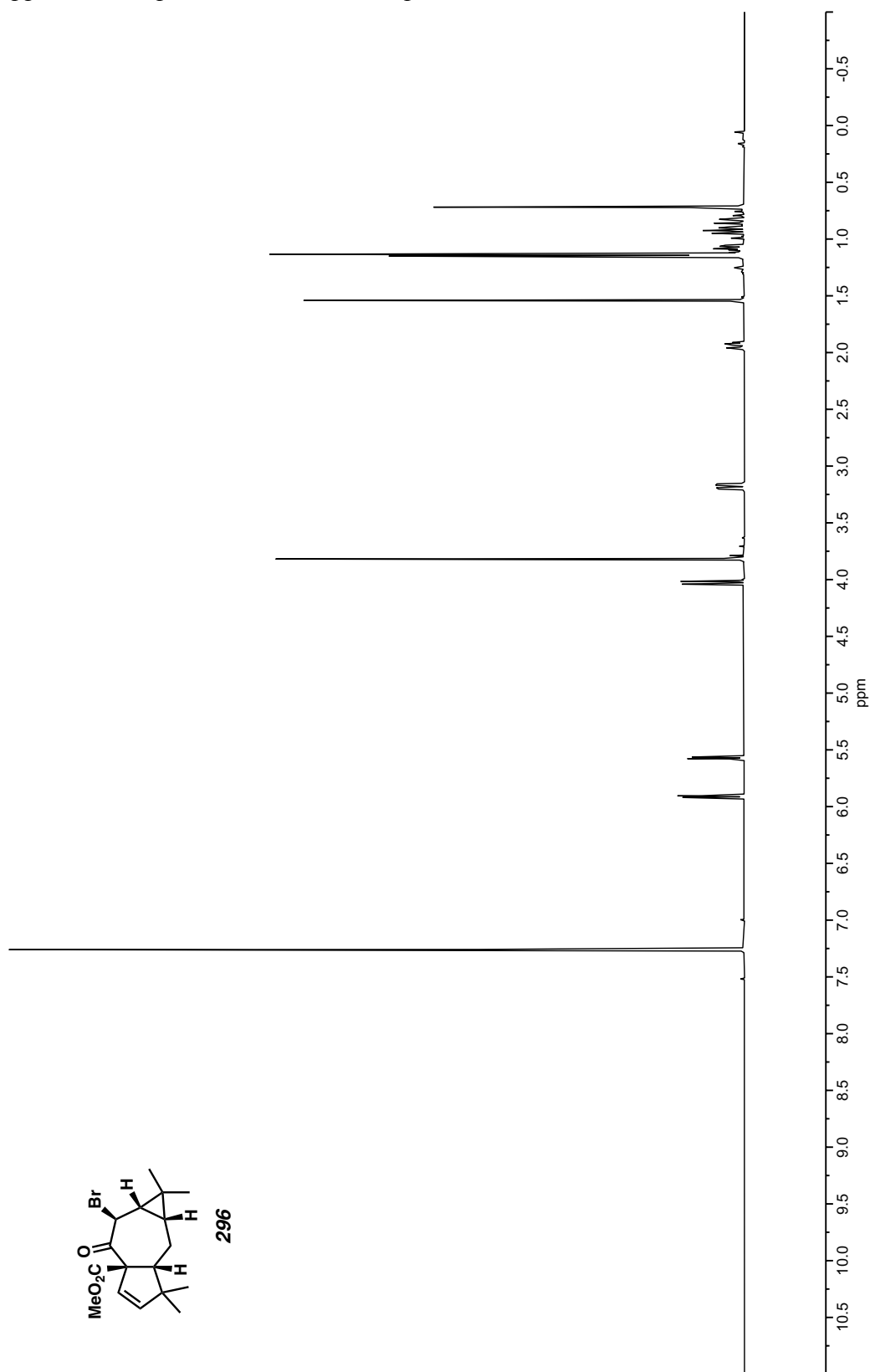


Figure A9.73 ¹H NMR (400 MHz, CDCl₃) of compound **296**.

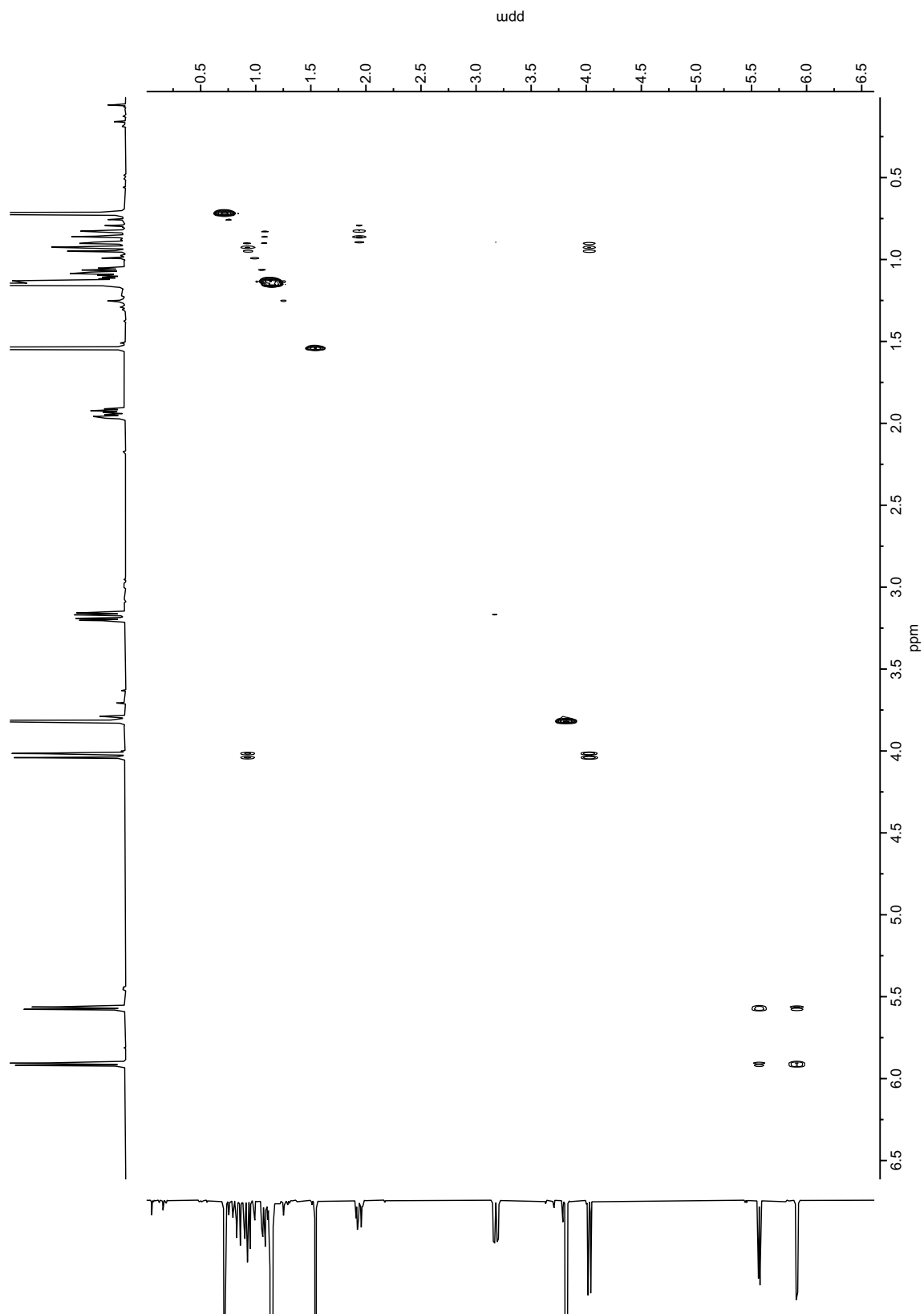


Figure A9.74 COSY NMR (400 MHz, CDCl_3) of compound **296**.

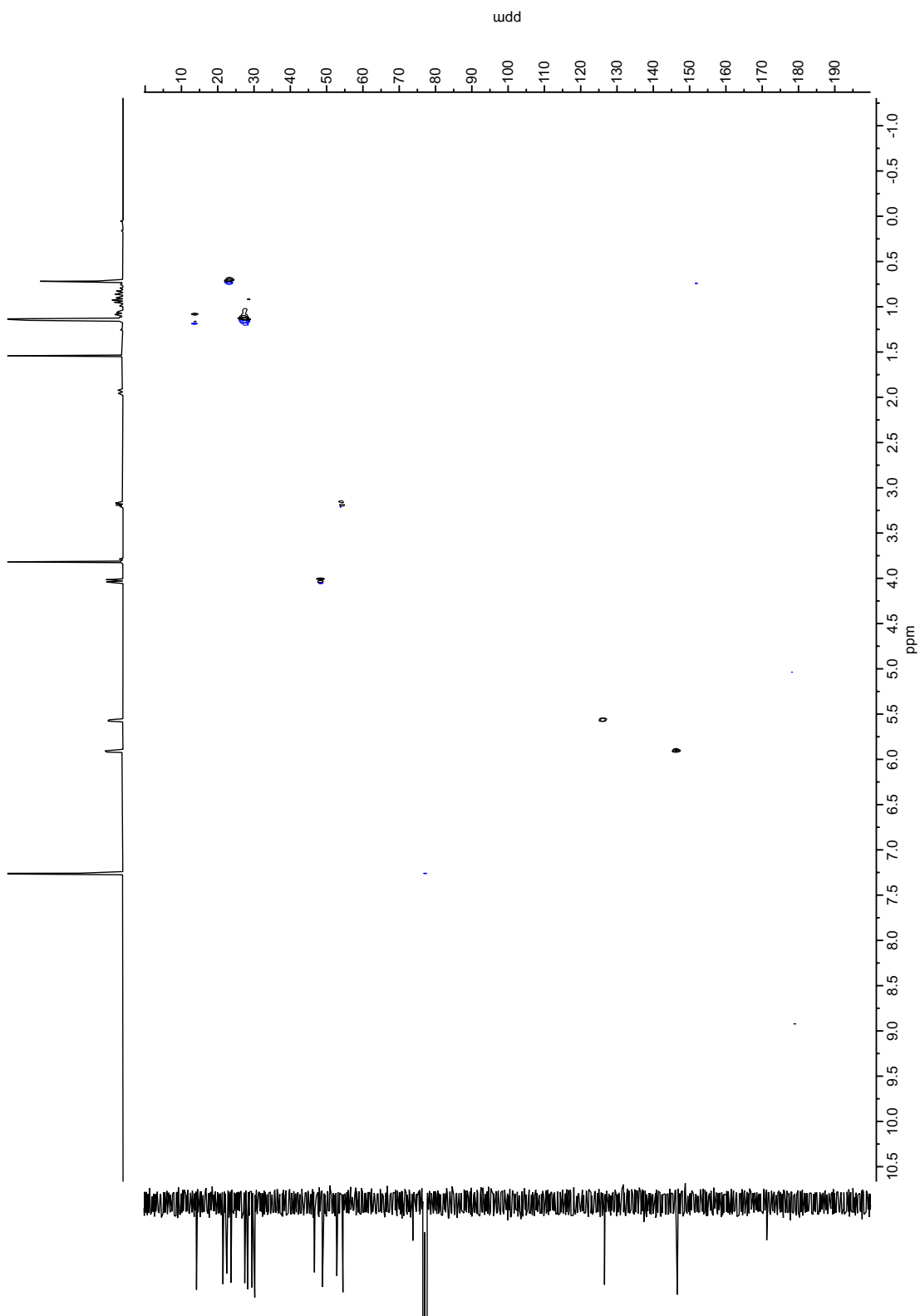


Figure A9.75 HSQC NMR (400 MHz, CDCl_3) of compound **296**.

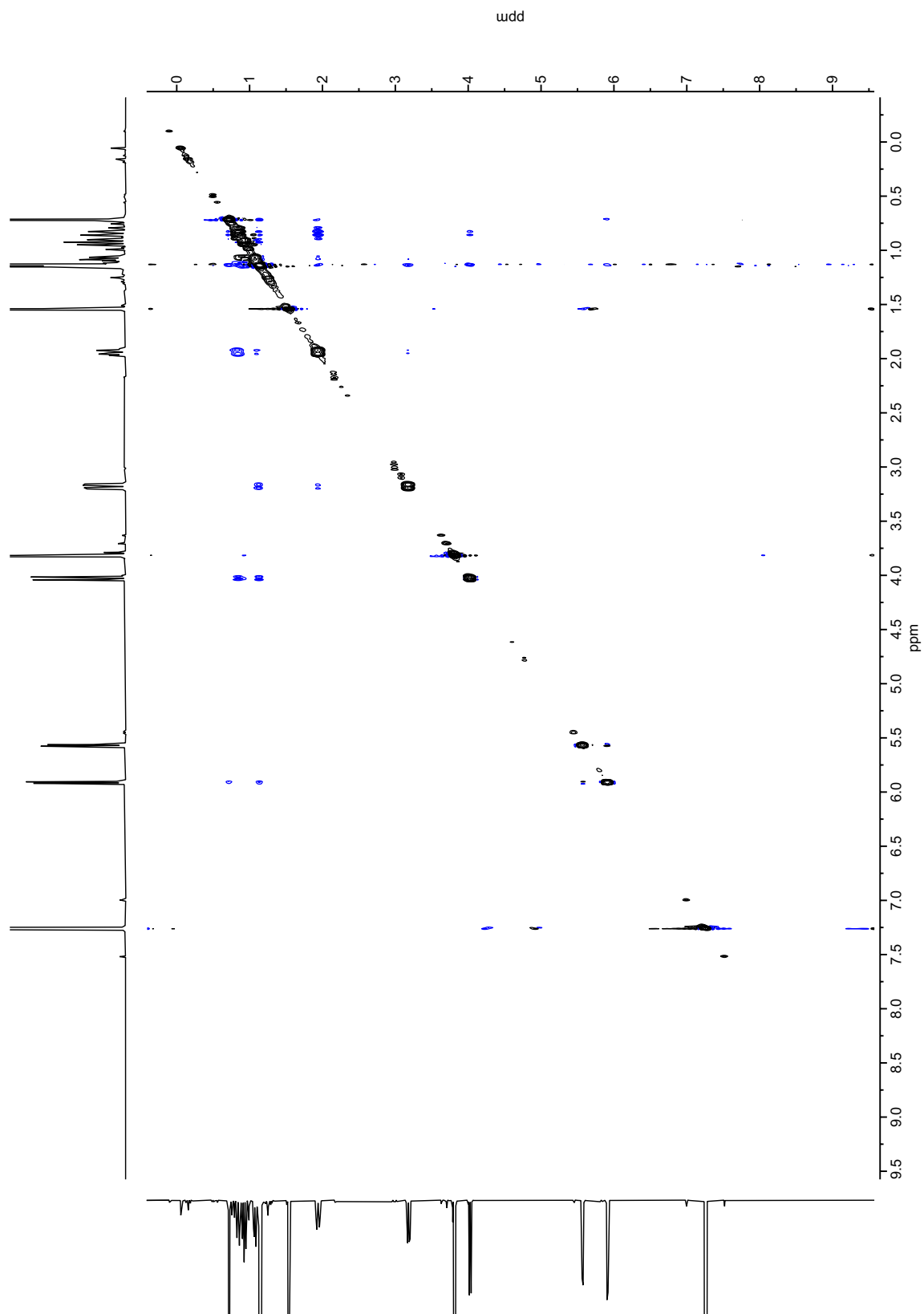


Figure A9.76 NOESY NMR (400 MHz, CDCl₃) of compound **296**.

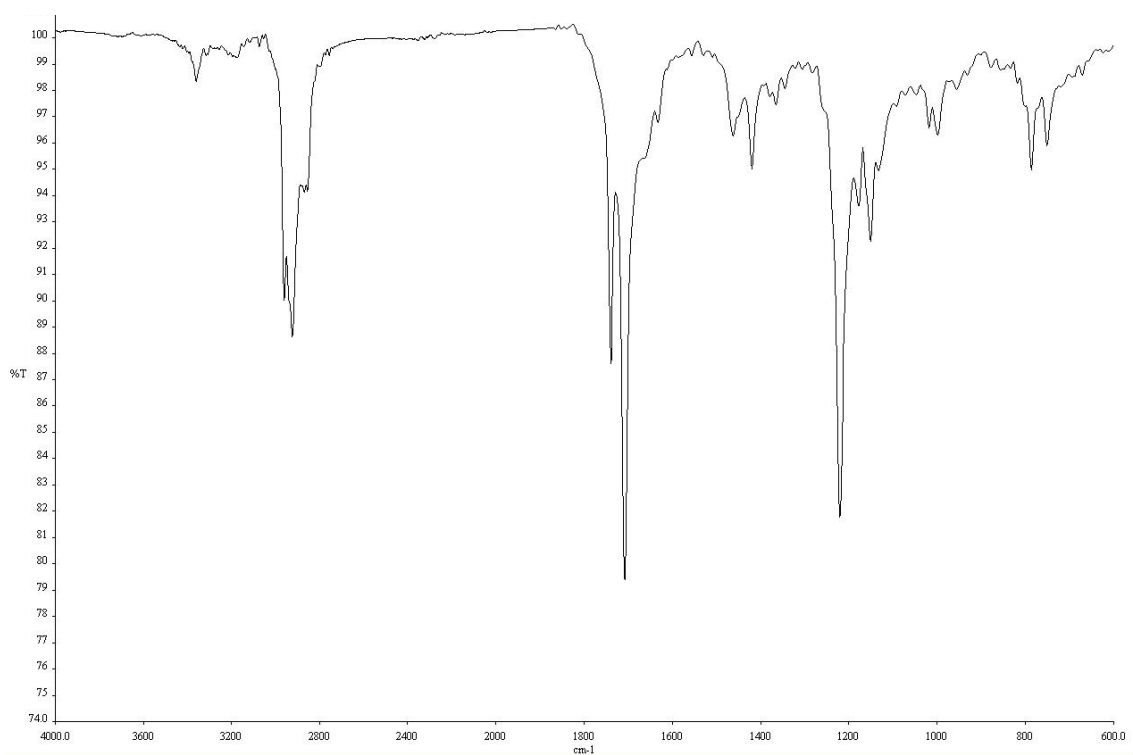


Figure A9.77 Infrared spectrum (Thin Film, NaCl) of compound **296**.

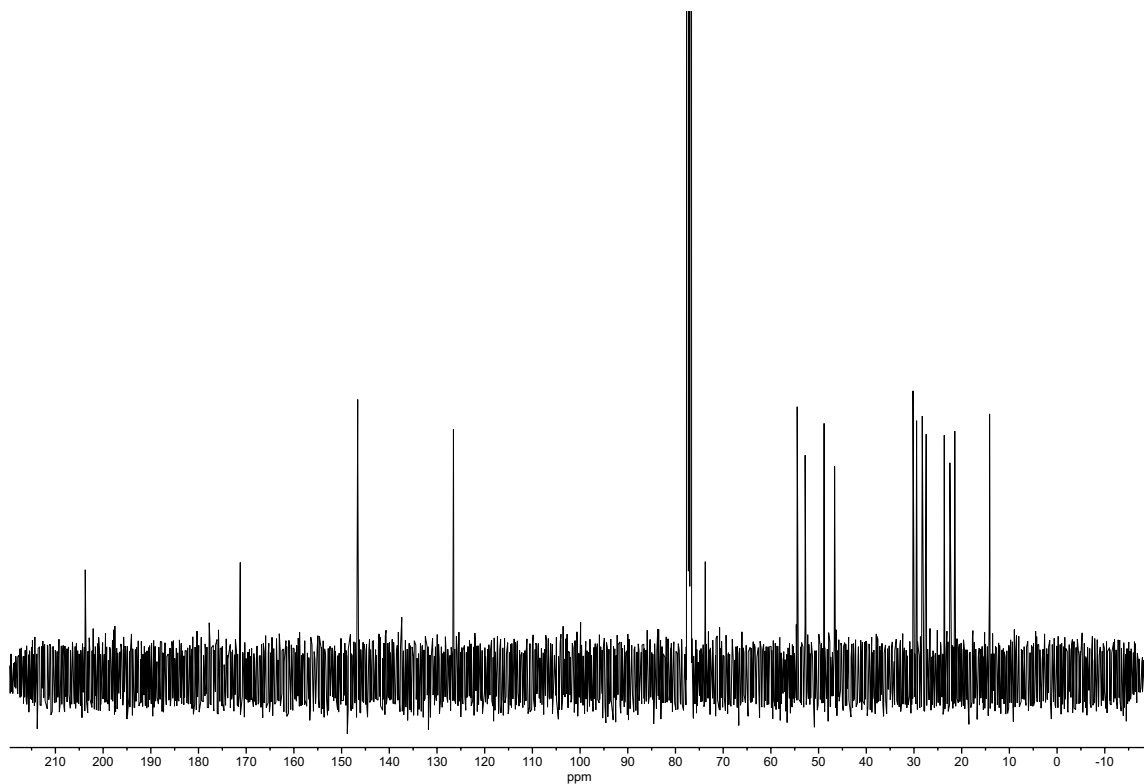


Figure A9.78 ¹³C NMR (100 MHz, CDCl₃) of compound **296**.

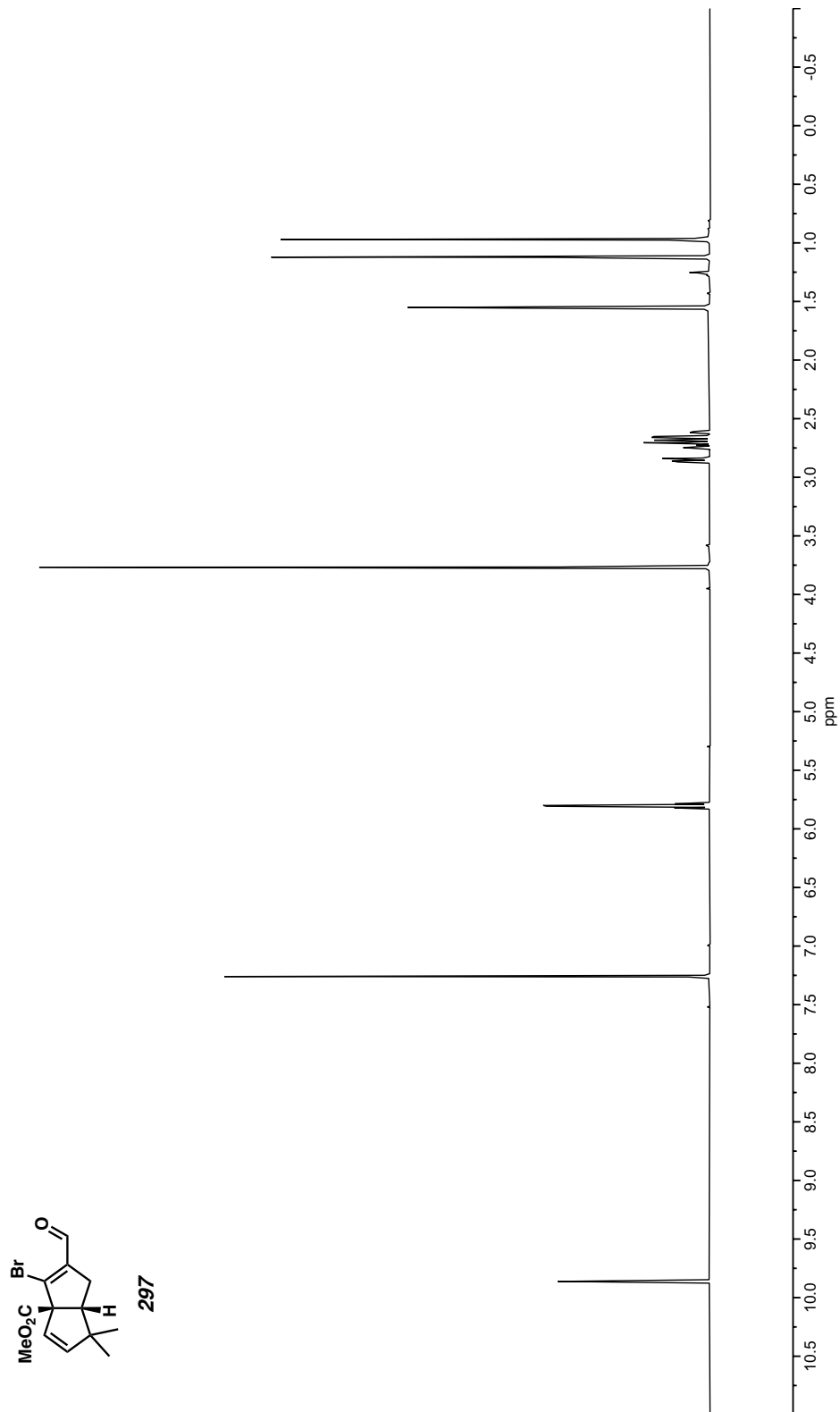


Figure A9.79 ¹H NMR (400 MHz, CDCl₃) of compound 297.

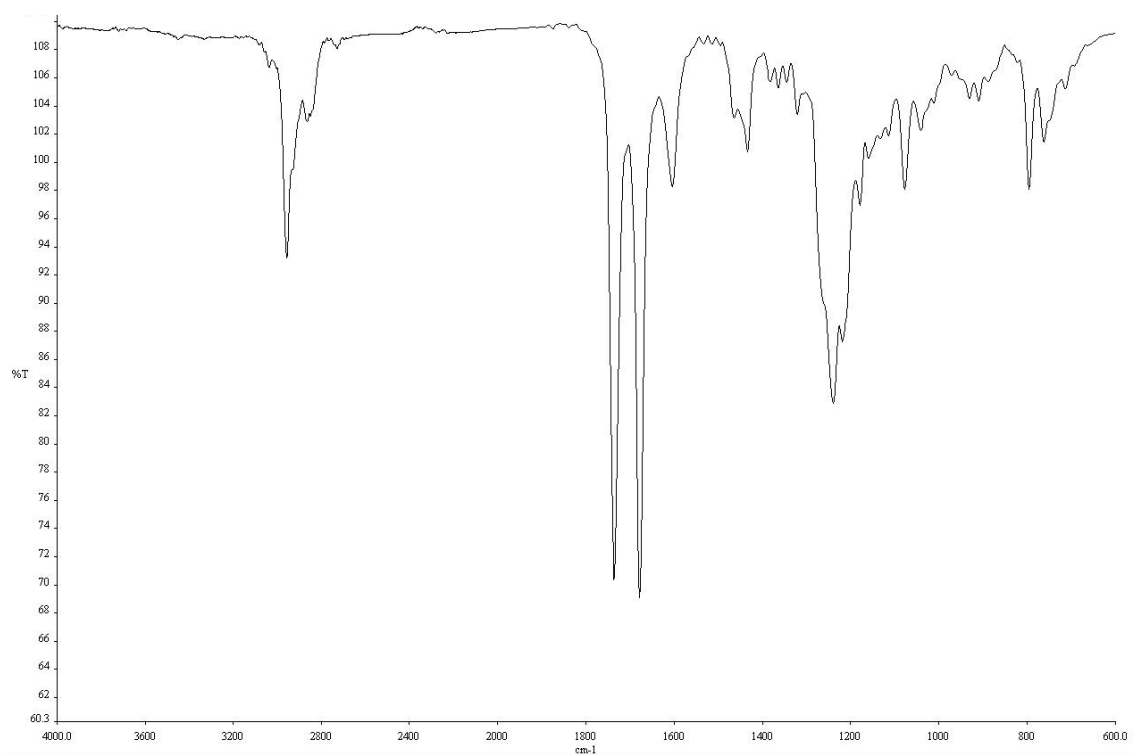


Figure A9.80 Infrared spectrum (Thin Film, NaCl) of compound **297**.

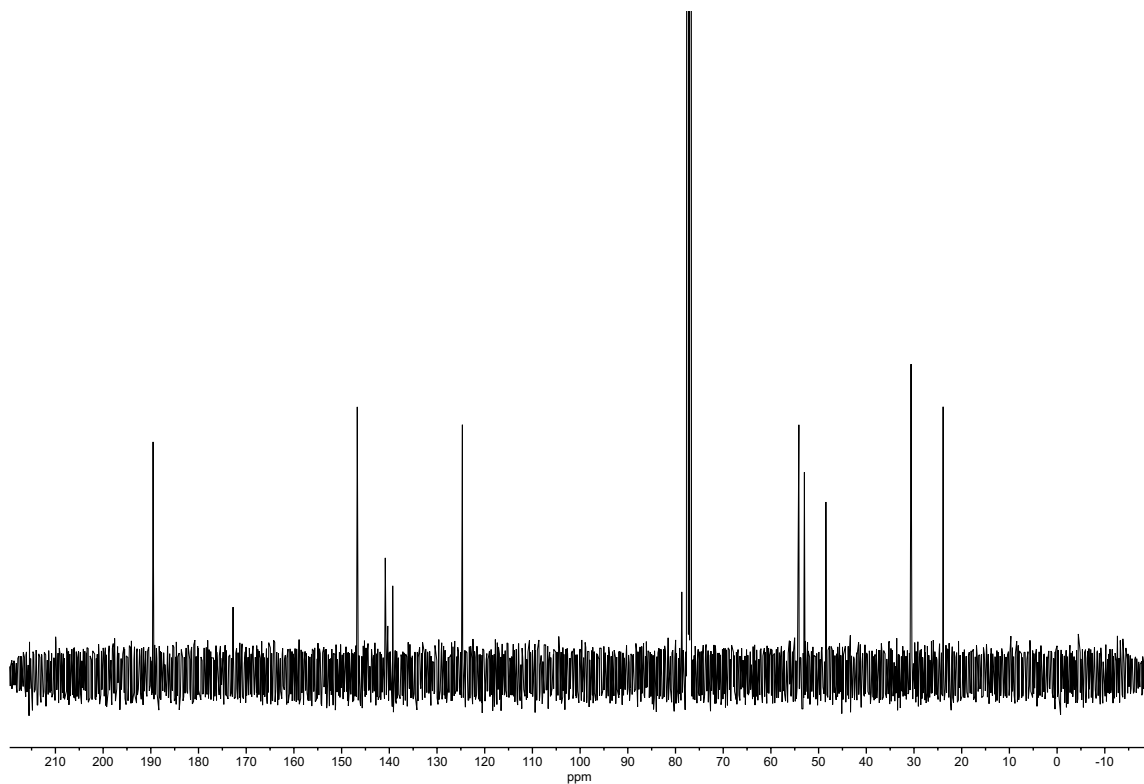


Figure A9.81 ¹³C NMR (100 MHz, CDCl₃) of compound **297**.

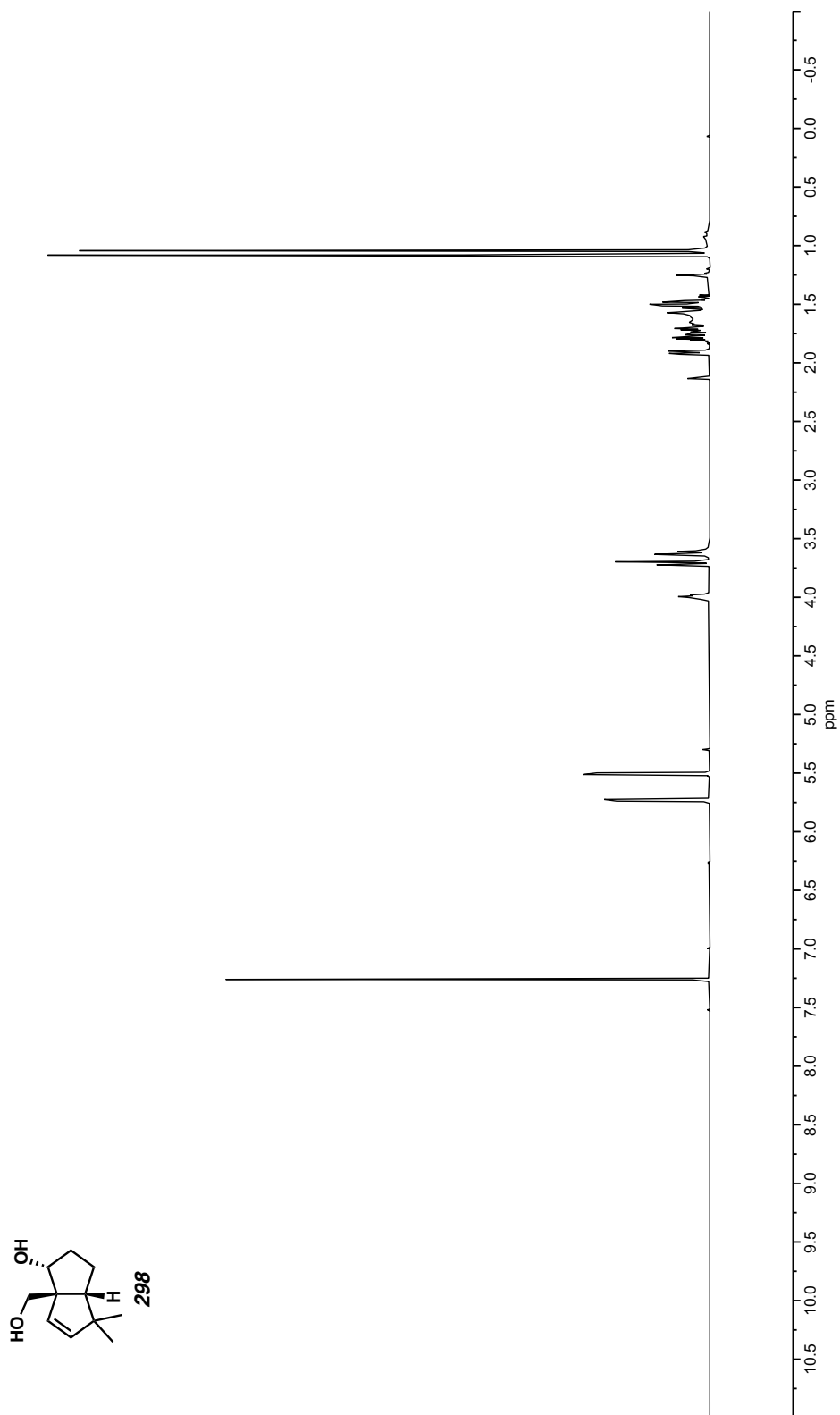


Figure A9.82 ^1H NMR (400 MHz, CDCl_3) of compound 298.

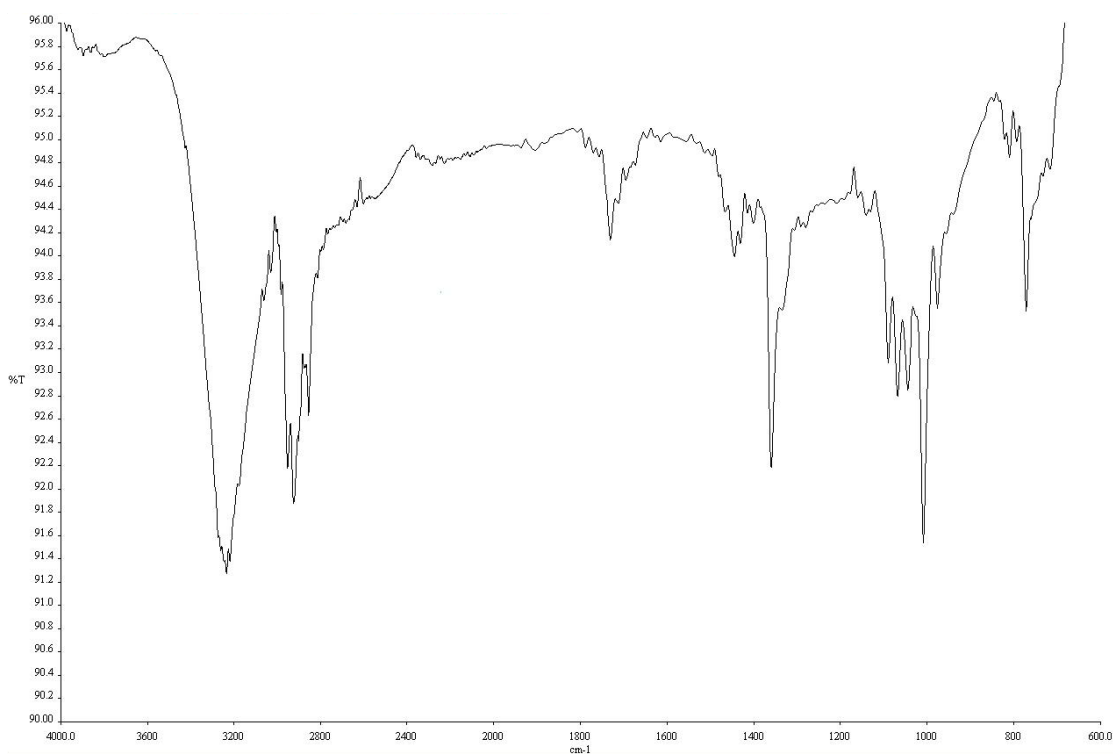


Figure A9.83 Infrared spectrum (Thin Film, NaCl) of compound **298**.

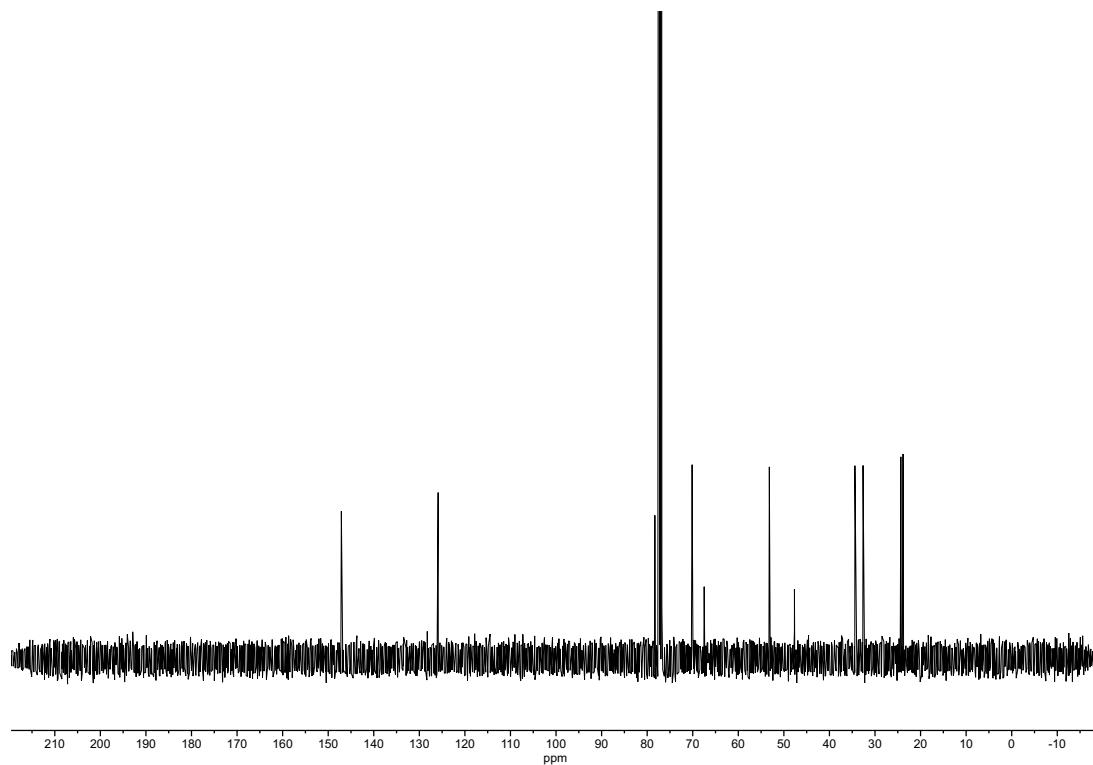


Figure A9.84 ¹³C NMR (100 MHz, CDCl₃) of compound **298**.

APPENDIX 10

Notebook Cross-Reference for New Compounds

Table A10.1. Notebook cross-reference for Chapter 1.

1	AS429
2	AS426
7	AS141
10	AS144
12	AS226/AS264
13	AS266
14	AS308
16	AS418
17	AS419
18	AS420
19	AS422
21	AS423
22	AS425
25	AS437
26	AS136
27	AS140
28	AS265
29	AS416
30	AS421
31	AS424

Table A10.2. Notebook cross-reference for Chapter 2.

12	AS226/AS264
37	AS411/AS412
38	AS363
51	AS261
52	AS308
54	AS318
56	AS319
57	AS319
58	AS342
59	AS358
60	AS360
61	AS362
62	AS117
64	AS243
65	AS262
66	AS263
67	AS334
68	AS355
69	AS361

Table A10.3. Notebook cross-reference for Appendix 5.

38	AS363	147	AS298
39	AS374	150	AS240
78	AS144	153	AS244
80	AS147	154	AS245
81	AS147	159	AS247
82	AS147	160	AS247
83	AS147	161	AS254/AS255
89	AS160	162	AS256
91	AS173	165	AS346
93	AS206	166	AS349
94	AS206	169	AS359
96	AS189	171	AS363
98	AS197	172	AS363
99	AS196	173	AS364
100	AS196	174	AS365
103	AS172	175	AS370
104	AS172	176	AS372
114	AS179	178	AS376/AS377
115	AS180	183	AS384/AS385
118	AS182	186	AS388/AS389
122	AS186	190	AS394
124	AS185	200	AS408
126	AS191	202	AS253
127	AS191	203	AS406/AS409

Table A10.4. Notebook cross-reference for Chapter 3.

204	AS149
205	ZPS-VI-239
207	AS151
208	AS151
210	ZPS-VI-171
211	ZPS-VI-171
212	AS153
213	AS153
214	AS153
215	AS153
220	ZPS-VI-213
221	ZPS-VI-231
223	AS148

Table A10.5. Notebook cross-reference for Chapter 4.

130	AS193/AS-C-4
131	AS194/AS-C-5
133	AS195/AS-C-7
236	AS195
241	AS-C-1
242	HN-473A
243	AS-C-8
244	HN02-489A
245	AS-C-6
246	AS-C-6
255	HN02-491A
256	HN02-491A

Table A10.6. Notebook cross-reference for Chapter 5.

62	AS117/KP95
89	AS160/KP88
269	ASCA70b
270	KP86
271	ASCA70/KP91
275	KP89
276	ASCA25
277	ASCA26
278	KP93
279	ASCA20
280	ASCA24
281	KP62
282	KP90
283	ASCA35
288	ASCA40
289	ASCA57
290	ASCA60
291	ASCA59
292	ASCA68
293	ASCA49
294	ASCA42
295	ASCA52
296	ASCA54
297	ASCA67
298	ASCA65

ABOUT THE AUTHOR

Adrian Eduard Samkian was born in Frankfurt am Main, Germany on December 13th, 1997 to Mario and Emik Samkian. After he turned five, Adrian, his parents, and his younger brother moved to Los Angeles, California. His interest in chemistry began around this time, and his early grade school years were spent studying chemistry textbooks and collecting laboratory glassware. In high school he developed an interest in organic chemistry, spending many hours synthesizing dye and fragrance chemicals in his parent's garage.

In the last two years of high school, Adrian joined the Oakcrest Institute of Science, where he conducted research under Dr. Marc Baum, developing a method to synthesize cyclic carbamates using nickel catalysis. In the fall of 2016, he started attending UC Berkeley as a chemistry major in the College of Chemistry. While an undergraduate at Cal, he conducted research in the lab of Professor Don Tilley, where he studied expanded helices and other polycyclic aromatic hydrocarbons in the context of organic materials.

In 2019, Adrian completed his studies at Cal and moved back to Southern California where he studied olefin metathesis catalysts in the lab of Professor Robert Grubbs. Having enjoyed his experience at Caltech immensely, he decided to start his graduate studies in the lab of Professor Brian Stoltz. His research there centered on the synthesis of complex natural products, specifically targeting the homoadamantane polycyclic polyprenylated acylphloroglucinols. In his fourth year of graduate study, he completed an internship at Merck & Co., which solidified his interest in industrial process chemistry. After completing his Ph.D., Adrian will work at Bristol Myers Squibb in New Jersey as an industrial process chemist.