ASYMMETRIC TRANSFORMATIONS FROM PALLADIUM ENOLATES AND PROGRESS TOWARD THE TOTAL SYNTHESIS OF HYPERMOIN A

Thesis by

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To my loving parents

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ABSTRACT

Research in the Stoltz group is centered around developing new methodologies for the asymmetric formation of stereocenters and the application of these technologies in complex natural product total synthesis. Herein we describe the development of new enantioselective transformations from Pd enolate intermediates and efforts toward the total synthesis of hypermoin A. Chapter 1 reports the development of an asymmetric intramolecular decarboxylative [4+2] cycloaddition from a catalytically generated chiral Pd enolate, forging four contiguous stereocenters in a single transformation. Mechanistic studies including quantum mechanics calculations, Eyring analysis, and KIE studies offer insight into the reaction mechanism. Appendix 2 discloses efforts toward the development of an asymmetric intermolecular decarboxylative double Michael addition. Chapter 2 describes an enantioselective cyclization of Pd enolates and isocyanates to form spirocyclic γ-lactams. This reaction proceeds under mild reaction conditions and utilizes a novel Meldrum's acid derivative to achieve catalyst turnover, delivering enantioenriched products in up to 97% yield and 96% ee. Chapter 3 outlines the ongoing progress toward the total synthesis of hypermoin A. A [4+2] cycloaddition and ring expansion strategy has been developed in a model system to form the key [3.2.2] bicycle and current efforts are dedicated to the application of this sequence in a more complex setting.

PUBLISHED CONTENT AND CONTRIBUTIONS

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TABLE OF CONTENTS

LIST OF FIGURES

CHAPTER 1

Catalytic Asymmetric Intramolecular [4+2] Cycloaddition of Pd Enolates

APPENDIX 1

Spectra Relevant to Chapter 1

APPENDIX 2

Catalytic Asymmetric Intermolecular Double Michael Addition of Pd Enolates

CHAPTER 2

An Enantioselective Spirocyclization of Pd Enolates and Isocyanates

APPENDIX 3

Spectra Relevant to Chapter 2

CHAPTER 3
Progress Toward the Total Synthesis of Hypermoin A

APPENDIX 4
Spectra Relevant to Chapter 3

LIST OF SCHEMES

CHAPTER 1

Catalytic Asymmetric Intramolecular [4+2] Cycloaddition of Pd Enolates

CHAPTER 2

An Enantioselective Spirocyclization of Pd Enolates and Isocyanates

CHAPTER 3

Progress Toward the Total Synthesis of Hypermoin A

LIST OF TABLES

CHAPTER 1

Catalytic Asymmetric Intramolecular [4+2] Cycloaddition of Pd Enolates

APPENDIX 2

Catalytic Asymmetric Intermolecular Double Michael Addition of Pd Enolates

CHAPTER 2

An Enantioselective Spirocyclization of Pd Enolates and Isocyanates

CHAPTER 3

Progress Toward the Total Synthesis of Hypermoin A

APPENDIX 5

Notebook Cross-Reference for New Compounds

LIST OF ABBREVIATIONS

$[\alpha]_D$	specific rotation at wavelength of sodium D line
ºC	degrees Celsius
Å	Angstrom
λ	wavelength
μ	micro
Aq	aqueous
Ar	aryl
atm	atmosphere
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bp	boiling point
br	broad
Bz	benzoyl
c	concentration for specific rotation measurements
calc'd	calculated
cm^{-1}	wavenumer(s)
d	doublet
D	deuterium
dba	dibenzylideneacetone
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine

DMF	*N,N*-dimethylformamide
dr	diastereomeric ratio
e.g.	for example (Latin exempli gratia)
ee	enantiomeric excess
EI+	electron impact
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
G	grams
GC	gas chromatography
h	hours
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	hertz
i.e.	that is (Latin id est)
IPA	isopropanol
i-Pr	*iso*-propyl
IR	infrared (spectroscopy)
J	coupling constant (NMR), exchange coupling constant (diradicals)
K	Kelvin (absolute temperature)

kcal	kilocalorie
KHMDS	potassium hexamethyldisilazide
L	liter; ligand
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
M	multiplet, milli
m/z	mass to charge ratio
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram(s)
MHz	megahertz
min	minutes
mol	mole(s)
n-Bu	*n*-butyl
NMR	nuclear magnetic resonance
Pd/C	palladium on carbon
Ph	phenyl
PHOX	phosphinooxazoline (ligand)
PHOX=O	phosphinooxazoline oxide (ligand)
ppm	parts per million
PTSA	*para*-toluenesulfonic acid

q	quartet
R	generic for any atom or functional groups
S	singlet
SCF	self-consistent field
SFC	supercritical fluid chromatography
t	triplet
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
*t*R	retention time
UV	ultraviolet
X	anionic ligand or electronegative element

CHAPTER 1

Catalytic Asymmetric Intramolecular [4+2] Cycloaddition of Pd Enolates†

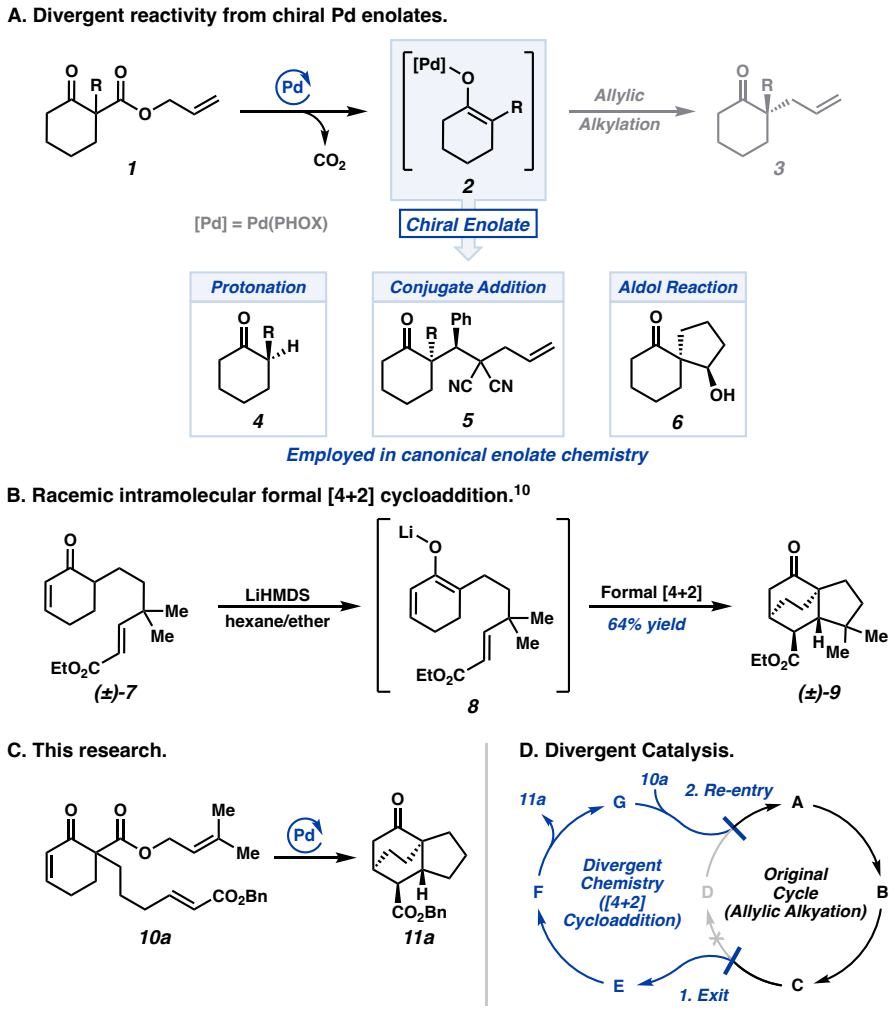
1.1 INTRODUCTION

Enantioselective construction of all-carbon quaternary stereogenic centers represents a central and ongoing challenge in synthetic organic chemistry.[1] The asymmetric allylic alkylation of enolate nucleophiles serves as a powerful strategy for accessing such motifs.[2]

A unique aspect of the Pd-catalyzed allylic alkylation methods developed by our group is the inner-sphere reductive elimination from a chiral O-bound Pd enolate intermediate (**2**), yielding enantioenriched ketones (**3**) (Figure 1.1A).[3,4] This intermediate is generated catalytically from achiral or racemic enolate precursors, such as allyl enol carbonates[5] and β-ketoesters[6] (**1**). The Pd enolate is accessed in the absence of a base, under neutral conditions, and in a regiospecific fashion. Conversely, canonical conditions for enolate formation are plagued by regioselectivity challenges and typically require the use of a strong base or Lewis acid. Given the inherent advantages of Pd enolates, we sought to exploit their reactivity beyond simple allylic alkylations in more general asymmetric transformations.

†This research was performed in collaboration with Cusumano, A. Q.; Chen, P.-J.; Strong, C. S.; Du, Y. E.. Portions of this chapter have been reproduced with permission from Stoltz, et al. *J. Am. Chem. Soc.* **2023**, *145*, 11301–11310.

Figure 1.1. *(A) Examples of chiral Pd enolate reactivity. (B) Lithium base-promoted intramolecular formal [4+2] cycloaddition. (C) Proposed asymmetric intramolecular [4+2] reaction. (D) Divergent catalytic cycle.*



Highlighting the utility of this concept, our lab has demonstrated the enantioselective protonation of Pd enolates as a valuable strategy to access ketones with tertiary stereocenters (**4**).[7] Building upon this success, we subsequently developed methods to construct quaternary centers via enantioselective conjugate additions [8] (**5**) and

intramolecular aldol reactions (**6**).[9] Taken together, these advances underscore the feasibility of employing Pd enolates as pro-stereogenic nucleophiles.

In a unique example of enolate reactivity, Fukumoto and coworkers reported a formal [4+2] reaction from in situ generated conjugated lithium enolate **8**, forging tricyclic adduct **9** in a racemic fashion (Figure 1.1B).[10] We envisioned that an analogous asymmetric transformation would be tractable from a chiral, conjugated Pd enolate – derived from the decarboxylation of unsaturated β-ketoester **10a** using an asymmetric ligand on Pd (Figure 1.1C).

To realize this transformation, we sought to develop a conceptual framework based on our mechanistic understanding to expand the general utility of the Pd enolate. As such, we employed a strategy of divergent catalysis (Figure 1.1D), where deviation occurs at the common Pd enolate (i.e., **C**, Figure 1.1D, cf. Scheme 1.1, vide infra), allowing for desired alternative reactivity in the diverged cycle. Subsequent re-entry into the original catalytic cycle turns over the catalyst allowing regeneration of the Pd enolate.

Applying this strategy of divergent catalysis, we developed a catalytic decarboxylative asymmetric intramolecular [4+2] cycloaddition from conjugated Pd enolates. Mechanistic studies including quantum mechanics calculations, Eyring analysis, and KIE studies offer insights into the reaction mechanism. This transformation enables access to tricyclic scaffolds bearing at least four contiguous stereocenters, at least one of which is quaternary.

1.2 RESULTS AND DISCUSSION

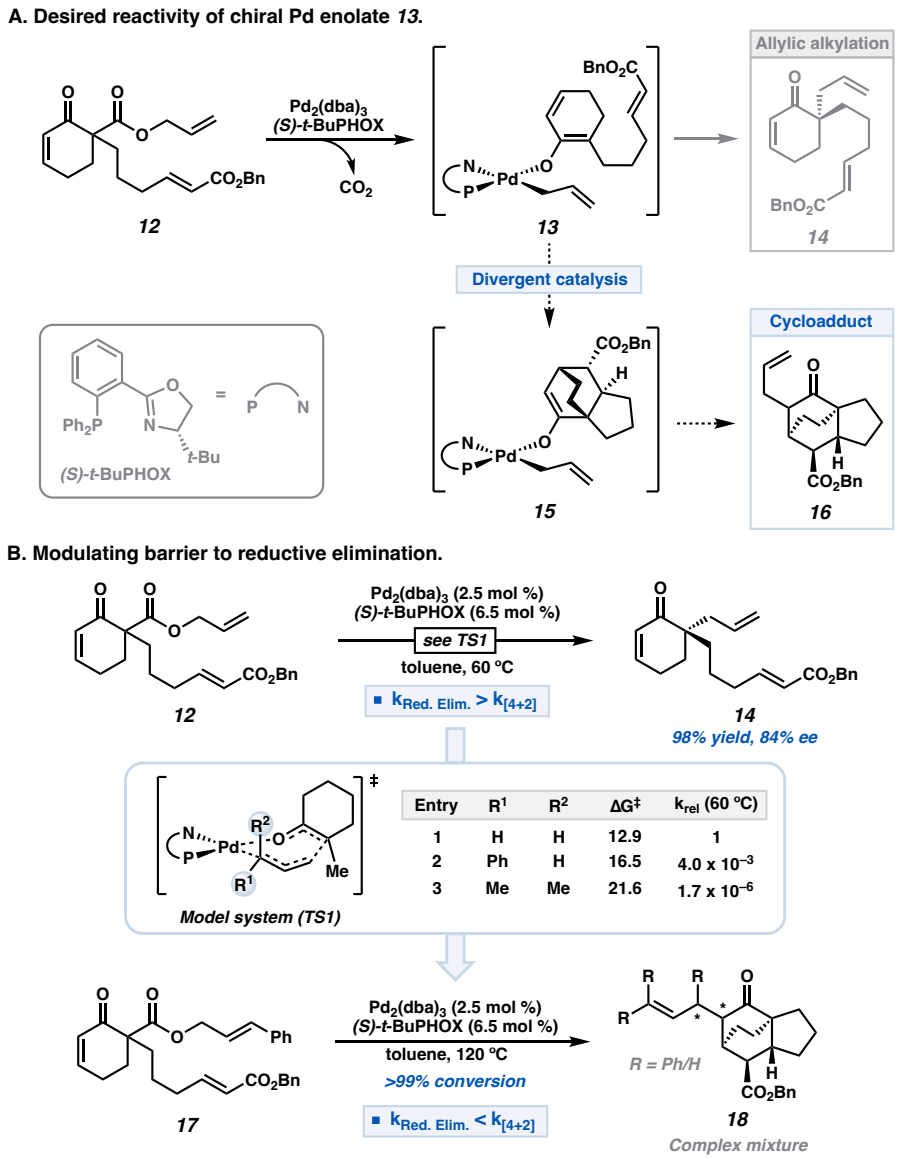
1.2.1 REACTION DESIGN AND OPTIMIZATION

Employing unsaturated β-ketoester **12** as a precursor for conjugated Pd enolate **13**, we hypothesized that the precedented allylic alkylation forming **14** could be interrupted by a [4+2] cycloaddition to generate **15** (Figure 1.2A). Alkylation of the transposed enolate (**15**) would then turn over the catalyst and forge tricyclic product **16**.

Unfortunately, the rate of direct allylic alkylation of enolate **13** supersedes the desired divergent reactivity. Treatment of β-ketoester **12** under our standard conditions produces ketone **14** in 98% yield and 84% ee (Figure 1.2B). This prompted us to redesign our exit strategy (Figure 1.1D). Increasing the rate of the cycloaddition through modification of the diene or dienophile could circumvent formation of premature allylic alkylation product **14** but would limit the generality of this transformation. Therefore, we sought to impede alkylation through modification of the allyl moiety.

Computational investigation of a model system (**TS1**) suggested that introducing terminal substitution on the allyl group raises the barrier to reductive elimination, decreasing the rate of allylic alkylation (Figure 1.2B, see 1.4 Experimental Section for computational details).[11] For example, phenyl substitution (entry 2, Figure 1.2B) slows the rate of inner-sphere reductive elimination by roughly three orders of magnitude. Inspired by these computational results, we explored the efficacy of cinnamyl ester substrate **17** in the transformation. In line with our hypothesis, the desired tricyclic core was observed (**18**), albeit as a complex mixture of isomers – hampering the synthetic utility. To this end, we sought to develop an alternative strategy for catalyst turnover that could potentially simplify the product outcomes.

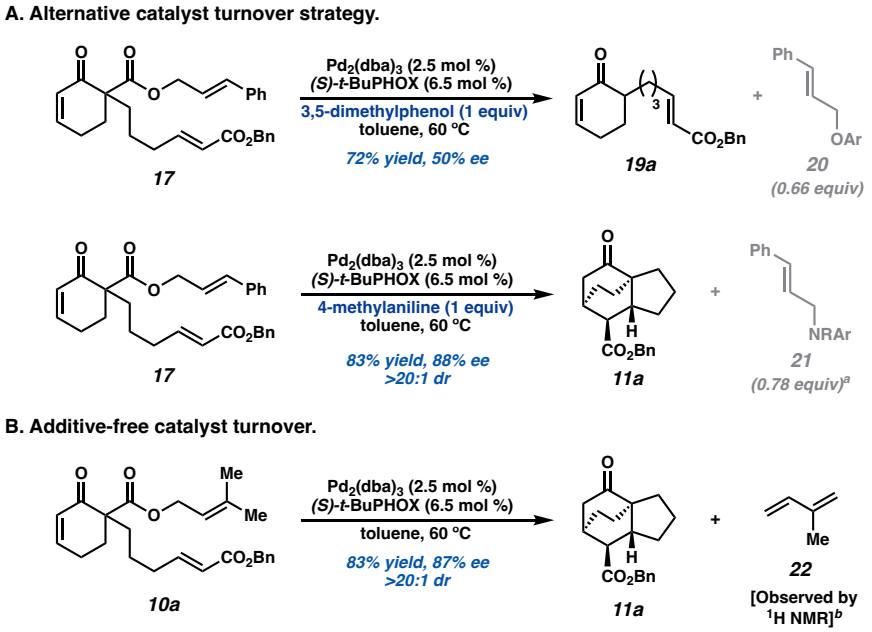
Figure 1.2. *(A) General reactivity paradigm from Pd enolate* ***13****. (B) Computed substituent effects on the rate of C–C bond formation and successful application.*[a]



[a] See 1.4 Experimental Section for computational details and discussion of other isomeric transition states. Yield determined by ^{1}H NMR with respect to 1,3,5-trimethoxybenzene as internal standard. Enantiomeric excess determined by chiral SFC.

Building upon previous findings from our group, we sought to employ stoichiometric acidic additives for catalyst turnover. The exogenous acid serves the dual purpose of protonating the final enolate (analogous to **15**) and turning over the catalyst by trapping the cinnamyl group. Addition of 3,5-dimethylphenol[9] exclusively yielded undesired protonation product **19a** along with aryl ether **20** (Figure 1.3A). To our delight, replacing the phenol additive with 4-methylaniline afforded the desired *endo* [4+2] cycloadduct (**11a**) as a single diastereomer in 83% yield and 88% ee.

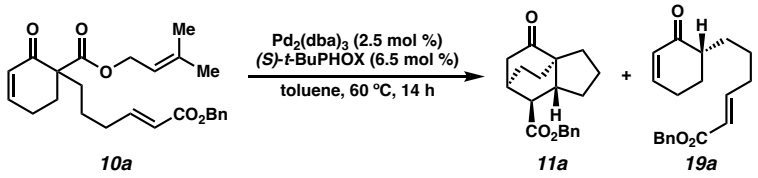
Figure 1.3. *(A) Sacrificial additives to enable catalyst turnover.*[a] *(B) Additive-free reaction with prenyl ester* ***10a****.*[b]



[a] Equivalents includes mixture of branched and linear constitutional isomers, as well as double-alkylation of aniline. [b] Isoprene (**22**) observed in 0.94:1 ratio with **11a** by ^{1}H NMR (J Young tube, toluene-d_8).

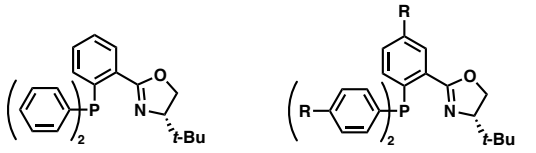
Seeking to improve the reaction yield, the competency of β-ketoester **10a**, derived from the commodity chemical prenyl alcohol, was explored. According to our computations, a substrate containing a di-substituted allyl fragment would be similarly effective in hindering premature allylic alkylation by increasing the barrier to reductive elimination (Figure 1.2B, entry 3). Perplexingly, while the desired tricyclic product was generated in 73% isolated yield and 88% ee, no alkylated 4-methylaniline (analogous to **21**) was observed as a byproduct (entry 8, Table 1.1).

Table 1.1. *Optimization of [4+2] reaction conditions.*[a]



10a *11a* *19a*

Entry	Deviation from standard conditions	Yield *11a* (%)[b]	ee *11a* (%)	Yield *19a* (%)[b]	ee *19a* (%)
1	none	96 (83)	87 (87)	–	–
2	THF	86	81	–	–
3	benzene	92	87	–	–
4	1,4-dioxane	12	–	63	49
5	40 °C	51	89	–	–
6	*(S)*-$(CF_3)_3$-*t*-BuPHOX	12	89	66	62
7	*(S)*-$(OMe)_3$-*t*-BuPHOX	40	88	26	65
8	4-methylaniline (1 equiv)	93 (73)	87 (88)	–	–
9	4-methylaniline (2 equiv)	78	87	–	–
10	3,5-dimethylphenol (1 equiv)	0	–	100	71



(S)-t-BuPHOX

[a] Conditions: 0.02 mmol **10a**, 2.5 mol % $Pd_2(dba)_3$, 6.5 mol % ligand, in 1.0 mL of solvent (0.02 M). [b] Yields determined by ^1H NMR with respect to 1,3,5-trimethoxybenzene as internal standard. Isolated yields on 0.2 mmol scale in parentheses.

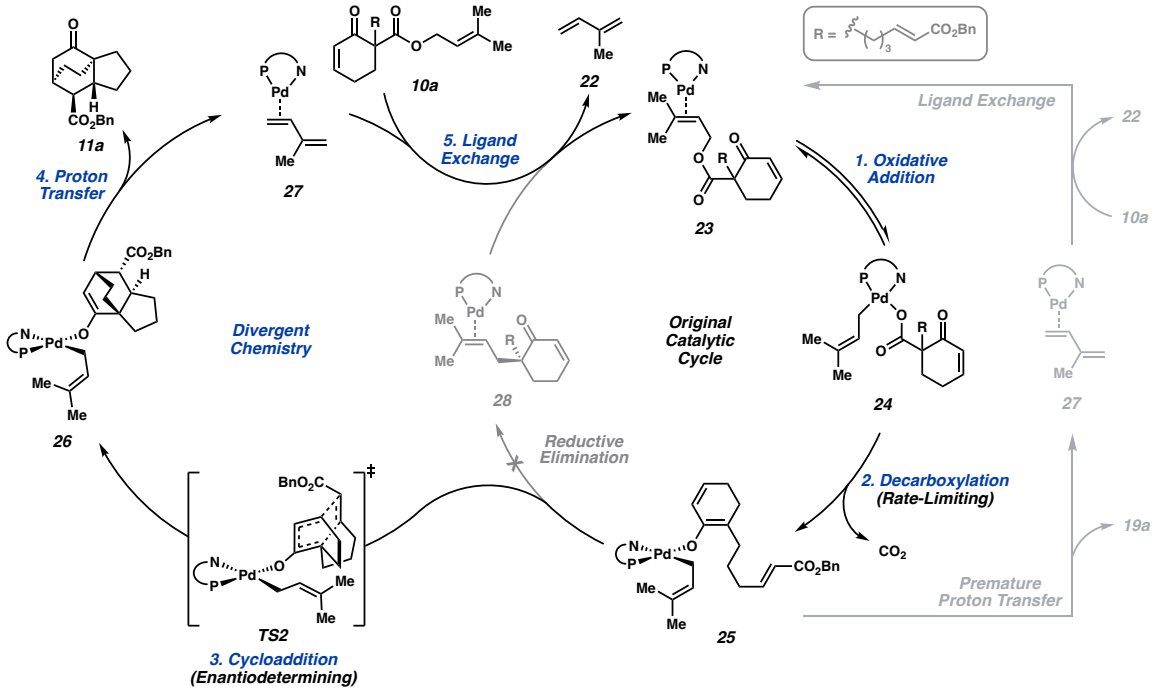
A control reaction excluding 4-methylaniline was carried out, and surprisingly, desired product **11a** was formed in 83% yield and 87% ee (Figure 1.3B). This suggests that an alternative catalyst turnover mechanism is operative. Further NMR experiments revealed the stoichiometric evolution of isoprene (**22**) accompanying formation of product **11a**. Intrigued by this unexpected finding and clean reaction profile, we pursued optimization of additive-free reaction conditions.

The reaction proceeds in THF and benzene albeit in slightly diminished yield and enantioselectivity (entries 2–3, Table 1.1). Employing 1,4-dioxane as the solvent, protonation product **19a** was obtained as the major product in 63% yield and 49% ee, while cycloadduct **11a** was observed in only 12% yield (entry 4, Table 1.1). Lowering the temperature to 40 ºC slightly improved the ee to 89% at the cost of decreased conversion (entry 5, Table 1.1). Modification of the electronic properties of the PHOX ligand deleteriously impacted the product distribution (entries 6–7, Table 1.1). Phenol and aniline additives do not improve the reaction (entries 8–10, Table 1.1). Ultimately, optimized reaction conditions were determined to be additive-free with *(S)-t*-BuPHOX in toluene at 60 ºC. The reaction affords **11a**, a bridged bicycle with a pendant fused ring, in 83% isolated yield and 87% ee. The transformation allows for the simultaneous construction of four contiguous stereocenters, including one all-carbon quaternary center. Gratifyingly, the reaction can be performed with reduced catalyst loading (0.625 mol %) on 1.0 mmol scale to afford **11a** in 59% yield and 89% ee. The ability to efficiently construct these complex building blocks on scale highlights the synthetic utility of this transformation.

1.2.2 PROPOSED MECHANISM

We sought to capitalize on these initial exciting results by constructing a mechanistic framework to inform rational design. Based on our lab's prior investigations of Pd-catalyzed decarboxylative asymmetric allylic alkylation reactions, we propose that oxidative addition of Pd^0 to β-ketoester **10a** proceeds through complex **23** to afford the η^1-allyl carboxylate resting state **24** (Scheme 1.1).[12] Rate-limiting decarboxylation ensues, affording O-bound Pd enolate **25**.[3,12] This chiral conjugated enolate then serves as the diene in a [4+2] cycloaddition (**TS2**) with the pendant dienophile to form tricyclic enolate **26**.

Scheme 1.1. *Proposed divergent catalytic cycle. Undesired reaction pathways in grey.*



Subsequent proton transfer would generate product **11a**. Concomitant isoprene generation, followed by ligand exchange, allows for re-entry into the original catalytic cycle at **23**. We

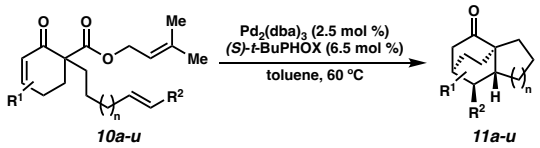
posit that the formation of undesired ketone **19a** arises from an off-cycle pathway, where catalyst turnover occurs prior to cycloaddition via premature proton transfer to **25**.

1.2.3 SUBSTRATE SCOPE

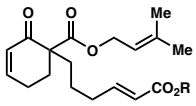
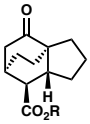
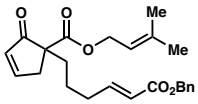
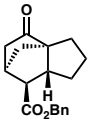
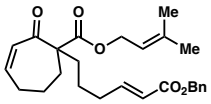
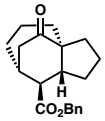
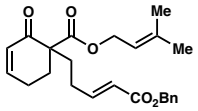
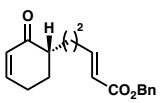
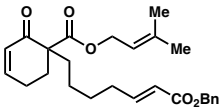
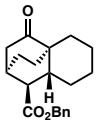
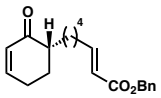
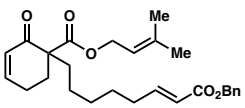
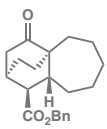
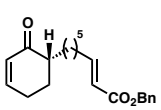
With a working mechanistic hypothesis in hand, we sought to draw further mechanistic insights from substrate design, while simultaneously exploring limits of the reaction. Considering the inverse relationship between diene ring size and Diels–Alder reaction rate[13,2], we explored whether this trend impacts the generality of our transformation. However, with cyclopentyl diene derived from enone **10c**, a decrease in yield and ee, relative to six-membered parent substrate **10a**, was noted (Table 1.2). In comparison to smaller ring sizes, seven-membered cyclic dienes require increased distortion energy to reach the desired transition state.[13] Despite this, seven-membered ring substrate **10d** leads to a high yield and improved ee. Thus, this transformation represents a powerful method to synthesize various challenging bicyclic cores.

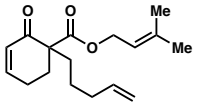
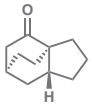
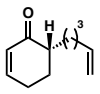
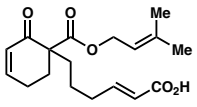
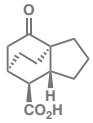
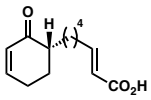
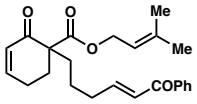
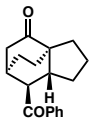
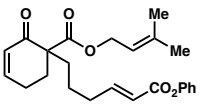
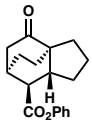
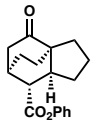
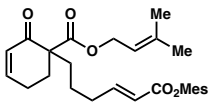
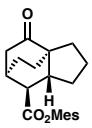
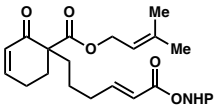
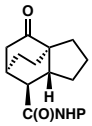
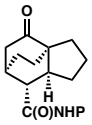
The dienophile tether length was subsequently modulated to test its influence on product distribution. The ethylene tethered substrate **10e** yields solely the premature protonation product **19e**, likely due to insurmountable developing ring strain in the cycloaddition transition state. In contrast to the propylene tethered substrate **10a**, the butylene tethered substrate **10f** leads to a near equal distribution of cycloadduct **11f** (42% yield) and premature protonation product **19f** (45% yield). Following this trend, the pentylene tethered substrate **10g** leads only to protonation product **19g**. Rationalizing this phenomenon, we propose that lengthening the tether increases conformational flexibility

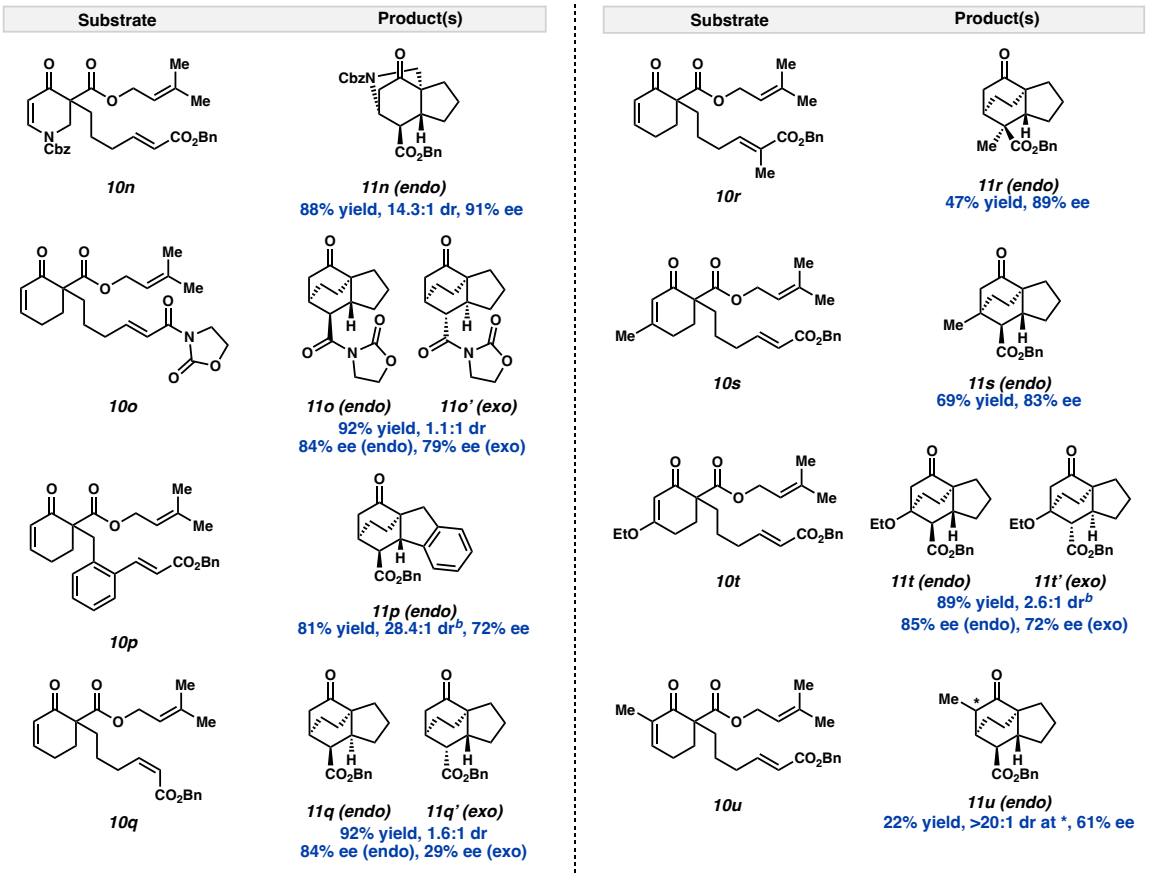
Table 1.2. *Substrate scope of the [4+2] reaction.*[a]



10a-u *11a-u*

Substrate	Product(s)		
 R = Bn *10a* R = Et *10b*	 *11a (endo)* 83% yield, 87% ee *11b (endo)* 85% yield, 88% ee		
 *10c*	 *11c (endo)* 65% yield, 65% ee		
 *10d*	 *11d (endo)* 83% yield, 97% ee		
 *10e*	 *11e (endo)* (not observed)	 *19e* 81% yield, 47% ee	
 *10f*	 *11f (endo)* 42% yield, 92% ee	 *19f* 45% yield, 51% ee	
 *10g*	 *11g (endo)* (not observed)	 *19g* 74% yield, 56% ee	

Substrate	Product(s)	
 *10h*	 *11h (endo)* (not observed)	 *19h* 33% yield, 58% ee
 *10i*	 *11i (endo)* (not observed)	 *19i* 80% yield, 7% ee
 *10j*	 *11j (endo)* 50% yield, 87% ee	
 *10k*	 *11k (endo)*	 *11k' (exo)* *11k'' (other)* 82% yield, 10.4:1.4:1 dr, 88% ee (endo)
 *10l*	 *11l (endo)* 90% yield, 89% ee	
 *10m*	 *11m (endo)*	 *11m' (exo)* 65% yield, 1.4:1 dr[b] 62% ee (endo), 62% ee (exo)



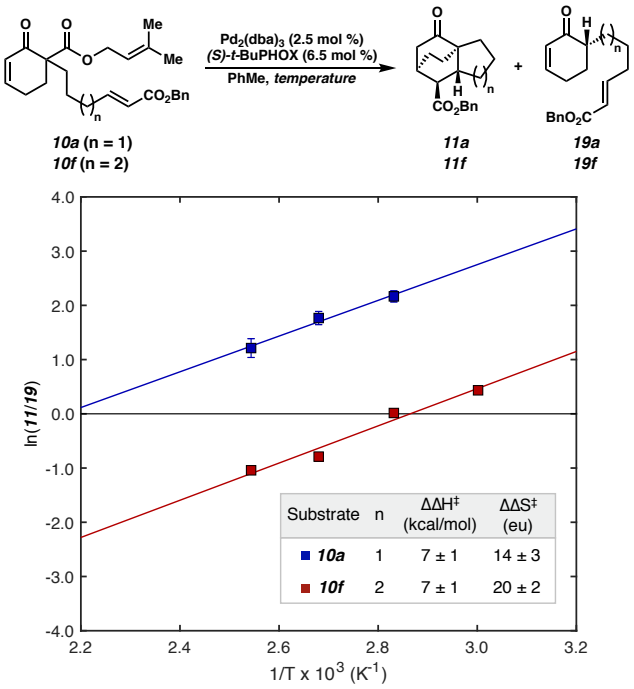
[a] Conditions: 0.2 mmol **10a**, 2.5 mol % $Pd_2(dba)_3$, 6.5 mol % ligand, in toluene (10 mL, 0.02 M), isolated yields, dr determined by ^1H NMR analysis of reaction crude. [b] dr determined by isolated yields of endo/exo products.

and imposes a greater entropic penalty to the highly organized [4+2] transition state. In contrast, increased tether length is inconsequential to the protonation process, which does not involve the dienophile.

Eyring analysis of product distributions from reactions of **10a** and **10f** further supports the hypothesis of an entropic preference for the formation of **19a/f** over **11a/f** (Figure 1.4). With **10a**, cycloaddition (**11a**) is enthalpically favored ($\Delta\Delta H^{\ddagger}$ = 7 kcal/mol) but entropically disfavored ($\Delta\Delta S^{\ddagger}$ = 14 eu) over protonation (**19a**). As anticipated,

increasing the tether length to four methylene units (**10f**) further increases the relative entropic penalty for cycloaddition ($\Delta\Delta S^{\ddagger}$ = 20 eu), while the differential enthalpy of activation remains similar ($\Delta\Delta H^{\ddagger}$ = 7 kcal/mol). Hence, entropy differences associated with tether length lead to the formation of differential amounts of undesired ketones **19a** and **19f**.

Figure 1.4. *Eyring analysis of **11**/**19** product ratio for propylene and butylene tethered substrates **10a** and **10f**.*[a]



T (°C)	*11a* : *19a*	*11f* : *19f*
60	–	1.5 : 1.0
80	8.7 : 1.0	1.0 : 1.0
100	5.9 : 1.0	1.0 : 2.2
120	3.4 : 1.0	1.0 : 2.8

[a] All data points collected in triplicate, error bars and ranges reflect a 95% confidence interval.[14] Reactions carried out on 0.02 mmol scale with product ratios determined by crude ^{1}H NMR analysis.

We then surveyed the scope of functional groups that are tolerated in this reaction (Table 1.2). The cycloaddition does not proceed in the absence of a π-acceptor (**10h**), and carboxylic acid **10i** exclusively affords undesired ketone **19i**. To our delight, a variety of functional groups are compatible, including ethyl ester **10b**, phenyl ketone **10j**, phenyl ester **10k**, mesityl ester **10l**, N-hydroxyphthalimido (NHP) ester **10m**, enecarbamate **10n**, and *N*-acyl oxazolidinone **10o**. Additionally, further conjugated cinnamic ester dienophile **10p** affords tetracycle **11p**. These results demonstrate the ability to tolerate varying dienophile electronics, incorporate additional functional handles, and access alternate ring systems.

The majority of the substrate scope is reflective of a stereospecific process, yielding only *endo* and *exo* diastereomers. We sought to exploit this property of the reaction to access other diastereomers of **11a** by employing *(Z)*-olefin dienophile **10q**. Gratifyingly, desired cycloadducts **11q** (*endo*) and **11q'** (*exo*) are furnished in a 1.6:1 ratio with a 92% combined yield, in 84% and 29% ee, respectively.

Further substitution patterns on the substrate were explored with the aim of increasing the stereochemical complexity of the products. Trisubstituted benzyl ester dienophile **10r** furnished cycloadduct **11r**, featuring two all-carbon quaternary centers, in 47% yield and 90% ee. β-Methyl (**10s**) and β-ethoxy (**10t**) α,β-unsaturated enones are also competent substrates, forging additional tetrasubstituted bridgehead stereocenters. Finally, we explored α-methyl substituted enone **10u**. The corresponding product **11u** was produced, bearing five contiguous stereocenters in >20:1 dr.

In summary, the transformation described herein represents a versatile method for the preparation of a variety of enantioenriched polycyclic scaffolds. Inspired by these

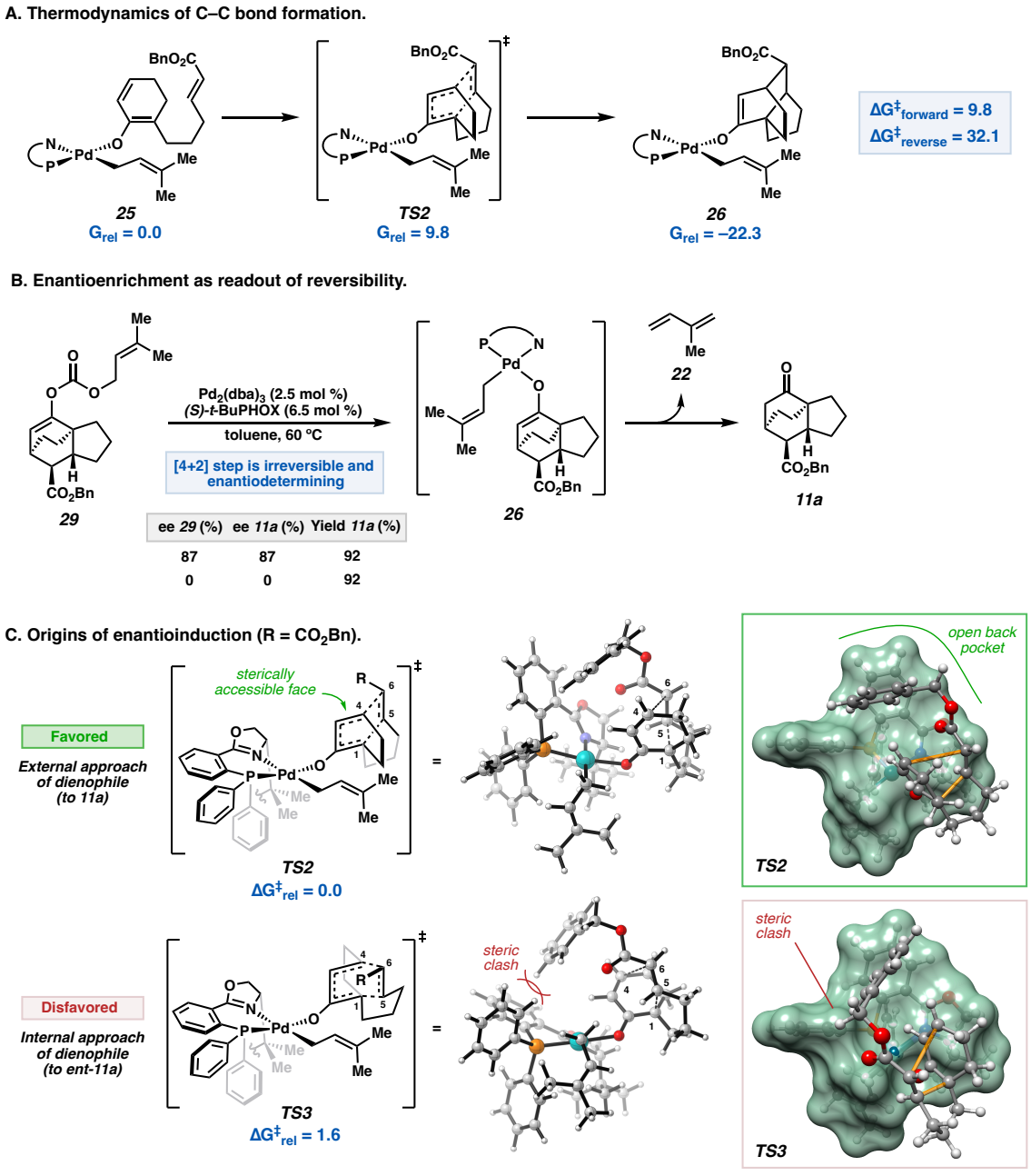
results, we sought to explore the origins of enantioinduction and the mechanism by which catalyst turnover is achieved.

1.2.4 [4+2] CYCLOADDITION

In order to probe the origins of enantioinduction in the transformation, we first aimed to elucidate the enantiodetermining step in the catalytic cycle. We hypothesized that either the cycloaddition is irreversible and dictates the stereochemical outcome, or a reversible [4+2] is coupled to a subsequent enantiodetermining step. First, we computationally evaluated the energetics of the [4+2] process. Cycloaddition directly from conjugated enolate **25** to transposed enolate **26** via **TS2** is achieved with a $\Delta G^{\ddagger}$ of 9.8 and ΔG of –22.3 kcal/mol (Figure 1.5A). The 32.1 kcal/mol barrier to the reverse process renders the cycloaddition step irreversible under the reaction conditions. Hence, our computations suggest that the cycloaddition step is enantiodetermining.

To assess this hypothesis experimentally, reaction product **11a** was converted to its corresponding prenyl enol carbonate **29**. Under the standard reaction conditions, Pd^0 undergoes oxidative addition to **29**, and decarboxylation affords target common intermediate **26** (Figure 1.5B).[5] When enantioenriched or racemic **29** is subjected to the reaction conditions, cycloadduct **11a** is obtained in high yield and identical enantiopurity to that of the respective enol carbonate precursor (**29**) (Figure 1.5B). No stereochemical resolution in product **11a** is observed from racemic enol carbonate **29**, indicating that a post-cycloaddition process is not responsible for enantioinduction. In addition to verifying the irreversibility of the cycloaddition step, these experiments also support the viability of enolate **26** as an intermediate in the catalytic cycle (Scheme 1.1).

Figure 1.5. *(A) Computed barriers.[a] (B) Experimentally verifying irreversibility of the C–C bond formation. (C) Origins of enantioinduction in the [4+2] cycloaddition step.*



[a] Gibbs free energies in kcal/mol. See Experimental Section in section 1.4 for details.

Considering the [4+2] cycloaddition as the enantiodetermining process, the origin of enantioinduction in this step was investigated. As such, the lowest energy *endo* transition states giving rise to each enantiomer of **11a** were evaluated (Figure 1.5C). The minimum energy pathway to each enantiomer of product features a transition state in which the dienophile tether is *syn* to the *t*-Bu group of the PHOX ligand – in accord with prior observations in inner-sphere allylic alkylation transition states.[3,15] From this orientation, the dienophile preferentially approaches the externally-exposed enantiotopic face of the diene to avoid steric clash between the benzyl ester and the phenyl groups of the PHOX ligand scaffold (Figure 1.5C). A 1.6 kcal/mol preference for external (**TS2**) over internal (**TS3**) approach is calculated, in accord with the experimentally observed 87% ee.[16] The major enantiomer of product (**11a**) predicted by computations matches that of the major enantiomer obtained experimentally, as confirmed by vibrational circular dichroism (VCD) spectroscopy (see 1.4 Experimental Section for details).

In summary, our investigations reveal C–C bond formation to be the enantiodetermining step, with enantioselectivity achieved by biasing *external* over *internal* dienophile approach (Figure 1.5).

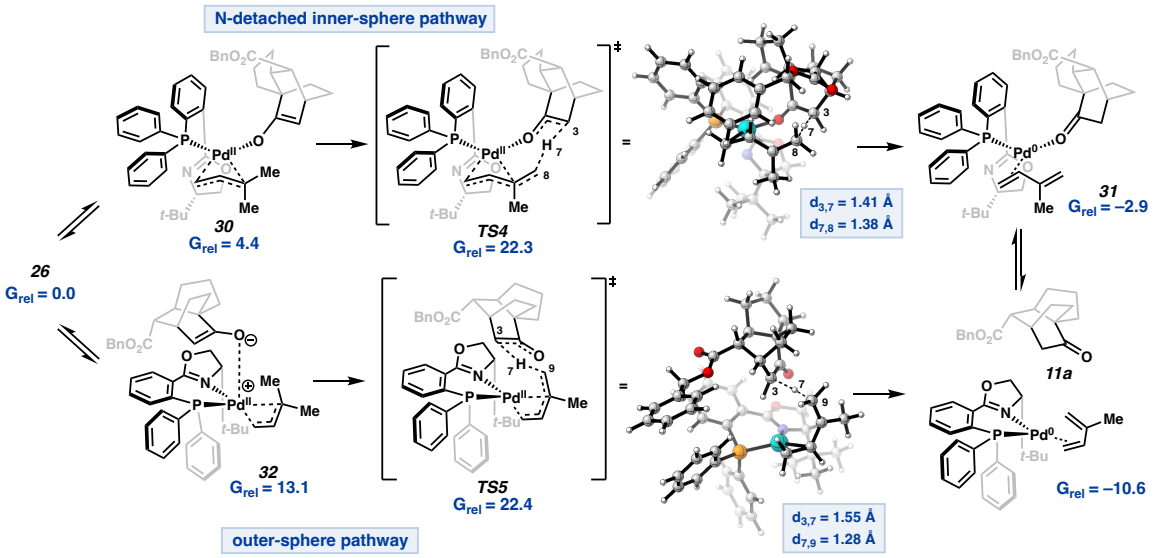
1.2.5 CATALYST TURNOVER

Our [4+2] transformation is rendered catalytic by a unique reduction of Pd^{II} to Pd^{0} that occurs concomitantly with formation of isoprene (**22**) and ketone **11a**. This observation motivated computational investigations to elucidate the catalyst turnover mechanism.

Of the numerous mechanisms explored, the minimum energy pathway involves isomerization of **26** to an N-detached π-allyl Pd species (**30**) and subsequent inner-sphere

proton transfer (**TS4**) (Figure 1.6). Additionally, a pathway featuring outer-sphere proton transfer (**TS5**) was found to be highly competitive for catalyst turnover. These two processes present very similar free energy barriers of 22.3 and 22.4 kcal/mol, respectively, which are readily surmountable at 60 °C. A single favored pathway is not identified as the energy difference between the two mechanisms is within error of computations. In both pathways, subsequent ligand exchange of isoprene (**22**) for starting material **10a** completes the catalytic cycle. Analysis of Intrinsic Bonding Orbitals (IBOs)[17] along the reaction coordinate suggest these processes are best conceptualized as the transfer of a proton, rather than a hydride, to the Pd enolate (see 1.4 Experimental Section for details).[18] Analogous mechanisms were found to be operative from pre-cycloaddition enolate **25**, giving rise to premature protonation product **19a**.

Figure 1.6. *Two lowest-energy pathways for catalyst turnover.*[a]



[a] Gibbs free energies in kcal/mol. See section 1.4 Experimental Section for details.

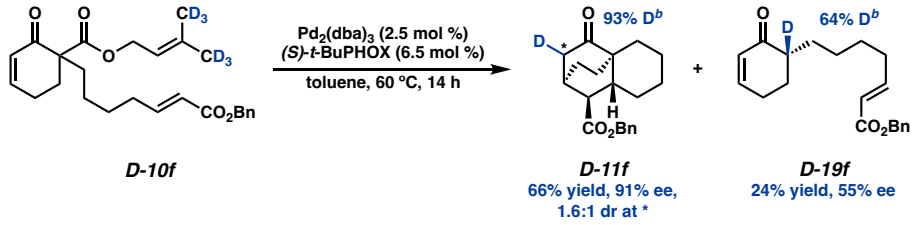
1.2.6 FURTHER MECHANISM-BASED DEVELOPMENTS

While this method allows access to a variety of complex scaffolds, premature protonation remains an outstanding challenge we sought to address. As such, we aimed to leverage our mechanistic insights surrounding this process to inhibit byproduct formation.

To that end, we turned our attention to butylene tethered substrate **10f** given its similar yield of desired **11f** (44%) and byproduct **19f** (42%). We envisioned favoring the formation of **11f** by modification of the ancillary prenyl moiety. By introducing a kinetic isotope effect, we aimed to slow down the protonation processes. To our delight, employing hexa-deutero prenyl ester **D-10f** (Figure 1.7A) increases the yield of desired cycloadduct **D-11f** to 66%, with 91% ee.[19] Next, cyclic analogs of the prenyl ester **10f** were prepared (Figure 1.7B). At one extreme, seven-membered exocycle **36** affords a product distribution which closely mirrors that of parent substrate **10f** (entry 5). Excitingly, contracting the ring by one methylene (**35**) shifts the distribution favorably toward **11f** (entry 4, 3:1 ratio of **11f**:**19f**). However, five- and four-membered exocycles (**34** and **33**), as well as acyclic bis-benzylic allylic ester **37**, afford unfavorable product distributions.

Figure 1.7. *(A) KIE study. (B) Prenyl ester modification.*

A. Leveraging kinetic isotope effect (KIE) to slow proton transfer.[a]

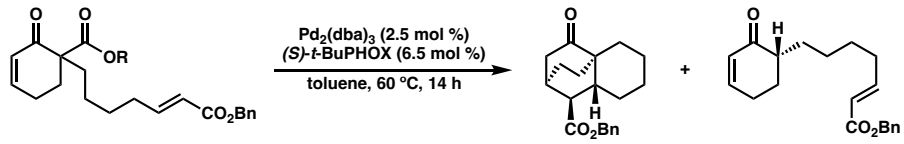


D-10f

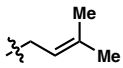
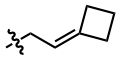
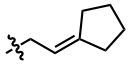
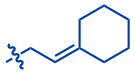
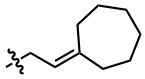
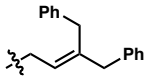
D-11f
66% yield, 91% ee, 1.6:1 dr at *

D-19f
24% yield, 55% ee

B. Modification of prenyl ester via cyclic and benzylic analogs.[c]



11f ***19f***

Entry	R		Yield 11f (%)	ee 11f (%)	Yield 19f (%)	ee 19f (%)
1		*(10f)*	44	91	42	40
2[d]		*(33)*	25	92	44	46
3		*(34)*	8	–	89	48
4		*(35)*	63	92	21	44
5		*(36)*	48	92	46	38
6[e]		*(37)*	14	94	86	60

[a] Conditions: 0.20 mmol **D-10f**, 2.5 mol % $Pd_2(dba)_3$, 6.5 mol % ligand, in 10 mL of solvent (0.02 M). [b] Deuterium incorporation determined by HRMS. [c] Conditions: 0.02 mmol substrate, 2.5 mol % $Pd_2(dba)_3$, 6.5 mol % ligand, in 1.0 mL of solvent (0.02 M). Yield determined by ^1H NMR with respect to 1,3,5-trimethoxybenzene as internal standard. [d] 21% of allylic alkylation product was also observed. [e] The corresponding benzylic diene was also observed (see 1.4 Experimental Section for details).

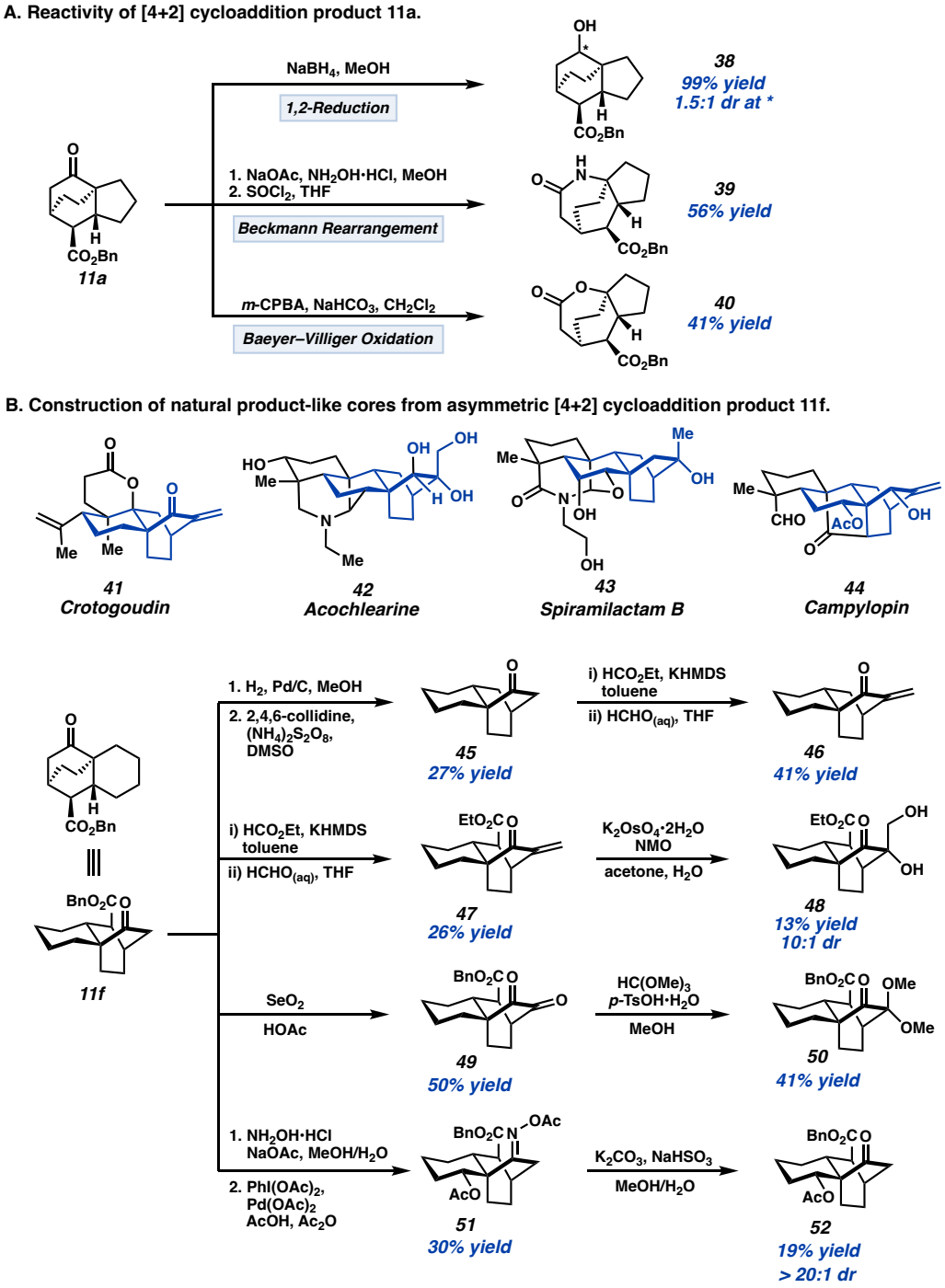
In summary, we find appropriate modification of the prenyl moiety to be effective in suppressing deleterious side reactions. This is particularly important as the ring system generated in this reaction is a scaffold relevant to natural product synthesis.

1.2.7 PRODUCT DERIVATIZATIONS

To assess the utility of the asymmetric intramolecular [4+2] products, we started by altering the oxidation state of ketone **11a** (Figure 1.8A) through a 1,2-reduction, which provided alcohol **38** in quantitative yield and in 1.5:1 dr. Subsequently, we explored ring expansion strategies to incorporate heteroatoms and to furnish different ring systems (Figure 1.8A). From ketone **11a**, oxime condensation and subsequent Beckmann rearrangement afforded lactam **39** as a single isomer in 56% yield over two steps. Analogously, Baeyer–Villiger oxidation furnished lactone **40** in 41% yield as a single isomer.

Furthermore, the tricyclic cycloaddition products closely resemble many members of the atisane family of diterpenoids (Figure 1.8B, **41**-**44**). Therefore, reactions to further functionalize these scaffolds were explored. First, hydrogenolysis followed by persulfate-mediated radical decarboxylation of **11f** afforded ketone **45** in 27% yield over two steps.[20] We were delighted to find that the exo-cyclic methylene motif presented in both crotogoudin (**41**) and campylopin (**44**) could be achieved through aldol condensations from both **45** and **11f** to yield crotogoudin-like enone **46** in 41% yield and analogous enone **47** in 26% yield.[21] Enone **47** can be further functionalized through dihydroxylation to furnish the primary and tertiary alcohol centers of the acochlearine (**42**) core in 13% yield and 10:1 dr (**48**).[22] A wider spectrum of natural product cores could also be accessed through

Figure 1.8. *(A) Oxidation state alterations, ring system adjustments, and heteroatom incorporation on* ***11a****. (B) Reaction sequences to construct natural product-like cores.*



oxidation at different sites of the tricyclic hydrocarbon backbone. For example, Riley oxidation of **11f** provided diketone **49** in 50% yield,[23] which can then be selectively mono-protected as acetal **50** in 41% yield.[24] Further manipulations to the exposed ketone of **50** could yield spiramilactam B (**43**)-like oxidation patterns. To that end, directed C–H oxidation following an oxime condensation of **11f** yielded oxime **51** in 30% yield. Deprotection of the oxime afforded the desired acetate on campylopin (**44**)-like tricycle **52** in 19% yield as a single diastereomer.[25] Overall, derivatization of cycloadduct **11f** allowed access to four natural product-like motifs, demonstrating the potential of applying this transformation to asymmetric natural product syntheses.

1.3 CONCLUSIONS

We developed an asymmetric decarboxylative [4+2] cycloaddition employing a key catalytically-generated chiral Pd enolate intermediate – analogous to those implicated in inner-sphere allylic alkylation reactions. To enable this transformation, we first systematically modified the allyl moiety to disfavor undesired allylic alkylation. This allows the conjugated Pd enolate to engage in a [4+2] cycloaddition with a pendant dienophile. Computational and experimental analysis supports the role of C–C bond formation as the enantiodetermining step. Further computational investigation reveals that the catalyst turnover occurs through a proton transfer from the prenyl group directly to the transposed enolate, forming the desired product and releasing isoprene. Building upon these mechanistic insights, we were able to further favor the desired [4+2] cycloaddition over premature protonation for challenging substrates relevant to complex natural product synthesis. In summary, our approach of divergent catalysis serves as a powerful framework

for rational design in asymmetric catalytic reactions. Studies applying this strategy more broadly in other synthetically relevant transformations are currently underway.

1.4 EXPERIMENTAL SECTION

1.4.1 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.[26] 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 $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 nm) was used for flash chromatography. ^{1}H NMR spectra were recorded on a Bruker 400 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer (100 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm). ^{2}H NMR spectra were recorded on a Bruker 400 MHz (61 MHz) spectrometer and are reported relative to residual $CDCl_3$ (δ 7.26 ppm). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as the peaks appear 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). 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. ^{13}C NMR spectra of deuterated compounds are complicated by the low intensity of peaks of deuterium-substituted carbon atoms. IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer or Nicolet 6700 FTIR 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. Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing Chiralpak (AD-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in Field Desorption (FD+) mode. Absolute stereochemical assignments were made by vibrational circular dichroism analysis for select compounds with related compounds assigned by analogy.

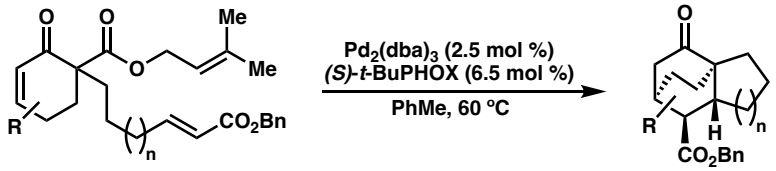
Reagents were purchased from commercial sources and used as received unless otherwise stated. Ligands were prepared according to literature procedures.[27]

List of Abbreviations: ee – enantiomeric excess, SFC – supercritical fluid chromatography, TLC – thin-layer chromatography, IPA – isopropanol, VCD – vibrational circular dichroism.

1.4.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

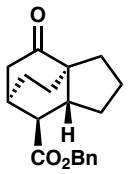
Pd-Catalyzed Decarboxylative Cycloadditions

General Procedure A: Asymmetric Pd-Catalyzed Decarboxylative Cycloadditions.



10 ***11***

In a nitrogen filled glovebox, an oven-dried 20 mL vial was charged with a stir bar, $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol, 2.5 mol %), *(S)*-*t*-BuPHOX (5.0 mg, 0.013 mmol, 6.5 mol %), and toluene (5 mL). The catalyst solution was stirred at 23 ºC for 20 min. A solution of substrate **10** (0.2 mmol, 1 equiv) in toluene (5 mL) was added to the vial. The resultant solution was then heated to 60 ºC for 14 h. The solution was then cooled to 23 ºC and concentrated under reduced pressure. The crude reaction mixture was loaded directly onto a flash column and the product (**11**) was isolated by silica gel flash column chromatography.



11a

benzyl (3a*R*,6*R*,7*S*,7a*R*)-4-oxooctahydro-3a,6-ethanoindene-7-carboxylate (11a)

Prepared from **10a** following General Procedure A. Purification by flash column chromatography (0–35% EtOAc/hexanes) afforded the title compound as a colorless oil (49.7 mg, 0.167 mmol, 83% yield, 87% ee). Absolute and relative stereochemistry were assigned by VCD (vida infra). 2D NMR studies independently confirm the relative stereochemistry (vida infra).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.31 (m, 5H), 5.14 (d, *J* = 1.6 Hz, 2H), 2.54 (dt, *J* = 18.8, 2.3 Hz, 1H), 2.51 – 2.47 (m, 2H), 2.21 (dddd, *J* = 10.6, 8.7, 7.2, 1.7 Hz, 1H), 2.14

– 2.04 (m, 3H), 1.86 (ddd, *J* = 13.0, 11.1, 6.8 Hz, 1H), 1.81 – 1.72 (m, 2H), 1.70 – 1.52 (m, 3H), 1.44 (ddt, *J* = 12.9, 10.9, 1.8 Hz, 1H), 1.22 (ddd, *J* = 13.9, 9.2, 4.9 Hz, 1H).

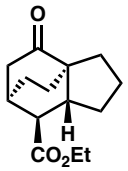
^{13}C NMR (100 MHz, $CDCl_3$): δ 215.1, 174.7, 136.0, 128.8, 128.5, 128.2, 66.7, 54.2, 47.5, 43.3, 41.3, 32.9, 29.1, 27.4, 26.5, 25.1, 22.6.

IR (Neat Film, NaCl): 2947, 2873, 1726, 1455, 1267, 1160 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{19}H_{22}O_3$ $[M]^+$: 298.1564, found 298.1576.

Optical Rotation: $[\alpha]_D^{21}$ –20.3 (c 1.00, $CHCl_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 4.21, major = 5.30



11b

ethyl (3a*R*,6*R*,7*S*,7a*R*)-4-oxooctahydro-3a,6-ethanoindene-7-carboxylate (11b)

Prepared from **10b** following General Procedure A. Purification by flash column chromatography (5–30% EtOAc/hexanes) afforded the title compound as a colorless oil (39.9 mg, 0.169 mmol, 84% yield, 88% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.15 (q, *J* = 7.1 Hz, 2H), 2.55 (dt, *J* = 18.8, 2.6 Hz, 1H), 2.49 – 2.44 (m, 1H), 2.42 (d, *J* = 8.6 Hz, 1H), 2.23 – 2.14 (m, 1H), 2.15 – 2.04 (m, 3H), 1.91 – 1.71 (m, 3H), 1.71 – 1.52 (m, 3H), 1.50 – 1.40 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.21 (dt, *J* = 9.2, 4.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 215.2, 174.9, 60.8, 54.2, 47.5, 43.3, 41.3, 32.9, 29.1, 27.4, 26.5, 25.1, 22.6, 14.4.

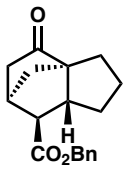
IR (Neat Film, NaCl): 2947, 2873, 1725, 1270, 1170 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{14}H_{20}O_3$ $[M]^+$: 236.1412, found 236.1415.

Optical Rotation: $[\alpha]_D^{21}$ –34.2 (c 1.00, $CHCl_3$).

Enantiomeric excess determined by converting ethyl ester to benzyl ester through saponification and Steglish esterification.

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 4.21, major = 5.30



11c

benzyl (3a*R*,6*R*,7*S*,7a*R*)-4-oxooctahydro-3a,6-methanoindene-7-carboxylate (11c)

Prepared from **10c** following General Procedure A. Purification by flash column chromatography (0–30% EtOAc/hexanes) afforded the title compound as a colorless oil (37.0 mg, 0.130 mmol, 65% yield, 65% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.29 (m, 5H), 5.13 (dd, *J* = 12.3, 7.9 Hz, 2H), 2.96 (t, *J* = 4.2, 1H), 2.92 (ddd, *J* = 5.2, 3.7, 1.4, 1H), 2.42 – 2.35 (m, 1H), 2.22 – 2.17 (m, 1H), 2.16 – 2.05 (m, 3H), 1.95 (ddtd, *J* = 12.9, 8.4, 5.1, 2.2 Hz, 1H), 1.90 – 1.80 (m, 2H), 1.66 (dt, *J* = 10.6, 1.6 Hz, 1H), 1.52 – 1.37 (m, 2H).

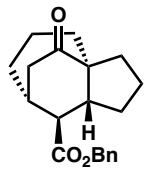
^{13}C NMR (100 MHz, $CDCl_3$): δ 213.9, 173.3, 136.0, 128.8, 128.5, 128.3, 67.8, 66.6, 52.4, 48.5, 41.8, 40.6, 40.5, 32.2, 27.5, 22.1.

IR (Neat Film, NaCl): 2960, 2358, 1739, 1164, 730, 668 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{18}H_{20}O_3$ $[M]^+$: 284.1414, found 284.1407.

Optical Rotation: $[\alpha]_D^{21}$ +20.0 (c 1.00, $CHCl_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 3.97, major = 4.33.



11d

benzyl (3a*R*,7*R*,8*S*,8a*R*)-10-oxooctahydro-1*H*-3a,7-ethanoazulene-8-carboxylate (11d)

Prepared from **10d** following General Procedure A. Purification by flash column chromatography (0–35% EtOAc/hexanes) afforded the title compound as a colorless oil (51.8 mg, 0.166 mmol, 83% yield, 97% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.31 (m, 5H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.12 (d, *J* = 12.3 Hz, 1H), 2.70 – 2.63 (m, 2H), 2.64 – 2.56 (m, 1H), 2.25 (ddd, *J* = 18.5, 2.0, 1.0 Hz, 1H), 2.08 (td, *J* = 10.5, 7.8 Hz, 1H), 2.03 – 1.94 (m, 1H), 1.93 – 1.79 (m, 3H), 1.78 – 1.60 (m, 4H), 1.59 – 1.43 (m, 4H).

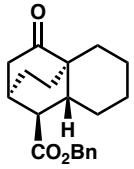
^{13}C NMR (100 MHz, $CDCl_3$): δ 215.7, 175.8, 136.0, 128.8, 128.5, 128.3, 66.7, 58.0, 50.2, 45.4, 41.0, 35.7, 33.6, 33.3, 32.0, 28.0, 21.8, 21.2.

IR (Neat Film, NaCl): 2934, 2873, 1727, 1713, 1455, 1161 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{20}H_{24}O_3$ $[M+H]^+$: 312.1720, found 312.1734.

Optical Rotation: $[\alpha]_D^{21}$ +21.4 (c 1.00, $CHCl_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 4.70, major = 6.23.



11f

benzyl (1*S*,2*R*,4a*R*,8a*R*)-4-oxooctahydro-2*H*-2,4a-ethanonaphthalene-1-carboxylate (11f).

Prepared from **10f** following General Procedure A. Purification by flash column chromatography (0–35% EtOAc/hexanes) afforded the title compound as a colorless oil (26.3 mg, 0.084 mmol, 42% yield, 92% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.29 (m, 5H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.10 (d, *J* = 12.2 Hz, 1H), 2.47 (dt, *J* = 17.0, 2.8 Hz, 2H), 2.28 – 2.19 (m, 2H), 2.14 (ddd, *J* = 19.7, 3.8, 1.8 Hz, 1H), 2.01 (dddd, *J* = 11.8, 6.8, 4.5, 1.7 Hz, 1H), 1.87 (ddtd, *J* = 12.8, 4.5, 3.4, 1.6 Hz, 1H), 1.83 – 1.71 (m, 1H), 1.71 – 1.56 (m, 4H), 1.51 – 1.11 (m, 5H).

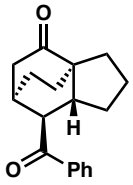
^{13}C NMR (100 MHz, $CDCl_3$): δ 216.3, 174.5, 136.0, 128.7, 128.4, 128.2, 66.7, 49.8, 45.1, 40.5, 37.1, 30.9, 30.0, 28.9, 26.2, 25.6, 21.7, 21.1.

IR (Neat Film, NaCl): 2928, 2856, 1721, 1170 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{20}H_{24}O_3$ $[M]^+$: 312.1720, found 312.1732.

Optical Rotation: $[\alpha]_D^{21}$ –15.5 (c 1.00, $CHCl_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 4.70, major = 6.23.



11j

(3a*R*,6*R*,7*S*,7a*R*)-7-benzoylhexahydro-3a,6-ethanoinden-4(1*H*)-one (11j)

Prepared from **10j** following General Procedure A. Purification by flash column chromatography (0–30% EtOAc/hexanes) afforded the title compound as a colorless oil (27.1 mg, 0.101 mmol, 50% yield, 87% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 – 7.94 (m, 2H), 7.61 – 7.56 (m, 1H), 7.51 – 7.46 (m, 2H), 3.42 (d, *J* = 8.5 Hz, 1H), 2.58 – 2.50 (m, 2H), 2.41 – 2.38 (m, 1H), 2.16 (ddd, *J* = 13.7, 11.1, 6.2 Hz, 1H), 2.08 – 1.87 (m, 4H), 1.82 – 1.74 (m, 1H), 1.70 – 1.50 (m, 4H), 1.25 (ddd, *J* = 14.0, 9.2, 5.1 Hz, 1H).

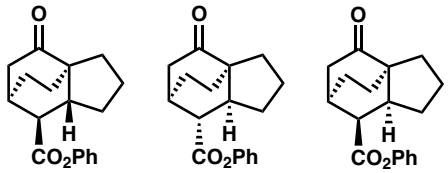
^{13}C NMR (100 MHz, $CDCl_3$): δ 214.9, 201.0, 136.4, 133.4, 128.9, 128.5, 54.2, 49.4, 41.4, 40.8, 34.1, 28.9, 27.8, 26.5, 25.6, 22.7.

IR (Neat Film, NaCl): 2945, 2871, 1720, 1677, 1447, 1217 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{18}H_{20}O_2$ $[M]^+$: 268.1463, found 268.1463.

Optical Rotation: $[\alpha]_D^{21}$ –32.7 (c 1.00, $CHCl_3$).

SFC conditions: 30% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 2.55, major = 3.40.



11k ***(endo-trans)*** ***11k'*** ***(exo-cis)*** ***11k"*** ***(endo-cis)***

phenyl (3a*R*,6*R*,7*S*,7a*R*)-4-oxooctahydro-3a,6-ethanoindene-7-carboxylate (11k, 11k' and 11k'')

Prepared from **10k** following General Procedure A. Purification by flash column chromatography (0–35% EtOAc/hexanes) afforded the title compound as a colorless oil (47.2 mg, 0.166 mmol, 83% yield, 14.8:1.6:1.0 *endo-trans*/*endo-cis*/*exo-trans*, 88% ee (*endo-trans*)). Crude analysis by ^{1}H NMR affords a 10.4:1.4:1.0 ratio of *endo-trans*/*exo-trans/endo-cis*. The diastereomers were subsequently separated by preparative HPLC (15% IPA/hexanes, 25 mL/min, Chiralpak AD-H column) for independent characterization. Absolute and relative stereochemistry were assigned/confirmed by VCD where applicable (vida infra) in addition to 2D NMR.

11k (endo-trans):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.34 (m, 2H), 7.25 – 7.20 (m, 1H), 7.09 – 7.04 (m, 2H), 2.70 (d, *J* = 8.7 Hz, 1H), 2.67 – 2.60 (m, 2H), 2.31 (dddd, *J* = 10.6, 8.8, 7.3, 1.7 Hz, 1H), 2.23 – 2.09 (m, 3H), 1.97 – 1.76 (m, 3H), 1.67 (ddddd, *J* = 13.5, 11.1, 9.0, 6.2, 4.5 Hz, 3H), 1.50 (ddt, *J* = 12.5, 10.6, 1.7 Hz, 1H), 1.31 – 1.17 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 214.8, 173.4, 150.7, 129.6, 126.0, 121.5, 54.2, 47.5, 43.4, 41.2, 32.9, 29.1, 27.3, 26.5, 25.0, 22.5.

IR (Neat Film, NaCl): 2948, 2872, 1750, 1721, 1592, 1492, 1192, 1144 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{18}H_{20}O_3$ $[M]^+$: 284.1412, found 284.1411.

Optical Rotation: $[\alpha]_D^{21}$ –16.7 (c 0.20, $CHCl_3$). *(single major enantiomer of 11j)*

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 4.09, major = 6.08.

11k' (exo-trans):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.34 (m, 2H), 7.25 – 7.19 (m, 1H), 7.06 – 7.01 (m, 2H), 3.30 (dt, *J* = 12.0, 2.3 Hz, 1H), 3.08 (dt, *J* = 19.5, 2.8 Hz, 1H), 2.58 (h, *J* = 2.8 Hz, 1H), 2.47 – 2.33 (m, 2H), 2.21 (dt, *J* = 19.6, 2.4 Hz, 1H), 2.08 – 2.01 (m, 2H), 1.93 – 1.71 (m, 5H), 1.70 – 1.59 (m, 1H), 1.04 (ddd, *J* = 12.8, 11.4, 6.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 215.2, 171.8, 150.6, 129.6, 126.0, 121.7, 54.6, 45.8, 44.0, 40.1, 31.4, 28.4, 28.2, 27.0, 26.3, 21.8.

IR ($CDCl_3$ solution): 2951, 2870, 1751, 1717, 1194, 1163, 1146 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{18}H_{20}O_3$ $[M]^+$: 284.1412, found 284.1417.

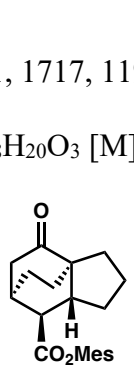
11k'' (endo-cis):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.36 (m, 2H), 7.27 – 7.22 (m, 1H), 7.12 – 7.07 (m, 2H), 2.76 – 2.67 (m, 1H), 2.58 (dt, *J* = 8.3, 1.7 Hz, 1H), 2.48 – 2.33 (m, 4H), 2.12 – 2.01 (m, 2H), 1.91 – 1.63 (m, 5H), 1.10 (ddd, *J* = 13.0, 11.2, 6.5 Hz, 1H), 1.01 (ddd, *J* = 12.4, 9.5, 2.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 215.1, 172.9, 150.9, 129.6, 126.1, 121.6, 53.8, 49.4, 46.0, 44.2, 32.7, 32.0, 28.6, 27.4, 22.6, 21.5.

IR ($CDCl_3$ solution): 2945, 2872, 1751, 1717, 1194, 1163, 1130 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{18}H_{20}O_3$ $[M]^+$: 284.1412, found 284.1407.



11l

mesityl (3a*R*,6*R*,7*S*,7a*R*)-4-oxooctahydro-3a,6-ethanoindene-7-carboxylate (11l)

Prepared from **10l** following General Procedure A. Purification by flash column chromatography (0–35% EtOAc/hexanes) afforded the title compound as a colorless oil (58.6 mg, 0.180 mmol, 90% yield, 89% ee).

^{1}H NMR (400 MHz, $CDCl_3$):) δ 6.87 (s, 2H), 2.75 (d, *J* = 8.8 Hz, 1H), 2.72 – 2.65 (m, 2H), 2.36 (dddd, *J* = 10.6, 8.9, 7.3, 1.6 Hz, 1H), 2.26 (s, 3H), 2.24 – 2.09 (m, 3H), 2.08 (s, 6H), 1.98 – 1.78 (m, 3H), 1.75 – 1.61 (m, 3H), 1.55 – 1.48 (m, 1H), 1.31 – 1.24 (m, 1H).

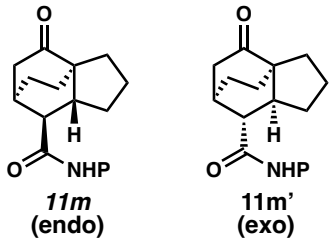
^{13}C NMR (100 MHz, $CDCl_3$): δ 214.8, 172.8, 145.9, 135.6, 129.5, 129.5, 54.2, 47.4, 43.5, 41.3, 33.2, 29.2, 27.5, 26.5, 25.1, 22.6, 20.9, 16.4.

IR (Neat Film, NaCl): 2946, 2873, 1747, 1723, 1485, 1458, 1189, 1137 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{21}H_{26}O_3$ $[M]^+$: 326.1877, found 326.1886.

Optical Rotation: $[\alpha]_D^{21}$ –25.8 (c 1.00, $CHCl_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 4.06, major = 4.33.



11m **(endo)** **11m' (exo)**

1,3-dioxoisoindolin-2-yl(3a*R*,6*R*,7*S*,7a*R*)-4-oxooctahydro-3a,6-ethanoindene-7-carboxylate (11m and 11m')

Prepared from **10m** following General Procedure A. Purification by flash column chromatography (0–35% EtOAc/hexanes) afforded the title compounds as colorless oils

(**Endo**: 37.7 mg, 0.106 mmol, 53% yield, 62% ee; **Exo**: 8.6 mg, 0.024 mmol, 12% yield, 62% ee).

11m (endo):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 – 7.85 (m, 2H), 7.83 – 7.75 (m, 2H), 2.84 (dd, *J* = 8.7, 1.3 Hz, 1H), 2.71 (m, 1H), 2.64 (dt, *J* = 18.9, 2.5 Hz, 1H), 2.46 – 2.28 (m, 1H), 2.28 – 2.18 (m, 2H), 2.13 (m, 1H), 1.98 – 1.76 (m, 3H), 1.76 – 1.60 (m, 3H), 1.56 – 1.48 (m, 1H), 1.34 – 1.19 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 214.0, 171.4, 162.1, 135.0, 129.0, 124.2, 54.1, 44.8, 43.3, 41.0, 33.2, 28.9, 27.2, 26.4, 24.9, 22.4.

IR (Neat Film, NaCl): 2948, 2873, 1782, 1742, 1718, 1466, 1362, 1185 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{20}H_{19}NO_5$ $[M]^+$: 353.1263, found 353.1251.

Optical Rotation: $[\alpha]_D^{21}$ –0.2 (c 1.00, $CHCl_3$).

SFC conditions: 30% IPA, 2.5 mL/min, Chiralpak IC column, l = 210 nm, t_R (min): minor = 4.03, major = 3.00

11m' (exo):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H), 2.77 (tt, *J* = 3.9, 2.2 Hz, 1H), 2.73 (d, *J* = 8.4 Hz, 1H), 2.47 – 2.28 (m, 4H), 2.19 – 2.02 (m, 2H), 1.92 – 1.71 (m, 4H), 1.71 – 1.61 (m, 1H), 1.11 (ddd, *J* = 13.1, 11.2, 6.6 Hz, 1H), 1.08 – 0.95 (m, 1H).

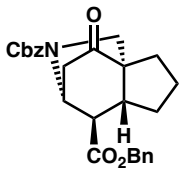
^{13}C NMR (100 MHz, $CDCl_3$): δ 214.2, 170.8, 162.1, 135.0, 129.1, 124.2, 53.7, 46.7, 46.0, 44.1, 32.9, 31.8, 28.4, 27.2, 22.5, 21.2.

IR (Neat Film, NaCl): 2947, 2868, 1809, 1784, 1743, 1717, 1466, 1362, 1185 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{20}H_{19}NO_5$ $[M]^+$: 353.1263, found 353.1261.

Optical Rotation: $[\alpha]_D^{21}$ –13.6 (c 0.81, $CHCl_3$).

SFC conditions: 30% IPA, 2.5 mL/min, Chiralpak IC column, l = 210 nm, t_R (min): minor = 4.98, major = 4.29.



11n

dibenzyl (3aR,4R,5R,7aS)-7-oxooctahydro-5,7a-(epiminomethano)indene-4,9-dicarboxylate (11n)

Prepared from **10n** following General Procedure A. Purification by flash column chromatography (0–40 % EtOAc/hexanes) afforded the title compound as a colorless oil (76.1 mg, 0.176 mmol, 88% yield, 14.3:1 endo/exo, 91% ee (endo)).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (dd, *J* = 7.1, 4.9 Hz, 10H), 5.21 – 5.07 (m, 4H), 4.90 – 4.74 (m, 1H), 3.49 (dd, *J* = 12.1, 5.8 Hz, 1H), 3.40 – 3.27 (m, 1H), 2.88 (t, *J* = 8.9 Hz, 1H), 2.66 – 2.42 (m, 2H), 2.30 (p, *J* = 9.3 Hz, 1H), 2.23 – 2.10 (m, 2H), 1.91 – 1.56 (m, 3H), 1.33 – 1.14 (m, 1H).

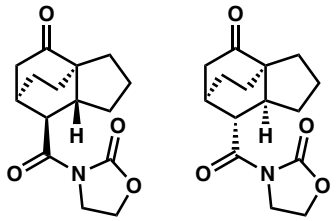
^{13}C NMR (100 MHz, $CDCl_3$): δ 210.1, 209.7, 172.2, 154.4, 136.3, 135.5, 128.9, 128.7, 128.7, 128.4, 128.4, 128.4, 128.3, 128.2, 128.1, 67.6, 67.2, 55.9, 55.8, 50.4, 50.0, 48.8, 48.6, 45.7, 45.6, 42.6, 42.6, 41.7, 41.6, 29.0, 28.9, 24.1, 22.9.

IR (Neat Film, NaCl): 3399, 2963, 2874, 2357, 1729, 1700, 1652, 1414, 1288, 1156, 1115, 748, 681 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{26}H_{27}NO_5$ $[M]^+$: 433.1889, found 433.1874.

Optical Rotation: $[\alpha]_D^{21}$ –39.8 (c 0.75, $CHCl_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, l = 210 nm, t_R (min): minor = 9.19, major = 11.59.



11o (endo) ***11o' (exo)***

3-((3a*R*,6*R*,7*S*,7a*R*)-4-oxooctahydro-3a,6-ethanoindene-7-carbonyl)oxazolidin-2-one (11o and 11o')

Prepared from **10o** following General Procedure A. Purification by flash column chromatography (0–90 % EtOAc/hexanes) afforded the title compound as a colorless oil (51.2 mg, 0.185 mmol, 92% yield, 1.1:1 endo/exo (ratio from crude ^{1}H NMR analysis), 84% ee (endo), 79% ee (exo)).

11o (endo):

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.43 (t, *J* = 8.1 Hz, 2H), 4.15 – 4.00 (m, 2H), 3.54 – 3.47 (m, 1H), 2.66 (ddd, *J* = 12.4, 8.3, 6.9 Hz, 1H), 2.52 – 2.25 (m, 4H), 1.92 – 1.68 (m, 5H), 1.67 – 1.53 (m, 2H), 1.08 (ddd, *J* = 12.9, 11.2, 6.4 Hz, 1H), 0.89 (tt, *J* = 12.3, 9.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 215.5, 173.8, 153.4, 62.1, 53.7, 48.3, 44.1, 44.0, 43.1, 33.8, 31.3, 28.7, 27.3, 22.8, 20.8.

IR (Neat Film, NaCl): 2942, 2867, 1775, 1714, 1693, 1387, 1267, 1222, 1040 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{15}H_{19}NO_4$ $[M]^+$: 277.1314, found 277.1321.

Optical Rotation: $[\alpha]_D^{21}$ –39.5 (c 1.00, $CHCl_3$).

SFC conditions: 20% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 4.15, major = 5.17.

11o' (exo):

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.43 (t, *J* = 8.1 Hz, 2H), 4.13 – 3.97 (m, 2H), 3.71 (d, *J* = 8.8 Hz, 1H), 2.59 – 2.41 (m, 2H), 2.35 (dd, *J* = 3.5, 2.3 Hz, 1H), 2.19 – 1.84 (m, 5H), 1.81 – 1.41 (m, 6H), 1.27 – 1.18 (m, 1H).

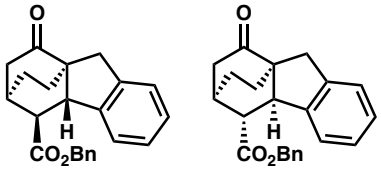
^{13}C NMR (100 MHz, $CDCl_3$): δ 214.9, 174.6, 153.5, 62.13, 54.1, 45.6, 43.1, 41.2, 40.6, 34.5, 28.4, 27.3, 26.5, 25.3, 22.7.

IR (Neat Film, NaCl): 2949, 2872, 1775, 1718, 1692, 1387, 1221,1040, 759 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{15}H_{19}NO_4$ $[M]^+$: 277.1314, found 277.1317.

Optical Rotation: $[\alpha]_D^{21}$ –5.8 (c 1.00, $CHCl_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 6.80, major = 6.38.



11p (endo) ***11p' (exo)***

benzyl (3*R*,4*S*,4a*S*,9a*S*)-1-oxo-1,2,3,4,4a,9-hexahydro-3,9a-ethanofluorene-4-carboxylate (11p and 11p')

Prepared from **10p** following General Procedure A. Purification by flash column chromatography (0–35% EtOAc/hexanes) afforded the title compounds as colorless oils (**Endo**: 56.8 mg, 0.156 mmol, 78% yield, 72% ee; **Exo**: 2.0 mg, 5.48 μmol, 3% yield).

11p (endo):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 – 7.20 (m, 5H), 7.14 – 7.05 (m, 4H), 5.13 (d, *J* = 2.4 Hz, 2H), 3.53 (dd, *J* = 9.4, 1.0 Hz, 1H), 3.16 (d, *J* = 15.7 Hz, 1H), 2.74 (dt, *J* = 9.3, 1.1 Hz, 1H), 2.61 (dt, *J* = 18.8, 2.4 Hz, 1H), 2.51 (ttd, *J* = 3.5, 2.2, 1.1 Hz, 1H), 2.31 (d, *J* = 15.8 Hz, 1H), 2.11 (ddd, *J* = 18.8, 3.5, 1.2 Hz, 1H), 1.70 – 1.56 (m, 2H), 1.54 – 1.45 (m, 1H), 1.42 – 1.34 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 214.0, 174.6, 142.3, 140.6, 135.8, 128.8, 128.6, 128.4, 127.3, 127.0, 125.5, 124.3, 67.1, 56.6, 47.8, 45.6, 42.1, 35.0, 33.2, 27.0, 24.8.

IR (Neat Film, NaCl): 2942, 2869, 1726, 1457, 1164 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{23}H_{22}O_3$ $[M+H]^+$: 346.1564, found 346.1571.

Optical Rotation: $[\alpha]_D^{21}$ +1.4 (c 1.00, $CHCl_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 6.74, major = 6.28.

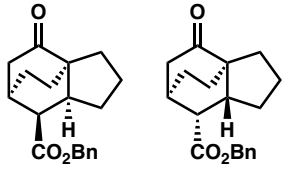
11p' (exo):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.34 (m, 5H), 7.24 (d, *J* = 7.1 Hz, 1H), 7.14 – 7.07 (m, 3H), 5.30 (d, *J* = 12.3 Hz, 1H), 5.25 (d, *J* = 12.3 Hz, 1H), 3.85 (d, *J* = 9.4 Hz, 1H), 3.46 (d, *J* = 14.7 Hz, 1H), 2.75 (d, *J* = 9.3 Hz, 1H), 2.69 – 2.65 (m, 1H), 2.44 (d, *J* = 14.9 Hz, 1H), 2.37 (dd, *J* = 18.7, 2.1 Hz, 1H), 2.19 (ddd, *J* = 18.6, 3.4, 2.1 Hz, 1H), 2.15 – 2.07 (m, 2H), 1.90 – 1.84 (m, 1H), 1.81 – 1.76 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 213.5, 174.0, 143.8, 142.7, 135.9, 128.8, 128.6, 128.4, 127.2, 126.6, 124.8, 122.5, 67.1, 56.4, 49.9, 48.3, 44.1, 35.3, 31.9, 27.5, 21.8.

IR (Neat Film, NaCl): 2918, 1727, 1161 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{23}H_{22}O_3$ $[M+H]^+$: 346.1569, found 346.1568.



11q (endo) *11q' (exo)*

benzyl (3a*R*,6*R*,7*S*,7a*S*)-4-oxooctahydro-3a,6-ethanoindene-7-carboxylate (11q and 11q')

Prepared from **10q** following General Procedure A. Purification by flash column chromatography (0–35% EtOAc/hexanes) afforded the title compound as a colorless oil (54.9 mg, 0.183 mmol, 92% yield, 1.6:1 endo/exo, 84% ee (endo), 29% ee (exo)). The *endo* (**11q**) and *exo* (**11q'**) diastereomers were subsequently separated by preparative TLC (25% EtOAc/hexanes) for independent characterization. Absolute and relative stereochemistry were assigned/confirmed by VCD (see below).

11q (endo):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.31 (m, 5H), 5.13 – 5.02 (m, 2H), 3.10 – 2.99 (m, 2H), 2.47 (h, *J* = 2.9 Hz, 1H), 2.36 – 2.21 (m, 2H), 2.15 (dt, *J* = 19.3, 2.3 Hz, 1H), 1.86 – 1.63 (m, 6H), 1.56 – 1.48 (m, 1H), 1.06 – 0.92 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 215.5, 172.9, 135.9, 128.7, 128.7, 128.5, 66.3, 54.4, 45.9, 44.0, 40.2, 31.4, 28.3, 28.1, 27.0, 26.4, 21.8.

IR (Neat Film, NaCl): 2940, 2868, 1728, 1456, 1174, 1166, 1146 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{19}H_{22}O_3$ $[M]^+$: 298.1564, found 298.1578.

Optical Rotation: $[\alpha]_D^{21}$ –32.4 (c 1.00, $CHCl_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 5.44, major = 6.53.

11q' (exo):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.31 (m, 5H), 5.14 (d, *J* = 12.3 Hz, 1H), 5.09 (d, *J* = 12.2 Hz, 1H), 3.01 (ddd, *J* = 11.7, 3.3, 1.4 Hz, 1H), 2.46 (h, *J* = 3.3 Hz, 1H), 2.35 – 2.25 (m, 3H), 2.14 (tdd, *J* = 11.6, 7.9, 1.6 Hz, 1H), 2.07 – 1.94 (m, 2H), 1.88 – 1.69 (m, 3H), 1.63 – 1.57 (m, 1H), 1.47 – 1.34 (m, 2H), 1.16 (ddd, *J* = 13.9, 9.1, 5.0 Hz, 1H).

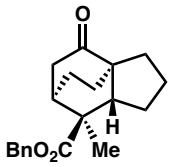
^{13}C NMR (100 MHz, $CDCl_3$): δ 215.5, 173.1, 136.0, 128.8, 128.5, 128.5, 66.3, 53.6, 45.4, 42.7, 41.2, 32.0, 26.4, 25.3, 24.4, 22.3, 21.8.

IR (Neat Film, NaCl): 2946, 2847, 1720, 1457, 1154 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{19}H_{22}O_3$ $[M]^+$: 298.1564, found 298.1578.

Optical Rotation: $[\alpha]_D^{21}$ –5.1 (c 1.00, $CHCl_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): minor = 7.01, major = 7.42.



11r

benzyl (3a*R*,6*R*,7*S*,7a*S*)-7-methyl-4-oxooctahydro-3a,6-ethanoindene-7-carboxylate (11r)

Prepared from **10r** following General Procedure A. Purification by flash column chromatography (0–30% EtOAc/hexanes) afforded the title compound as a colorless oil (29.4 mg, 0.094 mmol, 47% yield, 89% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.29 (m, 5H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.10 (d, *J* = 12.4 Hz, 1H), 2.49 – 2.38 (m, 2H), 2.32 (dt, *J* = 18.9, 2.8 Hz, 1H), 2.19 – 2.10 (m, 2H),

2.01 – 1.92 (m, 1H), 1.85 – 1.66 (m, 4H), 1.65 – 1.55 (m, 1H), 1.49 – 1.31 (m, 5H), 1.13 (ddd, *J* = 14.5, 9.1, 6.0 Hz, 1H).

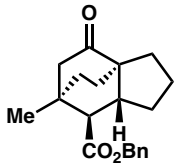
^{13}C NMR (100 MHz, $CDCl_3$): δ 215.2, 177.8, 136.1, 128.7, 128.4, 128.0, 66.8, 54.37, 45.8, 44.7, 43.4, 37.3, 26.5, 24.4, 24.1, 22.7, 22.4, 20.8.

IR (Neat Film, NaCl): 2951, 2875, 1723, 1454, 1239, 1212, 1106 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{20}H_{24}O_3$ $[M]^+$: 312.1725, found 312.1732.

Optical Rotation: $[\alpha]_D^{21}$ –15.3 (c 1.00, $CHCl_3$).

SFC conditions: 40% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): minor = 2.68, major = 3.51.



11s

benzyl (3aR,6R,7R,7aR)-6-methyl-4-oxooctahydro-3a,6-ethanoindene-7-carboxylate (11s)

Prepared from **10s** following General Procedure A. Purification by flash column chromatography (0–25% EtOAc/hexanes) afforded the title compound as a colorless oil (43.6 mg, 0.140 mmol, 69% yield, 83% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.29 (m, 5H), 5.13 (d, *J* = 1.1 Hz, 2H), 2.86 (dd, *J* = 18.5, 3.5 Hz, 1H), 2.37 (dd, *J* = 8.8, 1.4 Hz, 1H), 2.29 – 2.15 (m, 1H), 2.15 – 2.04 (m, 1H), 2.01 – 1.70 (m, 3H), 1.84 (dd, *J* = 18.7, 1.4 Hz, 1H), 1.68 – 1.36 (m, 4H), 1.30 – 1.15 (m, 2H), 0.94 (s, 3H).

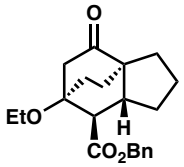
^{13}C NMR (100 MHz, $CDCl_3$): δ 214.5, 174.9, 135.9, 128.8, 128.5, 128.5, 66.7, 54.2, 52.6, 47.0, 44.9, 38.0, 36.0, 28.7, 26.3, 26.0, 23.8, 22.8.

IR (Neat Film, NaCl): 2949, 2873, 1750, 1498, 1454, 1384, 1324, 1155, 1114, 977, 754, 698, 678, 556 cm^{-1}.

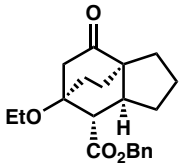
HRMS (MM: FD+): *m/z* calc'd for $C_{20}H_{24}O_3$ $[M]^+$: 312.1703, found 312.1720.

Optical Rotation: $[\alpha]_D^{21}$ –68.2 (c 0.75, $CHCl_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): minor = 10.23, major = 12.31.



11t (endo)



11t' (exo)

benzyl (3a*R*,6*S*,7*R*,7a*R*)-6-ethoxy-4-oxooctahydro-3a,6-ethanoindene-7-carboxylate (11t and 11t')

Prepared from **10t** following General Procedure A. Purification by flash column chromatography (0–50% EtOAc/hexanes) afforded the title compounds as colorless oils (**Endo**: 44.0 mg, 0.128 mmol, 64% yield, 85% ee; **Exo**: 17.0 mg, 0.050 mmol, 25% yield, 72% ee). Absolute and relative stereochemistry were assigned/confirmed by VCD (see below).

11t (endo):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.28 (m, 5H), 5.16 (d, *J* = 1.5 Hz, 2H), 3.55 – 3.32 (m, 2H), 3.17 (dd, *J* = 18.5, 3.1 Hz, 1H), 2.86 (dd, *J* = 8.5, 1.5 Hz, 1H), 2.38 – 2.25 (m,

2H), 2.16 – 2.02 (m, 1H), 2.02 – 1.86 (m, 3H), 1.87 – 1.39 (m, 5H), 1.20 (ddd, *J* = 14.1, 9.1, 5.1 Hz, 1H), 1.03 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 210.8, 173.7, 136.0, 128.7, 128.4, 128.3, 78.2, 66.8, 58.0, 54.2, 51.9, 45.1, 45.1, 30.7, 28.8, 25.8, 24.8, 22.9, 15.8.

IR (Neat Film, NaCl): 2944, 2875, 1726, 1458, 1390, 1320, 1282, 1153, 1110, 1039, 746, 700 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{21}H_{26}O_4$ $[M]^+$: 342.1832, found 342.1826.

Optical Rotation: $[\alpha]_D^{21}$ –47.4 (c 0.75, $CHCl_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 4.73, major = 5.13.

11t' (exo):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.28 (m, 5H), 5.19 (d, *J* = 1.1 Hz, 2H), 3.57 – 3.35 (m, 2H), 2.69 (dd, *J* = 7.8, 1.7 Hz, 1H), 2.60 – 2.47 (m, 1H), 2.47 – 2.44 (m, 2H), 2.39 (ddd, *J* = 12.5, 7.9, 6.9 Hz, 1H), 2.28 (ddd, *J* = 13.5, 9.4, 4.6 Hz, 1H), 1.92 – 1.78 (m, 3H), 1.77 – 1.66 (m, 1H), 1.67 – 1.58 (m, 1H), 1.11 (ddd, *J* = 11.3, 6.6, 3.7 Hz, 1H), 1.03 (t, *J* = 6.9 Hz, 3H), 0.89 (tt, *J* = 12.4, 9.6 Hz, 1H).

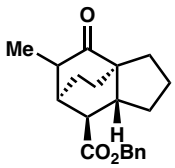
^{13}C NMR (100 MHz, $CDCl_3$): δ 211.5, 173.4, 136.0, 128.7, 128.4, 128.3, 66.9, 58.1, 54.1, 52.8, 47.5, 46.8, 31,0, 27.7, 26.5, 25.9, 23.1, 15.7.

IR (Neat Film, NaCl): 2946, 1721, 1451, 1390, 1328, 1154, 1117, 767, 698 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{21}H_{26}O_4$ $[M]^+$: 342.1833, found 342.1826.

Optical Rotation: $[\alpha]_D^{21}$ +1.8 (c 0.75, $CHCl_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): minor = 3.29, major = 4.04.



11u

benzyl (3a*R*,6*R*,7*S*,7a*R*)-5-methyl-4-oxooctahydro-3a,6-ethanoindene-7-carboxylate (11u)

Prepared from **10u** following General Procedure A. Purification by flash column chromatography (0–25% EtOAc/hexanes) afforded the title compound as a colorless oil (13.6 mg, 0.044 mmol, 22% yield, 61% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.32 (m, 5H), 5.14 (ddd, *J* = 17.8, 12.2 Hz, 2H), 2.61 (dd, *J* = 3.7, 2.1 Hz, 1H), 2.45 – 2.30 (m, 3H), 2.21 – 2.06 (m, 4H), 1.90 – 1.63 (m, 3H), 1.61 – 1.35 (m, 2H), 1.32 – 1.16 (m, 1H), 0.97 (d, *J* = 7.7 Hz, 3H).

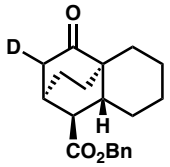
^{13}C NMR (100 MHz, $CDCl_3$): δ 217.7, 174.8, 135.9, 128.7, 128.6, 128.5, 66.8, 54.2, 48.3, 46.9, 42.2, 38.1, 29.7, 28.9, 26.6, 24.1, 22.5, 15.8.

IR (Neat Film, NaCl): 2943, 2873, 1718, 1455, 1197, 1171 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{20}H_{24}O_3$ $[M]^+$: 312.1725, found 312.1730.

Optical Rotation: $[\alpha]_D^{21}$ +10.9 (c 0.75, $CHCl_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 5.84, major = 5.43.



***D*-11f**

benzyl (1*S*,2*R*,4a*R*,8a*R*)-4-oxooctahydro-2*H*-2,4a-ethanonaphthalene-1-carboxylate-3-*d* (*D*-11f)

Prepared from ***D*-10f** following General Procedure A. Purification by flash column chromatography (0–30% EtOAc/hexanes) afforded the title compound as a colorless oil (41.3 mg, 0.132 mmol, 66% yield, 91% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.30 (m, 5H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.11 (d, *J* = 12.2 Hz, 1H), 2.51 – 2.41 (m, 1.6H), 2.36 – 2.10 (m, 2.7H), 2.02 (dddd, *J* = 11.8, 9.1, 5.3, 2.9 Hz, 1H), 1.91 – 1.83 (m, 1H), 1.82 – 1.71 (m, 1H), 1.70 – 1.55 (m, 4H), 1.52 – 1.11 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 216.4, 174.5, 136.0, 128.8, 128.4, 128.2, 77.5, 77.2, 76.8, 66.7, 49.9, 45.1, 40.5, 37.1, 31.0, 30.9, 30.8, 30.0, 28.9, 26.2, 25.6, 21.8, 21.2.

**Partial deuteration complicates ^{13}C NMR spectrum. Peaks are listed as they appear.*

^{2}H NMR (61 MHz, $CHCl_3$): δ 2.46, 2.14.

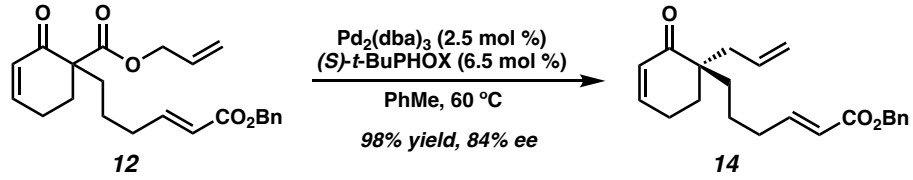
**Trace D-exchanged water observed in spectrum.*

IR (Neat Film, NaCl): 2928, 2858, 1723, 1169 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{20}H_{23}DO_3$ $[M+H]^+$: 313.1783, found 313.1795.

Optical Rotation: $[\alpha]_D^{21}$ –21.3 (c 1.00, $CHCl_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 5.07, major = 6.38.



12 ***14***

benzyl (*S*,*E*)-6-(1-allyl-2-oxocyclohex-3-en-1-yl)hex-2-enoate (14)

Prepared from **12** (0.02 mmol) following General Procedure A. Purification by preparatory thin layer chromatography (25% EtOAc/hexanes) afforded the title compound as a colorless oil (10.1 mg, 0.0196 mmol, 98% yield, 84 % ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.29 (m, 5H), 6.97 (dt, *J* = 15.6, 6.9 Hz, 1H), 6.85 (dt, *J* = 10.1, 3.9 Hz, 1H), 5.91 (dt, *J* = 10.0, 2.0 Hz, 1H), 5.85 (dt, *J* = 15.7, 1.6 Hz, 1H), 5.69 (ddt, *J* = 16.6, 10.5, 7.3 Hz, 1H), 5.17 (s, 2H), 5.09 – 5.00 (m, 2H), 2.41 – 2.29 (m, 3H), 2.26 – 2.13 (m, 3H), 1.87 (t, *J* = 6.1 Hz, 2H), 1.63 – 1.23 (m, 4H).

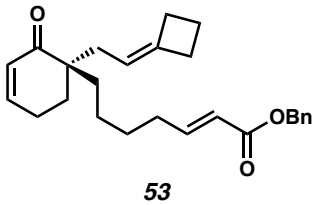
^{13}C NMR (100 MHz, $CDCl_3$): δ 202.9, 166.6, 149.6, 148.7, 136.3, 134.0, 129.0, 128.7, 128.3, 128.3, 121.4, 118.3, 66.2, 47.6, 39.1, 33.9, 32.9, 30.8, 23.1, 22.4.

IR (Neat Film, NaCl): 2936, 2358, 1718, 1669, 1262, 992 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{22}H_{26}O_3$ $[M]^+$: 338.1881, found 338.1877.

Optical Rotation: $[\alpha]_D^{21}$ –0.69 (c 0.62, $CHCl_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): minor = 14.49, major = 11.94.



53

benzyl (*E*)-7-(1-(2-cyclobutylideneethyl)-2-oxocyclohex-3-en-1-yl)hept-2-enoateenoate (53)

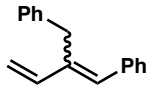
Prepared from **33** following General Procedure A, with the modification of being on 0.1 mmol scale. Purification by preparatory thin layer chromatography (20% EtOAc/hexanes) afforded the title compound as a clear oil (2.4 mg, 0.006 mmol, 6% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.29 (m, 5H), 6.99 (dt, *J* = 15.6, 6.9 Hz, 1H), 6.83 (dt, *J* = 10.0, 3.9 Hz, 1H), 5.92 – 5.81 (m, 2H), 5.17 (s, 2H), 5.01 – 4.92 (m, 1H), 2.67 – 2.54 (m, 3H), 2.40 – 2.30 (m, 2H), 2.27 – 1.99 (m, 4H), 1.96 – 1.82 (m, 3H), 1.63 – 1.49 (m, 3H), 1.49 – 1.36 (m, 3H), 1.32 – 1.13 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 203.6, 166.6, 150.1, 148.5, 143.1, 136.3, 129.1, 128.7, 128.3, 128.3, 121.1, 115.4, 66.2, 48.3, 34.1, 33.1, 32.3, 31.2, 30.8, 29.6, 28.8, 23.6, 23.2, 17.1.

IR (Neat Film, NaCl): 2929, 1720, 1670, 1185 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{26}H_{32}O_3$ $[M]^+$: 392.2351, found 392.2341.



54

(2-vinylprop-1-ene-1,3-diyl)dibenzene (54)

Prepared from **37** following General Procedure A, with the modification of being on 0.1 mmol scale. Purification by flash column chromatography (0–35% EtOAc/hexanes) afforded the title compound as a colorless oil (6.5 mg, 0.03 mmol, 29% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.18 (m, 11.5H), 6.91 – 6.80 (m, 1.15H), 6.56 (ddd, *J* = 17.4, 10.8, 0.9 Hz, 0.15H), 6.45 (s, 1H), 5.42 – 5.33 (m, 1H), 5.19 – 5.13 (m, 1.15H), 5.11 – 5.06 (m, 0.15H), 3.90 (s, 0.3H), 3.73 (s, 2H).

**Isolated as an apparent 1:0.15 mixture of alkene isomers.*

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.5, 140.2, 139.9, 137.7, 137.5, 137.3, 134.2, 133.8, 131.8, 129.6, 128.9, 128.8, 128.7, 128.5, 128.2, 128.2, 127.3, 127.0, 126.2, 126.1, 116.4, 114.8, 40.3, 33.2.

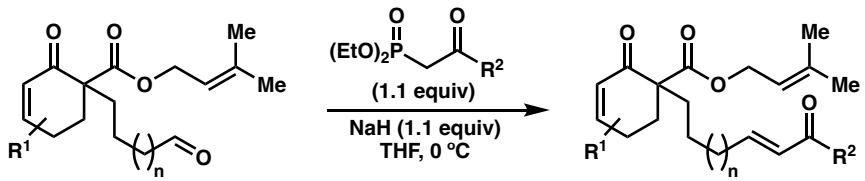
**Isolated as an apparent 1:0.15 mixture of alkene isomers.*

IR (Neat Film, NaCl): 3060, 3023, 2919, 1601, 1493, 1455, 1165, 1074 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{17}H_{16}$ $[M]^+$: 220.1252, found 220.1257.

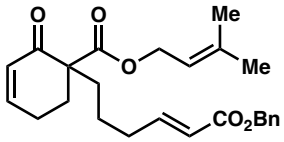
Preparation of Unsaturated β-Ketoester Starting Materials

General Procedure B: Horner–Wadsworth–Emmons Olefination



55 ***10***

To a suspension of NaH (60% by weight in mineral oil, 1.1 equiv) in THF (0.5 M) at 0 ºC was dropwise added a solution of the appropriate phosphonate ester (1.1 equiv) in THF (1.0 M). Stirred at 0 ºC was continued for 30 minutes. To the reaction was then dropwise added a solution of aldehyde **55** (1.0 equiv) in THF (0.5 M). Upon complete consumption of starting material (as determined by TLC), the reaction mixture was diluted with a saturated solution of $NaHCO_3$ and extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product (**10**) was purified by silica gel flash column chromatography.



10a

3-methylbut-2-en-1-yl (*E*)-1-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (10a)

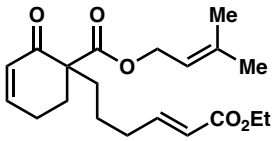
Prepared from **55** and benzyl 2-(diethoxyphosphoryl)acetate [28] following General Procedure B. Purification by flash column chromatography (20% EtOAc/hexanes) afforded the title compound as a colorless oil (0.410 g, 1.00 mmol, 67 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.29 (m, 5H), 6.98 (dt, *J* = 15.7, 6.9 Hz, 1H), 6.90 – 6.84 (m, 1H), 6.02 (ddd, *J* = 10.1, 2.5, 1.5 Hz, 1H), 5.87 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.31 – 5.24 (m, 1H), 5.17 (s, 2H), 4.58 (dt, *J* = 7.2, 1.0 Hz, 2H), 2.55 – 2.41 (m, 2H), 2.37 – 2.27 (m, 1H), 2.22 (qd, *J* = 7.3, 1.6 Hz, 2H), 1.97 – 1.86 (m, 2H), 1.77 – 1.69 (m, 4H), 1.67 (d, *J* = 1.4 Hz, 3H), 1.55 – 1.38 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 171.6, 166.5, 149.3, 149.3, 139.7, 136.3, 129.4, 128.7, 128.3, 128.3, 121.5, 118.3, 66.2, 62.3, 57.0, 33.5, 32.7, 30.5, 25.8, 23.9, 23.2, 18.2.

IR (Neat Film, NaCl): 3034, 2938, 1723, 1684, 1653, 1455, 1384, 1246, 1174, 1166 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{25}H_{30}O_5$ $[M]^+$: 410.2088, found 410.2097.



10b

3-methylbut-2-en-1-yl (*E*)-1-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (10b)

Prepared from **55** and ethyl 2-(diethoxyphosphoryl)acetate following General Procedure B. Purification by flash column chromatography (20% EtOAc/hexanes) afforded the title compound as a colorless oil (0.291 g, 0.835 mmol, 47 % yield).

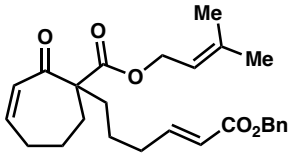
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 – 6.85 (m, 2H), 6.02 (ddd, *J* = 10.0, 2.6, 1.5 Hz, 1H), 5.81 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.31 – 5.24 (m, 1H), 4.64 – 4.54 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.55 – 2.41 (m, 2H), 2.37 – 2.27 (m, 1H), 2.21 (qd, *J* = 7.3, 1.6 Hz, 2H), 1.98 –

1.87 (m, 2H), 1.78 – 1.69 (m, 4H), 1.68 (s, 3H), 1.55 – 1.37 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 171.6, 166.8, 149.3, 148.5, 139.7, 129.4, 121.8, 118.3, 62.3, 60.3, 57.0, 33.5, 32.6, 30.5, 25.8, 23.9, 23.3, 18.2, 14.4.

IR (Neat Film, NaCl): 2934, 1714, 1682, 1168 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{20}H_{28}O_5$ $[M]^+$: 348.1937, found 348.1943.



10d

3-methylbut-2-en-1-yl (*E*)-1-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-2-oxocyclohept-3-ene-1-carboxylate (10d)

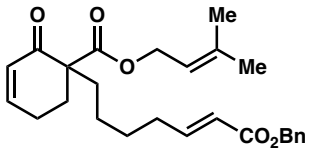
Prepared from cyclohept-2-en-1-one following General Procedures B–D. Note that inseparable impurities plagued the β-ketoester and aldehyde intermediates. Fortunately, these intermediates could be brought through the sequence in sub-optimal purity to still afford the title compound **10d** as a colorless oil (265 mg, 0.62 mmol, 3.2% yield from cyclohept-2-en-1-one) after a final purification by flash column chromatography (20% EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.30 (m, 5H), 6.97 (dt, J = 15.6, 6.9 Hz, 1H), 6.36 (ddd, J = 12.3, 5.5, 3.9 Hz, 1H), 5.98 (ddd, J = 12.3, 2.4, 1.4 Hz, 1H), 5.86 (dt, J = 15.6, 1.6 Hz, 1H), 5.28 (ddp, J = 8.6, 5.7, 1.4 Hz, 1H), 5.17 (s, 2H), 4.57 (d, J = 7.2 Hz, 2H), 2.47 – 2.27 (m, 3H), 2.19 (qd, J = 7.2, 1.6 Hz, 2H), 1.99 – 1.79 (m, 3H), 1.77 – 1.69 (m, 4H), 1.69 – 1.61 (m, 4H), 1.43 – 1.32 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.1, 172.9, 166.5, 149.3, 143.2, 139.7, 136.3, 131.6, 128.7, 128.3, 128.3, 121.5, 118.2, 66.2, 63.9, 62.2, 36.5, 32.6, 32.3, 31.2, 25.8, 24.3, 23.0, 18.2.

IR (Neat Film, NaCl): 2927, 1720, 1686, 1453, 1162 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{26}H_{32}O_5$ $[M]^+$: 424.2244, found 424.2241.



10f

3-methylbut-2-en-1-yl (*E*)-1-(7-(benzyloxy)-7-oxohept-5-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (10f)

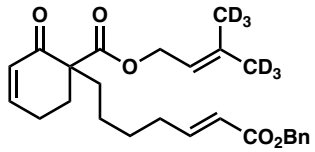
Prepared from **56** and benzyl 2-(diethoxyphosphoryl)acetate[28] following General Procedure B. Purification by flash column chromatography (15–20% EtOAc/hexanes) afforded the title compound as a colorless oil (652 mg, 1.54 mmol, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.30 (m, 5H), 6.99 (ddd, *J* = 15.5, 7.3, 6.3 Hz, 1H), 6.90 – 6.84 (m, 1H), 6.01 (d, *J* = 10.1 Hz, 1H), 5.85 (d, *J* = 15.6 Hz, 1H), 5.30 – 5.25 (m, 1H), 5.17 (s, 2H), 4.58 (d, *J* = 6.6 Hz, 2H), 2.55 – 2.40 (m, 2H), 2.36 – 2.26 (m, 1H), 2.24 – 2.16 (m, 2H), 1.96 – 1.86 (m, 2H), 1.77 – 1.65 (m, 7H), 1.47 (p, *J* = 7.4 Hz, 2H), 1.38 – 1.24 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 171.6, 166.5, 149.7, 149.2, 139.4, 136.2, 129.2, 128.6, 128.2, 128.2, 121.1, 118.2, 66.0, 62.1, 56.9, 33.5, 32.0, 30.2, 28.4, 25.7, 24.2, 23.7, 18.1.

IR (Neat Film, NaCl): 2932, 2861, 1722, 1684, 1653, 1456, 1263, 1181 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{26}H_{32}O_5$ $[M]^+$: 424.2244, found 424.2247.



D-10f

3-(methyl-*d*$_3$)but-2-en-1-yl-4,4,4-*d*$_3$ (*E*)-1-(7-(benzyloxy)-7-oxohept-5-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (*D*-10f)

Prepared from ***D*-56** and benzyl 2-(diethoxyphosphoryl)acetate[28] following General Procedure B. Purification by flash column chromatography (15–20% EtOAc/hexanes) afforded the title compound as a colorless oil (201 mg, 0.467 mmol, 48 % yield).

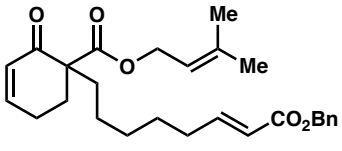
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.30 (m, 5H), 6.99 (dt, *J* = 15.6, 6.9 Hz, 1H), 6.90 – 6.85 (m, 1H), 6.01 (ddd, *J* = 10.1, 2.6, 1.5 Hz, 1H), 5.85 (dt, *J* = 15.6, 1.5 Hz, 1H), 5.27 (t, *J* = 7.1 Hz, 1H), 5.17 (s, 2H), 4.58 (dd, *J* = 7.2, 1.7 Hz, 2H), 2.55 – 2.41 (m, 2H), 2.36 – 2.27 (m, 1H), 2.25 – 2.15 (m, 2H), 1.98 – 1.85 (m, 2H), 1.73 (ddd, *J* = 13.6, 11.2, 5.3 Hz, 1H), 1.51 – 1.42 (m, 2H), 1.37 – 1.25 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 171.7, 166.6, 149.8, 149.3, 139.4, 136.3, 129.4, 128.7, 128.3, 128.3, 121.2, 118.4, 66.2, 62.3, 57.0, 33.6, 32.2, 30.3, 28.5, 24.3, 23.9.

^{2}H NMR (61 MHz, $CHCl_3$): δ 1.69, 1.65.

IR (Neat Film, NaCl): 2930, 1720, 1683, 1264, 1167 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{26}H_{26}D_6O_5$ $[M]^+$: 430.2621, found 430.2622.



10g

3-methylbut-2-en-1-yl (*E*)-1-(8-(benzyloxy)-8-oxooct-6-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (10g)

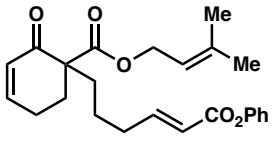
Prepared from **57** and benzyl 2-(diethoxyphosphoryl)acetate[28] following General Procedure B. Purification by flash column chromatography (10–25% EtOAc/hexanes) afforded the title compound as a colorless oil (773 mg, 1.76 mmol, 65 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.29 (m, 5H), 6.99 (dt, *J* = 15.6, 6.9 Hz, 1H), 6.89 – 6.84 (m, 1H), 6.01 (ddd, *J* = 10.0, 2.5, 1.5 Hz, 1H), 5.85 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.28 (ddp, *J* = 8.6, 5.7, 1.4 Hz, 1H), 5.17 (s, 2H), 4.63 – 4.53 (m, 2H), 2.55 – 2.40 (m, 2H), 2.36 – 2.26 (m, 1H), 2.19 (qd, *J* = 7.1, 1.6 Hz, 2H), 1.98 – 1.84 (m, 2H), 1.77 – 1.69 (m, 4H), 1.67 (s, 3H), 1.49 – 1.41 (m, 2H), 1.36 – 1.23 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.5, 171.7, 166.6, 150.1, 149.3, 139.5, 136.3, 129.4, 128.7, 128.3, 128.3, 121.2, 118.4, 66.2, 62.2, 57.1, 33.7, 32.3, 30.3, 29.6, 27.8, 25.8, 24.4, 23.9, 18.2.

IR (Neat Film, NaCl): 2929, 2858, 1721, 1684, 1654, 1456, 1264, 1168 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{27}H_{34}O_5$ $[M]^+$: 438.2401, found 438.2396.



10k

3-methylbut-2-en-1-yl (*E*)-2-oxo-1-(6-oxo-6-phenoxyhex-4-en-1-yl)cyclohex-3-ene-1-carboxylate (10k)

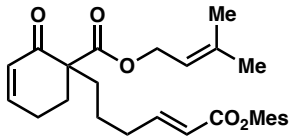
Prepared from **55** and benzyl 2-(diethoxyphosphoryl)acetate [29] following General Procedure B. Purification by flash column chromatography (20% EtOAc/hexanes) afforded the title compound as a colorless oil (409 mg, 1.03 mmol, 57 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (t, *J* = 8.0 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.18 – 7.10 (m, 3H), 6.91 – 6.87 (m, 1H), 6.05 – 6.00 (m, 2H), 5.29 (tt, *J* = 7.1, 1.3 Hz, 1H), 4.61 (d, *J* = 7.1 Hz, 2H), 2.56 – 2.44 (m, 2H), 2.37 – 2.27 (m, 3H), 2.00 – 1.92 (m, 2H), 1.82 – 1.73 (m, 4H), 1.69 (s, 3H), 1.63 – 1.46 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 171.6, 165.1, 150.9, 150.9, 149.3, 139.7, 129.5, 129.4, 125.8, 121.8, 121.1, 118.3, 62.4, 57.0, 33.6, 32.8, 30.5, 25.8, 23.9, 23.2, 18.2.

IR (Neat Film, NaCl): 2930, 1732, 1684, 1652, 1458, 1245, 1195 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{24}H_{28}O_5$ $[M]^+$: 396.1931, found 396.1945.



10l

3-methylbut-2-en-1-yl (*E*)-1-(6-(mesityloxy)-6-oxohex-4-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (10l)

Prepared from **55** and mesityl 2-(diethoxyphosphoryl)acetate [30] following General Procedure B. Purification by flash column chromatography (20% EtOAc/hexanes) afforded the title compound as a colorless oil (597 mg, 1.36 mmol, 76% yield).

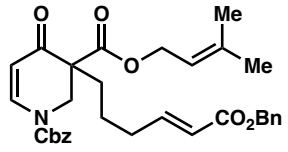
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (dt, *J* = 15.7, 6.8 Hz, 1H), 6.92 – 6.84 (m, 3H), 6.09 – 6.01 (m, 2H), 5.32 – 5.26 (m, 1H), 4.61 (d, *J* = 5.6 Hz, 2H), 2.57 – 2.43 (m, 2H), 2.39 –

2.27 (m, 3H), 2.26 (s, 3H), 2.09 (s, 6H), 2.01 – 1.92 (m, 2H), 1.79 (ddd, *J* = 13.6, 11.9, 4.8 Hz, 1H), 1.73 (s, 3H), 1.69 (s, 3H), 1.64 – 1.46 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 171.6, 164.6, 150.7, 149.3, 146.0, 139.7, 135.3, 130.0, 129.4, 129.3, 120.7, 118.3, 62.4, 57.0, 33.6, 32.8, 30.5, 25.8, 23.9, 23.2, 20.9, 18.2, 16.4.

IR (Neat Film, NaCl: 2920, 1733, 1684, 1458, 1248, 1192, 1140 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{27}H_{34}O_5$ $[M]^+$: 438.2401, found 438.2401.



10n

1-benzyl 3-(3-methylbut-2-en-1-yl) (*E*)-3-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-4-oxo-3,4-dihydropyridine-1,3(2*H*)-dicarboxylate (10n)

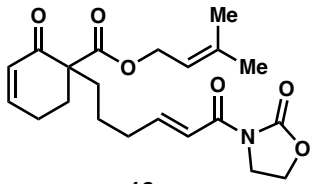
Prepared from **58** and benzyl 2-(diethoxyphosphoryl)acetate[28] following General Procedure B. Purification by flash column chromatography (20-30% EtOAc/hexanes) afforded the title compound as a colorless oil (181.3 mg, 0.332 mmol, 55% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.44 – 7.28 (m, 10H), 6.94 (dt, *J* = 15.5, 6.8 Hz, 1H), 5.85 (dt, *J* = 15.7, 1.6 Hz, 1H), 5.42 – 5.21 (m, 4H), 5.17 (s, 2H), 4.67 – 4.51 (m, 3H), 3.71 (d, *J* = 13.6 Hz, 1H), 2.20 (q, *J* = 7.3 Hz, 2H), 2.07 – 1.92 (m, 1H), 1.69 – 1.58 (m, 1H), 1.71 (s, 3H), 1.66 (s, 3H), 1.49 – 1.40 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.5, 169.5, 166.4, 148.7, 142.7, 140.1, 136.2, 135.0, 129.0, 128.9, 128.7, 128.6, 128.4, 128.3, 121.7, 118.0, 106.5, 69.4, 66.2, 62.8, 55.3, 48.3, 32.4, 31.3, 25.8, 23.0, 18.2.

IR (Neat Film, NaCl): 2938, 2338, 1726, 1676, 1604, 1456, 1388, 1303, 1201, 975 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{32}H_{35}NO_7$ $[M]^+$: 545.2414, found 545.2408.



10o

3-methylbut-2-en-1-yl (*E*)-2-oxo-1-(6-oxo-6-(2-oxooxazolidin-3-yl)hex-4-en-1-yl)cyclohex-3-ene-1-carboxylate (10o)

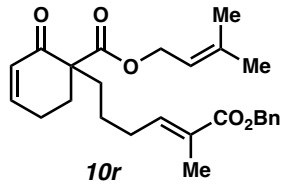
Prepared from **55** and diethyl (2-oxo-2-(2-oxooxazolidin-3-yl)ethyl)phosphonate [31] following General Procedure B. Purification by flash column chromatography (0-80% EtOAc/hexanes) afforded the title compound as a colorless oil (275.1 mg, 0.706 mmol, 71% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 15.6 Hz, 1H), 7.12 (dt, *J* = 15.4, 6.7 Hz, 1H), 6.87 (ddd, *J* = 7.8, 6.0, 3.9 Hz, 1H), 6.01 (dt, *J* = 10.3, 2.0 Hz, 1H), 5.28 (tt, *J* = 7.2, 1.3 Hz, 1H), 4.62 – 4.54 (m, 2H), 4.41 (dd, *J* = 8.5, 7.6 Hz, 2H), 4.11 – 4.02 (m, 2H), 2.55 – 2.40 (m, 2H), 2.38 – 2.25 (m, 3H), 2.00 – 1.86 (m, 2H), 1.82 – 1.69 (m, 2H), 1.73 (s, 3H), 1.68 (s, 3H), 1.50 (dtd, *J* = 17.3, 12.4, 7.6 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 171.6, 165.3, 153.6, 150.9, 149.4, 139.6, 129.3, 120.5, 118.3, 62.3, 62.2, 57.0, 42.8, 33.4, 33.1, 30.3, 25.8, 23.9, 23.3, 18.2.

IR (Neat Film, NaCl): 2927, 1774, 1724, 1684, 1636, 1385, 1359, 1222, 1042 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{21}H_{27}NO_6$ $[M]^+$: 389.1838, found 389.1827.



10r

3-methylbut-2-en-1-yl (*E*)-1-(6-(benzyloxy)-5-methyl-6-oxohex-4-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (10r)

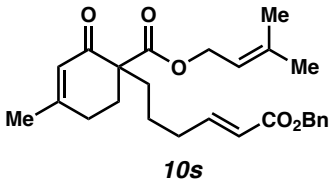
Prepared from **55** and benzyl 2-(diethoxyphosphoryl)propanoate[32] following General Procedure B. Purification by flash column chromatography (0–30% EtOAc/hexanes) afforded the title compound as a colorless oil (220 mg, 0.518 mmol, 29% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.29 (m, 5H), 6.87 (dddd, *J* = 10.1, 4.9, 3.0, 1.1 Hz, 1H), 6.78 (tq, *J* = 7.5, 1.5 Hz, 1H), 6.01 (ddd, *J* = 10.1, 2.5, 1.5 Hz, 1H), 5.31 – 5.24 (m, 1H), 5.18 (s, 2H), 4.58 (d, *J* = 6.9 Hz, 2H), 2.55 – 2.41 (m, 2H), 2.36 – 2.26 (m, 1H), 2.19 (qd, *J* = 7.5, 1.1 Hz, 2H), 1.98 – 1.87 (m, 2H), 1.85 (s, 3H), 1.79 – 1.69 (m, 4H), 1.67 (s, 3H), 1.53 – 1.37 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 171.6, 168.0, 149.3, 142.3, 139.6, 136.5, 129.3, 128.6, 128.2, 128.1, 128.1, 118.3, 66.3, 62.3, 57.0, 33.7, 30.4, 29.2, 25.8, 23.9, 23.9, 18.2, 12.6.

IR (Neat Film, NaCl): 2930, 1711, 1686, 1452, 1265, 1180 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{26}H_{32}O_5$ $[M]^+$: 424.2250, found 424.2250.



10s

3-methylbut-2-en-1-yl (*E*)-1-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-4-methyl-2-oxocyclohex-3-ene-1-carboxylate (10s)

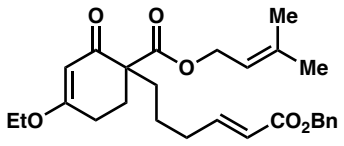
Prepared from **59** and benzyl 2-(diethoxyphosphoryl)acetate[28] following General Procedure B. Purification by flash column chromatography (15–20–25% EtOAc/hexanes) afforded the title compound as a colorless oil (827.2 mg, 2.16 mmol, 64% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.28 (m, 5H), 6.98 (dt, *J* = 15.6, 6.8 Hz, 1H), 5.87 (dq, *J* = 2.7, 1.3 Hz, 1H), 5.86 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.27 (tp, *J* = 7.1, 1.4 Hz, 1H), 5.16 (s, 2H), 4.64 – 4.51 (m, 2H), 2.52 – 2.36 (m, 2H), 2.28 – 2.14 (m, 3H), 1.98 – 1.83 (m, 5H), 1.72 (s, 4H), 1.67 (s, 3H), 1.54 – 1.34 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 171.7, 166.5, 161.4, 149.3, 139.6, 136.3, 128.7, 128.3, 128.3, 126.1, 121.5, 118.4, 66.2, 62.3, 55.9, 33.5, 32.7, 30.2, 28.8, 25.8, 24.2, 23.3, 18.2.

IR (Neat Film, NaCl): 3032, 2938, 1723, 1674, 1438, 1379, 1264, 1212, 1168, 1013, 741, 698 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{26}H_{32}O_5$ $[M]^+$: 424.2235, found 424.2244.



10t

3-methylbut-2-en-1-yl (*E*)-1-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-4-ethoxy-2-oxocyclohex-3-ene-1-carboxylate (10t)

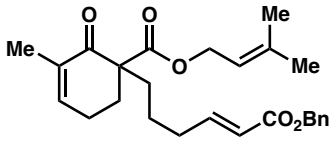
Prepared from **60** and benzyl 2-(diethoxyphosphoryl)acetate[28] following General Procedure B. Purification by flash column chromatography (30% EtOAc/hexanes) afforded the title compound as a colorless oil (814.7 mg, 1.79 mmol, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.28 (m, 5H), 6.98 (dt, *J* = 15.6, 6.8 Hz, 1H), 5.86 (dt, *J* = 15.7, 1.6 Hz, 1H), 5.34 (d, *J* = 1.2 Hz, 1H), 5.28 (dddt, *J* = 7.0, 5.6, 2.8, 1.4 Hz, 1H), 5.16 (s, 2H), 4.66 – 4.52 (m, 2H), 3.89 (qd, *J* = 7.1, 1.6 Hz, 2H), 2.61 (dddd, *J* = 17.9, 10.1, 4.9, 1.2 Hz, 1H), 2.46 – 2.27 (m, 2H), 2.21 (qd, *J* = 7.3, 1.6 Hz, 2H), 2.02 – 1.83 (m, 2H), 1.82 – 1.72 (m, 1H), 1.71 (s, 3H), 1.67 (s, 3H), 1.45 (dddd, *J* = 13.3, 11.2, 6.4, 2.7 Hz, 2H), 1.35 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.8, 176.6, 171.8, 166.5, 149.4, 139.5, 136.3, 128.7, 128.3, 128.3, 121.4, 118.5, 102.3, 66.2, 64.5, 62.3, 56.0, 33.8, 32.7, 28.7, 26.6, 25.8, 23.3, 18.2, 14.3.

IR (Neat Film, NaCl): 2939, 1721, 1655, 1608, 1446, 1380, 1314, 1242, 1190, 1026, 736 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{27}H_{34}O_6$ $[M]^+$: 454.2349, found 454.2350.



10u

3-methylbut-2-en-1-yl (*E*)-1-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-3-methyl-2-oxocyclohex-3-ene-1-carboxylate (10u)

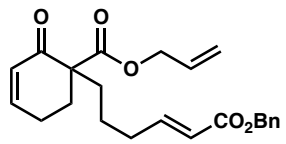
Prepared from **61** and benzyl 2-(diethoxyphosphoryl)acetate[28] following General Procedure B. Purification by flash column chromatography (10–25% EtOAc/hexanes) afforded the title compound as a colorless oil (1176.8 mg, 2.77 mmol, 71% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.26 (m, 5H), 6.98 (dt, *J* = 15.6, 6.8 Hz, 1H), 6.59 (ddt, *J* = 4.7, 3.1, 1.3 Hz, 1H), 5.87 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.27 (tdq, *J* = 7.1, 2.8, 1.5 Hz, 1H), 5.17 (s, 2H), 4.57 (d, *J* = 6.7 Hz, 2H), 2.50 – 2.36 (m, 2H), 2.33 – 2.16 (m, 3H), 1.98 – 1.83 (m, 2H), 1.78 (q, *J* = 1.7 Hz, 3H), 1.77 – 1.64 (m, 1H), 1.72 (s, 3H), 1.67 (s, 3H) 1.61 – 1.34 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.0, 171.9, 166.5, 149.4, 143.8, 139.6, 136.3, 135.4, 128.7, 128.3, 128.3, 121.5, 118.3, 66.2, 62.2, 56.9, 33.6, 32.7, 30.9, 25.8, 23.6, 23.4, 18.2, 16.6.

IR (Neat Film, NaCl): 2921, 1721, 1677, 1450, 1377, 1248, 1168, 728 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{26}H_{32}O_5$ $[M]^+$: 424.2244, found 424.2244.



12

allyl (*E*)-1-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (12)

Prepared from **62** and benzyl 2-(diethoxyphosphoryl)acetate[28] following General Procedure B. Purification by flash column chromatography (20–25% EtOAc/hexanes) afforded the title compound as a colorless oil (599.1 mg, 1.41 mmol, 46% yield).

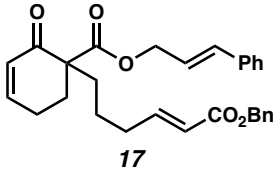
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.26 (m, 5H), 6.98 (dt, *J* = 15.6, 6.9 Hz, 1H), 6.89 (dddd, *J* = 10.1, 4.8, 3.1, 1.0 Hz, 1H), 6.03 (ddd, *J* = 10.1, 2.5, 1.6 Hz, 1H), 5.93 – 5.77 (m,

2H), 5.27 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.21 (dq, *J* = 10.4, 1.3 Hz, 1H), 5.17 (s, 2H), 4.60 (dq, *J* = 5.6, 1.6 Hz, 2H), 2.57 – 2.42 (m, 2H), 2.39 – 2.27 (m, 1H), 2.22 (qd, *J* = 7.3, 1.6 Hz, 2H), 2.02 – 1.87 (m, 2H), 1.77 (ddd, *J* = 13.7, 11.7, 5.2 Hz, 1H), 1.57 – 1.40 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.0, 171.2, 166.5, 149.5, 149.1, 136.2, 131.7, 129.3, 128.7, 128.3, 128.3, 127.8, 127.1, 121.6, 118.7, 66.2, 65.9, 57.0, 33.4, 32.6, 30.3, 23.8, 23.2.

IR (Neat Film, NaCl): 2937, 2357, 1723, 1684, 1456, 1262, 1165, 992 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{23}H_{27}O_5$ $[M]^+$: 383.1871, found 383.1853.



17

cinnamyl 1-((*E*)-6-(benzyloxy)-6-oxohex-4-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (17)

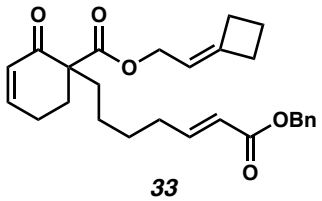
Prepared from **63** and benzyl 2-(diethoxyphosphoryl)acetate[28] following General Procedure B. Purification by flash column chromatography (20% EtOAc/hexanes) afforded the title compound as a colorless oil (569 mg, 1.24 mmol, 67% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.34 (m, 6H), 7.34 – 7.29 (m, 3H), 7.27 – 7.24 (m, 1H), 6.97 (dt, *J* = 15.6, 6.9 Hz, 1H), 6.89 (dddd, *J* = 10.1, 4.8, 3.1, 1.0 Hz, 1H), 6.62 (d, *J* = 15.9 Hz, 1H), 6.22 (dt, *J* = 15.9, 6.4 Hz, 1H), 6.04 (ddd, *J* = 10.1, 2.5, 1.6 Hz, 1H), 5.86 (dt, *J* = 15.7, 1.6 Hz, 1H), 5.16 (s, 2H), 4.76 (dt, *J* = 6.4, 1.4 Hz, 2H), 2.56 – 2.45 (m, 2H), 2.37 – 2.28 (m, 1H), 2.22 (ddd, *J* = 7.4, 7.4, 1.6 Hz, 2H), 1.95 (ddt, *J* = 16.8, 7.9, 5.7 Hz, 2H), 1.78 (ddd, *J* = 13.7, 11.7, 5.0 Hz, 1H), 1.56 – 1.42 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.0, 171.4, 166.5, 149.5, 149.1, 136.2, 136.2, 134.7, 129.3, 128.7, 128.7, 128.3, 128.3, 126.8, 122.6, 121.6, 66.2, 65.9, 57.0, 33.4, 32.6, 30.3, 23.8, 23.2.

IR (Neat Film, NaCl): 3034, 2942, 1718, 1700, 1684, 1247, 1166 cm^{-1}

HRMS (MM: FD+): *m/z* calc'd for $C_{29}H_{30}O_5$ $[M]^+$: 458.2088, found 458.2082.



33

22-cyclobutylideneethyl (*E*)-1-(7-(benzyloxy)-7-oxohept-5-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylatecarboxylate (33)

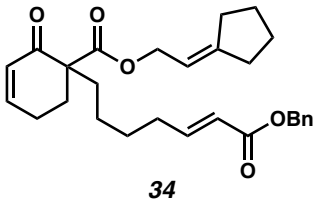
Prepared from **64** and benzyl 2-(diethoxyphosphoryl)acetate[28] following General Procedure B. Purification by flash column chromatography (5–60% EtOAc/hexanes) afforded the title compound as a colorless oil (354 mg, 0.81 mmol, 39.8% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.29 (m, 5H), 6.99 (dt, *J* = 14.9, 1.0 Hz, 1H), 6.91 – 6.84 (m, 1H), 6.02 (d, *J* = 1.2 Hz, 1H), 5.86 (d, *J* = 15.7 Hz, 1H), 5.24 – 5.13 (m, 3H), 4.51 – 4.41 (m, 2H), 2.75 – 2.62 (m, 4H), 2.56 – 2.39 (m, 2H), 2.36 – 2.27 (m, 1H), 2.25 – 2.16 (m, 2H), 2.02 – 1.84 (m, 4H), 1.73 (ddd, *J* = 13.6, 11.2, 5.3 Hz, 1H), 1.47 (p, *J* = 7.5 Hz, 2H), 1.40 – 1.23 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 171.6, 166.6, 149.8, 149.3, 148.8, 136.3, 129.4, 128.7, 128.3, 128.3, 121.2, 114.0, 66.2, 62.3, 57.1, 33.6, 32.2, 31.2, 30.3, 29.6, 28.5, 24.3, 23.9, 17.1.

IR (Neat Film, NaCl): 2945, 1722, 1687, 1446, 1169 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{27}H_{32}O_5$ $[M]^+$: 436.2250, found 436.2222.



34

2-cyclopentylideneethyl (*E*)-1-(7-(benzyloxy)-7-oxohept-5-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (34)

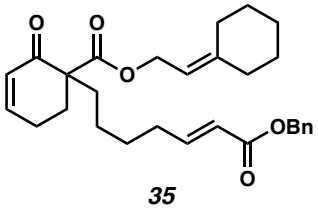
Prepared from **65** and benzyl 2-(diethoxyphosphoryl)acetate[28] following General Procedure B. Purification by flash column chromatography (10–60% EtOAc/hexanes) afforded the title compound as a colorless oil (1.40 g, 4.41 mmol, 38.9% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.28 (m, 5H), 6.99 (dt, *J* = 15.6, 6.9 Hz, 1H), 6.91 – 6.83 (m, 1H), 6.01 (ddd, *J* = 10.1, 2.6, 1.5 Hz, 1H), 5.85 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.37 (tp, *J* = 7.0, 2.2 Hz, 1H), 5.17 (s, 2H), 4.60 – 4.53 (m, 2H), 2.56 – 2.39 (m, 2H), 2.37 – 2.15 (m, 7H), 1.98 – 1.85 (m, 2H), 1.78 – 1.54 (m, 5H), 1.53 – 1.41 (m, 2H), 1.40 – 1.22 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 171.7, 166.6, 151.1, 149.8, 149.3, 136.3, 129.4, 128.7, 128.3, 128.3, 121.2, 113.8, 66.2, 63.7, 57.1, 33.9, 33.6, 32.2, 30.3, 29.0, 28.5, 26.4, 26.2, 24.3, 23.9.

IR (Neat Film, NaCl): 2946, 1719, 1686, 1457, 1165 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{28}H_{34}O_5$ $[M]^+$: 450.2406, found 450.2394.



35

2-cyclohexylideneethyl (*E*)-1-(7-(benzyloxy)-7-oxohept-5-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (35)

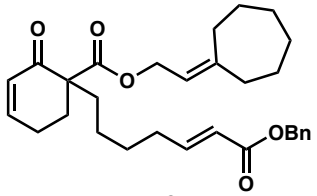
Prepared from **66** and benzyl 2-(diethoxyphosphoryl)acetate[28] following General Procedure B. Purification by flash column chromatography (10–60% EtOAc/hexanes) afforded the title compound as a colorless oil (81 mg, 0.17 mmol, 32.9% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.27 (m, 5H), 6.99 (dt, *J* = 15.6, 6.9 Hz, 1H), 6.87 (dddd, *J* = 10.1, 5.2, 2.5, 1.1 Hz, 1H), 6.01 (ddd, *J* = 10.1, 2.6, 1.5 Hz, 1H), 5.85 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.23 (tp, *J* = 7.3, 1.2 Hz, 1H), 5.17 (s, 2H), 4.59 (d, *J* = 7.2 Hz, 2H), 2.56 – 2.39 (m, 2H), 2.36 – 2.26 (m, 1H), 2.25 – 2.13 (m, 4H), 2.12 – 2.03 (m, 2H), 1.98 – 1.84 (m, 2H), 1.78 – 1.66 (m, 1H), 1.63 – 1.42 (m, 8H), 1.41 – 1.21 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 171.6, 166.6, 149.8, 149.3, 147.7, 136.3, 129.4, 128.7, 128.3, 128.3, 121.2, 114.9, 66.2, 61.5, 57.0, 37.1, 33.6, 32.2, 30.4, 29.2, 28.5, 28.5, 27.9, 26.7, 24.3, 23.9.

IR (Neat Film, NaCl): 2929, 2853, 1723, 1681, 1456, 1385, 1266, 1184 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{29}H_{36}O_5$ $[M]^+$: 464.2563, found 464.2543.



36

2-cycloheptylideneethyl (*E*)-1-(7-(benzyloxy)-7-oxohept-5-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (36)

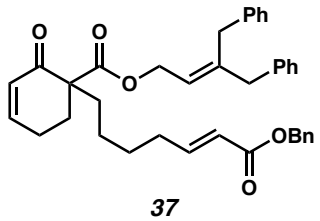
Prepared from **67** and benzyl 2-(diethoxyphosphoryl)acetate[28] following General Procedure B. Purification by flash column chromatography (5–70% EtOAc/hexanes) afforded the title compound as a colorless oil (135 mg, 0.28 mmol, 30% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.29 (m, 5H), 6.99 (dt, *J* = 15.7, 6.9 Hz, 1H), 6.91 – 6.82 (m, 1H), 6.01 (ddd, *J* = 10.2, 2.6, 1.5 Hz, 1H), 5.85 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.27 (tt, *J* = 7.1, 1.3 Hz, 1H), 5.17 (s, 2H), 4.59 (d, *J* = 7.1 Hz, 2H), 2.57 – 2.39 (m, 2H), 2.36 – 2.16 (m, 7H), 1.98 – 1.84 (m, 2H), 1.73 (ddd, *J* = 13.6, 11.3, 5.2 Hz, 1H), 1.61 – 1.43 (m, 10H), 1.31 (dddd, *J* = 13.2, 11.8, 8.6, 6.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 171.7, 166.6, 149.8, 149.3, 149.0, 136.3, 129.4, 128.7, 128.3, 128.3, 121.2, 118.4, 66.2, 62.0, 57.0, 37.7, 33.6, 32.2, 30.4, 30.2, 29.8, 29.1, 28.9, 28.5, 27.3, 24.3, 23.9.

IR (Neat Film, NaCl): 2919, 2361, 1722, 1682, 1651, 1443, 1234, 1187 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{30}H_{38}O_5$ $[M]^+$: 478.2719, found 478.2716.



37

3-benzyl-4-phenylbut-2-en-1-yl (*E*)-1-(7-(benzyloxy)-7-oxohept-5-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (37)

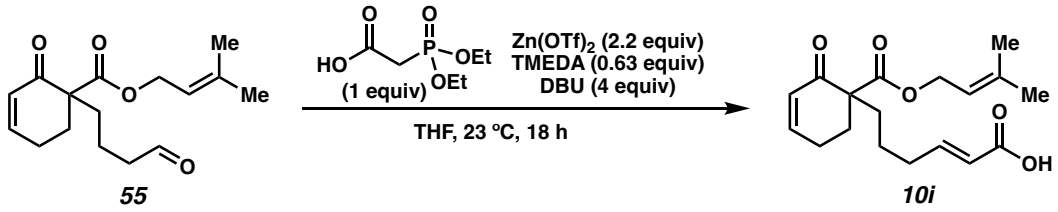
Prepared from **68** and benzyl 2-(diethoxyphosphoryl)acetate[28] following General Procedure B. Purification by flash column chromatography (5–70% EtOAc/hexanes) afforded the title compound as a colorless oil (205 mg, 0.36 mmol, 39% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.24 (m, 9H), 7.23 – 7.17 (m, 2H), 7.09 (dd, *J* = 11.6, 7.3 Hz, 4H), 6.98 (dt, *J* = 15.6, 6.9 Hz, 1H), 6.89 – 6.80 (m, 1H), 6.02 (d, *J* = 10.1 Hz, 1H), 5.85 (d, *J* = 16.1 Hz, 1H), 5.51 (t, *J* = 7.2 Hz, 1H), 5.17 (s, 2H), 4.83 – 4.69 (m, 2H), 3.36 (s, 2H), 3.23 (s, 2H), 2.55 – 2.40 (m, 2H), 2.37 – 2.24 (m, 1H), 2.18 (q, *J* = 7.2 Hz, 2H), 2.00 – 1.85 (m, 2H), 1.75 (ddd, *J* = 13.5, 11.1, 5.2 Hz, 1H), 1.46 (p, *J* = 7.4 Hz, 1H), 1.38 – 1.22 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 171.6, 166.6, 149.8, 149.3, 144.8, 139.0, 138.8, 136.3, 129.4, 129.3, 128.8, 128.7, 128.7, 128.5, 128.3, 128.3, 126.5, 126.4, 121.7, 121.3, 66.2, 61.9, 57.1, 42.9, 35.8, 33.6, 32.1, 30.3, 28.5, 24.3, 23.9.

IR (Neat Film, NaCl): 3027, 2931, 1722, 1682, 1493, 1387, 1264, 1165 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{38}H_{40}O_5$ $[M]^+$: 576.2876, found 576.2857.



(*E*)-6-(1-(((3-methylbut-2-en-1-yl)oxy)carbonyl)-2-oxocyclohex-3-en-1-yl)hex-2-enoic acid (10i)[33]

To a suspension of $Zn(OTf)_2$ (6.6 mmol, 2.2 equiv) in THF (15 mL) was added (diethoxyphosphinyl)acetic acid (3 mmol, 1 equiv), followed by the addition of TMEDA (1.89 mmol, 0.63 equiv), DBU (12 mmol, 4 equiv), and then a solution of aldehyde **55** (3 mmol, 1 equiv) in THF (2 mL). The solution was stirred at 23 ºC for 18 h, and the reaction was diluted with 1 M HCl and extracted with dichloromethane (4x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

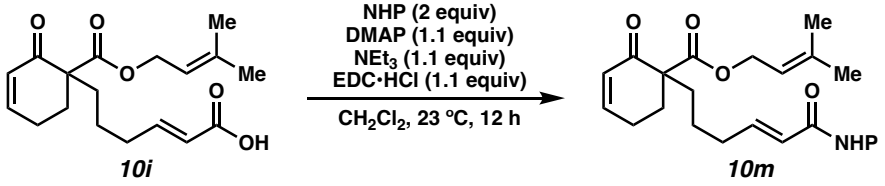
Purification by silica gel flash column chromatography (35% EtOAc/hexanes with 3% AcOH) afforded the title compound as a white solid (137.4 mg, 0.43 mmol, 43% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (dt, *J* = 15.7, 6.8 Hz, 1H), 6.93 – 6.84 (m, 1H), 6.03 (ddd, *J* = 10.2, 2.6, 1.5 Hz, 1H), 5.83 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.28 (tp, *J* = 7.2, 1.4 Hz, 1H), 4.66 – 4.53 (m, 2H), 2.58 – 2.40 (m, 2H), 2.37 – 2.28 (m, 1H), 2.25 (qd, *J* = 7.3, 1.6 Hz, 2H), 1.98 – 1.87 (m, 2H), 1.80 – 1.68 (m, 1H), 1.73 (s, 3H), 1.68 (s, 3H), 1.61 – 1.37 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 171.6, 170.2, 151.4, 149.3, 139.7, 129.4, 120.8, 118.3, 62.4, 57.0, 33.5, 32.7, 30.5, 25.8, 23.9, 23.1, 18.2.

IR (Neat Film, NaCl): 2929, 1725, 1694, 1424, 1384, 1236, 1171 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{18}H_{24}O_5$ $[M]^+$: 320.1624, found 320.1636.



3-methylbut-2-en-1-yl (*E*)-1-(6-((1,3-dioxoisoindolin-2-yl)oxy)-6-oxohex-4-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (10m)[34]

To a round bottom flask was added crude acid **10i** (assumed quantitative yield from previous reaction, 1 mmol, 1 equiv), DMAP (1.1 mmol, 1.1 equiv), NHP (2 mmol, 2 equiv), dichloromethane (9.5 mL), and triethylamine (1.1 mmol, 1.1 equiv). EDC•HCl (1.1 mmol, 1.1 equiv) was then added under N_2 atmosphere in a single portion, and the reaction was stirred vigorously at 23 ºC for 12 h. The reaction mixture was diluted with dichloromethane and washed with 0.5 N HCl, saturated aqueous $NaHCO_3$, and brine. The combined organic

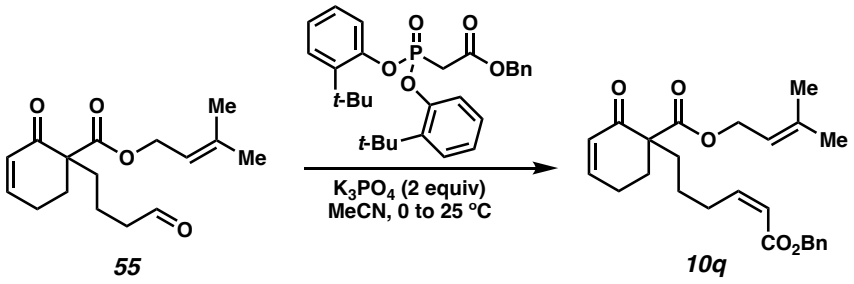
layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (30–35% EtOAc/hexanes) afforded the title compound as a colorless oil (109.6 mg, 0.48 mmol, 24% yield over two steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 – 7.84 (m, 2H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.30 (dd, *J* = 15.8, 6.7 Hz, 1H), 6.89 (dddd, *J* = 10.1, 4.9, 3.0, 1.1 Hz, 1H), 6.10 (dt, *J* = 15.8, 1.6 Hz, 1H), 6.04 (ddd, *J* = 10.1, 2.5, 1.5 Hz, 1H), 5.29 (tdt, *J* = 5.7, 2.8, 1.4 Hz, 1H), 4.67 – 4.55 (m, 2H), 2.58 – 2.40 (m, 2H), 2.35 (m, 3H), 2.03 – 1.89 (m, 2H), 1.87 – 1.74 (m, 1H), 1.74 (s, 3H), 1.69 (d, *J* = 1.3 Hz, 3H), 1.66 – 1.45 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 162.4, 162.2, 155.2, 149.3, 139.8, 134.8, 129.4, 129.1, 124.1, 118.3, 116.0, 62.4, 57.0, 33.5, 33.3, 30.6, 25.9, 23.9, 23.0, 18.3.

IR (Neat Film, NaCl): 1771, 1744, 1682, 1185 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{26}H_{27}NO_7$ $[M]^+$: 465.1788, found 465.1779.



3-methylbut-2-en-1-yl (*Z*)-1-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (10q)

To a solution of benzyl 2-(bis(2-(*tert*-butyl)phenoxy)phosphoryl)acetate[35] (890 mg, 1.80 mmol, 1.00 equiv) in MeCN (18 mL, 0.1 M) was added K_2CO_3 (783 mg, 3.69 mmol, 2.05 equiv). The reaction was cooled to 0 ºC and a solution of **55** (500 mg, 1.80 mmol, 1.00 equiv) in MeCN (18 mL, 0.1 M) was dropwise added. The reaction was gradually warmed

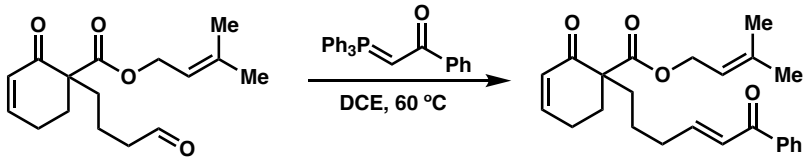
to 25 ºC and stirring was continued until consumption of **55** as determined by TLC (around 16 h). The reaction mixture was filtered through a plug of Celite® to remove solids and volatiles were removed in vacuo. Purification by flash column chromatography (0–40% EtOAc/hexanes) afforded the title compound as a colorless oil (482 mg, 1.17 mmol, 65 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.29 (m, 5H), 6.90 – 6.84 (m, 1H), 6.24 (dt, *J* = 11.5, 7.4 Hz, 1H), 6.01 (ddd, *J* = 10.1, 2.5, 1.6 Hz, 1H), 5.83 (dt, *J* = 11.5, 1.7 Hz, 1H), 5.28 (ddp, *J* = 8.6, 5.7, 1.4 Hz, 1H), 5.15 (s, 2H), 4.59 (d, *J* = 7.2 Hz, 2H), 2.68 (qd, *J* = 7.4, 1.8 Hz, 2H), 2.53 – 2.41 (m, 2H), 2.35 – 2.26 (m, 1H), 1.98 – 1.87 (m, 2H), 1.79 – 1.71 (m, 4H), 1.67 (s, 3H), 1.52 – 1.37 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 171.7, 166.2, 150.5, 149.3, 139.5, 136.3, 129.3, 128.7, 128.3, 128.3, 119.9, 118.4, 65.9, 62.3, 57.1, 33.4, 30.3, 29.4, 25.8, 24.2, 23.8, 18.2.

IR (Neat Film, NaCl): 2918, 1714, 1447, 1178, 1161 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{25}H_{30}O_5$ $[M]^+$: 410.2093, found 410.2108.



55 ***10j***

3-methylbut-2-en-1-yl (*E*)-2-oxo-1-(6-oxo-6-phenylhex-4-en-1-yl)cyclohex-3-ene-1-carboxylate (10j)

(2-oxo-2-phenylethyl)triphenylphosphonium bromide[36] (996 mg, 2.16 mmol, 1.2 equiv) was stirred in 26 mL of a 3:2 CH_2Cl_2/2 M aq. NaOH mixture for 30 minutes at 23 ºC. The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The

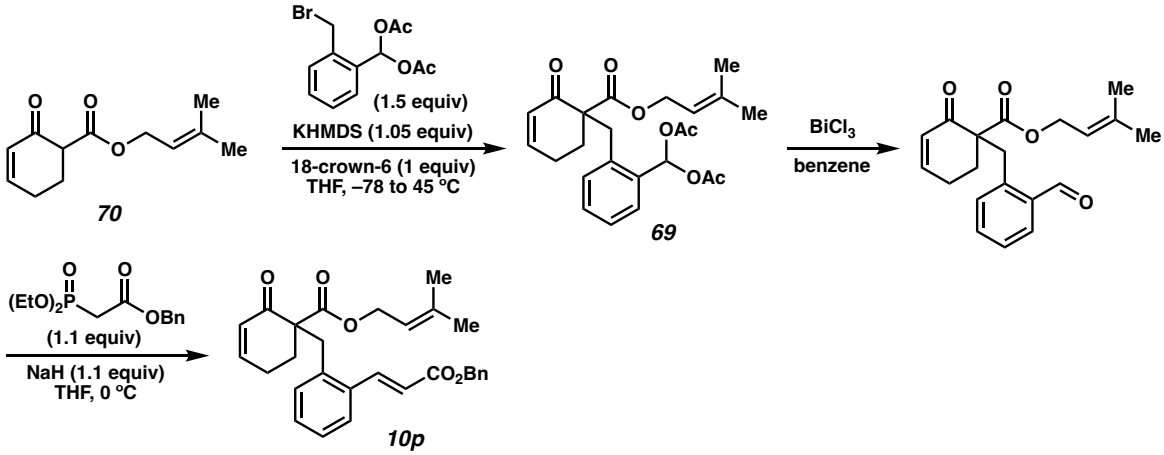
combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and solvent was removed in vacuo. To a solution of this crude ylide in DCE (22 mL, 0.1 M) was added aldehyde **55** (500 mg, 1.80 mmol, 1 equiv). The reaction was stirred at 65 ºC for 36 hours. Upon complete consumption of **55**, as determined by TLC, volatiles were removed in vacuo. Purification by flash column chromatography (30% EtOAc/hexanes) afforded the title compound as a colorless oil (330 mg, 0.867 mmol, 48% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 – 7.90 (m, 2H), 7.60 – 7.51 (m, 1H), 7.46 (tt, *J* = 6.8, 1.5 Hz, 2H), 7.02 (dt, *J* = 15.4, 6.7 Hz, 1H), 6.93 – 6.85 (m, 2H), 6.03 (ddd, *J* = 10.2, 2.6, 1.5 Hz, 1H), 5.30 – 5.25 (m, 1H), 4.59 (d, *J* = 7.1 Hz, 2H), 2.55 – 2.43 (m, 2H), 2.38 – 2.27 (m, 3H), 2.01 – 1.91 (m, 2H), 1.80 (ddd, *J* = 13.6, 12.0, 4.7 Hz, 1H), 1.72 (s, 3H), 1.67 (s, 3H), 1.63 – 1.47 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 191.0, 171.6, 149.3, 149.1, 139.7, 138.1, 132.8, 129.4, 128.7, 128.7, 126.4, 118.3, 62.4, 57.0, 33.6, 33.2, 30.5, 25.8, 23.9, 23.4, 18.2.

IR (Neat Film, NaCl): 2931, 1724, 1671, 1619, 1447, 1229, 1177 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{24}H_{28}O_4$ $[M]^+$: 380.1988, found 380.1982.



(2-((1-(((3-methylbut-2-en-1-yl)oxy)carbonyl)-2-oxocyclohex-3-en-1-yl)methyl)phenyl)methylene diacetate (69)

An oven dried round bottom flask was charged with KHMDS (837 mg, 4.20 mmol, 1.05 equiv), 18-crown-6 (1.06 g, 4.00 mmol, 1.0 equiv), and THF (21 mL). The mixture was cooled to –78 ºC and a solution of enone **70** (830 mg, 4.00 mmol, 1.0 equiv) in THF (10 mL) was added. The reaction mixture was stirred for 15 minutes then (2-(bromomethyl)phenyl)methylene diacetate[37] (1.86 g, 6.00 mmol, 1.5 equiv) was added in a minimal amount of THF (*ca* 5 mL). The solution was slowly warmed to 45 ºC and stirred for 14 h. Upon complete consumption of starting material (as determined by TLC), the solution was cooled to 23 ºC, diluted with a saturated aqueous solution of NH_4Cl, and the reaction mixture was extracted thrice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (20–60% EtOAc/hexanes) afforded the title compound as a colorless oil (1.00 g, 2.33 mmol, 58% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.58 – 7.52 (m, 1H), 7.30 – 7.24 (m, 2H), 7.21 – 7.16 (m, 1H), 6.88 – 6.82 (m, 1H), 6.07 (ddd, *J* = 10.1, 2.8, 1.3 Hz, 1H), 5.24 (ddq, *J* = 8.6, 5.7, 1.4 Hz, 1H), 4.56 (d, *J* = 7.2 Hz, 2H), 3.52 (d, *J* = 14.8 Hz, 1H), 3.45 (d, *J* = 14.8 Hz, 1H), 2.53 – 2.41 (m, 1H), 2.36 (dddd, *J* = 13.6, 4.9, 2.6, 1.3 Hz, 1H), 2.29 – 2.19 (m, 1H), 2.12 (s, 3H), 2.10 (s, 3H), 1.86 (ddd, *J* = 13.6, 10.4, 5.3 Hz, 1H), 1.73 (s, 3H), 1.67 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.4, 171.1, 168.8, 168.8, 149.6, 139.7, 135.5, 134.9, 131.5, 129.6, 129.5, 127.6, 127.2, 118.2, 88.4, 62.5, 58.2, 34.2, 30.2, 25.9, 24.1, 21.0, 21.0, 18.2.

IR (Neat Film, NaCl): 2935, 1759, 1731, 1682, 1447, 1371, 1236, 1206 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{24}H_{28}O_7$ $[M]^+$: 428.1835, found 428.1833.

3-methylbut-2-en-1-yl (*E*)-1-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-2-oxocyclohept-3-ene-1-carboxylate (10p)

To a solution of diacetate **69** (500 mg, 1.17 mmol, 1 equiv) in benzene (11.7 mL, 0.1 M) was added bismuth chloride (38 mg, 0.12 mmol, 0.1 equiv). The reaction mixture was heated to 35 ºC for 3 hours. Upon cooling to 25 ºC, the reaction mixture was diluted with water and the layers were separated. The aqueous layer was extracted twice with chloroform. The combined organic layers were washed with brine, dried over Na_2SO_4, and volatiles were removed in vacuo. The crude aldehyde was used directly in the subsequent Horner–Wadsworth–Emmons olefination.

To a suspension of NaH (52 mg, 1.29 mmol, 60% by weight in mineral oil, 1.1 equiv) in THF (2.6 mL, 0.5 M) at 0 ºC was dropwise added a solution of benzyl 2-(diethoxyphosphoryl)acetate[28] (369 mg, 1.29 mmol, 1.1 equiv) in THF (1.3 mL, 1.0 M). Stirring at 0 ºC was continued for 30 minutes. To the reaction was then dropwise added a solution of the crude aldehyde in THF (2.4 mL, 0.5 M). Upon complete consumption of starting material (as determined by TLC), the reaction mixture was diluted with a saturated solution of $NaHCO_3$ and extracted with EtOAc (3x). The combined organic layers were

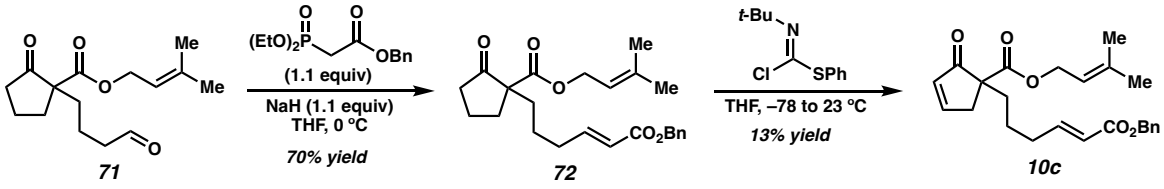
dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (5–40% EtOAc/hexanes) afforded the title compound as a colorless oil (230 mg, 0.502 mmol, 43% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 15.7 Hz, 1H), 7.57 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.44 – 7.31 (m, 5H), 7.27 – 7.17 (m, 3H), 6.85 – 6.80 (m, 1H), 6.40 (d, *J* = 15.7 Hz, 1H), 6.06 (ddd, *J* = 10.1, 2.9, 1.2 Hz, 1H), 5.28 – 5.21 (m, 3H), 4.56 – 4.49 (m, 2H), 3.57 (d, *J* = 14.3 Hz, 1H), 3.31 (d, *J* = 14.4 Hz, 1H), 2.51 – 2.39 (m, 1H), 2.30 – 2.16 (m, 2H), 1.82 – 1.70 (m, 4H), 1.65 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.1, 170.4, 166.7, 149.7, 143.2, 139.7, 136.7, 136.2, 134.7, 132.1, 130.0, 129.3, 128.7, 128.4, 128.3, 127.5, 126.8, 119.4, 118.2, 66.5, 62.5, 58.4, 35.4, 30.2, 25.9, 24.1, 18.2.

IR (Neat Film, NaCl): 3028, 2927, 1720, 1686, 1629, 1168 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{29}H_{30}O_5$ $[M]^+$: 458.2088, found 458.2086.



3-methylbut-2-en-1-yl (*E*)-1-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-2-oxocyclopentane-1-carboxylate (72)

Prepared from **71** and benzyl 2-(diethoxyphosphoryl)acetate[28] following General Procedure B. Purification by flash column chromatography (15% EtOAc/hexanes) afforded the title compound as a colorless oil (1.40 g, 3.51 mmol, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (dt, *J* = 5.6, 2.7 Hz, 1H), 7.42 – 7.26 (m, 5H), 6.95 (dt, *J* = 15.6, 6.9 Hz, 1H), 6.16 (dt, *J* = 5.8, 2.2 Hz, 1H), 5.85 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.27 (tdq, *J* = 7.2, 2.9, 1.5 Hz, 1H), 5.16 (s, 2H), 4.59 (d, *J* = 7.1 Hz, 2H), 3.33 – 3.19 (m, 1H), 2.68 – 2.51 (m, 1H), 2.21 (qd, *J* = 7.3, 1.6 Hz, 2H), 1.99 (ddd, *J* = 13.7, 12.3, 4.5 Hz, 1H), 1.82 – 1.70 (m, 1H), 1.73 (s, 3H), 1.67 (s, 3H), 1.53 – 1.23 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.7, 170.6, 166.4, 163.9, 148.9, 139.6, 136.2, 132.4, 128.7, 128.4, 128.3, 121.7, 118.3, 66.2, 62.7, 58.0, 39.5, 34.0, 32.4, 25.9, 23.2, 18.2.

IR (Neat Film, NaCl): 2932, 2356, 1715, 1263, 1164, 976, 754 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{24}H_{28}O_5$ $[M]^+$: 396.1920, found 396.1931.

3-methylbut-2-en-1-yl (*E*)-1-(6-(benzyloxy)-6-oxohex-4-en-1-yl)-2-oxocyclopent-3-ene-1-carboxylate (10c)

A flame dried round bottom flask was charged with *i*-Pr_2NH (0.35 mL, 2.5 mmol, 1.25 equiv) and THF (8.0 mL, 0.25 M). The solution was cooled to –78 ºC and *n*-BuLi (0.96 mL, 2.4 mmol, 1.2 equiv) was added dropwise and the resultant solution was stirred for 30 min. Ketoester **72** (797 mg, 2.00 mmol, 1.0 equiv) in THF (8.0 mL, 0.25 M) was added dropwise and the mixture was stirred for 1 h. *N-tert*-Butylbenzenesulfinimidoyl chloride[38] (560.9 mg, 2.6 mmol, 1.3 equiv) in THF (4.0 mL, 0.5 M) was added dropwise and the solution was slowly warmed to 23 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution and extracted with Et_2O (25 mL x 3). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was

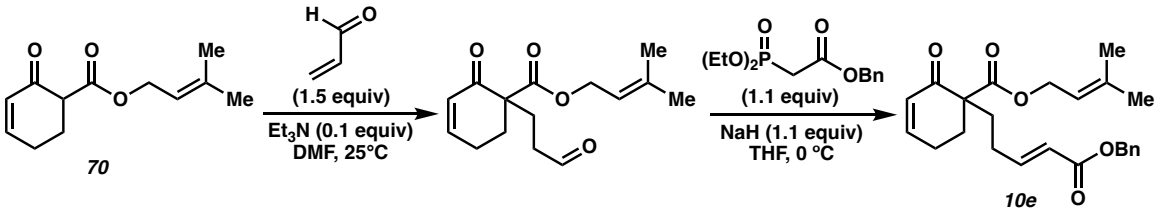
purified by column chromatography (SiO_2, 0–40% EtOAc/Hexanes) to afford enone **10b** as a colorless oil (100 mg, 0.25 mmol, 13% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (dt, *J* = 5.6, 2.7 Hz, 1H), 7.42 – 7.26 (m, 5H), 6.95 (dt, *J* = 15.6, 6.9 Hz, 1H), 6.16 (dt, *J* = 5.8, 2.2 Hz, 1H), 5.85 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.27 (tdq, *J* = 7.2, 2.9, 1.5 Hz, 1H), 5.16 (s, 2H), 4.59 (d, *J* = 7.1 Hz, 2H), 3.33 – 3.19 (m, 1H), 2.68 – 2.51 (m, 1H), 2.21 (qd, *J* = 7.3, 1.6 Hz, 2H), 1.99 (ddd, *J* = 13.7, 12.3, 4.5 Hz, 1H), 1.82 – 1.70 (m, 1H), 1.73 (s, 3H), 1.67 (s, 3H), 1.53 – 1.23 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.7, 170.6, 166.4, 163.9, 148.9, 139.6, 136.2, 132.4, 128.7, 128.4, 128.3, 121.7, 118.3, 66.2, 62.7, 58.0, 39.5, 34.0, 32.4, 25.9, 23.2, 18.2.

IR (Neat Film, NaCl): 2932, 2356, 1715, 1263, 1164, 976, 754 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{24}H_{28}O_5$ $[M]^+$: 396.1920, found 396.1931.



3-methylbut-2-en-1-yl (*E*)-1-(5-(benzyloxy)-5-oxopent-3-en-1-yl)-2-oxocyclohex-3-ene-1-carboxylate (10e)

To a solution of enone **70** (1.04 g, 5.00 mmol, 1.0 equiv) in DMF (10 mL, 0.5 M) at 25°C was added dropwise triethylamine (0.07 mL, 0.50 mmol, 0.1 equiv) followed by acrolein (0.50 mL, 7.50 mmol, 1.5 equiv). Upon consumption of starting material (as determined by TLC), the reaction mixture was diluted with water and extracted thrice with diethyl ether. The combined organic layers were washed with water followed by brine, dried over Na_2SO_4, and volatiles were removed in vacuo. The crude aldehyde was used directly in the

subsequent Horner–Wadsworth–Emmons olefination. To a suspension of NaH (132 mg, 3.30 mmol, 60% by weight in mineral oil, 1.1 equiv) in THF (6 mL, 0.5 M) at 0 ºC was dropwise added a solution of benzyl 2-(diethoxyphosphoryl)acetate (945 mg, 3.30 mmol, 1.1 equiv) in THF (3.0 mL, 1.0 M). Stirred at 0 ºC was continued for 30 minutes. To the reaction was then dropwise added a solution of the crude aldehyde in THF (6.0 mL, 0.5 M). Upon complete consumption of starting material (as determined by TLC), the reaction mixture was diluted with a saturated solution of $NaHCO_3$ and extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (10–20% EtOAc/hexanes) afforded the title compound as a colorless oil (490 mg, 1.24 mmol, 41% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.29 (m, 5H), 6.99 (dt, *J* = 15.7, 6.8 Hz, 1H), 6.93 – 6.84 (m, 1H), 6.03 (ddd, *J* = 10.1, 2.5, 1.5 Hz, 1H), 5.88 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.27 (ddt, *J* = 7.2, 5.8, 1.4 Hz, 1H), 5.17 (s, 2H), 4.59 (d, *J* = 7.1 Hz, 2H), 2.56 – 2.41 (m, 2H), 2.38 – 2.13 (m, 3H), 2.08 – 1.81 (m, 3H), 1.73 (s, 3H), 1.67 (s, 3H).

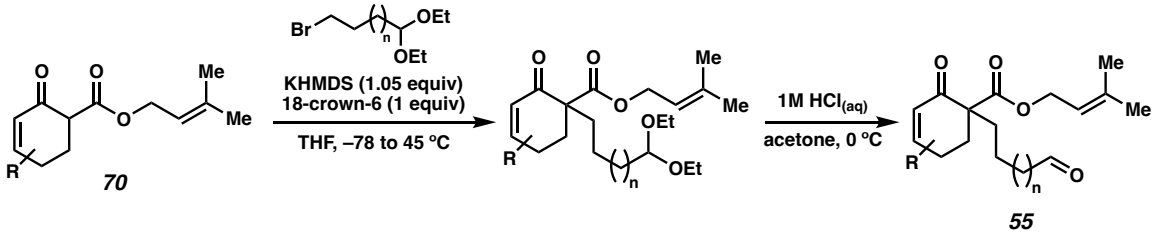
^{13}C NMR (100 MHz, $CDCl_3$): δ 196.0, 171.4, 166.4, 149.3, 148.9, 139.9, 136.2, 129.4, 128.7, 128.3, 121.5, 118.2, 66.2, 62.4, 56.6, 32.2, 30.7, 27.6, 25.8, 23.8, 18.2.

IR (Neat Film, NaCl): 3032, 2934, 1737, 1681, 1445, 1384, 1265, 1175, 1137 cm^{-1}.

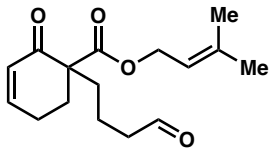
HRMS (MM: FD+): *m/z* calc'd for $C_{24}H_{28}O_5$ $[M]^+$: 396.1937, found 396.1926.

Preparation of Aldehyde Precursors

General Procedure C: Alkylation of β-Ketoesters



An oven dried round bottom flask was charged with KHMDS (1.05 equiv), 18-crown-6 (1.0 equiv), and THF (0.2 M with respect to KHMDS). The mixture was cooled to –78 ºC and a solution of acyclated enone **70** (1.0 equiv) in THF (0.4 M) was added. The reaction mixture was stirred for 15 minutes and then the appropriate alkyl bromide (1.5 equiv) was added neat dropwise. The solution was slowly warmed to 45 ºC and stirred for 14 h. Upon complete consumption of starting material (as determined by TLC), the solution was cooled to 23 ºC, diluted with a saturated aqueous solution of NH_4Cl and the reaction mixture was extracted thrice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude diethyl acetal which was used directly in the next step. A round bottom flask was charged with the crude acetal and acetone (0.5 M), then cooled to 0 ºC. Aqueous 1 M HCl (1:1 volume with respect to acetone) was added and stirring was continued for 1 h. Upon complete consumption of starting material (as determined by TLC), the reaction mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography to afford the respective aldehyde product (**55**).



55

3-methylbut-2-en-1-yl 2-oxo-1-(4-oxobutyl)cyclohex-3-ene-1-carboxylate (55)

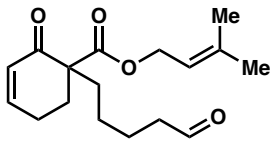
Prepared from **70** and 4-bromo-1,1-diethoxybutane[39] following General Procedure C. Purification by flash column chromatography (25% EtOAc/hexanes) afforded the title compound as a colorless oil (1.81 g, 6.50 mmol, 49% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (t, *J* = 1.5 Hz, 1H), 6.89 (dddd, *J* = 10.1, 4.4, 3.1, 1.1 Hz, 1H), 6.02 (ddd, *J* = 10.1, 2.5, 1.6 Hz, 1H), 5.31 – 5.25 (m, 1H), 4.59 (d, *J* = 6.8 Hz, 2H), 2.55 – 2.43 (m, 4H), 2.39 – 2.30 (m, 1H), 2.02 – 1.94 (m, 1H), 1.89 (ddd, *J* = 12.5, 11.7, 4.5 Hz, 1H), 1.78 (dd, *J* = 11.6, 4.9 Hz, 1H), 1.73 (s, 3H), 1.71 – 1.59 (m, 5H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.2, 196.2, 171.5, 149.5, 139.7, 129.3, 118.3, 62.4, 57.0, 44.2, 33.2, 30.3, 25.8, 23.8, 18.2, 17.5.

IR (Neat Film, NaCl): 2942, 1732, 1716, 1456, 1180 cm^{-1}

HRMS (MM: FD+): *m/z* calc'd for $C_{16}H_{22}O_4$ $[M]^+$: 278.1518, found 278.1509.



56

3-methylbut-2-en-1-yl 2-oxo-1-(5-oxopentyl)cyclohex-3-ene-1-carboxylate (56)

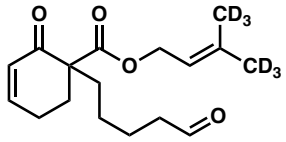
Prepared from **70** and 5-bromo-1,1-diethoxypentane[39] following General Procedure C. Purification by flash column chromatography (10–25% EtOAc/hexanes) afforded the title compound as a colorless oil (648 mg, 2.22 mmol, 38% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 6.91 – 6.84 (m, 1H), 6.01 (ddd, *J* = 10.1, 2.6, 1.6 Hz, 1H), 5.27 (tdq, *J* = 7.1, 2.8, 1.4 Hz, 1H), 4.58 (d, *J* = 7.1 Hz, 2H), 2.54 – 2.40 (m, 4H), 2.36 – 2.27 (m, 1H), 1.98 – 1.86 (m, 2H), 1.78 – 1.60 (m, 10H), 1.40 – 1.26 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.6, 196.4, 171.7, 149.4, 139.6, 129.3, 118.3, 62.3, 57.0, 43.7, 33.6, 30.4, 25.8, 24.3, 23.8, 22.5, 18.2.

IR (Neat Film, NaCl): 2941, 1733, 1717, 1456, 1219 cm^{-1}

HRMS (MM: FD+): *m/z* calc'd for $C_{16}H_{22}O_4$ $[M]^+$: 293.1747, found 293.1768.



D-56

3-(methyl-*d*$_3$)but-2-en-1-yl-4,4,4-*d*$_3$ 2-oxo-1-(5-oxopentyl)cyclohex-3-ene-1-carboxylate (*D*-56)

Prepared from ***D*-70** and 5-bromo-1,1-diethoxypentane[39] following General Procedure C. Purification by flash column chromatography (10–25% EtOAc/hexanes) afforded the title compound as a colorless oil (290 mg, 0.971 mmol, 42% yield).

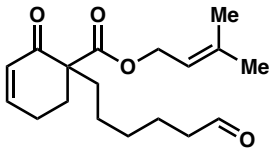
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (t, *J* = 1.7 Hz, 1H), 6.90 – 6.85 (m, 1H), 6.01 (ddd, *J* = 10.1, 2.6, 1.6 Hz, 1H), 5.27 (t, *J* = 7.2 Hz, 1H), 4.58 (dd, *J* = 7.2, 1.8 Hz, 2H), 2.55 – 2.41 (m, 4H), 2.36 – 2.26 (m, 1H), 1.97 – 1.86 (m, 2H), 1.74 (ddd, *J* = 13.6, 11.6, 5.1 Hz, 1H), 1.68 – 1.60 (m, 2H), 1.40 – 1.24 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.6, 196.4, 171.7, 149.4, 139.4, 129.3, 118.4, 62.3, 57.0, 43.7, 33.6, 30.4, 24.3, 23.9, 22.5.

^{2}H NMR (61 MHz, $CHCl_3$): δ 1.69, 1.65.

IR (Neat Film, NaCl): 2941, 1726, 1682, 1238, 1186 cm^{-1}

HRMS (MM: FD+): *m/z* calc'd for $C_{17}H_{18}D_6O_4$ $[M]^+$: 298.2051, found 298.2052.



57

3-methylbut-2-en-1-yl 2-oxo-1-(6-oxohexyl)cyclohex-3-ene-1-carboxylate (57)

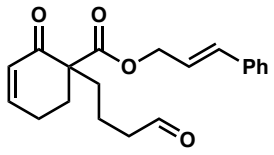
Prepared from **70** and 6-bromo-1,1-diethoxyhexane[39] following General Procedure C. Purification by flash column chromatography (10–25% EtOAc/hexanes) afforded the title compound as a colorless oil (838 mg, 2.73 mmol, 32% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (t, *J* = 1.8 Hz, 1H), 6.90 – 6.85 (m, 1H), 6.01 (ddd, *J* = 10.0, 2.5, 1.5 Hz, 1H), 5.30 – 5.25 (m, 1H), 4.62 – 4.55 (m, 2H), 2.54 – 2.39 (m, 4H), 2.36 – 2.27 (m, 1H), 1.98 – 1.84 (m, 2H), 1.73 (t, *J* = 1.2 Hz, 4H), 1.69 – 1.59 (m, 5H), 1.39 – 1.24 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.8, 196.5, 171.7, 149.3, 139.5, 129.4, 118.4, 62.3, 57.1, 43.9, 33.6, 30.3, 29.6, 25.8, 24.4, 23.9, 21.9, 18.2.

IR (Neat Film, NaCl): 2934, 2864, 1733, 1717, 1684, 1456, 1220 cm^{-1}

HRMS (MM: FD+): *m/z* calc'd for $C_{18}H_{26}O_4$ $[M]^+$: 306.1831, found 306.1854.



63

cinnamyl 2-oxo-1-(4-oxobutyl)cyclohex-3-ene-1-carboxylate (63)

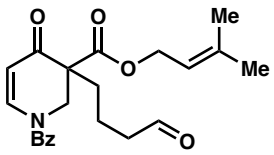
Prepared from **73** and 4-bromo-1,1-diethoxybutane[39] following General Procedure C. Purification by flash column chromatography (10–25% EtOAc/hexanes) afforded the title compound as a colorless oil (0.607 g, 1.86 mmol, 49% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (t, *J* = 1.5 Hz, 1H), 7.38 – 7.35 (m, 2H), 7.35 – 7.30 (m, 2H), 7.28 – 7.24 (m, 1H), 6.91 (dddd, *J* = 10.1, 4.3, 3.1, 1.1 Hz, 1H), 6.63 (dt, *J* = 16.0, 1.4 Hz, 1H), 6.23 (dt, *J* = 15.8, 6.4 Hz, 1H), 6.05 (ddd, *J* = 10.1, 2.4, 1.7 Hz, 1H), 4.77 (dt, *J* = 6.5, 1.1 Hz, 2H), 2.57 – 2.45 (m, 4H), 2.42 – 2.32 (m, 1H), 2.05 – 1.98 (m, 1H), 1.93 (ddd, *J* = 13.2, 11.7, 5.1 Hz, 1H), 1.80 (ddd, *J* = 13.2, 11.1, 5.5 Hz, 1H), 1.73 – 1.63 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.1, 196.0, 171.3, 149.7, 136.2, 134.7, 129.2, 128.8, 128.3, 126.8, 122.7, 66.0, 57.1, 44.1, 33.3, 30.1, 23.8, 17.5.

IR (Neat Film, NaCl): 2941, 1732, 1717, 1700, 1181, 734, 701 cm^{-1}

HRMS (MM: FD+): *m/z* calc'd for $C_{20}H_{22}O_4$ $[M]^+$: 326.1513, found 326.1510.



58

1-benzyl 3-(3-methylbut-2-en-1-yl) 4-oxo-3-(4-oxobutyl)-3,4-dihydropyridine-1,3(2*H*)-dicarboxylate (58)

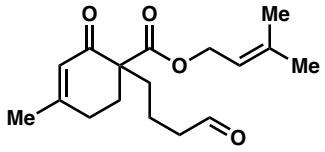
Prepared from **74** and 4-bromo-1,1-diethoxybutane[39] following General Procedure C. Purification by flash column chromatography (15–30% EtOAc/hexanes) afforded the title compound as a colorless oil (603.9 mg, 1.46 mmol, 60% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (t, *J* = 1.4 Hz, 1H), 7.80 (s, 1H), 7.40 (d, *J* = 3.5 Hz, 5H), 5.27 (m, 4H), 4.61 (m, 3H), 3.78 (d, *J* = 13.6 Hz, 1H), 2.45 (tt, *J* = 6.8, 1.7 Hz, 2H), 2.03 – 1.90 (m, 1H), 1.72 (s, 3H), 1.67 (s, 3H), 1.70 – 1.60 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.6, 190.5, 169.4, 142.7, 140.1, 135.0, 129.0, 128.9, 128.6, 118.0, 106.5, 69.4, 62.8, 55.4, 48.2, 43.9, 31.1, 25.8, 18.2, 17.2.

IR (Neat Film, NaCl): 2945, 2338, 1727, 1670, 1604, 1389, 1302, 1201, 932 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{23}H_{27}NO_6$ $[M]^+$: 413.1838, found 413.1852.



59

3-methylbut-2-en-1-yl 4-methyl-2-oxo-1-(4-oxobutyl)cyclohex-3-ene-1-carboxylate (59)

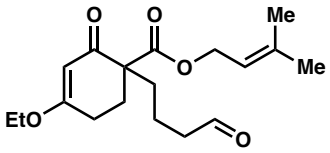
Prepared from **75** and 4-bromo-1,1-diethoxybutane[39] following General Procedure C. Purification by flash column chromatography (25–50% EtOAc/hexanes) afforded the title compound as a colorless oil (1141.4 mg, 3.90 mmol, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 5.87 (dt, *J* = 2.6, 1.2 Hz, 1H), 5.27 (tp, *J* = 7.1, 1.4 Hz, 1H), 4.58 (d, *J* = 7.2 Hz, 2H), 2.45 (ddd, *J* = 8.0, 4.8, 1.7 Hz, 4H), 2.29 – 2.18 (m, 1H), 1.92 (s, 3H), 2.00 – 1.84 (m, 2H), 1.72 (s, 3H), 1.67 (s, 3H), 1.79 – 1.54 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.2, 195.9, 171.7, 161.6, 139.6, 126.0, 118.3, 62.3, 56.0, 44.2, 33.2, 30.0, 28.7, 25.8, 24.2, 18.2, 17.5.

IR (Neat Film, NaCl): 3426, 2936, 2730, 1725, 1672, 1637, 1440, 1380, 1348, 1311, 1272, 1233, 1214, 1177, 1104, 1050, 1016, 986, 939, 870, 842, 820, 776 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{17}H_{24}O_4$ $[M]^+$: 292.1682, found 292.1669.



60

3-methylbut-2-en-1-yl 4-ethoxy-2-oxo-1-(4-oxobutyl)cyclohex-3-ene-1-carboxylate (60)

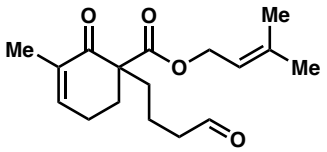
Prepared from **76** and 4-bromo-1,1-diethoxybutane[39] following General Procedure C. Purification by flash column chromatography (30–40% EtOAc/hexanes) afforded the title compound as a colorless oil (653.2 mg, 2.03 mmol, 21% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (t, *J* = 1.5 Hz, 1H), 5.34 (d, *J* = 1.1 Hz, 1H), 5.29 (tp, *J* = 7.2, 1.4 Hz, 1H), 4.66 – 4.53 (m, 2H), 3.86 (q, *J* = 7.18, 2H), 2.61 (dddd, *J* = 17.8, 10.3, 4.7, 1.3 Hz, 1H), 2.50 – 2.30 (m, 4H), 2.02 – 1.87 (m, 2H), 1.82 – 1.73 (m, 1H), 1.72 (s, 3H), 1.68 (s, 3H), 1.67 – 1.58 (m, 2H), 1.35 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.9, 195.5, 176.5, 171.5, 139.1, 118.1, 101.9, 64.3, 62.0, 55.7, 43.9, 33.1, 28.2, 26.3, 25.5, 17.9, 17.2, 13.9.

IR (Neat Film, NaCl): 2939, 2728, 1723, 1659, 1608, 1447, 1380, 1315, 1242, 1179, 1108, 1027, 942, 816, 769 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{18}H_{26}O_5$ $[M]^+$: 322.1790, found 322.1775.



61

3-methylbut-2-en-1-yl 3-methyl-2-oxo-1-(4-oxobutyl)cyclohex-3-ene-1-carboxylate (61)

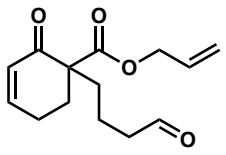
Prepared from **77** and 4-bromo-1,1-diethoxybutane[39] following General Procedure C. Purification by flash column chromatography (15–20% EtOAc/hexanes) afforded the title compound as a colorless oil (1.14 g, 3.90 mmol, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 6.64 – 6.57 (m, 1H), 5.27 (tt, *J* = 7.1, 1.4 Hz, 1H), 4.64 – 4.51 (m, 2H), 2.51 – 2.36 (m, 4H), 2.36 – 2.22 (m, 1H), 2.01 – 1.92 (m, 1H), 1.87 (m, 1H), 1.83-1.53 (m, 3H) 1.78 (s, 3H), 1.73 (s, 3H), 1.67 (d, *J* = 1.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.2, 196.9, 171.9, 143.9, 139.6, 135.3, 118.3, 62.2, 57.0, 44.2, 33.3, 30.7, 25.8, 23.5, 18.2, 17.7, 16.6.

IR (Neat Film, NaCl): 3500, 2925, 2333, 1725, 1681, 1449, 1361, 1182 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{17}H_{24}O_4$ $[M]^+$: 292.1680, found 292.1669.



62

allyl 2-oxo-1-(4-oxobutyl)cyclohex-3-ene-1-carboxylate (62)

Prepared from allyl 2-oxocyclohex-3-ene-1-carboxylate [40] and 4-bromo-1,1-diethoxybutane[39] following General Procedure C. Purification by flash column chromatography (15–30% EtOAc/hexanes) afforded the title compound as a colorless oil (773.2 mg, 3.09 mmol, 21% yield).

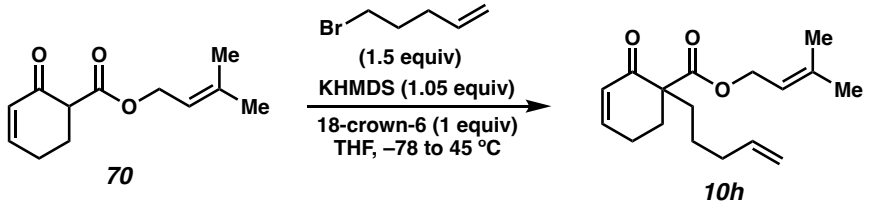
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (t, *J* = 1.4 Hz, 1H), 6.91 (dddd, *J* = 10.1, 4.4, 3.1, 1.1 Hz, 1H), 6.03 (dt, *J* = 10.1, 2.0 Hz, 1H), 5.86 (ddt, *J* = 17.1, 10.2, 5.6 Hz, 1H), 5.28 (dq, *J*

= 17.2, 1.6 Hz, 1H), 5.22 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.60 (dq, *J* = 5.4, 1.6 Hz, 2H), 2.58 – 2.43 (m, 4H), 2.43 – 2.30 (m, 1H), 2.07 – 1.95 (m, 1H), 1.91 (ddd, *J* = 13.2, 11.6, 5.2 Hz, 1H), 1.79 (ddd, *J* = 13.2, 10.9, 5.6 Hz, 1H), 1.75 – 1.56 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.1, 196.0, 171.2, 149.7, 131.7, 129.2, 118.7, 65.9, 57.1, 44.1, 33.1, 30.1, 23.7, 17.4.

IR (Neat Film, NaCl): 2947, 2732, 1726, 1680, 1238, 1184 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{14}H_{19}O_4$ $[M]^+$: 251.1281, found 251.1278.



3-methylbut-2-en-1-yl 2-oxo-1-(pent-4-en-1-yl)cyclohex-3-ene-1-carboxylate (10h)

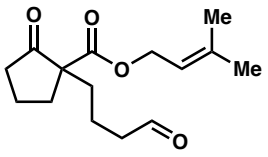
Prepared from **70** and 5-bromopent-1-ene following General Procedure C (without hydrolysis step). Purification by flash column chromatography (0-20% EtOAc/hexanes) afforded the title compound as a colorless oil (93.8 mg, 0.34 mmol, 23% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (dddd, *J* = 10.1, 4.8, 3.1, 1.1 Hz, 1H), 6.01 (ddd, *J* = 10.1, 2.5, 1.6 Hz, 1H), 5.78 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.28 (tdq, *J* = 7.1, 2.9, 1.4 Hz, 1H), 5.00 (dq, *J* = 17.1, 1.6 Hz, 1H), 4.94 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H), 4.59 (dd, *J* = 7.2, 3.7 Hz, 1H), 4.64 – 4.53 (m, 2H), 2.57 – 2.41 (m, 2H), 2.38 – 2.24 (m, 2H), 2.12 – 2.01 (m, 2H), 2.00 – 1.86 (m, 2H), 1.77 – 1.69 (m, 1H), 1.73 (s, 3H), 1.68 (s, 3H), 1.51 – 1.28 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.5, 171.7, 149.3, 139.5, 138.4, 129.4, 118.4, 114.9, 62.2, 57.1, 34.2, 33.4, 30.3, 25.8, 24.0, 23.9, 18.2.

IR (Neat Film, NaCl): 2928, 1726, 1683, 1440, 1383, 1186, 912 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{17}H_{24}O_3$ $[M]^+$: 276.1725, found 276.1718.



71

3-methylbut-2-en-1-yl 2-oxo-1-(4-oxobutyl)cyclopentane-1-carboxylate (71)

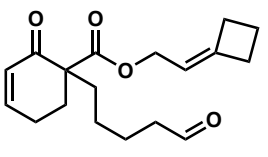
Prepared from 3-methylbut-2-en-1-yl 2-oxocyclopentane-1-carboxylate[41] and 4-bromo-1,1-diethoxybutane[39] following General Procedure C. Purification by flash column chromatography (20–25% EtOAc/hexanes) afforded the title compound as a colorless oil (1.86 g, 6.97 mmol, 87% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (t, *J* = 1.4 Hz, 1H), 5.29 (tp, *J* = 7.3, 1.4 Hz, 1H), 4.59 (d, *J* = 7.2 Hz, 2H), 2.58 – 2.47 (m, 1H), 2.44 (tt, *J* = 7.0, 1.5 Hz, 2H), 2.44 – 2.36 (m, 1H), 2.31 – 2.18 (m, 1H), 2.11 – 1.85 (m, 4H), 1.74 (s, 3H), 1.68 (s, 3H), 1.67 – 1.48 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 214.8, 201.9, 171.0, 139.7, 118.2, 62.5, 60.4, 44.0, 38.0, 33.2, 33.0, 25.9, 19.8, 18.2, 17.6.

IR (Neat Film, NaCl): 3456, 2954, 2724, 1745, 1721, 1446, 1406, 1384, 1154, 953 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{15}H_{22}O_4$ $[M]^+$: 266.1525, found 266.1513.



64

2-cyclobutylideneethyl 2-oxo-1-(5-oxopentyl)cyclohex-3-ene-1-carboxylate (64)

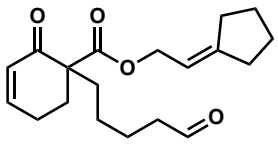
Prepared from **78** and 5-bromo-1,1-diethoxypentane[39] following General Procedure C. Purification by flash column chromatography (10–60% EtOAc/hexanes) afforded the title compound as a colorless oil (649 mg, 2.13 mmol, 29% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (t, *J* = 1.7 Hz, 1H), 6.94 – 6.83 (m, 1H), 6.02 (ddd, *J* = 10.1, 2.6, 1.5 Hz, 1H), 5.20 (tp, *J* = 7.1, 2.3 Hz, 1H), 4.46 (ddt, *J* = 7.4, 2.3, 1.1 Hz, 2H), 2.69 (dt, *J* = 16.0, 8.4 Hz, 4H), 2.56 – 2.40 (m, 4H), 2.37 – 2.26 (m, 1H), 2.03 – 1.84 (m, 4H), 1.75 (ddd, *J* = 13.6, 11.6, 5.1 Hz, 1H), 1.64 (p, *J* = 7.5 Hz, 2H), 1.42 – 1.26 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.6, 196.4, 171.6, 149.4, 148.9, 129.4, 114.0, 62.3, 57.0, 43.7, 33.6, 31.2, 30.4, 29.6, 24.3, 23.9, 22.5, 17.1.

IR (Neat Film, NaCl): 2941, 1726, 1681, 1446, 1387, 1240, 1171, 1103 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{18}H_{24}O_4$ $[M]^+$: 304.1675, found 304.1677.



65

2-cyclopentylideneethyl 2-oxo-1-(5-oxopentyl)cyclohex-3-ene-1-carboxylate (65)

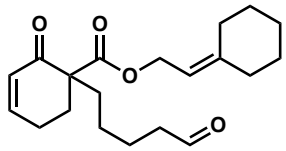
Prepared from **79** and 5-bromo-1,1-diethoxypentane[39] following General Procedure C. Purification by flash column chromatography (10–60% EtOAc/hexanes) afforded the title compound as a colorless oil (1.40 g, 4.40 mmol, 39% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (t, *J* = 1.7 Hz, 3H), 6.92 – 6.83 (m, 1H), 6.02 (ddd, *J* = 10.1, 2.6, 1.6 Hz, 1H), 5.41 – 5.32 (m, 1H), 4.64 – 4.50 (m, 2H), 2.56 – 2.39 (m, 4H), 2.37 – 2.20 (m, 5H), 1.99 – 1.83 (m, 2H), 1.80 – 1.57 (m, 7H), 1.45 – 1.22 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.6, 196.4, 171.7, 151.1, 149.4, 129.4, 113.8, 63.8, 57.0, 43.7, 33.9, 33.6, 30.4, 29.0, 26.4, 26.2, 24.3, 23.9, 22.5.

IR (Neat Film, NaCl): 2947, 2725, 1729, 1697, 1456, 1356, 1215 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{19}H_{26}O_4$ $[M]^+$: 318.1831, found 318.1809.



66

2-cyclohexylideneethyl 2-oxo-1-(5-oxopentyl)cyclohex-3-ene-1-carboxylate (66)

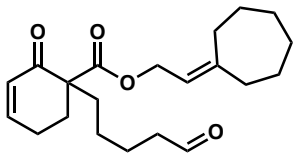
Prepared from **80** and 5-bromo-1,1-diethoxypentane[39] following General Procedure C. Purification by flash column chromatography (10–50% EtOAc/hexanes) afforded the title compound as a colorless oil (177 mg, 0.53 mmol, 25% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (t, *J* = 1.7 Hz, 1H), 6.93 – 6.83 (m, 1H), 6.02 (ddd, *J* = 10.1, 2.6, 1.6 Hz, 1H), 5.23 (tt, *J* = 7.2, 1.2 Hz, 1H), 4.60 (d, *J* = 7.2 Hz, 2H), 2.56 – 2.39 (m, 4H), 2.37 – 2.26 (m, 1H), 2.20 – 2.13 (m, 2H), 2.12 – 2.05 (m, 2H), 1.99 – 1.85 (m, 2H), 1.74 (ddd, *J* = 13.6, 11.7, 5.0 Hz, 1H), 1.64 (p, *J* = 7.5 Hz, 2H), 1.58 – 1.46 (m, 6H), 1.43 – 1.20 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.6, 196.4, 171.6, 149.3, 147.7, 129.4, 114.8, 61.5, 57.0, 43.7, 37.1, 33.6, 30.4, 29.2, 28.5, 27.9, 26.7, 24.3, 23.9, 22.5.

IR (Neat Film, NaCl): 2929, 2858, 1731, 1446, 1170, 938 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{20}H_{28}O_4$ $[M]^+$: 332.1988, found 332.1991.



67

2-cycloheptylideneethyl 2-oxo-1-(5-oxopentyl)cyclohex-3-ene-1-carboxylate (67)

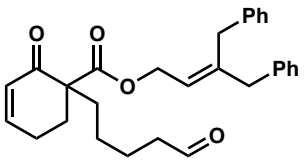
Prepared from **81** and 5-bromo-1,1-diethoxypentane[39] following General Procedure C. Purification by flash column chromatography (10–70% Et_2O/hexanes) afforded the title compound as a colorless oil (349 mg, 1.01 mmol, 15% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (t, *J* = 1.7 Hz, 1H), 6.91 – 6.84 (m, 1H), 6.02 (ddd, *J* = 10.1, 2.6, 1.6 Hz, 1H), 5.28 (tt, *J* = 7.1, 1.3 Hz, 1H), 4.60 (d, *J* = 7.1 Hz, 2H), 2.56 – 2.40 (m, 4H), 2.38 – 2.20 (m, 5H), 1.98 – 1.87 (m, 2H), 1.76 (ddd, *J* = 13.7, 12.0, 4.8 Hz, 1H), 1.65 (p, *J* = 7.5 Hz, 2H), 1.57 (q, *J* = 5.4 Hz, 4H), 1.50 (dt, *J* = 5.2, 2.4 Hz, 4H), 1.42 – 1.27 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.6, 196.4, 171.7, 149.4, 149.0, 129.4, 118.4, 62.1, 57.0, 43.7, 37.7, 33.6, 30.4, 30.2, 29.8, 29.1, 28.9, 27.3, 24.3, 23.9, 22.5.

IR (Neat Film, NaCl): 2923, 2854, 1737, 1681, 1443, 1385, 1235, 1172 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{21}H_{30}O_4$ $[M]^+$: 346.2144, found 346.2139.



68

3-benzyl-4-phenylbut-2-en-1-yl 2-oxo-1-(5-oxopentyl)cyclohex-3-ene-1-carboxylate (68)

Prepared from **82** and 5-bromo-1,1-diethoxypentane[39] following General Procedure C. Purification by flash column chromatography (10–60% Et_2O/hexanes) afforded the title compound as a colorless oil (425 mg, 0.955 mmol, 18% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (t, *J* = 1.7 Hz, 1H), 7.32 – 7.27 (m, 4H), 7.21 (tt, *J* = 7.5, 2.3 Hz, 2H), 7.15 – 7.03 (m, 4H), 6.90 – 6.82 (m, 1H), 6.02 (ddd, *J* = 10.2, 2.5, 1.6 Hz, 1H), 5.51 (d, *J* = 7.4 Hz, 1H), 4.83 – 4.70 (m, 2H), 3.36 (s, 2H), 3.24 (s, 2H), 2.54 – 2.24 (m, 5H), 2.00 – 1.86 (m, 2H), 1.77 (ddd, *J* = 13.6, 11.6, 5.1 Hz, 1H), 1.63 (p, *J* = 7.5 Hz, 2H), 1.44 – 1.22 (m, 2H).

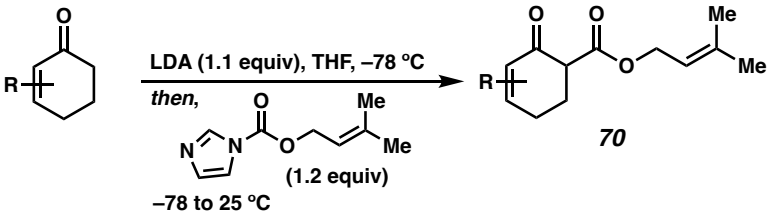
^{13}C NMR (100 MHz, $CDCl_3$): δ 202.5, 196.2, 171.6, 149.4, 144.8, 139.0, 138.8, 129.4, 129.3, 128.8, 128.7, 128.5, 126.5, 126.4, 121.7, 62.0, 57.0, 43.7, 42.9, 35.8, 33.6, 30.4, 24.3, 23.9, 22.5.

IR (Neat Film, NaCl): 2923, 1723, 1684, 1493, 1451, 1386, 1231 cm^{-1}.

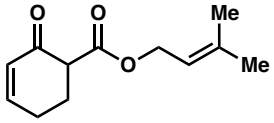
HRMS (MM: FD+): *m/z* calc'd for $C_{29}H_{32}O_4$ $[M]^+$: 444.2301, found 444.2300.

β-Ketoesters Synthesis

General Procedure D: Prenyl β-ketoesters Synthesis through Acylation



A flame dried round bottom flask was charged with iPr_2NH (1.1 equiv) and THF (1.75 M). The solution was cooled to 0 ºC and *n*-BuLi (2.5 M in hexanes, 1.05 equiv) was added dropwise. The resultant solution was stirred for 30 min at 0 ºC. The corresponding cyclohexenone (1.0 equiv) in THF (1.25 M) was added dropwise and stirring was continued at 0 ºC for 30 minutes. The solution was cooled to –78 ºC, and the appropriate N-acyl imidazole (1.2 equiv) in THF (3.25 M) was added dropwise. After 2 h, the reaction was gradually warmed to 23 ºC and diluted with 2 M aqueous HCl until reaching a pH < 7. The reaction mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography to afford the corresponding acylated enone.



70

3-methylbut-2-en-1-yl 2-oxocyclohex-3-ene-1-carboxylate (70)

Prepared from 2-cyclohexen-1-one and 3-methylbut-2-en-1-yl 1H-imidazole-1-carboxylate [42] following General Procedure D. Purification by flash column

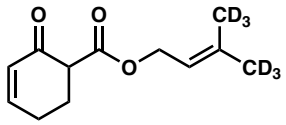
chromatography (25% EtOAc/hexanes) afforded the title compound as a colorless oil (6.65 g, 31.9 mmol, 41% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 – 6.97 (m, 1H), 6.07 (dt, *J* = 10.2, 2.0 Hz, 1H), 5.37 – 5.32 (m, 1H), 4.65 (d, *J* = 7.1 Hz, 2H), 3.42 – 3.39 (m, 1H), 2.55 – 2.45 (m, 1H), 2.44 – 2.34 (m, 2H), 2.26 – 2.18 (m, 1H), 1.75 (s, 3H), 1.71 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 170.2, 150.7, 139.6, 129.3, 118.4, 62.3, 53.6, 25.9, 25.8, 24.5, 18.2.

IR (Neat Film, NaCl): 3033, 2934, 1736, 1682, 1447, 1387, 1302, 1233, 1159, 1123 cm^{-1}

HRMS (MM: FD+): *m/z* calc'd for $C_{12}H_{16}O_3$ $[M]^+$: 208.1099, found 208.1090.



D-70

3-(methyl-*d*$_3$)but-2-en-1-yl-4,4,4-*d*$_3$ 2-oxocyclohex-3-ene-1-carboxylate (D-70)

Prepared from 2-cyclohexen-1-one and 3-(methyl-*d*$_3$)but-2-en-1-yl-4,4,4-*d*$_3$ 1*H*-imidazole-1-carboxylate [43] following General Procedure D. Purification by flash column chromatography (25% EtOAc/hexanes) afforded the title compound as a colorless oil (1.00 g, 4.67 mmol, 37% yield). *Note that 1.0 equiv of the N-acyl imidazole can be employed*.

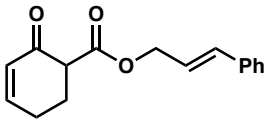
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (dt, *J* = 10.0, 3.7 Hz, 1H), 6.06 (dt, *J* = 10.2, 2.1 Hz, 1H), 5.34 (t, *J* = 7.2 Hz, 1H), 4.65 (d, *J* = 7.2 Hz, 2H), 3.40 (dd, *J* = 9.7, 5.0 Hz, 1H), 2.54 – 2.44 (m, 1H), 2.44 – 2.32 (m, 2H), 2.22 (ddt, *J* = 13.7, 8.8, 3.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 170.2, 150.7, 139.4, 129.3, 118.4, 62.3, 53.6, 25.8, 24.5.

^{2}H NMR (61 MHz, $CHCl_3$): δ 1.72, 1.67.

IR (Neat Film, NaCl): 2942, 1736, 1681, 1388, 1164 cm^{-1}

HRMS (MM: FD+): *m/z* calc'd for $C_{12}H_{10}D_6O_3$ $[M]^+$: 214.1476, found 214.1476.



73

cinnamyl 2-oxocyclohex-3-ene-1-carboxylate (73)

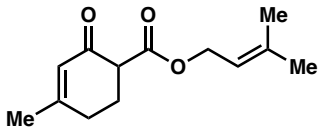
Prepared from 2-cyclohexen-1-one and cinnamyl 1*H*-imidazole-1-carboxylate[42] following General Procedure D. Purification by flash column chromatography (15–25% EtOAc/hexanes) afforded the title compound as a colorless oil (0.98 g, 3.82 mmol, 39% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.37 (m, 2H), 7.34 – 7.30 (m, 2H), 7.28 – 7.24 (m, 1H), 7.01 (dt, *J* = 10.3, 3.8 Hz, 1H), 6.67 (dt, *J* = 15.9, 1.3 Hz, 1H), 6.29 (dt, *J* = 15.9, 6.4 Hz, 1H), 6.09 (dt, *J* = 10.2, 2.0 Hz, 1H), 4.83 (d, *J* = 6.5 Hz, 2H), 3.47 (dd, *J* = 10.2, 4.9 Hz, 1H), 2.57 – 2.47 (m, 1H), 2.47 – 2.34 (m, 2H), 2.28 – 2.21 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9, 169.9, 150.8, 136.3, 134.6, 129.3, 128.7, 128.2, 126.8, 122.9, 65.9, 53.6, 25.8, 24.5.

IR (Neat Film, NaCl): 3024, 2940, 1734, 1676, 1304, 1223, 1157, 1123, 969 cm^{-1}

HRMS (MM: FD+): *m/z* calc'd for $C_{16}H_{16}NaO_3$ $[M+Na]^+$: 279.0997, found 279.0983.



75

3-methylbut-2-en-1-yl 4-methyl-2-oxocyclohex-3-ene-1-carboxylate (75)

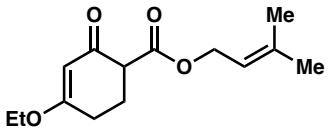
Prepared from 3-methylcyclohex-2-en-1-one and 3-methylbut-2-en-1-yl 1H-imidazole-1-carboxylate[42] following General Procedure D. Purification by flash column chromatography (10–20% EtOAc/hexanes) afforded the title compound as a colorless oil (2.95 g, 13.3 mmol, 17% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.91 (h, *J* = 1.4 Hz, 1H), 5.35 (tp, *J* = 7.1, 1.6 Hz, 1H), 4.65 (d, *J* = 7.2 Hz, 2H), 3.37 – 3.27 (m, 1H), 2.48 – 2.24 (m, 3H), 2.21 – 2.15 (m, 1H), 1.97 (s, 3H), 1.75 (d, *J* = 1.3 Hz, 3H), 1.70 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9, 170.5, 163.0, 139.5, 126.0, 118.5, 62.3, 52.6, 29.5, 25.9, 25.7, 24.5, 18.2.

IR (Neat Film, NaCl): 2938, 1732, 1668, 1632, 1434, 1378, 1357, 1302, 1246, 1216, 1170, 1152, 1018 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{13}H_{18}O_3$ $[M]^+$: 222.1257, found 222.1251.



76

3-methylbut-2-en-1-yl 4-ethoxy-2-oxocyclohex-3-ene-1-carboxylate (76)

Prepared from 3-ethoxycyclohex-2-en-1-one and 3-methylbut-2-en-1-yl 1H-imidazole-1-carboxylate[42] following General Procedure D. Purification by flash column chromatography (25–30% EtOAc/hexanes) afforded the title compound as a colorless oil (2.84 g, 9.51 mmol, 19% yield).

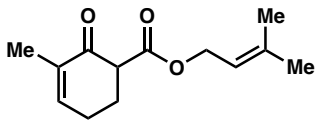
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.38 (s, 1H), 5.37 – 5.32 (m, 1H), 4.72 – 4.59 (m, 2H), 3.91 (qd, *J* = 7.0, 2.3 Hz, 2H), 3.36 – 3.27 (m, 1H), 2.56 (ddd, *J* = 16.6, 6.2, 4.5 Hz, 1H),

2.47 – 2.27 (m, 2H), 2.24 – 2.08 (m, 1H), 1.75 (s, 3H), 1.70 (s, 3H), 1.36 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.0, 177.7, 170.6, 139.4, 118.5, 102.3, 64.6, 62.3, 52.5, 27.5, 25.9, 24.3, 18.2, 14.2.

IR (Neat Film, NaCl): 2980, 2357, 1730, 1648, 1605, 1380, 1192, 1026, 668 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{14}H_{20}O_4$ $[M]^+$: 252.1363, found 252.1356.



77

3-methylbut-2-en-1-yl 3-methyl-2-oxocyclohex-3-ene-1-carboxylate (77)

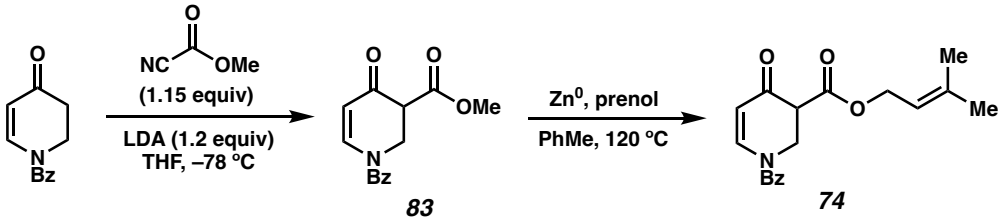
Prepared from 2-methylcyclohex-2-en-1-one[44] and 3-methylbut-2-en-1-yl 1H-imidazole-1-carboxylate[42] following General Procedure D. Purification by flash column chromatography (10–20% EtOAc/hexanes) afforded the title compound as a colorless oil (1.09 g, 4.90 mmol, 23% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 – 6.69 (m, 1H), 5.35 (tdq, *J* = 7.2, 2.9, 1.5 Hz, 1H), 4.65 (d, *J* = 7.2 Hz, 2H), 3.42 – 3.36 (m, 1H), 2.48 – 2.11 (m, 5H), 1.79 (d, *J* = 1.6 Hz, 3H), 1.75 (s, 3H), 1.70 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.7, 170.6, 145.5, 139.5, 135.4, 118.5, 62.2, 53.8, 26.3, 25.9, 24.6, 18.2, 16.2.

IR (Neat Film, NaCl): 2925, 1736, 1676, 1449, 1381, 1249, 1151 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{13}H_{18}O_3$ $[M]^+$: 222.1255, found 222.1251.



1-benzyl 3-methyl 4-oxo-3,4-dihydropyridine-1,3(2*H*)-dicarboxylate (83)

A flame dried round bottom flask was charged with *i*-Pr_2NH (2.52 mL, 18.0 mmol, 1.2 equiv) and THF (167 mL, 0.1 M). The solution was cooled to –78 ºC and *n*-BuLi (7.20 mL, 18.0 mmol, 1.2 equiv) was added dropwise. The resultant solution was slowly warmed to 0 ºC over 1 h and then cooled to –78 ºC. The LDA solution was added dropwise to a solution of 1-benzoyl-2,3-dihydropyridin-4(1*H*)-one[45] (3.47 g, 15.0 mmol, 1.0 equiv) in THF (239 mL, 0.06 M) at –78 ºC. The resultant solution was stirred for 1 h. Then methyl cyanoformate (1.37 mL, 17.25 mmol, 1.15 equiv) was added dropwise. Upon complete consumption of starting material (as determined by TLC), the reaction was diluted with a saturated solution of NH_4Cl and the product was extracted with EtOAc (3 x 200 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 20–30% EtOAc/Hexanes) to afford acylated enone **83** (1.17 g, 4.05 mmol, 27% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.39 (d, *J* = 2.3 Hz, 5H), 5.40 (s, 1H), 5.28 (s, 1H), 4.39 (dd, *J* = 13.6, 8.9 Hz, 1H), 4.18 (dd, *J* = 13.6, 5.4 Hz, 1H), 3.76 (s, 3H), 3.51 (dd, *J* = 8.9, 5.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 187.8, 168.2, 143.6, 134.8, 129.1, 128.9, 128.8, 128.7, 106.8, 69.6, 52.9, 50.6, 44.4.

IR (Neat Film, NaCl): 2952, 2332, 1734, 1670, 1601, 1388, 1293, 1213 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{15}H_{15}NO_5$ $[M]^+$: 289.0950, found 289.0948.

1-benzyl 3-(3-methylbut-2-en-1-yl) 4-oxo-3,4-dihydropyridine-1,3(2*H*)-dicarboxylate (74)

A flame dried round bottom flask equipped with a reflux condenser was charged with Zn^0 dust (51.5 mg, 0.787 mmol, 0.2 equiv), acylated enone **83** (1.14 g, 3.40 mmol, 1.0 equiv), and toluene (19.7 mL, 0.2 M). To the stirred solution, prenyl alcohol was added neat (2.00 mL, 19.68 mmol, 5.0 equiv). The resultant solution was heated to reflux for 3 days. The solution was cooled to 23 ºC, filtered through a celite plug and eluted with CH_2Cl_2, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 15–25% EtOAc/Hexanes) to afford acylated enone **74** (883 mg, 2.57 mmol, 65% yield).

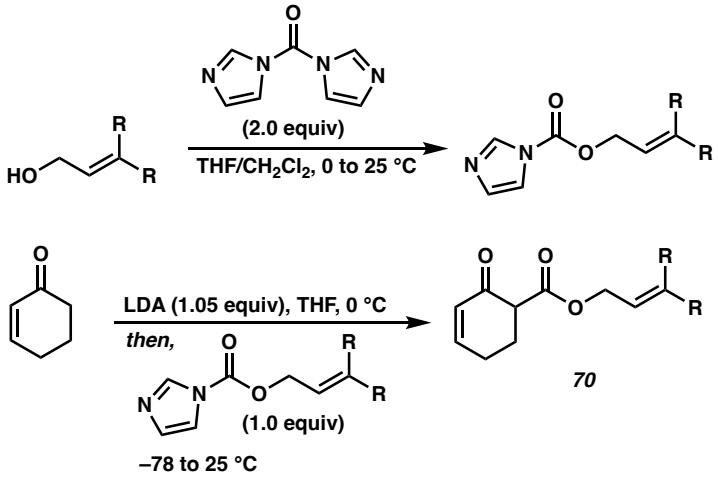
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.39 (m, 5H), 5.39 (s, 1H), 5.32 (tp, *J* = 7.3, 1.4 Hz, 1H), 5.27 (s, 2H), 4.65 (dd, *J* = 7.3, 2.9 Hz, 2H), 4.38 (dd, *J* = 13.6, 8.9 Hz, 1H), 4.17 (dd, *J* = 13.5, 5.4 Hz, 1H), 3.48 (dd, *J* = 9.1, 5.3 Hz, 1H), 1.74 (s, 3H), 1.69 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 187.9, 167.8, 143.5, 140.1, 134.9, 129.0, 128.9, 128.8, 128.7, 118.0, 106.9, 69.5, 62.8, 50.8, 44.5, 25.9, 18.2.

IR (Neat Film, NaCl): 2965, 1727, 1676, 1599, 1388, 1293, 1209, 940 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{19}H_{21}HO_5$ $[M]^+$: 343.1420, found 343.1420.

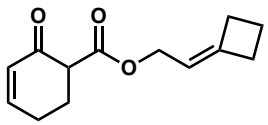
General Procedure E: Substituted β-Ketoesters Synthesis through Acylation[42]



To a solution of di(1*H*-imidazol-1-yl)methanone (2.0 equiv) in THF (2.0 M) at 0 °C was added dropwise a solution of the corresponding alcohol (1.0 equiv) in CH_2Cl_2 (1.0 M). After 3 h, the reaction mixture was gradually warmed to 25 °C. Upon consumption of starting material (as determined by TLC), the reaction mixture was concentrated under reduced pressure then filtered through a silica plug and eluted with 50% EtOAc/Hexanes. The resulting solution was concentrated under reduced pressure.

A flame dried round bottom flask was charged with iPr_2NH (1.1 equiv) and THF (1.75 M). The solution was cooled to 0 ºC and *n*-BuLi (2.5 M in hexanes, 1.05 equiv) was added dropwise. The resultant solution was stirred for 30 min at 0 ºC. 2-cyclohexen-1-one (1.0 equiv) in THF (1.25 M) was added dropwise and stirring was continued at 0 ºC for 30 minutes. The solution was cooled to –78 ºC, and the corresponding crude 1*H*-imidazole-1-carboxylate (1.2 equiv) in THF (3.25 M) was added dropwise. After 2 h, the reaction was gradually warmed to 23 ºC and diluted with 2 M aqueous HCl until reaching a pH < 7. The reaction mixture was extracted three times with EtOAc. The combined organic layers were

washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography to afford the corresponding acylated enone.



78

2-cyclobutylideneethyl 2-oxocyclohex-3-ene-1-carboxylate (78)

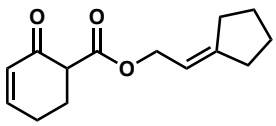
Prepared from 2-cyclohexen-1-one and 2-cyclobutylideneethan-1-ol[46] following General Procedure E. Purification by flash column chromatography (5–50% EtOAc/hexanes) afforded the title compound as a colorless oil (2.02 g, 9.19 mmol, 31.7% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00 (dt, *J* = 10.1, 3.7 Hz, 1H), 6.07 (dt, *J* = 10.2, 2.0 Hz, 1H), 5.27 (tp, *J* = 6.9, 2.2 Hz, 1H), 4.53 (d, *J* = 7.2 Hz, 2H), 3.45 – 3.36 (m, 1H), 2.80 – 2.65 (m, 4H), 2.56 – 2.31 (m, 3H), 2.28 – 2.15 (m, 1H), 1.98 (p, *J* = 8.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 170.1, 150.7, 148.9, 129.3, 114.1, 62.3, 53.6, 31.2, 29.6, 25.8, 24.5, 17.1.

IR (Neat Film, NaCl): 2947, 1737, 1681, 1457, 1397, 1301, 1229, 1163, 1123 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{13}H_{16}O_3$ $[M]^+$: 220.1099, found 220.1093.



79

2-cyclopentylideneethyl 2-oxocyclohex-3-ene-1-carboxylate (79)

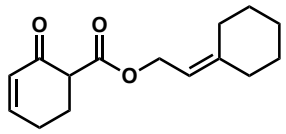
Prepared from 2-cyclohexen-1-one and 2-cyclopentylideneethan-1-ol[47] following General Procedure E. Purification by flash column chromatography (5–50% EtOAc/hexanes) afforded the title compound as a colorless oil (2.69 g, 11.46 mmol, 31.9% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (dt, *J* = 10.1, 3.8 Hz, 1H), 6.07 (dt, *J* = 10.2, 2.0 Hz, 1H), 5.50 – 5.40 (m, 1H), 4.64 (dt, *J* = 7.2, 1.1 Hz, 2H), 3.45 – 3.37 (m, 1H), 2.57 – 2.15 (m, 8H), 1.75 – 1.58 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 170.2, 151.2, 150.7, 129.3, 113.8, 63.8, 53.6, 34.0, 29.0, 26.4, 26.2, 25.8, 24.5.

IR (Neat Film, NaCl): 2946, 2869, 1782, 1681, 1455, 1387, 1304, 1224, 1156 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{14}H_{18}O_3$ $[M]^+$: 234.1256, found 234.1255.



80

2-cyclohexylideneethyl 2-oxocyclohex-3-ene-1-carboxylate (80)

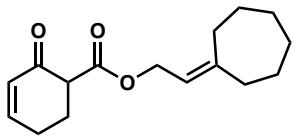
Prepared from 2-cyclohexen-1-one and 2-cyclohexylideneethan-1-ol[47] following General Procedure E, with the modification of 1.5 equiv of di(1*H*-imidazol-1-yl)methanone and 1.2 equiv of 2-cyclohexylideneethyl 1*H*-imidazole-1-carboxylate being used. Purification by flash column chromatography (5–30% EtOAc/hexanes) afforded the title compound as a colorless oil (535 mg, 2.15 mmol, 28% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ7.04 – 6.95 (m, 1H), 6.07 (dt, J = 10.1, 2.0 Hz, 1H), 5.29 (tt, J = 7.2, 1.2 Hz, 1H), 4.67 (d, J = 7.2 Hz, 2H), 3.45 – 3.36 (m, 1H), 2.56 – 2.30 (m, 3H), 2.27 – 2.15 (m, 3H), 2.14 – 2.08 (m, 2H), 1.60 – 1.48 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 170.2, 150.6, 147.5, 129.3, 115.0, 61.5, 53.6, 37.1, 29.2, 28.5, 27.9, 26.7, 25.8, 24.5.

IR (Neat Film, NaCl): 2930, 2852, 1735, 1683, 1447, 1388, 1298, 1169, 1122 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{15}H_{20}O_3$ $[M]^+$: 248.1412, found 248.1418.



81

2-cycloheptylideneethyl 2-oxocyclohex-3-ene-1-carboxylate (81)

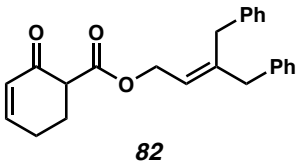
Prepared from 2-cyclohexen-1-one and 2-cycloheptylideneethan-1-ol[48] following General Procedure E. Purification by flash column chromatography (5–50% EtOAc/hexanes) afforded the title compound as a colorless oil (1.73 g, 5.43 mmol, 28.1% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (dt, *J* = 10.0, 3.8 Hz, 1H), 6.07 (dt, *J* = 10.1, 2.0 Hz, 1H), 5.34 (tt, *J* = 7.1, 1.3 Hz, 1H), 4.66 (d, *J* = 7.0 Hz, 2H), 3.45 – 3.37 (m, 1H), 2.57 – 2.15 (m, 8H), 1.63 – 1.44 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 170.2, 150.6, 148.8, 129.3, 118.5, 62.1, 53.6, 37.8, 30.2, 29.9, 29.1, 28.8, 27.3, 25.8, 24.5.

IR (Neat Film, NaCl): 2923, 2853, 1736, 1681, 1442, 1388, 1300, 1231, 1155, 1122, 1076 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{26}H_{22}O_3$ $[M]^+$: 262.1569, found 262.1577.



82

3-benzyl-4-phenylbut-2-en-1-yl 2-oxocyclohex-3-ene-1-carboxylate (82)

Prepared from 2-cyclohexen-1-one and 3-benzyl-4-phenylbut-2-en-1-ol [49] following General Procedure E. Purification by flash column chromatography (5–50% EtOAc/hexanes) afforded the title compound as a colorless oil (1.96 g, 5.43 mmol, 21.3% yield).

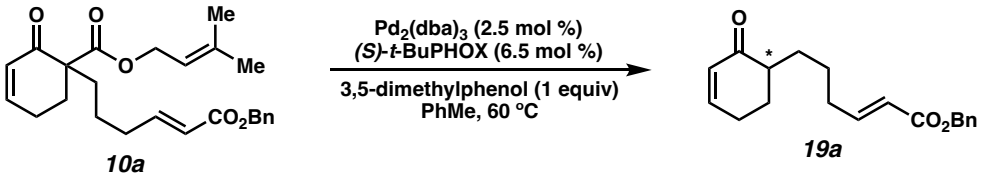
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.25 (m, 4H), 7.24 – 7.18 (m, 2H), 7.17 – 7.07 (m, 4H), 7.03 – 6.97 (m, 1H), 6.08 (dt, *J* = 10.1, 2.0 Hz, 1H), 5.59 (tt, *J* = 7.1, 1.1 Hz, 1H), 4.86 – 4.80 (m, 2H), 3.48 – 3.35 (m, 3H), 3.26 (s, 2H), 2.55 – 2.32 (m, 3H), 2.30 – 2.15 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9, 170.1, 150.7, 144.4, 139.0, 138.9, 129.3, 129.3, 128.9, 128.7, 128.5, 126.5, 126.4, 121.9, 62.0, 53.6, 42.9, 35.9, 25.8, 24.5.

IR (Neat Film, NaCl): 3026, 2927, 1738, 1681, 1493, 1388, 1304, 1230, 1157, 1123 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{24}H_{24}O_3$ $[M]^+$: 360.1725, found 360.17302.

Protonated Enone Byproducts



benzyl (*R*,*E*)-6-(2-oxocyclohex-3-en-1-yl)hex-2-enoate (19a)

In a nitrogen filled glovebox, an oven-dried 20 mL vial was charged with a stir bar, $Pd_2(dba)_3$ (0.46 mg, 0.50 μmol, 2.5 mol %), *(S)-t*-BuPHOX (0.50 mg, 1.3 μmol, 6.5 mol %), and toluene (0.5 mL). The catalyst solution was stirred at 23 ºC for 20 min. A solution of substrate **10a** (8.2 mg, 0.020 mmol, 1 equiv) and 3,5-dimethylphenol (2.4 mg, 0.020 mmol, 1 equiv) in toluene (0.5 mL) was added to the vial. The resultant solution was then heated to 60 ºC for 14 h. The solution was then cooled to 23 ºC and concentrated under reduced pressure. NMR analysis of the crude reaction mixture affords an NMR yield of 100% (with respect to 1,3,5-trimethoxybenzene as an internal standard). The sample was purified by preparatory TLC (25% EtOAc/hexanes) to afford **19a** (71% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.29 (m, 5H), 7.01 (dt, *J* = 15.7, 6.9 Hz, 1H), 6.92 (dddd, *J* = 10.1, 4.5, 3.5, 0.9 Hz, 1H), 5.98 (ddd, *J* = 10.1, 2.3, 1.7 Hz, 1H), 5.88 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.17 (s, 2H), 2.46 – 2.34 (m, 2H), 2.32 – 2.20 (m, 3H), 2.09 (dqd, *J* = 13.3, 4.8, 1.0 Hz, 1H), 1.89 – 1.80 (m, 1H), 1.75 (dddd, *J* = 13.3, 11.0, 8.4, 5.8 Hz, 1H), 1.55 – 1.35 (m, 3H).

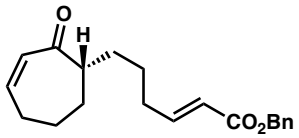
^{13}C NMR (100 MHz, $CDCl_3$): δ 201.6, 166.6, 149.7, 149.6, 136.3, 129.7, 128.7, 128.3, 128.3, 121.4, 66.2, 46.5, 32.5, 29.0, 28.0, 25.6, 25.3.

IR (Neat Film, NaCl): 2921, 1712, 1673, 1257 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{19}H_{22}O_3$ $[M]^+$: 298.1569, found 298.1565.

Optical Rotation: $[\alpha]_D^{21}$ +3.5 (c 0.20, $CHCl_3$).

SFC conditions: 40% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): minor = 3.81, major = 4.34.



19d

benzyl (*R*,*E*)-7-(2-oxocyclohex-3-en-1-yl)hept-2-enoate (19d)

Isolated as a byproduct from the reaction of **10d** to **11d** as a colorless oil (10.4 mg, 0.0332 mmol, 17% yield, 67% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.22 (m, 5H), 6.93 (dt, *J* = 15.7, 6.9 Hz, 1H), 6.53 (ddd, *J* = 12.0, 6.7, 4.0 Hz, 1H), 5.94 (ddd, *J* = 11.9, 2.5, 0.9 Hz, 1H), 5.80 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.10 (s, 3H), 2.59 – 2.49 (m, 1H), 2.42 – 2.25 (m, 2H), 2.14 (tdd, *J* = 7.7, 4.8, 1.4 Hz, 2H), 1.90 – 1.48 (m, 5H), 1.44 – 1.29 (m, 4H).

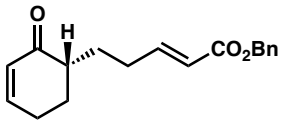
^{13}C NMR (100 MHz, $CDCl_3$): δ 205.7, 166.5, 149.6, 146.0, 136.2, 132.8, 128.6, 128.2, 128.2, 121.2, 66.0, 51.7, 32.4, 31.1, 29.9, 29.5, 25.8, 25.4.

IR (Neat Film, NaCl): 2917, 1719, 1671, 1266, 1165 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{20}H_{24}O_3$ $[M]^+$: 312.1720, found 312.1734.

Optical Rotation: $[\alpha]_D^{21}$ –0.6 (c 1.00, $CHCl_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 8.23, major = 7.63.



19e

benzyl (*S*,*E*)-5-(2-oxocyclohex-3-en-1-yl)pent-2-enoate (19e)

Isolated as the major byproduct from the reaction of **10e** to **11e**. Purification by flash column chromatography (0–45% EtOAc/hexanes) afforded the title compound as a colorless oil (46.1 mg, 0.16 mmol, 81% yield, 47% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.28 (m, 5H), 7.01 (dt, *J* = 15.6, 6.9 Hz, 1H), 6.92 (dddd, *J* = 10.0, 4.4, 3.6, 1.0 Hz, 1H), 5.98 (dt, *J* = 10.0, 2.0 Hz, 1H), 5.90 (dt, *J* = 15.7, 1.6 Hz, 1H), 5.17 (s, 2H), 2.44 – 2.24 (m, 5H), 2.15 – 1.96 (m, 2H), 1.82 – 1.69 (m, 1H), 1.62 – 1.44 (m, 1H).

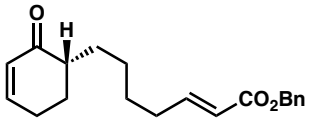
^{13}C NMR (100 MHz, $CDCl_3$): δ 201.3, 166.5, 149.6, 149.4, 136.2, 129.7, 128.7, 128.3, 128.3, 121.6, 66.2, 45.9, 29.7, 28.2, 27.8, 25.4.

IR (Neat Film, NaCl): 3032, 2932, 1719, 1675, 1455, 1386, 1265, 1171 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{18}H_{20}O_3$ $[M]^+$: 284.1412, found 284.1407.

Optical Rotation: $[\alpha]_D^{21}$ +11.8 (c 1.00, $CHCl_3$).

SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak AS-H column, λ = 210 nm, t_R (min): minor = 5.69, major = 6.54.



19f

benzyl (*R*,*E*)-7-(2-oxocyclohex-3-en-1-yl)hept-2-enoate (19f)

Isolated as a byproduct from the reaction of **10f** to **11f** as a colorless oil (28.1 mg, 0.090 mmol, 45% yield, 51% ee). Absolute stereochemistry proposed based on VCD analysis (vide infra).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.29 (m, 5H), 7.00 (dt, *J* = 15.6, 6.9 Hz, 1H), 6.90 (dddd, *J* = 10.0, 4.5, 3.5, 0.9 Hz, 1H), 5.97 (dt, *J* = 10.1, 2.0 Hz, 1H), 5.86 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.17 (s, 2H), 2.42 – 2.33 (m, 2H), 2.29 – 2.18 (m, 3H), 2.08 (dqd, *J* = 13.3, 4.8, 0.9 Hz, 1H), 1.88 – 1.80 (m, 1H), 1.78 – 1.69 (m, 1H), 1.52 – 1.29 (m, 5H).

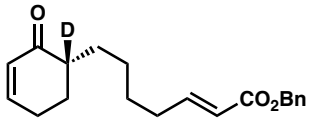
^{13}C NMR (100 MHz, $CDCl_3$): δ 201.8, 166.6, 150.0, 149.5, 136.3, 129.6, 128.6, 128.3, 128.3, 121.2, 66.1, 46.6, 32.2, 29.0, 28.2, 27.9, 26.6, 25.2.

IR (Neat Film, NaCl): 2927, 2859, 1716, 1675, 1652, 1262, 1172 cm^{-1}

HRMS (MM: FD+): *m/z* calc'd for $C_{20}H_{24}O_3$ $[M]^+$: 312.1725, found 312.1737.

Optical Rotation: $[\alpha]_D^{21}$ +4.1 (c 1.00, $CHCl_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 7.77, major = 8.44.



***D*-19f**

benzyl (*R*,*E*)-7-(2-oxocyclohex-3-en-1-yl-1-*d*)hept-2-enoate (*D*-19f)

Isolated as a byproduct from the reaction of ***D*-10f** to ***D*-11f** as a colorless oil (14.9 mg, 0.0475 mmol, 24% yield, 55% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.29 (m, 5H), 7.00 (dt, *J* = 15.6, 7.0 Hz, 1H), 6.91 (dddd, *J* = 10.1, 4.5, 3.5, 0.9 Hz, 1H), 5.97 (dddd, *J* = 10.0, 2.3, 1.6, 0.6 Hz, 1H), 5.86 (dt,

J = 15.6, 1.6 Hz, 1H), 5.17 (s, 2H), 2.44 – 2.33 (m, 2H), 2.28 – 2.18 (m, 2.5H), 2.09 (ddt, *J* = 13.3, 5.8, 4.5 Hz, 1H), 1.87 – 1.70 (m, 2H), 1.53 – 1.27 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.9, 166.6, 150.0, 149.6, 129.7, 129.7, 128.7, 128.3, 128.3, 121.2, 66.2, 46.6, 32.3, 29.0, 28.9, 28.2, 27.9, 27.8, 26.7, 26.6, 25.3, 25.2.

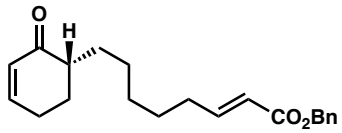
^{2}H NMR (61 MHz, $CHCl_3$): δ 2.25.

IR (Neat Film, NaCl): 2929, 2857, 1714, 1697, 1267, 1174 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{20}H_{23}DO_3$ $[M+H]^+$: 313.1783, found 313.1788.

Optical Rotation: $[\alpha]_D^{21}$ +5.8 (c 0.50, $CHCl_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 7.96, major = 8.67.



19g

benzyl (*R*,*E*)-8-(2-oxocyclohex-3-en-1-yl)oct-2-enoate (19g)

Isolated as the major product from the reaction of **10g** to **11g** as a colorless oil (50.5 mg, 0.155 mmol, 77% yield, 56% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.29 (m, 5H), 7.01 (dt, *J* = 15.6, 6.9 Hz, 1H), 6.91 (dddd, *J* = 10.0, 4.5, 3.5, 0.9 Hz, 1H), 5.97 (dt, *J* = 10.0, 2.0 Hz, 1H), 5.86 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.17 (s, 2H), 2.45 – 2.33 (m, 2H), 2.30 – 2.16 (m, 3H), 2.09 (dqd, *J* = 14.5, 5.0, 0.9 Hz, 1H), 1.86 – 1.70 (m, 2H), 1.51 – 1.42 (m, 2H), 1.41 – 1.28 (m, 5H).

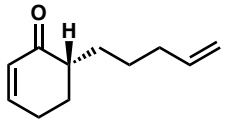
^{13}C NMR (100 MHz, $CDCl_3$): δ 202.0, 166.7, 150.2, 149.5, 136.3, 129.7, 128.7, 128.3, 128.3, 121.1, 66.1, 46.6, 32.3, 29.3, 29.1, 28.0, 27.9, 26.8, 25.2.

IR (Neat Film, NaCl): 2927, 2859, 1718, 1677, 1555, 1450, 1257, 1165 cm^{-1}

HRMS (MM: FD+): *m/z* calc'd for $C_{21}H_{26}O_3$ $[M]^+$: 326.1877, found 326.1891.

Optical Rotation: $[\alpha]_D^{21}$ +7.0 (c 1.00, $CHCl_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 9.70, major = 10.46.



19h

6-(pent-4-en-1-yl)cyclohex-2-en-1-one (19h)

Isolated as the major product from the reaction of **10h** to **11h** as a colorless oil. Purification by flash column chromatography (0–15% EtOAc/hexanes) afforded the title compound as a colorless oil (11.0 mg, 0.067 mmol, 33% yield, 58% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91 (dddd, *J* = 10.1, 4.4, 3.5, 0.9 Hz, 1H), 5.97 (dt, *J* = 10.0, 2.1 Hz, 1H), 5.81 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.01 (dq, *J* = 17.2, 1.8 Hz, 1H), 4.94 (dd, *J* = 10.1, 1.3 Hz, 1H), 2.45 – 2.24 (m, 3H), 2.16 – 1.98 (m, 2=3H), 1.95 – 1.69 (m, 2H), 1.55 – 1.31 (m, 3H).

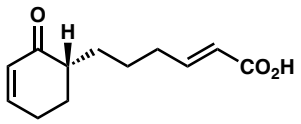
^{13}C NMR (100 MHz, $CDCl_3$): δ 202.0, 149.5, 138.8, 129.7, 114.7, 46.6, 34.0, 28.8, 27.9, 26.4, 25.2.

IR (Neat Film, NaCl): 2925, 2859, 1677, 1639, 1456, 1387, 1215, 912 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{11}H_{16}O$ $[M]^+$: 164.1201, found 164.1201.

Optical Rotation: $[\alpha]_D^{21}$ –111.5 (c 1.00, $CHCl_3$).

SFC conditions: 3% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 4.41, major = 4.11.



19i

(*E*)-6-(2-oxocyclohex-3-en-1-yl)hex-2-enoic acid (19i)

Isolated as the major product from the reaction of **10i** to **11i** as a colorless oil. Purification by flash column chromatography (35% EtOAc/hexanes with 3% AcOH) afforded the title compound as a white solid (33.2 mg, 0.16 mmol, 80% yield, 9% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (dtd, *J* = 15.5, 7.0, 1.5 Hz, 1H), 6.97 – 6.87 (m, 1H), 5.98 (dq, *J* = 10.1, 1.9 Hz, 1H), 5.84 (dt, *J* = 15.6, 1.6 Hz, 1H), 2.49 – 2.35 (m, 2H), 2.34 – 2.19 (m, 3H), 2.16 – 2.04 (m, 1H), 1.92 – 1.81 (m, 1H), 1.81 – 1.70 (m, 1H), 1.63 – 1.48 (m, 2H), 1.48 – 1.35 (m, 1H).

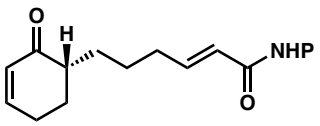
^{13}C NMR (100 MHz, $CDCl_3$): δ 201.7, 171.5, 151.9, 149.7, 129.7, 120.9, 46.5, 32.5, 29.0, 28.0, 25.5.

IR (Neat Film, NaCl): 2928, 2857, 1731, 1454, 1155 cm^{-1}

HRMS (MM: FD+): *m/z* calc'd for $C_{12}H_{17}O_3$ $[M]^+$: 209.1178, found 209.1168.

Optical Rotation: $[\alpha]_D^{21}$ 2.2 (c 1.00, $CHCl_3$).

SFC conditions: 30% IPA, 2.5 mL/min, Chiralpak IC column, l = 210 nm, t_R (min): minor = 3.30, major = 4.02



19m

1,3-dioxoisoindolin-2-yl (*E*)-6-(2-oxocyclohex-3-en-1-yl)hex-2-enoate (19m)

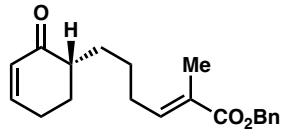
Isolated as a byproduct product from the reaction of **10m** to **11m** as a colorless oil. Purification by flash column chromatography (0–35% EtOAc/hexanes) afforded the title compound as a white solid (7.7 mg, 0.022 mmol, 11% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.32 (dt, *J* = 15.8, 6.9 Hz, 1H), 6.93 (dddd, *J* = 10.1, 4.5, 3.5, 1.0 Hz, 1H), 6.10 (dt, *J* = 15.8, 1.6 Hz, 1H), 5.99 (ddd, *J* = 10.0, 2.3, 1.7 Hz, 1H), 2.50 – 2.25 (m, 5H), 2.12 (m, 1H), 1.95 – 1.84 (m, 1H), 1.78 (m, 1H), 1.59 (m, 2H), 1.45 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.5, 162.5, 162.2, 155.6, 149.7, 134.9, 129.7, 129.1, 124.1, 115.9, 46.5, 33.2, 29.1, 28.1, 25.4, 25.3.

IR (Neat Film, NaCl): 2931, 1770, 1745, 1673, 1466, 1360, 1186 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{20}H_{19}NO_5$ $[M]^+$: 353.1263, found 353.1242.



19r

benzyl (*R*,*E*)-2-methyl-6-(2-oxocyclohex-3-en-1-yl)hex-2-enoate (19r)

Isolated as a byproduct from the reaction of **10r** to **11r** as a colorless oil (23.2 mg, 0.0743 mmol, 37% yield, 59% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.29 (m, 5H), 6.91 (dddd, *J* = 10.1, 4.5, 3.5, 0.9 Hz, 1H), 6.81 (td, *J* = 7.5, 1.5 Hz, 1H), 5.97 (dt, *J* = 10.0, 1.9 Hz, 1H), 5.18 (s, 2H), 2.45 – 2.34 (m, 2H), 2.32 – 2.17 (m, 3H), 2.09 (dqd, *J* = 13.4, 4.9, 1.0 Hz, 1H), 1.90 – 1.81 (m, 4H), 1.80 – 1.71 (m, 1H), 1.55 – 1.36 (m, 3H).

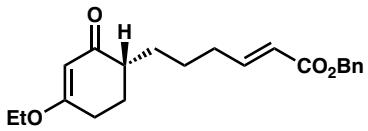
^{13}C NMR (100 MHz, $CDCl_3$): δ 201.7, 168.1, 149.6, 142.7, 136.6, 129.7, 128.6, 128.2, 128.1, 127.9, 66.3, 46.6, 29.2, 29.0, 28.0, 26.2, 25.2, 12.6.

IR (Neat Film, NaCl): 3033, 2932, 2861, 1710, 1677, 1256 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{20}H_{24}O_3$ $[M]^+$: 312.1725, found 312.1729.

Optical Rotation: $[\alpha]_D^{21}$ +8.6 (c 1.00, $CHCl_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 5.89, major = 6.22.



19t

benzyl (*E*)-6-(4-ethoxy-2-oxocyclohex-3-en-1-yl)hex-2-enoate (19t)

Isolated as a byproduct from the reaction of **10t** to **11t** as a colorless oil (5.2 mg, 0.015 mmol, 8% yield, 45% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.27 (m, 5H), 7.01 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.87 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.31 (s, 1H), 5.17 (s, 2H), 3.88 (qd, *J* = 7.1, 1.4 Hz, 2H), 2.41 (dd, *J* = 7.2, 5.3 Hz, 2H), 2.29 – 2.13 (m, 3H), 2.06 (dq, *J* = 13.2, 5.2 Hz, 1H), 1.86 (ddt, *J* = 13.3, 11.1, 5.2 Hz, 1H), 1.78 – 1.64 (m, 1H), 1.59 – 1.37 (m, 3H), 1.35 (t, *J* = 7.0 Hz, 3H).

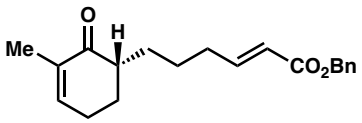
^{13}C NMR (100 MHz, $CDCl_3$): δ 201.4, 176.9, 166.6, 149.7, 136.3, 128.7, 128.3, 128.3, 121.3, 102.3, 66.1, 64.4, 45.1, 32.5, 29.3, 28.2, 26.4, 25.7, 14.3.

IR (Neat Film, NaCl): 2919, 1718, 1648, 1605, 1456, 1377, 1260, 1190, 732 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{21}H_{26}O_4$ $[M]^+$: 342.1828, found 342.1826.

Optical Rotation: $[\alpha]_D^{21}$ –5.5 (c 0.34, $CHCl_3$).

SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 10.17, major = 11.69.



19u

benzyl (*E*)-6-(3-methyl-2-oxocyclohex-3-en-1-yl)hex-2-enoate (19u)

Isolated as a byproduct from the reaction of **10u** to **11u** as a colorless oil (23.6 mg, 0.075 mmol, 37% yield, 46% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.28 (m, 5H), 7.01 (dt, *J* = 15.5, 6.9 Hz, 1H), 6.71 – 6.63 (m, 1H), 5.88 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.17 (s, 2H), 2.33 (ddq, *J* = 6.3, 4.8, 2.0 Hz, 2H), 2.29 – 2.19 (m, 3H), 2.10 – 2.01 (m, 1H), 1.88 – 1.77 (m, 1H), 1.76 (q, *J* = 1.7 Hz, 3H), 1.74 – 1.69 (m, 1H), 1.56 – 1.34 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.9, 166.6, 149.8, 144.5, 136.3, 135.3, 128.68, 128.3, 128.3, 121.3, 66.2, 46.6, 32.5, 29.2, 28.4, 25.7, 25.2, 16.3.

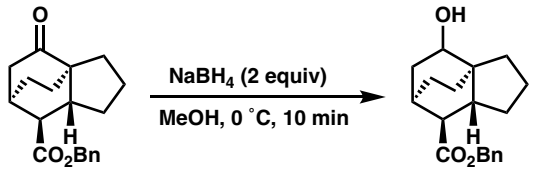
IR (Neat Film, NaCl): 2925, 1718, 1670, 1455, 1262, 1172, 1013 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{20}H_{24}O_3$ $[M]^+$: 312.1725, found 312.1721.

Optical Rotation: $[\alpha]_D^{21}$ –14.7 (c 0.35, $CHCl_3$).

SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak OJ-H column, λ = 210 nm, t_R (min): minor = 7.18, major = 7.62.

Product Derivatizations



11a ***38***

benzyl (3a*R*,6*R*,7*S*,7a*R*)-4-hydroxyoctahydro-3a,6-ethanoindene-7-carboxylate (38)

To a solution of ketone **11a** (0.125 mmol, 1 equiv) in methanol (4.4 mL) was added $NaBH_4$ (0.25 mmol, 2 equiv) at 0 ºC. The reaction was allowed to stir for 10 min at 0 ºC and then was diluted with water. The aqueous layer was extracted with dichloromethane (3x), and the combined organic layers were dried over Na_2SO_4. Concentration under reduced pressure afforded the title compound as a colorless oil (37.6 mg, 0.125 mmol, 99% yield).

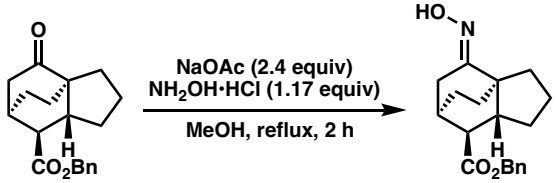
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.30 (m, 5H), 5.19 – 5.05 (m, 2H), 3.76 (dd, *J* = 8.9, 5.3 Hz, 0.4H, minor), 3.69 (dt, *J* = 8.9, 1.5 Hz, 0.6H, major), 2.35 – 2.24 (m, 1H), 2.15 – 1.95 (m, 2H), 1.95 – 1.83 (m, br, 1H), 1.83 – 1.56 (m, 6H), 1.53 – 1.23 (m, 5H), 1.15 – 1.01 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 175.6, 136.3, 128.6, 128.2, 128.2, 128.0, 128.0, 75.6, 70.3, 66.3, 66.3, 49.21, 48.1, 44.5, 44.2, 43.2, 36.8, 35.0, 34.9, 34.0, 30.5, 30.3, 30.1, 29.6, 29.0, 26.7, 26.3, 22.8, 22.8, 20.3.

IR (Neat Film, NaCl): 3438, 3032, 2942, 2865, 1730, 1455, 1162 cm^{-1}

HRMS (MM: FD+): *m/z* calc'd for $C_{19}H_{24}O_3$ $[M]^+$: 300.1725, found 300.1730.

Optical Rotation: $[\alpha]_D^{21}$ –31.1 (c 1.00, $CHCl_3$).



11a ***84***

benzyl (3a*R*,6*R*,7*S*,7a*R*,*E*)-4-(hydroxyimino)octahydro-3a,6-ethanoindene-7-carboxylate (84)

To a stirred solution of ketone **11a** (0.125 mmol, 1 equiv) in methanol (1.25 mL) was added NaOAc (0.3 mmol, 2.4 equiv), NH_2OH•HCl (0.15 mmol. 1.17 equiv), and water (0.05 mL). The reaction was brought to reflux for 2 h and was subsequently cooled to 23 ºC and concentrated under reduced pressure. The crude mixture was then diluted with water and extracted with EtOAc (3x), washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried with Na_2SO_4, and concentrated under reduced pressure. The material was used in the next step without further purification assuming quantitative yield.

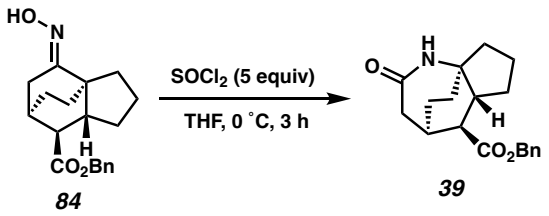
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.28 (m, 5H), 5.20 – 5.06 (m, 2H), 2.52 – 2.46 (m, 2H), 2.43 – 2.39 (m, 1H), 2.39 – 2.36 (m, 1H), 2.15 (dtd, *J* = 10.2, 8.2, 1.8 Hz, 1H), 2.07 (ddt, *J* = 11.9, 8.3, 4.1 Hz, 1H), 1.98 (ddd, *J* = 13.0, 11.0, 8.0 Hz, 1H), 1.82 – 1.71 (m, 3H), 1.67 (ddd, *J* = 10.9, 3.6, 1.8 Hz, 1H), 1.48 (dddd, *J* = 12.5, 7.8, 6.5, 3.7 Hz, 2H), 1.36 (dddd, *J* = 23.6, 11.1, 8.8, 2.6 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 165.4, 136.2, 128.7, 128.4, 128.2, 66.5, 48.2, 45.7, 44.4, 30.6, 29.2, 28.9, 28.1, 27.2, 25.5, 22.6.

IR (Neat Film, NaCl): 2945, 1731, 1161 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{19}H_{23}NO_3$ $[M]^+$: 313.1678, found 313.1676.

Optical Rotation: $[\alpha]_D^{21}$ –22.0 (c 0.37, $CHCl_3$).



84 *39*

benzyl (4*R*,5*S*,5a*R*,8a*R*)-2-oxooctahydro-1*H*-4,8a-ethanocyclopenta[*b*]azepine-5-carboxylate (39)

To a solution of **84** (0.125 mmol, 1 equiv) in THF (1.25 mL) at 0 ºC was added a solution of $SOCl_2$ (0.625 mmol, 5 equiv) in THF (0.23 mL). The reaction was stirred for 3 h at 0 ºC, followed by dilution with water. Aqueous solution NH_4OH was added to the reaction mixture until neutral, and the aqueous layer was extracted with dichloromethane (3x). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography (35% EtOAc/hexanes) afforded the title compound as a colorless oil (22 mg, 0.167 mmol, 56% yield over two steps).

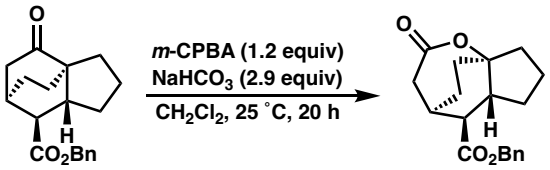
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.27 (m, 5H), 6.67 (s, 1H, br), 5.15 (q, *J* = 12.3 Hz, 2H), 2.73 (dt, *J* = 18.1, 1.6 Hz, 1H), 2.62 (tdd, *J* = 9.9, 8.0, 1.4 Hz, 1H), 2.48 (dd, *J* = 18.4, 6.9 Hz, 1H), 2.40 – 2.32 (m, 2H), 2.29 – 2.16 (m, 1H), 1.95 (dtd, *J* = 12.7, 8.7, 2.2 Hz, 1H), 1.82 – 1.62 (m, 7H), 1.62 – 1.52 (m, 1H), 1.44 – 1.30 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 174.2, 135.9, 128.8, 128.4, 128.3, 66.7, 59.9, 48.8, 48.5, 39.2, 33.3, 31.1, 29.8, 25.1, 23.3.

IR (Neat Film, NaCl): 3182, 3055, 2934, 1727, 1648, 1456, 1398, 1167 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{19}H_{23}NO_3$ $[M]^+$: 313.1678, found 313.1678.

Optical Rotation: $[\alpha]_D^{21}$ –5.5 (c 0.89, $CHCl_3$).



11a ***40***

benzyl (4*R*,5*S*,5a*R*,8a*R*)-2-oxooctahydro-4,8a-ethanocyclopenta[*b*]oxepine-5-carboxylate (40)

To a solution ketone **11a** (37 mg, 0.13 mmol, 1 equiv) in CH_2Cl_2 (1.25 mL, 0.1 M) at 0°C was added $NaHCO_3$ (30.8 mg, 0.37 mmol, 2.9 equiv). Subsequently, *m*-CPBA (31 mg, 0.15 mmol, 1.2 equiv) was added and the reaction was allowed to warm to 25 °C. Upon complete consumption of starting material (as determined by TLC), the reaction mixture was diluted with a saturated solution of $Na_2S_2O_3$ and extracted with Et_2O (3x). The combined organic layers were washed with a saturated solution of $NaHCO_3$ followed by brine, dried over Na_2SO_4, and volatiles were removed in vacuo. Purification by preparatory thin layer chromatography (30% EtOAc/hexanes) afforded the title compound as a clear oil (16 mg, 0.05 mmol, 41% yield).

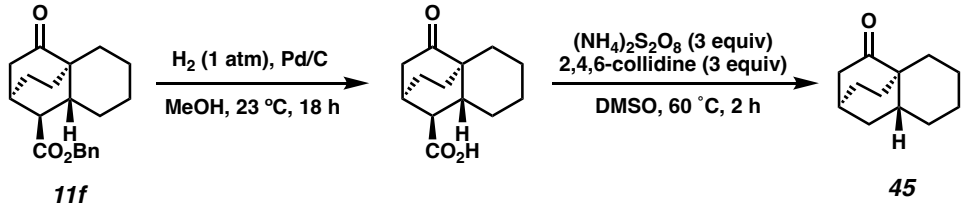
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.29 (m, 5H), 5.22 – 5.10 (m, 2H), 2.97 (ddd, *J* = 19.0, 2.5, 1.4 Hz, 1H), 2.83 – 2.61 (m, 2H), 2.41 – 2.32 (m, 2H), 2.28 – 2.09 (m, 3H), 2.05 – 1.93 (m, 1H), 1.81 – 1.56 (m, 5H), 1.40 – 1.26 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 172.9, 135.7, 128.8, 128.6, 128.3, 88.4, 66.9, 47.8, 46.5, 39.6, 39.1, 32.8, 30.4, 29.7, 24.9, 22.7.

IR (Neat Film, NaCl): 2943, 2873, 1722, 1255, 1189, 1167 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{19}H_{22}O_4$ $[M]^+$: 314.1518, found 314.1521.

Optical Rotation: $[\alpha]_D^{21}$ –15.8 (c 1.00, $CHCl_3$).



11f *45*

(2*S*,4a*R*,8a*R*)-octahydro-2*H*-2,4a-ethanonaphthalen-9-one (45)

A vial containing ketone **11f** (0.72 mmol, 1 equiv) and Pd/C (10 wt. % with 67% H_2O, 0.072 mmol, 0.1 equiv) was evacuated and backfilled with H_2. Methanol (1.06 mL) was subsequently added, and the reaction was stirred at 23 ºC overnight. The crude reaction mixture was filtered through a silica plug and concentrated under reduced pressure to afford the corresponding acid as a white solid, which was used without further purification.

To a solution of the crude acid (0.62 mmol, 1 equiv) in DMSO (1.24 mL) was added $(NH_4)_2S_2O_8$ (1.86 mmol, 3 equiv) and 2,4,6-collidine (1.86 mmol, 3 equiv). The mixture was purged with N_2 for 5 min and was subsequently sealed and heated to 60 ºC for 2 h with stirring. The reaction mixture was diluted with dichloromethane, washed with brine (1x), and the aqueous layer was extracted with dichloromethane (3x). The combined organic layers were washed with brine (3x), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography (15% EtOAc/hexanes) afforded the title compound as a white solid (30.2 mg, 0.167 mmol, 27% yield).

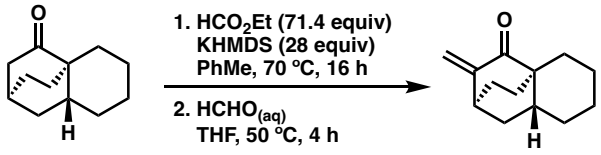
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 – 2.21 (m, 3H), 2.13 – 2.07 (m, 1H), 1.93 (dddd, *J* = 13.3, 10.6, 3.8, 2.8 Hz, 1H), 1.75 – 1.58 (m, 6H), 1.53 (dd, *J* = 13.6, 4.0 Hz, 1H), 1.47 – 1.38 (m, 2H), 1.38 – 1.28 (m, 1H), 1.27 – 1.17 (m, 1H), 1.17 – 1.05 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 218.6, 44.9, 43.9, 34.5, 34.1, 30.6, 29.0, 27.7, 25.9, 25.9, 21.8, 21.4.

IR (Neat Film, NaCl): 2925, 1716 cm^{-1}

HRMS (MM: FI+): *m/z* calc'd for $C_{12}H_{18}O$ $[M]^+$: 178.1358, found 178.1359.

Optical Rotation: $[\alpha]_D^{21}$ –59.9 (c 0.89, $CHCl_3$).



45 ***46***

(2*S*,4a*R*,8a*R*)-10-methyleneoctahydro-2*H*-2,4a-ethanonaphthalen-9-one (46)

To a solution of ketone **45** (0.056 mmol, 1 equiv) and ethyl formate (4 mmol, 71.4 equiv) in toluene (3.2 mL) was added a solution of KHMDS (0.5 M in toluene, 1.6 mmol, 28 equiv) at 23 ºC. The reaction mixture was stirred at 70 ºC for 16 h. Upon cooling to 0 ºC, THF (6.4 mL) and formalin (37% in water, 3.2 mL) was added, and then the reaction was heated to 50 ºC for 4 h. The reaction mixture was diluted with a saturated aqueous solution of NH_4Cl, extracted with EtOAc (3x), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by preparatory thin layer chromatography (30% EtOAc/hexanes, 2x) afforded the title compound as a yellow oil (4.4 mg, 0.023 mmol, 41% yield).

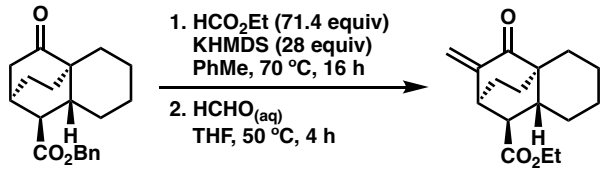
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.93 (d, *J* = 1.8 Hz, 1H), 5.15 (d, *J* = 1.8 Hz, 1H), 2.66 (p, *J* = 3.0 Hz, 1H), 2.39 – 2.19 (m, 1H), 1.98 (dddd, *J* = 13.2, 10.6, 3.9, 2.8 Hz, 1H), 1.81 – 1.61 (m, 6H), 1.51 – 1.42 (m, 2H), 1.41 – 1.31 (m, 2H), 1.23 – 1.15 (m, 2H), 1.11 (dt, *J* = 12.9, 3.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.3, 147.9, 116.3, 45.0, 36.1, 35.0, 34.7, 30.8, 29.0, 26.5, 26.0, 21.6, 21.3.

IR (Neat Film, NaCl): 2926, 2859, 1708, 1630, 1464, 1449 cm^{-1}

HRMS (MM: FD+): *m/z* calc'd for $C_{13}H_{18}O$ $[M]^+$: 190.1358, found 190.1353.

Optical Rotation: $[\alpha]_D^{21}$ –34.2 (c 0.29, $CHCl_3$).



11f ***47***

ethyl (1*S*,2*S*,4a*R*,8a*R*)-3-methylene-4-oxooctahydro-2*H*-2,4a-ethanonaphthalene-1-carboxylate (47)

To a solution of **11f** (0.192 mmol, 1 equiv) and ethyl formate (13.71 mmol, 71.4 equiv) in toluene (11.1 mL) was added a solution of KHMDS (0.5 M in toluene, 5.49 mmol, 28 equiv) at 23 ºC. The reaction mixture was stirred at 70 ºC for 16 h. Upon cooling to 0 ºC, THF (22.2 mL) and formalin (37% in water, 11.1 mL) was added, and then the reaction was heated to 50 ºC for 4 h. The reaction mixture was diluted with a saturated aqueous solution of NH_4Cl, extracted with EtOAc (3x), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by preparatory thin layer chromatography (30% EtOAc/hexanes, 2x) afforded the title compound as a yellow oil (13.1 mg, 0.05 mmol, 26% yield).

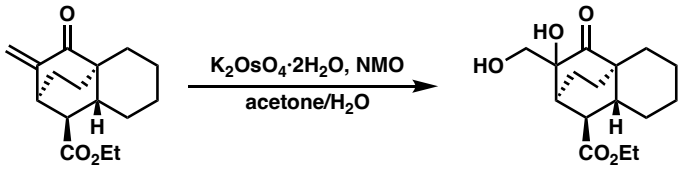
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.99 (d, *J* = 1.7 Hz, 1H), 5.17 (d, *J* = 1.7 Hz, 1H), 4.21 – 4.01 (m, 2H), 3.04 (td, *J* = 3.1, 2.0 Hz, 1H), 2.27 (ddd, *J* = 14.2, 11.4, 5.4 Hz, 1H), 2.21 (dd, *J* = 6.8, 2.0 Hz, 1H), 2.01 (dddd, *J* = 11.6, 6.5, 4.4, 1.7 Hz, 1H), 1.92 – 1.75 (m, 3H), 1.73 – 1.65 (m, 2H), 1.56 – 1.50 (m, 1H), 1.47 – 1.31 (m, 2H), 1.29 – 1.16 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 203.7, 173.8, 144.3, 119.0, 60.8, 51.1, 45.0, 39.1, 37.2, 30.3, 28.9, 26.2, 25.8, 21.3, 21.1, 14.4.

IR (Neat Film, NaCl): 2927, 2867, 1732, 1708, 1449, 1180 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{16}H_{22}O_3$ $[M]^+$: 262.1569, found 262.1576.

Optical Rotation: $[\alpha]_D^{21}$ –3.9 (c 0.38, $CHCl_3$).



47 ***48***

ethyl (1*R*,2*S*,4a*R*,8a*R*)-3-hydroxy-3-(hydroxymethyl)-4-oxooctahydro-2*H*-2,4a-ethanonaphthalene-1-carboxylate (48)

A flame dried vial was charged with enone **47** (14.7 mg, 0.056 mmol, 1 equiv) and acetone (2.3 mL, 0.024 M) and water (0.6 mL, 0.094 M). NMO (50 wt. % in H_2O) (23 µL, 0.112 mmol, 2 equiv) was added and the solution was cooled to 0 ºC. $K_2OsO_4 \cdot 2H_2O$ (2.1 mg, 0.006 mmol, 0.1 equiv) was added to the solution. The resultant solution was slowly warmed to 23 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction was quenched with a saturated solution of $Na_2S_2O_3$ and stirred for 30 min. The mixture was then diluted with CH_2Cl_2 and the product was extracted with CH_2Cl_2 (2 x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparatory thin layer chromatography (50% EtOAc/hexanes) afforded the title compound as a colorless oil (2.1 mg, 0.007 mmol,13% yield, 10:1 dr). In the ^1H NMR, peaks that correspond to the minor diastereomer closely resemble the major diastereomer. dr was determine through integration of ^1H NMR peaks 2.69 ppm (major) and 2.96 ppm (minor).

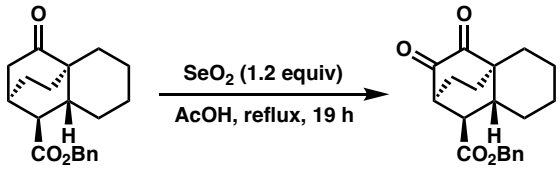
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.15 (q, *J* = 7.1 Hz, 2H), 3.81 (dd, *J* = 11.8, 2.6 Hz, 1H), 3.54 (dd, *J* = 11.9, 2.7 Hz, 1H), 2.71 – 2.67 (m, 1H), 2.38 – 2.24 (m, 2H), 2.10 (d, *J* = 7.3 Hz, 1H), 1.94 – 1.64 (m, 7H), 1.47 – 1.18 (m, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 218.4, 174.8, 75.8, 65.8, 61.0, 48.9, 45.4, 37.3, 37.2, 30.3, 28.3, 25.6, 22.5, 21.0, 14.3.

IR (Neat Film, NaCl): 3468, 2930, 2355, 1716, 1197, 1033 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{16}H_{24}O_5$ $[M]^+$: 296.1624, found 296.1619.

Optical Rotation: $[\alpha]_D^{21}$ 2.1 (c 0.24, $CHCl_3$).



11f ***49***

benzyl (1*R*,2*S*,4a*R*,8a*R*)-3,4-dioxooctahydro-2*H*-2,4a-ethanonaphthalene-1-carboxylate (49)

To a solution of **11f** (0.064 mmol, 1 equiv) in glacial acetic acid (0.1 mL) was added SeO_2 (0.077 mmol, 1.2 equiv). The reaction was brought to reflux for 19 h. After cooling to 23 ºC, the reaction mixture was filtered and concentrated under reduced pressure. The resulting crude mixture was dissolved in EtOAc and washed with water (5x), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by preparatory thin layer chromatography (30% EtOAc/hexanes) afforded the title compound as a yellow oil (10.4 mg, 0.031 mmol, 48% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.28 (m, 5H), 5.19 – 5.04 (m, 2H), 3.00 (m, 1H), 2.54 (dd, *J* = 6.4, 2.3 Hz, 1H), 2.40 (ddd, *J* = 14.6, 10.3, 6.9 Hz, 1H), 2.02 (m, 3H), 1.80 –

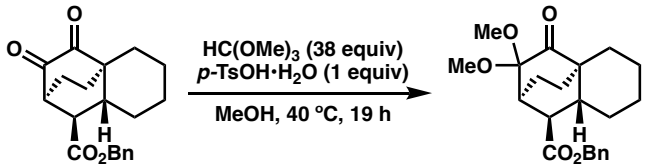
1.69 (m, 2H), 1.68 – 1.50 (m, 3H), 1.48 – 1.38 (m, 1H), 1.33 (dt, *J* = 13.4, 3.5 Hz, 1H), 1.29 – 1.15 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7, 196.1, 173.2, 135.4, 128.8, 128.6, 128.4, 67.4, 49.9, 48.0, 46.3, 37.9, 30.2, 28.3, 25.5, 22.7, 20.5, 20.2.

IR (Neat Film, NaCl): 2932, 2857, 1731, 1454, 1155 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{20}H_{22}O_4$ $[M]^+$: 326.1518, found 326.1532.

Optical Rotation: $[\alpha]_D^{21}$ –49.2 (c 1.04, $CHCl_3$).



49 ***50***

benzyl (1*R*,2*S*,4a*R*,8a*R*)-3,3-dimethoxy-4-oxooctahydro-2*H*-2,4a-ethanonaphthalene-1-carboxylate (50)

To a solution of diketone **49** (0.031 mmol, 1 equiv) in methanol (0.13 mL) was added $HC(OMe)_3$ (1.2 mmol, 38 equiv) and *p*-TsOH•H_2O (0.031 mmol, 1 equiv). The reaction was stirred for 19 h at 40 ºC, followed by dilution with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with EtOAc (4x), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by preparatory thin layer chromatography (30% EtOAc/hexanes) afforded the title compound as a yellow oil (4.7 mg, 0.013 mmol, 41% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.29 (m, 5H), 5.26 (d, *J* = 12.3 Hz, 1H), 5.02 (d, *J* = 12.3 Hz, 1H), 3.20 (s, 3H), 3.06 (s, 3H), 2.93 (dt, *J* = 4.2, 2.2 Hz, 1H), 2.29 – 2.11 (m,

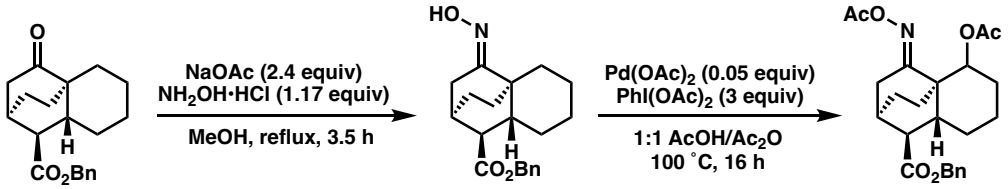
3H), 1.98 – 1.89 (m, 1H), 1.83 (dddd, J = 13.8, 11.4, 6.7, 2.4 Hz, 1H), 1.70 – 1.58 (m, 4H), 1.54 (d, J = 3.9 Hz, 1H), 1.31 (dd, J = 10.8, 2.4 Hz, 1H), 1.27 – 1.19 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 209.0, 173.5, 136.5, 128.6, 128.5, 128.2, 97.4, 66.4, 50.4, 48.8, 48.4, 45.5, 36.4, 34.9, 30.0, 29.1, 25.5, 23.1, 21.0, 21.0.

IR (Neat Film, NaCl): 2933, 2855, 1736, 1449, 1172 cm^{-1}

HRMS (MM: FD+): *m/z* calc'd for $C_{22}H_{28}O_5$ $[M]^+$: 372.1937, found 372.1931.

Optical Rotation: $[\alpha]_D^{21}$ –26.2 (c 0.42, $CHCl_3$).



benzyl (1*S*,2*R*,4a*S*,8a*R*,*E*)-5-acetoxy-4-(acetoxyimino)octahydro-2*H*-2,4a-ethanonaphthalene-1-carboxylate (51)

To a stirred solution of ketone **11f** (0.096 mmol, 1 equiv) in methanol (0.93 mL) was added NaOAc (0.23 mmol, 2.4 equiv), NH_2OH•HCl (0.111 mmol, 1.17 equiv), and water (0.033 mL). The reaction was brought to reflux for 3.5 h and was subsequently cooled to 23 ºC and concentrated under reduced pressure. The crude mixture was then diluted with water and extracted with EtOAc (3x), washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried with Na_2SO_4, and concentrated under reduced pressure. The crude oxime was dissolved in a 1:1 mixture of AcOH/Ac_2O (0.78 mL). The reaction vessel was sealed and stirred at 23 ºC for 2 h. $Pd(OAc)_2$ (0.0048 mmol, 0.05 equiv) and $PhI(OAc)_2$ (0.288 mmol, 3 equiv) were subsequently added, and the reaction was heated to 100 ºC for 16 h. The reaction mixture was cooled to 23 ºC, filtered through a silica plug, and the filtrate was

diluted with EtOAc. The organic layer was washed with a saturated solution of $NaHCO_3$ until not acidic, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by preparatory thin layer chromatography (30% EtOAc/hexanes) afforded the title compound (**51**) as a yellow oil (12.3 mg, 0.0288 mmol, 30% yield over two steps).

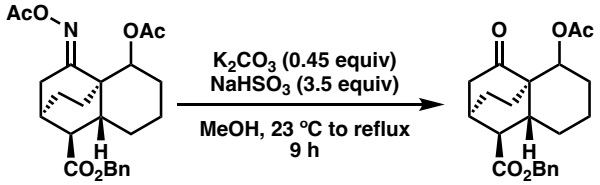
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.27 (m, 5H), 5.31 – 5.20 (m, 1H), 5.20 – 5.02 (m, 2H), 2.62 (dt, *J* = 20.2, 3.5 Hz, 1H), 2.40 – 2.29 (m, 2H), 2.27 – 2.17 (m, 1H), 2.14 (s, 3H), 2.02 (s, 3H), 1.89 (m, 1H), 1.83 – 1.69 (m, 4H), 1.62 (t, *J* = 2.8 Hz, 2H), 1.46 – 1.28 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 170.6, 170.4, 168.9, 135.9, 128.8, 128.5, 128.2, 71.7, 66.9, 49.6, 42.2, 39.1, 29.5, 28.9, 28.6, 26.9, 25.5, 23.0, 21.4, 20.2, 16.7.

IR (Neat Film, NaCl): 2930, 1764, 1731, 1456, 1371, 1248, 1210 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{24}H_{29}NO_6$ $[M]^+$: 427.1995, found 427.2017.

Optical Rotation: $[\alpha]_D^{21}$ –27.6 (c 1.00, $CHCl_3$).



51 ***52***

benzyl (1*S*,2*R*,4a*R*,8a*R*)-5-acetoxy-4-oxooctahydro-2*H*-2,4a-ethanonaphthalene-1-carboxylate (52)

To a solution of **51** (0.029 mmol, 1 equiv) in methanol (0.06 mL) in a loosely capped vial was added K_2CO_3 (0.013 mmol, 0.45 equiv) at 23 ºC in three portions over 6 h. $NaHSO_3$ (0.1 mmol, 3.5 equiv) and water (0.06 mL) were subsequently added, and the vial was

sealed and heated to 80 ºC for 3 h. The reaction mixture was diluted with $CHCl_3$, rinsed with 1 M HCl, and the aqueous layer was extracted with $CHCl_3$ (3x). The combined organic layers were neutralized with a saturated solution of $NaHCO_3$, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by preparatory thin layer chromatography (35% EtOAc/hexanes) afforded the title compound as a colorless oil (1.8 mg, 0.0056 mmol, 19% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.30 (m, 5H), 5.19 – 5.06 (m, 3H), 2.48 (m, 1H), 2.41 (dt, *J* = 19.2, 2.8 Hz, 1H), 2.29 (dt, *J* = 6.9, 2.0 Hz, 1H), 2.16 – 2.04 (m, 3H), 1.98 (s, 3H), 1.94 – 1.89 (m, 1H), 1.87 – 1.79 (m, 3H), 1.78 – 1.73 (m, 1H), 1.71 (m, 2H), 1.46 – 1.29 (m, 3H).

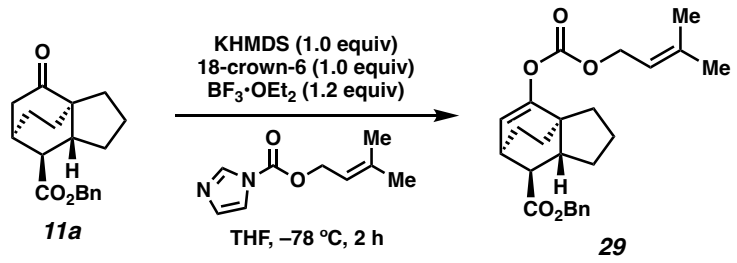
^{13}C NMR (100 MHz, $CDCl_3$): δ 212.2, 173.9, 170.2, 135.9, 128.8, 128.5, 128.3, 70.8, 66.9, 49.4, 48.5, 40.5, 37.9, 30.7, 29.0, 26.7, 25.8, 22.9, 21.3, 15.7.

IR (Neat Film, NaCl): 2928, 1781, 1375, 1246, 1173 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{22}H_{26}O_5$ $[M]^+$: 370.1780, found 370.1774.

Optical Rotation: $[\alpha]_D^{21}$ –18.3 (c 0.18, $CHCl_3$).

Preparation of Additional Compounds



benzyl (3a*R*,6*R*,7*S*,7a*R*)-4-oxooctahydro-3a,6-ethanoindene-7-carboxylate (29)

42

To a solution of KHMDS (40 mg, 0.20 mmol, 1.0 equiv) and 18-crown-6 (53 mg, 0.20 mmol, 1 equiv) in THF (2.0 mL) at –78 ºC was added a solution of **11a** (60 mg, 0.20 mmol, 1 equiv). Stirring was continued at –78 ºC for 30 minutes, then a pre-mixed solution of 3-methylbut-2-en-1-yl 1*H*-imidazole-1-carboxylate (43 mg, 0.24 mmol, 1.2 equiv) and boron trifluoride diethyl etherate (30 μL, 0.24 mmol, 1.2 equiv) in THF (1.2 mL) was added dropwise. After two additional hours of stirring at –78 ºC, EtOAc and saturated aqueous NH_4Cl were added. The layers were separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and solvent was removed in vacuo. The crude mixture was purified by silica gel flash column chromatography (0–40% EtOAc/hexanes) to afford enol carbonate **29** as a colorless oil (44 mg, 0.11 mmol, 55% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.29 (m, 5H), 5.70 (d, *J* = 6.8 Hz, 1H), 5.42 – 5.36 (m, 1H), 5.09 (d, *J* = 3.6 Hz, 2H), 4.65 (d, *J* = 7.3 Hz, 2H), 3.08 – 2.96 (m, 1H), 2.25 (d, *J*

= 5.6 Hz, 1H), 2.07 – 1.97 (m, 2H), 1.91 – 1.79 (m, 3H), 1.77 (s, 3H), 1.73 (s, 3H), 1.63 – 1.54 (m, 2H), 1.52 – 1.38 (m, 3H), 1.35 – 1.28 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 155.6, 153.5, 140.6, 136.4, 128.7, 128.2, 128.0, 117.9, 112.8, 66.3, 65.3, 51.3, 48.1, 48.1, 35.5, 28.4, 28.4, 27.3, 25.9, 24.6, 22.8, 18.3.

IR (Neat Film, NaCl): 2953, 2870, 1754, 1735, 1241, 1226, 1150 cm^{-1}

HRMS (MM: FD+): *m/z* calc'd for $C_{25}H_{30}O_5$ $[M]^+$: 410.2093, found 410.2094.

SFC conditions: 20% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): minor = 3.05, major = 3.40.

1.4.3 DETERMINATION OF ABSOLUTE AND RELATIVE STEREOCHEMISTRY BY VCD SPECTROSCOPY

Experimental Protocol: A solution of the compound of interest (50 mg/mL) in $CDCl_3$ was loaded into a front-loading SL-4 cell (International Crystal Laboratories) possessing BaF_2 windows and a 100 mm path length. Infrared (IR) and VCD spectra were acquired on a BioTools ChiralIR-2X VCD spectrometer as a set of 24 one-hour blocks (24 blocks, 3120 scans per block) in dual PEM mode. A 15-minute acquisition of neat (+)-α-pinene control yielded a VCD spectrum in agreement with literature spectra. IR and VCD spectra were background corrected using a 30-minute block IR acquisition of the empty instrument chamber under gentle N_2 purge, and were solvent corrected using a 16-hour (16 blocks, 3120 scans per block) IR/VCD acquisition of $CDCl_3$ in the same 100 μm BaF2 cell. The reported spectra represent the result of block averaging.

Both enantiomers of compounds **11a**, **11q**, and **11q'** were prepared from the *(S)* and *(R)* enantiomers of the *t*-BuPHOX ligand. Data were collected for both enantiomers of

compounds at identical concentration and the final reported VCD spectra are the half-difference of the spectra of the compounds derived from the *(S)* minus *(R)* enantiomer of ligand. Due to limited sample size, spectra of cycloadducts **11k'** and **11k''** were collected at concentrations of 11.7 and 9.3 mg/mL, respectively.

Computational Protocol: An arbitrarily chosen enantiomer of the compound of interest was subjected to an exhaustive initial molecular mechanics-based conformational search (OPLS_2005 force field, $CHCl_3$ solvent, 10.0 kcal/mol cutoff, "Enhanced" torsional sampling) as implemented in MacroModel program.[50] The resulting ensemble of conformers was subsequently optimized using the B3PW91 functional, cc-pVTZ(-f) basis, and implicit PBF solvation model for chloroform using the Jaguar program.[51] Harmonic frequencies computed at the B3PW91/cc-pVTZ(-f)/PBF(chloroform) level were scaled by 0.98. The resultant structurally unique conformers possessing all positive Hessian eigenvalues were Boltzmann weighted by relative free energy at 298.15 K. The predicted IR and VCD frequencies and intensities of the retained conformers were convolved using Lorentzian line shapes (γ = 4 cm^{-1}) and summed using the respective Boltzmann weights to yield the final predicted IR and VCD spectra. The predicted VCD of the opposite enantiomer was generated by inversion of sign.

VCD Analysis for diastereomers 11a, 11q, and 11q'

Figure 1.9. *Three diastereomers* ***11a***, ***11q***, *and* ***11q'*** *to be compared to spectra computed from all eight possible stereoisomers.*

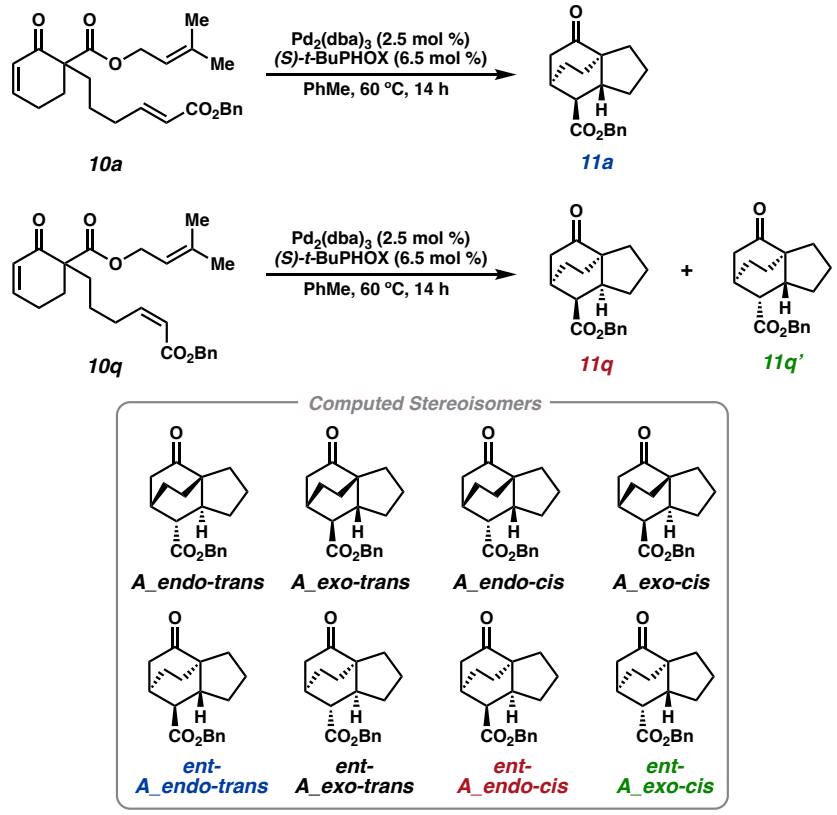
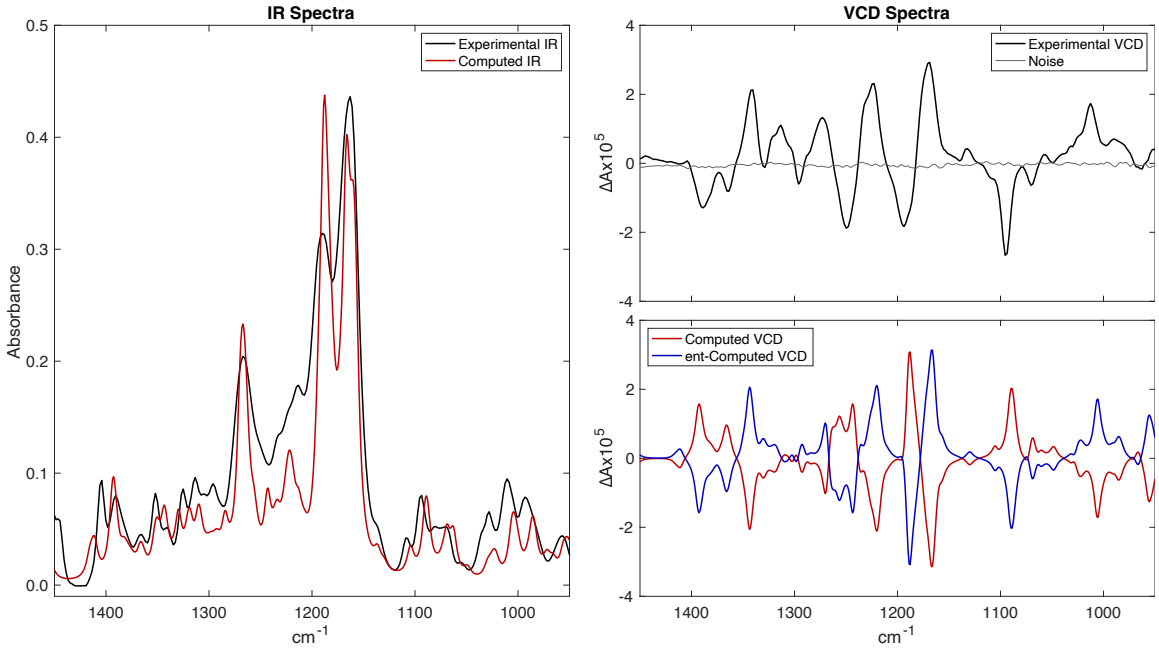


***Figure 1.10**. Comparison of experimental VCD and IR spectra for product **11a** to computed spectra for **A_endo-trans**.*[a]



[a] Experimental IR spectrum in good agreement with computed spectrum. Experimental VCD spectrum for **11a** is in excellent agreement with computed spectrum for ***ent*-A_endo-trans**.

***Figure 1.11**. Overlayed experimental and calculated VCD spectra for **11a** – assigned as **ent-A_endo-trans**.*

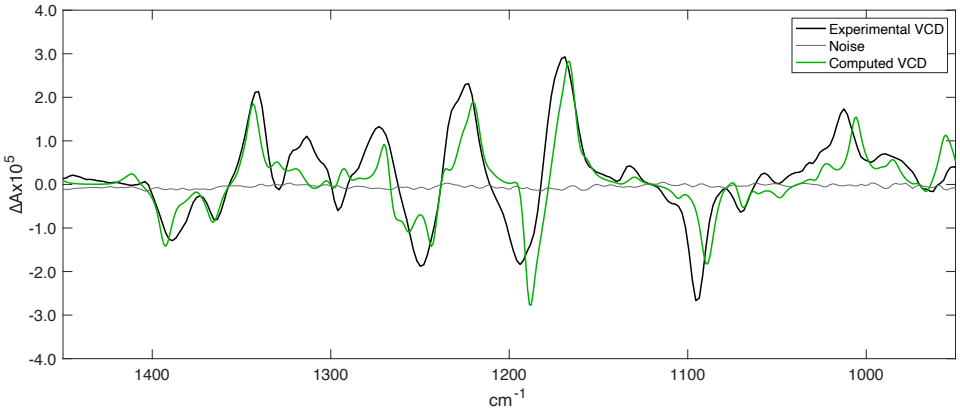
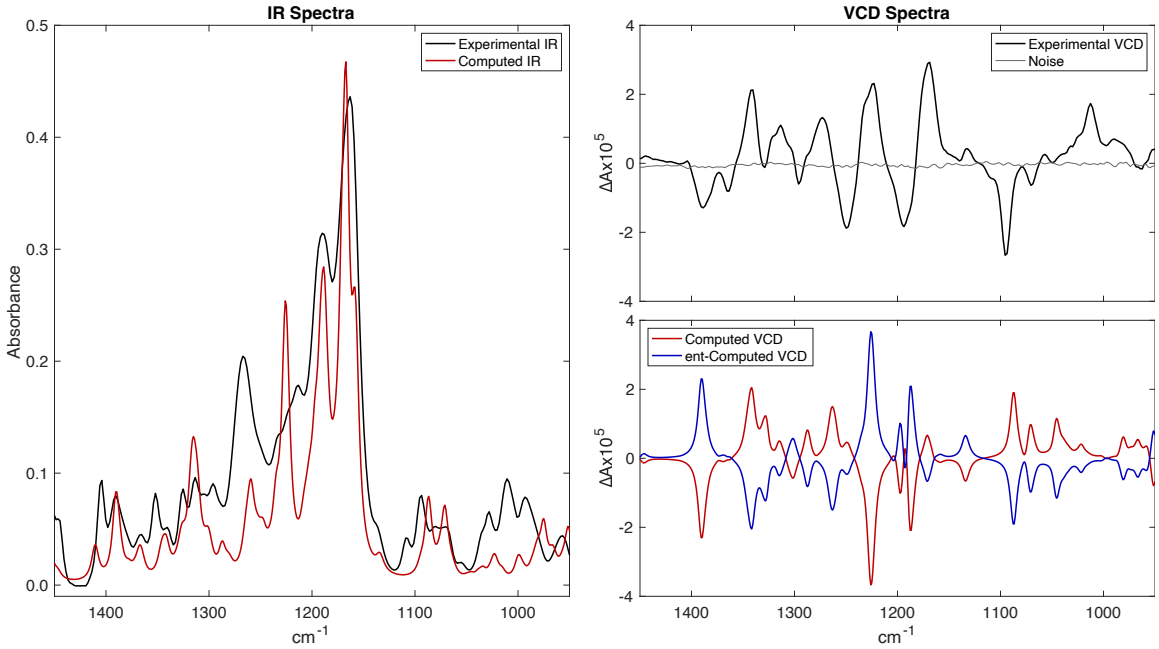
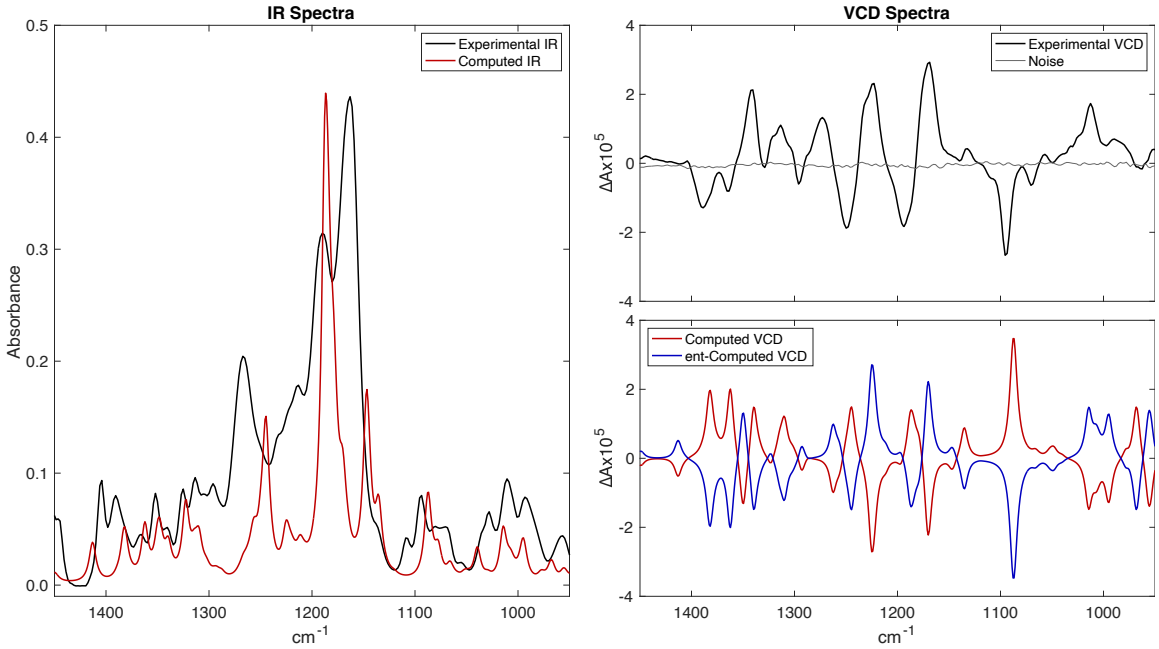


***Figure 1.12**. Comparison of experimental VCD and IR spectra for product **11a** to computed spectra for **A_exo-trans**.*[a]



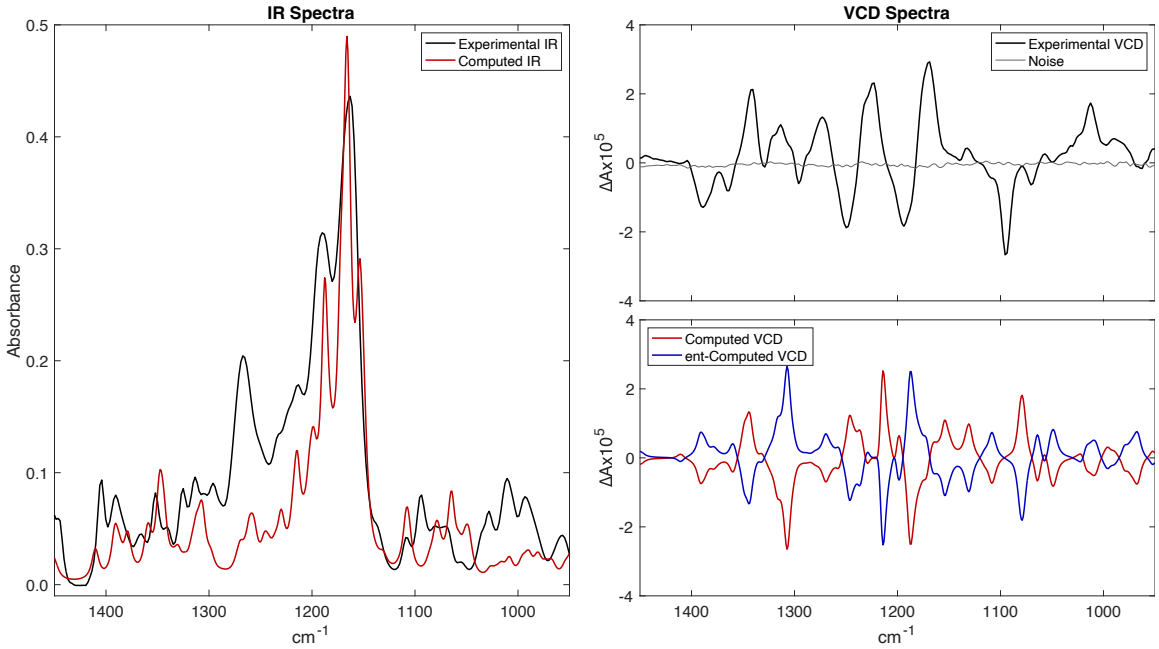
[a] A shift of –3 cm^{-1} along x-axis applied to computed spectra in fitting. Experimental data from **11a** do not match computed data of **A_exo-trans**.

***Figure 1.13**. Comparison of experimental VCD and IR spectra for product **11a** to computed spectra for **A_endo-cis**.*[a]



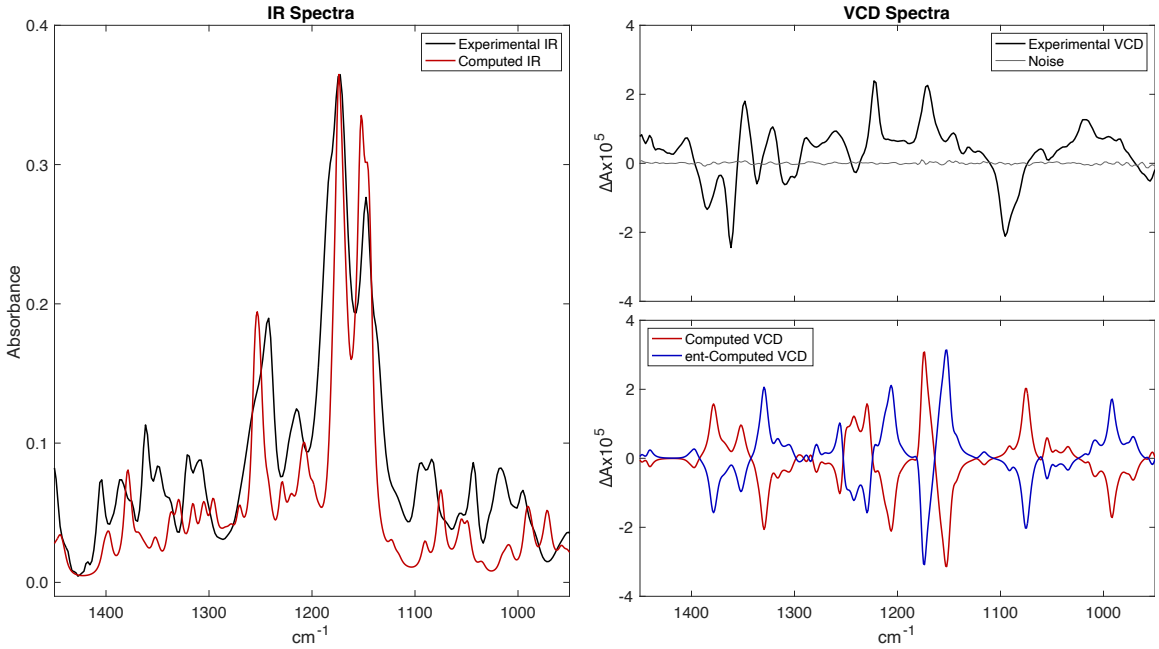
[a] Experimental data from **11a** do not match computed data of **A_endo-cis**.

Figure 1.14. Comparison of experimental VCD and IR spectra for product **11a** to computed spectra for **A_exo-cis**.[a]



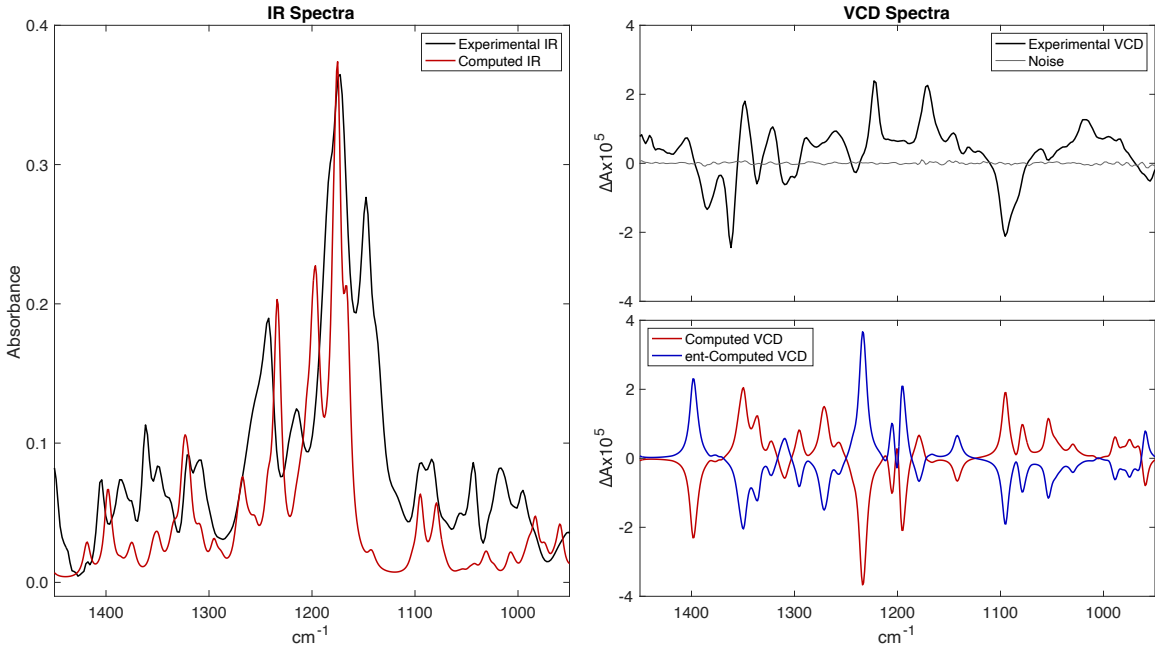
[a] A shift of –3 cm-1 along x-axis applied to computed spectra in fitting. Experimental data from **11a** do not match computed data of **A_exo-cis**.

***Figure 1.15**. Comparison of experimental VCD and IR spectra for product **11q** to computed spectra for **A_endo-trans**.*[a]



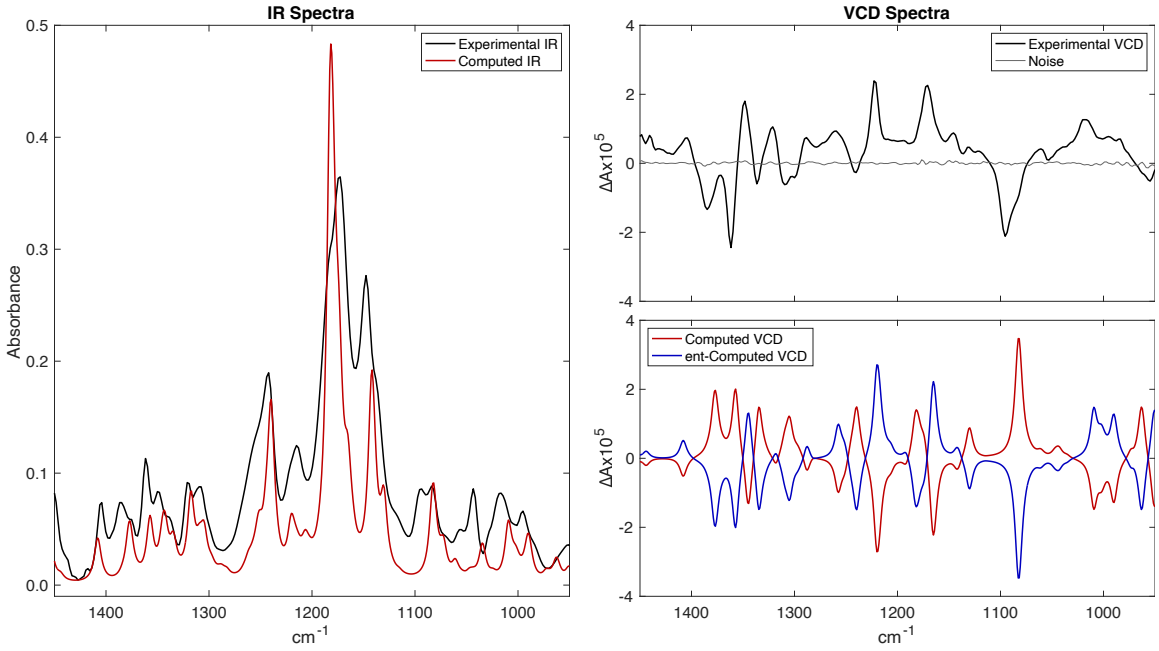
[a] A shift of +14 cm^{-1} along x-axis applied to computed spectra in fitting. The IR spectrum of **11q** contains similar features to the calculated spectrum for **A_endo-trans**; however, the VCD spectrum displays large discrepancies at 1174, 1152, 1330, 1076, and 992 cm^{-1}. **11q** is <u>not</u> assigned as **A_endo-trans**.

***Figure 1.16**. Comparison of experimental VCD and IR spectra for product **11q** to computed spectra for **A_exo-trans**.*



[a] Experimental data from **11q** do not match computed data of **A_exo-trans**.

Figure 1.17. *Comparison of experimental VCD and IR spectra for product* ***11q*** *to computed spectra for* ***A_endo-cis****.*



[a] A shift of +5 cm^{-1} along x-axis applied to computed spectra in fitting. The IR spectrum of **11q** is in good agreement with that of the computed IR spectrum of **A_endo-cis**. Experimental VCD spectrum for **11q** is in excellent agreement with computed spectrum for ***ent*-A_endo-cis**.

Figure 1.18. *Overlayed experimental and calculated VCD spectra for* ***11q*** *– assigned as* ***ent-A_endo-cis****.*

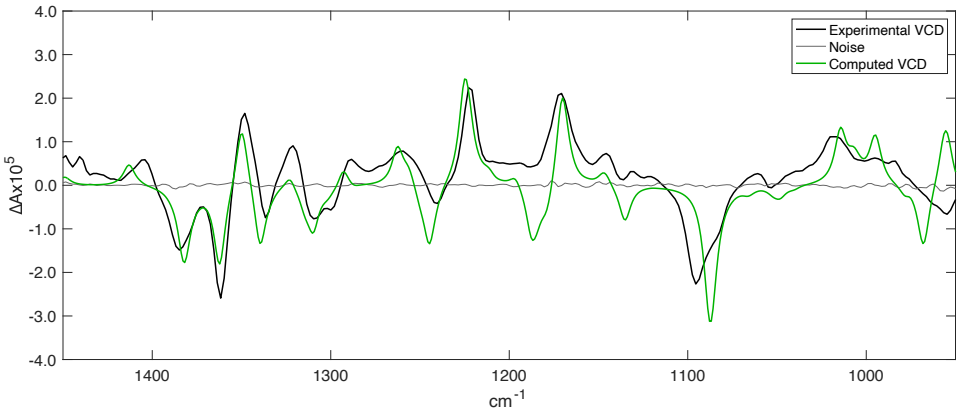
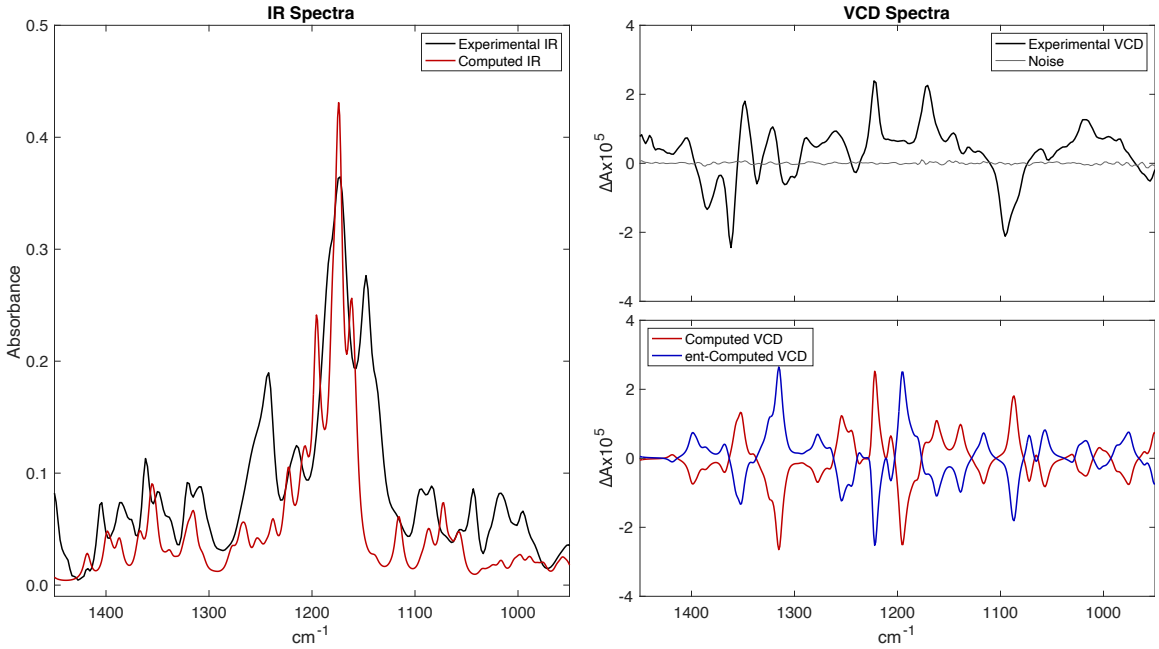
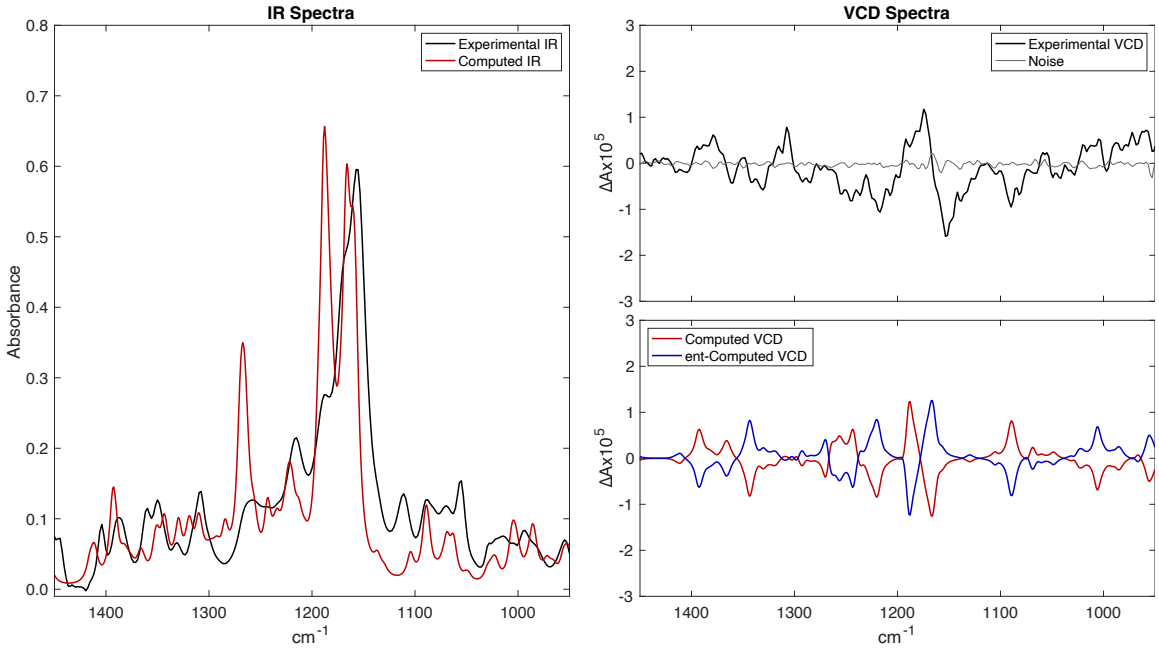


***Figure 1.19**. Comparison of experimental VCD and IR spectra for product **11q** to computed spectra for **A_exo-cis**.*[a]



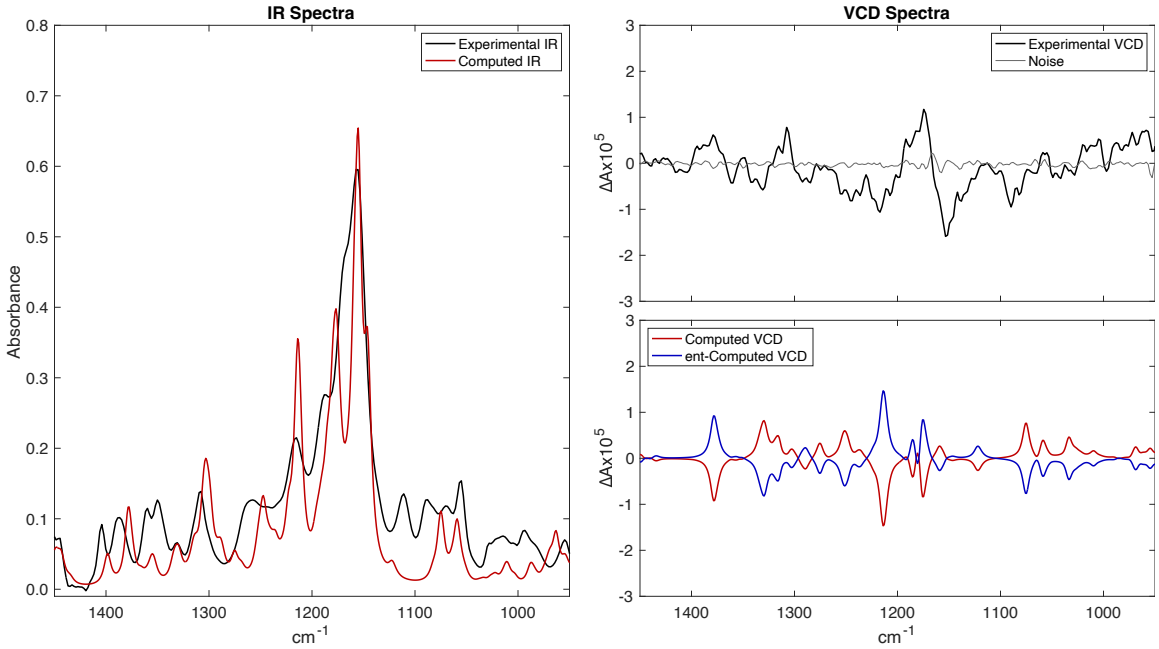
[a] Experimental data from **11q** do not match computed data of **A_exo-cis**.

***Figure 1.20**. Comparison of experimental VCD and IR spectra for product **11q'** to computed spectra for **A_endo-trans**.*[a]



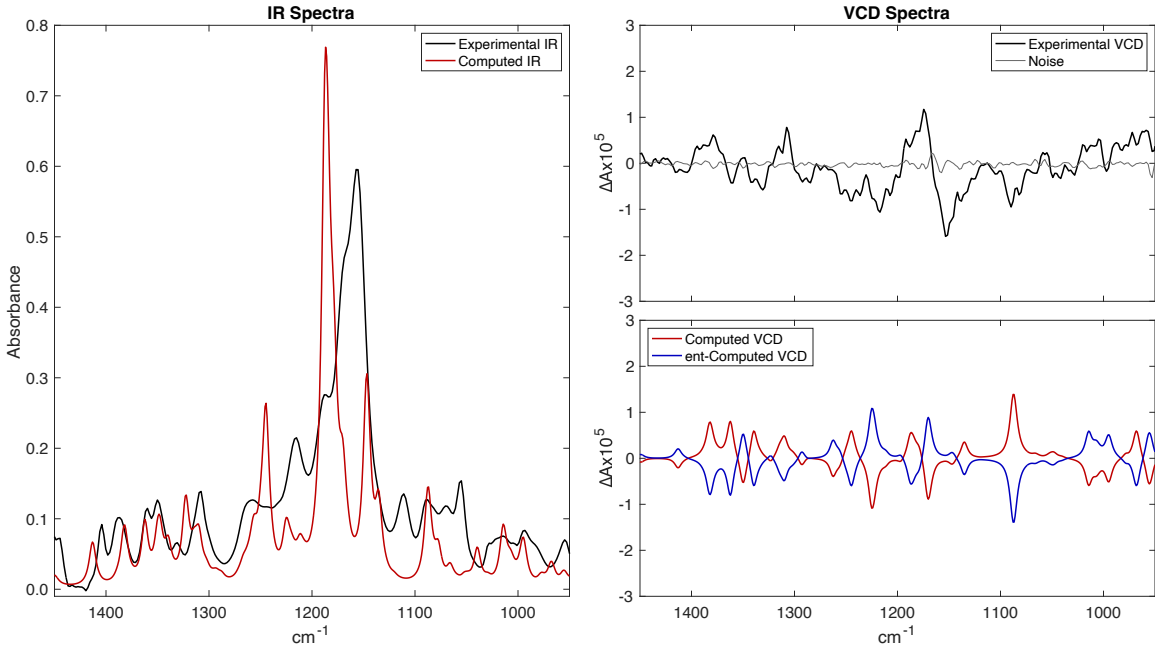
[a] The VCD spectrum was baseline-corrected with a shift of +7 cm^{-1} along y-axis. Experimental data from **11q'** do not match computed data of **A_endo-trans**.

***Figure 1.21**. Comparison of experimental VCD and IR spectra for product **11q'** to computed spectra for **A_exo-trans**.*[a]



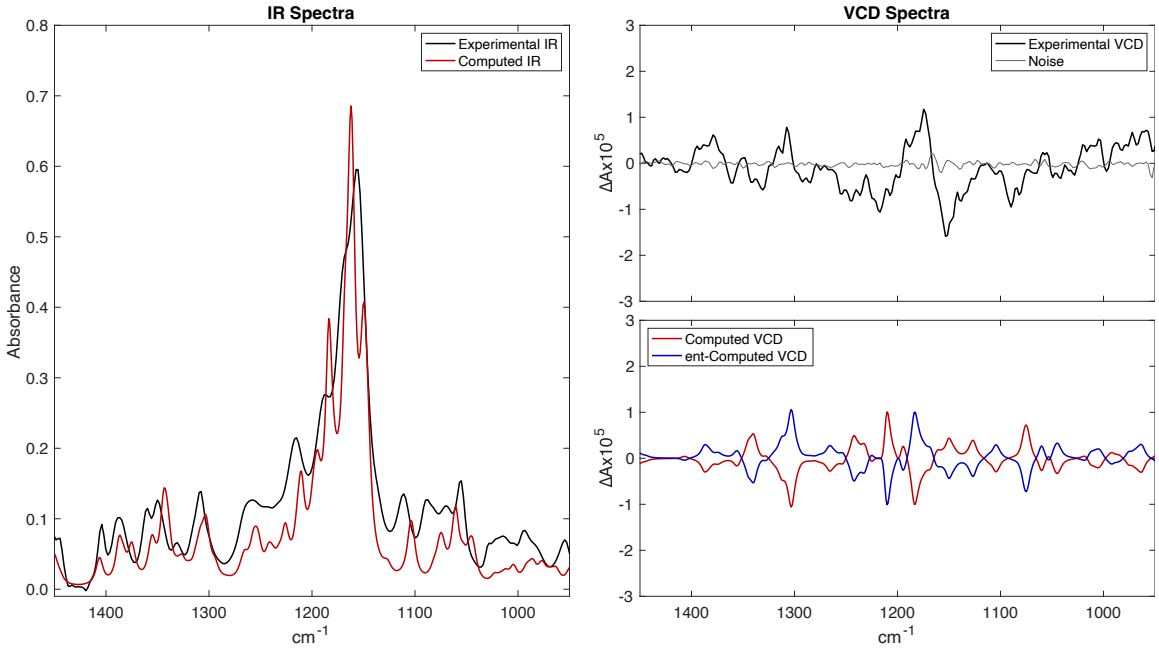
[a] The VCD spectrum of **11q'** was baseline-corrected with a shift of +7 cm^{-1} along y-axis. A shift of -15 cm^{-1} along x-axis applied to computed spectra in fitting. Experimental data from **11q'** do not match computed data of **A_exo-trans**.

Figure 1.22. *Comparison of experimental VCD and IR spectra for product* ***11q'*** *to computed spectra for* ***A_endo-cis****.*[a]



[a] The VCD spectrum of **11q'** was baseline-corrected with a shift of +7 cm^{-1} along y-axis. Experimental data from **11q'** do not match computed data of **A_endo-cis**.

Figure 1.23. *Comparison of experimental VCD and IR spectra for product* ***11q'*** *to computed spectra for* ***A_exo-cis****.*[a]



[a] The VCD spectrum of **11q'** was baseline-corrected with a shift of +7 cm^{-1} along y-axis. A shift of +7 cm^{-1} along x-axis applied to computed spectra in fitting. Experimental VCD spectrum for **11q'** is in good agreement with computed spectrum for ***ent*-A_exo-cis**.

Figure 1.24. *Overlayed experimental and calculated VCD spectra for* ***11q'*** *– assigned as* ***ent-A_exo-cis****.*

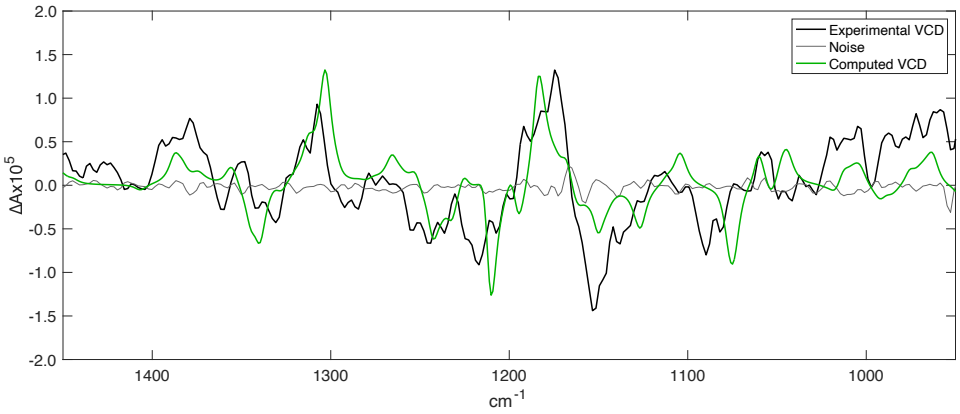


Figure 1.25. *Three diastereomers* ***11k****,* ***11k'****, and* ***11k''*** *to be compared to spectra computed from all eight possible stereoisomers.*

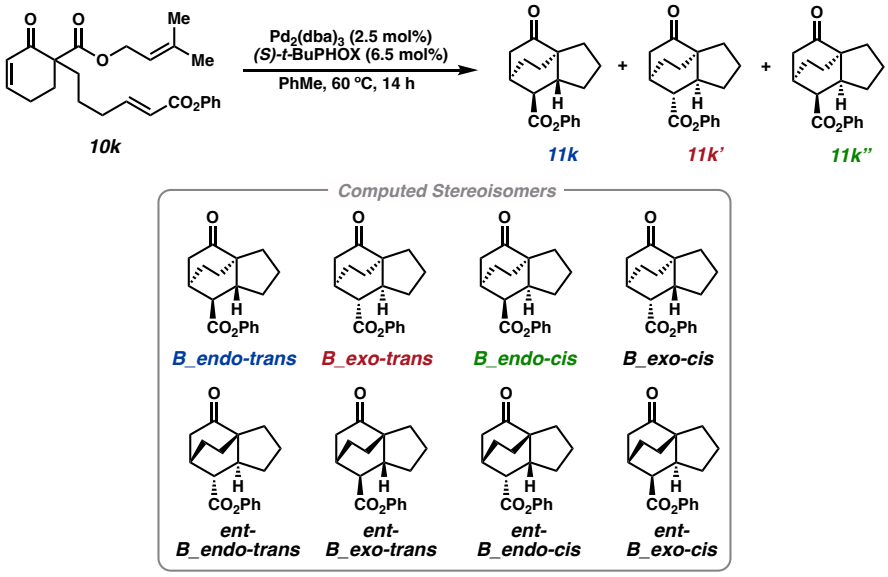
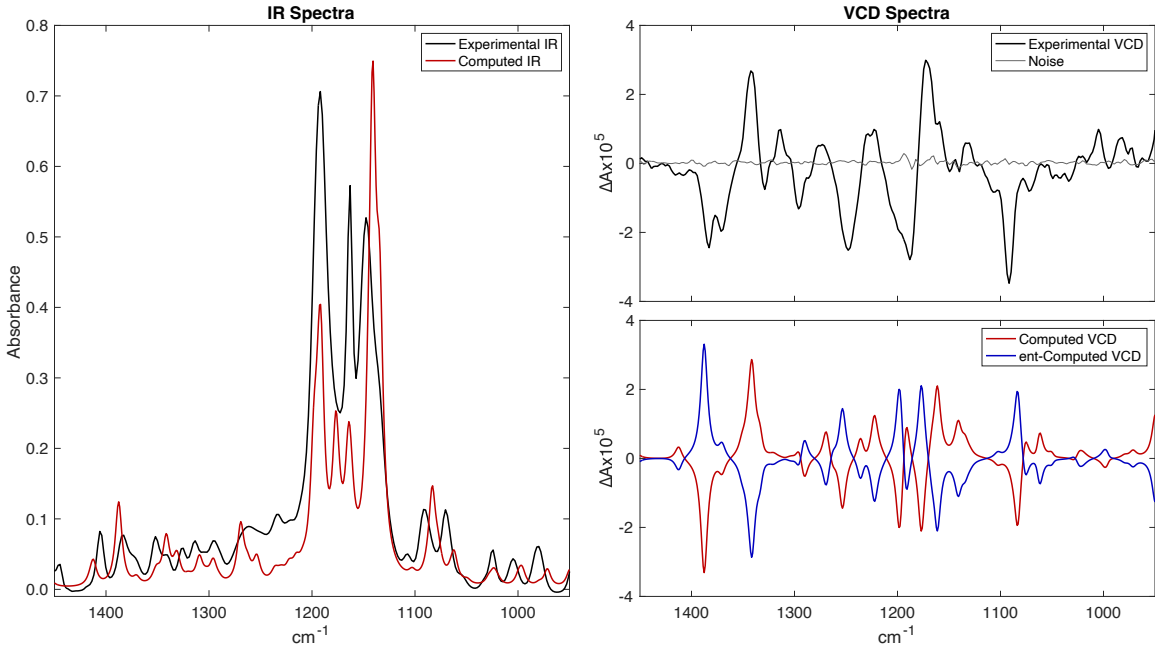


Figure 1.26. Experimental VCD and IR spectra for product **11k** compared to computed spectra for **B_endo-trans**.[a]



[a] Experimental IR spectrum in good agreement with computed spectrum. Experimental VCD spectrum for **11k** is in excellent agreement with computed spectrum for **B_endo-trans**.

Figure 1.27. *Overlayed experimental and calculated VCD spectra for* ***11k*** *– assigned as* ***B_endo-trans****.*

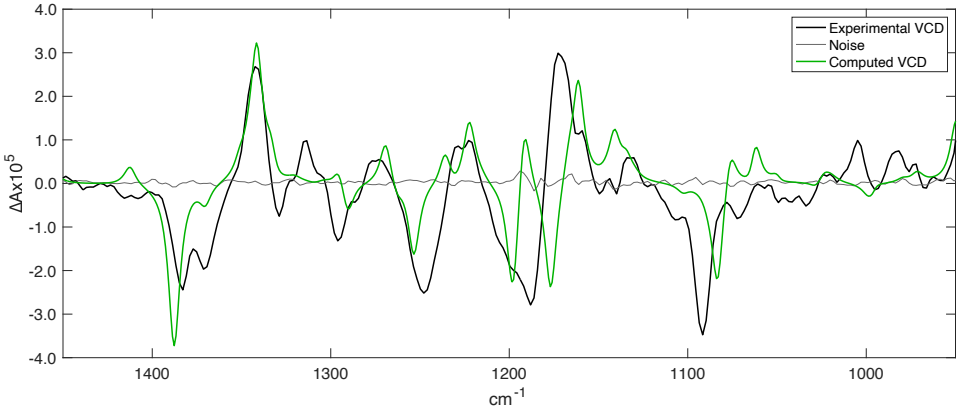
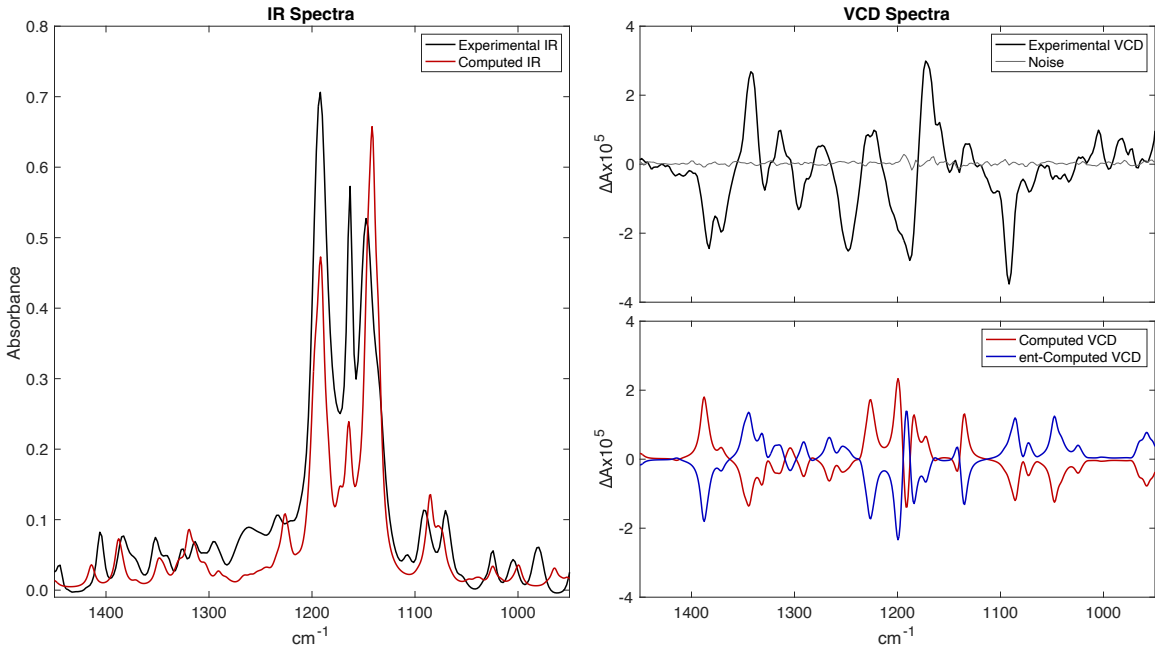
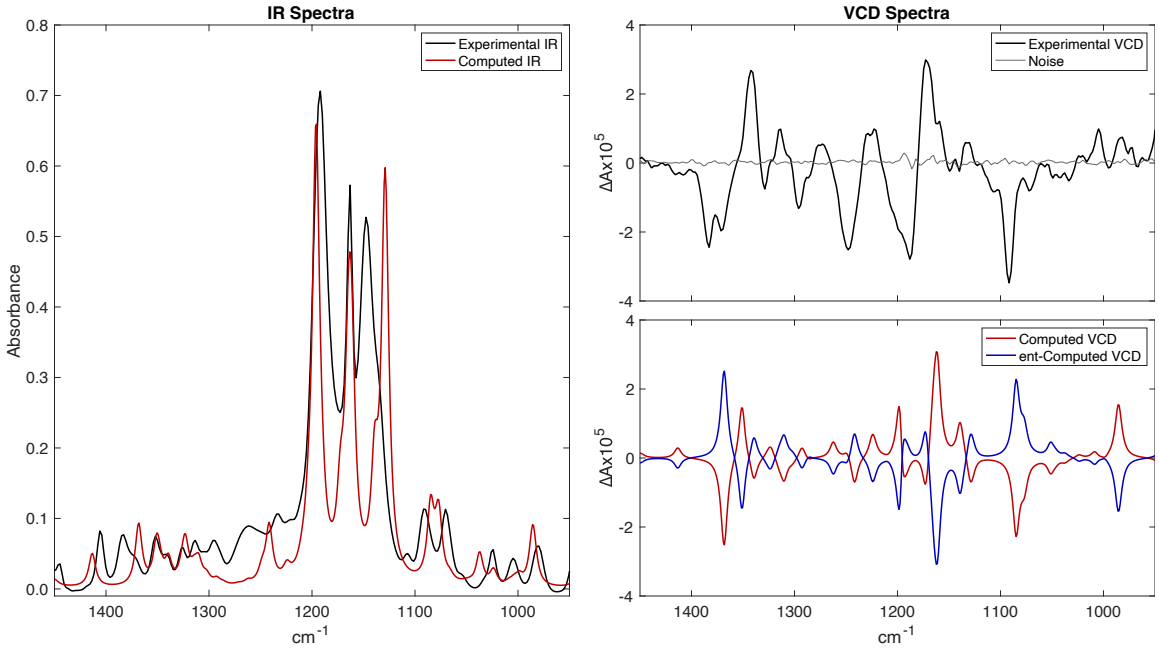


Figure 1.28. *Experimental VCD and IR spectra for product* ***11k*** *compared to computed spectra for* ***B_exo-trans****.*[a]



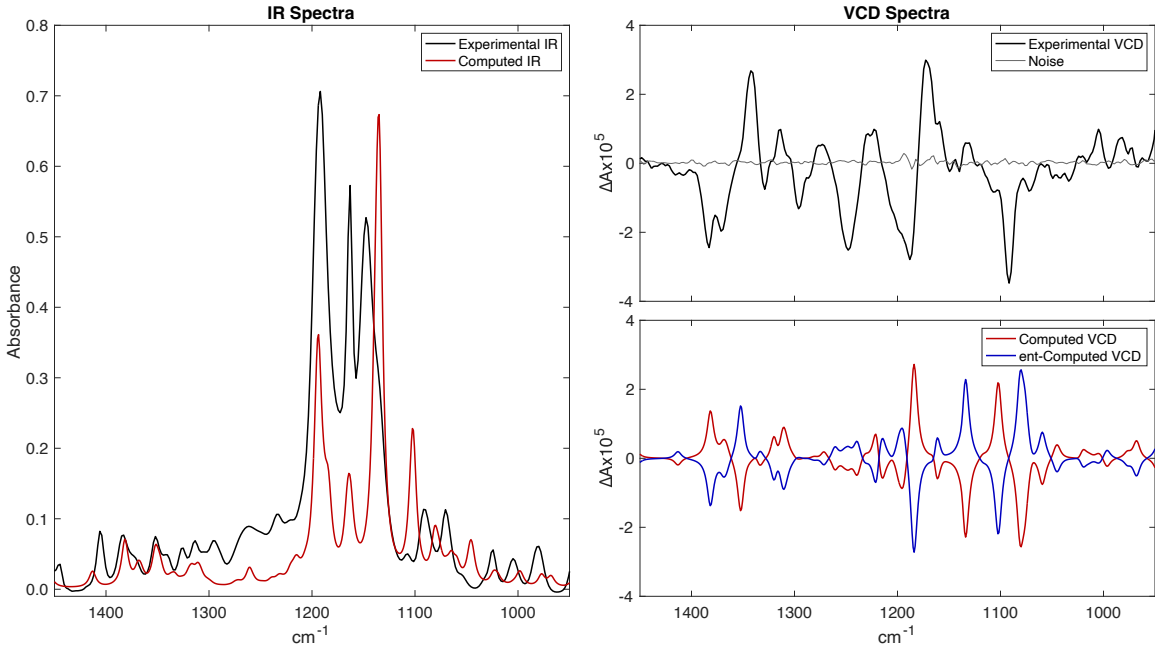
[a] Experimental IR spectrum in good agreement with computed spectrum. However, VCD spectrum contain key sign mismatches in regions around 1400 and 1100 cm^{-1}. Hence, **11k** is not assigned as **B_exo-trans**.

Figure 1.29. Experimental VCD and IR spectra for product **11k** compared to computed spectra for **B_endo-cis**.[a]



[a] Experimental data do not match computed data and **11k** is not assigned as **B_endo-cis**.

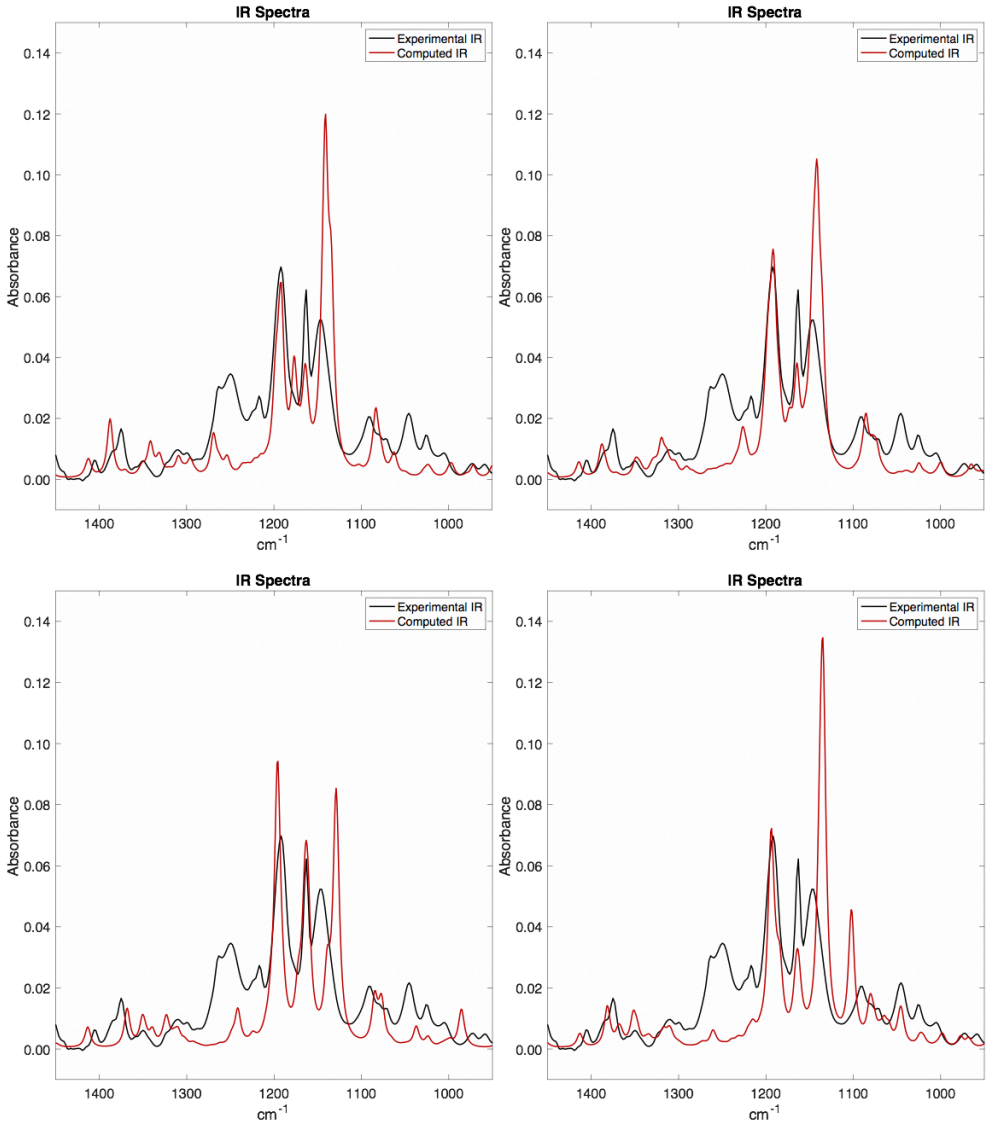
***Figure 1.30**. Experimental VCD and IR spectra for product **11k** compared to computed spectra for **B_exo-cis**.*[a]



[a] Experimental data do not match computed data and **11k** is not assigned as **B_exo-cis**.

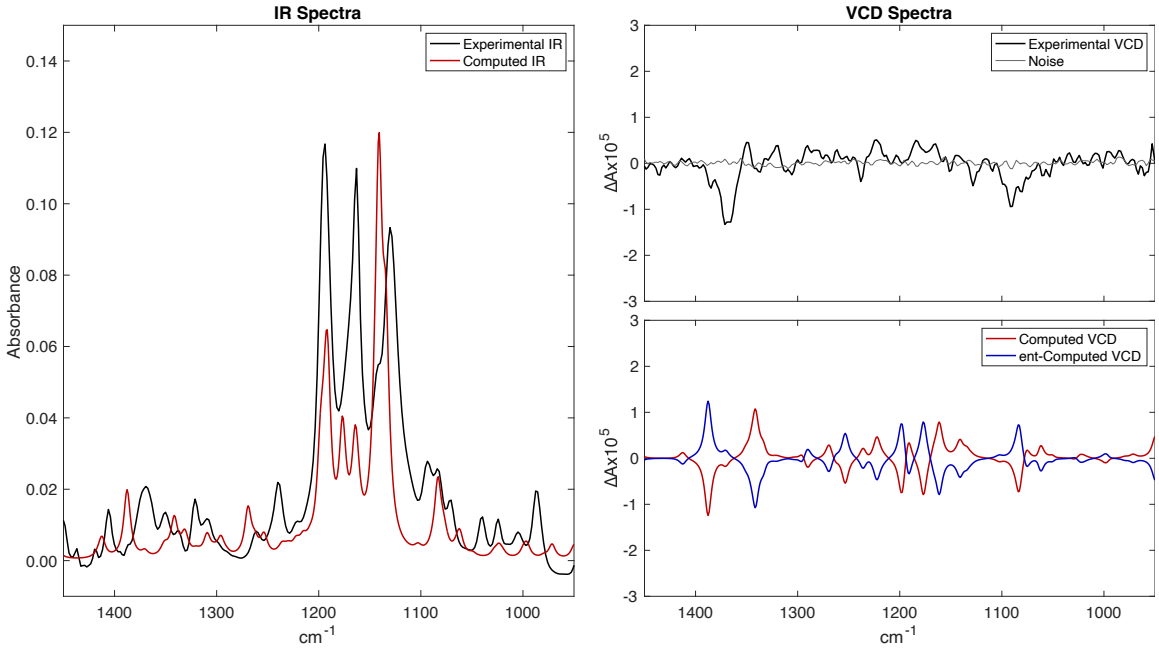
Due to limited sample size (< 3 mg), useful VCD spectra of **11k'** were unable to be obtained. Enantiomeric series was assigned by analogy to the **11a**, **11q** and **11q'** series. The 1000–1500 cm^{-1} region of the IR spectra are still analyzed to support relative stereochemical assignments made by 2D NMR.

Figure 1.31. *Experimental IR spectrum for product* ***11k'*** *compared to computed spectra for* ***B_endo-trans*** *(top left),* ***B_exo-trans*** *(top right),* ***B_endo-cis*** *(bottom left),* ***B_exo-cis*** *(bottom right).*[a]



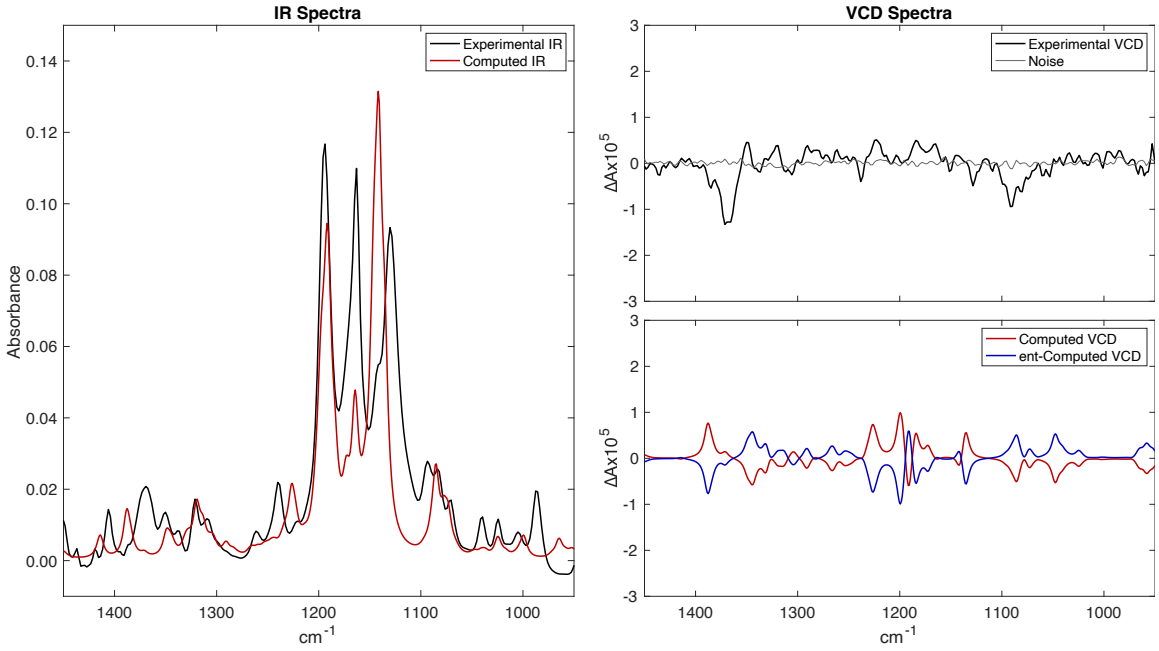
[a] The trans relationship is supported, in accord with 2D NMR data. In contrast to endo-cis and exo-cis, the computed IR spectra for both endo-trans and exo-trans are similar and do not offer key features for distinguishing the two. Given the trans stereochemistry, with **11k** known as **B_endo-trans**, **11k'** is assigned as **B_exo-trans** with absolute stereochemistry assigned based on analogy to **11q'**.

Figure 1.32. *Experimental VCD and IR spectra for product* ***11k″*** *compared to computed spectra for* ***B_endo-trans****.*[a]



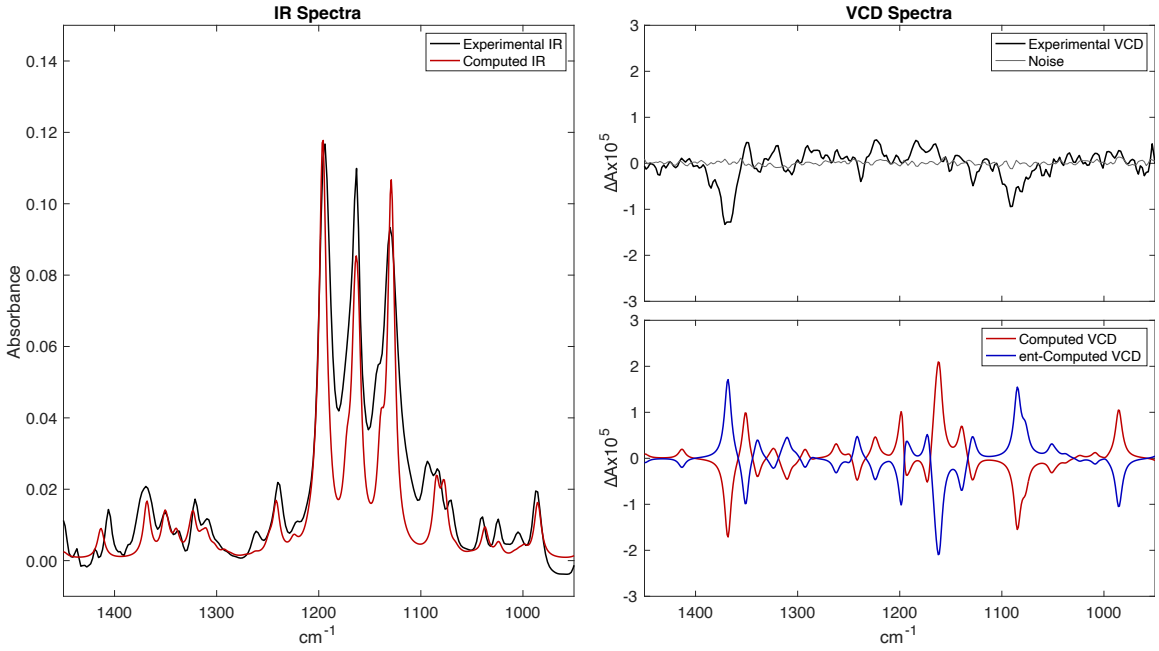
[a] Experimental data do not match computed data and **11k″** is not assigned as **B_endo-trans**.

Figure 1.33. *Experimental VCD and IR spectra for product* ***11k″*** *compared to computed spectra for* ***B_exo-trans****.*[a]



[a] Experimental data do not match computed data and **11k″** is not assigned as **B_exo-trans**.

Figure 1.34. *Experimental VCD and IR spectra for product* ***11k″*** *compared to computed spectra for* ***B_endo-cis***.[a]



[a] Experimental IR spectrum is in agreement with the computed spectrum of **B_endo-cis**. Assignment of absolute stereochemistry is based the on the sign of the three most intense peaks in VCD spectrum, 1368, 1350, and 1085 cm^{-1}. These match **B_endo-cis**, the same enantiomeric series as **11k**.

Figure 1.35. *Overlayed experimental and calculated VCD spectra for* ***11k″*** *– assigned as* ***B_endo-cis***.

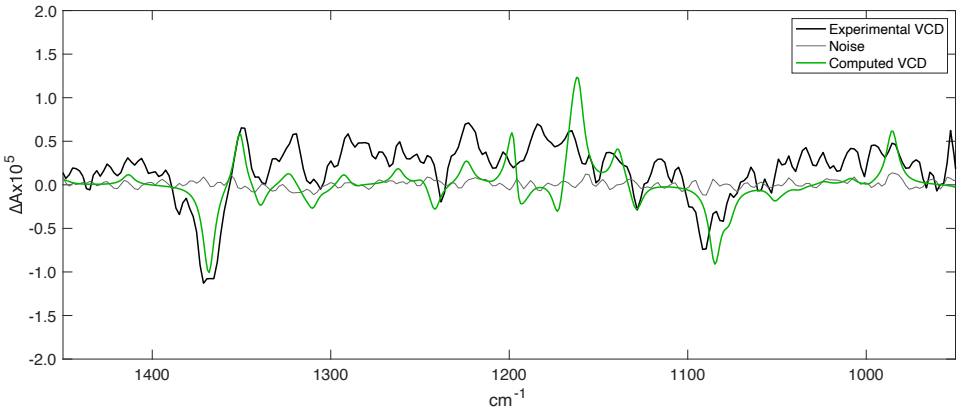
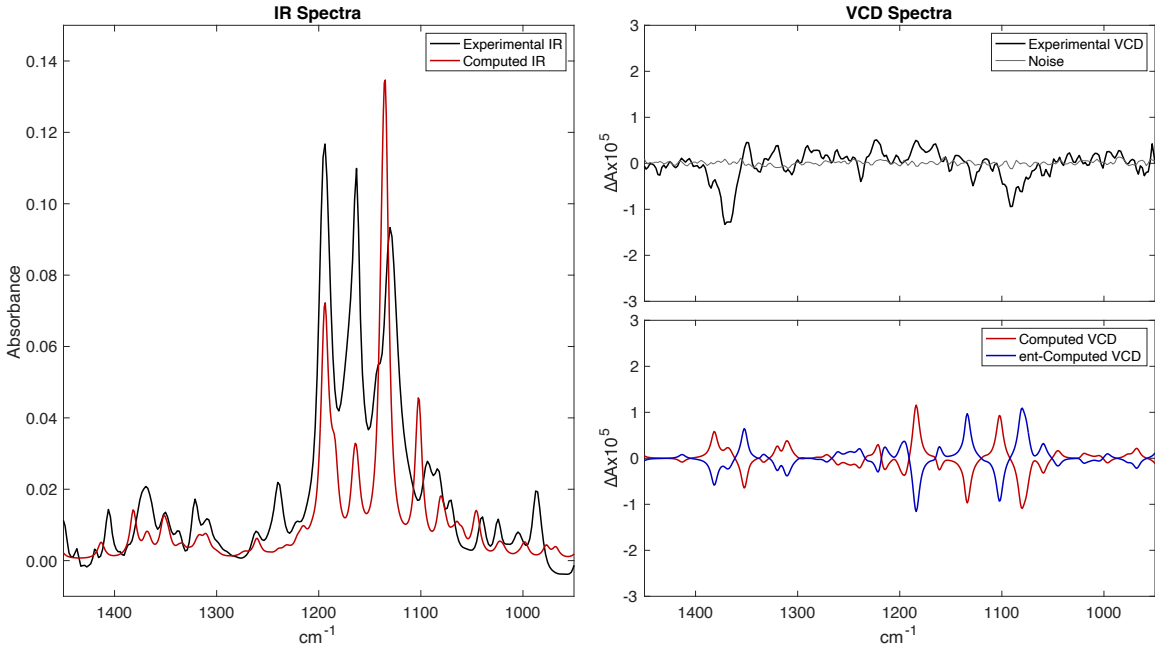


Figure 1.36. *Experimental VCD and IR spectra for product* ***11k″*** *compared to computed spectra for* ***B_exo-cis***.[a]



[a] Experimental data do not match computed data and **11k″** is not assigned as **B_exo-cis**.

1.4.4 2D NMR ANALYSIS OF SELECT COMPOUNDS

Figure 1.37. *^{1}H-^{1}H COSY NMR spectrum of* ***11a*** *(400 MHz, $CDCl_3$).*

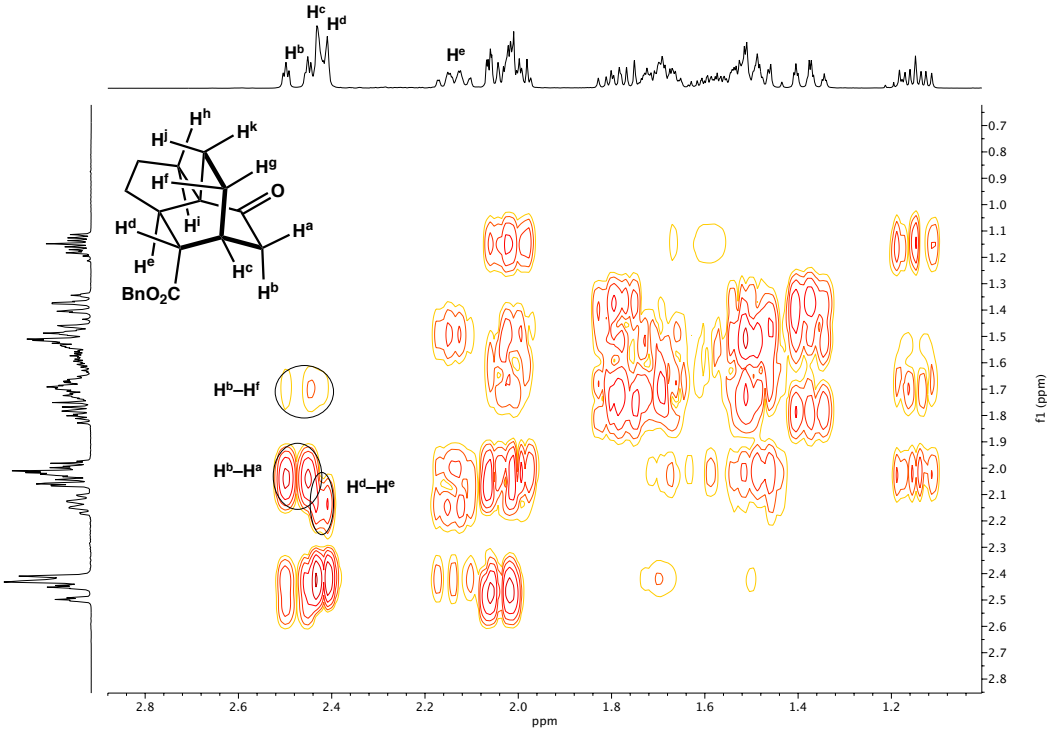


Figure 1.38. *^{1}H-^{13}C HSQC NMR spectrum of* ***11a*** *(400 MHz, $CDCl_3$).*

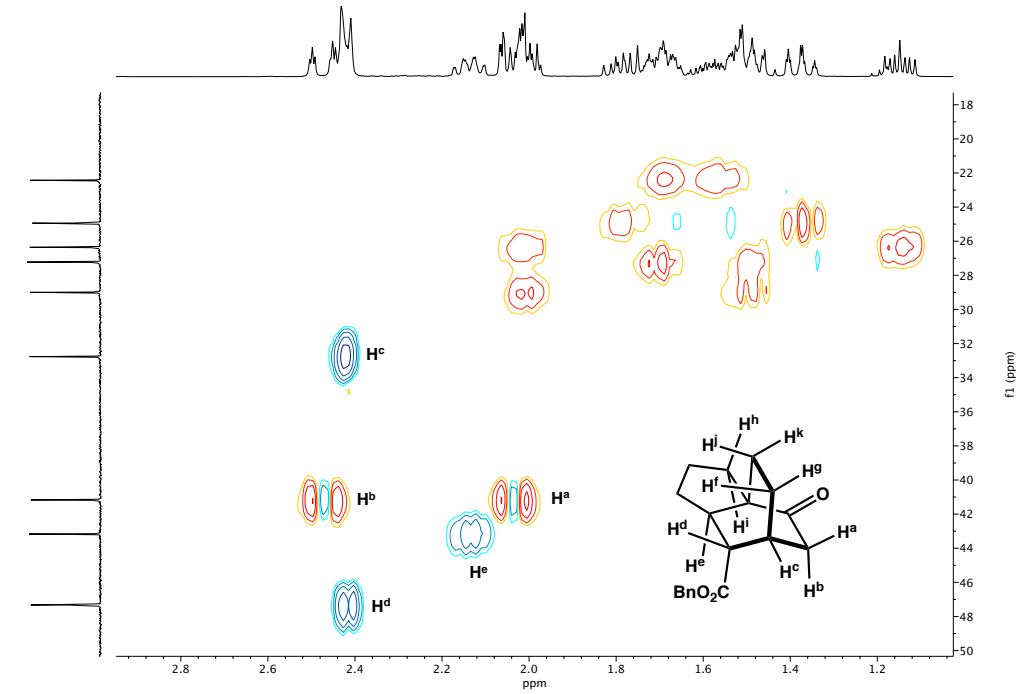


Figure 1.39. *^{1}H-^{1}H NOESY NMR spectrum of* ***11a*** *(400 MHz, $CDCl_3$).*

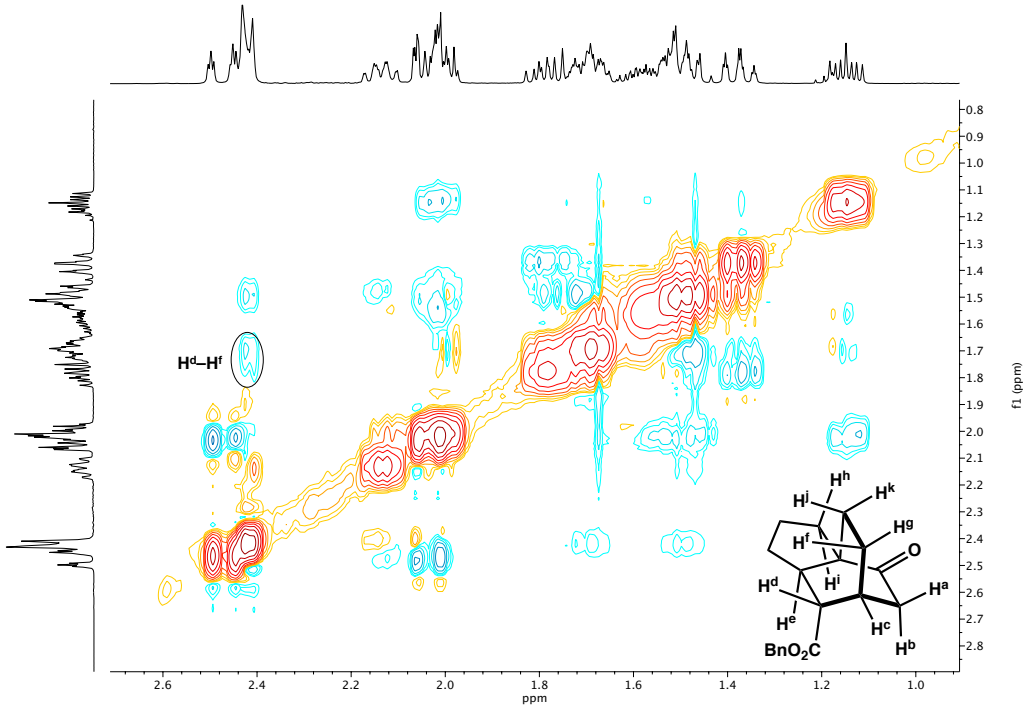


Figure 1.40. *^{1}H-^{1}H COSY NMR spectrum of* ***11p*** *(400 MHz, $CDCl_3$).*

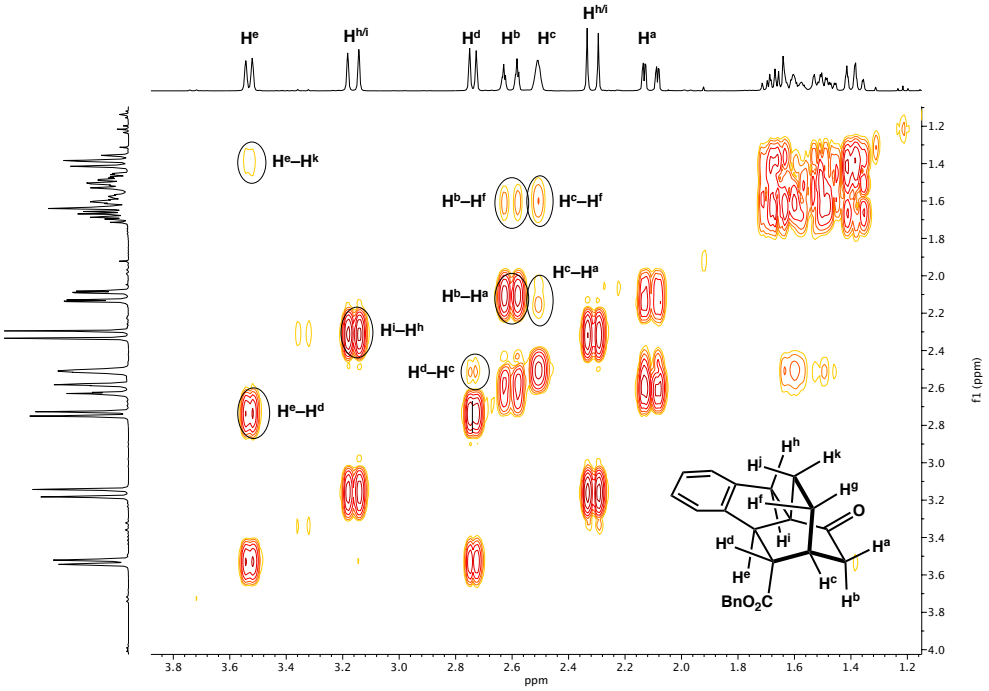


Figure 1.41. *^{1}H-^{13}C HSQC NMR spectrum of* ***11p*** *(400 MHz, $CDCl_3$).*

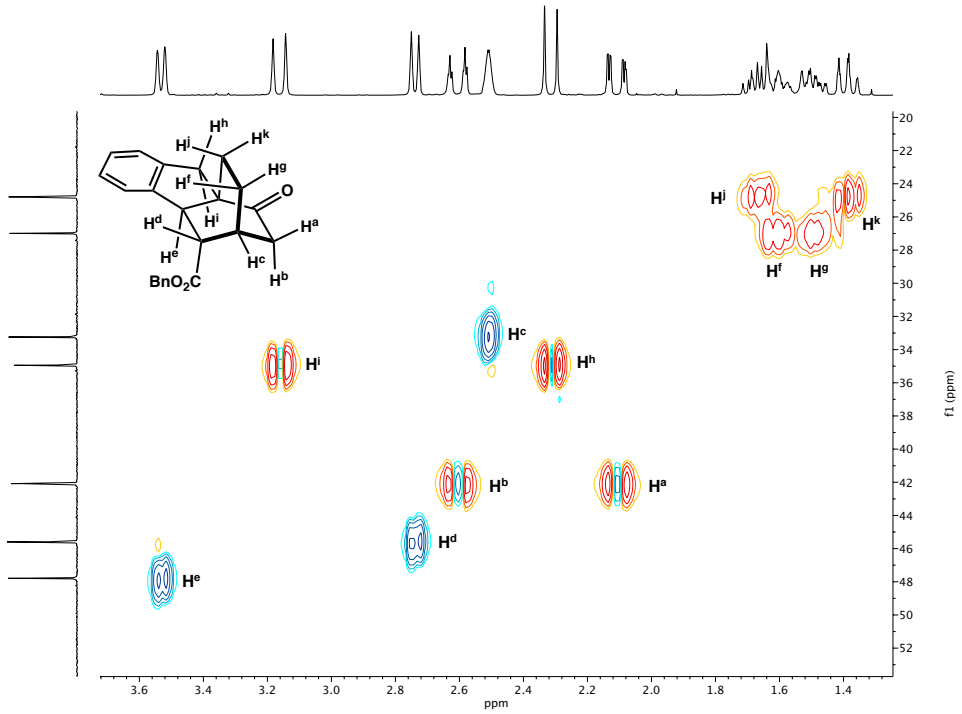


Figure 1.42. *^{1}H-^{1}H NOESY NMR spectrum of* ***11p*** *(400 MHz, $CDCl_3$).*

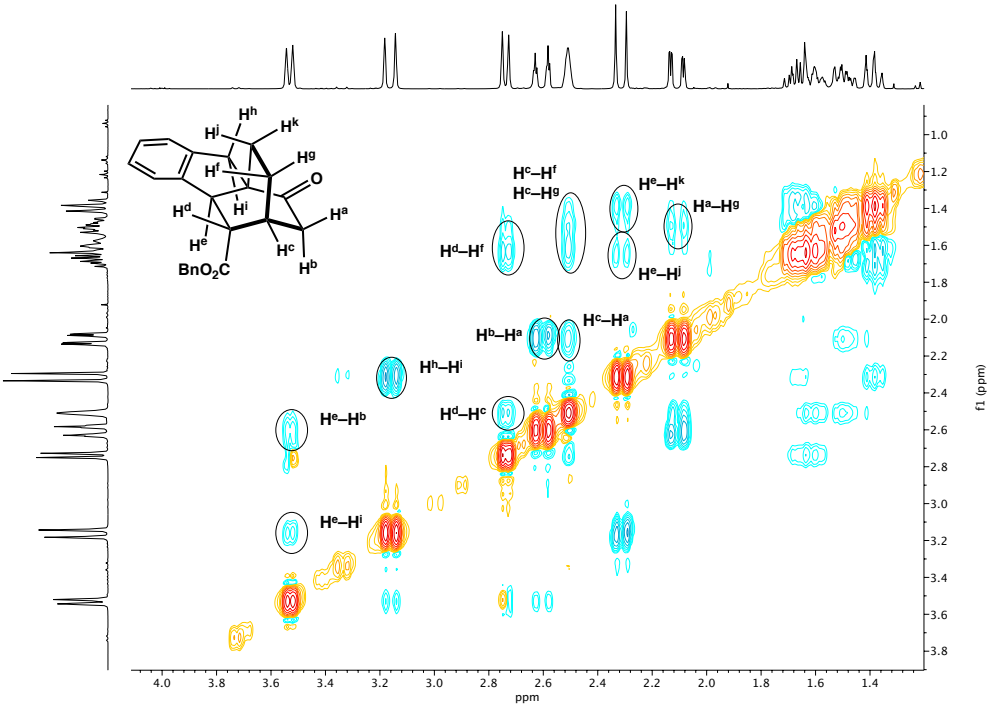


Figure 1.43. *^{1}H-^{1}H COSY NMR spectrum of* ***11q*** *(400 MHz, $CDCl_3$).*

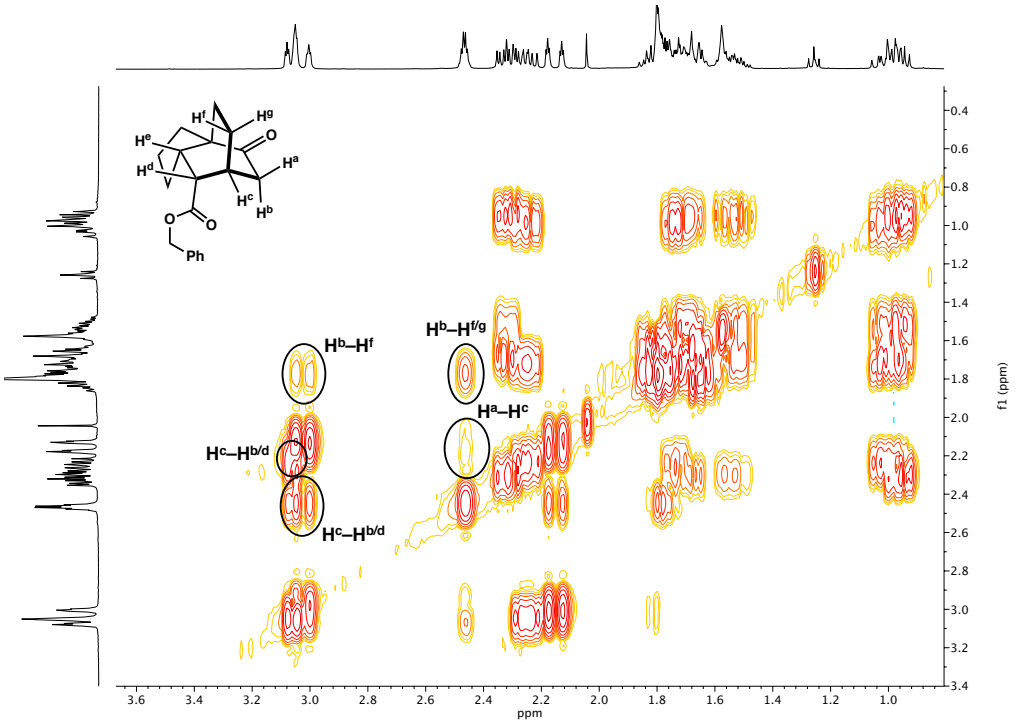


Figure 1.44. *^{1}H-^{13}C HSQC NMR spectrum of* ***11q*** *(400 MHz, $CDCl_3$).*

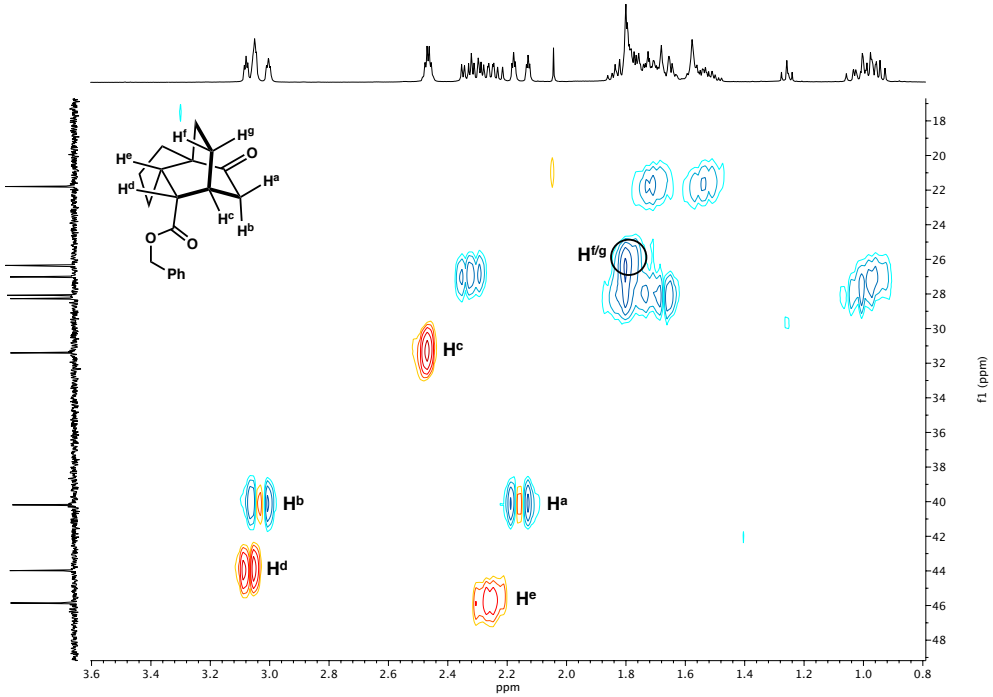


Figure 1.45. *^{1}H-^{1}H NOESY NMR spectrum of* ***11q*** *(400 MHz, $CDCl_3$).*

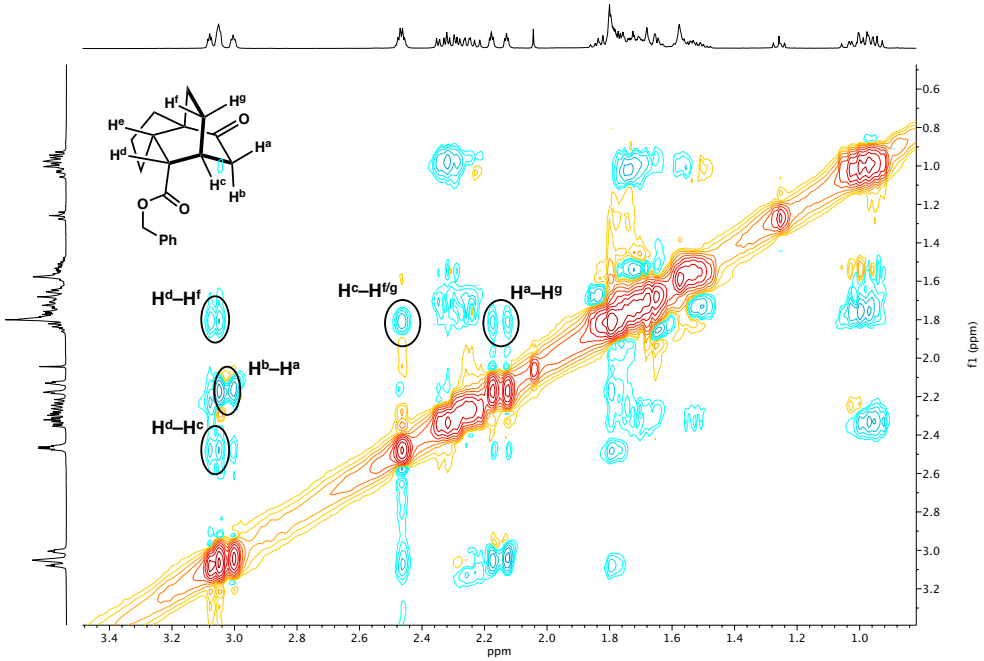


Figure 1.46. *^{1}H-^{1}H COSY NMR spectrum of* ***11q'*** *(400 MHz, $CDCl_3$).*

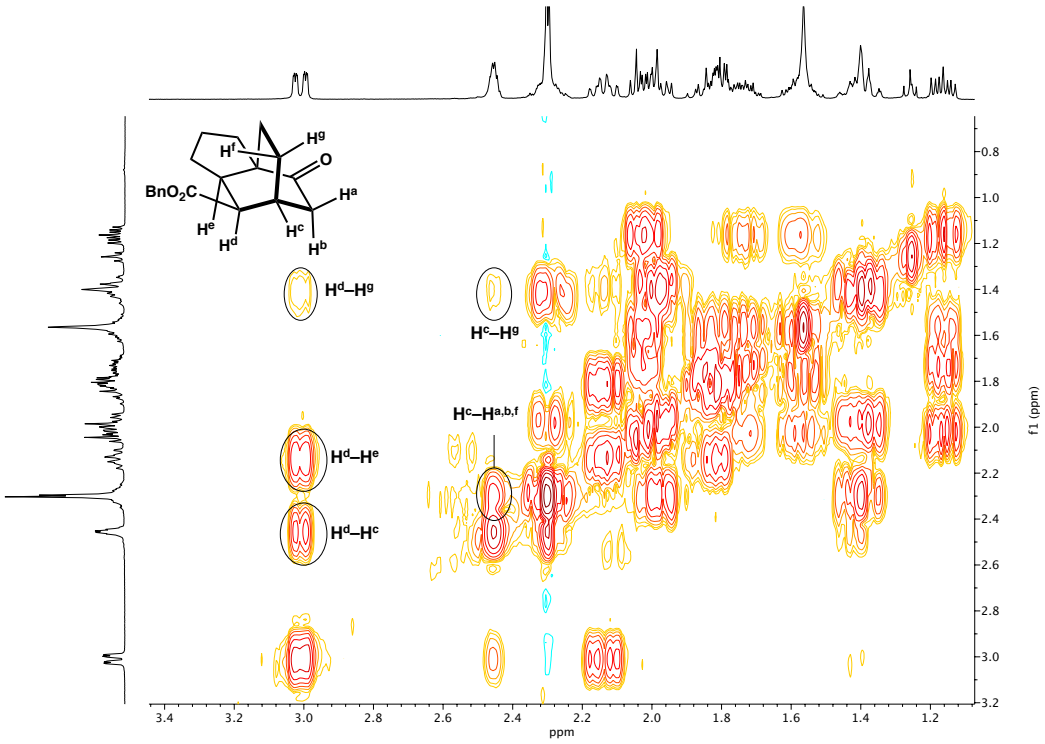


Figure 1.47. *^{1}H-^{13}C HSQC NMR spectrum of* ***11q'*** *(400 MHz, $CDCl_3$).*

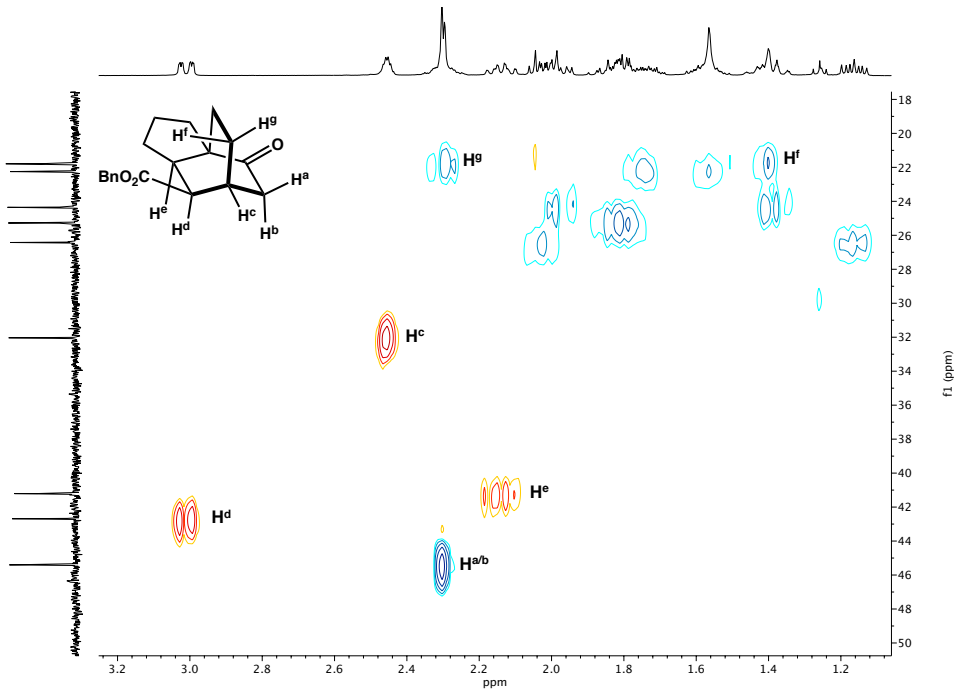
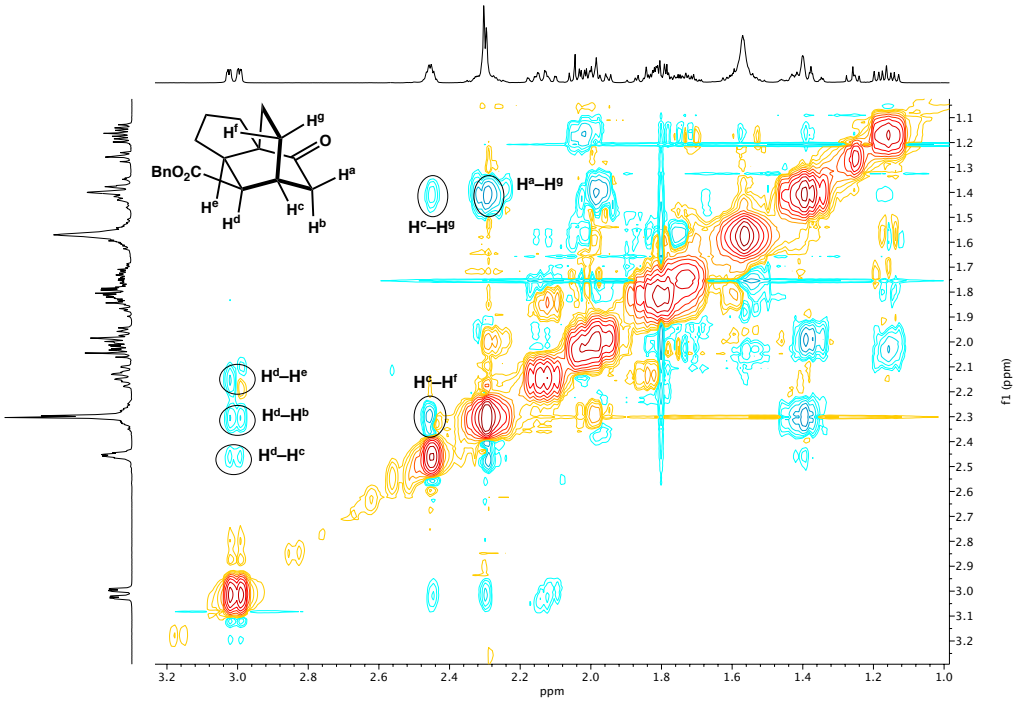


Figure 1.48. *^{1}H-^{1}H NOESY NMR spectrum of* ***11q'*** *(400 MHz, $CDCl_3$).*



1.4.5 GENERAL COMPUTATIONAL DETAILS

General Notes

All quantum mechanics calculations were carried out with the ORCA program.[52] Geometry optimizations, harmonic frequency calculations, and single-point energy evaluations were carried out with density functional theory (DFT). The PBE0 functional[53] paired with Becke–Johnson damped D4 dispersion corrections[54], henceforth referred to as PBE0-D4, was used as it has proven a robust method for such systems in our prior studies.[55] For geometry optimization and harmonic frequency calculations, Pd is described by the def2-TZVP basis set[56] and the ECP28MWB small-core (18 explicit valence electrons) quasi-relativistic pseudopotential,[57] while C, H, N, and P are assigned the def2-SVP basis. Diffuse functions are added to oxygen (ma-def2-SVP). Herein, we refer to this composite

basis set as BS1. Geometry optimization and harmonic frequency calculations were carried out with the CPCM implicit solvation model for toluene (PhMe, $\varepsilon = 2.4$). For all calculations employing CPCM, surface charges are described by the improved Gaussian charge scheme of Neese and coworkers with a scaled Van der Waals cavity ($\alpha = 1.2$).[58] All Hessians were computed analytically. Stationary points are characterized by the correct number of imaginary vibrational modes (zero for minima and one for saddle points). Intrinsic reaction coordinate (IRC) analysis confirms the nature of transition states.[59] Cartesian coordinates of all optimized structures are included as ".xyz" files are available online in a compressed in a zip file format.

Electronic energies are further refined with single-point calculations employing the PBE0-D4 functional[60] and the def2-TZVPP basis set on all atoms (with the ECP28MWB pseudopotential for Pd) with additional diffuse functions on O (ma-def2-TZVPP). This mixed basis is henceforth referred to as BS2. Solvation was accounted for with CPCM as mentioned above (PhMe, $\varepsilon = 2.4$). Final Gibbs free energies were obtained by applying thermodynamic corrections obtained at the optimization level of theory to these refined electronic energies. Thermodynamic corrections from harmonic frequency calculations employ the quasi-ridged rotor harmonic oscillator approach to correct for the breakdown of the harmonic oscillator approximation at low vibrational frequencies.[61] Note that free energies are adjusted to a 1 M standard state. The translational (S_{trans}) and rotational entropy (S_{rot}) contributions to the Gibbs free energy calculated for a complex in condensed phase are *ca.* 40–60% of the values obtained assuming an ideal gas.[62] As suggested in the literature, S_{trans} and S_{rot} obtained by ideal gas treatment are scaled by a factor of 0.5 to

obtain the final condensed phase values.[63] Hence, the Gibbs free energy at 333.15 K is calculated as:

$$G^*_{solv} = E^{BS2}_{el,solv} + ZPE + E_{trans} + E_{rot} + E_{vib} + k_bT - T\left(S_{el} + S_{vib} + \frac{1}{2}S_{trans} + \frac{1}{2}S_{rot}\right) + \Delta G^{0\rightarrow *}$$

The resolution of identity (RI) and Chain-of-Spheres (COS) approximations are employed for efficient evaluation of Coulomb and exchange integrals, respectively.[64] The def2/J auxiliary basis[65] is employed for all atoms except oxygen, for which a suitable auxiliary was obtained via the automatic generation algorithm in the ORCA program (keyword: *AutoAux*). [66] Very fine grid settings are employed in all calculations (optimization/frequency calculations: DefGrid2, single point calculations: DefGrid3).

Conformer searching was carried out for each stationary point using the meta-dynamics-based CREST program (using GNF-FF) from the Grimme group. Duplicate conformers were removed, and low energy conformers were subsequently optimized and energies evaluated at the cheaper PBE0-D4/def2-TZVP (Pd), ma-def2-SVP (O), def2-SVP/CPCM(PhMe)//PBE-D4/def2-TZVP (Pd), ma-def2-SV(P) (O), def2-SV(P) level of theory. The final low energy conformers were further optimized at the level of theory mentioned prior. Note that for enantiodetermining transition states (such as TS2 and TS3) conformer searching also explicitly includes rotation about the Pd–O–C–C(enolate) dihedral, consideration of s-cis and s-trans ester conformations, as well as all permutations of the considered stereochemical elements.

Finally, conformational entropy[67] (entropy arising from multiple low energy thermally populated conformers) is accounted for by the *mixture of components* model of DeTar.[68] Conformational entropy (S_{conf}) is defined as:

$$S_{conf} = -R \sum \chi_i \ln (\chi_i)$$

where χ_i is the mole fraction (thermal population) of the ith conformer based on its relative free energy within the conformer ensemble. Given the computational demand for computing free energies for large ensembles of conformers, χ_i was derived from the free energies initially computed during the conformer screening process (PBE0-D4/def2-TZVP (Pd), ma-def2-SVP (O), def2-SVP/CPCM(PhMe)//PBE-D4/def2-TZVP (Pd), ma-def2-SV(P) (O), def2-SV(P))

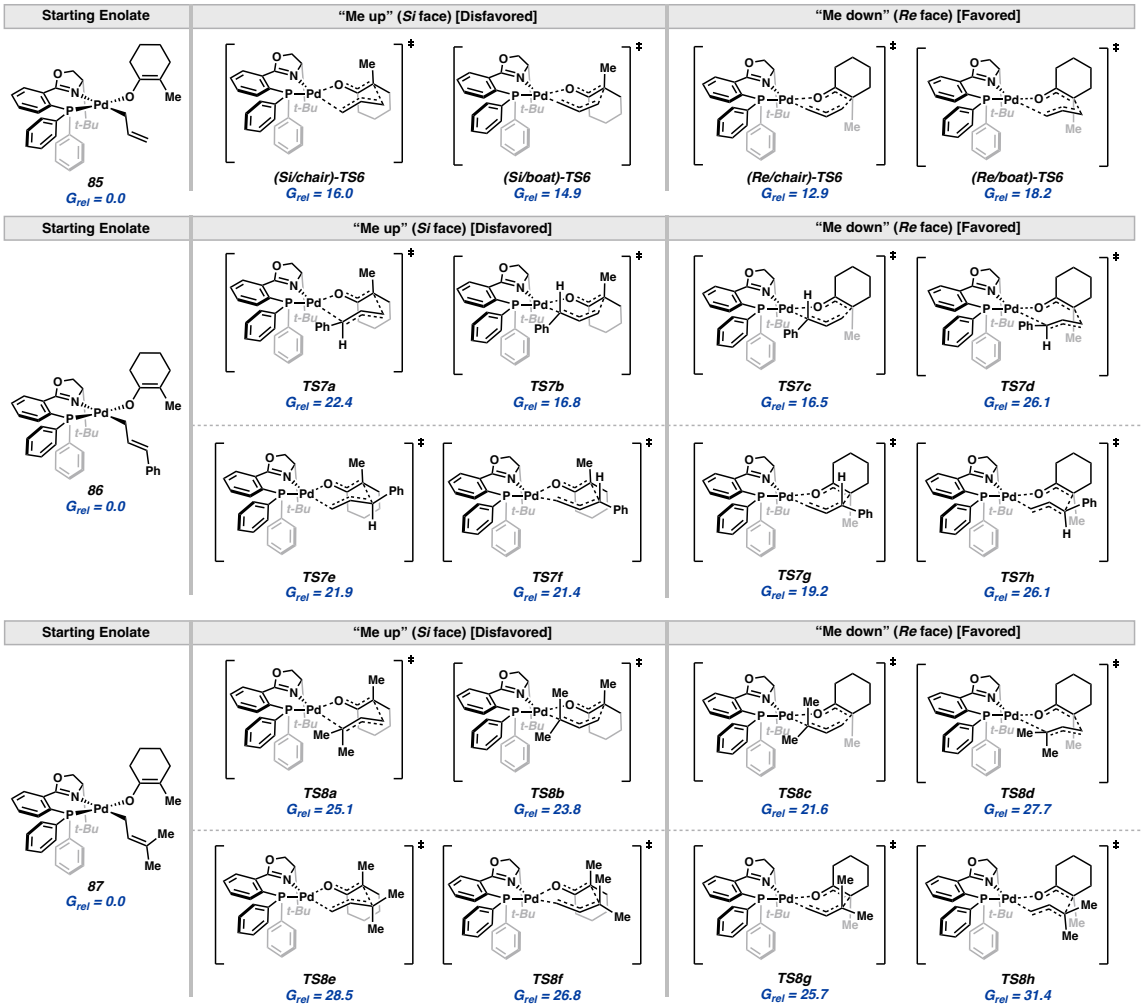
$$G_{final} = G^*_{solv} - TS_{conf}$$

For the systems at hand, values of TS_{conf} (at 333.15 K) can be on the order of magnitude of a few kcal/mol.

Comparison of Barrier Heights to Inner-sphere Reductive Elimination

Employing cyclohexanone-derived Pd enolate as a model system (**85, 86, 87**), the barrier to inner-sphere reductive elimination was investigated while varying substitution on the allyl moiety (Figure 1.49).

Figure 1.49. *Relative free energies for various inner-sphere reductive elimination transition states from allyl (**85**), cinnamyl (**86**), and prenyl (**87**) complexes.*[a]



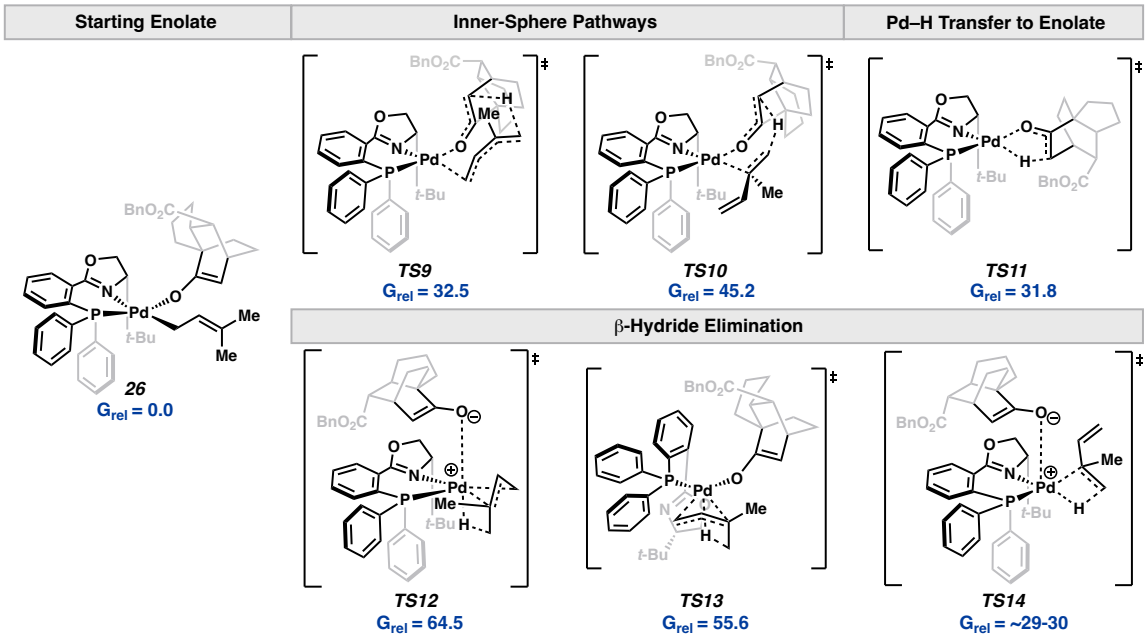
[a] Gibbs free energies in kcal/mol computed at the PBE0-D4/BS2/CPCM(PhMe)//PBE0-D4/BS1/CPCM(PhMe) level of theory at 333.15 K.

Mechanism of Catalyst Turnover

Of all the sampled transition states, we found the outer-sphere and N-detached inner-sphere pathways to be highly competitive and lowest in energy. Additional transition states were

also explored, and the lowest energy pathway of each type of mechanism are shown in the following table.

Figure 1.50. *Relative free energies for various proton transfer transition states from post-cycloaddition enolate* ***26****.*[a]

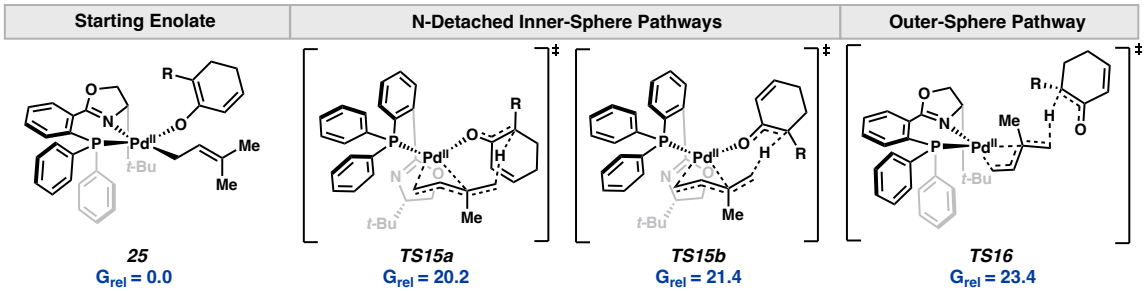


[a] Gibbs free energies in kcal/mol computed at the PBE0-D4/BS2/CPCM(PhMe)//PBE0-D4/BS1/CPCM(PhMe) level of theory at 333.15 K.

Mechanism of Premature Protonation

Analogous to the catalyst turnover mechanism, N-detached inner-sphere pathways were found to be lowest-energy for premature protonation. Of these transition states (**TS15a** and **TS15b**) that would yield enantiomeric protonation products, the lowest-energy **TS15a** provides the enantiomer consistent with the major reaction product. In addition, an outer-sphere pathway (**TS16**) was also found to be competitive.

Figure 1.51. *Relative free energies for various proton transfer transition states from pre-cycloaddition enolate* ***25****.*[a]

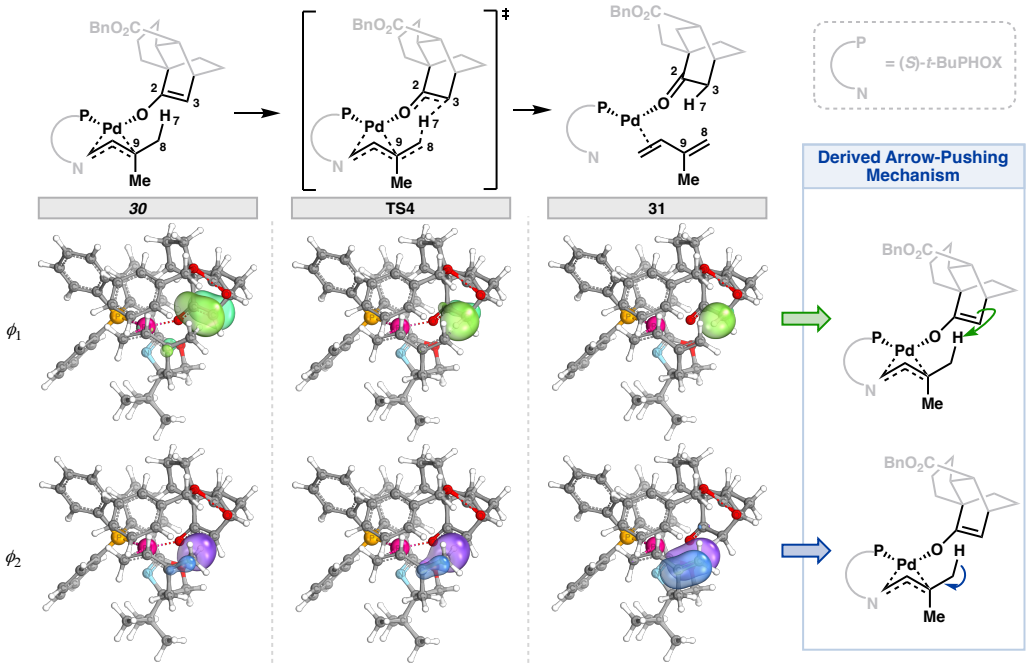


[a] Gibbs free energies in kcal/mol computed at the PBE0-D4/BS2/CPCM(PhMe)//PBE0-D4/BS1/CPCM(PhMe) level of theory at 333.15 K.

Intrinsic Bonding Orbital (IBO) Analysis of Inner-sphere Proton Transfer

IBO analysis along the reaction coordinate of the N-detached inner-sphere proton transfer to post-cycloaddition enolate confirms the role of prenyl as a proton source.

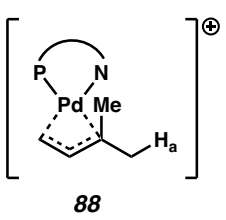
Figure 1.52. *IBO analysis of N-detached inner-sphere mechanism and corresponding derived arrow-pushing mechanism.*



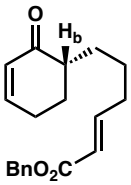
pKa Calculations and Thermodynamics of Outer-Sphere Proton Transfer

The pK_a values of the π-allyl Pd complex **88** and ketones were calculated, and the results verify that the proton transfers to both pre- and post-cycloaddition enolates are thermodynamically favorable.

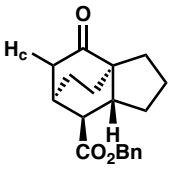
Figure 1.53. *Computed pKa values of cationic π-allyl Pd complex* ***88*** *and ketones* ***19a*** *and* ***11a****.*



88

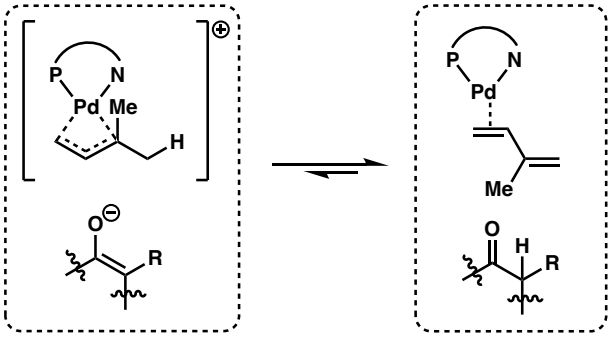


19a



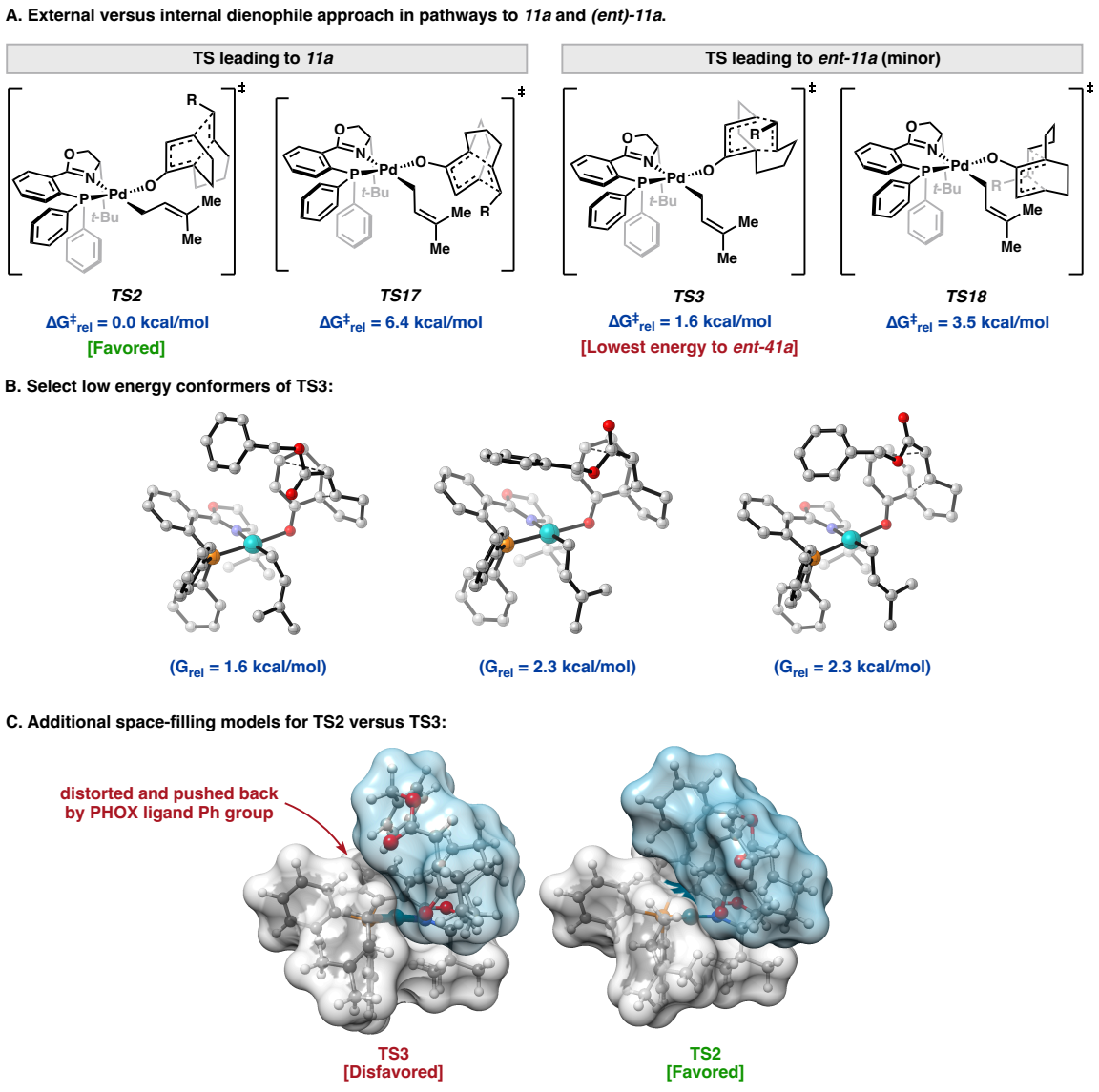
11a

Compound	Proton	pK_a in water	pK_a in DMSO
88	H_a	20.0	19.5
19a	H_b	30.1	30.3
11a	H_c	31.3	30.8



Enantiodetermining [4+2] cycloaddition

Figure 1.54. *(A) Comparison of internal versus external dienophile approach to both enantiotopic diene faces. (B) Select low energy conformers of* ***TS3*** *(allyl isomers not pictured). (C) Additional space-filling models for* ***TS2*** *and* ***TS3****.*



1.5 REFERENCES AND NOTES

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APPENDIX 1

Spectra Relevant to Chapter 1: Catalytic Asymmetric Intramolecular [4+2] Cycloaddition of Pd Enolates

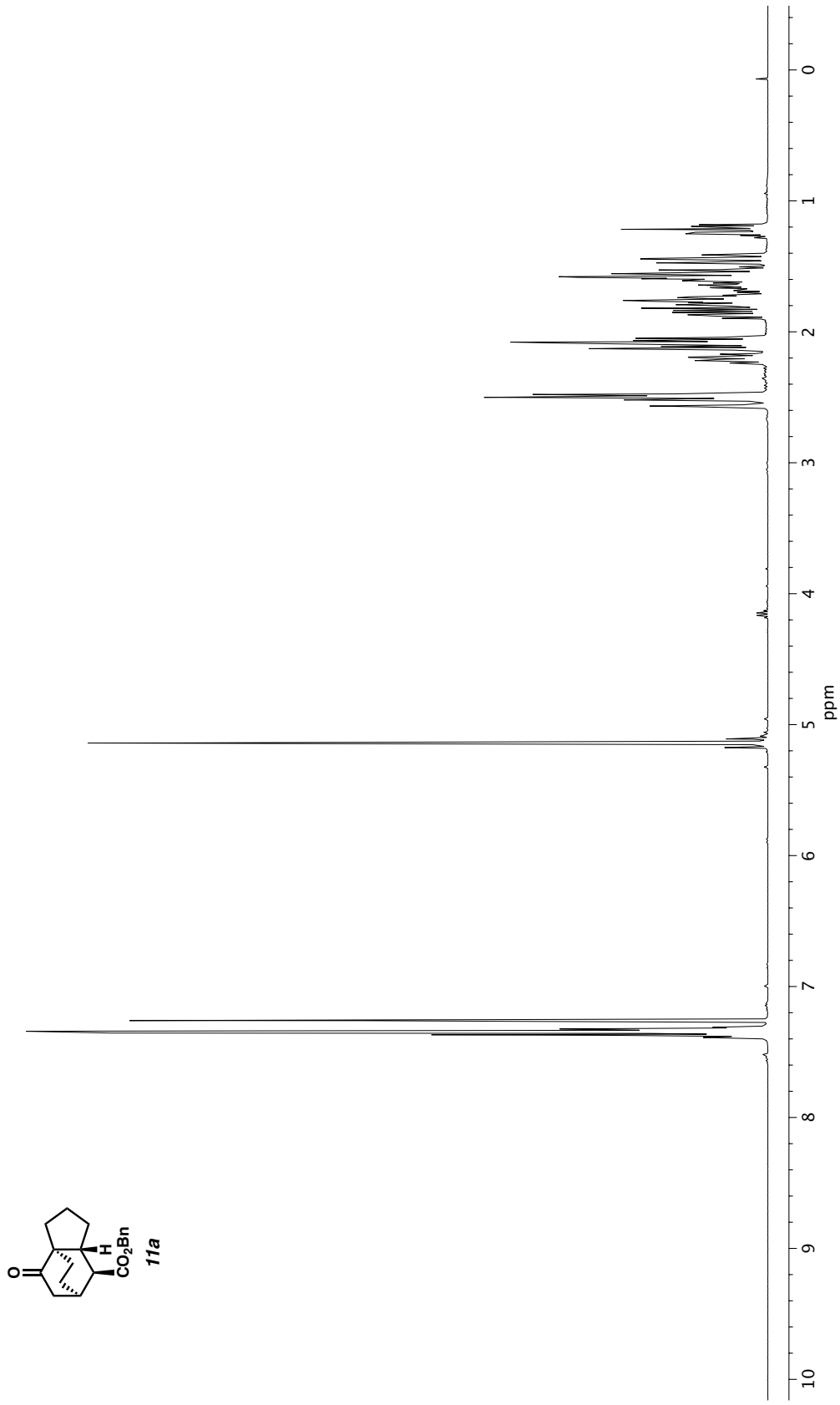


Figure A1.1. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***11a****.*

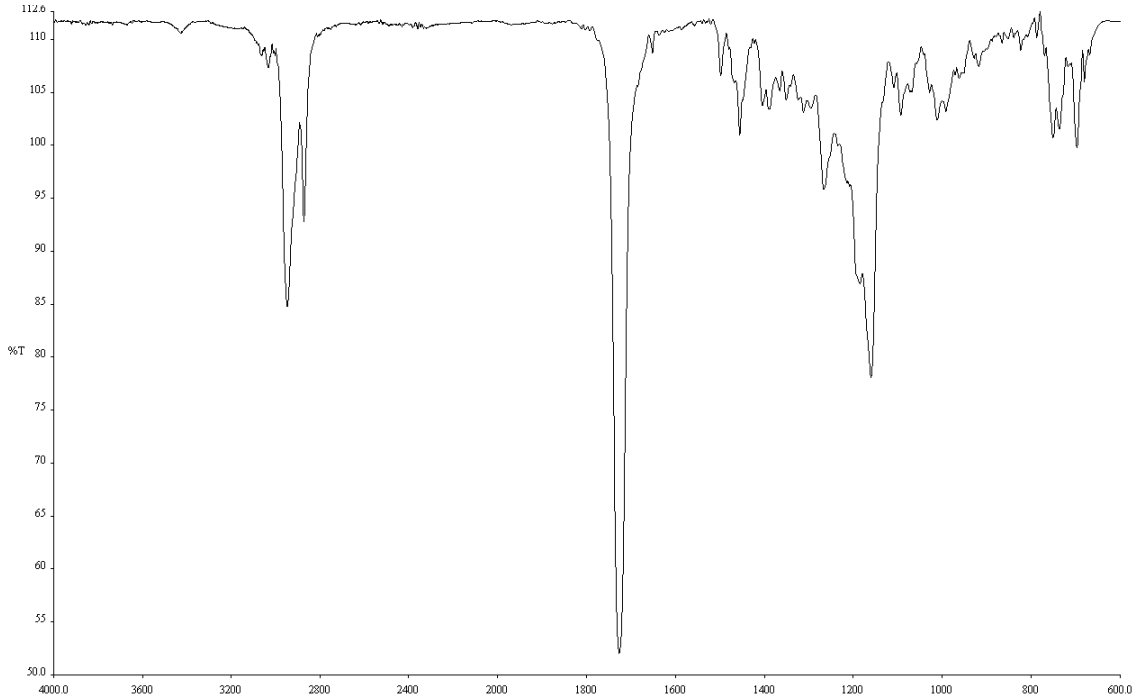


Figure A1.2. *Infrared spectrum (Thin Film, NaCl) of compound* ***11a****.*

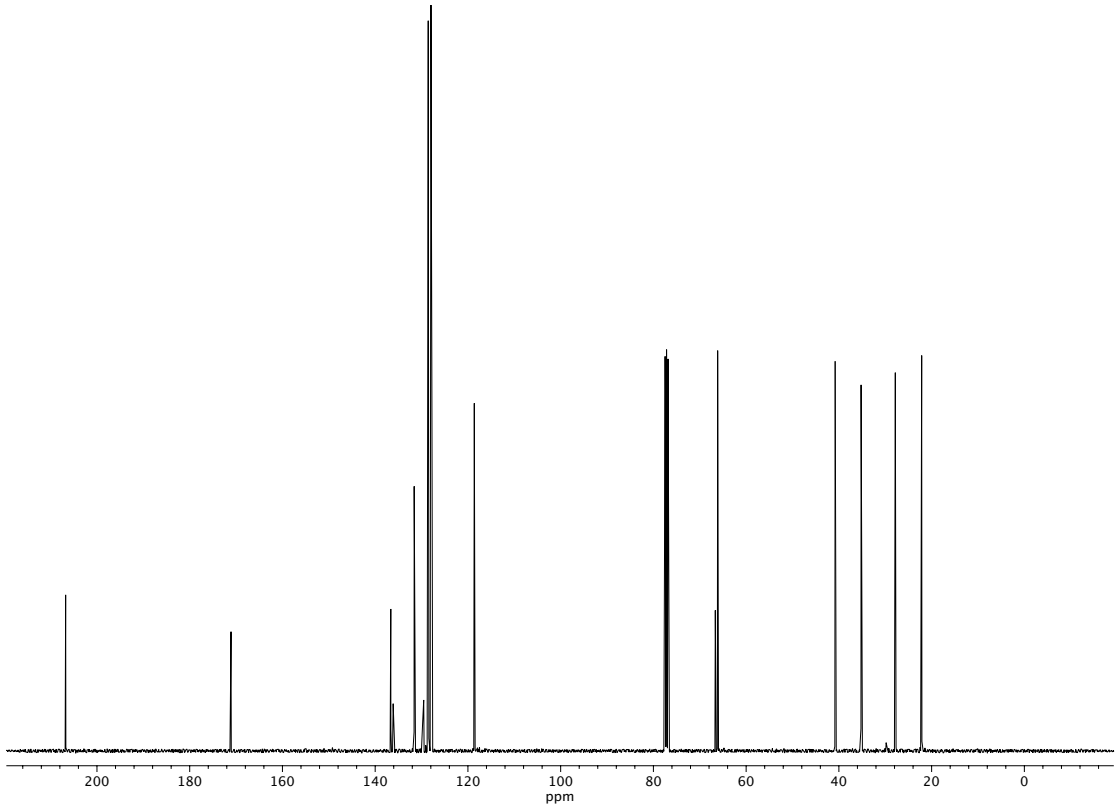
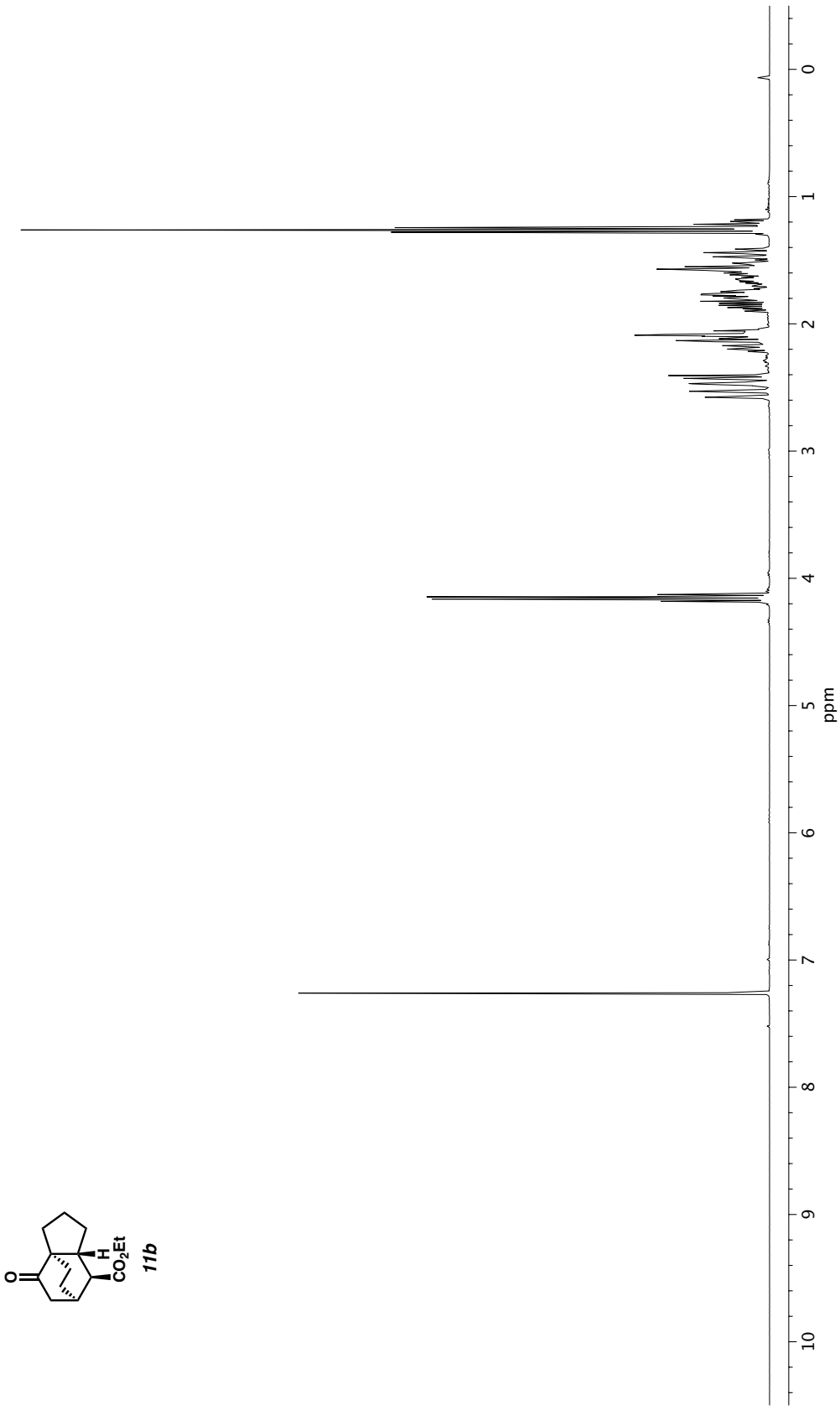


Figure A1.3. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11a****.*



11b

Figure A1.4. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***11b****.*

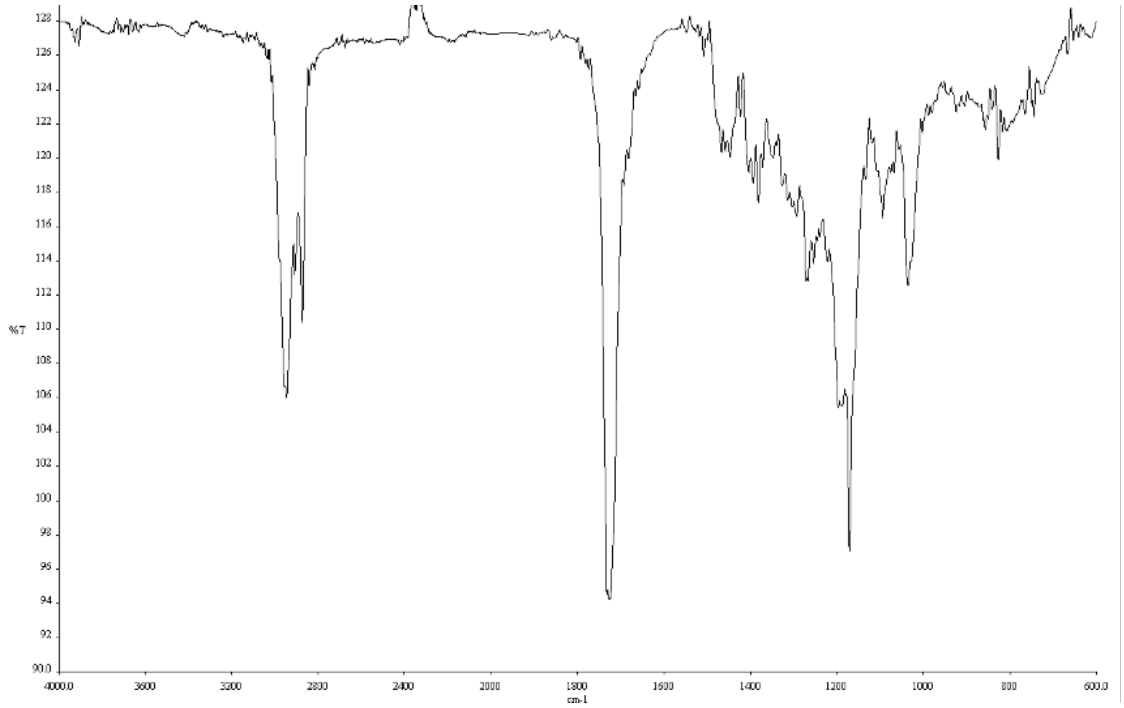


Figure A1.5. *Infrared spectrum (Thin Film, NaCl) of compound* ***11b****.*

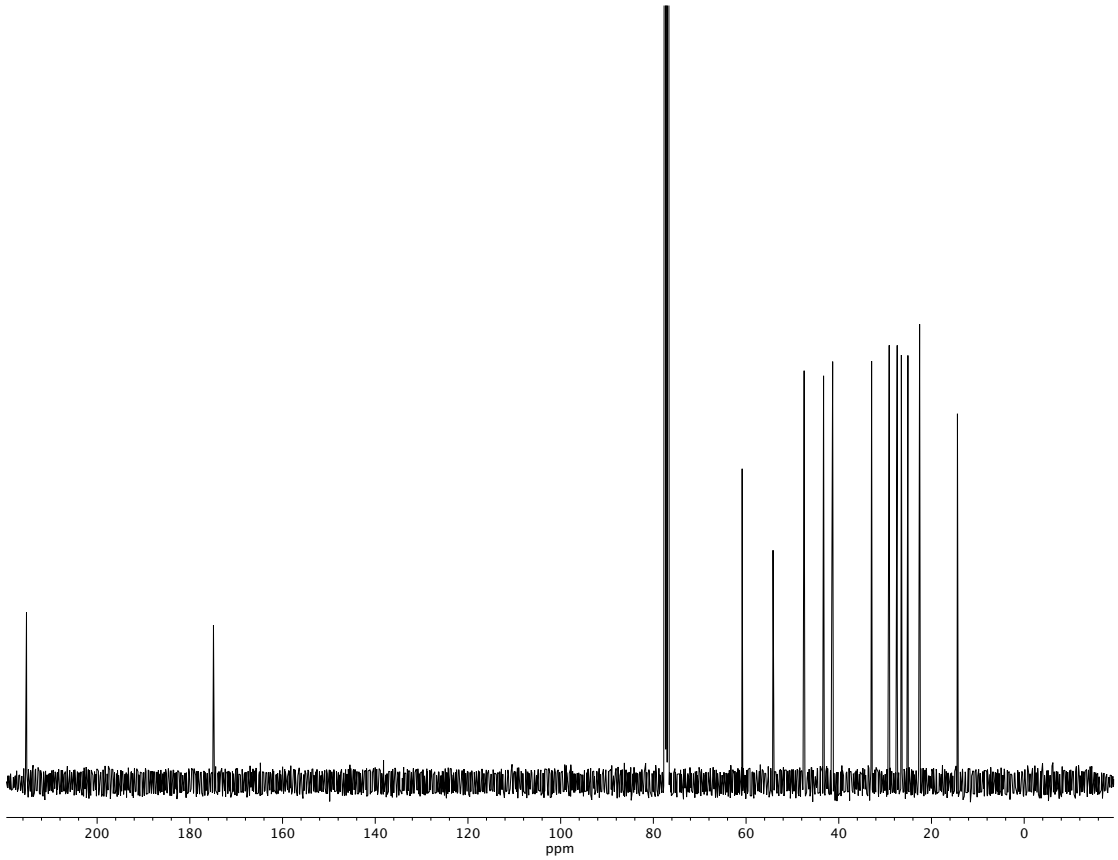


Figure A1.6. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11b****.*

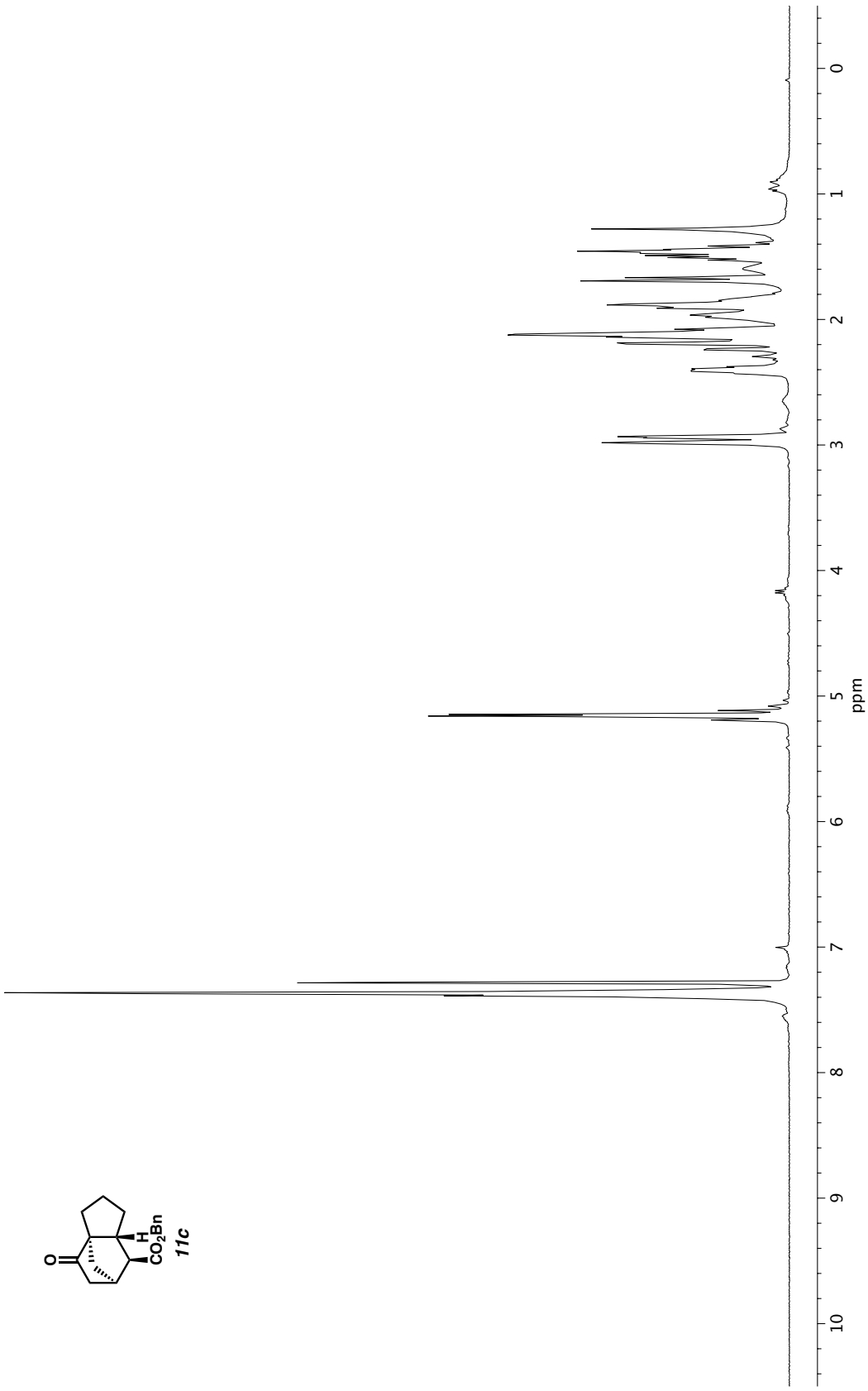


Figure A1.7. *^1H NMR (400 MHz, $CDCl_3$) of compound **11c**.*

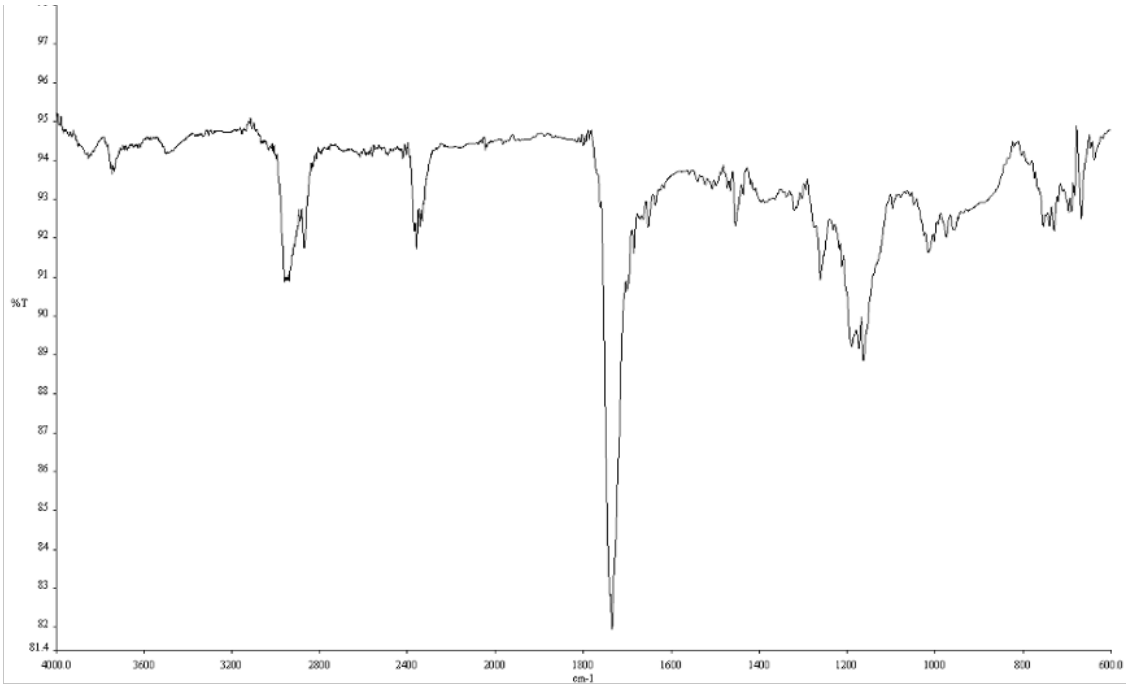


Figure A1.8. *Infrared spectrum (Thin Film, NaCl) of compound* ***11c****.*

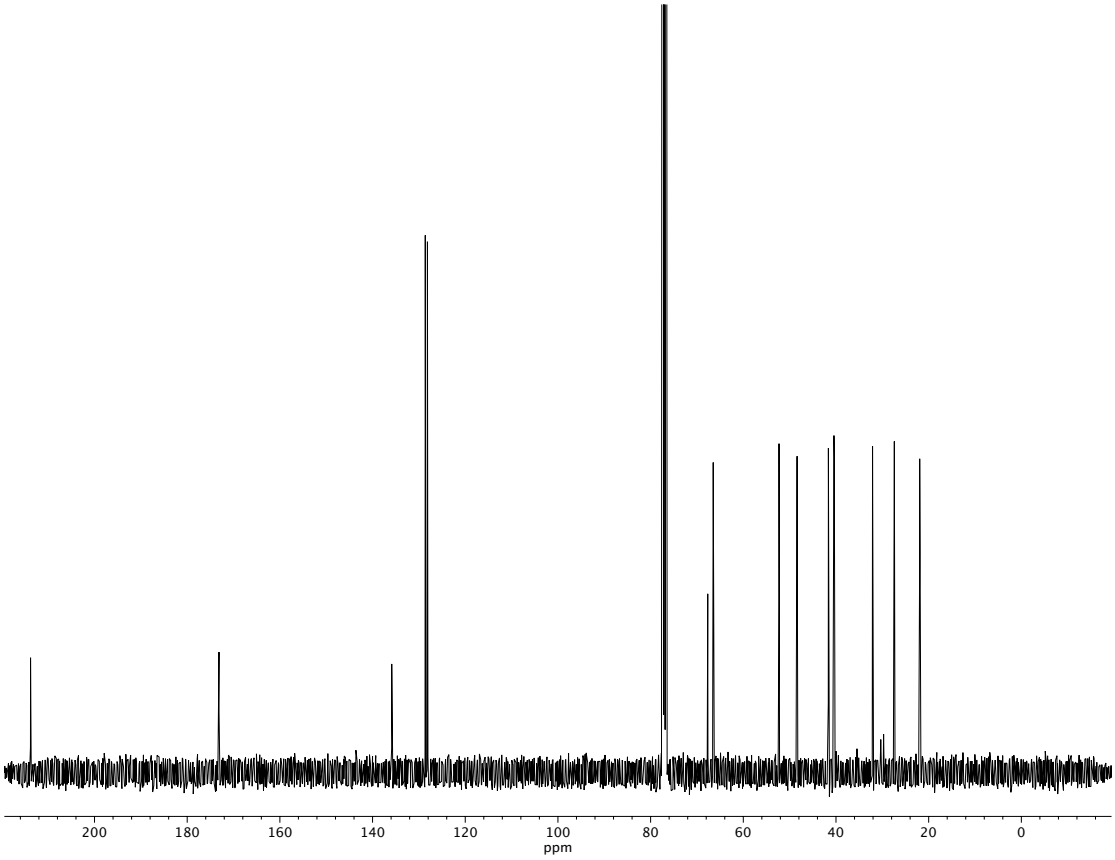


Figure A1.9. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11c****.*

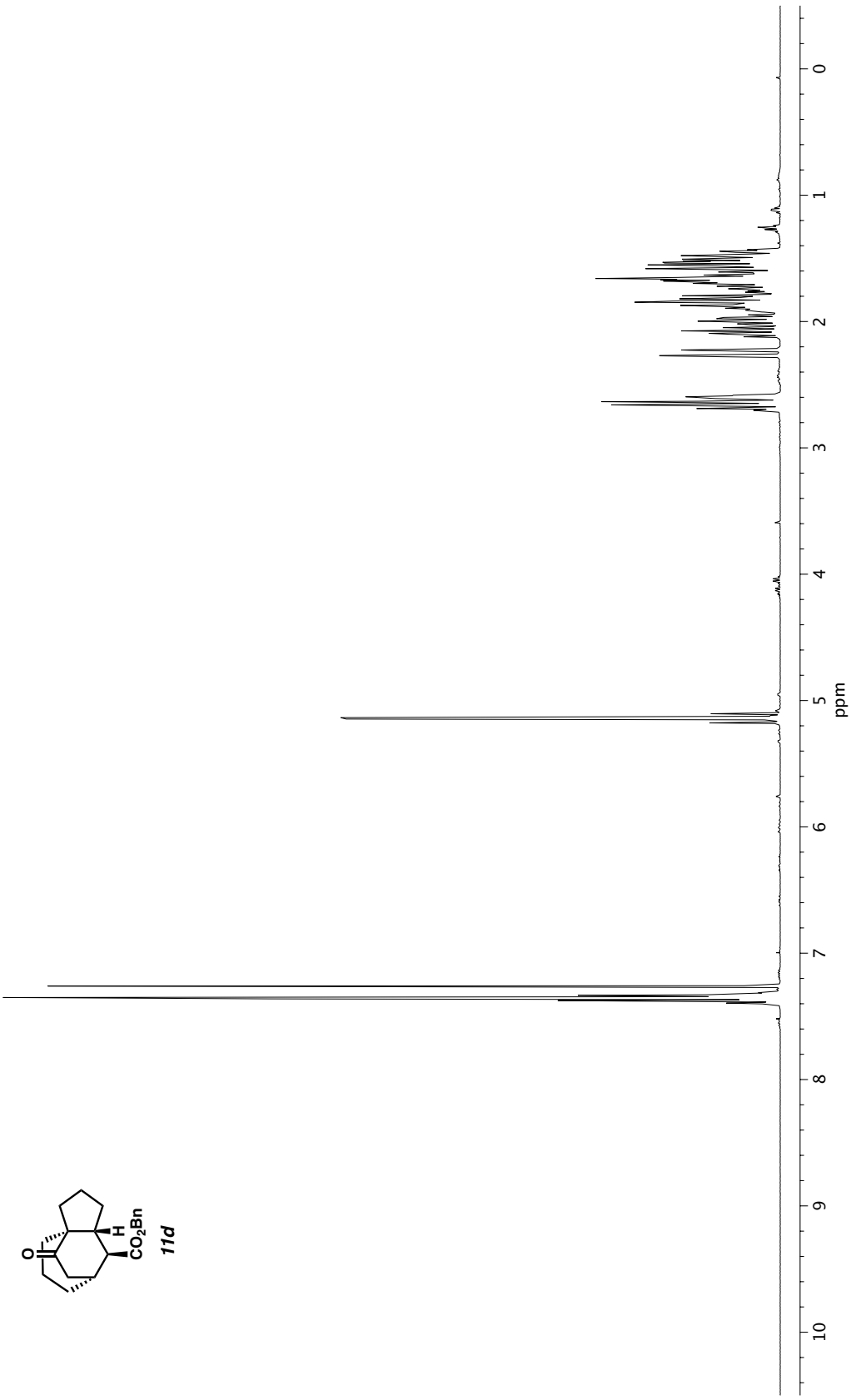


Figure A1.10. *^1H NMR (400 MHz, $CDCl_3$) of compound **11d**.*

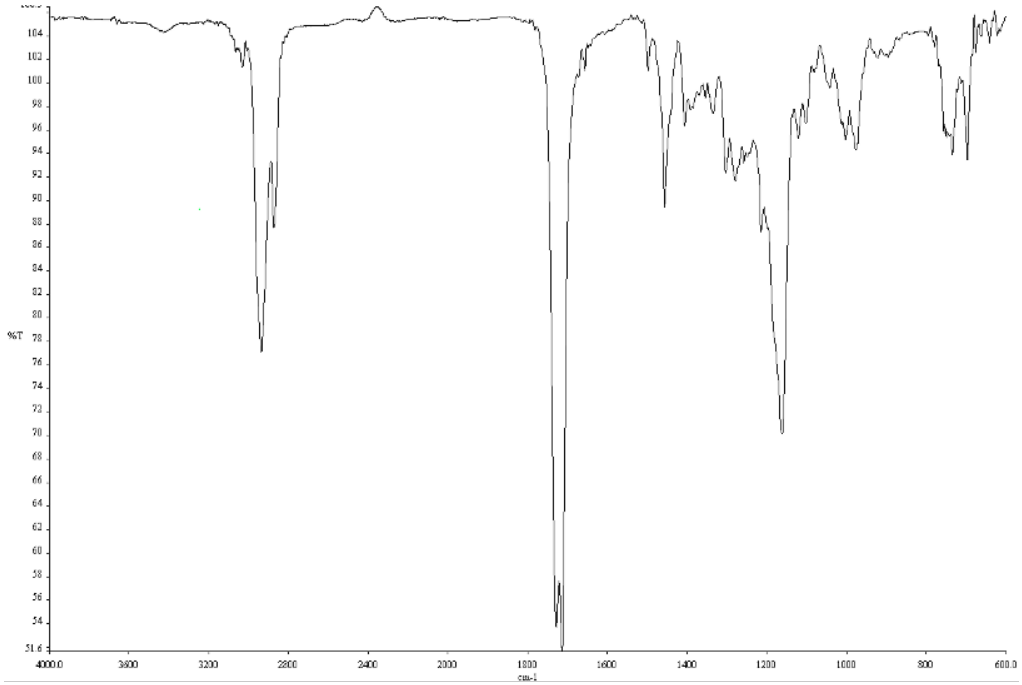


Figure A1.11. *Infrared spectrum (Thin Film, NaCl) of compound* ***11d****.*

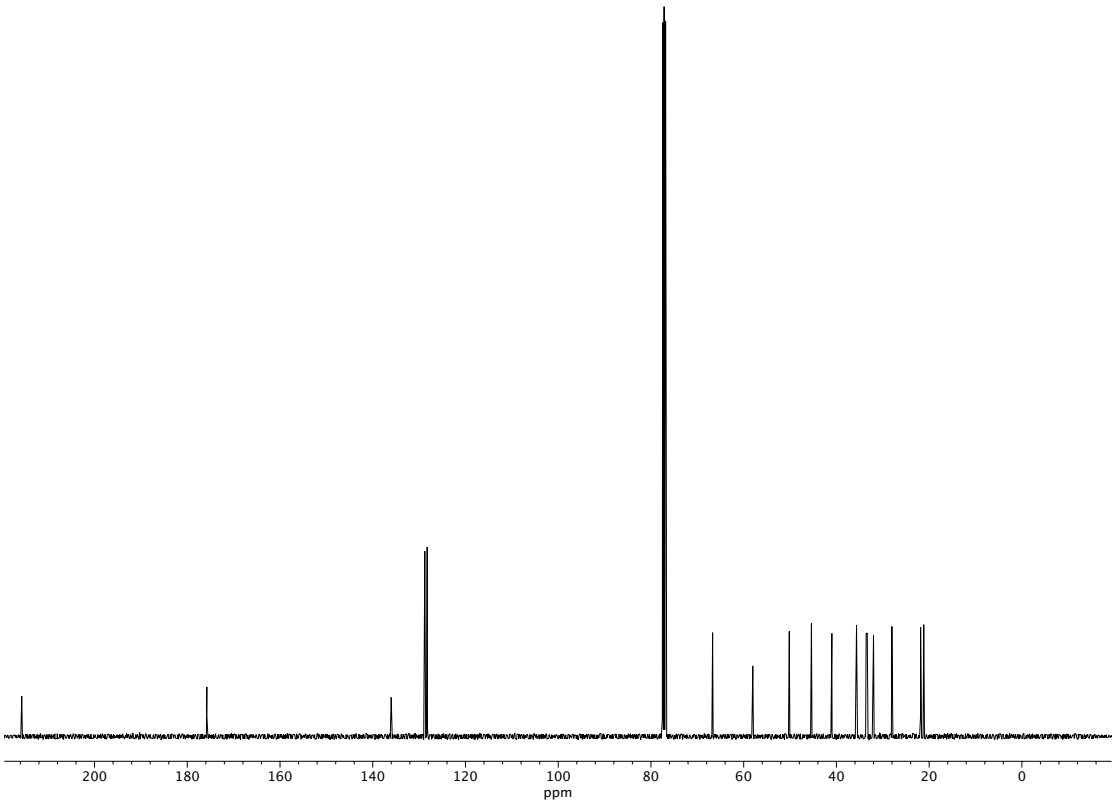


Figure A1.12. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11d****.*

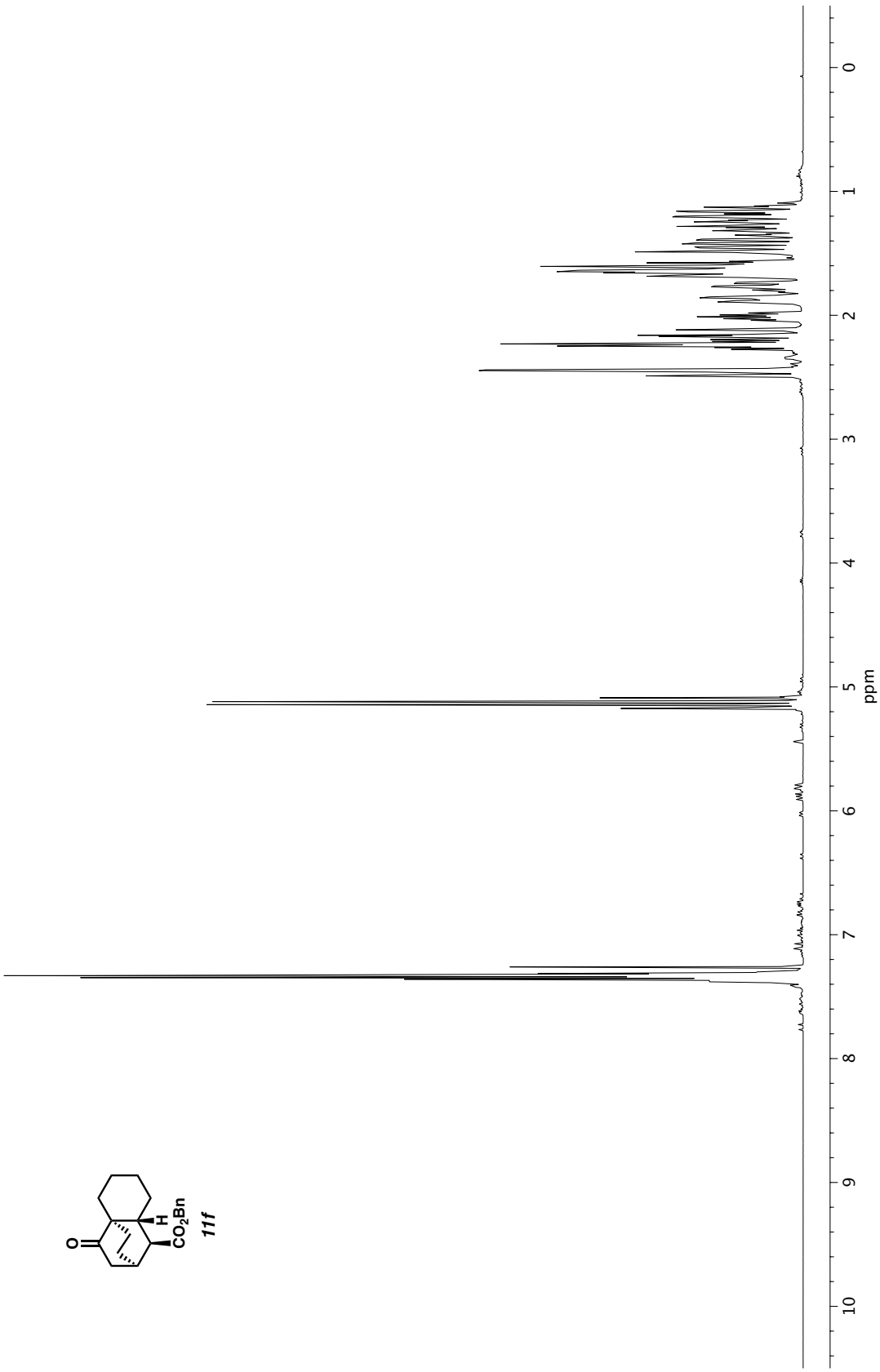


Figure A1.13. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***11f****.*

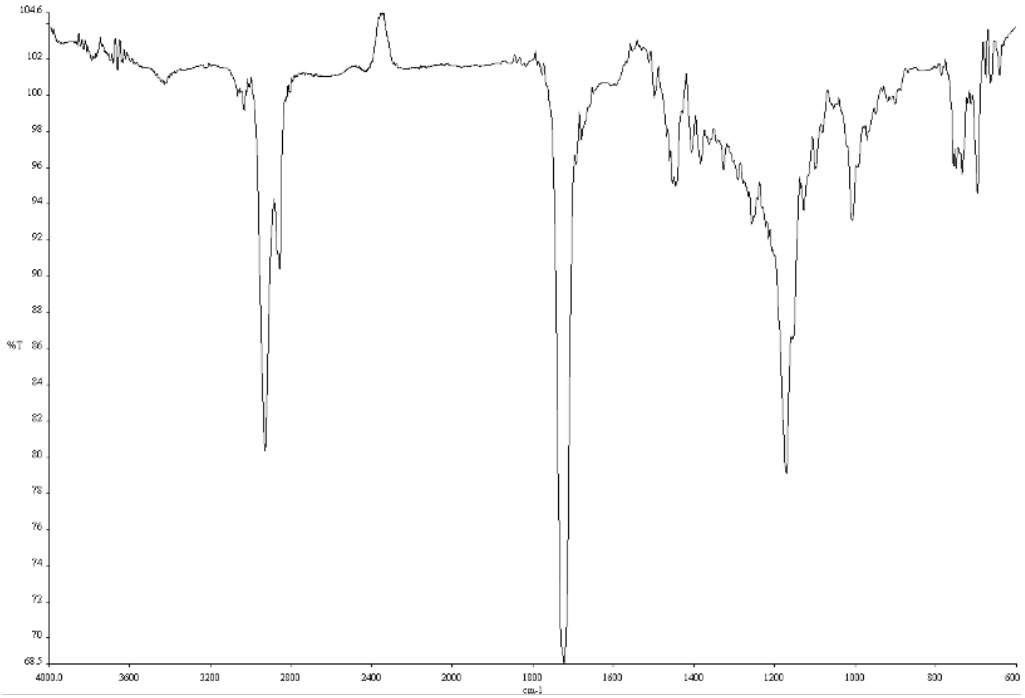


Figure A1.14. *Infrared spectrum (Thin Film, NaCl) of compound* ***11f****.*

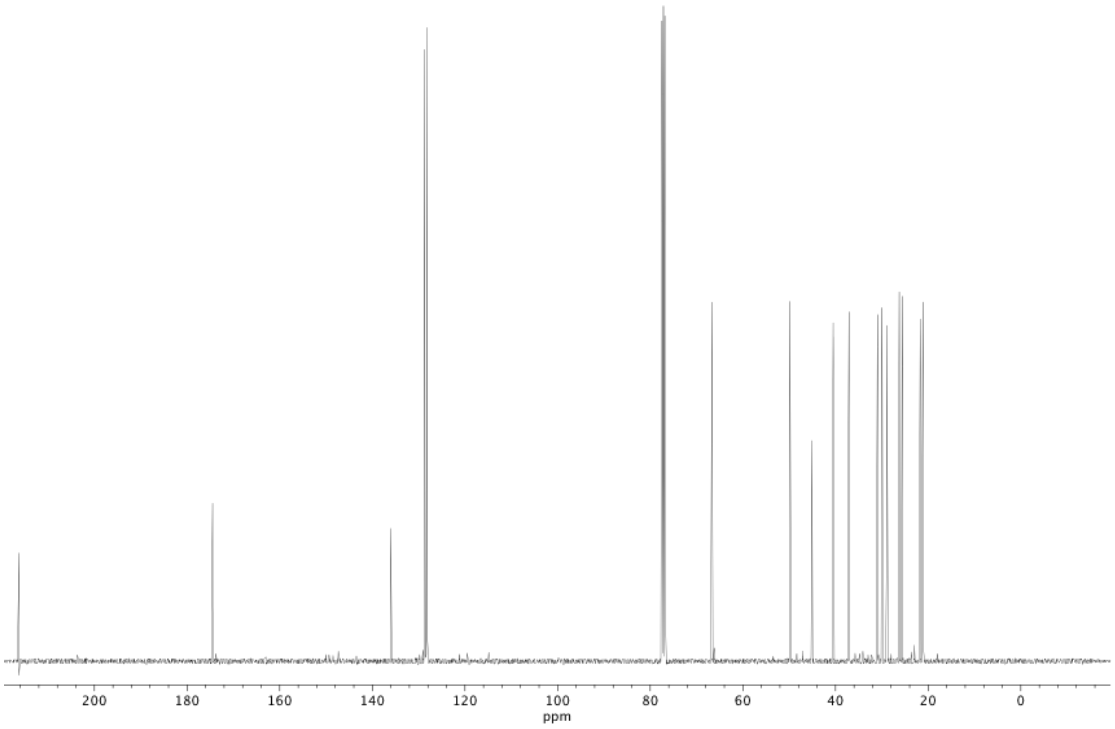


Figure A1.15. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11f****.*

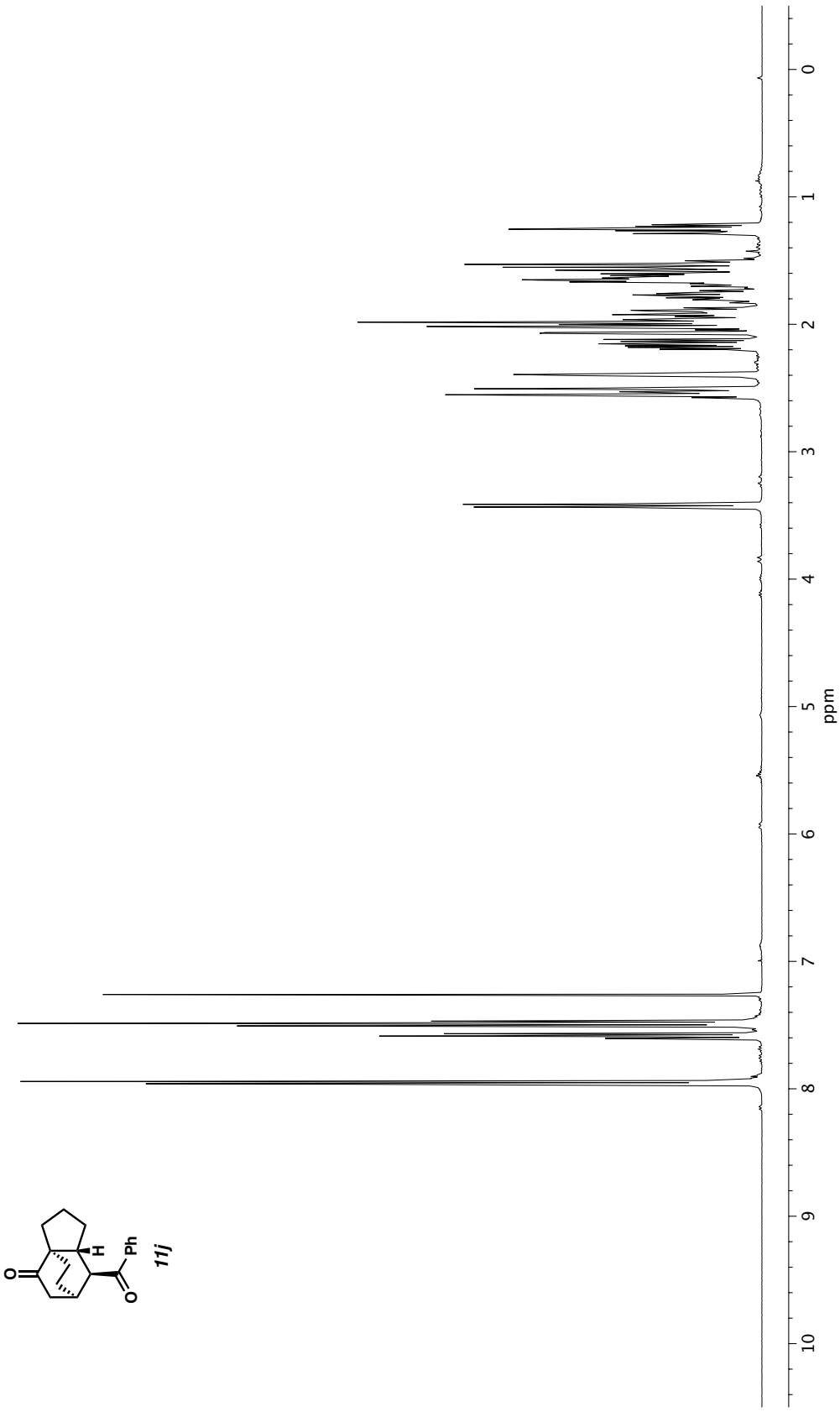


Figure A1.16. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***11j****.*

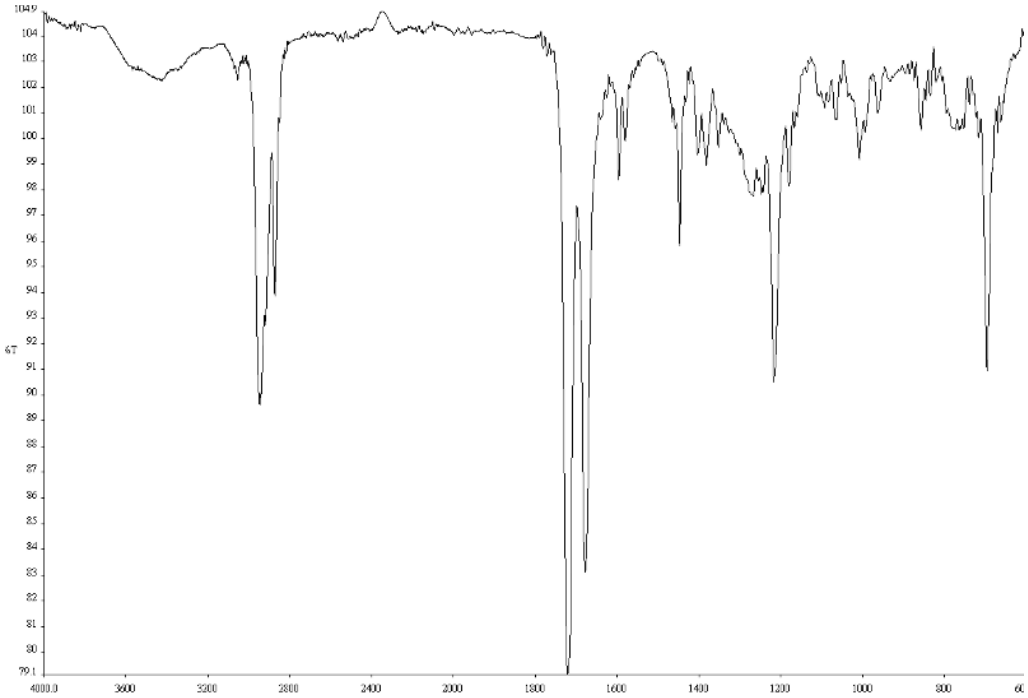


Figure A1.17. *Infrared spectrum (Thin Film, NaCl) of compound* ***11j****.*

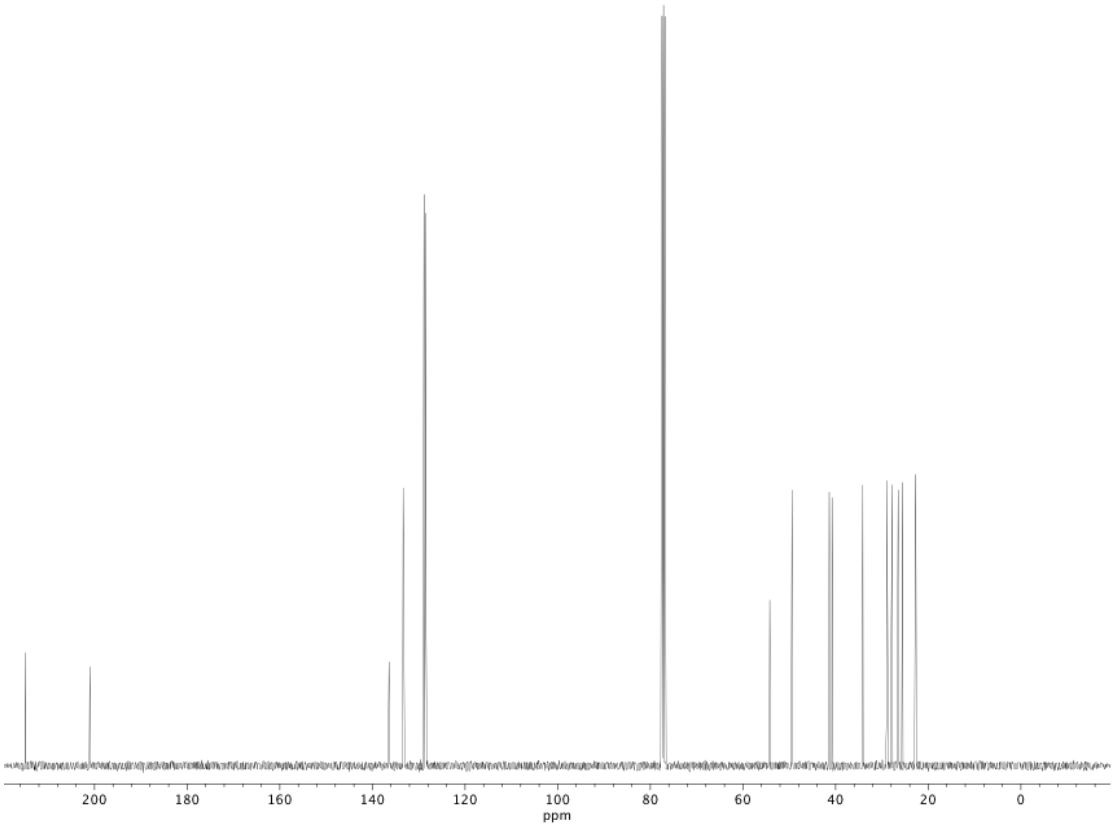


Figure A1.18. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11j****.*

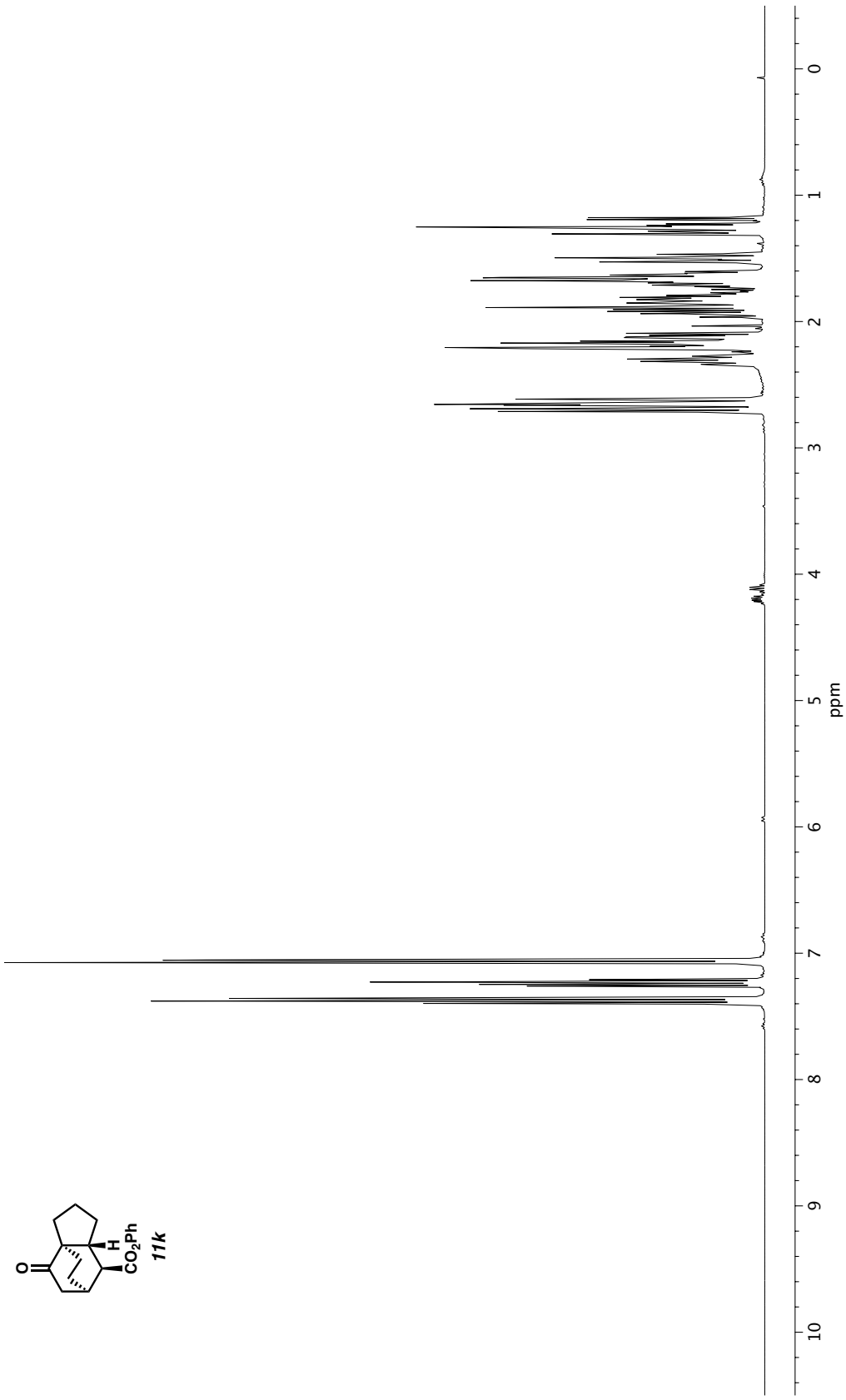


Figure A1.19. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***11k****.*

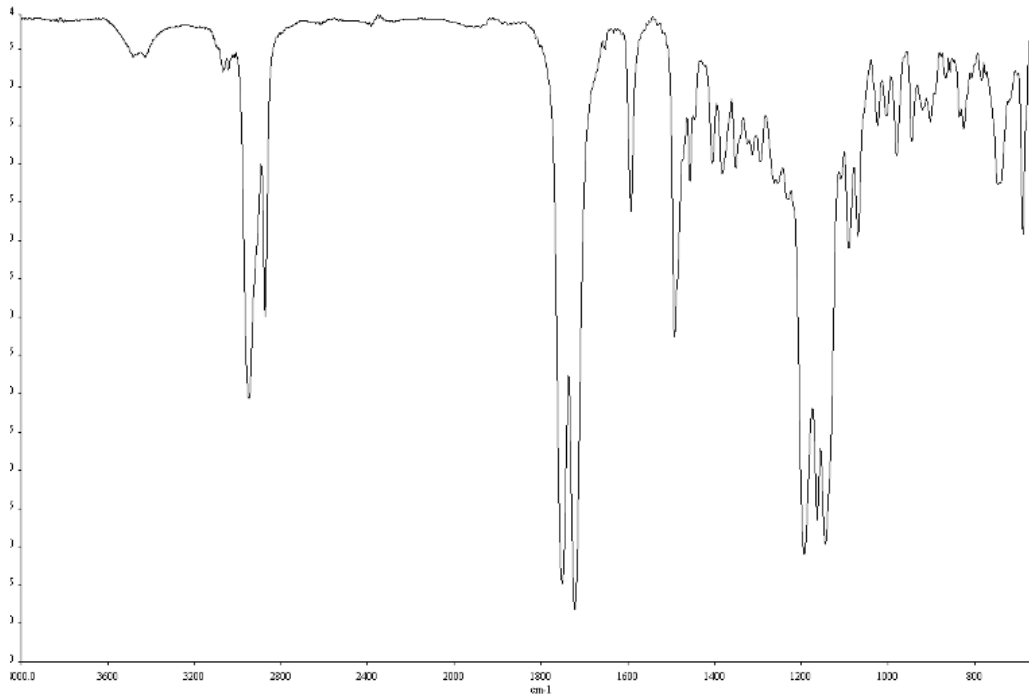


Figure A1.20. *Infrared spectrum (Thin Film, NaCl) of compound* ***11k****.*

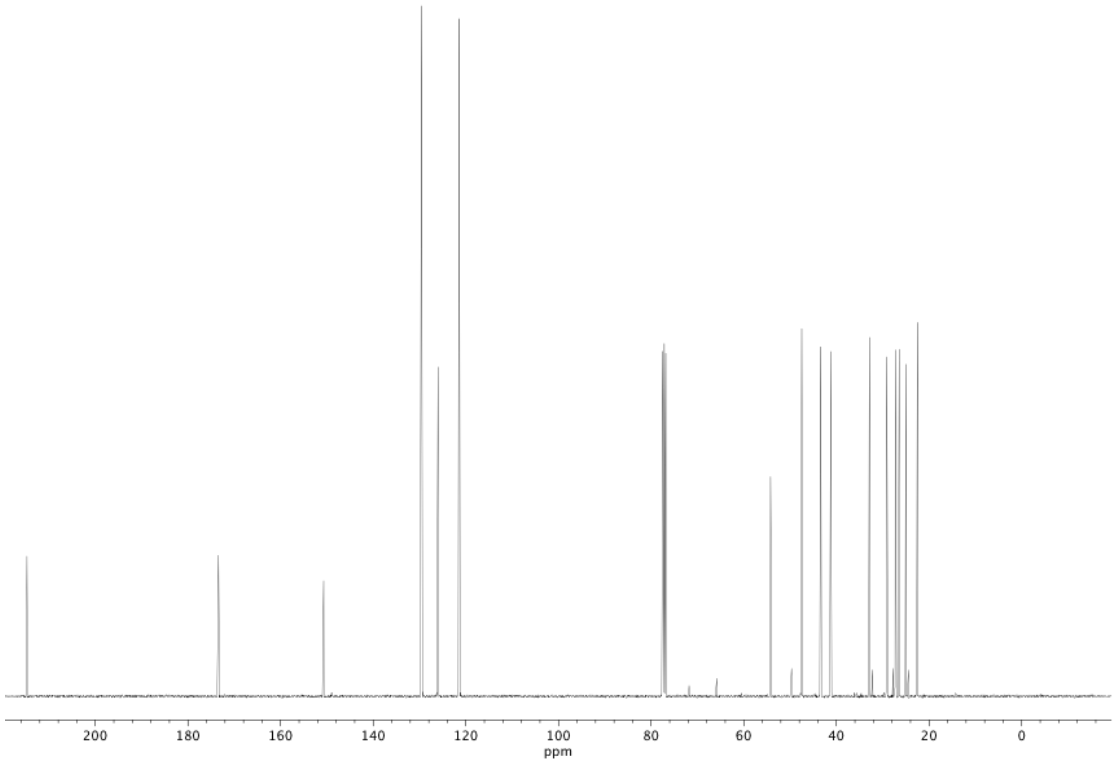


Figure A1.21. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11k****.*

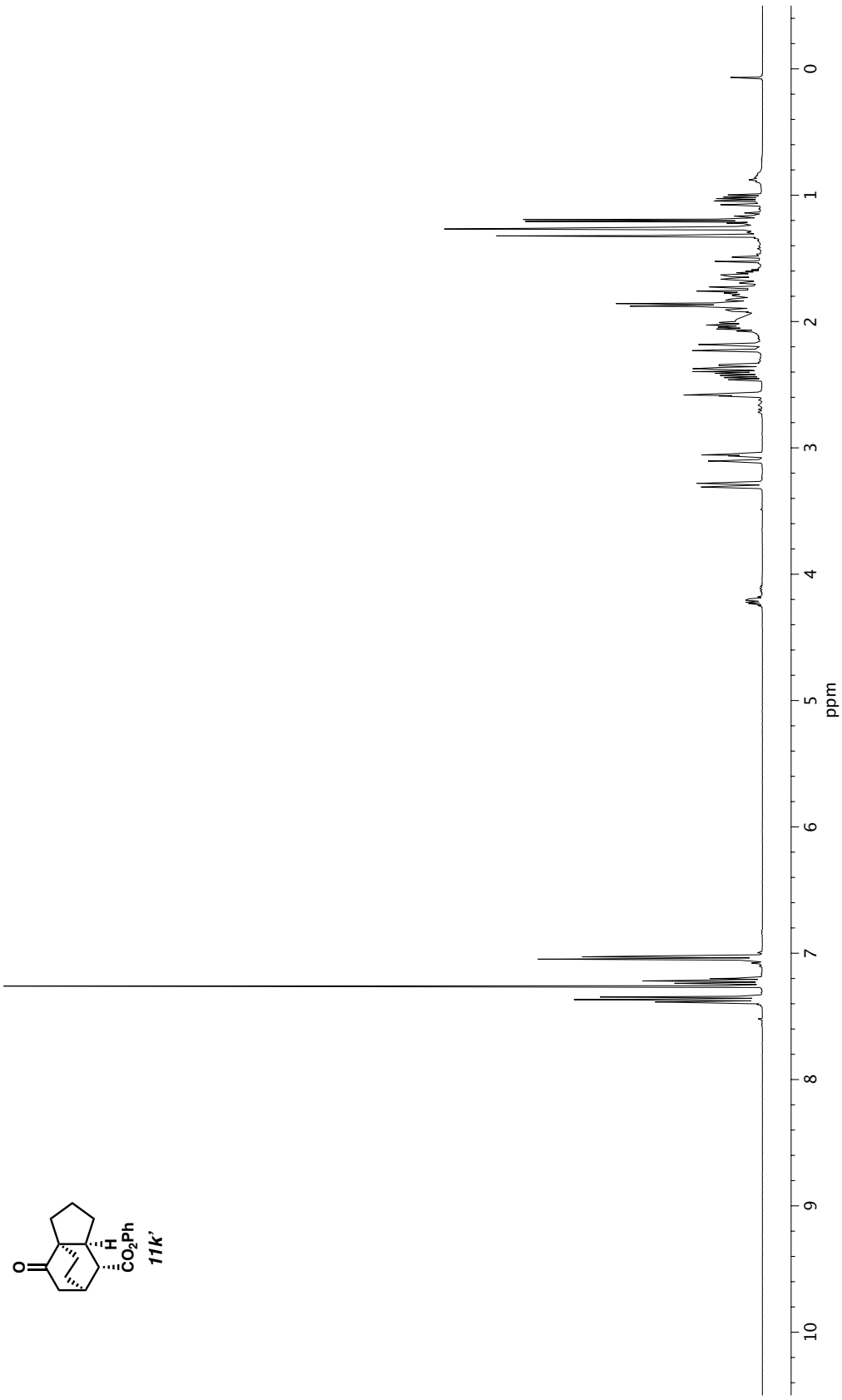


Figure A1.22. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***11k'*** *.*

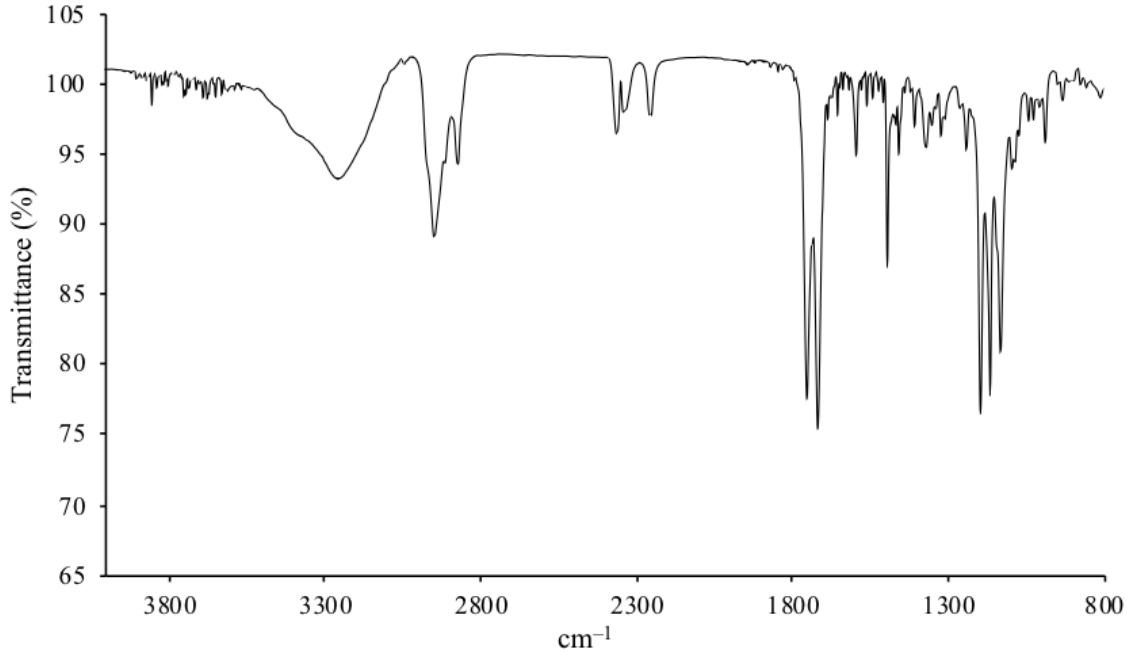


Figure A1.23. *Infrared spectrum ($CDCl_3$ solution) of compound* ***11k'***.

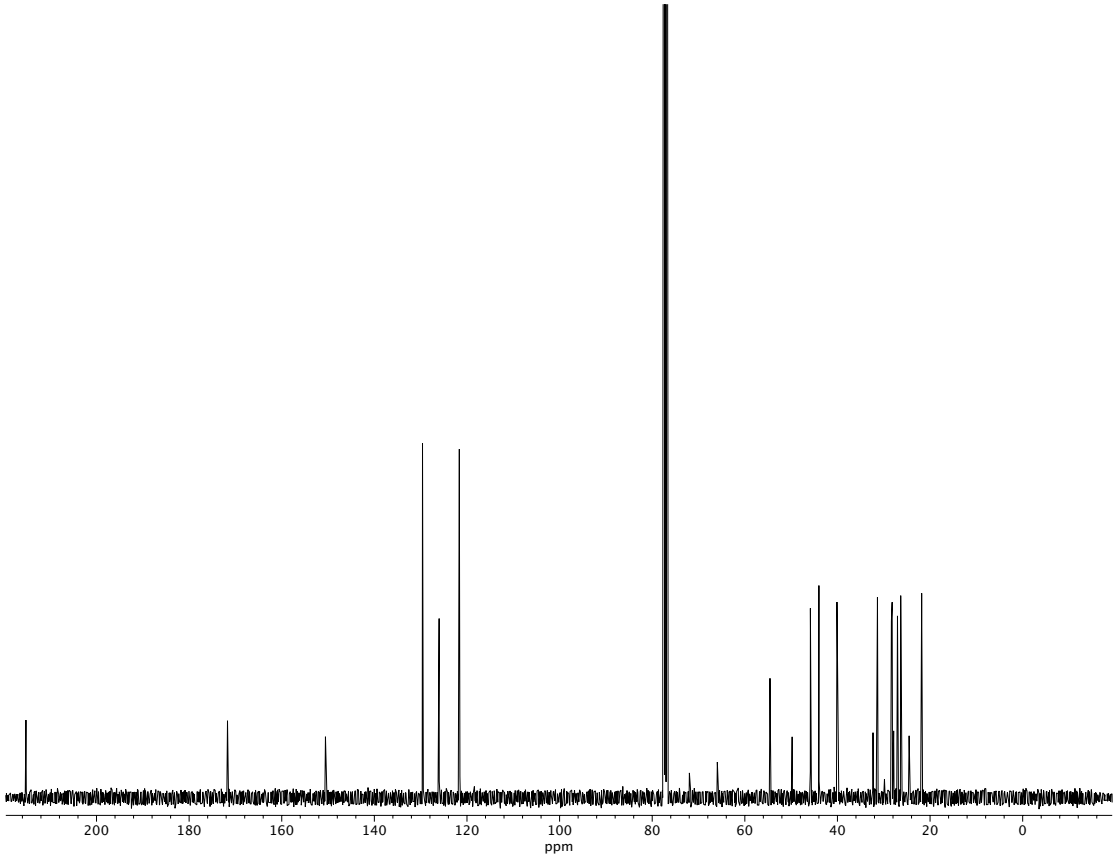


Figure A1.24. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11k'***.

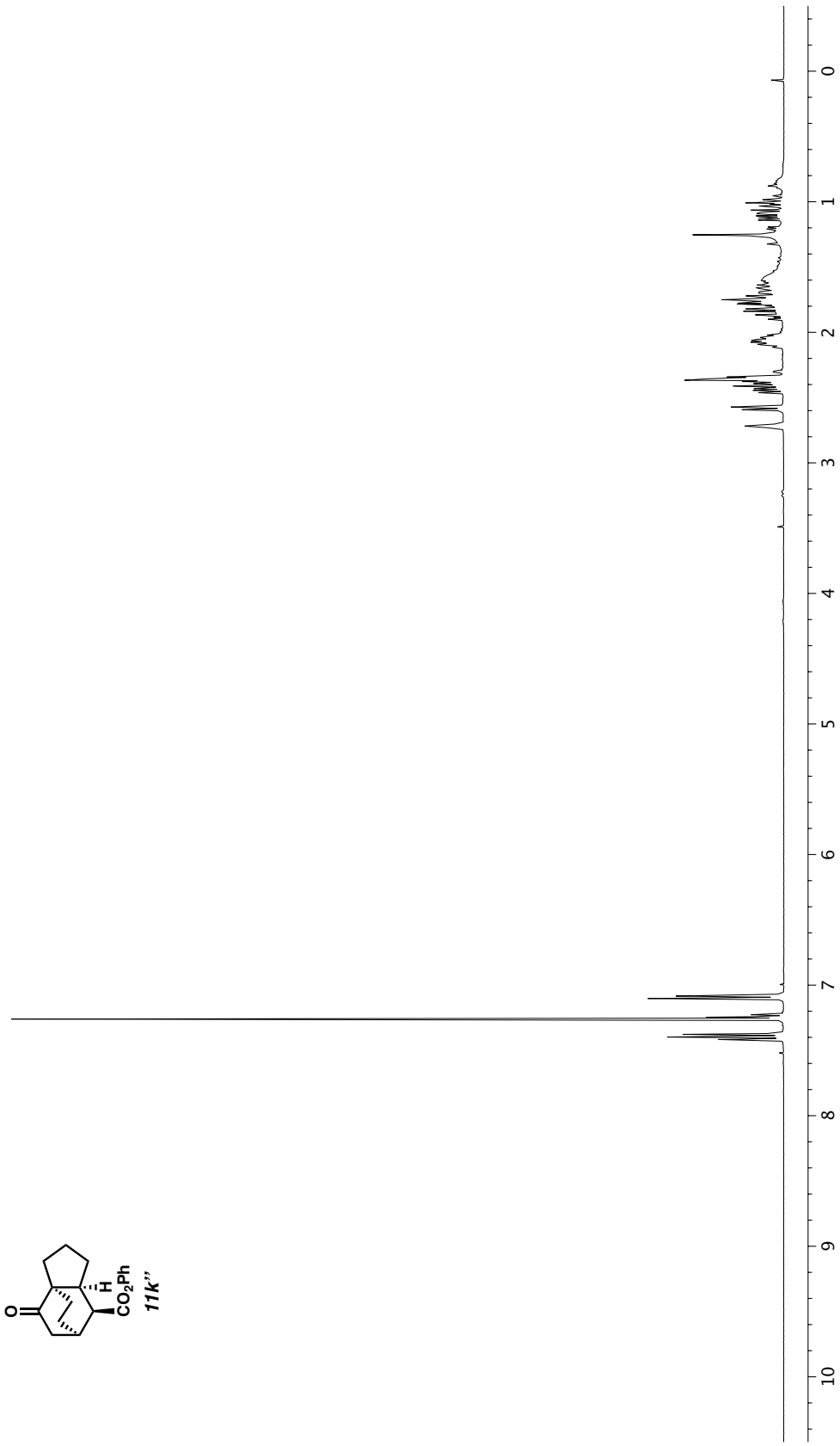


Figure A1.25. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***11k''*** *.*

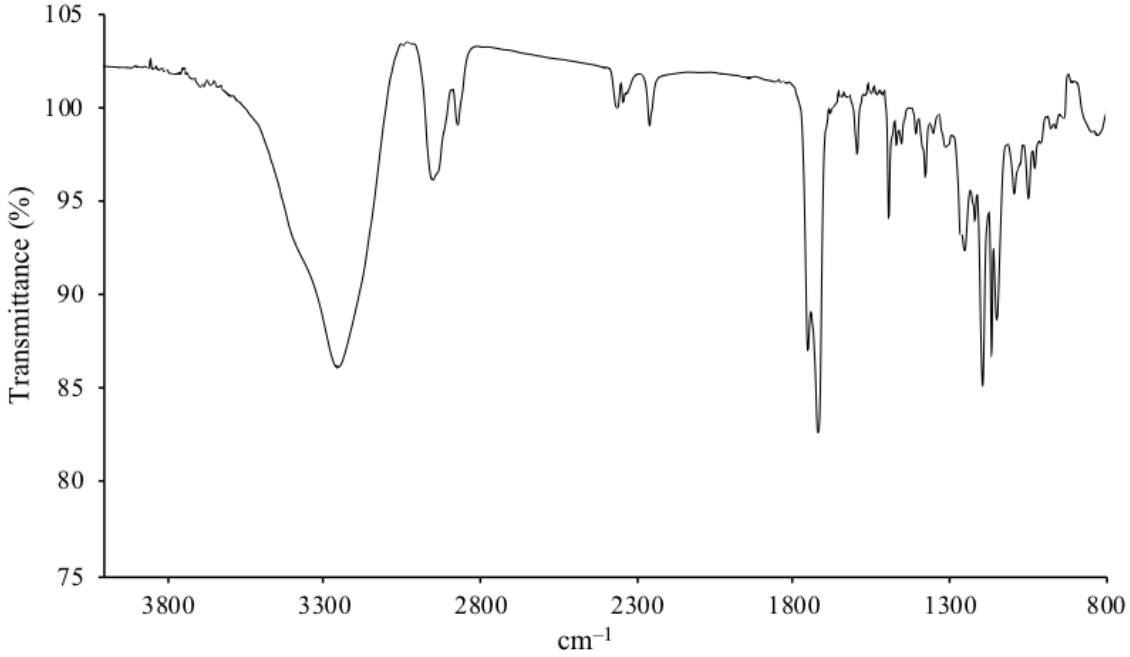


Figure A1.26. *Infrared spectrum ($CDCl_3$ solution) of compound* ***11k''***.

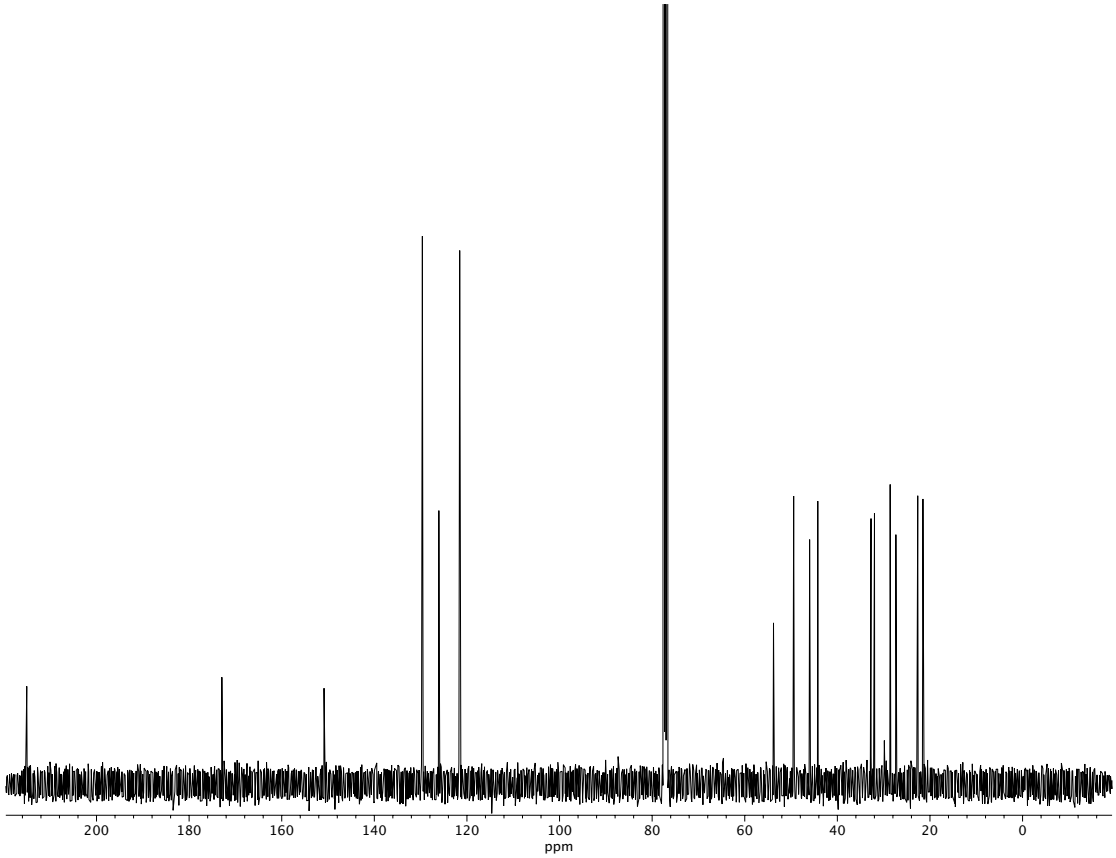


Figure A1.27. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11k''***.

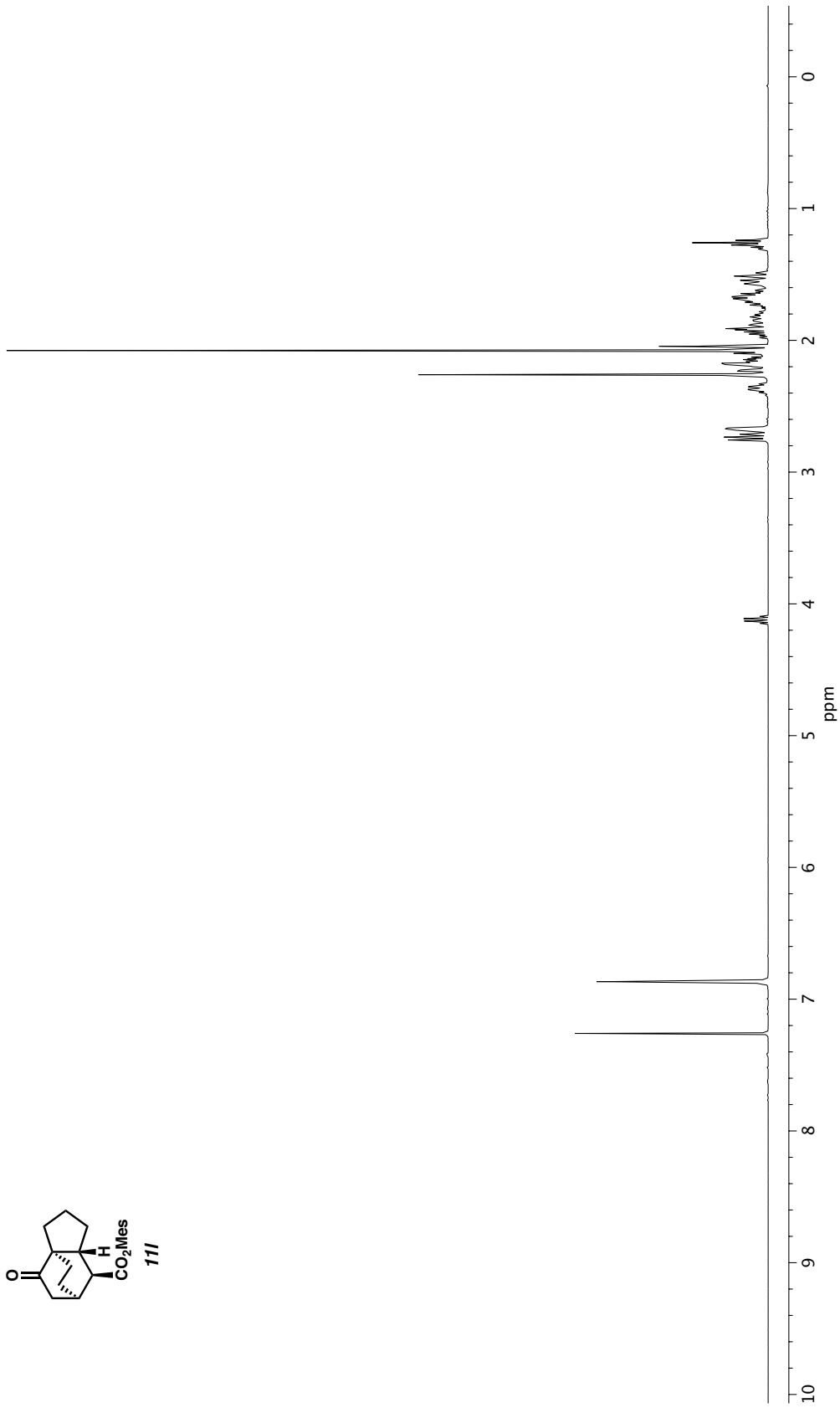


Figure A1.28. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***11l****.*

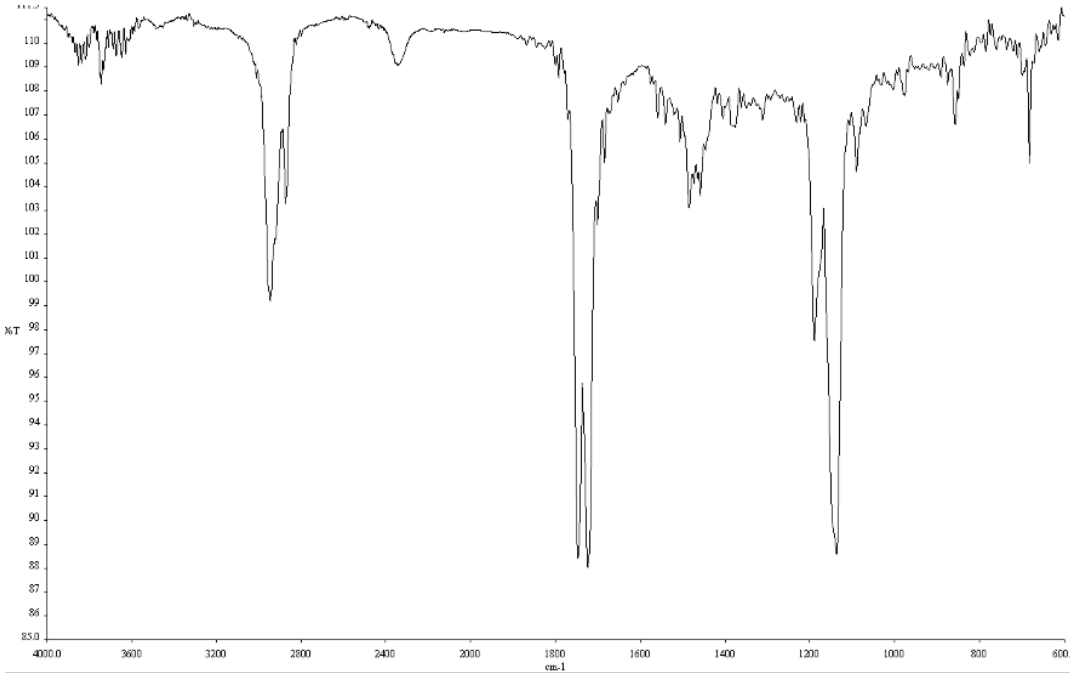


Figure A1.29. *Infrared spectrum (Thin Film, NaCl) of compound* ***11l****.*

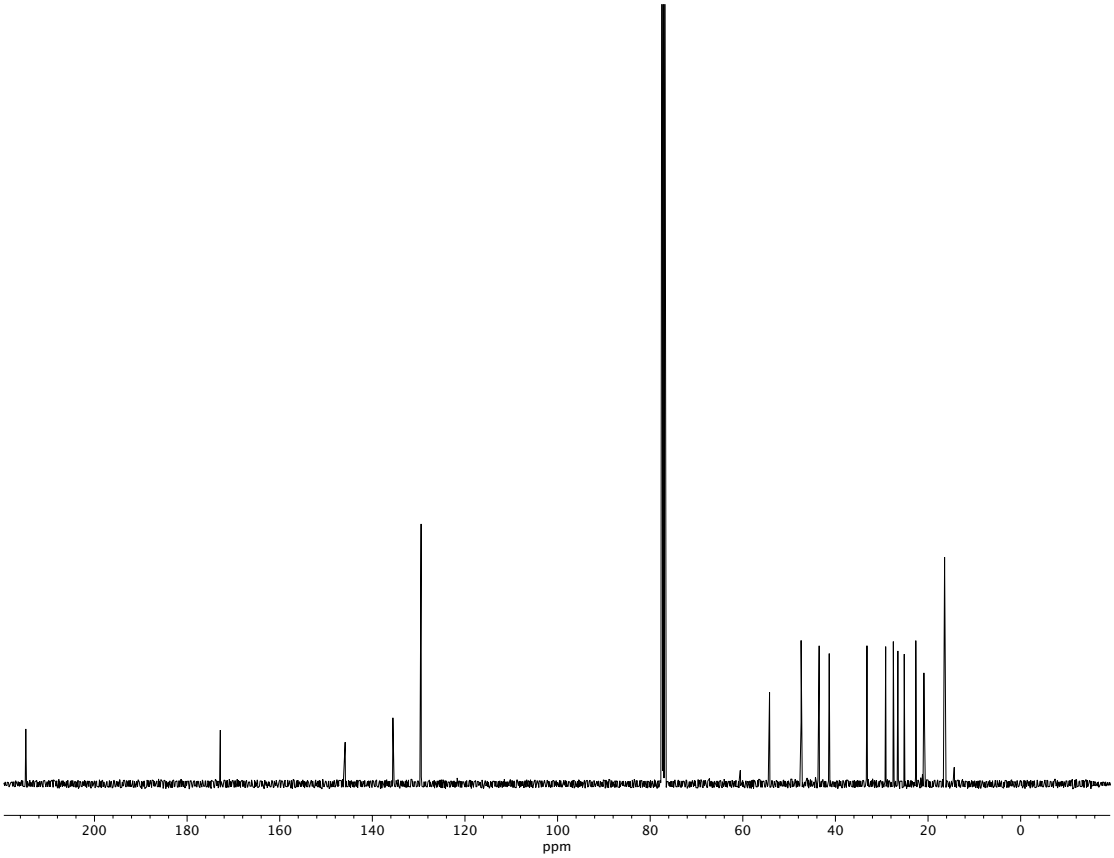


Figure A1.30. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11l****.*

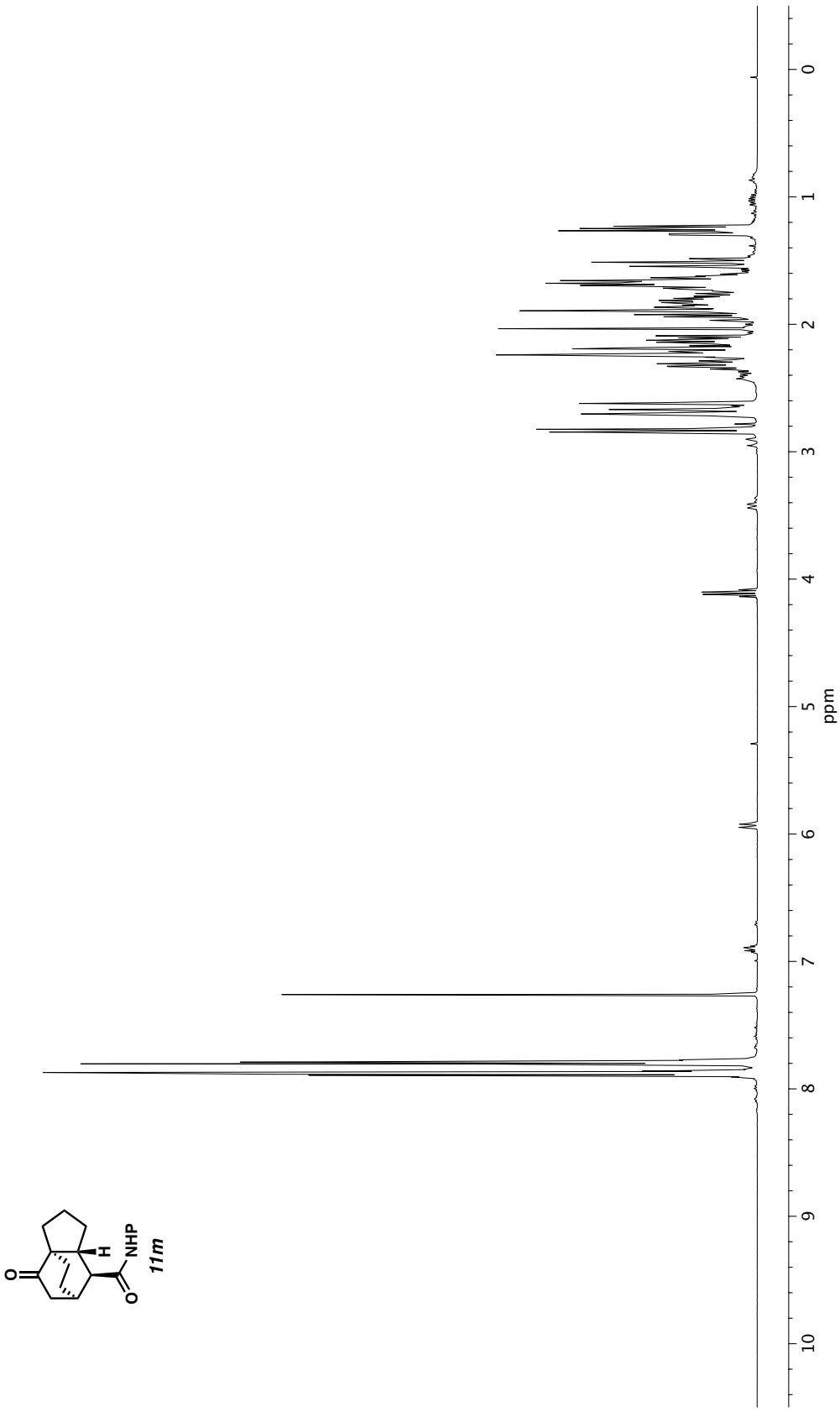


Figure A1.31. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***11m****.*

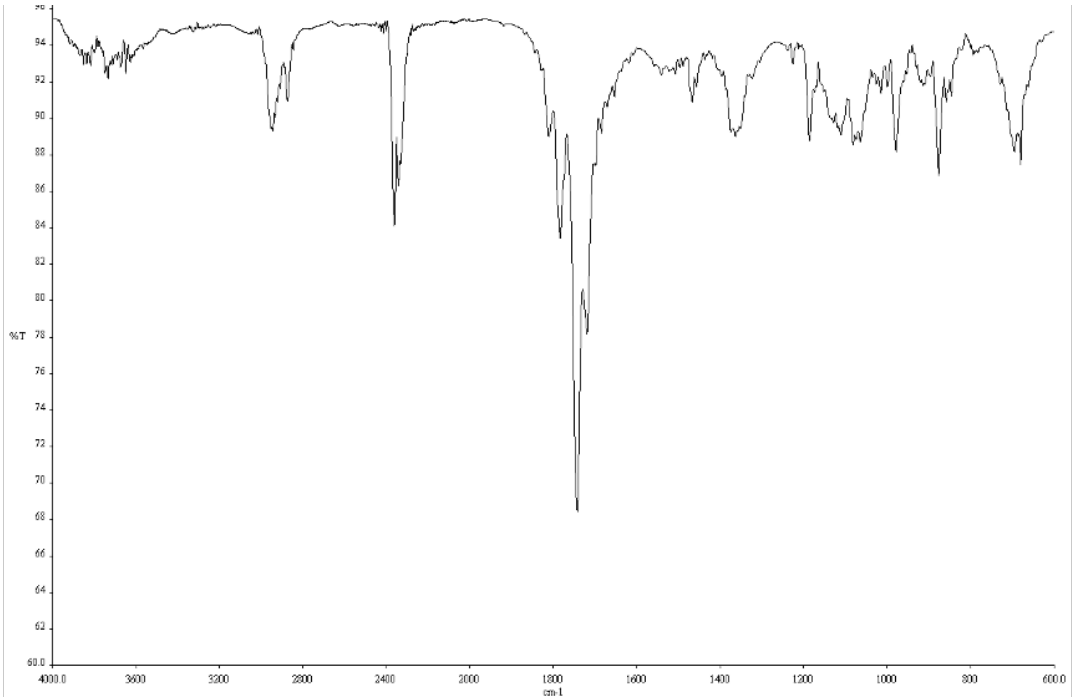


Figure A1.32. *Infrared spectrum (Thin Film, NaCl) of compound* ***11m****.*

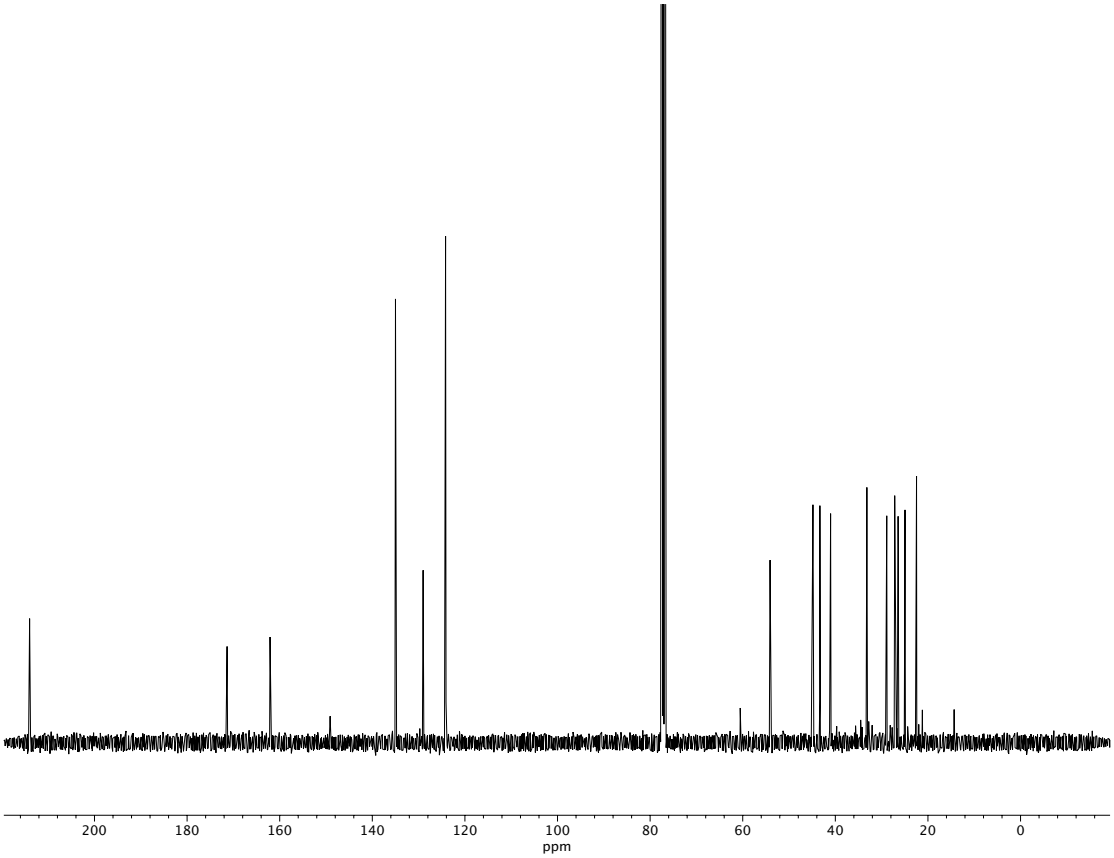


Figure A1.33. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11m****.*

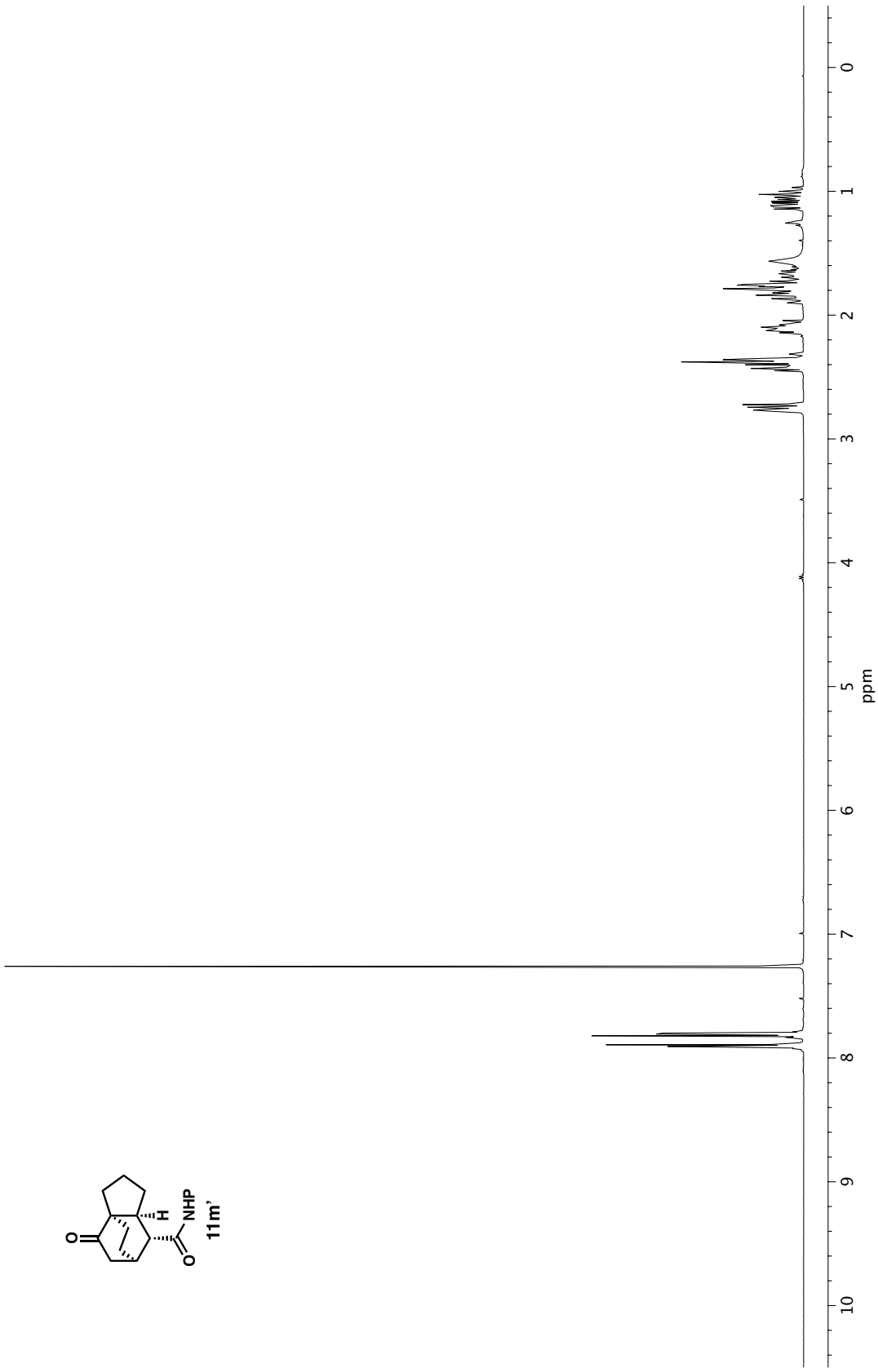


Figure A1.34. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***11m'*** .

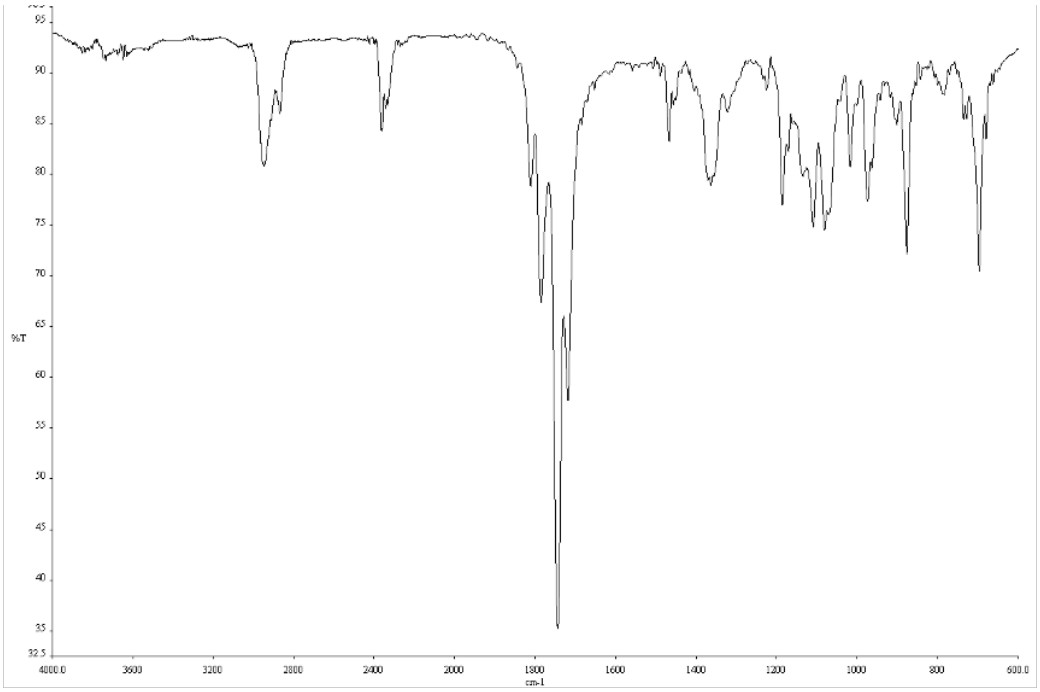


Figure A1.35. *Infrared spectrum (Thin Film, NaCl) of compound* ***11m′****.*

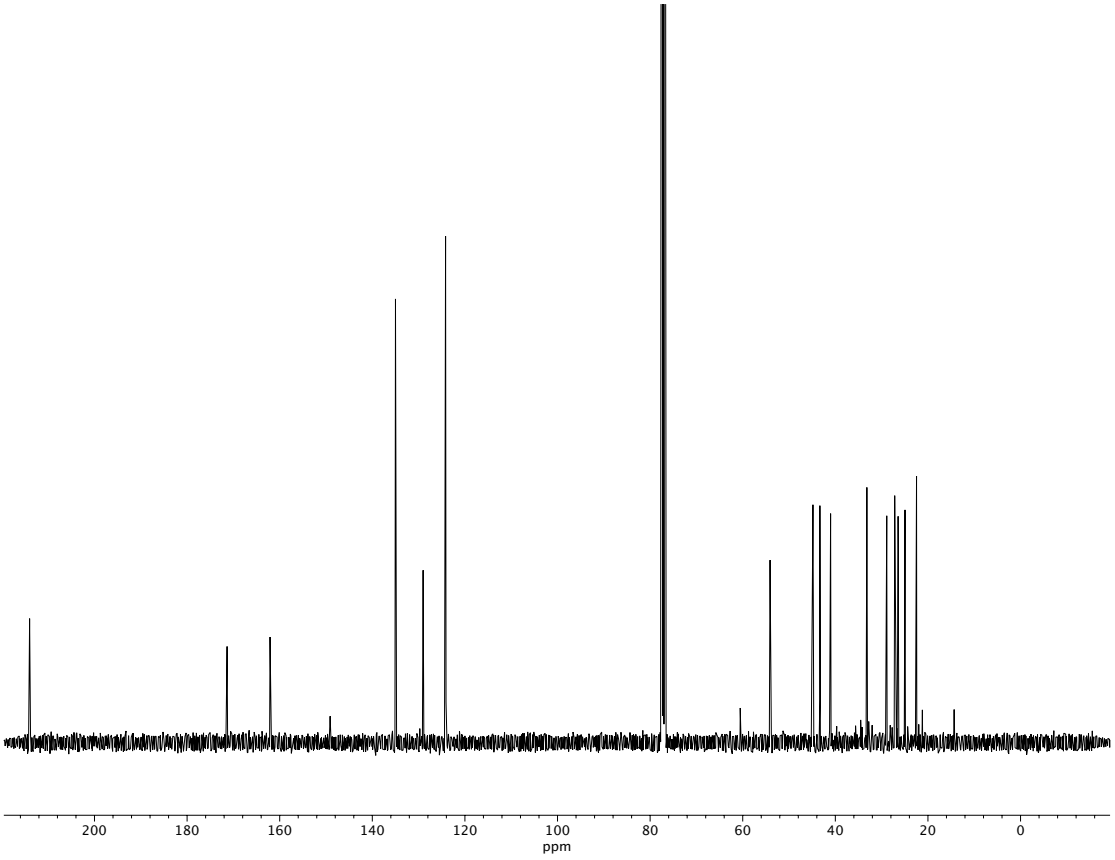


Figure A1.36. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11m′****.*

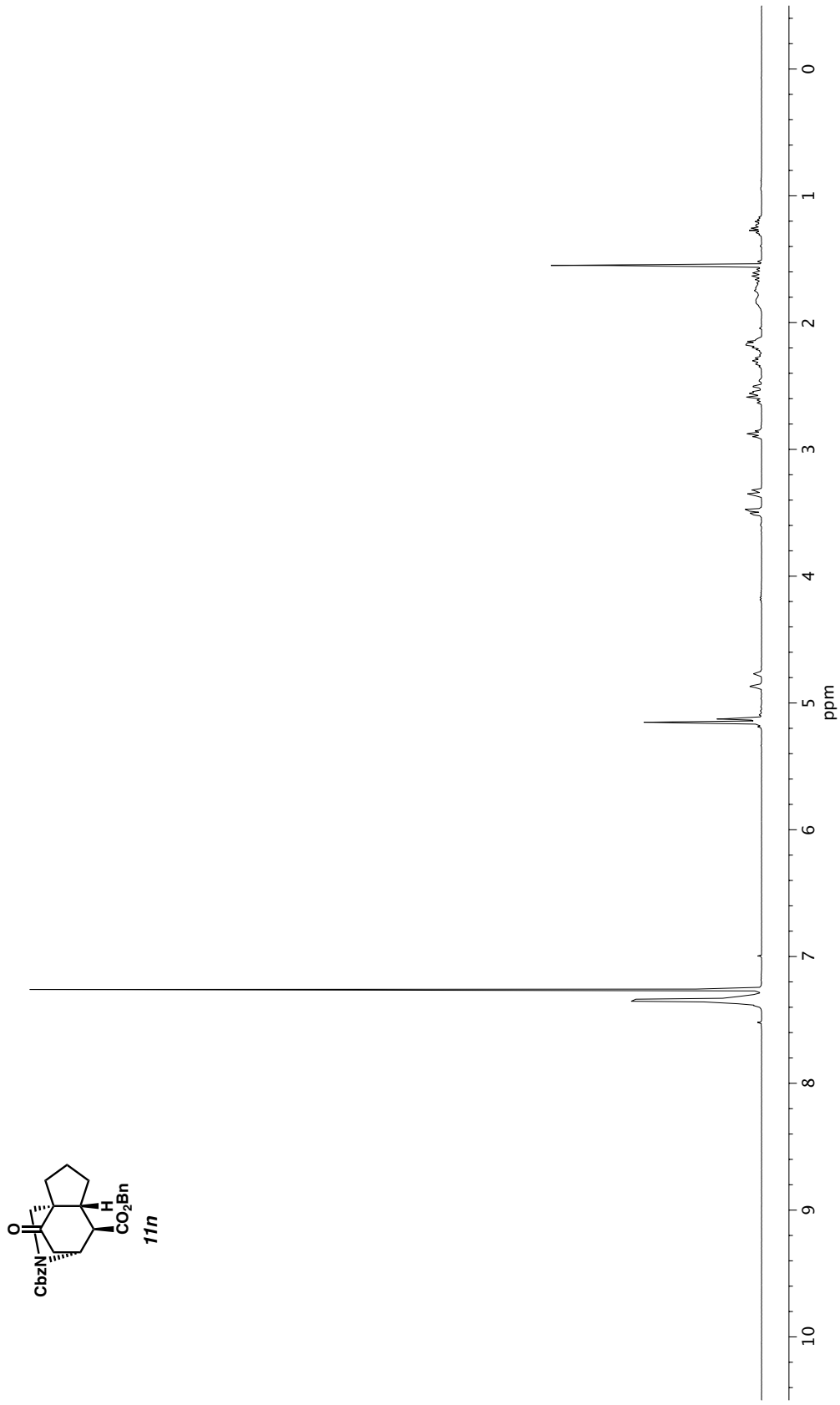


Figure A1.37. *^{1}H NMR (400 MHz, $CDCl_3$) of compound **11n**.*

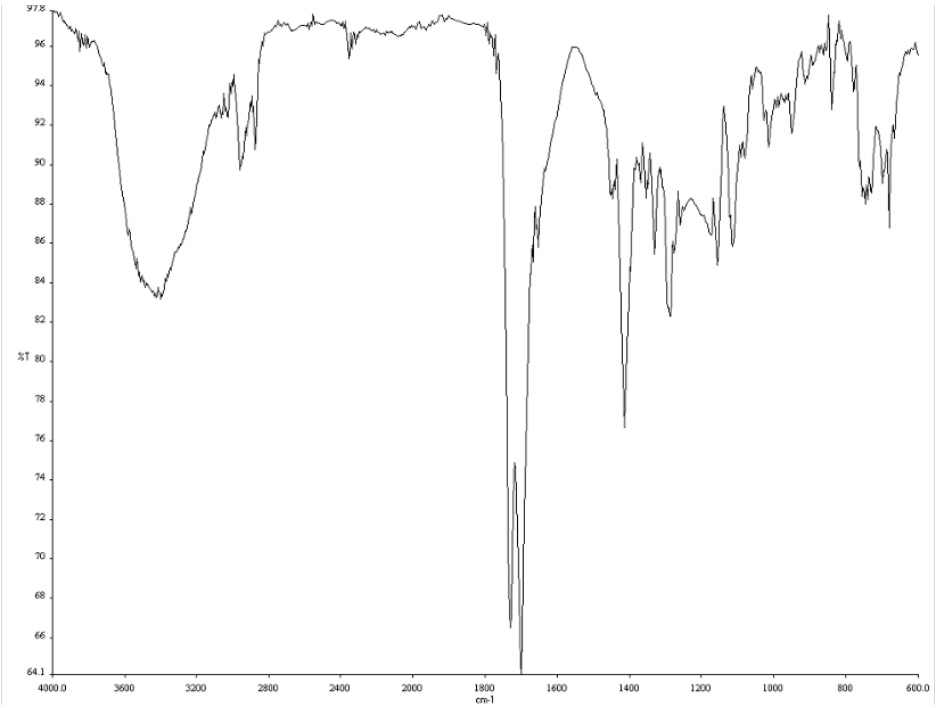


Figure A1.38. *Infrared spectrum (Thin Film, NaCl) of compound* ***11n****.*

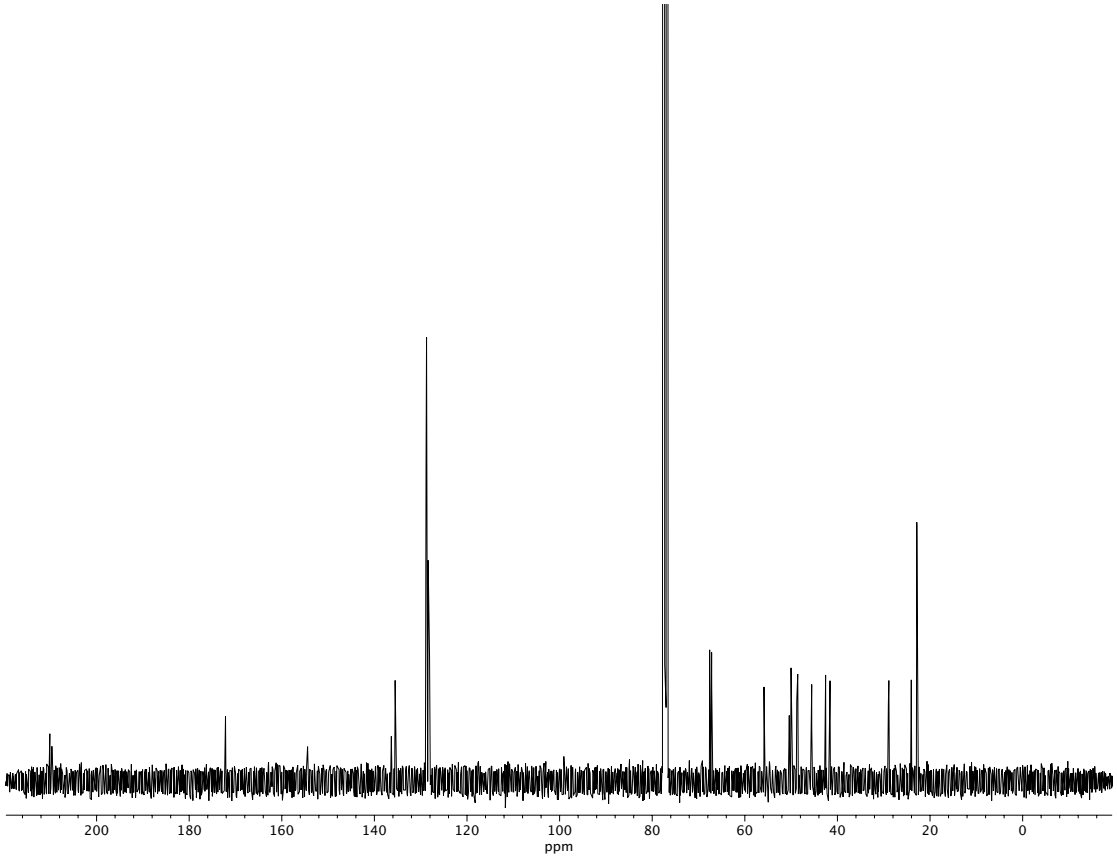
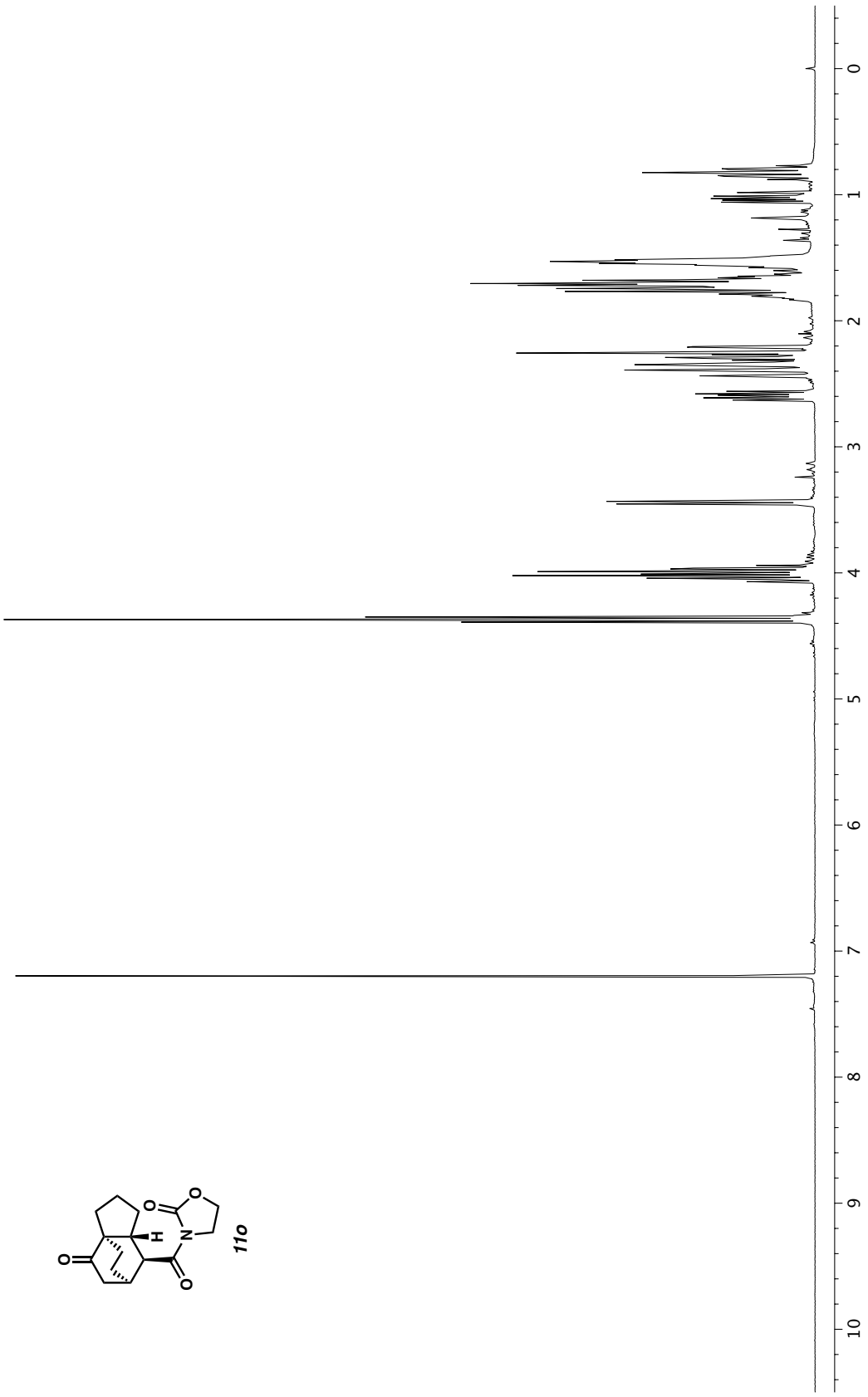


Figure A1.39. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11n****.*



11o

Figure A1.40. *^{1}H NMR (400 MHz, $CDCl_3$) of compound **11o**.*

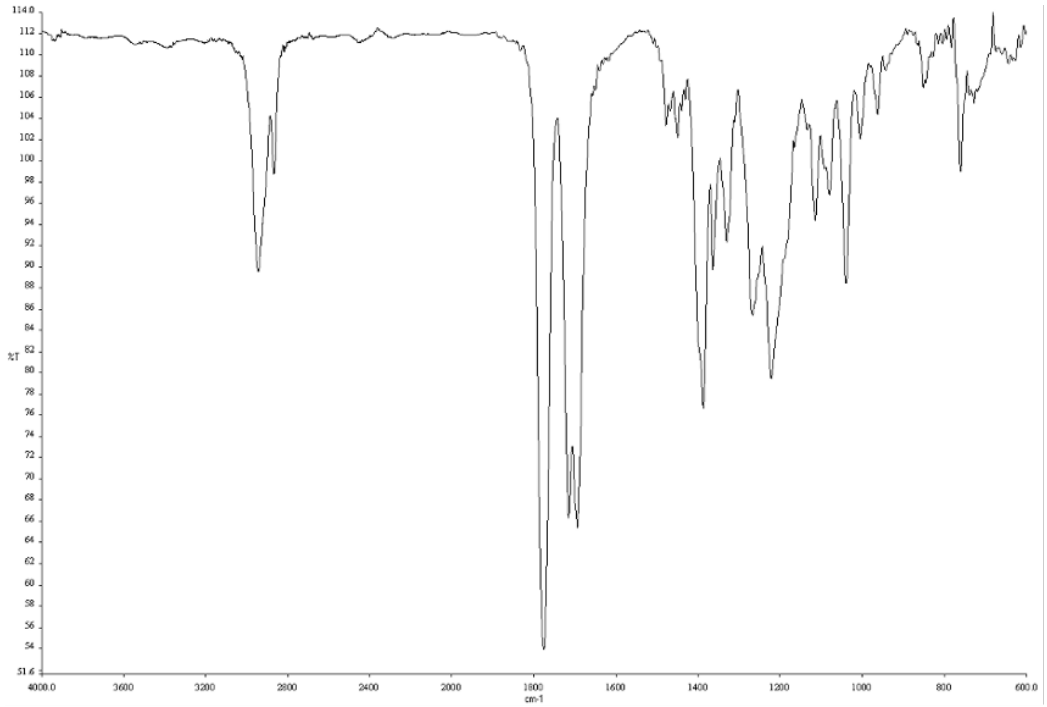


Figure A1.41. *Infrared spectrum (Thin Film, NaCl) of compound* ***11o****.*

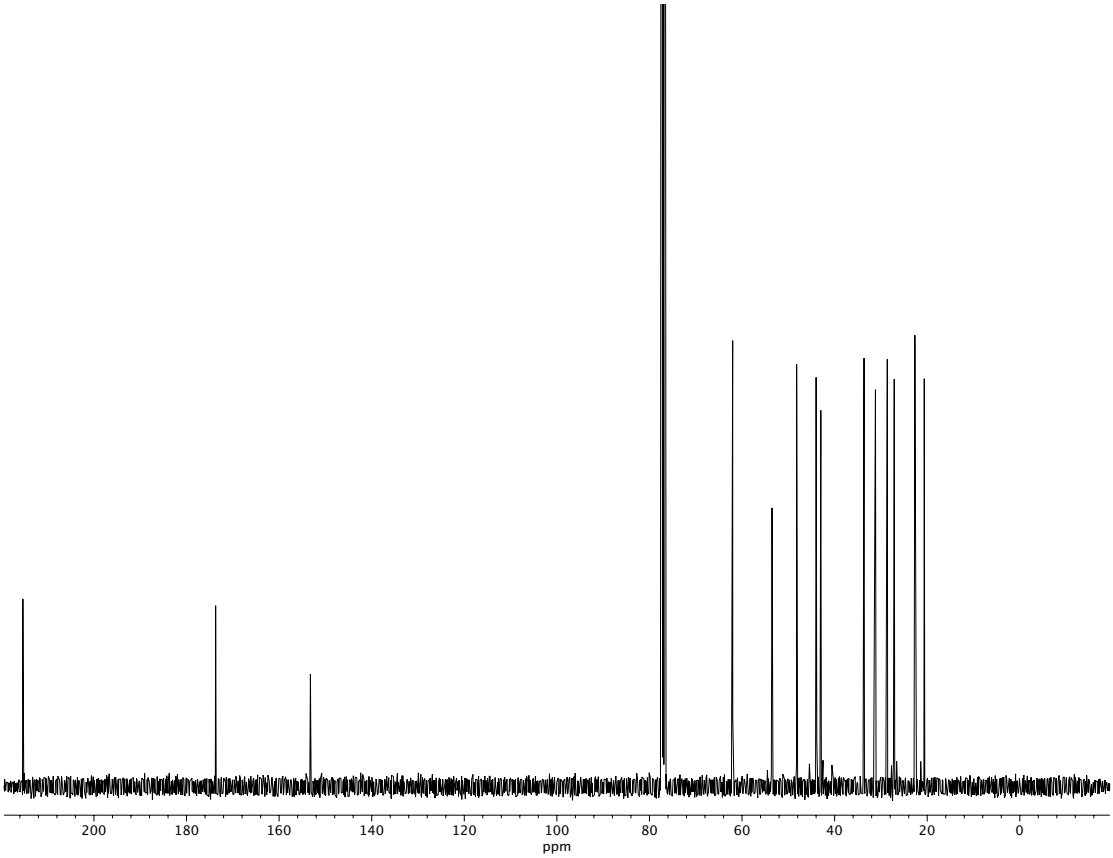


Figure A1.42. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11o****.*

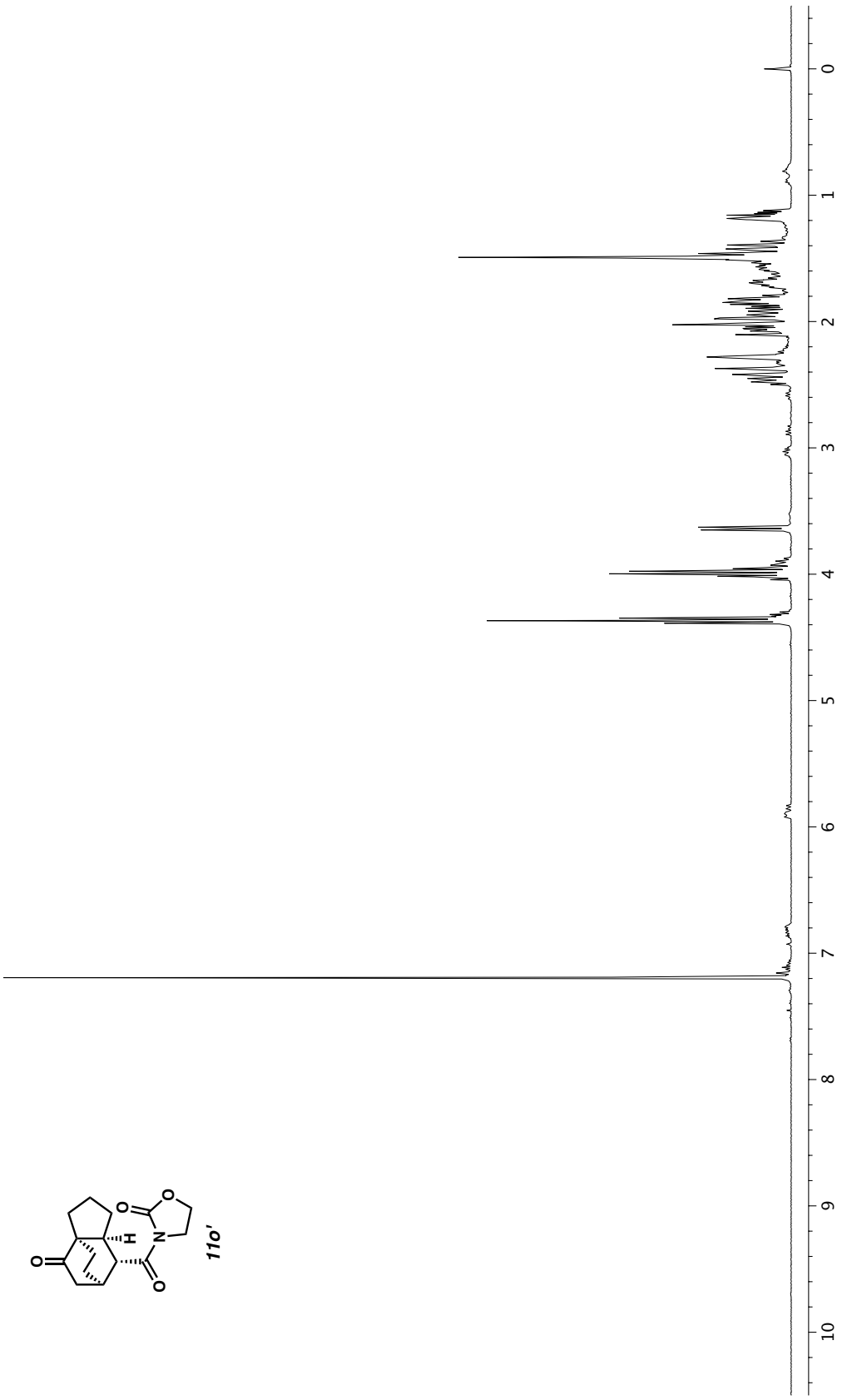


Figure A1.43. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***11o'*** .

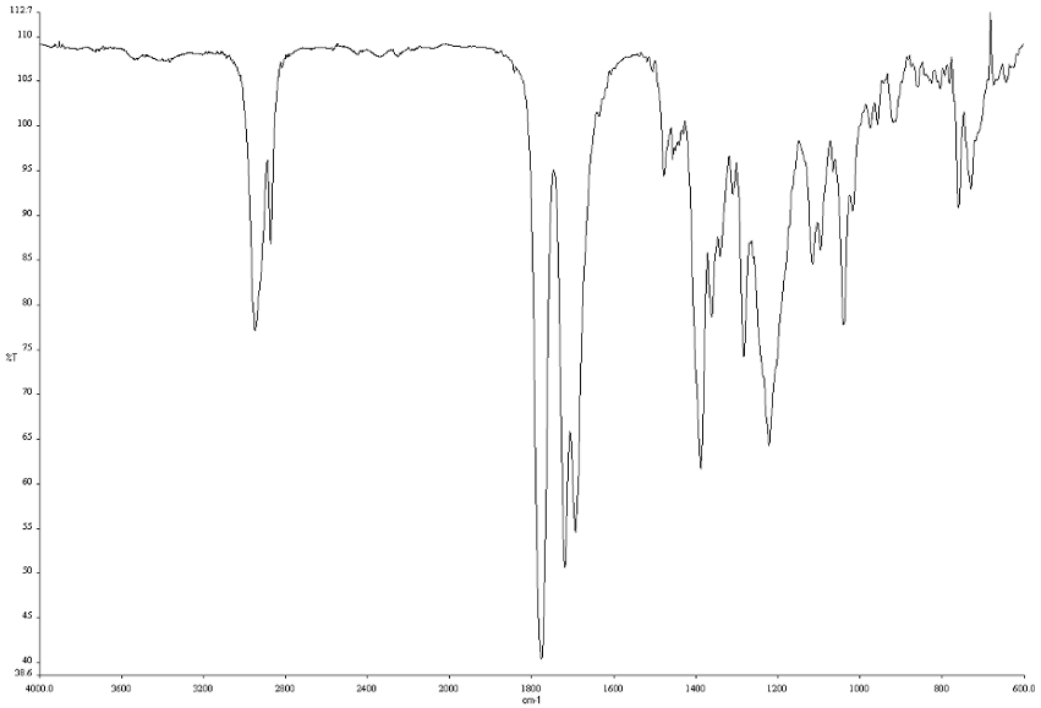


Figure A1.44. *Infrared spectrum (Thin Film, NaCl) of compound* ***11o′****.*

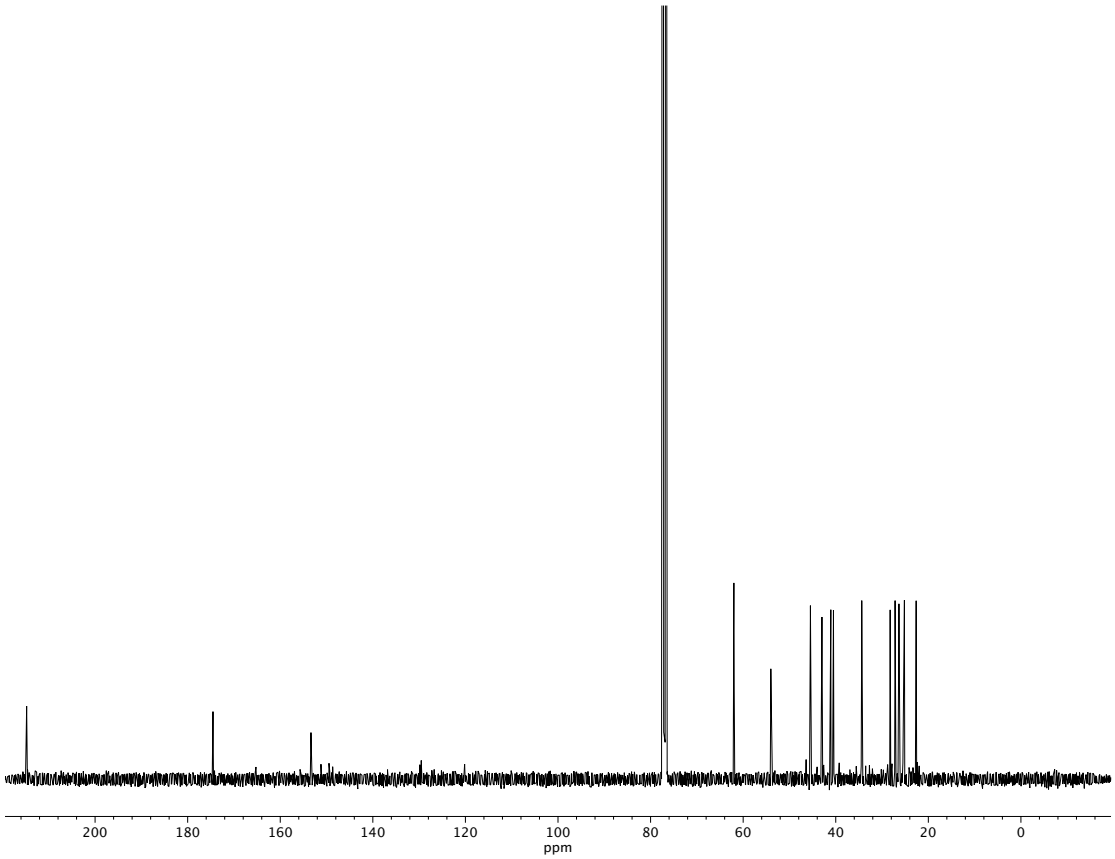


Figure A1.45. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11o′****.*

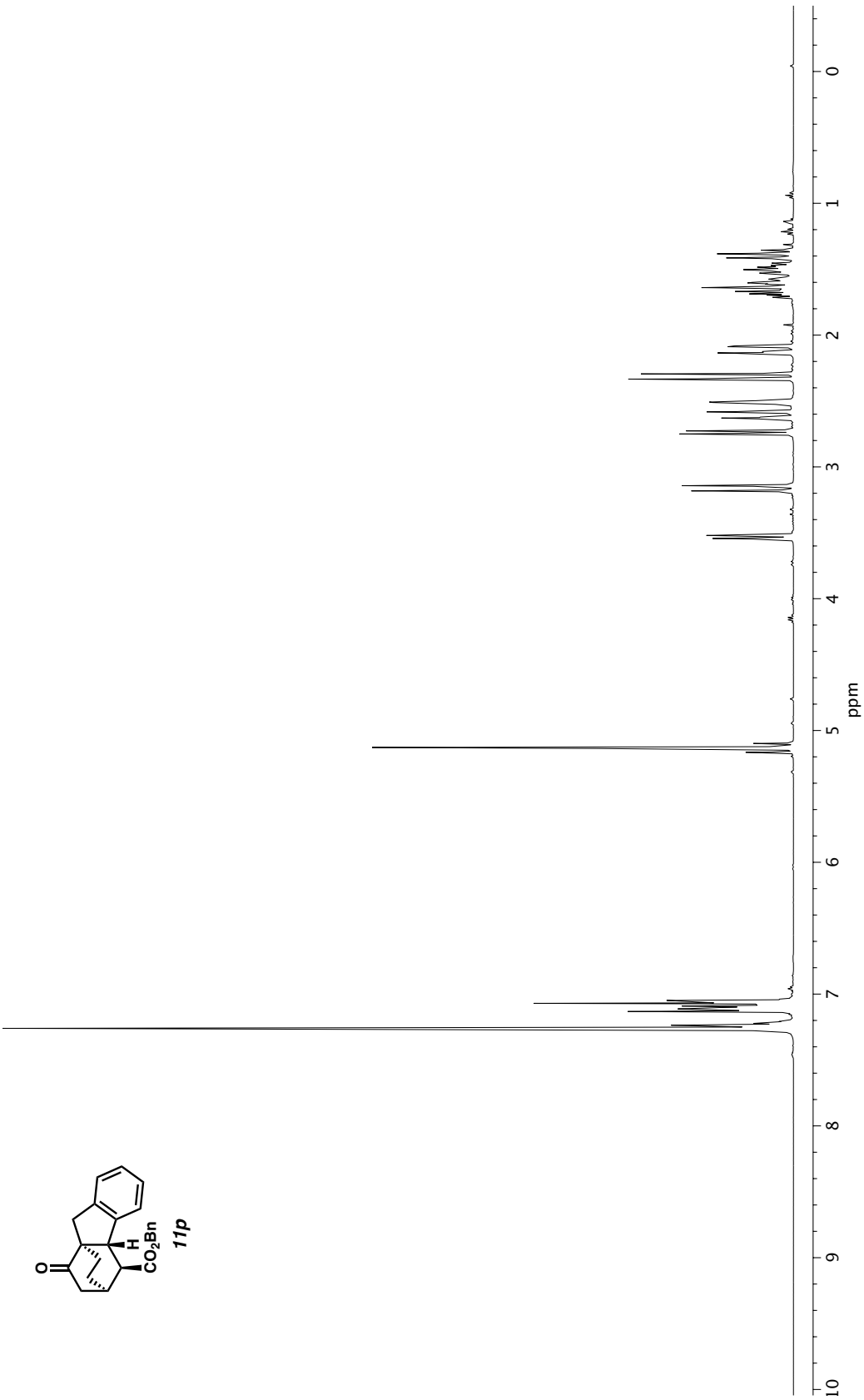


Figure A1.46. *^1H NMR (400 MHz, $CDCl_3$) of compound **11p**.*

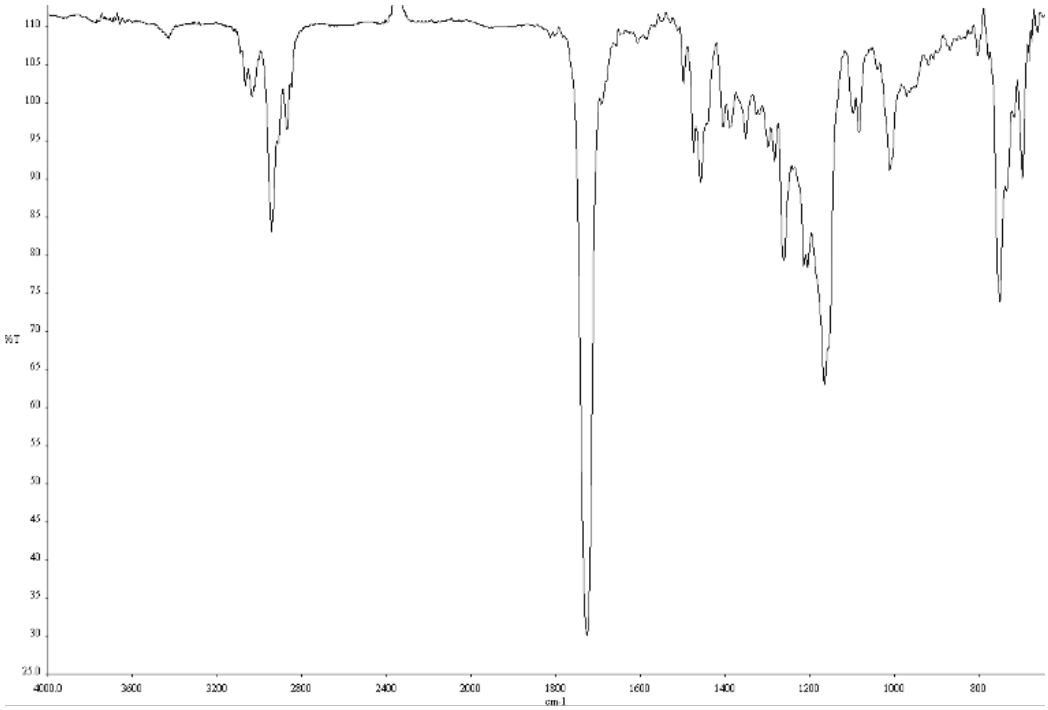


Figure A1.47. *Infrared spectrum (Thin Film, NaCl) of compound* ***11p****.*

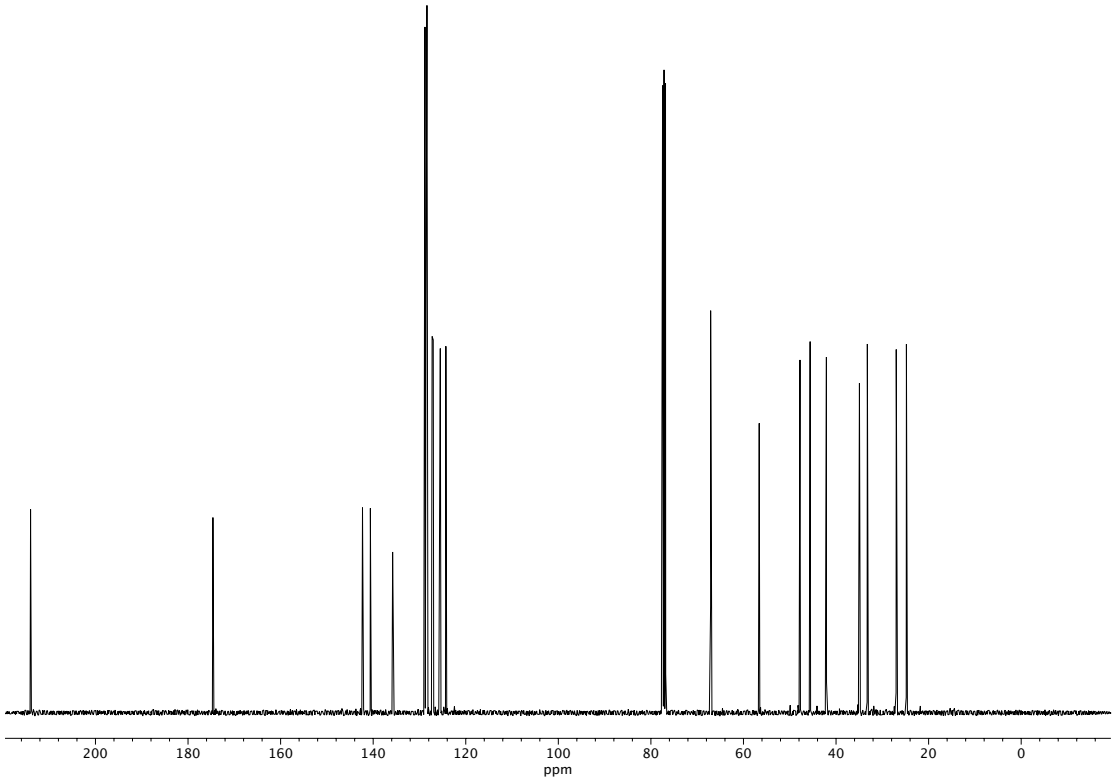


Figure A1.48. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11p****.*

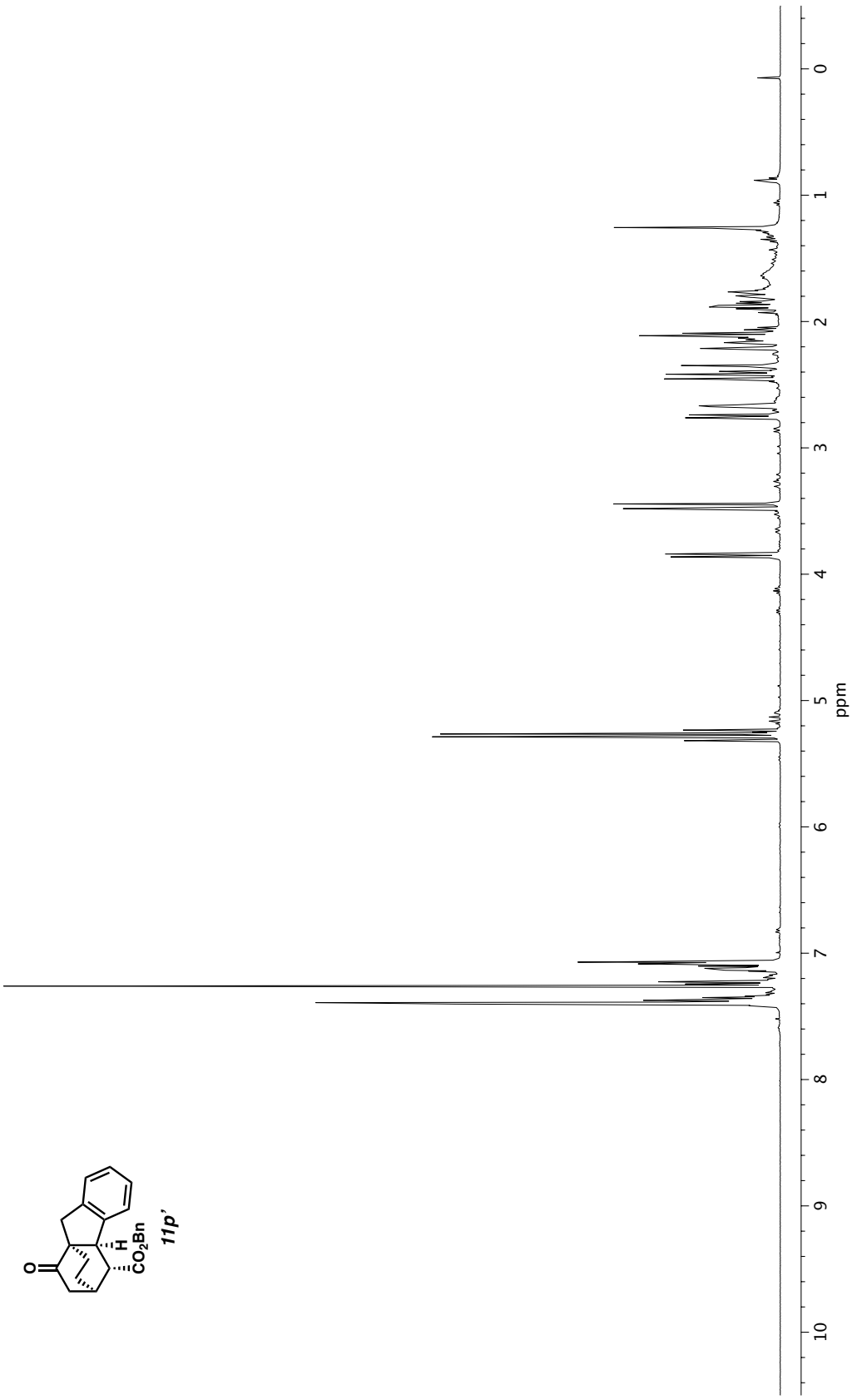


Figure A1.49. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***11p'*** .

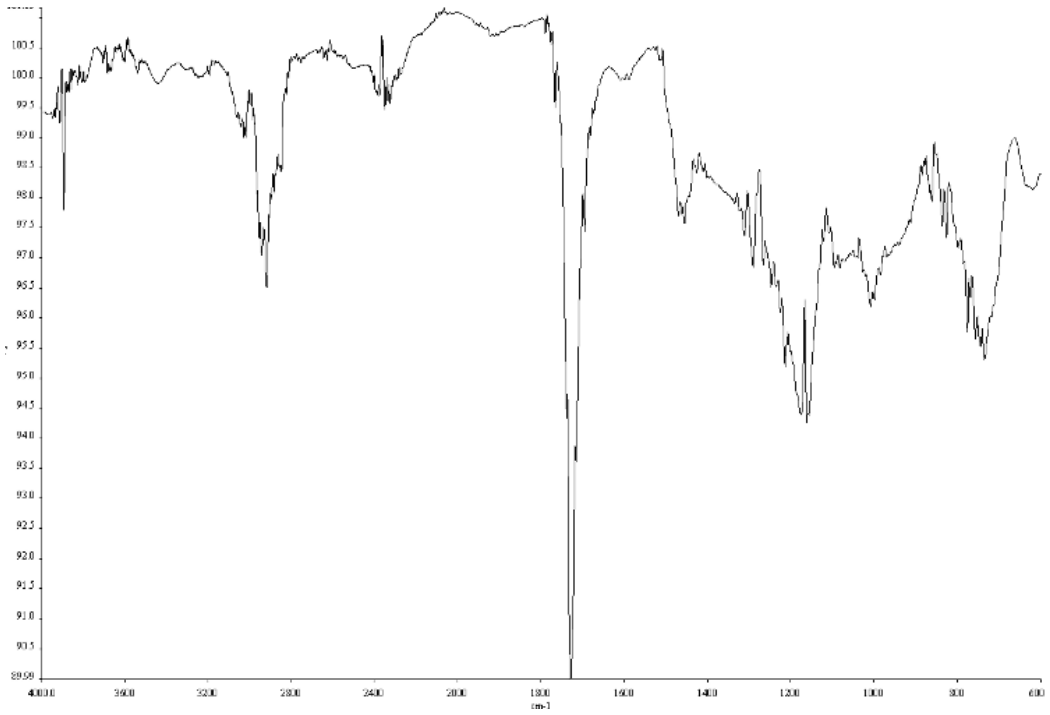


Figure A1.50. *Infrared spectrum (Thin Film, NaCl) of compound* ***11p′****.*

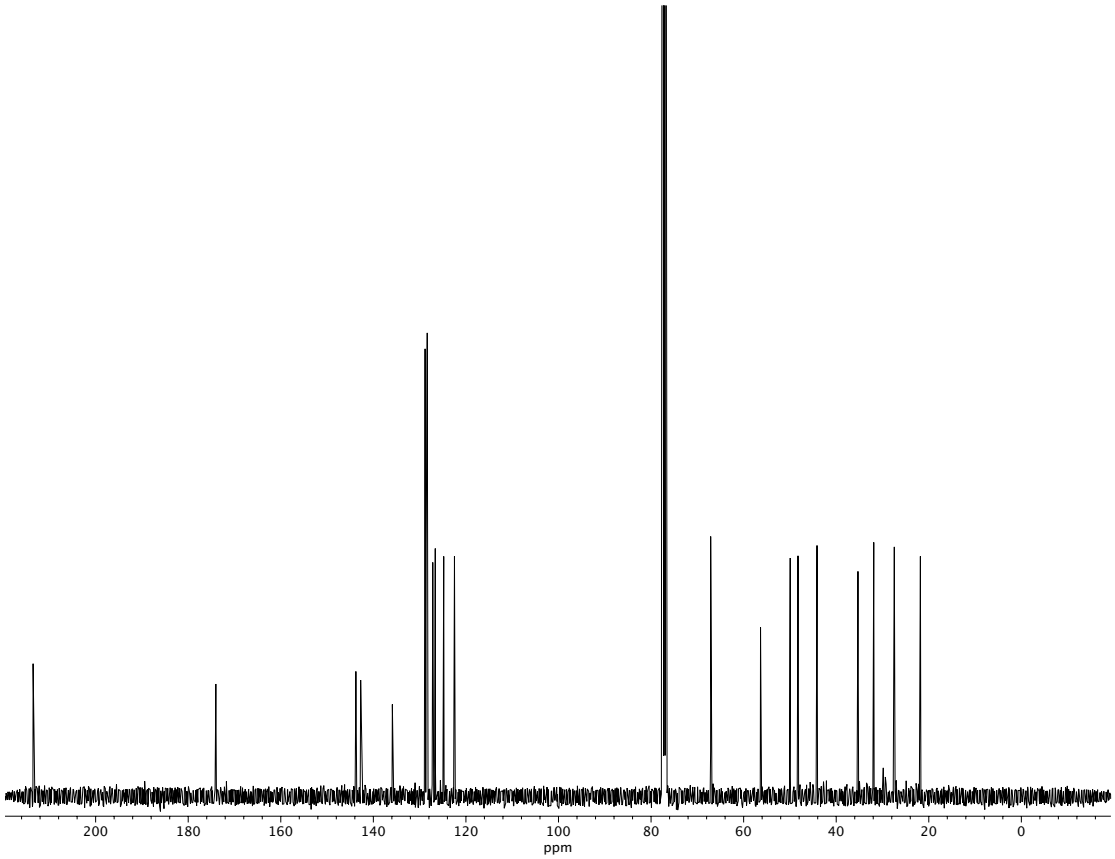


Figure A1.51. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11p′****.*

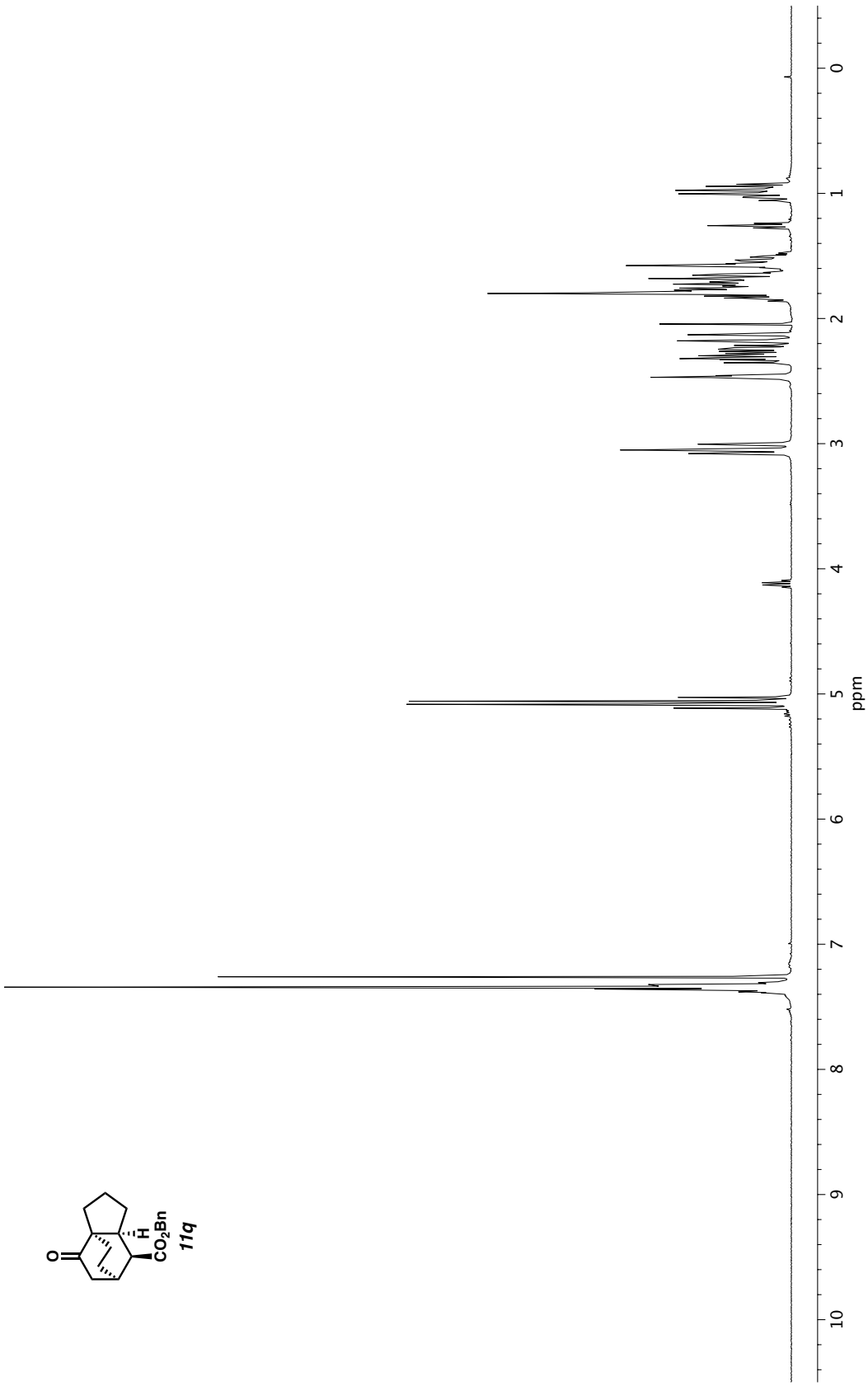


Figure A1.52. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***11q***.

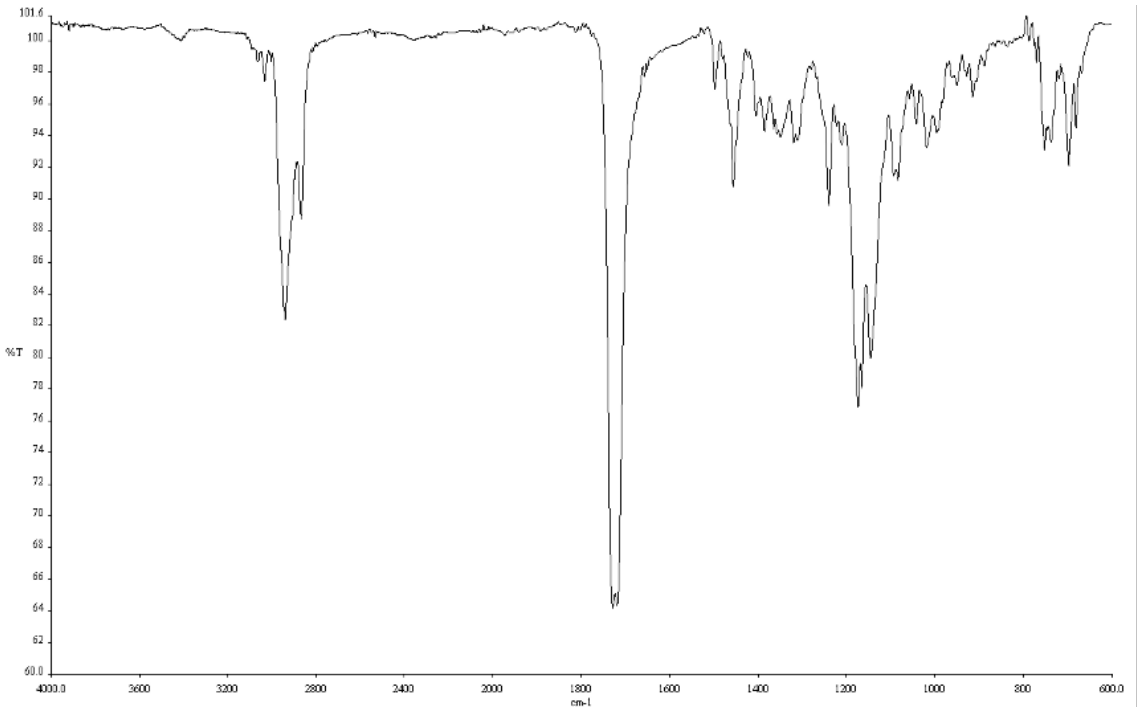


Figure A1.53. *Infrared spectrum (Thin Film, NaCl) of compound* ***11q****.*

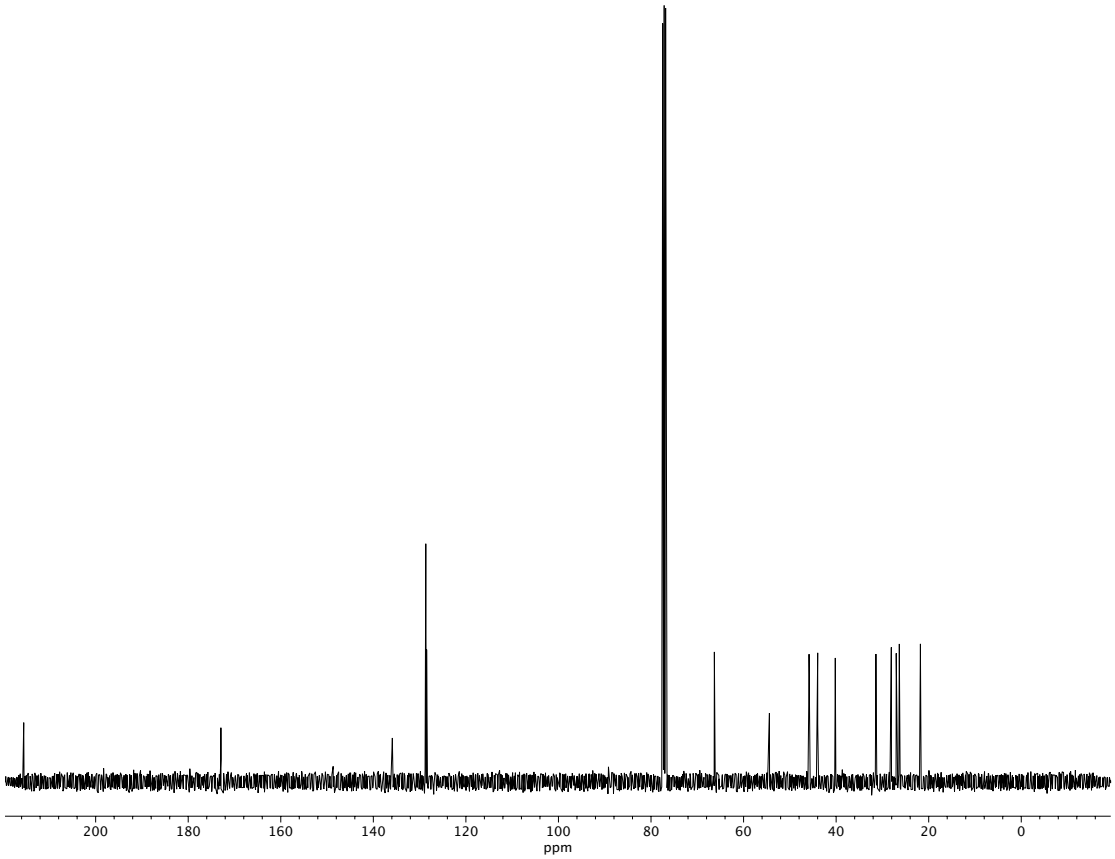


Figure A1.54. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11q****.*

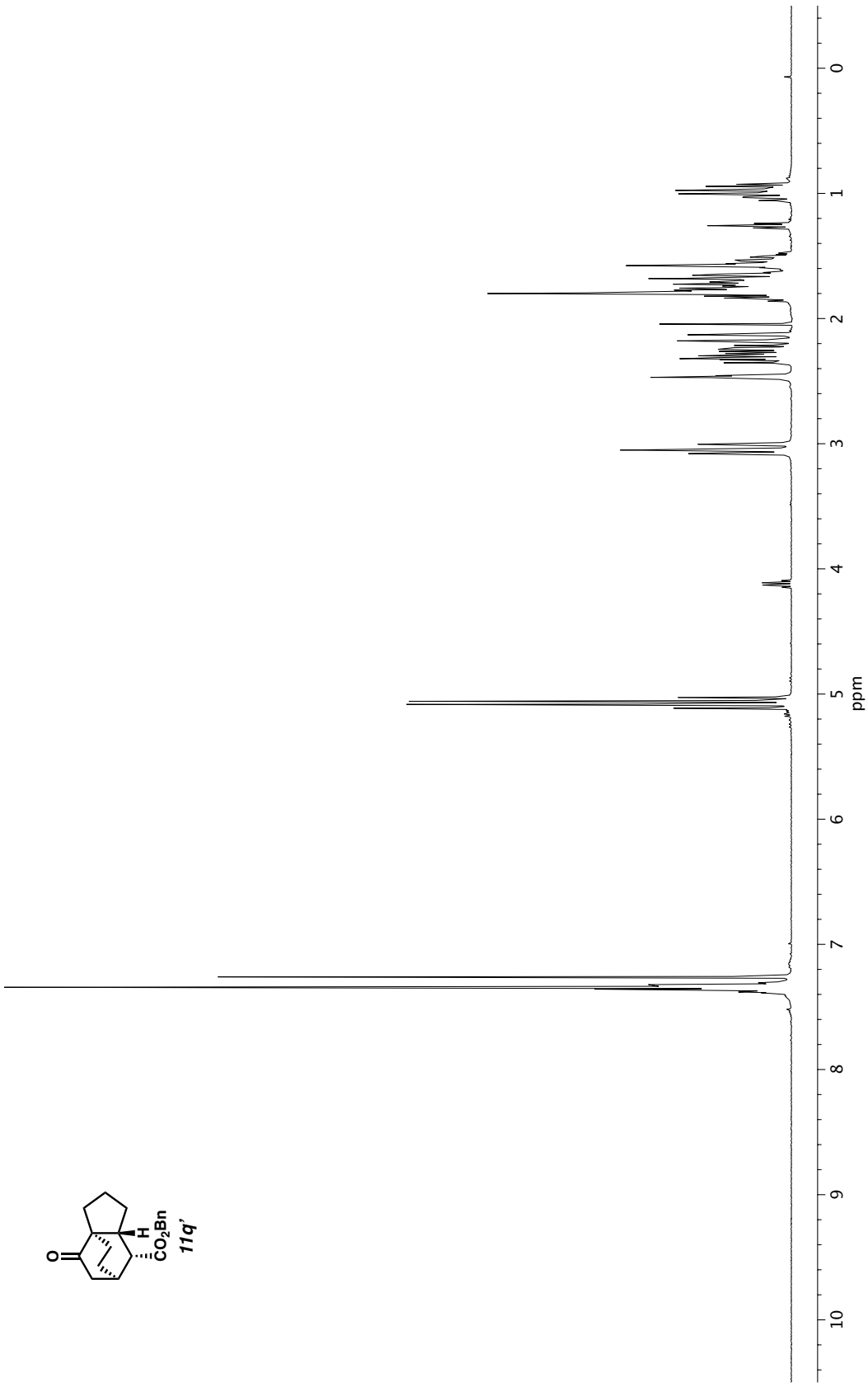


Figure A1.55. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***11q'*** *.*

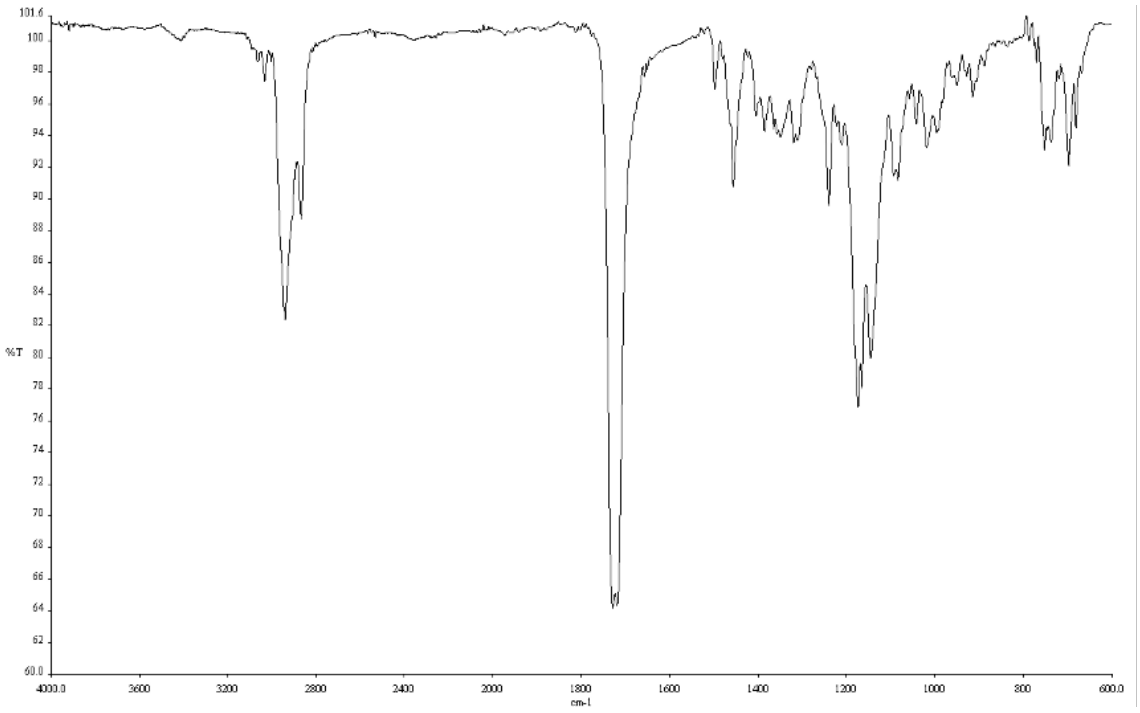


Figure A1.56. *Infrared spectrum (Thin Film, NaCl) of compound* ***11q'****.*

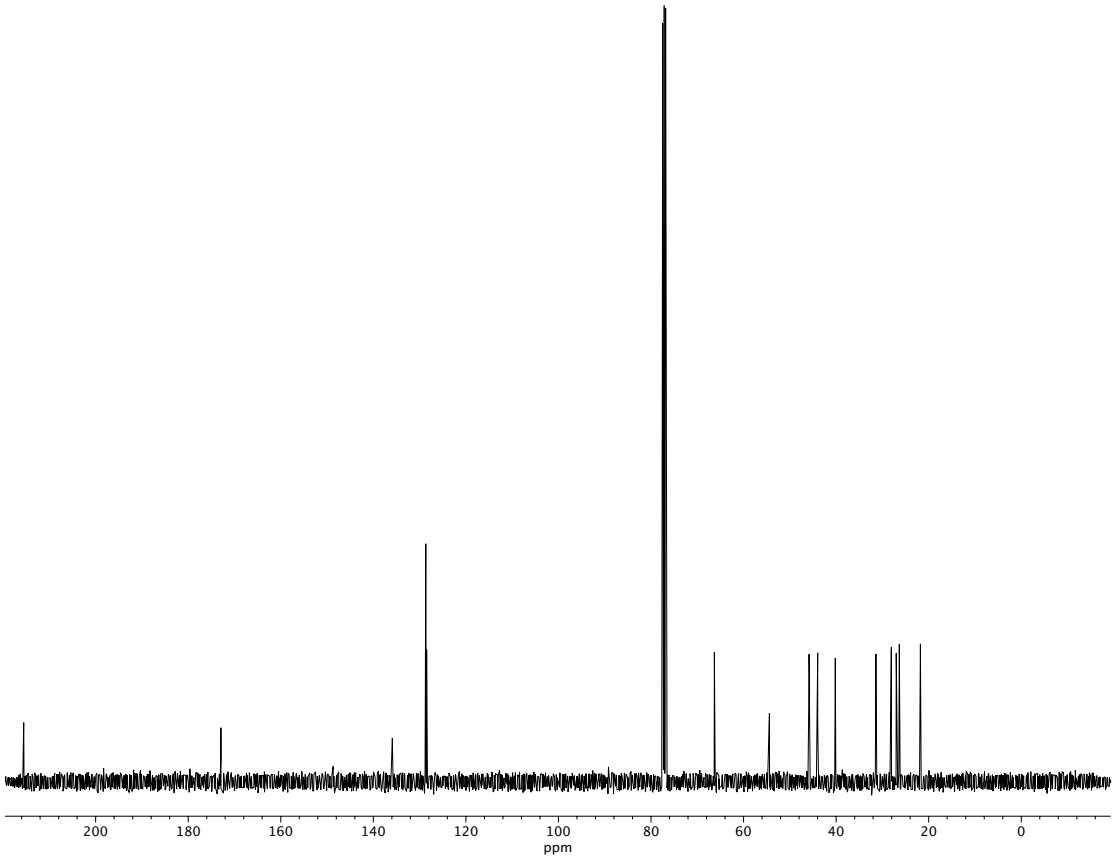


Figure A1.57. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11q'****.*

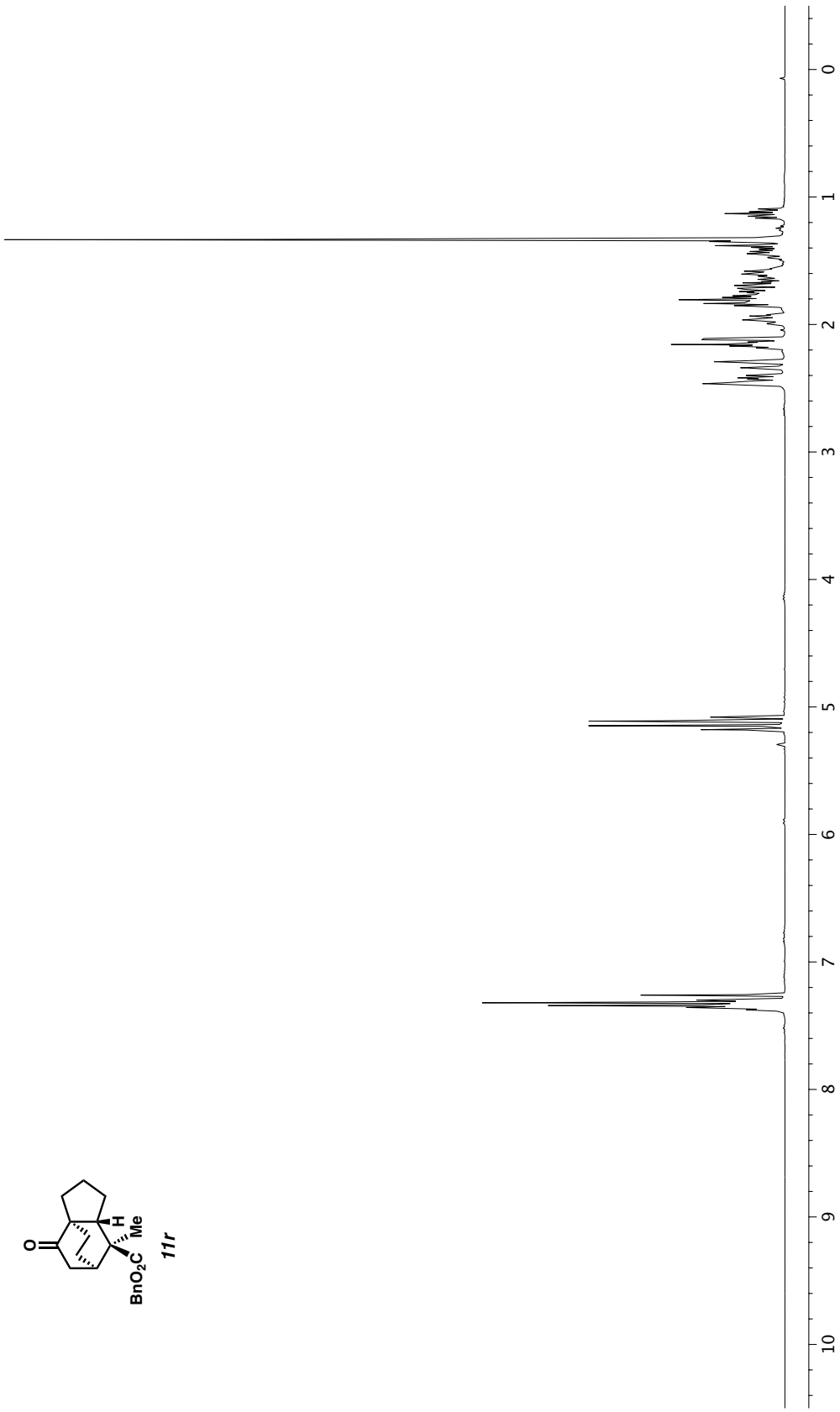


Figure A1.58. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***11r****.*

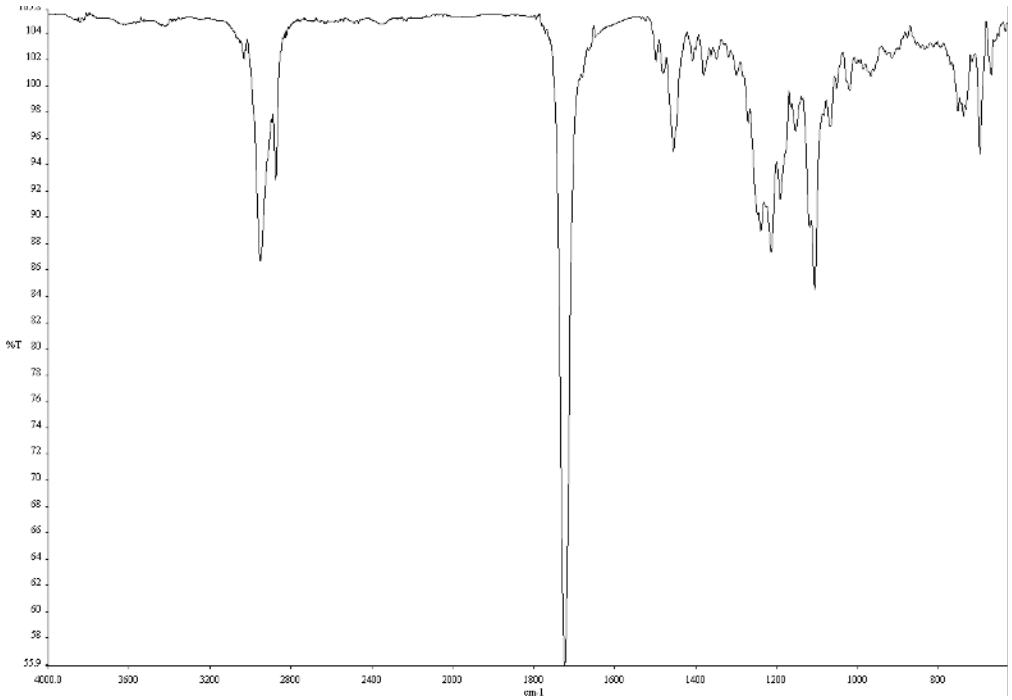


Figure A1.59. *Infrared spectrum (Thin Film, NaCl) of compound* ***11r****.*

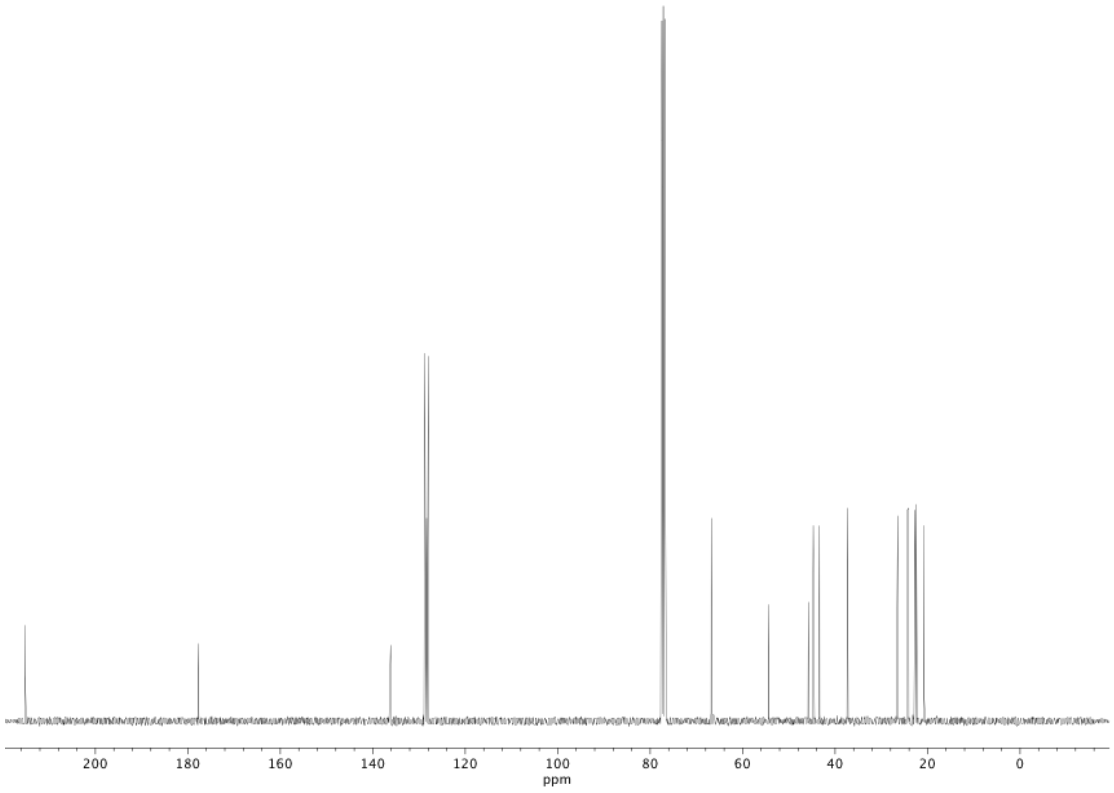


Figure A1.60. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11r****.*

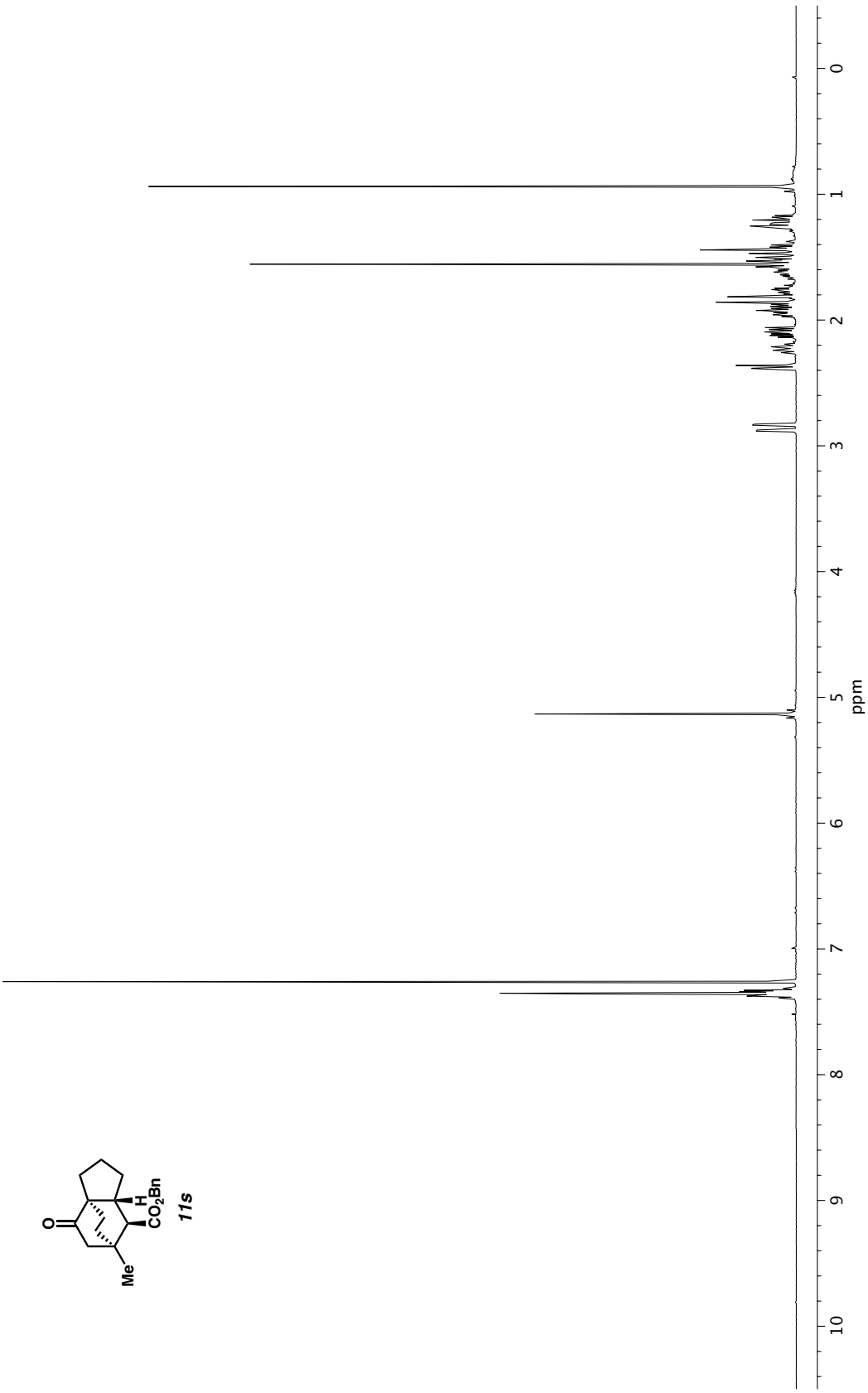


Figure A1.61. *^{1}H NMR (400 MHz, $CDCl_3$) of compound **11s**.*

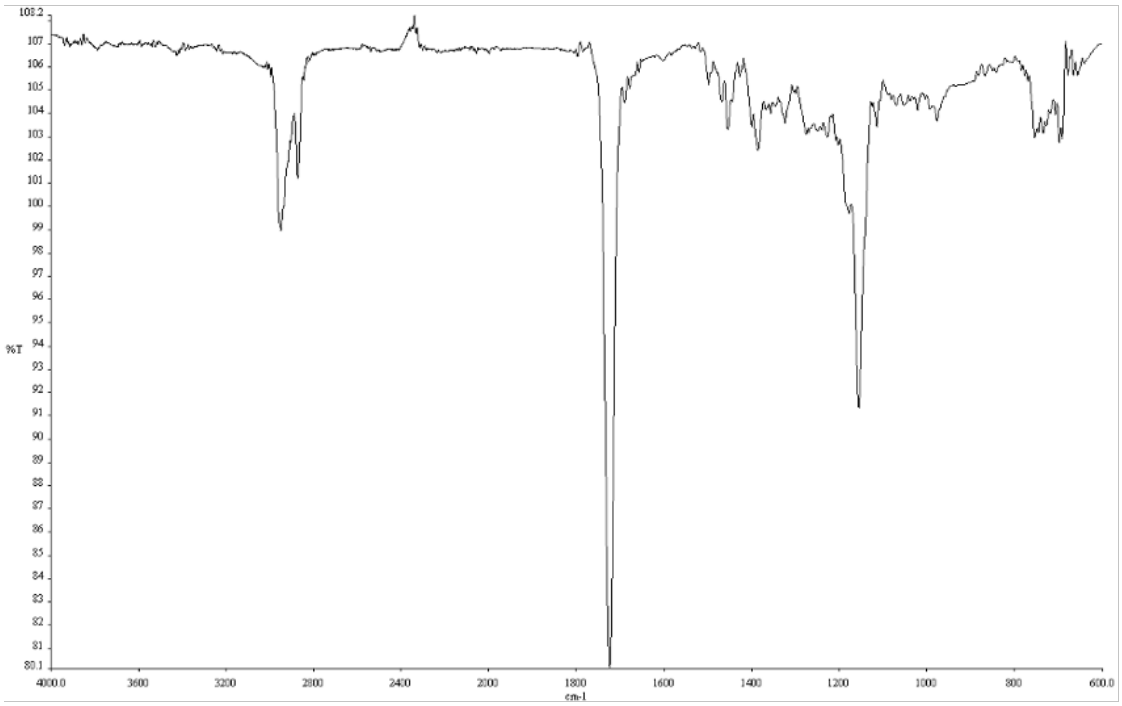


Figure A1.62. *Infrared spectrum (Thin Film, NaCl) of compound* ***11s****.*

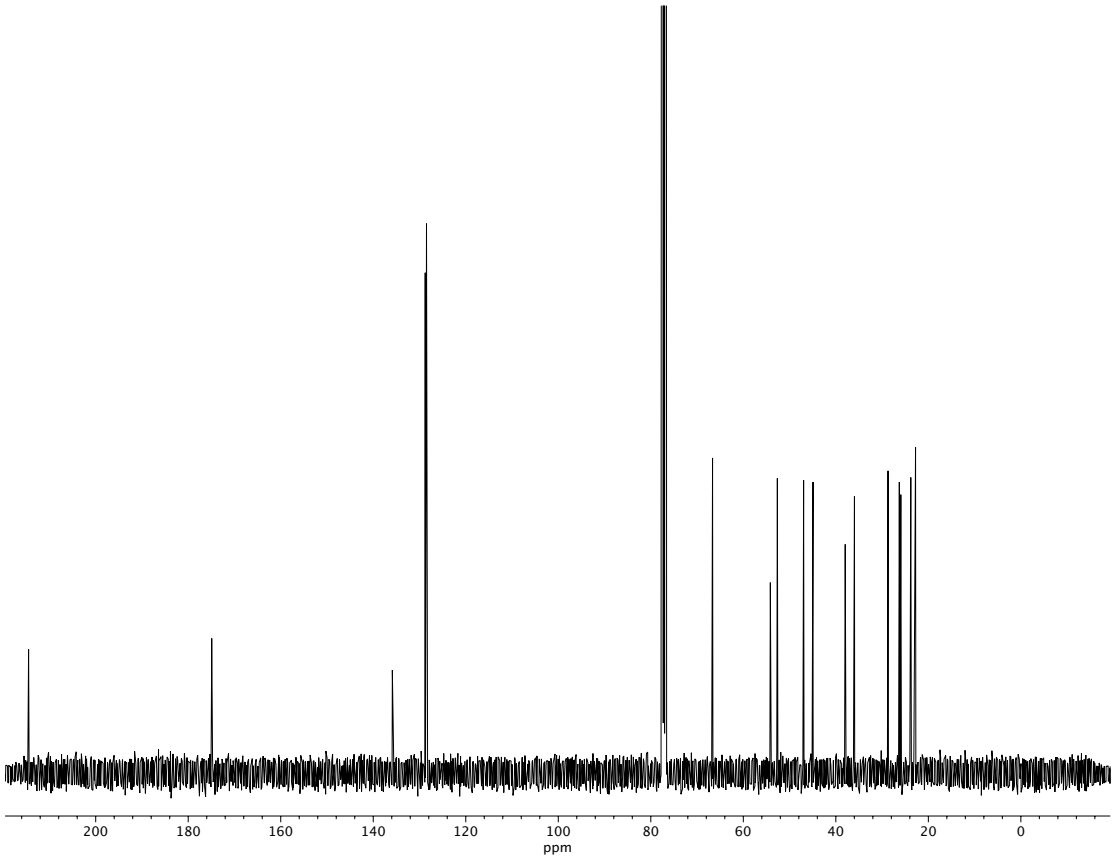


Figure A1.63. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11s****.*

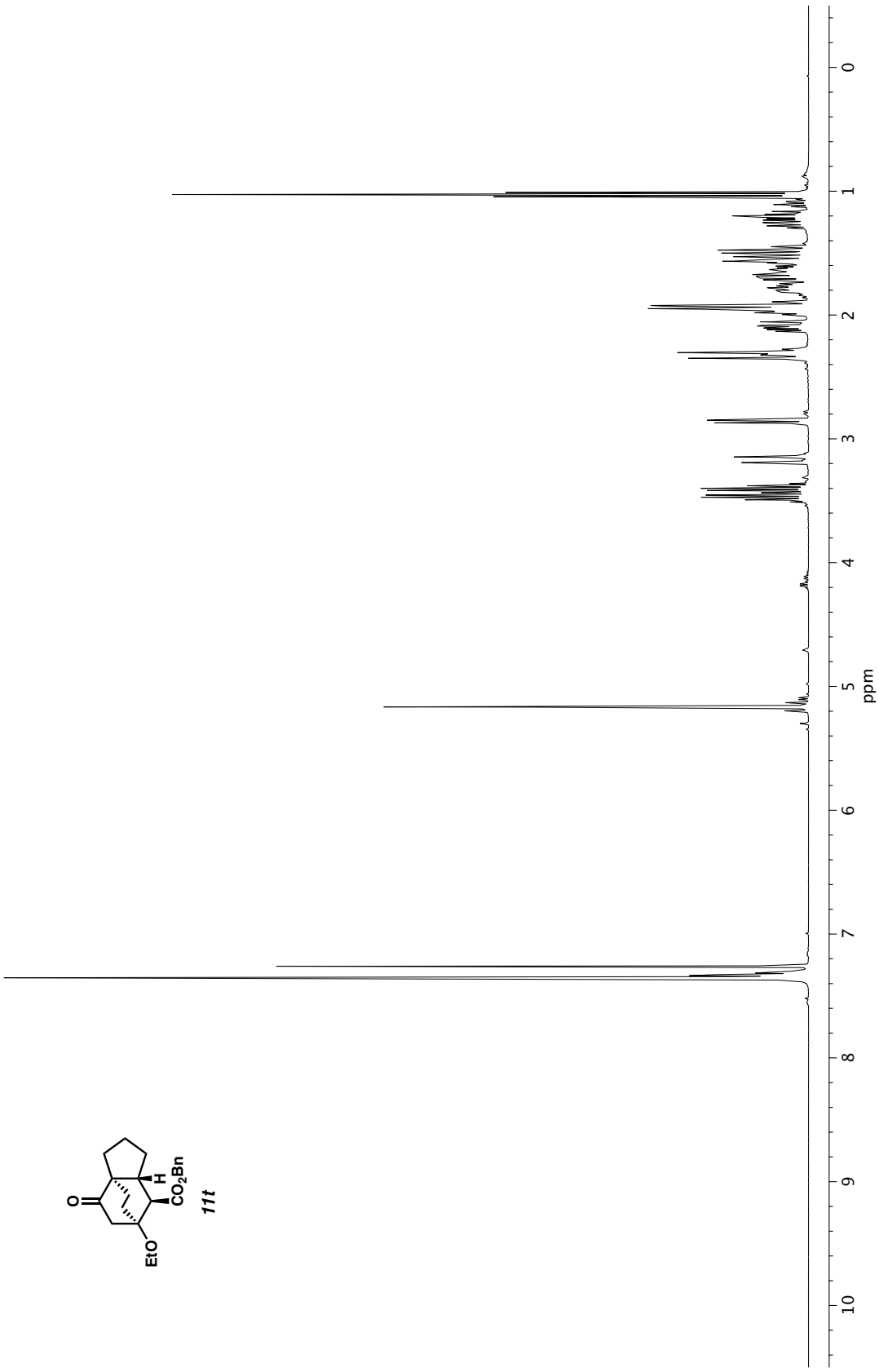


Figure A1.64. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***11t****.*

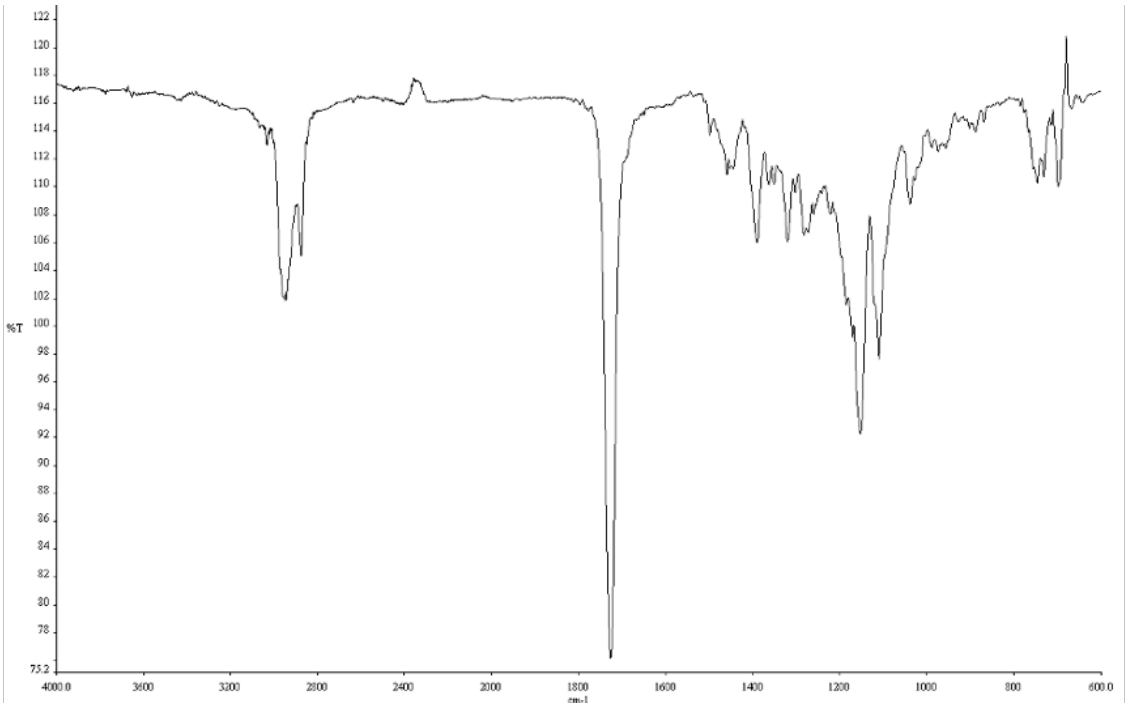


Figure A1.65. *Infrared spectrum (Thin Film, NaCl) of compound* ***11t****.*

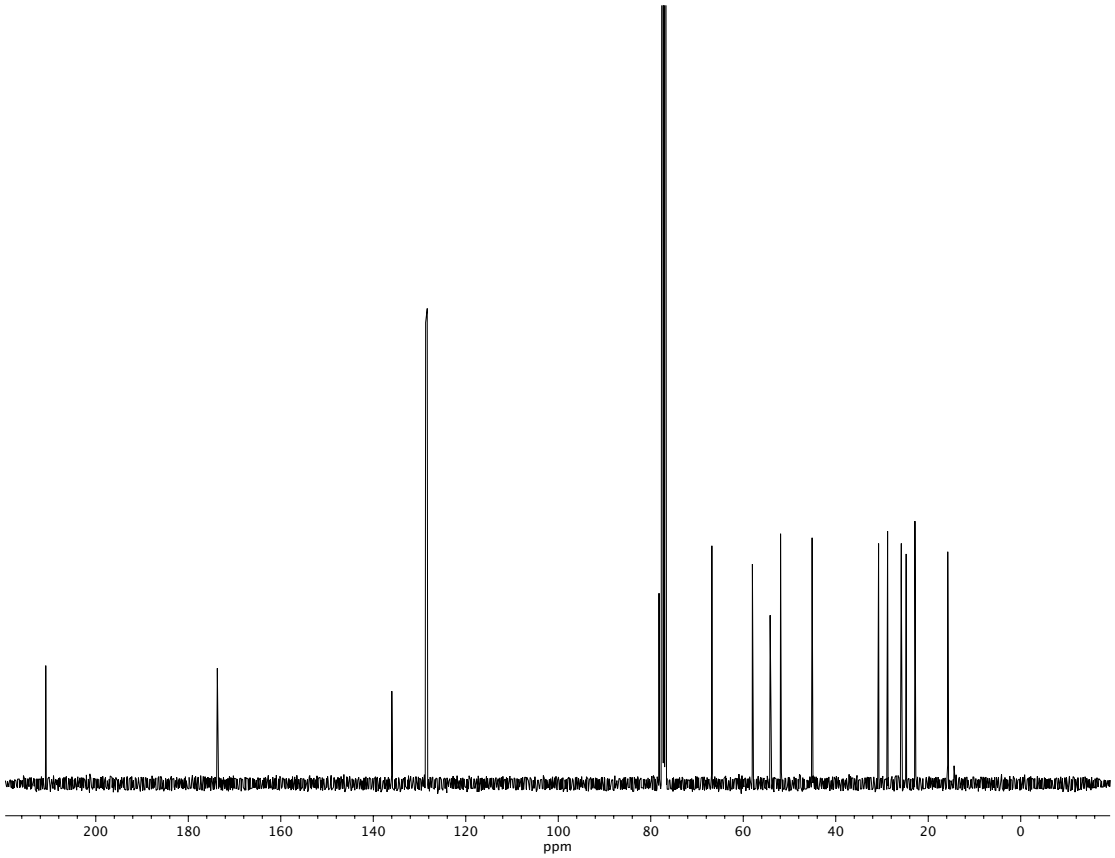


Figure A1.66. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11t****.*

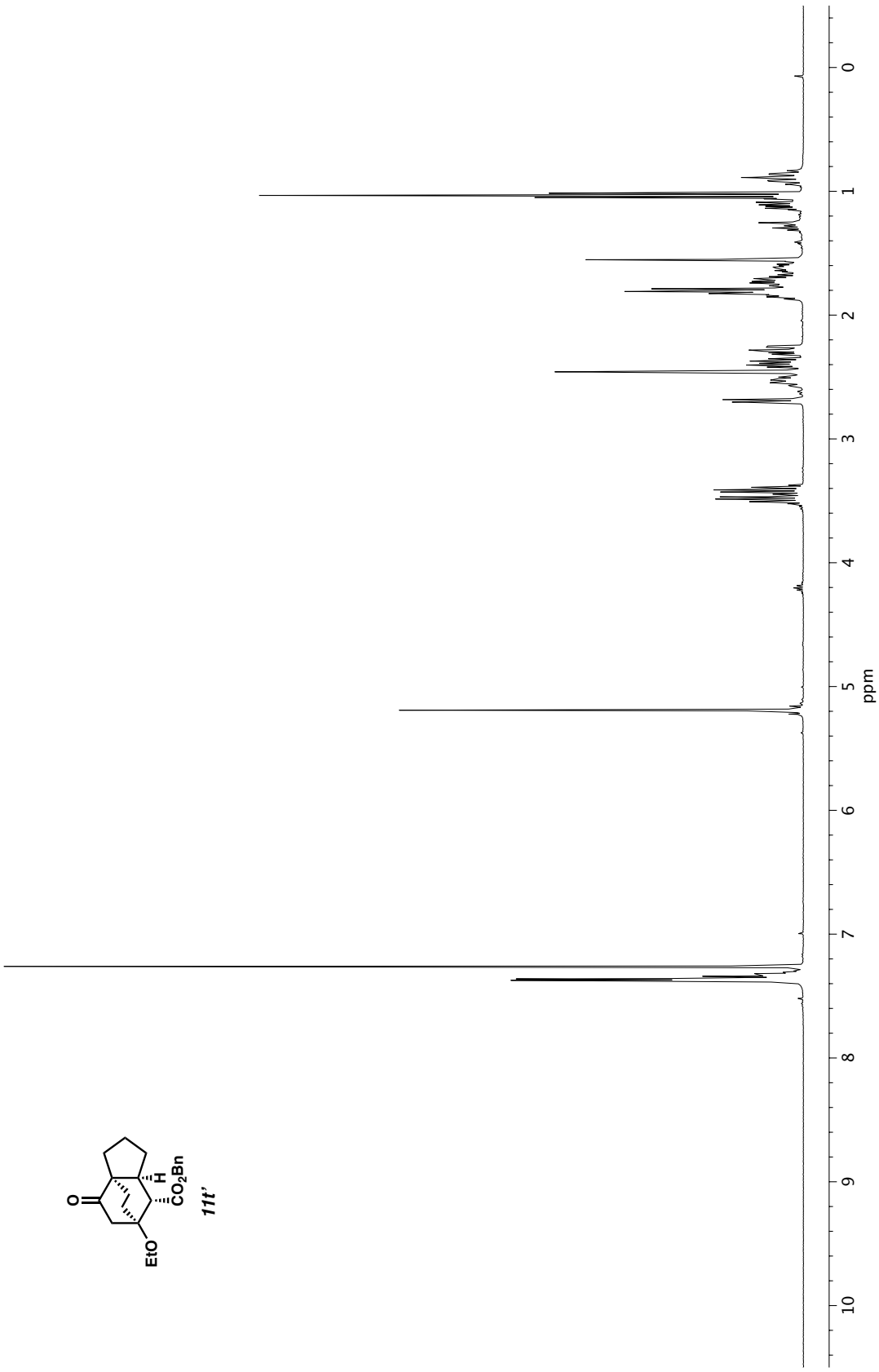


Figure A1.67. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***11t'*** *.*

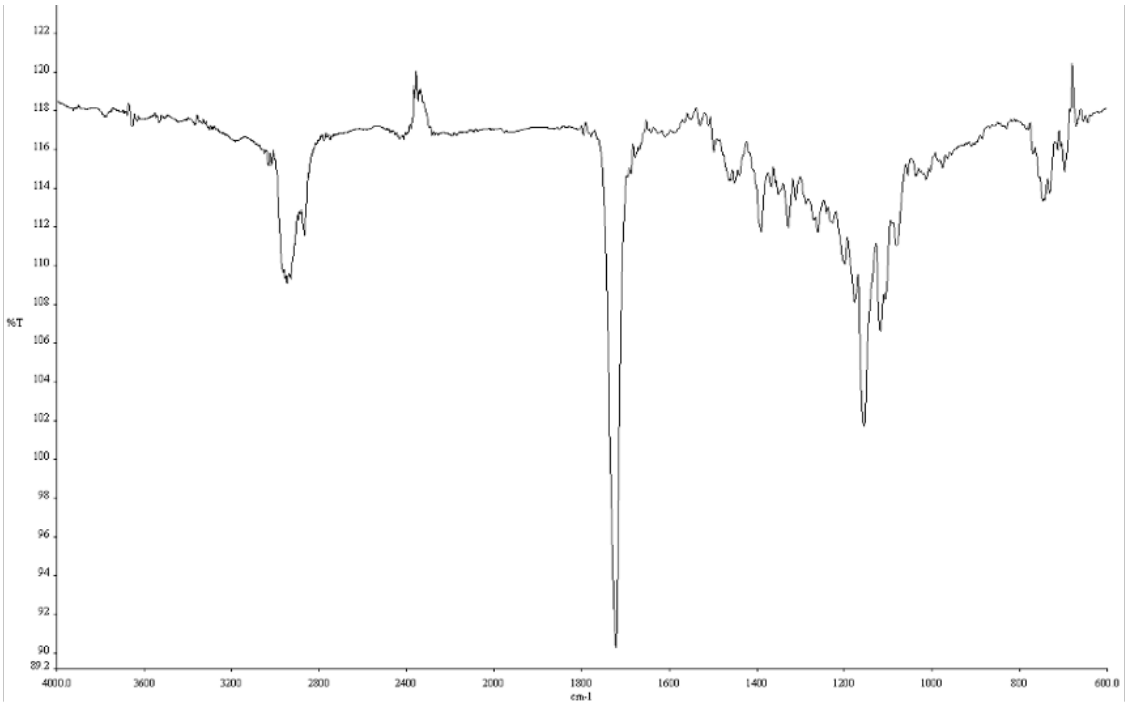


Figure A1.68. *Infrared spectrum (Thin Film, NaCl) of compound* ***11t'****.*

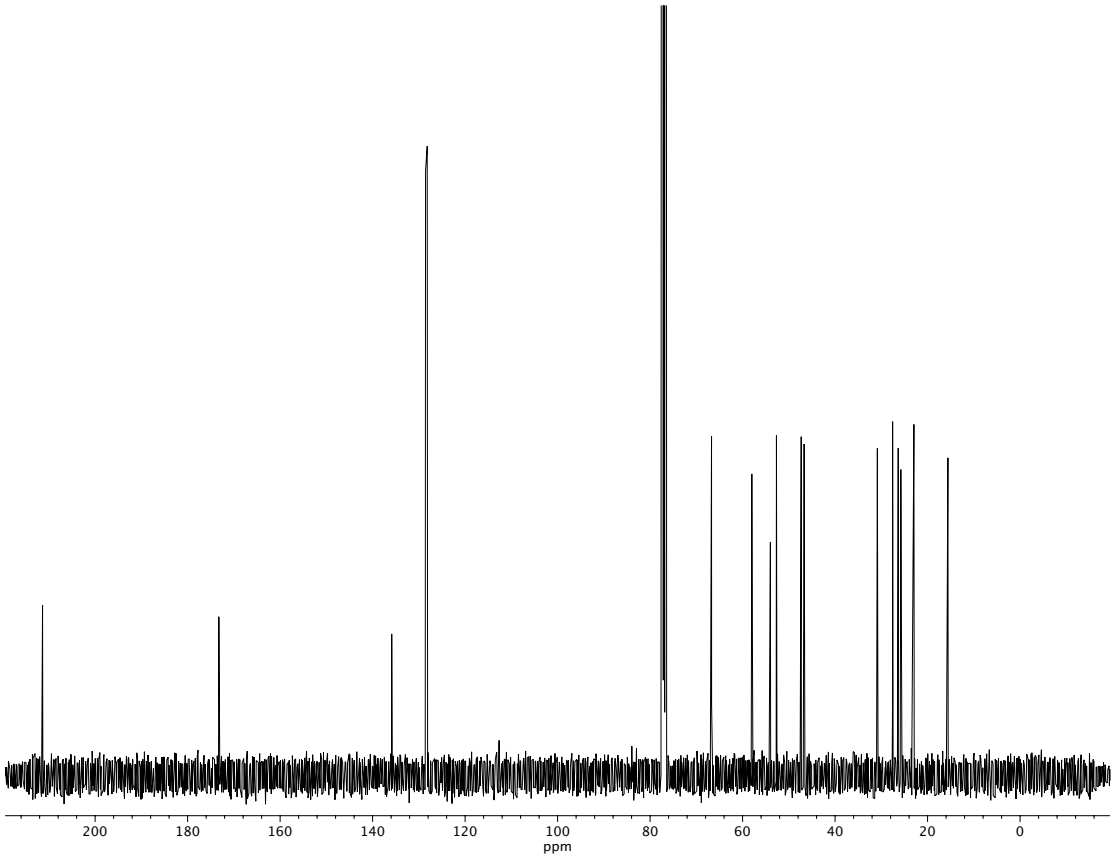


Figure A1.69. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11t'****.*

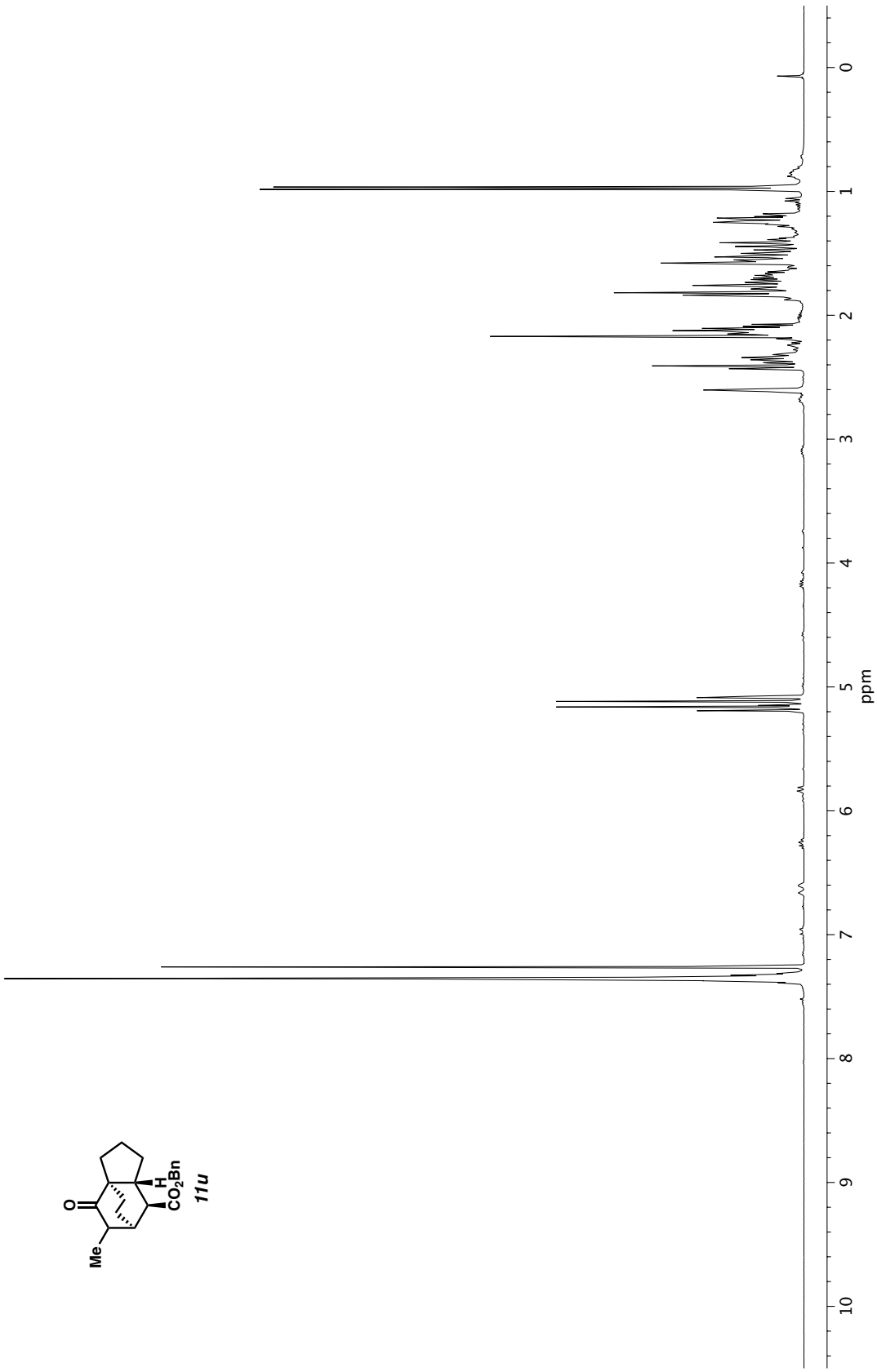


Figure A1.70. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***11u****.*

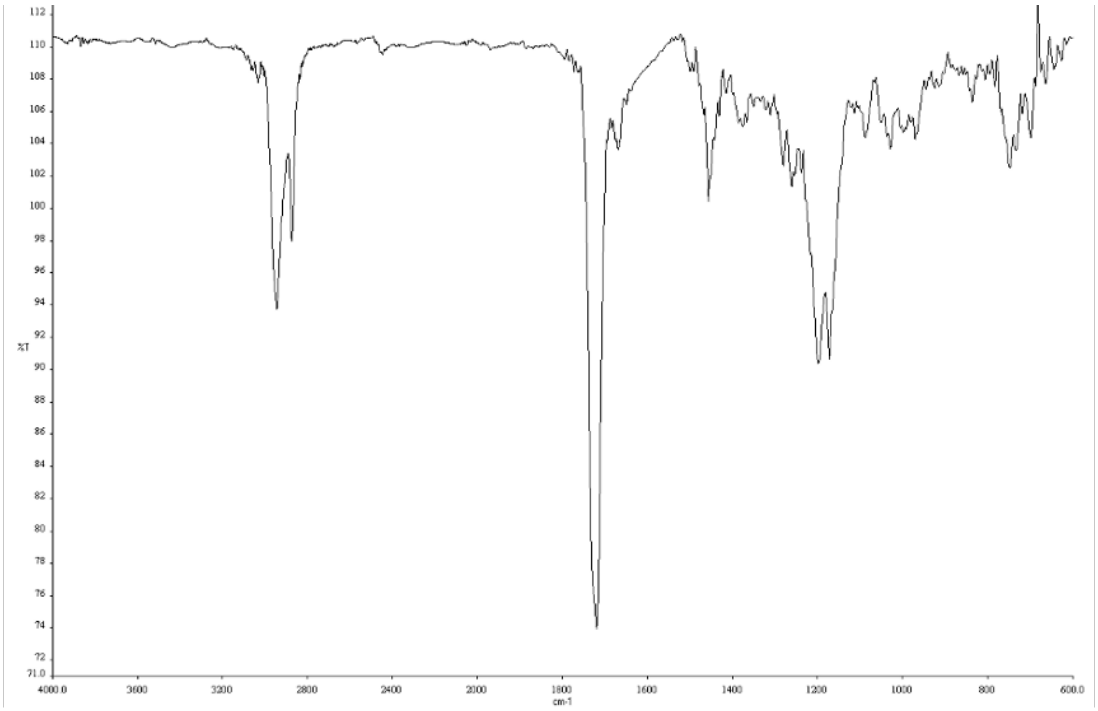


Figure A1.71. *Infrared spectrum (Thin Film, NaCl) of compound* ***11u****.*

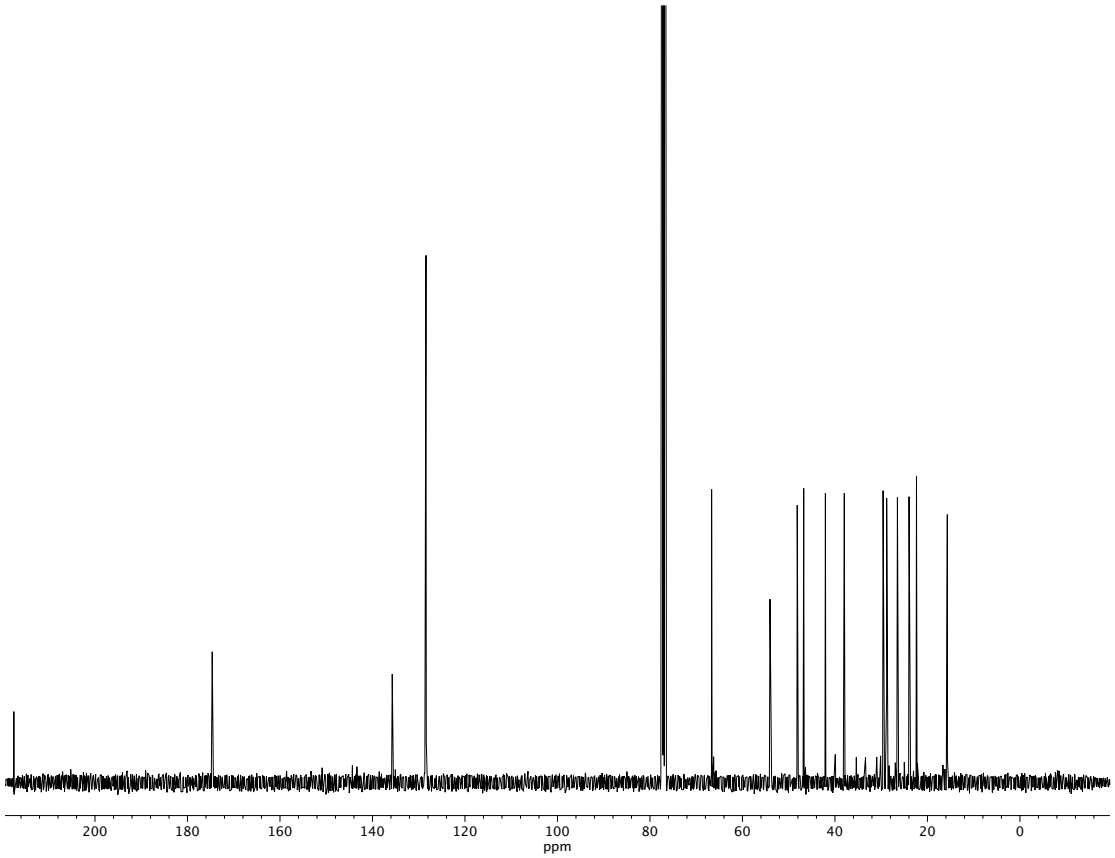


Figure A1.72. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11u****.*

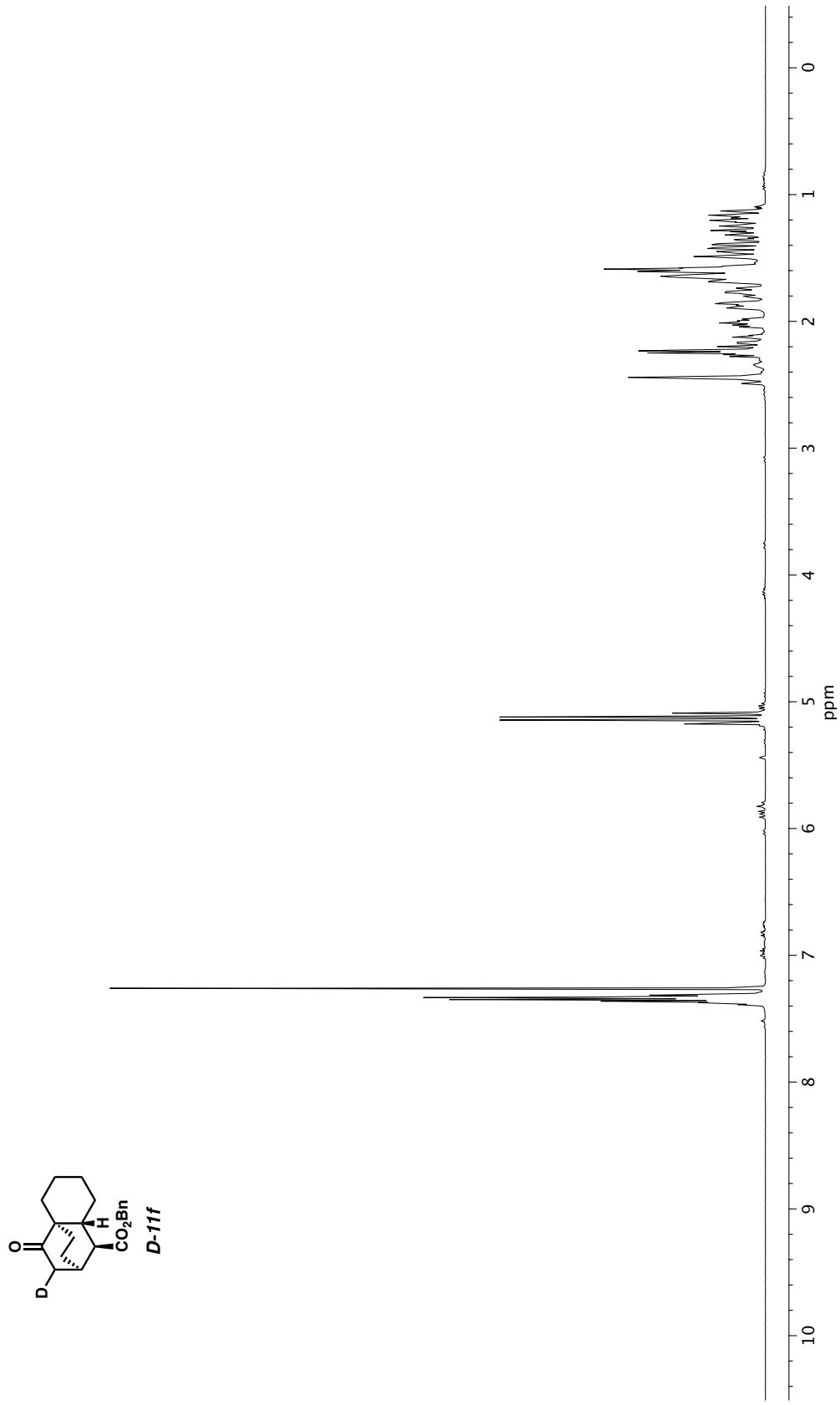


Figure A1.73. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***D-11f****.*

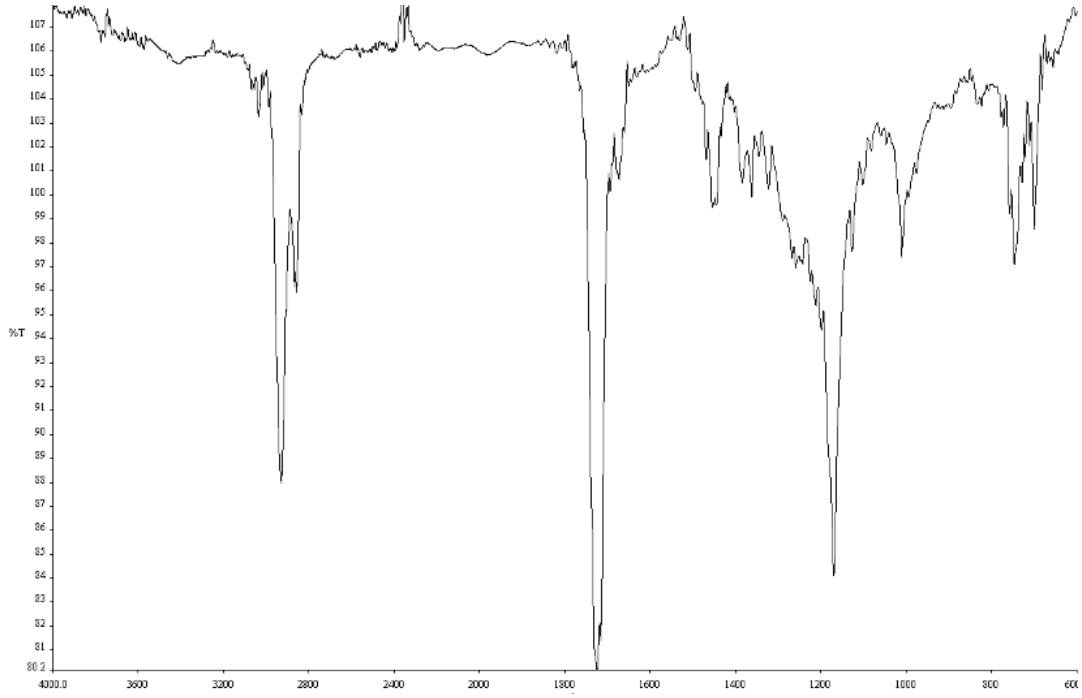


Figure A1.74. *Infrared spectrum (Thin Film, NaCl) of compound* ***D-11f****.*

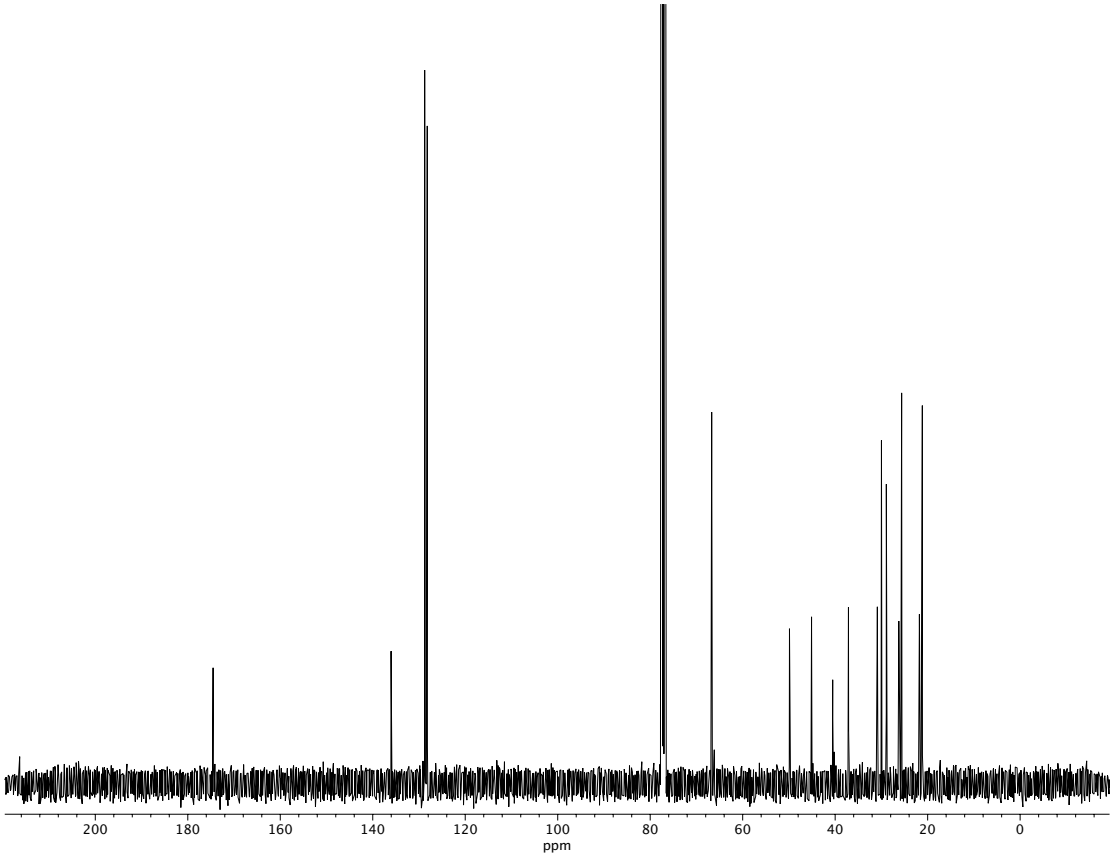


Figure A1.75. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***D-11f****.*

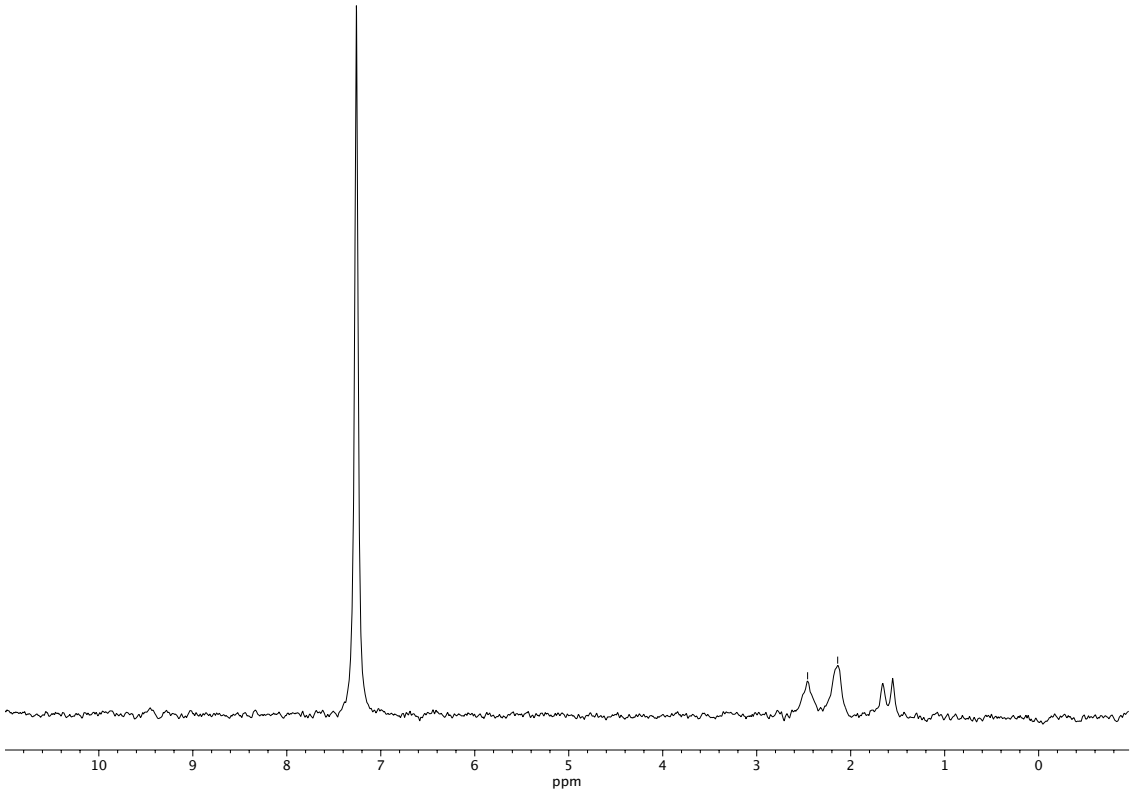


Figure A1.76. *^{2}H NMR (61 MHz, $CDCl_3$) of compound* ***D-11f****.*

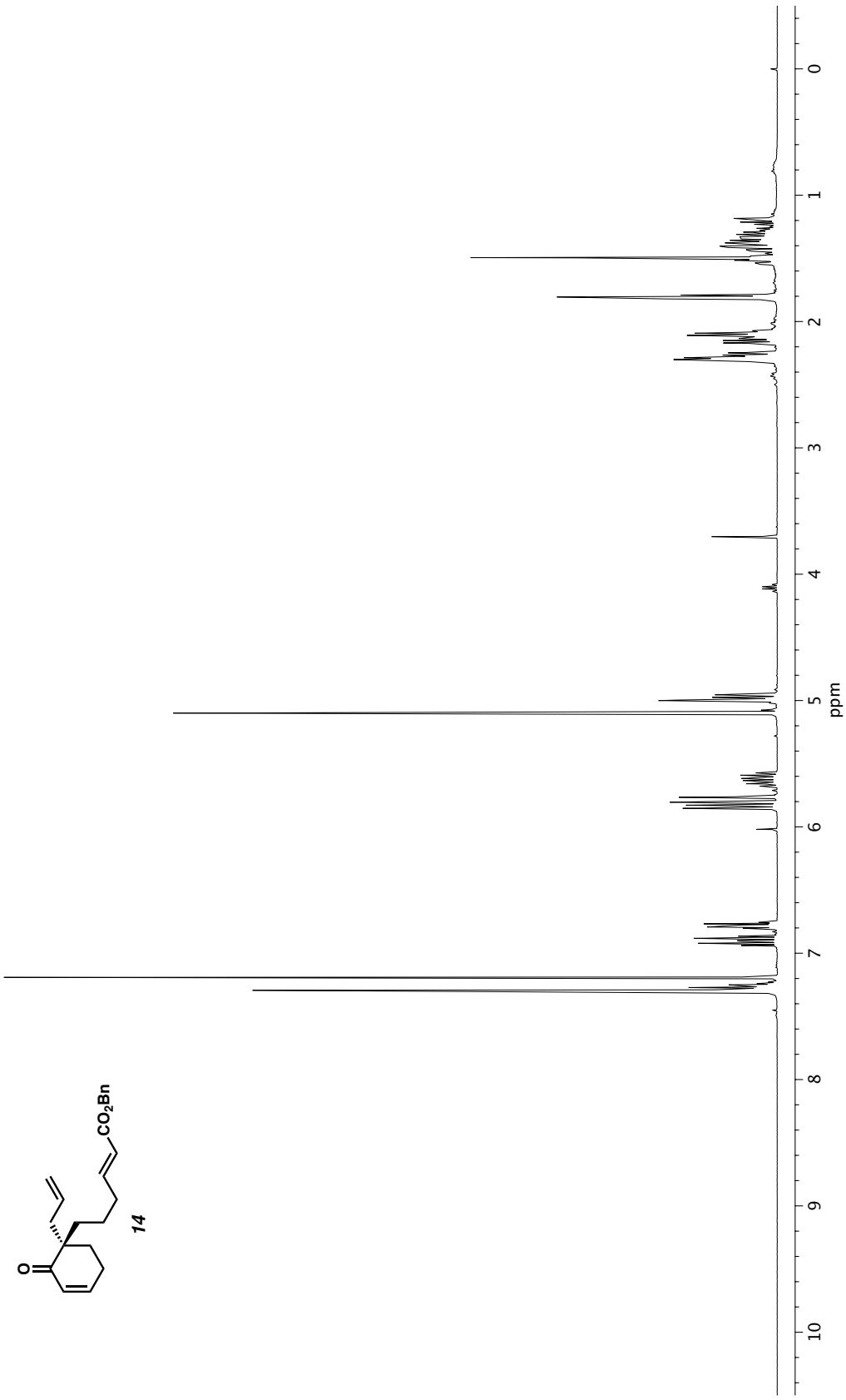


Figure A1.77. *^{1}H NMR (400 MHz, $CDCl_3$) of compound **14**.*

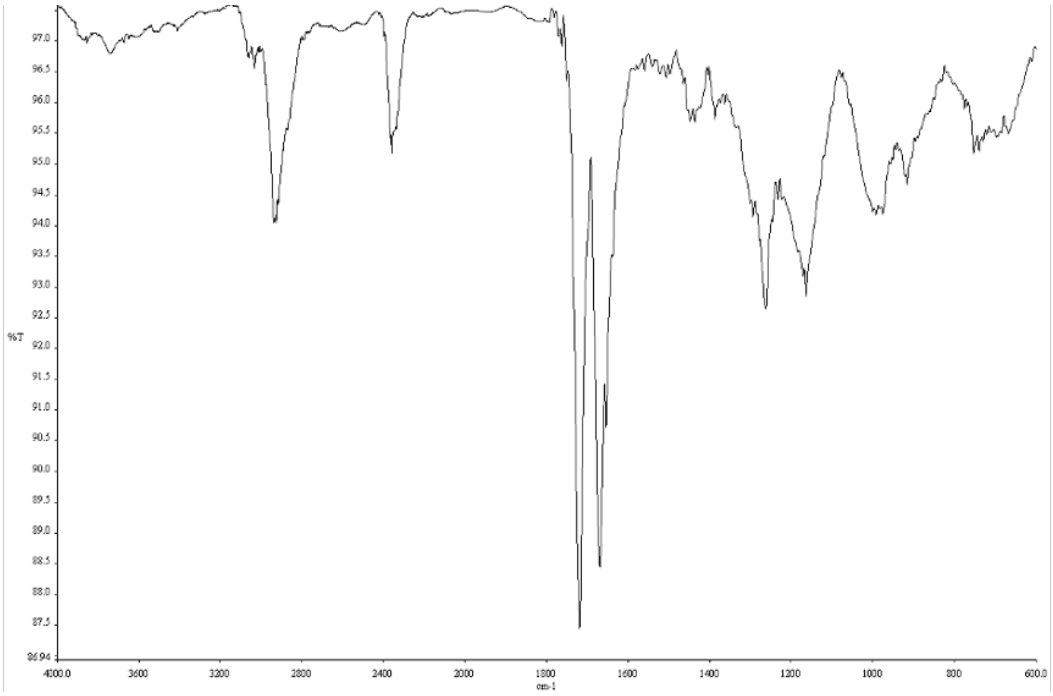


Figure A1.78. *Infrared spectrum (Thin Film, NaCl) of compound* ***14****.*

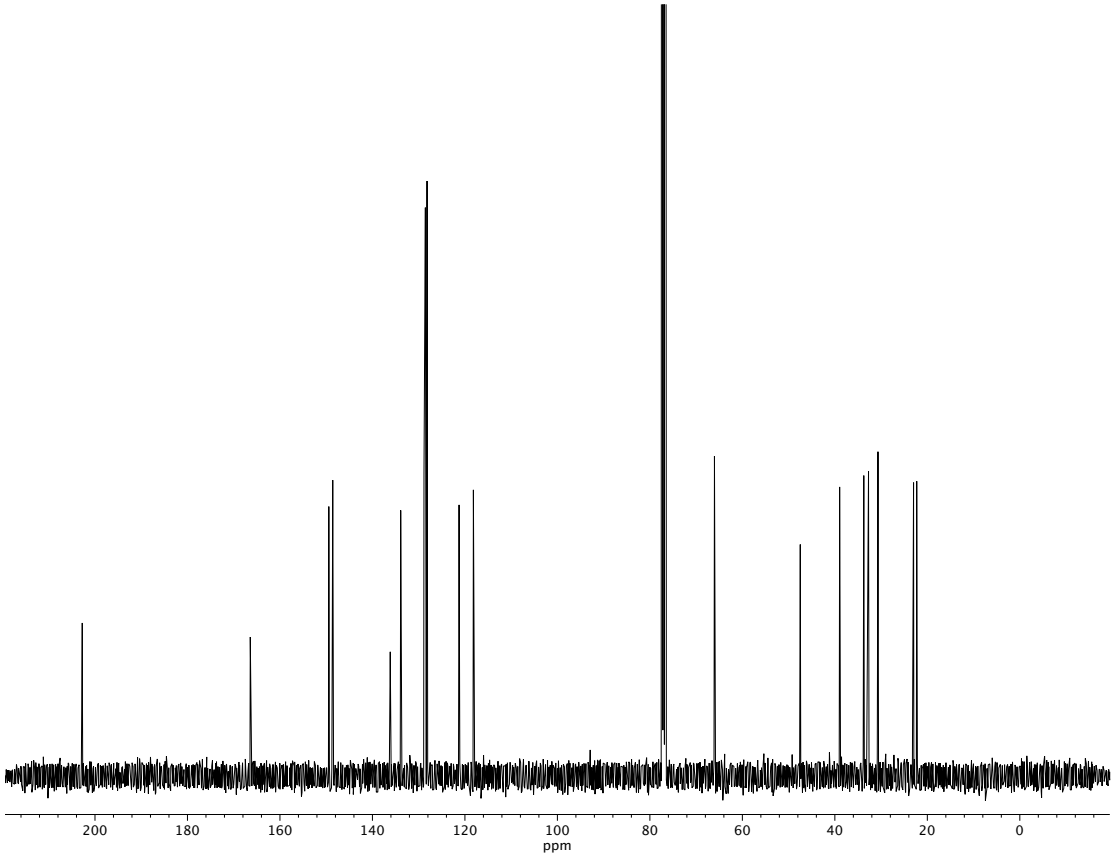


Figure A1.79. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***14****.*

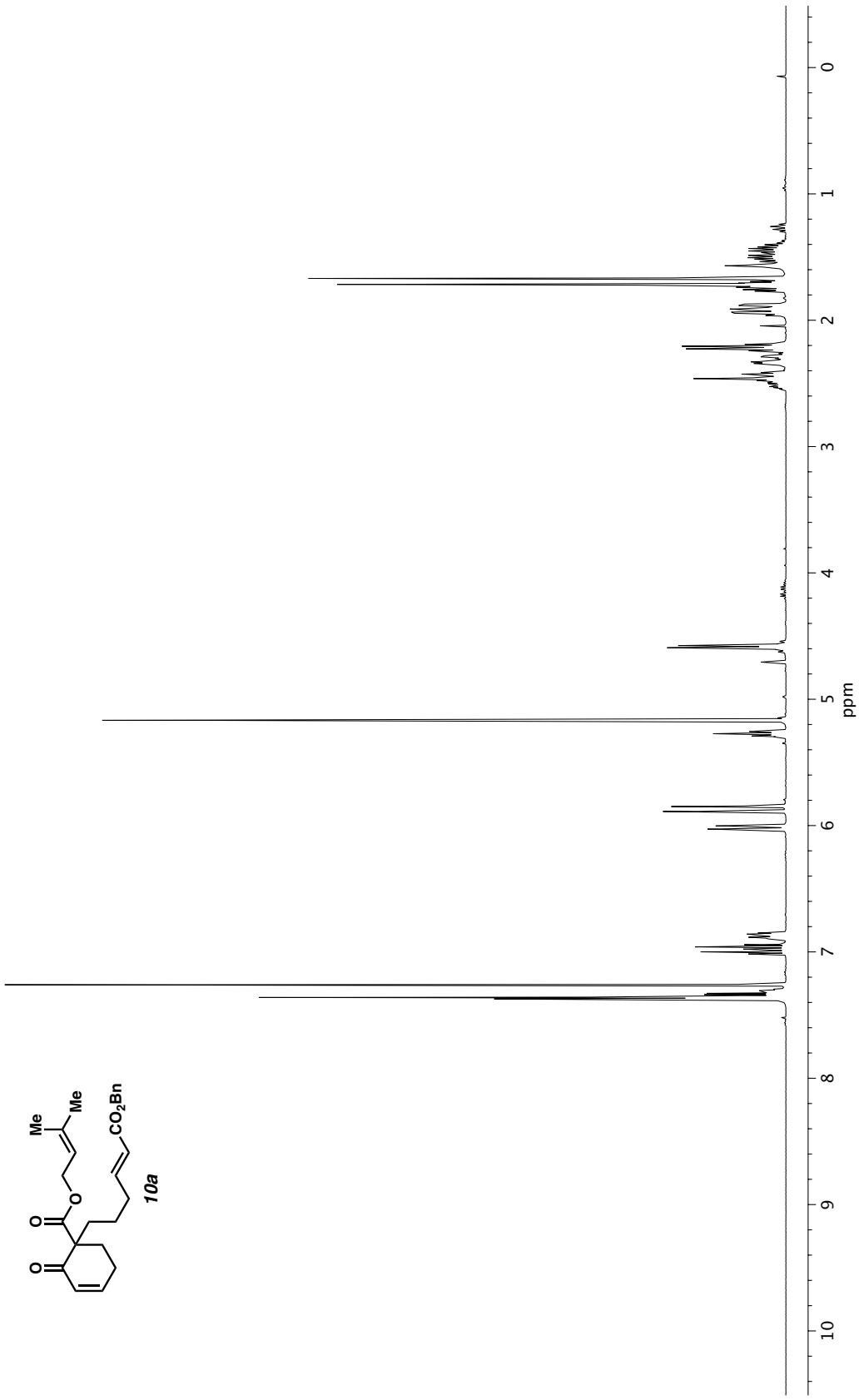


Figure A1.80. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***10a****.*

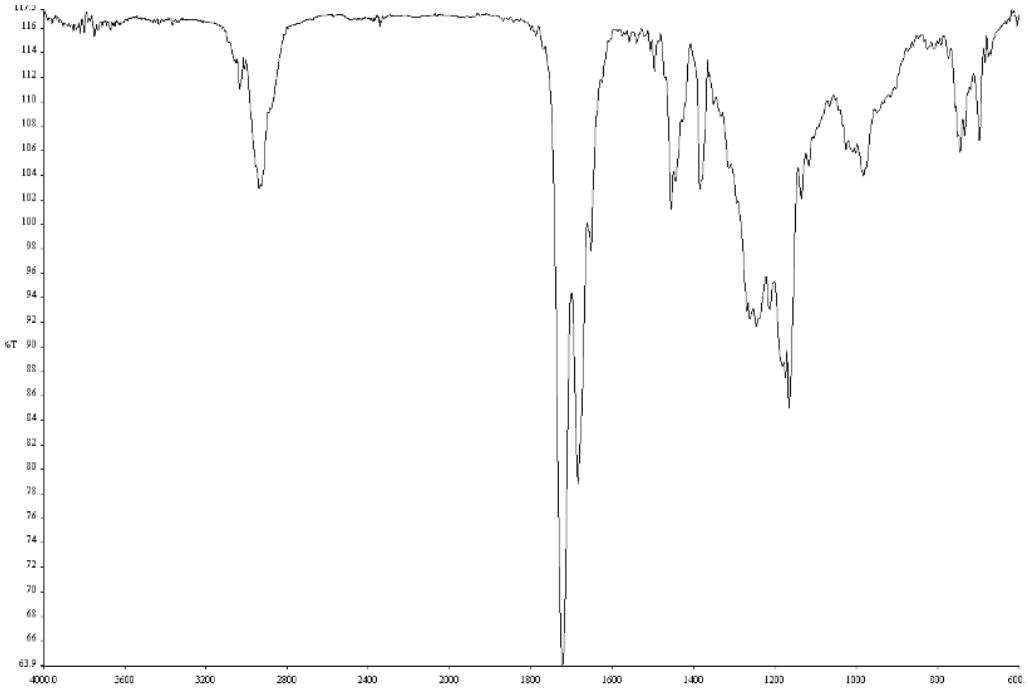


Figure A1.81. *Infrared spectrum (Thin Film, NaCl) of compound* ***10a****.*

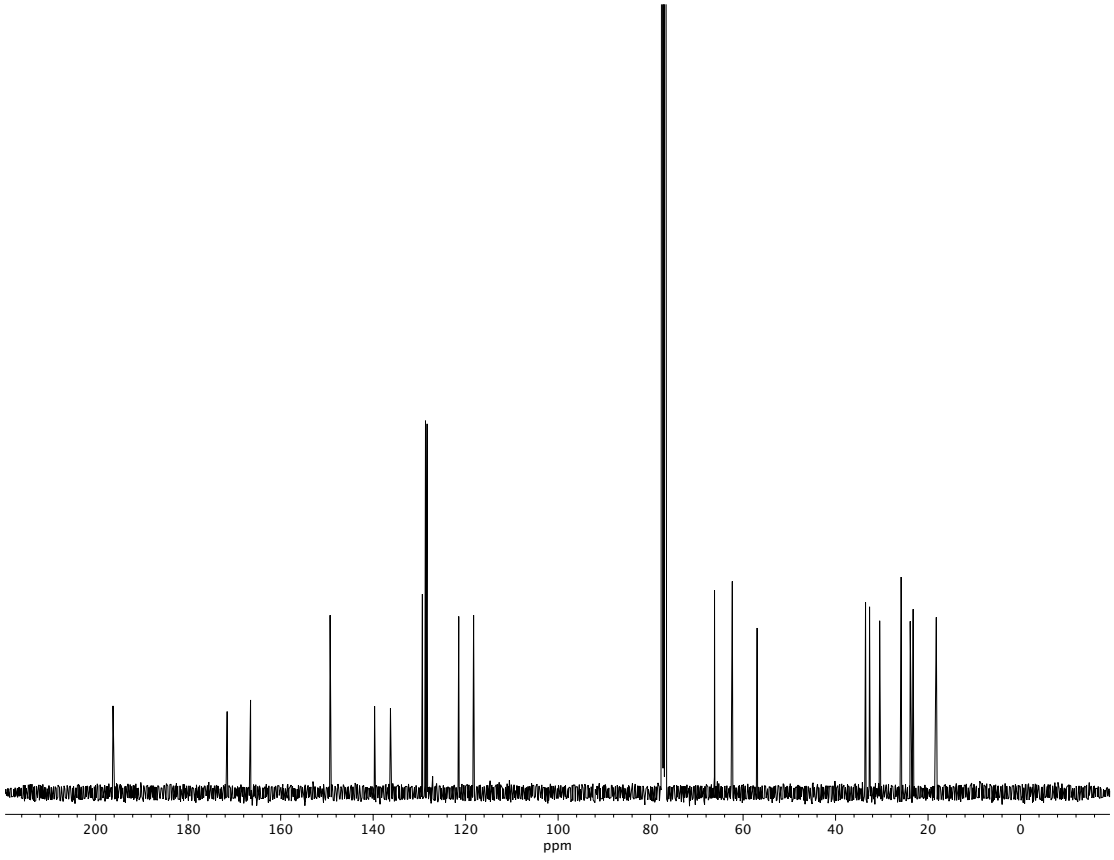


Figure A1.82. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10a****.*

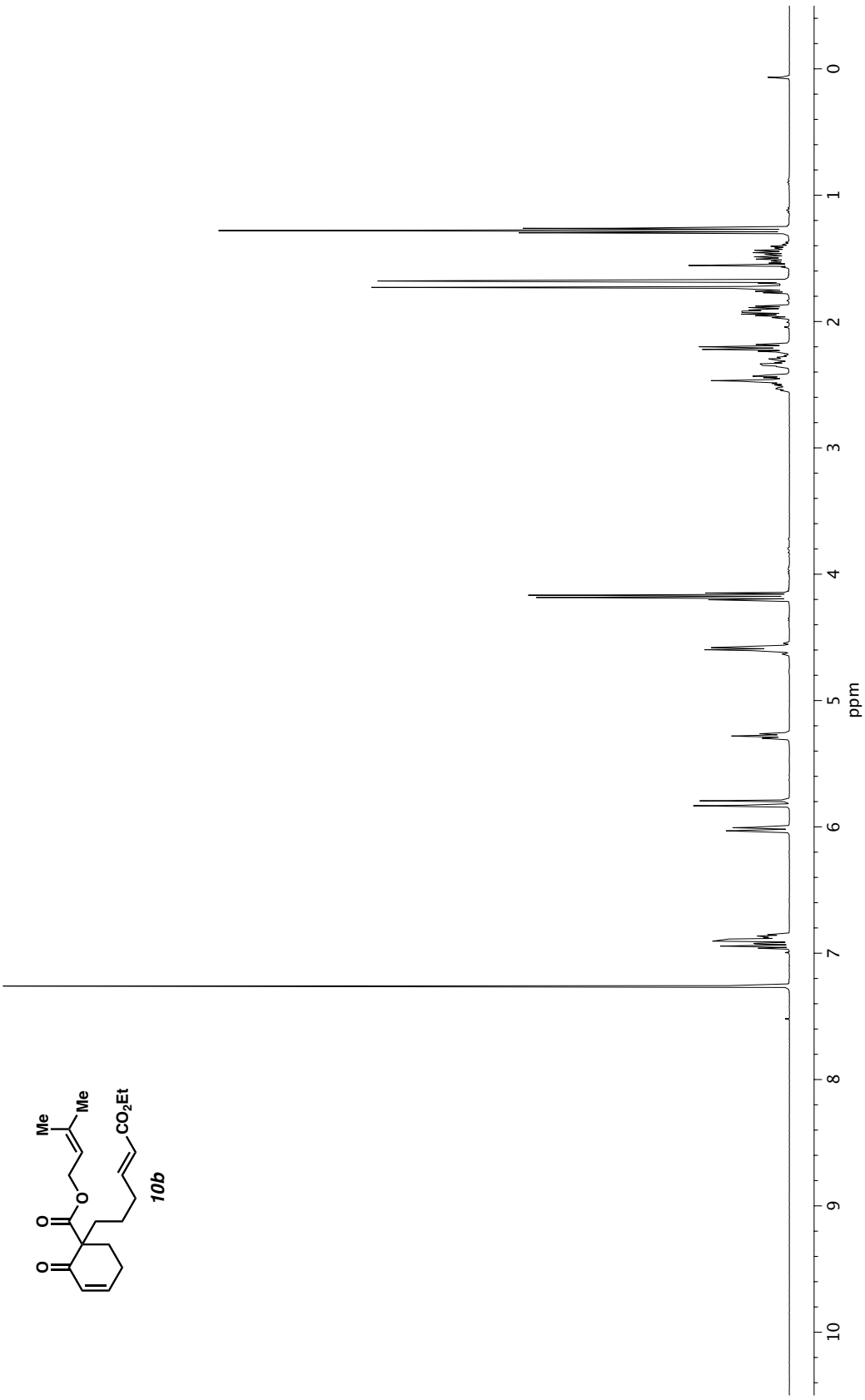


Figure A1.83. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***10b****.*

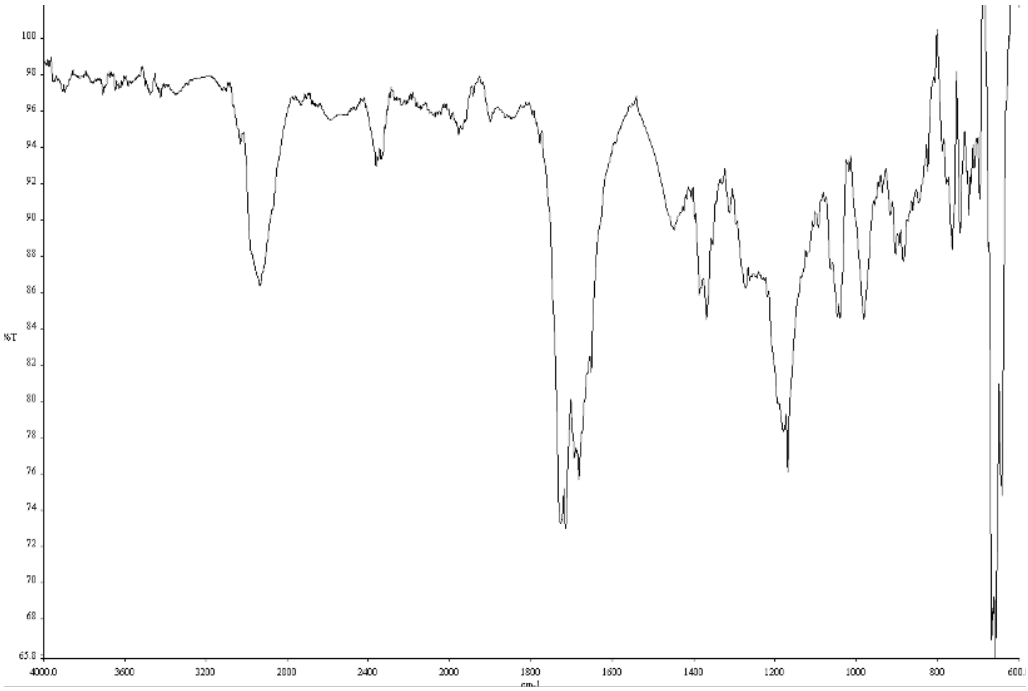


Figure A1.84. *Infrared spectrum (Thin Film, NaCl) of compound* ***10b****.*

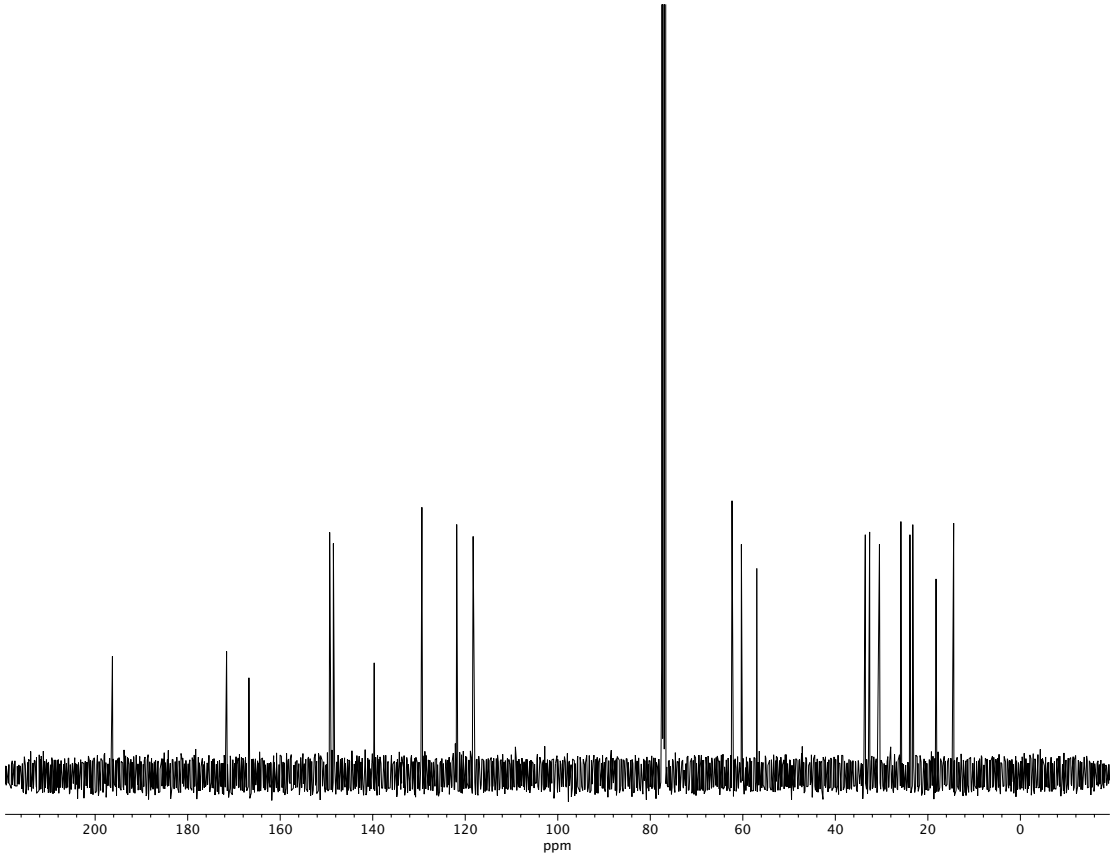


Figure A1.85. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10b****.*

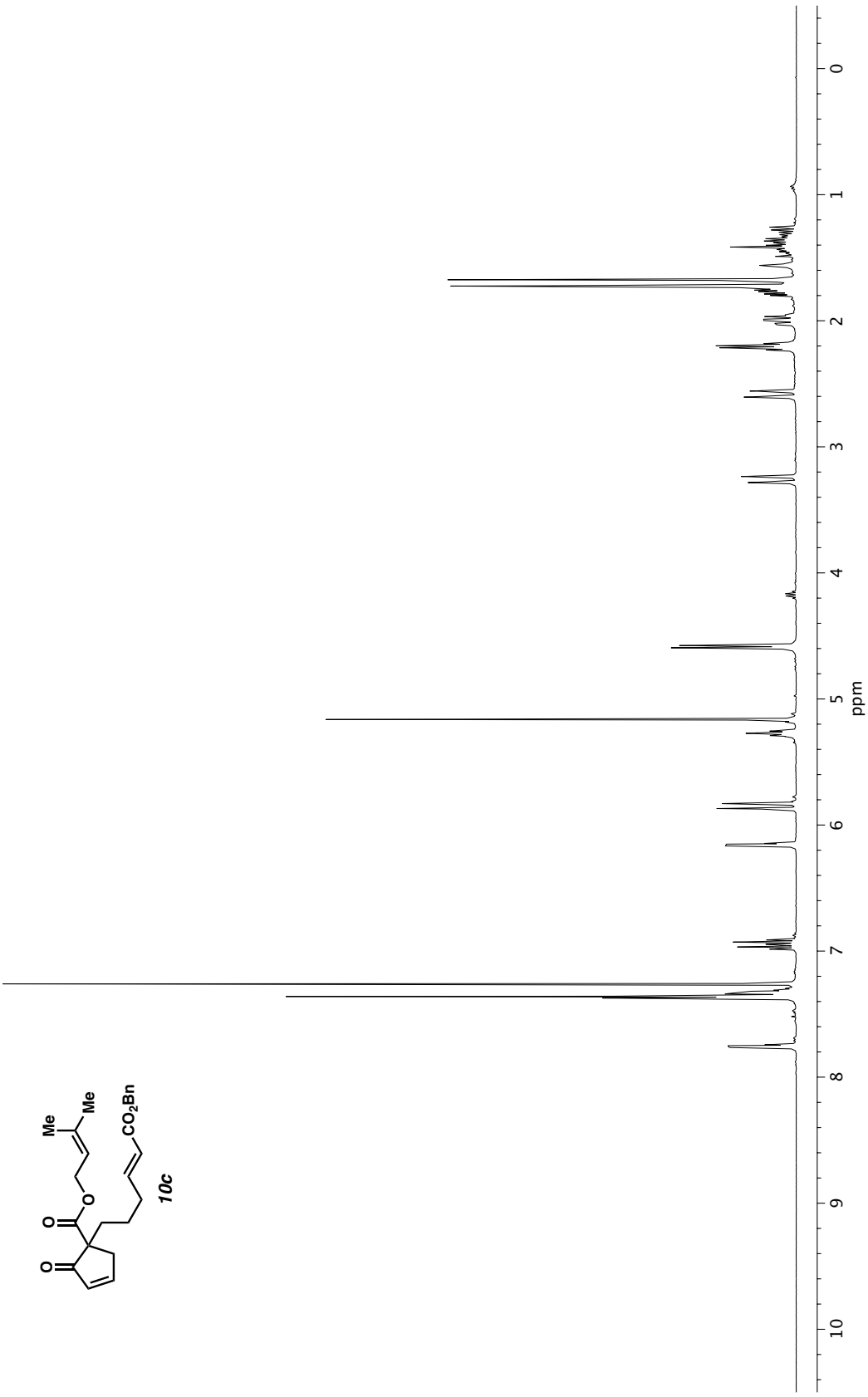


Figure A1.86. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***10c****.*

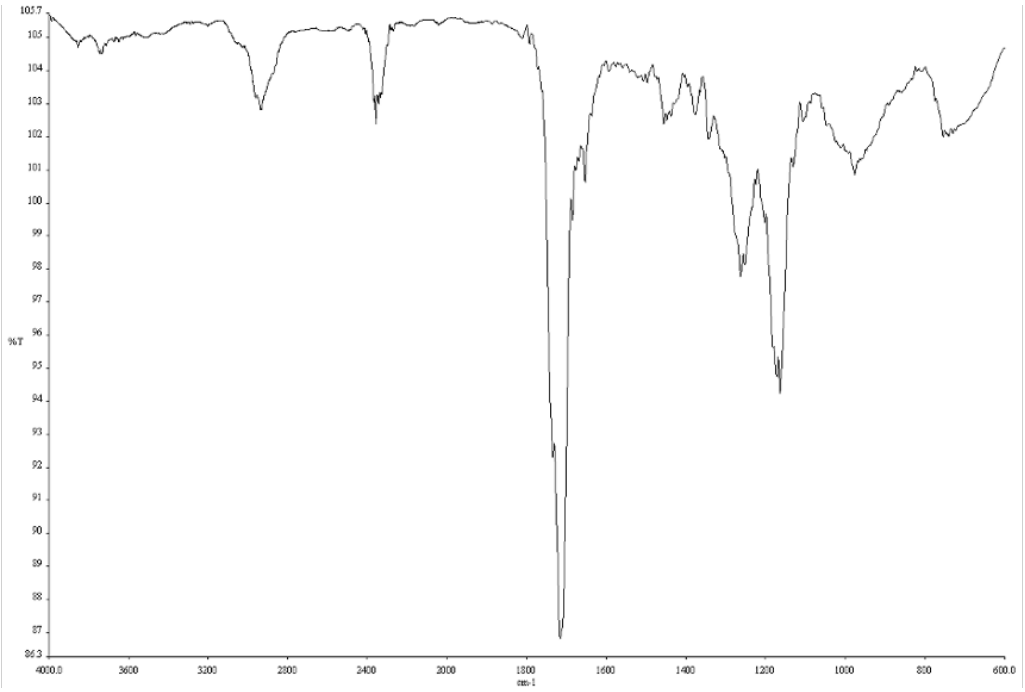


Figure A1.87. *Infrared spectrum (Thin Film, NaCl) of compound* ***10c****.*

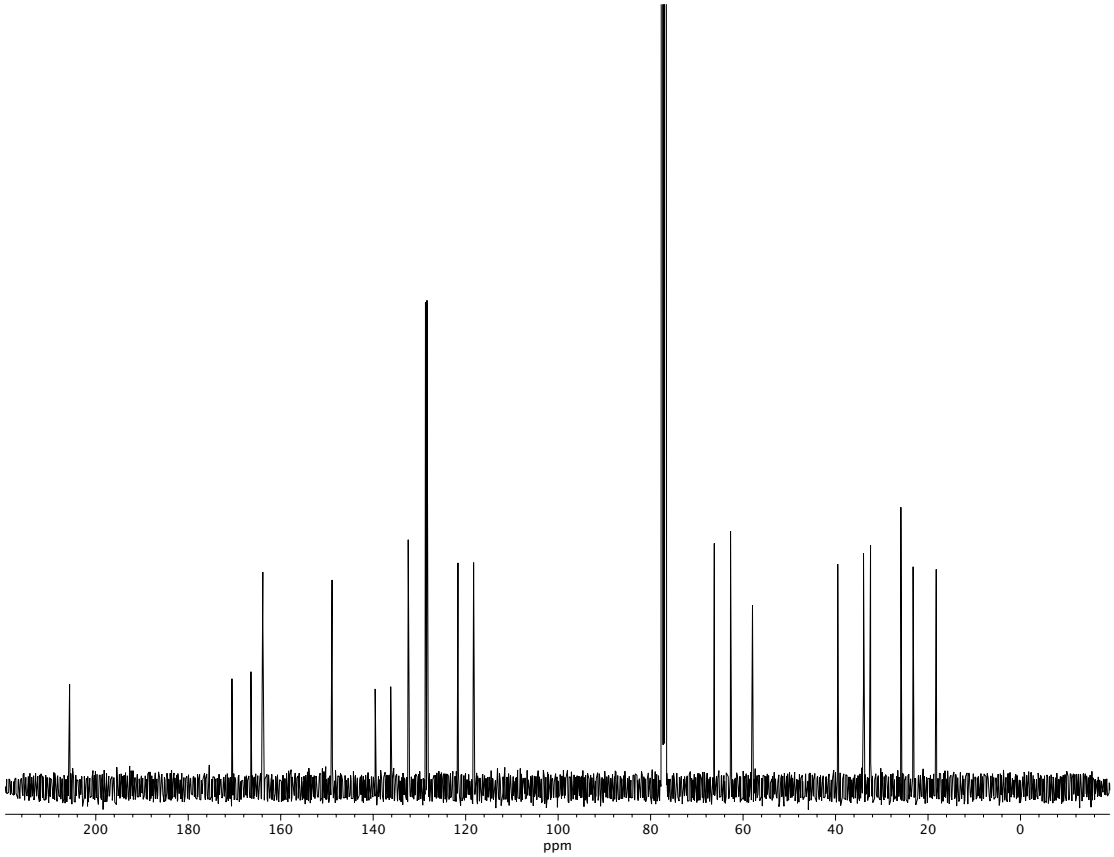


Figure A1.88. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10c****.*

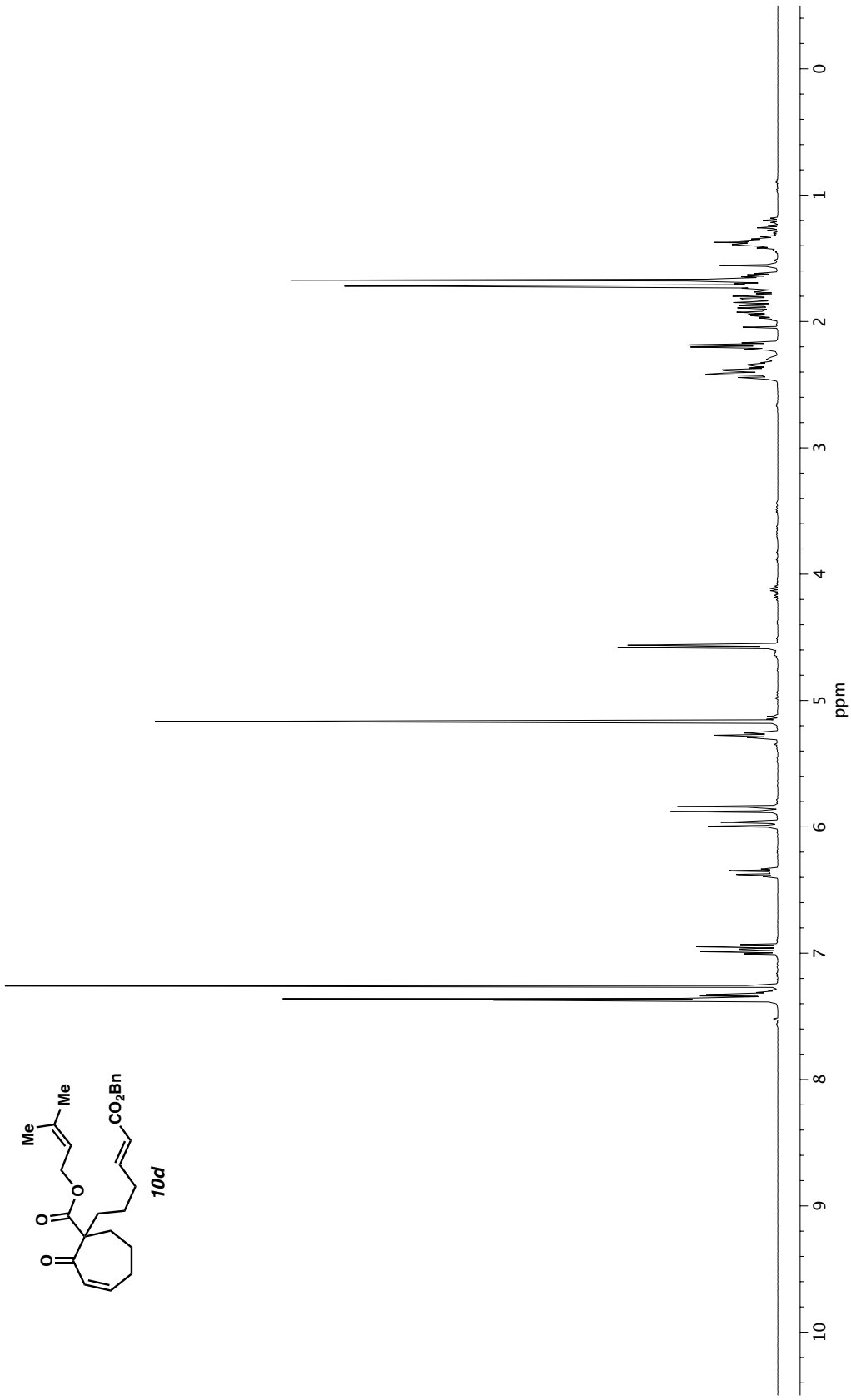


Figure A1.89. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***10d****.*

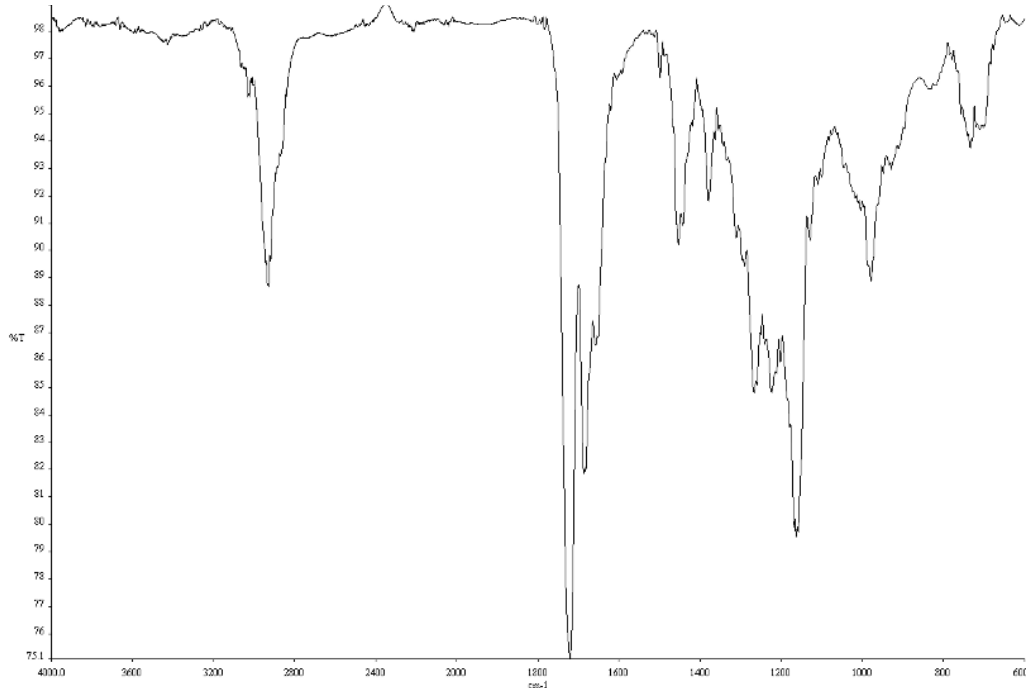


Figure A1.90. *Infrared spectrum (Thin Film, NaCl) of compound* ***10d****.*

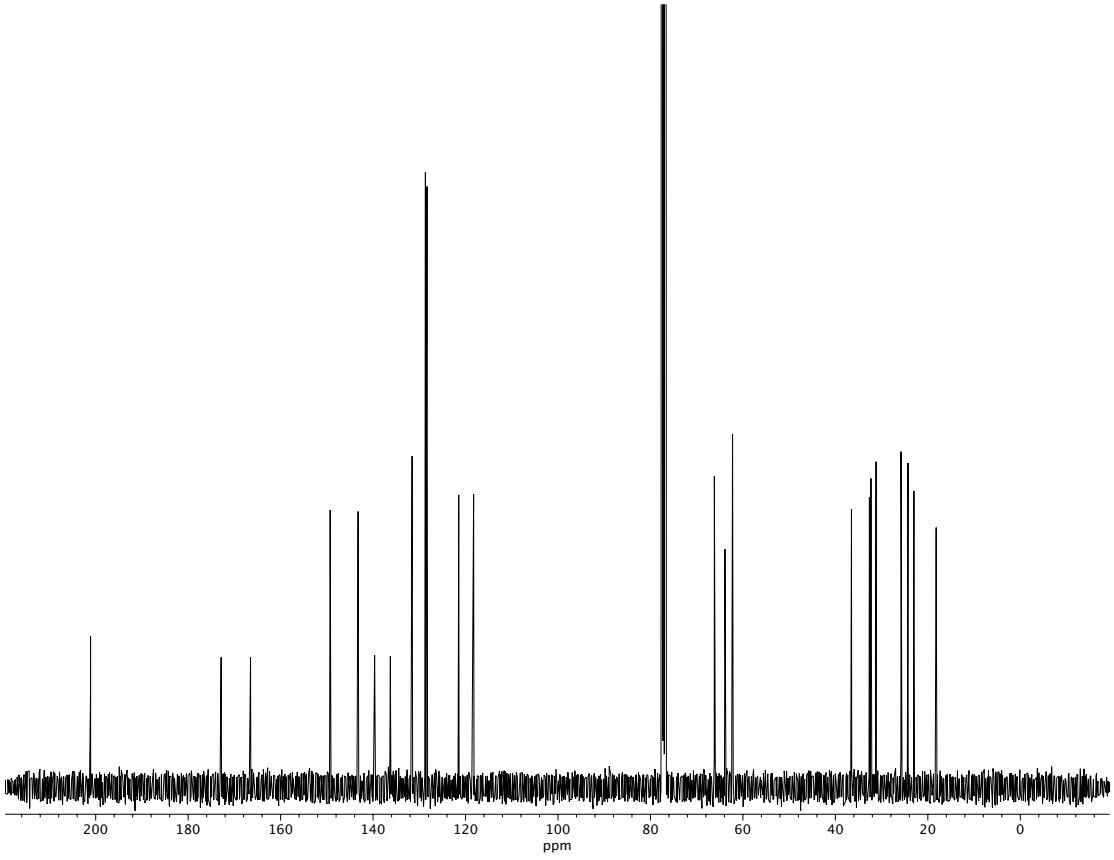


Figure A1.91. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10d****.*

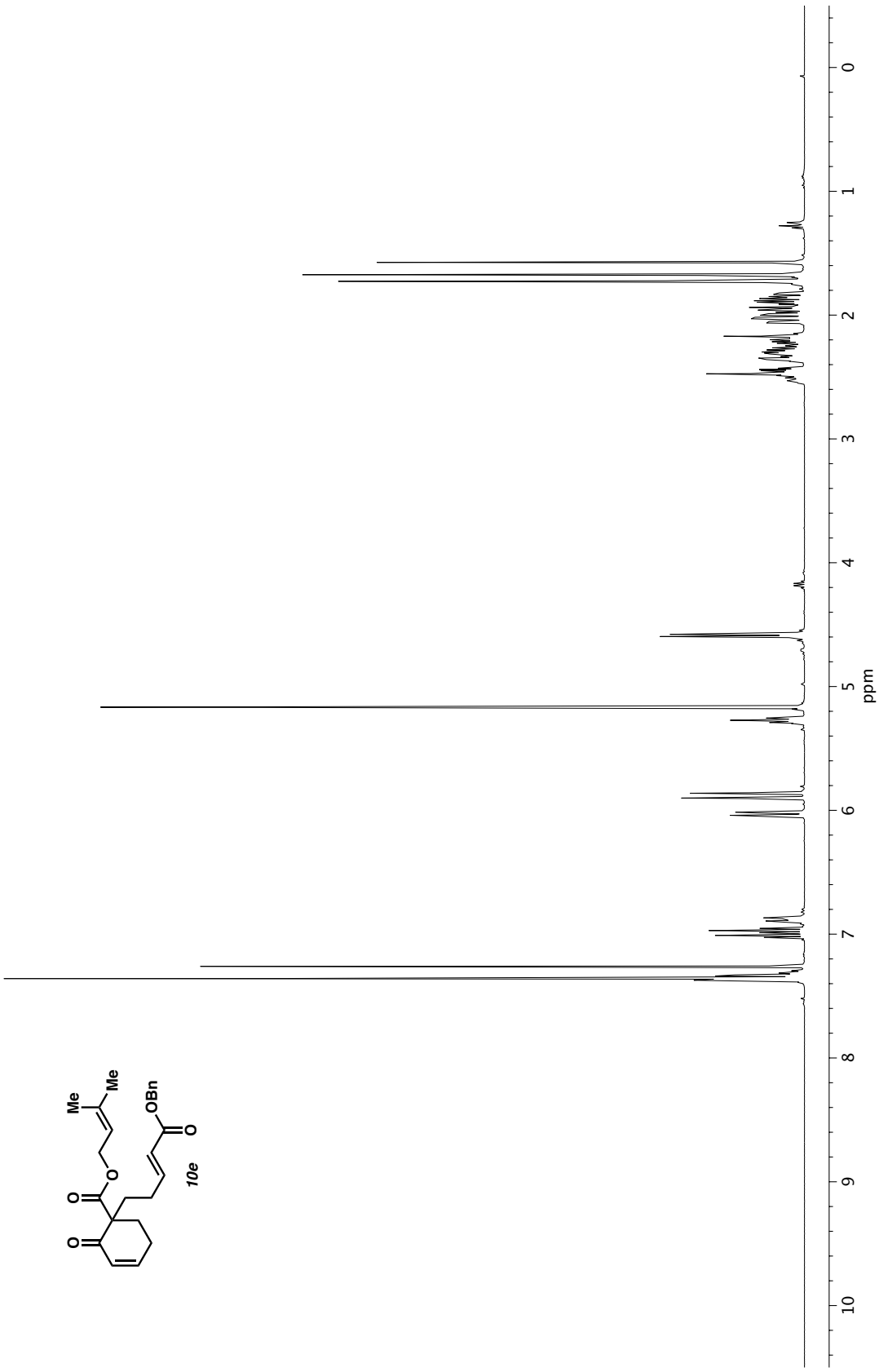


Figure A1.92. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***10e****.*

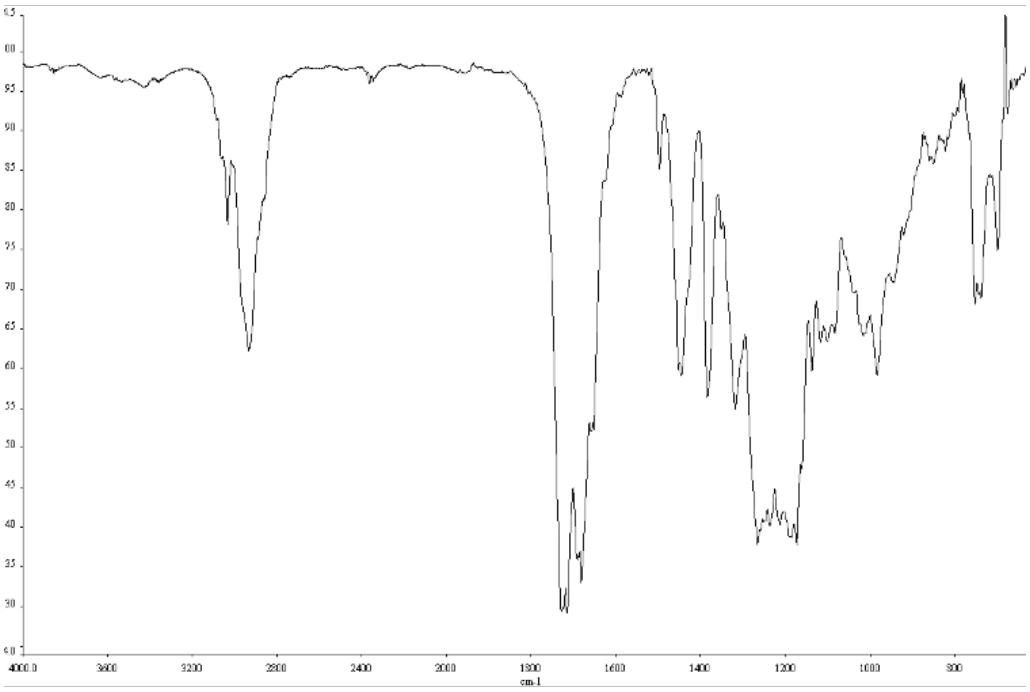


Figure A1.93. *Infrared spectrum (Thin Film, NaCl) of compound* ***10e****.*

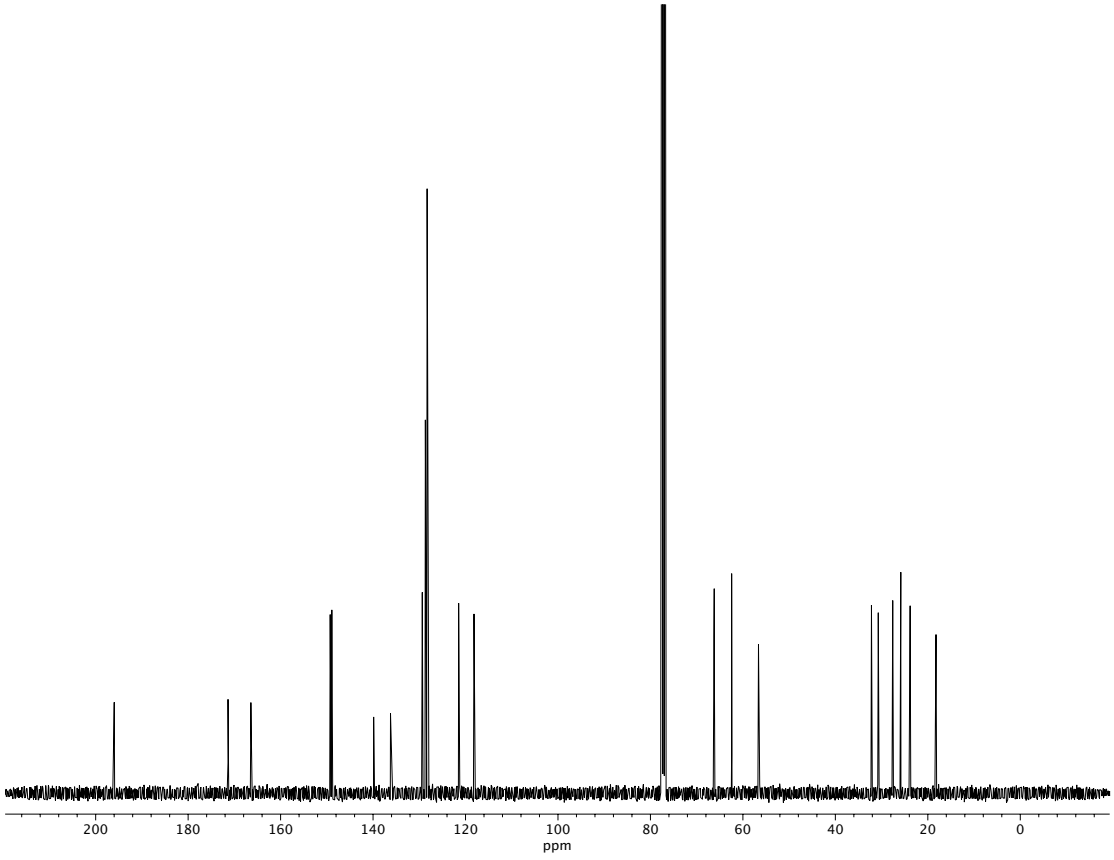


Figure A1.94. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10e****.*

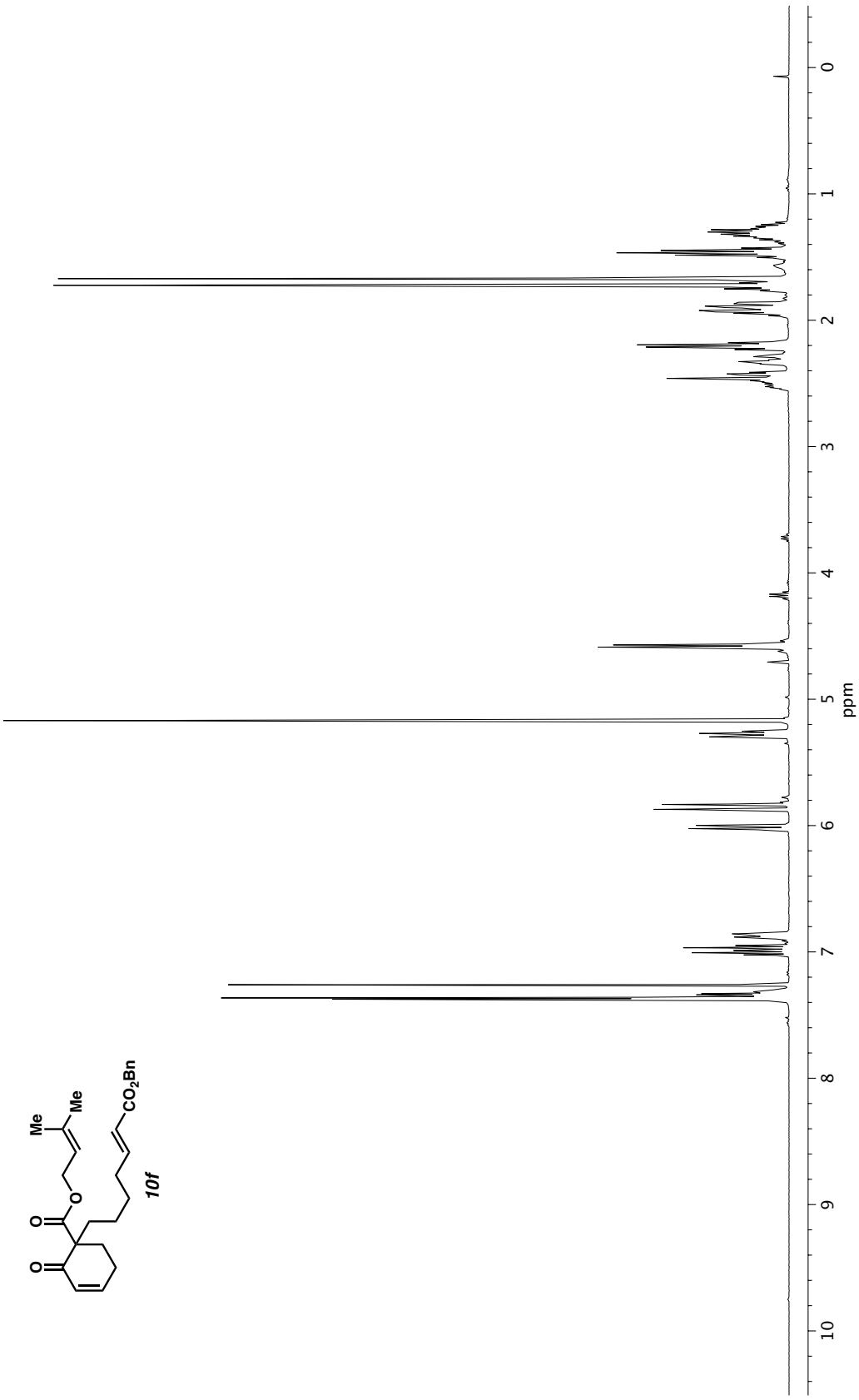


Figure A1.95. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***10f****.*

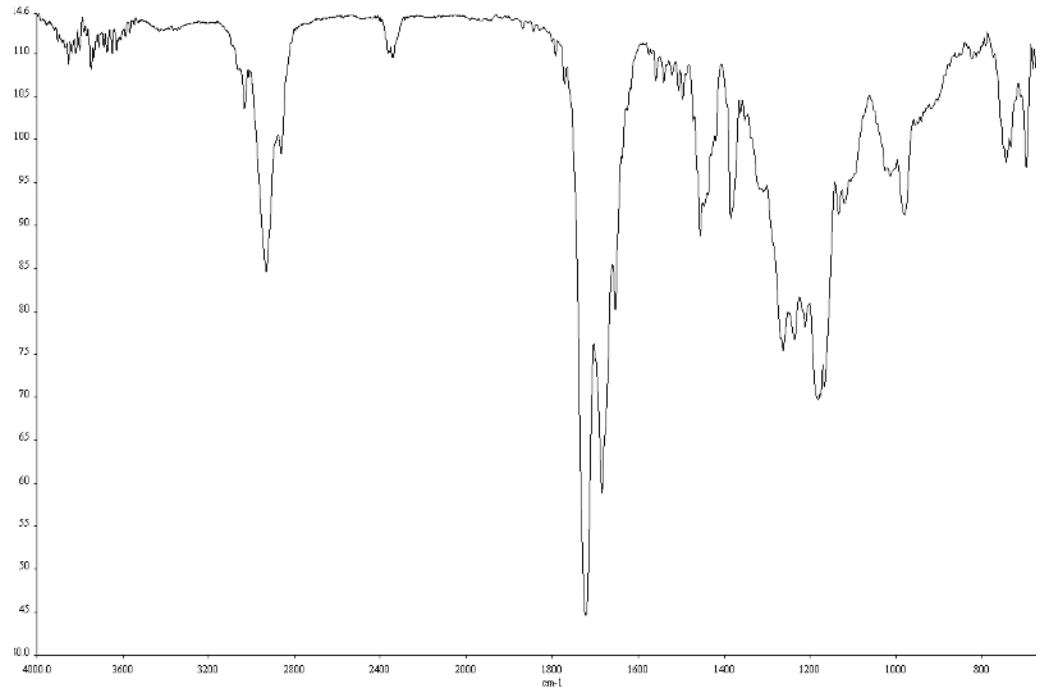


Figure A1.96. *Infrared spectrum (Thin Film, NaCl) of compound* ***10f****.*

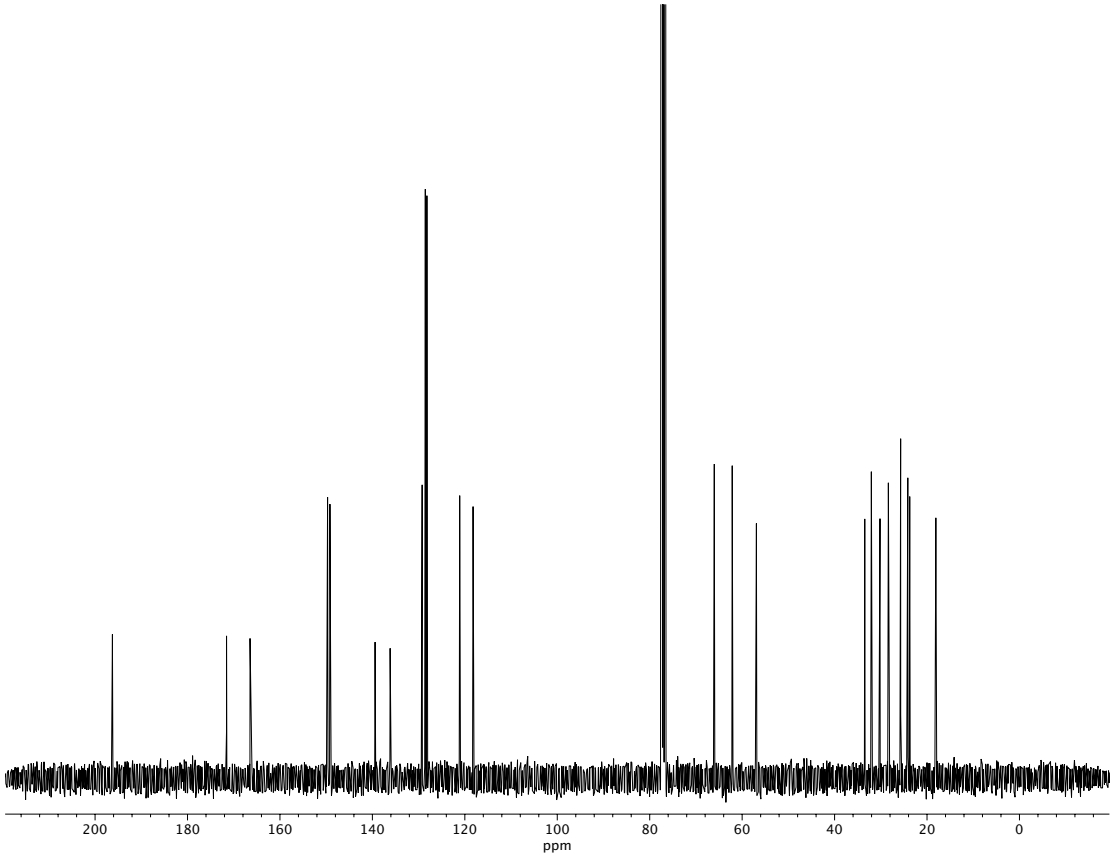


Figure A1.97. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10f****.*

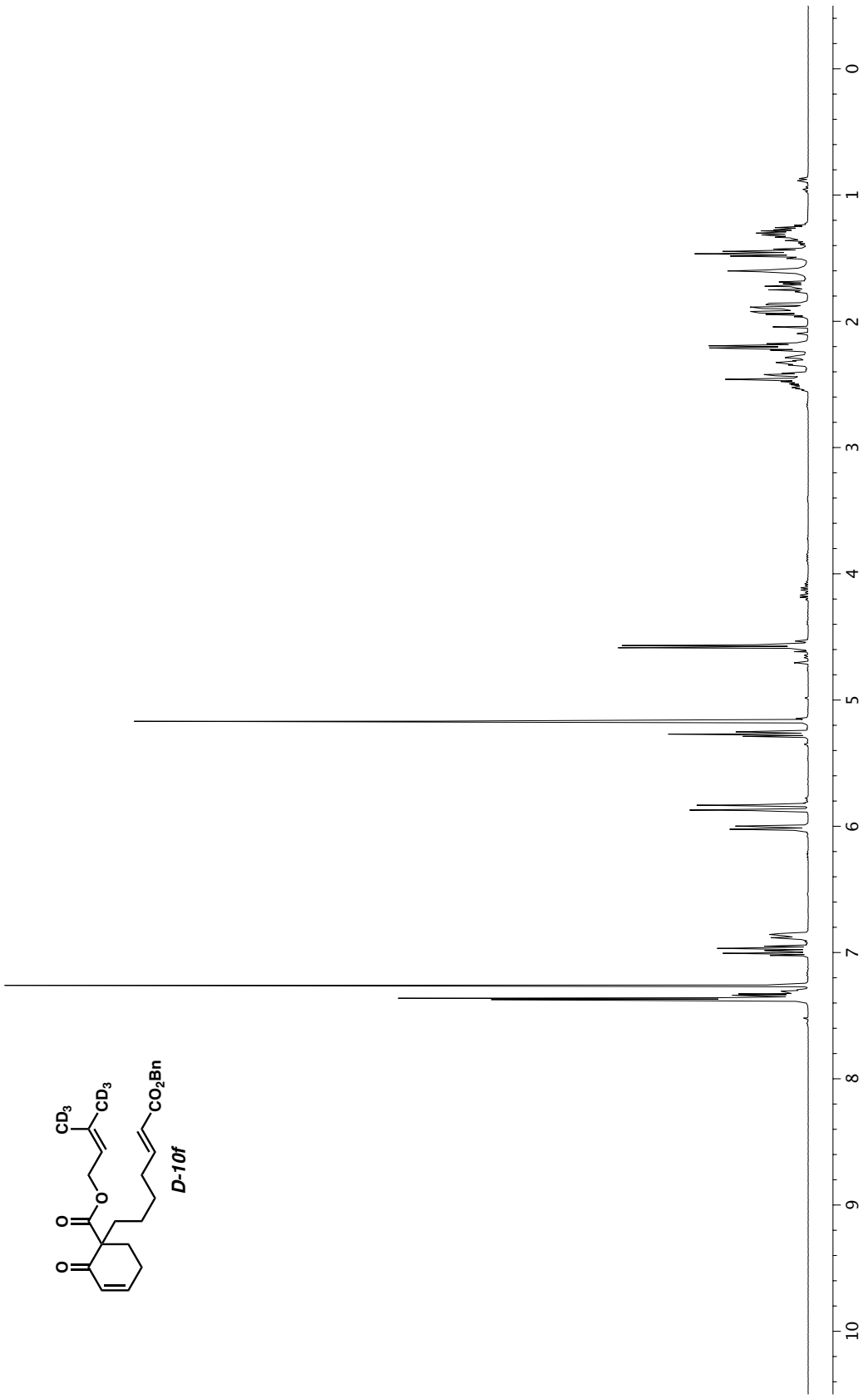


Figure A1.98. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***D-10f****.*

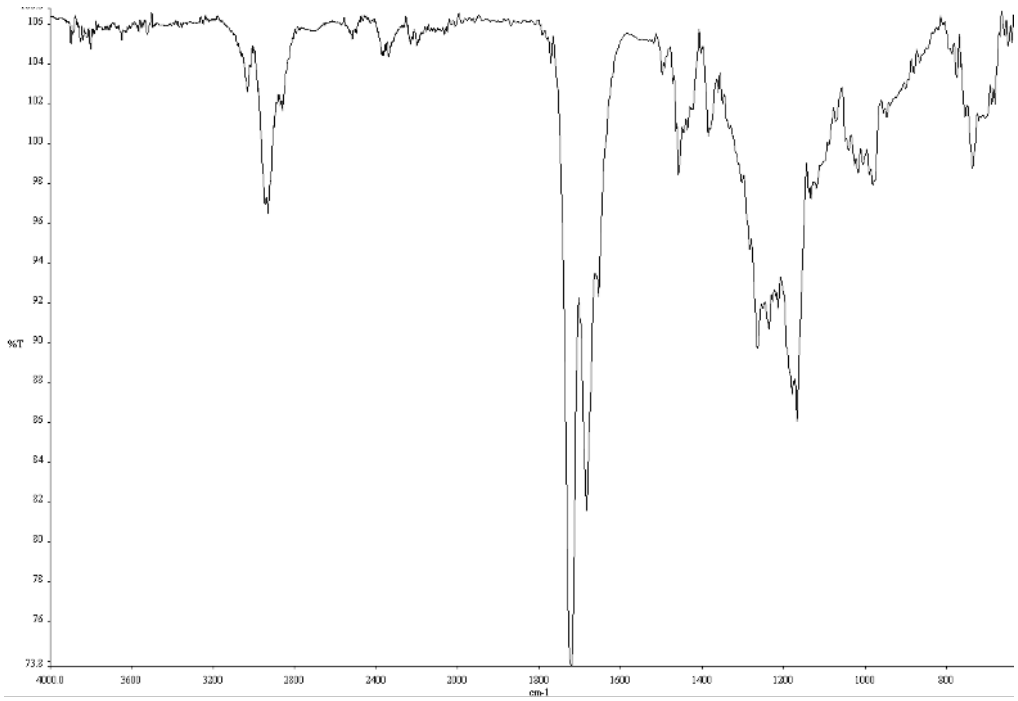


Figure A1.99. *Infrared spectrum (Thin Film, NaCl) of compound* ***D-10f****.*

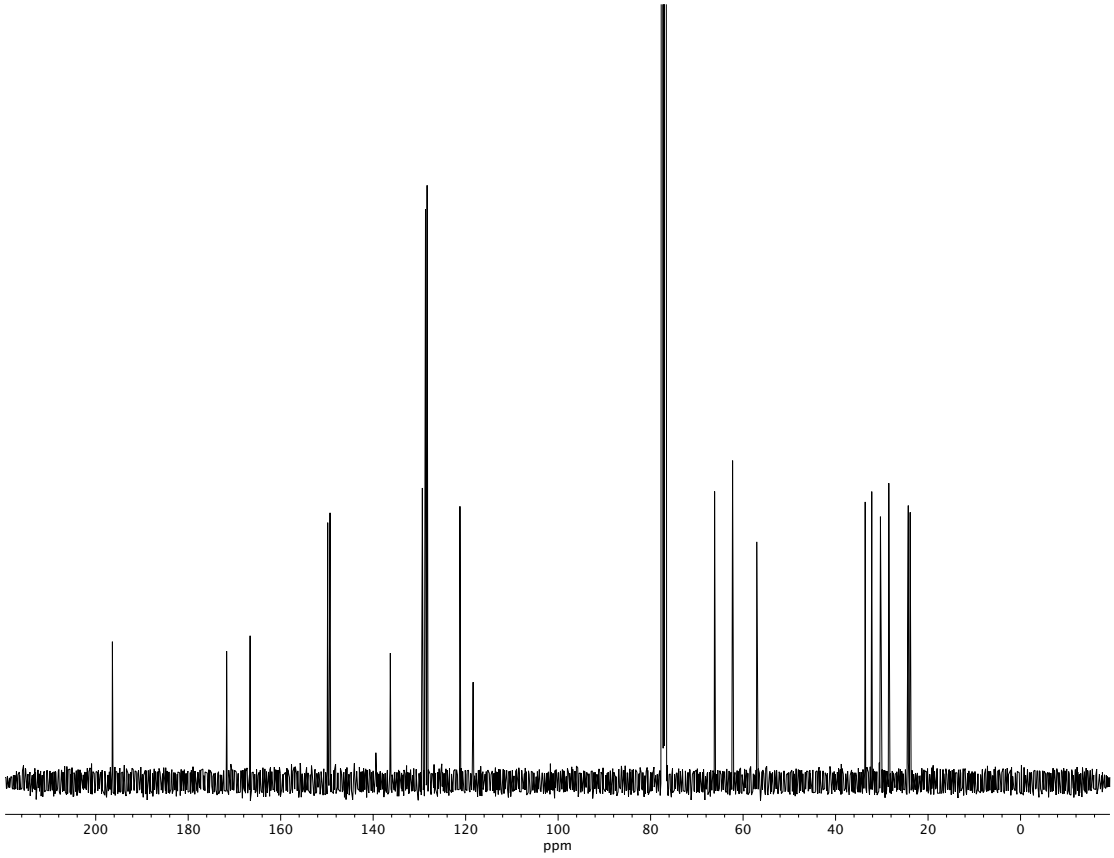


Figure A1.100. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***D-10f****.*

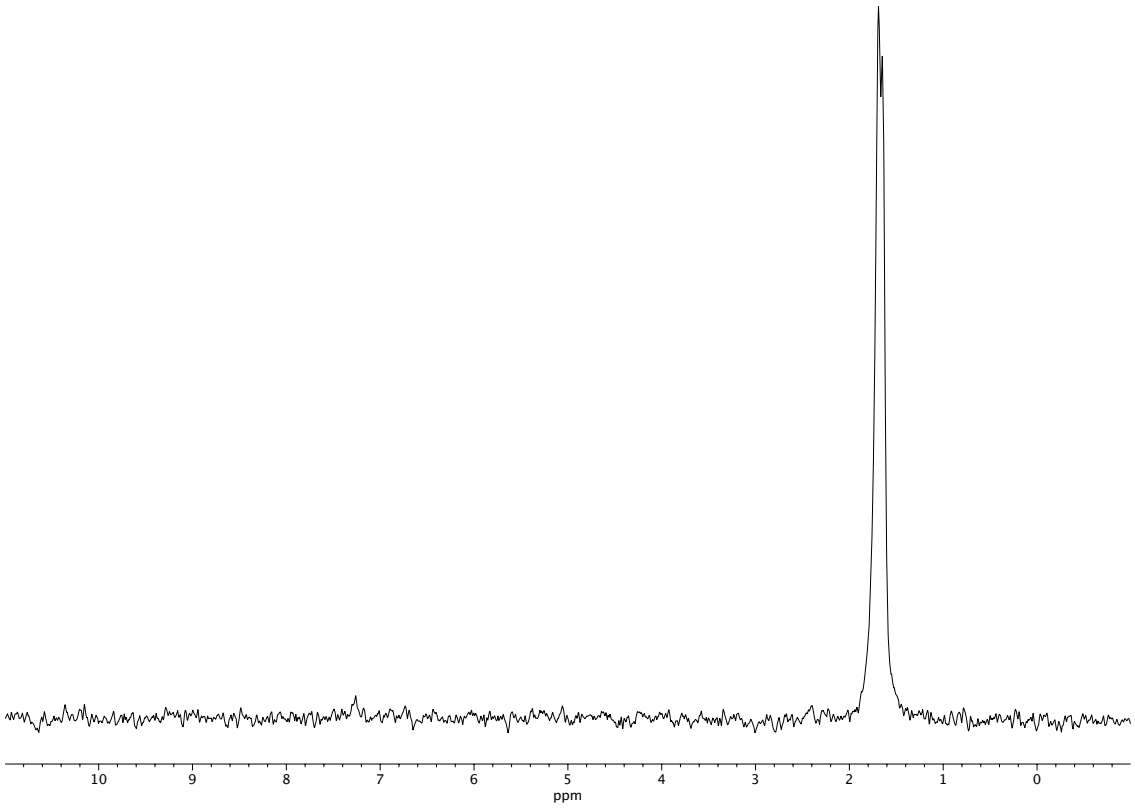


Figure A1.101. *^{2}H NMR (61 MHz, $CDCl_3$) of compound* ***D-10f****.*

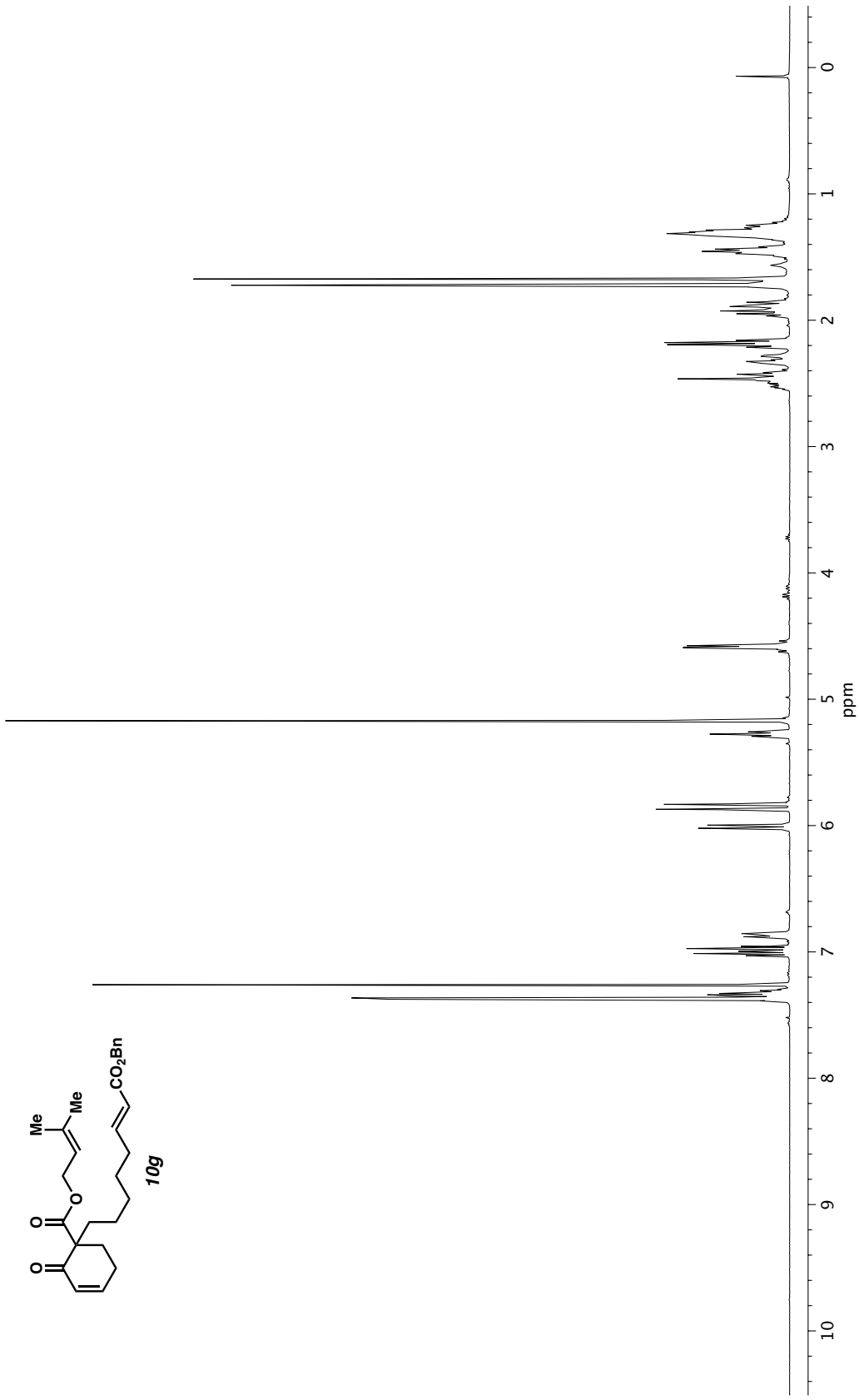


Figure A1.102. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***10g****.*

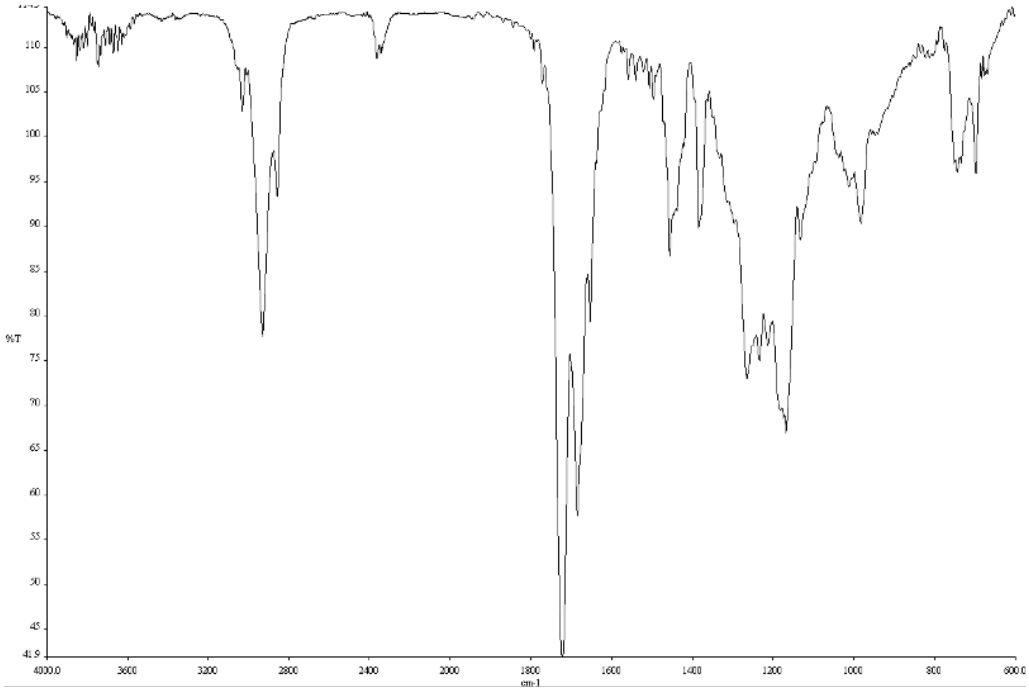


Figure A1.103. *Infrared spectrum (Thin Film, NaCl) of compound* ***10g****.*

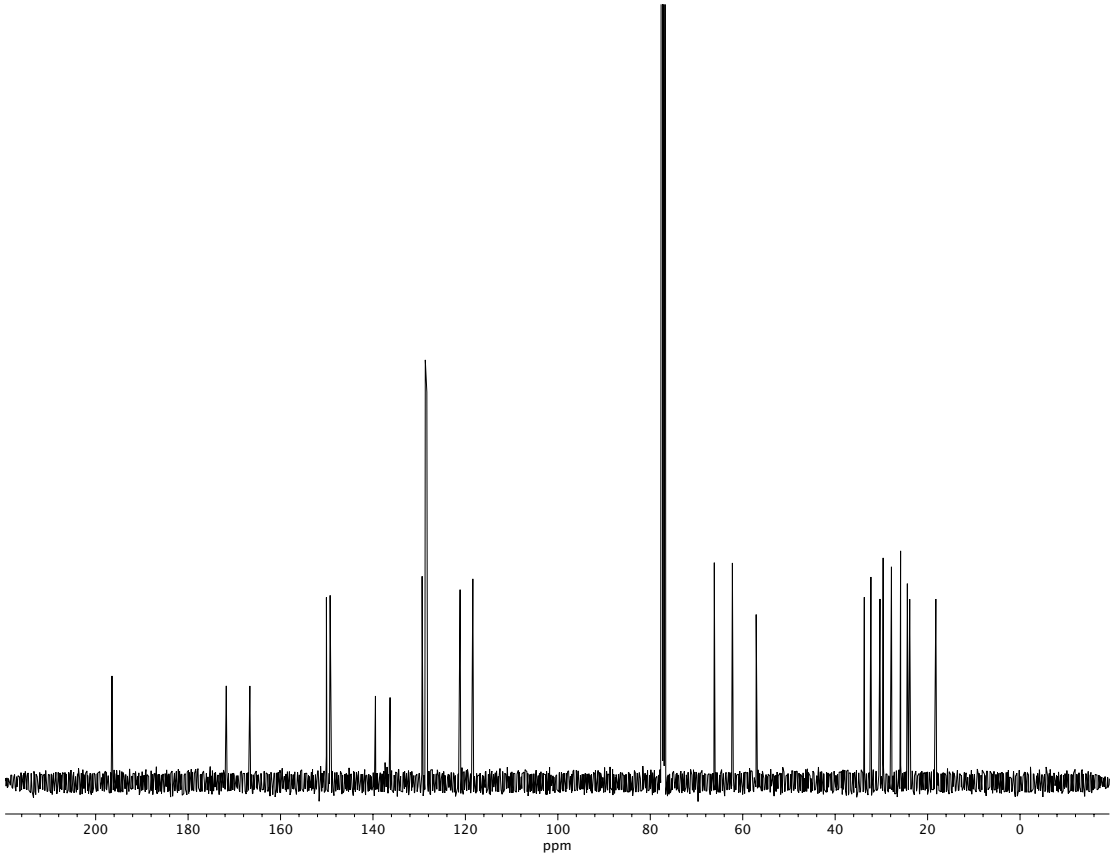


Figure A1.104. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10g****.*

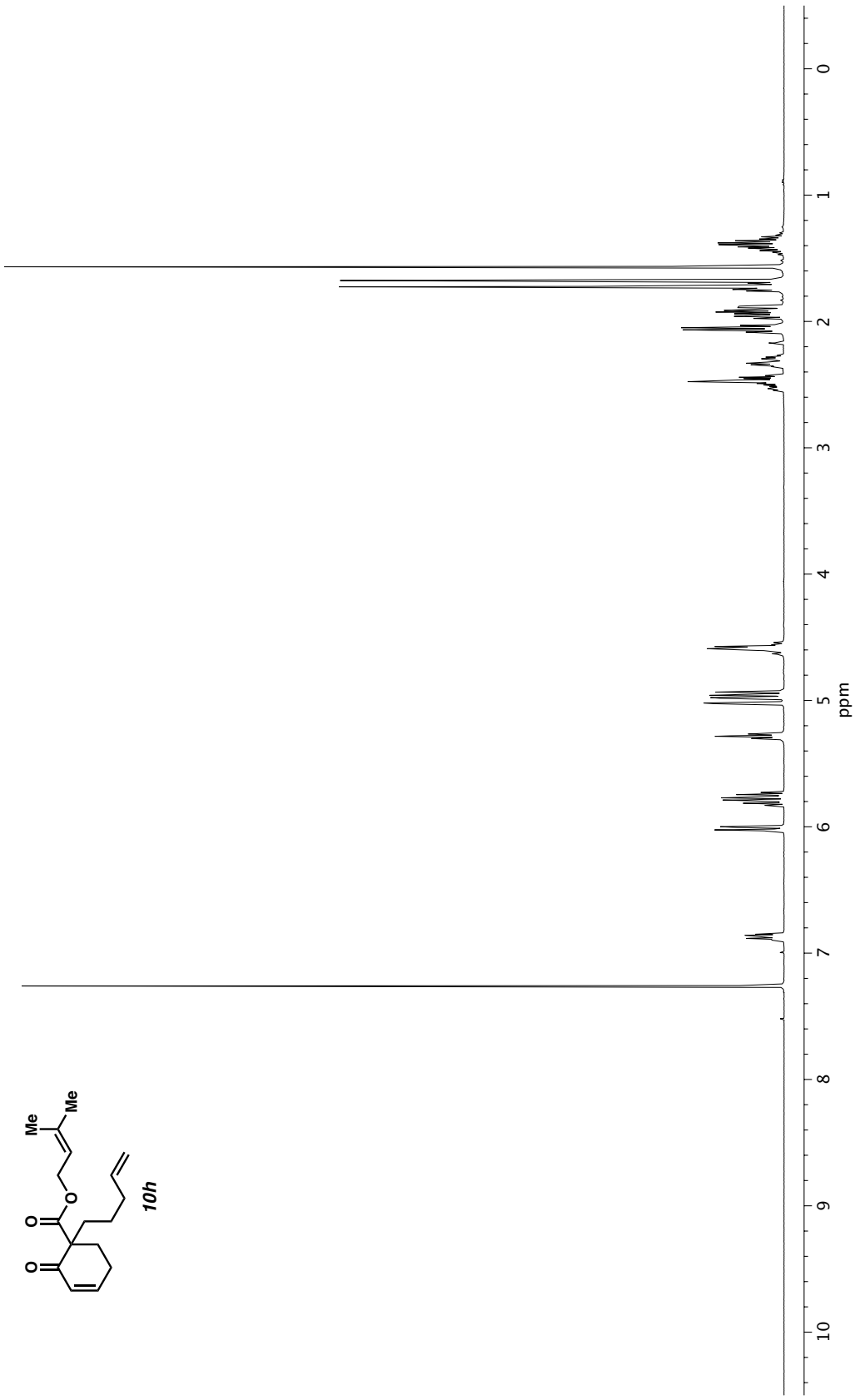


Figure A1.105. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***10h****.*

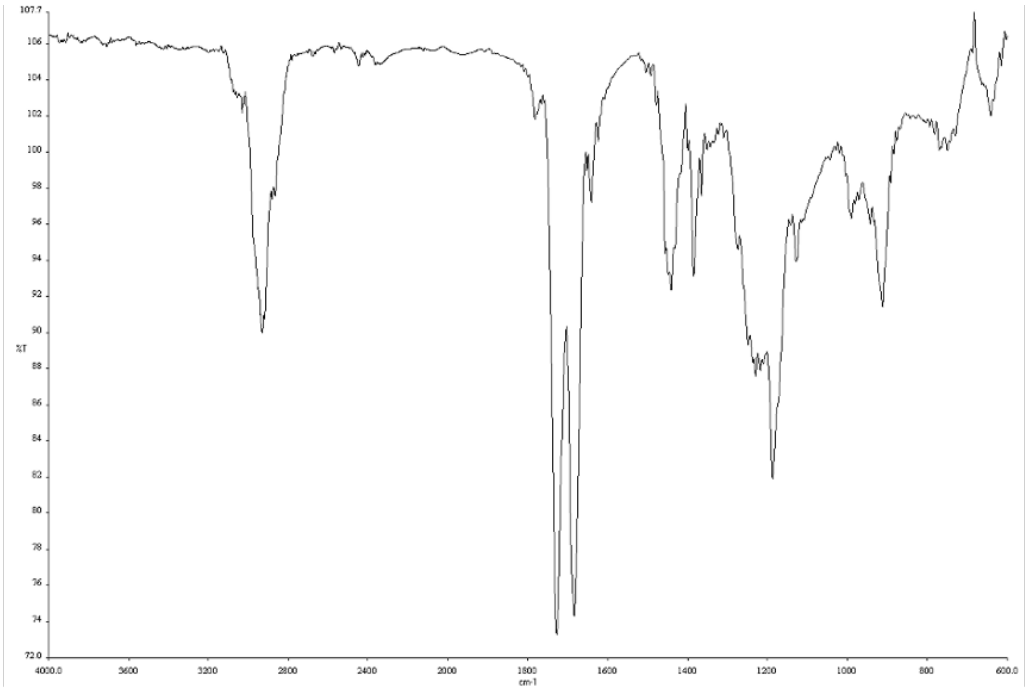


Figure A1.106. *Infrared spectrum (Thin Film, NaCl) of compound* ***10h****.*

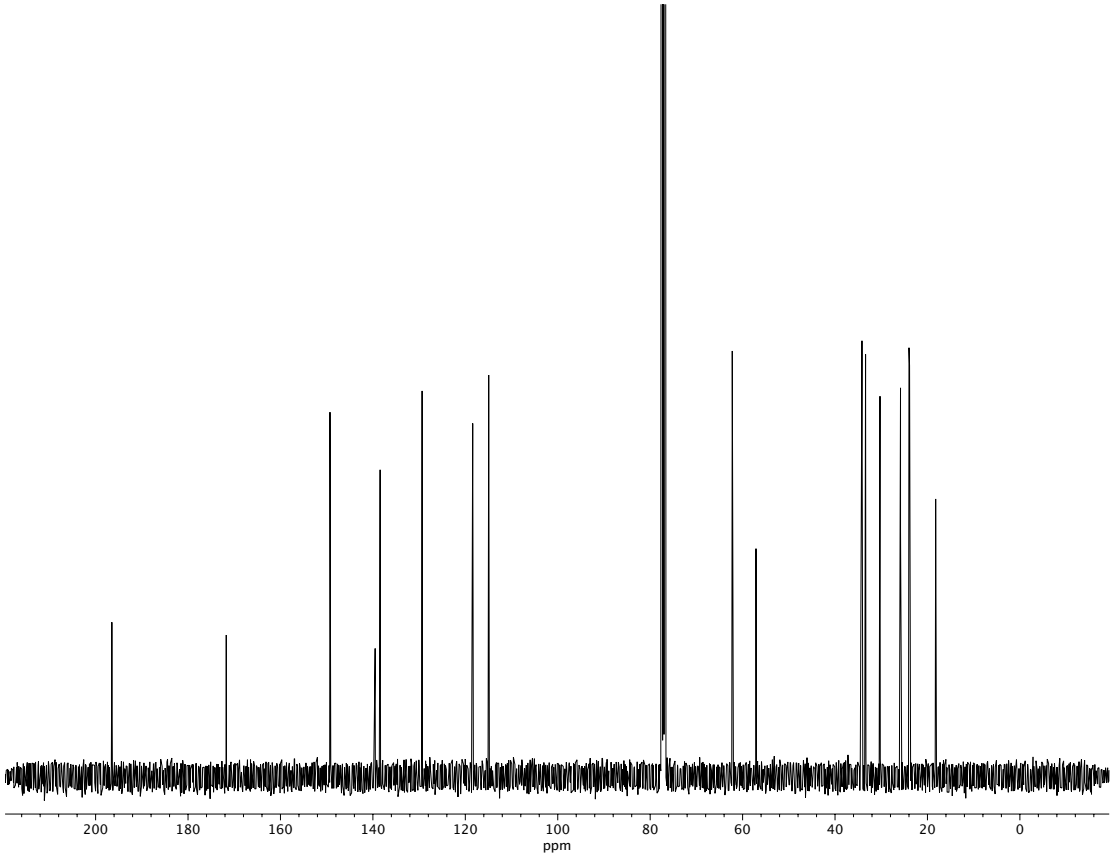


Figure A1.107. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10h****.*

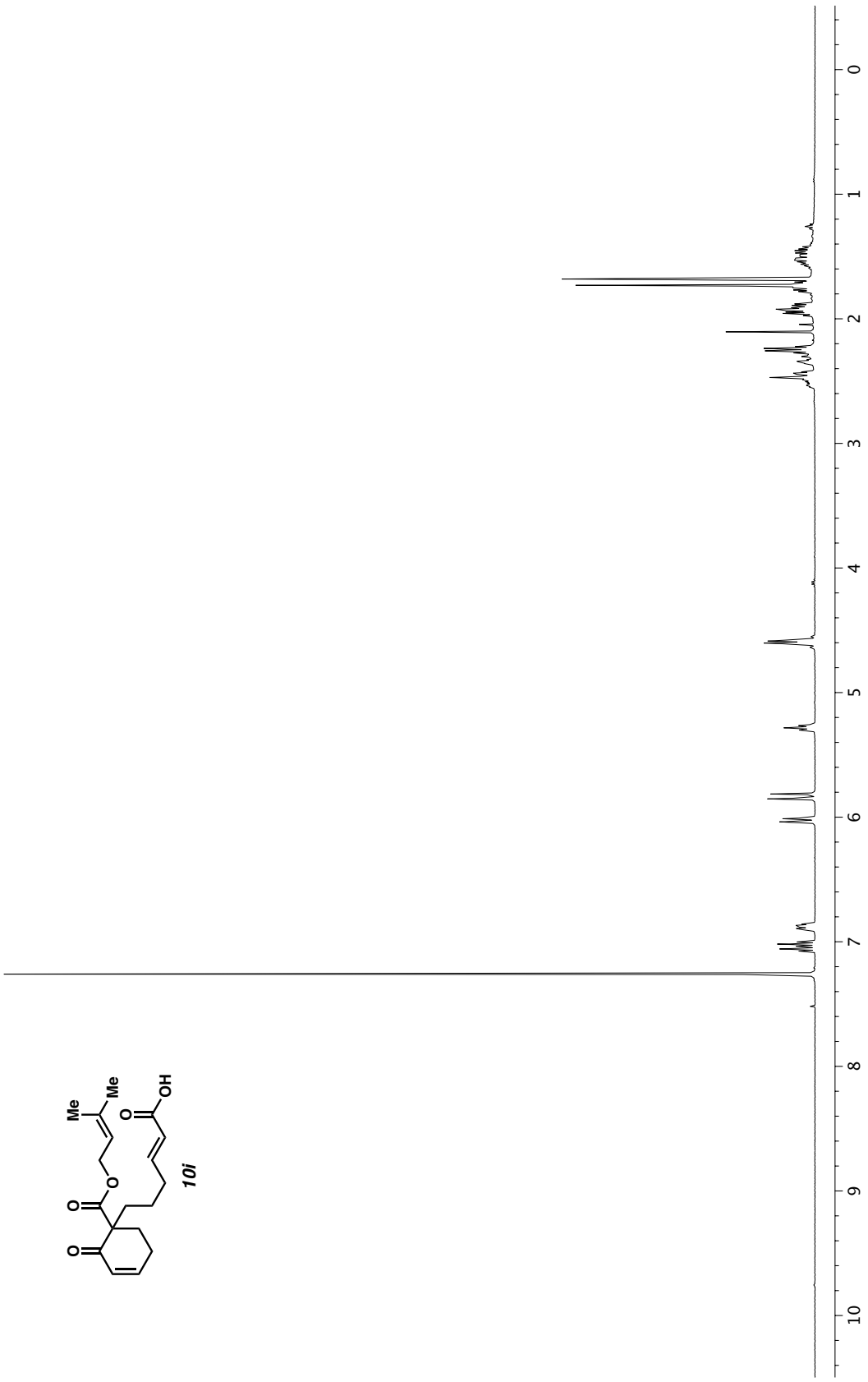


Figure A1.108. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***10i****.*

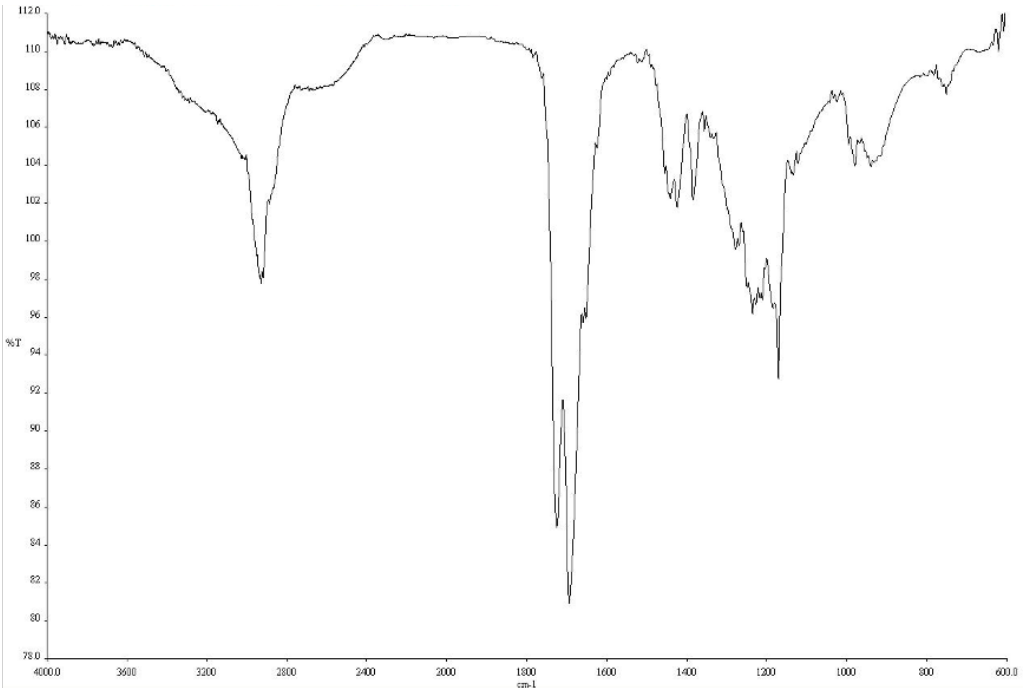


Figure A1.109. *Infrared spectrum (Thin Film, NaCl) of compound* ***10i****.*

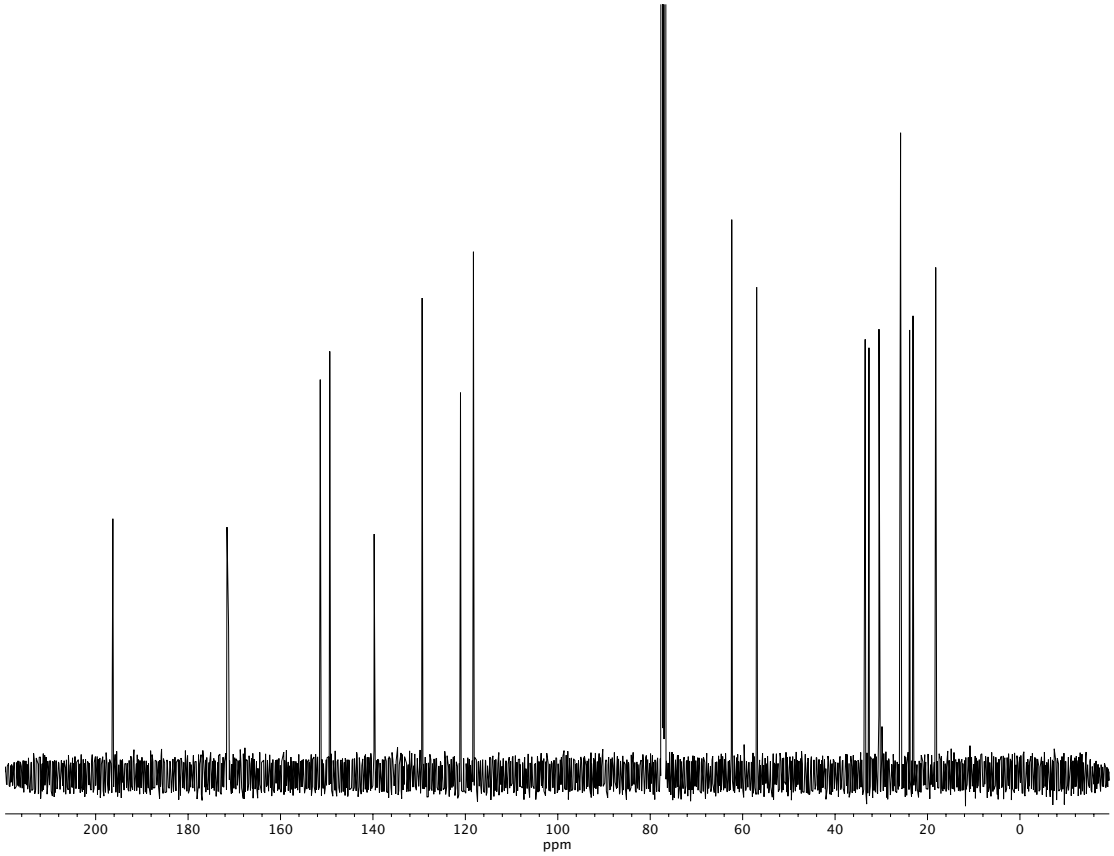


Figure A1.110. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10i****.*

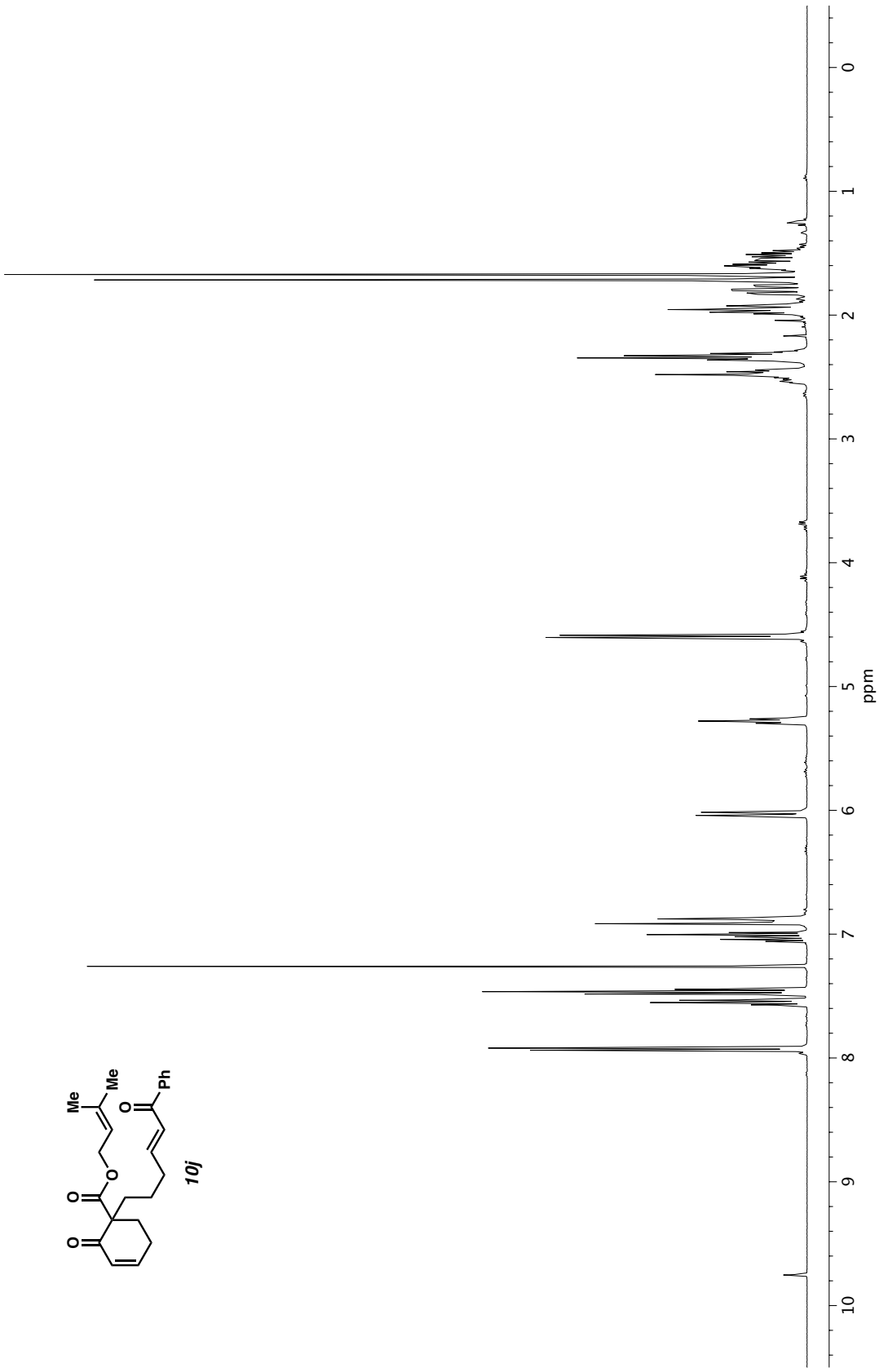


Figure A1.111. *^1H NMR (400 MHz, $CDCl_3$) of compound **10j**.*

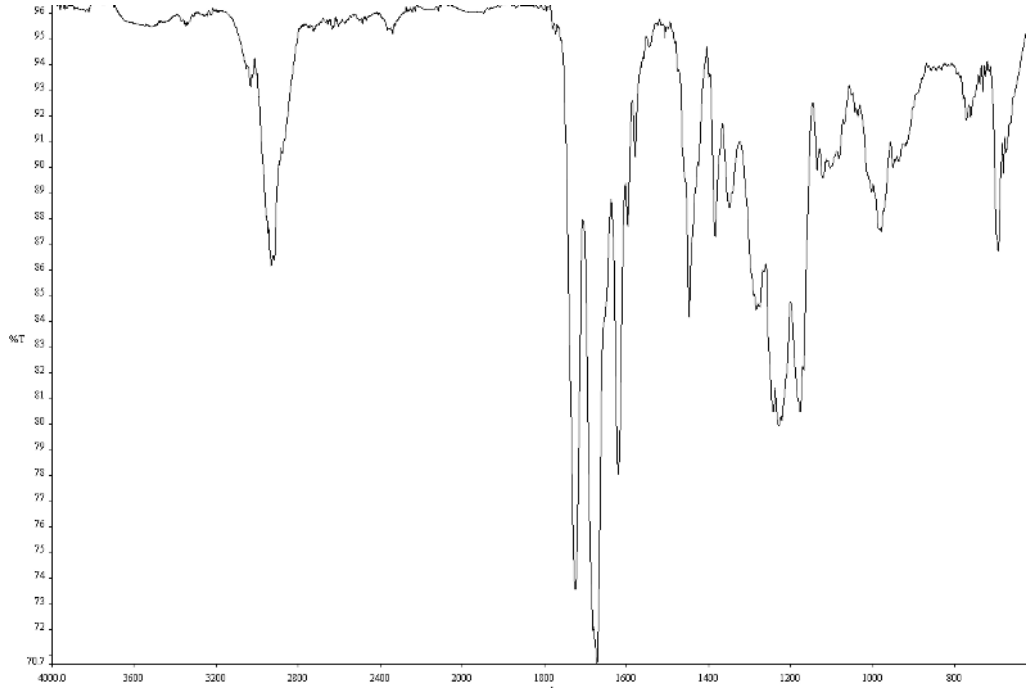


Figure A1.112. *Infrared spectrum (Thin Film, NaCl) of compound* ***10j****.*

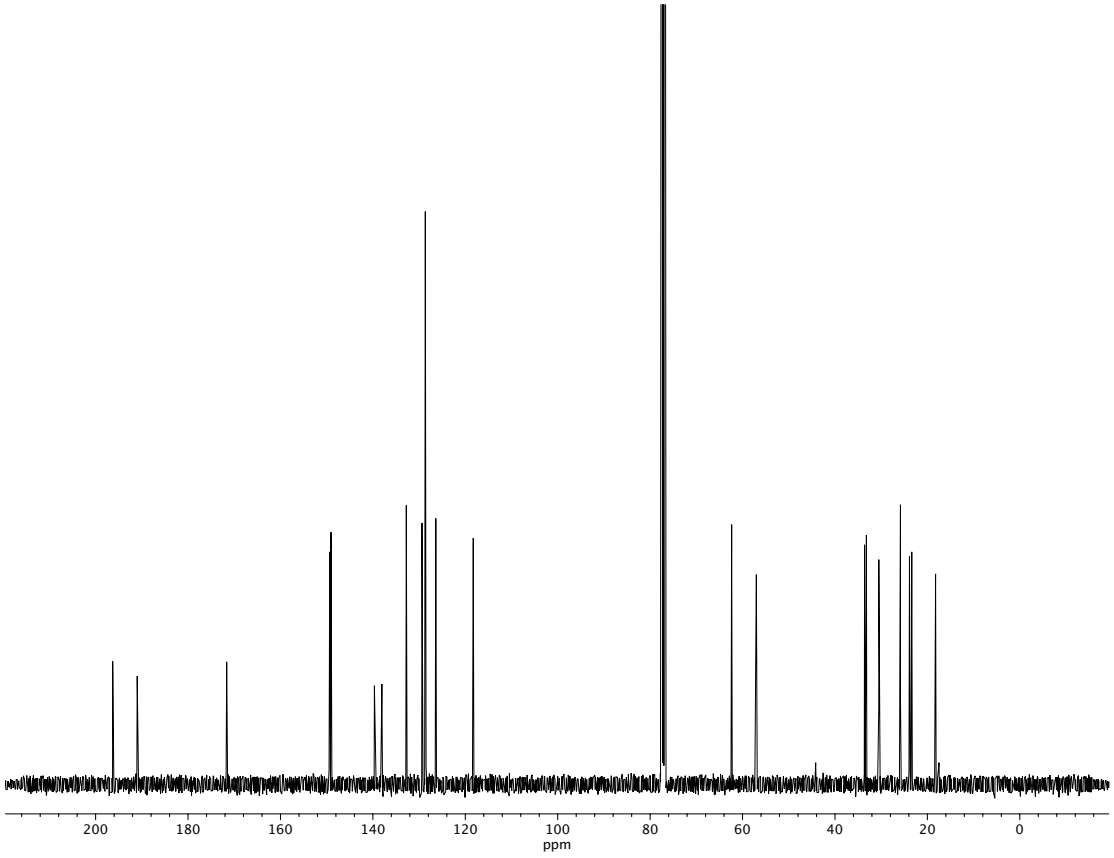


Figure A1.113. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10j****.*

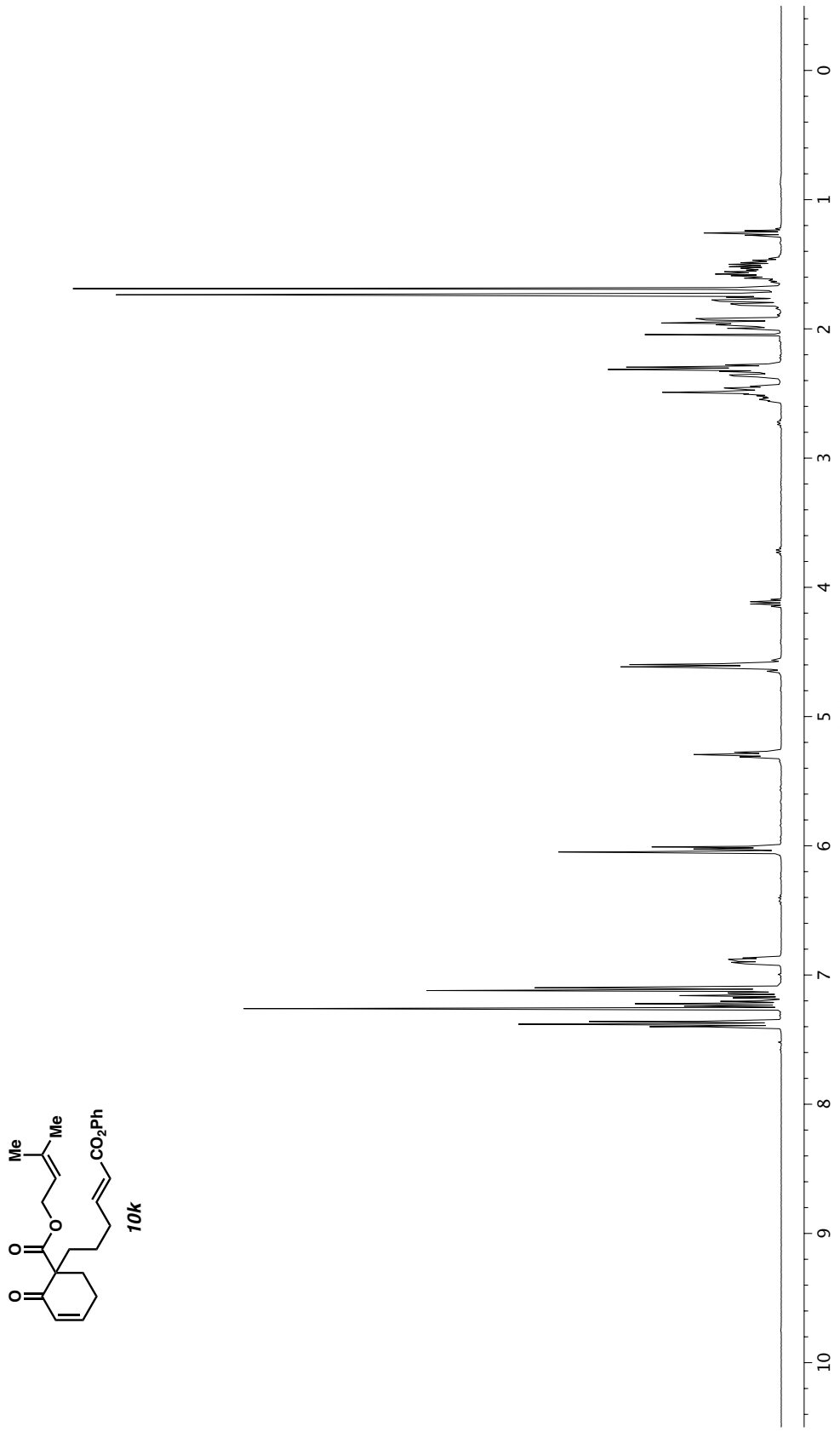


Figure A1.114. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***10k****.*

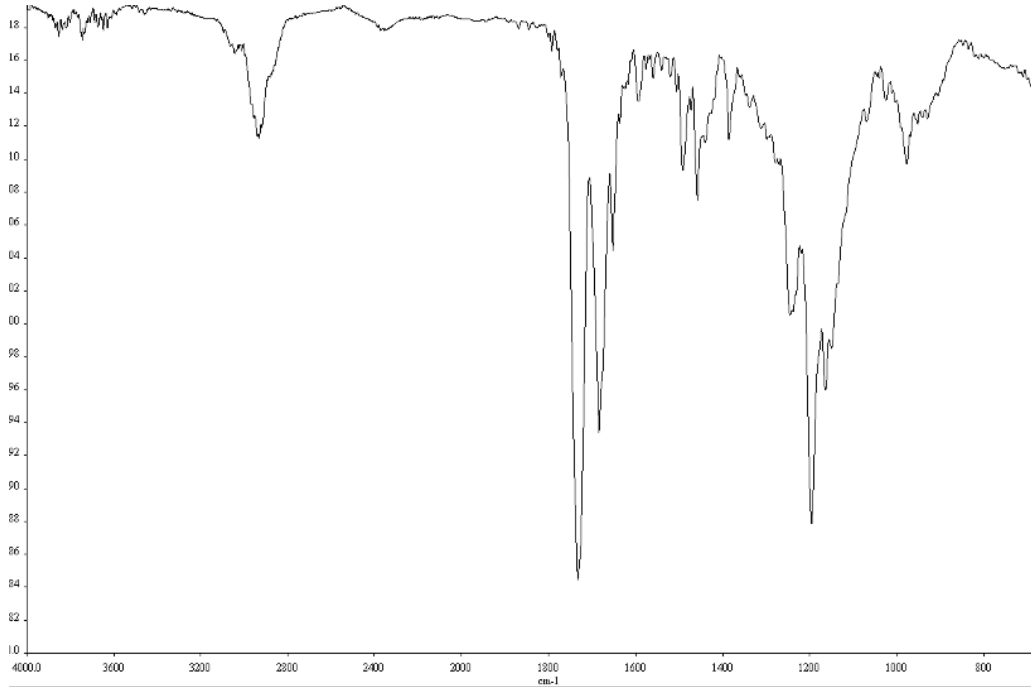


Figure A1.115. *Infrared spectrum (Thin Film, NaCl) of compound* ***10k****.*

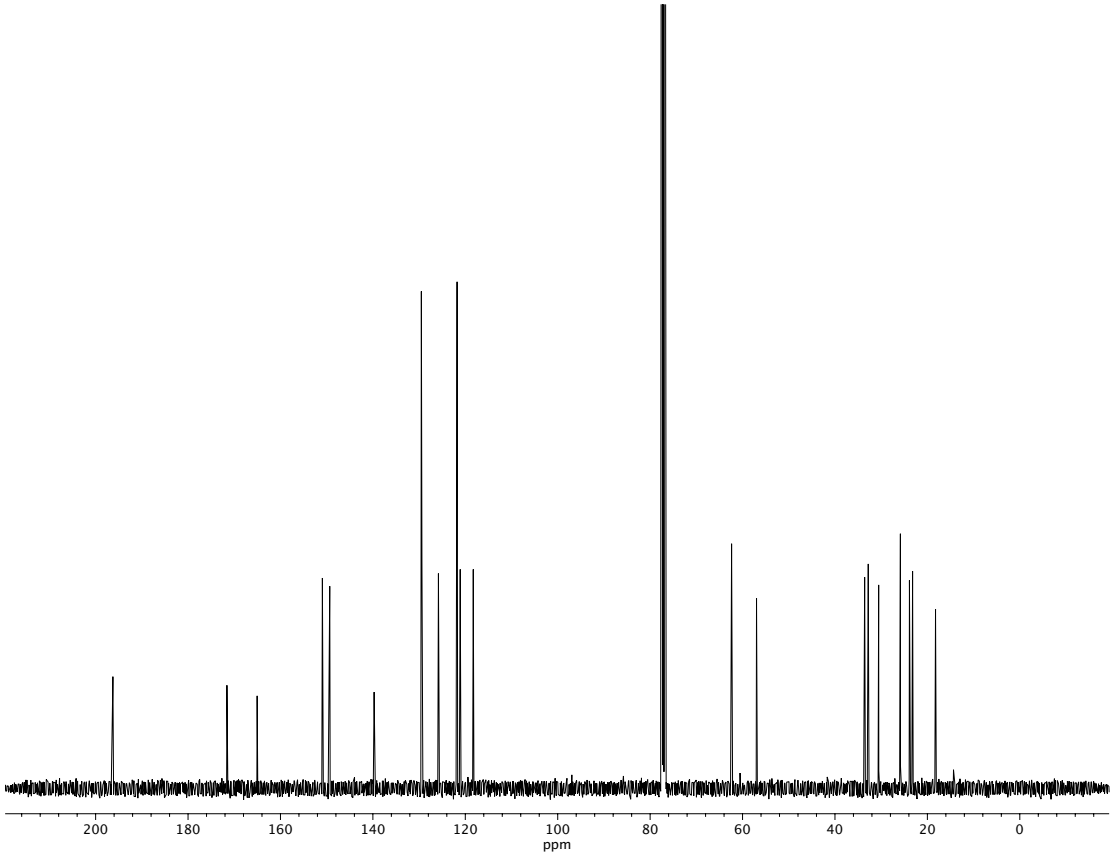


Figure A1.116. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10k****.*

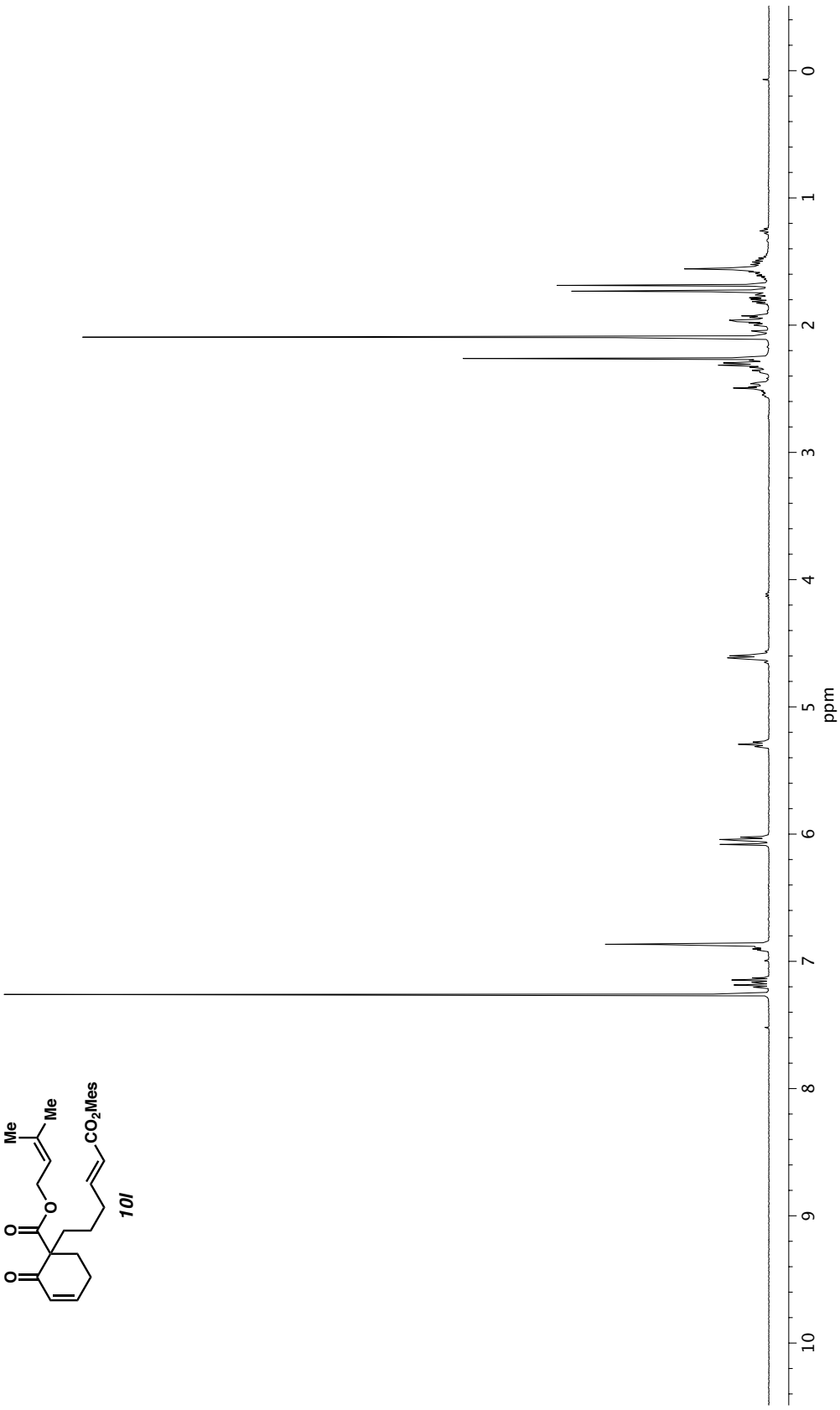


Figure A1.117. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***10l****.*

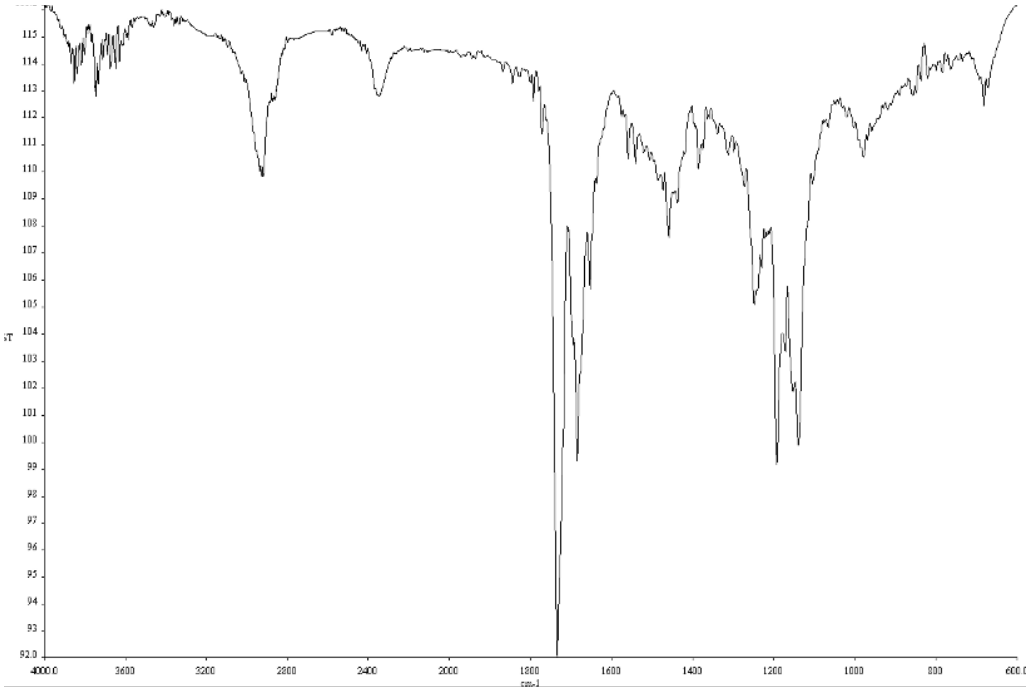


Figure A1.118. *Infrared spectrum (Thin Film, NaCl) of compound* ***10l****.*

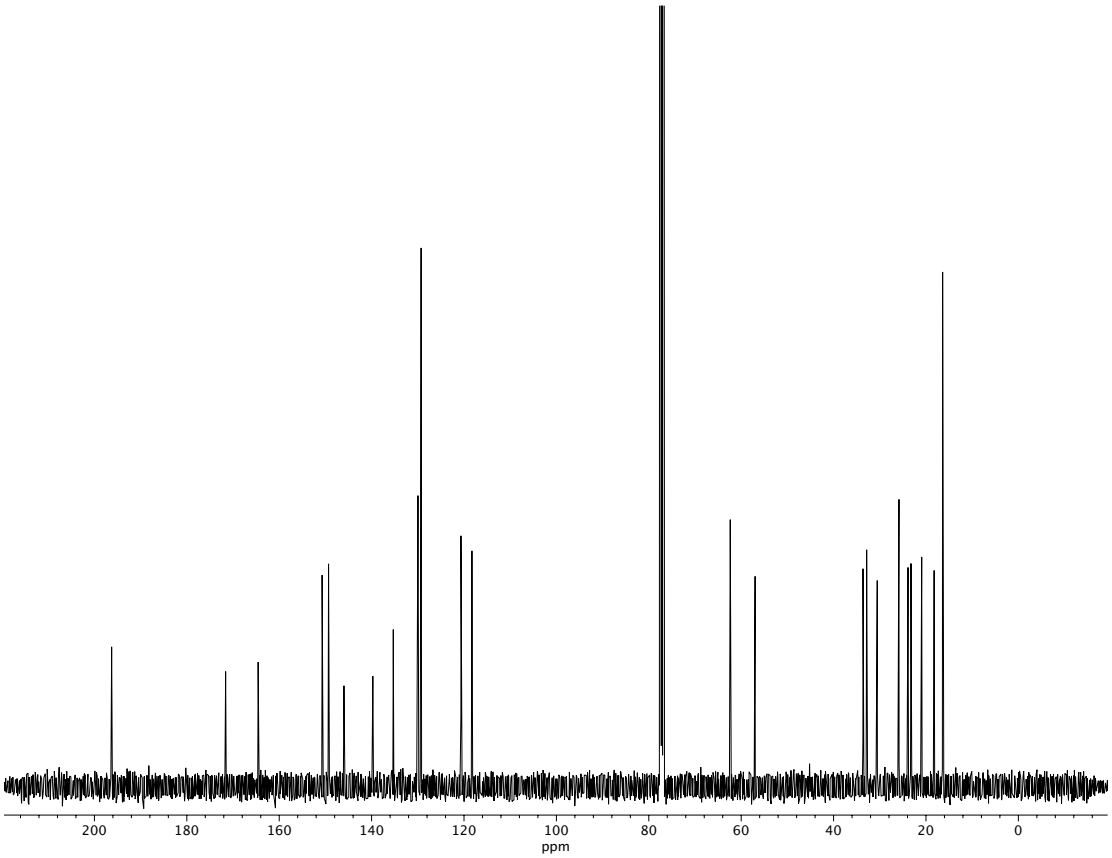


Figure A1.119. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10l****.*

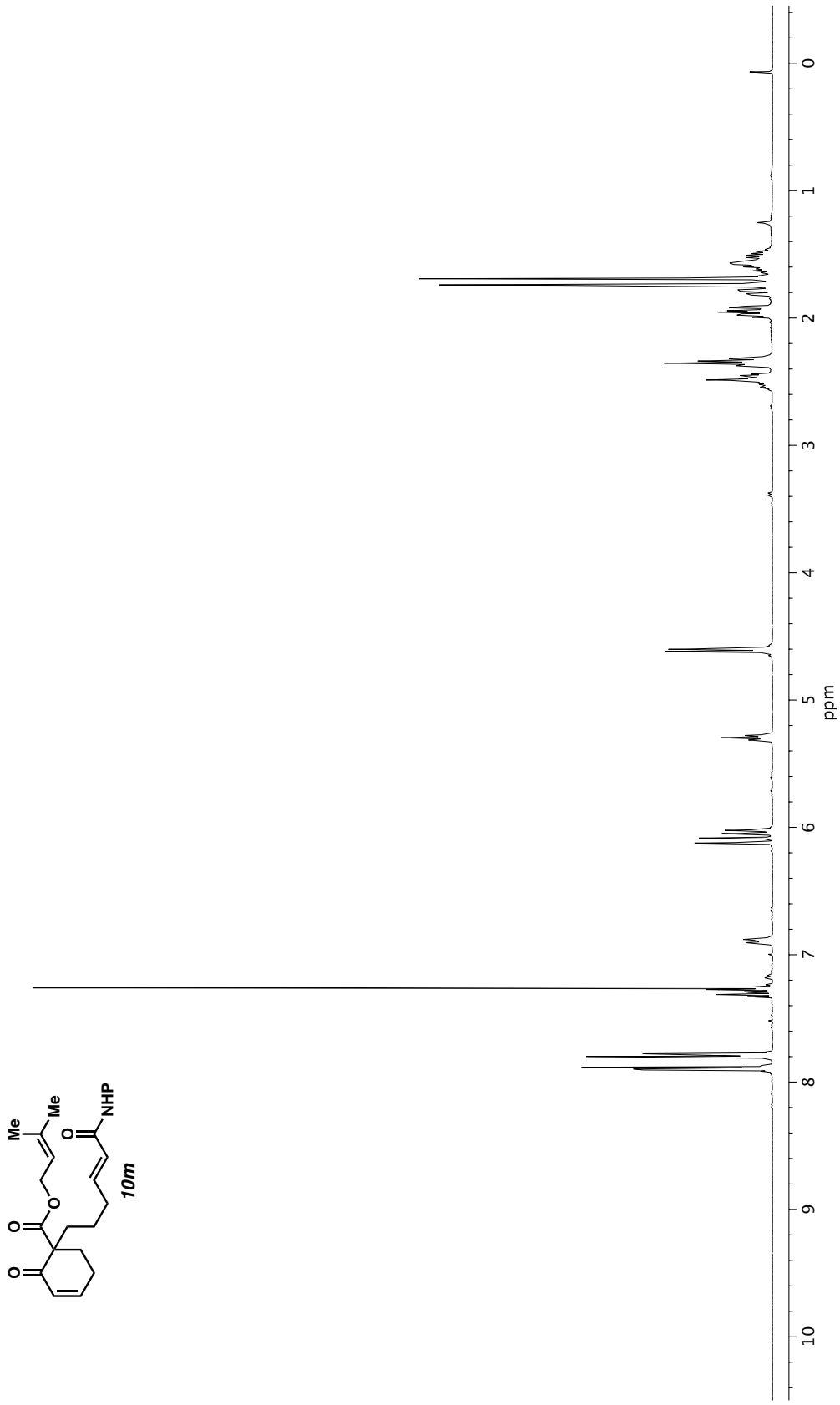


Figure A1.120. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***10m****.*

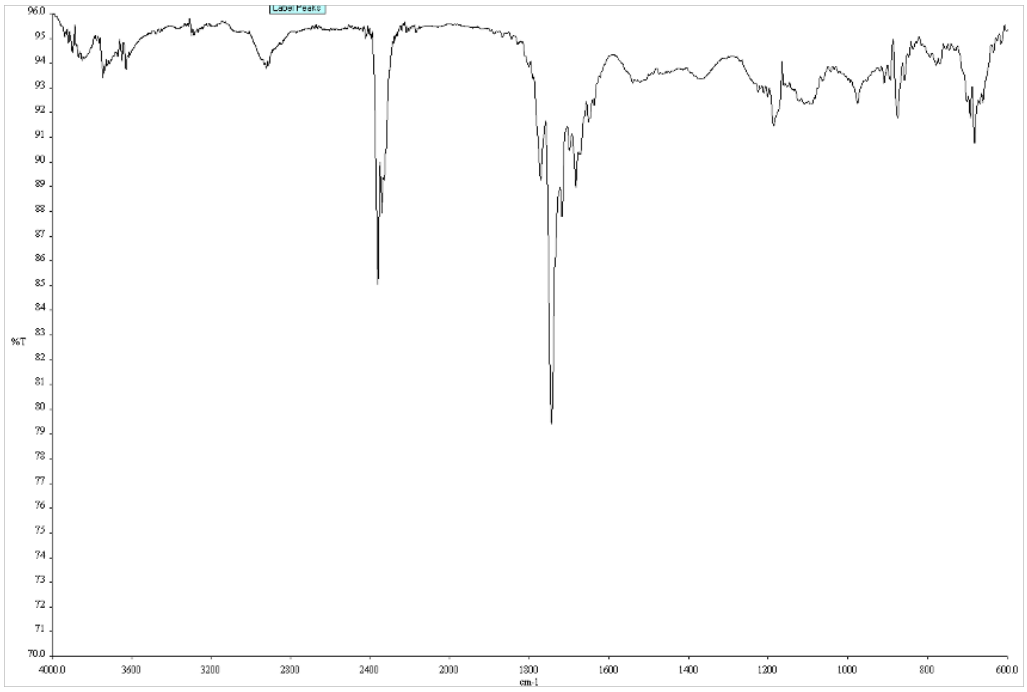


Figure A1.121. *Infrared spectrum (Thin Film, NaCl) of compound* ***10m****.*

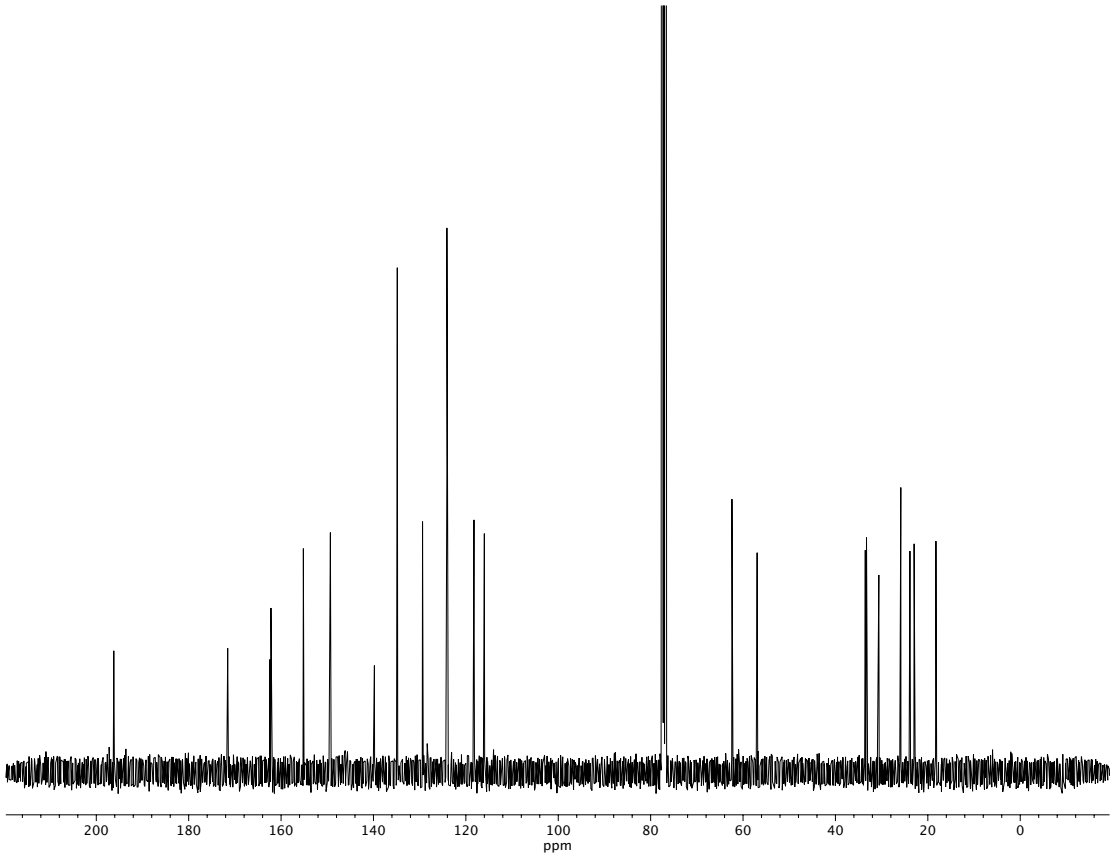


Figure A1.122. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10m****.*

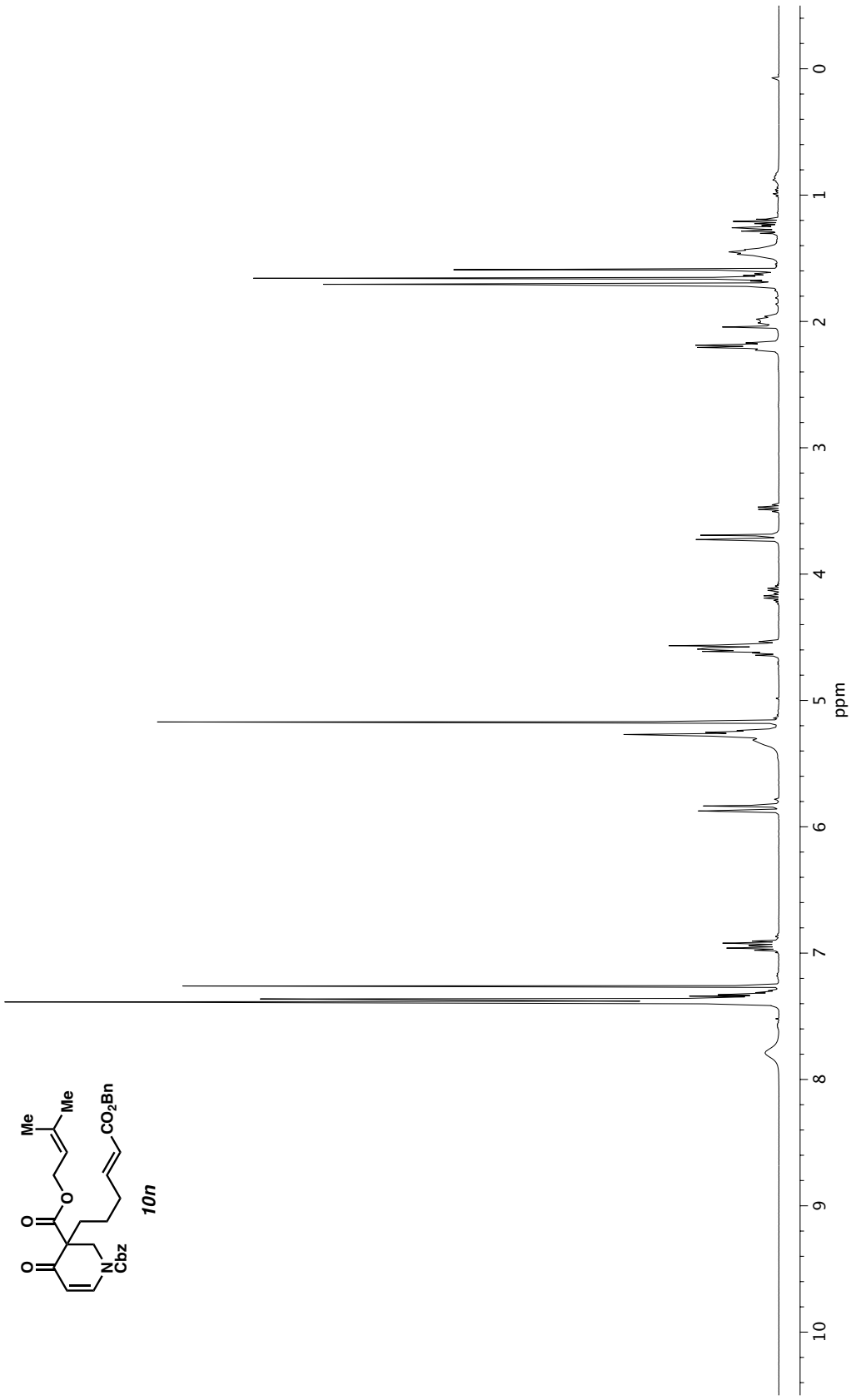


Figure A1.123. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***10n****.*

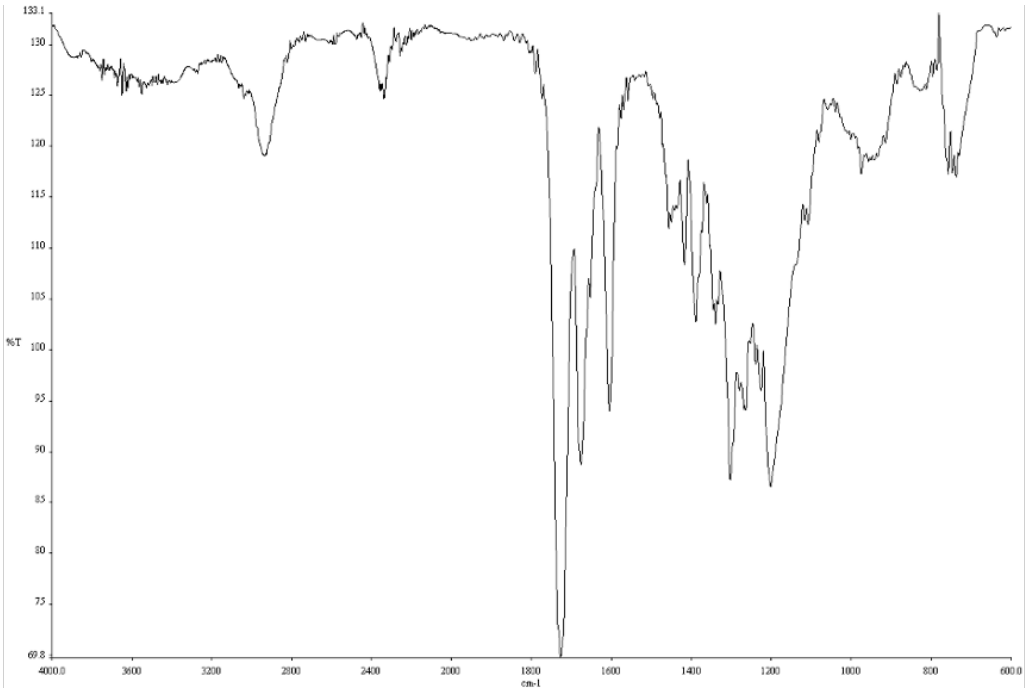


Figure A1.124. *Infrared spectrum (Thin Film, NaCl) of compound* ***10n****.*

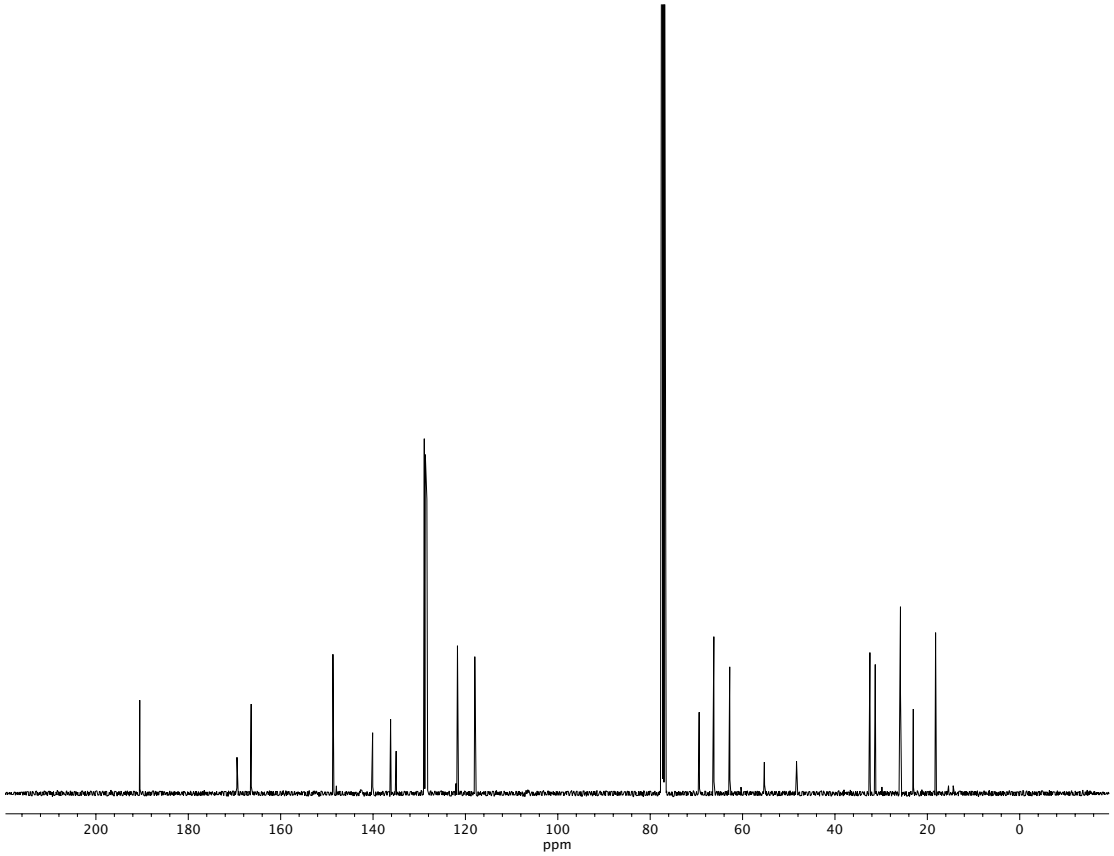


Figure A1.125. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10n****.*

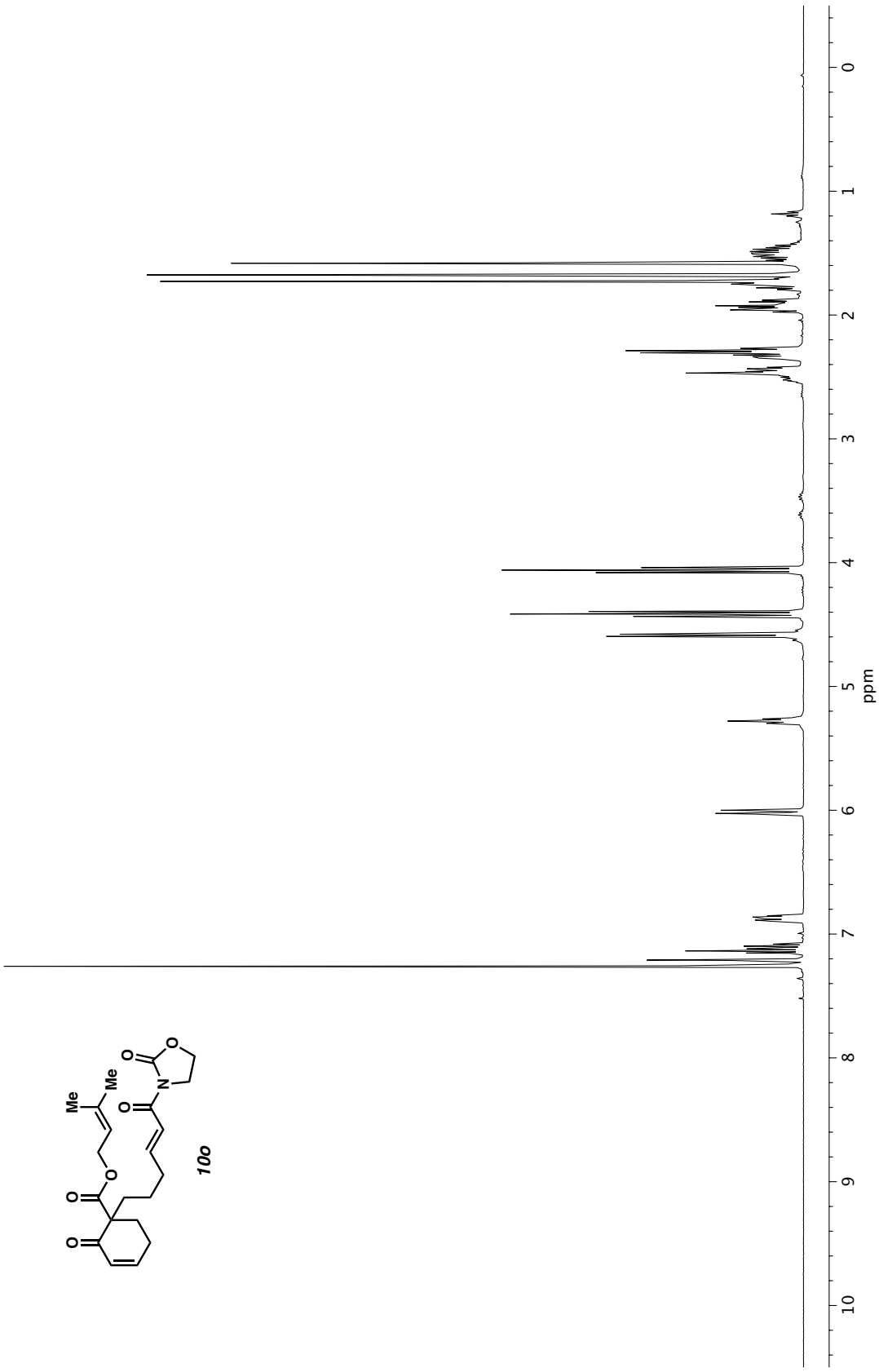


Figure A1.126. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***10o***.

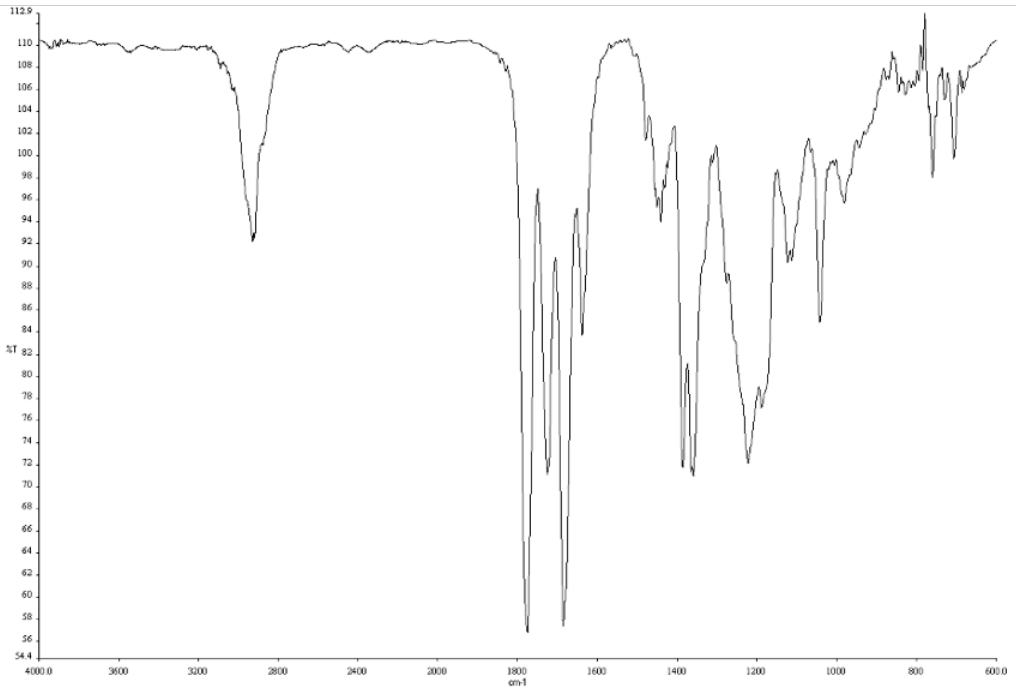


Figure A1.127. *Infrared spectrum (Thin Film, NaCl) of compound* ***10o****.*

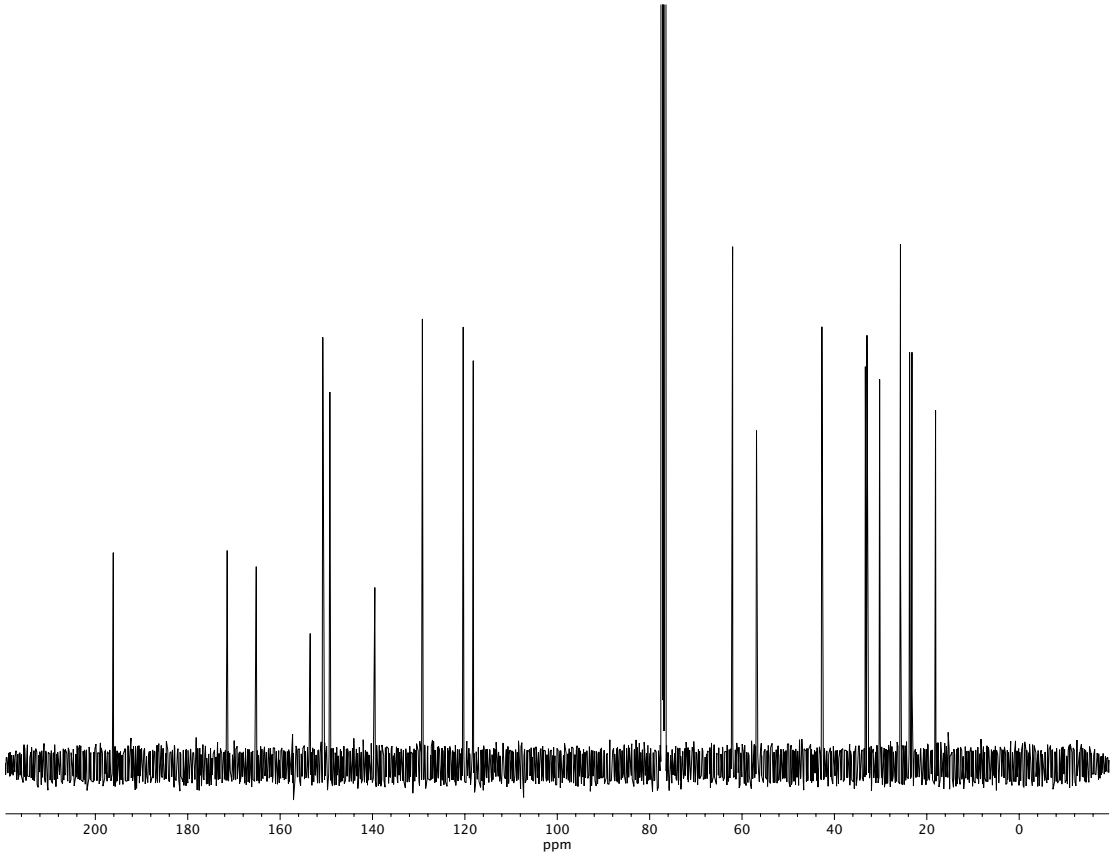


Figure A1.128. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10o****.*

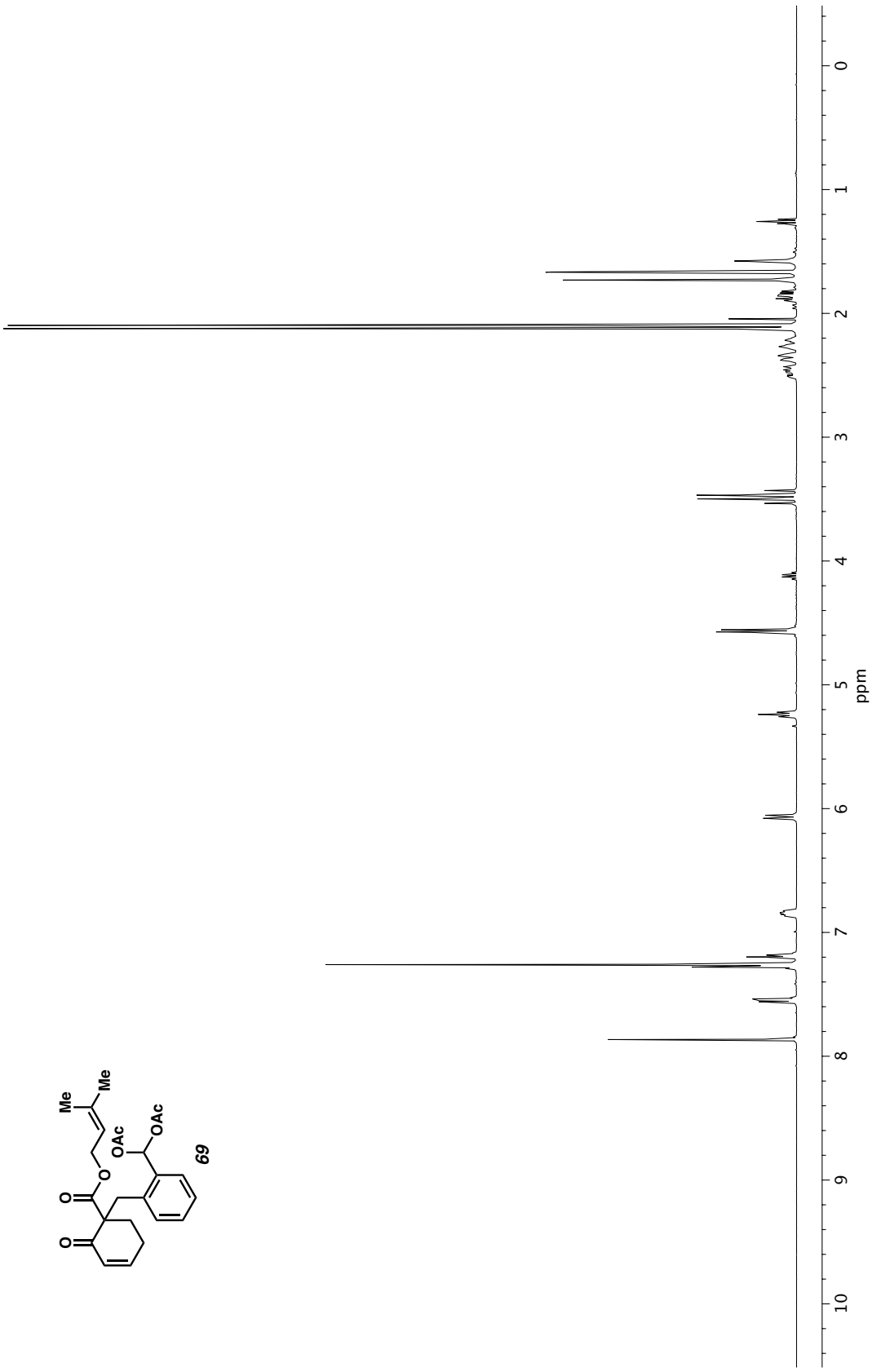


Figure A1.129. *^1H NMR (400 MHz, $CDCl_3$) of compound **69**.*

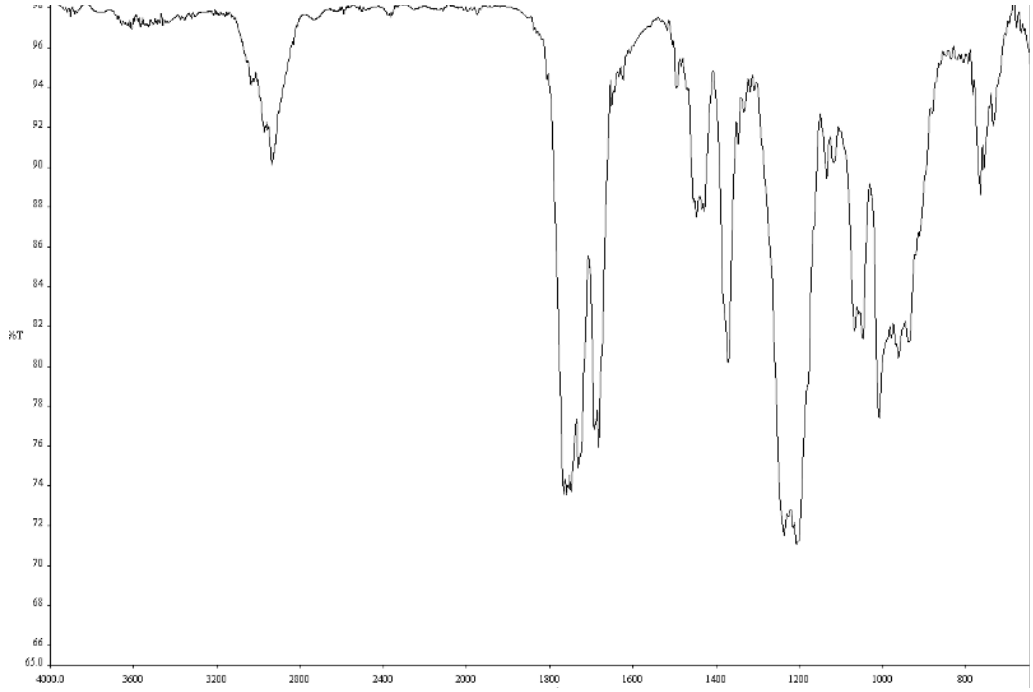


Figure A1.130. *Infrared spectrum (Thin Film, NaCl) of compound* ***69****.*

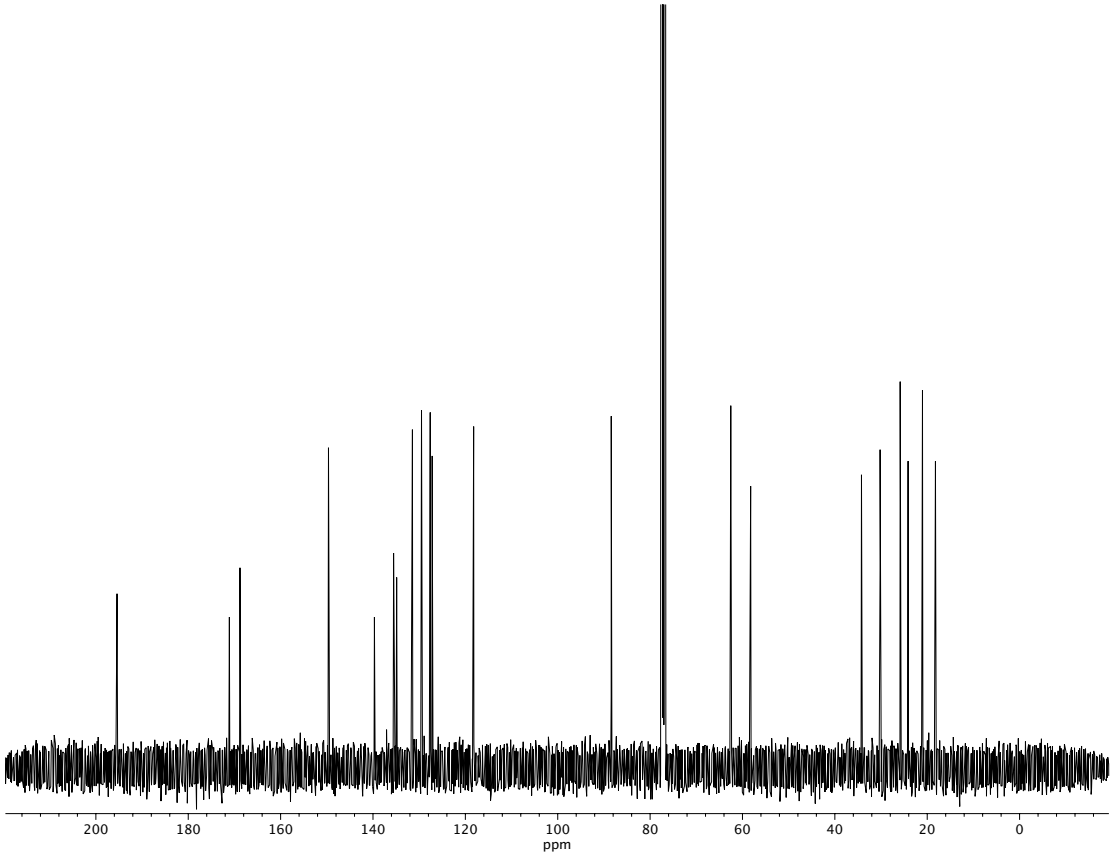


Figure A1.131. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***69****.*

Figure A1.132. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***10p***.

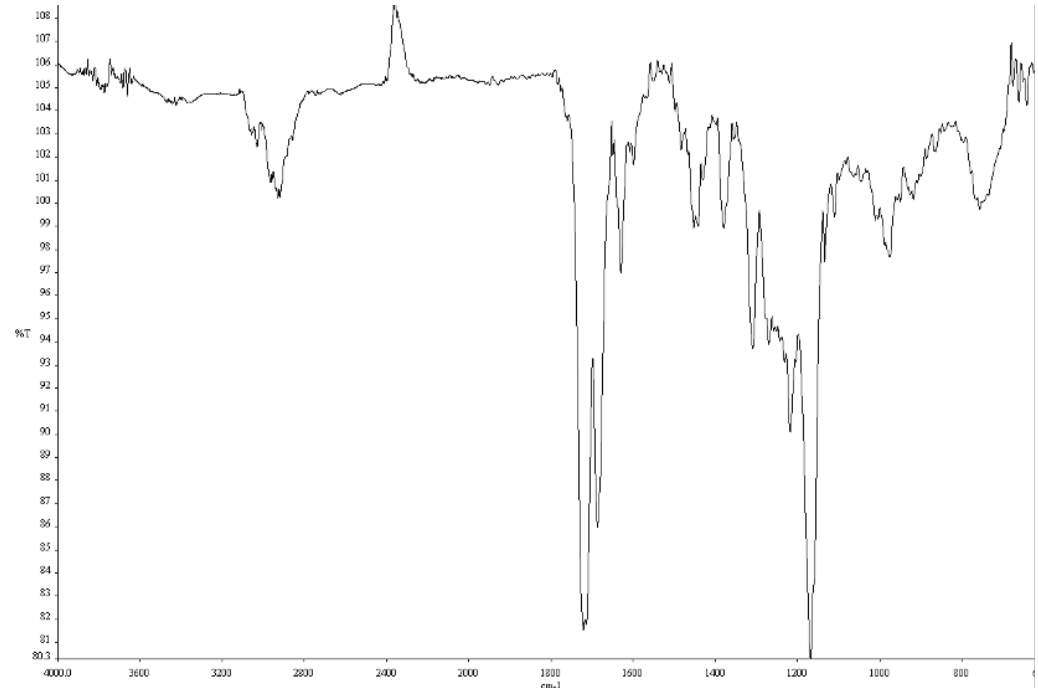


Figure A1.133. *Infrared spectrum (Thin Film, NaCl) of compound* ***10p****.*

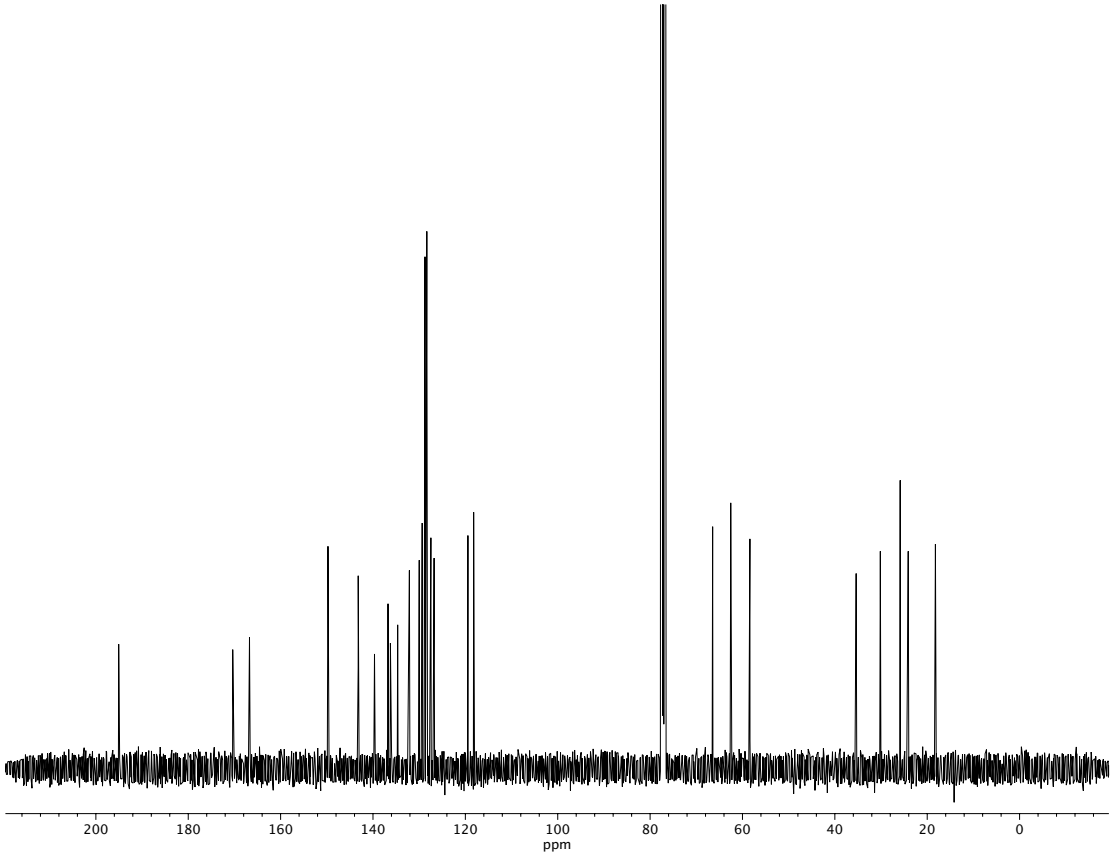


Figure A1.134. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10p****.*

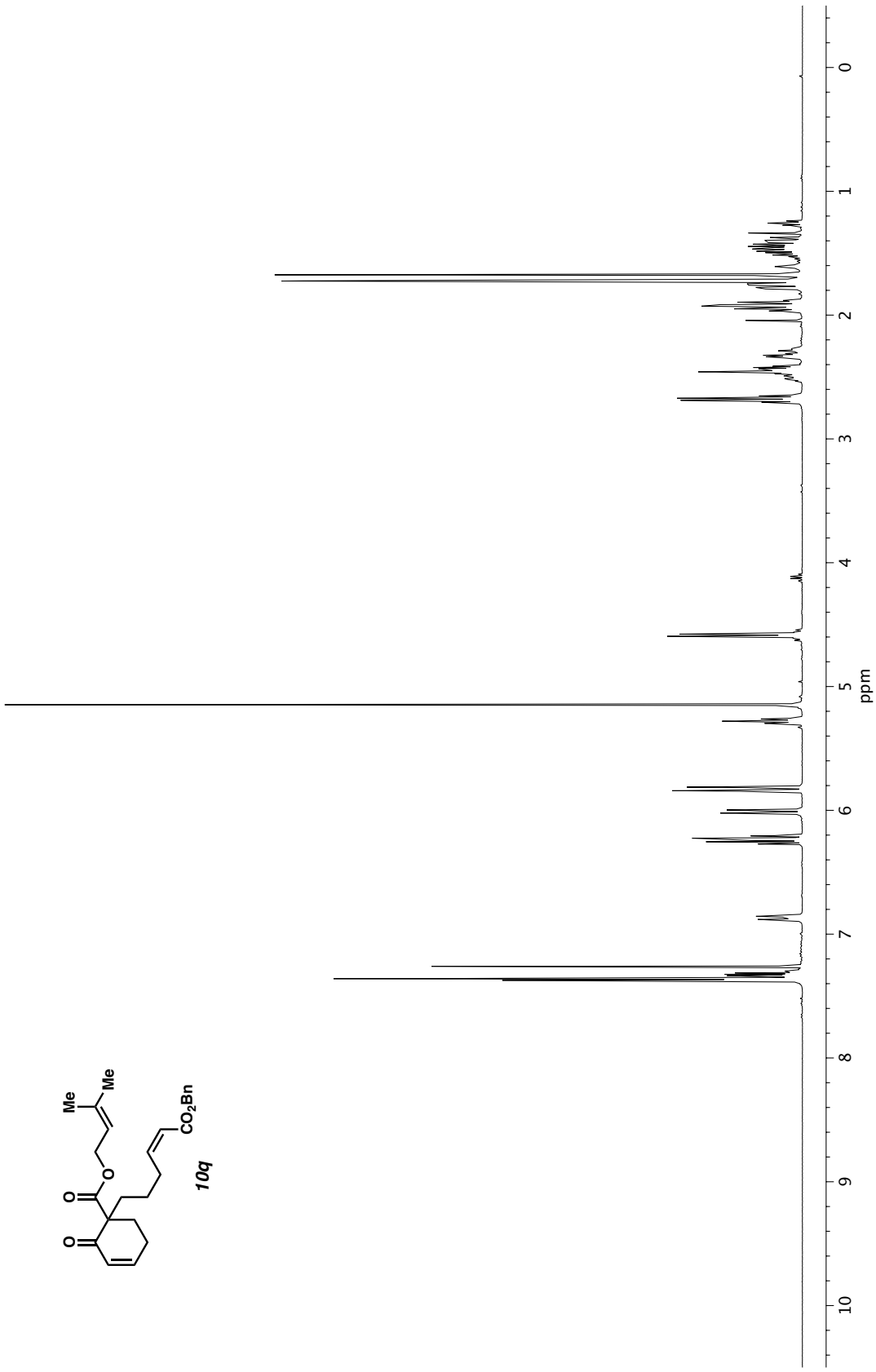


Figure A1.135. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***10q***.

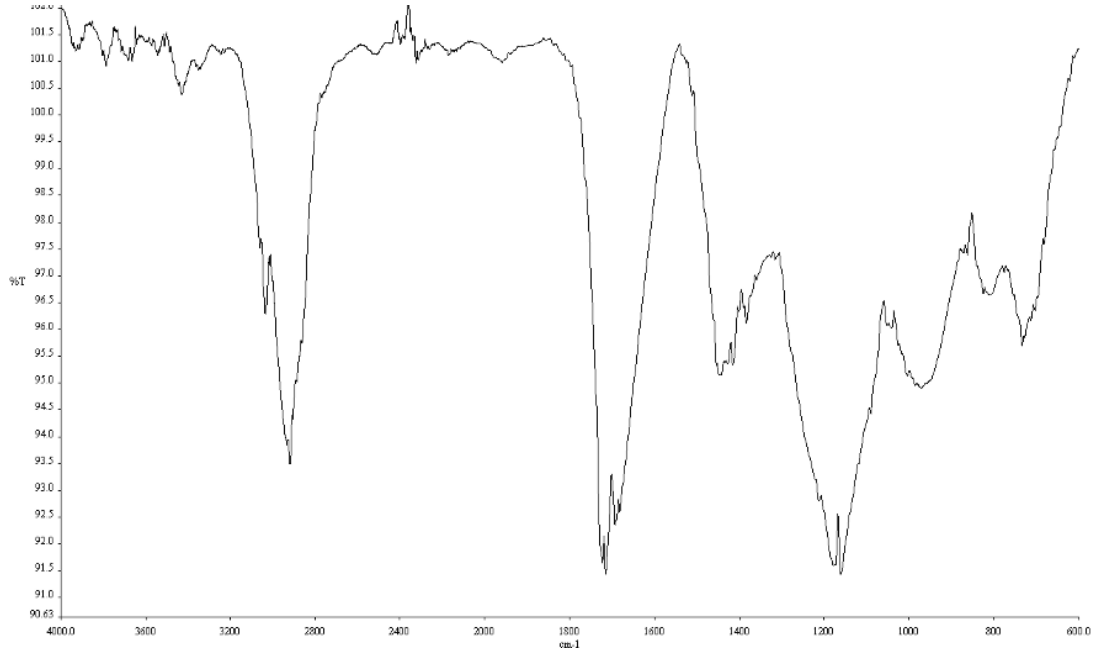


Figure A1.136. *Infrared spectrum (Thin Film, NaCl) of compound* ***10q****.*

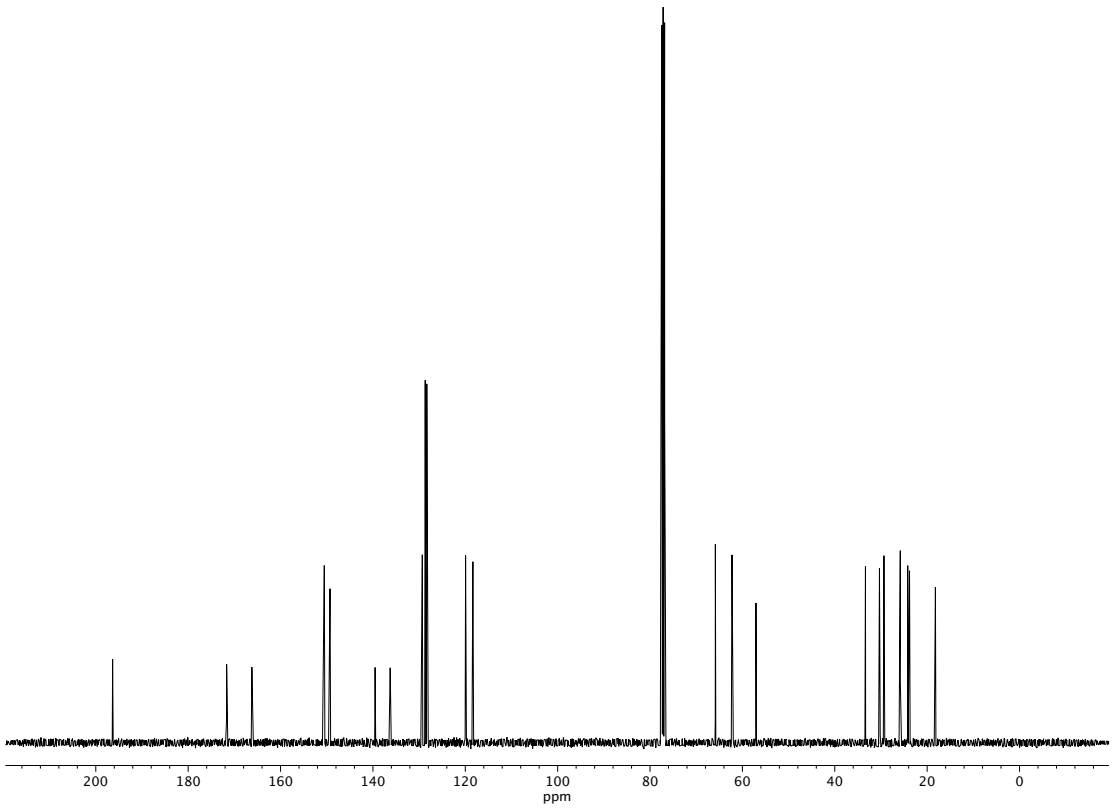


Figure A1.137. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10q****.*

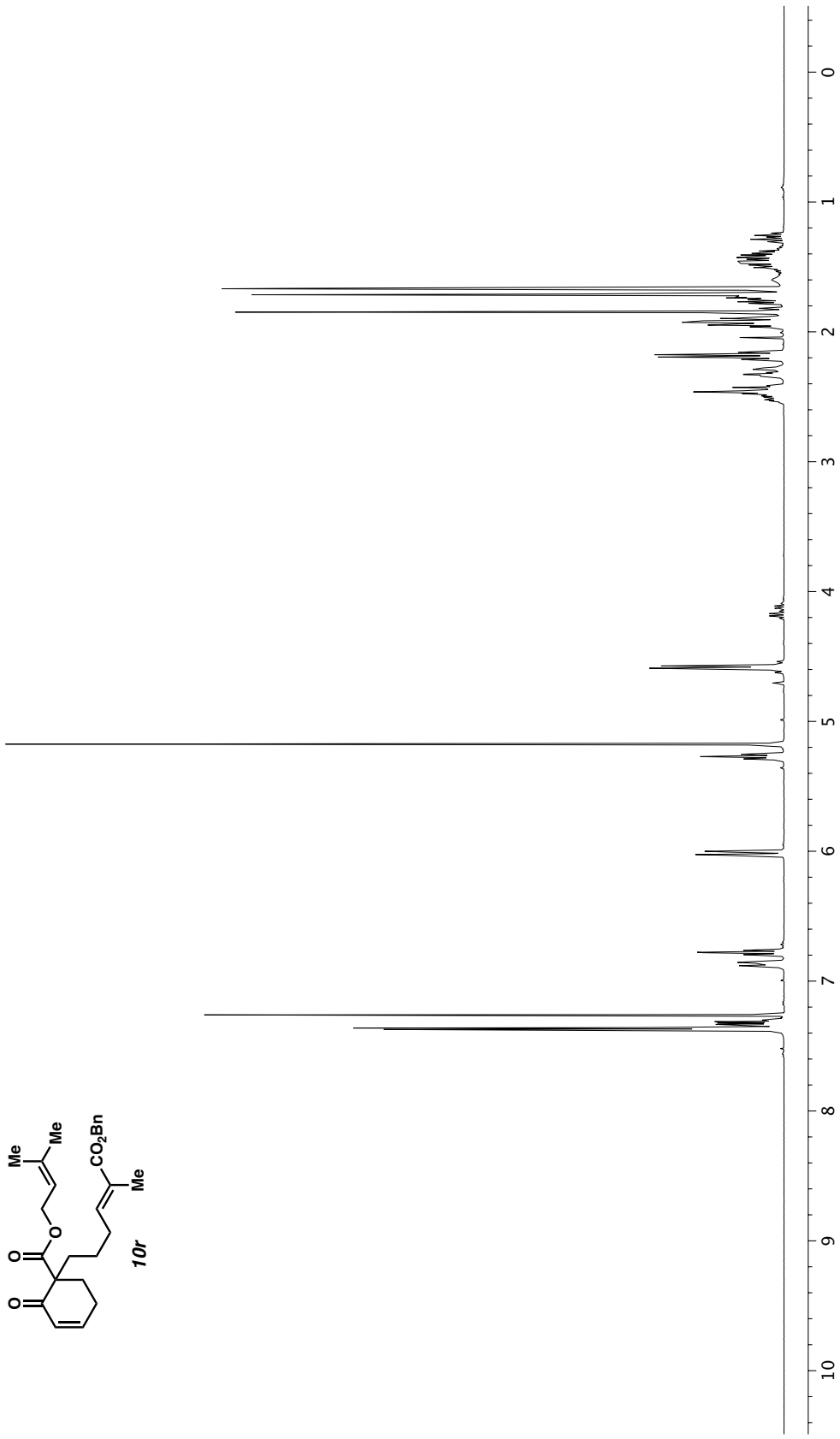


Figure A1.138. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***10r****.*

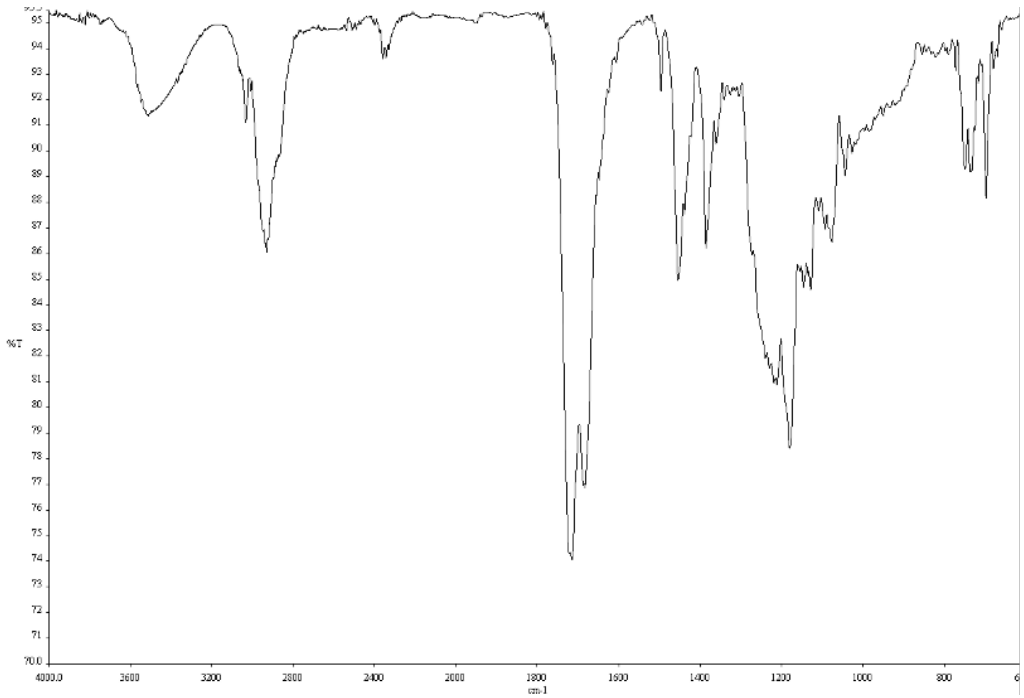


Figure A1.139. *Infrared spectrum (Thin Film, NaCl) of compound* ***10r****.*

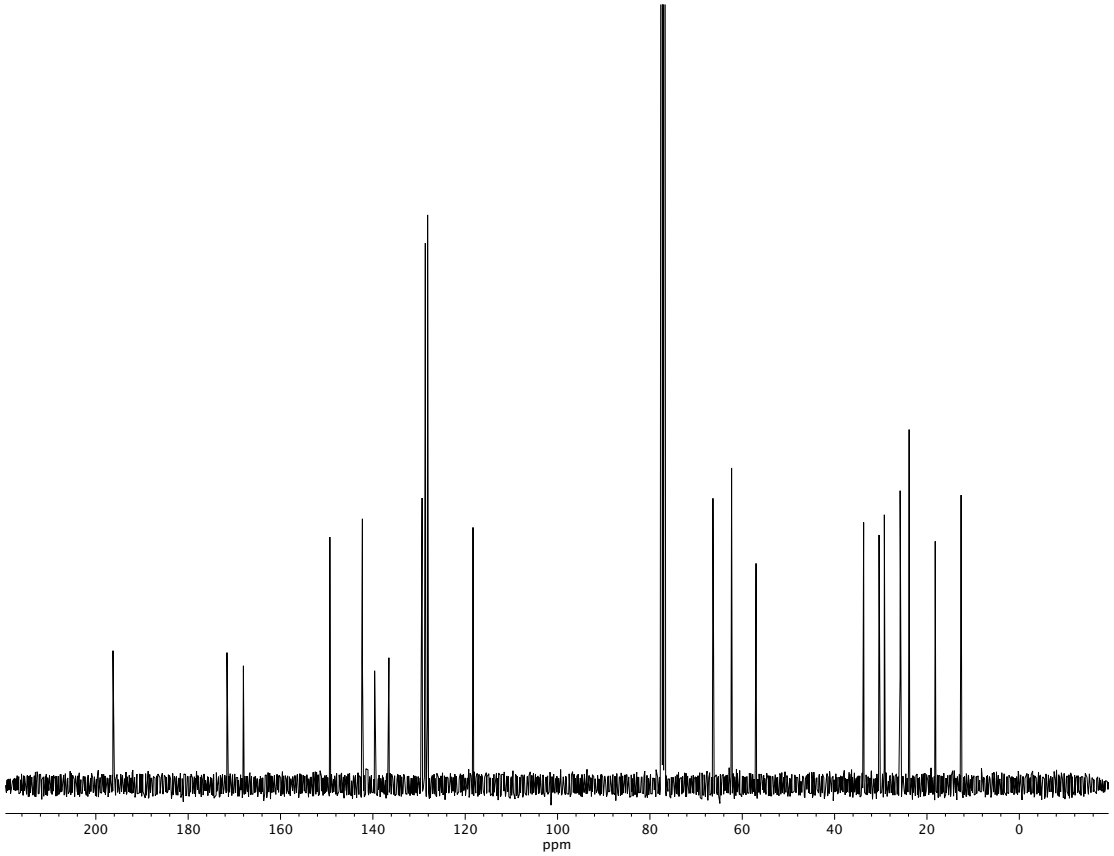


Figure A1.140. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10r****.*

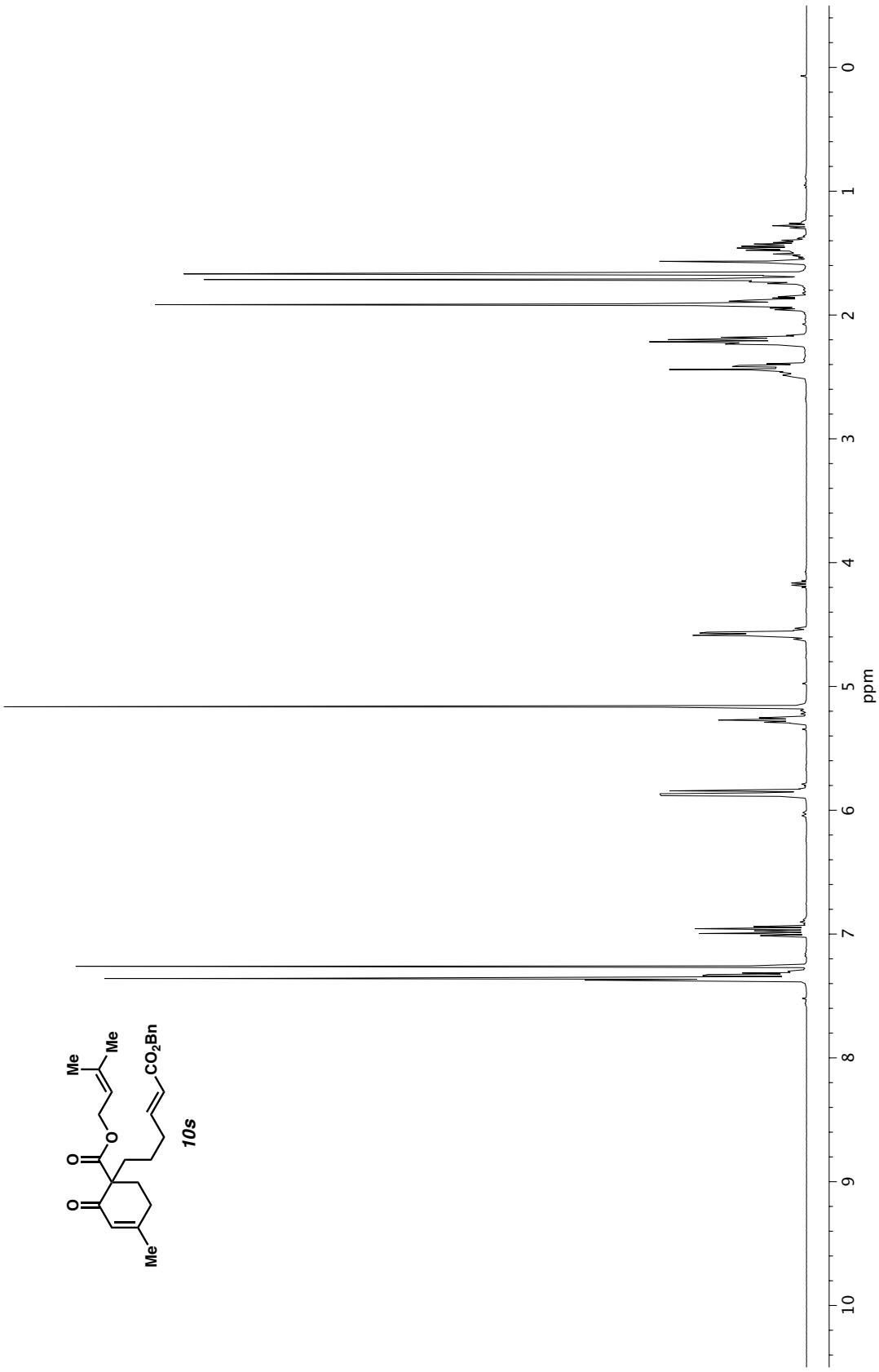


Figure A1.141. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***10s****.*

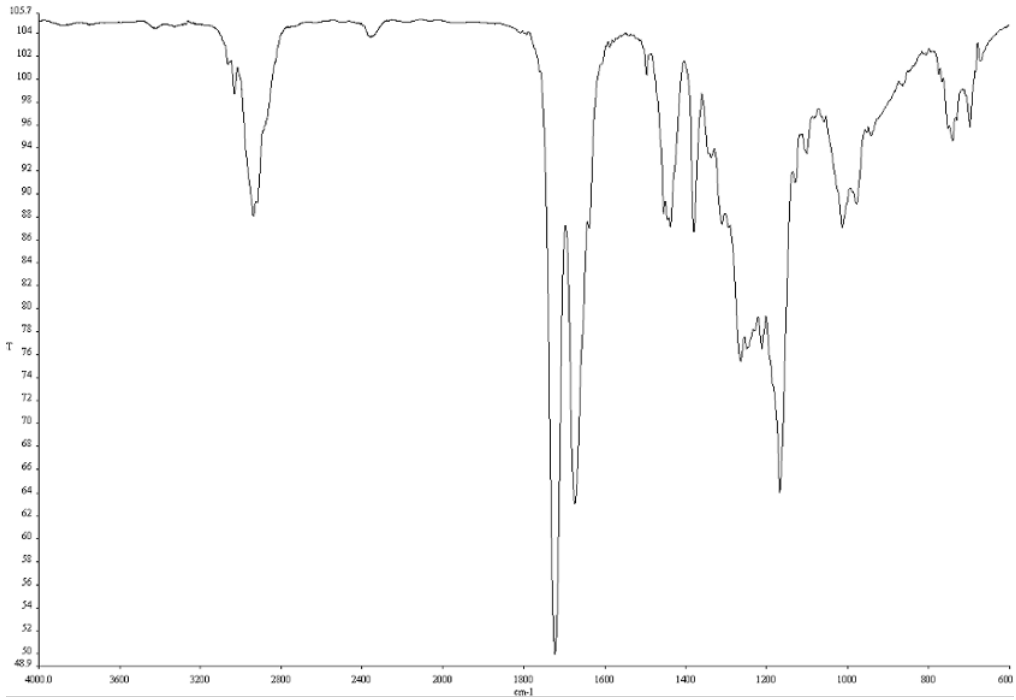


Figure A1.142. *Infrared spectrum (Thin Film, NaCl) of compound* ***10s****.*

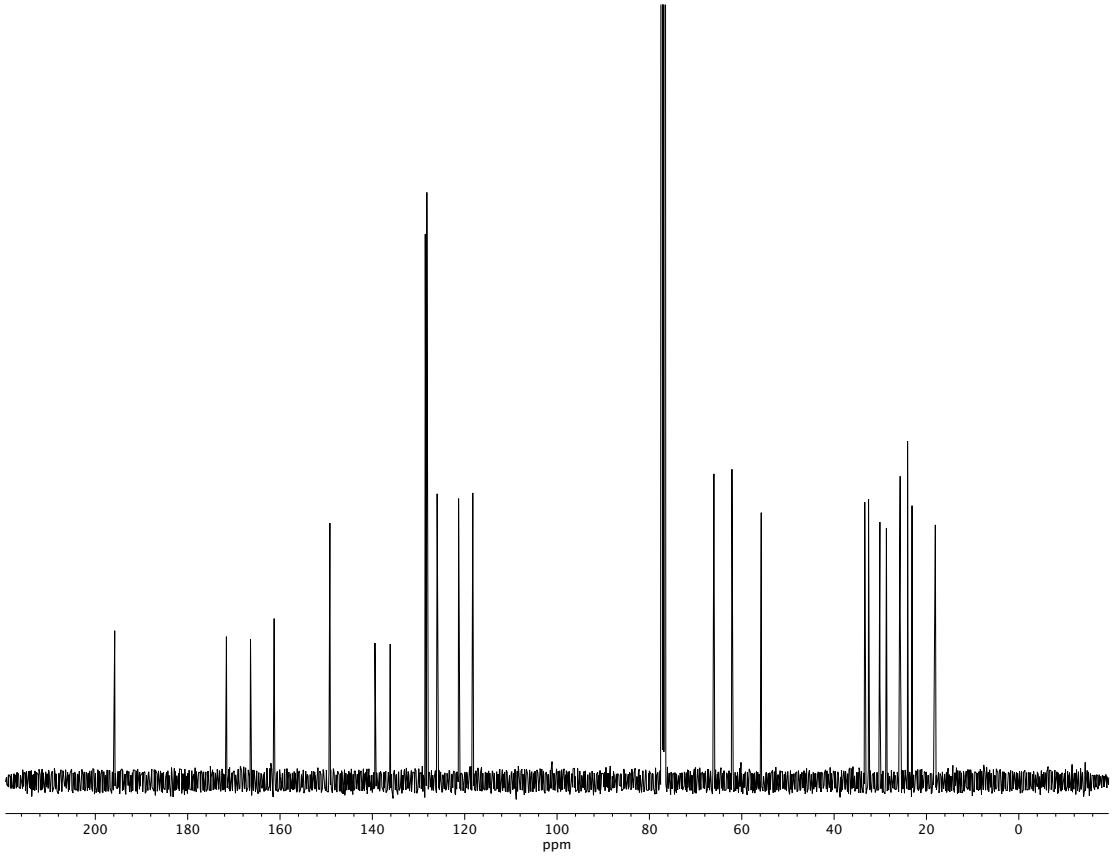


Figure A1.143. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10s****.*

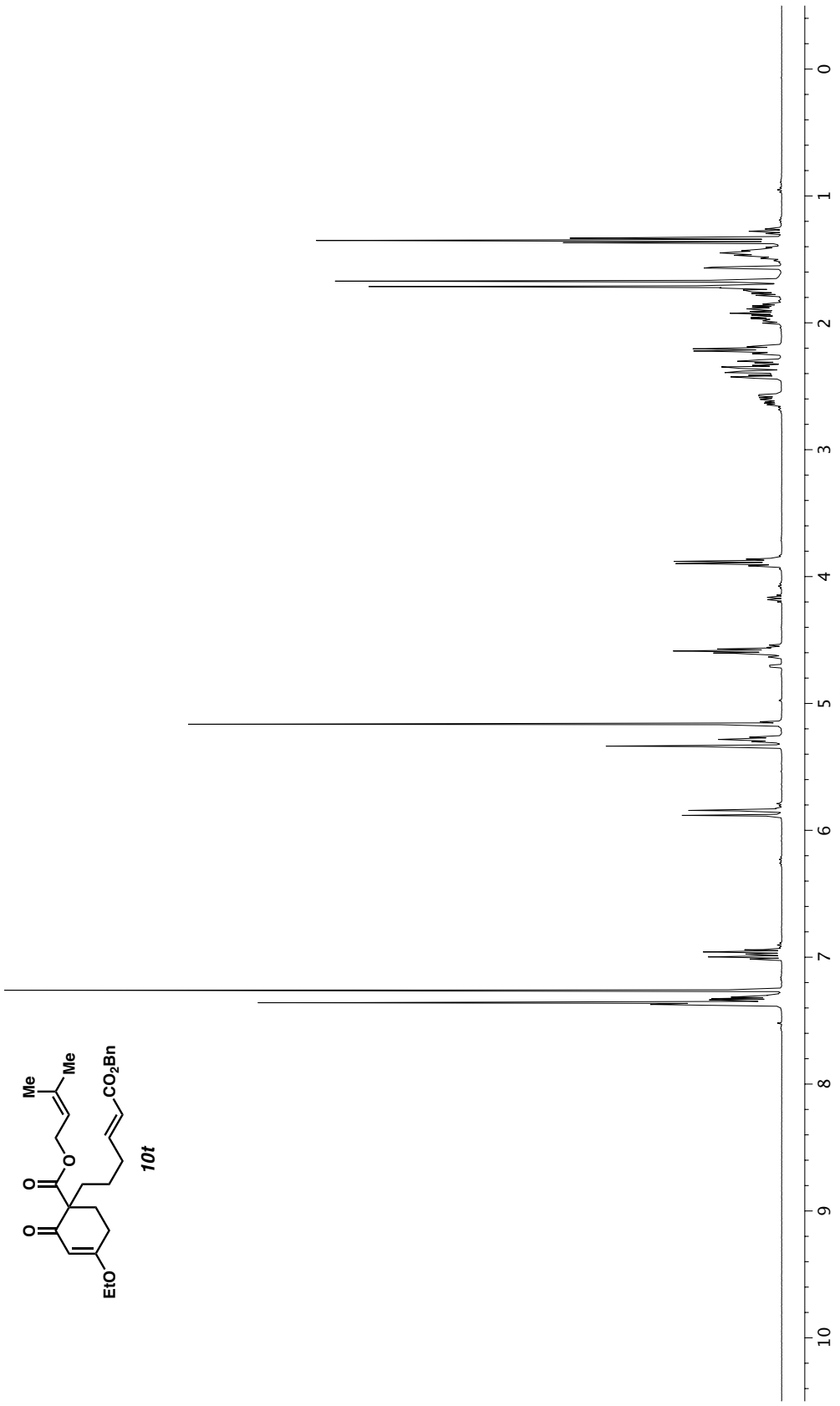


Figure A1.144. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***10t****.*

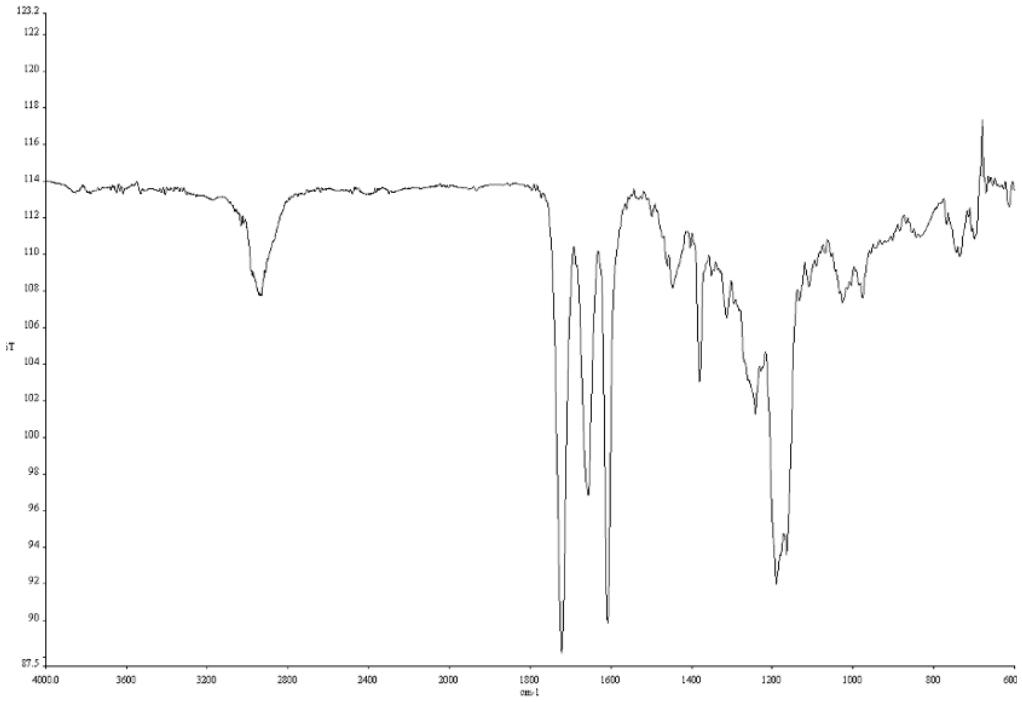


Figure A1.145. *Infrared spectrum (Thin Film, NaCl) of compound* ***10t****.*

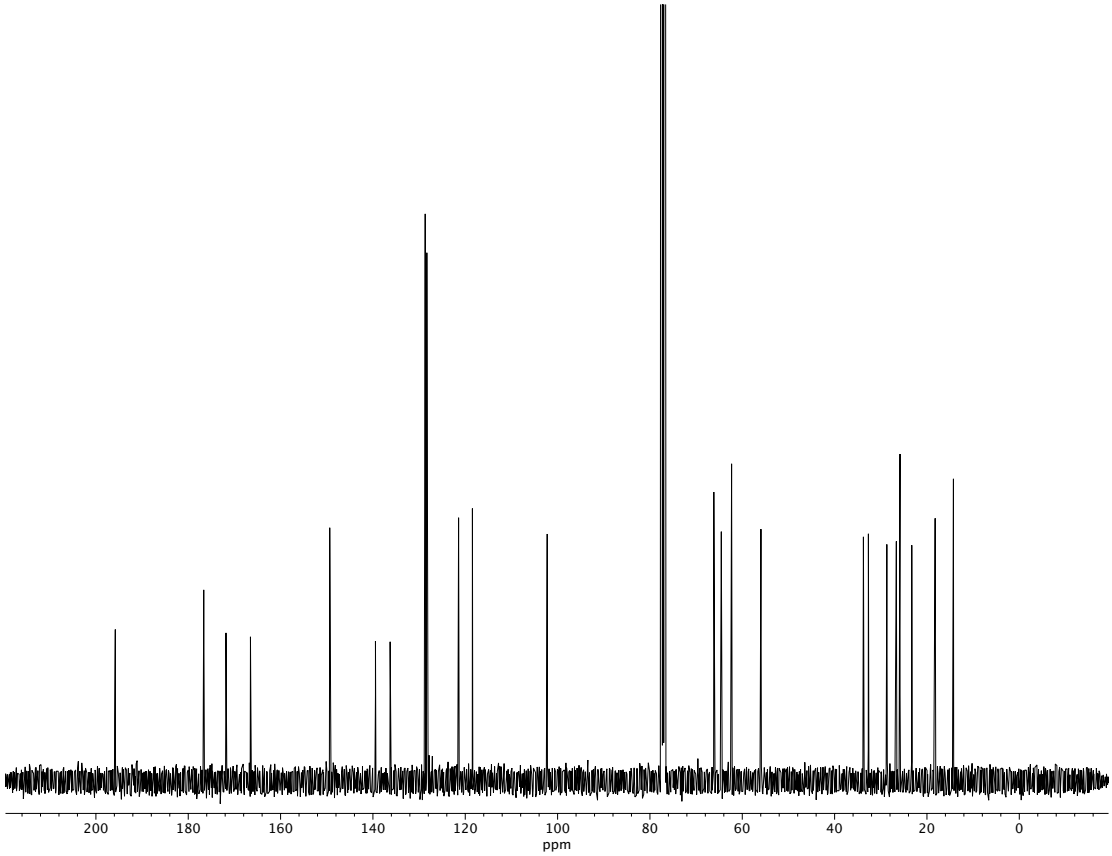


Figure A1.146. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10t****.*

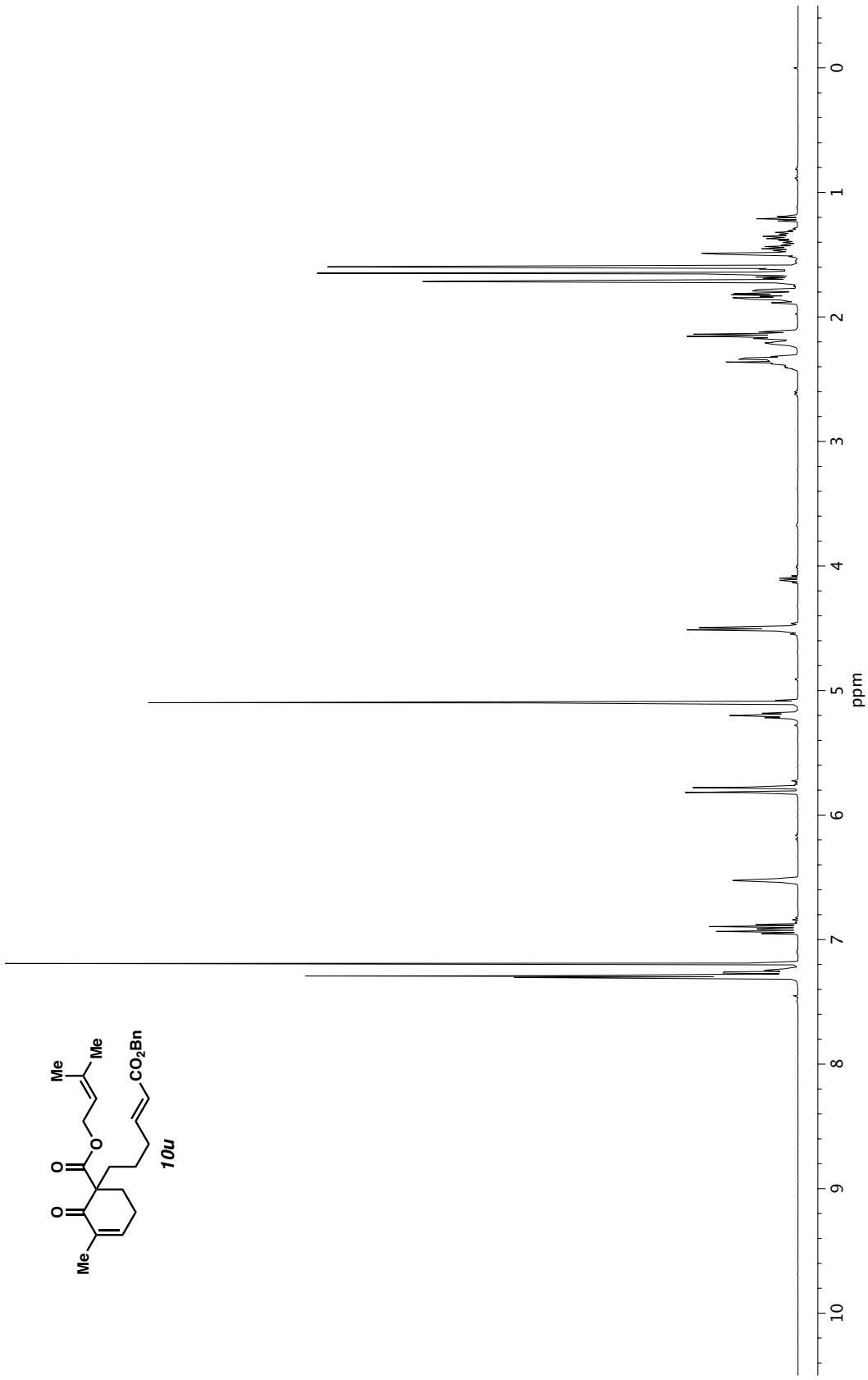


Figure A1.147. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***10u****.*

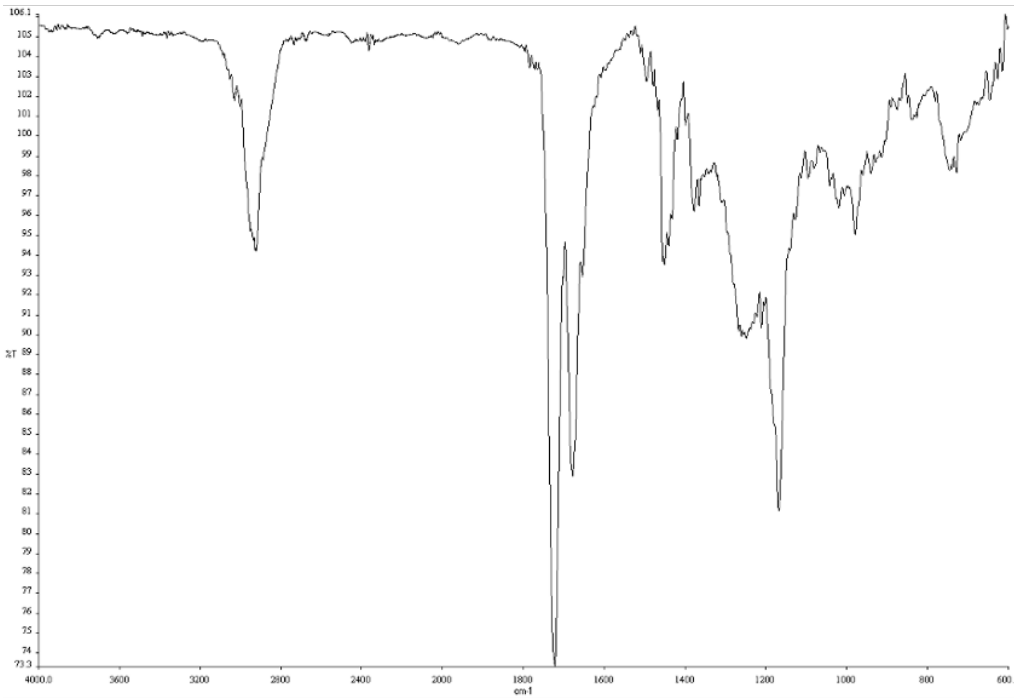


Figure A1.148. *Infrared spectrum (Thin Film, NaCl) of compound* ***10u****.*

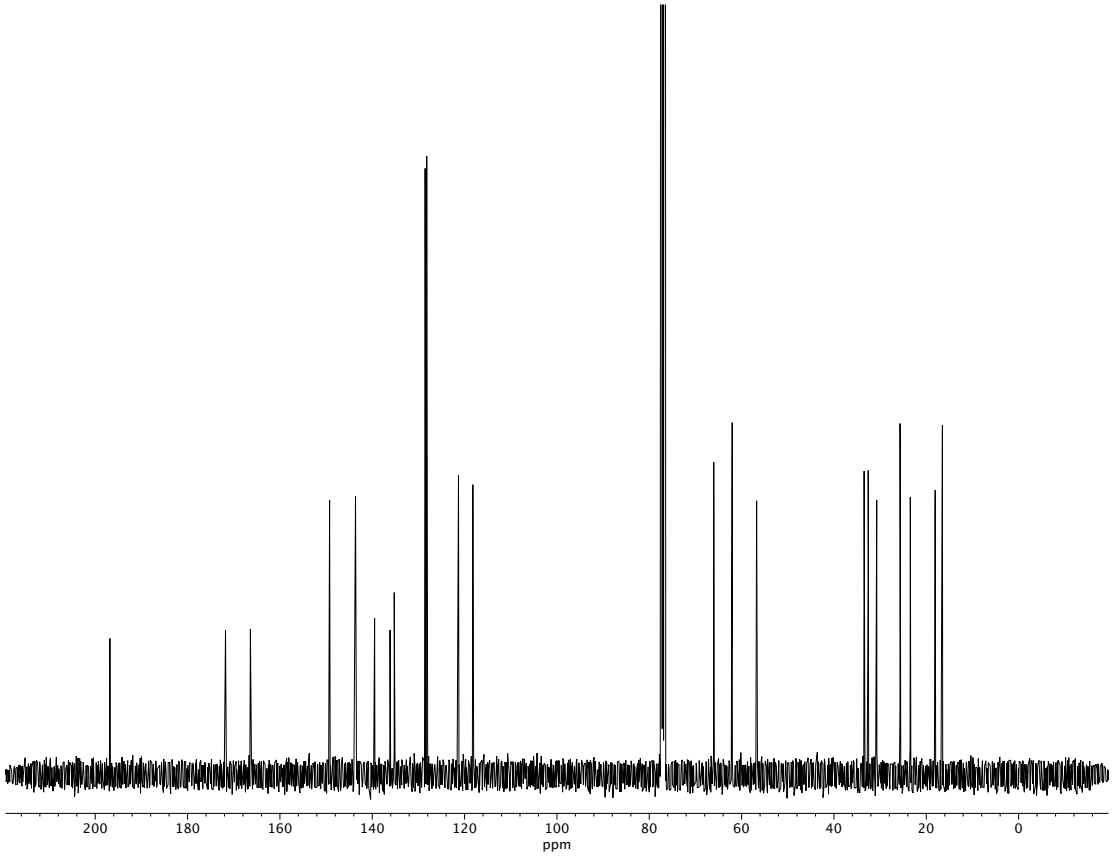


Figure A1.149. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10u****.*

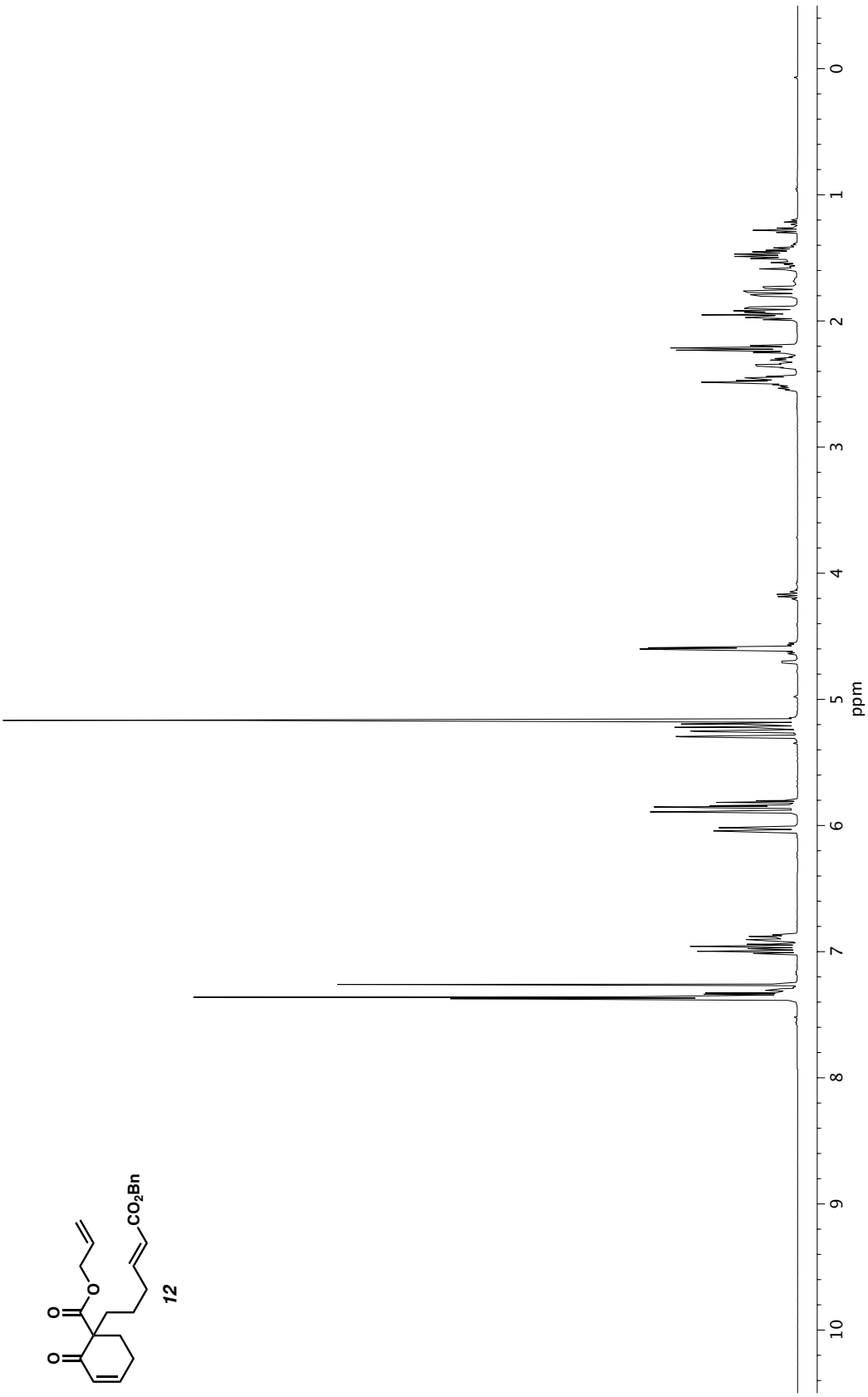


Figure A1.150. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***12****.*

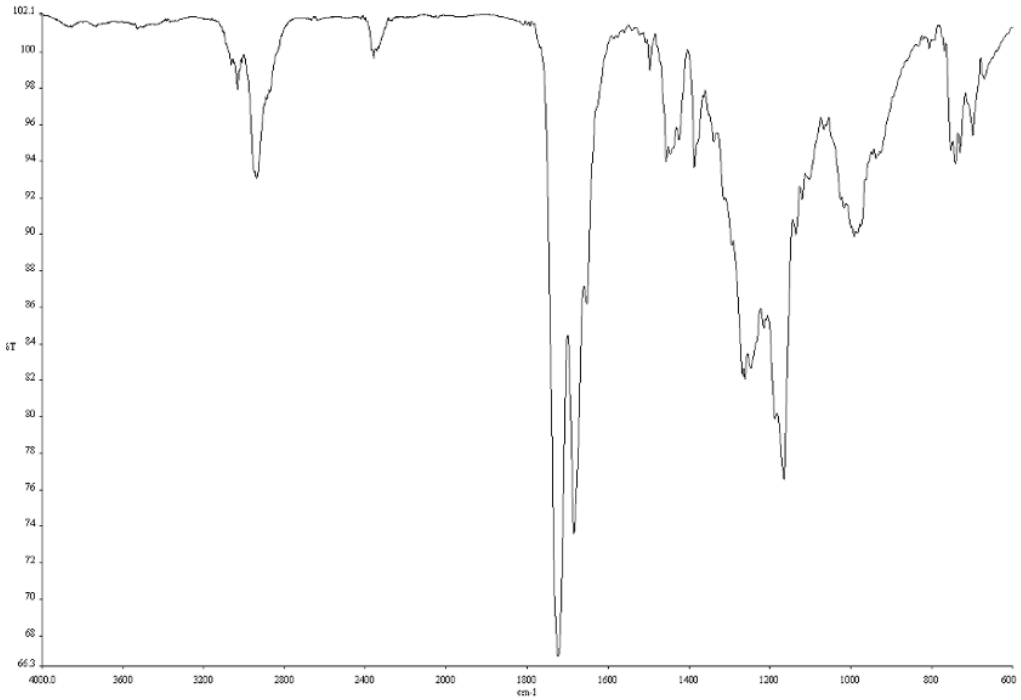


Figure A1.151. *Infrared spectrum (Thin Film, NaCl) of compound* ***12****.*

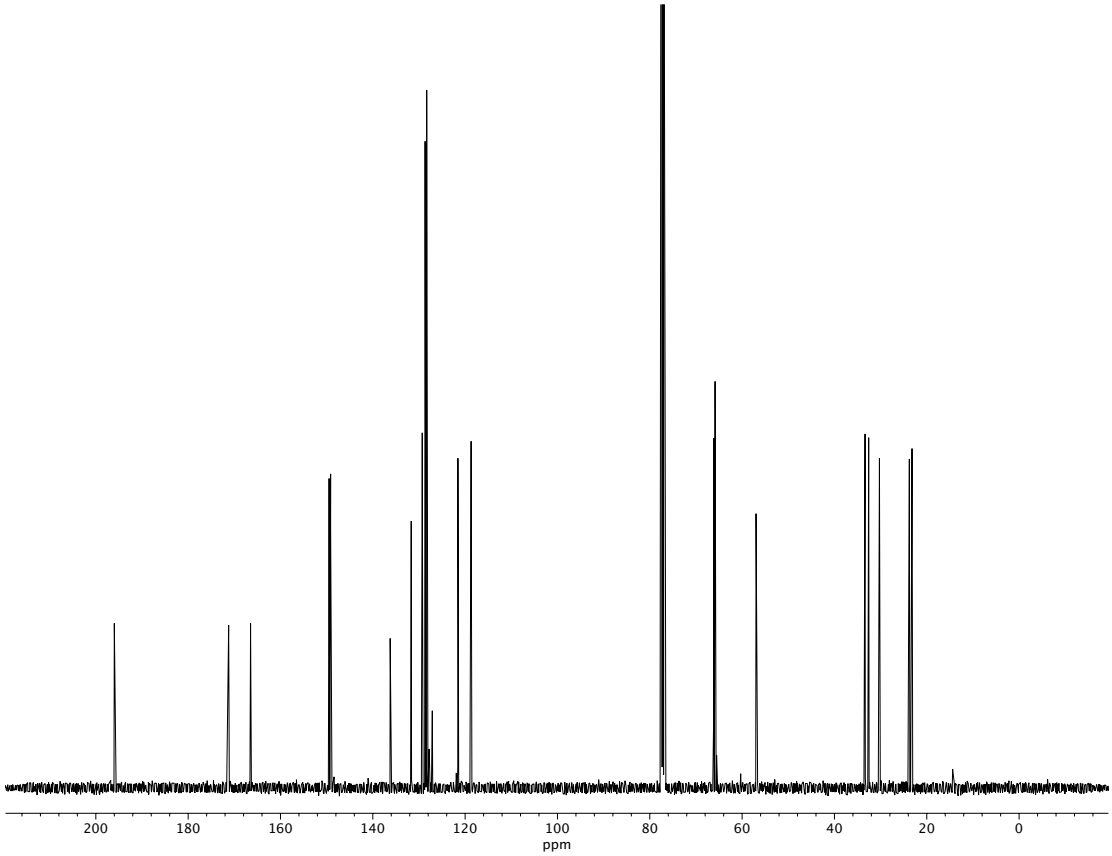


Figure A1.152. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***12****.*

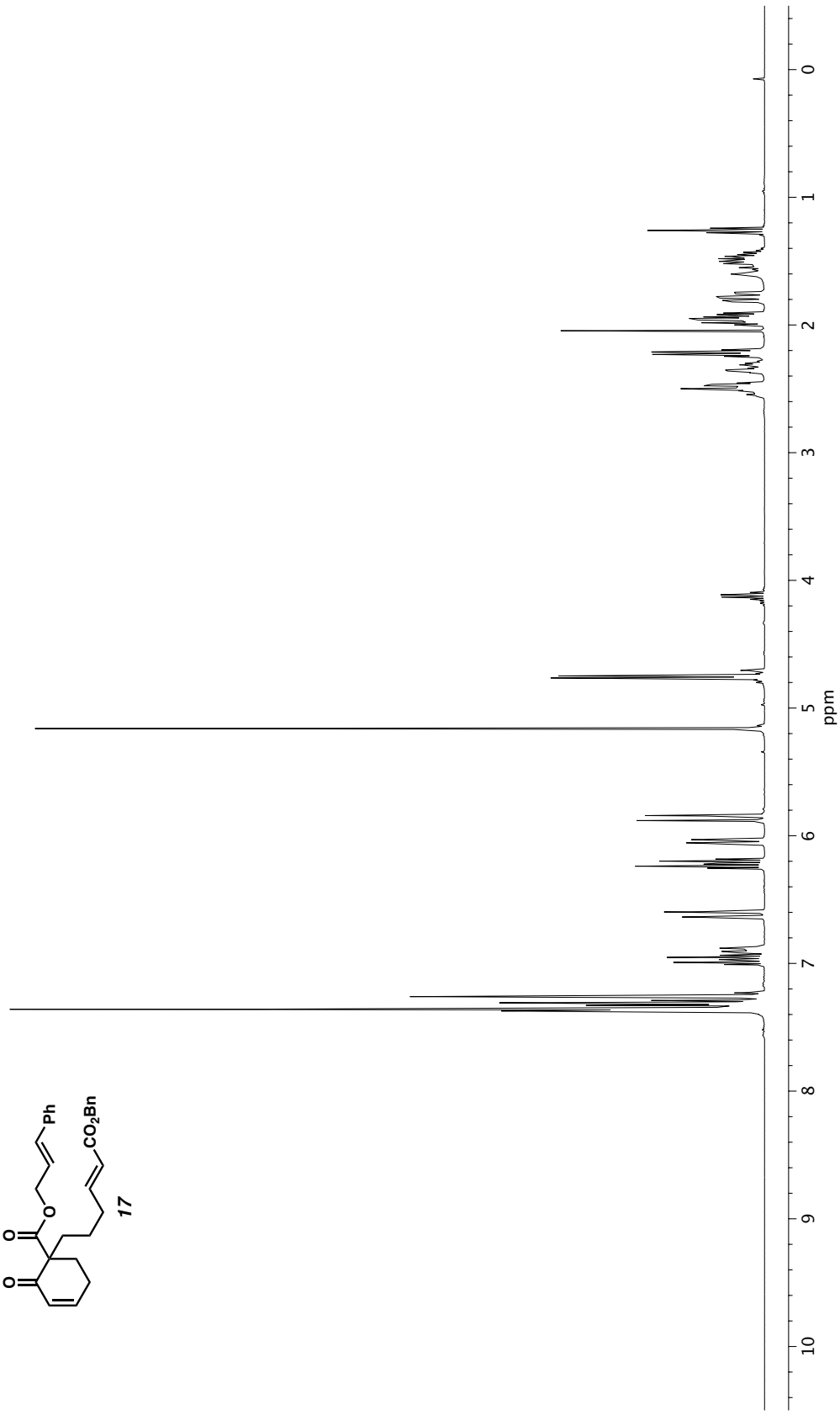


Figure A1.153. *^1H NMR (400 MHz, $CDCl_3$) of compound **17**.*

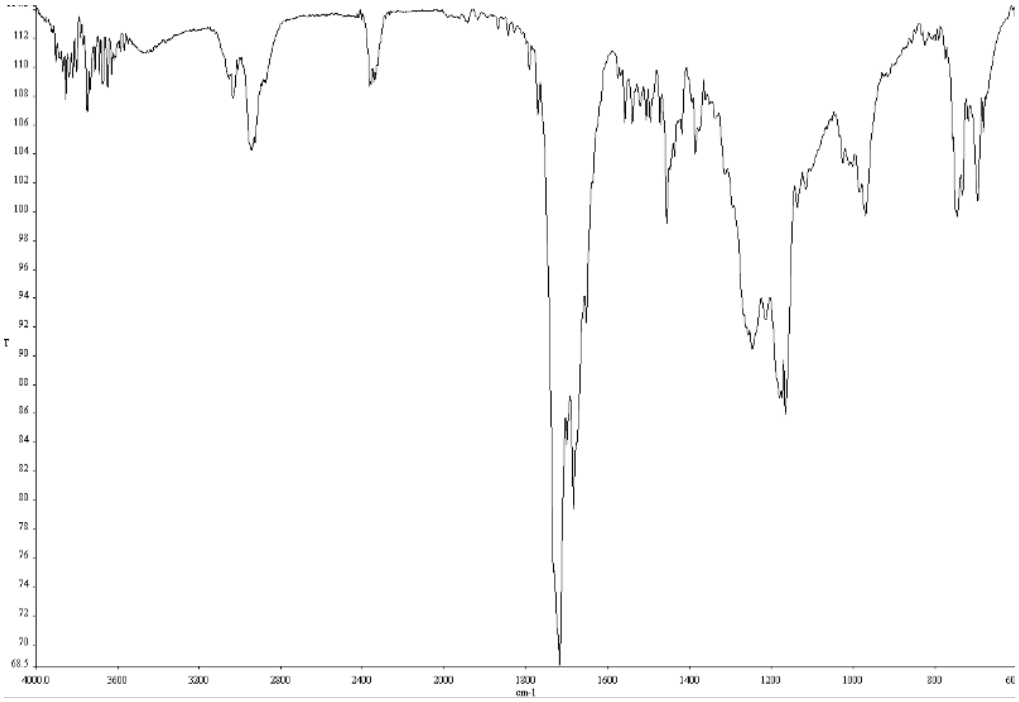


Figure A1.154. *Infrared spectrum (Thin Film, NaCl) of compound* ***17****.*

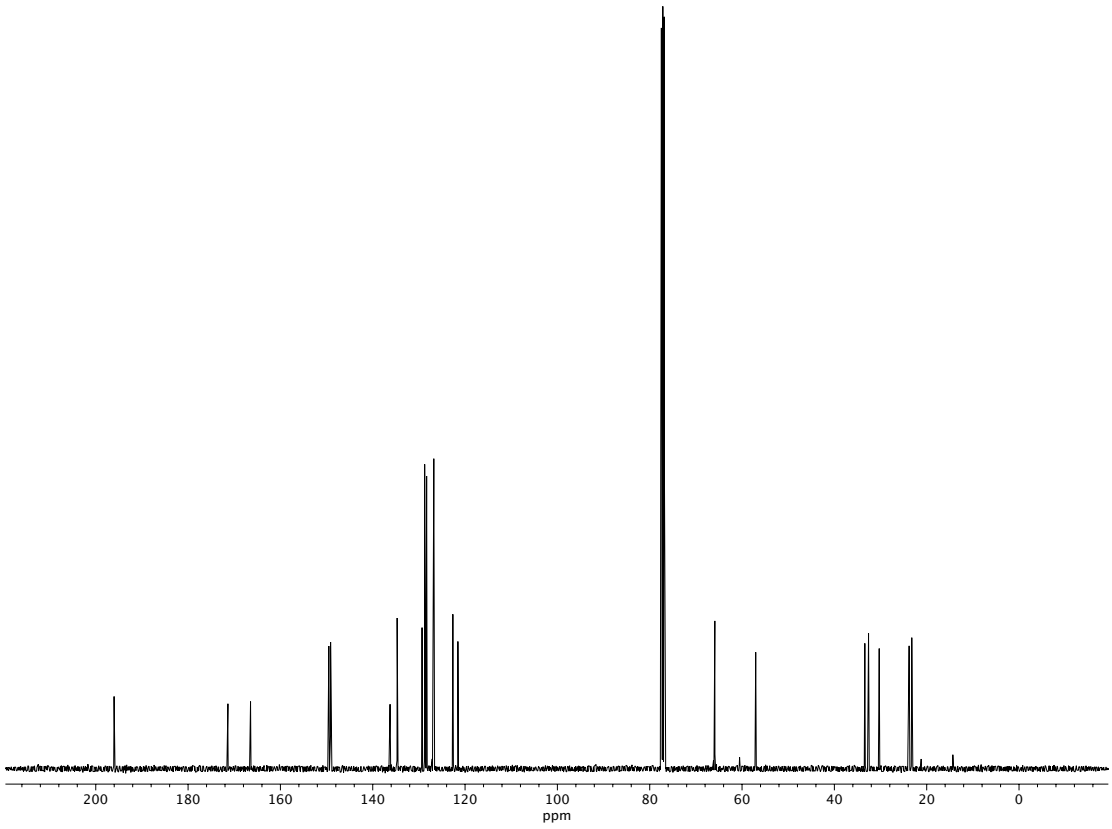


Figure A1.155. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***17****.*

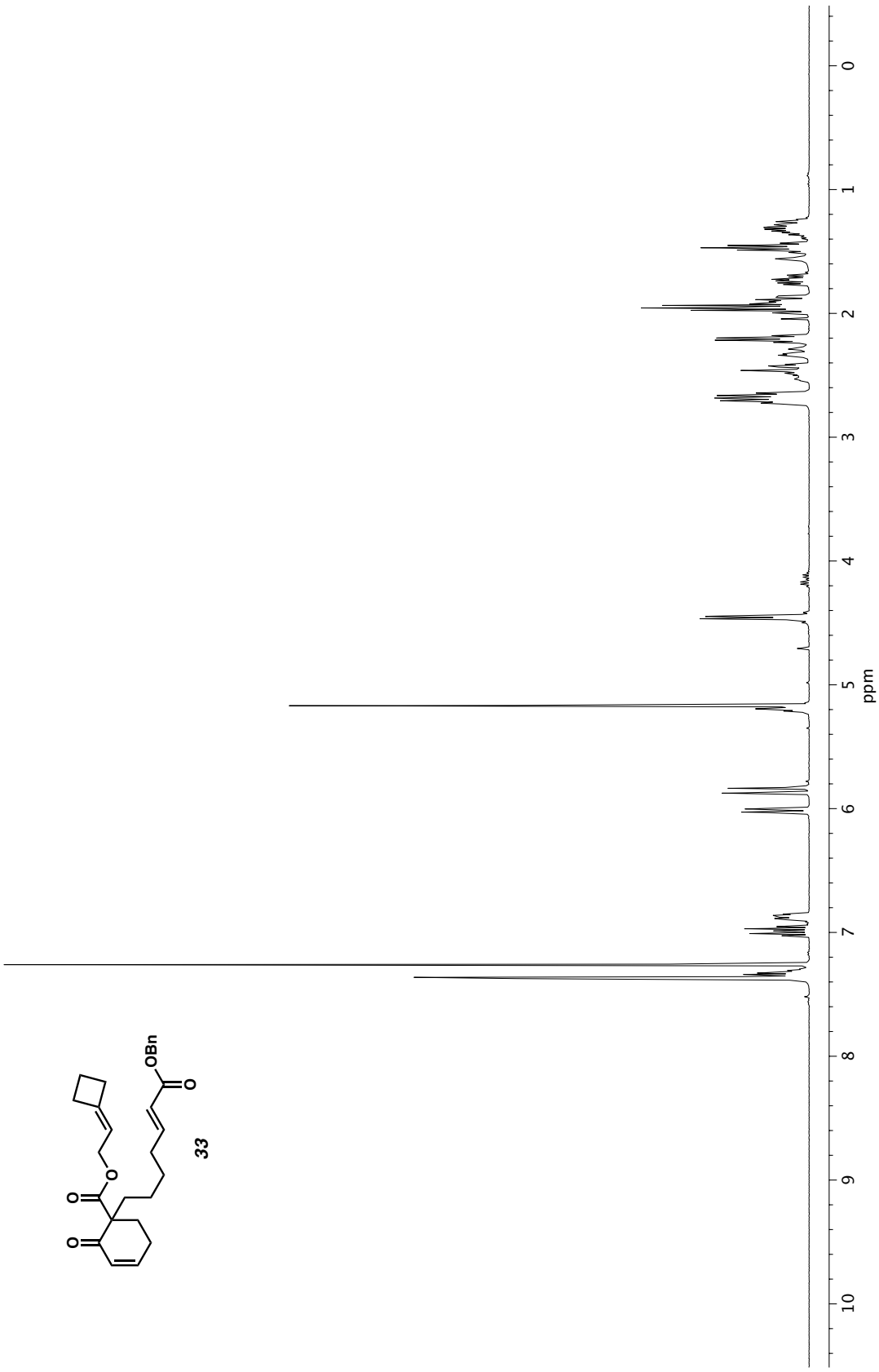


Figure A1.156. *^1H NMR (400 MHz, $CDCl_3$) of compound **33**.*

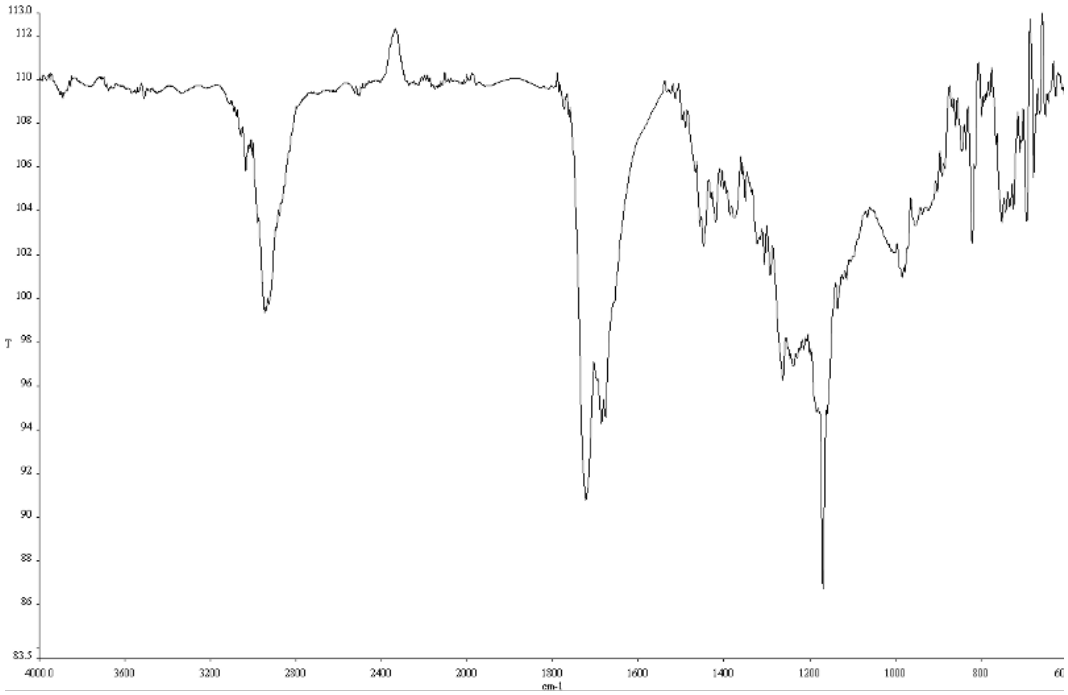


Figure A1.157. *Infrared spectrum (Thin Film, NaCl) of compound* ***33****.*

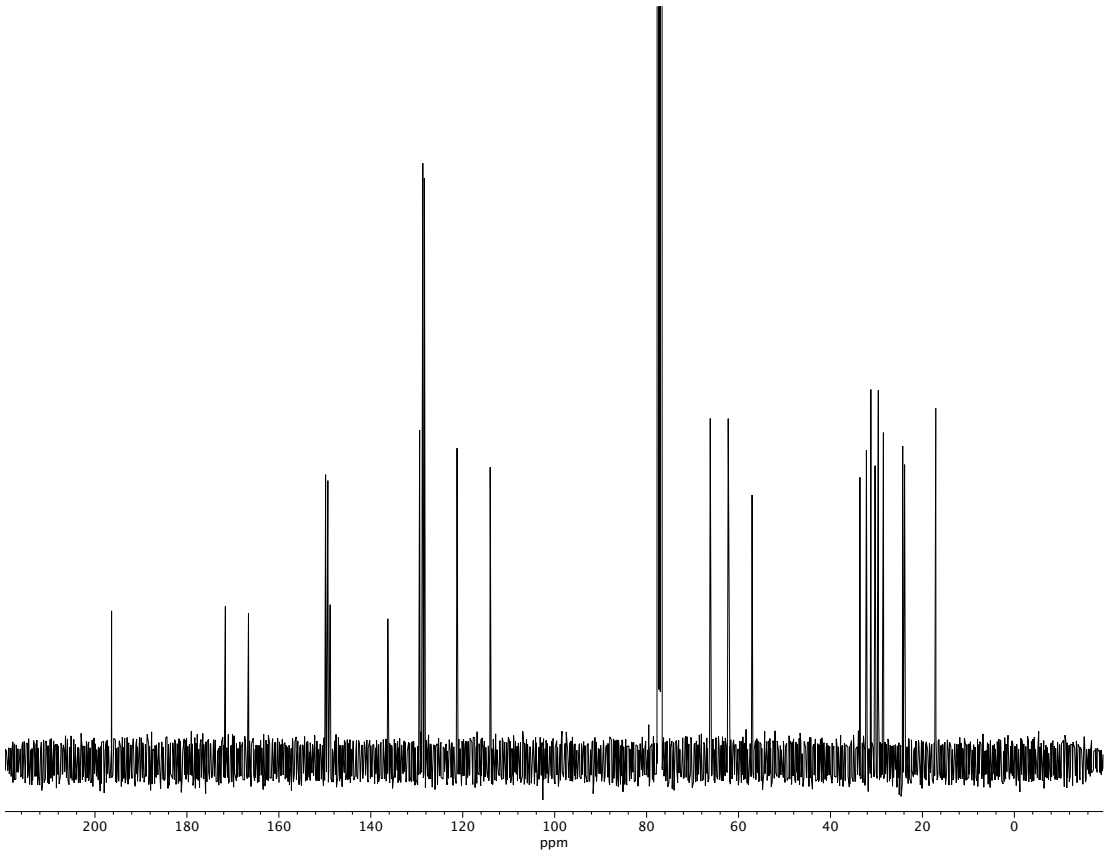


Figure A1.158. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***33****.*

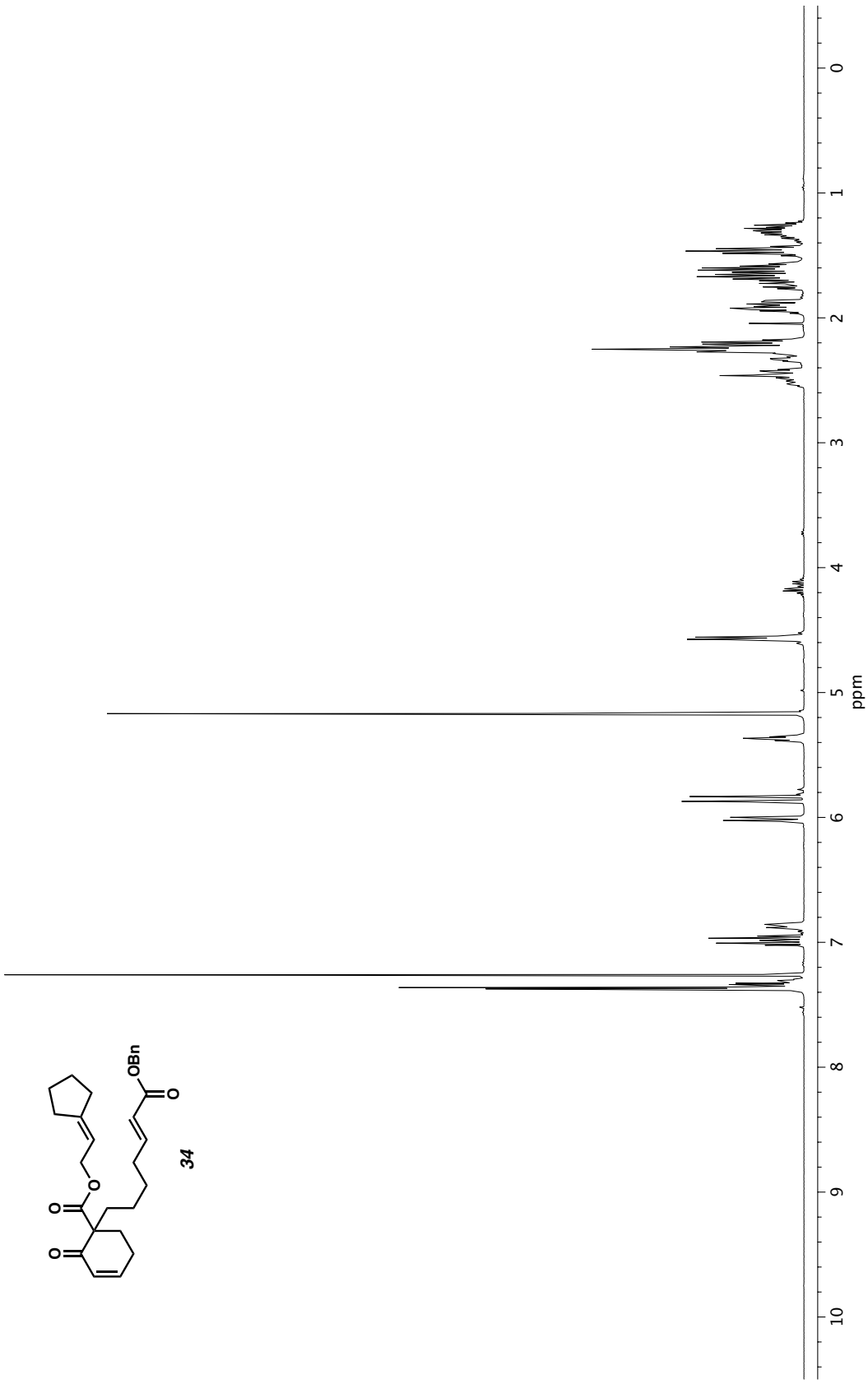


Figure A1.159. *^1H NMR (400 MHz, $CDCl_3$) of compound **34**.*

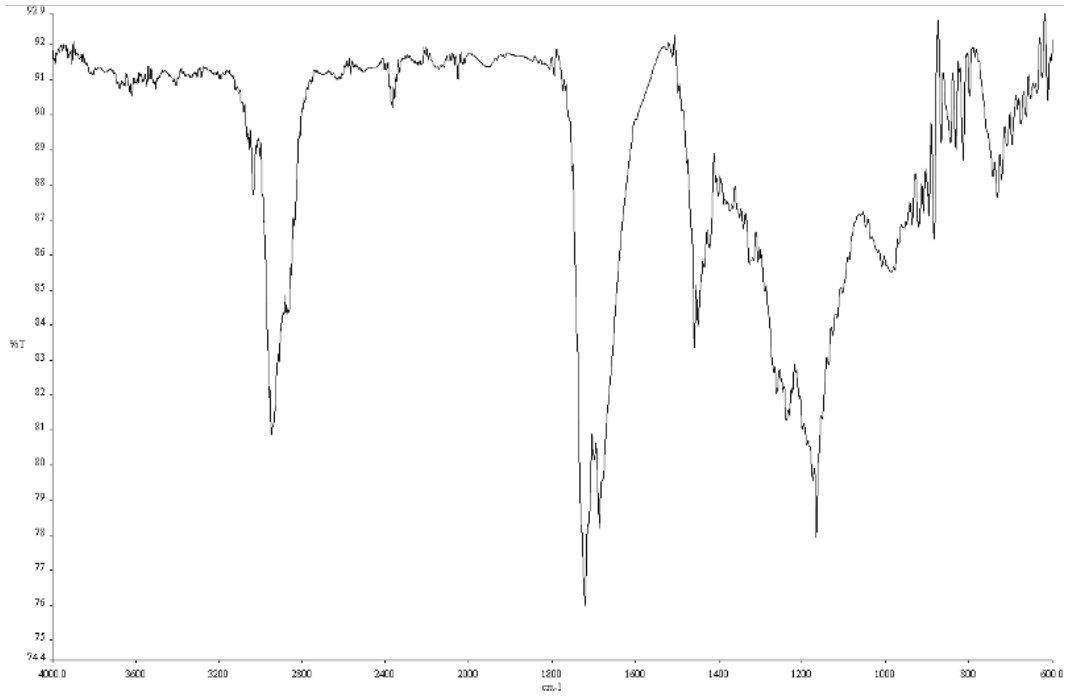


Figure A1.160. *Infrared spectrum (Thin Film, NaCl) of compound* ***34****.*

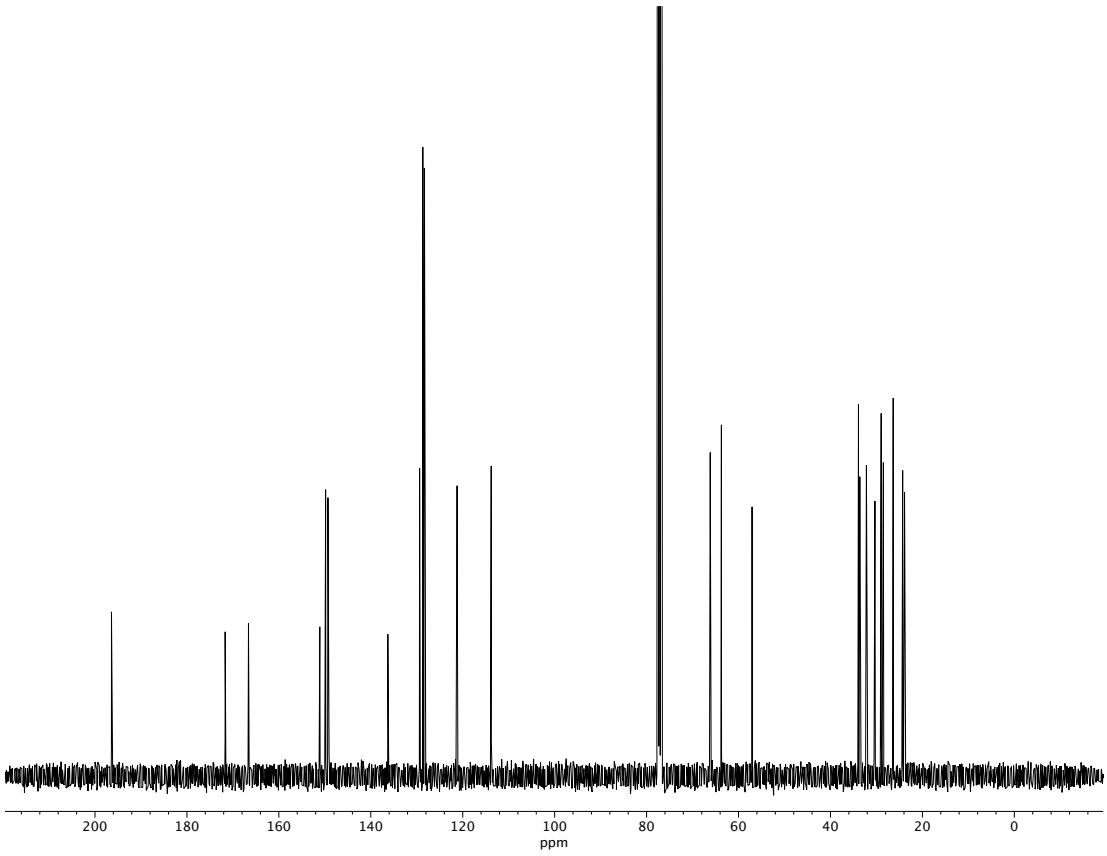


Figure A1.161. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***34****.*

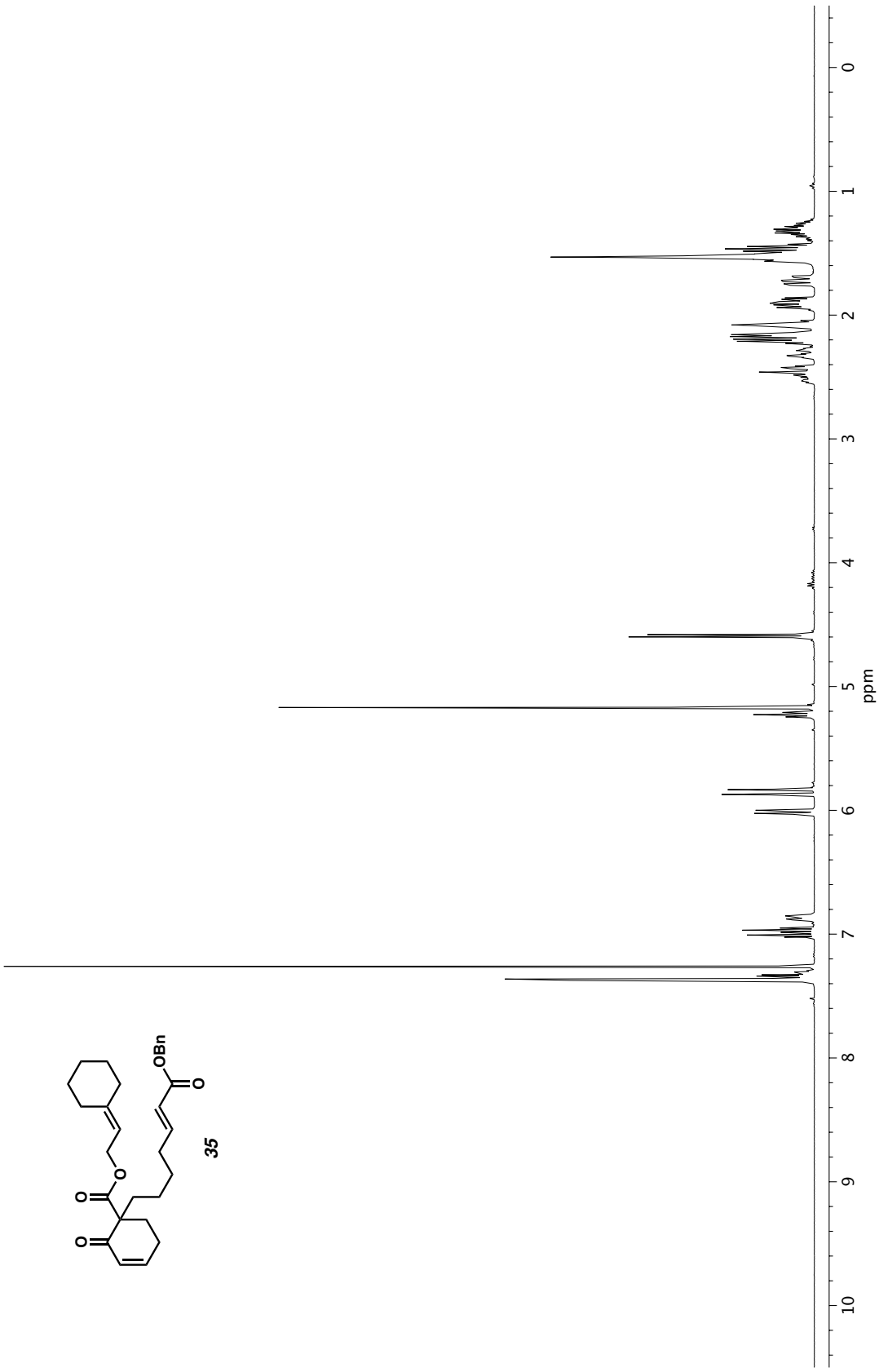


Figure A1.162. *^1H NMR (400 MHz, $CDCl_3$) of compound **35**.*

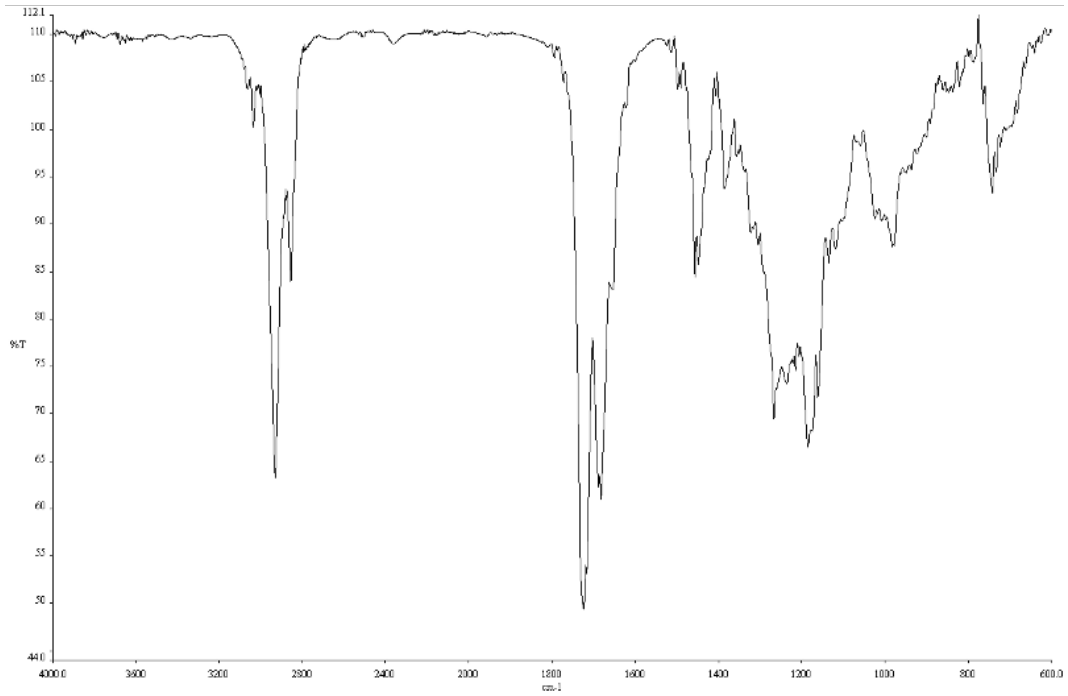


Figure A1.163. *Infrared spectrum (Thin Film, NaCl) of compound* ***35****.*

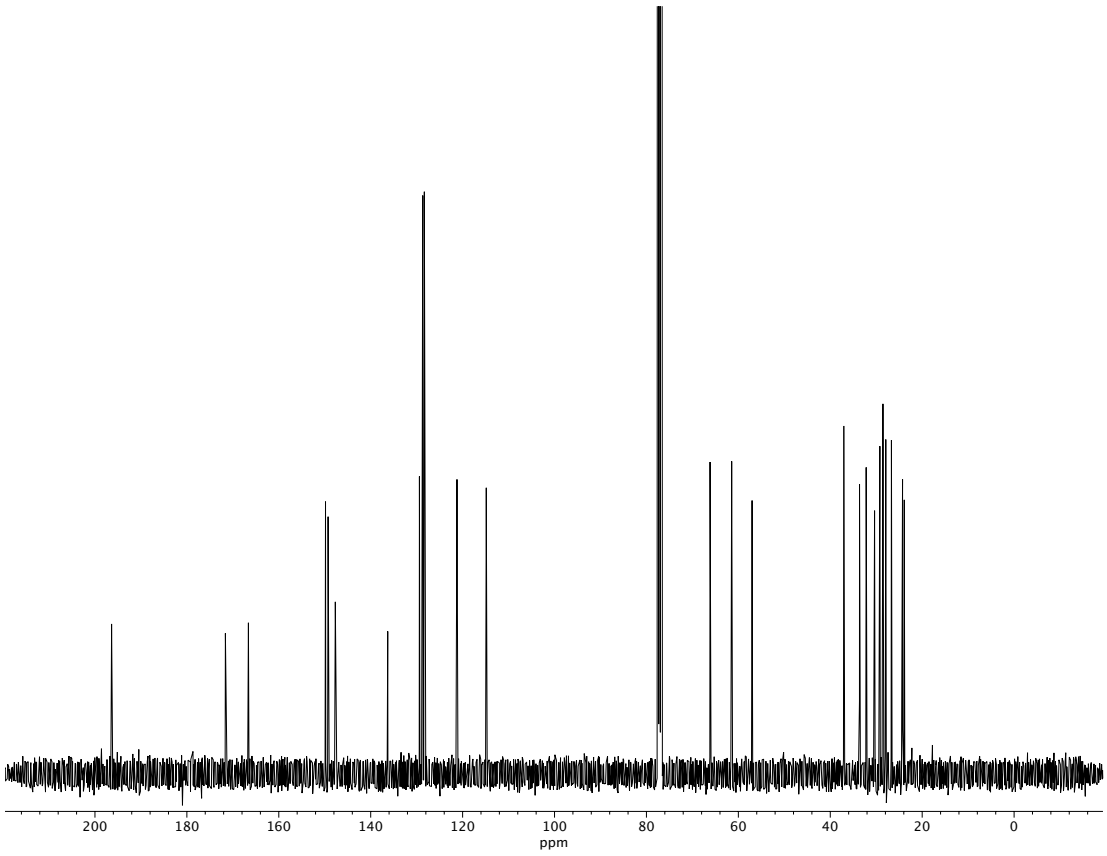


Figure A1.164. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***35****.*

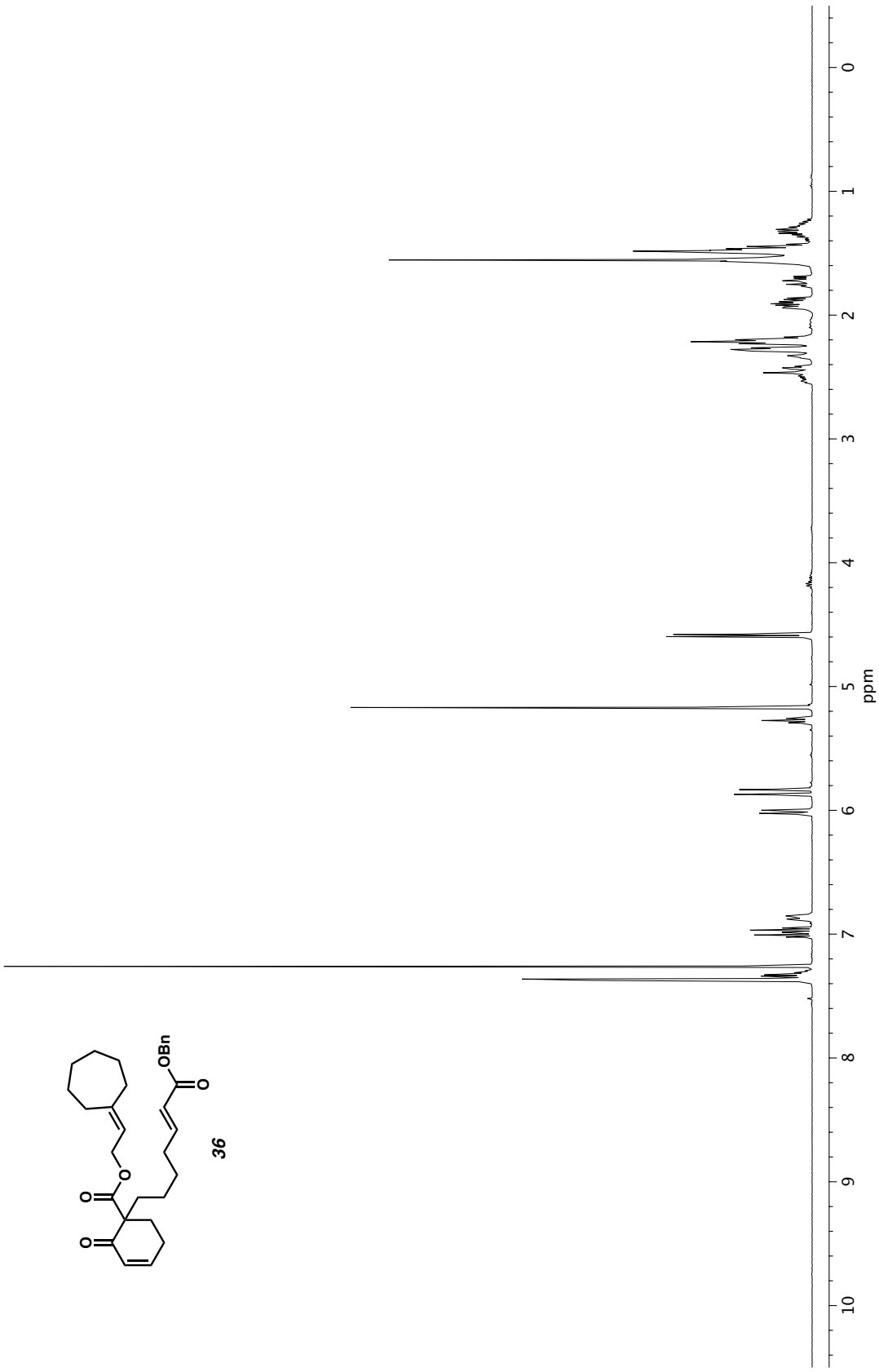


Figure A1.165. *^1H NMR (400 MHz, $CDCl_3$) of compound **36**.*

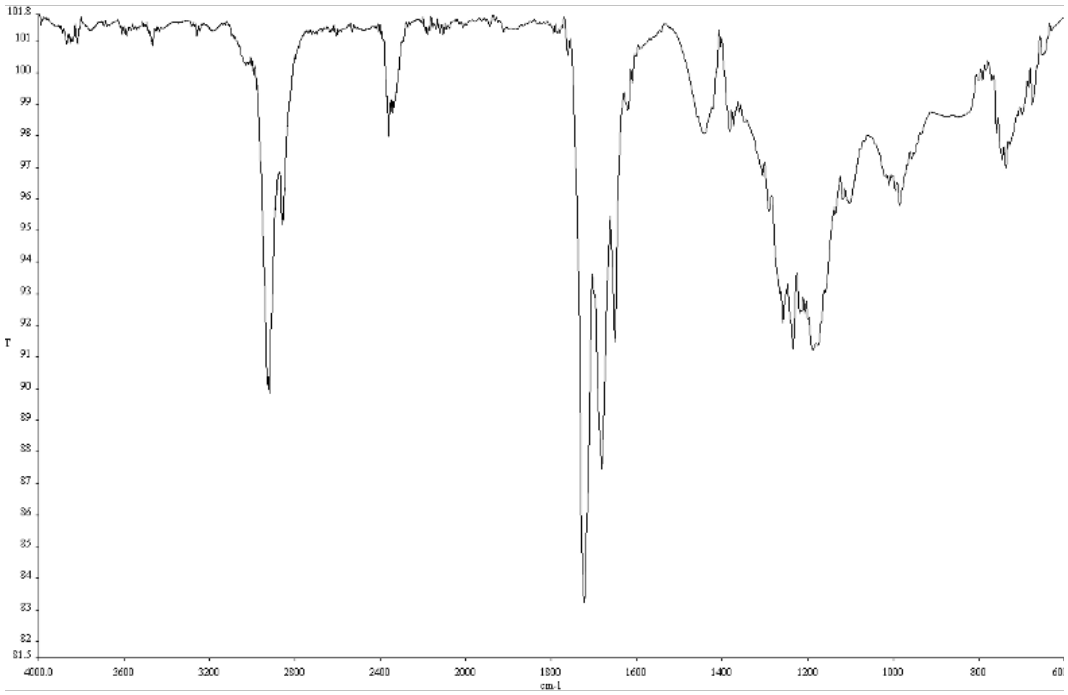


Figure A1.166. *Infrared spectrum (Thin Film, NaCl) of compound* ***36****.*

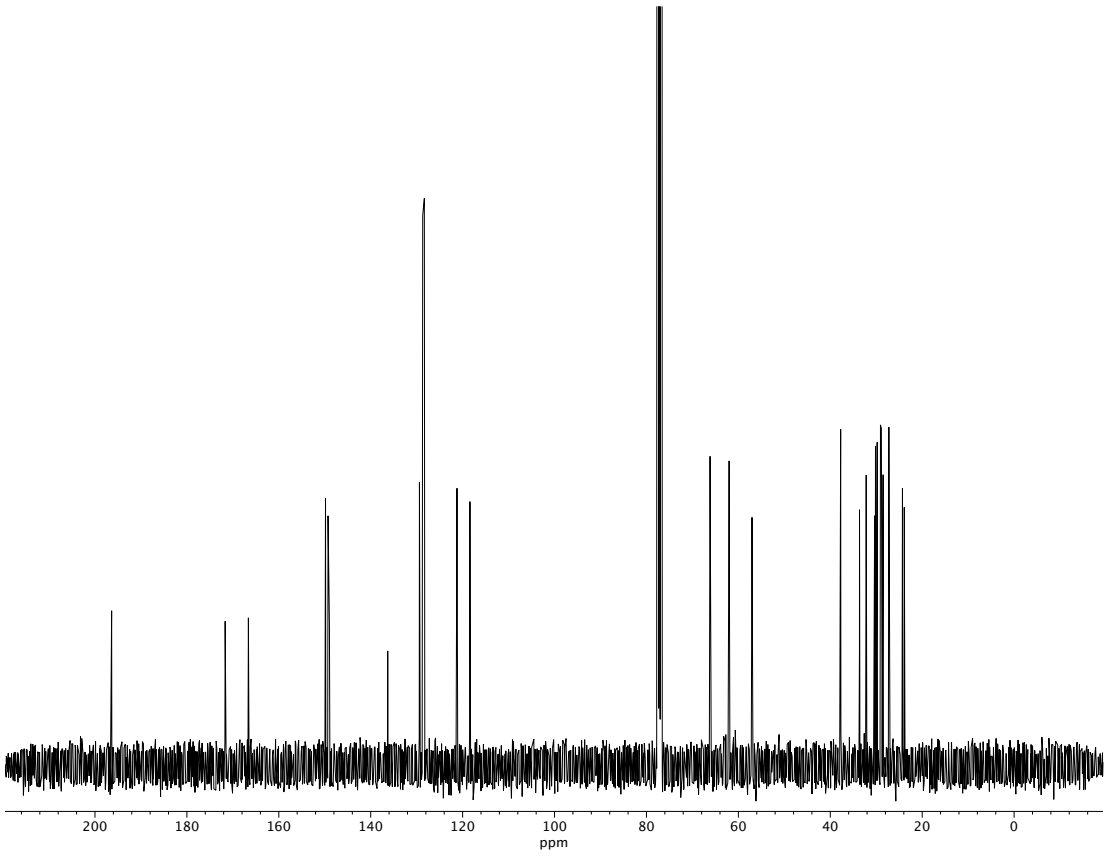


Figure A1.167. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***36****.*

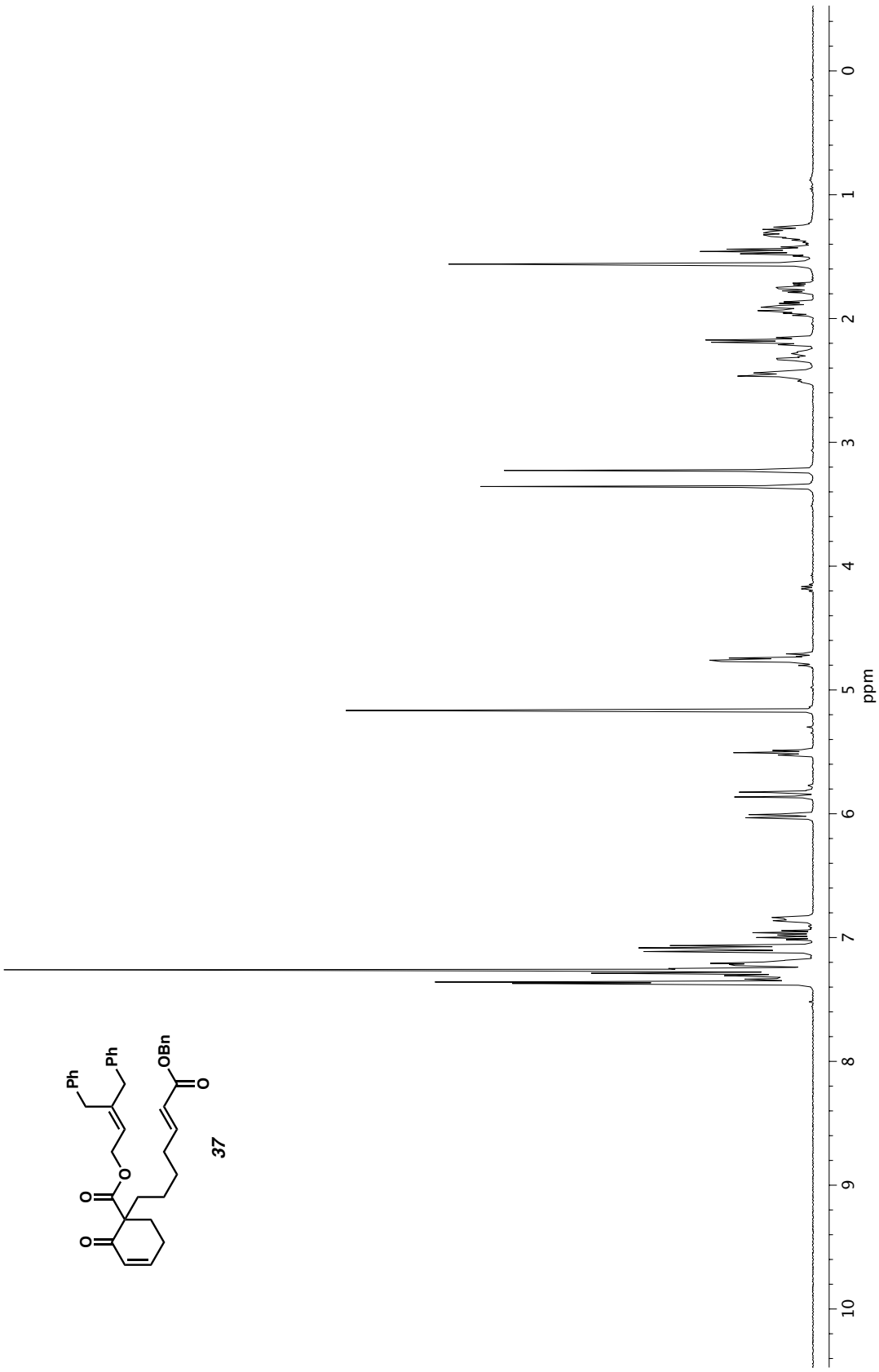


Figure A1.168. *^1H NMR (400 MHz, $CDCl_3$) of compound **37**.*

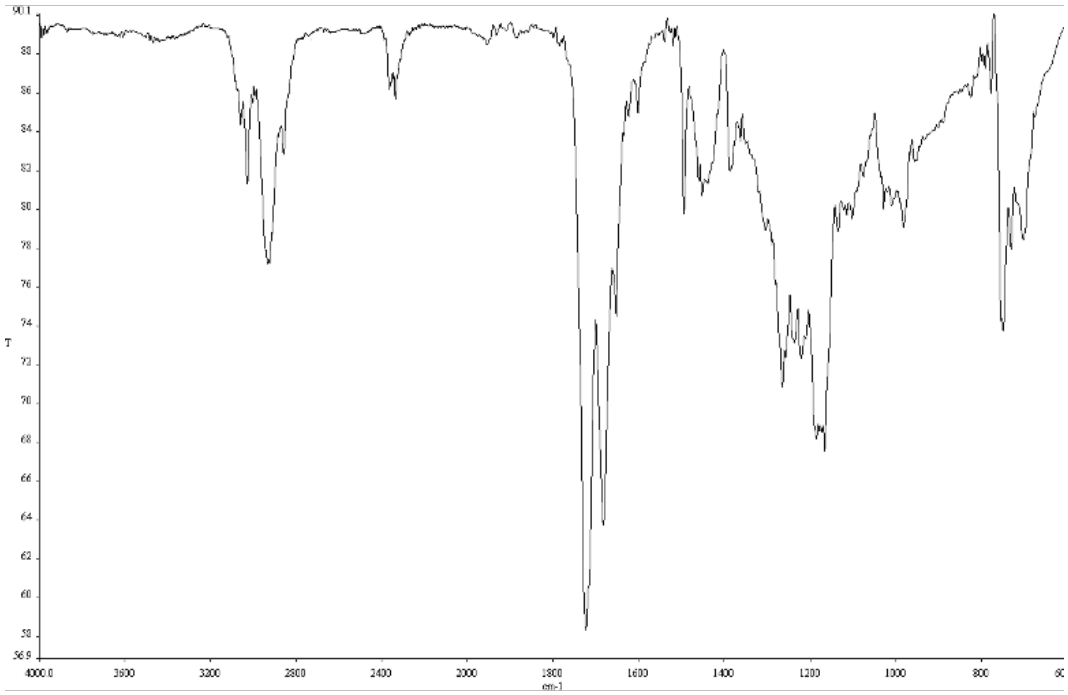


Figure A1.169. *Infrared spectrum (Thin Film, NaCl) of compound* ***37****.*

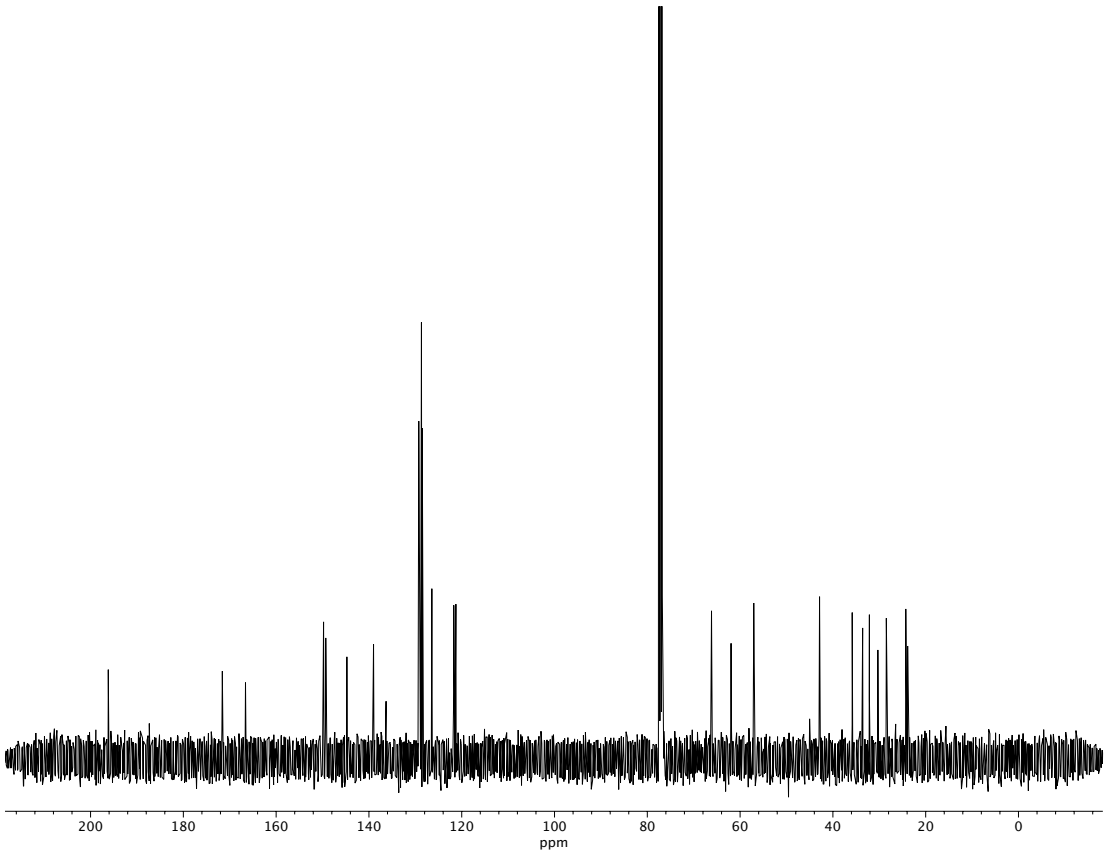


Figure A1.170. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***37****.*

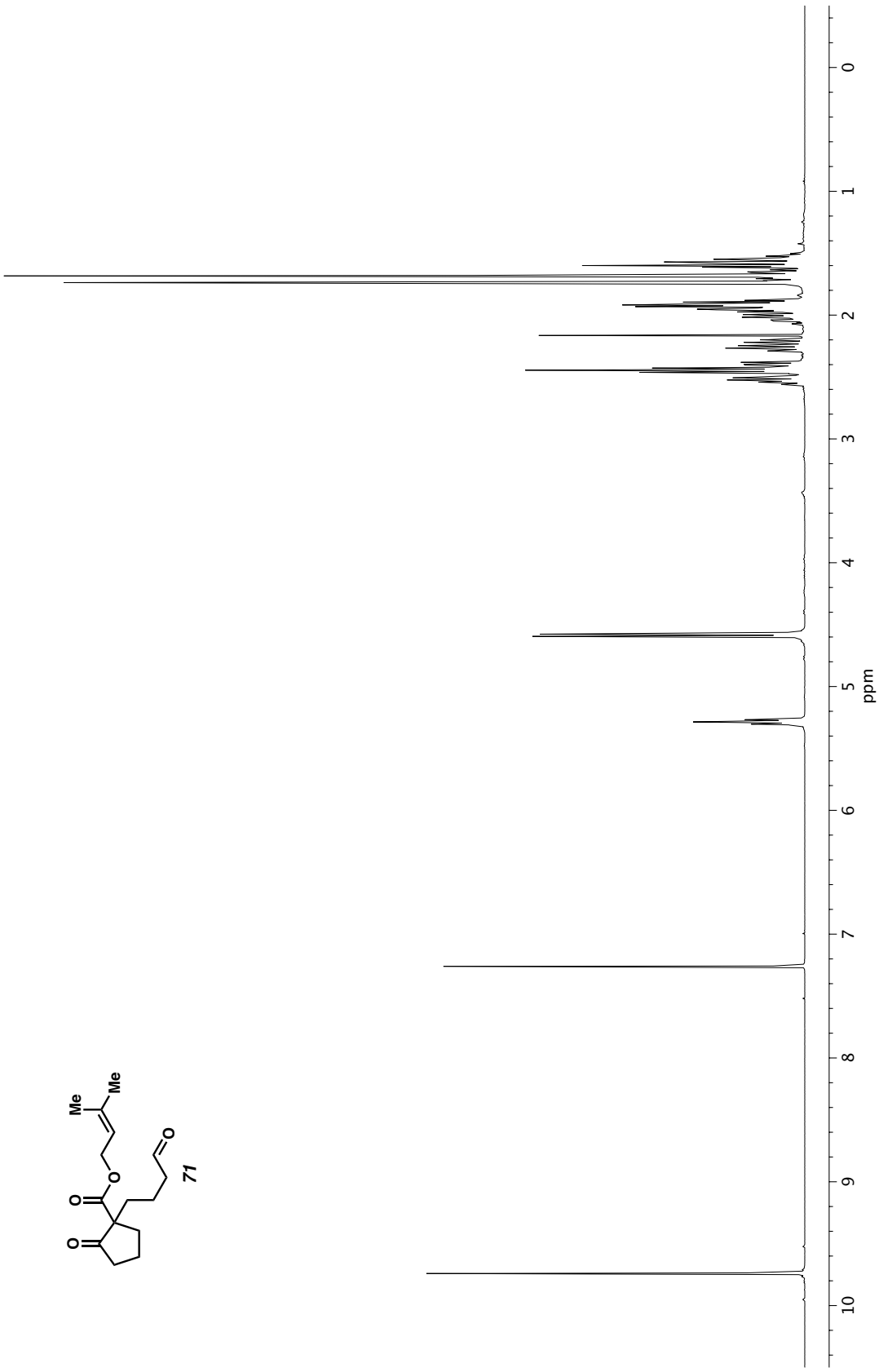


Figure A1.171. *^1H NMR (400 MHz, $CDCl_3$) of compound **71**.*

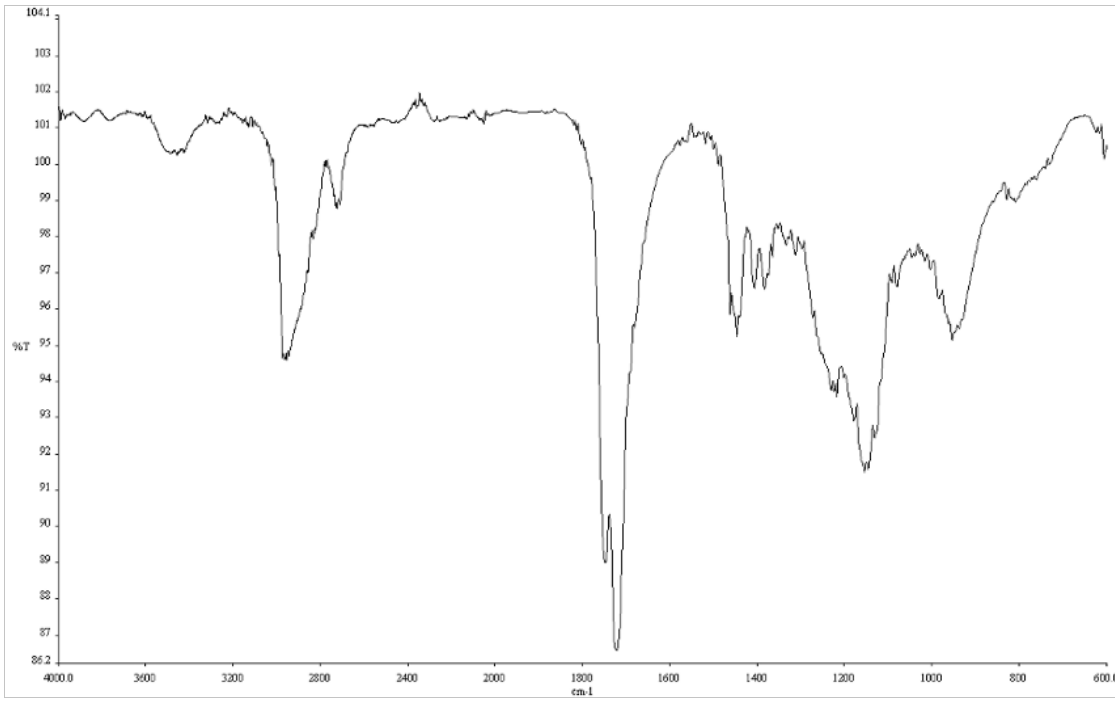


Figure A1.172. *Infrared spectrum (Thin Film, NaCl) of compound* ***71****.*

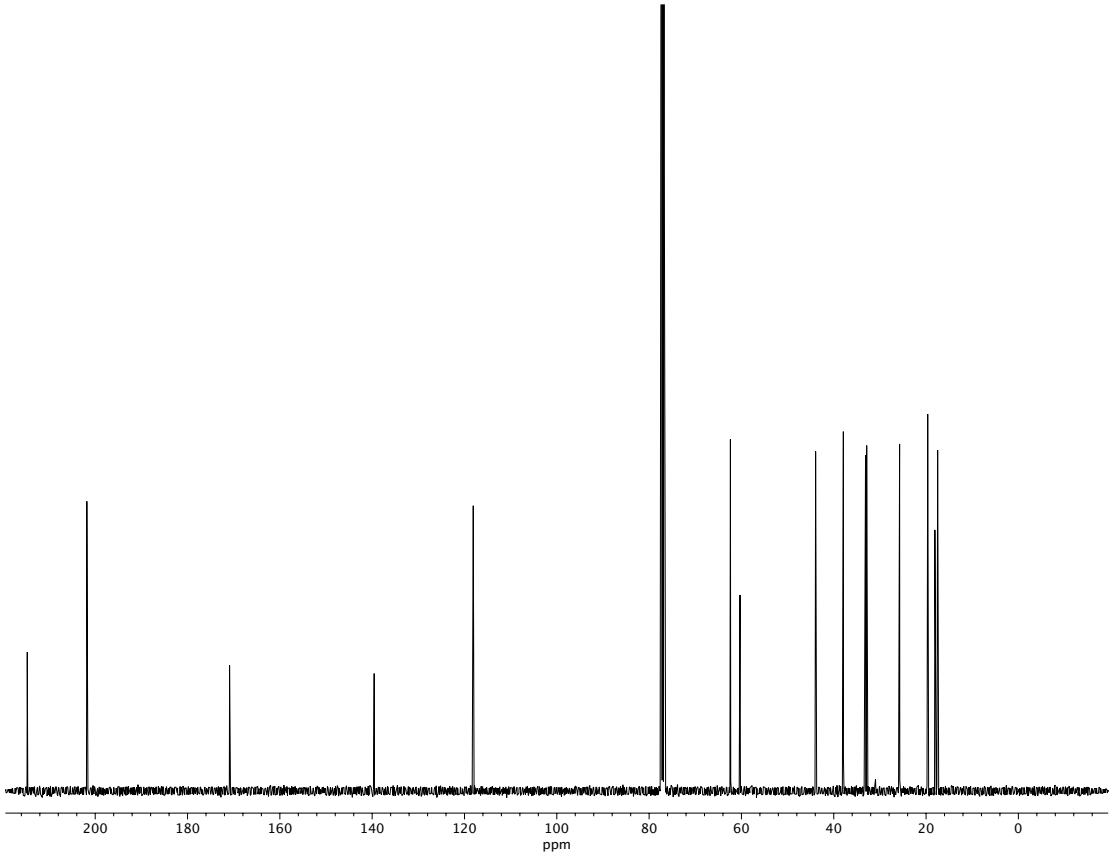


Figure A1.173. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***71****.*

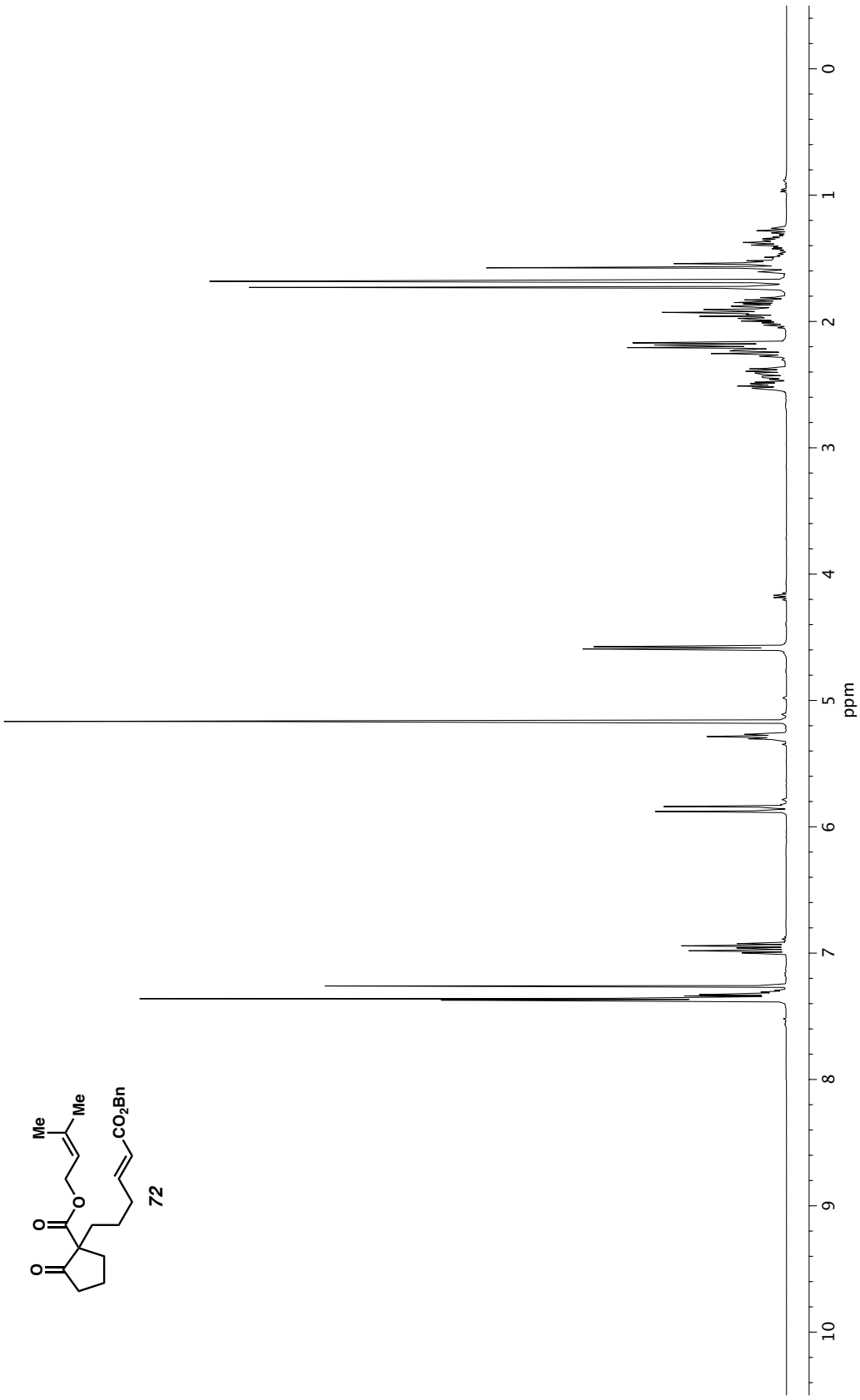


Figure A1.174. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***72****.*

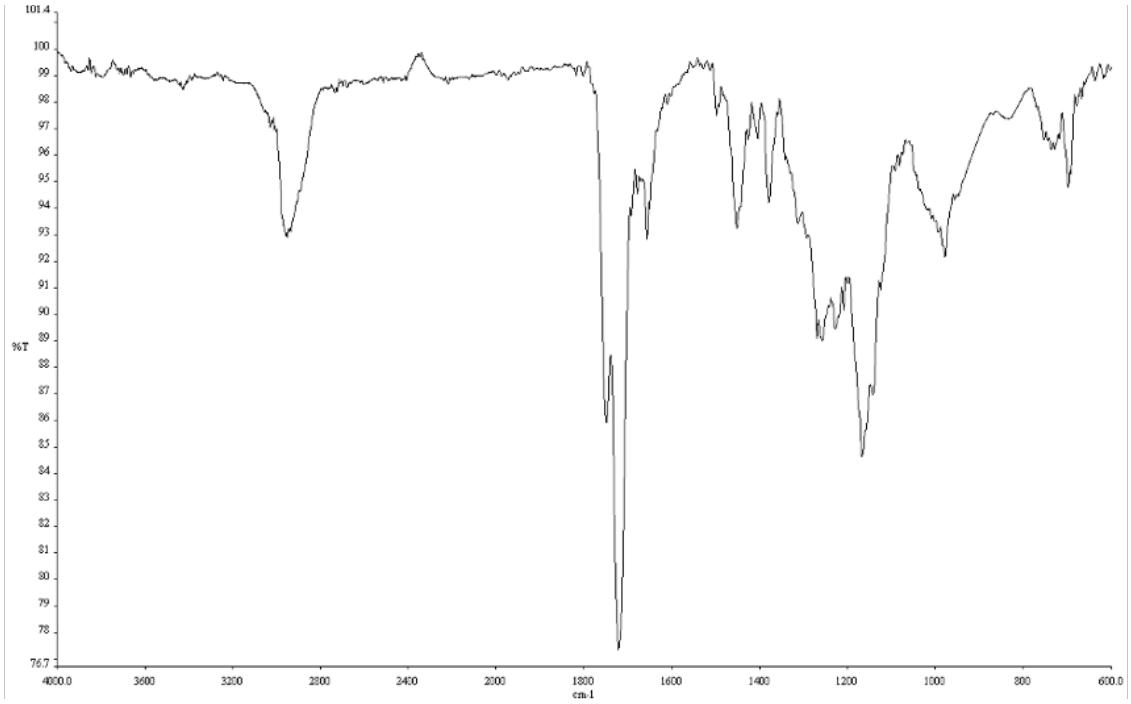


Figure A1.175. *Infrared spectrum (Thin Film, NaCl) of compound* ***72****.*

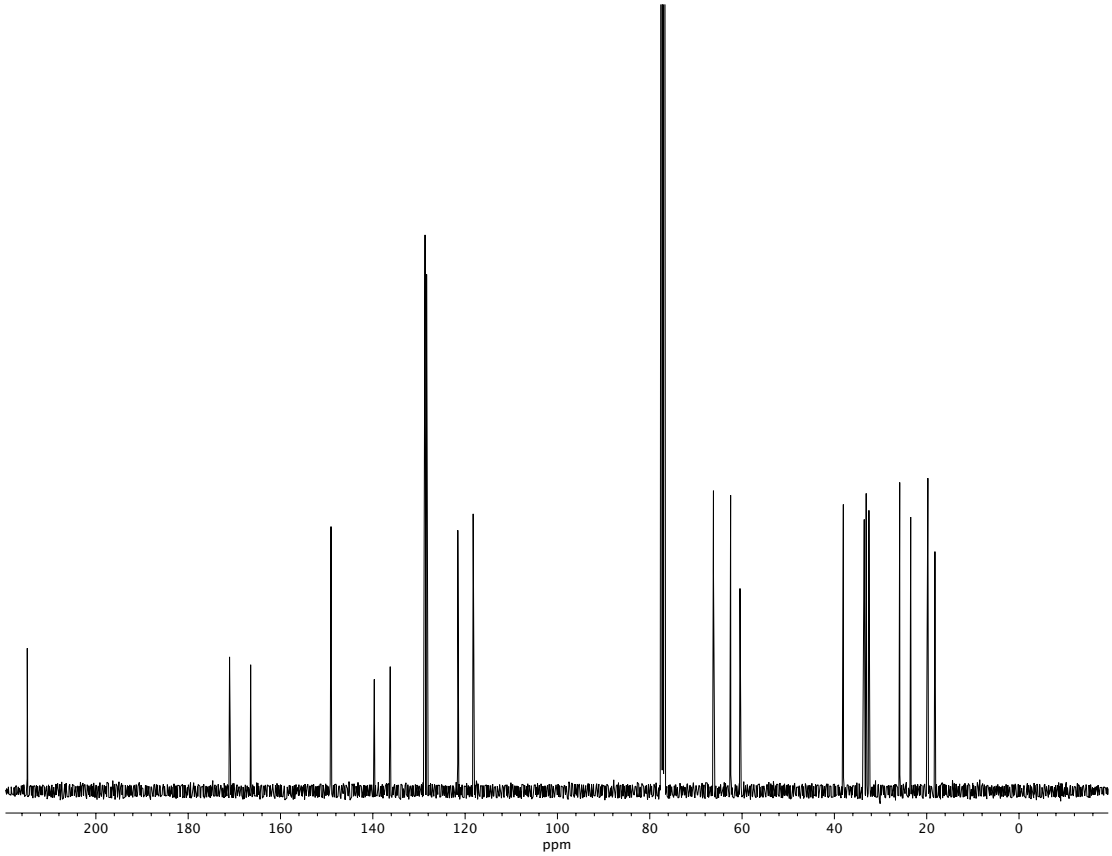


Figure A1.176. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***72****.*

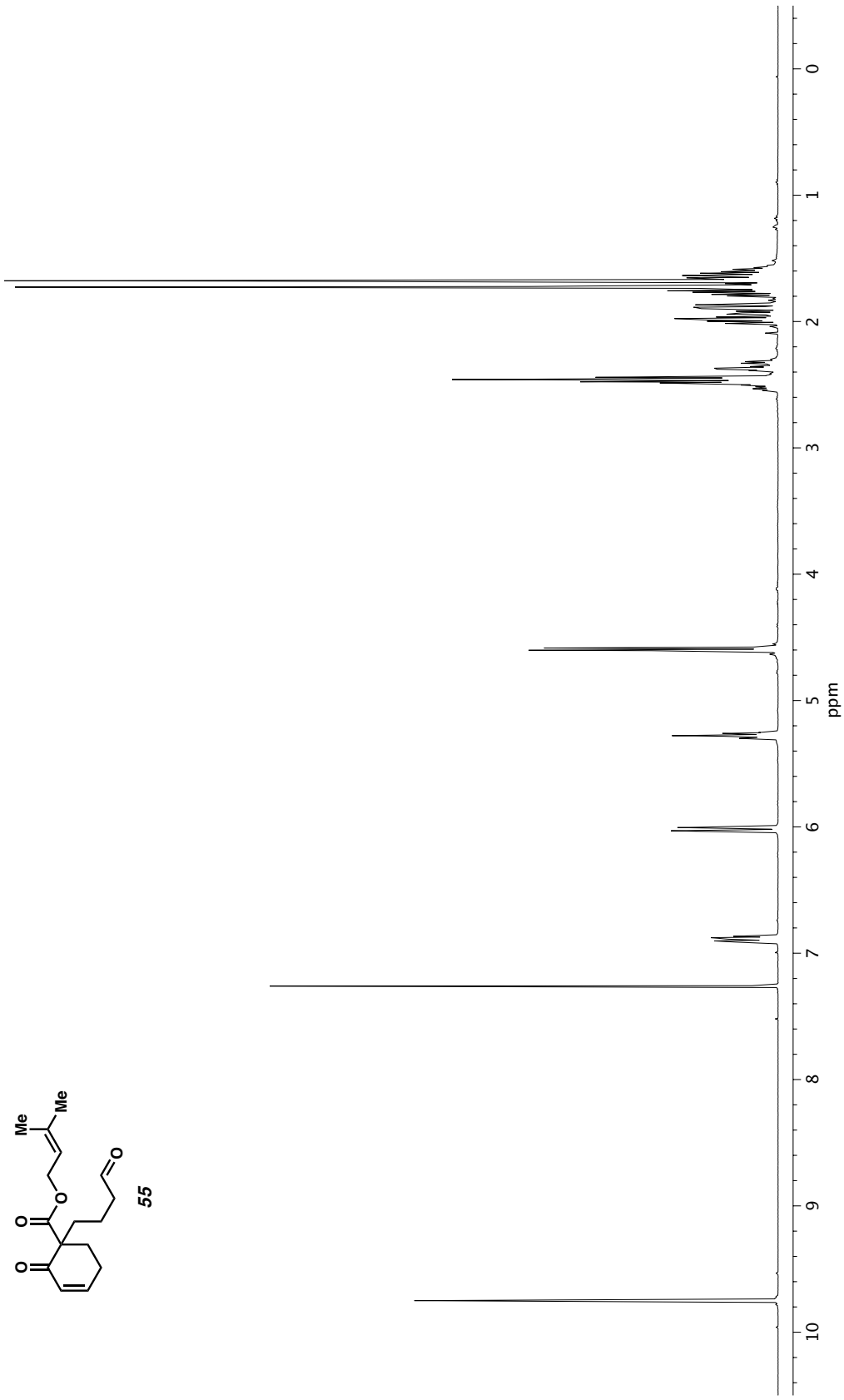


Figure A1.177. *^1H NMR (400 MHz, $CDCl_3$) of compound **55**.*

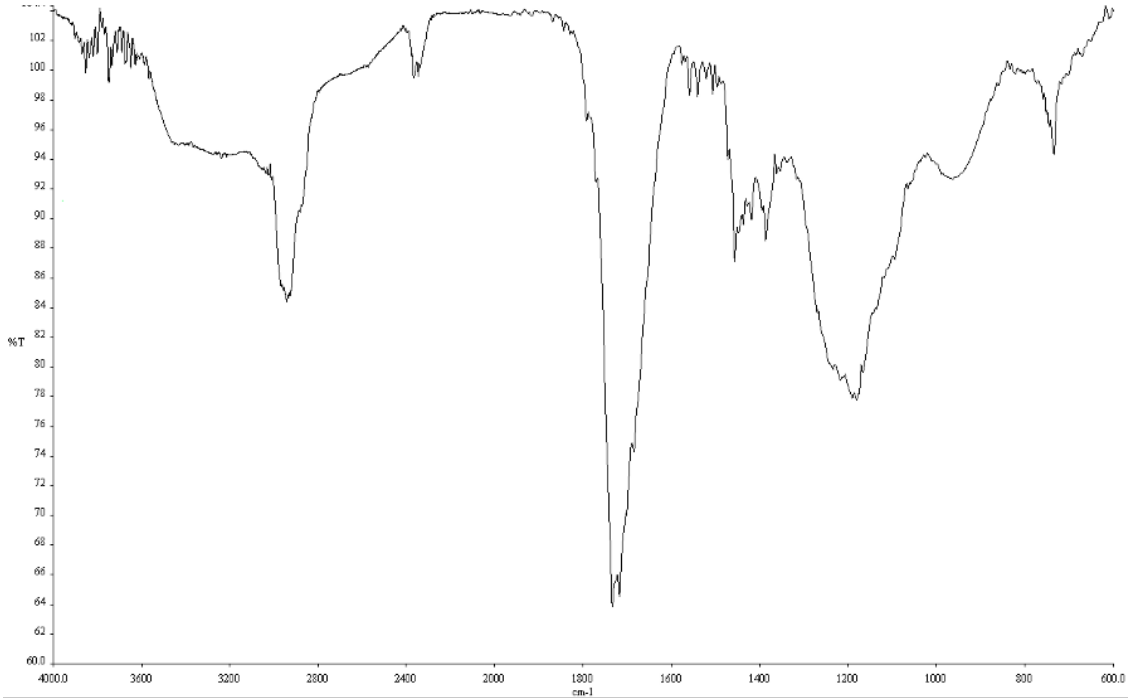


Figure A1.178. *Infrared spectrum (Thin Film, NaCl) of compound* ***55****.*

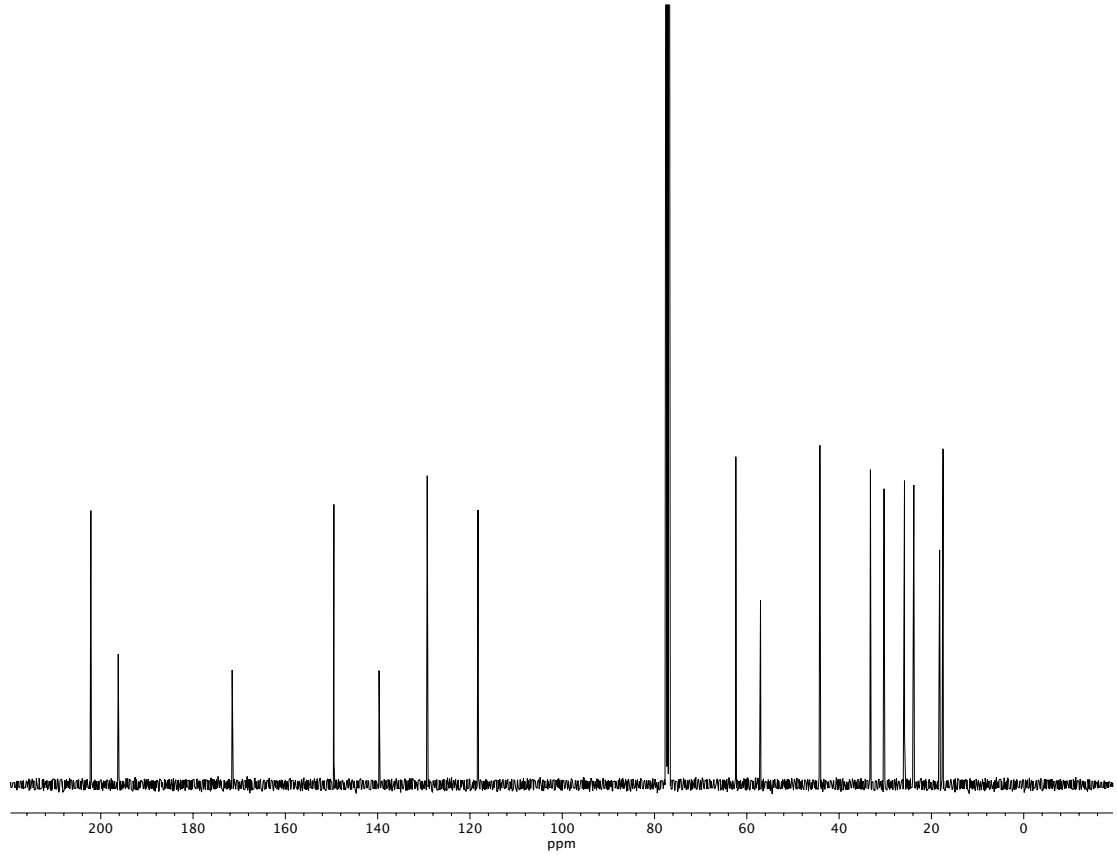


Figure A1.179. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***55****.*

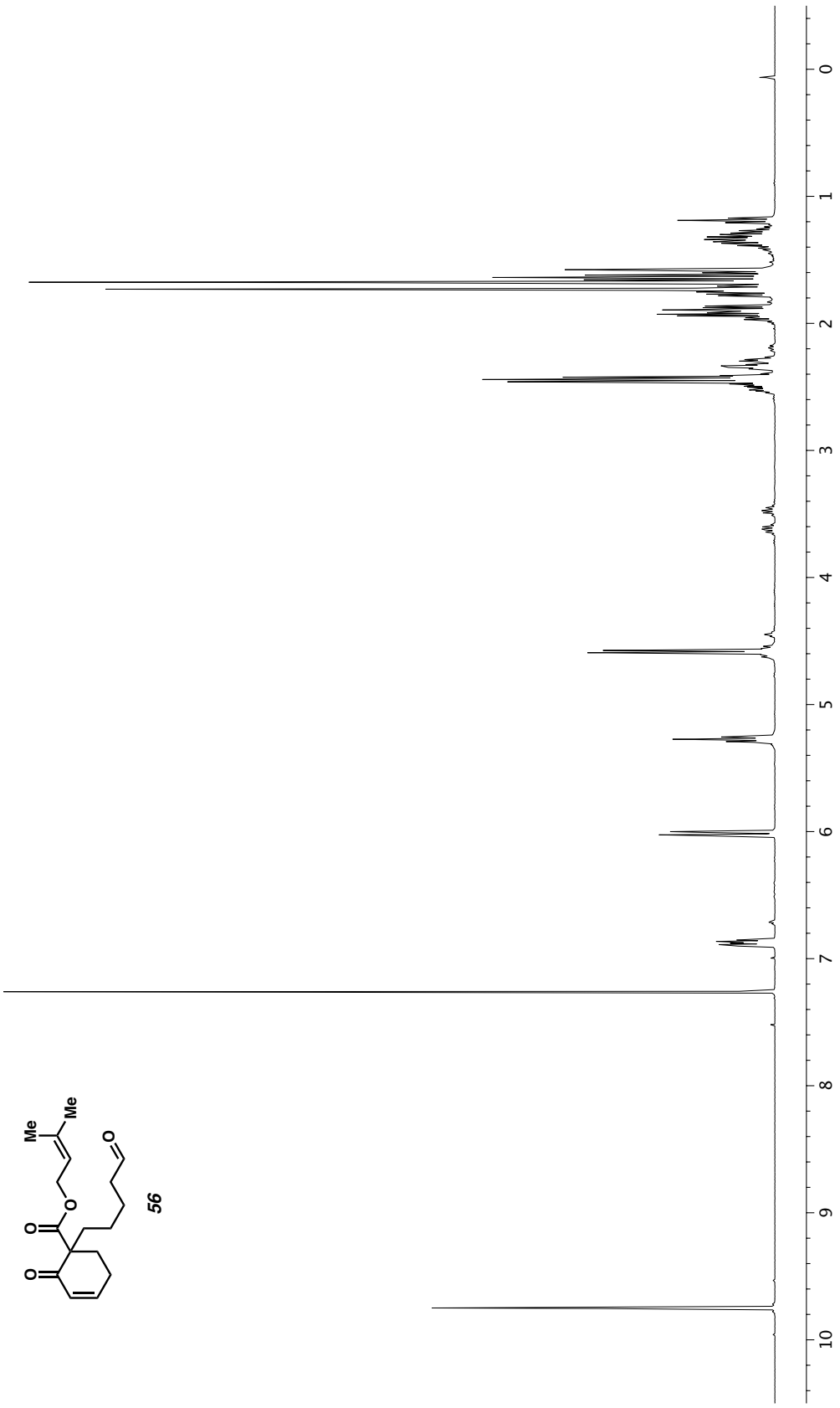


Figure A1.180. *^1H NMR (400 MHz, $CDCl_3$) of compound **56**.*

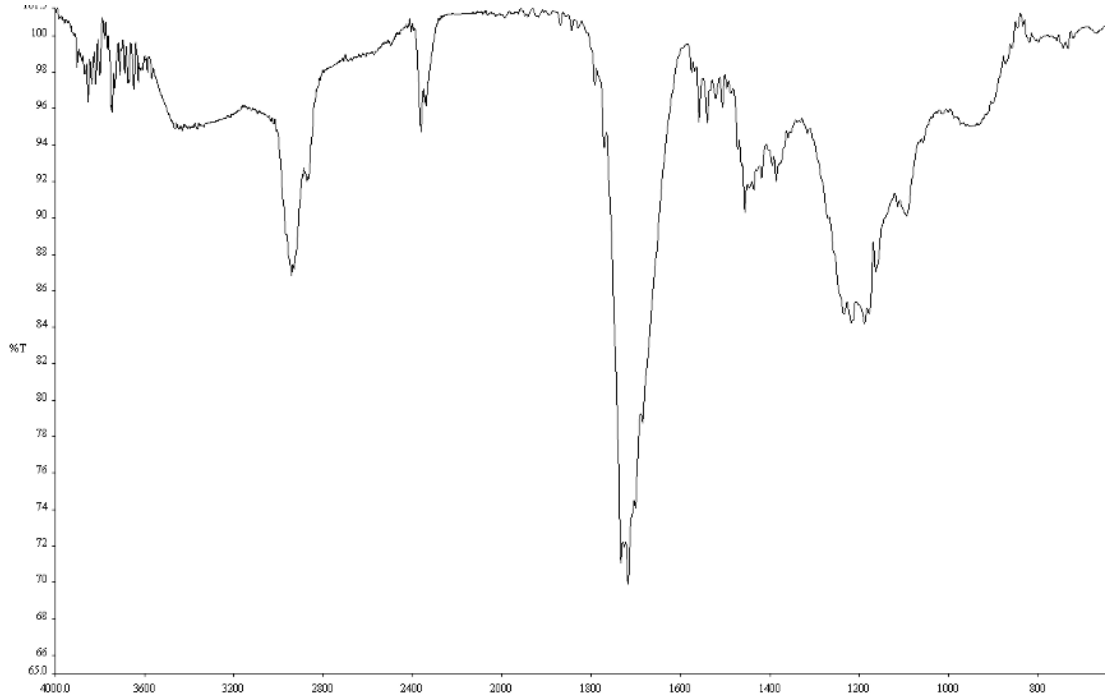


Figure A1.181. *Infrared spectrum (Thin Film, NaCl) of compound* ***56****.*

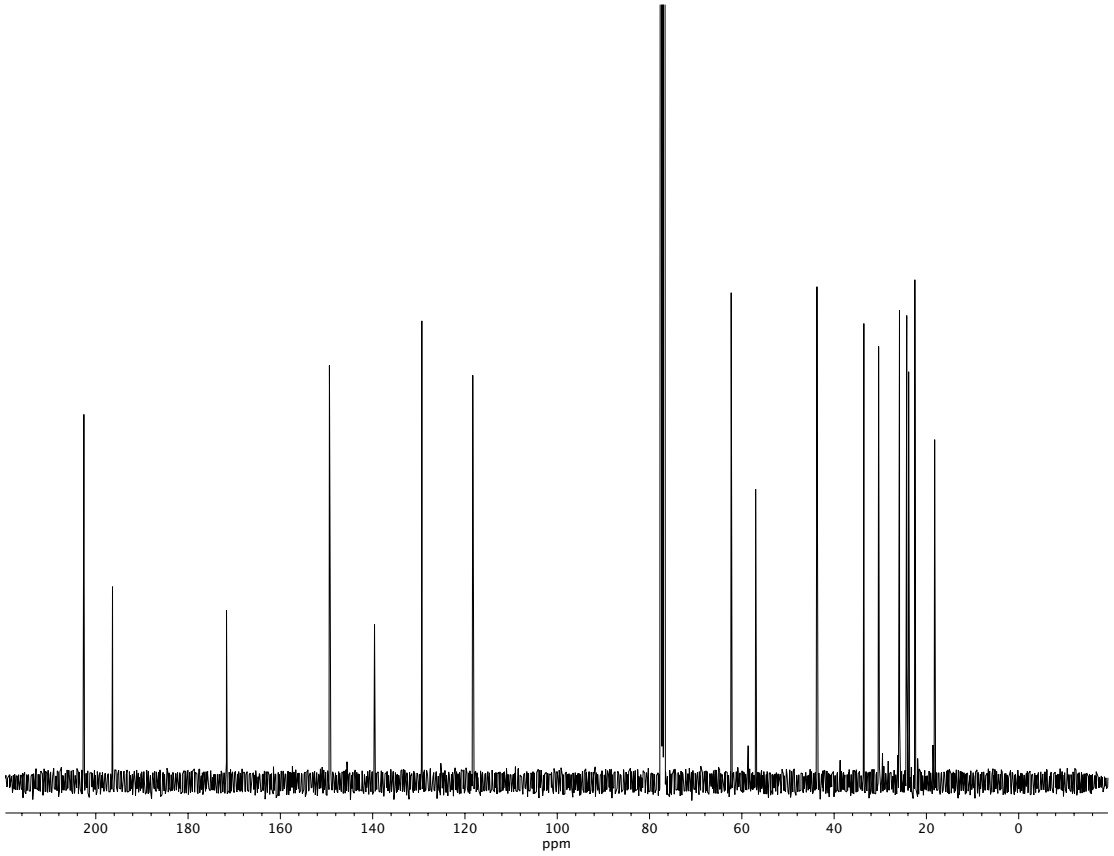


Figure A1.182. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***56****.*

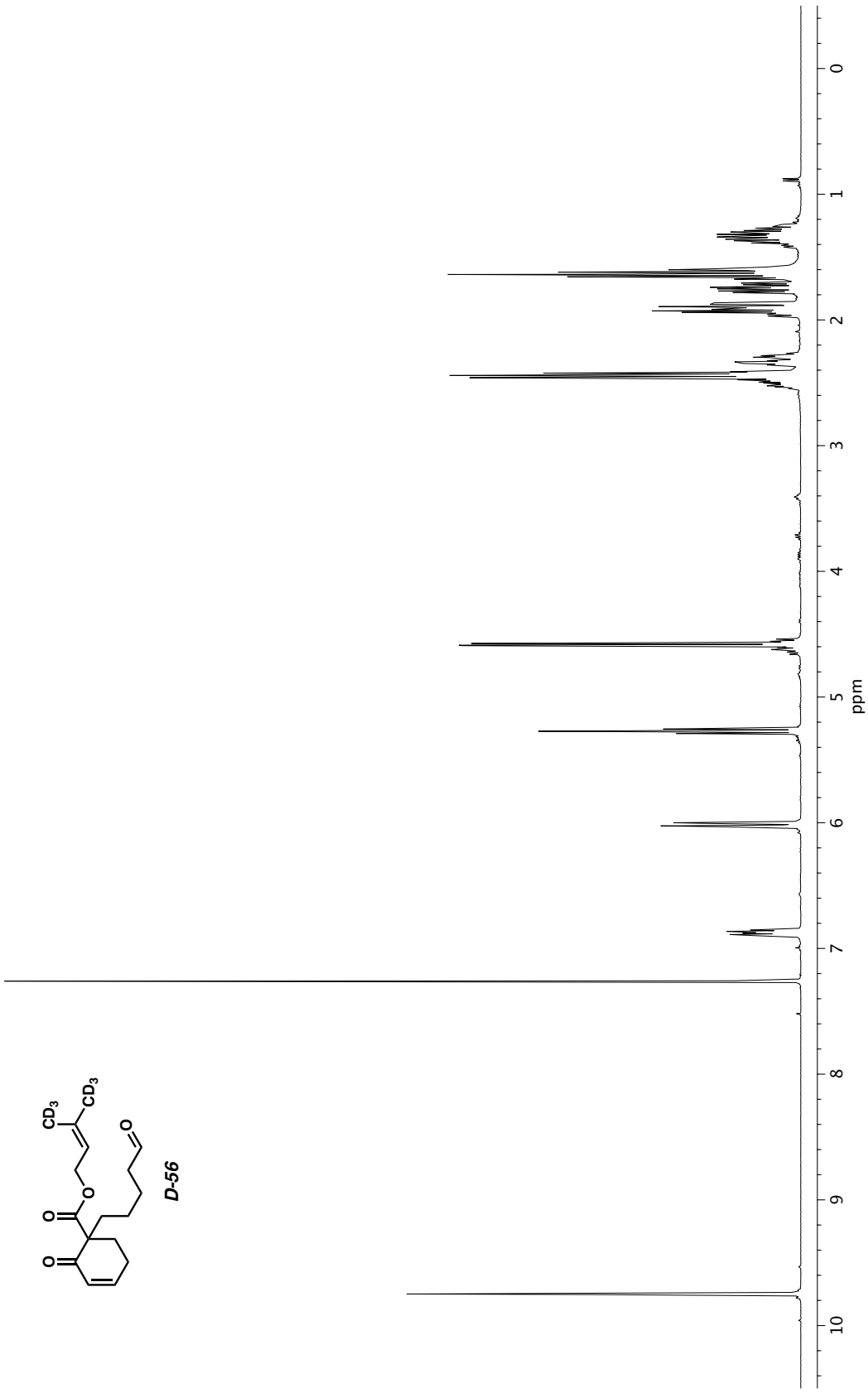


Figure A1.183. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***D-56****.*

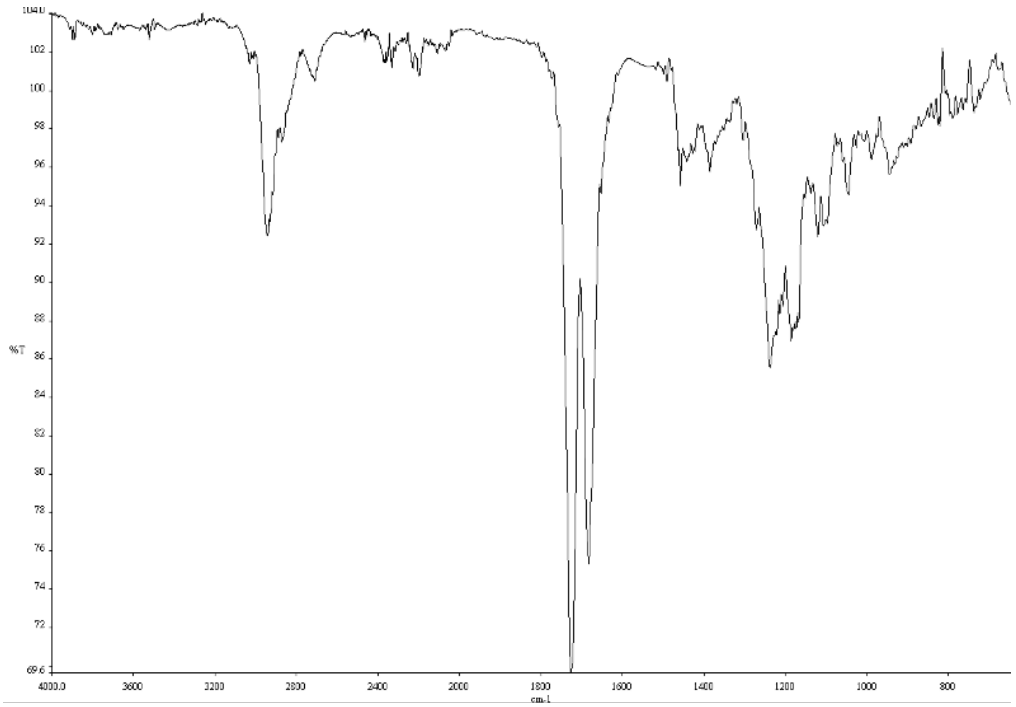


Figure A1.184. *Infrared spectrum (Thin Film, NaCl) of compound* ***D-56***.

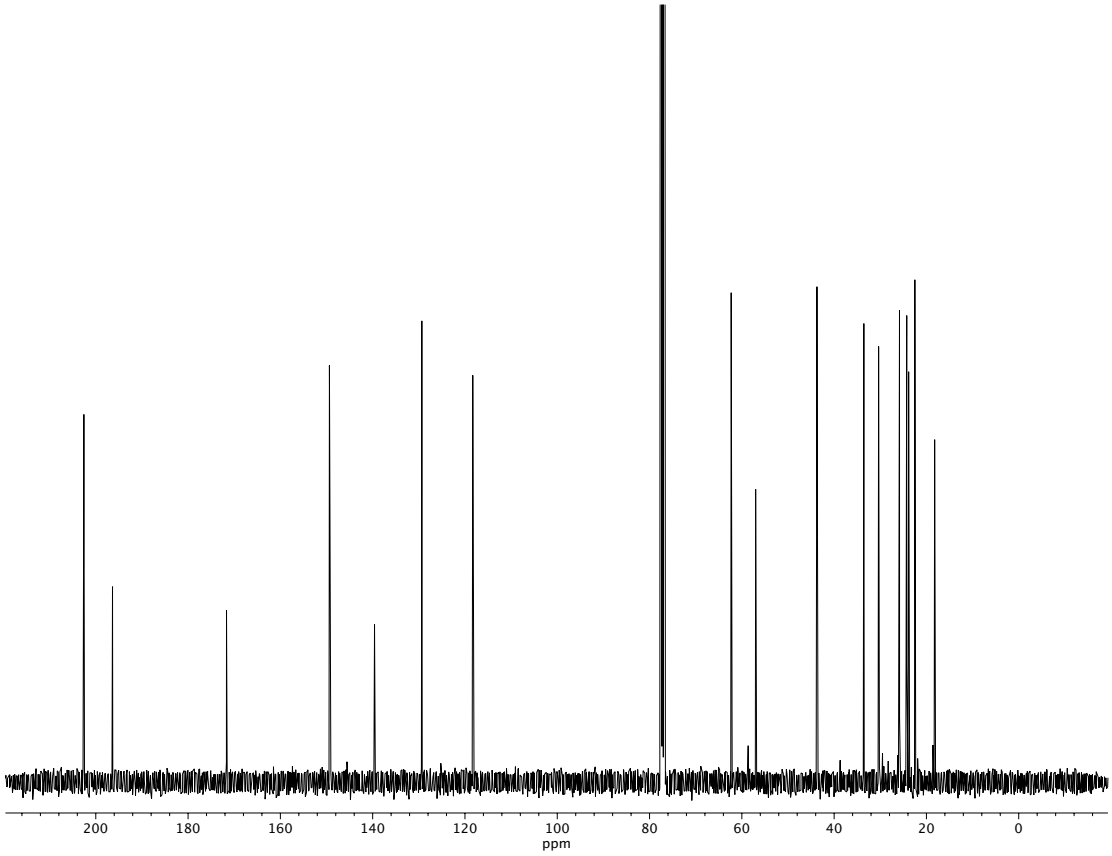


Figure A1.185. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***D-56***.

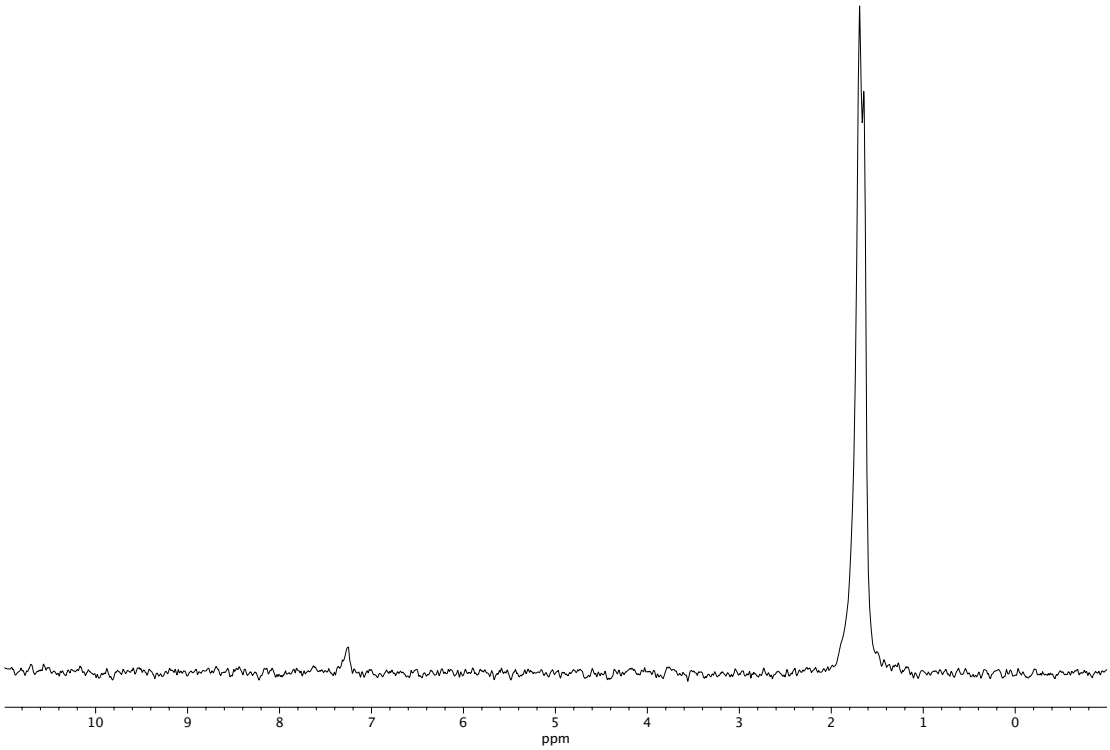


Figure A1.186. *^{2}H NMR (61 MHz, $CHCl_3$) of compound* ***D-56****.*

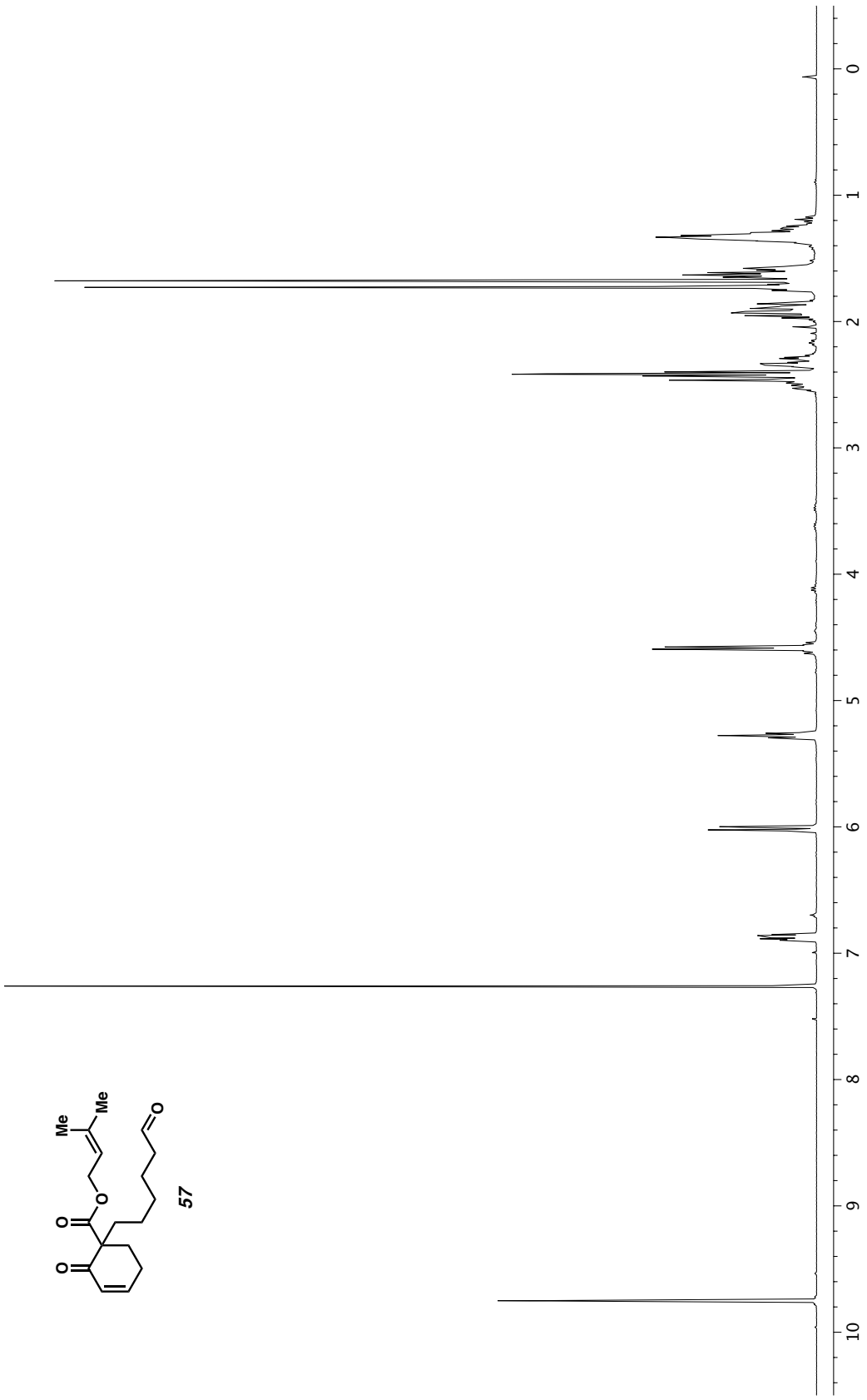


Figure A1.187. *^1H NMR (400 MHz, $CDCl_3$) of compound **57**.*

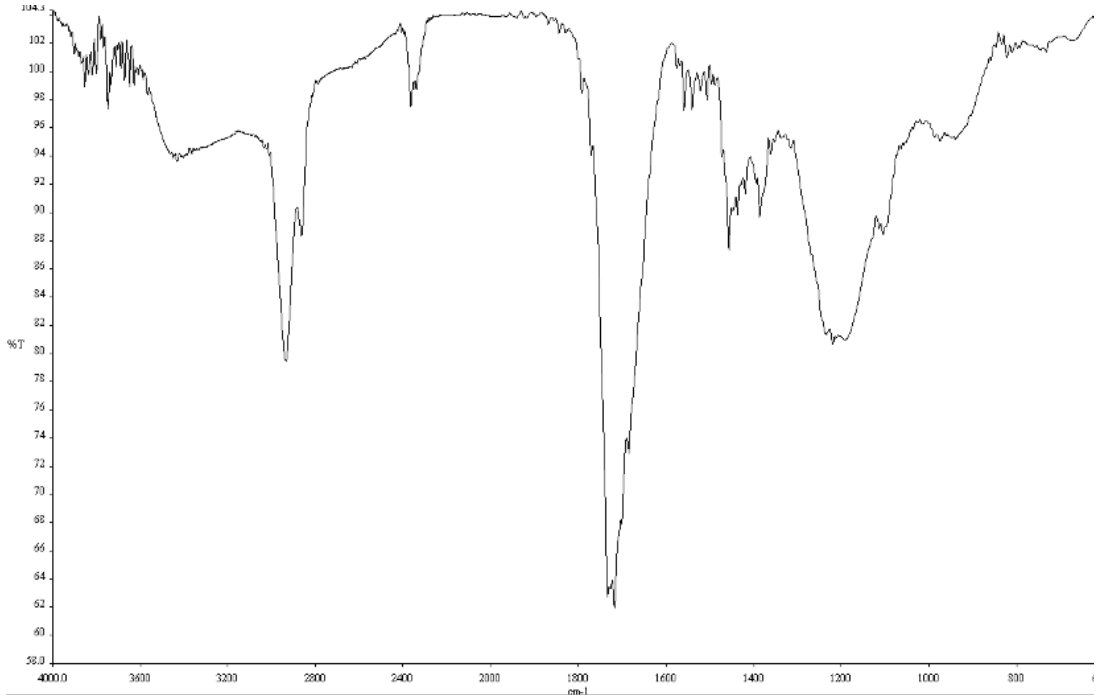


Figure A1.188. *Infrared spectrum (Thin Film, NaCl) of compound* ***57****.*

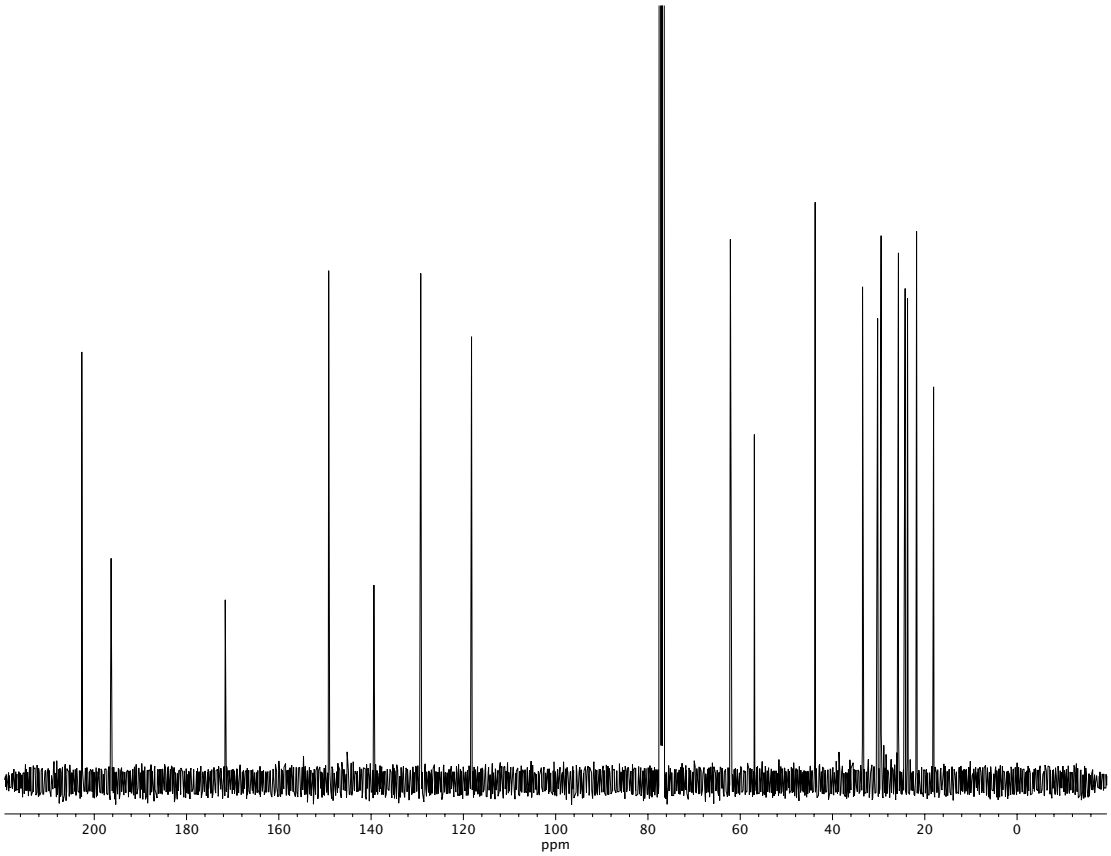


Figure A1.189. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***57****.*

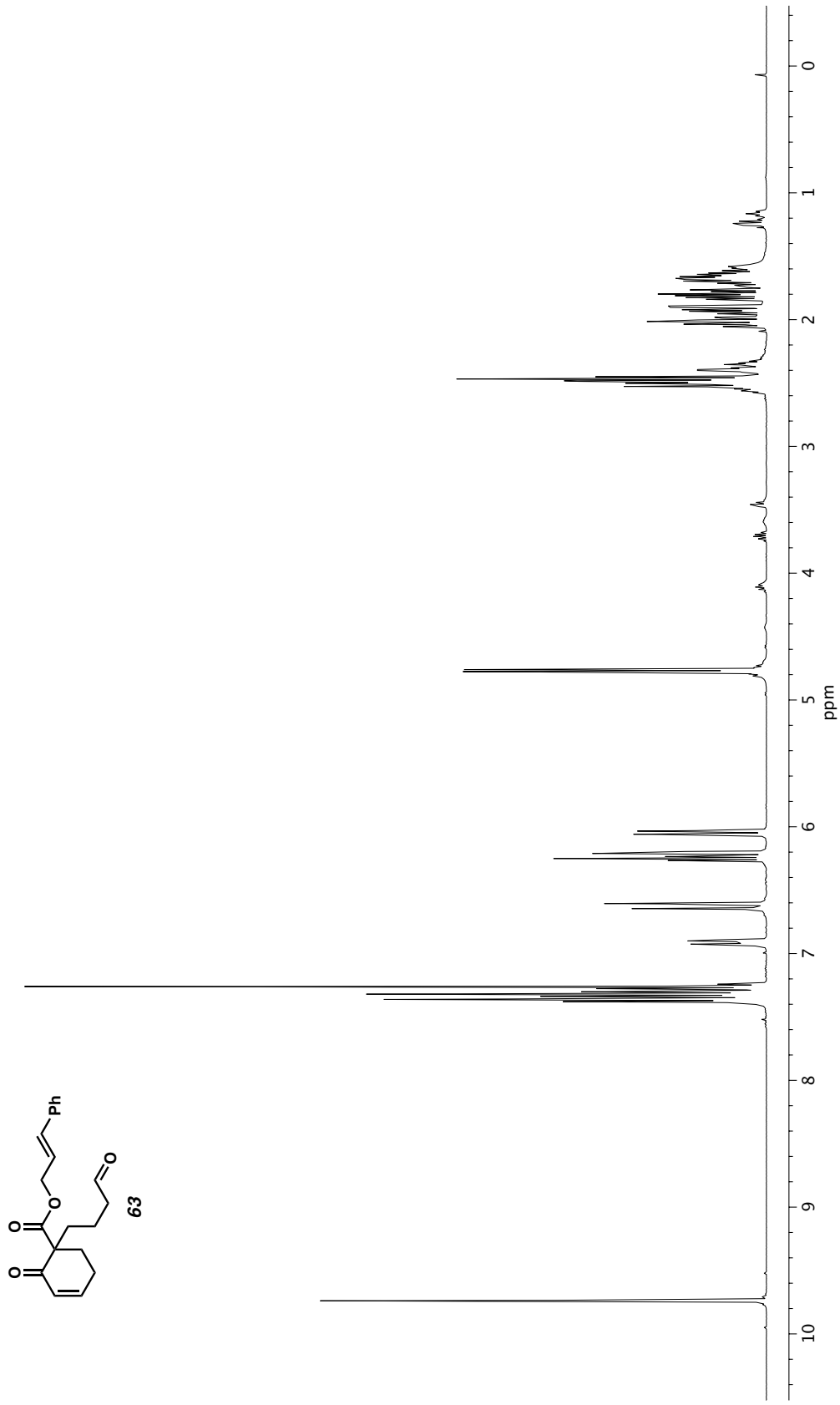


Figure A1.190. *^1H NMR (400 MHz, $CDCl_3$) of compound **63**.*

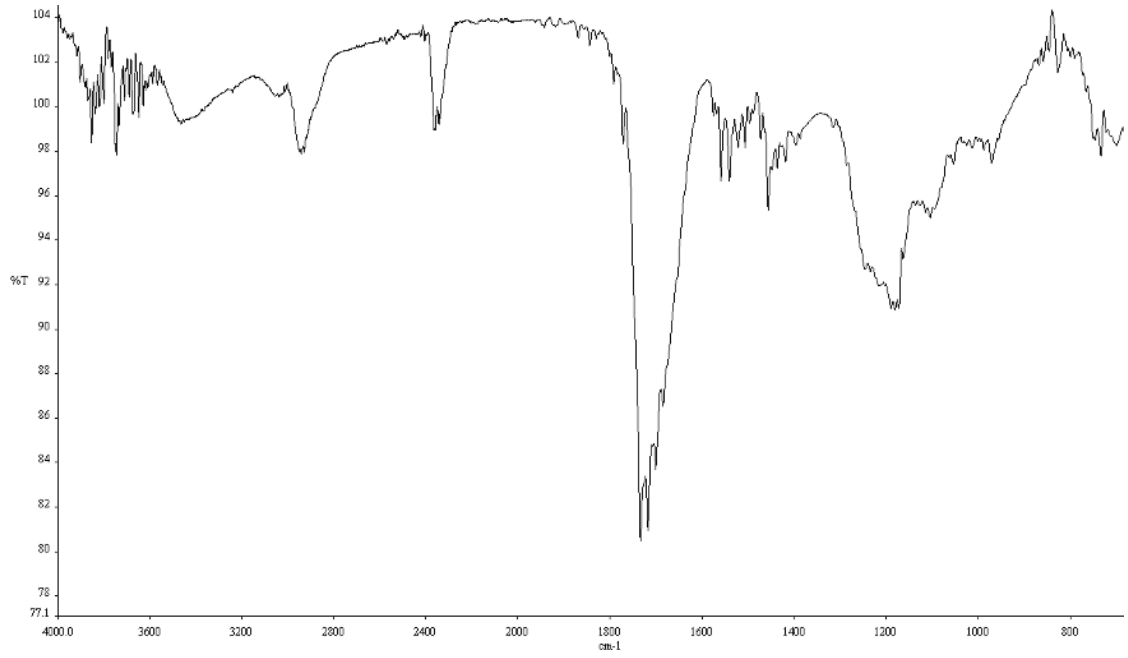


Figure A1.191. *Infrared spectrum (Thin Film, NaCl) of compound* ***63****.*

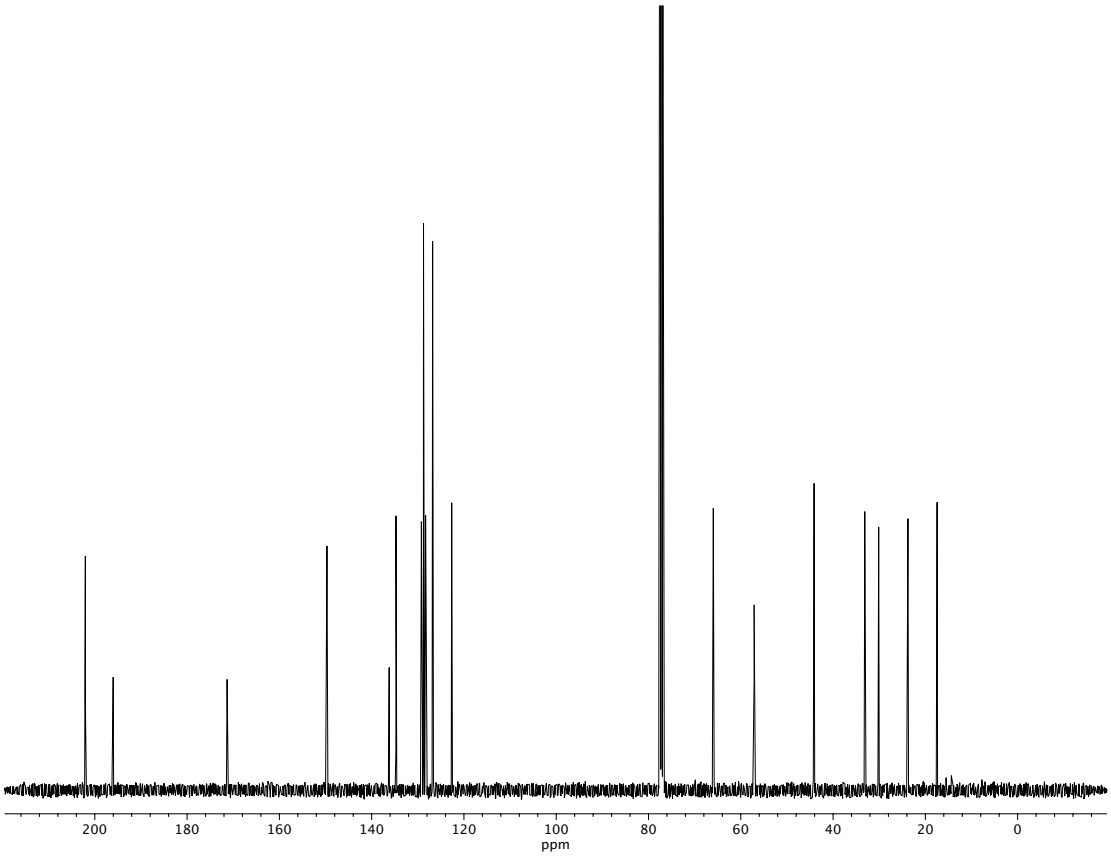


Figure A1.192. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***63****.*

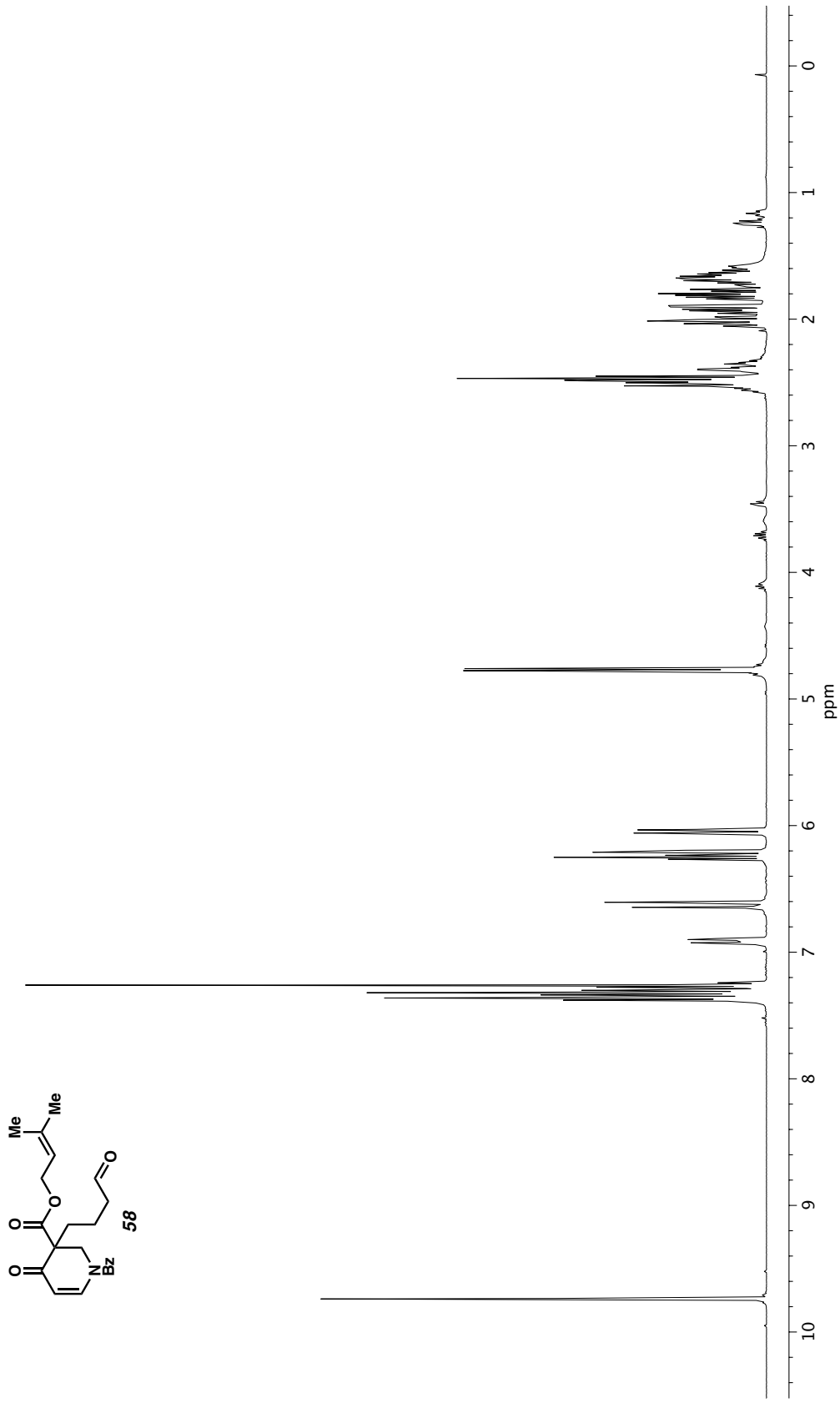


Figure A1.193. *^1H NMR (400 MHz, $CDCl_3$) of compound **58**.*

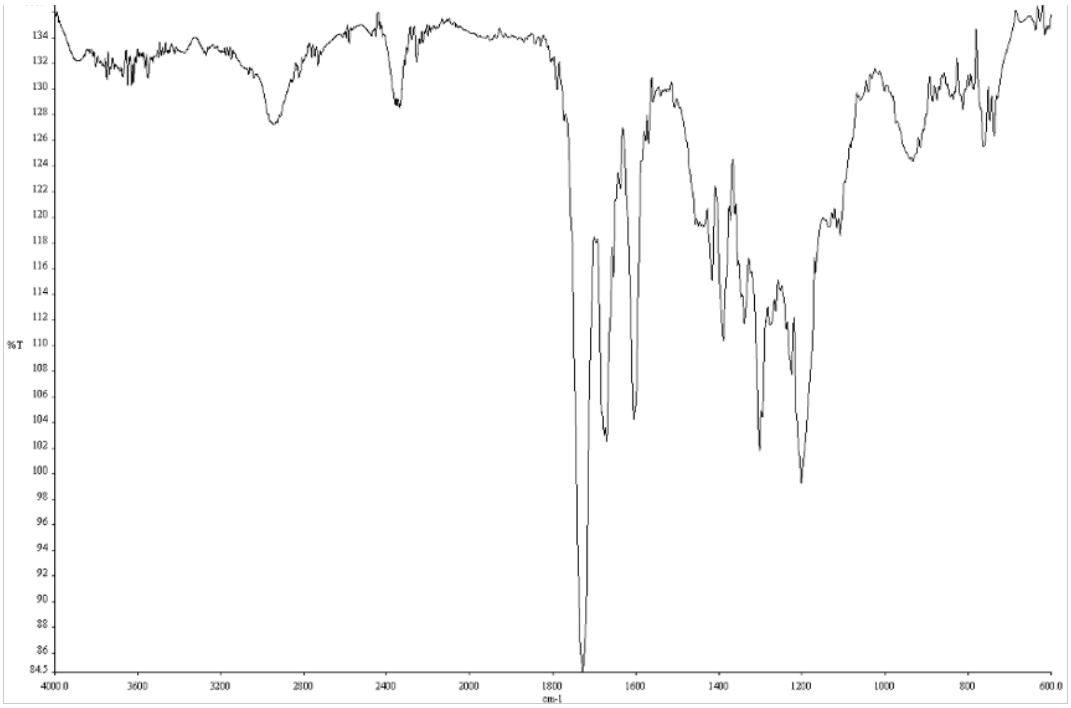


Figure A1.194. *Infrared spectrum (Thin Film, NaCl) of compound* ***58****.*

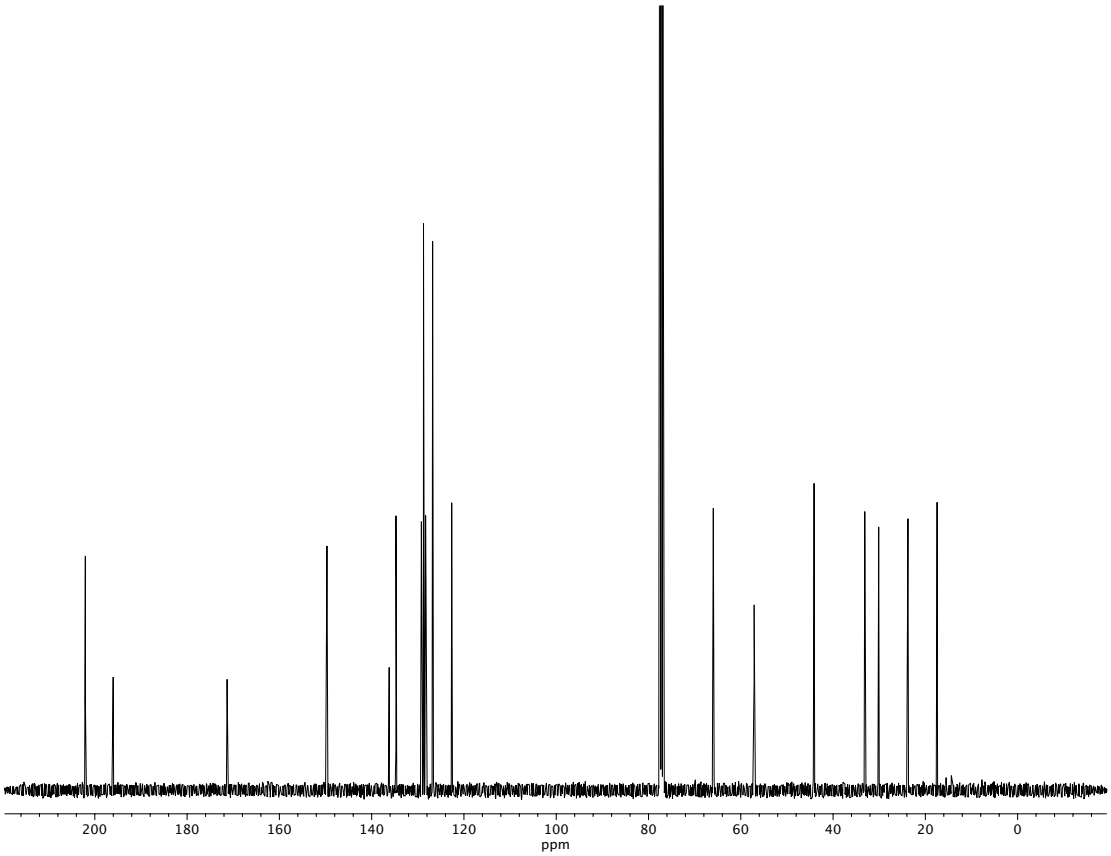


Figure A1.195. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***58****.*

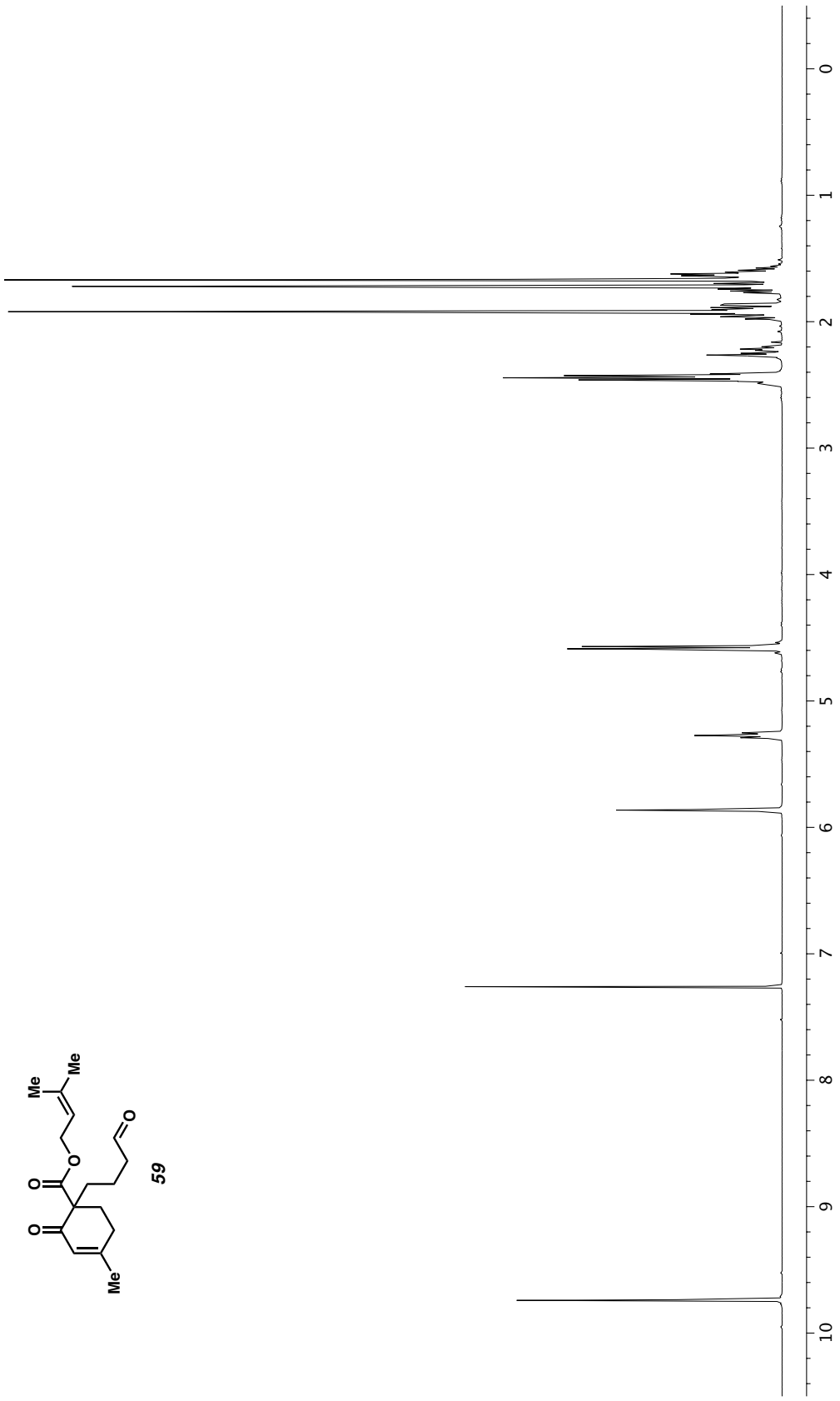


Figure A1.196. *^1H NMR (400 MHz, $CDCl_3$) of compound **59**.*

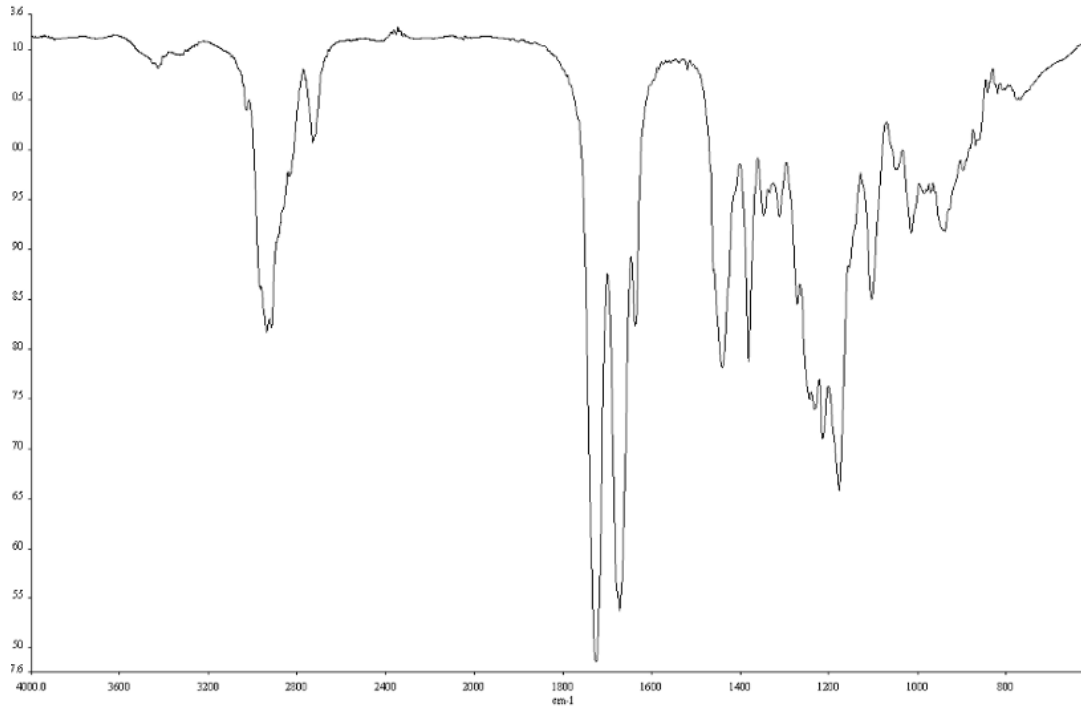


Figure A1.197. *Infrared spectrum (Thin Film, NaCl) of compound* ***59****.*

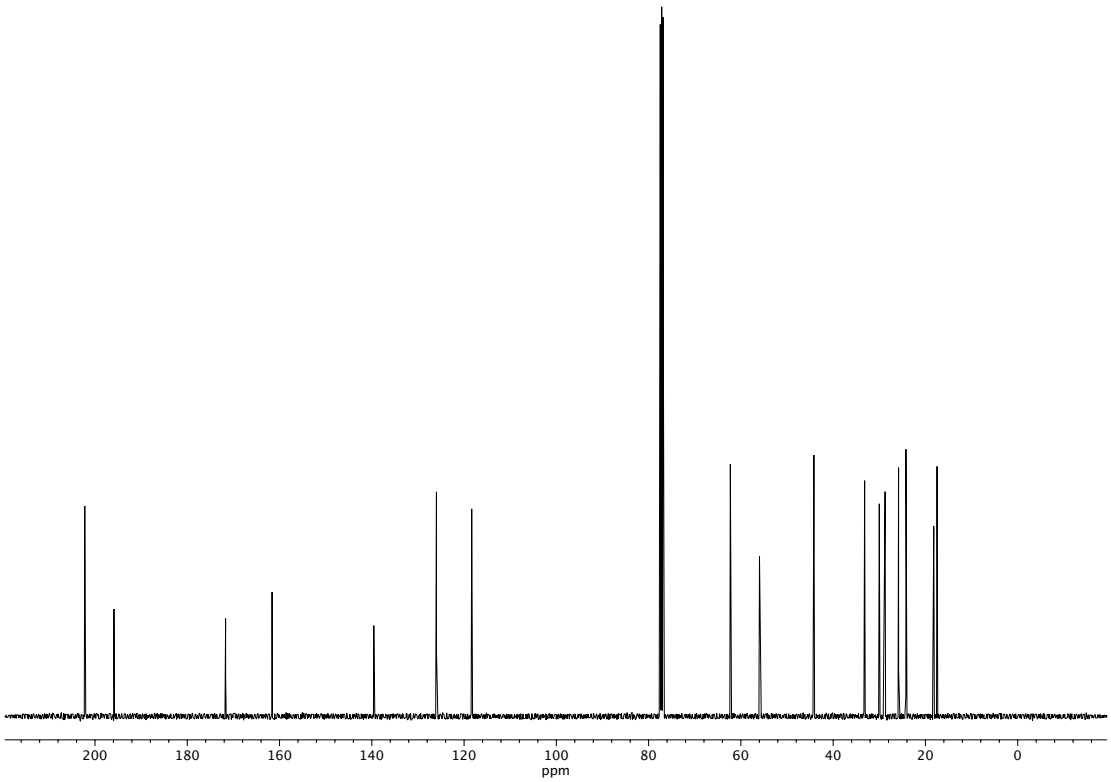
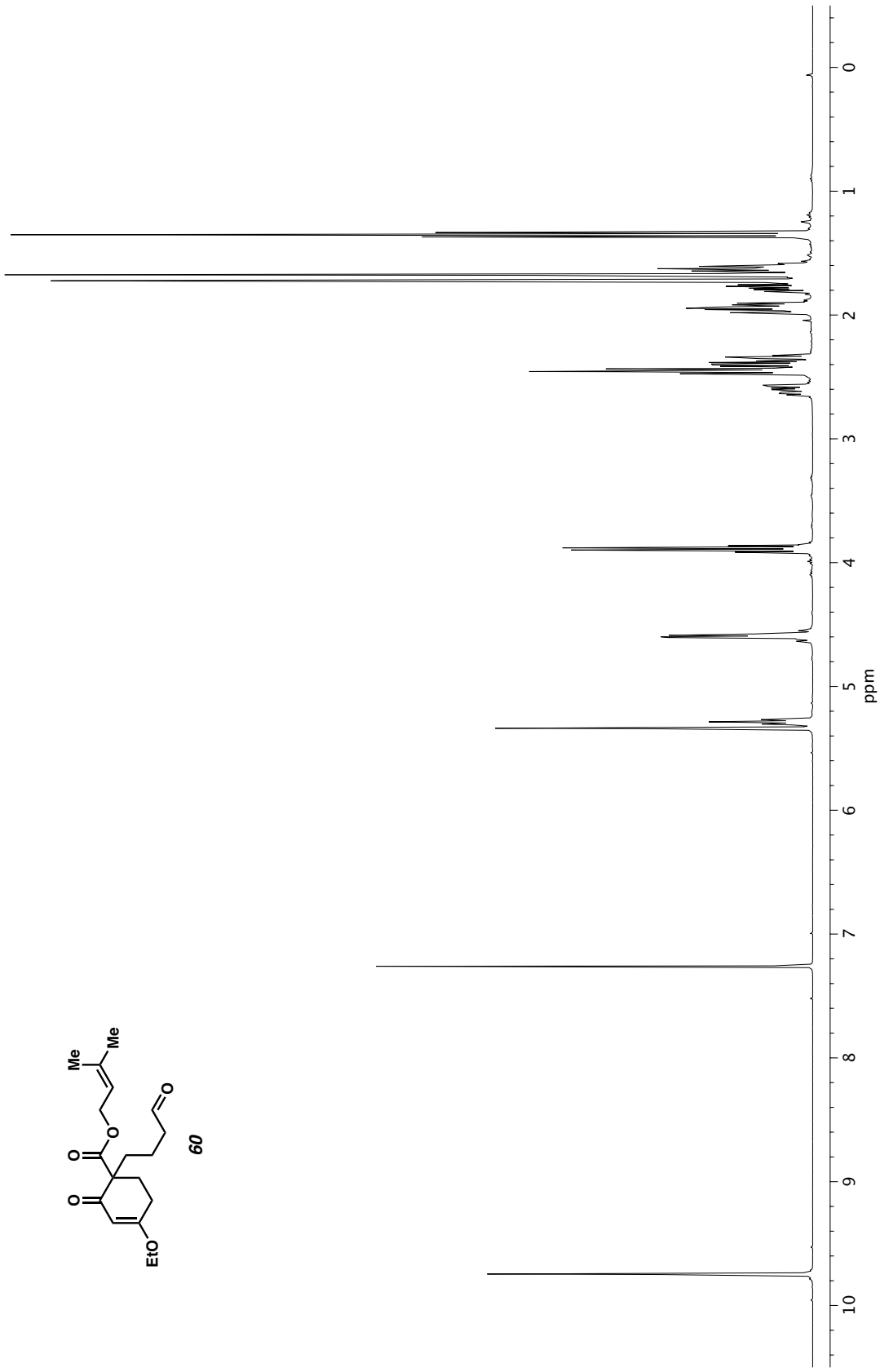


Figure A1.198. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***59****.*



60

Figure A1.199. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***60****.*

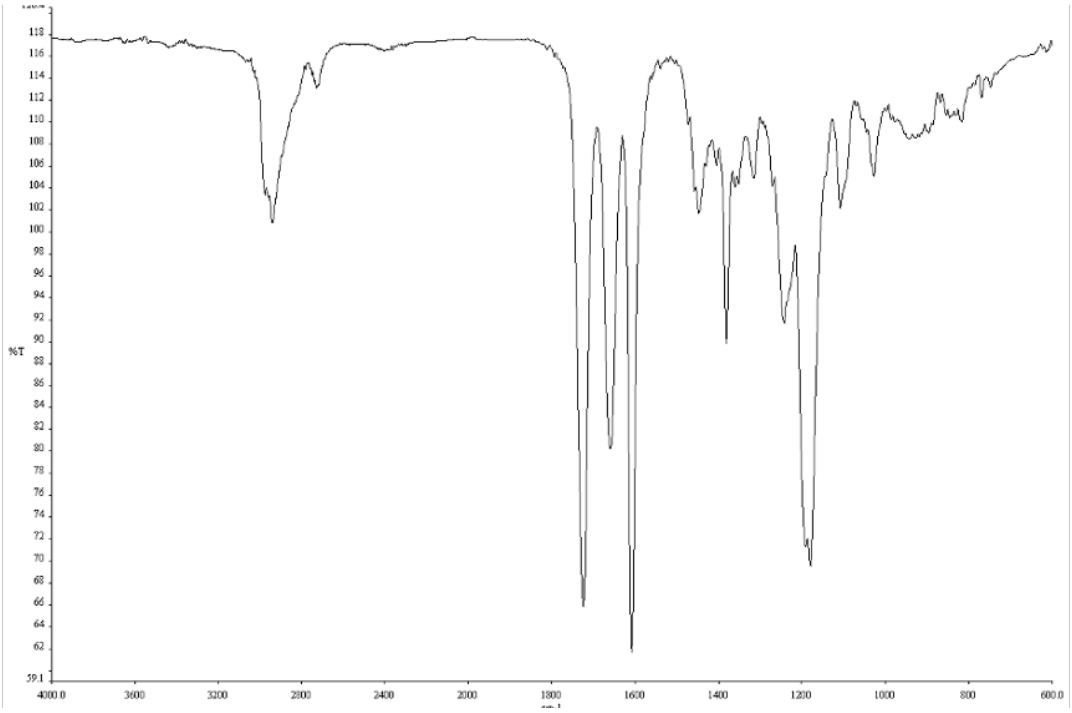


Figure A1.200. *Infrared spectrum (Thin Film, NaCl) of compound* ***60****.*

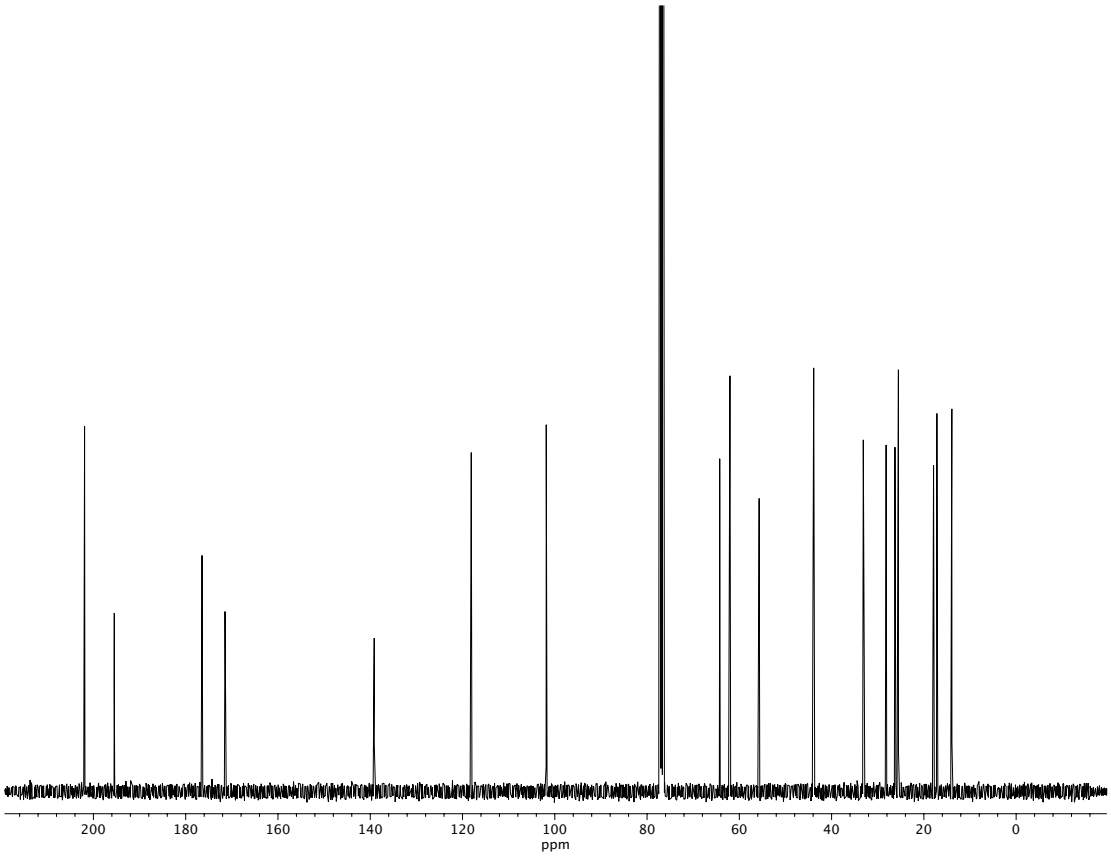


Figure A1.201. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***60****.*

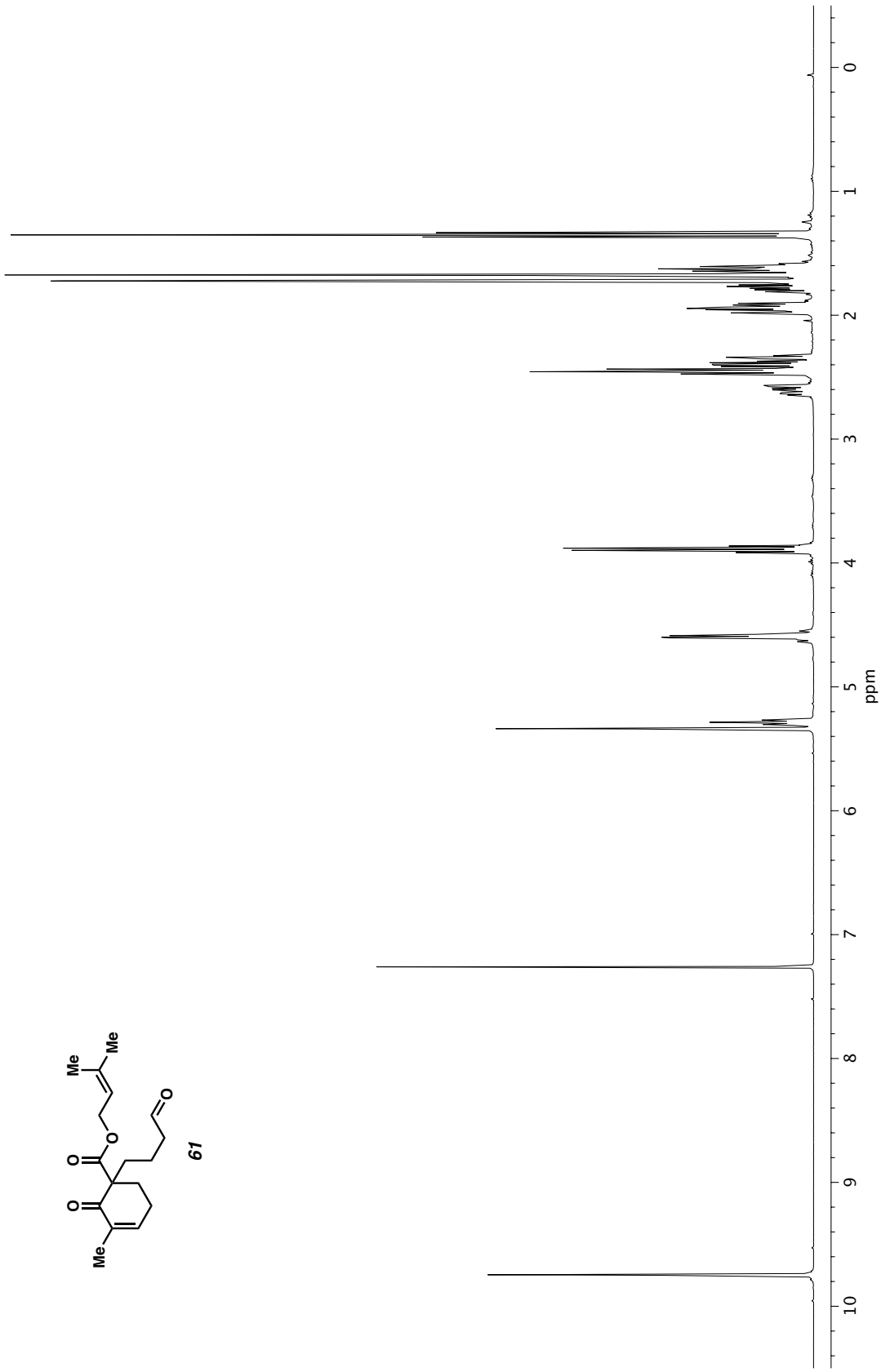


Figure A1.202. *^1H NMR (400 MHz, $CDCl_3$) of compound **61**.*

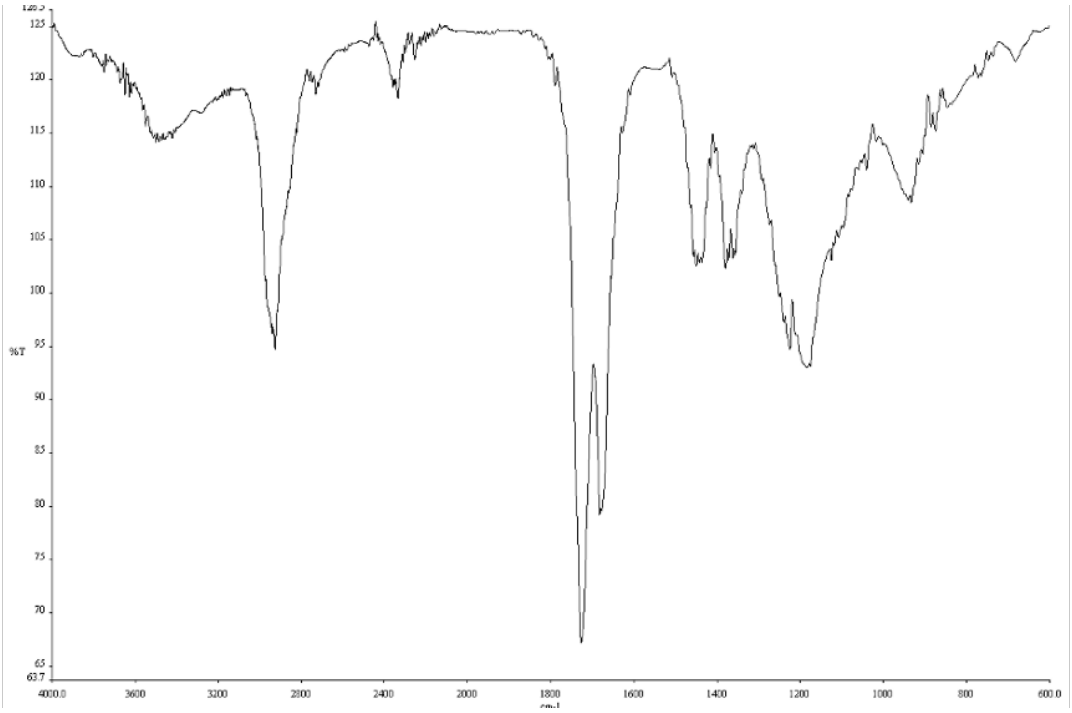


Figure A1.203. *Infrared spectrum (Thin Film, NaCl) of compound* ***61****.*

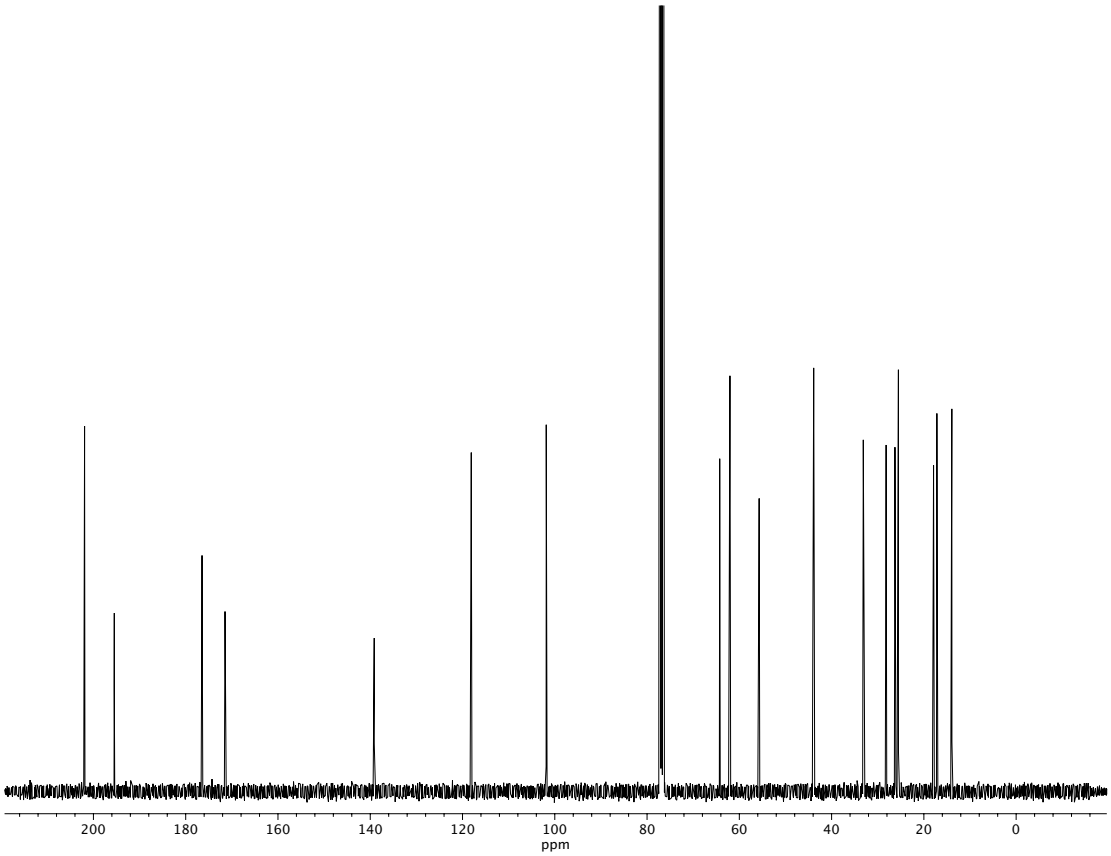


Figure A1.204. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***61****.*

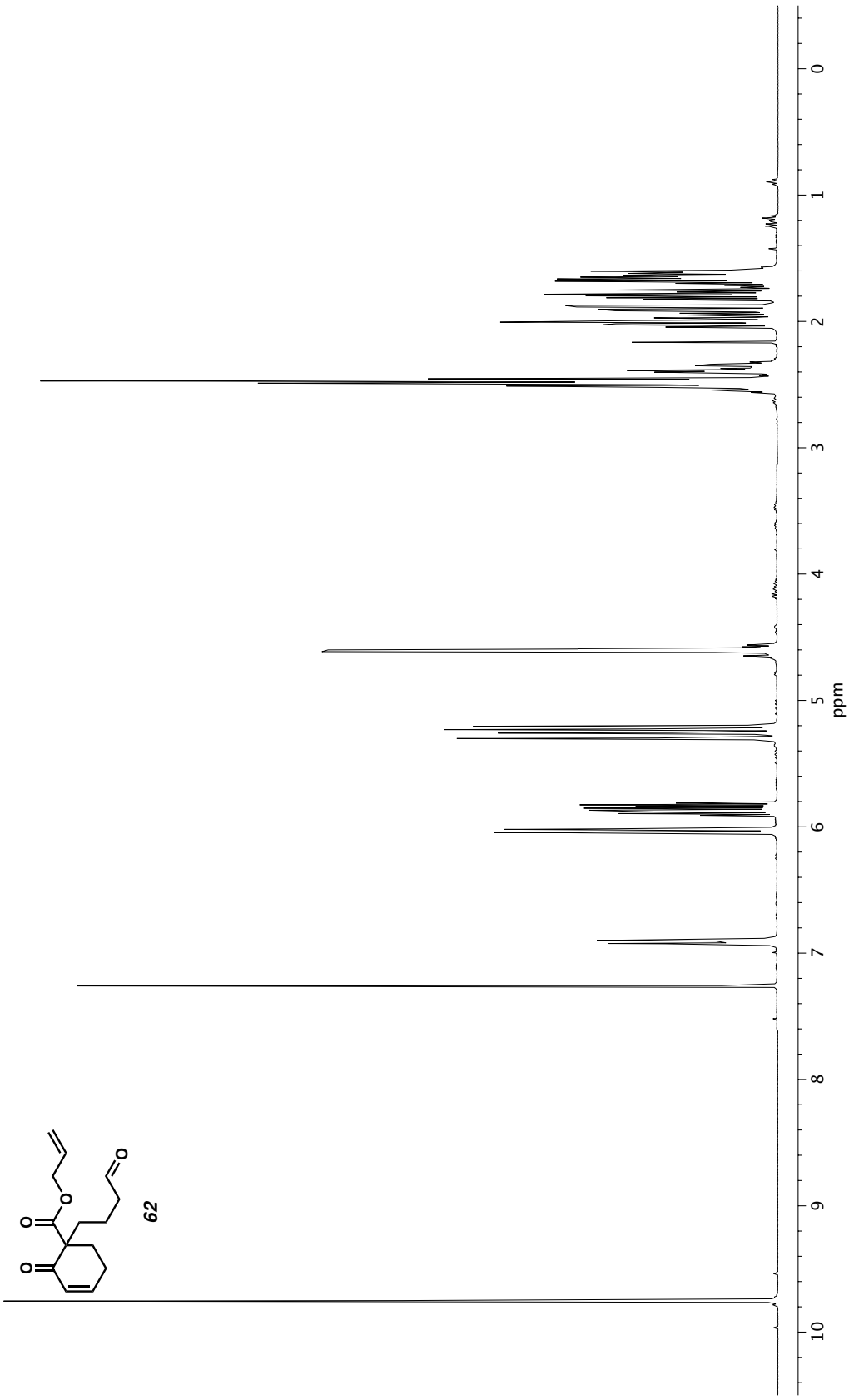


Figure A1.205. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***62****.*

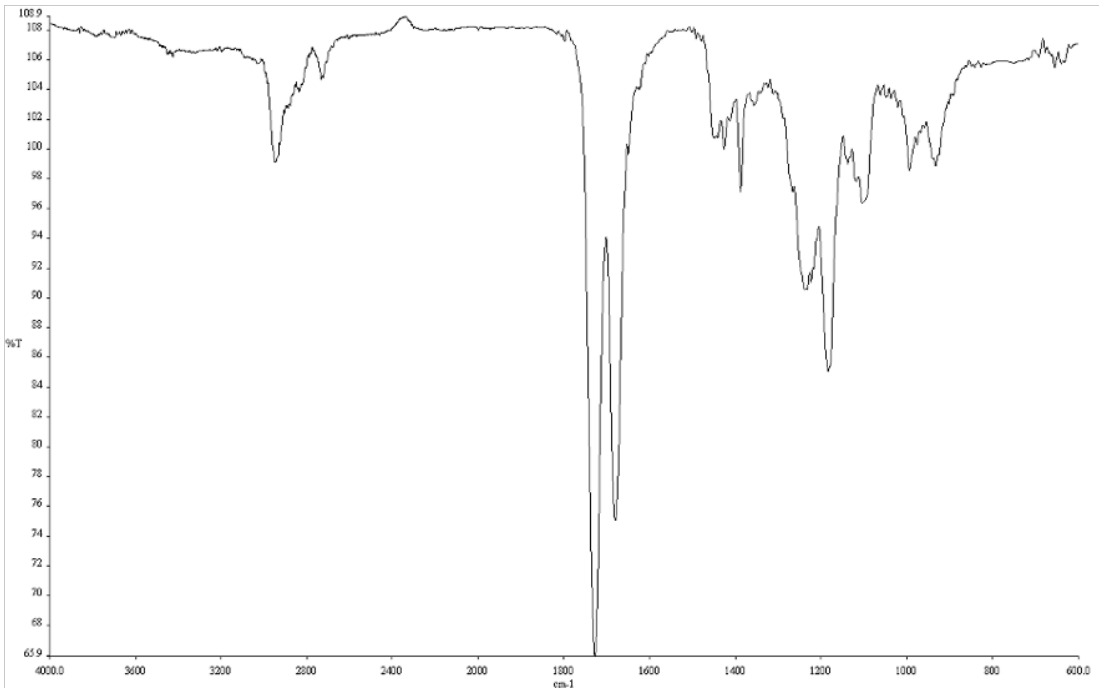


Figure A1.206. *Infrared spectrum (Thin Film, NaCl) of compound* ***62****.*

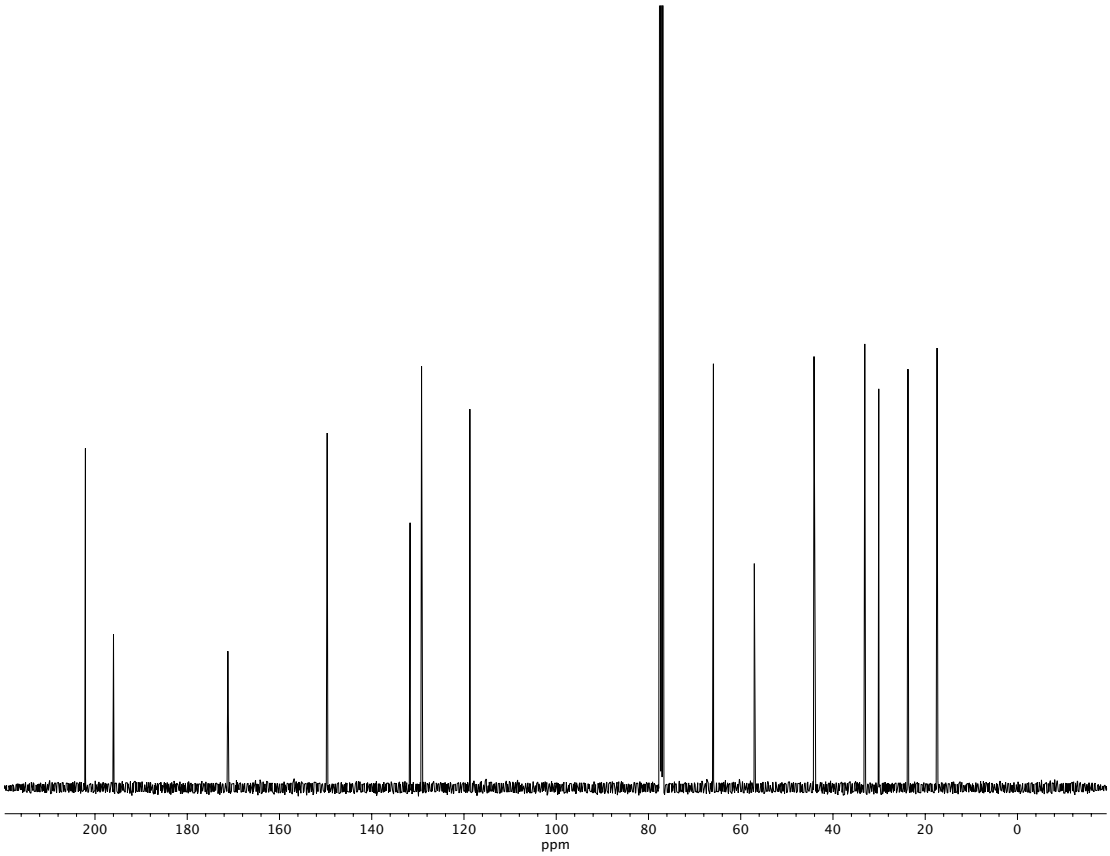


Figure A1.207. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***62****.*

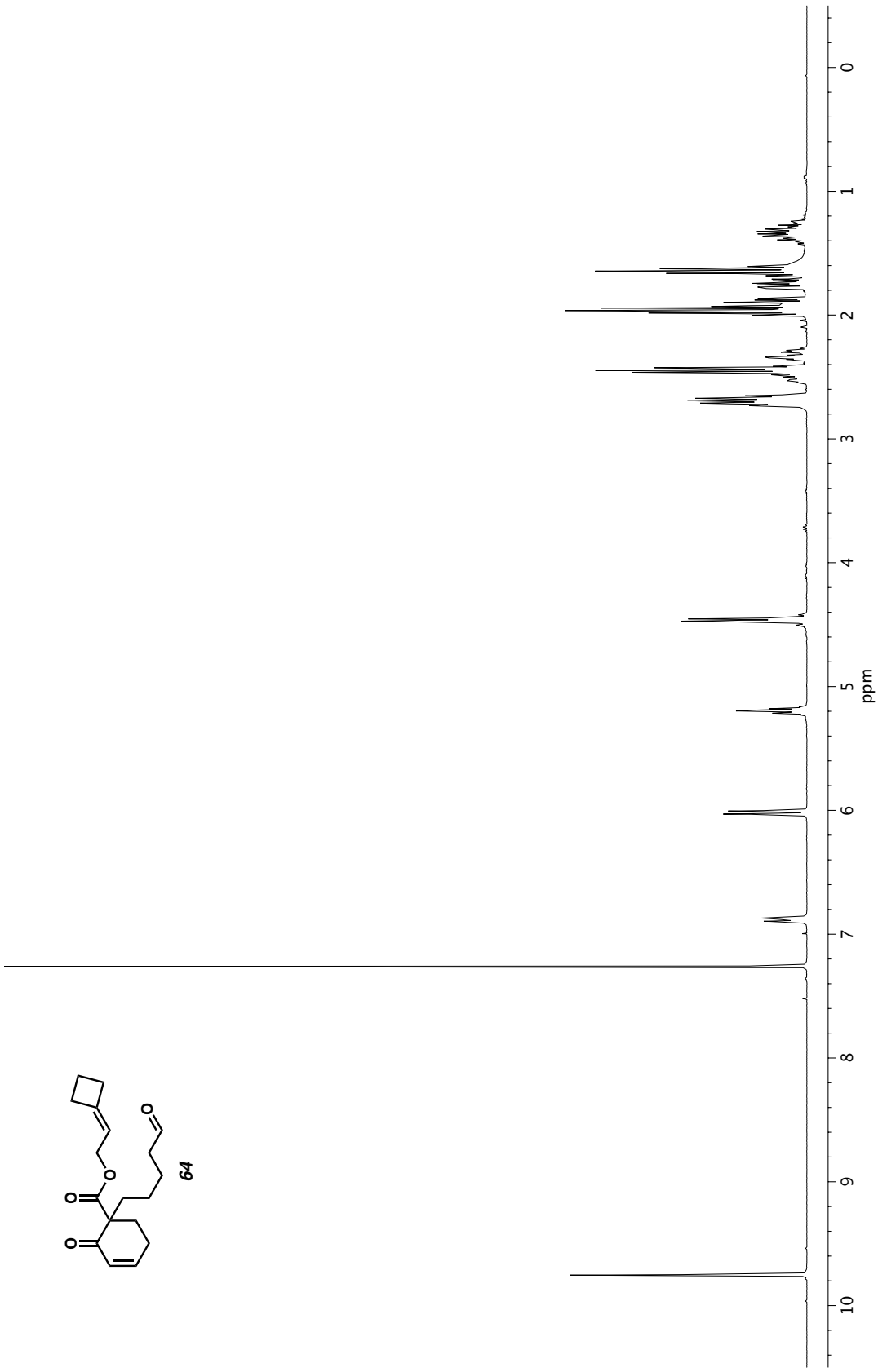


Figure A1.208. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***64****.*

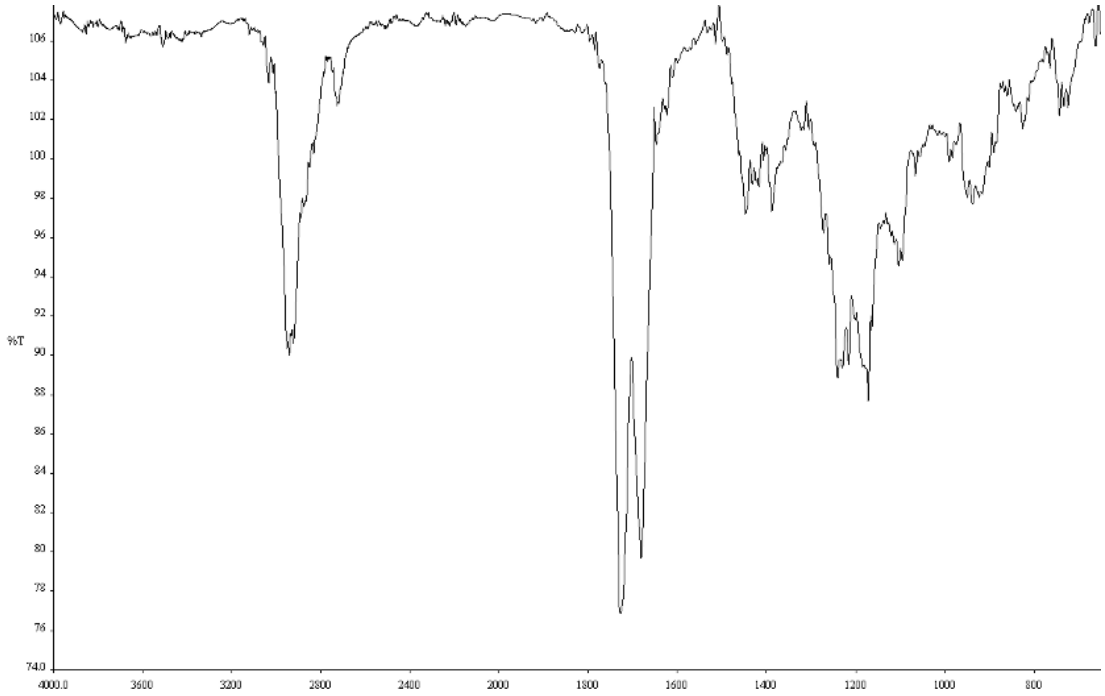


Figure A1.209. *Infrared spectrum (Thin Film, NaCl) of compound* ***64****.*

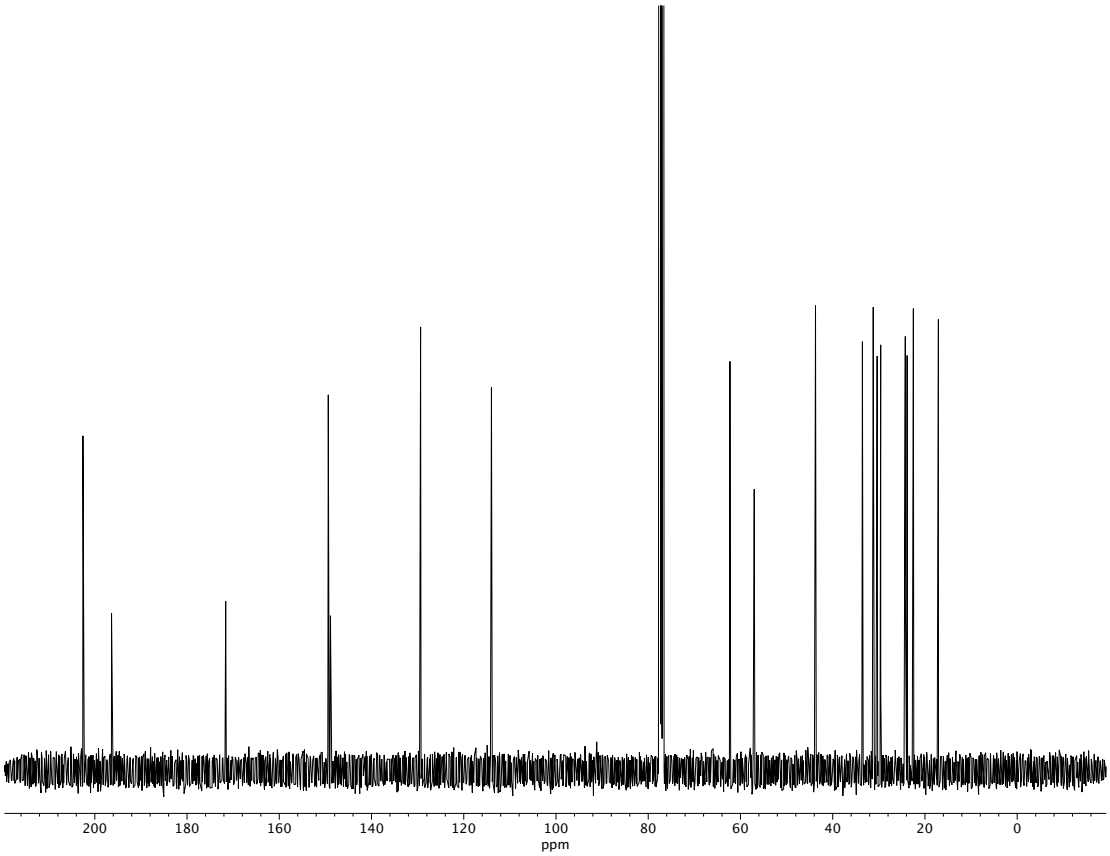


Figure A1.210. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***64****.*

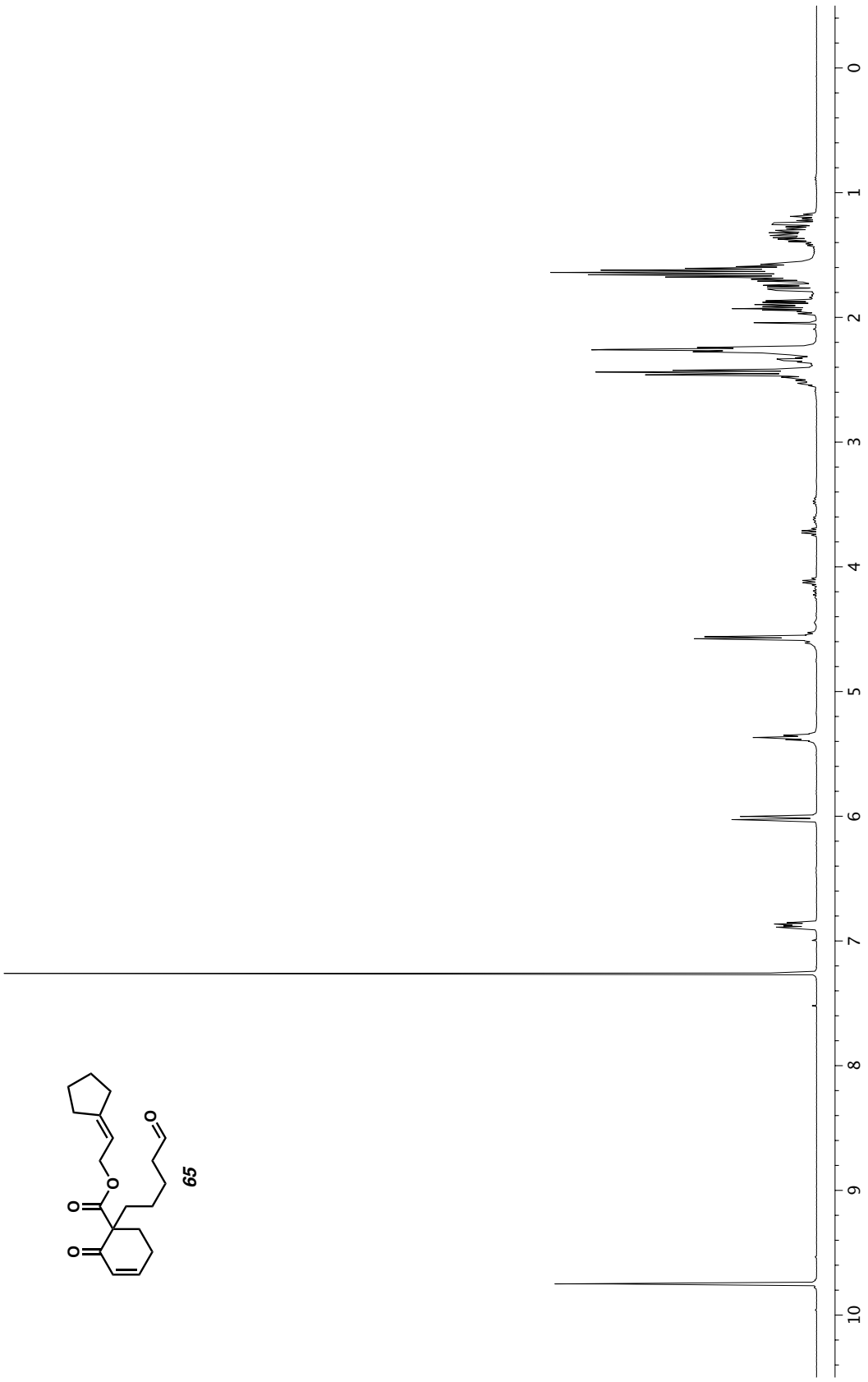


Figure A1.211. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***65****.*

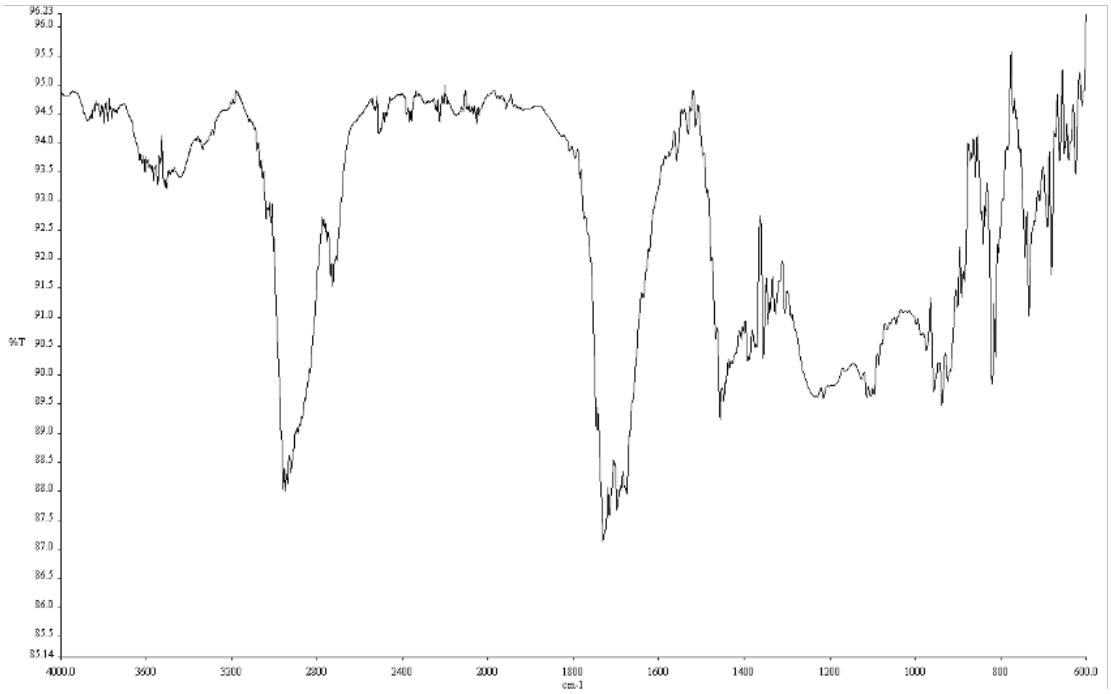


Figure A1.212. *Infrared spectrum (Thin Film, NaCl) of compound* ***65****.*

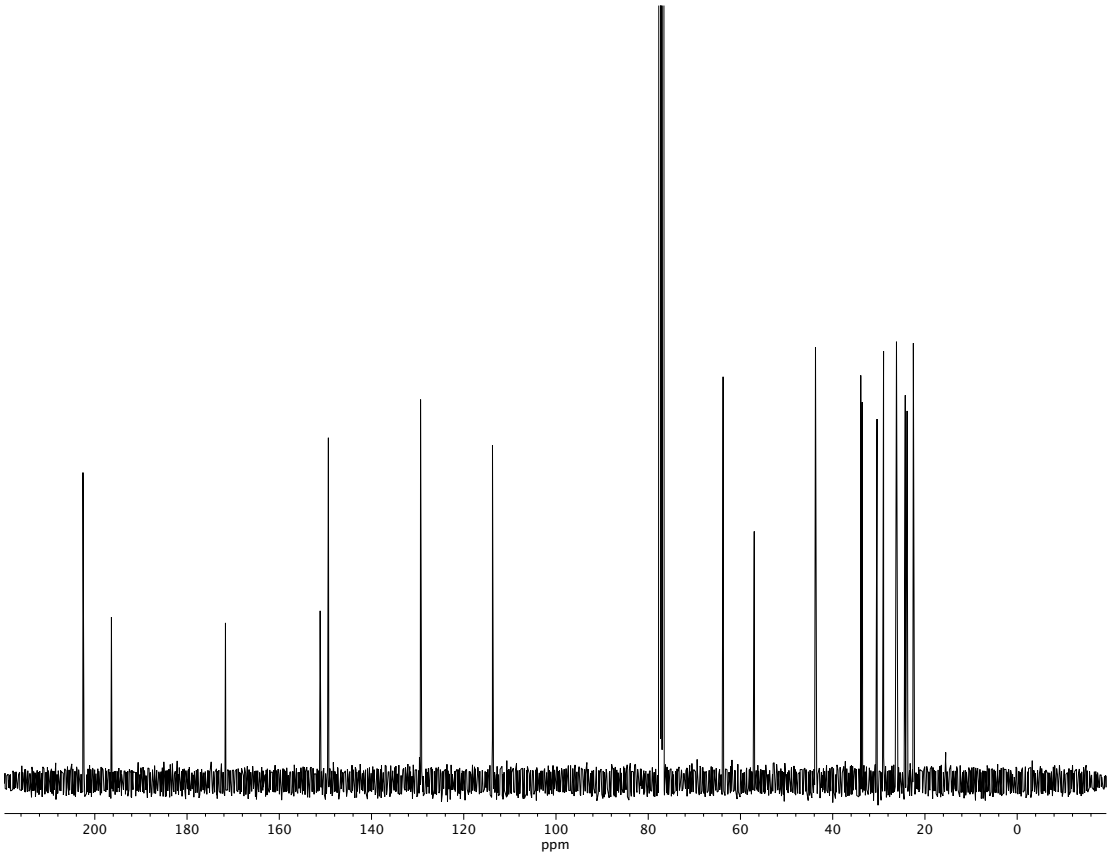


Figure A1.213. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***65****.*

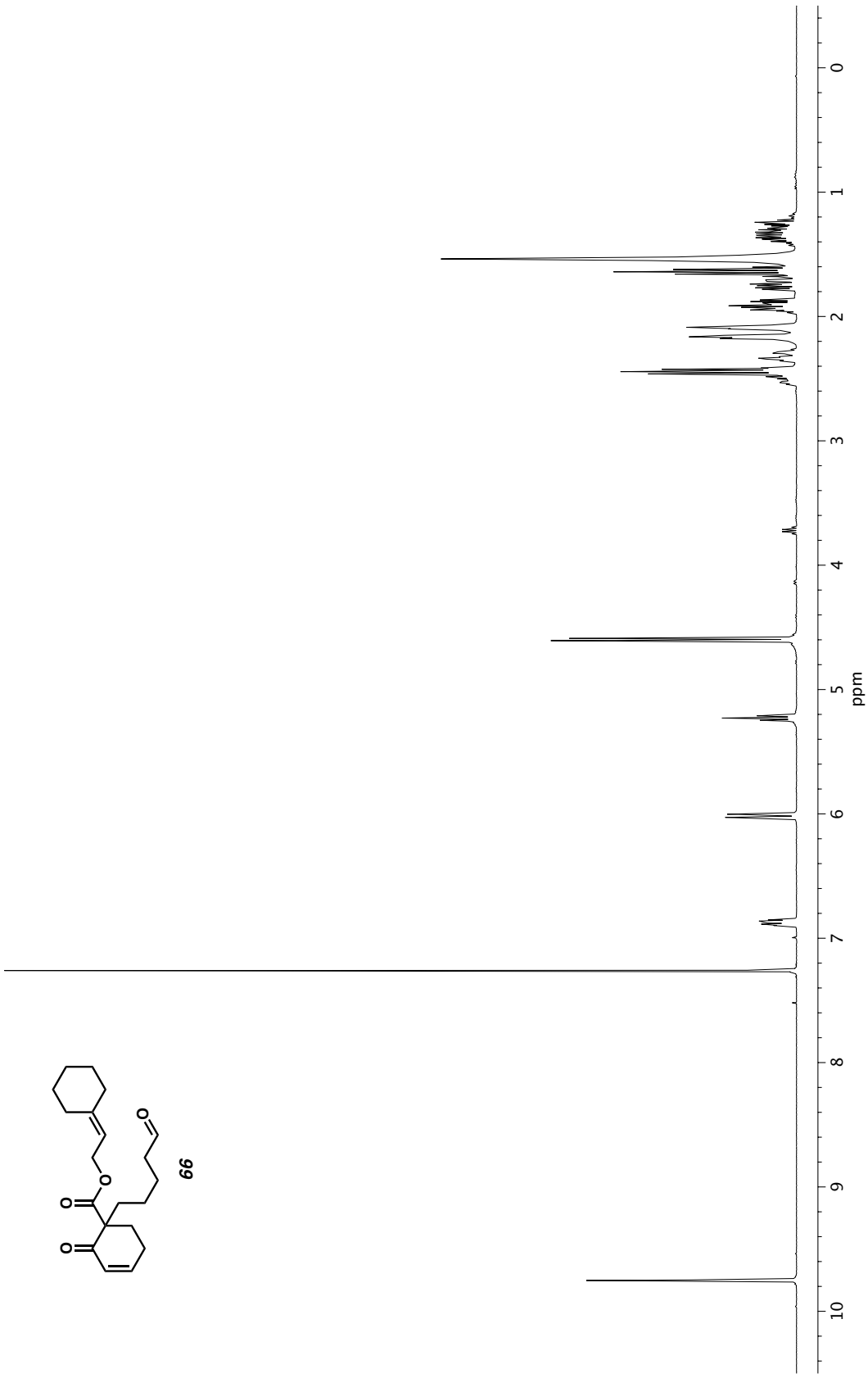


Figure A1.214. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***66****.*

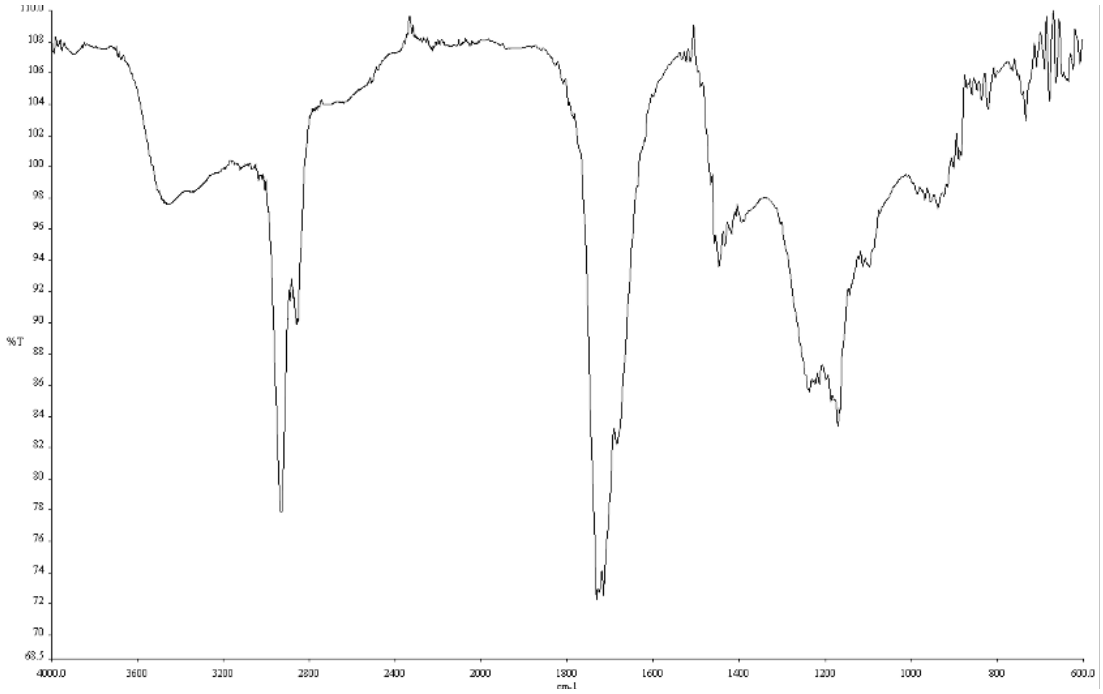


Figure A1.215. *Infrared spectrum (Thin Film, NaCl) of compound* ***66****.*

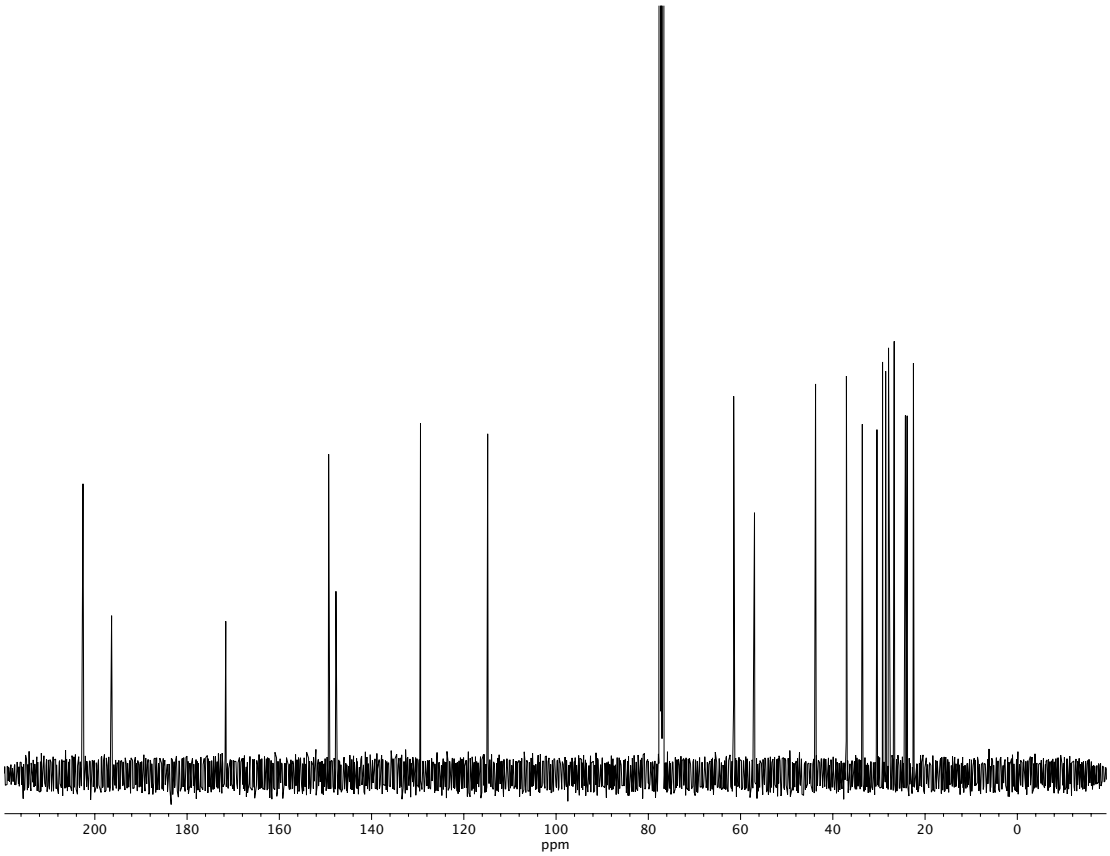


Figure A1.216. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***66****.*

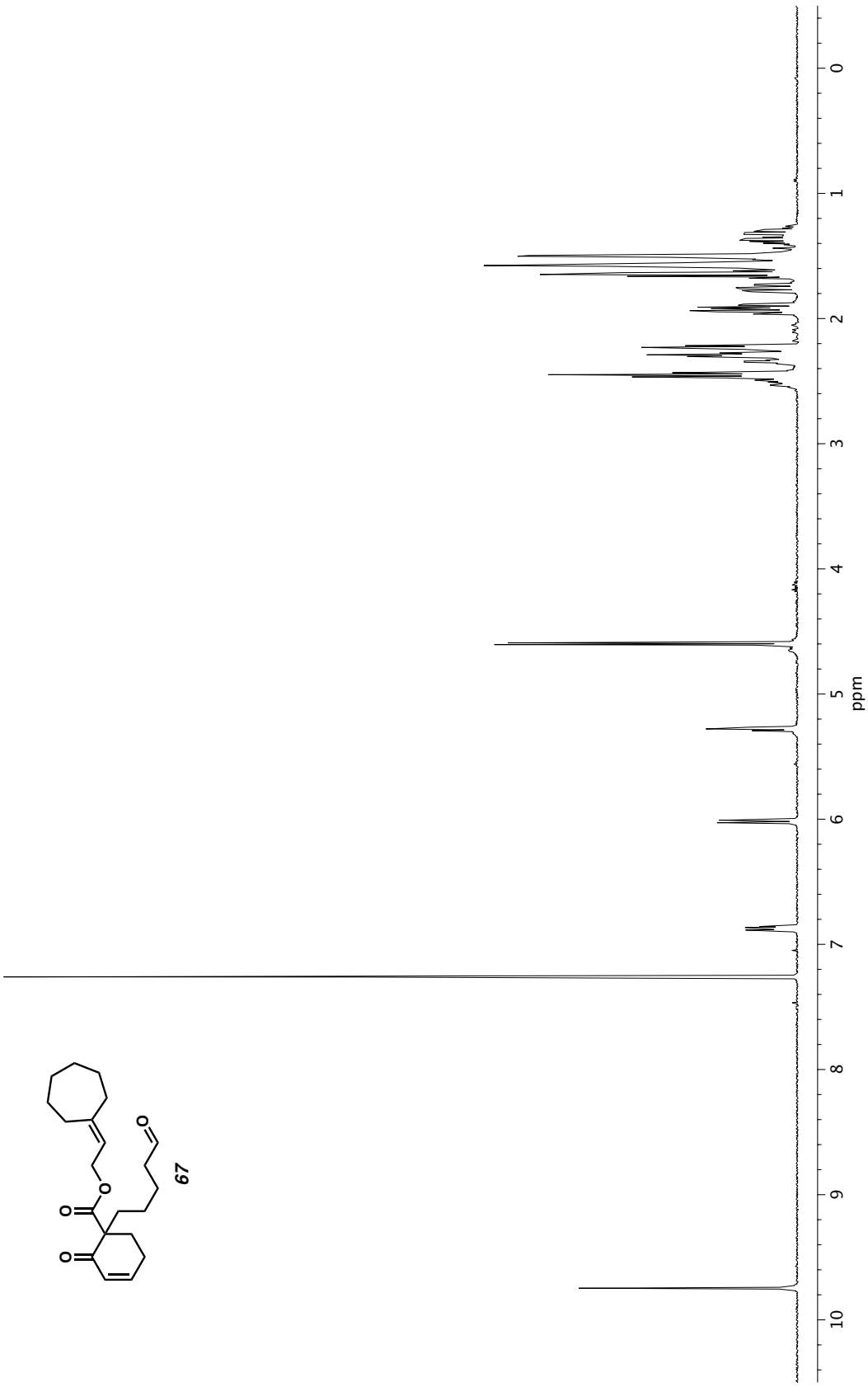


Figure A1.217. *^1H NMR (400 MHz, $CDCl_3$) of compound **67**.*

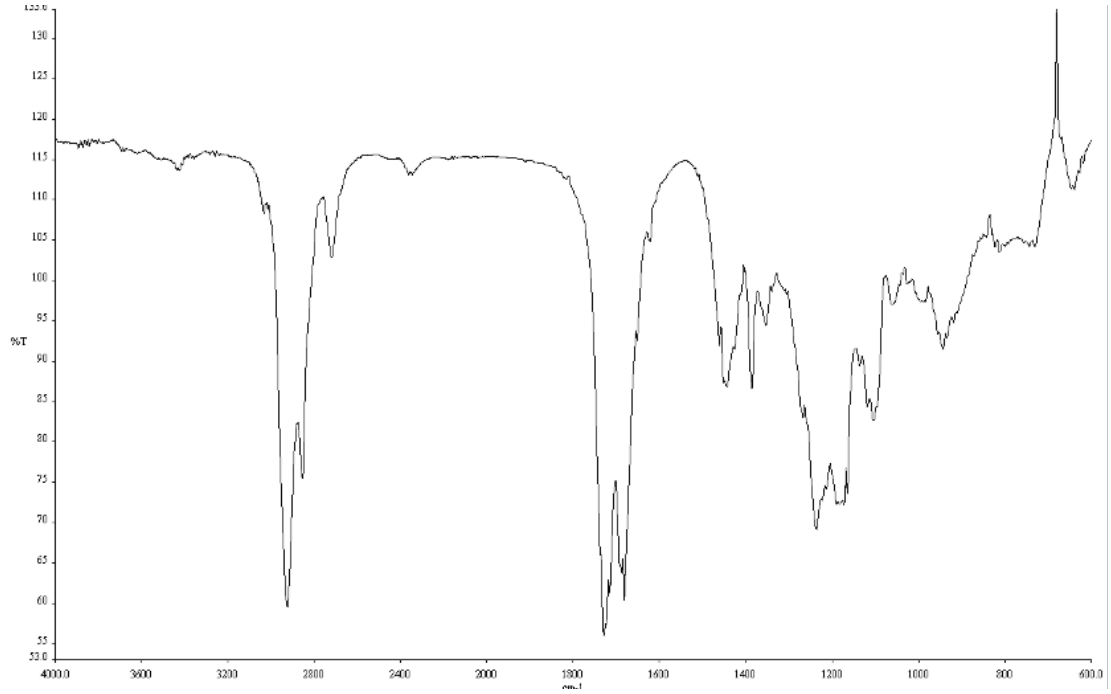


Figure A1.218. *Infrared spectrum (Thin Film, NaCl) of compound* ***67****.*

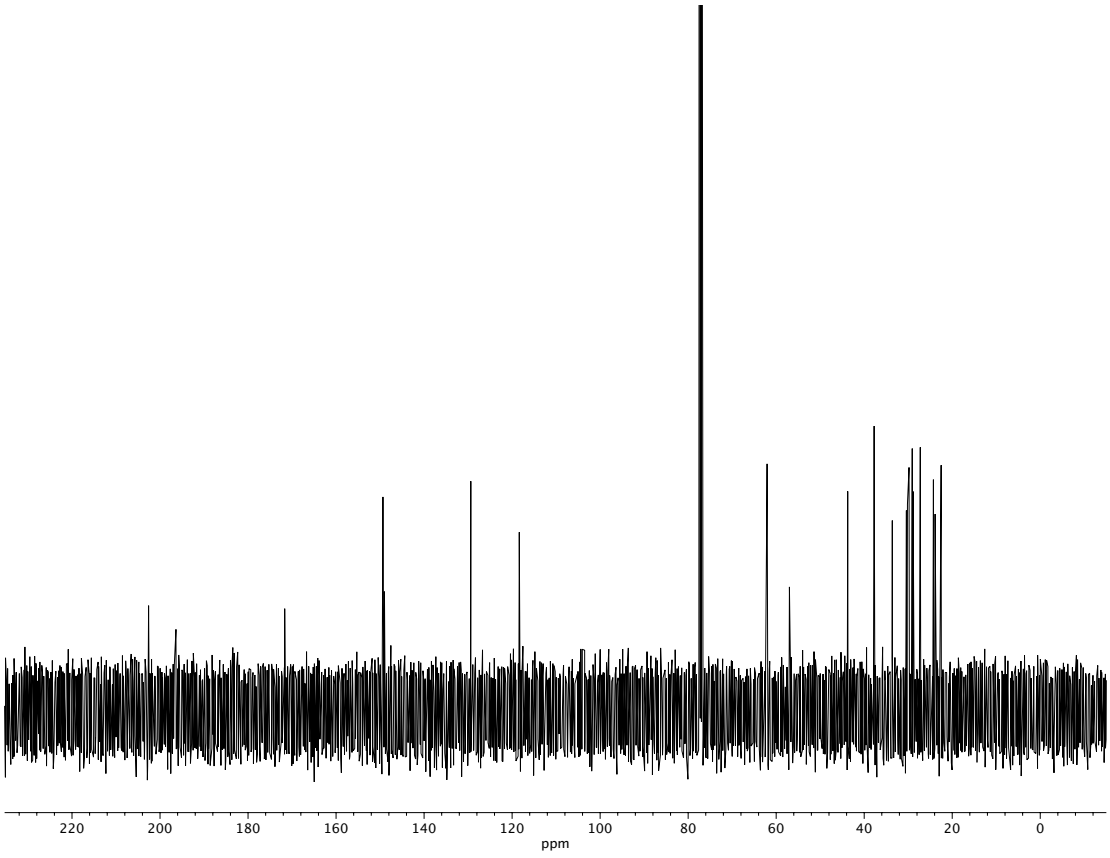


Figure A1.219. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***67****.*

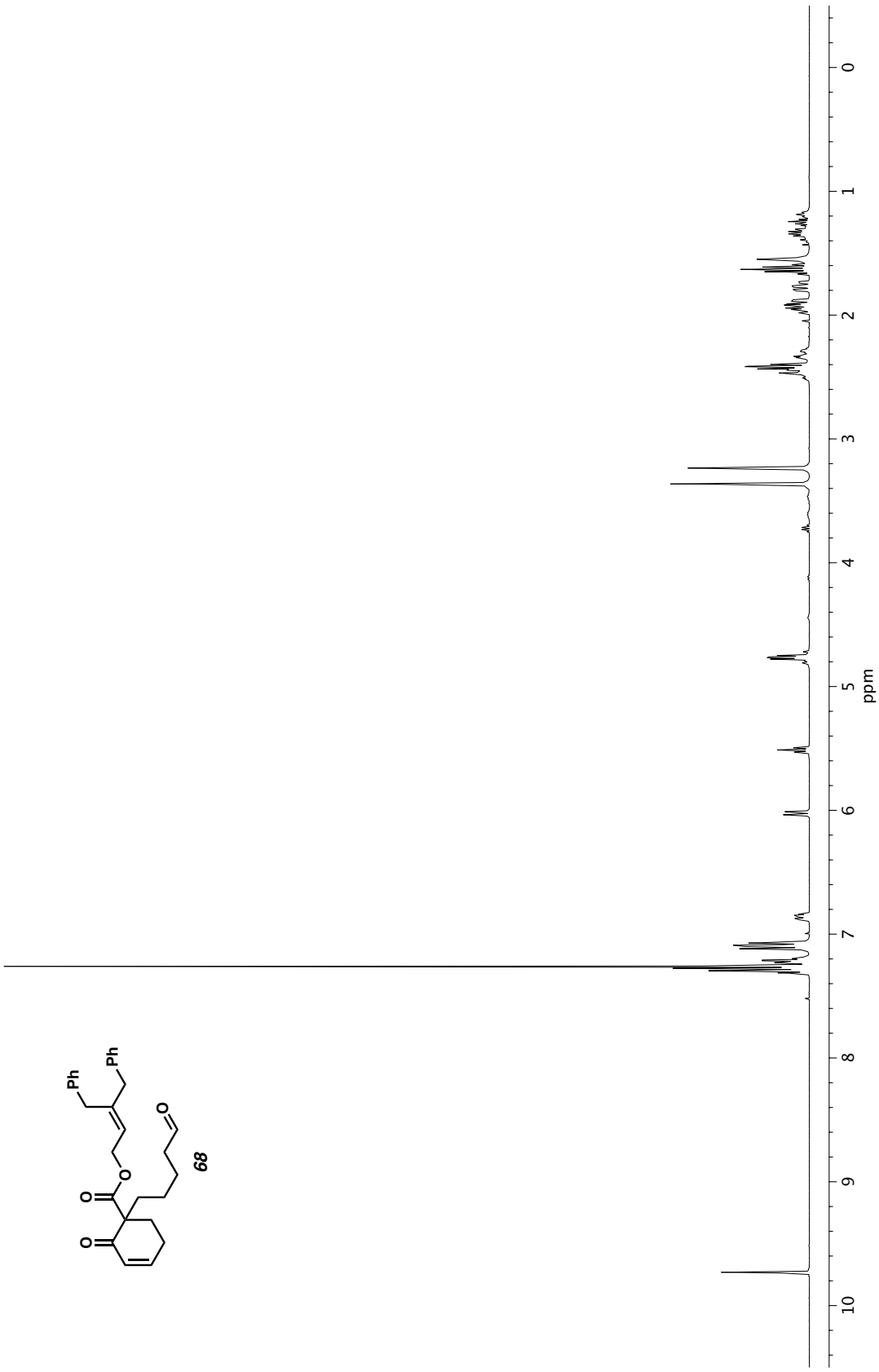


Figure A1.220. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***68****.*

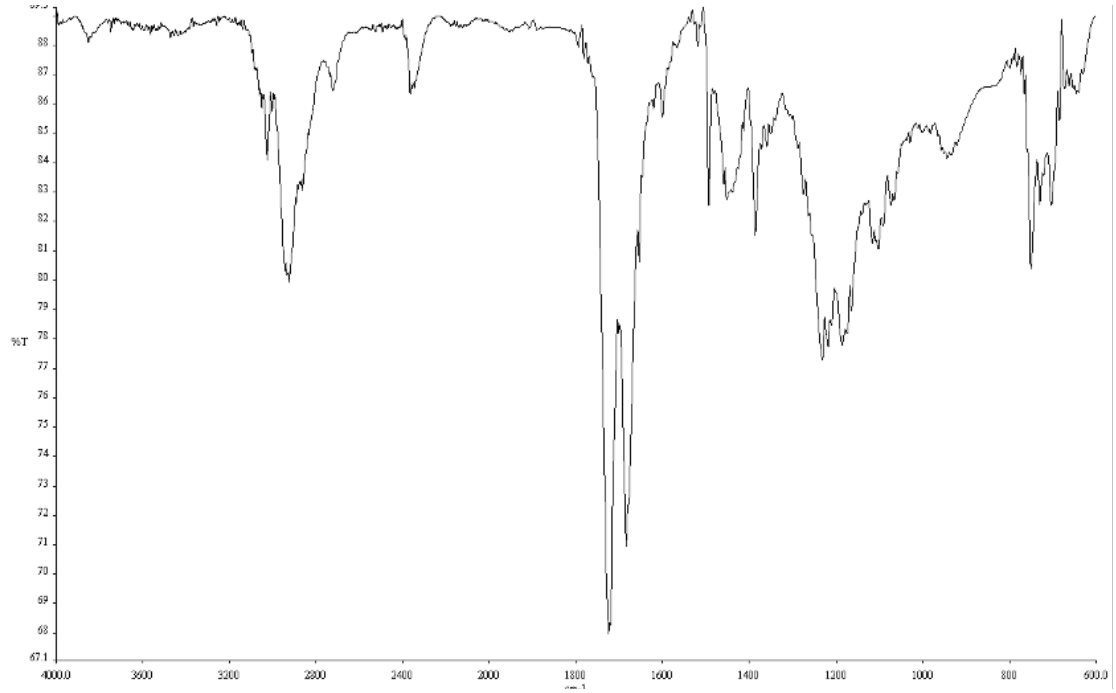


Figure A1.221. *Infrared spectrum (Thin Film, NaCl) of compound* ***68****.*

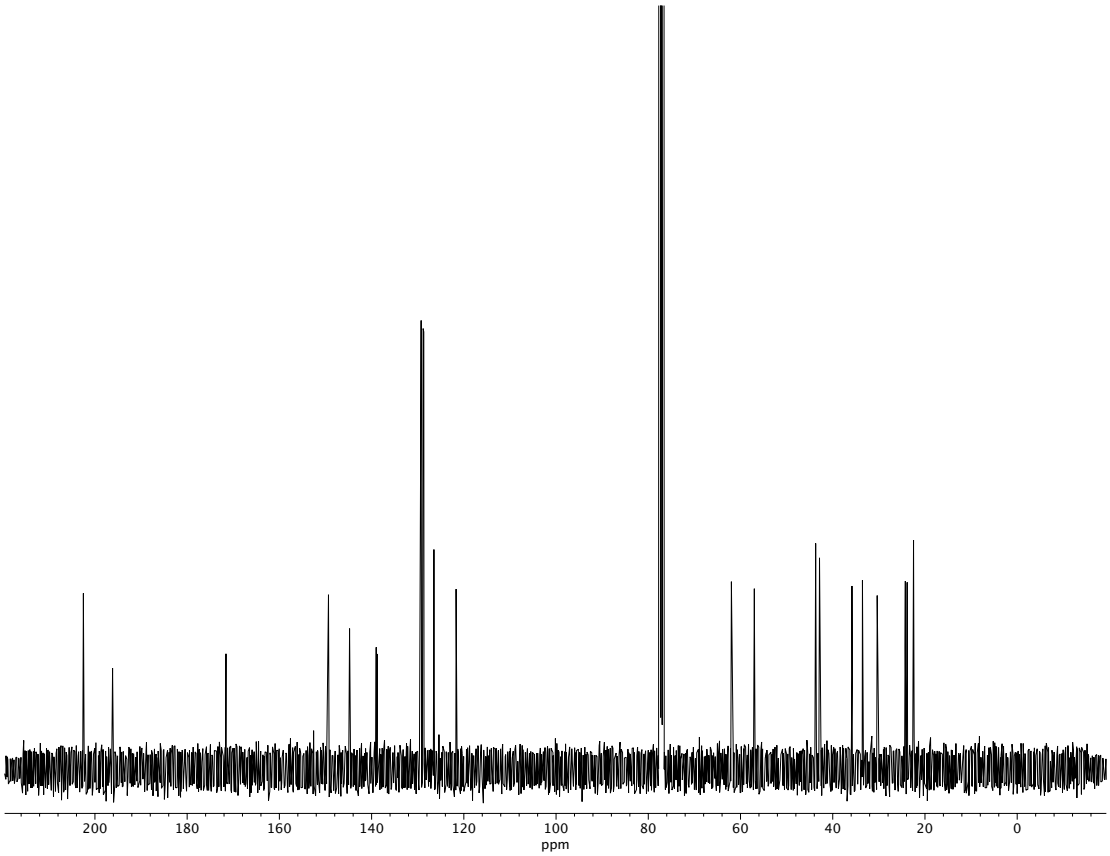
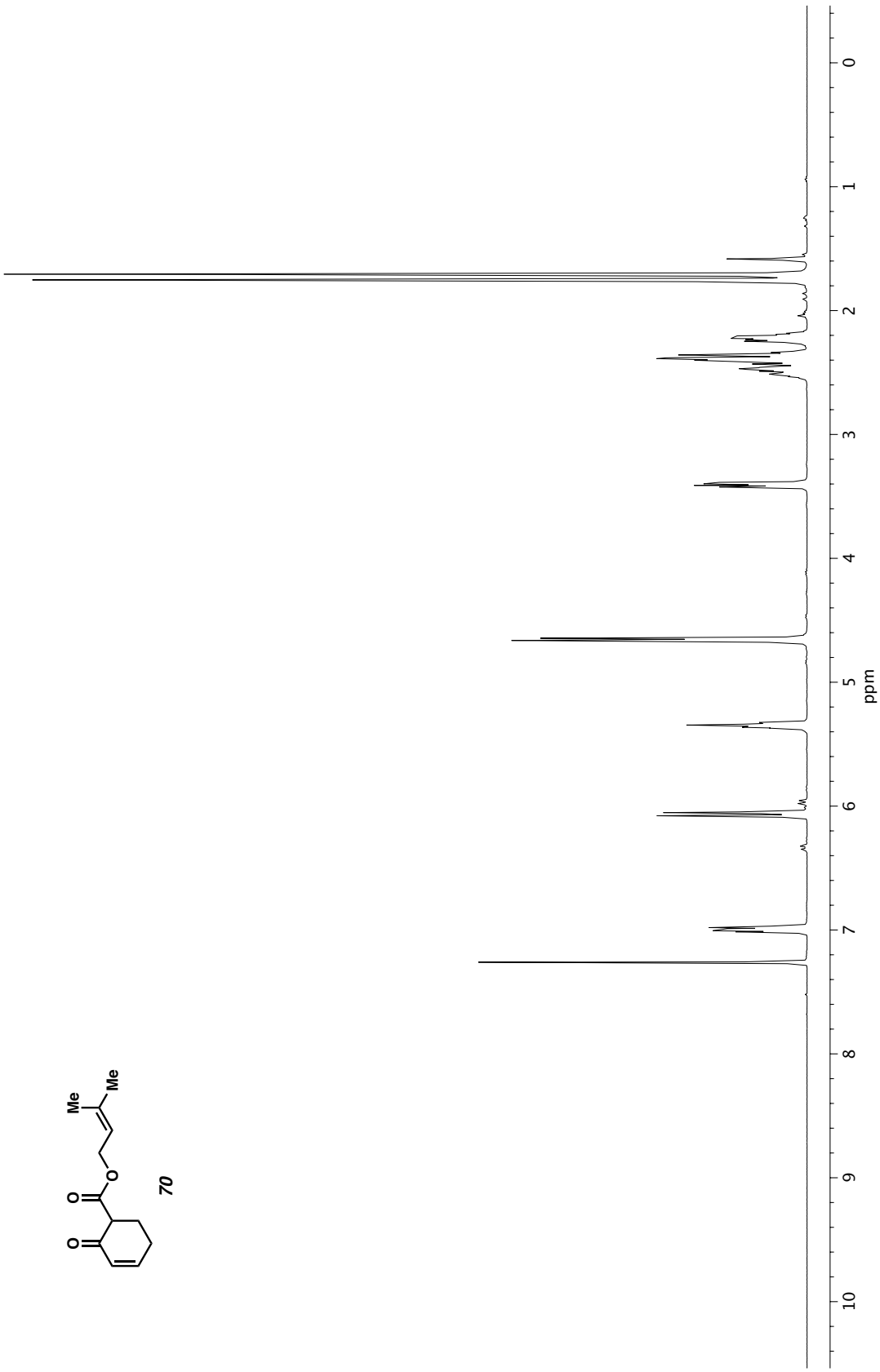


Figure A1.222. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***68****.*



70

Figure A1.223. *^1H NMR (400 MHz, $CDCl_3$) of compound **70**.*

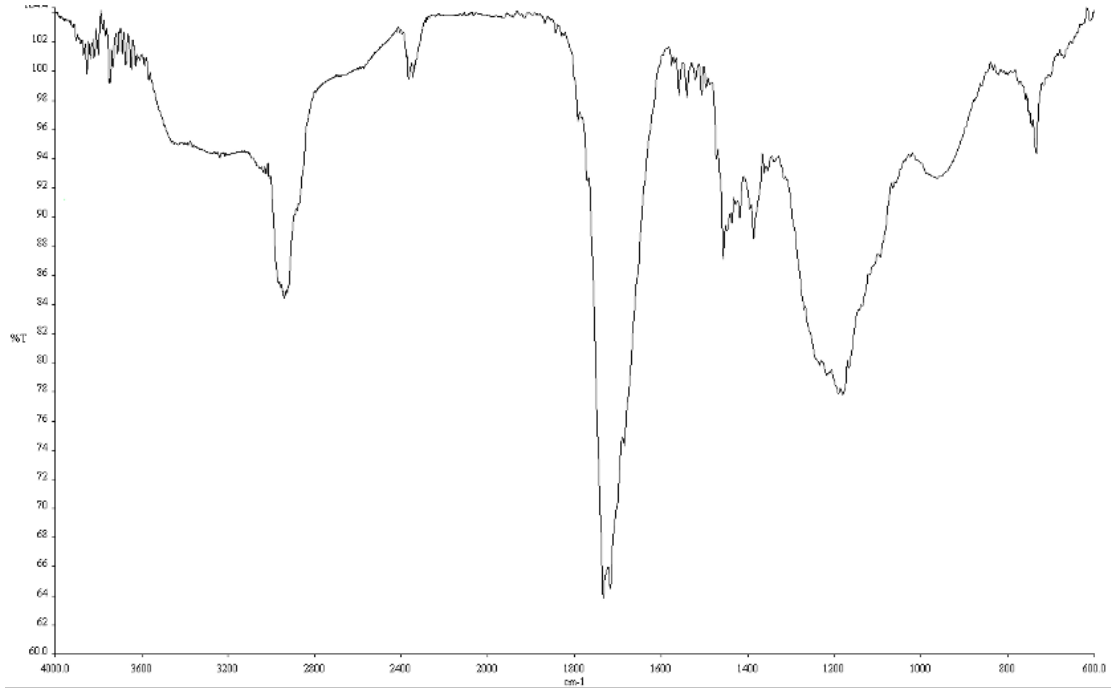


Figure A1.224. *Infrared spectrum (Thin Film, NaCl) of compound* ***70****.*

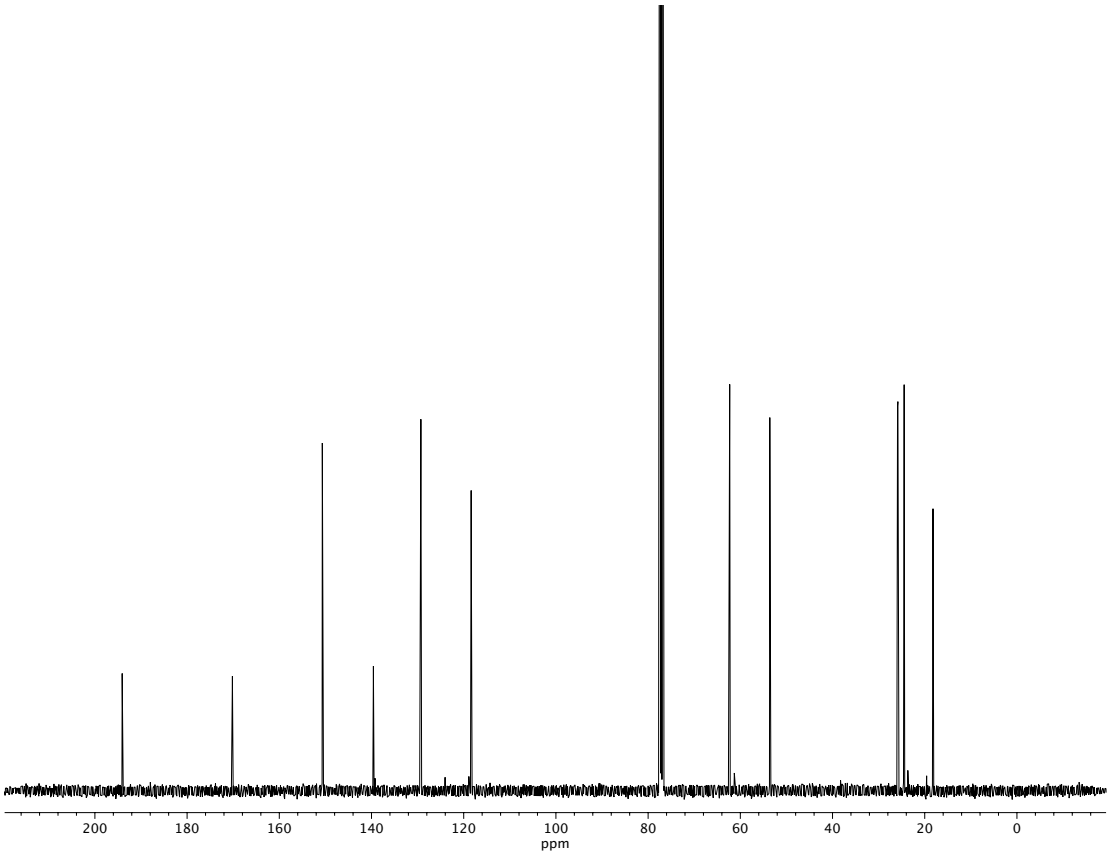


Figure A1.225. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***70****.*

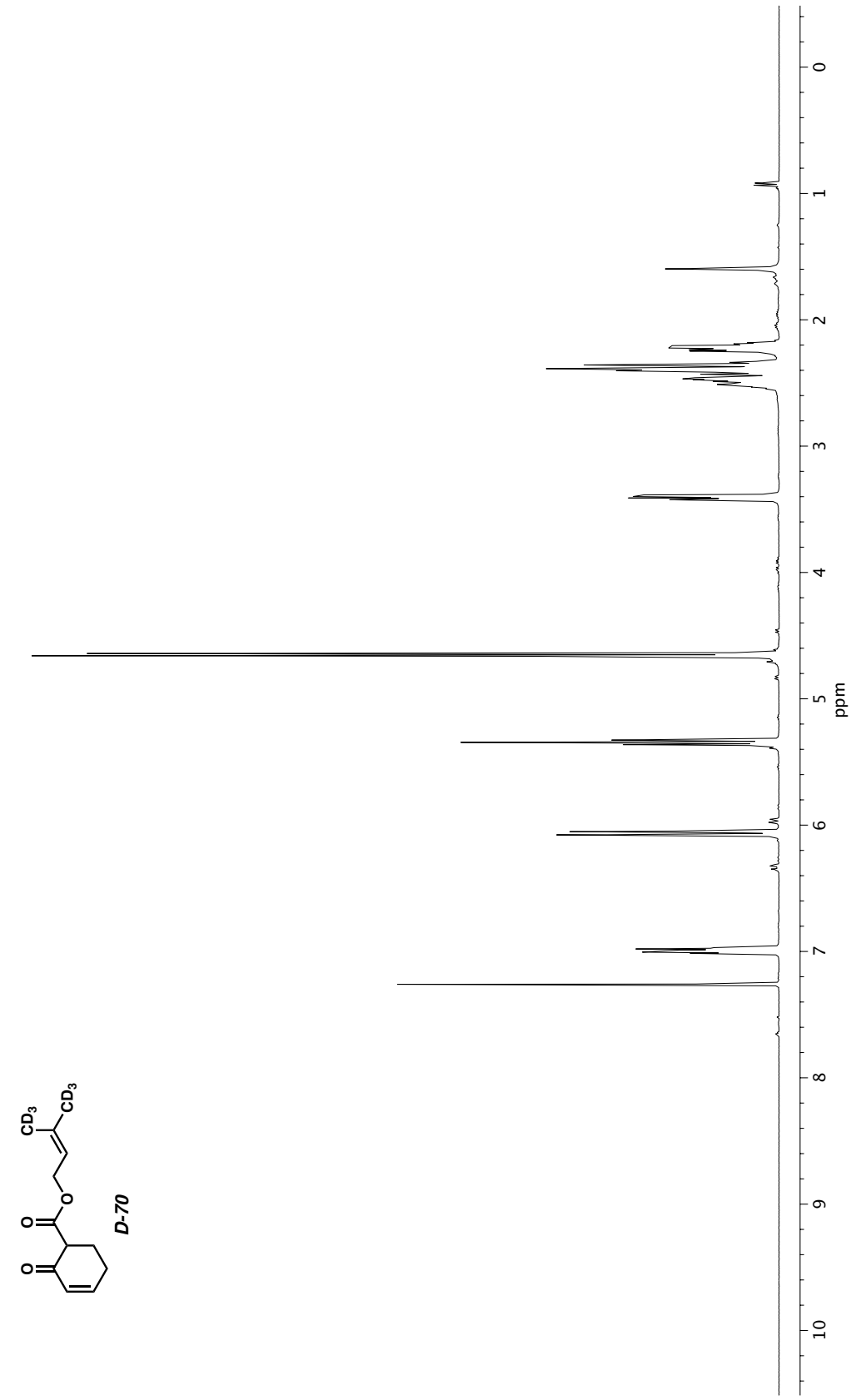


Figure A1.226. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***D-70****.*

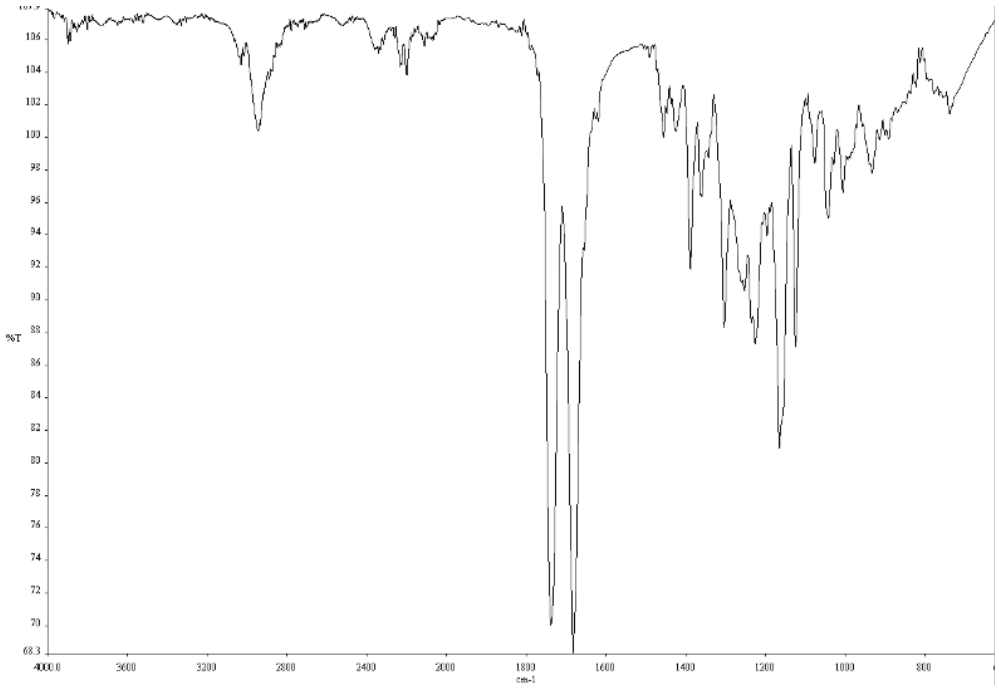


Figure A1.227. *Infrared spectrum (Thin Film, NaCl) of compound* ***D-70****.*

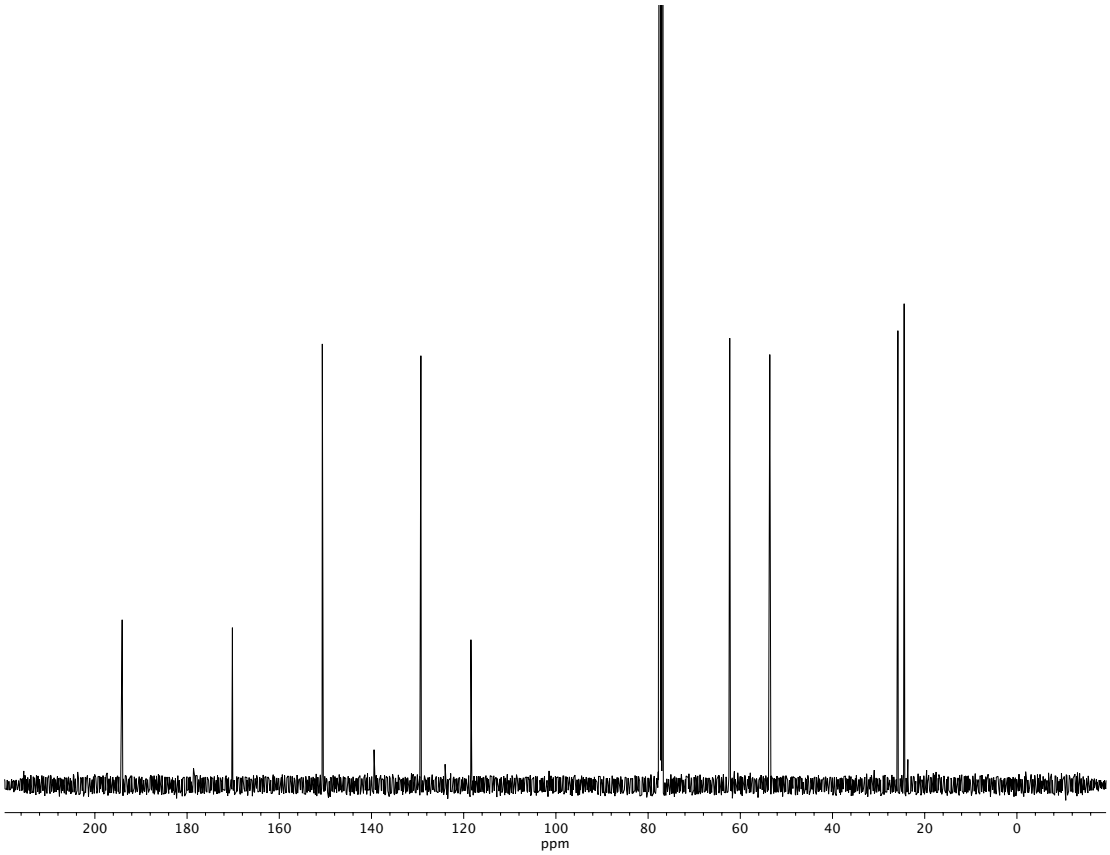


Figure A1.228. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***D-70****.*

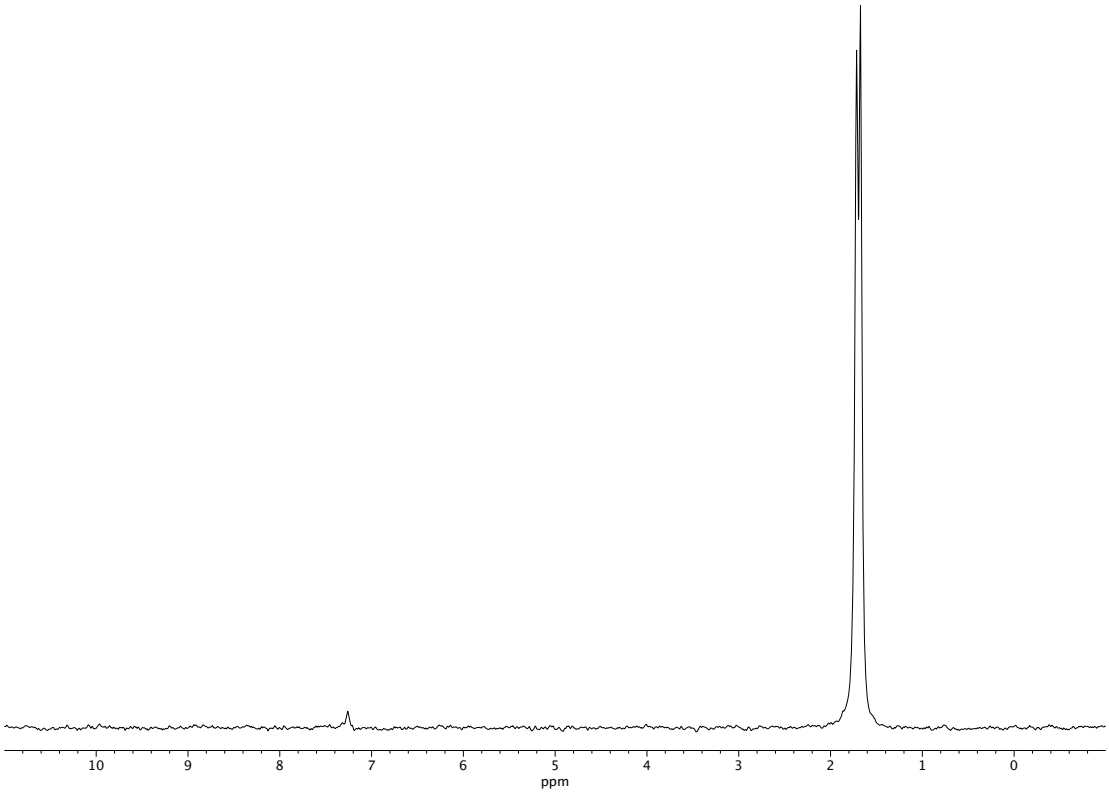


Figure A1.229. *^{2}H NMR (61 MHz, $CHCl_3$) of compound* ***D-70****.*

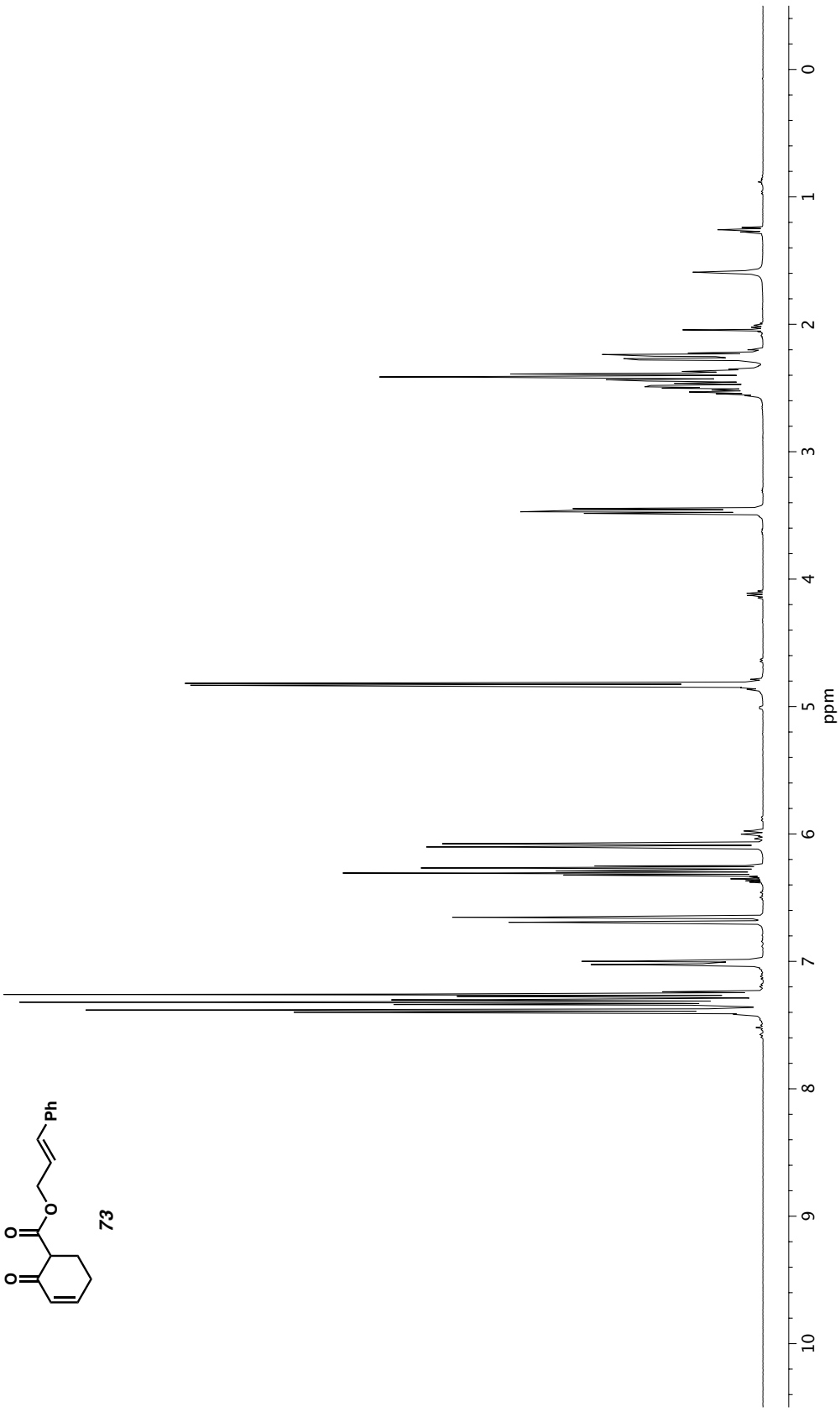


Figure A1.230. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***73****.*

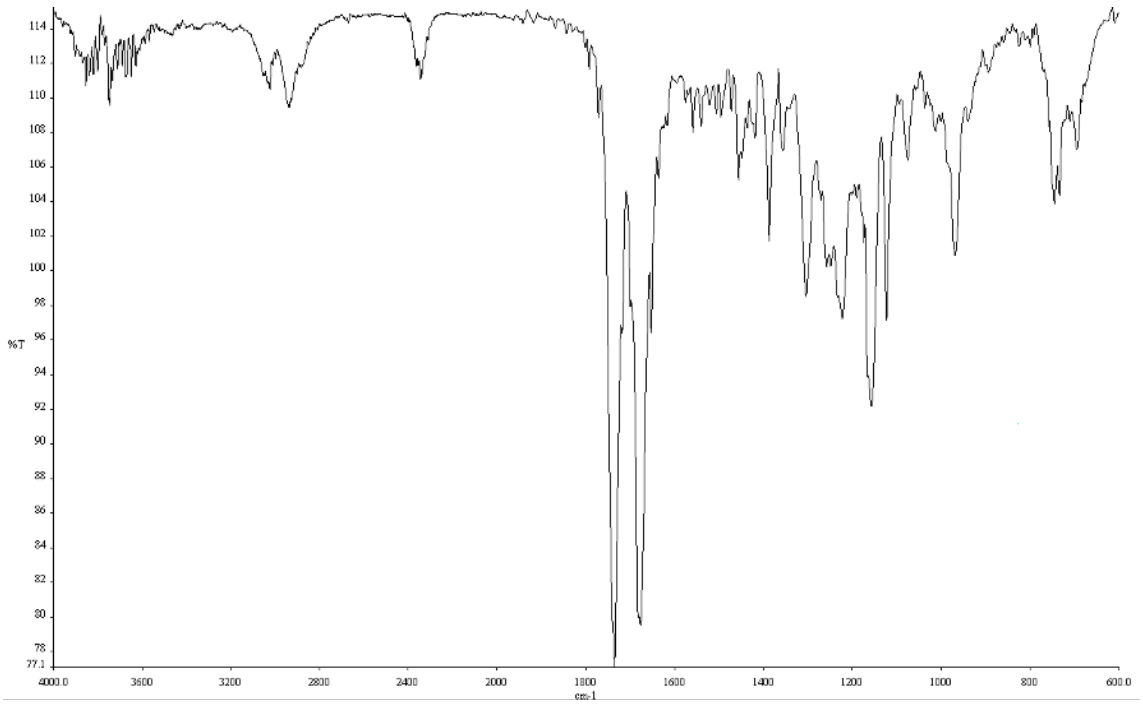


Figure A1.231. *Infrared spectrum (Thin Film, NaCl) of compound* ***73****.*

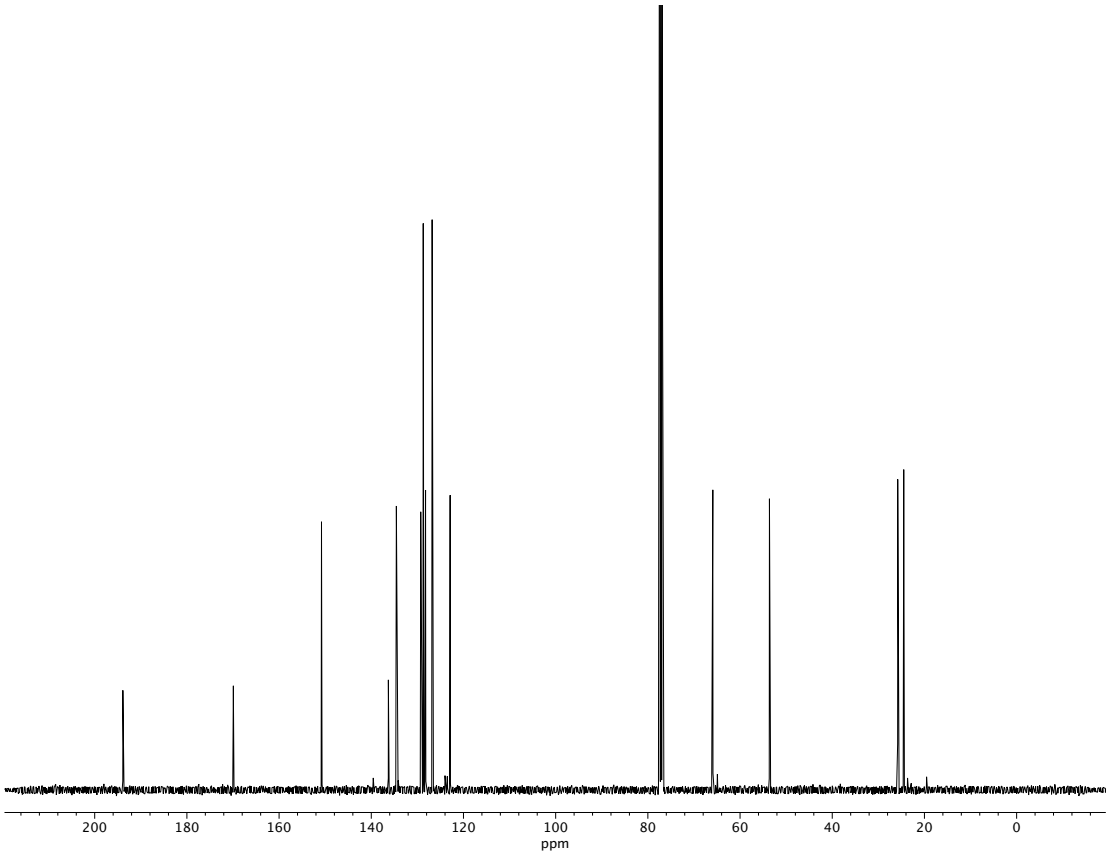


Figure A1.232. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***73****.*

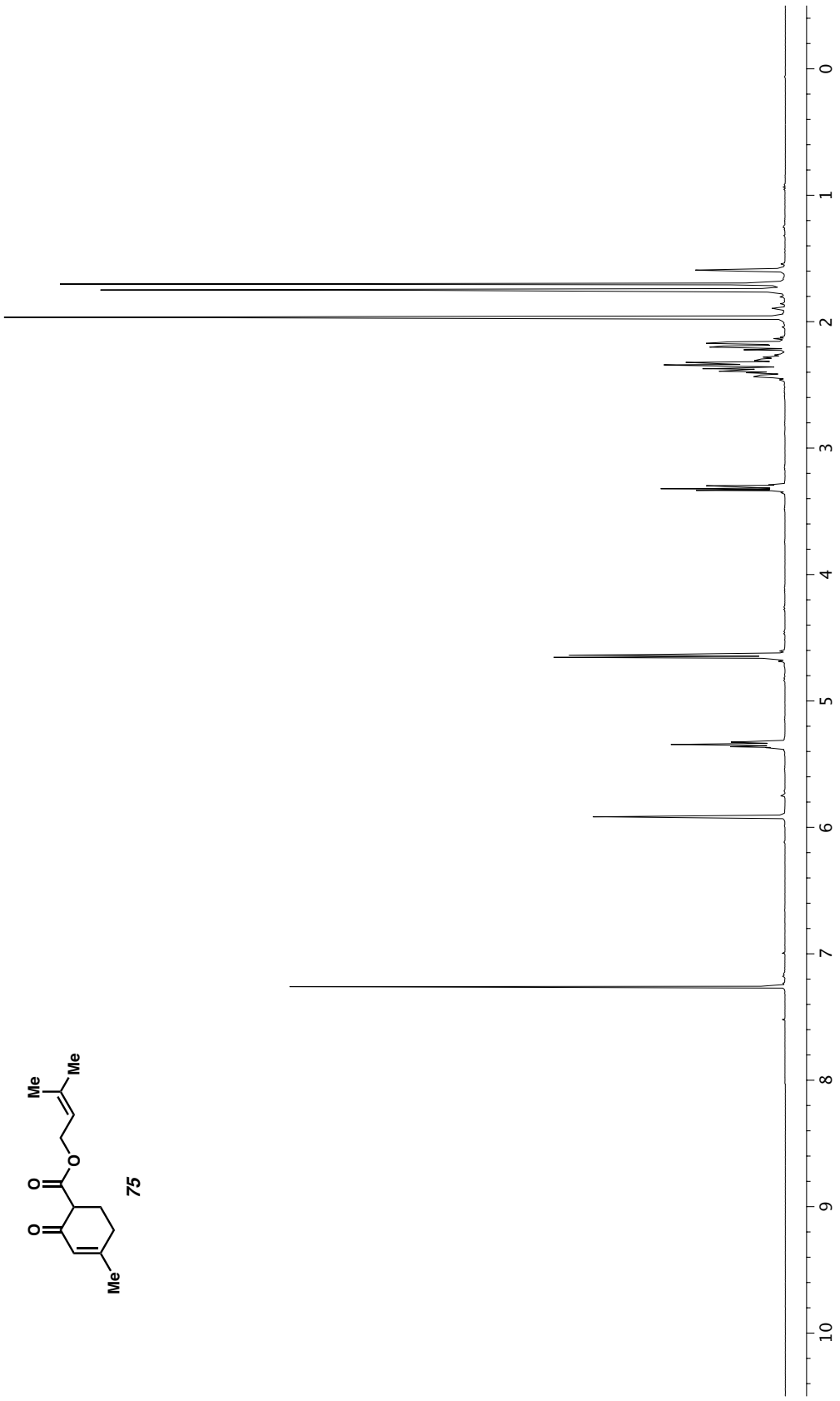


Figure A1.233. *^1H NMR (400 MHz, $CDCl_3$) of compound **75**.*

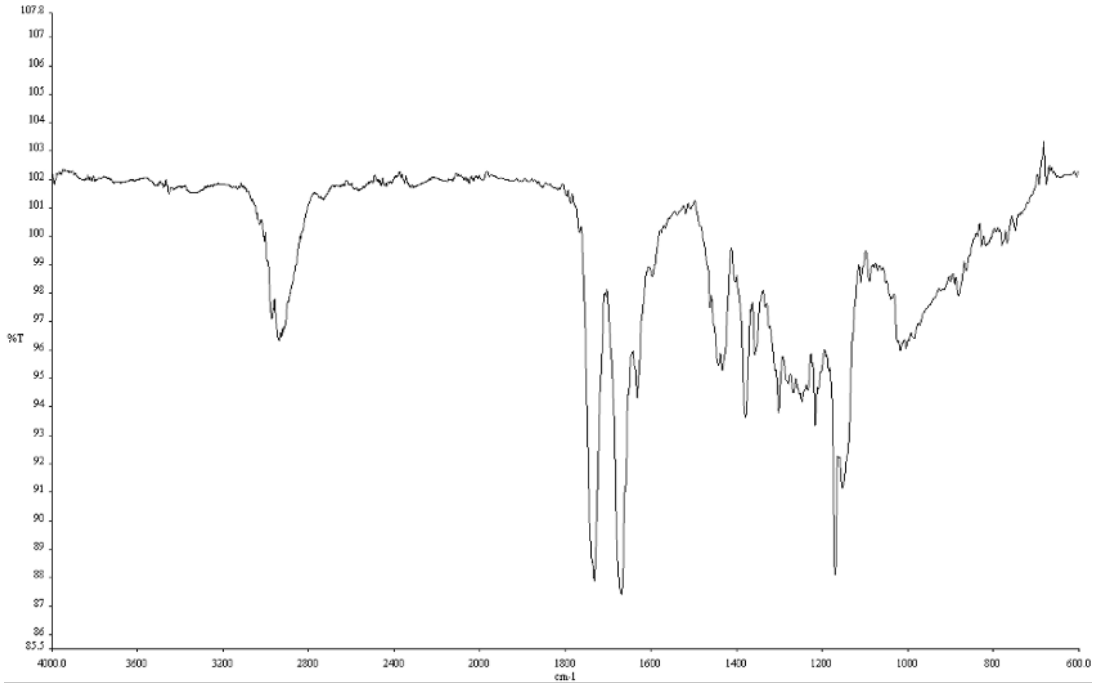


Figure A1.234. *Infrared spectrum (Thin Film, NaCl) of compound* ***75****.*

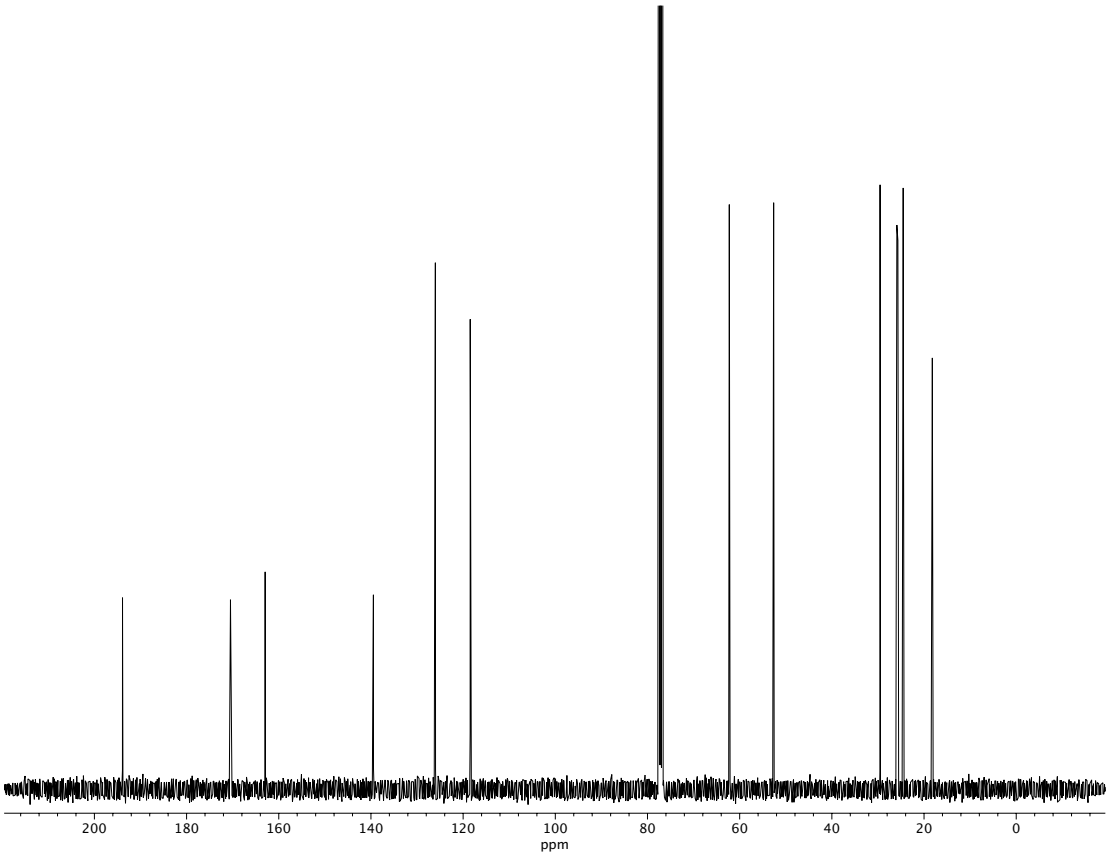


Figure A1.235. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***75****.*

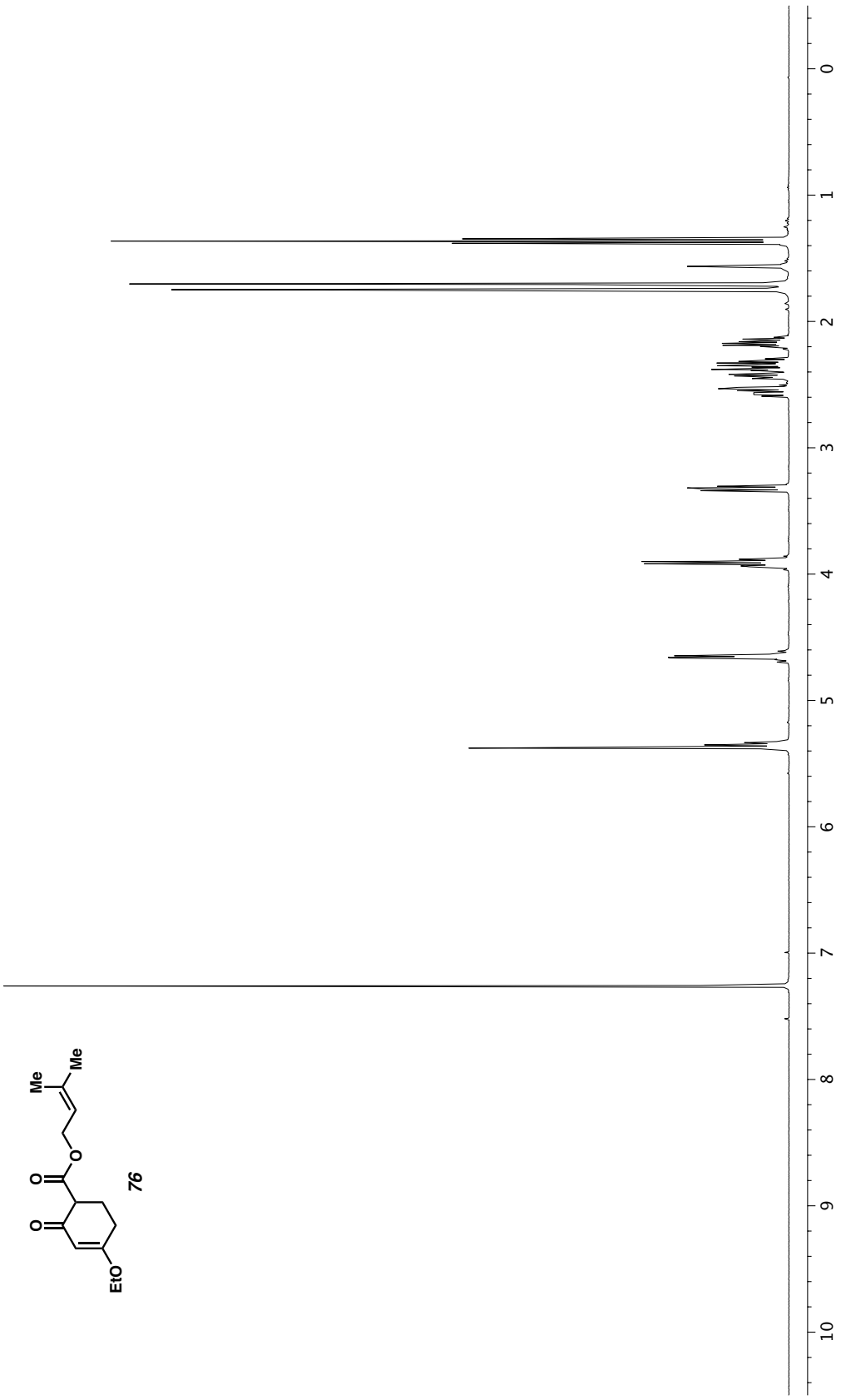


Figure A1.236. *^1H NMR (400 MHz, $CDCl_3$) of compound **76**.*

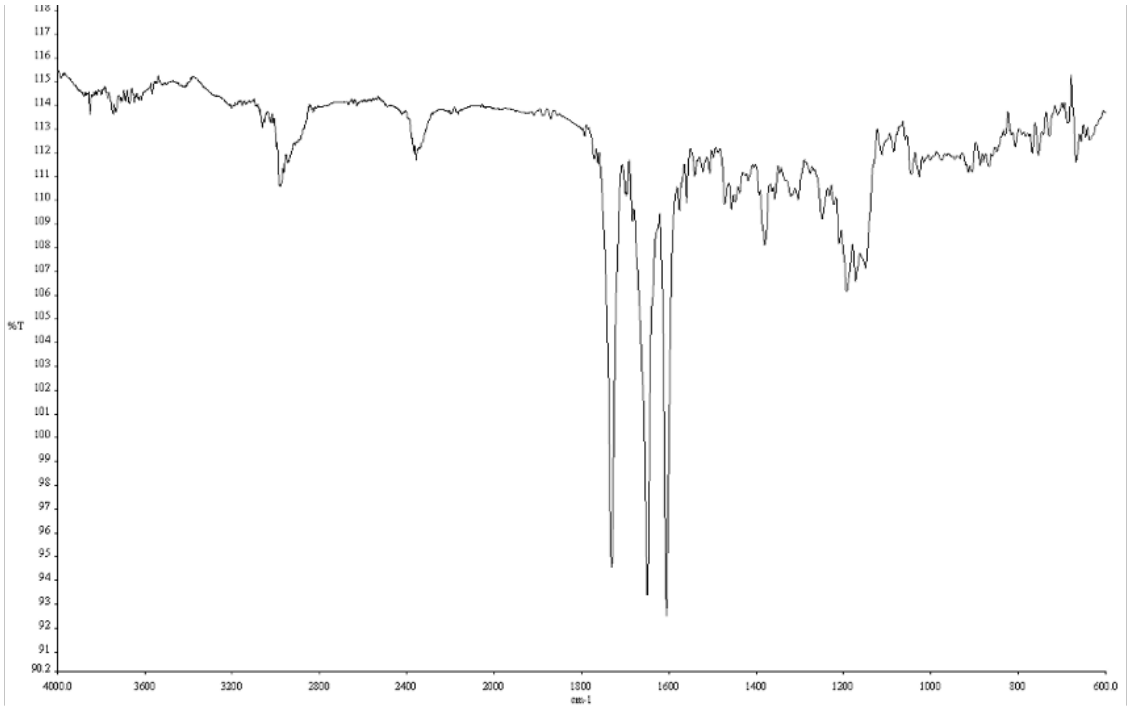


Figure A1.237. *Infrared spectrum (Thin Film, NaCl) of compound* ***76****.*

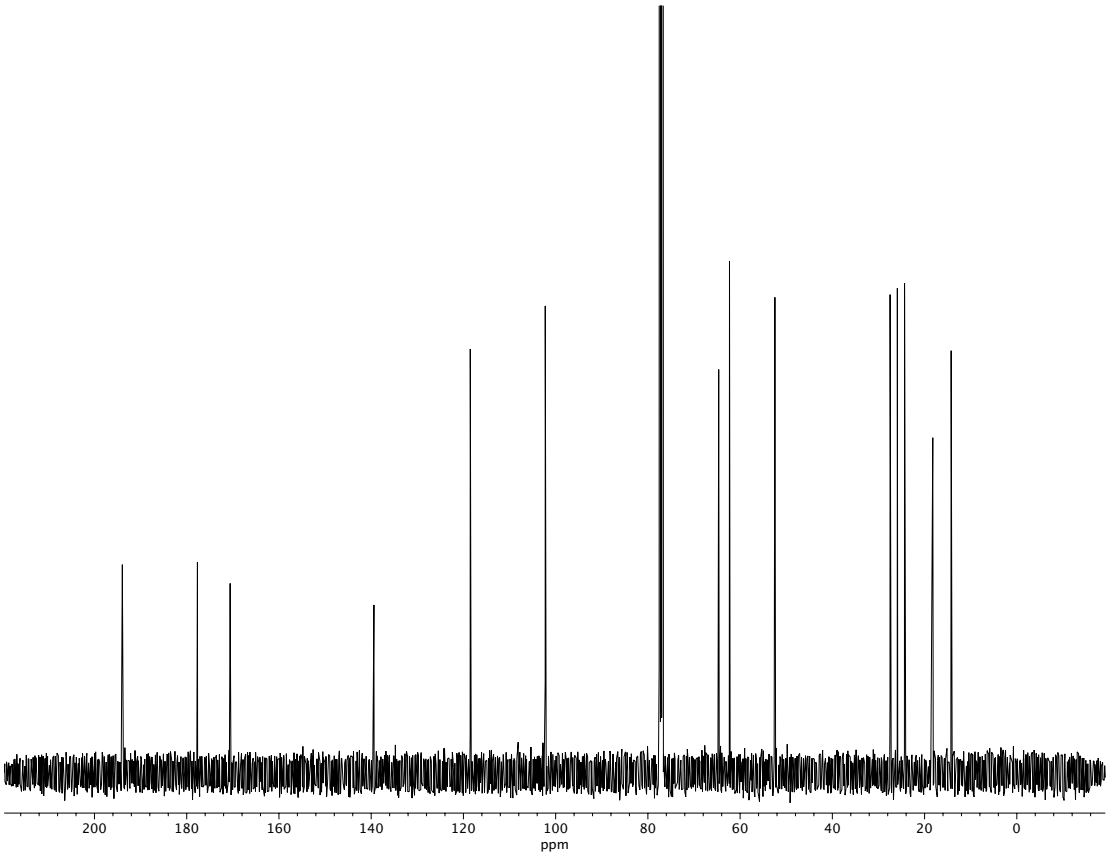
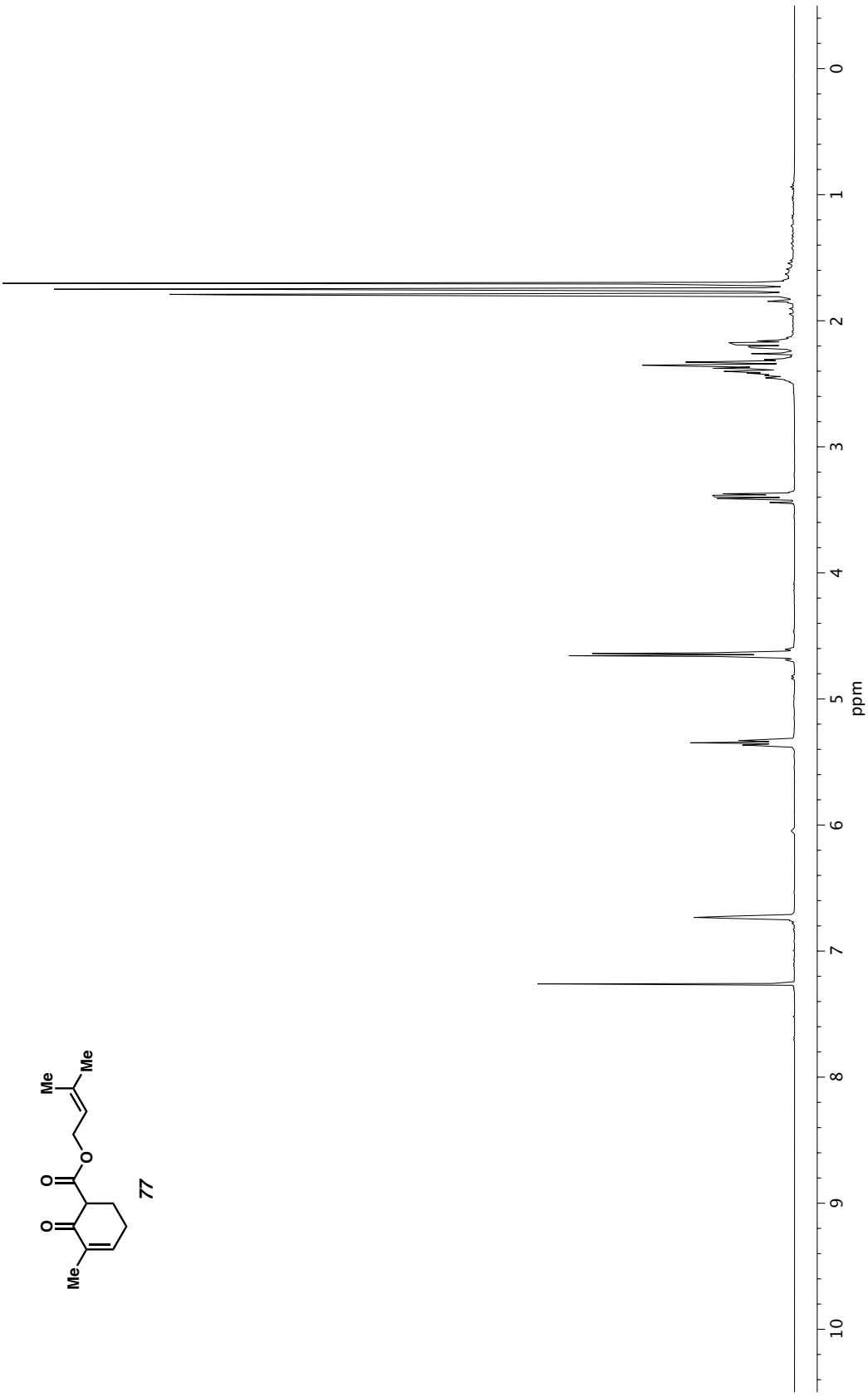


Figure A1.238. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***76****.*



77

Figure A1.239. *^1H NMR (400 MHz, $CDCl_3$) of compound **77**.*

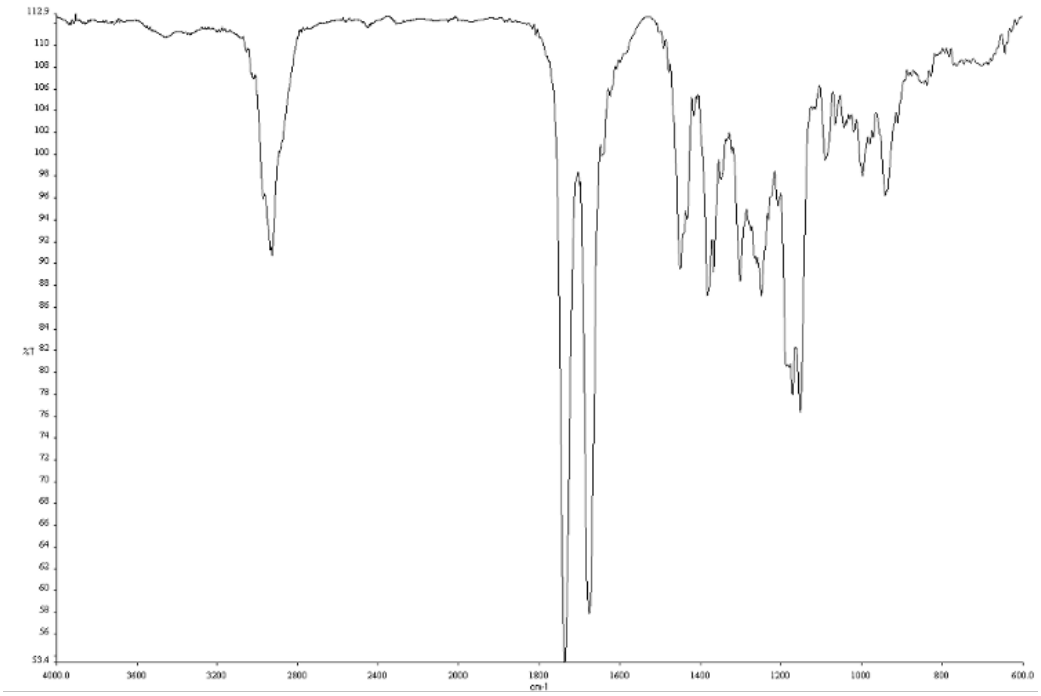


Figure A1.240. *Infrared spectrum (Thin Film, NaCl) of compound* ***77****.*

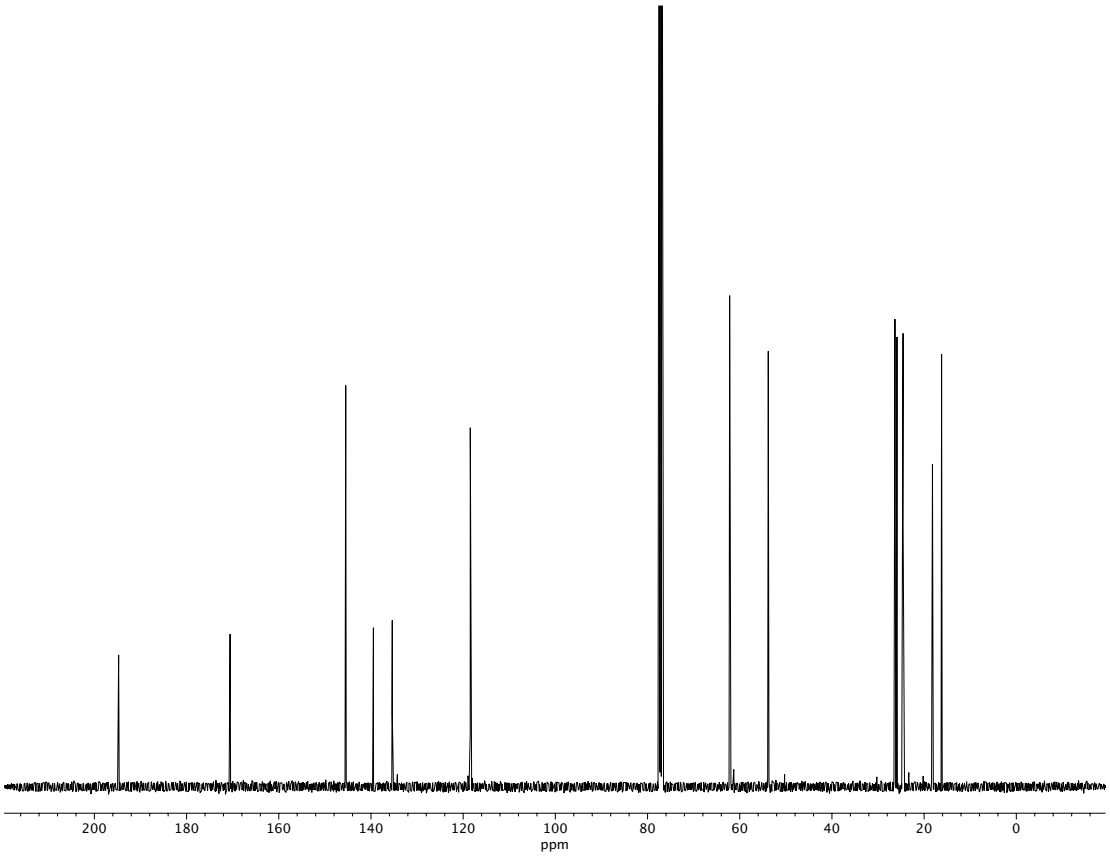


Figure A1.241. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***77****.*

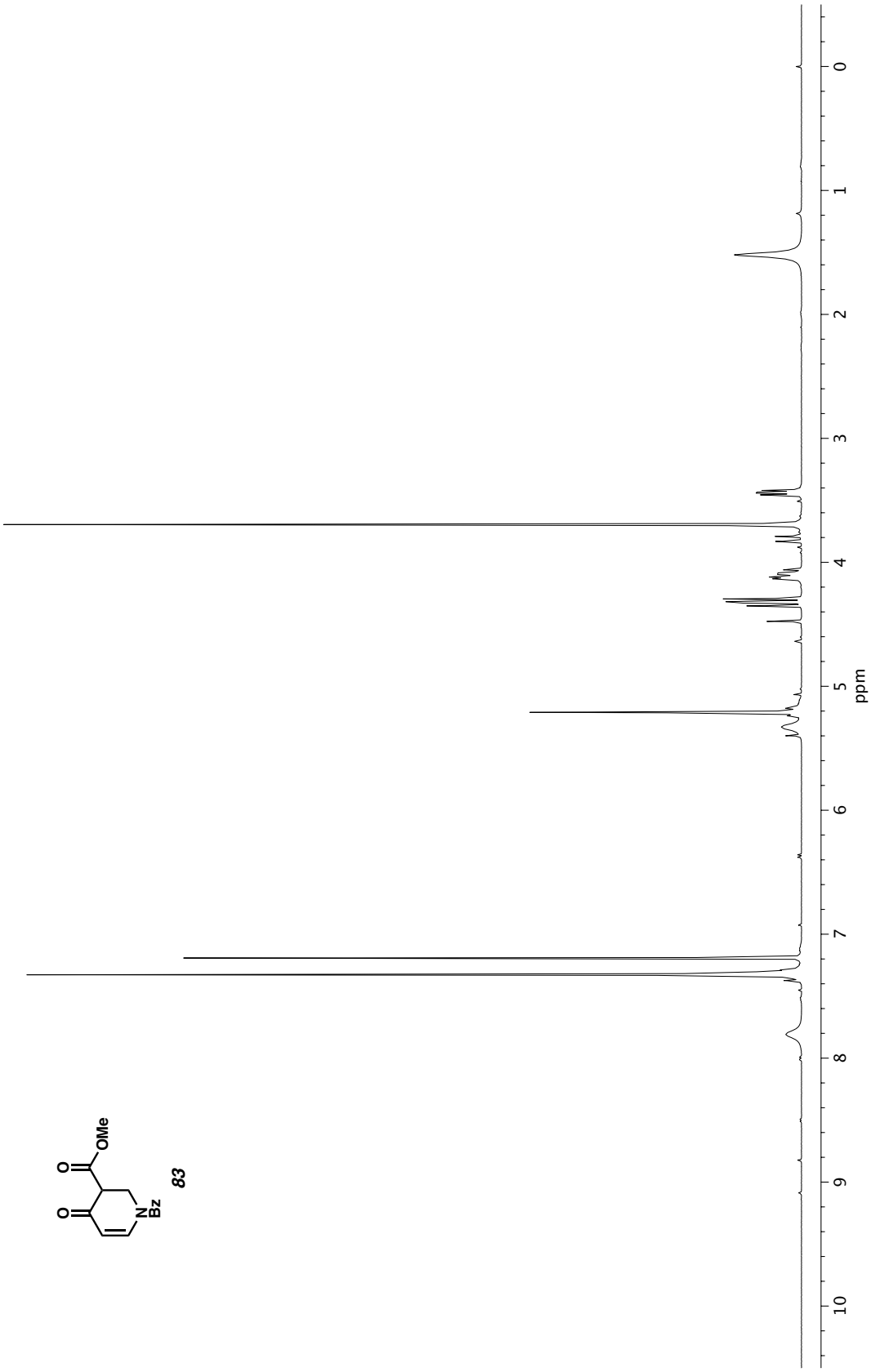


Figure A1.242. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***83****.*

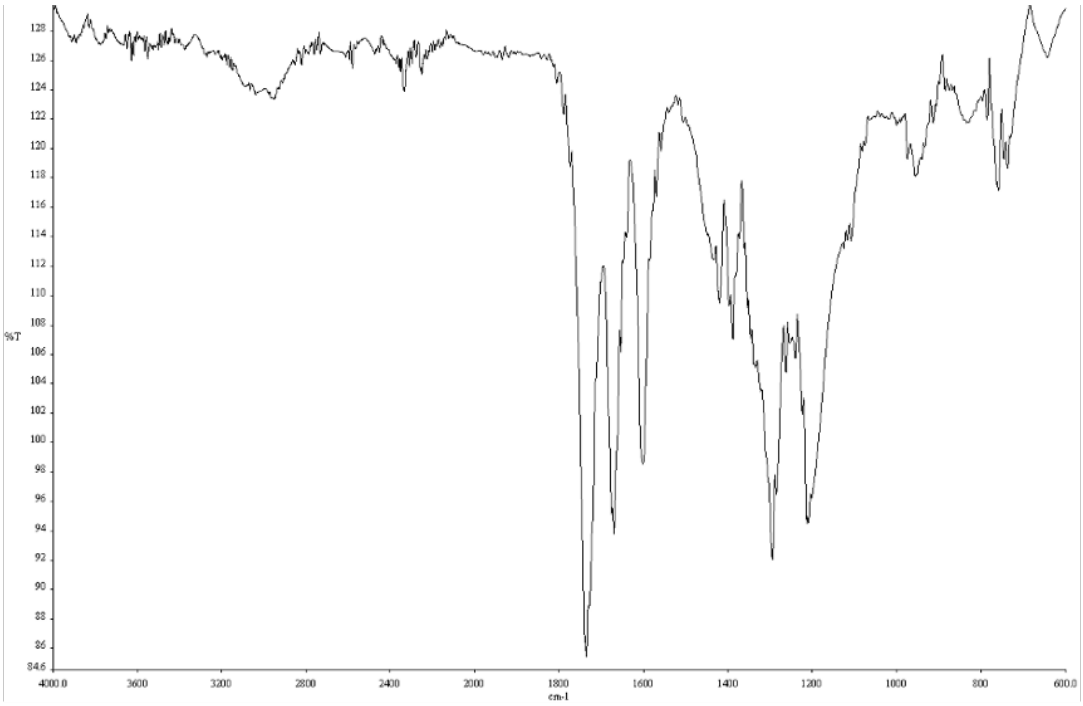


Figure A1.243. *Infrared spectrum (Thin Film, NaCl) of compound* ***83****.*

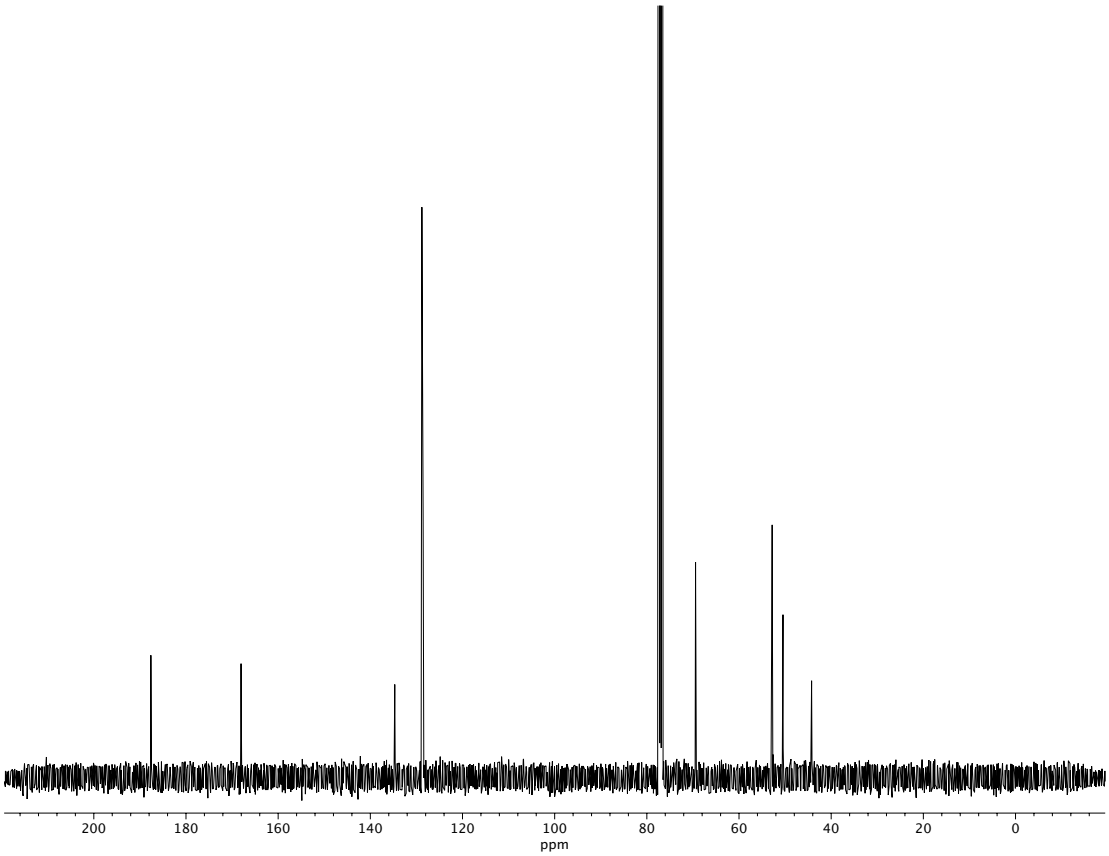


Figure A1.244. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***83****.*

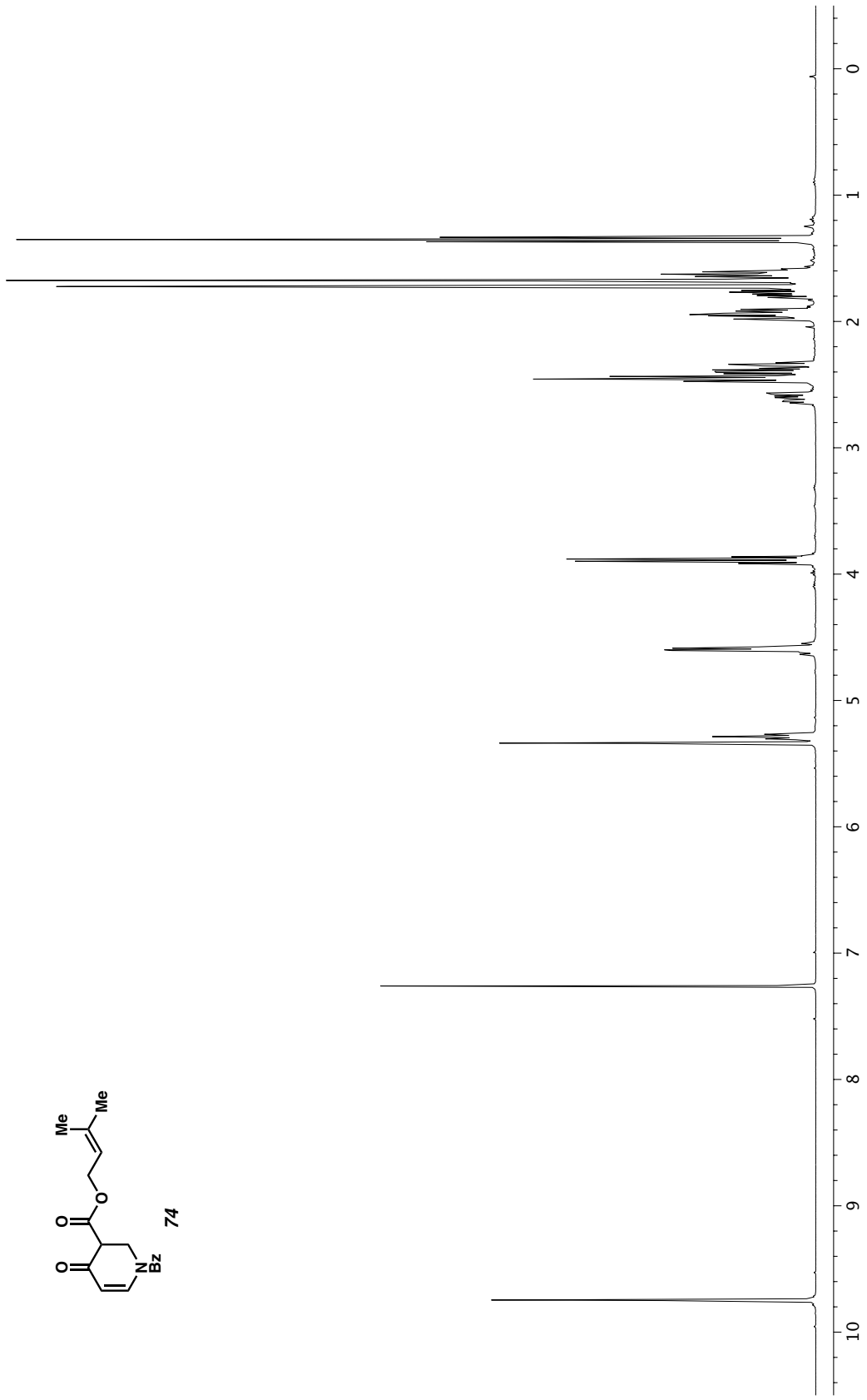


Figure A1.245. *^1H NMR (400 MHz, $CDCl_3$) of compound **74**.*

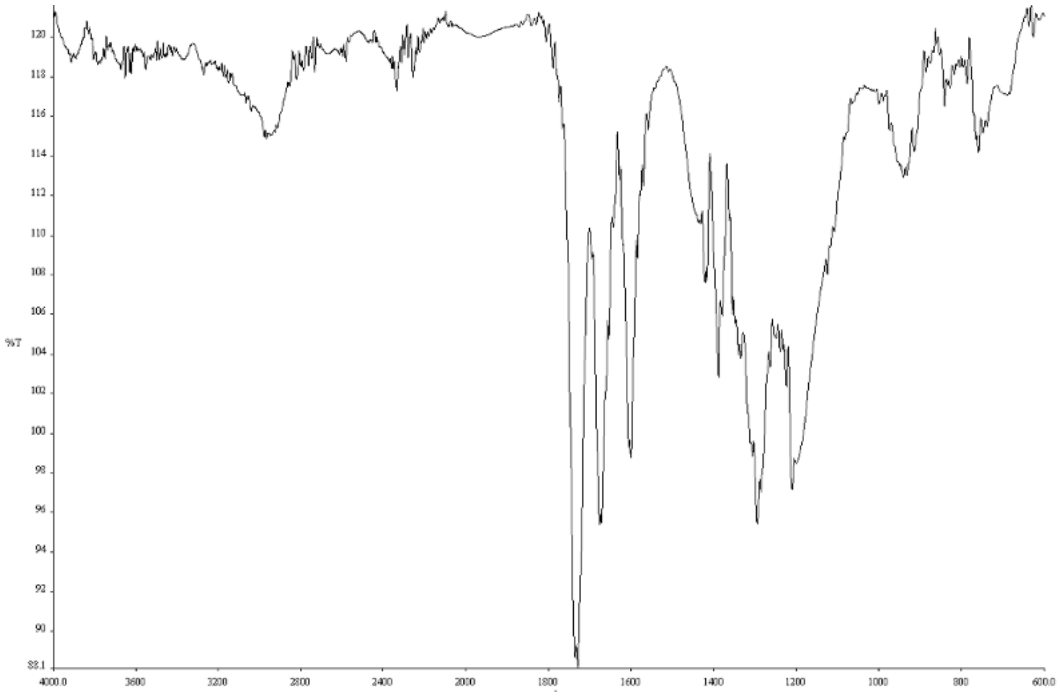


Figure A1.246. *Infrared spectrum (Thin Film, NaCl) of compound* ***74****.*

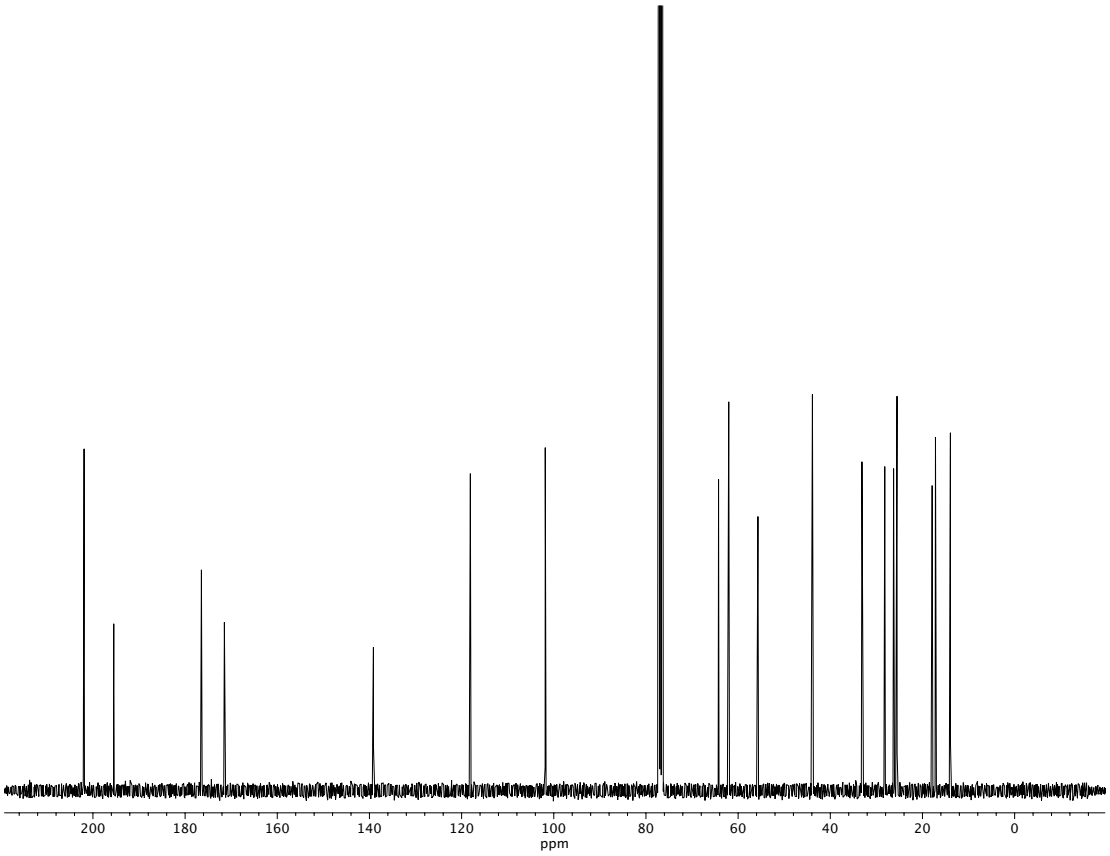


Figure A1.247. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***74****.*

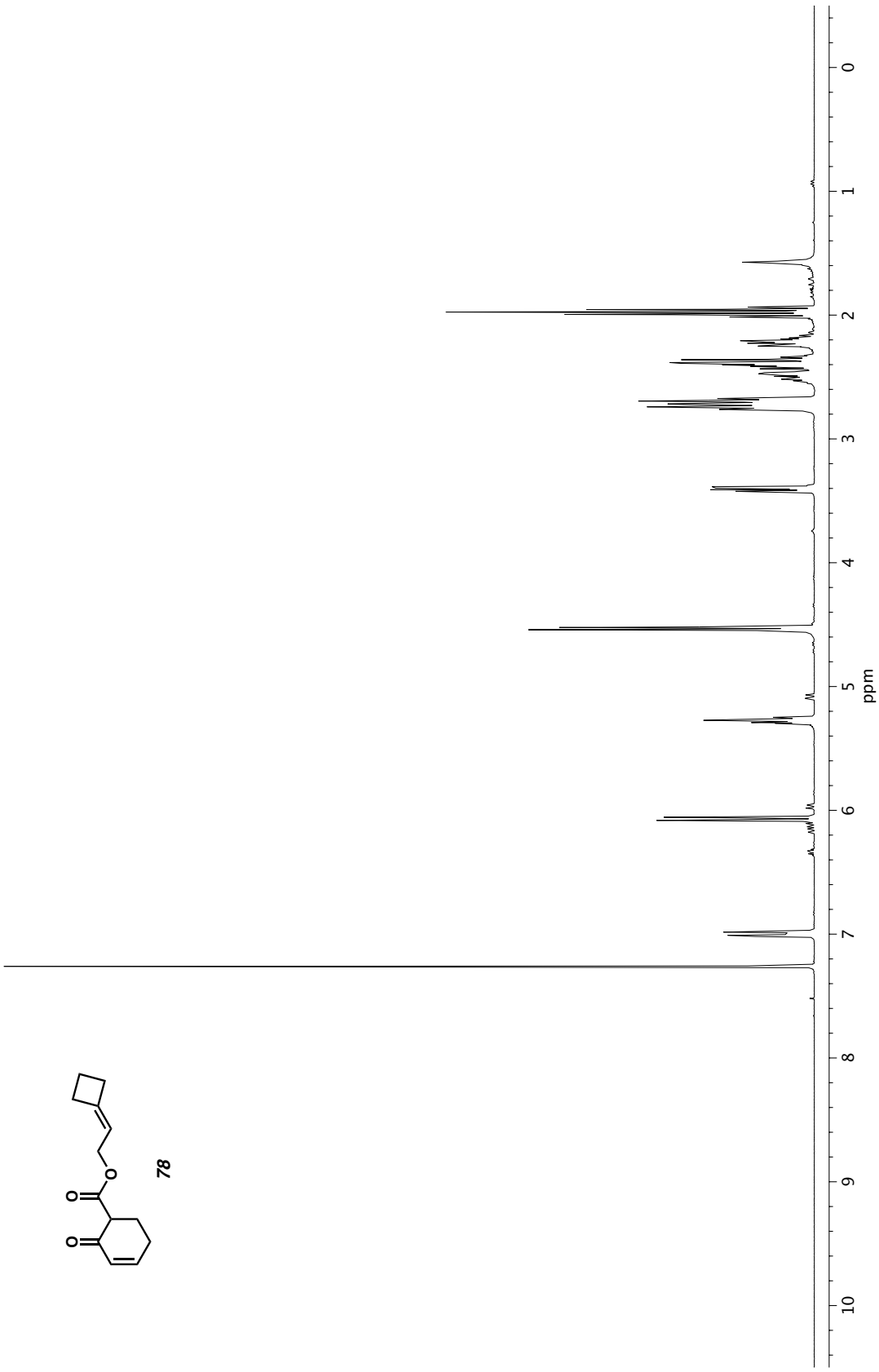


Figure A1.248. *^1H NMR (400 MHz, $CDCl_3$) of compound **78**.*

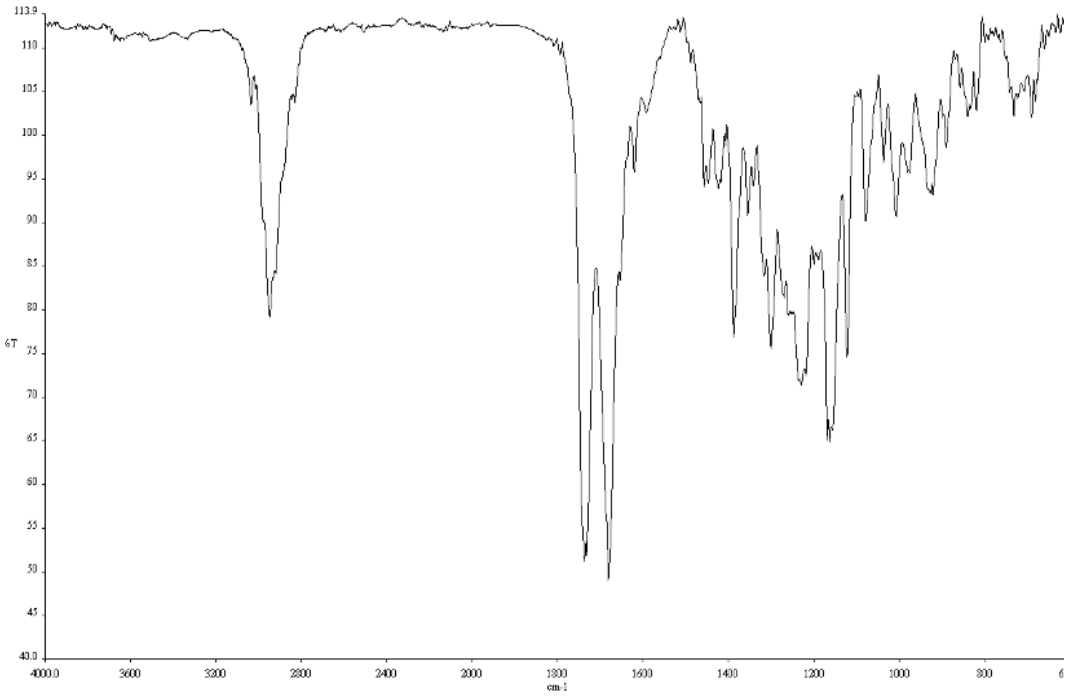


Figure A1.249. *Infrared spectrum (Thin Film, NaCl) of compound* ***78****.*

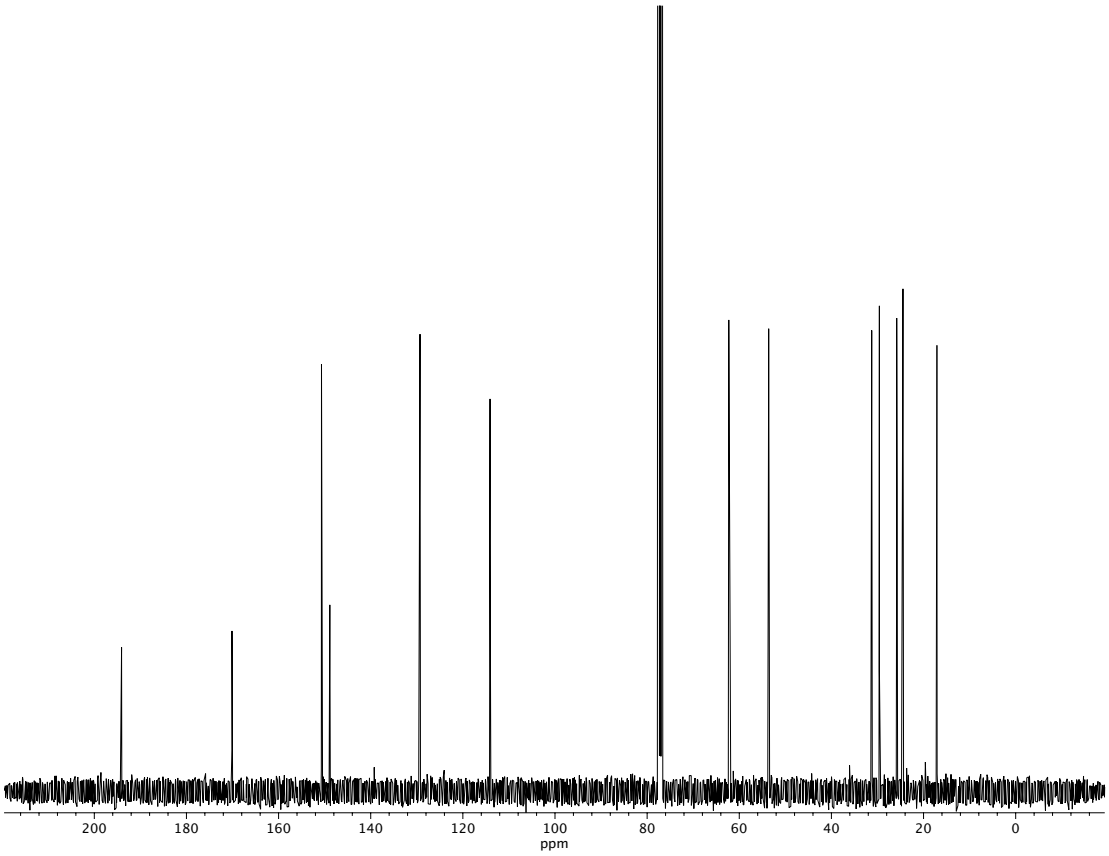


Figure A1.250. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***78****.*

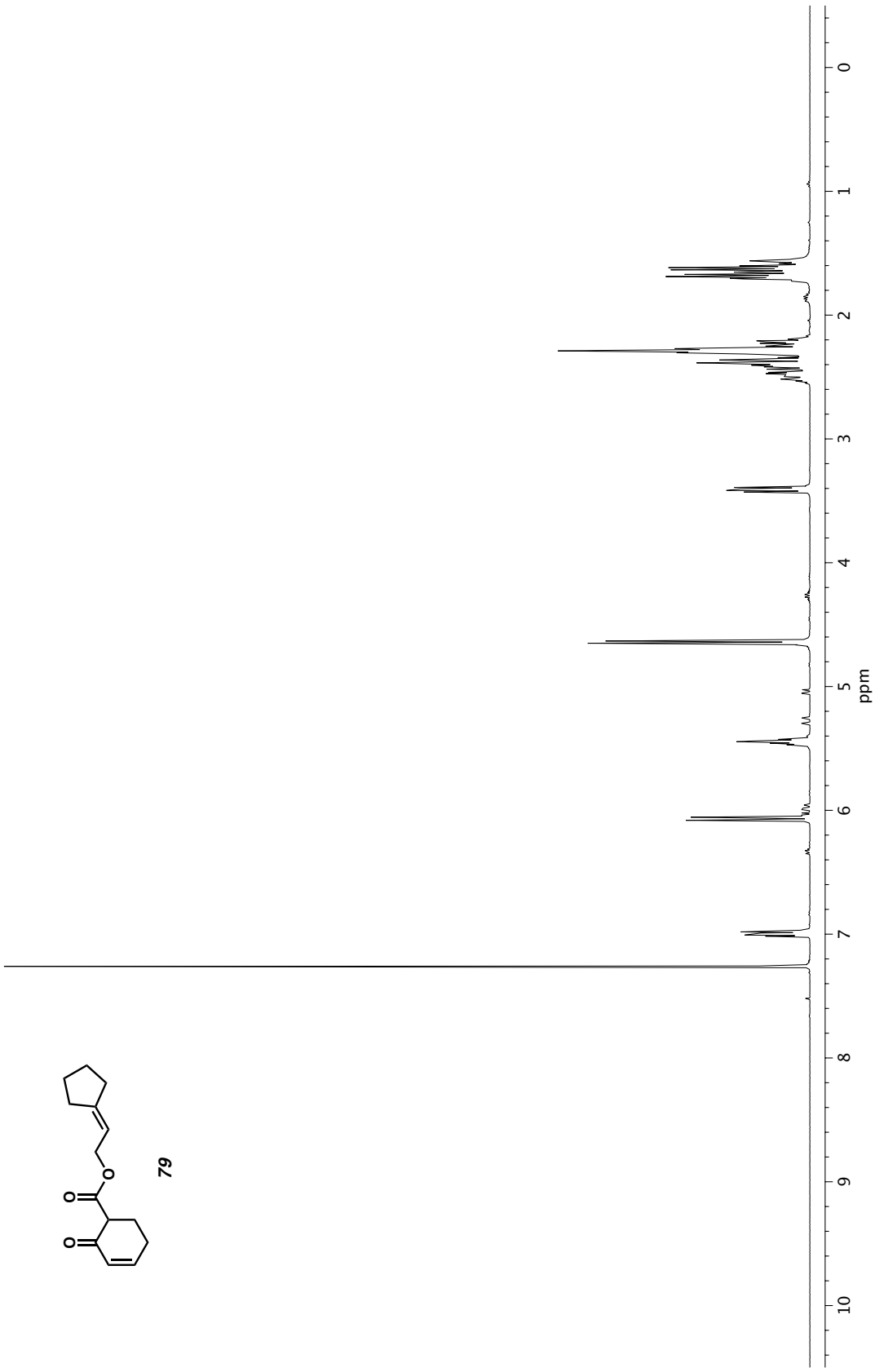


Figure A1.251. *^1H NMR (400 MHz, $CDCl_3$) of compound **79**.*

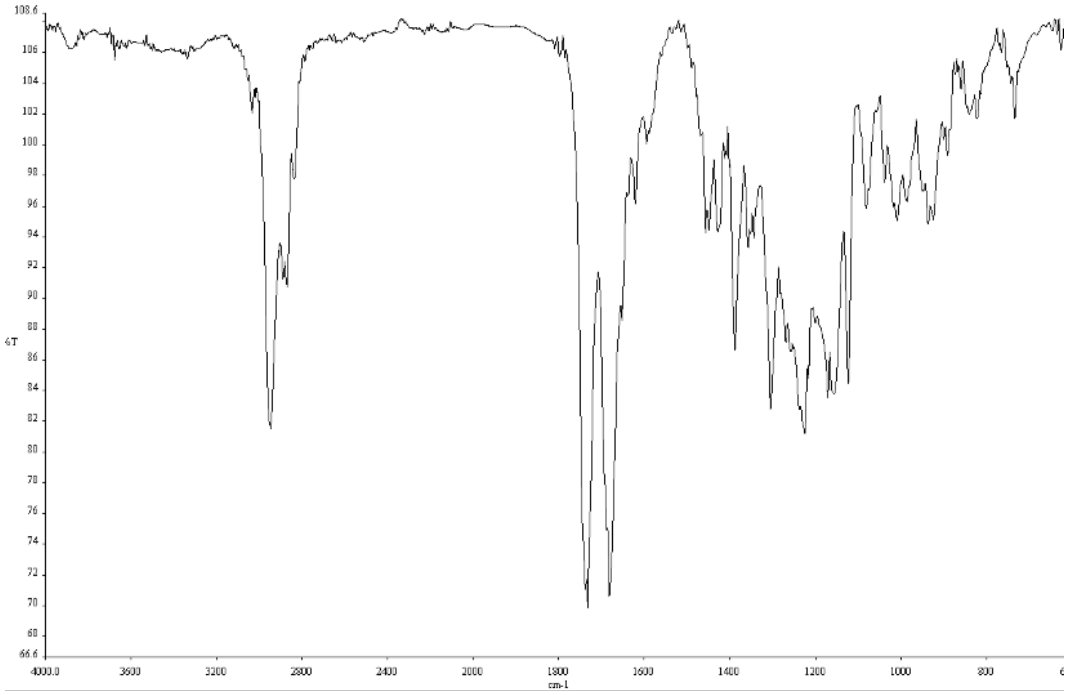


Figure A1.252. *Infrared spectrum (Thin Film, NaCl) of compound* ***79****.*

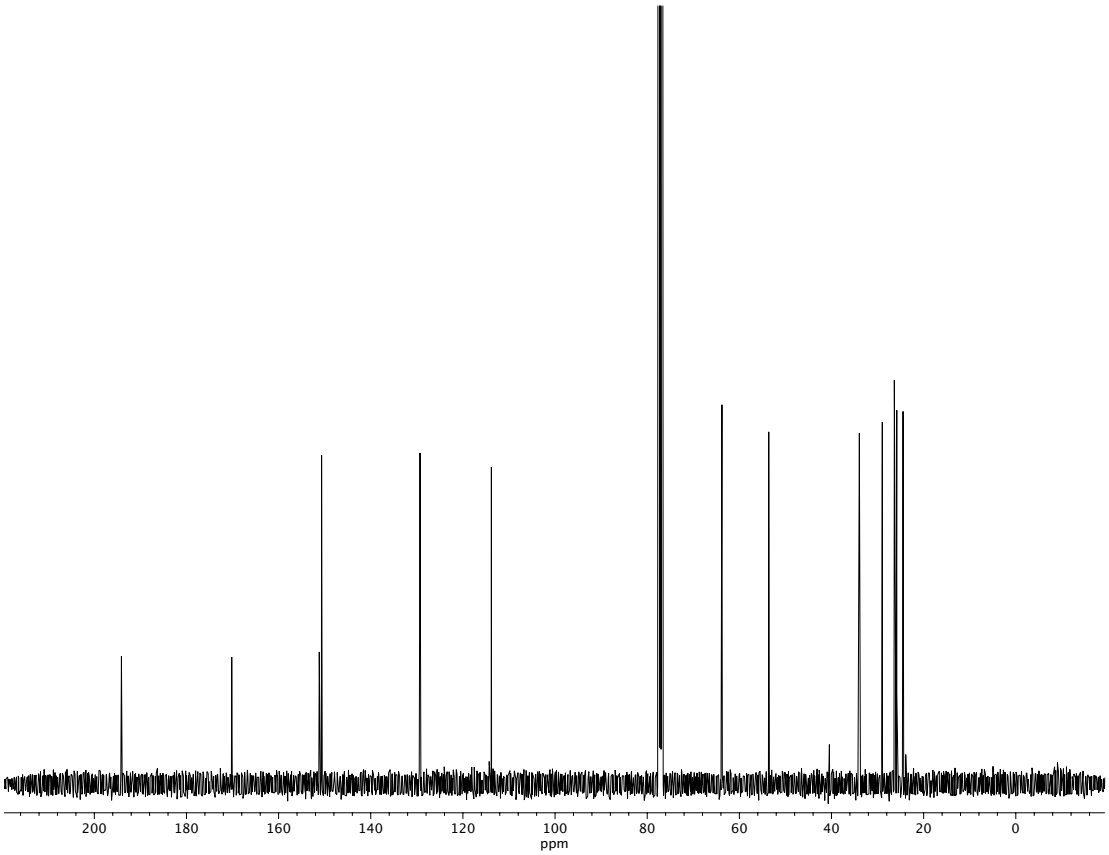


Figure A1.253. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***79****.*

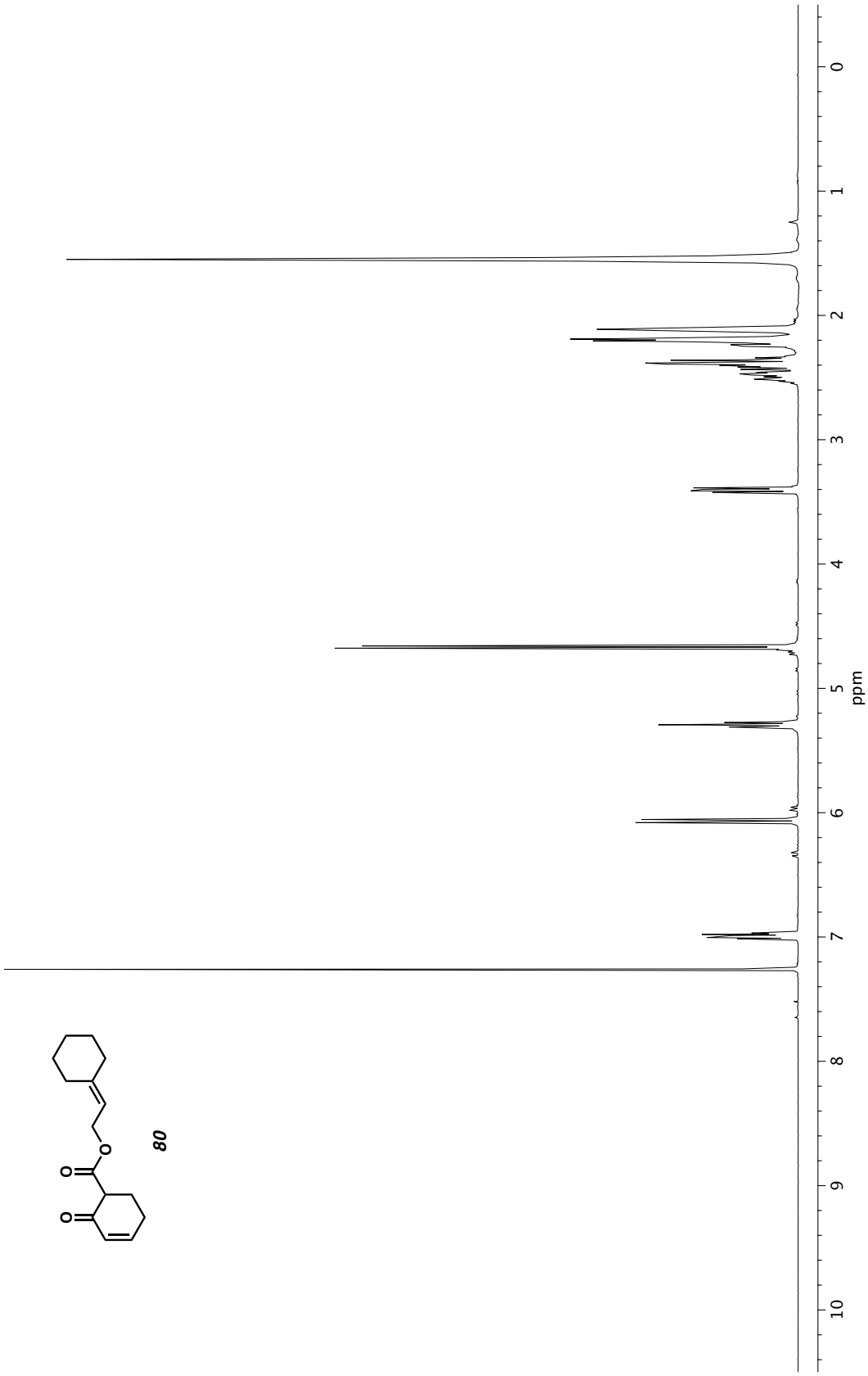


Figure A1.254. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***80****.*

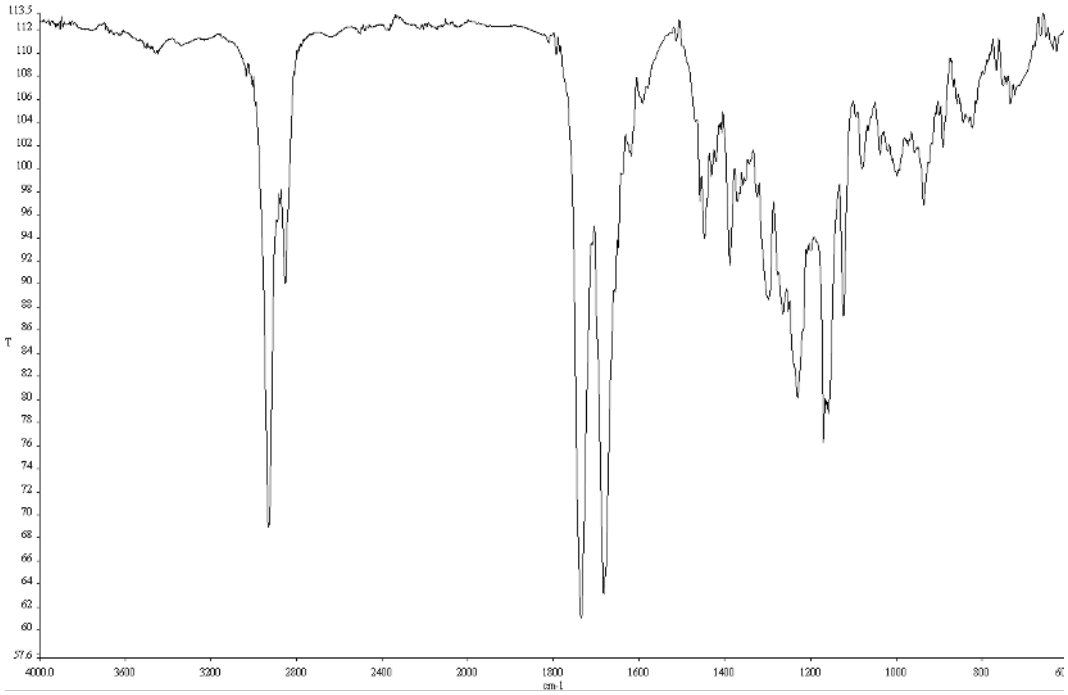


Figure A1.255. *Infrared spectrum (Thin Film, NaCl) of compound* ***80****.*

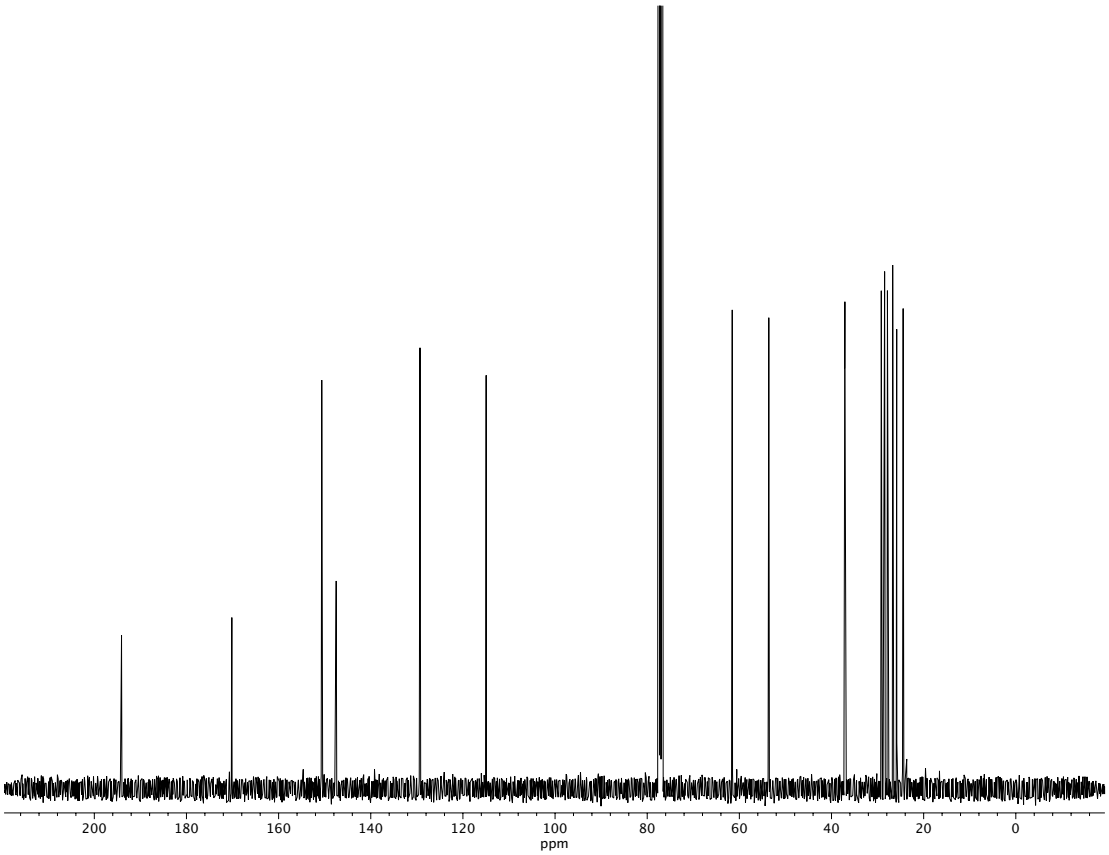


Figure A1.256. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***80****.*

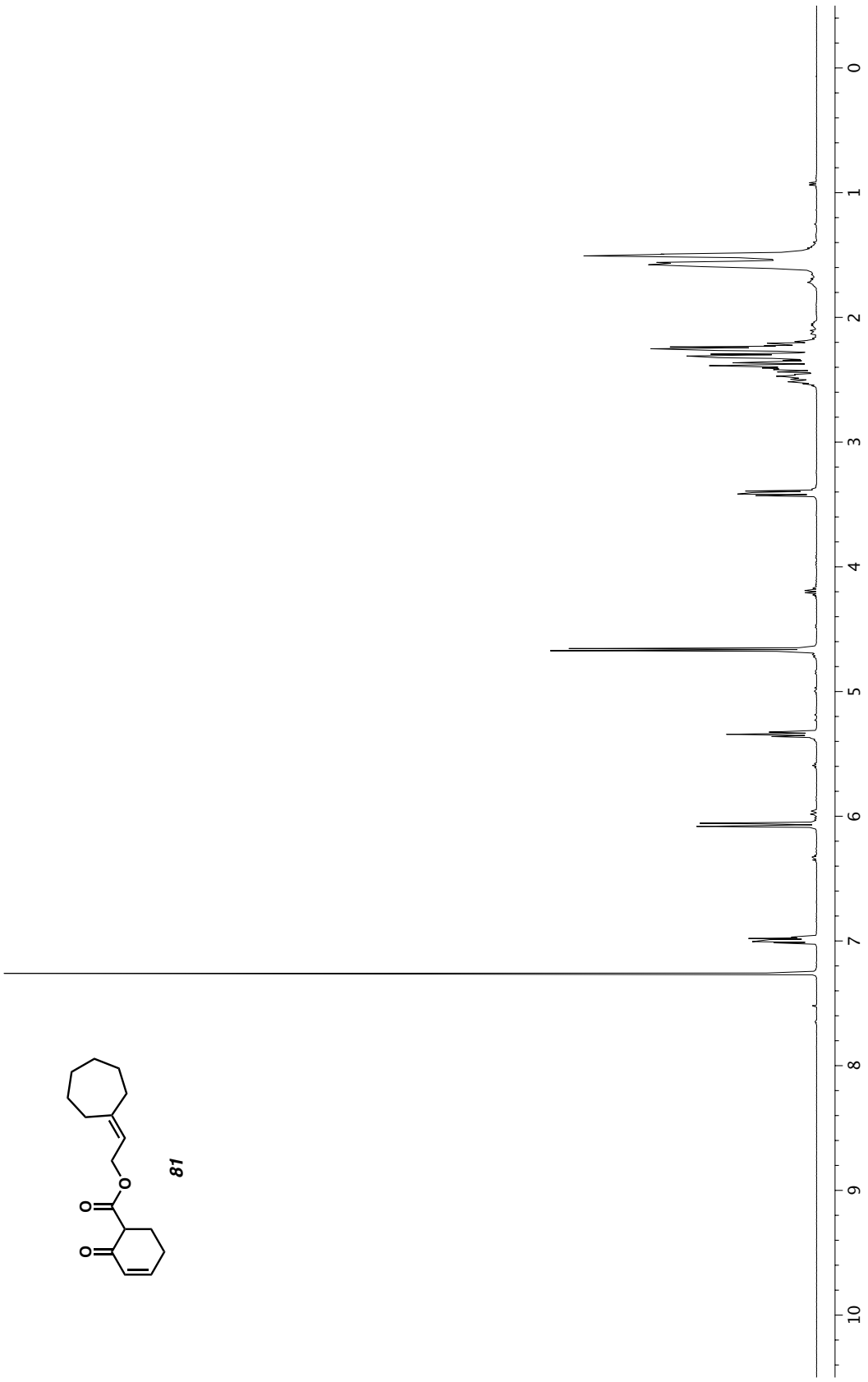


Figure A1.257. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***81****.*

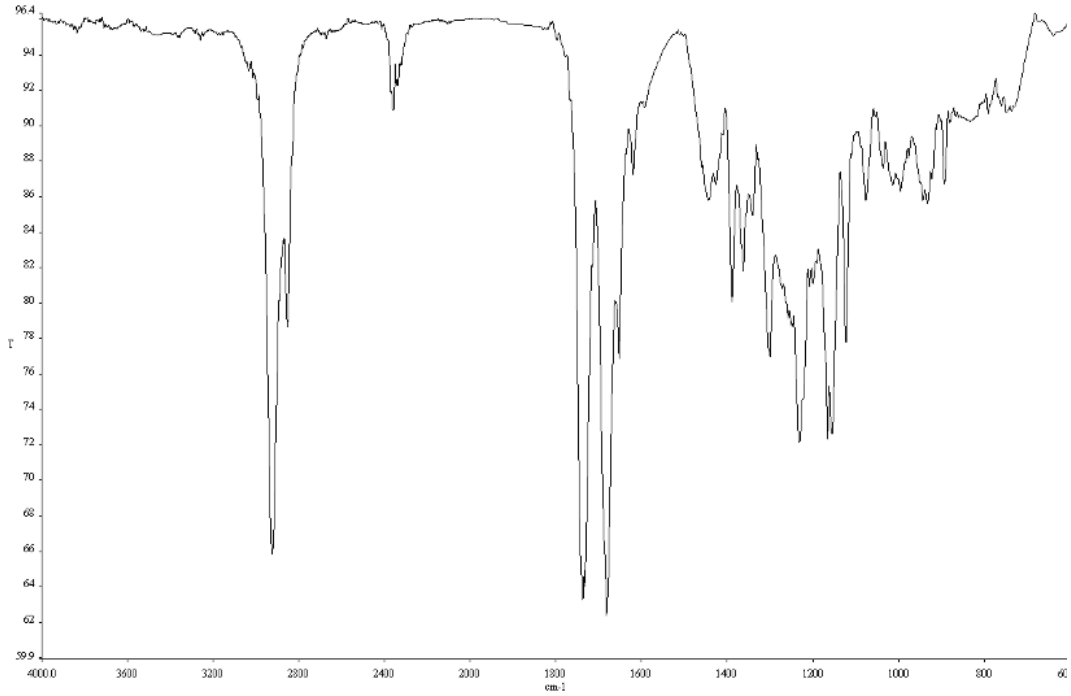


Figure A1.258. *Infrared spectrum (Thin Film, NaCl) of compound* ***81***.

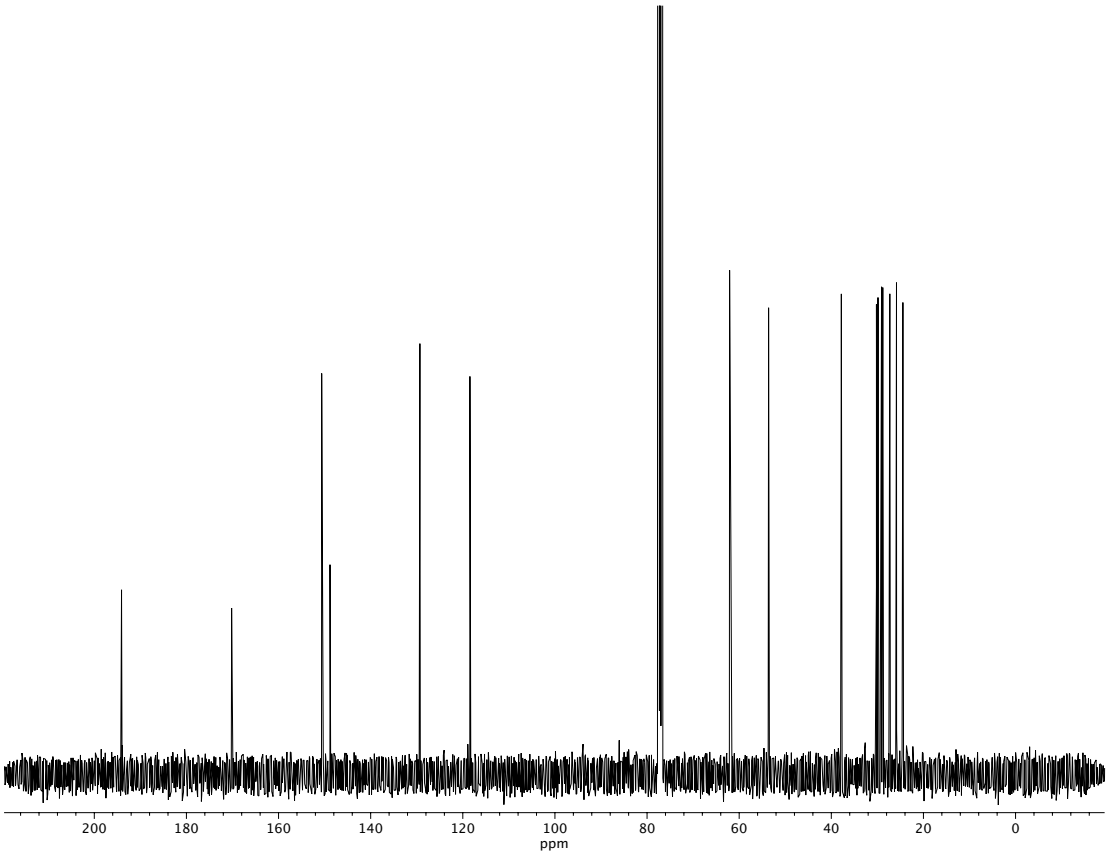


Figure A1.259. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***81***.

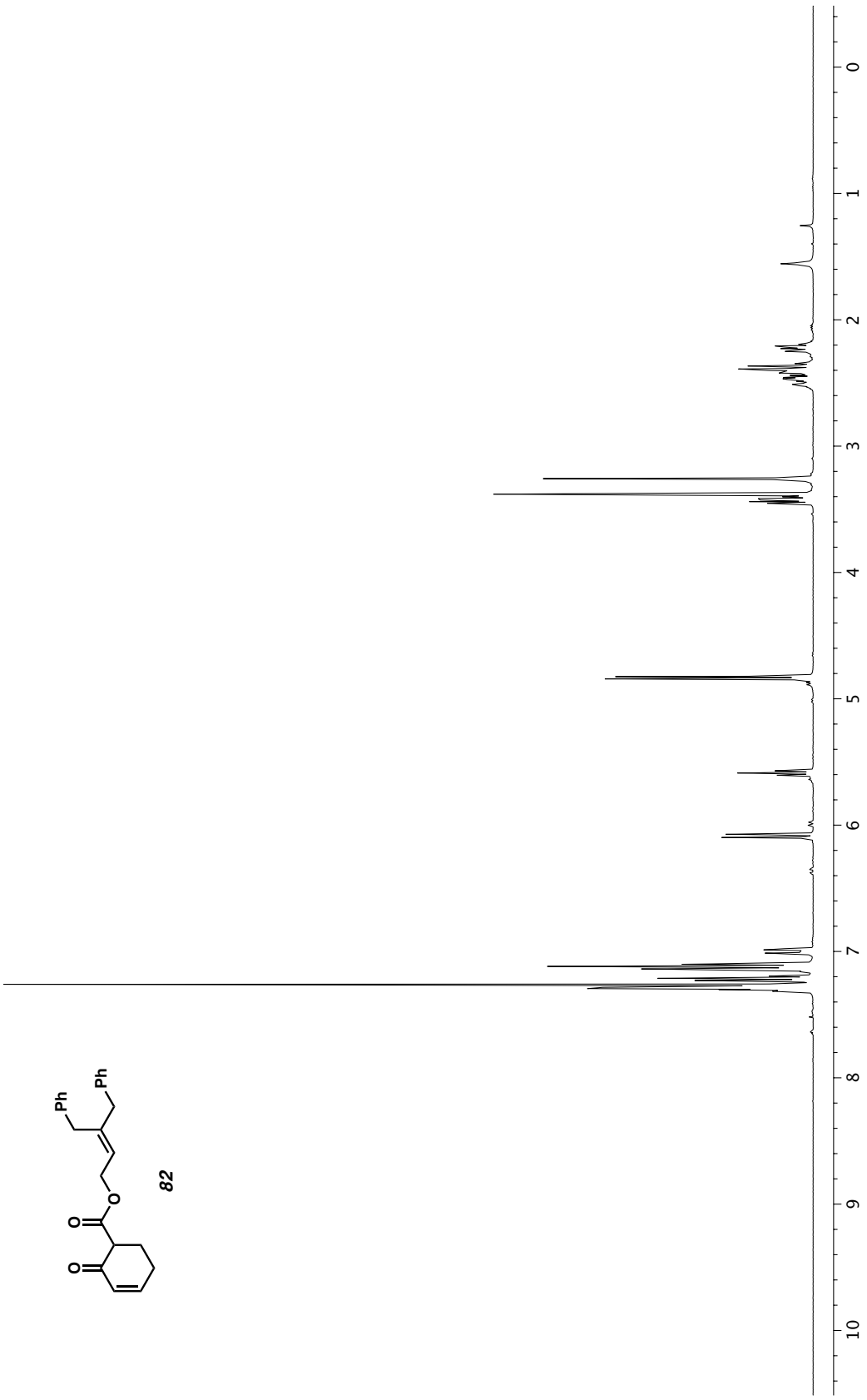


Figure A1.260. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***82****.*

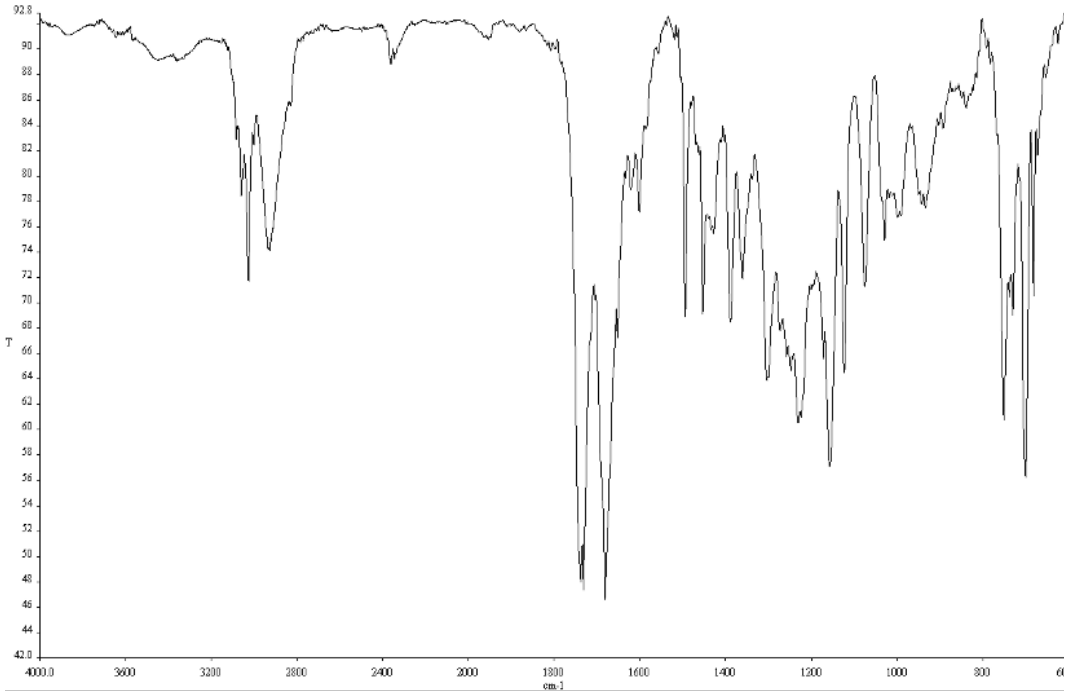


Figure A1.261. *Infrared spectrum (Thin Film, NaCl) of compound* ***82****.*

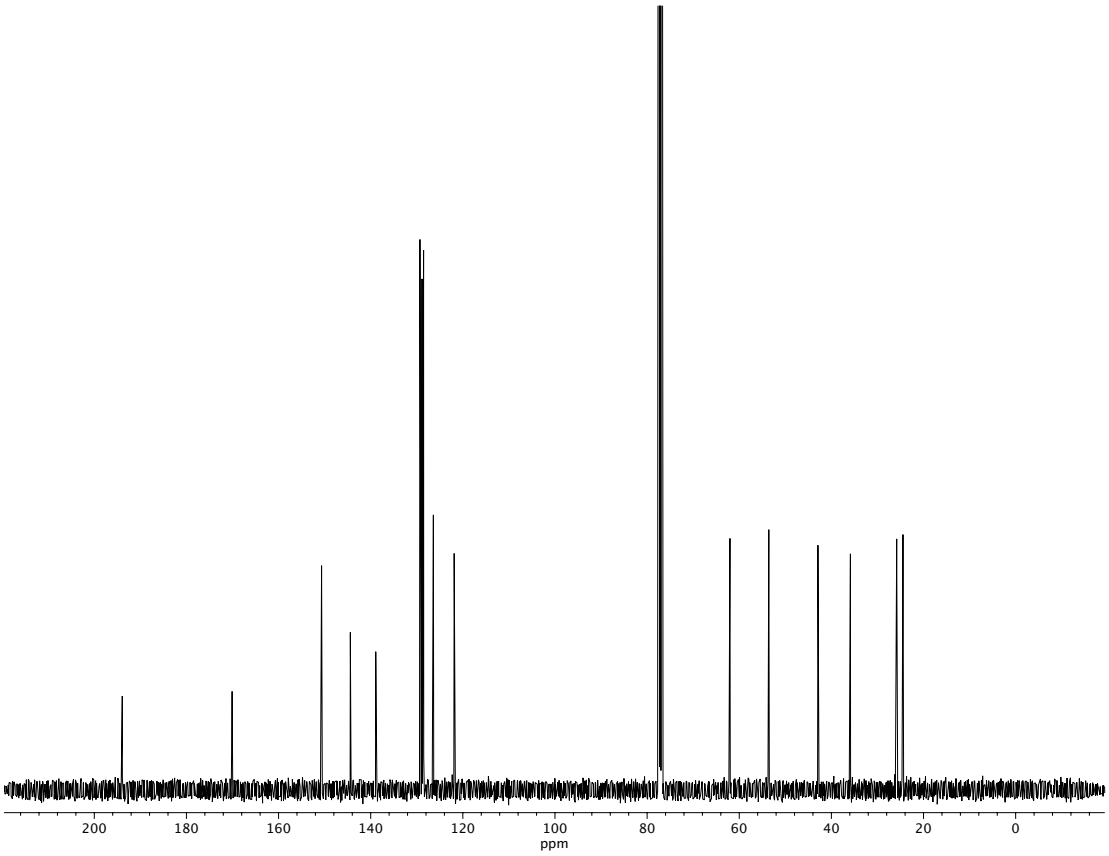


Figure A1.262. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***82****.*

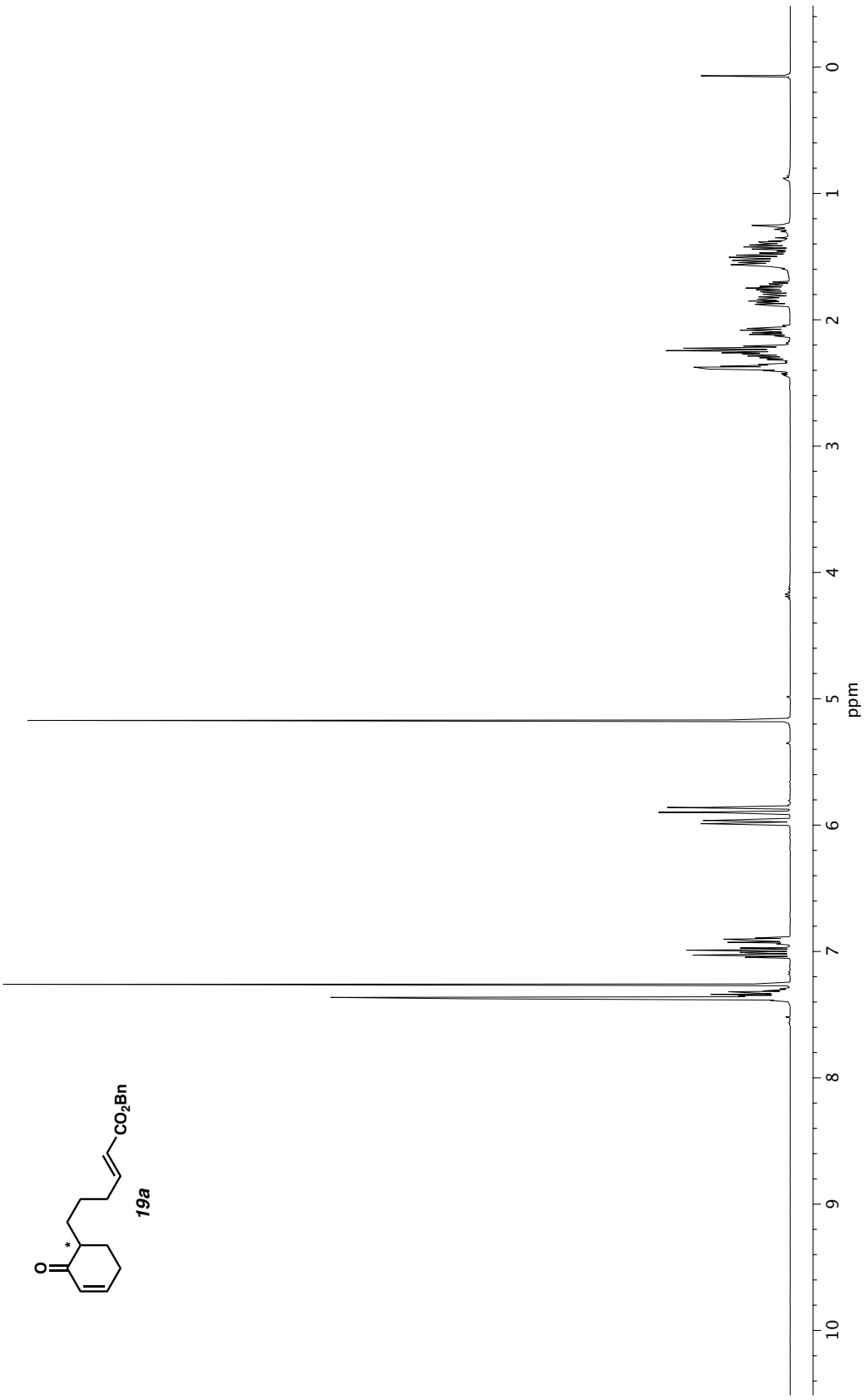


Figure A1.263. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***19a****.*

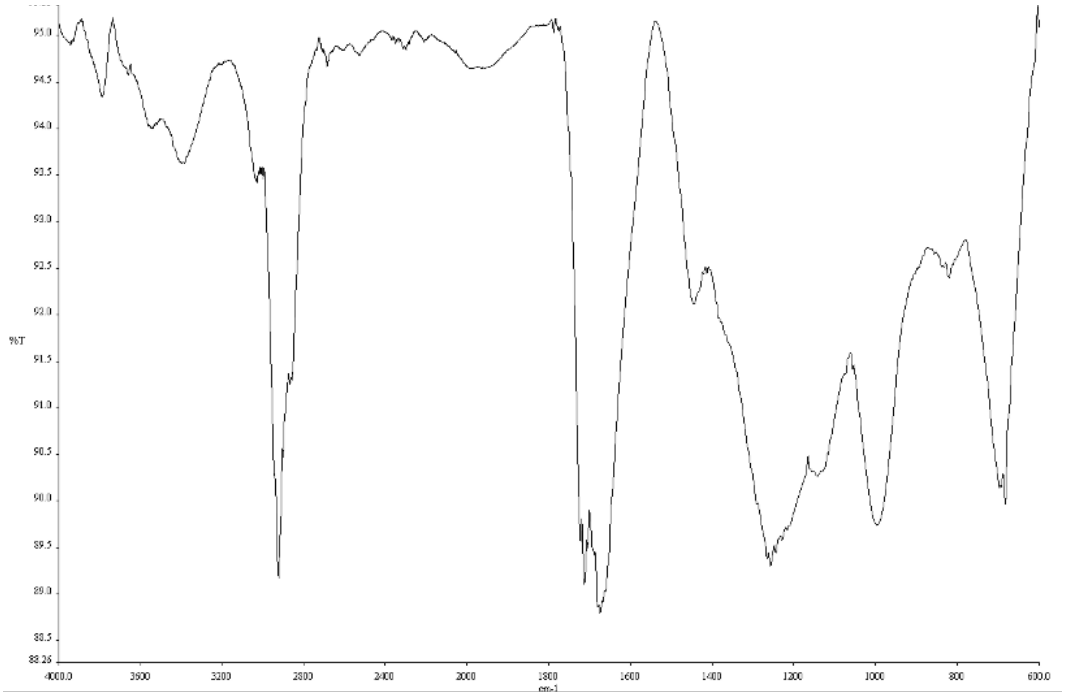


Figure A1.264. *Infrared spectrum (Thin Film, NaCl) of compound* ***19a****.*

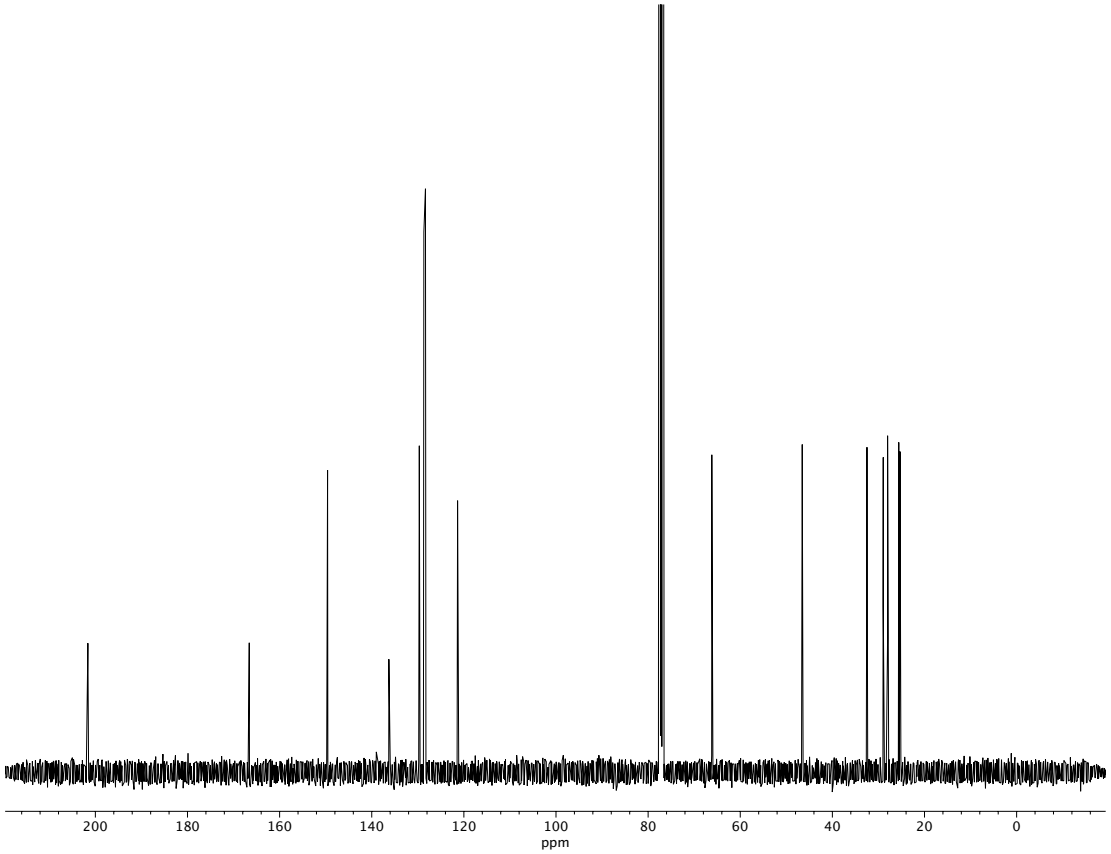


Figure A1.265. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***19a****.*

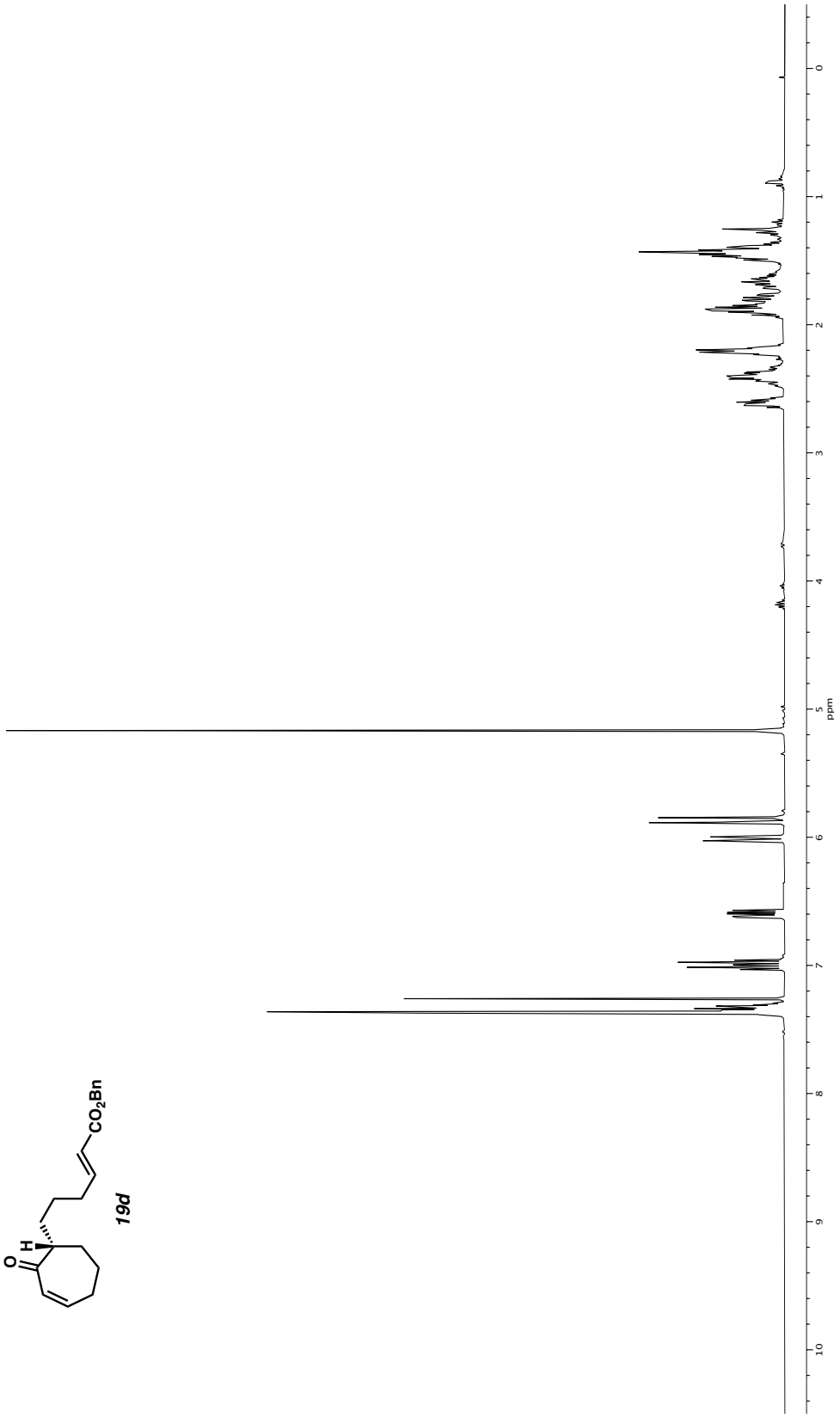


Figure A1.266. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***19d****.*

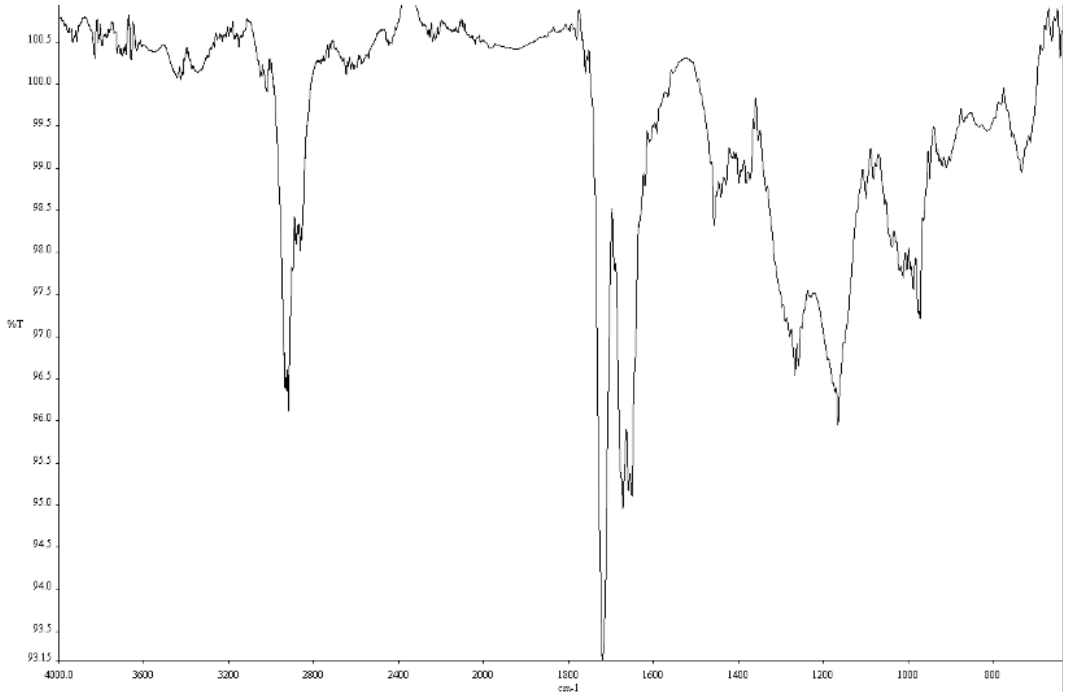


Figure A1.267. *Infrared spectrum (Thin Film, NaCl) of compound* ***19d****.*

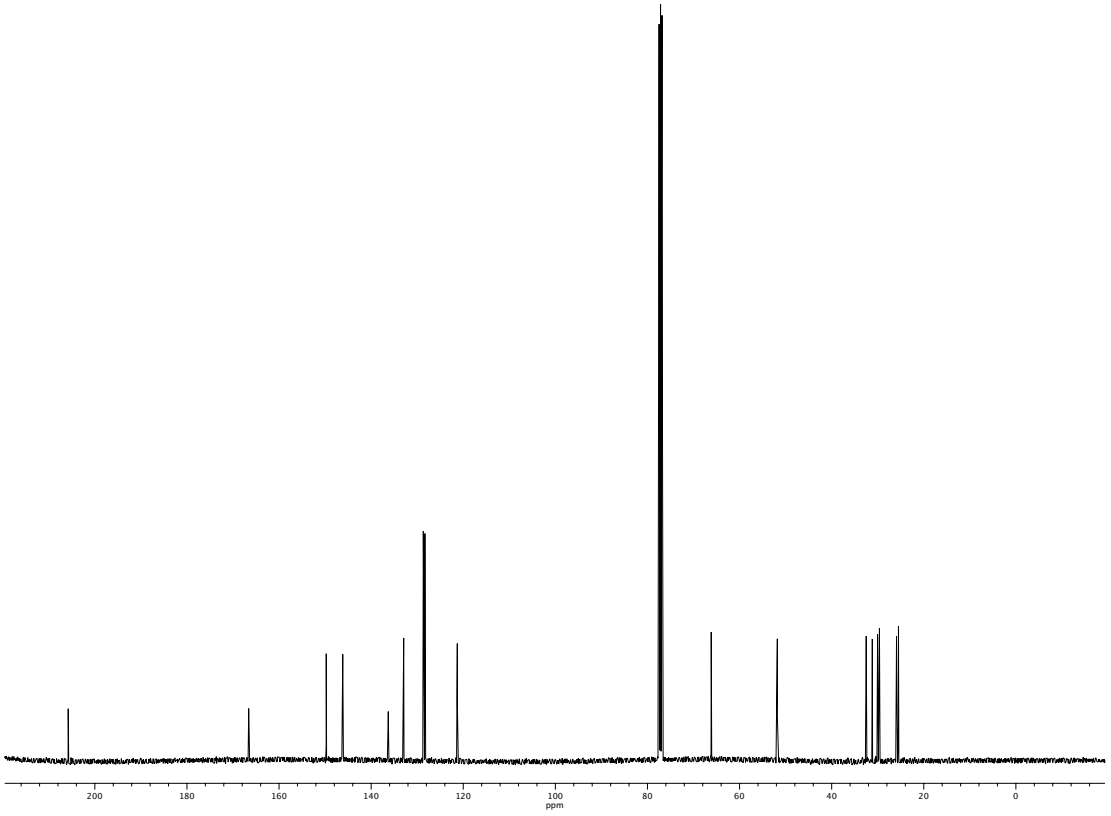


Figure A1.268. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***19d****.*

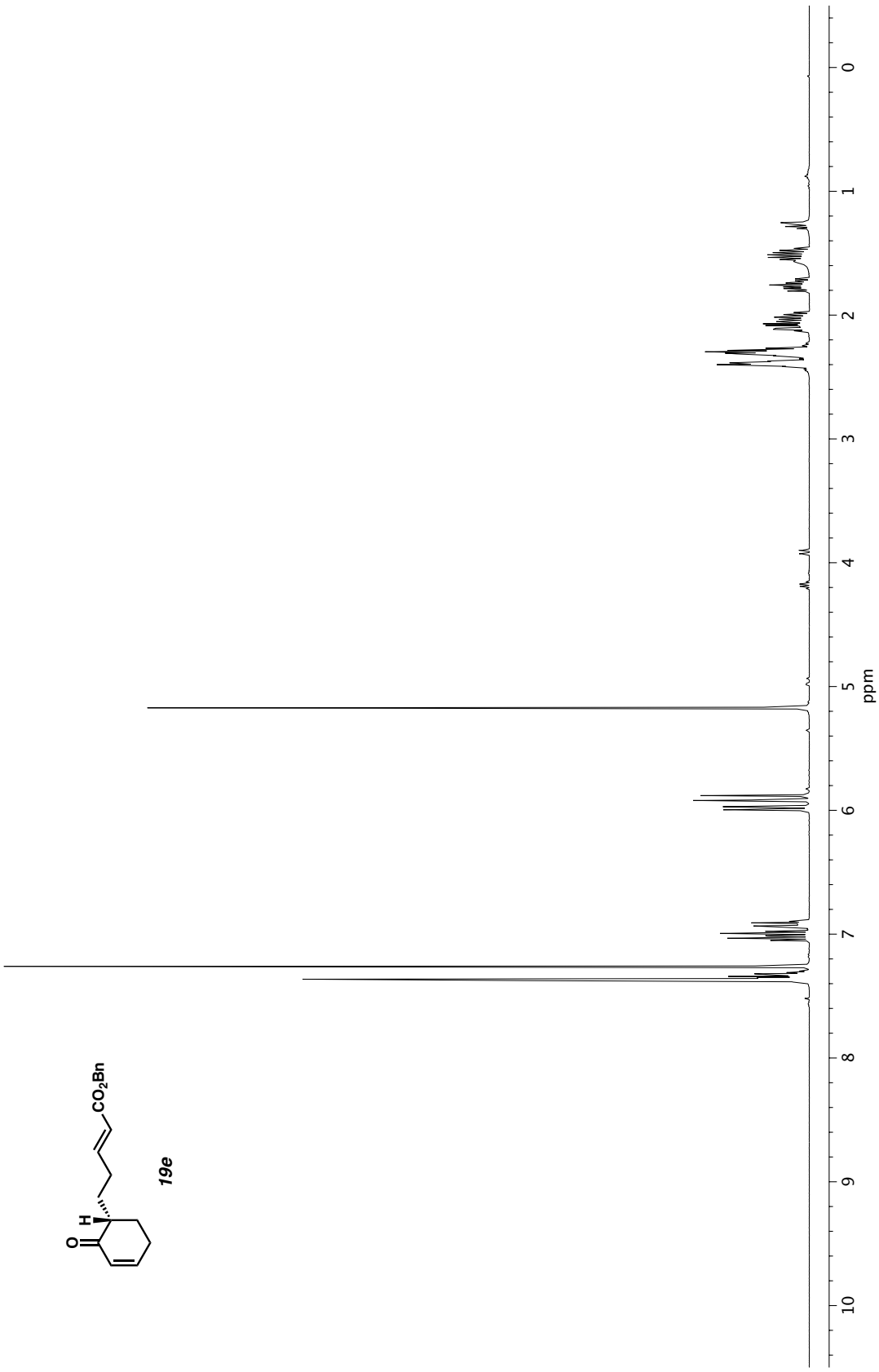


Figure A1.269. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***19e****.*

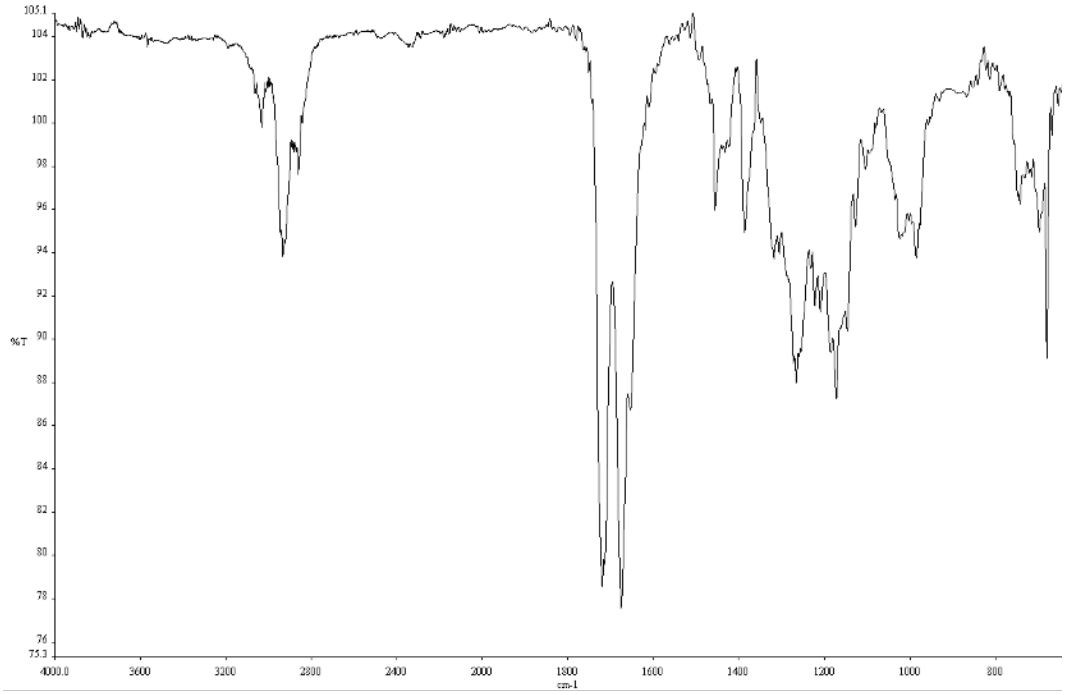


Figure A1.270. *Infrared spectrum (Thin Film, NaCl) of compound* ***19e****.*

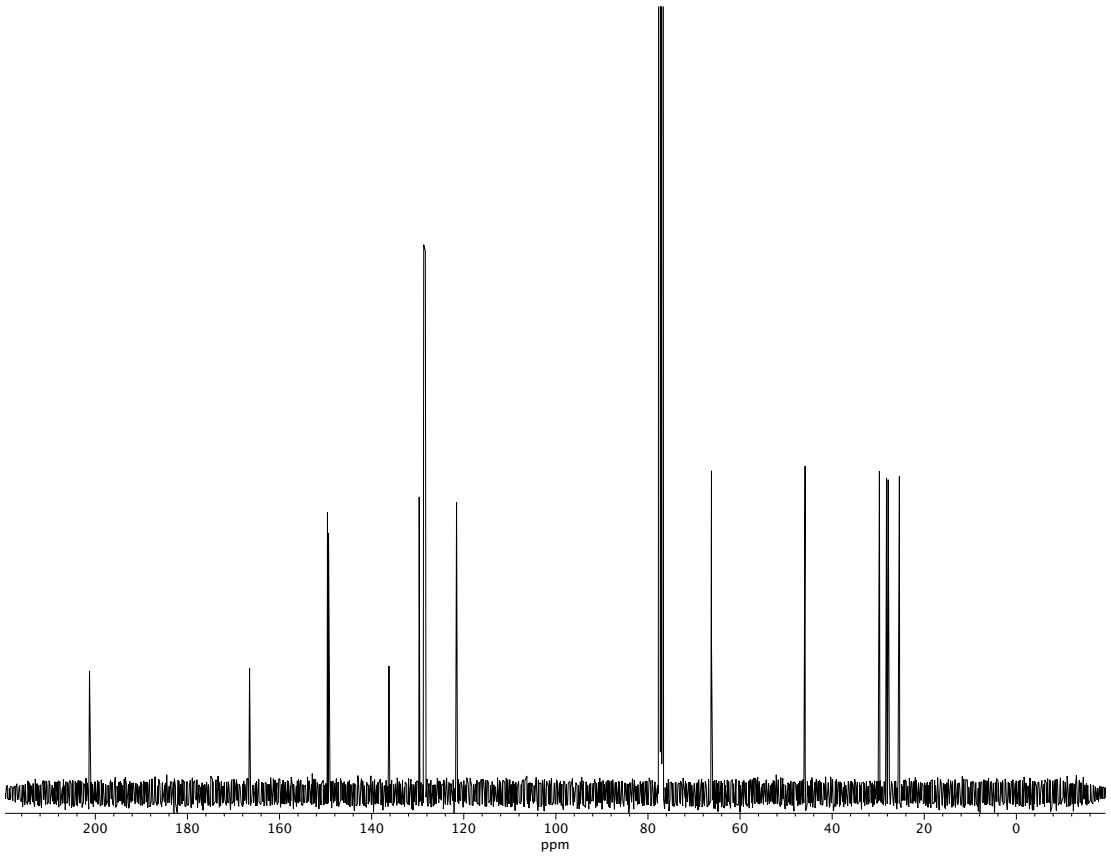


Figure A1.271. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***19e****.*

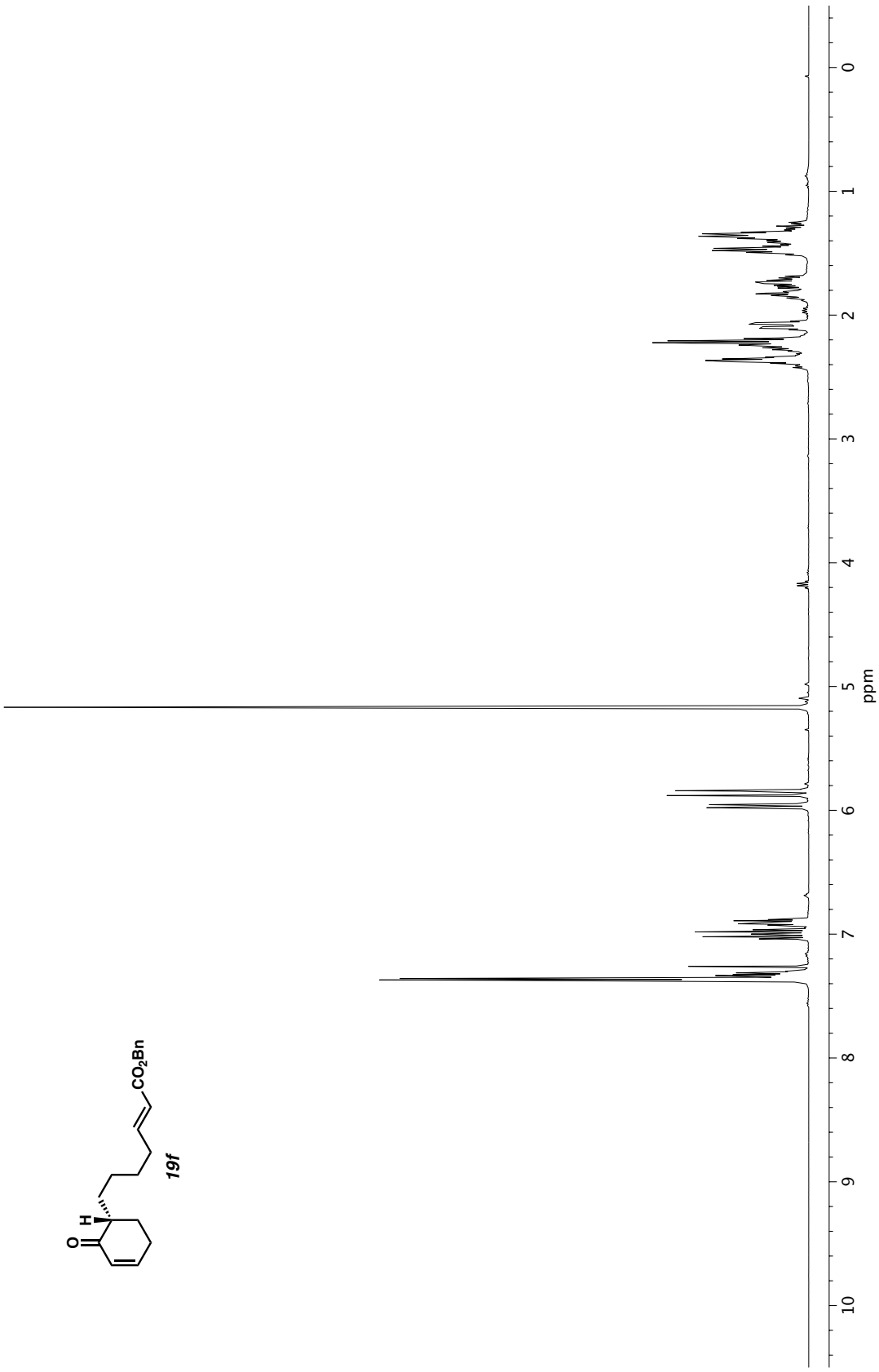


Figure A1.272. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***19f****.*

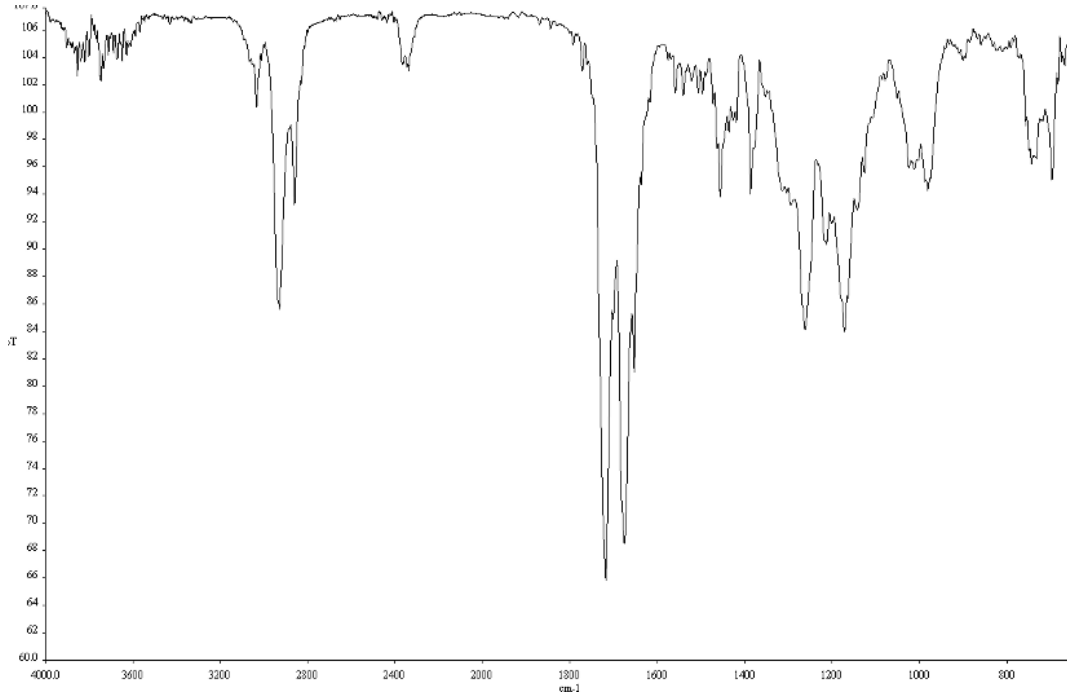


Figure A1.273. *Infrared spectrum (Thin Film, NaCl) of compound* ***19f****.*

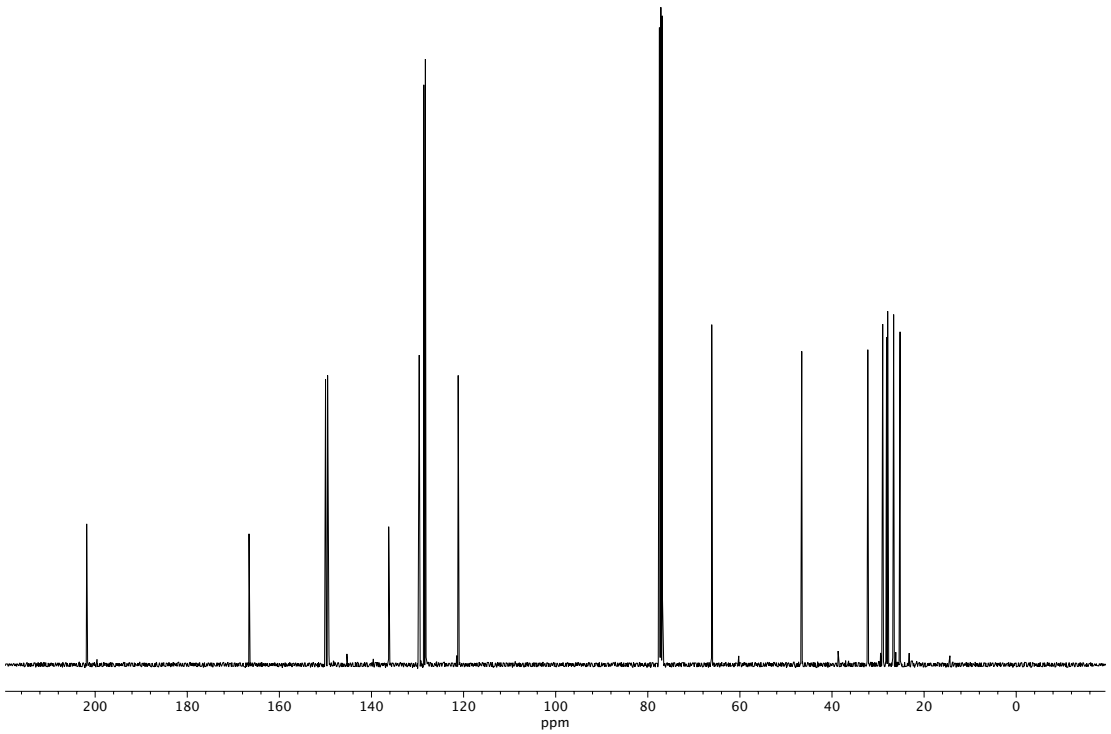


Figure A1.274. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***19f****.*

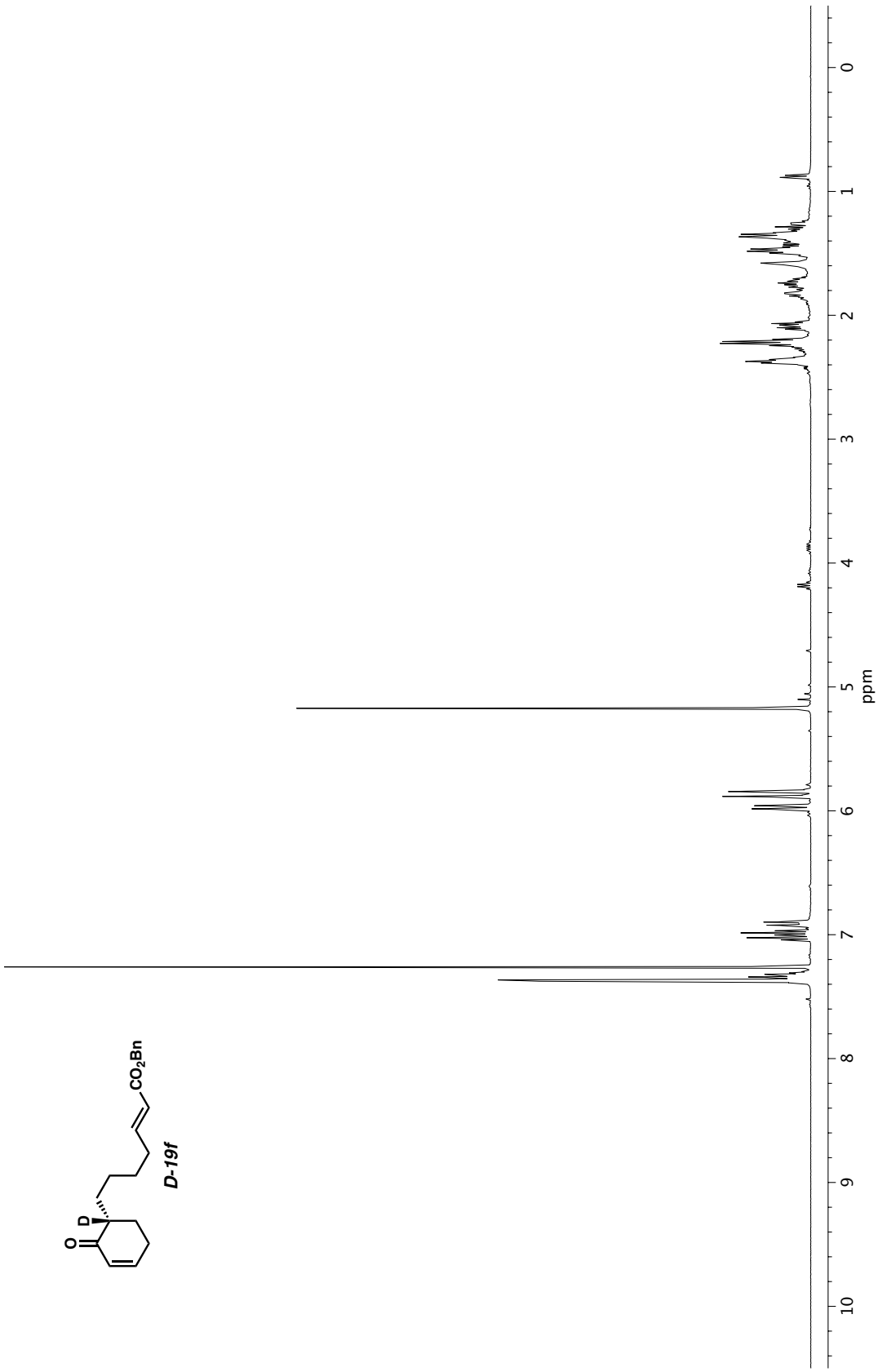


Figure A1.275. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***D-19f****.*

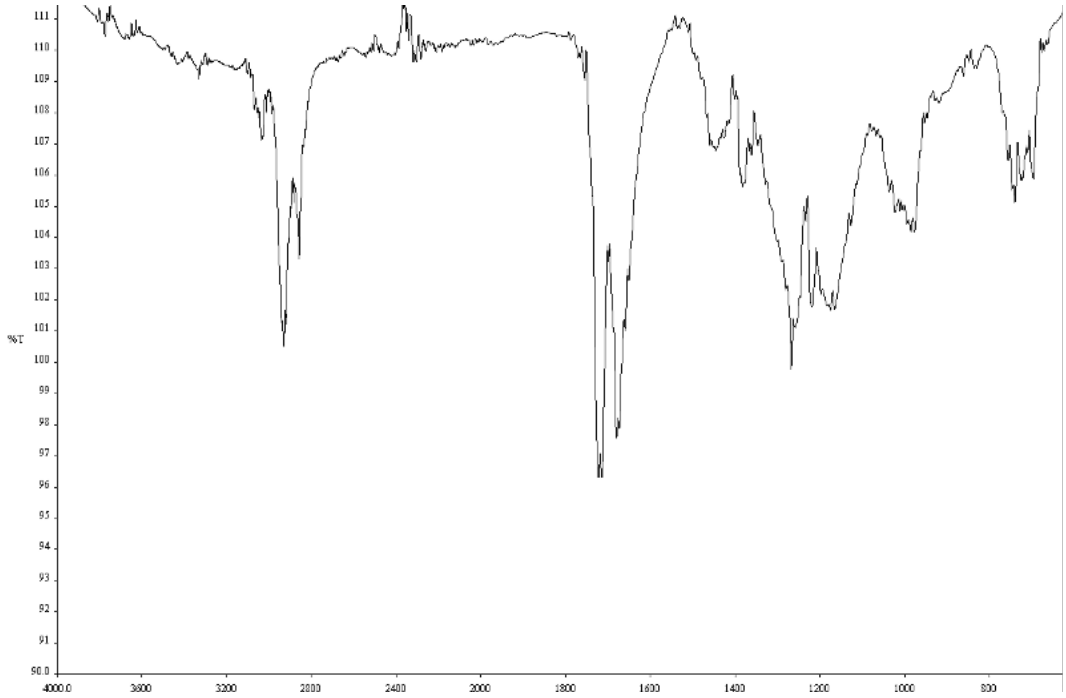


Figure A1.276. *Infrared spectrum (Thin Film, NaCl) of compound* ***D-19f****.*

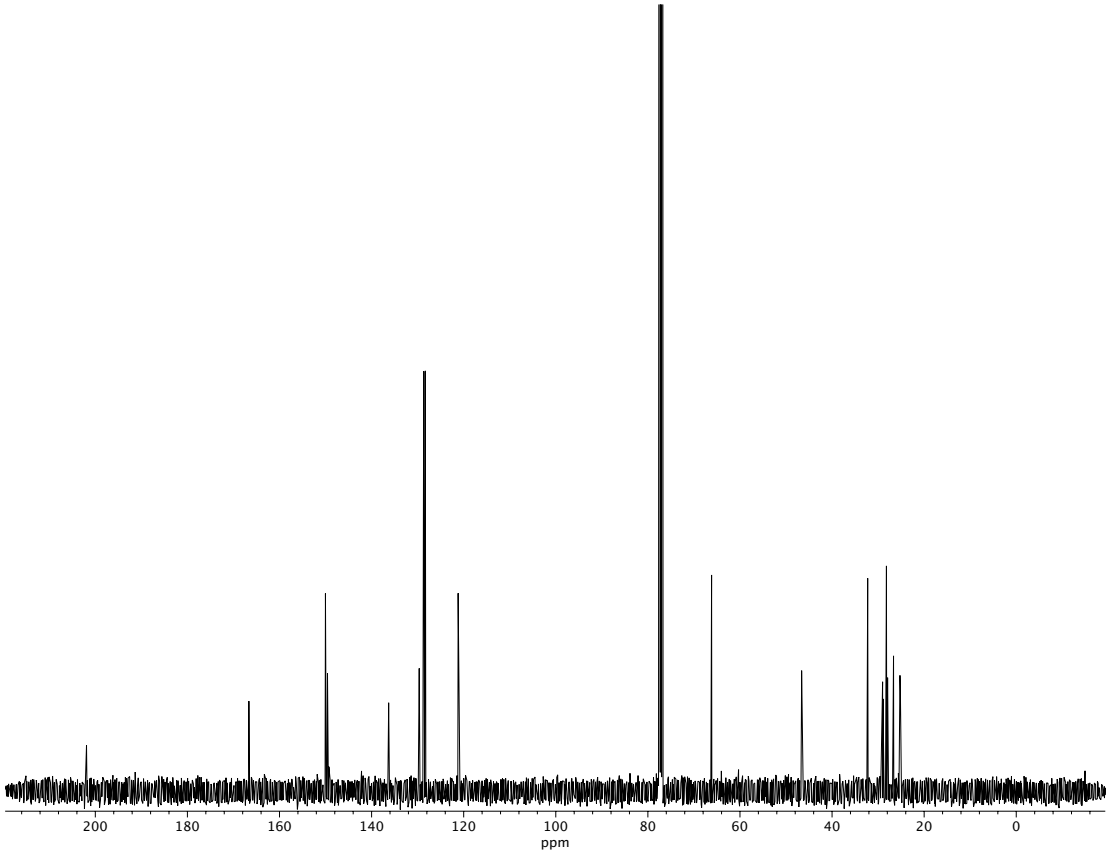


Figure A1.277. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***D-19f****.*

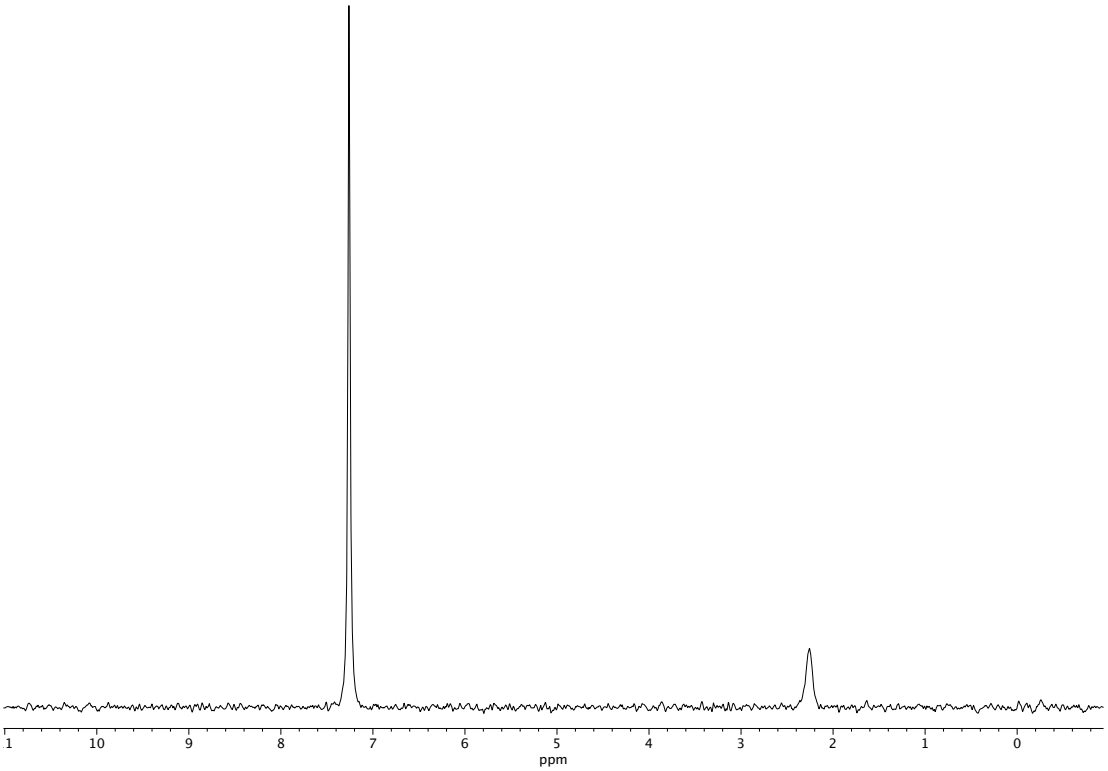


Figure A1.278. *^{2}H NMR (61 MHz, $CHCl_3$) of compound* ***D-19f****.*

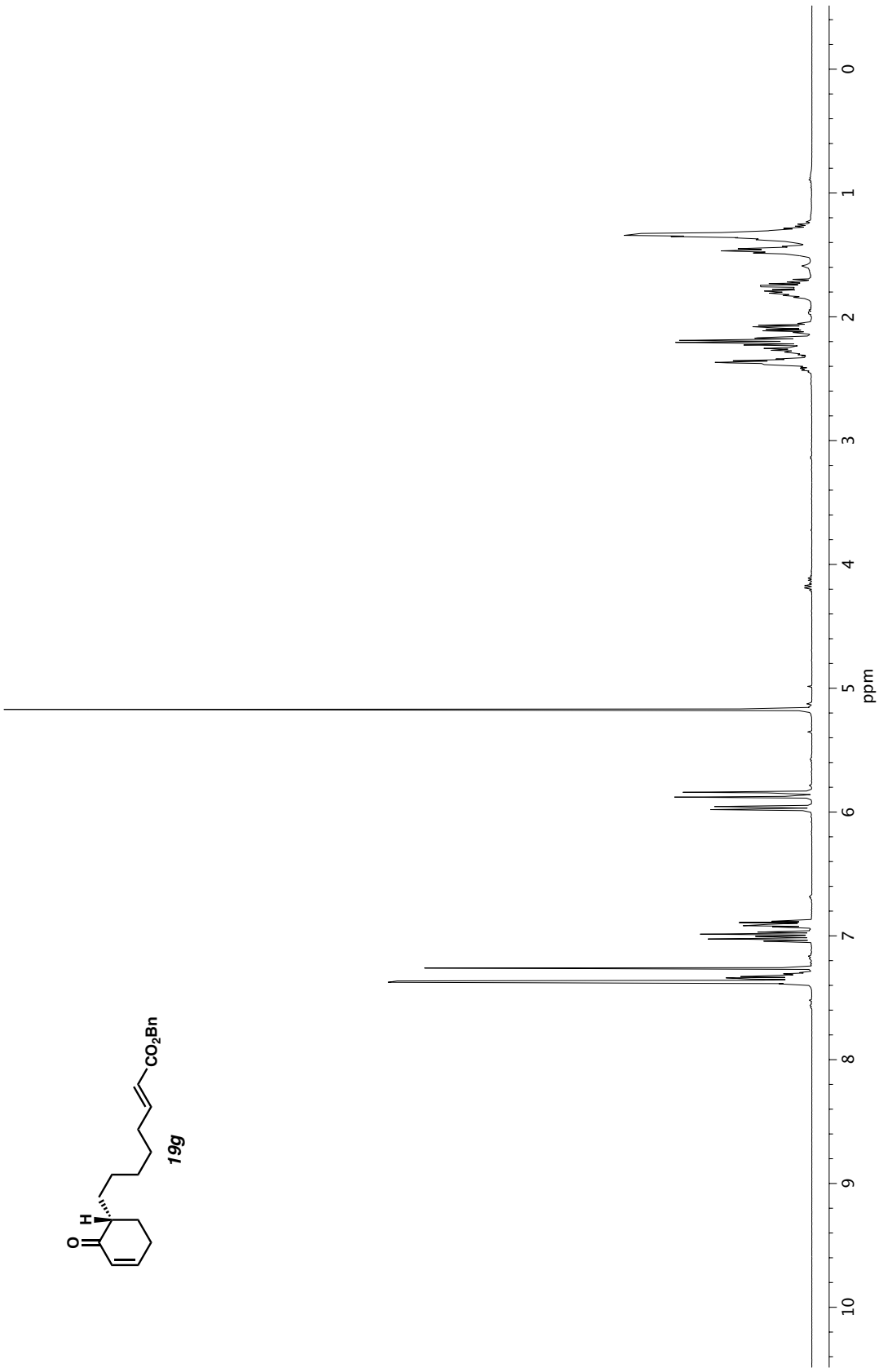


Figure A1.279. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***19g****.*

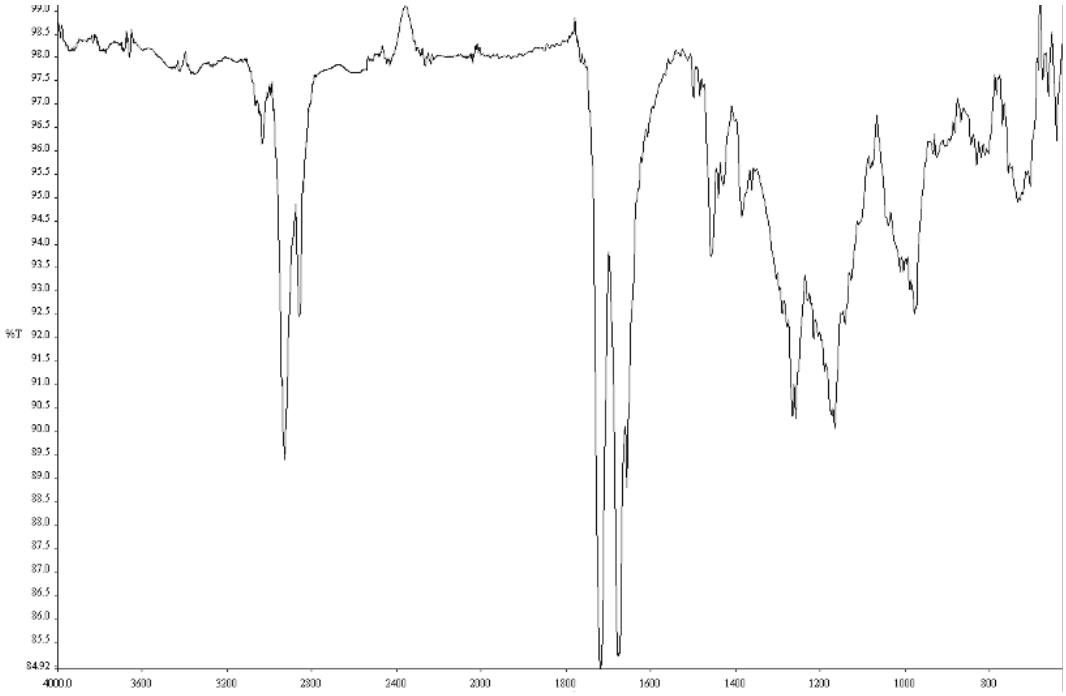


Figure A1.280. *Infrared spectrum (Thin Film, NaCl) of compound* ***19g****.*

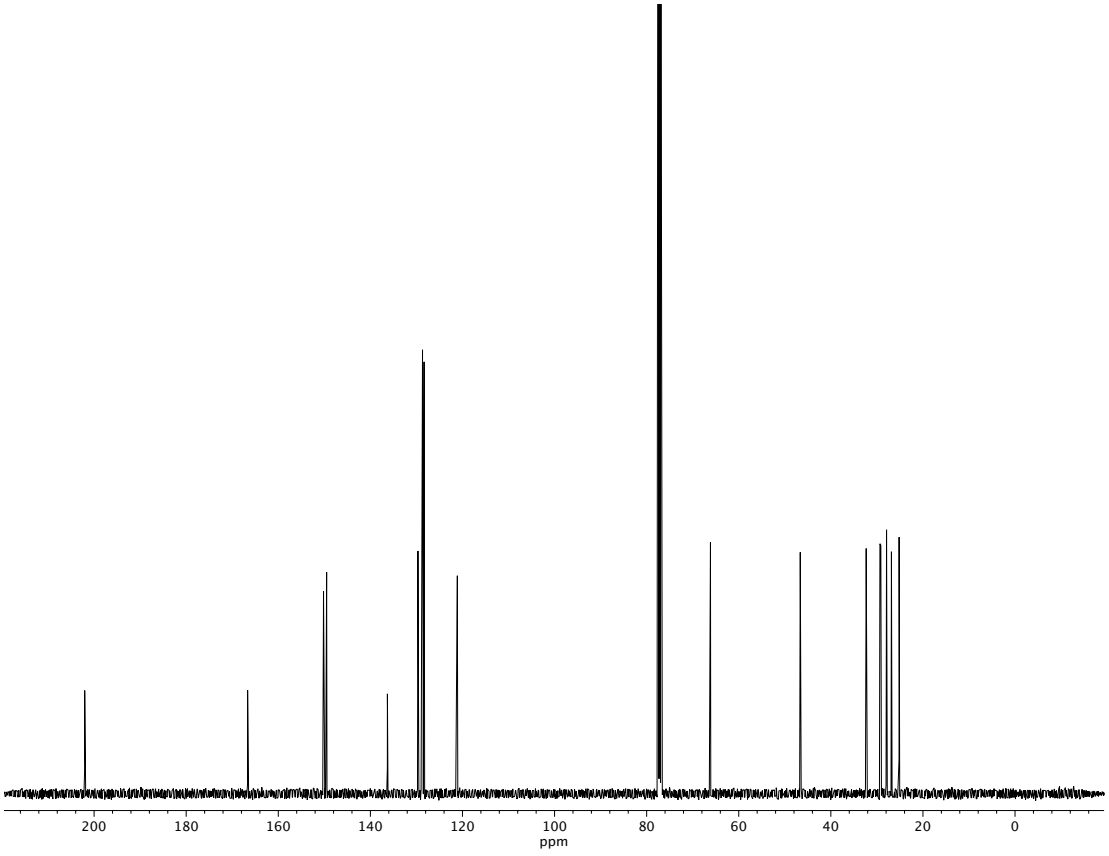


Figure A1.281. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***19g****.*

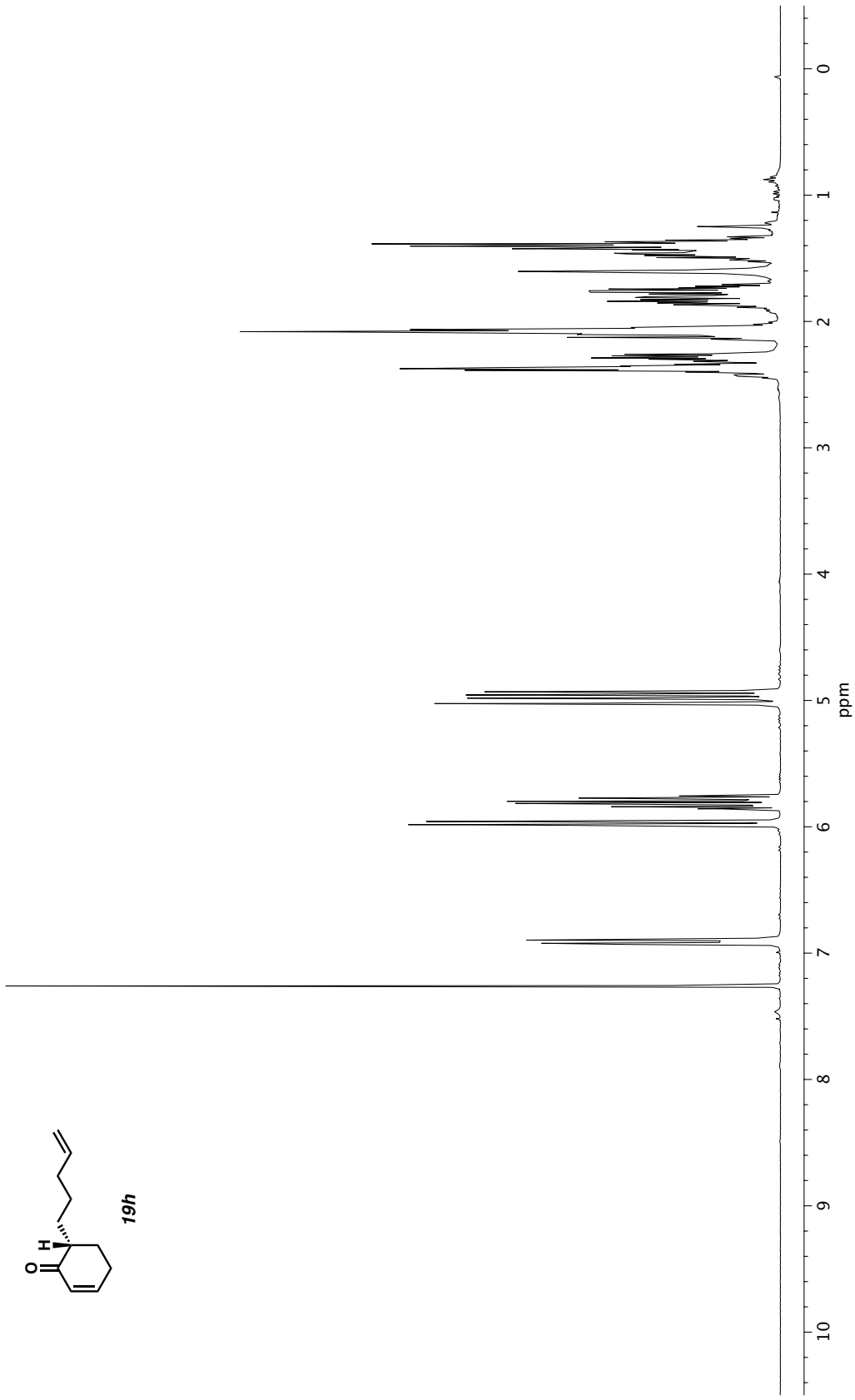


Figure A1.282. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***19h****.*

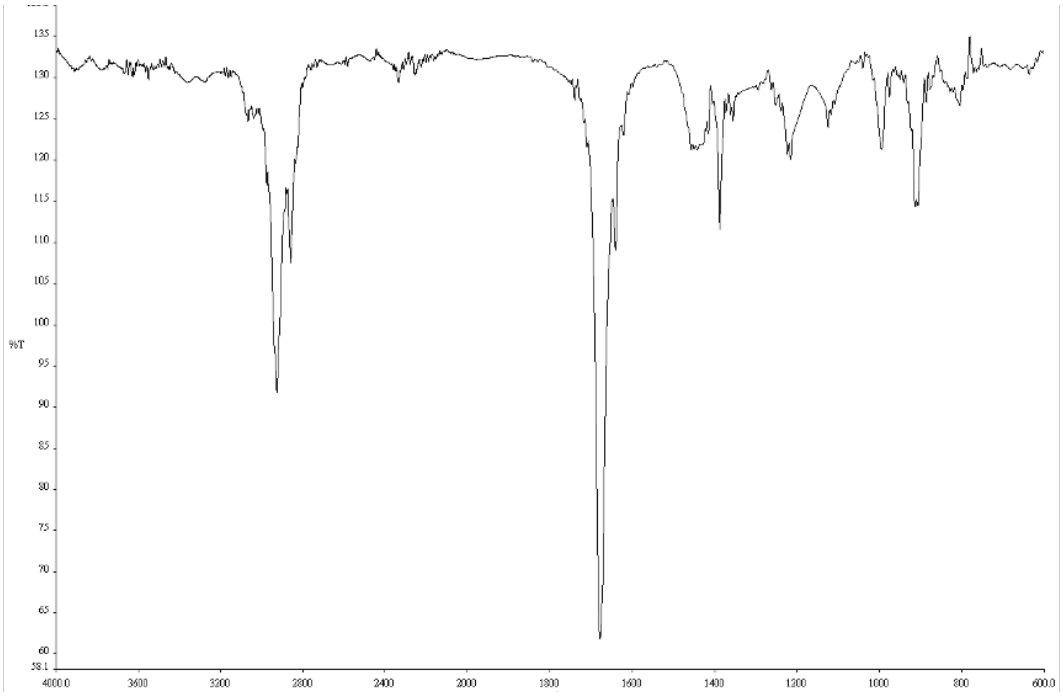


Figure A1.283. *Infrared spectrum (Thin Film, NaCl) of compound* ***19h****.*

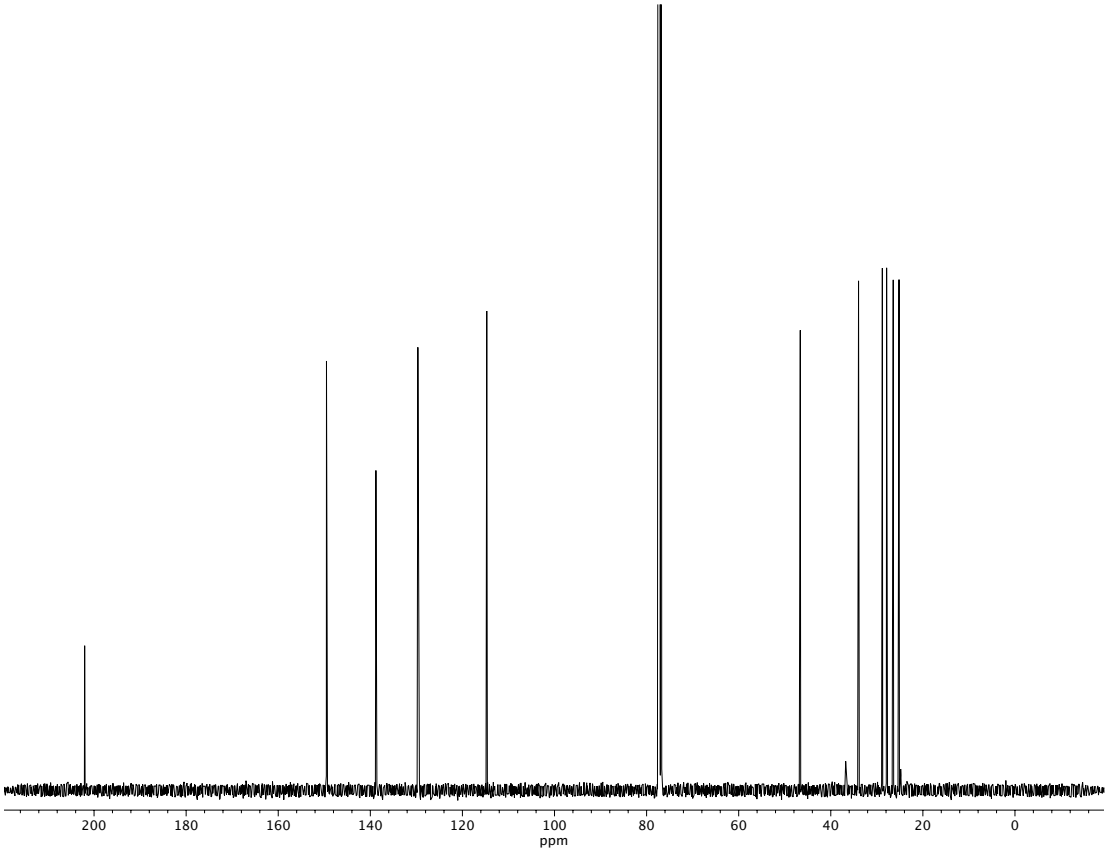


Figure A1.284. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***19h****.*

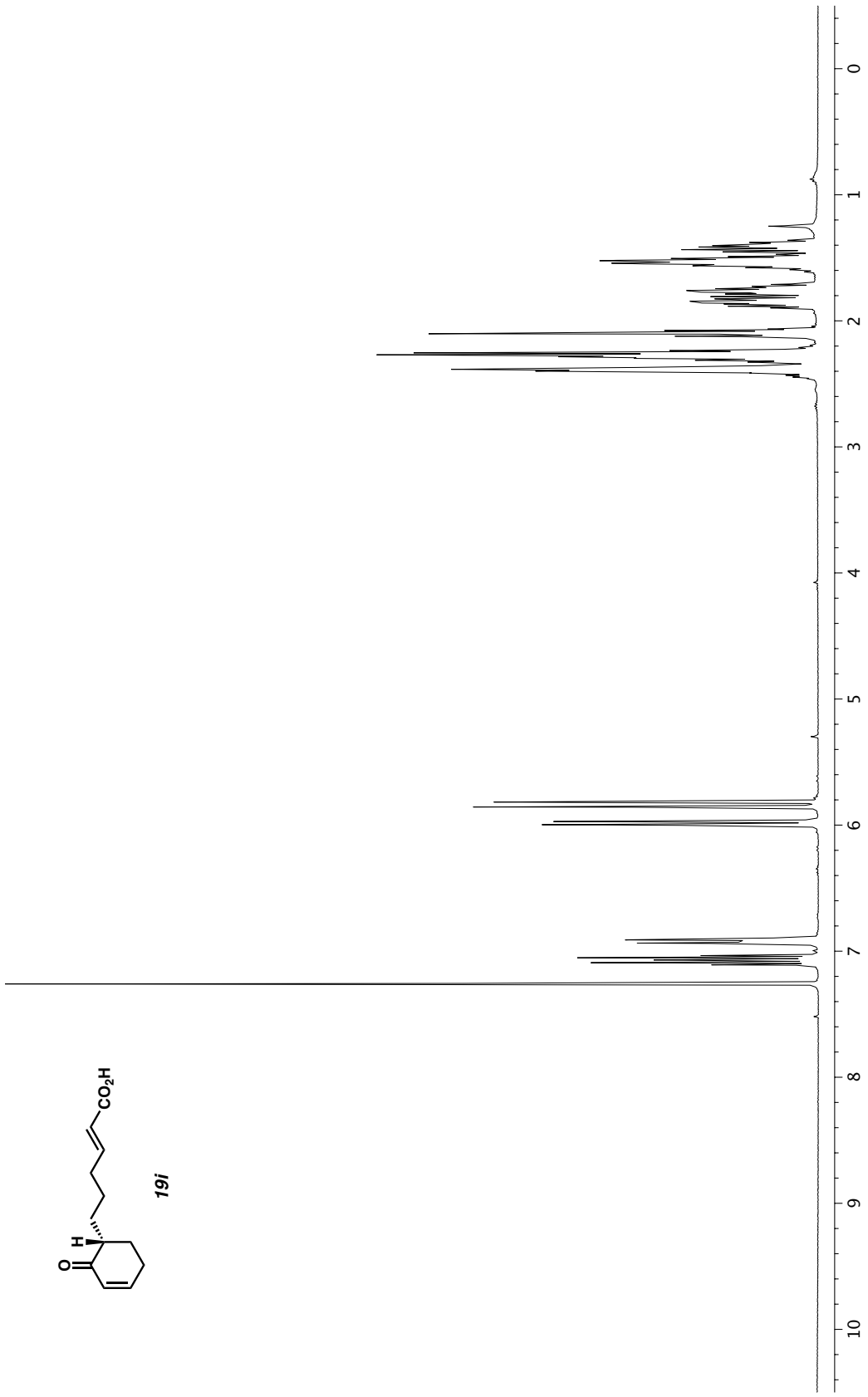


Figure A1.285. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***19i****.*

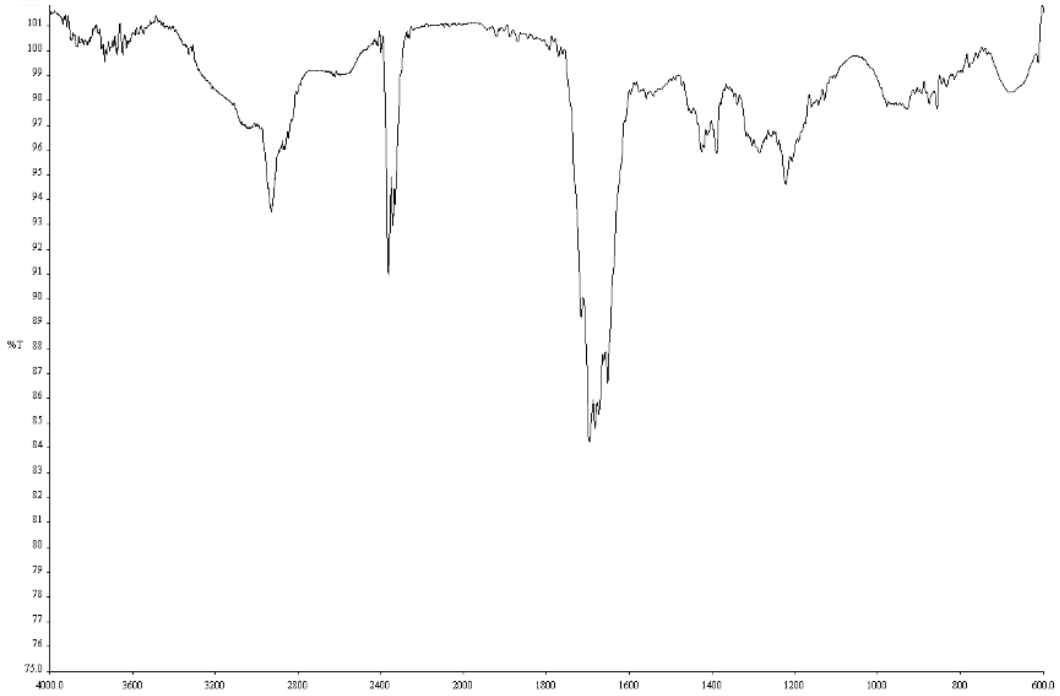


Figure A1.286. *Infrared spectrum (Thin Film, NaCl) of compound* ***19i****.*

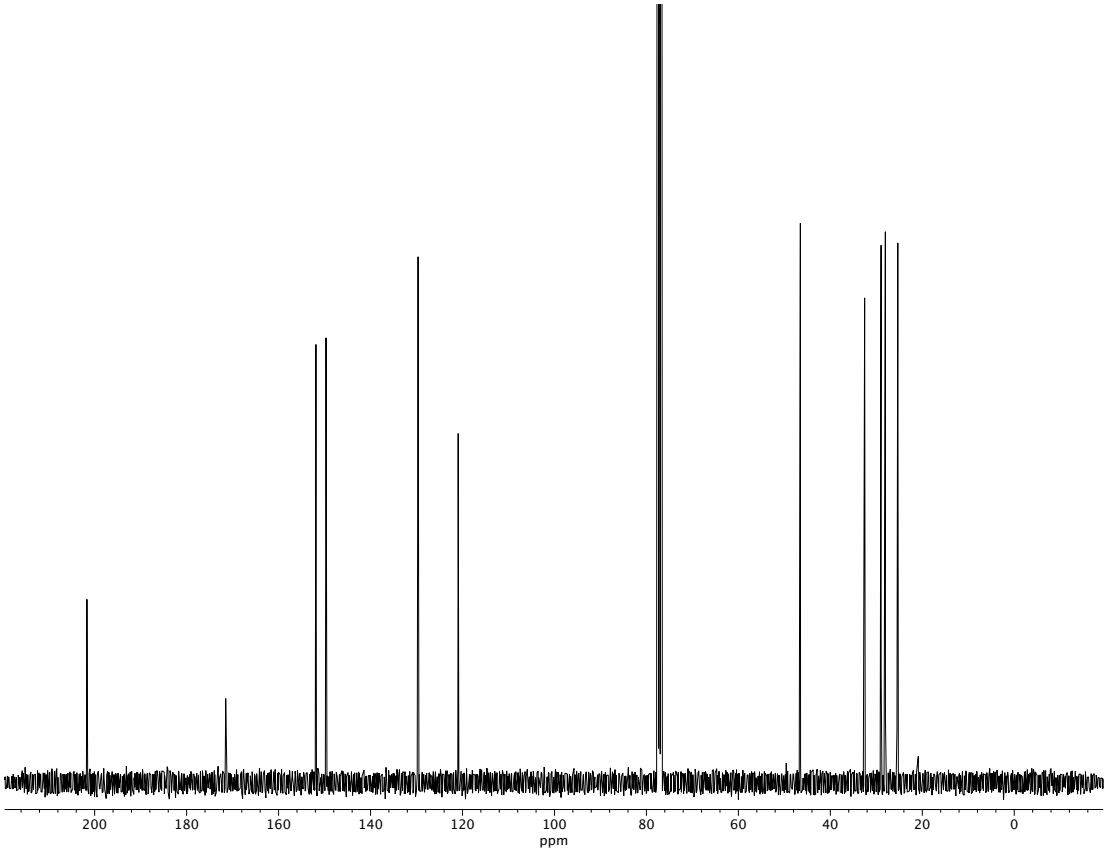


Figure A1.287. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***19i****.*

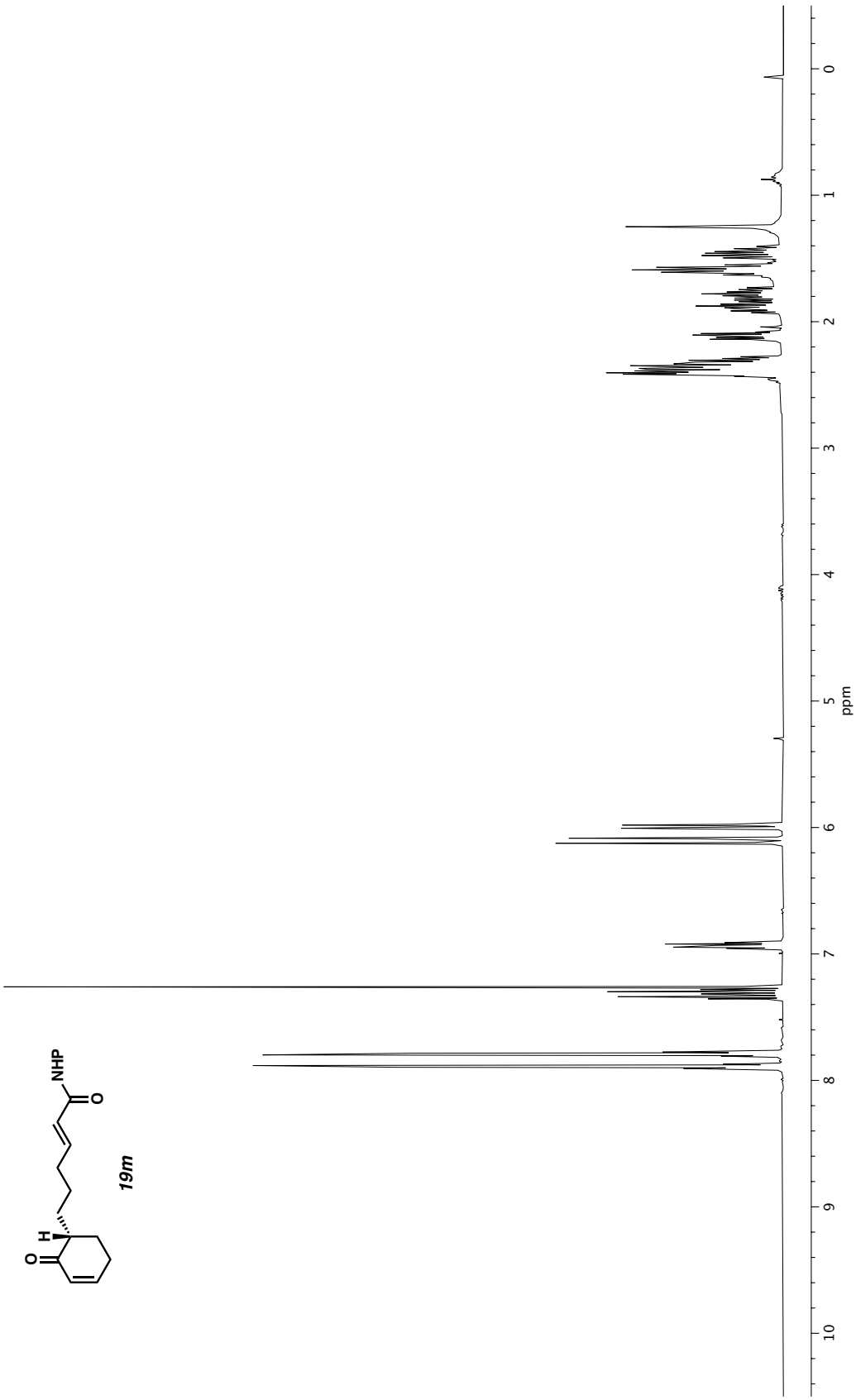


Figure A1.288. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***19m****.*

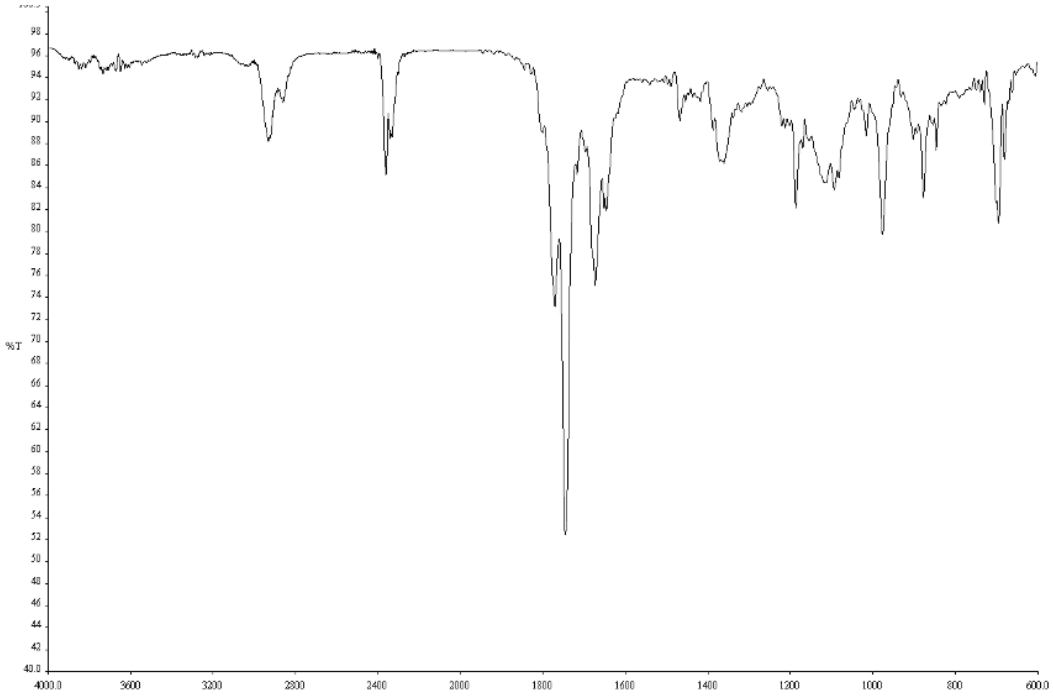


Figure A1.289. *Infrared spectrum (Thin Film, NaCl) of compound* ***19m****.*

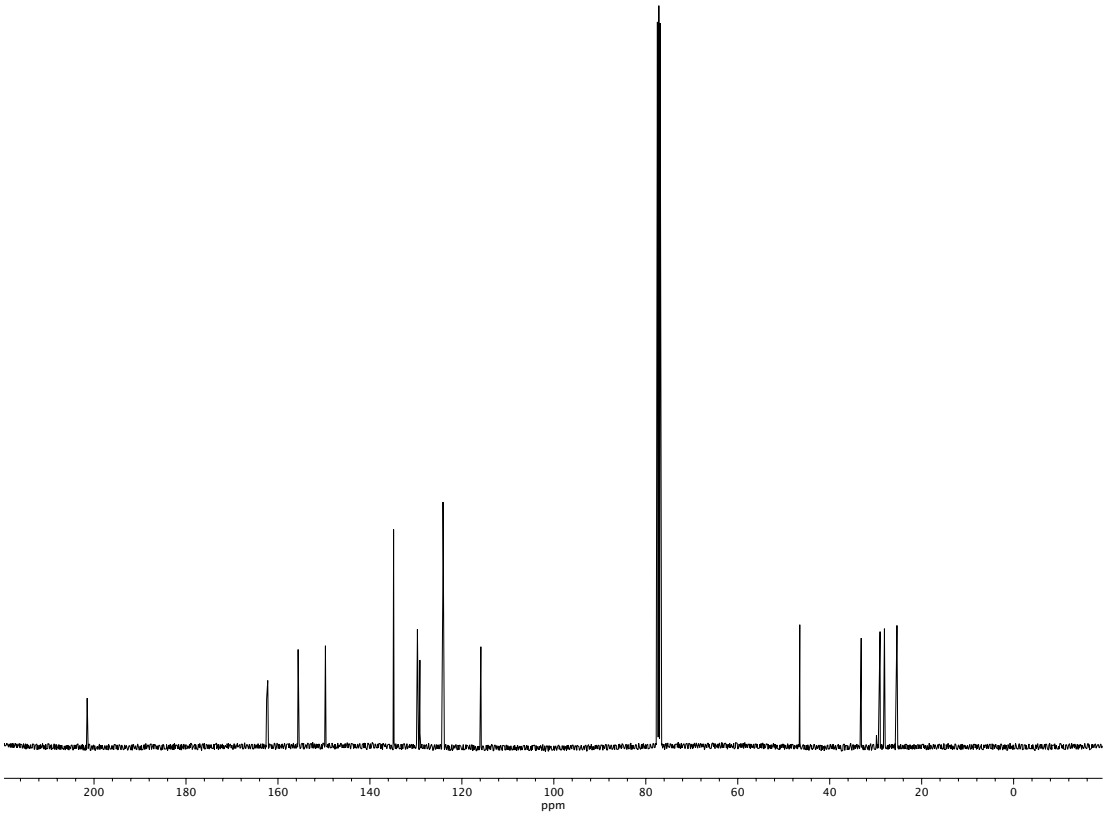


Figure A1.290. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***19m****.*

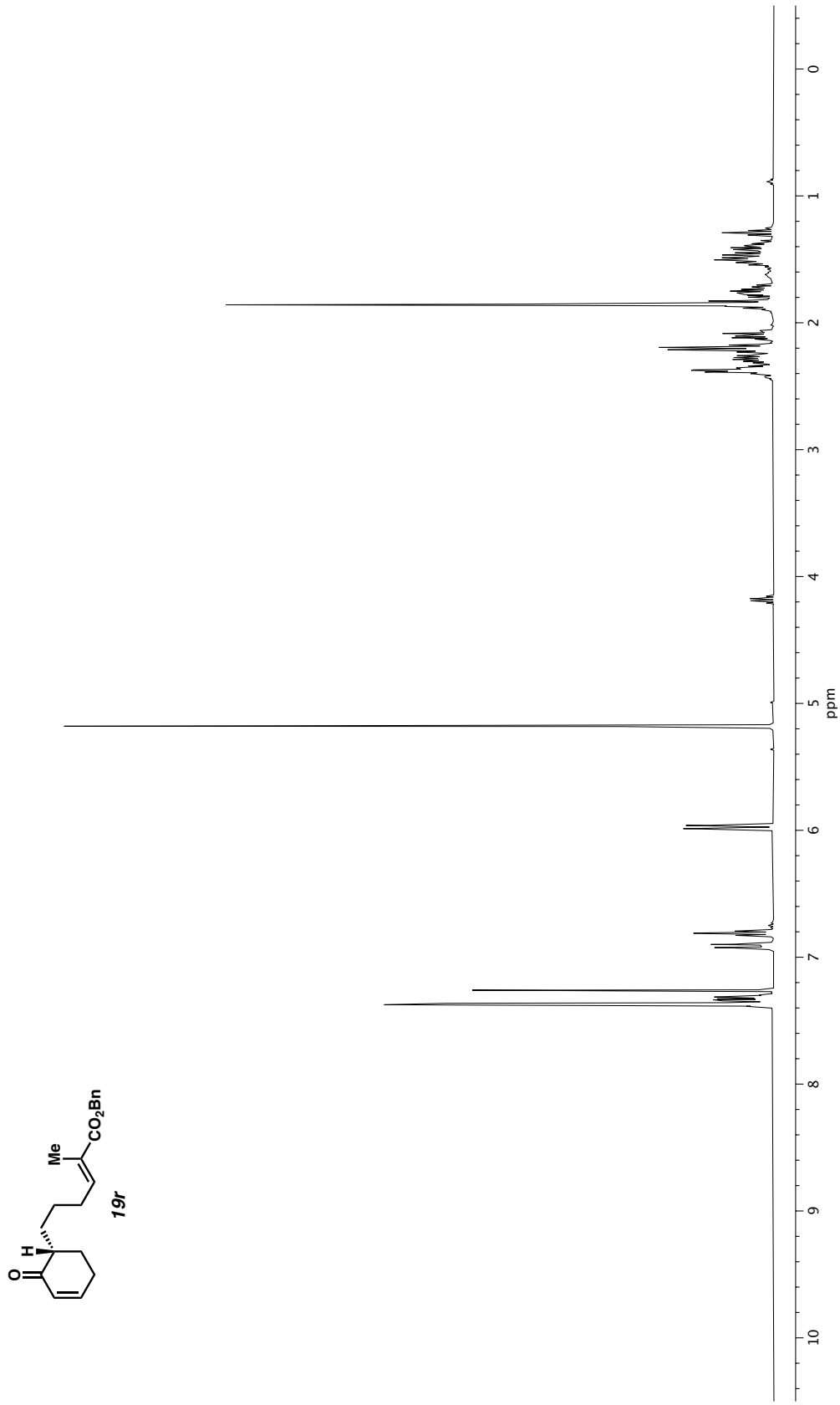


Figure A1.291. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***19r****.*

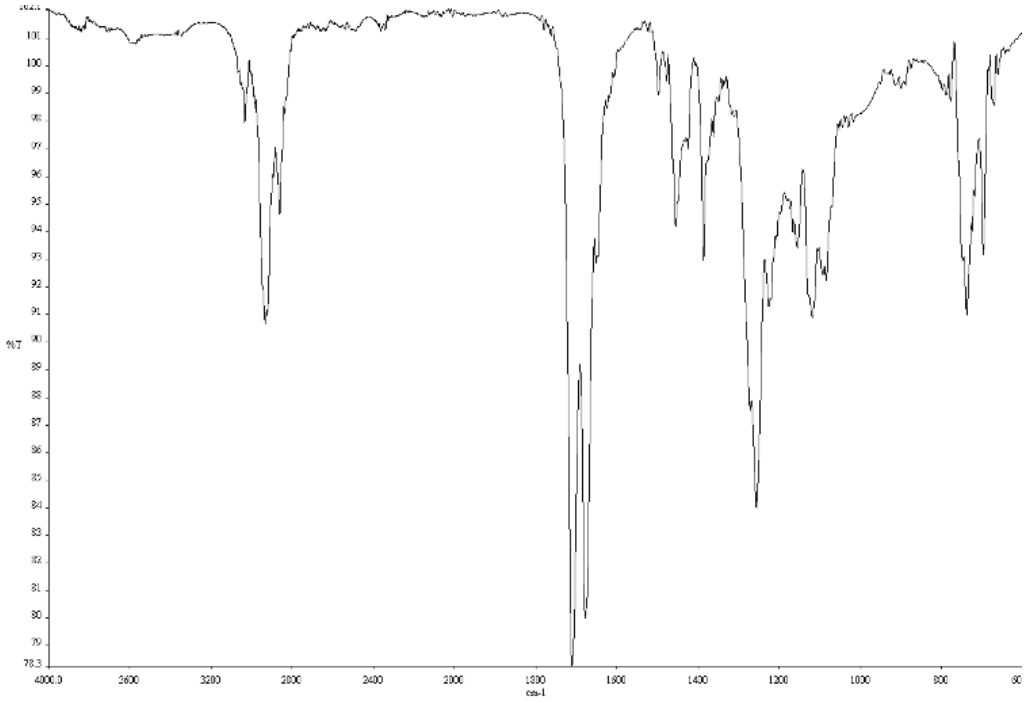


Figure A1.292. *Infrared spectrum (Thin Film, NaCl) of compound* ***19r****.*

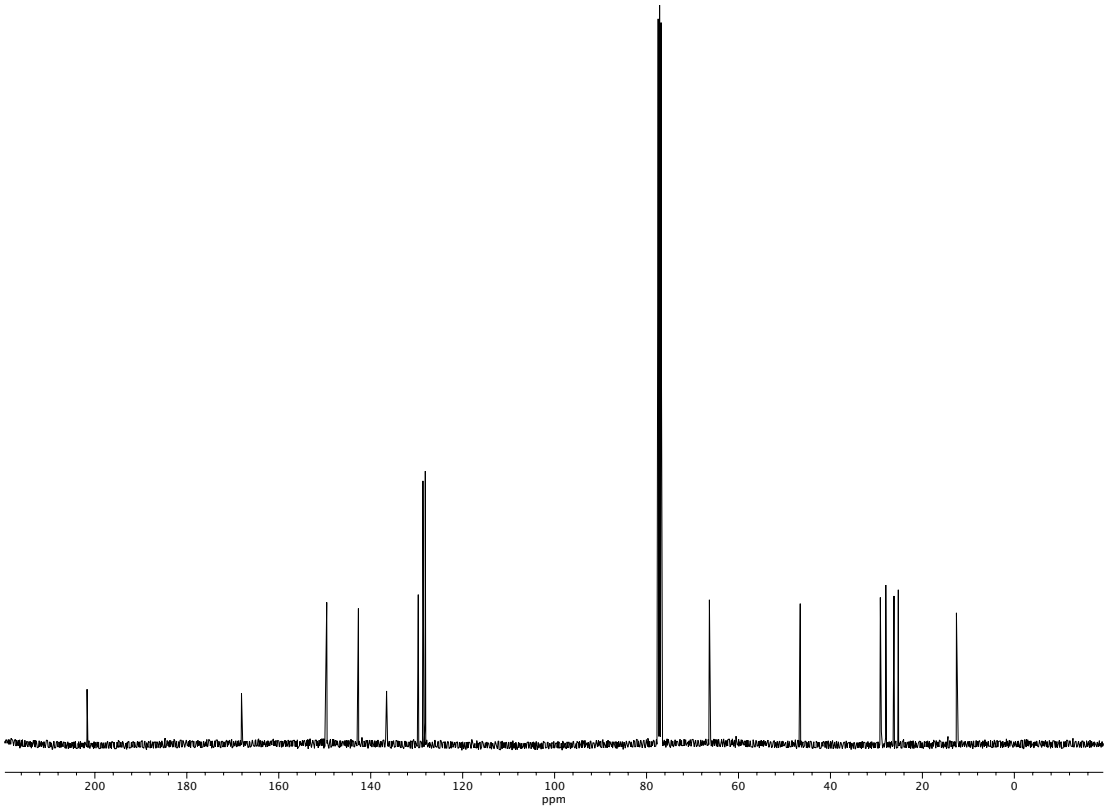


Figure A1.293. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***19r****.*

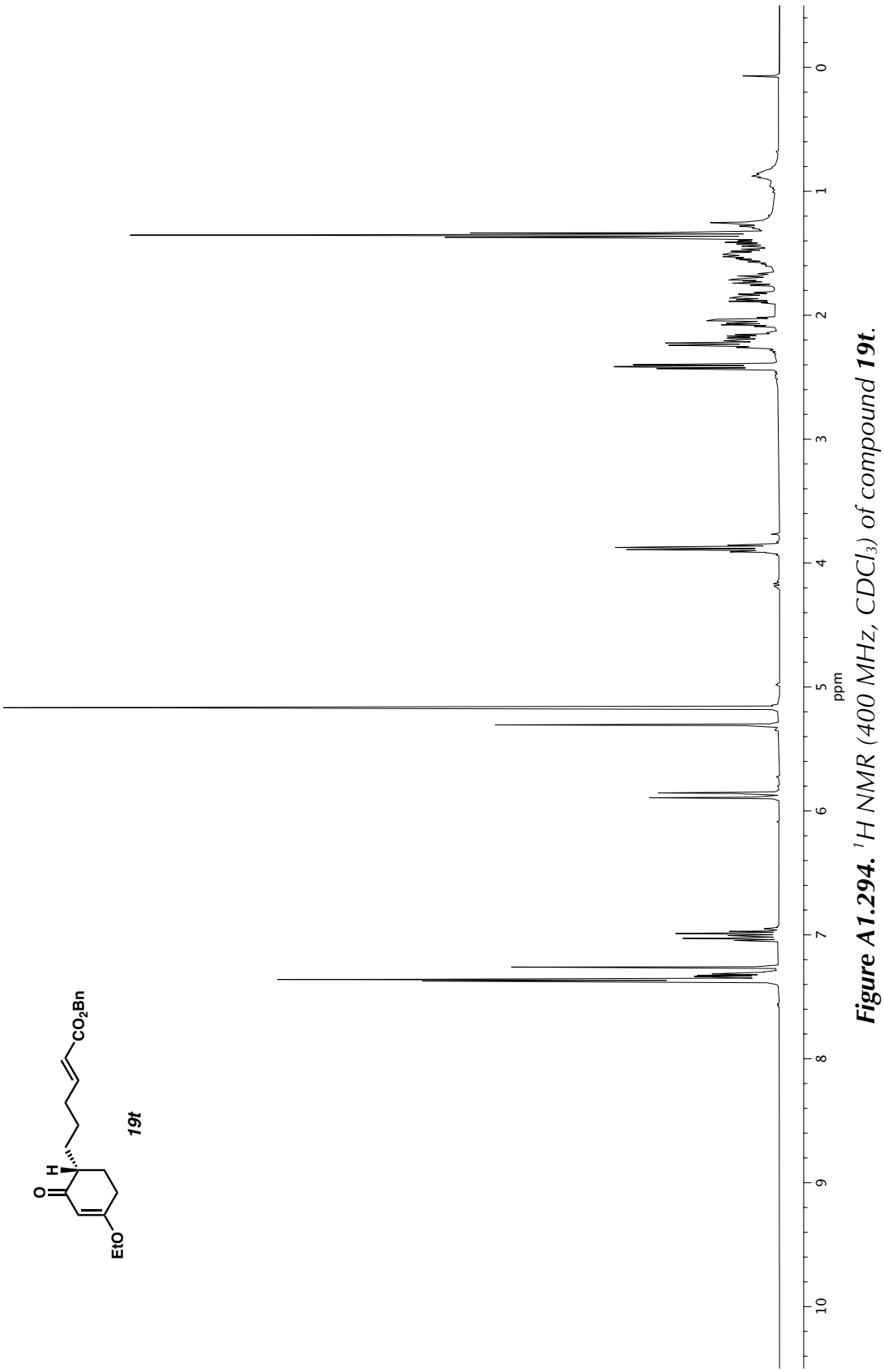


Figure A1.294. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***19t****.*

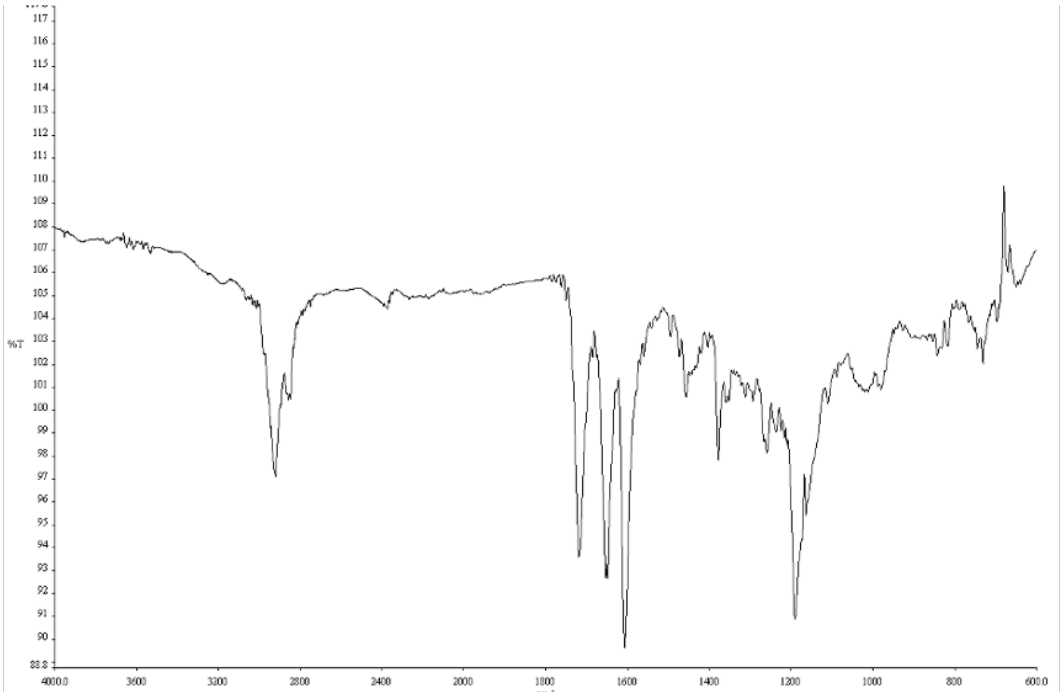


Figure A1.295. *Infrared spectrum (Thin Film, NaCl) of compound* ***19t****.*

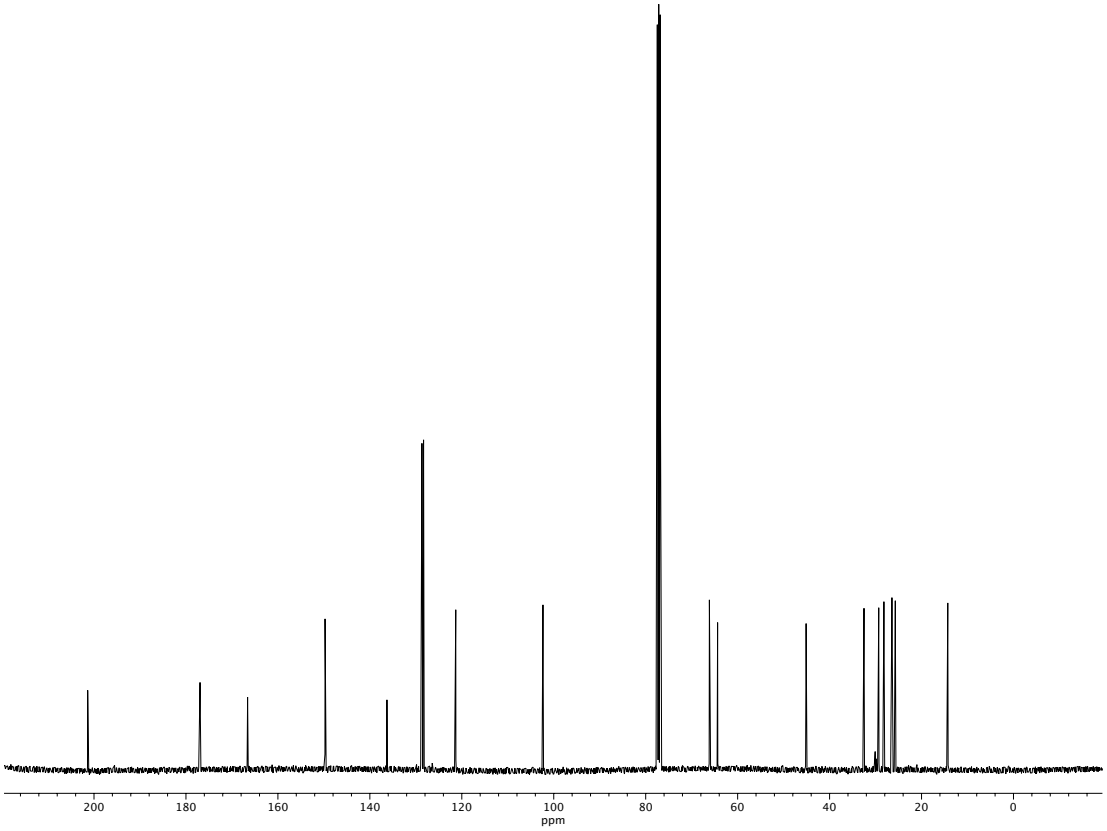


Figure A1.296. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***19t****.*

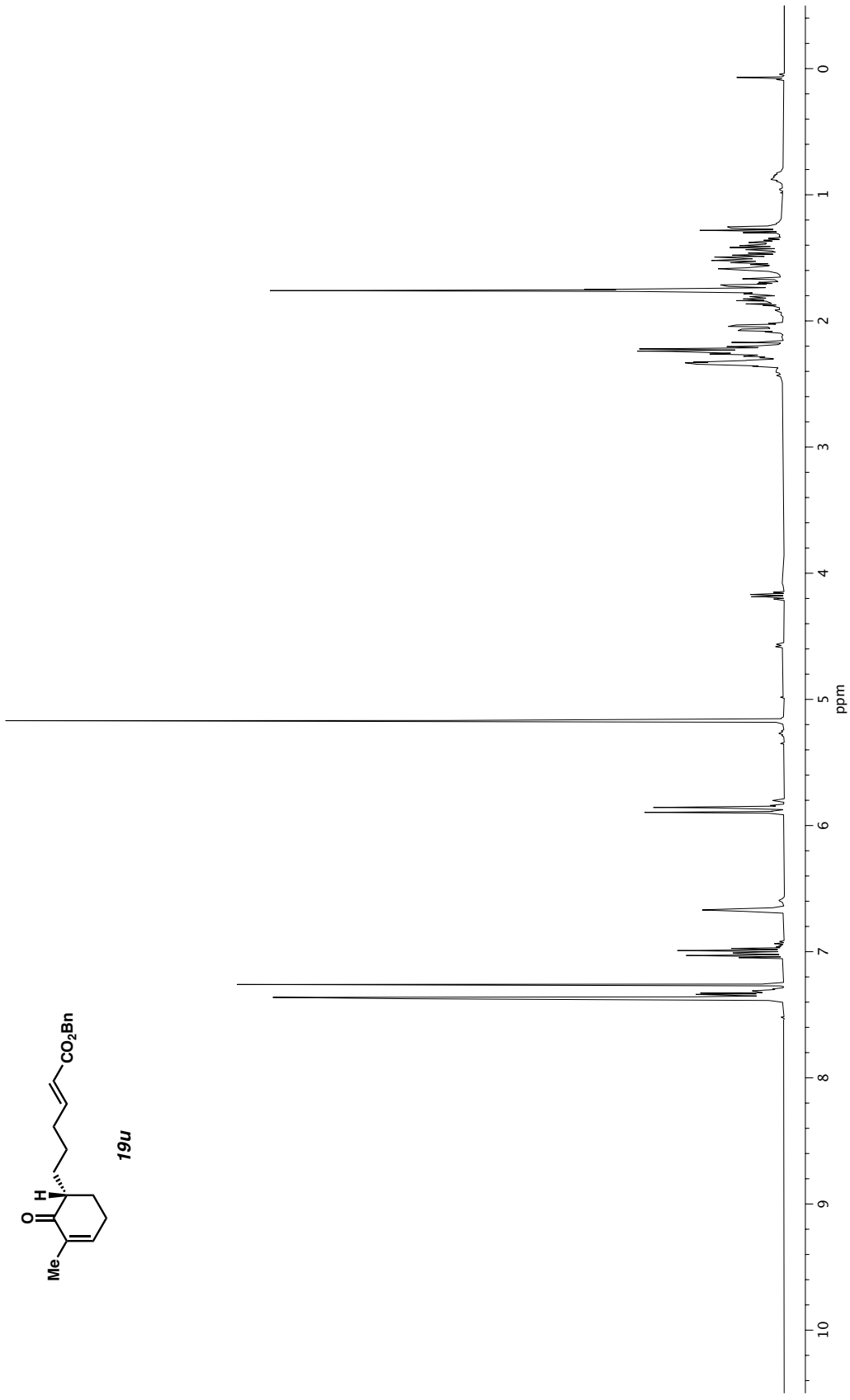


Figure A1.297. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***19u****.*

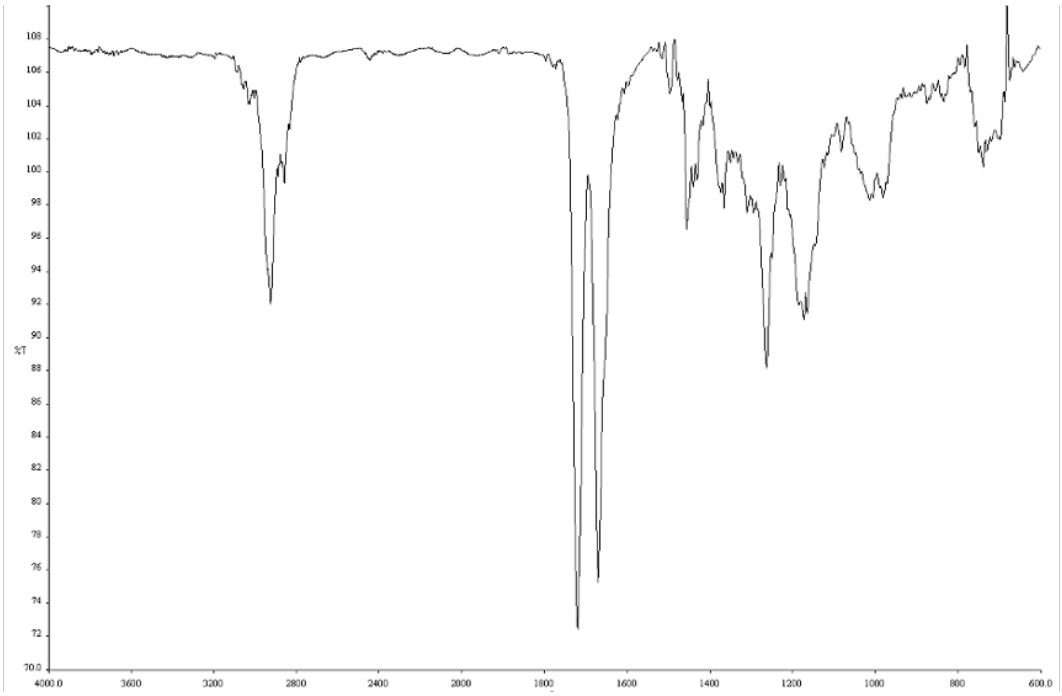


Figure A1.298. *Infrared spectrum (Thin Film, NaCl) of compound* ***19u****.*

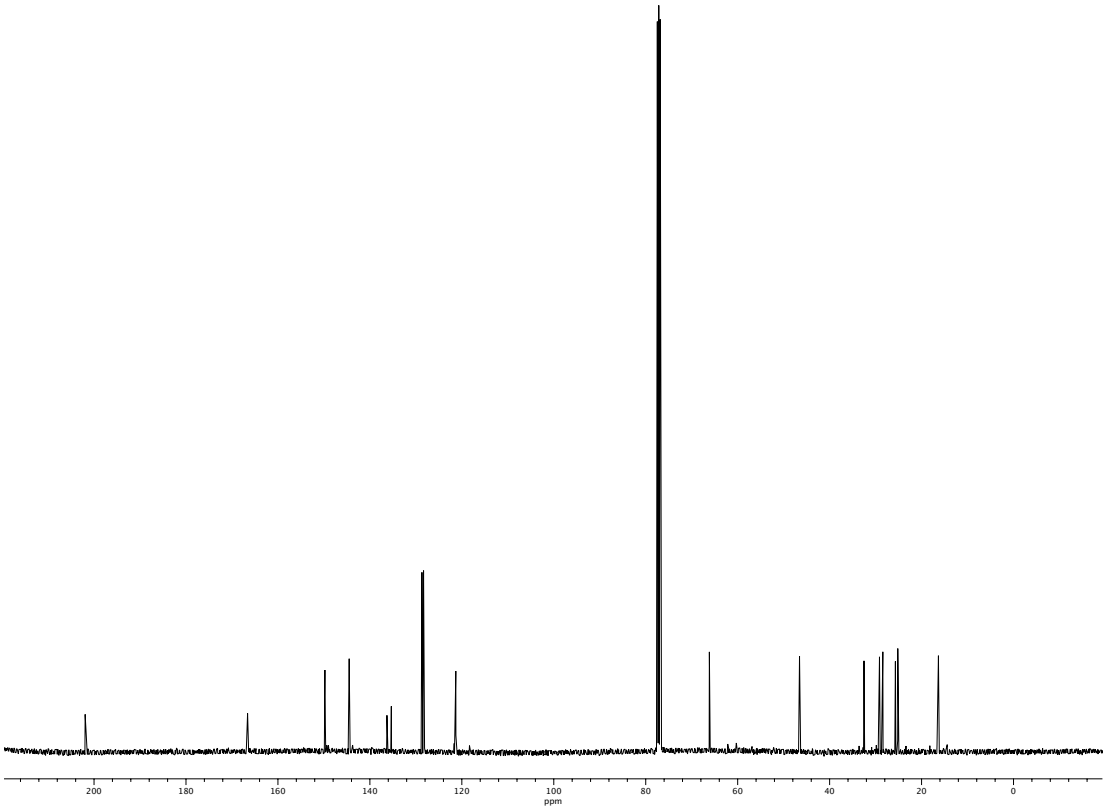


Figure A1.299. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***19u****.*

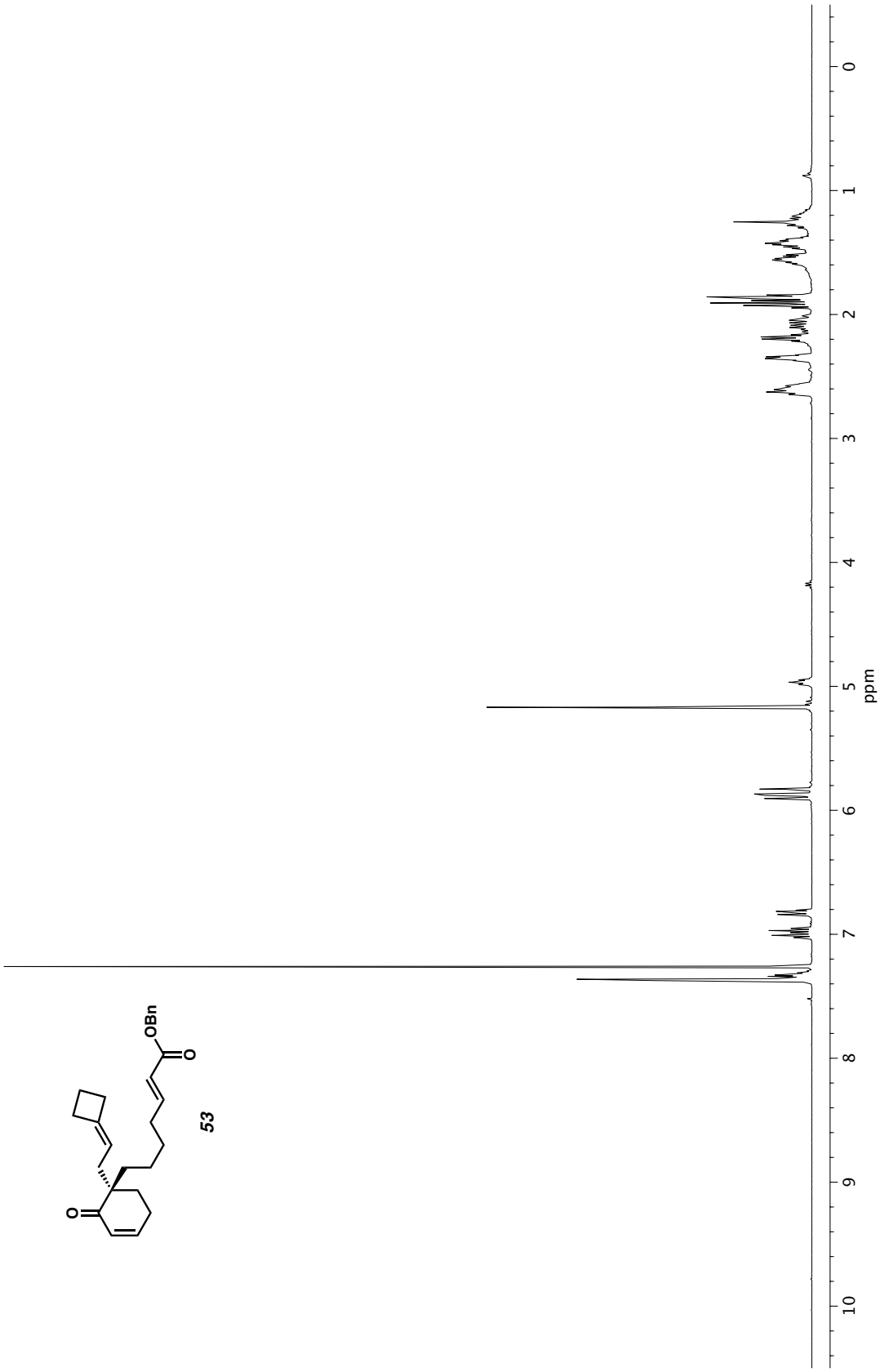


Figure A1.300. *^1H NMR (400 MHz, $CDCl_3$) of compound **53**.*

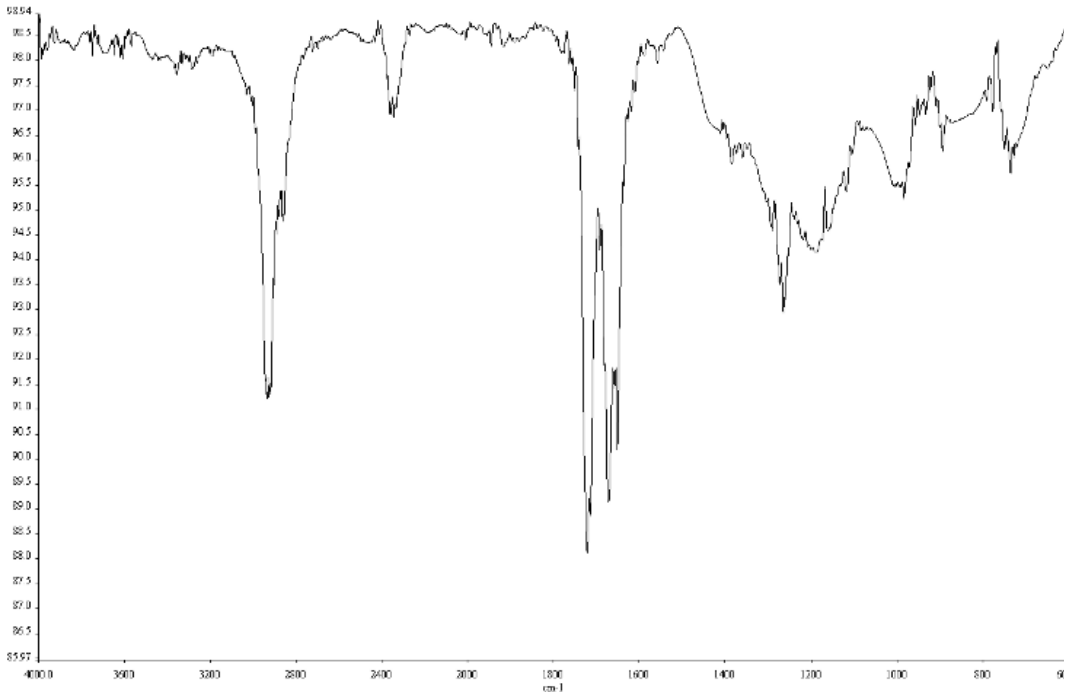


Figure A1.301. *Infrared spectrum (Thin Film, NaCl) of compound* ***53****.*

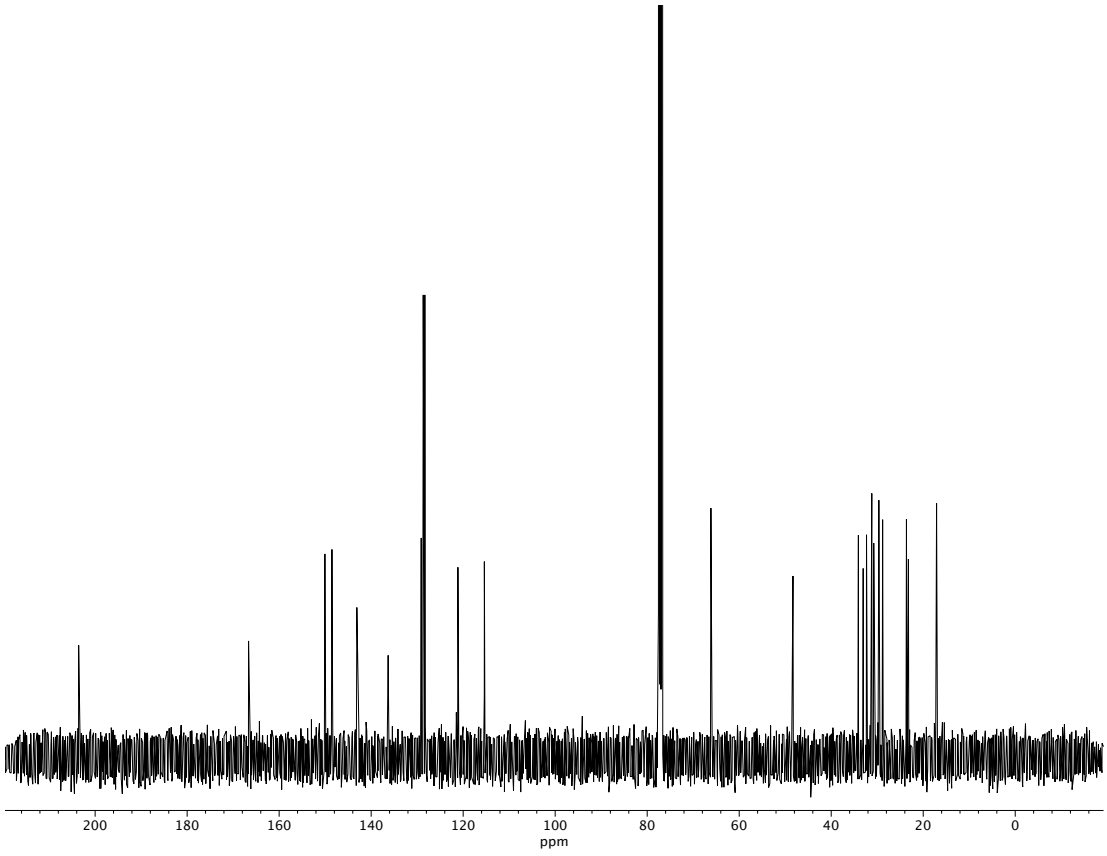


Figure A1.302. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***53****.*

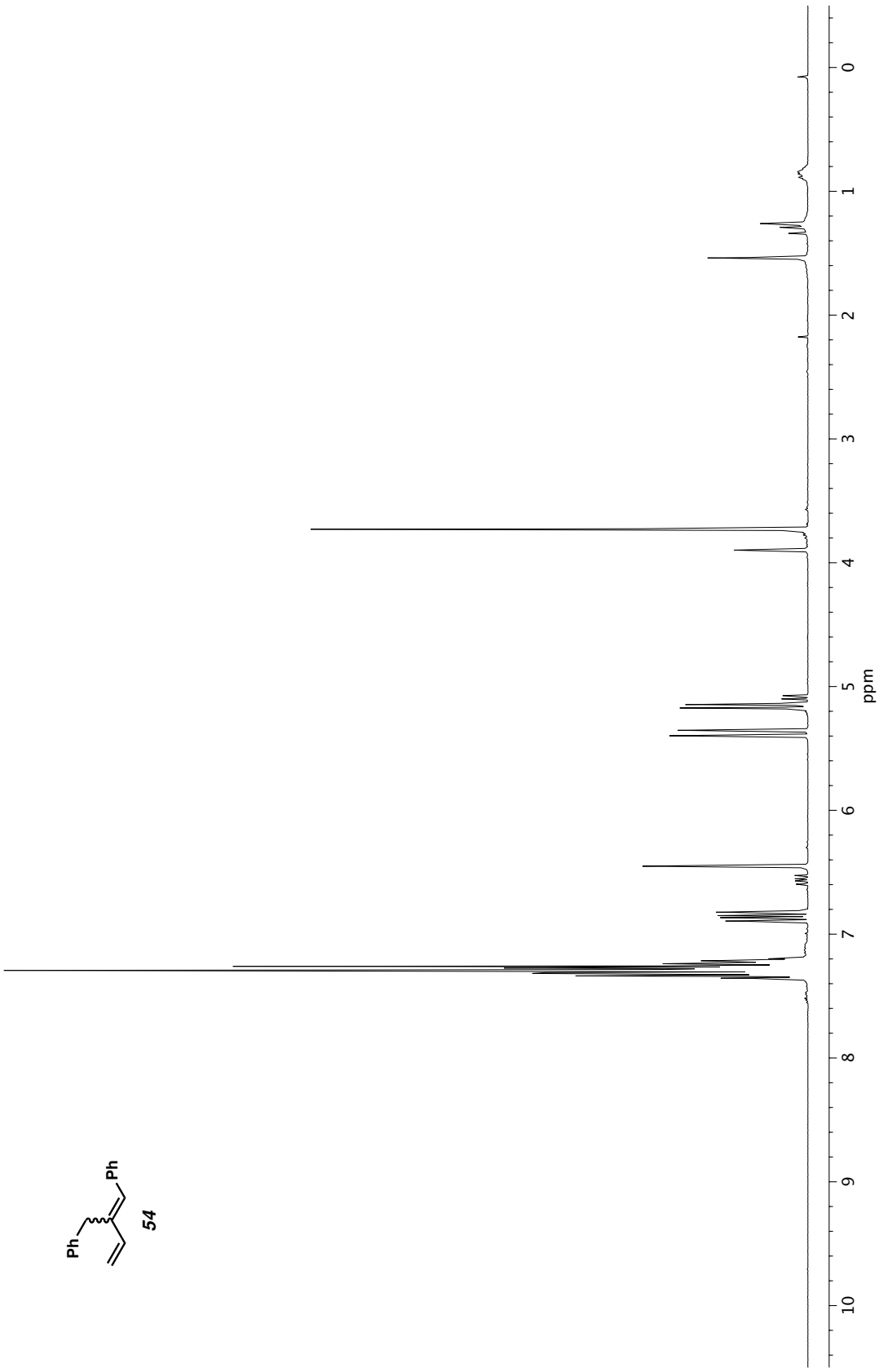


Figure A1.303. *^1H NMR (400 MHz, $CDCl_3$) of compound **54**.*

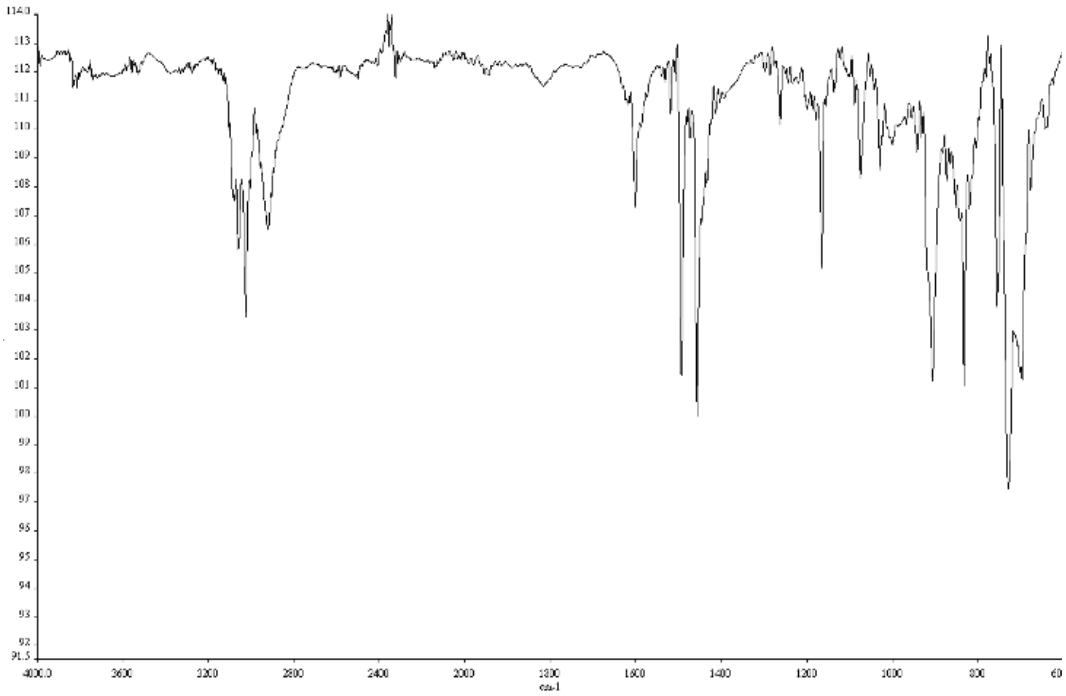


Figure A1.304. *Infrared spectrum (Thin Film, NaCl) of compound* ***54****.*

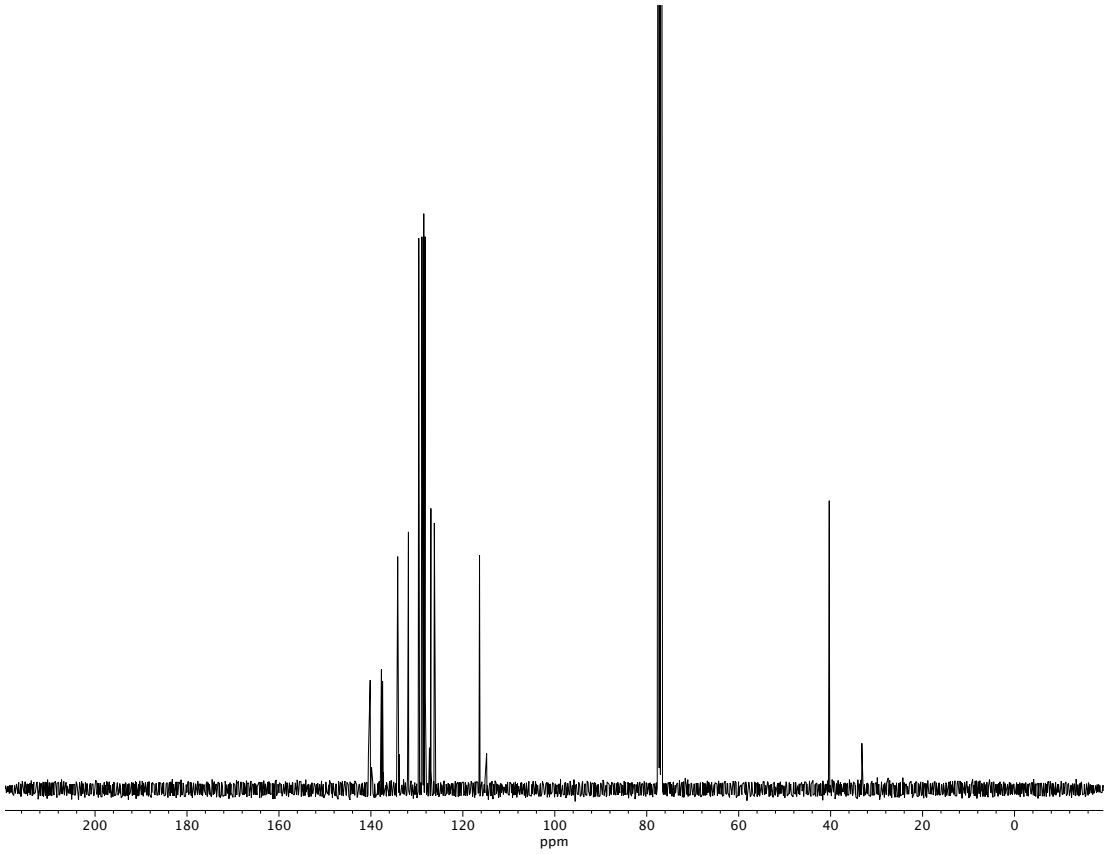


Figure A1.305. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***54****.*

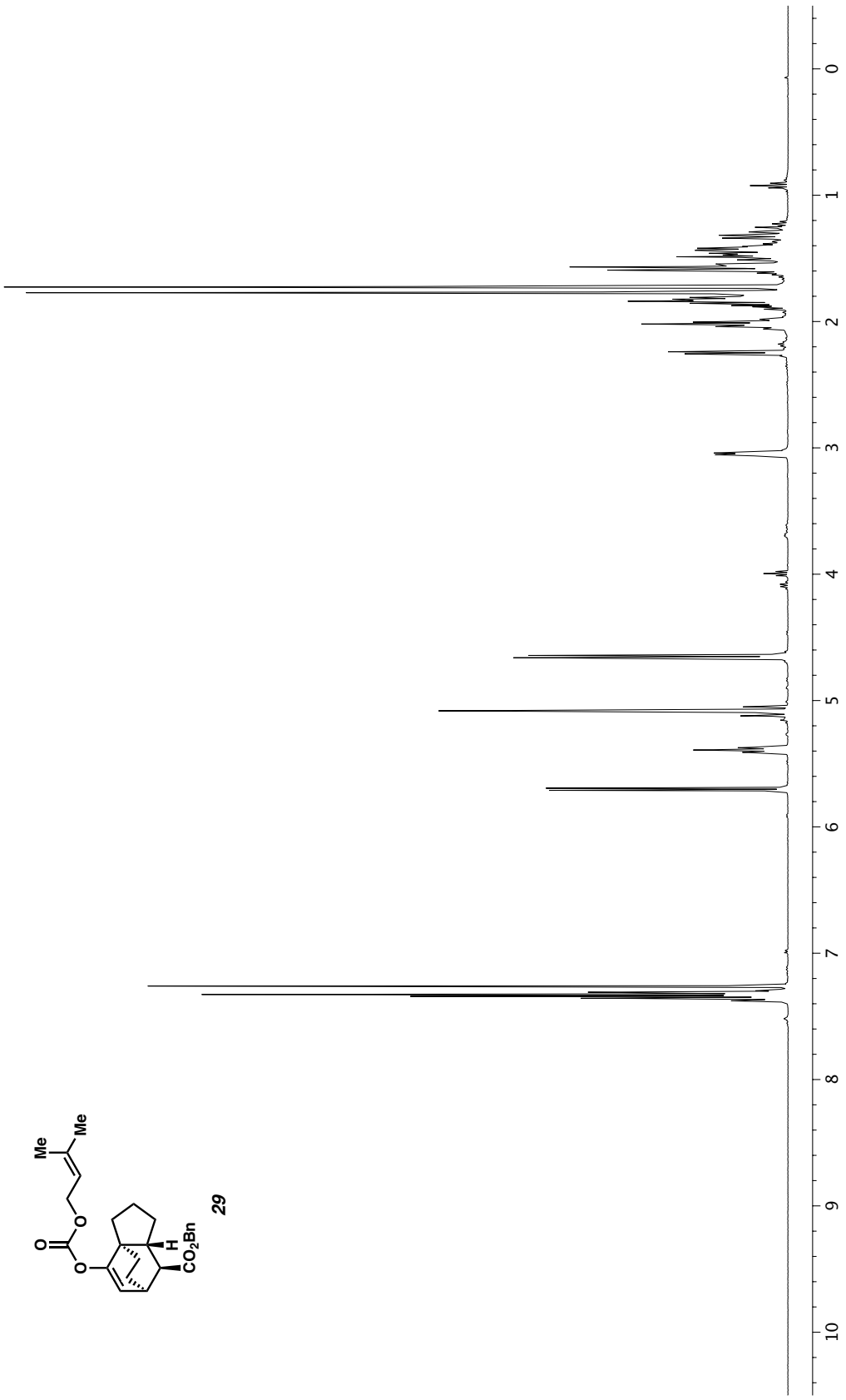


Figure A1.306. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***29****.*

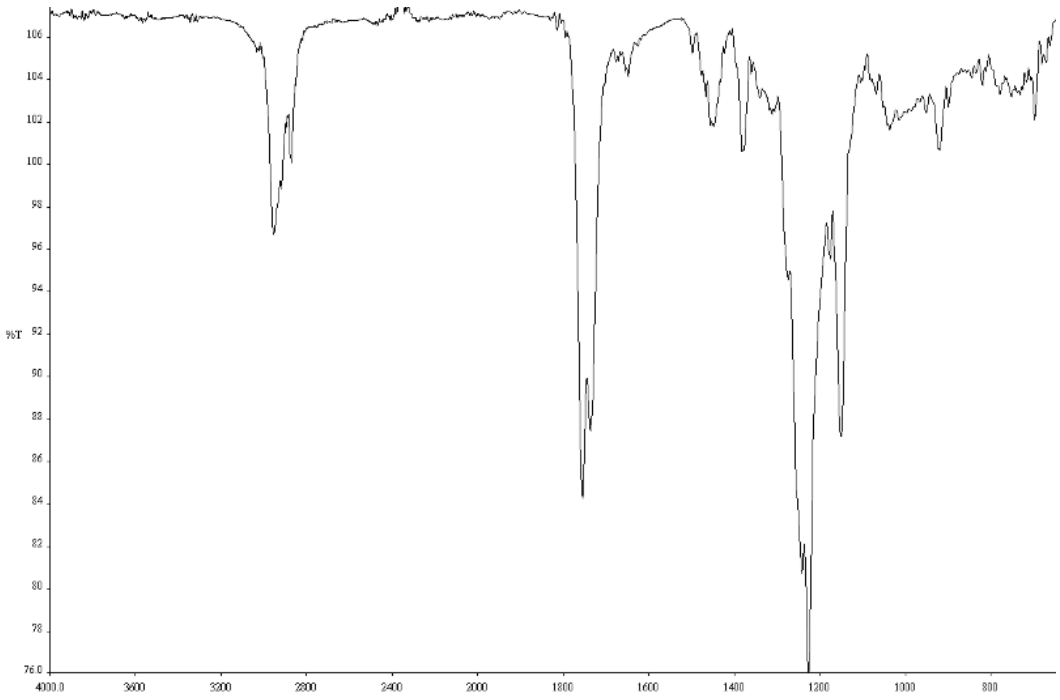


Figure A1.307. *Infrared spectrum (Thin Film, NaCl) of compound* ***29****.*

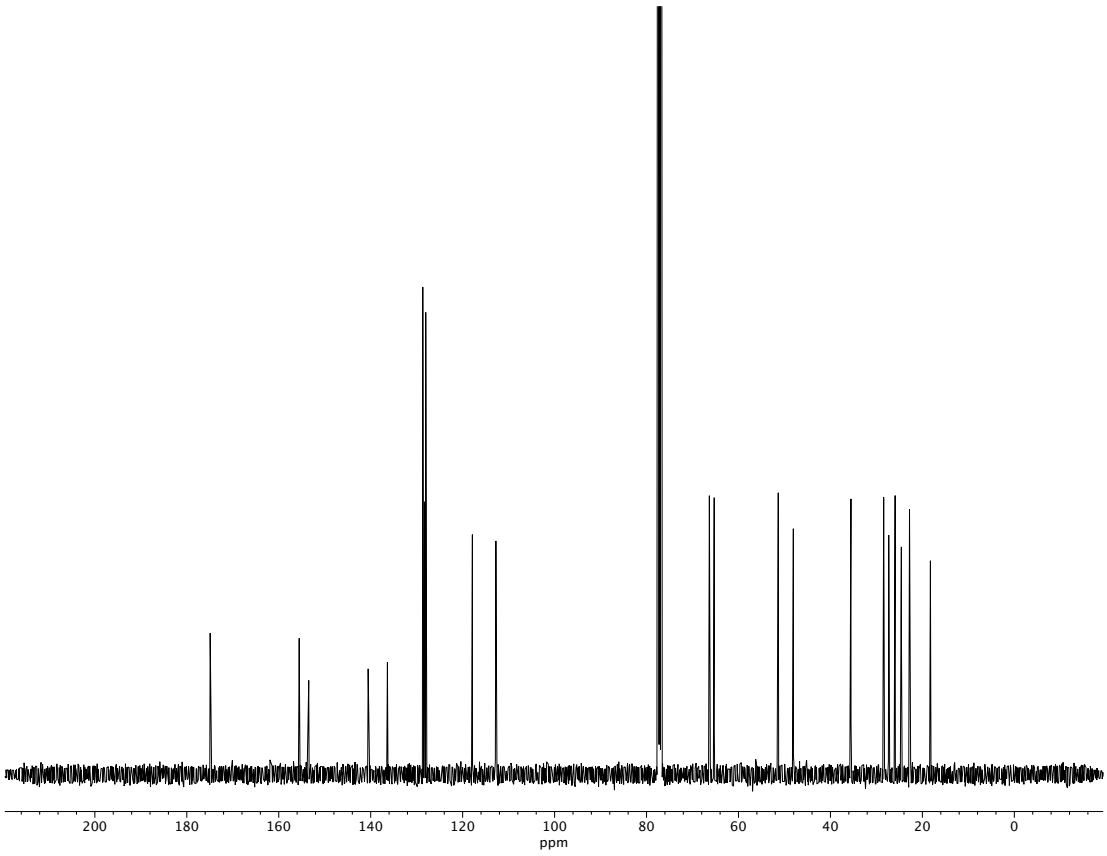


Figure A1.308. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***29****.*

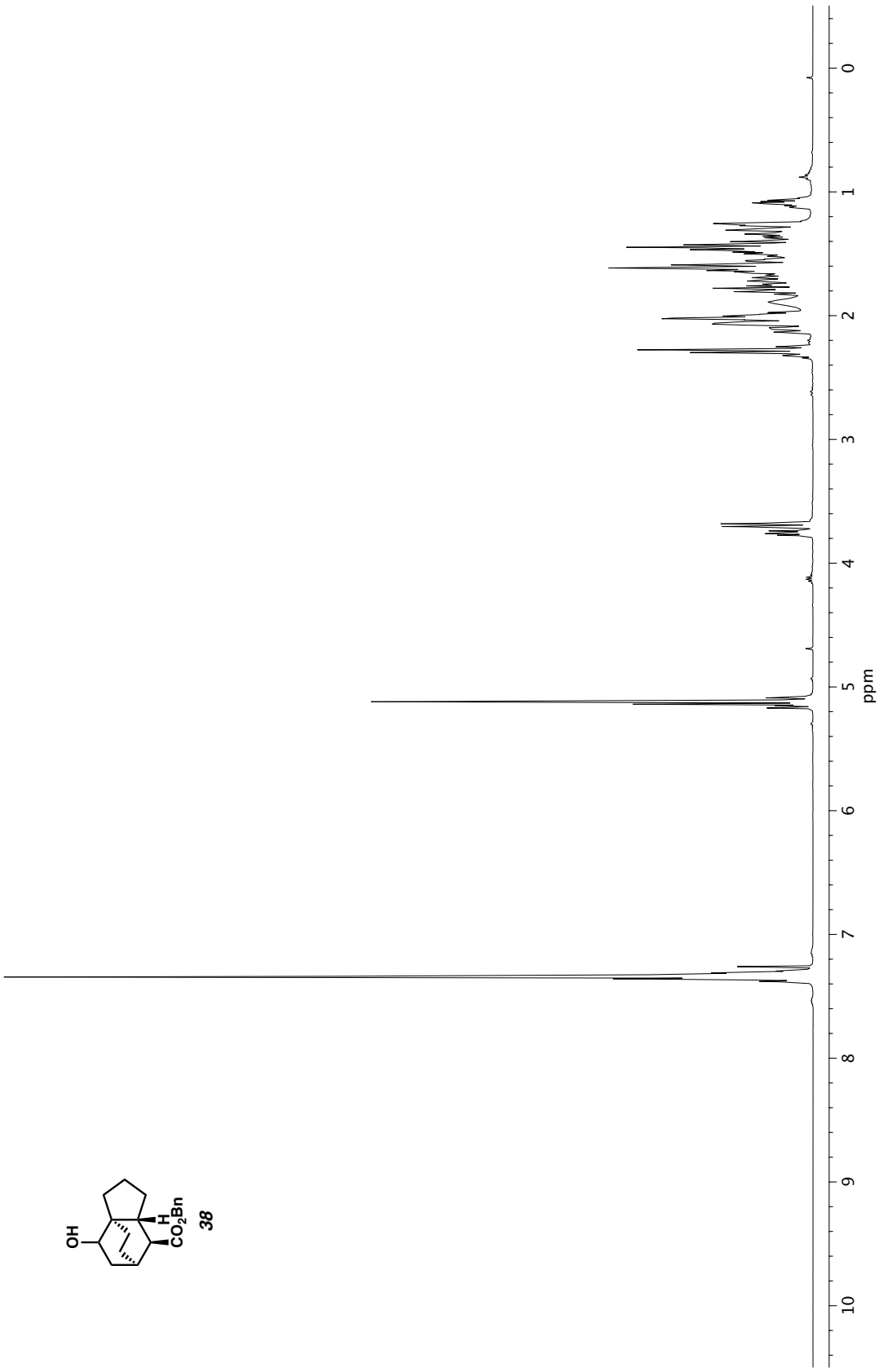


Figure A1.309. *^1H NMR (400 MHz, $CDCl_3$) of compound **38**.*

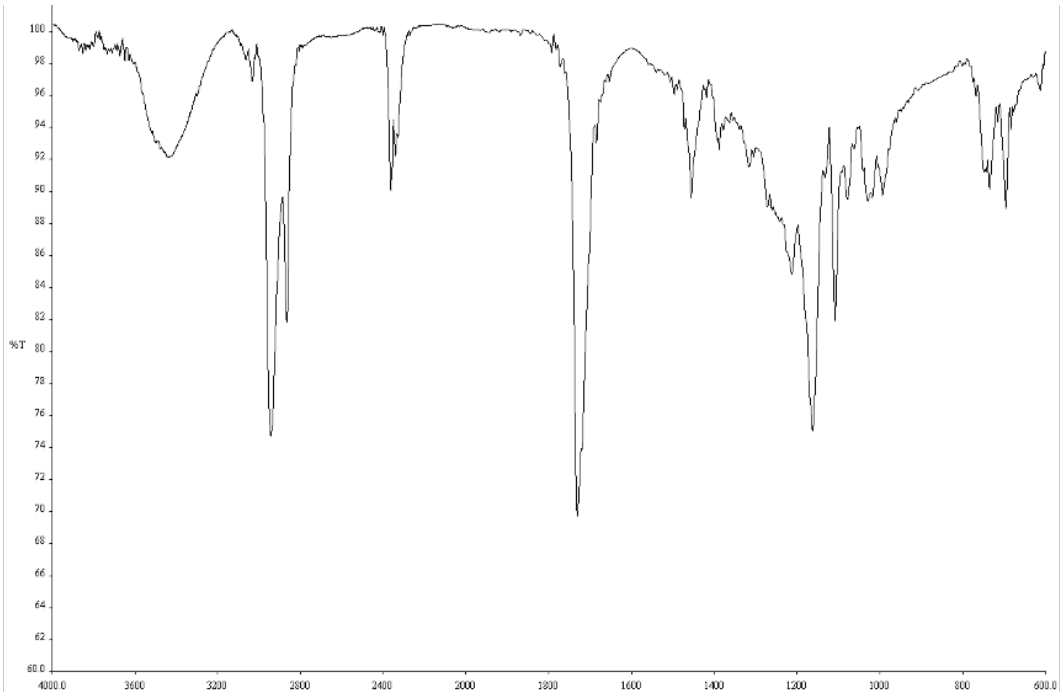


Figure A1.310. *Infrared spectrum (Thin Film, NaCl) of compound* ***38****.*

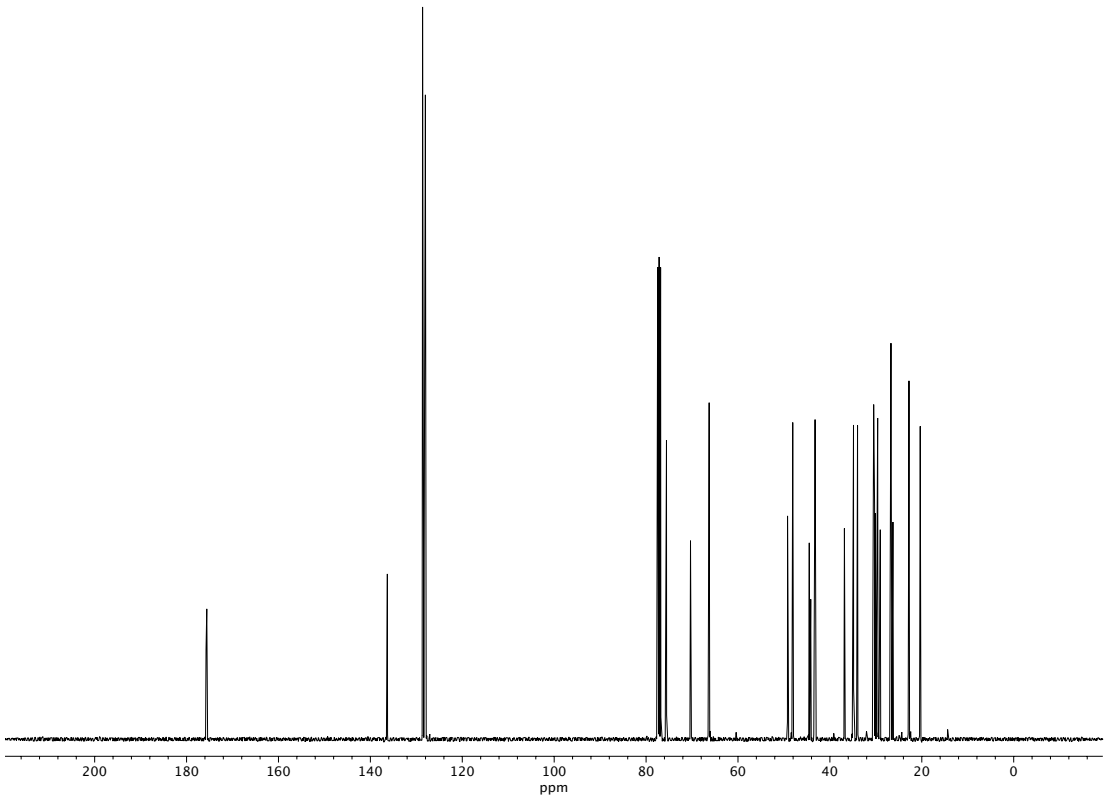


Figure A1.311. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***38****.*

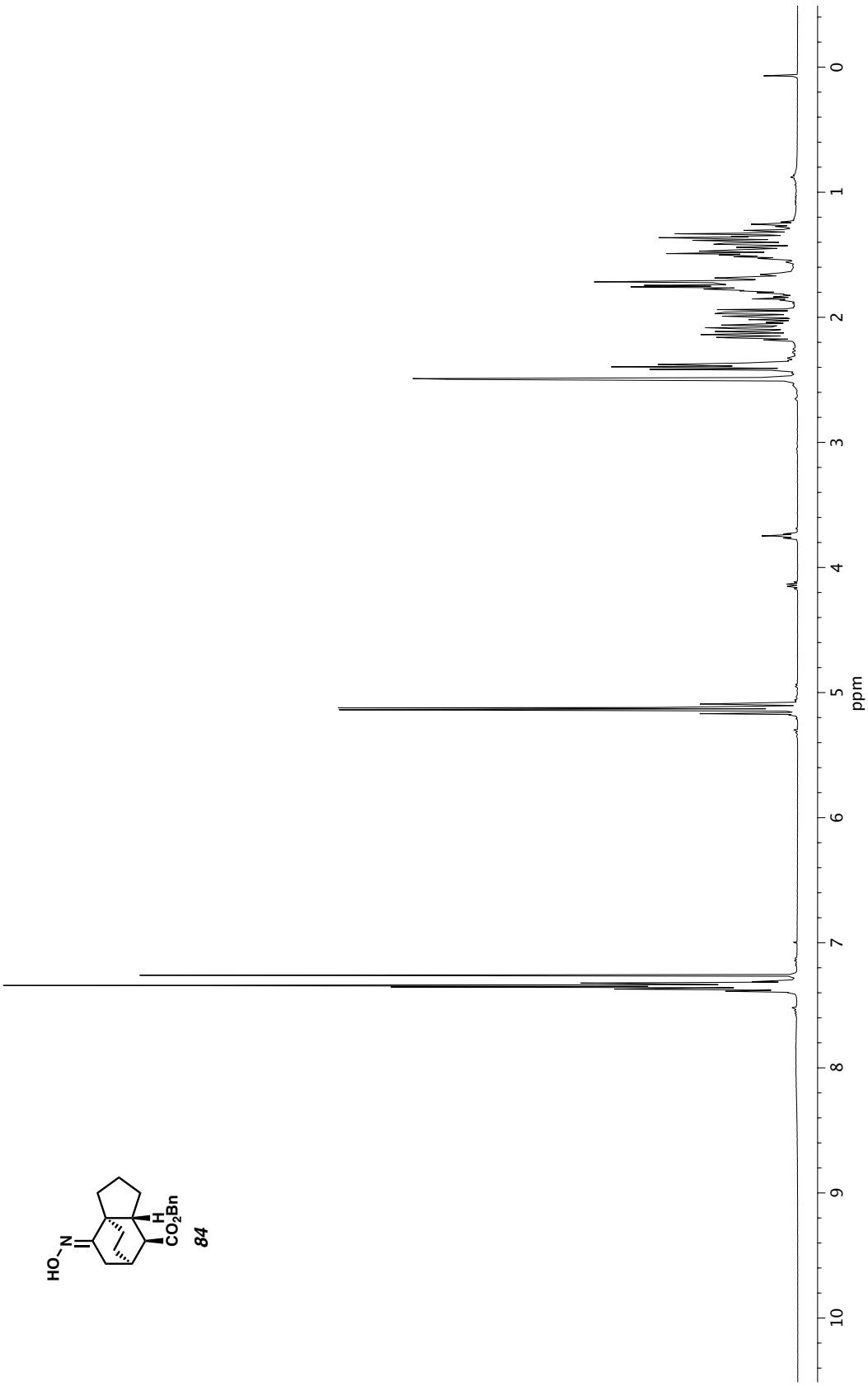


Figure A1.312. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***84****.*

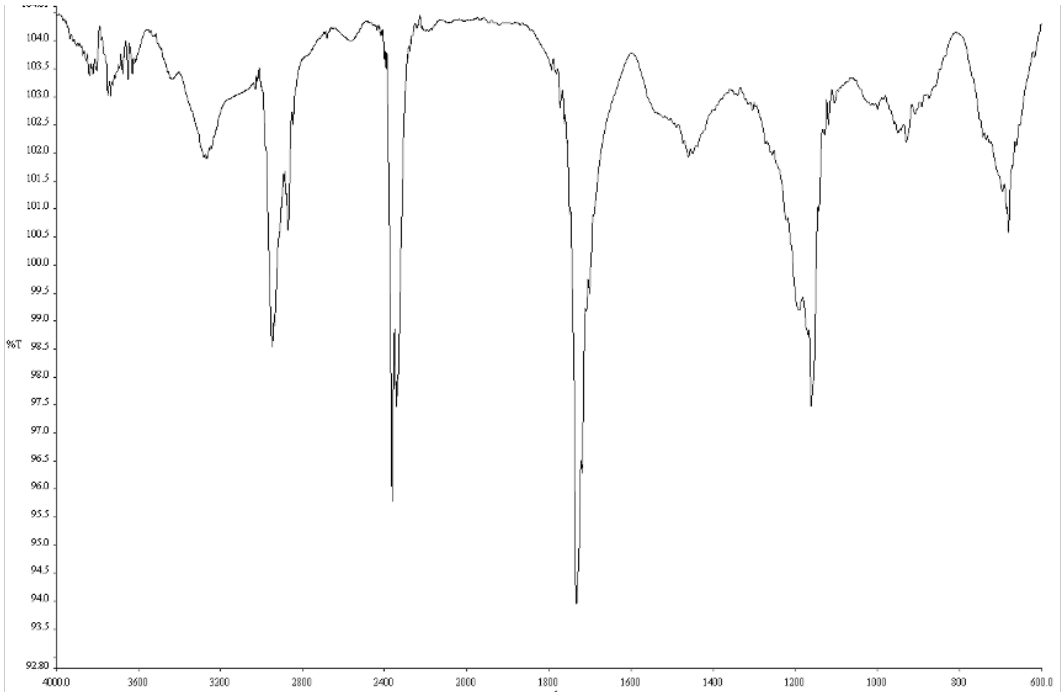


Figure A1.313. *Infrared spectrum (Thin Film, NaCl) of compound* ***84****.*

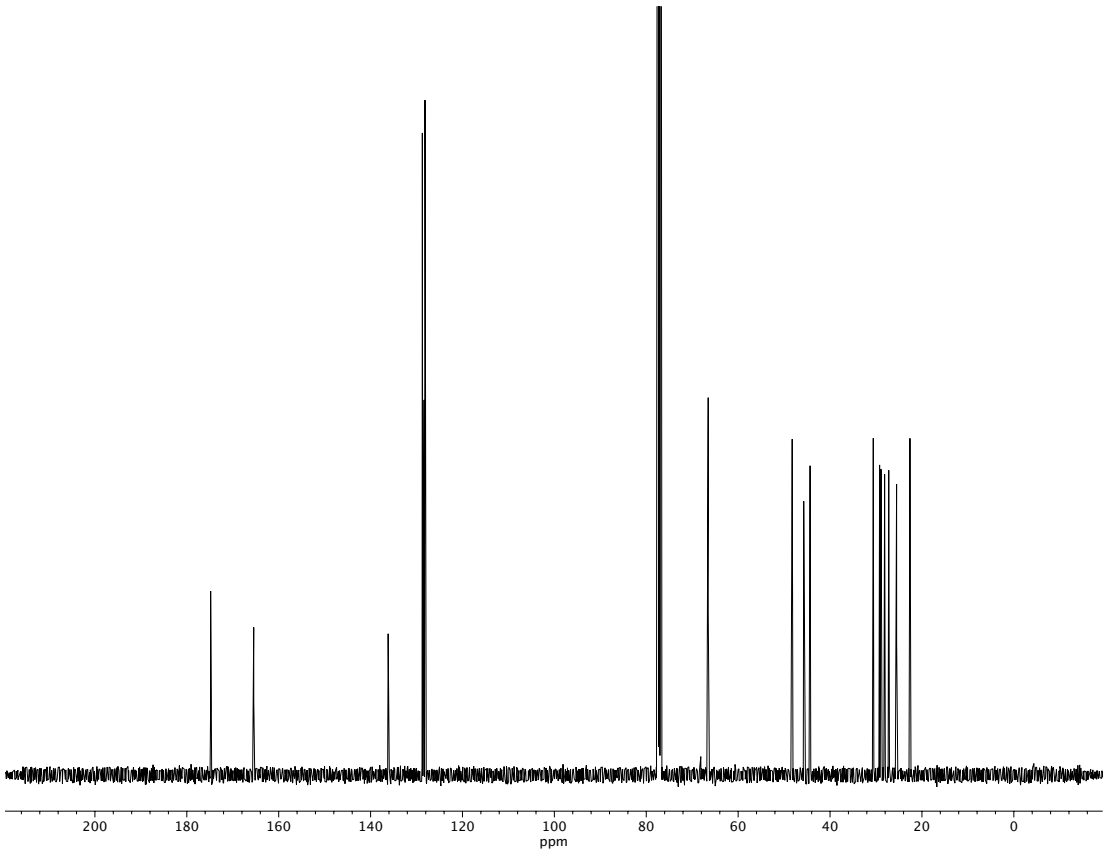


Figure A1.314. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***84****.*

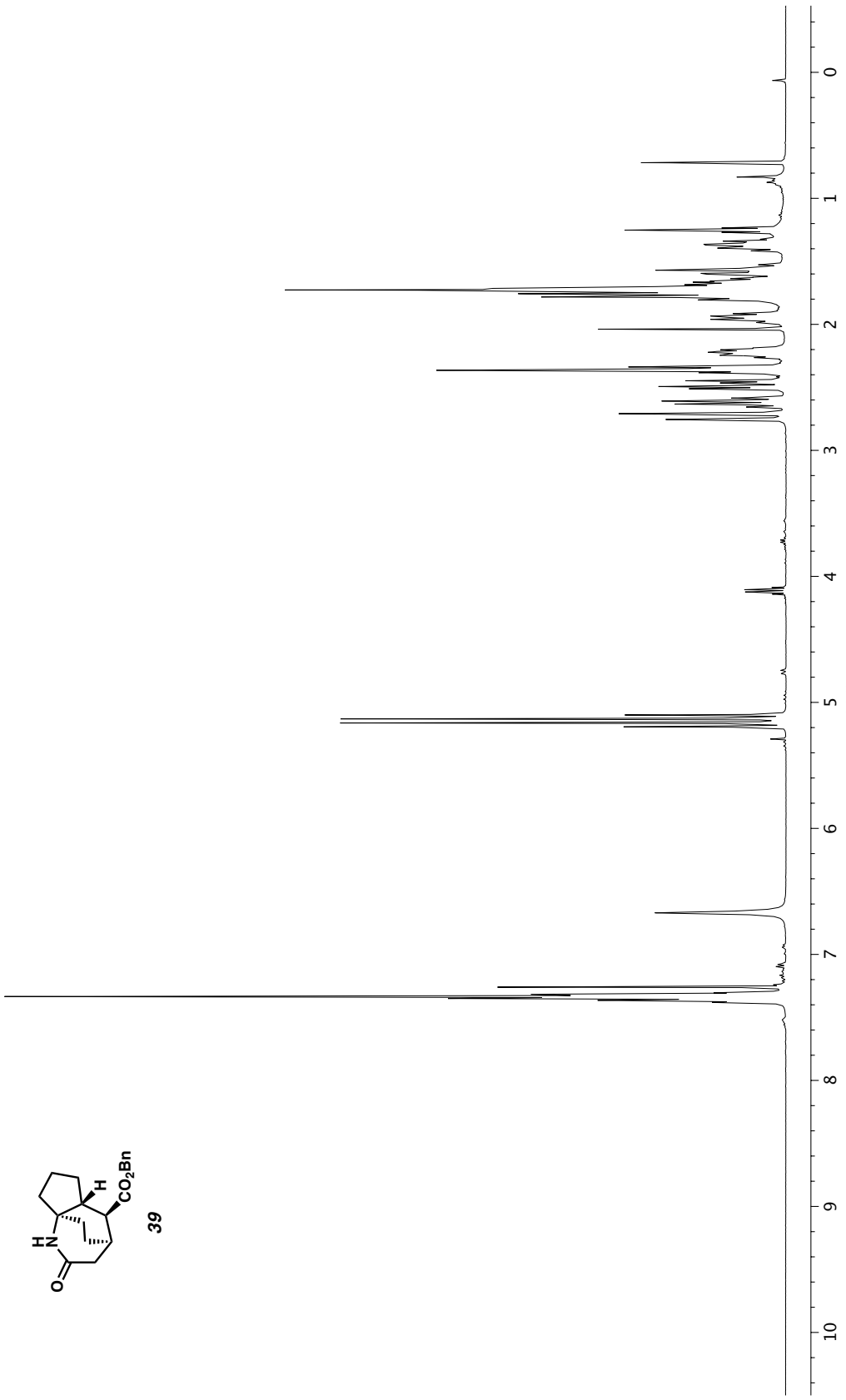


Figure A1.315. *^1H NMR (400 MHz, $CDCl_3$) of compound **39**.*

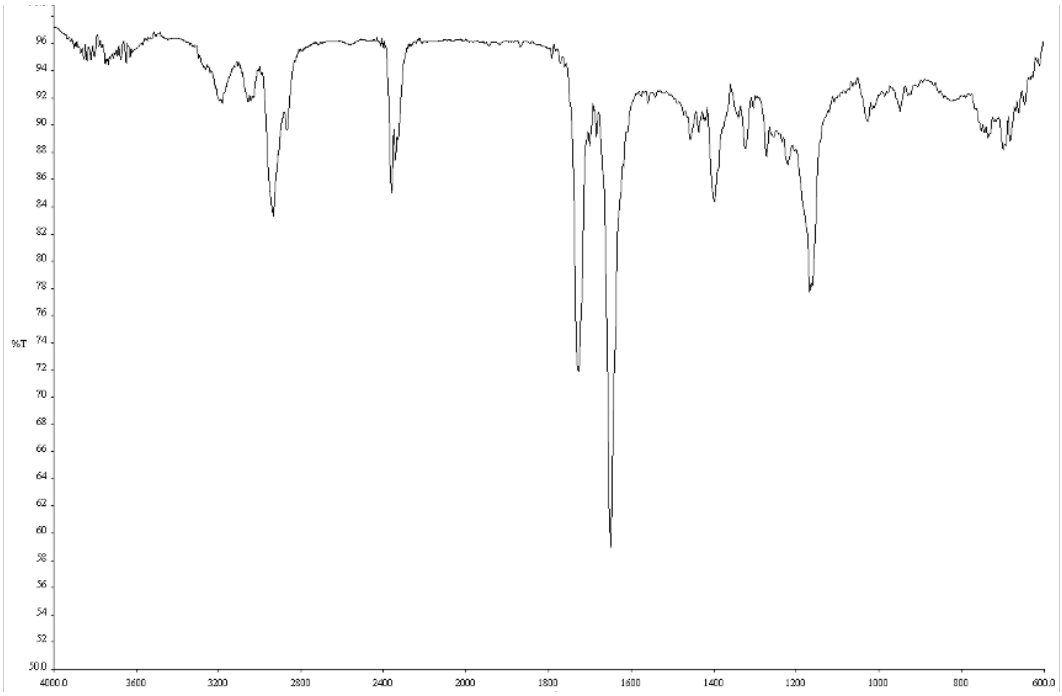


Figure A1.316. *Infrared spectrum (Thin Film, NaCl) of compound* ***39****.*

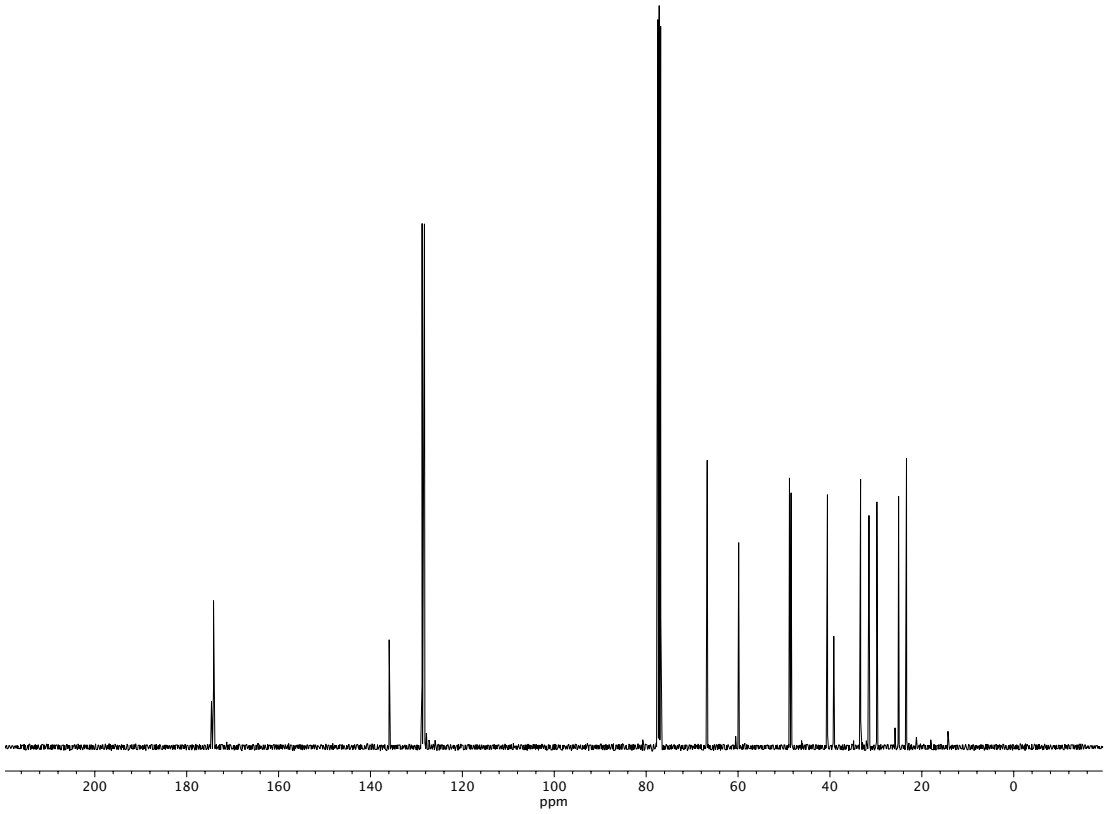


Figure A1.317. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***39****.*

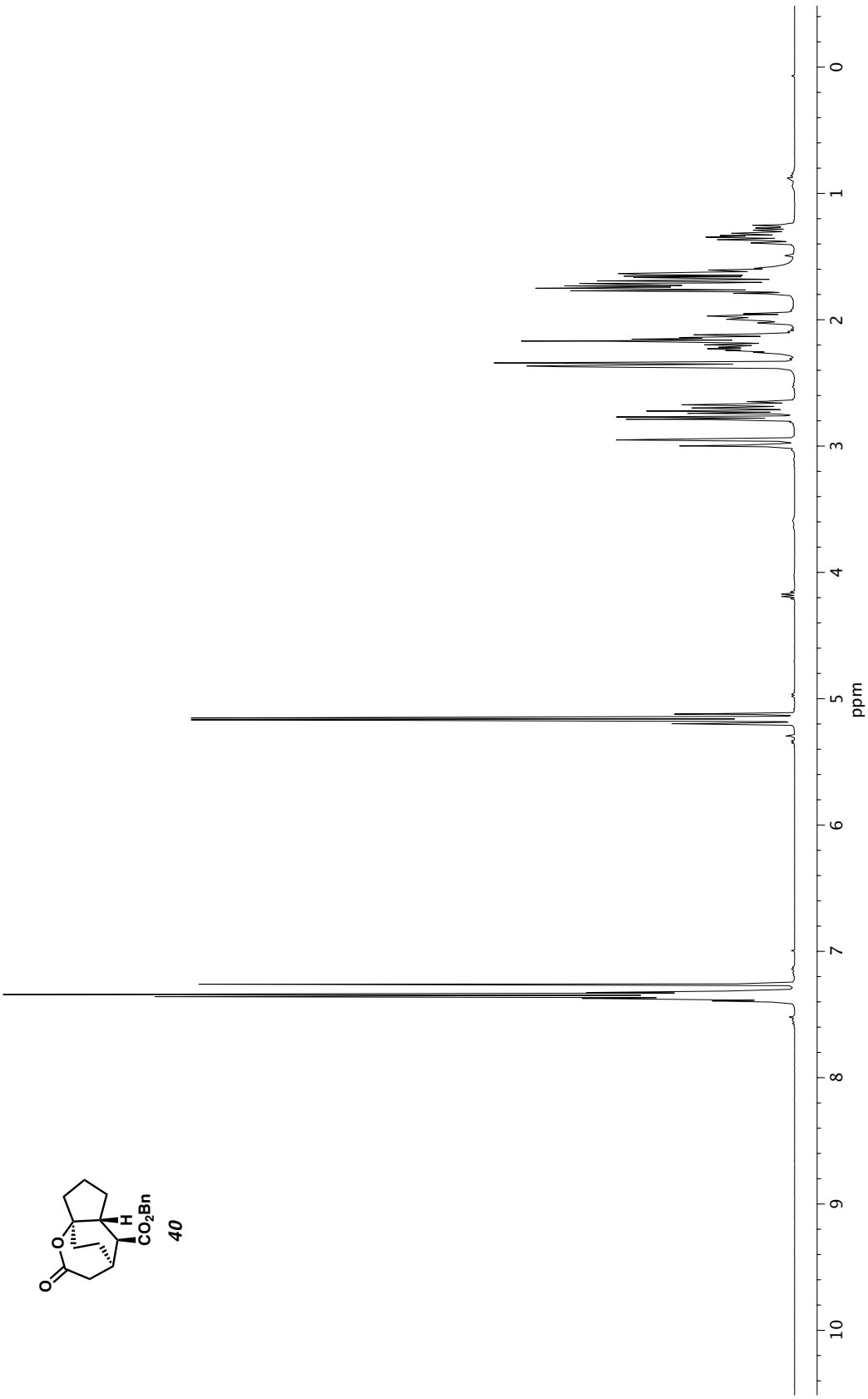


Figure A1.318. *^1H NMR (400 MHz, $CDCl_3$) of compound **40**.*

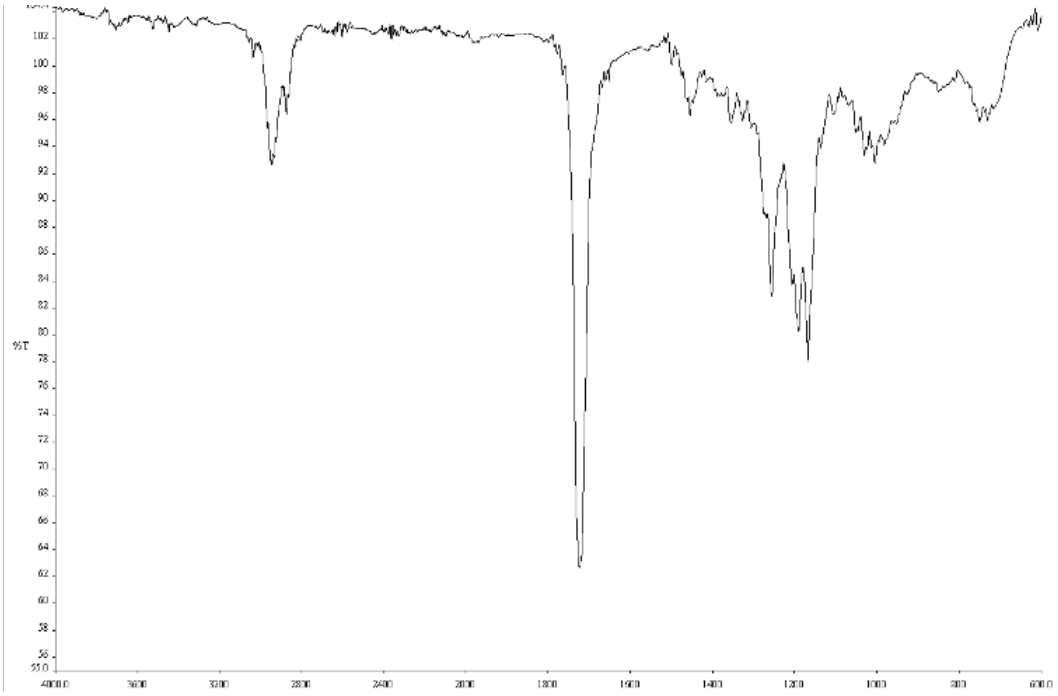


Figure A1.319. *Infrared spectrum (Thin Film, NaCl) of compound* ***40****.*

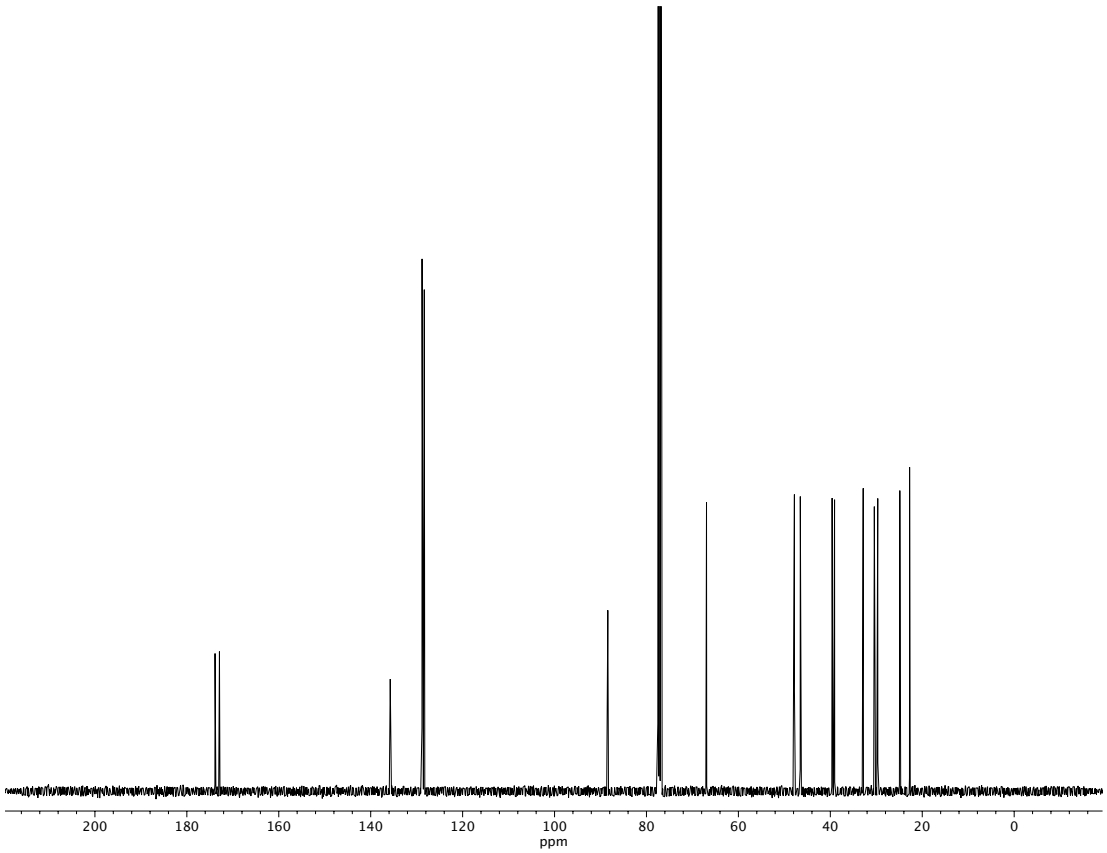


Figure A1.320. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***40****.*

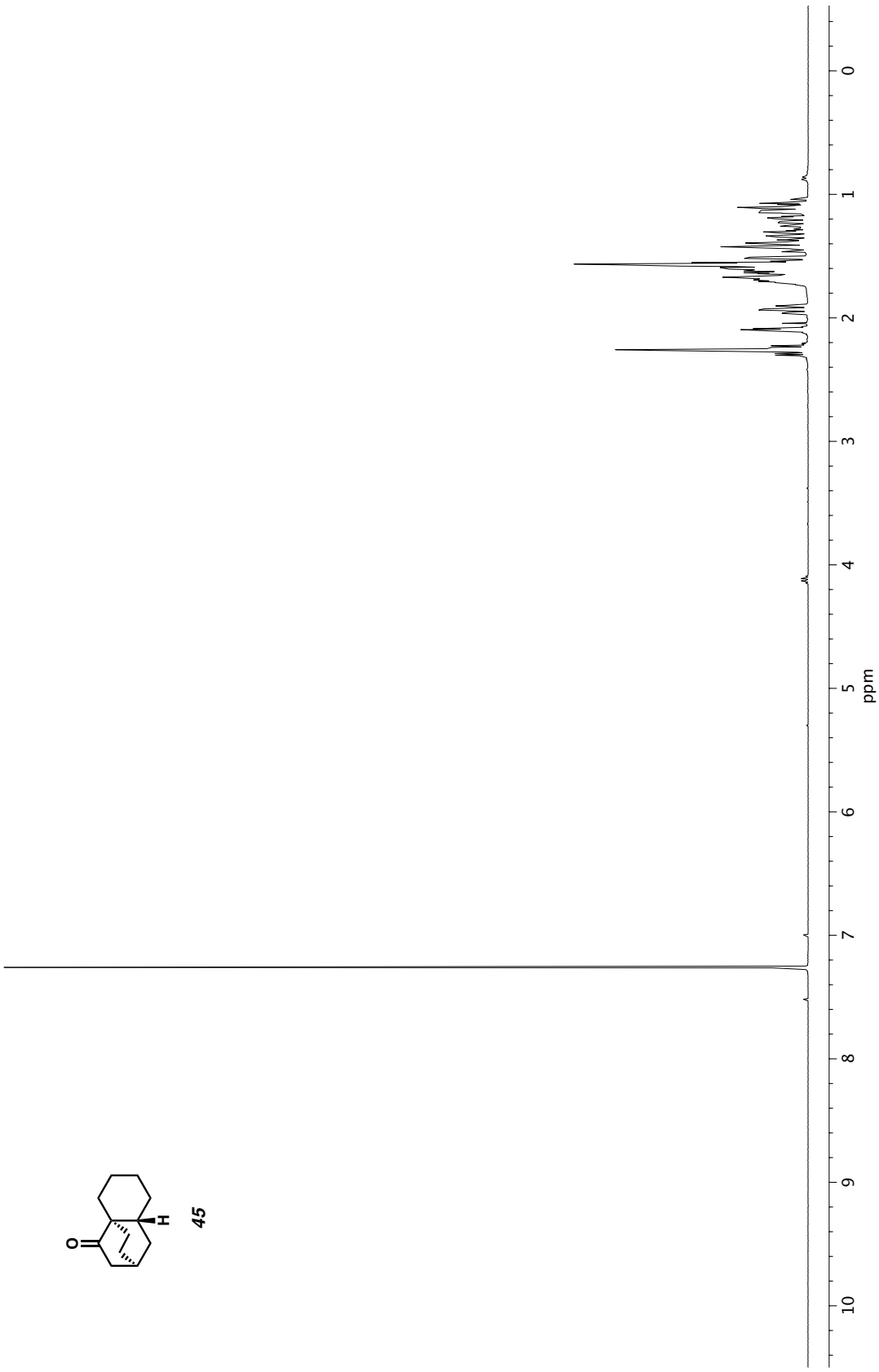


Figure A1.321. *^1H NMR (400 MHz, $CDCl_3$) of compound **45**.*

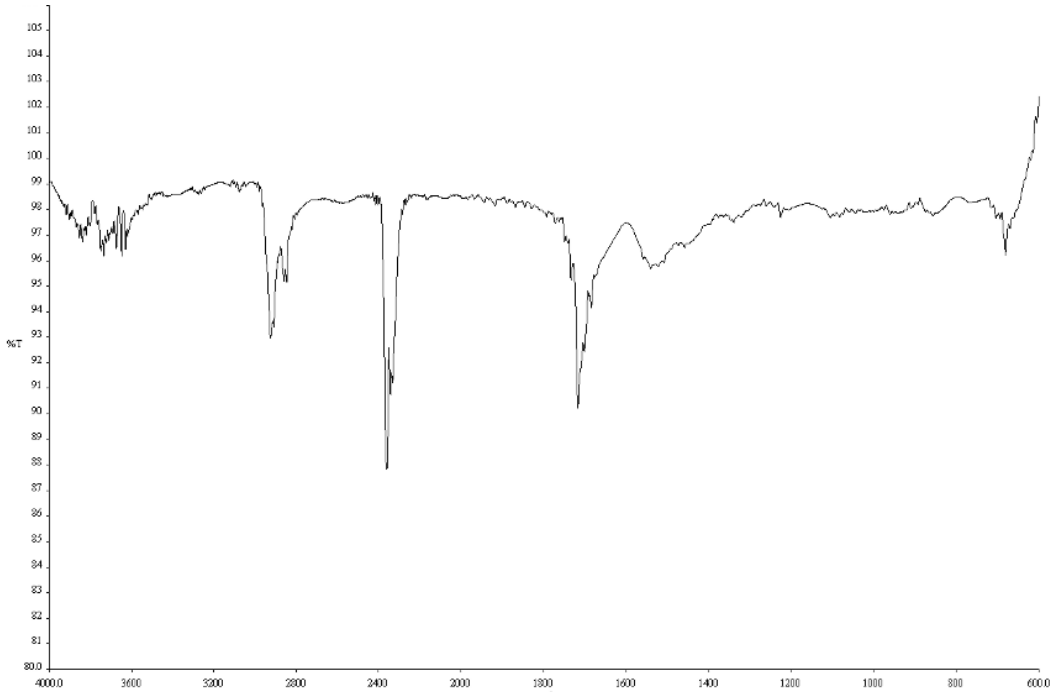


Figure A1.322. *Infrared spectrum (Thin Film, NaCl) of compound* ***45****.*

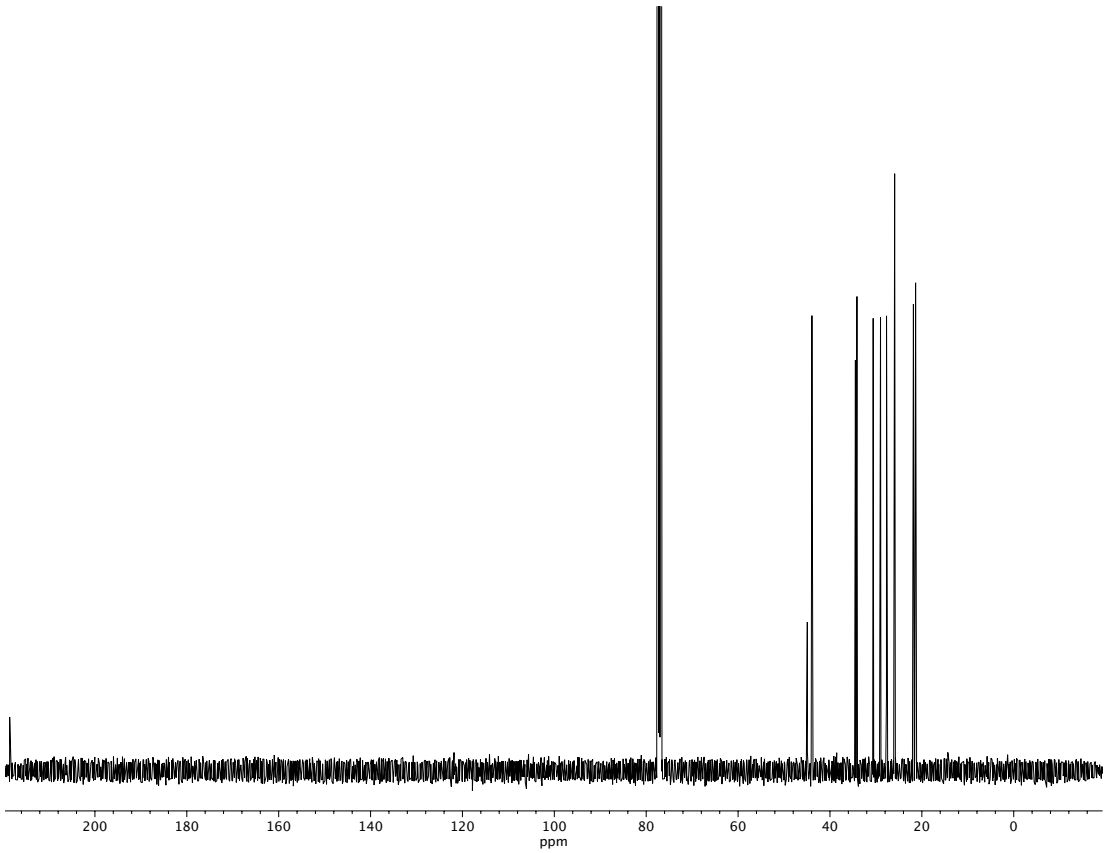


Figure A1.323. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***45****.*

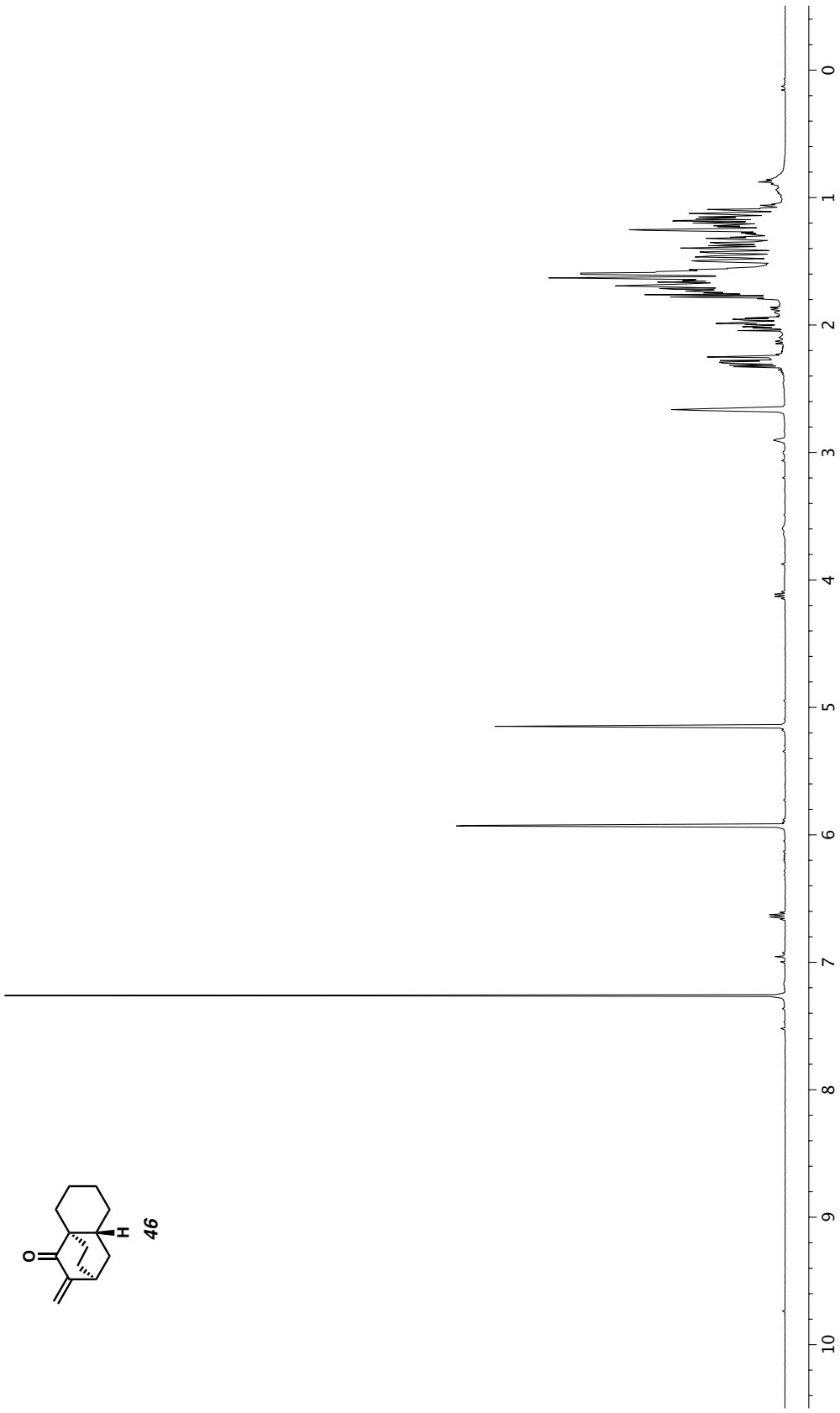


Figure A1.324. *^1H NMR (400 MHz, $CDCl_3$) of compound **46**.*

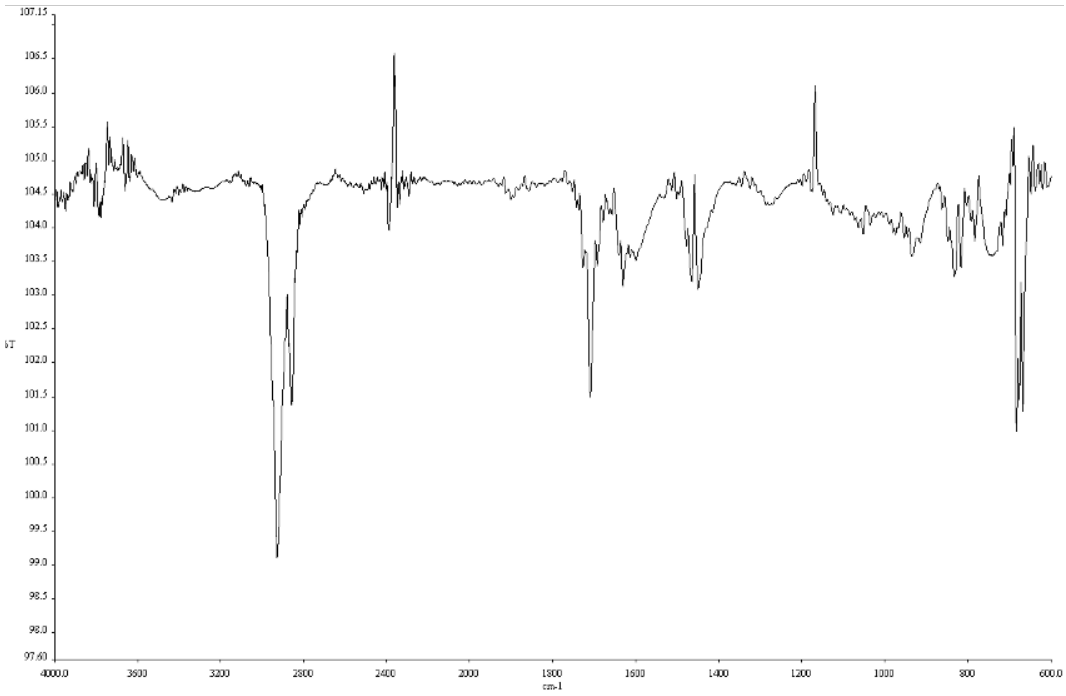


Figure A1.325. *Infrared spectrum (Thin Film, NaCl) of compound* ***46****.*

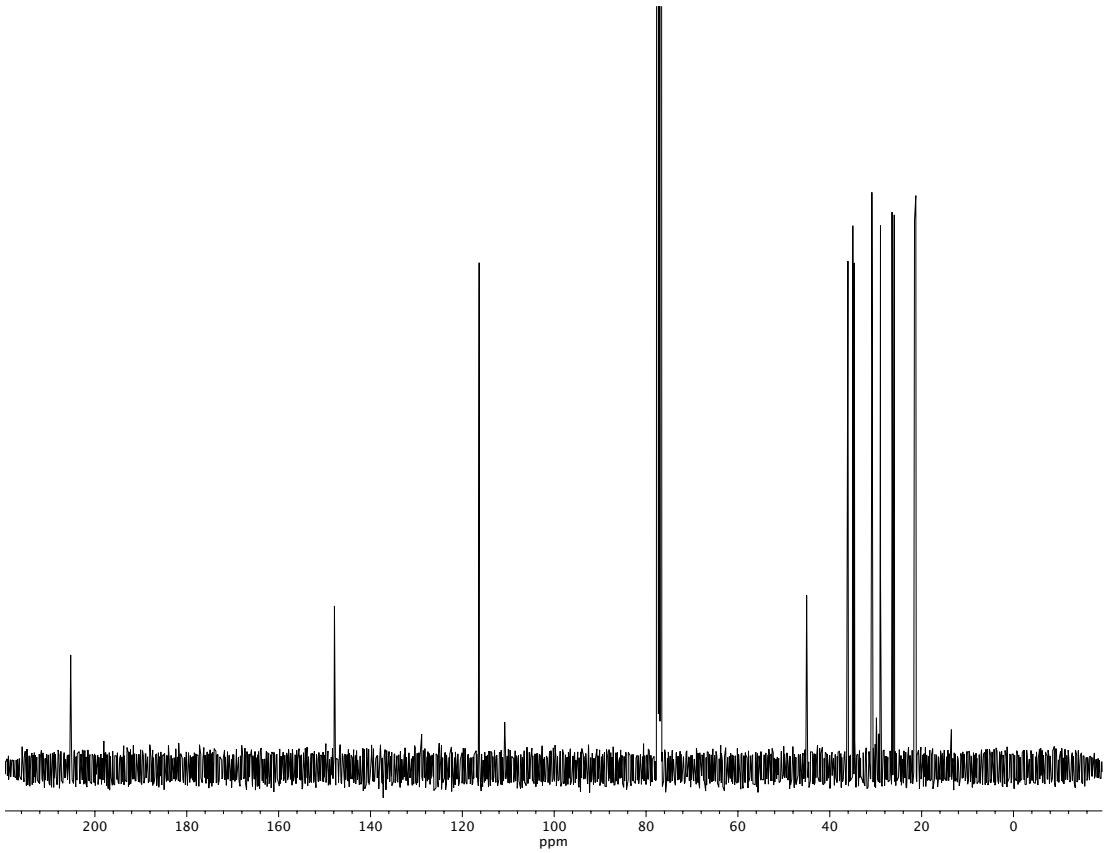


Figure A1.326. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***46****.*

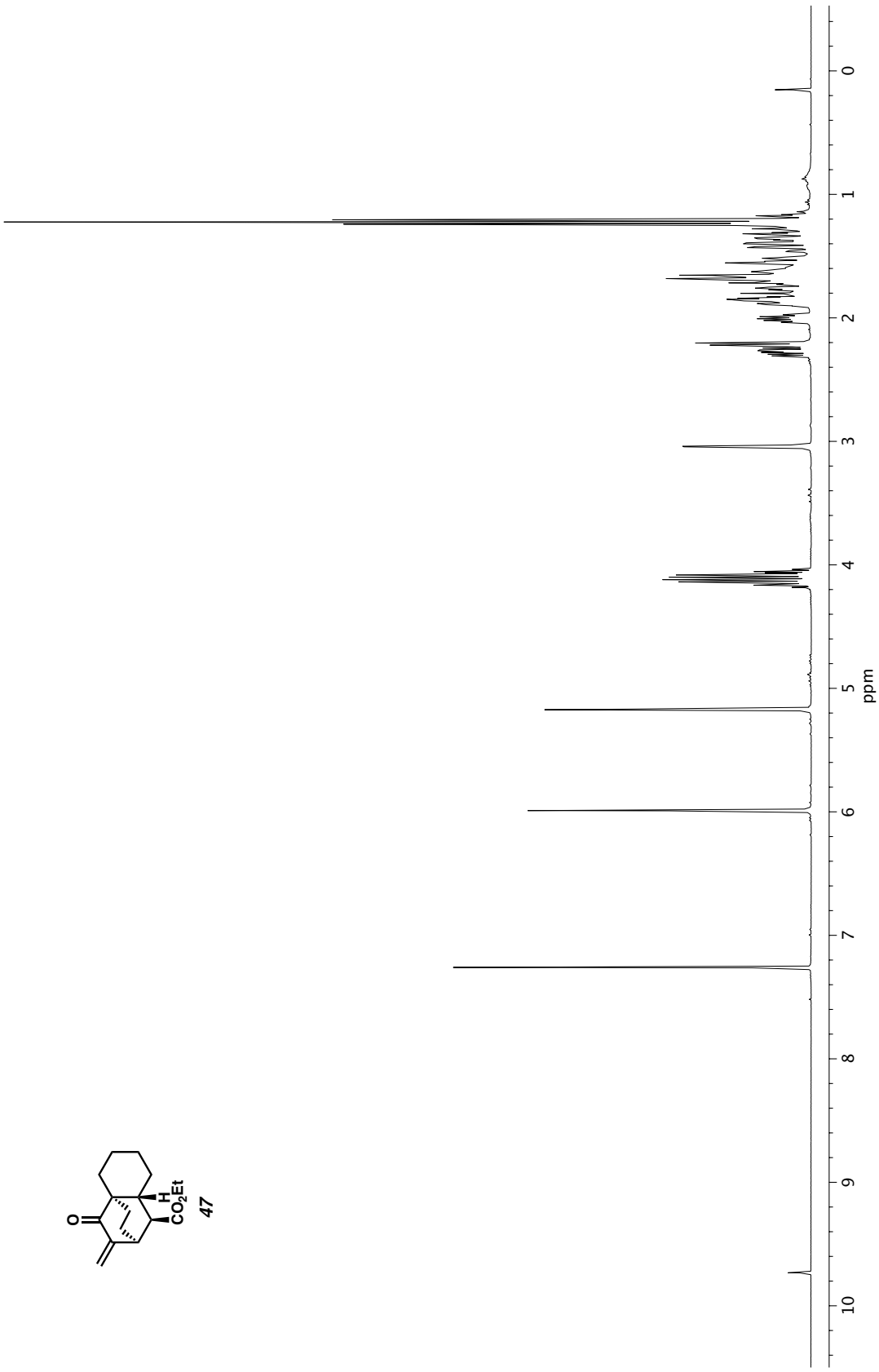


Figure A1.327. *^1H NMR (400 MHz, $CDCl_3$) of compound **47**.*

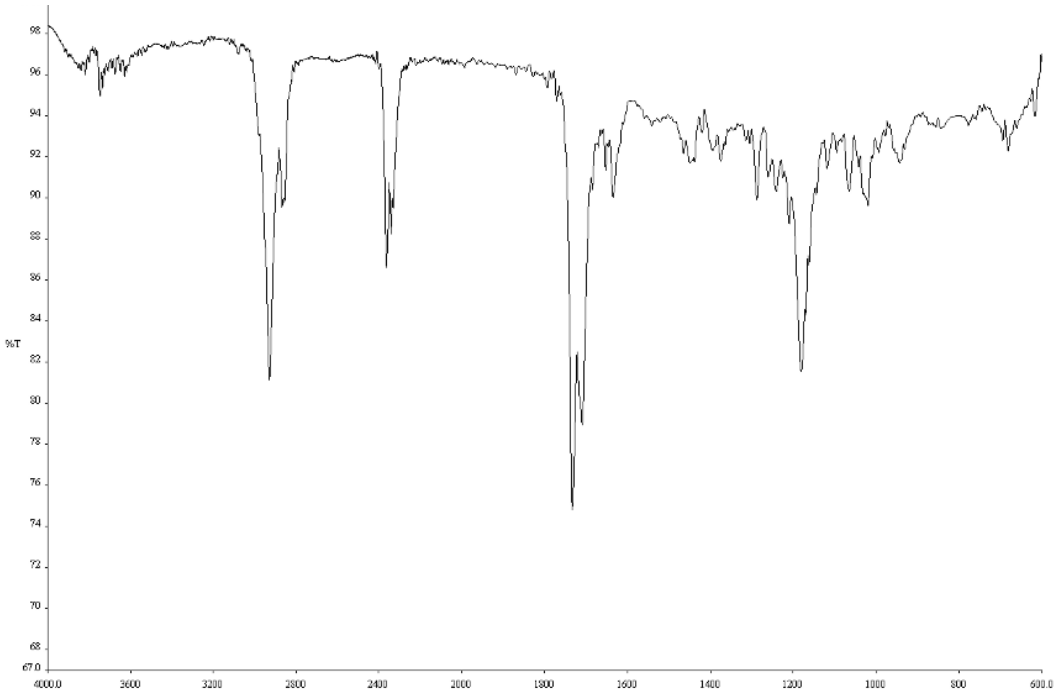


Figure A1.328. *Infrared spectrum (Thin Film, NaCl) of compound* ***47****.*

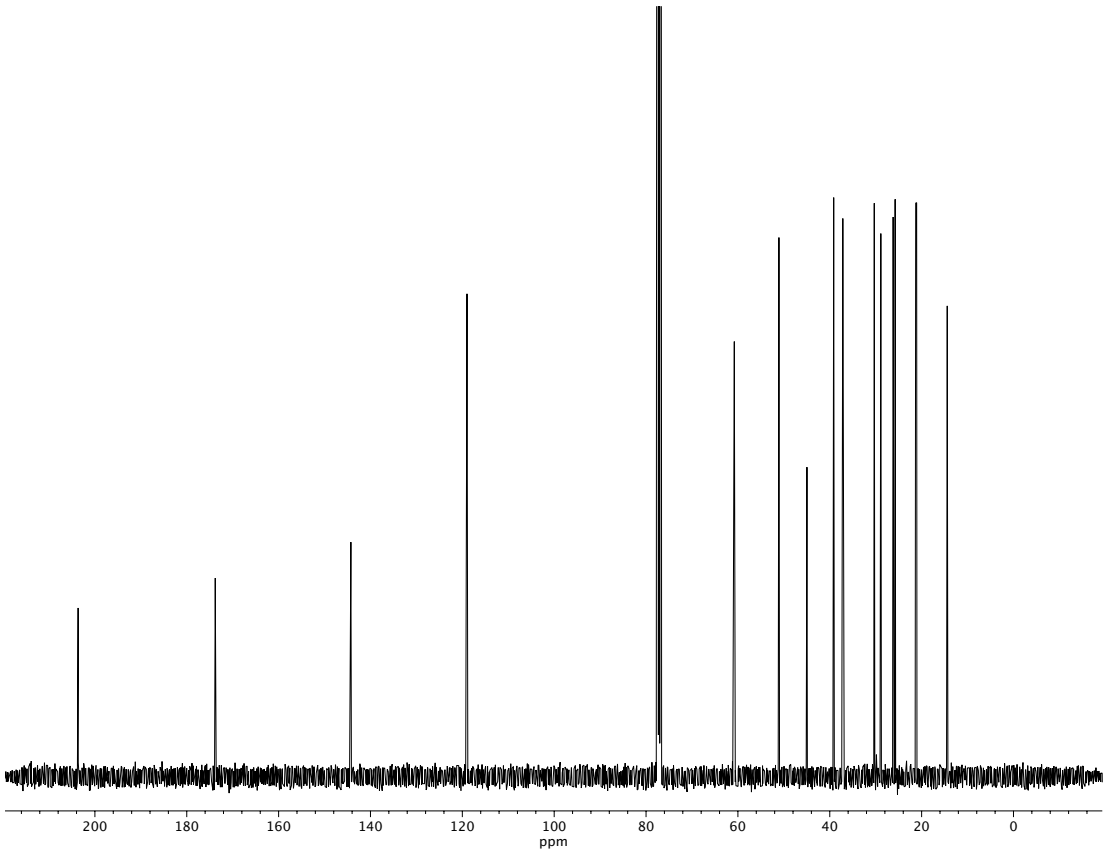


Figure A1.329. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***47****.*

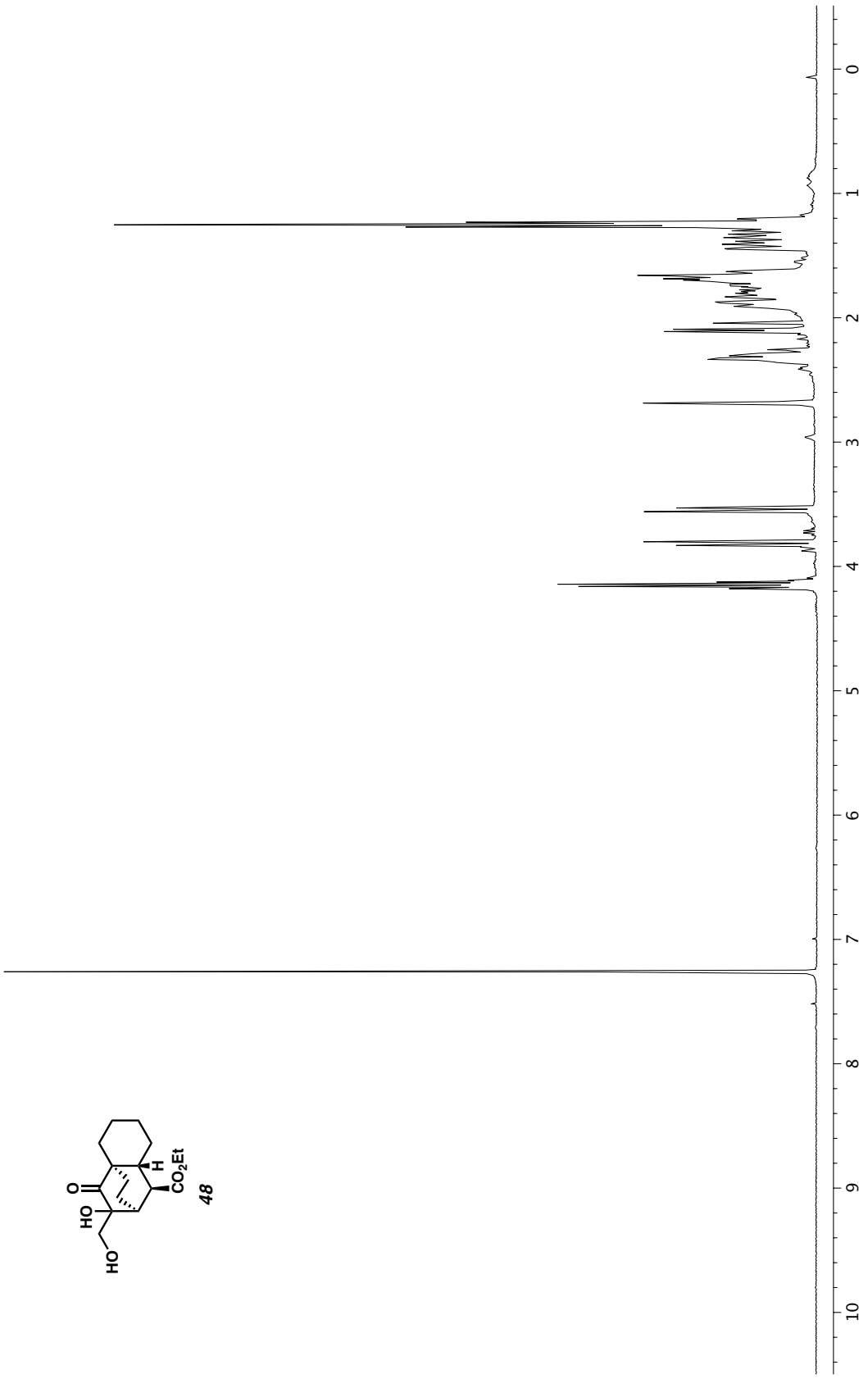


Figure A1.330. *^1H NMR (400 MHz, $CDCl_3$) of compound **48**.*

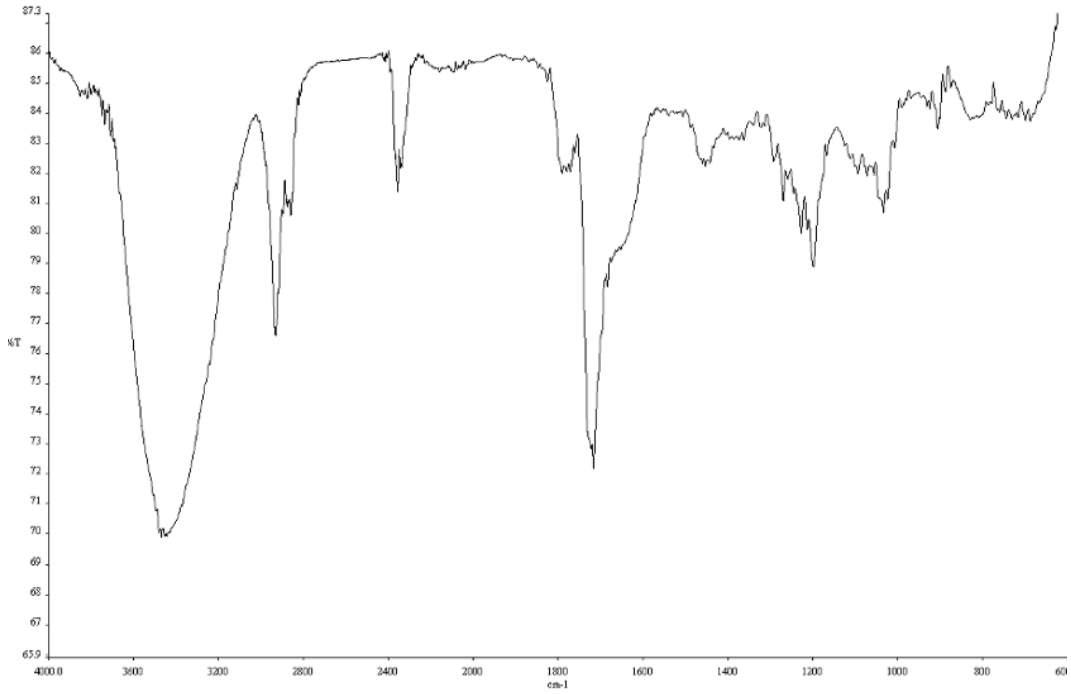


Figure A1.331. *Infrared spectrum (Thin Film, NaCl) of compound* ***48****.*

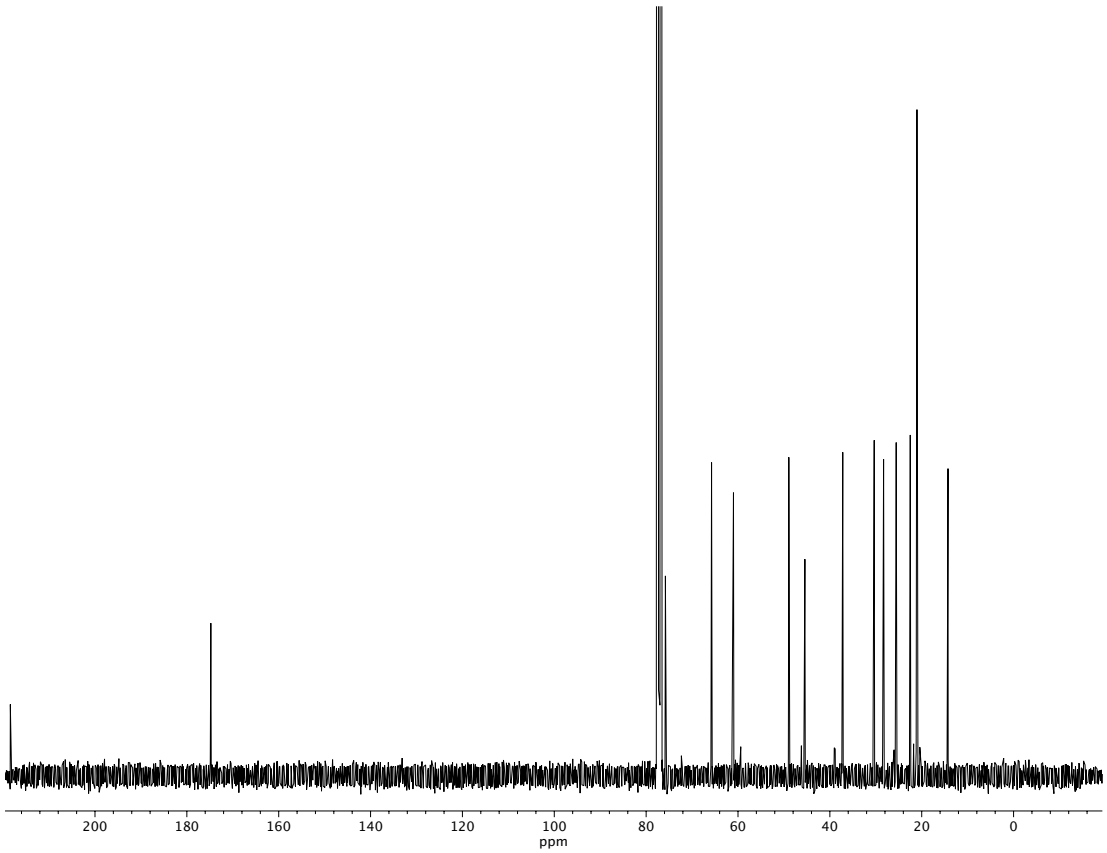


Figure A1.332. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***48****.*

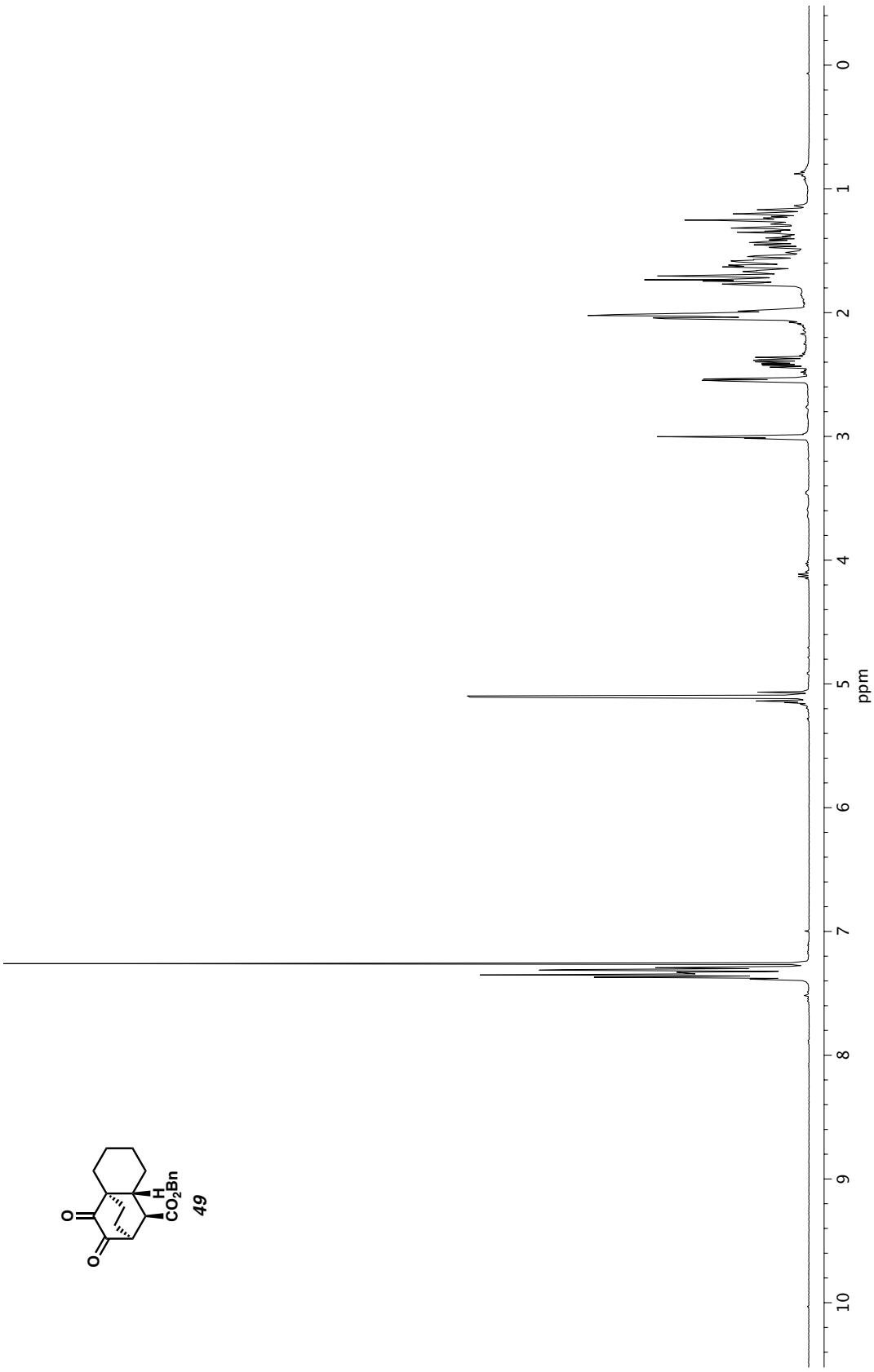


Figure A1.333. *^1H NMR (400 MHz, $CDCl_3$) of compound **49**.*

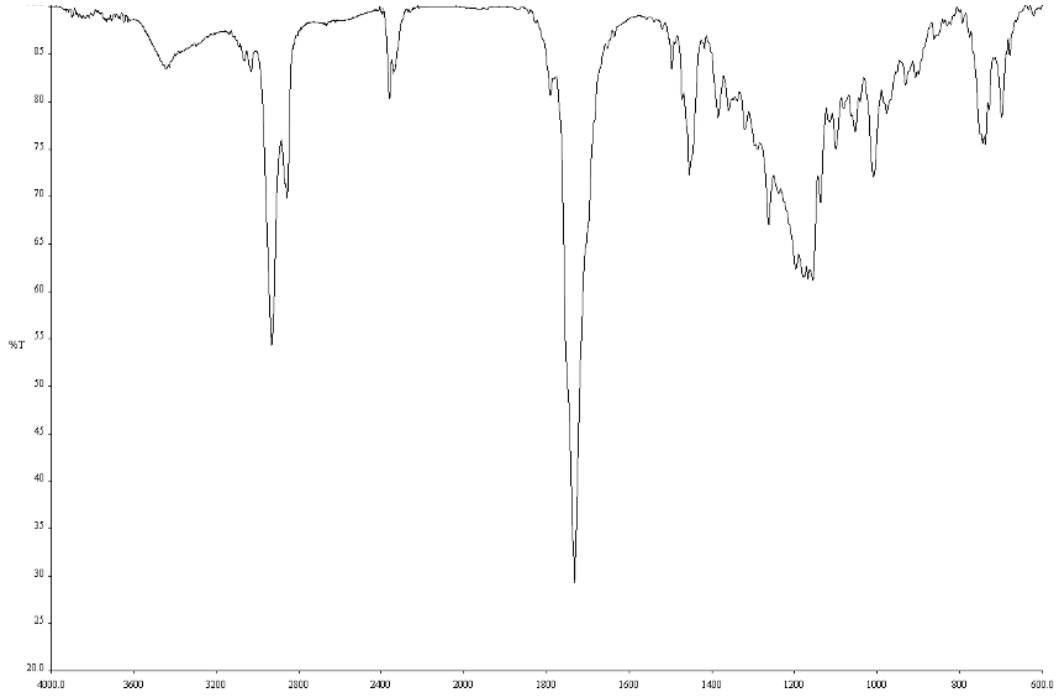


Figure A1.334. *Infrared spectrum (Thin Film, NaCl) of compound* ***49****.*

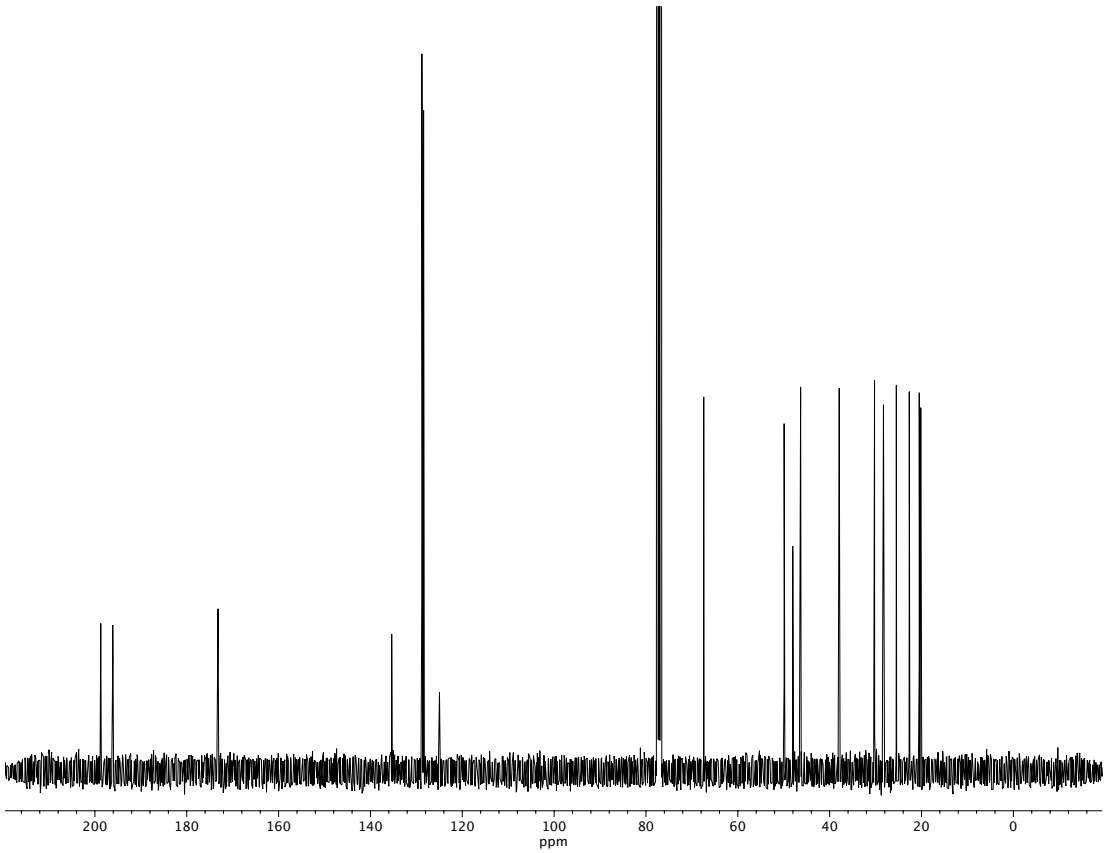


Figure A1.335. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***49****.*

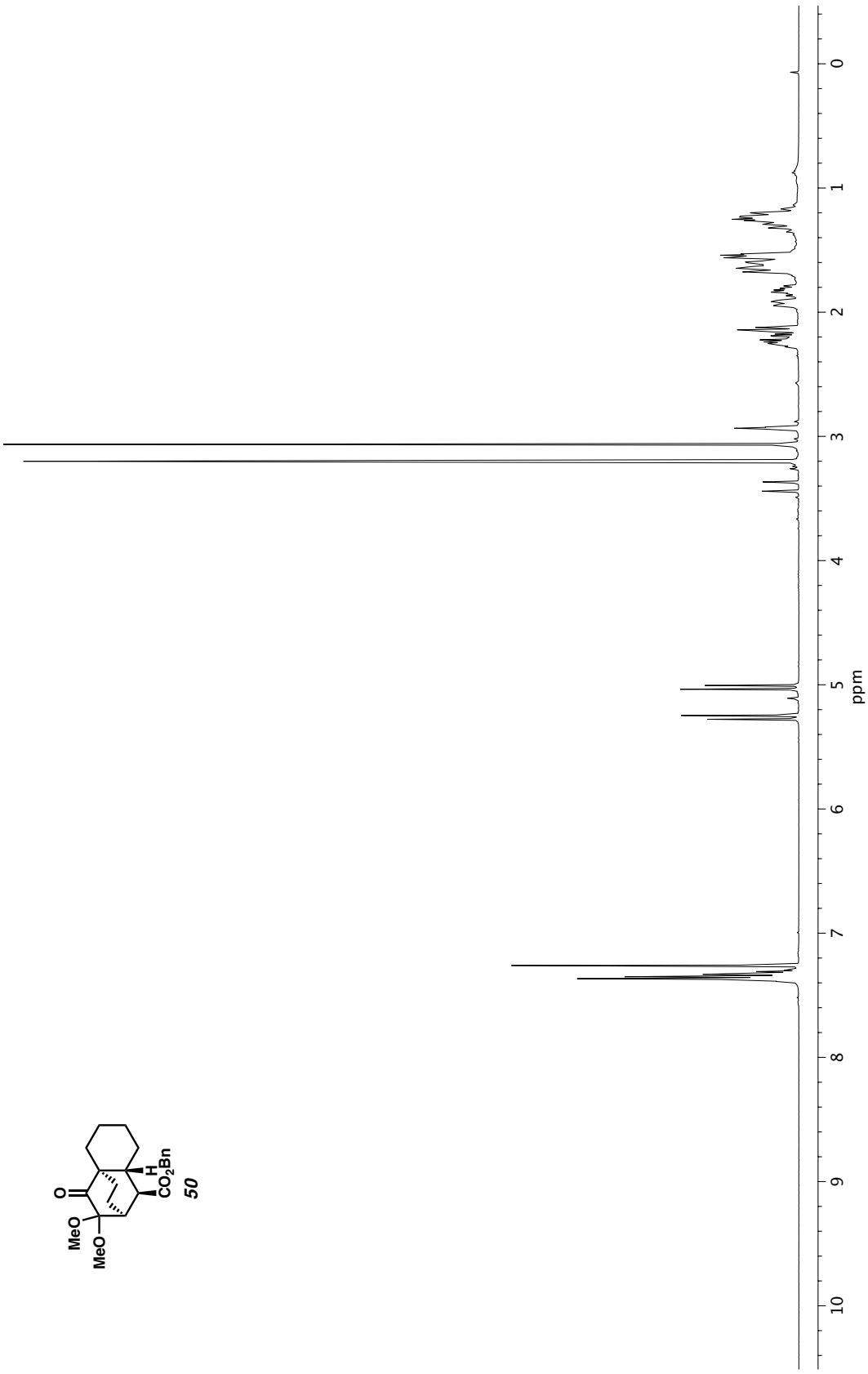


Figure A1.336. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***50****.*

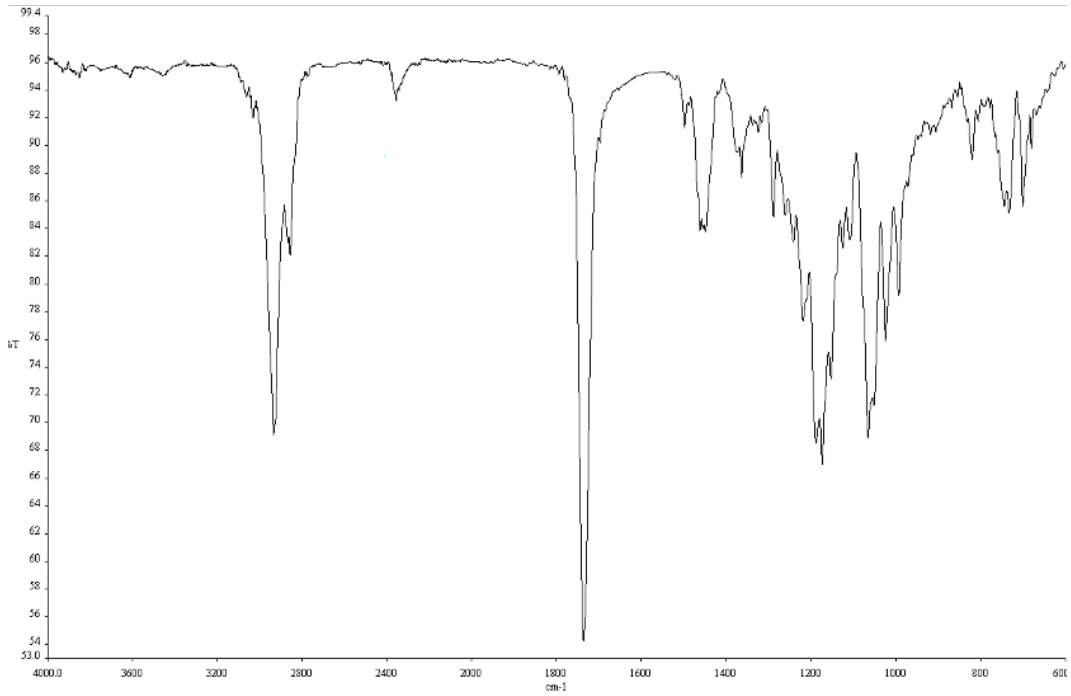


Figure A1.337. *Infrared spectrum (Thin Film, NaCl) of compound* ***50****.*

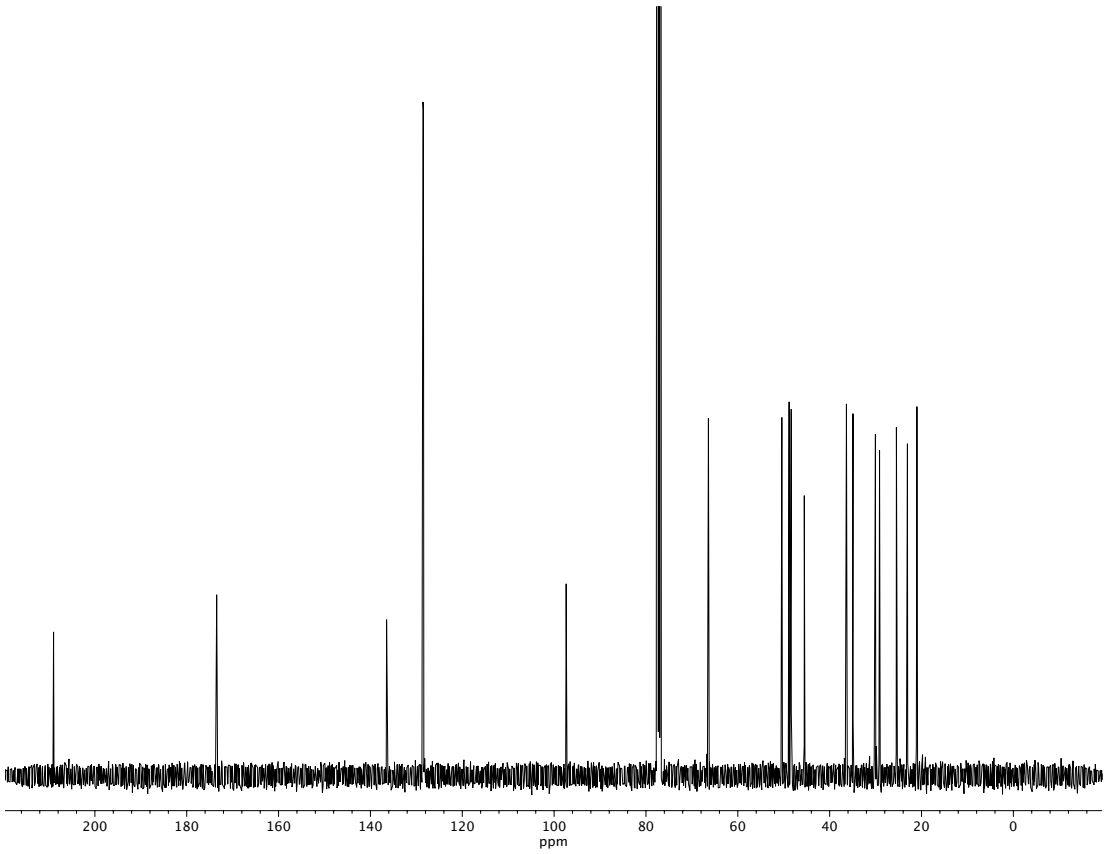


Figure A1.338. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***50****.*

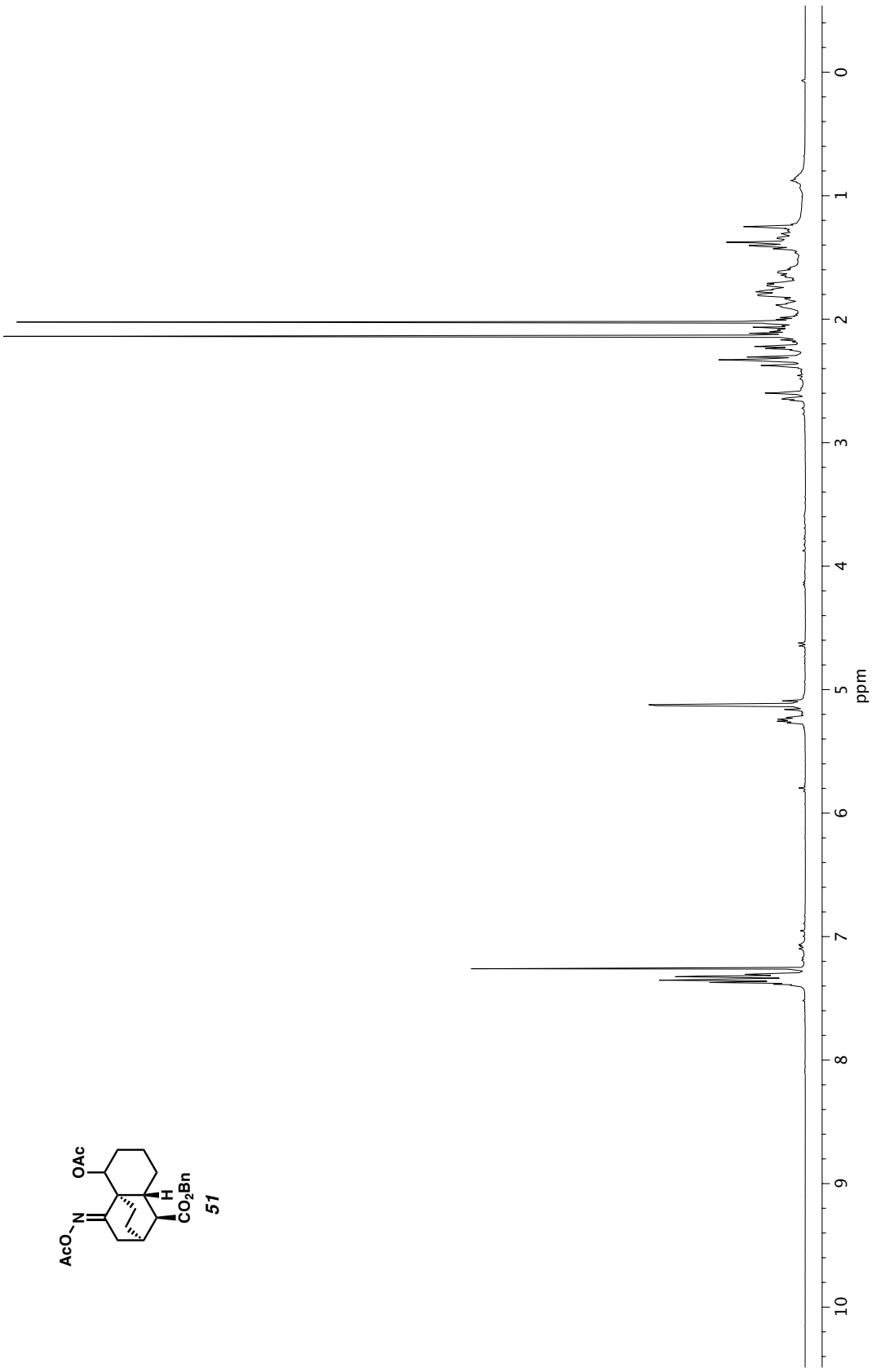


Figure A1.339. *^{1}H NMR (400 MHz, $CDCl_3$) of compound **51**.*

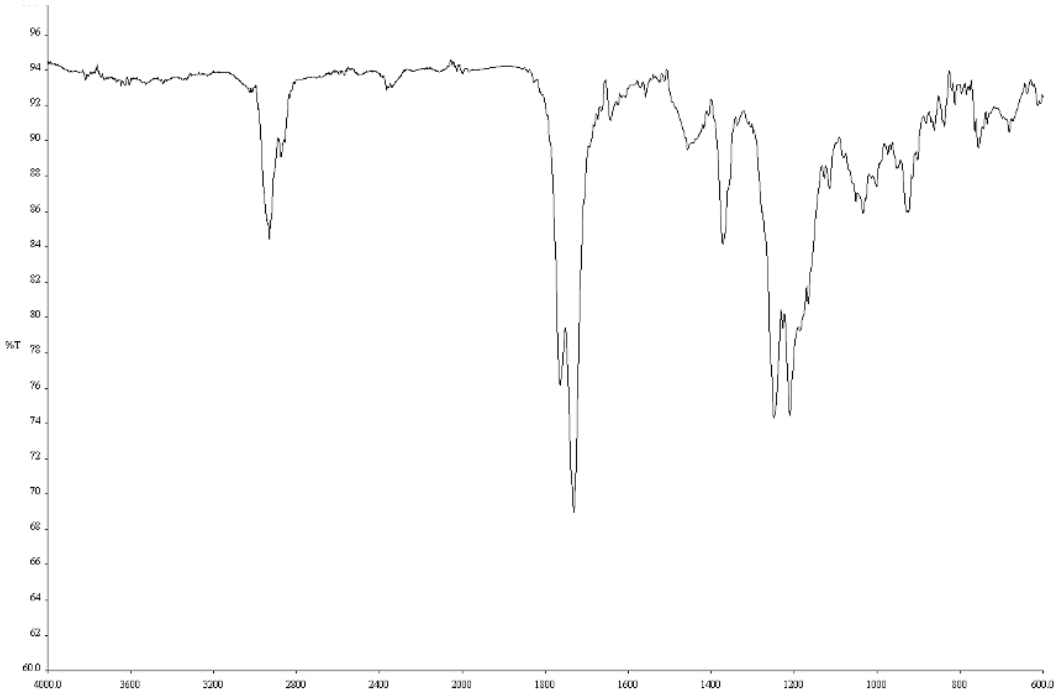


Figure A1.340. *Infrared spectrum (Thin Film, NaCl) of compound* ***51****.*

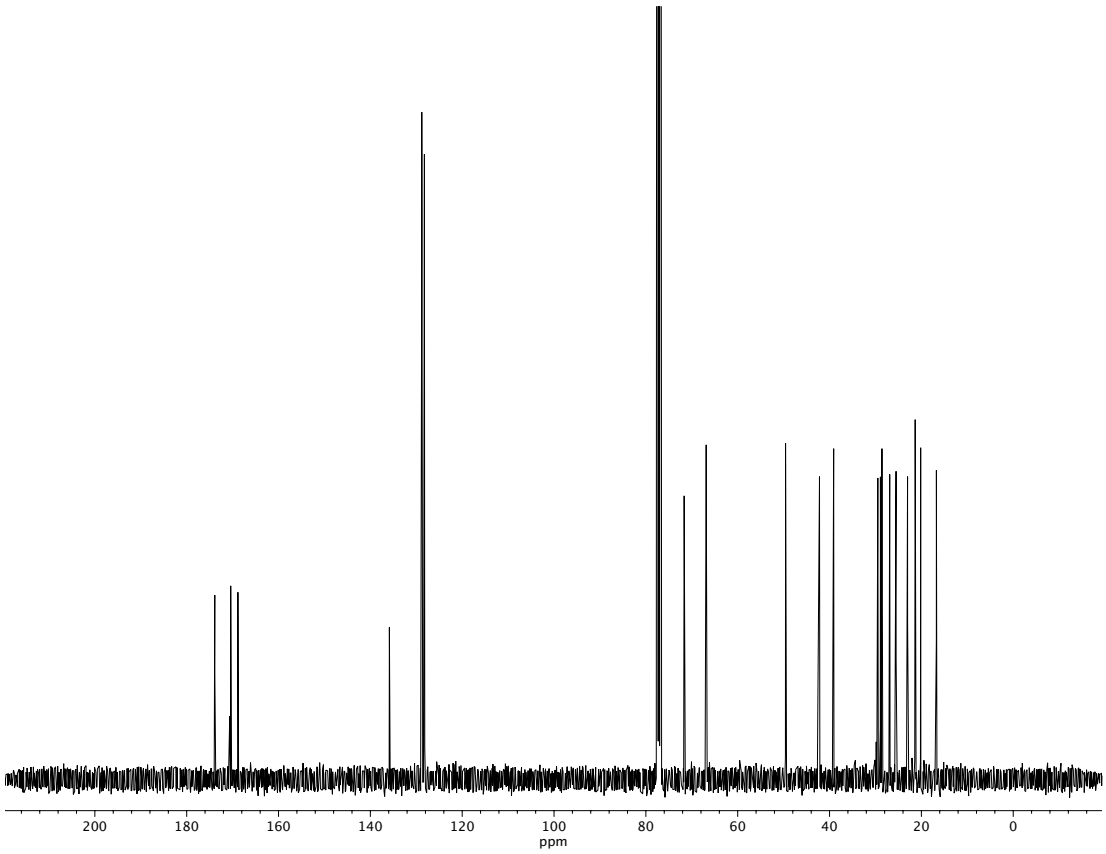


Figure A1.341. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***51****.*

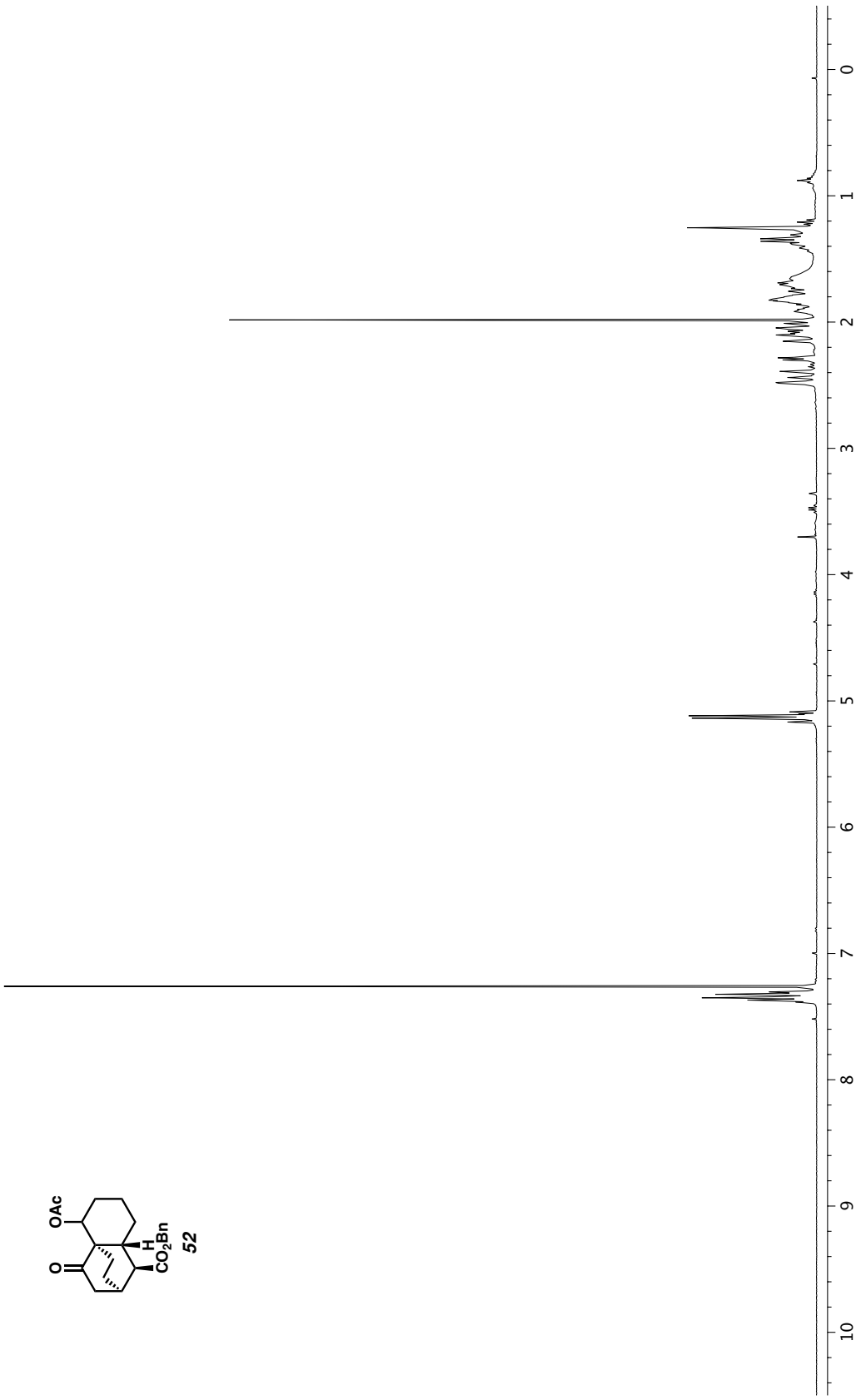


Figure A1.342. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***52****.*

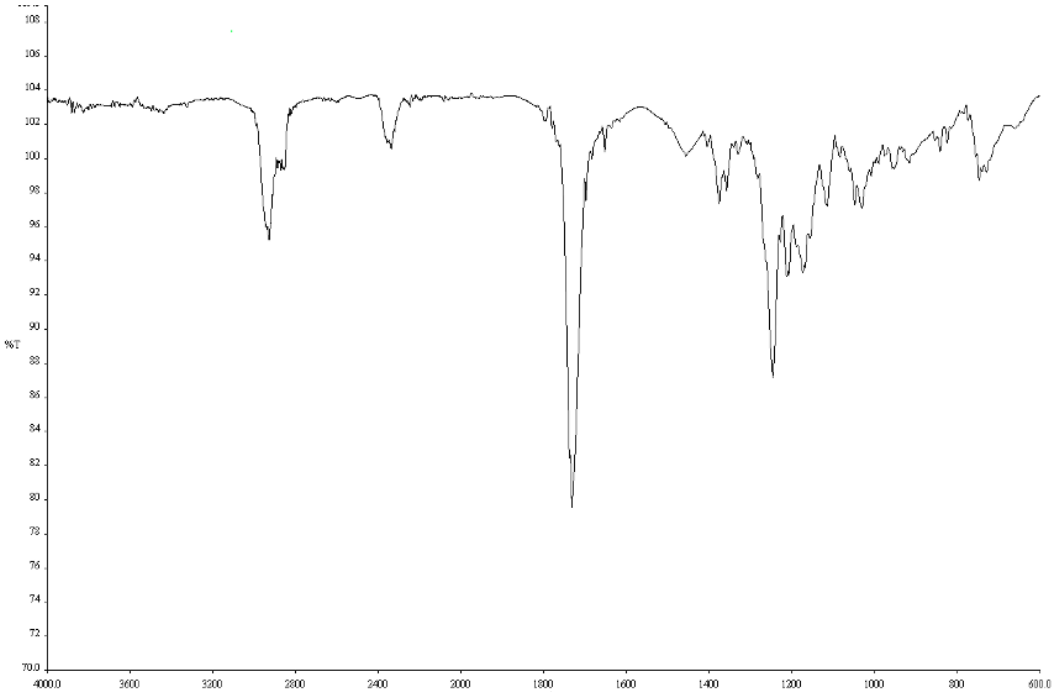


Figure A1.343. *Infrared spectrum (Thin Film, NaCl) of compound* ***52****.*

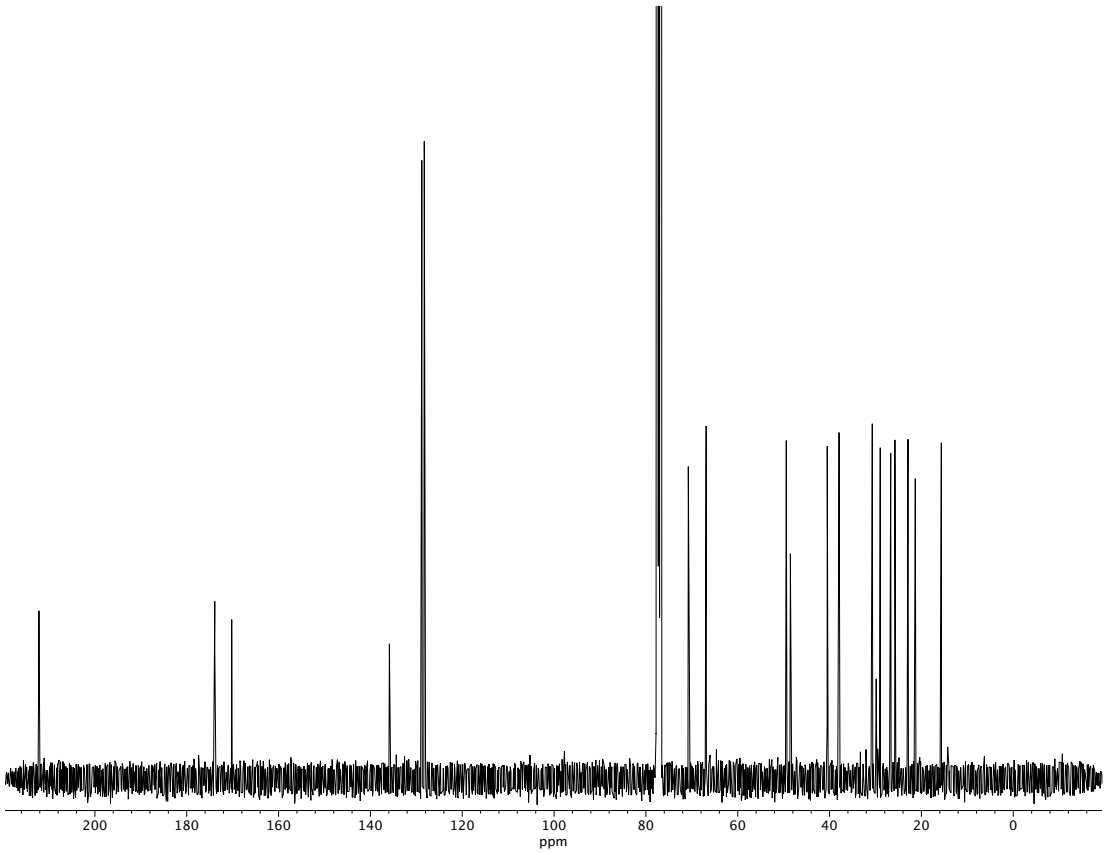


Figure A1.344. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***52****.*

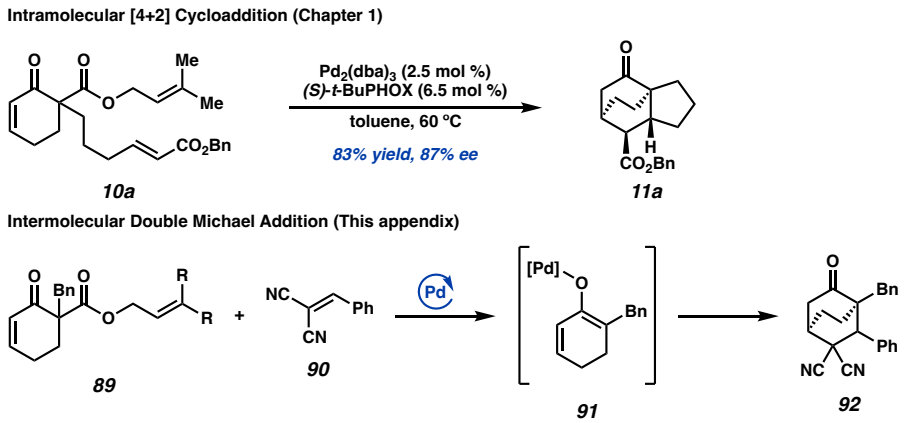
APPENDIX 2

Catalytic Asymmetric Intermolecular Double Michael Addition of Pd Enolates†

A2.1 INTRODUCTION

Having developed an intramolecular [4+2] cycloaddition from chiral Pd enolate intermediates (Chapter 1),[1] we sought to expand this approach to intermolecular systems. We envisioned starting from β-ketoester **89** and under Pd catalyzed conditions forming Pd enolate intermediate **91** analogously to the intramolecular system. In the presence of an external dienophile (**90**) a double Michael addition or net [4+2] cycloaddition is proposed to yield bicycle **92** (Figure A2.1).

Figure A2.1. *Proposed asymmetric intermolecular double Michael addition.*



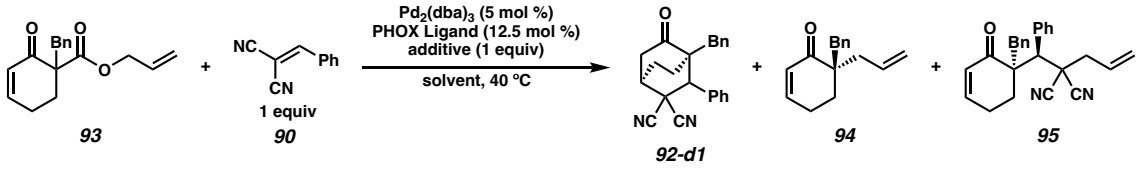
†This research was performed in collaboration with Chan, M. and Barbor, J. P.

A2.2 RESULTS AND DISCUSSION

A2.2.1 REACTION DESIGN AND OPTIMIZATION

Previous reports using saturated β-ketoesters (*i.e.* **1**) demonstrated that from the Pd enolate intermediate conjugate addition with **90** could occur prior to allylic alkylation to yield products analogous to **95**.[2] We hypothesized that in the presence of an additive to trap the allyl fragment, a second intramolecular Michael addition could take place to form desired bicycle **92**. Therefore, initial optimization efforts utilized allyl β-ketoester **93** and dienophile **90** (Table A2.1).

Table A2.1. *Initial optimization with allyl β-ketoester* ***93***.



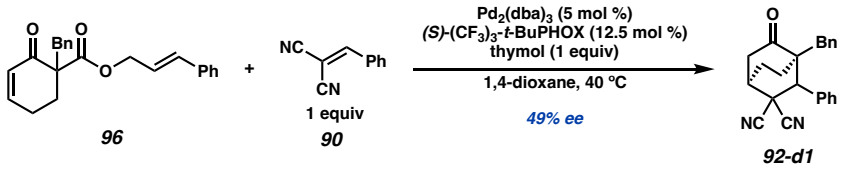
Entry	Ligand	Additive	Solvent	ee *92-d1* (%)
1	*(S)*-$(CF_3)_3$-*t*-BuPHOX	3,5-dimethylphenol	1,4-dioxane	60
2	*(S)*-*t*-BuPHOX	3,5-dimethylphenol	1,4-dioxane	49
3	*(S)*-$(CF_3)_3$-*t*-BuPHOX	p-toluidine	1,4-dioxane	61
4	*(S)*-$(CF_3)_3$-*t*-BuPHOX	2,6-dimethoxyphenol	toluene	66
5	*(S)*-*t*-BuPHOX	2,6-dimethoxyphenol	toluene	41
6	*(S)*-$(CF_3)_3$-*t*-BuPHOX	thymol	toluene	34

Reaction mixtures from these transformations were very complex with the formation of two diastereomers of bicycle **92**[3], allylic alkylation product **94**, and conjugate addition product **95**. Ligand, additive, and solvent were all explored during reaction optimization. Modest ee's were observed using either *(S)*-*t*-BuPHOX or the more electron poor *(S)*-$(CF_3)_3$-*t*-BuPHOX with different additive and solvent combinations (Table A2.1). Both phenol (Table A2.1, entries 1, 2, 4–6) and aniline (Table A2.1, entry 3) additives were

competent in the reaction. In contrast, phenol additives only resulted in protonation of the Pd enolate intermediate in the intramolecular [4+2] cycloaddition (see Chapter 1, Table 1.1, entry 10).[1] Finally, both 1,4-dioxane (Table A2.1, entries 1–3) and toluene (Table A2.1, entries 4–6) performed similarly in the reaction. Due to the complex reaction profile and modest ee's, we evaluated changes to both the β-ketoester and dienophile.

The analogous cinnamyl β-ketoester **96** was explored in this transformation (Figure A2.2). Under Pd catalyzed conditions product **92-d1** was still formed with a modest 49% ee. However, due to the formation of additional diastereomers and constitutional isomers of the allylic alkylation and conjugate addition side products, the reaction profile was even more complex than with allyl β-ketoester **93**. Therefore, we decided not to continue optimization with cinnamyl β-ketoesters.

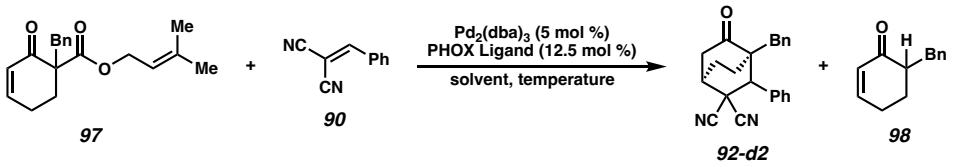
Figure A2.2. *Double Michael addition with cinnamyl β-ketoester* ***96***.



Next, prenyl β-ketoester **97** with dienophile **90** was evaluated in the transformation (Table A2.2). Unlike the allyl or cinnamyl systems, no conversion of starting material was observed at 40 ºC (Table A2.2, entry 1). Excitingly, when the reaction temperature was increased to 100 ºC formation of the desired bicycle occurred in an excellent 82% ee of **92-d2** (Table A2.2, entry 2). Interestingly, the major diastereomer (**92-d2**) isolated was different than the major diastereomer (**92-d1**) previously observed with allyl β-ketoester **93** and cinnamyl β-ketoester **96**. Different high boiling solvents were also evaluated and

performed similarly (Table A2.2, entries 3–5). Switching to a more electron poor ligand *(S)*-$(CF_3)_3$-*t*-BuPHOX, the ee of the reaction increased to 94% (Table A2.2, entry 6). Utilizing two equivalents of the dienophile further improved the reaction yield to a modest 33% of the major diastereomer (Table A2.2, entry 7). Despite these improvements, protonation product **98** was still observed in high yield, and the diastereoselectivity and yield of the desired product was not able to be further improved.

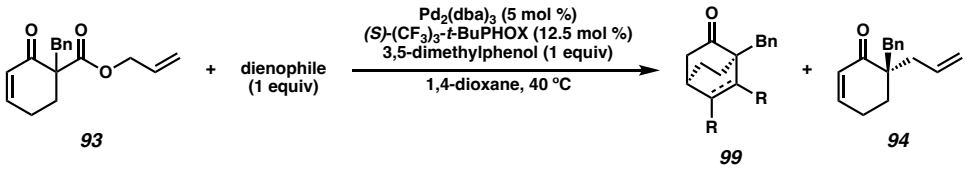
Table A2.2. *Initial optimization with prenyl β-ketoester* ***97****.*



Entry	Ligand	Equiv *90*	Solvent	Temp (° C)	ee *92-d2* (%)	yield *92-d2* (%)	dr (*92-d2*:*92-d1*)
1	*(S)*-*t*-BuPHOX	1	toluene	40	–	–	–
2	*(S)*-*t*-BuPHOX	1	toluene	100	82	15	–
3	*(S)*-*t*-BuPHOX	1	*m*-xylenes	150	73	17	1.1:1
4	*(S)*-*t*-BuPHOX	1	1,4-dioxane	100	80	14	2.8:1
5	*(S)*-*t*-BuPHOX	1	ethyl benzene	150	76	22	1.4:1
6	*(S)*-$(CF_3)_3$-*t*-BuPHOX	1	toluene	100	92	22	1.8:1
7	*(S)*-$(CF_3)_3$-*t*-BuPHOX	2	toluene	100	94	33	2.4:1
8	*(S)*-$(CF_3)_3$-*t*-BuPHOX	2	toluene	80	92	15	2.5:1

Finally, with allyl β-ketoester **93**, we explored the efficacy of different dienophiles (Table A2.3). With maleic anhydride (Table A2.3, entry 1) or quinone (Table A2.3, entry 2), the only **93** was recovered after heating overnight. It is hypothesized that coordination of the dienophile to Pd resulted in inhibition of the catalyst. In contrast, only allylic alkylation product **94** was formed when using an acrylate dienophile (Table A2.3, entry 3). When employing alkynyl dienophiles (Table A2.3, entries 4–6), nonspecific decomposition was observed.

Table A2.3. *Evaluation of additional dienophiles.*



Entry	Dienophile	Product (*99*)	Allylic Alkylation (*94*)	SM (*93*) Remaining
1	maleic anhydride	No	No	Yes
2	quinone	No	No	Yes
3	methyl methacrylate	No	Yes	No
4[a]	EtO_2C—≡—CO_2Et	No	No	No
5[a]	Ph—≡—COH	No	No	No
6[a]	EtO_2C—≡—Me	No	Yes	No

[a] In Toluene at 100 ºC with 3 equiv of dienophile.

A2.3 CONCLUSIONS

In conclusion, the development of an intermolecular Diels–Alder/double Michael addition proved challenging. Product formation occurred in modest to excellent ee with various β-ketoester starting materials. Interestingly, the substitution on the allyl group on the β-ketoester influenced the diastereoselectivity greatly. However, we were plagued with complex reaction profiles and low yields under all explored conditions. Furthermore, the narrow scope of tolerated dienophile classes limits the utility of the transformation. As such, further optimization was not preformed.

A2.4 EXPERIMENTAL SECTION

A2.4.1 MATERIALS AND METHODS

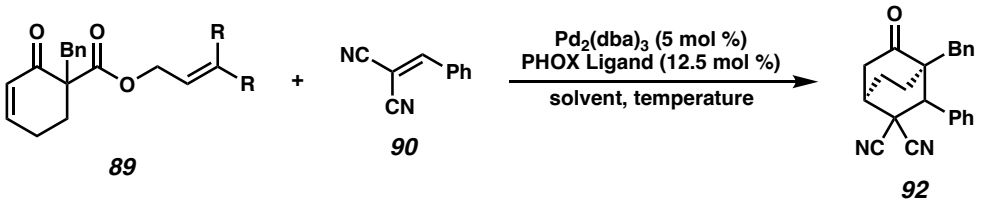
Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[4] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 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 $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 nm) was used for flash chromatography. ^{1}H NMR spectra were recorded on a Bruker 400 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer (100 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as the peaks appear 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). Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing Chiralpak (AD-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd.

Reagents were purchased from commercial sources and used as received unless otherwise stated. Ligands were prepared according to literature procedures.[5]

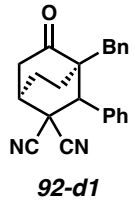
List of Abbreviations: ee – enantiomeric excess, SFC – supercritical fluid chromatography, TLC – thin-layer chromatography.

A2.4.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

General Procedure A: Asymmetric Pd-Catalyzed Decarboxylative Double Michael Additions.



In a nitrogen filled glovebox, an oven-dried 4 mL vial was charged with a stir bar, $Pd_2(dba)_3$ (0.05 mmol, 5 mol %), PHOX ligand (0.13 mmol, 12.5 mol %), and solvent (0.4 mL). The catalyst solution was stirred at 23 ºC for 20 min. A solution of substrate **89** (0.1 mmol, 1 equiv) in solvent (0.3 mL) and a solution of dienophile **90** (0.1 mmol, 1 equiv) in solvent (0.3 mL) were added to the vial. The resultant solution was then heated to desired temperature for 14 h. The solution was then cooled to 23 ºC and concentrated under reduced pressure. The crude reaction mixture was loaded directly onto a preparatory TLC plate and the product(s) was isolated.



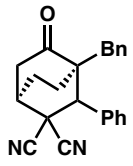
(1*R*,4*S*)-4-benzyl-5-oxo-3-phenylbicyclo[2.2.2]octane-2,2-dicarbonitrile (92-d1)

Prepared from **93** following General Procedure A. Purification by preparatory TLC (10% EtOAc/hexanes) afforded the title compound as a colorless oil. Absolute and relative stereochemistry not determined.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.42 (m, 3H), 7.19 (dd, *J* = 5.0, 1.9 Hz, 5H), 6.83 – 6.76 (m, 2H), 3.53 (s, 1H), 3.07 (dt, *J* = 19.7, 3.1 Hz, 1H), 3.00 (d, *J* = 14.7 Hz, 1H), 2.86 (p, *J* = 3.1 Hz, 1H), 2.68 (dd, *J* = 19.6, 3.3 Hz, 1H), 2.63 (d, *J* = 14.3 Hz, 1H), 2.37 – 2.23 (m, 1H), 2.06 – 1.90 (m, 2H), 1.69 (ddd, *J* = 15.3, 12.3, 5.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 210.2, 135.8, 135.6, 130.9, 129.7, 129.6, 128.3, 127.0, 116.7, 113.5, 55.8, 48.4, 42.4, 41.0, 37.0, 36.4, 28.3, 20.7.

SFC Conditions: 10% IPA, 2.5 mL/min, Chiralpack AD-H column, λ = 210 nm, t_R (min): major = 8.43, t_R (min): minor = 6.59.



92-d2

(1*R*,4*S*)-4-benzyl-5-oxo-3-phenylbicyclo[2.2.2]octane-2,2-dicarbonitrile (92-d2)

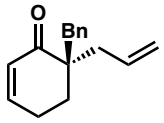
Prepared from **97** following General Procedure A. Purification by preparatory TLC (20% EtOAc/hexanes, followed by second preparatory TLC purification with 2% EtOAc/toluene) afforded the title compound as a colorless oil. Absolute and relative stereochemistry not determined.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.40 (m, 3H), 7.18 (dd, *J* = 5.1, 2.0 Hz, 5H), 6.82 – 6.77 (m, 2H), 3.53 (s, 1H), 3.04 (dt, *J* = 19.9, 3.3 Hz, 1H), 2.97 (d, *J* = 14.1 Hz, 1H), 2.86 (p, *J* = 3.0 Hz, 1H), 2.66 (dt, *J* = 19.2, 3.3 Hz, 1H), 2.60 (d, *J* = 14.1 Hz, 1H), 2.30 (tdt, *J*

= 10.6, 5.0, 2.7 Hz, 1H), 1.97 (dddd, *J* = 15.0, 11.7, 9.1, 5.5 Hz, 2H), 1.69 (ddd, *J* = 15.3, 12.3, 5.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 208.7, 136.4, 134.0, 130.7, 129.7, 128.0, 126.4, 116.5, 114.3, 51.6, 49.8, 41.3, 40.5, 37.8, 36.1, 23.6, 22.1.

SFC Conditions: 10% IPA, 2.5 mL/min, Chiralpack AD-H column, λ = 210 nm, t_R (min): major = 7.15, t_R (min): minor = 5.19.

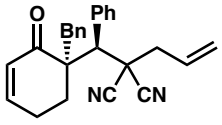


94

(*S*)-6-allyl-6-benzylcyclohex-2-en-1-one (94)

Undesired side product prepared from **93** following General Procedure A. Purification by preparatory TLC (10% EtOAc/hexanes) afforded the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.15 (m, 3H), 7.12 (d, *J* = 7.3 Hz, 2H), 6.86 (dt, *J* = 9.9, 4.0 Hz, 1H), 5.97 (dt, *J* = 9.9, 2.1 Hz, 1H), 5.77 (td, *J* = 17.1, 7.5 Hz, 1H), 5.14 – 5.08 (m, 1H), 5.06 (d, *J* = 17.0 Hz, 1H), 3.11 (d, *J* = 13.5 Hz, 1H), 2.67 (d, *J* = 13.5 Hz, 1H), 2.45 (dd, *J* = 13.9, 6.7 Hz, 1H), 2.39 (d, *J* = 5.7 Hz, 2H), 2.11 (dd, *J* = 13.9, 7.8 Hz, 1H), 1.91 – 1.82 (m, 1H), 1.77 (dt, *J* = 13.6, 6.4 Hz, 1H).



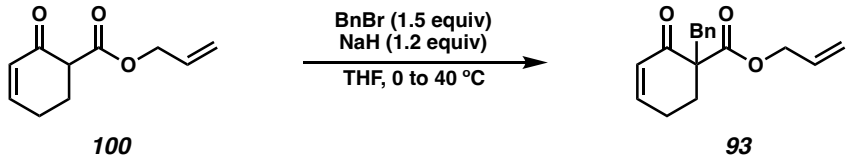
95

2-allyl-2-((*S*)-((*S*)-1-benzyl-2-oxocyclohex-3-en-1-yl)(phenyl)methyl)malononitrile (95)

Undesired side product prepared from **93** following General Procedure A. Purification by preparatory TLC (10% EtOAc/hexanes) afforded the title compound as a colorless oil.

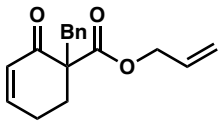
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 7.9 Hz, 1H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.12 (dd, *J* = 8.3, 6.3 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 2H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.83 – 6.74 (m, 1H), 6.64 (d, *J* = 7.4 Hz, 2H), 6.15 (d, *J* = 10.4 Hz, 1H), 5.87 (ddt, *J* = 17.1, 10.2, 7.2 Hz, 1H), 5.39 (d, *J* = 10.1 Hz, 1H), 5.28 (dd, *J* = 16.8, 1.5 Hz, 1H), 4.24 (s, 1H), 2.98 (ddd, *J* = 13.8, 10.8, 6.1 Hz, 1H), 2.74 (dd, *J* = 13.8, 5.5 Hz, 1H), 2.70 (s, 2H), 2.59 – 2.45 (m, 3H), 2.34 (dddd, *J* = 17.0, 10.8, 5.8, 2.9 Hz, 1H).

General Procedure B: Alkylation of β-ketoesters.



100 ***93***

A flame dried flask was charged with NaH (60% dispersion in mineral oil, 1.2 equiv) and THF (0.3 M) and cooled to 0 ºC. β-ketoester **100** (1 equiv) was added dropwise (dissolved in minimal THF if necessary) and the resulting solution was stirred for 1 h. Benzyl bromide (1.5 equiv) was added dropwise, and the reaction was slowly heated to 40 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction mixture was cooled to 0 ºC and diluted with a saturated solution of NH_4Cl and extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product (**93**) was purified by silica gel flash column chromatography.

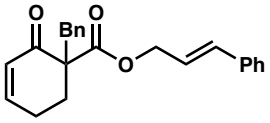


92

allyl 1-benzyl-2-oxocyclohex-3-ene-1-carboxylate (93)

Prepared from allyl 2-oxocyclohex-3-ene-1-carboxylate [6] (**100**) following General Procedure B. Purification by flash column chromatography (10% EtOAc/hexanes) afforded the title compound as a colorless oil (533 mg, 1.97 mmol, 71% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.21 (m, 3H), 7.18 – 7.14 (m, 2H), 6.88 (dt, *J* = 8.6, 3.0 Hz, 1H), 6.10 – 6.03 (m, 1H), 5.85 (ddt, *J* = 16.3, 10.8, 5.6 Hz, 1H), 5.28 (d, *J* = 17.2 Hz, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 4.64 – 4.54 (m, 2H), 3.26 (s, 2H), 2.57 – 2.46 (m, 1H), 2.39 (dt, *J* = 13.8, 3.9 Hz, 1H), 2.35 – 2.24 (m, 1H), 1.84 (ddd, *J* = 13.9, 10.2, 5.3 Hz, 1H).



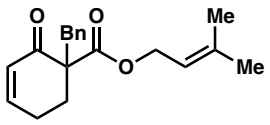
96

cinnamyl 1-benzyl-2-oxocyclohex-3-ene-1-carboxylate (96)

Prepared from cinnamyl 2-oxocyclohex-3-ene-1-carboxylate **73** following General Procedure B. Purification by flash column chromatography (10% EtOAc/hexanes) afforded the title compound as a colorless oil (216 mg, 0.62 mmol, 31% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.0 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 3H), 7.17 (dd, *J* = 7.7, 1.9 Hz, 2H), 6.91 – 6.85 (m, 1H), 6.62 (d, *J* = 15.9 Hz, 1H), 6.21 (dt, *J* = 15.8, 6.4 Hz, 1H), 6.08 (ddd, *J* = 10.1, 2.7, 1.4 Hz, 1H), 4.75 (dt, *J* = 6.5, 1.3 Hz, 2H), 3.32 (d, *J* = 13.7 Hz, 1H), 3.24 (d, *J* = 13.7 Hz, 1H),

2.59 – 2.47 (m, 1H), 2.41 (dt, *J* = 13.6, 4.0 Hz, 1H), 2.35 – 2.25 (m, 1H), 1.85 (ddd, *J* = 13.7, 10.2, 5.4 Hz, 1H).



97

3-methylbut-2-en-1-yl 1-benzyl-2-oxocyclohex-3-ene-1-carboxylate (97)

Prepared from 3-methylbut-2-en-1-yl 2-oxocyclohex-3-ene-1-carboxylate **70** following General Procedure B. Purification by flash column chromatography (10–15% EtOAc/hexanes) afforded the title compound as a colorless oil (3.35 g, 11.2 mmol, 74% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.20 (m, 3H), 7.17 – 7.14 (m, 2H), 6.86 (dddd, *J* = 10.1, 5.3, 2.6, 1.3 Hz, 1H), 6.05 (ddd, *J* = 10.1, 2.8, 1.4 Hz, 1H), 5.28 (tdt, *J* = 7.2, 2.9, 1.4 Hz, 1H), 4.62 (ddt, *J* = 12.2, 7.2, 0.9 Hz, 1H), 4.55 (ddt, *J* = 12.3, 7.2, 0.9 Hz, 1H), 3.26 (d, *J* = 13.7 Hz, 1H), 3.22 (d, *J* = 13.7 Hz, 1H), 2.55 – 2.46 (m, 1H), 2.36 (dddd, *J* = 13.7, 5.0, 2.8, 1.3 Hz, 1H), 2.31 – 2.23 (m, 1H), 1.81 (ddd, *J* = 13.7, 10.3, 5.3 Hz, 1H), 1.76 (q, *J* = 1.1 Hz, 3H), 1.69 (d, *J* = 1.3 Hz, 3H).

A2.5 REFERENCES AND NOTES

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(2) Streuff, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. A Palladium-Catalysed Enolate Alkylation Cascade for the Formation of Adjacent Quaternary and Tertiary Stereocentres. *Nat. Chem.* **2010**, *2*, 192–196.

(3) Relative and absolute stereochemistry of the product diastereomers (**92-d1** and **92-d2**) was not determined.

(4) Pangborn, A. M.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. Safe and Convenient Procedure for Solvent Purification. *Organometallics* **1996**, *15*, 1518–1520.

(5) McDougal, N. T.; Streuff, J.; Mukherjee, H.; Virgil, S. C.; Stoltz, B. M. Rapid Synthesis of an Electron-deficient *t*-BuPHOX Ligand: Cross-coupling of Aryl Bromides with Secondary Phosphine Oxides. *Tetrahedron Lett*. **2010**, *51*, 5550–5554.

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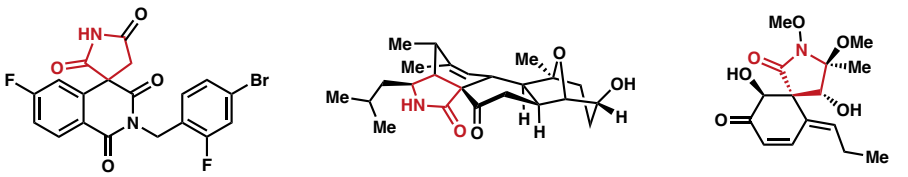
CHAPTER 2

An Enantioselective Spirocyclization of Pd Enolates and Isocyanates†

2.1 INTRODUCTION

Since their first description by von Baeyer over 120 years ago,[1] spirocyclic compounds have found widespread utility as chiral ligands,[2] pharmaceuticals,[3] and optoelectronic materials.[4] Spirocyclic frameworks are also found within nature and feature in a variety of bioactive natural products.[5] Due to their inherently high Fsp^3, or fraction of sp^3 carbon atoms, and their ability to project functionality along multiple distinct spatial vectors, spiranes are of increased interest in modern medicinal chemistry campaigns.[3] While the development of new stereoselective methods for the construction of spirocyclic compounds remains an ongoing challenge, many new asymmetric technologies have been developed for the synthesis of spirocyclic oxindoles.[5] In comparison, there are far fewer asymmetric methods for the synthesis of saturated spirocyclic γ-lactams, despite the prevalence of this motif in a range of biologically active small molecules and natural products (Figure 2.1).[6,7]

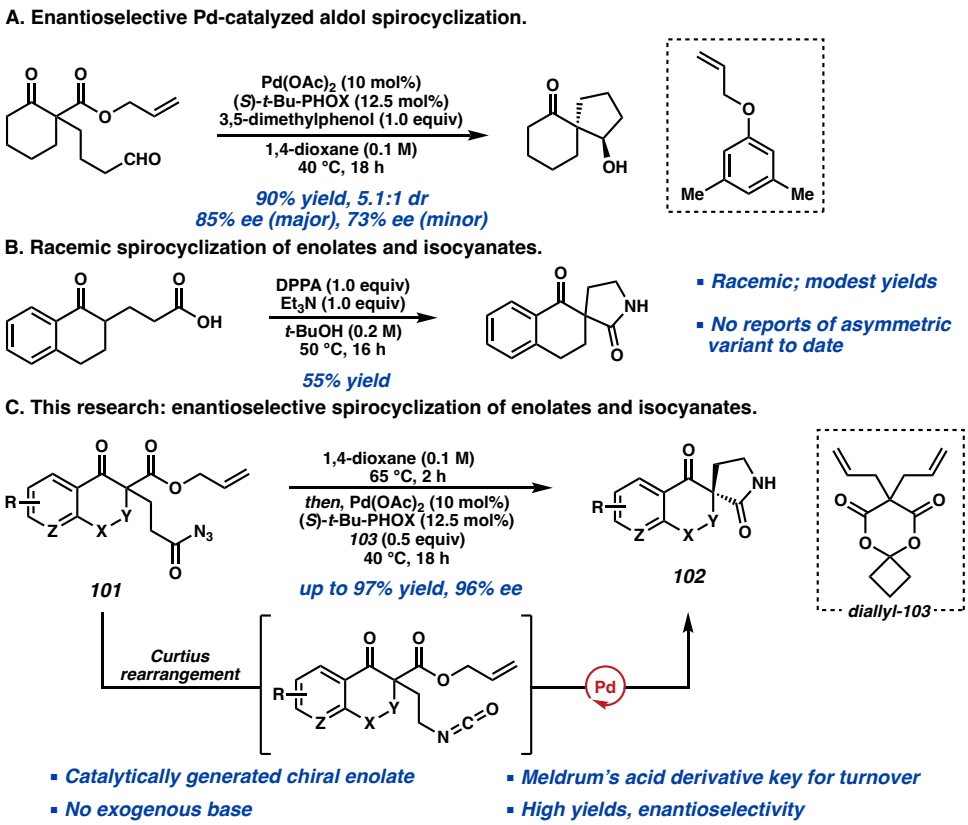
Figure 2.1. *Natural products and pharmaceuticals bearing a spirocyclic lactam.*



†This research was performed in collaboration with Barbor, J. P.; Chan, M.; Ang, H. R. Portions of this chapter have been reproduced with permission from Stoltz, et al. *Angew. Chem. Int. Ed.* **2025**, e202502583.

In 2020, our group disclosed an enantioselective Pd-catalyzed aldol cyclization, enabling the general asymmetric construction of spiranes bearing a 1,3-dioxygenation pattern (Scheme 2.1A).[8] Following decarboxylative enolate formation, chiral Pd enolates can undergo an intramolecular aldol cyclization, which upon further oxidation delivers a variety of 1,3-diketospiranes in good yields and enantioselectivity. Bronsted acidic additives, namely phenols, were found to be essential for catalyst turnover, serving as a proton-donor for the putative Pd-alkoxide and facilitating Pd reduction by trapping the allyl group. Following this report, we sought to expand this strategy toward other classes of electrophiles and hypothesized that we may be able to achieve similar success with isocyanates, enabling access to chiral spirocyclic lactams.

Scheme 2.1. *Construction of spiranes via enolate addition.*



An uncatalyzed and racemic variant of our targeted reaction was reported by Xue and coworkers in 2015 (Scheme 2.1B).[9] Upon treatment with DPPA and triethylamine, δ-keto acids could undergo a Curtius rearrangement and subsequent nucleophilic cyclization, delivering spirocyclic lactams in modest to good yields. Within the context of catalysis, isocyanates are well-precedented to undergo a variety of polymerization reactions in the presence of transition metal catalysts,[10] and there is a well-established body of literature pertaining to the reactions of isocyanates with Pd π-allyl intermediates.[11] However, there appears to be a general lack of research into controlled, stereoselective additions of metal enolates and isocyanates. In fact, we have been unable to find any general reports detailing the stereoselective addition of an enolate to an isocyanate,[12] which we attribute to the unforgiving propensity of isocyanates to decompose or self-condense and their inherent incompatibility with many strong bases.[10c] Given the mild, base-free, and regiospecific nature under which we can generate chiral Pd enolates from allyl β-keto esters, we envisioned that this decarboxylative enolate formation would be an appropriate manifold for the development of a general asymmetric spirocyclization of Pd enolates and isocyanates (Scheme 2.1C).

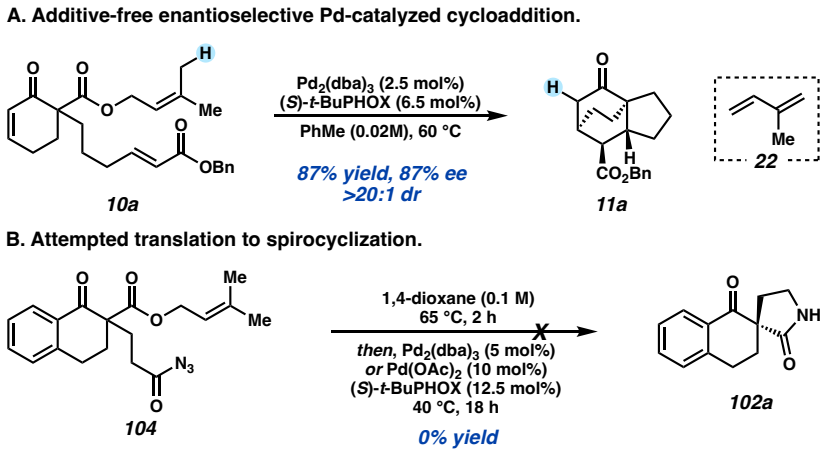
2.2 RESULTS AND DISCUSSION

2.2.1 REACTION DESIGN AND OPTIMIZATION

Inspired by a recent disclosure from our group, we decided to first explore reactivity with a prenyl β-keto ester. In 2023, our group reported an asymmetric decarboxylative Pd-catalyzed [4+2] cycloaddition (see Chapter 1).[13] Rather than adding an exogenous additive, we found that use of a prenylated β-keto ester enabled proton-transfer from the prenyl

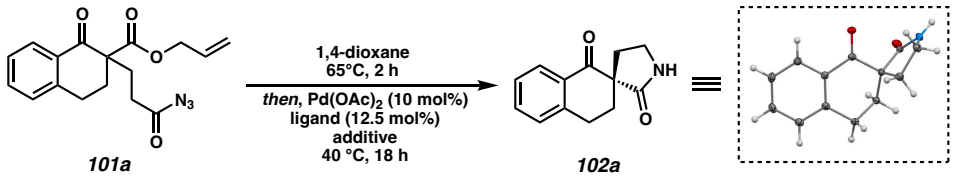
group following cycloaddition, generating isoprene and turning over the catalytic cycle (Scheme 2.2A). Unfortunately, subjecting prenylated starting material **104** to a Curtius rearrangement followed by treatment with a Pd/PHOX catalyst resulted in a complex mixture of undesired byproducts (Scheme 2.2B).

Scheme 2.2. *Attempted additive-free spirocyclization.*

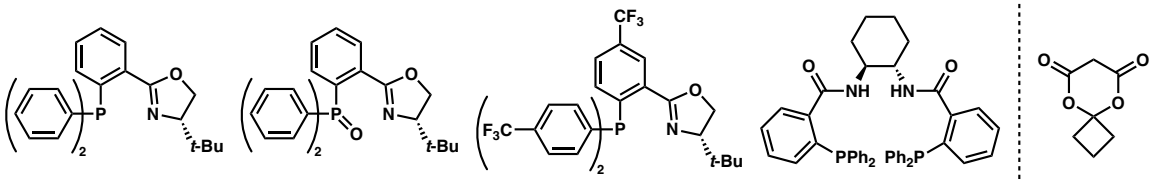


Alternatively, Curtius rearrangement of allyl β-keto ester **101a** followed by treatment with a Pd/PHOX catalyst generated the desired product **102a** in 89% ee, albeit in a modest 10% yield (Table 2.1, entry 1). Akin to the previously developed aldol spirocyclization, we did not observe reductive elimination of the allyl group onto the amidate following cyclization.[8] Unable to force reductive elimination of the allyl, we decided to explore alternative strategies to achieve turnover.

Table 2.1. *Reaction optimization.*[a]



Entry	Ligand	Additive	Result
1	(*S*)-*t*-Bu-PHOX	–	10% yield, 89% ee
2	(*S*)-*t*-Bu-PHOX	phenol (1.0 equiv)	17% yield, 39% ee
3	(*S*)-*t*-Bu-PHOX	Meldrum's acid (0.5 equiv)	59% yield, 93% ee
4	(*S*)-*t*-Bu-PHOX	Meldrum's acid (1.0 equiv)	19% yield, 85% ee
5	(*S*)-*t*-Bu-PHOX	dimedone (0.5 equiv)	43% yield, 31% ee
6	(*S*)-*t*-Bu-PHOX	acacH (0.5 equiv)	32% yield, 58% ee
7	(*S*)-*t*-Bu-PHOX	*103* (0.5 equiv)	99(93[b])% yield, 96% ee
8	(*S*)-$(CF_3)_3$-*t*-Bu-PHOX	*103* (0.5 equiv)	89% yield, 83% ee
9	(*S*,*S*)-DACH-Ph	*103* (0.5 equiv)	99% yield, 10% ee
10[c]	(*S*)-*t*-Bu-PHOX	*103* (0.5 equiv)	85% yield, 98% ee

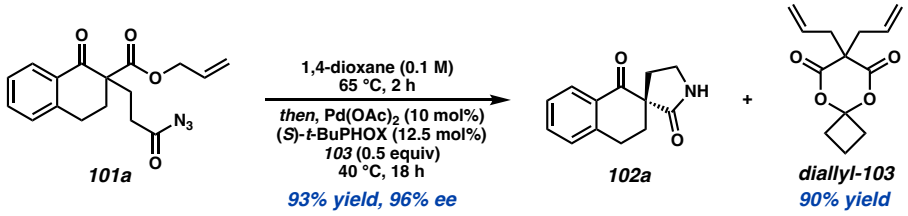


[a] Reactions performed on 0.05 mmol scale and yields determined by ^{1}H NMR integration against an internal standard (1,3,5-trimethoxybenzene). [b] 0.2 mmol scale, isolated yield. [c] 1.0 mmol scale, isolated yield.

Drawing inspiration from the previously developed aldol spirocyclization, we decided to explore phenol as an additive.[8] Predictably, inclusion of phenol in this reaction generated significant amounts of carbamate side products, with only a marginally improved 17% yield of our desired product (Table 2.1, entry 2).[14,15] Pursuing alternative additives that may be less reactive toward the isocyanate, we decided to assess the use of Meldrum's acid, as we have previously demonstrated that this additive can be used for enantioselective protonation.[16] Gratifyingly, inclusion of 50 mol% of Meldrum's acid delivered a 59% yield

of product **102a** in 93% ee, highlighting that cyclization to form the γ-lactam kinetically outcompetes protonation of the enolate (Table 2.1, entry 3). Increasing equivalents of Meldrum's acid resulted in lower conversion (Table 2.1, entry 4). Use of similar 1,3-dicarbonyl compounds, like dimedone or acacH, also resulted in poorer reaction performance, with the ee of the product dropping significantly (Table 2.1, entries 5 and 6); however, use of Meldrum's acid derivative **103** resulted in near quantitative yield of the desired product and excellent 96% ee (Table 2.1, entry 7).[17] On 0.2 mmol scale, 90% of **103** added to the reaction could be reisolated as the diallylated byproduct (**diallyl-103**), confirming the ultimate fate of **103** and the allyl group (Scheme 2.3).

Scheme 2.3. *Isolation of reaction byproduct.*



(*S*)-*t*-Bu-PHOX was found to be the optimal ligand for this transformation, with a more electron-deficient PHOX ligand or DACH-Ph affording diminished ee (Table 2.1, entry 8, 9). Additionally, we were pleased to find that the reaction also performs well on scale, with a 1.0 mmol scale reaction generating an 85% yield of product with 98% ee (Table 2.1, entry 10).

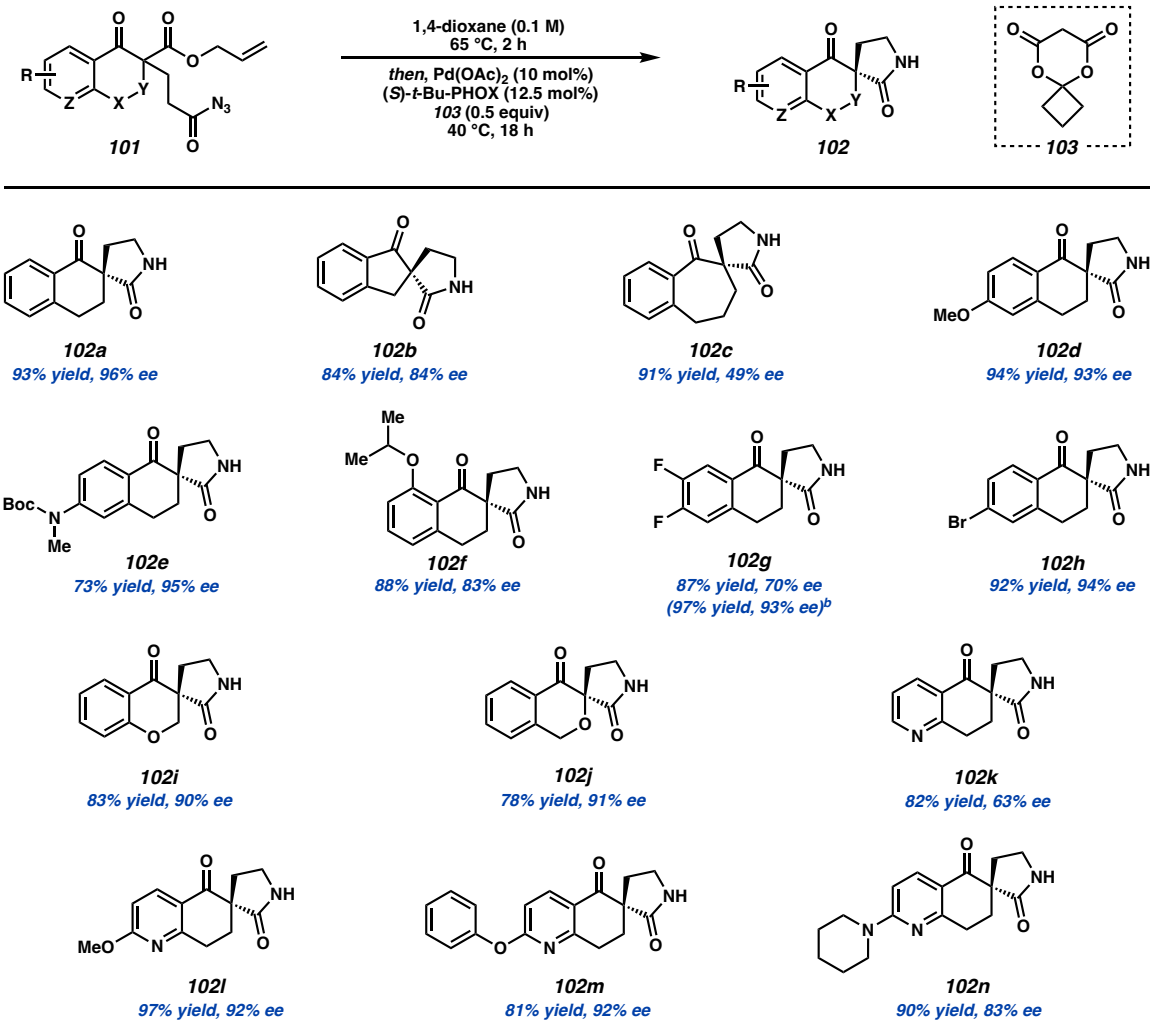
2.2.2 SUBSTRATE SCOPE

With optimized reaction conditions in hand, we explored the scope of the transformation (Scheme 2.4). Ring contraction from the model system to an indanone derived substrate (**102b**) was well tolerated. Ring-expanded benzosuberone product **102c**

was formed in an excellent 91% yield, albeit in a diminished 49% ee. Electron donating groups para to the ketone performed well (**102d** and **102e**). Additionally, incorporation of an *ortho*-isopropyl ether (**102f**) was successful, demonstrating that this reaction can accommodate a moderate amount of steric bulk near the ketone. Gratifyingly, a compound bearing an aryl bromide can withstand the reaction conditions without any evidence of protodehalogenation, generating **102h** in 92% yield and 94% ee. Heterocyclic chromanone **102i** and isochromanone **102j** were also competent substrates. Saturated ketone, α,β-unsaturated ketone, or *N*-benzoylated lactam starting materials all furnished product in good to excellent yield but suffered from low enantioselectivity under these reaction conditions (See Section 2.4.1 Materials and Methods, Scheme S2.7).

Although di-fluorinated (**102g**) and pyridine-containing (**102k**) compounds were able to be synthesized in excellent yields, the ee of these products was notably diminished. Increasing electron density by substitution of the pyridine derivative with a methoxy (**102l**), phenoxy (**102m**), or piperidine (**102n**) allowed for the synthesis of these complex heterocyclic spiranes in excellent yields and enantioselectivities. Given the overall trends of the scope of this reaction, we postulate that it is necessary for substrates to be electron rich to obtain products with high ee using (*S*)-*t*-Bu-PHOX. Excitingly, **102g** could be synthesized in 97% yield and 93% ee with the more electron-deficient (*S*)-$(CF_3)_3$-*t*-Bu-PHOX, indicating that further tuning of the catalyst can potentially improve the performance of this reaction across electronically diverse substrates.[18]

Scheme 2.4. *Reaction scope.*[a]



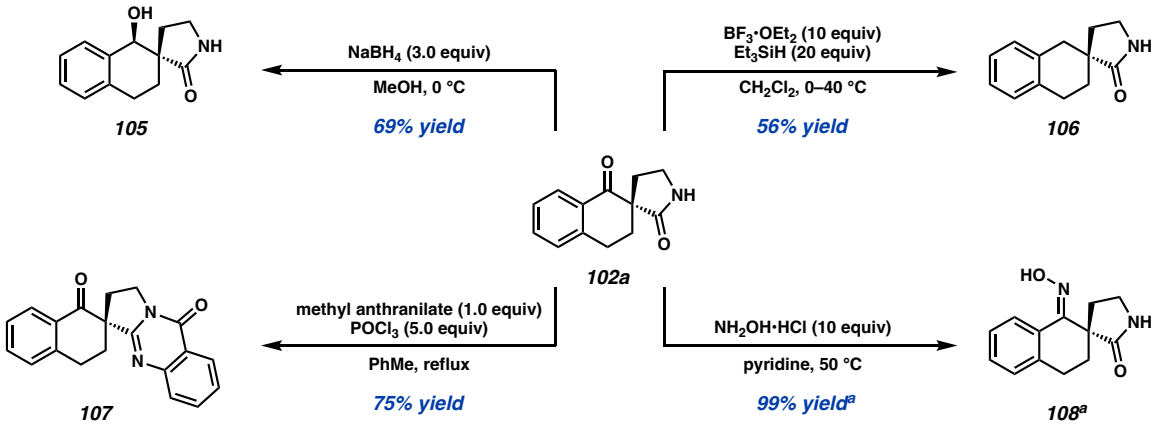
[a] Reactions performed on 0.2 mmol scale, isolated yield. [b] Reaction performed on 0.05 mmol scale with (*S*)-$(CF_3)_3$-*t*-Bu-PHOX, isolated yield.

2.2.3 PRODUCT DERIVATIZATIONS

To highlight the utility of these spirocyclic compounds, we explored various transformations to further diversify the products obtained from the reaction (Scheme 2.5). Diastereoselective reduction of the ketone with $NaBH_4$ to alcohol **105** can be achieved in 69% yield and >20:1 dr. Selective ketone reduction with BF_3•Et_2O and Et_3SiH yielded

lactam **106** in 56% yield. Owing to the fact that this reaction affords unprotected lactam products, **102a** could directly undergo a heterocyclic annulation to deliver pentacyclic pyrimidone **107** in 75% yield. Furthermore, oxime **108** can be selectively formed as a single stereoisomer in 99% yield.

Scheme 2.5. *Product derivatizations.*

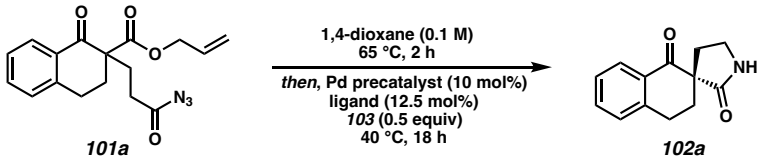


[a] Oxime geometry not determined.

2.2.4 MECHANISTIC STUDIES

Throughout the development of this reaction, we observed a stark correlation between the choice of Pd-precatalyst and enantioselectivity (Table 2.2). Interestingly, use of $Pd_2(dba)_3$ in place of $Pd(OAc)_2$ under otherwise identical reaction conditions affords a similarly excellent yield of product but with a severely diminished 15% ee (Table 2.2, entries 1 and 2). To further probe this effect, we first explored the impact of the ancillary ligands for each of these precatalysts.

Table 2.2. *Investigation of reaction dependence on Pd-precatalyst.*[a]



101a ***102a***

Entry	Pd Precatalyst	Ligand	Additive	Yield (%)	ee (%)
1	$Pd(OAc)_2$	(*S*)-*t*-Bu-PHOX	—	99	96
2[b]	$Pd_2(dba)_3$	(*S*)-*t*-Bu-PHOX	—	99	15
3[b]	$Pd_2(dba)_3$	(*S*)-*t*-Bu-PHOX	[N(*n*-Bu)$_4$]OAc (20 mol%)	94	3
4	$Pd(dba)_2$	(*S*)-*t*-Bu-PHOX	—	97	15
5	[Pd((*S*)-*t*-BuPHOX)dba]	—	—	98	11
6	$Pd(OAc)_2$	(*S*)-*t*-Bu-PHOX/ (*S*)-*t*-Bu-PHOX=O (1:1)	—	39	83
7[c]	$Pd(OAc)_2$	(*S*)-*t*-Bu-PHOX	—	94	84
8	$Pd(OAc)_2$	(*S*)-*t*-Bu-PHOX (40 mol%)	—	19	90
9	$Pd(TFA)_2$	(*S*)-*t*-Bu-PHOX	—	9	76
10	$Pd(TFA)_2$ (8 mol%)/ $Pd_2(dba)_3$ (1 mol%)	(*S*)-*t*-Bu-PHOX	—	96	74

[a] Reactions performed on 0.05 mmol scale and yields determined by ^{1}H NMR integration against an internal standard (1,3,5-trimethoxybenzene). [b] 5 mol% $Pd_2(dba)_3$. [c] O_2 balloon.

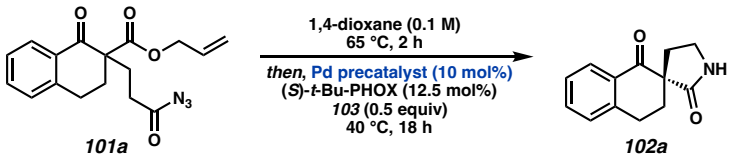
Addition of acetate in the form of [N(*n*-Bu)$_4$]OAc to a reaction utilizing $Pd_2(dba)_3$ did not restore ee (Table 2.2, entry 3); likewise, alteration of the amount of dibenzylideneacetone (dba) did not have any significant impact on reaction performance (Table 2.2, entries 4 and 5), indicating that neither of these ancillary ligands alter the enantioselectivity of the reaction. Because reduction of $Pd(OAc)_2$ to Pd(0) with a phosphine ligand necessitates the formation of the corresponding phosphine oxide with adventitious water,[19] we were curious if the oxidized variant of our ligand played a supporting role in the reaction mechanism. Yet, utilizing a 1:1 ratio of (*S*)-*t*-Bu-PHOX to the phosphine oxide derivative, (*S*)-*t*-Bu-PHOX=O, resulted in diminished product ee and significant unreacted starting material (Table 2.2, entry 6), eliminating the possibility that (*S*)-*t*-Bu-PHOX=O might serve some beneficial function as a supporting ligand.

We were surprised that use of such a small excess of PHOX ligand with $Pd(OAc)_2$ afforded product in both high yield and ee, as typically, full reduction of $Pd(OAc)_2$ to Pd(0) requires three to four times the amount of phosphine relative to Pd(II),[16] and previous research within our group has demonstrated that a 1:4 ratio of $Pd(OAc)_2$ to PHOX ligand is required for high enantioselectivity in allylic alkylation reactions utilizing $Pd(OAc)_2$.[20] To probe whether this reaction might be a Pd(II)-only mechanism, we performed an experiment with an O_2 balloon (Table 2.2, entry 7). While we only obtained a 19% yield of product, indicating that the reaction is likely not a Pd(II)-only mechanism, we observed a similar 90% ee. Conversely, increasing equivalents of (*S*)-*t*-BuPHOX in an effort to force the reduction of $Pd(OAc)_2$ to Pd(0) resulted in diminished ee (Table 2.2, entry 8).

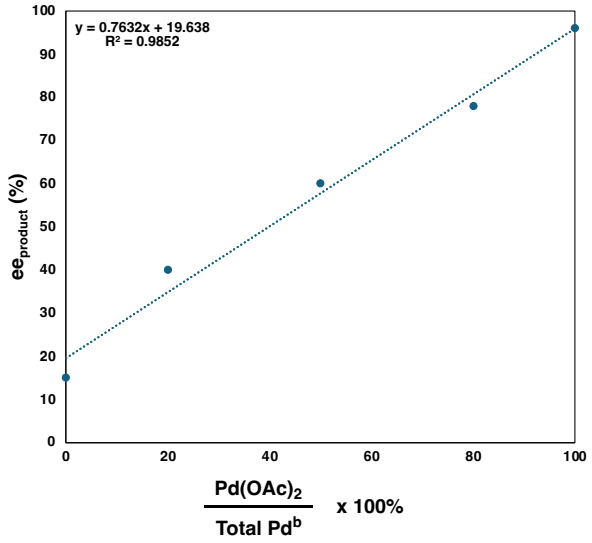
We decided to survey alternative Pd(II) precatalysts that might also be effective, and we found that while $Pd(TFA)_2$ alone affords only a 9% yield of product, enantioselectivity was improved to 76% ee as compared to the nearly racemic $Pd_2(dba)_3$ reactions (Table 2.2, entry 9). Curiously, replacing a small amount of the total palladium loading with $Pd_2(dba)_3$ restored the yield to 96% while maintaining 74% ee (Table 2.2, entry 10). To explore this effect further, we mixed varying amounts of $Pd(OAc)_2$ and $Pd_2(dba)_3$, keeping the total Pd concentration at 10 mol%, and we observed a nearly linear relationship between increased $Pd(OAc)_2$ loading and product ee (Table 2.3). In a more traditional nonlinearity experiment,[21] we observed a negative nonlinear effect (Table 2.4). Taken together, we posit that it is mechanistically important for some amount of Pd(II) to be present in the reaction mixture to obtain product with high ee, and these findings implicate the formation of catalytically relevant higher-order species. These results suggest

a remarkable mechanistic departure from previously studied decarboxylative Pd enolate reactions and warrant further investigation to determine if this pathway is more generalizable.

Table 2.3. *Exploration of mixed precatalysts.*[a]

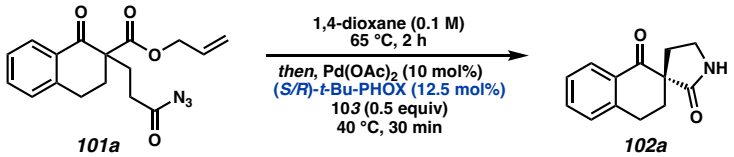


Entry	$Pd(OAc)_2$ (mol%)	$Pd_2(dba)_3$ (mol%)	Yield (%)	ee (%)
1	0	5	99	15
2	2	4	95	40
3	5	2.5	96	60
4	8	1	98	78
5	10	0	99	96

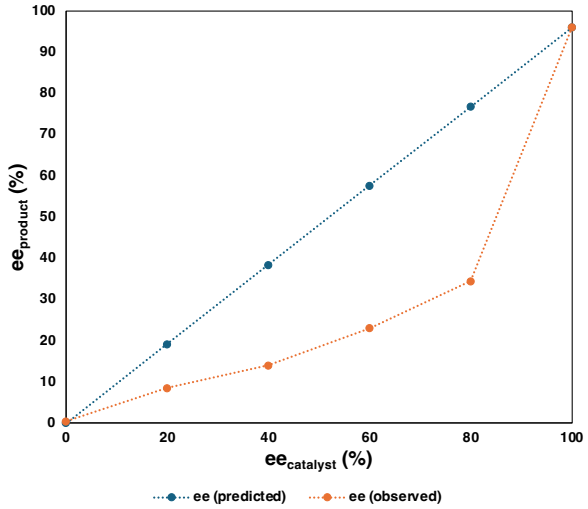


[a] Reactions performed on 0.05 mmol scale and yields determined by ^{1}H NMR integration against an internal standard (1,3,5-trimethoxybenzene). [b] Total Pd is the molar amount of Pd by combination of $Pd(OAc)_2$ and $Pd_2(dba)_3$.

Table 2.4. *Nonlinearity experiment.*[a]



Entry	ee_{cat} (%)	$ee_{predicted}$ (%)	$ee_{observed}$ (%)
1	100	96	96
2	80	77	34
3	60	58	23
4	40	38	14
5	20	19	9
6	0	0	0



[a] Reactions performed on 0.05 mmol scale and yields determined by ^{1}H NMR integration against an internal standard (1,3,5-trimethoxybenzene).

2.3 CONCLUSIONS

In conclusion, we have developed a novel asymmetric cyclization of isocyanates and Pd enolates for the synthesis of spirocyclic γ-lactams. To the best of our knowledge, this transformation is the first example of an asymmetric enolate addition to an isocyanate. This reaction tolerates a variety of functional groups, including aryl bromides and electron-rich heterocyclic motifs. The importance of the Pd(II) precatalyst was explored through

preliminary mechanistic investigations, which revealed both a negative non-linear effect and strong correlation between the presence of Pd(II) in the reaction and high enantioselectivity. In the future, we intend to perform additional mechanistic studies, both kinetic and computational, to obtain a deeper understanding of this unusual catalytic cycle. Ultimately, we aim to leverage these findings for the development of new reactions derived from this decarboxylative Pd enolate formation.

2.4 EXPERIMENTAL SECTION

2.4.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under a nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[22] 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, iodine, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) was used for silica gel flash chromatography. Teledyne Isco RediSep Gold High Performance C18 columns were used for reverse phase flash chromatography. ^{1}H NMR spectra were recorded on Bruker 400 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer (101 MHz) and are reported relative to residual $CHCl_3$ (δ 77.16 ppm).^{19}F NMR spectra were recorded on a Varian Mercury 300 MHz spectrometer (282 MHz) and referenced to an external standard (hexafluorobenzene; ^{19}F NMR (282 MHz, $CDCl_3$) δ -161.64.[23] Data for ^{1}H 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. Data for ^{13}C NMR, ^{11}B and ^{19}F NMR are reported in terms of chemical shifts (δ ppm). 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. Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system or an Agilent 1260 Infinity II supercritical CO_2 analytical chromatography system utilizing utilizing Chiralpak (IC-3, AD-3, ID- 3, IF-3, IG-3, IH-3) or Chiralcel (OD-3, OJ-3) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Center for Catalysis and Chemical Synthesis, using an Agilent 6230 Series TOF LC/MS with an Agilent Jet Stream source in electrospray mode (ESI), and the Caltech Mass Spectral Facility, using a JEOL JMS-T2000 AccuTOF GC-Alpha time-of-flight mass spectrometer using Field Desorption (FD) ionization (ions detected are $M^{+\bullet}$). The Caltech Chemistry Division Mass Spectrometry laboratory acknowledges DOW Chemical Company (DOW Next Generation Instrumentation Grant) and the NSF CRIF program for providing funds that enabled the purchase of this instrumentation.

Low-temperature diffraction data (f-and w-scans) were collected on a Bruker AXS D8 VENTURE KAPPA diffractometer coupled to a PHOTON II CPAD detector with Cu K_a radiation (l = 1.54178 Å) from an IμS micro-source for the structures of compounds V21281, V22396, and V22221. The structure was solved by direct methods using SHELXS[24] and refined against F^2 on all data by full-matrix least squares with SHELXL-2017 or SHELXL-2019[25] using established refinement techniques.[26] 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).

Reagents were purchased from commercial sources and used as received unless otherwise stated. Compound **103** was prepared according to a literature procedure.[27]

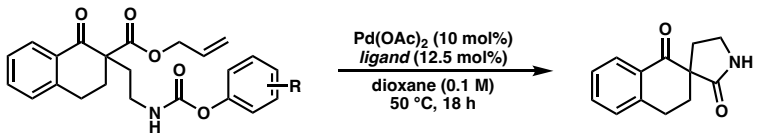
List of Abbreviations

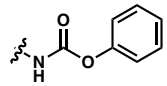
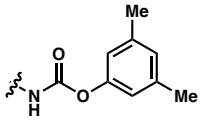
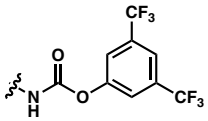
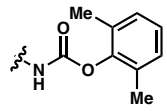
TLC – thin-layer chromatography, ee – enantiomeric excess, SFC – supercritical fluid chromatography, LDA – lithium diisopropylamide, ethyl acetate – ethyl acetate, TFA – trifluoroacetic acid, THF – tetrahydrofuran, MeCN – acetonitrile, IPA – isopropanol, MeOH – methanol

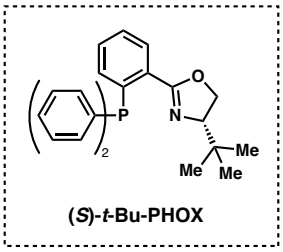
2.4.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

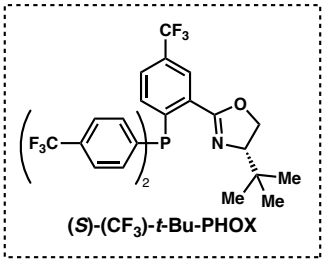
Additional Optimization Data

Table 2.5. *Assessment of alternative carbamate electrophiles.*[a]



substrate	(*S*)-*t*-Bu-PHOX	(*S*)-(CF$_3$)-*t*-Bu-PHOX
	*15% yield* *46% ee*	*0% yield*
	*trace yield* *ND ee*	*0% yield*
	*16% yield* *32% ee*	*64% yield* *14% ee*
	*trace yield* *ND ee*	*0% yield*

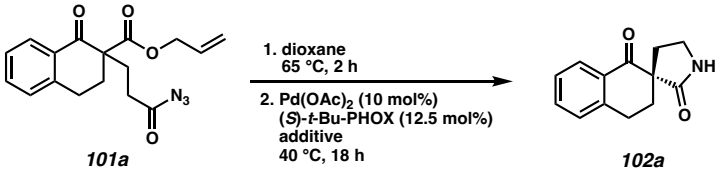




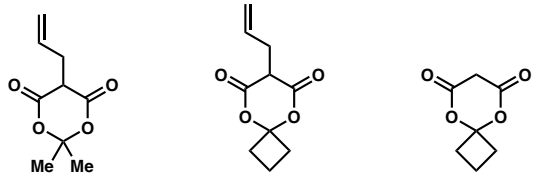
[a] Yields determined by ^{1}H NMR integration against an internal standard.

Note: adding various bases to encourage blocked isocyanate reactivity was unsuccessful;[28] in a few instances, we observed improved enantioselectivity that was found to be irreproducible.

Table 2.6. *Assessment of alternative additives.*[a]

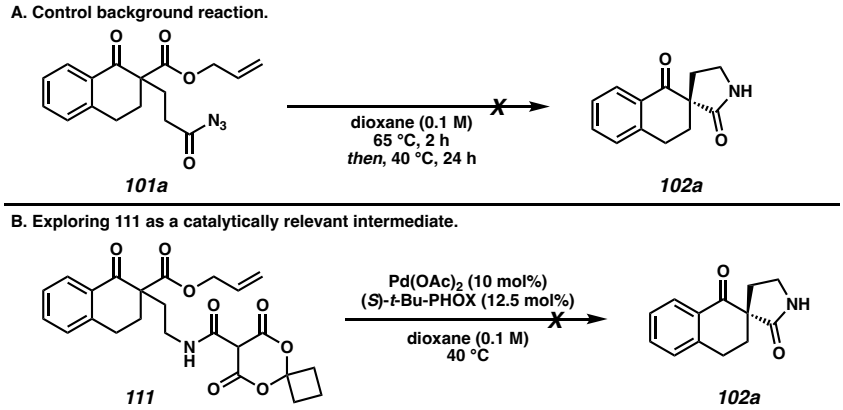


entry	additive	result
1	acac	32% yield, 58% ee
2	dimethyl malonate	0% yield, ND ee
3	methylsulfonylacetone	0% yield, ND ee
4	*109* (1.0 equiv)	98% yield, 54% ee
5	*110* (1.0 equiv)	91% yield, 57% ee
6	*103* (1.0 equiv)	93% yield, 92% ee

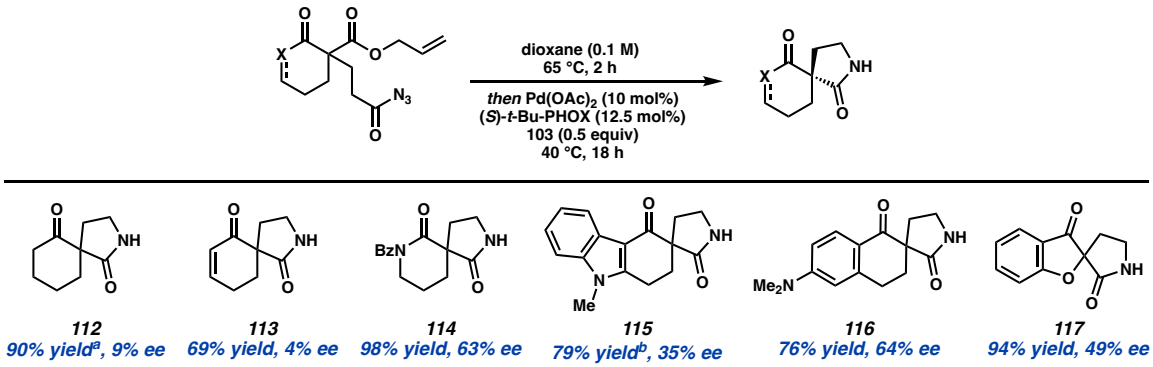


[a] Yields determined by ^{1}H NMR integration against an internal standard.

Scheme 2.6. *Control reactions.*

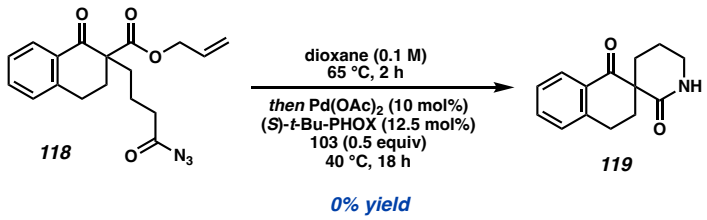


Scheme 2.7. *Failed substrates.*



[a] Yield determined by ^{1}H NMR integration against internal standard (1,3,5-trimethoxybenzene); **112** was found to be volatile. [b] Reaction performed at 50 °C.

Scheme 2.8. *Failed δ-lactam synthesis.*[a]

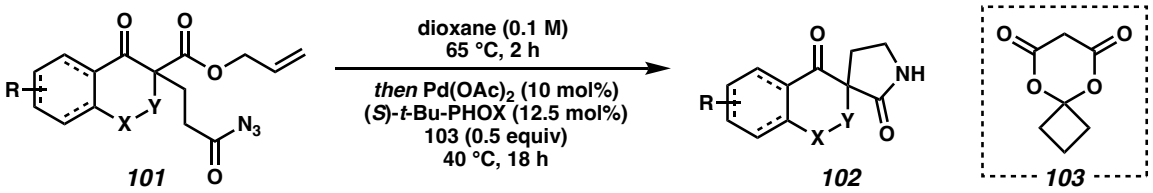


[a] Reaction performed on 0.05 mmol scale.

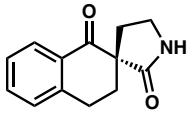
Note: only protonation of the enolate was observed; isocyanate unstable to characterization, confirmed identity via IR.

Pd-Catalyzed Decarboxylative Spirocyclization

General Procedure A: *Asymmetric Pd-Catalyzed Decarboxylative Spirocyclization*



In a nitrogen-filled glovebox, an oven-dried 2-dram vial was charged with a stir bar, **101** (0.2 mmol), and dioxane (0.8 mL, 0.25 M). The vial was sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 65 °C. After 2 h, the solution was cooled and pumped into the glovebox. To a separate oven-dried 2-dram vial, $Pd(OAc)_2$ (0.02 mmol, 10 mol%) and (*S*)-*t*-Bu-PHOX (0.025 mmol, 12.5 mol%) was taken up in dioxane (0.8 mL, 0.25 M) and stirred at 23 °C for 20 minutes. The reaction vial is charged with a solution of **103** (0.1 mmol, 0.5 equiv) in dioxane (0.4 mL, 0.5 M) and the Pd stock solution (0.8 mL), sealed, removed from the glovebox, and heated to 40 °C for 18 h. The reaction mixture was then cooled, concentrated under reduced pressure, and purified on silica gel chromatography to afford product **102**.



102a

3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-1,2'-dione (102a)

Prepared from **101a** following General Procedure A. Purification by flash column chromatography (0–10% acetone/dichloromethane) afforded the title compound as a light yellow solid (40.0 mg, 0.19 mmol, 93% yield, 96% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.49 (td, *J* = 7.5, 1.5 Hz, 1H), 7.42 – 7.29 (m, 1H), 7.25 (d, *J* = 7.1 Hz, 1H), 6.42 (s, 1H), 3.51 (dt, *J* = 9.7, 7.5 Hz, 1H), 3.45 – 3.36 (m, 1H), 3.29 (ddd, *J* = 16.8, 6.5, 4.7 Hz, 1H), 2.96 (ddd, *J* = 16.9, 9.4, 4.7 Hz, 1H), 2.61 (m, 2H), 2.19 – 2.02 (m, 2H).

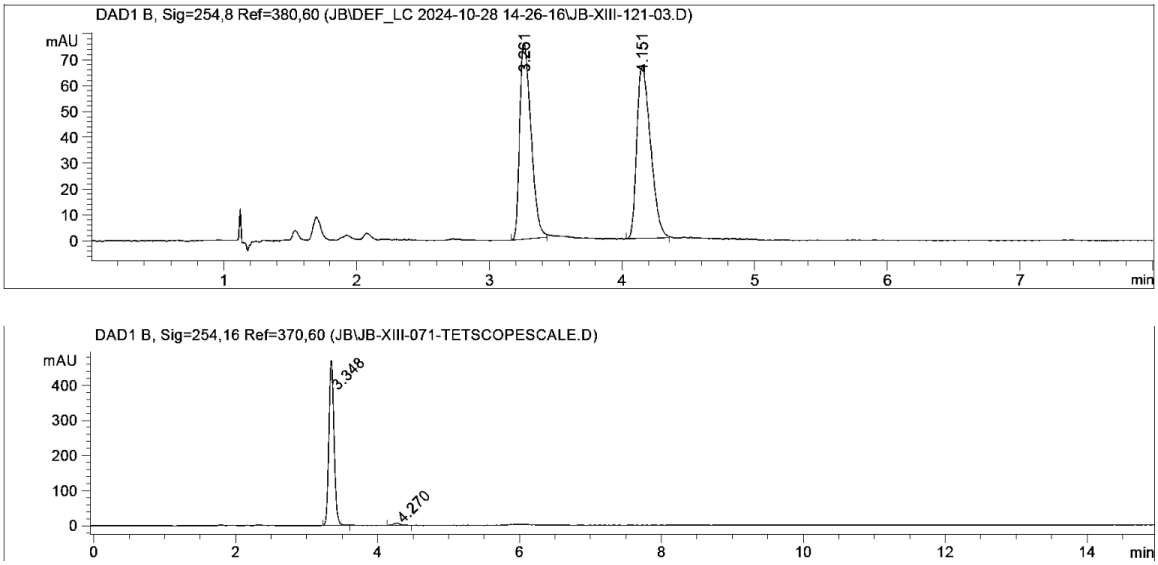
^{13}C NMR (100 MHz, $CDCl_3$): δ 196.5, 177.1, 144.0, 134.0, 131.1, 128.8, 128.3, 127.0, 55.1, 39.5, 32.0, 31.4, 25.7.

IR (neat film, NaCl): 3238, 1701, 1570, 1598, 1360, 1290, 1229, 1071 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{13}H_{14}NO_2$ $[M+H]^+$: 216.1019, found 216.1018.

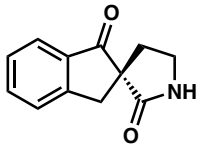
Optical Rotation: $[\alpha]_D^{24}$ = 82.20 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 3.35, t_R (min): minor = 4.27.



```
Signal 2: DAD1 B, Sig=254,16 Ref=370,60

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   3.348 BB    0.0795 2394.81299  469.36411  98.2383
   2   4.270 BB    0.1104   42.94566    6.08255   1.7617
```



102b

spiro[indene-2,3'-pyrrolidine]-1,2'(3*H*)-dione (102b)

Prepared from **101b** following General Procedure A. Purification by flash column chromatography (0–50% ethyl acetate/dichloromethane) afforded the title compound as a light yellow solid (33.8 mg, 0.17 mmol, 84% yield, 81% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.7 Hz, 1H), 7.61 (td, *J* = 7.4, 1.3 Hz, 1H), 7.48 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.43 – 7.34 (m, 1H), 6.65 (s, 1H), 3.81 – 3.68 (m, 2H), 3.41 (tdd, *J* = 9.1, 3.0, 1.1 Hz, 1H), 2.99 (d, *J* = 17.1 Hz, 1H), 2.63 (ddd, *J* = 12.9, 7.6, 3.0 Hz, 1H), 2.25 (ddd, *J* = 12.8, 8.8, 7.9 Hz, 1H).

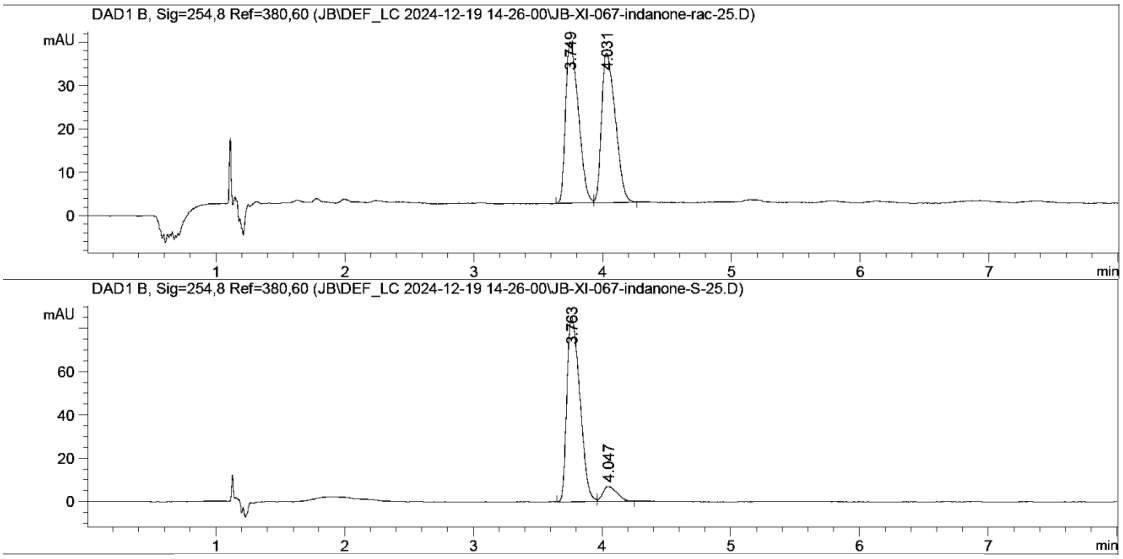
^{13}C NMR (100 MHz, $CDCl_3$): δ 204.7, 176.7, 153.8, 135.5, 135.1, 127.9, 126.5, 124.8, 58.0, 40.0, 37.8, 32.7.

IR (neat film, NaCl): 3246, 1693, 1278 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{12}H_{12}NO_2$ $[M+H]^+$: 202.0863, found 202.0859.

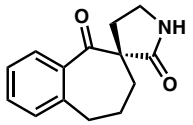
Optical Rotation: $[\alpha]_D^{24}$ = 114.40 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 3.76, t_R (min): minor = 4.05.



Signal 2: DAD1 B, Sig=254,8 Ref=380,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.763	BV	0.1164	598.70044	85.81369	91.8425
2	4.047	VB	0.1059	53.17688	6.97777	8.1575



102c

8,9-dihydrospiro[benzo[7]annulene-6,3'-pyrrolidine]-2',5(7*H*)-dione (2c)

Prepared from **101c** following General Procedure A. Purification by flash column chromatography (0–100% ethyl acetate/hexanes) afforded the title compound as an off-white solid (41.5 mg, 0.18 mmol, 91% yield, 49% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.41 (td, *J* = 7.5, 1.5 Hz, 1H), 7.30 (td, *J* = 7.5, 1.2 Hz, 1H), 7.13 (dd, *J* = 7.5, 1.1 Hz, 1H), 6.17 (s, 1H), 3.77 – 3.55 (m, 1H), 3.39 (dddd, *J* = 9.4, 8.5, 3.9, 1.0 Hz, 1H), 2.90 (ddd, *J* = 14.3, 6.2, 4.1 Hz, 1H), 2.75 (ddd, *J* = 14.3, 10.5, 6.8 Hz, 1H), 2.59 (dddd, *J* = 12.0, 8.0, 4.0, 1.6 Hz, 1H), 2.31 – 2.12 (m, 2H), 2.07 – 1.85 (m, 2H), 1.77 (dddd, *J* = 14.7, 5.4, 3.8, 1.2 Hz, 1H).

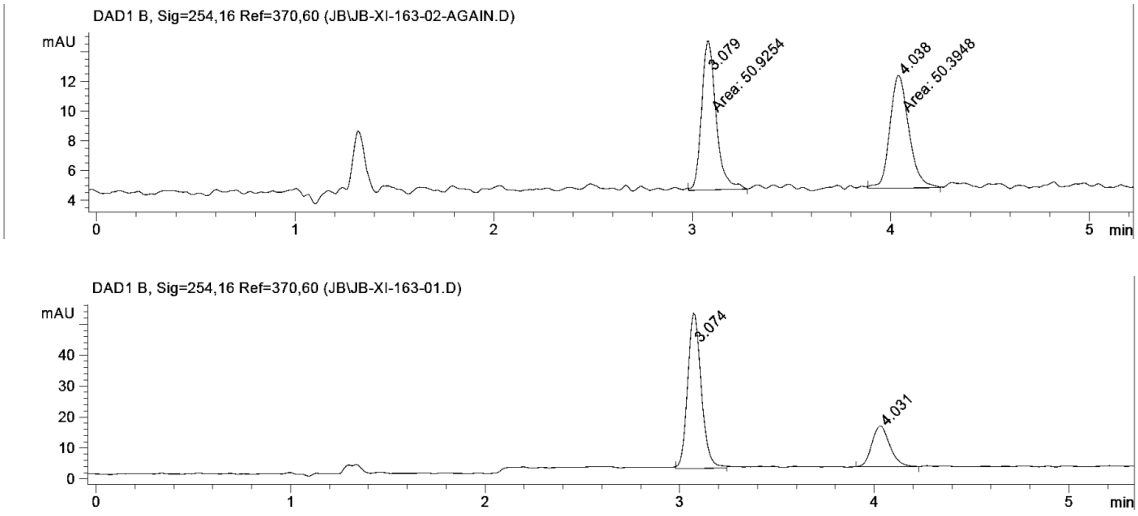
^{13}C NMR (100 MHz, $CDCl_3$): δ 209.8, 177.8, 139.8, 137.7, 132.2, 128.6, 128.0, 127.2, 58.2, 39.8, 39.8, 31.8, 31.1, 29.8, 29.7, 22.1.

IR (neat film, NaCl): 3228, 2942, 1698, 1671, 1597, 1448, 1348, 1280, 1254, 1066, 960 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{14}H_{16}NO_2$ $[M+H]^+$: 230.1176, found 230.1174.

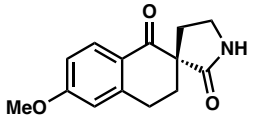
Optical Rotation: $[\alpha]_D^{24}$ = 36.40 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 3.07, t_R (min): minor = 4.03.



Signal 2: DAD1 B, Sig=254,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.074	BB	0.0774	246.12061	50.04628	74.4296
2	4.031	BB	0.1029	84.55526	13.16238	25.5704



102d

6-methoxy-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-1,2'-dione (102d)

Prepared from **101d** following General Procedure A. Purification by flash column chromatography (0–10% acetone/dichloromethane) afforded the title compound as an off-white solid (46.0 mg, 0.188 mmol, 94% yield, 93% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.8 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.69 (d, *J* = 2.6 Hz, 1H), 6.14 (s, 1H), 3.86 (s, 3H), 3.61 – 3.46 (m, 1H), 3.39 (dddd, *J* = 9.4, 8.4, 3.5, 1.0 Hz, 1H), 3.27 (ddd, *J* = 16.8, 6.7, 4.7 Hz, 1H), 2.91 (ddd, *J* = 16.7, 9.3, 4.6 Hz, 1H), 2.66 – 2.53 (m, 2H), 2.14 – 2.01 (m, 2H).

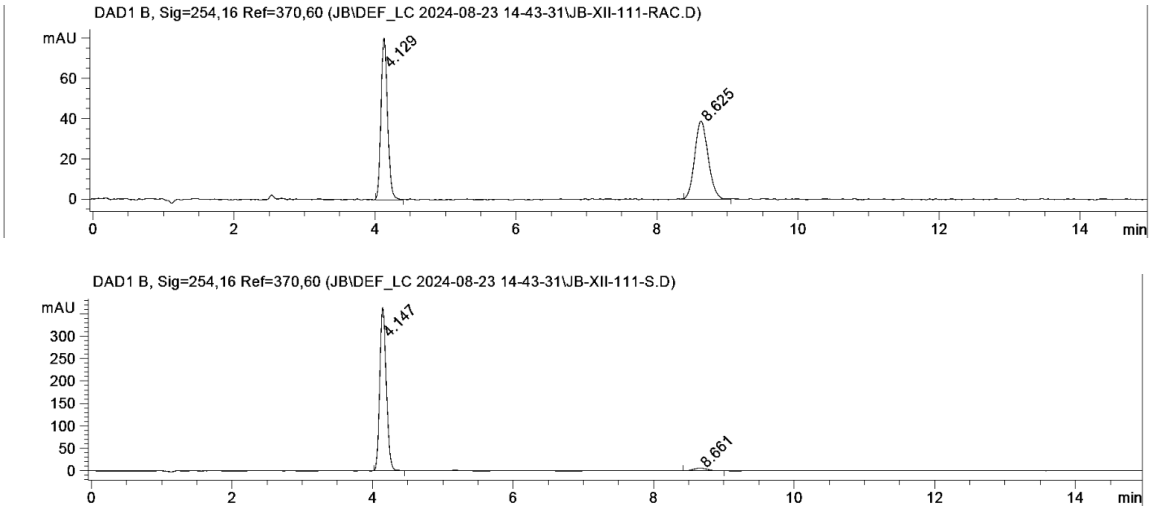
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 177.3, 164.1, 146.6, 130.8, 124.7, 113.7, 112.6, 55.6, 54.7, 39.5, 32.2, 31.6, 26.1.

IR (neat film, NaCl): 3320, 2921, 1695, 1661, 1598, 1230 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{14}H_{16}NO_3$ $[M+H]^+$: 246.1125, found 246.1123.

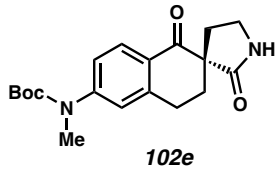
Optical Rotation: $[\alpha]_D^{24}$ = 71.93 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 4.15, t_R (min): minor = 8.66.



Signal 2: DAD1 B, Sig=254,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.147	BB	0.0997	2352.88525	362.41766	96.6103
2	8.661	BB	0.1910	82.55418	6.21419	3.3897



102e

***tert*-butyl (*S*)-(1,2'-dioxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidin]-6-yl)(methyl)carbamate (102e)**

Prepared from **101e** following General Procedure A. Purification by flash column chromatography (20% acetone/CH_2Cl_2) afforded the title compound as an off-white solid (51.0 mg, 0.15 mmol, 73% yield, 95% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.5 Hz, 1H), 7.22 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.19 (d, *J* = 2.2 Hz, 1H), 5.70 (s, 1H), 3.57 – 3.49 (m, 1H), 3.40 (dddd, *J* = 9.3, 8.3, 3.4, 1.0 Hz, 1H), 3.30 (s, 4H), 2.94 (ddd, *J* = 16.8, 9.2, 4.7 Hz, 1H), 2.66 – 2.56 (m, 2H), 2.15 – 2.04 (m, 2H), 1.49 (s, 9H).

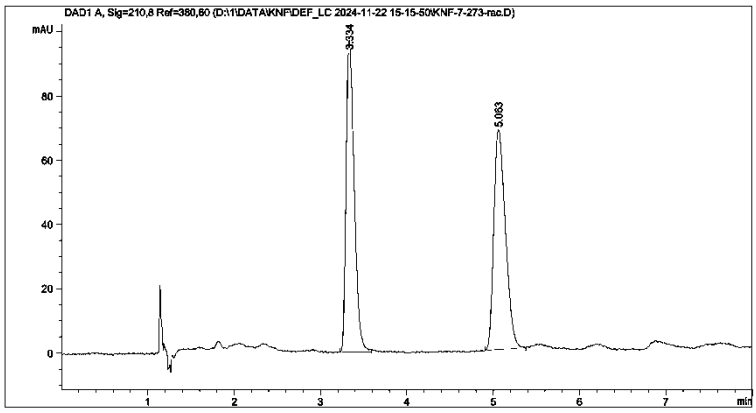
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.6, 176.8, 154.2, 148.7, 144.7, 128.9, 127.5, 123.8, 123.1, 81.4, 54.7, 39.4, 36.9, 32.2, 31.6, 28.4, 25.9.

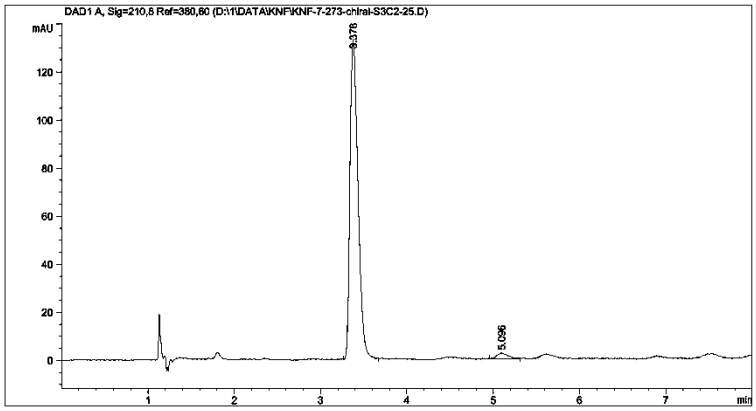
IR (Neat Film, NaCl): 3228, 2940, 1702, 1670, 1601, 1352, 1152 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{19}H_{24}N_2O_4$ $[M+H]^+$: 345.1800, found 345.1800.

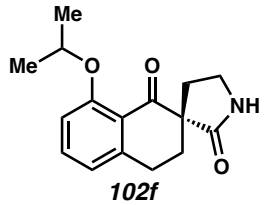
Optical Rotation: $[\alpha]_D^{21}$ 64.12 (c 1.0, $CHCl_3$).

SFC conditions: 25% IPA, 2.5 mL/min, Chiralpak AD3 column, λ = 210 nm, t_R (min): minor = 5.10, major = 3.38.





Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.378	BB	0.1048	870.29437	132.23550	97.5950
2	5.096	BB	0.1353	21.44655	2.33188	2.4050



102f

(*S*)-8-isopropoxy-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-1,2'-dione (102f)

Prepared from **101f** following General Procedure A. Purification by flash column chromatography (0–40% ethyl acetate/dichloromethane) afforded the title compound as an off-white solid (48.1 mg, 0.18 mmol, 88% yield, 82% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (dd, *J* = 8.5, 7.4 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.80 – 6.66 (m, 1H), 6.42 (s, 1H), 4.55 (p, *J* = 6.1 Hz, 1H), 3.60 – 3.49 (m, 1H), 3.42 – 3.30 (m, 1H), 3.19 (ddd, *J* = 16.4, 6.4, 4.5 Hz, 1H), 2.87 (ddd, *J* = 15.9, 10.1, 4.4 Hz, 1H), 2.63 (ddd, *J* = 12.9, 7.7, 3.1 Hz, 1H), 2.58 – 2.43 (m, 1H), 2.10 – 1.92 (m, 2H), 1.37 (dd, *J* = 9.7, 6.0 Hz, 6H).

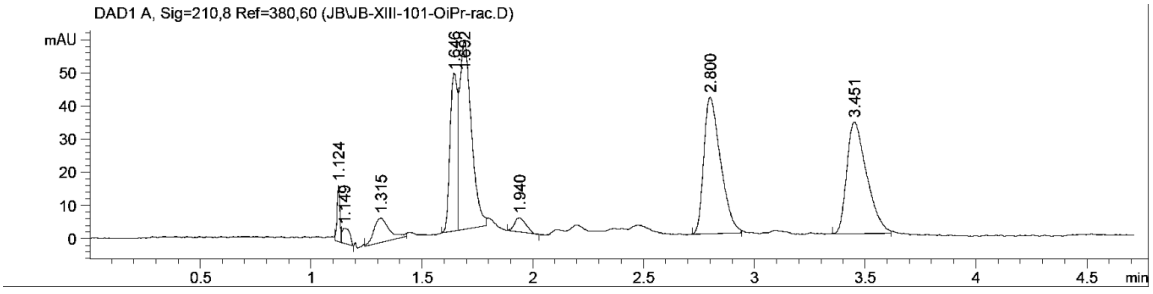
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.1, 177.7, 159.8, 146.6, 134.3, 121.8, 120.5, 113.9, 113.8, 71.8, 56.6, 56.6, 39.6, 32.8, 31.5, 26.9, 22.2, 22.1.

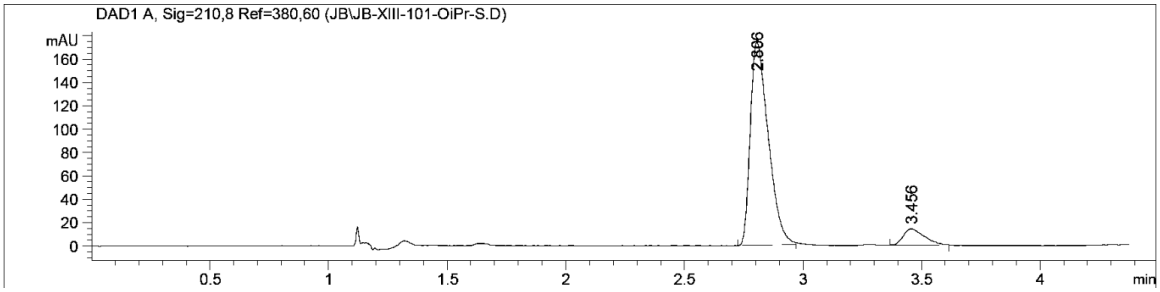
IR (neat film, NaCl): 3217, 2977, 2931, 2361, 2246, 1698, 1592, 1462, 1271, 1207, 1113, 919, 730 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{16}H_{20}NO_3$ $[M+H]^+$: 274.1438, found 274.1434.

Optical Rotation: $[\alpha]_D^{24}$ = 127.86 (c 1.0, $CHCl_3$).

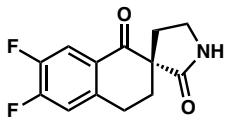
SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 210 nm, t_R (min): major = 2.81, t_R (min): minor = 3.46.





Signal 1: DAD1 A, Sig=210,8 Ref=380,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.806	BB	0.0799	915.93970	173.97523	91.3563
2	3.456	BB	0.0866	86.66156	14.02055	8.6437



102g

6,7-difluoro-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-1,2'-dione (102g)

Prepared from **101g** following General Procedure A. Purification by flash column chromatography (0–10% acetone/dichloromethane) afforded the title compound as an off-white solid (43.5 mg, 0.17 mmol, 87% yield, 68% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 10.6, 8.3 Hz, 1H), 7.05 (dd, *J* = 10.4, 7.1 Hz, 1H), 6.06 (s, 1H), 3.68 – 3.47 (m, 1H), 3.41 (dddd, *J* = 9.4, 8.3, 3.9, 1.0 Hz, 1H), 3.38 – 3.25 (m, 1H), 3.03 – 2.85 (m, 1H), 2.68 (ddd, *J* = 12.9, 7.8, 3.9 Hz, 1H), 2.58 (ddd, *J* = 13.2, 8.1, 4.8 Hz, 1H), 2.16 – 2.04 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.4, 176.4, 157.5 – 151.6 (dd, *J* = 259.0, 13.5 Hz), 149.7 (dd, *J* = 249.7, 13.2 Hz), 141.9 (dd, *J* = 7.4, 3.6 Hz), 128.2, 117.3 (d, *J* = 17.5 Hz), 117.0 (dd, *J* = 17.8, 2.2 Hz), 54.3, 39.4, 31.9, 31.5, 25.2.

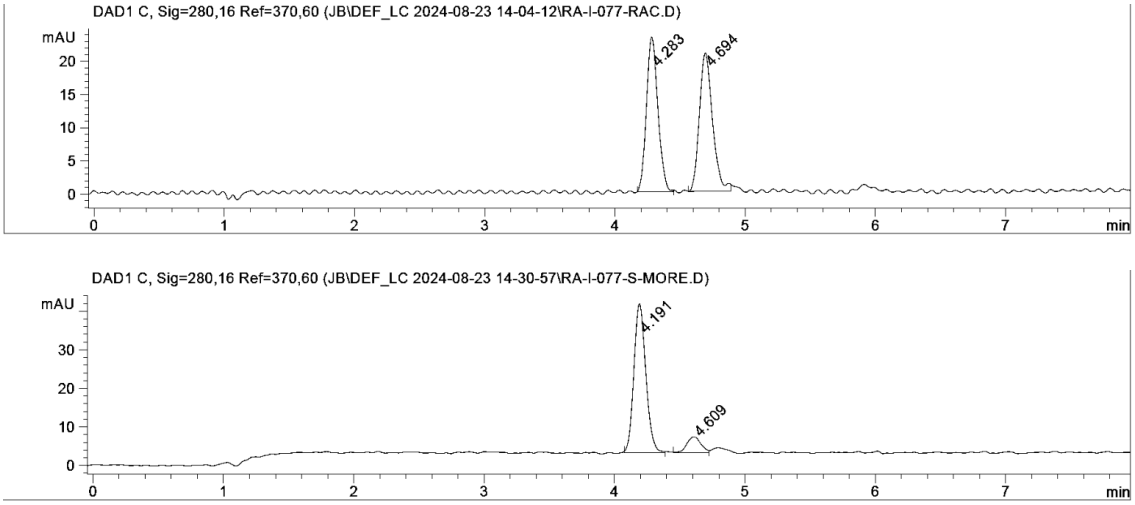
^{19}F NMR (282 MHz, $CDCl_3$): δ -128.25, -138.98.

IR (neat film, NaCl): 3248, 1698, 1674, 1616, 1509, 1355, 1330, 1283 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{13}H_{12}F_2NO_2$ $[M+H]^+$: 252.0831, found 252.0830.

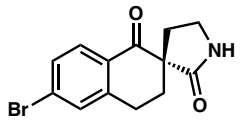
Optical Rotation: $[\alpha]_D^{24}$ = 68.40 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 280 nm, t_R (min): major = 4.28, t_R (min): minor = 4.61.



Signal 3: DAD1 C, Sig=280,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.191	BB	0.0984	246.48422	38.63472	88.6709
2	4.609	BV	0.1166	31.49216	4.14871	11.3291



102h

(*S*)-6-bromo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-1,2'-dione (102h)

Prepared from **101h** following General Procedure A. Purification by flash column chromatography (0–20% acetone/dichloromethane) afforded the title compound as an off-white solid (54.3 mg, 0.18 mmol, 92% yield, 94% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 – 7.86 (m, 1H), 7.53 – 7.41 (m, 2H), 6.52 (s, 1H), 3.56 – 3.45 (m, 1H), 3.45 – 3.19 (m, 2H), 2.91 (ddd, *J* = 17.0, 8.7, 4.7 Hz, 1H), 2.71 – 2.51 (m, 2H), 2.15 – 2.01 (m, 2H).

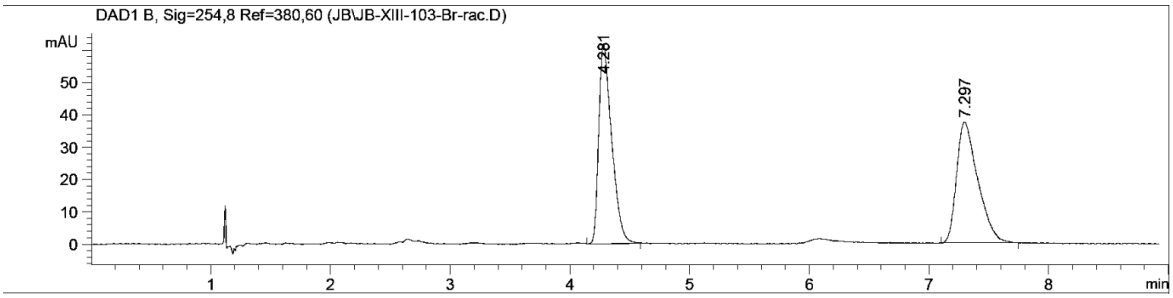
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.7, 176.7, 145.8, 131.8, 130.5, 130.0, 129.9, 129.3, 54.9, 39.5, 31.9, 31.3, 25.5.

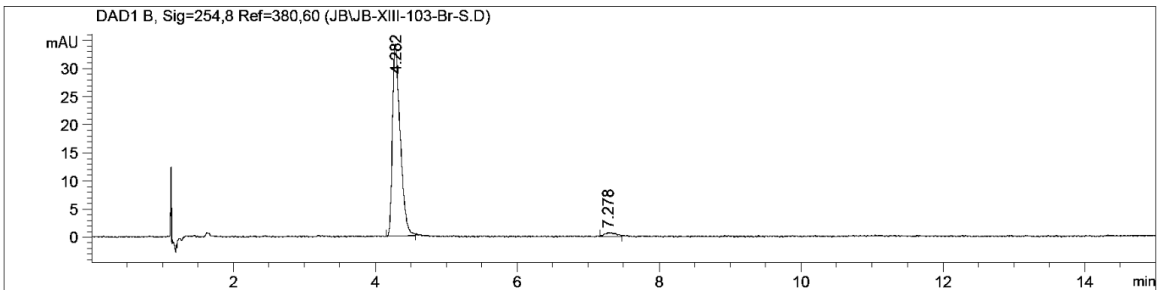
IR (neat film, NaCl): 3233, 2930, 2893, 2362, 1701, 1672, 1586, 1430, 1353, 1289, 1226, 1079, 911, 735 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{13}H_{13}NO_2Br$ $[M+H]^+$: 294.0124, found 294.0125.

Optical Rotation: $[\alpha]_D^{24}$ = 85.81 (c 1.0, $CHCl_3$).

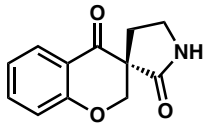
SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 4.28, t_R (min): minor = 7.28.





Signal 2: DAD1 B, Sig=254,8 Ref=380,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.282	BB	0.1104	258.49854	34.11715	96.9706
2	7.278	BB	0.1403	8.07555	6.90994e-1	3.0294



102i

(*R*)-spiro[chromane-3,3'-pyrrolidine]-2',4-dione (102i)

Prepared from **101i** following General Procedure A. Purification by flash column chromatography (75% EtOAc/hexanes) afforded the title compound as an off-white solid (35.9 mg, 0.17 mmol, 83% yield, 90% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.52 (ddd, *J* = 8.4, 7.2, 1.8 Hz, 1H), 7.06 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H), 7.01 (dd, *J* = 8.4, 1.3 Hz, 1H), 5.89 (s, 1H), 4.78 (d, *J* = 11.7 Hz, 1H), 4.39 (d, *J* = 11.8 Hz, 1H), 3.53 (dtd, *J* = 9.6, 7.6, 0.7 Hz, 1H), 3.44 (dddd, *J* = 9.6, 8.6, 3.2, 1.1 Hz, 1H), 2.52 (ddd, *J* = 13.4, 7.6, 3.2 Hz, 1H), 2.30 (ddd, *J* = 13.4, 8.5, 7.7 Hz, 1H).

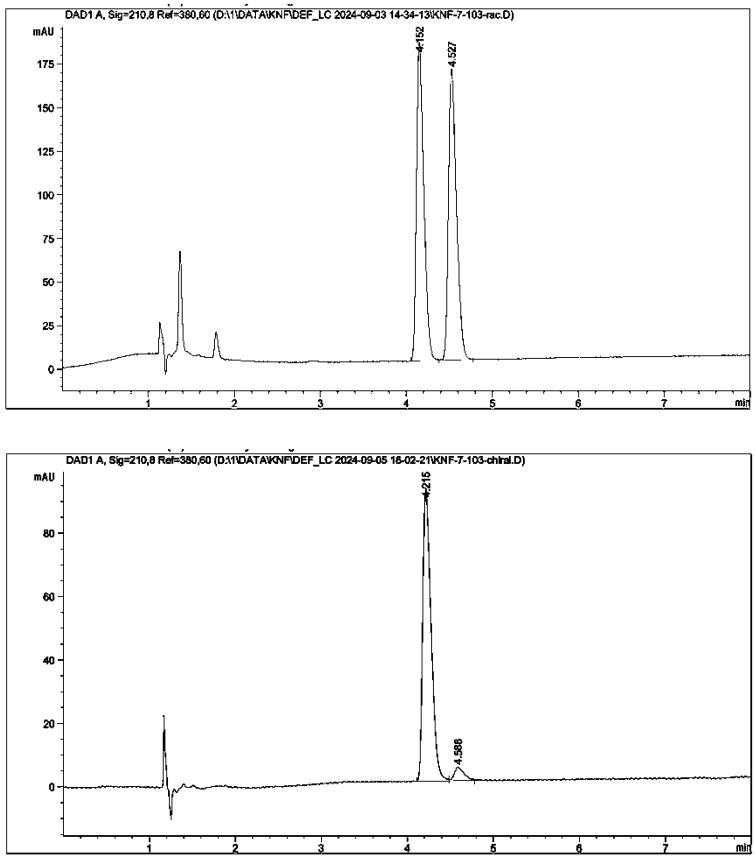
^{13}C NMR (100 MHz, $CDCl_3$): δ 190.6, 173.7, 161.5, 136.6, 128.0, 122.0, 119.7, 118.1, 72.4, 54.4, 39.4, 30.0.

IR (Neat Film, NaCl): 3247, 2902, 1704, 1680, 1605, 1477, 1301 cm^{-1}.

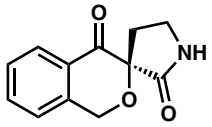
HRMS (MM: ESI+): *m/z* calc'd for $C_{12}H_{11}NO_3$ $[M+H]^+$: 218.0812, found 218.0811.

Optical Rotation: $[\alpha]_D^{21}$ 62.22 (c 1.0, $CHCl_3$).

SFC conditions: 20% IPA, 2.5 mL/min, Chiralpak AD3 column, λ = 210 nm, t_R (min): minor = 4.59, major = 4.22.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.215	BB	0.1015	622.31726	92.45192	94.9860
2	4.588	BB	0.1029	32.84975	4.31077	5.0140



102j

(*R*)-spiro[isochromane-3,3'-pyrrolidine]-2',4-dione (2j)

Prepared from **101j** following General Procedure A. Purification by flash column chromatography (0–50% ethyl acetate/dichloromethane) afforded the title compound as an off-white solid (34.1 mg, 0.16 mmol, 78% yield, 91% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.58 (td, *J* = 7.6, 1.4 Hz, 1H), 7.49 – 7.37 (m, 1H), 7.19 (s, 1H), 5.98 (s, 1H), 5.63 (d, *J* = 15.3 Hz, 1H), 4.88 (d, *J* = 15.3 Hz, 1H), 3.52 (td, *J* = 6.6, 1.0 Hz, 2H), 2.91 (dt, *J* = 13.3, 6.8 Hz, 1H), 2.30 (dt, *J* = 13.3, 6.4 Hz, 1H).

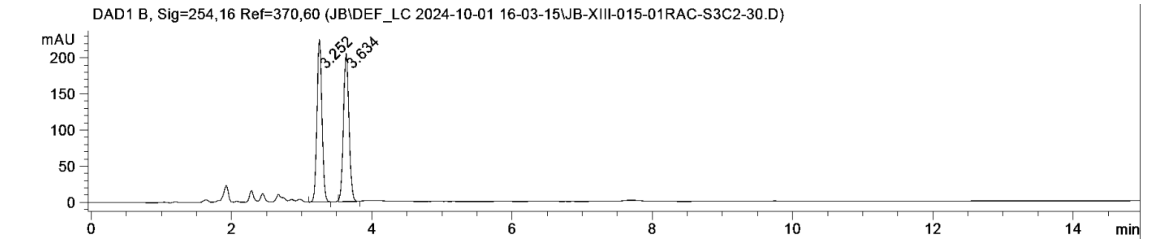
^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 173.3, 141.6, 134.6, 128.6, 127.9, 127.1, 124.5, 83.9, 64.4, 39.2, 32.3.

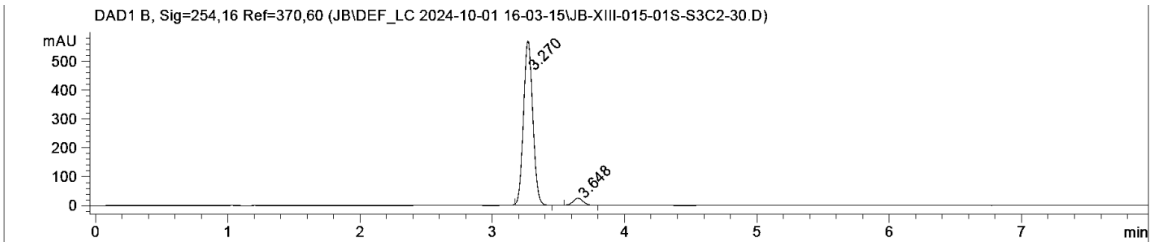
IR (neat film, NaCl): 3252, 2954, 2901, 2246, 1706, 1684, 1603, 1441, 1284, 1222, 1123, 1055, 886, 755 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{12}H_{12}NO_3$ $[M+H]^+$: 218.0812, found 218.0807.

Optical Rotation: $[\alpha]_D^{24}$ = 50.98 (c 1.0, $CHCl_3$).

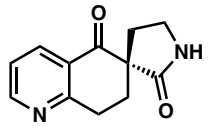
SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 3.27, t_R (min): minor = 3.65.





Signal 2: DAD1 B, Sig=254,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.270	BB	0.0774	2791.60864	567.28564	95.3423
2	3.648	BB	0.0842	136.37683	24.77287	4.6577



102k

7',8'-dihydro-5'*H*-spiro[pyrrolidine-3,6'-quinoline]-2,5'-dione (102k)

Prepared from **101k** following General Procedure A. Purification by flash column chromatography (0–30% acetone/dichloromethane) afforded the title compound as an off-white solid (35.3 mg, 0.16 mmol, 82% yield, 63% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (dd, *J* = 4.8, 1.9 Hz, 1H), 8.29 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.29 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.59 (s, 1H), 3.67 – 3.46 (m, 2H), 3.42 (dddd, *J* = 9.5, 8.3, 4.1, 1.0 Hz, 1H), 3.12 (ddd, *J* = 17.7, 8.4, 5.0 Hz, 1H), 2.78 – 2.43 (m, 2H), 2.33 – 2.02 (m, 2H).

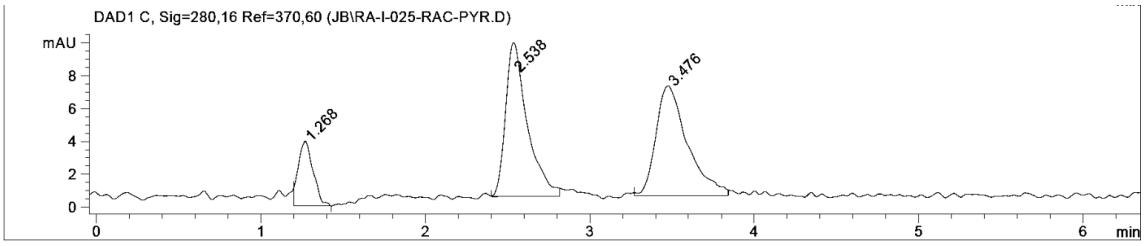
^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 176.4, 163.3, 154.0, 136.0, 126.9, 122.5, 54.8, 54.8, 46.1, 39.4, 31.6, 30.3, 30.3, 28.9.

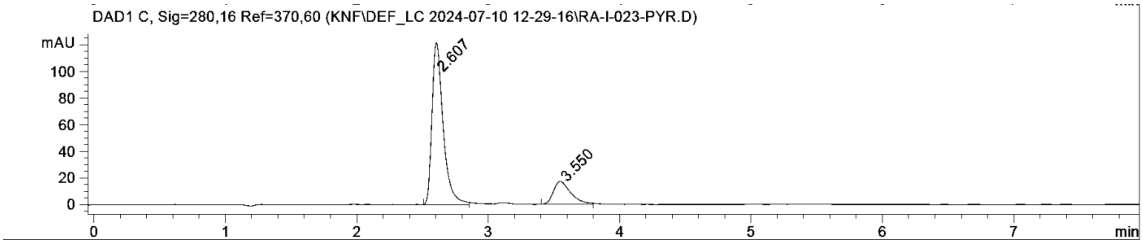
IR (neat film, NaCl): 2930, 2603, 2496, 1645, 1396, 1035 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{12}H_{13}N_2O_2$ $[M+H]^+$: 217.0972, found 217.0971.

Optical Rotation: $[\alpha]_D^{24}$ = 81.71 (c 0.42, $CHCl_3$).

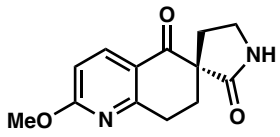
SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack ID-3 column, λ = 280 nm, t_R (min): major = 2.61, t_R (min): minor = 3.55.





Signal 3: DAD1 C, Sig=280,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.607	BB	0.0927	718.46594	121.98861	81.6541
2	3.550	BB	0.1408	161.42337	17.31181	18.3459



102l

2'-methoxy-7',8'-dihydro-5'*H*-spiro[pyrrolidine-3,6'-quinoline]-2,5'-dione (102l)

Prepared from **101l** following General Procedure A. Purification by flash column chromatography (0–50% ethyl acetate/dichloromethane) afforded the title compound as an off-white solid (48.0 mg, 0.195 mmol, 97% yield, 92% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.7 Hz, 1H), 6.65 (dd, *J* = 8.7, 0.7 Hz, 1H), 6.34 (s, 1H), 3.99 (s, 3H), 3.51 (dddd, *J* = 9.5, 7.8, 7.1, 0.8 Hz, 1H), 3.45 – 3.30 (m, 2H), 2.97 (ddd, *J* = 17.8, 8.4, 5.0 Hz, 1H), 2.70 – 2.53 (m, 2H), 2.16 – 2.01 (m, 2H).

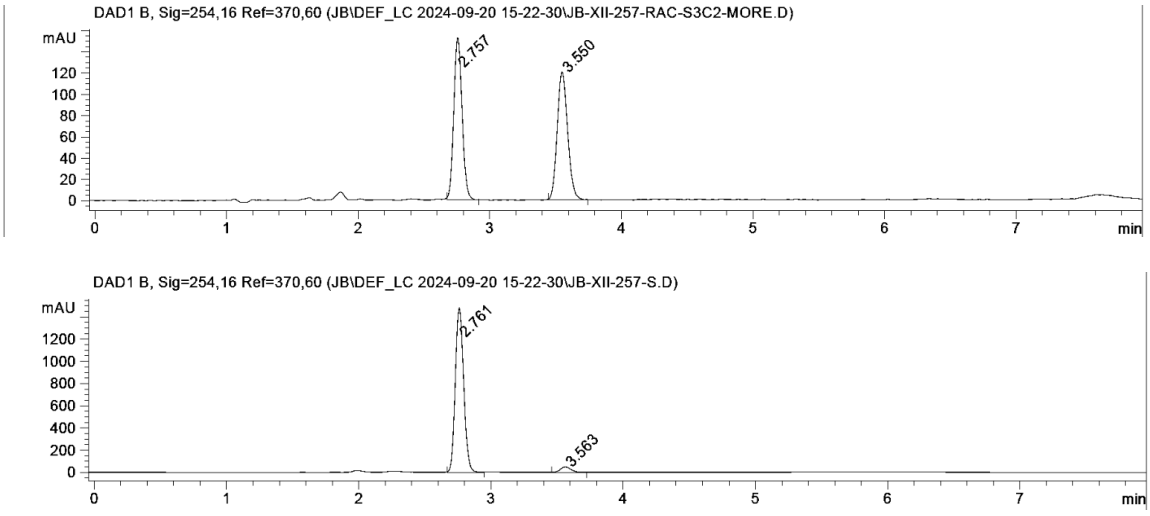
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 176.8, 166.6, 163.7, 138.6, 121.4, 110.4, 54.4, 54.2, 39.5, 31.8, 30.5, 28.9.

IR (neat film, NaCl): 3305, 2942, 1700, 1669, 1591, 1412, 1347, 1329, 1266, 1235, 1013, 906, 734 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{13}H_{15}N_2O_3$ $[M+H]^+$: 247.1077, found 247.1073.

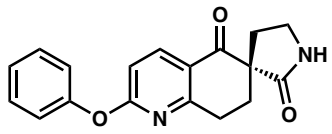
Optical Rotation: $[\alpha]_D^{24}$ = 92.99 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 2.76, t_R (min): minor = 3.56.



Signal 2: DAD1 B, Sig=254,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.761	BB	0.0718	6538.02100	1472.38684	96.0605
2	3.563	BB	0.0853	268.12891	47.92621	3.9395



102m

(*S*)-2'-phenoxy-7',8'-dihydro-5'*H*-spiro[pyrrolidine-3,6'-quinoline]-2,5'-dione (102m)

Prepared from **101m** following General Procedure A. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as an off-white solid (50.1 mg, 0.16 mmol, 81% yield, 95% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.7 Hz, 1H), 7.41 (tt, *J* = 7.6, 2.2 Hz, 2H), 7.30 – 7.19 (m, 1H), 6.74 (d, *J* = 8.6 Hz, 2H), 6.47 (s, 1H), 3.62 – 3.45 (m, 1H), 3.43 – 3.18 (m, 2H), 2.93 (ddd, *J* = 17.9, 8.2, 5.0 Hz, 1H), 2.66 (ddd, *J* = 12.9, 7.9, 4.1 Hz, 1H), 2.57 (ddd, *J* = 13.5, 8.2, 5.1 Hz, 1H), 2.07 (dddd, *J* = 18.4, 8.3, 7.2, 4.5 Hz, 2H).

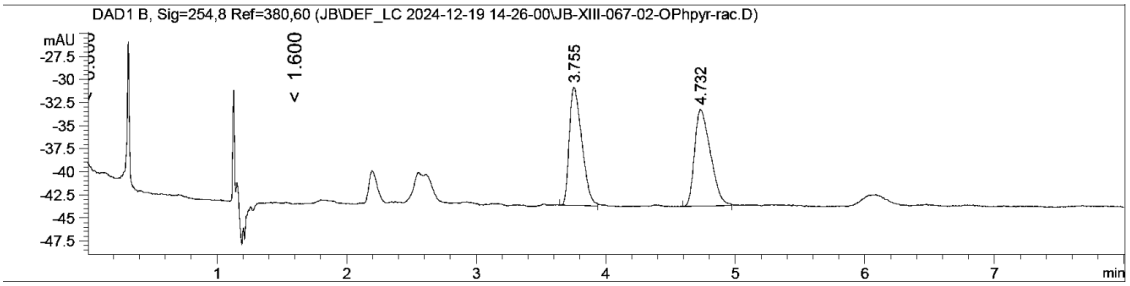
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.1, 176.6, 166.1, 164.1, 153.3, 139.8, 129.9, 125.5, 122.7, 121.6, 109.8, 54.5, 39.5, 31.7, 30.4, 28.8.

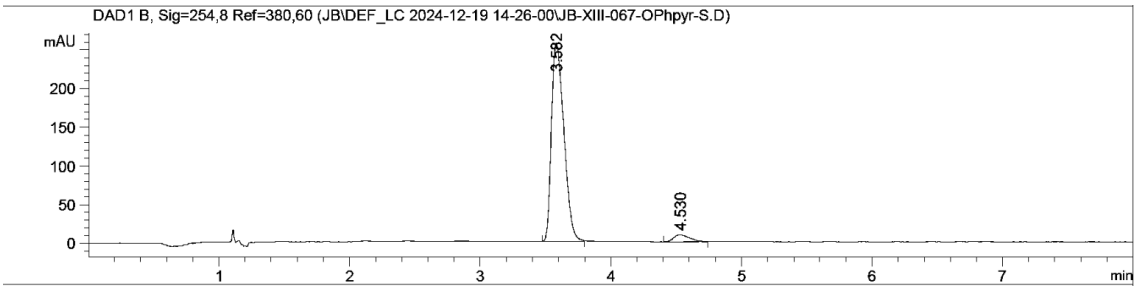
IR (neat film, NaCl): 3227, 2939, 1698, 1672, 1509, 1488, 1452, 1346, 1260, 1201, 934, 909, 774, 727 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{18}H_{17}N_2O_3$ $[M+H]^+$: 309.1234, found 309.1243.

Optical Rotation: $[\alpha]_D^{24}$ = 86.14 (c 1.0, $CHCl_3$).

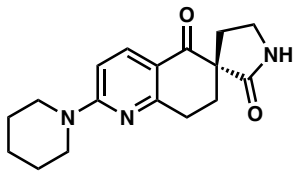
SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 3.58, t_R (min): minor = 4.53.





Signal 2: DAD1 B, Sig=254,8 Ref=380,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.582	BB	0.1063	1699.03015	256.45801	95.8033
2	4.530	BB	0.1157	74.42605	9.06856	4.1967



102n

(*S*)-2'-(piperidin-1-yl)-7',8'-dihydro-5'*H*-spiro[pyrrolidine-3,6'-quinoline]-2,5'-dione (102n)

Prepared from **101n** following General Procedure A. Purification by flash column chromatography (0–75% ethyl acetate/hexanes) afforded the title compound as an off-white solid (53.6 mg, 0.18 mmol, 90% yield, 82% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 9.1 Hz, 1H), 6.52 (d, *J* = 9.1 Hz, 1H), 6.25 (s, 1H), 3.70 (dd, *J* = 6.3, 4.4 Hz, 4H), 3.57 – 3.44 (m, 1H), 3.37 (dddd, *J* = 9.4, 8.4, 3.7, 1.0

Hz, 1H), 3.21 (ddd, *J* = 17.4, 6.6, 4.9 Hz, 1H), 2.86 (ddd, *J* = 17.3, 9.3, 4.9 Hz, 1H), 2.64 – 2.50 (m, 2H), 2.13 – 1.97 (m, 2H), 1.80 – 1.66 (m, 2H), 1.63 (m, 4H).

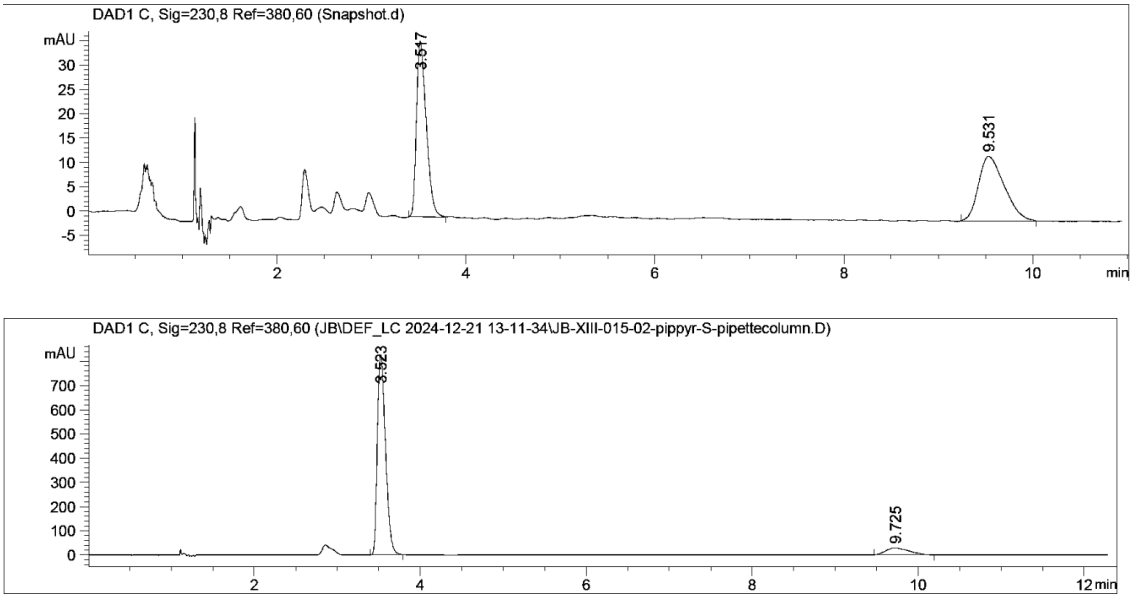
^{13}C NMR (100 MHz, $CDCl_3$): δ 194.5, 177.6, 164.4, 159.9, 137.3, 116.5, 105.0, 54.2, 45.8, 39.6, 32.2, 30.6, 29.2, 25.8, 24.8.

IR (neat film, NaCl): 3226, 2932, 2855, 2239, 1697, 1653, 1587, 1496, 1345, 1239, 1126, 1021, 913, 728 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{17}H_{22}N_3O_2$ $[M+H]^+$: 300.1707, found 300.1709.

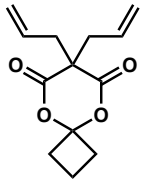
Optical Rotation: $[\alpha]_D^{24}$ = 77.89 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 230 nm, t_R (min): major = 3.52, t_R (min): minor = 9.73.



Signal 3: DAD1 C, Sig=230,8 Ref=380,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.523	BB	0.1057	5633.90088	824.67969	91.3230
2	9.725	BB	0.2889	535.30133	27.64777	8.6770



diallyl-103a

7,7-diallyl-5,9-dioxaspiro[3.5]nonane-6,8-dione(diallyl-103a)

Isolated from a reaction with **101a** following General Procedure A. Purification by flash column chromatography (0–10% acetone/dichloromethane) afforded the title compound as a clear oil (21.0 mg, 0.09 mmol, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.65 (ddt, *J* = 17.3, 10.1, 7.4 Hz, 2H), 5.23 – 5.13 (m, 4H), 2.72 – 2.66 (m, 4H), 2.65 – 2.57 (m, 4H), 1.89 (tt, *J* = 9.8, 7.2 Hz, 2H).

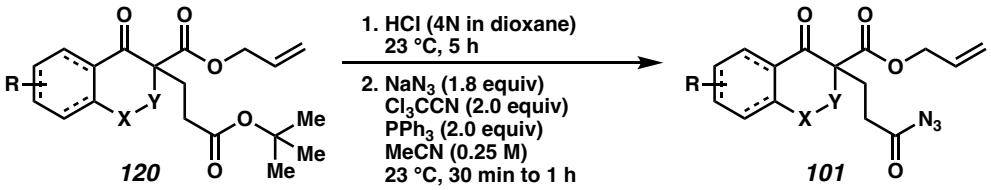
^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 130.6, 121.4, 104.5, 53.6, 41.4, 37.7, 10.7.

IR (neat film, NaCl): 2956, 1782, 1750, 1285, 1246, 1157, 995, 929 cm^{-1}.

HMRS (FD+): *m/z* calc'd for $C_{13}H_{16}O_4$ $[M]^{+\bullet}$: 236.1043, found 236.1041.

Preparation of Acyl Azide Starting Materials

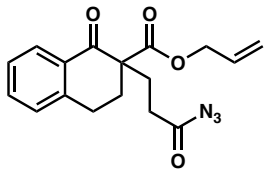
General Procedure B: Synthesis of Acyl Azides



To a flask containing ester intermediate **120** was added HCl (4N in dioxane) at 23 °C. The resultant solution was stirred for 5 h, or until full consumption of starting material by TLC analysis. The crude mixture was concentrated under reduced pressure, then dissolved in ethyl acetate, washed with water twice, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude carboxylic acid intermediate was used without further purification.

Acyl azides were synthesized according to a modified literature procedure.[29] To a solution of the carboxylic acid intermediate in acetonitrile (0.25 M) at 23 °C was added sodium azide (1.8 equiv) and triphenylphosphine (2.0 equiv). Trichloroacetonitrile (2.0 equiv) was added dropwise, and the reaction was stirred for 30 minutes to an hour, or until starting material was consumed by TLC analysis. The crude reaction mixture was concentrated under reduced pressure, then dissolved in ethyl acetate and washed with water, saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and concentrated again under reduced pressure. The product (**101**) was purified by silica gel chromatography.

Note: occasionally, upon addition of trichloroacetonitrile, the reaction gently exotherms, in which case the reaction flask was cooled with an ice bath at 0 °C until completion of the dropwise addition.



101a

allyl 2-(3-azido-3-oxopropyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (101a)

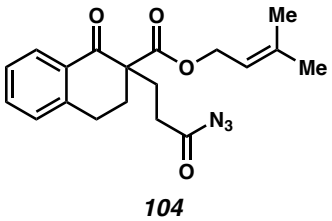
Prepared from **121** following General Procedure B. Purification by flash column chromatography (0–30% ethyl acetate/hexanes) afforded the title compound as a clear oil (642 mg, 1.96 mmol, 64% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (m, 1H), 7.48 (m, 1H), 7.36 – 7.28 (m, 1H), 7.25 – 7.18 (m, 1H), 5.78 (ddt, *J* = 17.5, 10.2, 5.6 Hz, 1H), 5.17 (m, 1H), 5.16 – 4.97 (m, 1H), 4.58 (ddt, *J* = 5.6, 3.4, 1.4 Hz, 2H), 3.21 – 2.84 (m, 2H), 2.73 – 2.41 (m, 3H), 2.38 – 2.17 (m, 2H), 2.11 (ddd, *J* = 13.6, 9.8, 5.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.1, 180.1, 171.3, 142.8, 133.9, 133.9, 132.0, 131.4, 128.9, 128.2, 128.2, 127.1, 127.1, 118.9, 118.8, 66.0, 56.7, 32.7, 31.7, 28.8, 26.0.

IR (neat film, NaCl): 3735, 2939, 2268, 2137, 1731, 1686, 1600, 1454, 1180, 929, 743 cm^{-1}.

HMRS (FD+): *m/z* calc'd for $C_{17}H_{17}N_3O_4$ $[M]^{+\bullet}$: 327.1214, found 327.1211.



104

3-methylbut-2-en-1-yl 2-(3-azido-3-oxopropyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (104)

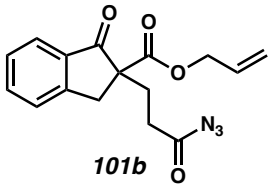
Prepared from **122** following General Procedure B. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (881 mg, 2.48 mmol, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.51 – 7.42 (m, 1H), 7.32 – 7.28 (m, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 5.20 (ddt, *J* = 7.2, 5.9, 1.4 Hz, 1H), 4.63 – 4.48 (m, 2H), 3.14 – 2.84 (m, 2H), 2.76 – 2.38 (m, 3H), 2.36 – 2.13 (m, 2H), 2.08 (ddd, *J* = 13.5, 10.2, 4.9 Hz, 1H), 1.68 (s, 3H), 1.58 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.3, 180.1, 171.5, 142.8, 133.7, 132.1, 130.2, 128.8, 128.1, 126.9, 117.9, 62.4, 56.6, 32.7, 31.9, 28.9, 26.0, 25.7, 18.1.

IR (neat film, NaCl): 2930, 2264, 2136, 1717, 1599, 1457, 1185, 1-71, 957, 766 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{19}H_{21}N_3O_4Na$ $[M+Na]^+$: 378.1424, found 378.1412.



101b

allyl 2-(3-azido-3-oxopropyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (101b)

Prepared from **123** following General Procedure B. Purification by flash column chromatography (10–15% EtOAc/hexanes) afforded the title compound (191 mg, 0.50 mmol, 51% yield).

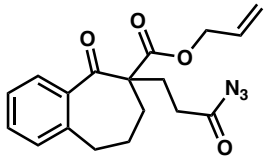
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.8 Hz, 1H), 7.65 (td, *J* = 7.4, 1.2 Hz, 1H), 7.49 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.42 (td, *J* = 7.4, 0.9 Hz, 1H), 5.82 (ddt, *J* = 17.3, 10.6, 5.5 Hz, 1H), 5.26 – 5.15 (m, 2H), 4.59 (dt, *J* = 5.5, 1.5 Hz, 2H), 3.70 (d, *J* = 17.3 Hz, 1H), 3.06

(d, *J* = 17.3 Hz, 1H), 2.61 – 2.51 (m, 1H), 2.51 – 2.30 (m, 2H), 2.27 (ddd, *J* = 14.0, 10.6, 4.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.8, 179.8, 170.5, 152.6, 135.8, 135.1, 131.5, 128.3, 126.6, 125.2, 118.7, 66.3, 59.3, 37.8, 32.5, 29.5.

IR (Neat Film, NaCl): 3423, 2269, 2137, 1713, 1173 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{16}H_{15}NO_4$ $[M+H]^+$: 286.1074, found 286.1067.



101c

allyl 6-(3-azido-3-oxopropyl)-5-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-6-carboxylate (101c)

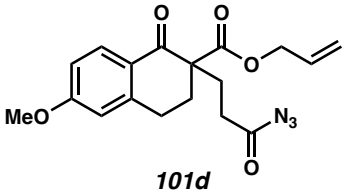
Prepared from **124** following General Procedure B. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (184 mg, 0.54 mmol, 49% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (m, 1H), 7.36 (m, 1H), 7.26 (m, 1H), 7.12 (m, 1H), 5.65 (ddd, *J* = 17.2, 10.3, 5.9 Hz, 1H), 5.28 – 5.03 (m, 2H), 4.46 (dd, *J* = 5.9, 1.3 Hz, 1H), 2.89 (dddd, *J* = 53.8, 15.7, 8.3, 4.2 Hz, 2H), 2.67 – 2.28 (m, 4H), 2.28 – 2.13 (m, 1H), 2.03 (m, 1H), 1.77 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.2, 180.0, 171.7, 140.0, 138.7, 131.5, 131.3, 129.3, 129.2, 126.7, 119.3, 66.2, 61.1, 33.1, 33.0, 32.5, 30.9, 23.9.

IR (neat film, NaCl): 2937, 2265, 2137, 1784, 1685, 1598, 1447, 1182, 959, 743 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{18}H_{20}N_1O_4$ $[M–N_2+H]^+$: 314.3487, found 314.3478.



101d

allyl 2-(3-azido-3-oxopropyl)-6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (101d)

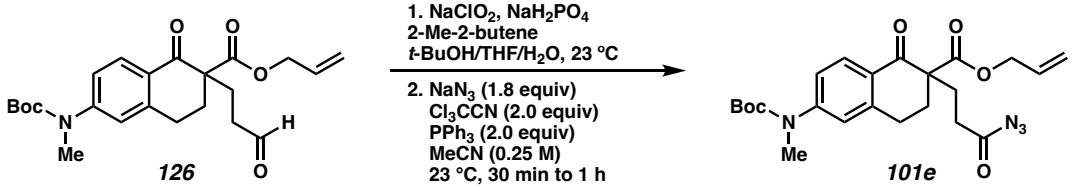
Prepared from **125** following General Procedure B. Purification by flash column chromatography (0–40% ethyl acetate/hexanes) afforded the title compound as a clear oil (513 mg, 1.44 mmol, 59% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.8 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.65 (d, *J* = 2.5 Hz, 1H), 5.87 – 5.73 (m, 1H), 5.25 – 5.11 (m, 2H), 4.58 (m, 2H), 3.85 (s, 3H), 3.11 – 2.80 (m, 2H), 2.74 – 2.39 (m, 3H), 2.38 – 2.14 (m, 2H), 2.15 – 1.95 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 180.2, 171.5, 164.0, 145.4, 131.5, 130.7, 125.5, 118.7, 113.8, 112.6, 66.0, 56.5, 55.6, 32.7, 31.6, 28.8, 26.3.

IR (neat film, NaCl): 2940, 2268, 2137, 1726, 1675, 1599, 1442, 1352, 1256, 1187, 1076, 931 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{18}H_{20}N_3O_5$ $[M+H]^+$: 330.1336, found 330.1337.



allyl 2-(3-azido-3-oxopropyl)-6-((*tert*-butoxycarbonyl)(methyl)amino)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (101e)

To a solution of aldehyde **126** (1.28 g, 3.07 mmol, 1 equiv) and 2-Me-2-butene (4.9 mL, 46 mmol, 15 equiv) in *t*-BuOH/THF (1:1 ratio, 30 mL, 0.1 M total) was added $NaClO_2$ (833 mg, 3 equiv, 9.2 mmol) and NaH_2PO_4 (2.21 g, 18.4 mmol, 6 equiv) in H_2O (8 mL, 0.4 M). The reaction was stirred for 2 hours at 23 ºC until starting material was consumed by TLC analysis. The reaction was quenched with 1 N HCl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude carboxylic acid intermediate was used without further purification.

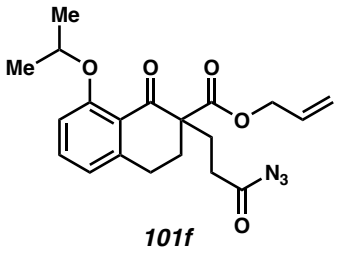
To a solution of the carboxylic acid intermediate in acetonitrile (16 mL, 0.25 M) at 23 °C was added sodium azide (242 mg, 3.7 mmol, 1.8 equiv) and triphenylphosphine (1.63 g, 6.2 mmol, 2.0 equiv). Trichloroacetonitrile (0.62 mL, 6.2 mmol, 2.0 equiv) was added dropwise, and the reaction was stirred for 30 minutes to an hour, or until starting material was consumed by TLC analysis. The crude reaction mixture was concentrated under reduced pressure, then dissolved in ethyl acetate and washed with water, saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and concentrated again under reduced pressure. Purification by flash column chromatography (20% EtOAc/hexanes) afforded the title compound as a clear oil (939 mg, 2.06 mmol, 66% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.6 Hz, 1H), 7.22 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.16 (d, *J* = 2.2 Hz, 1H), 5.80 (ddt, *J* = 17.1, 10.4, 5.6 Hz, 1H), 5.19 (dq, *J* = 9.8, 1.4 Hz, 1H), 5.15 (dq, *J* = 2.8, 1.4 Hz, 1H), 4.58 (dt, *J* = 5.6, 1.4 Hz, 2H), 3.28 (s, 3H), 3.02 (ddd, *J* = 17.3, 10.0, 4.8 Hz, 1H), 2.91 (dt, *J* = 17.4, 5.1 Hz, 1H), 2.69 – 2.42 (m, 3H), 2.35 – 2.16 (m, 2H), 2.09 (ddd, *J* = 13.6, 9.8, 4.9 Hz, 1H), 1.48 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.0, 180.1, 171.3, 154.1, 148.6, 143.4, 131.4, 128.8, 128.3, 123.8, 123.1, 118.8, 81.4, 66.0, 56.6, 36.9, 32.7, 31.6, 28.8, 28.4, 26.1.

IR (Neat Film, NaCl): 2976, 2935, 2264, 2139, 1704, 1601, 1356, 1153 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{23}H_{28}N_4O_6$ $[M+H]^+$: 457.2082, found 457.2078.



101f

allyl 2-(3-azido-3-oxopropyl)-8-isopropoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (101f)

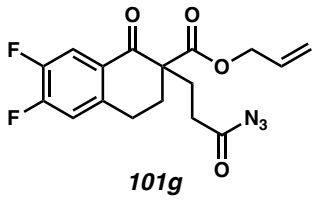
Prepared from **127** following General Procedure B. Purification by flash column chromatography (0–40% ethyl acetate/hexanes) afforded the title compound as a clear oil (343 mg, 0.89 mmol, 59% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.27 (m, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.73 (dd, *J* = 7.6, 1.0 Hz, 1H), 5.76 (ddt, *J* = 17.2, 10.5, 5.5 Hz, 1H), 5.22 – 5.09 (m, 2H), 4.65 – 4.47 (m, 3H), 3.27 – 2.75 (m, 2H), 2.63 (ddd, *J* = 16.9, 10.6, 5.4 Hz, 1H), 2.55 – 2.40 (m, 2H), 2.23 (dddd, *J* = 56.7, 14.1, 10.5, 5.4 Hz, 2H), 2.07 – 1.88 (m, 1H), 1.37 (dd, *J* = 16.1, 6.0 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.4, 180.3, 171.6, 159.2, 144.8, 133.8, 131.6, 123.4, 120.6, 118.5, 113.7, 71.8, 65.8, 57.7, 32.7, 31.1, 29.2, 26.6, 22.2, 22.1.

IR (neat film, NaCl): 2979, 2933, 2263, 2138, 1731, 1694, 1592, 1454, 1270, 1182, 1111, 922, 763 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{20}H_{23}N_3O_5Na$ $[M+Na]^+$: 408.1530, found 408.1515.



101g

allyl 2-(3-azido-3-oxopropyl)-6,7-difluoro-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (101g)

Prepared from **128** following General Procedure B. Purification by flash column chromatography (0–30% ethyl acetate/hexanes) afforded the title compound as a clear oil (416 mg, 1.14 mmol, 64% yield).

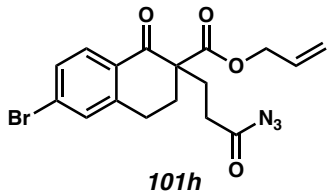
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 10.6, 8.2 Hz, 1H), 7.01 (dd, *J* = 10.3, 7.1 Hz, 1H), 5.79 (ddt, *J* = 17.6, 10.0, 5.7 Hz, 1H), 5.24 – 5.11 (m, 2H), 4.65 – 4.53 (m, 2H), 3.06 – 2.84 (m, 2H), 2.71 – 2.38 (m, 3H), 2.36 – 2.15 (m, 2H), 2.10 (ddd, *J* = 13.7, 10.3, 5.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 192.90, 179.93, 170.85, 153.95 (dd, *J* = 258.9, 13.6 Hz), 149.76 (dd, *J* = 250.2, 13.1 Hz), 140.37 (dd, *J* = 7.3, 3.6 Hz), 131.21, 130.04 – 126.31 (m), 119.17, 117.28 (d, *J* = 17.5 Hz), 116.94 (dd, *J* = 17.9, 2.2 Hz), 66.26, 56.18, 32.54, 31.74, 28.82, 25.57.

^{19}F NMR (282 MHz, $CDCl_3$): δ -128.23, -138.48.

IR (neat film, NaCl): 3067, 2937, 2269, 2139, 1731, 1619, 1511, 1356, 1284, 1170, 1072, 919, 786 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{17}H_{16}F_2O_4$ $[M–N_3+H]^+$: 321.0933, found 321.0936.



101h

allyl 2-(3-azido-3-oxopropyl)-6-bromo-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (101h)

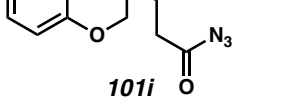
Prepared from **129** following General Procedure B. Purification by flash column chromatography (0–30% ethyl acetate/hexanes) afforded the title compound as a clear oil (484 mg, 1.19 mmol, 67% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.4 Hz, 1H), 7.46 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.40 (s, 1H), 5.79 (m, *J* = 17.2, 9.9, 5.6 Hz, 1H), 5.22 – 5.13 (m, 2H), 4.58 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.16 – 2.79 (m, 2H), 2.64 (ddd, *J* = 16.6, 10.3, 5.5 Hz, 1H), 2.55 (dt, *J* = 13.7, 4.8 Hz, 1H), 2.46 (ddd, *J* = 16.7, 10.1, 5.5 Hz, 1H), 2.26 (dddd, *J* = 40.0, 14.1, 10.2, 5.5 Hz, 2H), 2.13 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.2, 180.0, 171.0, 144.5, 131.8, 131.3, 130.9, 130.6, 129.9, 129.1, 119.1, 66.2, 56.6, 32.6, 31.5, 28.8, 25.8.

IR (neat film, NaCl): 2939, 2271, 2138, 1728, 1688, 1587, 1443, 1349, 1183, 1071, 905 cm^{-1}.

HMRS (FD+): *m/z* calc'd for $C_{17}H_{16}N_3O_4Br$ $[M]^{+\bullet}$: 405.0319, found 405.0329.



101i

allyl 3-(3-azido-3-oxopropyl)-4-oxochromane-3-carboxylate (101i)

A solution of **130** (507 mg, 1.41 mmol, 1 equiv) in acetone (0.5 M, 2.8 mL) was cooled to 0 ºC. Concentrated HCl (2.8 mL) was added. Upon complete consumption of starting material (as determined by TLC), the reaction mixture was diluted with brine and extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude carboxylic acid which was used directly in the next step.

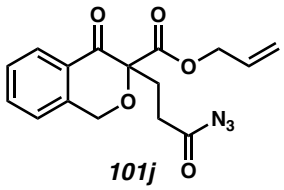
To a solution of the carboxylic acid intermediate in acetonitrile (0.25 M) at 23 °C was added sodium azide (1.8 equiv) and triphenylphosphine (2.0 equiv). Trichloroacetonitrile (2.0 equiv) was added dropwise, and the reaction was stirred for 30 minutes to an hour, or until starting material was consumed by TLC analysis. The crude reaction mixture was concentrated under reduced pressure, then dissolved in ethyl acetate and washed with water, saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and concentrated again under reduced pressure. Purification by flash column chromatography (15% EtOAc/hexanes) afforded the title compound as a clear oil (148 mg, 0.45 mmol, 64% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.50 (ddd, *J* = 8.6, 7.2, 1.7 Hz, 1H), 7.06 (td, *J* = 7.7, 1.1 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 5.81 (ddt, *J* = 17.1, 10.2, 5.6 Hz, 1H), 5.25 – 5.17 (m, 2H), 4.80 (d, *J* = 11.7 Hz, 1H), 4.68 – 4.59 (m, 2H), 4.31 (d, *J* = 11.7 Hz, 1H), 2.70 – 2.50 (m, 2H), 2.31 (ddd, *J* = 14.2, 10.1, 5.8 Hz, 1H), 2.15 (ddd, *J* = 14.3, 10.3, 5.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 189.7, 179.6, 169.0, 161.0, 136.5, 131.1, 128.0, 122.2, 120.1, 119.0, 117.9, 72.1, 66.5, 56.3, 32.4, 25.0.

IR (Neat Film, NaCl): 3076, 2937, 2264, 2136, 1713, 1606, 1458, 1220 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{16}H_{15}NO_5$ $[M+H]^+$: 302.1023, found 302.1012.



101j

allyl 3-(3-azido-3-oxopropyl)-4-oxoisochromane-3-carboxylate (101j)

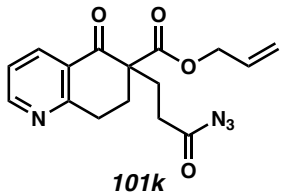
Prepared from **131** following General Procedure B. Purification by flash column chromatography (0–30% ethyl acetate/hexanes) afforded the title compound as a clear oil (400 mg, 1.22 mmol, 64% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.58 (m, 1H), 7.41 (m, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 5.92 – 5.76 (m, 1H), 5.41 – 5.16 (m, 2H), 4.90 (d, *J* = 16.1 Hz, 1H), 4.63 (m, 2H), 2.64 – 2.38 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.0, 179.8, 167.8, 141.0, 134.7, 131.0, 128.4, 128.0, 127.4, 124.4, 119.3, 84.1, 66.6, 64.3, 31.2.

IR (neat film, NaCl): 2948, 2270, 2139, 1741, 1701, 1603, 1449, 1287, 1210, 1051, 756 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{16}H_{15}NO_5Na$ $[M–N_2+Na]^+$: 324.0842, found 324.0831.



101k

allyl 6-(3-azido-3-oxopropyl)-5-oxo-5,6,7,8-tetrahydroquinoline-6-carboxylate (101k)

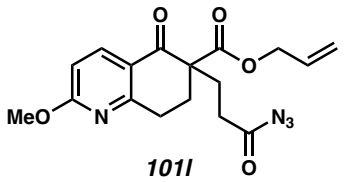
Prepared from **132** following General Procedure B. Purification by flash column chromatography (0–40% ethyl acetate/hexanes) afforded the title compound as a clear oil (0.193 mg, 0.59 mmol, 27% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (dd, *J* = 4.8, 1.9 Hz, 1H), 8.34 – 8.26 (m, 1H), 7.31 (dd, *J* = 7.9, 4.7 Hz, 1H), 5.78 (ddt, *J* = 17.6, 10.0, 5.7 Hz, 1H), 5.22 – 5.13 (m, 2H), 4.58 (dt, *J* = 5.2, 1.4 Hz, 2H), 3.29 – 3.09 (m, 2H), 2.74 – 2.56 (m, 2H), 2.47 (ddd, *J* = 16.7, 10.1, 5.4 Hz, 1H), 2.29 (dddd, *J* = 42.9, 14.1, 10.3, 5.4 Hz, 2H), 2.15 (ddd, *J* = 13.9, 9.6, 6.1 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.8, 179.9, 170.8, 162.0, 154.0, 136.0, 131.2, 127.9, 122.6, 119.3, 66.3, 56.5, 32.5, 30.6, 29.3, 28.8.

IR (neat film, NaCl): 2949, 2272, 2138, 1713, 1694, 1584, 1442, 1181, 1089, 943, 759 cm^{-1}.

HMRS (FD+): *m/z* calc'd for $C_{16}H_{16}N_4O_4$ $[M]^{+\bullet}$: 328.1166, found 328.1154.



101l

allyl 6-(3-azido-3-oxopropyl)-2-methoxy-5-oxo-5,6,7,8-tetrahydroquinoline-6-carboxylate (101l)

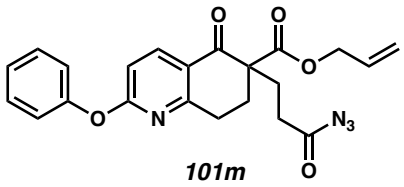
Prepared from **133** following General Procedure B. Purification by flash column chromatography (0–30% ethyl acetate/hexanes) afforded the title compound as a clear oil (259 mg, 0.72 mmol, 42% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.7 Hz, 1H), 6.66 (d, *J* = 8.7 Hz, 1H), 5.81 (ddt, *J* = 17.4, 10.2, 5.7 Hz, 1H), 5.26 – 5.15 (m, 2H), 4.59 (d, *J* = 5.6 Hz, 2H), 3.98 (s, 3H), 3.14 – 2.94 (m, 2H), 2.78 – 2.54 (m, 2H), 2.48 (ddd, *J* = 16.8, 10.1, 5.5 Hz, 1H), 2.32 (ddd, *J* = 14.1, 10.1, 5.6 Hz, 1H), 2.21 (ddd, *J* = 14.2, 10.4, 5.5 Hz, 1H), 2.14 – 1.97 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 180.1, 171.2, 166.5, 162.4, 138.5, 131.4, 122.1, 119.0, 110.6, 66.2, 56.1, 54.2, 32.6, 30.5, 29.2, 28.7.

IR (neat film, NaCl): 2945, 2267, 2139, 1727, 1592, 1480, 1329, 1267, 1183, 1072, 1020, 842, 784 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{=17}H_{19}N_2O_5$ $[M–N_2+H]^+$: 331.1288, found 331.1301.



101m

allyl 6-(3-azido-3-oxopropyl)-5-oxo-2-phenoxy-5,6,7,8-tetrahydroquinoline-6-carboxylate (101m)

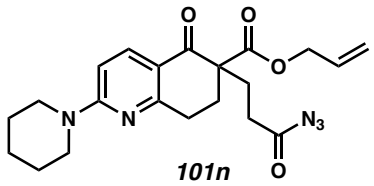
Prepared from **134** following General Procedure B. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (164 mg, 0.39 mmol, 44% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.6 Hz, 1H), 7.47 – 7.33 (m, 2H), 7.26 (s, 1H), 7.19 – 7.11 (m, 2H), 6.76 (d, *J* = 8.7 Hz, 1H), 5.81 (m, 1H), 5.22 (dd, *J* = 8.4, 1.4 Hz, 1H), 5.19 (m, 1H), 4.59 (m, 2H), 3.18 – 2.86 (m, 2H), 2.75 – 2.38 (m, 3H), 2.27 (dddd, *J* = 43.3, 14.1, 10.2, 5.5 Hz, 2H), 2.09 (ddd, *J* = 13.9, 9.8, 5.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5, 180.0, 171.0, 166.1, 162.8, 153.3, 139.8, 131.3, 129.9, 125.6, 123.5, 121.6, 119.1, 110.0, 66.2, 56.2, 32.6, 30.5, 29.1, 28.7.

IR (neat film, NaCl): 2946, 2266, 2137, 1727, 1579, 1489, 1451, 1414, 1314, 1257, 1196, 1071, 941, 777 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{22}H_{21}N_2O_5$ $[M–N_2+H]^+$: 393.1445, found 393.1446.



101n

allyl 6-(3-azido-3-oxopropyl)-5-oxo-2-(piperidin-1-yl)-5,6,7,8-tetrahydroquinoline-6-carboxylate (101n)

Prepared from **135** following General Procedure B. Purification by flash column chromatography (0–30% ethyl acetate/hexanes) afforded the title compound as a clear oil (1.18 g, 2.87 mmol, 66% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 9.1 Hz, 1H), 6.53 (d, *J* = 9.1 Hz, 1H), 5.92 – 5.76 (m, 1H), 5.34 – 5.14 (m, 2H), 4.64 – 4.56 (m, 2H), 3.70 (m, 4H), 3.02 – 2.77 (m, 2H), 2.69 – 2.40 (m, 3H), 2.38 – 2.19 (m, 2H), 2.13 – 1.86 (m, 1H), 1.76 – 1.66 (m, 2H), 1.67 – 1.57 (m, 4H).

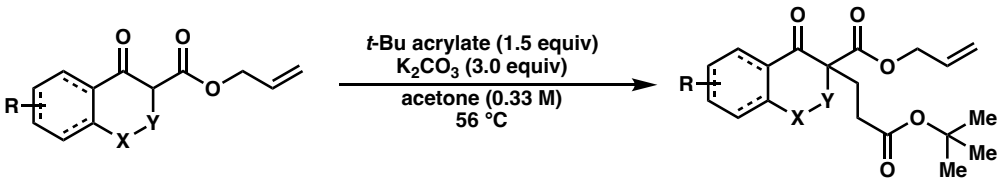
^{13}C NMR (100 MHz, $CDCl_3$): δ 192.8, 180.3, 171.8, 163.4, 159.8, 137.3, 131.7, 118.7, 117.1, 105.1, 66.0, 56.0, 45.8, 32.8, 30.5, 29.5, 28.8, 25.9, 24.8.

IR (neat film, NaCl): 2938, 2855, 2266, 2137, 1729, 1662, 1589, 1498, 1408, 1249, 1088, 1024, 941, 817 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{21}H_{26}N_5O_4$ $[M+H]^+$: 412.2132, found 412.2113.

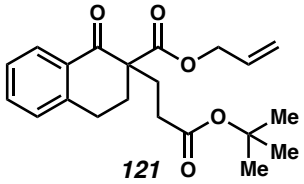
Preparation of *tert*-Butyl Ester Intermediates

General Procedure C: Michael Addition of tert-Butyl Acrylate



136 *120*

To a flask containing intermediate **136** was added acetone (0.33 M), *t*-butyl acrylate (1.5 equiv) and K_2CO_3 (3.0 equiv). The reaction was heated to 56 °C for 5 h, or until complete consumption of starting material by TLC analysis. The reaction was cooled, filtered through a small Celite plug, concentrated, and purified via silica gel chromatography to afford ester **120**.



121

allyl 2-(3-(*tert*-butoxy)-3-oxopropyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (121)

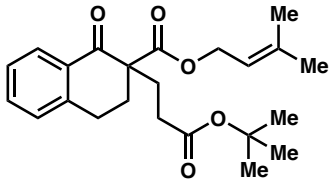
Prepared from **137** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (11.65 g, 32.5 mmol, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (m, 1H), 7.46 (m, 1H), 7.30 (m, 1H), 7.20 (m, 1H), 5.86 – 5.71 (m, 1H), 5.21 – 5.09 (m, 2H), 4.65 – 4.51 (m, 2H), 3.11 – 2.89 (m, 2H), 2.57 (m, 1H), 2.51 – 2.39 (m, 1H), 2.38 – 2.04 (m, 4H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 172.5, 171.5, 142.9, 133.7, 132.1, 131.6, 128.8, 128.2, 127.0, 118.4, 80.5, 65.8, 56.9, 31.2, 31.1, 29.0, 28.2, 25.9.

IR (neat film, NaCl): 2974, 2365, 1729, 1686, 1601, 1365, 1228, 1154, 947 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{21}H_{26}O_5Na$ $[M+Na]^+$: 381.1672, found 381.1676.



122

3-methylbut-2-en-1-yl 2-(3-(*tert*-butoxy)-3-oxopropyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (122)

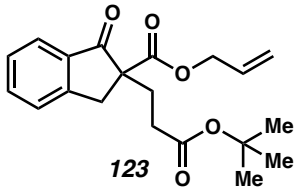
Prepared from **138** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (1.18 g, 3.10 mmol, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (dt, *J* = 8.0, 1.3 Hz, 1H), 7.58 – 7.38 (m, 1H), 7.32 (d, *J* = 1.4 Hz, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 5.22 (ddt, *J* = 7.2, 5.8, 1.4 Hz, 1H), 4.65 – 4.49 (m, 2H), 3.10 – 2.87 (m, 2H), 2.60 – 2.39 (m, 2H), 2.38 – 2.20 (m, 2H), 2.20 – 1.97 (m, 2H), 1.68 (s, 3H), 1.58 (s, 3H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.4, 172.6, 171.8, 143.0, 139.9, 133.6, 132.3, 128.8, 128.2, 126.9, 118.2, 80.5, 62.3, 56.9, 31.5, 31.2, 29.2, 28.2, 26.0, 25.8, 18.1.

IR (neat film, NaCl): 2974, 2361, 1729, 1691, 1601, 1454, 1367, 1226, 1164, 941, 741 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{23}H_{30}O_5Na$ $[M+Na]^+$: 409.1985, found 409.1977.



123

allyl 2-(3-(*tert*-butoxy)-3-oxopropyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (123)

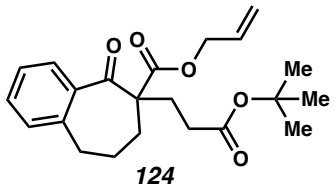
Prepared from **139** following General Procedure C. Purification by flash column chromatography (20% EtOAc/hexanes) afforded the title compound as a clear oil (772 mg, 2.24 mmol, 39% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.63 (td, *J* = 7.5, 1.2 Hz, 1H), 7.48 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.40 (td, *J* = 7.2, 0.9 Hz, 1H), 5.83 (ddt, *J* = 17.3, 10.5, 5.5 Hz, 1H), 5.23 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.18 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.60 (dt, *J* = 5.5, 1.5 Hz, 2H), 3.70 (d, *J* = 17.4 Hz, 1H), 3.09 (d, *J* = 17.3 Hz, 1H), 2.38 – 2.21 (m, 4H), 1.44 (s, 2H), 1.41 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.1, 172.1, 170.7, 152.8, 135.6, 135.3, 131.7, 128.1, 126.5, 125.0, 118.5, 80.7, 66.2, 59.7, 37.3, 31.1, 30.0, 28.2.

IR (Neat Film, NaCl): 3427, 2980, 2340, 1715, 1605, 1453, 1368, 1168 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{20}H_{24}O_5$ $[M+Na]^+$: 367.1516, found 367.1527.



124

allyl 6-(3-(*tert*-butoxy)-3-oxopropyl)-5-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-6-carboxylate (124)

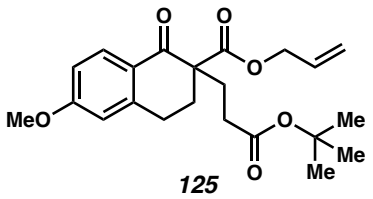
Prepared from **140** following General Procedure C. Purification by flash column chromatography (0–10% ethyl acetate/hexanes) afforded the title compound as a clear oil (409 mg, 1.10 mmol, 79% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (m, 1H), 7.35 (m, 1H), 7.29 – 7.20 (m, 3H), 7.11 (m, 1H), 5.66 (ddt, *J* = 17.3, 10.4, 5.8 Hz, 1H), 5.23 – 5.10 (m, 2H), 4.47 (dt, *J* = 5.7, 1.1 Hz, 2H), 3.09 – 2.61 (m, 2H), 2.58 – 2.12 (m, 5H), 2.10 – 1.95 (m, 1H), 1.92 – 1.72 (m, 2H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.4, 172.4, 171.9, 140.2, 138.8, 131.5, 131.3, 129.3, 129.2, 126.6, 119.0, 80.6, 66.0, 61.4, 33.1, 32.8, 31.6, 30.9, 28.2, 24.0.

IR (neat film, NaCl): 2935, 1730, 1685, 1449, 1366, 1253, 1153, 1090, 958 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{22}H_{29}O_5Na$ $[M+Na]^+$: 395.1829, found 395.1831.



125

allyl 2-(3-(*tert*-butoxy)-3-oxopropyl)-6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (125)

Prepared from **141** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (1.02 g, 2.62 mmol, 94% yield).

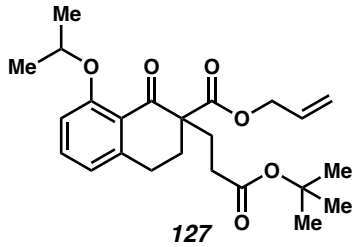
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.8 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.65 (d, *J* = 2.5 Hz, 1H), 5.88 – 5.74 (m, 1H), 5.24 – 5.12 (m, 2H), 4.66 – 4.53 (m, 2H),

3.85 (s, 3H), 3.07 – 2.86 (m, 2H), 2.56 (ddd, *J* = 13.6, 5.9, 4.8 Hz, 1H), 2.50 – 2.01 (m, 5H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 172.6, 171.7, 163.9, 145.5, 131.7, 130.7, 125.6, 118.4, 113.7, 112.5, 80.5, 65.8, 56.7, 55.6, 31.2, 29.0, 28.2, 26.3.

IR (neat film, NaCl): 2934, 1729, 1600, 1450, 1366, 1257, 1155, 1080, 934, 850, 681 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{22}H_{28}O_6Na$ $[M+Na]^+$: 411.1778, found 411.1775.



127

allyl 2-(3-(*tert*-butoxy)-3-oxopropyl)-8-isopropoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (127)

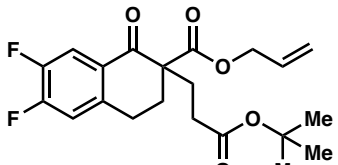
Prepared from **142** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (637 mg, 1.53 mmol, 86% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (dd, *J* = 8.3, 7.6 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.72 (dd, *J* = 7.6, 1.0 Hz, 1H), 5.77 (ddt, *J* = 17.3, 10.7, 5.4 Hz, 1H), 5.22 – 5.00 (m, 2H), 4.65 – 4.47 (m, 3H), 3.20 – 2.71 (m, 2H), 2.62 – 2.20 (m, 4H), 2.20 – 2.09 (m, 1H), 2.06 – 1.88 (m, 1H), 1.43 (s, 9H), 1.36 (dd, *J* = 14.1, 6.0 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 172.6, 171.8, 159.2, 145.0, 133.7, 131.7, 123.6, 120.6, 118.2, 113.7, 80.4, 71.8, 65.6, 58.0, 31.1, 30.6, 29.4, 28.2, 26.6, 22.2, 22.2.

IR (neat film, NaCl): 2976, 2932, 1780, 1693, 1592, 1453, 1367, 1270, 1154, 1112, 921, 848, 764 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{24}H_{33}O_6$ $[M+H]^+$: 417.2272, found 417.2274.



128

allyl 2-(3-(*tert*-butoxy)-3-oxopropyl)-6,7-difluoro-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (128)

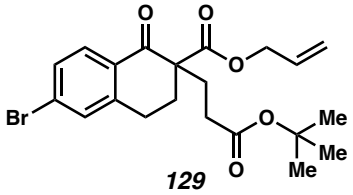
Prepared from **143** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (1.07 g, 2.71 mmol, 73% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (m, 1H), 7.00 (m, 1H), 5.86 – 5.72 (m, 1H), 5.23 – 5.11 (m, 2H), 4.65 – 4.51 (m, 2H), 3.05 – 2.84 (m, 2H), 2.55 (m, 1H), 2.50 – 2.37 (m, 1H), 2.36 – 2.16 (m, 3H), 2.16 – 2.05 (m, 1H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 192.99, 172.29, 171.03, 153.83 (dd, *J* = 258.5, 13.5 Hz), 149.68 (dd, *J* = 249.9, 13.3 Hz), 140.48 (dd, *J* = 7.3, 3.6 Hz), 131.38, 129.45 – 128.95 (m), 118.83, 117.22 (d, *J* = 17.5 Hz), 116.88 (dd, *J* = 17.7, 2.2 Hz), 80.68, 66.07, 56.42, 31.26, 30.97, 28.98, 28.18, 25.53.

IR (neat film, NaCl): 3434, 2935, 2356, 1750, 1435, 1213, 1097, 991, 665 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{21}H_{24}F_2O_5$ $[M+Na]^+$: 417.1484, found 417.1492.



129

allyl 6-bromo-2-(3-(*tert*-butoxy)-3-oxopropyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (129)

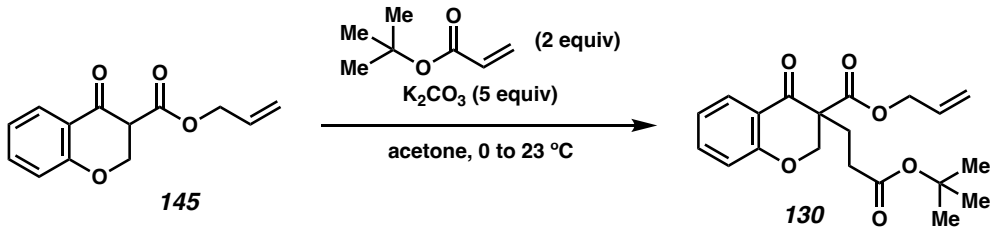
Prepared from **144** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (772 mg, 1.77 mmol, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.4 Hz, 1H), 7.47 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.42 (d, *J* = 1.9 Hz, 1H), 6.05 – 5.59 (m, 1H), 5.25 – 5.15 (m, 2H), 4.61 (dq, *J* = 5.6, 1.5 Hz, 2H), 3.11 – 2.89 (m, 2H), 2.58 (m, 1H), 2.52 – 2.39 (m, 1H), 2.41 – 2.09 (m, 4H), 1.45 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.3, 172.4, 171.2, 144.6, 131.8, 131.5, 131.0, 130.5, 129.9, 129.0, 118.8, 80.7, 66.0, 56.8, 31.1, 31.0, 29.0, 28.2, 25.8.

IR (neat film, NaCl): 2975, 2360, 1780, 1691, 1587, 1367, 1226, 1154, 1089 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{21}H_{25}BrO_5Na$ $[M+Na]^+$: 459.0778, found 459.0783.



145 ***130***

allyl 3-(3-(*tert*-butoxy)-3-oxopropyl)-4-oxochromane-3-carboxylate (130)

48 reactions performed in parallel and combined for purification. Yield significantly decreased at larger scale. A solution of b-ketoester **145** (20 mg, 0.09 mmol, 1 equiv) in

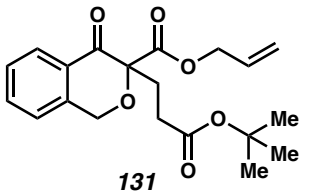
acetone (0.3 mL, 0.3 M) was cooled to 0 ºC. To the reaction K_2CO_3 (59 mg, 0.43 mmol, 5 equiv) and *t*-Bu acrylate (25 mL, 0.17 mmol, 2 equiv) were added, and the reaction was slowly warmed to 23 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction was filtered over celite with acetone and concentrated. Purification by flash column chromatography (10% EtOAc/hexanes) afforded the title compound (500 mg, 1.38 mmol, 33% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.49 (ddd, *J* = 8.4, 7.2, 1.8 Hz, 1H), 7.05 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H), 6.97 (dd, *J* = 8.3, 1.0 Hz, 1H), 5.82 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.24 – 5.16 (m, 2H), 4.81 (d, *J* = 11.7 Hz, 1H), 4.70 – 4.58 (m, 2H), 4.32 (d, *J* = 11.6 Hz, 1H), 2.52 – 2.34 (m, 2H), 2.29 (ddd, *J* = 14.0, 10.1, 5.8 Hz, 1H), 2.12 (ddd, *J* = 14.1, 10.5, 5.4 Hz, 1H), 1.43 (s, 10H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 189.8, 171.9, 169.2, 161.0, 136.3, 131.3, 128.0, 122.1, 120.3, 118.8, 117.9, 80.9, 72.0, 66.4, 56.5, 30.9, 28.2, 25.5.

IR (Neat Film, NaCl): 3437, 2980, 2932, 1731, 1607, 1479, 1217 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{20}H_{24}O_6$ $[M+Na]^+$: 383.1465, found 383.1470.



131

allyl 3-(3-(*tert*-butoxy)-3-oxopropyl)-4-oxochromane-3-carboxylate (131)

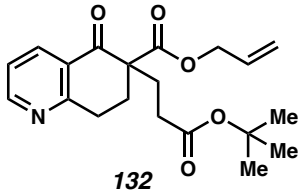
Prepared from **146** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (686 mg, 1.90 mmol, 39% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.56 (td, *J* = 7.5, 1.4 Hz, 1H), 7.44 – 7.35 (m, 1H), 7.16 (dt, *J* = 7.7, 0.9 Hz, 1H), 5.84 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.34 – 5.15 (m, 3H), 4.94 – 4.85 (m, 1H), 4.71 – 4.57 (m, 2H), 2.66 – 2.10 (m, 4H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.3, 172.1, 168.1, 141.1, 134.5, 131.2, 128.5, 127.9, 127.4, 124.4, 119.1, 84.6, 80.5, 66.4, 64.2, 30.5, 29.7, 28.2.

IR (neat film, NaCl): 2973, 1781, 1603, 1364, 1230, 1169, 707 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{20}H_{24}O_6Na$ $[M+Na]^+$: 383.1465, found 383.1467.



132

allyl 6-(3-(*tert*-butoxy)-3-oxopropyl)-5-oxo-5,6,7,8-tetrahydroquinoline-6-carboxylate (132)

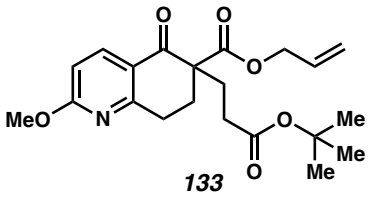
Prepared from **147** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (830 mg, 2.31 mmol, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (dd, *J* = 4.7, 1.9 Hz, 1H), 8.29 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.30 (dd, *J* = 7.9, 4.8 Hz, 1H), 5.86 – 5.72 (m, 1H), 5.23 – 5.13 (m, 2H), 4.59 (dq, *J* = 5.7, 1.5 Hz, 2H), 3.27 – 3.09 (m, 2H), 2.62 (dt, *J* = 13.9, 5.0 Hz, 1H), 2.54 – 2.41 (m, 1H), 2.38 – 2.26 (m, 2H), 2.26 – 2.10 (m, 2H), 1.44 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.9, 172.3, 171.0, 162.2, 153.9, 136.0, 131.4, 127.9, 122.5, 119.0, 80.7, 66.2, 56.7, 31.0, 30.2, 29.3, 29.0, 28.2.

IR (neat film, NaCl): 2977, 1729, 1697, 1584, 1456, 1367, 1229, 1171, 1155, 937 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{20}H_{26}NO_5$ $[M+H]^+$: 360.1805, found 360.1813.



133

allyl 6-(3-(*tert*-butoxy)-3-oxopropyl)-5-oxo-5,6,7,8-tetrahydroquinoline-6-carboxylate (133)

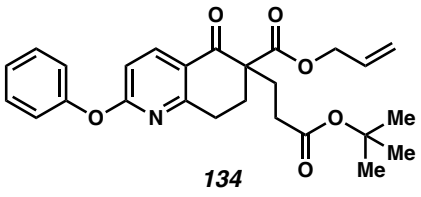
Prepared from **148** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (670 mg, 1.72 mmol, 61% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.7 Hz, 1H), 6.66 (d, *J* = 8.7 Hz, 1H), 5.82 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.26 – 5.14 (m, 2H), 4.60 (dt, *J* = 5.6, 1.5 Hz, 2H), 3.98 (s, 3H), 3.14 – 2.94 (m, 2H), 2.59 (dt, *J* = 13.8, 5.3 Hz, 1H), 2.50 – 2.02 (m, 5H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 172.4, 171.3, 166.4, 162.5, 138.6, 131.6, 122.2, 118.7, 110.4, 80.6, 66.0, 56.4, 54.2, 31.1, 30.1, 29.2, 28.9, 28.2.

IR (neat film, NaCl): 2977, 2365, 1780, 1683, 1480, 1415, 1329, 1265, 1154, 1020 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{21}H_{28}NO_6$ $[M+H]^+$: 390.1911, found 390.1913.



134

allyl 6-(3-(*tert*-butoxy)-3-oxopropyl)-5-oxo-2-phenoxy-5,6,7,8-tetrahydroquinoline-6-carboxylate (134)

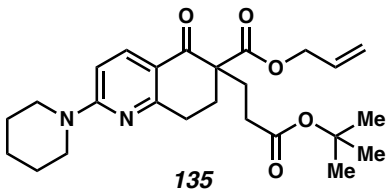
Prepared from **149** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (395 mg, 0.87 mmol, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (dd, *J* = 8.7, 0.8 Hz, 1H), 7.42 (ddd, *J* = 8.4, 7.4, 0.8 Hz, 2H), 7.19 – 7.11 (m, 2H), 6.75 (d, *J* = 8.6 Hz, 1H), 5.82 (dddd, *J* = 11.4, 10.5, 5.2, 0.8 Hz, 1H), 5.27 – 5.15 (m, 2H), 4.60 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.10 – 2.90 (m, 2H), 2.62 – 2.02 (m, 6H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 172.4, 171.2, 166.0, 162.9, 153.3, 139.8, 131.5, 129.9, 125.5, 123.6, 121.6, 118.8, 109.9, 80.7, 66.1, 56.5, 31.0, 30.1, 29.1, 28.9, 28.2.

IR (neat film, NaCl): 2973, 2351, 1729, 1685, 1579, 1455, 1315, 1256, 1156 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{26}H_{30}NO_6$ $[M+H]^+$: 452.2068, found 452.2072.



135

allyl 6-(3-(*tert*-butoxy)-3-oxopropyl)-5-oxo-2-(piperidin-1-yl)-5,6,7,8-tetrahydroquinoline-6-carboxylate (135)

Prepared from **150** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (1.94 g, 4.39 mmol, 94% yield).

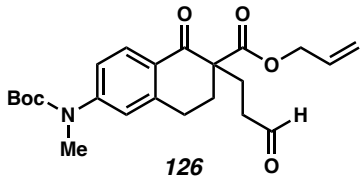
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 9.1 Hz, 1H), 6.52 (d, *J* = 9.1 Hz, 1H), 5.84 (ddt, *J* = 17.4, 10.7, 5.5 Hz, 1H), 5.34 – 5.13 (m, 2H), 4.59 (dd, *J* = 5.5, 1.5 Hz, 2H), 3.69 (m, 4H), 3.03 – 2.79 (m, 2H), 2.54 (ddd, *J* = 13.7, 6.1, 5.0 Hz, 1H), 2.47 – 2.21 (m, 3H), 2.22 – 2.11 (m, 1H), 2.06 (ddd, *J* = 13.9, 8.6, 5.2 Hz, 1H), 1.69 (d, *J* = 4.8 Hz, 2H), 1.66 – 1.54 (m, 6H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.0, 172.6, 171.9, 163.5, 159.8, 137.4, 131.8, 118.4, 117.2, 105.0, 80.4, 65.8, 56.2, 45.8, 31.2, 30.1, 29.5, 29.0, 28.2, 25.8, 24.8.

IR (neat film, NaCl): 2937, 2855, 1729, 1663, 1589, 1496, 1406, 1249, 1154, 1085, 1022, 949, 698 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{25}H_{35}N_2O_5$ $[M+H]^+$: 443.2540, found 443.2551.

Preparation of aldehyde S13.



126

allyl 6-((*tert*-butoxycarbonyl)(methyl)amino)-2-(3-hydroxy-3λ2-propyl)-1-oxo-1,2,3,4- tetrahydronaphthalene-2-carboxylate (126)

Prepared from **151**. To a solution of **151** (1.42 g, 3.95 mmol) was added acrolein (0.4 mL, 5.9 mmol, 1.5 equiv) and triethylamine (80 uL, 0.6 mmol, 0.15 equiv) in DMF (3.2 mL, 1.2 M). The reaction was stirred at 23 °C until starting material was consumed by TLC, at which point the reaction was quenched with water and extracted with diethyl ether (x3), dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification

by flash column chromatography (30% ethyl acetate/hexanes) afforded the title compound (1.33 g, 3.21 mmol, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.22 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.16 (d, *J* = 2.2 Hz, 1H), 5.81 (ddt, *J* = 17.3, 10.5, 5.6 Hz, 1H), 5.23 – 5.14 (m, 2H), 4.59 (dt, *J* = 5.6, 1.4 Hz, 2H), 3.29 (s, 3H), 3.09 – 2.97 (m, 1H), 2.92 (dt, *J* = 17.4, 5.2 Hz, 1H), 2.79 – 2.68 (m, 1H), 2.65 – 2.51 (m, 2H), 2.35 – 2.18 (m, 2H), 2.11 (ddd, *J* = 13.7, 9.8, 4.9 Hz, 1H), 1.49 (s, 9H).

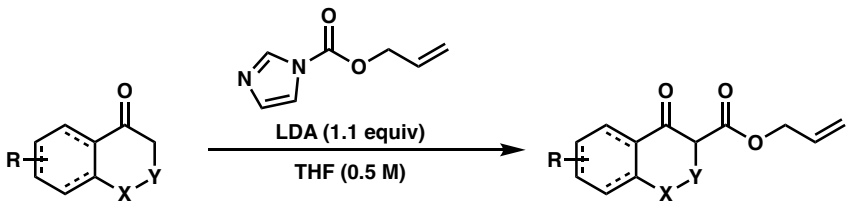
^{13}C NMR (100 MHz, $CDCl_3$): δ 201.3, 194.3, 171.6, 154.2, 148.6, 143.5, 131.5, 128.8, 128.4, 123.9, 123.1, 118.8, 81.5, 66.0, 56.6, 39.8, 36.9, 31.8, 28.4, 26.3, 26.2.

IR (Neat Film, NaCl): 2941, 2346, 1703, 1600, 1357, 1164 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{23}H_{29}NO_6$ $[M+H]^+$: 416.2068, found 416.2067.

Preparation of New β-Keto Ester Intermediates

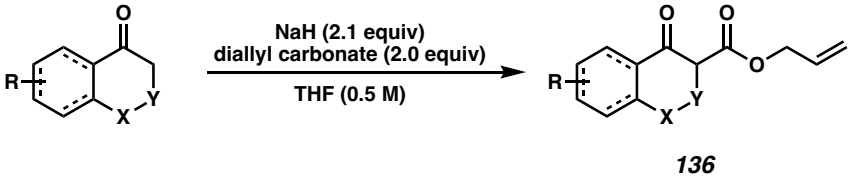
General Procedure D: Acylation of Ketones using N-Acyl Imidazole Reagent



136

A flame dried round bottom flask was charged with *i*-Pr_2NH (1.1 equiv) and THF (1.75 M). The solution was cooled to 0 ºC and *n*-BuLi (2.5 M in hexanes, 1.05 equiv) was added dropwise. The resultant solution was stirred for 30 min at 0 ºC. Then, ketone (1.0 equiv) in THF (1.25 M) was added dropwise and stirring was continued at 0 ºC for 30 minutes. The solution was cooled to –78 ºC, and the N-acyl imidazole reagent (1.2 equiv) in THF (3.25 M) was added dropwise. After 2 h, the reaction was gradually warmed to 23 ºC and diluted with 2 M aqueous HCl until reaching a pH < 7. The reaction mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography to afford the acylated ketone **136**.

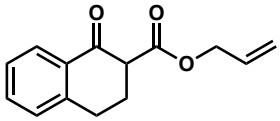
General Procedure E: Acylation of Ketones using Diallyl Carbonate



136

A flame dried round bottom flask was charged with NaH (2.1 equiv) and THF (0.625 M). Diallyl carbonate was added, followed by a solution of ketone (1.0 equiv) in THF (2.5 M)

dropwise. The solution was heated to reflux for 2 h or until complete conversion by TLC, at which point the reaction was cooled and quenched with 1 M aqueous HCl until neutral. The reaction mixture was extracted three times with EtOAc, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography to afford the acylated ketone **136**.

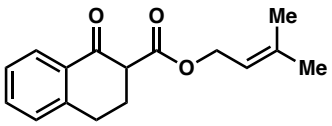


137

allyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (137)

Prepared from 3,4-dihydronaphthalen-1(2*H*)-one following General Procedure D. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (622 mg, 2.70 mmol, 54% yield). All characterization data match those reported in the literature.[30]

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (7:3) δ 12.39 (s, 0.7H), 8.05 (dd, *J* = 7.9, 1.5 Hz, 0.3H), 7.81 (dd, *J* = 7.5, 1.6 Hz, 1=0.7H), 7.50 (m, 0.3H), 7.42 – 7.27 (m, 2H), 7.21 – 7.10 (m, 0.7H), 6.14 – 5.82 (m, 1H), 5.52 – 5.34 (m, 1H), 5.33 – 5.07 (m, 1H), 4.83 – 4.52 (m, 2H), 3.65 (dd, *J* = 10.5, 4.7 Hz, 0.3H), 3.04 (dt, *J* = 13.6, 5.0 Hz, 0.6H), 2.82 (dd, *J* = 8.9, 6.6 Hz, 1.4H), 2.65 – 2.56 (m, 1.4H), 2.55 – 2.17 (m, 0.6H).



138

3-methylbut-2-en-1-yl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (138)

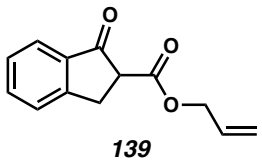
Prepared from 3,4-dihydronaphthalen-1(2*H*)-one following General Procedure D, using a prenyl variant of the N-acyl imidazole reagent instead. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (1.15 g, 4.75 mmol, 47% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (6:4) δ 12.46 (s, 0.6H), 8.05 (dd, *J* = 7.9, 1.4 Hz, 0.4H), 7.80 (dd, *J* = 7.4, 1.7 Hz, 0.6H), 7.49 (td, *J* = 7.5, 1.5 Hz, 0.4H), 7.36 – 7.22 (m, 2H), 7.21 – 7.11 (m, 0.6H), 5.48 – 5.25 (m, 1H), 4.85 – 4.48 (m, 2H), 3.61 (dd, *J* = 10.3, 4.7 Hz, 0.4H), 3.12 – 2.93 (m, 0.8H), 2.80 (dd, *J* = 8.9, 6.6 Hz, 1.2H), 2.57 (dd, *J* = 8.8, 6.6 Hz, 1.2H), 2.53 – 2.14 (m, 0.8H), 1.79 (s, 2.4H), 1.75 (s, 3.6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.4, 172.9, 170.4, 165.1, 143.8, 139.6, 139.6, 139.2, 134.0, 132.0, 130.6, 130.2, 128.9, 127.9, 127.5, 127.0, 126.7, 124.4, 118.8, 118.4, 118.3, 97.3, 64.7, 62.4, 61.6, 54.7, 27.9, 27.8, 26.6, 26.0, 25.9, 20.7, 18.3, 18.2.

IR (neat film, NaCl): 2938, 2342, 1739, 1643, 1453, 1392, 1268, 1210, 1082, 956, 759 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{16}H_{18}O_3Na$ $[M+Na]^+$: 281.1148, found 281.1140.

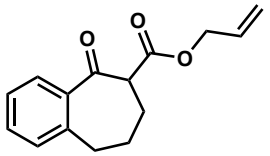


139

allyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (139)

Prepared from 2,3-dihydro-1*H*-inden-1-one following General Procedure D. Purification by flash column chromatography (5–10% EtOAc/hexanes) afforded the title compound as a clear oil (1.24 g, 5.72 mmol, 57% yield). All characterization data match those reported in the literature.[31]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.63 (td, *J* = 7.5, 1.3 Hz, 1H), 7.51 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.40 (ddd, *J* = 7.9, 7.1, 0.9 Hz, 1H), 5.94 (ddt, *J* = 17.3, 10.5, 5.7 Hz, 1H), 5.37 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.26 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.70 (tt, *J* = 5.9, 1.5 Hz, 2H), 3.76 (dd, *J* = 8.3, 4.1 Hz, 1H), 3.63 – 3.52 (m, 1H), 3.39 (dd, *J* = 17.3, 8.2 Hz, 1H).

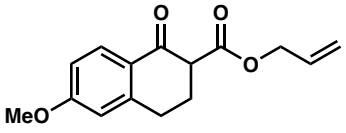


140

allyl 5-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-6-carboxylate (140)

Prepared from 6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one following General Procedure D. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (339 mg, 1.39 mmol, 28% yield). All characterization data match those reported in the literature.[32]

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (7:3) δ 12.59 (s, 0.7H), 7.75 (dd, *J* = 7.7, 1.5 Hz, 0.3H), 7.67 – 7.58 (m, 0.7H), 7.43 (td, *J* = 7.5, 1.5 Hz, 0.3H), 7.39 – 7.29 (m, 1.7H), 7.25 – 7.03 (m, 1H), 6.22 – 5.74 (m, 1H), 5.38 (m, 1H), 5.33 – 5.20 (m, 1H), 4.74 (m, 1.4H), 4.70 – 4.59 (m, 0.6H), 3.85 (dd, *J* = 10.5, 4.4 Hz, 0.3H), 3.01 – 2.90 (m, 0.6H), 2.65 (t, *J* = 6.8 Hz, 1.4H), 2.26 – 1.99 (m, 3.7H), 1.85 (ddd, *J* = 8.9, 6.8, 5.5 Hz, 0.3H).

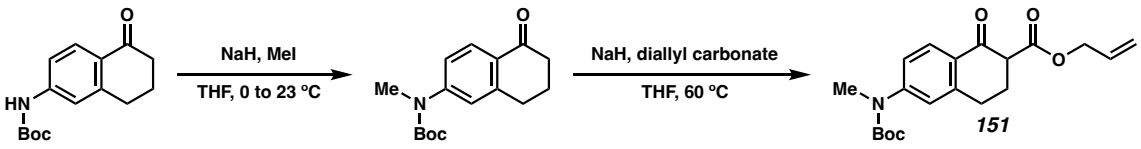


141

allyl 6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (141)

Prepared from 6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one following General Procedure D. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (751 mg, 2.89 mmol, 58% yield). All characterization data match those reported in the literature.[33]

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (3:7) δ 12.44 (s, 0.3H), 8.03 (d, *J* = 8.8 Hz, 0.7H), 7.74 (d, *J* = 8.6 Hz, 0.3H), 6.82 (ddd, *J* = 16.3, 8.7, 2.6 Hz, 1H), 6.70 (dd, *J* = 5.9, 2.5 Hz, 1H), 6.07 – 5.86 (m, 1H), 5.48 – 5.12 (m, 2H), 4.86 – 4.62 (m, 2H), 3.86 (s, 2H), 3.84 (s, 1H), 3.60 (dd, *J* = 10.3, 4.7 Hz, 0.7H), 3.16 – 2.91 (m, 1.4H), 2.79 (m, 0.6H), 2.63 – 2.56 (m, 0.6H), 2.54 – 2.26 (m, 1.4H).



allyl 6-((*tert*-butoxycarbonyl)(methyl)amino)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (151)

A solution of *tert*-butyl (5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)carbamate (466 mg, 1.8 mmol, 1 equiv) and THF (1.2 M, 1.5 mL) was cooled 0 ºC. NaH (60% dispersion in mineral oil, 86 mg, 2.1 mmol, 1.2 equiv) was added portion wise. Then MeI (0.13 mL, 2.1 mmol, 1.2 equiv) was added dropwise, and the reaction was slowly warmed to 23 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction mixture was diluted with water and extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude *N*-Me aniline which was used directly in the next step. To NaH (60% dispersion in mineral oil, 150 mg, 3.7 mmol, 2.1 equiv) in THF (2.1 mL, 1.8 M) diallyl carbonate (0.51 mL, 3.6

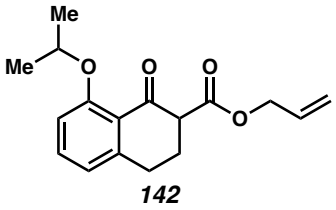
mmol, 2 equiv) was added. Crude *N*-Me aniline in THF (1.5 mL, 1.2 M) was added, and the reaction was heated to 60 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction mixture was cooled to 23 ºC and diluted with a saturated solution of NH_4Cl and extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (15% EtOAc/hexanes) afforded the title compound (376 mg, 1.05 mmol, 59% yield). Mixture of enol-keto tautomers. Used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 12.38 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.22 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.20 (d, *J* = 2.1 Hz, 1H), 7.15 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.11 (d, *J* = 2.2 Hz, 1H), 6.06 – 5.88 (m, 2H), 5.36 (ddq, *J* = 16.8, 13.6, 1.6 Hz, 2H), 5.26 (ddq, *J* = 13.1, 10.5, 1.3 Hz, 2H), 4.73 (dt, *J* = 5.6, 1.5 Hz, 2H), 4.69 (ddt, *J* = 6.1, 4.7, 1.4 Hz, 1H), 3.62 (dd, *J* = 10.3, 4.8 Hz, 1H), 3.30 (s, 2H), 3.28 (s, 3H), 3.10 – 2.91 (m, 2H), 2.80 (dd, *J* = 8.9, 6.6 Hz, 2H), 2.65 – 2.57 (m, 2H), 2.57 – 2.45 (m, 1H), 2.36 (ddt, *J* = 13.5, 5.8, 4.7 Hz, 1H), 1.49 (s, 7H), 1.47 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 192.2, 172.4, 170.1, 165.3, 154.6, 154.2, 148.8, 145.9, 144.3, 140.2, 132.4, 131.9, 128.6, 128.3, 126.8, 124.9, 124.0, 123.1, 123.0, 118.6, 118.3, 96.5, 81.5, 80.9, 66.0, 65.2, 54.6, 37.2, 36.9, 34.8, 31.7, 28.5, 28.4, 28.0, 28.0, 26.5, 22.8, 20.7, 14.3.

IR (Neat Film, NaCl): 2976, 2937, 1738, 1704, 1602, 1433, 1352, 1150 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{20}H_{25}NO_5$ $[M+H]^+$: 360.1805, found 360.1806.



142

allyl 8-isopropoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (142)

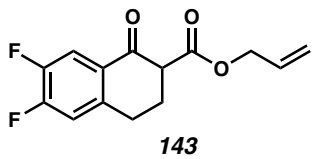
Prepared from 8-isopropoxy-3,4-dihydronaphthalen-1(2H)-one following General Procedure E. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (500 mg, 1.73 mmol, 98% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (4:6) δ 12.68 (s, 0.4H), 7.35 (dd, *J* = 8.4, 7.6 Hz, 0.6H), 7.22 (dd, *J* = 8.4, 7.4 Hz, 0.4H), 6.92 – 6.80 (m, 1H), 6.78 (m, 1H), 5.96 (m, H), 5.51 – 5.28 (m, 1H), 5.27 – 5.00 (m, 2H), 4.70 (ddt, *J* = 16.2, 5.6, 1.5 Hz, 2H), 4.55 (m, 1H), 3.61 (dd, *J* = 10.4, 4.9 Hz, 0.6H), 3.23 – 2.84 (m, 1H), 2.71 (dd, *J* = 8.8, 5.9 Hz, 1H), 2.53 – 2.47 (m, 1H), 2.46 – 2.18 (m, 1H), 1.44 – 1.32 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.6, 172.3, 170.4, 167.7, 159.5, 157.0, 146.1, 143.2, 134.2, 132.6, 132.1, 131.3, 122.6, 120.7, 120.6, 118.4, 118.1, 115.9, 113.7, 97.6, 72.8, 71.8, 65.8, 65.0, 56.5, 29.7, 28.8, 26.2, 22.3, 22.1, 22.1, 20.8.

IR (neat film, NaCl): 2975, 2937, 1740, 1684, 1592, 1463, 1383, 1267, 1116, 989, 922 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{16}H_{20}O_3$ $[M+H]^+$: 274.1438, found 274.1434.



143

allyl 6,7-difluoro-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (143)

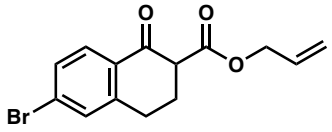
Prepared from 6,7-difluoro-3,4-dihydronaphthalen-1(2*H*)-one following General Procedure D. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (976 mg, 3.67 mmol, 56% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (7:3) δ 12.23 (s, 0.7H), 7.74 (dd, *J* = 10.5, 8.2 Hz, 0.3H), 7.49 (dd, *J* = 11.0, 8.1 Hz, 0.7H), 6.95 (dd, *J* = 10.4, 7.2 Hz, 0.3H), 6.87 (dd, *J* = 10.4, 7.5 Hz, 0.7H), 6.02 – 5.72 (m, 1H), 5.39 – 5.21 (m, 1H), 5.22 – 5.01 (m, 1H), 4.79 – 4.46 (m, 2H), 3.51 (dd, *J* = 9.9, 4.8 Hz, 0.3H), 2.88 (dt, *J* = 17.9, 7.4 Hz, 0.6H), 2.66 (dd, *J* = 9.1, 6.5 Hz, 1.4H), 2.49 (dd, *J* = 9.1, 6.6 Hz, 1.4H), 2.45 – 2.12 (m, 0.6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 172.2, 169.5, 163.5, 163.5, 163.5, 155.4, 155.3, 152.8, 152.8, 152.7, 152.6, 151.0, 150.9, 150.5, 150.4, 150.3, 150.1, 148.5, 148.4, 148.1, 148.0, 141.4, 141.4, 141.3, 141.3, 136.6, 136.5, 136.5, 136.5, 132.2, 132.1, 131.7, 128.9, 128.9, 128.8, 126.9, 126.8, 126.8, 126.8, 118.8, 118.5, 118.4, 117.5, 117.3, 117.3, 116.8, 116.8, 116.6, 116.6, 116.4, 113.9, 113.9, 113.8, 113.7, 97.1, 97.1, 68.1, 66.1, 65.4, 53.8, 50.1, 27.2, 27.1, 27.1, 27.1, 26.4, 20.5.

IR (neat film, NaCl): 2938, 2340, 1744, 1693, 1651, 1590, 1511, 1387, 1327, 1250, 1076, 926, 804 cm^{-1}.

HMRS (ESI–): *m/z* calc'd for $C_{14}H_{12}F2O_3$ $[M–H]^–$: 265.0682, found 265.0686.



144

allyl 6-bromo-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (144)

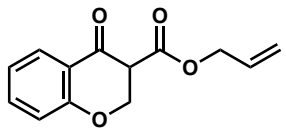
Prepared from 6-bromo-3,4-dihydronaphthalen-1(2*H*)-one following General Procedure E. Purification by flash column chromatography (0–10% ethyl acetate/hexanes) afforded the title compound as a clear oil (639 mg, 2.07 mmol, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (6:4) δ 12.35 (s, 0.6H), 7.91 (d, *J* = 8.3 Hz, 0.4H), 7.65 (d, *J* = 8.3 Hz, 0.6H), 7.52 – 7.38 (m, 1.4H), 7.34 (dt, *J* = 2.0, 0.9 Hz, 0.6H), 6.17 – 5.79 (m, 1H), 5.48 – 5.33 (m, 1H), 5.33 – 5.16 (m, 1H), 4.77 – 4.50 (m, 2H), 3.63 (dd, *J* = 10.1, 4.7 Hz, 0.4H), 3.14 – 2.89 (m, 0.8H), 2.80 (m, 1.2H), 2.67 – 2.53 (m, 1.2H), 2.54 – 2.25 (m, 0.8H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 192.3, 172.3, 169.7, 164.6, 145.4, 141.5, 132.2, 131.9, 131.8, 131.7, 130.7, 130.6, 129.9, 129.6, 129.4, 129.1, 126.1, 125.1, 119.1, 118.8, 118.4, 97.2, 68.6, 66.1, 65.4, 54.4, 27.6, 27.5, 26.3, 20.5.

IR (neat film, NaCl): 2341, 1613, 1259, 1212, 824 cm^{-1}.

HMRS (FD+): *m/z* calc'd for $C_{14}H_{13}BrO_3$ $[M]^{+\bullet}$: 308.0043, found 308.0052.



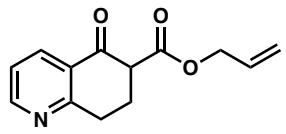
145

allyl 4-oxochromane-3-carboxylate (145)

Prepared from chroman-4-one following General Procedure D. Purification by flash column chromatography (0–5% ethyl acetate/hexanes) afforded the title compound as a clear oil (1.47 g, 6.3 mmol, 42% yield). All characterization data match those reported in the literature.[34]

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.95 (s, 0.4H), 7.93 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.66 (dd, *J* = 7.7, 1.7 Hz, 0.6H), 7.51 (ddd, *J* = 8.4, 7.2, 1.8 Hz, 1H), 7.33 (ddd, *J* = 8.2, 7.4, 1.7 Hz,

0.6H), 7.06 (ddd, *J* = 8.0, 7.2, 1.1 Hz, 1H), 7.02 – 6.97 (m, 1H), 6.87 (dd, *J* = 8.2, 1.1 Hz, 0.6H), 6.01 – 5.94 (m, 0.6H), 5.94 – 5.85 (m, 1H), 5.37 (dq, *J* = 17.2, 1.5 Hz, 0.6H), 5.34 – 5.28 (m, 1.6H), 5.24 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.99 (s, 1.2H), 4.81 (dd, *J* = 11.7, 8.4 Hz, 1H), 4.71 (m, 3.2H), 4.65 (dd, *J* = 11.6, 4.5 Hz, 1H), 3.78 (dd, *J* = 8.4, 4.4 Hz, 1H).



147

allyl 5-oxo-5,6,7,8-tetrahydroquinoline-6-carboxylate (147)

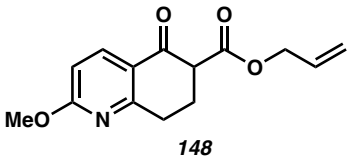
Prepared from 7,8-dihydroquinolin-5(6*H*)-one following General Procedure D. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (580 mg, 2.56 mmol, 51% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (9:1) δ 12.29 (s, 0.9H), 8.71 (dd, *J* = 4.8, 1.9 Hz, 0.1H), 8.50 (dd, *J* = 4.9, 1.8 Hz, 0.9H), 8.30 (dd, *J* = 7.9, 1.9 Hz, 0.1H), 8.03 (dd, *J* = 7.8, 1.8 Hz, 0.9H), 7.31 (dd, *J* = 8.0, 4.7 Hz, 0.1H), 7.23 (dd, *J* = 7.8, 4.9 Hz, 0.9H), 6.00 (m, 1H), 5.39 (m, 1H), 5.30 (m, 1H), 4.75 (d, *J* = 5.6 Hz, 1.8H), 4.70 (ddd, *J* = 4.4, 2.9, 1.4 Hz, 0.2H), 3.69 (dd, *J* = 10.0, 4.8 Hz, 0.1H), 3.32 – 3.10 (m, 0.2H), 3.04 (dd, *J* = 8.8, 7.1 Hz, 1.8H), 2.73 (dd, *J* = 8.8, 7.1 Hz, 1.8H), 2.61 – 2.36 (m, 0.2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.0, 172.2, 169.5, 163.7, 162.9, 159.5, 154.2, 150.6, 135.7, 132.1, 131.7, 131.7, 127.7, 125.9, 122.6, 122.0, 118.9, 118.6, 97.6, 66.2, 65.5, 54.0, 30.7, 30.6, 25.1, 20.0.

IR (neat film, NaCl): 2948, 1743, 1692, 1654, 1380, 1321, 1269, 1209, 1085, 980, 805 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{13}H_{14}NO_3$ $[M+H]^+$: 232.0968, found 232.0969.



148

allyl 2-methoxy-5-oxo-5,6,7,8-tetrahydroquinoline-6-carboxylate (148)

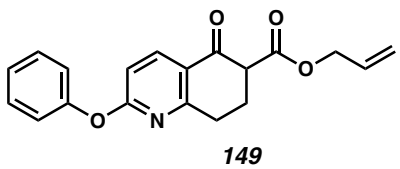
Prepared from 2-methoxy-7,8-dihydroquinolin-5(6*H*)-one following General Procedure E. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a yellow oil (1.504 g, 5.76 mmol, 91% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (15:85) δ 12.37 (s, 0.15H), 8.15 (d, *J* = 8.7 Hz, 0.85H), 7.91 (d, *J* = 8.5 Hz, 0.15H), 6.67–6.61 (m, 1H), 6.14 – 5.75 (m, 1H), 5.54 – 5.11 (m, 2H), 4.81 – 4.57 (m, 2H), 3.98 (s, 2.55H), 3.95 (s, 0.45H), 3.61 (dd, *J* = 10.1, 4.8 Hz, 0.85H), 3.19 – 2.95 (m, 1.7H), 2.94 – 2.62 (m, 0.6H), 2.57 – 2.25 (m, 1.7H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.9, 172.3, 169.9, 166.6, 165.1, 165.0, 163.3, 159.0, 138.2, 134.7, 132.3, 131.8, 122.1, 119.1, 118.7, 118.3, 110.5, 108.6, 94.5, 66.0, 65.2, 54.2, 53.9, 53.8, 30.7, 30.5, 25.2, 20.0.

IR (neat film, NaCl): 2945, 1740, 1681, 1591, 1479, 1331, 1267, 1200, 1023, 925, 834 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{14}H_{16}NO_4$ $[M+H]^+$: 262.1074, found 262.1070.



149

allyl 5-oxo-2-phenoxy-5,6,7,8-tetrahydroquinoline-6-carboxylate (149)

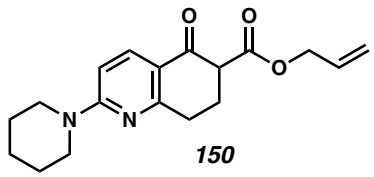
Prepared from 2-phenoxy-7,8-dihydroquinolin-5(6*H*)-one following General Procedure E. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a yellow oil (1.067 g, 3.30 mmol, 58% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (4:6) δ 12.35 (s, 0.4H), 8.27 (d, *J* = 8.6 Hz, 0.6H), 8.01 (d, *J* = 8.6 Hz, 0.4H), 7.42 (m, 2H), 7.31 – 7.21 (m, 1H), 7.16 (m, 1.8H), 6.76 (d, *J* = 8.7 Hz, 0.6H), 6.68 (t, *J* = 8.6 Hz, 0.6H), 6.16 – 5.86 (m, 1H), 5.45 – 5.35 (m, 1H), 5.33 – 5.22 (m, 1H), 4.77 – 4.62 (m, 2H), 3.62 (m, 0.6H), 3.35 – 2.96 (m, 1.6H), 2.97 – 2.86 (m, 0.4H), 2.69 (m, 0.4H), 2.60 – 2.29 (m, 1.6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.7, 169.7, 166.2, 163.6, 159.5, 153.9, 153.2, 139.7, 138.4, 135.8, 132.9, 132.1, 131.8, 130.0, 125.7, 125.3, 123.5, 121.6, 121.3, 118.9, 118.5, 110.7, 109.9, 108.4, 95.8, 67.5, 66.1, 66.0, 65.4, 53.8, 30.4, 30.0, 25.1, 19.9.

IR (neat film, NaCl): 2938, 1739, 1685, 1580, 1450, 1259, 1076, 990 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{19}H_{18}NO_4$ $[M+H]^+$: 324.1230, found 324.1229.



150

allyl 5-oxo-2-(piperidin-1-yl)-5,6,7,8-tetrahydroquinoline-6-carboxylate (150)

Prepared from 2-(piperidin-1-yl)-7,8-dihydroquinolin-5(6*H*)-one following General Procedure E. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a yellow oil (1.46 g, 4.64 mmol, 74% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (5:95) δ 12.41 (s, 0.05H), 7.95 (dd, *J* = 9.1, 1.5 Hz, 0.95H), 7.72 (dd, *J* = 8.9, 1.5 Hz, 0.05H), 6.48 (dd, *J* = 9.0, 1.5

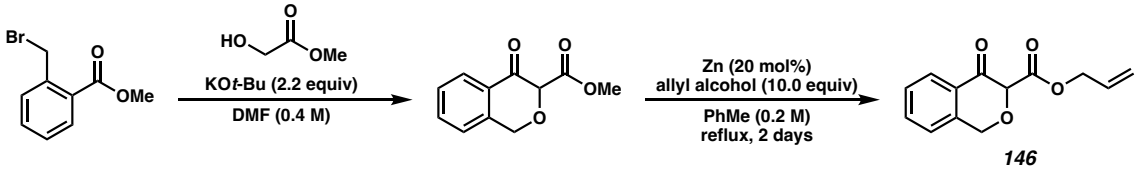
Hz, 0.95H), 6.44 (dd, *J* = 8.8, 1.5 Hz, 0.05H), 6.05 – 5.73 (m, 1H), 5.30 (dt, *J* = 17.2, 1.6 Hz, 1H), 5.19 (dt, *J* = 10.5, 1.5 Hz, 1H), 4.80 – 4.43 (m, 2H), 3.78 – 3.57 (m, 3.75H), 3.59 (t, *J* = 4.7 Hz, 0.25H), 3.51 (ddd, *J* = 10.3, 4.8, 1.5 Hz, 1H), 3.07 – 2.79 (m, 2H), 2.78 – 2.56 (m, 0.25H), 2.53 – 2.20 (m, 1.75H), 1.65 (m, 2H), 1.58 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 170.4, 164.1, 159.7, 136.8, 133.2, 132.5, 131.9, 118.3, 117.0, 104.8, 103.7, 92.3, 65.6, 64.7, 53.7, 45.6, 31.0, 25.7, 25.3, 24.6.

IR (neat film, NaCl): 2935, 2853, 1739, 1662, 1593, 1498, 1417, 1249, 1120, 1023 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{18}H_{22}N_2O_3Na$ $[M+Na]^+$: 337.1523, found 337.1518.

Preparation of ß-Keto Ester **146**



A flame dried round bottom flask under N_2 was charged with KO*t*-Bu (2.2 equiv), methyl 2-(bromomethyl)benzoate (1.0 equiv, 10 mmol) and DMF (0.4 M). After cooling to 0 °C, methyl 2-hydroxyacetate was added. The ice bath was then removed, and the reaction was allowed to continue stirring for 18 h. The reaction was quenched with 1 N HCl, extracted with EtOAc three times, and the combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude methyl ester intermediate was used without further purification.

To the crude intermediate in PhMe (0.2 M) was added Zn powder (20 mol%) and allyl alcohol (5.0 equiv). The reaction was refluxed for 24 h, at which point more allyl alcohol (5.0 equiv) was added. After an additional day of refluxing, the reaction was cooled,

filtered over Celite, and concentrated. The crude product was purified by flash silica gel column chromatography (0–15% ethyl acetate/hexanes) to afford the acylated ketone **146** (1.126 g, 4.84 mmol, 48% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (1:1) δ 10.36 (s, 0.5H), 8.06 (dd, *J* = 7.9, 1.3 Hz, 0.5H), 7.73 – 7.64 (m, 0.5H), 7.60 (td, *J* = 7.6, 1.4 Hz, 0.5H), 7.49 – 7.40 (m, 0.5H), 7.40 – 7.32 (m, 1H), 7.21 (dt, *J* = 7.5, 0.9 Hz, 0.5H), 7.16 – 7.07 (m, 0.5H), 5.98 (dddt, *J* = 31.0, 17.1, 10.4, 5.9 Hz, 1H), 5.50 – 5.34 (m, 1H), 5.33 – 5.22 (m, 1.5H), 5.02 (s, 1H), 4.99 (s, 0.5H), 4.94 (s, 0.5H), 4.78 (ddt, *J* = 25.7, 5.8, 1.4 Hz, 2H).

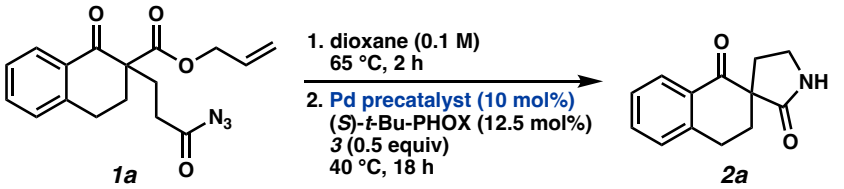
^{13}C NMR (100 MHz, $CDCl_3$): δ 188.5, 167.7, 166.1, 152.7, 141.2, 134.8, 133.0, 131.7, 131.3, 130.9, 130.7, 128.7, 128.4, 128.2, 127.7, 127.2, 127.1, 124.5, 124.3, 124.0, 123.5, 122.6, 119.8, 119.7, 119.4, 80.9, 68.4, 67.9, 66.6, 66.1, 62.3.

IR (neat film, NaCl): 1752, 1701, 1400, 1273, 744 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{13}H_{14}NO_3$ $[M+H]^+$: 262.1074, found 262.1070.

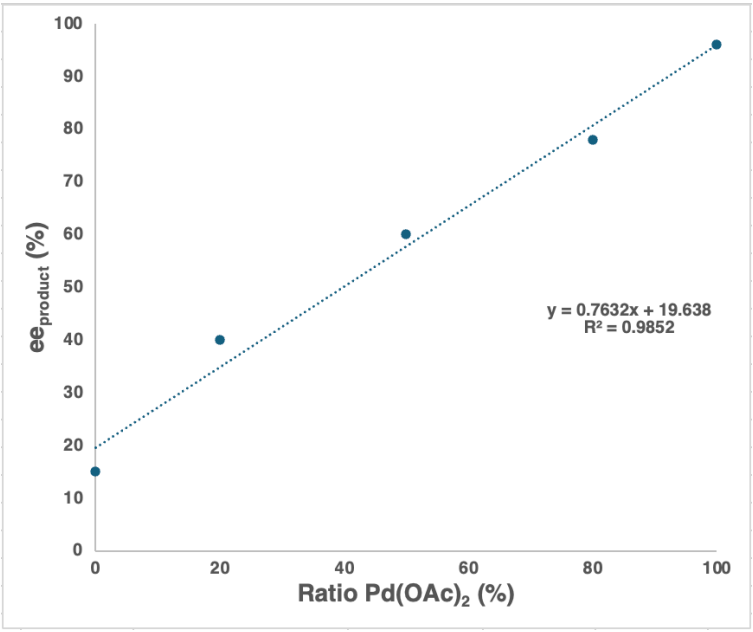
Mechanistic Experiments

Mixed Precatalyst Experiment



entry	$Pd(OAc)_2$ (mol%)	$Pd_2(dba)_3$ (mol%)	yield (%)[a]	ee (%)
1	0	5	99	15
2	2	4	95	40
3	5	2.5	96	60
4	8	1	98	78
5	10	0	99	96

[a]Yield determined by ^{1}H NMR integration against internal standard.



In a nitrogen-filled glovebox, five oven-dried 1-dram vials were charged with a stir bar, **101a** (16.4 mg, 0.05 mmol) in dioxane (0.2 mL), and ***3*** (3.9 mg, 0.025 mmol) in dioxane (0.1 mL). In a separate oven-dried 2-dram vial, $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) and (*S*)-*t*-BuPHOX (14.5 mg, 0.0375 mmol) in dioxane (1.2 mL) were stirred for 20 min at 23 °C. In another oven-dried 2-dram vial, $Pd_2(dba)_3$ (13.7 mg, 0.015 mmol) and (*S*)-*t*-BuPHOX

(0.0375 mmol) in dioxane (1.2 mL) were stirred for 20 min at 23 °C. To each reaction vial containing **101a** and **103** was added the corresponding volume of Pd-stock solutions, such that the mol% of Pd is as represented in the table and graph above:

Vial 01: Pd_2dba_3 solution (0.20 mL, 5 mol%)

Vial 02: Pd_2dba_3 solution (0.16 mL, 4 mol%), $Pd(OAc)_2$ solution (0.04 mL, 2 mol%)

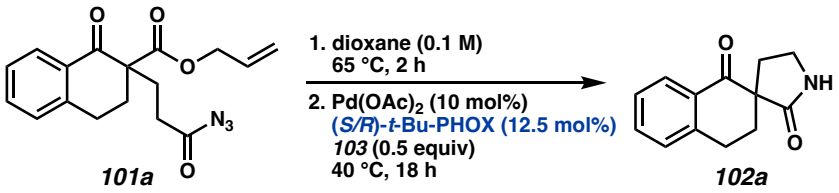
Vial 02: Pd_2dba_3 solution (0.10 mL, 2.5 mol%), $Pd(OAc)_2$ solution (0.10 mL, 5 mol%)

Vial 02: Pd_2dba_3 solution (0.04 mL, 1 mol%), $Pd(OAc)_2$ solution (0.16 mL, 8 mol%)

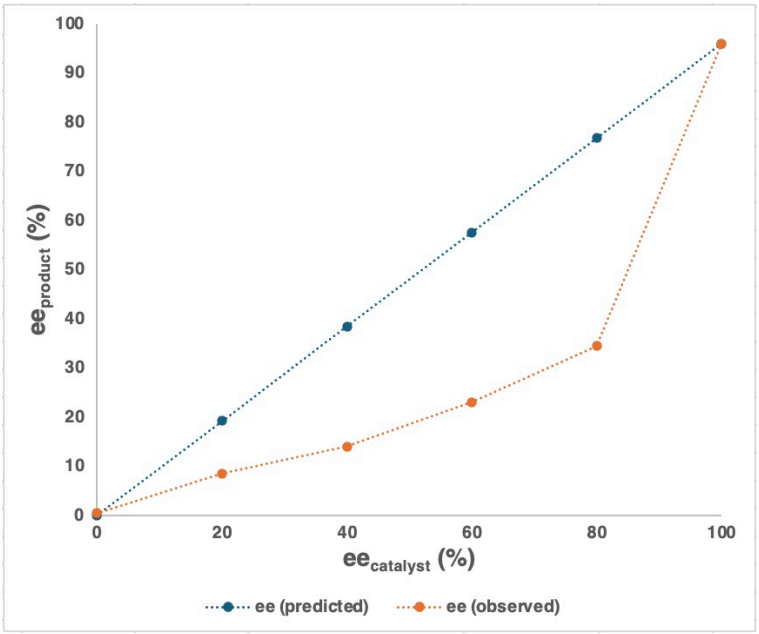
Vial 02: $Pd(OAc)_2$ solution (0.20 mL, 10 mol%)

The vials were sealed, removed from the glovebox, and heated to 40 °C for 18 h. The reaction mixtures were then cooled, 1,3,5-trimethoxybenzene (0.33 equiv) was added to each reaction, and the crude reactions mixtures were concentrated under reduced pressure. The yield was determined by ^1H NMR integration against 1,3,5-trimethoxybenzene as an internal standard, and the ee was determined utilizing SFC (30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 3.35, t_R (min): minor = 4.27).

Nonlinearity Experiment



entry	ee_{cat} (%)	$ee_{predicted}$ (%)	$ee_{observed}$ (%)
1	100	96	96
2	80	77	34
3	60	58	23
4	40	38	14
5	20	19	9
6	0	0	0



In a nitrogen-filled glovebox, five oven-dried 1-dram vials were charged with a stir bar, **101a** (16.4 mg, 0.05 mmol) in dioxane (0.2 mL), and **103** (3.9 mg, 0.025 mmol) in dioxane (0.1 mL). In five separate oven-dried 1-dram vials was added $Pd(OAc)_2$ (2.2 mg, 0.01 mmol). Stock solutions were prepared of (*S*)-*t*-BuPHOX (19.4 mg, 0.05 mmol) in dioxane (1.6 mL) and (*R*)-*t*-BuPHOX (9.7 mg, 0.025 mmol) in dioxane (0.8 mL), and the corresponding volume of (*S*)- or (*R*)-*t*-BuPHOX stock solutions was added to each vial of

$Pd(OAc)_2$, such that the ee of the resulting Pd solution is as represented in the table and graph above:

Vial 01: (*R*)-*t*-BuPHOX stock solution (0.04 mL, 1.25 mol%), (*S*)-*t*-BuPHOX stock solution (0.36 mL, 11.25 mol%)

Vial 02: (*R*)-*t*-BuPHOX stock solution (0.08 mL, 2.5 mol%), (*S*)-*t*-BuPHOX stock solution (0.32 mL, 10 mol%)

Vial 03: (*R*)-*t*-BuPHOX stock solution (0.12 mL, 3.75 mol%), (*S*)-*t*-BuPHOX stock solution (0.28 mL, 8.75 mol%)

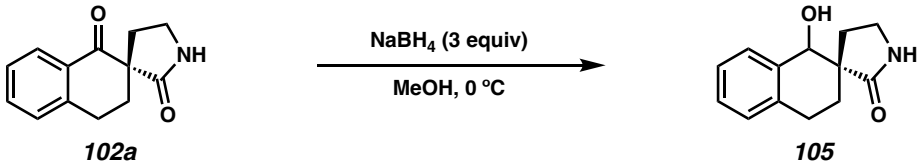
Vial 04: (*R*)-*t*-BuPHOX stock solution (0.16 mL, 5 mol%), (*S*)-*t*-BuPHOX stock solution (0.24 mL, 7.5 mol%)

Vial 05: (*R*)-*t*-BuPHOX stock solution (0.20 mL, 6.25 mol%), (*S*)-*t*-BuPHOX stock solution (0.20 mL, 6.25 mol%)

The vials were sealed and stirred for 20 min at 23 °C. To each reaction vial, the corresponding Pd stock solution (0.2 mL) was added. The reaction vials were sealed, from the glovebox, and heated to 40 °C for 30 min, at which point the reactions were quenched by opening to air and concentrated. The ee of each reaction product was determined utilizing SFC (30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 3.35, t_R (min): minor = 4.27).

Product Derivatizations

*Preparation of alcohol **105***



102a ***105***

(2*S*)-1-hydroxy-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidin]-2'-one (105)

A flame dried vial under N_2 was charged with ketone **102a** (1 equiv, 0.05 mmol, 10.8 mg) and MeOH (0.03 M, 1.8 mL) at 0 ºC. $NaBH_4$ (2 equiv, 0.1 mmol, 3.8 mg) was added to the reaction. After two hours, starting material was not consumed and additional $NaBH_4$ (1 equiv, 0.05 mmol, 1.9 mg) was added to the reaction. Following complete consumption of starting material as determined by TLC, the reaction was diluted with water. The reaction mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% acetone/CH_2Cl_2) afforded the title compound **105** as a white solid (7.5 mg, 0.035 mmol, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.24 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.24 – 7.15 (m, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 6.42 (s, 1H), 4.94 (s, 1H), 4.59 (s, 1H), 3.45 – 3.30 (m, 2H), 3.04 (ddd, *J* = 17.8, 7.1, 2.3 Hz, 1H), 2.00 (ddd, *J* = 13.1, 7.3, 3.8 Hz, 1H), 1.81 (dt, *J* = 13.2, 8.3 Hz, 1H), 1.71 (dd, *J* = 13.6, 5.9 Hz, 1H).

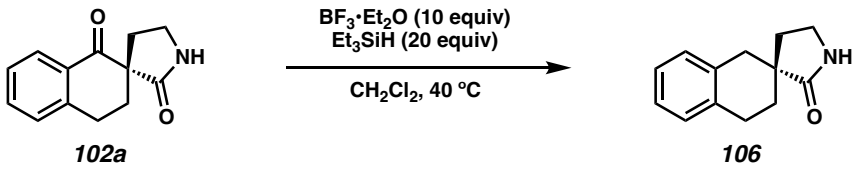
^{13}C NMR (100 MHz, $CDCl_3$): δ 182.8, 135.5, 135.4, 130.6, 129.2, 128.4, 126.3, 72.9, 44.8, 39.1, 29.3, 25.0, 22.8.

IR (Neat Film, NaCl): 3300, 2929, 1684, 1456, 1285 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{13}H_{15}NO_2$ $[M+Na]^+$: 240.0995, found 240.0985.

Optical Rotation: $[\alpha]_D^{21}$ –36.0 (c 0.75, $CHCl_3$).

*Preparation of lactam **106***



102a ***106***

(R)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidin]-2'-one (106)

A flame dried vial under N_2 was charged with ketone **102a** (1 equiv, 0.05 mmol, 10.8 mg) and CH_2Cl_2 (0.1 M, 0.5 mL) at 0 ºC. Et_3SiH (10 equiv, 0.5 mmol, 62 µL) then BF_3•Et_2O (20 equiv, 1 mmol, 0.16 mL) was added to the reaction. The reaction was heated to 40 ºC. Following complete consumption of starting material as determined by TLC, the reaction was cooled to 23 ºC and diluted with saturated aqueous $NaHCO_3$. The reaction mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% acetone/CH_2Cl_2) afforded the title compound **106** as a white solid (5.6 mg, 0.028 mmol, 56% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 – 7.05 (m, 4H), 6.18 (s, 1H), 3.37 (ddd, J = 7.6, 6.1, 0.9 Hz, 2H), 3.10 (d, J = 16.4 Hz, 1H), 2.94 (ddd, J = 17.3, 6.5, 2.7 Hz, 1H), 2.84 (dddd, J = 17.4, 12.1, 5.9, 1.6 Hz, 1H), 2.63 (dd, J = 16.4, 2.3 Hz, 1H), 2.14 – 1.99 (m, 2H), 1.94 (dt, J = 12.7, 6.0 Hz, 1H), 1.74 (ddt, J = 13.3, 5.9, 2.5 Hz, 1H).

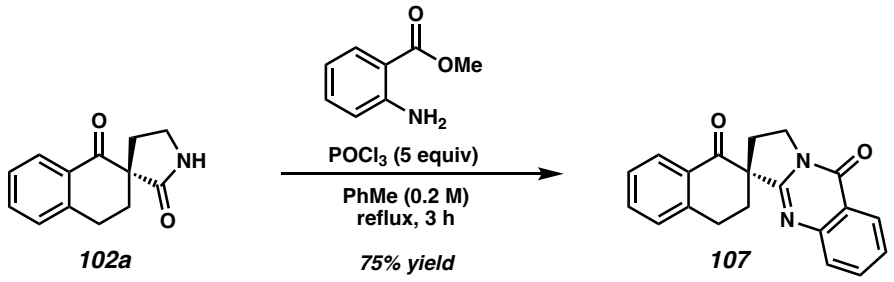
^{13}C NMR (100 MHz, $CDCl_3$): 182.4, 135.4, 134.5, 129.7, 129.0, 126.1, 126.0, 42.7, 39.0, 36.2, 31.7, 29.2, 25.8.

IR (Neat Film, NaCl): 3224, 3012, 2926, 2352, 1694, 1455, 1297 cm^{-1}.

HRMS (MM: ESI+): m/z calc'd for $C_{13}H_{15}NO$ $[M+H]^+$: 202.1226, found 202.1217.

Optical Rotation: $[\alpha]_D^{21}$ –9.2 (c 0.53, $CHCl_3$).

*Preparation of pyrimidone **107***



(*R*)-1',2',3,4-tetrahydro-1*H*,9'*H*-spiro[naphthalene-2,3'-pyrrolo[2,1-*b*]quinazoline]-1,9'-dione (107)

To a vial containing **102a** (21.5 mg, 0.1 mmol) in toluene (0.5 mL, 0.2 M) added methyl anthranilate (13 uL, 0.1 mmol, 1.0 equiv) and $POCl_3$ (47 uL, 0.5 mmol, 5.0 equiv). The vial was capped and heated to 110 °C for 3 h, at which point the reaction had reached completion by TLC analysis. The reaction mixture was cooled and poured over a cold solution of saturated $NaHCO_3$. The crude mixture was extracted three times with ethyl acetate, and the combined organics were dried over Na_2SO_4, filtered, concentrated, and dried under reduced pressure. The crude material was purified on column chromatography (0–50% ethyl acetate/hexanes) to afford **107** (23.7 mg, 0.075 mmol, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (dd, J = 8.0, 1.5 Hz, 1H), 8.06 (dd, J = 7.9, 1.4 Hz, 1H), 7.69 (ddd, J = 8.5, 7.0, 1.6 Hz, 1H), 7.65 – 7.59 (m, 1H), 7.55 (td, J = 7.5, 1.5 Hz, 1H), 7.45 (ddd, J = 8.2, 7.0, 1.3 Hz, 1H), 7.40 – 7.29 (m, 2H), 4.37 (ddd, J = 11.8, 8.7, 2.8 Hz, 1H), 4.16 (ddd, J = 12.1, 9.0, 7.5 Hz, 1H), 3.36 (dt, J = 16.6, 4.8 Hz, 1H), 3.11 (ddd, J =

16.3, 10.8, 4.3 Hz, 1H), 2.98 (ddd, J = 13.5, 10.8, 4.5 Hz, 1H), 2.69 (ddd, J = 13.1, 7.6, 2.8 Hz, 1H), 2.34 – 2.22 (m, 2H).

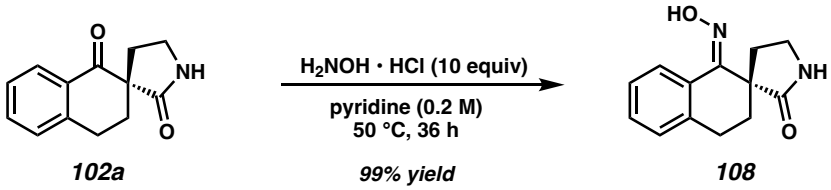
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.8, 161.0, 159.9, 149.4, 143.8, 134.4, 134.1, 130.5, 128.9, 128.6, 127.6, 127.3, 126.7, 126.5, 121.3, 58.1, 44.0, 32.4, 30.9, 25.7.

IR (neat film, NaCl): 2928, 1673, 1614, 1468, 1320, 1221, 774, 683 cm^{-1}.

HMRS (ESI+): m/z calc'd for $C_{20}H_{17}N_2O_2$ $[M+H]^+$: 317,1285, found 317.1275.

Optical Rotation: $[\alpha]_D^{24}$ = 14.21 (c 1.0, $CHCl_3$).

*Preparation of oxime **108***



102a ***99% yield*** ***108***

(*S*,*E*)-1-(hydroxyimino)-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidin]-2'-one (108)

To a vial containing **102a** (21.5 mg, 0.1 mmol) in pyridine (0.5 mL, 0.2 M) added hydroxylamine HCl (70 mg, 1.0 mmol, 10 equiv). The vial was capped and heated to 50 °C for 36 h, at which point the reaction had reached completion by TLC analysis. The reaction mixture was cooled, concentrated under reduced pressure, and then partitioned between water and ethyl acetate. The crude mixture was extracted three times with ethyl acetate, and the combined organics were dried over Na_2SO_4, filtered, concentrated, and dried under reduced pressure to afford **108** (22.9 mg, 0.10 mmol, 99% yield).

^{1}H NMR (400 MHz, CD_3OD): δ 7.94 (dd, J = 8.3, 1.4 Hz, 1H), 7.30 – 7.19 (m, 1H), 7.19 – 6.95 (m, 2H), 4.60 (s, 2H), 3.62 – 3.41 (m, 2H), 2.95 – 2.77 (m, 2H), 2.65 (dddd, J = 12.7,

10.0, 7.5, 1.2 Hz, 1H), 2.22 (ddd, J = 12.7, 8.4, 3.2 Hz, 1H), 2.03 (dddd, J = 13.0, 10.3, 5.9, 1.2 Hz, 1H), 1.93 (t, J = 4.1 Hz, 1H), 1.90 (t, J = 4.1 Hz, 1H).

^{13}C NMR (100 MHz, CD_3OD): δ 182.6, 154.3, 139.7, 132.5, 129.8, 129.1, 127.4, 125.7, 40.6, 33.4, 30.9, 27.1.

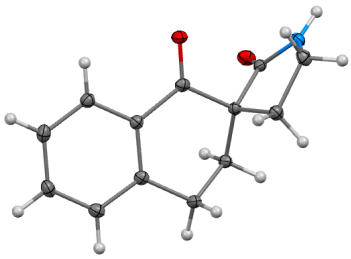
IR (neat film, NaCl): 3265, 2913, 2512, 2070, 1669, 1163, 978, 830, 773, 687 cm^{-1}.

HMRS (ESI+): m/z calc'd for $C_{13}H_{15}N_2O_2$ $[M+H]^+$: 231.1128, found 231.1126.

Optical Rotation: $[\alpha]_D^{24}$ = 50.32 (c 1.0, $CHCl_3$).

Crystal Structure Analysis of (*S*)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-1,2'-dione (102a) (sample No.: V24106)

Compound **102a** was crystallized from a mixture of dichloromethane and pentane at 23 °C to provide crystals suitable for X-ray analysis. Compound V24106 (CCDC 2414202) crystallizes in the monoclinic space group $P2_1$ with one molecule in the asymmetric unit.



Empirical formula	C13 H13 N O2	
Formula weight	215.24	
Temperature	101(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 6.9799(8) Å	a= 90°.
	b = 6.1366(5) Å	b= 105.205(7)°.
	c = 12.9790(12) Å	g = 90°.
Volume	536.47(9) Å3	
Z	2	
Density (calculated)	1.332 Mg/m3	
Absorption coefficient	0.730 mm-1	
F(000)	228	
Crystal size	0.200 x 0.200 x 0.100 mm3	
Theta range for data collection	3.529 to 74.548°.	
Index ranges	-8<=h<=8, -7<=k<=7, -15<=l<=16	

Reflections collected	11830
Independent reflections	2157 [R(int) = 0.0460]
Completeness to theta = 67.679°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7538 and 0.6123
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	2157 / 2 / 148
Goodness-of-fit on F2	1.067
Final R indices [I>2sigma(I)]	R1 = 0.0290, wR2 = 0.0740
R indices (all data)	R1 = 0.0294, wR2 = 0.0744
Absolute structure parameter	-0.05(13)
Extinction coefficient	n/a
Largest diff. peak and hole	0.161 and -0.205 e.Å-3

Table 2.7. *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for V24106. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U(eq)
N(1)	1891(2)	7872(2)	5903(1)	14(1)
C(1)	2707(2)	5936(3)	5824(1)	12(1)
O(1)	1974(2)	4411(2)	5235(1)	17(1)
C(2)	4792(2)	5877(3)	6599(1)	11(1)
C(3)	5210(2)	8322(3)	6870(1)	14(1)
C(4)	3131(2)	9317(3)	6693(1)	16(1)
C(5)	4621(2)	4699(3)	7611(1)	12(1)
O(2)	3133(2)	4913(2)	7929(1)	18(1)
C(6)	6324(2)	3348(3)	8200(1)	12(1)
C(7)	6133(3)	2167(3)	9098(1)	14(1)
C(8)	7667(3)	855(3)	9653(1)	17(1)
C(9)	9402(3)	700(3)	9313(1)	17(1)
C(10)	9604(2)	1876(3)	8432(1)	15(1)
C(11)	8077(2)	3216(3)	7865(1)	13(1)
C(12)	8296(2)	4492(3)	6908(1)	14(1)
C(13)	6290(2)	4788(3)	6095(1)	13(1)

Table 2.8. *Bond lengths [Å] and angles [°] for V24106.*

N(1)-C(1)	1.333(2)
N(1)-C(4)	1.457(2)
N(1)-H(1N)	0.886(18)
C(1)-O(1)	1.231(2)
C(1)-C(2)	1.537(2)
C(2)-C(13)	1.525(2)
C(2)-C(5)	1.532(2)
C(2)-C(3)	1.551(2)
C(3)-C(4)	1.535(2)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-O(2)	1.221(2)
C(5)-C(6)	1.486(2)
C(6)-C(11)	1.405(2)
C(6)-C(7)	1.408(2)
C(7)-C(8)	1.382(2)
C(7)-H(7)	0.9500
C(8)-C(9)	1.396(3)
C(8)-H(8)	0.9500
C(9)-C(10)	1.390(3)
C(9)-H(9)	0.9500
C(10)-C(11)	1.394(2)
C(10)-H(10)	0.9500
C(11)-C(12)	1.509(2)
C(12)-C(13)	1.527(2)

C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900

C(1)-N(1)-C(4)	114.20(14)
C(1)-N(1)-H(1N)	123.6(16)
C(4)-N(1)-H(1N)	122.0(16)
O(1)-C(1)-N(1)	127.51(15)
O(1)-C(1)-C(2)	123.79(15)
N(1)-C(1)-C(2)	108.71(14)
C(13)-C(2)-C(5)	112.16(14)
C(13)-C(2)-C(1)	111.58(13)
C(5)-C(2)-C(1)	107.40(12)
C(13)-C(2)-C(3)	114.31(13)
C(5)-C(2)-C(3)	108.32(13)
C(1)-C(2)-C(3)	102.44(13)
C(4)-C(3)-C(2)	103.69(13)
C(4)-C(3)-H(3A)	111.0
C(2)-C(3)-H(3A)	111.0
C(4)-C(3)-H(3B)	111.0
C(2)-C(3)-H(3B)	111.0
H(3A)-C(3)-H(3B)	109.0
N(1)-C(4)-C(3)	103.11(13)
N(1)-C(4)-H(4A)	111.1
C(3)-C(4)-H(4A)	111.1
N(1)-C(4)-H(4B)	111.1
C(3)-C(4)-H(4B)	111.1
H(4A)-C(4)-H(4B)	109.1
O(2)-C(5)-C(6)	121.53(14)

O(2)-C(5)-C(2)	120.25(14)
C(6)-C(5)-C(2)	118.21(13)
C(11)-C(6)-C(7)	120.39(15)
C(11)-C(6)-C(5)	121.15(14)
C(7)-C(6)-C(5)	118.45(14)
C(8)-C(7)-C(6)	120.23(15)
C(8)-C(7)-H(7)	119.9
C(6)-C(7)-H(7)	119.9
C(7)-C(8)-C(9)	119.46(16)
C(7)-C(8)-H(8)	120.3
C(9)-C(8)-H(8)	120.3
C(10)-C(9)-C(8)	120.54(16)
C(10)-C(9)-H(9)	119.7
C(8)-C(9)-H(9)	119.7
C(9)-C(10)-C(11)	120.83(15)
C(9)-C(10)-H(10)	119.6
C(11)-C(10)-H(10)	119.6
C(10)-C(11)-C(6)	118.54(15)
C(10)-C(11)-C(12)	120.84(14)
C(6)-C(11)-C(12)	120.62(14)
C(11)-C(12)-C(13)	110.96(13)
C(11)-C(12)-H(12A)	109.4
C(13)-C(12)-H(12A)	109.4
C(11)-C(12)-H(12B)	109.4
C(13)-C(12)-H(12B)	109.4
H(12A)-C(12)-H(12B)	108.0
C(2)-C(13)-C(12)	111.33(13)
C(2)-C(13)-H(13A)	109.4
C(12)-C(13)-H(13A)	109.4
C(2)-C(13)-H(13B)	109.4

C(12)-C(13)-H(13B)	109.4
H(13A)-C(13)-H(13B)	108.0

Symmetry transformations used to generate equivalent atoms:

Table 2.9. *Anisotropic displacement parameters ($Å^2$ x 10^3) for V24106. The anisotropic displacement factor exponent takes the form: -2p2[$h^2 a^{*2} U^{11}$ + ... + 2 h k a^* b^* U^{12}]*

	U11	U22	U33	U23	U13	U12
N(1)	11(1)	14(1)	17(1)	2(1)	2(1)	3(1)
C(1)	10(1)	14(1)	12(1)	1(1)	4(1)	-1(1)
O(1)	13(1)	17(1)	19(1)	-4(1)	1(1)	-2(1)
C(2)	10(1)	11(1)	12(1)	0(1)	1(1)	0(1)
C(3)	13(1)	12(1)	17(1)	-1(1)	2(1)	-1(1)
C(4)	17(1)	12(1)	19(1)	-2(1)	3(1)	2(1)
C(5)	11(1)	12(1)	13(1)	-2(1)	2(1)	-2(1)
O(2)	14(1)	24(1)	20(1)	6(1)	8(1)	4(1)
C(6)	12(1)	11(1)	13(1)	-1(1)	2(1)	-1(1)
C(7)	15(1)	14(1)	16(1)	1(1)	5(1)	-1(1)
C(8)	20(1)	14(1)	15(1)	3(1)	2(1)	-2(1)
C(9)	16(1)	13(1)	19(1)	1(1)	-1(1)	2(1)
C(10)	13(1)	14(1)	18(1)	-2(1)	3(1)	1(1)
C(11)	12(1)	12(1)	13(1)	-2(1)	2(1)	-2(1)
C(12)	11(1)	17(1)	16(1)	3(1)	5(1)	1(1)
C(13)	11(1)	14(1)	13(1)	0(1)	3(1)	1(1)

Table 2.10. *Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for V24106.*

	x	y	z	U(eq)
H(1N)	660(30)	8230(40)	5550(16)	17
H(3A)	5996	8511	7619	17
H(3B)	5935	8996	6390	17
H(4A)	2705	9325	7362	20
H(4B)	3093	10826	6417	20
H(7)	4946	2272	9322	17
H(8)	7543	64	10262	20
H(9)	10452	-216	9687	20
H(10)	10797	1765	8214	18
H(12A)	9214	3715	6568	17
H(12B)	8876	5939	7143	17
H(13A)	6464	5690	5494	15
H(13B)	5775	3347	5807	15

Table 2.11. *Torsion angles [°] for V24106.*

C(4)-N(1)-C(1)-O(1)	178.91(16)
C(4)-N(1)-C(1)-C(2)	-1.57(19)
O(1)-C(1)-C(2)-C(13)	41.0(2)
N(1)-C(1)-C(2)-C(13)	-138.59(14)
O(1)-C(1)-C(2)-C(5)	-82.34(19)
N(1)-C(1)-C(2)-C(5)	98.11(16)
O(1)-C(1)-C(2)-C(3)	163.67(15)
N(1)-C(1)-C(2)-C(3)	-15.87(17)
C(13)-C(2)-C(3)-C(4)	146.75(14)
C(5)-C(2)-C(3)-C(4)	-87.42(14)
C(1)-C(2)-C(3)-C(4)	25.89(16)
C(1)-N(1)-C(4)-C(3)	18.53(19)
C(2)-C(3)-C(4)-N(1)	-26.88(16)
C(13)-C(2)-C(5)-O(2)	-157.93(15)
C(1)-C(2)-C(5)-O(2)	-35.0(2)
C(3)-C(2)-C(5)-O(2)	74.98(18)
C(13)-C(2)-C(5)-C(6)	23.5(2)
C(1)-C(2)-C(5)-C(6)	146.42(15)
C(3)-C(2)-C(5)-C(6)	-103.61(16)
O(2)-C(5)-C(6)-C(11)	-176.14(16)
C(2)-C(5)-C(6)-C(11)	2.4(2)
O(2)-C(5)-C(6)-C(7)	4.9(2)
C(2)-C(5)-C(6)-C(7)	-176.55(15)
C(11)-C(6)-C(7)-C(8)	-0.4(2)
C(5)-C(6)-C(7)-C(8)	178.63(15)
C(6)-C(7)-C(8)-C(9)	-0.4(3)
C(7)-C(8)-C(9)-C(10)	0.9(3)

C(8)-C(9)-C(10)-C(11)	-0.6(3)
C(9)-C(10)-C(11)-C(6)	-0.2(2)
C(9)-C(10)-C(11)-C(12)	-179.98(16)
C(7)-C(6)-C(11)-C(10)	0.7(2)
C(5)-C(6)-C(11)-C(10)	-178.30(15)
C(7)-C(6)-C(11)-C(12)	-179.55(15)
C(5)-C(6)-C(11)-C(12)	1.5(2)
C(10)-C(11)-C(12)-C(13)	149.00(15)
C(6)-C(11)-C(12)-C(13)	-30.8(2)
C(5)-C(2)-C(13)-C(12)	-52.74(18)
C(1)-C(2)-C(13)-C(12)	-173.29(14)
C(3)-C(2)-C(13)-C(12)	71.06(18)
C(11)-C(12)-C(13)-C(2)	56.21(19)

Symmetry transformations used to generate equivalent atoms:

Table 2.12. *Hydrogen bonds for V24106 [Å and °].*

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...O(1)#1	0.886(18)	1.994(19)	2.8742(18)	173(2)

Symmetry transformations used to generate equivalent atoms:

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

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(14) We briefly explored phenolic carbamates as alternative electrophiles to isocyanates with the hypothesis that an electron deficient variant might be sufficiently electrophilic to outcompete allylic alkylation, or that these carbamates could act as blocked isocyanates under tailored reaction conditions; ultimately, this approach yielded limited success, generating product **102a** in both diminished yields and enantioselectivities (See Section 2.4.1 Materials and Methods).

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(17) Substoichiometric use of additive **103** (less than 0.5 equiv) delivers oligomeric byproducts arising from condensation of the unprotonated product with the isocyanate starting material.

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APPENDIX 3

Spectra Relevant to Chapter 2: An Enantioselective Spirocyclization of Pd Enolates and Isocyanates

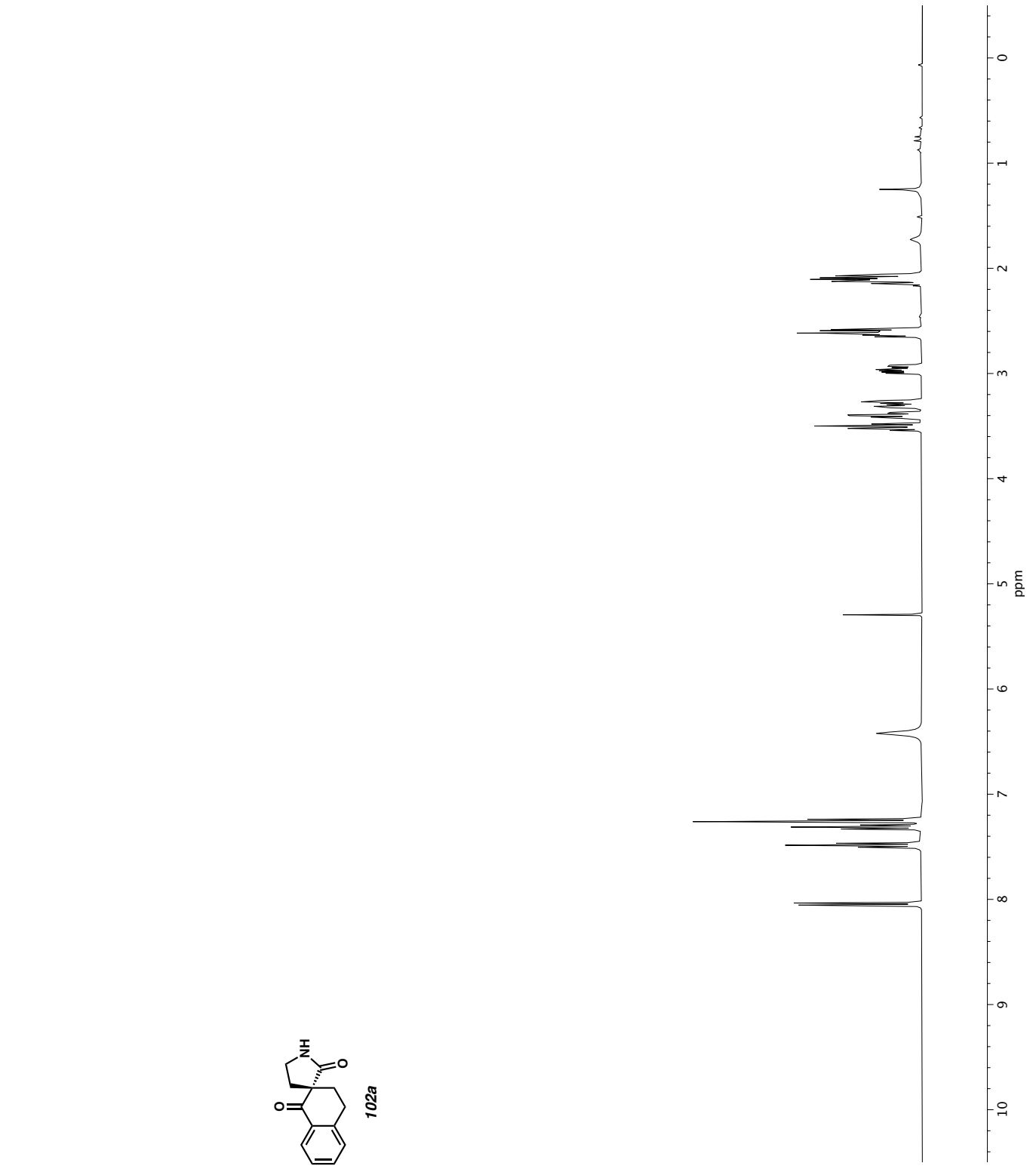


Figure A3.1. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***102a***.

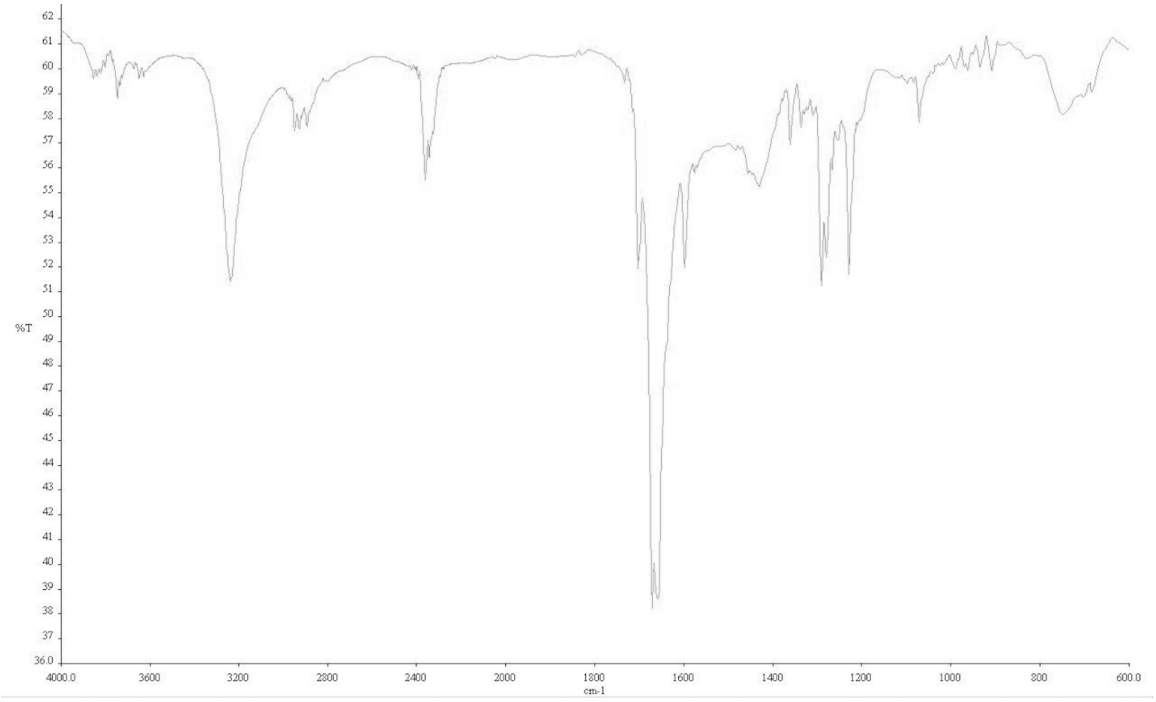


Figure A3.2. *Infrared spectrum (Thin Film, NaCl) of compound* ***102a****.*

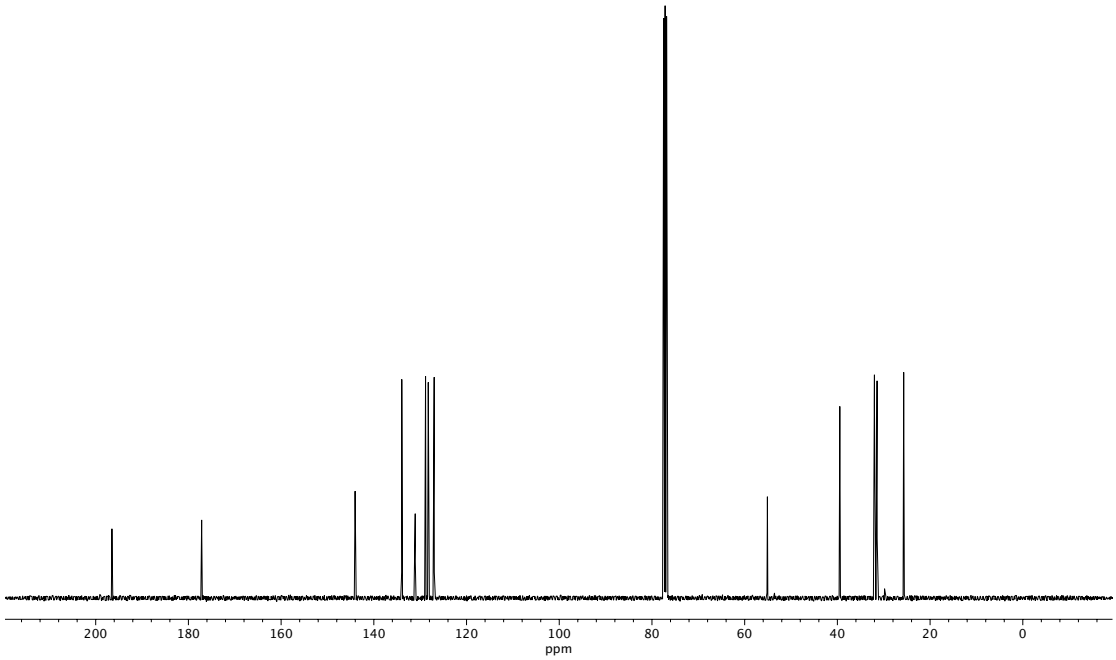
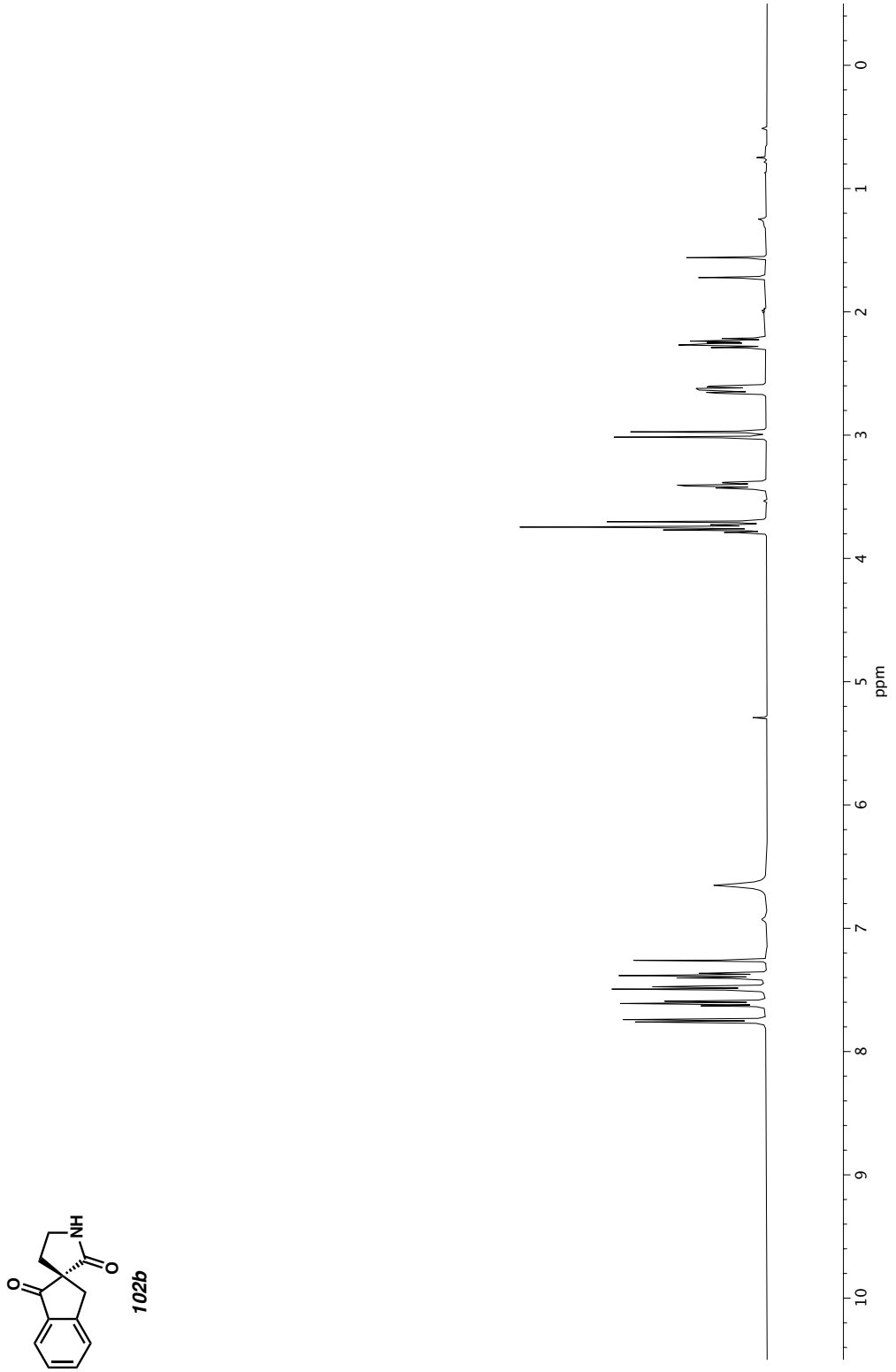


Figure A3.3. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***102a****.*



102b

Figure A3.4. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***102b****.*

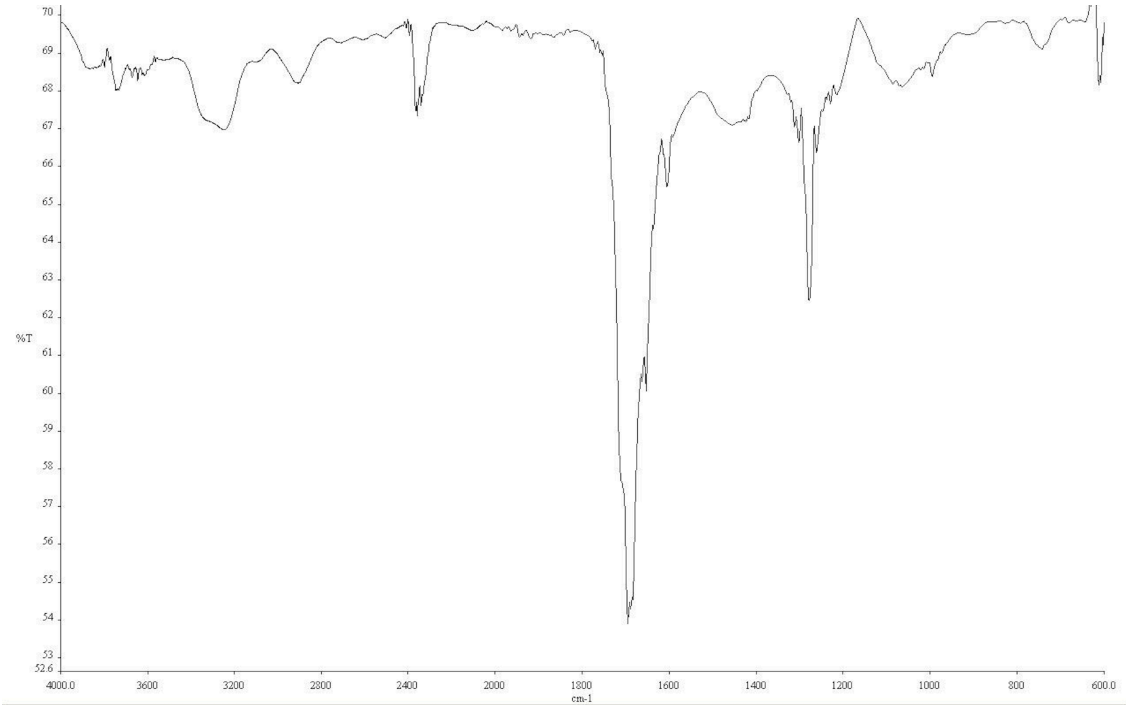


Figure A3.5. *Infrared spectrum (Thin Film, NaCl) of compound* ***102b****.*

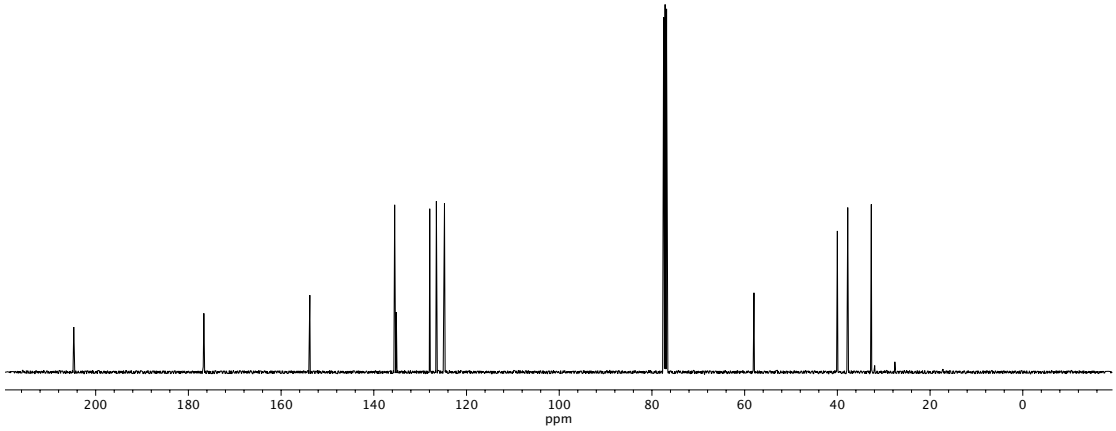


Figure A3.6. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***102b****.*

Figure A3.7. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***102c****.*

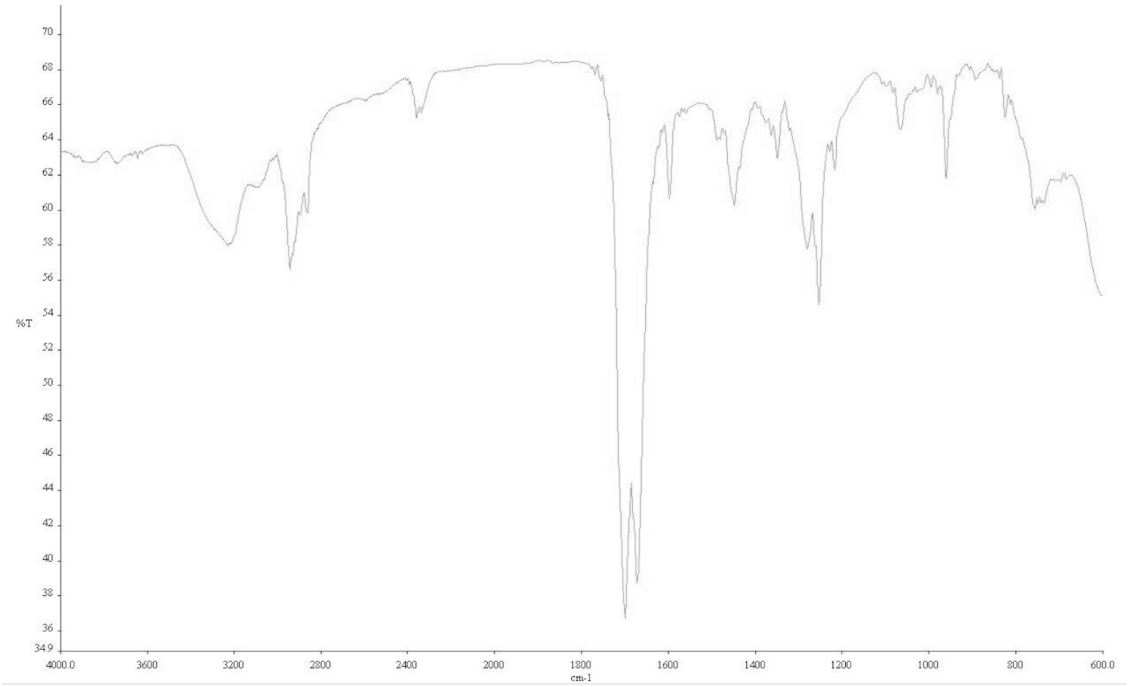


Figure A3.8. *Infrared spectrum (Thin Film, NaCl) of compound* ***102c****.*

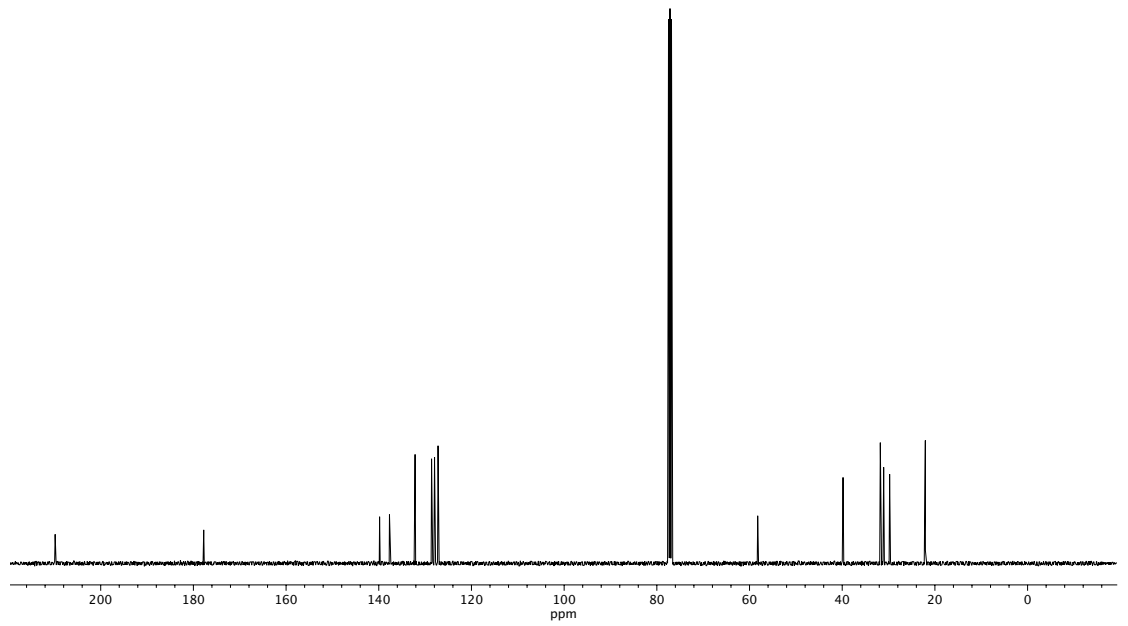


Figure A3.9. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***102c****.*

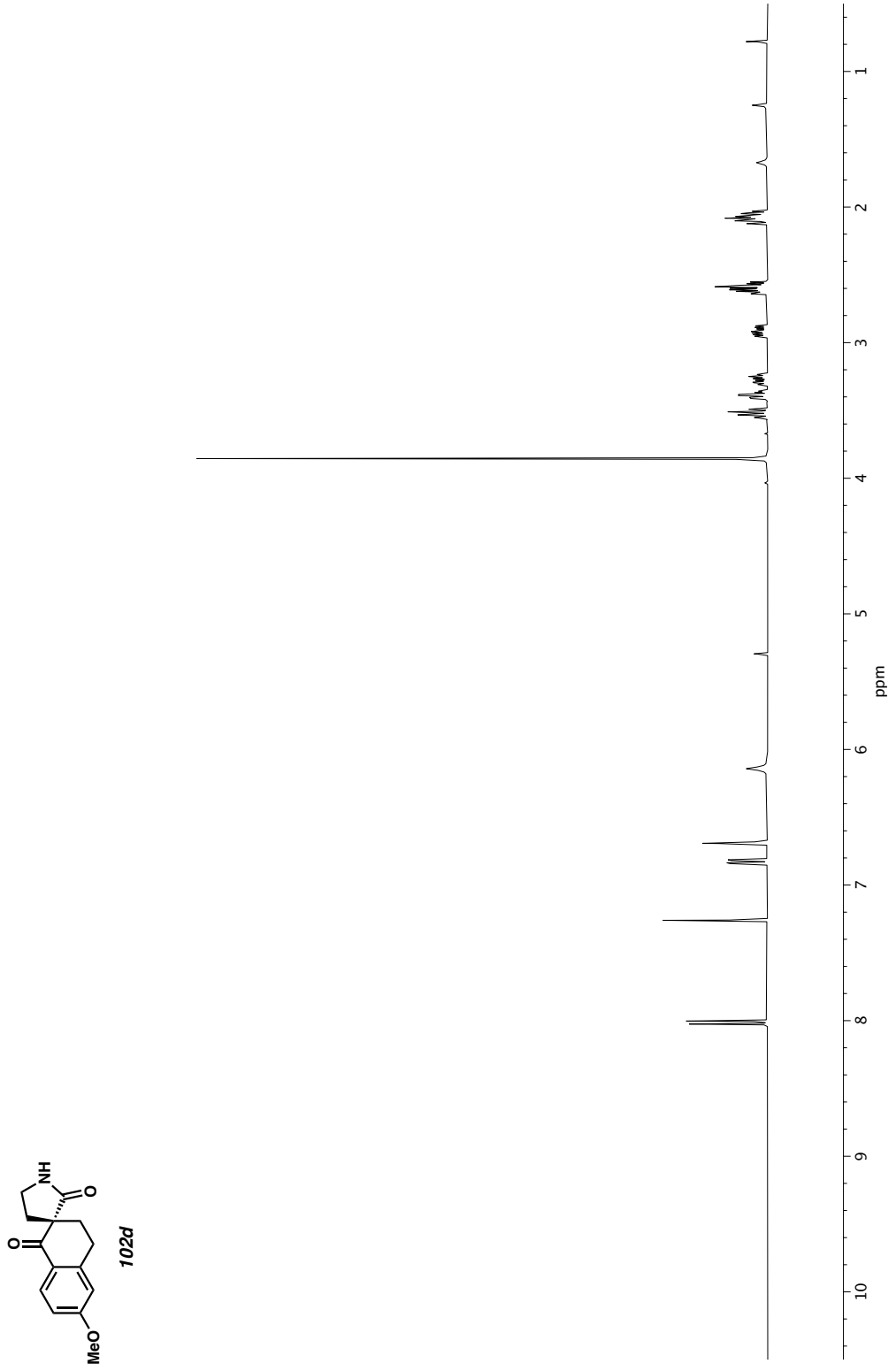


Figure A3.10. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***102d****.*

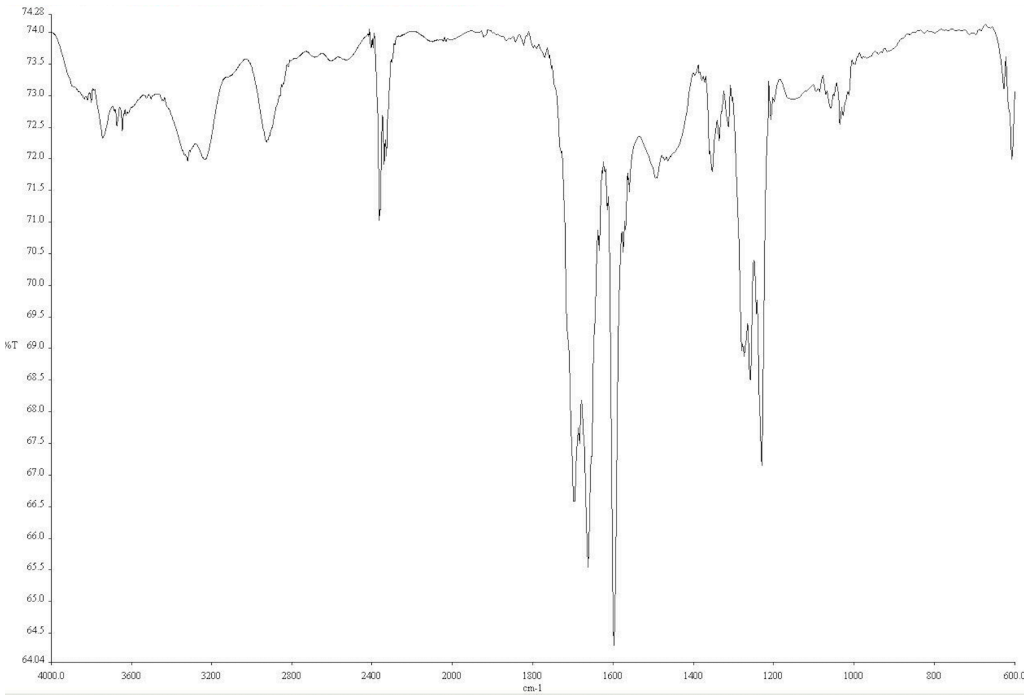


Figure A3.11. *Infrared spectrum (Thin Film, NaCl) of compound* ***102d****.*

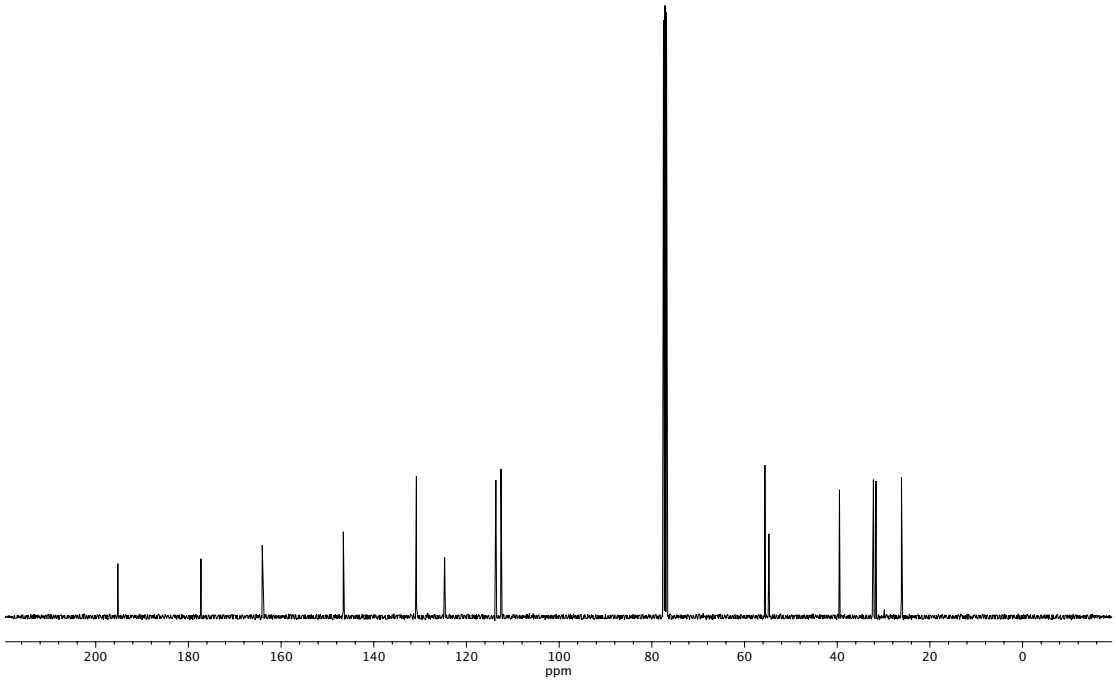


Figure A3.12. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***102d****.*

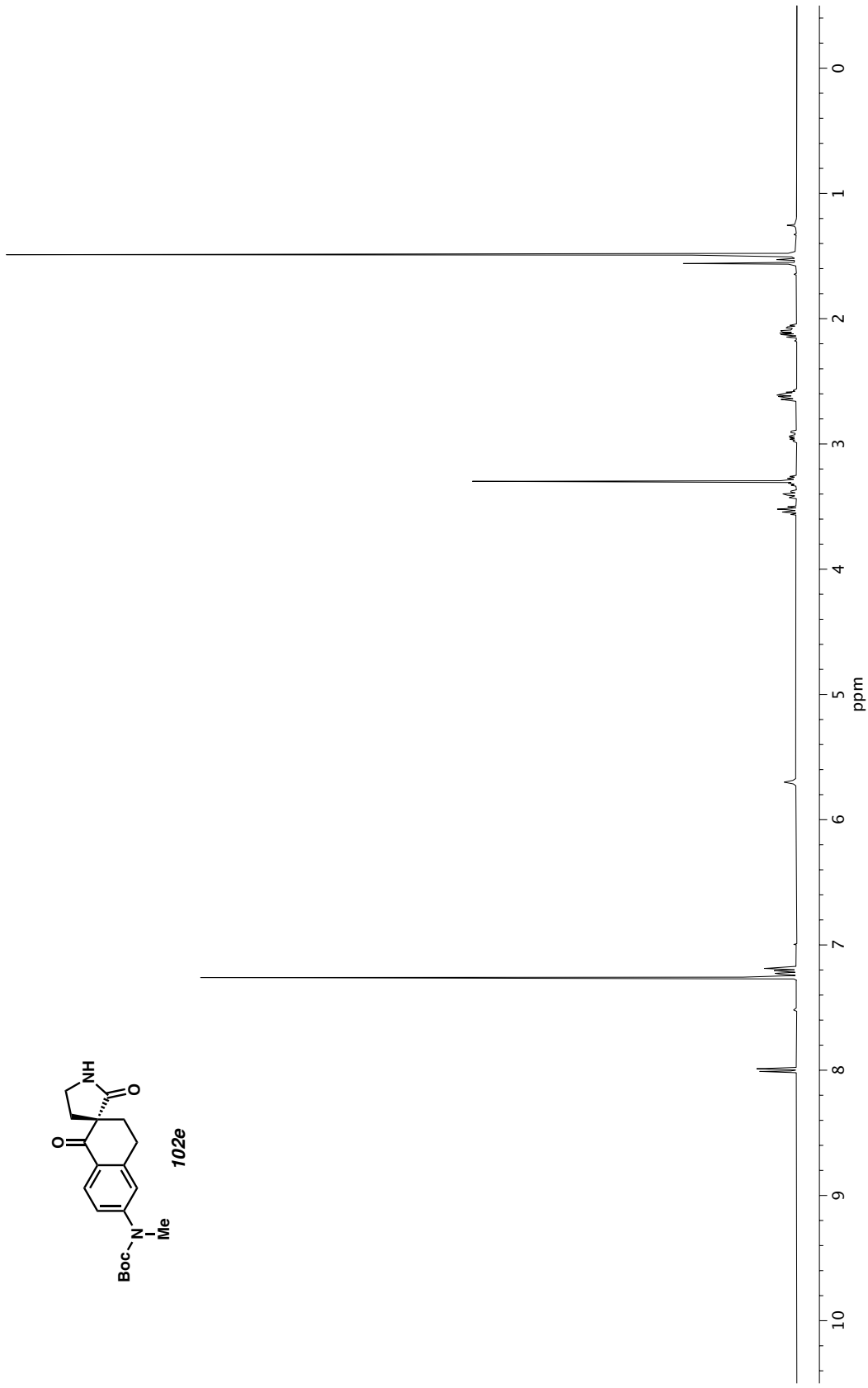


Figure A3.13. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***102e****.*

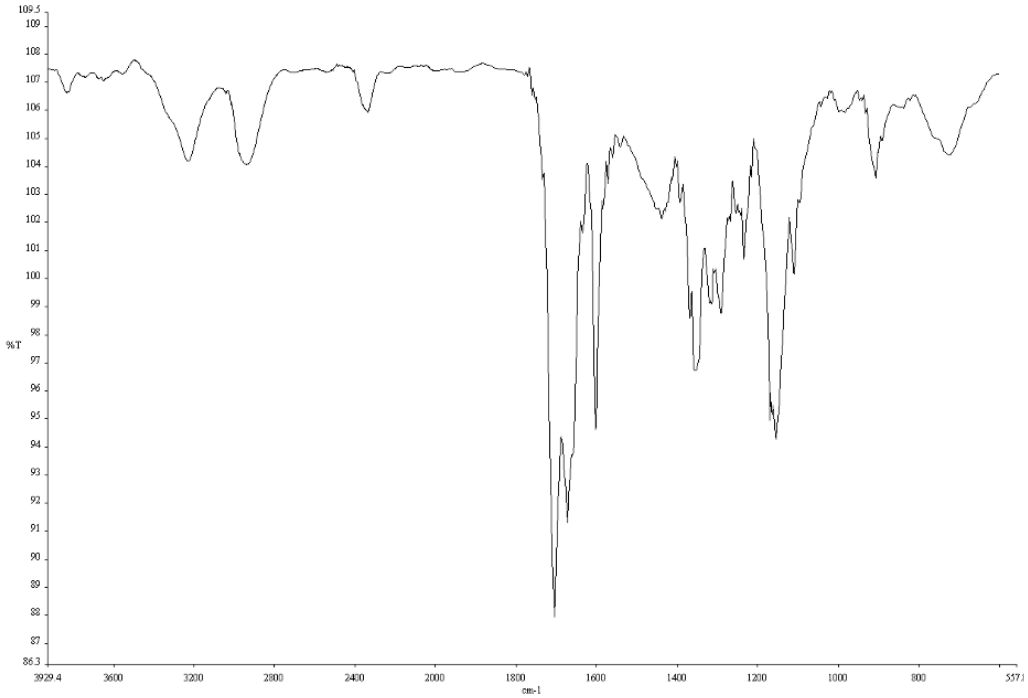


Figure A3.14. *Infrared spectrum (Thin Film, NaCl) of compound* ***102e****.*

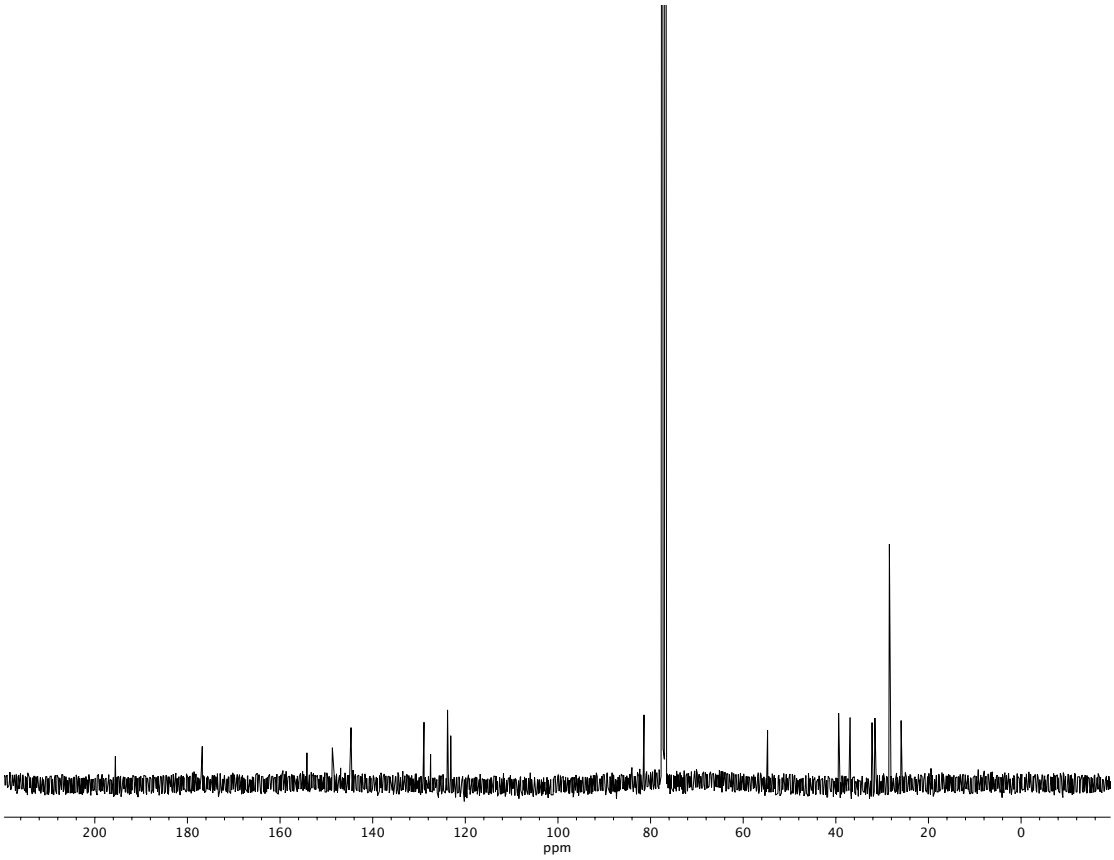


Figure A3.15. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***102e****.*

Figure A3.16. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***102f****.*

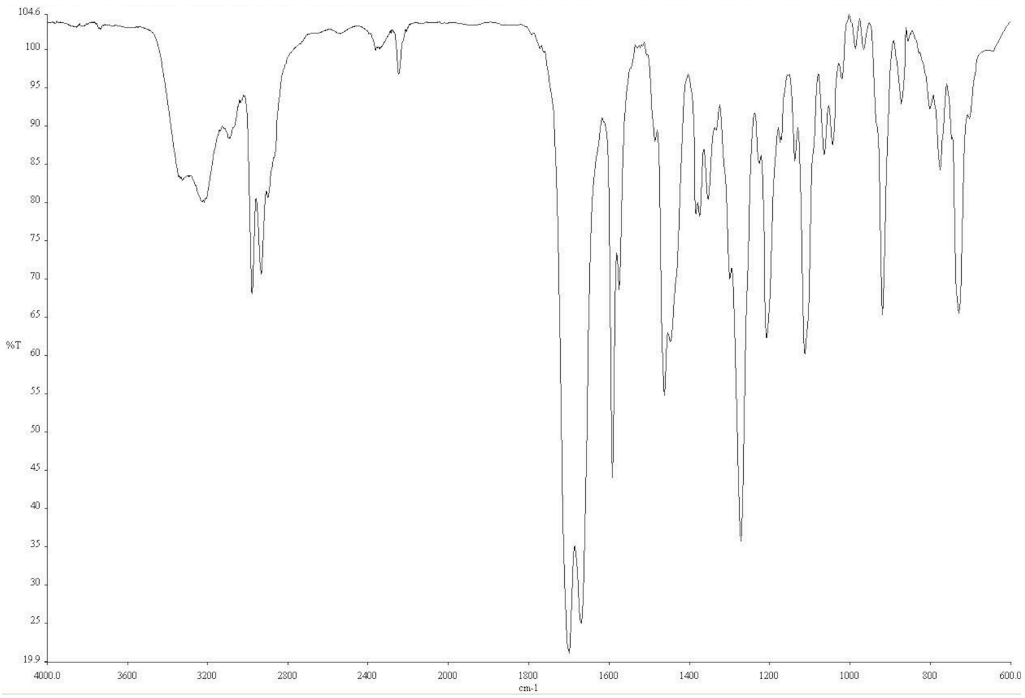


Figure A3.17. *Infrared spectrum (Thin Film, NaCl) of compound* ***102f****.*

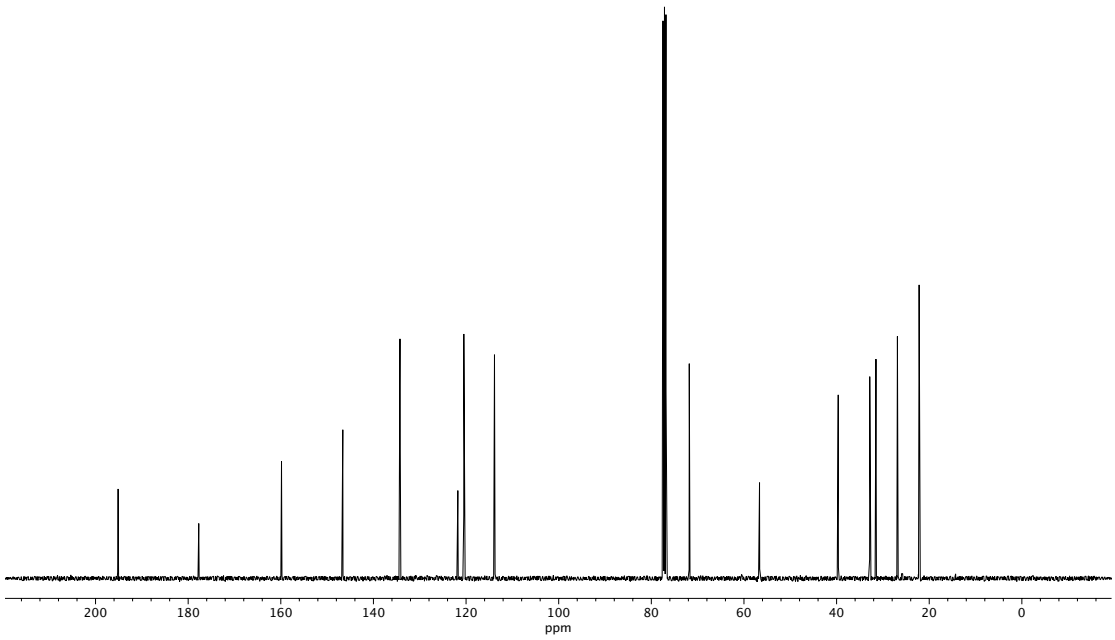


Figure A3.18. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***102f****.*

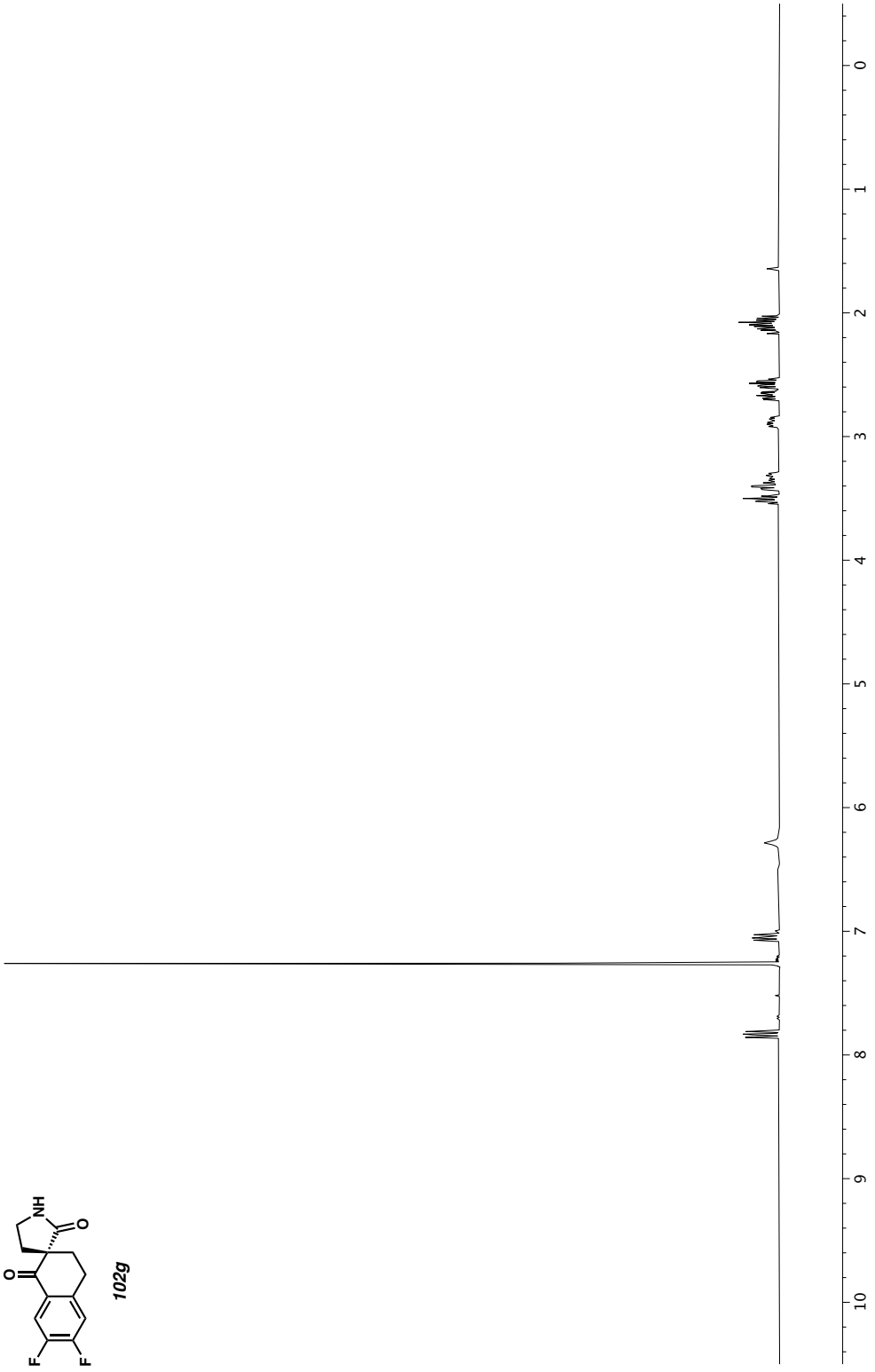


Figure A3.19. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***102g****.*

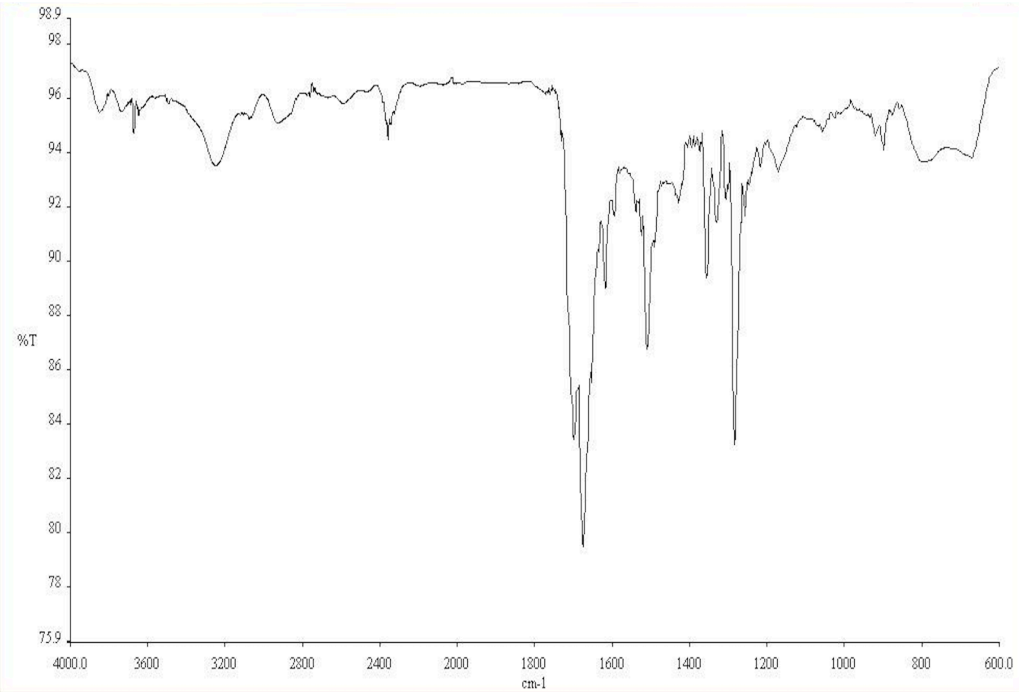


Figure A3.20. *Infrared spectrum (Thin Film, NaCl) of compound* ***102g****.*

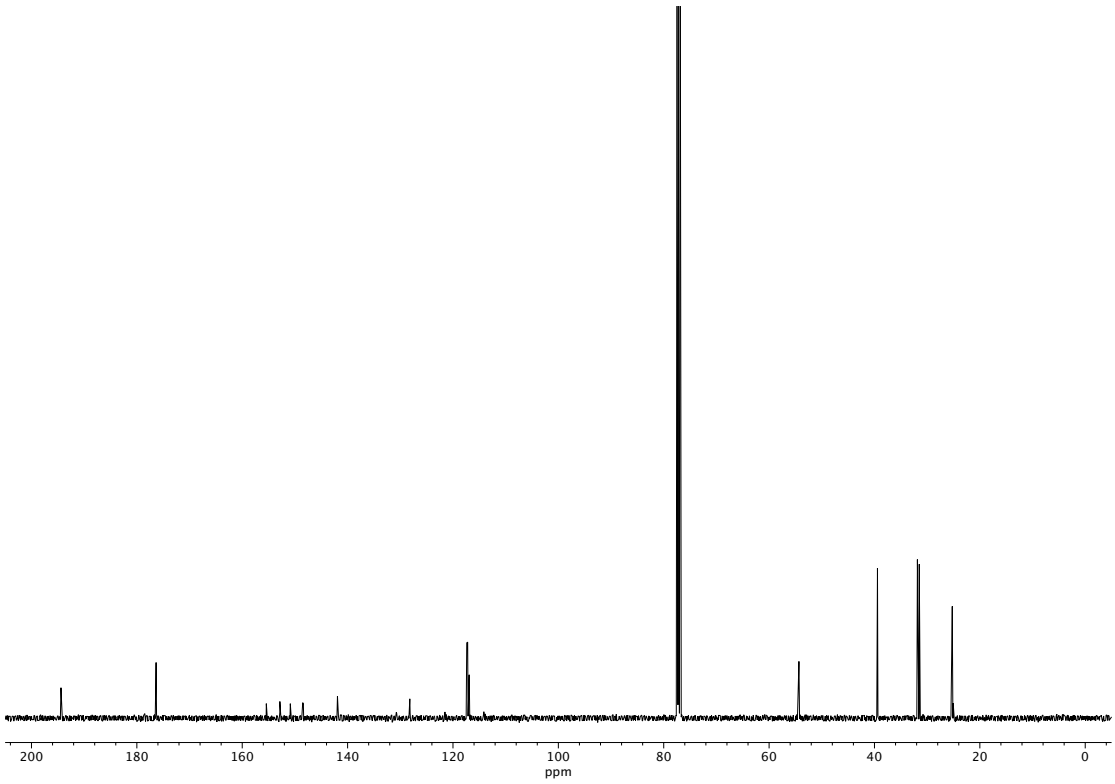


Figure A3.21. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***102g****.*

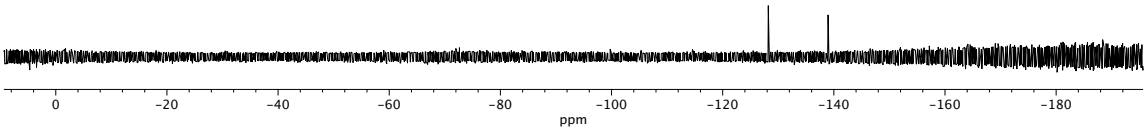


Figure A3.22. *^{19}F NMR (282 MHz, $CDCl_3$) of compound* ***102g****.*

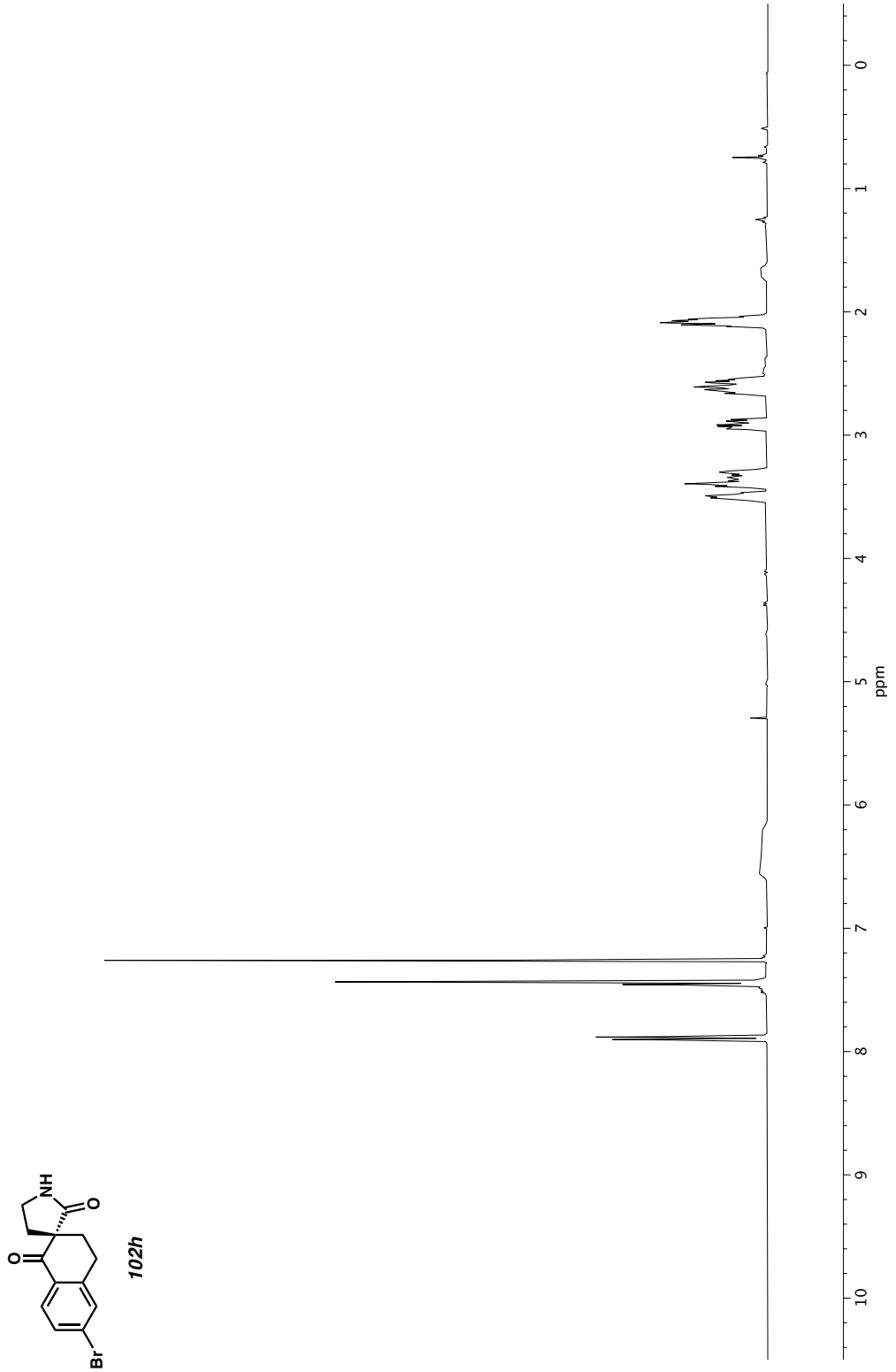


Figure A3.23. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***102h***.

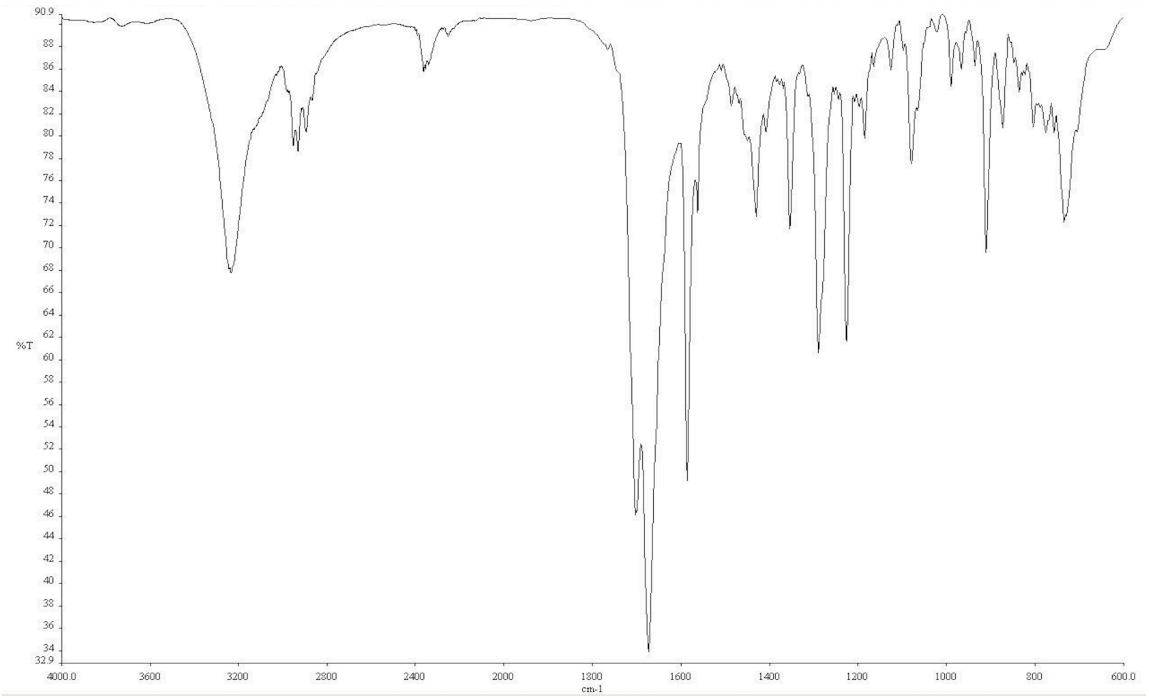


Figure A3.24. *Infrared spectrum ($CDCl_3$ solution) of compound* ***102h****.*

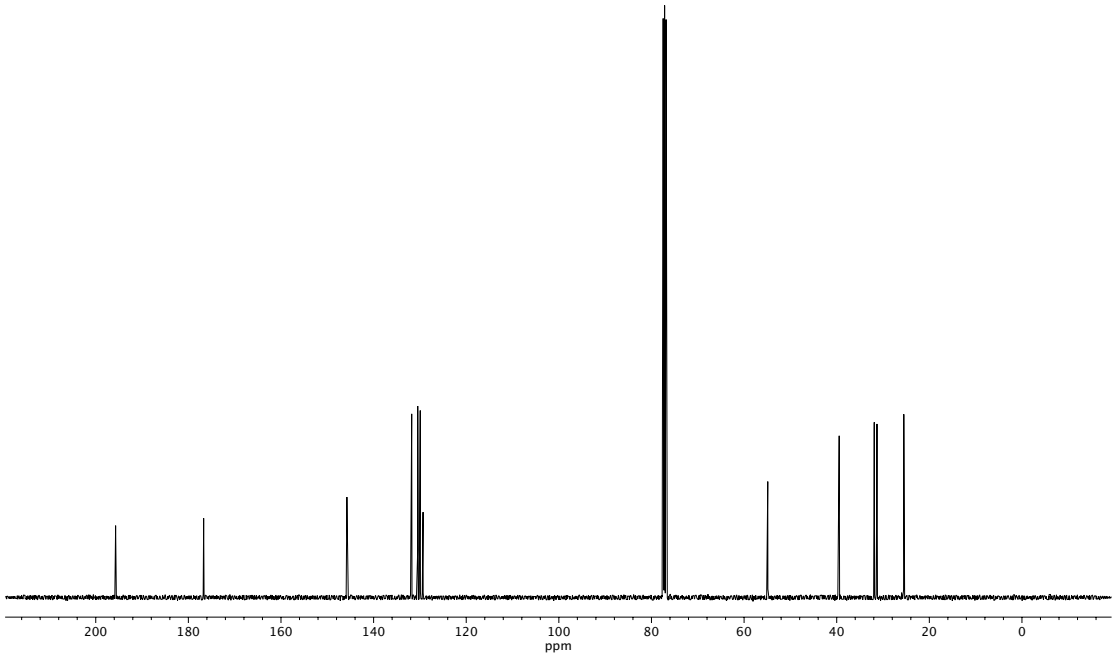


Figure A3.25. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***102h****.*

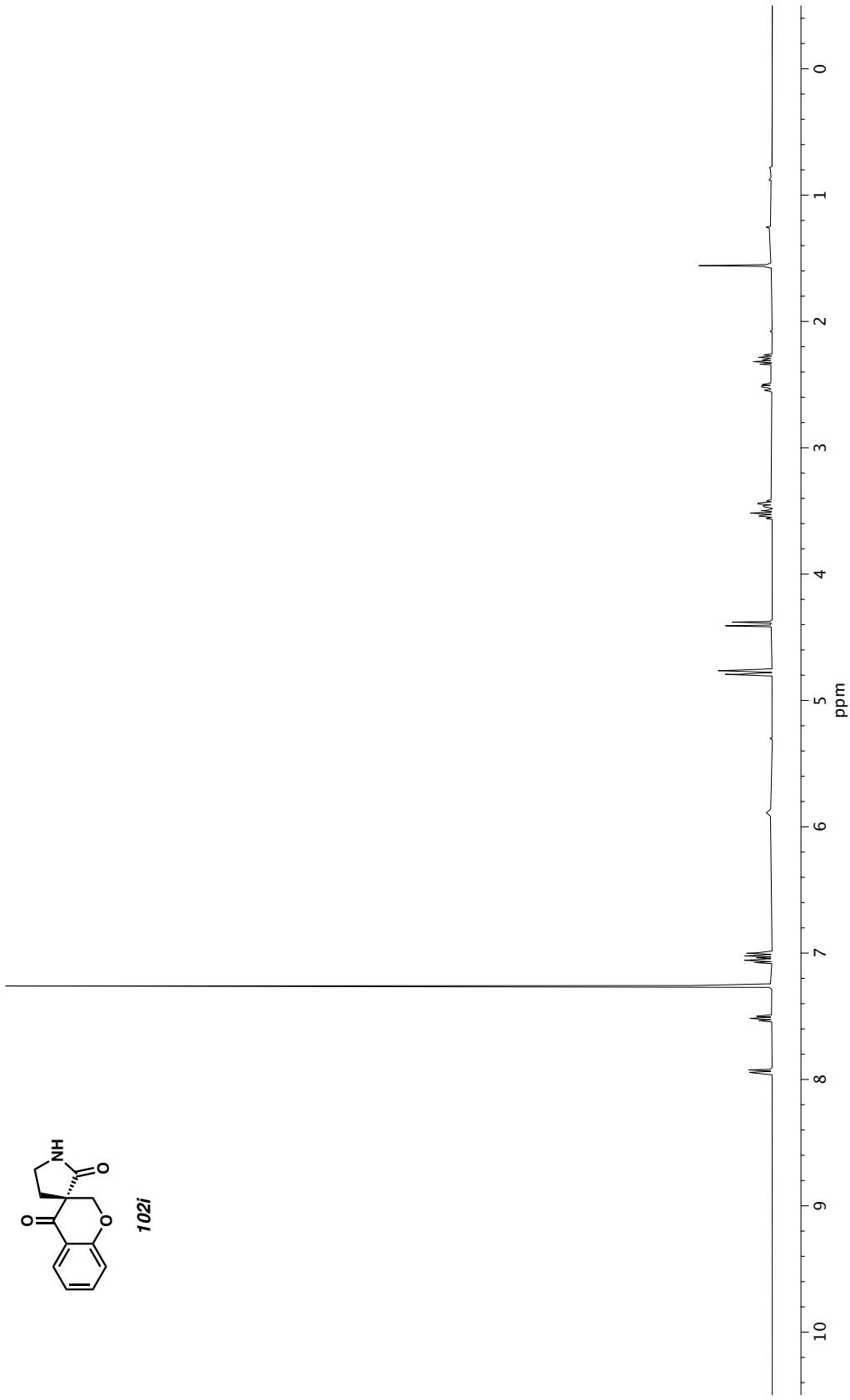


Figure A3.26. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***102i****.*

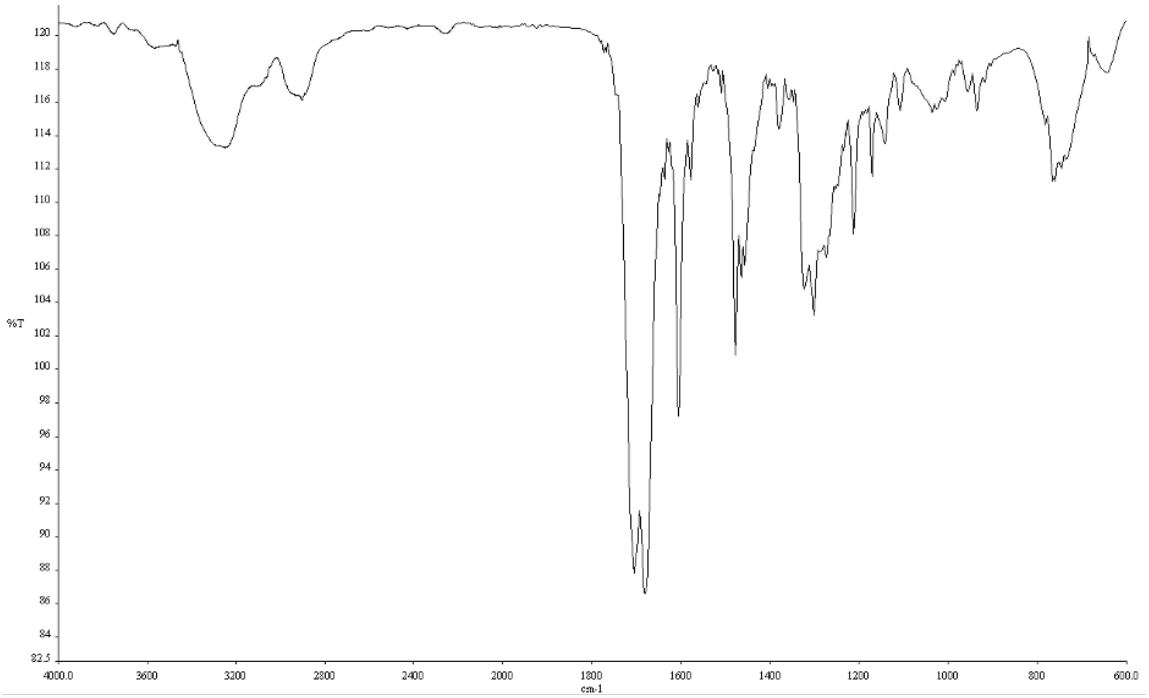


Figure A3.27. *Infrared spectrum ($CDCl_3$ solution) of compound* ***102i****.*

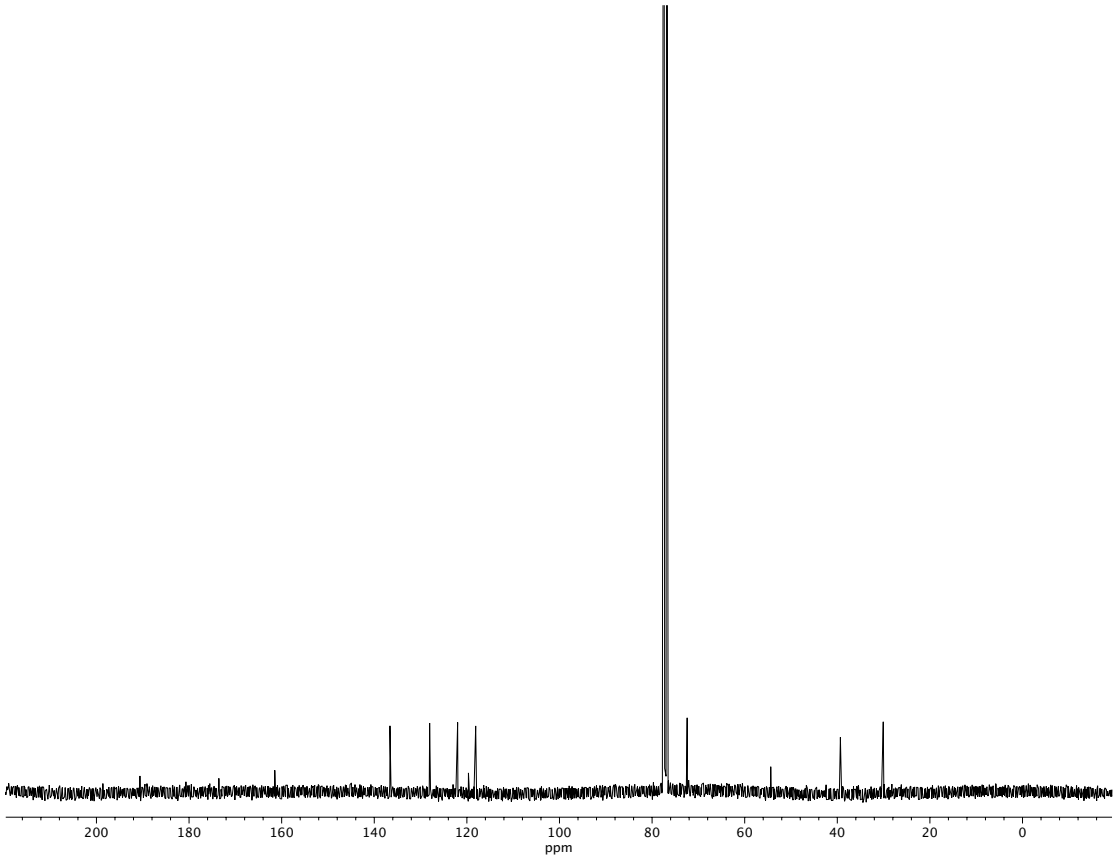


Figure A3.28. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***102i****.*

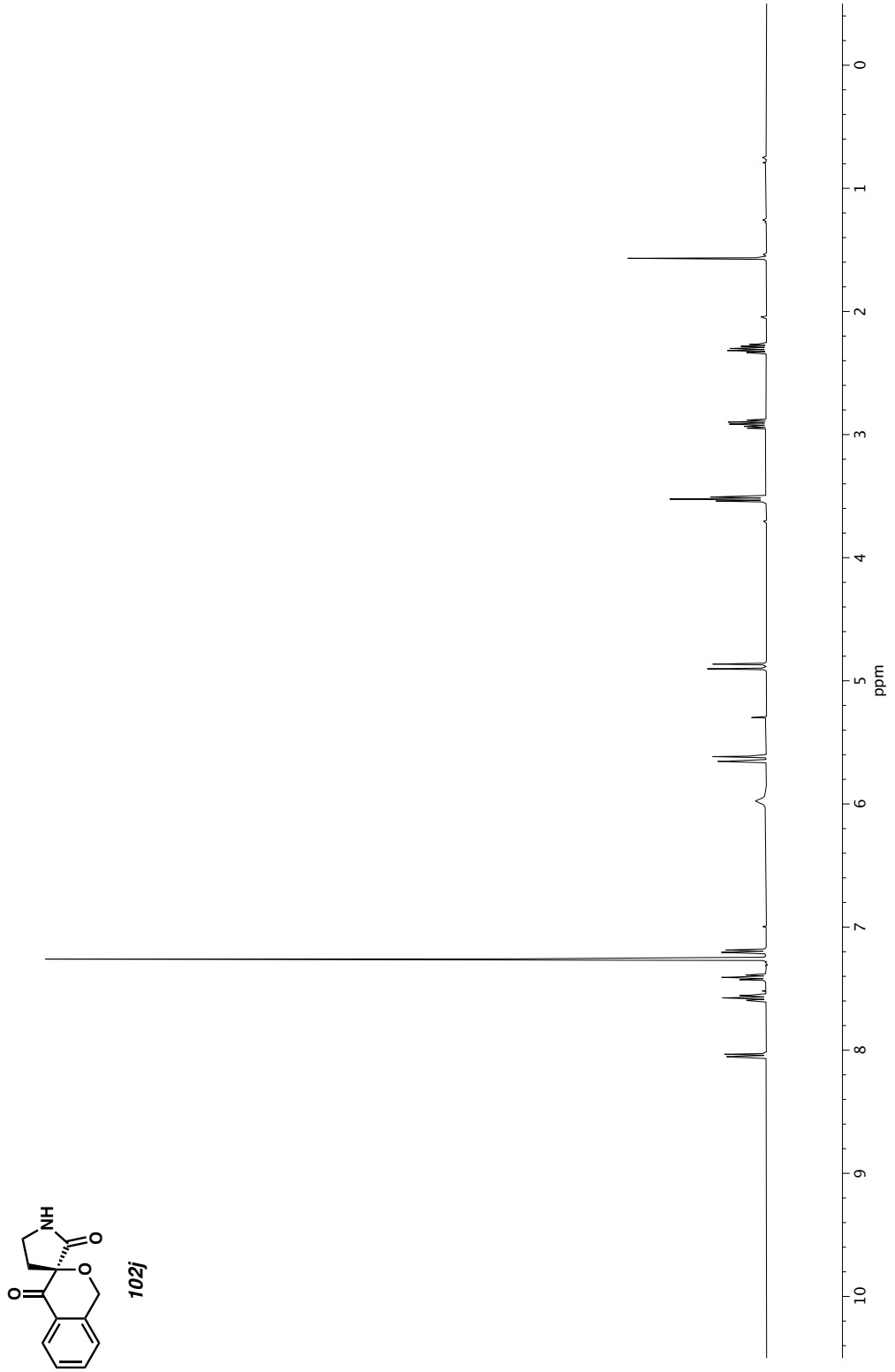


Figure A3.29. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***102j****.*

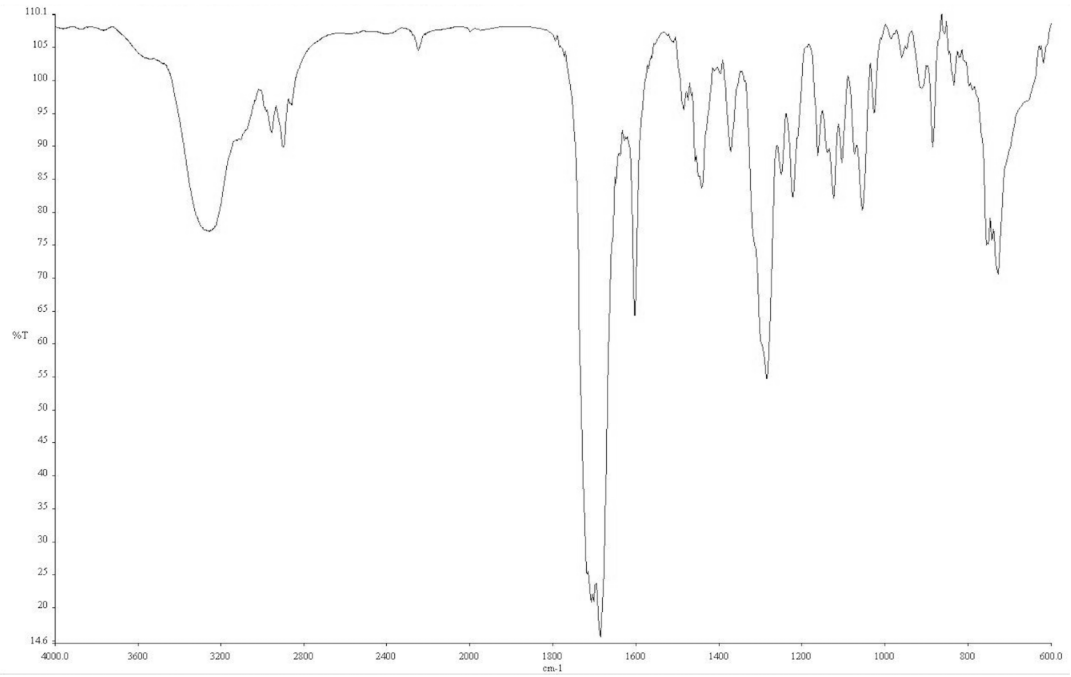


Figure A3.30. *Infrared spectrum (Thin Film, NaCl) of compound* ***102j****.*

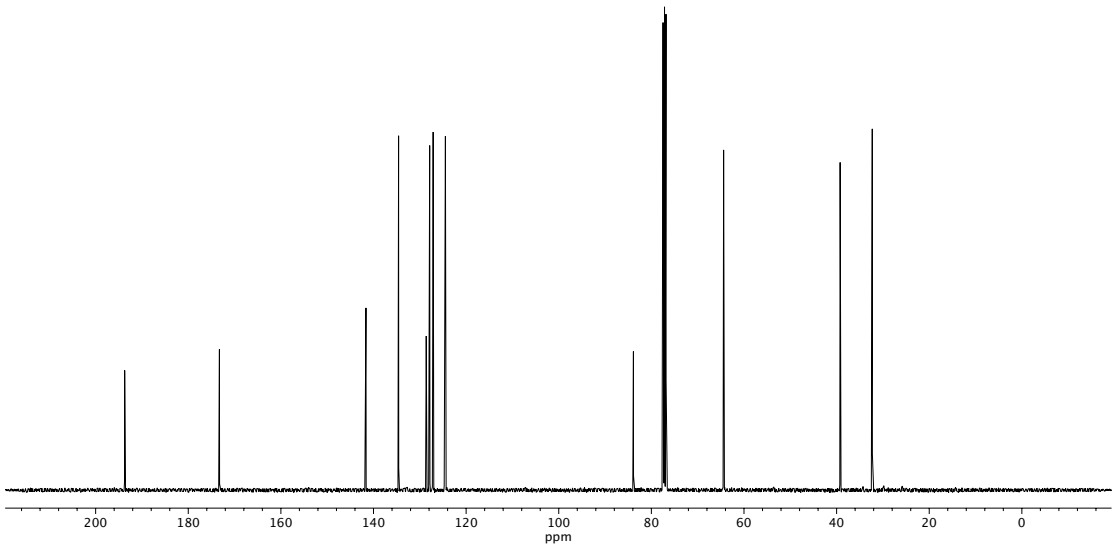


Figure A3.31. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***102j****.*

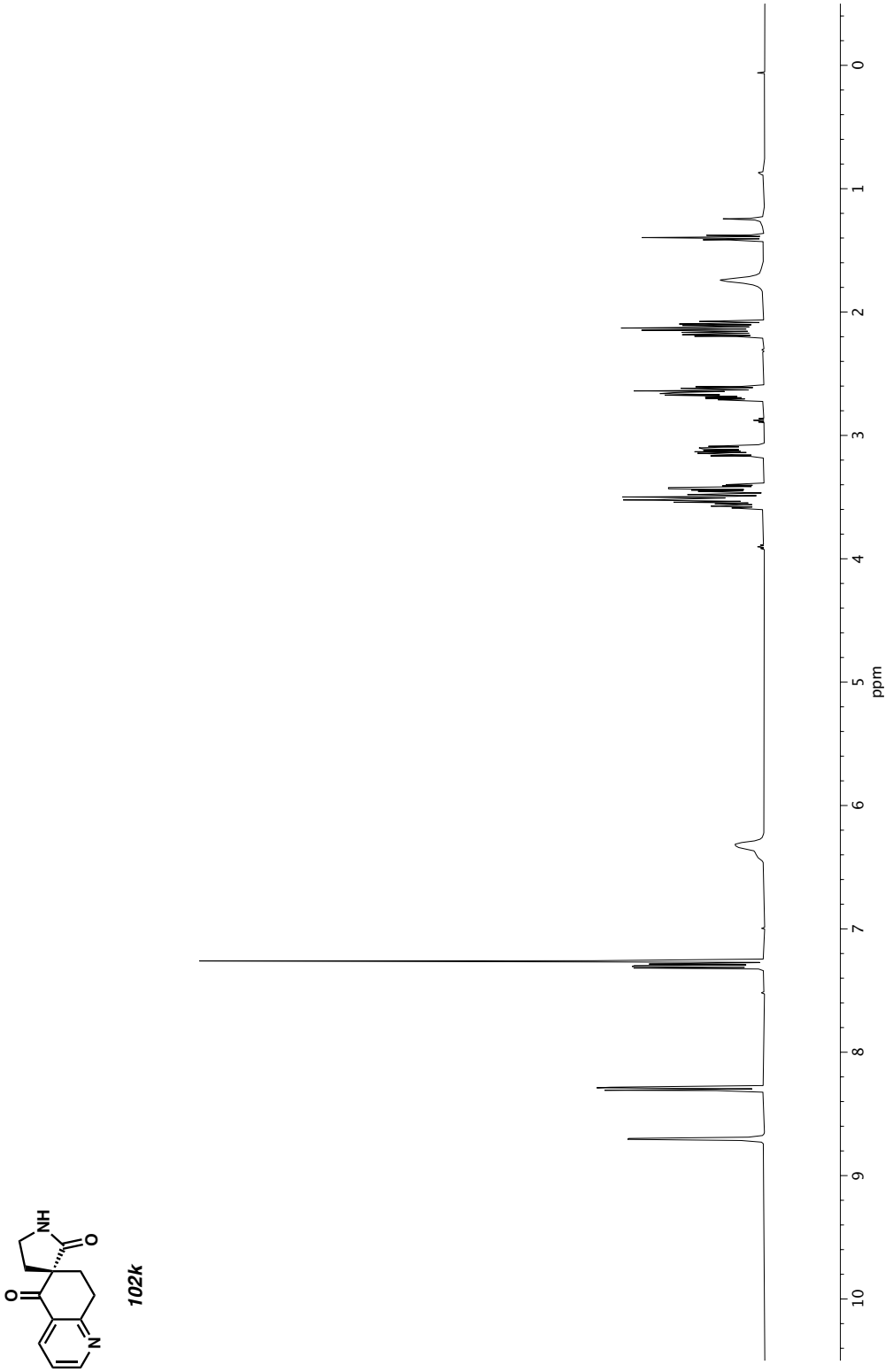


Figure A3.32. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***102k****.*

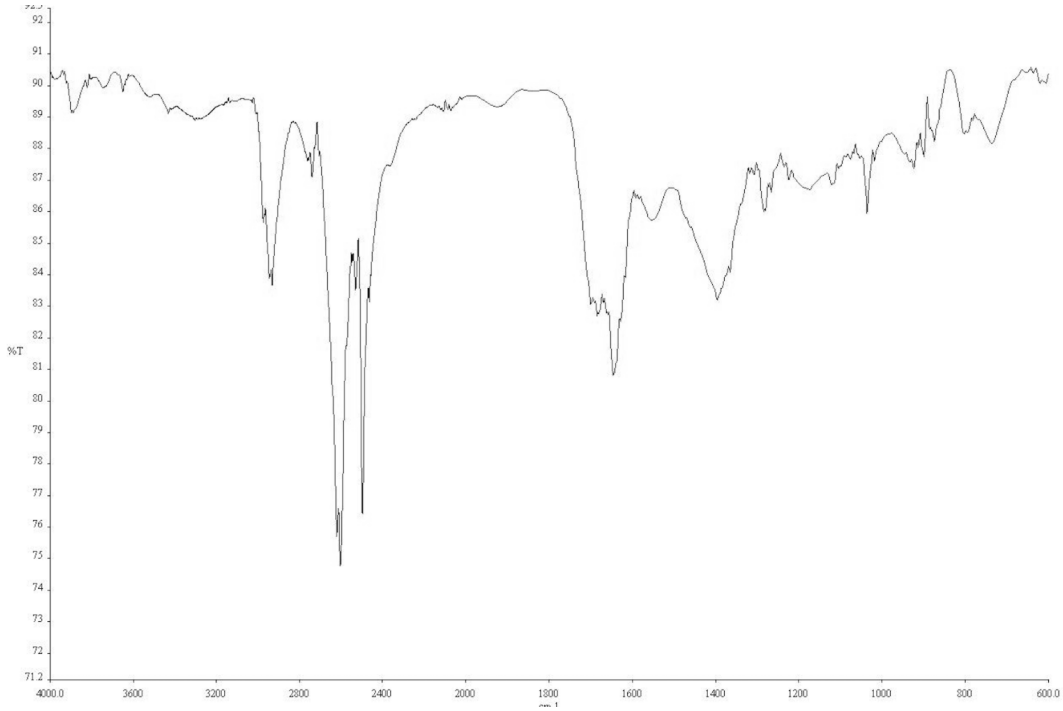


Figure A3.33. *Infrared spectrum (Thin Film, NaCl) of compound* ***102k****.*

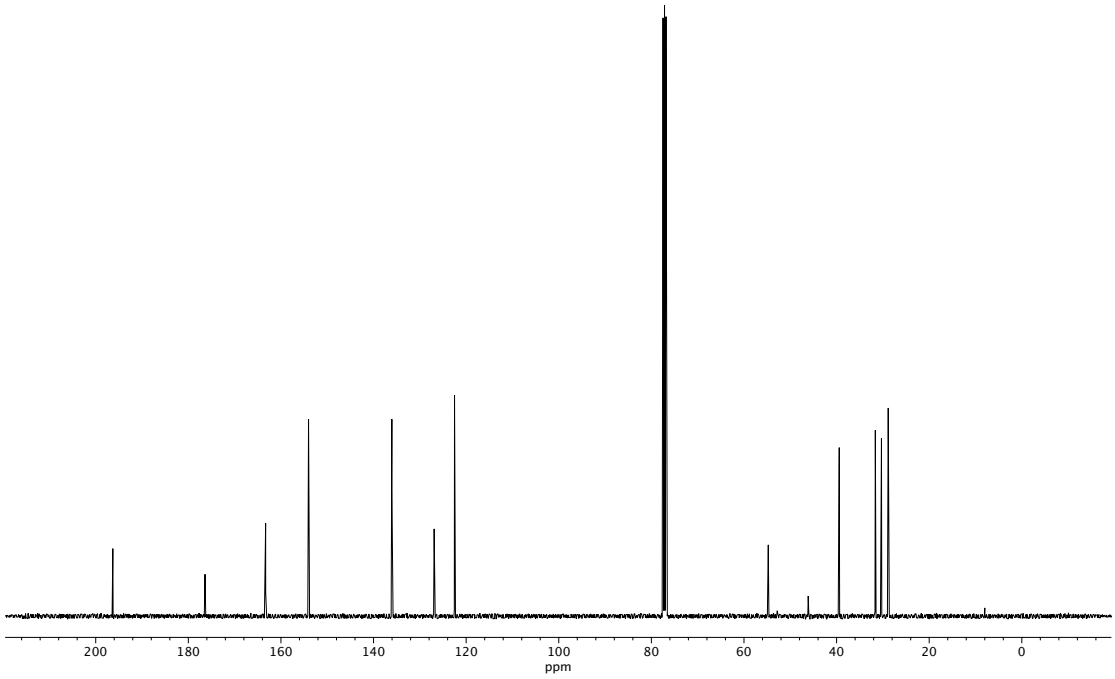


Figure A3.34. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***102k****.*

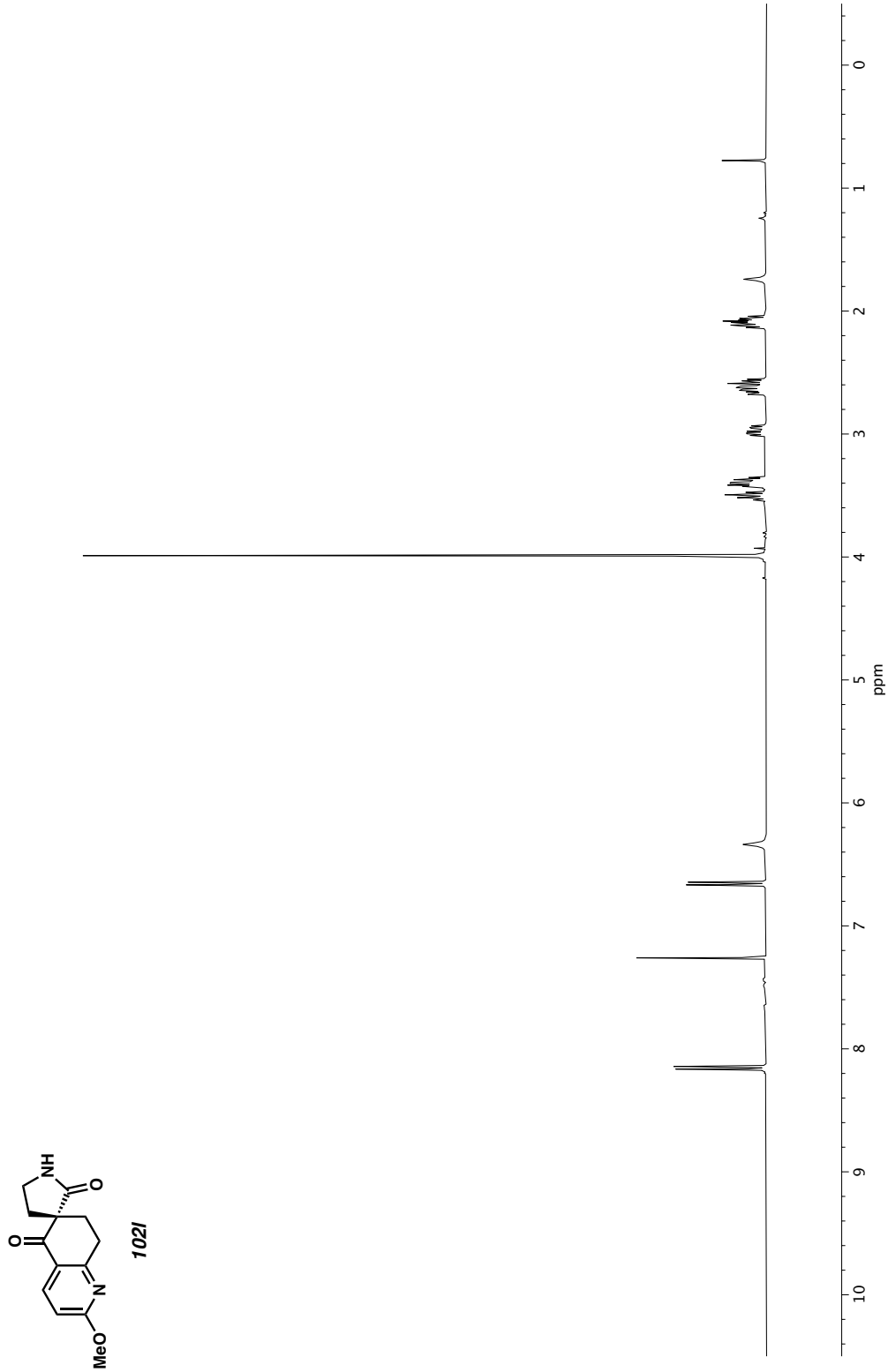


Figure A3.35. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***102l****.*

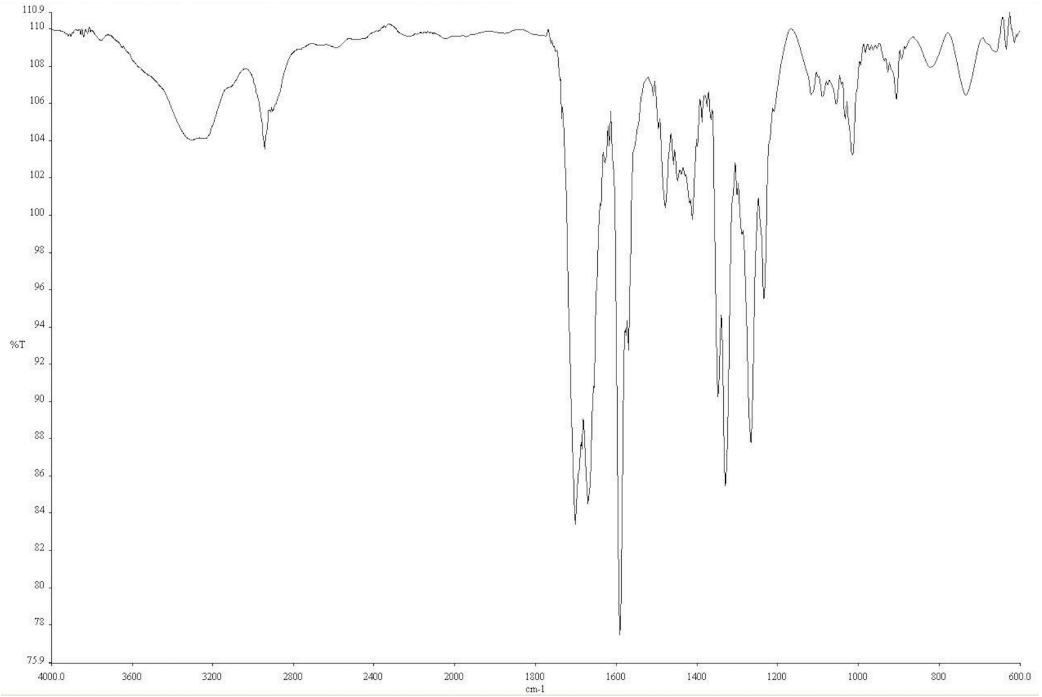


Figure A3.36. *Infrared spectrum (Thin Film, NaCl) of compound* ***102l****.*

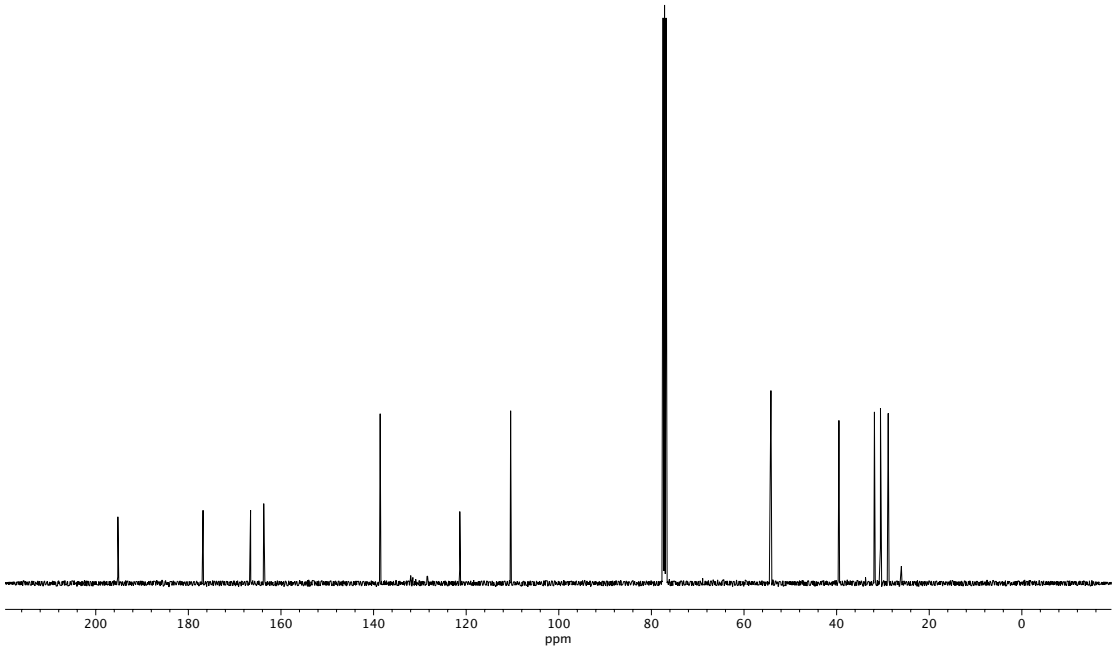


Figure A3.37. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***102l****.*

Figure A3.38. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***102m****.*

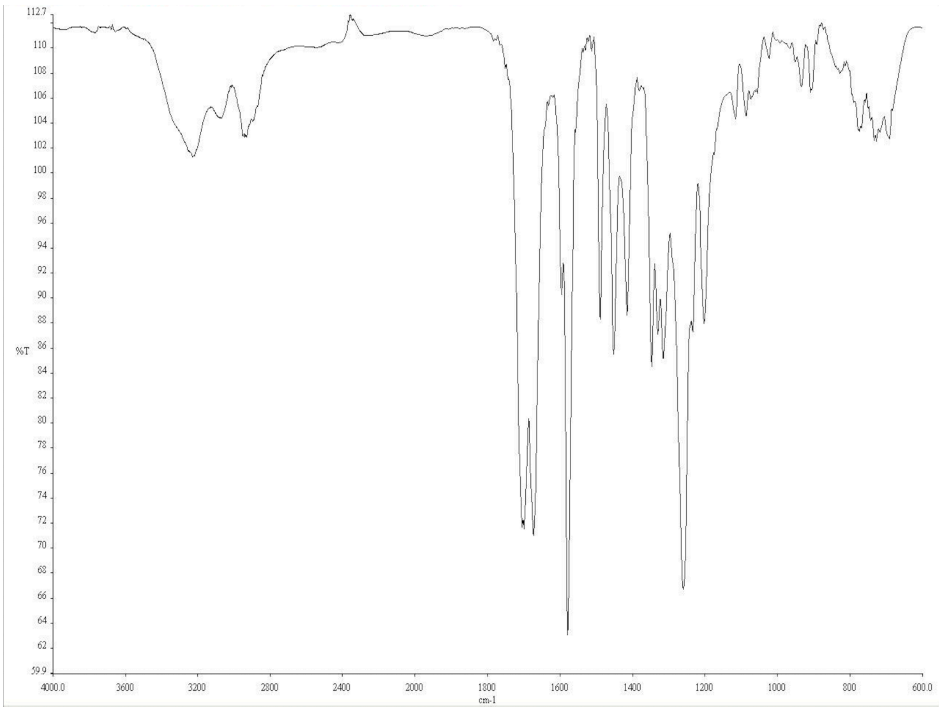


Figure A3.39. *Infrared spectrum (Thin Film, NaCl) of compound* ***102m****.*

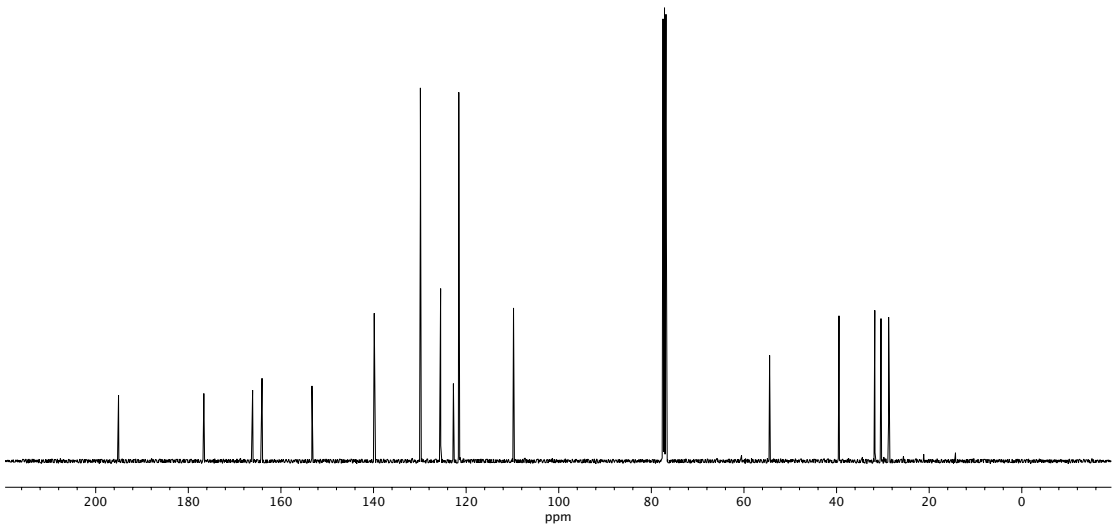


Figure A3.40. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***102m****.*

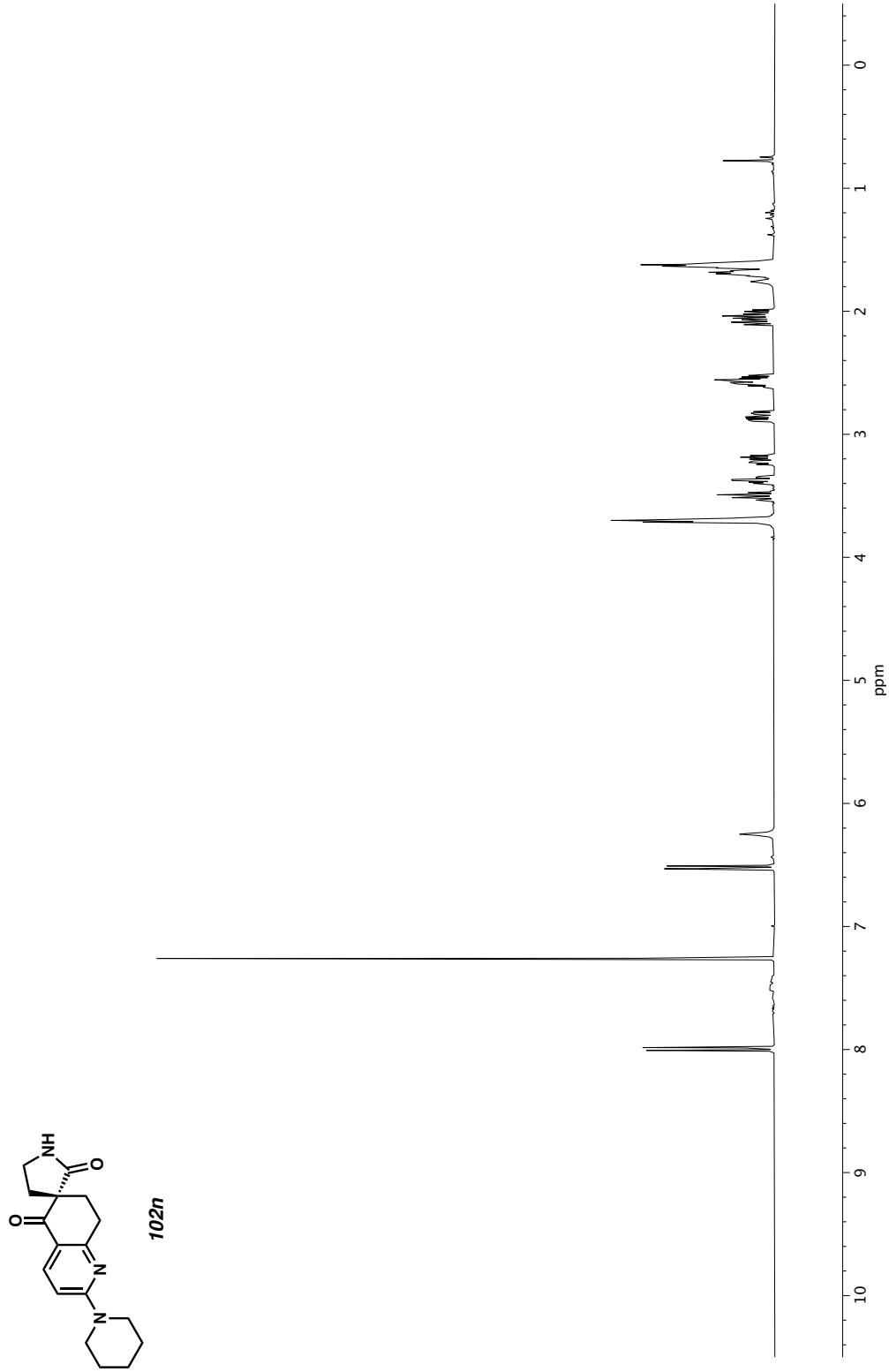


Figure A3.41. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***102n***.

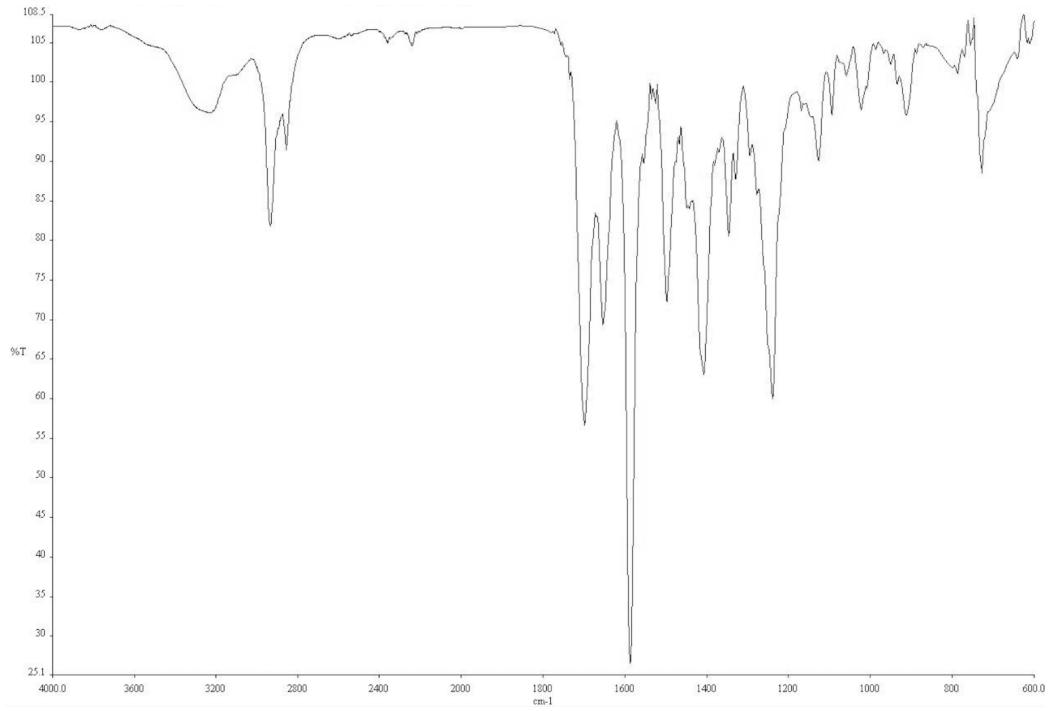


Figure A3.42. *Infrared spectrum (Thin Film, NaCl) of compound* ***102n****.*

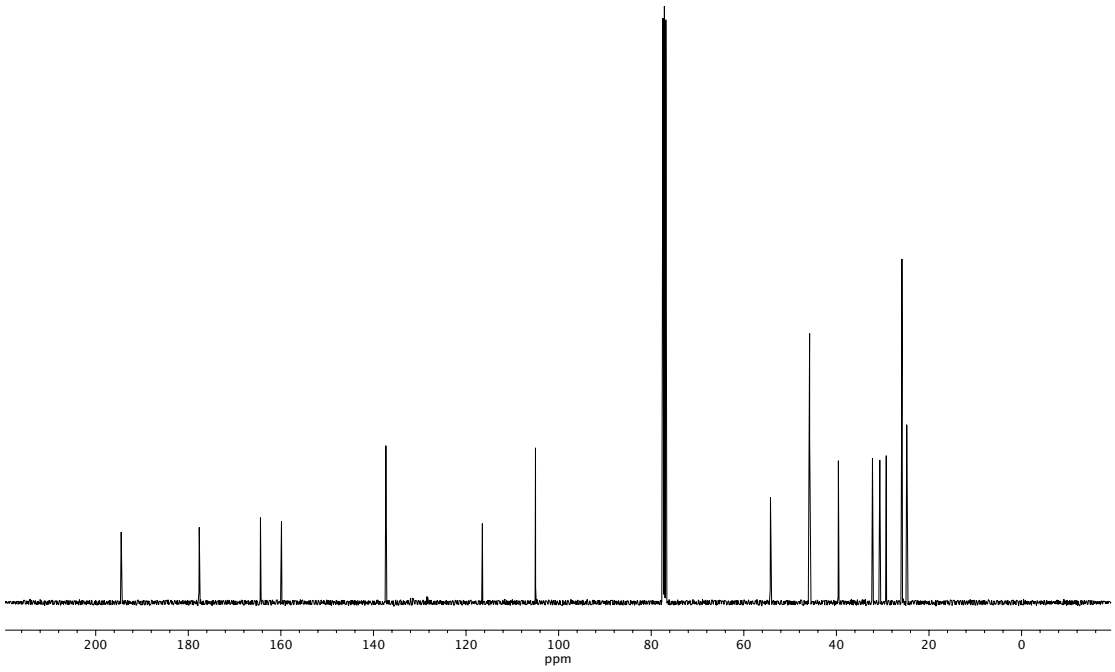


Figure A3.43. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***102n****.*

Figure A3.44. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***diallyl-103a***.

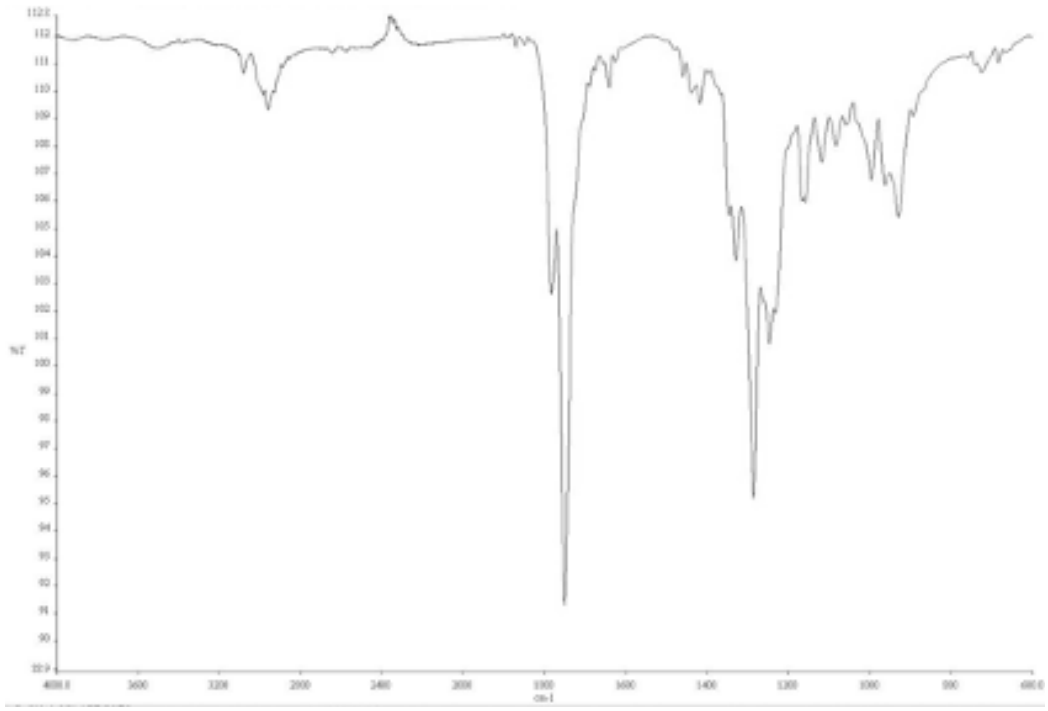


Figure A3.45. *Infrared spectrum (Thin Film, NaCl) of compound* ***diallyl-103a****.*

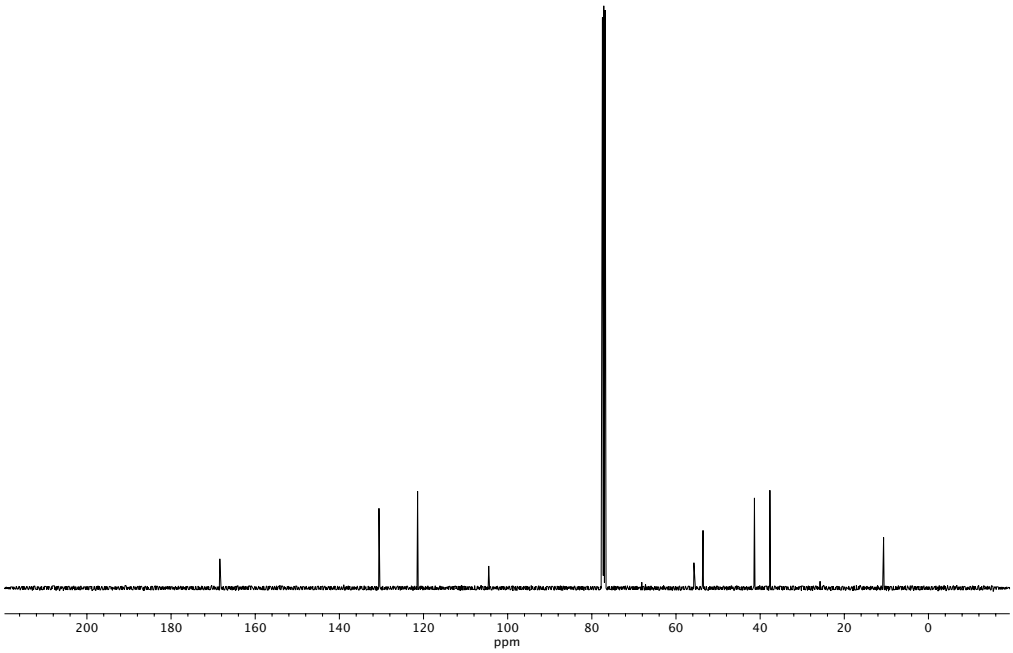


Figure A3.46. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***diallyl-103a****.*

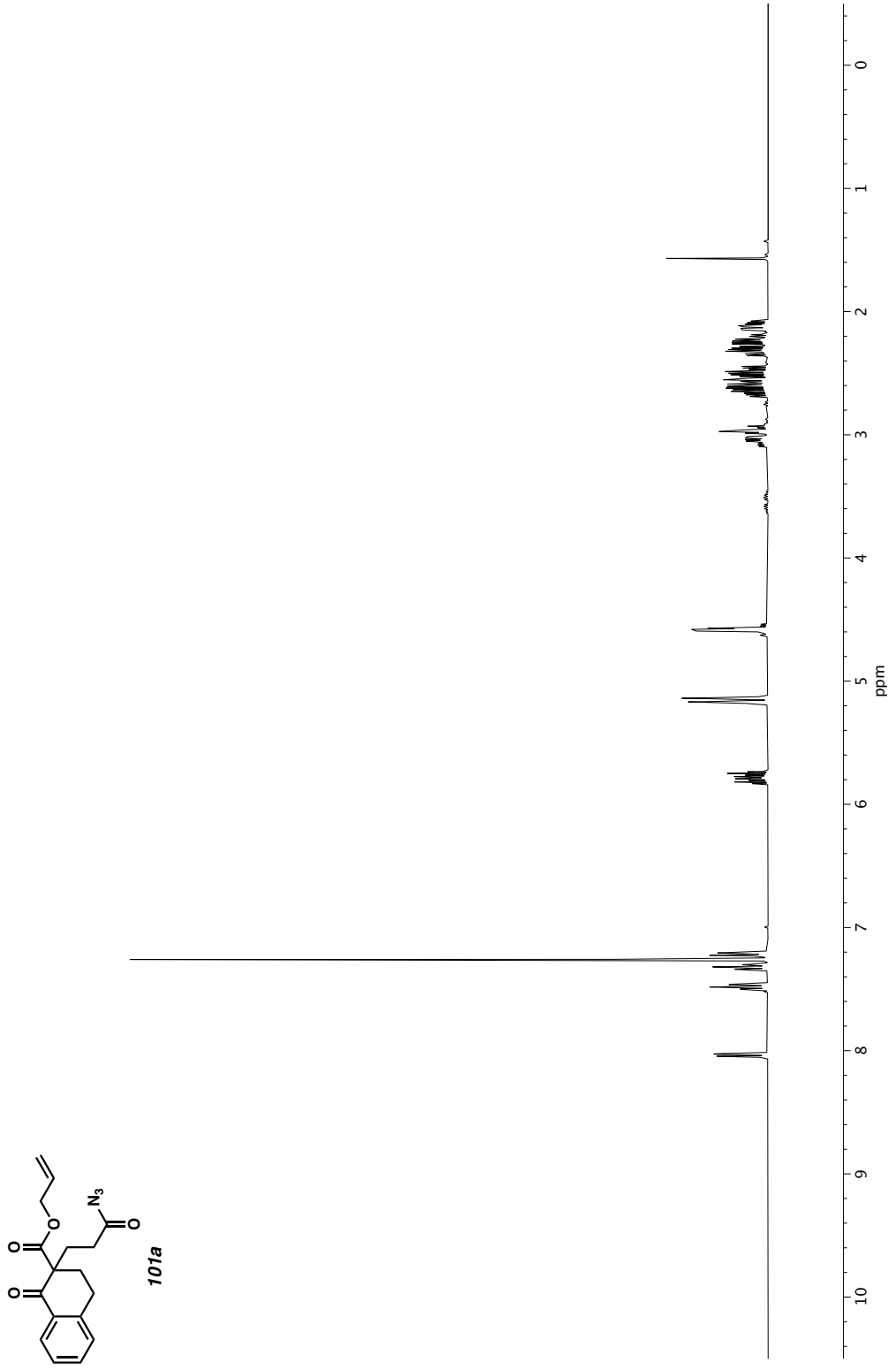


Figure A3.47. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***101a****.*

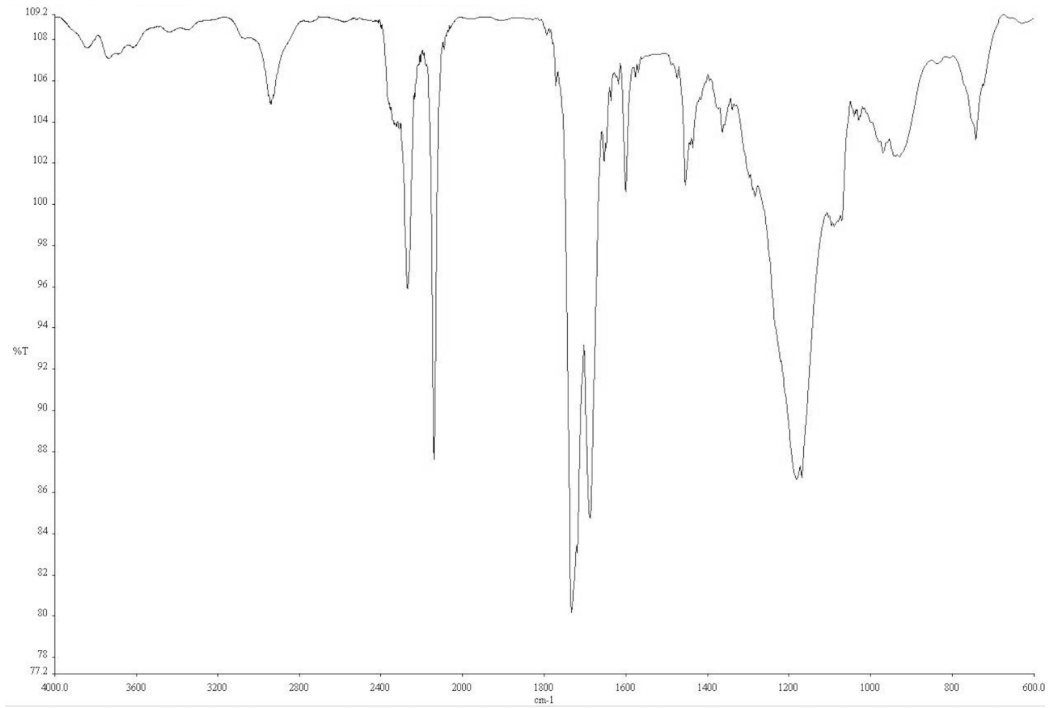


Figure A3.48. *Infrared spectrum (Thin Film, NaCl) of compound* ***101a****.*

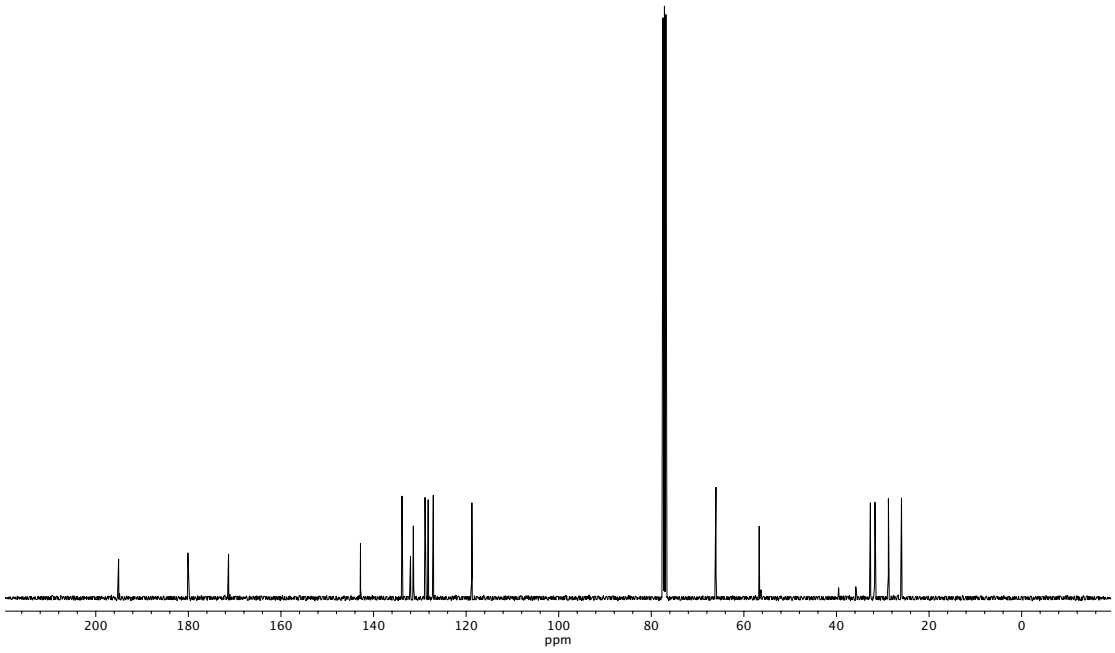


Figure A3.49. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***101a****.*

Figure A3.50. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***104****.*

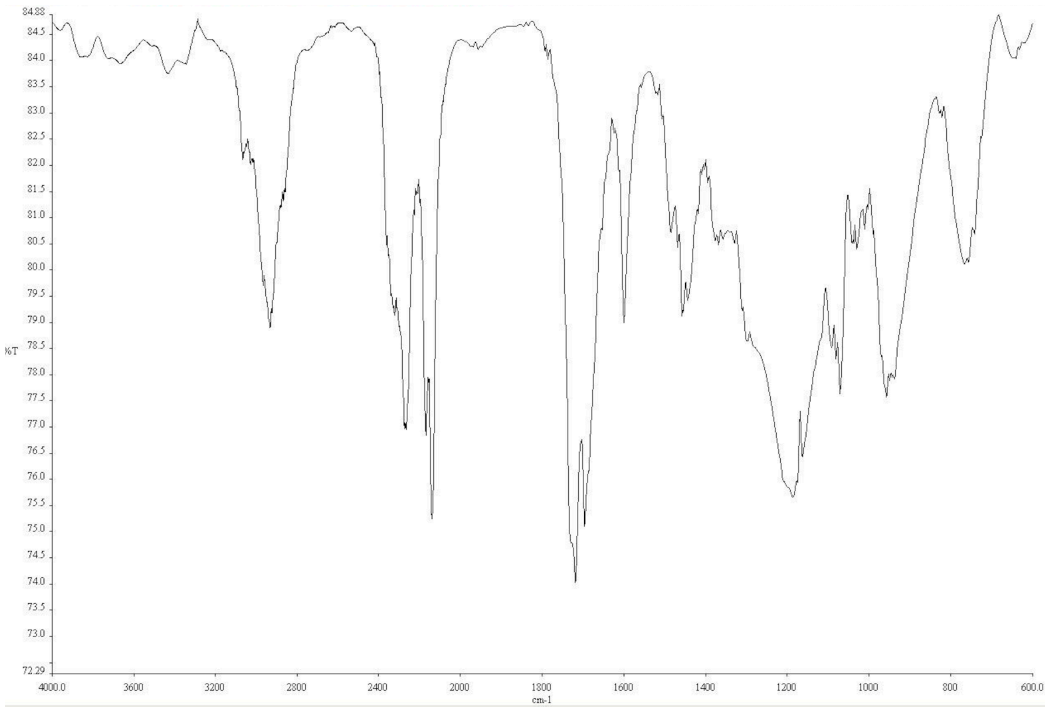


Figure A3.51. *Infrared spectrum (Thin Film, NaCl) of compound* ***104****.*

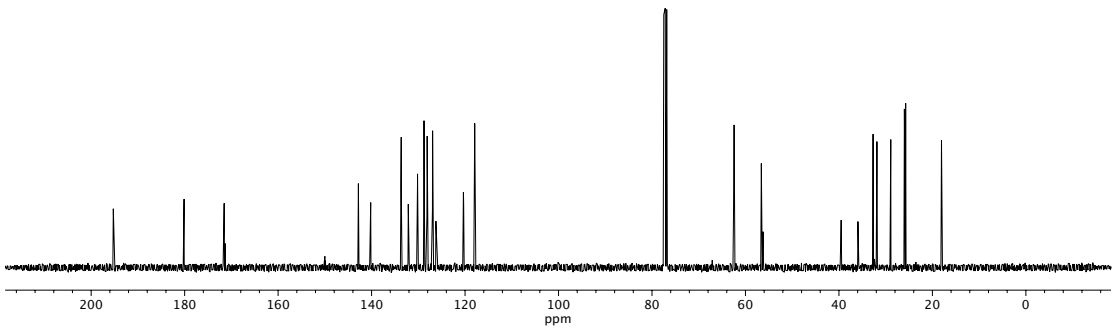


Figure A3.52. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***104****.*

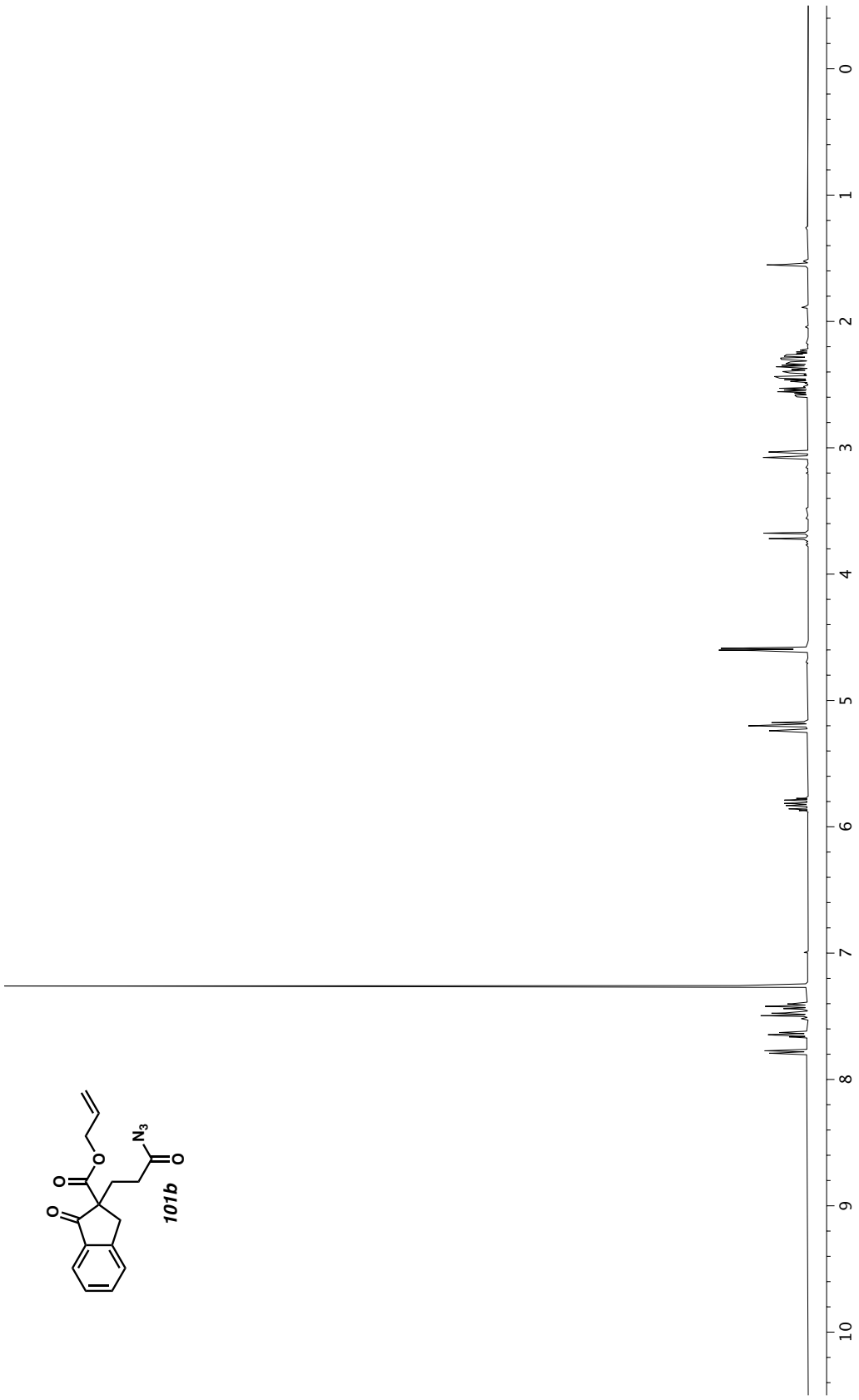


Figure A3.53. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***101b****.*

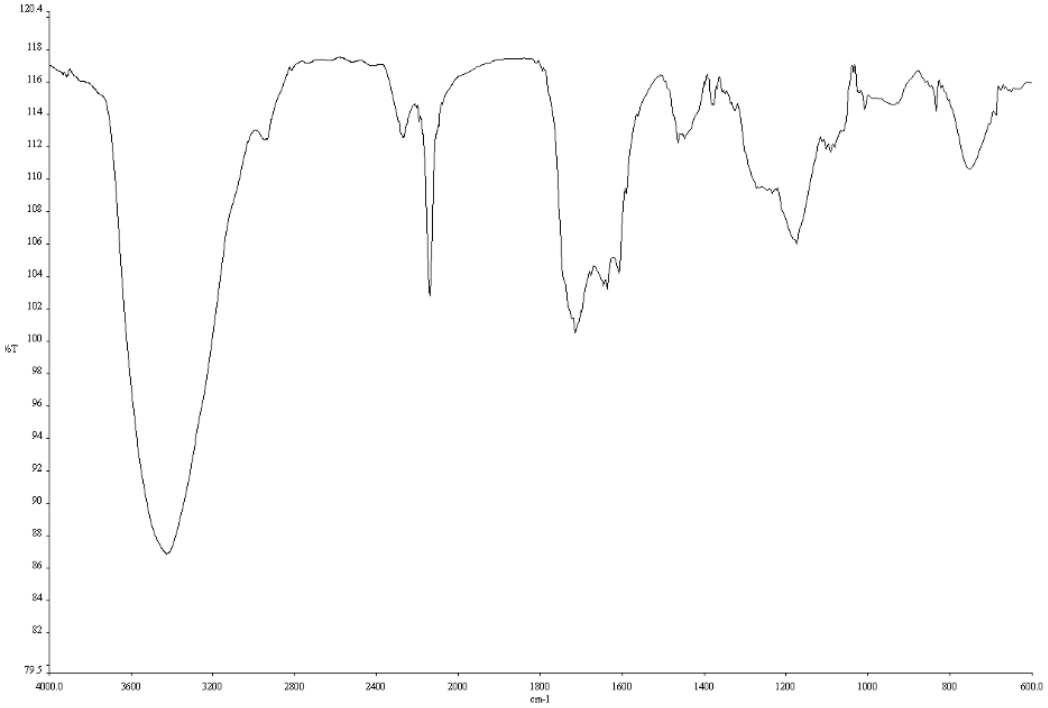


Figure A3.54. *Infrared spectrum (Thin Film, NaCl) of compound* ***101b****.*

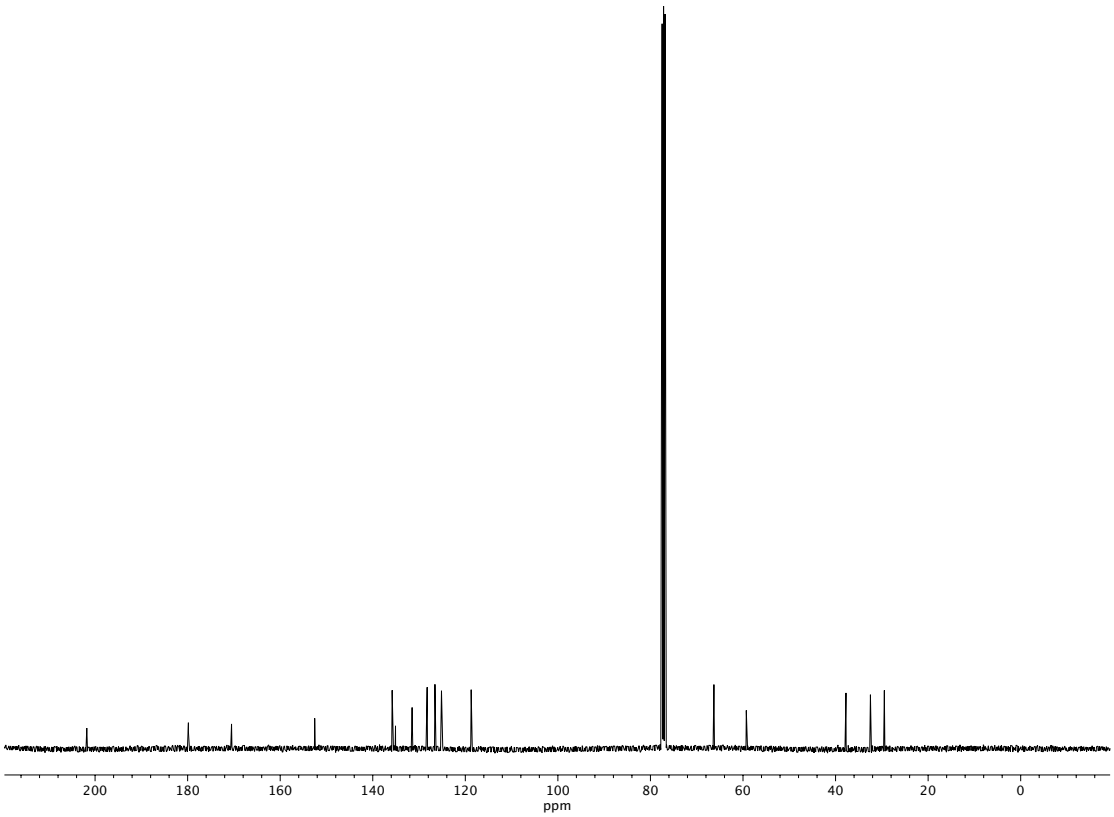


Figure A3.55. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***101b****.*

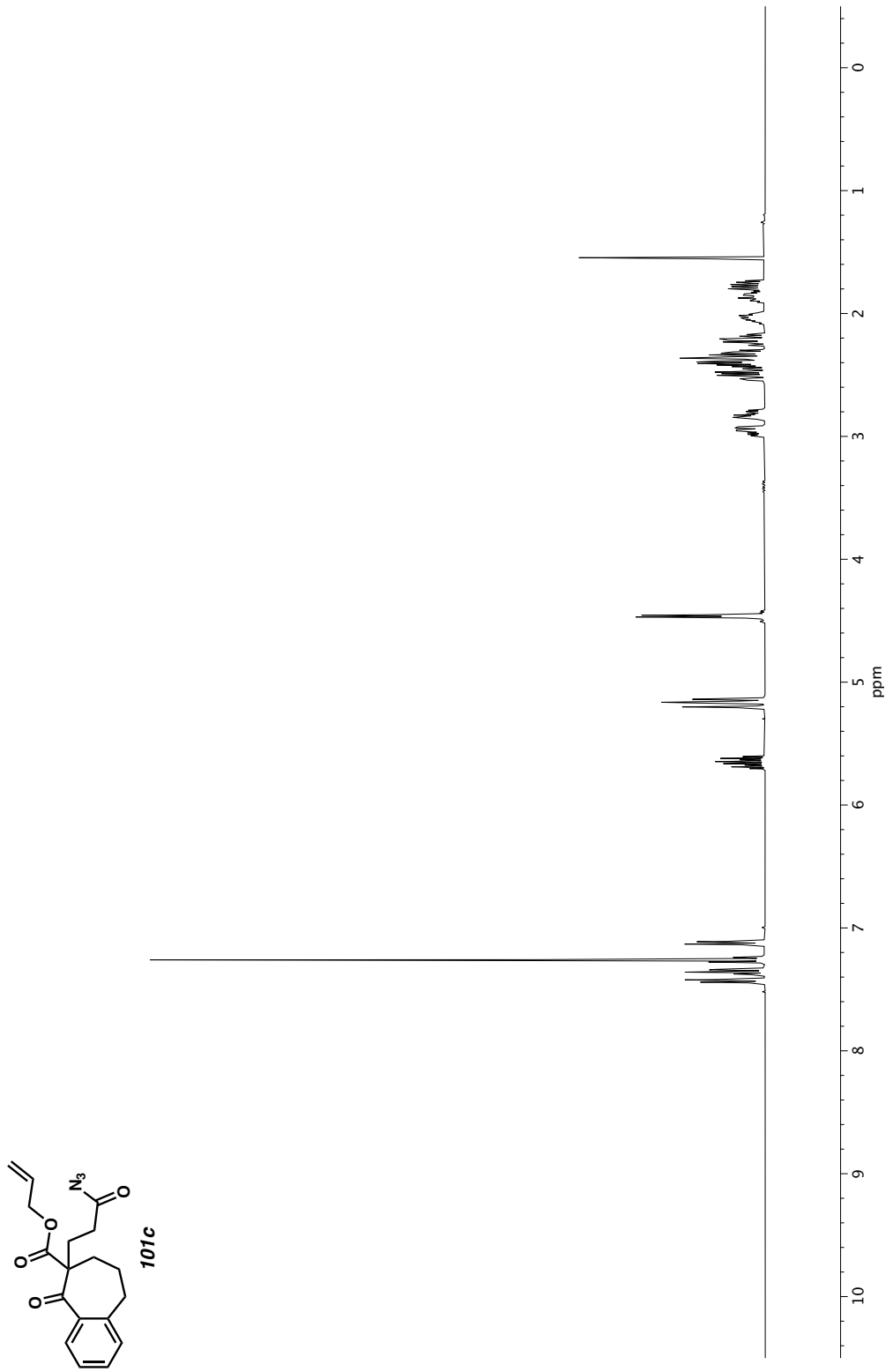


Figure A3.56. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***101c****.*

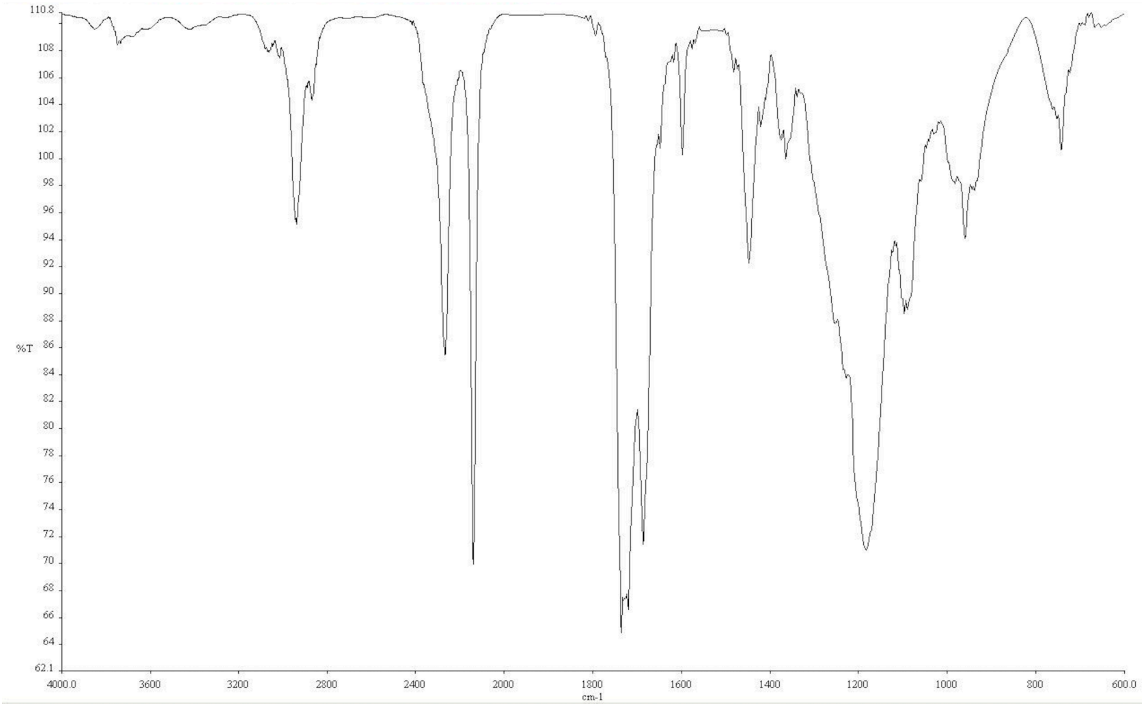


Figure A3.57. *Infrared spectrum (Thin Film, NaCl) of compound* ***101c****.*

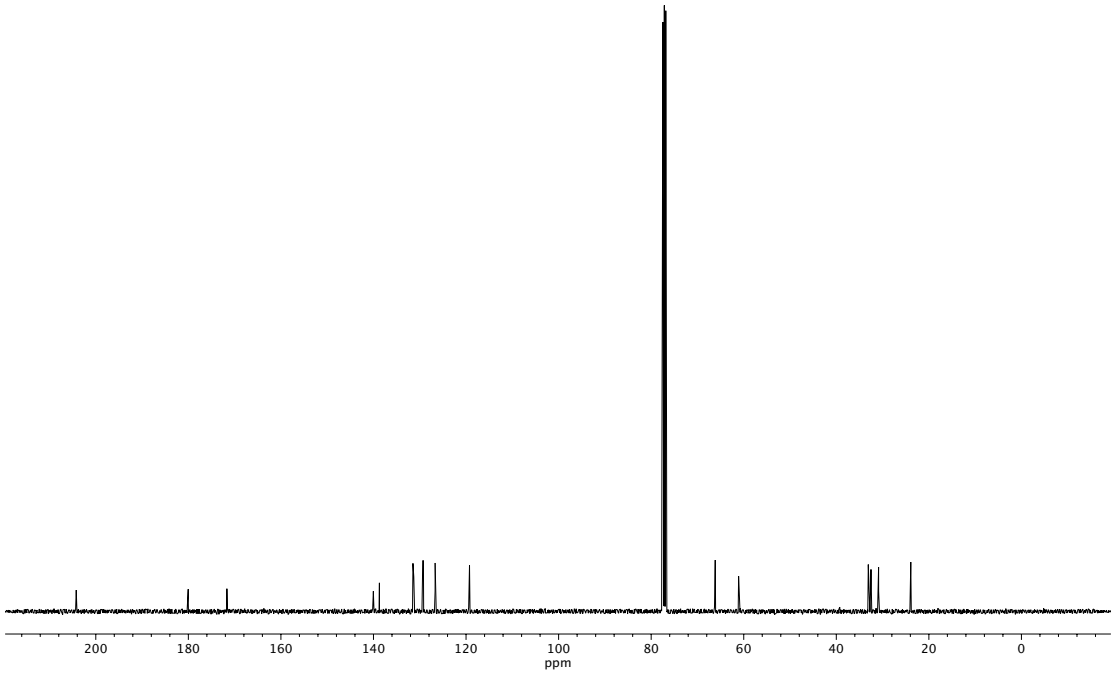


Figure A3.58. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***101c****.*

Figure A3.59. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***101d****.*

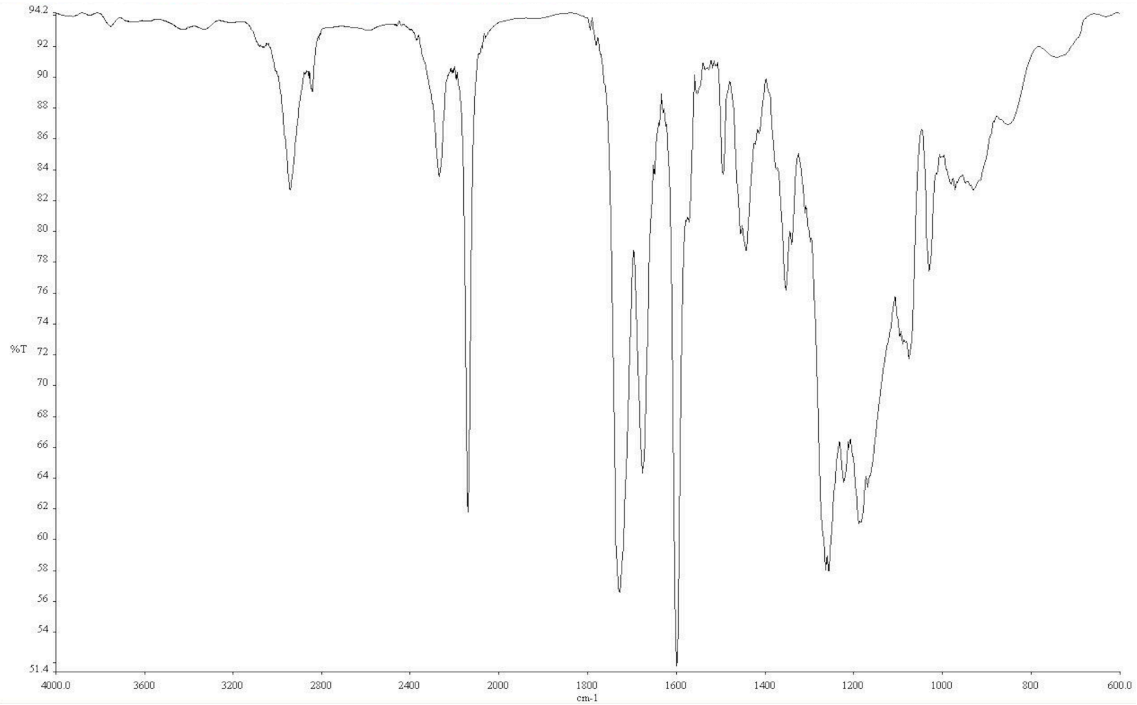


Figure A3.60. *Infrared spectrum (Thin Film, NaCl) of compound* ***101d****.*

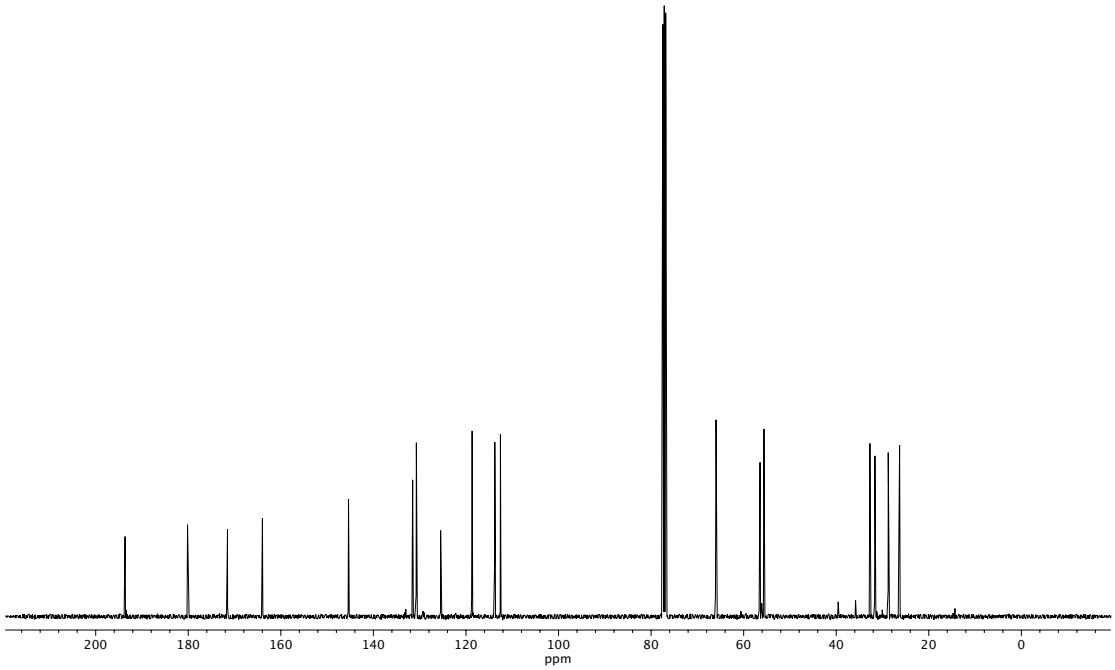


Figure A3.61. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***101d****.*

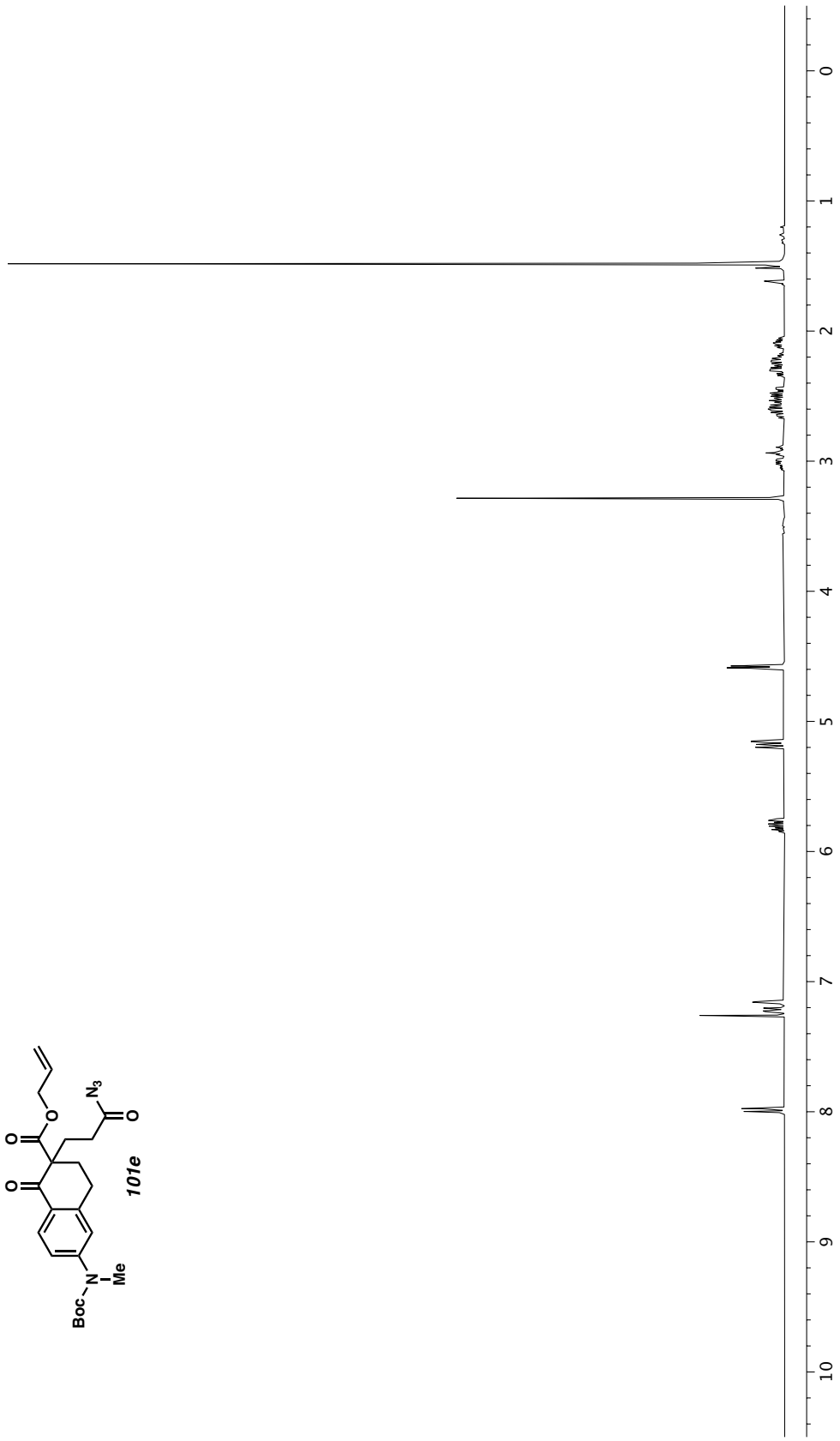


Figure A3.62. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***101e****.*

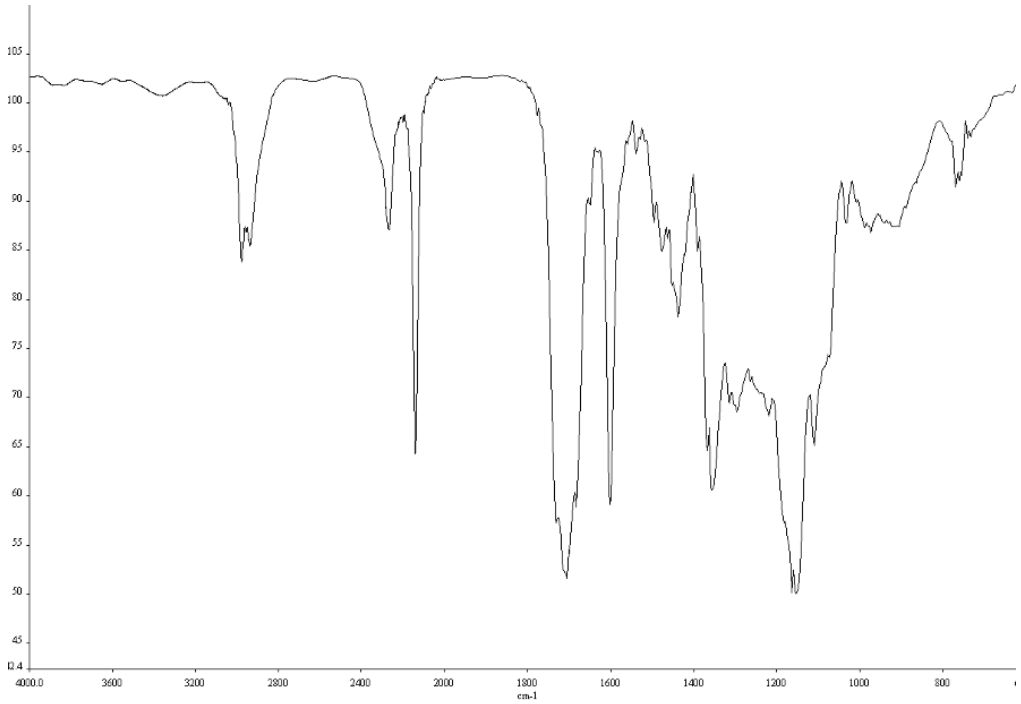


Figure A3.63. *Infrared spectrum (Thin Film, NaCl) of compound* ***101e****.*

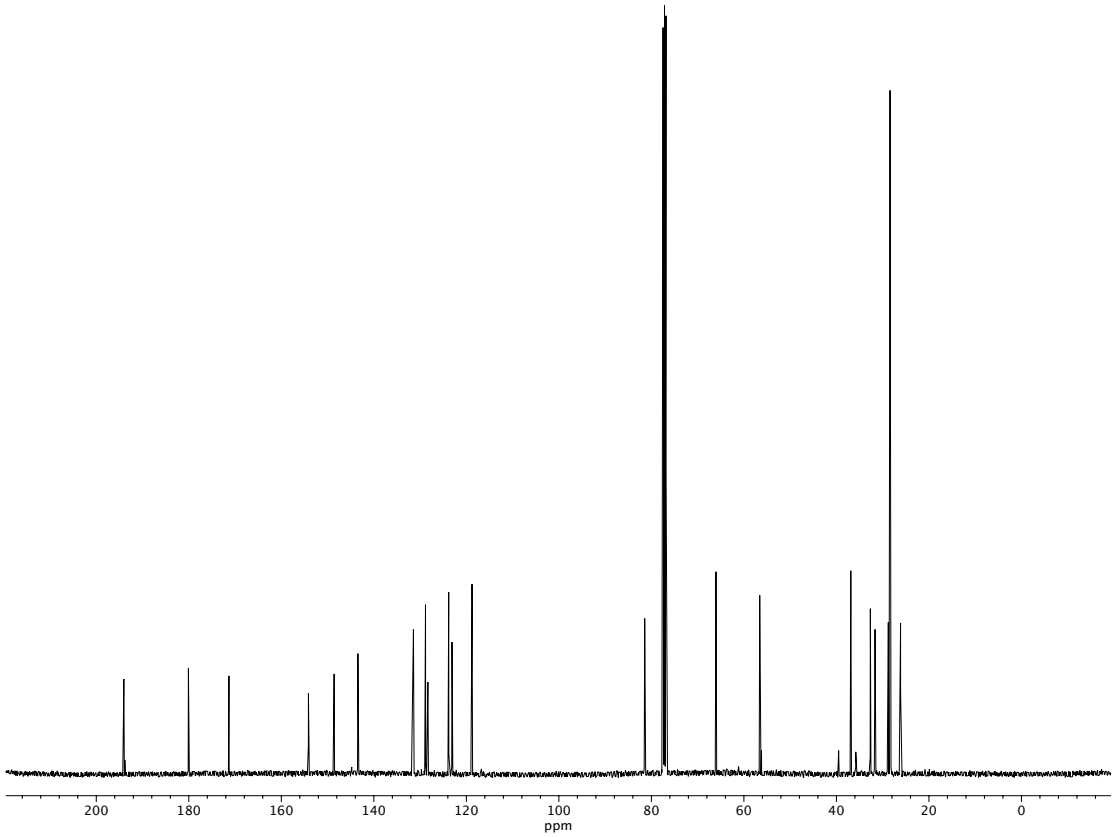


Figure A3.64. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***101e****.*

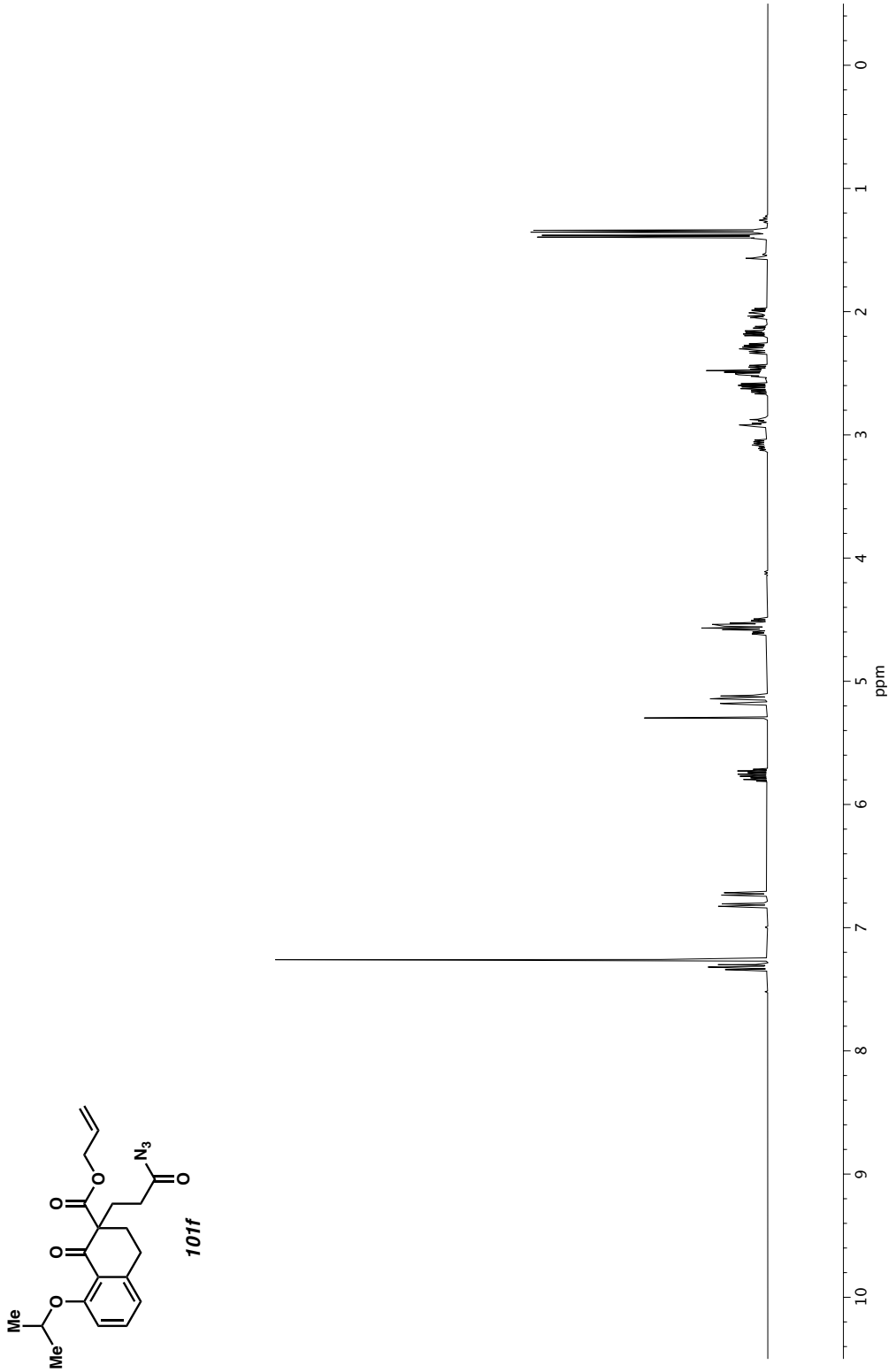


Figure A3.65. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***101f****.*

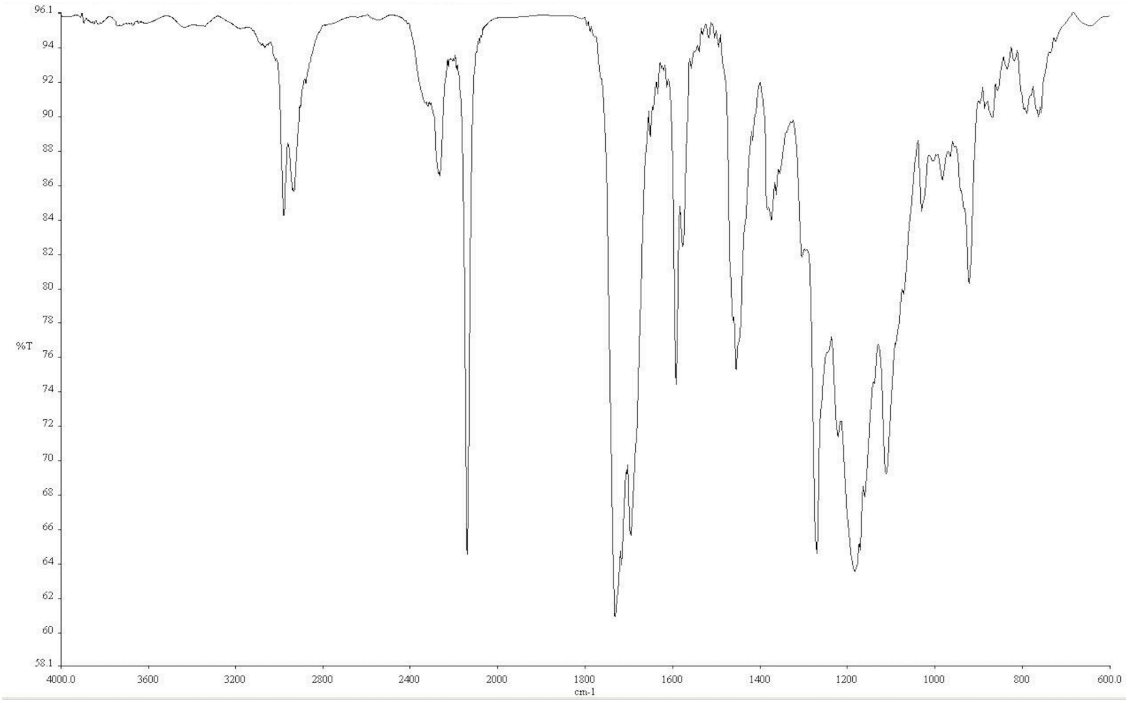


Figure A3.66. *Infrared spectrum (Thin Film, NaCl) of compound* ***101f****.*

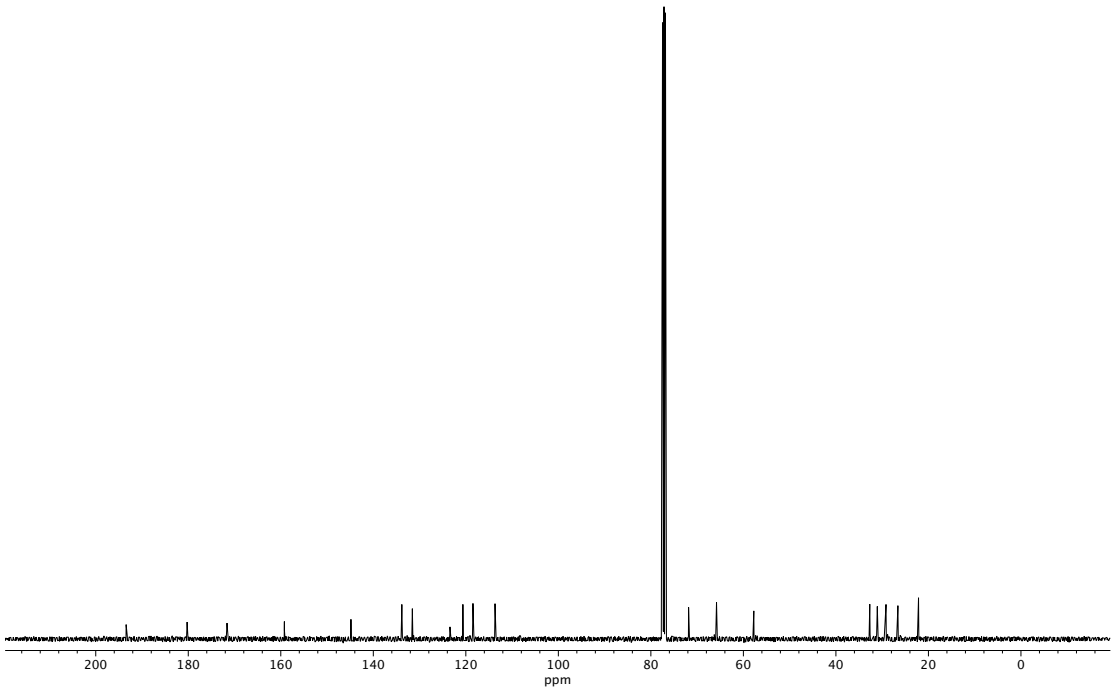


Figure A3.67. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***101f****.*

Figure A3.68. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***101g****.*

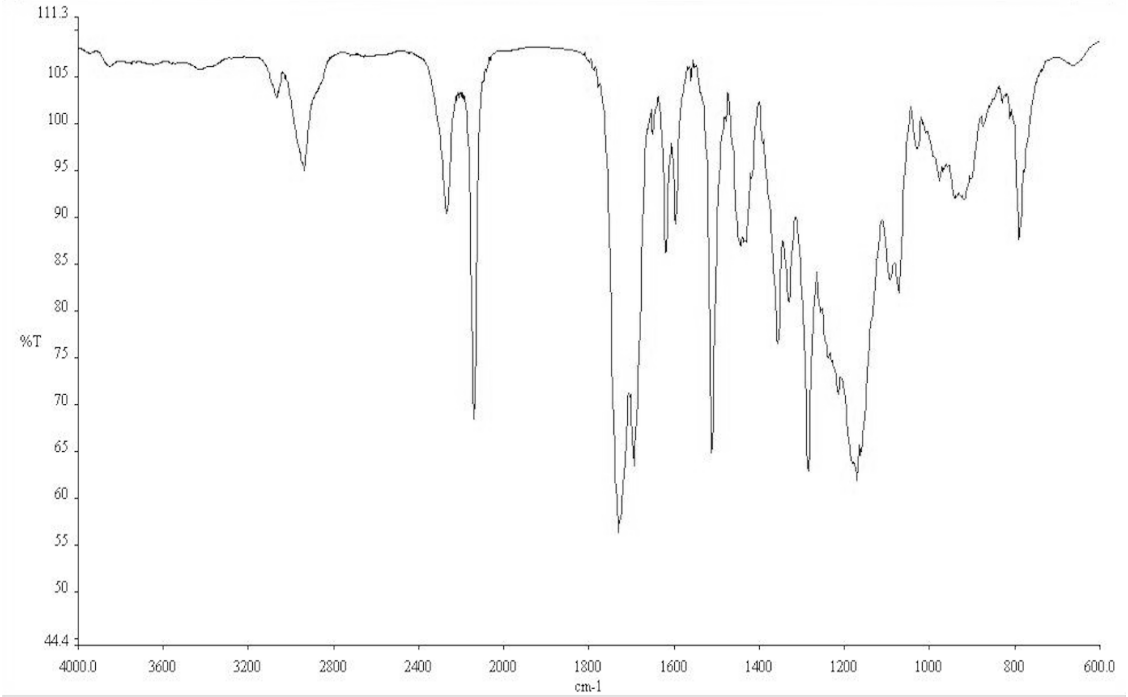


Figure A3.69. *Infrared spectrum (Thin Film, NaCl) of compound* ***101g****.*

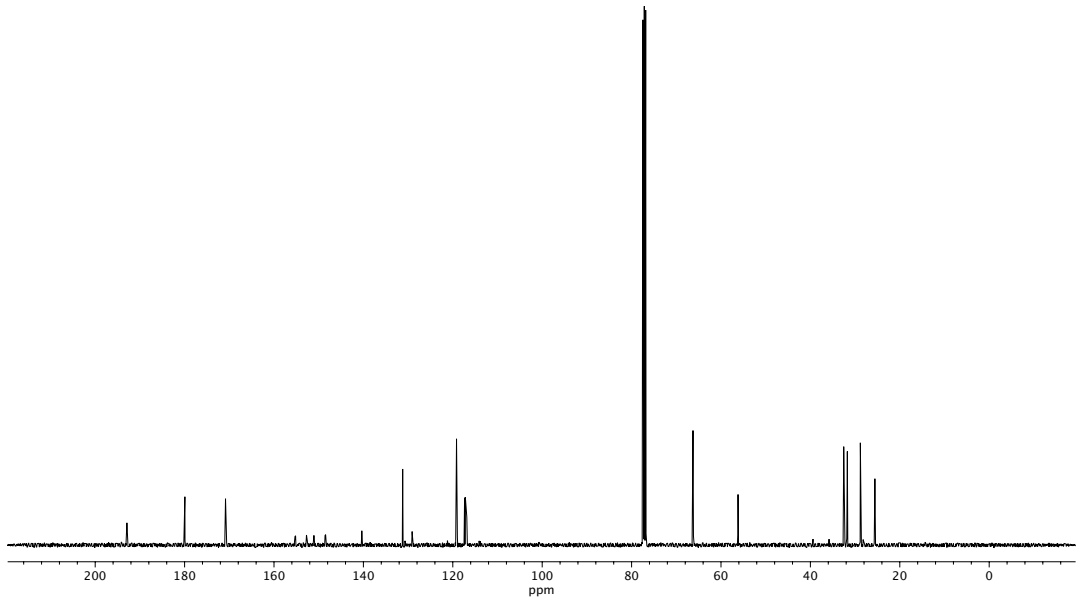


Figure A3.70. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***101g****.*

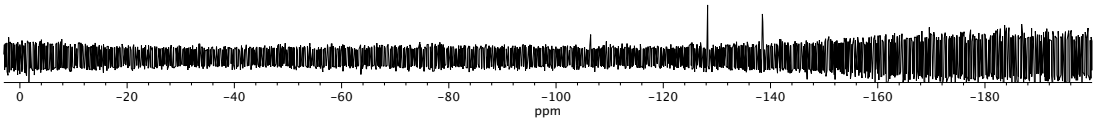


Figure A3.71 *^{19}F NMR (282 MHz, $CDCl_3$) of compound* ***101g***.

Figure A3.72. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***101h****.*

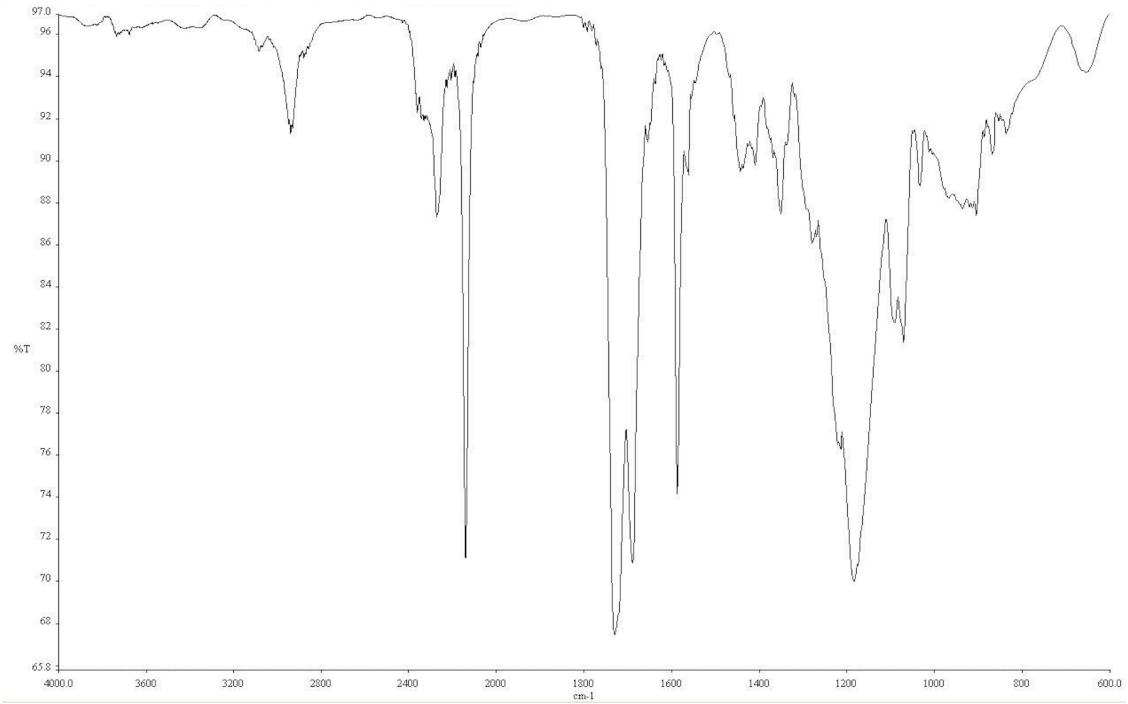


Figure A3.73. *Infrared spectrum (Thin Film, NaCl) of compound* ***101h****.*

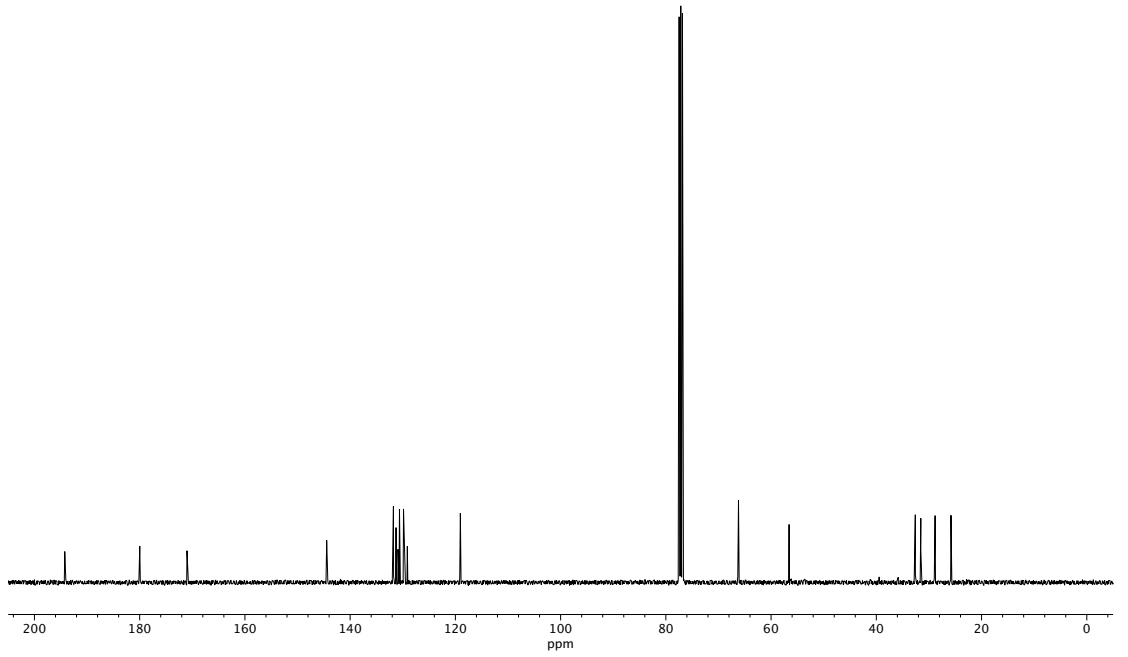


Figure A3.74. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***101h****.*

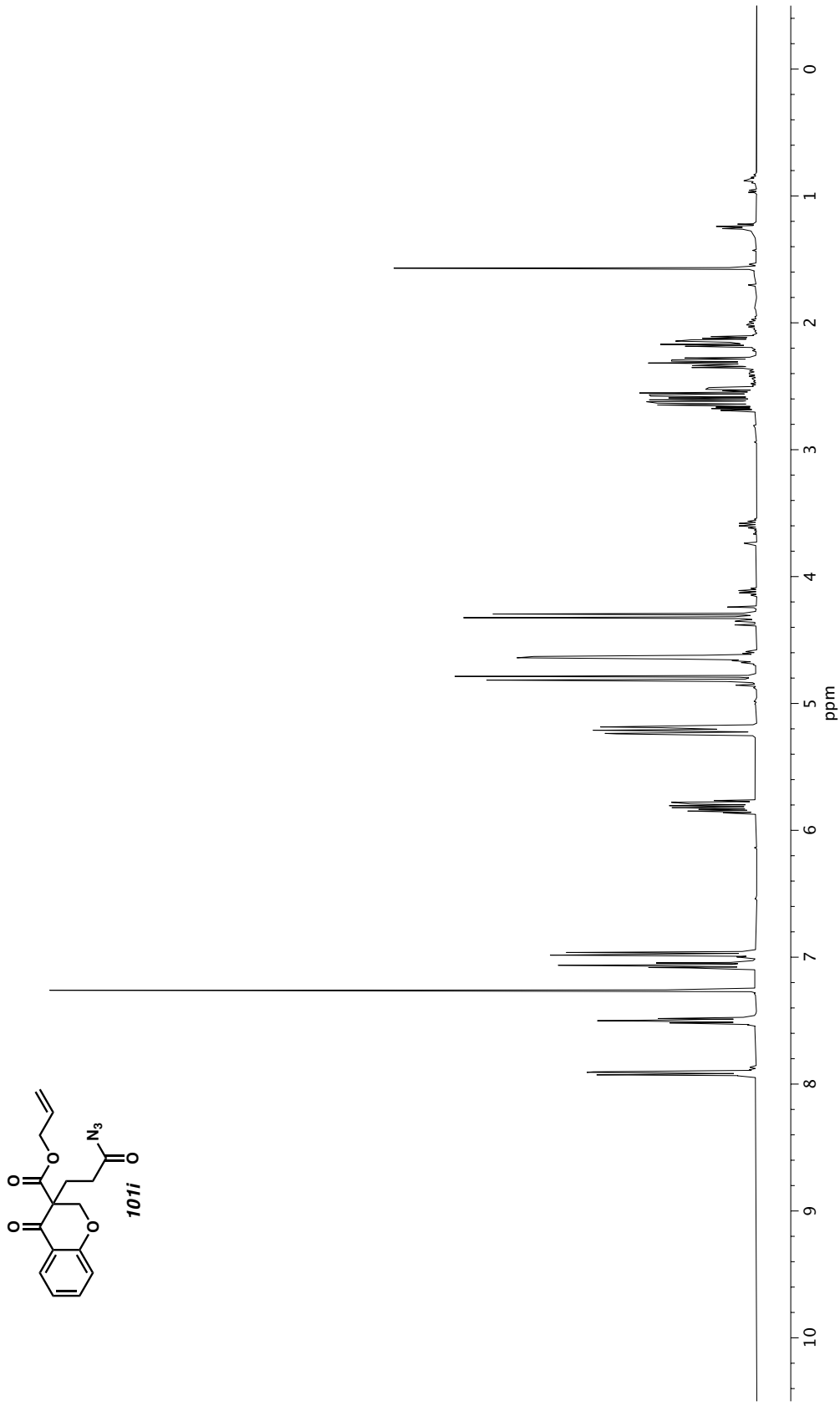


Figure A3.75. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***101i****.*

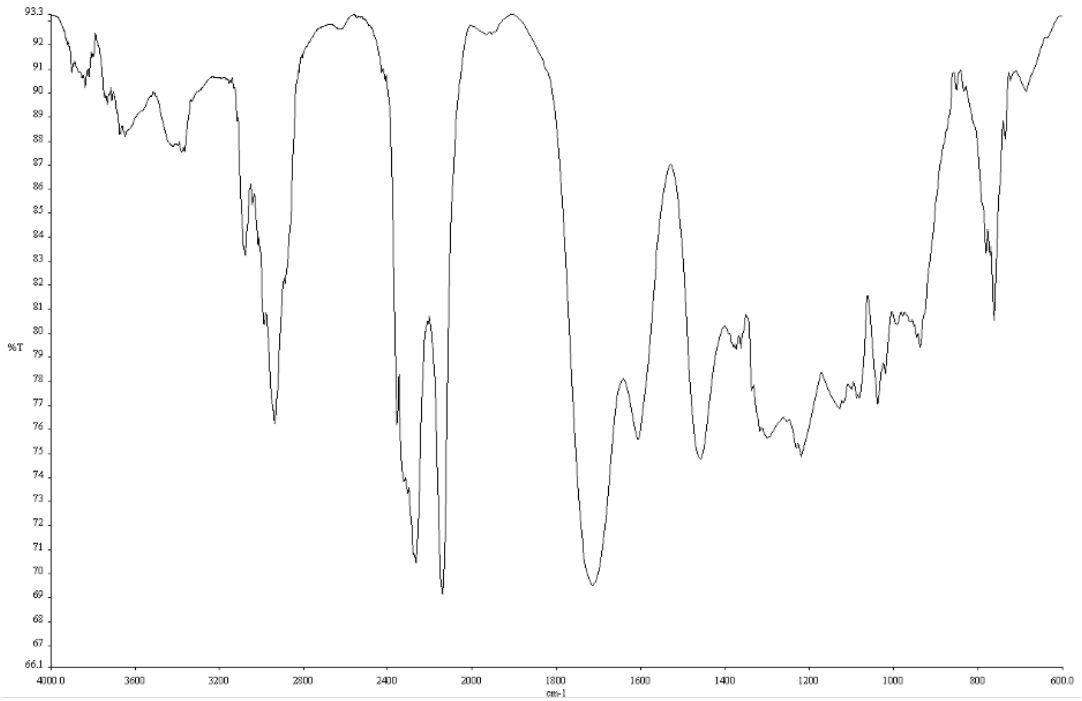


Figure A3.76. *Infrared spectrum (Thin Film, NaCl) of compound* ***101i****.*

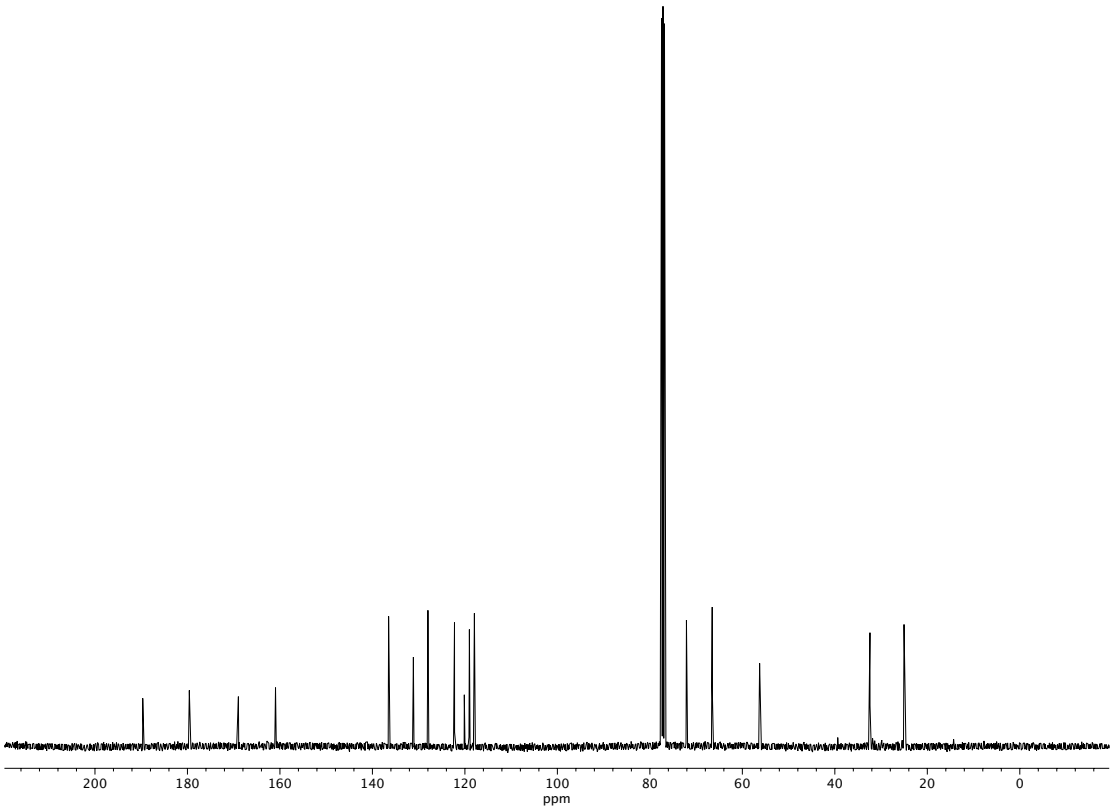


Figure A3.77. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***101i****.*

Figure A3.78. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***101j****.*

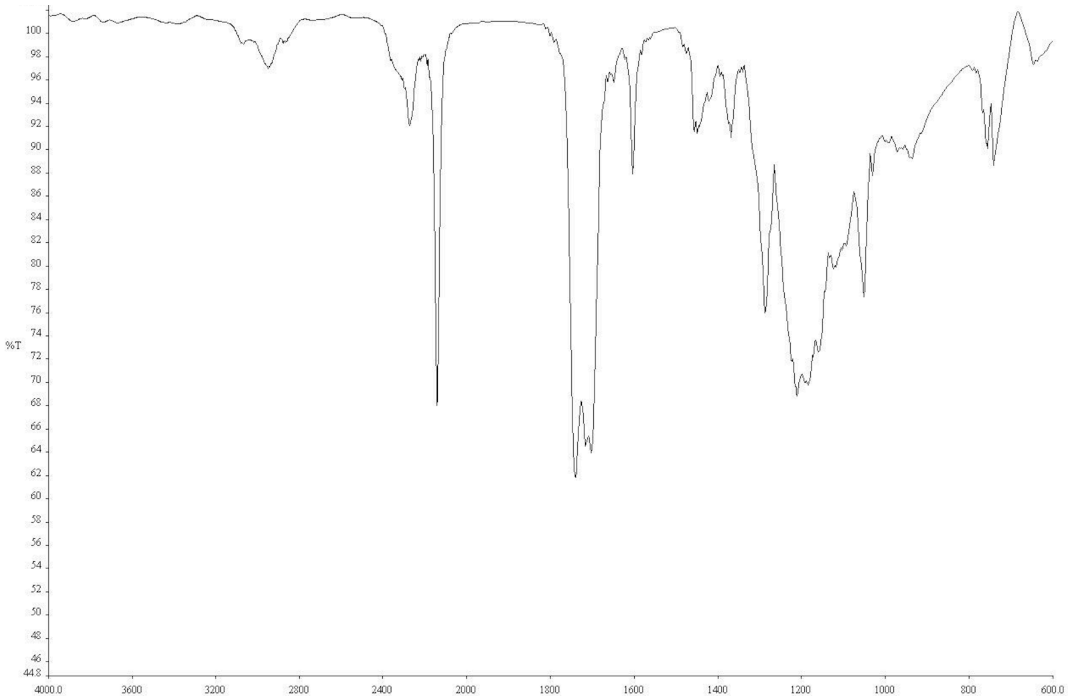


Figure A3.79. *Infrared spectrum (Thin Film, NaCl) of compound* ***101j****.*

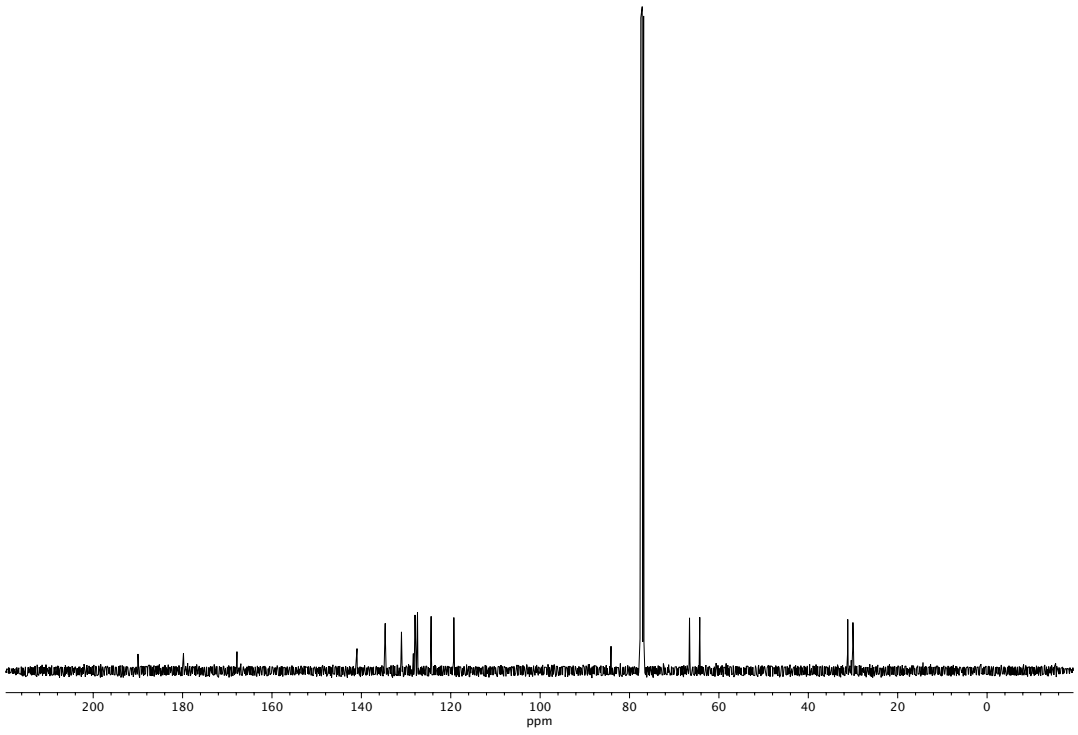


Figure A3.80. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***101j****.*

Figure A3.81. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***101k****.*

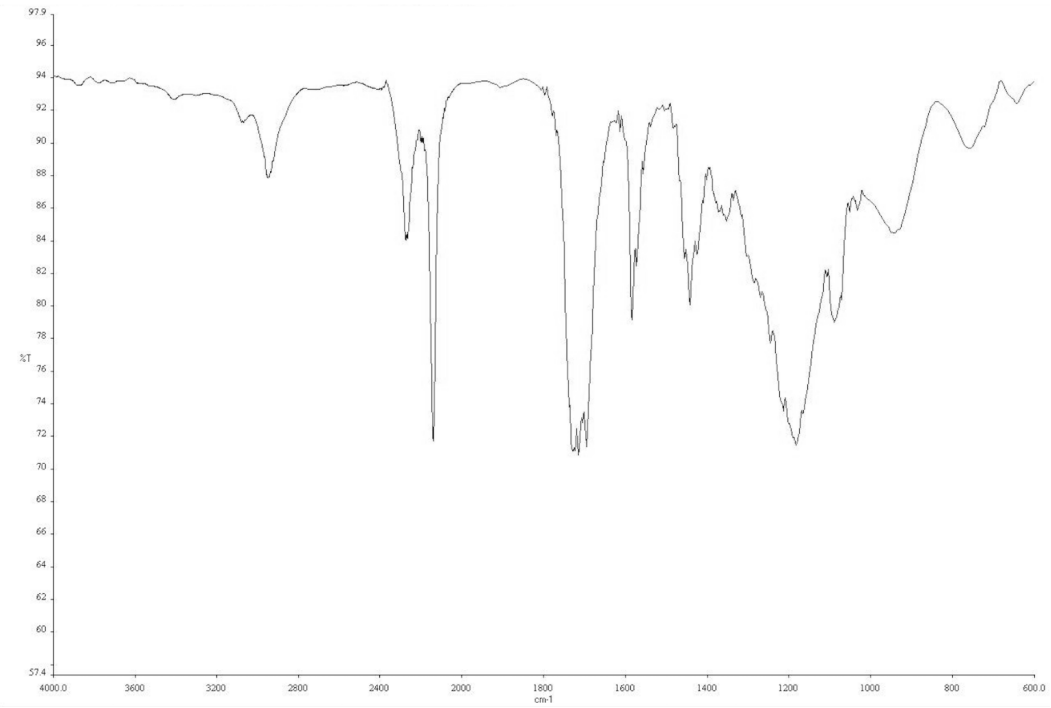


Figure A3.82. *Infrared spectrum (Thin Film, NaCl) of compound* ***101k****.*

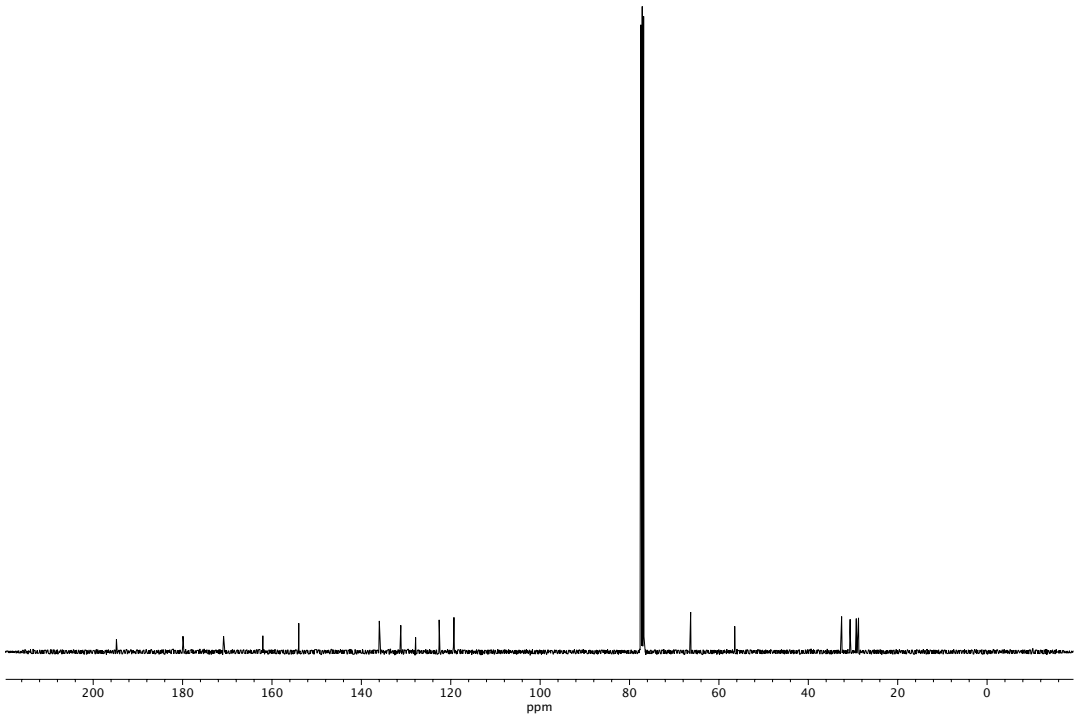


Figure A3.83. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***101k****.*

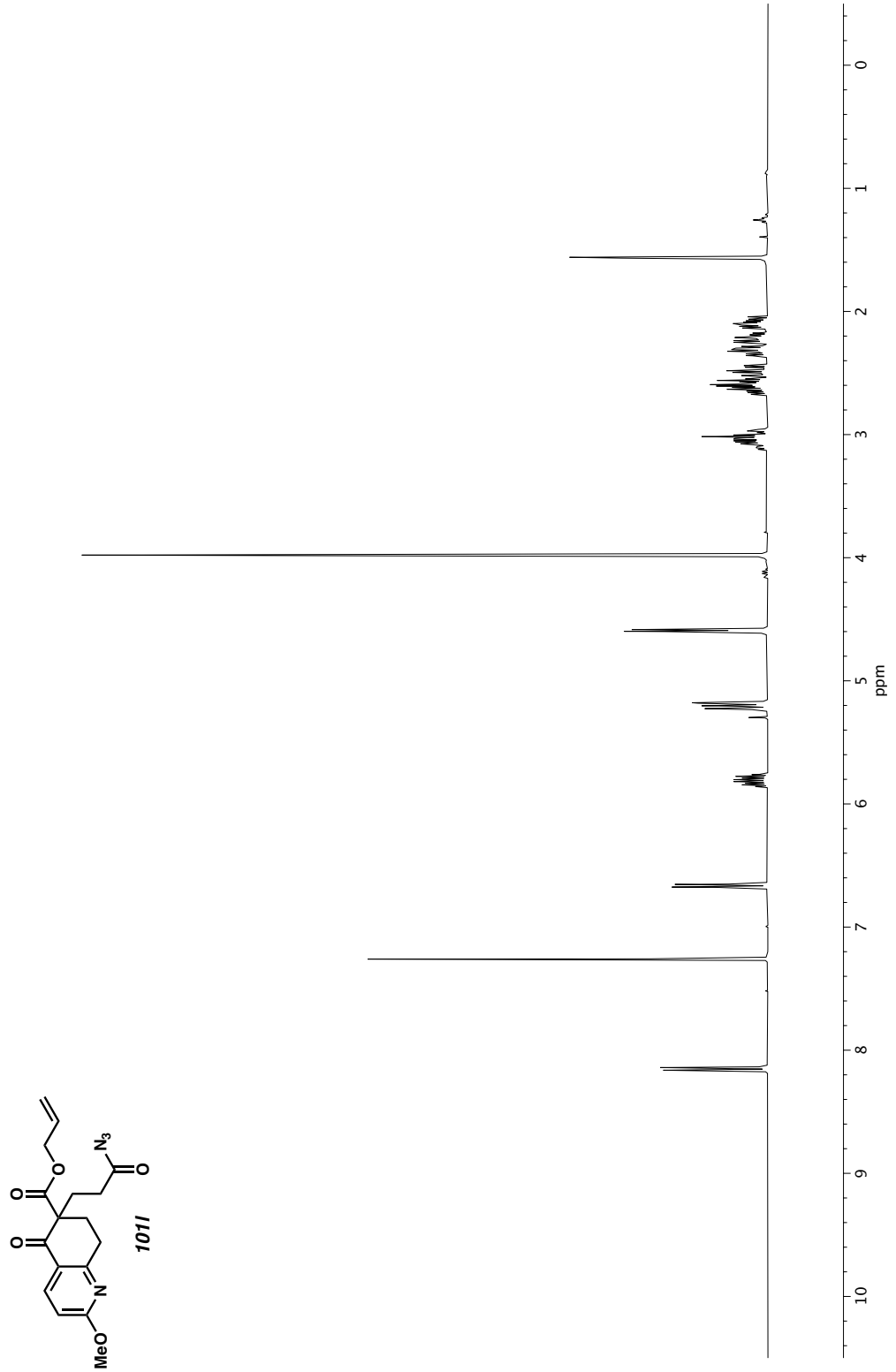


Figure A3.84. *^1H NMR (400 MHz, $CDCl_3$) of compound **1011**.*

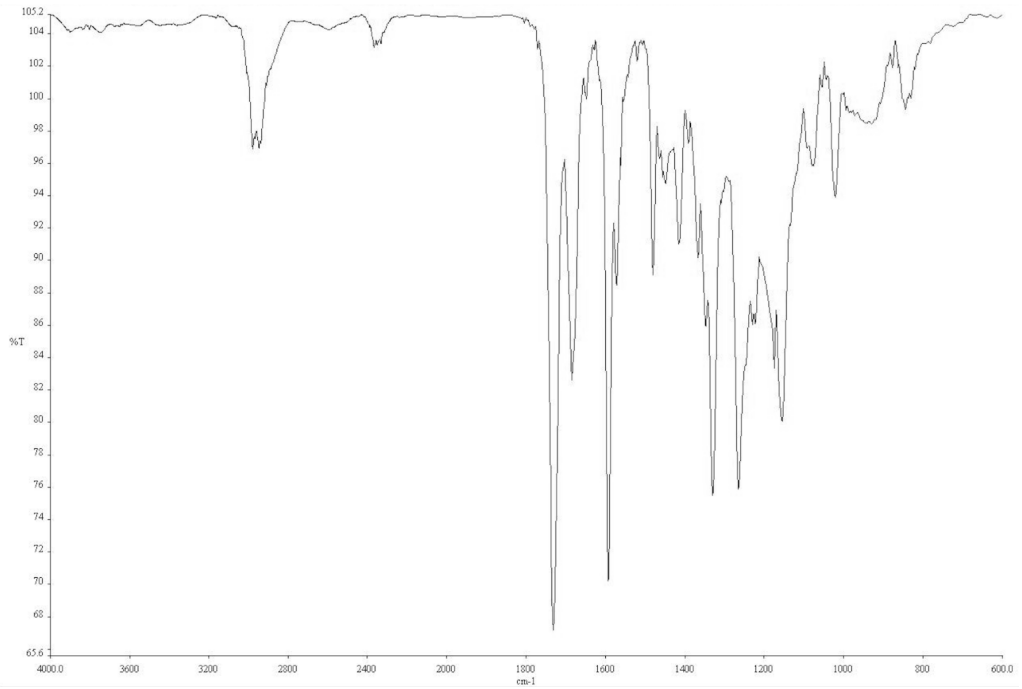


Figure A3.85. *Infrared spectrum (Thin Film, NaCl) of compound* ***101l****.*

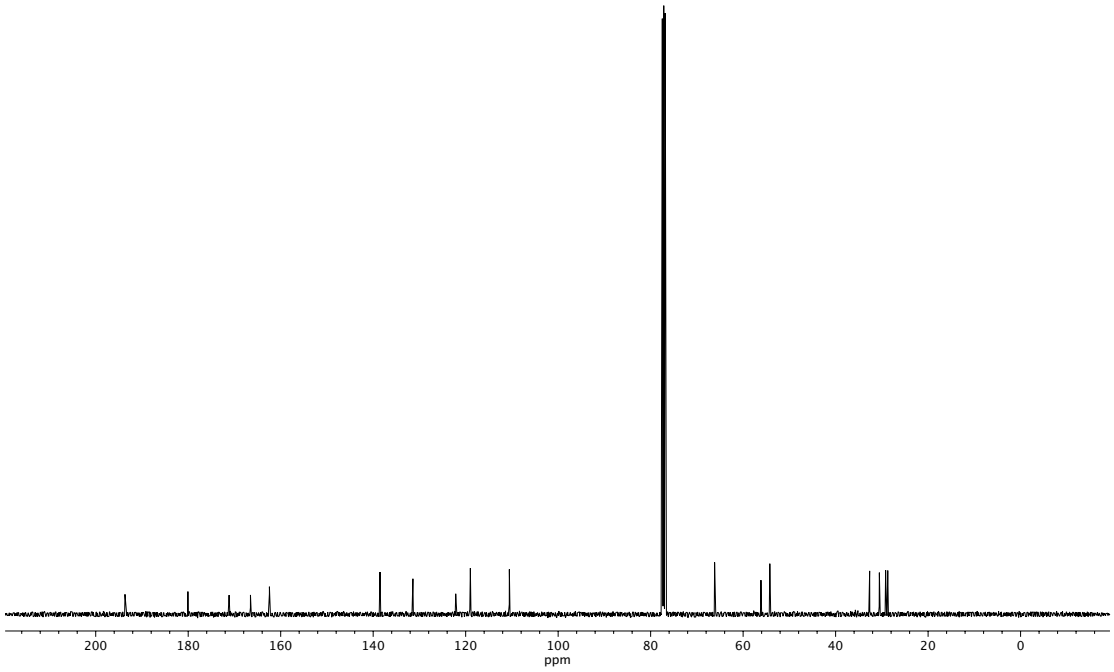


Figure A3.86. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***101l****.*

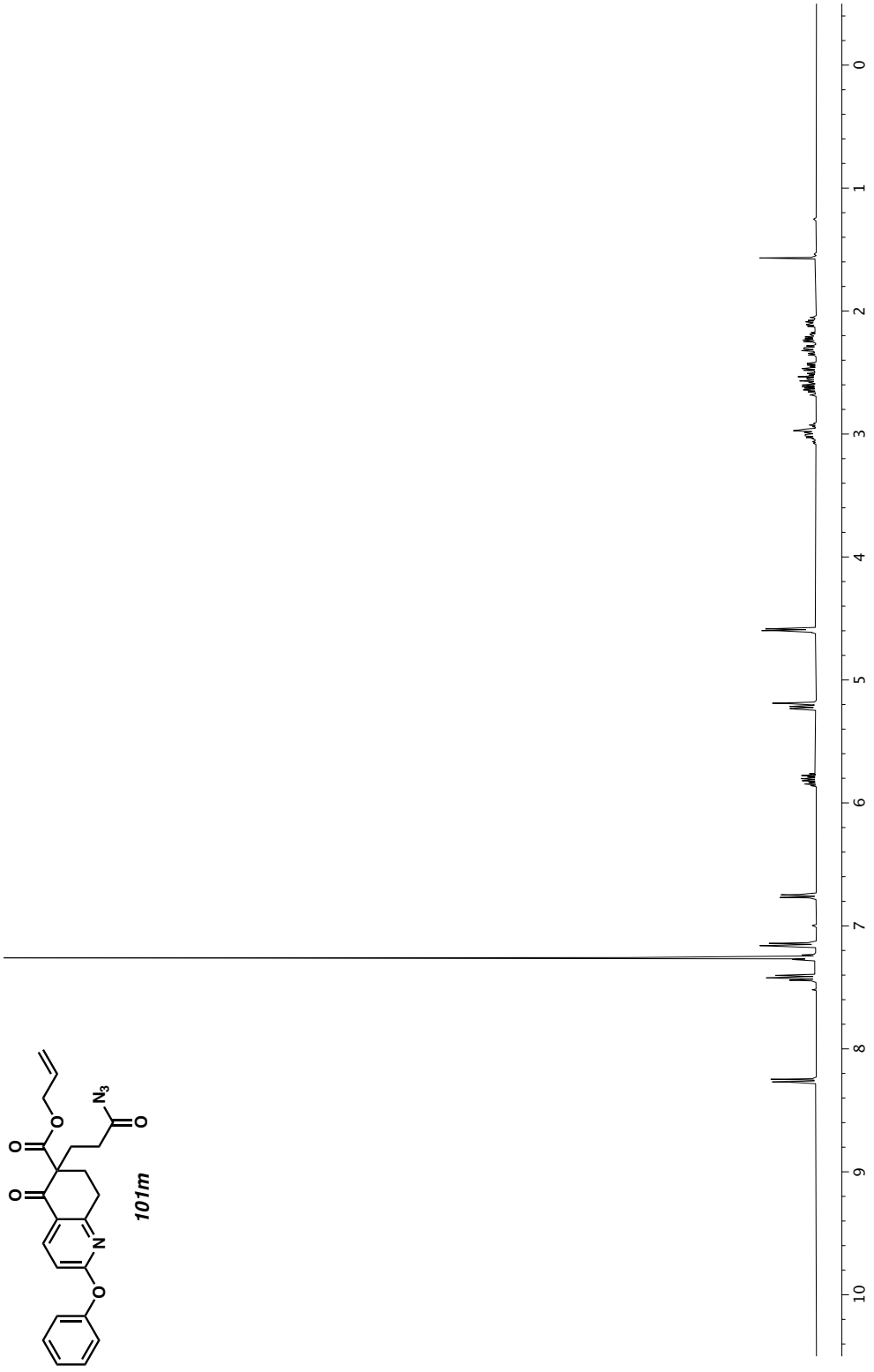


Figure A3.87. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***101m****.*

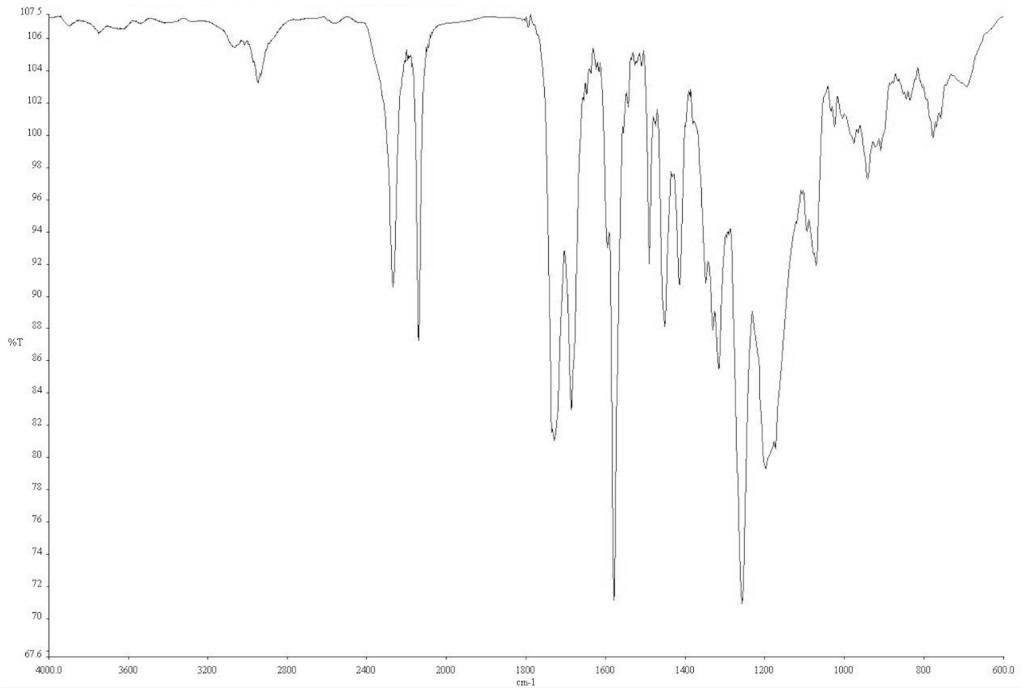


Figure A3.88. *Infrared spectrum (Thin Film, NaCl) of compound* ***101m****.*

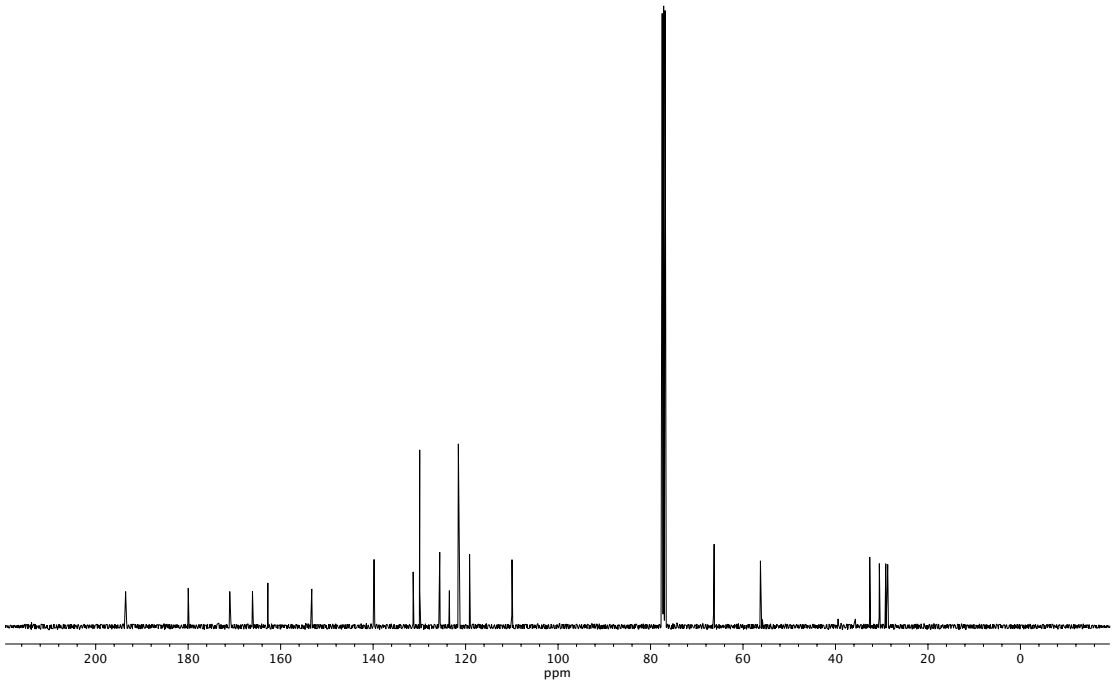


Figure A3.89. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***101m****.*

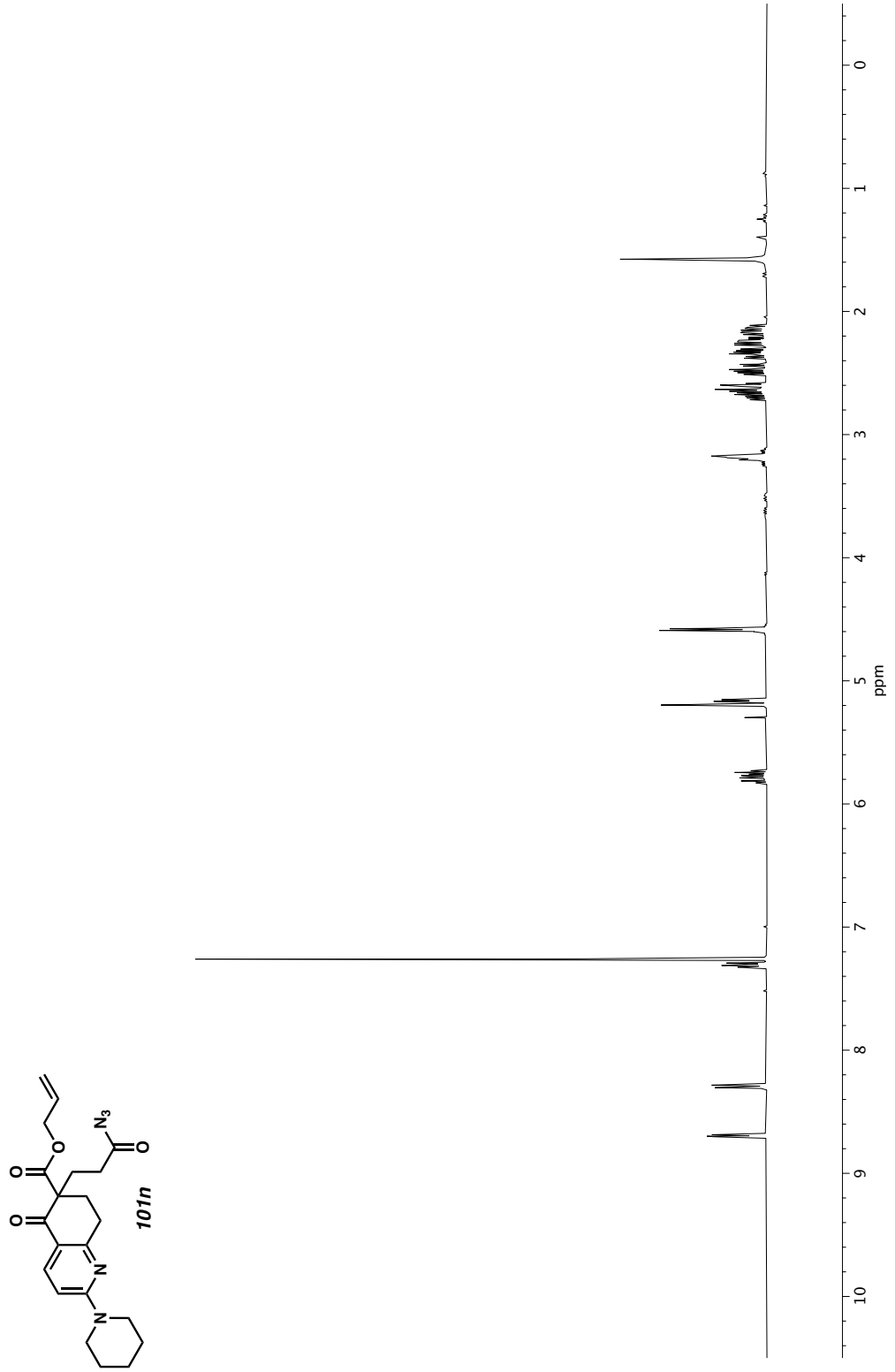


Figure A3.90. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***101n****.*

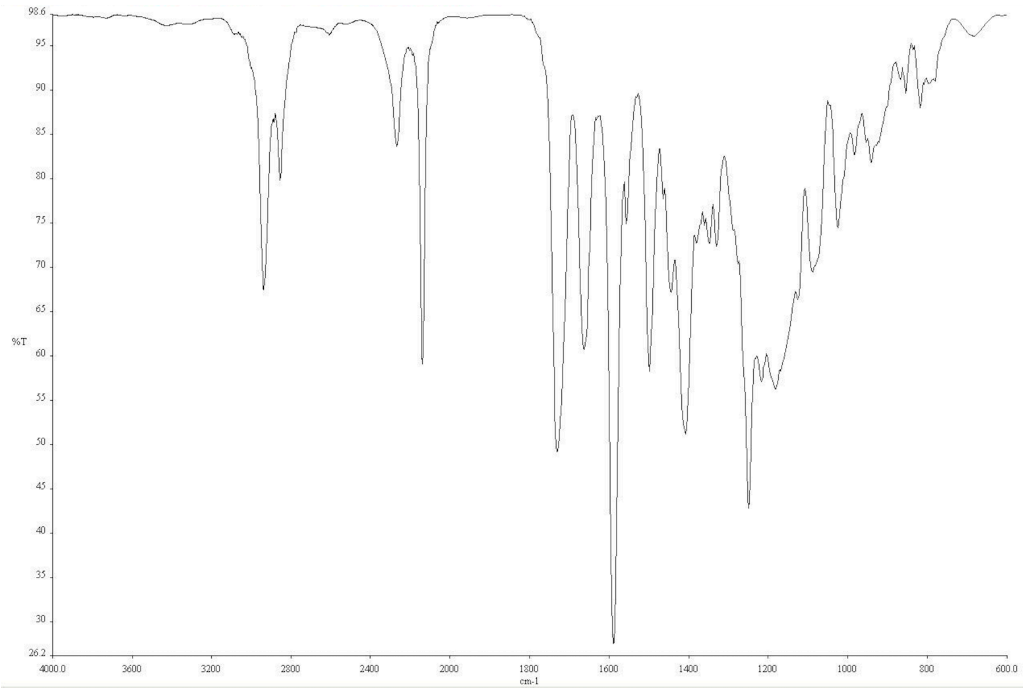


Figure A3.91. *Infrared spectrum (Thin Film, NaCl) of compound* ***101n****.*

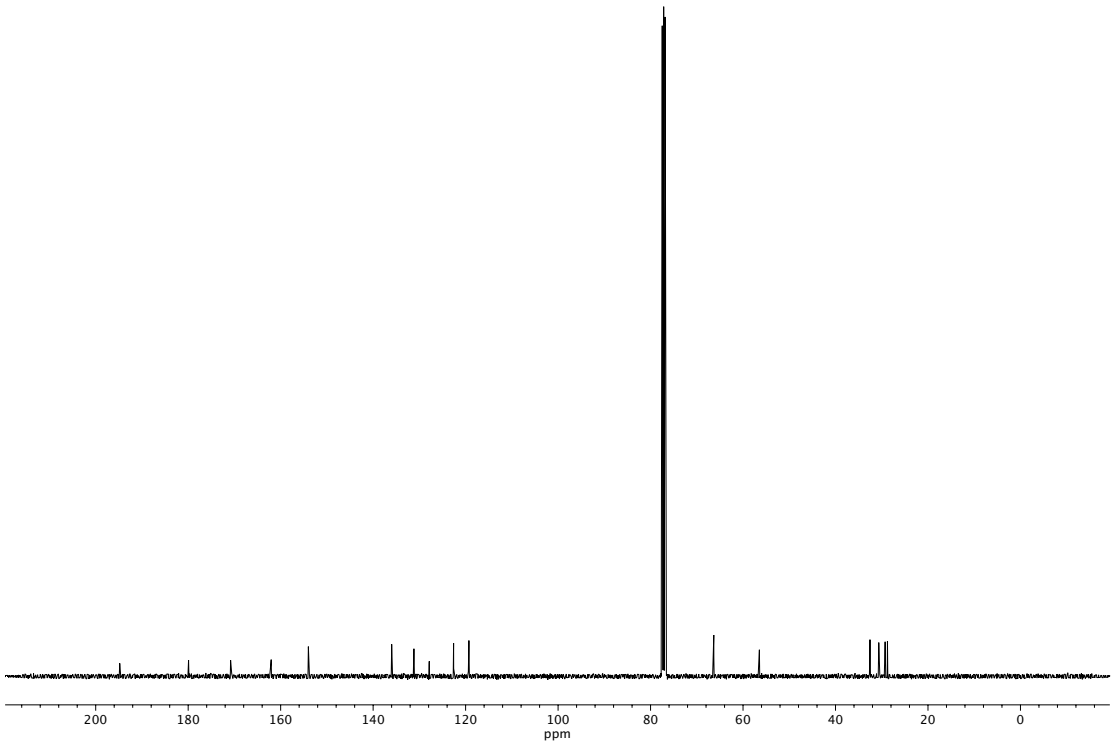


Figure A3.92. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***101n****.*

Figure A3.93. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***121***.

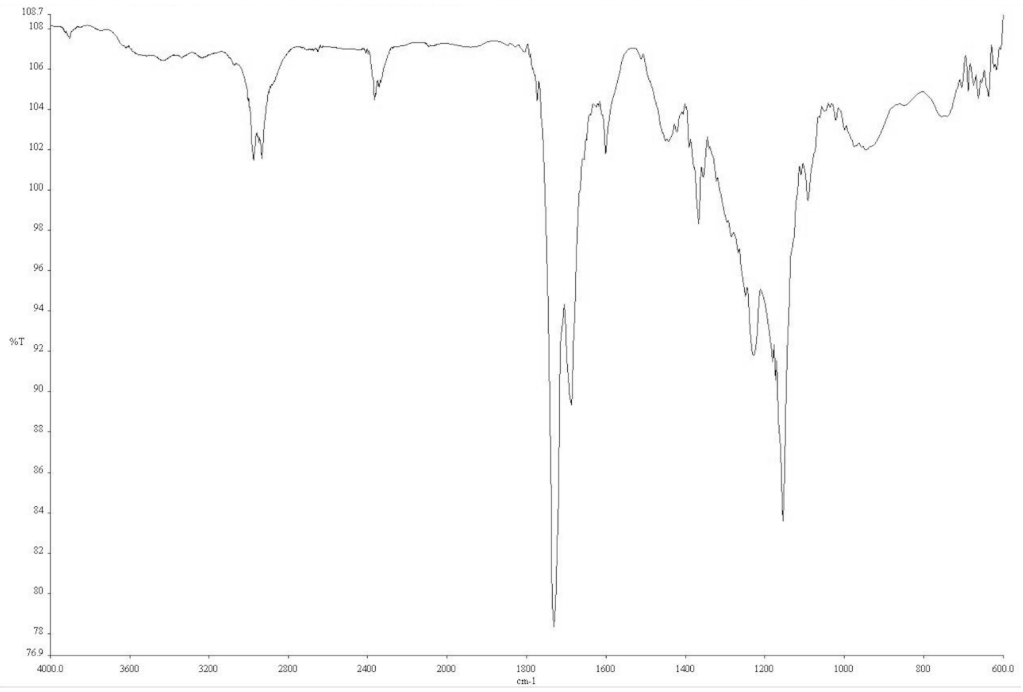


Figure A3.94. *Infrared spectrum (Thin Film, NaCl) of compound* ***121***.

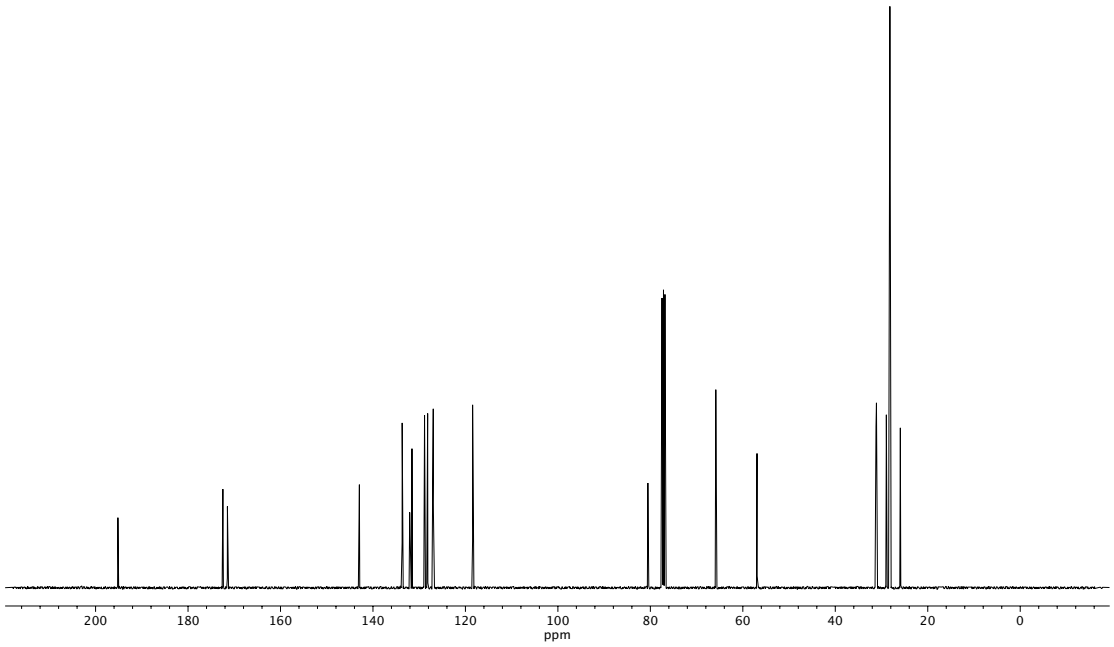


Figure A3.95. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***121***.

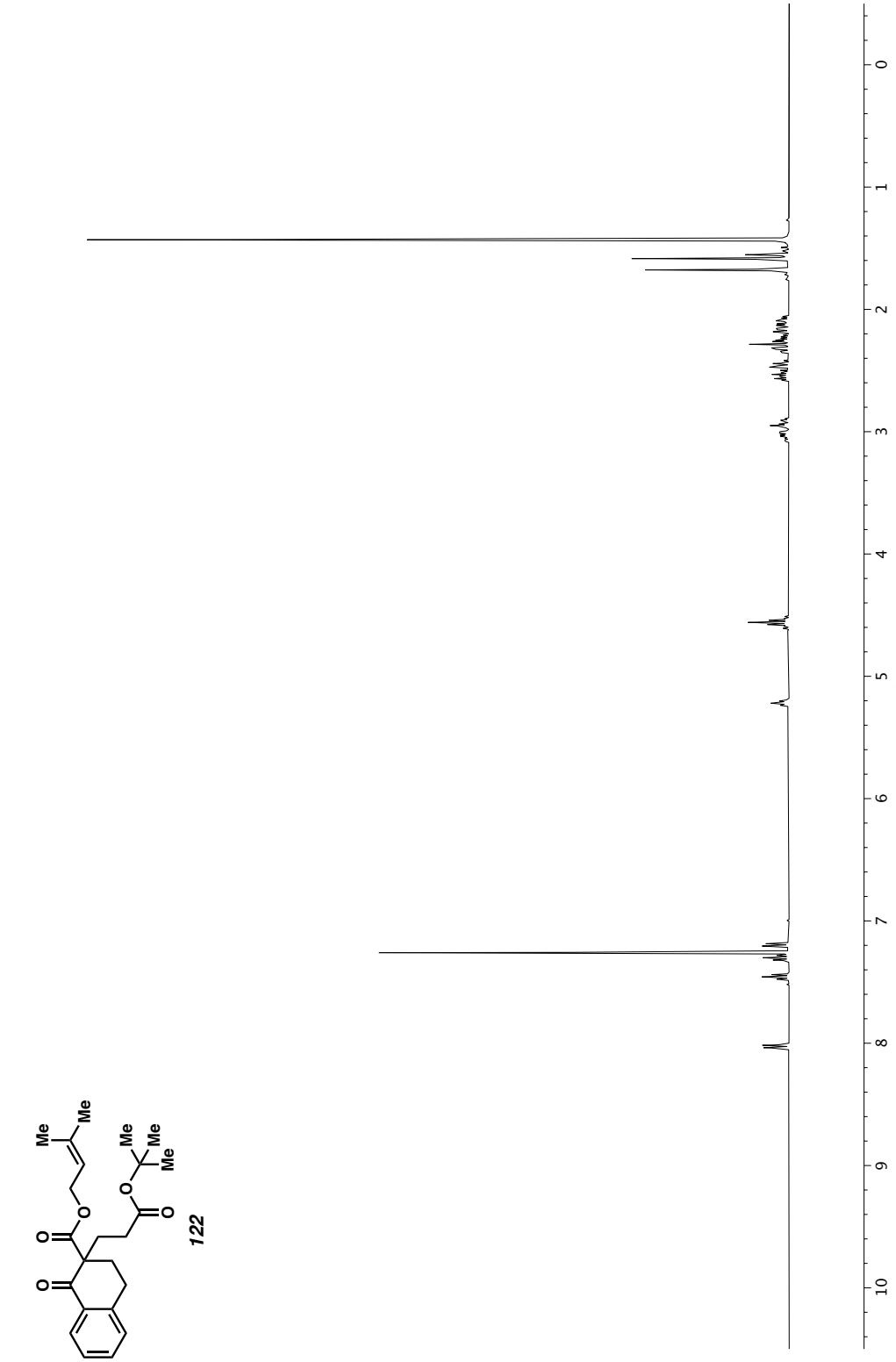


Figure A3.96. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***122***.

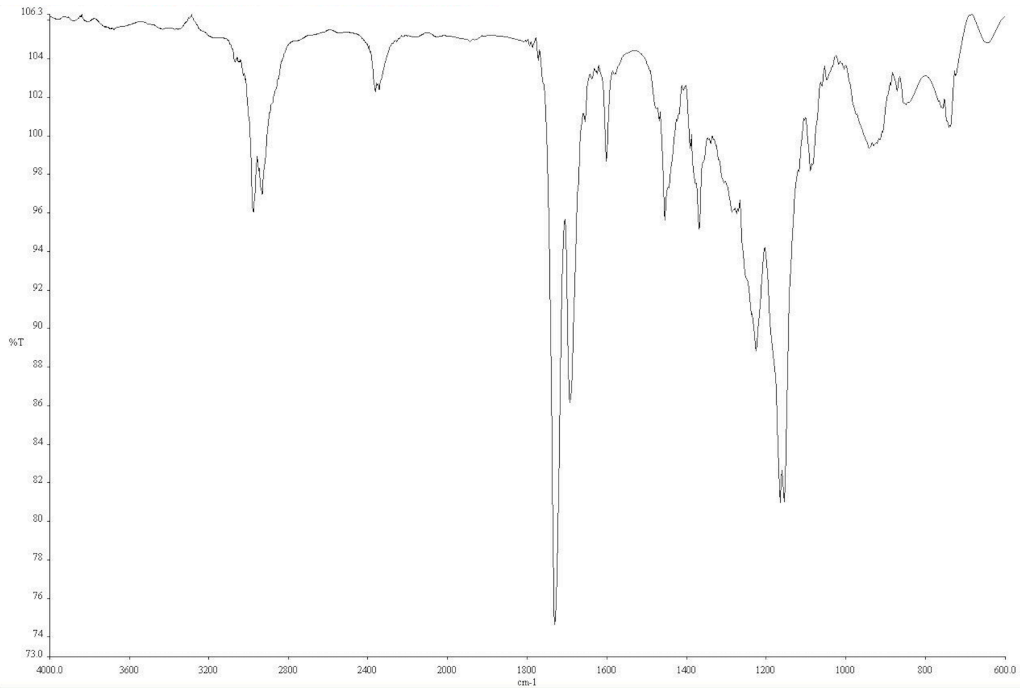


Figure A3.97. *Infrared spectrum (Thin Film, NaCl) of compound* ***122****.*

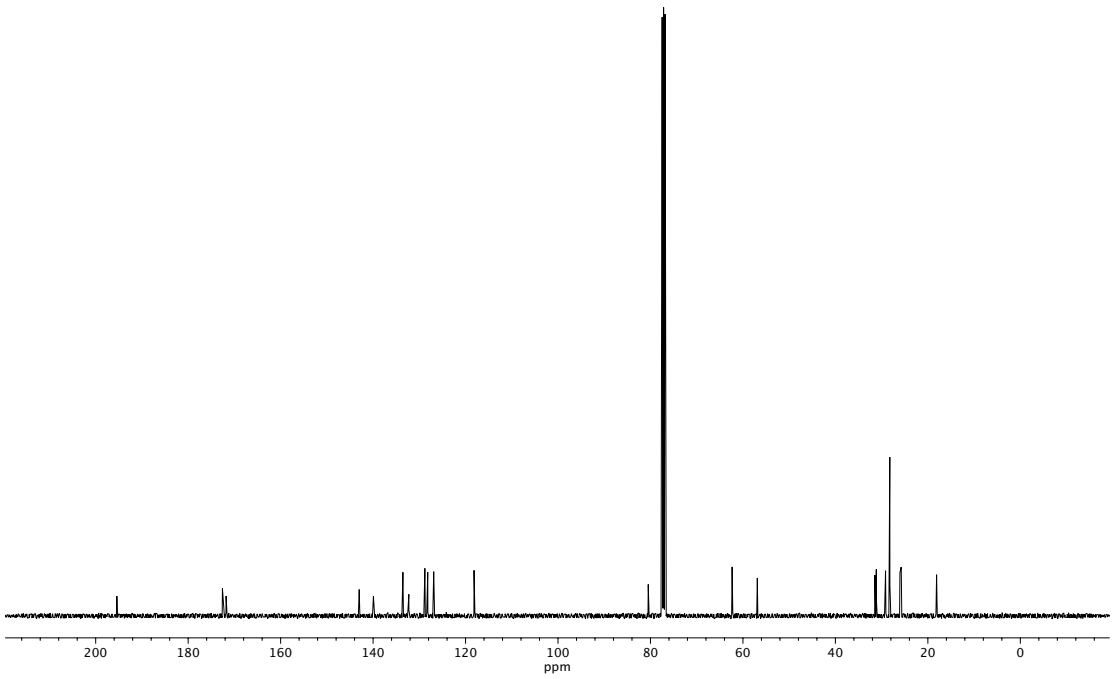


Figure A3.98. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***122****.*

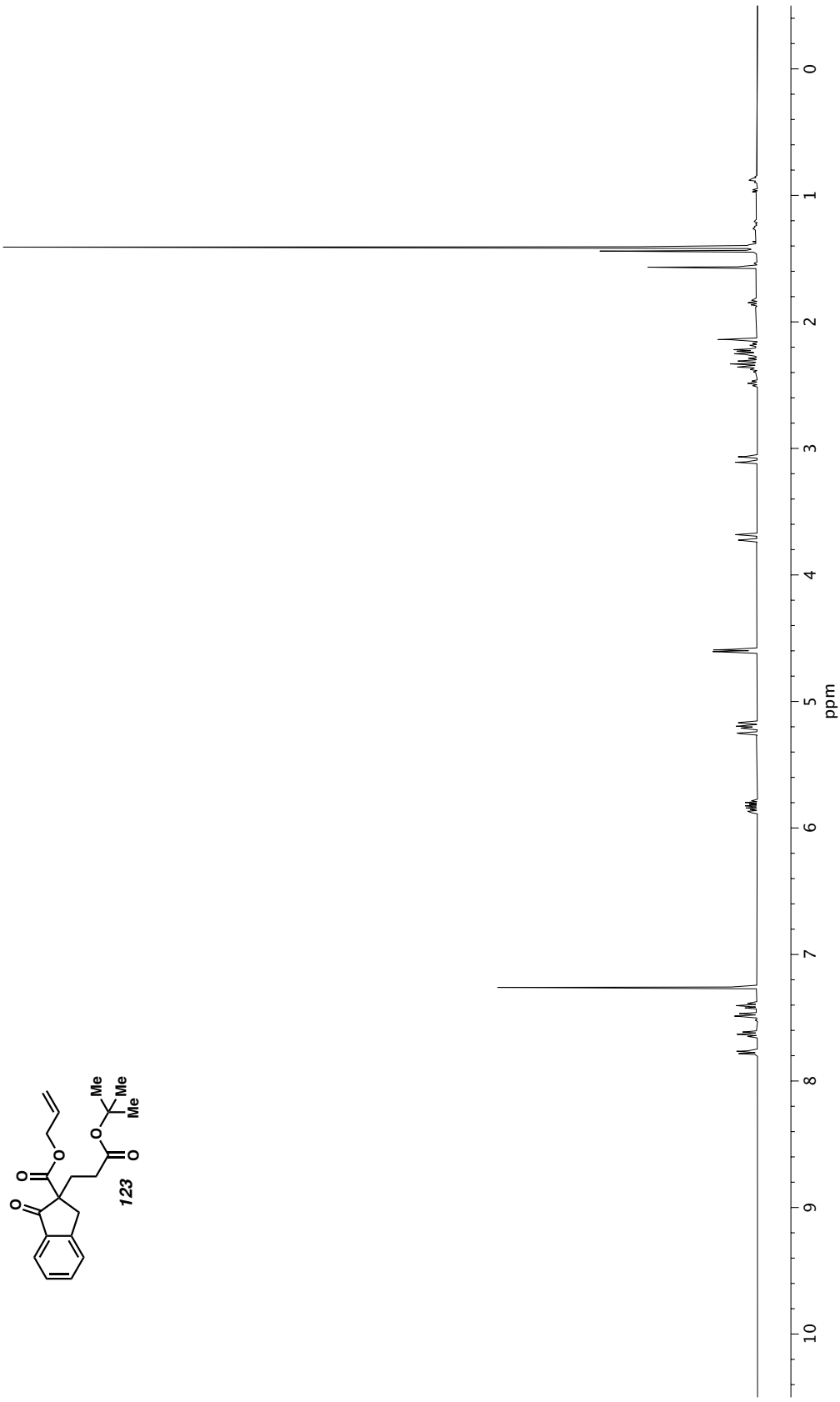


Figure A3.99. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***123****.*

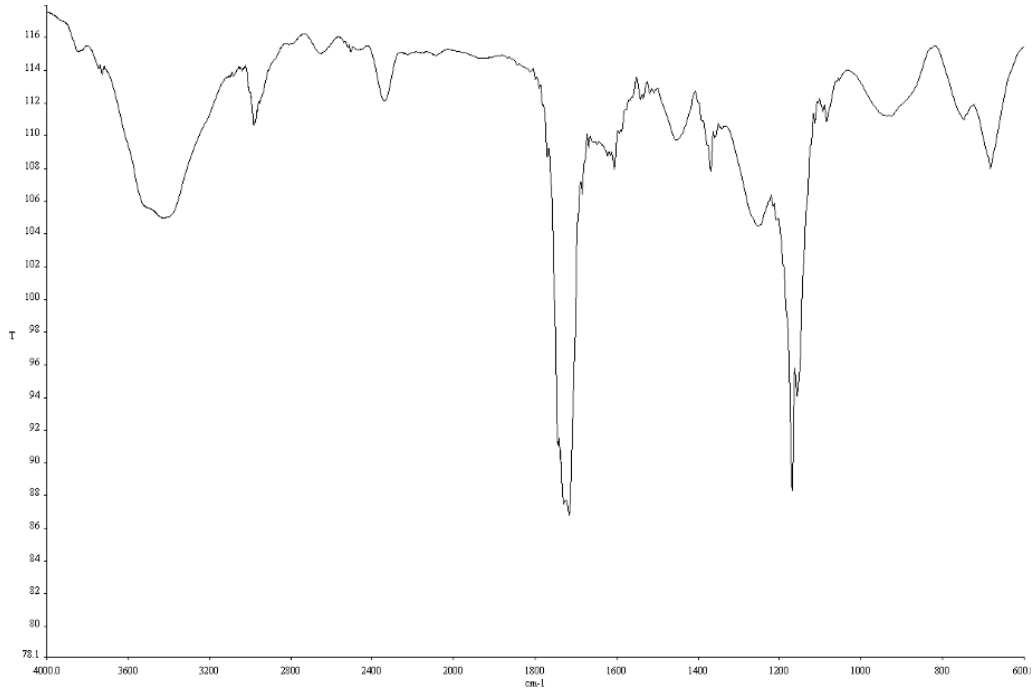


Figure A3.100. *Infrared spectrum (Thin Film, NaCl) of compound* ***123****.*

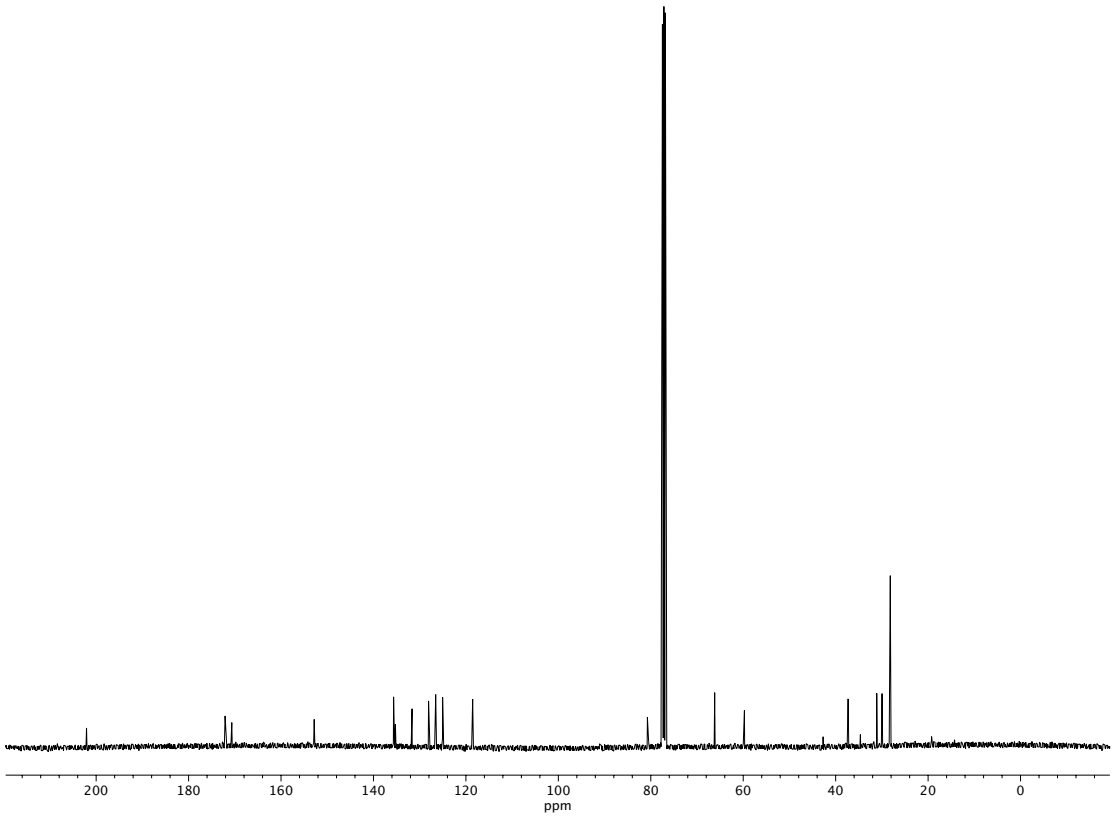
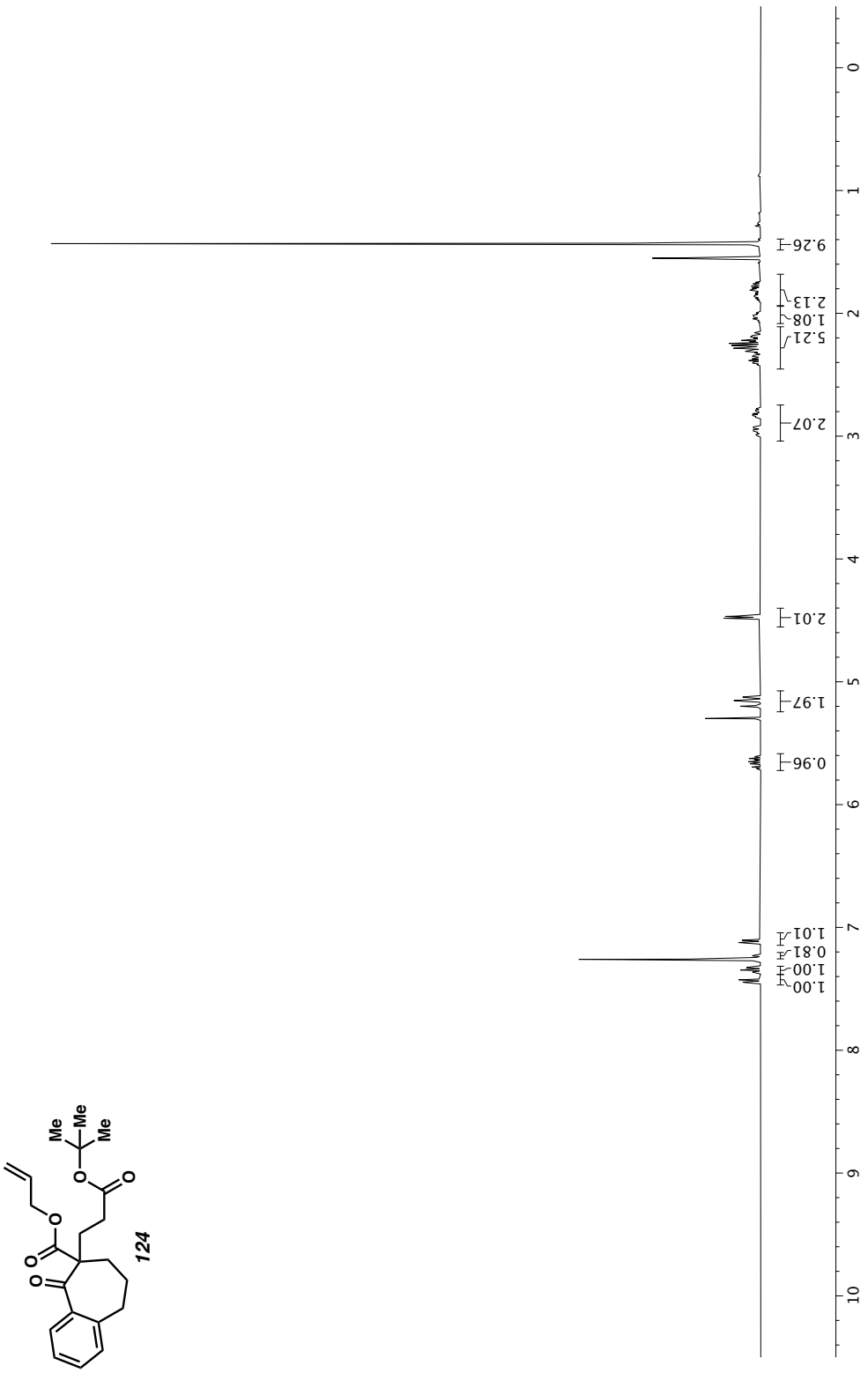


Figure A3.101. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***123****.*



124

Figure A3.102. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***124****.*

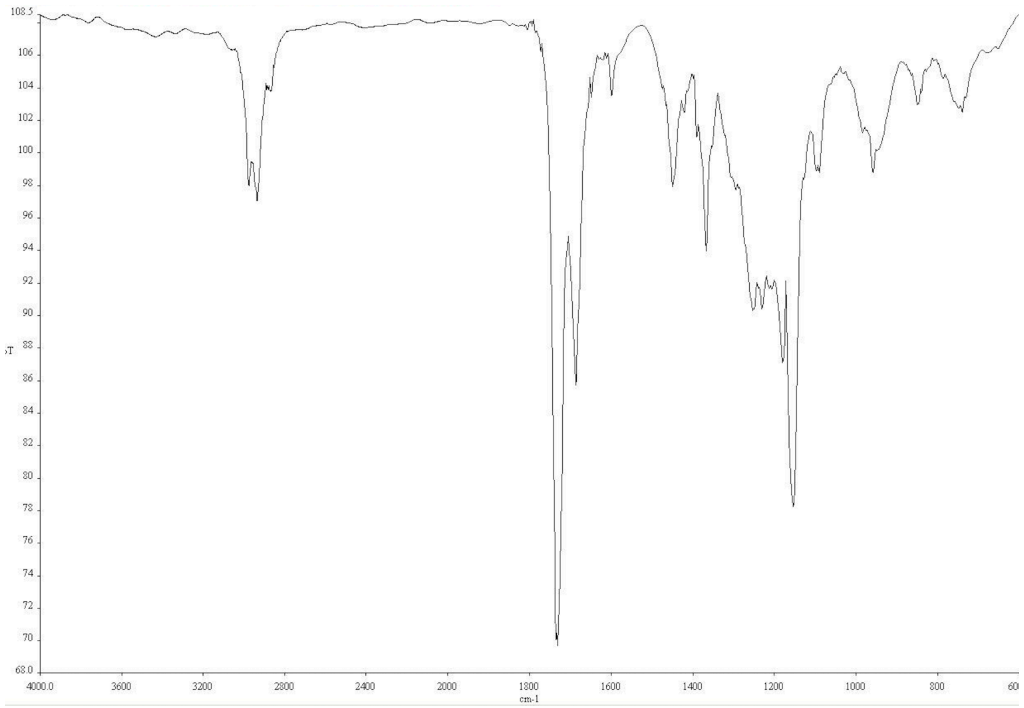


Figure A3.103. *Infrared spectrum (Thin Film, NaCl) of compound* ***124****.*

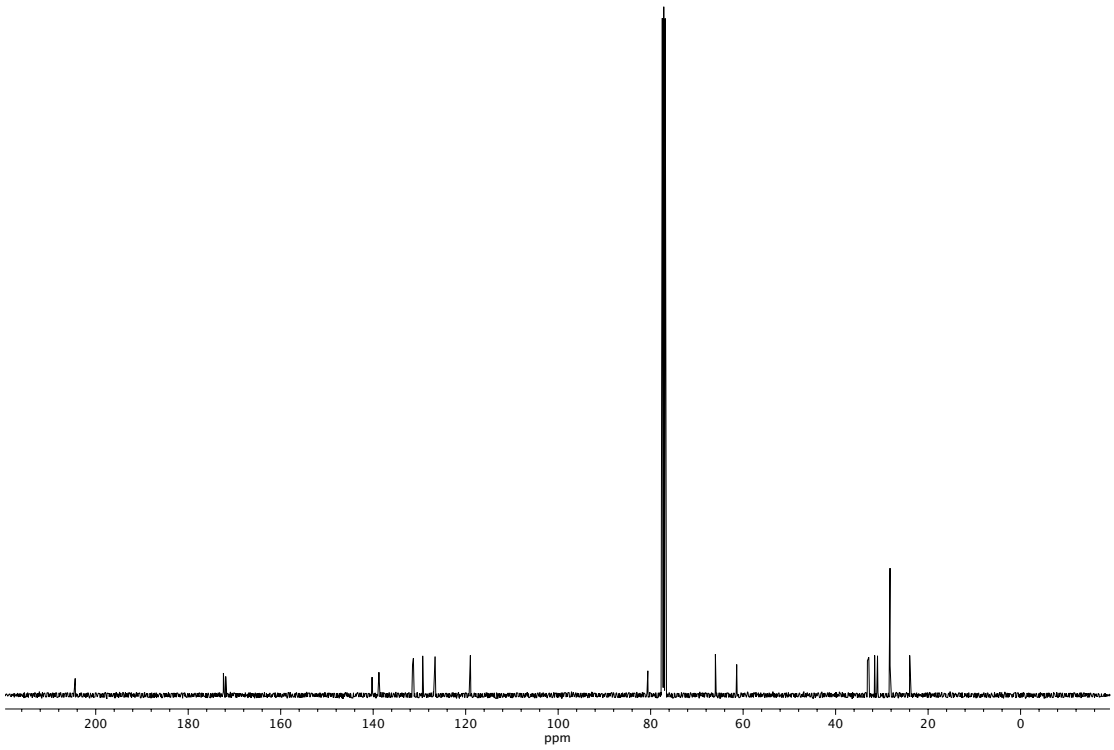


Figure A3.104. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***124****.*

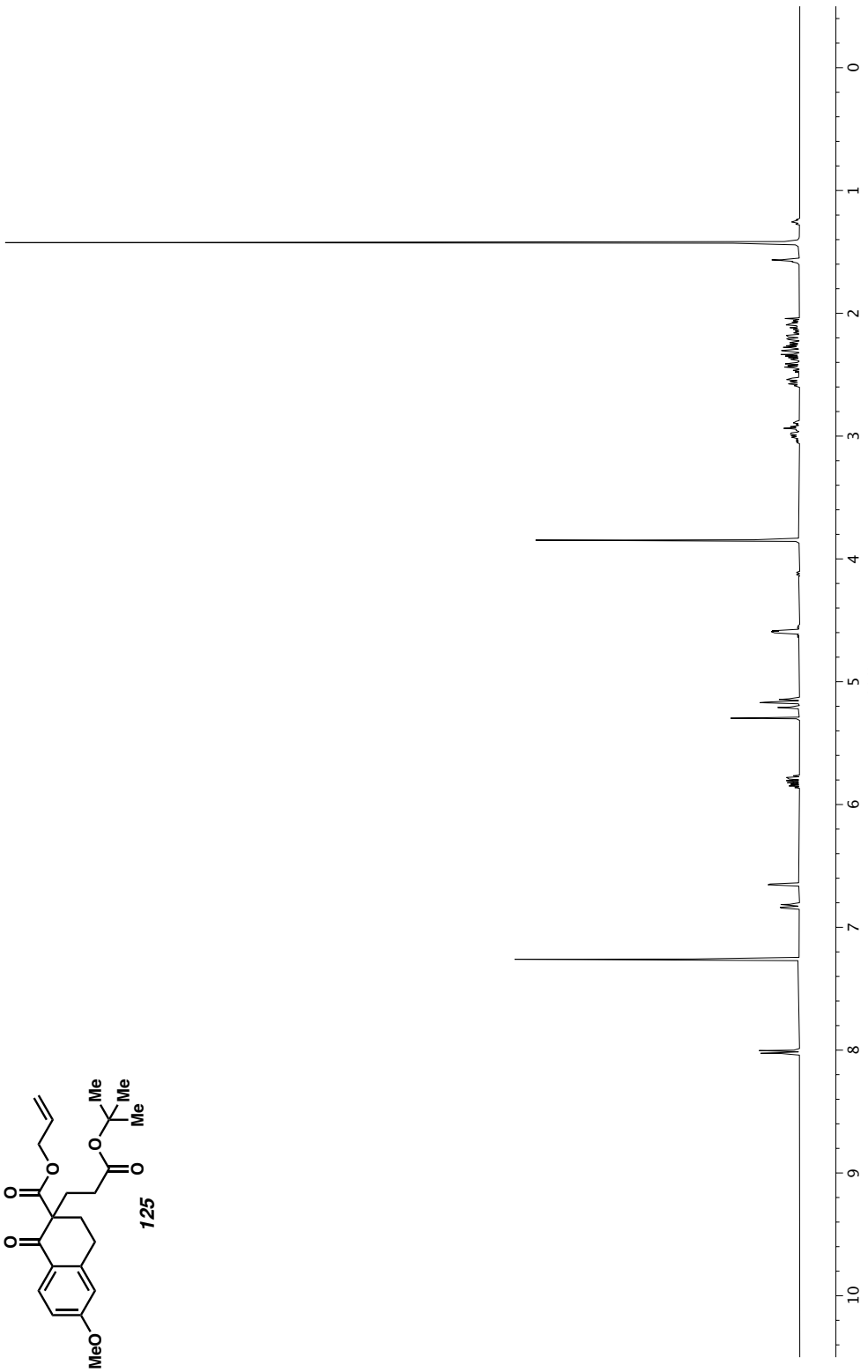


Figure A3.105. *^1H NMR (400 MHz, $CDCl_3$) of compound **125**.*

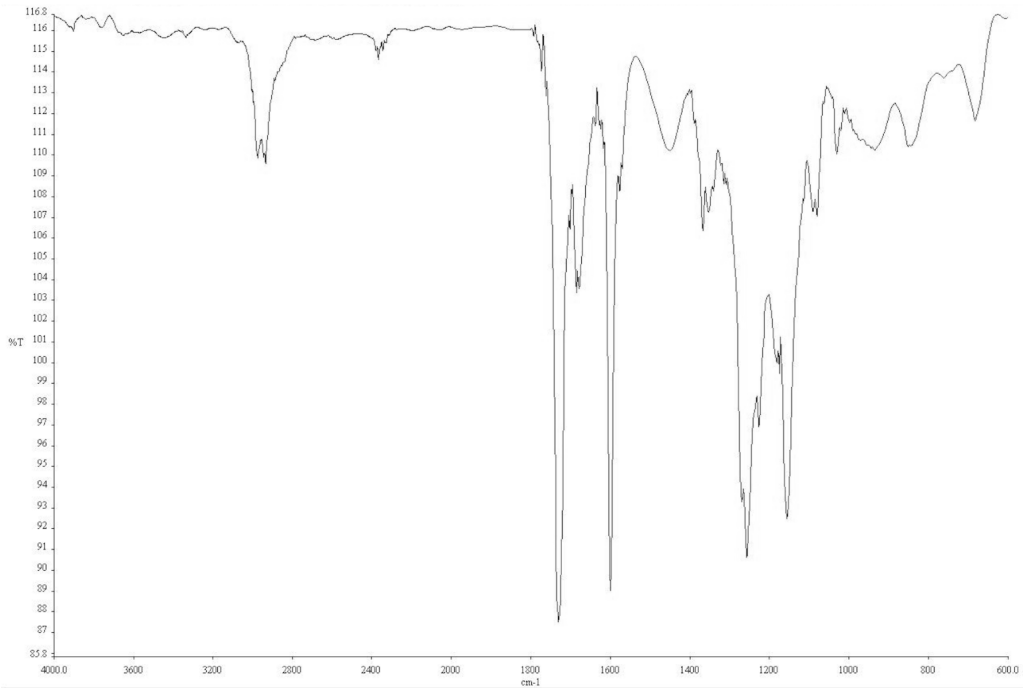


Figure A3.106. *Infrared spectrum (Thin Film, NaCl) of compound* ***125****.*

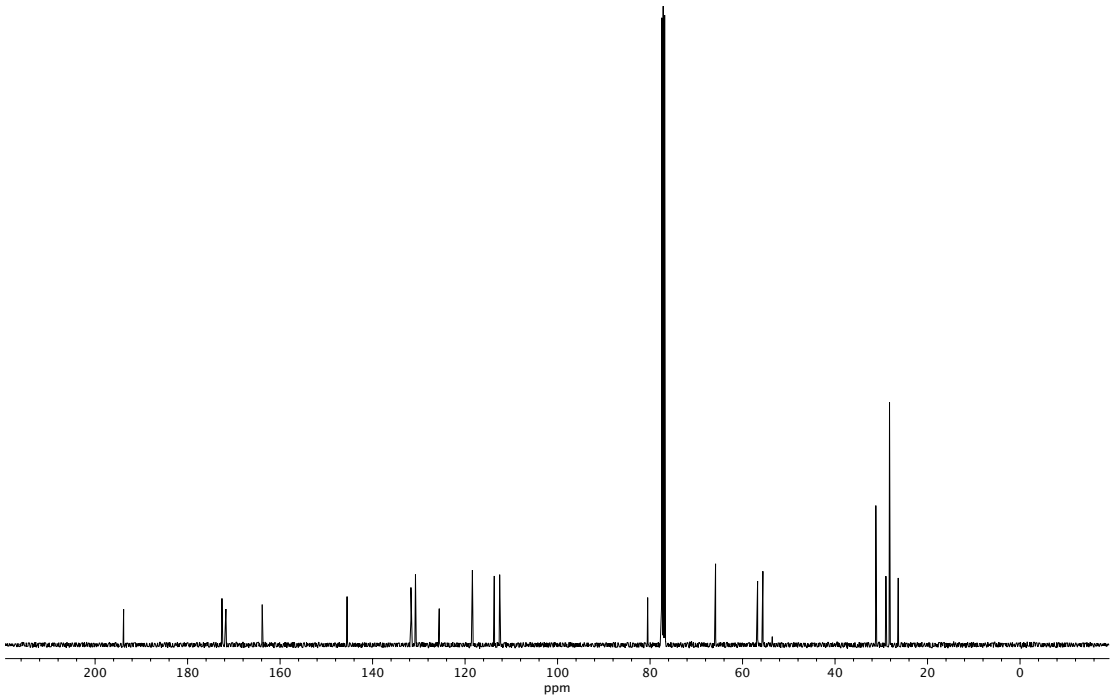


Figure A3.107. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***125****.*

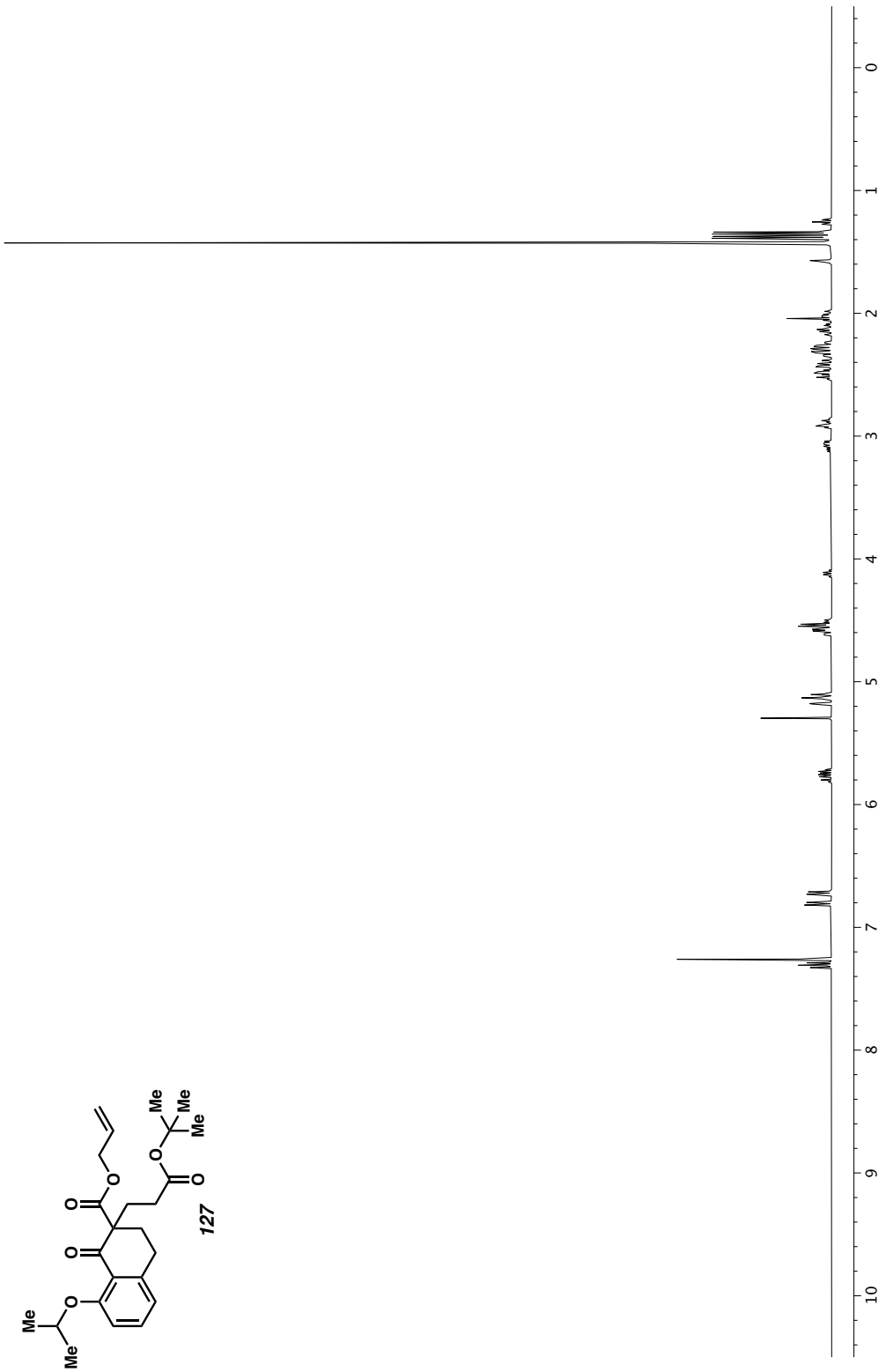


Figure A3.108. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***127****.*

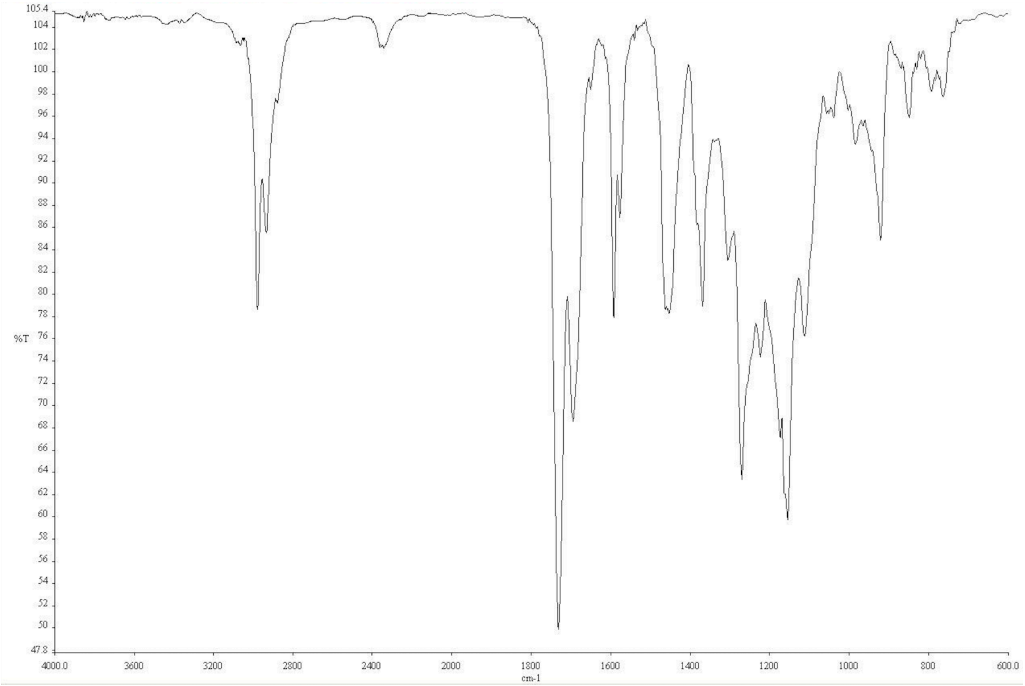


Figure A3.109. *Infrared spectrum (Thin Film, NaCl) of compound* ***127****.*

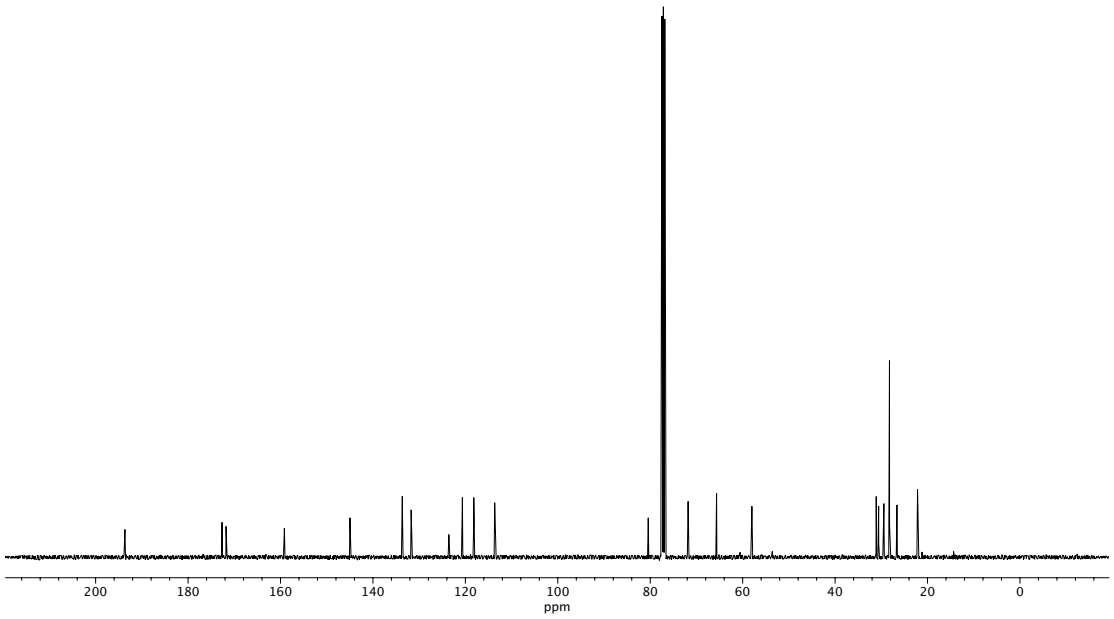


Figure A3.110. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***127****.*

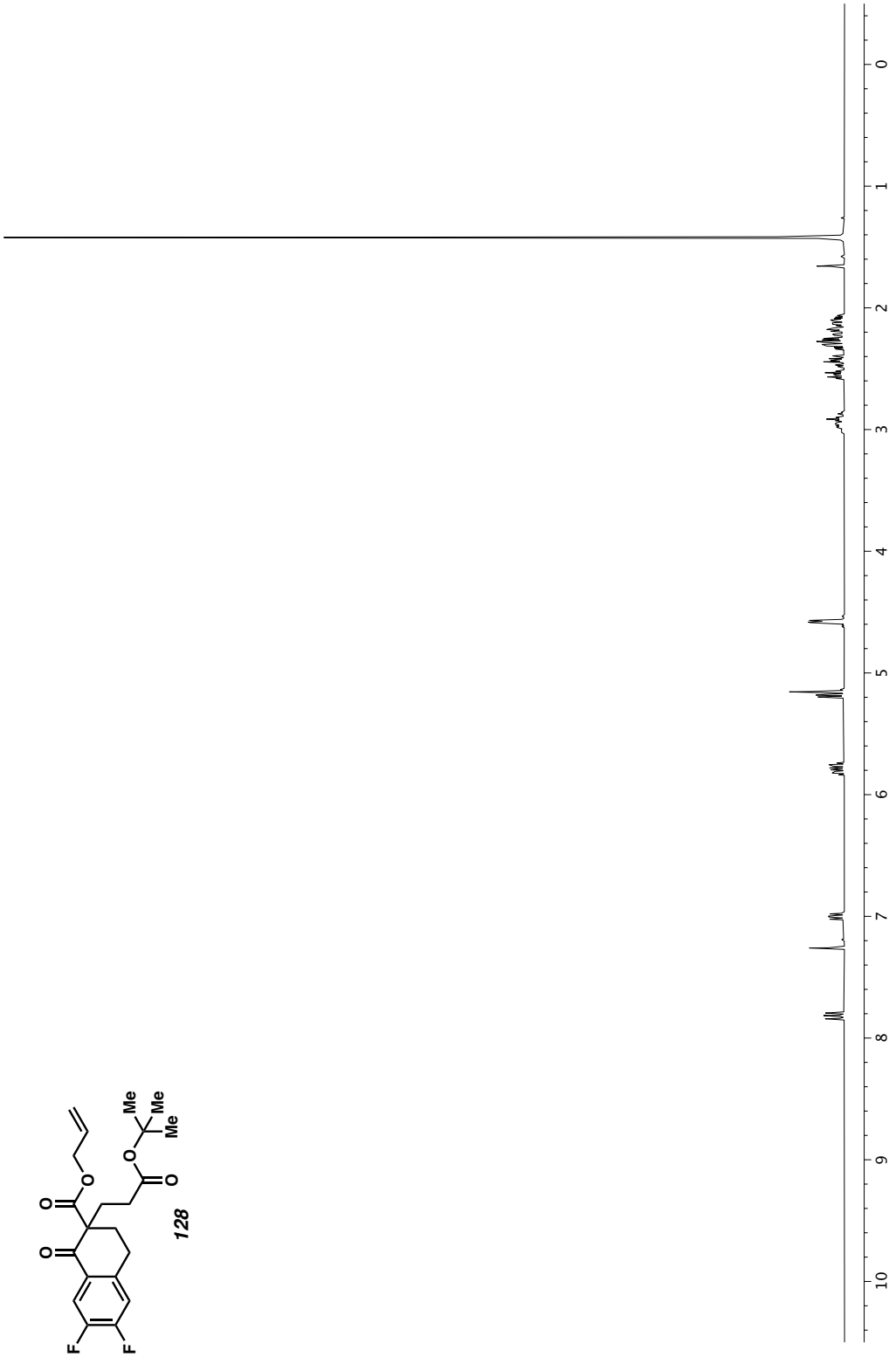


Figure A3.111. *^{1}H NMR (400 MHz, $CDCl_3$) of compound **128**.*

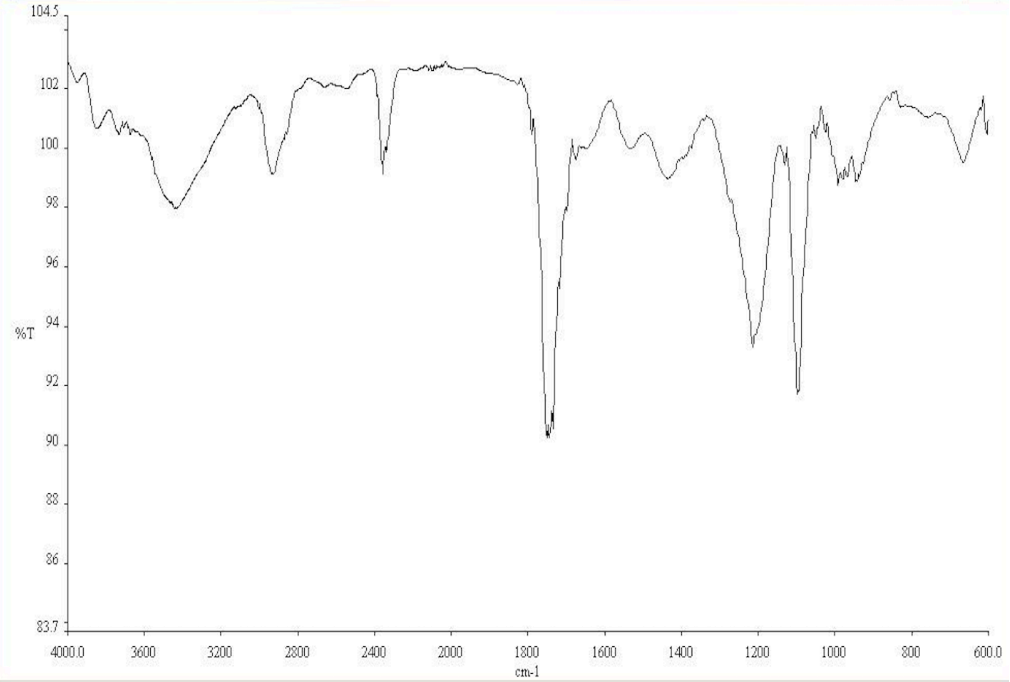


Figure A3.112. *Infrared spectrum (Thin Film, NaCl) of compound* ***128****.*

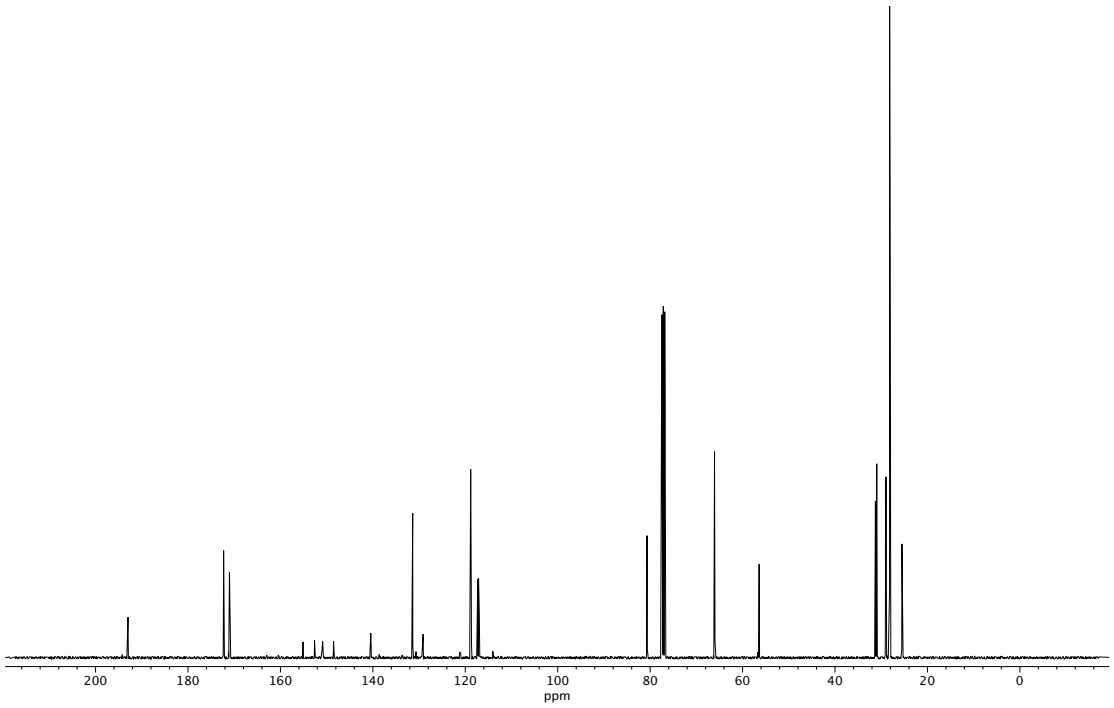


Figure A3.113. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***128****.*

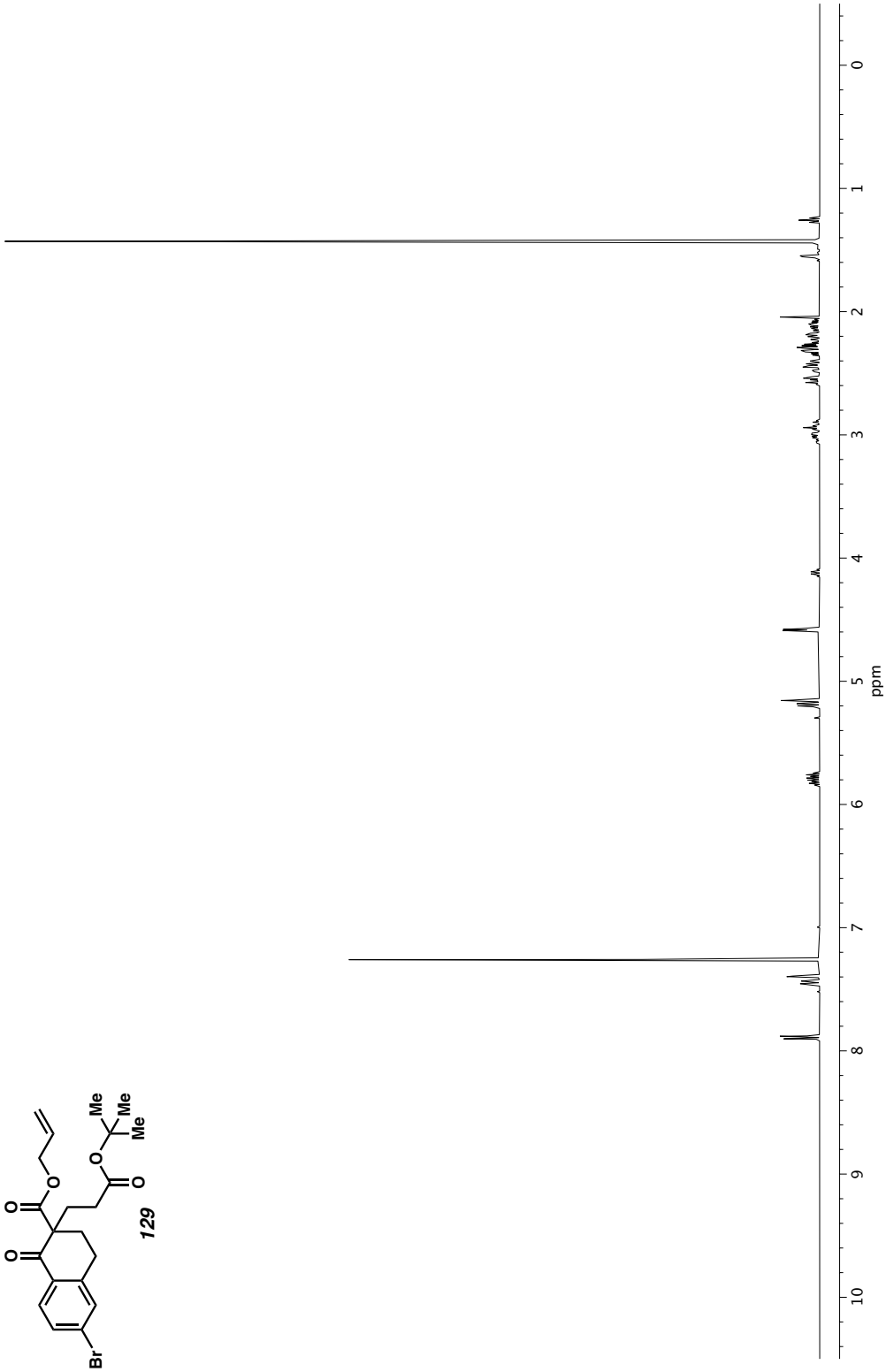


Figure A3.114. *^1H NMR (400 MHz, $CDCl_3$) of compound **129**.*

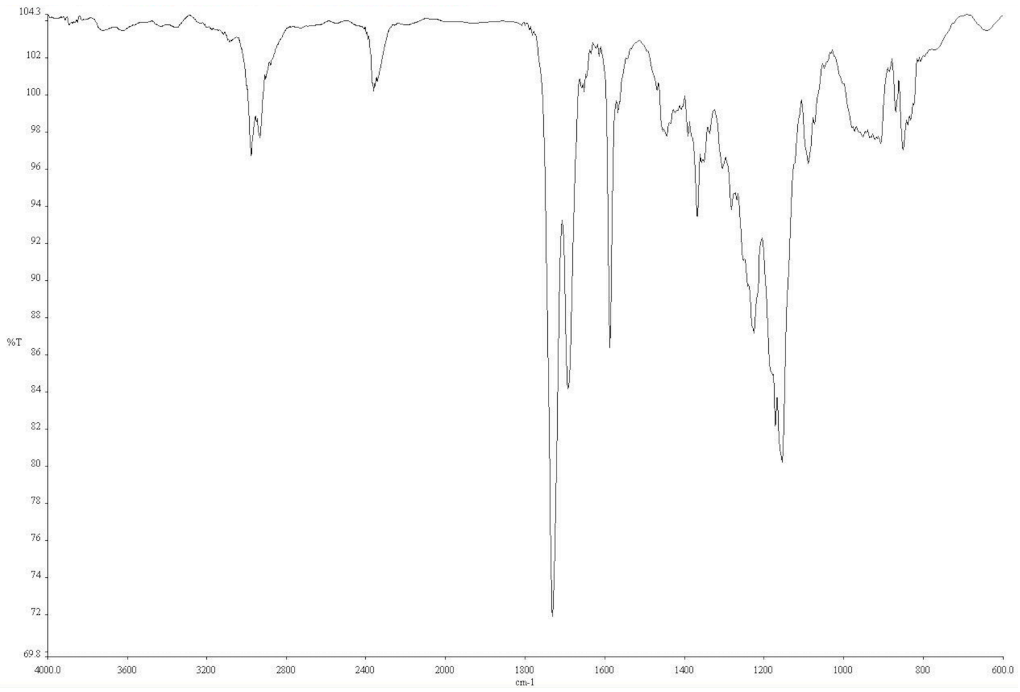


Figure A3.115. *Infrared spectrum (Thin Film, NaCl) of compound* ***129****.*

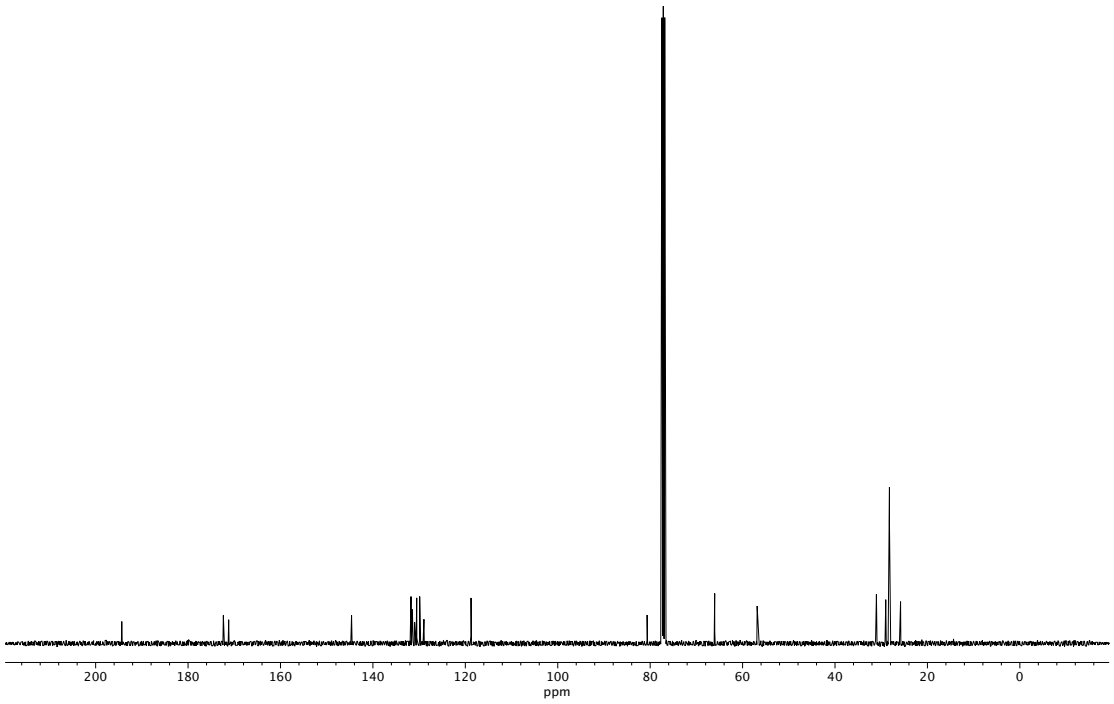


Figure A3.116. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***129****.*

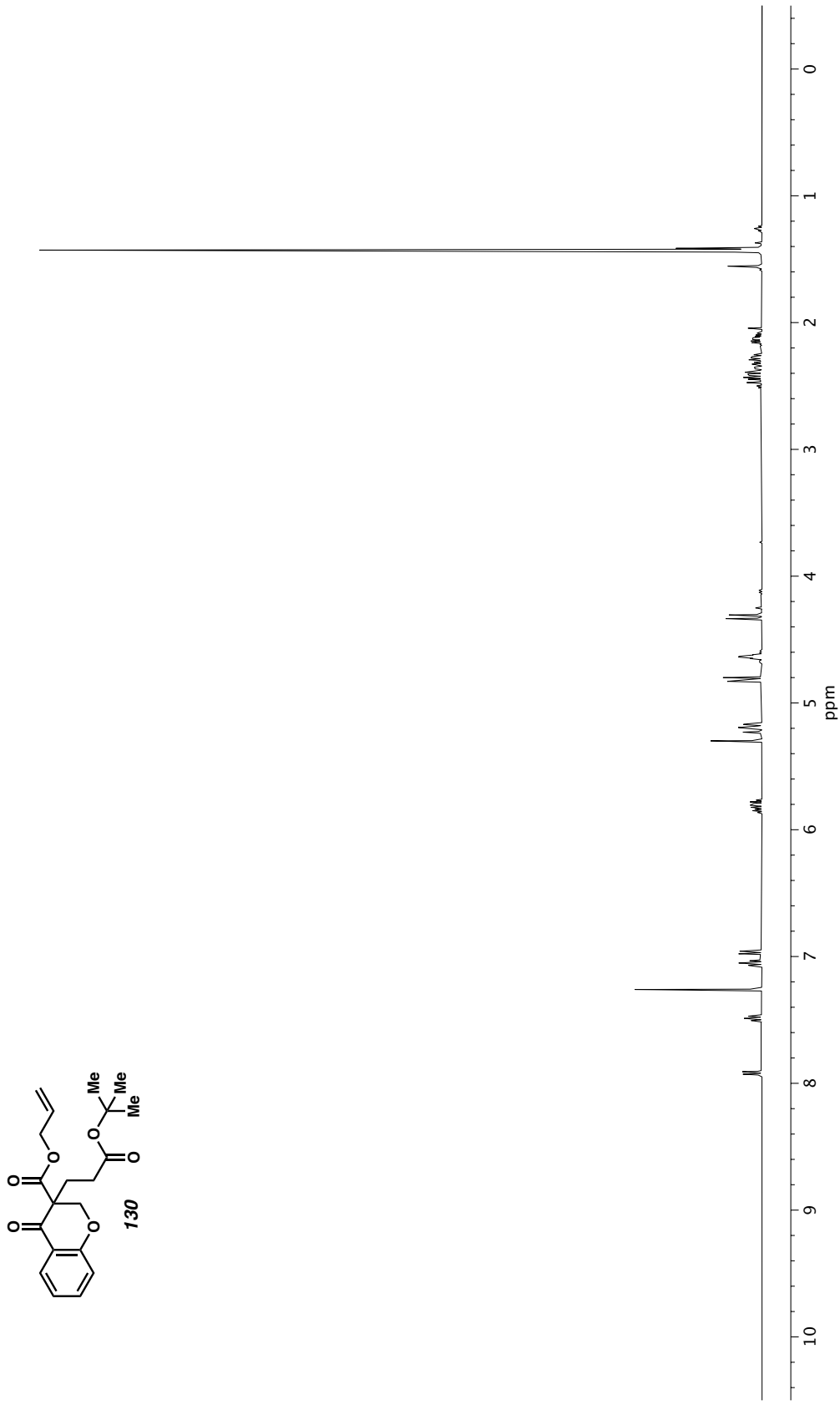


Figure A3.117. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***130***.

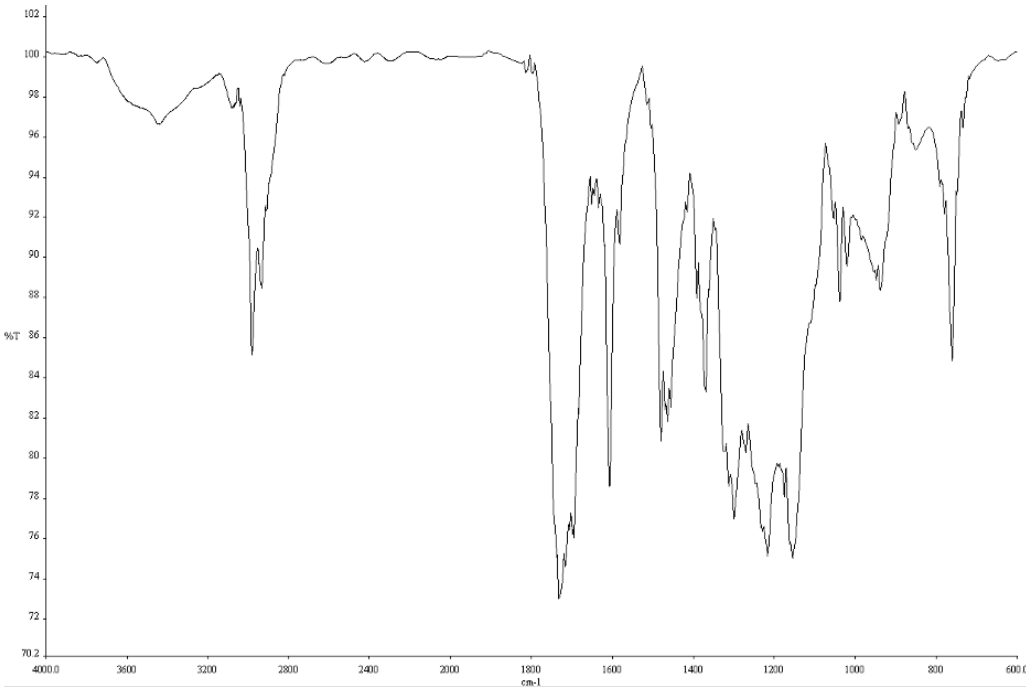


Figure A3.118. *Infrared spectrum (Thin Film, NaCl) of compound* ***130****.*

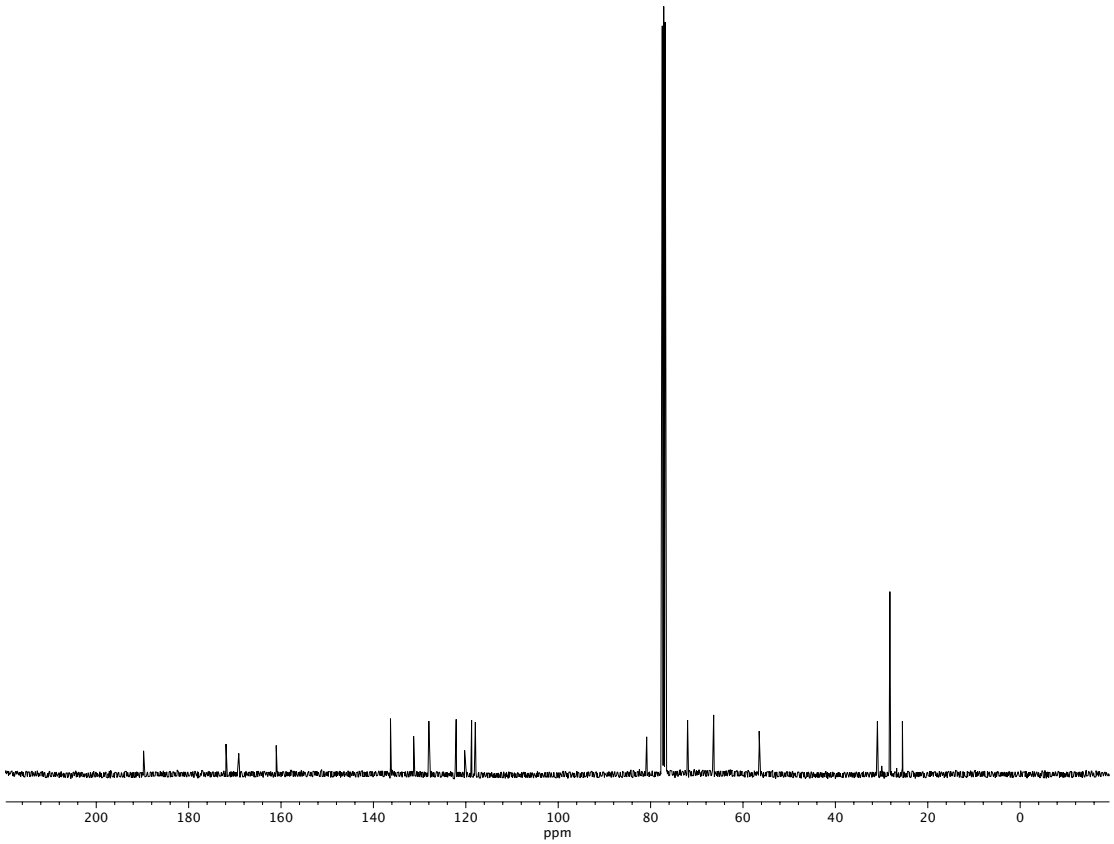


Figure A3.119. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***130****.*

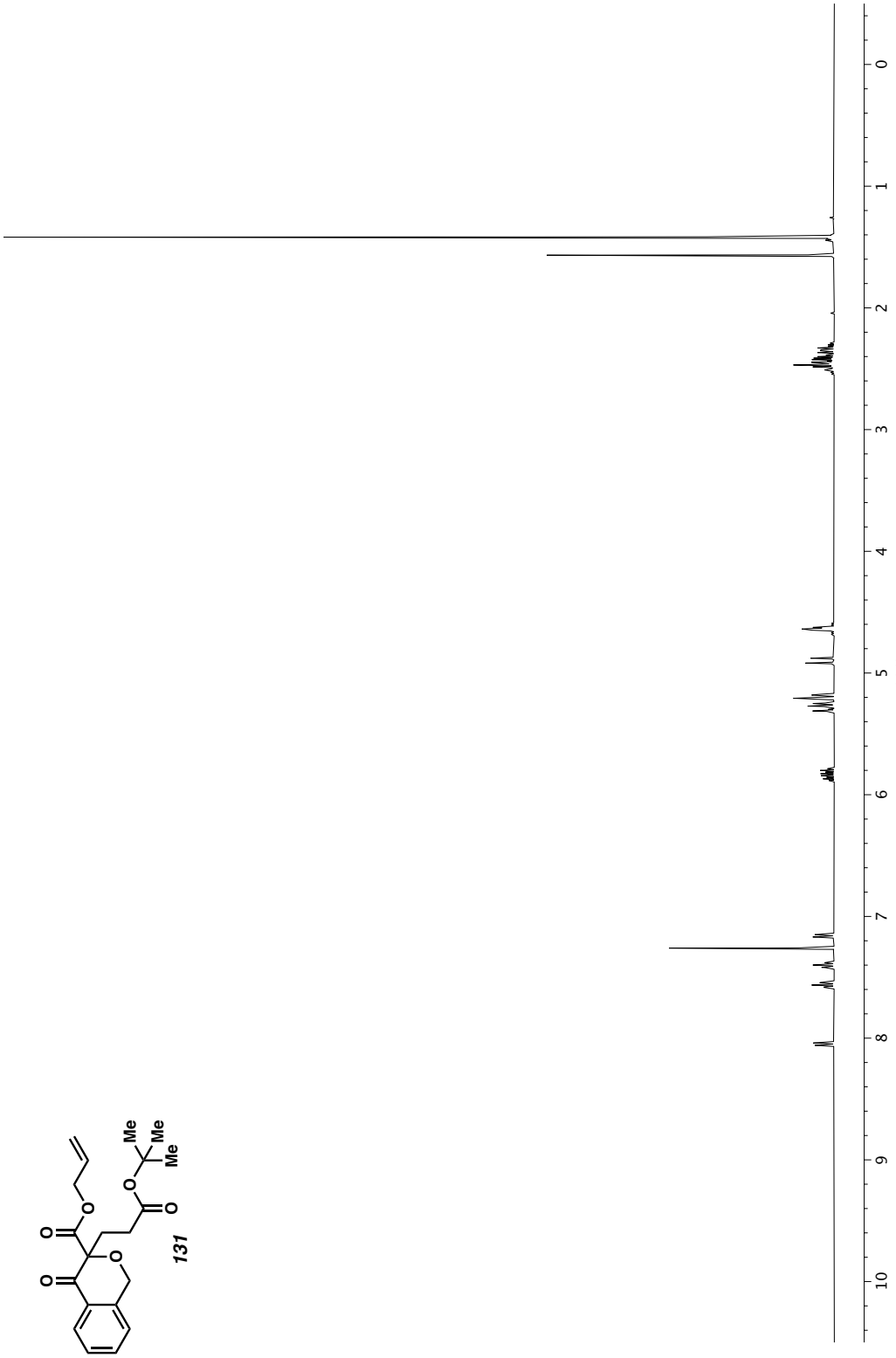


Figure A3.120. *^{1}H NMR (400 MHz, $CDCl_3$) of compound **131**.*

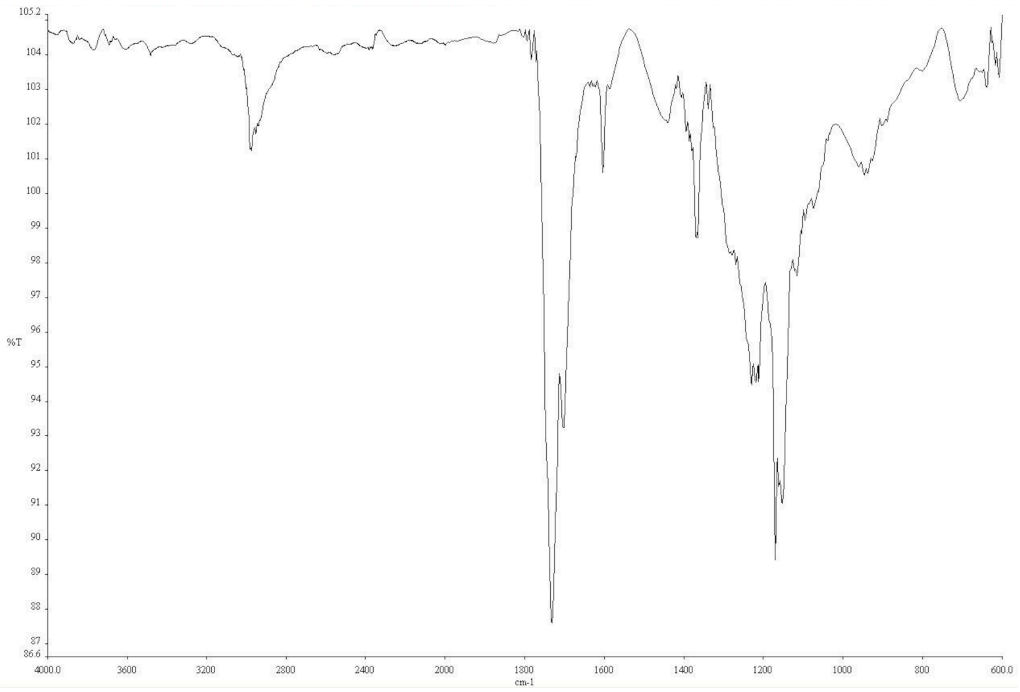


Figure A3.121. *Infrared spectrum (Thin Film, NaCl) of compound* ***131****.*

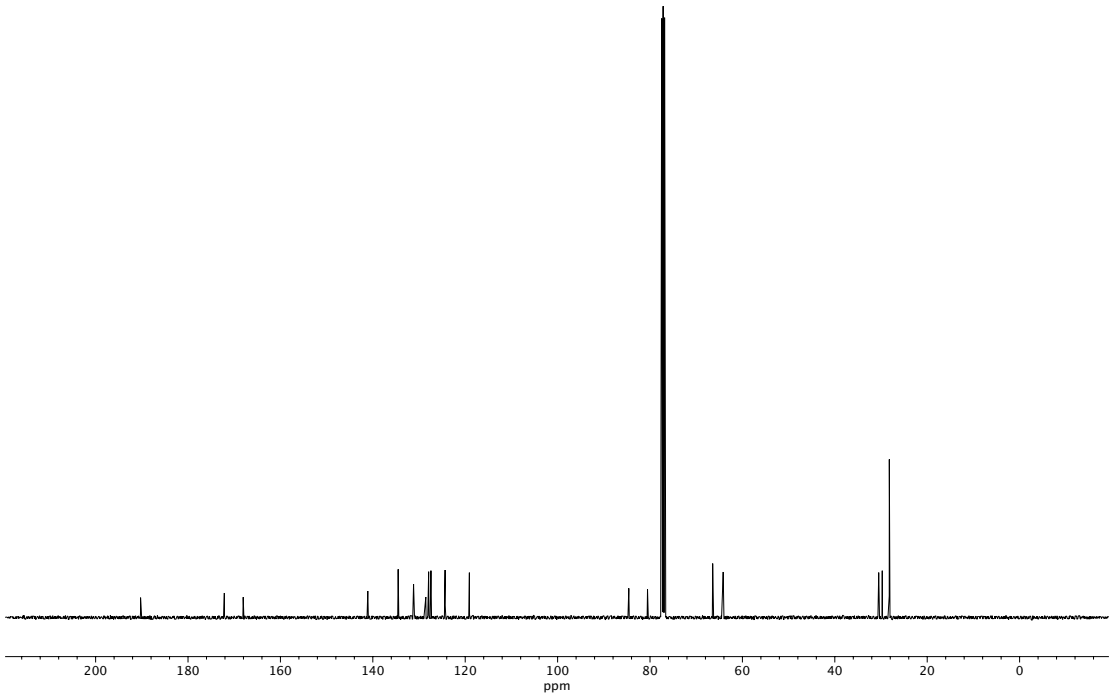


Figure A3.122. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***131****.*

Figure A3.123. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***132***.

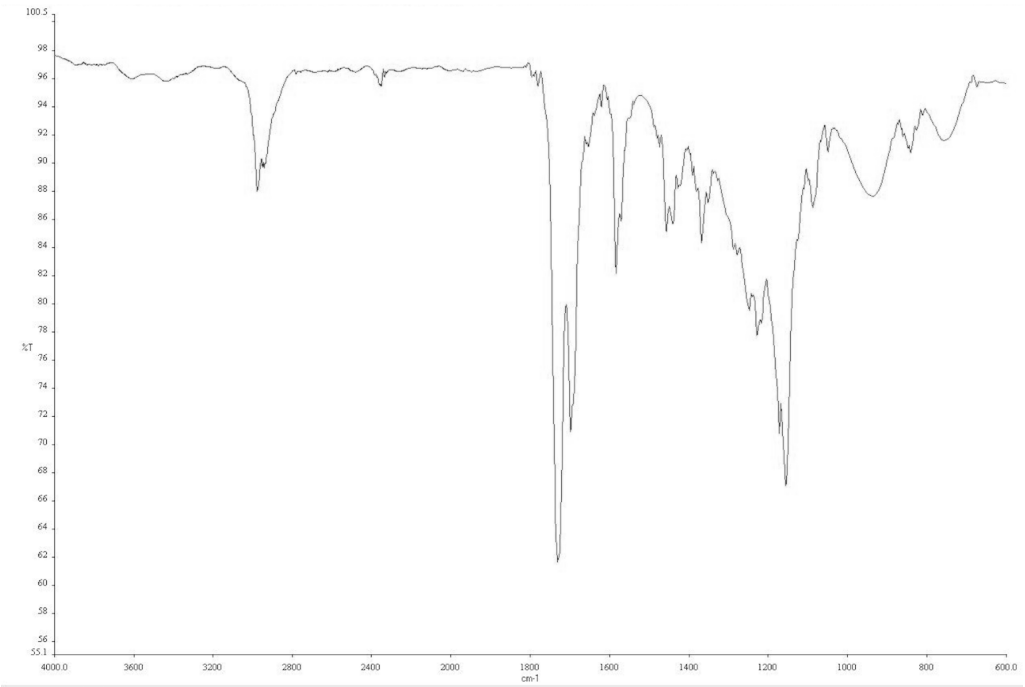


Figure A3.124. *Infrared spectrum (Thin Film, NaCl) of compound* ***132****.*

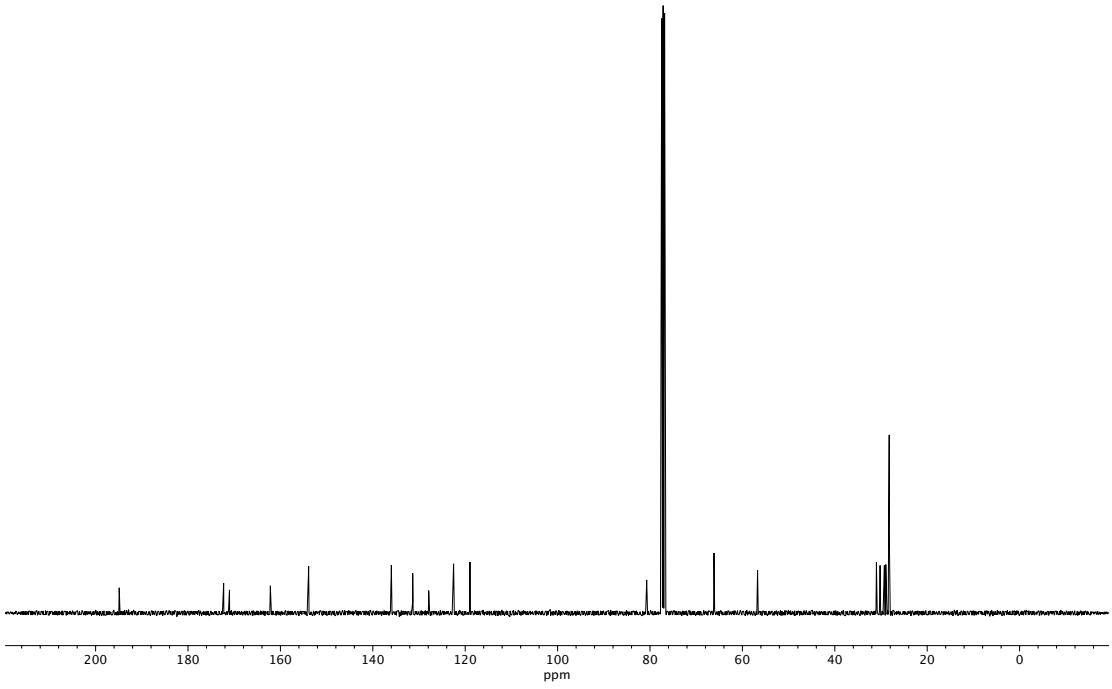


Figure A3.125. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***132****.*

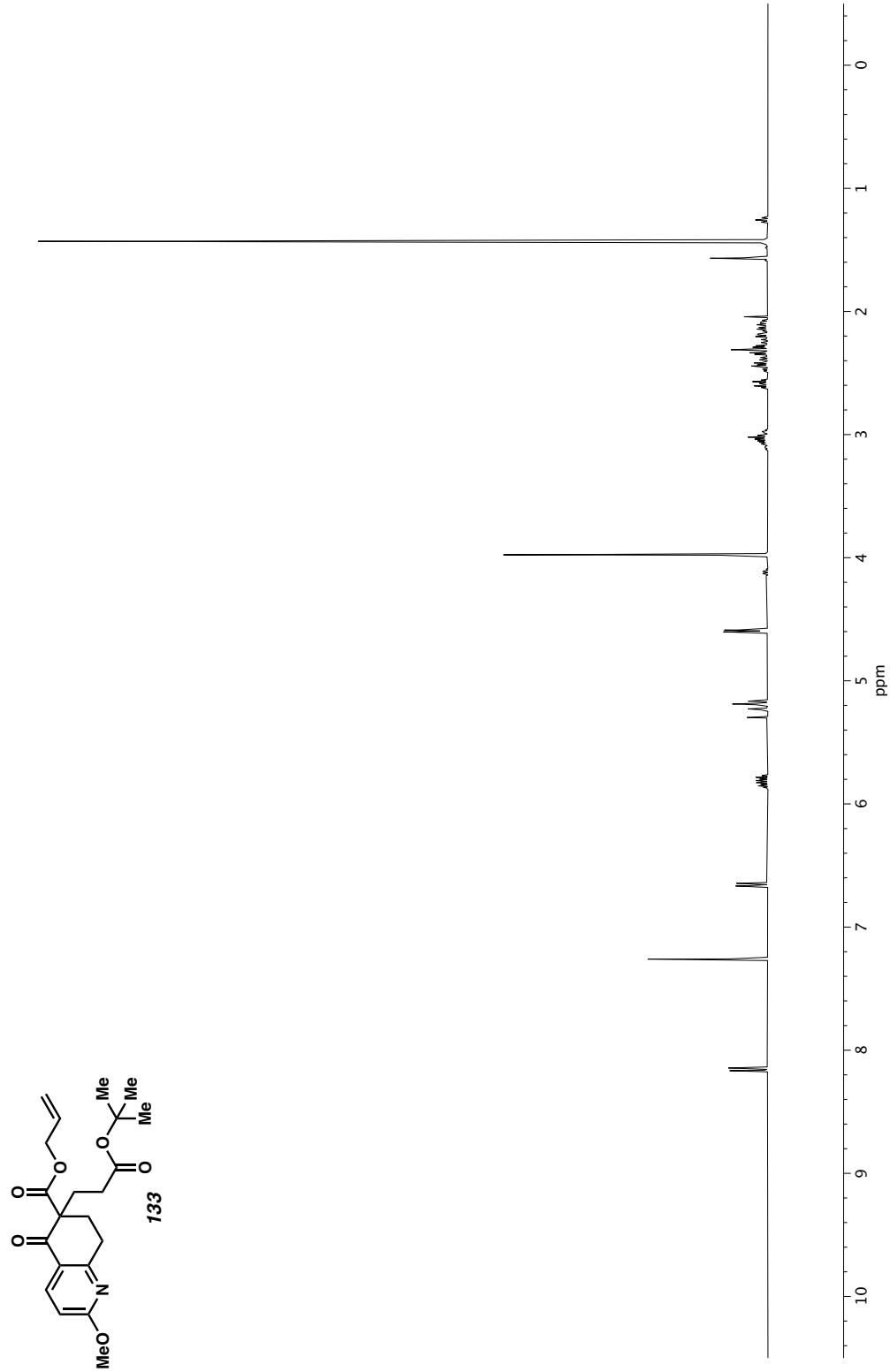


Figure A3.126. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***133****.*

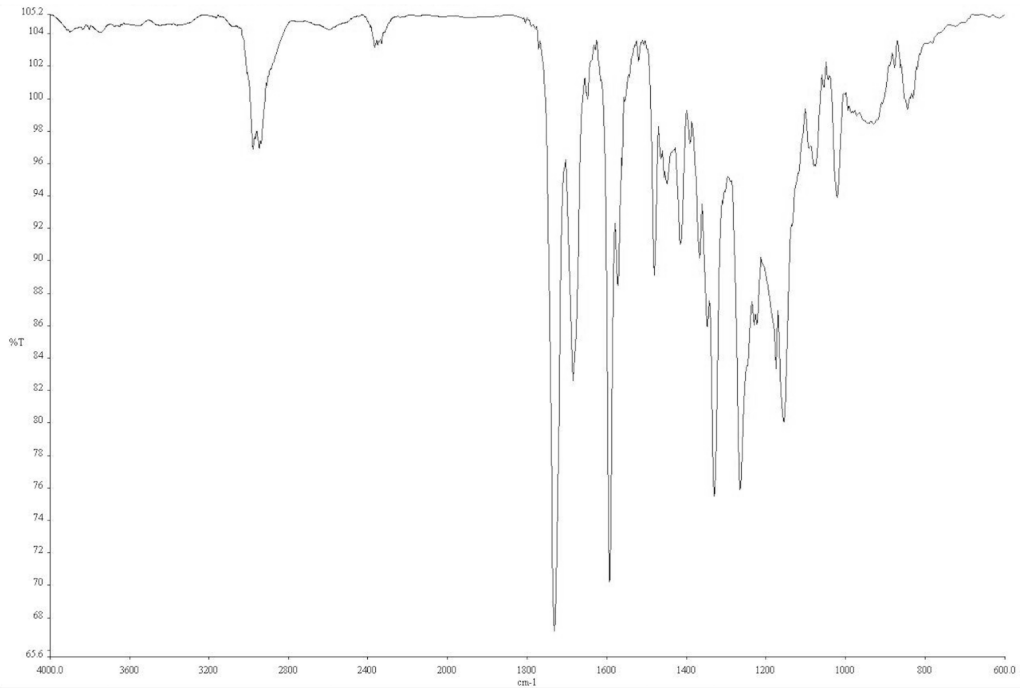


Figure A3.127. *Infrared spectrum (Thin Film, NaCl) of compound* ***133****.*

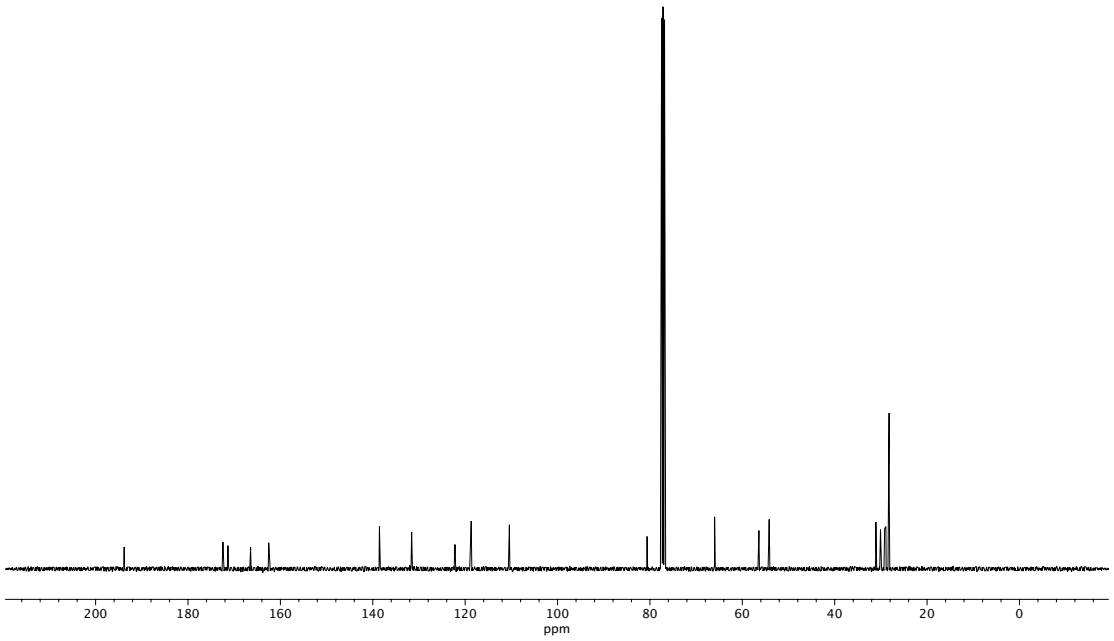


Figure A3.128. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***133****.*

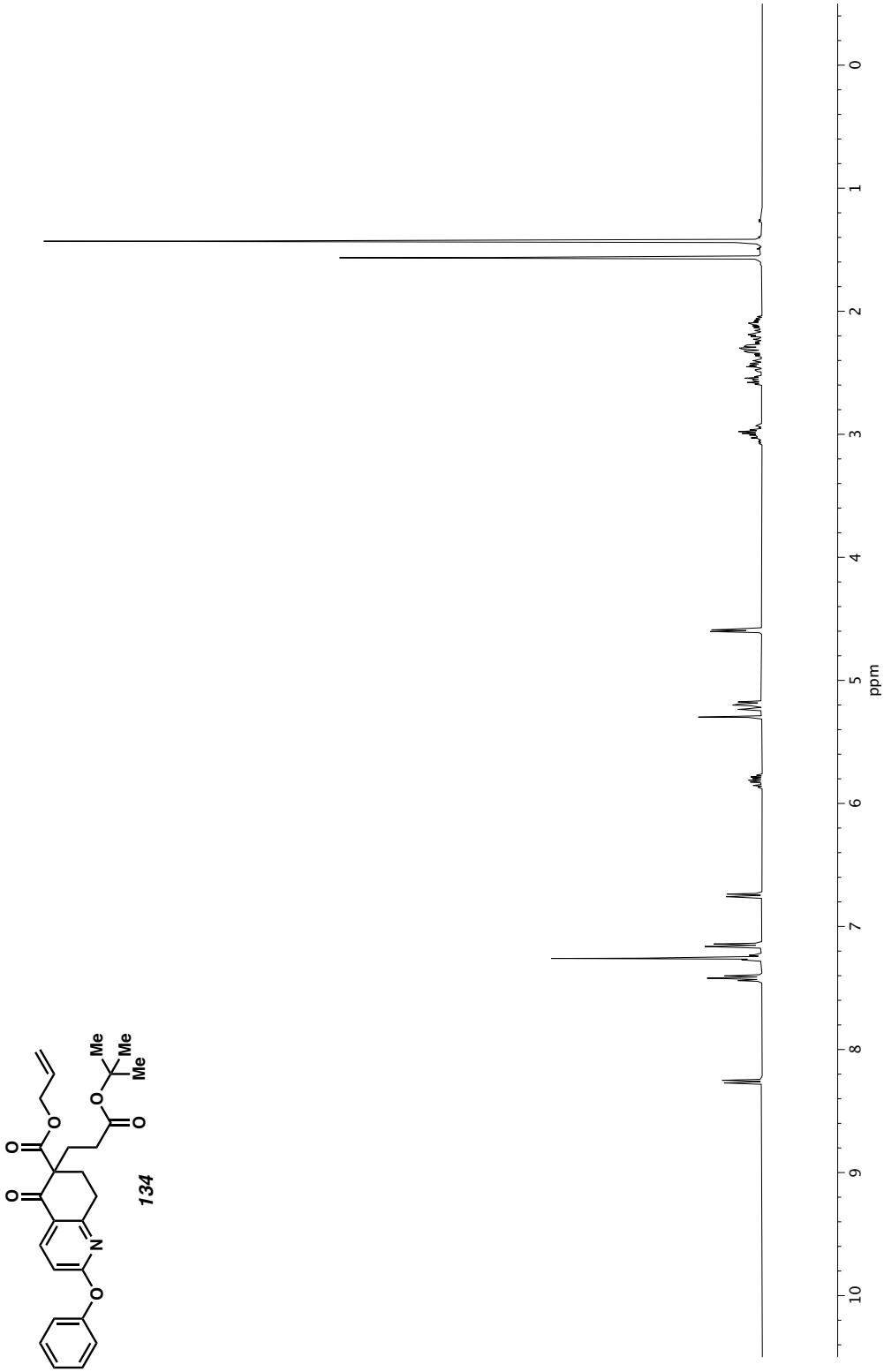


Figure A3.129. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***134****.*

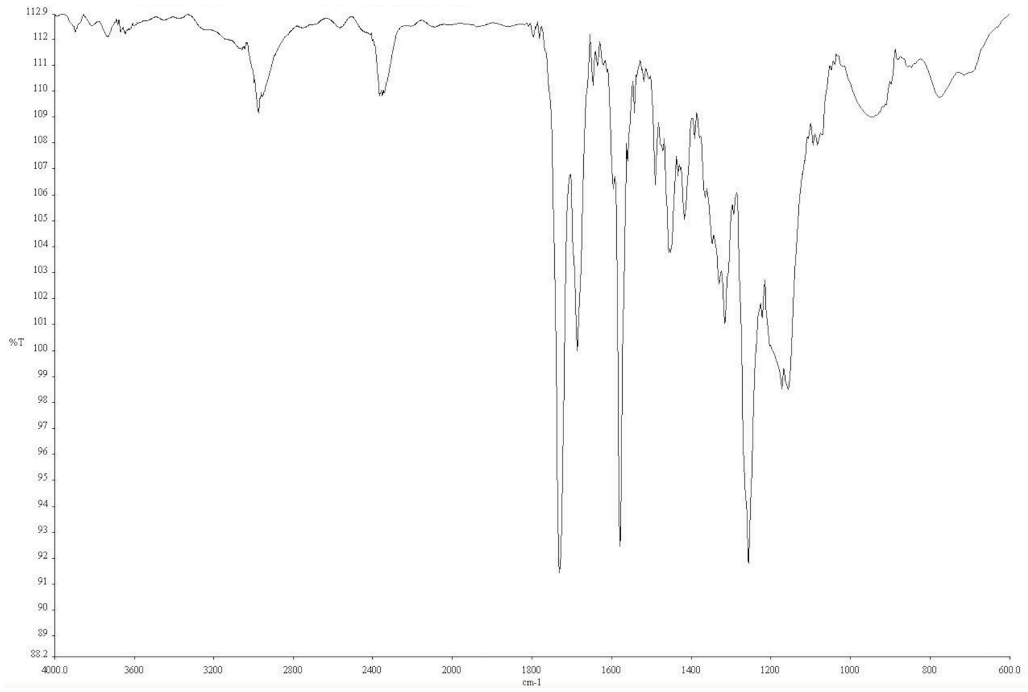


Figure A3.130. *Infrared spectrum (Thin Film, NaCl) of compound* ***134****.*

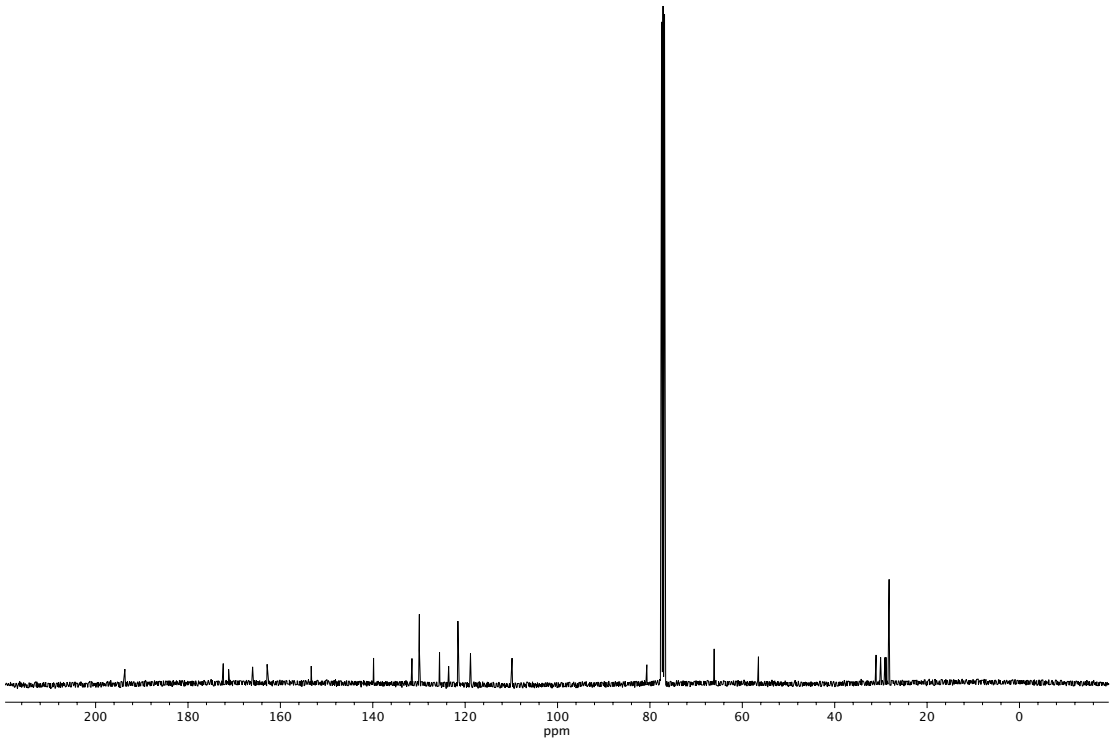


Figure A3.131. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***134****.*

Figure A3.132. *^{1}H NMR (400 MHz, $CDCl_3$) of compound **135**.*

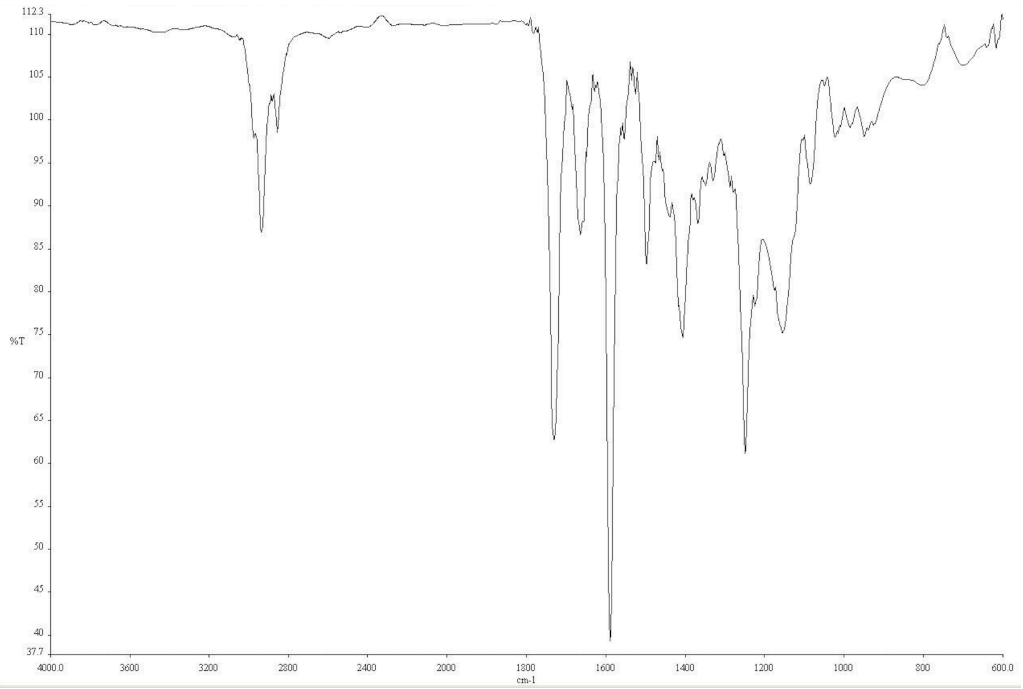


Figure A3.133. *Infrared spectrum (Thin Film, NaCl) of compound* ***135****.*

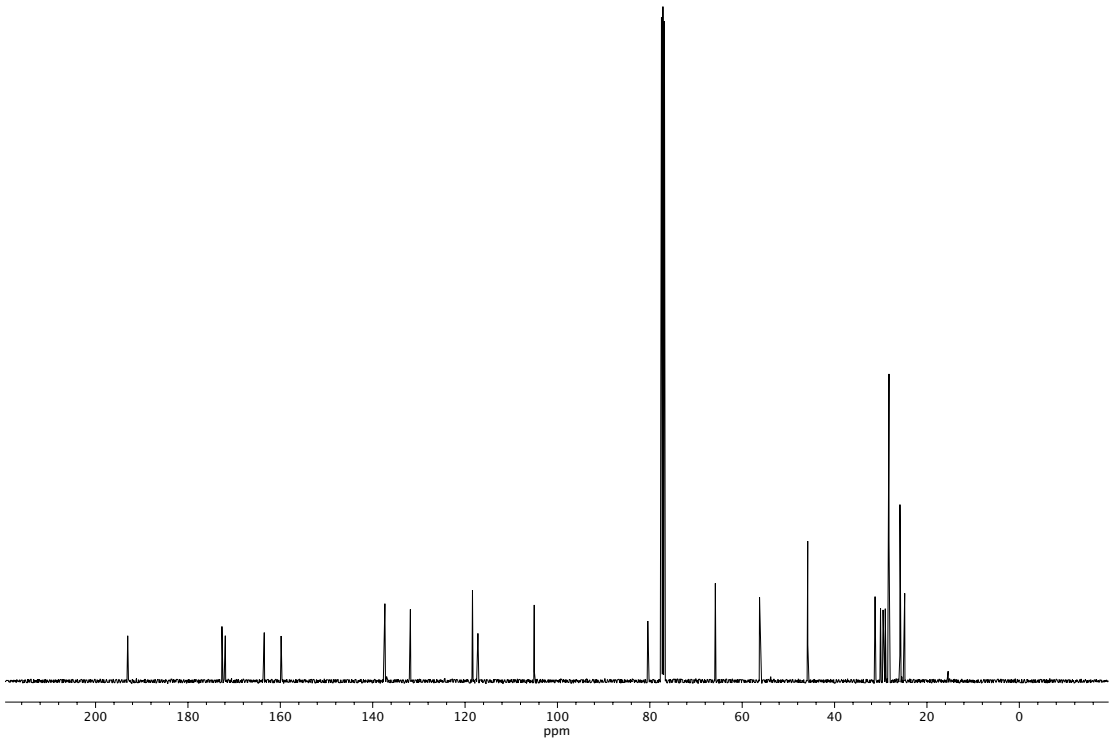


Figure A3.134. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***135****.*

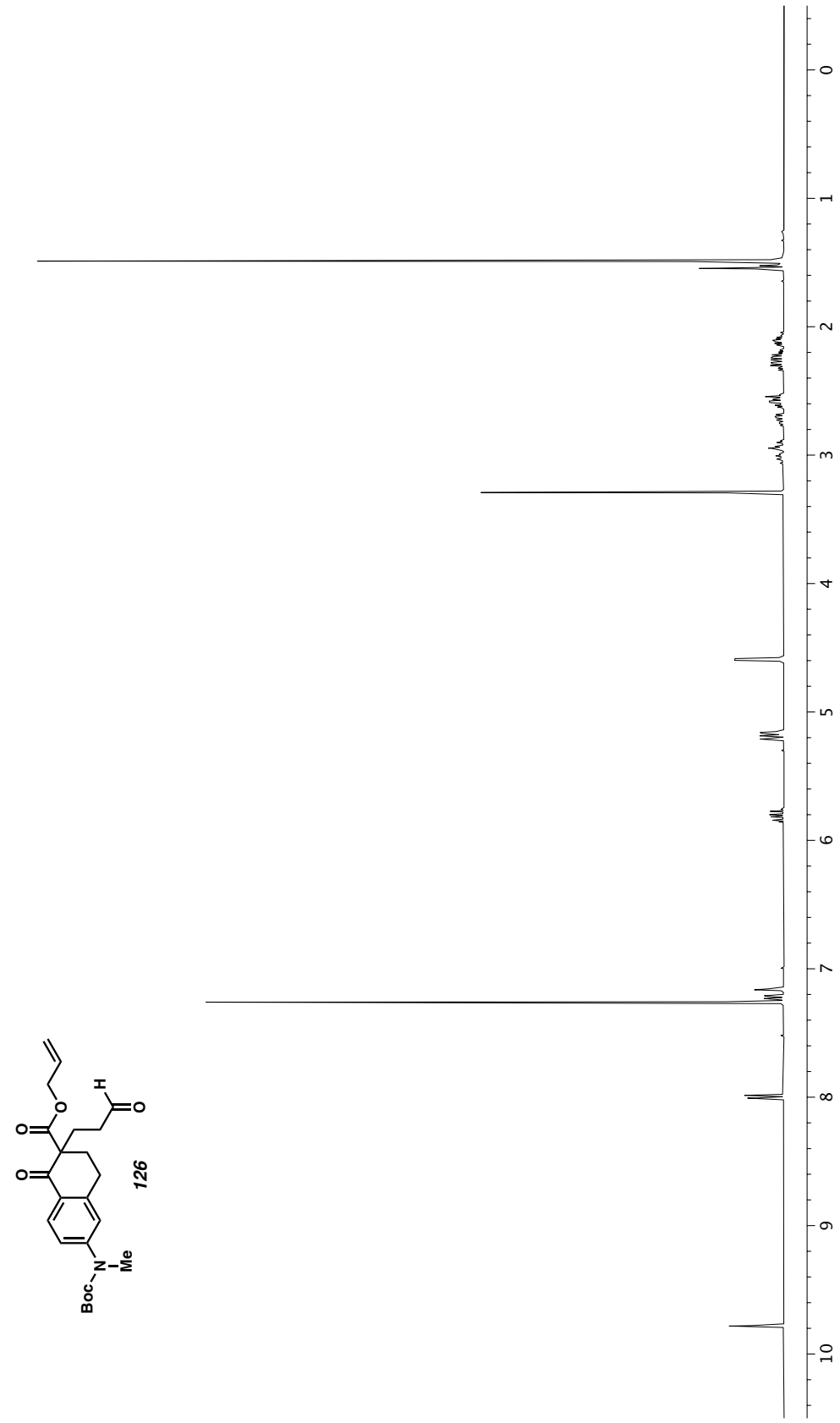


Figure A3.135. *^{1}H NMR (400 MHz, $CDCl_3$) of compound **126**.*

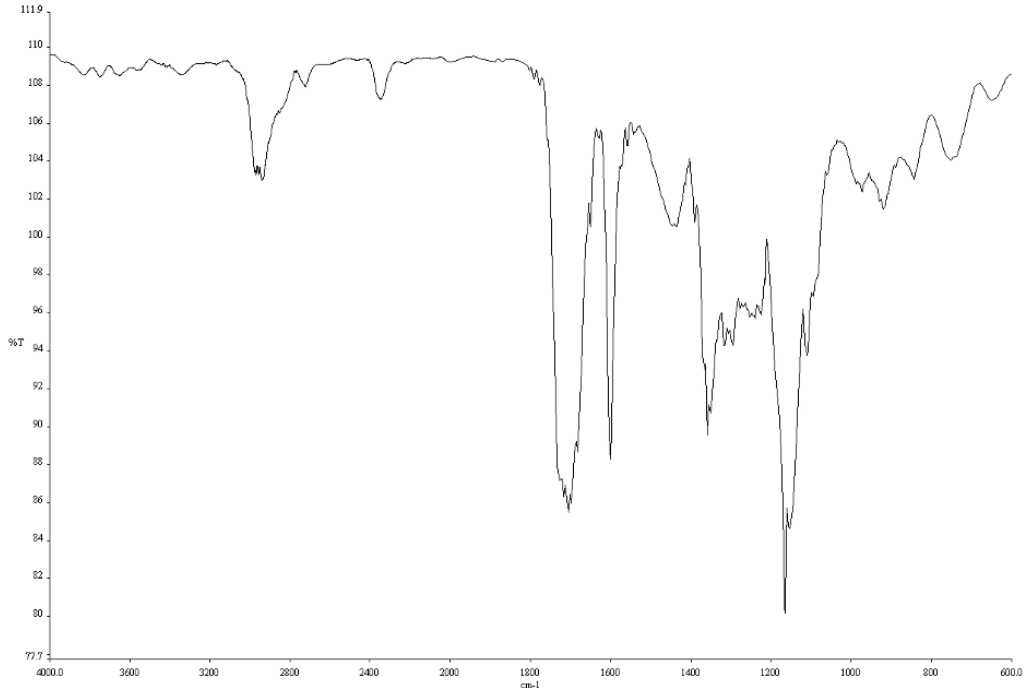


Figure A3.136. *Infrared spectrum (Thin Film, NaCl) of compound* ***126****.*

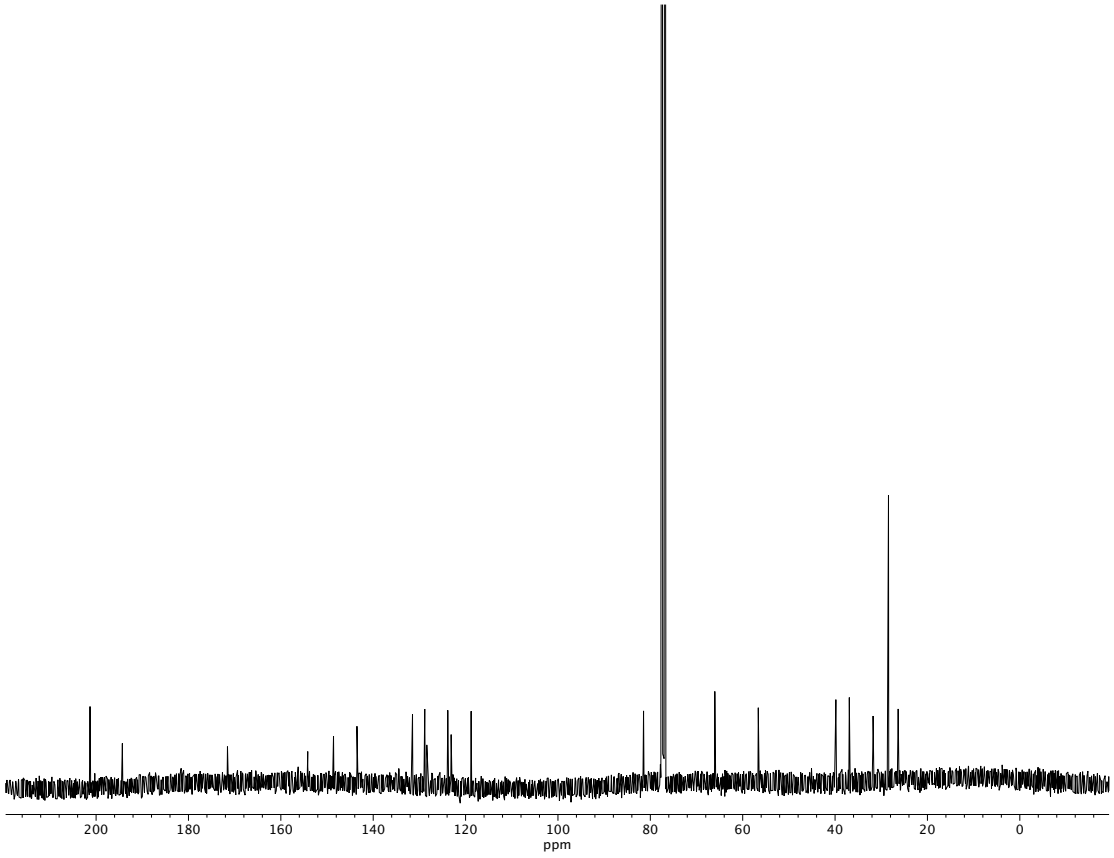


Figure A3.137. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***126****.*

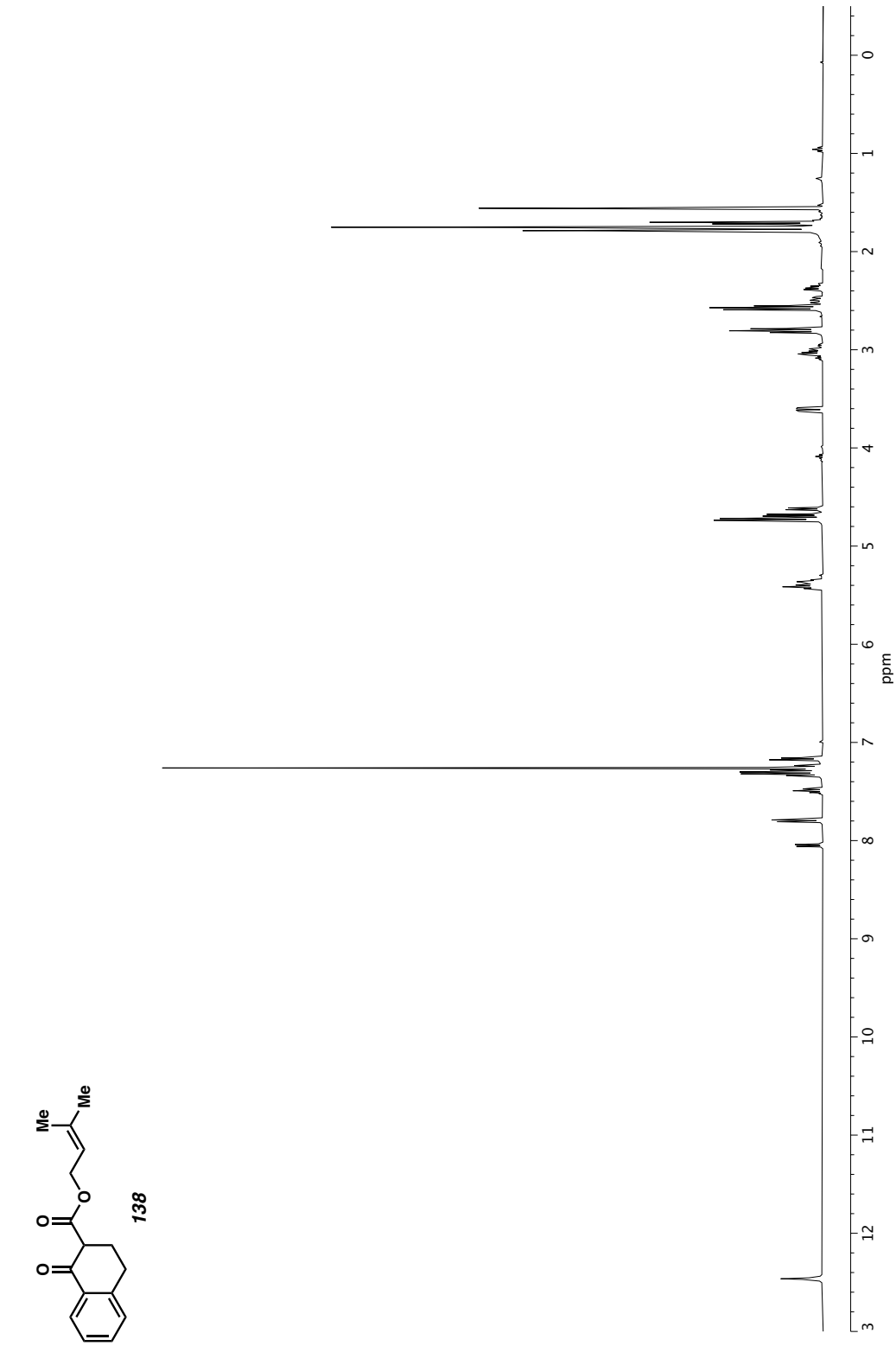


Figure A3.138. *^{1}H NMR (400 MHz, $CDCl_3$) of compound **138**.*

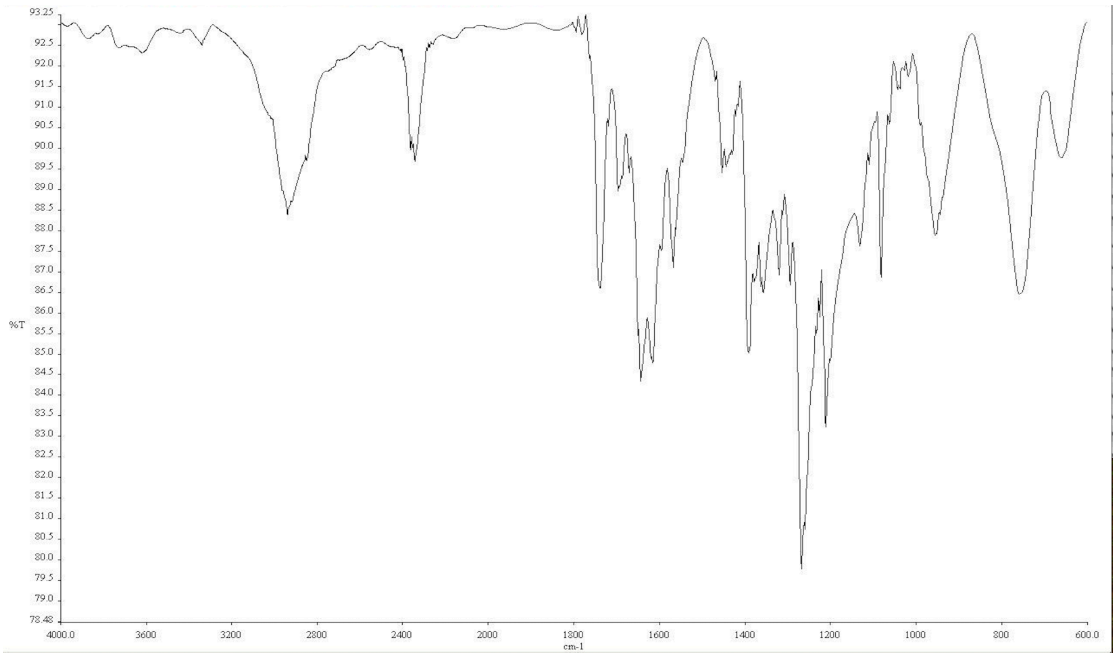


Figure A3.139. *Infrared spectrum (Thin Film, NaCl) of compound* ***138****.*

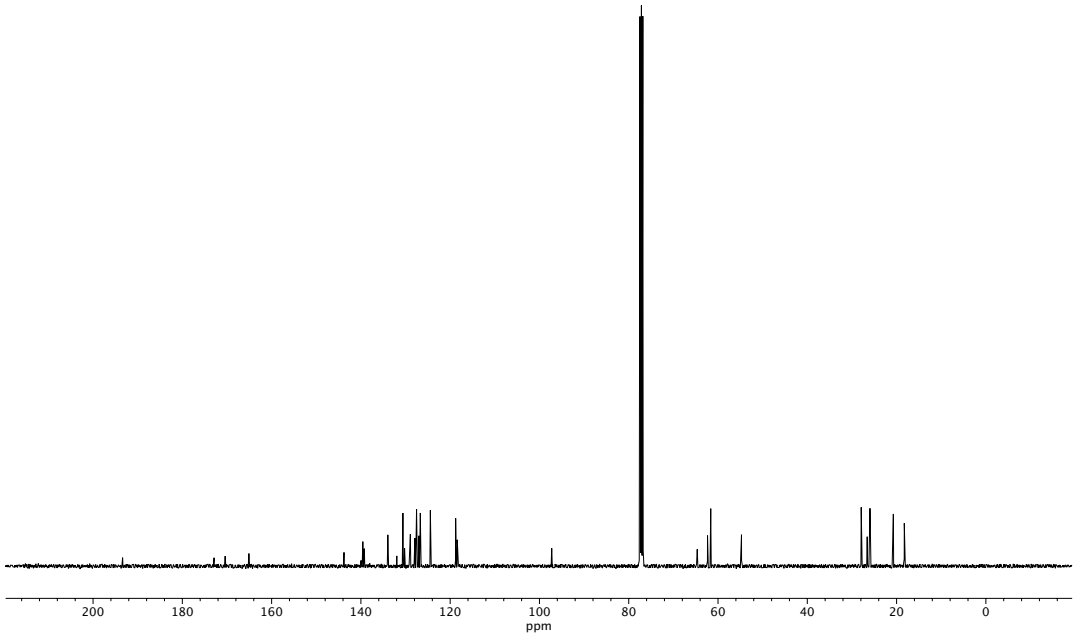


Figure A3.140. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***138****.*

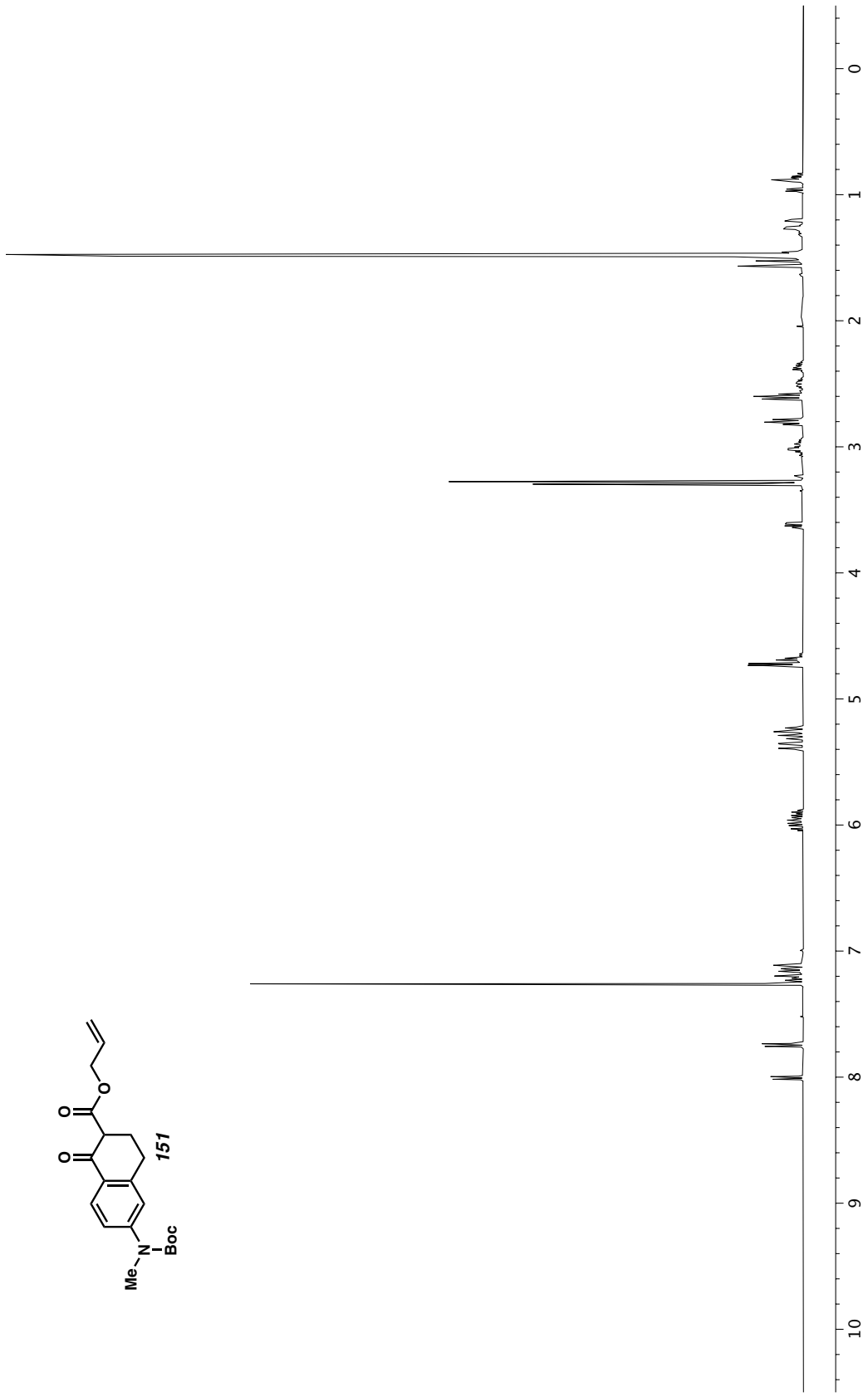


Figure A3.141. *^{1}H NMR (400 MHz, $CDCl_3$) of compound **151**.*

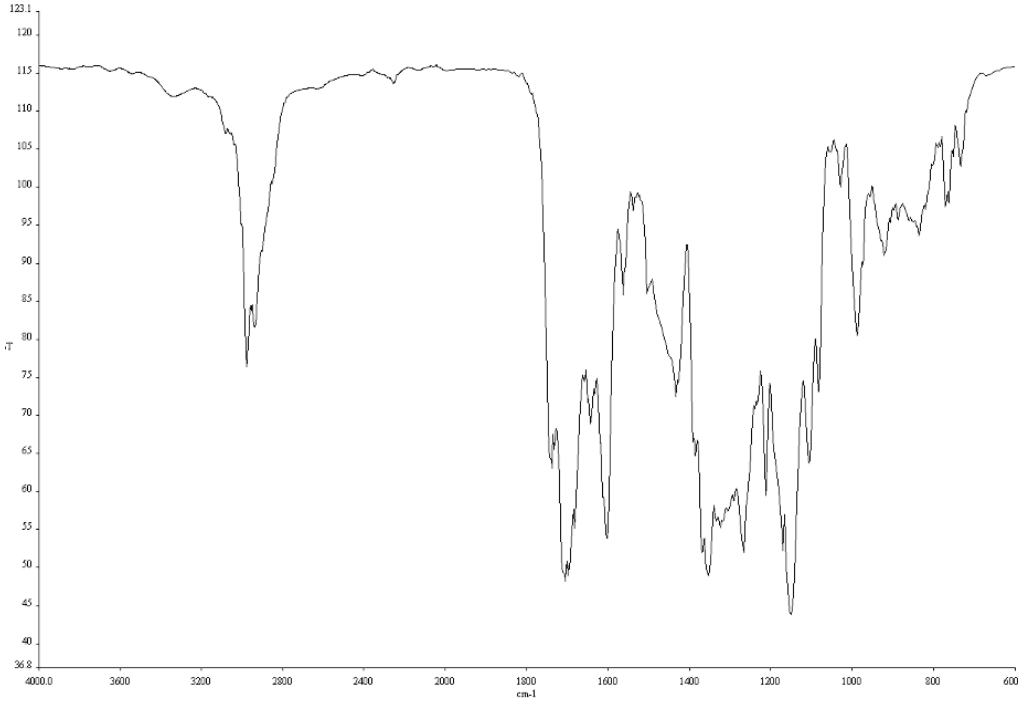


Figure A3.142. *Infrared spectrum (Thin Film, NaCl) of compound* ***151****.*

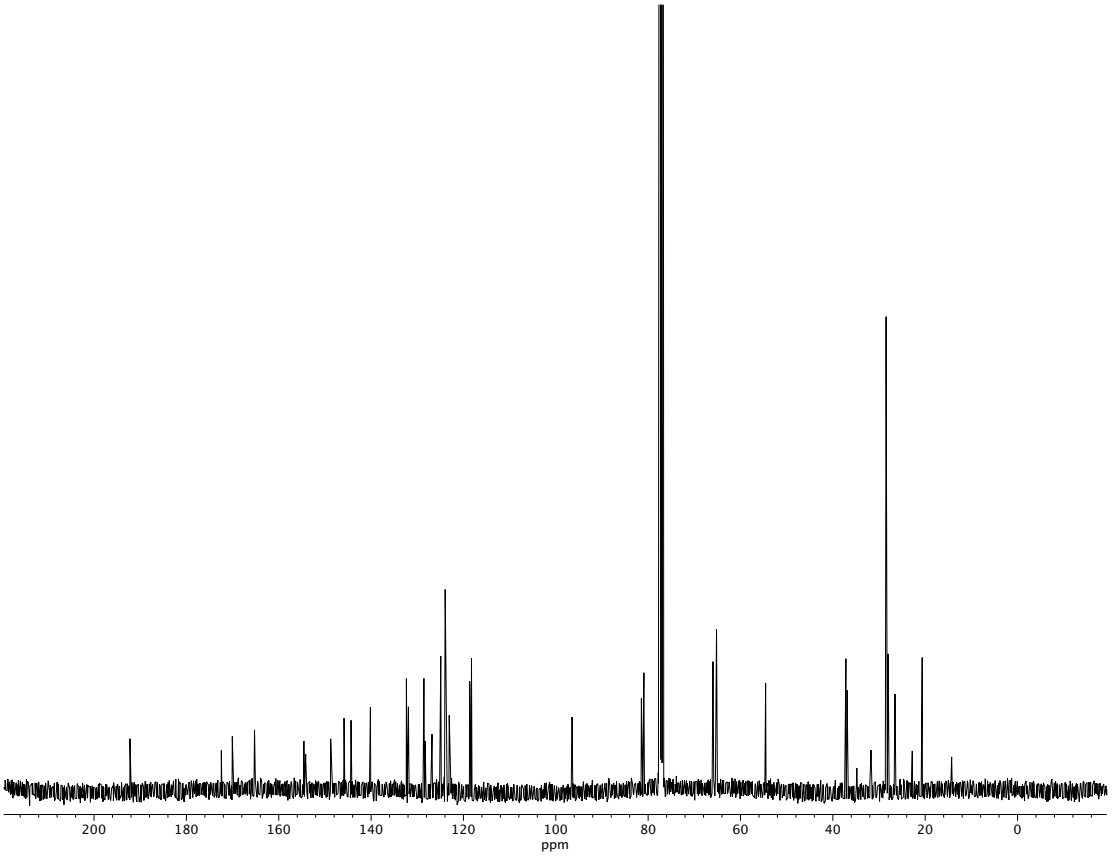


Figure A3.143. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***151****.*

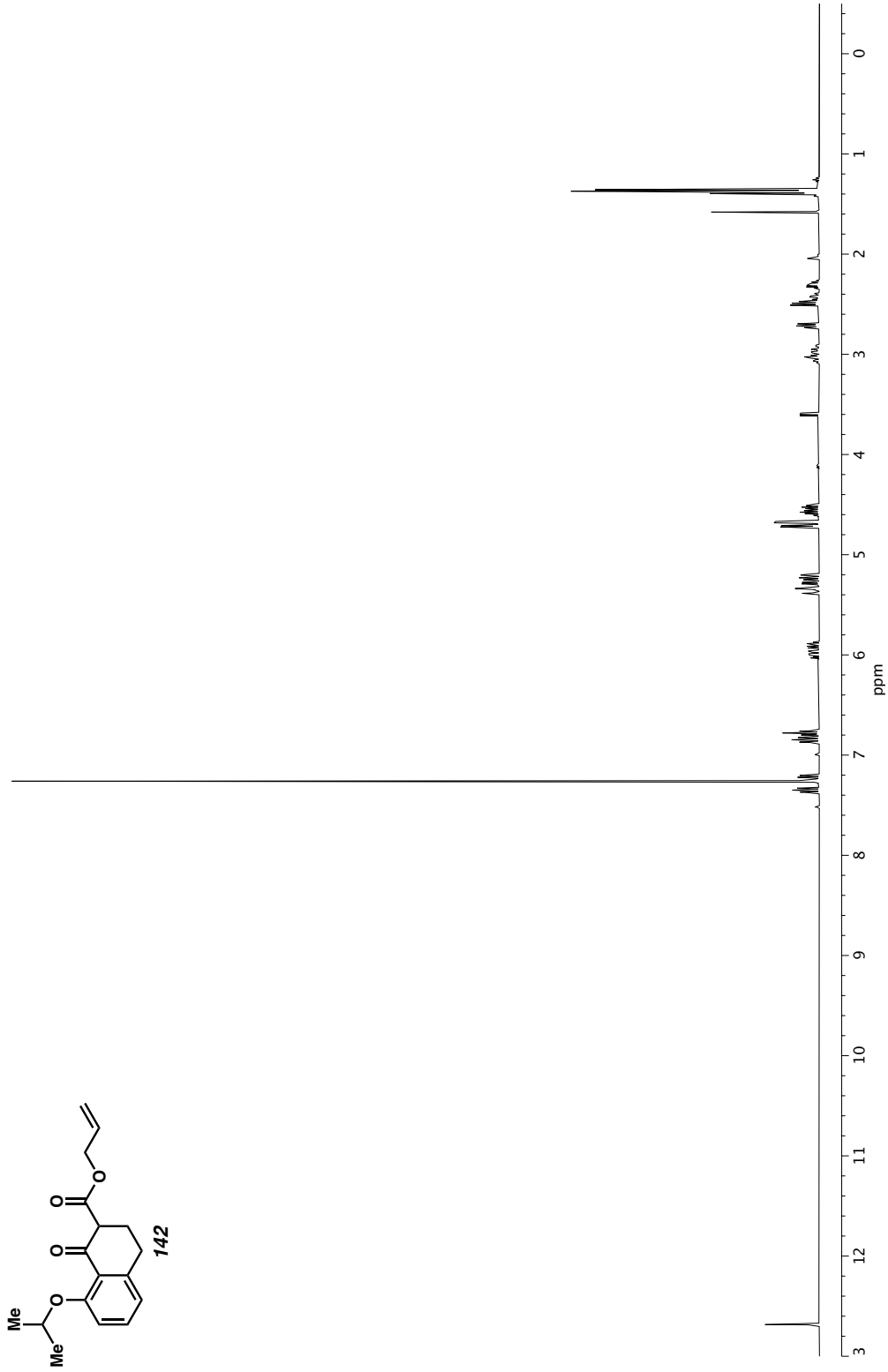


Figure A3.144. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***142****.*

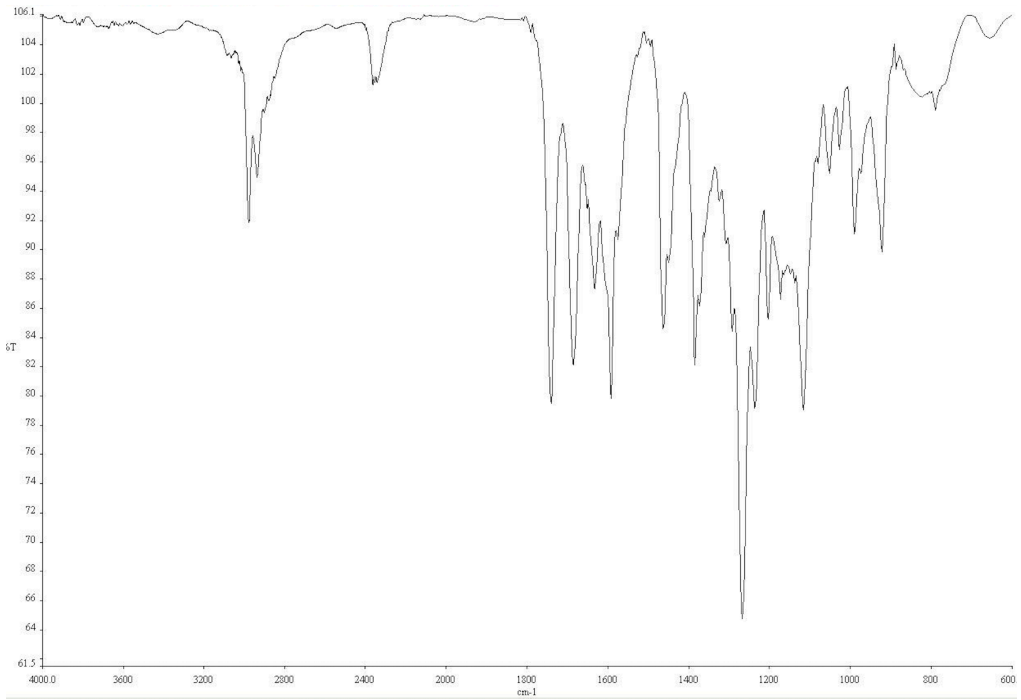


Figure A3.145. *Infrared spectrum (Thin Film, NaCl) of compound* ***142****.*

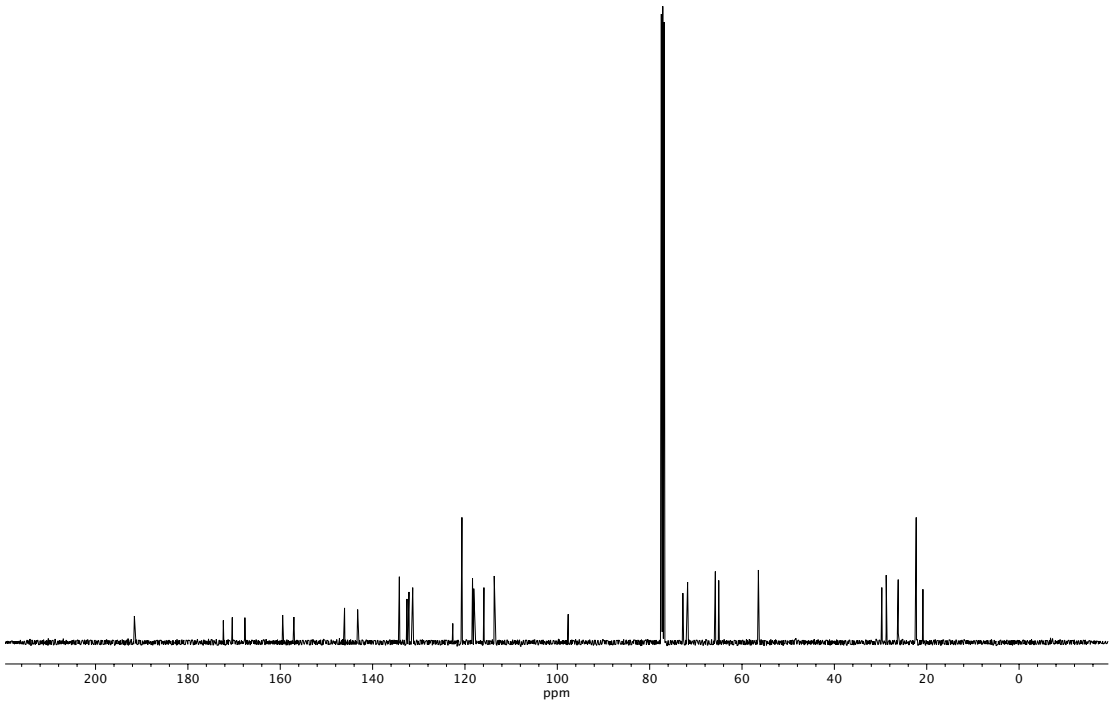


Figure A3.146. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***142****.*

Figure A3.147. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***143***.

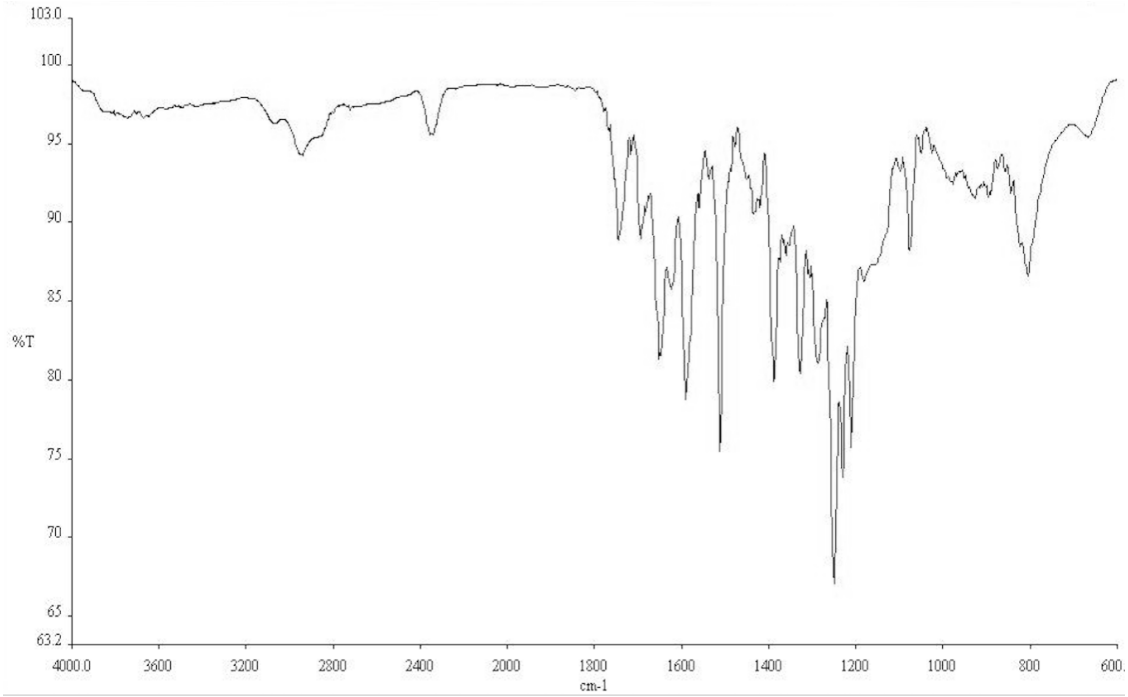


Figure A3.148. *Infrared spectrum (Thin Film, NaCl) of compound* ***143****.*

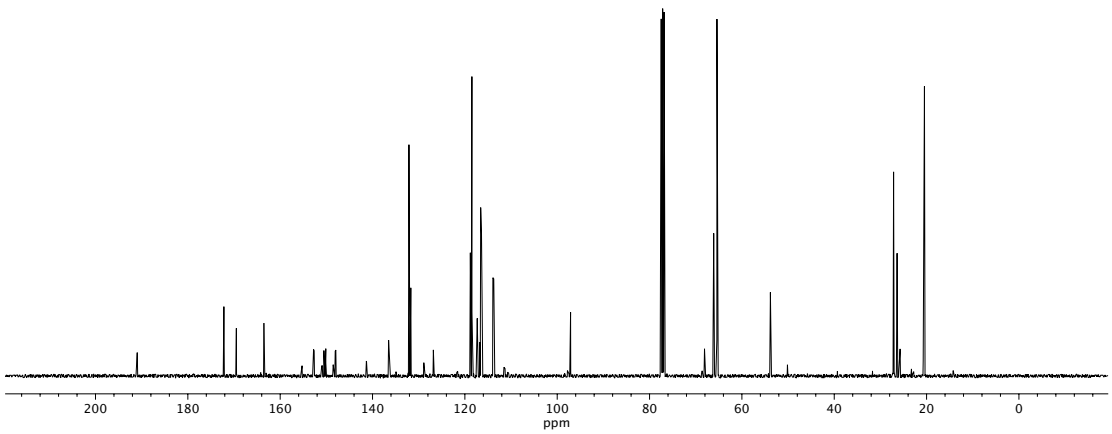


Figure A3.149. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***143****.*

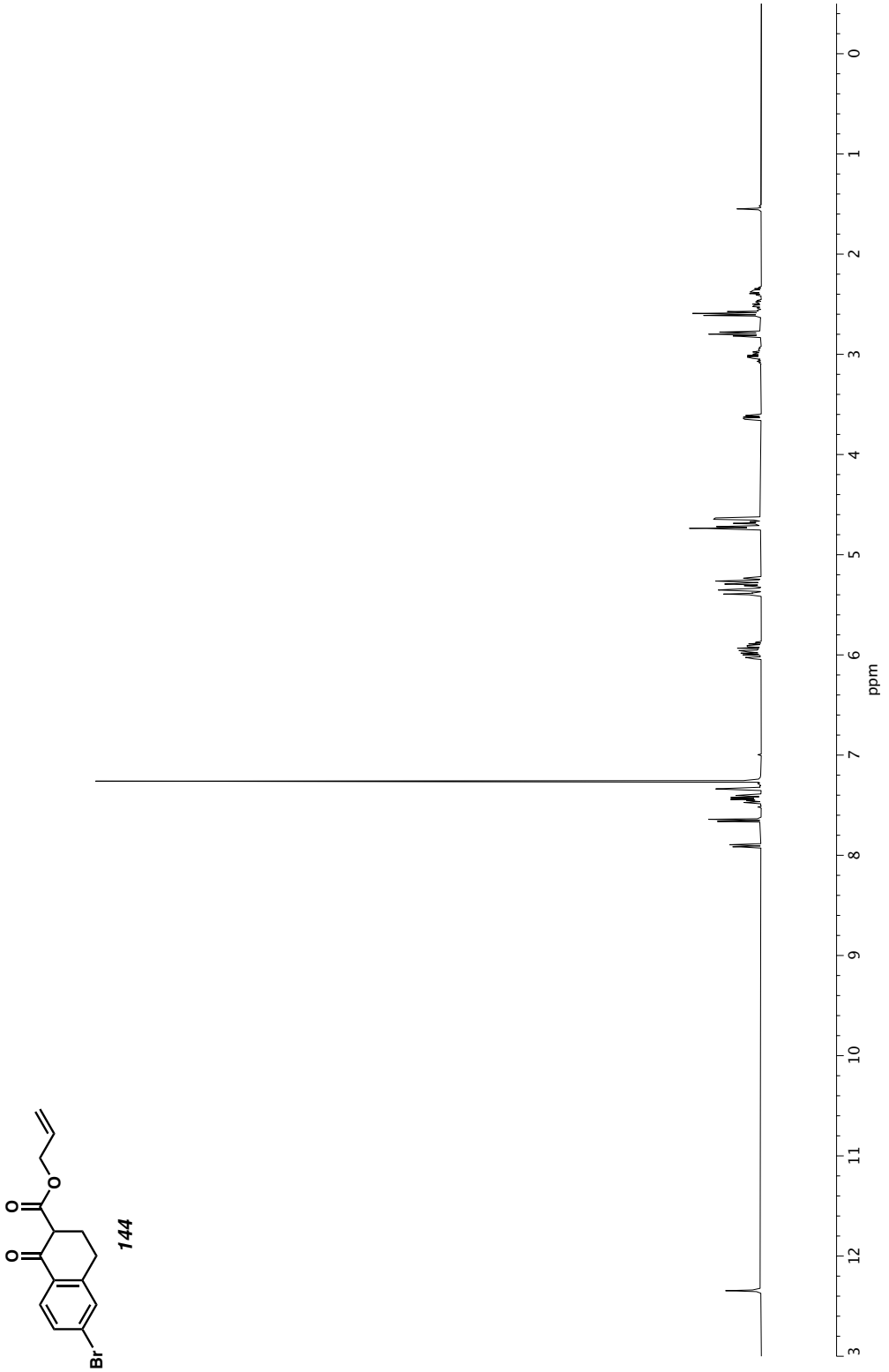


Figure A3.150. *^{1}H NMR (400 MHz, $CDCl_3$) of compound **144**.*

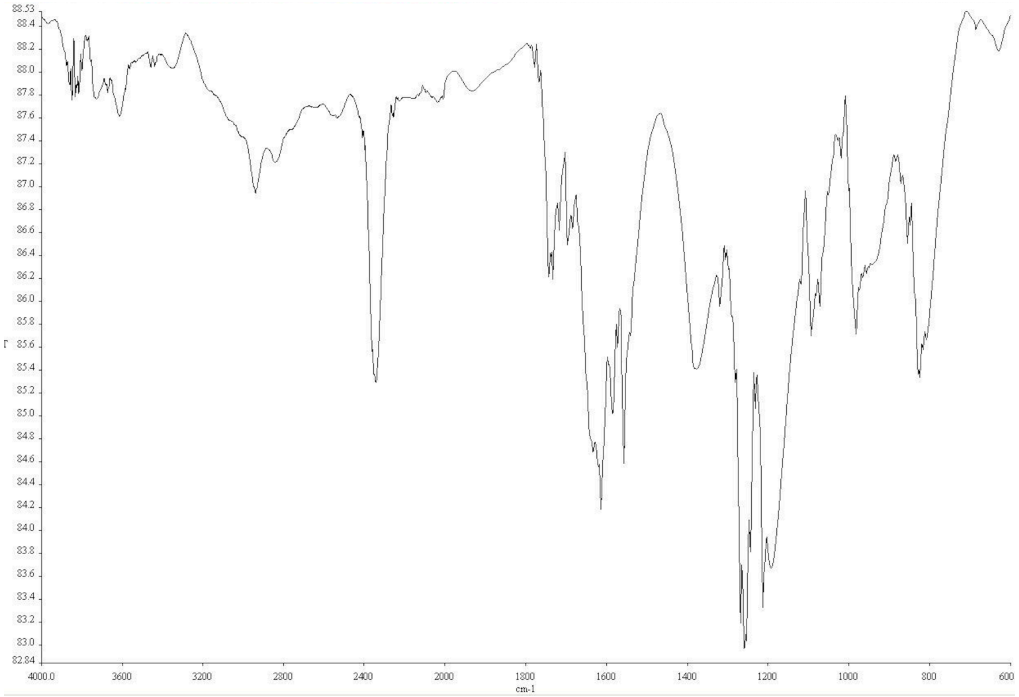


Figure A3.151. *Infrared spectrum (Thin Film, NaCl) of compound* ***144****.*

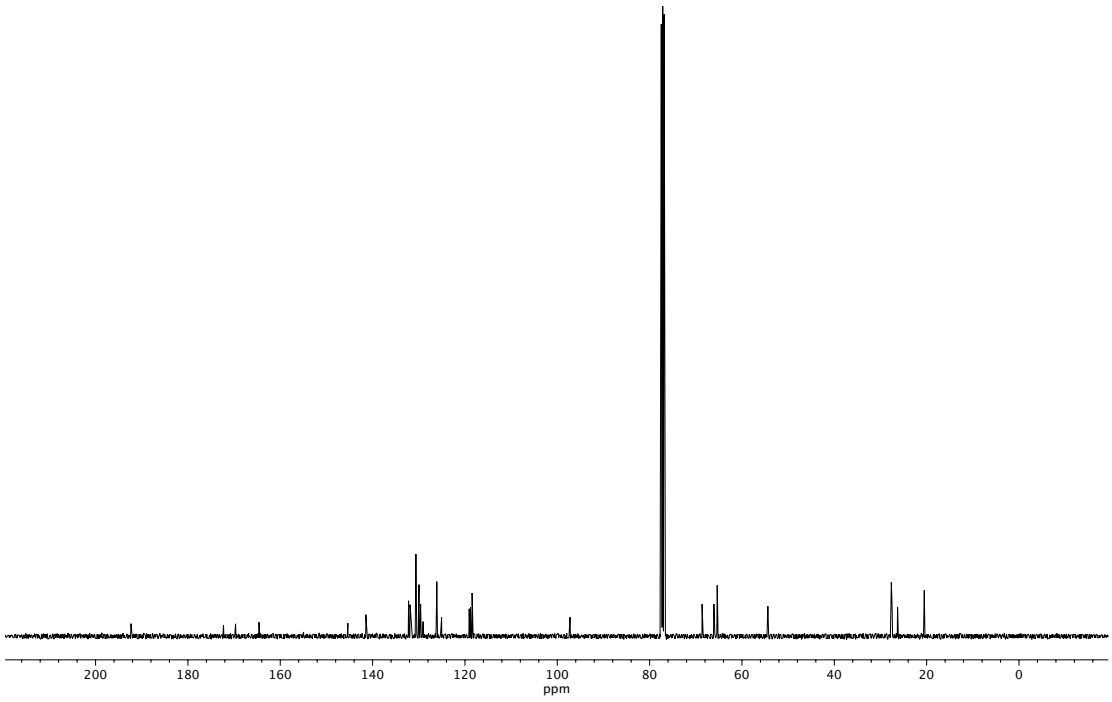


Figure A3.152. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***144****.*

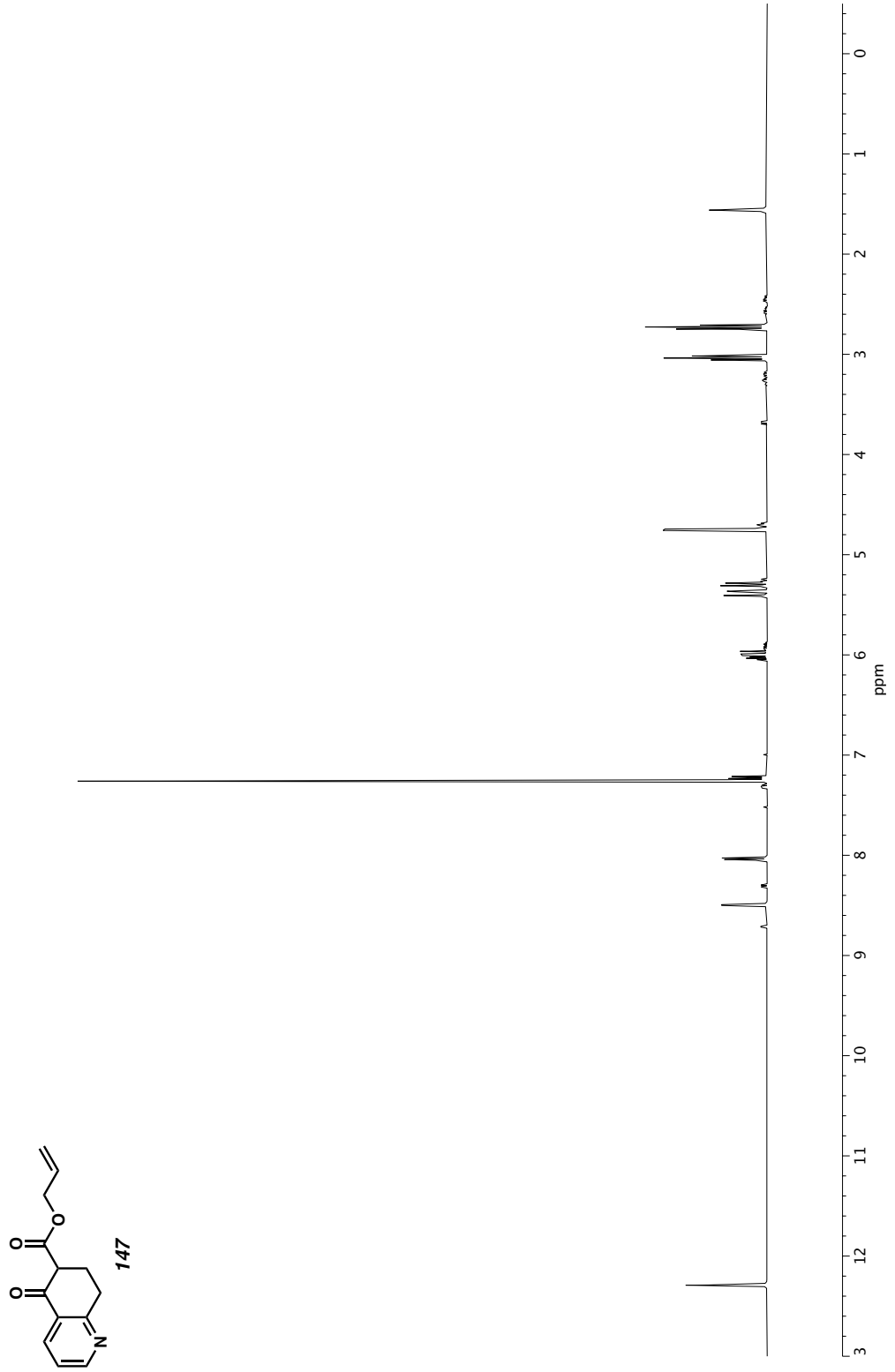


Figure A3.153. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***147****.*

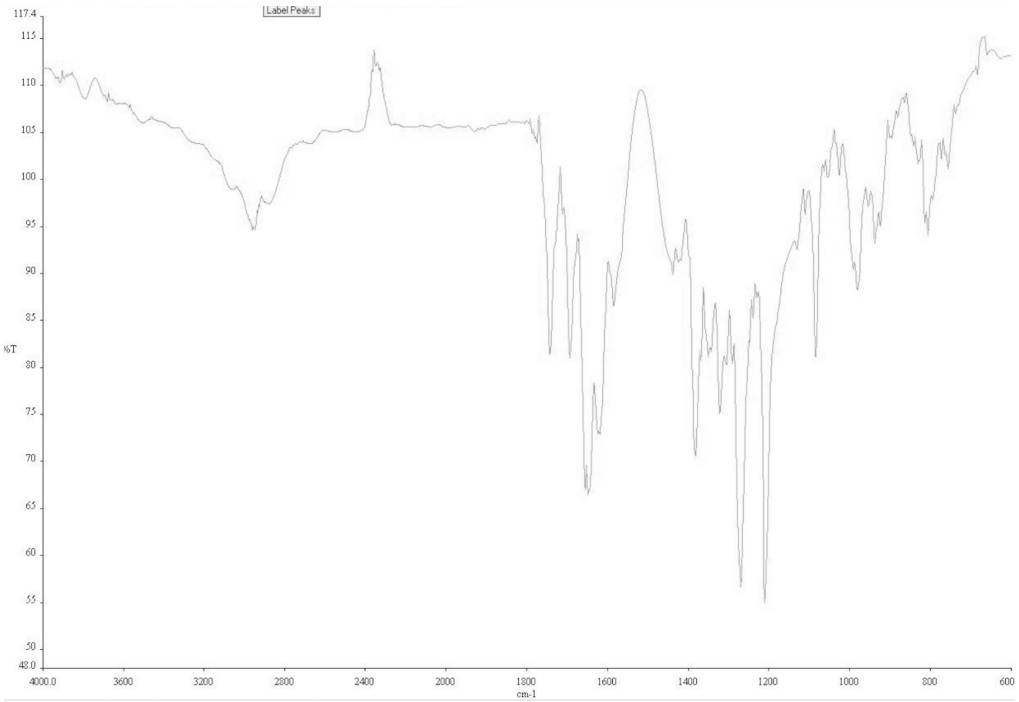


Figure A3.154. *Infrared spectrum (Thin Film, NaCl) of compound* ***147****.*

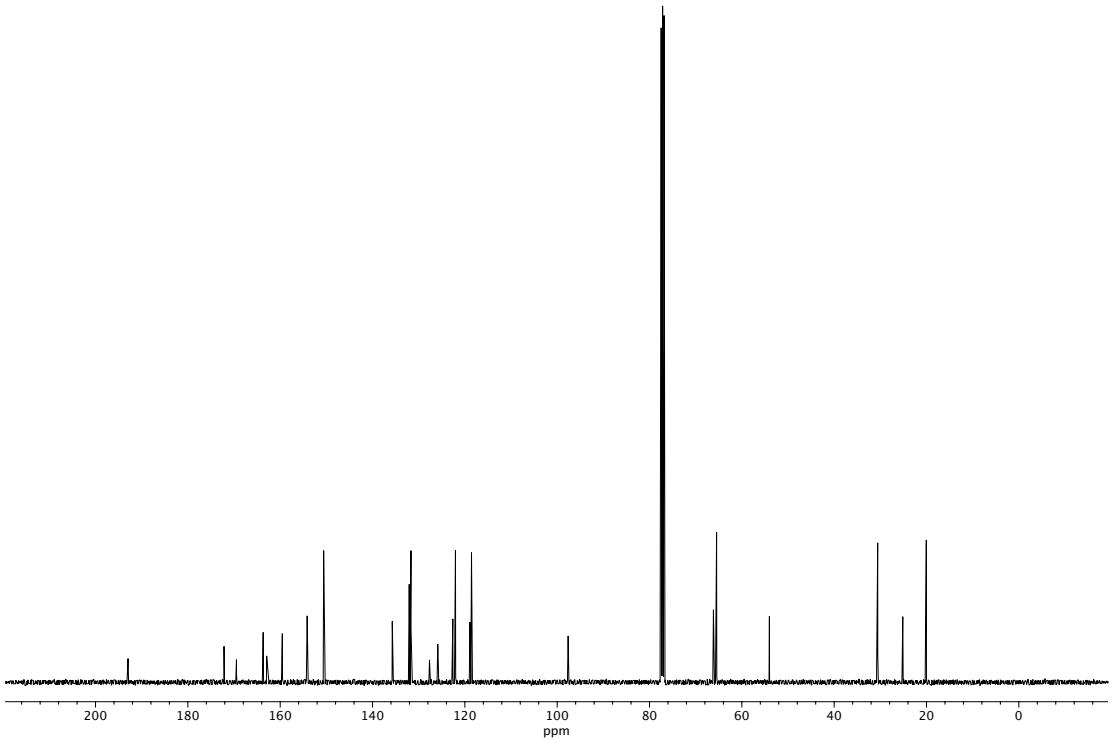


Figure A3.155. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***147****.*

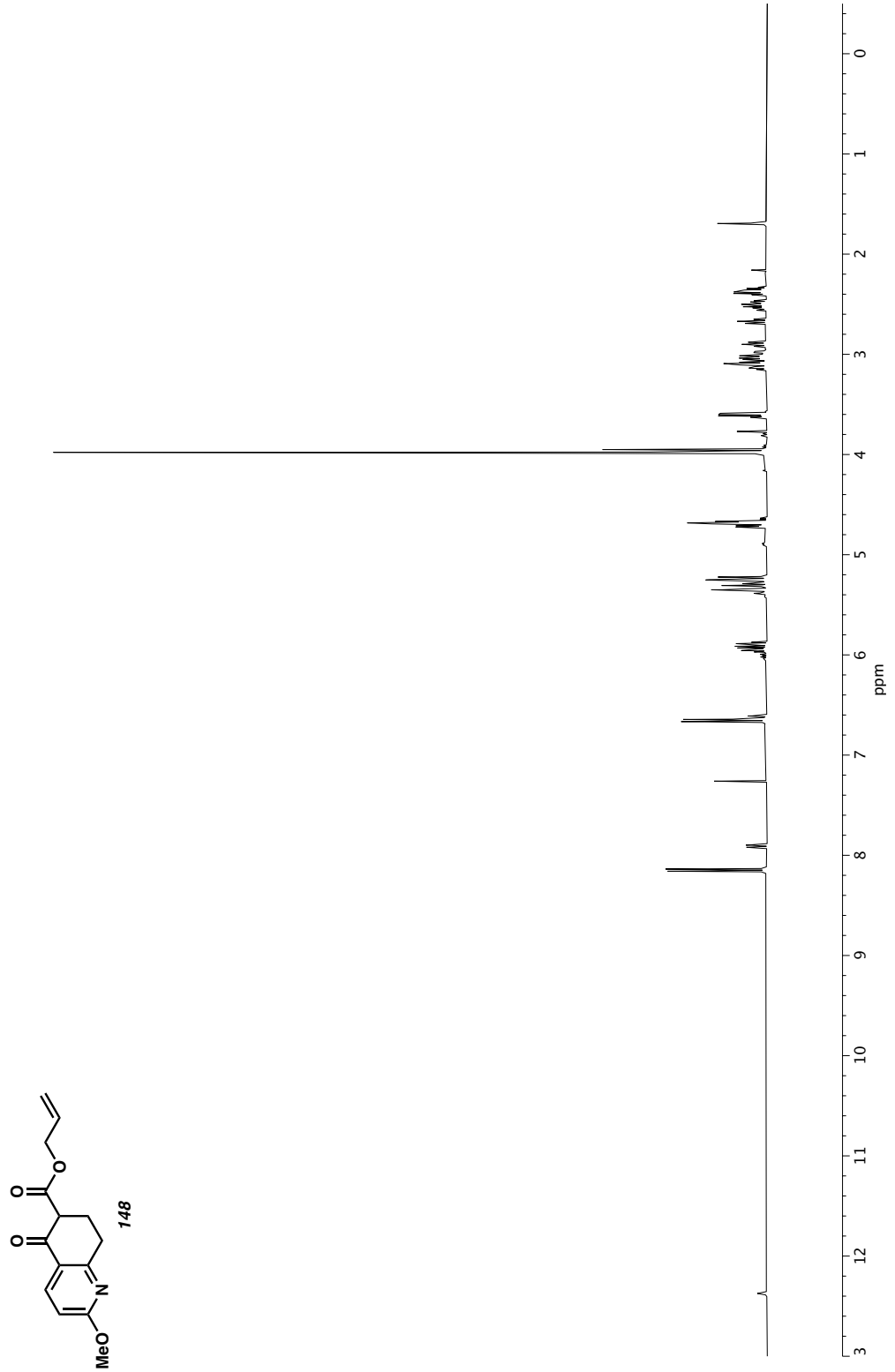


Figure A3.156. *^{1}H NMR (400 MHz, $CDCl_3$) of compound **148**.*

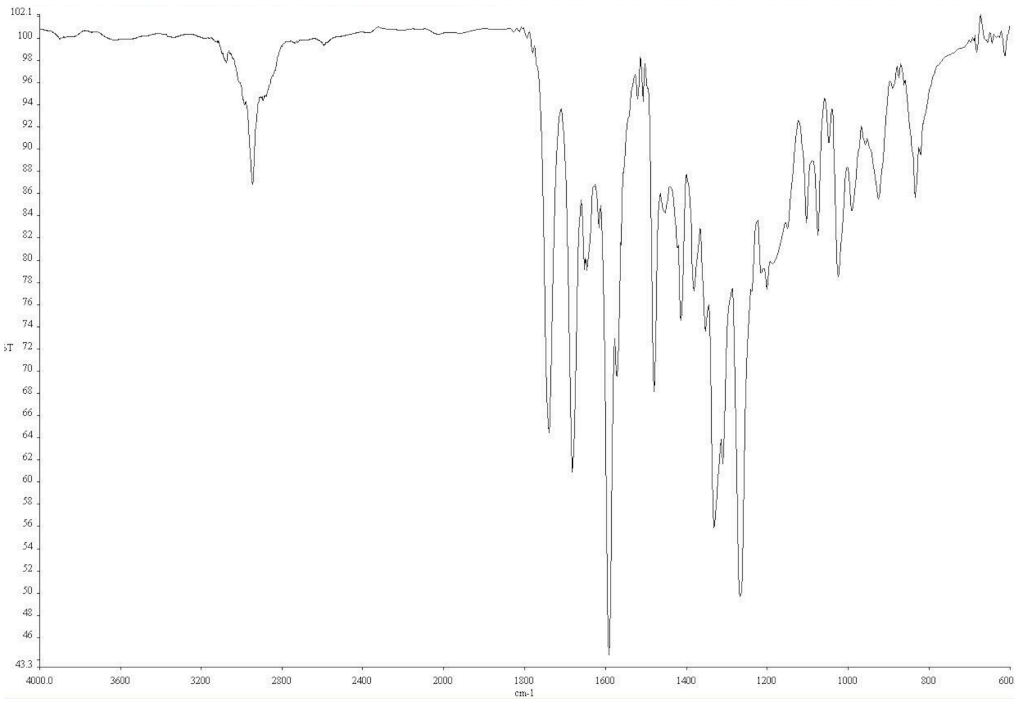


Figure A3.157. *Infrared spectrum (Thin Film, NaCl) of compound* ***148****.*

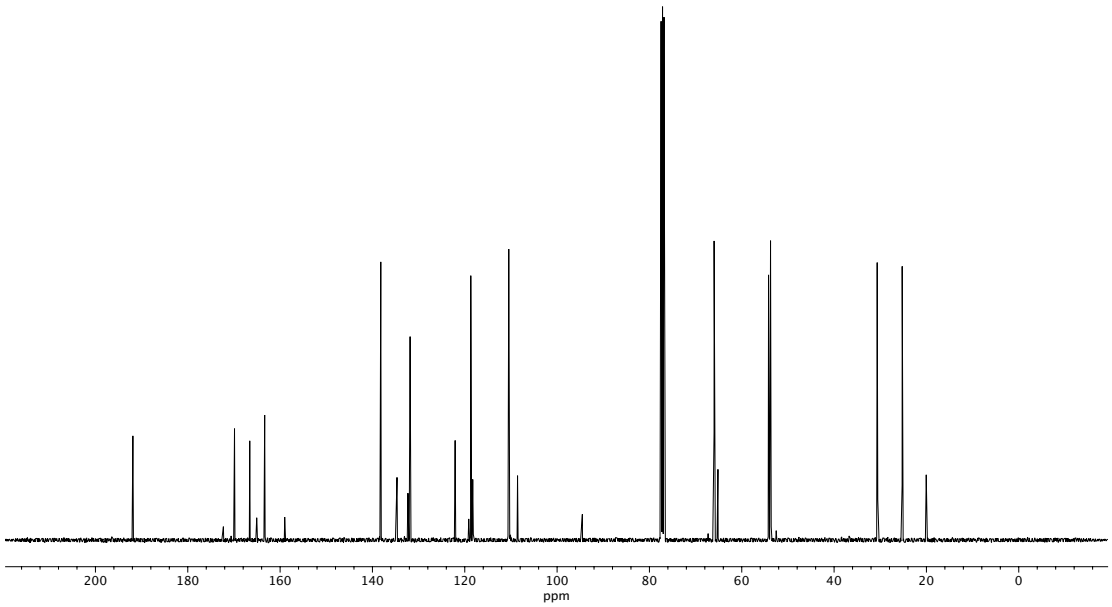


Figure A3.158. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***148****.*

Figure A3.159. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***149***.

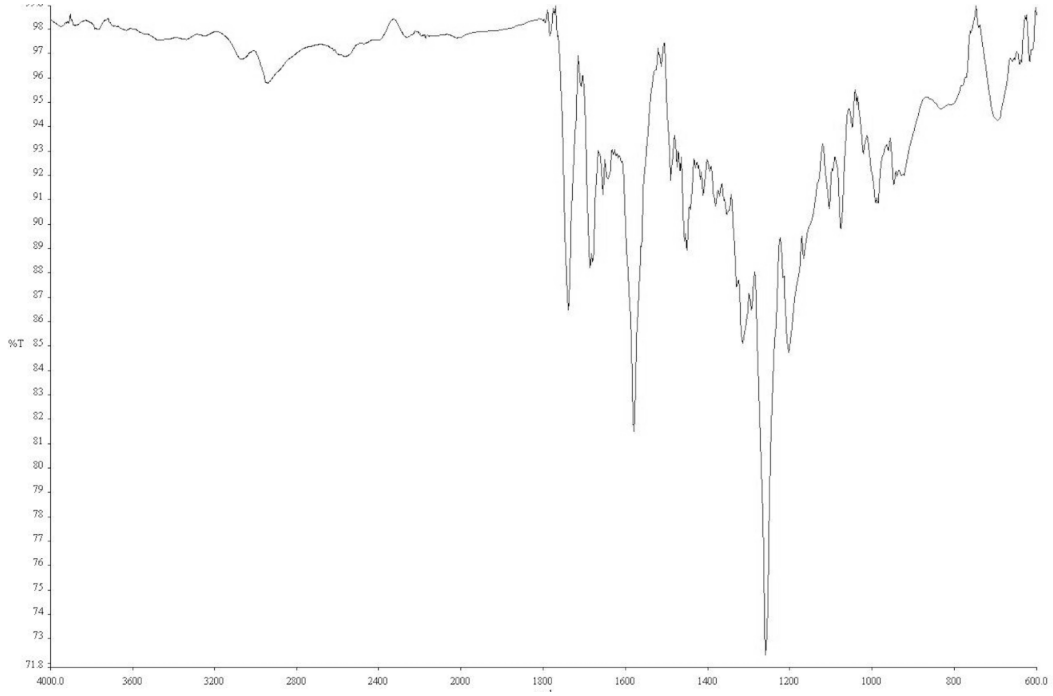


Figure A3.160. *Infrared spectrum (Thin Film, NaCl) of compound* ***149****.*

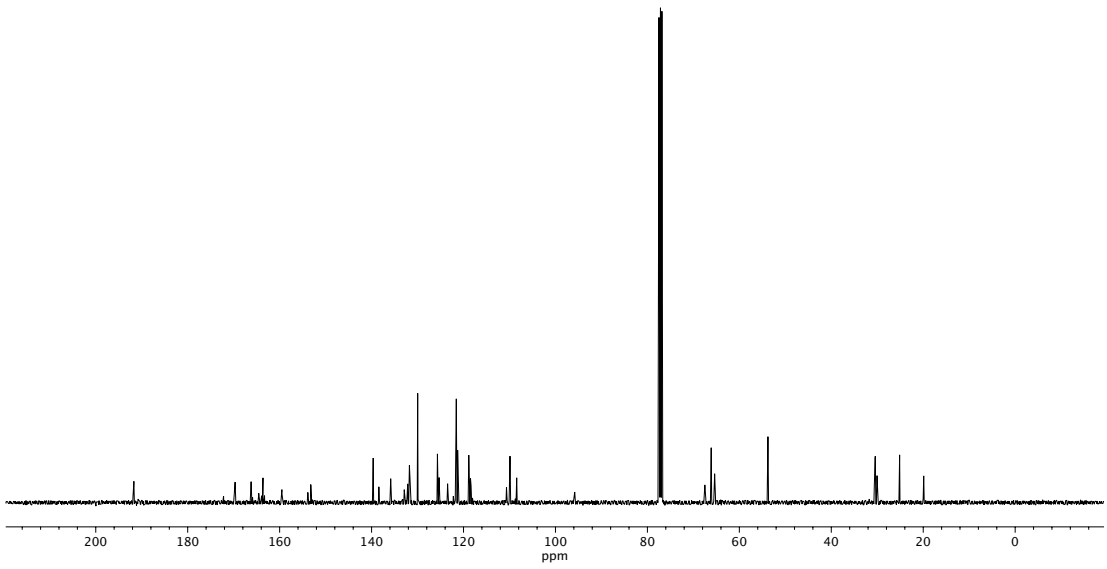


Figure A3.161. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***149****.*

Figure A3.162. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***150****.*

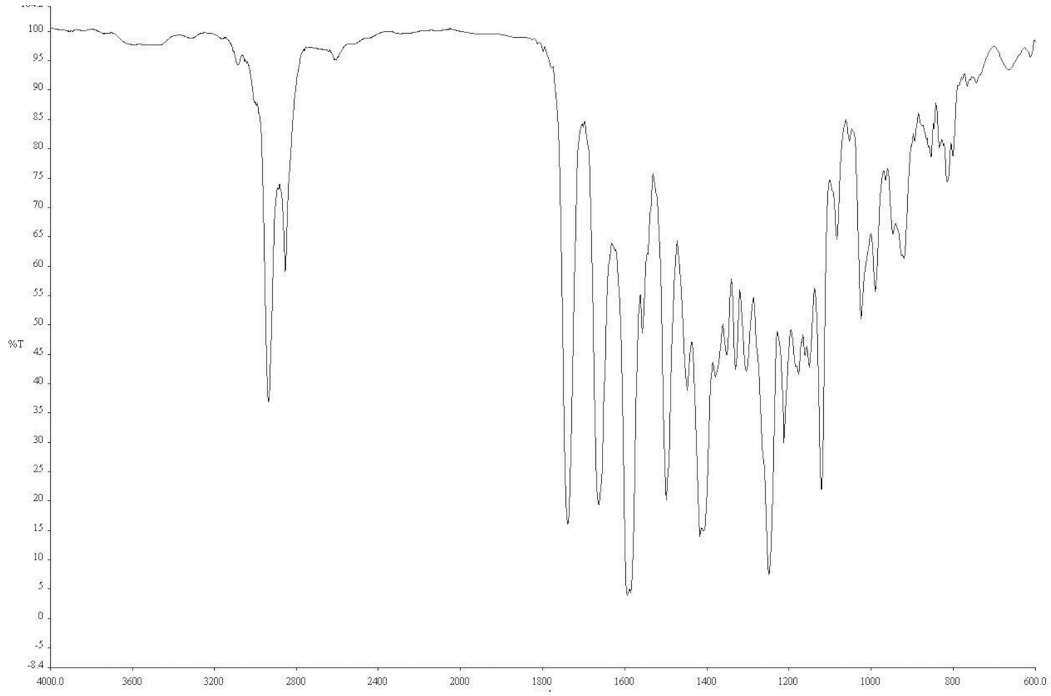


Figure A3.163. *Infrared spectrum (Thin Film, NaCl) of compound* ***150****.*

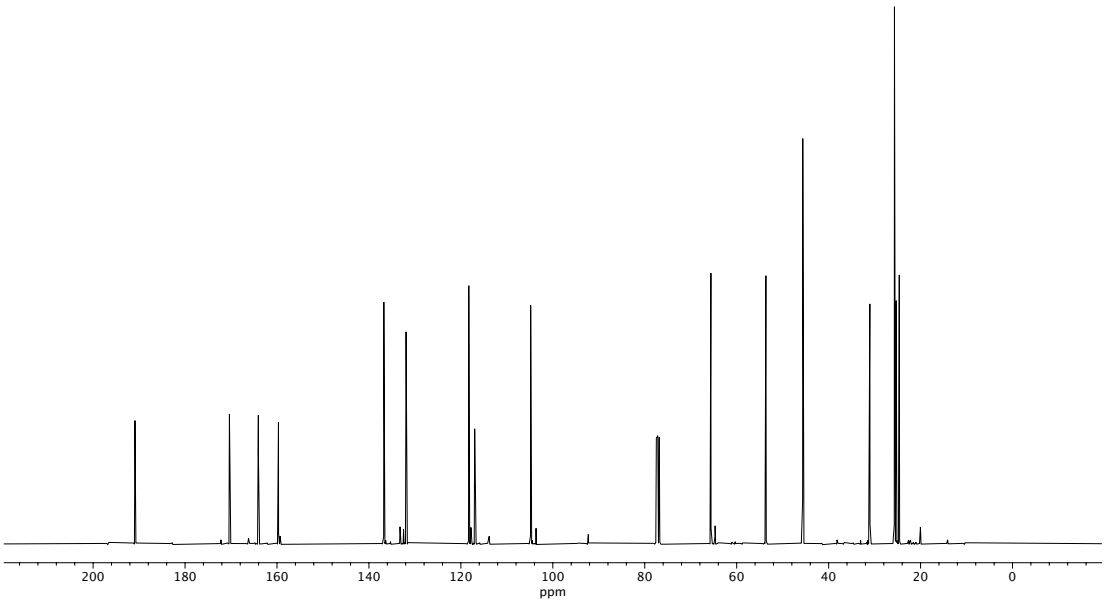


Figure A3.164. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***150****.*

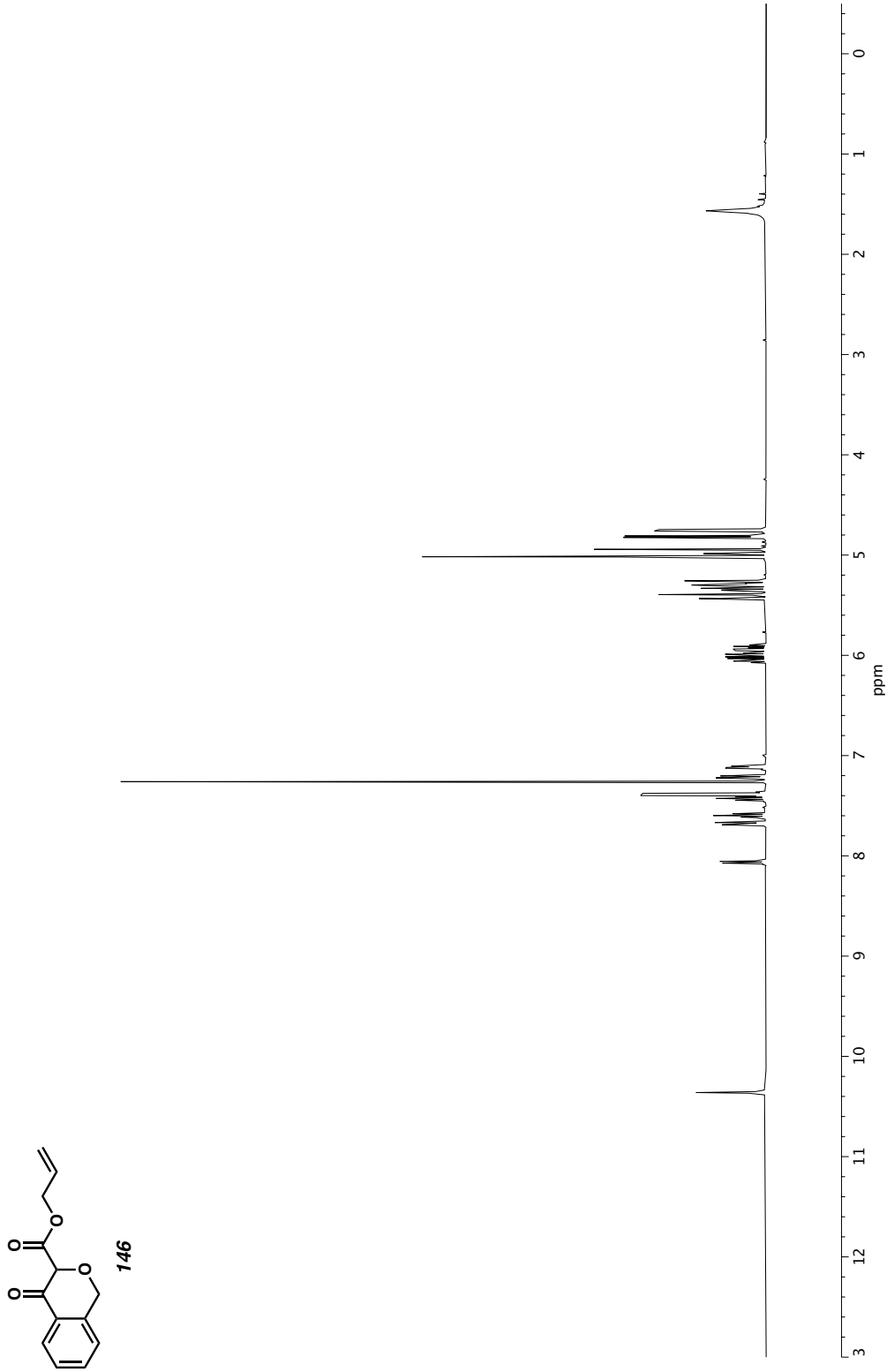


Figure A3.165. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***146****.*

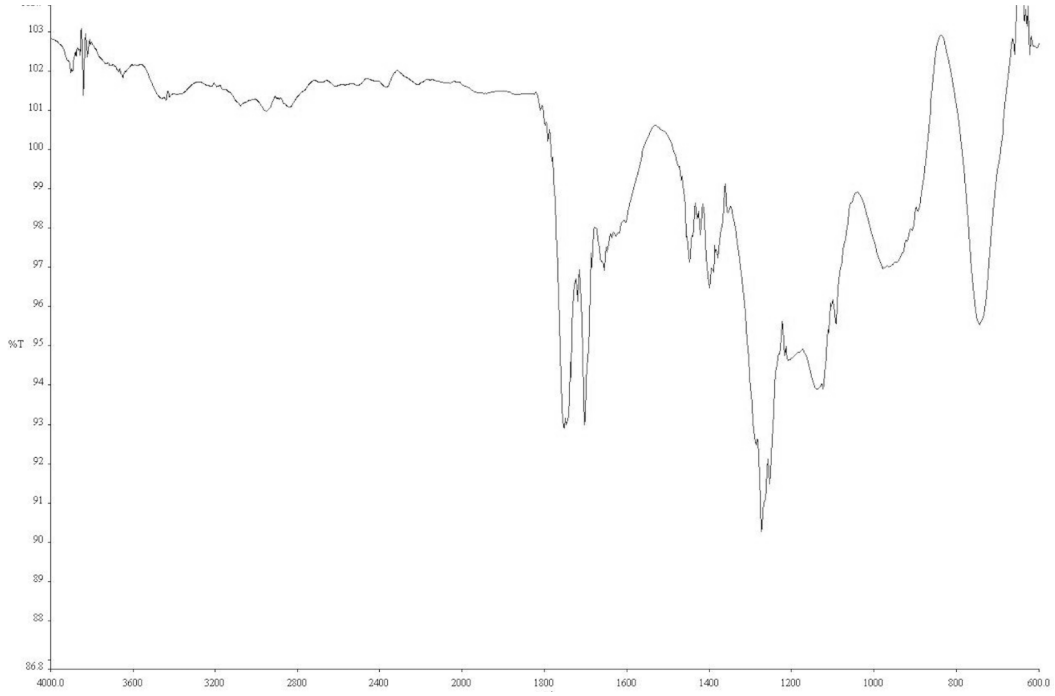


Figure A3.166. *Infrared spectrum (Thin Film, NaCl) of compound* ***146****.*

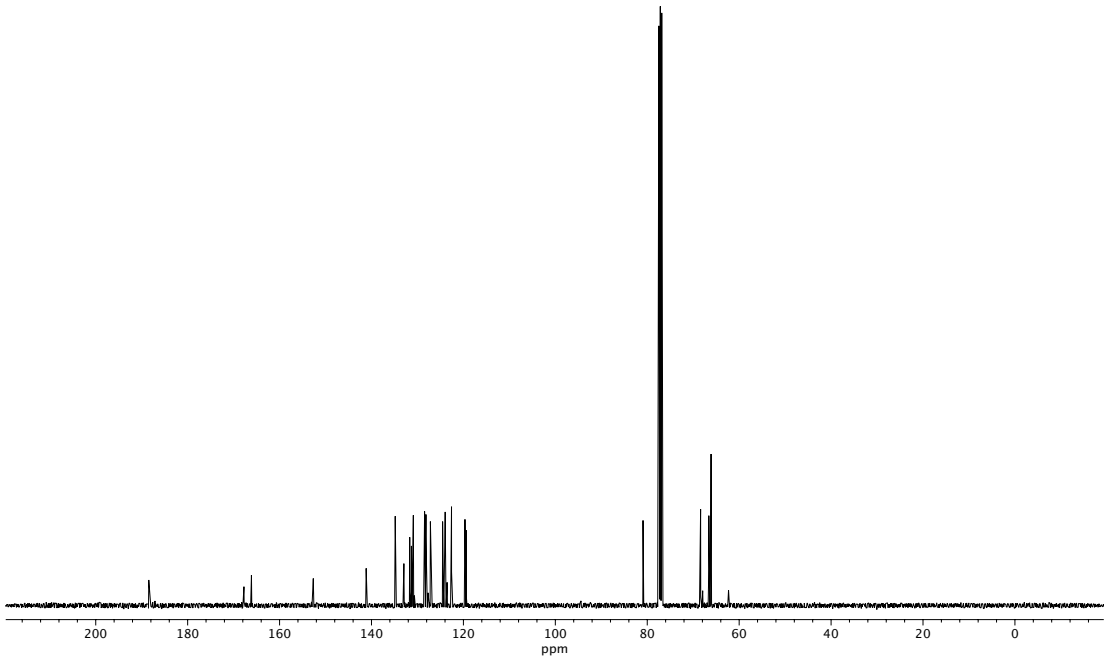


Figure A3.167. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***146****.*

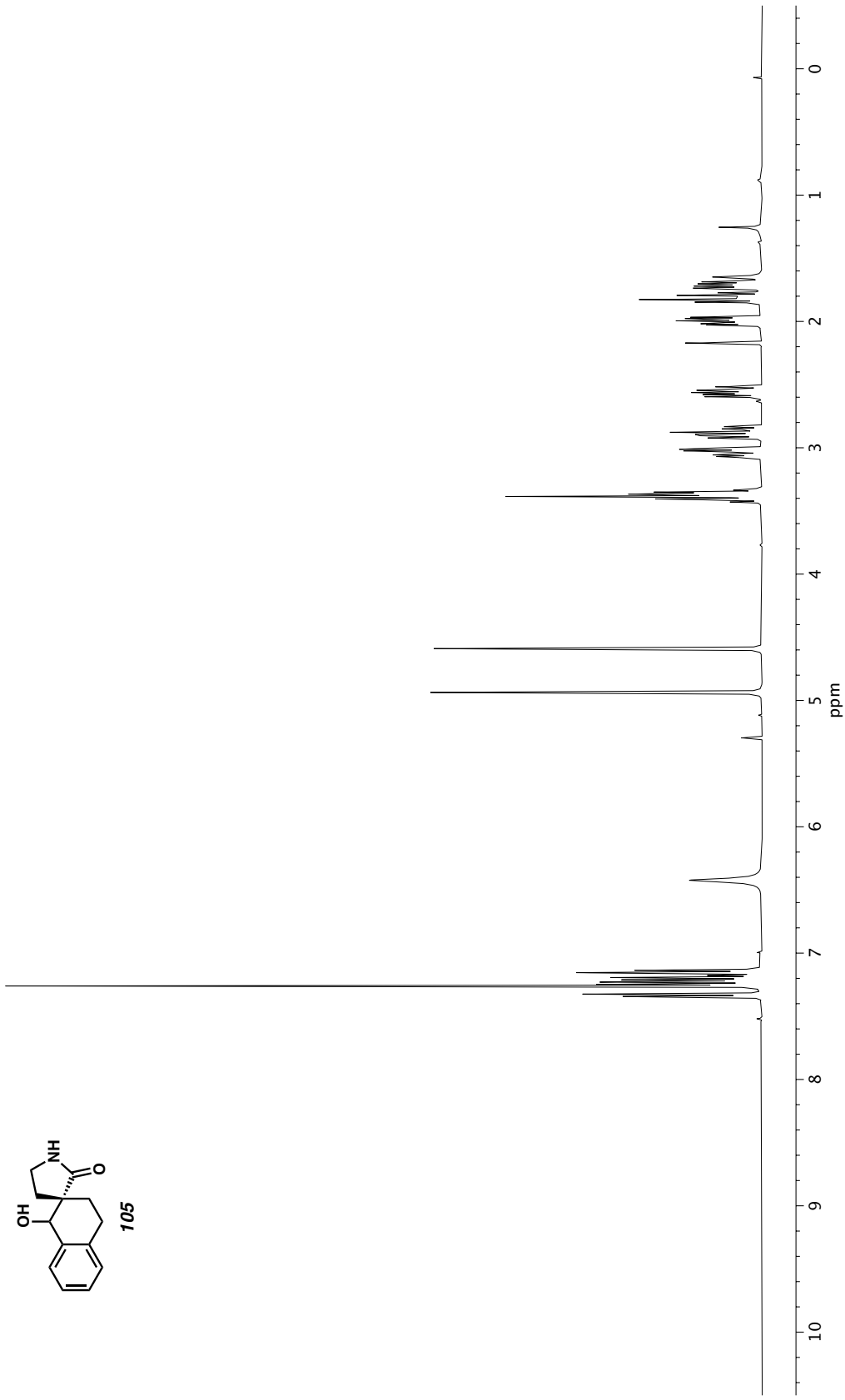


Figure A3.168. *^{1}H NMR (400 MHz, $CDCl_3$) of compound **105**.*

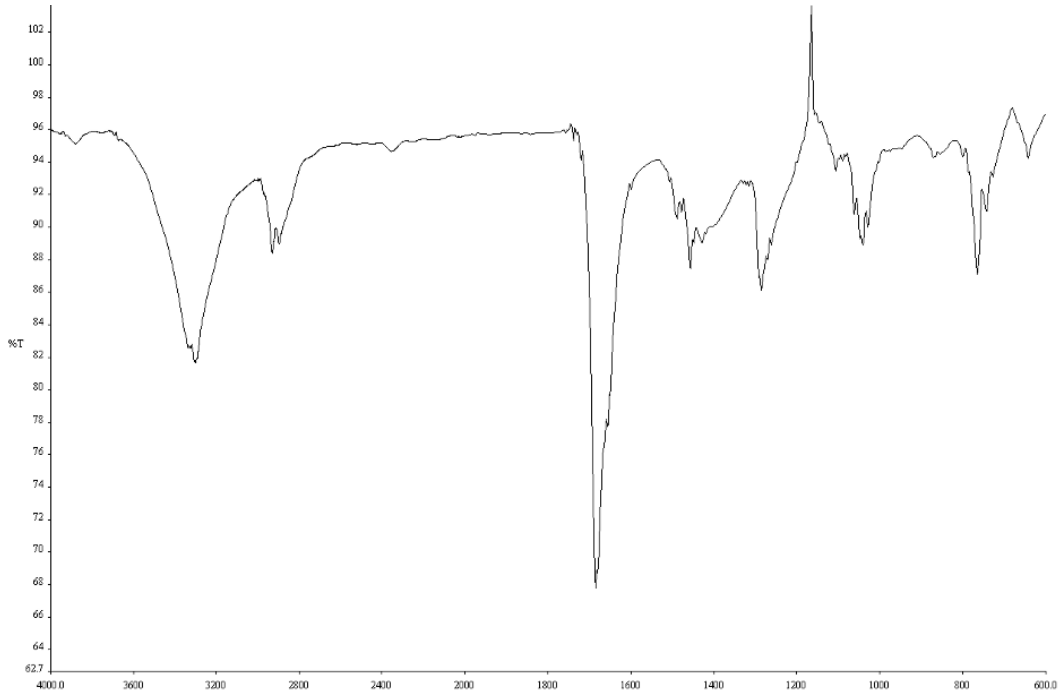


Figure A3.169. *Infrared spectrum (Thin Film, NaCl) of compound* ***105****.*

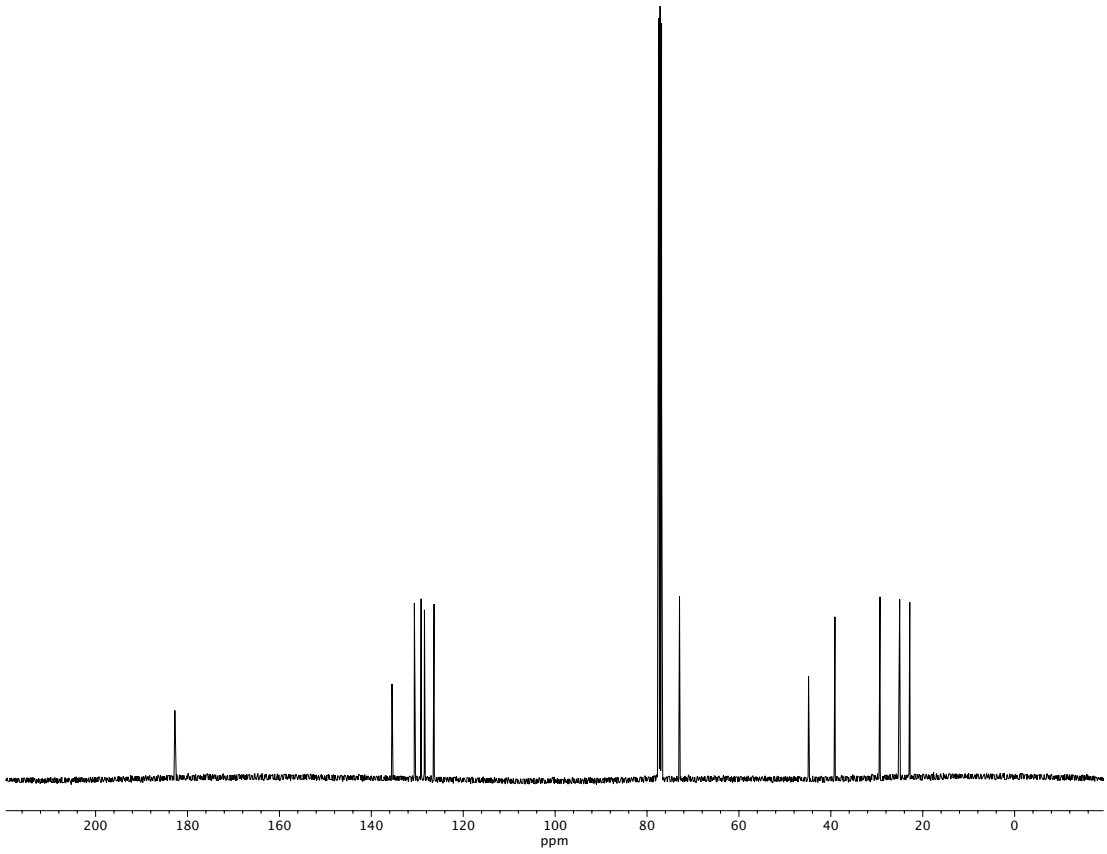


Figure A3.170. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***105****.*

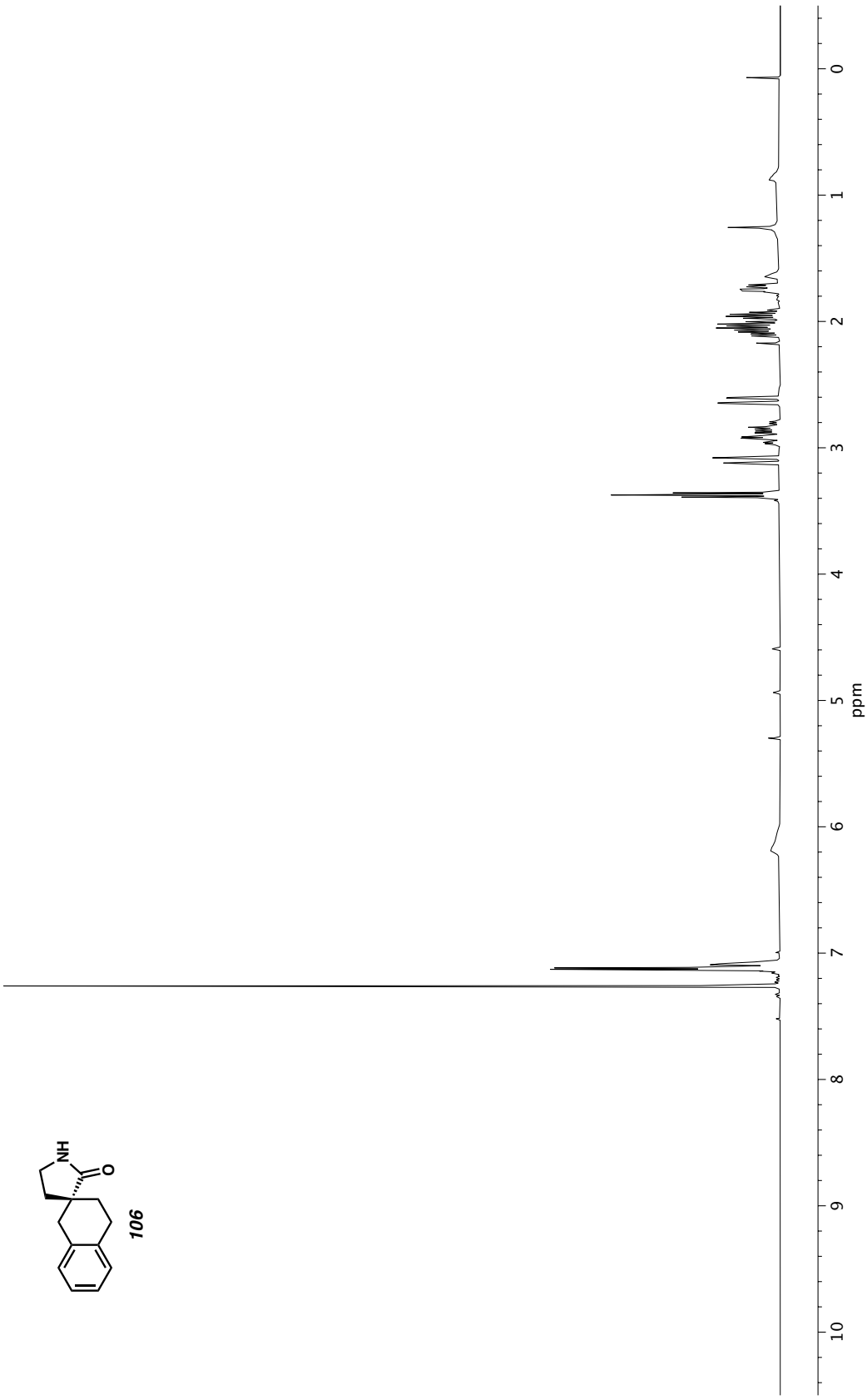


Figure A3.171. *^{1}H NMR (400 MHz, $CDCl_3$) of compound **106**.*

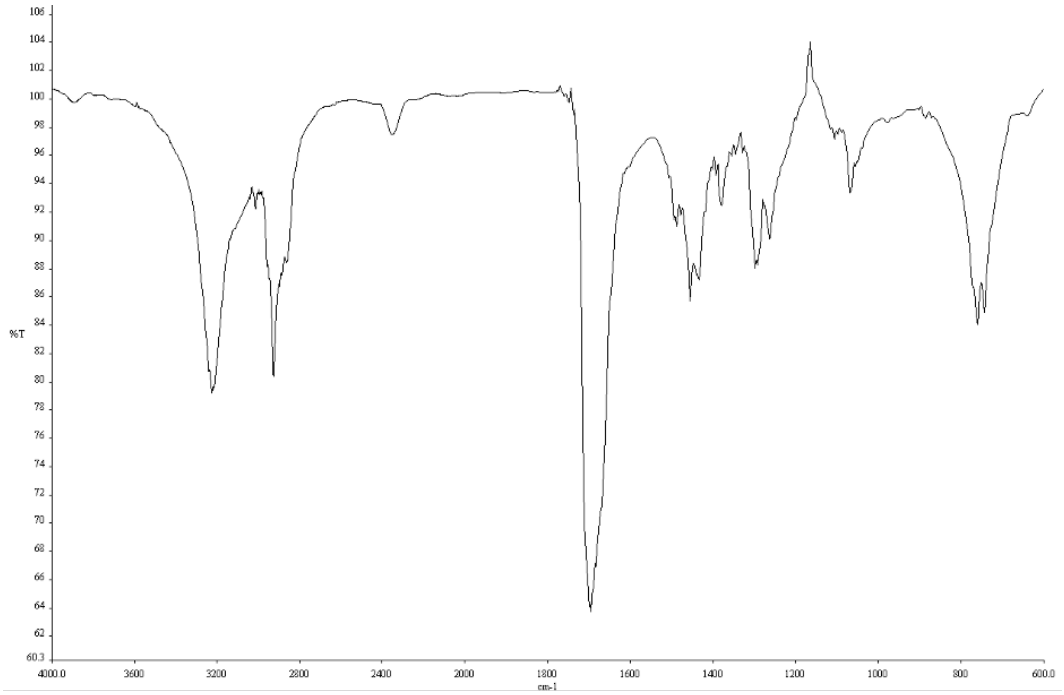


Figure A3.172. *Infrared spectrum (Thin Film, NaCl) of compound* ***106****.*

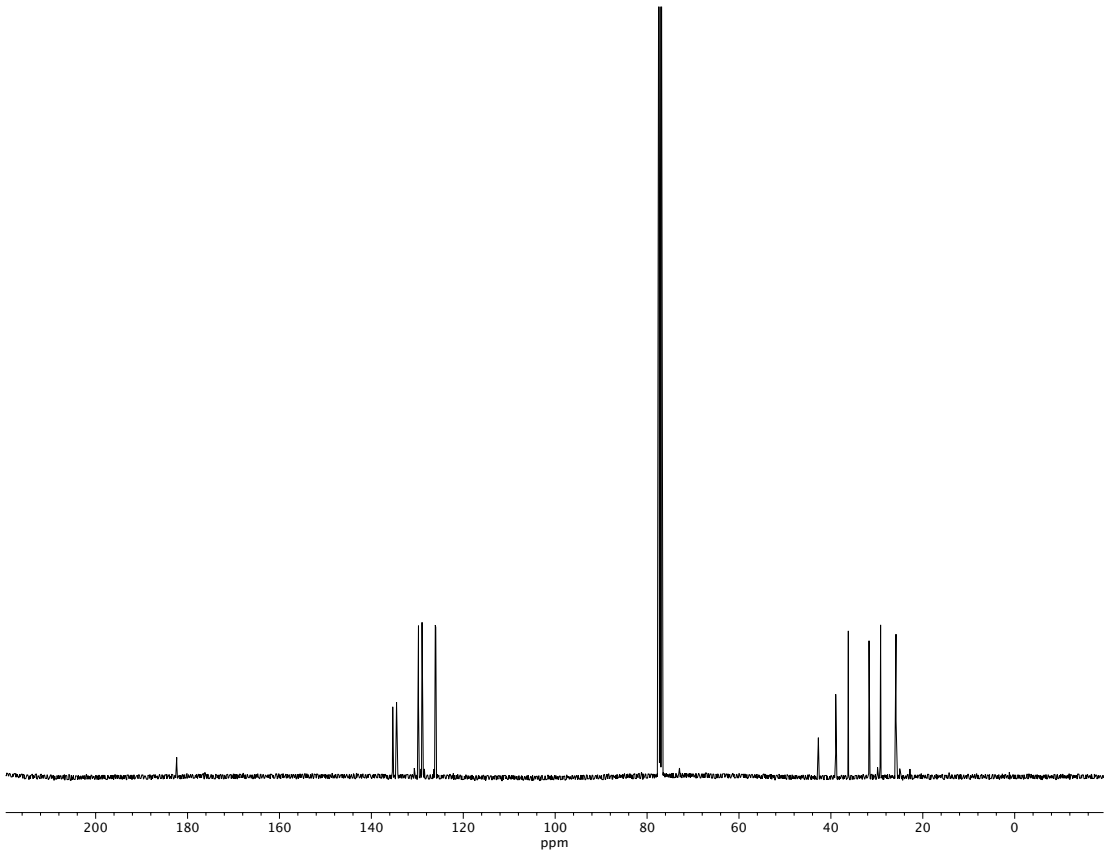


Figure A3.173. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***106****.*

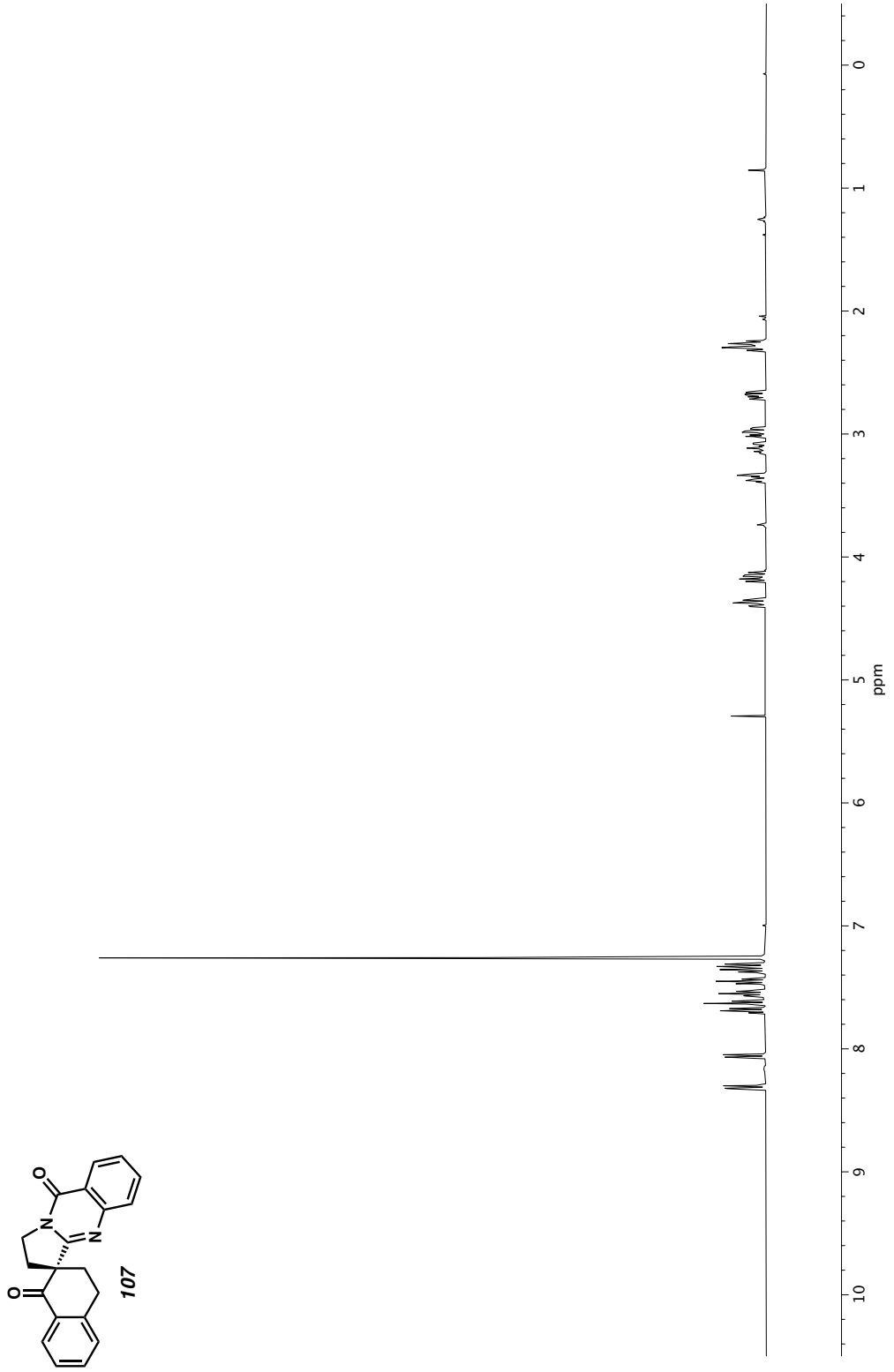


Figure A3.174. *^{1}H NMR (400 MHz, $CDCl_3$) of compound **107**.*

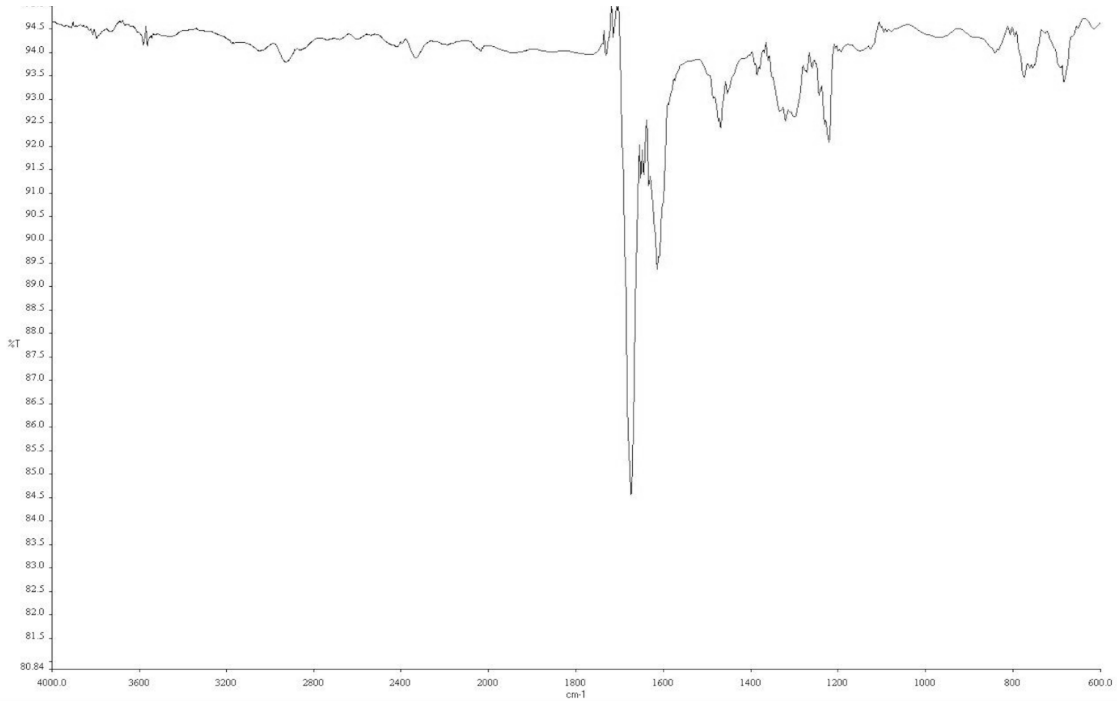


Figure A3.175. *Infrared spectrum (Thin Film, NaCl) of compound* ***107****.*

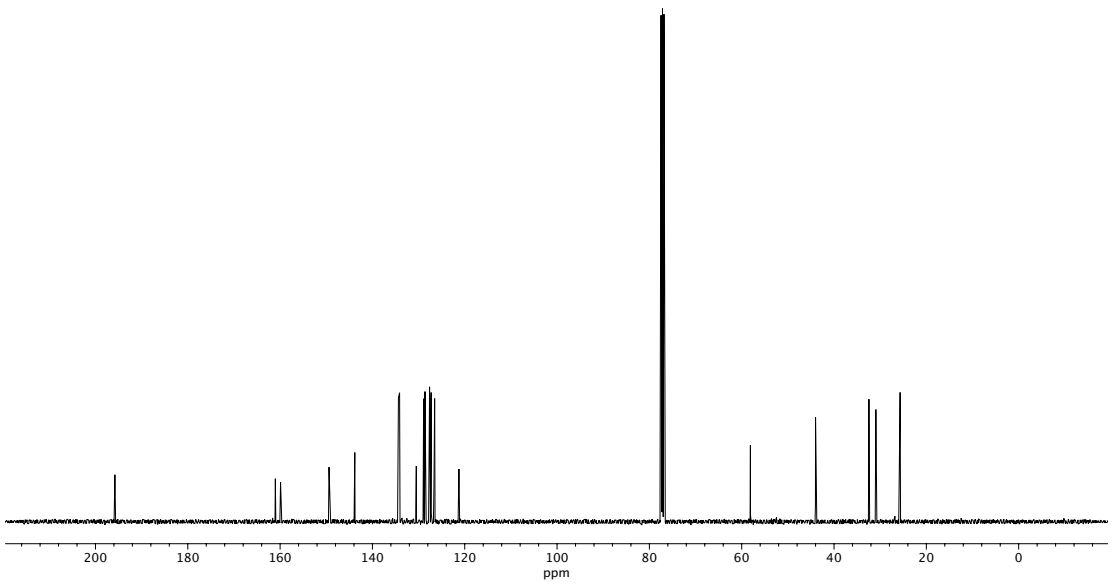


Figure A3.176. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***107****.*

Figure A3.177. *^1H NMR (400 MHz, CD_3OD) of compound* ***108****.*

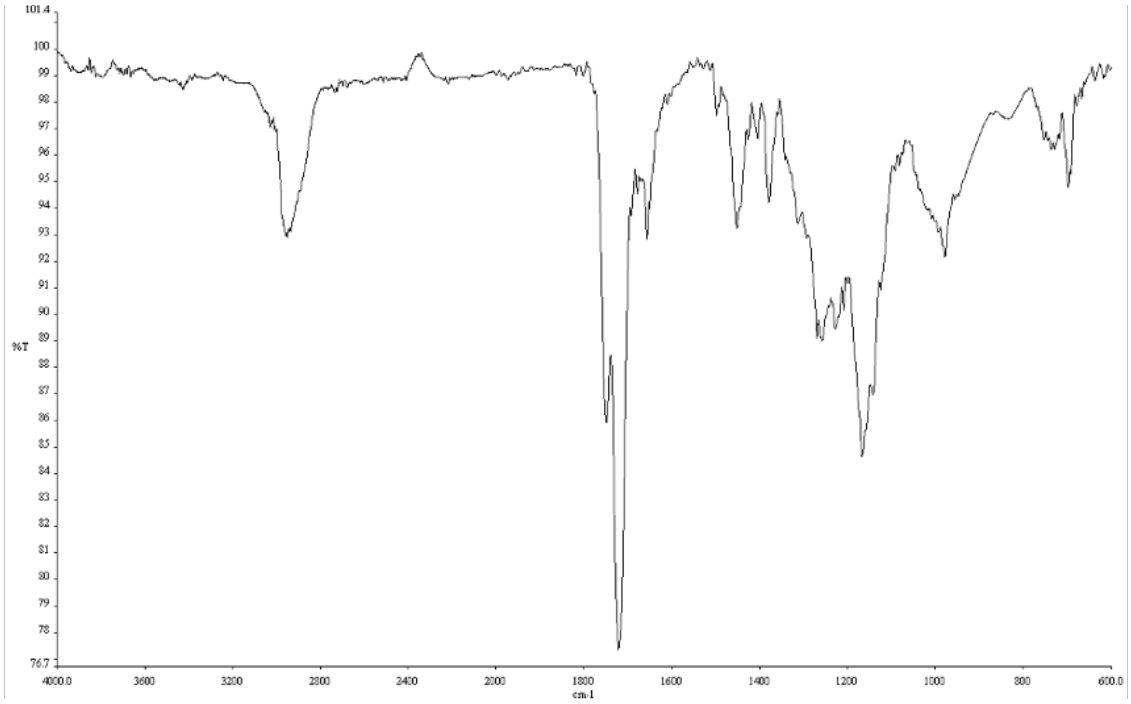


Figure A3.178. *Infrared spectrum (Thin Film, NaCl) of compound* ***108****.*

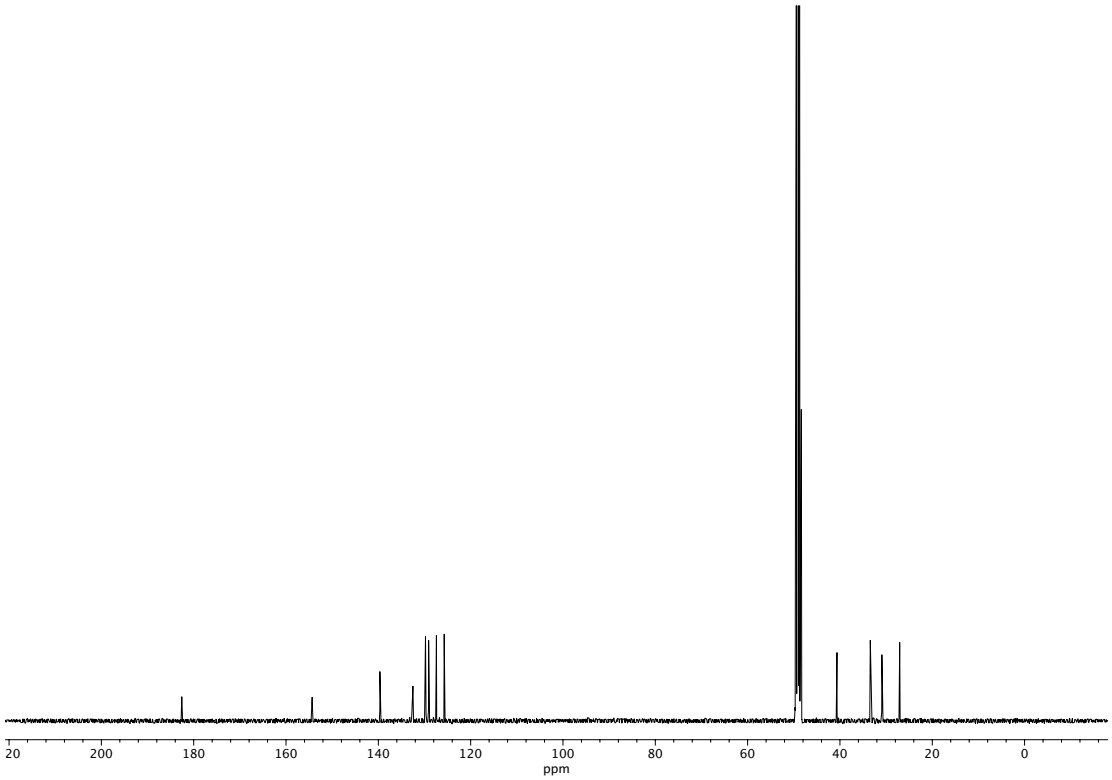


Figure A3.179. *^{13}C NMR (100 MHz, CD_3OD) of compound* ***108****.*

CHAPTER 3

Progress Toward the Total Synthesis of Hypermoin A†

3.1 INTRODUCTION

Within organic chemistry, the total synthesis of natural products is a prominent area of research. Natural product synthesis provides a platform to apply methodologies already developed in complex settings, and challenges encountered during total synthetic endeavors inspire the development of new methods to address limitations in the existing literature. Excitingly, the impacts of natural product total synthesis reach beyond the field of organic chemistry.[1] Natural products often display biological activities that can serve as a starting point for the discovery of new drugs.[2,3] However, isolation of a natural product from its natural source often provides low quantities of the desired compound. This further highlights the value of developing efficient and scalable processes to synthesize natural products from cheap and available materials.[3] Moreover, modular synthetic routes provide a means to access analogs for structural activity-relationship studies.

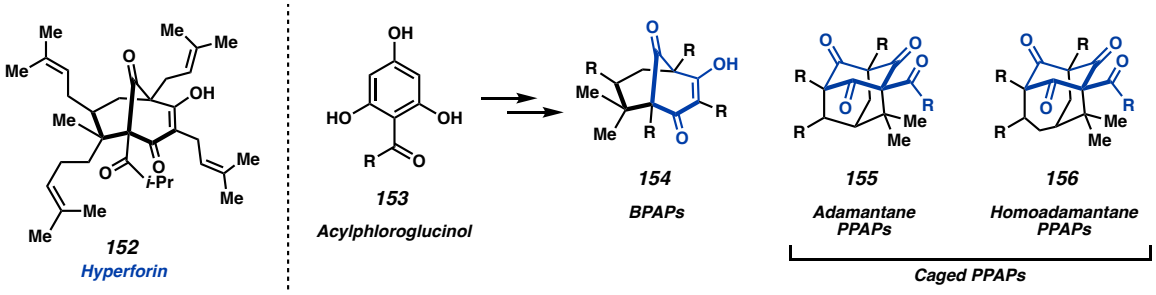
Polycyclic polyprenylated acylphloroglucinols (PPAPs) are a large class of biologically active natural products with over 400 members isolated primarily from the genera *Hypericum* and *Garcinia* (Figure 3.1).[4] In 1971 hyperforin (**152**) was the first PPAP to be isolated.[5] Since its isolation, it was determined that hyperforin is the major antidepressant compound in St. John's wort, and it has been explored for use as an antidepressant drug.[6] Hyperforin has been the target of multiple elegant total syntheses,

†Unpublished research performed in collaboration with Chen, P.-J., Nair, V. N.; Grogan, Z. R.; Ahmad, J; Bottcher, S. E.

highlighting the synthetic interest in these structurally complex bioactive PPAP natural products.[7]

Biosynthetically PPAPs arise from acylphloroglucinols (**153**) and undergo a series of functionalizations to provide a diverse set of structures. Based on structure, PPAPs can be subdivided further into bicyclic polyprenylated acylphloroglucinols (BPAPs), caged PPAPs (**155**, **156**), and other rearranged PPAPs (Figure 3.1).[4a] The bicyclo[3.3.1]nonane BPAPs (**154**) and *seco*-BPAPs represent approximately 60% of known PPAPs and have been the target of many successful syntheses.[4c,7,8] Within the caged PPAP natural product class, there have been three completed syntheses of adamantane PPAPs[9] and only one disclosed synthesis of a homoadamantane PPAP.[10] Furthermore, rearranged PPAPs contain unique structures often with highly oxidized polycyclic scaffolds and multiple syntheses of compounds within this subclass have been achieved.[11]

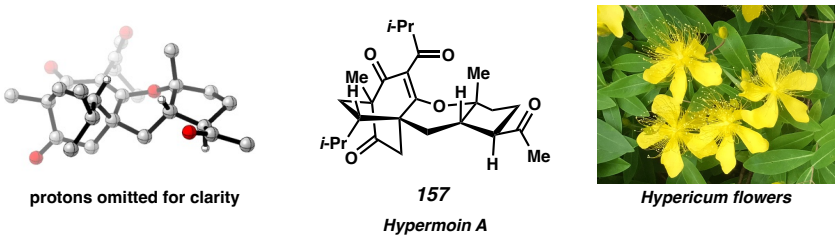
Figure 3.1. *PPAP natural products.*



We are particularly interested in rearranged PPAPs as their unique structural features present new challenges not addressed in the current literature. The approaches previously used in total synthetic endeavors toward other PPAPs often do not lend

themselves well to these rearranged PPAPs due to their uncommon structures. Therefore, these systems represent an exciting manifold to explore new synthetic strategies. To this end, we identified rearranged norPPAP hypermoin A (**157**), isolated in 2021 from the flowers of *Hypericum monogynum*, as an appealing target (Figure 3.2).[12] **157** contains a bicyclo[3.2.2]nonane fused to a 6/5 polycyclic skeleton that is unprecedented in PPAP natural products. It is decorated with six stereocenters including two all-carbon quaternary stereocenters. In preliminary biological testing hypermoin A demonstrated reversal of multidrug resistance activity in HepG2/ADR and MCF-7/ADR cancer cell lines.

Figure 3.2. *Hypermoin A.*

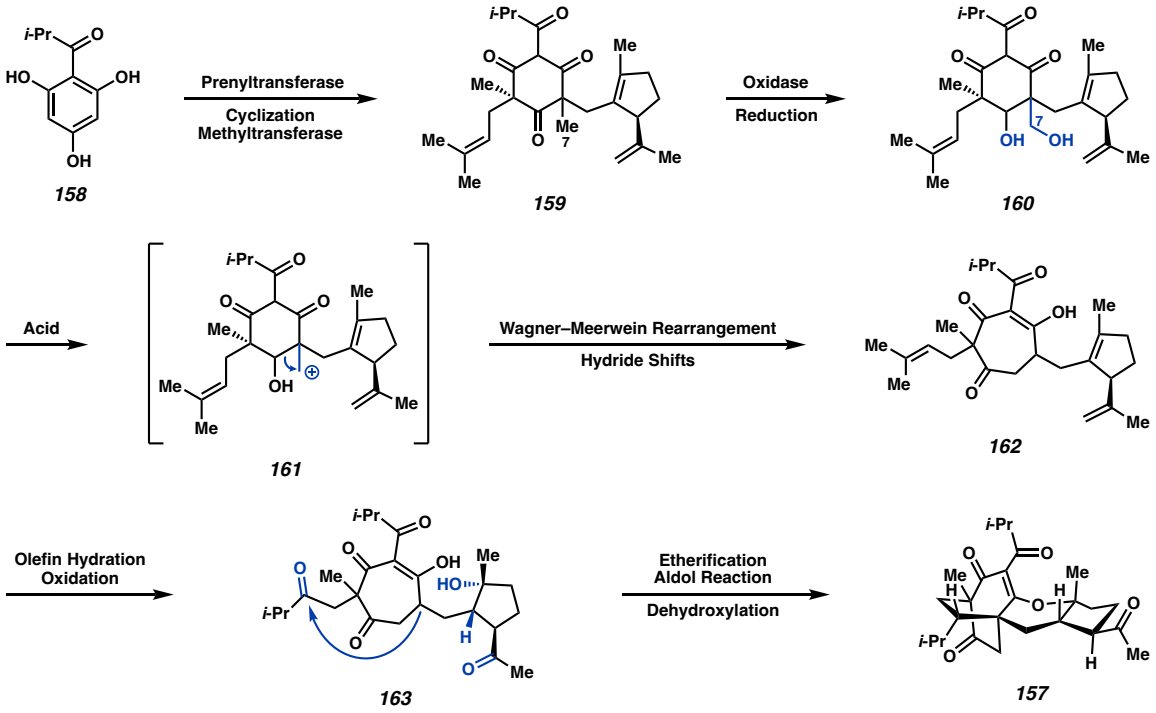


- Rearranged norPPAP with a novel tetracyclic skeleton
- Contains six stereocenters including two quaternary stereocenters
- Rare bicyclo[3.2.2]nonane core

The proposed biosynthesis of **157** begins from acylphloroglucinol **158** which undergoes prenylation, cyclization, and installation of two methyl groups to yield **159** (Scheme 3.1).[12] Oxidation of the methyl group at C-7 and reduction of one ketone forges diol **160**. A Wagner–Meerwein rearrangement and hydride shifts result in the ring expanded 7-membered ring (**162**). Final olefin hydration and oxidation events forming **163** are followed by an etherification to form the central tetrahydropyran ring. An

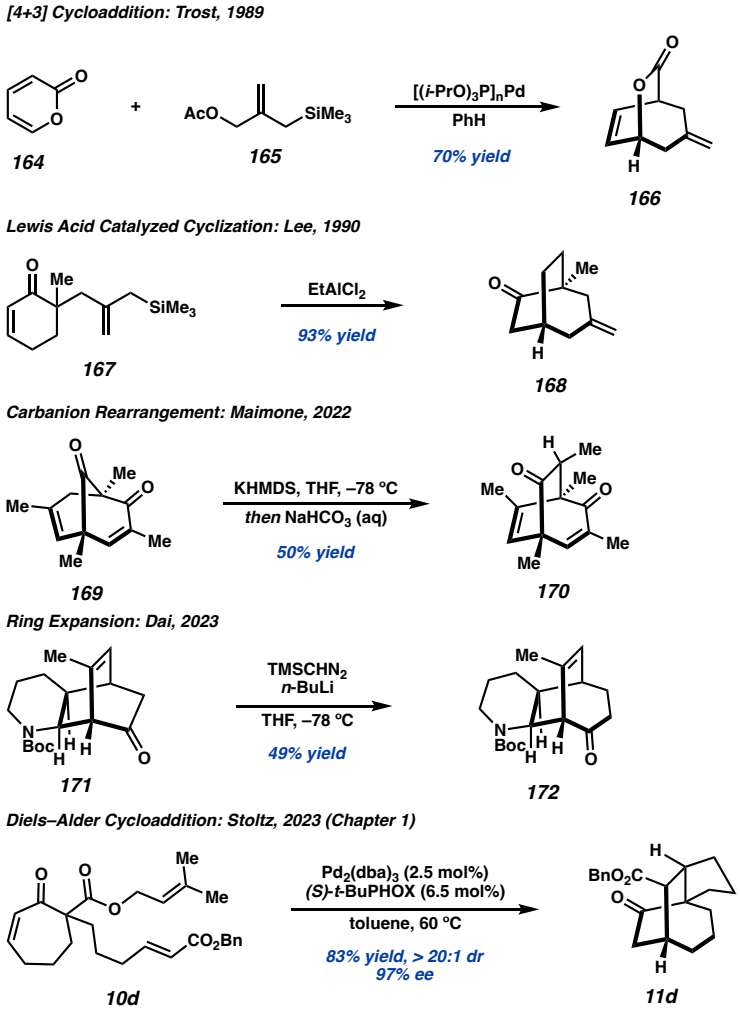
intramolecular aldol reaction forges the [3.2.2] bicycle, and finally, dehydroxylation yields natural product **157**.

Scheme 3.1. *Proposed biosynthesis.*



A key challenge in the total synthesis of **157** is the construction of the [3.2.2] bicyclic core. While this is an uncommon ring system in PPAP natural products, related carbonyl containing [3.2.2] bicycles have been previously synthesized (Scheme 3.2). Trost and coworkers reported an intermolecular Pd catalyzed [4+3] cycloaddition with pyrones (**164**) to yield a [3.2.2] bicycle containing a lactone bridge (**166**) in 70% yield.[13] Additionally, an intramolecular Lewis acid catalyzed cyclization was disclosed in 1990 by Lee.[14] An enone containing a tethered allyl silane (**167**) was subjected to $EtAlCl_2$ forming bridged bicycle **168** via a 7-(allylendo)-exo-trig cyclization. Furthermore, starting with a [3.3.1] bicycle already in place, Maimone and coworkers reported a base mediated

Scheme 3.2. *Prior art for constructing [3.2.2] bicycles.*



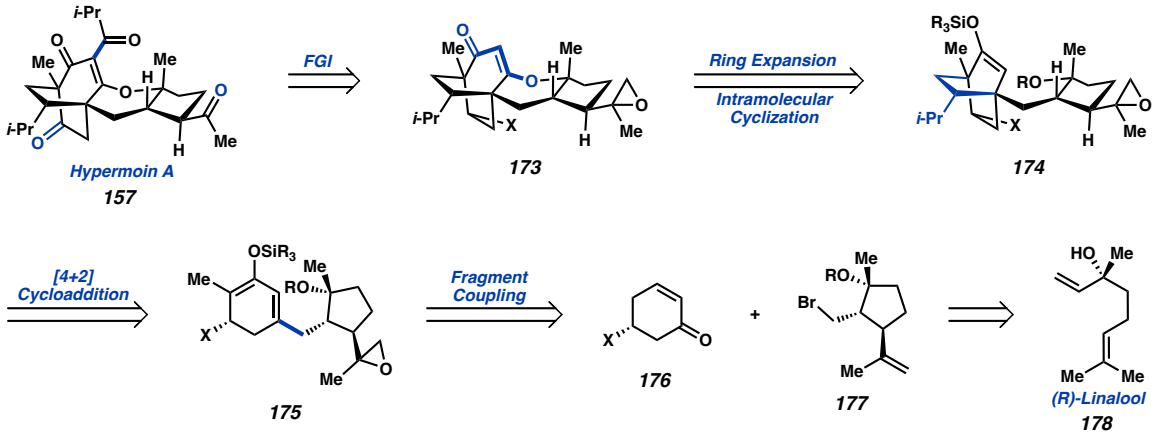
carbanion rearrangement to access the corresponding structurally rearranged [3.2.2] bicycle **170** in 50% yield.[15] Again beginning from a bridged bicyclic system, Dai and coworkers utilized a ring expansion approach from [2.2.2] bicycle **171**.[16] Using $TMSCHN_2$, a single methylene was introduced resulting in the desired 7-membered ring. Finally, the Pd catalyzed asymmetric intramolecular [4+2] cycloaddition reported by our group allows access to an enantioenriched cycloadduct containing a [3.2.2] bicycle (**11d**) when starting from cycloheptenone **10d** (see Chapter 1).[17] However, this intramolecular approach we

developed is not applicable in our synthetic endeavors toward hypermoin A due to the positioning of the tether between the diene and dienophile. With these literature precedents in mind, we opted to pursue a ring expansion approach most similar to that reported by Dai and coworkers.

3.2 RETROSYNTHETIC ANALYSIS

Retrosynthetic disconnection of **157** begins with late-stage functional group interconversion and oxidative manipulations from **173** (Scheme 3.3). The 7/6/6/5 skeleton is proposed to be formed via a ring expansion cascade sequence from [2.2.2] bicycle **174**. The bicycle will be forged from a [4+2] cycloaddition between siloxy diene **175** and a dienophile containing a functional handle to form the requisite *i*-Pr group. Finally, 1,2-addition and enone transposition occurs between two fragments, cyclopentane **177**, derived from *(R)*-linalool (**178**), and chiral enone **176**.

Scheme 3.3. *Retrosynthetic analysis of* ***157****.*

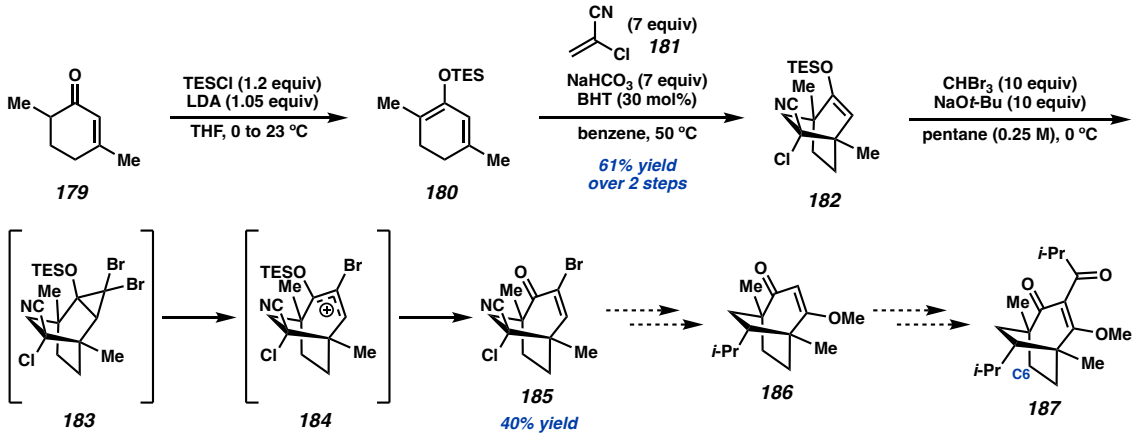


3.3 FORMATION OF THE [3.2.2] BICYCLIC CORE

Preliminary investigations involved employing a model system to explore reactions to access the [3.2.2] bicycle through a [4+2] cycloaddition and ring expansion (Scheme

3.4). From enone **179** silyl enol ether formation provided access to siloxy diene **180**. Preliminary investigation of the [4+2] cycloaddition revealed that an excess of ketene equivalent **181** and $NaHCO_3$ and 30 mol% butylated hydroxytoluene (BHT) were necessary for sufficient formation of cycloadduct **182**. We then envisioned a cyclopropanation followed by ring expansion via cyclopropane cleavage would reveal the requisite [3.2.2] bicyclic core. To our delight, using a large excess of $CHBr_3$ and NaO*t*-Bu in pentane directly yielded ring expanded product **185**. This intermediate contains the fully constructed [3.2.2] bicycle and synthetic handles for installation of the requisite functionality. The α-bromo enone is poised to undergo an oxa-Michael addition and elimination sequence and an acylation reaction. We propose accessing the *i*-Pr via conversion of the chloro-nitrile motif to a ketone, Wittig olefination, and hydrogenation. However, in this model system we lack a handle for the formation of the isolated ketone at C6 in the [3.2.2] bicycle of hypermoin A.

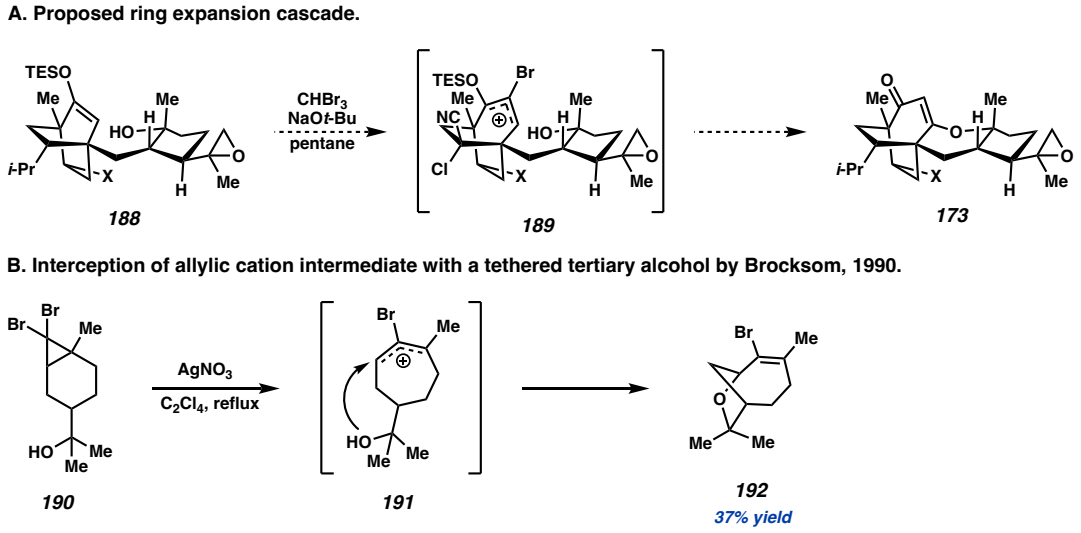
Scheme 3.4. *Initial study with a model system to access a [3.2.2] bicycle.*



Excitingly, in the cyclopropanation/ring expansion step we envision being able to further leverage the key allylic cation in a more complex setting (Scheme 3.5A). We

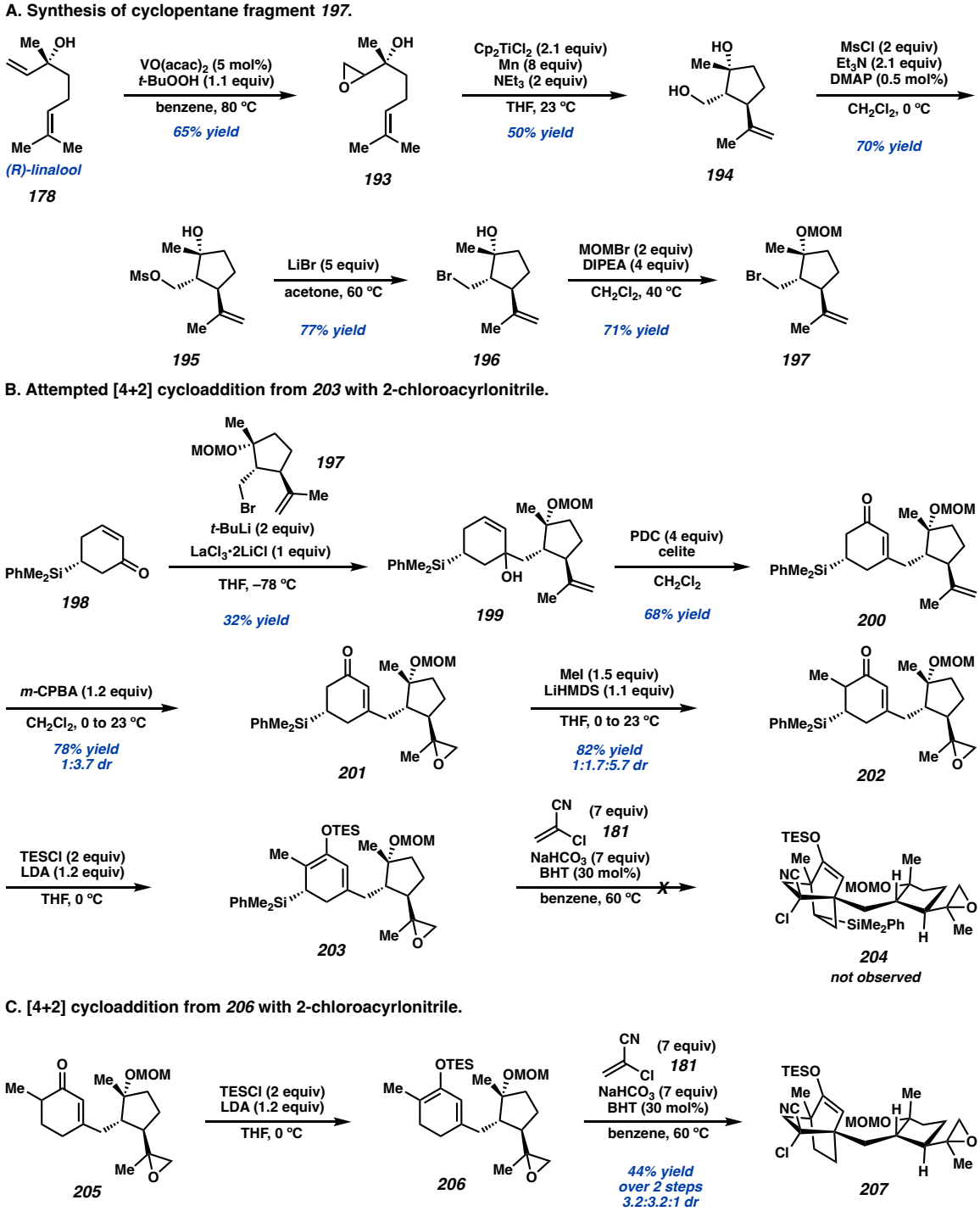
propose intercepting cationic intermediate **189** with a pendant alcohol to form the tetrahydropyran ring. It has previously been demonstrated that tethered tertiary alcohols can intercept allylic cations generated from cleavage of dibromocyclopropanes to ultimately form bridged bicyclic scaffolds (Scheme 3.5B).[18] Successful application of the proposed cascade would form the full tetracyclic ring system of hypermoin A.

Scheme 3.5. *(A) Proposed ring expansion cascade sequence from advanced intermediate* ***188*** *to form the full skeleton of hypermoin A. (B) Prior art intercepting allylic cations with tertiary alcohols by Brocksom and coworkers.*



We thus aimed to explore the key [4+2] cycloaddition and proposed ring expansion cascade in a more elaborate system. Synthesis of the cyclopentane fragment began from *(R)*-linalool (**178**) following known epoxidation and radical mediated cyclization steps to form **194** (Scheme 3.6A).[19] Mesylation of the primary alcohol is achieved in 70% yield, and a Finkelstein reaction with LiBr yields **196**. Finally, protection of the tertiary alcohol provides access to alkyl bromide **197** in 71% yield. This fragment contains all the requisite stereochemistry for the 5-membered ring found in **157**.

Scheme 3.6. *(A) Synthesis of cyclopentane fragment* ***197****. (B) Attempted [4+2] cycloaddition from intermediate* ***203****. (C) Successful [4+2] cycloaddition from* ***206****.*



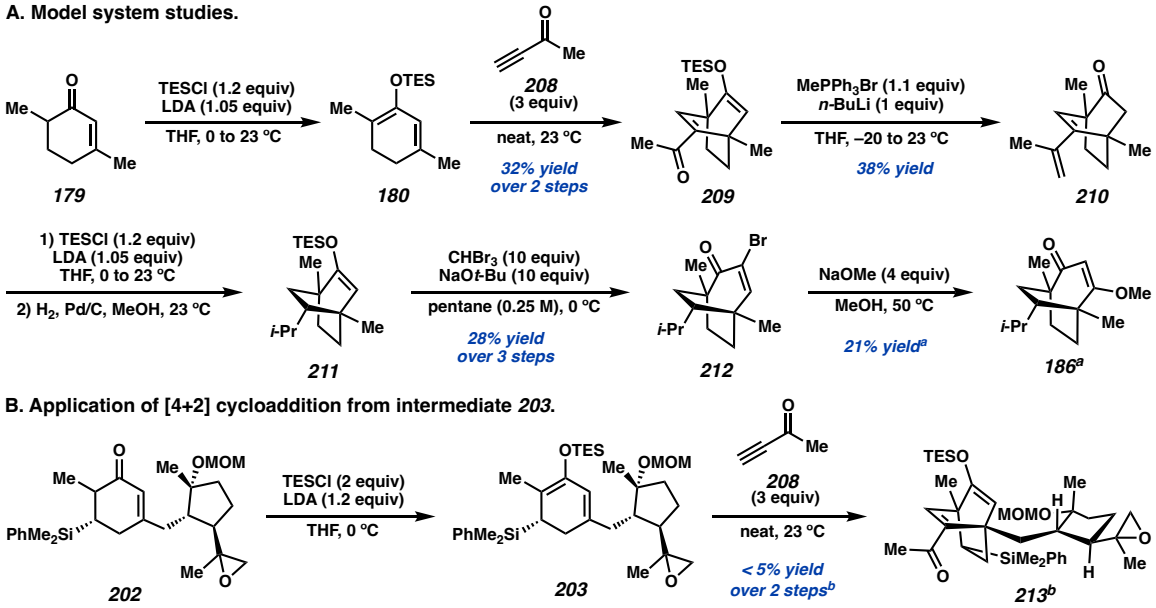
1,2-addition of **197** to chiral enone **198**[20] proved quite challenging and we were unable to improve the yield beyond 31% yield (Scheme 3.6B). The use of different additives, varying solvent, and altering temperature did not improve the yield of product **199**. Regardless of the low yield, we were able to advance **199** further in the synthesis through PDC oxidation, yielding transposed enone **200** in 68% yield. Epoxidation of the isopropenyl moiety is hypothesized to protect the olefin from cyclopropanation in the later stages of our proposed sequence while still providing a functional handle capable of undergoing oxidative transformations to form the required methyl ketone moiety.[21] Enolate alkylation installs the methyl group in 82% yield. With this advanced intermediate (**202**) in hand, we were poised to explore the [4+2] cycloaddition and ring expansion developed in the model system. Formation of silyl oxy diene **203** proceeded smoothly, and it was subjected crude to the previously developed [4+2] cycloaddition conditions. Unfortunately, the desired [4+2] cycloaddition with dienophile **181** did not occur from diene **203** and only recovered enone **202** and decomposition was observed.

To explore the compatibility of the functionality on the diene in the desired transformation, we performed the analogous [4+2] cycloaddition from intermediate **206** which does not contain the $SiMe_2Ph$ group (Scheme 3.6C). Interestingly, the [4+2] cycloaddition performed well with a 44% yield and 3.2:3.2:1 dr over two steps. Unfortunately, initial attempts at further advancing **207** to the desired [3.2.2] bicycle were unsuccessful. The success of the [4+2] cycloaddition from **206** indicated that the $SiMe_2Ph$ functional handle was likely incompatible with the previously developed [4+2] cycloaddition. We hypothesized that alterations to the diene and/or dienophile were needed to recover reactivity. At the same time, we were unable to elaborate **185** further and install

required functional groups in the model system, which we attributed to undesired reactivity of the chloro-nitrile moiety. Therefore, we decided to explore alternative dienophiles for the [4+2] cycloaddition.

Returning to the model system, we found that we could successfully perform the [4+2] cycloaddition with ynone **208** (Scheme 3.7). Methylenation and hydrogenation formed the *i*-Pr group as a single diastereomer with the desired stereochemistry (**211**). The same ring expansion previously discussed was employed to furnish the [3.2.2] bicyclic structure now with the *i*-Pr moiety in place (**212**) in 28% yield over 3 steps. Subjection of α-bromo enone **212** to NaOMe in MeOH resulted in the formation of vinylogous ester **186**. This same transformation resulted in no conversion at 23 ºC and only decomposition at elevated temperatures when carried out from **185** highlighting that the dienophile change may eliminate challenges experienced when the chloro-nitrile moiety was present.

Scheme 3.7. *(A) Model system studies. [4+2] cycloaddition with ynone* ***208*** *and further advancement to [3.2.2] bicycle* ***186****. (B) [4+2] cycloaddition from diene* ***203****.*

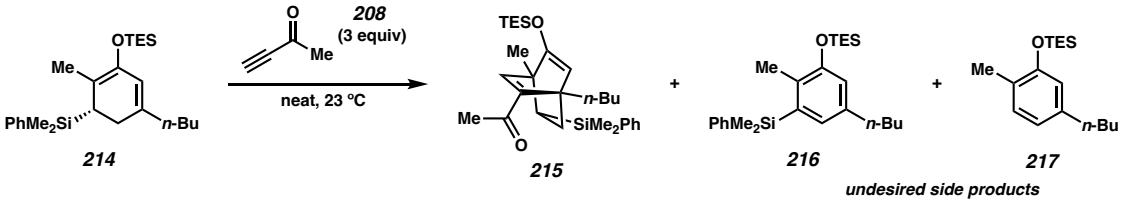


[a]Tentative assignment. Structure of proposed product **186** is in agreement with ^{1}H NMR data. [b] Tentative assignment. Structure of proposed product **213** is in agreement with ^{1}H NMR and HRMS data.

Excited by the successful [4+2] cycloaddition with ynone **208** and functional group compatibility through multiple sequential steps in the model system, we applied this Diels–Alder in a more complex system. We were able to access desired product **213** albeit in extremely low yield (Scheme 3.7B). In effort to further improve this transformation, we are currently exploring a variety of reaction conditions in a model system containing the $SiMe_2Ph$ functional handle (Table 3.1). So far, these efforts have been unsuccessful, and the major mass balance was recovered enone and aromatization of the diene (**216** and **217**). However, we are continuing to evaluate different reaction conditions with this dienophile and others. Furthermore, we are also exploring different substitution on the enol ether.

However, in our attempts so far either no desired product was observed (i.e., acetyl enol ether) or issues synthesizing the enol ether prevented testing the [4+2] cycloaddition (i.e., methyl enol ether, other silyl enol ethers).

Table 3.1. *Ongoing optimization of the [4+2] cycloaddition in a model system.*

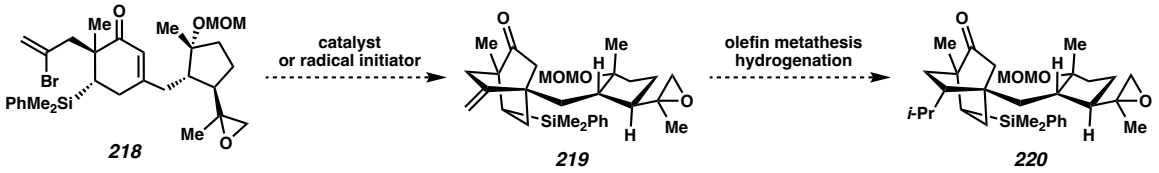


Entry	Variation to Conditions	% yield[a]	216/217 Observed
1	none	23[b]	trace
2	CH_2Cl_2 (1 M), 5 equiv *208*	7	Yes
3	Et_2O (1 M), 5 equiv *208*	–	Yes
4	CH_2Cl_2 (0.66 M), 5 equiv *208*, $AlCl_3$ or $BF_3{\cdot}Et_2O$ or I_2 or $TiCl_4$ (0.25 equiv)	–	No
5	10 equiv *208*, 5 equiv 2,6-lutidine	13	No
6	10 equiv *208*, 5 equiv $NaHCO_3$	19	No

[a] Yield over two steps determined by ^{1}H NMR with respect to 1,3,5-trimethoxybenzene as internal standard. [b] Isolated yield.

Additionally, we are currently investigating an alternative approach to form the [2.2.2] bicycle via an intramolecular cyclization (Figure 3.8). We envision metalation of the vinyl Br (**218**) followed by 1,4-addition into the enone to construct [2.2.2] bicycle **219**. Alternatively, generation of a radical from vinyl Br **218** could result in the same cyclization product. Olefin metathesis followed by hydrogenation would yield the *i*-Pr group. Intermediate **220** can then be subjected to the same proposed ring expansion and endgame sequence. Efforts are currently ongoing to explore this method to access the desired [2.2.2] bicycle.

Scheme 3.8. *Alternative approach for the formation of the [2.2.2] bicycle.*

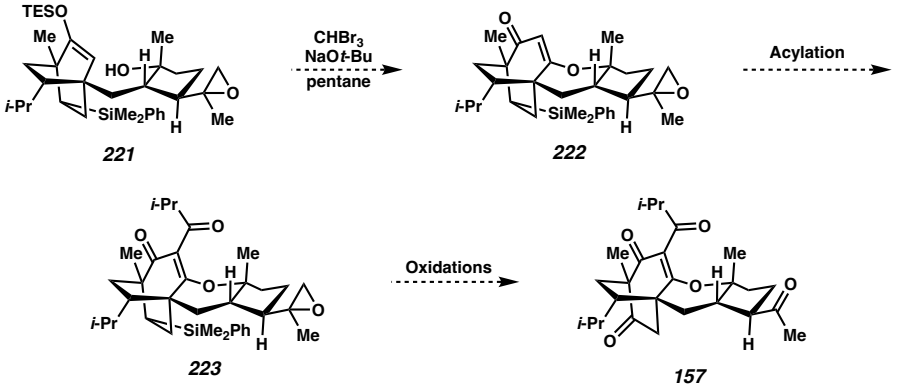


3.4 SUMMARY AND FUTURE DIRECTIONS

We have successfully developed a [4+2] cycloaddition and ring expansion sequence in model systems to form the desired [3.2.2] bicyclic ring system found in hypermoin A. When applying the first generation [4+2] cycloaddition with ketene equivalent **181** as the dienophile and **203** as the diene, no product was observed. It was determined that functional group incompatibility with the silane on the diene and dienophile was problematic. This led us to revisit potential dienophiles for the transformation; we ultimately found that ynone **208** performed well in the [4+2] cycloaddition and sequential steps in a model system. Unfortunately, low yields with diene **203** have again hindered exploration of further steps. Optimization efforts are ongoing to improve material throughput in the [4+2] cycloaddition. Additionally, we are exploring alternative approaches to access the [2.2.2] bicycle.

Following successful formation of the [2.2.2] bicycle and installation of the *i*-Pr moiety according to aforementioned methods (see Schemes 3.7B and 3.8), we will explore the endgame to access hypermoin A (Scheme 3.9). We propose a ring expansion cascade to construct the full ring system (**222**), and acylation will provide **223**. Finally, a Tamao–Fleming oxidation will convert the silane to the corresponding alcohol. Oxidation of the alcohol and the epoxide to the desired ketones will yield hypermoin A.

Scheme 3.9. *Proposed endgame toward the synthesis of hypermoin A.*



In conclusion, efforts are ongoing to apply a [4+2] cycloaddition and ring expansion approach that was successful in model systems to advanced intermediates. Implementation of this strategy would form the full framework of hypermoin A with appropriate handles for the final functional group interconversions. Completion of this route would result in the first asymmetric total synthesis of hypermoin A.

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.[22] 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 $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 nm) was used for flash chromatography. ^{1}H NMR spectra were recorded on a Bruker 400 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer (100 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm). ^{2}H NMR spectra were recorded on a Bruker 400 MHz (61 MHz) spectrometer and are reported relative to residual $CDCl_3$ (δ 7.26 ppm). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as the peaks appear 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). 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. ^{13}C NMR spectra of deuterated compounds are complicated by the low intensity of peaks of deuterium-

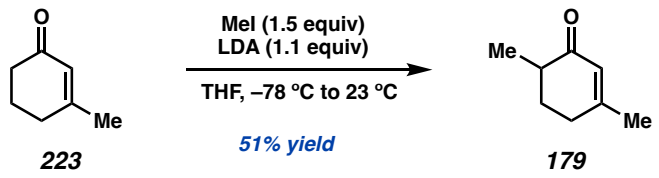
substituted carbon atoms. IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer or Nicolet 6700 FTIR spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating 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-600H High Resolution Mass Spectrometer in Field Desorption (FD+) mode.

Reagents were purchased from commercial sources and used as received unless otherwise stated.

List of Abbreviations: TLC – thin-layer chromatography.

3.5.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

3.5.2.1 MODEL SYSTEM STUDIES: FIRST GENERATION [4+2] CYCLOADDITION

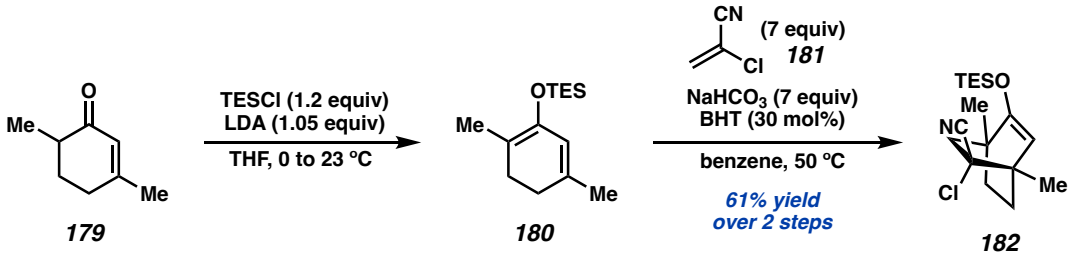


223 ***179***

3,6-dimethylcyclohex-2-en-1-one (179)

A flame dried round bottom flask was charged with *i*-Pr_2NH (6.7 mL, 48 mmol, 1.2 equiv) and THF (28 mL, 1.75 M). The solution was cooled to 0 ºC and *n*-BuLi (18.3 mL, 44 mmol, 1.1 equiv) was added dropwise. The resultant solution was stirred for 30 min at 0 ºC. Enone **223** (4.5 mL, 40 mmol, 1.0 equiv) in THF (32 mL, 1.25 M) was added dropwise and stirring was continued at 0 ºC for 30 minutes. The solution was cooled to –78 ºC, and MeI (3.7 mL, 60 mmol, 1.5 equiv) was added dropwise. The reaction was gradually warmed to 23 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction was diluted with a saturated solution of NH_4Cl and the product was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (SiO_2, 5–15% EtOAc/Hexanes) to afford the corresponding methylated enone **179** as a colorless oil (2.54 g, 20.5 mmol, 51% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86 (d, *J* = 1.2 Hz, 1H), 2.45 – 2.22 (m, 3H), 2.11 – 2.02 (m, 1H), 1.95 (t, *J* = 1.1 Hz, 3H), 1.79 – 1.64 (m, 1H), 1.14 (d, *J* = 6.8 Hz, 3H).



2-chloro-1,4-dimethyl-5-((triethylsilyl)oxy)bicyclo[2.2.2]oct-5-ene-2-carbonitrile (182)

A flame dried round bottom flask was charged with *i*-Pr_2NH (5.9 mL, 42.0 mmol, 1.1 equiv) and THF (28 mL, 1.5 M). The solution was cooled to 0 ºC and *n*-BuLi (16.0 mL, 40.1 mmol, 1.05 equiv) was added dropwise. The resultant solution was stirred for 30 min at 0 ºC. Enone **179** (4.74 g, 38.2 mmol, 1.0 equiv) in THF (38 mL, 1.0 M) was added dropwise and stirring was continued at 0 ºC for 30 minutes. The solution was cooled to –78 ºC, and TESCl (7.7 mL, 45.8 mmol, 1.2 equiv) was added dropwise. The reaction was gradually warmed to 23 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction was diluted with a saturated solution of NH_4Cl and the product was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude silyloxy diene **180** was used without further purification.

A flame dried round bottom flask was charged with crude diene **180** (9.35 g, 39.2 mmol, 1 equiv) and benzene (39.2 mL, 1.0 M) at 23 ºC. $NaHCO_3$ (23.1 g, 274 mmol, 7 equiv) and BHT (2.59 g, 11.8 mmol, 0.3 equiv) were added to the reaction mixture. Then dienophile **181** (21.9 mL, 274 mmol, 7 equiv) was added and the resulting mixture was heated to 50 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction was *slowly* diluted with a saturated solution of citric acid and the product was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over

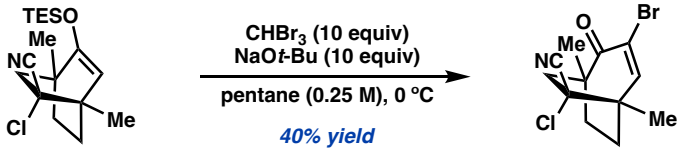
Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (SiO_2, 0–5% EtOAc/Hexanes) to afford the corresponding bicycle **182** as a colorless oil (7.76 g, 23.8 mmol, 61% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.66 (s, 1H), 2.44 (d, *J* = 14.7 Hz, 1H), 2.09 (dd, *J* = 14.7, 2.1 Hz, 1H), 1.98 – 1.85 (m, 1H), 1.52 – 1.43 (m, 3H), 1.42 (s, 3H), 1.08 (s, 3H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.71 (q, *J* = 8.0 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 120.3, 103.1, 63.9, 54.2, 44.5, 38.3, 33.8, 31.8, 22.0, 19.8, 6.8, 5.0.

IR (Neat Film, NaCl): 3646, 3063, 2959, 2912, 2876, 2346, 1633, 1466, 1455, 1355, 1246, 1118, 1011, 829 cm^{-1}.

HRMS (ES+): *m/z* calc'd for $C_{17}H_{28}ClNOSi$ $[M]^+$: 326.1707, found 326.1711.



182 ***185***

3-bromo-6-chloro-1,5-dimethyl-2-oxobicyclo[3.2.2]non-3-ene-6-carbonitrile (185)

A flame dried round bottom flask was charged with silyl enol ether **182** (163 mg, 0.5 mmol, 1 equiv) and pentane (2.0 mL, 0.25 M). The resulting solution was cooled to 0 ºC and NaO*t*-Bu (480 mg, 5.0 mmol, 10 equiv) was added. Then $CHBr_3$ (0.44 mL, 5.0 mmol, 10 equiv) was added fast dropwise, rate of addition was monitored to ensure bubbling of the reaction mixture was kept to a minimum. Upon complete consumption of starting material (as determined by TLC), the reaction was *slowly* diluted with brine and the product was extracted three times with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash

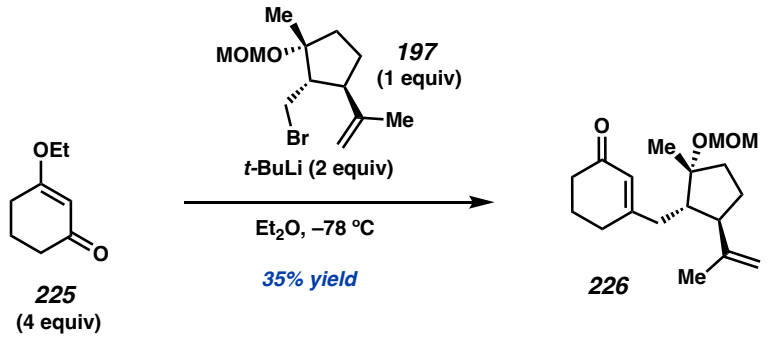
silica gel column chromatography (SiO_2, 0–4–7% EtOAc/Hexanes) to afford α-bromo enone **185** as a white solid (60.5 mg, 0.2 mmol, 40% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (s, 1H), 2.75 (d, *J* = 16.0 Hz, 1H), 2.46 (dd, *J* = 15.9, 2.1 Hz, 1H), 2.17 – 1.91 (m, 3H), 1.73 – 1.67 (m, 1H), 1.65 (s, 3H), 1.30 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.0, 151.5, 129.6, 118.9, 61.4, 49.0, 47.2, 46.7, 34.4, 28.0, 26.5, 25.5.

IR (Neat Film, NaCl): 3438, 2938, 2870, 2232, 1693, 1650, 1464, 1254, 850 cm^{-1}.

HRMS (FD+): *m/z* calc'd for $C_{12}H_{23}NOClBr$ $[M]^+$: 300.9869, found 300.9870.



3-(((1*S*,2*R*,5*R*)-2-(methoxymethoxy)-2-methyl-5-(prop-1-en-2 yl)cyclopentyl)methyl)cyclohex-2-en-1-one (226)

Vinylogous ester **225** (2.1 mL, 14.43 mmol, 4 equiv) was azeotroped with benzene (1 mL) 2 times and placed under high vacuum for 3 h to remove trace benzene. Alkyl bromide **197** (1.00 g, 3.61 mmol, 1 equiv, 1:4.8 ratio of *i*-Pr to isopropenyl) was azeotroped with benzene (1 mL) 2 times and placed under high vacuum for 3 h to remove trace benzene. Both vials are backfilled with N_2, then enone **225** was dissolved in Et_2O (72 mL, 0.2 M) and cooled to –78 ºC. Alkyl bromide **197** was dissolved in THF (4.5 mL, 0.8 M) and cooled to –78 ºC. *t*-BuLi (1.7 M in pentane, 4.2 mL, 2 equiv) was added dropwise and the resulting solution

was stirred for 15 minutes. The alkyl Li solution was added as fast as possible via cannula to the stirring solution of **225**. Upon complete consumption of starting material (as determined by TLC), the reaction was diluted with a saturated solution of NH_4Cl and the product was extracted three times with Et_2O. The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (SiO_2, 20% EtOAc/Hexanes) to afford enone **226** as a colorless oil (369 mg, 1.26 mmol, 35% yield, 1:5.3 ratio of *i*-Pr to isopropenyl). The mixture of *i*-Pr to isopropenyl were not separated as they can be separated during the subsequent steps.

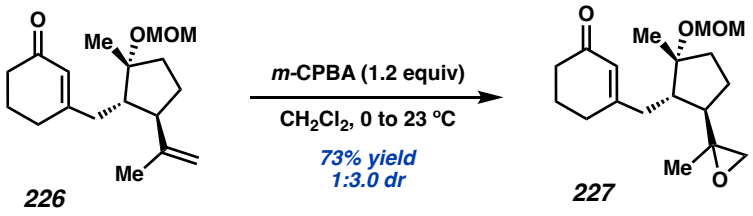
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.95 (t, *J* = 1.3 Hz, 1H), 4.72 – 4.65 (m, 4H), 3.37 (s, 3H), 2.61 – 2.50 (m, 2H), 2.38 – 2.23 (m, 4H), 2.21 – 2.14 (m, 1H), 2.07 – 1.86 (m, 4H), 1.77 (ddd, *J* = 10.5, 7.0, 6.0 Hz, 1H), 1.65 (dd, *J* = 1.3, 0.8 Hz, 3H), 1.56 – 1.41 (m, 2H), 1.28 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 199.8, 166.9, 147.3, 127.4, 111.5, 91.4, 85.4, 55.6, 52.4, 51.3, 37.4, 36.8, 36.7, 30.0, 27.9, 23.4, 22.9, 19.0.

IR (Neat Film, NaCl): 3068, 2950, 1668, 1622, 1458, 1374, 1248, 1142, 1036 cm^{-1}.

HRMS (FD+): *m/z* calc'd for $C_{18}H_{28}O_3$ $[M]^+$: 292.2033, found 292.2024.

Optical Rotation: $[\alpha]_D^{21}$ –23.2 (c 1.00, $CHCl_3$).



3-(((1S,2R,5R)-2-(methoxymethoxy)-2-methyl-5-((R)-2-methyloxiran-2-yl)cyclopentyl)methyl)cyclohex-2-en-1-one (227)

A flame dried 1 dram vial was charged with enone **226** (369 mg, 1.26 mmol, 1 equiv, 1:5.3 ratio of *i*-Pr to isopropenyl) and CH_2Cl_2 (6.3 mL, 0.2 M) and cooled to 0 ºC. *m*-CPBA (261 mg, 1.51 mmol, 1.2 equiv) was added to the reaction which was slowly warmed to 23 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction was filtered over celite with CH_2Cl_2. The crude reaction mixture was diluted with approximately 1:1 $Na_2S_2O_3$ and $NaHCO_3$ solutions. The layers were separated, and the product was extracted three times with CH_2Cl_2. The combined organic layer was washed with $NaHCO_3$ two times, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (SiO_2, 40% EtOAc/Hexanes) to afford enone **227** as a colorless oil (284 mg, 0.92 mmol, 73% yield, 1:3.0 dr). Diastereomers are inconsequential and, therefore, are not separated.

^{1}H NMR (400 MHz, $CDCl_3$) mixture of diastereomers: δ 5.98 (t, *J* = 1.3 Hz, 0.3H, minor), 5.94 (p, *J* = 1.3 Hz, 1H, major), 4.69 – 4.61 (m, 2.7H), 3.34 (s, 4H), 2.69 – 2.47 (m, 4H), 2.41 – 2.24 (m, 6.7H), 2.08 – 1.83 (m, 6.7H), 1.81 – 1.73 (m, 0.6H, minor), 1.62 – 1.50 (m, 2.3H), 1.50 – 1.39 (m, 1.6H), 1.26 (s, 0.9H, minor), 1.26 (s, 6H, major), 1.24 (s, 0.9H, minor).

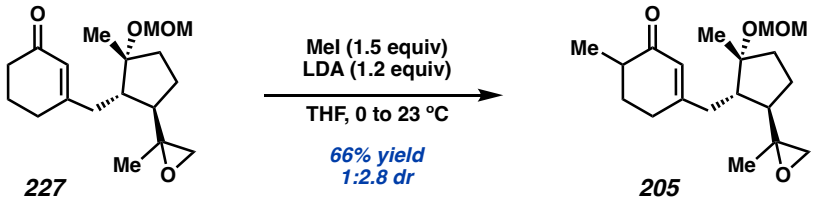
^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer: δ 199.8, 166.6, 127.2, 91.4, 85.6, 58.5, 55.7, 53.1, 50.0, 49.8, 38.0, 37.5, 36.7, 29.9, 25.6, 23.1, 22.8, 19.5.

^{13}C NMR (100 MHz, $CDCl_3$) minor diastereomer: δ 199.9, 166.7, 127.2, 91.4, 85.6, 58.0, 55.7, 53.2, 50.1, 49.4, 37.5, 37.1, 36.6, 30.2, 25.3, 23.3, 22.8, 18.5.

IR (Neat Film, NaCl): 3498, 2954, 1666, 1622, 1376, 1326, 1142, 1088, 1034, 918 cm^{-1}.

HRMS (FD+): *m/z* calc'd for $C_{18}H_{28}O_4$ $[M]^+$: 308.1982, found 308.1970.

Optical Rotation: $[\alpha]_D^{21}$ –26.6 (c 1.00, $CHCl_3$).



3-(((1*S*,2*R*,5*R*)-2-(methoxymethoxy)-2-methyl-5-((*R*)-2-methyloxiran-2-yl)cyclopentyl)methyl)-6-methylcyclohex-2-en-1-one (205)

A flame dried round bottom flask was charged with *i*-Pr_2NH (0.17 mL, 1.22 mmol, 1.25 equiv) and THF (0.67 mL, 1.75 M). The solution was cooled to 0 ºC and *n*-BuLi (0.47 mL, 1.18 mmol, 1.2 equiv) was added dropwise. The resultant solution was stirred for 30 min at 0 ºC. The corresponding enone **227** (302.0 mg, 0.98 mmol, 1.0 equiv) in THF (0.78 mL, 1.25 M) was added dropwise and stirring was continued at 0 ºC for 30 minutes. MeI (0.09 mL, 1.47 mmol, 1.5 equiv) was added dropwise. The reaction was gradually warmed to 23 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction was diluted with a saturated solution of NH_4Cl and the product was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (SiO_2, 30% EtOAc/Hexanes) to afford the

corresponding methylated enone **205** as a yellow oil (207 mg, 0.64 mmol, 66% yield, 1:2.8 dr). Diastereomers are inconsequential and, therefore, are not separated.

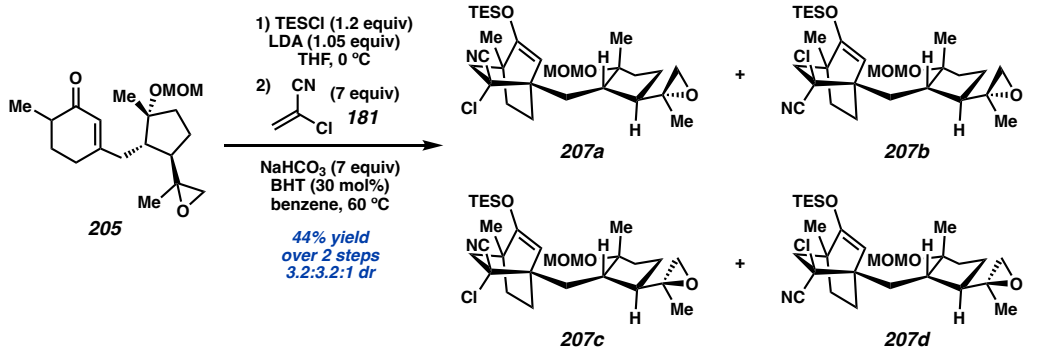
^{1}H NMR (400 MHz, $CDCl_3$) mixture of diastereomers: δ 5.96 (s, 0.3H, minor), 5.91 (s, 1H, major), 4.70 – 4.62 (m, 2.8H), 3.35 (m, 4H), 2.69 – 2.47 (m, 4H), 2.45 – 2.21 (m, 5H), 2.12 – 1.64 (m, 7H), 1.59 – 1.39 (m, 4H), 1.28 – 1.24 (m, 8H), 1.13 (d, J = 6.8 Hz, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) mixture of diastereomers: δ 202.2, 202.2, 165.3, 126.7, 126.7, 91.4, 85.6, 85.6, 58.5, 58.5, 58.0, 55.7, 53.3, 53.2, 53.2, 50.2, 50.1, 50.1, 50.1, 49.9, 49.4, 49.4, 41.0, 40.9, 40.9, 40.8, 37.9, 37.6, 36.9, 36.7, 36.7, 31.1, 31.0, 30.9, 30.9, 30.1, 29.6, 29.4, 25.6, 25.5, 25.3, 25.2, 23.3, 23.2, 23.1, 23.1, 19.4, 18.5, 18.5, 15.2.

IR (Neat Film, NaCl): 2960, 2928, 1666, 1456, 1034 cm^{-1}.

HRMS (FD+): *m/z* calc'd for $C_{19}H_{30}O_4$ $[M]^+$: 322.2139, found 322.2127.

Optical Rotation: $[\alpha]_D^{21}$ –22.1 (c 1.00, $CHCl_3$).



(1R,4R)-2-chloro-1-(((1R,5S)-2-(methoxymethoxy)-2-methyl-5-(2-methyloxiran-2-yl)cyclopentyl)methyl)-4-methyl-5-((triethylsilyl)oxy)bicyclo[2.2.2]oct-5-ene-2-carbonitrile (207a, 207b, 207c, 207d)

A flame dried round bottom flask was charged with *i*-Pr_2NH (0.07 mL, 0.47 mmol, 1.25 equiv) and THF (0.47 mL, 1.0 M). The solution was cooled to 0 ºC and *n*-BuLi (0.18 mL, 0.45 mmol, 1.2 equiv) was added dropwise. The resultant solution was stirred for 30 min at 0 ºC. Enone **205** (120 mg, 0.37 mmol, 1.0 equiv) in THF (0.47 mL, 0.8 M) was added dropwise and stirring was continued at 23 ºC for 30 minutes. The solution was cooled to 0 ºC, and TESCl (0.13 mL, 0.74 mmol, 2 equiv) was added dropwise. Upon complete consumption of starting material (as determined by TLC), the reaction was diluted with a saturated solution of NH_4Cl and the product was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude silyloxy diene **206** was used without further purification.

A flame dried round bottom flask was charged with crude diene **206** (162 mg, 0.37 mmol, 1 equiv) and benzene (0.37 mL, 1.0 M) at 23 ºC. $NaHCO_3$ (219 mg, 2.6 mmol, 7 equiv) and BHT (24.6 mg, 0.11 mmol, 0.3 equiv) were added to the reaction mixture. Then dienophile **181** (0.21 mL, 2.6 mmol, 7 equiv) was added and the resulting mixture was heated to 60 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction was *slowly* diluted with a saturated solution of citric acid and the product was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (SiO_2, 0–5–10–15–50% EtOAc/Hexanes) to afford the corresponding bicycle **207-d1**, **207-d2**, and **207-d3** as colorless oils (88.1 mg, 0.17 mmol, 44% yield, 3.2:3.2:1 dr (d1:d2:d3)). Stereochemistry of the diastereomers was not able to be assigned.

Diastereomer 1 (207-d1):

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.77 (s, 1H), 4.73 – 4.68 (m, 2H), 3.40 (s, 3H), 2.80 (d, *J* = 4.7 Hz, 1H), 2.67 (d, *J* = 4.7 Hz, 1H), 2.47 (d, *J* = 14.7 Hz, 1H), 2.36 (dd, *J* = 15.2, 5.1 Hz, 1H), 2.11 (dd, *J* = 14.6, 3.2 Hz, 1H), 2.05 – 1.91 (m, 3H), 1.87 – 1.76 (m, 2H), 1.68 – 1.61 (m, 2H), 1.56 – 1.41 (m, 4H), 1.35 (s, 3H), 1.30 (s, 3H), 1.08 (s, 3H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.71 (q, *J* = 7.9 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 158.2, 120.4, 101.5, 91.4, 85.5, 65.3, 58.1, 55.9, 54.5, 53.9, 53.9, 48.4, 48.0, 38.2, 37.1, 34.2, 33.9, 29.5, 25.3, 24.2, 19.9, 18.0, 6.8, 5.0.

IR (Neat Film, NaCl): 3504, 2958, 2878, 2358, 1734, 1628, 1460, 1282, 1038, 750 cm^{-1}.

HRMS (FD+): *m/z* calc'd for $C_{28}H_{46}ClNO_4Si$ $[M]^+$: 523.2879, found 523.2889.

Optical Rotation: $[\alpha]_D^{21}$ –5.9 (c 0.8, $CHCl_3$).

Diastereomer 2 (207-d2):

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.93 (s, 1H), 4.74 – 4.68 (m, 2H), 3.39 (s, 3H), 2.82 – 2.74 (m, 2H), 2.64 (d, *J* = 4.6 Hz, 1H), 2.47 (d, *J* = 14.7 Hz, 1H), 2.14 – 1.91 (m, 3H), 1.79 (td, *J* = 9.5, 6.2 Hz, 1H), 1.67 (dqq, *J* = 14.0, 6.6, 3.2 Hz, 3H), 1.54 – 1.40 (m, 5H), 1.35 (s, 3H), 1.27 (d, *J* = 0.6 Hz, 3H), 1.09 (s, 3H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.76 – 0.65 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8, 120.4, 101.4, 91.3, 86.1, 65.1, 58.1, 55.8, 55.2, 54.5, 53.6, 48.9, 47.9, 38.1, 37.0, 34.0, 33.7, 29.0, 25.2, 23.8, 19.8, 17.5, 6.8, 5.0.

IR (Neat Film, NaCl): 3466, 2958, 2930, 2878, 2358, 2342, 1734, 1632, 1460, 1036, 828 cm^{-1}.

HRMS (FD+): *m/z* calc'd for $C_{28}H_{46}ClNO_4Si$ $[M]^+$: 523.2879, found 523.2888.

Optical Rotation: $[\alpha]_D^{21}$ –13.7 (c 0.33, $CHCl_3$).

Diastereomer 3 (207-d3):

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.21 (s, 1H), 4.73 – 4.67 (m, 2H), 3.40 (s, 3H), 2.52 (s, 2H), 2.47 (d, *J* = 14.6 Hz, 1H), 2.31 (dd, *J* = 15.2, 4.8 Hz, 1H), 2.18 (dd, *J* = 15.2, 3.5 Hz, 1H), 2.10 (dd, *J* = 14.8, 3.1 Hz, 1H), 2.00 – 1.87 (m, 2H), 1.86 – 1.77 (m, 2H), 1.72 – 1.64 (m, 2H), 1.53 – 1.42 (m, 4H), 1.32 (s, 3H), 1.31 (s, 3H), 1.08 (s, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.74 (q, *J* = 8.0 Hz, 6H).

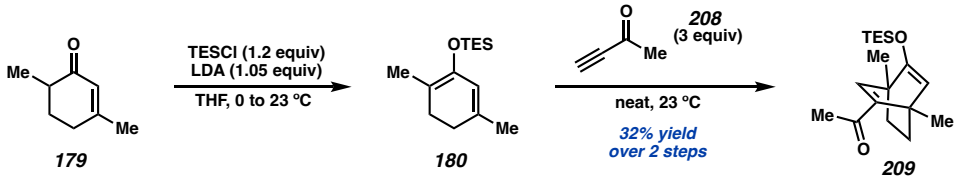
^{13}C NMR (151 MHz, $CDCl_3$): δ 157.7, 120.8, 102.1, 91.3, 86.3, 65.2, 58.1, 55.8, 54.7, 53.7, 53.3, 48.0, 47.6, 38.0, 36.7, 34.0, 34.0, 29.2, 26.0, 23.7, 20.0, 17.6, 7.2, 6.8, 6.3, 4.7.

IR (Neat Film, NaCl): 3482, 2956, 2928, 2878, 2360, 1730, 1630, 1458, 1378, 1088, 1038, 740 cm^{-1}.

HRMS (FD+): *m/z* calc'd for $C_{28}H_{46}ClNO_4Si$ $[M]^+$: 523.2879, found 523.2878.

Optical Rotation: $[\alpha]_D^{21}$ –5.8 (c 0.23, $CHCl_3$).

3.5.2.2 MODEL SYSTEM STUDIES: SECOND GENERATION [4+2] CYCLOADDITION



1-(1,4-dimethyl-5-((triethylsilyl)oxy)bicyclo[2.2.2]octa-2,5-dien-2-yl)ethan-1-one (209)

A flame dried round bottom flask was charged with *i*-Pr_2NH (1.33 mL, 9.5 mmol, 1.1 equiv) and THF (5.7 mL, 1.6 M). The solution was cooled to 0 ºC and *n*-BuLi (3.6 mL, 9.0 mmol, 1.05 equiv) was added dropwise. The resultant solution was stirred for 30 min at 0 ºC. Enone **179** (1.07 g, 8.6 mmol, 1.0 equiv) in THF (8.1 mL, 1 M) was added dropwise and stirring was continued at 0 ºC for 30 minutes. The solution was cooled to –78 ºC, and TESCl (1.7 mL, 10.3 mmol, 1.2 equiv) was added dropwise. Upon complete consumption

of starting material (as determined by TLC), the reaction was diluted with a saturated solution of NH_4Cl and the product was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude silyl oxy diene **180** was used without further purification.

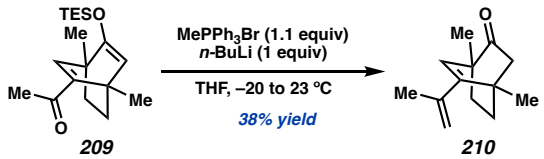
A flame dried vial was charged with crude diene **180** (1 g, 4.2 mmol, 1 equiv) and 3-butyn-2-one (**208**) (1 mL, 12.8 mmol, 3 equiv) at 23 ºC and the resulting mixture was stirred at 23 ºC overnight. Upon complete consumption of starting material (as determined by TLC), the crude product was directly purified by flash silica gel column chromatography (SiO_2, 0–5% EtOAc/Hexanes) to afford the corresponding bicycle **209** as a pale yellow oil (412.6 mg, 1.4 mmol, 32% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80 (s, 1H), 4.82 (s, 1H), 2.20 (s, 3H), 1.65 (s, 3H), 1.59 – 1.48 (m, 1H), 1.41 (s, 3H), 1.37 – 1.32 (m, 1H), 1.32 – 1.25 (m, 1H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.71 – 0.54 (q, 6H, *J* = 8.3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 159.4, 152.1, 150.8, 111.2, 45.4, 43.7, 37.3, 35.5, 28.0, 22.5, 18.6, 6.8, 5.0.

IR (Neat Film, NaCl): 2932, 2870, 1724, 1676, 1596, 1450, 1366, 1254, 1196, 1080, 682 cm^{-1}.

HRMS: Mass not detected.



209 ***210***

1,4-dimethyl-5-(prop-1-en-2-yl)bicyclo[2.2.2]oct-5-en-2-one (210)

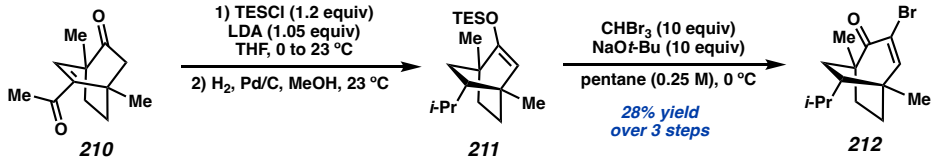
A flame dried vial was charged with $MePPh_3Br$ (64.3 mg, 0.18 mmol, 1.1 equiv) and THF (1.6 mL, 1 M). The solution was cooled to –20 ºC and *n*-BuLi (0.07 mL, 0.16 mmol, 1 equiv) was added dropwise. The resultant solution was stirred for 5 min at –20 ºC, and this solution was added dropwise to a solution of enone **209** (50 mg, 0.16 mmol, 1.0 equiv) in THF (0.5 mL, 0.33 M) at –20 ºC. The reaction mixture was warmed gradually to 23 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction was diluted with water and the product was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (SiO_2, 0–5% EtOAc/Hexanes) to afford the corresponding bicycle **210** as a colorless oil (12 mg, 0.06 mmol, 38% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.59 (s, 1H), 4.88 (dt, *J* = 3.0, 1.5 Hz, 1H), 4.69 (dq, *J* = 1.7, 0.8 Hz, 1H), 2.04 (dd, *J* = 18.2, 2.3 Hz, 1H), 1.95 (d, *J* = 18.2 Hz, 1H), 1.85 (dd, *J* = 1.6, 0.9 Hz, 3H), 1.74 – 1.67 (m, 1H), 1.62 (dd, *J* = 10.2, 2.6 Hz, 1H), 1.57 (d, *J* = 6.0 Hz, 1H), 1.54 – 1.51 (m, 1H), 1.27 (s, 3H), 1.21 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 213.6, 154.5, 144.0, 128.0, 113.9, 49.7, 48.3, 40.0, 35.1, 31.8, 24.0, 22.7, 17.8.

IR (Neat Film, NaCl): 2950, 2876, 2344, 1700, 1672, 1452, 1416, 1186, 1120, 1006, 724 cm^{-1}.

HRMS (FI+): *m/z* calc'd for $C_{13}H_{18}O$ $[M]^+$: 190.1352, found 190.13614.



3-bromo-6-isopropyl-1,5-dimethylbicyclo[3.2.2]non-3-en-2-one (212)

A flame dried vial was charged with *i*-Pr_2NH (0.03 mL, 0.22 mmol, 1.1 equiv) and THF (0.12 mL, 1.8 M). The solution was cooled to 0 ºC and *n*-BuLi (0.082 mL, 0.21 mmol, 1.05 equiv) was added dropwise. The resultant solution was stirred for 30 min at 0 ºC. Ketone **210** (37.6 mg, 0.2 mmol, 1.0 equiv) in THF (0.2 mL, 1.0 M) was added dropwise and stirring was continued at 0 ºC for 30 minutes. The solution was cooled to –78 ºC, and TESCl (0.04 mL, 0.24 mmol, 1.2 equiv) was added dropwise. The reaction was gradually warmed to 23 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction was diluted with a saturated solution of NH_4Cl and the product was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude silyl enol ether was used without further purification.

A flame dried vial was charged with silyl enol ether (22 mg, 0.072 mmol, 1 equiv) and Pd/C (2.0 mg,10 wt%). The vial was evacuated and backfilled with H_2, and MeOH (1.2 mL, 0.06 M) was added. The reaction mixture was stirred vigorously at 23 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction was filtered through a short plug of celite and concentrated under reduced pressure. The crude isopropyl compound **211** was used without further purification.

A vial was charged with silyl enol ether **211** (0.072 mmol, 1 equiv) and pentane (0.35 mL, 0.25 M). The resulting solution was cooled to 0 ºC and NaO*t*-Bu (69 mg, 0.72 mmol, 10 equiv) was added. Then $CHBr_3$ (0.067 mL, 0.72 mmol, 10 equiv) was added fast dropwise. The reaction mixture was then stirred at 23 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction was diluted with brine and the product was

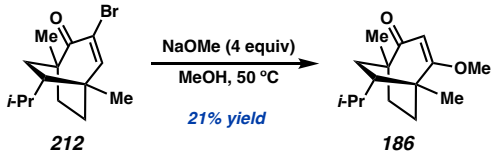
extracted three times with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (SiO_2, 0–5% EtOAc/Hexanes) to afford α-bromo enone **212** as a colorless oil (5.7 mg, 0.02 mmol, 28% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (s, 1H), 2.06 (dtq, *J* = 10.1, 7.0, 3.5 Hz, 1H), 1.79 – 1.70 (m, 1H), 1.70 – 1.58 (m, 3H), 1.57 – 1.51 (m, 1H), 1.50 – 1.43 (m, 1H), 1.38 (m, 1H), 1.23 (s, 3H), 1.23 (s, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.69 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 199.0, 159.0, 126.3, 47.8, 47.2, 42.1, 39.0, 30.2, 29.3, 27.7, 27.2, 27.0, 21.4, 17.3.

IR (Neat Film, NaCl): 2960, 2932, 2868, 1680, 1464, 1372, 1068, 850 cm^{-1}.

HRMS (FI+): *m/z* calc'd for $C_{14}H_{21}OBr$ $[M]^+$: 284.0770, found 284.0771.

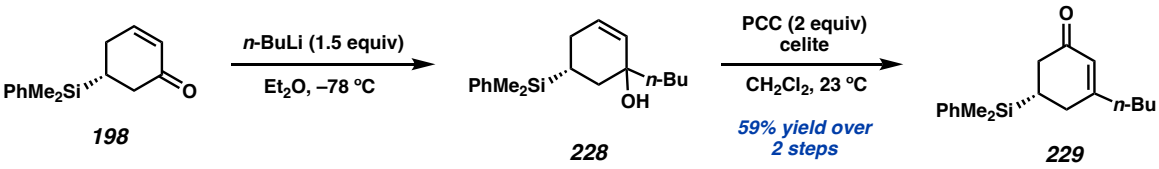


212 *186*

1-(1,4-dimethyl-5-((triethylsilyl)oxy)bicyclo[2.2.2]octa-2,5-dien-2-yl)ethan-1-one (186)

A flame dried vial was charged with α-bromo enone **212** (5.8 mg, 0.02 mmol, 1 equiv), sodium methoxide (4.4 mg, 0.08 mmol, 4 equiv), and methanol (1 mL, 0.02 M) and the resulting mixture was stirred at reflux overnight. The crude product was diluted with water, and the product was extracted three times with EtOAc. The combined organic layers were further washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (SiO_2, 0–10% EtOAc/Hexanes) to afford the corresponding β-methoxy enone **186** as a colorless oil (1.0 mg, 0.004 mmol, 21% yield). Tentative assignment.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.60 (s, 1H), 3.58 (s, 3H), 2.13 – 2.03 (m, 1H), 1.70 – 1.66 (m, 1H), 1.63 (dd, *J* = 10.4, 7.5 Hz, 1H), 1.54 – 1.47 (m, 1H), 1.45 (d, *J* = 11.7 Hz, 1H), 1.41 – 1.34 (m, 1H), 1.24 (s, 3H), 1.20 (s, 3H), 1.18 – 1.14 (m, 1H), 1.03 (d, *J* = 10.7 Hz, 1H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.70 (d, *J* = 6.9 Hz, 3H).



(*S*)-3-butyl-5-(dimethyl(phenyl)silyl)cyclohex-2-en-1-one (229)

A round bottom flask was charged with chiral enone **198**[20] (1.00 g, 4.34 mmol, 1 equiv) and Et_2O (10.0 mL, 0.43 M) and cooled to –78 °C. *n*-BuLi (2.6 mL, 6.51 mmol, 1.5 equiv) was added dropwise. Upon complete consumption of starting material (as determined by TLC), the reaction was diluted with H_2O and the product was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude allylic alcohol **228** was used without further purification.

A round bottom flask open to air was charged with celite and CH_2Cl_2 (17 mL, 0.25 M). PCC (1.87 g, 8.68 mmol, 2 equiv) was added to the slurry and stirred until the PCC is evenly dispersed. Crude allylic alcohol **228** was added to the mixture using minimal CH_2Cl_2 to transfer. Upon complete consumption of starting material (as determined by TLC), the reaction was filtered over celite with Et_2O. The crude reaction mixture was washed with 1 M NaOH, 1 M HCl, saturated $NaHCO_3$ x3, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude

product was purified by flash silica gel column chromatography (SiO_2, 10% EtOAc/Hexanes) to afford enone **229** as a colorless oil (734 mg, 2.56 mmol, 59% yield).

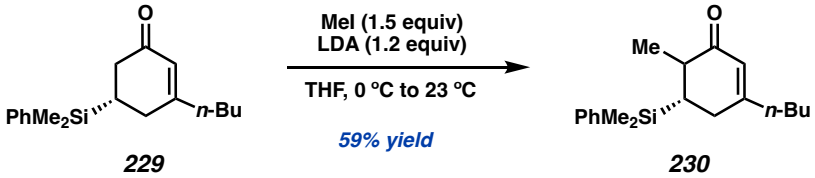
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.27 (m, 2H), 7.24 – 7.16 (m, 3H), 5.64 (d, J = 1.1 Hz, 1H), 2.24 – 2.17 (m, 1H), 2.00 – 1.86 (m, 5H), 1.47 – 1.20 (m, 4H), 1.18 – 1.07 (m, 2H), 0.72 (t, J = 7.2 Hz, 3H), 0.15 (s, 3H), 0.15 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 200.3, 167.5, 136.4, 134.1, 129.5, 128.1, 125.1, 38.1, 37.7, 31.0, 29.2, 23.0, 22.5, 14.0, -5.1, -5.2.

IR (Neat Film, NaCl): 2956, 2932, 2870, 2358, 1670, 1628, 1426, 1252, 1112, 816, 774 cm^{-1}.

HRMS (FD+): *m/z* calc'd for $C_{18}H_{26}OSi$ $[M]^+$: 286.1747, found 286.1756.

Optical Rotation: $[\alpha]_D^{21}$ –36.7 (c 1.00, $CHCl_3$).



229 ***230***

(5S)-3-butyl-5-(dimethyl(phenyl)silyl)-6-methylcyclohex-2-en-1-one (230)

A flame dried round bottom flask was charged with *i*-Pr_2NH (0.44 mL, 3.16 mmol, 1.25 equiv) and THF (1.8 mL, 1.75 M). The solution was cooled to 0 ºC and *n*-BuLi (1.2 mL, 3.04 mmol, 1.2 equiv) was added dropwise. The resultant solution was stirred for 30 min at 0 ºC. The corresponding enone **229** (725 mg, 2.53 mmol, 1.0 equiv) in THF (2.0 mL, 1.25 M) was added dropwise and stirring was continued at 0 ºC for 30 minutes. MeI (0.24 mL, 3.80 mmol, 1.5 equiv) was added dropwise. The reaction was gradually warmed to 23 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction was diluted with a saturated solution of NH_4Cl and the product was extracted three times

with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (SiO_2, 5% EtOAc/Hexanes) to afford the corresponding methylated enone **230** as a colorless oil (451 mg, 1.50 mmol, 59% yield).

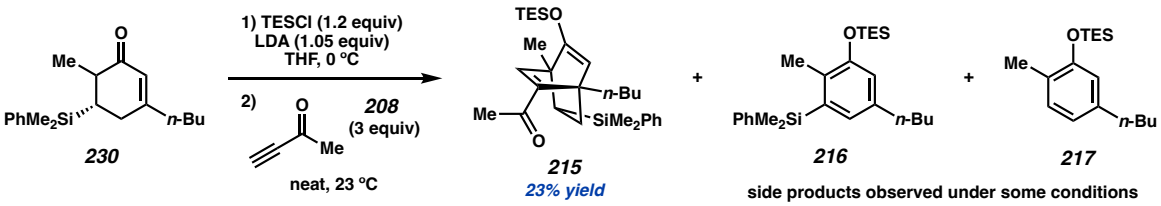
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.46 (m, 2H), 7.39 – 7.33 (m, 3H), 5.78 (p, *J* = 1.4 Hz, 1H), 2.37 – 2.27 (m, 2H), 2.24 – 2.14 (m, 1H), 2.10 (t, *J* = 7.8 Hz, 2H), 1.47 – 1.37 (m, 3H), 1.35 – 1.24 (m, 2H), 1.13 (d, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H), 0.34 (s, 3H), 0.32 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.6, 165.4, 137.8, 133.9, 129.3, 128.1, 124.6, 42.0, 37.5, 30.4, 29.2, 28.9, 22.5, 16.6, 14.0, -3.2, -3.5.

IR (Neat Film, NaCl): 2958, 2930, 2860, 2358, 1668, 1426, 1252, 1112, 814 cm^{-1}.

HRMS (FD+): *m/z* calc'd for $C_{19}H_{28}OSi$ $[M]^+$: 300.1904, found 300.1900.

Optical Rotation: $[\alpha]_D^{21}$ –57.4 (c 1.00, $CHCl_3$).



1-((1*S*,8*R*)-1-butyl-8-(dimethyl(phenyl)silyl)-4-methyl-5-((triethylsilyl)oxy)bicyclo[2.2.2]octa-2,5-dien-2-yl)ethan-1-one (215)

A flame dried vial was charged with *i*-Pr_2NH (0.04 mL, 0.31 mmol, 1.25 equiv) and THF (0.15 mL, 2.0 M). The solution was cooled to 0 ºC and *n*-BuLi (0.12 mL, 0.30 mmol, 1.2 equiv) was added dropwise. The resultant solution was stirred for 30 min at 0 ºC. Enone **230** (74.9 mg, 0.25 mmol, 1.0 equiv) in THF (0.25 mL, 1.0 M) was added dropwise and stirring was continued at 0 ºC for 30 minutes. The solution was cooled to –78 ºC and TESCl

(0.05 mL, 0.30 mmol, 1.2 equiv) was added dropwise. The reaction was gradually warmed to 23 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction was diluted with a saturated solution of NH_4Cl and the product was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

The crude diene (20.7 mg, 0.05 mmol, 1 equiv) was transferred to a vial and was placed under high vacuum to remove trace solvent and then backfilled with N_2. Dienophile **208** (12 µL, 0.15 mmol, 3 equiv) was added and the mixture was stirred neat at 23 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction mixture was loaded directly onto silica for flash silica gel column chromatography (SiO_2, 0–2.5–5% EtOAc/Hexanes) to afford product **215** (5.4 mg, 0.012 mmol, 23% yield). Aromatization side products **216** and **217** were observed under some reaction conditions tested (see Table 3.1).

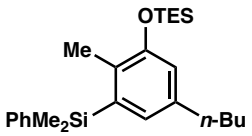
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 – 7.47 (m, 2H), 7.36 (dd, *J* = 5.1, 1.9 Hz, 3H), 6.81 (s, 1H), 4.98 (s, 1H), 2.45 (ddd, *J* = 13.1, 11.3, 4.2 Hz, 1H), 2.24 (s, 3H), 1.69 – 1.53 (m, 2H), 1.46 – 1.33 (m, 5H), 1.29 (s, 3H), 1.05 (dd, *J* = 10.3, 3.9 Hz, 1H), 1.01 (t, *J* = 7.9 Hz, 9H), 0.96 (t, *J* = 7.2 Hz, 3H), 0.70 (m, 6H), 0.38 (s, 3H), 0.27 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 199.2, 157.2, 154.6, 148.8, 140.5, 133.7, 128.7, 127.7, 109.9, 49.2, 47.0, 40.7, 34.3, 33.7, 29.2, 28.2, 25.9, 23.7, 19.7, 14.3, 6.8, 5.0, -2.9, -3.5.

IR (Neat Film, NaCl): 3066, 2956, 2926, 2876, 1670, 1646, 1492, 1358, 1252, 1208, 1110 cm^{-1}.

HRMS (FD+): *m/z* calc'd for $C_{29}H_{46}O_2Si_2$ $[M]^+$: 482.3031, found 482.3046.

Optical Rotation: $[\alpha]_D^{21}$ 28.3 (c 1.00, $CHCl_3$).



216

(5-butyl-2-methyl-3-((triethylsilyl)oxy)phenyl)dimethyl(phenyl)silane (216)

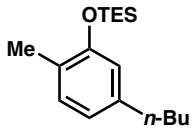
Tentative assignment. Suspected mixture of rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (ddd, J = 6.2, 3.4, 2.0 Hz, 2H), 7.34 – 7.29 (m, 3H), 6.91 (d, J = 1.8 Hz, 1H), 6.67 (d, J = 1.7 Hz, 1H), 2.56 – 2.50 (m, 2H), 2.07 (s, 3H), 1.62 – 1.51 (m, 2H), 1.41 – 1.31 (m, 2H), 1.01 – 0.96 (m, 9H), 0.93 (t, J = 7.3 Hz, 3H), 0.79 – 0.70 (m, 6H), 0.55 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.6, 141.4, 140.5, 139.1, 138.4, 135.0, 135.0, 132.5, 129.7, 129.7, 129.2, 128.7, 128.6, 121.0, 119.7, 36.7, 36.3, 35.1, 34.6, 23.6, 23.4, 17.5, 17.2, 15.0, 14.9, 7.7, 7.7, 6.4, 6.4, 0.4, -0.0. Additional peaks due to suspected mixture of rotamers.

IR (Neat Film, NaCl): 3066, 3046, 2956, 2930, 2876, 1562, 1458, 1410, 1282, 1248, 1142, 812, 776, 730 cm^{-1}.

HRMS (FD+): *m/z* calc'd for $C_{25}H_{40}OSi_2$ $[M]^+$: 412.2612, found 412.2612.



217

(5-butyl-2-methylphenoxy)triethylsilane (217)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (dd, *J* = 7.6, 0.8 Hz, 1H), 6.67 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.59 (d, *J* = 1.7 Hz, 1H), 2.52 (t, *J* = 7.6 Hz, 2H), 2.17 (s, 3H), 1.62 – 1.50 (m, 2H),

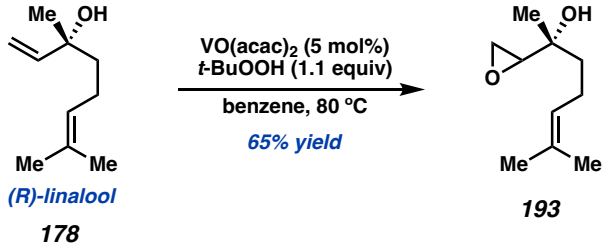
1.39 – 1.28 (m, 2H), 1.00 (t, J = 7.9 Hz, 9H), 0.92 (t, J = 7.4 Hz, 3H), 0.76 (qd, J = 7.8, 0.9 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 141.6, 130.6, 125.8, 121.2, 118.7, 35.3, 33.8, 22.4, 16.4, 14.1, 6.9, 5.5.

IR (Neat Film, NaCl): 2956, 2930, 2876, 1578, 1414, 1274, 1004, 834, 732 cm^{-1}.

HRMS (FI+): *m/z* calc'd for $C_{17}H_{30}OSi$ $[M]^+$: 278.2060, found 278.2078.

3.5.2.3 PROGRESS TOWARD HYPERMOIN A



(R)-linalool
178

193

(2*R*)-6-methyl-2-(oxiran-2-yl)hept-5-en-2-ol (193)

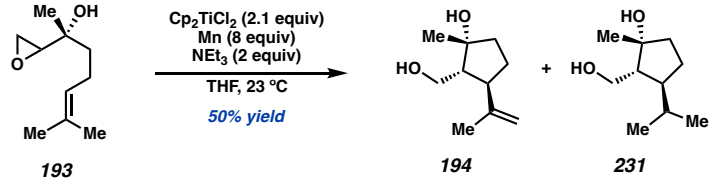
Procedure adapted from Opatz and coworkers.[19] A round bottom flask is equipped with a reflux condenser and charged with *(R)*-linalool (7.1 mL, 40 mmol, 1 equiv) and benzene (154 mL, 0.26 M). The solution is heated to 65 ºC. $VO(acac)_2$ (530 mg, 2 mmol, 5 mol%) is added and the reaction mixture is heated to 80 ºC for 10 min. Then *t*-BuOOH (5.5 M in decane, 8.0 mL, 44 mmol, 1.1 equiv) was added dropwise via syringe pump over 1 h. Upon complete consumption of starting material (as determined by TLC), the reaction was cooled to 23 ºC. The reaction mixture was washed with saturated $NaHCO_3$ and brine and then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (SiO_2, 20% EtOAc/Hexanes) to afford epoxide **193** as a pale yellow oil (4.39 g, 25.8 mmol, 65% yield, 1.5:1 dr). All characterization data match those reported in the literature.

Diastereomer 1:

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.16 – 5.07 (m, 1H), 2.93 (dd, *J* = 3.9, 2.8 Hz, 1H), 2.85 (dd, *J* = 5.1, 2.8 Hz, 1H), 2.74 (dd, *J* = 5.1, 4.0 Hz, 1H), 2.18 – 2.07 (m, 2H), 1.69 (s, 3H), 1.62 (s, 3H), 1.65–1.55 (m, 2H), 1.32 (s, 3H).

Diastereomer 2:

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.16 – 5.07 (m, 1H), 2.97 (dd, *J* = 4.1, 2.8 Hz, 1H), 2.77 (dd, *J* = 5.1, 2.8 Hz, 1H), 2.70 (dd, *J* = 5.1, 4.1 Hz, 1H), 2.18 – 2.07 (m, 2H), 1.69 (s, 3H), 1.63 (s, 3H), 1.65–1.55 (m, 2H), 1.20 (s, 3H).

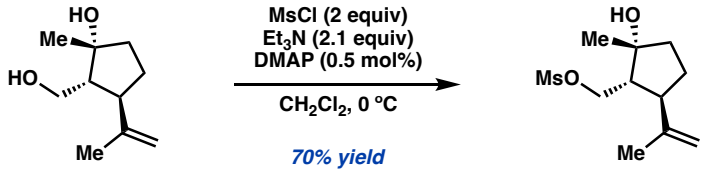


(1*R*,2*R*,3*R*)-2-(hydroxymethyl)-1-methyl-3-(prop-1-en-2-yl)cyclopentan-1-ol (194)

Procedure adapted from Opatz and coworkers.[19] A round bottom flask is charged with Mn (12.51 g, 228 mmol, 8 equiv), Cp_2TiCl_2 (14.88 g, 60 mmol, 2.1 equiv), and THF (150 mL, 0.4 M). The mixture is stirred for 30 minutes until it turns from a dark red to green color. A solution of epoxide **193** (4.84 g, 28.5 mmol, 1 equiv) and NEt_3 (7.9 mL, 57 mmol, 2 equiv) in THF (100 mL, 0.3 M) was added to the reaction mixture. Upon complete consumption of starting material (as determined by TLC), the reaction mixture was filtered to remove insoluble metals and then concentrated under reduced pressure to ~100 mL. The crude reaction mixture was diluted with Et_2O and 2N HCl and then filtered to remove the precipitate. The organic layer was separated and concentrated to approximately half the volume. 2N HCl was added and the mixture was stirred for 10 min. The mixture was separated, and the organic layer was washed with 2N HCl two times and then with brine.

The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (SiO_2, 45% EtOAc/Hexanes) to afford diol **194** as an orange waxy solid (2.43 g, 14.3 mmol, 50% yield) as a mixture with the reduced compound **231**. This mixture could be used without further purification in subsequent steps. To separate the products, the mixture was dissolved in hexanes with minimal Et_2O and cooled to –20 ºC. The formed precipitate was filtered off and washed with hexanes (–20 ºC). This was repeated 2 times to yield pure **194** as a white solid (767 mg, 4.45 mmol). All characterization data match those reported in the literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.78 (dq, *J* = 2.5, 0.9 Hz, 1H), 4.76 (dq, *J* = 2.8, 1.5 Hz, 1H), 3.91 (dt, *J* = 11.3, 3.5 Hz, 1H), 3.72 (ddd, *J* = 11.4, 7.0, 5.1 Hz, 1H), 2.87 (dt, *J* = 10.9, 8.7 Hz, 1H), 1.95 (dtd, *J* = 12.7, 8.3, 5.8 Hz, 1H), 1.84 – 1.72 (m, 2H), 1.72 (s, 3H), 1.60 (ddd, *J* = 10.8, 5.0, 3.2 Hz, 1H), 1.55 – 1.46 (m, 1H), 1.41 (s, 3H).



194 ***195***

((1*R*,2*R*,5*R*)-2-hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclopentyl)methyl methanesulfonate (195)

A round bottom flask was charged with diol **194** (757 mg, 4.45 mmol, 1 equiv), DMAP, (2.7 mg, 0.02 mmol, 0.5 mol%), and CH_2Cl_2 (23 mL, 0.2 M) and the mixture was cooled to 0 ºC. Et_3N (1.3 mL, 9.34 mmol, 2.1 equiv) was added dropwise which was followed by a dropwise addition of MsCl (0.69 mL, 8.89 mmol, 2 equiv). Upon complete consumption

of starting material (as determined by TLC), the reaction mixture was washed with saturated brine two times. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (SiO_2, 40% EtOAc/Hexanes) to afford mesylate **195** as a pale yellow oil (775 mg, 3.12 mmol, 70% yield).

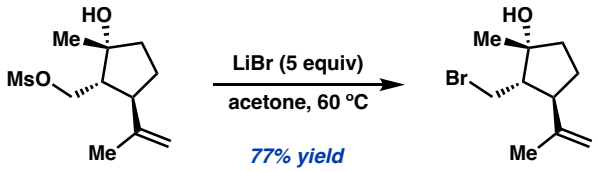
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.76 (q, *J* = 1.2 Hz, 2H), 4.44 (dd, *J* = 10.1, 8.9 Hz, 1H), 4.19 (dd, *J* = 10.1, 4.1 Hz, 1H), 3.00 (s, 3H), 2.52 (dt, *J* = 11.1, 8.6 Hz, 1H), 2.02 – 1.87 (m, 2H), 1.87 – 1.73 (m, 2H), 1.70 (t, *J* = 1.1 Hz, 3H), 1.52 (dddd, *J* = 12.6, 9.3, 8.5, 6.0 Hz, 1H), 1.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9, 111.6, 79.6, 69.4, 50.9, 48.9, 41.7, 37.3, 28.6, 28.2, 19.0.

IR (Neat Film, NaCl): 3538, 2964, 1644, 1456, 1352, 1172, 976, 944 cm^{-1}.

HRMS (FD+): *m/z* calc'd for $C_{11}H_{20}O_4S$ $[M]^+$: 248.1077, found 248.1088.

Optical Rotation: $[\alpha]_D^{21}$ –18.4 (c 1.00, $CHCl_3$).



195 ***196***

(1*R*,2*S*,3*R*)-2-(bromomethyl)-1-methyl-3-(prop-1-en-2-yl)cyclopentan-1-ol (196)

A round bottom flask was charged with mesylate **195** (775 mg, 3.12 mmol, 1 equiv) and acetone (15.6 mL, 0.2 M). LiBr (1.36 g, 15.6 mmol, 5 equiv) was added and the solution was heated to 60 ºC. Upon complete consumption of starting material (as determined by TLC, after ~3 hours product decomposition results in lower yields), the reaction mixture

was cooled to 23 ºC and concentrated. The crude residue was diluted with CH_2Cl_2 and H_2O. The product was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (SiO_2, 10% EtOAc/Hexanes) to afford alkyl bromide **196** as a colorless oil (561 mg, 2.41 mmol, 77% yield).

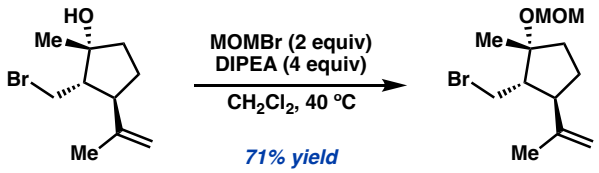
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.77 (dh, *J* = 3.7, 1.1 Hz, 2H), 3.56 (dd, *J* = 10.3, 8.9 Hz, 1H), 3.42 (dd, *J* = 10.3, 3.5 Hz, 1H), 2.46 (ddd, *J* = 10.4, 9.1, 7.5 Hz, 1H), 1.98 (ddd, *J* = 11.0, 9.0, 3.5 Hz, 1H), 1.92 – 1.72 (m, 3H), 1.70 (t, *J* = 1.1 Hz, 3H), 1.51 – 1.42 (m, 1H), 1.48 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.0, 111.7, 79.9, 53.4, 52.5, 41.9, 31.9, 29.7, 28.1, 19.3.

IR (Neat Film, NaCl): 3450, 3072, 2962, 2872, 1642, 1458, 1376, 1168, 896 cm^{-1}.

HRMS (FI+): *m/z* calc'd for $C_{10}H_{17}OBr$ $[M]^+$: 232.0457, found 232.0468.

Optical Rotation: $[\alpha]_D^{21}$ –16.2 (c 1.00, $CHCl_3$).



196 ***197***

(1*R*,2*S*,3*R*)-2-(bromomethyl)-1-(methoxymethoxy)-1-methyl-3-(prop-1-en-2-yl)cyclopentane (197)

A round bottom flask was charged with alcohol **196** (561 mg, 2.41 mmol, 1 equiv) and CH_2Cl_2 (12.0 mL, 0.2 M) and the mixture is cooled to 0 ºC. DIPEA (1.7 mL, 9.62 mmol, 4 equiv) was added followed by a dropwise addition of MOMBr (0.39 mL, 4.81 mmol, 2

equiv). The reaction mixture was then slowly heated to 40 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction mixture was cooled to 23 ºC diluted with saturated NH_4Cl. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (SiO_2, 0–5% EtOAc/Hexanes) to afford MOM protected alkyl bromide **197** as a colorless oil (474 mg, 1.71 mmol, 71% yield).

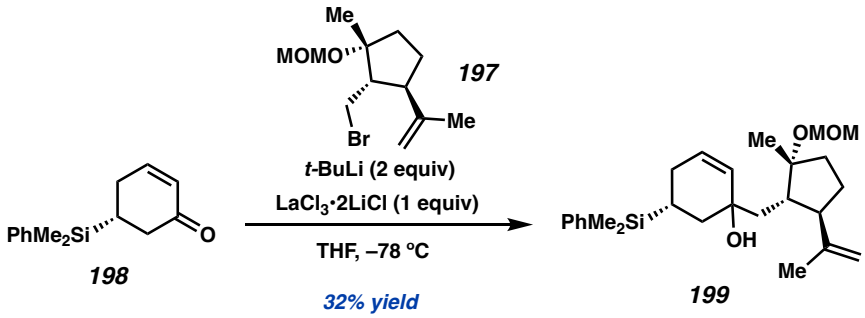
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.76 (m, 2H), 4.72 (q, *J* = 7.2 Hz, 2H), 3.71 (dd, *J* = 10.2, 8.1 Hz, 1H), 3.39 (s, 3H), 3.32 (dd, *J* = 10.3, 4.0 Hz, 1H), 2.60 – 2.49 (m, 1H), 2.07 – 2.00 (m, 2H), 1.94 – 1.83 (m, 1H), 1.72 (t, *J* = 1.1 Hz, 3H), 1.64 – 1.55 (m, 1H), 1.53 – 1.41 (m, 1H), 1.49 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 111.5, 91.4, 85.1, 56.0, 55.6, 52.3, 37.4, 30.7, 27.8, 24.3, 19.1.

IR (Neat Film, NaCl): 3072, 2962, 1458, 1142, 1086, 1038, 918, 894 cm^{-1}.

HRMS (FI+): *m/z* calc'd for $C_{12}H_{21}O_2Br$ $[M]^+$: 276.0719, found 276.0735. Unable to obtain a mass difference <5 ppm with various ionization methods.

Optical Rotation: $[\alpha]_D^{21}$ –36.9 (c 1.00, $CHCl_3$).



(5R)-5-(dimethyl(phenyl)silyl)-1-(((1S,2R,5R)-2-(methoxymethoxy)-2-methyl-5-(prop-1-en-2-yl)cyclopentyl)methyl)cyclohex-2-en-1-ol (199)

Enone **198**[20] (115.2 mg, 0.5 mmol, 1 equiv) was azeotroped with benzene (0.5 mL) 2 times and placed under high vacuum for 3 h to remove trace benzene. Alkyl bromide **197** (138.6 mg, 0.5 mmol, 1 equiv) was azeotroped with benzene (0.5 mL) 2 times and placed under high vacuum for 3 h to remove trace benzene. Both vials are backfilled with N_2, then enone **198** was dissolved in THF (2.5 mL, 0.2 M) and cooled to –78 ºC. $LaCl_3$•2LiCl (0.6 M in THF, 0.83 mL, 1 equiv) was added dropwise and the resulting solution was stirred 30 minutes. Alkyl bromide **197** was dissolved in THF (0.63 mL, 0.8 M) and cooled to –78 ºC. *t*-BuLi (1.7 M in pentane, 0.69 mL, 2 equiv) was added dropwise and the resulting solution was stirred for 15 minutes. Both solutions were warmed to –40 ºC and enone **198** and $LaCl_3$•2LiCl solution was added as fast as possible via cannula to the stirring solution of the alkyl Li generated from **197**. Upon complete consumption of starting material (as determined by TLC), silica gel was added followed by MeOH (~0.1 mL). The slurry was filtered over celite with CH_2Cl_2, and the resulting solution was concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (SiO_2, 10–15% EtOAc/Hexanes) to afford allylic alcohol **199** as a colorless oil (67.9 mg, 0.16 mmol, 32% yield).

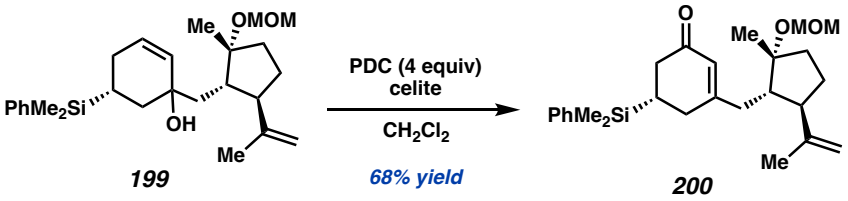
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.46 (m, 2H), 7.36 – 7.32 (m, 3H), 5.66 (ddd, J = 10.2, 4.0, 2.8 Hz, 1H), 5.59 (dq, J = 10.2, 1.9 Hz, 1H), 4.77 (dq, J = 3.8, 1.2 Hz, 2H), 4.71 (s, 2H), 3.37 (s, 3H), 2.40 (dt, J = 10.2, 8.6 Hz, 1H), 2.01 – 1.81 (m, 5H), 1.77 – 1.68 (m, 2H), 1.67 (s, 3H), 1.65 – 1.55 (m, 3H), 1.53 – 1.40 (m, 2H), 1.26 (s, 3H), 1.14 (dddd, *J* = 14.3, 9.8, 7.2, 2.3 Hz, 1H), 0.27 (s, 3H), 0.27 (s, 3H).

^{13}C NMR (100 MHz, CDCl3): δ 148.4, 137.8, 134.7, 134.2, 134.1, 129.1, 127.9, 127.8, 127.6, 111.5, 91.7, 86.1, 70.4, 55.8, 54.3, 49.0, 40.2, 37.6, 37.2, 28.7, 26.0, 25.1, 19.5, 19.2, -5.2, -5.4.

IR (Neat Film, NaCl): 3464, 2938, 2354, 1710, 1374, 1246, 1078, 1040, 834 cm^{-1}.

HRMS (FD+): *m/z* calc'd for $C_{26}H_{40}O_3Si$ $[M]^+$: 428.2741, found 428.2740.

Optical Rotation: $[\alpha]_D^{21}$ –56.0 (c 1.00, $CHCl_3$).



(*S*)-5-(dimethyl(phenyl)silyl)-3-(((1*S*,2*R*,5*R*)-2-(methoxymethoxy)-2-methyl-5-(prop-1-en-2-yl)cyclopentyl)methyl)cyclohex-2-en-1-one (200)

A round bottom flask open to air was charged with celite and CH_2Cl_2 (0.6 mL, 0.25 M). PDC (238 mg, 0.63 mmol, 4 equiv) was added to the slurry and stirred until the PCC is evenly dispersed. Allylic alcohol **199** (67.9 mg, 0.16 mmol, 1 equiv) was added to the mixture using minimal CH_2Cl_2 to transfer. Upon complete consumption of starting material (as determined by TLC), the reaction was filtered over celite with Et_2O. The crude reaction mixture was washed with 1 M NaOH, 1 M HCl, saturated $NaHCO_3$ x3, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (SiO_2, 10–15% EtOAc/Hexanes) to afford enone **200** as a colorless oil (45. mg, 0.11 mmol, 68% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.45 (m, 2H), 7.40 – 7.33 (m, 3H), 5.91 – 5.85 (m, 1H), 4.66 (d, *J* = 1.0 Hz, 2H), 4.61 (ddd, *J* = 7.3, 2.2, 1.3 Hz, 2H), 3.35 (s, 3H), 2.58 – 2.45

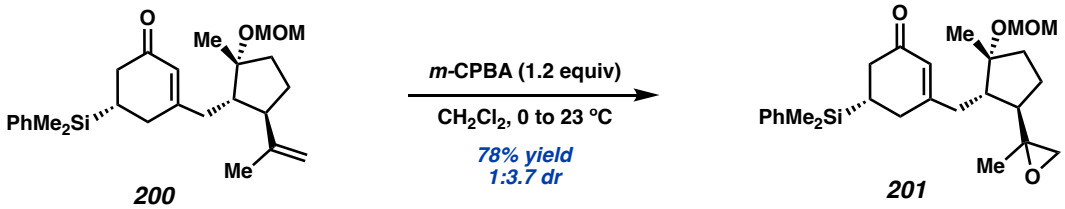
(m, 2H), 2.35 (ddd, *J* = 16.3, 2.7, 1.7 Hz, 1H), 2.16 – 1.98 (m, 5H), 1.88 (ddt, *J* = 12.7, 10.2, 7.5 Hz, 1H), 1.68 (dt, *J* = 10.5, 6.6 Hz, 1H), 1.57 (dd, *J* = 1.4, 0.8 Hz, 3H), 1.55 – 1.37 (m, 3H), 1.25 (s, 3H), 0.32 (s, 6H).

^{13}C NMR (100 MHz, CDCl3): δ 200.0, 167.7, 147.3, 136.4, 134.0, 129.5, 128.1, 126.8, 111.5, 91.4, 85.5, 55.6, 52.3, 51.5, 37.9, 36.7, 36.6, 31.3, 28.1, 23.4, 22.8, 18.8, -5.2, -5.4.

IR (Neat Film, NaCl): 3420, 3068, 2954, 1666, 1426, 1376, 1252, 1144, 1038, 814 cm^{-1}.

HRMS (FD+): *m/z* calc'd for $C_{26}H_{38}O_3Si$ $[M]^+$: 426.2585, found 426.2582.

Optical Rotation: $[\alpha]_D^{21}$ 26.0 (c 1.00, $CHCl_3$).



(*S*)-5-(dimethyl(phenyl)silyl)-3-(((1*S*,2*R*,5*R*)-2-(methoxymethoxy)-2-methyl-5-((*R*)-2-methyloxiran-2-yl)cyclopentyl)methyl)cyclohex-2-en-1-one (201)

A flame dried 1 dram vial was charged with enone **200** (45.9 mg, 0.11 mmol, 1 equiv) and CH_2Cl_2 (0.54 mL, 0.2 M) and cooled to 0 ºC. *m*-CPBA (22.3 mg, 0.13 mmol, 1.2 equiv) was added to the reaction which was slowly warmed to 23 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction was filtered over celite with CH_2Cl_2. The crude reaction mixture was diluted with approximately 1:1 $Na_2S_2O_3$ and $NaHCO_3$ solutions. The layers were separated, and the product was extracted three times with CH_2Cl_2. The combined organic layer was washed with $NaHCO_3$ two times, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (SiO_2, 25–30%

EtOAc/Hexanes) to afford enone **201** as a colorless oil (37.2 mg, 0.08 mmol, 78% yield, 1:3.7 dr). Diastereomers are inconsequential and, therefore, are not separated.

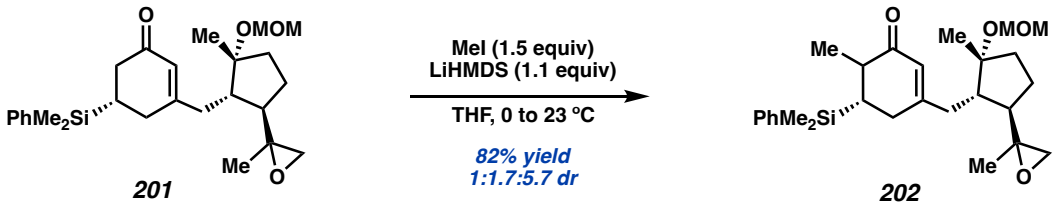
^{1}H NMR (400 MHz, $CDCl_3$) major diastereomer: δ 7.52 – 7.45 (m, 2H), 7.42 – 7.34 (m, 3H), 5.89 (d, *J* = 1.9 Hz, 1H), 4.66 – 4.60 (m, 2H), 3.33 (s, 3H), 2.62 – 2.33 (m, 4H), 2.30 – 2.10 (m, 4H), 2.07 – 1.68 (m, 3H), 1.62 – 1.50 (m, 2H), 1.51 – 1.39 (m, 2H), 1.22 (s, 3H), 1.18 (s, 3H), 0.33 (d, *J* = 2.6 Hz, 6H).

^{13}C NMR (100 MHz, CDCl3) major diastereomer: δ 199.8, 167.1, 136.2, 133.9, 129.5, 128.0, 126.5, 91.3, 85.5, 58.3, 55.6, 53.1, 50.0, 49.8, 37.9, 37.6, 36.6, 30.9, 25.4, 23.1, 22.8, 19.0, -5.3, -5.5.

IR (Neat Film, NaCl): 2954, 2354, 1730, 1666, 1250, 1144, 1038, 834 cm^{-1}.

HRMS (FD+): *m/z* calc'd for $C_{26}H_{38}O_4Si$ $[M]^+$: 442.2534, found 442.2533.

Optical Rotation: $[\alpha]_D^{21}$ 11.1 (c 1.00, $CHCl_3$).



(5*S*)-5-(dimethyl(phenyl)silyl)-3-(((1*S*,2*R*,5*R*)-2-(methoxymethoxy)-2-methyl-5-((*R*)-2-methyloxiran-2-yl)cyclopentyl)methyl)-6-methylcyclohex-2-en-1-one (202)

A flame dried round bottom flask was charged with LHMDS (107.9 mg, 0.64 mmol, 1.1 equiv) and THF (0.37 mL, 1.75 M). The solution was cooled to 0 ºC and enone **201** (259.4 mg, 0.59 mmol, 1.0 equiv) in THF (0.47 mL, 1.25 M) was added dropwise and stirring was continued at 0 ºC for 30 minutes. MeI (55 µL, 0.88 mmol, 1.5 equiv) was added dropwise. The reaction was gradually warmed to 23 ºC. Upon complete consumption of starting

material (as determined by TåLC), the reaction was diluted with a saturated solution of NH_4Cl and the product was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (SiO_2, 25% EtOAc/Hexanes) to afford the corresponding methylated enone **202** as a colorless oil (219 mg, 0.48 mmol, 82% yield, 1:1.7:5.7 dr). Diastereomers are inconsequential and, therefore, are not separated.

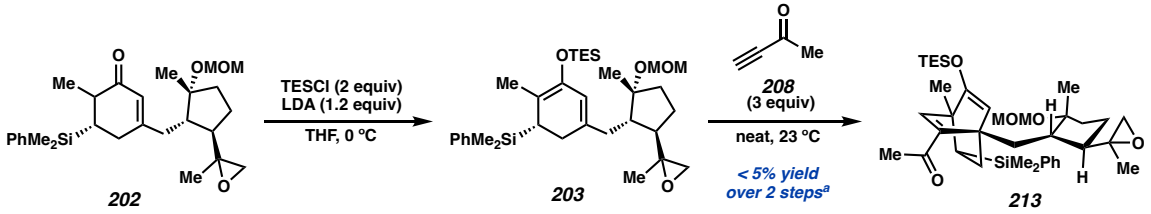
^{1}H NMR (400 MHz, $CDCl_3$) major diastereomer: δ 7.52 – 7.45 (m, 2H), 7.40 – 7.33 (m, 3H), 5.86 (s, 1H), 4.68 – 4.58 (m, 2H), 3.33 (s, 3H), 2.61 – 2.38 (m, 3H), 2.39 – 2.06 (m, 4H), 2.06 – 1.76 (m, 3H), 1.79 – 1.57 (m, 1H), 1.57 – 1.45 (m, 1H), 1.47 – 1.36 (m, 2H), 1.19 (s, 3H), 1.18 (s, 3H), 1.14 (d, J = 6.9 Hz, 3H), 0.37 (s, 3H), 0.35 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) all diastereomers: δ 202.0, 165.2, 137.7, 133.8, 133.7, 129.3, 129.2, 129.2, 128.0, 127.9, 125.9, 91.3, 85.3, 58.3, 57.7, 55.5, 55.5, 53.0, 52.9, 50.0, 49.8, 49.0, 42.1, 42.0, 37.2, 36.6, 36.5, 36.3, 31.6, 30.9, 30.9, 29.1, 29.0, 27.9, 25.2, 25.0, 23.2, 23.0, 22.7, 19.0, 18.3, 16.1, 15.9, 14.1, -3.0, -3.1, -3.7, -4.01, -4.03.

IR (Neat Film, NaCl): 2958, 1666, 1460, 1374, 1252, 1144, 1090, 1036, 770 cm^{-1}.

HRMS (FD+): *m/z* calc'd for $C_{27}H_{40}O_4Si$ $[M]^+$: 456.2680, found 466.2687.

Optical Rotation: $[\alpha]_D^{21}$ –1.1 (c 1.00, $CHCl_3$).



1-((1*S*,8*R*)-8-(dimethyl(phenyl)silyl)-1-(((1*R*,2*R*,5*S*)-2-(methoxymethoxy)-2-methyl-5-(2-methyloxiran-2-yl)cyclopentyl)methyl)-4-methyl-5-((triethylsilyl)oxy)bicyclo[2.2.2]octa-2,5-dien-2-yl)ethan-1-one (213)

A flame dried vial was charged with *i*-Pr_2NH (19 µL, 0.14 mmol, 1.25 equiv) and THF (0.14 mL, 1.0 M). The solution was cooled to 0 ºC and *n*-BuLi (53 µL, 0.13 mmol, 1.2 equiv) was added dropwise. The resultant solution was stirred for 30 min at 0 ºC. Enone **202** (50.0 mg, 0.11 mmol, 1.0 equiv) in THF (0.14 mL, 0.8 M) was added dropwise and stirring was continued at 23 ºC for 30 minutes. The solution was cooled to 0 ºC and TESCl (37 µL, 0.22 mmol, 2.0 equiv) was added dropwise. Upon complete consumption of starting material (as determined by TLC), the reaction was diluted with a saturated solution of NH_4Cl and the product was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

The crude diene **203** was transferred to a vial and was placed under high vacuum to remove trace solvent and then backfilled with N_2. Dienophile **208** (26 µL, 0.33 mmol, 3 equiv) was added and the mixture was stirred neat at 23 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction mixture was loaded directly onto silica for flash silica gel column chromatography (SiO_2, 10–15–25% EtOAc/Hexanes) and the fractions containing product were them purified further via preparatory TLC (10% EtOAc/Toluene x3) to afford product **213** (less than 3.0 mg, 0.005 mmol, 4% yield, 1:1.6 dr). Diastereomers were inseparable and relative stereochemistry was unable to be assigned.

^{1}H NMR (600 MHz, $CDCl_3$) mixture of diastereomers: δ 7.47 – 7.43 (m, 4H), 7.33 – 7.29 (m, 5.6H), 6.70 (s, 0.7H, minor), 6.69 (s, 1H, major), 5.28 (s, 1H, major), 5.25 (s,

0.7H, minor), 4.79 (d, J = 7.1 Hz, 1H, major), 4.74 (d, J = 7.1 Hz, 0.7H, minor), 4.59 (d, J = 7.1 Hz, 0.7H, minor), 4.56 (d, J = 7.1 Hz, 1H, major), 3.38 (s, 2.1H, minor), 3.37 (s, 3H, major), 2.69 (q, J = 4.9 Hz, 2H), 2.61 – 2.54 (m, 1.6H), 2.38 (d, J = 4.6 Hz, 0.7H), 2.28 – 2.24 (m, 2H), 2.21 (s, 3H, major), 2.19 (s, 2.1H, minor), 2.17 – 1.91 (m, 6H), 1.80 – 1.73 (m, 1H), 1.64 (s, 1H), 1.52 – 1.32 (m, 8H), 1.31 (s, 2.1H, minor), 1.31 (s, 3H, major), 1.25 (s, 2.1H, minor), 1.24 (s, 3H, major), 1.17 (s, 2.1H, minor), 1.15 (s, 3H, major), 0.96 – 0.92 (m, 15.3H), 0.70 – 0.58 (m, 10.2H), 0.33 (s, 5H), 0.23 (s, 3H, major), 0.23 (s, 2.1H, minor). **HRMS (FD+):** *m/z* calc'd for $C_{37}H_{58}O_5Si_2$ $[M]^+$: 638.3817, found 638.3840.

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APPENDIX 4

Spectra Relevant to Chapter 3: Progress Toward the Total Synthesis of Hypermoin A

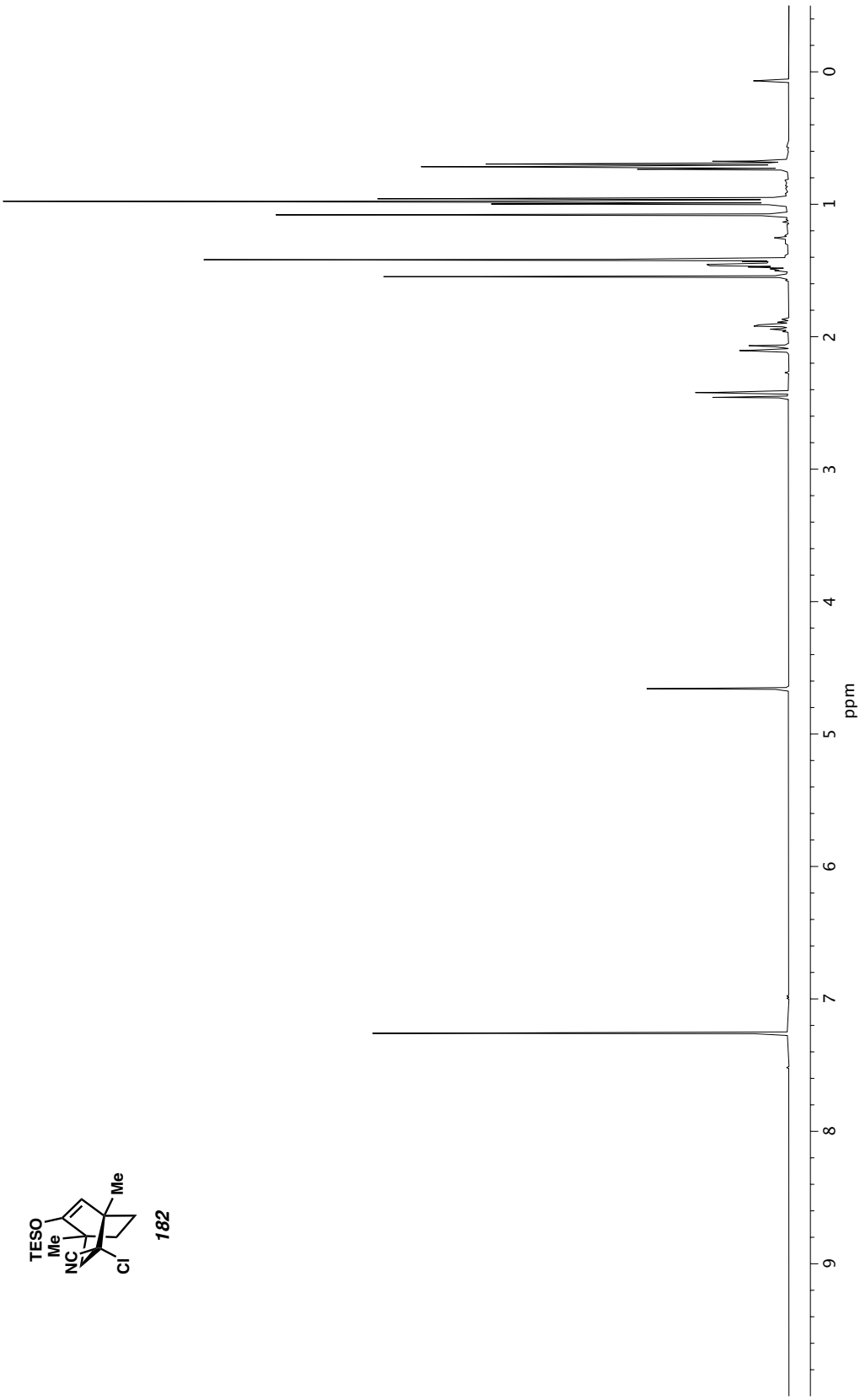


Figure A4.1. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***182****.*

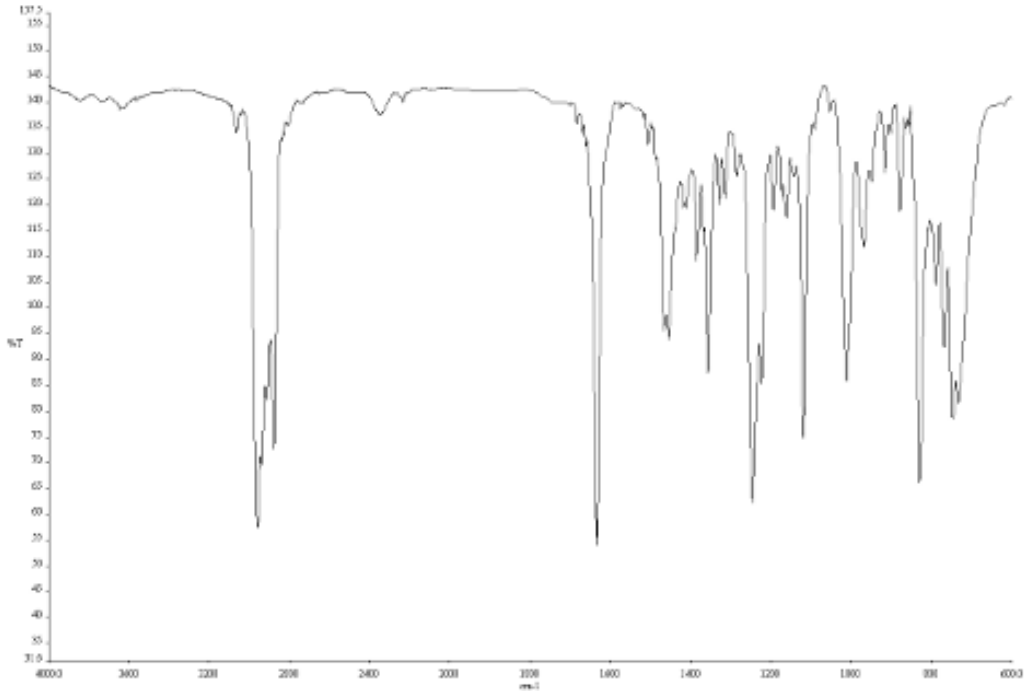


Figure A4.2. *Infrared spectrum (Thin Film, NaCl) of compound* ***182****.*

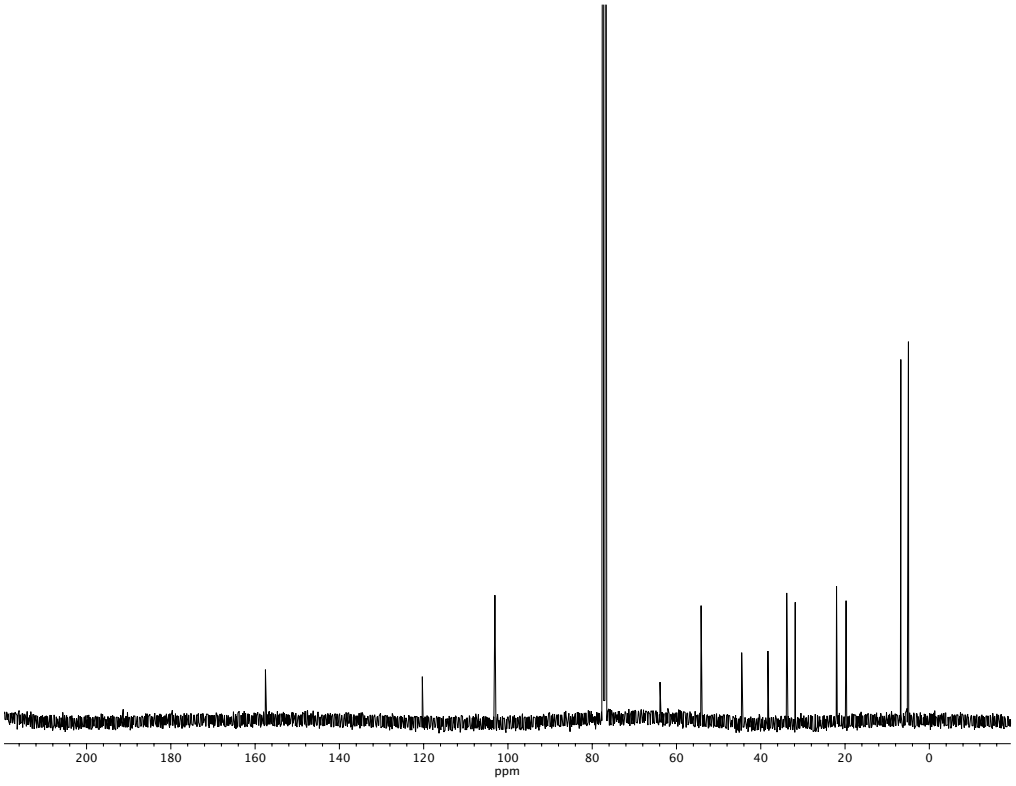


Figure A4.3. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***182****.*

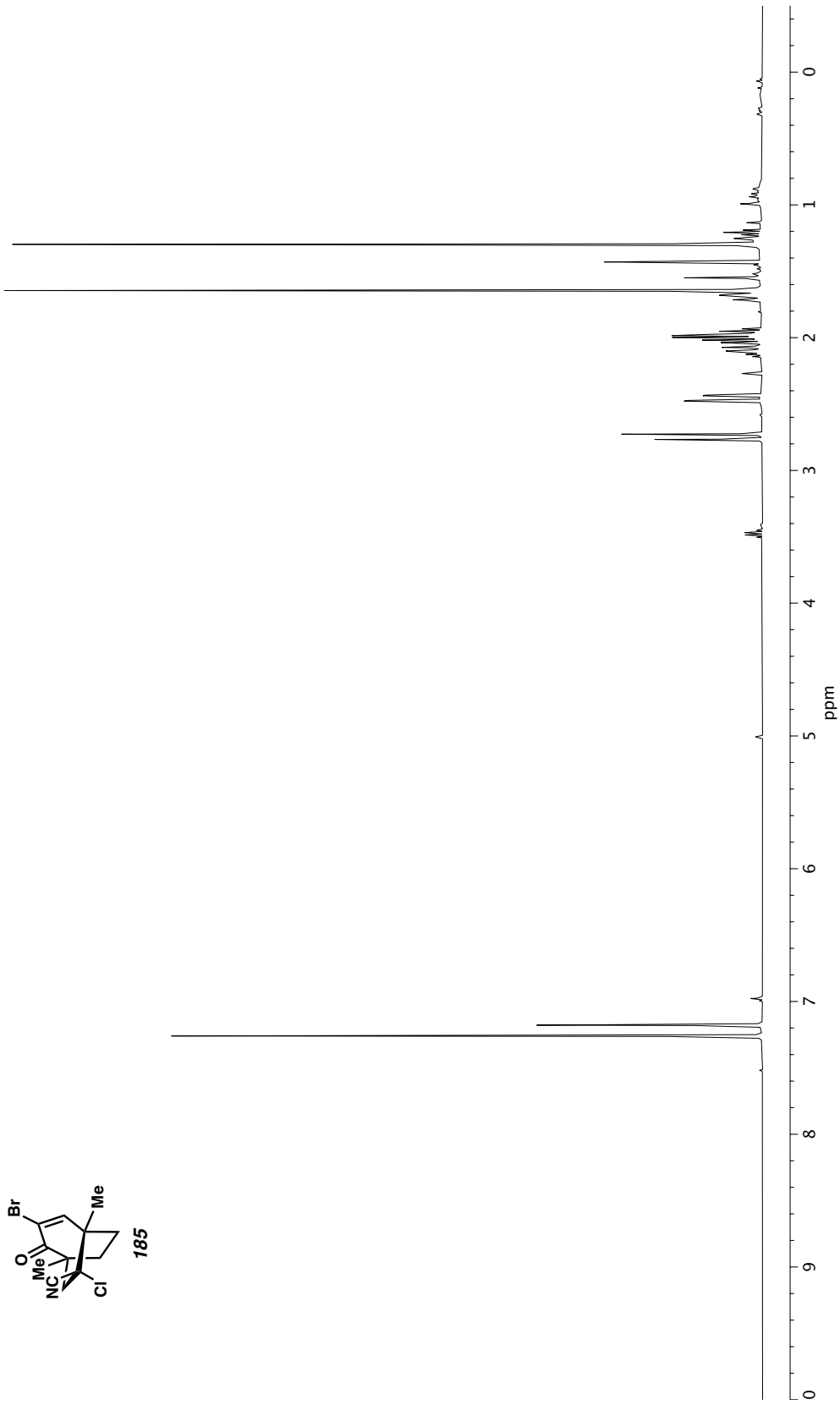


Figure A4.4. *^1H NMR (400 MHz, $CDCl_3$) of compound **185**.*

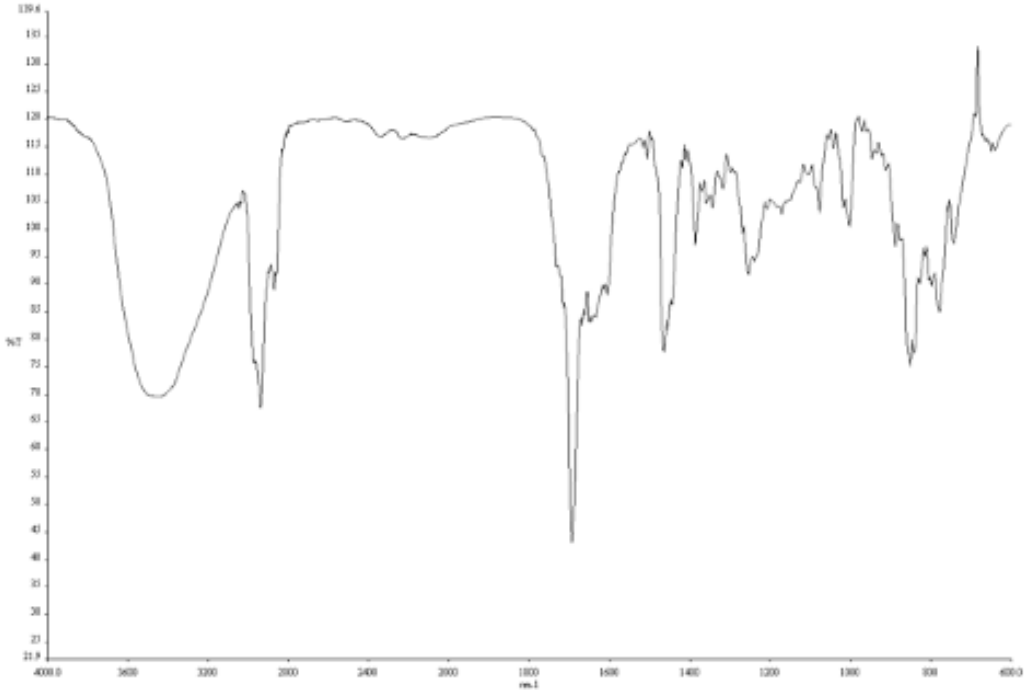


Figure A4.5. *Infrared spectrum (Thin Film, NaCl) of compound* ***185****.*

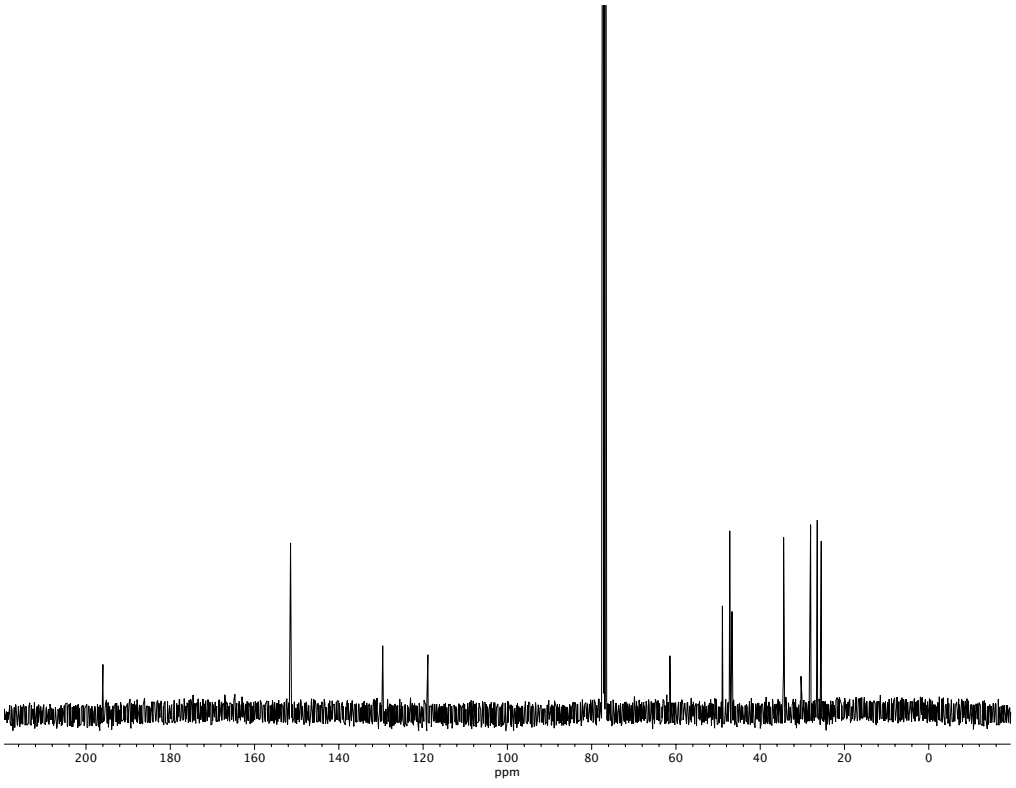


Figure A4.6. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***185****.*

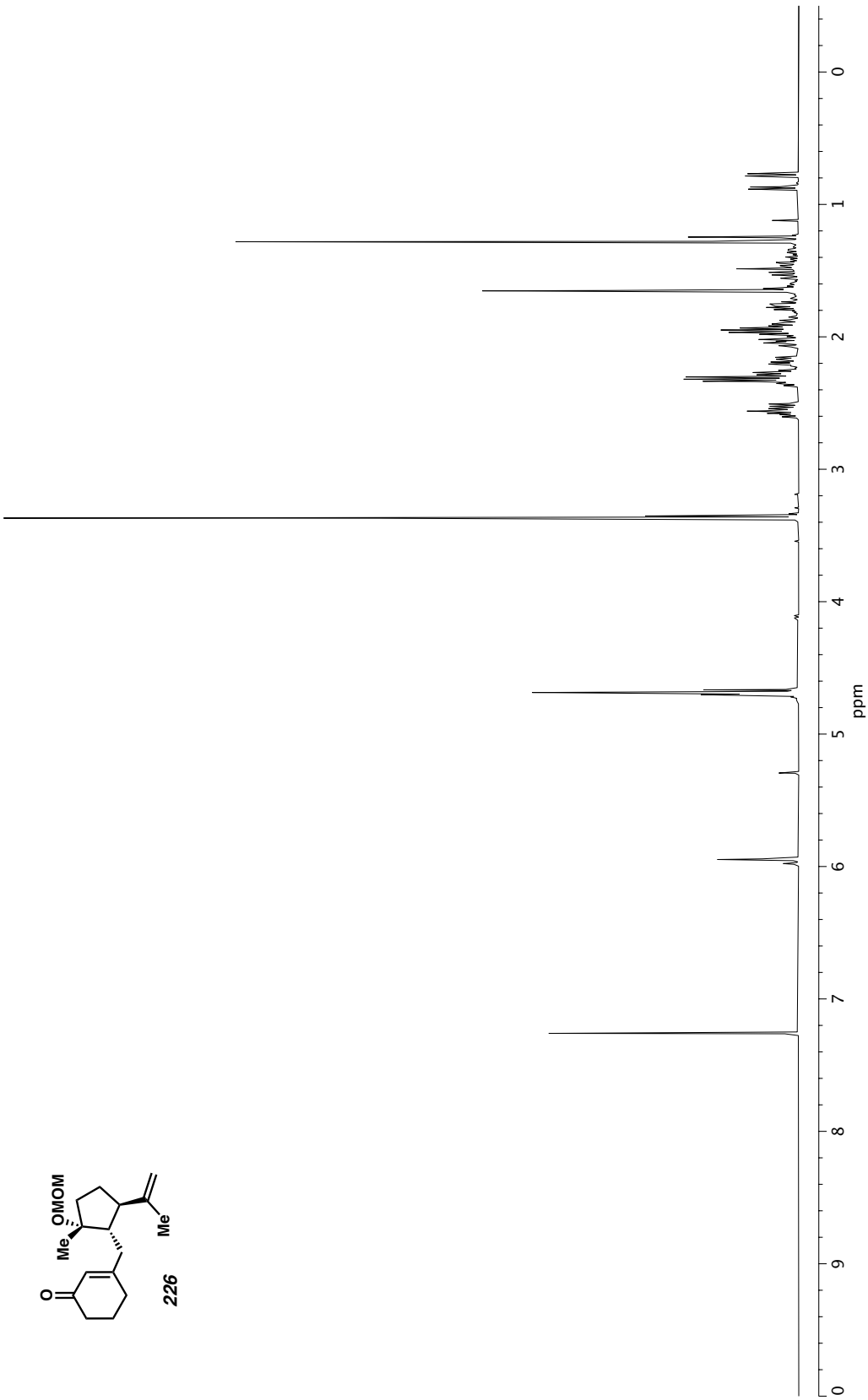


Figure A4.7. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***226****.*

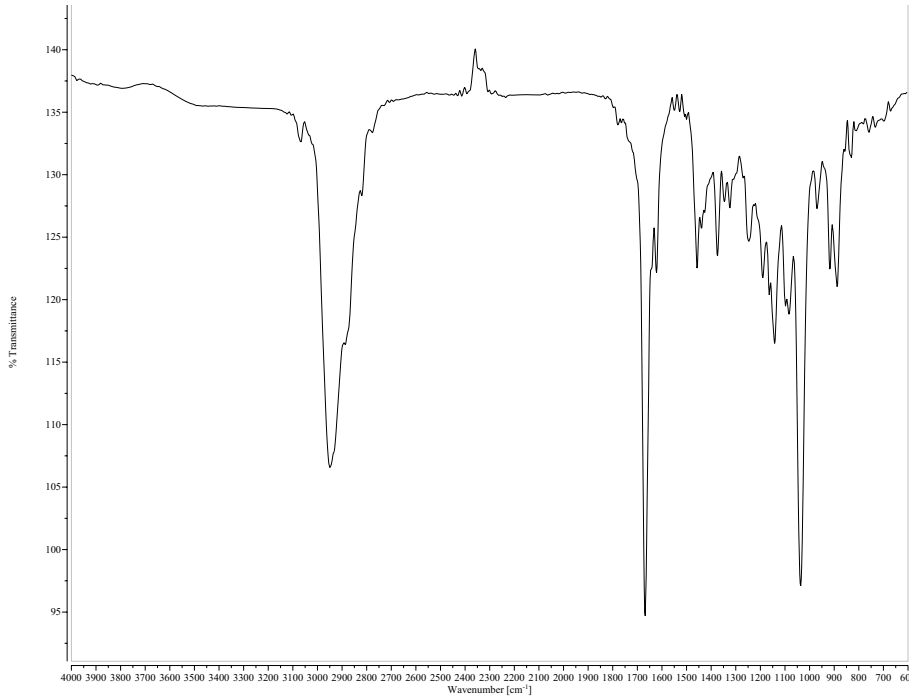


Figure A4.8. *Infrared spectrum (Thin Film, NaCl) of compound* ***226****.*

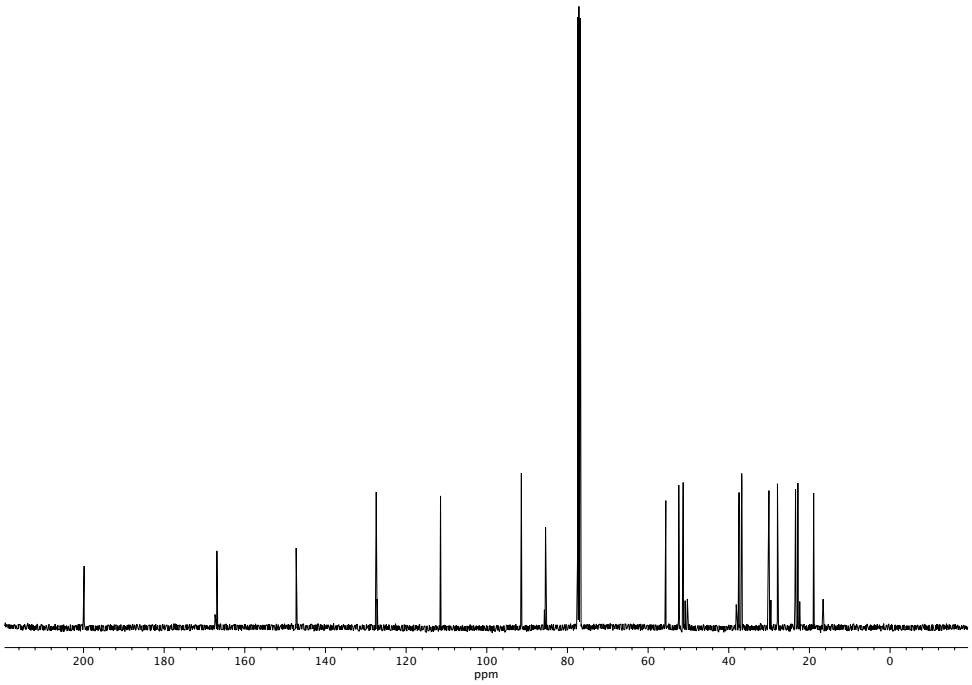


Figure A4.9. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***226****.*

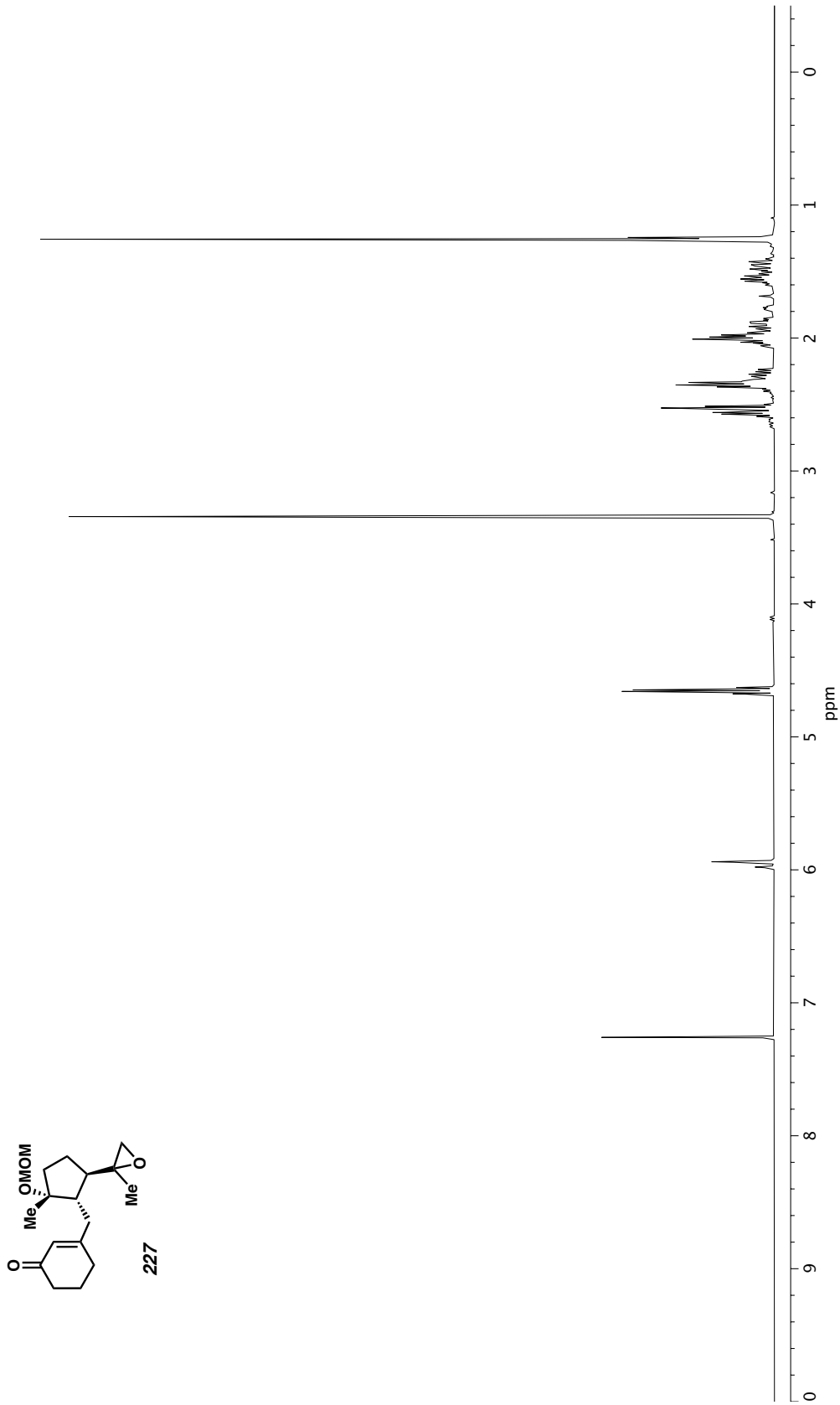


Figure A4.10. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***227****.*

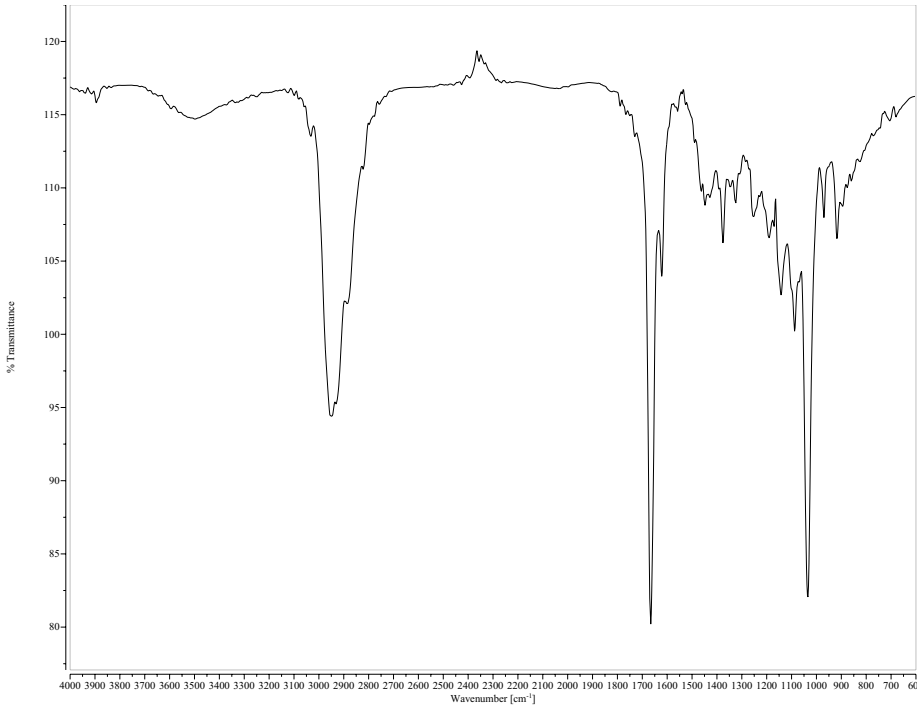


Figure A4.11. *Infrared spectrum (Thin Film, NaCl) of compound* ***227****.*

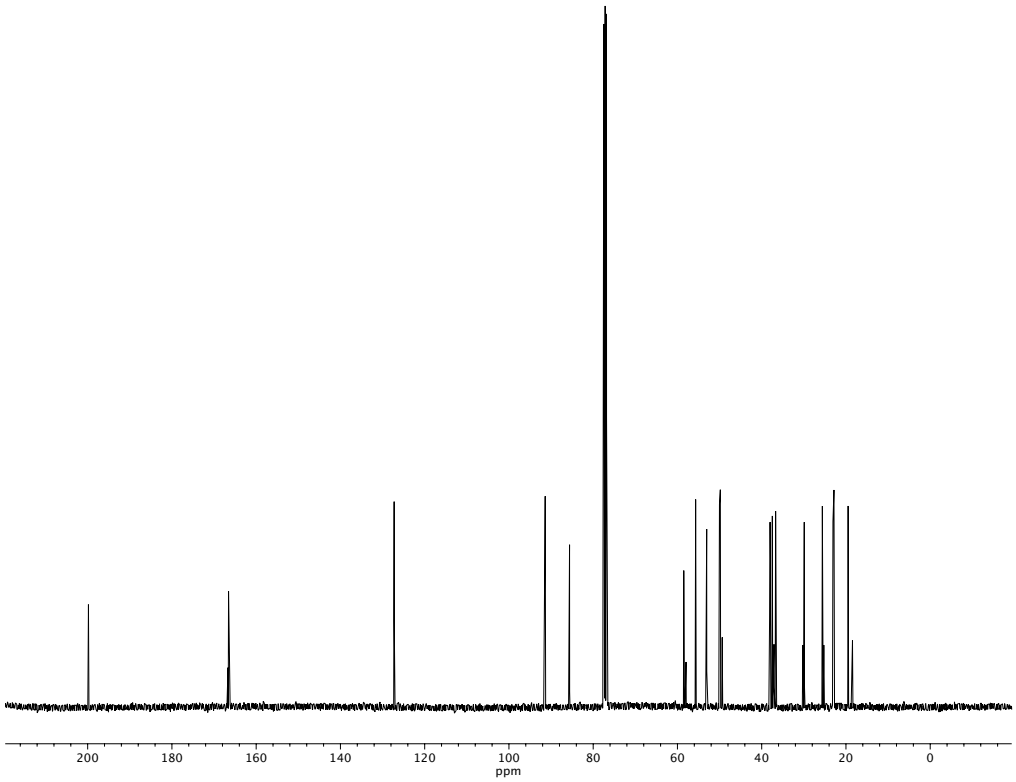


Figure A4.12. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***227****.*

Figure A4.13. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***205****.*

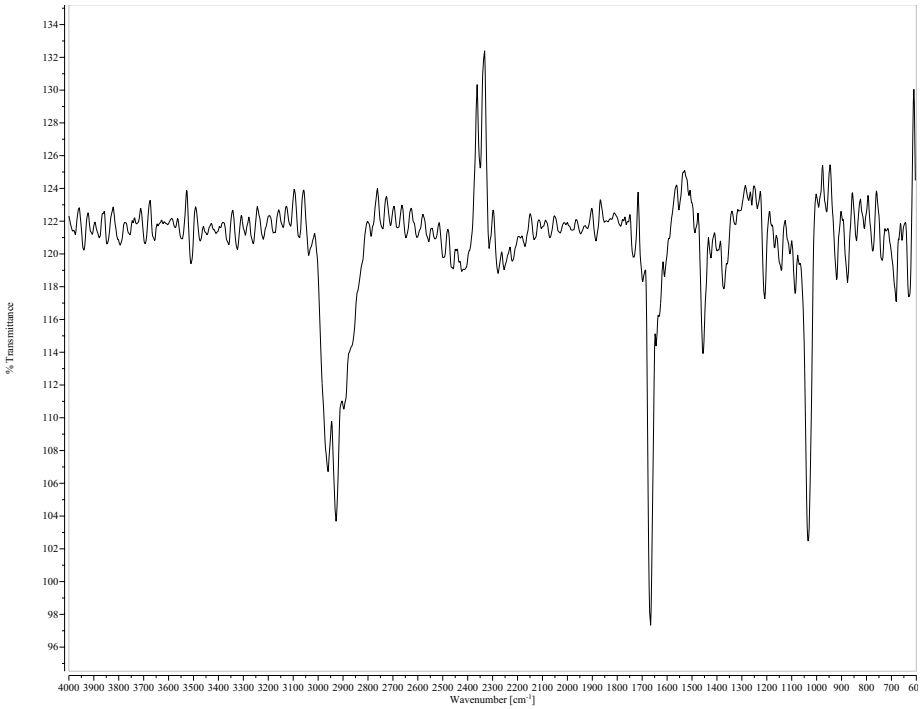


Figure A4.14. *Infrared spectrum (Thin Film, NaCl) of compound* ***205****.*

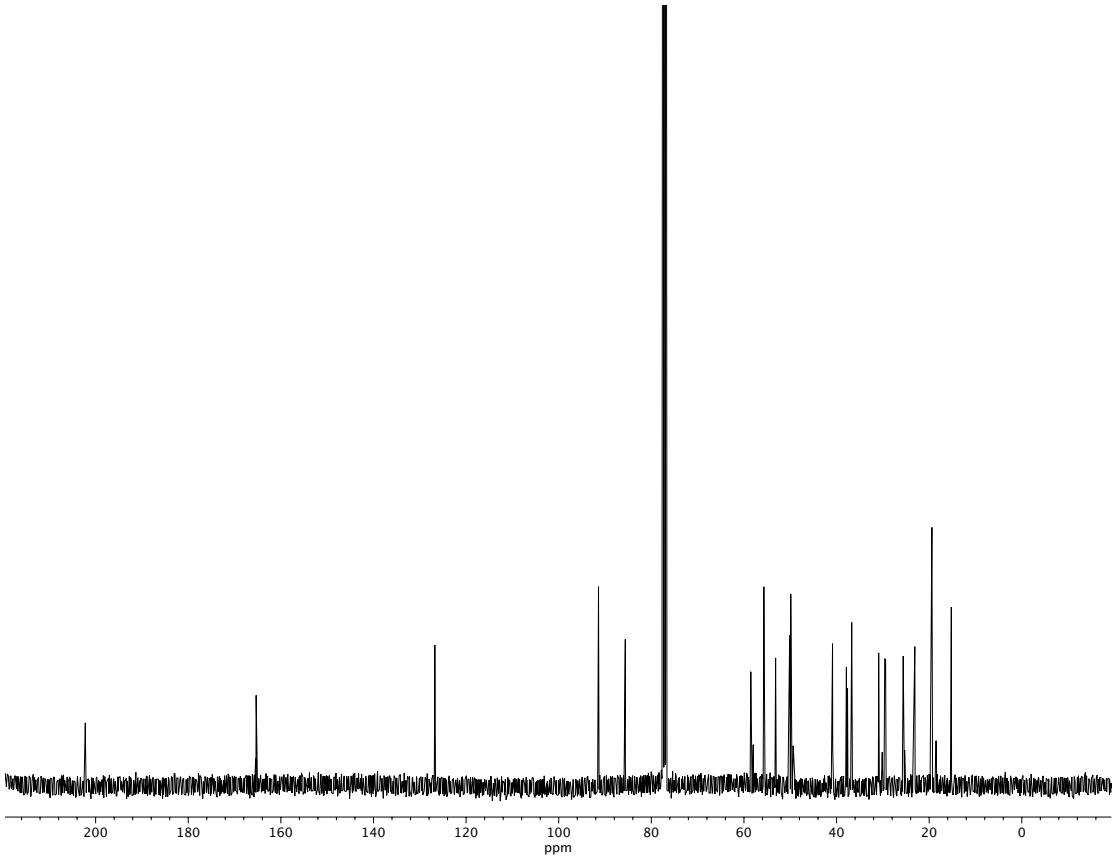


Figure A4.15. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***205****.*

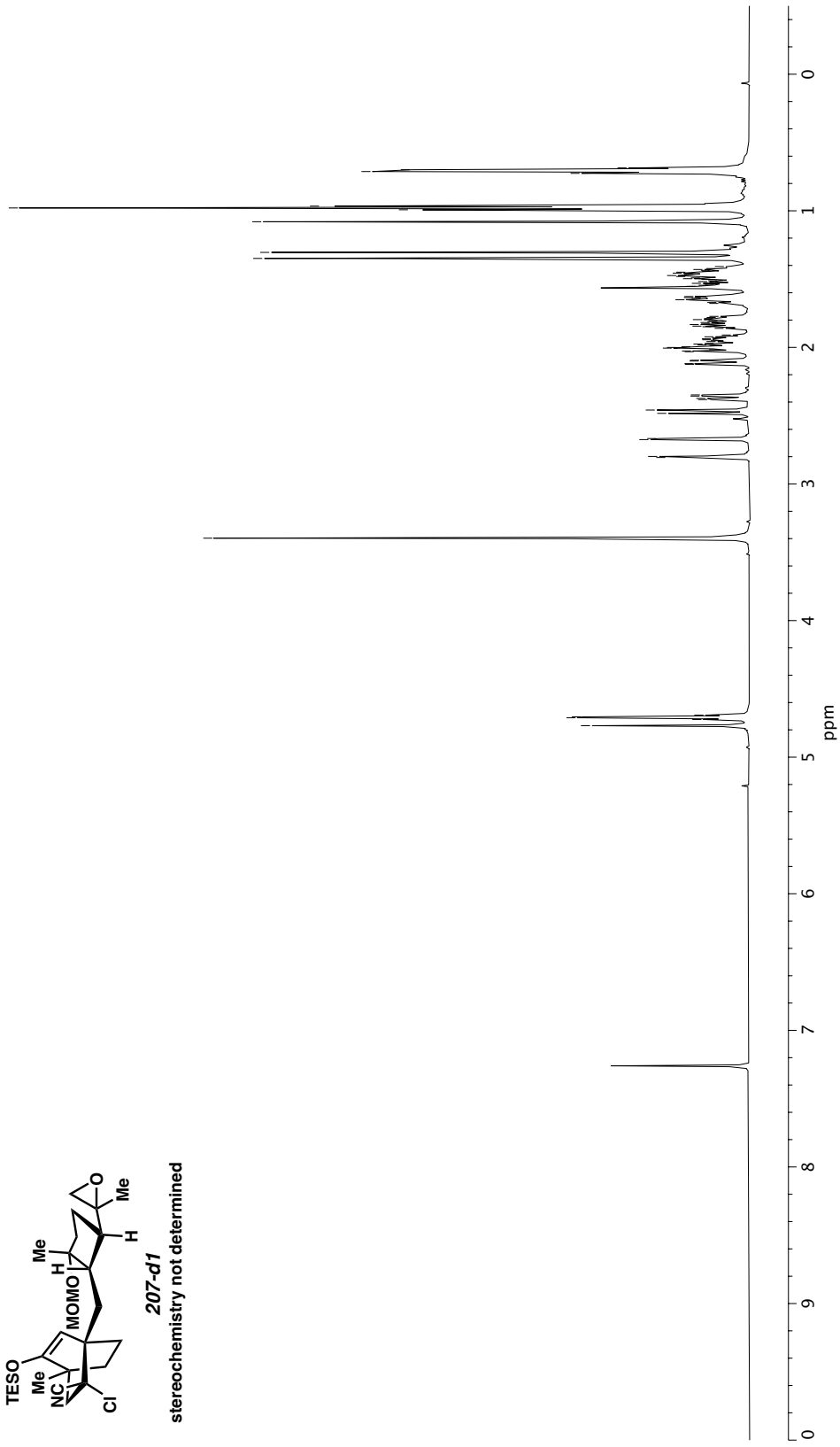


Figure A4.16. *^1H NMR (600 MHz, $CDCl_3$) of compound* ***207-d1***.

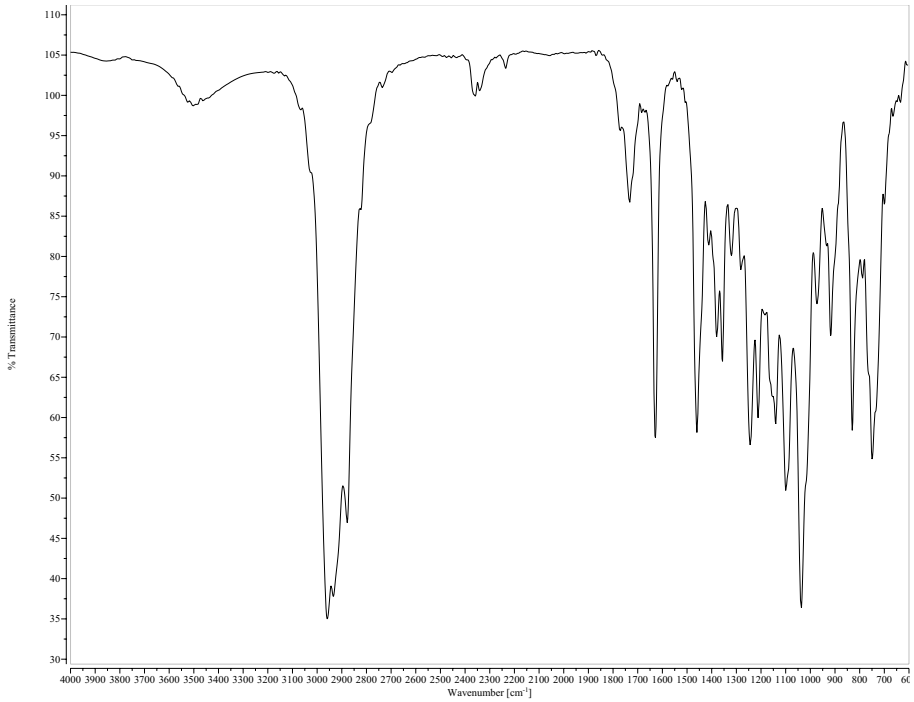


Figure A4.17. *Infrared spectrum (Thin Film, NaCl) of compound* ***207-d1***.

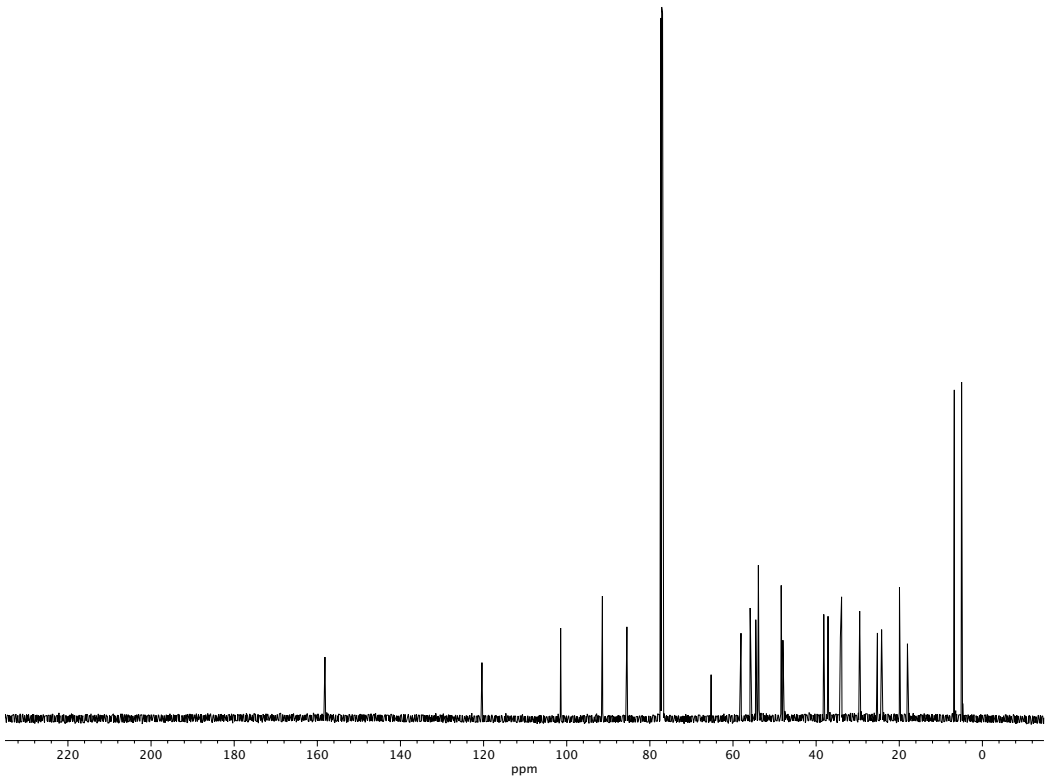


Figure A4.18. *^{13}C NMR (151 MHz, $CDCl_3$) of compound* ***207-d1***.

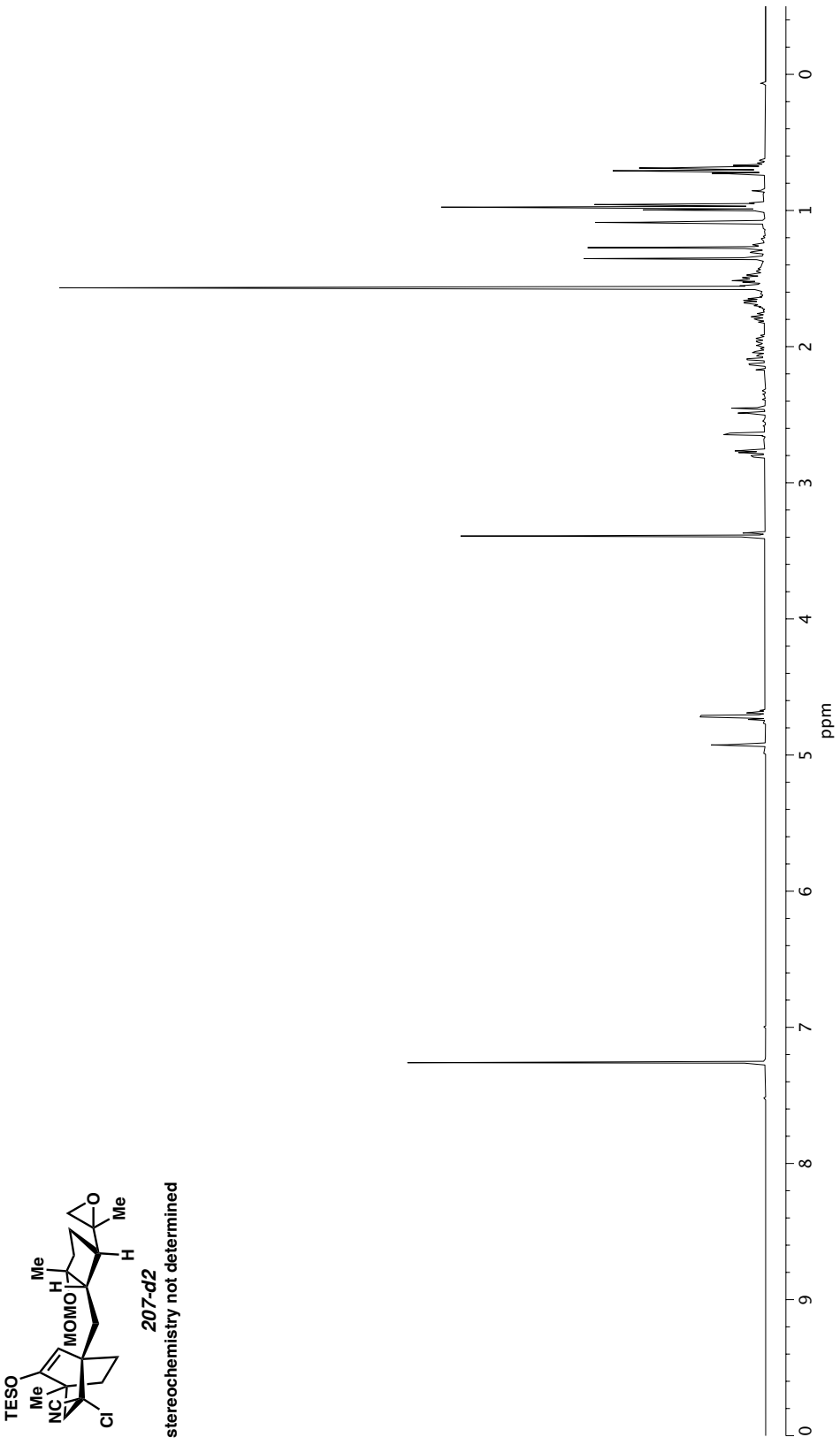


Figure A4.19. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***207-d2***.

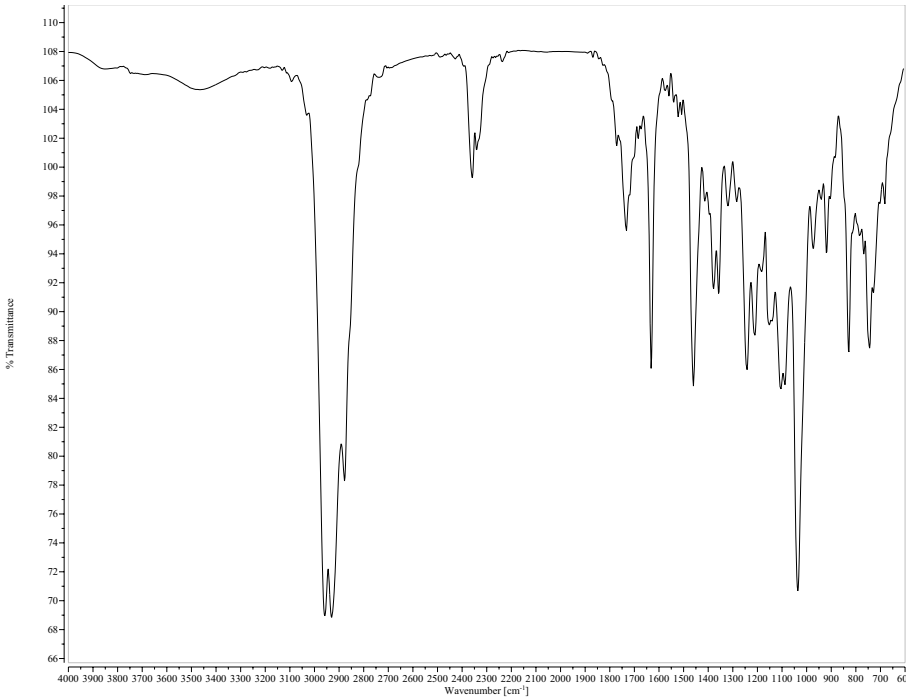


Figure A4.20. *Infrared spectrum (Thin Film, NaCl) of compound* ***207-d2****.*

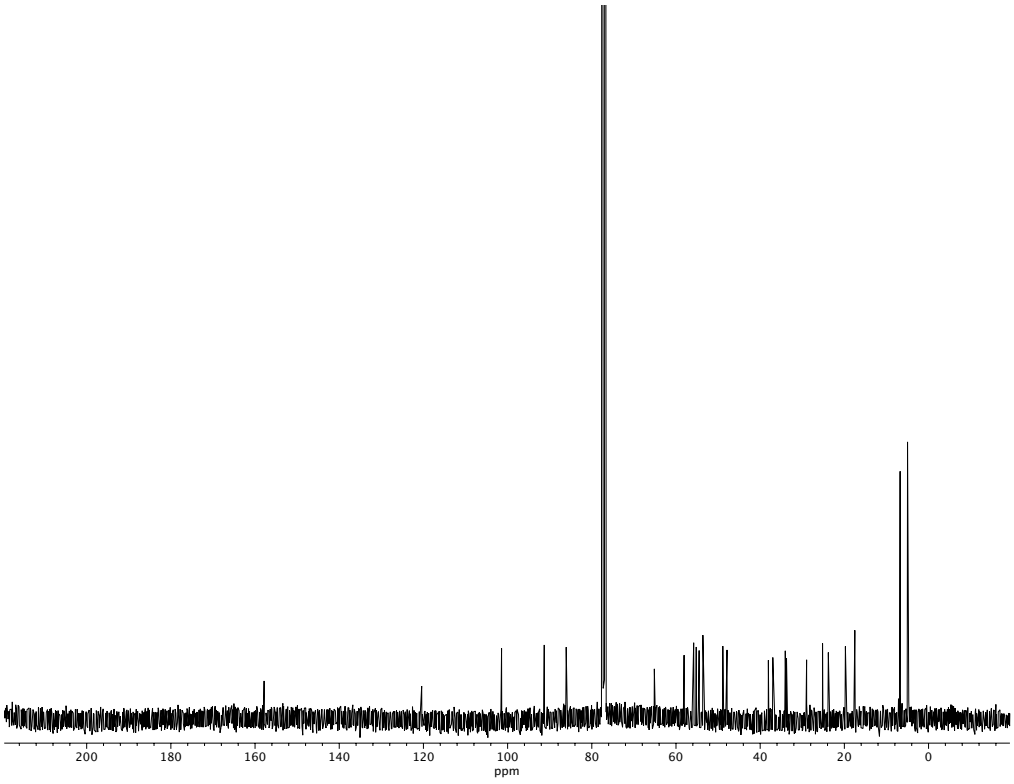


Figure A4.21. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***207-d2****.*

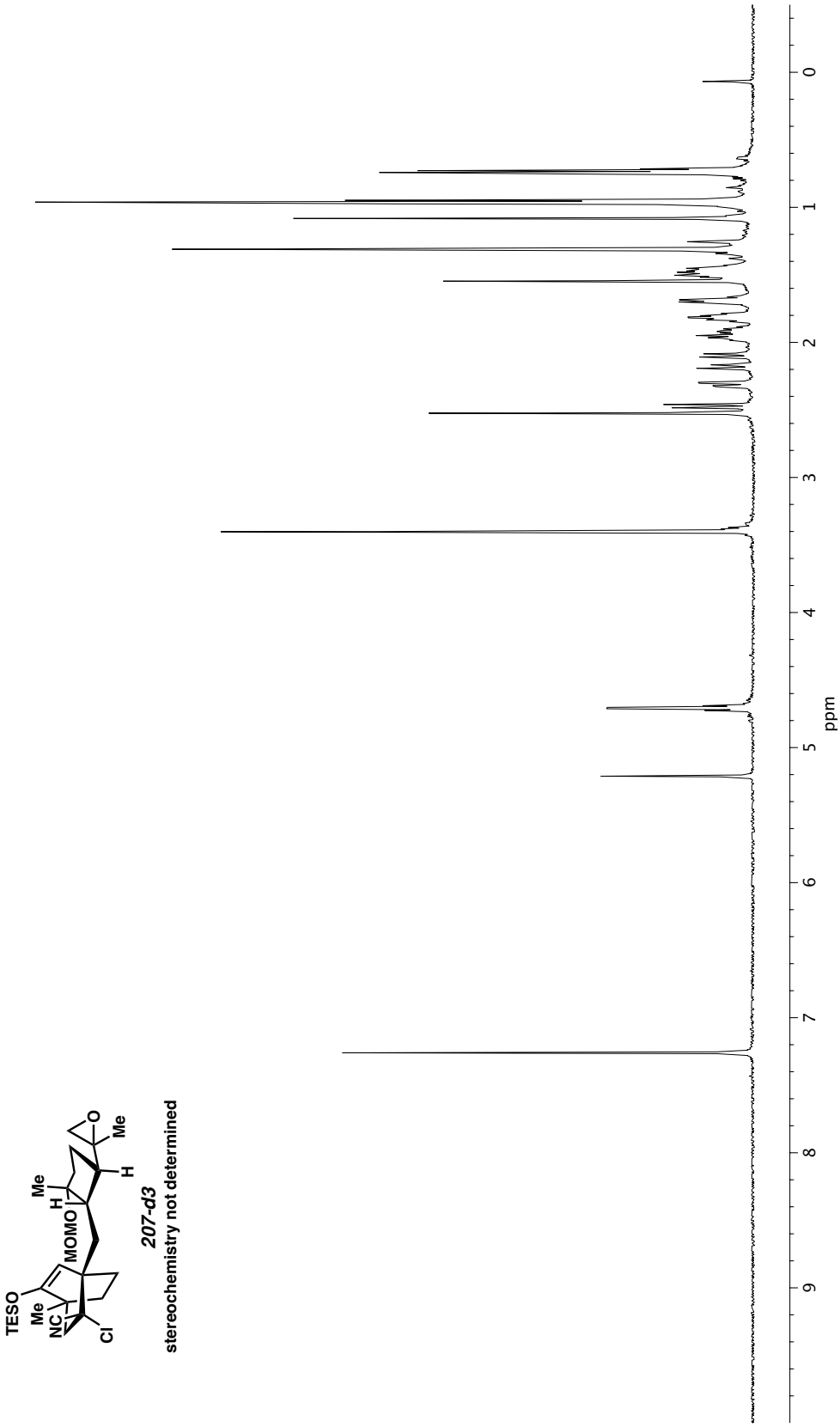


Figure A4.22. *^1H NMR (600 MHz, $CDCl_3$) of compound* ***207-d3***.

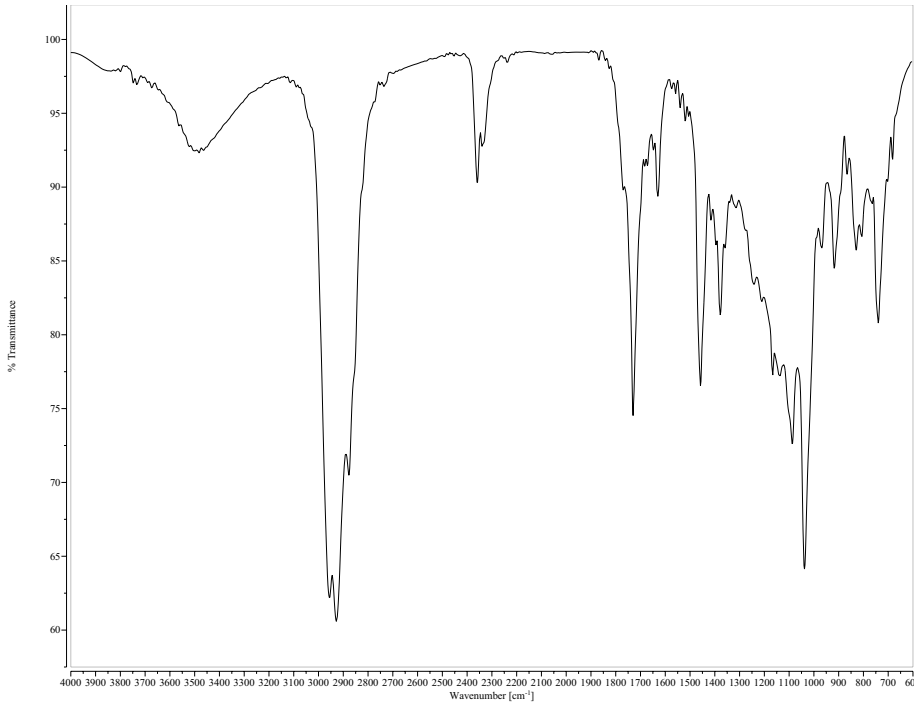


Figure A4.23. *Infrared spectrum ($CDCl_3$ solution) of compound* ***207-d3****.*

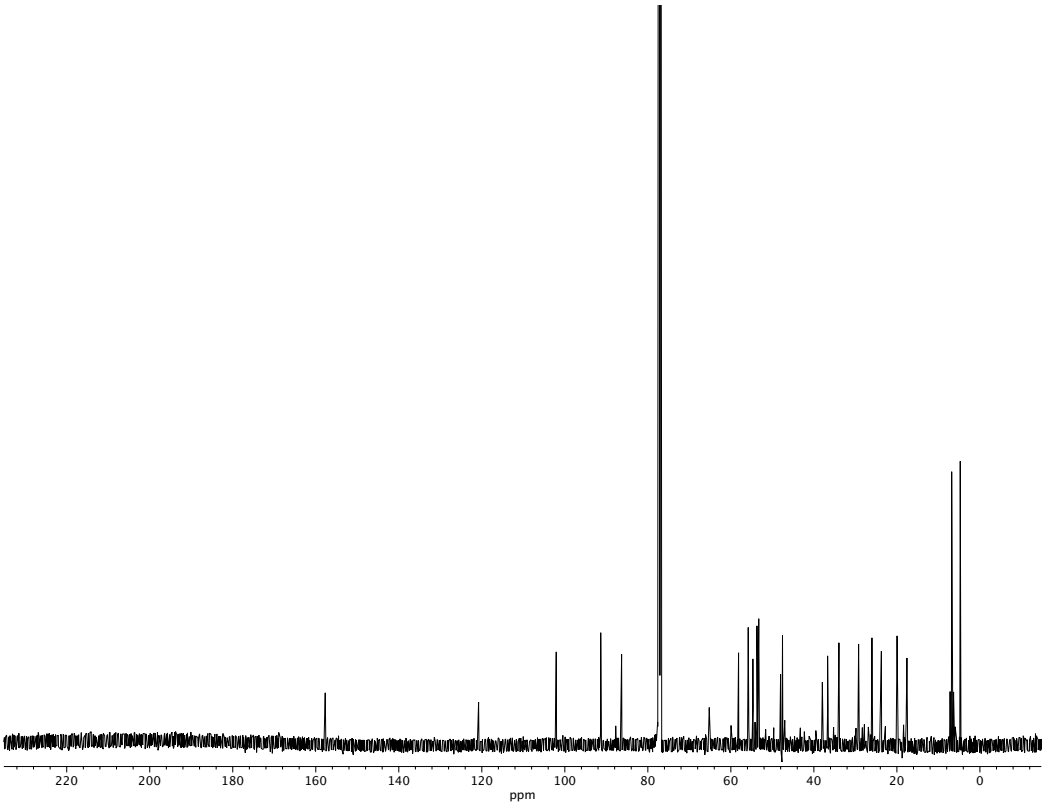


Figure A4.24. *^{13}C NMR (151 MHz, $CDCl_3$) of compound* ***207-d3****.*

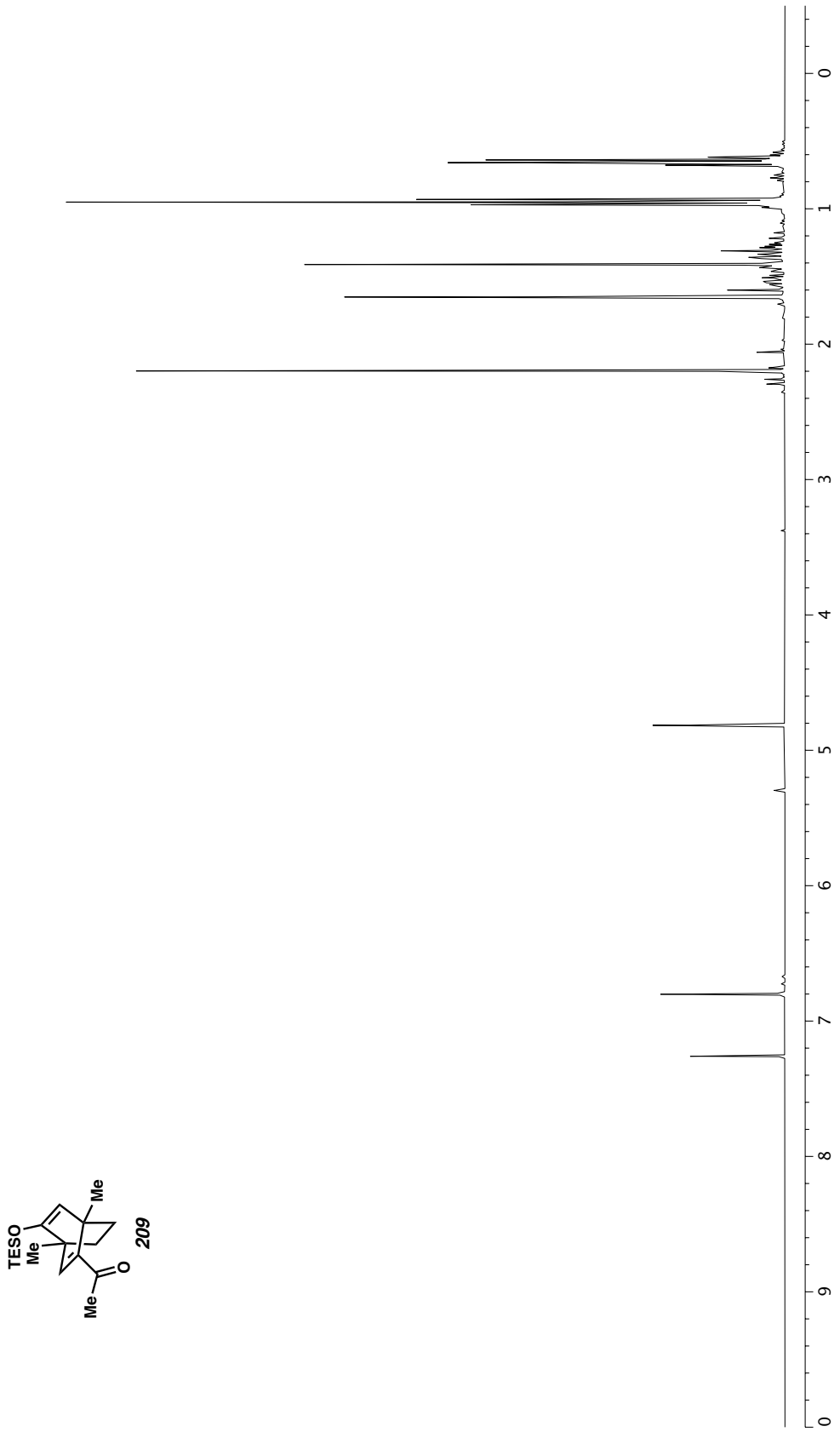


Figure A4.25. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***209***.

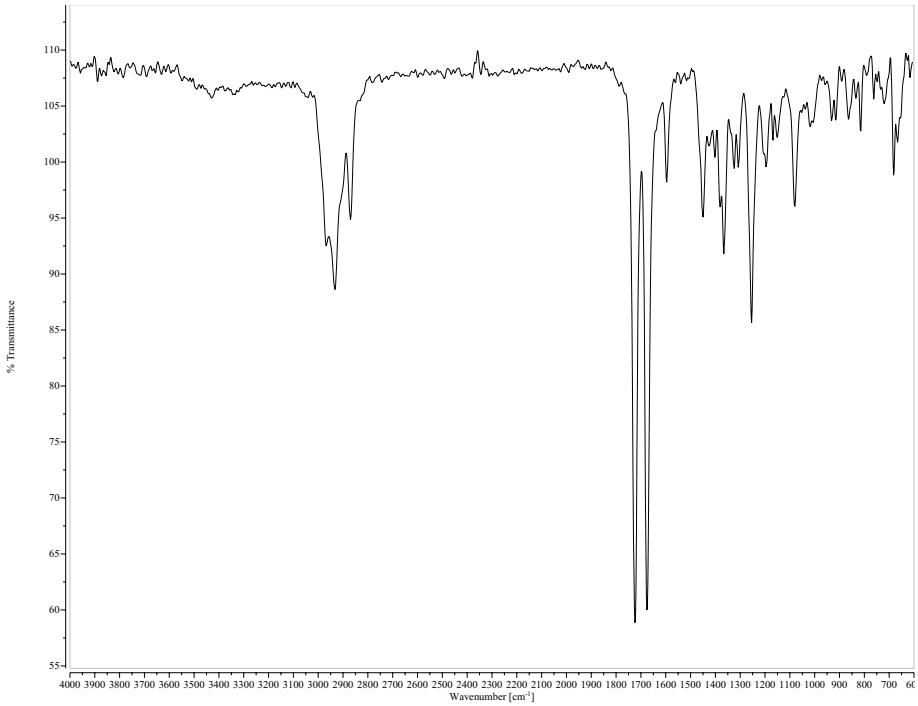


Figure A4.26. *Infrared spectrum ($CDCl_3$ solution) of compound* ***209***.

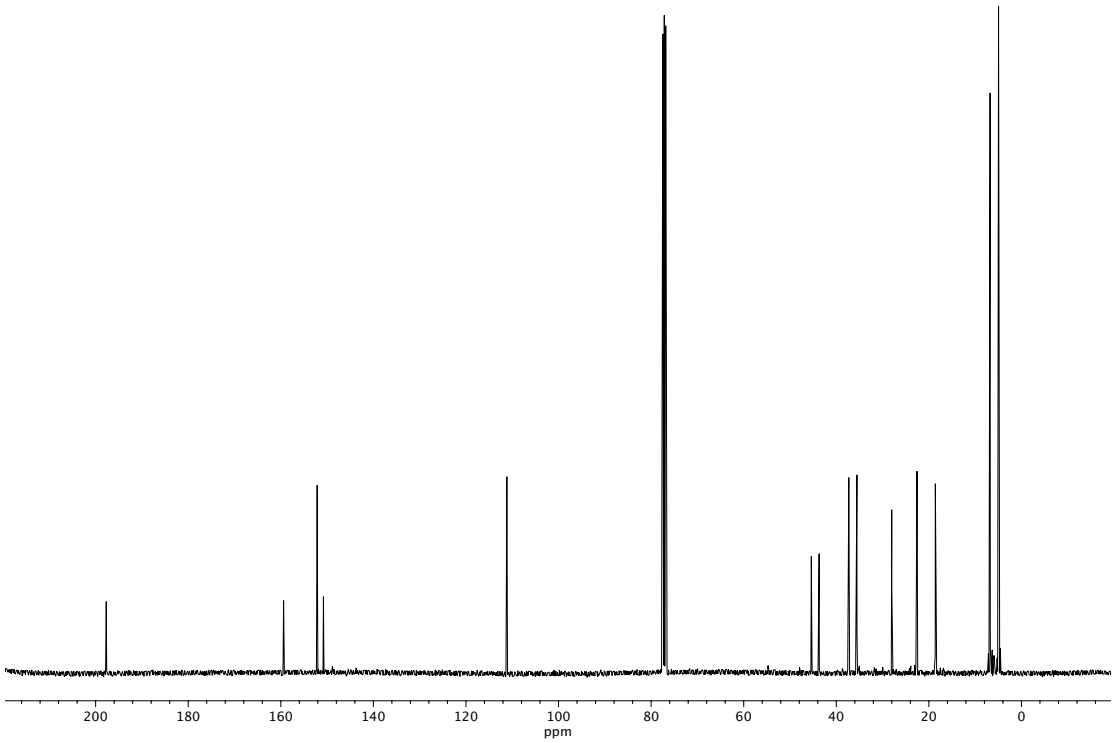


Figure A4.27. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***209***.

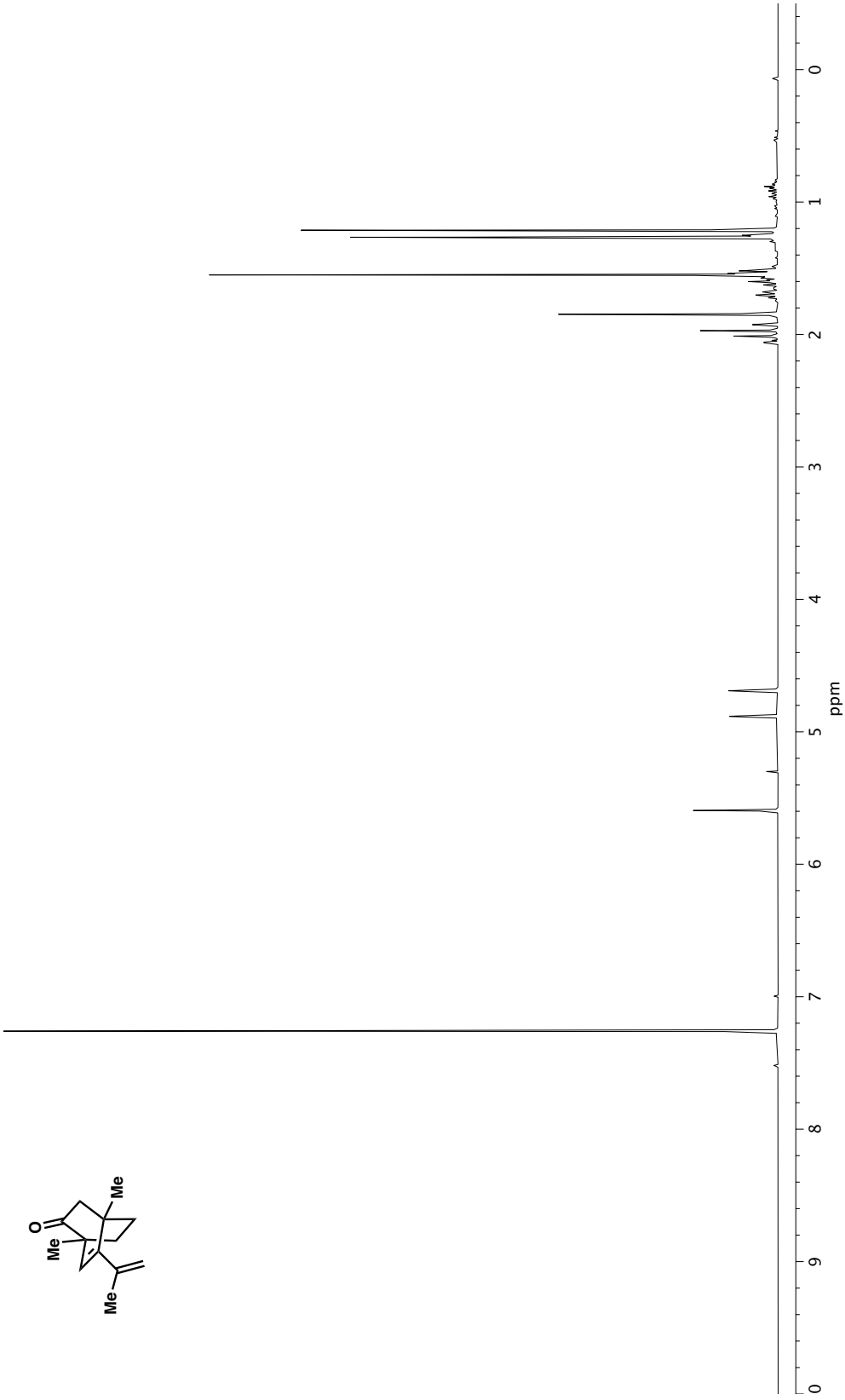


Figure A4.28. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***210****.*

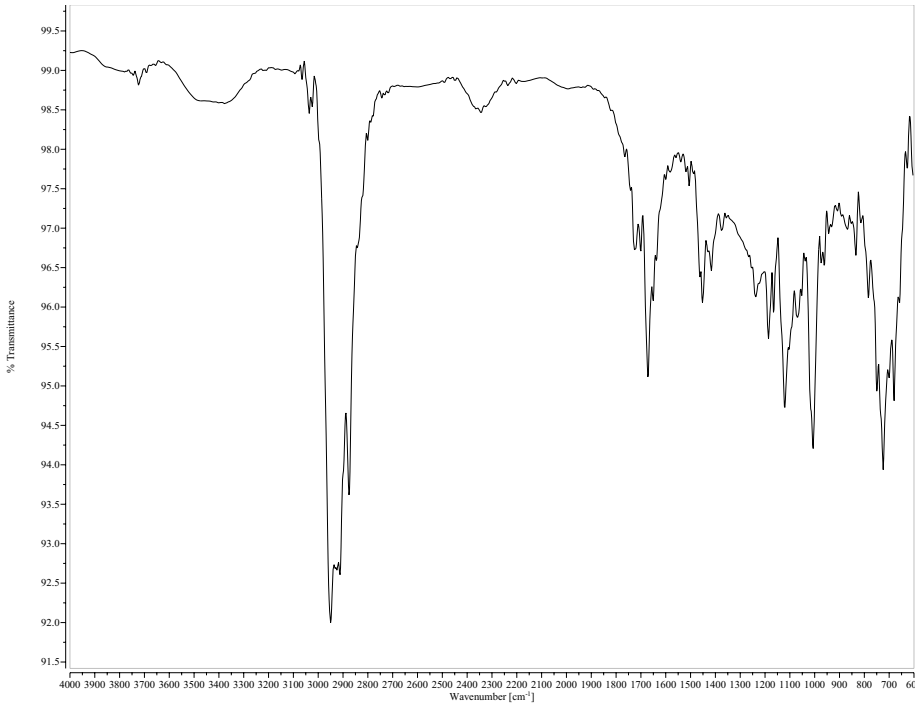


Figure A4.29. *Infrared spectrum (Thin Film, NaCl) of compound* ***210****.*

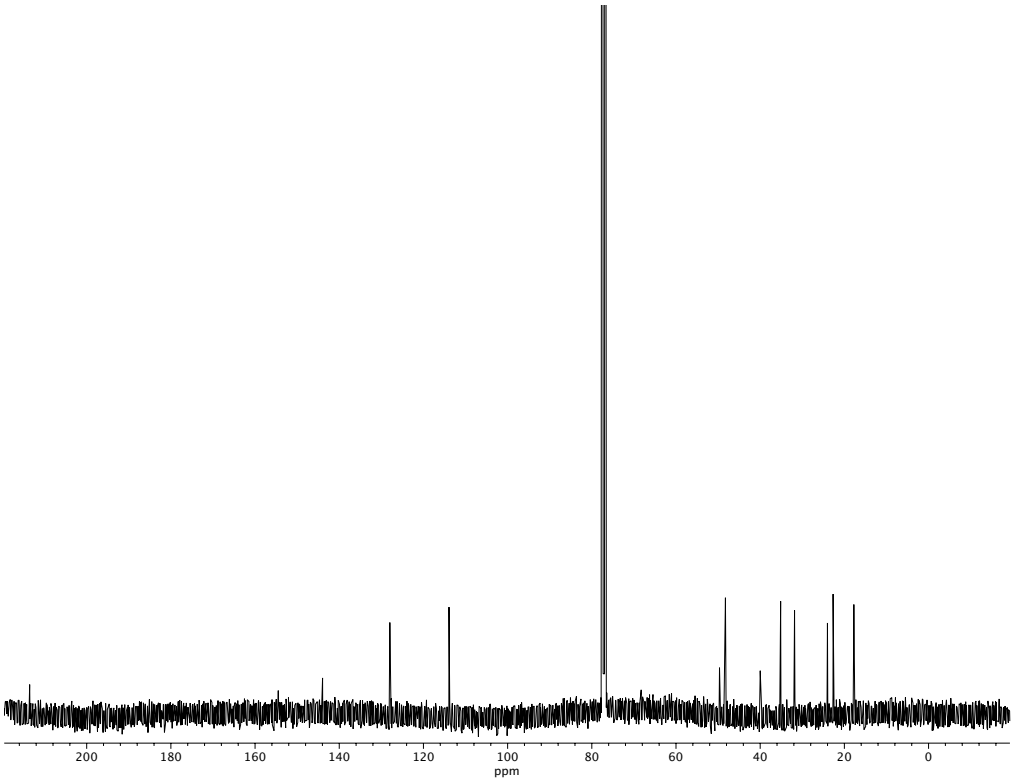
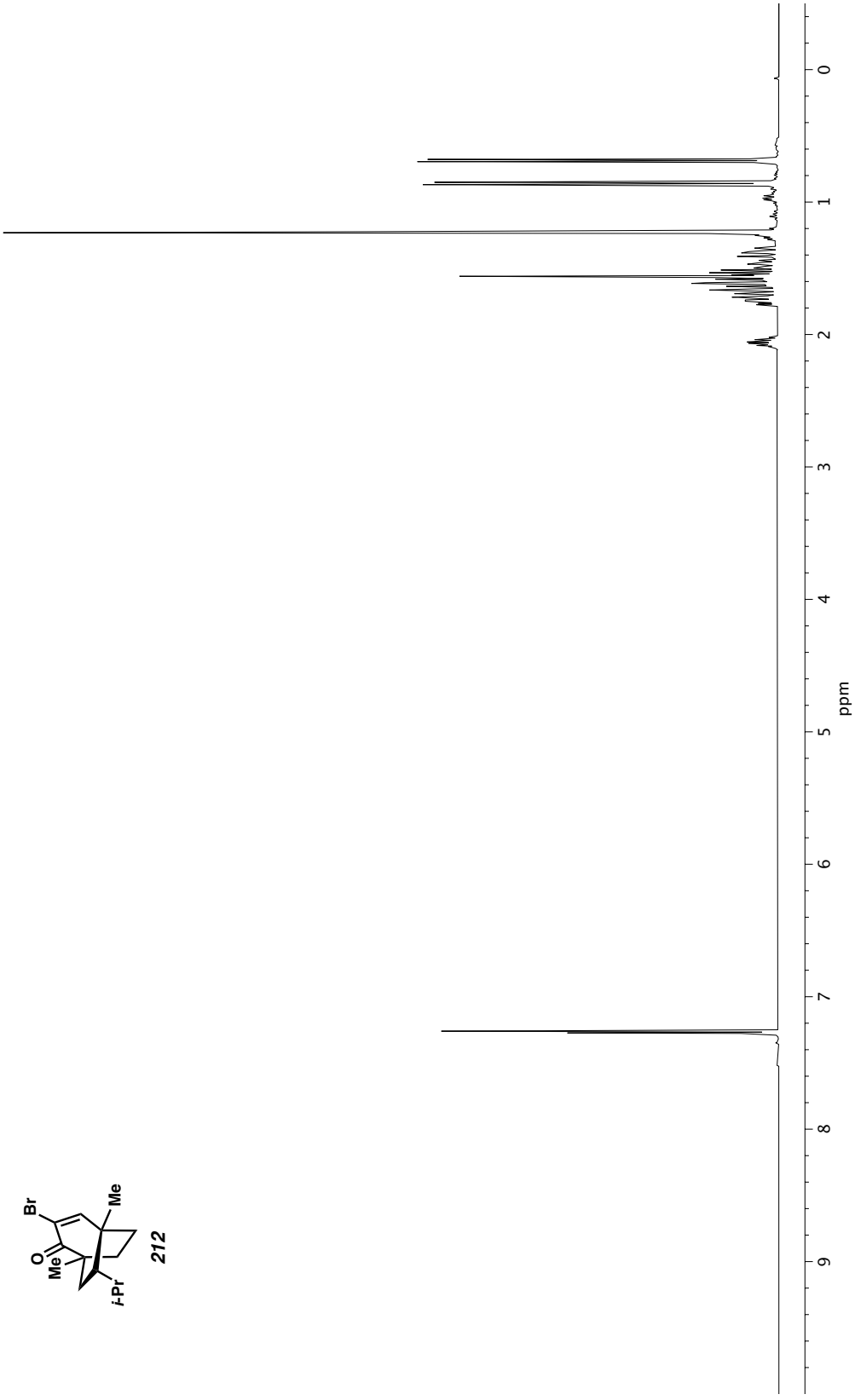


Figure A4.30. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***210****.*



212

Figure A4.31. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***212****.*

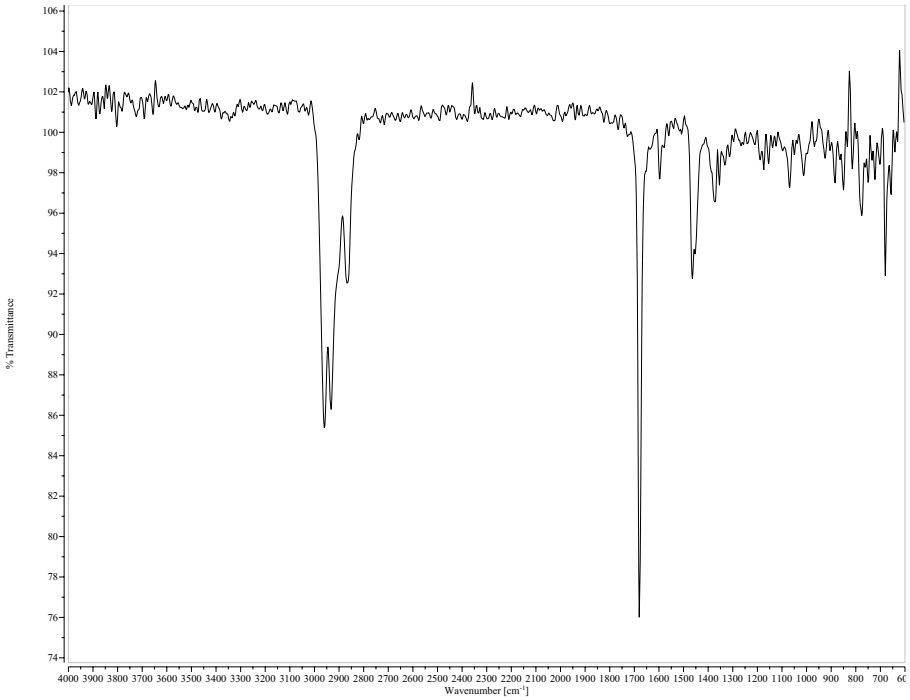


Figure A4.32. *Infrared spectrum (Thin Film, NaCl) of compound* ***212****.*

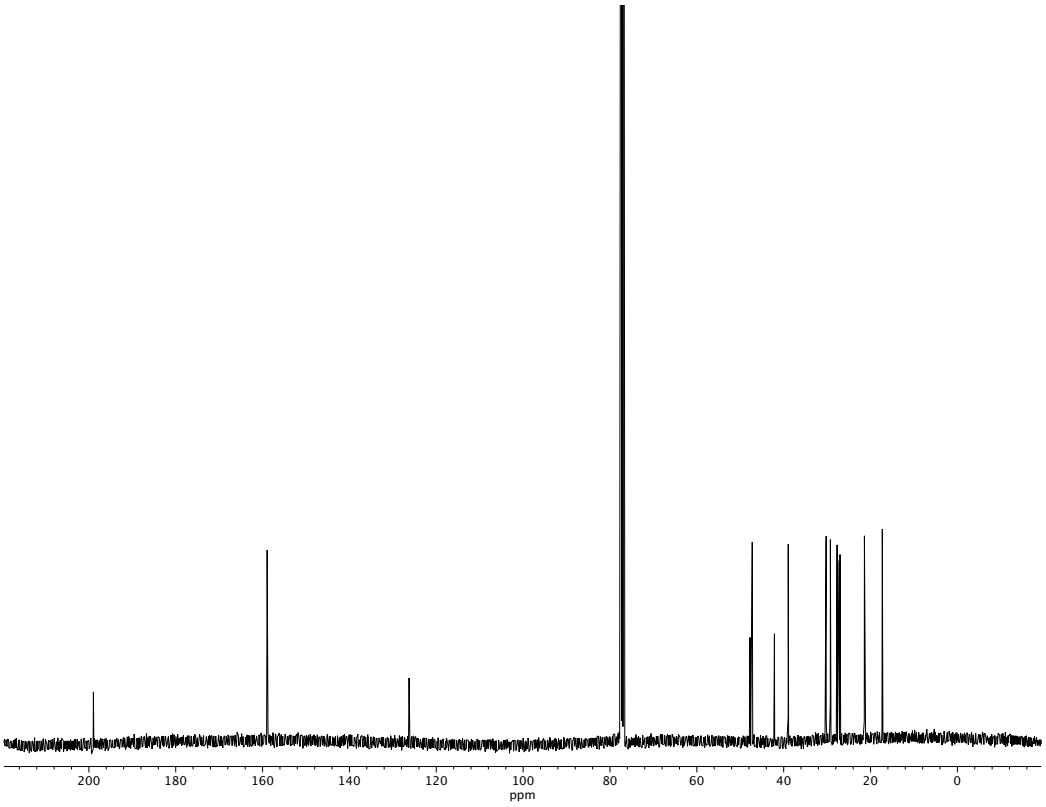


Figure A4.33. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***212****.*

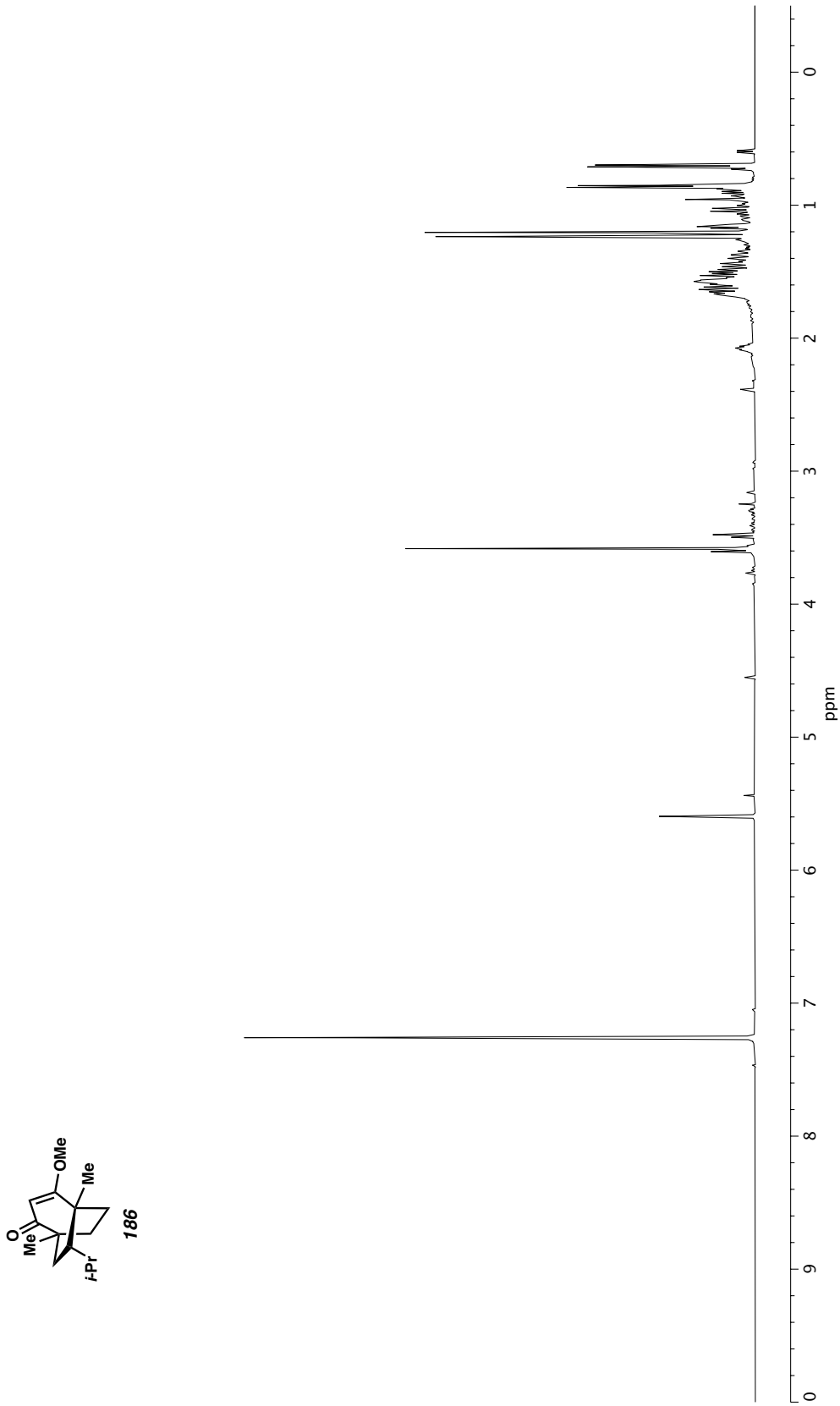


Figure A4.34. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***186****.*

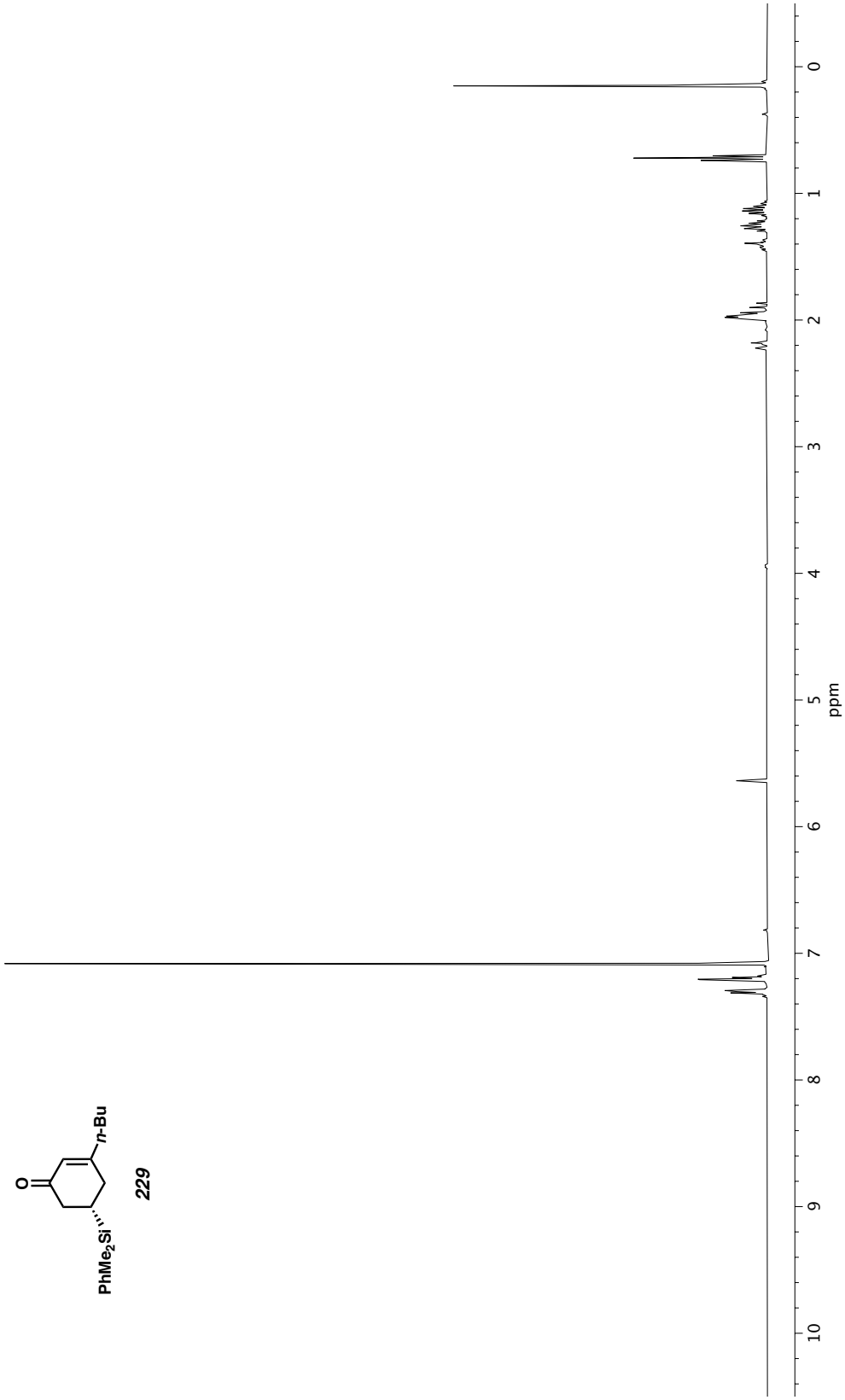


Figure A4.35. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***229***.

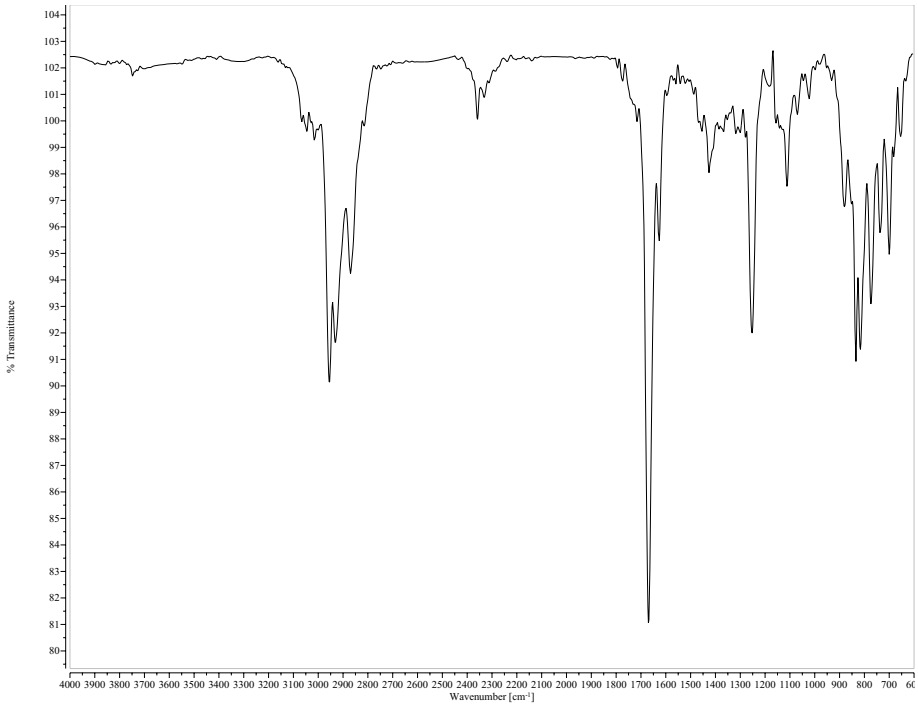


Figure A4.36. *Infrared spectrum (Thin Film, NaCl) of compound* ***229***.

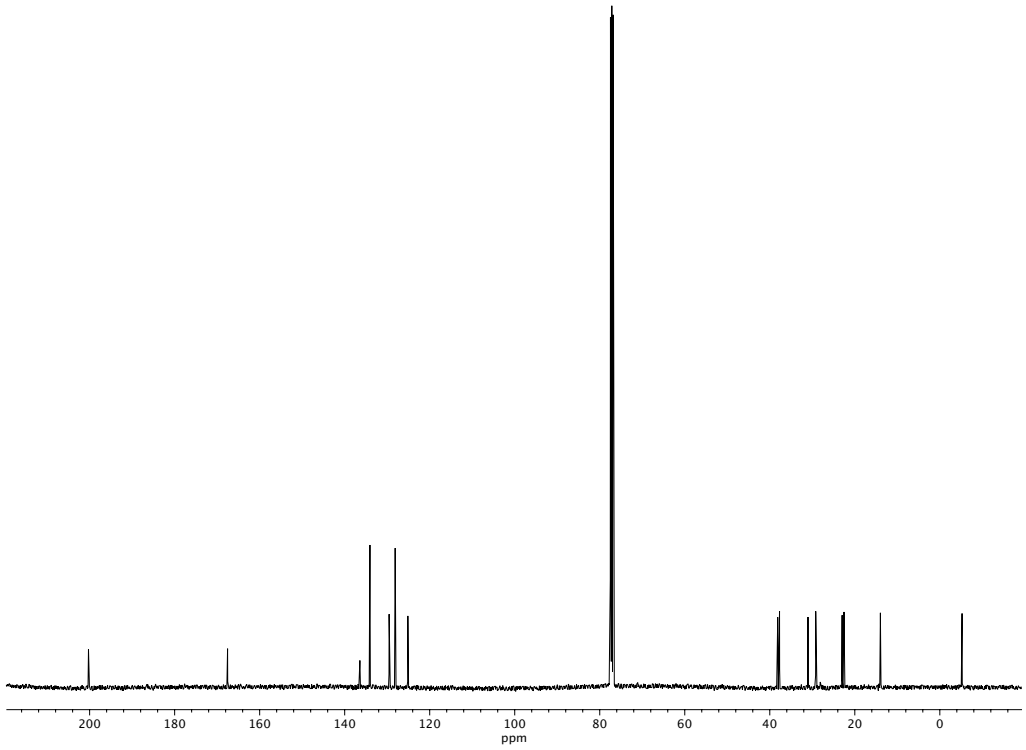


Figure A4.37. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***229***.

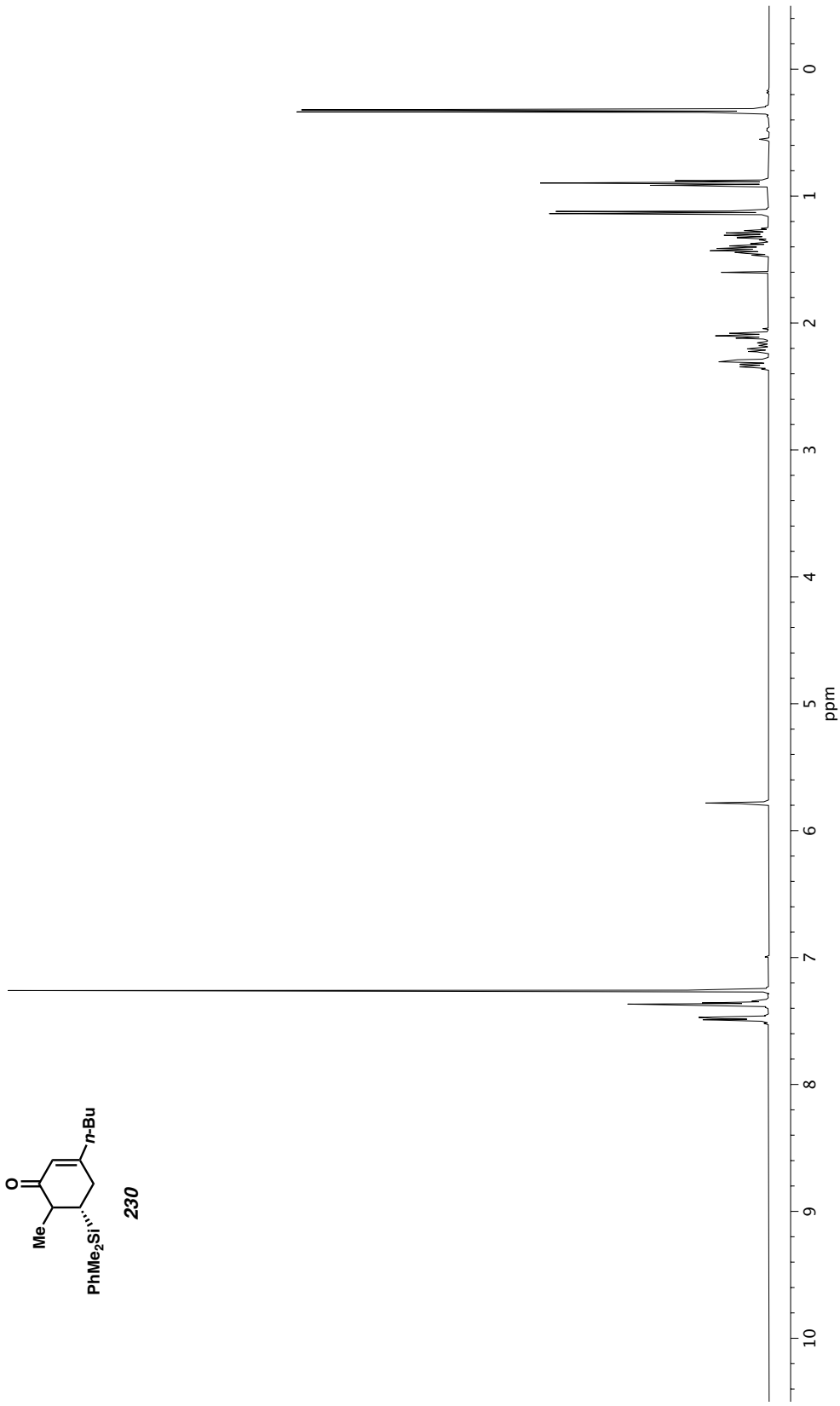


Figure A4.38. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***230***.

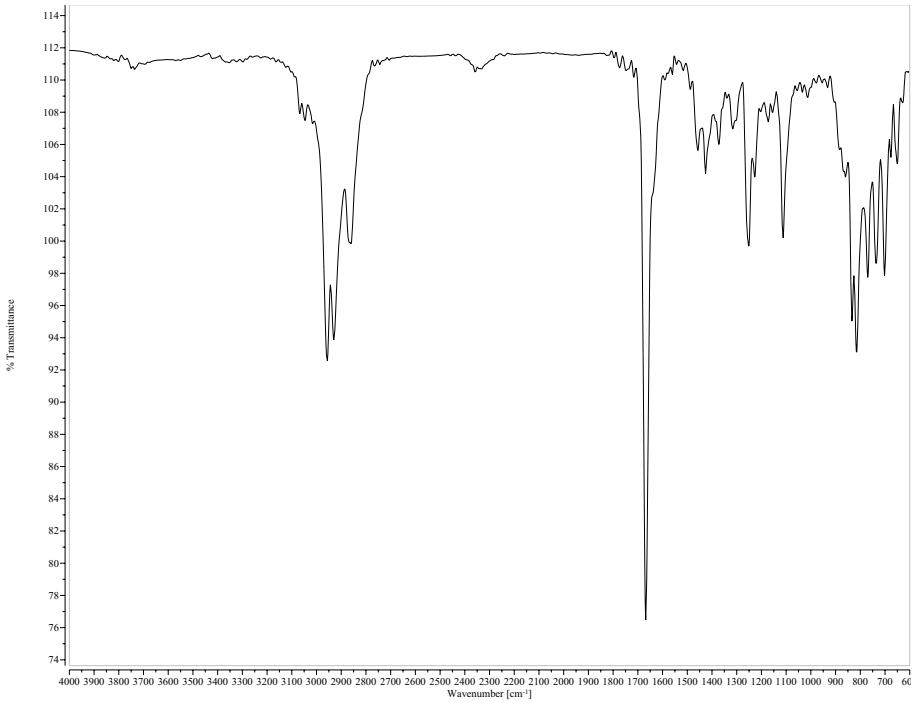


Figure A4.39. *Infrared spectrum (Thin Film, NaCl) of compound* ***230****.*

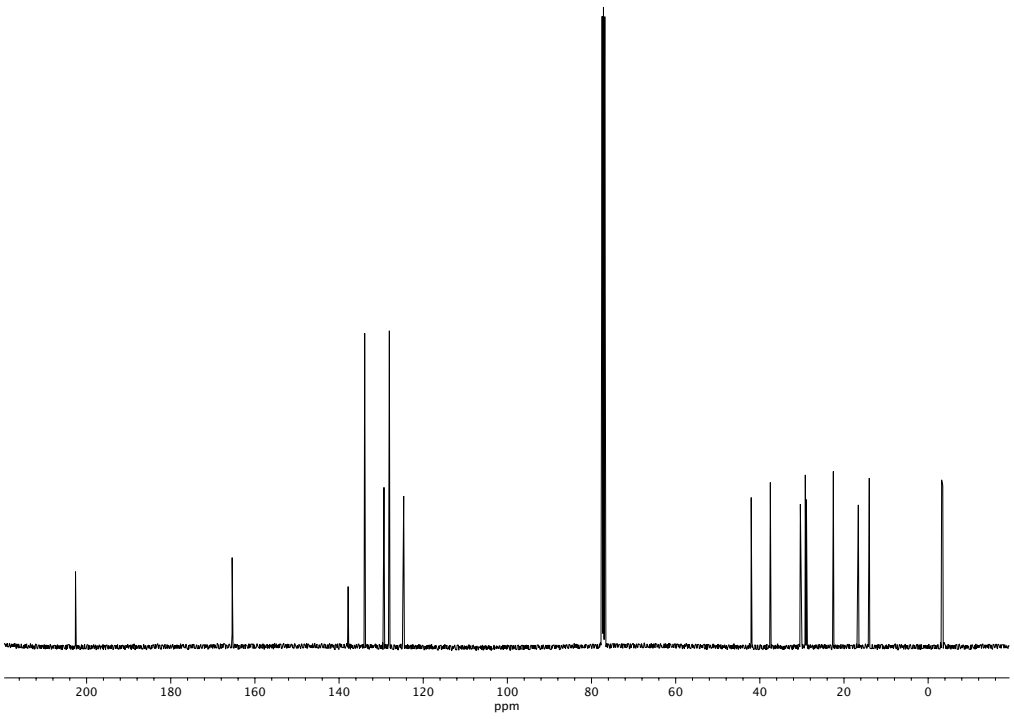


Figure A4.40. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***230****.*

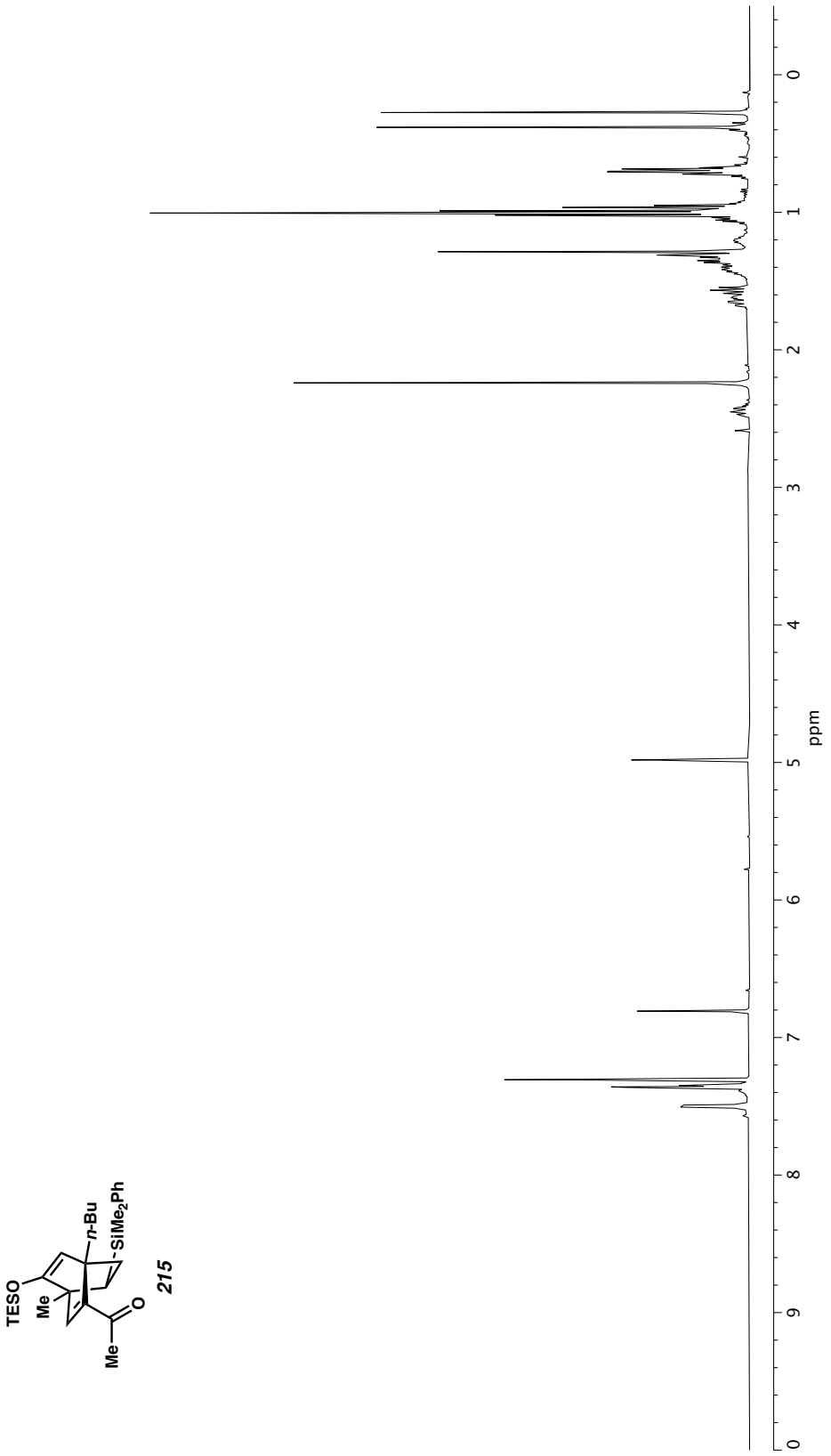


Figure A4.41. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***215****.*

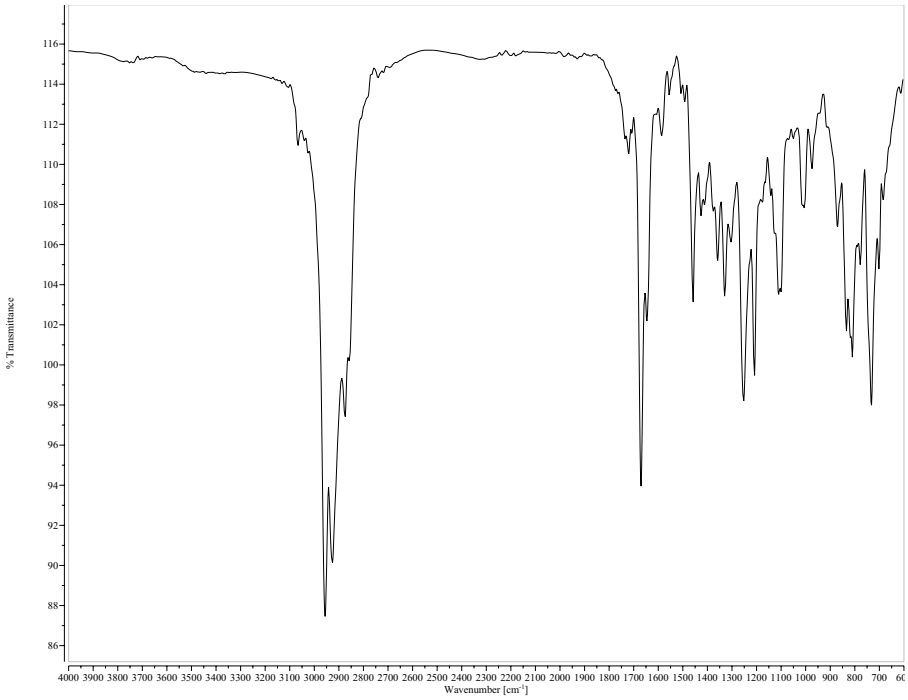


Figure A4.42. *Infrared spectrum (Thin Film, NaCl) of compound* ***215****.*

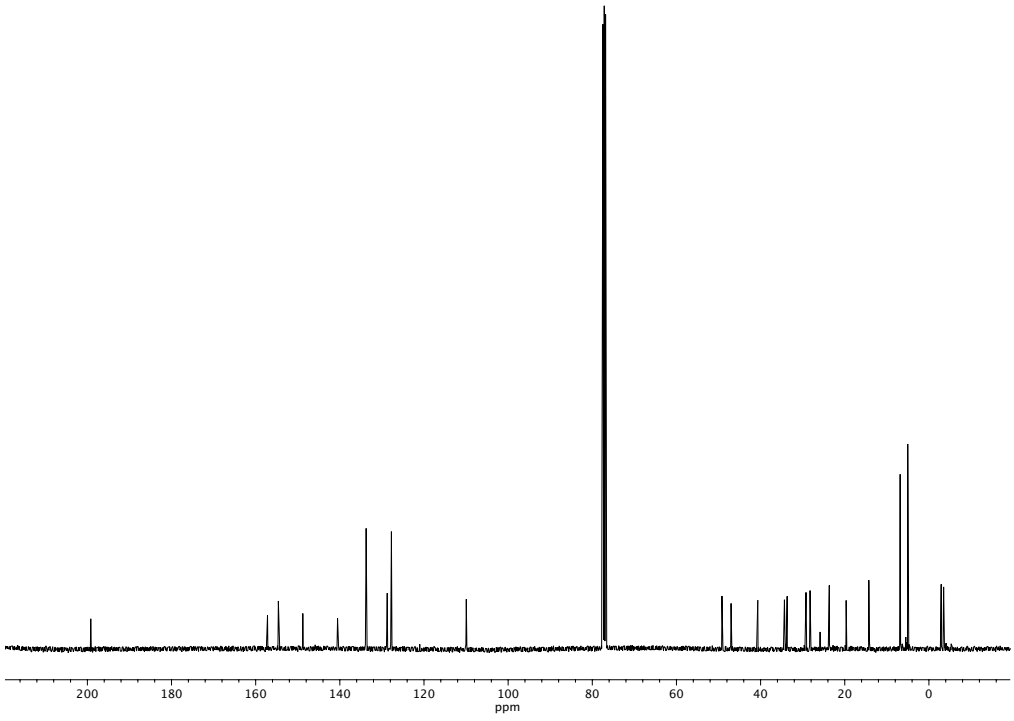


Figure A4.43. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***215****.*

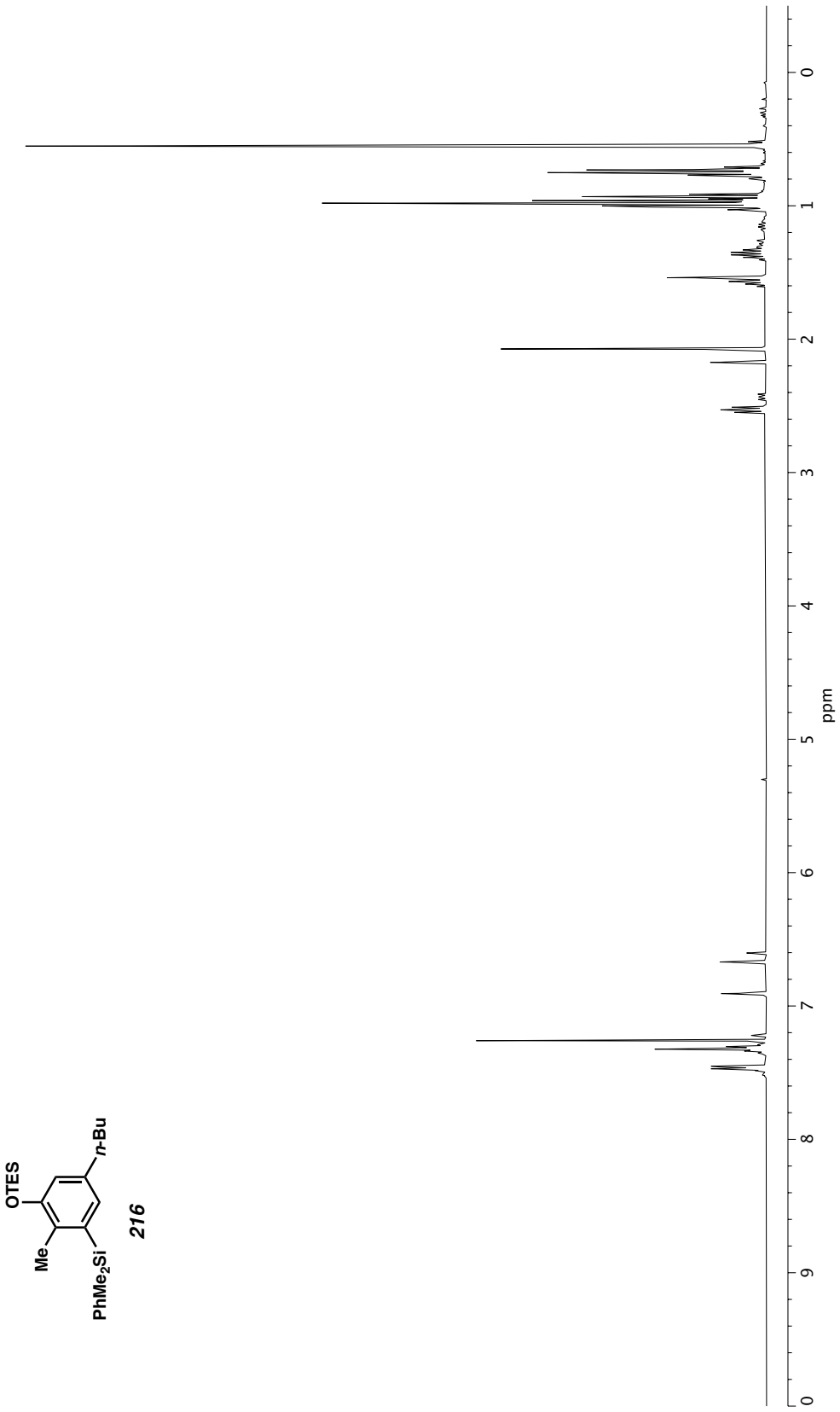


Figure A4.44. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***216****.*

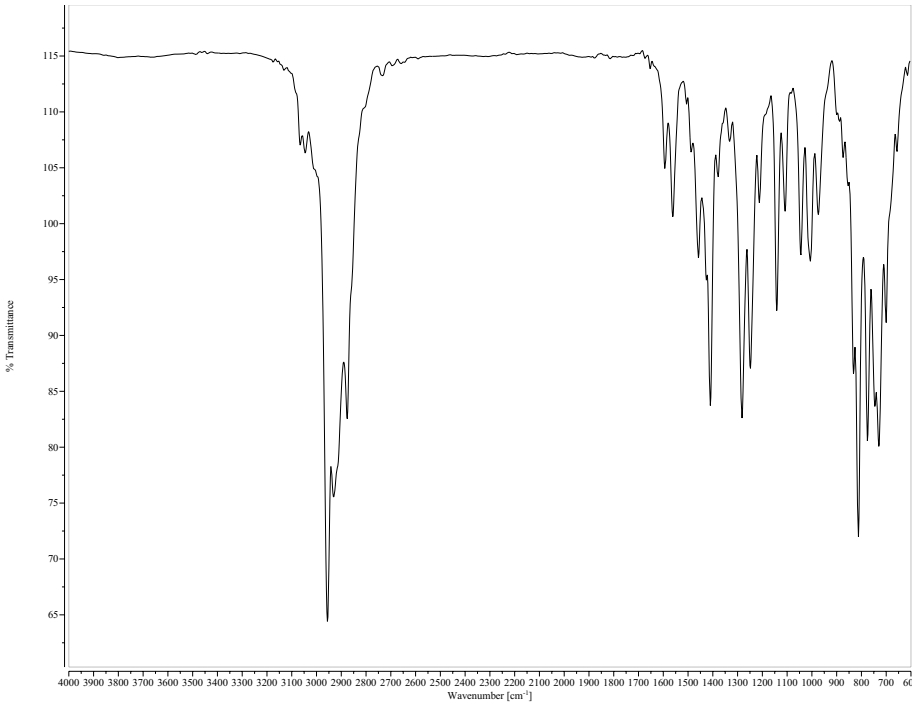


Figure A4.45. *Infrared spectrum (Thin Film, NaCl) of compound* ***216****.*

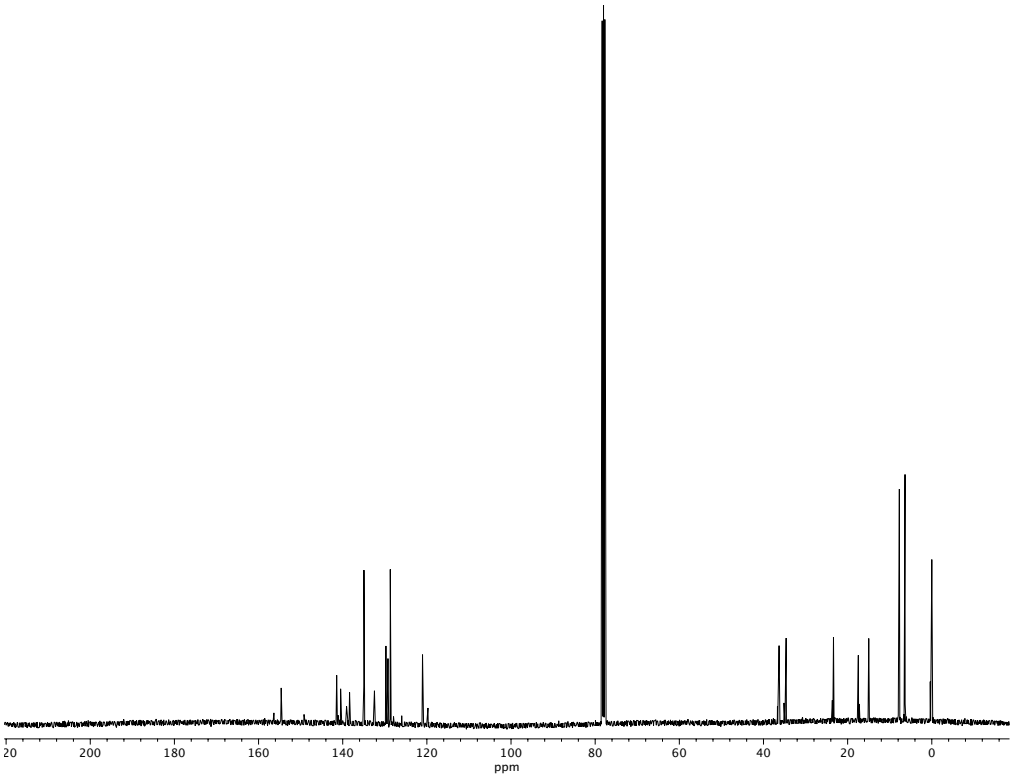


Figure A4.46. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***216****.*

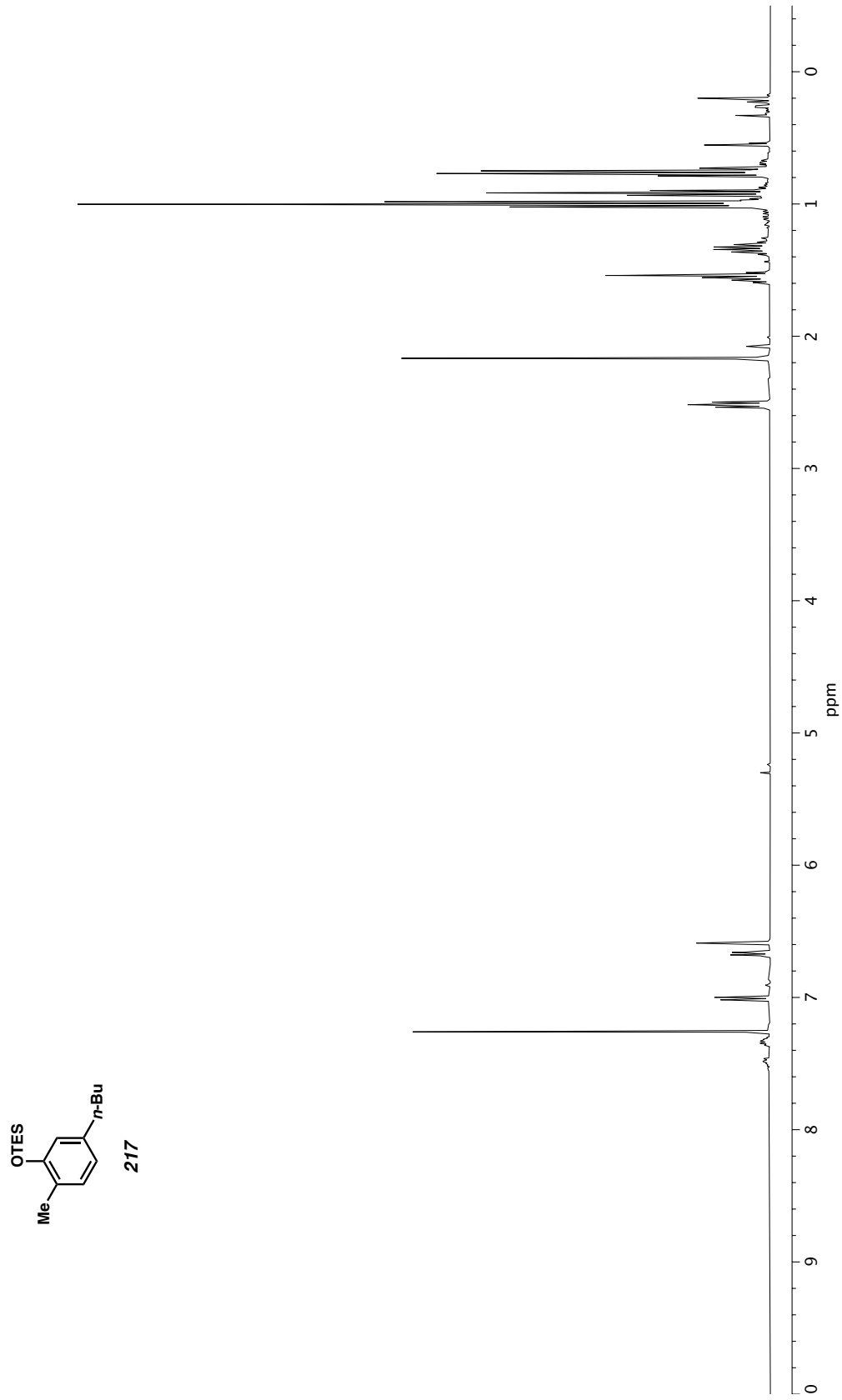


Figure A4.47. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***217****.*

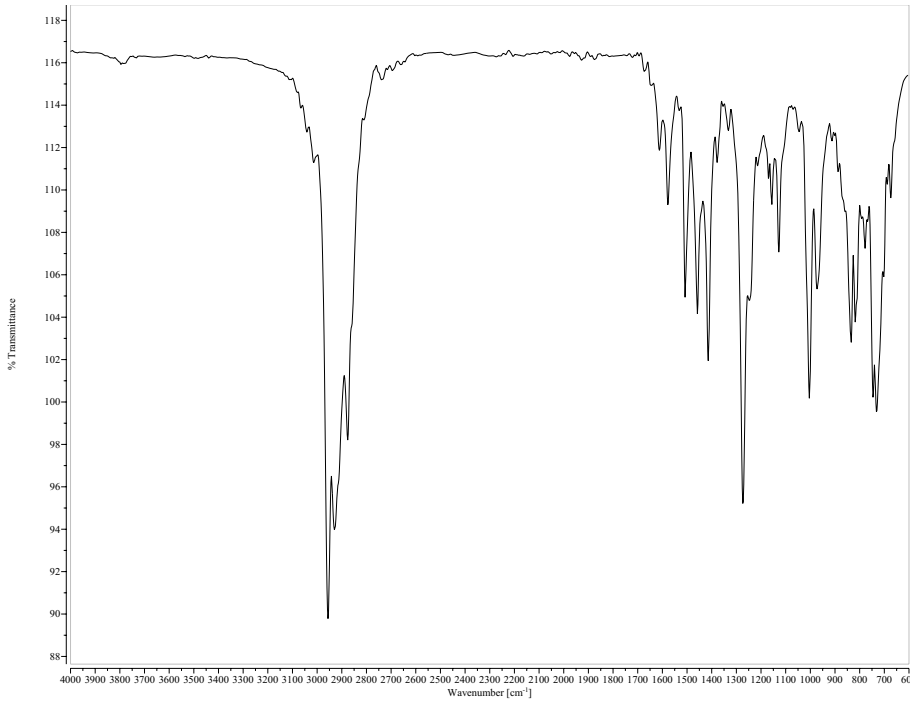


Figure A4.48. *Infrared spectrum (Thin Film, NaCl) of compound* ***217****.*

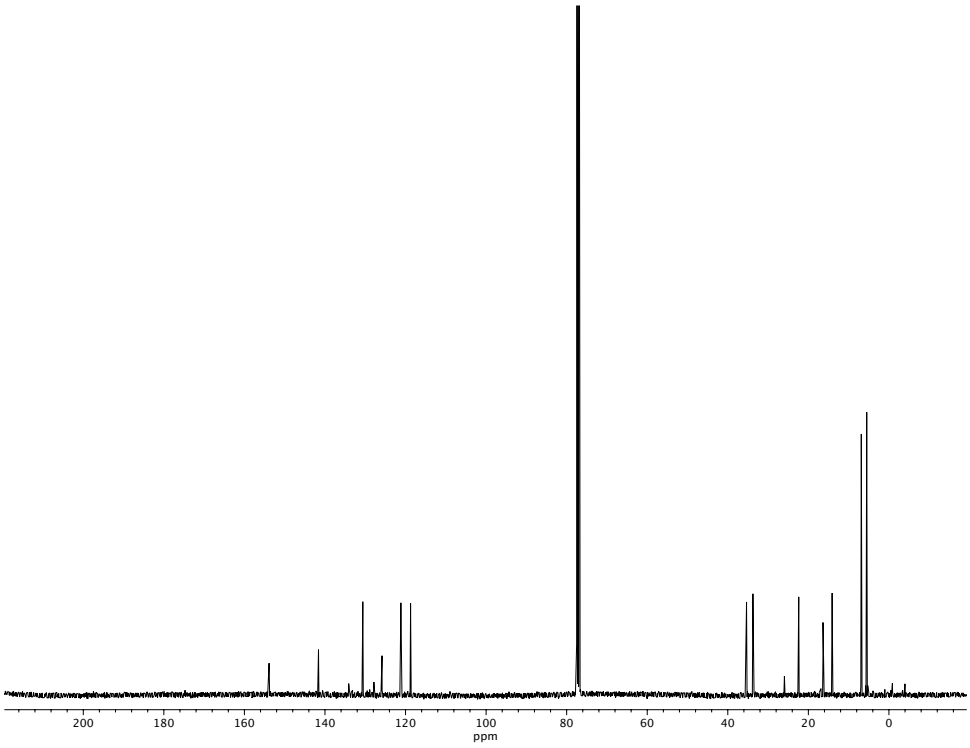


Figure A4.49. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***217****.*

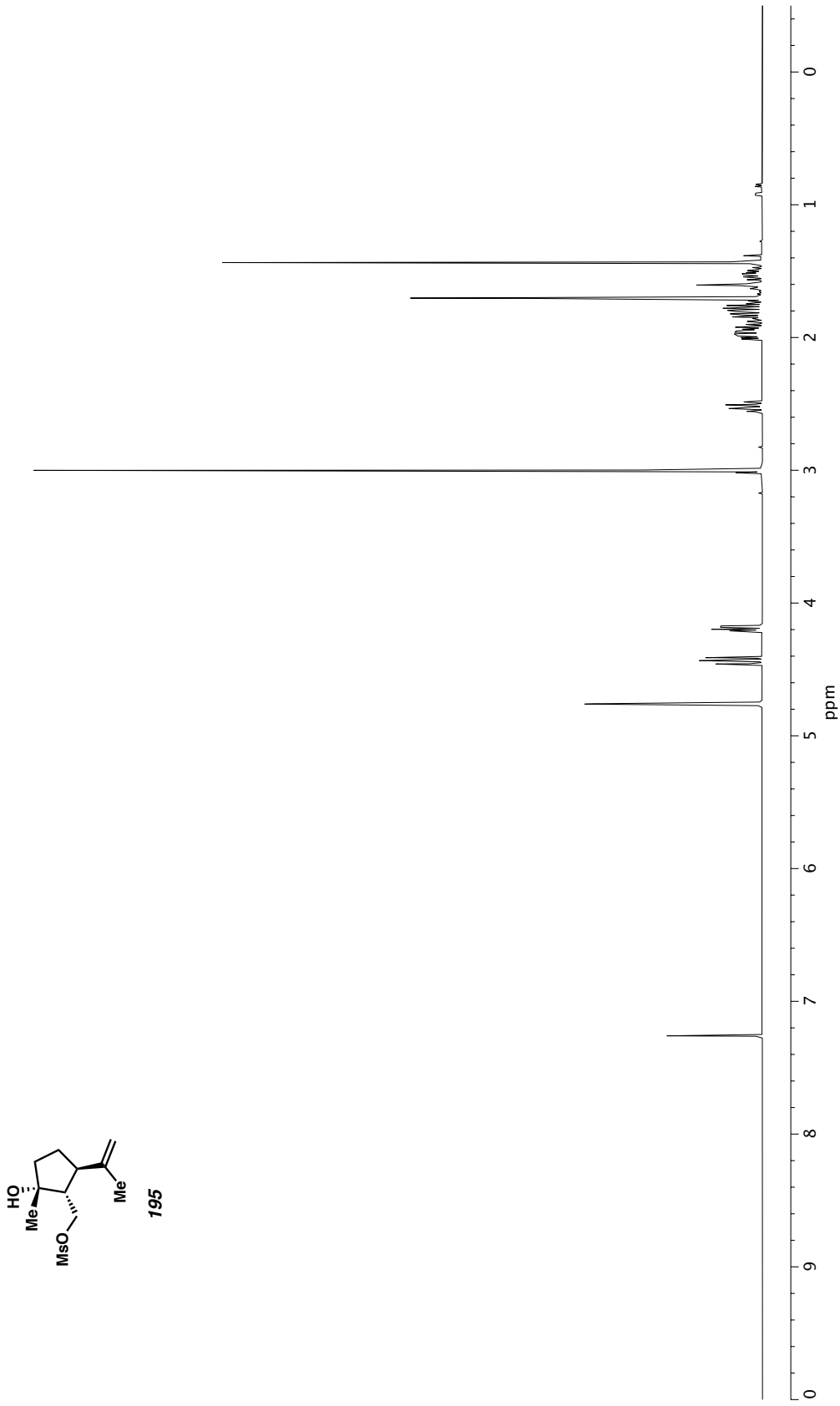


Figure A4.50. *^1H NMR (400 MHz, $CDCl_3$) of compound **195**.*

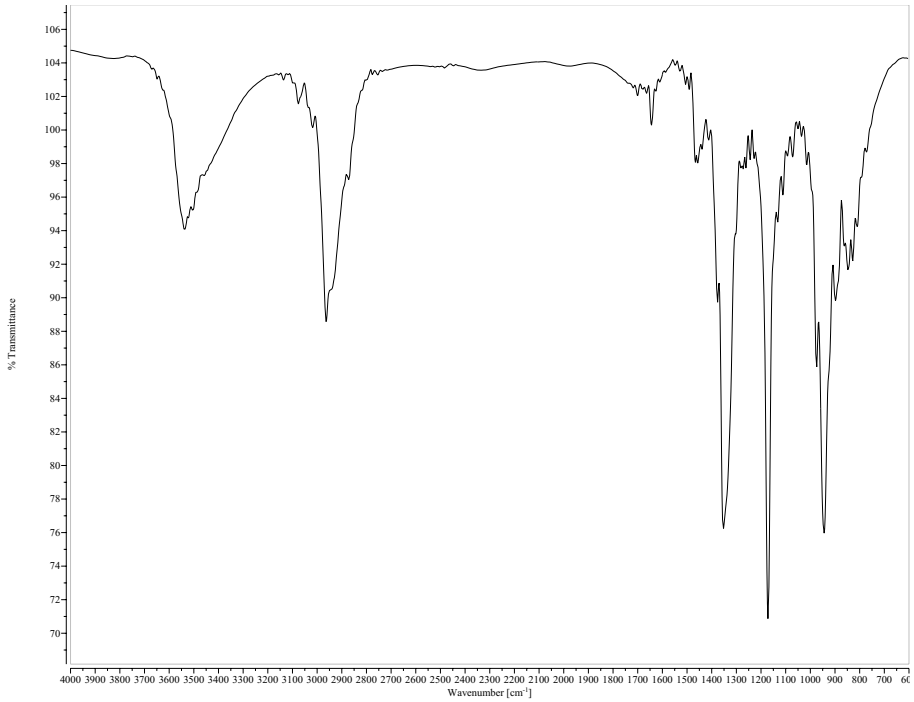


Figure A4.51. *Infrared spectrum (Thin Film, NaCl) of compound* ***195****.*

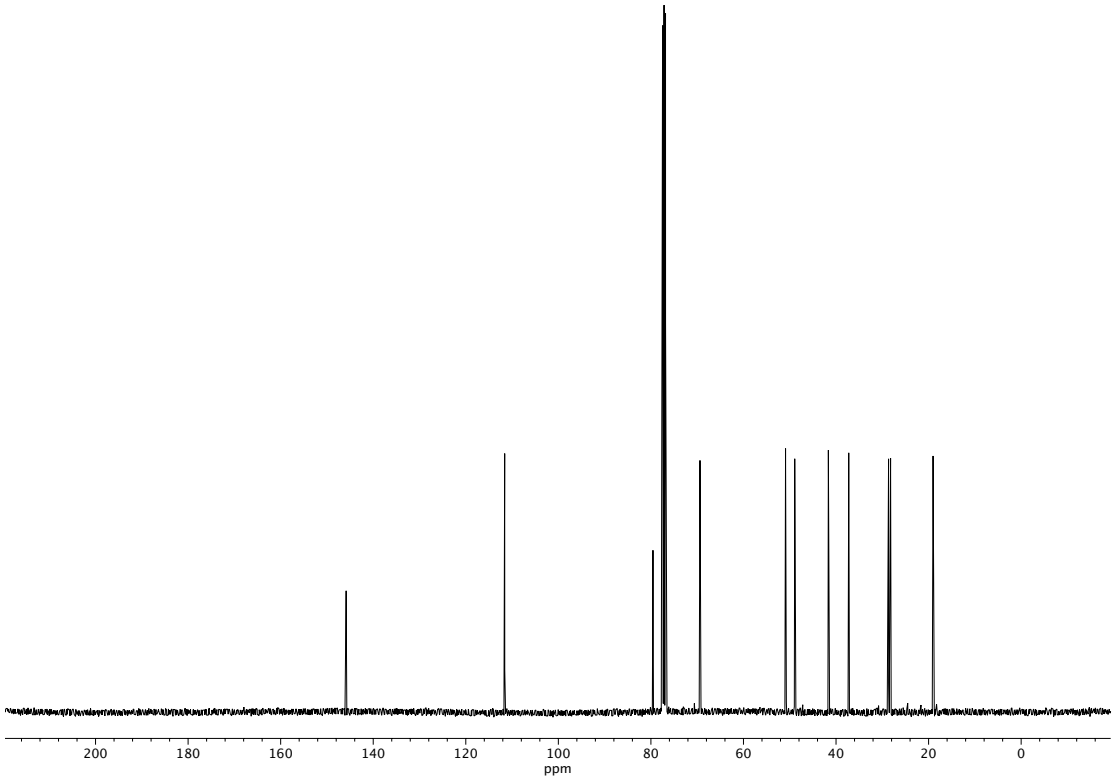


Figure A4.52. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***195****.*

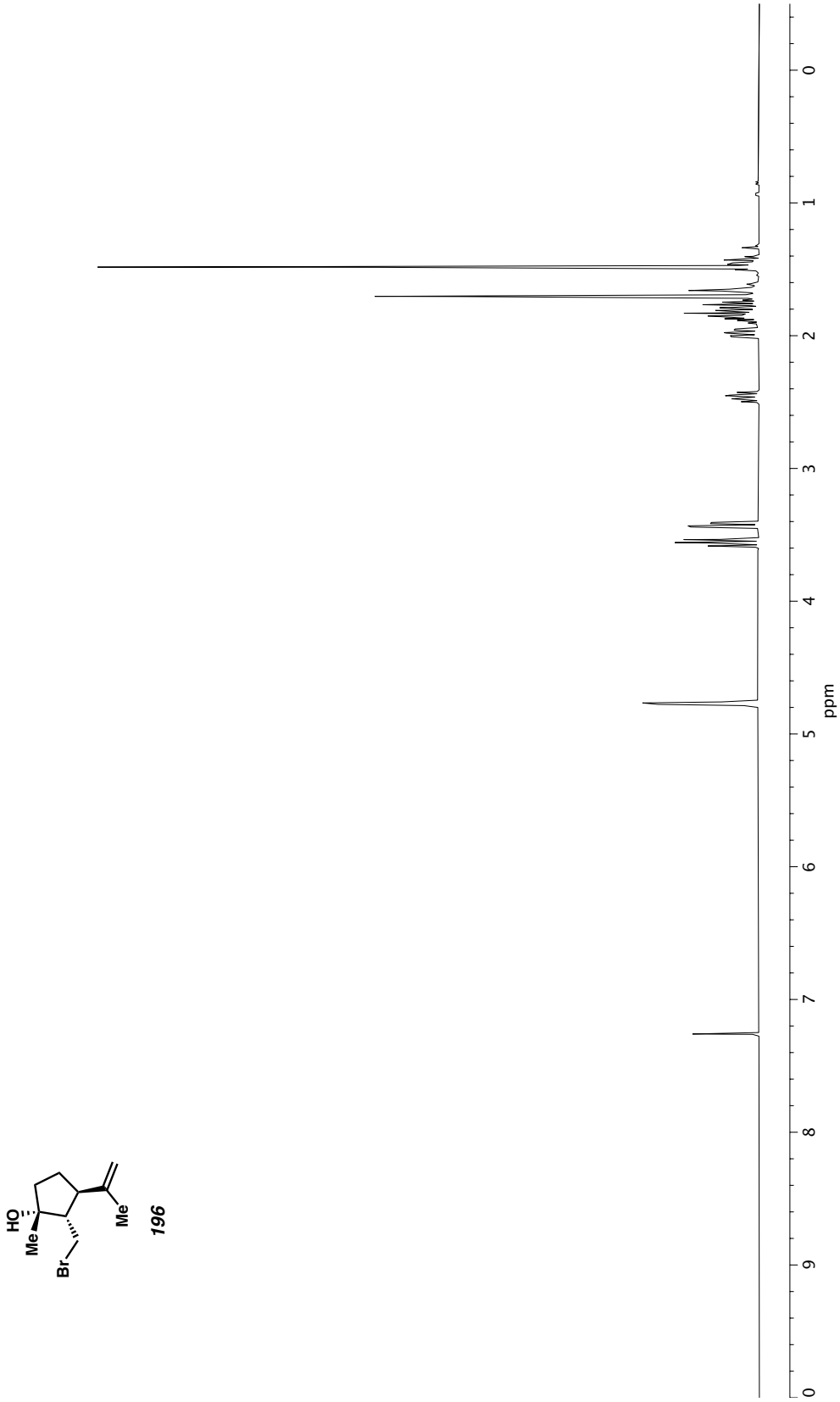


Figure A4.53. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***196****.*

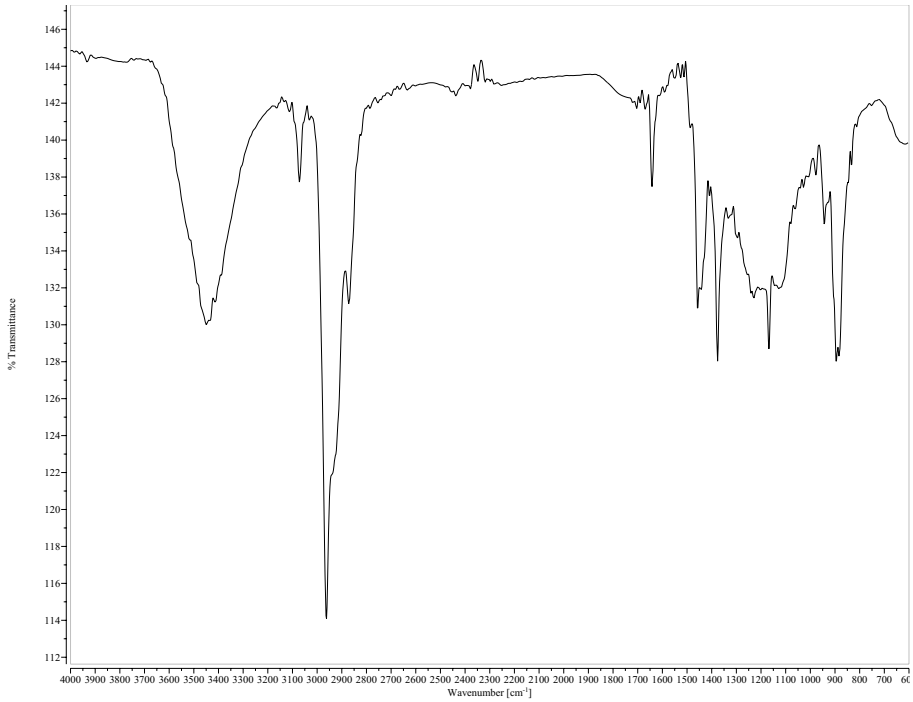


Figure A4.54. *Infrared spectrum (Thin Film, NaCl) of compound* ***196****.*

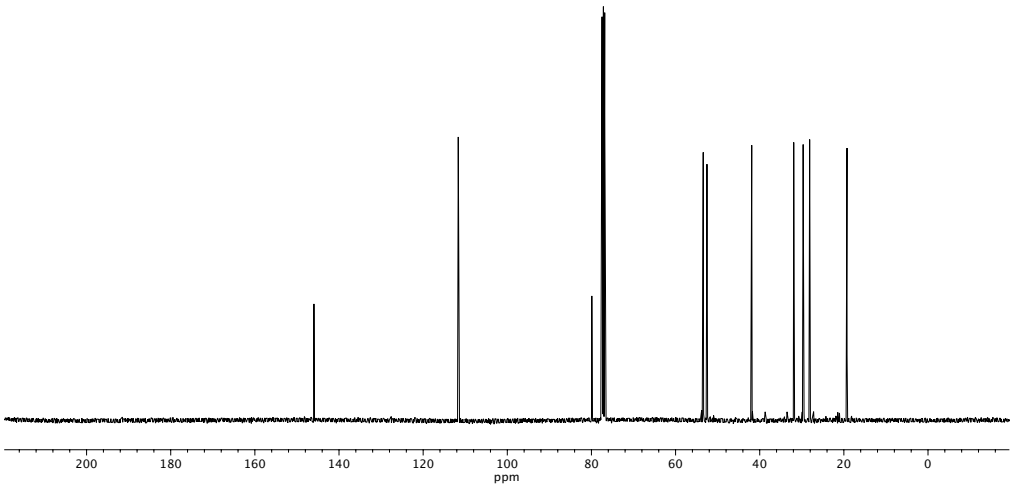


Figure A4.55. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***196****.*

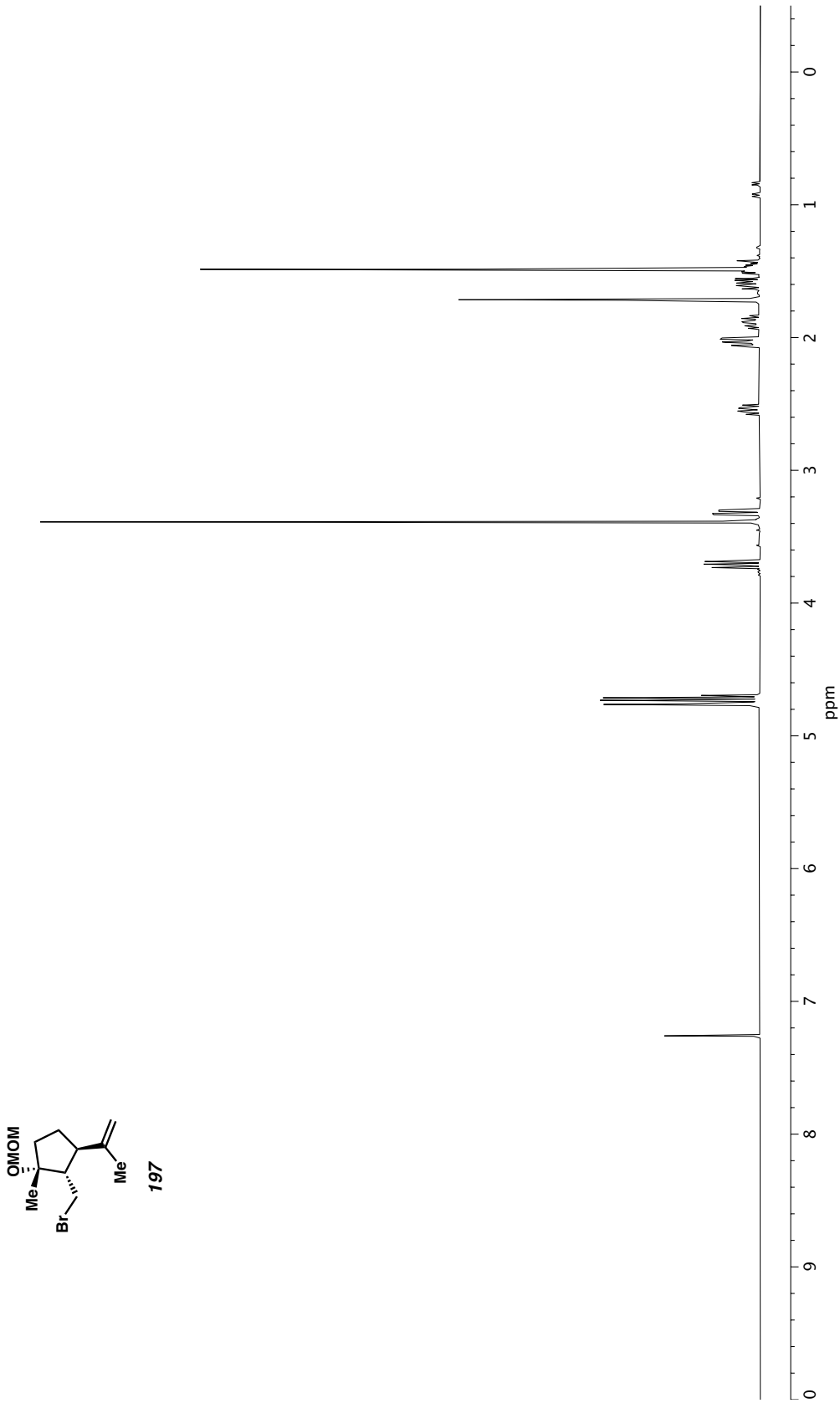


Figure A4.56. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***197****.*

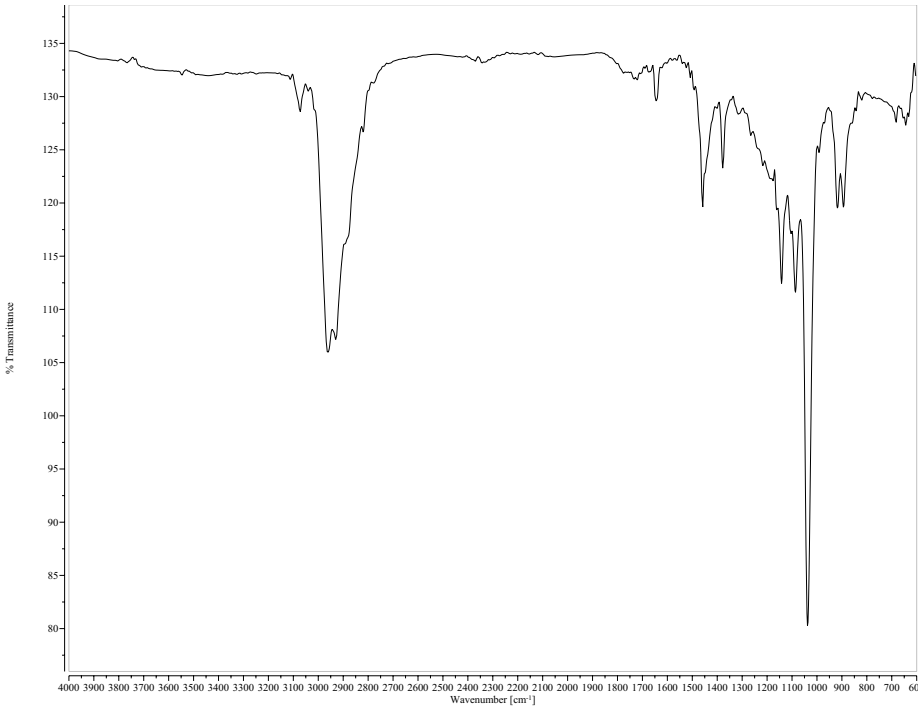


Figure A4.57. *Infrared spectrum (Thin Film, NaCl) of compound* ***197****.*

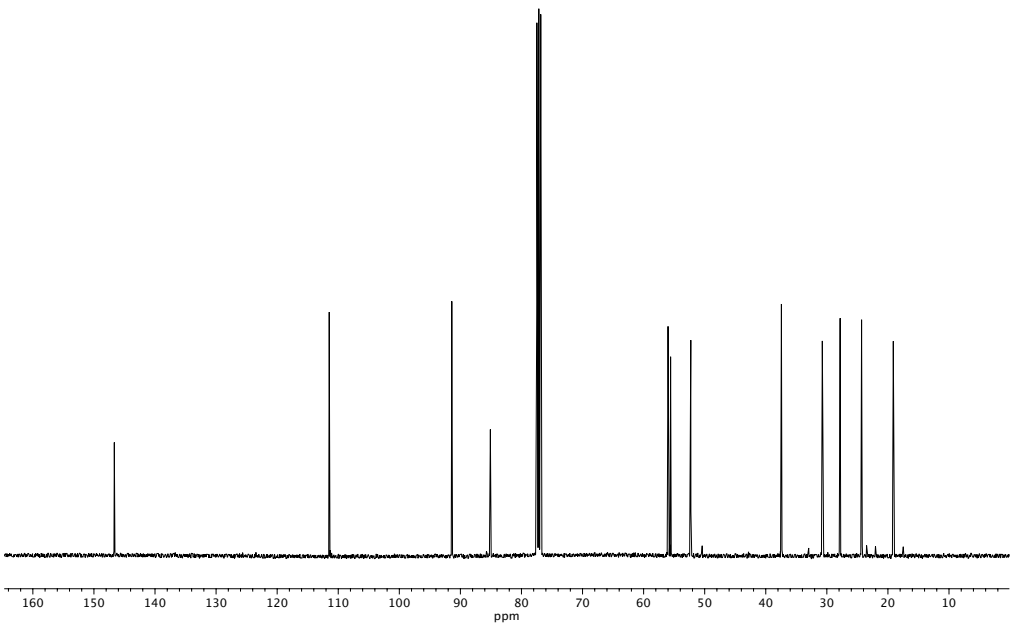


Figure A4.58. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***197****.*

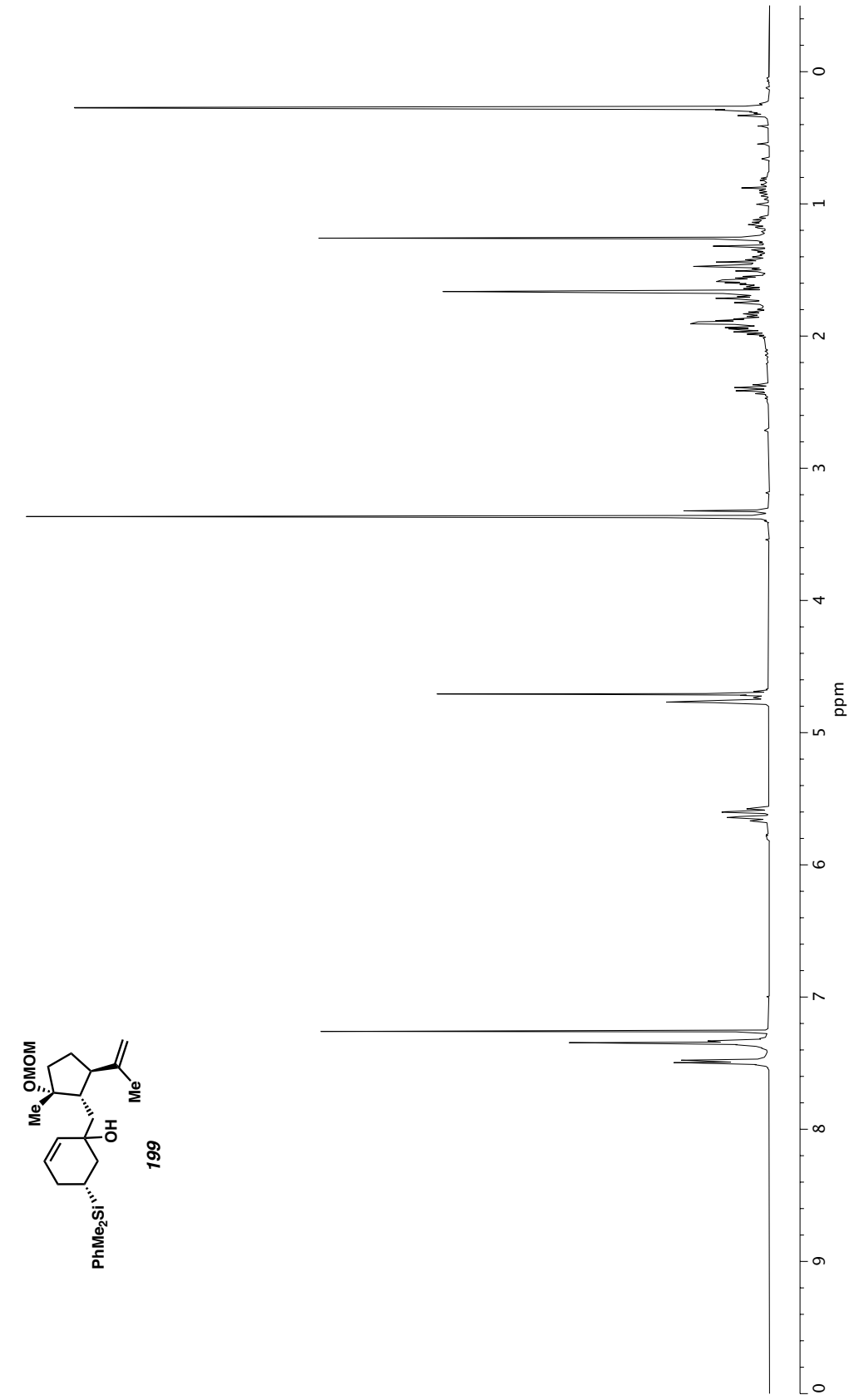


Figure A4.59. *^{1}H NMR (400 MHz, $CDCl_3$) of compound **199**.*

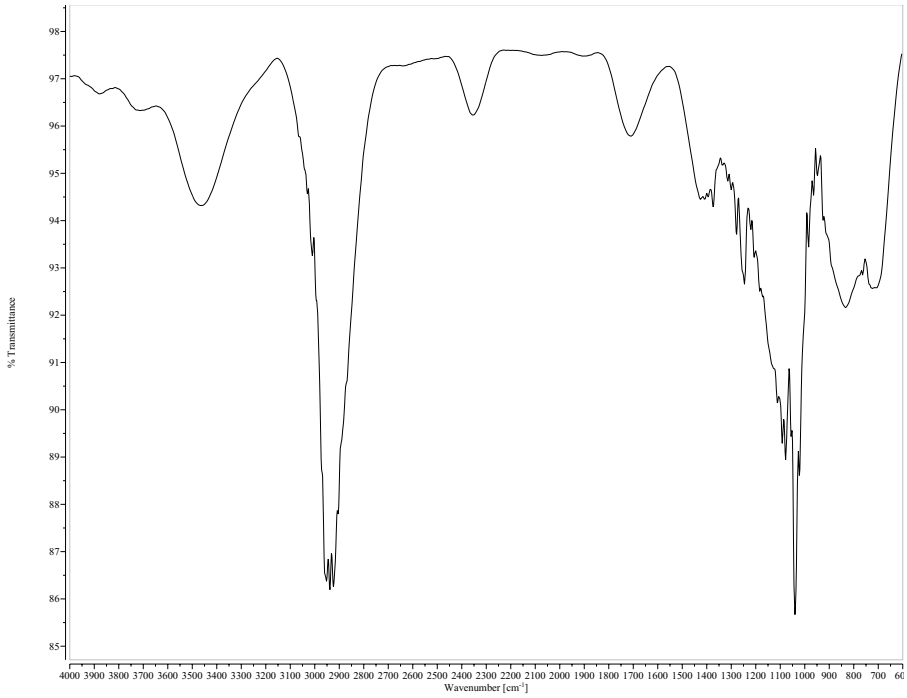


Figure A4.60. *Infrared spectrum (Thin Film, NaCl) of compound* ***199****.*

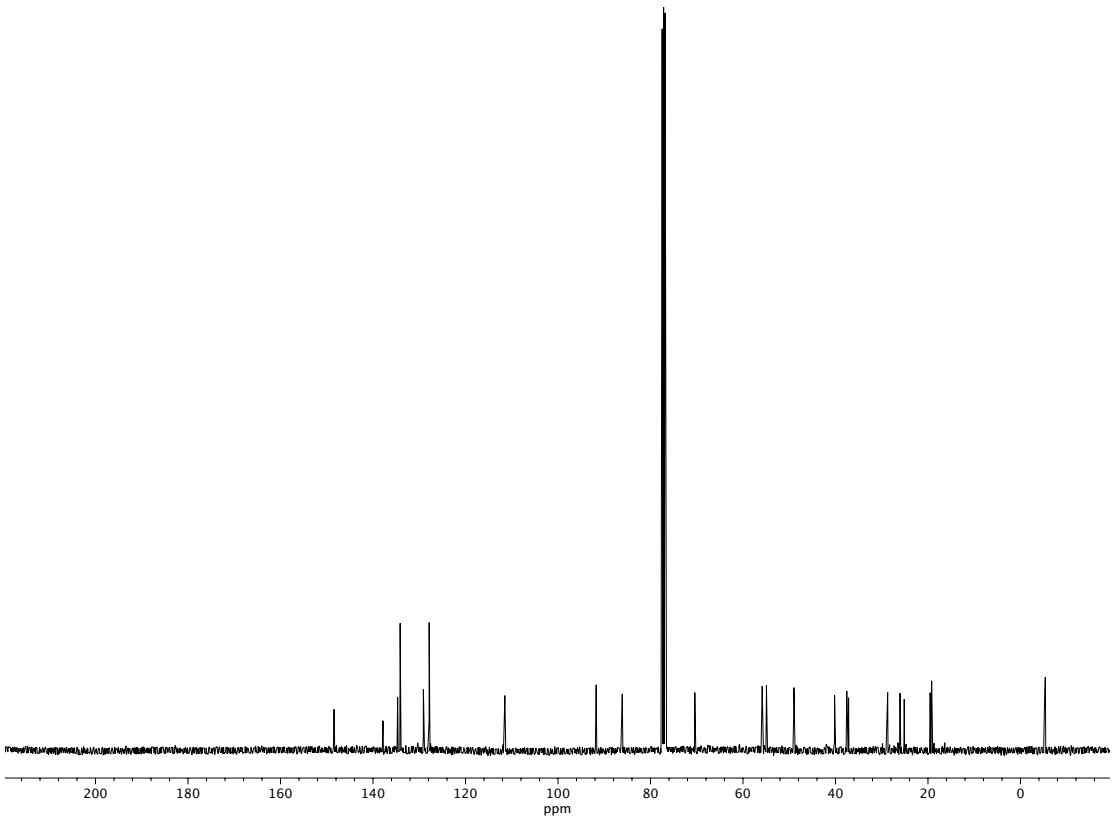


Figure A4.61. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***199****.*

Figure A4.62. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***200***.

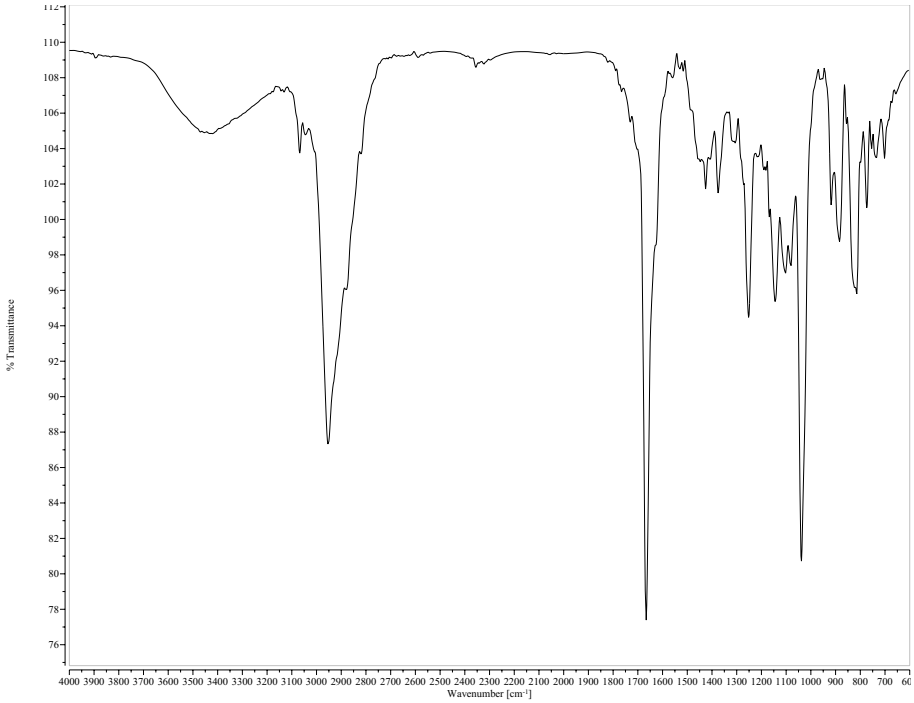


Figure A4.63. *Infrared spectrum (Thin Film, NaCl) of compound* ***200****.*

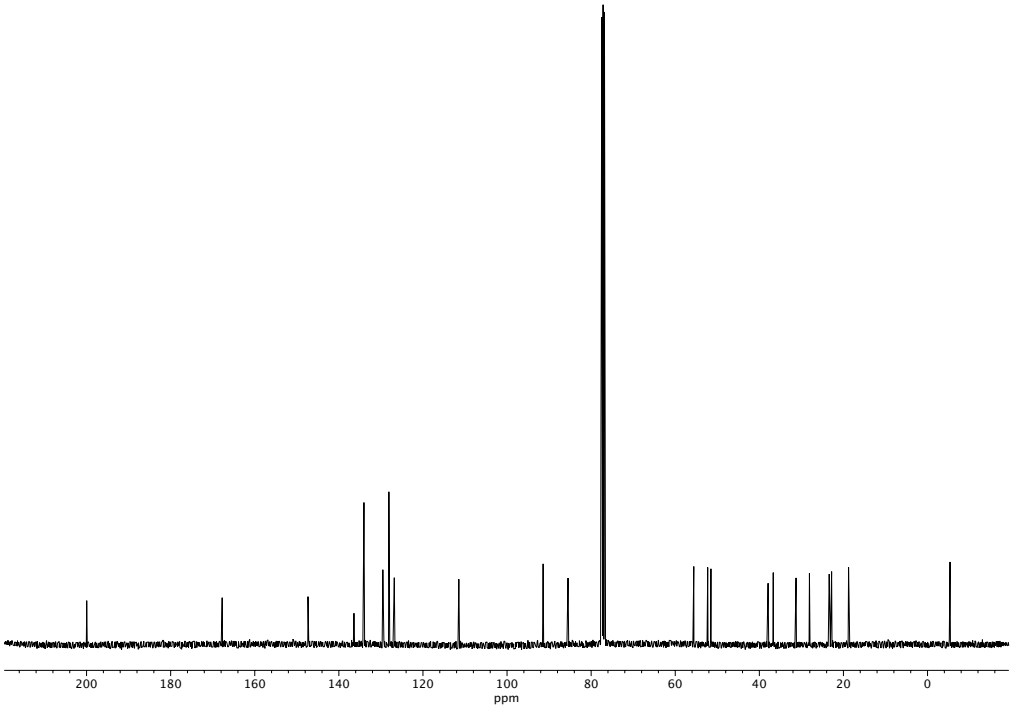


Figure A4.64. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***200****.*

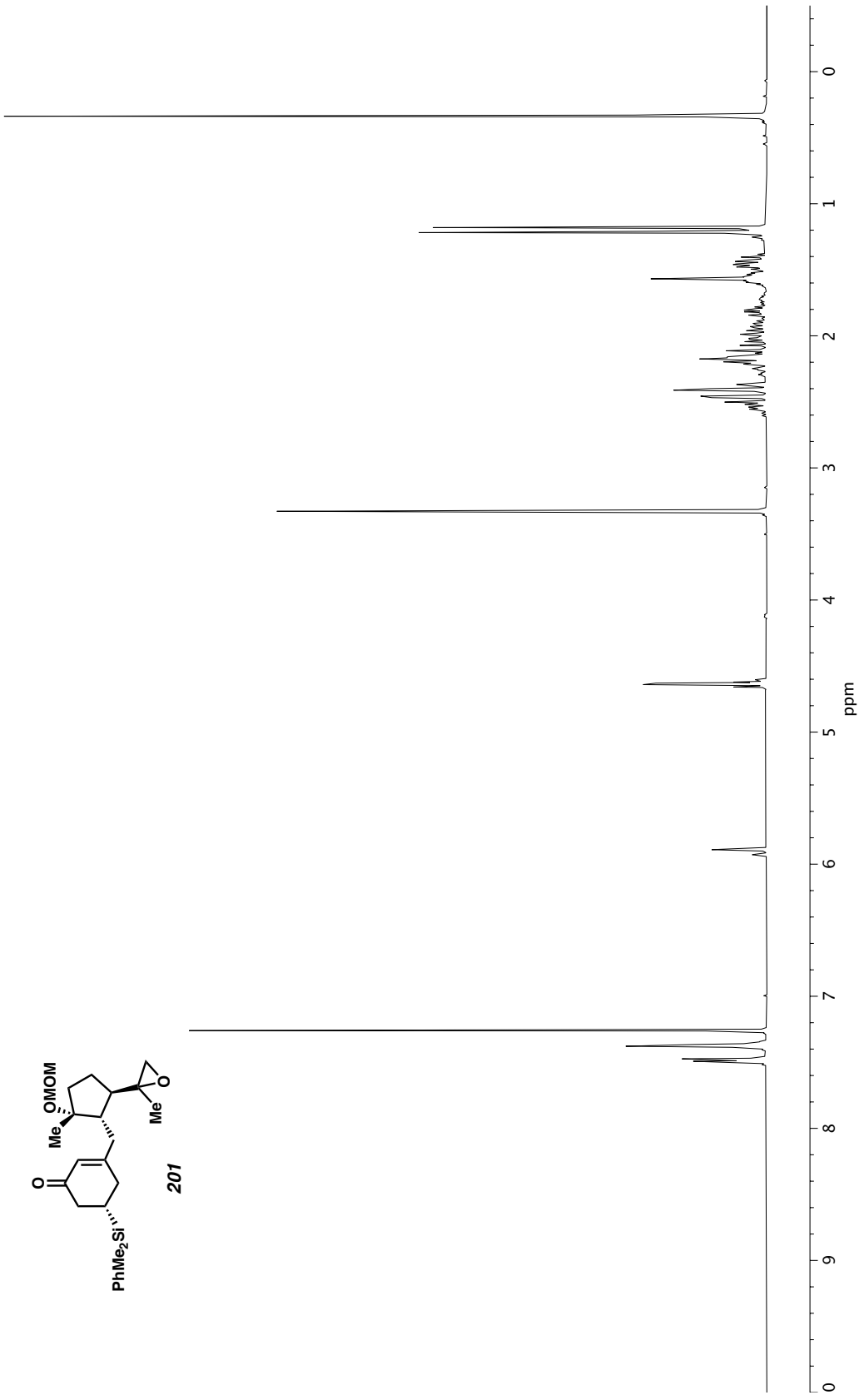


Figure A4.65. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***201****.*

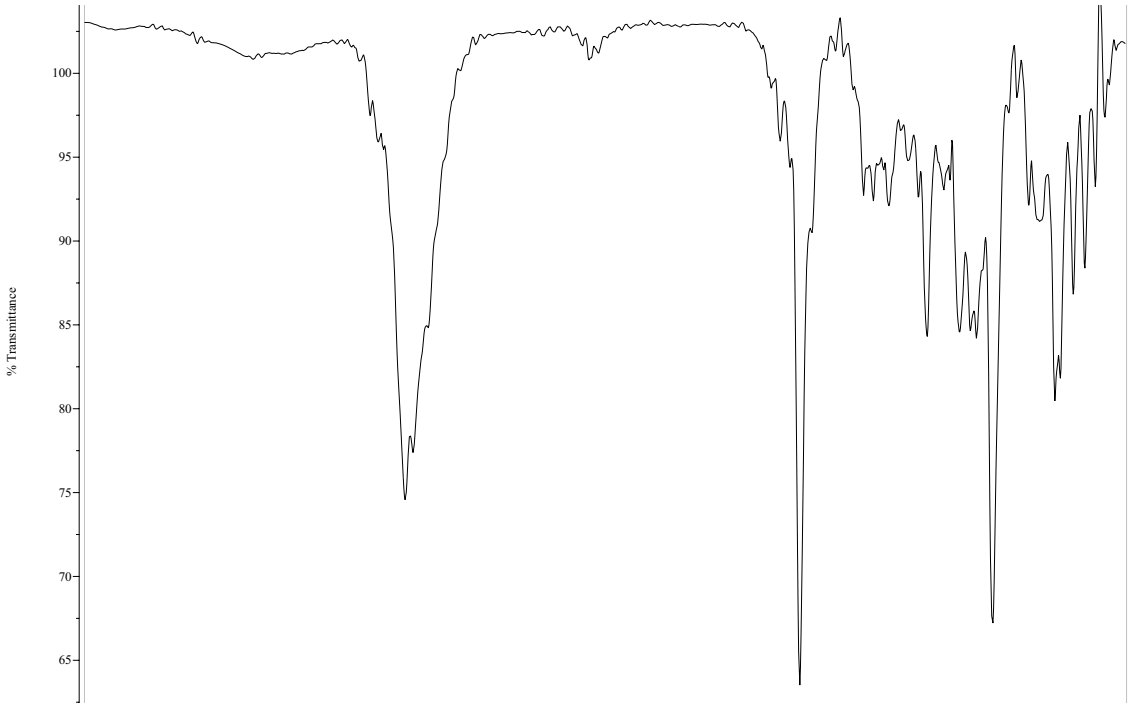


Figure A4.66. *Infrared spectrum (Thin Film, NaCl) of compound* ***201***.

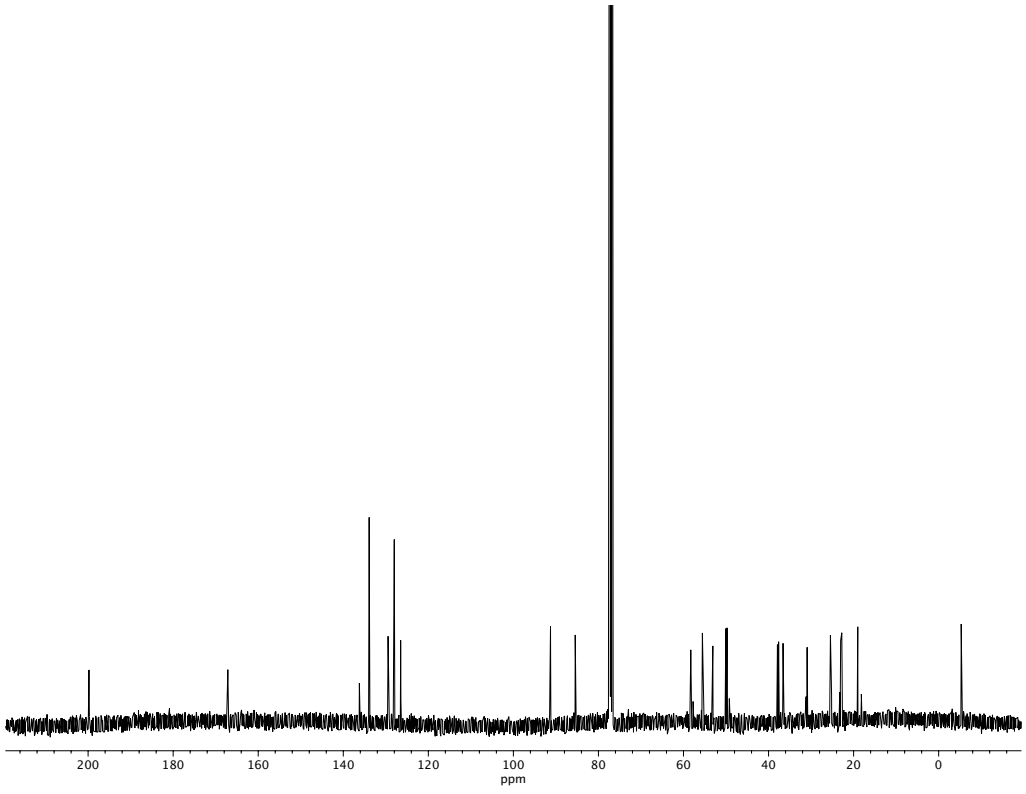


Figure A4.67. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***201***.

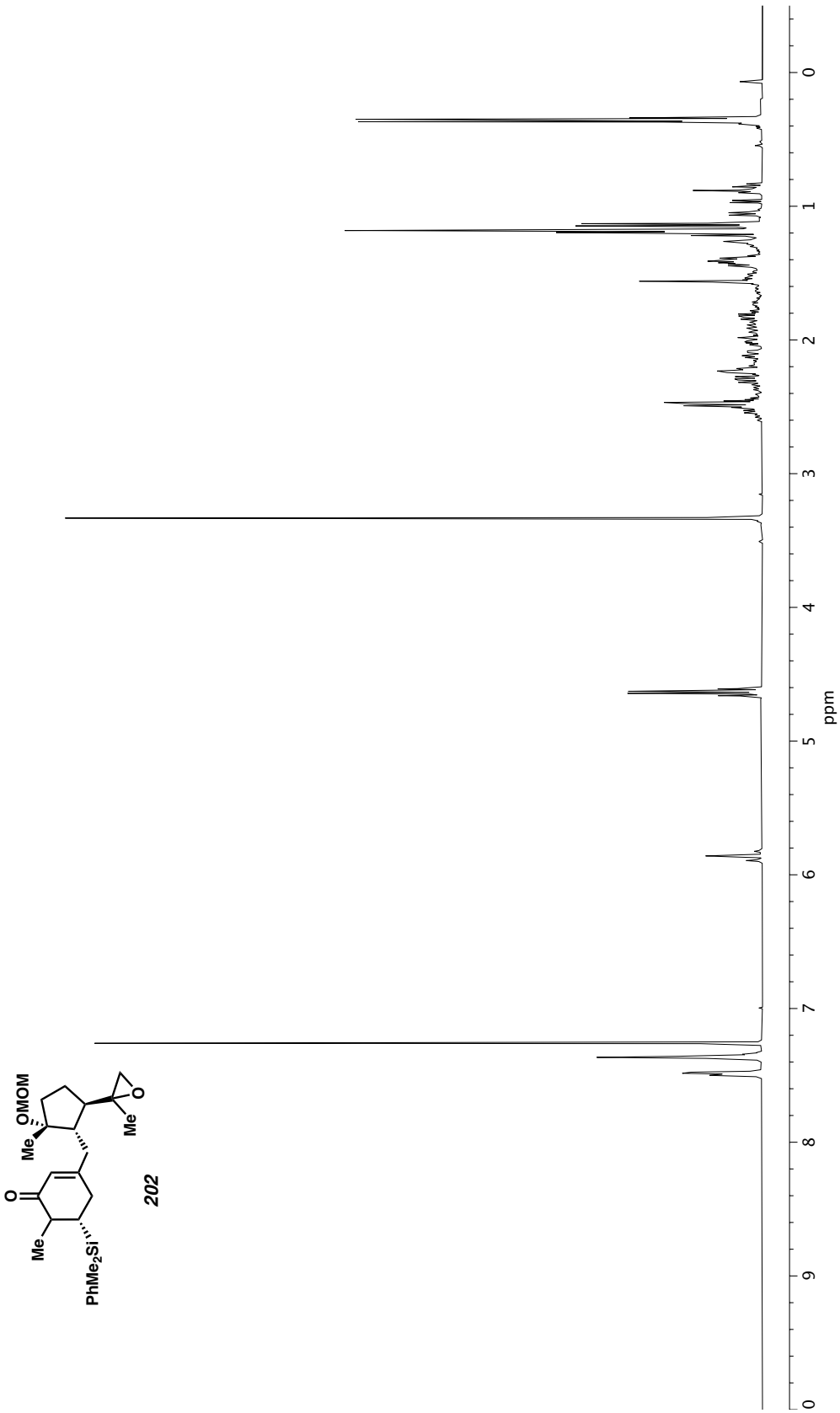


Figure A4.68. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***202***.

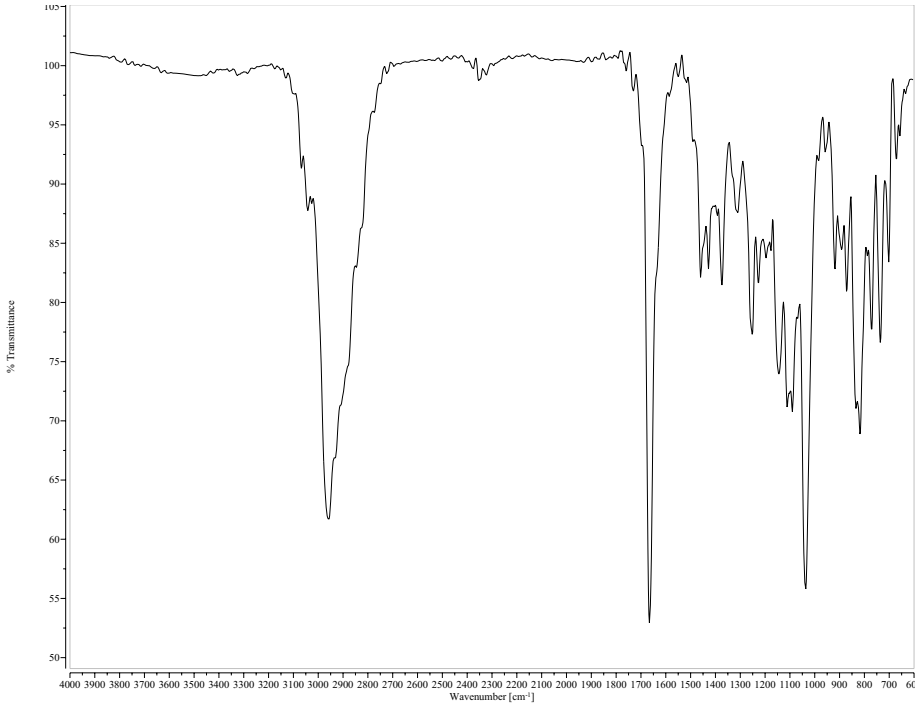


Figure A4.69. *Infrared spectrum (Thin Film, NaCl) of compound* ***202****.*

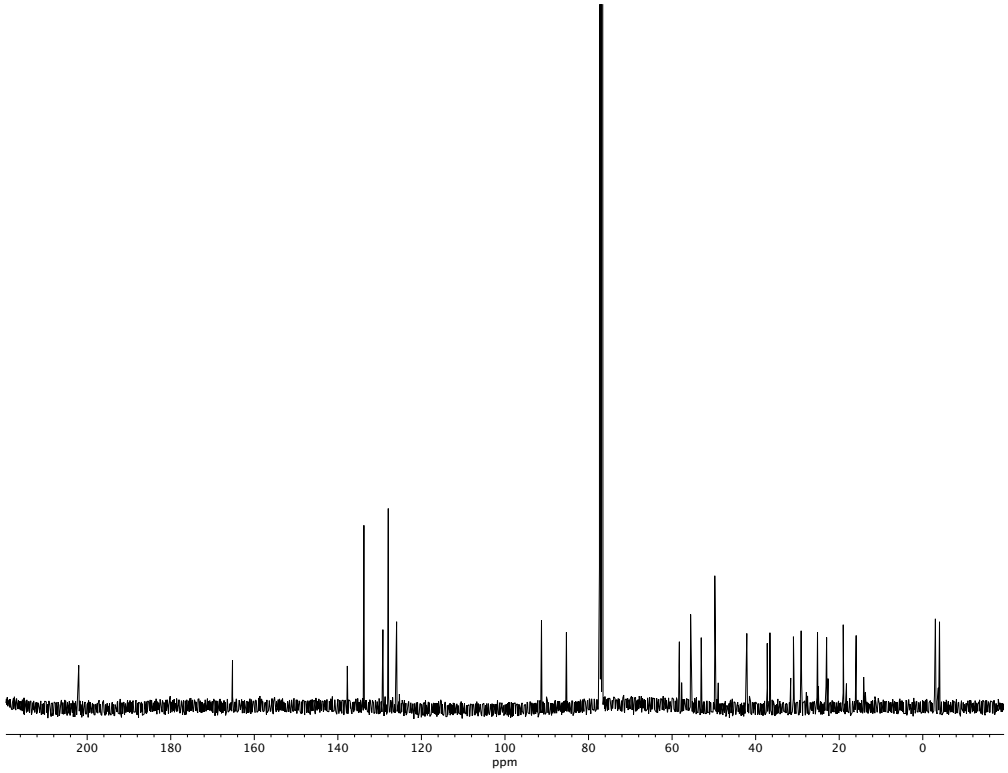


Figure A4.70. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***202****.*

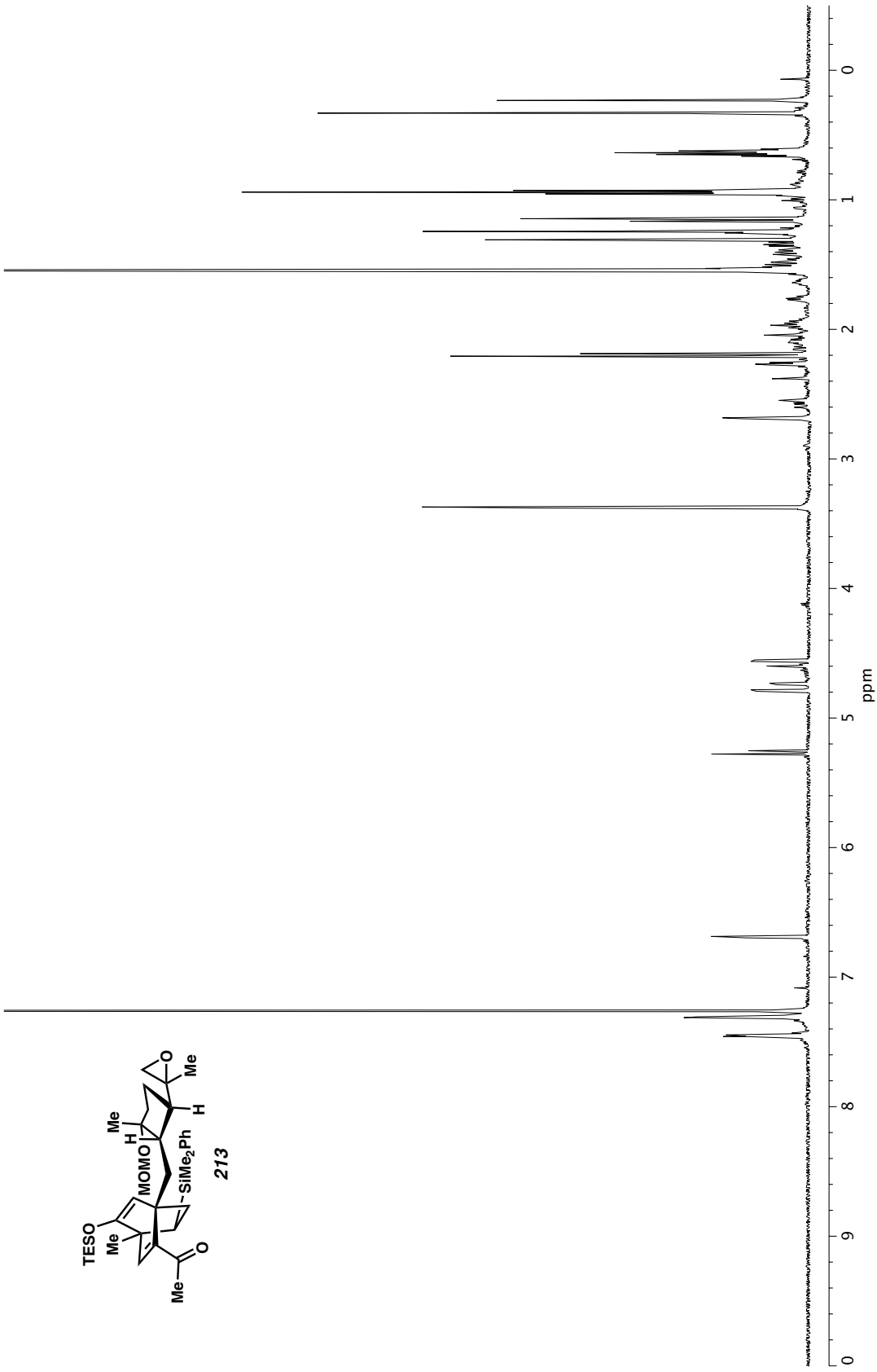


Figure A4.71. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***213***.

APPENDIX 5

Notebook Cross-Reference for New Compounds.

Table A5.1 *Notebook cross-reference for Chapter 1.*

Compound	Notebook Ref.
10a	AQC3-189
10b	AQC5-245
10c	KNF-2-145
10d	AQC4-33
10e	CS-I-153
10f	AQC4-274
10g	AQC3-213
10h	KNF-2-219
10i	RC-I-99
10j	AQC4-109
10k	AQC3-263
10l	AQC3-277
10m	RC-I-75
10n	KNF-3-033
10o	KNF-2-207
10p	AQC4-55
10q	AQC3-281
10r	AQC4-67
10s	KNF-1-287
10t	KNF-2-157
10u	ED-2-043
11a	AQC3-291
11b	AQC5-251
11c	KNF-2-151
11d	AQC4-35_p1
11f	AQC4-19_p1
11j	AQC4-117
11k	AQC3-265B_p4
11k'	AQC3-265B_p3
11k"	AQC3-265B_p1
11l	AQC3-287
11m	RC-I-181A
11m'	RC-I-181A
11n	KNF-3-043-B
11o	KNF-2-221A
11p	AQC4-61

Compound	Notebook Ref.
11o'	KNF-2-221B
11p'	AQC4-181_p2
11q	AQC3-275_p2
11r	AQC4-69_p1
11s	KNF-1-295
11t	KNF-2-161_A
11t'	KNF-2-161_B
11u	KNF-2-229_C
12	KNF-1-289
14	KNF-1-293
17	AQC3-137
19a	AQC3-229
19d	AQC4-35-p2
19e	CS-I-163
19f	AQC4-19_p2
19g	AQC4-21
19h	KNF-3-031
19i	RC-I-119A
19m	RC-1-181A
19r	AQC4-69-p2
19t	KNF-2-161-C
19u	KNF-2-229-D
29	AQC4-75
33	CS-I-225
34	CS-I-223
35	CS-I-183
36	CS-I-271
37	CS-I-257
38	RC-I-111
39	RC-I-129
40	CS-I-51
45	RC-II-35
46	RC-II-39
47	RC-II-41
48	KNF-3-177
49	RC-I-301

50	RC-II-67
51	RC-II-65
52	RC-II-77
53	CS-I-229
54	CS-I-279
55	AQC3-187
56	AQC3-201
57	AQC3-203
58	KNF-3-029
59	KNF-1-283
60	KNF-2-155
61	KNF-2-277
62	KNF-1-275-B
63	AQC3-129
64	CS-I-217
65	CS-I-215
66	CS-I-179
67	CS-I-267
68	CS-I-249
69	AQC4-159
70	AQC3-183
71	KNF-2-121
72	KNF-2-123
73	AQC3-117
74	KNF-2-155
75	KNF-1-279
76	KNF-2-147
77	ED-2-035
78	CS-I-207
79	CS-I-203
80	CS-I-175
81	CS-I-253
82	CS-I-237
83	KNF-2-283
84	RC-I-113
D-10f	AQC4-143
D-11f	AQC4-153_p1
D-19f	AQC4-153_p2

D-56	AQC4-139
D-70	AQC4-133

Table A5.2 *Notebook cross-reference for Appendix 2.*

Compound	Notebook Ref.
92-d1	KNF-1-157 R2E
92-d2	KNF-5-033
94	KNF-1-157 R1A
95	KNF-1-157 R1C
92	KNF-1-153
96	KNF-1-151
97	KNF-4-143

Table A5.3 *Notebook cross-reference for Chapter 2.*

Compound	Notebook Ref.
102a	JB-X-237
102b	JB-XI-061
102c	JB-XI-163-01
102d	JB-XI-111-01
102e	KNF-7-273
102f	JB-XIII-101
102g	RA-I-077
102h	JB-XIII-103
102i	KNF-7-103
102j	JB-XIII-0101
102k	RA-I-023
102l	JB-XII-257
102m	JB-XIII-067
102n	JB-XIII-015-02
101a	JB-IX-151
104	JB-VIII-055-02
101b	KNF-6-121
101c	JB-XI-197
101d	JB-XII-109
101e	KNF-7-271
101f	JB-XIII-077
101g	RA-I-065
101h	JB-XIII-089
101i	KNF-7-099
101j	JB-XII-303
101k	RA-I-017
101l	JB-XII-251
101m	JB-XIII-025
101n	JB-XII-299
121	JB-VIII-261
122	JB-XIII-107
123	KNF-6-105
124	JB-XI-145
125	JB-XII-029
127	JB-XIII-057
128	RA-I-061

Compound	Notebook Ref.
129	JB-XIII-085
130	KNF-7-073
131	JB-XII-279
132	RA-I-011
133	JB-XII-235
134	JB-XII-293
135	JB-XII-281
126	KNF-7-261
138	JB-XIII-097
151	KNF-7-211-B
142	JB-XIII-049
143	RA-I-059
144	JB-XIII-063
147	RA_I-009
148	JB-XII-223
149	JB-XII-273
150	JB-XII-275
146	JB-XII-265
105	KNF-7-287
106	KNF-7-223
107	JB-XIII-173
108	JB-XIII-079
Diallyl-103a	JB-X-237

Table A5.4 *Notebook cross-reference for Chapter 3.*

Compound	Notebook Ref.
179	KNF-3-233
182	KNF-4-187
185	KNF-4-119
226	KNF-8-067
227	KNF-8-069
205	KNF-8-073
207-d1	KNF-8-089-d1
207-d2	KNF-8-089-d2
207-d2	KNF-8-089-d3
209	RC-V-225
210	RC-V-189
212	RC-V-253
186	RC-VI-023
229	KNF-8-017
230	KNF-8-023
215	RC-V-173B
216	KNF-8-027B
217	KNF-0-027A
193	KNF-8-033
194	KNF-8-035
195	KNF-8-051
196	KNF-8-057
197	KNF-8-059
199	KNF-8-061
200	KNF-8-063
201	KNF-8-065
202	KNF-7-231
213	KNF-7-253B1

ABOUT THE AUTHOR

Kali Flesch was born in Waukesha, WI in 1998 to Toni and Danny Flesch. She became interested in chemistry during her sophomore year high school chemistry class taught by Mr. Erling Antony. Performing experiments in the laboratory and learning about chemical reactivity in this class motivated her to study chemistry as an undergraduate.

In the fall of 2016 Kali began her undergraduate studies at the University of Wisconsin – Madison as a chemistry major. During her freshman year, she joined the laboratory of Prof. Shannon Stahl and worked alongside Dr. Chase Salazar. She studied the mechanism of palladium-catalyzed aerobic oxidation reactions with the ultimate goal of increasing catalyst turnover. Kali spent the summer of 2019 in Nagoya, Japan in the laboratory of Prof. Kenichiro Itami at Nagoya University as a part of the International Research Experiences for Students Fellowship through the NSF Center for Selective C–H Functionalization. She joined a team developing the C6-selective direct arylation of thieno[2,3-*d*]pyrimidines. These research experiences motivated Kali to continue her studies of chemistry in graduate school.

Kali moved to Pasadena, California to pursue graduate studies at the California Institute of Technology under the advisory of Prof. Brian Stoltz. Her research focused on the development of novel asymmetric transformations from Pd enolate intermediates and natural product total synthesis. Upon the completion of her Ph.D. at Caltech, Kali will join the process chemistry team at Sanofi in Boston, Massachusetts.