PROGRESS TOWARD THE CORTISTATIN A CARBOCYLIC CORE

AND

THE DEVELOPMENT OF THE CATALYTIC ENANTIOSELECTIVE ALKYLATION OF 3-HALOOXINDOLES

Thesis by

Sandy Ma

In Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy

CALIFORNIA INSTITUTE OF TECHNOLOGY

Pasadena, California

2011

(Defended September 27, 2010)

To my parents

ACKNOWLEDGEMENTS

I would like to first acknowledge my undergraduate adviser Prof. Robert Waymouth for his invaluable instruction and inspiring my interest in chemistry.

I would like to thank my adviser, Prof. Brian Stoltz. Brian has always taken the time to read through my many drafts of papers, proposals, fellowships, and this thesis. I have always appreciated Brian's advice and support.

I would also like to thank my committee members, Prof. John Bercaw, Prof. Peter Dervan, and Prof. Sarah Reisman for all of their help. They have provided me with helpful feedback and discussions pertaining to my proposals and research.

I would also like to thank my coworkers on the projects that I have worked on. I am indebted to Drs. Qi "Charles" Liu and Corinne Baumgartner for their hard work and help on the cortistatin project A. I would also like to thank Drs. Shyam Krishnan and Xiaoqing Han for all their help and contributions on the oxindole project. Moreover, I would also like to acknowledge Dr. Scott Virgil for all of his help.

I would also like to thank all of the past and present Stoltz group members that I've had the pleasure to work with. They have been invaluable with answering my chemistry questions, proofreading my various drafts, and keeping me sane over the past years. I wish everyone the very best in their respective futures.

I would also like to thank the chemistry department staff for keeping things running smoothly and appreciate everything that they have done for me.

On a personal level, I would like to acknowledge Michael Alton for his advice and support during my graduate studies. My Caltech and non-Caltech friends have also provided me with support over the years. I would also like to thank my parents for

everything that they have done for me. To show my appreciation for their sacrifices, I have dedicated this thesis in their honor.

ABSTRACT

Biologically active natural products often contain interesting and complex structural features and functionalities that make them attractive targets for synthetic chemists. As such, these natural products can serve as inspiration for the development of new reaction methodology.

Cortistatin A contains a unique rearranged steroidal core and possesses potent anti-angiogenic activity. These features have made cortistatin A the target of many synthetic efforts, including ours. The progress toward the synthesis of the cortistatin A carbocyclic core via an enyne-ene metathesis is discussed. Our studies towards the construction of the cortistatin A carbocyclic core yielded an interesting result, wherein an attempted S_N2 inversion of a secondary mesylate afforded product with retention of stereochemistry.

Oxindole derived motifs are also prevalent in biologically active molecules. More specifically, 3,3-disubstituted oxindoles can be used to access pyrrolidinylspirooxindole and pyrrolidinoindoline cores. Herein, the development of a catalytic enantioselective malonate alkylation of 3-halooxindoles to access enantiopure 3,3-disubstituted oxindoles is detailed. We then demonstrate that the enantiopure 3,3-disubstituted oxindoles derived from this novel transformation can be used towards the construction of pyrrolidinylspirooxindole and pyrrolidinoindoline cores.

TABLE OF CONTENTS

LIST OF FIGURES

CHAPTER 1

CHAPTER 2

APPENDIX 1

APPENDIX 2

CHAPTER 3

APPENDIX 3

APPENDIX 4

APPENDIX 6

LIST OF SCHEMES

CHAPTER 1

CHAPTER 2

CHAPTER 3

APPENDIX 5

APPENDIX 6

LIST OF TABLES

APPENDIX 2

CHAPTER 3

APPENDIX 4

APPENDIX 7

LIST OF ABBREVIATIONS

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
Ac	acetyl
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl group
atm	atmosphere(s)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOX	bisoxazoline
br	broad
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	butyl or *norm*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
c	concentration of sample for measurement of optical rotation
^{13}C	carbon-13 isotope
°C	degrees Celsius
calc'd	calculated
CAN	ceric ammonium nitrate

Cbz	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
cf.	consult or compare to (Latin: *confer*)
cm^{-1}	wavenumber(s)
comp	complex
conc.	concentrated
Cy	cyclohexyl
CSA	camphor sulfonic acid
d	doublet
d	dextrorotatory
D	deuterium
dba	dibenzylideneacetone
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DIBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
2,6-DTBP	2,6-di-*tert*-butylphenol

ee	enantiomeric excess
E^+	electrophile
E	trans (entgegen) olefin geometry
e.g.	for example (Latin: *exempli gratia*)
EI	electron impact
eq	equation
ESI	electrospray ionization
Et	ethyl
et al.	and others (Latin: *et alii*)
FAB	fast atom bombardment
Fmoc	fluorenylmethyloxycarbonyl
g	gram(s)
h	hour(s)
^1H	proton
^2H	deuterium
^3H	tritium
[H]	reduction
HMDS	hexamethyldisilamide or hexamethyldisilazide
$h\nu$	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IBX	2-iodoxybenzoic acid

IC_{50}	half maximal inhibitory concentration (50%)
i.e.	that is (Latin: *id est*)
IR	infrared spectroscopy
J	coupling constant
k	rate constant
kcal	kilocalorie(s)
kg	kilogram(s)
L	liter or neutral ligand
l	levorotatory
LA	Lewis acid
LDA	lithium diisopropylamide
m	multiplet or meter(s)
M	molar or molecular ion
m	meta
μ	micro
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
MM	mixed method
mol	mole(s)
MOM	methoxymethyl

mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
m/*z*	mass-to-charge ratio
N	normal or molar
NBS	*N*-bromosuccinimide
nm	nanometer(s)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu^-	nucleophile
o	ortho
[O]	oxidation
p	para
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PHOX	phosphinooxazoline
pK_a	acid dissociation constant
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl

n-Pr	propyl or *norm*-propyl
psi	pounds per square inch
py	pyridine
q	quartet
R	alkyl group
ref	reference
R_f	retention factor
s	singlet or seconds
S	sinister
sat.	saturated
Su	succinimide
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBAT	tetra-*n*-butylammonium difluorotriphenylsilicate
TBCHD	2,4,4,5-tetrabromo-2,5-cyclohexadienone
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
temp	temperature
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl

TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
tol	tolyl
Ts	*para*-toluenesulfonyl (tosyl)
UV	ultraviolet
w/v	weight per volume
v/v	volume per volume
X	anionic ligand or halide
Z	cis (zusammen) olefin geometry

CHAPTER 1

Inspiration from Natural Products

1.1 INTRODUCTION

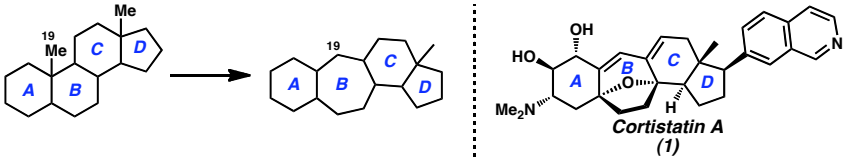
Biologically active natural products often contain interesting and complex structural features and functionalities that make them attractive targets for synthetic chemists. Furthermore, these natural products can serve as inspiration for the development of new synthetic methodologies.[1] Herein, we will discuss our efforts toward the synthesis of several natural product scaffolds.

1.2 CORTISTATIN A

Cortistatin A (**1**) is a potent anti-angiogenic agent that features a unique rearranged steroid core (Figure 1.1) and has become a target for numerous synthetic efforts since its isolation in 2006.[2] These collective efforts utilized a variety of methods to construct the cortistatin A carbocyclic core, resulting in one semi-synthesis, three total syntheses, two formal syntheses, and numerous syntheses of the pentacyclic cortistatin core.[3] A select number of these efforts will be discussed here and are only meant to illustrate some

general approaches that have been directed towards the synthesis of cortistatin A. For convenience, these strategies are organized by method for B ring formation.

Figure 1.1 Rearranged steroid core of cortistatin A

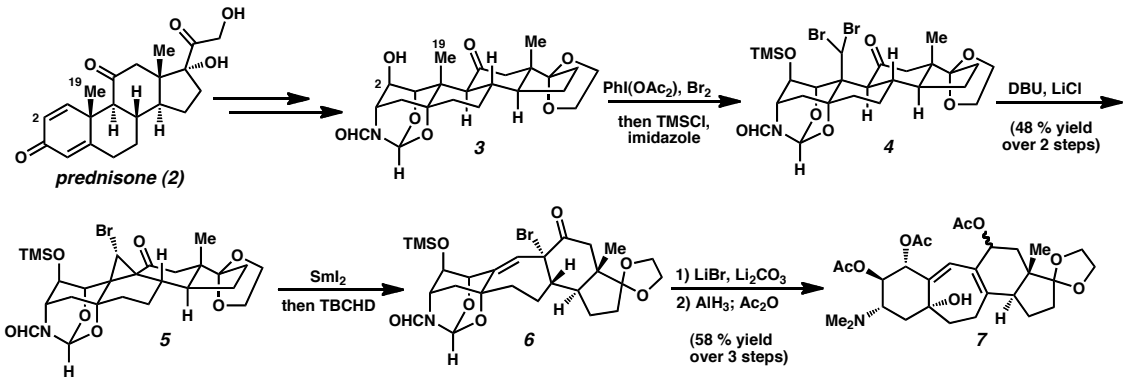


One approach that has been used by several groups is to rely on ring expansion strategies to access the 7-membered B ring by C(19) methyl group incorporation. Baran utilized cyclopropane fragmentation to construct the 7-membered B ring en route to the first synthesis of (+)-cortistatin A (Scheme 1.1).[4] This semi-synthesis began with the commercially available steroid prednisone (**2**). To prepare the key ring-expansion step, an alcohol-directed double C–H functionalization was triggered by treatment of secondary alcohol **3** with $PhI(OAc)_2$ and Br_2 and irradiation with a sunlamp. Because the resulting dibromo alcohol is unstable, this intermediate was directly silylated with TMSCl to yield the C(19)-dibromomethyl species **4**, which upon subsequent exposure to DBU and LiCl yielded bromocyclopropane **5** in 48% overall yield. Regioselective ring fragmentation of bromocyclopropane **5** was achieved with SmI_2 followed by treatment with 2,4,4,5-tetrabromo-2,5-cyclohexadienone (TBCHD) to trap the intermediate enolate, yielding α-bromoketone **6**. Dehydrobromination of **6** with Li_2CO_3 followed by alane reduction and acylation produced **7**. With the 7-membered B-ring installed, this intermediate was then elaborated to cortistatin A.

Shair's approach to the total synthesis of (+)-cortistatin A also featured a cyclopropane fragmentation to construct the 7-membered B ring. The key step was a highly diastereoselective aza-Prins cyclization to construct the cortistatin A core.[5] Corey[6]

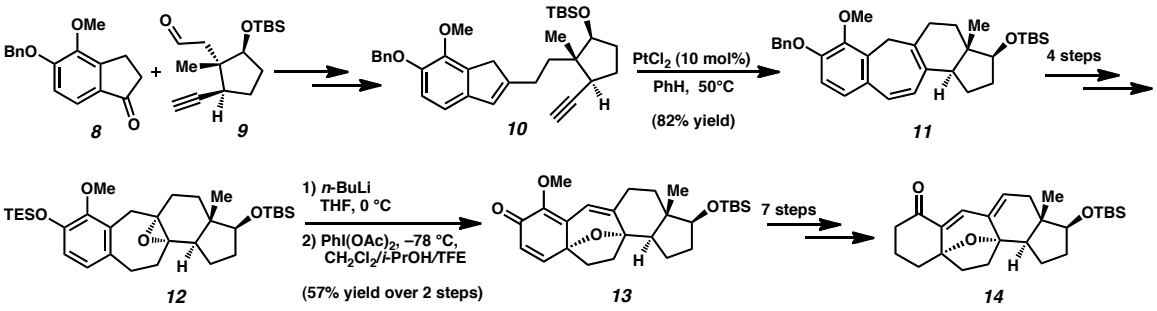
and Magnus[7] have also pursued routes that contained ring expansion strategies to access the 7-membered B ring in their respective model system studies.

Scheme 1.1 Baran's semi-synthesis of (+)-cortistatin A



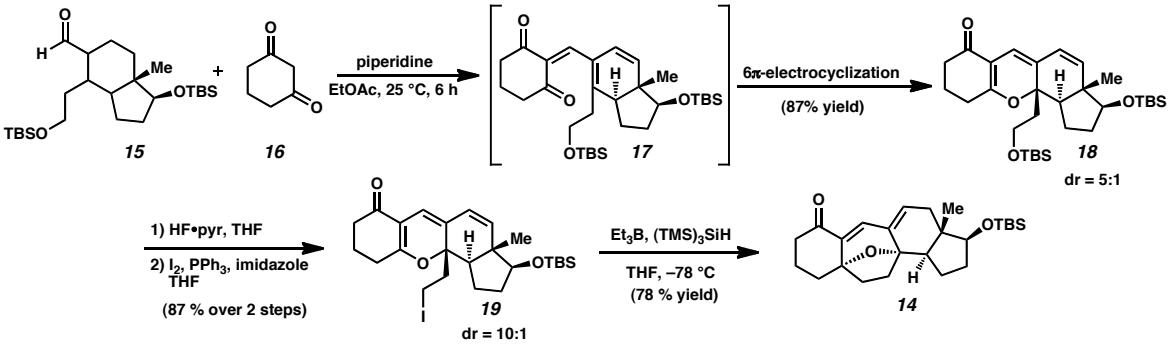
Oxidative dearomatization has also been employed for the construction of the bridging ether moiety contained in the B ring by the Sarpong,[8] Sorensen,[9] and Danishefsky[10] groups. Sarpong's second approach in the formal synthesis of (±)-cortistatin A featured an enyne cycloisomerization to form the 7-membered B ring followed by an oxidative dearomatization to construct the ether bridge (Scheme 1.2).[8b] Sarpong's synthesis commenced from indanone **8** and aldehyde **9**, which were converted to alkynyl indene **10** through a series of steps. Enyne cycloisomerization catalyzed by $PtCl_2$ produced benzocycloheptadiene **11**. After a series of steps to install an epoxide moiety and to selectively reduce an olefin, **12** was then treated with *n*-BuLi to effect a regioselective ring opening, affording an intermediate alcohol. This intermediate alcohol subsequently underwent oxidative dearomatization with $PhI(OAc)_2$ to furnish the ether bridge of pentacycle **13**. Pentacycle **13** was then elaborated to ketone **14**, a known intermediate that intercepts the synthesis of (+)-cortistatin A reported by Nicolaou.[11] Sorensen has also reported a synthesis of the pentacylic core of cortistatin A that featured a tandem oxidative dearomatization/intramolecular dipolar cycloaddition.[9]

Scheme 1.2 Sarpong's formal synthesis of (±)-cortistatin A



The research groups of Hirama,[12] Danishefsky,[13] and Gung[14] have independently considered an alternate route that relied on pericyclic transformations to construct the [3.2.1]oxabicylic ring B ring. Hirama's synthesis commenced from aldehyde **15**, which was derived from enantioenriched Hajos-Parrish ketone (Scheme 1.3).[12] Bicycle **15** was treated with cyclohexane-1,3-dione (**16**) in the presence of base to effect a Knoevenagel condensation to form intermediate **17**. This intermediate **17** underwent spontaneous 6π-electrocyclization to form 2-H-pyran **18** in 87% yield. Conversion of the TBS ether to the iodide yielded iodide **19**, which was then treated with triethylborane and $(TMS)_3SiH$ to give ketone **14**, the intermediate from the synthesis of (+)-cortistatin A reported by Nicolaou.[11]

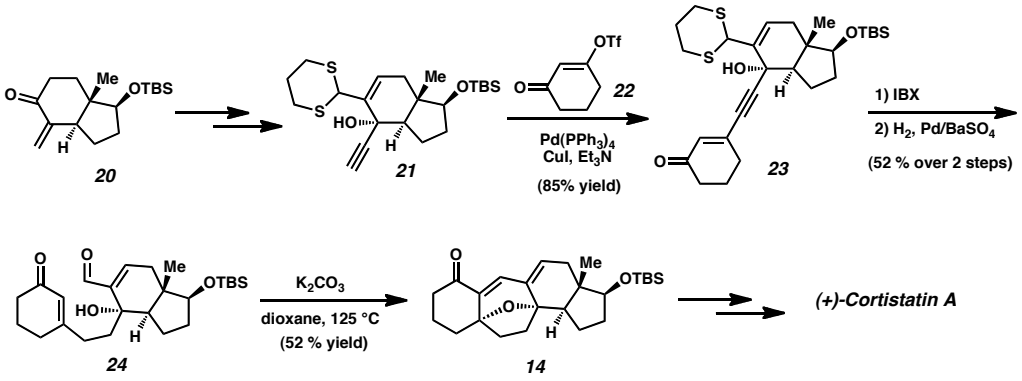
Scheme 1.3 Hirama's synthesis of the pentacyclic core of (+)-cortistatin A



A cascade sequence in which the 7-membered B ring and the tetrahydrofuran ring are simultaneously constructed has been pursued by the Nicolaou group (Scheme 1.4).[11] The

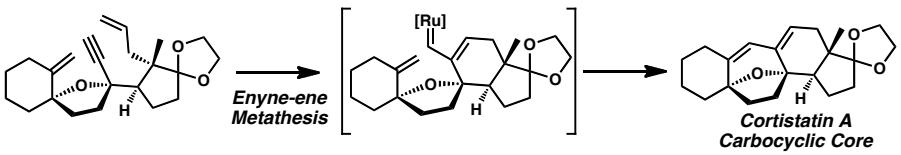
synthesis started from known enone **20**, which was derived from enantiopure Hajos-Parrish ketone. Enone **20** was converted to alkyne **21**, which was then coupled to triflate **22** via a Sonogashira coupling to yield **23**. Dithiane cleavage followed by alkyne hydrogenation afforded **24**. The key step was triggered by treatment of **24** with K_2CO_3 in refluxing dioxane to induce an oxy-Michael addition of the tertiary alcohol into the enone moiety followed by an intramolecular aldol, furnishing dienone **14** in 52% yield. This dieonone was then elaborated to (+)-cortistatin A.

Scheme 1.4 Nicolaou's total synthesis of (+)-cortistatin A



Given the promising biological activity and intriguing structure of cortistatin A, we set out to develop our own novel approach towards the construction of the carbocylic core.[15] It was envisioned that an enyne-ene metathesis would allow rapid access to the carbocylic core (Scheme 1.5). Our synthetic efforts for the construction of the cortistatin A are discussed in this thesis.

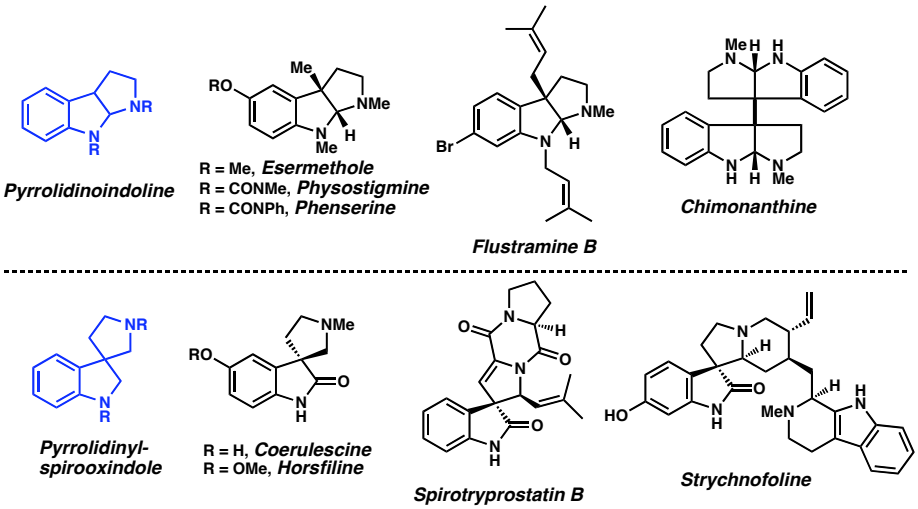
Scheme 1.5 Proposed approach to the cortistatin A carbocyclic core



1.3 OXINDOLE DERIVED STRUCTURAL MOTIFS

Pyrrolidinoindolines and pyrrolidinylspirooxindoles are structural motifs that are prevalent in a large family of alkaloid natural products that have strong bioactivity profiles and interesting structural properties (Figure 1.2).[17]

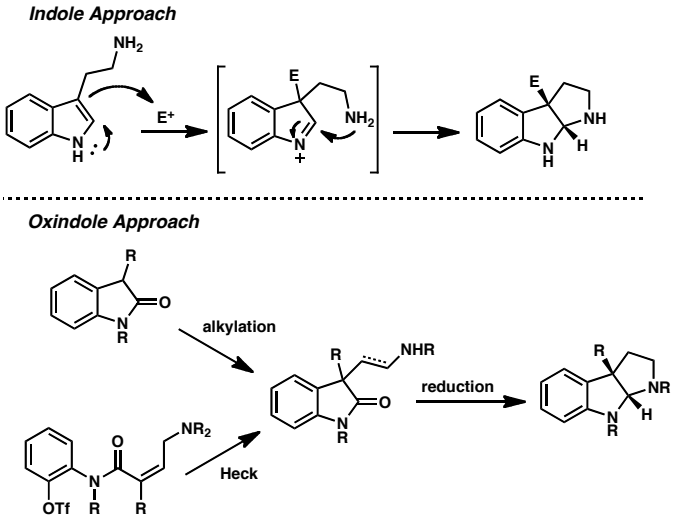
Figure 1.2 Natural products that contain pyrrolidinoindoline and pyrrolidinylspirooxindole cores



There have been many approaches toward the pyrrolidinoindoline core; however there are two general strategies that are most commonly used and are highlighted in Scheme 1.6. The first approach (Indole Approach, Scheme 1.6) involves electrophilic attack at the indole C(3) position of tryptamine or tryptophan (not shown) followed by cyclization by the pendant amine to form the pyrrolidinoindoline core, a mechanism postulated to occur in nature. Many synthetic groups have exploited this first approach to access racemic and enantiopure pyrrolidinoindolines.[16] The second approach (Oxindole Approach, Scheme 1.6) relies on the reduction of a 3,3-disubstituted oxindole to form the pyrrolidinoindoline core. There have been many synthetic methods developed for the construction of 3,3-disubstituted oxindoles,[17] Two of the more common strategies are

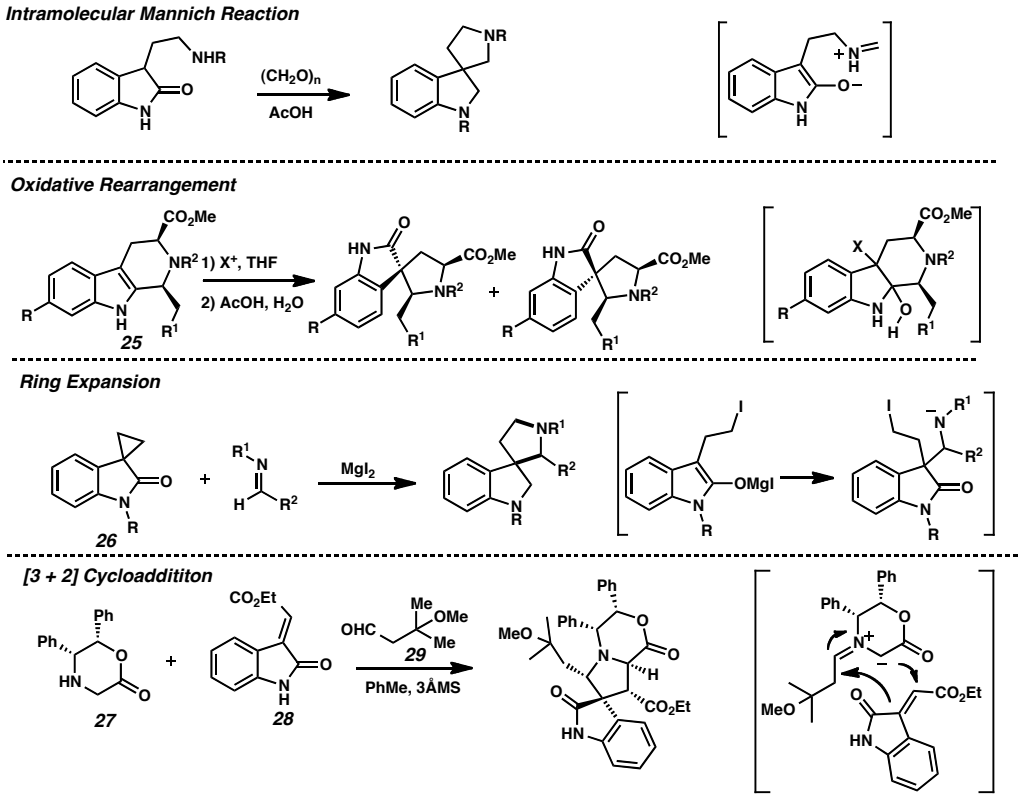
shown in Scheme 1.6: alkylation of the 3-substituted oxindole and an intramolecular Heck cyclization.

Scheme 1.6 General strategies for accessing pyrrolidinoindoline core



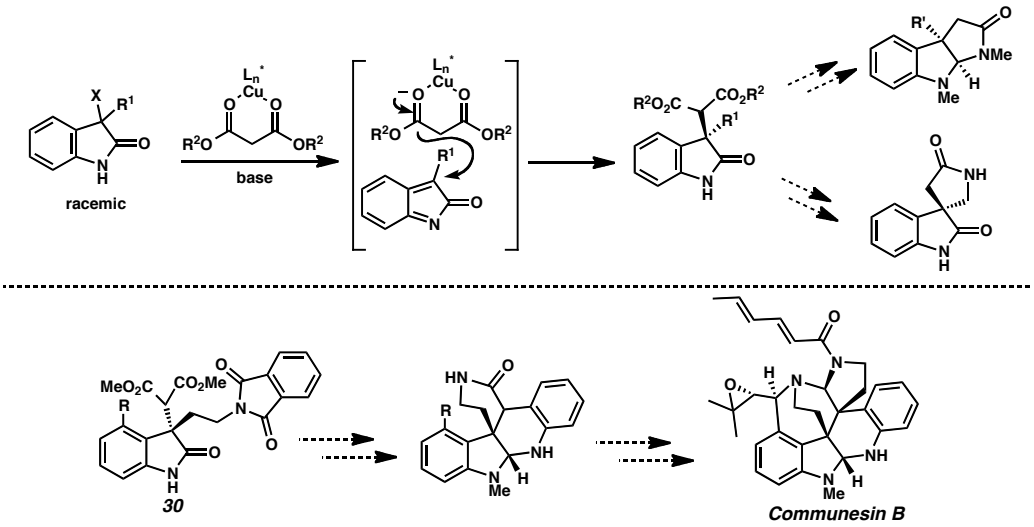
There have also been many methods developed for the construction of pyrrolidinylspirooxindole cores;[18] several common methods are featured in Scheme 1.7. One of the earliest methods involves an intramolecular Mannich reaction, a strategy inspired by the hypothesis that the isomerization of pyrrolidinylspirooxindoles in nature is from a Mannich/retro-Mannich reaction.[19] The second method is an oxidative rearrangement of a tetrahydro-β-carboline **25**, where treatment with a suitable oxidant in combination with a hydroxide source results in an oxidative rearrangement to the pyrrolidinylspirooxindole core.[20] A MgI_2 ring expansion strategy has also been utilized to construct the spirocylic core from imines and spirocyclopropyl oxindoles **26**, wherein MgI_2 is postulated to serve a dual role of Lewis acid activation as well as nucleophilic counterion to promote ring expansion.[21] The final strategy that is also widely employed for this spirocyclic motif is a three component [3+2] cycloaddition reaction of morpholine **27**, oxindolylideneacetate **28**, and aldehyde **29**.[22]

Scheme 1.7 General methods for accessing pyrrolidinylspirooxindole core



Because of the significance of pyrrolidinylspirooxindole and pyrrolidinoindoline cores, we devised a method to access both cores by using 3,3-disubstituted oxindoles (Scheme 1.8). Herein, we will discuss our efforts to pursue these motifs through the development of a novel asymmetric copper-catalyzed malonate addition into oxindoles to access these 3,3-disubstituted oxindoles.[23] Furthermore, another important application is that these disubstituted oxindoles, such as **30**, can also be used to access more complex biologically active molecules, such as communesin B.[24,25]

Scheme 1.8 Proposed strategy to access pyrrolidinylspirooxindole and pyrrolidinoindoline cores and application to communesin B



1.4 CONCLUSION

We have briefly discussed the role of complex and structurally interesting natural products as an inspiration for method development and total syntheses. We have also briefly highlighted the current strategies available for accessing the key structural motifs discussed in this thesis: cortistatin A and pyrrolidinylspirooxindole and pyrrolidinoindoline cores. Our progress toward the synthesis of the cortistatin A carbocyclic core via an enyne-ene metathesis is discussed in Chapter 2 of this thesis, whereas the synthesis of the pyrrolidinylspirooxindole and pyrrolidinoindoline cores via enantiopure 3,3-disubstituted oxindoles derived from a novel copper-catalyzed malonate alkylation is discussed in Chapter 3.

1.5 NOTES AND REFERENCES FOR TEXT

(1) Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Nature* **2008**, *455*, 323–332.

(2) (a) Aoki, S.; Watanabe, Y.; Tanabe, D.; Setiawan, A.; Arai, M.; Kobayashi, M. *Tetrahedron Lett*. **2007**, *48*, 4485–4488. (b) Watanabe, Y.; Aoki, S.; Tanabe, D.; Setiawan, A.; Kobayashi, M. *Tetrahedron* **2007**, *63*, 4074–4079. (c) Aoki, S.; Watanabe, Y.; Tanabe, D.; Arai, M.; Suna, H.; Miyamoto, K.; Tsujibo, H.; Tsujikawa, K.; Yamamoto, H.; Kobayashi, M. *Bioorg. Med. Chem*. **2007**, *15*, 6758–6762. (d) Aoki, S.; Watanabe, Y.; Sanagawa, M.; Setiawan, A.; Kotoku, N.; Kobayashi, M. *J. Am. Chem. Soc*. **2006**, *128*, 3148–3149.

(3) For a recent review of synthetic strategies towards cortistatin A, please see: Narayan, A. R. H.; Simmons, E. M.; Sarpong. R. *Eur. J. Org. Chem*. **2010**, 3553–3567.

(4) Shenvi, R. A.; Guerrero, C. A.; Shi, J.; Li, C.-C.; Baran, P. S. *J. Am. Chem. Soc*. **2008**, *130*, 7241–7243.

(5) Lee, H. M.; Nieto-Oberhuber, C.; Shair, M. D. *J. Am. Chem. Soc*. **2008**, *130*, 16864–16866.

(6) Kürti, L.; Czakó, B.; Corey, E. J. *Org. Lett*. **2008**, *10*, 5247–5250.

(7) Magnus, P.; Littich, R. *Org. Lett*. **2009**, *11*, 3938–3941.

(8) (a) Simmons, E. M.; Hardin, A. R.; Guo, X.; Sarpong, R. *Angew. Chem. Int. Ed*. **2008**, *47*, 6650–6653. (b) Simmons, E. M.; Hardin-Narayan, A. R.; Guo, X.; Sarpong, R. *Tetrahedron* **2010**, *66*, 4696–4700.

(9) Frie, J. L.; Jeffrey, C. S.; Sorensen, E. J. *Org. Lett*. **2009**, *11*, 5394–5397.

(10) Dai, M.; Danishefsky, S. J. *Heterocycles* **2009**, *77*, 157–161.

(11) Nicolaou, K. C.; Sun, Y.-P.; Peng, X.-S.; Polet, D.; Chen, D. Y.-K. *Angew. Chem. Int. Ed.* **2008**, *47*, 7310–7313.

(12) Yamashita, S.; Iso, K.; Hirama, M. *Org. Lett.* **2008**, *10*, 3413–3415

(13) (a) Dai, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**, *49*, 6610–6612. (b) Dai, M.; Wang, Z.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**, *49*, 6613–6616.

(14) Craft, D. T.; Gung, B. W. *Tetrahedron Lett.* **2008**, *49*, 5931–5934

(15) Baumgartner, C.; Ma, S.; Liu, Q.; Stoltz, B. M. *Org. Biomol. Chem.* **2010**, *8*, 2915–2917.

(16) For select, recent examples, please see: (a) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5482–5487. (b) Tan, G. H.; Zhu, X.; Ganesan, A. *Org. Lett.* **2003**, *5*, 1801–1803. (c) Lopez-Alvarado, P.; Caballero, E.; Avendano, C.; Menendez, J. C. *Org. Lett.* **2006**, *8*, 4303–4306. (d) Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143–11144.

(17) Please refer to Chapter 3 for more detailed discussion on the synthesis of 3,3-disubstituted oxindoles.

(18) For reviews on the synthesis of pyrrolidinylspirooxindole, please see (a) Galliford, C.V.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8748–8758. (b) Marti, C.; Carriera, E. M. *Eur. J. Org. Chem.* **2003**, 2209–2219.

(19) (a) Wenkert, E.: Udelhofen, J. H.; Bhattacharayya, N. K. *J. Am. Chem. Soc.* **1959**, *81*, 3763–3768. (b) Seaton, J. C.; Nair, M. D.; Edwards, O. E.; Marion, L. *Can. J. Chem.* **1960**, *38*, 1035–1042. (c) Bascop, S. I.; Sapi, J.; Laronze, J. Y.; Levy, J. *Heterocycles* **1994**, *38*, 725–732. (d) Nussbaum, F. v.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2000**, *39*, 2175–2178.

(20) (a) Yu, P.; Cook, J. M. *Tetrahedron Lett.* **1997**, *38*, 8799–8802. (b) Pellegrini, C.; Strässlet, C.; Weber, M.; Borschberg, H.-J. *Tetrahedron: Asymmetry* **1994**, *5*, 1979–1992. (c) Edmonson, S. D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1138–1140. (d) Edmondson, S. D.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 2147–2155.

(21) (a) Lerchner, A.; Carreira, E. M. *J. Am. Chem. Soc.* **2002**, *124*, 14826–14827. (b) Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505–11515.

(22) Sehahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666–5667.

(23) Ma, S.; Han, X.; Krishnan, S.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 8037–8041.

(24) For isolation of communesin B, please see: Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsamura, E.; Imachi, M.; Ito, T.; Hasegawa, T. *Tetrahedron Lett.* **1993**, *34*, 2355–2358.

(25) (a) Siengalewicz, P.; Gaich, T., Mulzer, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 8170–8176. (b) May, J. A; Zeidan, R. K.; Stoltz, B. M. *Tetrahedron Lett.* **2003**, *44*, 1203–1205. (c) Crawley, S. L.; Funk, R. L. *Org. Lett.* **2003**, *5*, 3169–3171.

CHAPTER 2

Efforts toward the Rapid Construction of the Cortistatin A Carbocylic Core[1]

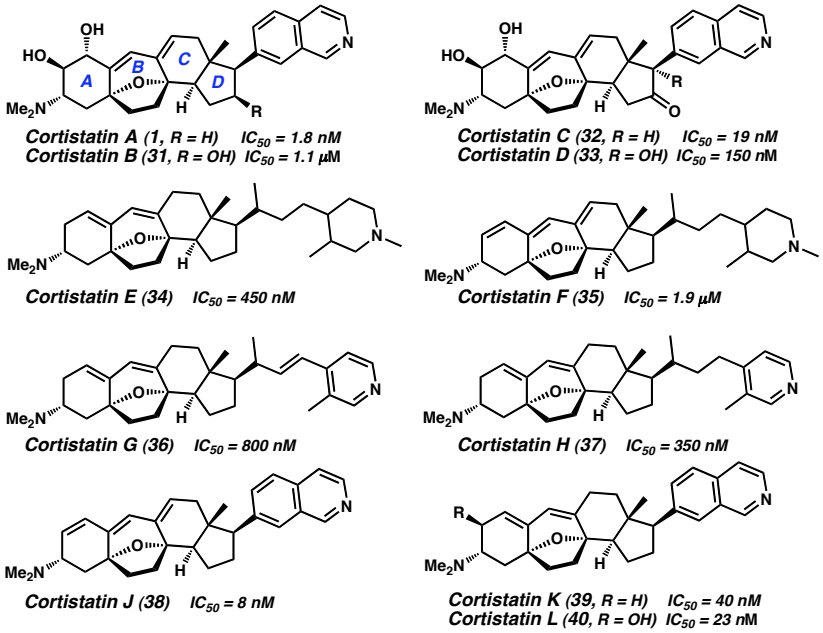
2.1 INTRODUCTION

The discovery of novel anti-angiogenic agents has become an active area of drug therapy research given their therapeutic applications in the treatment of cancer, autoimmune diseases, macular degeneration, and other diseases.[1] A series of unique *abeo*-9(10,19)-androstane-type steroidal alkaloids were isolated from the marine sponge *Corticium simplex* in 2006 and 2007,[2] some of which possessed significant anti-angiogenic activity (Figure 2.1). The most potent member, cortistatin A (**1**), demonstrated a highly selective growth inhibition of human umbilical vein endothelial cells (IC_{50} = 1.88 nM, selectivity index > 3000) with relatively no general toxicity toward other cell types. The biological activity, as well as the intriguing molecular structure of **1**

[1] This work was performed in collaboration with Drs. Corinne Baumgartner and Qi (Charles) Liu.

has led to several total syntheses[3] and efforts toward the construction of the cortistatin A core.[4]

Figure 2.1 Cortistatin family of natural products

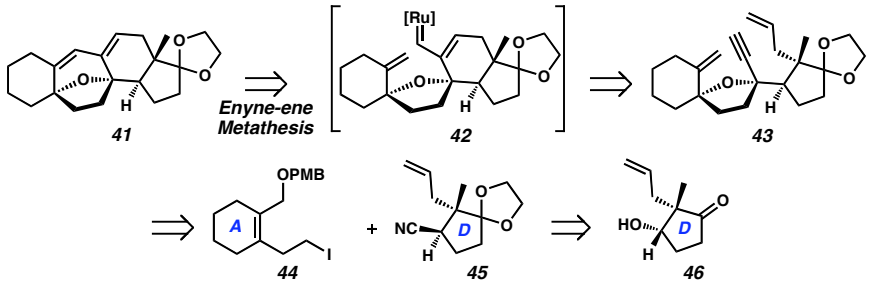


2.2 SYNTHETIC APPROACH OF CORTISTATIN A CORE

2.2.1 Retrosynthetic Analysis

In our approach to the synthesis of cortistatin A (**1**), we envisioned that the [6,7,6,5] core could arise via an intramolecular tandem enyne-ene metathesis (Scheme 2.1).[5] To examine the feasibility of such a step, we focused on the synthesis of alkynyl diene **43** as a model precursor for the key enyne-ene metathesis to give pentacyclic model diene **41**. Alkynyl diene **43** could arise from alkyl iodide **44** and nitrile **45**. Nitrile **45**, in turn, could be derived from ketone **46**, which has been synthesized in enantiopure form,[6] thus providing a direct route for an asymmetric synthesis of the cortistatin A carbocyclic core.

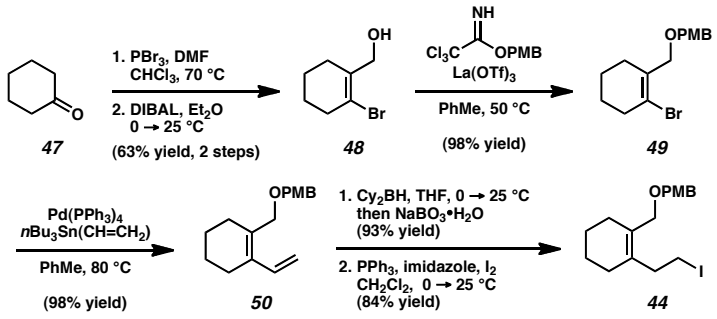
Scheme 2.1 Retrosynthetic analysis of cortistatin A core



2.2.2 Synthesis of A-ring Portion of Cortistatin A Core

Our synthesis of the A-ring portion of cortistatin A commenced from cyclohexanone **47,** which was converted to the allylic alcohol **48** through treatment with PBr_3 and DMF followed by a DIBAL reduction of the resulting aldehyde (Scheme 2.2).[7] PMB protection of the allylic alcohol yielded ether **49**, which was coupled to vinyltributylstannane to afford diene **50**. Hydroboration of diene **50** and subsequent exposure of the resultant primary alcohol to triphenylphosphine and iodine produced iodide **44**.

Scheme 2.2 Synthesis of A-ring

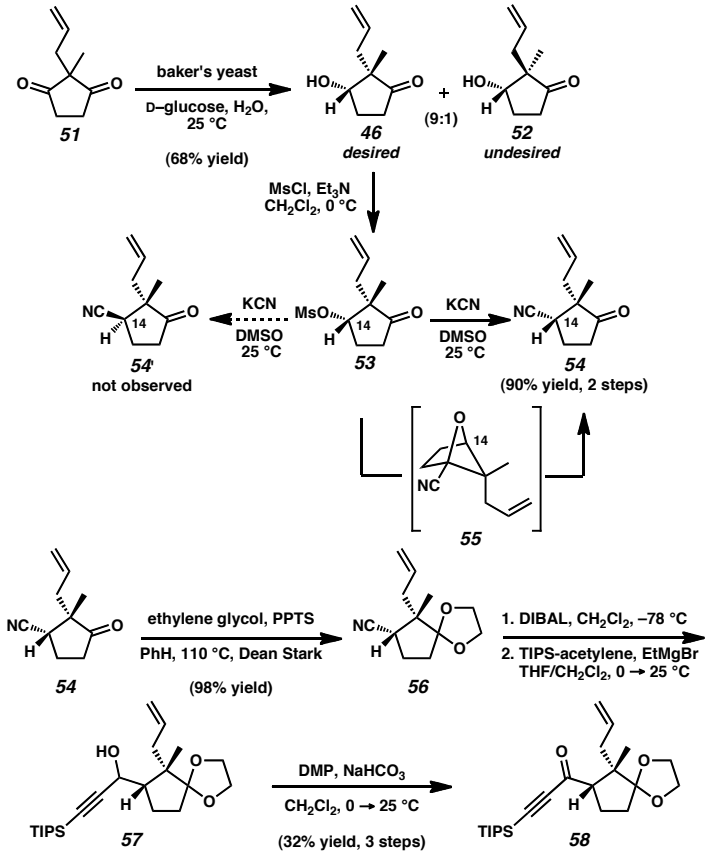


2.2.3 Synthesis of D-ring Portion of Cortistatin A Core

With the A-ring precursor **44** in hand, we set out to make the D-ring portion in an asymmetric manner (Scheme 2.3). Treatment of dione **51** with baker's yeast provided a 9:1 mixture of chromatographically separable alcohols **46** and **52**.[5] We envisioned that subjecting the major product alcohol **46**[8] to S_N2 displacement conditions would install the final carbon of the D-ring moiety and set the desired absolute and relative stereochemistry. However, mesylation of alcohol **46** followed by treatment with potassium cyanide in DMSO surprisingly afforded nitrile **54**, a product with net retention of stereochemistry at C(14). This unexpected result was confirmed via NOESY correlations of alcohol **46**, alcohol **52**, and nitrile **54** and by x-ray diffractometry of crystalline compounds derived from alcohol **46** and nitrile **54**.[9,10] A possible explanation for this unexpected outcome is that the mechanism proceeds via oxetane **55**, which is postulated to arise from reversible cyanohydrin formation of mesylate **53**.

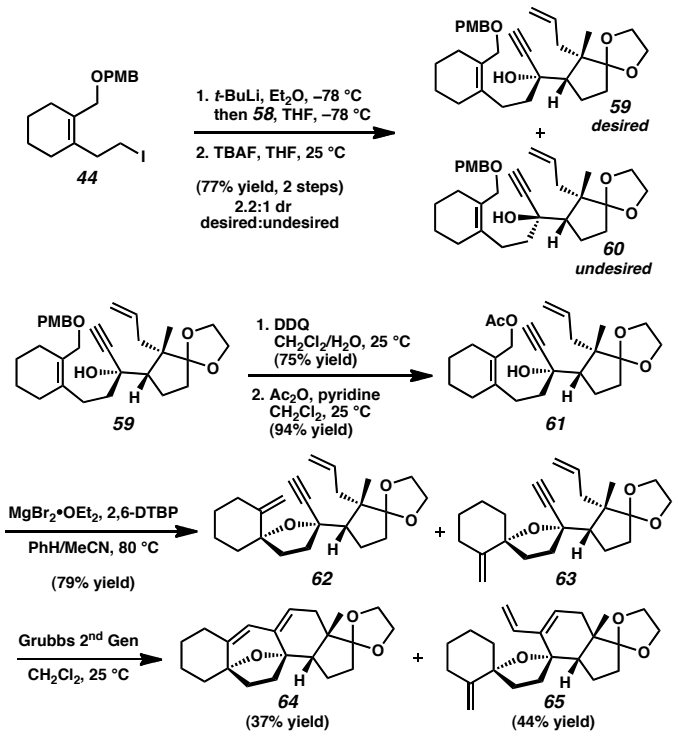
Despite this unusual result, we wished to continue the synthesis of the model system due to our interest in testing the enyne-ene metathesis. To advance ketone **54**, we protected the ketone as the acetal to give **56**. Nitrile **56** was then reduced to the aldehyde and after treatment with TIPS-acetylene and EtMgBr, afforded alcohol **57** as a mixture of diastereomers. Alcohol **57** was oxidized with Dess-Martin periodinane (DMP) to give ketone **58**.

Scheme 2.3 Asymmetric synthesis of D-ring piece



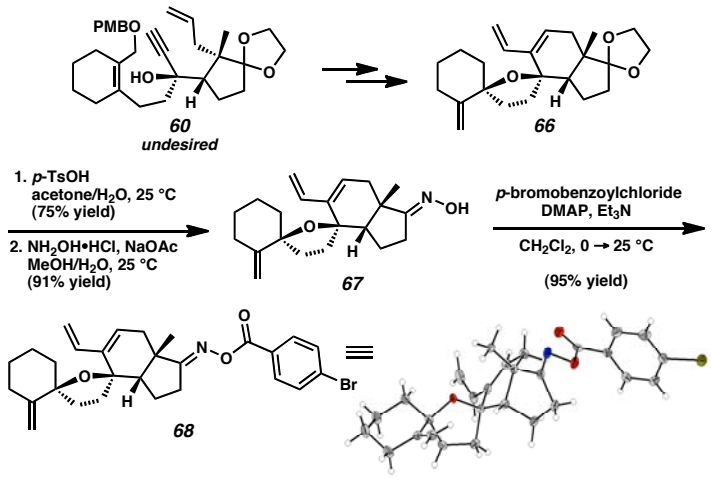
With our A-ring (**44**) and epi-D-ring (**58**) precusors in hand, we then coupled the two together by treating vinyl iodide **44** with *t*-BuLi and adding the resultant lithio species to ketone **58** (Scheme 2.4). Subsequent TIPS cleavage with TBAF gave a 2.2:1 mixture of the desired alcohol **59** (Felkin-Anh product) and the undesired alcohol **60**. After separation by column chromatography, PMB ether **59** was converted to allylic acetate **61**. Treatment of **61** with $MgBr_2$ gave the substituted tetrahydrofurans **62** and **63**, which were inseparable by column chromatography. Nonetheless, subjection of the mixture of **62** and **63** to Grubbs second-generation catalyst produced the desired enyne-ene metathesis product **64**, which contains the desired [6,7,6,5]-core, in 37% yield and the enyne metathesis product **65** in 44% yield.

Scheme 2.4 Enyne-ene metathesis



We planned to establish the absolute and relative stereochemistry of our metathesis products via derivatization to give compounds suitable for x-ray crystallography analysis. Attempts to convert the enyne-ene product **64** or the enyne product **65** to crystalline compounds were not successful. However, we were able to derivatize the undesired alcohol **60** by proceeding through a similar route as outlined in Scheme 2.4 for **59** to ultimately afford enyne product **66**. Enyne product **66** was then transformed to oxime **67**, which was acylated with *p*-bromobenzoylchloride to furnish **68**, a compound that was amenable to x-ray diffraction (Scheme 2.5). As a result, we were able to assign the relative and absolute stereochemistry of enyne product **66** and thereby, the relative and absolute stereochemistry of enyne-ene product **64** as well.[11]

Scheme 2.5 Determination of relative and absolute stereochemistry



2.3 CONCLUSION

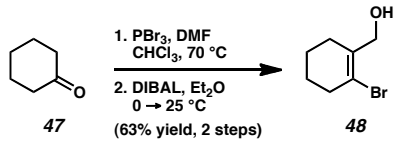
Herein, we have established the enyne-ene metathesis as a rapid method for the construction of the carbocylic core of cortistatin A. We have also reported an unusual reaction in which an attempted S_N2 displacement of a secondary mesylate on our five-membered D-ring piece gave a product with retention of stereochemistry. Further studies directed toward the synthesis of cortistatin A and related analogs are underway and will be reported in due course.

2.4 EXPERIMENTAL SECTION

2.4.1 Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All other commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. ICN Silica gel (particle size 0.032-0.063 mm) was used for flash column chromatography. Analytical chiral HPLC was performed on a Chiralcel OD-H column (250 mm x 4.6 mm, 5 mm particle size, 0.8 mL/min flow rate) obtained from Daicel Chemical Industries, Ltd. ^{1}H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) or a Varian Inova 500 (at 500 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz) or a Varian Inova 500 (at 125 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm using either a 100 mm or 50 mm path-length cell. High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility.

2.4.2 Preparative Procedures and Spectroscopic Data



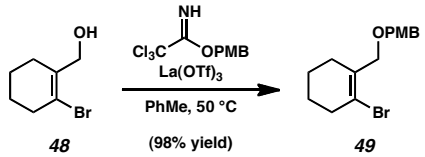
47 *48*

(2-Bromocyclohex-1-enyl)methanol (**48**).[7]

The allylic alcohol was synthesized according to a similar procedure.[12] To a solution of DMF (7.4 mL, 95.0 mmol, 3.0 equiv) in $CHCl_3$ (25 mL) was added PBr_3 (8.1 mL, 86.0 mmol, 2.7 equiv) dropwise at 0 °C. The mixture was stirred at 70 °C for 30 min, then cyclohexanone (**47**) (3.3 mL, 32.0 mmol, 1.0 equiv) was added dropwise over 30 min. After the resulting dark red solution was stirred at 70 °C for 1.5 h, it was poured into 4 M aq NaOAc (40 mL). Solid NaOH was added to the mixture to adjust the pH to 7.0 and the aqueous layer was extracted with hexanes. The combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated and the crude product was used in the next step without further purification. R_f = 0.80 (4:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.02 (s, 1H), 2.77-2.72 (m, 2H), 2.30-2.25 (m, 2H), 1.80-1.65 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 143.9, 128.6, 39.1, 25.2, 24.5, 21.3; IR (Neat Film NaCl) 2937, 1681, 1619, 1449, 1340, 1208, 972 cm^{-1}.

The crude product was dissolved in Et_2O (60 mL) and the solution was cooled to 0 °C. DIBAL (5.7 mL, 32.0 mmol, 1.0 equiv) was added slowly, and the mixture was stirred at 25 °C for 12 h. The reaction was quenched with H_2O (1.5 mL), 3 M aq NaOH (1.5 mL) and H_2O (3.0 mL), and stirred vigorously for 20 min. Na_2SO_4 (ca. 20 g) was added, and the mixture was stirred for an additional 1 h. The white solid was removed by filtration and the filtrate was concentrated to afford a yellow oil, which was purified by flash chromatography (4:1 hexanes/EtOAc) to give **48** as a clear oil (3.85 g, 63% yield

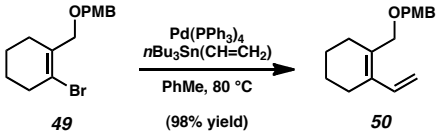
over 2 steps). R_f = 0.30 (4:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22 (s, 2H), 2.52-2.50 (m, 2H), 2.28-2.24 (m, 2H), 1.69 (quintet, *J* = 3.0 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 121.0, 66.1, 36.9, 29.0, 24.9, 22.5.



48 *49*

1-(((2-Bromocyclohex-1-enyl)methoxy)methyl)-4-methoxybenzene (**49**).

To a solution of **48** (1.01 g, 5.29 mmol, 1.0 equiv) in toluene (21 mL) was added 4-methoxybenzyl 2,2,2-trichloroacetimidate[13] (2.24 g, 7.93 mmol, 1.5 equiv) and $La(OTf)_3$ (164 mg, 0.28 mmol, 0.053 equiv). The mixture was stirred at 50 °C for 12 h. The reaction mixture was concentrated, and the crude residue was purified by flash chromatography (hexanes → 99:1 → 98:2 hexanes/EtOAc) to give **49** as a colorless oil (1.60 g, 98% yield). R_f = 0.40 (99:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2H), 6.90-6.84 (m, 2H), 4.41 (s, 2H), 4.15 (s, 2H), 3.80 (s, 3H), 2.52-2.49 (m, 2H), 2.24-2.20 (m, 2H), 1.71-1.64 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 133.5, 130.8, 129.6, 122.3, 114.0, 73.2, 72.0, 55.5, 37.1, 29.2, 25.0, 22.5; IR (Neat Film NaCl) 2934, 2858, 2836, 1613, 1586, 1513, 1464, 1332, 1302, 1246, 1173, 1112, 1077, 1037, 972, 820 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{19}BrO_2$ $[M]^+$: 310.0568, found 310.0563.

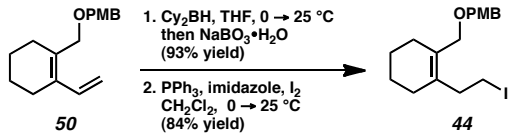


49 *50*

1-Methoxy-4-(((2-vinylcyclohex-1-enyl)methoxy)methyl)benzene (**50**).

A Schlenk flask was charged with $Pd(PPh_3)_4$ (281 mg, 0.24 mmol, 0.1 equiv), evacuated and refilled with Ar. **49** (755 mg, 2.44 mmol, 1.0 equiv) in toluene (10 mL)

and tributyl(vinyl)tin (1.0 mL, 3.41 mmol, 1.4 equiv) were added. The mixture was stirred at 80 °C for 2 d. The reaction mixture was concentrated, and the crude residue was purified by flash chromatography (hexanes → 99:1 → 98:2 hexanes/EtOAc) to give **50** as a colorless oil (618 mg, 98% yield). R_f = 0.50 (99:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H), 6.90-6.88 (m, 2H), 6.83 (dd, *J* = 17.1, 10.8 Hz, 1H), 5.20 (dd, *J* = 17.1, 1.2 Hz, 1H), 5.01 (d, *J* = 10.8 Hz, 1H), 4.42 (s, 2H), 4.09 (s, 2H), 3.81 (s, 3H), 2.23-2.21 (m, 4H), 1.68-1.62 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 134.4, 133.9, 133.1, 130.9, 129.6, 114.0, 112.3, 71.9, 69.1, 55.5, 29.3, 25.3, 22.8, 22.7; IR (Neat Film NaCl) 3088, 2999, 2930, 2857, 2835, 1698, 1637, 1613, 1586, 1514, 1464, 1357, 1302, 1248, 1173, 1136, 1064, 1037, 986, 896, 820 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{22}O_2$ $[M]^+$: 258.1620, found 258.1623.



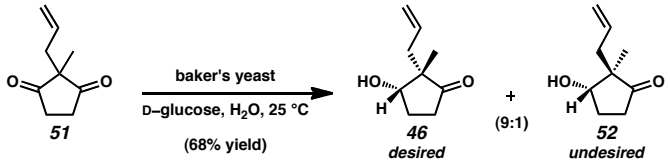
1-(((2-(2-Iodoethyl)cyclohex-1-enyl)methoxy)methyl)-4-methoxybenzene (**44**).

A round bottom flask was cooled to 0 °C and charged with BH_3•THF (3.6 mL, 1 M in THF, 3.54 mmol, 1.5 equiv). Cyclohexene (0.73 mL, 7.20 mmol, 3.05 equiv) was added and the mixture was allowed to warm to 25 °C over 30 min. Then **50** (610 mg, 2.36 mmol, 1.0 equiv) in THF (5 mL) was added at 0 °C, and the mixture was allowed to warm to 25 °C over 5 h. The reaction was quenched with $NaBO_3$•H_2O (4.48 g, 44.9 mmol, 19 equiv) in H_2O (20 mL), and the mixture was stirred at 25 °C for 12 h. The aqueous layer was extracted with EtOAc, and the combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (9:1 → 7:1 → 5:1 hexanes/EtOAc) to give 2-(2-((4-

methoxybenzyloxy)methyl)cyclohex-1-enyl)ethanol as a colorless oil (608 mg, 93% yield). R_f = 0.20 (9:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.26 (m, 2H), 6.88-6.86 (m, 2H), 4.43 (s, 2H), 3.88 (s, 2H), 3.79 (s, 3H), 3.61 (t, *J* = 6.0 Hz, 2H), 2.66 (br s, 1H), 2.31 (t, *J* = 6.0 Hz, 2H), 2.10 (br s, 2H), 2.01 (br s, 2H), 1.61-1.58 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 133.9, 130.9, 130.3, 129.9, 114.0, 72.6, 70.2, 60.5, 55.5, 36.8, 29.8, 29.5, 23.2, 23.1; IR (Neat Film NaCl) 3401, 2998, 2929, 2858, 2835, 1664, 1613, 1586, 1514, 1464, 1442, 1365, 1352, 1302, 1249, 1174, 1138, 1110, 1038, 821 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{25}O_3$ $[M+H]^+$: 277.1804, found 277.1811.

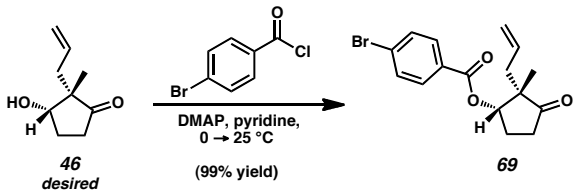
To a solution of PPh_3 (527 mg, 2.01 mmol, 1.5 equiv) and imidazole (273 mg, 4.02 mmol, 3.0 equiv) in CH_2Cl_2 (8 mL) was added I_2 (544 mg, 2.14 mmol, 1.6 equiv) at 0 °C. The mixture was stirred at 0 °C for 30 min. Then 2-(2-((4-methoxybenzyloxy)methyl)cyclohex-1-enyl)ethanol (370 mg, 1.34 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added, and the mixture was allowed to warm to 25 °C over 2 h and stirred at 25 °C for 16 h. After addition of 5% aq $Na_2S_2O_3$, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the crude residue was purified by flash chromatography (99:1 → 95:5 → 9:1 hexanes/EtOAc) to give **44** as a pale yellow oil (436 mg, 84% yield). R_f = 0.50 (99:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.26 (m, 2H), 6.89-6.87 (m, 2H), 4.41 (s, 2H), 3.89 (s, 2H), 3.80 (s, 3H), 3.12 (t, *J* = 8.5 Hz, 2H), 2.60 (t, *J* = 8.5 Hz, 2H), 2.07 (br s, 2H), 2.01 (br s, 2H), 1.60-1.58 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 135.1, 131.0, 130.7, 129.6, 114.0, 72.2, 69.8, 55.5, 38.2, 29.5, 28.5, 23.0, 22.9, 4.6; IR (Neat Film NaCl) 2998, 2927, 2855,

2833, 1612, 1586, 1513, 1463, 1354, 1302, 1248, 1172, 1134, 1068, 1037, 820 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{23}IO_2$ $[M]^+$: 386.0743, found 386.0733.



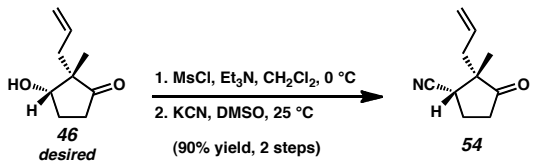
(2*S*, 3*S*)-2-allyl-3-hydroxy-2-methylcyclopentanone (**46**).[6]

To a solution of D-glucose (30.0 g) in H_2O (200 mL) was added dry active baker's yeast (20.0 g) at 35 °C. The suspension was stirred open to the air at 33 °C for 45 min. Dione **51** (1.71 g, 11.2 mmol, 1.0 equiv) was added dropwise, and the mixture was vigorously stirred at 25 °C for 5 d. The mixture was filtered over Celite, and the Celite was washed with H_2O and CH_2Cl_2. The filtrate was diluted with H_2O and extracted with CH_2Cl_2 in a continuous extractor for 48 h. The organic phase was concentrated and the crude residue was purified by flash chromatography (9:1 → 7:1 → 3:1 hexanes/EtOAc) to afford separated diastereoisomers **46** and **52** (1.16 g, 68% yield, 9 : 1 dr). **46** was isolated as a colorless oil. R_f = 0.27 (7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, 1H), 5.17-5.10 (m, 2H), 4.13-4.10 (m, 1H), 2.51-2.43 (m, 1H), 2.37-2.16 (m, 4H), 1.97 (dddd, *J* = 13.0, 9.5, 9.5, 3.5 Hz, 1H), 1.90 (s, 1H), 0.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.9, 134.6, 118.4, 77.7, 53.4, 35.7, 34.3, 28.0 20.0; HRMS (EI+) *m/z* calc'd for $C_9H_{14}O_2$ $[M]^+$: 154.0994, found 154.0993; $[\alpha]_D^{24.6}$ +98.4° (*c* 1.01, $CHCl_3$, >99% ee). Analytical chiral HPLC assay with the benzoate of **46**: Chiralcel OD-H column, 1:9 2-propanol:hexanes, 0.8 mL/min, λ = 254 nm, isocratic method. **46-benzoate**: t_{fast} = 13.93 min (**(+)-46-benzoate**), t_{slow} = 15.51 min (**(–)-46-benzoate**). Enantioenriched **46-benzoate**: t_{fast} = 13.93 min (**(+)-46-benzoate**, >99%) (the trace corresponding to **(–)-46-benzoate** was below the threshold of detection).



(1*S*, 2*S*)-2-allyl-2-methyl-3-oxocyclopentyl 4-bromobenzoate (**69**).

To a suspension of alcohol **46** (150 mg, 0.97 mmol, 1 equiv) and DMAP (11.9 mg, 0.097 mmol, 0.1 equiv) in pyridine (9 mL) cooled to 0 °C, *p*-bromobenzoylchloride (320 mg, 1.46 mmol, 1.5 equiv) was added. The reaction was allowed to gradually warm to 25 °C and quenched with water after 18 hours. The reaction mixture was extracted with CH_2Cl_2, the combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the crude residue was purified by flash chromatography (hexanes → 90:10 hexanes/EtOAc) to afford **69** (335 mg, 99% yield) as a white solid. MP: 55-57 °C; R_f = 0.52 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 9.0 Hz, 2H), 5.72 (dddd, J = 17.0, 10.5, 7.5, 7.5 Hz, 1H), 5.37 (m, 1H), 5.04-4.99 (m, 2H), 2.49-2.33 (comp. m, 5H), 2.20 (m, 1H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.0, 165.0, 133.1, 132.1, 131.2, 128.9, 128.6, 118.8, 79.9, 52.4, 35.9, 34.1, 25.9, 20.1; IR (Neat Film NaCl) 3076, 2976, 1742, 1721, 1590, 1484, 1398, 1271, 1113, 1102, 1012, 756 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{17}O_3Br$ [M^+]: 336.0361, found 336.0350; $[\alpha]_D^{25.0}$ +162.2° (*c* 0.61, $CHCl_3$).

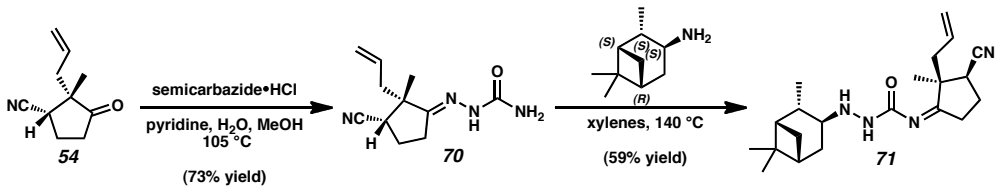


(1*S*, 2*S*)-2-allyl-2-methyl-3-oxocyclopentanecarbonitrile (**54**).

To a solution of **46** (805 mg, 5.22 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) was added MsCl (0.8 mL, 10.4 mmol, 2.0 equiv) and Et_3N (1.5 mL, 10.4 mmol, 2.0 equiv) at 0 °C.

The mixture was stirred at 0 °C for 1 h. After addition of H_2O, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the crude mesylate was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (dddd, J = 11.4, 8.7, 7.2, 7.2 Hz, 1H), 5.16-5.10 (m, 2H), 5.02 (m, 1H), 3.05 (s, 3H), 2.45-2.28 (m, 6H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.0, 132.5, 119.2, 85.9, 52.4, 38.8, 35.4, 33.7, 26.4, 19.7; HRMS (FAB+) *m/z* calc'd for $C_{10}H_{17}SO_4$ $[M]^+$: 233.0848, found 233.0844.

The resulting yellow oil was dissolved in DMSO (16 mL), KCN (680 mg, 10.4 mmol, 2.0 equiv) was added, and the mixture was stirred at 25 °C for 5 d. After addition of brine, the aqueous layer was extracted with EtOAc. The combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (8:1 → 6:1 hexanes/EtOAc) to give **54** (765 mg, 90% yield) as a yellow oil. R_f = 0.33 (7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (dddd, J = 17.5, 10.0, 7.5, 7.5 Hz, 1H), 5.21-5.15 (m, 2H), 2.94-2.90 (m, 1H), 2.52-2.21 (m, 6H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.3, 131.8, 120.4, 119.4, 51.2, 39.1, 38.4, 35.5, 23.5, 21.2; IR (Neat Film NaCl) 3079, 2978, 2917, 2848, 2240, 1743, 1640, 1457, 1406, 1378, 1298, 1268, 1196, 1148, 1111, 1049, 994, 923 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{10}H_{13}NO$ $[M]^+$: 163.0997, found 163.0997; $[\alpha]_D^{24.3}$ +46.8° (*c* 0.80, $CHCl_3$).

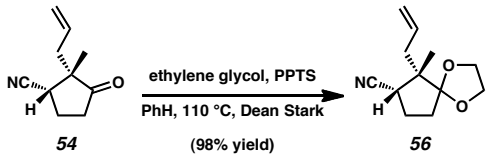


(Isopinocampheylamine)-semicarbazone 71.

Semicarbazide•HCl (51.2 mg, 0.46 mmol, 1.5 equiv) was added to a solution of ketone **54** (50 mg, 0.31 mmol, 1 equiv) in pyridine (2.7 mL), water (1.3 mL), and MeOH (0.4 mL). The reaction mixture was heated to 105 °C for 1 h and then cooled to 25 °C. After addition of water, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (CH_2Cl_2 → 9:1 CH_2Cl_2/MeOH) to afford the semicarbazone **70** (49.7 mg, 73% yield) as a white solid. R_f = 0.53 (10:1 CH_2Cl_2/MeOH); ^{1}H NMR (500 MHz, MeOD) δ 5.87 (dddd, *J* = 17.5, 10.0, 7.5, 7.5 Hz, 1H), 5.19-5.12 (m, 2H), 3.00 (m, 1H), 2.57-2.36 (m, 4H), 2.31 (m, 1H), 2.17 (m, 1H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 158.8, 133.2, 119.5, 117.8, 40.7, 39.1, 25.4, 24.9, 22.1; IR (Neat Film NaCl) 3215, 1691, 1490 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{11}H_{17}N_4O$ $[M+H]^+$: 221.1402, found 221.1408; $[\alpha]_D^{25.0}$ +60.5° (*c* 0.615, MeOH).

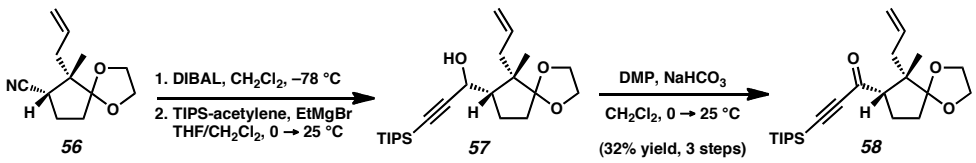
To a solution of the semicarbazone **70** (30 mg, 0.136 mmol, 1 equiv) in xylenes (1.3 mL) was added (1*S*, 2*S*, 3*S*, 5*R*)-(+)-isopinocampheylamine (27.5 uL, 0.163 mmol, 1.2 equiv). The reaction mixture was refluxed for 18 hours. Upon cooling, the reaction mixture was concentrated and purified by column chromatography (100:1 → 1:100 hexanes/EtOAc) to give **71** as a light brown solid (28.5 mg, 59% yield). MP: 230-232 °C from $CDCl_3$; R_f = 0.67 (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 5.92 (d, *J* = 9.0 Hz, 1H), 5.80 (dddd, *J* = 17.5, 15.0, 7.5, 7.5 Hz, 1H), 5.21-5.14 (m, 2H), 4.17 (m, 1H), 2.74 (dd, *J* = 7.0, 7.0 Hz, 1H), 2.63-2.52 (m, 2H), 2.45-2.40 (m, 4H), 2.30-2.17 (m, 2H), 1.97 (m, 1H), 1.86-1.83 (m, 2H), 1.60 (ddd, *J* = 13.5, 6.0, 2.5 Hz, 1H), 1.24 (s, 3H), 1.23 (s, 3H), 1.13 (d, *J* = 7.5 Hz, 3H), 1.05 (s, 3H), 0.92 (d, *J* = 10 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 156.1, 132.8, 119.5, 119.5, 48.4, 48.4, 48.0, 46.7, 41.8, 41.0,

40.0, 38.5, 37.9, 35.4, 28.2, 25.9, 25.4, 23.5, 23.5, 20.9; IR (Neat Film NaCl) 3414, 3192, 3080, 2911, 1669, 1659, 1534 cm $^{-1}$; HRMS (EI+) *m/z* calc'd for $C_{21}H_{32}ON_4$ [M^+]: 356.2576, found 356.2584; $[\alpha]_D^{25.0}$ +96.3 (c 1.09, $CHCl_3$).



(6*S*,7*S*)-6-allyl-6-methyl-1,4-dioxaspiro[4.4]nonane-7-carbonitrile (**56**).

To a solution of **54** (800 mg, 4.90 mmol, 1.0 equiv) in benzene (49 mL) was added PPTS (308 mg, 1.23 mmol, 0.25 equiv) and ethylene glycol (1.9 mL, 34.3 mmol, 7.0 equiv). The flask was fitted with a Dean-Stark trap, and the mixture was refluxed at 110 °C for 2 d. The volatiles were removed, and the crude residue was purified by flash chromatography (95:5 → 9:1 hexanes/EtOAc) to give **56** (997 mg, 98% yield) as a pale yellow oil. R_f = 0.42 (7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 (dddd, *J* = 17.5, 10.0, 7.5, 7.5 Hz, 1H), 5.19-5.14 (m, 1H), 5.11-5.08 (m, 1H), 4.00-3.94 (m, 2H), 3.93-3.88 (m, 2H), 2.75-2.72 (m, 1H), 2.47 (dd, *J* = 14.0, 7.5 Hz, 1H), 2.28 (ddt, *J* = 14.0, 7.0, 1.5 Hz, 1H), 2.17-2.08 (m, 1H), 2.04-1.96 (m, 2H), 1.93-1.86 (m, 1H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.5, 121.5, 118.6, 118.0, 65.7, 65.1, 49.1, 37.8, 37.3, 32.7, 23.8, 19.9; IR (Neat Film NaCl) 3077, 2979, 2916, 2888, 2849, 2237, 1639, 1462, 1439, 1380, 1310, 1290, 1202, 1173, 1148, 1132, 1043, 1005, 950, 928 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{12}H_{18}NO_2$ [M+H]$^+$: 208.1338, found 208.1331; $[\alpha]_D^{26.4}$ +78.0° (*c* 0.85, $CHCl_3$).



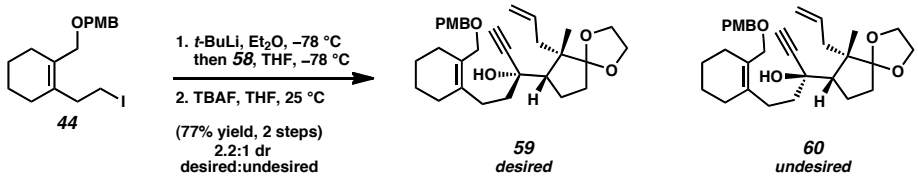
Compound 58.

To a solution of **56** (500 mg, 2.41 mmol, 1.0 equiv) in CH_2Cl_2 (23 mL) was added DIBAL (3.6 mL, 1 M in CH_2Cl_2, 3.62 mmol, 1.5 equiv) at –78 °C. The mixture was stirred at –78 °C for 1 h. Rochelle's salt (7.5 mL) was added and the mixture was stirred at 25 °C for 40 min. The phases were separated, and the aqueous layer was extracted with EtOAc. The combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the crude product was used in the next step without further purification.

The resulting colorless oil was dissolved in CH_2Cl_2 (12 mL) and added to a solution of TIPS-acetylene (3.2 mL, 14.5 mmol, 6.0 equiv) and ethylmagnesium bromide (3.2 mL, 3.0 M in Et_2O, 9.64 mmol, 4.0 equiv) in THF (29 mL) at 0 °C. The mixture was allowed to warm to 25 °C slowly and stirred at 25 °C for 24 h. After addition of saturated aq NH_4Cl, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (98:2 → 9:1 hexanes/EtOAc) to give **57** as a mixture of two diastereomers.

To a solution of **57** in CH_2Cl_2 (10 mL), DMP (601 mg, 1.43 mmol, 1.0 equiv) and $NaHCO_3$ (132 mg, 1.57 mmol, 1.1 equiv) were added at 0 °C. The mixture was allowed to warm to 25 °C over 2 h and stirred at 25 °C for 10 h. After addition of saturated aq $NaHCO_3$, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (98:2 hexanes/EtOAc) to give **58** as a colorless oil (298 mg, 32% yield over 3 steps). R_f = 0.60 (9:1 hexanes/EtOAc); ^{1}H NMR

(500 MHz, $CDCl_3$) δ 5.92-5.83 (m, 1H), 4.99-4.95 (m, 2H), 3.95-3.88 (m, 4H), 3.00 (t, *J* = 9.0 Hz, 1H), 2.38-2.26 (m, 2H), 2.11 (dd, *J* = 14.5, 8.0 Hz, 1H), 1.96-1.89 (m, 1H), 1.79-1.70 (m, 2H), 1.22 (s, 3H), 1.17-1.05 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.0, 135.7, 119.7, 117.6, 105.9, 96.7, 66.0, 64.5, 60.7, 50.6, 37.8, 32.0, 20.4, 19.6, 18.8, 11.4; IR (Neat Film NaCl) 3075, 2945, 2867, 2146, 1665, 1463, 1384, 1346, 1307, 1201, 1126, 1074, 1044, 998, 950, 917, 883 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{23}H_{38}O_3Si$ $[M]^+$: 390.2590, found 390.2585; $[\alpha]_D^{19.1}$ +44.5° (*c* 1.03, $CHCl_3$).



Compounds 59 and 60.

To a solution of **44** (159 mg, 0.41 mmol, 1.5 equiv) in Et_2O (4.2 mL), *t*-BuLi (0.63 mL 0.88 mmol, 3.2 equiv) was added dropwise at –78 °C. The mixture was stirred at –78 °C for 30 min. A solution of **58** (107 mg, 0.27 mmol, 1.0 equiv) in THF (2.7 mL) was added, and the mixture was stirred at –78 °C for 1 h. After addition of saturated aq NH_4Cl, the aqueous layer was extracted with Et_2O. The combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (9:1 hexanes/EtOAc) to give the tertiary alcohol as a mixture of two diastereomers.

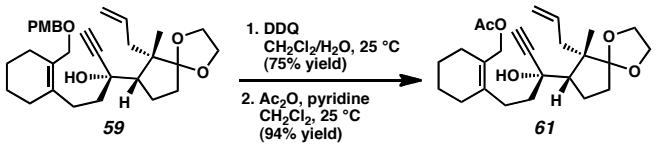
To a solution of this alcohol (147 mg, 0.23 mmol, 1.0 equiv) in THF (2.3 mL), TBAF (0.27 mL, 1 M in THF, 1.2 equiv) was added at 25 °C. The mixture was stirred at 25 °C for 1 h. After addition of H_2O, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. The

filtrate was concentrated, and the residue was purified by flash chromatography (8:1 → 1:1 hexanes/EtOAc) to give separated diastereomers **59** and **60** as colorless oils (104 mg, 77% yield, 2.2:1 dr).

Compound 59: R_f = 0.31 (7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.27 (m, 2H), 6.87-6.85 (m, 2H), 6.14 (dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, 1H), 5.04 (dd, *J* = 17.0, 2.0 Hz, 1H), 5.01-4.98 (m, 1H), 4.40 (ABq, *J* = 11.5 Hz, 2H), 4.00-3.87 (m, 6H), 3.80 (s, 3H), 3.35 (s, 1H), 2.63 (dd, *J* = 14.5, 7.5 Hz, 1H), 2.55-2.50 (m, 1H), 2.49 (s, 1H), 2.30 (ddd, *J* = 12.5, 12.5, 5.0 Hz, 1H), 2.22 (ddd, *J* = 12.5, 12.5, 5.0 Hz, 1H), 2.08-2.01 (m, 5H), 1.85-1.54 (m, 10H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 138.4, 136.1, 131.2, 129.7, 128.3, 119.8, 115.8, 114.0, 87.6, 74.8, 71.9, 71.3, 70.0, 65.4, 64.5, 55.5, 54.0, 49.1, 41.5, 37.8, 31.3, 30.1, 28.3, 28.3, 23.3, 23.2, 22.7, 19.9; IR (Neat Film NaCl) 3436, 3294, 3065, 2929, 2879, 2836, 1997, 1633, 1612, 1584, 1514, 1462, 1302, 1248, 1173, 1140, 1070, 1036, 1006, 949, 907, 821 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{31}H_{43}O_5$ $[M+H]^+$: 495.3110, found 495.3133; $[\alpha]_D^{23.7}$ +6.4° (*c* 1.02, $CHCl_3$).

Compound 60: R_f = 0.39 (7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.26 (m, 2H), 6.88-6.86 (m, 2H), 6.16 (dddd, *J* = 17.0, 10.0, 7.5, 6.5 Hz, 1H), 5.05 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.99 (dd, *J* = 10.0, 1.0 Hz, 1H), 4.41 (ABq, *J* = 11.5 Hz, 2H), 4.00-3.87 (m, 6H), 3.82 (s, 3H), 2.68 (dd, *J* = 14.5, 8.0 Hz, 1H), 2.52 (s, 1H), 2.52-2.48 (m, 1H), 2.45 (s, 1H), 2.34-2.25 (m, 2H), 2.12-1.96 (m, 5H), 1.90-1.85 (m, 1H), 1.80-1.57 (m, 9H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 138.4, 136.4, 131.0, 129.7, 128.4, 119.9, 116.1, 114.0, 86.4, 75.6, 74.4, 72.0, 70.1, 65.8, 64.2, 55.5, 55.3, 49.6, 42.5, 37.4, 31.8, 30.0, 28.6, 27.6, 23.3, 23.2, 23.0, 21.7; IR (Neat Film NaCl) 3436, 3302, 2930, 2884, 2832, 1995, 1638, 1613, 1514, 1458, 1302, 1248, 1174, 1141, 1068, 1037,

1003, 951, 907 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{31}H_{43}O_5$ $[M+H]^+$: 495.3110, found 495.3124; $[\alpha]_D^{23.5}$ +32.3° (*c* 0.98, $CHCl_3$).

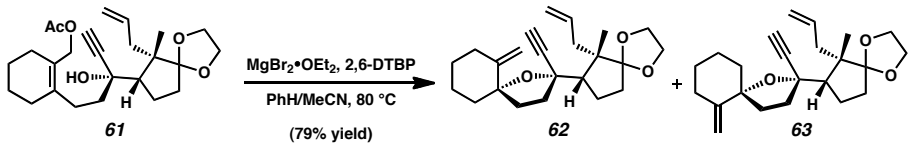


Acetate 61.

To a solution of **59** (65 mg, 0.13 mmol, 1.0 equiv) in CH_2Cl_2 (13 mL) and H_2O (1.3 mL) was added DDQ (45 mg, 0.20 mmol, 1.5 equiv). The mixture was stirred at 25 °C for 1 h. After addition of saturated aq $NaHCO_3$, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (3:1 hexanes/EtOAc) to give the allylic alcohol as a colorless oil (37 mg, 75% yield). R_f = 0.11 (4:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 6.13 (dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, 1H), 5.05-4.98 (m, 2H), 4.11 (ABq, *J* = 11.5 Hz, 2H), 3.97-3.86 (m, 4H), 3.47 (br s, 1H), 2.62 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.58 (s, 1H), 2.52 (dd, *J* = 15.0, 6.5 Hz, 1H), 2.36 (ddd, *J* = 12.5, 12.5, 5.0 Hz, 1H), 2.24 (ddd, *J* = 12.0, 12.0, 5.5 Hz, 1H), 2.14-1.99 (m, 5H), 1.88-1.54 (m, 11H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 135.3, 130.7, 119.8, 115.9, 87.4, 75.0, 71.4, 65.4, 64.5, 63.1, 54.0, 49.2, 41.4, 37.7, 31.2, 29.9, 28.1, 28.1, 23.3, 23.3, 22.6, 19.9; IR (Neat Film NaCl) 3401, 3304, 3070, 2919, 2884, 1995, 1724, 1636, 1459, 1434, 1377, 1318, 1274, 1246, 1217, 1176, 1138, 1070, 1038, 1003, 982, 937, 758 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{35}O_4$ $[M+H]^+$: 375.2535, found 375.2546; $[\alpha]_D^{26.2}$ +12.5° (*c* 0.67, $CHCl_3$).

To a solution of the allylic alcohol (44 mg, 0.12 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL), pyridine (39 μL, 0.48 mmol, 4.0 equiv) and Ac_2O (45 μL, 0.48 mmol, 4.0 equiv)

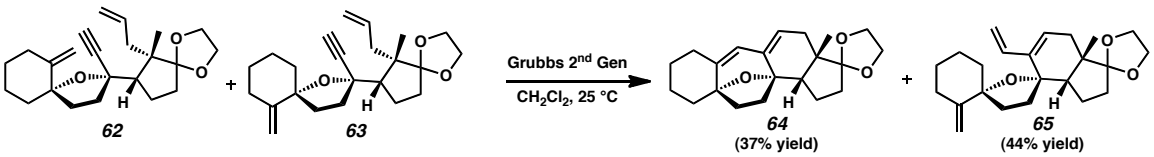
were added. The mixture was stirred at 25 °C for 24 h. After addition of H_2O, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with 10% aq HCl, saturated aq $NaHCO_3$ and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (8:1 hexanes/EtOAc) to give **61** as a colorless oil (46 mg, 94% yield). R_f = 0.28 (7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.14 (dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, 1H), 5.06-4.98 (m, 2H), 4.59 (ABq, *J* = 11.5 Hz, 2H), 3.98-3.88 (m, 4H), 3.35 (s, 1H), 2.66-2.62 (m, 1H), 2.57 (s, 1H), 2.56-2.52 (m, 1H), 2.36-2.23 (m, 2H), 2.10-2.03 (m, 4H), 2.06 (s, 3H), 1.89-1.71 (m, 6H), 1.62-1.55 (m, 5H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 138.3, 137.9, 126.1, 119.8, 115.9, 87.3, 75.0, 71.2, 65.4, 65.0, 64.5, 54.0, 49.2, 41.5, 37.7, 31.3, 30.1, 28.4, 28.1, 23.1, 23.0, 22.7, 21.4, 19.9; IR (Neat Film NaCl) 3468, 3272, 3069, 2930, 2884, 1735, 1636, 1455, 1436, 1378, 1239, 1176, 1144, 1073, 1023, 952 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{23}H_{33}O_3$ $[M\text{-}OAc]^+$: 357.2430, found 357.2440; $[\alpha]_D^{28.0}$ +4.0° (*c* 0.62, $CHCl_3$).



Compounds 62 and 63.

To a solution of **61** (43 mg, 0.10 mmol, 1.0 equiv) in benzene (5 mL), 2,6-DTBP (0.14 mL 0.62 mmol, 6.0 equiv), $MgBr_2$•OEt_2 (107 mg, 0.41 mmol, 4.0 equiv) and MeCN (1.0 mL) were added, and the mixture was stirred at 80 °C for 2 d. After addition of brine, the aqueous layer was extracted with EtOAc. The combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (hexanes → 199:1 → 99:1 hexanes/EtOAc) to give **62** and **63** as

a mixture of two diastereomers as a colorless oil (29 mg, 79% yield). R_f = 0.45 (99:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23-6.13 (m, 1H), 5.19 (d, *J* = 2.5 Hz, 0.5H), 5.02-4.92 (m, 2H), 4.88 (d, *J* = 2.0 Hz, 0.5H), 4.67 (s, 1H), 3.97-3.86 (m, 4H), 2.56-2.34 (m, 4H), 2.24-1.23 (m, 16H), 1.11 (s, 1.5H), 1.04 (s, 1.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 152.2, 138.6, 138.5, 120.5, 120.3, 115.5, 115.5, 106.2, 105.4, 88.0, 87.5, 87.3, 86.7, 80.7, 80.1, 74.5, 74.4, 65.9, 65.8, 64.1, 64.1, 55.3, 54.7, 48.8, 48.6, 42.0, 39.9, 38.7, 38.4, 38.4, 38.2, 35.0, 34.9, 34.9, 33.7, 31.7, 31.4, 28.1, 28.0, 25.2, 24.7, 22.0, 21.2, 20.9, 20.7; IR (Neat Film NaCl) 3304, 3071, 2972, 2934, 2879, 2853, 1735, 1649, 1636, 1460, 1446, 1396, 1376, 1315, 1300, 1274, 1217, 1202, 1173, 1145, 1120, 1068, 1046, 1011, 947, 899 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{33}O_3$ $[M+H]^+$: 357.2430, found 357.2439.



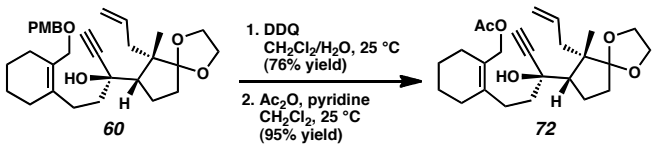
Compounds 64 and 65.

To a solution of **62** and **63** (24 mg, 0.067 mmol, 1.0 equiv) in CH_2Cl_2 (6.5 mL), Grubbs 2nd generation catalyst (8.6 mg, 0.010 mmol, 15 mol%) was added. The mixture was stirred at 25 °C for 2 d. The solvent was concentrated, and the residue was purified by flash chromatography (99:1 → 98:2 → 9:1 hexanes/EtOAc) to give **64** as a beige solid (8.2 mg, 37% yield) and **65** as a colorless oil (10.5 mg, 44% yield).

Compound 64: R_f = 0.47 (9:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 (d, *J* = 2.0 Hz, 1H), 5.20 (t, *J* = 4.0 Hz, 1H), 3.95-3.88 (m, 4H), 2.32-2.28 (m, 2H), 2.24-2.12 (m, 3H), 2.05-1.78 (m, 10H), 1.74-1.60 (m, 4H), 0.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 137.3, 120.3, 120.1, 117.2, 81.4, 80.7, 65.6, 64.6, 51.0, 46.4, 39.8, 38.9,

35.5, 34.0, 31.7, 31.3, 26.1, 24.4, 23.1, 19.9; IR (Neat Film NaCl) 2919, 2858, 1995, 1727, 1465, 1451, 1427, 1375, 1310, 1279, 1259, 1202, 1175, 1158, 1098, 1070, 1024, 942, 912, 871 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{21}H_{29}O_3$ $[M+H]^+$: 329.2117, found 329.2122; $[\alpha]_D^{21.3}$ +176.8° (*c* 0.97, $CHCl_3$).

Compound 65: R_f = 0.42 (99:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 6.54 (dd, *J* = 17.5, 10.5 Hz, 1H), 5.85 (t, *J* = 4.0 Hz, 1H), 5.35 (dd, *J* = 17.0, 2.0 Hz, 1H), 4.98 (dd, *J* = 10.5, 2.0 Hz, 1H), 4.94 (d, *J* = 2.0 Hz, 1H), 4.67 (s, 1H), 3.92-3.87 (m, 4H), 2.43-2.38 (m, 1H), 2.34-2.24 (m, 2H), 2.16-2.05 (m, 3H), 2.02-1.60 (m, 11H), 1.54-1.48 (m, 2H), 0.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 139.8, 136.7, 122.5, 120.5, 113.8, 105.3, 85.4, 84.4, 65.6, 64.6, 51.5, 46.3, 40.4, 36.4, 35.0, 34.0, 33.2, 31.2, 28.6, 24.4, 23.9, 20.9; IR (Neat Film NaCl) 2930, 2853, 1995, 1736, 1648, 1460, 1442, 1372, 1311, 1261, 1200, 1151, 1137, 1078, 1030, 1009, 946, 894 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{33}O_3$ $[M+H]^+$: 357.2430, found 357.2445.



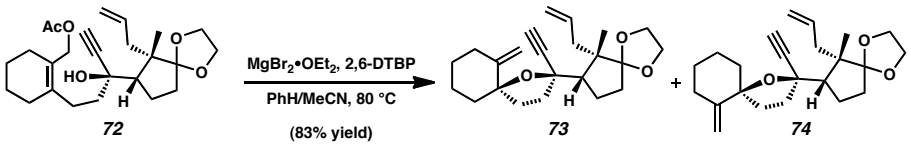
Compound 72.

To a solution of **60** (33 mg, 0.07 mmol, 1.0 equiv) in CH_2Cl_2 (7.0 mL) and H_2O (0.7 mL), DDQ (23 mg, 0.10 mmol, 1.5 equiv) was added. The mixture was stirred at 25 °C for 1 h. After addition of saturated aq $NaHCO_3$, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (4:1 hexanes/EtOAc) to give the allylic alcohol as a colorless oil (19 mg, 76% yield). R_f = 0.20 (4:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 6.16 (dddd, *J*

= 17.0, 10.0, 8.0, 6.5 Hz, 1H), 5.09-5.04 (m, 1H), 5.01-4.98 (m, 1H), 4.13 (ABq, *J* = 11.5 Hz, 2H), 3.95-3.86 (m, 4H), 2.68 (dd, *J* = 14.5, 8.5 Hz, 1H), 2.59 (s, 1H), 2.52-2.47 (m, 1H), 2.42-2.32 (m, 1H), 2.31-2.14 (m, 1H), 2.13-1.91 (m, 5H), 1.90-1.55 (m, 12H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 135.5, 130.8, 119.8, 116.4, 86.4, 75.7, 74.5, 65.8, 64.2, 63.2, 55.3, 49.6, 42.5, 37.3, 31.8, 29.9, 28.3, 27.5, 23.3, 23.2, 23.0, 21.6; IR (Neat Film NaCl) 3402, 3305, 3072, 2919, 2884, 1718, 1635, 1459, 1436, 1377, 1320, 1276, 1246, 1216, 1176, 1138, 1070, 1039, 1002, 981, 952, 758 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{35}O_4$ $[M+H]^+$: 375.2535, found 375.2544; $[\alpha]_D^{26.1}$ +38.6° (*c* 0.62, $CHCl_3$).

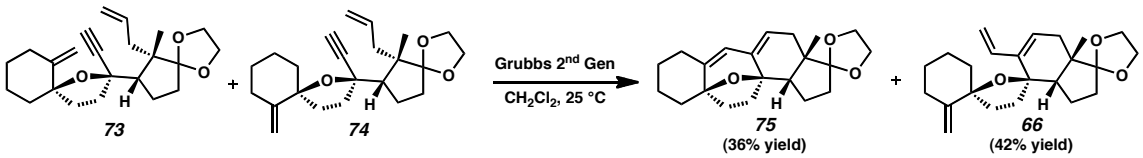
To a solution of the allylic alcohol (18 mg, 0.05 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), pyridine (15 μL, 0.19 mmol, 4.0 equiv) and Ac_2O (18 μL, 0.19 mmol, 4.0 equiv) were added. The mixture was stirred at 25 °C for 21 h. After addition of H_2O, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with 10% aq HCl, saturated aq $NaHCO_3$ and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (8:1 hexanes/EtOAc) to give **72** as a colorless oil (19 mg, 95% yield). R_f = 0.34 (7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.17 (dddd, *J* = 18.0, 10.0, 8.0, 6.5 Hz, 1H), 5.08-5.04 (m, 1H), 5.01-4.99 (m, 1H), 4.60 (ABq, *J* = 12.0 Hz, 2H), 3.96-3.87 (m, 4H), 2.69 (dd, *J* = 14.5, 8.0 Hz, 1H), 2.58 (s, 1H), 2.54-2.49 (m, 1H), 2.41 (s, 1H), 2.34 (t, *J* = 8.0 Hz, 2H), 2.12 (t, *J* = 9.0 Hz, 1H), 2.06 (s, 3H), 2.05-2.02 (m, 4H), 1.92-1.68 (m, 6H), 1.68-1.57 (m, 4H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 138.3, 138.0, 126.2, 119.8, 116.3, 86.1, 75.8, 74.4, 65.8, 65.0, 64.2, 55.2, 49.6, 42.6, 37.4, 31.8, 30.1, 28.3, 27.7, 23.1, 22.7, 22.7, 21.6, 21.4; IR (Neat Film NaCl) 3481, 3303, 3071, 2924, 2856, 1736, 1636, 1461, 1436, 1378, 1318, 1239, 1177, 1143, 1075, 1024, 953

cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{23}H_{33}O_3$ $[M\text{-}OAc]^+$: 357.2430, found 357.2426; $[\alpha]_D^{27.9}$ +44.6° (*c* 0.42, $CHCl_3$).



Compounds 73 and 74.

To a solution of **72** (31 mg, 0.08 mmol, 1.0 equiv) in benzene (4 mL), 2,6-DTBP (0.10 mL, 0.45 mmol, 6.0 equiv), $MgBr_2 \bullet OEt_2$ (77 mg, 0.30 mmol, 4.0 equiv) and MeCN (0.6 mL) were added, and the mixture was stirred at 80 °C for 2 d. After addition of brine, the aqueous layer was extracted with EtOAc. The combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (99:1 hexanes/EtOAc) to give **73** and **74** as a mixture of two diastereomers as a colorless oil (22 mg, 83% yield). R_f = 0.46 (99:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 6.20 (dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, 1H), 5.23 (d, *J* = 2.5 Hz, 0.4H), 5.02-4.91 (m, 2.6H), 4.71 (s, 0.4H), 4.65 (s, 0.6H), 3.97-3.86 (m, 4H), 2.75-2.71 (m, 1H), 2.60-2.54 (m, 1H), 2.47 (s, 0.4H), 2.47 (s, 0.6H), 2.42-2.36 (m, 1H), 2.21-1.29 (m, 16H), 1.12 (s, 1.2H), 1.07 (s, 1.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 152.4, 138.9, 138.8, 120.0, 119.9, 115.1, 115.1, 106.6, 106.0, 87.9, 87.7, 87.5, 87.1, 81.5, 81.5, 74.7, 74.6, 65.7, 65.7, 64.3, 64.2, 57.2, 56.4, 49.3, 49.3, 42.1, 41.9, 41.6, 40.6, 37.8, 37.5, 34.9, 34.8, 34.5, 33.8, 32.4, 32.4, 28.1, 27.9, 25.2, 24.6, 23.0, 22.9, 22.0, 21.9; IR (Neat Film NaCl) 3302, 3070, 2972, 2935, 2879, 2858, 1649, 1636, 1459, 1446, 1396, 1375, 1298, 1243, 1174, 1137, 1105, 1075, 1050, 1002, 950, 899 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{33}O_3$ $[M+H]^+$: 357.2430, found 357.2426.



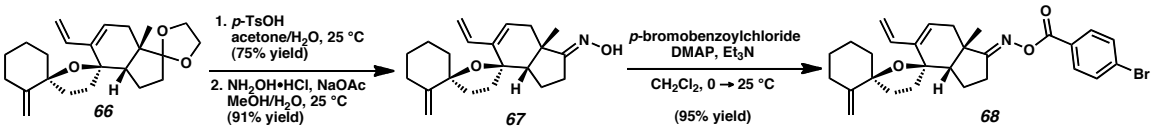
Compounds 75 and 66.

To a solution of **73** and **74** (20 mg, 0.056 mmol, 1.0 equiv) in CH_2Cl_2 (2.8 mL), Grubbs 2nd generation catalyst (7 mg, 0.008 mmol, 15 mol%) was added. The mixture was stirred at 25 °C for 2 d. The solvent was concentrated, and the residue was purified by flash chromatography (99:1 → 98:2 → 9:1 hexanes/EtOAc) to give **75** as a white solid (6.7 mg, 36% yield) and **66** as a colorless oil (8.3 mg, 42% yield).

Compound 75: R_f = 0.42 (9:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 (s, 1H), 5.34 (d, *J* = 5.5 Hz, 1H), 3.91-3.88 (m, 4H), 2.31-2.25 (m, 2H), 2.18-2.05 (m, 4H), 1.96-1.70 (m, 10H), 1.61-1.48 (m, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 139.8, 120.1, 119.7, 118.2, 83.4, 79.5, 65.6, 64.6, 49.5, 46.1, 37.4, 35.5, 34.3, 34.0, 31.7, 30.1, 26.2, 24.4, 24.2, 19.5; IR (Neat Film NaCl) 2924, 2853, 1995, 1726, 1623, 1461, 1377, 1310, 1259, 1153, 1072, 1055, 946, 907 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{21}H_{28}O_3$ $[M]^+$: 328.2039, found 328.2038; $[\alpha]_D^{24.3}$ −159.9° (*c* 0.90, $CHCl_3$).

Compound 66: R_f = 0.42 (99:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.43 (ddd, *J* = 17.0, 11.0, 1.0 Hz, 1H), 5.92 (dd, *J* = 5.5, 2.0 Hz, 1H), 5.35 (dd, *J* = 17.0, 2.0 Hz, 1H), 5.04 (d, *J* = 2.0 Hz, 1H), 5.00 (dd, *J* = 11.0, 2.0 Hz, 1H), 4.69 (s, 1H), 3.96-3.85 (m, 4H), 2.44-2.39 (m, 1H), 2.26 (dd, *J* = 12.0, 8.0 Hz, 1H), 2.15-2.01 (m, 3H), 1.97-1.82 (m, 4H), 1.80-1.73 (m, 2H), 1.70-1.65 (m, 2H), 1.61-1.52 (m, 2H), 1.50-1.43 (m, 2H), 1.31-1.25 (m, 2H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 138.0, 137.0, 124.4, 120.4, 114.2, 105.5, 85.7, 83.0, 65.6, 64.8, 50.2, 44.7, 40.8, 34.9, 34.3, 33.9, 33.2, 31.0, 28.5, 24.7, 23.8, 19.4; IR (Neat Film NaCl) 3079, 2932, 2876, 2858, 1736, 1648,

1619, 1460, 1446, 1374, 1317, 1305, 1263, 1200, 1152, 1087, 1068, 1055, 1021, 1009, 950, 893, 755 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{33}O_3$ $[M+H]^+$: 357.2430, found 357.2429; $[\alpha]_D^{24.2}$ +3.1° (*c* 0.93, $CHCl_3$).



Compound 68.

To a solution of **66** (31 mg, 0.09 mmol, 1.0 equiv) in acetone (0.9 mL) was added H_2O (2.4 μL, 0.13 mmol, 1.5 equiv) and *p*-TsOH (3.3 mg, 0.02 mmol, 0.2 equiv) at 25 °C. The mixture was stirred at 25°C for 15 h, and the solvent was concentrated. After addition of EtOAc, the organic phase was washed with saturated aq $NaHCO_3$, H_2O and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the crude residue was purified by flash chromatography (99:1 → 98:2 hexanes/EtOAc) to afford the desired product that was used directly in the next step.

To the resulting ketone (15 mg, 0.05 mmol, 1.0 equiv) dissolved in MeOH/H_2O (3 mL, 5:1) was added NaOAc (38 mg, 0.45 mmol, 10 equiv) and $NH_2OH•H_2O$ (34 mg, 0.49 mmol, 11 equiv) at 25 °C. The mixture was stirred at 25°C for 14 h, and the solvent was concentrated. After addition of H_2O, the aqueous layer was extracted with EtOAc. The combined organic phases were washed with brine, dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (5:1 hexanes/EtOAc) to give **67**.

To a solution of oxime **67** (14 mg, 0.04 mmol, 1.0 equiv) in CH_2Cl_2 (0.4 mL), *p*-bromobenzoylchloride (11 mg, 0.05 mmol, 1.2 equiv), DMAP (1 mg, 0.01 mmol, 0.2 equiv), and Et_3N (12 μL, 0.08 mmol, 2.0 equiv) were added at 0 °C. The mixture was

stirred at 0 °C for 2 h. After addition of saturated aq NH_4Cl, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (99:1 → 98:2 → 95:5 hexanes/EtOAc) to give **68** as a white solid (20 mg, 95% yield). MP: 91-93 °C from ethyl acetate/heptane; R_f = 0.38 (95:5 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91-7.88 (m, 2H), 7.60-7.57 (m, 2H), 6.43 (ddd, *J* = 17.0, 10.5, 1.0 Hz, 1H), 5.89 (dd, *J* = 5.5, 2.0 Hz, 1H), 5.37 (dd, *J* = 17.0, 2.0 Hz, 1H), 5.06 (dd, *J* = 11.0, 2.0 Hz, 1H), 4.95 (d, *J* = 2.0 Hz, 1H), 4.66 (s, 1H), 2.83 (dd, *J* = 19.5, 8.5 Hz, 1H), 2.67-2.60 (m, 1H), 2.43-2.38 (m, 1H), 2.25 (dd, *J* = 13.0, 6.5 Hz, 1H), 2.20 (d, *J* = 19.0 Hz, 1H), 2.13-2.01 (m, 4H), 1.96-1.75 (m, 4H), 1.71-1.61 (m, 2H), 1.58 (s, 3H), 1.54-1.41 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.7, 163.5, 154.1, 138.8, 136.4, 132.1, 131.3, 128.6, 128.5, 122.4, 115.0, 105.4, 85.9, 81.8, 53.3, 44.3, 40.8, 34.8, 34.4, 33.9, 32.5, 28.5, 27.4, 24.5, 24.5, 22.4; IR (Neat Film NaCl) 3079, 2932, 2855, 1746, 1648, 1590, 1483, 1447, 1398, 1379, 1320, 1254, 1174, 1069, 1011, 906, 875, 750, 732 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{28}H_{33}BrO_3N$ $[M+H]^+$: 510.1644, found 510.1644; $[\alpha]_D^{22.9}$ +30.4° (*c* 0.90, $CHCl_3$).

NOTES AND REFERENCES

(1) (a) Ferrara, N; Kerbel, R. S. *Nature* **2005**, *438*, 967–974. (b) Folkman, J. *Nature Reviews Drug Discovery* **2007**, *6*, 273–286, and references therein.

(2) (a) Aoki, S.; Watanabe, Y.; Tanabe, D.; Setiawan, A.; Arai, M.; Kobayashi, M. *Tetrahedron Lett*. **2007**, *48*, 4485–4488. (b) Watanabe, Y.; Aoki, S.; Tanabe, D.; Setiawan, A.; Kobayashi, M. *Tetrahedron* **2007**, *63*, 4074–4079. (c) Aoki, S.; Watanabe, Y.; Tanabe, D.; Arai, M.; Suna, H.; Miyamoto, K.; Tsujibo, H.; Tsujikawa, K.; Yamamoto, H.; Kobayashi, M. *Bioorg. Med. Chem*. **2007**, *15*, 6758–6762. (d) Aoki, S.; Watanabe, Y.; Sanagawa, M.; Setiawan, A.; Kotoku, N.; Kobayashi, M. *J. Am. Chem. Soc*. **2006**, *128*, 3148–3149.

(3) (a) Shenvi, R. A.; Guerrero, C. A.; Shi, J.; Li, C.-C.; Baran, P. S. *J. Am. Chem. Soc*. **2008**, *130*, 7241–7243. (b) Nicolaou, K. C.; Sun, Y.-P.; Peng, X.-S.; Polet, D.; Chen, D. Y.-K. *Angew. Chem. Int. Ed*. **2008**, *47*, 7310–7313. (c) Lee, H. M.; Nieto-Oberhuber, C.; Shair, M. D. *J. Am. Chem. Soc*. **2008**, *130*, 16864–16866. (d) Simmons, E. M.; Hardin-Narayan, A. R.; Guo, X.; Sarpong, R. *Tetrahedron* **2010**, *66*, 4696–4700.

(4) (a) Shi, J.; Shigeshisa, H.; Guerrero, C. A.; Shenvi, R. A.; Li, C.-C.; Baran, P. S. *Angew. Chem. Int. Ed*. **2009**, *48*, 4328–4331. (b) Liu, L.; Gao, Y.; Che, C.; Wu, N.; Wang, D. Z.; Li, C.-C.; Yang, Z. *Chem. Commun*. **2009**, 662–664. (c) Frie, J. L.; Jeffrey, C. S.; Sorensen, E. J. *Org. Lett*. **2009**, *11*, 5394–5397. (d) Magnus, P.; Littich, R. *Org. Lett*. **2009**, *11*, 3938–3941. (e) Simmons, E. M.; Hardin, A. R.; Guo, X.; Sarpong, R. *Angew. Chem. Int. Ed*. **2008**, *47*, 6650–6653. (f)

Yamashita, S.; Iso, K.; Hirama, M. *Org. Lett.* **2008**, *10*, 3413–3415. (g) Craft, D. T.; Gung, B. W. *Tetrahedron Lett.* **2008**, *49*, 5931–5934. (h) Dai, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**, *49*, 6610–6612. (i) Kürti, L.; Czakó, B.; Corey, E. J. *Org. Lett.* **2008**, *10*, 5247–5250.

(5) (a) Kim, S.-H.; Bowden, N.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801–10802. (b) Kim, S.-H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073–1081. (c) Choi, T.-L.; Grubbs, R. H. *Chem. Comm.* **2001**, 2648–2649.

(6) Brooks, D. W.; Mazdiyasni, H.; Grothaus, P. G. *J. Org. Chem.* **1987**, *52*, 3223–3232.

(7) (a) Rajamannar, T.; Balasubramanian, K. K. *Tetrahedron Lett.* **1988**, *29*, 5789–5792. (b) Chavan, S. P.; Chavan, S. P.; Sonawane, H. R.; Kalkote, U. R.; Sudrik, S. G.; Gonnade, R. G.; Bhadbhade, M. M. *Eur. J. Org. Chem.* **2007**, 3277–3280.

(8) The enantiomeric excess of the benzoate derivative of alcohol **46** was determined by chiral HPLC to be >99% ee. See Experimental Section for details.

(9) See Experimental Section for details.

(10) It is worth noting that we did not realize the actual result of our "S_N2" reaction until a much later point in the synthesis. This unexpected result highlights the sometimes unexpected reactivity of individual organic substrates even under conventional reaction conditions.

(11) From this result, the D-ring relative stereochemistry was unambiguously assigned.

(12) Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999–10003.

(13) Audis, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 3738–3740.

APPENDIX 1

Spectra Relevant to Chapter 2

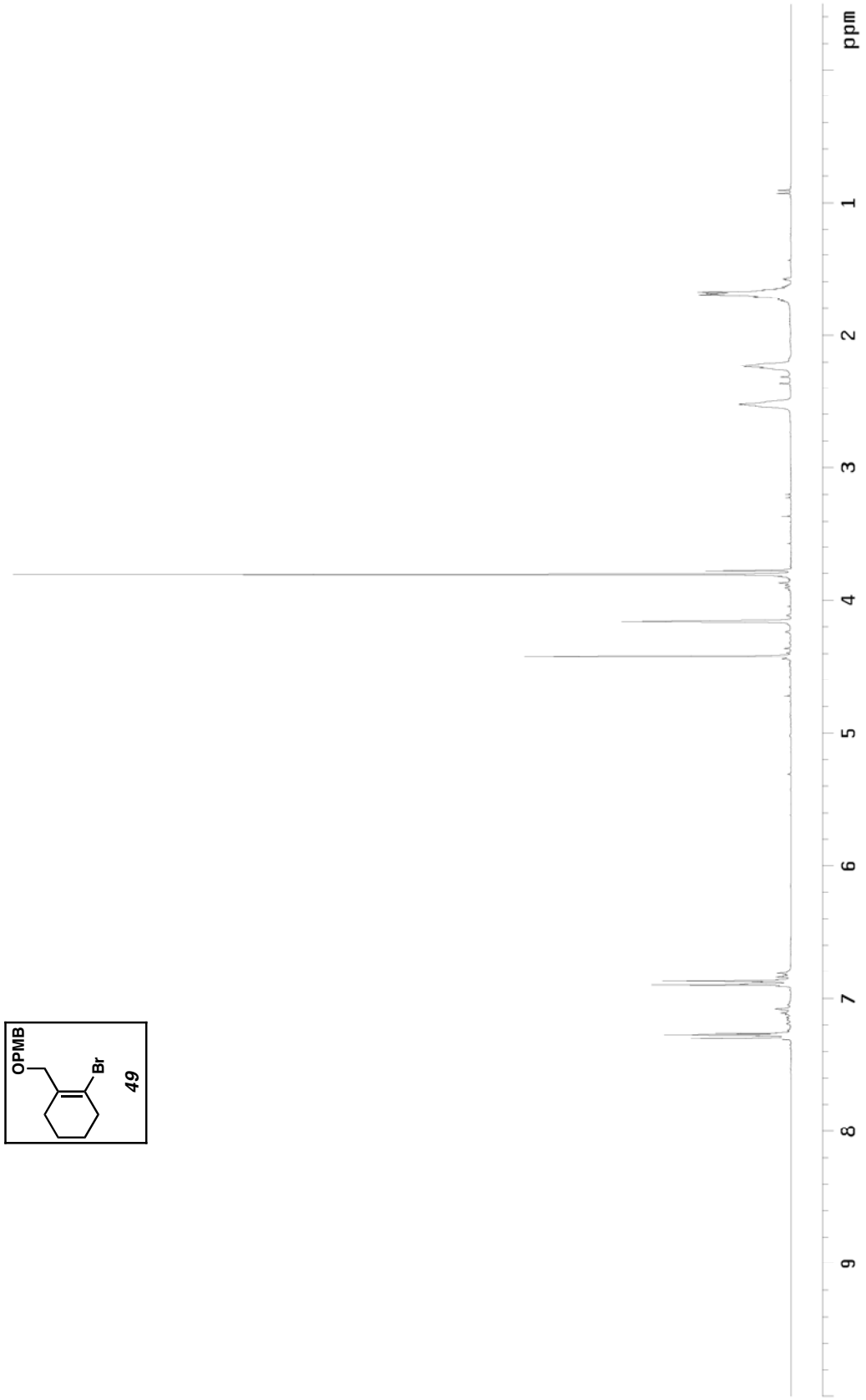


Figure A1.1.1 ^{1}H NMR (300 MHz, $CDCl_3$) of bromide **49**.

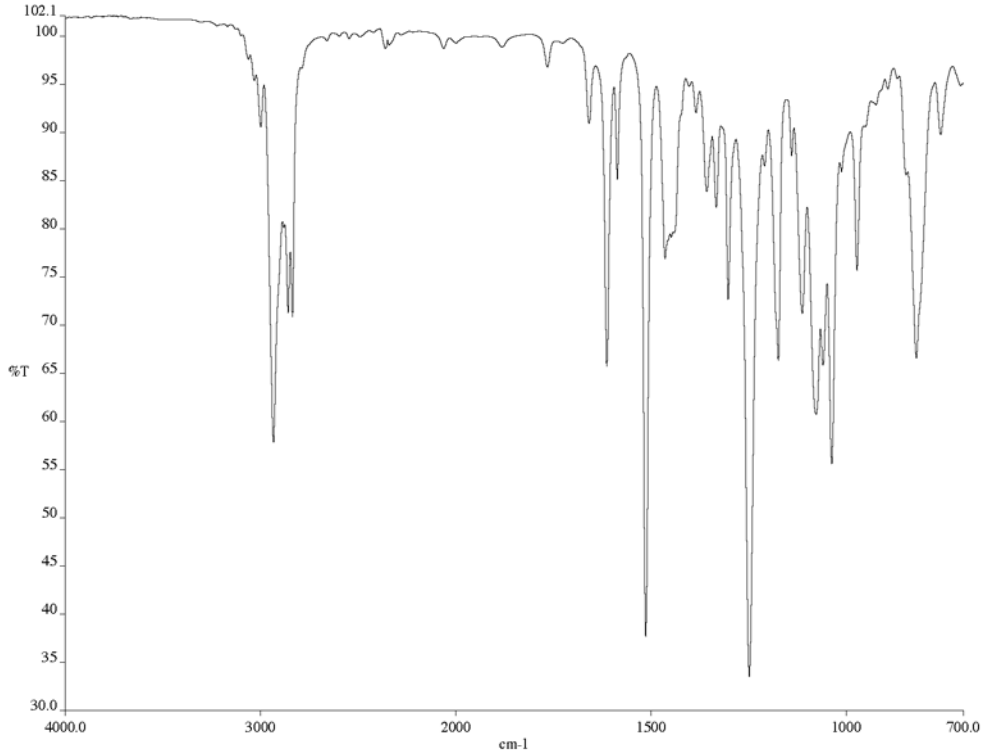


Figure A1.1.2 Infrared spectrum (thin film/NaCl) of bromide **49**.

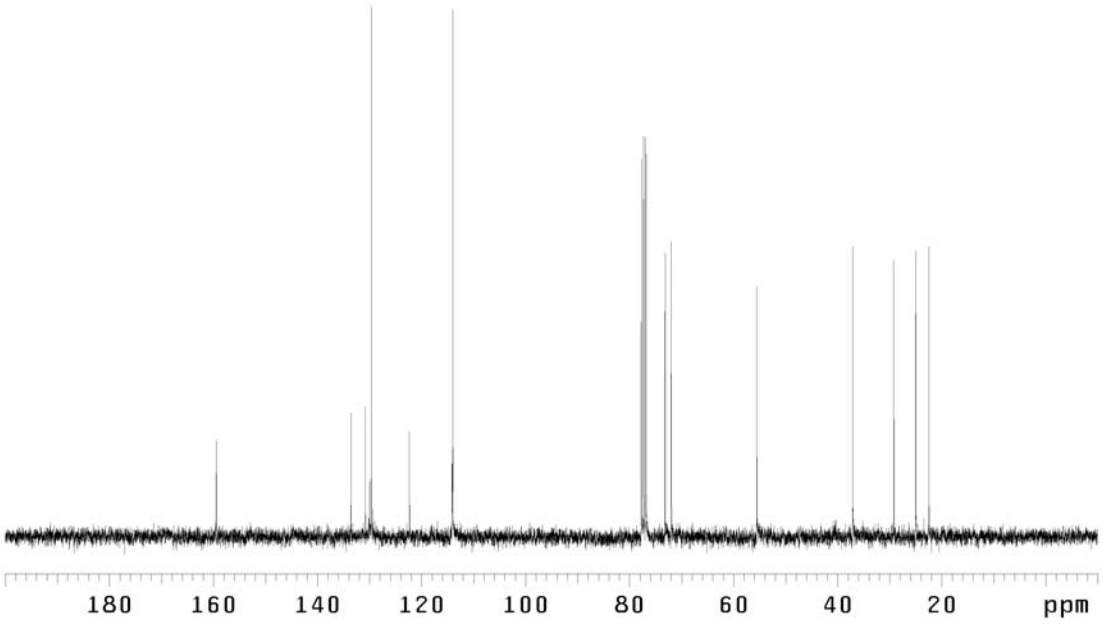


Figure A1.1.3 ^{13}C NMR (75 MHz, $CDCl_3$) of bromide **49**.

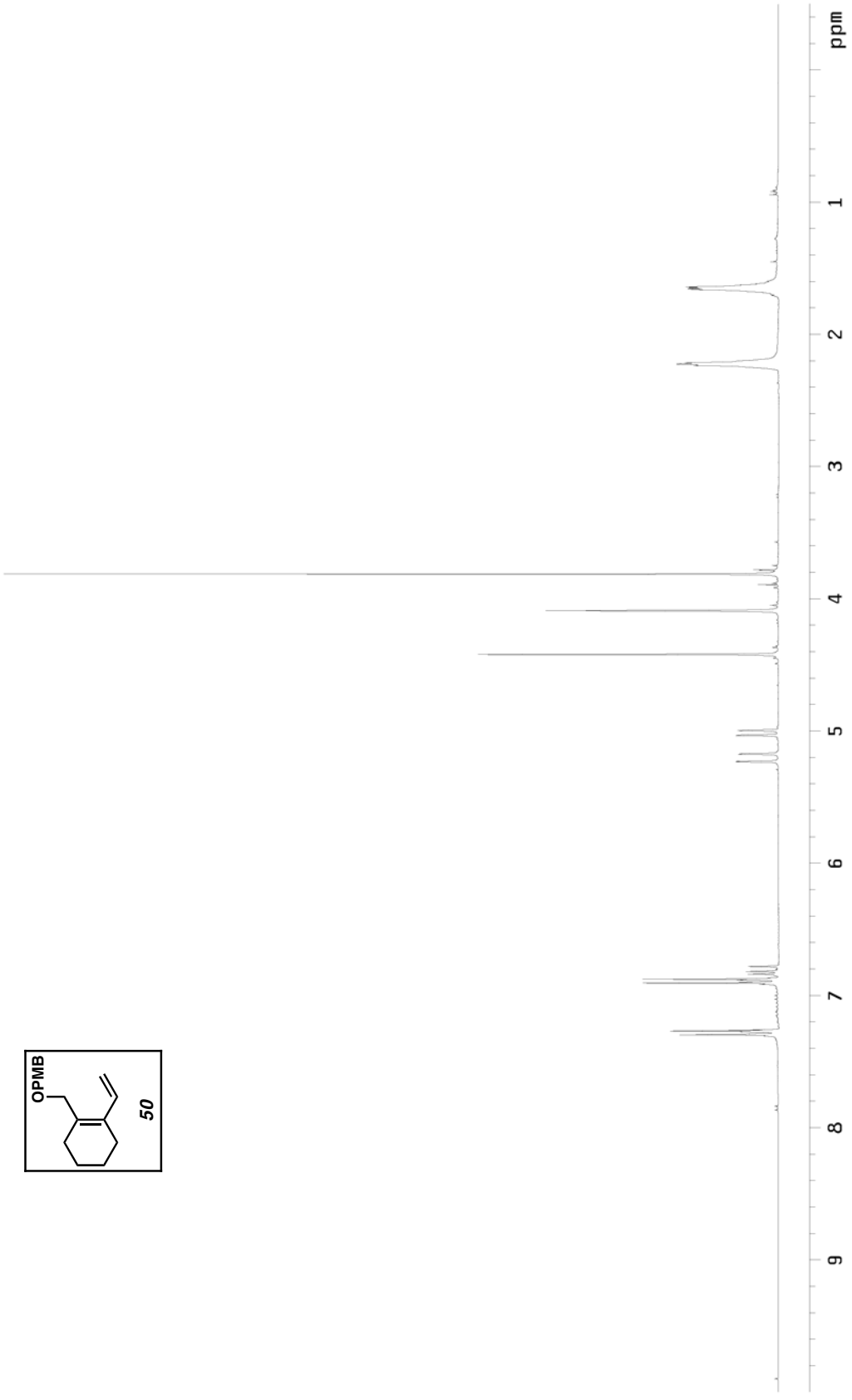


Figure A1.2.1 ^{1}H NMR (300 MHz, $CDCl_3$) of diene **50**.

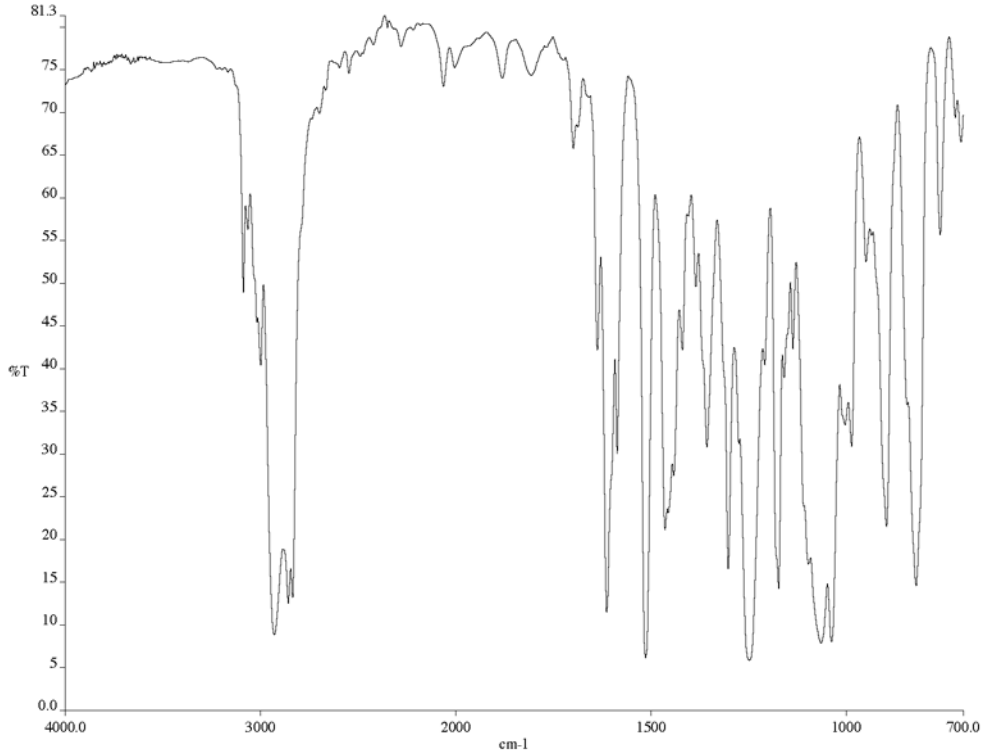


Figure A1.2.2 Infrared spectrum (thin film/NaCl) of diene **50**.

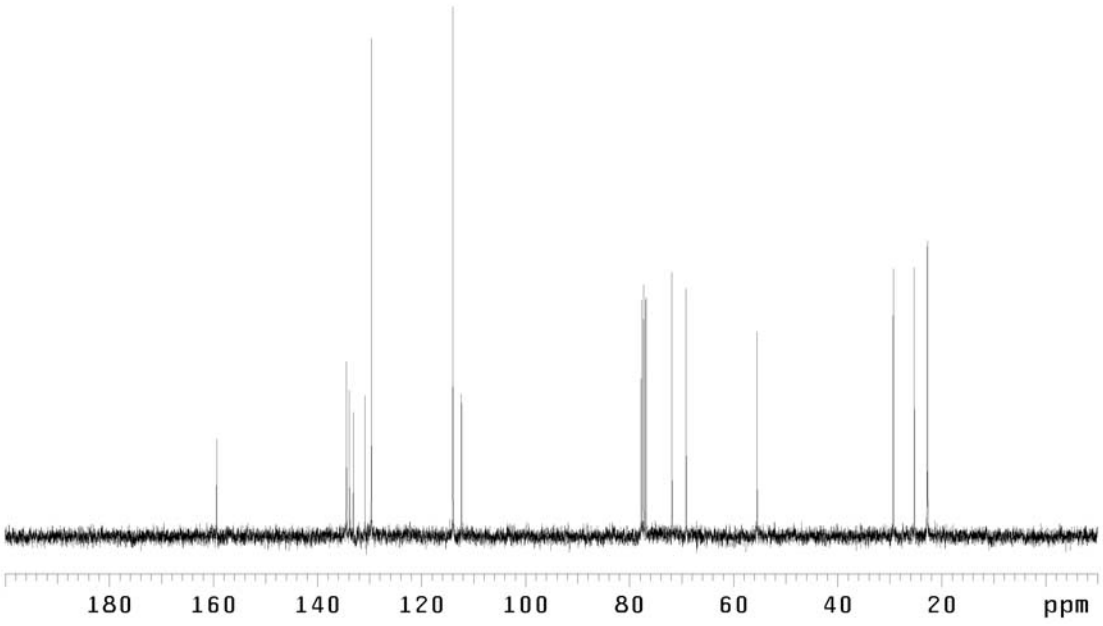


Figure A1.2.3 ^{13}C NMR (75 MHz, $CDCl_3$) of diene **50**.

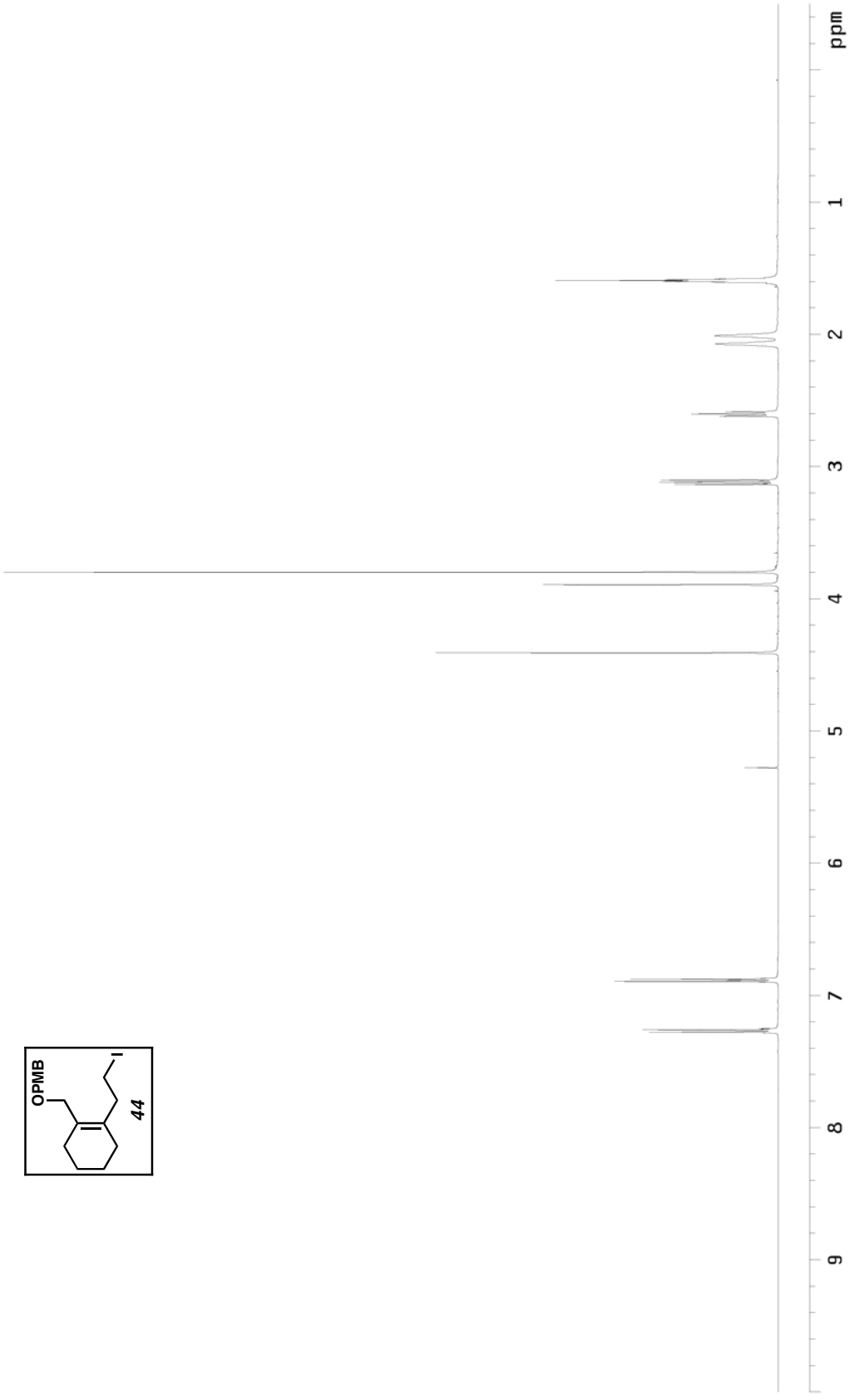


Figure A1.3.1 ^{1}H NMR (500 MHz, $CDCl_3$) of iodide **44**.

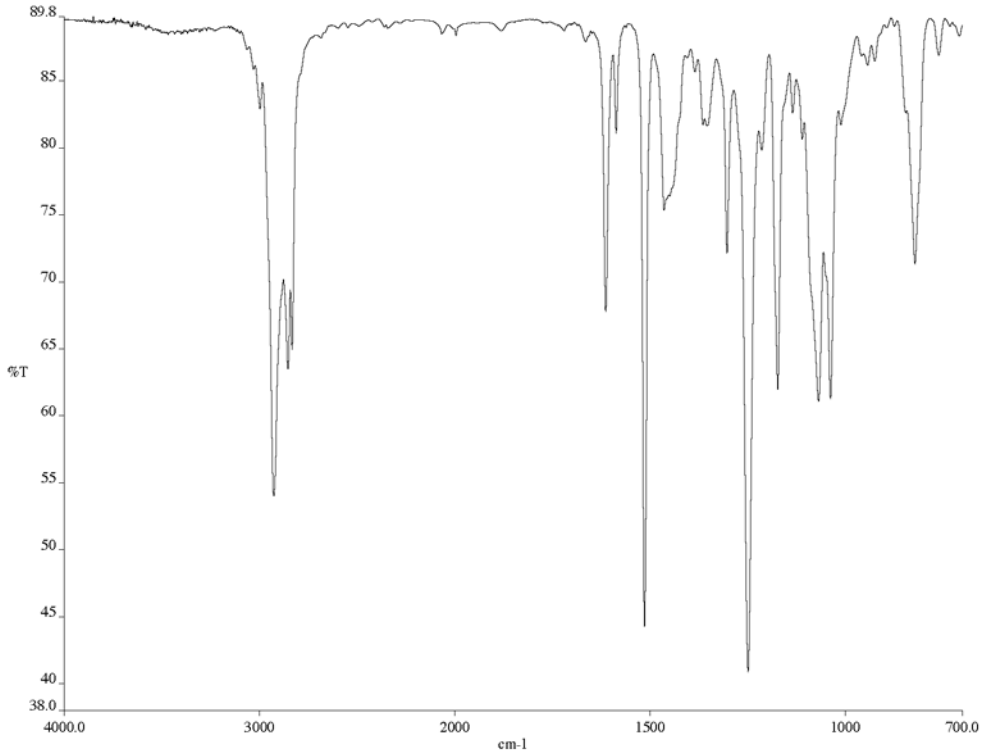


Figure A1.3.2 Infrared spectrum (thin film/NaCl) of iodide **44**.

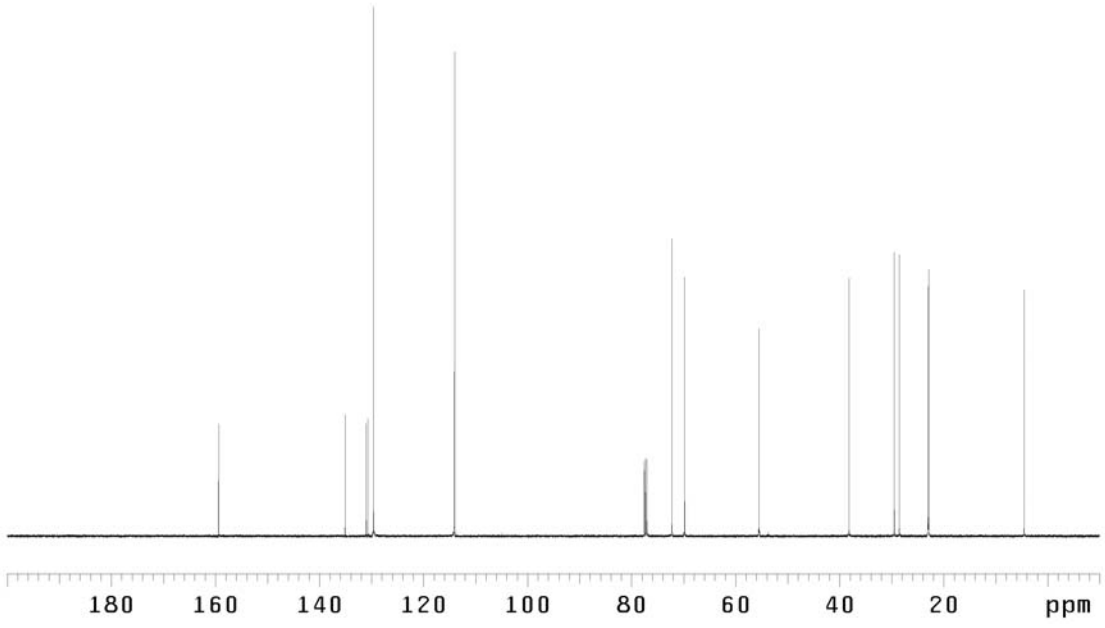


Figure A1.3.3 ^{13}C NMR (125 MHz, $CDCl_3$) of iodide **44**.

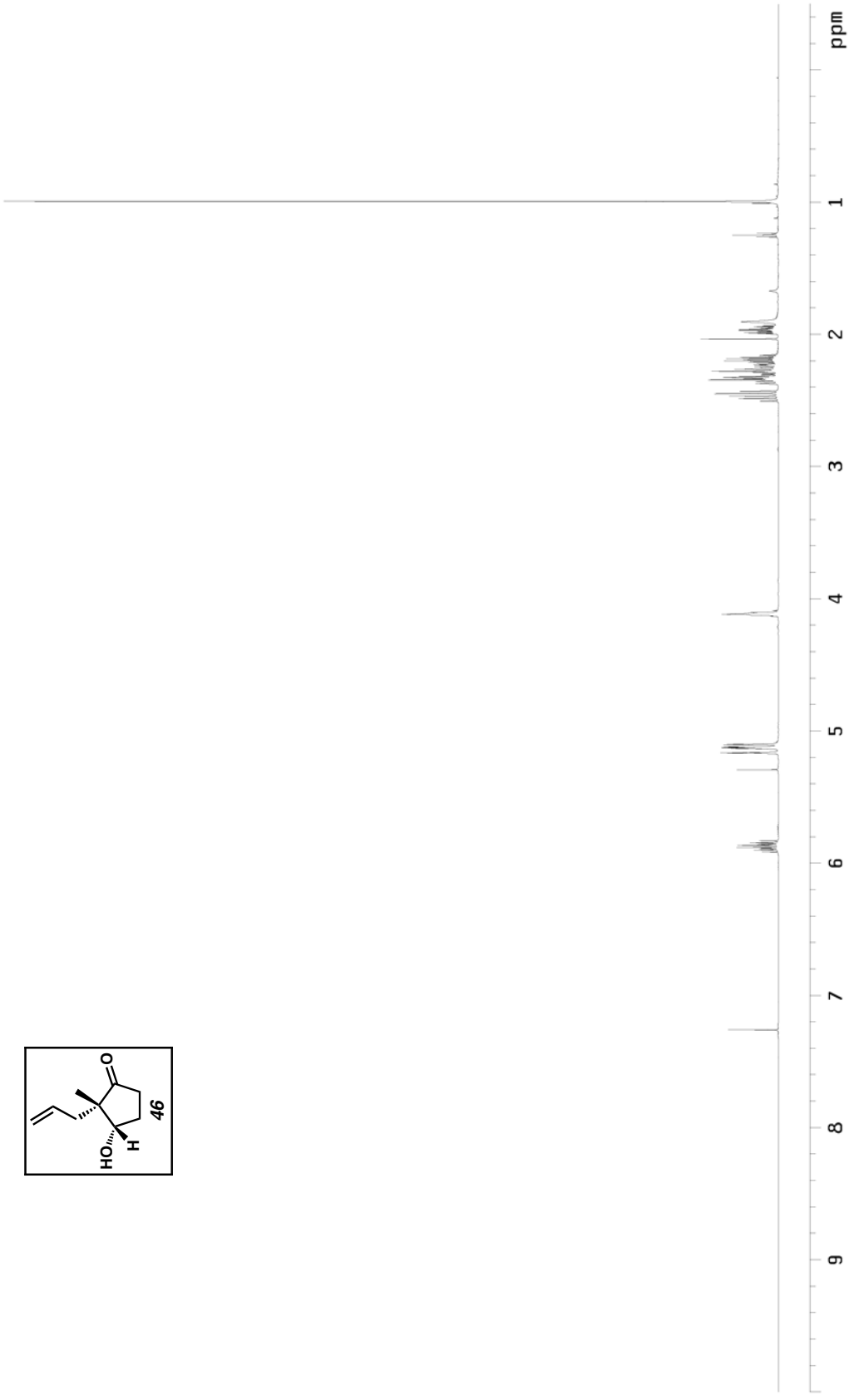


Figure A1.4.1 ^{1}H NMR (500 MHz, $CDCl_3$) of alcohol **46**.

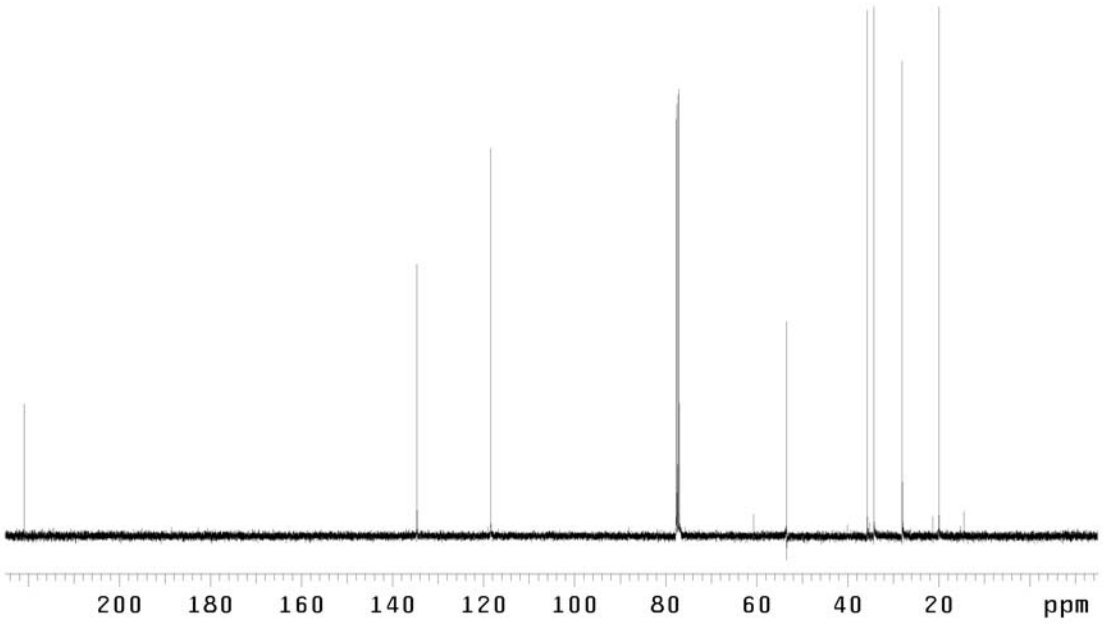


Figure A1.4.2 ^{13}C NMR (125 MHz, $CDCl_3$) of alcohol **46**.

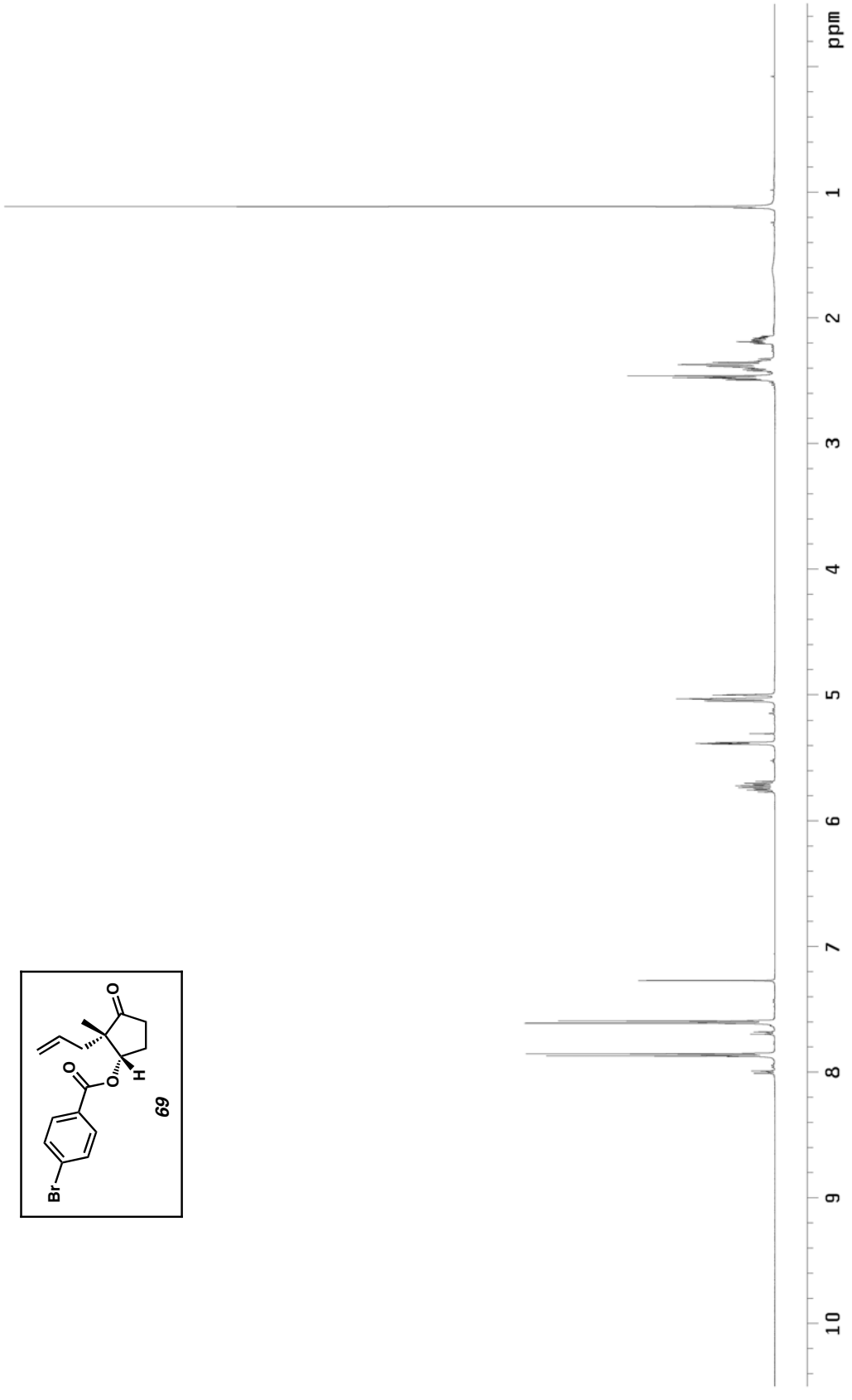


Figure A1.5.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **69**.

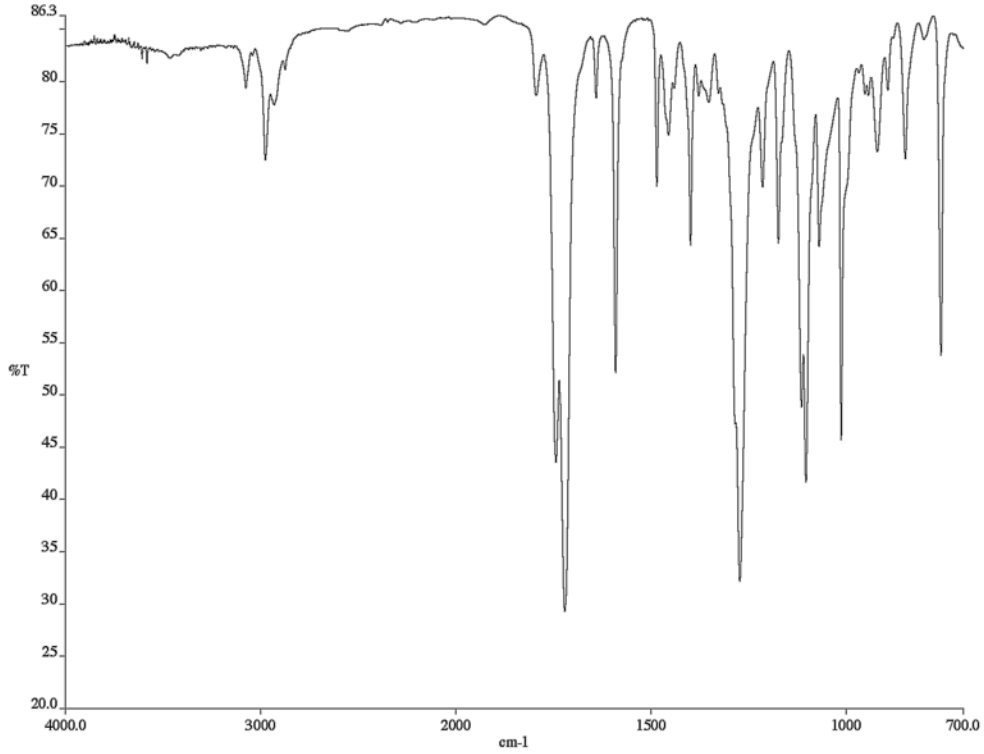


Figure A1.5.2 Infrared spectrum (thin film/NaCl) of compound **69**.

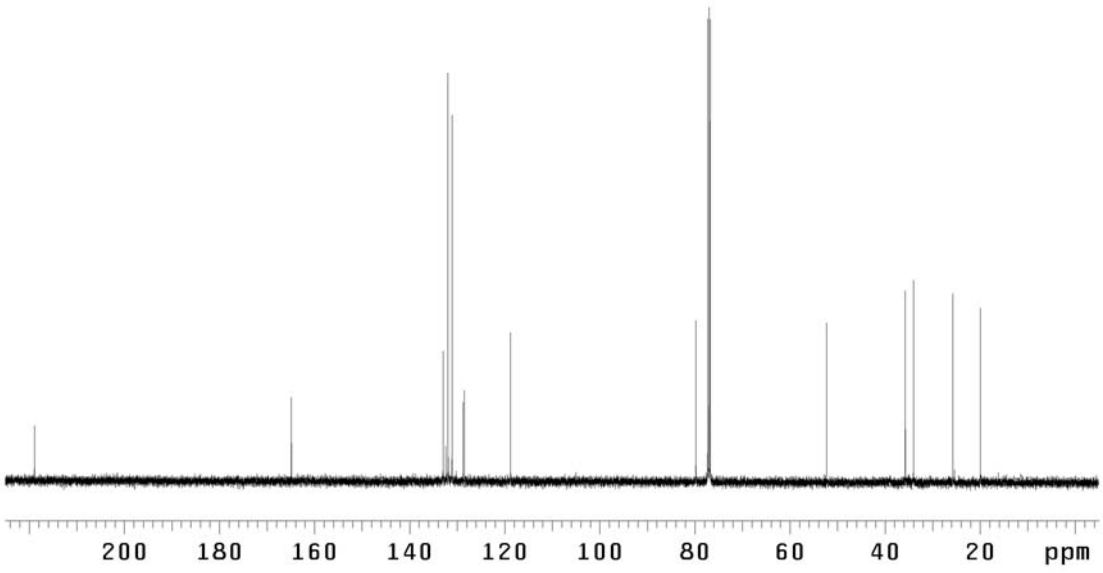


Figure A1.5.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **69**.

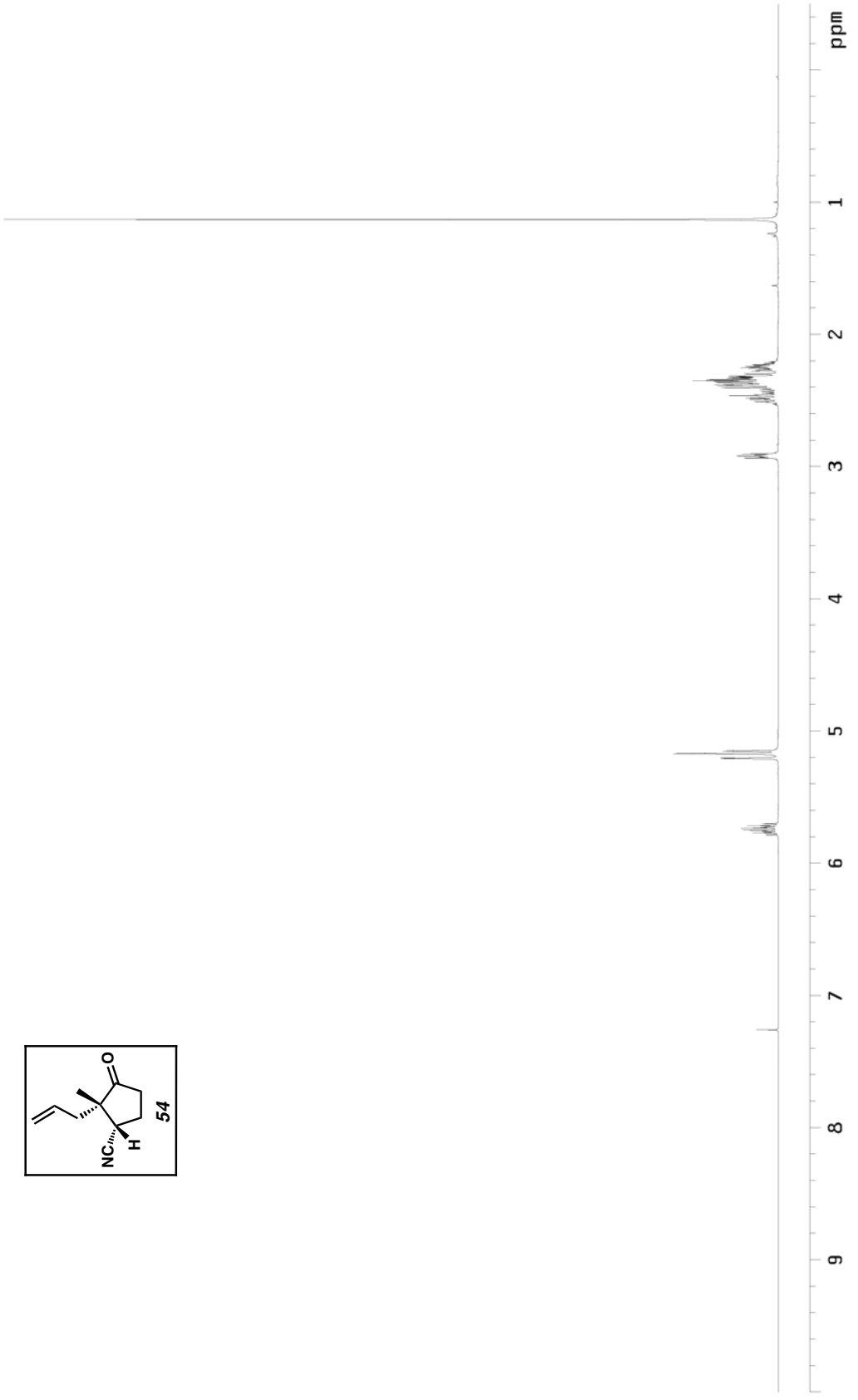


Figure A1.6.1 ^{1}H NMR (500 MHz, $CDCl_3$) of nitrile **54**.

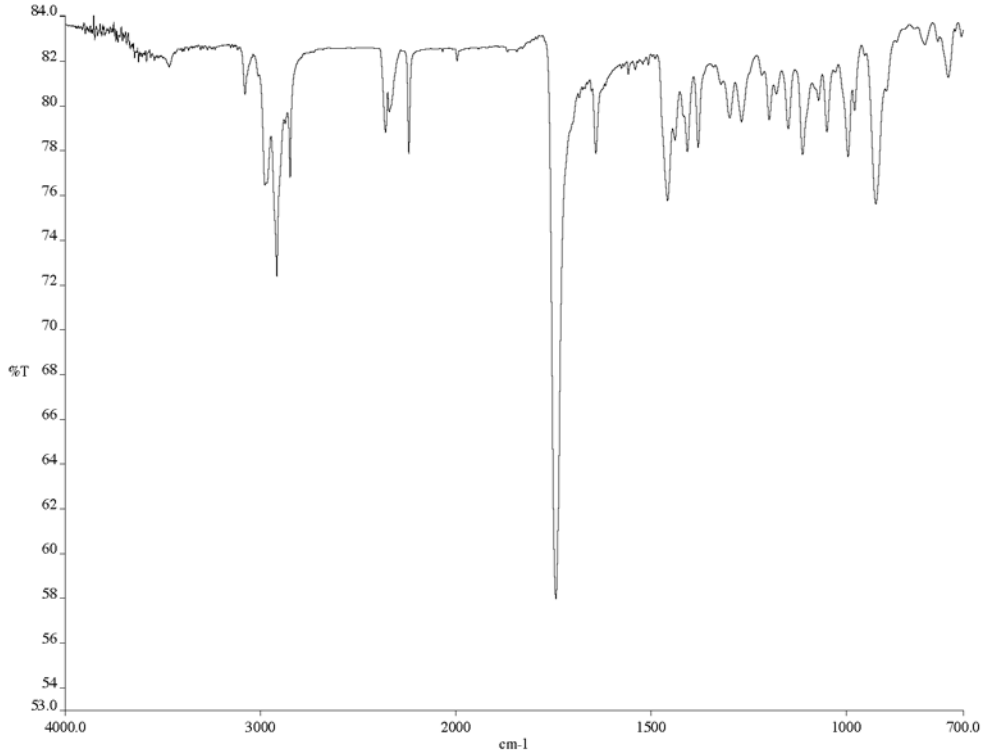


Figure A1.6.2 Infrared spectrum (thin film/NaCl) of nitrile **54**.

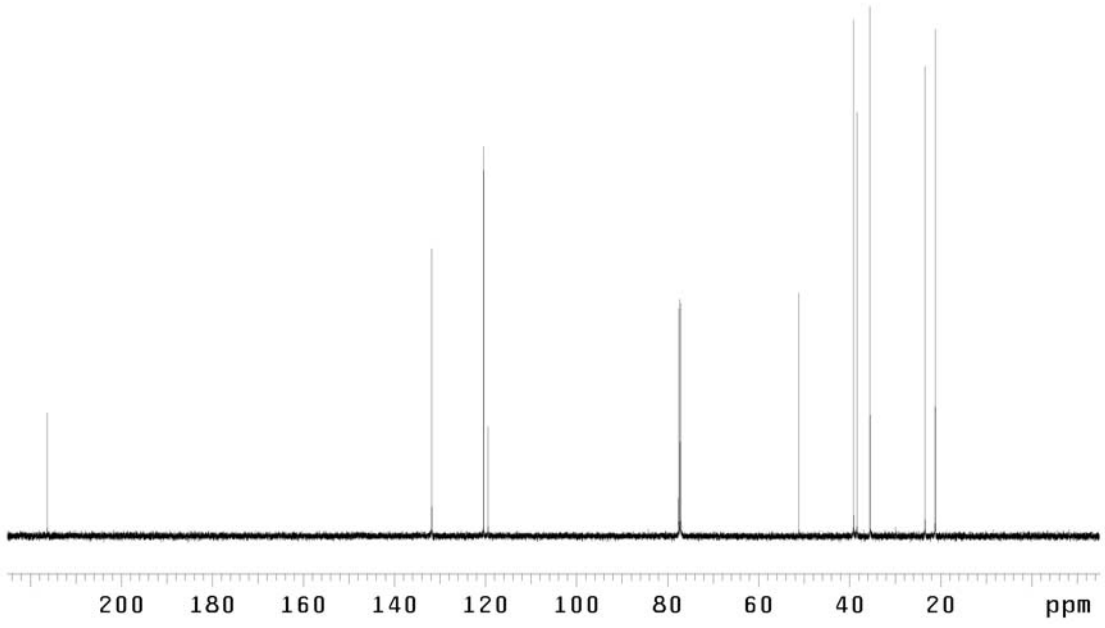


Figure A1.6.3 ^{13}C NMR (125 MHz, $CDCl_3$) of nitrile **54**.

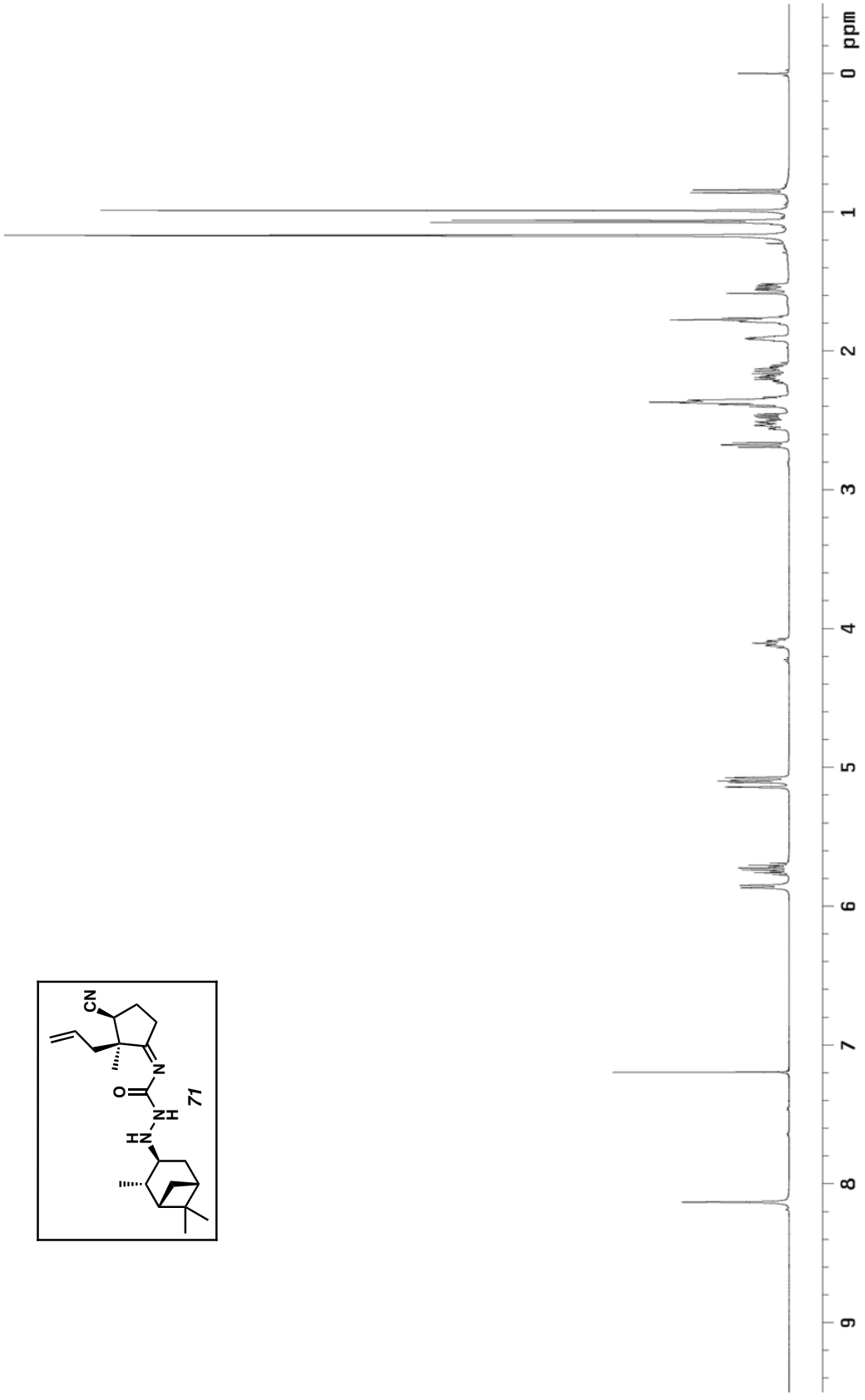


Figure A1.7.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **71**.

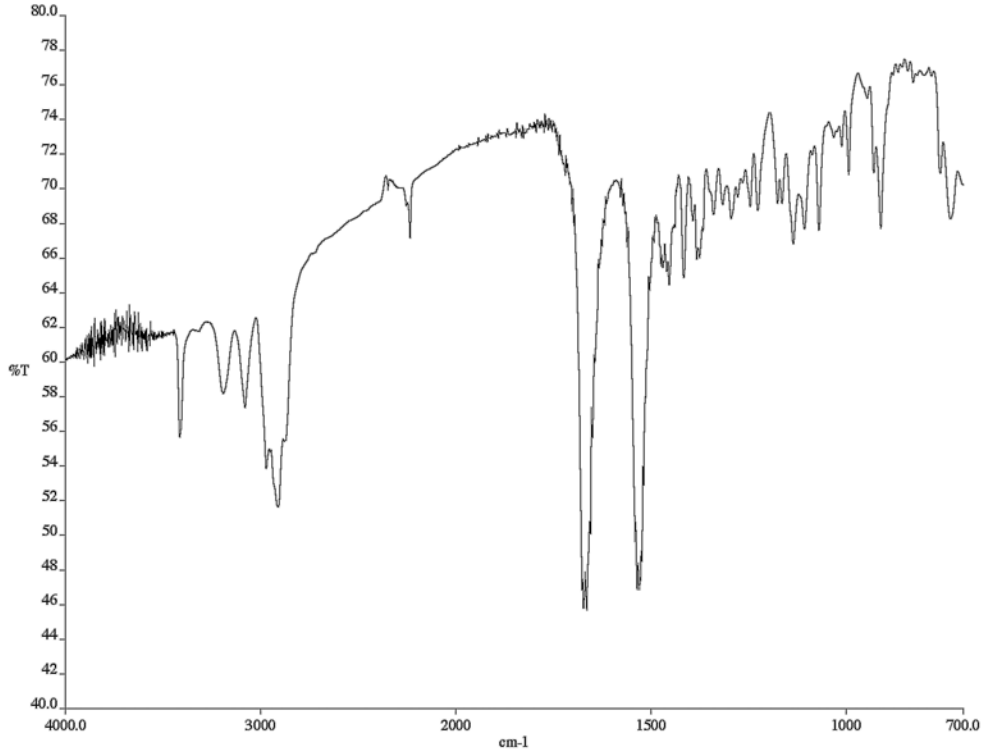


Figure A1.7.2 Infrared spectrum (thin film/NaCl) of compound **71**.

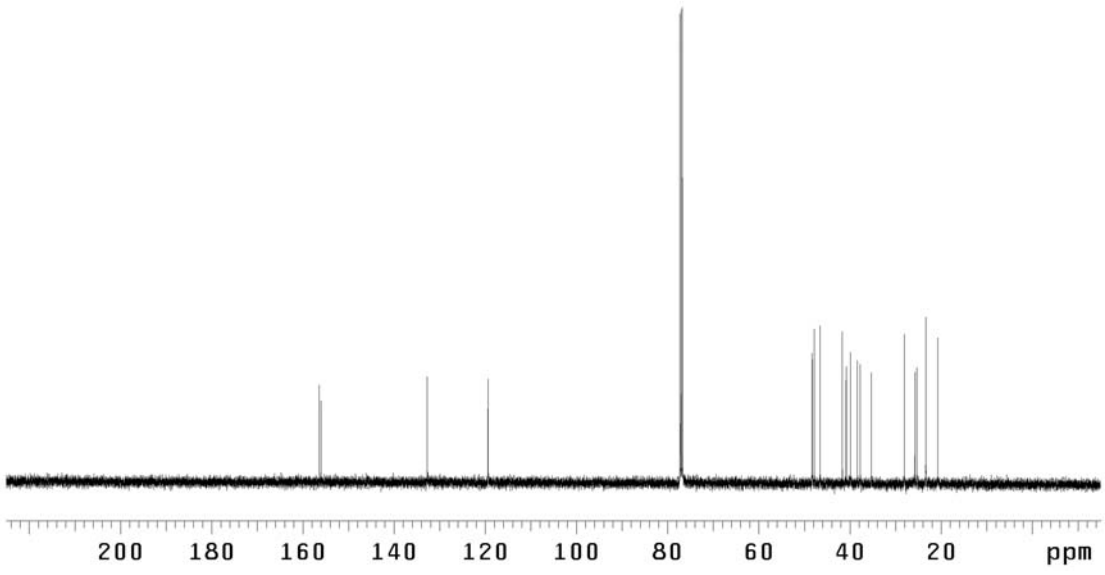


Figure A1.7.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **71**.

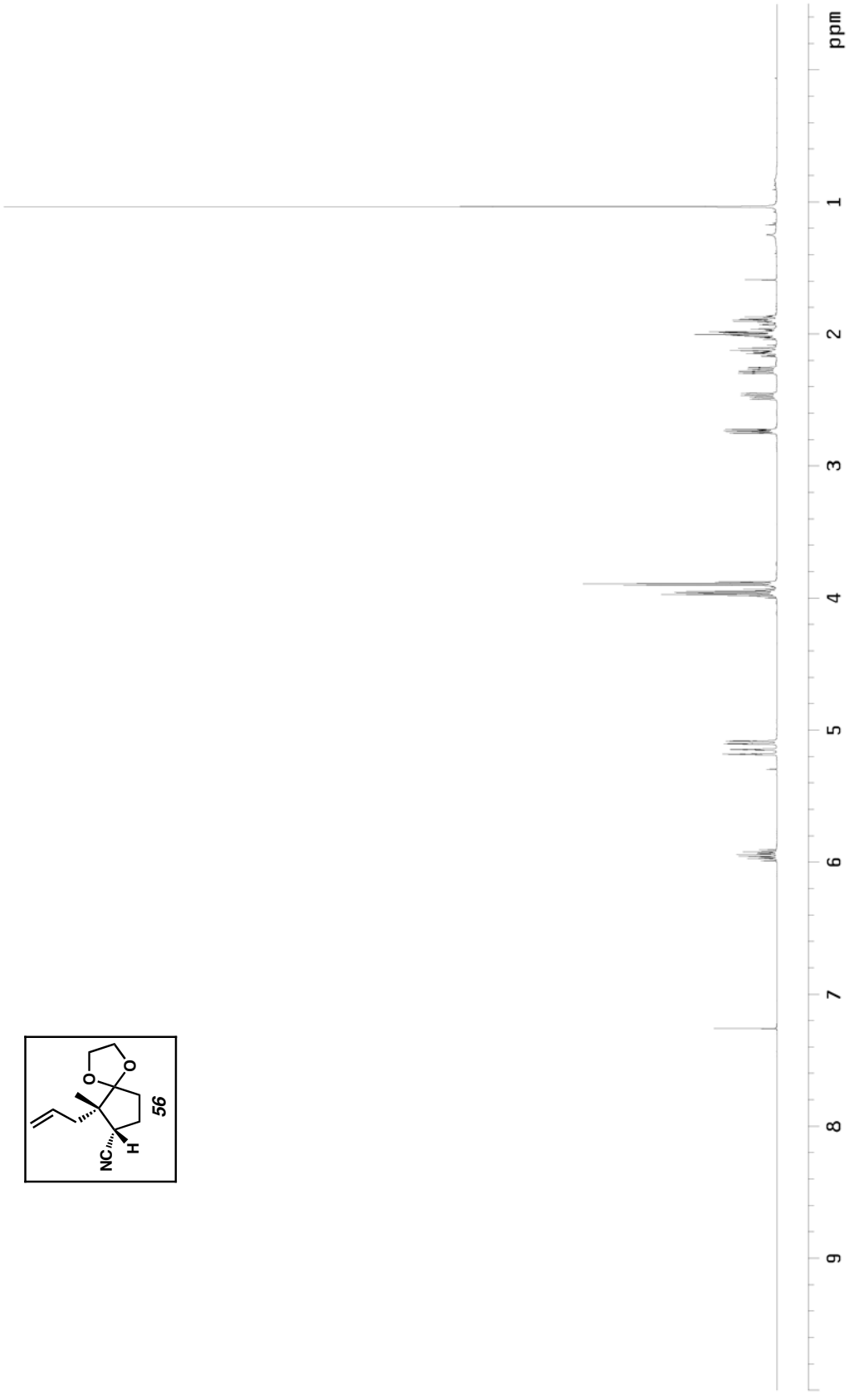


Figure A1.8.1 ^{1}H NMR (500 MHz, $CDCl_3$) of ketal **56**.

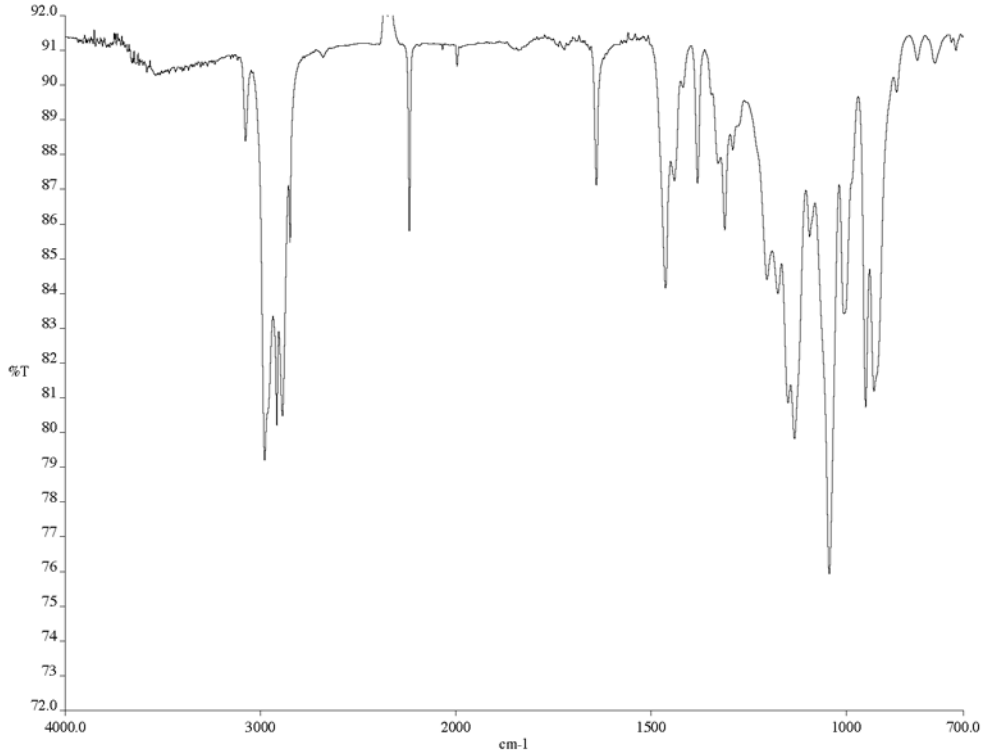


Figure A1.8.2 Infrared spectrum (thin film/NaCl) of ketal **56**.

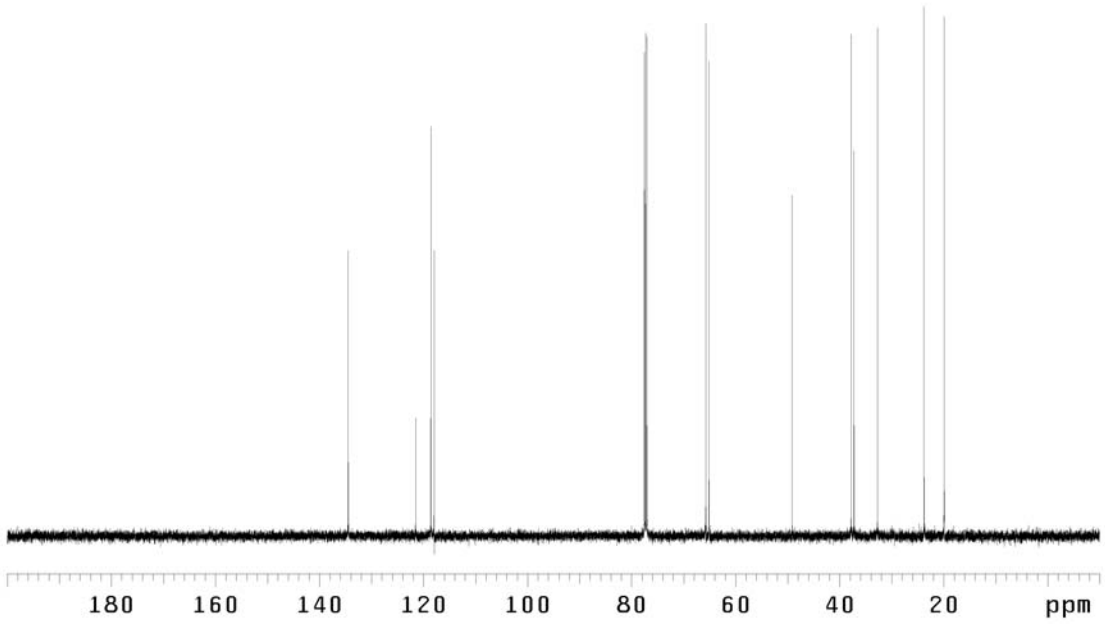


Figure A1.8.3 ^{13}C NMR (125 MHz, $CDCl_3$) of ketal **56**.

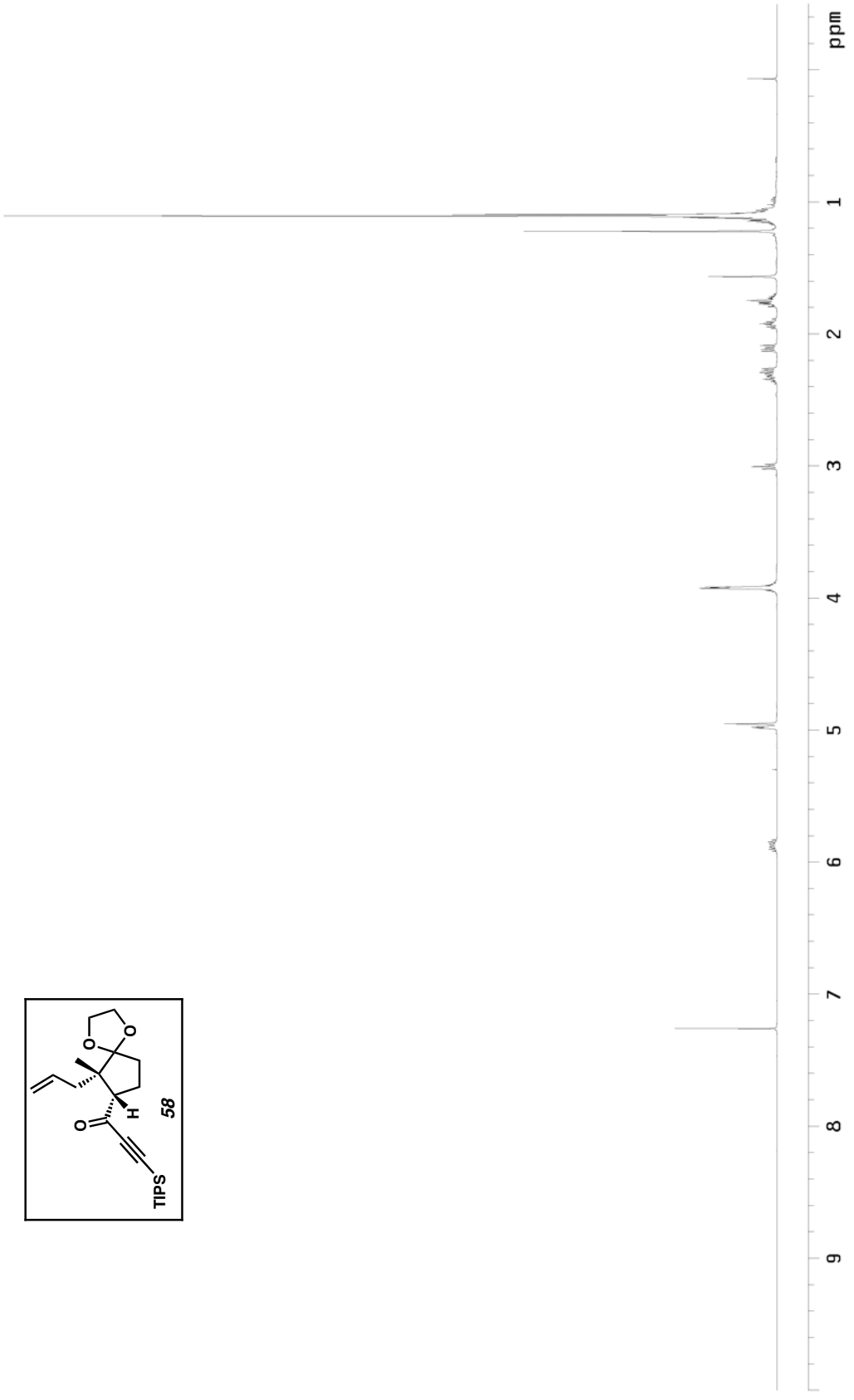


Figure A1.9.1 ^{1}H NMR (500 MHz, $CDCl_3$) of ynone **58**.

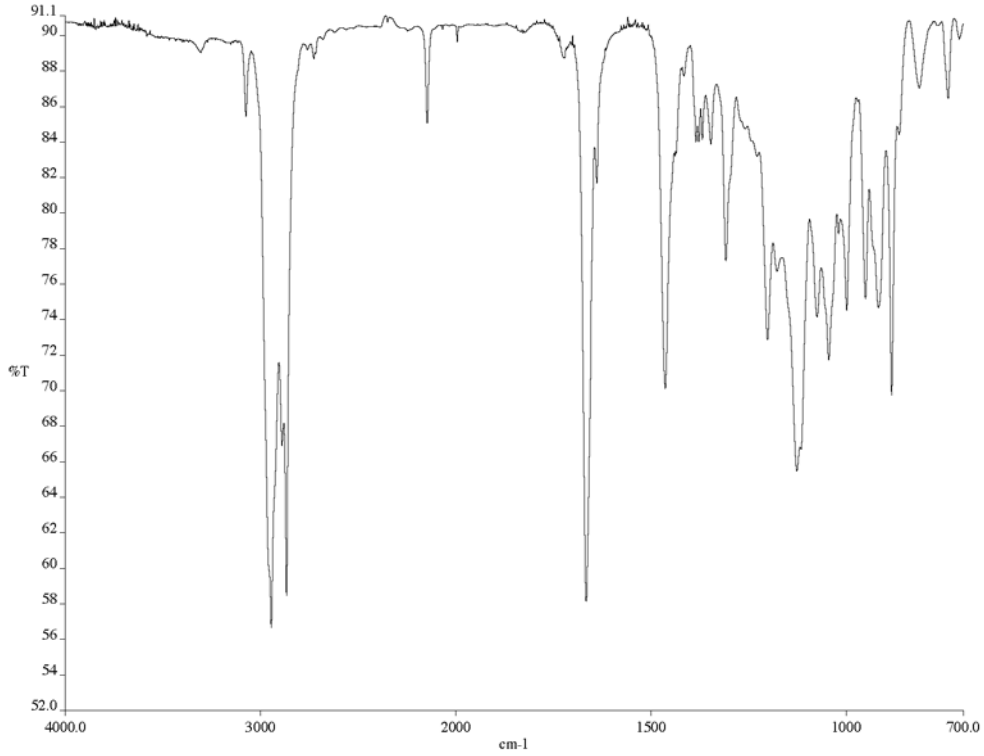


Figure A1.9.2 Infrared spectrum (thin film/NaCl) of ynone **58**.

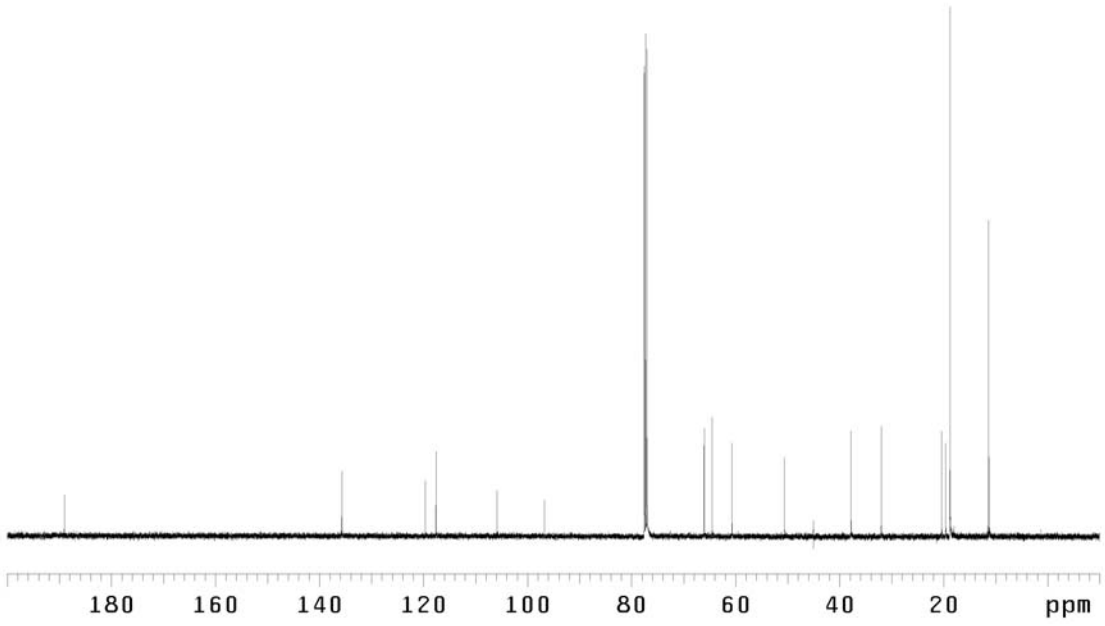


Figure A1.9.3 ^{13}C NMR (125 MHz, $CDCl_3$) of ynone **58**.

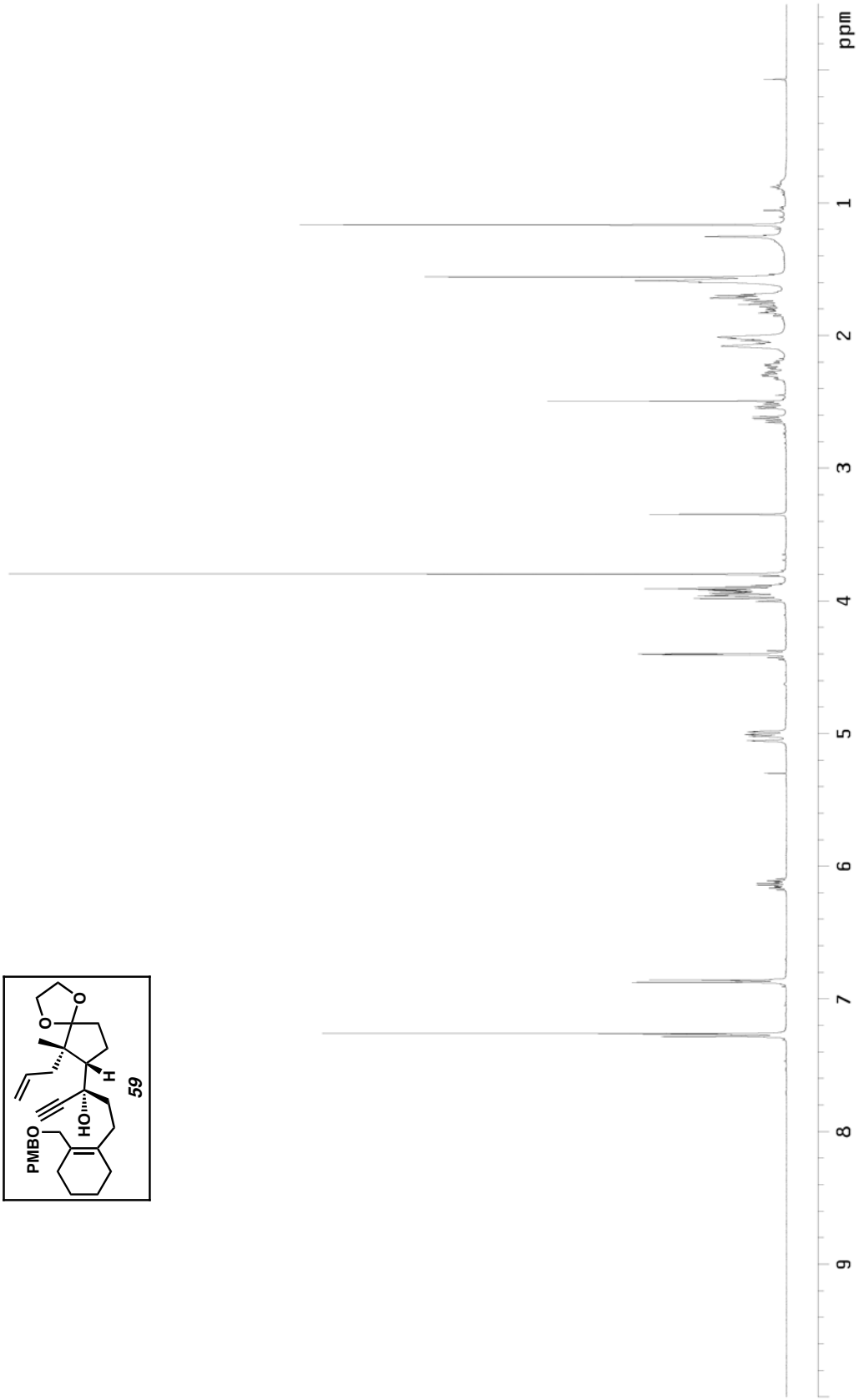


Figure A1.10.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **59**.

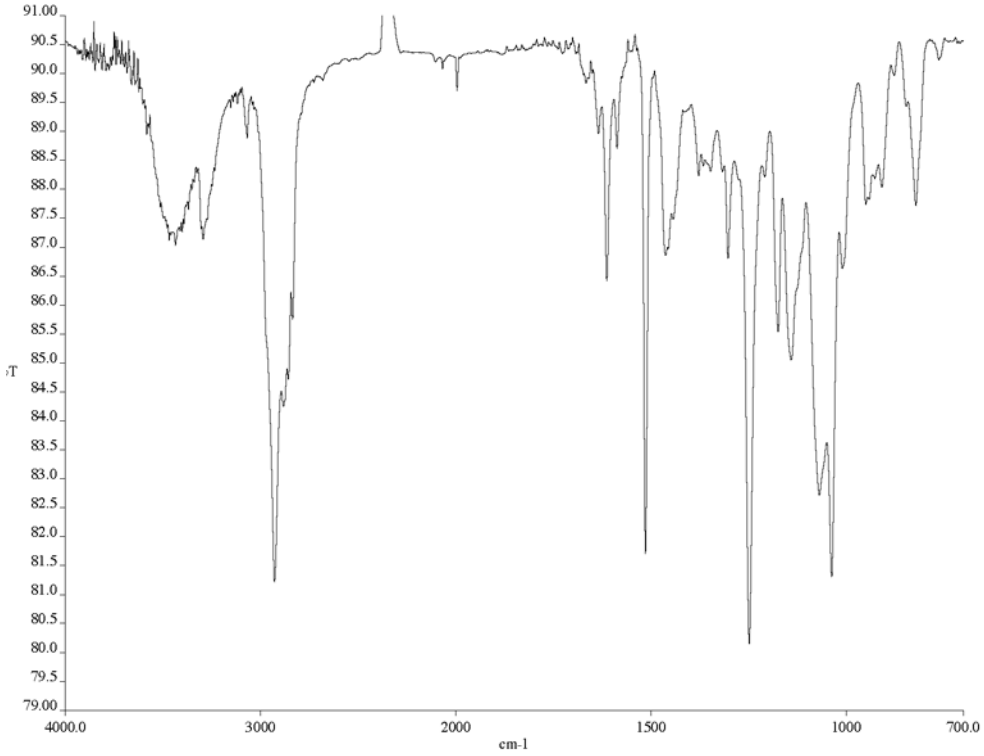


Figure A1.10.2 Infrared spectrum (thin film/NaCl) of compound **59**.

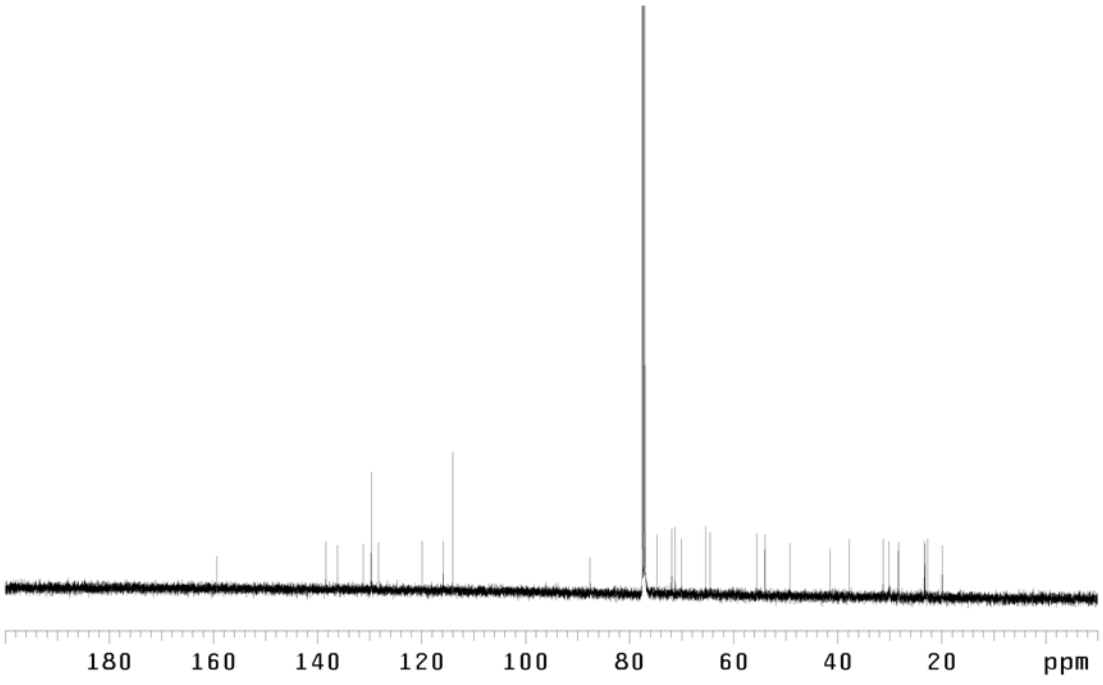


Figure A1.10.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **59**.

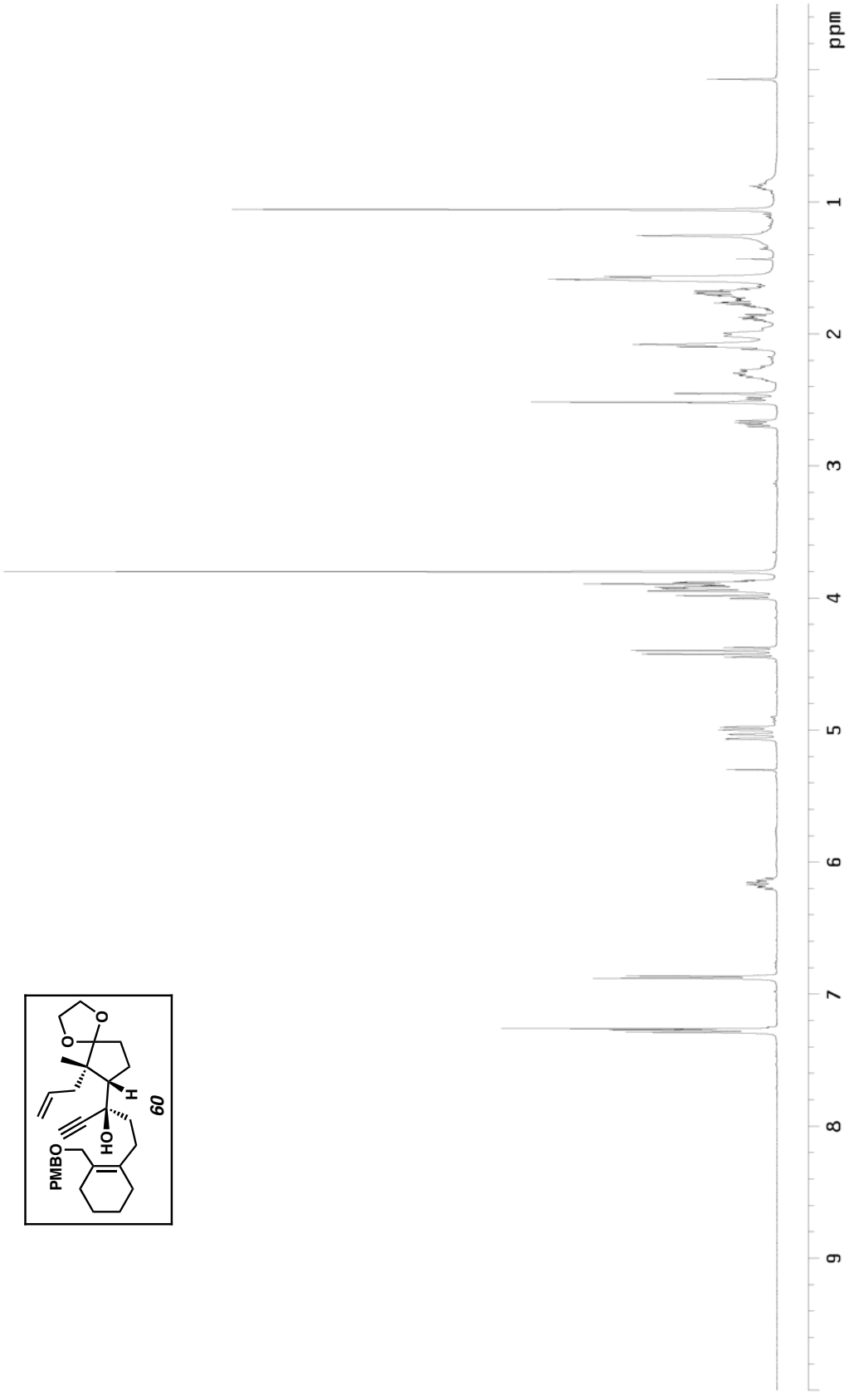


Figure A1.11.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **60**.

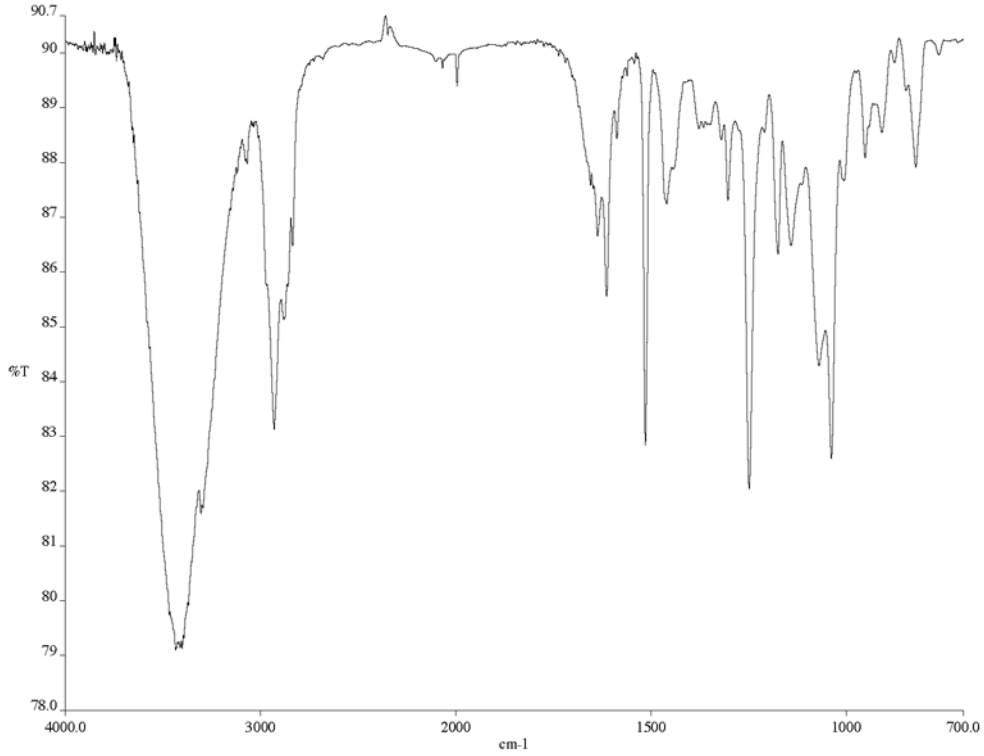


Figure A1.11.2 Infrared spectrum (thin film/NaCl) of compound **60**.

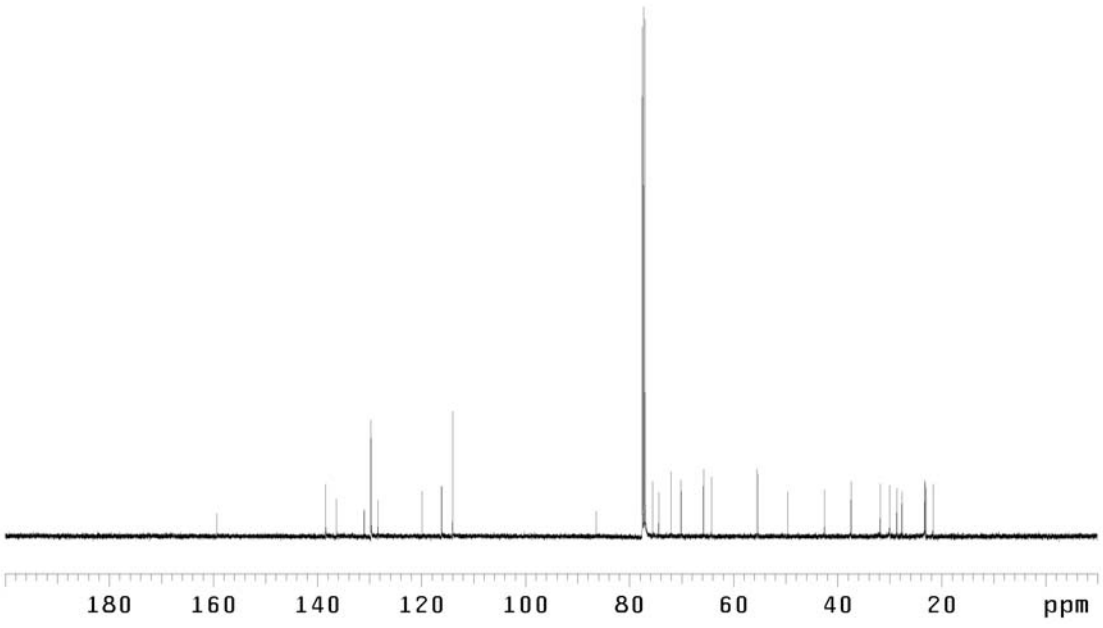


Figure A1.11.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **60**.

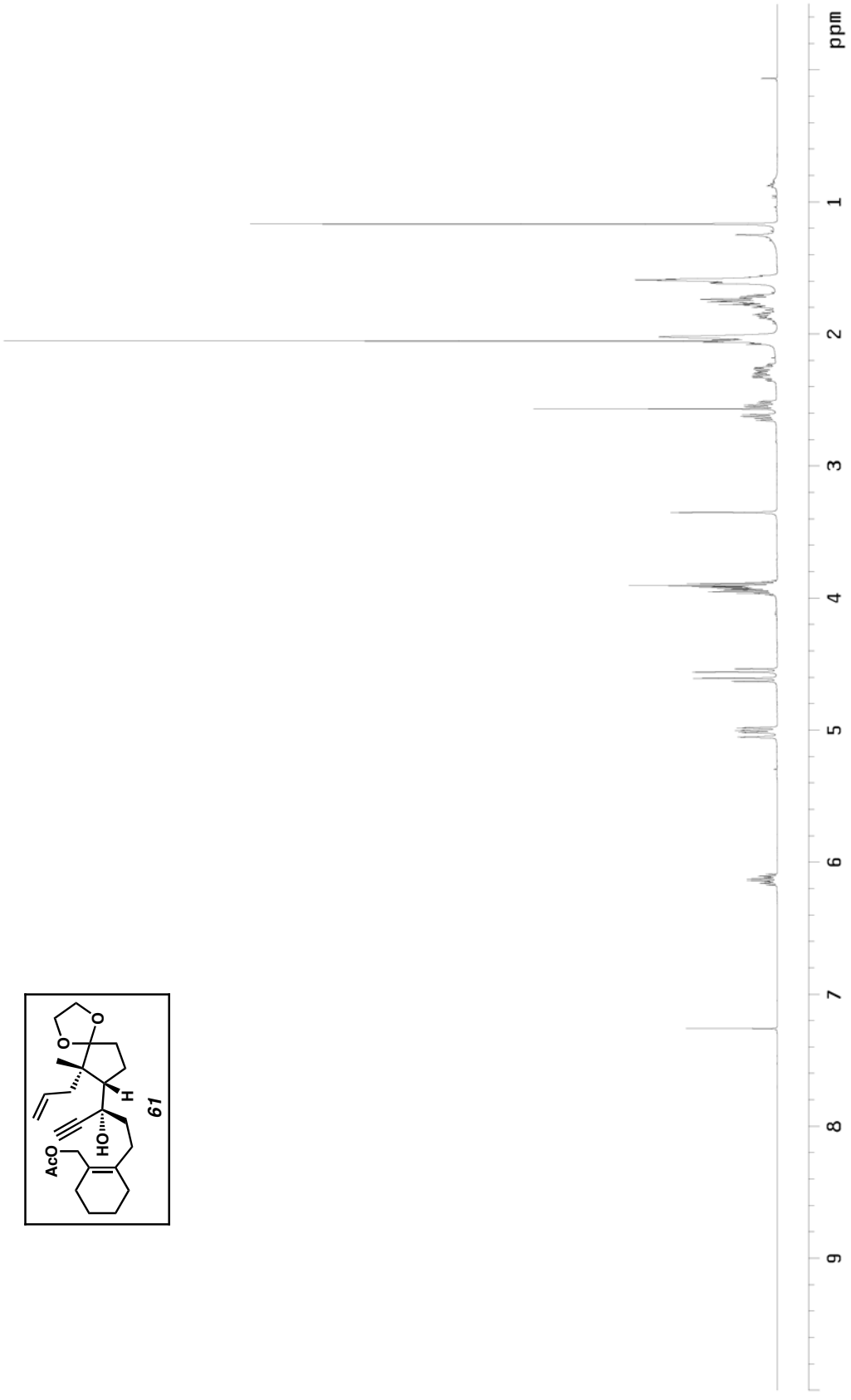


Figure A1.12.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **61**.

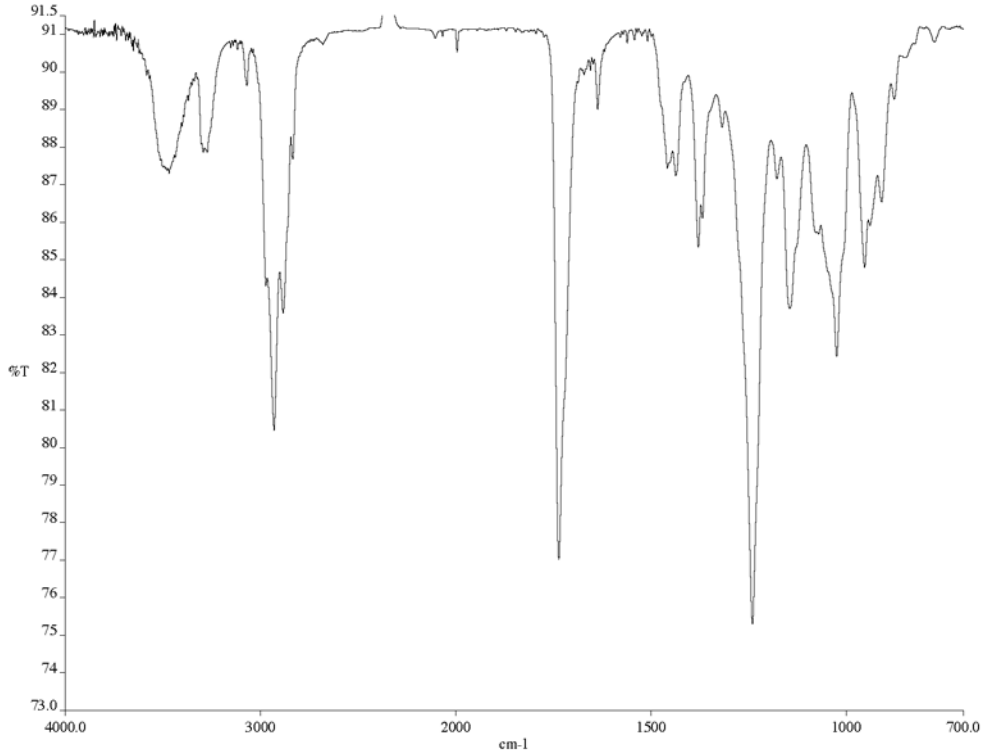


Figure A1.12.2 Infrared spectrum (thin film/NaCl) of compound **61**.

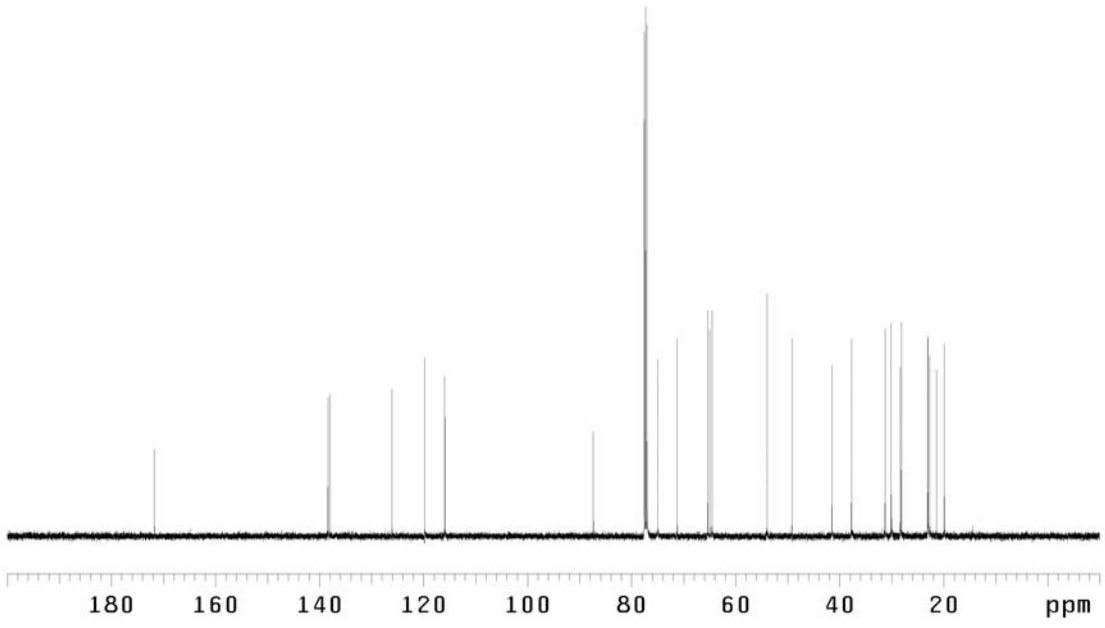


Figure A1.12.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **61**.

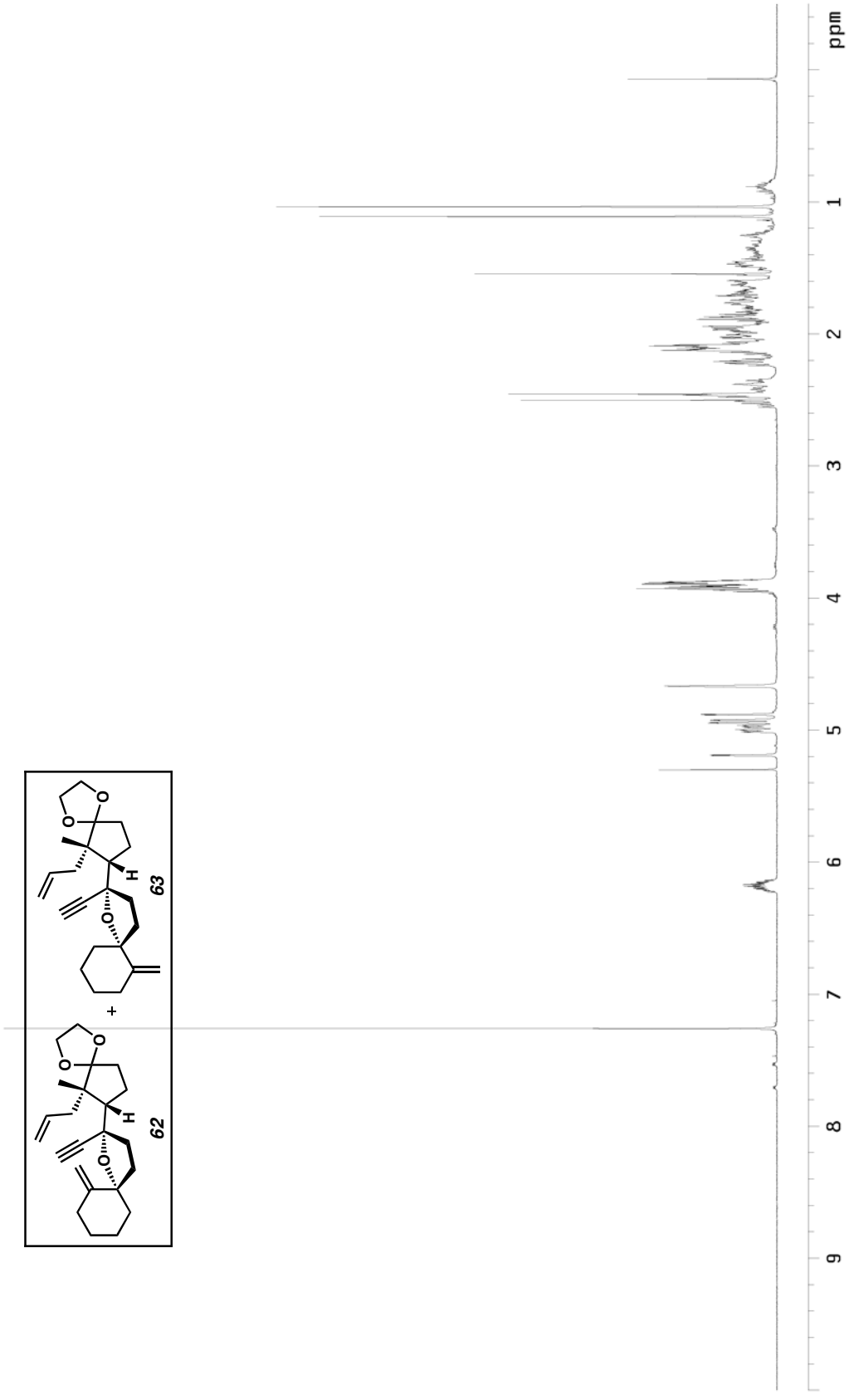


Figure A1.13.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **62** and **63**.

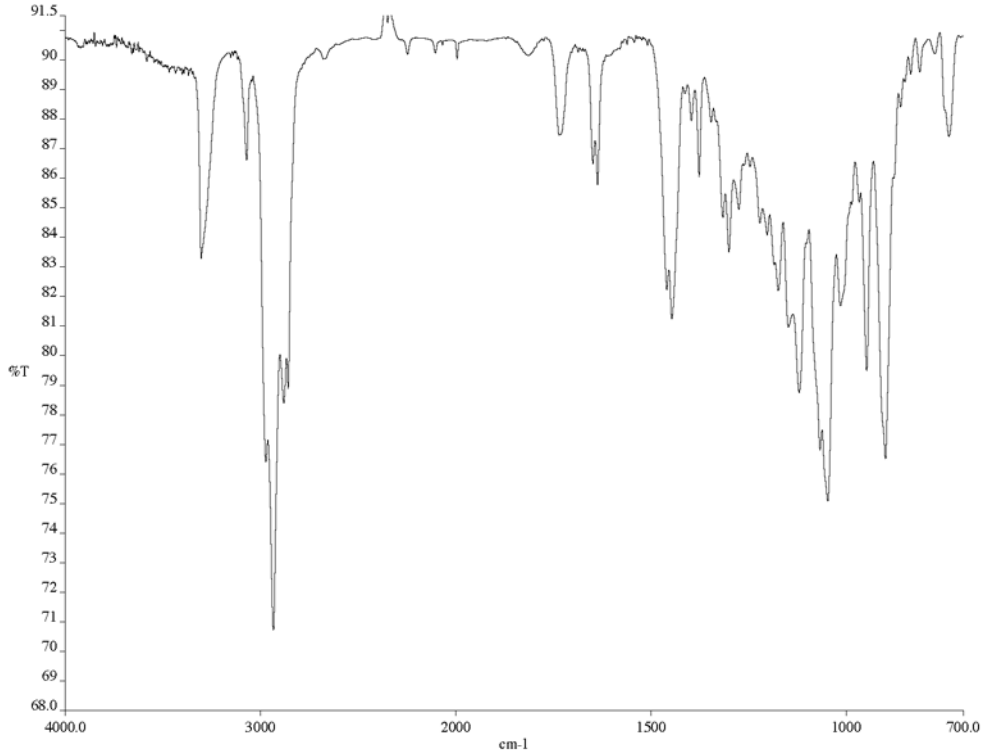


Figure A1.13.2 Infrared spectrum (thin film/NaCl) of compounds **62** and **63**.

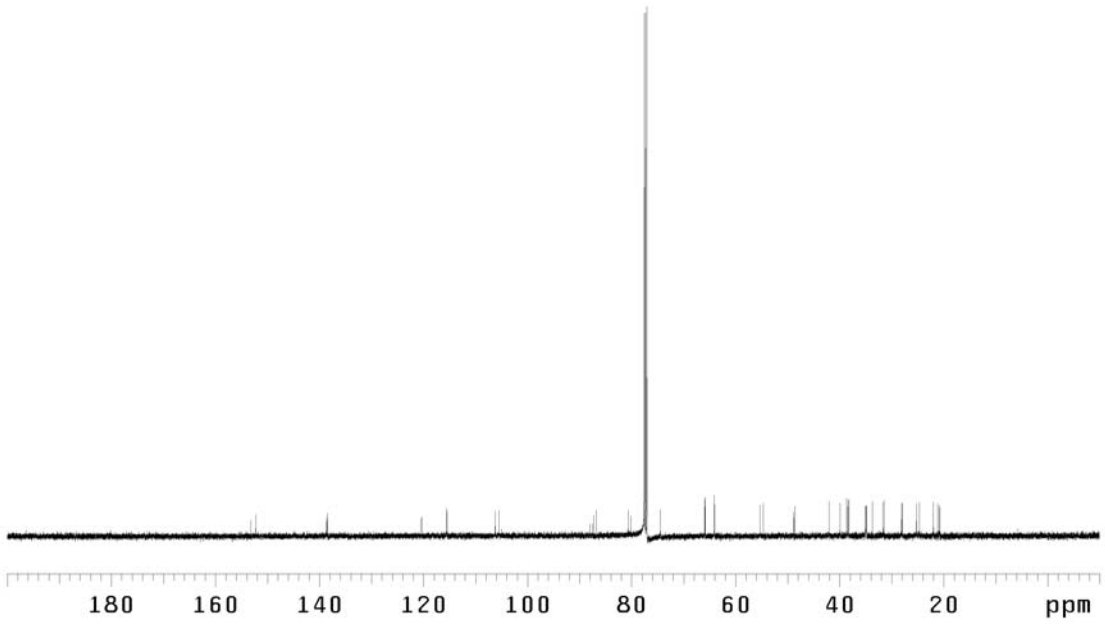


Figure A1.13.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **62** and **63**.

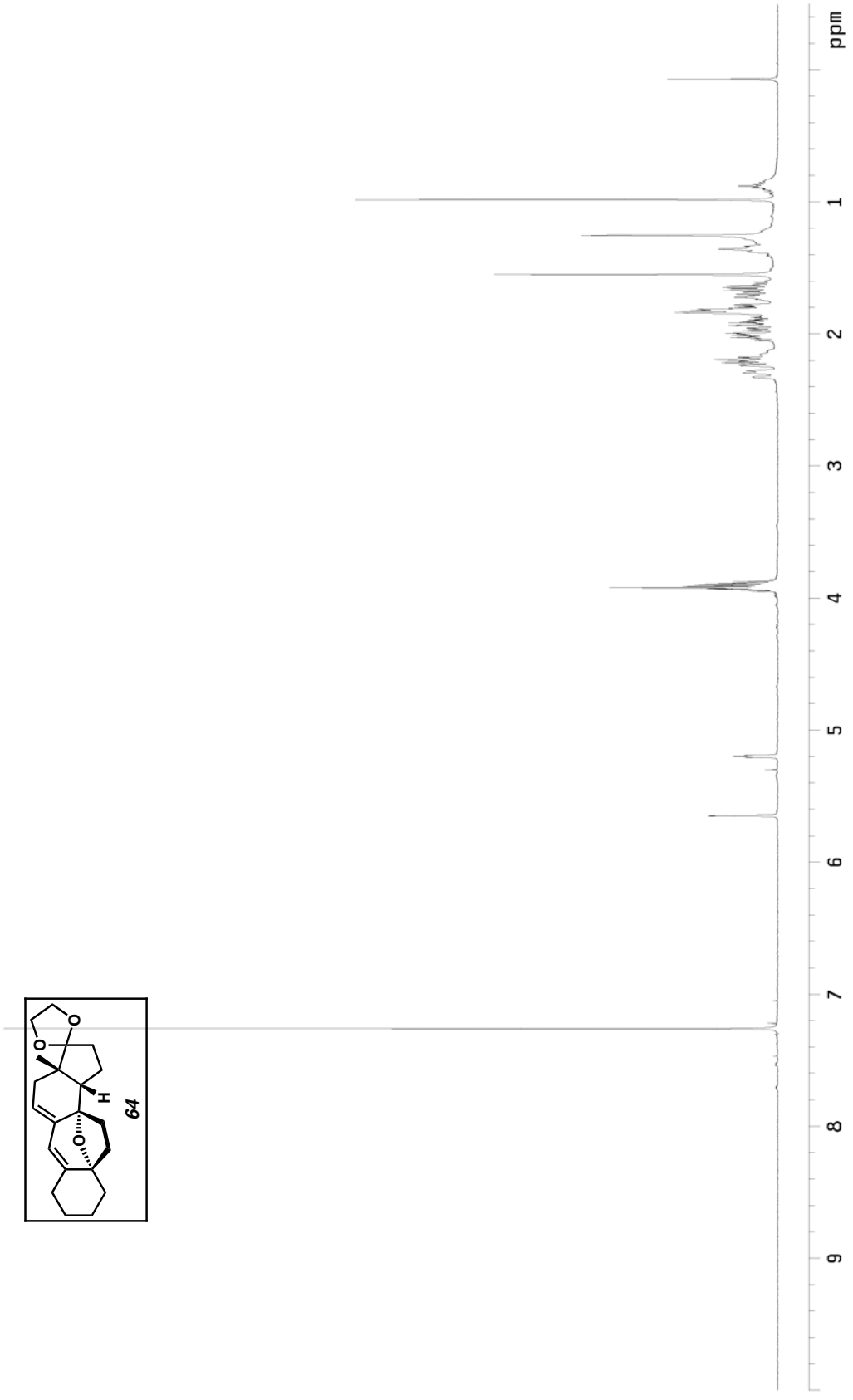


Figure A1.14.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **64**.

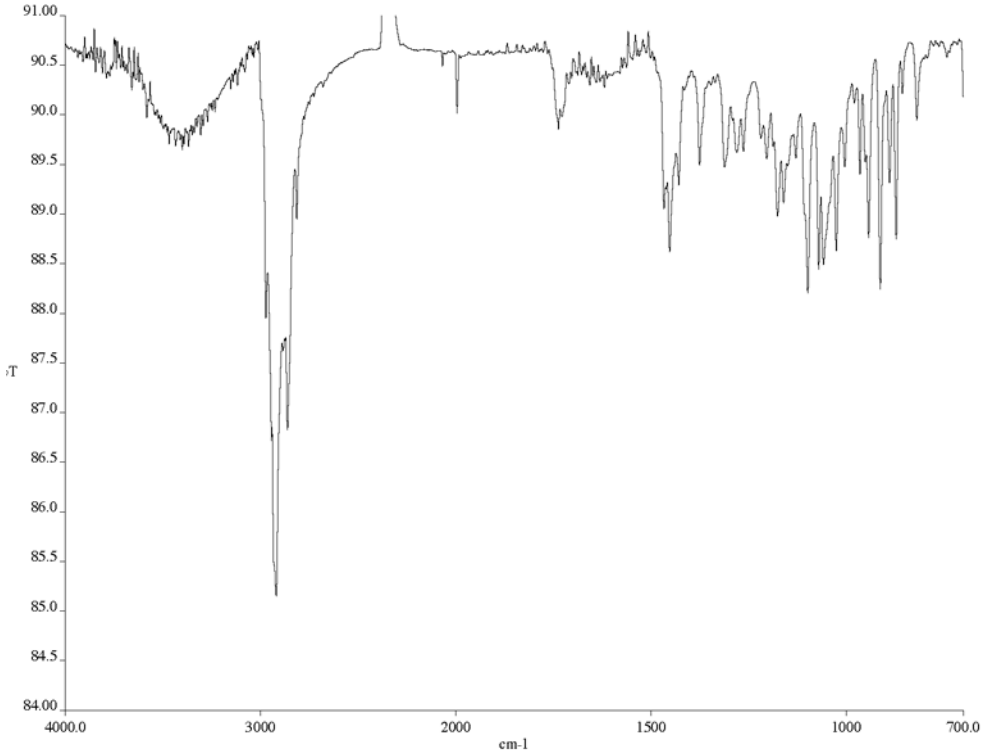


Figure A1.14.2 Infrared spectrum (thin film/NaCl) of compound **64**.

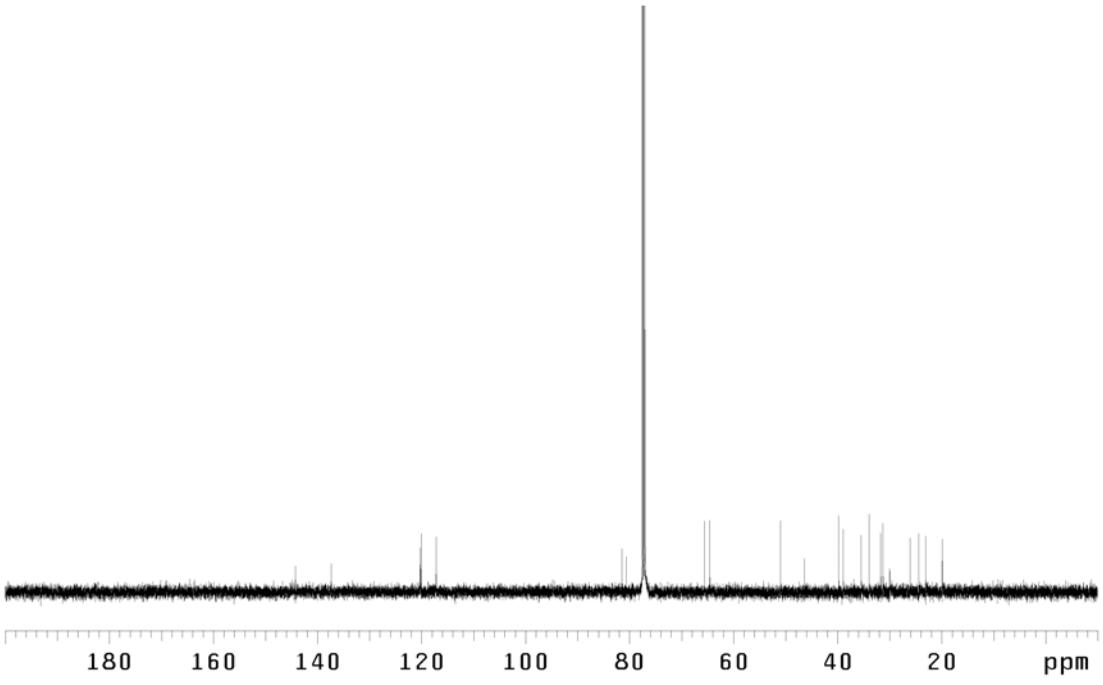


Figure A1.14.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **64**.

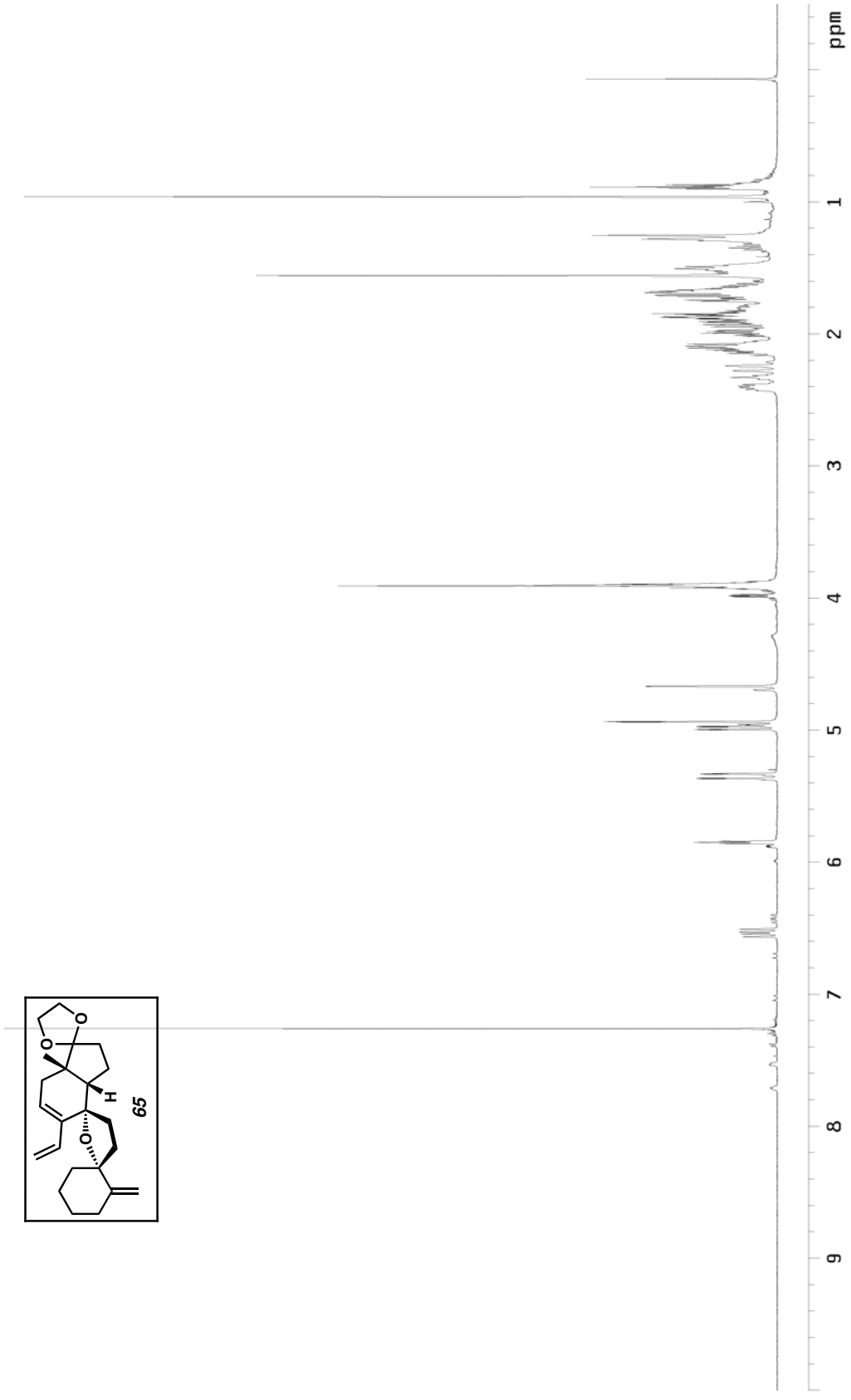


Figure A1.15.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **65**.

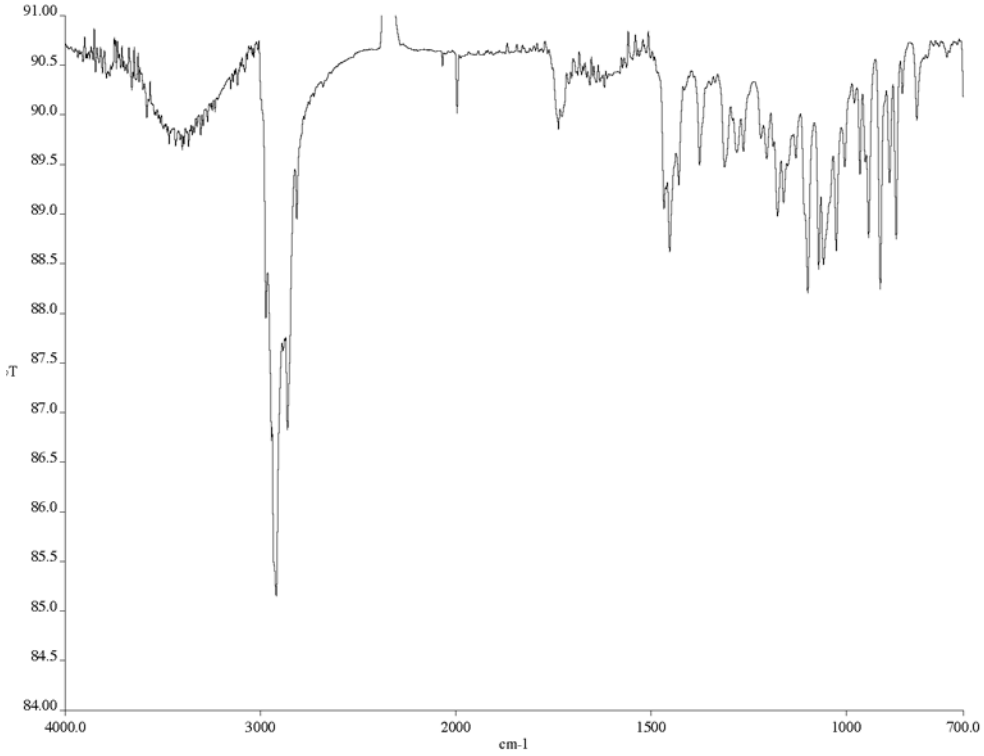


Figure A1.15.2 Infrared spectrum (thin film/NaCl) of compound **65**.

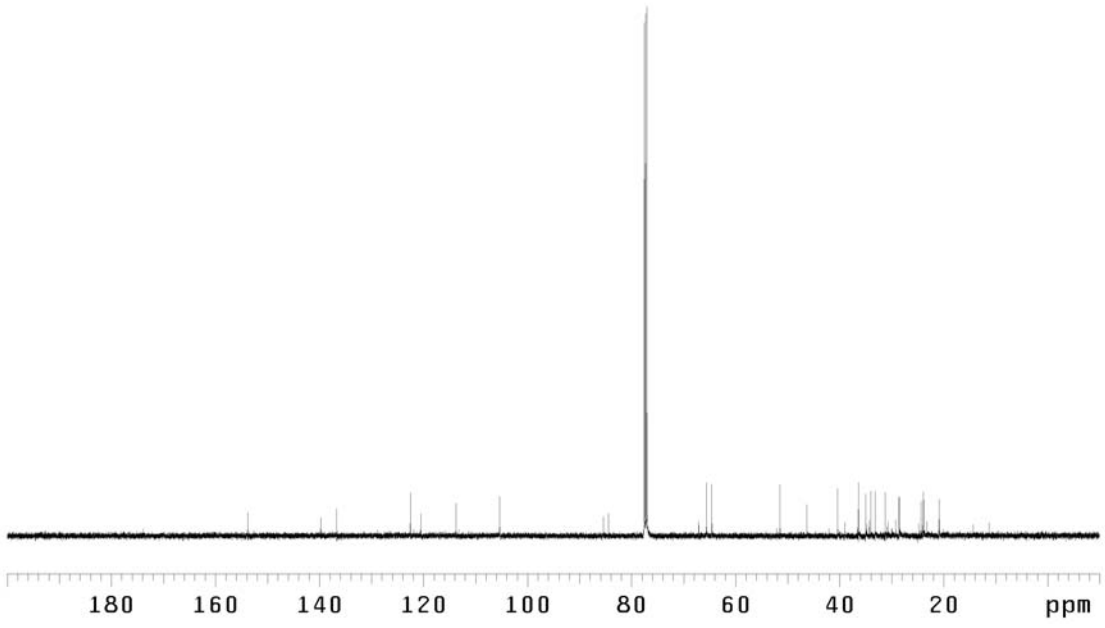


Figure A1.15.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **65**.

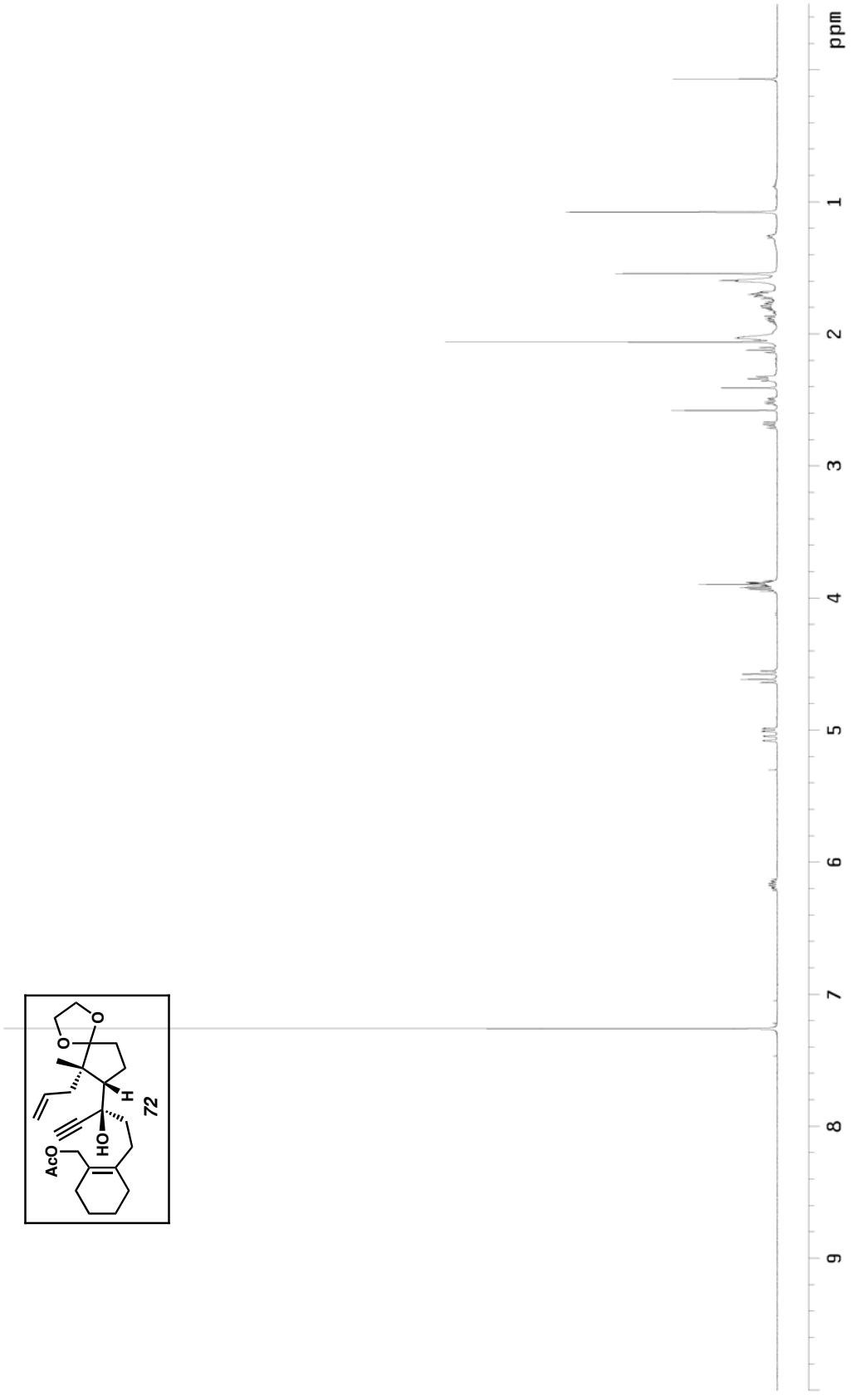


Figure A1.16.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **72**.

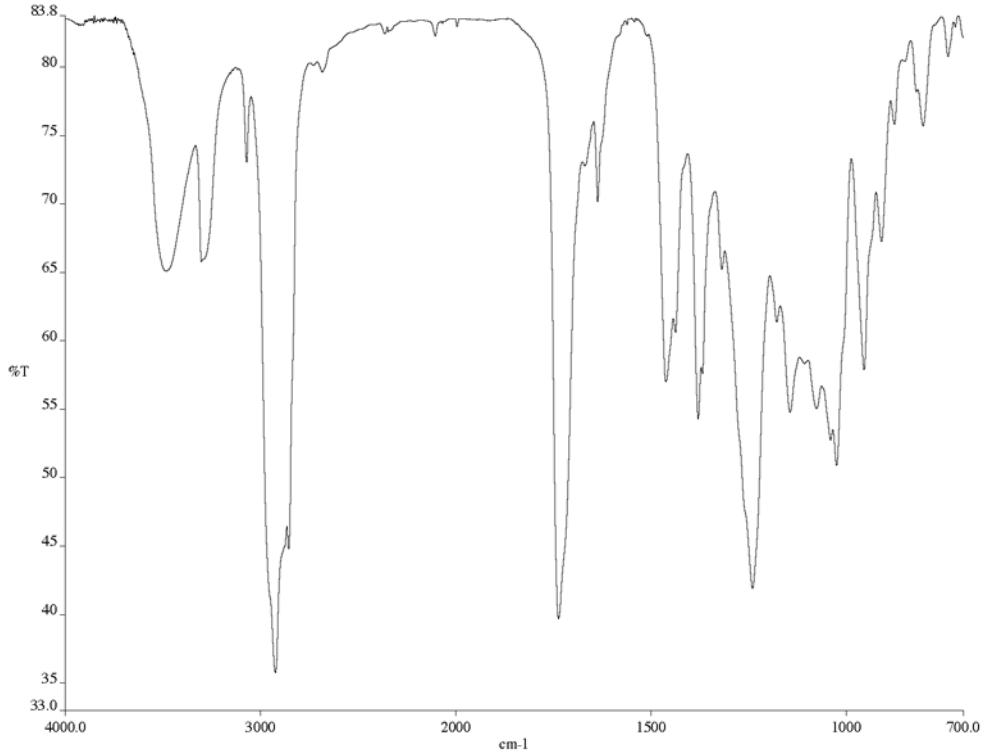


Figure A1.16.2 Infrared spectrum (thin film/NaCl) of compound **72**.

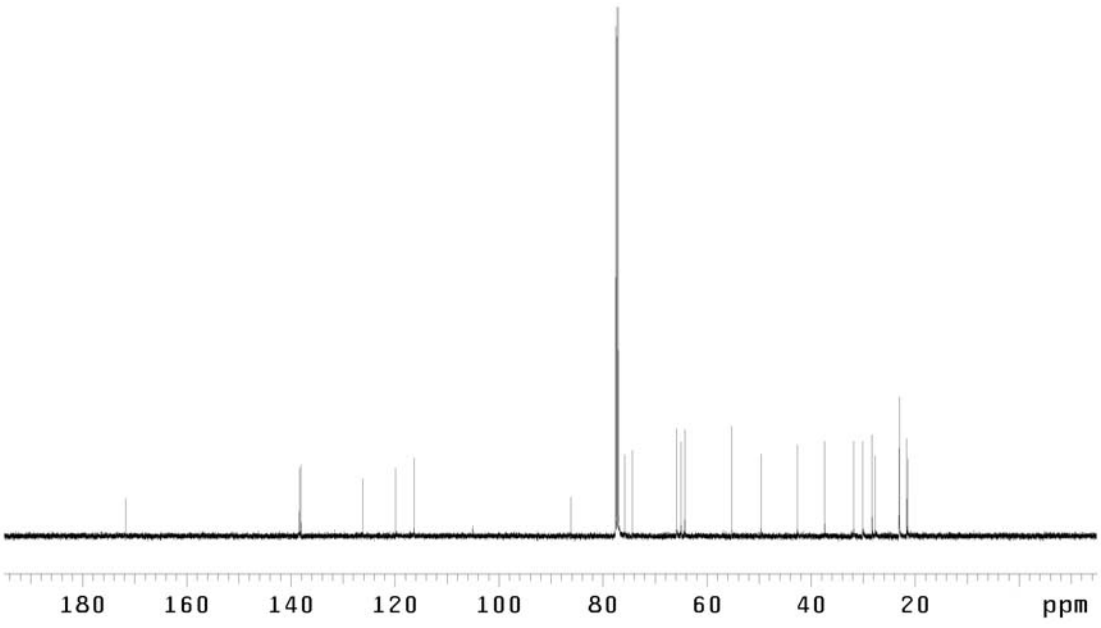


Figure A1.16.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **72**.

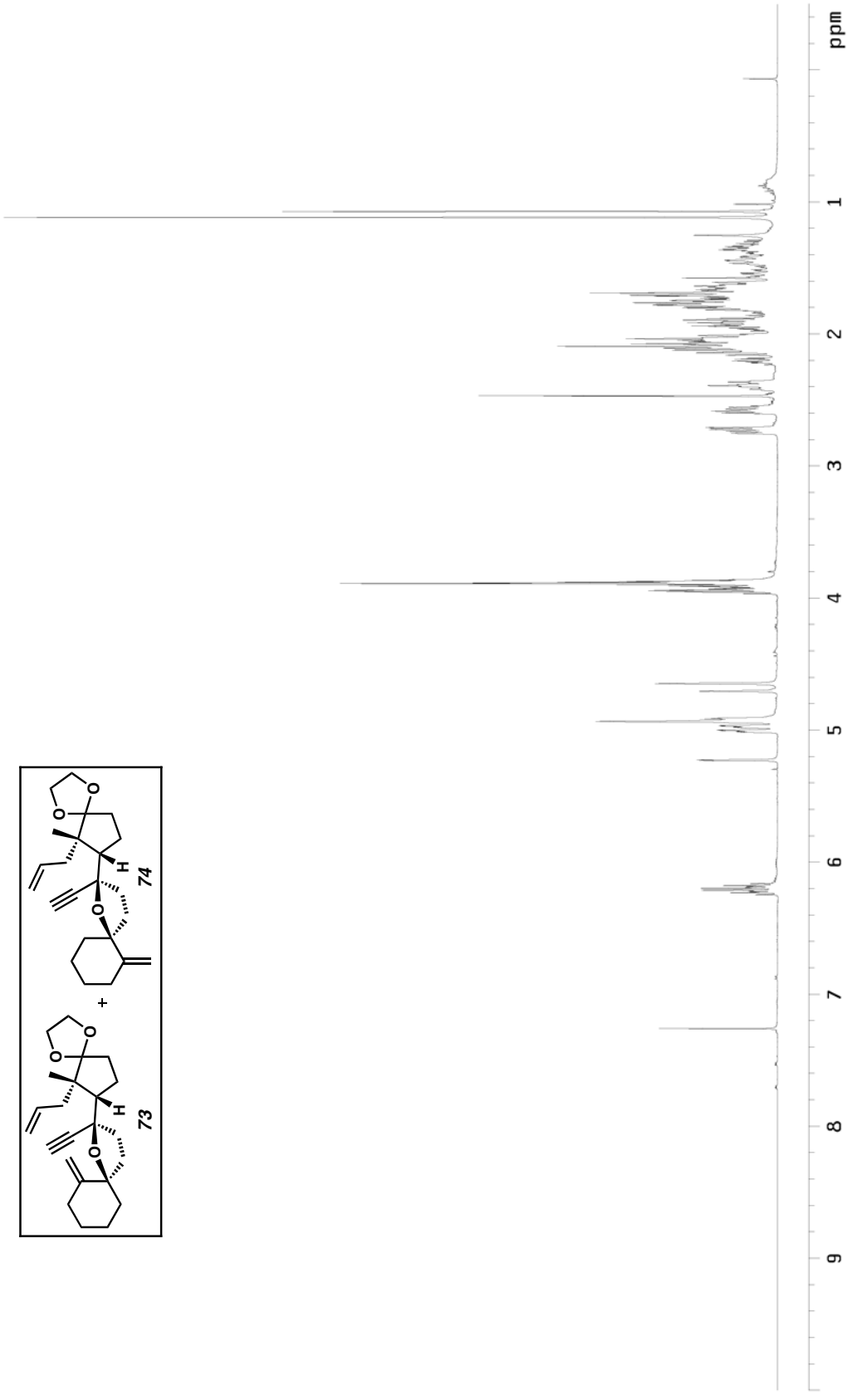


Figure A1.17.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **73** and **74**.

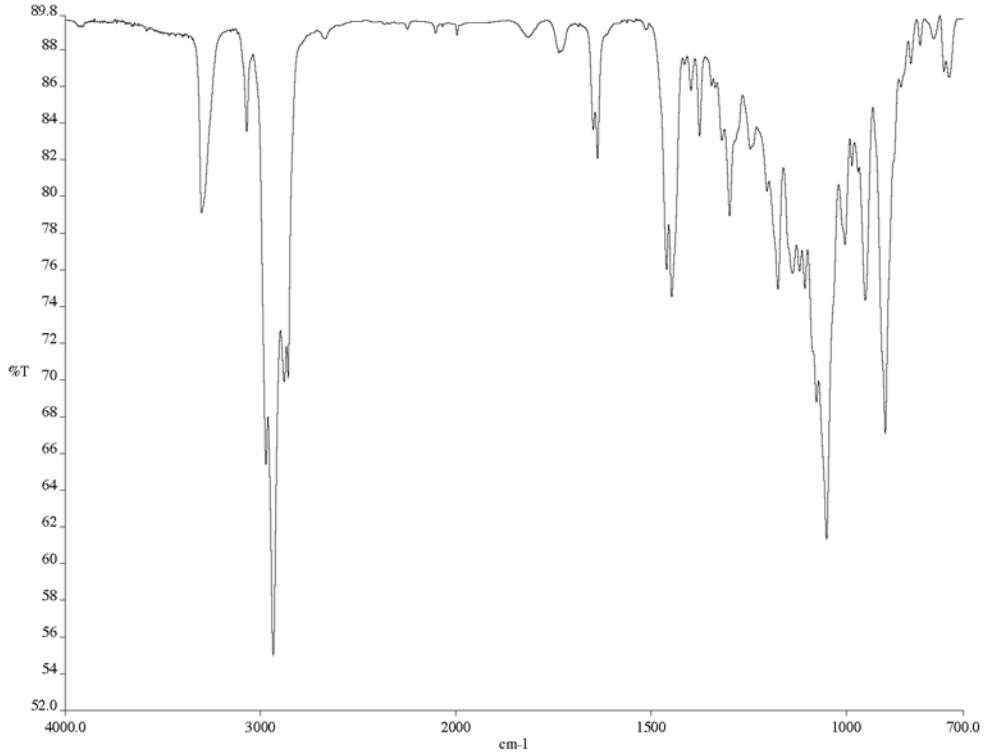


Figure A1.17.2 Infrared spectrum (thin film/NaCl) of compounds **73** and **74**.

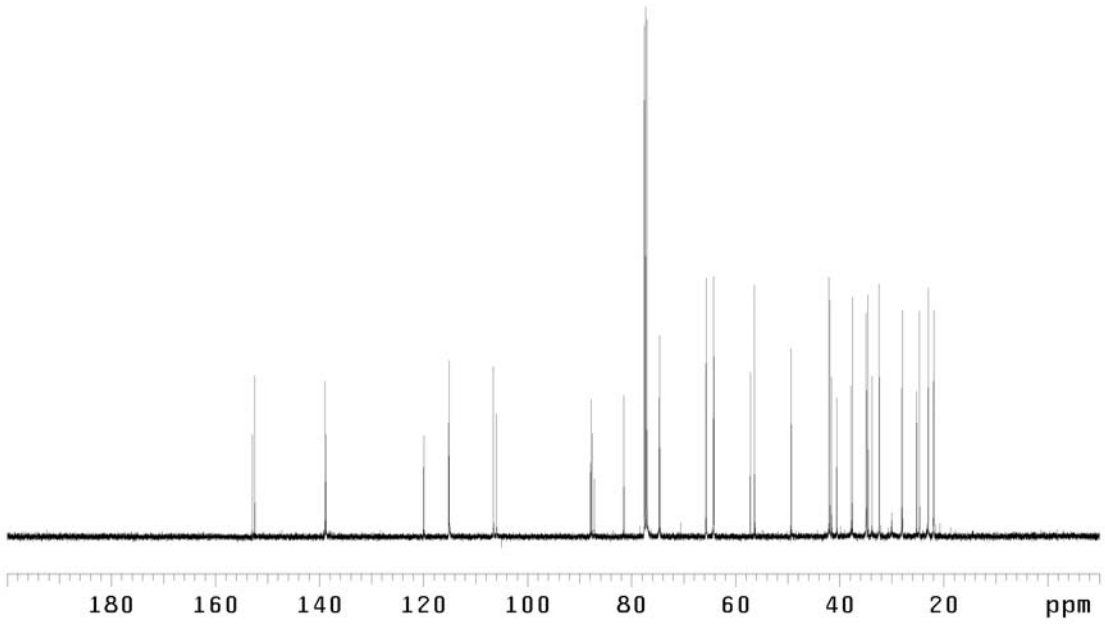


Figure A1.17.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **73** and **74**.

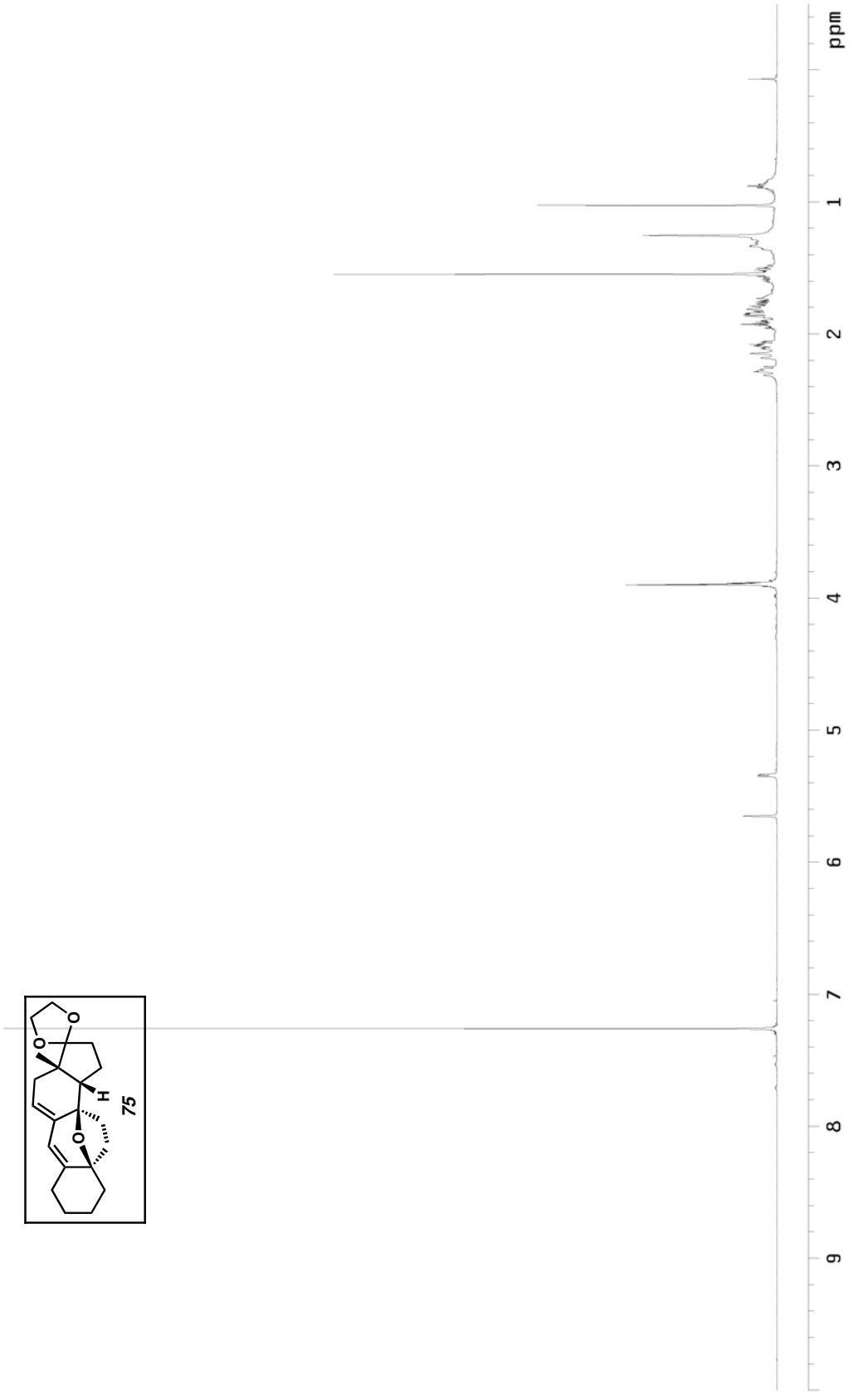


Figure A1.18.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **75**.

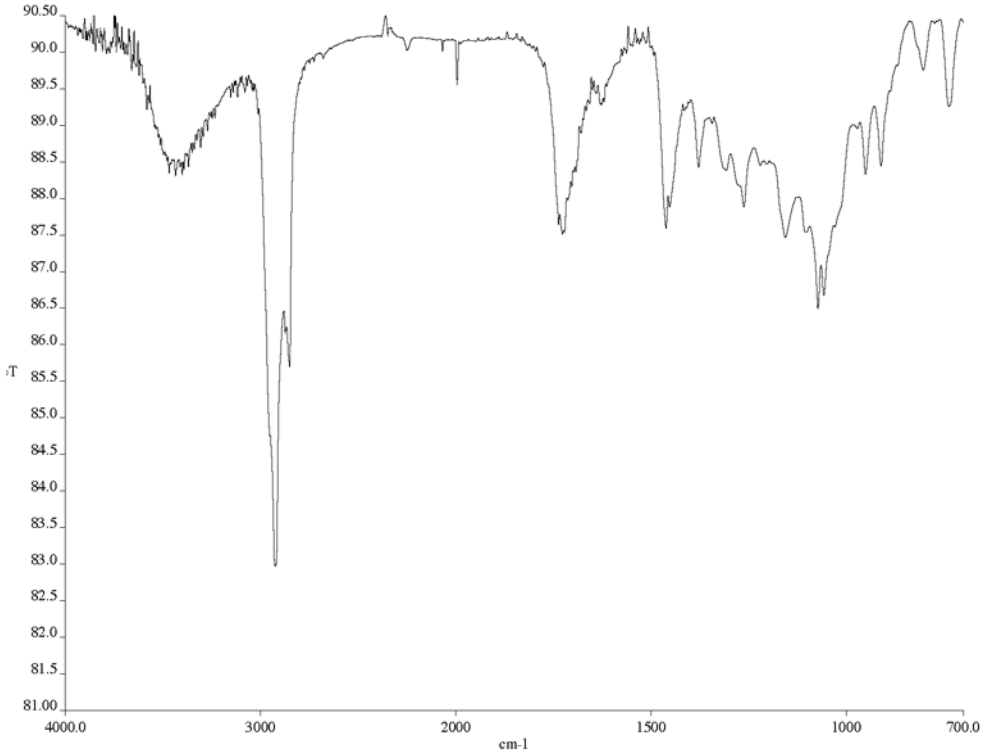


Figure A1.18.2 Infrared spectrum (thin film/NaCl) of compound **75**.

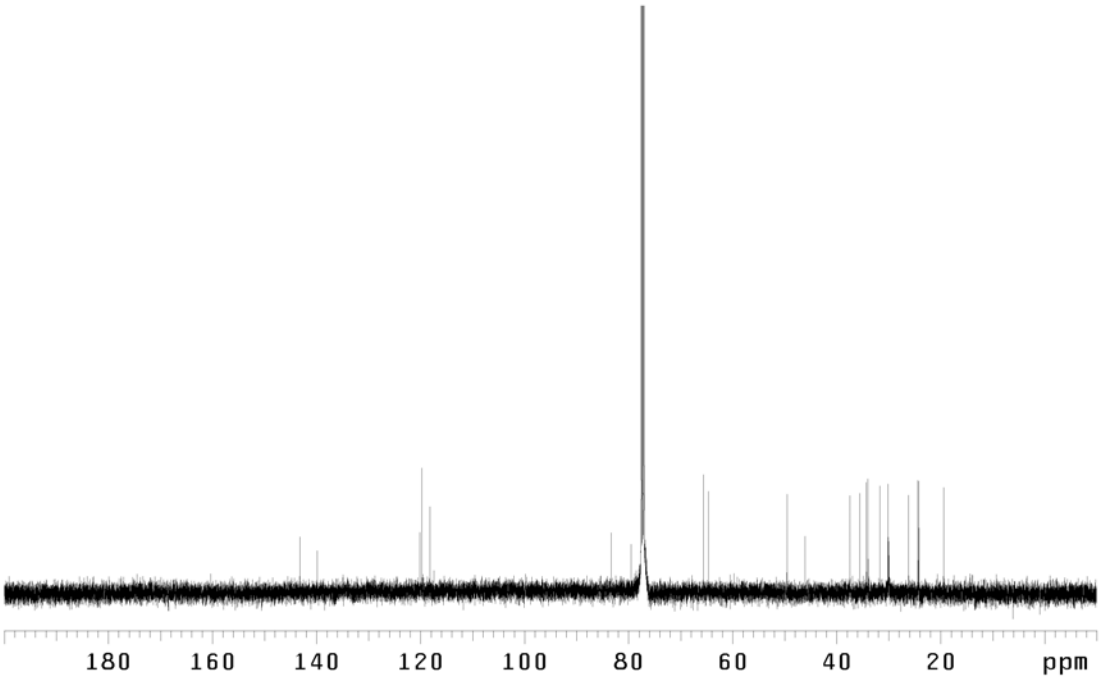


Figure A1.18.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **75**.

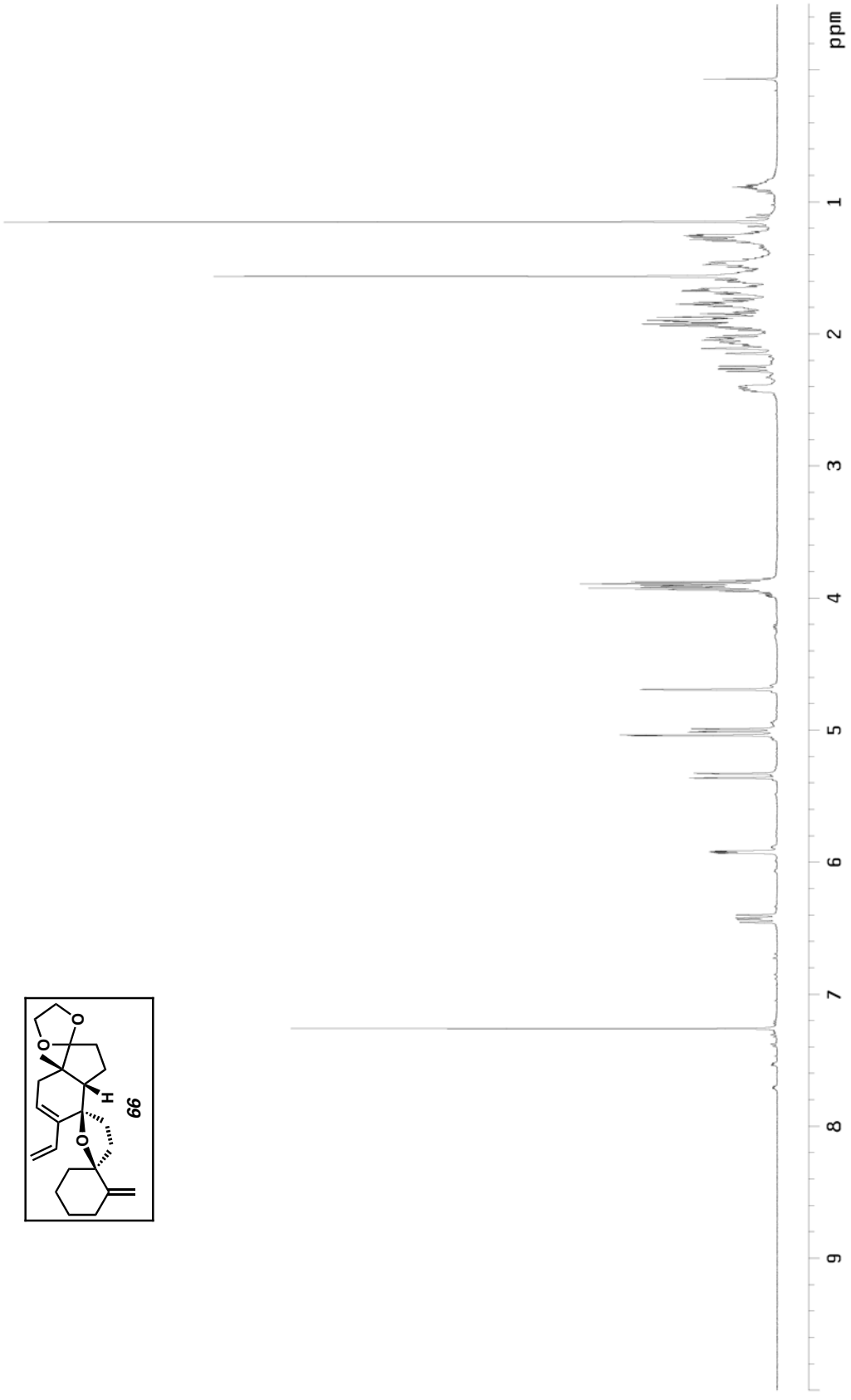


Figure A1.19.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **66**.

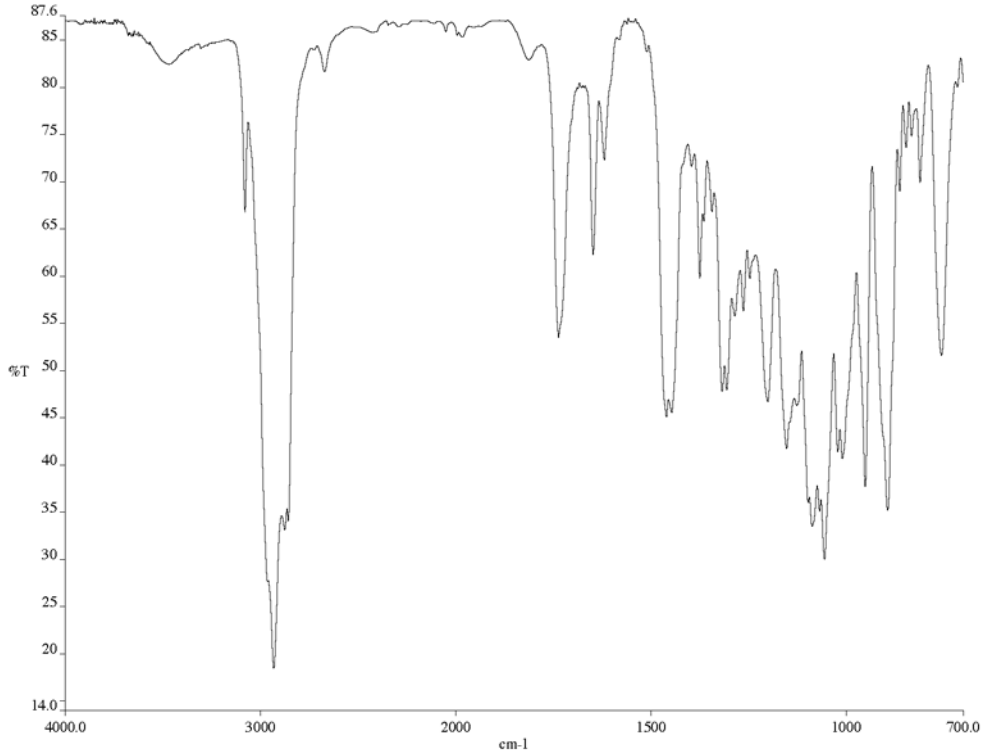


Figure A1.19.2 Infrared spectrum (thin film/NaCl) of compound **66**.

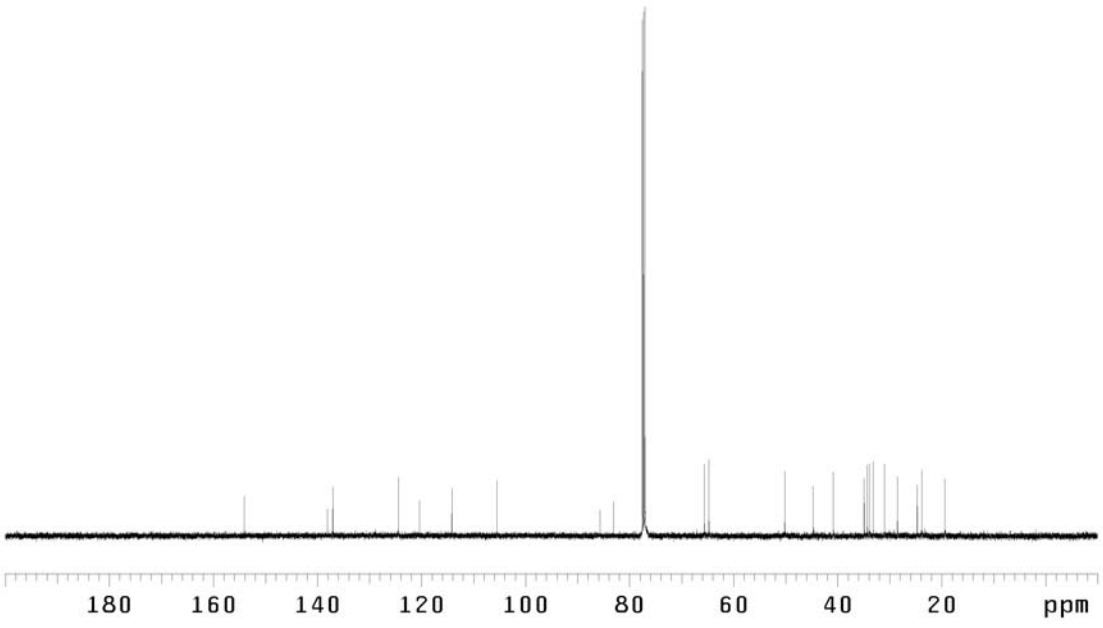


Figure A1.19.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **66**.

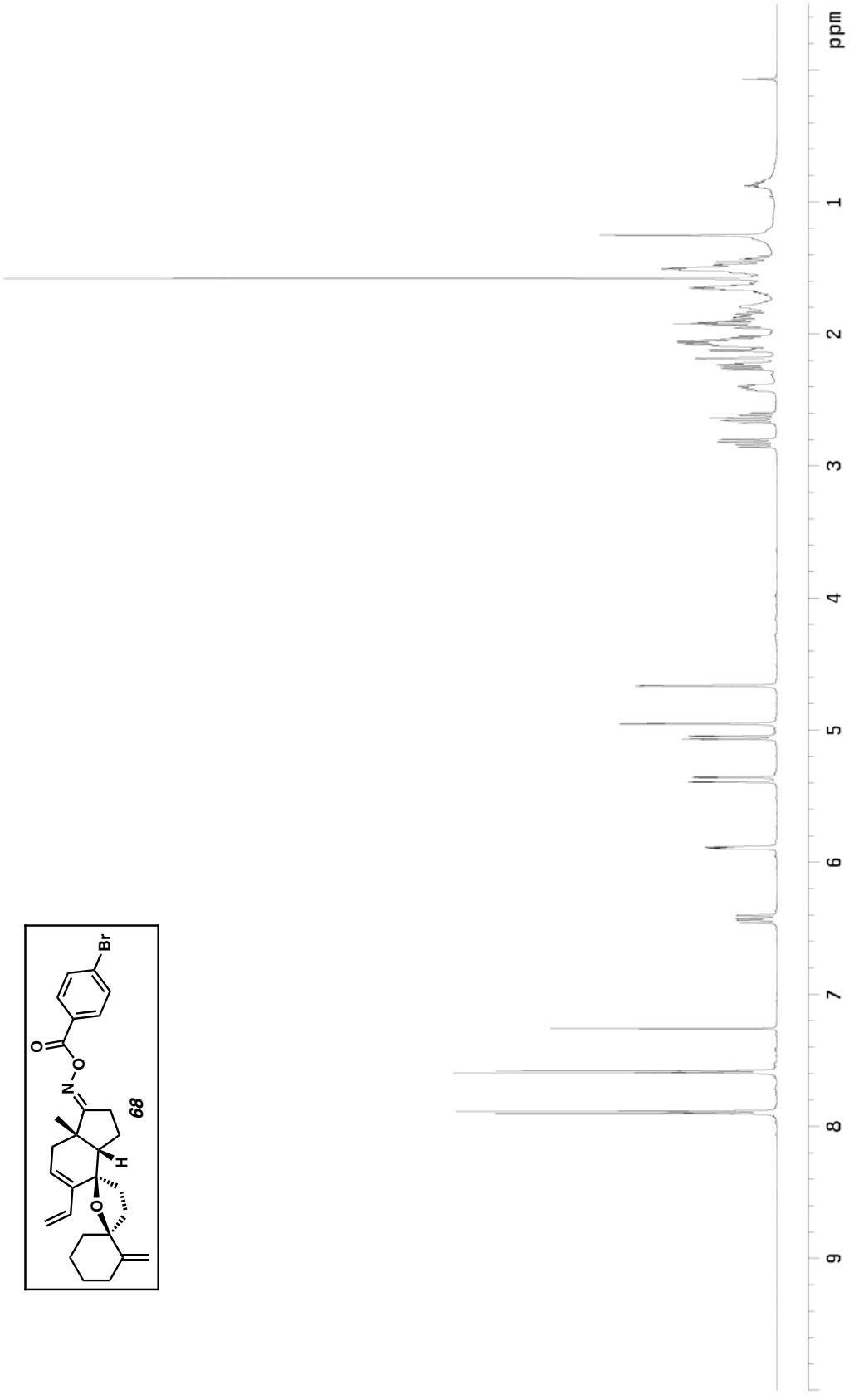


Figure A1.20.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **68**.

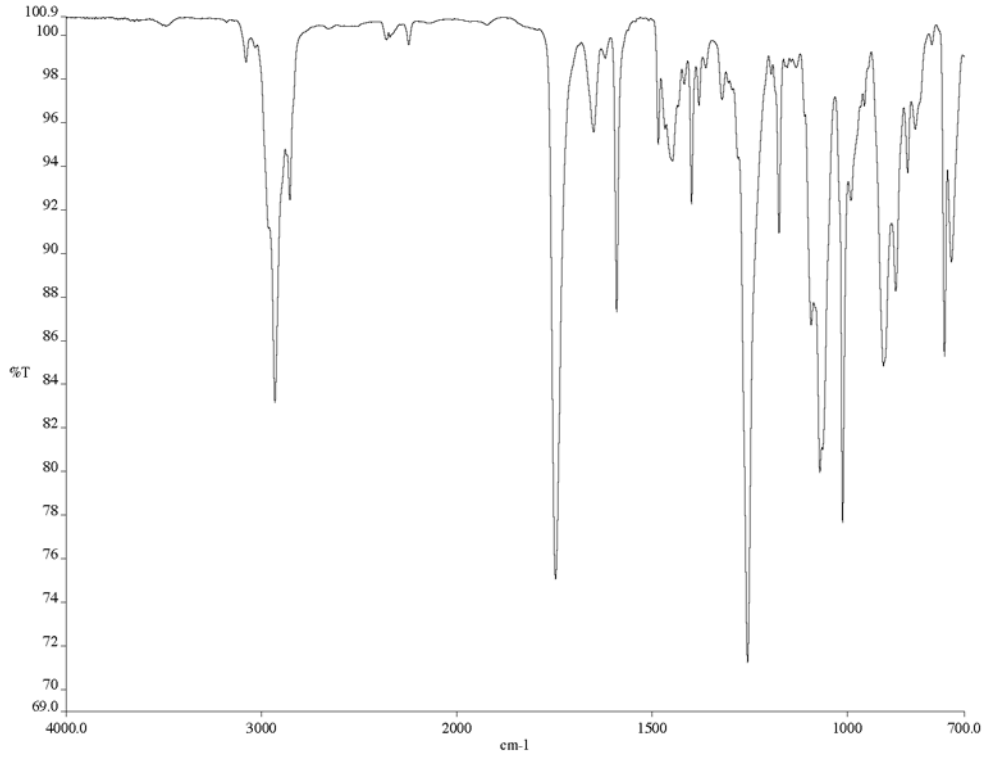


Figure A1.20.2 Infrared spectrum (thin film/NaCl) of compound **68**.

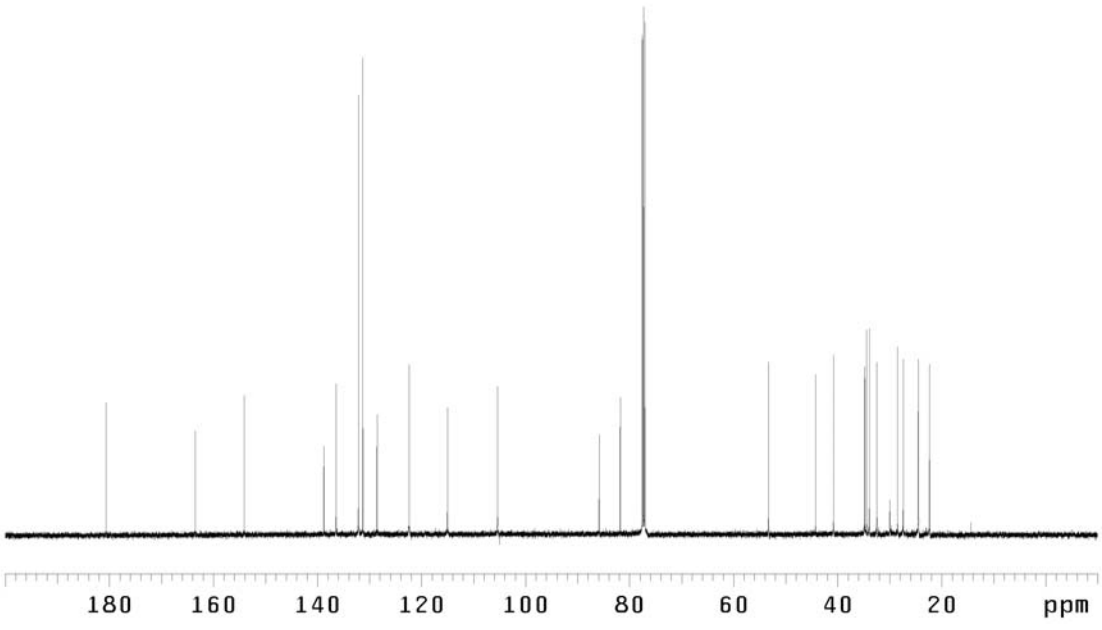


Figure A1. 20.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **68**.

APPENDIX 2

X-Ray Crystallography Reports Relevant to Chapter 2

A2.1 CRYSTAL STRUCTURE OF BROMOBENZOATE 69

Figure A2.1 ORTEP drawing of bromobenzoate ***69*** *(shown with 50% probability ellipsoids)*

NOTE: Crystallographic data have been deposited in the Cambridge Database (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 748731.

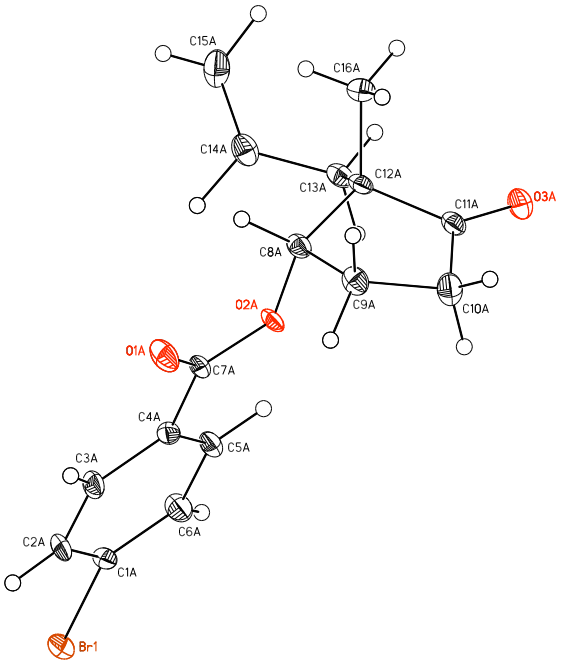


Table A2.1 Crystal data and structure refinement for bromobenzoate ***69*** *(CCDC 748731)*

Empirical formula	$C_{16}H_{17}O_3Br$
Formula weight	337.21
Crystallization Solvent	Ethylacetate/hexanes
Crystal Habit	Block
Crystal size	0.20 x 0.19 x 0.12 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker KAPPA APEX II
Wavelength	0.71073 Å MoKα
Data Collection Temperature	100(2) K
θ range for 9810 reflections used in lattice determination	2.57 to 32.19°
Unit cell dimensions	a = 5.7803(2) Å b = 24.8200(11) Å β= 91.528(2)° c = 10.2688(4) Å
Volume	1472.71(10) $Å^3$
Z	4
Crystal system	Monoclinic
Space group	$P2_1$
Density (calculated)	1.521 Mg/m^3
F(000)	688
Data collection program	Bruker APEX2 v2009.7-0
θ range for data collection	1.64 to 33.46°
Completeness to θ = 33.46°	99.5 %
Index ranges	$-8 \le h \le 8, -38 \le k \le 38, -15 \le l \le 15$
Data collection scan type	ω scans; 24 settings
Data reduction program	Bruker SAINT-Plus v7.66A
Reflections collected	50019
Independent reflections	11399 [R_{int}= 0.0523]
Absorption coefficient	2.795 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.7303 and 0.6048

Table A2.1 (cont.)

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 2008)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 2008)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	11399 / 1 / 497
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.549
Final R indices [I>2σ(I), 10256 reflections]	R1 = 0.0342, *w*R2 = 0.0548
R indices (all data)	R1 = 0.0391, *w*R2 = 0.0551
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.002
Average shift/error	0.000
Absolute structure determination	Anomalous differences
Absolute structure parameter	-0.002(4)
Largest diff. peak and hole	1.491 and -0.868 e.Å^{-3}

Special Refinement Details

Crystals were mounted on a glass fiber using Paratone oil then placed on the diffractometer under a nitrogen stream at 100K.

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Table A2.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for bromobenzoate ***69*** *(CCDC 748731). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor*

	x	y	z	U_{eq}
Br(1)	-5722(1)	10484(1)	7314(1)	20(1)
O(1A)	3014(3)	8952(1)	4870(1)	21(1)
O(2A)	1258(2)	9232(1)	3005(1)	13(1)
O(3A)	481(3)	8879(1)	-881(1)	21(1)
C(1A)	-3491(4)	10098(1)	6357(2)	16(1)
C(2A)	-1783(4)	9818(1)	7039(2)	18(1)
C(3A)	-181(4)	9531(1)	6351(2)	16(1)
C(4A)	-277(4)	9526(1)	4994(2)	13(1)
C(5A)	-1992(4)	9816(1)	4325(2)	16(1)
C(6A)	-3612(4)	10104(1)	5017(2)	19(1)
C(7A)	1506(4)	9206(1)	4312(2)	14(1)
C(8A)	3137(4)	8985(1)	2287(2)	14(1)
C(9A)	2776(4)	8379(1)	2168(2)	16(1)
C(10A)	1086(5)	8306(1)	1019(2)	20(1)
C(11A)	1370(4)	8804(1)	188(2)	14(1)
C(12A)	2987(3)	9200(1)	892(2)	12(1)
C(13A)	2137(4)	9788(1)	735(2)	15(1)
C(14A)	3483(4)	10178(1)	1570(2)	19(1)
C(15A)	5129(4)	10500(1)	1170(2)	25(1)
C(16A)	5370(4)	9131(1)	272(2)	18(1)
Br(2)	10449(1)	1109(1)	9526(1)	17(1)
O(1B)	1925(3)	2677(1)	6729(1)	19(1)
O(2B)	3746(2)	2396(1)	4938(1)	14(1)
O(3B)	4473(3)	2717(1)	1036(1)	20(1)
C(1B)	8350(4)	1522(1)	8492(2)	14(1)
C(2B)	6529(4)	1780(1)	9089(2)	14(1)
C(3B)	4972(4)	2074(1)	8329(2)	14(1)
C(4B)	5222(4)	2106(1)	6990(2)	13(1)
C(5B)	7069(4)	1847(1)	6407(2)	15(1)
C(6B)	8642(4)	1553(1)	7162(2)	16(1)
C(7B)	3462(4)	2427(1)	6236(2)	14(1)
C(8B)	1873(4)	2633(1)	4148(2)	14(1)
C(9B)	2249(4)	3239(1)	4008(2)	17(1)
C(10B)	3958(4)	3293(1)	2913(2)	19(1)
C(11B)	3642(4)	2799(1)	2092(2)	15(1)
C(12B)	2028(4)	2400(1)	2764(2)	14(1)
C(13B)	2906(4)	1823(1)	2681(2)	17(1)
C(14B)	1288(5)	1414(1)	3231(3)	28(1)
C(15B)	1665(5)	1147(1)	4312(2)	33(1)
C(16B)	-348(4)	2463(1)	2074(2)	21(1)

*Table A2.3 Bond lengths [Å] and angles [°] for bromobenzoate **69** (CCDC 748731)*

Br(1)-C(1A)	1.901(2)	C(6B)-H(6B)	0.96(2)
O(1A)-C(7A)	1.207(3)	C(8B)-C(9B)	1.527(3)
O(2A)-C(7A)	1.348(2)	C(8B)-C(12B)	1.539(3)
O(2A)-C(8A)	1.464(2)	C(8B)-H(8B)	1.05(2)
O(3A)-C(11A)	1.214(3)	C(9B)-C(10B)	1.523(3)
C(1A)-C(6A)	1.376(3)	C(9B)-H(9B1)	0.98(3)
C(1A)-C(2A)	1.383(3)	C(9B)-H(9B2)	0.97(3)
C(2A)-C(3A)	1.378(3)	C(10B)-C(11B)	1.498(3)
C(2A)-H(2A)	0.91(3)	C(10B)-H(10C)	0.91(3)
C(3A)-C(4A)	1.393(3)	C(10B)-H(10D)	0.92(3)
C(3A)-H(3A)	0.91(2)	C(11B)-C(12B)	1.536(3)
C(4A)-C(5A)	1.392(3)	C(12B)-C(13B)	1.523(3)
C(4A)-C(7A)	1.490(3)	C(12B)-C(16B)	1.537(3)
C(5A)-C(6A)	1.389(3)	C(13B)-C(14B)	1.501(3)
C(5A)-H(5A)	0.97(2)	C(13B)-H(13C)	1.00(3)
C(6A)-H(6A)	0.84(3)	C(13B)-H(13D)	0.99(2)
C(8A)-C(9A)	1.523(3)	C(14B)-C(15B)	1.306(4)
C(8A)-C(12A)	1.528(3)	C(14B)-H(14B)	0.92(3)
C(8A)-H(8A)	1.00(3)	C(15B)-H(15C)	1.03(3)
C(9A)-C(10A)	1.523(3)	C(15B)-H(15D)	1.15(4)
C(9A)-H(9A1)	1.01(3)	C(16B)-H(16D)	0.91(3)
C(9A)-H(9A2)	0.92(3)	C(16B)-H(16E)	0.99(3)
C(10A)-C(11A)	1.512(3)	C(16B)-H(16F)	0.93(3)
C(10A)-H(10A)	0.87(3)		
C(10A)-H(10B)	0.96(3)	C(7A)-O(2A)-C(8A)	114.89(16)
C(11A)-C(12A)	1.526(3)	C(6A)-C(1A)-C(2A)	121.9(2)
C(12A)-C(16A)	1.542(3)	C(6A)-C(1A)-Br(1)	119.68(18)
C(12A)-C(13A)	1.545(3)	C(2A)-C(1A)-Br(1)	118.43(15)
C(13A)-C(14A)	1.499(3)	C(1A)-C(2A)-C(3A)	118.7(2)
C(13A)-H(13A)	0.92(2)	C(1A)-C(2A)-H(2A)	116.9(16)
C(13A)-H(13B)	1.03(2)	C(3A)-C(2A)-H(2A)	124.4(16)
C(14A)-C(15A)	1.317(3)	C(2A)-C(3A)-C(4A)	120.6(2)
C(14A)-H(14A)	1.09(2)	C(2A)-C(3A)-H(3A)	124.2(14)
C(15A)-H(15A)	1.03(3)	C(4A)-C(3A)-H(3A)	115.1(14)
C(15A)-H(15B)	0.84(3)	C(5A)-C(4A)-C(3A)	119.8(2)
C(16A)-H(16A)	0.96(2)	C(5A)-C(4A)-C(7A)	122.45(18)
C(16A)-H(16B)	0.90(3)	C(3A)-C(4A)-C(7A)	117.73(19)
C(16A)-H(16C)	0.98(3)	C(4A)-C(5A)-C(6A)	119.67(19)
Br(2)-C(1B)	1.893(2)	C(4A)-C(5A)-H(5A)	119.1(15)
O(1B)-C(7B)	1.205(2)	C(6A)-C(5A)-H(5A)	121.2(15)
O(2B)-C(7B)	1.349(2)	C(1A)-C(6A)-C(5A)	119.3(2)
O(2B)-C(8B)	1.460(2)	C(1A)-C(6A)-H(6A)	120.3(19)
O(3B)-C(11B)	1.214(2)	C(5A)-C(6A)-H(6A)	120.3(19)
C(1B)-C(6B)	1.382(3)	O(1A)-C(7A)-O(2A)	123.61(19)
C(1B)-C(2B)	1.389(3)	O(1A)-C(7A)-C(4A)	123.73(18)
C(2B)-C(3B)	1.384(3)	O(2A)-C(7A)-C(4A)	112.66(17)
C(2B)-H(2B)	0.97(2)	O(2A)-C(8A)-C(9A)	110.64(17)
C(3B)-C(4B)	1.389(3)	O(2A)-C(8A)-C(12A)	107.53(16)
C(3B)-H(3B)	1.02(3)	C(9A)-C(8A)-C(12A)	105.44(17)
C(4B)-C(5B)	1.394(3)	O(2A)-C(8A)-H(8A)	104.5(14)
C(4B)-C(7B)	1.493(3)	C(9A)-C(8A)-H(8A)	112.6(14)
C(5B)-C(6B)	1.386(3)	C(12A)-C(8A)-H(8A)	116.1(14)
C(5B)-H(5B)	0.95(2)	C(8A)-C(9A)-C(10A)	105.23(17)

C(8A)-C(9A)-H(9A1)	110.4(15)	C(4B)-C(5B)-H(5B)	117.2(14)
C(10A)-C(9A)-H(9A1)	113.3(16)	C(1B)-C(6B)-C(5B)	119.09(19)
C(8A)-C(9A)-H(9A2)	104.6(17)	C(1B)-C(6B)-H(6B)	117.5(12)
C(10A)-C(9A)-H(9A2)	110.3(17)	C(5B)-C(6B)-H(6B)	123.4(12)
H(9A1)-C(9A)-H(9A2)	112(2)	O(1B)-C(7B)-O(2B)	123.66(18)
C(11A)-C(10A)-C(9A)	105.27(18)	O(1B)-C(7B)-C(4B)	123.84(17)
C(11A)-C(10A)-H(10A)	113.6(16)	O(2B)-C(7B)-C(4B)	112.48(16)
C(9A)-C(10A)-H(10A)	111.6(18)	O(2B)-C(8B)-C(9B)	110.13(17)
C(11A)-C(10A)-H(10B)	104.5(16)	O(2B)-C(8B)-C(12B)	107.51(15)
C(9A)-C(10A)-H(10B)	115.4(17)	C(9B)-C(8B)-C(12B)	105.75(17)
H(10A)-C(10A)-H(10B)	106(2)	O(2B)-C(8B)-H(8B)	110.9(13)
O(3A)-C(11A)-C(10A)	125.81(19)	C(9B)-C(8B)-H(8B)	111.3(13)
O(3A)-C(11A)-C(12A)	124.67(18)	C(12B)-C(8B)-H(8B)	111.2(13)
C(10A)-C(11A)-C(12A)	109.51(18)	C(8B)-C(9B)-C(10B)	104.67(17)
C(11A)-C(12A)-C(8A)	103.70(16)	C(8B)-C(9B)-H(9B1)	113.6(15)
C(11A)-C(12A)-C(16A)	105.93(16)	C(10B)-C(9B)-H(9B1)	111.3(15)
C(8A)-C(12A)-C(16A)	108.58(17)	C(8B)-C(9B)-H(9B2)	108.8(15)
C(11A)-C(12A)-C(13A)	111.70(17)	C(10B)-C(9B)-H(9B2)	114.5(15)
C(8A)-C(12A)-C(13A)	115.95(16)	H(9B1)-C(9B)-H(9B2)	104(2)
C(16A)-C(12A)-C(13A)	110.34(16)	C(11B)-C(10B)-C(9B)	105.77(18)
C(14A)-C(13A)-C(12A)	113.09(18)	C(11B)-C(10B)-H(10C)	113.6(18)
C(14A)-C(13A)-H(13A)	106.0(15)	C(9B)-C(10B)-H(10C)	111.0(17)
C(12A)-C(13A)-H(13A)	112.2(14)	C(11B)-C(10B)-H(10D)	106.2(17)
C(14A)-C(13A)-H(13B)	110.8(13)	C(9B)-C(10B)-H(10D)	114.3(17)
C(12A)-C(13A)-H(13B)	111.0(13)	H(10C)-C(10B)-H(10D)	106(2)
H(13A)-C(13A)-H(13B)	103(2)	O(3B)-C(11B)-C(10B)	126.52(19)
C(15A)-C(14A)-C(13A)	125.7(2)	O(3B)-C(11B)-C(12B)	123.54(18)
C(15A)-C(14A)-H(14A)	119.8(13)	C(10B)-C(11B)-C(12B)	109.92(16)
C(13A)-C(14A)-H(14A)	114.6(13)	C(13B)-C(12B)-C(11B)	111.92(17)
C(14A)-C(15A)-H(15A)	123.3(16)	C(13B)-C(12B)-C(16B)	111.32(18)
C(14A)-C(15A)-H(15B)	126(2)	C(11B)-C(12B)-C(16B)	105.89(17)
H(15A)-C(15A)-H(15B)	111(3)	C(13B)-C(12B)-C(8B)	115.68(17)
C(12A)-C(16A)-H(16A)	107.9(13)	C(11B)-C(12B)-C(8B)	102.97(16)
C(12A)-C(16A)-H(16B)	103.1(17)	C(16B)-C(12B)-C(8B)	108.33(17)
H(16A)-C(16A)-H(16B)	121(2)	C(14B)-C(13B)-C(12B)	113.81(19)
C(12A)-C(16A)-H(16C)	109.8(15)	C(14B)-C(13B)-H(13C)	108.5(15)
H(16A)-C(16A)-H(16C)	114(2)	C(12B)-C(13B)-H(13C)	109.8(15)
H(16B)-C(16A)-H(16C)	100(2)	C(14B)-C(13B)-H(13D)	115.9(13)
C(7B)-O(2B)-C(8B)	114.71(15)	C(12B)-C(13B)-H(13D)	107.0(13)
C(6B)-C(1B)-C(2B)	121.61(19)	H(13C)-C(13B)-H(13D)	101(2)
C(6B)-C(1B)-Br(2)	119.43(15)	C(15B)-C(14B)-C(13B)	124.8(3)
C(2B)-C(1B)-Br(2)	118.95(15)	C(15B)-C(14B)-H(14B)	113.3(18)
C(3B)-C(2B)-C(1B)	118.93(19)	C(13B)-C(14B)-H(14B)	121.8(18)
C(3B)-C(2B)-H(2B)	121.1(14)	C(14B)-C(15B)-H(15C)	117.1(17)
C(1B)-C(2B)-H(2B)	120.0(14)	C(14B)-C(15B)-H(15D)	111.6(19)
C(2B)-C(3B)-C(4B)	120.32(19)	H(15C)-C(15B)-H(15D)	130(3)
C(2B)-C(3B)-H(3B)	125.2(14)	C(12B)-C(16B)-H(16D)	109(2)
C(4B)-C(3B)-H(3B)	114.5(14)	C(12B)-C(16B)-H(16E)	108.6(15)
C(3B)-C(4B)-C(5B)	120.00(19)	H(16D)-C(16B)-H(16E)	111(2)
C(3B)-C(4B)-C(7B)	117.12(17)	C(12B)-C(16B)-H(16F)	106.8(19)
C(5B)-C(4B)-C(7B)	122.87(18)	H(16D)-C(16B)-H(16F)	107(3)
C(6B)-C(5B)-C(4B)	120.04(19)	H(16E)-C(16B)-H(16F)	115(2)
C(6B)-C(5B)-H(5B)	122.7(14)		

Table A2.4 Anisotropic displacement parameters ($Å^2$ x 10^4) for bromobenzoate ***69*** *(CCDC 748731). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	180(1)	281(1)	141(1)	-48(1)	47(1)	-19(1)
O(1A)	232(8)	281(8)	112(7)	32(6)	-21(6)	68(6)
O(2A)	137(7)	205(7)	56(6)	9(5)	12(5)	28(6)
O(3A)	222(8)	282(8)	115(7)	11(6)	-30(6)	-17(6)
C(1A)	158(11)	189(10)	128(9)	-31(7)	49(8)	-37(8)
C(2A)	226(12)	229(11)	72(9)	-16(8)	0(8)	-37(9)
C(3A)	199(12)	182(10)	95(9)	11(7)	-29(8)	-22(9)
C(4A)	156(11)	131(9)	116(9)	3(7)	15(8)	-31(8)
C(5A)	176(11)	222(10)	90(9)	-4(7)	7(8)	-5(8)
C(6A)	156(11)	259(11)	146(10)	-6(8)	1(8)	40(9)
C(7A)	149(10)	206(10)	67(8)	12(7)	-1(7)	-23(8)
C(8A)	114(10)	204(10)	110(9)	-4(7)	5(8)	37(8)
C(9A)	174(11)	185(10)	136(10)	20(7)	-17(8)	36(8)
C(10A)	274(13)	176(10)	162(10)	2(8)	-32(9)	-30(9)
C(11A)	124(10)	199(10)	103(9)	-7(7)	16(7)	28(8)
C(12A)	107(10)	178(9)	90(8)	11(7)	28(7)	21(7)
C(13A)	155(11)	187(10)	107(9)	26(7)	18(8)	31(8)
C(14A)	260(12)	167(10)	142(10)	6(7)	-7(8)	24(8)
C(15A)	312(13)	215(10)	215(11)	-28(10)	-61(9)	-34(11)
C(16A)	157(11)	227(11)	171(11)	-15(8)	49(8)	-21(9)
Br(2)	155(1)	231(1)	120(1)	17(1)	-15(1)	31(1)
O(1B)	169(8)	282(8)	112(7)	-12(6)	13(6)	69(6)
O(2B)	138(7)	214(7)	73(6)	1(5)	-6(5)	37(5)
O(3B)	189(8)	308(8)	108(7)	-13(6)	39(6)	0(6)
C(1B)	132(10)	175(9)	109(9)	4(7)	-22(7)	-29(7)
C(2B)	151(11)	185(10)	96(9)	-4(7)	14(8)	-9(8)
C(3B)	147(10)	160(9)	104(9)	-11(7)	1(8)	9(8)
C(4B)	123(10)	162(9)	97(9)	7(7)	8(7)	3(8)
C(5B)	142(11)	230(11)	86(9)	6(7)	24(7)	-23(8)
C(6B)	147(10)	221(10)	107(9)	-2(7)	29(8)	24(8)
C(7B)	139(10)	168(9)	99(9)	1(7)	6(7)	-17(7)
C(8B)	111(10)	211(10)	100(9)	-6(7)	-18(7)	42(8)
C(9B)	210(13)	180(10)	119(10)	-16(7)	-7(8)	36(9)
C(10B)	237(13)	193(10)	143(10)	10(8)	16(9)	-23(9)
C(11B)	107(9)	229(10)	100(9)	10(7)	-26(7)	43(8)
C(12B)	121(10)	191(10)	98(9)	-2(7)	8(7)	-4(8)
C(13B)	205(12)	185(11)	123(10)	-34(8)	10(8)	11(9)
C(14B)	316(15)	247(12)	285(13)	-41(9)	57(11)	-20(10)
C(15B)	474(17)	272(12)	254(12)	-22(11)	68(11)	2(13)
C(16B)	127(11)	312(12)	172(11)	-17(9)	-38(8)	-28(9)

*Table A2.5 Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for bromobenzoate **69** (CCDC 748731)*

	x	y	z	U_{iso}
H(2A)	-1800(40)	9837(10)	7920(30)	19(6)
H(3A)	940(40)	9322(8)	6720(20)	6(5)
H(5A)	-2050(40)	9806(10)	3380(20)	21(6)
H(6A)	-4590(50)	10297(11)	4620(30)	32(8)
H(8A)	4560(40)	9079(10)	2800(20)	16(6)
H(9A1)	2190(50)	8227(10)	3010(30)	26(7)
H(9A2)	4210(50)	8245(11)	1970(30)	28(7)
H(10A)	1340(40)	8007(11)	600(20)	22(6)
H(10B)	-530(50)	8305(11)	1230(30)	27(7)
H(13A)	2250(40)	9909(9)	-110(20)	16(6)
H(13B)	390(40)	9816(9)	900(20)	15(6)
H(14A)	3020(40)	10180(9)	2600(20)	16(6)
H(15A)	5660(50)	10512(12)	220(30)	34(7)
H(15B)	5910(50)	10717(13)	1640(30)	42(9)
H(16A)	5740(40)	8753(9)	280(20)	9(5)
H(16B)	6260(50)	9374(11)	700(30)	26(7)
H(16C)	5340(40)	9291(10)	-600(30)	26(7)
H(2B)	6370(40)	1755(9)	10030(20)	8(6)
H(3B)	3590(50)	2285(10)	8670(20)	24(7)
H(5B)	7220(40)	1895(9)	5490(20)	15(6)
H(6B)	9970(40)	1377(8)	6815(19)	0(5)
H(8B)	260(40)	2549(10)	4550(20)	14(6)
H(9B1)	2840(40)	3412(10)	4810(30)	24(7)
H(9B2)	770(50)	3410(10)	3840(30)	21(7)
H(10C)	3730(50)	3606(11)	2470(30)	29(7)
H(10D)	5480(50)	3295(11)	3190(30)	29(7)
H(13C)	3180(50)	1728(10)	1760(30)	29(7)
H(13D)	4500(40)	1820(9)	3050(20)	11(6)
H(14B)	-80(50)	1319(12)	2800(30)	36(8)
H(15C)	3230(50)	1209(13)	4790(30)	49(9)
H(15D)	280(60)	822(16)	4460(30)	74(11)
H(16D)	-280(50)	2319(12)	1260(30)	42(8)
H(16E)	-740(40)	2851(10)	2030(20)	20(6)
H(16F)	-1380(50)	2253(12)	2530(30)	35(8)

A2.2 CRYSTAL STRUCTURE OF SEMICARBAZONE 71

*Figure A2.2 ORTEP drawing of semicarbazone **71** (shown with 50% probability ellipsoids)*

NOTE: Crystallographic data have been deposited in the Cambridge Database (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 749151.

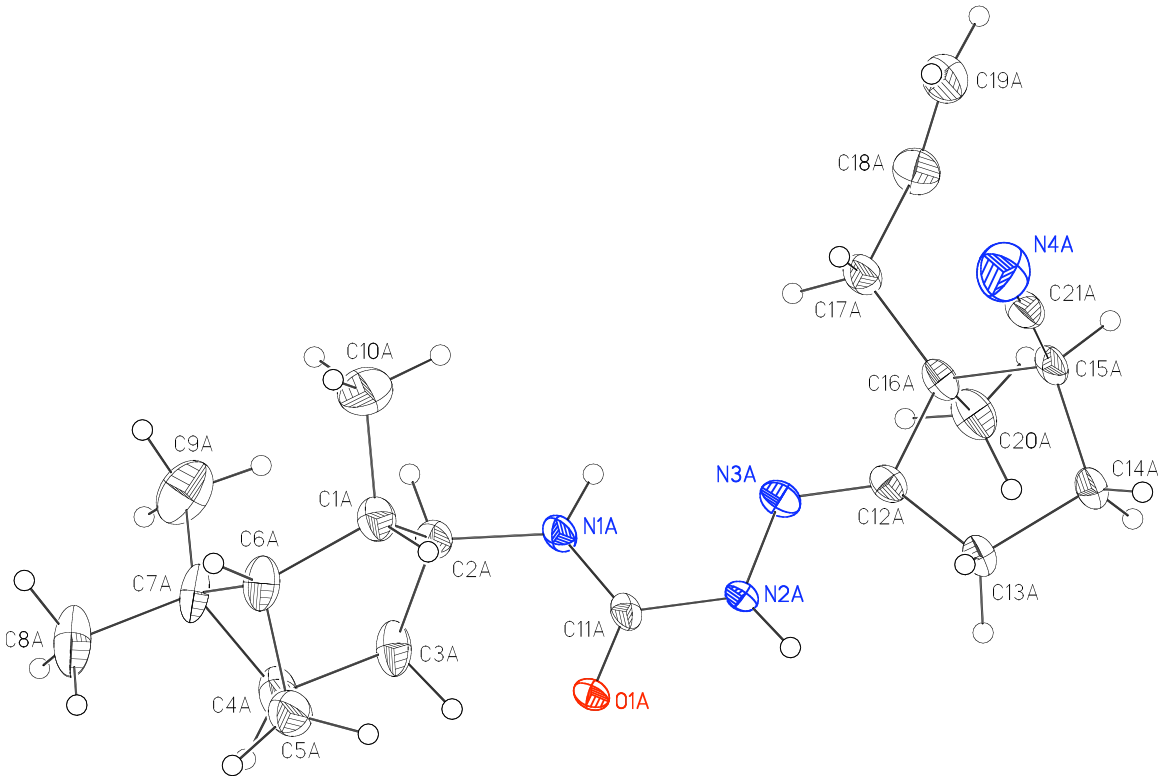


*Table A2.6 Crystal data and structure refinement for semicarbazone **71** (CCDC 749151)*

Empirical formula	$C_{21}H_{32}N_4O$
Formula weight	356.51
Crystallization Solvent	Methanol or $CDCl_3$
Crystal Habit	Blade
Crystal size	0.23 x 0.19 x 0.07 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker KAPPA APEX II
Wavelength	0.71073 Å MoKα
Data Collection Temperature	100(2) K
θ range for 9942 reflections used in lattice determination	2.40 to 18.72°
Unit cell dimensions	a = 17.5462(8) Å b = 11.0229(5) Å β= 103.274(3)° c = 32.8065(15) Å
Volume	6175.6(5) $Å^3$
Z	12
Crystal system	Monoclinic
Space group	$P2_1$
Density (calculated)	1.150 Mg/m^3
F(000)	2328
Data collection program	Bruker APEX2 v2009.7-0
θ range for data collection	1.19 to 26.40°
Completeness to θ = 26.40°	99.7 %
Index ranges	$-21 \le h \le 21, -13 \le k \le 13, -34 \le l \le 41$
Data collection scan type	ω scans; 9 settings
Data reduction program	Bruker SAINT-Plus v7.66A
Reflections collected	80862
Independent reflections	25063 [R_{int}= 0.0604]
Absorption coefficient	0.072 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9950 and 0.9836

Table A2.6 (cont.)

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 2008)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 2008)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	25063 / 1 / 1429
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	1.387
Final R indices [I>2σ(I), 16797 reflections]	R1 = 0.0574, *w*R2 = 0.0734
R indices (all data)	R1 = 0.0950, *w*R2 = 0.0768
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.001
Average shift/error	0.000
Absolute structure determination	Known stereo center
Absolute structure parameter	-1.1(8)
Largest diff. peak and hole	0.397 and -0.495 e.Å^{-3}

Special Refinement Details

Crystals were mounted on a glass fiber using Paratone oil then placed on the diffractometer under a nitrogen stream at 100K.

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

*Table A2.7 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for semicarbazone **71** (CCDC 749151). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor*

	x	y	z	U_{eq}
O(1A)	7744(1)	7491(2)	-623(1)	19(1)
N(1A)	7679(1)	7837(2)	55(1)	20(1)
N(2A)	8454(1)	9017(2)	-263(1)	18(1)
N(3A)	8711(1)	9598(2)	120(1)	20(1)
N(4A)	11284(2)	9439(3)	640(1)	44(1)
C(1A)	7344(2)	5620(3)	62(1)	25(1)
C(2A)	7064(2)	6947(3)	83(1)	21(1)
C(3A)	6290(2)	7237(3)	-227(1)	27(1)
C(4A)	5796(2)	6113(3)	-387(1)	35(1)
C(5A)	6318(2)	5254(3)	-586(1)	32(1)
C(6A)	6647(2)	4782(3)	-131(1)	29(1)
C(7A)	5843(2)	5153(3)	-32(1)	29(1)
C(8A)	5227(2)	4132(3)	-179(1)	46(1)
C(9A)	5784(2)	5562(3)	405(1)	46(1)
C(10A)	7790(2)	5197(3)	492(1)	45(1)
C(11A)	7937(2)	8061(3)	-291(1)	18(1)
C(12A)	9246(2)	10395(3)	136(1)	19(1)
C(13A)	9655(2)	10762(3)	-201(1)	25(1)
C(14A)	10291(2)	11677(3)	17(1)	24(1)
C(15A)	10413(2)	11377(3)	484(1)	20(1)
C(16A)	9574(2)	11094(3)	540(1)	20(1)
C(17A)	9547(2)	10385(3)	937(1)	25(1)
C(18A)	9913(2)	11036(3)	1330(1)	30(1)
C(19A)	10563(2)	10716(3)	1592(1)	37(1)
C(20A)	9120(2)	12298(3)	524(1)	30(1)
C(21A)	10913(2)	10289(3)	584(1)	25(1)
O(1B)	5794(1)	9309(2)	2246(1)	20(1)
N(1B)	5529(1)	9319(2)	1529(1)	20(1)
N(2B)	4860(1)	8065(2)	1881(1)	16(1)
N(3B)	4447(1)	7649(2)	1491(1)	16(1)
N(4B)	4165(2)	3472(2)	1322(1)	40(1)
C(1B)	6910(2)	9856(3)	1548(1)	26(1)
C(2B)	6066(2)	10301(3)	1465(1)	23(1)
C(3B)	5923(2)	11493(2)	1678(1)	28(1)
C(4B)	6680(2)	12191(3)	1841(1)	33(1)
C(5B)	7278(2)	11333(3)	2124(1)	37(1)
C(6B)	7490(2)	10886(3)	1713(1)	28(1)
C(7B)	7233(2)	12156(3)	1526(1)	25(1)
C(8B)	7898(2)	13081(3)	1644(1)	47(1)
C(9B)	6862(2)	12332(3)	1066(1)	42(1)
C(10B)	7086(2)	9230(3)	1166(1)	40(1)
C(11B)	5424(2)	8931(3)	1902(1)	19(1)
C(12B)	3915(2)	6866(3)	1496(1)	15(1)

C(13B)	3688(2)	6307(2)	1869(1)	18(1)
C(14B)	2986(2)	5494(3)	1678(1)	21(1)
C(15B)	3109(2)	5171(2)	1240(1)	18(1)
C(16B)	3415(2)	6365(2)	1087(1)	16(1)
C(17B)	3888(2)	6205(3)	756(1)	23(1)
C(18B)	3417(2)	5609(3)	364(1)	27(1)
C(19B)	3258(2)	6063(3)	-10(1)	43(1)
C(20B)	2728(2)	7252(3)	928(1)	26(1)
C(21B)	3695(2)	4206(3)	1283(1)	24(1)
O(1C)	4461(1)	7744(2)	2683(1)	19(1)
N(1C)	4432(1)	8248(2)	3354(1)	21(1)
N(2C)	5096(1)	9446(2)	2973(1)	18(1)
N(3C)	5393(1)	10056(2)	3350(1)	18(1)
N(4C)	7874(2)	9740(3)	3700(1)	44(1)
C(1C)	3172(2)	7090(3)	3216(1)	39(1)
C(2C)	4034(2)	7139(3)	3450(1)	27(1)
C(3C)	4199(2)	7017(3)	3933(1)	44(1)
C(4C)	3461(2)	7003(3)	4099(1)	42(1)
C(5C)	2889(2)	7973(3)	3847(1)	59(1)
C(6C)	2629(2)	6966(3)	3514(1)	38(1)
C(7C)	2897(2)	6016(3)	3866(1)	29(1)
C(8C)	2236(2)	5760(3)	4094(1)	62(1)
C(9C)	3240(2)	4828(3)	3789(1)	54(1)
C(10C)	2997(2)	6069(3)	2873(1)	68(1)
C(11C)	4647(2)	8417(3)	2991(1)	19(1)
C(12C)	5894(2)	10884(3)	3340(1)	17(1)
C(13C)	6230(2)	11309(3)	2979(1)	22(1)
C(14C)	6915(2)	12159(3)	3180(1)	24(1)
C(15C)	7107(2)	11793(3)	3646(1)	20(1)
C(16C)	6294(2)	11538(3)	3744(1)	20(1)
C(17C)	6330(2)	10771(3)	4133(1)	26(1)
C(18C)	6857(2)	11291(3)	4523(1)	36(1)
C(19C)	7499(2)	10755(3)	4735(1)	50(1)
C(20C)	5876(2)	12754(2)	3770(1)	30(1)
C(21C)	7562(2)	10660(3)	3691(1)	29(1)
O(1D)	2448(1)	9568(2)	5706(1)	22(1)
N(1D)	2316(1)	9676(2)	5000(1)	18(1)
N(2D)	1502(1)	8460(2)	5286(1)	17(1)
N(3D)	1058(1)	8271(2)	4883(1)	20(1)
N(4D)	652(2)	4479(3)	4404(1)	60(1)
C(1D)	2777(2)	11266(3)	4583(1)	20(1)
C(2D)	2861(2)	10713(3)	5029(1)	19(1)
C(3D)	3710(2)	10347(3)	5254(1)	22(1)
C(4D)	4331(2)	10852(3)	5040(1)	22(1)
C(5D)	4082(2)	10468(3)	4566(1)	28(1)
C(6D)	3561(2)	11630(3)	4505(1)	21(1)
C(7D)	4155(2)	12180(3)	4890(1)	19(1)
C(8D)	4852(2)	12740(3)	4756(1)	29(1)
C(9D)	3880(2)	13079(2)	5179(1)	27(1)
C(10D)	2184(2)	12297(3)	4504(1)	34(1)
C(11D)	2111(2)	9260(3)	5346(1)	18(1)

C(12D)	474(2)	7556(3)	4856(1)	21(1)
C(13D)	242(2)	6823(3)	5192(1)	23(1)
C(14D)	-443(2)	6031(3)	4963(1)	30(1)
C(15D)	-393(2)	6062(3)	4497(1)	30(1)
C(16D)	-126(2)	7383(3)	4440(1)	33(1)
C(17D)	223(2)	7589(3)	4064(1)	43(1)
C(18D)	-391(2)	7406(3)	3647(1)	49(1)
C(19D)	-294(2)	6585(3)	3380(1)	45(1)
C(20D)	-821(2)	8254(3)	4432(1)	49(1)
C(21D)	182(2)	5186(3)	4432(1)	41(1)
O(1E)	8957(1)	2962(2)	3954(1)	23(1)
N(1E)	9111(1)	3343(2)	3298(1)	23(1)
N(2E)	8234(1)	4448(2)	3577(1)	18(1)
N(3E)	7975(1)	4992(2)	3189(1)	18(1)
N(4E)	5416(2)	4619(3)	2676(1)	55(1)
C(1E)	10250(2)	2757(3)	3021(1)	27(1)
C(2E)	9728(2)	2424(3)	3323(1)	24(1)
C(3E)	9377(2)	1128(3)	3264(1)	33(1)
C(4E)	9790(2)	320(3)	3006(1)	34(1)
C(5E)	9751(2)	979(3)	2585(1)	40(1)
C(6E)	10510(2)	1644(3)	2813(1)	26(1)
C(7E)	10692(2)	505(3)	3114(1)	25(1)
C(8E)	11099(2)	-491(3)	2910(1)	45(1)
C(9E)	11128(2)	605(3)	3568(1)	39(1)
C(10E)	10950(2)	3556(3)	3238(1)	39(1)
C(11E)	8786(2)	3545(3)	3621(1)	19(1)
C(12E)	7421(2)	5765(3)	3167(1)	18(1)
C(13E)	7004(2)	6137(3)	3498(1)	25(1)
C(14E)	6339(2)	6964(3)	3272(1)	29(1)
C(15E)	6223(2)	6629(3)	2803(1)	23(1)
C(16E)	7076(2)	6398(3)	2754(1)	18(1)
C(17E)	7123(2)	5644(3)	2367(1)	24(1)
C(18E)	6728(2)	6220(3)	1957(1)	38(1)
C(19E)	6120(2)	5790(3)	1699(1)	50(1)
C(20E)	7492(2)	7645(2)	2755(1)	27(1)
C(21E)	5757(2)	5505(3)	2722(1)	32(1)
O(1F)	843(1)	4083(2)	974(1)	19(1)
N(1F)	996(1)	4228(2)	1681(1)	17(1)
N(2F)	1800(1)	3005(2)	1398(1)	16(1)
N(3F)	2191(1)	2699(2)	1802(1)	16(1)
N(4F)	2312(2)	-1390(2)	2133(1)	43(1)
C(1F)	746(2)	6432(2)	1750(1)	19(1)
C(2F)	393(2)	5148(2)	1665(1)	17(1)
C(3F)	-154(2)	4784(3)	1953(1)	29(1)
C(4F)	-428(2)	5865(3)	2172(1)	30(1)
C(5F)	308(2)	6554(3)	2408(1)	31(1)
C(6F)	284(2)	7212(3)	1992(1)	27(1)
C(7F)	-618(2)	6985(3)	1875(1)	25(1)
C(8F)	-1046(2)	7979(3)	2062(1)	39(1)
C(9F)	-1067(2)	6794(3)	1428(1)	38(1)
C(10F)	832(2)	7029(3)	1338(1)	32(1)

C(11F)	1186(2)	3806(2)	1337(1)	17(1)
C(12F)	2708(2)	1885(3)	1827(1)	16(1)
C(13F)	2914(2)	1165(2)	1478(1)	21(1)
C(14F)	3567(2)	290(3)	1693(1)	25(1)
C(15F)	3440(2)	166(3)	2140(1)	21(1)
C(16F)	3206(2)	1474(3)	2251(1)	19(1)
C(17F)	2743(2)	1528(3)	2595(1)	26(1)
C(18F)	3191(2)	970(3)	3000(1)	31(1)
C(19F)	3482(2)	1543(3)	3349(1)	60(1)
C(20F)	3944(2)	2261(3)	2370(1)	27(1)
C(21F)	2813(2)	-706(3)	2140(1)	27(1)

*Table A2.8 Bond lengths [Å] and angles [°] for semicarbazone **71** (CCDC 749151)*

O(1A)-C(11A)	1.235(3)	C(1B)-C(6B)	1.537(4)
N(1A)-C(11A)	1.337(3)	C(2B)-C(3B)	1.536(4)
N(1A)-C(2A)	1.477(3)	C(3B)-C(4B)	1.522(4)
N(2A)-C(11A)	1.379(3)	C(4B)-C(5B)	1.552(4)
N(2A)-N(3A)	1.389(3)	C(4B)-C(7B)	1.571(4)
N(3A)-C(12A)	1.278(3)	C(5B)-C(6B)	1.559(4)
N(4A)-C(21A)	1.132(4)	C(6B)-C(7B)	1.553(4)
C(1A)-C(10A)	1.521(4)	C(7B)-C(9B)	1.515(4)
C(1A)-C(6A)	1.548(4)	C(7B)-C(8B)	1.530(4)
C(1A)-C(2A)	1.550(4)	C(12B)-C(13B)	1.503(4)
C(2A)-C(3A)	1.532(4)	C(12B)-C(16B)	1.528(4)
C(3A)-C(4A)	1.535(4)	C(13B)-C(14B)	1.536(4)
C(4A)-C(5A)	1.561(4)	C(14B)-C(15B)	1.542(4)
C(4A)-C(7A)	1.563(4)	C(15B)-C(21B)	1.464(4)
C(5A)-C(6A)	1.559(4)	C(15B)-C(16B)	1.548(4)
C(6A)-C(7A)	1.573(4)	C(16B)-C(17B)	1.520(4)
C(7A)-C(9A)	1.529(4)	C(16B)-C(20B)	1.546(4)
C(7A)-C(8A)	1.558(4)	C(17B)-C(18B)	1.510(4)
C(12A)-C(13A)	1.506(4)	C(18B)-C(19B)	1.295(4)
C(12A)-C(16A)	1.527(4)	O(1C)-C(11C)	1.235(3)
C(13A)-C(14A)	1.552(4)	N(1C)-C(11C)	1.342(3)
C(14A)-C(15A)	1.531(4)	N(1C)-C(2C)	1.478(3)
C(15A)-C(21A)	1.477(4)	N(2C)-C(11C)	1.390(3)
C(15A)-C(16A)	1.557(4)	N(2C)-N(3C)	1.398(3)
C(16A)-C(17A)	1.530(4)	N(3C)-C(12C)	1.273(3)
C(16A)-C(20A)	1.543(4)	N(4C)-C(21C)	1.150(4)
C(17A)-C(18A)	1.486(4)	C(1C)-C(6C)	1.520(4)
C(18A)-C(19A)	1.308(4)	C(1C)-C(2C)	1.532(4)
O(1B)-C(11B)	1.238(3)	C(1C)-C(10C)	1.570(4)
N(1B)-C(11B)	1.348(3)	C(2C)-C(3C)	1.549(4)
N(1B)-C(2B)	1.482(3)	C(3C)-C(4C)	1.517(4)
N(2B)-C(11B)	1.365(3)	C(4C)-C(7C)	1.549(4)
N(2B)-N(3B)	1.395(3)	C(4C)-C(5C)	1.566(5)
N(3B)-C(12B)	1.274(3)	C(5C)-C(6C)	1.550(4)
N(4B)-C(21B)	1.141(4)	C(6C)-C(7C)	1.549(4)
C(1B)-C(10B)	1.522(4)	C(7C)-C(9C)	1.487(4)
C(1B)-C(2B)	1.524(4)	C(7C)-C(8C)	1.544(4)

C(12C)-C(13C)	1.513(4)	C(6E)-C(7E)	1.584(4)
C(12C)-C(16C)	1.531(4)	C(7E)-C(9E)	1.514(4)
C(13C)-C(14C)	1.547(4)	C(7E)-C(8E)	1.543(4)
C(14C)-C(15C)	1.543(3)	C(12E)-C(13E)	1.499(4)
C(15C)-C(21C)	1.472(4)	C(12E)-C(16E)	1.520(4)
C(15C)-C(16C)	1.556(4)	C(13E)-C(14E)	1.531(4)
C(16C)-C(17C)	1.521(4)	C(14E)-C(15E)	1.551(4)
C(16C)-C(20C)	1.539(4)	C(15E)-C(21E)	1.475(4)
C(17C)-C(18C)	1.509(4)	C(15E)-C(16E)	1.562(4)
C(18C)-C(19C)	1.321(4)	C(16E)-C(17E)	1.534(4)
O(1D)-C(11D)	1.240(3)	C(16E)-C(20E)	1.555(4)
N(1D)-C(11D)	1.347(3)	C(17E)-C(18E)	1.505(4)
N(1D)-C(2D)	1.479(3)	C(18E)-C(19E)	1.291(4)
N(2D)-C(11D)	1.366(3)	O(1F)-C(11F)	1.243(3)
N(2D)-N(3D)	1.388(3)	N(1F)-C(11F)	1.332(3)
N(3D)-C(12D)	1.279(3)	N(1F)-C(2F)	1.458(3)
N(4D)-C(21D)	1.153(4)	N(2F)-C(11F)	1.371(3)
C(1D)-C(6D)	1.512(4)	N(2F)-N(3F)	1.388(3)
C(1D)-C(10D)	1.523(4)	N(3F)-C(12F)	1.266(3)
C(1D)-C(2D)	1.560(4)	N(4F)-C(21F)	1.154(4)
C(2D)-C(3D)	1.557(4)	C(1F)-C(6F)	1.525(4)
C(3D)-C(4D)	1.530(4)	C(1F)-C(10F)	1.541(4)
C(4D)-C(7D)	1.552(4)	C(1F)-C(2F)	1.544(4)
C(4D)-C(5D)	1.572(4)	C(2F)-C(3F)	1.547(4)
C(5D)-C(6D)	1.559(4)	C(3F)-C(4F)	1.525(4)
C(6D)-C(7D)	1.562(4)	C(4F)-C(5F)	1.546(4)
C(7D)-C(8D)	1.523(4)	C(4F)-C(7F)	1.560(4)
C(7D)-C(9D)	1.525(4)	C(5F)-C(6F)	1.539(4)
C(12D)-C(13D)	1.497(4)	C(6F)-C(7F)	1.560(4)
C(12D)-C(16D)	1.532(4)	C(7F)-C(9F)	1.512(4)
C(13D)-C(14D)	1.536(4)	C(7F)-C(8F)	1.534(4)
C(14D)-C(15D)	1.553(4)	C(12F)-C(13F)	1.502(4)
C(15D)-C(21D)	1.447(5)	C(12F)-C(16F)	1.532(4)
C(15D)-C(16D)	1.553(4)	C(13F)-C(14F)	1.539(4)
C(16D)-C(17D)	1.515(4)	C(14F)-C(15F)	1.538(4)
C(16D)-C(20D)	1.547(4)	C(15F)-C(21F)	1.461(4)
C(17D)-C(18D)	1.548(4)	C(15F)-C(16F)	1.565(4)
C(18D)-C(19D)	1.298(4)	C(16F)-C(20F)	1.532(4)
O(1E)-C(11E)	1.243(3)	C(16F)-C(17F)	1.534(4)
N(1E)-C(11E)	1.333(4)	C(17F)-C(18F)	1.511(4)
N(1E)-C(2E)	1.470(3)	C(18F)-C(19F)	1.305(4)
N(2E)-C(11E)	1.372(3)		
N(2E)-N(3E)	1.386(3)	C(11A)-N(1A)-C(2A)	124.8(2)
N(3E)-C(12E)	1.282(3)	C(11A)-N(2A)-N(3A)	119.0(3)
N(4E)-C(21E)	1.136(4)	C(12A)-N(3A)-N(2A)	116.0(3)
C(1E)-C(6E)	1.524(4)	C(10A)-C(1A)-C(6A)	112.8(3)
C(1E)-C(2E)	1.542(4)	C(10A)-C(1A)-C(2A)	110.4(3)
C(1E)-C(10E)	1.546(4)	C(6A)-C(1A)-C(2A)	110.6(2)
C(2E)-C(3E)	1.550(4)	N(1A)-C(2A)-C(3A)	111.6(2)
C(3E)-C(4E)	1.523(4)	N(1A)-C(2A)-C(1A)	112.4(2)
C(4E)-C(5E)	1.549(4)	C(3A)-C(2A)-C(1A)	114.1(2)
C(4E)-C(7E)	1.554(4)	C(2A)-C(3A)-C(4A)	113.8(2)
C(5E)-C(6E)	1.553(4)	C(3A)-C(4A)-C(5A)	107.0(3)

C(3A)-C(4A)-C(7A)	111.3(3)	C(8B)-C(7B)-C(4B)	111.7(3)
C(5A)-C(4A)-C(7A)	88.0(2)	C(6B)-C(7B)-C(4B)	86.0(2)
C(4A)-C(5A)-C(6A)	85.8(2)	O(1B)-C(11B)-N(1B)	124.6(3)
C(1A)-C(6A)-C(5A)	106.1(2)	O(1B)-C(11B)-N(2B)	120.3(3)
C(1A)-C(6A)-C(7A)	115.0(3)	N(1B)-C(11B)-N(2B)	115.1(3)
C(5A)-C(6A)-C(7A)	87.7(2)	N(3B)-C(12B)-C(13B)	128.4(3)
C(9A)-C(7A)-C(8A)	108.2(3)	N(3B)-C(12B)-C(16B)	120.5(3)
C(9A)-C(7A)-C(4A)	119.7(3)	C(13B)-C(12B)-C(16B)	111.2(2)
C(8A)-C(7A)-C(4A)	110.1(3)	C(12B)-C(13B)-C(14B)	104.1(2)
C(9A)-C(7A)-C(6A)	121.8(3)	C(13B)-C(14B)-C(15B)	104.1(2)
C(8A)-C(7A)-C(6A)	109.9(3)	C(21B)-C(15B)-C(14B)	108.8(2)
C(4A)-C(7A)-C(6A)	85.3(2)	C(21B)-C(15B)-C(16B)	111.1(2)
O(1A)-C(11A)-N(1A)	125.2(3)	C(14B)-C(15B)-C(16B)	103.9(2)
O(1A)-C(11A)-N(2A)	119.4(3)	C(17B)-C(16B)-C(12B)	111.9(2)
N(1A)-C(11A)-N(2A)	115.5(3)	C(17B)-C(16B)-C(15B)	114.9(2)
N(3A)-C(12A)-C(13A)	128.5(3)	C(12B)-C(16B)-C(15B)	101.2(2)
N(3A)-C(12A)-C(16A)	120.6(3)	C(17B)-C(16B)-C(20B)	110.1(2)
C(13A)-C(12A)-C(16A)	110.8(3)	C(12B)-C(16B)-C(20B)	108.2(2)
C(12A)-C(13A)-C(14A)	104.3(2)	C(15B)-C(16B)-C(20B)	110.2(2)
C(15A)-C(14A)-C(13A)	104.1(2)	C(18B)-C(17B)-C(16B)	112.2(2)
C(21A)-C(15A)-C(14A)	109.6(3)	C(19B)-C(18B)-C(17B)	126.5(3)
C(21A)-C(15A)-C(16A)	109.9(2)	N(4B)-C(21B)-C(15B)	178.4(4)
C(14A)-C(15A)-C(16A)	104.0(2)	C(11C)-N(1C)-C(2C)	123.1(3)
C(12A)-C(16A)-C(17A)	113.8(2)	C(11C)-N(2C)-N(3C)	117.2(2)
C(12A)-C(16A)-C(20A)	108.4(2)	C(12C)-N(3C)-N(2C)	116.3(2)
C(17A)-C(16A)-C(20A)	110.6(3)	C(6C)-C(1C)-C(2C)	111.9(3)
C(12A)-C(16A)-C(15A)	100.1(2)	C(6C)-C(1C)-C(10C)	110.4(3)
C(17A)-C(16A)-C(15A)	114.7(2)	C(2C)-C(1C)-C(10C)	113.1(3)
C(20A)-C(16A)-C(15A)	108.6(2)	N(1C)-C(2C)-C(1C)	112.6(3)
C(18A)-C(17A)-C(16A)	113.6(2)	N(1C)-C(2C)-C(3C)	107.7(2)
C(19A)-C(18A)-C(17A)	125.2(3)	C(1C)-C(2C)-C(3C)	116.1(3)
N(4A)-C(21A)-C(15A)	176.6(4)	C(4C)-C(3C)-C(2C)	113.2(3)
C(11B)-N(1B)-C(2B)	125.9(3)	C(3C)-C(4C)-C(7C)	109.3(3)
C(11B)-N(2B)-N(3B)	119.6(2)	C(3C)-C(4C)-C(5C)	107.4(3)
C(12B)-N(3B)-N(2B)	115.9(2)	C(7C)-C(4C)-C(5C)	87.7(2)
C(10B)-C(1B)-C(2B)	111.8(3)	C(6C)-C(5C)-C(4C)	86.1(3)
C(10B)-C(1B)-C(6B)	112.5(3)	C(1C)-C(6C)-C(7C)	114.4(3)
C(2B)-C(1B)-C(6B)	111.3(2)	C(1C)-C(6C)-C(5C)	105.3(3)
N(1B)-C(2B)-C(1B)	111.3(2)	C(7C)-C(6C)-C(5C)	88.3(2)
N(1B)-C(2B)-C(3B)	112.6(2)	C(9C)-C(7C)-C(8C)	107.4(3)
C(1B)-C(2B)-C(3B)	116.6(2)	C(9C)-C(7C)-C(6C)	122.3(3)
C(4B)-C(3B)-C(2B)	111.8(2)	C(8C)-C(7C)-C(6C)	110.6(3)
C(3B)-C(4B)-C(5B)	108.5(3)	C(9C)-C(7C)-C(4C)	117.7(3)
C(3B)-C(4B)-C(7B)	112.2(3)	C(8C)-C(7C)-C(4C)	110.8(3)
C(5B)-C(4B)-C(7B)	86.8(2)	C(6C)-C(7C)-C(4C)	86.7(2)
C(4B)-C(5B)-C(6B)	86.4(2)	O(1C)-C(11C)-N(1C)	124.6(3)
C(1B)-C(6B)-C(7B)	114.7(2)	O(1C)-C(11C)-N(2C)	120.2(3)
C(1B)-C(6B)-C(5B)	105.6(3)	N(1C)-C(11C)-N(2C)	115.2(3)
C(7B)-C(6B)-C(5B)	87.2(2)	N(3C)-C(12C)-C(13C)	129.6(3)
C(9B)-C(7B)-C(8B)	107.1(3)	N(3C)-C(12C)-C(16C)	119.8(3)
C(9B)-C(7B)-C(6B)	121.9(3)	C(13C)-C(12C)-C(16C)	110.4(2)
C(8B)-C(7B)-C(6B)	111.5(3)	C(12C)-C(13C)-C(14C)	104.9(2)
C(9B)-C(7B)-C(4B)	117.6(3)	C(15C)-C(14C)-C(13C)	103.7(2)

C(21C)-C(15C)-C(14C)	108.0(3)	C(19D)-C(18D)-C(17D)	121.1(4)
C(21C)-C(15C)-C(16C)	109.2(2)	N(4D)-C(21D)-C(15D)	176.3(4)
C(14C)-C(15C)-C(16C)	104.4(2)	C(11E)-N(1E)-C(2E)	121.0(3)
C(17C)-C(16C)-C(12C)	112.8(2)	C(11E)-N(2E)-N(3E)	119.1(2)
C(17C)-C(16C)-C(20C)	111.5(3)	C(12E)-N(3E)-N(2E)	115.2(2)
C(12C)-C(16C)-C(20C)	109.2(2)	C(6E)-C(1E)-C(2E)	112.3(2)
C(17C)-C(16C)-C(15C)	114.2(3)	C(6E)-C(1E)-C(10E)	112.2(3)
C(12C)-C(16C)-C(15C)	99.6(2)	C(2E)-C(1E)-C(10E)	111.4(3)
C(20C)-C(16C)-C(15C)	108.9(2)	N(1E)-C(2E)-C(1E)	109.8(2)
C(18C)-C(17C)-C(16C)	113.5(2)	N(1E)-C(2E)-C(3E)	111.2(2)
C(19C)-C(18C)-C(17C)	124.0(3)	C(1E)-C(2E)-C(3E)	114.6(3)
N(4C)-C(21C)-C(15C)	174.7(4)	C(4E)-C(3E)-C(2E)	112.6(3)
C(11D)-N(1D)-C(2D)	120.1(2)	C(3E)-C(4E)-C(5E)	107.0(3)
C(11D)-N(2D)-N(3D)	118.9(2)	C(3E)-C(4E)-C(7E)	112.6(3)
C(12D)-N(3D)-N(2D)	115.1(2)	C(5E)-C(4E)-C(7E)	88.6(2)
C(6D)-C(1D)-C(10D)	112.7(2)	C(4E)-C(5E)-C(6E)	86.2(2)
C(6D)-C(1D)-C(2D)	111.6(2)	C(1E)-C(6E)-C(5E)	106.5(3)
C(10D)-C(1D)-C(2D)	111.4(2)	C(1E)-C(6E)-C(7E)	113.4(2)
N(1D)-C(2D)-C(3D)	111.4(2)	C(5E)-C(6E)-C(7E)	87.4(2)
N(1D)-C(2D)-C(1D)	108.7(2)	C(9E)-C(7E)-C(8E)	107.4(3)
C(3D)-C(2D)-C(1D)	114.8(2)	C(9E)-C(7E)-C(4E)	119.5(3)
C(4D)-C(3D)-C(2D)	113.1(2)	C(8E)-C(7E)-C(4E)	110.8(3)
C(3D)-C(4D)-C(7D)	112.2(2)	C(9E)-C(7E)-C(6E)	122.7(3)
C(3D)-C(4D)-C(5D)	106.9(2)	C(8E)-C(7E)-C(6E)	109.9(3)
C(7D)-C(4D)-C(5D)	87.2(2)	C(4E)-C(7E)-C(6E)	85.0(2)
C(6D)-C(5D)-C(4D)	85.8(2)	O(1E)-C(11E)-N(1E)	123.4(3)
C(1D)-C(6D)-C(5D)	106.8(2)	O(1E)-C(11E)-N(2E)	119.4(3)
C(1D)-C(6D)-C(7D)	115.5(2)	N(1E)-C(11E)-N(2E)	117.2(3)
C(5D)-C(6D)-C(7D)	87.3(2)	N(3E)-C(12E)-C(13E)	129.1(3)
C(8D)-C(7D)-C(9D)	107.8(2)	N(3E)-C(12E)-C(16E)	119.8(3)
C(8D)-C(7D)-C(4D)	111.1(2)	C(13E)-C(12E)-C(16E)	111.0(3)
C(9D)-C(7D)-C(4D)	118.9(2)	C(12E)-C(13E)-C(14E)	104.9(2)
C(8D)-C(7D)-C(6D)	110.8(2)	C(13E)-C(14E)-C(15E)	104.4(2)
C(9D)-C(7D)-C(6D)	120.5(2)	C(21E)-C(15E)-C(14E)	108.5(3)
C(4D)-C(7D)-C(6D)	86.4(2)	C(21E)-C(15E)-C(16E)	110.5(3)
O(1D)-C(11D)-N(1D)	123.2(3)	C(14E)-C(15E)-C(16E)	103.3(2)
O(1D)-C(11D)-N(2D)	120.0(3)	C(12E)-C(16E)-C(17E)	113.7(2)
N(1D)-C(11D)-N(2D)	116.8(3)	C(12E)-C(16E)-C(20E)	108.3(2)
N(3D)-C(12D)-C(13D)	129.0(3)	C(17E)-C(16E)-C(20E)	111.5(2)
N(3D)-C(12D)-C(16D)	121.0(3)	C(12E)-C(16E)-C(15E)	100.3(2)
C(13D)-C(12D)-C(16D)	110.0(3)	C(17E)-C(16E)-C(15E)	114.0(2)
C(12D)-C(13D)-C(14D)	105.1(2)	C(20E)-C(16E)-C(15E)	108.4(2)
C(13D)-C(14D)-C(15D)	104.8(2)	C(18E)-C(17E)-C(16E)	114.2(2)
C(21D)-C(15D)-C(16D)	111.7(3)	C(19E)-C(18E)-C(17E)	125.0(3)
C(21D)-C(15D)-C(14D)	109.1(3)	N(4E)-C(21E)-C(15E)	177.2(4)
C(16D)-C(15D)-C(14D)	103.0(2)	C(11F)-N(1F)-C(2F)	122.2(2)
C(17D)-C(16D)-C(12D)	112.5(3)	C(11F)-N(2F)-N(3F)	119.7(2)
C(17D)-C(16D)-C(20D)	110.9(3)	C(12F)-N(3F)-N(2F)	115.1(2)
C(12D)-C(16D)-C(20D)	108.4(3)	C(6F)-C(1F)-C(10F)	112.8(2)
C(17D)-C(16D)-C(15D)	115.2(3)	C(6F)-C(1F)-C(2F)	111.9(2)
C(12D)-C(16D)-C(15D)	100.1(3)	C(10F)-C(1F)-C(2F)	110.4(2)
C(20D)-C(16D)-C(15D)	109.0(3)	N(1F)-C(2F)-C(1F)	112.0(2)
C(16D)-C(17D)-C(18D)	111.8(3)	N(1F)-C(2F)-C(3F)	110.1(2)

C(1F)-C(2F)-C(3F)	114.0(2)	N(3F)-C(12F)-C(13F)	128.3(3)
C(4F)-C(3F)-C(2F)	113.1(2)	N(3F)-C(12F)-C(16F)	121.2(3)
C(3F)-C(4F)-C(5F)	107.6(3)	C(13F)-C(12F)-C(16F)	110.5(2)
C(3F)-C(4F)-C(7F)	111.8(2)	C(12F)-C(13F)-C(14F)	105.4(2)
C(5F)-C(4F)-C(7F)	87.6(2)	C(15F)-C(14F)-C(13F)	103.7(2)
C(6F)-C(5F)-C(4F)	86.3(2)	C(21F)-C(15F)-C(14F)	109.4(3)
C(1F)-C(6F)-C(5F)	106.7(3)	C(21F)-C(15F)-C(16F)	111.6(3)
C(1F)-C(6F)-C(7F)	114.3(2)	C(14F)-C(15F)-C(16F)	104.1(2)
C(5F)-C(6F)-C(7F)	87.8(2)	C(20F)-C(16F)-C(12F)	109.6(2)
C(9F)-C(7F)-C(8F)	107.1(3)	C(20F)-C(16F)-C(17F)	110.5(2)
C(9F)-C(7F)-C(4F)	118.9(3)	C(12F)-C(16F)-C(17F)	111.6(2)
C(8F)-C(7F)-C(4F)	111.7(3)	C(20F)-C(16F)-C(15F)	109.2(2)
C(9F)-C(7F)-C(6F)	122.2(3)	C(12F)-C(16F)-C(15F)	100.7(2)
C(8F)-C(7F)-C(6F)	110.5(2)	C(17F)-C(16F)-C(15F)	114.7(2)
C(4F)-C(7F)-C(6F)	85.1(2)	C(18F)-C(17F)-C(16F)	112.0(3)
O(1F)-C(11F)-N(1F)	124.5(3)	C(19F)-C(18F)-C(17F)	126.5(3)
O(1F)-C(11F)-N(2F)	119.3(3)	N(4F)-C(21F)-C(15F)	178.8(4)
N(1F)-C(11F)-N(2F)	116.2(3)		

*Table A2.9 Anisotropic displacement parameters ($Å^2$ x 10^4) for semicarbazone **71** (CCDC 749151). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1A)	224(13)	220(12)	128(11)	-48(10)	16(10)	-60(10)
N(1A)	219(16)	216(15)	160(15)	-73(12)	51(13)	-73(12)
N(2A)	205(16)	190(14)	133(14)	-20(12)	-3(12)	-60(12)
N(3A)	190(16)	199(15)	191(15)	-54(12)	26(12)	18(12)
N(4A)	320(20)	480(20)	530(20)	58(17)	124(16)	33(16)
C(1A)	210(20)	243(19)	300(20)	0(16)	59(16)	-10(15)
C(2A)	240(20)	211(18)	200(18)	-27(15)	62(15)	-32(15)
C(3A)	200(20)	151(17)	480(20)	17(17)	107(17)	9(15)
C(4A)	220(20)	300(20)	500(20)	66(18)	23(18)	-43(16)
C(5A)	290(20)	410(20)	280(20)	-40(18)	88(17)	-76(17)
C(6A)	320(20)	155(18)	430(20)	-9(16)	141(18)	-27(15)
C(7A)	270(20)	192(18)	480(20)	44(17)	199(18)	-50(16)
C(8A)	330(20)	310(20)	770(30)	80(20)	220(20)	-67(18)
C(9A)	570(30)	410(20)	490(30)	20(20)	330(20)	70(20)
C(10A)	490(30)	400(20)	410(20)	130(20)	-30(20)	0(20)
C(11A)	100(18)	155(17)	250(20)	39(15)	-11(15)	8(14)
C(12A)	143(18)	183(18)	223(18)	-20(15)	11(15)	21(14)
C(13A)	230(20)	240(19)	260(20)	-13(16)	11(16)	-91(16)
C(14A)	230(20)	207(18)	263(19)	-21(16)	19(16)	-77(15)
C(15A)	230(20)	128(17)	228(19)	-64(15)	17(15)	-57(15)
C(16A)	136(18)	206(18)	255(19)	-65(15)	28(15)	-3(14)
C(17A)	230(20)	310(20)	205(19)	-70(16)	63(15)	-70(16)
C(18A)	390(20)	280(20)	260(20)	-107(17)	102(18)	-30(17)
C(19A)	430(30)	360(20)	320(20)	-45(18)	69(19)	-110(19)

C(20A)	270(20)	254(19)	370(20)	-97(17)	59(17)	-2(16)
C(21A)	190(20)	320(20)	220(20)	-19(17)	20(16)	-49(17)
O(1B)	197(13)	204(12)	164(12)	-30(10)	-11(10)	-54(10)
N(1B)	242(16)	184(15)	182(15)	-9(12)	55(13)	-79(12)
N(2B)	192(15)	186(14)	118(14)	29(11)	43(12)	-71(12)
N(3B)	156(15)	176(14)	148(14)	-27(12)	0(12)	-13(12)
N(4B)	530(20)	304(18)	370(20)	-36(15)	93(17)	30(16)
C(1B)	240(20)	231(19)	330(20)	22(16)	86(16)	8(15)
C(2B)	177(19)	217(18)	310(20)	-28(16)	71(16)	-63(15)
C(3B)	180(20)	173(18)	480(20)	13(17)	83(17)	-39(15)
C(4B)	340(20)	250(20)	410(20)	-48(18)	126(18)	-21(17)
C(5B)	330(20)	450(20)	300(20)	-30(19)	18(18)	-57(18)
C(6B)	180(20)	370(20)	290(20)	6(17)	62(16)	-30(16)
C(7B)	181(19)	233(19)	330(20)	54(16)	57(16)	-84(15)
C(8B)	390(30)	410(20)	630(30)	-10(20)	140(20)	-70(19)
C(9B)	500(30)	410(20)	380(20)	62(19)	130(20)	80(20)
C(10B)	320(20)	420(20)	460(20)	-33(19)	117(19)	31(18)
C(11B)	190(20)	88(16)	290(20)	13(15)	35(17)	29(14)
C(12B)	114(17)	179(17)	151(17)	-15(14)	31(14)	48(14)
C(13B)	202(19)	192(17)	148(17)	2(14)	44(14)	-48(14)
C(14B)	218(19)	203(18)	212(18)	-13(15)	50(15)	-71(15)
C(15B)	142(18)	175(17)	202(18)	-4(15)	-6(14)	-75(14)
C(16B)	151(18)	197(17)	117(16)	-35(14)	21(14)	-3(14)
C(17B)	220(20)	267(19)	228(19)	-61(15)	73(15)	-90(15)
C(18B)	300(20)	320(20)	224(19)	-80(16)	96(17)	-86(16)
C(19B)	680(30)	300(20)	240(20)	-15(18)	0(20)	-110(20)
C(20B)	250(20)	240(18)	250(19)	-23(15)	2(15)	-31(15)
C(21B)	310(20)	191(19)	205(19)	-30(15)	15(17)	-52(16)
O(1C)	196(13)	211(12)	147(12)	-57(10)	-5(10)	-75(10)
N(1C)	259(17)	196(15)	176(15)	-15(12)	54(13)	-97(12)
N(2C)	193(15)	222(15)	109(14)	40(12)	-5(12)	-72(12)
N(3C)	176(15)	186(15)	164(14)	-11(12)	6(12)	-11(12)
N(4C)	350(20)	470(20)	510(20)	121(18)	111(16)	46(16)
C(1C)	490(30)	330(20)	320(20)	98(18)	9(19)	-132(19)
C(2C)	270(20)	410(20)	132(18)	16(16)	24(16)	-170(17)
C(3C)	330(20)	600(30)	360(20)	130(20)	15(19)	-120(20)
C(4C)	520(30)	510(20)	260(20)	-40(19)	174(19)	-220(20)
C(5C)	580(30)	370(20)	760(30)	-190(20)	40(30)	-30(20)
C(6C)	280(20)	380(20)	480(20)	20(20)	71(19)	14(18)
C(7C)	270(20)	300(20)	310(20)	89(17)	107(17)	-19(17)
C(8C)	530(30)	810(30)	600(30)	-90(20)	250(20)	-250(20)
C(9C)	610(30)	360(20)	600(30)	80(20)	60(20)	-30(20)
C(10C)	810(40)	890(30)	330(20)	-170(20)	110(20)	-480(30)
C(11C)	90(18)	206(19)	260(20)	143(16)	13(15)	49(14)
C(12C)	154(18)	183(17)	164(17)	-4(14)	23(14)	16(14)
C(13C)	220(19)	253(19)	201(18)	-17(15)	65(15)	-65(15)
C(14C)	230(20)	247(18)	240(19)	11(16)	28(15)	-64(15)
C(15C)	193(19)	197(18)	195(18)	-42(15)	27(15)	-78(15)
C(16C)	260(20)	194(18)	142(17)	18(14)	49(15)	-45(15)
C(17C)	270(20)	280(20)	245(19)	-57(16)	86(16)	-80(16)
C(18C)	460(30)	380(20)	230(20)	-7(18)	61(19)	-174(19)

C(19C)	600(30)	540(30)	300(20)	100(20)	-30(20)	-310(20)
C(20C)	310(20)	253(19)	340(20)	-82(17)	87(17)	-52(16)
C(21C)	200(20)	450(20)	240(20)	15(18)	54(16)	-93(18)
O(1D)	224(13)	267(13)	153(12)	-22(10)	19(10)	-104(10)
N(1D)	208(16)	215(15)	130(14)	-47(12)	44(12)	-86(12)
N(2D)	203(16)	149(14)	146(15)	67(12)	16(12)	-39(12)
N(3D)	207(16)	180(15)	196(16)	10(12)	1(13)	-30(12)
N(4D)	570(30)	380(20)	900(30)	-210(20)	280(20)	-99(18)
C(1D)	214(19)	229(18)	156(17)	-7(15)	18(15)	-30(15)
C(2D)	179(19)	234(18)	141(17)	22(14)	25(14)	-38(15)
C(3D)	200(19)	241(18)	215(18)	32(15)	34(15)	-6(15)
C(4D)	199(19)	242(19)	246(19)	23(15)	87(15)	6(15)
C(5D)	330(20)	236(19)	330(20)	-75(16)	208(17)	-65(16)
C(6D)	220(20)	249(18)	180(18)	57(15)	98(15)	-27(15)
C(7D)	189(19)	144(17)	250(19)	-12(15)	97(15)	11(14)
C(8D)	250(20)	252(19)	370(20)	43(16)	81(17)	-43(16)
C(9D)	290(20)	212(19)	300(20)	-9(16)	44(17)	-9(16)
C(10D)	290(20)	400(20)	310(20)	88(18)	33(17)	2(18)
C(11D)	130(18)	171(18)	237(19)	57(16)	47(15)	1(14)
C(12D)	220(20)	181(18)	196(18)	-4(15)	-11(15)	-19(15)
C(13D)	200(20)	282(19)	206(18)	-18(16)	38(15)	-70(15)
C(14D)	300(20)	340(20)	260(20)	-19(17)	84(17)	-118(17)
C(15D)	260(20)	400(20)	250(20)	-130(18)	71(17)	-140(18)
C(16D)	360(20)	380(20)	250(20)	-6(17)	92(18)	-169(18)
C(17D)	530(30)	490(20)	230(20)	-97(19)	1(19)	-300(20)
C(18D)	440(30)	560(30)	450(30)	60(20)	20(20)	-140(20)
C(19D)	540(30)	500(30)	360(20)	-150(20)	190(20)	-80(20)
C(20D)	350(30)	510(30)	540(30)	50(20)	-50(20)	10(20)
C(21D)	420(30)	410(30)	390(20)	-120(20)	100(20)	-230(20)
O(1E)	245(14)	259(13)	175(12)	20(11)	34(10)	95(10)
N(1E)	229(16)	265(16)	202(16)	47(13)	85(13)	106(13)
N(2E)	175(16)	206(15)	156(14)	5(12)	52(12)	70(12)
N(3E)	175(15)	196(15)	160(15)	42(12)	-2(12)	11(12)
N(4E)	340(20)	480(20)	740(30)	162(19)	-68(18)	-70(17)
C(1E)	260(20)	290(20)	280(20)	50(17)	78(17)	7(16)
C(2E)	270(20)	215(19)	270(19)	7(16)	150(16)	48(15)
C(3E)	290(20)	300(20)	450(20)	37(18)	228(19)	61(17)
C(4E)	400(20)	220(20)	440(20)	-56(18)	179(19)	-54(18)
C(5E)	440(30)	450(20)	340(20)	-130(20)	140(20)	-40(20)
C(6E)	260(20)	290(20)	280(20)	-33(16)	147(16)	18(16)
C(7E)	250(20)	185(18)	340(20)	-61(16)	128(17)	15(15)
C(8E)	510(30)	320(20)	610(30)	-80(20)	310(20)	21(19)
C(9E)	440(30)	380(20)	360(20)	69(19)	104(19)	87(19)
C(10E)	390(20)	270(20)	530(30)	-61(18)	140(20)	-10(17)
C(11E)	124(19)	212(18)	230(20)	-28(16)	31(16)	-43(14)
C(12E)	156(18)	173(17)	208(18)	34(15)	37(15)	-25(14)
C(13E)	300(20)	235(19)	213(19)	79(16)	67(16)	102(16)
C(14E)	250(20)	320(20)	300(20)	85(17)	79(16)	145(17)
C(15E)	240(20)	169(18)	269(19)	58(15)	19(16)	35(15)
C(16E)	156(18)	186(18)	174(17)	6(14)	-16(14)	23(14)
C(17E)	310(20)	211(18)	173(18)	2(15)	0(16)	12(15)

C(18E)	480(30)	350(20)	260(20)	-5(18)	-26(19)	101(19)
C(19E)	610(30)	410(20)	390(20)	-30(20)	-50(20)	190(20)
C(20E)	250(20)	290(20)	260(19)	62(16)	45(16)	-16(16)
C(21E)	170(20)	370(20)	360(20)	149(19)	-50(17)	35(17)
O(1F)	204(13)	197(12)	144(12)	22(10)	-13(10)	60(10)
N(1F)	194(16)	172(14)	142(14)	45(12)	51(12)	91(12)
N(2F)	175(15)	157(14)	151(15)	-29(11)	26(12)	74(12)
N(3F)	175(15)	138(14)	149(14)	16(12)	9(12)	-12(12)
N(4F)	530(20)	264(18)	450(20)	-10(15)	30(18)	35(16)
C(1F)	178(19)	179(18)	230(18)	-20(15)	58(15)	28(14)
C(2F)	213(19)	144(17)	172(17)	22(14)	86(14)	22(14)
C(3F)	310(20)	253(19)	340(20)	-34(17)	153(17)	-3(16)
C(4F)	270(20)	400(20)	280(20)	-77(18)	183(17)	37(17)
C(5F)	340(20)	360(20)	238(19)	-2(17)	79(17)	-21(18)
C(6F)	360(20)	270(20)	229(19)	-60(16)	140(17)	-14(17)
C(7F)	210(20)	218(19)	350(20)	-62(17)	136(17)	33(15)
C(8F)	370(20)	340(20)	510(20)	-85(19)	190(20)	43(18)
C(9F)	240(20)	510(20)	370(20)	-40(20)	35(18)	111(18)
C(10F)	380(20)	292(19)	320(20)	-33(17)	164(17)	-4(17)
C(11F)	160(19)	93(17)	270(20)	-49(15)	76(16)	-67(14)
C(12F)	172(18)	150(17)	138(17)	-26(14)	12(14)	-20(14)
C(13F)	270(20)	177(17)	179(18)	36(15)	50(15)	67(15)
C(14F)	250(20)	275(19)	202(19)	-27(16)	7(16)	109(16)
C(15F)	240(20)	174(18)	199(18)	-14(15)	10(15)	70(15)
C(16F)	198(19)	212(18)	135(17)	26(14)	14(14)	46(15)
C(17F)	290(20)	277(19)	224(19)	44(16)	75(16)	95(16)
C(18F)	350(20)	340(20)	280(20)	43(17)	137(18)	79(17)
C(19F)	950(40)	600(30)	190(20)	-60(20)	10(20)	290(30)
C(20F)	230(20)	320(20)	225(19)	5(16)	-29(15)	-11(16)
C(21F)	340(20)	210(20)	210(20)	4(16)	-9(17)	97(17)

*Table A2.10 Hydrogen bonds for semicarbazone **71** (CCDC 749151) [Å and °]*

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2A)-H(2A)...O(1F)#1	0.88	2.05	2.879(3)	156.2
N(2B)-H(2B)...O(1C)	0.88	2.06	2.895(3)	159.2
N(2C)-H(2C)...O(1B)	0.88	2.16	2.926(3)	144.7
N(2D)-H(2D)...O(1E)#2	0.88	2.02	2.842(3)	154.0
N(2E)-H(2E)...O(1D)#3	0.88	2.04	2.879(3)	159.6
N(2F)-H(2F)...O(1A)#4	0.88	2.04	2.892(3)	162.4

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,y+1/2,-z
#2 -x+1,y+1/2,-z+1
#3 -x+1,y-1/2,-z+1
#4 -x+1,y-1/2,-z

A2.3 CRYSTAL STRUCTURE OF COMPOUND 68

*Figure A2.3 ORTEP drawing of **68** (shown with 50% probability ellipsoids)*

NOTE: Crystallographic data have been deposited in the Cambridge Database (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 751261.

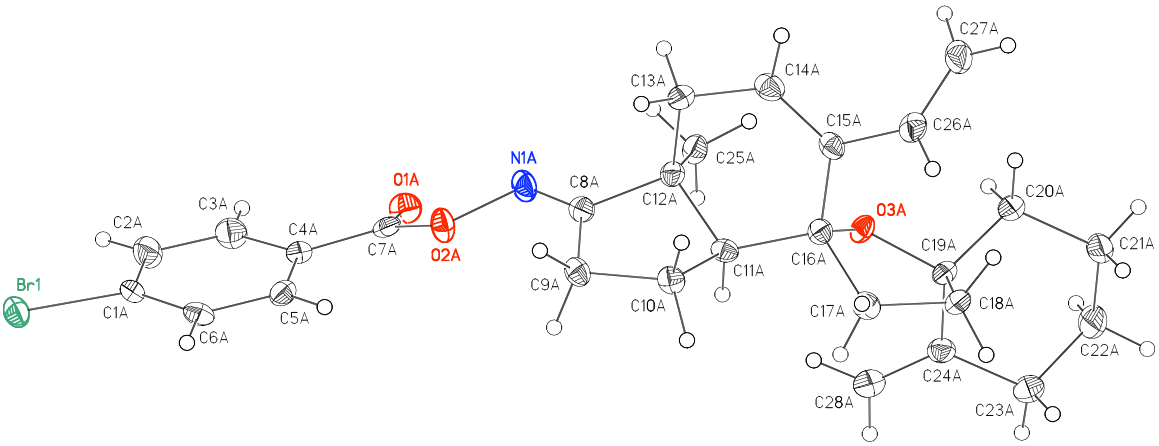


*Table A2.11 Crystal data and structure refinement for **68** (CCDC 751261)*

Empirical formula	$C_{28}H_{32}NO_3Br$
Formula weight	510.46
Crystallization Solvent	Ethyl acetate/heptane
Crystal Habit	Plate
Crystal size	0.43 x 0.29 x 0.06 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker KAPPA APEX II
Wavelength	0.71073 Å MoKα
Data Collection Temperature	100(2) K
θ range for 9936 reflections used in lattice determination	2.45 to 29.34°
Unit cell dimensions	a = 11.4503(6) Å b = 6.5371(3) Å β= 92.180(3)° c = 33.2116(16) Å
Volume	2484.1(2) $Å^3$
Z	4
Crystal system	Monoclinic
Space group	$P2_1$
Density (calculated)	1.365 Mg/m^3
F(000)	1064
Data collection program	Bruker APEX2 v2.1-0
θ range for data collection	1.78 to 29.74°
Completeness to θ = 29.74°	92.7 %
Index ranges	$-15 \le h \le 15, -9 \le k \le 8, -45 \le l \le 45$
Data collection scan type	ω scans; 12 settings
Data reduction program	Bruker SAINT-Plus v7.34A
Reflections collected	36895
Independent reflections	12339 [R_{int}= 0.0299]
Absorption coefficient	1.684 mm^{-1}
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7459 and 0.6043

Table A2.11 (cont.)

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 2008)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 2008)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	12339 / 1 / 851
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.004
Final R indices [I>2σ(I), 10737 reflections]	R1 = 0.0294, *w*R2 = 0.0515
R indices (all data)	R1 = 0.0387, *w*R2 = 0.0534
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.004
Average shift/error	0.000
Absolute structure determination	Anomalous differences
Absolute structure parameter	0.010(3)
Largest diff. peak and hole	0.567 and -0.323 e.Å^{-3}

Special Refinement Details

Crystals were mounted on a glass fiber using Paratone oil then placed on the diffractometer under a nitrogen stream at 100K.

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

*Table A2.12 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **68** (CCDC 751261). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor*

	x	y	z	U_{eq}
Br(1)	9880(1)	4696(1)	6209(1)	25(1)
O(1A)	5451(1)	6756(2)	7478(1)	23(1)
O(2A)	5684(1)	3349(2)	7575(1)	22(1)
O(3A)	2616(1)	1547(2)	9151(1)	16(1)
N(1A)	4587(1)	3471(3)	7783(1)	21(1)
C(1A)	8722(2)	4832(3)	6603(1)	19(1)
C(2A)	7995(2)	6497(3)	6600(1)	26(1)
C(3A)	7114(2)	6605(3)	6872(1)	24(1)
C(4A)	6956(2)	5006(3)	7142(1)	17(1)
C(5A)	7709(2)	3330(3)	7145(1)	18(1)
C(6A)	8614(2)	3241(3)	6876(1)	19(1)
C(7A)	5961(2)	5189(3)	7415(1)	18(1)
C(8A)	4548(2)	1987(3)	8028(1)	17(1)
C(9A)	5449(2)	392(3)	8140(1)	19(1)
C(10A)	4921(2)	-796(3)	8492(1)	18(1)
C(11A)	4020(2)	710(3)	8657(1)	16(1)
C(12A)	3463(2)	1686(3)	8273(1)	16(1)
C(13A)	2673(2)	121(3)	8050(1)	21(1)
C(14A)	1993(2)	-1189(3)	8328(1)	21(1)
C(15A)	2193(2)	-1397(3)	8723(1)	17(1)
C(16A)	3145(2)	-182(3)	8949(1)	16(1)
C(17A)	3741(2)	-1358(3)	9298(1)	19(1)
C(18A)	2950(2)	-1009(3)	9650(1)	18(1)
C(19A)	2504(2)	1203(3)	9579(1)	16(1)
C(20A)	1211(2)	1504(3)	9666(1)	20(1)
C(21A)	983(2)	1475(4)	10117(1)	26(1)
C(22A)	1717(2)	3101(4)	10336(1)	29(1)
C(23A)	3015(2)	2774(4)	10266(1)	26(1)
C(24A)	3269(2)	2688(3)	9822(1)	19(1)
C(25A)	2809(2)	3671(3)	8346(1)	20(1)
C(26A)	1497(2)	-2920(3)	8943(1)	21(1)
C(27A)	347(2)	-3031(4)	8921(1)	29(1)
C(28A)	4103(2)	3791(3)	9665(1)	22(1)
Br(2)	-2285(1)	2168(1)	8941(1)	36(1)
O(1B)	-950(1)	9378(2)	7531(1)	31(1)
O(2B)	443(1)	6988(2)	7431(1)	18(1)
O(3B)	3401(1)	8260(2)	5769(1)	16(1)
N(1B)	925(1)	8429(2)	7145(1)	18(1)
C(1B)	-1789(2)	3793(3)	8502(1)	23(1)
C(2B)	-2342(2)	5616(3)	8420(1)	26(1)
C(3B)	-1924(2)	6859(3)	8121(1)	23(1)
C(4B)	-967(2)	6258(3)	7904(1)	17(1)
C(5B)	-446(2)	4380(3)	7983(1)	21(1)
C(6B)	-857(2)	3129(3)	8284(1)	24(1)
C(7B)	-527(2)	7736(3)	7601(1)	18(1)

C(8B)	1817(2)	7590(3)	6996(1)	15(1)
C(9B)	2336(2)	5503(3)	7062(1)	19(1)
C(10B)	3311(2)	5349(3)	6756(1)	16(1)
C(11B)	3001(2)	6989(3)	6438(1)	13(1)
C(12B)	2511(2)	8767(3)	6690(1)	14(1)
C(13B)	3533(2)	9804(3)	6923(1)	16(1)
C(14B)	4496(2)	10366(3)	6650(1)	16(1)
C(15B)	4681(2)	9463(3)	6298(1)	16(1)
C(16B)	3964(2)	7645(3)	6148(1)	14(1)
C(17B)	4730(2)	5831(3)	6026(1)	16(1)
C(18B)	3948(2)	4750(3)	5711(1)	18(1)
C(19B)	3273(2)	6497(3)	5500(1)	17(1)
C(20B)	3800(2)	7176(4)	5098(1)	22(1)
C(21B)	3187(2)	9075(4)	4927(1)	27(1)
C(22B)	1869(2)	8762(4)	4873(1)	29(1)
C(23B)	1334(2)	7992(4)	5265(1)	26(1)
C(24B)	1987(2)	6118(3)	5411(1)	20(1)
C(25B)	1773(2)	10291(3)	6445(1)	19(1)
C(26B)	5595(2)	10177(3)	6028(1)	19(1)
C(27B)	6582(2)	11094(3)	6135(1)	25(1)
C(28B)	1499(2)	4268(4)	5414(1)	28(1)

Table A2.13 Bond lengths [Å] and angles [°] for ***68*** *(CCDC 751261)*

Br(1)-C(1A)	1.8994(16)	C(11A)-C(12A)	1.544(3)
O(1A)-C(7A)	1.202(2)	C(11A)-H(11A)	0.952(18)
O(2A)-C(7A)	1.358(2)	C(12A)-C(25A)	1.522(3)
O(2A)-N(1A)	1.459(2)	C(12A)-C(13A)	1.536(3)
O(3A)-C(19A)	1.450(2)	C(13A)-C(14A)	1.497(3)
O(3A)-C(16A)	1.458(2)	C(13A)-H(13A)	0.91(2)
N(1A)-C(8A)	1.269(2)	C(13A)-H(13B)	0.99(2)
C(1A)-C(2A)	1.370(3)	C(14A)-C(15A)	1.332(3)
C(1A)-C(6A)	1.390(3)	C(14A)-H(14A)	0.949(19)
C(2A)-C(3A)	1.381(3)	C(15A)-C(26A)	1.485(3)
C(2A)-H(2A)	0.91(2)	C(15A)-C(16A)	1.523(3)
C(3A)-C(4A)	1.394(3)	C(16A)-C(17A)	1.529(3)
C(3A)-H(3A)	0.93(2)	C(17A)-C(18A)	1.525(3)
C(4A)-C(5A)	1.394(3)	C(17A)-H(17A)	0.94(2)
C(4A)-C(7A)	1.487(2)	C(17A)-H(17B)	0.89(2)
C(5A)-C(6A)	1.394(3)	C(18A)-C(19A)	1.549(3)
C(5A)-H(5A)	0.86(2)	C(18A)-H(18A)	0.937(18)
C(6A)-H(6A)	0.86(2)	C(18A)-H(18B)	0.99(2)
C(8A)-C(9A)	1.504(3)	C(19A)-C(24A)	1.518(3)
C(8A)-C(12A)	1.522(2)	C(19A)-C(20A)	1.531(3)
C(9A)-C(10A)	1.544(3)	C(20A)-C(21A)	1.530(3)
C(9A)-H(9A1)	1.008(19)	C(20A)-H(20A)	0.95(2)
C(9A)-H(9A2)	0.92(2)	C(20A)-H(20B)	0.963(18)
C(10A)-C(11A)	1.542(3)	C(21A)-C(22A)	1.523(3)
C(10A)-H(10A)	0.98(2)	C(21A)-H(21A)	1.00(2)
C(10A)-H(10B)	1.00(2)	C(21A)-H(21B)	0.93(2)
C(11A)-C(16A)	1.535(2)	C(22A)-C(23A)	1.528(3)

C(22A)-H(22A)	0.956(19)	C(16B)-C(17B)	1.538(2)
C(22A)-H(22B)	0.96(2)	C(17B)-C(18B)	1.524(3)
C(23A)-C(24A)	1.517(3)	C(17B)-H(17C)	0.989(19)
C(23A)-H(23A)	0.93(2)	C(17B)-H(17D)	0.989(19)
C(23A)-H(23B)	1.01(2)	C(18B)-C(19B)	1.534(3)
C(24A)-C(28A)	1.319(3)	C(18B)-H(18C)	0.925(18)
C(25A)-H(25A)	0.93(2)	C(18B)-H(18D)	0.940(18)
C(25A)-H(25B)	0.947(18)	C(19B)-C(24B)	1.512(3)
C(25A)-H(25C)	0.978(19)	C(19B)-C(20B)	1.549(2)
C(26A)-C(27A)	1.318(3)	C(20B)-C(21B)	1.525(3)
C(26A)-H(26A)	0.962(18)	C(20B)-H(20C)	0.98(2)
C(27A)-H(27A)	0.96(2)	C(20B)-H(20D)	0.99(2)
C(27A)-H(27B)	0.96(2)	C(21B)-C(22B)	1.527(3)
C(28A)-H(28A)	0.96(2)	C(21B)-H(21C)	0.95(2)
C(28A)-H(28B)	0.960(18)	C(21B)-H(21D)	0.982(19)
Br(2)-C(1B)	1.9068(18)	C(22B)-C(23B)	1.544(3)
O(1B)-C(7B)	1.197(2)	C(22B)-H(22C)	1.03(2)
O(2B)-C(7B)	1.356(2)	C(22B)-H(22D)	0.99(2)
O(2B)-N(1B)	1.4602(18)	C(23B)-C(24B)	1.506(3)
O(3B)-C(16B)	1.448(2)	C(23B)-H(23C)	0.98(2)
O(3B)-C(19B)	1.462(2)	C(23B)-H(23D)	1.09(2)
N(1B)-C(8B)	1.276(2)	C(24B)-C(28B)	1.332(3)
C(1B)-C(2B)	1.371(3)	C(25B)-H(25D)	0.97(2)
C(1B)-C(6B)	1.382(3)	C(25B)-H(25E)	0.95(2)
C(2B)-C(3B)	1.384(3)	C(25B)-H(25F)	0.917(19)
C(2B)-H(2B)	0.96(2)	C(26B)-C(27B)	1.317(3)
C(3B)-C(4B)	1.390(3)	C(26B)-H(26B)	0.968(18)
C(3B)-H(3B)	0.93(2)	C(27B)-H(27C)	0.94(2)
C(4B)-C(5B)	1.386(3)	C(27B)-H(27D)	0.924(18)
C(4B)-C(7B)	1.497(3)	C(28B)-H(28C)	0.98(2)
C(5B)-C(6B)	1.389(3)	C(28B)-H(28D)	0.99(2)
C(5B)-H(5B)	0.954(17)		
C(6B)-H(6B)	0.93(2)	C(7A)-O(2A)-N(1A)	110.85(14)
C(8B)-C(9B)	1.500(3)	C(19A)-O(3A)-C(16A)	112.66(13)
C(8B)-C(12B)	1.523(2)	C(8A)-N(1A)-O(2A)	108.37(15)
C(9B)-C(10B)	1.542(3)	C(2A)-C(1A)-C(6A)	121.97(17)
C(9B)-H(9B1)	1.01(2)	C(2A)-C(1A)-Br(1)	118.22(14)
C(9B)-H(9B2)	0.91(2)	C(6A)-C(1A)-Br(1)	119.79(15)
C(10B)-C(11B)	1.536(2)	C(1A)-C(2A)-C(3A)	119.70(19)
C(10B)-H(10C)	0.97(2)	C(1A)-C(2A)-H(2A)	120.0(15)
C(10B)-H(10D)	1.05(2)	C(3A)-C(2A)-H(2A)	120.3(15)
C(11B)-C(12B)	1.550(2)	C(2A)-C(3A)-C(4A)	119.87(19)
C(11B)-C(16B)	1.553(2)	C(2A)-C(3A)-H(3A)	119.9(12)
C(11B)-H(11B)	0.982(19)	C(4A)-C(3A)-H(3A)	120.3(12)
C(12B)-C(25B)	1.522(3)	C(3A)-C(4A)-C(5A)	119.94(17)
C(12B)-C(13B)	1.537(3)	C(3A)-C(4A)-C(7A)	116.90(17)
C(13B)-C(14B)	1.501(2)	C(5A)-C(4A)-C(7A)	123.17(17)
C(13B)-H(13C)	0.94(2)	C(4A)-C(5A)-C(6A)	120.18(18)
C(13B)-H(13D)	1.013(17)	C(4A)-C(5A)-H(5A)	120.2(13)
C(14B)-C(15B)	1.333(2)	C(6A)-C(5A)-H(5A)	119.6(13)
C(14B)-H(14B)	0.919(19)	C(1A)-C(6A)-C(5A)	118.30(18)
C(15B)-C(26B)	1.479(2)	C(1A)-C(6A)-H(6A)	119.2(12)
C(15B)-C(16B)	1.518(3)	C(5A)-C(6A)-H(6A)	122.4(12)

O(1A)-C(7A)-O(2A)	124.34(16)	H(17A)-C(17A)-H(17B)	103.5(17)
O(1A)-C(7A)-C(4A)	124.33(17)	C(17A)-C(18A)-C(19A)	103.01(15)
O(2A)-C(7A)-C(4A)	111.30(16)	C(17A)-C(18A)-H(18A)	112.1(12)
N(1A)-C(8A)-C(9A)	130.38(16)	C(19A)-C(18A)-H(18A)	113.7(11)
N(1A)-C(8A)-C(12A)	119.39(16)	C(17A)-C(18A)-H(18B)	112.3(10)
C(9A)-C(8A)-C(12A)	110.20(15)	C(19A)-C(18A)-H(18B)	107.0(11)
C(8A)-C(9A)-C(10A)	104.49(15)	H(18A)-C(18A)-H(18B)	108.6(15)
C(8A)-C(9A)-H(9A1)	107.4(10)	O(3A)-C(19A)-C(24A)	110.49(15)
C(10A)-C(9A)-H(9A1)	112.5(9)	O(3A)-C(19A)-C(20A)	106.65(15)
C(8A)-C(9A)-H(9A2)	108.3(13)	C(24A)-C(19A)-C(20A)	111.14(16)
C(10A)-C(9A)-H(9A2)	114.4(14)	O(3A)-C(19A)-C(18A)	104.67(14)
H(9A1)-C(9A)-H(9A2)	109.3(16)	C(24A)-C(19A)-C(18A)	109.63(15)
C(11A)-C(10A)-C(9A)	103.62(15)	C(20A)-C(19A)-C(18A)	114.02(17)
C(11A)-C(10A)-H(10A)	110.7(12)	C(21A)-C(20A)-C(19A)	112.60(17)
C(9A)-C(10A)-H(10A)	110.6(11)	C(21A)-C(20A)-H(20A)	110.6(12)
C(11A)-C(10A)-H(10B)	109.5(11)	C(19A)-C(20A)-H(20A)	104.5(13)
C(9A)-C(10A)-H(10B)	112.4(12)	C(21A)-C(20A)-H(20B)	111.5(10)
H(10A)-C(10A)-H(10B)	109.8(16)	C(19A)-C(20A)-H(20B)	110.4(11)
C(16A)-C(11A)-C(10A)	116.40(15)	H(20A)-C(20A)-H(20B)	106.8(16)
C(16A)-C(11A)-C(12A)	114.80(16)	C(22A)-C(21A)-C(20A)	110.32(18)
C(10A)-C(11A)-C(12A)	103.24(14)	C(22A)-C(21A)-H(21A)	109.6(12)
C(16A)-C(11A)-H(11A)	106.9(10)	C(20A)-C(21A)-H(21A)	109.0(11)
C(10A)-C(11A)-H(11A)	108.2(11)	C(22A)-C(21A)-H(21B)	111.1(12)
C(12A)-C(11A)-H(11A)	106.8(10)	C(20A)-C(21A)-H(21B)	109.8(11)
C(8A)-C(12A)-C(25A)	113.01(16)	H(21A)-C(21A)-H(21B)	106.9(17)
C(8A)-C(12A)-C(13A)	107.94(14)	C(21A)-C(22A)-C(23A)	110.63(18)
C(25A)-C(12A)-C(13A)	111.08(17)	C(21A)-C(22A)-H(22A)	110.0(13)
C(8A)-C(12A)-C(11A)	100.06(15)	C(23A)-C(22A)-H(22A)	108.0(13)
C(25A)-C(12A)-C(11A)	114.26(15)	C(21A)-C(22A)-H(22B)	113.0(13)
C(13A)-C(12A)-C(11A)	109.85(15)	C(23A)-C(22A)-H(22B)	109.4(13)
C(14A)-C(13A)-C(12A)	113.34(16)	H(22A)-C(22A)-H(22B)	105.6(17)
C(14A)-C(13A)-H(13A)	111.0(13)	C(24A)-C(23A)-C(22A)	112.07(18)
C(12A)-C(13A)-H(13A)	109.9(14)	C(24A)-C(23A)-H(23A)	109.1(14)
C(14A)-C(13A)-H(13B)	106.5(12)	C(22A)-C(23A)-H(23A)	111.1(15)
C(12A)-C(13A)-H(13B)	110.2(13)	C(24A)-C(23A)-H(23B)	107.9(11)
H(13A)-C(13A)-H(13B)	105.6(16)	C(22A)-C(23A)-H(23B)	107.6(12)
C(15A)-C(14A)-C(13A)	126.25(19)	H(23A)-C(23A)-H(23B)	108.9(17)
C(15A)-C(14A)-H(14A)	116.7(10)	C(28A)-C(24A)-C(23A)	122.11(19)
C(13A)-C(14A)-H(14A)	117.0(10)	C(28A)-C(24A)-C(19A)	123.53(17)
C(14A)-C(15A)-C(26A)	118.61(18)	C(23A)-C(24A)-C(19A)	114.34(16)
C(14A)-C(15A)-C(16A)	121.67(17)	C(12A)-C(25A)-H(25A)	109.8(14)
C(26A)-C(15A)-C(16A)	119.67(15)	C(12A)-C(25A)-H(25B)	111.2(11)
O(3A)-C(16A)-C(15A)	109.22(14)	H(25A)-C(25A)-H(25B)	109.0(15)
O(3A)-C(16A)-C(17A)	102.84(13)	C(12A)-C(25A)-H(25C)	110.8(11)
C(15A)-C(16A)-C(17A)	113.64(17)	H(25A)-C(25A)-H(25C)	109.6(18)
O(3A)-C(16A)-C(11A)	106.80(16)	H(25B)-C(25A)-H(25C)	106.4(15)
C(15A)-C(16A)-C(11A)	111.10(14)	C(27A)-C(26A)-C(15A)	124.3(2)
C(17A)-C(16A)-C(11A)	112.64(15)	C(27A)-C(26A)-H(26A)	117.8(12)
C(18A)-C(17A)-C(16A)	104.19(16)	C(15A)-C(26A)-H(26A)	117.9(11)
C(18A)-C(17A)-H(17A)	115.0(11)	C(26A)-C(27A)-H(27A)	123.0(13)
C(16A)-C(17A)-H(17A)	113.6(11)	C(26A)-C(27A)-H(27B)	121.6(14)
C(18A)-C(17A)-H(17B)	111.6(12)	H(27A)-C(27A)-H(27B)	115.3(19)
C(16A)-C(17A)-H(17B)	109.1(12)	C(24A)-C(28A)-H(28A)	121.0(11)

C(24A)-C(28A)-H(28B)	122.5(12)	C(14B)-C(13B)-C(12B)	111.46(14)
H(28A)-C(28A)-H(28B)	116.4(17)	C(14B)-C(13B)-H(13C)	108.0(12)
C(7B)-O(2B)-N(1B)	111.98(13)	C(12B)-C(13B)-H(13C)	108.1(13)
C(16B)-O(3B)-C(19B)	110.09(13)	C(14B)-C(13B)-H(13D)	113.7(10)
C(8B)-N(1B)-O(2B)	107.64(14)	C(12B)-C(13B)-H(13D)	108.9(10)
C(2B)-C(1B)-C(6B)	121.98(19)	H(13C)-C(13B)-H(13D)	106.5(15)
C(2B)-C(1B)-Br(2)	119.10(16)	C(15B)-C(14B)-C(13B)	124.51(17)
C(6B)-C(1B)-Br(2)	118.88(16)	C(15B)-C(14B)-H(14B)	116.6(11)
C(1B)-C(2B)-C(3B)	118.8(2)	C(13B)-C(14B)-H(14B)	118.8(11)
C(1B)-C(2B)-H(2B)	119.8(13)	C(14B)-C(15B)-C(26B)	122.04(17)
C(3B)-C(2B)-H(2B)	121.1(13)	C(14B)-C(15B)-C(16B)	122.20(16)
C(2B)-C(3B)-C(4B)	120.5(2)	C(26B)-C(15B)-C(16B)	115.76(15)
C(2B)-C(3B)-H(3B)	123.5(13)	O(3B)-C(16B)-C(15B)	106.58(13)
C(4B)-C(3B)-H(3B)	116.0(13)	O(3B)-C(16B)-C(17B)	102.99(13)
C(5B)-C(4B)-C(3B)	119.69(18)	C(15B)-C(16B)-C(17B)	112.54(15)
C(5B)-C(4B)-C(7B)	123.00(17)	O(3B)-C(16B)-C(11B)	108.18(14)
C(3B)-C(4B)-C(7B)	117.29(18)	C(15B)-C(16B)-C(11B)	113.62(14)
C(4B)-C(5B)-C(6B)	120.14(19)	C(17B)-C(16B)-C(11B)	112.12(15)
C(4B)-C(5B)-H(5B)	118.8(10)	C(18B)-C(17B)-C(16B)	102.24(15)
C(6B)-C(5B)-H(5B)	121.0(10)	C(18B)-C(17B)-H(17C)	109.4(10)
C(1B)-C(6B)-C(5B)	118.8(2)	C(16B)-C(17B)-H(17C)	109.8(11)
C(1B)-C(6B)-H(6B)	120.8(13)	C(18B)-C(17B)-H(17D)	111.1(11)
C(5B)-C(6B)-H(6B)	120.2(13)	C(16B)-C(17B)-H(17D)	112.2(11)
O(1B)-C(7B)-O(2B)	125.01(17)	H(17C)-C(17B)-H(17D)	111.6(15)
O(1B)-C(7B)-C(4B)	124.45(17)	C(17B)-C(18B)-C(19B)	103.96(16)
O(2B)-C(7B)-C(4B)	110.48(15)	C(17B)-C(18B)-H(18C)	113.2(10)
N(1B)-C(8B)-C(9B)	130.76(17)	C(19B)-C(18B)-H(18C)	107.3(11)
N(1B)-C(8B)-C(12B)	119.15(16)	C(17B)-C(18B)-H(18D)	115.6(12)
C(9B)-C(8B)-C(12B)	110.07(15)	C(19B)-C(18B)-H(18D)	111.2(11)
C(8B)-C(9B)-C(10B)	104.83(15)	H(18C)-C(18B)-H(18D)	105.3(15)
C(8B)-C(9B)-H(9B1)	107.5(12)	O(3B)-C(19B)-C(24B)	108.84(14)
C(10B)-C(9B)-H(9B1)	113.9(11)	O(3B)-C(19B)-C(18B)	105.67(14)
C(8B)-C(9B)-H(9B2)	110.3(13)	C(24B)-C(19B)-C(18B)	115.96(16)
C(10B)-C(9B)-H(9B2)	110.9(13)	O(3B)-C(19B)-C(20B)	105.53(15)
H(9B1)-C(9B)-H(9B2)	109.2(17)	C(24B)-C(19B)-C(20B)	106.69(15)
C(11B)-C(10B)-C(9B)	104.67(15)	C(18B)-C(19B)-C(20B)	113.60(15)
C(11B)-C(10B)-H(10C)	111.0(11)	C(21B)-C(20B)-C(19B)	111.40(16)
C(9B)-C(10B)-H(10C)	108.5(11)	C(21B)-C(20B)-H(20C)	109.6(12)
C(11B)-C(10B)-H(10D)	110.9(10)	C(19B)-C(20B)-H(20C)	109.6(10)
C(9B)-C(10B)-H(10D)	110.9(11)	C(21B)-C(20B)-H(20D)	110.3(12)
H(10C)-C(10B)-H(10D)	110.7(16)	C(19B)-C(20B)-H(20D)	108.5(12)
C(10B)-C(11B)-C(12B)	103.40(13)	H(20C)-C(20B)-H(20D)	107.3(16)
C(10B)-C(11B)-C(16B)	117.90(15)	C(20B)-C(21B)-C(22B)	111.96(19)
C(12B)-C(11B)-C(16B)	114.11(15)	C(20B)-C(21B)-H(21C)	111.9(14)
C(10B)-C(11B)-H(11B)	106.7(10)	C(22B)-C(21B)-H(21C)	109.3(14)
C(12B)-C(11B)-H(11B)	107.0(11)	C(20B)-C(21B)-H(21D)	114.8(13)
C(16B)-C(11B)-H(11B)	107.1(10)	C(22B)-C(21B)-H(21D)	108.8(11)
C(25B)-C(12B)-C(8B)	113.31(16)	H(21C)-C(21B)-H(21D)	99.4(18)
C(25B)-C(12B)-C(13B)	112.21(16)	C(21B)-C(22B)-C(23B)	111.45(17)
C(8B)-C(12B)-C(13B)	107.00(14)	C(21B)-C(22B)-H(22C)	107.1(11)
C(25B)-C(12B)-C(11B)	114.00(15)	C(23B)-C(22B)-H(22C)	109.7(11)
C(8B)-C(12B)-C(11B)	100.96(14)	C(21B)-C(22B)-H(22D)	111.1(12)
C(13B)-C(12B)-C(11B)	108.56(15)	C(23B)-C(22B)-H(22D)	110.5(11)

H(22C)-C(22B)-H(22D)	106.9(15)	C(12B)-C(25B)-H(25F)	111.4(12)
C(24B)-C(23B)-C(22B)	109.21(17)	H(25D)-C(25B)-H(25F)	106.3(16)
C(24B)-C(23B)-H(23C)	111.4(12)	H(25E)-C(25B)-H(25F)	107.2(17)
C(22B)-C(23B)-H(23C)	107.7(11)	C(27B)-C(26B)-C(15B)	126.88(18)
C(24B)-C(23B)-H(23D)	109.6(12)	C(27B)-C(26B)-H(26B)	118.9(12)
C(22B)-C(23B)-H(23D)	108.0(10)	C(15B)-C(26B)-H(26B)	114.2(12)
H(23C)-C(23B)-H(23D)	110.8(16)	C(26B)-C(27B)-H(27C)	118.3(13)
C(28B)-C(24B)-C(23B)	122.51(19)	C(26B)-C(27B)-H(27D)	121.7(12)
C(28B)-C(24B)-C(19B)	123.6(2)	H(27C)-C(27B)-H(27D)	119.9(18)
C(23B)-C(24B)-C(19B)	113.42(18)	C(24B)-C(28B)-H(28C)	122.3(12)
C(12B)-C(25B)-H(25D)	110.2(12)	C(24B)-C(28B)-H(28D)	125.2(14)
C(12B)-C(25B)-H(25E)	113.4(13)	H(28C)-C(28B)-H(28D)	112.5(18)
H(25D)-C(25B)-H(25E)	108.0(16)		

*Table A2.14 Anisotropic displacement parameters ($Å^2x\ 10^4$) for **68** (CCDC 751261). The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	171(1)	340(1)	240(1)	61(1)	49(1)	14(1)
O(1A)	226(8)	228(8)	242(7)	-29(6)	5(6)	38(6)
O(2A)	202(8)	223(8)	235(7)	39(6)	98(6)	43(6)
O(3A)	206(8)	175(7)	111(6)	-14(5)	19(5)	42(5)
N(1A)	169(9)	259(9)	214(8)	-4(7)	75(7)	38(7)
C(1A)	114(9)	277(10)	172(8)	9(9)	0(6)	-32(9)
C(2A)	219(12)	283(12)	289(11)	119(9)	19(9)	-18(9)
C(3A)	218(12)	241(12)	275(11)	37(8)	7(9)	52(9)
C(4A)	148(9)	209(11)	145(8)	-1(7)	-19(7)	-4(8)
C(5A)	213(11)	180(10)	148(9)	18(8)	-16(8)	-23(8)
C(6A)	127(11)	188(11)	251(10)	0(8)	-26(8)	22(8)
C(7A)	182(10)	228(12)	126(9)	9(7)	-55(7)	-12(8)
C(8A)	161(10)	177(10)	161(9)	-46(8)	17(7)	7(8)
C(9A)	161(11)	204(11)	211(10)	-21(8)	48(8)	20(8)
C(10A)	172(11)	160(11)	212(10)	17(7)	20(8)	40(8)
C(11A)	143(10)	145(9)	184(9)	-28(7)	-9(7)	-1(8)
C(12A)	162(10)	186(11)	143(9)	-14(7)	11(7)	14(8)
C(13A)	184(11)	294(13)	150(9)	-11(8)	-13(8)	0(9)
C(14A)	178(11)	219(10)	233(10)	-57(8)	10(8)	-18(8)
C(15A)	151(10)	177(10)	197(9)	-51(7)	37(7)	-6(8)
C(16A)	157(9)	177(9)	156(8)	-11(8)	19(6)	33(9)
C(17A)	176(12)	176(11)	225(10)	12(8)	13(8)	17(9)
C(18A)	197(11)	216(10)	133(9)	11(7)	-15(8)	-9(8)
C(19A)	174(11)	196(10)	119(9)	1(7)	-11(7)	4(8)
C(20A)	189(11)	256(12)	156(10)	-25(8)	-3(8)	-16(9)
C(21A)	200(12)	381(14)	201(11)	-49(9)	41(8)	-61(10)
C(22A)	288(13)	406(14)	190(11)	-95(10)	57(9)	-42(10)
C(23A)	252(12)	343(13)	184(10)	-61(9)	-18(8)	-66(10)
C(24A)	162(10)	222(11)	180(9)	-11(7)	-11(7)	30(8)
C(25A)	196(12)	237(11)	173(10)	36(9)	39(8)	81(9)
C(26A)	258(12)	207(10)	160(9)	-64(9)	22(8)	-27(9)

C(27A)	274(13)	387(14)	208(10)	-83(10)	64(9)	-106(11)
C(28A)	239(12)	214(10)	217(11)	-2(9)	-32(9)	-1(9)
Br(2)	413(2)	417(1)	249(1)	114(1)	22(1)	-142(1)
O(1B)	310(9)	274(9)	358(8)	122(7)	139(6)	123(7)
O(2B)	207(7)	163(7)	182(6)	31(5)	62(5)	17(6)
O(3B)	174(7)	197(7)	114(6)	-16(5)	-22(5)	15(5)
N(1B)	214(9)	180(8)	145(8)	27(6)	32(6)	-8(7)
C(1B)	234(12)	298(11)	168(9)	74(8)	-25(8)	-129(9)
C(2B)	172(12)	376(13)	243(11)	45(9)	36(9)	16(10)
C(3B)	175(11)	283(13)	235(10)	40(9)	13(8)	45(9)
C(4B)	143(10)	215(10)	159(9)	-7(8)	-17(7)	-14(8)
C(5B)	207(11)	225(12)	188(9)	-24(8)	8(8)	-4(9)
C(6B)	293(13)	187(11)	252(11)	39(9)	-3(9)	1(9)
C(7B)	186(11)	177(11)	175(9)	-27(7)	5(7)	-5(8)
C(8B)	182(10)	147(10)	126(8)	-20(7)	-11(7)	-10(7)
C(9B)	260(12)	171(10)	143(10)	24(8)	27(8)	7(9)
C(10B)	217(11)	118(10)	147(9)	10(7)	6(8)	30(8)
C(11B)	128(9)	119(9)	151(8)	-3(7)	-4(7)	4(8)
C(12B)	149(10)	128(9)	149(9)	15(7)	14(7)	28(7)
C(13B)	211(10)	113(9)	140(8)	-19(8)	8(7)	45(9)
C(14B)	150(10)	120(10)	206(9)	8(7)	-36(7)	-12(7)
C(15B)	136(9)	140(10)	192(9)	39(8)	-26(7)	17(8)
C(16B)	147(10)	150(10)	112(8)	2(7)	-16(7)	13(7)
C(17B)	157(11)	151(10)	178(10)	-19(8)	28(8)	25(8)
C(18B)	188(10)	185(9)	161(8)	-45(9)	28(7)	-15(10)
C(19B)	154(10)	223(10)	135(9)	-26(7)	22(7)	-19(8)
C(20B)	169(11)	345(12)	153(9)	-8(9)	33(7)	-16(10)
C(21B)	226(12)	403(14)	191(11)	69(9)	30(9)	-11(9)
C(22B)	208(13)	464(14)	200(11)	65(10)	-32(9)	19(11)
C(23B)	166(12)	413(13)	195(10)	20(9)	-3(8)	6(10)
C(24B)	156(11)	332(12)	121(9)	-12(8)	17(7)	-19(9)
C(25B)	190(11)	189(11)	194(10)	26(8)	39(8)	41(8)
C(26B)	216(11)	171(11)	178(9)	16(7)	7(8)	19(8)
C(27B)	217(12)	251(11)	280(12)	8(9)	43(9)	-45(9)
C(28B)	206(12)	388(16)	237(11)	-67(9)	-2(8)	-79(10)

*Table A2.15 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **68** (CCDC 751261).*

	x	y	z	U_{iso}
H(2A)	8090(20)	7530(40)	6420(6)	46(7)
H(3A)	6631(17)	7750(30)	6875(5)	21(5)
H(5A)	7636(16)	2370(30)	7318(5)	19(5)
H(6A)	9130(16)	2280(30)	6884(5)	14(5)
H(9A1)	6192(16)	1130(30)	8224(5)	9(4)

H(9A2)	5578(17)	-390(40)	7916(6)	32(6)
H(10A)	4537(17)	-2050(30)	8393(5)	20(5)
H(10B)	5518(18)	-1140(30)	8708(6)	23(5)
H(11A)	4434(16)	1770(30)	8798(5)	11(5)
H(13A)	2186(19)	780(30)	7868(6)	26(6)
H(13B)	3150(19)	-820(30)	7890(6)	33(6)
H(14A)	1390(16)	-2010(30)	8208(5)	13(5)
H(17A)	3887(16)	-2730(40)	9238(5)	22(5)
H(17B)	4449(17)	-840(30)	9347(5)	16(5)
H(18A)	3347(16)	-1190(30)	9900(5)	15(5)
H(18B)	2253(18)	-1920(30)	9638(5)	15(5)
H(20A)	1020(19)	2800(30)	9553(6)	26(6)
H(20B)	738(16)	510(30)	9521(5)	10(5)
H(21A)	1189(17)	100(30)	10228(5)	25(6)
H(21B)	192(19)	1670(30)	10156(5)	23(6)
H(22A)	1605(18)	3030(30)	10619(6)	29(6)
H(22B)	1500(18)	4480(40)	10258(6)	33(6)
H(23A)	3470(20)	3800(40)	10388(6)	42(7)
H(23B)	3246(18)	1420(30)	10390(6)	24(6)
H(25A)	3265(18)	4530(40)	8510(6)	29(6)
H(25B)	2092(17)	3420(30)	8469(5)	10(5)
H(25C)	2614(16)	4360(30)	8091(5)	19(5)
H(26A)	1914(16)	-3920(30)	9106(5)	11(5)
H(27A)	-133(18)	-2070(30)	8774(5)	20(6)
H(27B)	-66(19)	-4110(40)	9050(6)	32(6)
H(28A)	4585(17)	4680(30)	9830(5)	26(5)
H(28B)	4280(16)	3720(30)	9385(6)	15(5)
H(2B)	-2960(20)	6060(30)	8585(6)	35(6)
H(3B)	-2231(19)	8150(30)	8059(6)	30(6)
H(5B)	220(16)	4000(30)	7835(5)	9(5)
H(6B)	-471(19)	1910(40)	8351(6)	31(6)
H(9B1)	1685(18)	4470(30)	7017(5)	26(5)
H(9B2)	2633(18)	5380(30)	7318(6)	26(6)
H(10C)	4053(18)	5650(30)	6894(5)	16(5)
H(10D)	3326(17)	3890(30)	6625(5)	17(5)
H(11B)	2347(16)	6450(30)	6271(5)	13(5)
H(13C)	3253(18)	11010(30)	7038(6)	26(6)
H(13D)	3796(15)	8890(30)	7156(5)	9(4)
H(14B)	4966(17)	11460(30)	6717(5)	17(5)
H(17C)	5440(17)	6340(30)	5898(5)	16(5)
H(17D)	4927(14)	4920(30)	6256(5)	12(4)
H(18C)	3404(16)	3890(30)	5822(5)	8(4)
H(18D)	4337(16)	3940(30)	5525(5)	14(5)
H(20C)	4639(18)	7460(30)	5143(5)	22(5)
H(20D)	3726(17)	6030(30)	4905(6)	25(6)
H(21C)	3340(20)	10240(40)	5090(6)	38(7)
H(21D)	3490(16)	9570(30)	4673(5)	28(5)
H(22C)	1738(17)	7690(30)	4649(5)	23(5)
H(22D)	1476(18)	10040(30)	4779(6)	28(6)
H(23C)	1393(17)	9100(30)	5462(6)	22(6)
H(23D)	420(20)	7600(30)	5197(6)	38(6)
H(25D)	1127(17)	9600(30)	6307(5)	20(5)

H(25E)	2200(18)	11000(30)	6249(6)	26(6)
H(25F)	1449(17)	11260(30)	6607(5)	18(5)
H(26B)	5413(16)	9950(30)	5745(6)	26(5)
H(27C)	6745(19)	11330(30)	6410(6)	34(6)
H(27D)	7097(17)	11540(30)	5947(5)	21(5)
H(28C)	670(20)	4050(30)	5341(6)	27(6)
H(28D)	1920(20)	2970(40)	5478(6)	36(7)

CHAPTER 3

Catalytic Enantioselective Stereoablative Alkylation of 3-Halooxindoles[1]

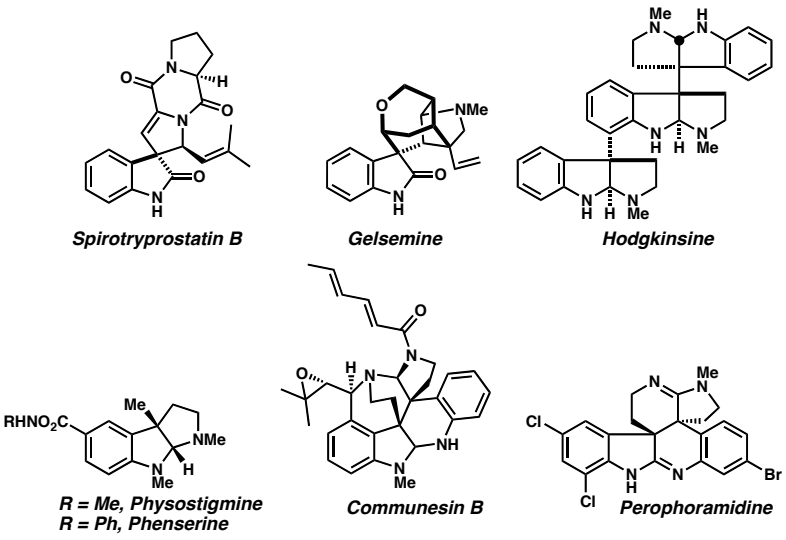
3.1 INTRODUCTION

The construction of all-carbon quaternary stereocenters remains one of the most challenging problems in asymmetric catalysis and has been an area of great interest in our laboratories.[1,2] Over the past several years, significant effort from many research groups has been directed toward the enantioselective synthesis of 3,3-disubstituted oxindoles and derivatives thereof, given the prevalence of this structural motif in biologically active molecules and their interesting molecular architectures (Figure 3.1).[3,4,5] Although a number of catalytic enantioselective approaches to this motif have been developed (Heck reaction,[6] cyanoamidation,[7] cycloadditions,[8] arylation,[9] alkylation,[10,11] acyl migration,[12] Claisen rearrangment,[13] aldol,[14] Mannich,[15] and conjugate addition reactions[15b]), we

[1] This work was performed in collaboration with Drs. Xiaoqing Han, Shyam Krishnan, and Scott Virgil.

pursued an alternative tactic.[16,17,18] In all of the reported systems that rely on stereoselective functionalization of an existing oxindole, this oxindole unit serves as a nucleophile. In contrast, we present herein an unusual strategy for the enantioselective synthesis of substituted oxindoles with C(3) quaternary stereocenters that employs the oxindole moiety as the electrophilic partner in a facile and rapid coupling to malonate nucleophiles.

Figure 3.1. Naturally occurring 3,3-disubstituted oxindoles and indolines bearing all-carbon quaternary stereocenters



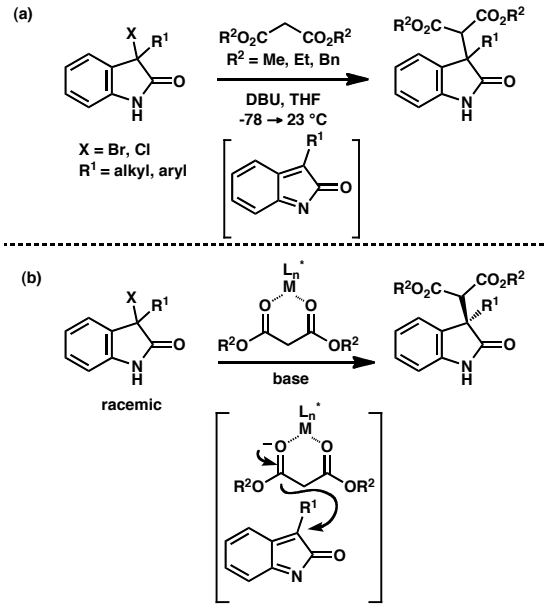
3.2 DEVELOPMENT OF CATALYTIC ENANTIOSELECTIVE ALKYLATION

3.2.1 Background and Initial Results

Despite an early report from Hinman and Bauman in 1964,[19] the use of 3-haloxindoles as electrophiles in substitution chemistry has been limited. Although the addition of carbon-based π- and heteroatom-nucleophiles to the C(3) position of oxindoles has been reported, no enantioselective methods exist.[20] We recently reported

the base-promoted addition of malonate esters to 3-halooxindoles by the in situ formation of a putative *o*-azaxylylene (Scheme 3.1a).[21] In light of these results and our general interest in stereoablative reactions,[22] we sought to develop a catalytic enantioselective system (Scheme 3.1b).[23] We hypothesized that a Lewis acid could facilitate the base-mediated reaction by lowering the pK_a of the N–H proton of the halooxindole and/or the C_α–H proton of the malonate. Through either pathway, complexation by a chiral Lewis acid could potentially lead to asymmetric induction.

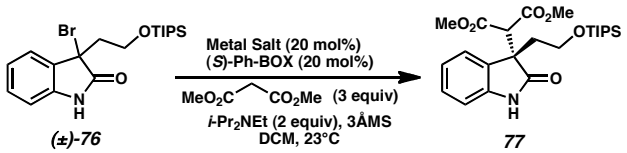
Scheme 3.1 (a) Base-mediated addition of malonates to halooxindoles via a reactive o-azaxylylene intermediate. (b) Proposed Lewis acid-catalyzed enantioselective alkylation of 3-halooxindoles. Only the malonate activation pathway is shown.



We reasoned that the key to implementing a catalytic enantioselective system would be to identify a base that would not promote competitive background reactions in the absence of a catalyst. In our initial experiments, we found that exposure of racemic bromooxindole (±)-**76** to *N*,*N*-diisopropylethylamine (*i*-Pr_2NEt) and dimethyl malonate in the absence of a Lewis acid did not result in formation of adduct **77**.[24] Encouraged by

this finding, we then surveyed a variety of chiral Lewis acids (e.g., Cu^{II}, Mg^{II}, La^{III}, and Ni^{II} complexes) that could potentially promote the asymmetric alkylation (Table 3.1). We found that several chiral Lewis acids could promote alkylation; however, only copper afforded adduct **77** with promising enantiomeric excess (Table 3.1, Entry 1). We also surveyed a variety of bases for the asymmetric alkylation of racemic bromooxindole (±)-**76** (Table 3.2) and found that *i*-Pr_2NEt provided desired adduct **77** with the best yield and ee. Alkyl amines, such as *N*-methyl-dicyclohexylamine, afforded adduct **77** with ee's comparable to that observed with *i*-Pr_2NEt albeit in diminished yields (Table 3.2, Entries 5, 8, and 10). Ultimately, the combination of copper(II) triflate and (*S*)-Ph-BOX (**78**) gave the most promising result, producing **77** in 63% yield and 77% ee (Table 3.3, entry 1).[25,26] Related bis(oxazoline) ligands **79**-**82** resulted in diminished yields and enantioselectivities (Table 3.3, entries 2-5). Given the strong electronic preference observed in related Lewis acid catalyzed processes, we investigated the effect of less coordinating counterions.[27] Although imparting only a moderate influence on chemical yield, a more pronounced counterion effect was observed with enantioselectivity. For example, using the hexafluoroantimonate (SbF_6^-) complex produced malonate adduct **77** in 72% yield and 84% ee in less than 10 min (Table 3.3, entry 9). Ultimately, we found that employing the preformed [Cu(**78**)] $(SbF_6)_2$ catalyst at low temperature (i.e., –40 °C) in the presence of 3Å molecular sieves[28] produced oxindole **77** in 77% yield and 88% ee (Table 3.4, entry 1).

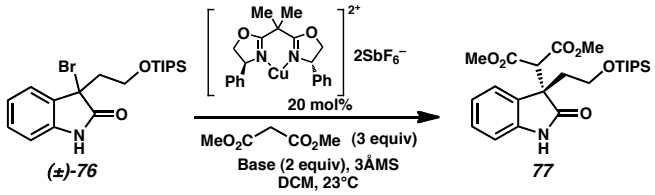
Table 3.1 Lewis acid metal screen for enantioselective malonate alkylation



Entry	Metal Salt	Yield[%][b]	ee[%][c]
1	$Cu(OTf)_2$	63	77
2	$Mg(OTf)_2$	41	0
3[a]	$La(OTf)_3$	93	0
4	$NiCl_2$	59	25

a. Performed with (*R*)-Ph-BOX. b. Isolated yield.
c. Measured by chiral HPLC.

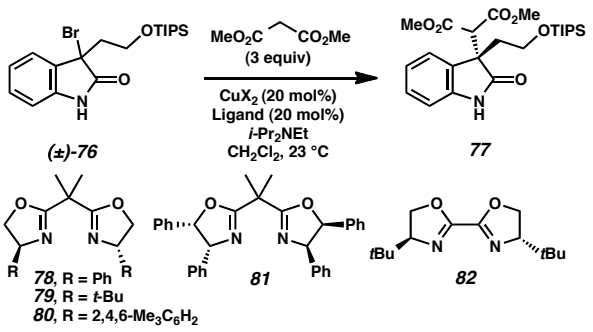
Table 3.2 Base optimization for enantioselective malonate alkylation



Entry	Base	Yield [%][b]	ee[%][c]	Entry	Base	Yield [%][b]	*ee*[%][c]
1[a]	Pyridine	--	--	7[a]	Imidazole	--	--
2[a]	2,6-di-*tert*-butylpyridine	--	--	8	TEA	74	82
3[a]	*N*-Methylmorpholine	--	--	9[a]	DABCO	--	--
4[a]	DMAP	--	--	10	*N,N*-Dimethylcyclohexylamine	40	81
5	*N*-Methyl-dicyclohexylamine	46	80	11	*i*-Pr_2NEt	60	83
6	Cs_2CO_3	30	60	12	NaH	73	32

a. No product observed. b. Isolated yield. c. Measured by chiral HPLC.

Table 3.3 Ligand screen for enantioselective malonate alkylation



Entry	X	Ligand	Yield[b][%]	*ee*[c][%]
1	OTf	***78***	63	77
2	OTf	**79**	45	6
3	OTf	***ent*-80**	24	–42
4	OTf	***81***	37	–64
5	OTf	***82***	49	13
6[a]	PF_6[d]	***78***	65	81
7	NTf_2[d]	***78***	65	79
8[a]	BF_4[d]	***78***	61	76
9	SbF_6[d]	***78***	72	84

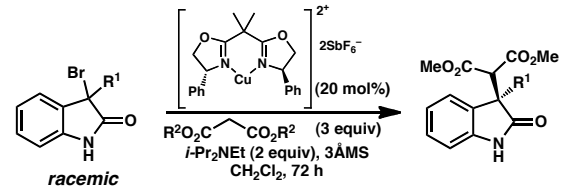
[a] Performed at –78 → 23 °C. [b] Yield of isolated product. [c] Determined by chiral-phase HPLC. [d] The catalyst was generated by in situ metathesis of [Cu(*78*)Cl_2] with the corresponding AgX salt.

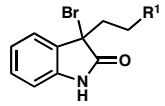
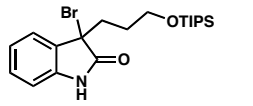
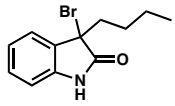
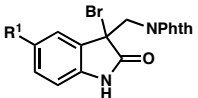
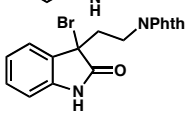
3.2.2 Substrate Scope

On examining the scope of the transformation, we found that malonate esters could be alkylated with various 3-alkyl and 3-aryl halooxindoles in good yields and high enantioselectivities (Tables 3.4 and 3.5).[29] Methyl, ethyl, and benzyl malonates were each added to bromide (±)-**76**, via the putative *o*-azaxylylene, with similar levels of selectivity and yield (Table 3.4, entries 1-3). Silyl ethers (entries 1-4 and 6), benzoate esters (entry 5), and phthalimides (entries 8-10) were all tolerated as substituents on the alkyl chain at C(3). Additionally, substituted alkyl chains of various lengths led to alkylation products in high enantioselectivities (entries 1 and 6). Finally, substitution of

the bromooxindole core at C(5) with a methoxy group produced the malonate addition product in 51% yield and 91% ee (entry 10).

Table 3.4

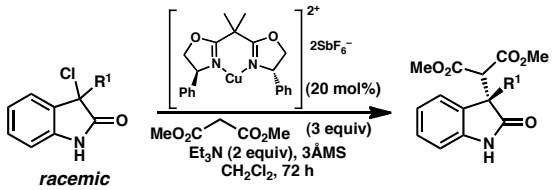


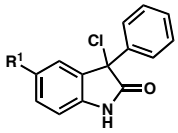
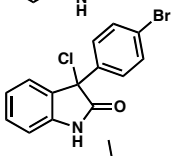
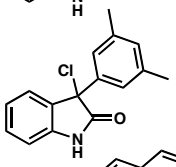
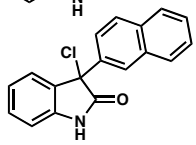
Entry	Substrate	R^1	R^2	Temp[°C]	Yield[a] [%]	*ee*[b] [%]
1		R^1 = OTIPS	R^2 = Me	–40	77	88
2		R^1 = OTIPS	R^2 = Et	–40	73	84
3		R^1 = OTIPS	R^2 = Bn	–40	78	88
4		R^1 = OTBDPS	R^2 = Me	–40	77	88
5		R^1 = OBz	R^2 = Me	–40	77	88
6			R^2 = Me	–20	47	86
7			R^2 = Me	–40	44	84
8		R^1 = H	R^2 = Me	–20	42	81
9		R^1 = OMe	R^2 = Me	–20	51	91
10			R^2 = Me	–20	63	94

[a] Yield of isolated product. [b] Determined by chiral-phase HPLC.

In addition to reactions with bromooxindoles, dimethyl malonate reacted smoothly with racemic 3-aryl chlorooxindoles to produce the C(3)-malonate adducts in good yields and enantioselectivities (Table 3.5). In these reactions, Et_3N proved to be a better base than *i*-Pr_2NEt in terms of both yield and enantioselectivity. Products with phenyl (entry 1), bromophenyl (entry 3), 3,5-dimethylphenyl (entry 4), and naphthyl substitution at C(3) (entry 5) were stereoselectively formed by this method. Additionally, methoxy substituents on the oxindole framework at C(5) were well tolerated (entry 2).

Table 3.5



Entry	Substrate	R^1	Temp(°C)	Yield[a] [%]	*ee*[b] [%]
1		R^1 = H	–20	76	–76[c]
2		R^1 = OMe	–20	76	84
3			0	76	76
4			–40	69	84
5			0	74	74

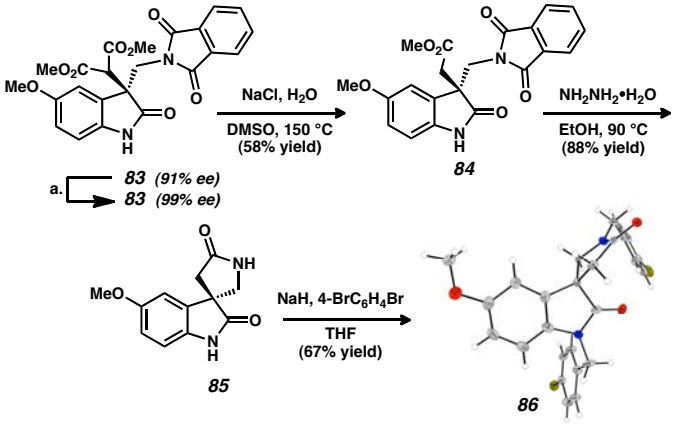
[a] Yield of isolated product. [b] Determined by chiral-phase HPLC. [c] (*R*)-Ph-BOX was employed as the ligand.

3.2.3 Applications to Natural Product Scaffolds

We proceeded to apply this new method for the enantioselective generation of C(3)-quaternary oxindoles to the synthesis of natural product scaffolds. To construct the pyrrolidinylspirooxindole core prevalent in a large family of biologically active alkaloids, we began with malonate adduct **83** (Table 3.4, entry 9), which could be recrystallized to 99% ee (Scheme 3.2). Oxindole malonate **83** was converted to phthalimidoester **84** by Krapcho decarboxylation.[30] Cleavage of phthalimide **84** with hydrazine resulted in rapid formation of spirocyclic bis(lactam) **85**. Double alkylation of oxindole **85** produced

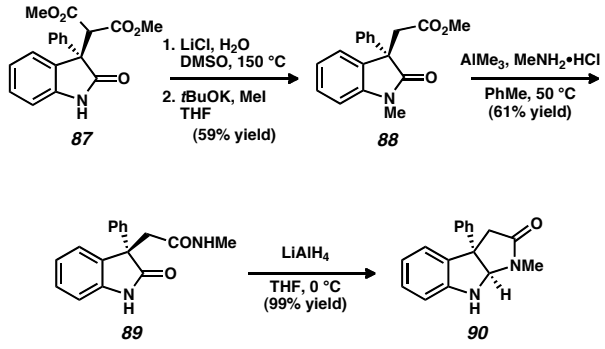
bis(*p*-bromobenzyl)lactam **86**, a crystalline compound amenable to single crystal x-ray analysis, which allowed for its determination of absolute configuration.[31]

Scheme 3.2



In addition to spirocyclic motifs, fused pyrrolidinoindolines are also a key moiety found in many natural products. To access this family, quaternary C(3)-aryl oxindole malonate adduct **87** was subjected to Krapcho decarboxylation and *N*-alkylation to give methyl ester **88** (Scheme 3.3). Finally, ester **88** was converted to *N*-methyl amide **89** and reduced with $LiAlH_4$ to provide lactam **90**, which contains the pyrrolidinoindoline core.

Scheme 3.3



3.3 CONCLUSION

In summary, we have discovered a unique copper-catalyzed enantioselective synthesis of C(3)-quaternary oxindoles. This stereoablative transformation most likely involves the in situ formation of a highly reactive *o*-azaxylylene from C(3)-halooxindoles followed by enantioselective malonate addition. Finally, we have demonstrated that our method is useful for the rapid and stereoselective construction of biologically active core structures. Mechanistic studies and further synthetic applications of our method are underway.

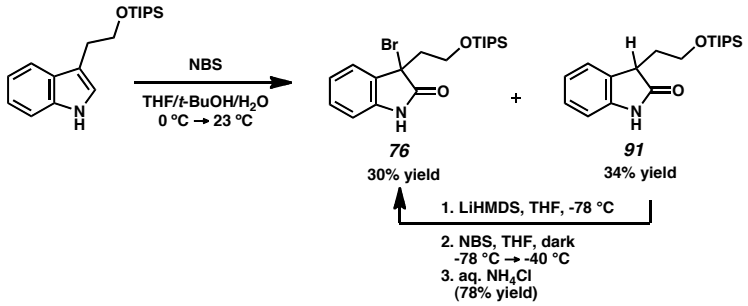
3.4 EXPERIMENTAL SECTION

3.4.1 Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, anisaldehyde, or ceric ammonium molybdate staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak AD column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 254 nm and flow rate of 1 mL/min, unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 125 MHz, respectively) and a Varian Mercury 300 spectrometer (at 300 MHz and 75 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were either obtained from the Caltech Mass Spectral Facility or an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric

pressure chemical ionization (APCI) or mixed (MM) ionization mode. Optical rotations were measured on either a Jasco P-1010 using a 50 mm path-length cell or Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. Melting points were determined using a Thomas capillary melting point apparatus and the values reported are uncorrected. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number.

3.4.2 General Synthesis of 3-Alkyl Bromooxindoles From Corresponding 3-Alkyl Indoles.

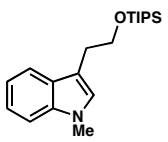


3-bromo-3-(2-((triisopropylsilyl)oxy)ethyl)indolin-2-one (76).

3-(2-(triisopropylsilyloxy)ethyl)-1*H*-indole (2.0 g, 6.3 mmol, 1.0 equiv) was dissolved in a mixture of THF (63 mL), *t*-BuOH (63 mL), and H_2O (1.3 mL). The solution was cooled to 0–5 ºC and solid *N*-bromosuccinimide (1.6 g, 8.9 mmol, 1.4 equiv) was added in small portions over 60 minutes. The reaction mixture was then allowed to warm to ambient temperature and concentrated under reduced pressure. The residue obtained was purified by column chromatography (SiO_2, 6% EtOAc in hexanes→10% EtOAc in hexanes) to afford bromooxindole **76** as an off-white solid (791 mg, 30% yield) and oxindole **91** as a colorless oil (712 mg, 34% yield).

3-(2-((triisopropylsilyl)oxy)ethyl)indolin-2-one (91): R_f = 0.30 (SiO_2, 25% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (br s, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.20 (tt, *J* = 8.0, 1.0 Hz, 1H), 7.02 (td, *J* = 7.5, 1.0 Hz, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 3.92 (m, 2H), 3.66 (app. t, *J* = 6.5 Hz, 1H), 2.25 (m, 1H), 2.07 (m, 1H), 1.04 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.5, 141.5, 129.7, 127.8, 124.6, 122.2, 109.6, 60.1, 42.8, 33.7, 18.1, 12.1; IR (neat film, NaCl) 3215, 2941, 2863, 1711, 1620, 1471, 1109, 747 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{32}NO_2Si[M+H]^+$: 334.2202, found 334.2202.

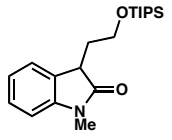
Oxindole **91** could be brominated to give bromooxindole **76** as follows: To a solution of oxindole **91** (485 mg, 1.5 mmol, 1.0 equiv) in THF (15 mL) that had been pre-cooled to –78 ºC was added a freshly prepared solution of LiHMDS (536 mg, 3.2 mmol, 2.2 equiv) in THF (4 mL) dropwise. The reaction mixture was then maintained at –78 ºC for 30 minutes, and then transferred via cannula to a solution of NBS (518 mg, 2.9 mmol, 2.0 equiv) in THF (10 mL) that had been pre-cooled to –78 ºC and wrapped in aluminum foil to exclude light. The reaction mixture was allowed to warm to –40 ºC and maintained at this temperature for 2 hours. The reaction mixture was then poured into saturated aqueous NH_4Cl (60 mL). 1 M aqueous $Na_2S_2O_3$ (40 mL) was then added, and the mixture was stirred for 10 minutes to reduce any excess NBS. The mixture was then extracted with EtOAc (3 × 100 mL). The combined EtOAc extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford a pale yellow solid. Purification by column chromatography (SiO_2, 10% EtOAc in hexanes) afforded bromooxindole **76** as a pale yellow solid (468 mg, 78% yield). R_f = 0.35 (SiO_2, 25% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.37 (dd, *J* = 7.5, 0.5 Hz, 1H), 7.26 (app. t, *J* = 5.0 Hz, 1H), 7.07 (app. dt, *J* = 7.5, 1.0 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 3.62 (m, 2H), 2.89 (m, 1H), 2.61 (m, 1H), 0.91 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 140.2, 130.1, 129.7, 124.8, 123.0, 111.0, 60.1, 55.8, 41.7, 17.8, 11.9; IR (neat film, NaCl) 3202, 2946, 2866, 1725, 1619, 1474, 1115 cm^{-1}; HMRS (FAB+) *m/z* calc'd for $C_{19}H_{31}BrNO_2Si$ $[M+H]^+$: 412.1307, found 412.1290.



92

1-methyl-3-(2-((triisopropylsilyl)oxy)ethyl)-1H-indole (92).

To NaH (53 mg, 60%, 1.3 mmol, 1.2 equiv) in DMF (1 mL) was added a solution of 3-(2-(triisopropylsilyloxy)ethyl)-1*H*-indole (350 mg, 1.1 mmol, 1.0 equiv) in DMF (4 mL) at ambient temperature. The solution was stirred for 20 min and then MeI (103 μL, 1.7 mmol, 1.5 equiv) was added dropwise. The solution was stirred for an additional 30 min at ambient temperature. Water (5 mL) and brine (5 mL) were added, and the mixture was extracted with a mixture of hexanes/EtOAc (1:2) (2 x 15 mL). The combined extracts were dried with $MgSO_4$ prior to concentration. The residue obtained was purified by column chromatography (SiO_2, 2% EtOAc in hexanes) to afford 1-methyl-3-(2-(triisopropylsilyloxy)ethyl)-1*H*-indole as a pale yellow viscous oil (303 mg, 83% yield). R_f = 0.66 (22% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.1. Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.23 (td, *J* = 7.2, 1.2 Hz, 1H), 7.11 (ddd, *J* = 6.9, 6.6, 1.2 Hz, 1H), 6.91(s, 1H), 3.94 (t, *J* = 7.2 Hz, 2H), 3.75 (s, 3H), 3.04 (t, *J* = 7.2 Hz, 2H), 1.15-1.05 (comp. m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.0, 128.2, 127.1, 121.5, 119.1, 118.8, 111.6, 109.2, 64.5, 32.7, 29.2, 18.2, 12.2; IR (neat film, NaCl) 3056, 2942, 2865, 1616, 1470, 1382, 1328, 1248, 1100, 1069, 1013, 918, 883 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{20}H_{33}NSi$ $[M]^+$: 331.2331, found 331.2320.

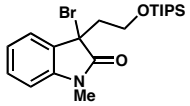


93

1-methyl-3-(2-((triisopropylsilyl)oxy)ethyl)indolin-2-one (93).

Prepared according to the procedure used for oxindole **91** using *N*-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO_2, 2% EtOAc in hexanes→5% EtOAc in hexanes). Isolated as a colorless viscous oil. 43% yield. R_f = 0.41 (17% EtOAc in

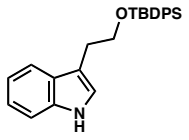
hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.24 (comp. m, 2H), 7.07-7.01 (m, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 4.00-3.86 (comp. m, 2H), 3.63 (t, *J* = 6.6 Hz, 1H), 3.19 (s, 3H), 2.23 (dq, *J* = 13.8, 6.6 Hz, 1H), 2.02 (dq, *J* = 13.8, 6.6 Hz, 1H), 1.08-1.01 (comp. m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 144.5, 129.3, 127.8, 124.2, 122.3, 108.0, 60.3, 42.4, 33.9, 26.2, 18.1, 12.1; IR (neat film, NaCl) 3056, 2941, 2865, 1712, 1613, 1494, 1468, 1375, 1344, 1263, 1263, 1193, 1095, 1019, 921 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{20}H_{33}NSi$ $[M+H]^+$: 348.2359, found 348.2376.



94

3-bromo-1-methyl-3-(2-((triisopropylsilyl)oxy)ethyl)indolin-2-one (94).

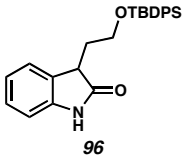
Prepared according to the procedure used for bromooxindole **76** using *N*-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO_2, 2% EtOAc in hexanes→5% EtOAc in hexanes). Isolated as a pale yellow viscous oil. 28% yield. R_f = 0.56 (17% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.31 (td, *J* = 7.8, 1.2 Hz, 1H), 7.08 (td, *J* = 7.5, 1.2 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 3.67-3.54 (m, 2H), 3.21 (s, 3H), 2.84 (ddd, *J* = 14.1, 7.2, 6.6 Hz, 1H), 2.60 (ddd, *J* = 13.8, 5.4, 4.5 Hz, 1H), 0.91 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 142.7, 130.1, 129.7, 124.8, 123.1, 108.8, 60.3, 55.3, 41.8, 26.8, 17.9, 11.9; IR (neat film, NaCl) 2943, 2891, 2866, 1732, 1614, 1494, 1471, 1422, 1372, 1344, 1244, 1137, 1104, 1071, 1018, 958 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{20}H_{33}NO_2Si^{81}Br$ $[M]^+$: 428.1443, found 428.1447.



95

3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-1H-indole (95).

To a solution of tryptophol (1.1 g, 6.6 mmol, 1.0 equiv) and imidazole (1.0 g, 14.6 mmol, 2.2 equiv) in DMF (25 mL) was added TIPSCl (1.9 mL, 7.3 mmol, 1.1 equiv) dropwise at ambient temperature. The reaction solution was stirred for 18 hours. Saturated aqueous $NaHCO_3$ (50 mL) was added and the mixture was extracted with EtOAc (2 x 50 mL). The combined extracts were dried with $MgSO_4$ prior to concentration. The residue obtained was purified by column chromatography (SiO_2, 9% EtOAc in hexanes) to afford 3-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-1*H*-indole as a yellow viscous oil (2.60 g, 98% yield). R_f = 0.60 (22% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 7.67 (dd, *J* = 7.5, 1.5 Hz, 4H), 7.44-7.40 (m, 3H), 7.38-7.32 (m, 5H), 7.18 (td, *J* = 7.5, 1.0 Hz, 1H), 7.06 (td, *J* = 7.5, 1.0 Hz, 1H), 7.00 (d, *J* = 2.5 Hz, 1H), 3.95 (t, *J* = 7.5 Hz, 2H), 3.05 (t, *J* = 7.5 Hz, 2H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.7, 134.1, 129.7, 127.8, 127.7, 122.3, 122.0, 119.3, 119.0, 113.1, 111.1, 64.6, 28.8, 27.0, 19.3.

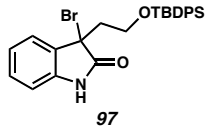


96

3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)indolin-2-one (96).

Prepared according to the procedure used for oxindole **91** using *N*-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO_2, 9% EtOAc in hexanes→17% EtOAc in hexanes). Isolated as a white solid. 57% yield. R_f = 0.30 (22% EtOAc in

hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (br s, 1H), 7.66 (dt, *J* = 6.5, 1.5 Hz, 2H), 7.52 (dt, *J* = 6.5, 1.5 Hz, 2H), 7.44-7.36 (comp. m, 4H), 7.33 (tt, *J* = 7.5, 1.0 Hz, 2H), 7.22 (tt, *J* = 8.0, 1.0 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 6.98 (td, *J* = 7.5, 1.0 Hz, 1H), 6.87 (d, *J* = 7.5 Hz, 1H), 3.86 (ddd, *J* = 12.5, 7.0, 5.5 Hz, 1H), 3.78 (dt, *J* = 10.5, 6.0 Hz, 1H), 3.69 (t, *J* = 7.5 Hz, 1H), 2.27 (dq, *J* = 14.0, 6.0 Hz, 1H), 2.19-2.12 (m, 1H), 1.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.3, 141.6, 135.8, 135.6, 133.6 (2 C), 129.8, 129.7, 129.4, 127.9, 127.8 (2 C), 124.7, 122.3, 109.7, 60.6, 42.9, 32.9, 26.9, 19.2; IR (neat film, NaCl) 3198, 3071, 2956, 2930, 2889, 2857, 1709, 1621, 1472, 1428, 1390, 1335, 1307, 1235, 1111, 1073, 953 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{26}H_{30}NO_2Si$ $[M+H]^+$: 416.2046, found 416.2033.

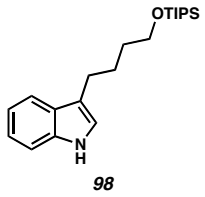


97

3-bromo-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)indolin-2-one (97).

Prepared according to the procedure used for bromooxindole **76** using *N*-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO_2, 9% EtOAc in hexanes→17% EtOAc in hexanes). Isolated as a white solid. 13% yield. R_f = 0.46 (22% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (br s, 1H), 7.50 (dt, *J* = 6.5, 1.5 Hz, 2H), 7.41 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.37-7.30 (comp. m, 5H), 7.28-7.23 (comp. m, 4 H), 7.10 (td, *J* = 8.0, 1.0 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 3.54-3.46 (m, 2H), 3.01 (ddd, *J* = 15.5, 9.0, 6.5 Hz, 1H), 2.60 (dt, *J* = 14.0, 4.0 Hz, 1H), 0.92 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 140.1, 135.7, 135.4, 133.1, 132.9, 130.3, 129.9, 129.7, 129.7, 127.8, 127.7, 125.2, 123.2, 110.8, 60.7, 55.4, 41.2, 26.6, 19.0; IR (neat film, NaCl) 3209, 3175, 3107, 2930, 2879, 2857, 1731, 1614, 1470, 1427, 1388, 1332, 1195, 1107, 1084,

824, 758, 748 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{26}H_{29}NO_2Si^{81}Br$ $[M+H]^+$: 496.1118, found 496.1130.



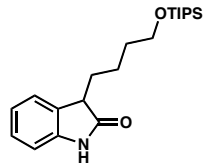
98

3-(4-((triisopropylsilyl)oxy)butyl)-1H-indole (98).

To a solution of indole-3-butyric acid (1.5 g, 7.4 mmol, 1.0 equiv) in THF (20 mL) at 0 ºC was added a solution of LAH (5.5 mL, 11 mmol, 2.0 M in THF, 1.5 equiv) dropwise. The reaction mixture was then allowed to warm to ambient temperature and stirred for 6 hours. Water (2 mL), 10 % aqueous NaOH (2 mL), and water (6 mL) were added in succession, and the mixture was stirred at ambient temperature for additional 30 min, filtered through Celite, concentrated under vacuum to get indole-3-butanol as a pale yellow viscous oil (1.40 g). The crude product was used for the next step without further purification.

To a solution of the above crude alcohol (1.4 g, 7.4 mmol) and imidazole (1.1 g, 16 mmol, 2.2 equiv) in DMF (20 mL) was added TIPSCl (1.7 mL, 8.1 mmol, 1.1 equiv) dropwise at ambient temperature. The reaction solution was stirred for 18 hours. Saturated aqueous $NaHCO_3$ (30 mL) was added and the mixture was extracted with EtOAc (4 x 30 mL). The combined extracts were dried with $MgSO_4$ prior to concentration. The residue obtained was purified by column chromatography (SiO_2, 5% EtOAc in hexanes) to afford 3-(4-(triisopropylsilyloxy)butyl)-1*H*-indole as a pale yellow viscous oil (2.50 g, 98% yield). R_f = 0.45 (22% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (br s, 1H), 7.62 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.35 (dt, *J* = 8.0, 1.0 Hz, 1H),

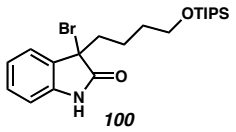
7.19 (td, *J* = 7.5, 1.0 Hz, 1H), 7.11 (td, *J* = 7.5, 1.0 Hz, 1H), 6.98 (t, *J* = 1.0 Hz, 1H), 3.74 (t, *J* = 6.5 Hz, 2H), 2.79 (t, *J* = 7.5 Hz, 2H), 1.84-1.78 (m, 2H), 1.70-1.64 (m, 2H), 1.14-1.01 (comp. m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.5, 127.8, 121.9, 121.2, 119.2 (2 C), 117.1, 111.1, 63.5, 33.1, 26.5, 25.1, 18.2, 12.2; IR (neat film, NaCl) 3420, 3057, 2941, 2864, 1458, 1420, 1382, 1351, 1336, 1246, 1228, 1105, 1070, 1012, 995, 969, 882, 796, 739 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{21}H_{35}NOSi$ [M+H]$^+$: 345.2488, found 345.2483.



99

3-(4-((triisopropylsilyl)oxy)butyl)indolin-2-one (99).

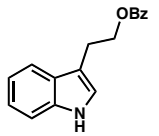
Prepared according to the procedure used for oxindole **91** using *N*-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO_2, 9% EtOAc in hexanes→17% EtOAc in hexanes). Isolated as a white solid. 15% yield. R_f = 0.11 (29% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (br s, 1H), 7.24 (d, *J* = 7.0 Hz, 1H), 7.20 (t, *J* = 7.0 Hz, 1H), 7.01 (td, *J* = 7.5, 1.0 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 3.70-3.61 (m, 2H), 3.48 (t, *J* = 6.5 Hz, 1H), 2.07-2.00 (m, 1H), 1.98-1.90 (m, 1H), 1.61-1.53 (m, 2H), 1.52-1.43 (m, 2H), 1.09-0.97 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.8, 141.7, 129.9, 127.9, 124.4, 122.4, 109.8, 63.2, 46.2, 33.0, 30.6, 22.4, 18.1, 12.1; IR (neat film, NaCl) 3209, 3091, 2942, 2892, 2866, 1711, 1621, 1486, 1472, 1383, 1338, 1233, 1106, 1070, 1015, 996, 883 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{21}H_{36}NO_2Si$ [M+H]$^+$: 362.2515, found 362.2498.



100

3-bromo-3-(4-((triisopropylsilyl)oxy)butyl)indolin-2-one (100).

Prepared according to the procedure used for bromooxindole **76** using *N*-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO_2, 9% EtOAc in hexanes→17% EtOAc in hexanes). Isolated as a pale yellow viscous oil. 15% yield. R_f = 0.34 (22% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.03 (br s, 1H), 7.37 (d, *J* = 7.0 Hz, 1H), 7.26 (td, *J* = 7.0, 1.0 Hz, 1H), 7.08 (td, *J* = 7.5, 0.5 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 3.65-3.56 (m, 2H), 2.42 (t, *J* = 8.0 Hz, 2H), 1.56-1.47 (m, 2H), 1.31-1.22 (m, 2H), 1.04-0.93 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 139.8, 130.5, 130.1, 124.9, 123.5, 110.8, 62.8, 56.9, 39.4, 32.6, 22.1, 18.1, 12.1; IR (neat film, NaCl) 3239, 2943, 2865, 2732, 1619, 1472, 1383, 1331, 1246, 1208, 1180, 1112, 1069, 1014, 996, 882, 749 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{21}H_{35}NO_2Si^{81}Br$ $[M+H]^+$: 442.1600, found 442.1583.

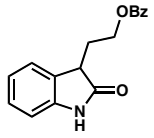


101

2-(1H-indol-3-yl)ethyl benzoate (101).

To a solution of benzoic acid (0.97 g, 7.9 mmol, 1.0 equiv) and EDCI (1.7 g, 8.7 mmol, 1.1 equiv) in CH_2Cl_2 (15 mL) was added DMAP (0.11 g, 0.87 mmol, 0.11 equiv) and tryptophol (1.5 g, 8.7 mmol, 1.1 equiv) at 23 ºC. The reaction mixture was stir at 23 ºC for 14 hours. Saturated aqueous $NaHCO_3$ solution (30 mL) was added and the mixture was extracted with CH_2Cl_2 (2 x 30 mL). The combined extracts were dried with $MgSO_4$

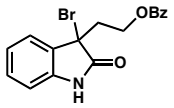
prior to concentration. Purification by flash chromatography (SiO_2, 9% EtOAc in hexanes→17% EtOAc in hexanes) afforded 2-(1*H*-indol-3-yl)ethyl benzoate as a yellow solid (1.05 g, 50% yield).[32] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09-8.03 (comp. m, 3H), 7.72-7.69 (m, 1H), 7.57 (tt, *J* = 7.5, 1.2 Hz, 1H), 7.48-7.41 (comp. m, 2H), 7.40-7.37 (m, 1H), 7.23 (td, *J* = 6.9, 1.5 Hz, 1H), 7.17 (td, *J* = 7.5, 1.5 Hz, 1H), 7.11 (d, *J* = 2.4 Hz, 1H), 4.63 (t, *J* = 7.5 Hz, 2H), 3.26 (td, *J* = 6.9, 0.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 136.3, 133.1, 130.5, 129.7, 128.5, 127.6, 122.3, 122.2, 119.6, 118.9, 112.2, 111.3, 65.2, 25.0.



102

2-(2-oxoindolin-3-yl)ethyl benzoate (102).

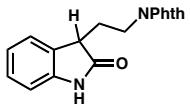
Prepared according to the procedure used for oxindole **91** using *N*-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO_2, 5% EtOAc in hexanes→25% EtOAc in hexanes). Isolated as a white solid. 47% yield. R_f = 0.21 (33% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (br s, 1H), 7.96-7.92 (comp. m, 2H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.02 (td, *J* = 7.5, 0.9 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 4.52 (dt, *J* = 11.4, 7.2 Hz, 1H), 4.41 (dt, *J* = 11.1, 6.8 Hz, 1H), 3.66 (t, *J* = 6.0 Hz, 1H), 2.48 (q, *J* = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.1, 166.5, 141.6, 133.1, 130.1, 129.7, 128.6, 128.4, 128.3, 124.4, 122.6, 110.2, 61.8, 43.4, 29.2; IR (neat film, NaCl) 3207, 3059, 2961, 1715, 1620, 1471, 1452, 1335, 1314, 1272, 1176, 1116, 1070, 1026 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{16}NO_3$ $[M+H]^+$: 282.1130, found 282.1126.



103

2-(3-bromo-2-oxoindolin-3-yl)ethyl benzoate (103).

Prepared according to the procedure used for bromooxindole **76** using *N*-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO_2, 5% EtOAc in hexanes→25% EtOAc in hexanes). Isolated as a pale yellow solid. 23% yield. $R_f = 0.48$ (33% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (br s, 1H), 7.86-7.81 (comp. m, 2H), 7.48 (td, *J* = 7.8, 1.2 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.25 (td, *J* = 7.5, 1.6 Hz, 1H), 7.07 (td, *J* = 7.5, 1.2 Hz, 1H), 6.85 (t, *J* = 7.1, 1H), 4.34 (dt, *J* = 11.7, 5.7 Hz, 1H), 4.16 (ddd, *J* = 11.4, 8.1, 4.8 Hz, 1H), 3.06 (ddd, *J* = 14.4, 8.4, 6.0 Hz, 1H), 2.89 (dt, *J* = 14.4, 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 166.2, 139.8, 133.3, 130.6, 129.6, 129.6, 129.5, 128.4, 125.0, 123.7, 111.2, 61.4, 54.5, 38.2; IR (neat film, NaCl) 3256, 3090, 3064, 3033, 2961, 1723, 1619, 1602, 1473, 1451, 1329, 1316, 1273, 1192, 1114, 1071, 1028, 752 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{15}N_2O_2{}^{81}Br$ $[M+H]^+$: 360.0296, found 360.0287.

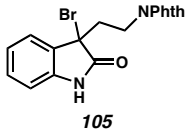


104

2-(2-(2-oxoindolin-3-yl)ethyl)isoindoline-1,3-dione (104).

Prepared from *N*-phthalimidotryptamine according to the procedure used for oxindole **91**. 54% yield. $R_f = 0.12$ (SiO_2, 50% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (bs, 1H), 7.75 (m, 2H), 7.66 (m, 2H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.08 (d, *J* = 7.7 Hz, 1H), 6.87 (t, *J* = 7.7 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 3.97 (m, 1H), 3.80 (m, 1H), 3.53 (t, *J* = 6.0 Hz, 1H), 2.51 (m, 1H), 2.32 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7,

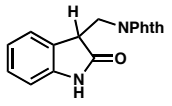
168.2, 141.3, 133.9, 132.1, 128.6, 128.0, 124.1, 123.2, 122.4, 109.7, 43.9, 35.2, 28.5; IR (Neat film, NaCl) 3271, 1772, 1711, 1621, 1471, 1398, 1220, 1022, 718 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{15}N_2O_3$ $[M+H]^+$: 307.1083, found 307.1076.



105

2-(2-(3-bromo-2-oxoindolin-3-yl)ethyl)isoindoline-1,3-dione (105).

Prepared from *N*-phthalimidotryptamine according to the procedure used for bromooxindole **76**. 9% yield. R_f = 0.31 (SiO_2, 50% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.71 (m, 2H), 7.62 (m, 2H), 7.28 (m, 1H), 7.06 (m, 1H), 6.80 (m, 2H), 3.81 (m, 1H), 3.65 (m, 1H), 3.01 (m, 1H), 2.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 167.8, 139.8, 134.0, 131.8, 130.2, 129.5, 124.4, 123.2, 123.1, 111.1, 54.2, 36.5, 34.6; IR (Neat film, NaCl) 3256, 1711, 1615, 1471, 1398, 1184, 716 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{14}BrN_2O_3$ $[M+H]^+$ 385.0188, found 385.0178.

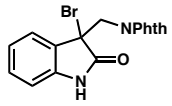


106

2-((2-oxoindolin-3-yl)methyl)isoindoline-1,3-dione (106).

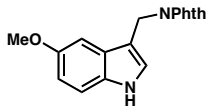
Prepared from *N*-(indol-3-yl)methyl]phthalimide according to the procedure used for oxindole **91** using *N*-bromosuccinimide (1.0 equiv).[33] Purified by flash chromatography (SiO_2, 25% EtOAc in hexanes→50% EtOAc in hexanes; then 9% EtOAc in DCM). Isolated as a pale yellow solid with 35% (w/w) of succinimide. 23% yield (corrected for succinimide). R_f = 0.17 (9% EtOAc in DCM); ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (br s, 1H), 7.90-7.86 (m, 2H), 7.76-7.71 (m, 2H), 7.22 (td, *J* = 7.5, 1.0 Hz, 1H), 7.19 (d, *J* = 7.0 Hz, 1H), 6.99 (td, *J* = 7.5, 1.0 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 4.20 (dd, *J* = 14.0, 9.0

Hz, 1H), 4.14 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.99 (dd, *J* = 9.0, 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5, 168.3, 141.6, 134.2, 132.1, 128.8, 126.6, 124.6, 123.7, 122.6, 110.1, 43.5, 38.2; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{13}N_2O_3$ $[M+H]^+$: 293.0926, found 293.0915.



107

2-((3-bromo-2-oxoindolin-3-yl)methyl)isoindoline-1,3-dione (107). Prepared from *N*-(indol-3-yl)methyl]phthalimide according to the procedure used for bromooxindole **76** using *N*-bromosuccinimide (1.0 equiv).[33] Purified by flash chromatography (SiO_2, 25% EtOAc in hexanes→50% EtOAc in hexanes, then 9% EtOAc in DCM). Isolated as a white solid. 22% yield. R_f = 0.30 (9% EtOAc in DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (br s, 1H), 7.76-7.72 (comp. m, 2H), 7.68-7.64 (comp. m, 2H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.20 (td, *J* = 8.0, 1.5 Hz, 1H), 7.02 (td, *J* = 7.5, 1.0 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 4.64 (ABq, *J* = 14.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 167.4, 140.3, 134.4, 131.5, 130.9, 127.4, 126.3, 123.8, 123.3, 110.8, 53.7, 43.9; IR (neat film, NaCl) 3268, 1778, 1734, 1719, 1617, 1472, 1389, 1335, 1192, 1142, 986, 967, 876 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{12}N_2O_3Br$ $[M+H]^+$: 371.0031, found 371.0044.

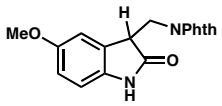


108

2-((5-methoxy-1H-indol-3-yl)methyl)isoindoline-1,3-dione (108).

CH_3I (0.89 mL, 14 mmol, 5.0 equiv) was added to a solution of 5-methoxy-gramine (0.58 g, 2.8 mmol, 1.0 equiv) in THF (25 mL) at 0 ºC over 30 min. After stirring of the reaction mixture at ambient temperature for 1 hour, the solvent was removed in vacuo.

The residue was heated with potassium phthalimide (0.53 g, 2.8 mmol, 1 equiv) at 140 ºC for 6 hours. Upon cooling to ambient temperature, the reaction mixture was then diluted with water (20 mL) and brine (20 mL) and then extracted with EtOAc (3 x 50 mL). The organic layers were collected and dried with $MgSO_4$. Purification by column chromatography (SiO_2, 33% EtOAc in hexanes) afforded *N*-(5-methoxy-indol-3-yl)methyl]phthalimide as a yellow solid (441 mg, 51% yield). R_f = 0.23 (33% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (br s, 1H), 7.81-7.78 (comp. m, 2H), 7.67-7.64 (comp. m, 2H), 7.44 (d, *J* = 2.5 Hz, 1H), 7.38 (d, *J* = 2.5 Hz, 1H), 7.22 (dd, *J* = 9.0, 0.5 Hz, 1H), 6.85 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.99 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 154.5, 133.9, 132.4, 131.1, 127.1, 125.9, 123.3, 113.0, 111.9, 111.3, 101.0, 55.9, 32.8; IR (neat film, NaCl) 3401, 2938, 1767, 1708, 1488, 1432, 1394, 1334, 1216, 1178, 1056 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{14}N_2O_3$ $[M]^+$: 306.1005, found 306.1007.

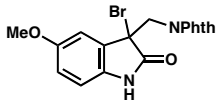


109

2-((5-methoxy-2-oxoindolin-3-yl)methyl)isoindoline-1,3-dione (109).

Prepared according to the procedure similar to that used to synthesize oxindole **91** using *N*-bromosuccinimide (1.6 equiv). Purified by column chromatography (SiO_2, 9% EtOAc in CH_2Cl_2 →17% EtOAc in CH_2Cl_2). Isolated as a white solid. 33% yield. R_f = 0.06 (9% EtOAc in DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89-7.85 (comp. m, 2H), 7.75-7.7.71 (comp. m, 2H), 7.73 (bs, 1H), 6.80 (s, 1H), 6.77 (d, *J* = 8.0, 1H), 6.74 (dd, *J* = 8.5, 2.0 Hz, 1H), 4.19 (dd, *J* = 14.0, 9.5 Hz, 1H), 4.12 (dd, *J* = 14.0, 7.0 Hz, 1H), 3.95 (dd, *J* = 9.0, 7.0 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 168.3,

155.9, 134.8, 134.3, 132.1, 127.8, 123.7, 113.6, 111.7, 110.3, 55.9, 43.8, 38.2; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{15}N_2O_4$ $[M+H]^+$: 323.1032, found 323.1024.

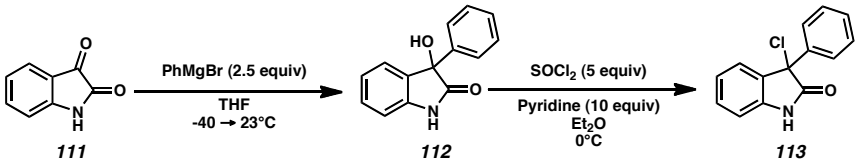


110

2-((3-bromo-5-methoxy-2-oxoindolin-3-yl)methyl)isoindoline-1,3-dione (110).

Prepared according to the procedure similar to that used to synthesize bromooxindole **76** using *N*-bromosuccinimide (1.6 equiv). Purified by column chromatography (SiO_2, 9% EtOAc in DCM) and then recrystallized from DCM. Isolated as a yellow solid. 78% yield. R_f = 0.18 (9% EtOAc in DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78-7.74 (comp. m, 2H), 7.69-7.65 (comp. m, 2H), 7.61 (br s, 1H), 7.07, (d, *J* = 2.5 Hz, 1H), 6.75 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.70 (d, *J* = 7.5, 1H), 4.62 (ABq, *J* = 15.0 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 167.4, 156.1, 134.4, 133.3, 131.6, 128.3, 123.8, 117.1, 111.9, 111.2, 56.0, 53.9, 43.9; IR (neat film, NaCl) 3271, 2997, 1777, 1721, 1492, 1389, 1299, 1205, 719 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{18}H_{14}N_2O_4Br$ $[M+H]^+$: 401.0137, found 401.0142.

3.4.3 General Synthesis of 3-Aryl Haloxindoles from Isatin



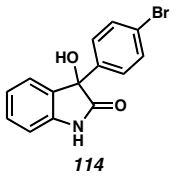
111 ***112*** ***113***

3-chloro-3-phenylindolin-2-one (113).

To a solution of isatin (**111**, 1.0 g, 6.8 mmol, 1.0 equiv) in THF (60 mL) cooled to –40 °C was added PhMgBr (3 M in Et_2O, 5.7 mL, 17 mmol, 2.5 equiv). The reaction mixture

was allowed to warm to ambient temperature. After 6 hours, 1 N hydrochloric acid (30 mL) was added dropwise to quench the reaction, and the phases were separated. The aqueous phase was extracted with ether (2 x 50 mL), dried with sodium sulfate and concentrated to afford **112** as a yellow solid in 99% yield.[34] No further purification was necessary. R_f = 0.18 (20% EtOAc in DCM); ^{1}H NMR (500 MHz, CD_3OD) δ 7.39-7.37 (comp. m, 2H), 7.33-7.26 (comp. m, 4H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.06 (ddd, *J* = 8.5, 8.5, 1.0 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 181.8, 143.2, 142.2, 135.0, 130.8, 129.4, 129.1, 126.8, 126.2, 124.2, 111.5, 79.5; IR (neat film, NaCl) 3312, 1711, 1622, 1473, 1183 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{14}H_{11}O_2N$ [M^+] 225.0790, found 255.0796.

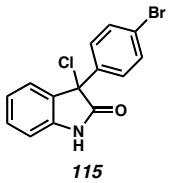
To a cooled (0 °C) solution of hydroxyoxindole **112** (322 mg, 1.4 mmol, 1.0 equiv) and pyridine (1.2 mL, 14 mmol, 3.0 equiv) in THF (10 mL) in flask equipped with a stirbar was added thionyl chloride (520 μL, 850 mg, 5.0 equiv) in a dropwise manner. The solution was stirred at 0 °C for one hour or until complete by TLC. Water (60 mL) then added and the mixture was extracted with EtOAc (3 x 100 mL). The combined extracts were washed with brine (1 x 100 mL), and then dried with $MgSO_4$ prior to concentration. Purification by flash chromatography (SiO_2, 10% EtOAc in hexanes) afforded chlorooxindole **113** as a white powder (83% yield). R_f = 0.27 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (bs, 1H), 7.56-7.54 (comp. m, 2H), 7.39-7.32 (comp. m, 5H), 7.14 (ddd, *J* = 7.6, 7.6, 0.9 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 139.9, 136.5, 131.0, 130.6, 129.1, 128.7, 127.6, 126.5, 123.9, 110.8, 66.8; IR (neat film, NaCl) 3247, 1729, 1619, 1472, 1322, 1211 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{14}H_{11}ONCl$ $[M+H]^+$: 244.0529, found 244.0539.



114

3-(4-bromophenyl)-3-hydroxyindolin-2-one (114).

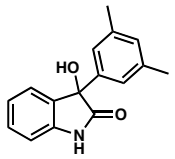
Prepared according to the procedure used for hydroxyoxindole **112**. Purified by flash chromatography (SiO_2, 50% EtOAc in hexanes). Isolated as a white powder. 80% yield. R_f = 0.33 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, CD_3OD) δ 7.38 (app. d, *J* = 8.5 Hz, 2H), 7.23-7.19 (comp. m, 3H), 7.08 (d, *J* = 7.3 Hz, 1H), 6.96 (dd, *J* = 7.6, 7.6 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 179.9, 141.9, 140.2, 133.2, 131.2, 129.8, 127.6, 124.9, 123.0, 121.7, 110.3, 77.8; IR (neat film, NaCl) 3234, 1718, 1621, 1472, 1184 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $C_{14}H_{10}BrNO_2$ [M]$^+$: 302.9895, found 302.9896.



115

3-(4-bromophenyl)-3-chloroindolin-2-one (115).

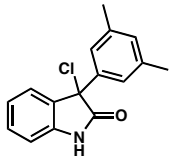
Prepared according to the procedure used for chlorooxindole **113**. Purified by flash chromatography (SiO_2, 20% EtOAc in hexanes). Isolated as a white solid. 63% yield. R_f = 0.67 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.49 (app. d, *J* = 8.8 Hz, 2H), 7.42 (app. d, *J* = 8.8 Hz, 2H), 7.53 (app. t, *J* = 6.1 Hz, 2H), 7.16 (dd, *J* = 7.6, 7.6 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 140.0, 135.6, 131.9, 130.9, 130.4, 129.4, 127.6, 126.3, 124.0, 111.2, 66.2; IR (neat film, NaCl) 3247, 1728, 1619, 1472, 1395, 1322, 1211, 1011 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $C_{14}H_{19}ONCl^{81}Br$ [M]$^+$: 322.9536, found 322.9521.



116

3-(3,5-dimethylphenyl)-3-hydroxyindolin-2-one (116).

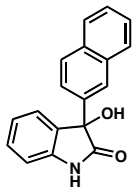
Prepared according to the procedure used for hydroxyoxindole **112**. Purified by flash chromatography (SiO_2, 20% EtOAc in DCM). Isolated as a pale yellow solid. 46% yield. R_f = 0.50 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, CD_3OD) δ 7.29 (ddd, *J* = 7.8, 7.8, 1.2 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.04 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H), 6.98-6.96 (comp. m, 3H), 6.92 (s, 1H), 2.26 (s, 6H); ^{13}C NMR (125 MHz, MeOD) δ 182.0, 143.2, 142.0, 139.2, 135.3, 130.8, 130.6, 126.2, 124.5, 124.2, 111.5, 79.5, 21.6; IR (neat film, NaCl) 3270, 1720, 1620, 1472, 1186, 1109 cm^{-1}; MS (EI$^+$) *m/z* calc'd for $C_{16}H_{15}O_2N$ $[M]^+$: 253.1103, found 253.1112.



117

3-chloro-3-(3,5-dimethylphenyl)indolin-2-one (117).

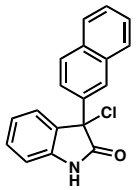
Prepared according to the procedure used for chlorooxindole **113**. Purified by flash chromatography (SiO_2, 20% EtOAc in hexanes). Isolated as a light yellow solid. 85% yield. R_f = 0.40 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.30 (comp. m, 2H), 7.14-7.11 (comp. m, 3H), 6.98-6.97 (comp. m, 2H), 2.30 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 140.0, 138.4, 136.2, 131.5, 130.9, 130.4, 126.3, 125.2, 123.8, 110.9, 67.0, 21.5; IR (neat film, NaCl) 3247, 1729, 1619, 1473, 1192 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{16}H_{15}ClNO$ $[M+H]^+$: 272.0842, found 272.0847.



118

3-hydroxy-3-(naphthalen-2-yl)indolin-2-one (118).

Prepared according to the procedure used for hydroxyoxindole **112**. Purified by flash chromatography (SiO_2, 50% EtOAc in hexanes). Isolated as a yellow solid. 86% yield. R_f = 0.46 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, CD_3OD) δ 7.84 (d, *J* = 1.5 Hz, 1H), 7.73-7.71 (comp. m, 2H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.38-7.36 (comp. m, 2H), 7.31 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.22 (ddd, *J* = 7.8, 7.8, 1.2 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.96 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 181.5, 143.2, 139.3, 134.8, 134.5, 134.5, 130.8, 129.2, 129.0, 128.6, 127.3, 127.2, 126.2, 125.6, 124.7, 124.1, 111.5, 79.5; IR (Neat Film, NaCl) 3235, 1727, 1711, 1619, 1471, 1339, 1180, 1109, 1074, 893, 929, 859, 811, 754, 740 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $C_{18}H_{13}O_2N$ [M]$^+$: 275.0946, found 275.0936.

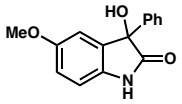


119

3-chloro-3-(naphthalen-2-yl)indolin-2-one (119).

Prepared according to the procedure used for chlorooxindole **113**. Purified by flash chromatography (SiO_2, 0% EtOAc in hexanes→40% EtOAc in hexanes). Isolated as a pale yellow solid. 67% yield. R_f = 0.30 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, CD_3OD) δ 7.83 (s, 1H), 7.72-7.68 (comp. m, 3H), 7.38 (comp. m, 2H), 7.29 (dd, *J* = 8.5,

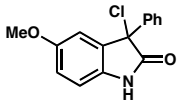
1.7 Hz, 1H), 7.22 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.96 (dd, *J* = 7.6, 7.6 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (125 MHz, MeOD) δ 180.4, 142.0, 138.2, 133.6, 133.4, 133.3, 129.6, 128.0, 127.9, 127.4, 126.1, 126.0, 125.0, 124.4, 123.5, 122.9, 110.3, 78.4; IR (neat film, NaCl) 3261, 1726, 1679, 1622, 1474, 1342, 1268, 1180, 1126, 1111, 933, 894, 810, 752 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $C_{18}H_{12}ONCl$ [M]$^+$:293.0607, found 293.0604.



120

3-hydroxy-5-methoxy-3-phenylindolin-2-one (120).

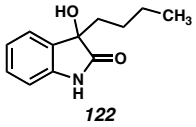
Prepared according to the procedure used for hydroxyoxindole **112**. Purified by flash chromatography (SiO_2, 20% EtOAc in hexanes→50% EtOAc in hexanes). Isolated as a pale pink solid. 86% yield. R_f = 0.25 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, CD_3OD) δ 7.39-7.36 (comp. m, 2H), 7.34-7.26 (comp. m, 3H), 6.91-6.85 (comp. m, 2H), 6.78 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 181.7, 157.8, 142.0, 136.1, 129.3, 129.0, 126.7, 115.6, 112.6, 111.9, 79.8, 56.2; IR (neat film, NaCl) 3271, 1708, 1489, 1203, 1026, 758, 733 cm^1; HRMS (EI$^+$) *m/z* calc'd for $C_{15}H_{13}NO_3$ [M]$^+$: 255.0895, found 255.0891.



121

3-chloro-5-methoxy-3-phenylindolin-2-one (121). Prepared according to the procedure used for chlorooxindole **113**. Purified by flash chromatography (SiO_2, 20% EtOAc in hexanes). Isolated as a white powder. 66% yield. R_f = 0.70 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.56 (comp. m, 2H), 7.40-7.26 (comp. m,

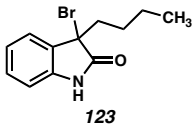
3H), 6.95 (app. s, 1H), 6.90-6.86 (comp. m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 156.8, 136.6, 133.2, 132.2, 129.2, 128.9, 127.6, 116.0, 112.6, 111.5, 67.2, 56.0; IR (neat film, NaCl) 3206, 2961, 1726, 1613, 1492, 1440, 1300, 1206, 1146, 1104, 1031, 959, 846, 814, 750, 734, 695 cm^{-1}; MS (FAB$^+$) *m/z* calc'd for $C_{15}H_{12}ClNO_2$ $[M]^+$: 273.0556, found 273.0557.



122

3-butyl-3-hydroxyindolin-2-one (122).

Prepared according to the procedure used for hydroxyoxindole **112**. Purified by flash chromatography (SiO_2, 33% EtOAc in hexanes→50% EtOAc in hexanes) and recrystallized from EtOAc and hexanes. Isolated as a white solid. 29% yield. R_f = 0.47 (33% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (br s, 1H), 7.37 (dd, *J* = 7.2, 0.6 Hz, 1H), 7.27 (td, *J* = 7.5, 1.2 Hz, 1H), 7.09 (td, *J* = 7.5, 1.2 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 2.76 (s, 1H), 1.99-1.90 (comp. m, 2H), 1.31-1.16 (comp. m, 3H), 1.12-1.04 (comp. m, 1H), 0.82 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.0, 140.6, 130.7, 129.7, 124.4, 123.3, 110.5, 77.2, 38.4, 25.3, 22.9, 13.9; IR (neat film, NaCl) 3401, 3189, 2951, 2934, 2860, 1718, 1624, 1474, 1400, 1338, 1234, 1194, 1103, 1083, 1059, 1010, 961, 774, 748 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{12}H_{15}NO_2$ $[M+H]^+$: 205.1103, found 205.1109.

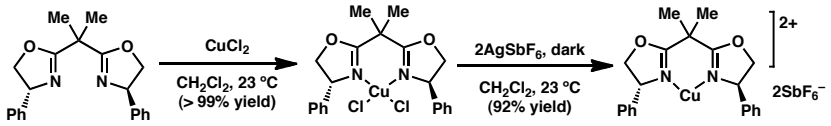


123

3-bromo-3-butylindolin-2-one (123).

To cooled solution (0 °C) of 3-butyl-3-hydroxyindolin-2-one (188 mg, 0.916 mmol, 1.0 equiv) and pyridine (0.89 mL, 0.99 mmol, 12 equiv) in THF (8 mL) in a flask equipped with a stirbar was added a solution of $POBr_3$ (1.0 g, 3.7 mg, 4.0 equiv) in THF (2 mL) in a dropwise manner. The reaction solution was stirred at 0 °C for 20 min. Water (20 mL) then added and the mixture was extracted with EtOAc (3 x 30 mL). The combined extracts were dried with $MgSO_4$ prior to concentration. Purification by flash chromatography (SiO_2, 10% EtOAc in hexanes) afforded 3-bromo-3-butylindolin-2-one as a pale yellow viscous oil (31% yield). R_f = 0.48 (33% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.45 (br s, 1H), 7.38 (dd, *J* = 7.2, 0.6 Hz, 1H), 7.27 (td, *J* = 7.5, 1.2 Hz, 1H), 7.09 (td, *J* = 7.8, 1.2 Hz, 1H), 6.98 (d, *J* = 7.1 Hz, 1H), 2.47-2.32 (comp. m, 2H), 1.37-1.00 (comp. m, 4H), 0.83 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 139.9, 130.6, 130.1, 124.8, 123.5, 111.0, 57.1, 39.3, 27.6, 22.6, 13.9; IR (neat film, NaCl) 3247, 2957, 2930, 2872, 1722, 1618, 1472, 1381, 1331, 1223, 1193, 1139, 1118, 1102, 1018, 863, 837 cm^{-1}; HRMS (FAB+) *m/z* calcd. for $C_{12}H_{15}BrNO$ $[M+H]^+$: 268.0337, found 268.0328.

3.4.4 Synthesis of [Cu((R)-Ph-BOX)(SbF$_6$)$_2$]

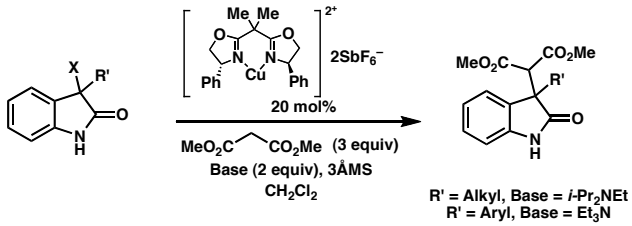


(*R*)-Ph-BOX (190 mg, 0.58 mmol, 1.0 equiv) was stirred in the presence of copper(II) chloride (82 mg, 0.61 mmol, 1.0 equiv) in CH_2Cl_2 (8 mL) for 24 hours at ambient temperature in a glovebox. The reaction mixture was then filtered through Celite, and the

green solution was concentrated under reduced pressure to afford [Cu((*R*)-Ph-BOX)Cl_2] as a light green powder (272 mg, >99% yield).

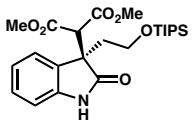
A 25 mL reaction flask equipped with a magnetic stir bar was charged with [Cu((*R*)-PhBOX)Cl_2] (103 mg, 0.22 mmol. 1.0 equiv) and silver hexafluoroantimonate (150 mg, 2.0 equiv) in a glovebox. The flask was wrapped with aluminum foil to prevent exposure to light, and CH_2Cl_2 (11 mL) was added. The flask was capped and the reaction mixture stirred in the glovebox for 14 hours, then filtered through a pad of Celite. The dark green filtrate was concentrated under reduced pressure to afford [Cu((*R*)-PhBOX)$(SbF_6)_2$] as a dark green powder (174 mg, 92% yield).[35]

3.4.5 General Procedure for Enantioselective Malonate Alkylation



A 1 dram vial equipped with a stirbar was charged with [Cu((*R*)-Ph-BOX)$(SbF_6)_2$] (17.4 mg, 0.02 mmol, 0.2 equiv) and 3ÅMS (32.3 mg) in the glovebox. After the reaction vial was removed from the glove box, DCM (0.25 mL of 0.5 mL added, 0.2 M solution) was added, and the mixture was allowed to stir for 15 minutes. Upon cooling to reaction temperature, malonate (34.3 uL, 0.3 mmol, 3.0 equiv) followed by halooxindole (0.1 mmol, 1.0 equiv) were dissolved in the remaining DCM and were added via syringe to give a dark blue-green solution.[36] Base (0.2 mmol, 2.0 equiv) was then added to give a dark brown solution. Upon completion of reaction, saturated aqueous ammonium

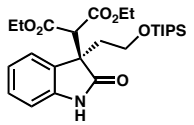
chloride solution (2 mL) was added. Upon extraction with DCM (3 x 2 mL), the combined organic layers were dried with sodium sulfate and purified as stated.



77

Malonate Adduct 77 (Table 3.4, Entry 1).

Purified by flash chromatography (SiO_2, 5% acetonitrile in benzene). Isolated as a white solid. 77% yield. R_f = 0.53 (17% acetonitrile in benzene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.21 (td, *J* = 7.7, 1.0 Hz, 1H), 7.01 (td, *J* = 7.6, 1.0 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 4.17 (s, 1H), 3.79 (s, 3H), 3.52 (s, 3H), 3.51 (m, 1H), 3.35 (m, 1H), 3.25 (m, 2H), 0.93 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.3, 168.0, 167.1, 141.4, 129.4, 128.6, 125.4, 122.5, 109.5, 58.9, 57.1, 52.6, 52.5, 50.9, 38.5, 17.9, 11.9; IR (neat film, NaCl) 3251, 2941, 2863, 1747, 1721, 1687, 1471, 1321, 1197, 1114 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{24}H_{38}NO_6Si$ $[M+H]^+$:464.2468, found 464.2468; $[\alpha]_D^{25}$ –28.6 (*c* 0.43, CH_2Cl_2, 88% ee).

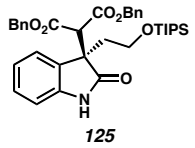


124

Malonate Adduct 124 (Table 3.4, Entry 2).

Purified by flash chromatography (SiO_2, 9% EtOAc in hexanes→17% EtOAc in hexanes). Isolated as a white solid. 73% yield. R_f = 0.24 (33% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (br s, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.20 (td, *J* = 8.0, 1.0 Hz, 1H), 7.00 (td, *J* = 7.5, 1.0 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 4.29-4.23 (m, 2H), 4.14 (s, 1H), 4.00-3.89 (m, 2H), 3.52 (ddd, *J* = 12.0, 8.0, 7.0 Hz, 1H), 3.36 (ddd, *J* = 13.5, 8.5,

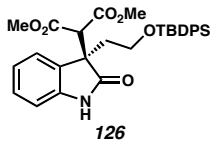
5.0 Hz, 1H), 2.32-2.21 (m, 2H), 1.29 (t, *J* = 7.0 Hz, 3H), 0.99 (t, *J* = 7.0 Hz, 3H), 0.93 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.5, 167.8, 166.9, 141.6, 129.7, 128.7, 125.9, 122.7, 109.5, 61.8 (2C), 59.1, 57.6, 51.0, 38.9, 18.1, 14.2, 13.8, 12.1; IR (neat film, NaCl) 3218, 2942, 2866, 1731, 1716, 1621, 1472, 1197 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{26}H_{42}NO_6Si$ $[M+H]^+$: 492.2781, found 492.2774; $[\alpha]_D^{25}$ –16.4 (*c* 0.78, CH_2Cl_2, 84% ee).



125

Malonate Adduct 125 (Table 3.4, Entry 3).

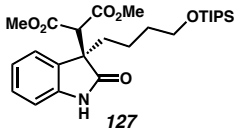
Purified by flash chromatography (SiO_2, 7% EtOAc in hexanes→17% EtOAc in hexanes). Isolated as a white solid. 78% yield. R_f = 0.25 (33% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (br s, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.33-7.23 (comp. m, 8H), 7.16 (td, *J* = 7.5, 1.0 Hz, 1H), 7.07 (dd, *J* = 8.0, 1.5 Hz, 2H), 6.94 (td, *J* = 7.5, 0.5 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 5.20 (ABq, *J* = 17.0 Hz, 2H), 4.91 (ABq, *J* = 18.5 Hz, 2H), 4.27 (s, 1H), 3.50 (dt, *J* = 9.5, 6.0 Hz, 1H), 3.50 (ddd, *J* = 10.0, 8.5, 5.0 Hz, 1H), 2.33-2.22 (m, 2H), 0.92 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3, 167.5, 166.6, 141.5, 135.2, 135.1, 129.4, 128.8, 128.7, 128.6, 128.43, 128.39, 125.7, 122.7, 109.8, 67.7, 67.5, 59.1, 57.6, 51.1, 38.9, 18.1, 12.1; IR (neat film, NaCl) 3251, 2941, 2863, 1747, 1721, 1687, 1471, 1321, 1197, 1114 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{24}H_{38}NO_6Si$ $[M+H]^+$: 464.2468, found 464.2468; $[\alpha]_D^{25}$ –17.7 (*c* 0.71, CH_2Cl_2, 88% ee).



126

Malonate Adduct 126 (Table 3.4, Entry 4).

Purified by flash chromatography (SiO_2, 5% acetonitrile in benzene). Isolated as a white solid. 78% yield. R_f = 0.48 (17% acetonitrile in benzene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (br s, 1 H), 7.51 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.42-7.39 (comp. m, 3H), 7.38-7.35 (comp. m, 2H), 7.33-7.28 (comp. m, 4H), 7.21 (td, *J* = 7.5, 1.5 Hz, 1H), 6.98 (td, *J* = 7.5, 1.0 Hz, 1H), 6.80 (d, *J* = 7.5 Hz, 1H), 4.13 (s, 1H), 3.73 (s, 3H), 3.51 (s, 3H), 3.46 (ddd, *J* = 14.0, 7.5, 6.5 Hz, 1H), 3.34 (ddd, *J* = 12.0, 7.5, 4.5 Hz, 1H), 2.38 (dt, *J* = 13.5, 8.0 Hz, 1H), 2.25 (ddd, *J* = 13.5, 6.5, 4.5 Hz, 1H), 0.94 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 168.1, 167.1, 141.5, 135.6, 135.5, 133.5, 133.4, 129.7, 129.6, 129.1, 128.6, 127.7 (2 C), 125.6, 122.6, 109.6, 59.8, 57.5, 52.7, 52.6, 51.0, 38.2, 26.8, 19.1; IR (neat film, NaCl) 3369, 3071, 2953, 2930, 2857, 1736, 1717, 1620, 1472, 1429, 1325, 1237, 1198, 1156, 1112, 1088, 1022, 823, 740 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{31}H_{36}NO_6Si$ $[M+H]^+$: 546.2312, found 546.2320; $[\alpha]_D^{25}$ –17.3 (*c* 0.94, CH_2Cl_2, 88% ee).

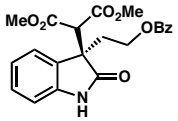


127

Malonate Adduct 127 (Table 3.4, Entry 6).

Purified by flash chromatography (SiO_2, 9% EtOAc in hexanes→17% EtOAc in hexanes). Isolated as a white solid. 47% yield. R_f = 0.16 (22% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (br s, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.20 (td, *J* = 7.5, 1.0 Hz, 1H), 7.01 (td, *J* = 7.5, 1.0 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 4.15 (s, 1H), 3.79 (s, 3H), 3.56-3.46 (comp. m, 2H), 3.51 (s, 3H), 1.96-1.89 (comp. m, 2H), 1.46-1.31 (comp. m, 2H), 1.18-1.08 (comp. m, 1H), 1.02-0.88 (comp. m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.6, 168.2, 167.3, 141.5, 129.9, 128.5, 125.2, 122.8, 109.4, 63.0, 57.2, 52.9, 52.8, 52.7, 36.4, 33.0, 20.0, 18.1, 12.1; IR (neat film, NaCl) 3248, 2944, 2866, 1736,

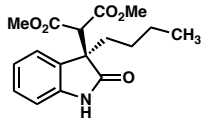
1716, 1620, 1472, 1436, 1326, 1225, 1155, 1109, 1058, 995, 883, 752 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{26}H_{42}NO_6Si$ $[M+H]^+$: 492.2781, found 492.2775; $[\alpha]_D^{25}$ –6.3 (*c* 0.58, CH_2Cl_2, 86% ee).



128

Malonate Adduct 128 (Table 3.4, Entry 5).

Purified by flash chromatography (SiO_2, 9% acetonitrile in benzene). Isolated as a white solid. 51% yield. R_f = 0.13 (33% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (br s, 1H), 7.85 (dd, *J* = 8.1, 1.2 Hz, 2H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.51 (tt, *J* = 7.5, 1.2 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.19 (td, *J* = 7.5, 1.2 Hz, 1H), 7.01 (td, *J* = 7.8, 1.2 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 4.19 (s, 1H), 4.08 (comp. m, 2H), 3.78 (s, 3H), 3.51 (s, 3H), 2.53 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 167.8, 166.9, 166.2, 141.6, 133.0, 129.9, 129.7, 130.1, 128.8, 128.3, 125.5, 122.9, 110.1, 60.7, 57.3, 52.8, 52.7, 51.2, 34.6; IR (neat film, NaCl) 3307, 2955, 1723, 1620, 1473, 1452, 1436, 1318, 1274, 1199, 1158, 1117, 1026, 756, 714 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{22}H_{22}NO_7$ $[M+H]^+$: 412.1396, found 412.1392; $[\alpha]_D^{25}$ –52.5 (*c* 1.40, CH_2Cl_2, 83% ee).

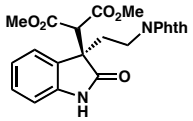


129

Malonate Adduct 129 (Table 3.4, Entry 7).

Purified by flash chromatography (SiO_2, 9% EtOAc in hexanes→17% EtOAc in hexanes). Isolated as a pale yellow solid. 47% yield. R_f = 0.22 (33% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 8.11 (br s, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.22

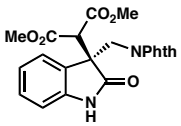
(td, *J* = 7.8, 2.0 Hz, 1H), 7.02 (td, *J* = 7.5, 1.5 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 4.15 (s, 1H), 3.79 (s, 3H), 3.50 (s, 3H), 1.93-1.87 (comp. m, 2H), 1.22-1.04 (comp. m, 3H), 0.81-0.72 (comp. m with a triplet at δ 0.75, *J* = 7.5 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.9, 168.2, 167.3, 141.6, 130.1, 128.5, 125.2, 122.7, 109.5, 57.3, 52.8, 52.7, 52.6, 36.2, 25.5, 22.8, 13.9; IR (neat film, NaCl) 3249, 2956, 2930, 2862, 1736, 1716, 1620, 1486, 1472, 1436, 1327, 1292, 1230, 1198, 1157, 1057, 1022, 755 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{22}NO_5$ $[M+H]^+$: 320.1498, found 320.1512; $[\alpha]_D^{25}$ –10.6 (*c* 1.46, CH_2Cl_2, 84% ee).



130

Malonated Adduct 130 (Table 3.4, Entry 10).

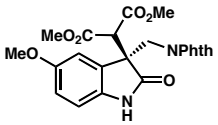
Purified by flash chromatography (SiO_2, 17% acetone in hexanes). Isolated as a white solid. 63% yield. R_f = 0.22 (33% acetone in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 7.73-7.70 (comp. m, 2H), 7.66-7.63 (comp. m, 2H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.07 (td, *J*= 7.5, 1.0 Hz, 1H), 6.88 (td, *J* = 7.5, 1.0 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 4.18 (s, 1H), 3.82 (s, 3H), 3.56 (t, *J* = 7.5 Hz, 2H), 3.50 (s, 3H), 2.52 (dt, *J* = 13.5, 8.0 Hz, 1H), 2.35 (quintet, *J* = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5, 167.9, 167.8, 166.9, 141.4, 133.9, 132.1, 128.9, 128.8, 125.4, 123.2, 122.9, 110.0, 57.0, 52.9, 52.7, 51.3, 33.6, 33.5; IR (neat film, NaCl) 3261, 3034, 2935, 1755, 1724, 1698, 1473, 1398, 1347, 1272, 1153, 1060, 719 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{21}N_2O_7$ $[M+H]^+$: 437.1349, found 437.1342; $[\alpha]_D^{25}$ –4.4 (*c* 0.56, MeOH, 94% ee).



131

Malonate Adduct 131 (Table 3.4, Entry 8).

Purified by flash chromatography (SiO_2, 5% acetonitrile in benzene→25% acetonitrile in benzene). Isolated as a white solid. 42% yield. R_f = 0.48 (17% acetonitrile in benzene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (br s, 1H), 7.70-7.74 (m, 2H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.68-7.64 (m, 2H), 7.18 (td, *J* = 7.5, 1.5 Hz, 1H), 7.00 (td, *J* = 8.0, 1.0 Hz, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 4.62 (d, *J* = 14.5 Hz, 1H), 4.30 (s, 1 H), 4.15 (d, *J* = 14.5 Hz, 1H), 3.90 (s, 3H), 3.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 168.1, 168.0, 167.3, 141.2, 134.2, 131.8, 129.3, 127.8, 126.5, 123.6, 122.7, 109.9, 54.7, 53.0, 52.9, 52.4, 41.3; IR (neat film, NaCl) 3340, 2954, 2924, 2853, 1776, 1732, 1718, 1618, 1472, 1434, 1394, 1354, 1316, 1295, 1225, 1197, 1158, 1001, 905 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{22}H_{19}N_2O_7$ $[M]^+$: 423.1192, found 423.1203; $[\alpha]_D^{25}$ –3.3 (*c* 0.55, CH_2Cl_2, 81% ee).

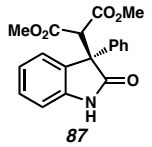


83

Malonate Adduct 83 (Table 3.4, Entry 9).

Purified by flash chromatography (SiO_2, 33% EtOAc in hexanes→50% EtOAc in hexanes; then 9% acetonitrile in benzene→17% acetonitrile in benzene). Isolated as a white solid. 42% yield. R_f = 0.22 (17% acetonitrile in benzene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89-7.76 (m, 2H), 7.69-7.66 (m, 2H), 7.48 (br s, 1H), 7.41 (d, *J* = 2.0 Hz, 1H), 6.75-6.71 (comp. m, 2H), 4.62 (d, *J* = 14.5 Hz, 1H), 4.30 (s, 1H), 4.10 (d, *J* = 14.5 Hz,

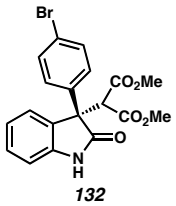
1H), 3.92 (s, 3H), 3.77 (s, 3H), 3.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 168.1, 168.0, 167.2, 155.7, 134.6, 134.1, 131.8, 129.1, 123.6, 114.6, 113.2, 110.4, 55.9, 54.6, 53.0, 52.9, 52.8, 41.3; IR (neat film, NaCl) 3350, 3003, 2954, 2840, 1776, 1722, 1602, 1488, 1468, 1435, 1394, 1331, 1301, 1265, 1206, 1160, 1051, 1032, 1004, 909, 815, 720 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{21}N_2O_8$ [M+H]$^+$: 453.1298, found 453.1319; $[\alpha]_D^{25}$ –2.3 (*c* 1.10, $CHCl_3$, 95% ee).



87

Malonate Adduct 87 (Table 3.5, Entry 1).

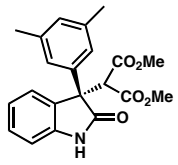
Purified by flash chromatography (SiO_2, 10% acetonitrile in toluene→15% acetonitrile in toluene). Isolated as a pale yellow solid. 76% yield. R_f = 0.22 (33% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (bs, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.25-7.16 (comp. m, 5H), 7.06 (ddd, *J* = 7.6, 7.6, 0.9 Hz, 1H), 6.84 (d, *J*= 7.8 Hz, 1H), 4.85 (s, 1H), 3.50 (s, 3H), 3.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 167.8, 167.3, 141.8, 137.3, 129.2, 128.7, 128.4, 128.0, 127.1, 122.8, 110.1, 58.5, 56.7, 52.7, 52.6; IR (neat film, NaCl) 3254, 2954, 1734, 1620, 1473, 1436, 1325, 1156, 1039, 912, 733 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{19}H_{18}NO_5$ [M+H]$^+$: 340.1185, found 340.1183; $[\alpha]_D^{25}$ –66.6 (*c* 1.12, CH_2Cl_2, 76% ee).



132

Malonate Adduct 132 (Table 3.5, Entry 3).

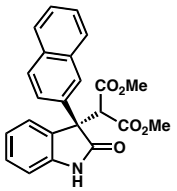
Purified by flash chromatography (SiO_2, toluene → 20% acetonitrile in toluene). Isolated as a 74% yield. Isolated as a pale yellow oil. 84% yield. R_f = 0.45 (20% acetonitrile in toluene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.6 Hz, 1H), 7.66 (s, 1H), 7.38 (app. d, *J* = 8.5 Hz, 2H), 7.33 (dd, *J* = 8.8, 8.8 Hz, 1H), 7.20 (app. d, *J* = 6.8 Hz, 2H), 7.15 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.93 (d, *J* = 7.6 Hz), 4.85 (s, 1H), 3.61 (s, 3H), 3.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 167.7, 167.2, 141.6, 136.5, 131.9, 129.6, 129.0, 128.4, 128.2, 123.2, 122.6, 110.2, 58.5, 56.3, 52.9, 52.8; IR (neat film, NaCl) 3307, 1736, 1619, 1472, 1435, 1323, 1158 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $C_{19}H_{16}O_5NBr$ [M]$^+$: 417.0212, found 417.0219; $[\alpha]_D^{25}$ +175.0 (*c* 1.52, CH_2Cl_2, 81% ee).



133

Malonate Adduct 133 (Table 3.5, Entry 4).

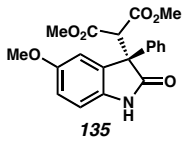
Purified by flash chromatography (SiO_2, toluene→10% acetonitrile in toluene). Isolated as a yellow oil. 69% yield. R_f = 0.25 (15% acetonitrile in toluene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (bs, 1H), 7.95 (d, *J* = 7.1 Hz, 1H), 7.29 (ddd, *J* = 7.8, 7.8, 1.2 Hz, 1H), 7.12 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.87-6.85 (comp. m, 3H), 4.90 (s, 1H), 3.60 (s, 3H), 3.38 (s, 3H), 2.21 (s, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 178.9, 167.9, 167.5, 141.8, 138.1, 137.3, 129.8, 129.1, 129.0, 128.3, 124.7, 122.8, 110.0, 58.4, 56.7, 52.6, 52.5, 21.6; IR (neat film, NaCl) 3248, 2956, 1737, 1718, 1618, 1473, 1324, 1199, 1155 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{21}H_{22}NO_5$ [M+H]$^+$: 368.1498, found 368.1507; $[\alpha]_D^{25}$ +181.7 (*c* 0.84, CH_2Cl_2, 84% ee).



134

Malonate Adduct 134 (Table 3.5, Entry 5).

Purified by flash chromatography (SiO_2, toluene→20% acetonitrile in toluene). Isolated as a light yellow solid. 74% yield. R_f = 0.65 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.8 Hz, 1H), 8.01 (s, 1H), 7.77-7.76 (comp. m, 2H), 7.70-7.68 (comp. m, 1H), 7.23 (bs, 1H), 7.58 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.45-7.39 (comp. m, 2H), 7.33 (ddd, *J* = 7.8, 7.8, 1.2 Hz, 1H), 7.19 (ddd, J = 7.8, 7.8, 1.0 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 5.05 (s, 1H), 3.52 (s. 3H), 3.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 167.9, 167.5, 141.9, 134.8, 133.3, 133.0, 129.4, 128.8, 128.6, 128.5, 127.7, 126.8, 126.6, 126.4, 124.6, 123.1, 110.2, 58.5, 56.9, 52.8, 52.7; IR (neat film, NaCl) 3256, 3059, 2953, 1732, 1619, 1597, 1472, 1435, 1323, 1294, 1198, 1157, 1037, 912, 732, 648 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $C_{23}H_{20}O_5N$ $[M+H]^+$: 390.1341, found 390.1354; $[\alpha]_D^{25}$ +171.8 (*c* 1.20, CH_2Cl_2, 74% ee).



135

Malonate Adduct 135 (Table 3.5, Entry 2).

Purified by flash chromatography (SiO_2, toluene → 10% acetonitrile in toluene). Isolated as an orange solid. 82% yield. R_f = 0.23 (15% acetonitrile in toluene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.6 (app. s, 1H), 7.24-7.23 (app. d, *J* = 6.6 Hz, 2H), 7.20-6.74 (comp. m, 5H), 4.92 (s, 1H), 3.83 (s, 3H), 3.57 (s, 3H), 3.45 (s, 3H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 178.3, 167.8, 167.3, 156.0, 137.3, 135.0, 130.0, 128.7, 128.0, 127.0, 114.9, 114.4, 110.3, 58.4, 57.1, 56.0, 52.7, 52.6; IR (neat film, NaCl) 3271, 2953, 1733, 1600, 1487, 1437, 1301, 1266, 1207, 1156, 1058, 1033 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $C_{20}H_{19}O_6N[M]^+$: 369.1212, found 369.1204; $[\alpha]_D^{25}$ +168.1 (*c* 1.09, CH_2Cl_2, 84% ee).

3.4.6 Chiral HPLC Assay conditions

Table 3.6

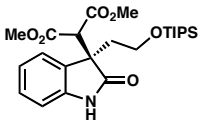
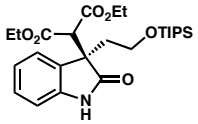
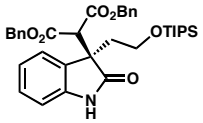
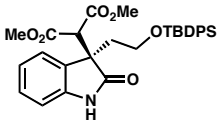
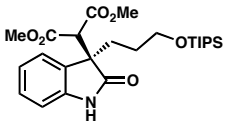
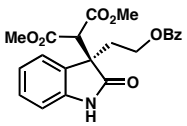
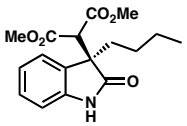
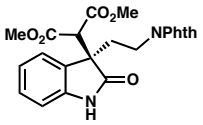
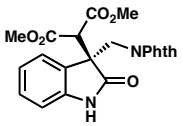
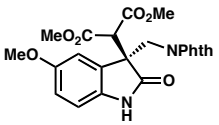
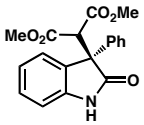
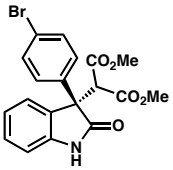
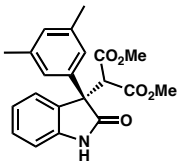
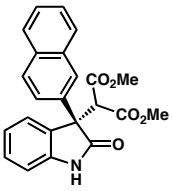
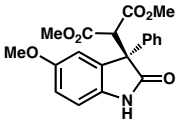
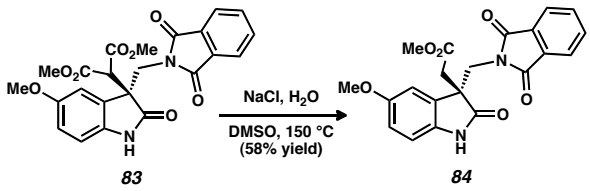
Malonate Adduct	Conditions	Time	*ee*
	5% IPA/Hexanes	28.9 min (major) 35.3 min (minor)	88%
	4% EtOH/Hexanes	16.4 min (major) 19.0 min (minor)	84%
	4% EtOH/Hexanes	24.4 min (major) 28.1 min (minor)	88%
	10% IPA/Hexanes	16.8 min (major) 24.4 min (minor)	88%
	5% IPA/Hexanes	17.7 min (major) 41.9 min (minor)	86%
	20% IPA/Hexanes	19.9 min (major) 33.1 min (minor)	83%
	10% IPA/Hexanes	19.5 min (major) 24.4 min (minor)	84%
	80% EtOH/Hexanes	17.2 min (major) 22.8 min (minor)	94%
	80% EtOH/Hexanes	18.6 min (major) 26.0 min (minor)	81%
	80% EtOH/Hexanes	21.7 min (major) 35.4 min (minor)	91%

Table 3.7

Malonate Adduct	Conditions	Time	*ee*
	20% IPA/Hexanes	7.6 min (major) 19.5 min (minor)	76%
	15% IPA/Hexanes	26.1 min (major) 37.5 min (minor)	–81%
	15% IPA/Hexanes	14.1 min (major) 34.5 min (minor)	–84%
	20% IPA/Hexanes	29.2 min (major) 41.2 min (minor)	–74%
	15% IPA/Hexanes	21.4 min (major) 40.5 min (minor)	–84%

3.4.7 Synthesis of Pyrrolidinone-spirooxindoles

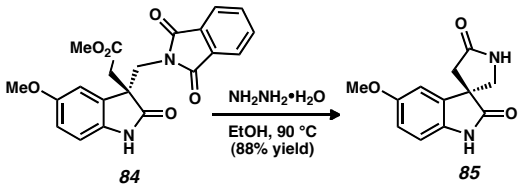


83 *84*

Phthalimidoester 84 (Scheme 3.2).

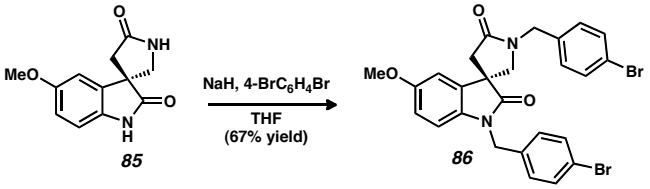
To a round bottom flask equipped with a stirbar, malonate adduct (99% ee, 115 mg, 0.25 mmol, 1 equiv) and sodium chloride (30 mg, 0.51 mmol, 2 equiv) were dissolved in water (23 μL, 1.3 mmol, 5 equiv) and DMSO (5 mL).[37] The reaction flask was then

heated to 150 °C for 5 hours. Upon cooling to ambient temperature, the reaction mixture was then diluted with water (5 mL) and brine (5 mL) and then extracted with EtOAc (3 x 20 mL). The organic layers were collected and dried with $MgSO_4$. Purification by column chromatography (SiO_2, 9% acetonitrile in benzene→17% acetonitrile in benzene) afforded phthalimidoester **84** as a pale yellow solid (57.5 mg, 58% yield). R_f = 0.09 (17% acetonitrile in benzene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 5.0, 3.0 Hz, 2H), 7.71 (dd, *J* = 5.0, 3.0 Hz, 2H), 7.54 (br s, 1H), 6.82 (d, *J* = 2.5 Hz, 1H), 6.79 (d, *J* = 9.0 Hz, 1H), 6.74 (dd, *J* = 9.0, 2.5 Hz, 1H), 4.00 (ABq, *J* = 14.0 Hz, 2H), 3.74 (s, 3H), 3.51 (s, 3H), 3.15 (ABq, *J* = 17.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.4, 170.2, 168.2, 155.7, 134.5, 134.3, 131.9, 130.8, 123.7, 113.7, 110.9, 110.5, 55.9, 51.9, 50.4, 43.1, 38.6; IR (neat film, NaCl) 3306, 2997, 2952, 2838, 1776, 1719, 1604, 1490, 1468, 1437, 1395, 1363, 1302, 1207, 1140, 1027, 928, 908, 812 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{21}H_{19}N_2O_6$ $[M+H]^+$: 395.1243, found 395.1243; $[\alpha]_D^{18.0}$ +26.1 (*c* 1.00, CH_2Cl_2).



Spirocyclic Oxindole 85 (Scheme 3.2). To a solution of phthalimidoester **84** (13 mg, 0.032 mmol, 1 equiv) in EtOH (3 mL) was added H_2NNH_2•H_2O (16 μL, 0.32, 10 equiv) at 23 °C. The reaction flask was then heated to 95 °C for 13 hours. Upon cooling to ambient temperature, reaction mixture was filtered though a short plug of celite and concentrated. Purification by preparative TLC (SiO_2, 9% MeOH in DCM) afforded spirocyclic oxindole **85** as a white solid (6.5 mg, 88% yield). R_f = 0.36 (9% MeOH in

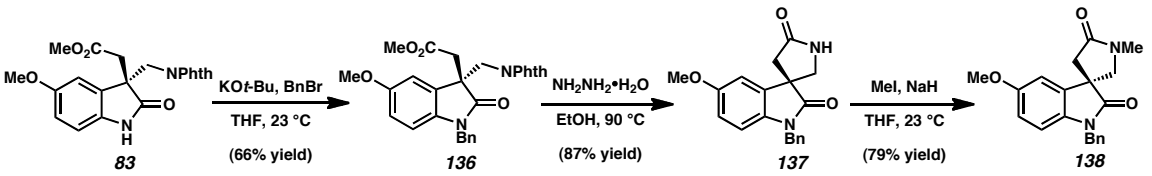
DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (br s, 1H), 6.95 (d, *J* = 2.0 Hz, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 6.80 (dd, *J* = 7.5, 2.0 Hz, 1H), 5.98 (bs, 1H), 3.87 (d, *J* = 9.5 Hz, 1H), 3.79 (s, 3H), 3.59 (dd, *J* = 9.5, 0.5 Hz, 1H), 2.98 (d, *J* = 16.5 Hz, 1H), 2.50 (d, *J* = 17.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 175.3, 156.7, 134.9, 132.9, 113.8, 110.7, 109.6, 56.1, 51.0, 50.4, 40.4; IR (neat film, NaCl) 3231, 2956, 2925, 2847, 1699, 1494, 1439, 1306, 1207, 1179, 1033 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{13}H_{13}N_2O_3$ $[M+H]^+$: 233.0926, found 233.0918; $[\alpha]_D^{23.0}$ +43.5 (*c* 0.65, MeOH).



Bis(*p*-Br-benzyl)lactam 86 (Scheme 3.2). To a cooled (0 °C) mixture of NaH (3.4 mg, 60 %, 0.84 mmol, 3.0 equiv) in THF (1 mL) was added a solution of spirocylic oxindole **85** (6.5 mg, 0.028 mmol, 1.0 equiv) in THF (2.0 mL) in a dropwise manner via syringe. The flask containing the oxindole was rinsed with THF (1 mL) and this solution was also added dropwise via syringe at 0 °C. The reaction was allowed to stir for 30 minutes at 23 °C before the addition of 4-bromobenzyl bromide (21 mg, 0.84 mmol, 3.0 equiv). After stirring for 14 hours at 23 °C, the reaction was quenched with brine (3 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were collected and dried with $MgSO_4$. Purification by column chromatography (SiO_2, 25% EtOAc in CH_2Cl_2) afforded bis(*p*-Br-benzyl)lactam **86** as a white solid (10.1 mg, 67% yield). Mp: 214.5-216 °C from CH_2Cl_2/hexanes; R_f = 0.66 (50% EtOAc in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (dt, *J* = 8.5, 2.5 Hz, 2H), 7.43 (dt, *J* = 9.0, 2.5 Hz, 2H), 7.22 (dt, *J* = 8.5, 2.5 Hz, 2H), 7.11 (dt, *J* = 8.5, 2.5 Hz, 2H), 6.71-6.68 (comp. m, 2H), 6.60 (d, *J* = 9.5 Hz, 1H), 4.80

(ABq, J = 16.0 Hz, 2H), 4.66 (d, J = 14.5 Hz, 1H), 4.41 (d, J = 15.0 Hz, 1H), 3.74 (d, J = 9.5 Hz, 1H), 3.69 (s, 3 H), 3.31 (d, J = 9.5 Hz, 1H), 3.12 (d, J = 17.0 Hz, 1H), 2.63 (d, J = 17.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4, 171.7, 156.9, 135.0, 134.9, 134.6, 134.4, 132.2, 130.2, 129.1, 122.1, 122.0, 113.5, 110.0, 109.4, 105.1, 55.9, 55.3, 47.1, 46.5, 43.7, 41.7; IR (neat film, NaCl) 2930, 1700, 1601, 1488, 1435, 1406, 1366, 1294, 1200, 1177, 1071, 1034, 1012, 798 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{26}H_{23}N_2O_3Br^{81}Br$ [M+H]$^+$: 571.0055, found 571.0048; $[\alpha]_D^{25.0}$ –46.7 (c 0.39, CH_2Cl_2).

3.4.8 Synthesis of Other Pyrrolidinone-spirooxindole: Further Confirmation of Absolute Stereochemistry



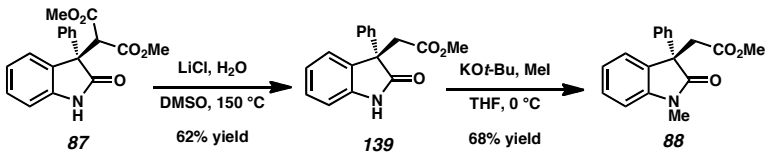
(*R*)-1-benzyl-5-methoxy-1'-methylspiro[indoline-3,3'-pyrrolidine]-2,5'-dione (138). To a solution of pthalimidoester **83**[38] (56 mg, 0.14 mmol, 1.0 equiv) in THF (2 mL) was added a solution of KO*t*-Bu (19 mg, 0.17 mmol, 1.2 equiv) in THF (1 mL) was added in a dropwise manner via syringe at 23 °C. The reaction was allowed to stir for 20 minutes before the addition of BnBr (51 μL, 0.43 mmol, 3.0 equiv) via syringe. After stirring for 3 hours at 23 °C, the reaction was quenched with saturated brine solution (5 mL) and extracted with EtOAc (3 x 15 mL). The organic layers were combined and dried with $MgSO_4$. Purification by column chromatography (SiO_2, 33% EtOAc in hexanes→50% EtOAc in hexanes) afforded **136** as a pale yellow solid (45.5 mg, 66% yield). R_f = 0.50 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86-7.82 (m, 2H), 7.73-7.69 (m, 2H), 7.43 (d, J = 7.5 Hz, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.25 (tt, J = 7.5, 2.0 Hz, 1H),

6.86 (d, J = 2.0 Hz, 1H), 6.65 (dd, J = 8.5, 2.0 Hz, 1H), 6.57 (d, J = 8.5 Hz, 1H), 4.93 (ABq, J = 16.0 Hz, 2H), 4.02 (ABq, J = 14.0 Hz, 2H), 3.70 (s, 3H), 3.45 (s, 3H), 3.20 (ABq, J = 17.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 170.1, 168.2, 155.8, 136.1, 135.8, 134.3, 131.9, 130.5, 128.8, 127.6 (2 C), 123.7, 113.3, 110.8, 110.0, 55.9, 51.9, 50.0, 44.5, 43.3, 38.7; IR (neat film, NaCl) 2951, 2930, 2858, 1776, 1717, 1602, 1496, 1456, 1435, 1394, 1333, 1298, 1206, 1178, 1144, 1077, 1029 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{28}H_{25}N_2O_6$ $[M+H]^+$: 485.1713, found 485.1707; $[\alpha]_D^{19.0}$ –17.7 (*c* 1.00, CH_2Cl_2).

To a solution of benzylated **136** (46 mg, 0.094 mmol, 1.0 equiv) in EtOH (5 mL) was added $H_2NNH_2 \bullet H_2O$ (46 μL, 0.94, 10 equiv) at 23 °C. The reaction flask was then heated to 95 °C for 18 hours. Upon cooling to ambient temperature, reaction mixture was filtered though a short plug of Celite and concentrated. Purification by column chromatography (SiO_2, 2% MeOH in DCM→3% MeOH in DCM) afforded spirocyclic lactam **137** as a white solid (26 mg, 87% yield). R_f = 0.59 (9% MeOH in DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.31 (comp. m, 2H), 7.29-7.25 (comp. m, 3H), 6.99 (d, J = 2.5 Hz, 1H), 6.72 (dd, J = 7.5, 2.5 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.35 (br s, 1H), 4.90 (s, 2H), 3.92 (d, J = 9.0 Hz, 1H), 3.76 (s, 3H), 3.50 (d, J = 9.5 Hz, 1H), 3.03 (d, J = 16.5 Hz, 1H), 2.51 (d, J = 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 175.6, 156.8, 135.6, 135.2, 134.5, 129.0, 128.0, 127.4, 113.4, 110.1, 109.6, 56.0, 51.2, 50.0, 44.3, 40.6; IR (neat film, NaCl) 3271, 2925, 1705, 1602, 1496, 1455, 1436, 1368, 1298, 1200, 1178, 1032 cm^{-1}; HRMS (ESI–APCI) m/z calc'd for $C_{19}H_{18}N_2O_3$ $[M+H]^+$: 323.1390, found 323.1393; $[\alpha]_D^{23.0}$ +64.7 (*c* 0.50, CH_2Cl_2).

To a mixture of NaH (9.9 mg, 60 %, 0.248 mmol, 3 equiv) in THF (0.5 mL) at 23 °C was added a solution of spirocyclic lactam **137** (24.7 mg, 0.0825 mmol, 1 equiv) in THF (2.0 mL) in a dropwise manner via syringe. The flask containing the spirocyclic lactam was rinsed with THF (2 x 1 mL), and the solution was also added dropwise via syringe at 23 °C. The reaction was allowed to stir for 30 minutes before the addition of MeI (16 μL, 0.25 mmol, 3.0 equiv) via syringe. After stirring for 14 hours at 23 °C, the reaction was quenched with water (30 μL) and concentrated under reduced pressure. Purification by column chromatography (SiO_2, 55% EtOAc in CH_2Cl_2) afforded **138** as a white solid (20 mg, 79% yield). Mp: 146.0-147.5 °C; R_f = 0.18 (33% EtOAc in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (td, *J* = 7.5, 1.5 Hz, 2H), 7.28-7.24 (comp. m, 3H), 6.87 (d, *J* = 3.0 Hz, 1H), 6.71 (dd, *J* = 7.5, 3.0 Hz, 1H), 6.65 (d, *J* = 7.5 Hz, 1H), 4.89 (ABq, *J* = 16.0 Hz, 2H), 3.88 (d, *J* = 9.5 Hz, 1H), 3.74 (s, 3H), 3.45 (d, *J* = 9.5 Hz, 1H), 3.07 (dd, *J* = 17.0, 0.5 Hz, 1H), 2.99 (s, 3H), 2.58 (d, *J* = 17.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7, 171.9, 156.8, 135.6, 135.3, 134.9, 129.0, 127.9, 127.4, 113.1, 110.1, 109.5, 58.1, 56.0, 47.2, 44.3, 41.6, 29.0; IR (neat film, NaCl) 3033, 2929, 2879, 2837, 1704, 1602, 1496, 1456, 1436, 1368, 1348, 1298, 1200, 1178, 1033, 977 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{20}H_{21}N_2O_3$ $[M+H]^+$: 337.1552, found 337.1567; $[\alpha]_D^{22.0}$ +37.3 (*c* 1.00, CH_2Cl_2)

3.4.9 Synthesis of Fused Indolinopyrrolidinone



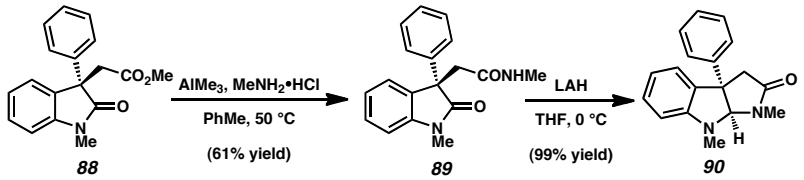
87 ***139*** ***88***

(*S*)-methyl 2-(1-methyl-2-oxo-3-phenylindolin-3-yl)acetate (88).

A round bottom flask equipped with a stirbar was charged with malonate adduct **87** (50 mg, 0.14 mmol, 1.0 equiv), lithium chloride (116 mg, 0.27 mmol, 2.0 equiv), water (12 μL, 0.68 mmol, 5.0 equiv), and DMSO (2 mL). The reaction flask was then heated at 150 °C for 12 hours. Upon cooling to ambient temperature, reaction mixture was diluted with water (10 mL) and then extracted with EtOAc (5 x 5 mL). The organic layers were collected and dried with $MgSO_4$. Purification by flash chromatography (SiO_2, 50% EtOAc in hexanes) afforded **139** as a colorless oil (62% yield). R_f = 0.41 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (br s, 1H), 7.31-7.21 (comp. m, 7H), 7.04 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H), 6.92 (dd, *J* = 7.8, 0.5 Hz, 1H), 3.54 (d, *J* = 16.1 Hz, 1H), 3.44 (s, 3H), 3.26 (d, *J* = 16.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.2, 170.3, 141.8, 139.1, 131.8, 128.9, 128.8, 127.8, 126.7, 124.9, 122.6, 110.3, 53.9, 51.9, 41.7; IR (neat film, NaCl) 3248, 1721, 1619, 1472, 1203 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{17}H_{16}NO_3$ $[M+H]^+$ 282.1130, found 282.1138.

To a cooled (0 °C) solution of methyl ester **139** (14.3 mg, 0.051 mmol, 1.0 equiv) in THF (5mL) was added a freshly prepared stock solution of KO*t*-Bu (6.8 mg, 0.061 mmol, 1.2 equiv) in THF in a dropwise manner via syringe. The reaction was allowed to stir for 15 minutes before addition of MeI (9.5 μL, 0.15 mmol, 3.0 equiv) via syringe. After stirring for one hour at 0 °C, the reaction was quenched with saturated brine (2 mL) and extracted with EtOAc (3 x 5 mL). The organic layers were collected and dried with $MgSO_4$. Purification by column chromatography (SiO_2, 20 % EtOAc in hexanes) afforded methyl ester **88** as a light yellow oil (68% yield. 56% yield over two steps). R_f = 0.57 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.24 (comp. m, 7H), 7.11 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 3.55 (d, *J* = 16.4 Hz, 1H),

3.45 (s, 3H), 3.27 (d, J = 16.4 Hz, 1H), 3.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 170.3, 144.8, 139.2, 131.2, 128.8, 127.8, 126.8, 124.6, 122.6, 108.6, 53.4, 51.8, 42.0, 26.8; IR (neat film, NaCl) 3065, 2951, 1744, 1716, 1612, 1494, 1470, 1349, 1200 cm^{-1}; HRMS (FAB$^+$) m/z calc'd for $C_{18}H_{18}NO_3$ $[M+H]^+$: 296.1273, found 296.1286.



Fused Indolinopyrrolidinone 90.

A freshly prepared stock solution of trimethylaluminum amine complex was prepared by adding trimethylaluminum (0.5 mL, 2 M in toluene) to a mixture of methyl amine hydrochloride (67.5 mg, 1 mmol) in toluene (4.5 mL) at 0 °C and allowing to warm to ambient temperature. After the methane evolution had ceased (about 1 hour), the aluminum amine complex solution (0.9 mL, 0.18 mmol, 3.0 equiv) was added to a solution of methyl ester **88** (18 mg, 0.061 mmol, 1 equiv) in toluene (2 mL) at ambient temperature, and the reaction mixture was immediately heated to 50 °C. The reaction was maintained at 50 °C for five days, where an additional freshly prepared trimethylaluminum amine complex (0.9 mL, 0.18 mmol, 3 equiv) was added after initial 72 hours. Reaction was then cooled to room temperature and quenched with aqueous solution of saturated Rochelle's salt (5 mL) and extracted with EtOAc (3 x 10 mL). The organic layers were combined and dried with $MgSO_4$. Purification by flash chromatography (SiO_2, 10% toluene in acetonitrile) afforded amide **89** isolated as a white solid (71% yield). R_f = 0.62 (10% toluene in acetonitrile); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.24 (comp. m, 7H), 7.10 (ddd, J = 7.3, 7.3, 1.0 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H),

6.17 (br s, 1H), 3.38 (d, J = 15.4 Hz, 1H), 3.28 (s, 3H), 3.03 (d, J = 15.4 Hz, 1H), 2.59 (d, J = 4.9, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 169.3, 143.6, 139.4, 132.0, 128.9, 128.7, 127.7, 126.6, 124.6, 123.0, 108.7, 54.3, 44.2, 26.8, 26.4; IR (neat film, NaCl) 3326, 2933, 1711, 1653, 1615, 1495, 1470, 1375, 1349 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{18}H_{19}O_2N_2$ [M+H]$^+$: 295.1447, found 295.1436.

To a cooled (0 °C) solution of methyl amide **89** (5.0 mg, 0.017 mmol, 1.0 equiv) in THF was added a solution of lithium aluminum hydride (2.0 M in hexanes, 12 equiv) in a dropwise fashion via syringe. The reaction was stirred for 1 hour and then quenched with brine solution. Following extraction with EtOAc (3 x 10 mL), the organic layers were collected and dried with $MgSO_4$. Purification by flash chromatography (SiO_2, 50% EtOAc in hexanes) afforded fused tricycle **90** as a white solid (92% yield). R_f = 0.24 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.30 (comp. m, 2H), 7.26-7.18 (comp. m, 4H), 7.05 (d, J = 7.3 Hz, 1H), 6.79 (ddd, J = 7.6, 7.6, 1.0 Hz, 1H), 6.55 (d, J = 7.8 Hz, 1H), 4.96 (s, 1H), 3.26 (d, J = 17.3 Hz, 1H), 3.11 (d, J = 17.3 Hz, 1H), 3.10 (s, 3H), 2.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 149.6, 144.5, 134.0, 129.3, 129.0, 127.3, 126.2, 125.0, 119.2, 108.1, 93.2, 53.9, 44.5, 35.4, 28.8; IR (neat film, NaCl) 3054, 2925, 1692, 1606, 1494 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{18}H_{19}ON_2$ [M+H]$^+$: 279.1497, found 279.1509.

3.5 NOTES AND REFERENCES FOR TEXT

(1) For reviews on the catalytic asymmetric construction of all-carbon quaternary stereocenters, see: (a) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369–396. (b) Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis; Christoffers, J.; Baro, A., Eds.; Wiley: Weinheim, 2005. (c) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473–1482. (d) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363–5367. (e) Ramon, D. J.; Yus, M. *Curr. Org. Chem.* **2004**, *8*, 149–183. (f) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969–5994.

(2) (a) Petrova, K. V.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 293–295. (b) Levine, S. R.; Krout, M. R.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 289–292. (c) Enquist, J. A. Jr.; Stoltz, B. M. *Nature* **2008**, *453*, 1228–1231. (d) White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810–811. (e) Behenna, D. C.; Stockdill, J. L.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 4077–4080. (f) McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738–7739. (g) Mohr, J. T.; Behenna, D. C.; Harned, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924–6927. (h) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045.

(3) (a) Galliford, C.V.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8748–8758. (b) Marti, C.; Carriera, E. M. *Eur. J. Org. Chem.* **2003**, 2209–2219. (c) May, J. A.; Stoltz, B. *Tetrahedron* **2006**, *62*, 15044–15045.

(4) For selected recent examples, see: (a) Overman, L. E.; Rosen, M. D. *Angew. Chem. Int. Ed.* **2000**, *39*, 4596–4599. (b) Lerchner, A.; Carreira, E. M. *J. Am.*

Chem. Soc. **2002**, *124*, 14826–14827. (c) Lin, H.; Danishesky, S. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 36–51. (d) Siengalewicz, P.; Gaich, T.; Mulzer, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 8170–8176. (e) Kawasaki, T.; Shinada, M.; Kamimura, D.; Ohzono, M.; Ogawa, A. *Chem. Commun.* **2006**, 420–422. (f) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5482–5487. (g) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590–4591. (h) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500–6503. (i) Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043–14053. (j) Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505–11515. (k) Onishi, T.; Sebahar, P. R.; Williams, R. M. *Org. Lett.* **2003**, *5*, 3135–3137. (l) Trost, B. M. Stiles, D. T. *Org. Lett.* **2007**, *9*, 2763–2766. (m) Miyake, F. Y.; Yakushijin; K.; Horne, D. A. *Org. Lett.* **2004**, *6*, 4249–4251. (n) Miyake, F. Y.; Yakshijin, K.; Horne, D. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 5357–5360. (o) Lo, M. M.-C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 16077–16086. (p) Bagul, T. D.; Lakshmaiah, G.; Kawabata, T.; Fuji, K. *Org. Lett.* **2002**, *4*, 249–251. (q) Edmondson, S.; Danishefsky, S. J.; Sepp-Lorenzino, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147–2155. (r) Sehahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666–5667.

(5) Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Nature* **2008**, *455*, 323–332.

(6) (a) Pinto, A.; Jia, Y.; Neuville, J.; Zhu, J. *Chem. Eur. J.* **2007**, *13*, 961–967. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2964. (c) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477–6487. (d) Ashimori, A.; Matsuura, T.; Overman, L. E.; Poon, D. J. *J.*

Org. Chem. **1993**, *58*, 6949–6951. (e) Busacca, C. A.; Grossbach, D.; So, R. C.; O'Brien, E. M.; Spinelli, E. M. *Org. Lett.* **2003**, *5*, 595–598.

(7) Yasui, Y.; Kamisaki, H.; Takemoto, Y. *Org. Lett.* **2008**, *10*, 3303–3306.

(8) Trost, B. M.; Cramer, N.; Silverman, S. M. *J. Am. Chem. Soc.* **2007**, *129*, 12396–12397.

(9) (a) Kundig, E. P.; Seidel, T. M.; Jia, Y.-x.; Bernardinelli, G. *Angew. Chem. Int. Ed.* **2007**, *46*, 8484–8487. (b) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402–3415.

(10) (a) Lee, T. B. K.; Wong, G. S. K. EP 438796A2, **1991** 19910731 US 90–46992. (b) Lee, T. B. K.; Wong, G. S. K. *J. Org. Chem.* **1991**, 56, 872–875.

(11) (a) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2007**, *129*, 14548–14549. (b) Trost, B. M.; Brennan, M. K. *Org. Lett.* **2006**, *8*, 2027–2030. (c) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590–4591. (d) Trost, B. M.; Frederiksen, M. U. *Angew. Chem. Int. Ed.* **2004**, *43*, 308–310.

(12) (a) Hills, I. D.; Fu, G. F. *Angew. Chem. Int. Ed.* **2003**, *42*, 3921–3924. (b) Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. *J. Am. Chem. Soc.* **2006**, *128*, 925–934. (c) Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368–13369.

(13) Linton, E. C.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 16162–16163.

(14) Ogawa, S.; Shibata, N.; Inagaki, J.; Nakamura, S. Toru, T.; Shiro, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 8666–8669.

(15) (a) Tian, X.; Jiang, K.; Peng, J.; Du, W.; Chen, Y.-C. *Org. Lett.* **2008**, *10*, 3583–3586. (b) He, R.; Ding, C.; Maruoka, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 4559–4561.

(16) For enzymatic desymmetrization methods, see: (a) Akai, S.; Tsujino, T.; Akiyama, E.; Tanimoto, K.; Naka, T.; Kita, Y. *J. Org. Chem.* **2004**, *69*, 2478–2486. (b) Nakazawa, K.; Hayashi, M.; Tanaka, M.; Aso, M.; Suemune, H. *Tetrahedron Asymmetry* **2001**, *12*, 897–901. (c) Akai, S.; Tsujino, T.; Naka, T.; Tanimoto, K.; Kita, Y. *Tetrahedron Lett.* **2001**, *42*, 7315–7317.

(17) For catalytic enantioselective methods that produce C(3)-quaternary oxindoles after additional functionalization steps, see: (a) Nagata, K.; Sano, D.; Itoh, T.; *Synlett* **2007**, 547–550. (b) Bella, M.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 3670–3671.

(18) Catalytic asymmetric fluorinations and hydroxylations have also been reported for the syntheses of fully substituted tertiary stereocenters at the C(3)-position of the oxindole core, see: (a) Ishimaru, T.; Shibata, N.; Horikawa, T.; Yasuda, N.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 4157–4161. (b) Hamashima, Y.; Sodeoka, M. *Synlett* **2006**, 1467–1478. (c) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164–10165. (d) Sano, D.; Nagata, K.; Itoh, T. *Org. Lett.* **2008**, *10*, 1593–1595. (e) Chen, J.-R.; Liu, X.-P.; Zhu, X.-Y.; Li, L.; Qiao, Y.-F.; Zhang, J.-M.; Xiao, W.-J. *Tetrahedron* **2007**, *63*, 10437–10444. (f) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 3353–3356. (g) Ishimaru, T.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *J. Am. Chem. Soc.* **2006**, *128*, 16488–16489. (h) Toullec, P. Y.; Jagt, R. B. C.; de Vries, J. G.; Feringa, B. L.;

Minnaard, A. J. *Org. Lett.* **2006**, *8*, 2715–2718. (i) Luppi, G.; Cozzi, P. G.; Monari, M.; Kaptein, B.; Broxterman, Q. B.; Tomasini, C. *J. Org. Chem.* **2005**, *70*, 7418–7421.

(19) Hinman, R. L.; Bauman, C. P. *J. Org. Chem.* **1964**, *29*, 2431–2437.

(20) (a) Cheung, C.-M.; Goldberg, F. W.; Magnus, P.; Russell, C. J.; Turnbull, R.; Lynch, V. *J. Am. Chem. Soc.* **2007**, *129*, 12320–12327. (b) England, D. B.; Merey, G.; Padwa, A. *Org. Lett.* **2007**, *9*, 3805–3807. (c) Magnus, P.; Turnbull, R. *Org. Lett.* **2006**, *8*, 3497–3499. (d) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2005**, *7*, 677–680. (e) Goldberg, F. W.; Magnus, P.; Turnbull, R. *Org. Lett.* **2005**, *7*, 4531–4534. (f) Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 5068–5069. (g) Fejes, I.; Toke, L.; Nyerges, M.; Pak, C. S. *Tetrahedron* **2000**, *56*, 639–644. (h) Rajeswaran, W. G.; Labroo, R. B.; Cohen, L. A. *J. Org. Chem.* **1999**, *64*, 1369–1371. (i) Beccalli, E. M.; Marchesini, A.; Pilati, T. *J. Chem. Soc. Perkin Trans. 1* **1994**, 579–587. (j) Labroo, R. B.; Labroo, V. M.; King, M. M. Cohen, L. A. *J. Org. Chem.* **1991**, *56*, 3637–3642. (k) Kornet, M. J.; Thio, A. P. *J. Med. Chem.* **1976**, *19*, 892–898.

(21) Krishnan, S.; Stoltz, B. M. *Tetrahedron Lett.* **2007**, *48*, 7571–7573.

(22) For a review of catalytic enantioselective stereoablative reactions, see: Mohr, J. T.; Ebner, D. C.; Stoltz, B. M. *Org. Biomol. Chem.* **2007**, *5*, 3571–3576.

(23) For select recent examples of malonate alkylation catalyzed by chiral Lewis acids, see: (a) Evans, D. A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*, 11583–11592. (b) Watanabe, M.; Ikagawa, A.; Wang, H.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* **2004**, *126*, 11148–11149. (c) Majima, K.; Takita, R.; Okada,

T.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 15837–15845. (d) Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Presekill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097–13105. (e) Kim, Y. S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohsima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6506–6507.

(24) See the Experimental Section for details.

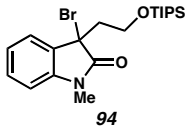
(25) For reviews on the use of bis(oxazoline) ligands in asymmetric catalysis, see: (a) Atodiresei, I.; Schiffers, I.; Bolm, C. *Tetrahedron: Asymmetry* **2006**, *17*, 620–633. (b) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561–3651. (c) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325–335. (d) Evans, D. A.; Rovis, T.; Johnson, J. S. *Pure Appl. Chem.* **1999**, *71*, 1407–1415. (e) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1–45. (f) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339–345. (g) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151–4202.

(26) For an example of bis(oxazoline)-mediated MeLi additions to electrophiles and an excellent discussion of the use of bisoxazolines in general, see: Denmark, S. D.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875–5878.

(27) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 798–800, and references therein.

(28) Exposure of racemic bromooxindole (±)-**76** to preformed [Cu(**78**)] $(SbF_6)_2$ in the presence of *i*-Pr_2NEt at –40°C without molecular sieves gave malonate adduct **77** in 68% yield and 86% ee.

(29) Consistent with our proposal of an *o*-azaxylylene intermediate, exposure of *N*-methyl bromooxindole **94** to our reaction conditions (see Table 3.4) failed to give a detectable amount of the malonate adduct.



94

(30) (a) Krapcho, A. P. *Synthesis* **1982**, 893–914. (b) Krapcho, A. P. *Synthesis* **1982**, 805–822.

(31) The absolute configuration depicted for all products in Tables 3.4 and 3.5 is derived by analogy from the X-ray analysis of **86**.

(32) Köhling, P.; Schmidt, A. M.; Eilbracht, P. *Org. Lett.* **2003**, *5*, 3213–3216.

(33) Takechi, H.; Machida, M.; Kanaoka, Y. *Chem. Pharm. Bull.* **1988**, *36*, 2853–2863.

(34) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164–10165.

(35) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635–1649.

(36) For compounds in Table 3.4 Entries 8–10, the bromooxindole was added in one portion as a solid due to low solubility in CH_2Cl_2.

(37) Malonate adduct **83** was recrystallized to 99% ee from CH_2Cl_2–hexanes (3.5:1).

(38) Malonate adduct **83** was recrystallized to 97% ee from CH_2Cl_2–hexanes (3.5:1).

APPENDIX 3

Spectra Relevant to Chapter 3

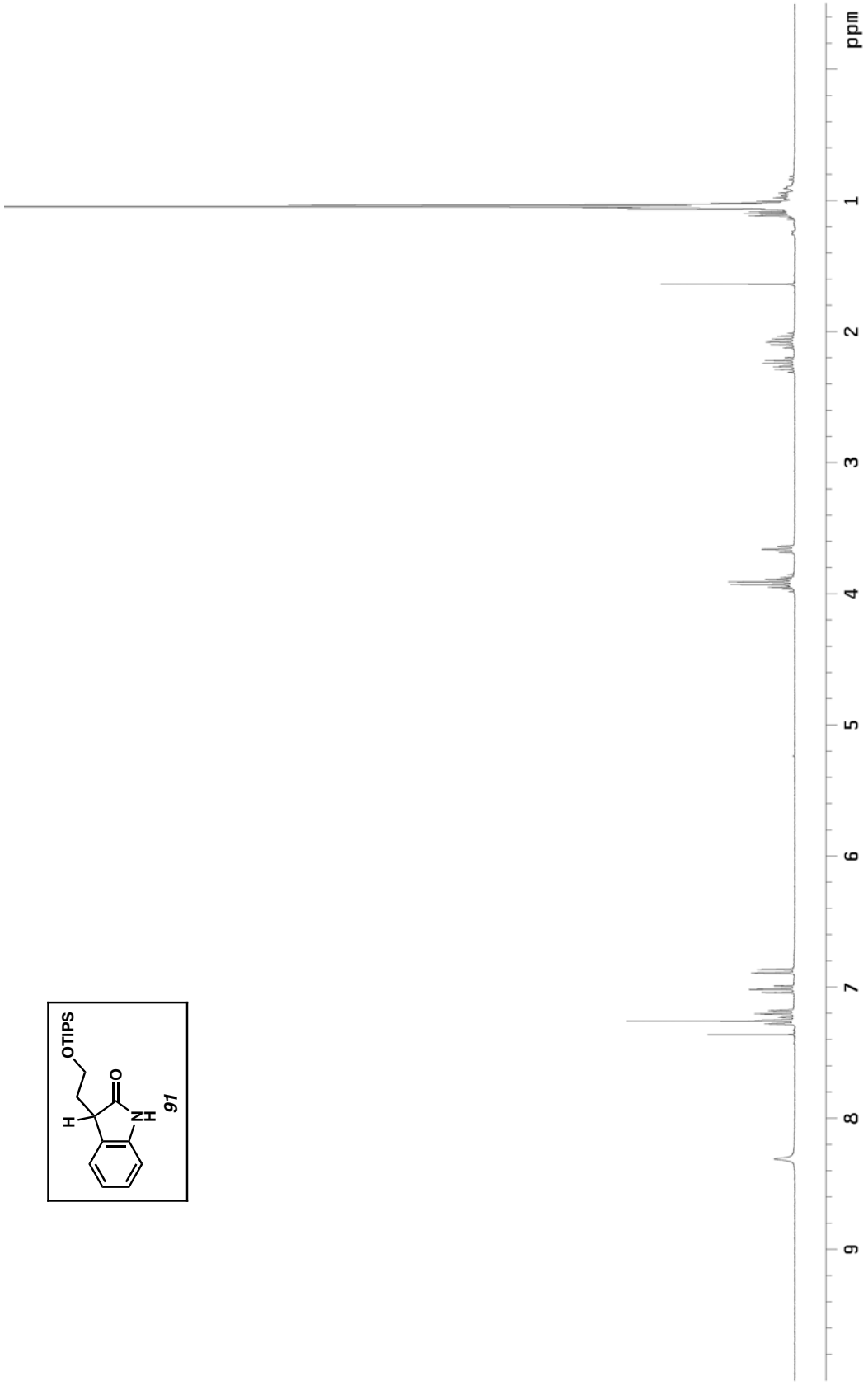


Figure A3.1.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **91**.

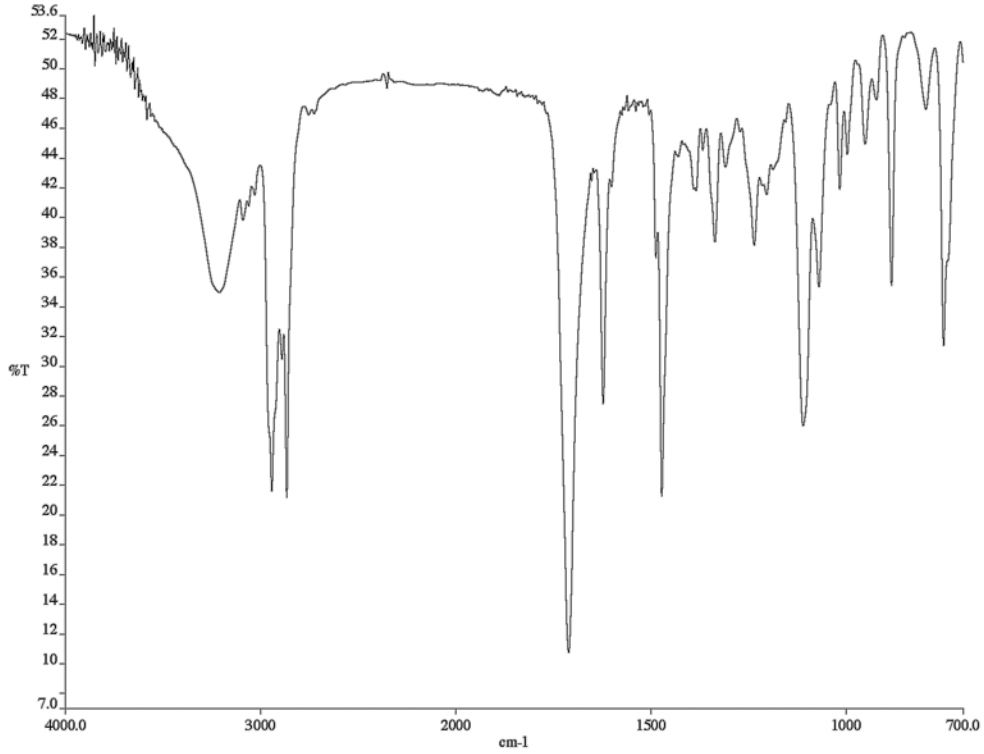


Figure A3.1.2 Infrared spectrum (thin film/NaCl) of compound **91**.

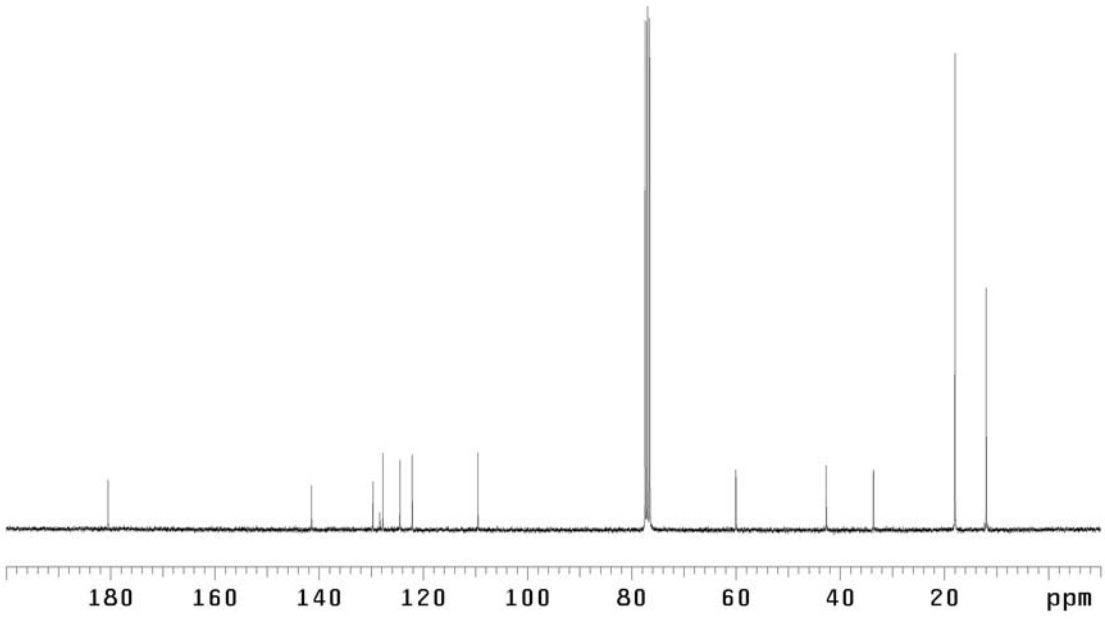


Figure A3.1.3 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **91**.

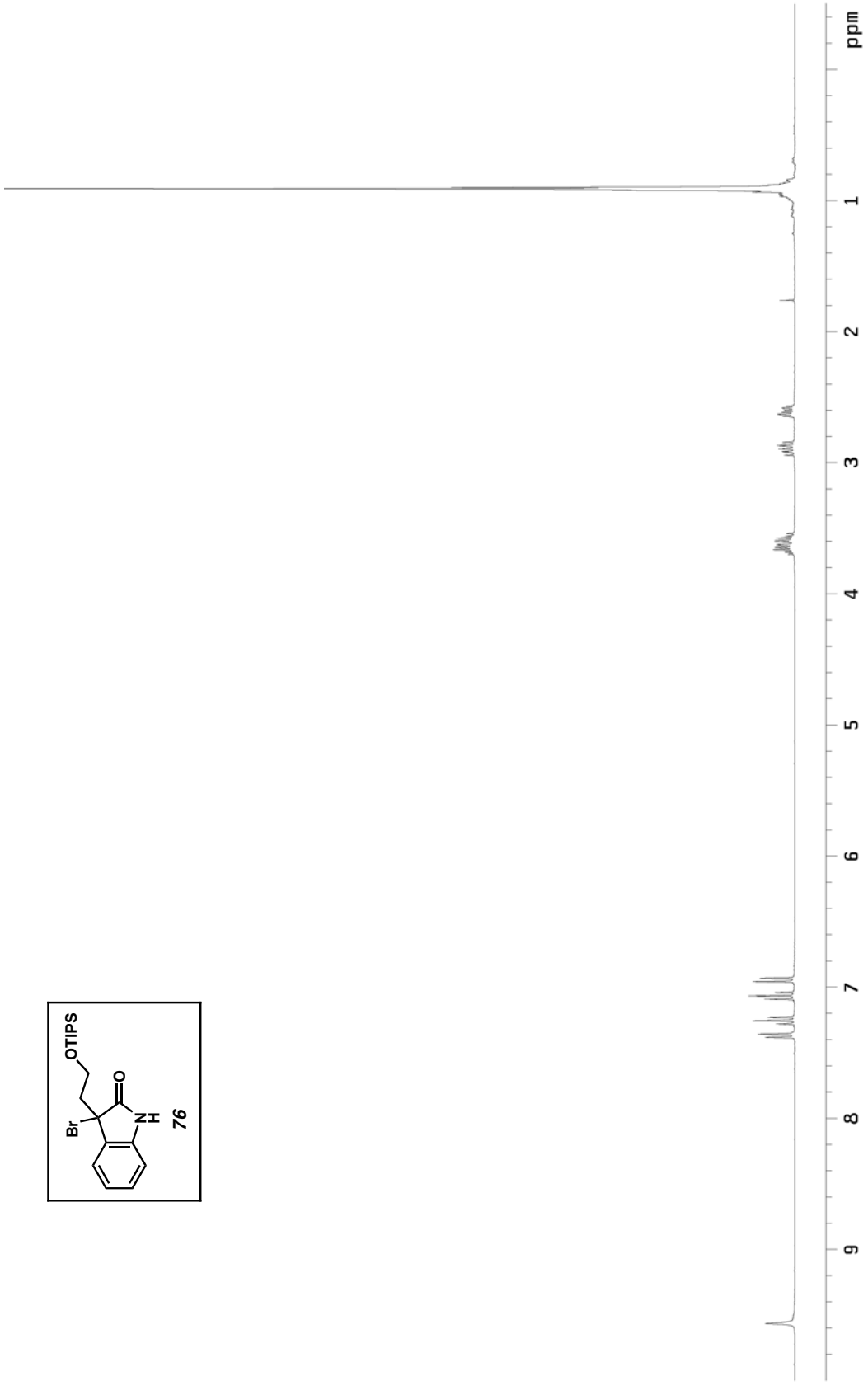


Figure A3.2.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **76**.

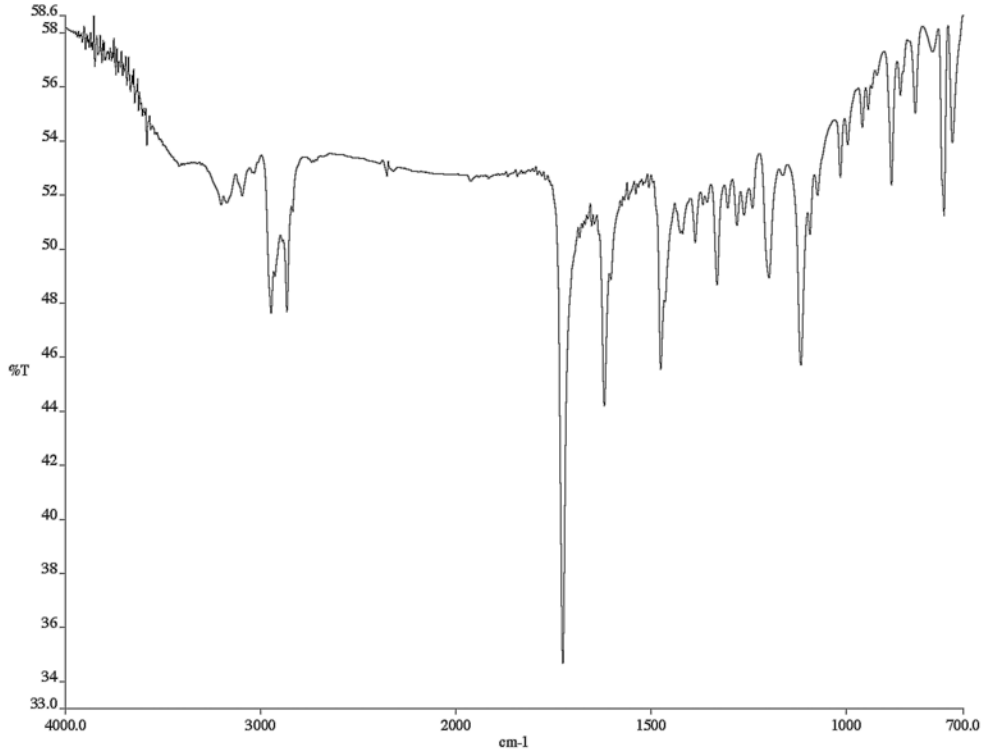


Figure A3.2.2 Infrared spectrum (thin film/NaCl) of compound **76**.

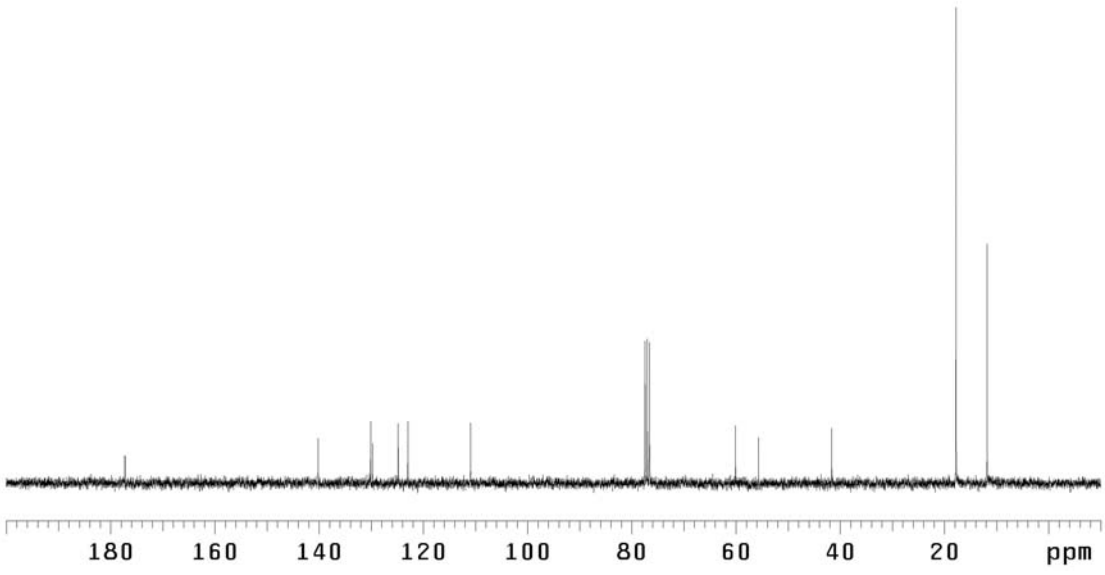


Figure A3.2.3 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **76**.

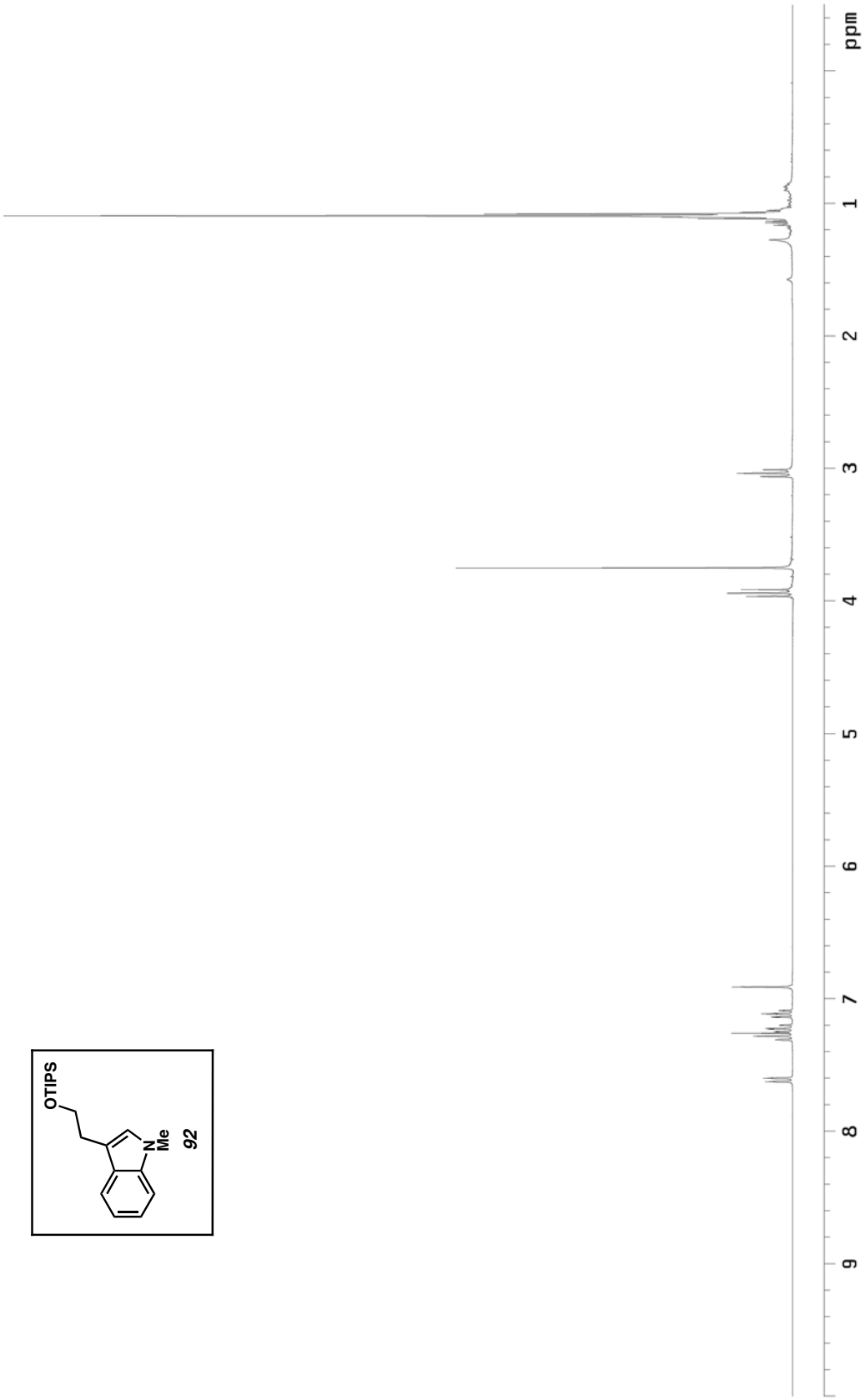


Figure A3.3.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **92**.

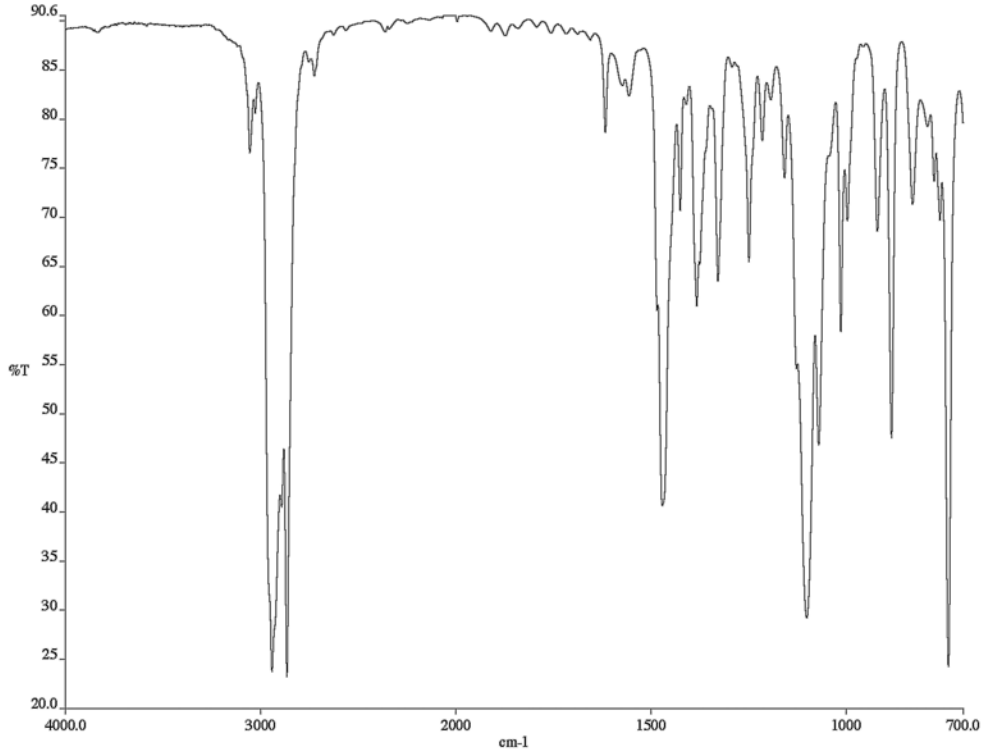


Figure A3.3.2 Infrared spectrum (thin film/NaCl) of compound **92**.

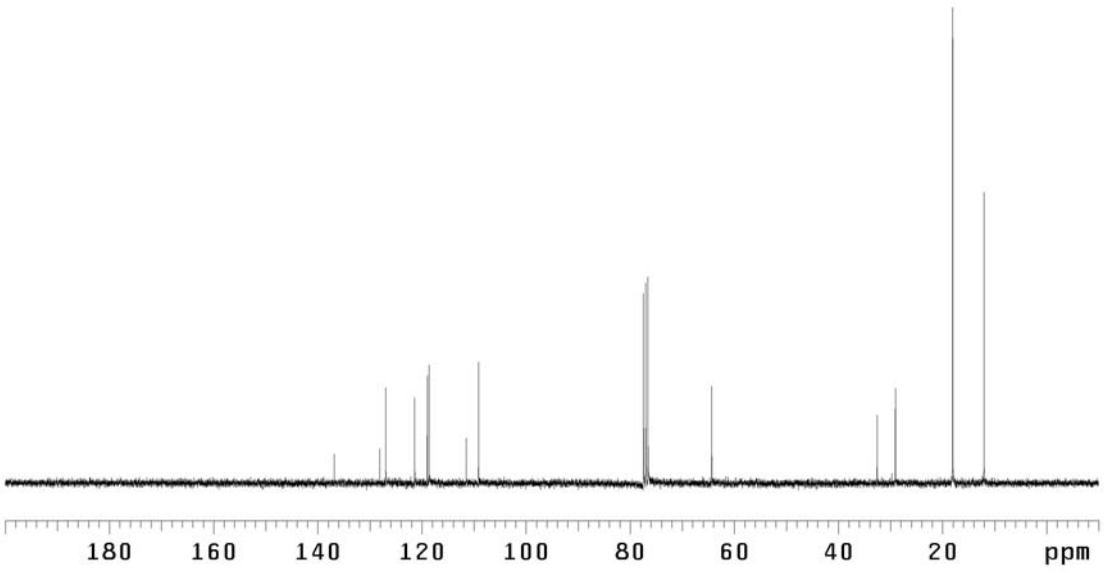


Figure A3.3.3 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **92**.

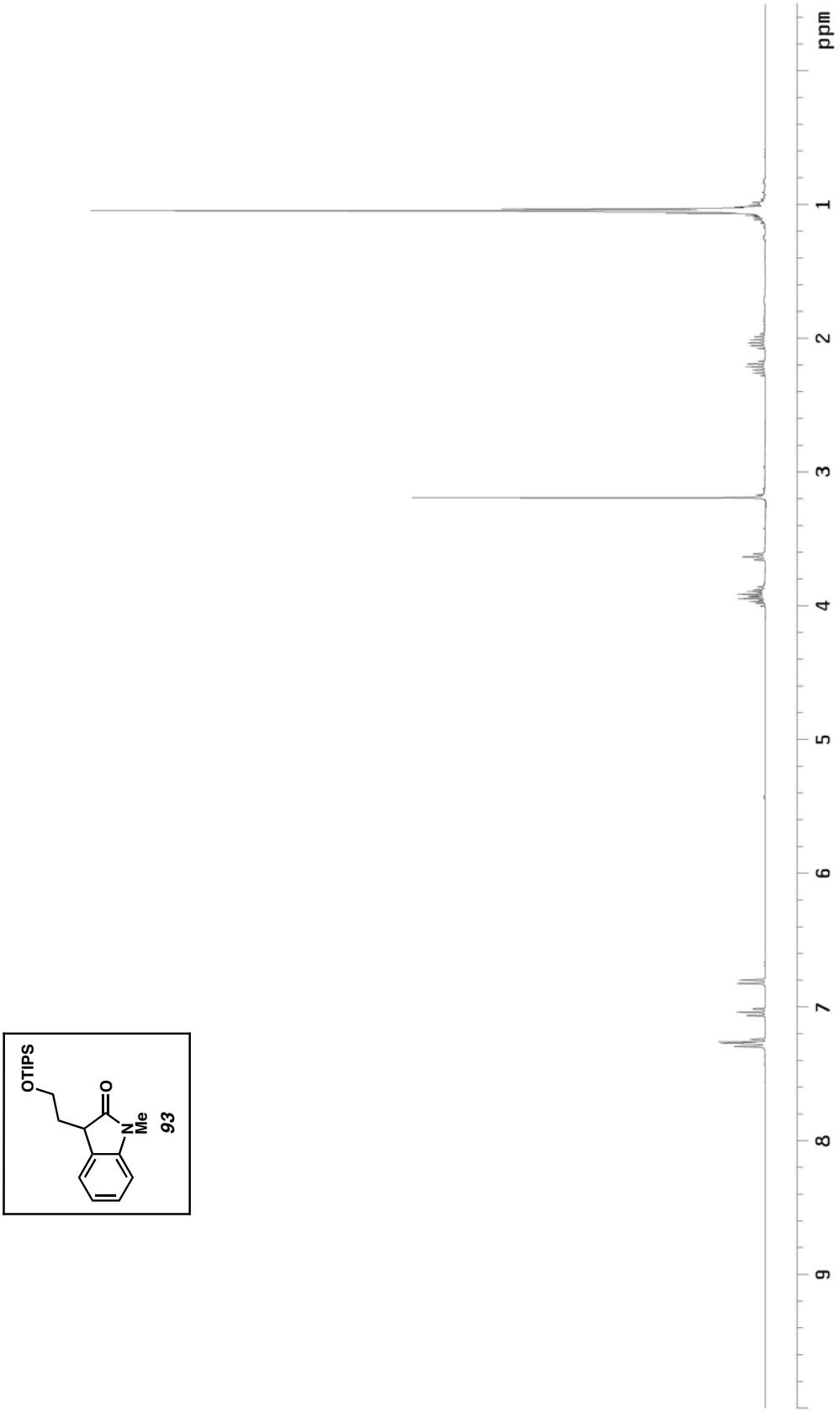


Figure A3.4.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **93**.

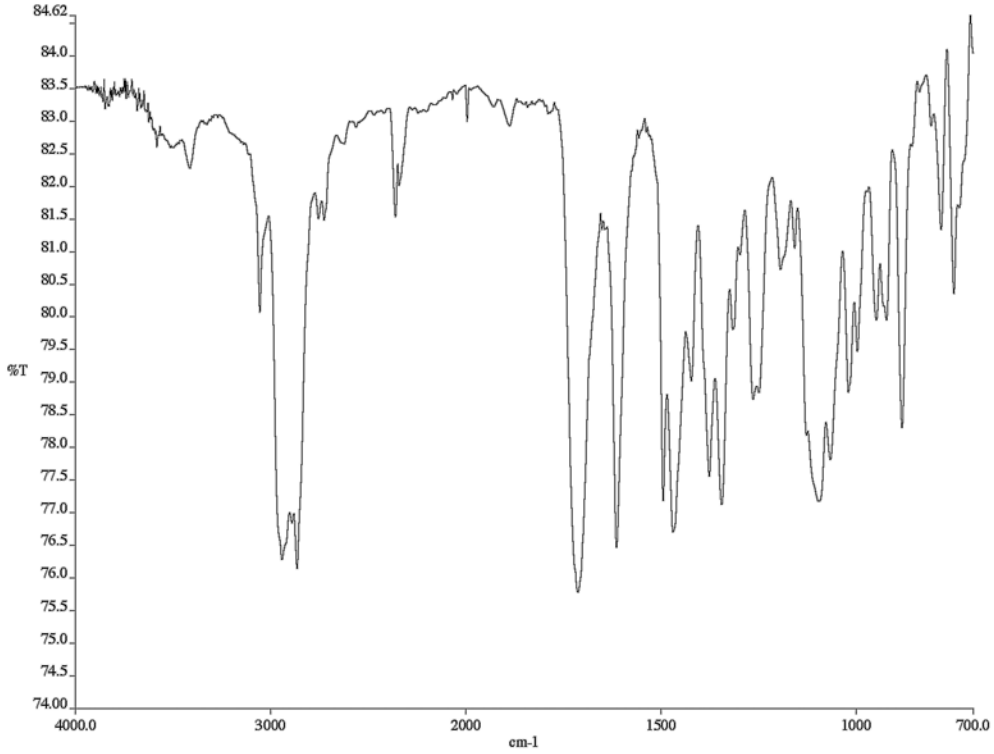


Figure A3.4.2 Infrared spectrum (thin film/NaCl) of compound **93**.

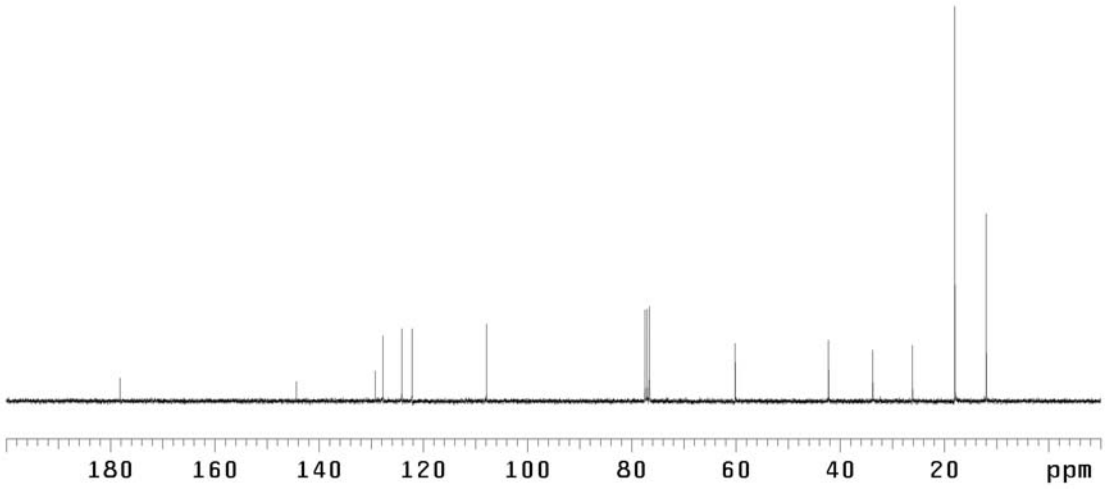


Figure A3.4.3 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **93**.

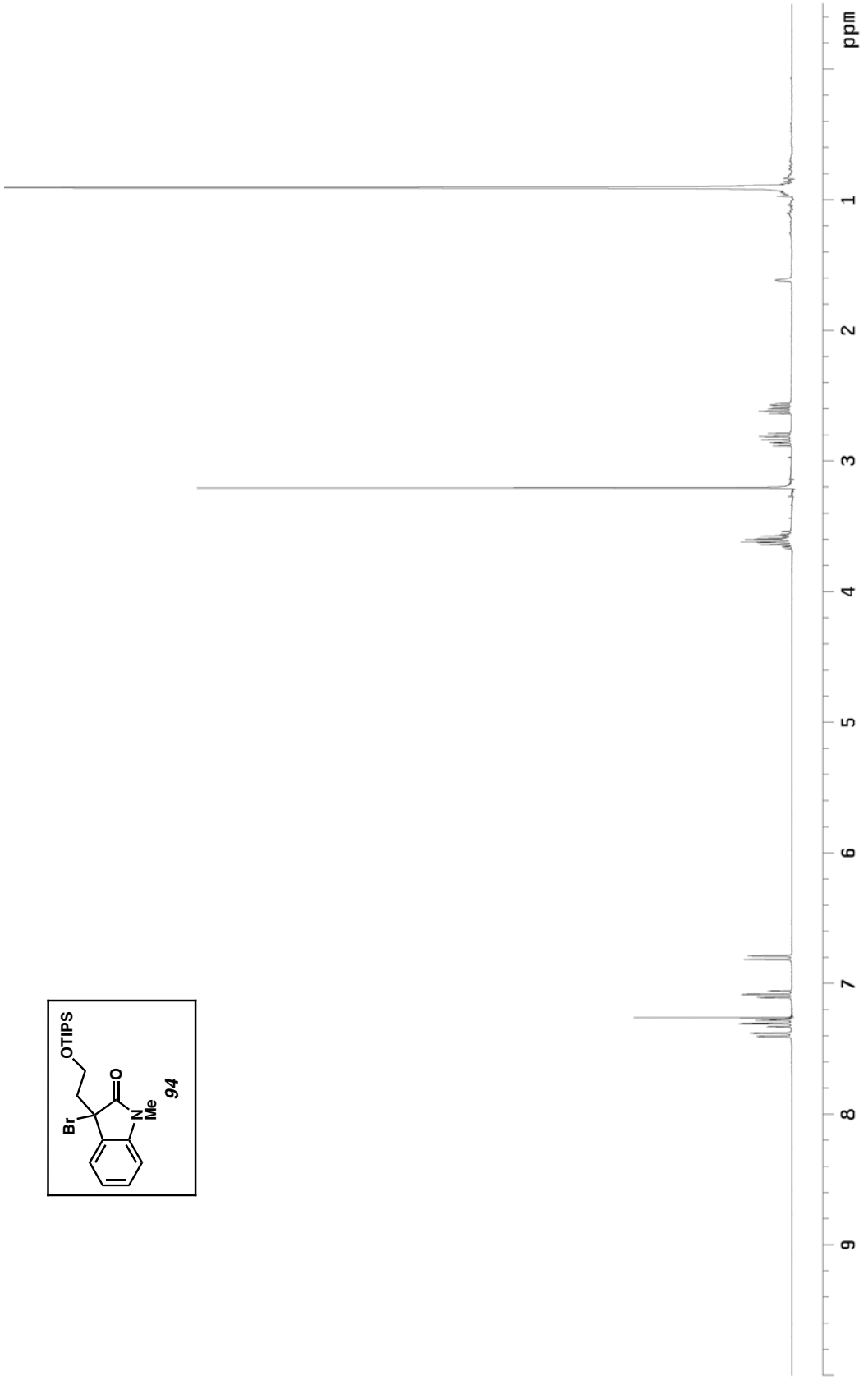


Figure A3.5.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **94**.

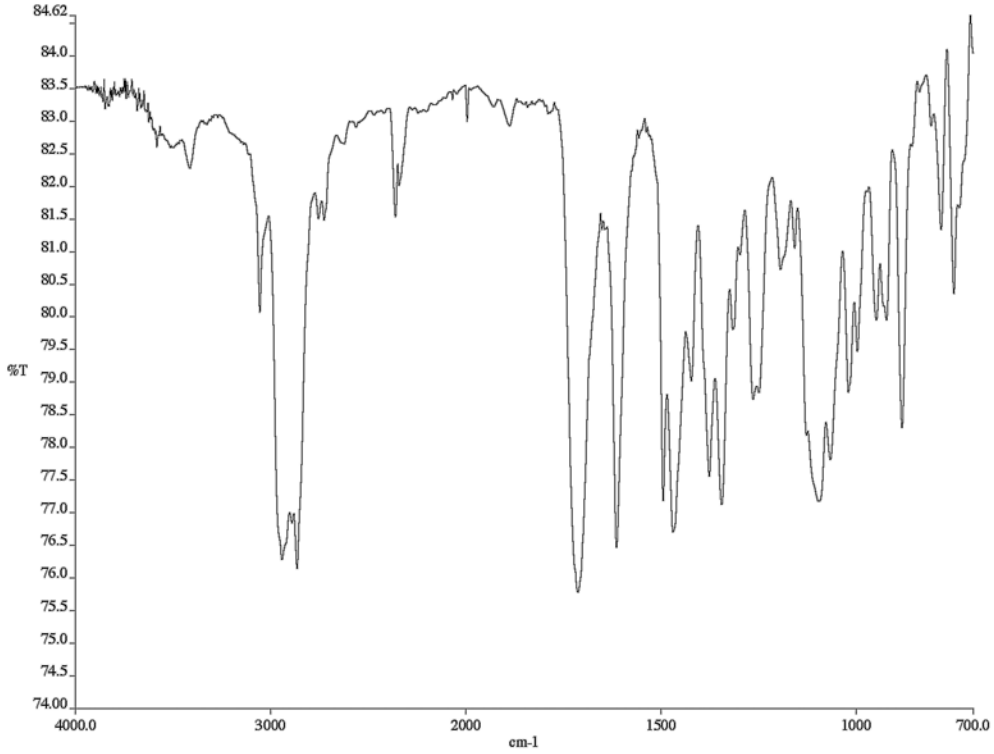


Figure A3.5.2 Infrared spectrum (thin film/NaCl) of compound **94**.

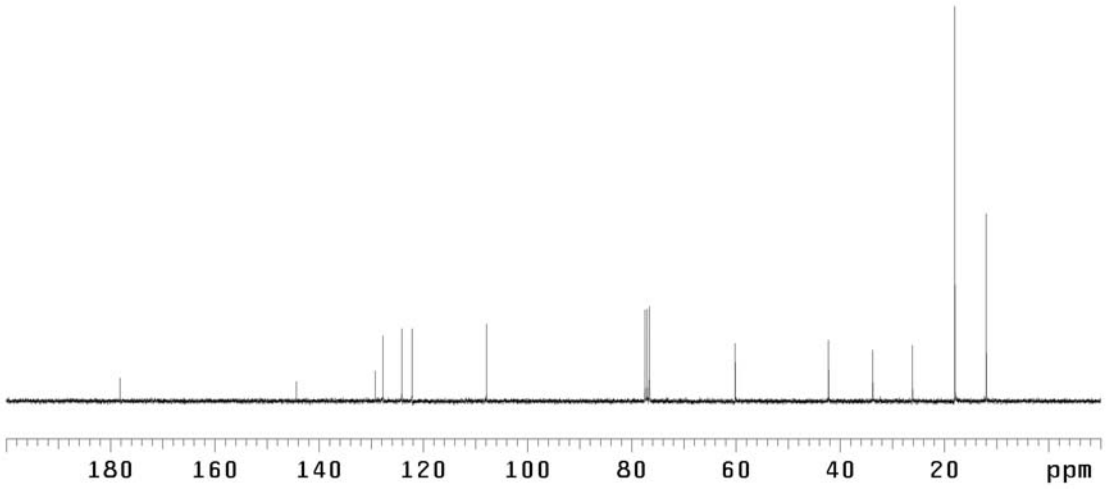


Figure A3.5.3 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **94**.

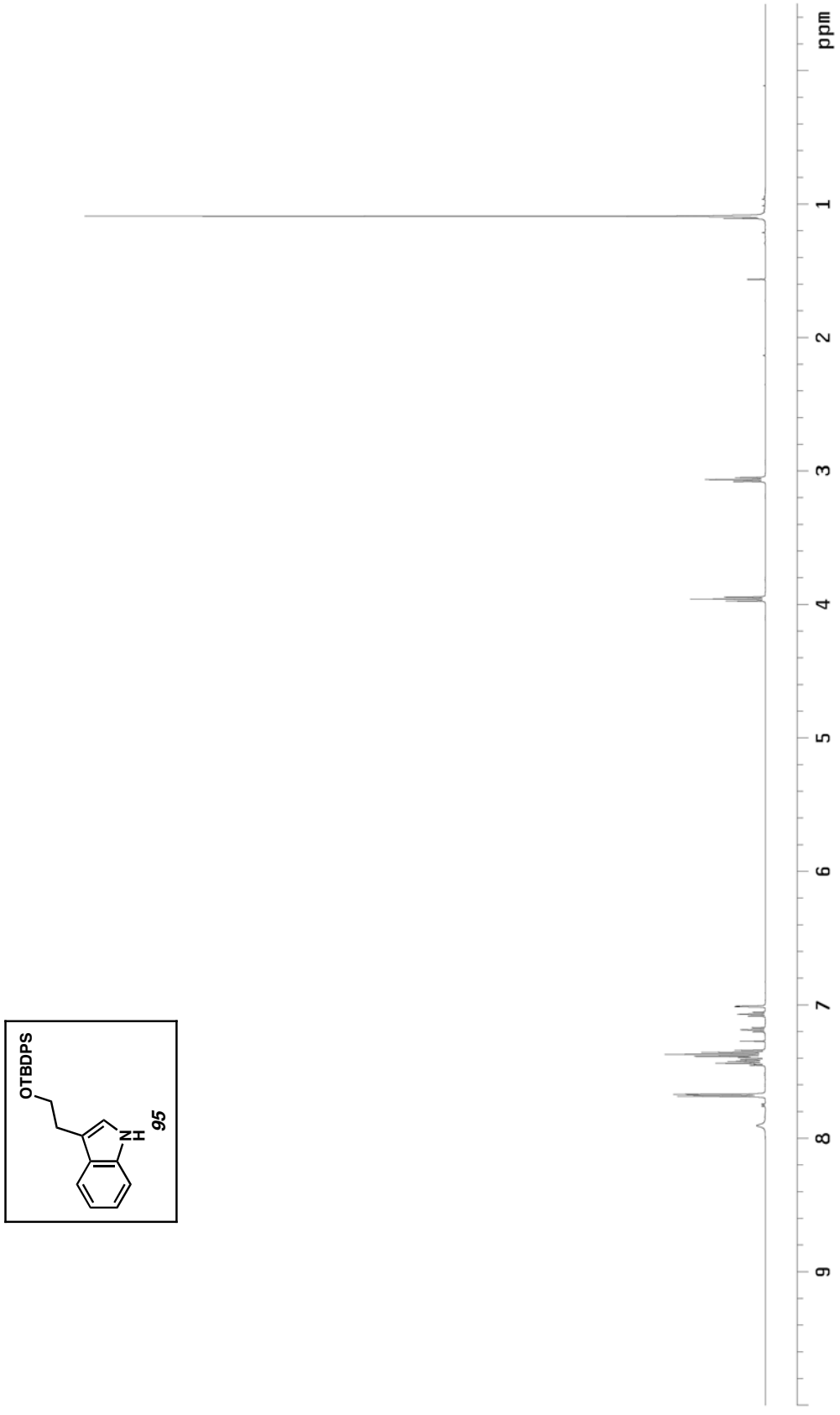


Figure A3.6.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **95**.

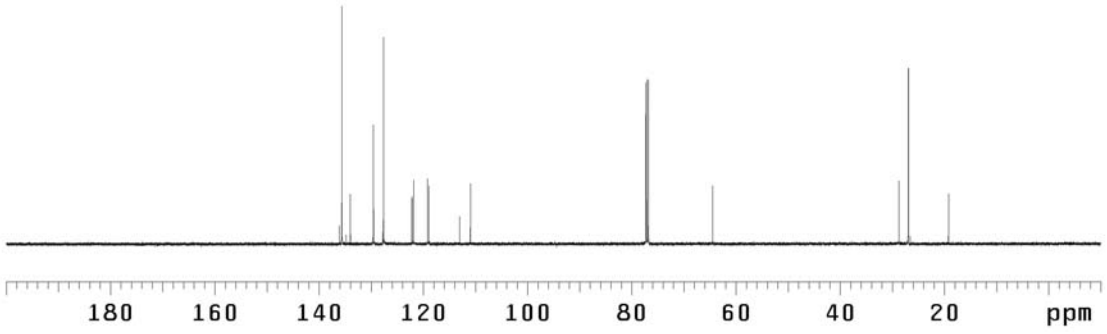


Figure A6.6.2 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **95**.

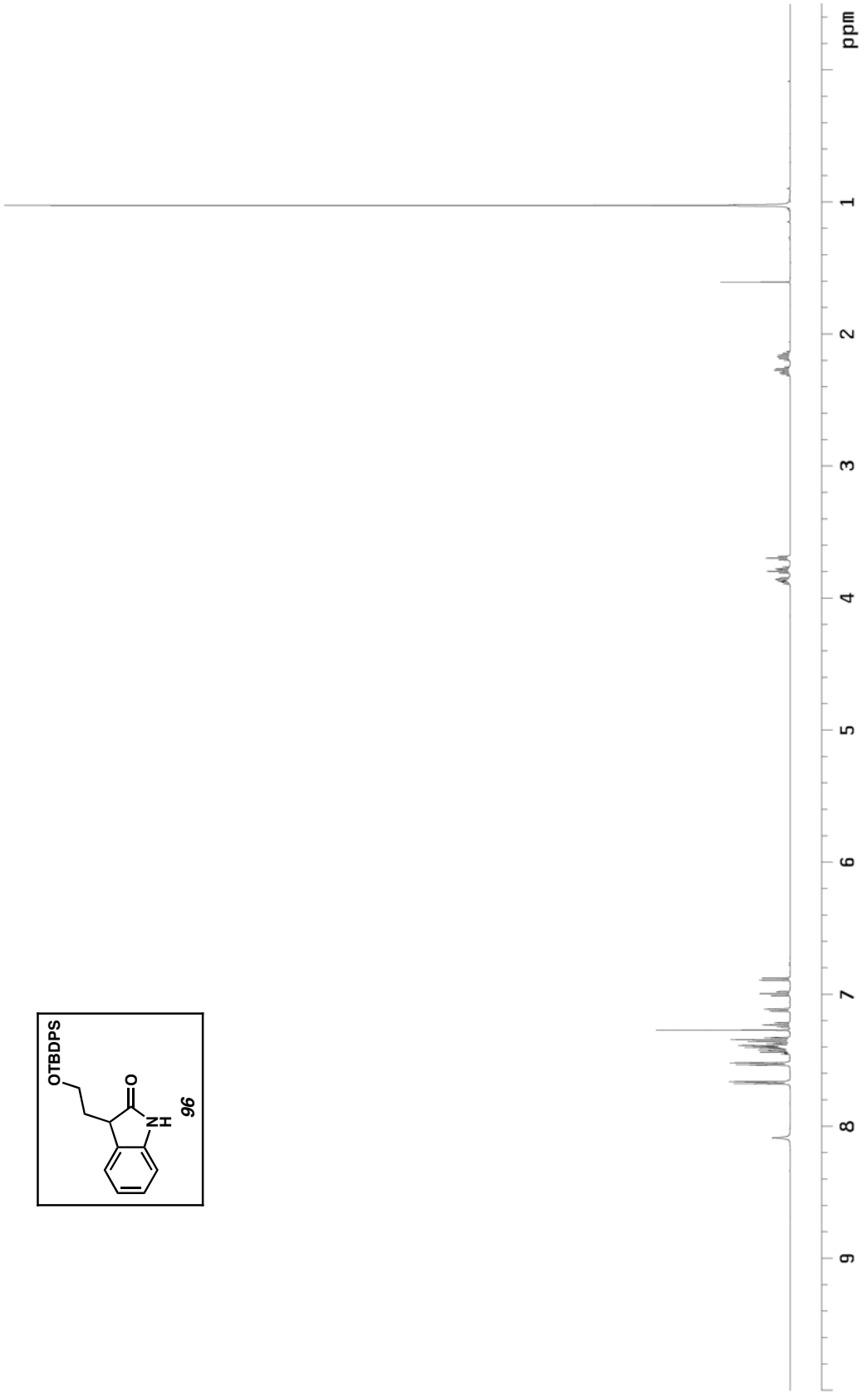


Figure A3.7.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **96**.

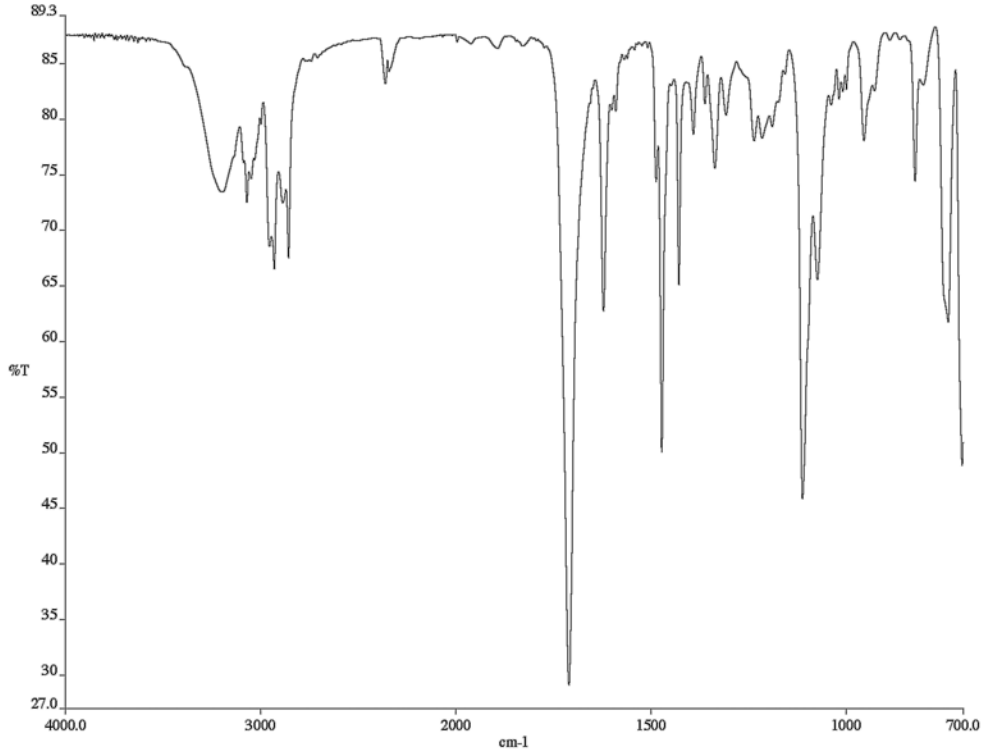


Figure A3.7.2 Infrared spectrum (thin film/NaCl) of compound **96**.

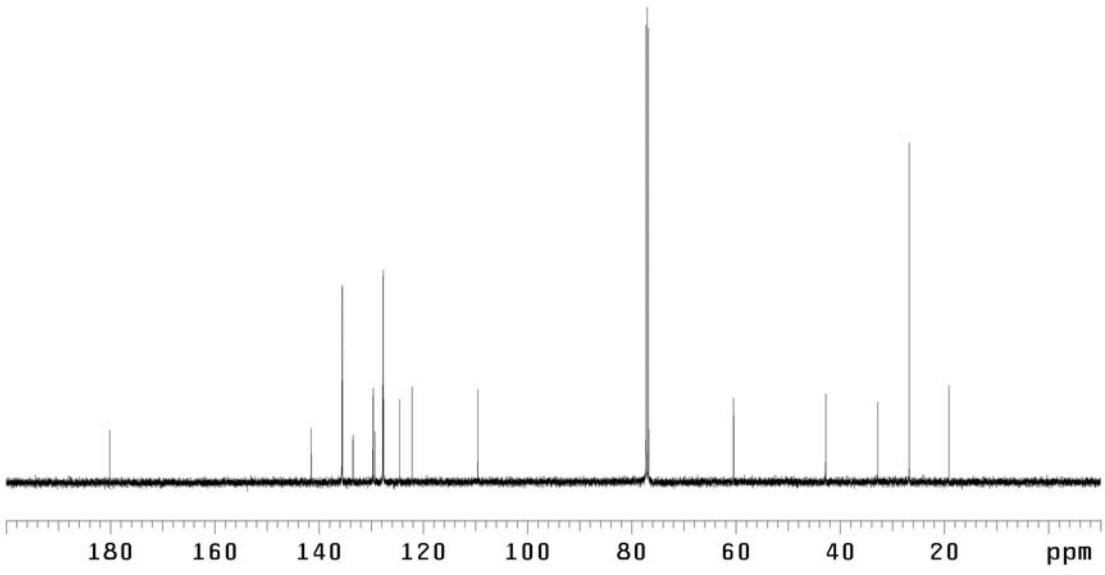


Figure A3.7.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **96**.

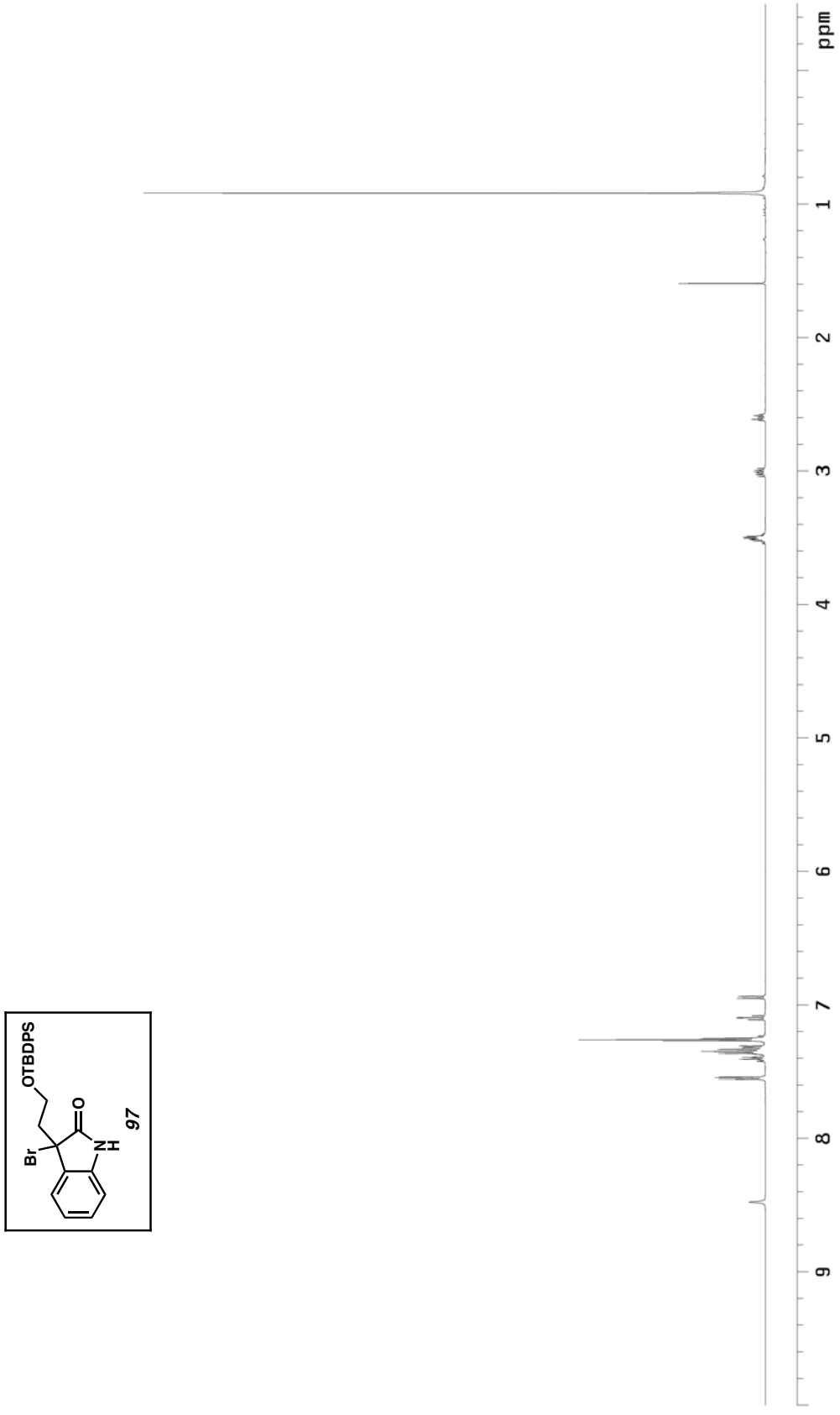


Figure A3.8.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **97**.

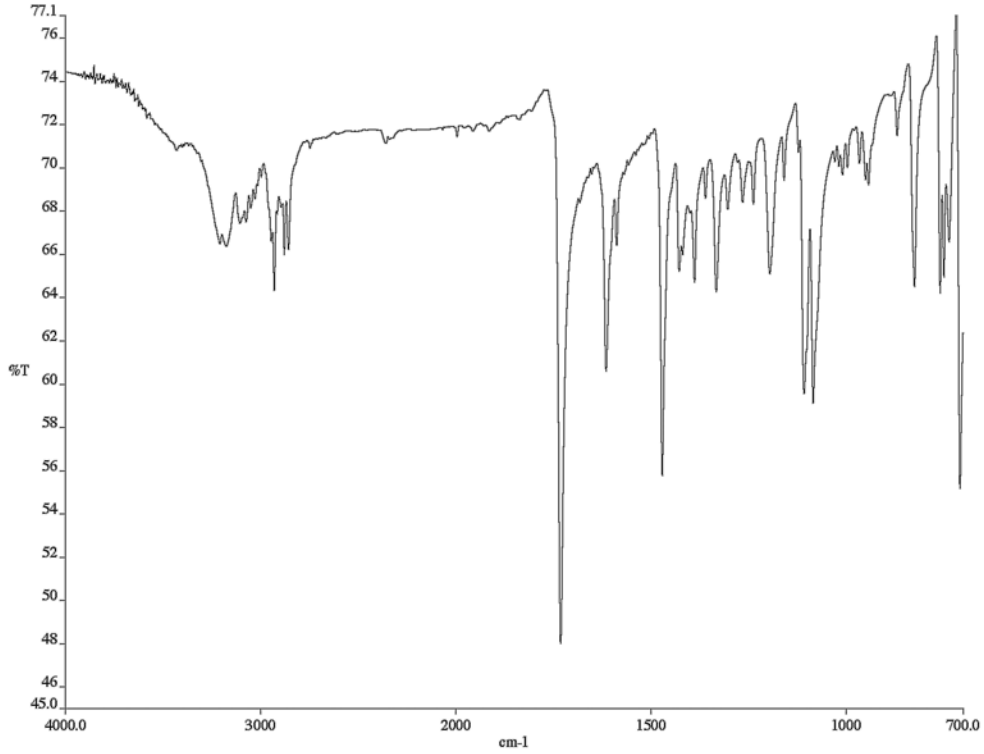


Figure A3.8.2 Infrared spectrum (thin film/NaCl) of compound **97**.

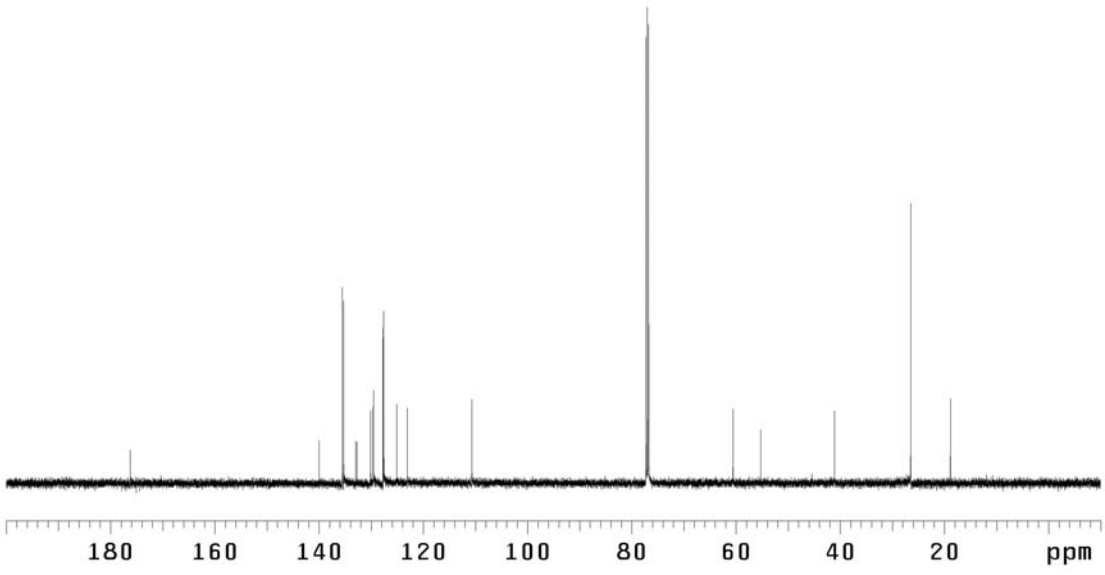


Figure A3.8.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **97**.

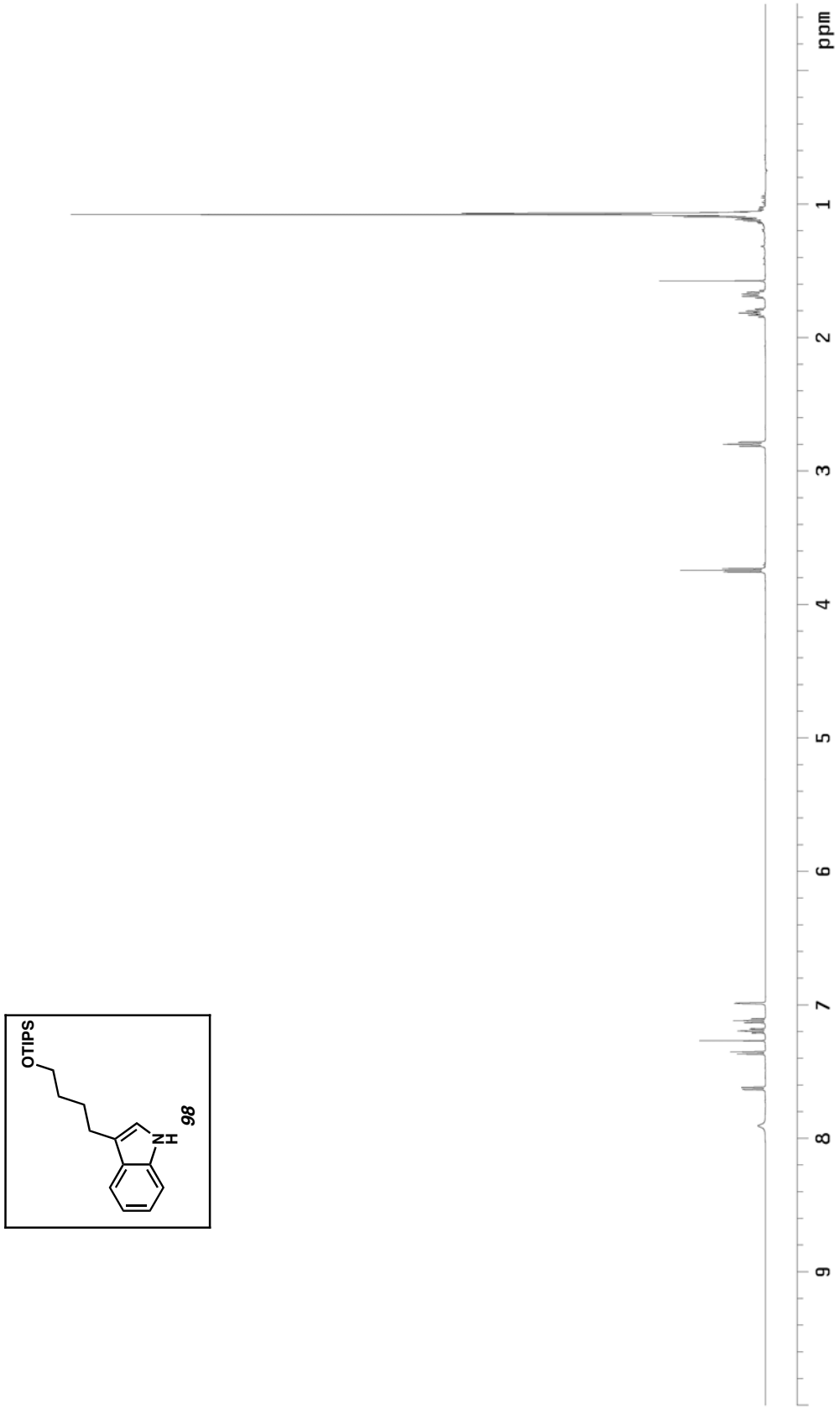


Figure A3.9.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **98**.

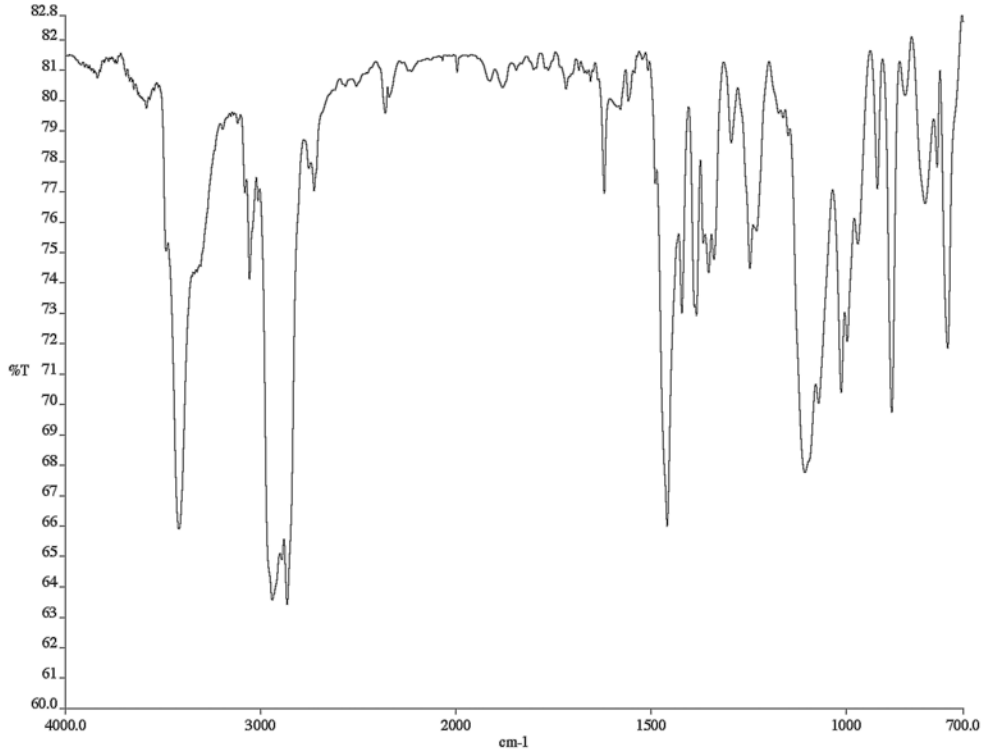


Figure A3.9.2 Infrared spectrum (thin film/NaCl) of compound **98**.

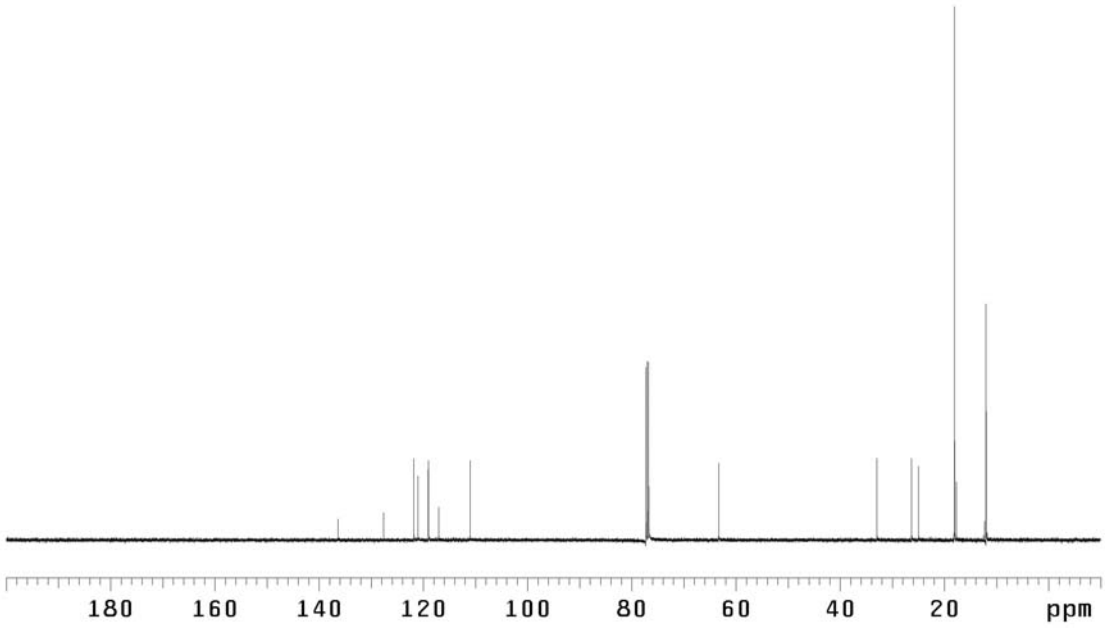


Figure A3.9.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **98**.

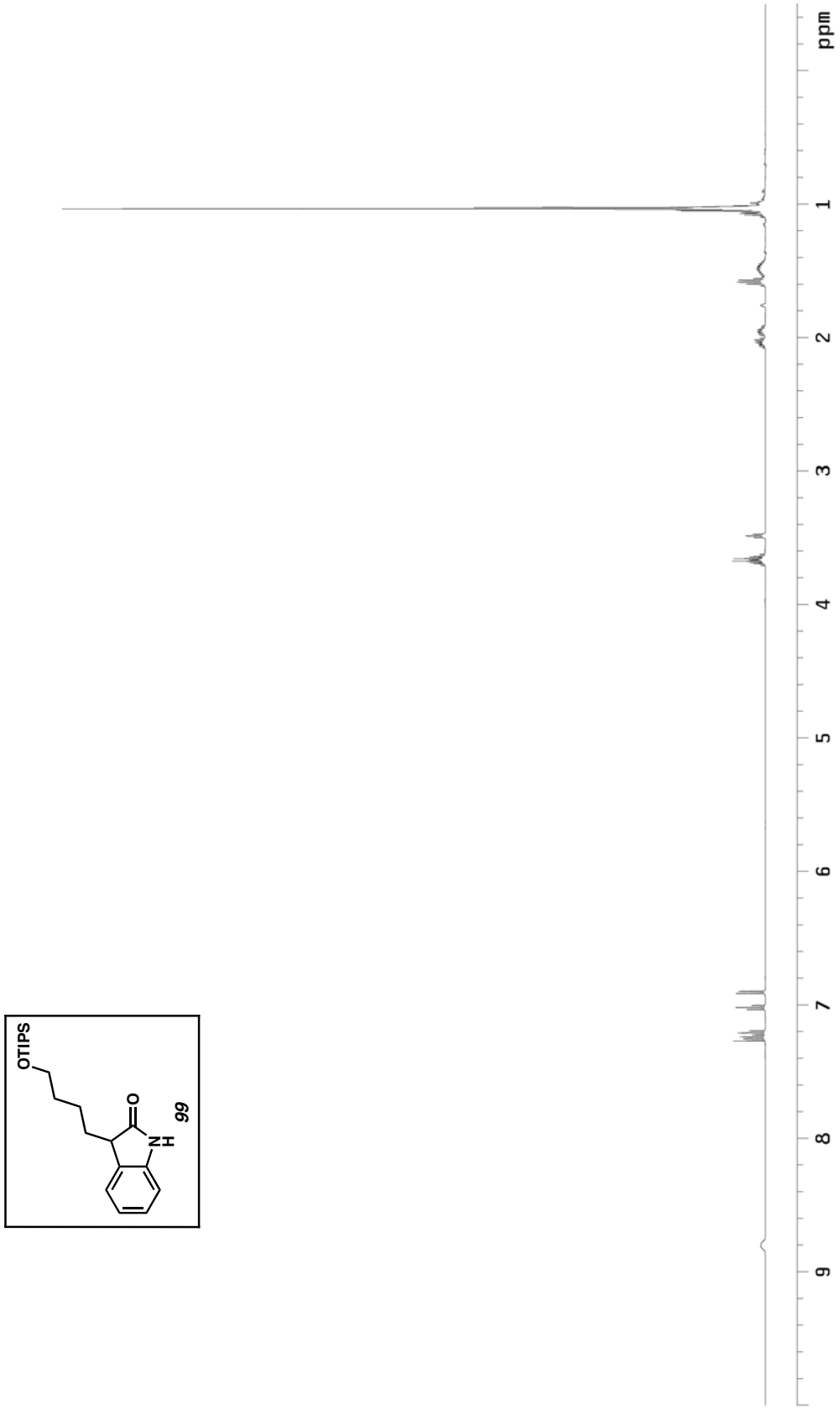


Figure A3.10.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **99**.

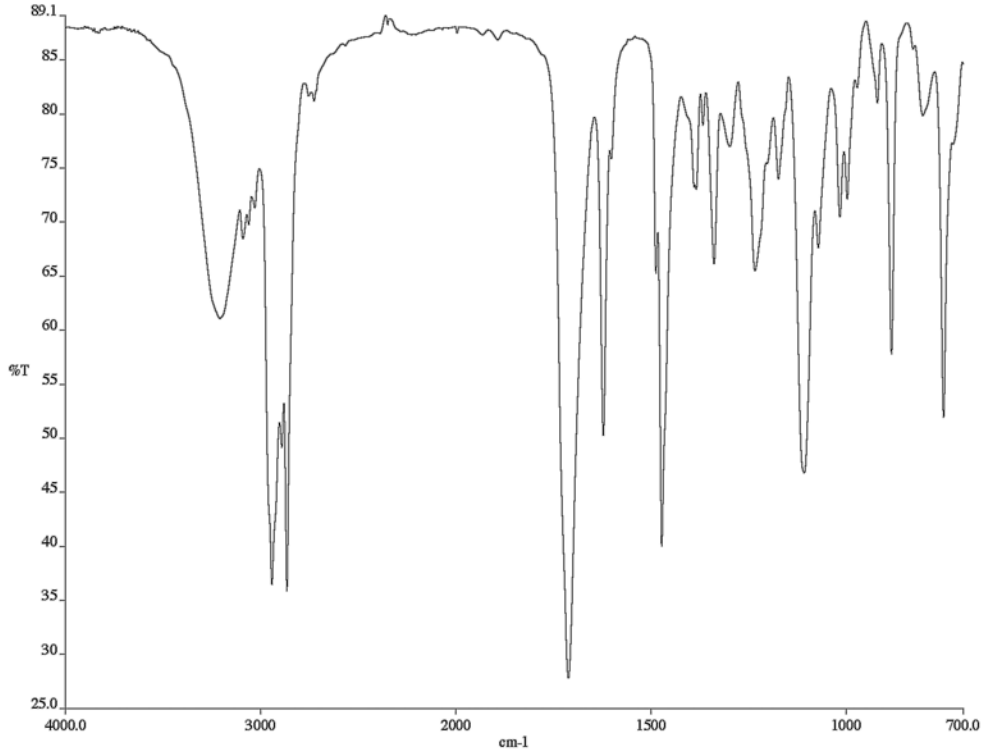


Figure A3.10.2 Infrared spectrum (thin film/NaCl) of compound **99**.

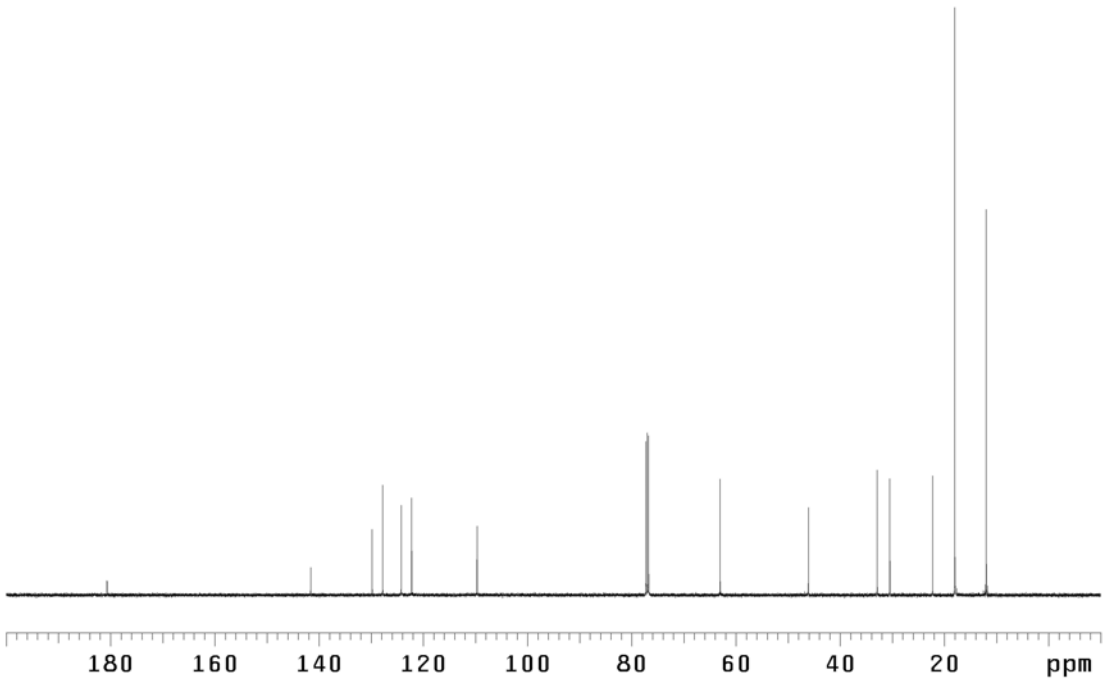


Figure A3.10.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **99**.

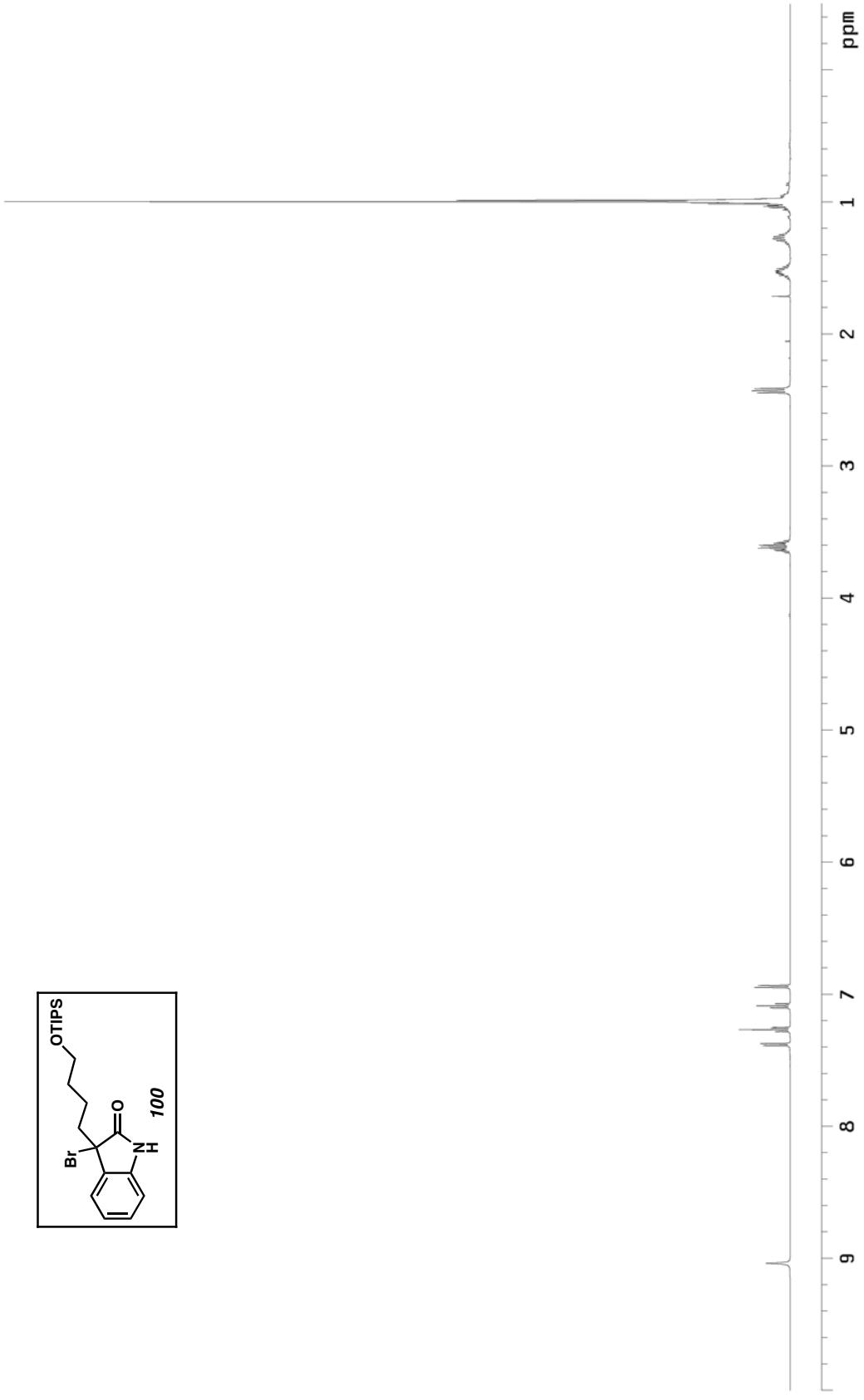


Figure A3.11.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **100**.

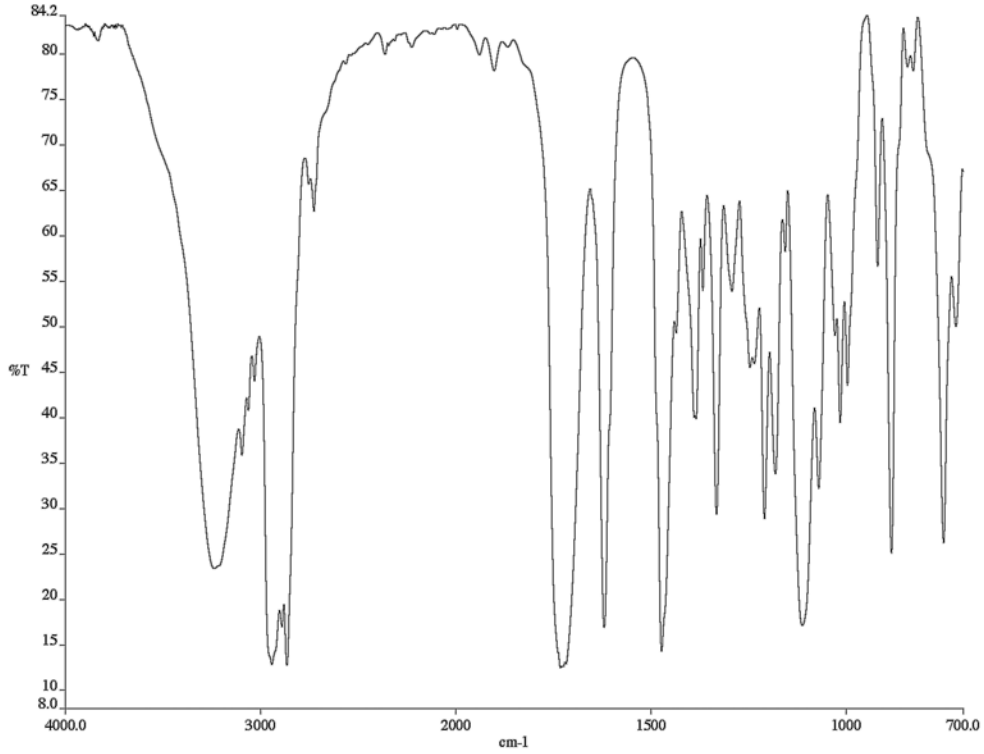


Figure A3.11.2 Infrared spectrum (thin film/NaCl) of compound **100**.

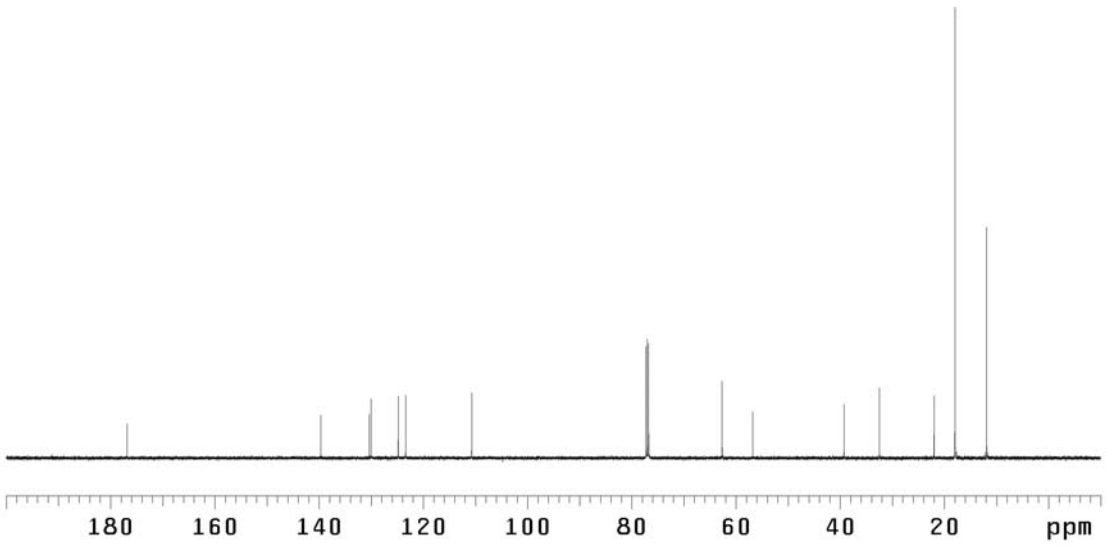
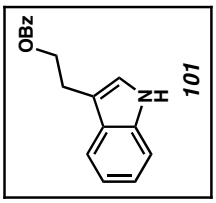


Figure A3.11.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **100**.



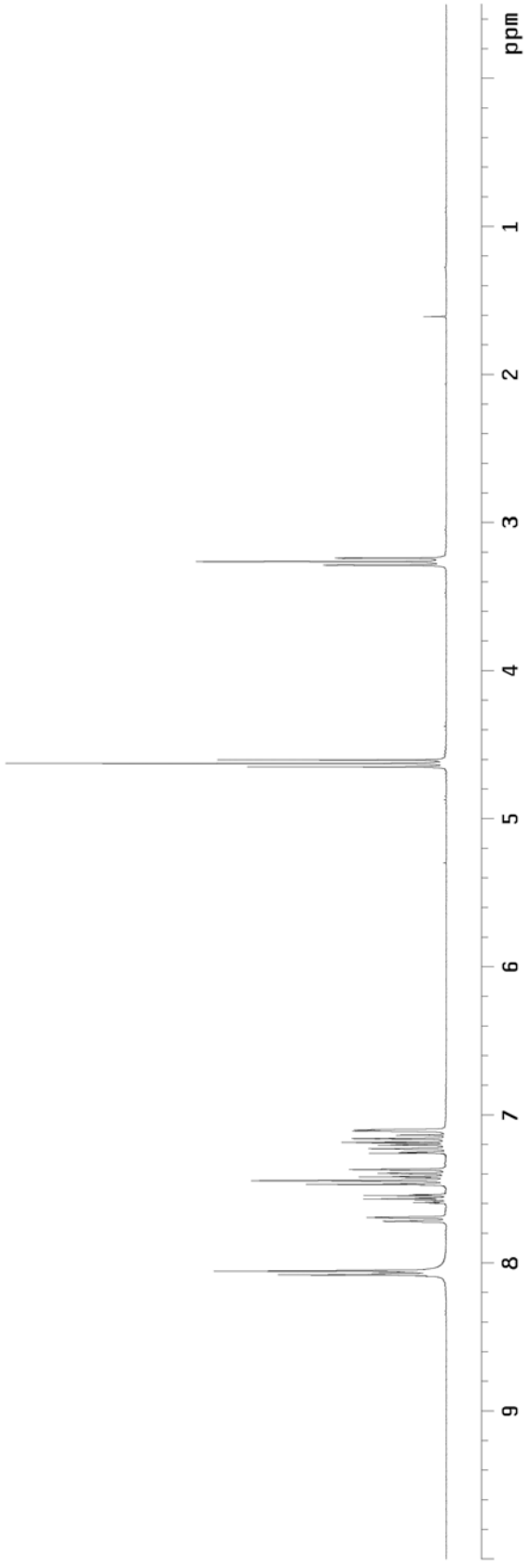


Figure A3.12.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **101**.

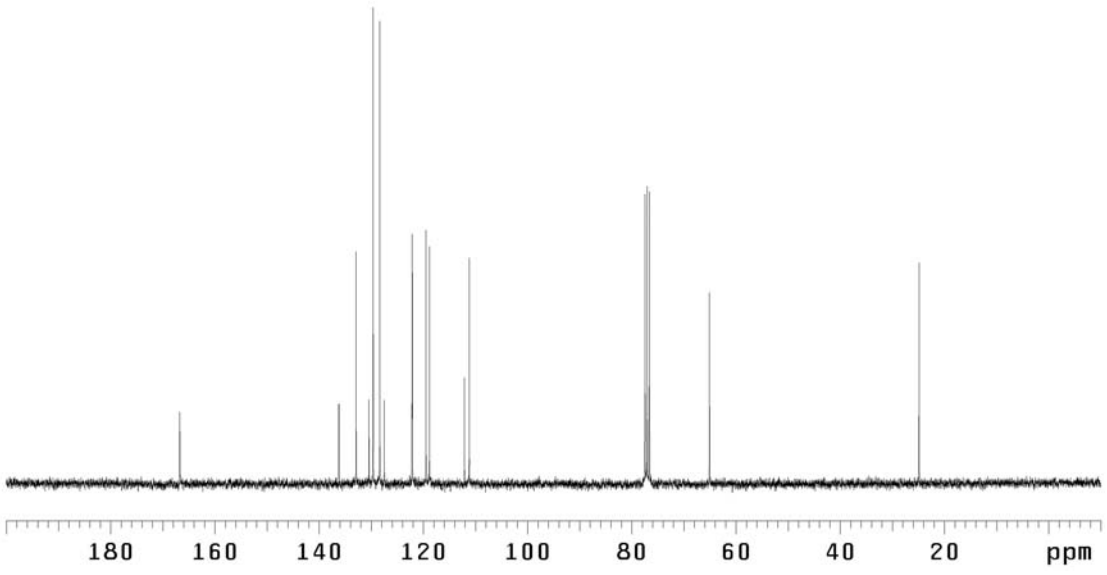


Figure A3.12.2 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **101**.

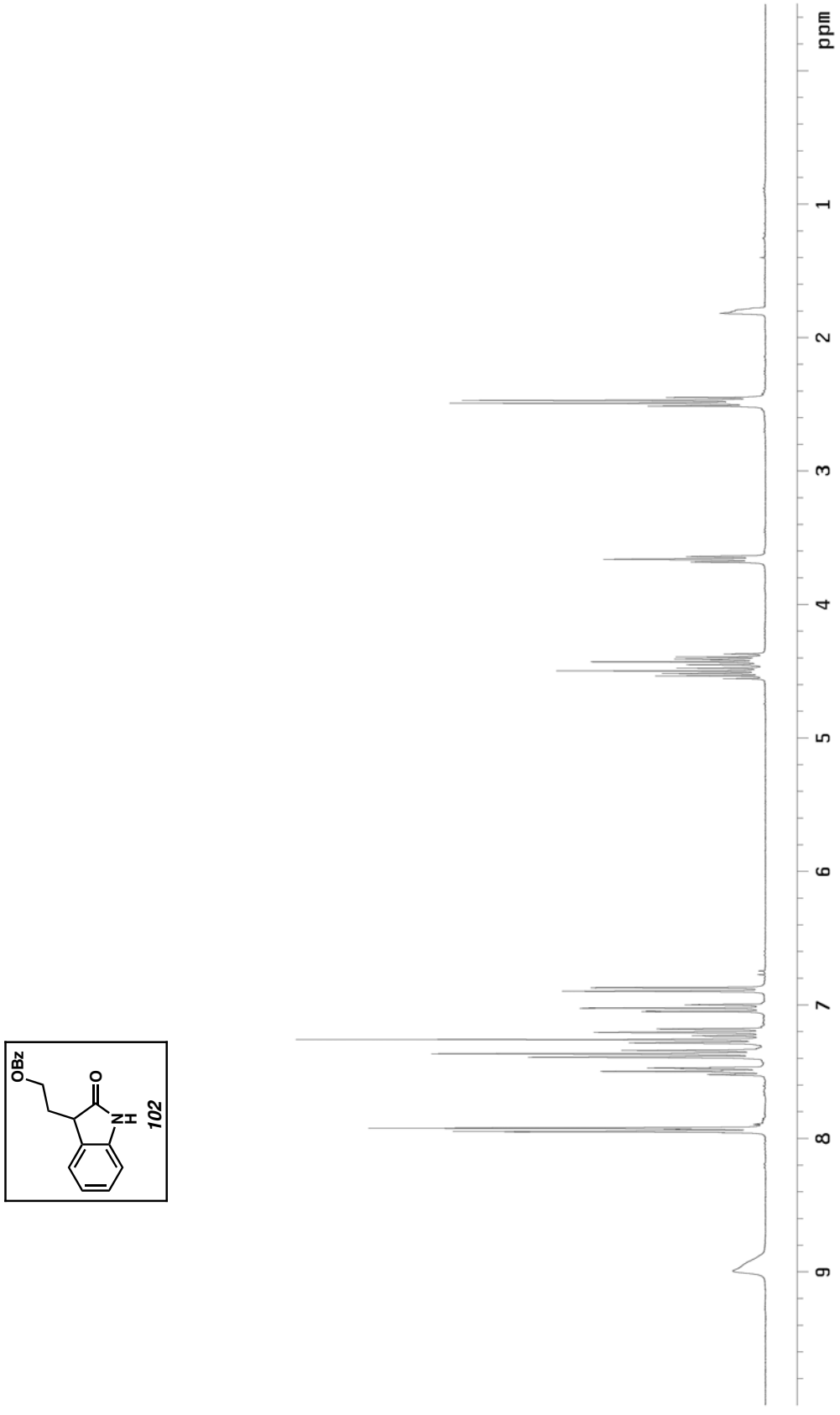


Figure A3.13.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **102**.

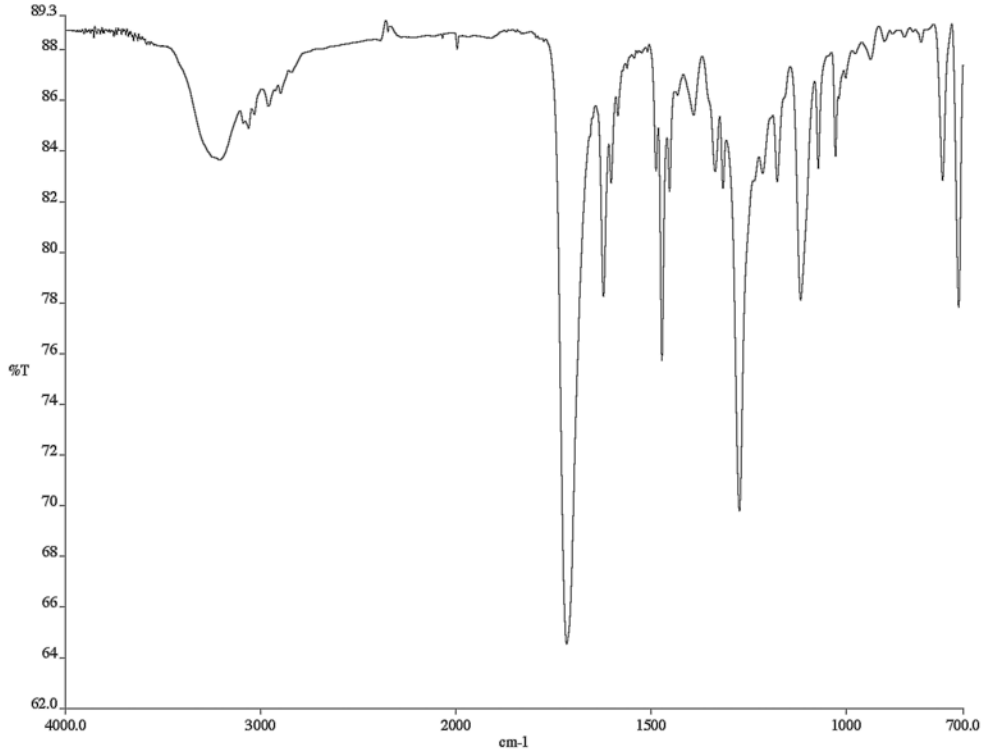


Figure A3.13.2 Infrared spectrum (thin film/NaCl) of compound **102**.

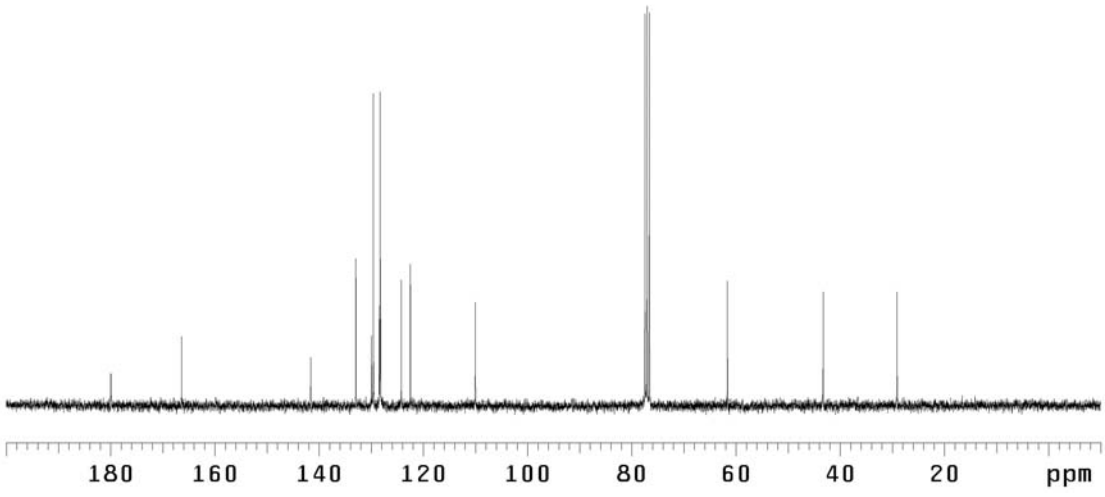


Figure A3.13.3 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **102**.

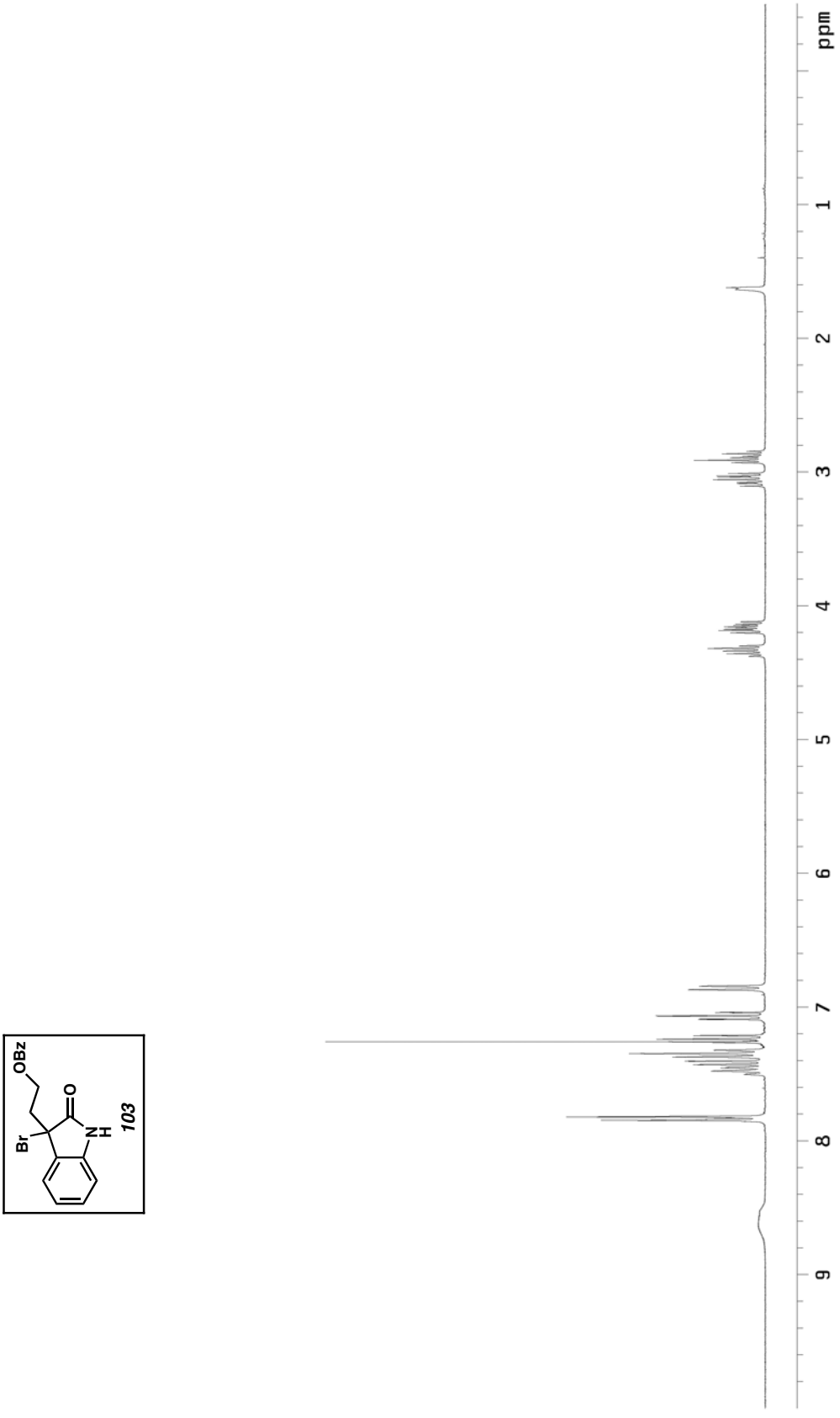


Figure A3.14.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **103**.

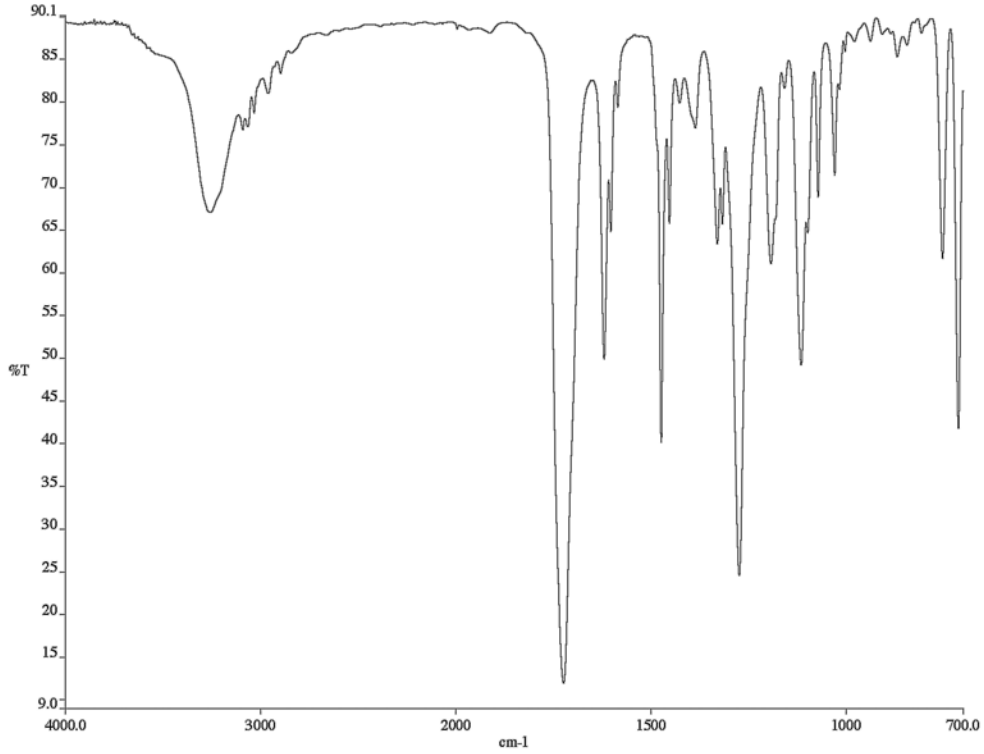


Figure A3.14.2 Infrared spectrum (thin film/NaCl) of compound **103**.

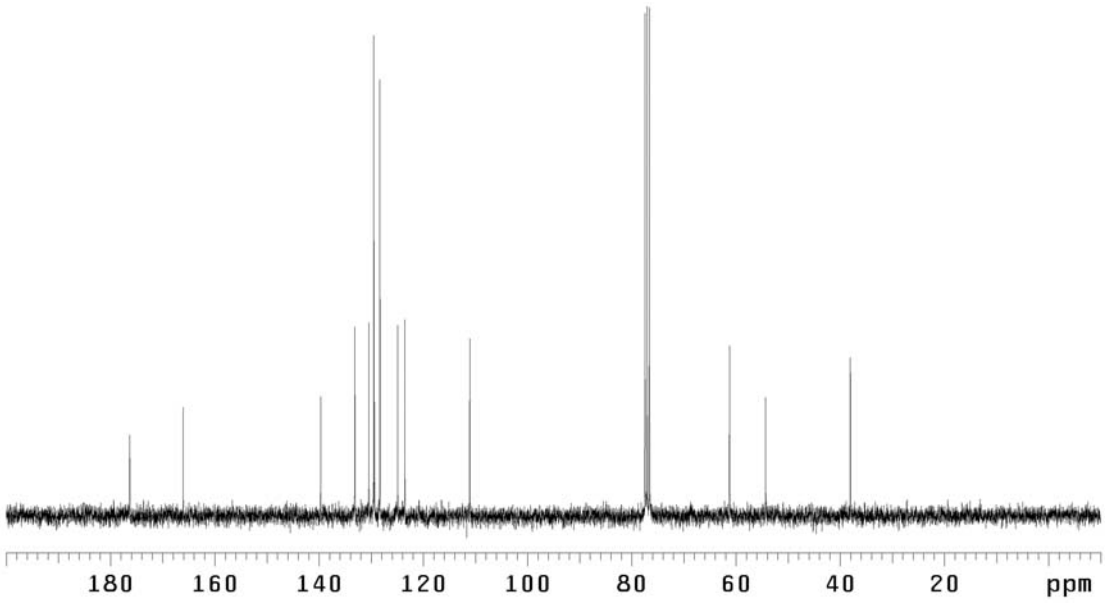


*Figure A3.14.*3 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **103**.

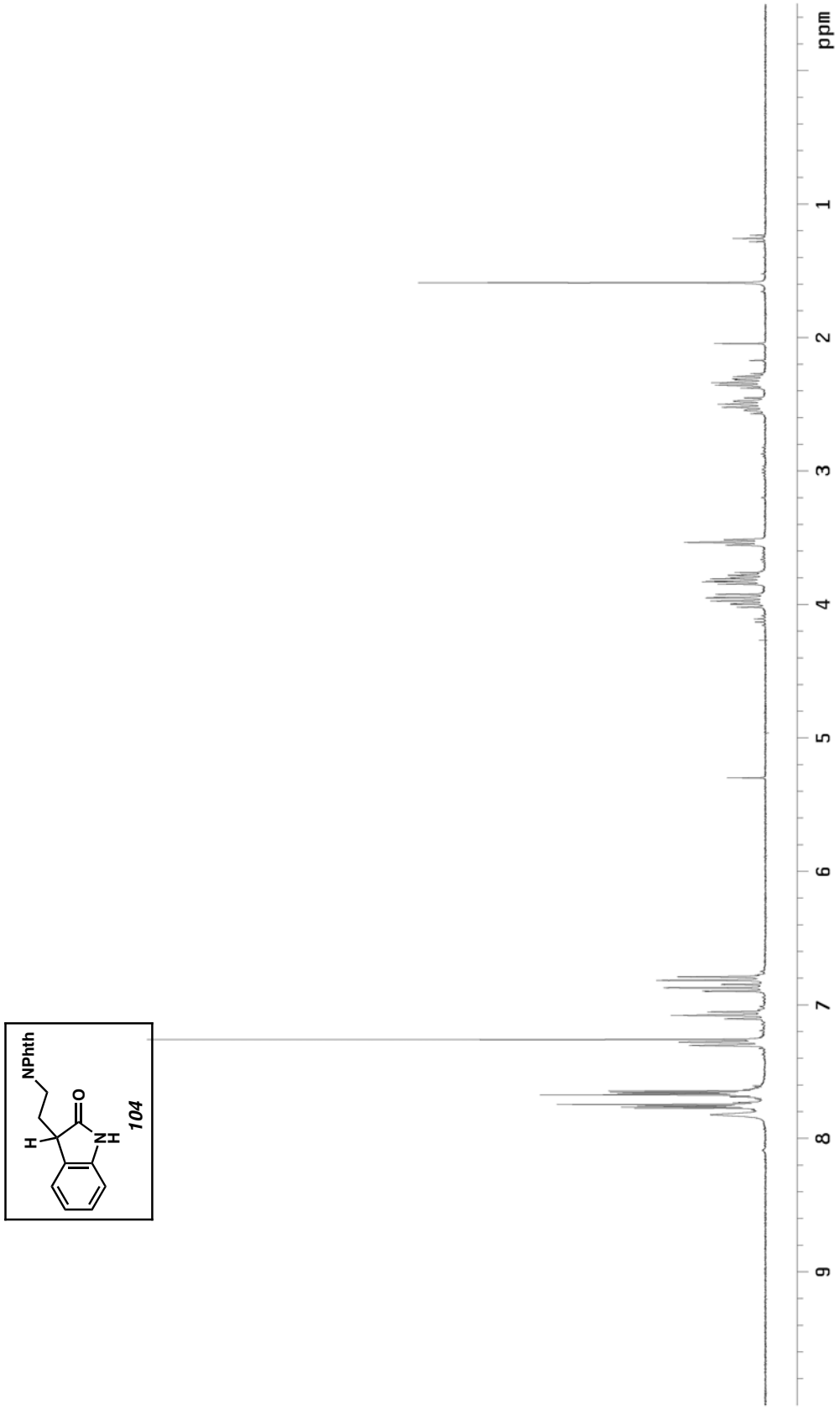


Figure A3.15.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **104**.

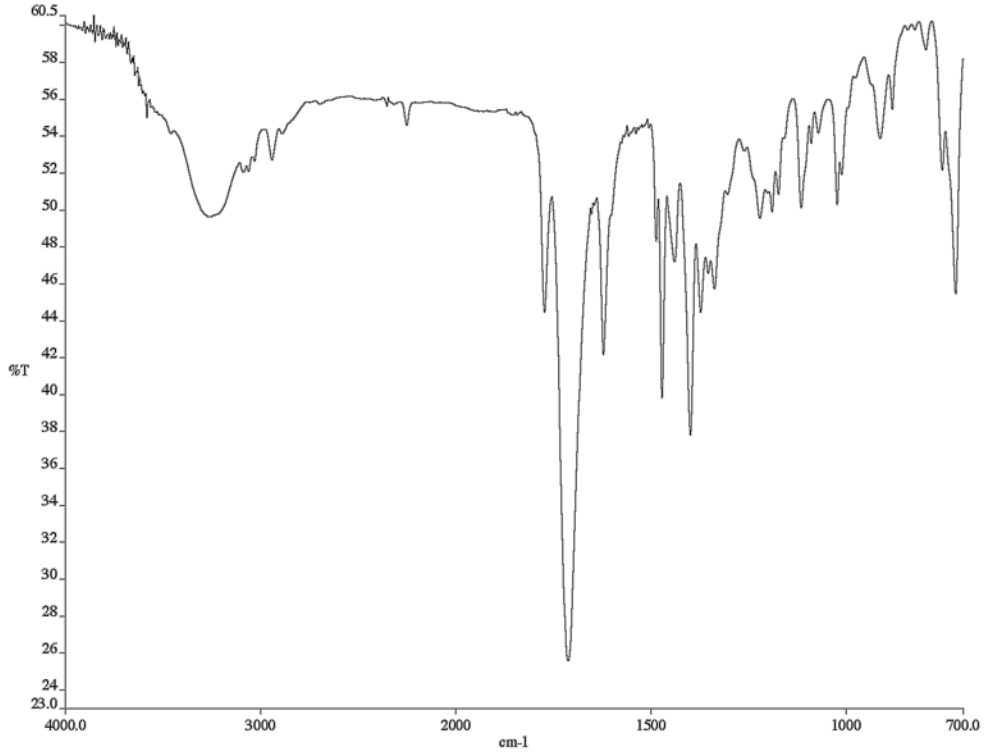


Figure A3.15.2 Infrared spectrum (thin film/NaCl) of compound **104**.

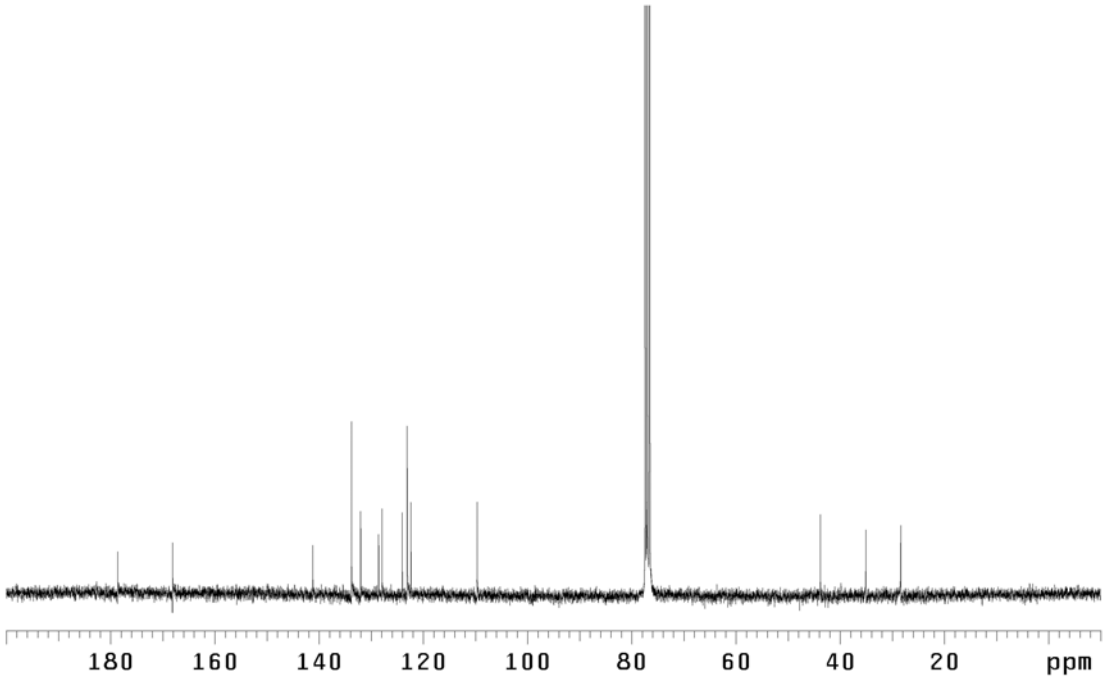
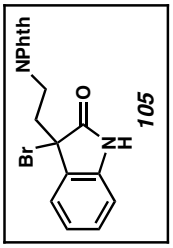


Figure A3.15.3 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **104**.



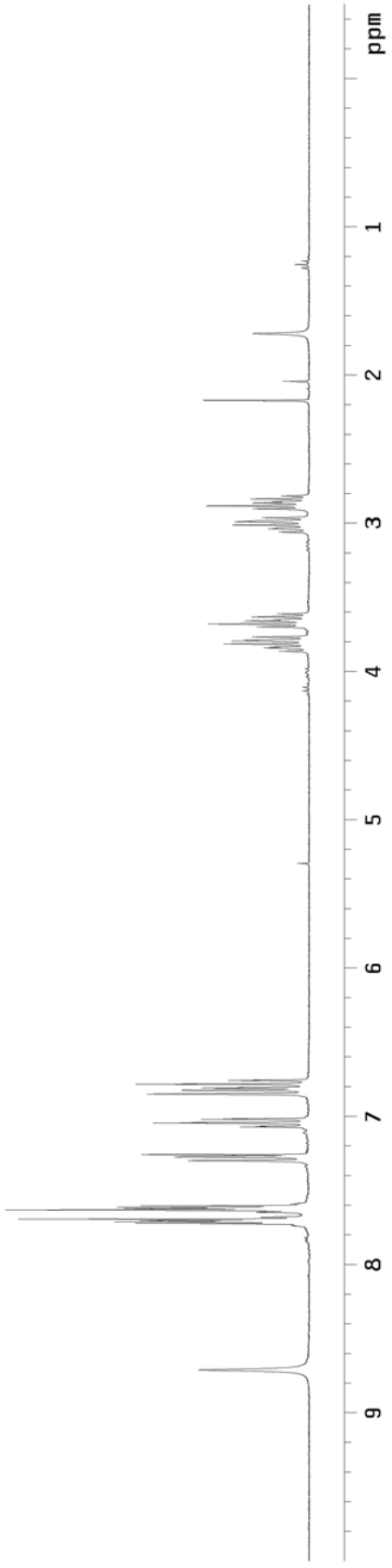


Figure A3.16.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **105**.

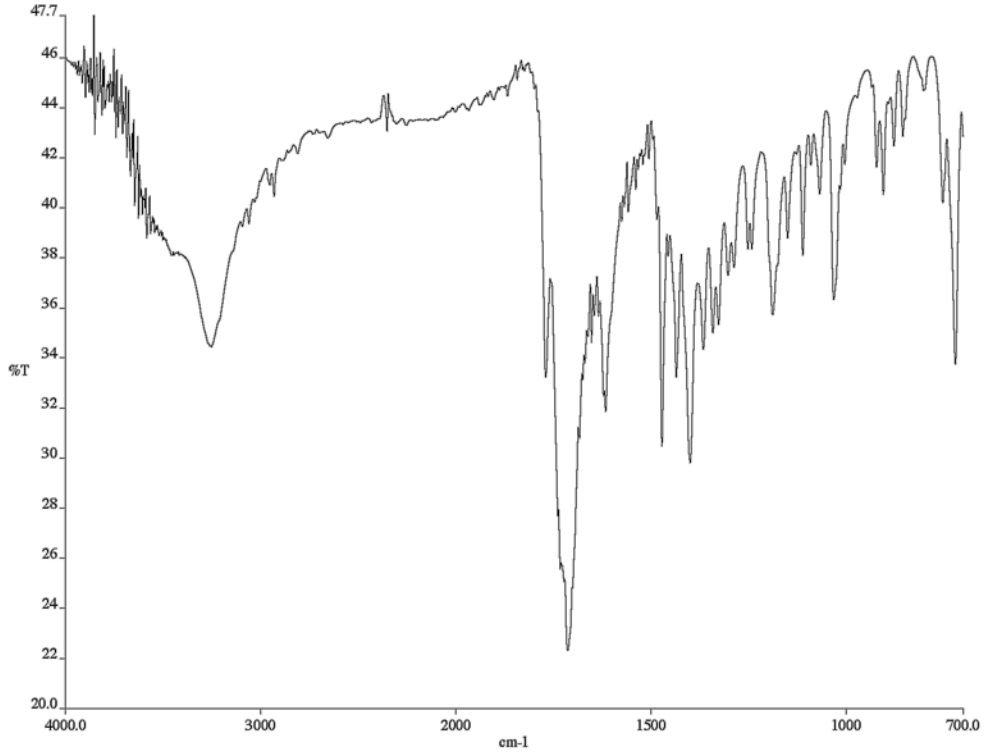


Figure A3.16.2 Infrared spectrum (thin film/NaCl) of compound **105**.

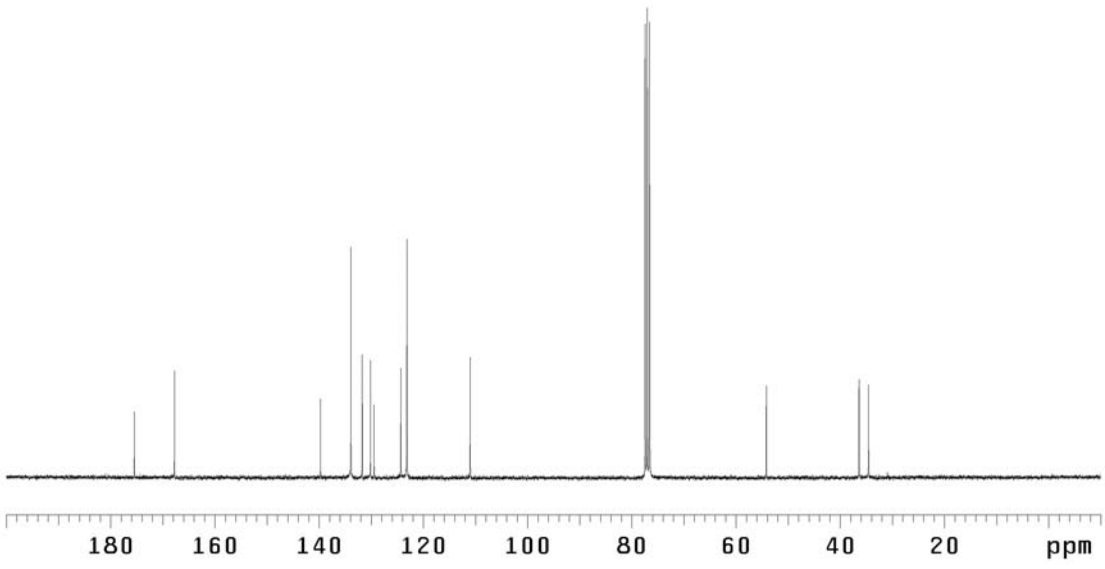


Figure A3.16.3 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **105**.

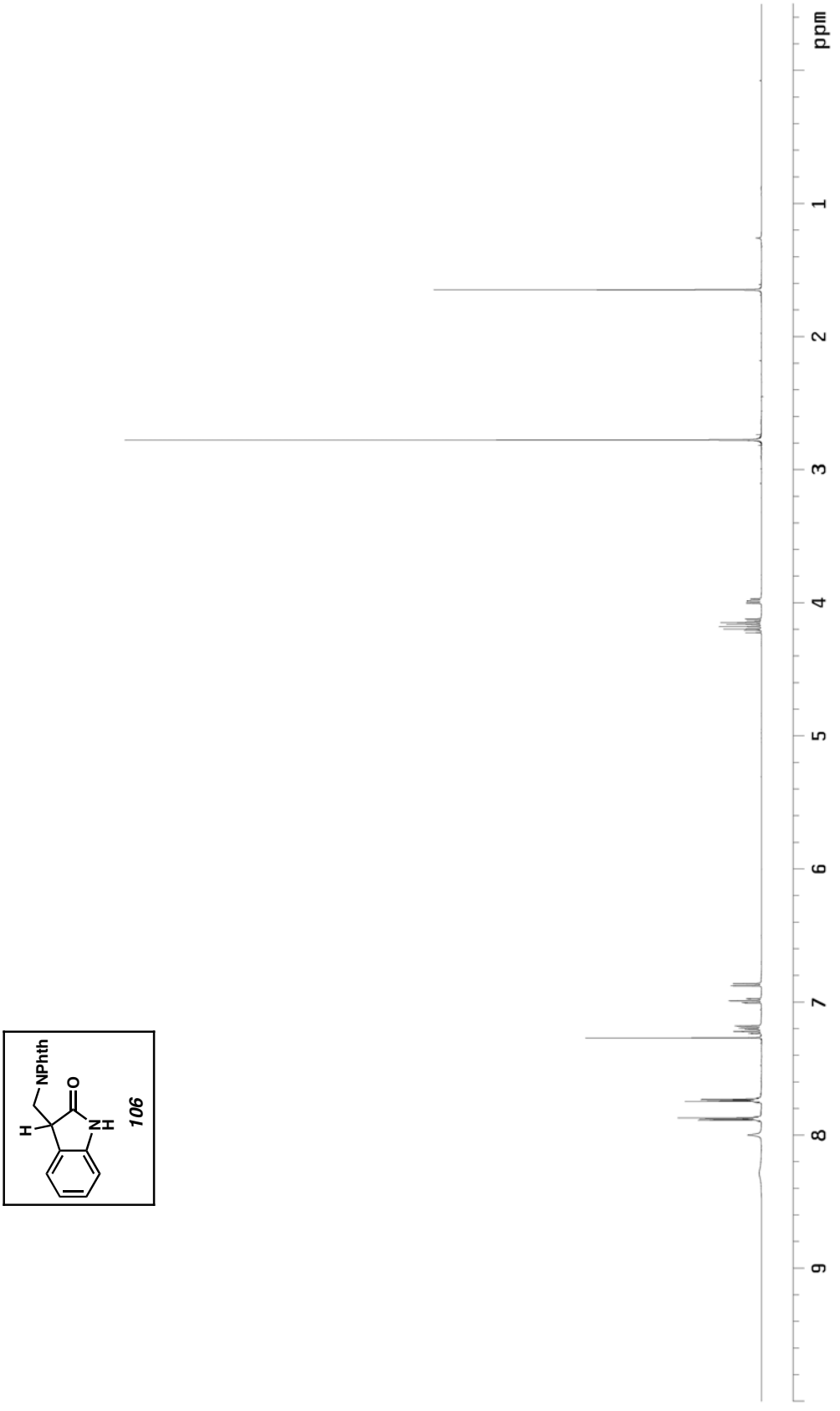


Figure A3.17.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **106** with succinimide impurity.

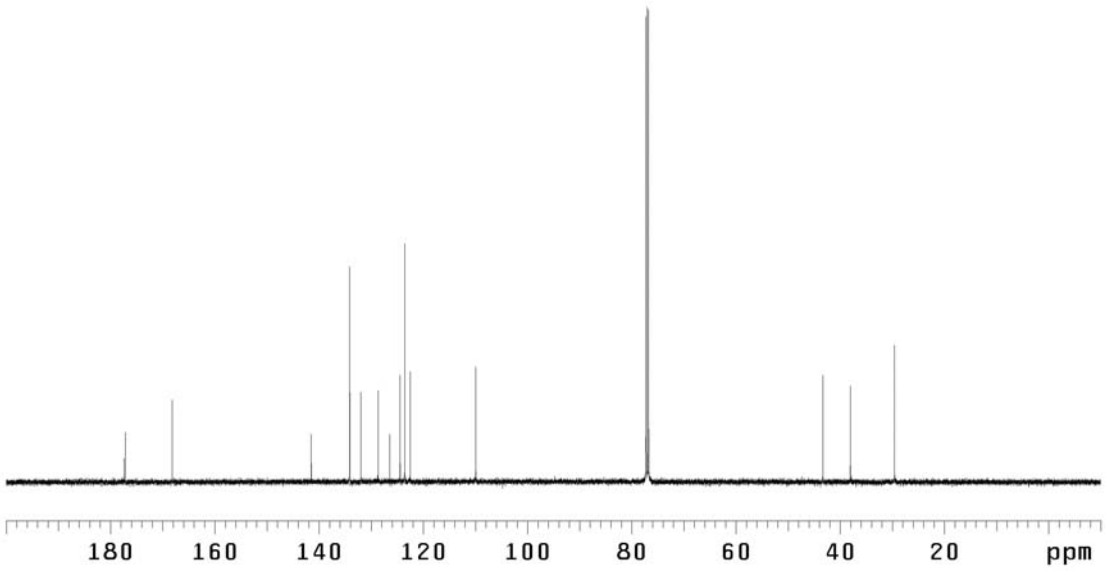


Figure A3.17.2 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **106** with succinimide impurity.

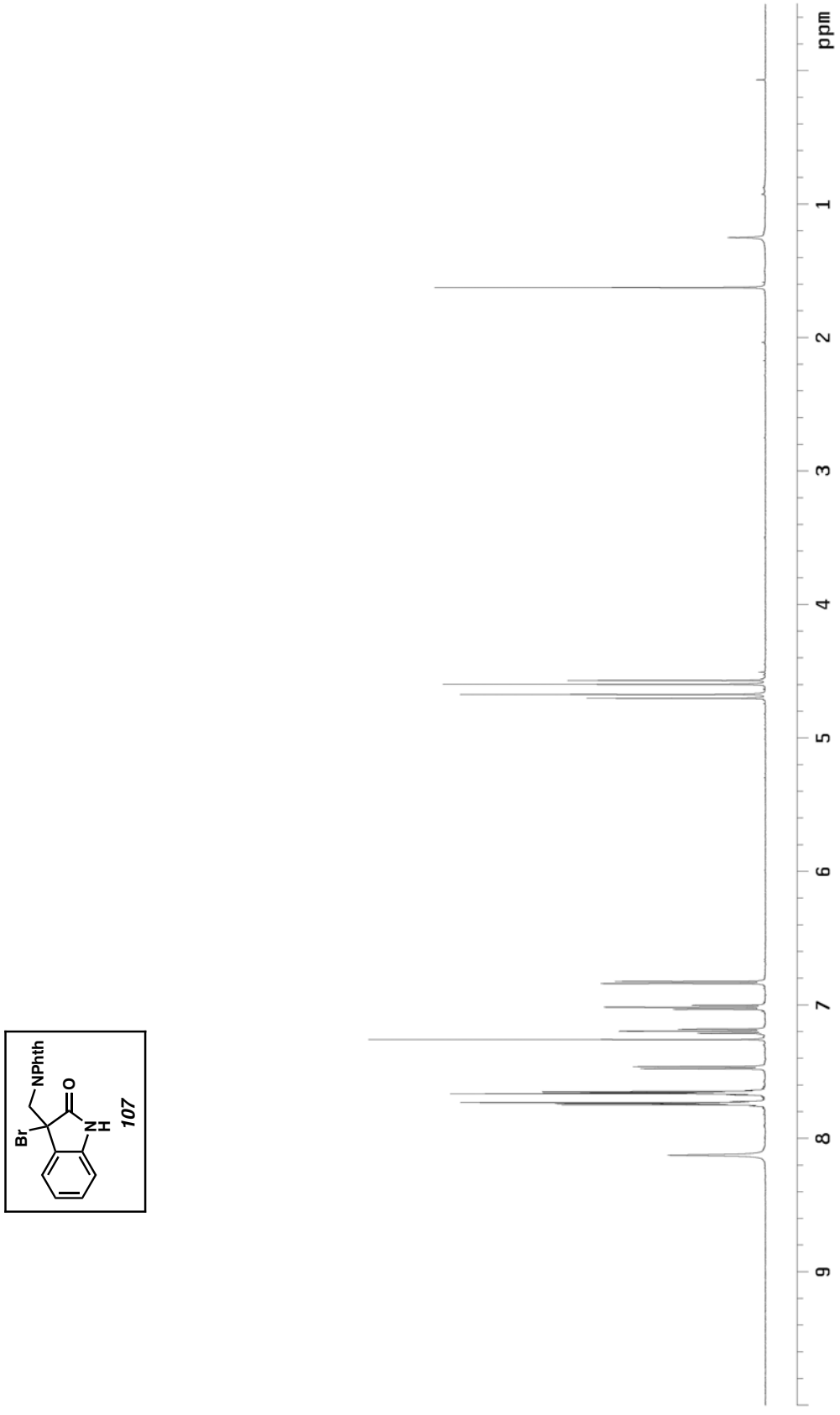


Figure A3.18.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **107**.

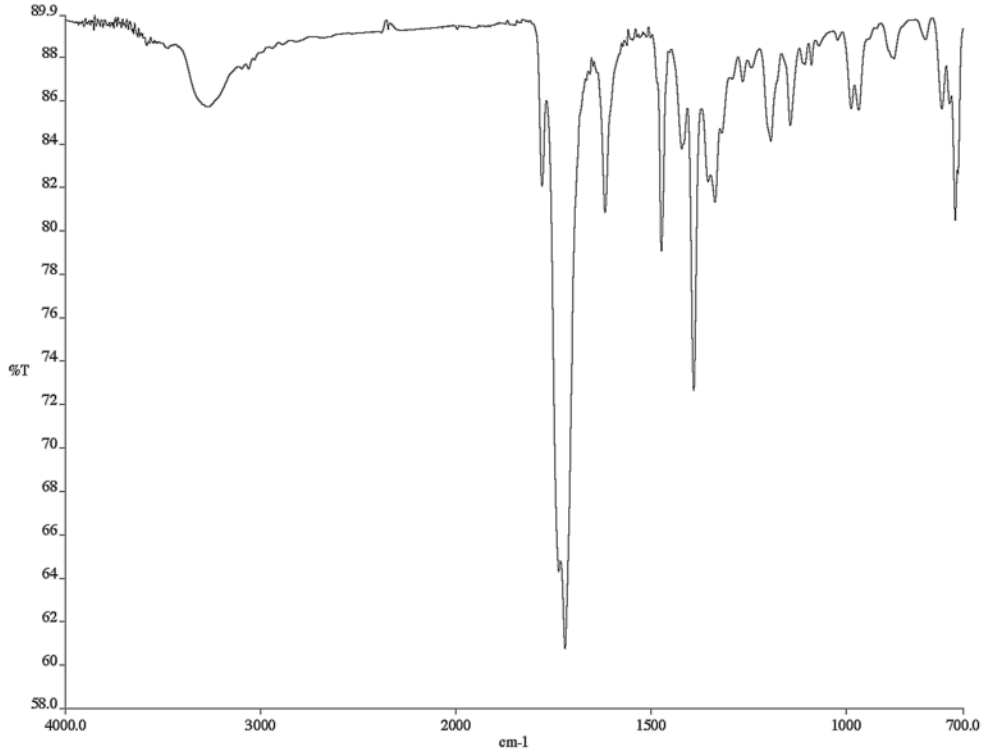


Figure A3.18.2 Infrared spectrum (thin film/NaCl) of compound **107**.

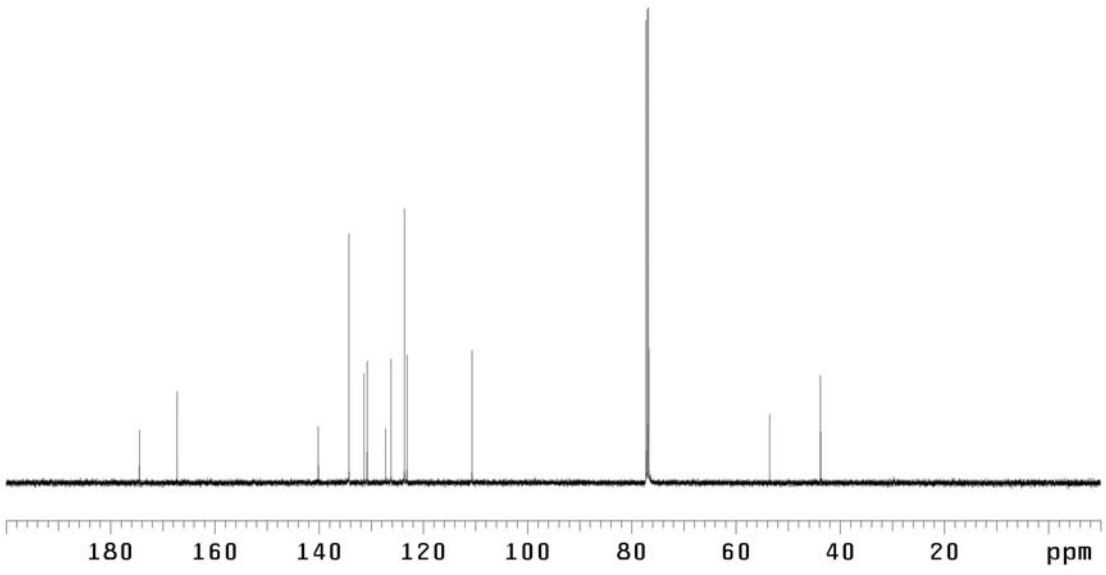


Figure A3.18.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **107**.

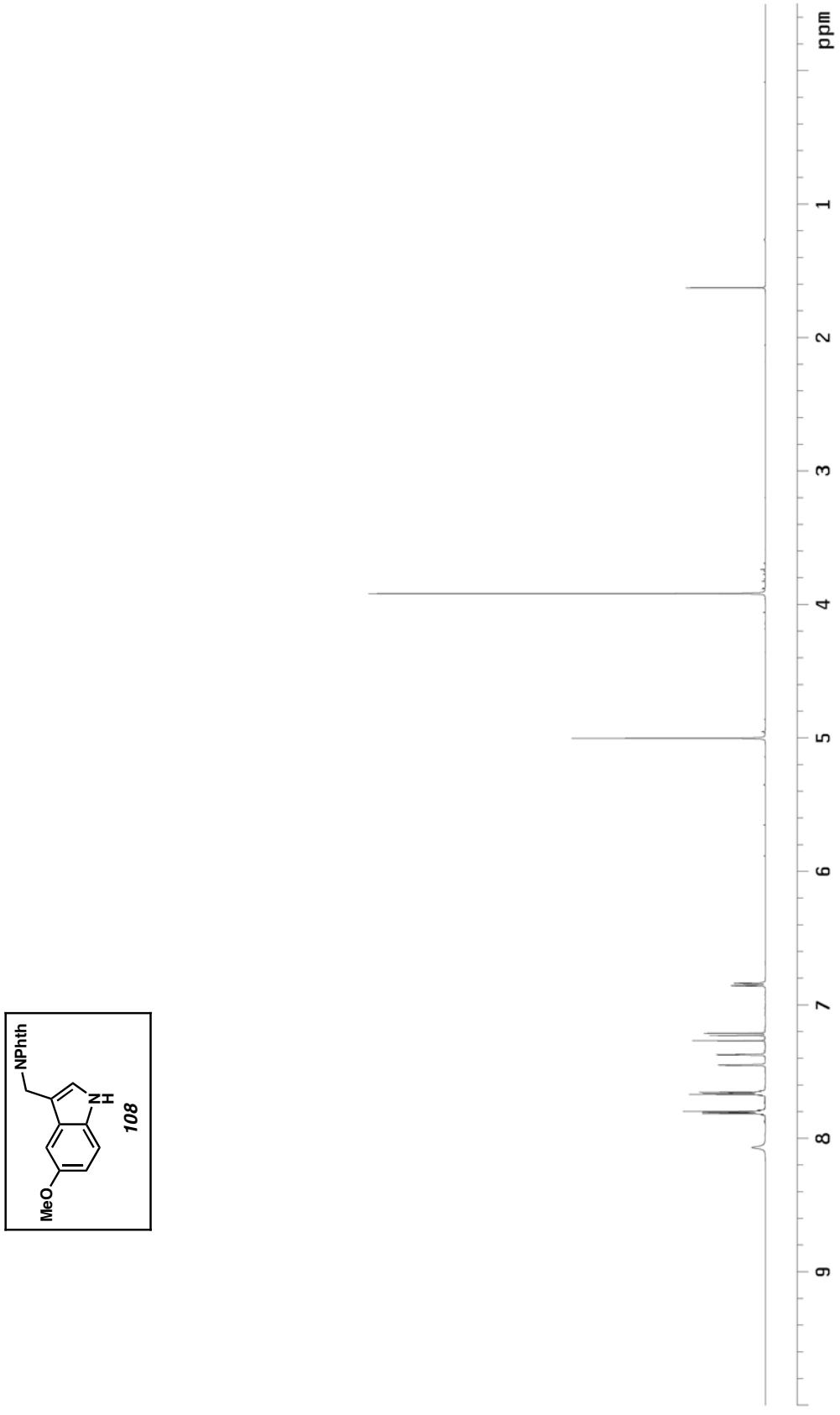


Figure A3.19.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **108**.

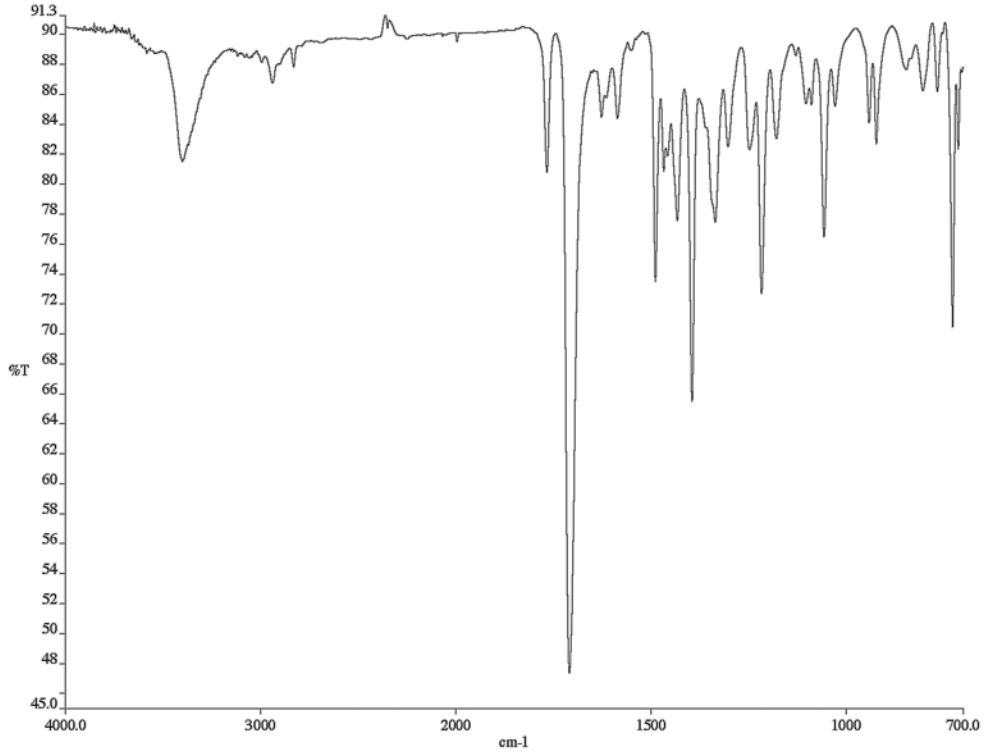


Figure A3.19.2 Infrared spectrum (thin film/NaCl) of compound **108**.

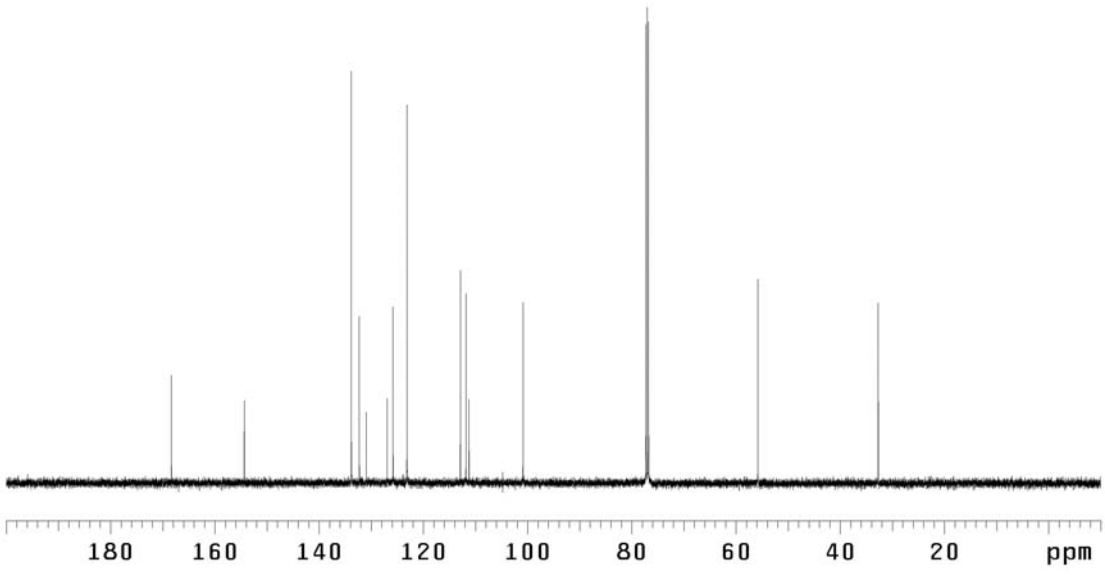


Figure A3.19.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **108**.

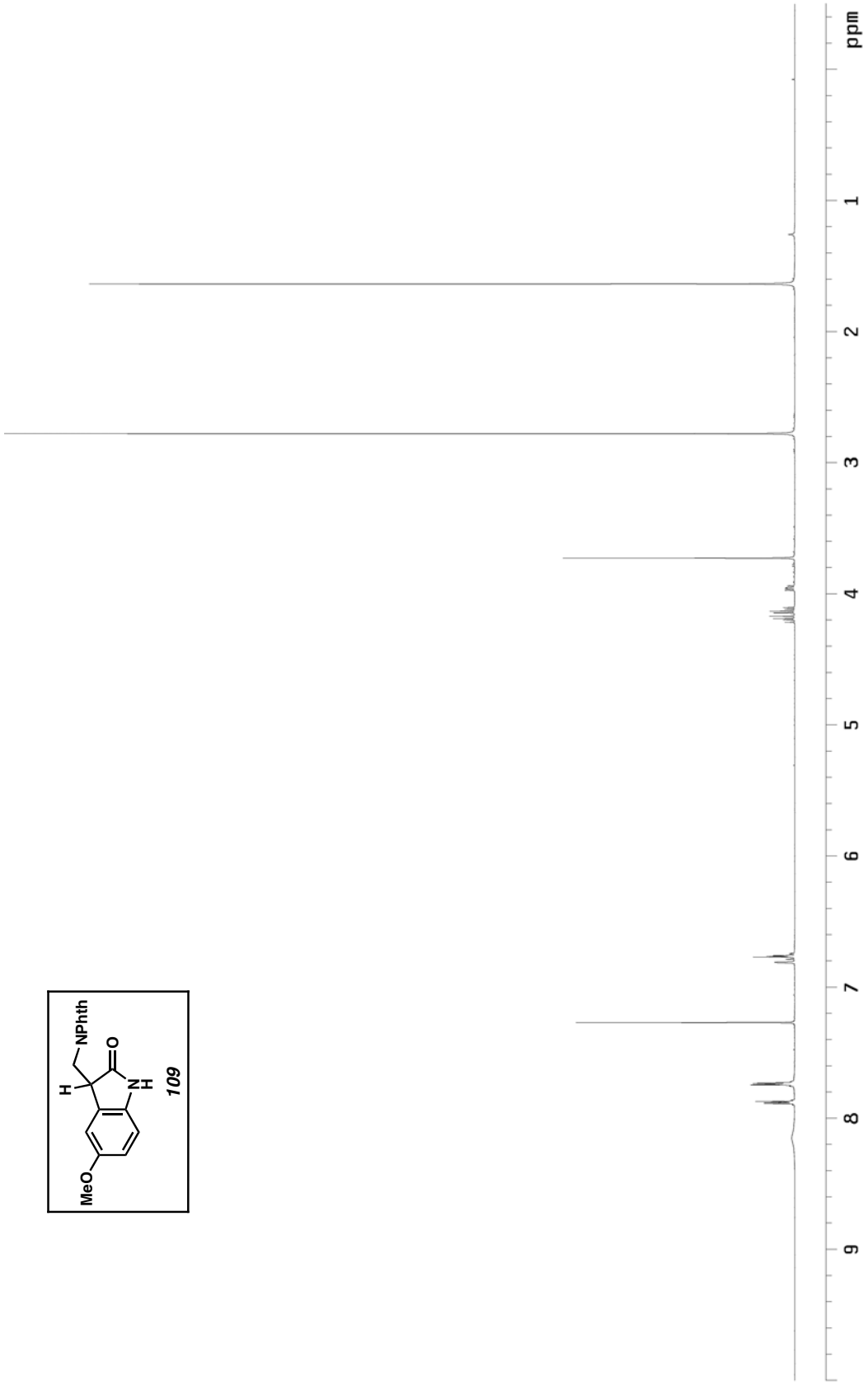


Figure A3.20.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **109** with succinimide impurity.

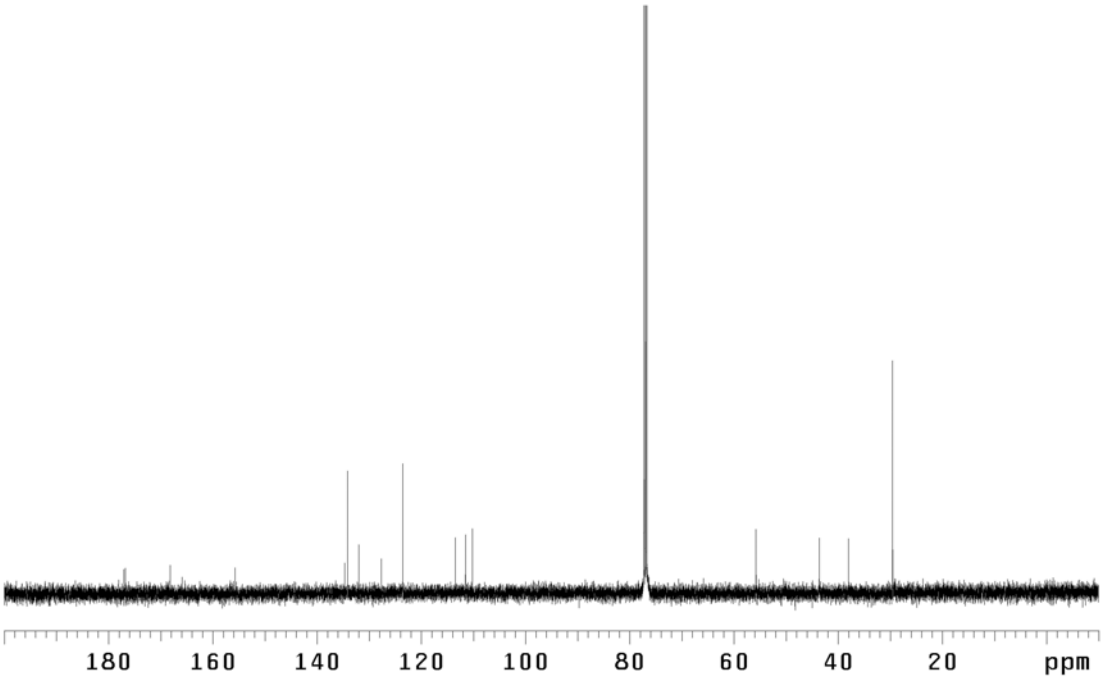


Figure A3.20.2 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **109** with succinimide impurity.

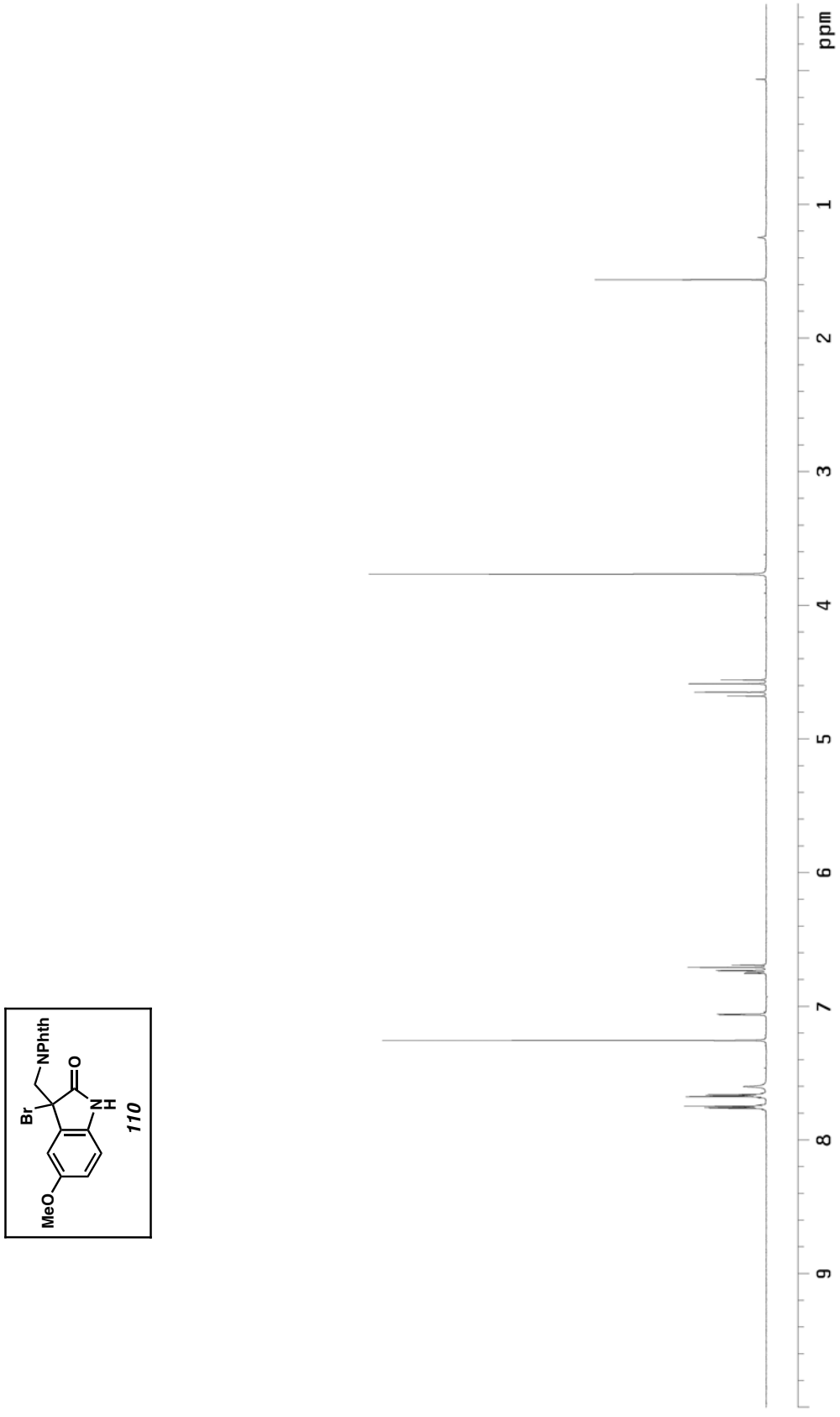


Figure A3.21.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **110**.

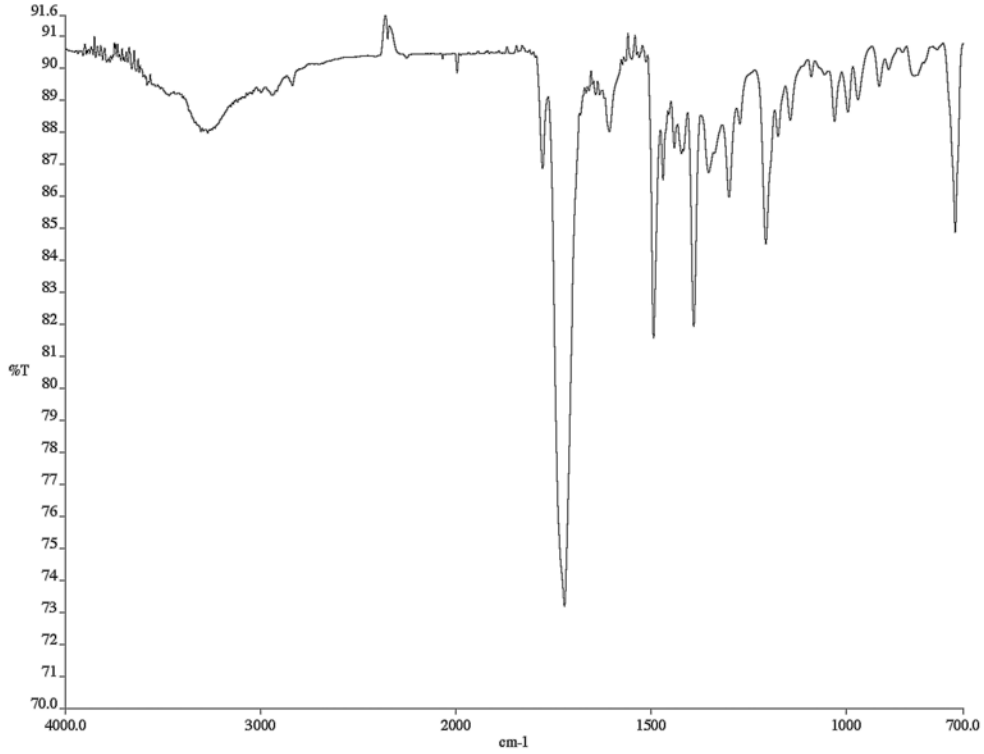


Figure A3.21.2 Infrared spectrum (thin film/NaCl) of compound **110**.

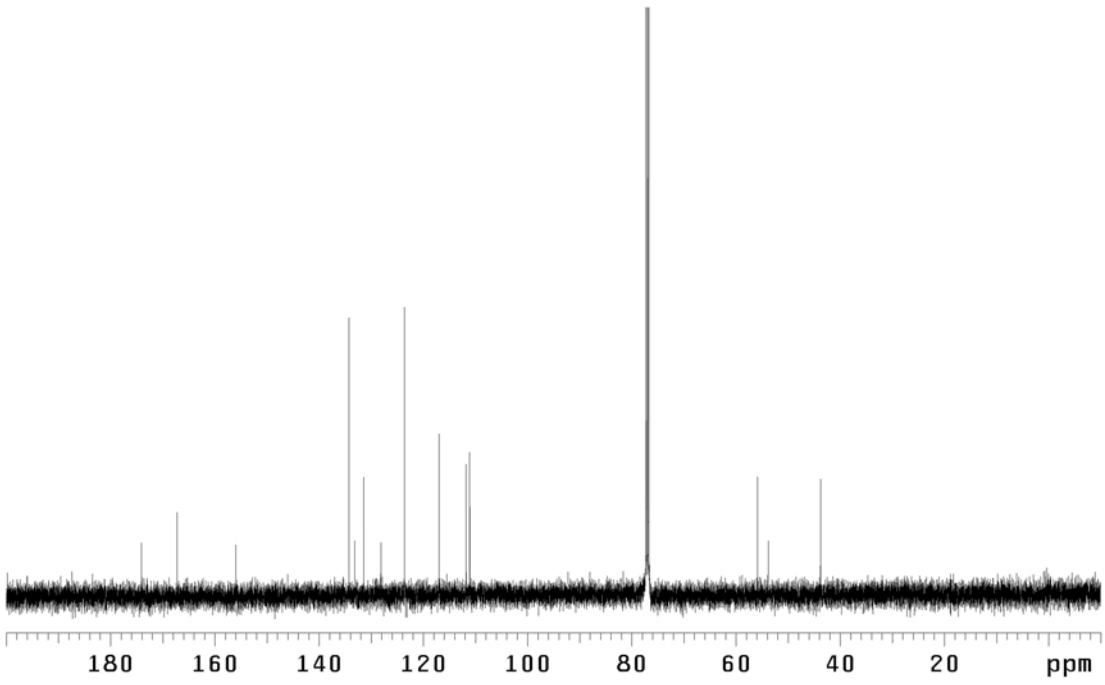
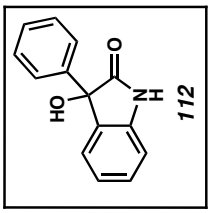


Figure A3.21.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **110**.



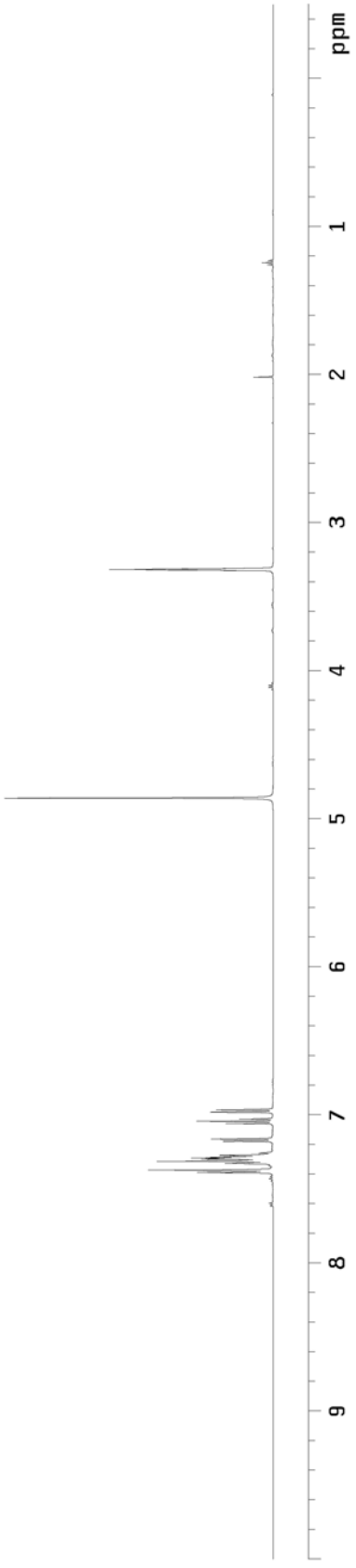


Figure A3.22.1 ^{1}H NMR (500 MHz, CD_3OD) of compound **112**.

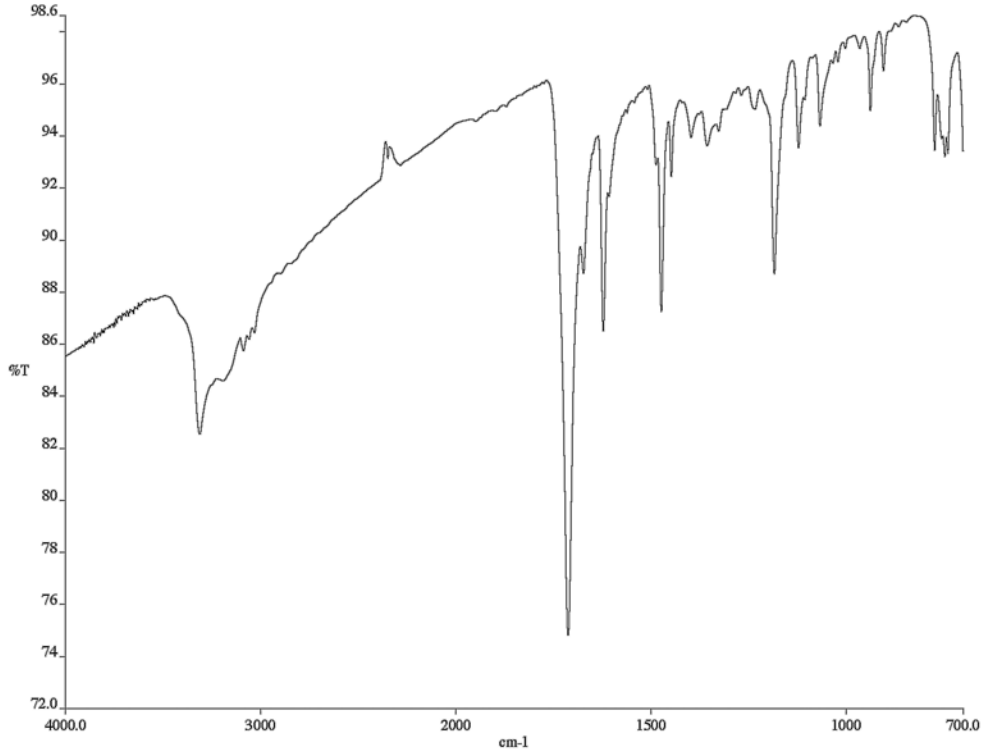


Figure A3.22.2 Infrared spectrum (thin film/NaCl) of compound **112**.

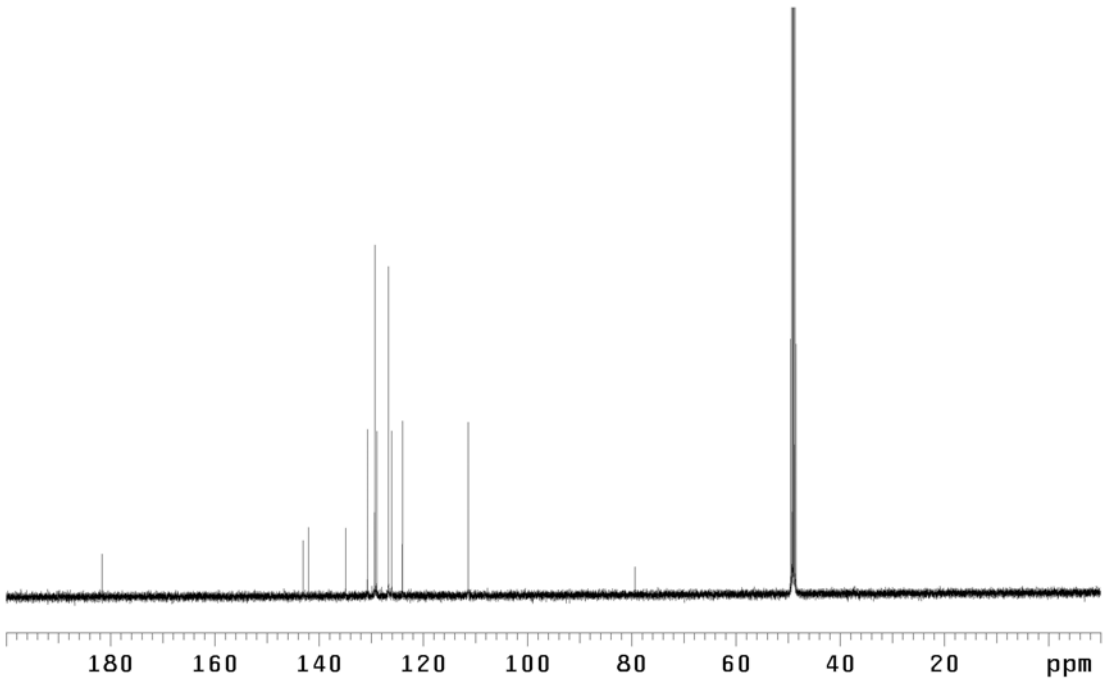
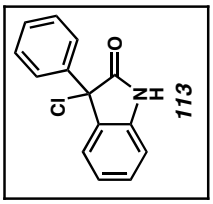


Figure A3.22.3 ^{13}C NMR (125 MHz, CD_3OD) of compound **112**.



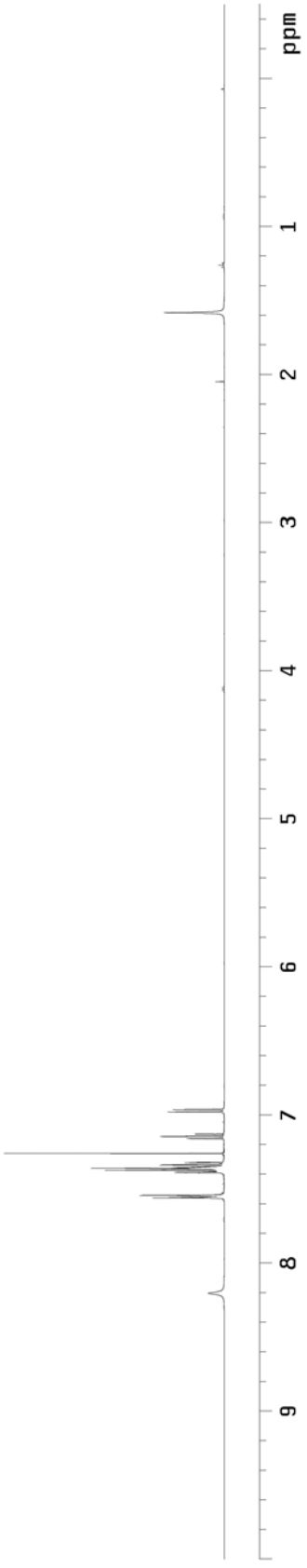


Figure A3.23.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **113**.

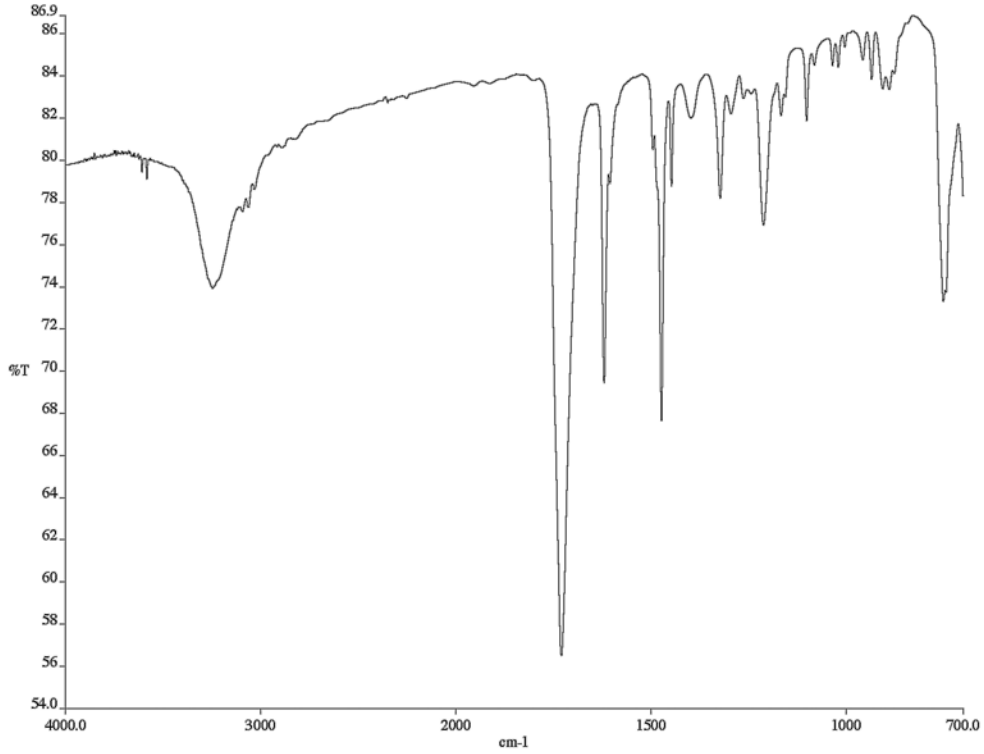


Figure A3.23.2 Infrared spectrum (thin film/NaCl) of compound **113**.

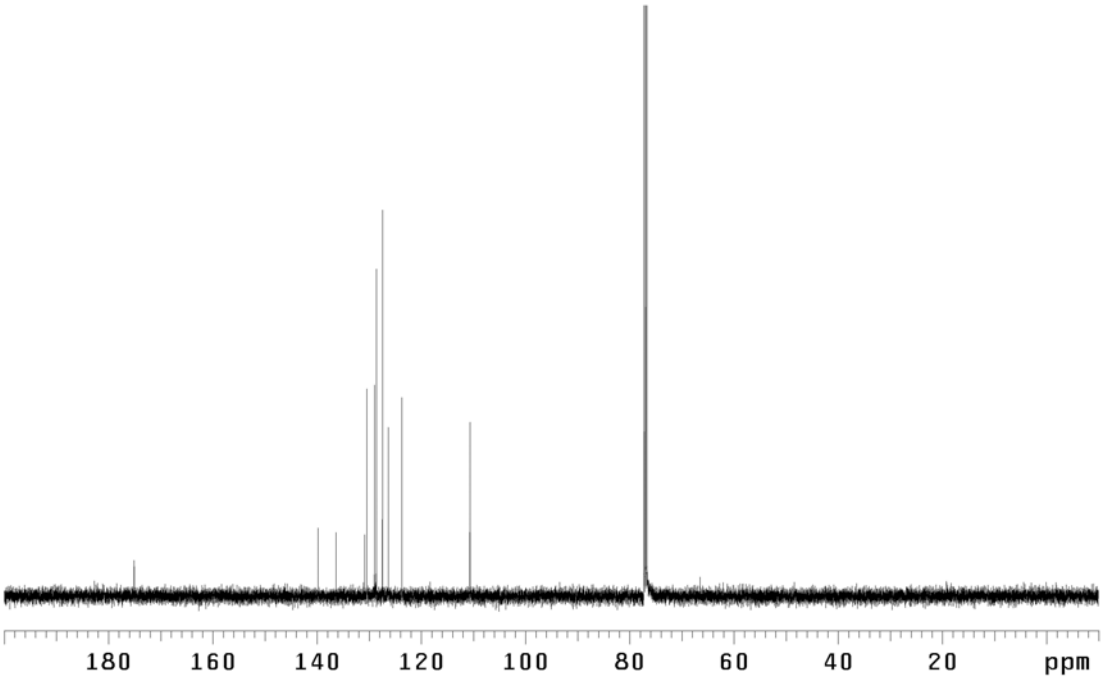


Figure A3.23.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **113**.

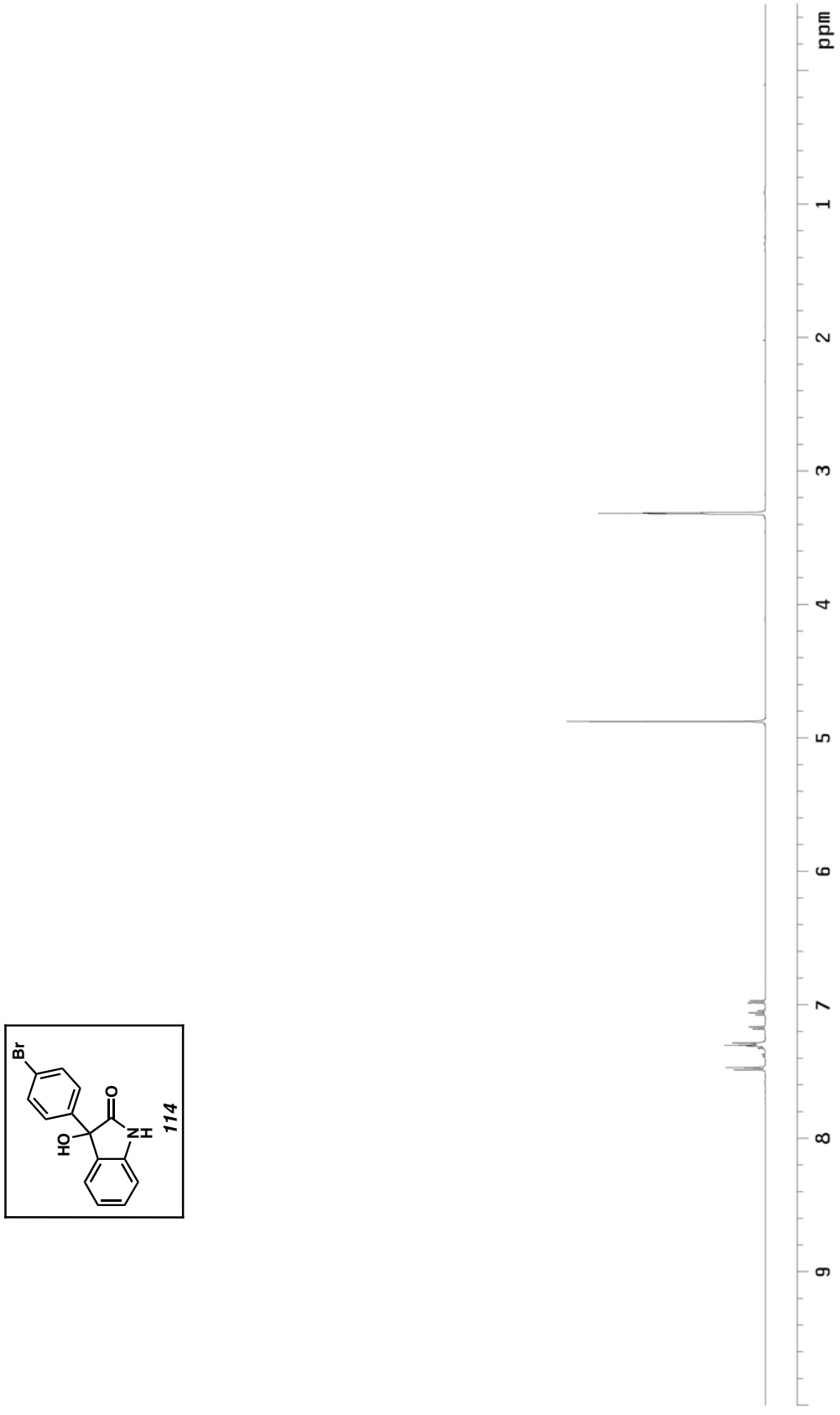


Figure A3.24.1 ^{1}H NMR (500 MHz, CD_3OD) of compound **114**.

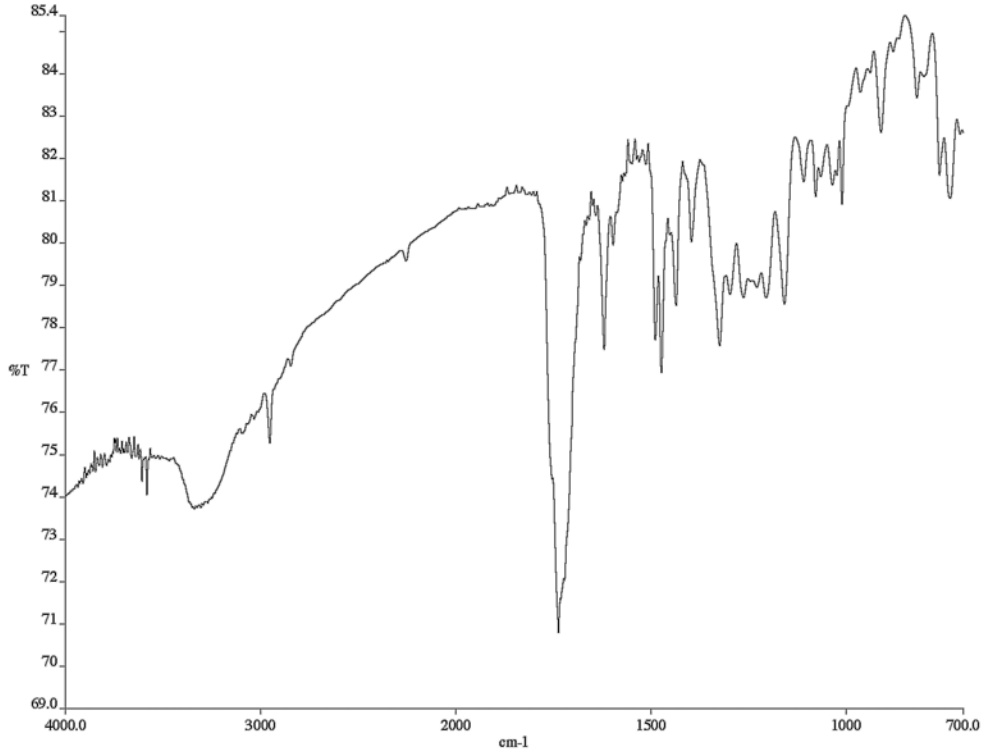


Figure A3.24.2 Infrared spectrum (thin film/NaCl) of compound **114**.

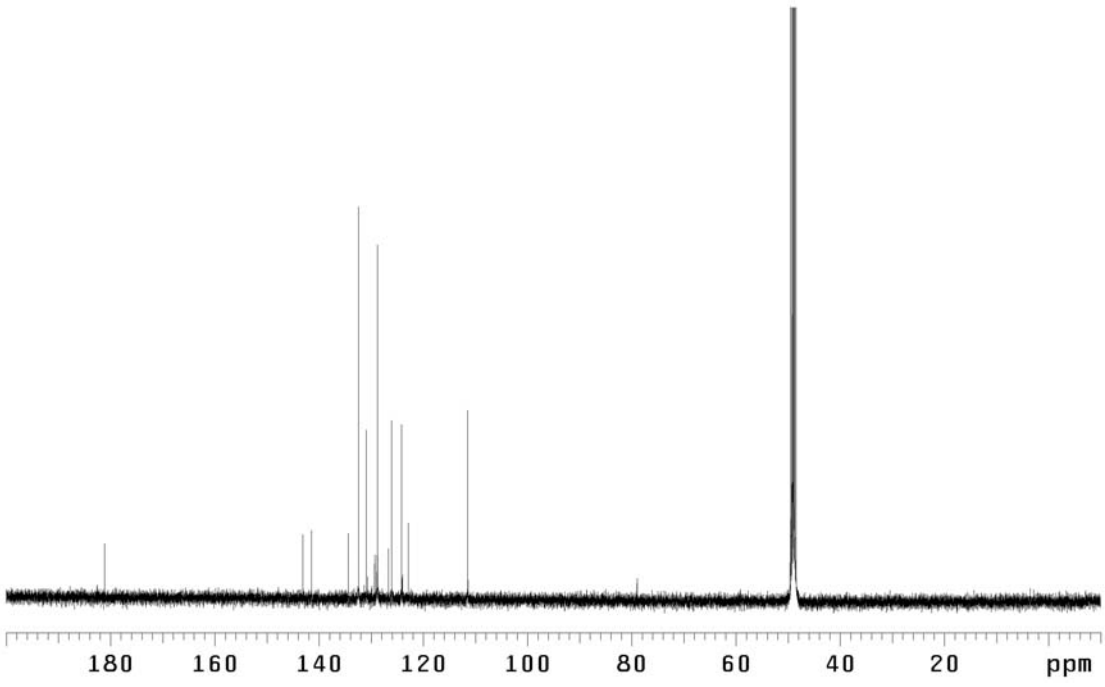
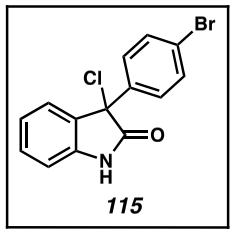


Figure A3.24.3 ^{13}C NMR (125 MHz, CD_3OD) of compound **114**.



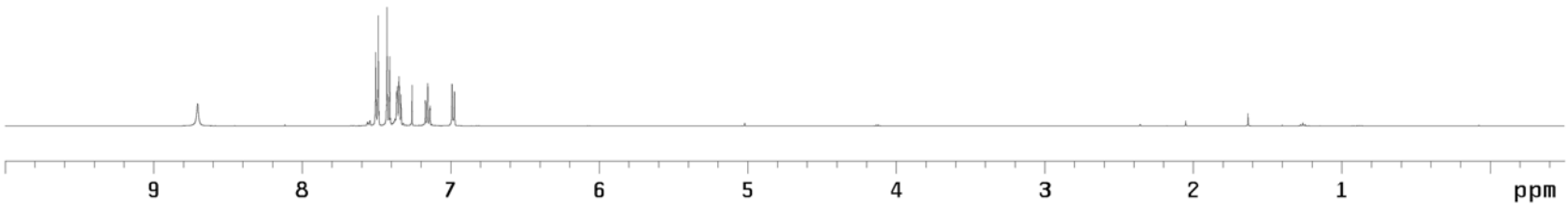


Figure A3.25.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **115**.

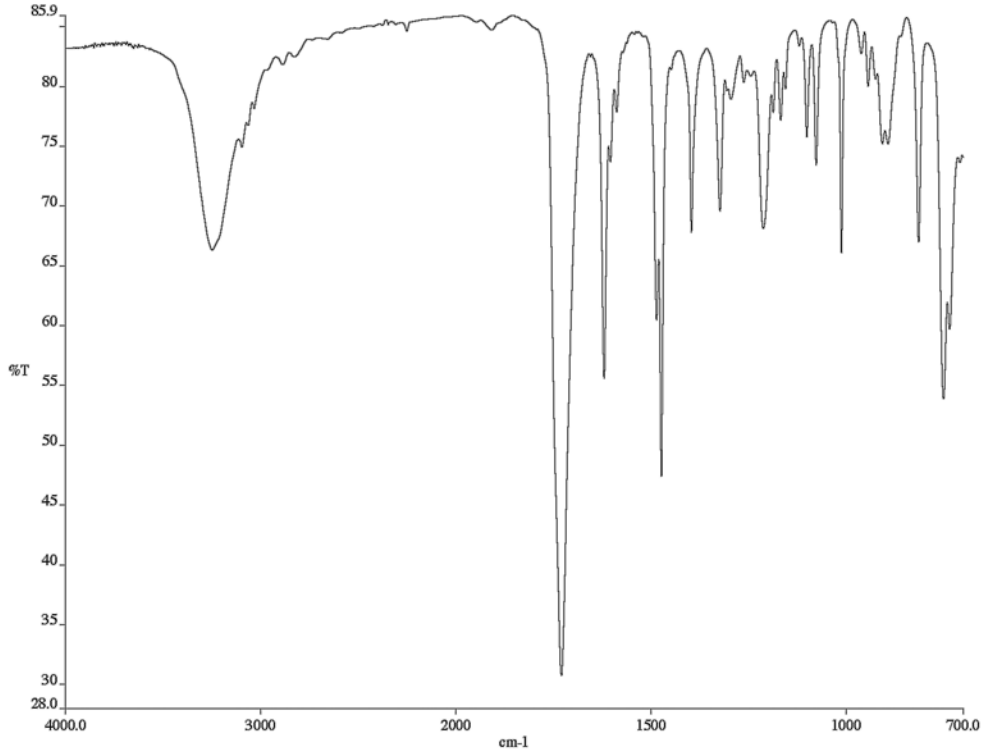


Figure A3.25.2 Infrared spectrum (thin film/NaCl) of compound **115**.

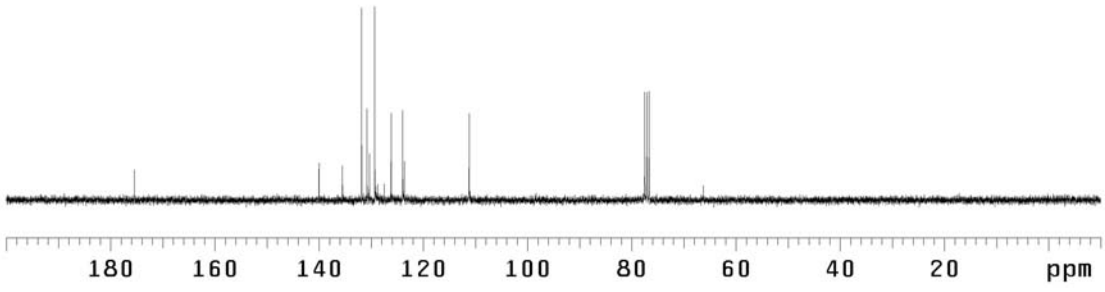
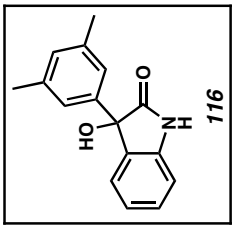


Figure A3.25.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **115**.



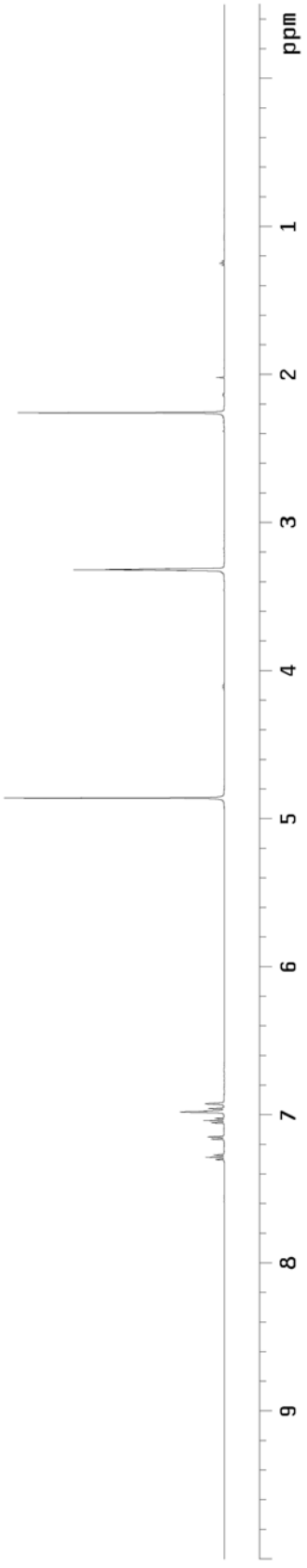


Figure A3.26.1 ^{1}H NMR (500 MHz, CD_3OD) of compound **116**.

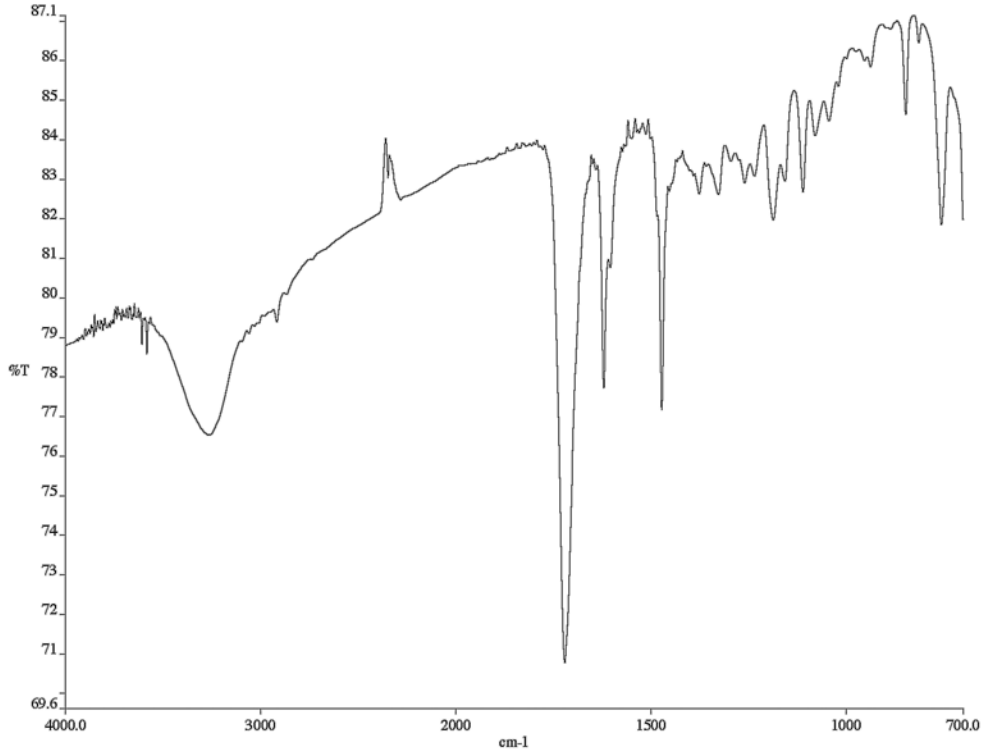


Figure A3.26.2 Infrared spectrum (thin film/NaCl) of compound **116**.

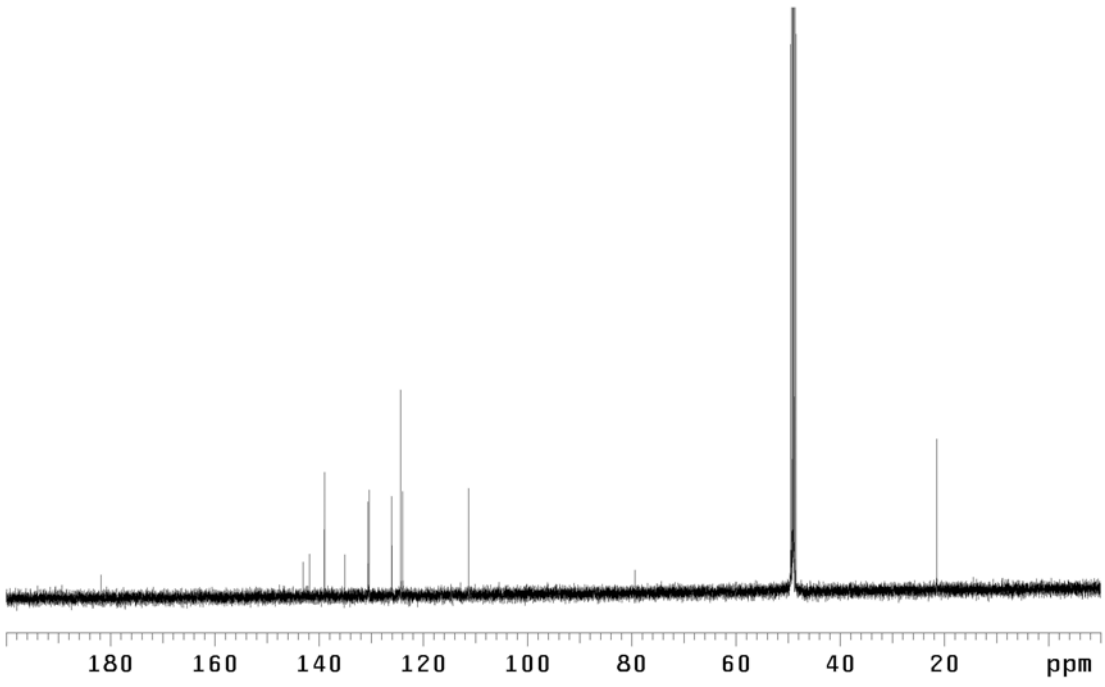
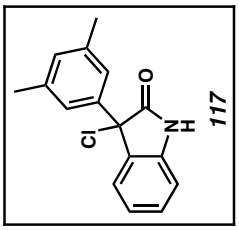


Figure A3.26.3 ^{13}C NMR (125 MHz, CD_3OD) of compound **116**.



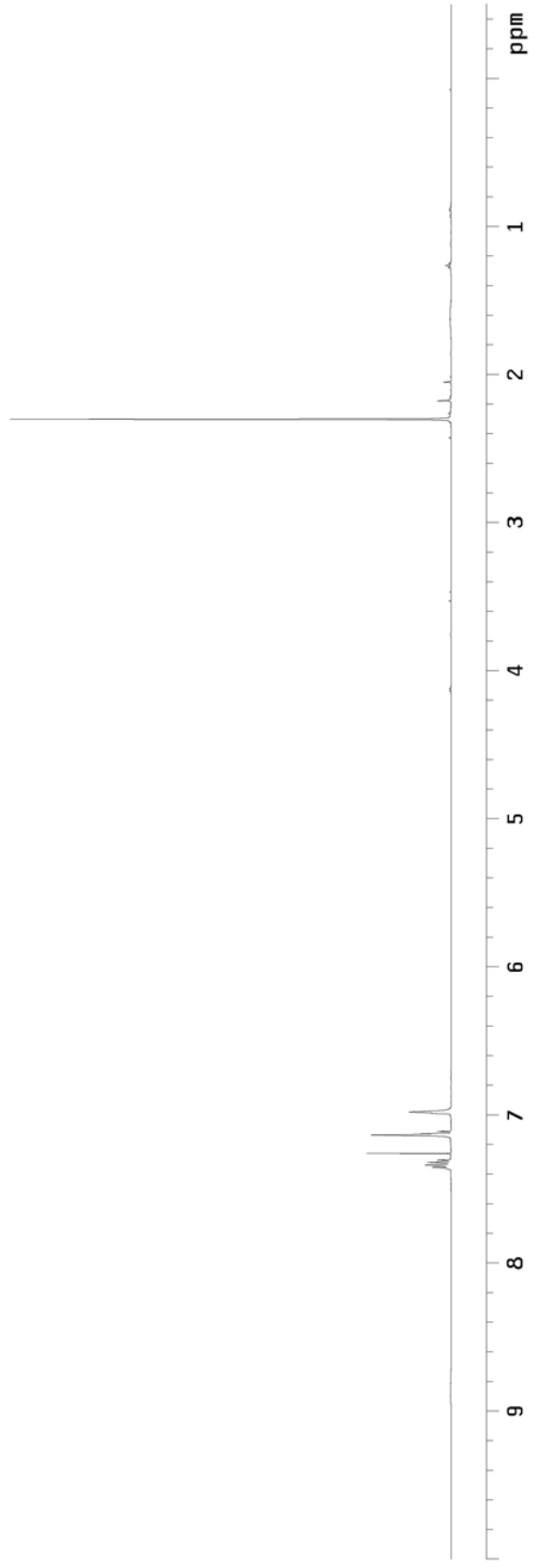


Figure A3.27.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **117**.

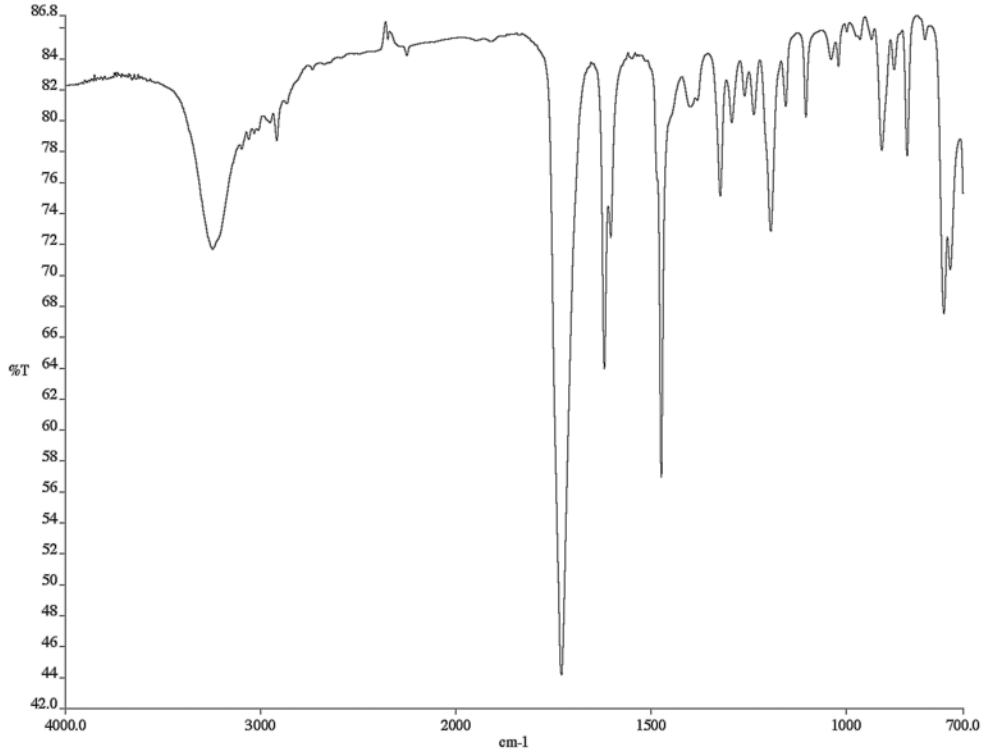


Figure A3.27.2 Infrared spectrum (thin film/NaCl) of compound **117**.

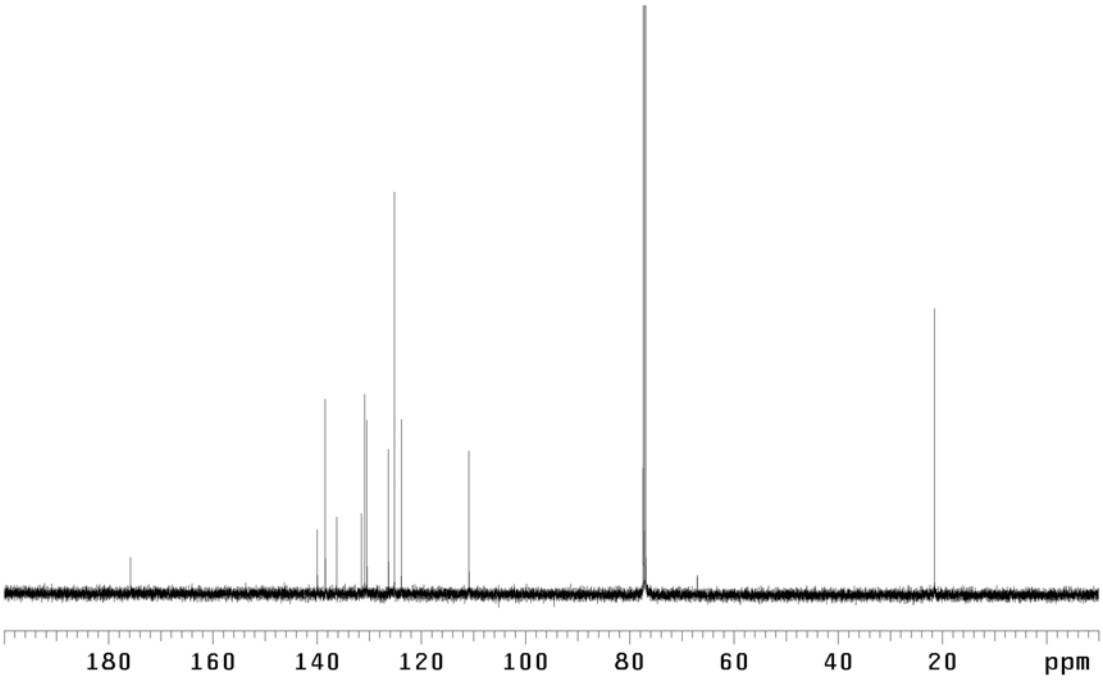


Figure A3.27.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **117**.

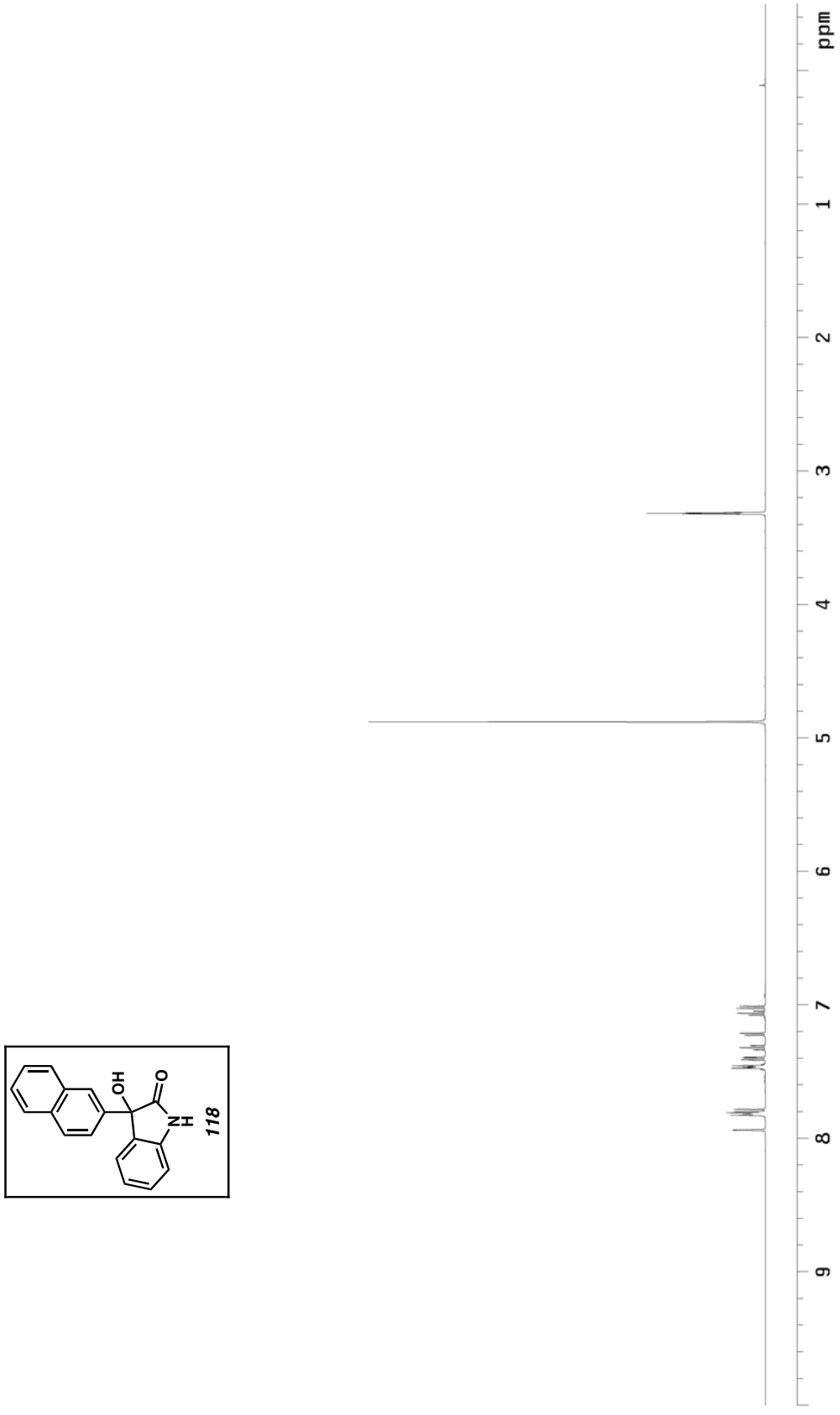


Figure A3.28.1 ^{1}H NMR (500 MHz, CD_3OD) of compound **118**.

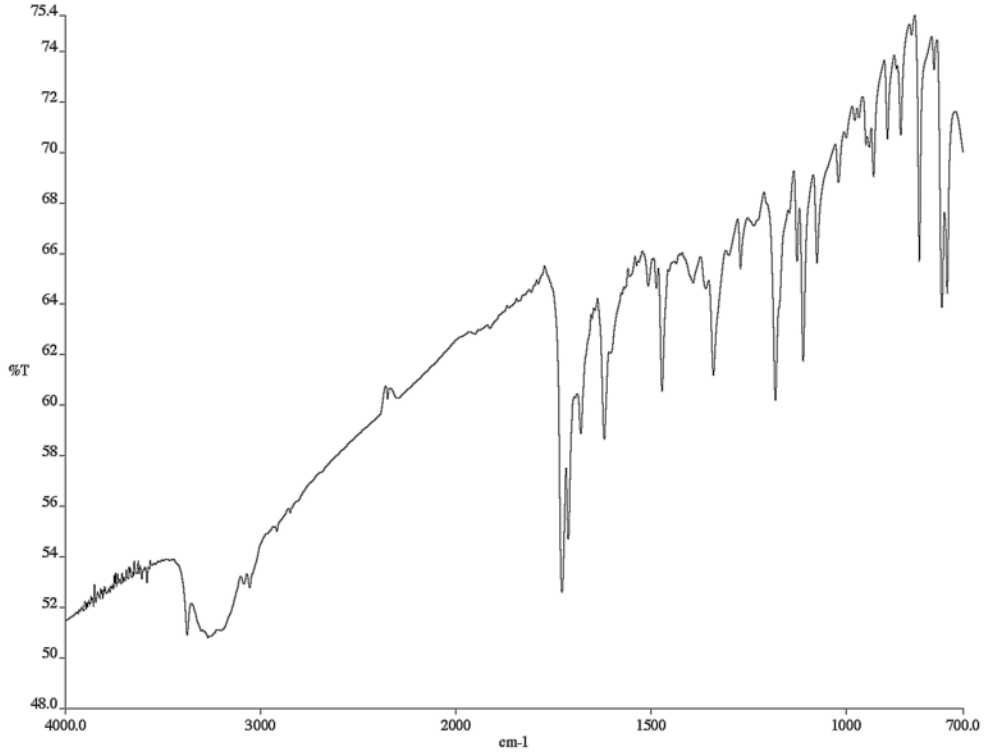


Figure A3.28.2 Infrared spectrum (thin film/NaCl) of compound **118**.

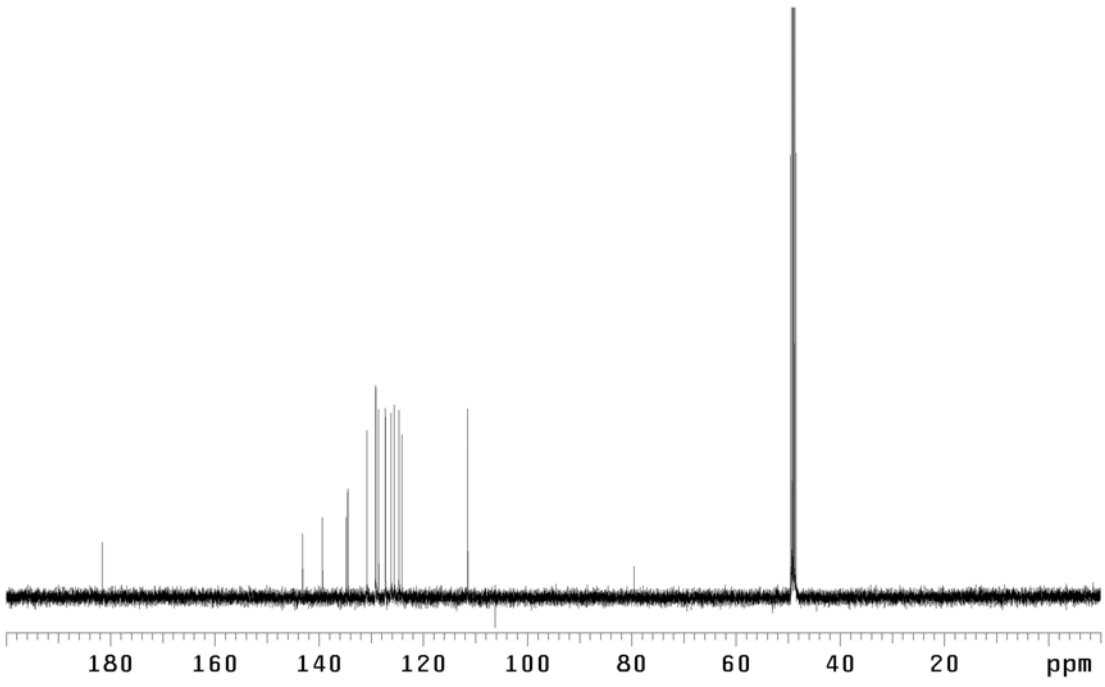
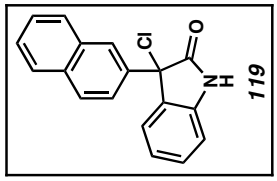


Figure A3.28.3 ^{13}C NMR (125 MHz, CD_3OD) of compound **118**.



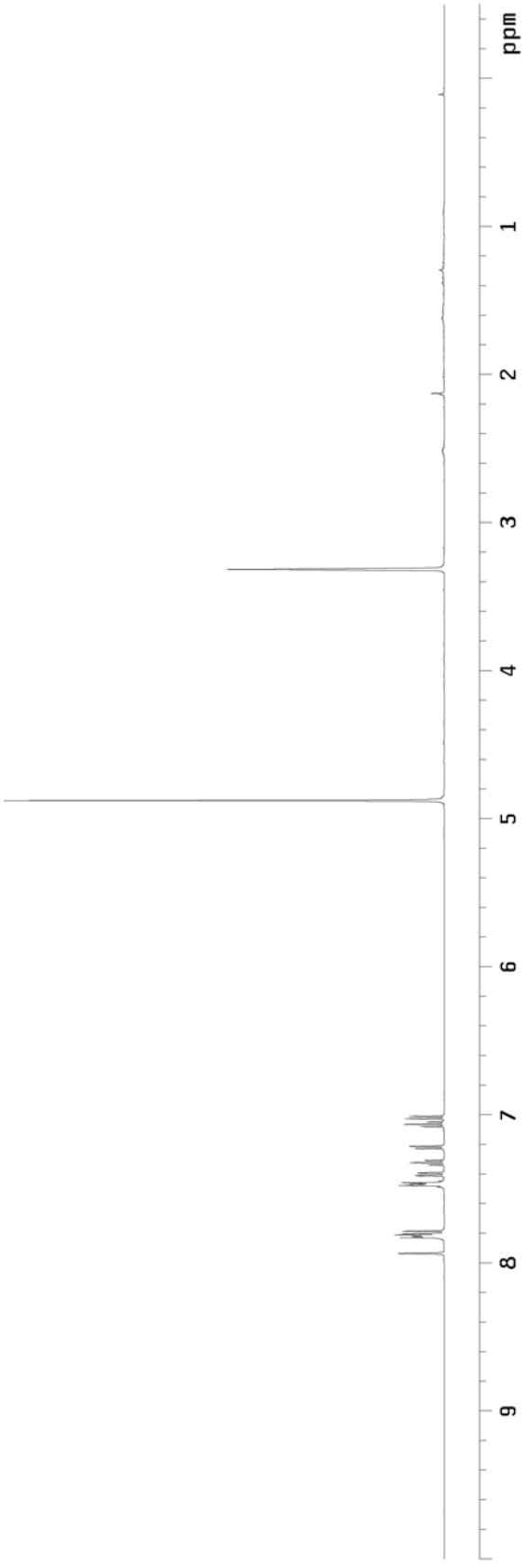


Figure A3.29.1 ^{1}H NMR (500 MHz, CD_3OD) of compound **119**.

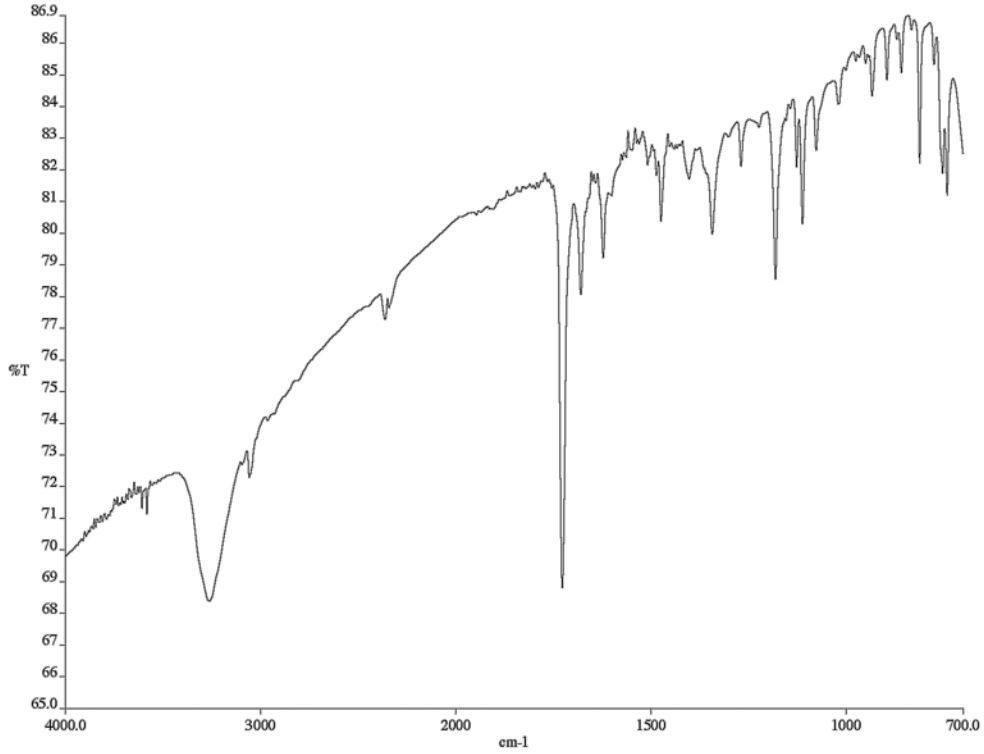


Figure A3.29.2 Infrared spectrum (thin film/NaCl) of compound **119**.

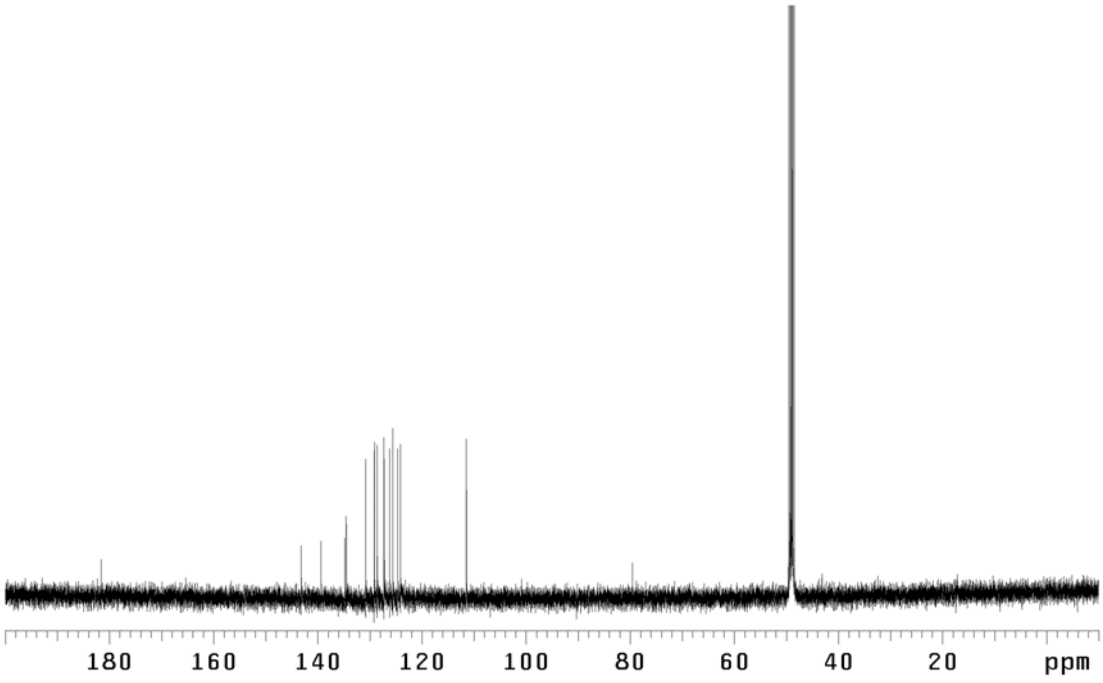
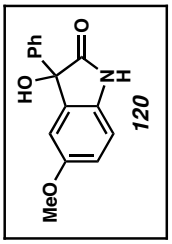


Figure A3.29.3 ^{13}C NMR (125 MHz, CD_3OD) of compound **119**.



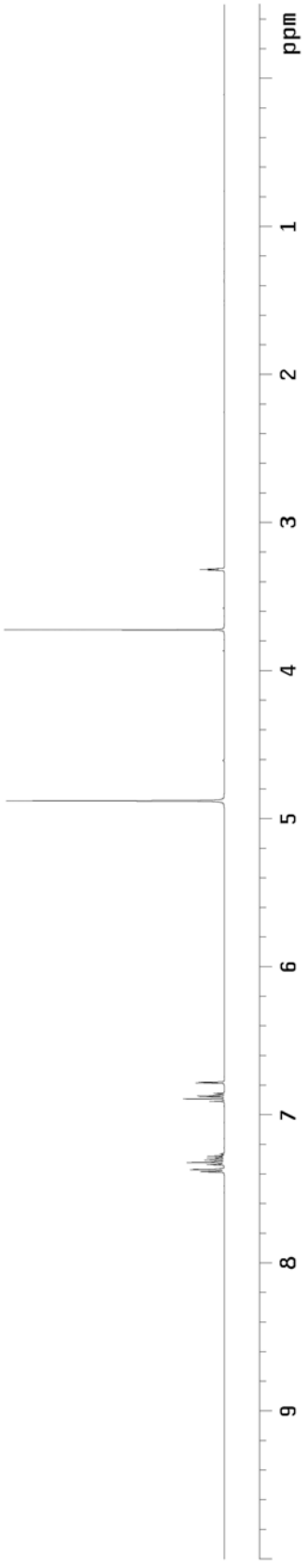


Figure A3.30.1 ^{1}H NMR (500 MHz, CD_3OD) of compound **120**.

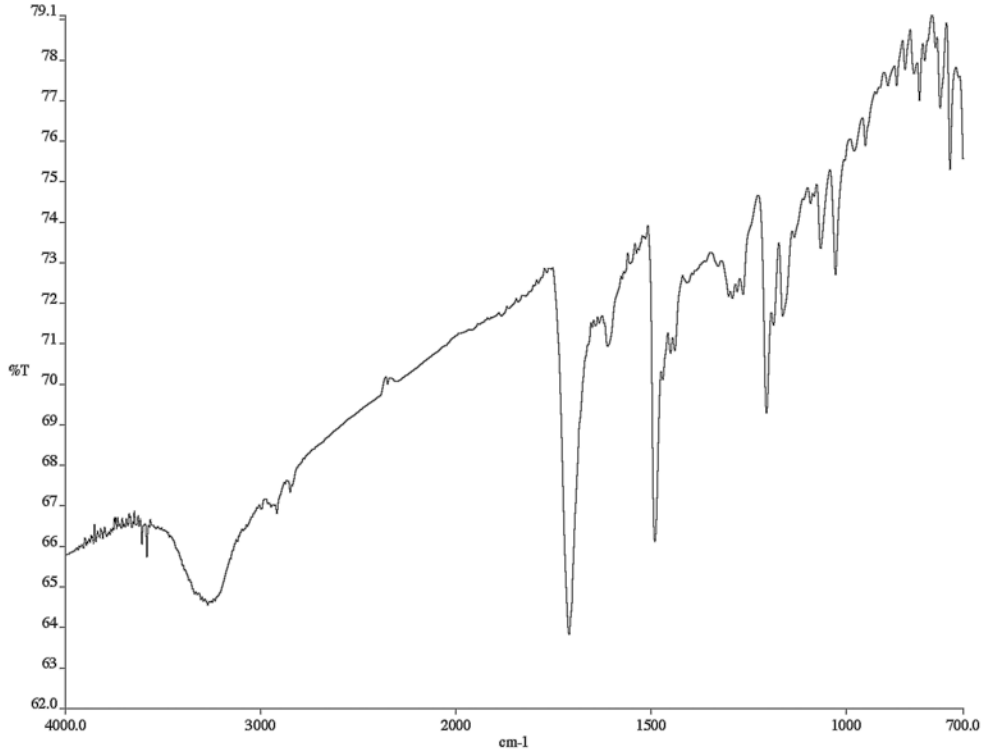


Figure A3.30.2 Infrared spectrum (thin film/NaCl) of compound **120**.

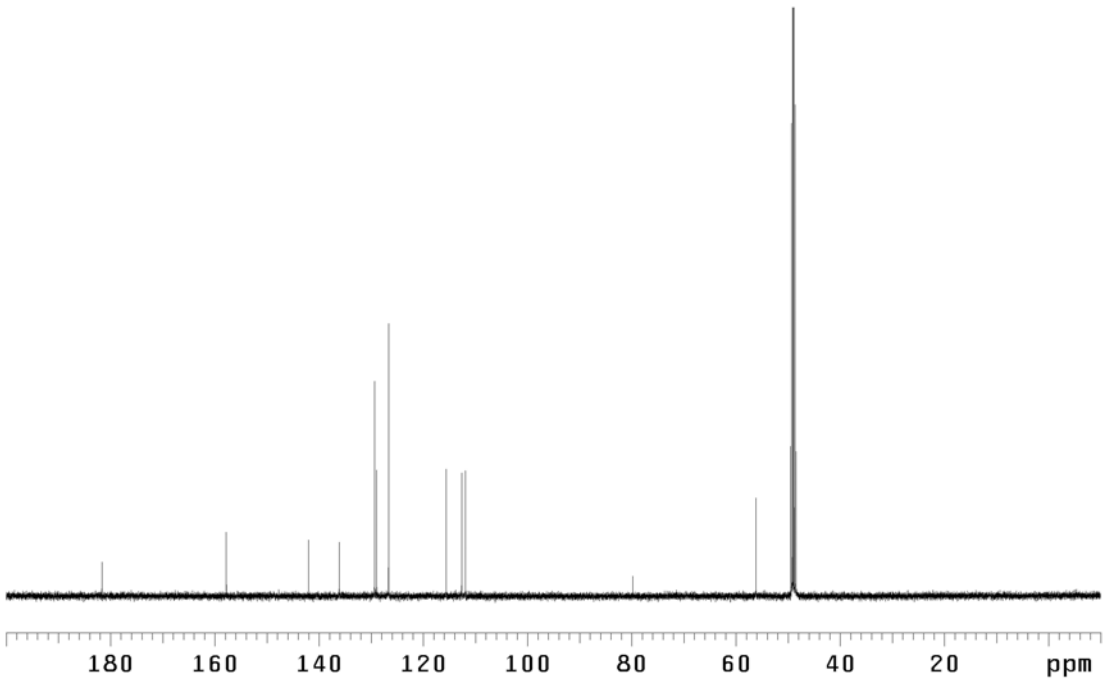


Figure A3.30.3 ^{13}C NMR (125 MHz, CD_3OD) of compound **120**.

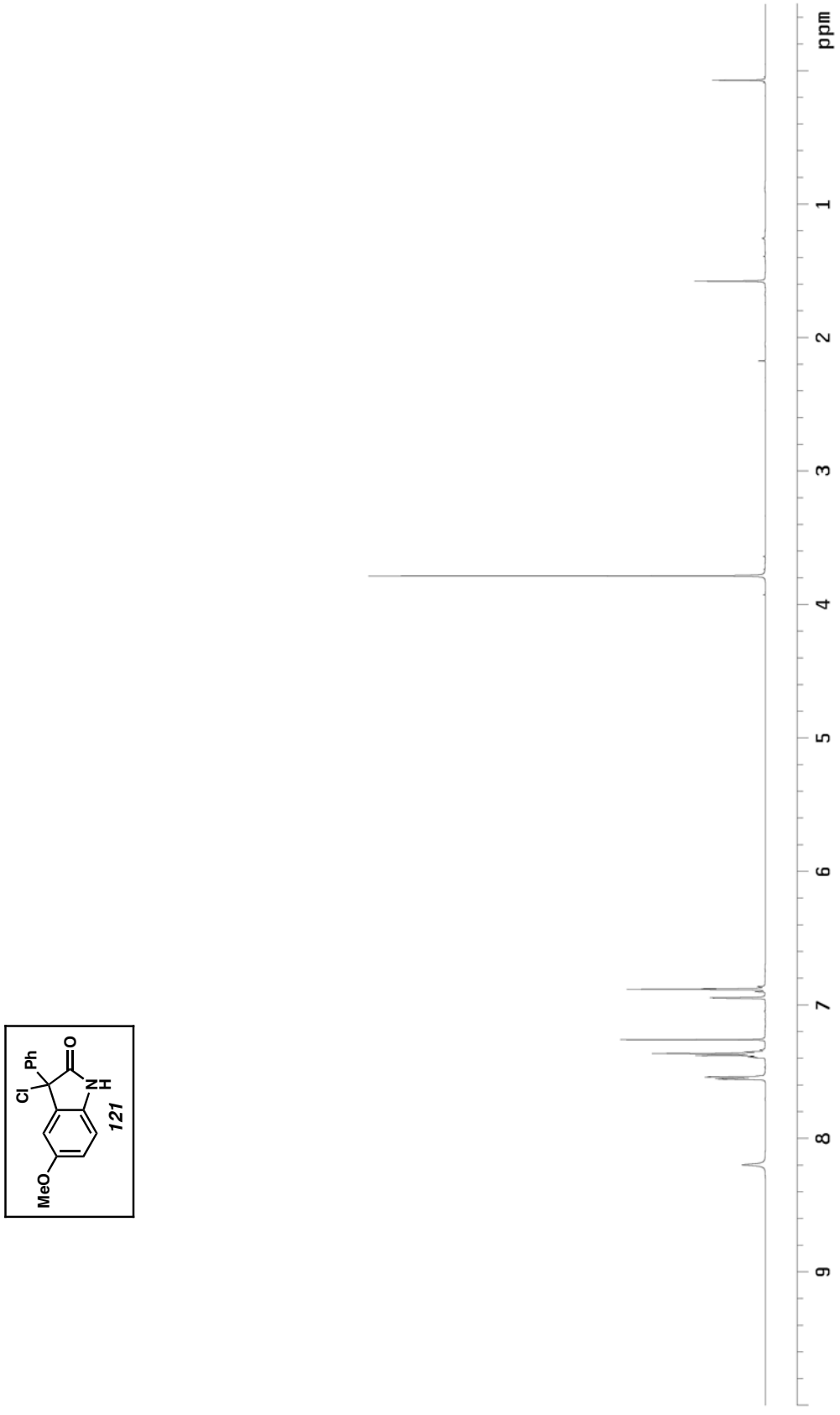


Figure A3.31.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **121**.

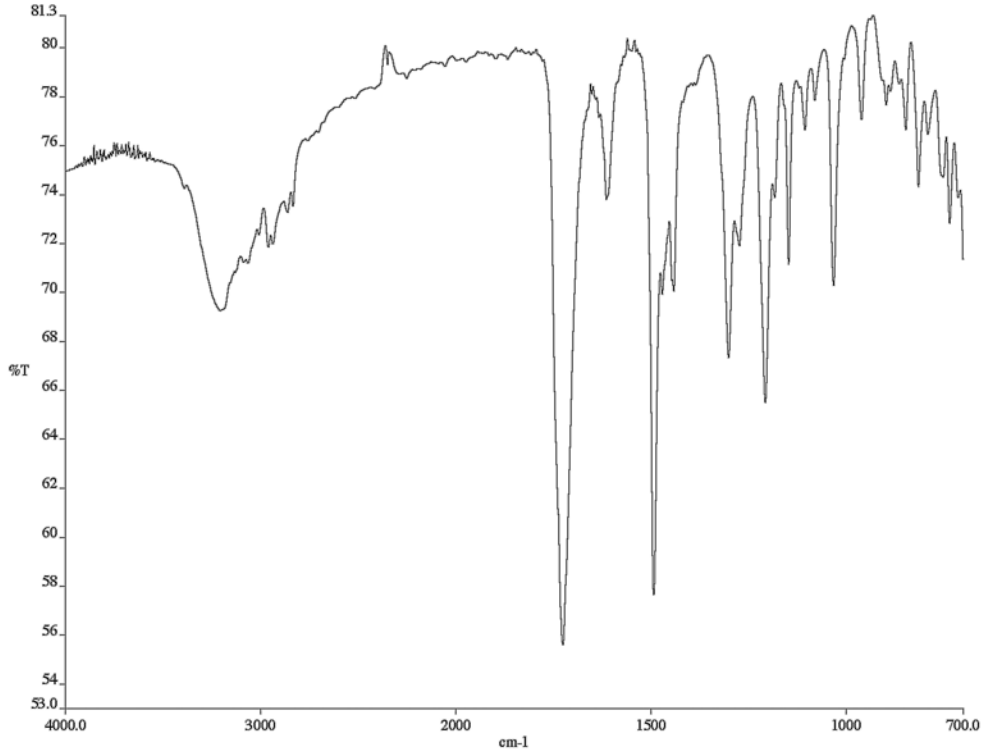


Figure A3.31.2 Infrared spectrum (thin film/NaCl) of compound **121**.

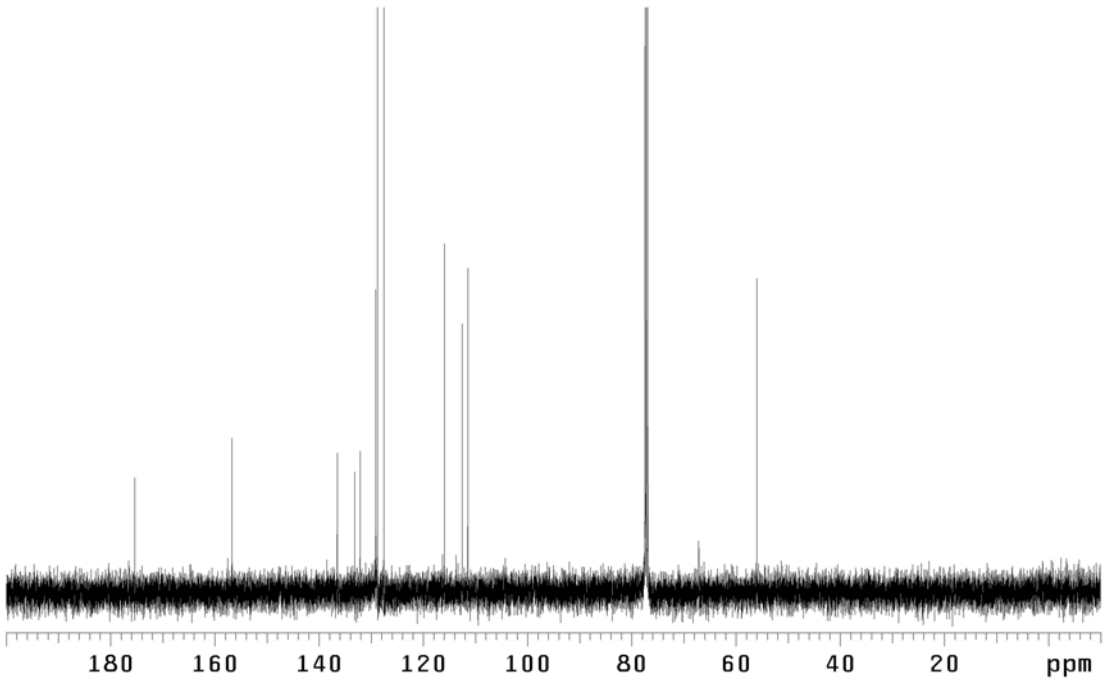


Figure A3.31.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **121**.

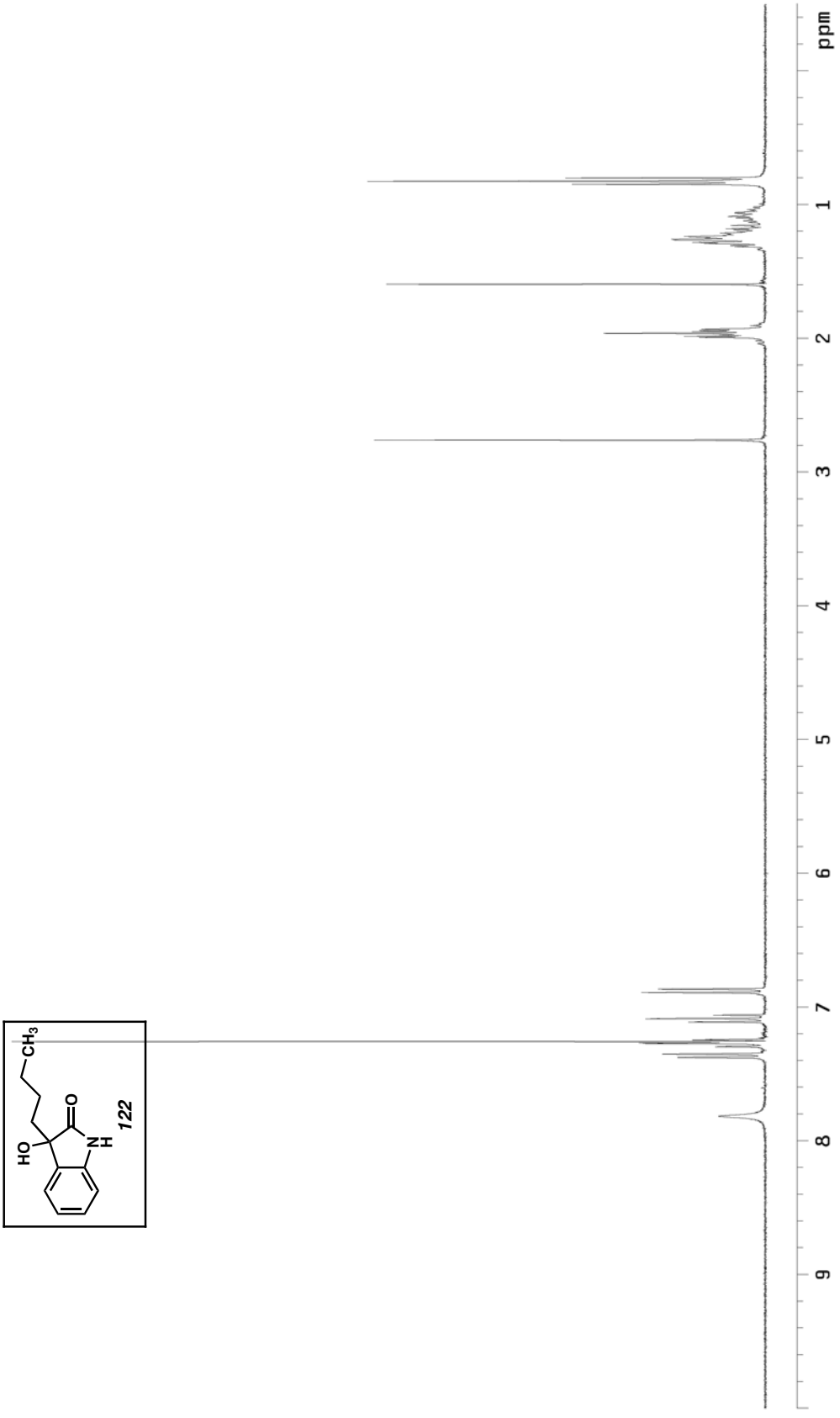


Figure A3.32.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **122**.

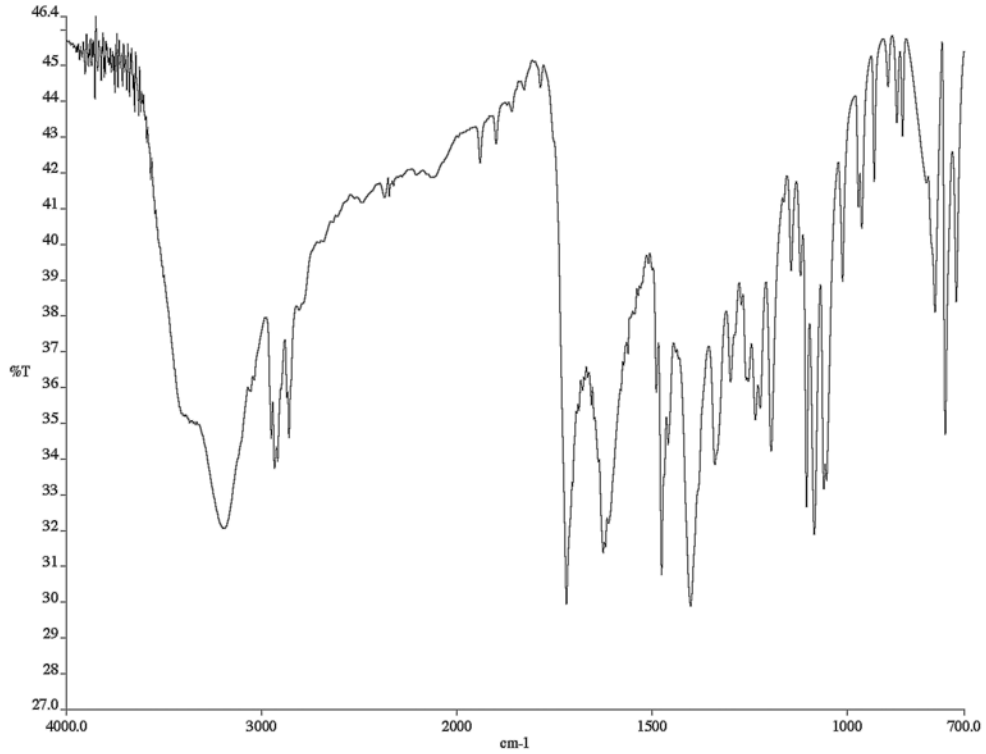


Figure A3.32.2 Infrared spectrum (thin film/NaCl) of compound **122**.

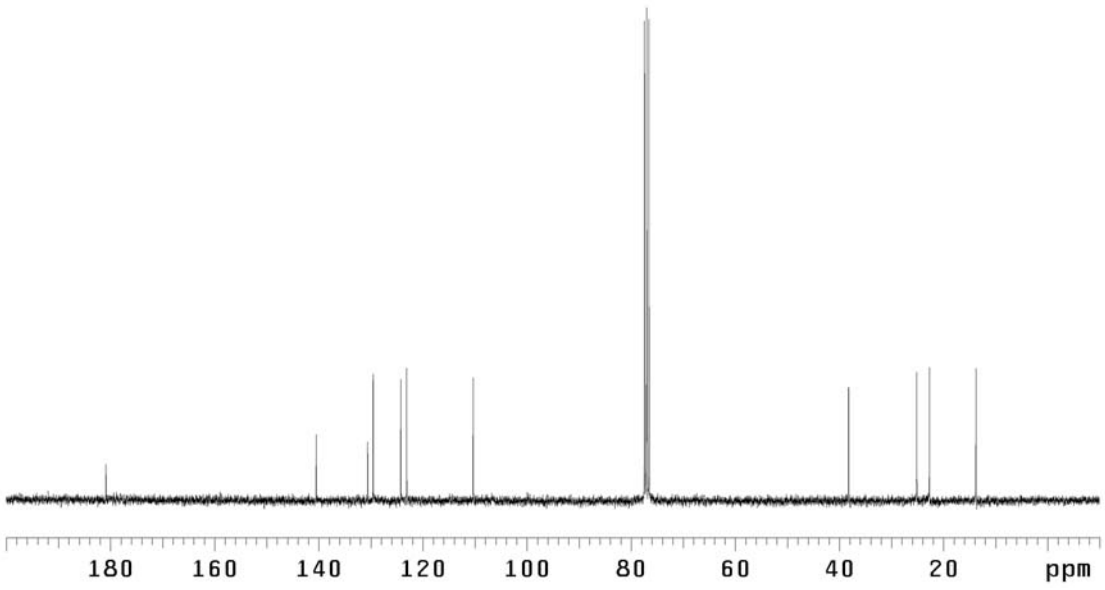


Figure A3.32.3 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **122**.

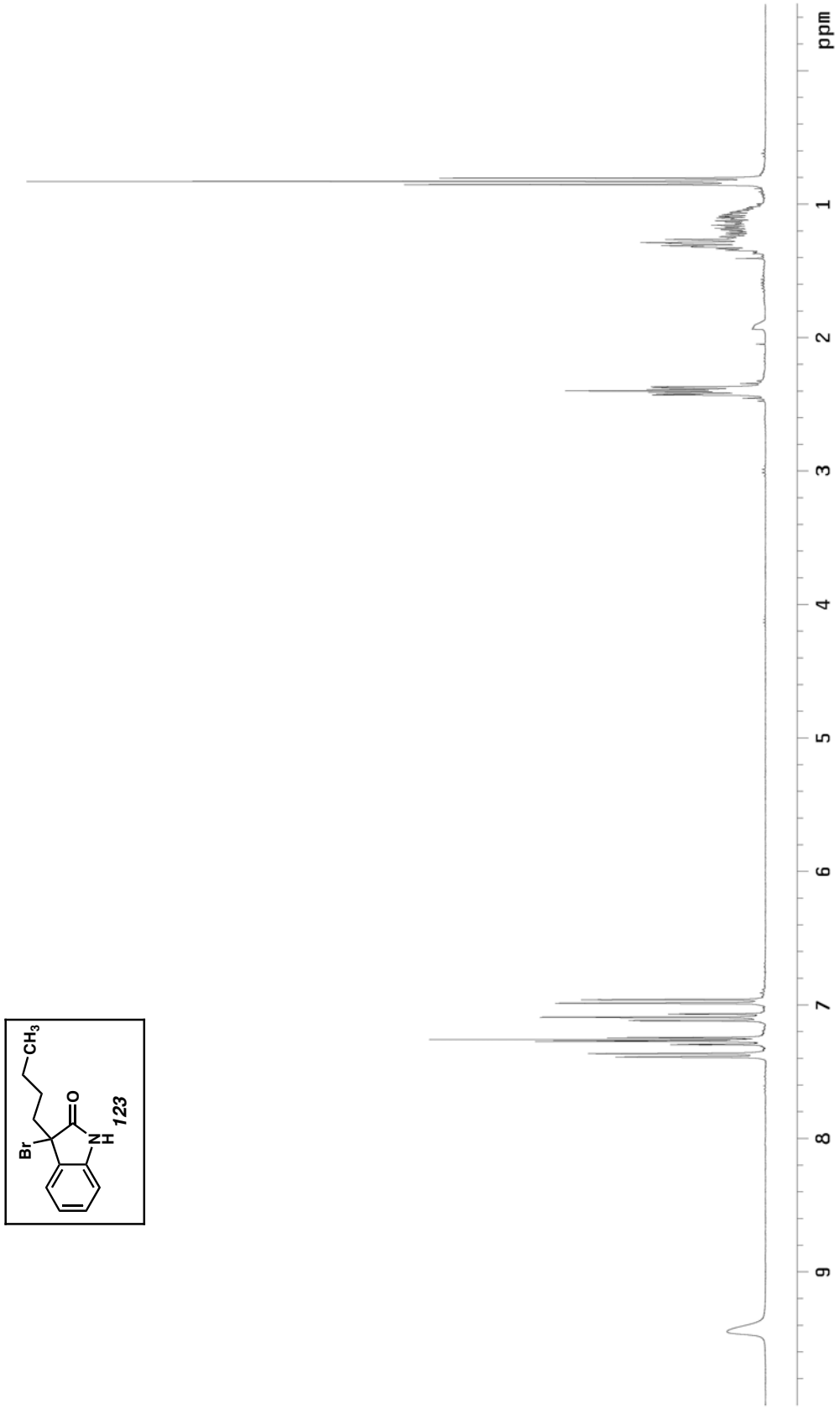


Figure A3.33.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **123**.

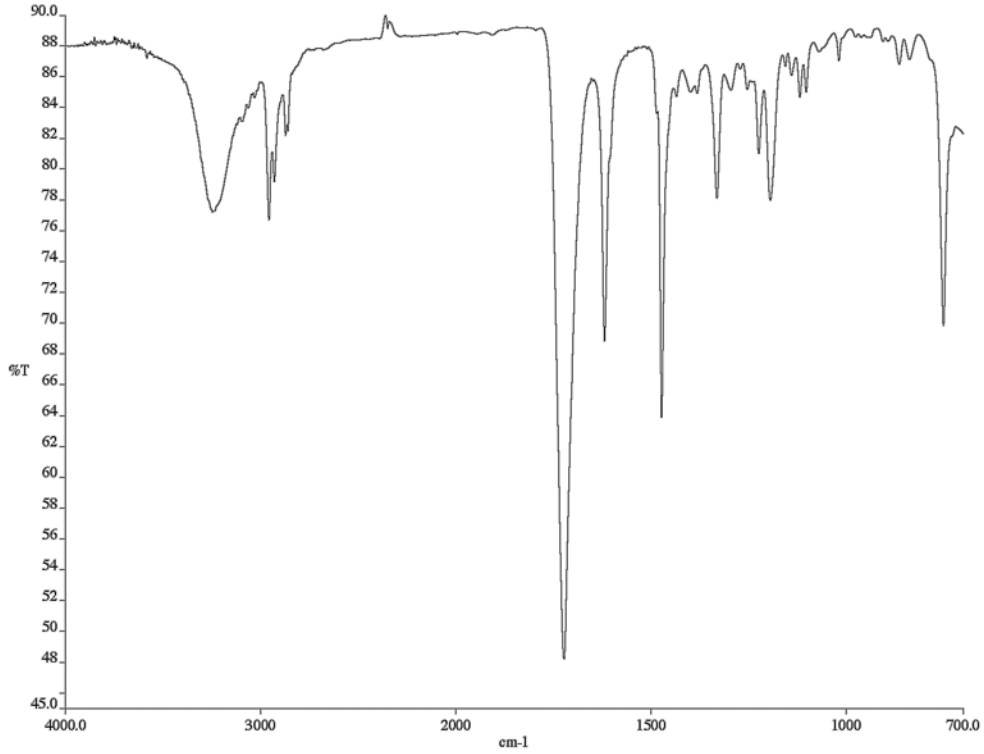


Figure A3.33.2 Infrared spectrum (thin film/NaCl) of compound **123**.

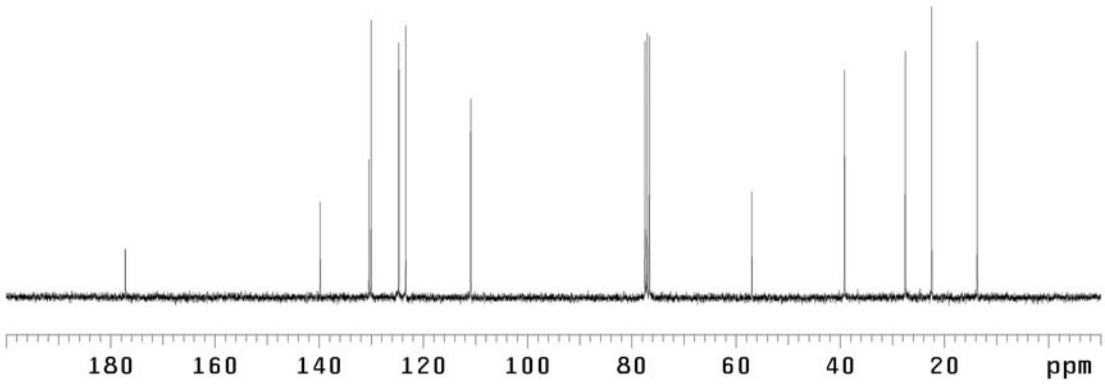


Figure A3.33.3 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **123**.

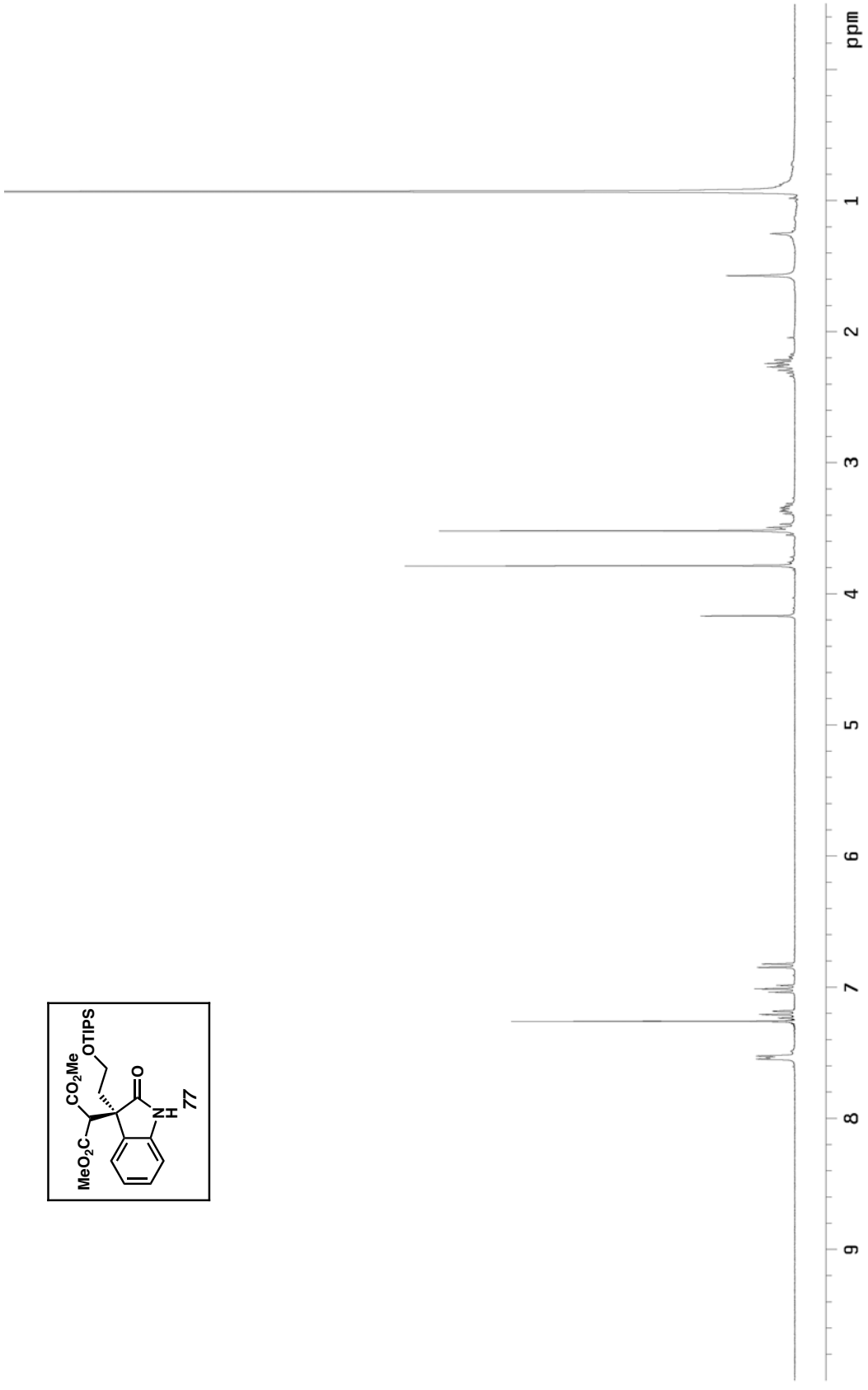


Figure A3.34.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **77** (Table 3.4, Entry 1).

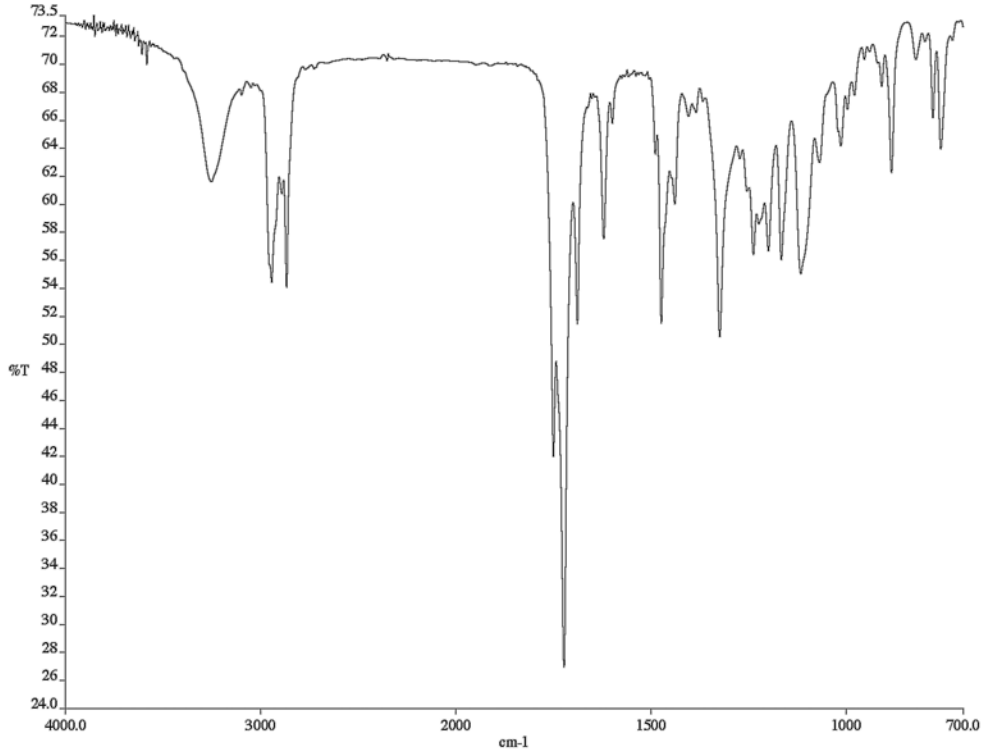


Figure A3.34.2 Infrared spectrum (thin film/NaCl) of compound **77** (Table 3.4, Entry 1).

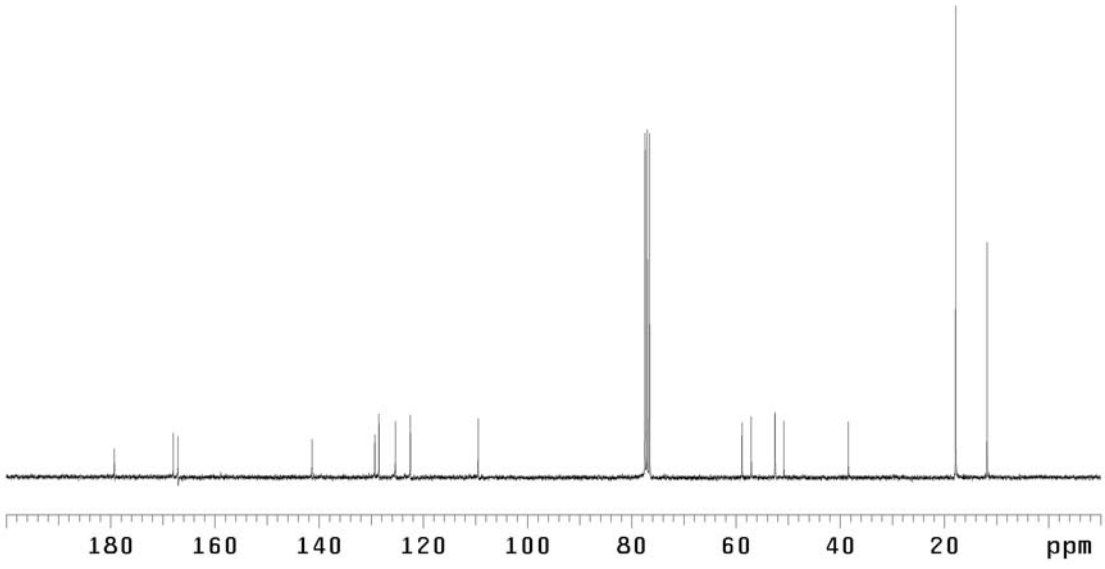


Figure A3.34.3 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **77** (Table 3.4, Entry 1).

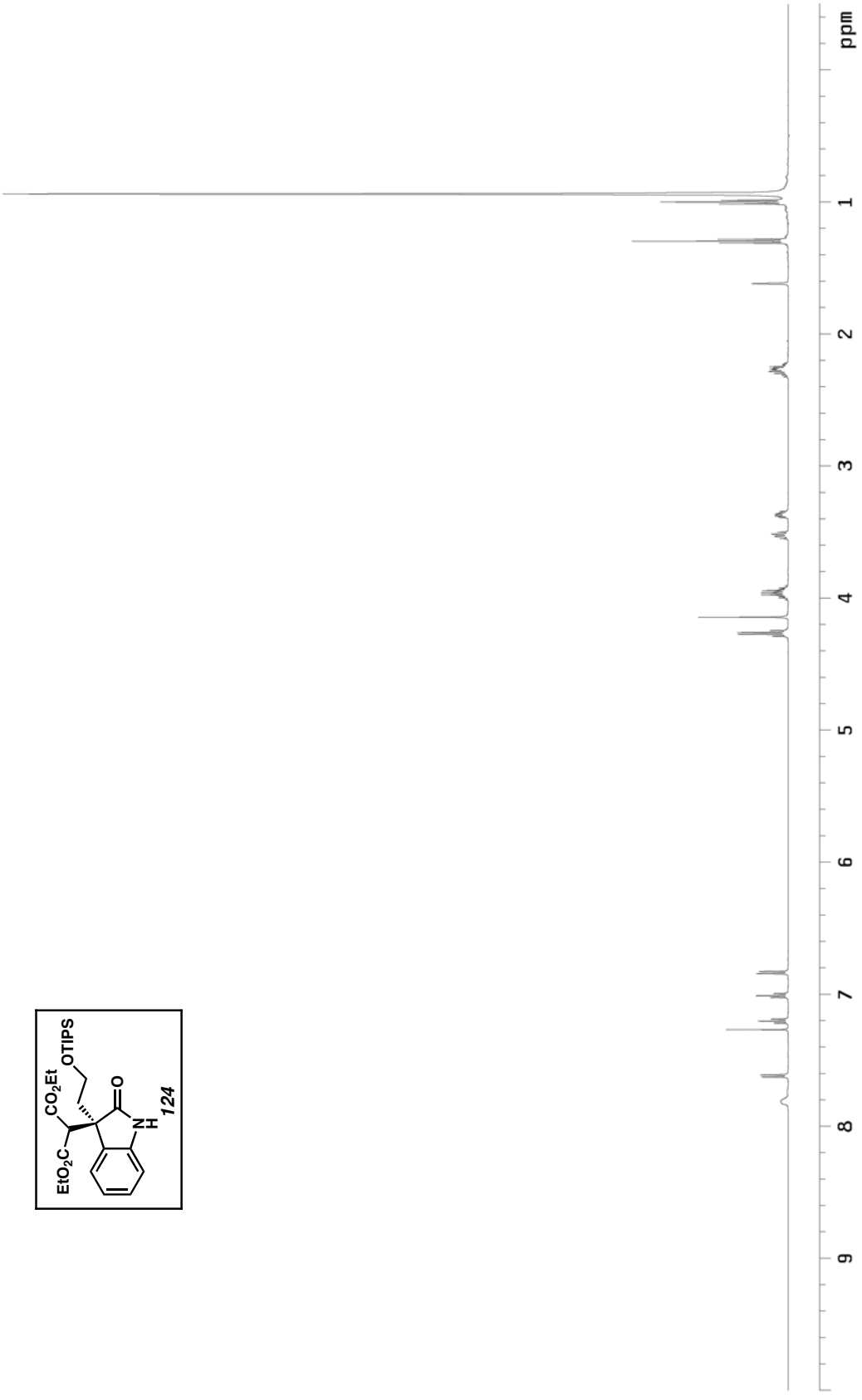


Figure A3.35.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **124** (Table 3.4, Entry 2).

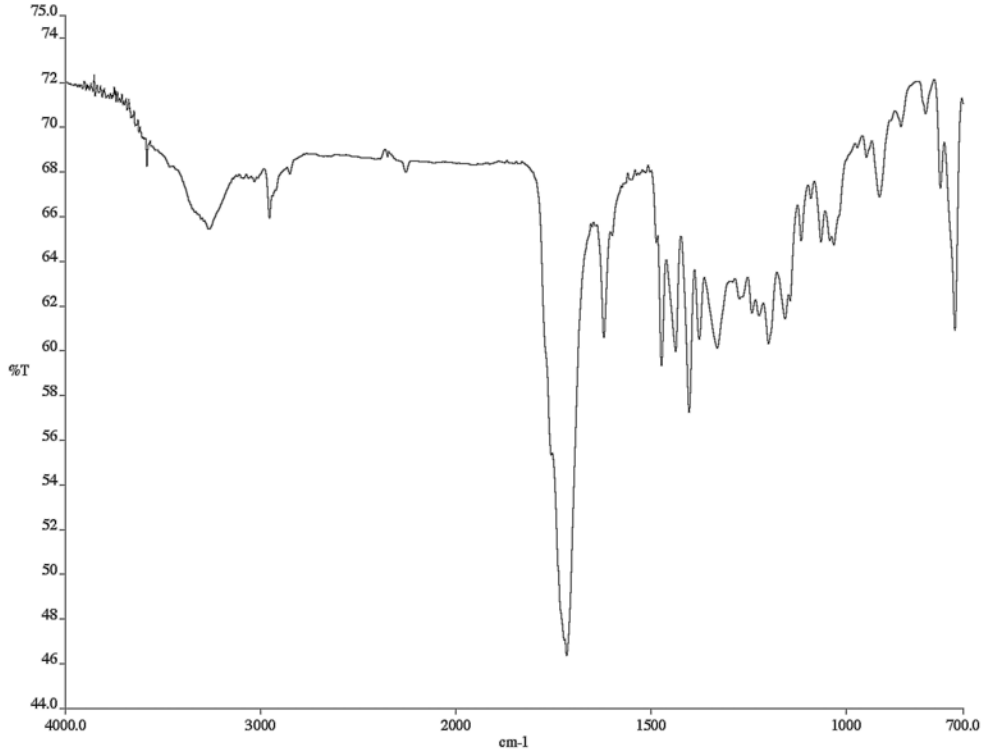


Figure A3.35.2 Infrared spectrum (thin film/NaCl) of compound **124** (Table 3.4, Entry 2).

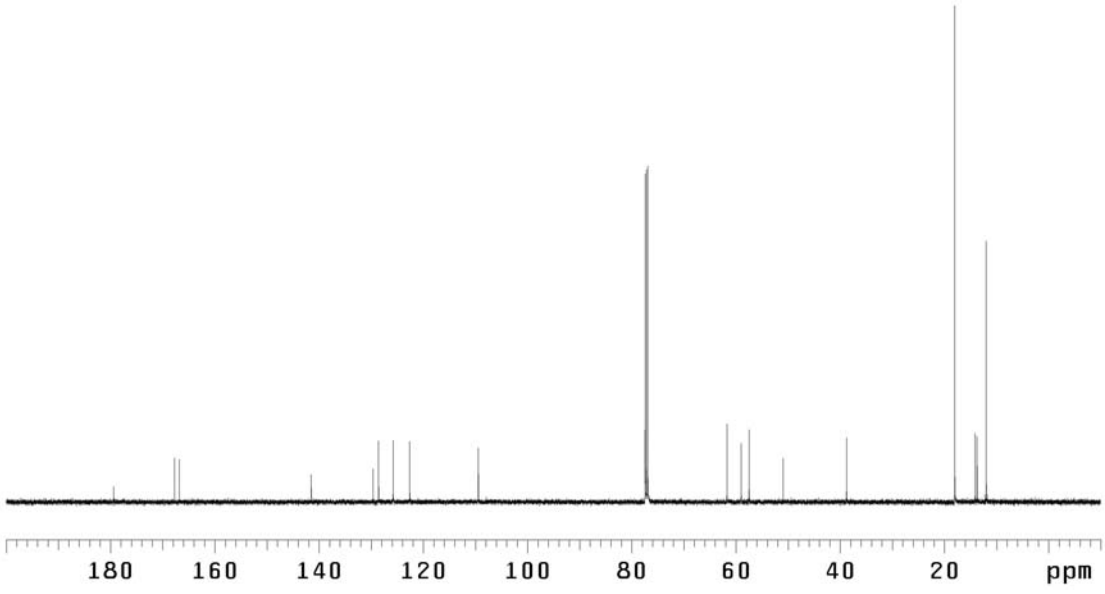


Figure A3.35.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **124** (Table 3.4, Entry 2).

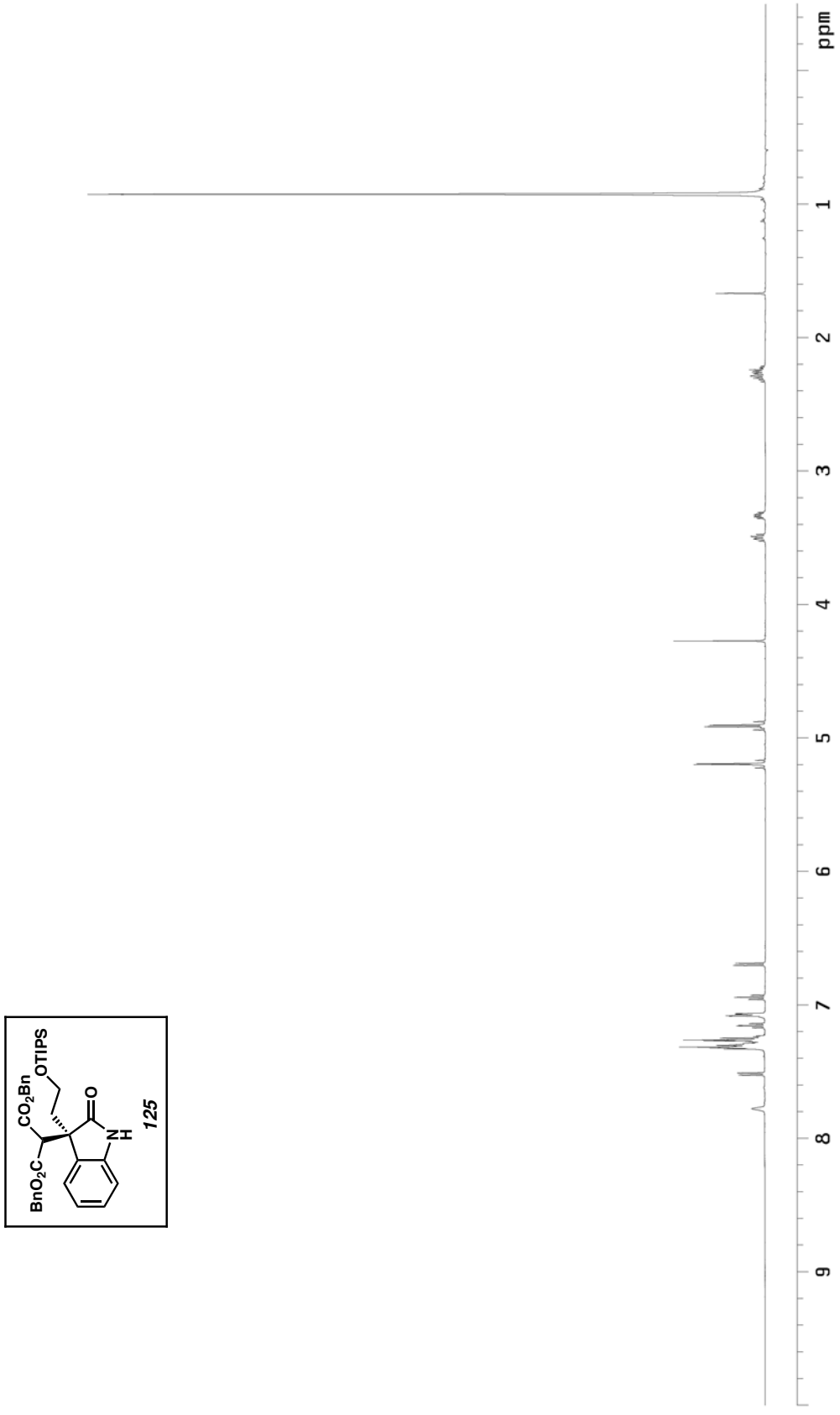


Figure A3.36.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **125** (Table 3.4, Entry 3).

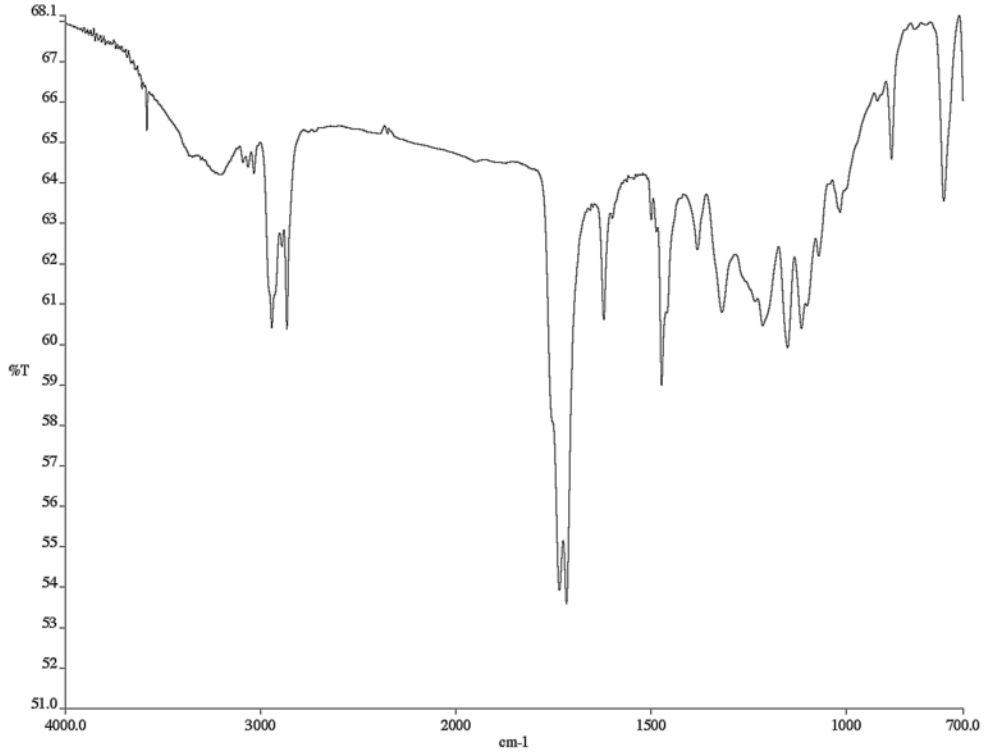


Figure A3.36.2 Infrared spectrum (thin film/NaCl) of compound **125** (Table 3.4, Entry 3).

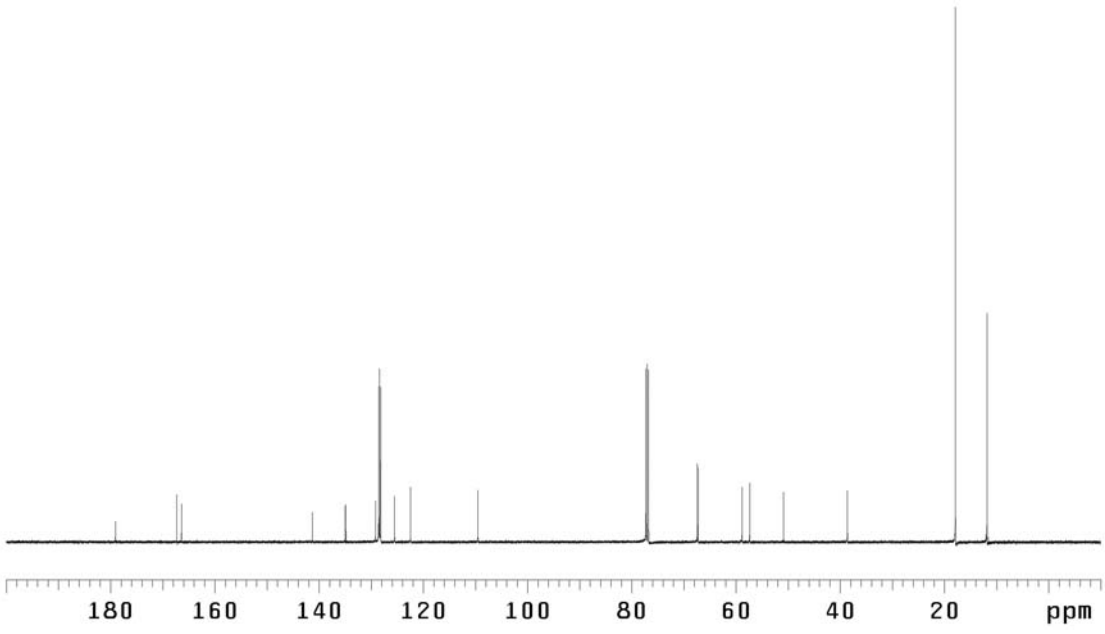
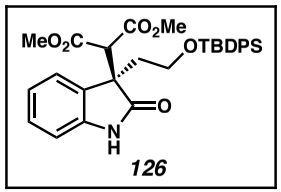


Figure A3.36.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **125** (Table 3.4, Entry 3).



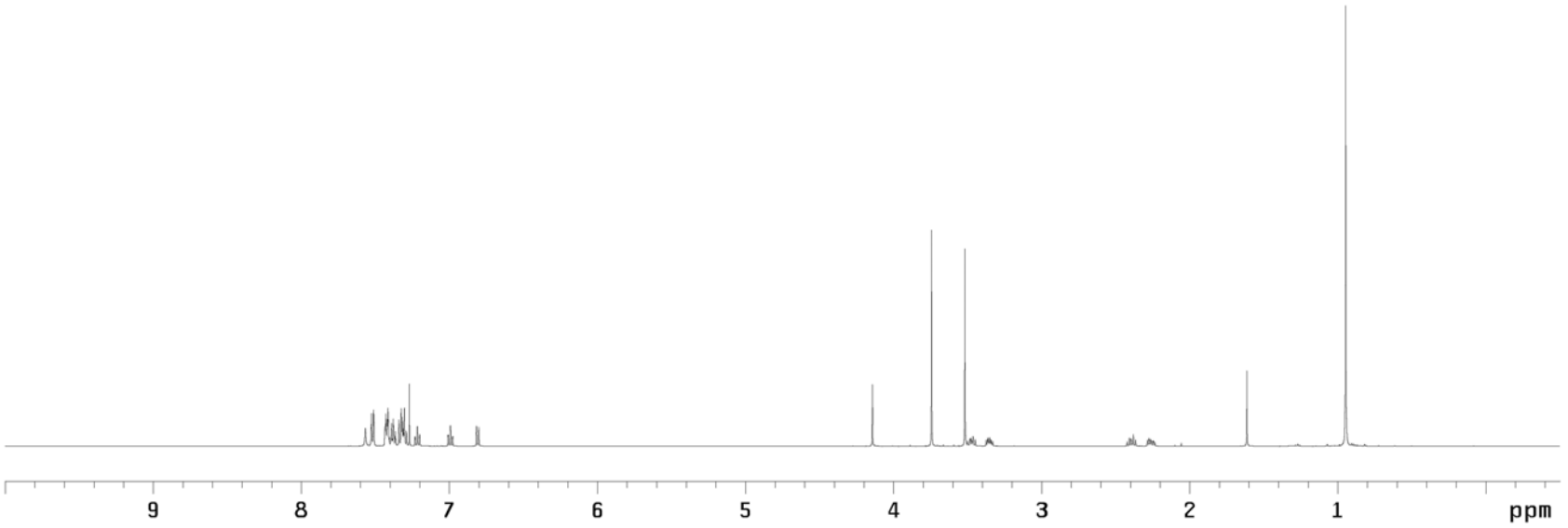


Figure A3.37.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **126** (Table 3.4, Entry 4).

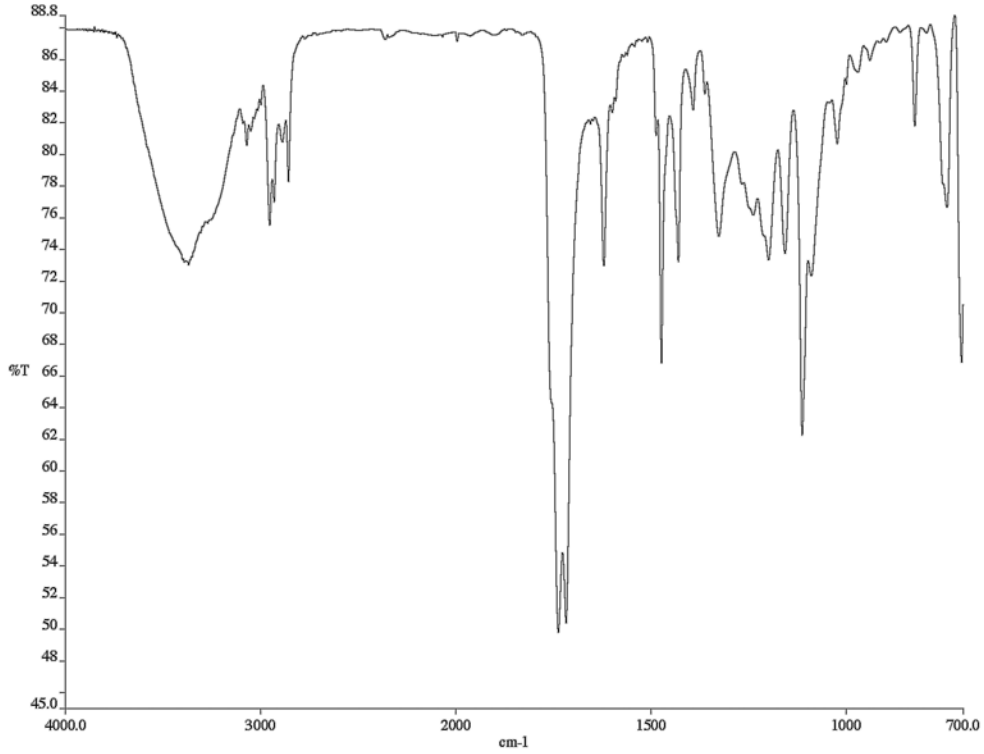


Figure A3.37.2 Infrared spectrum (thin film/NaCl) of compound **126** (Table 3.4, Entry 4).

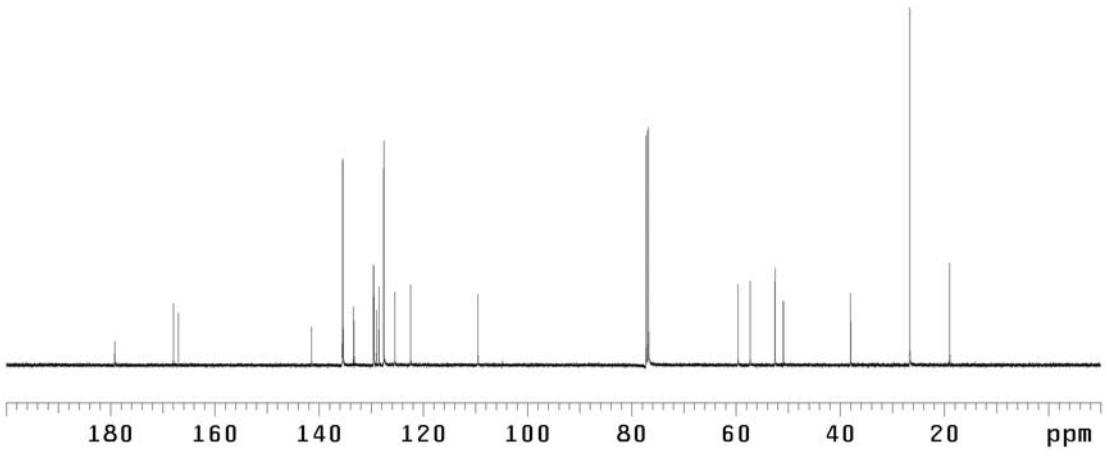


Figure A3.37.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **126** (Table 3.4, Entry 4)

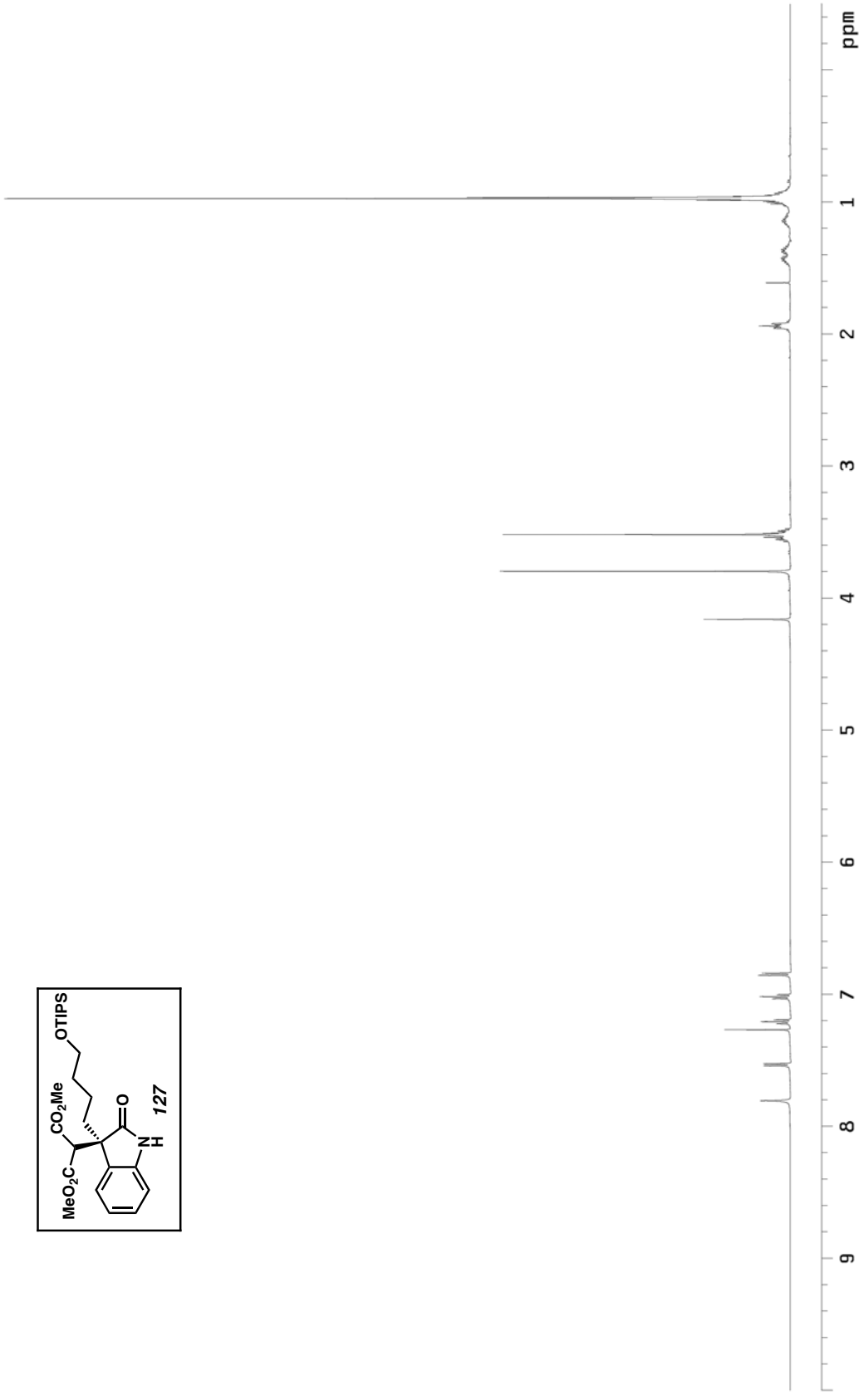


Figure A3.38.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **127** (Table 3.4, Entry 6).

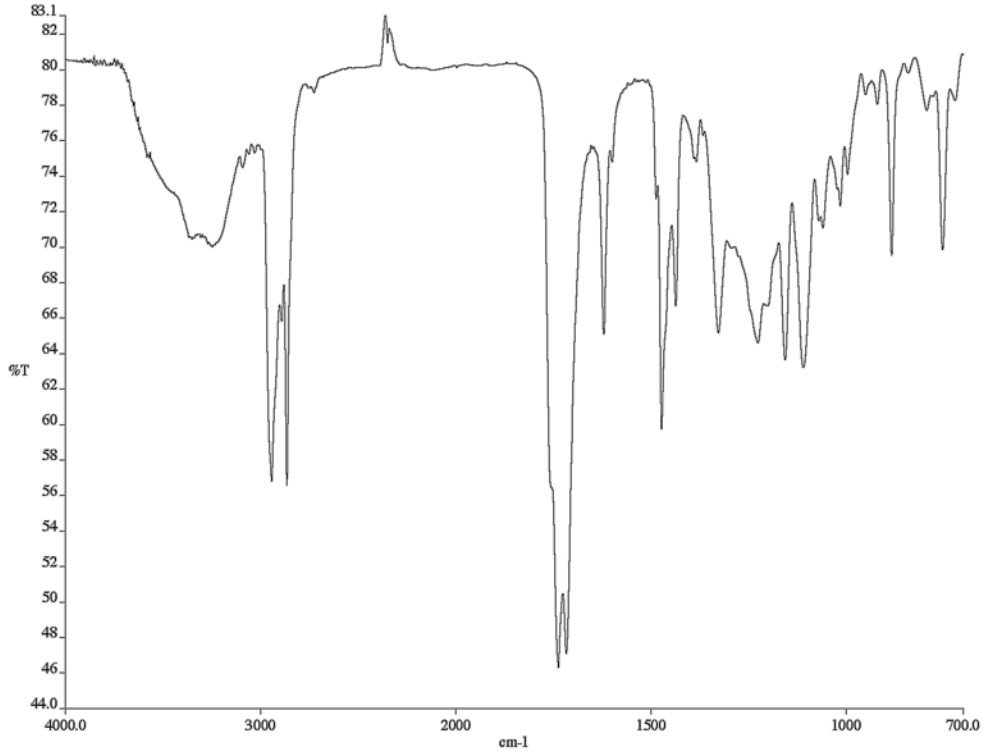


Figure A3.38.2 Infrared spectrum (thin film/NaCl) of compound **127** (Table 3.4, Entry 6)

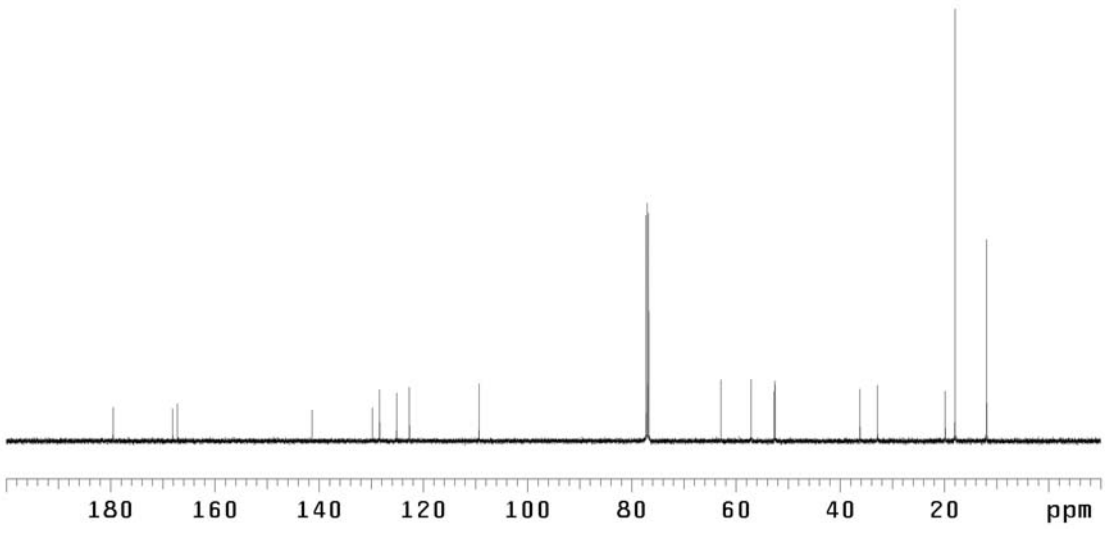


Figure A3.38.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **127** (Table 3.4, Entry 6).

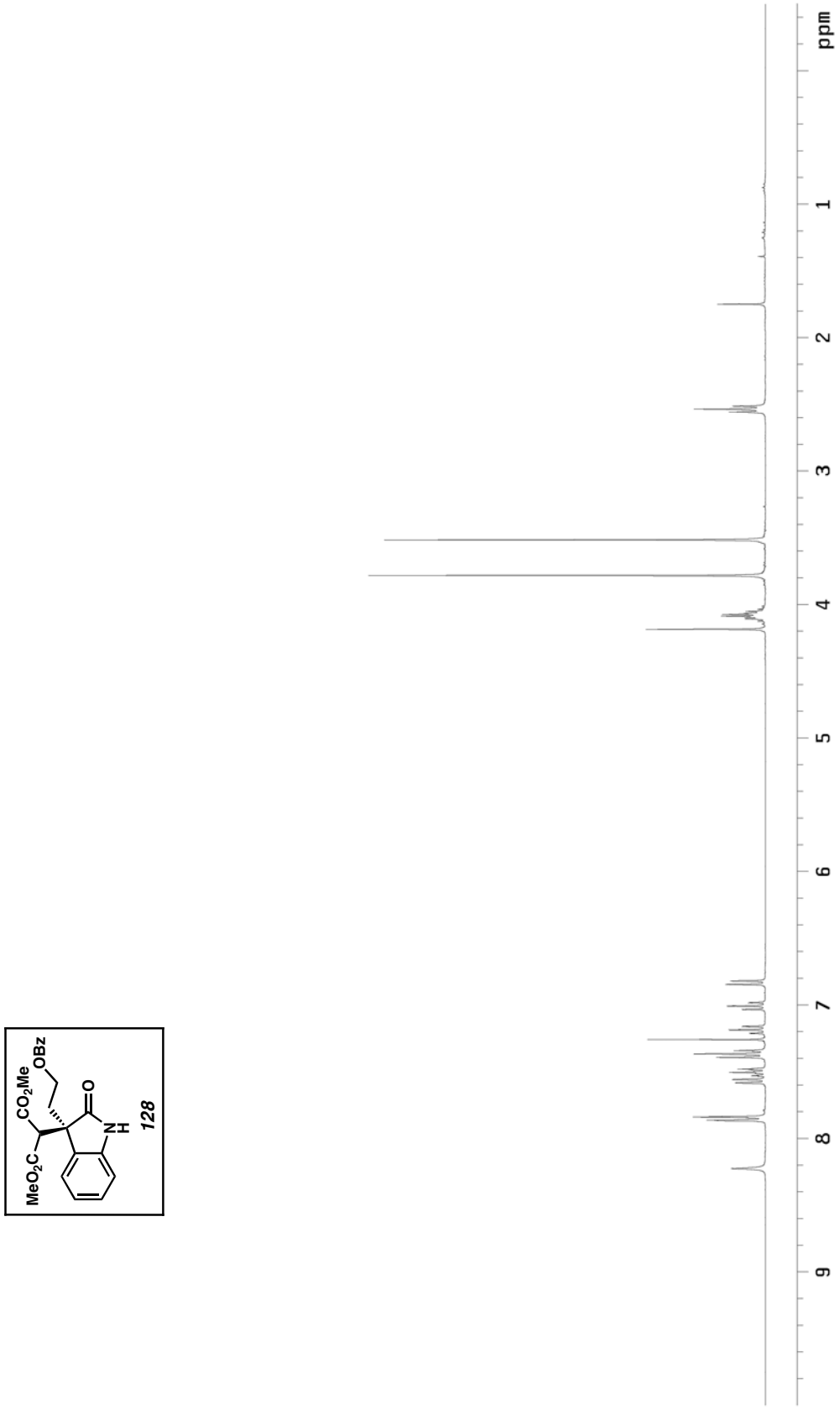


Figure A3.39.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **128** (Table 3.4, Entry5).

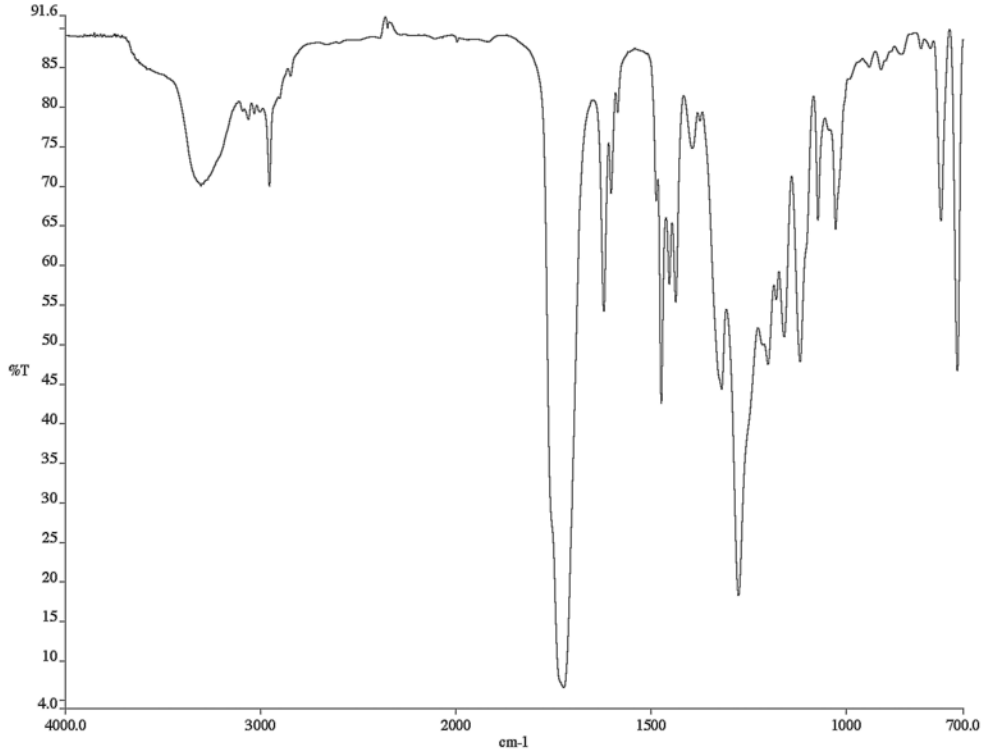


Figure A3.39.2 Infrared spectrum (thin film/NaCl) of compound **128** (Table 3.4, Entry 5).

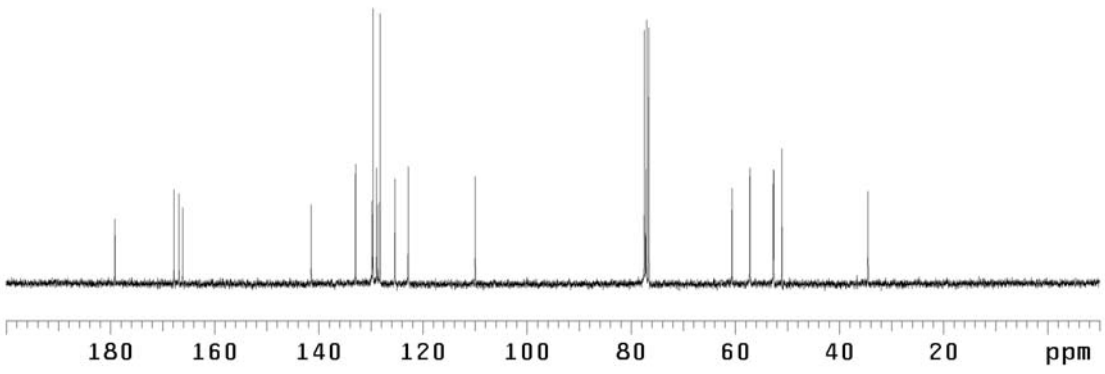


Figure A3.39.3 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **128** (Table 3.4, Entry 5).

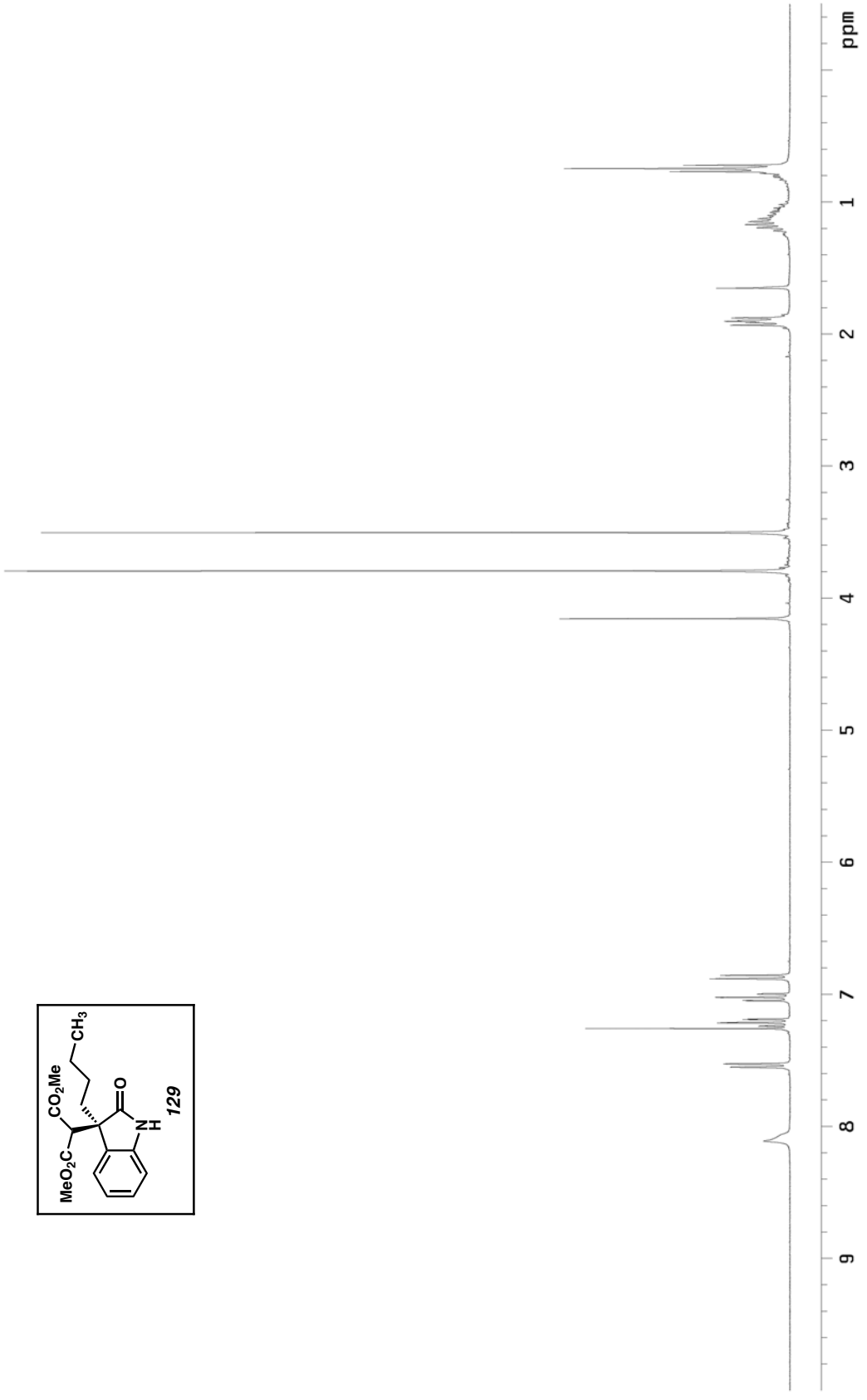


Figure A3.40.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **129** (Table 3.4, Entry 7).

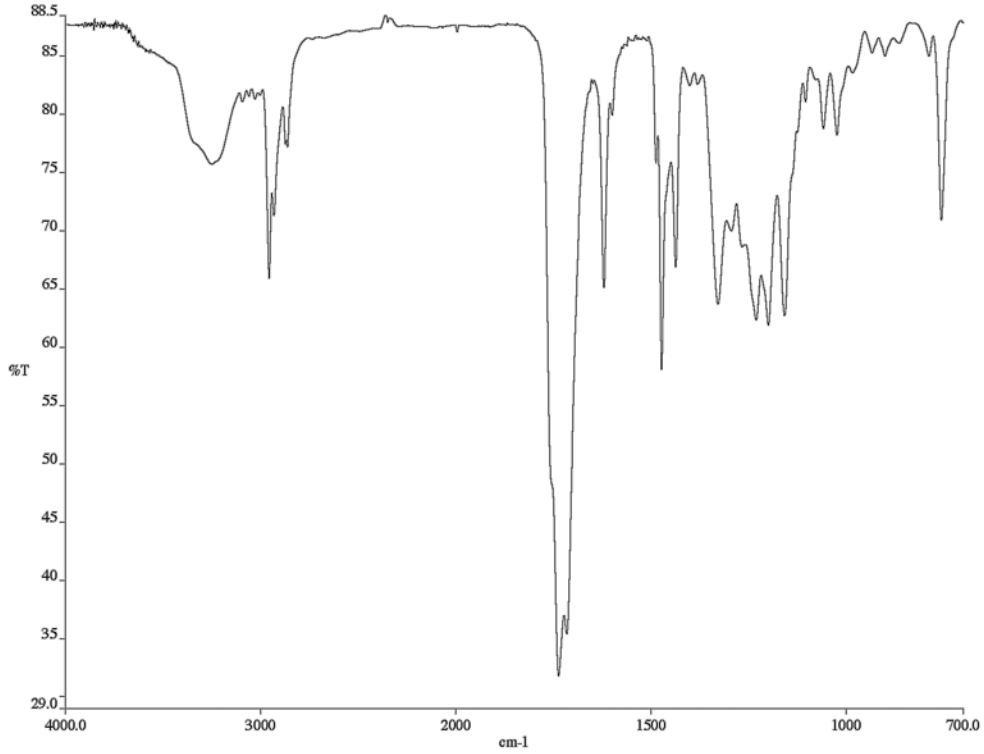


Figure A3.40.2 Infrared spectrum (thin film/NaCl) of compound **129** (Table 3.4, Entry 7).

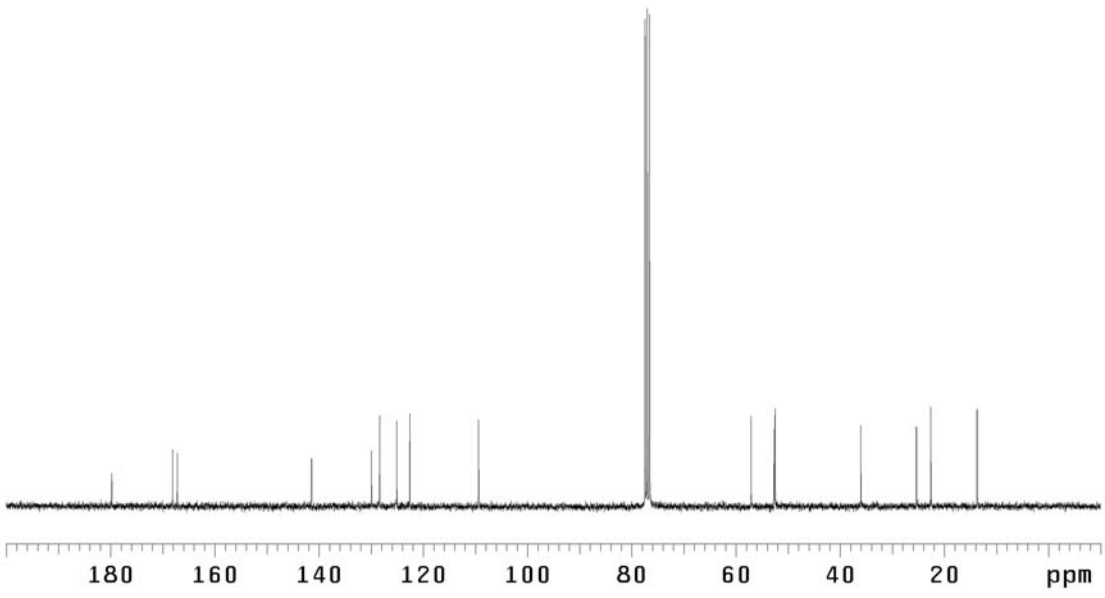


Figure A3.40.3 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **129** (Table 3.4, Entry 7).

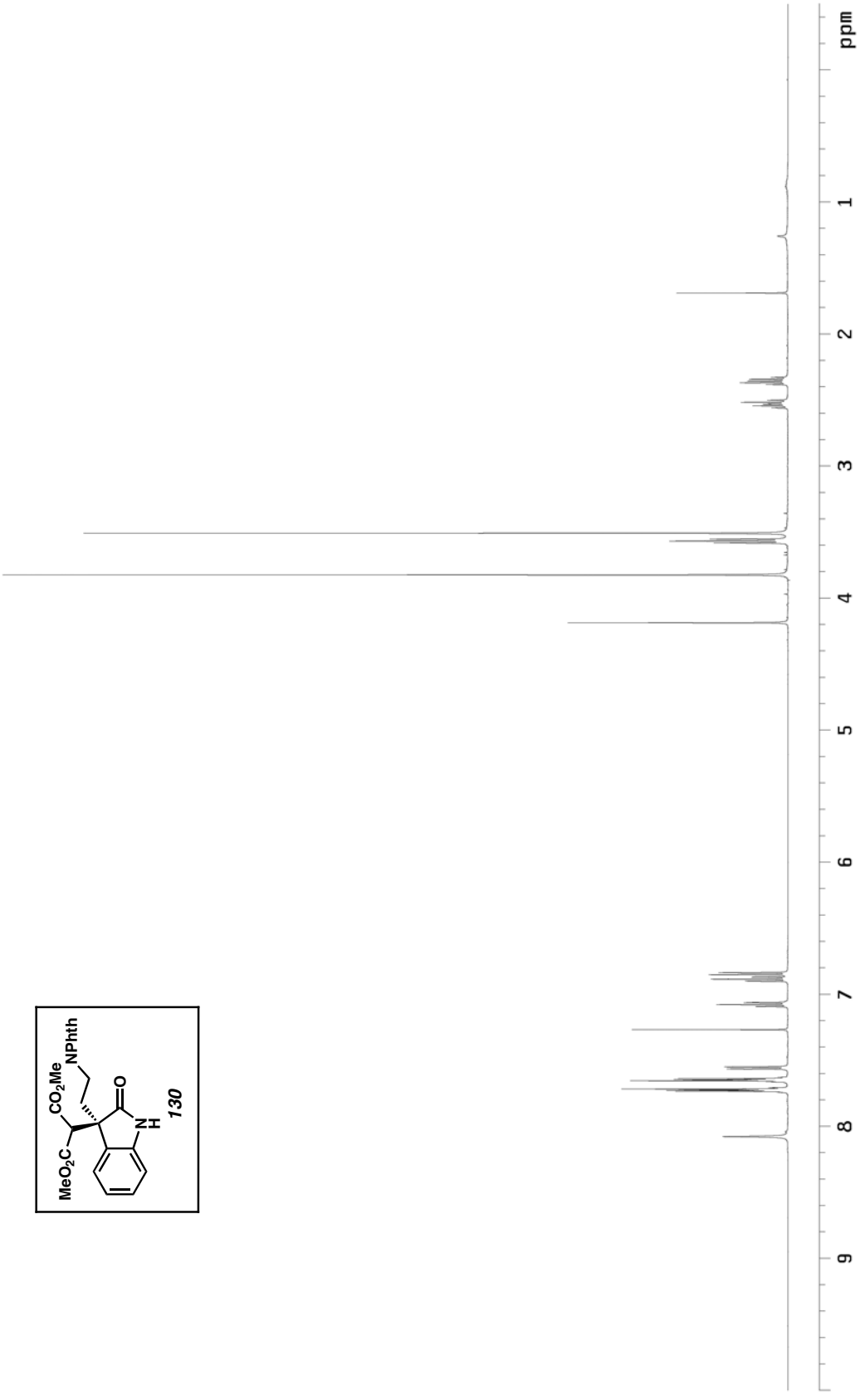


Figure A3.41.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **130** (Table 3.4, Entry 10).

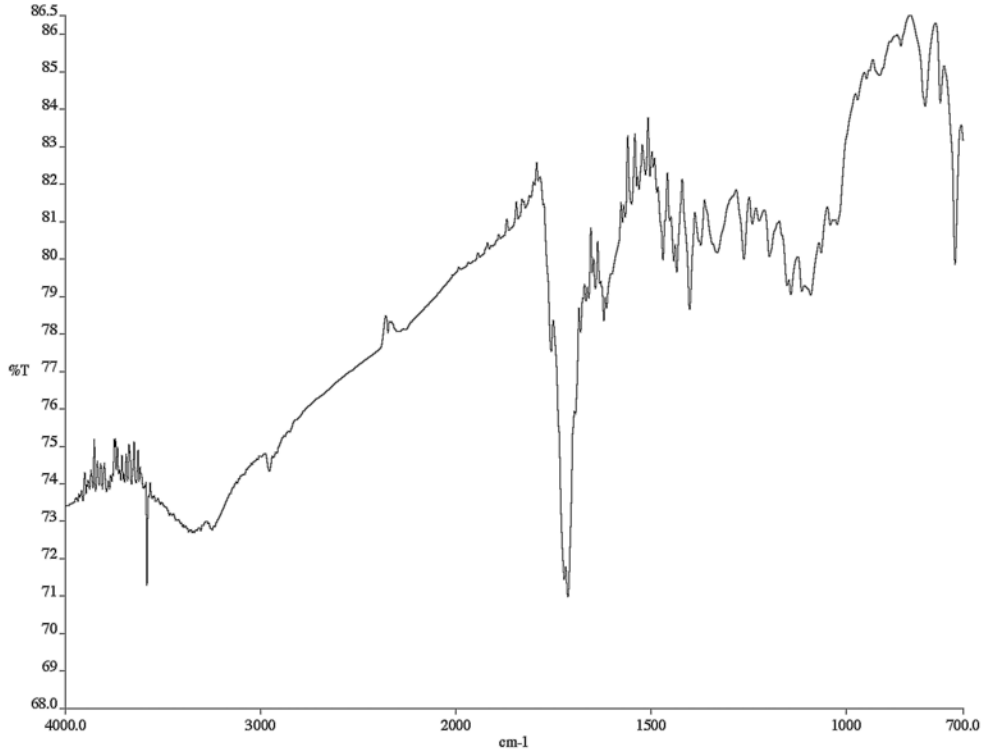


Figure A3.41.2 Infrared spectrum (thin film/NaCl) of compound **130** (Table 3.4, Entry 10).

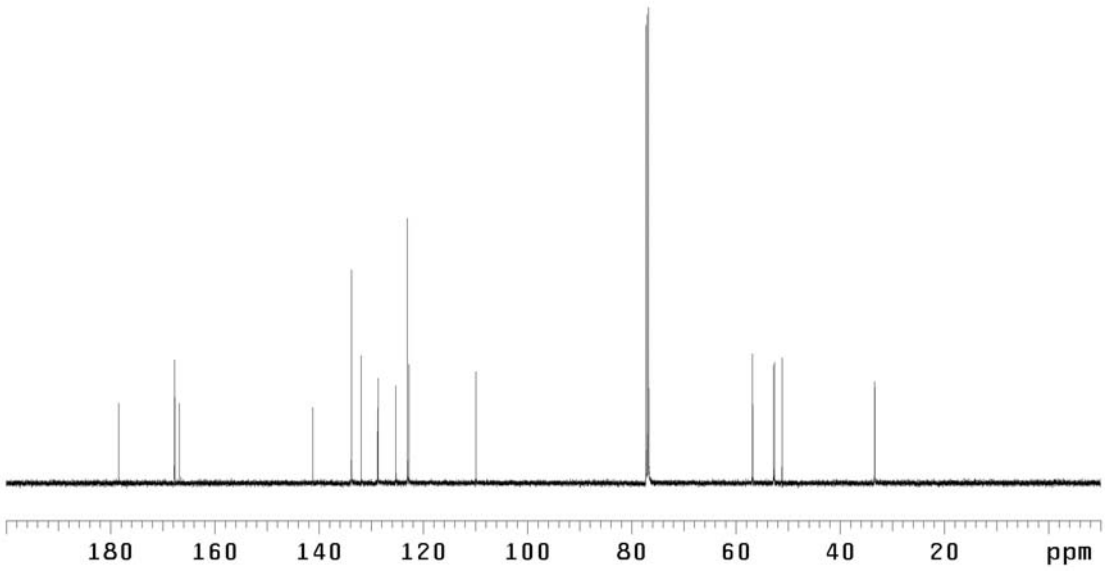


Figure A3.41.3 ^{13}C NMR (500 MHz, $CDCl_3$) of compound **130** (Table 3.4, Entry 10).

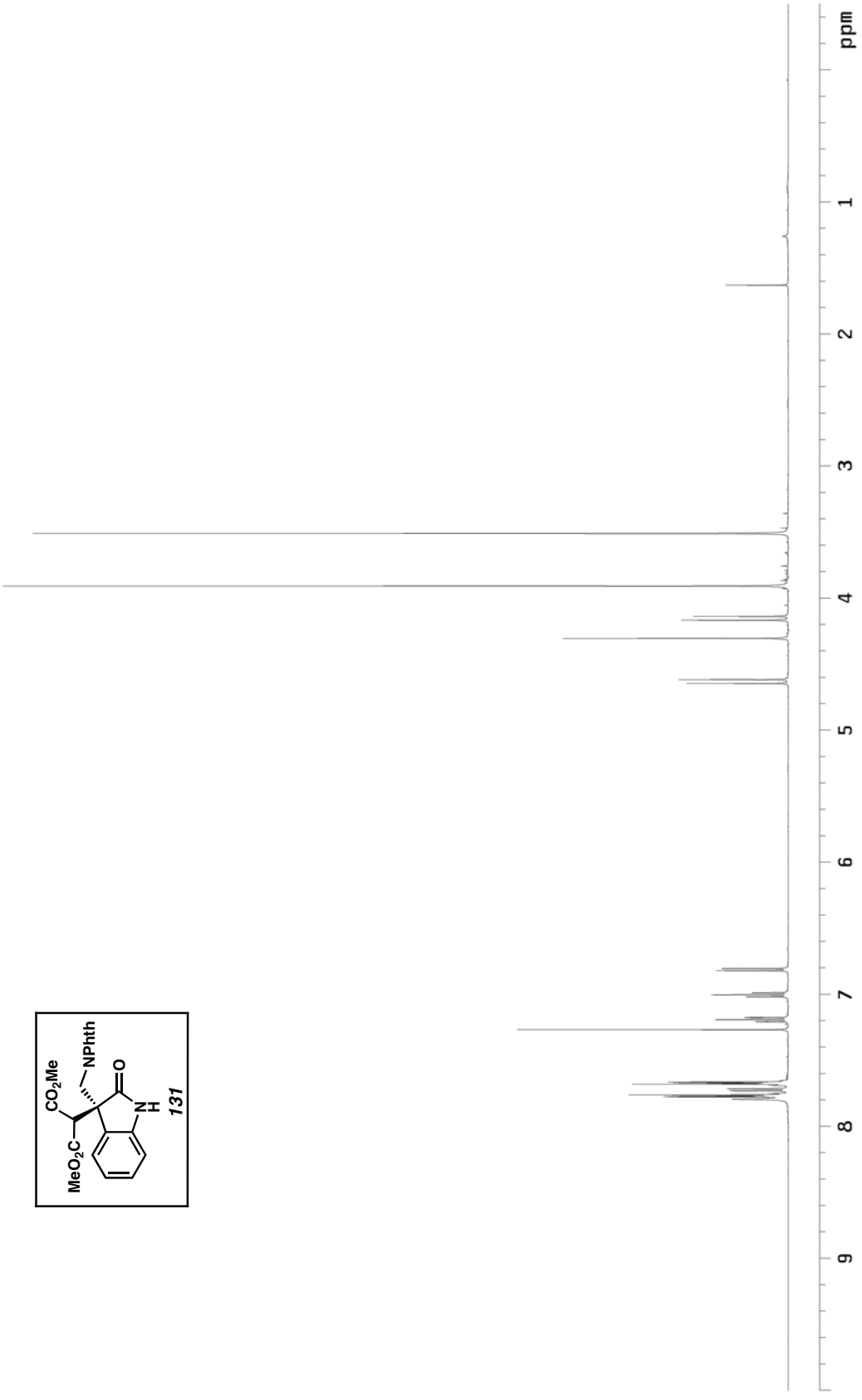


Figure A3.42.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **131** (Table 3.4, Entry 8).

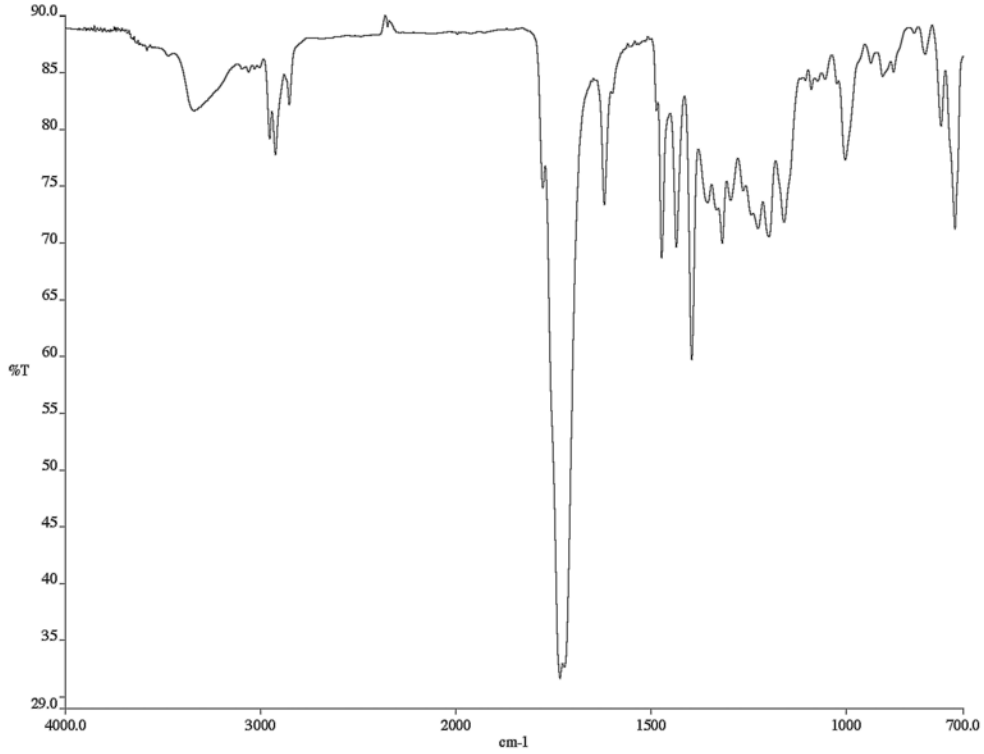


Figure A3.42.2 Infrared spectrum (thin film/NaCl) of compound **131** (Table 3.4, Entry 8).

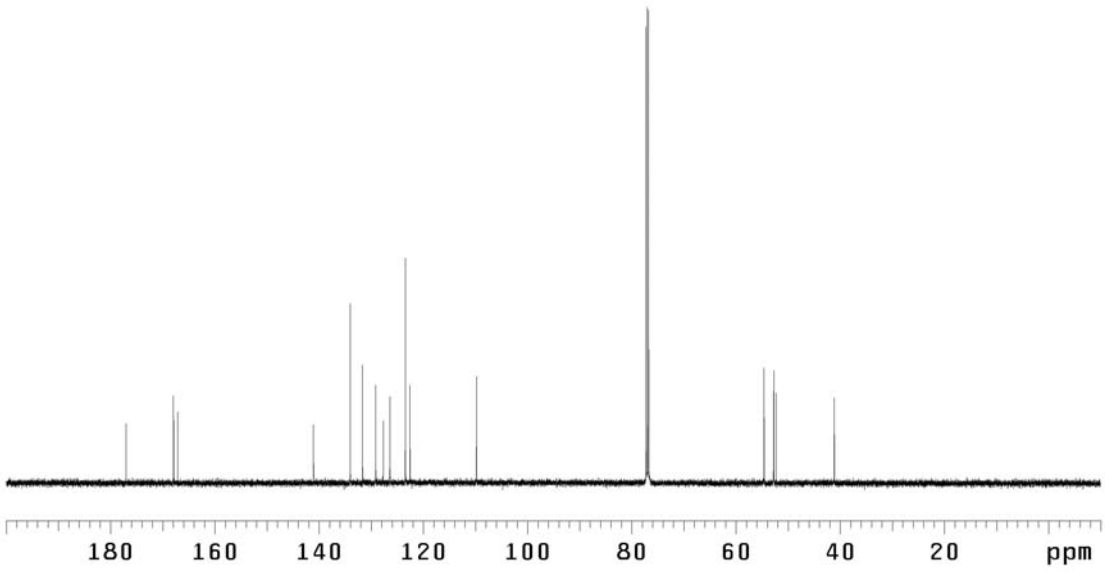
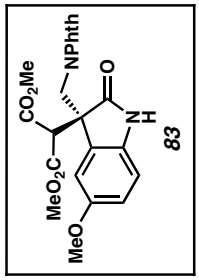


Figure A3.42.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **131** (Table 3.4, Entry 8).



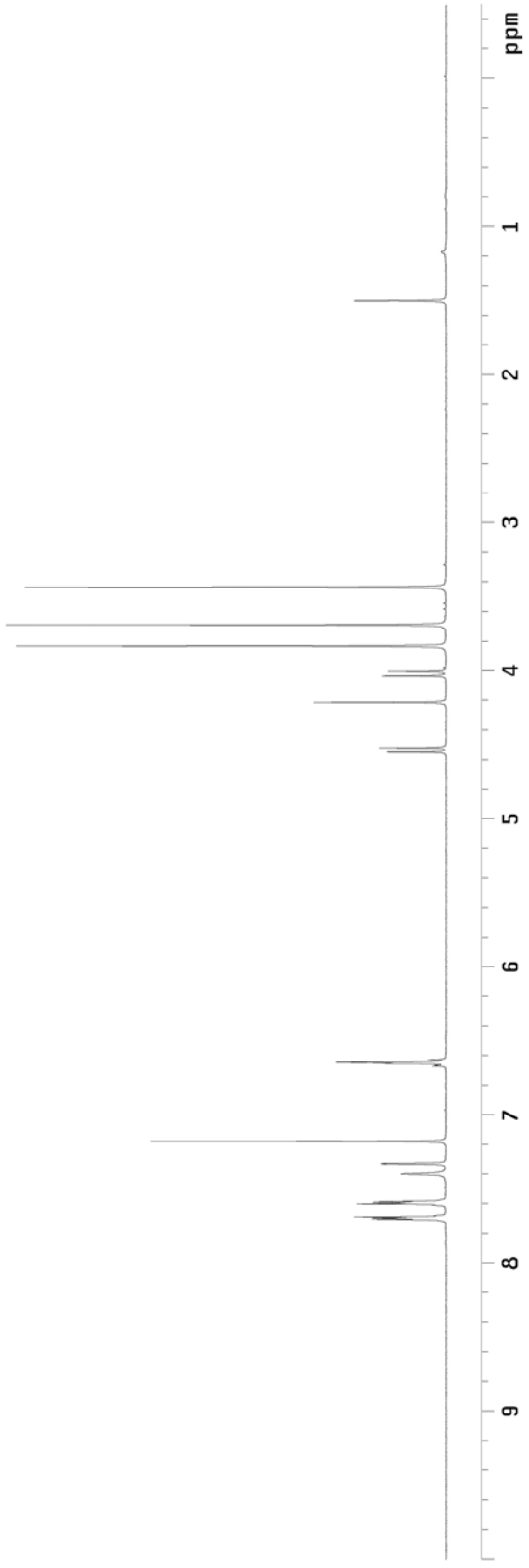


Figure A3.43.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **83** (Table 3.4, Entry 9).

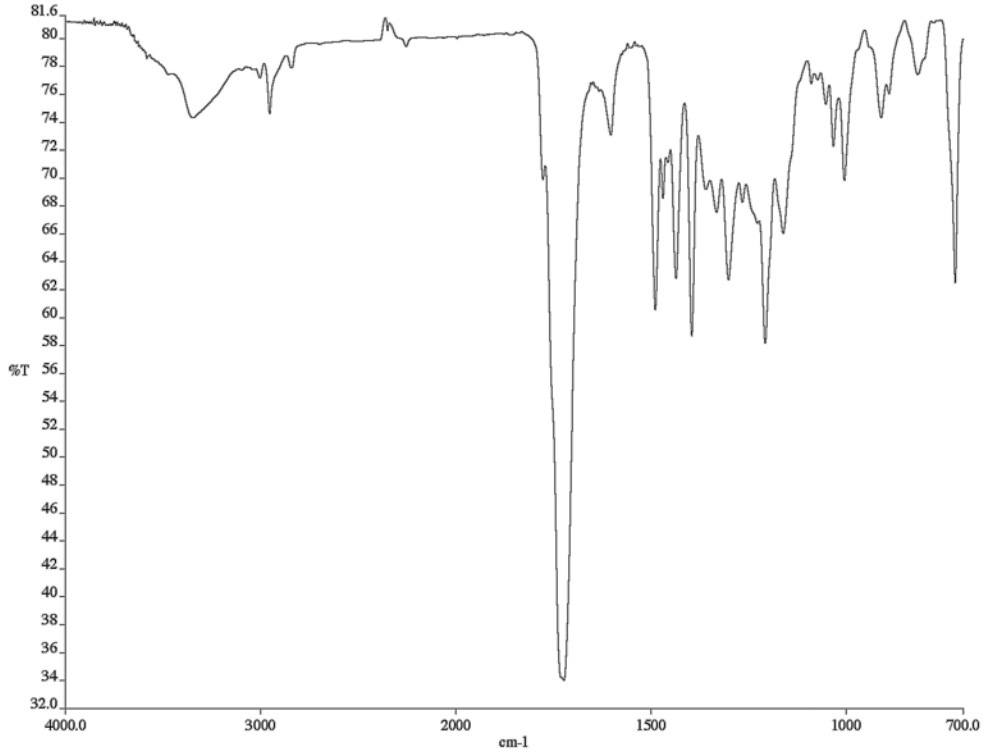


Figure A3.43.2 Infrared spectrum (thin film/NaCl) of compound **83** (Table 3.4, Entry 9).

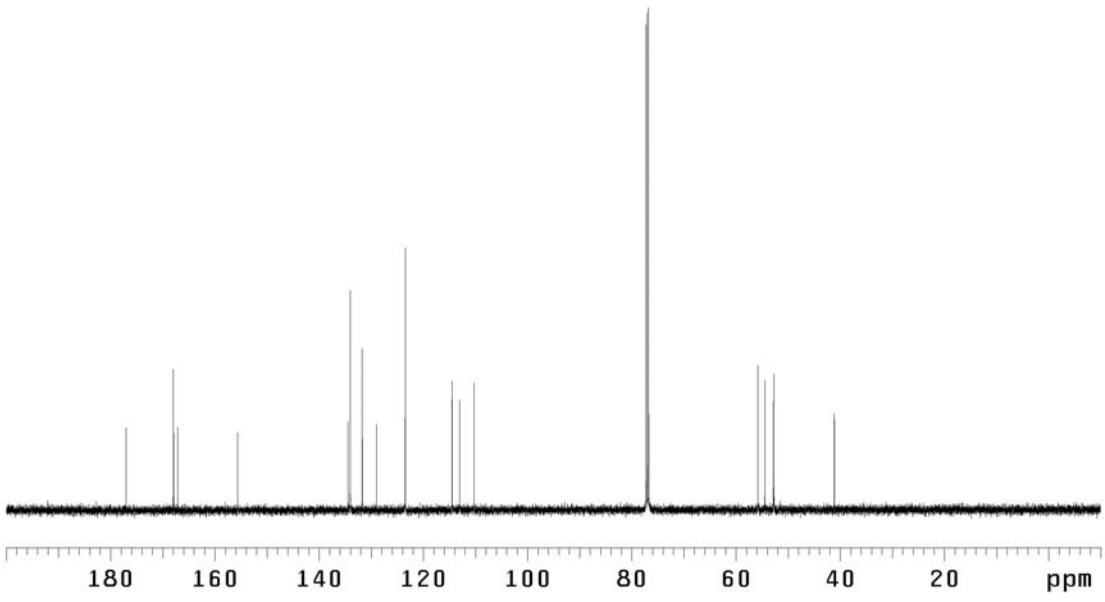


Figure A3.43.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **83** (Table 3.4, Entry 9).

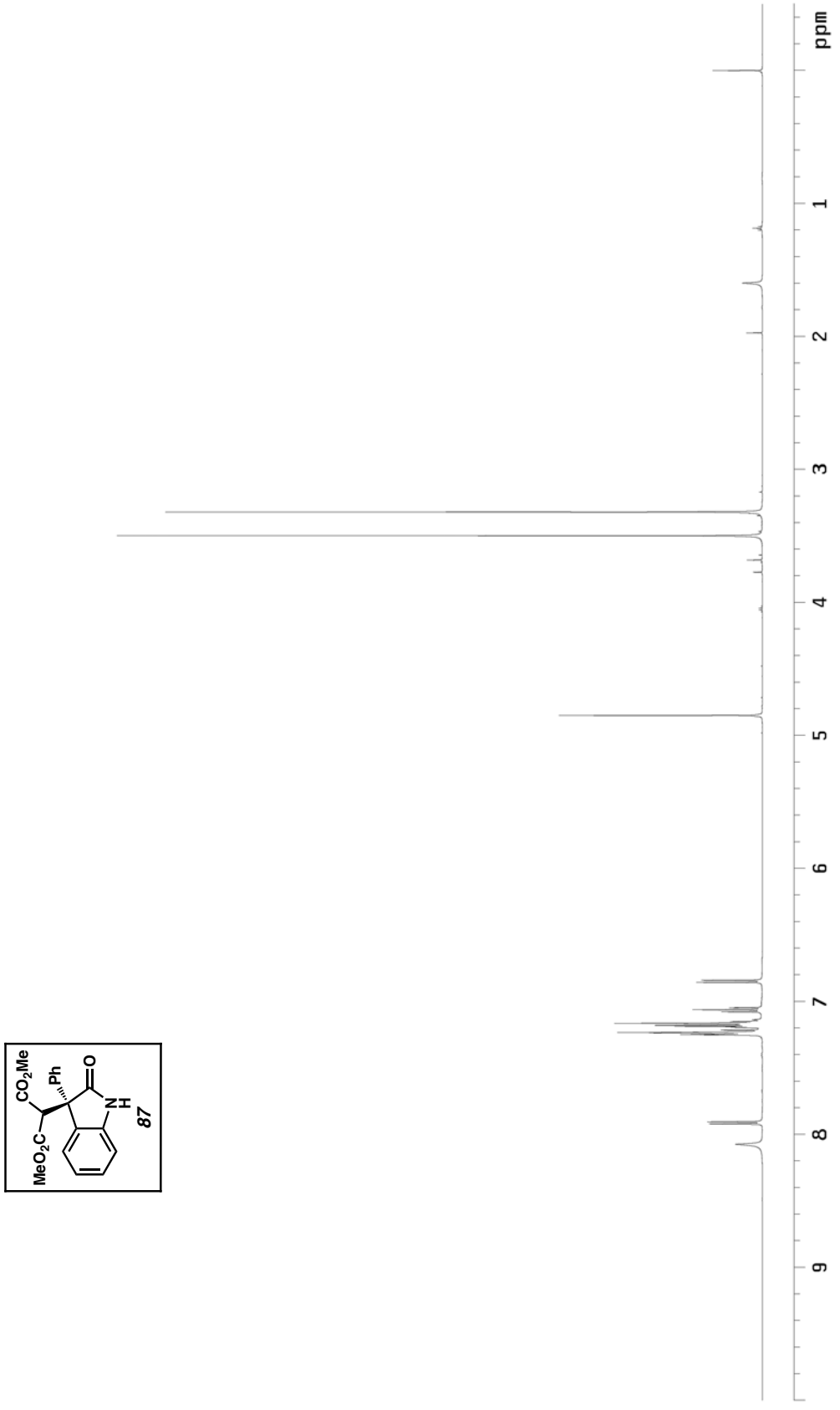


Figure A3.44.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **87** (Table 3.5, Entry 1).

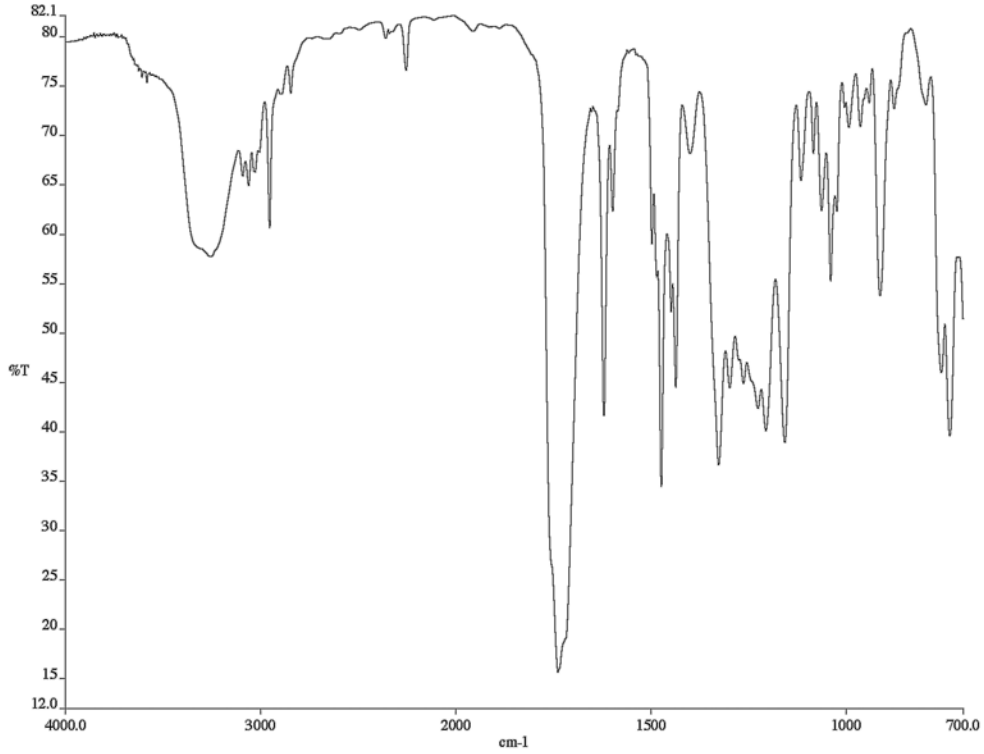


Figure A3.44.2 Infrared spectrum (thin film/NaCl) of compound **87** (Table 3.5, Entry 1).

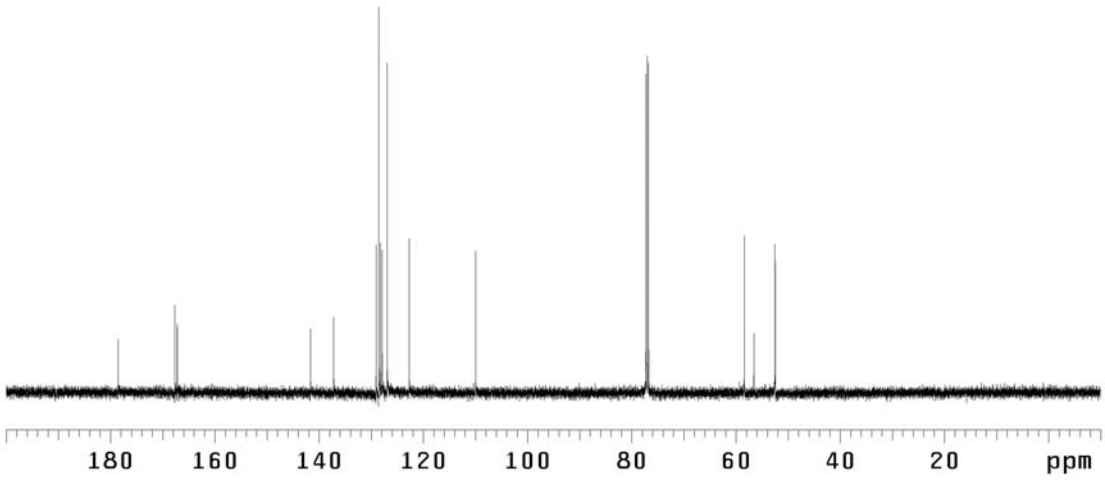
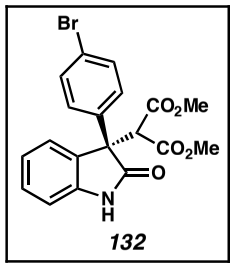


Figure A3.44.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **87** (Table 3.5, Entry 1).



132

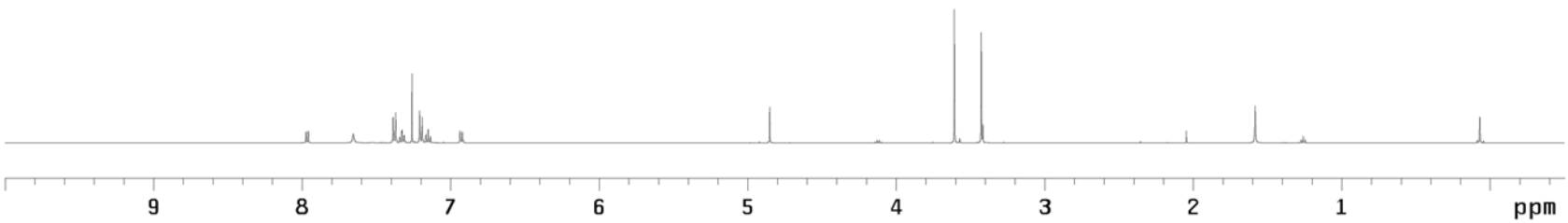


Figure A3.45.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **132** (Table 3.5, Entry 3).

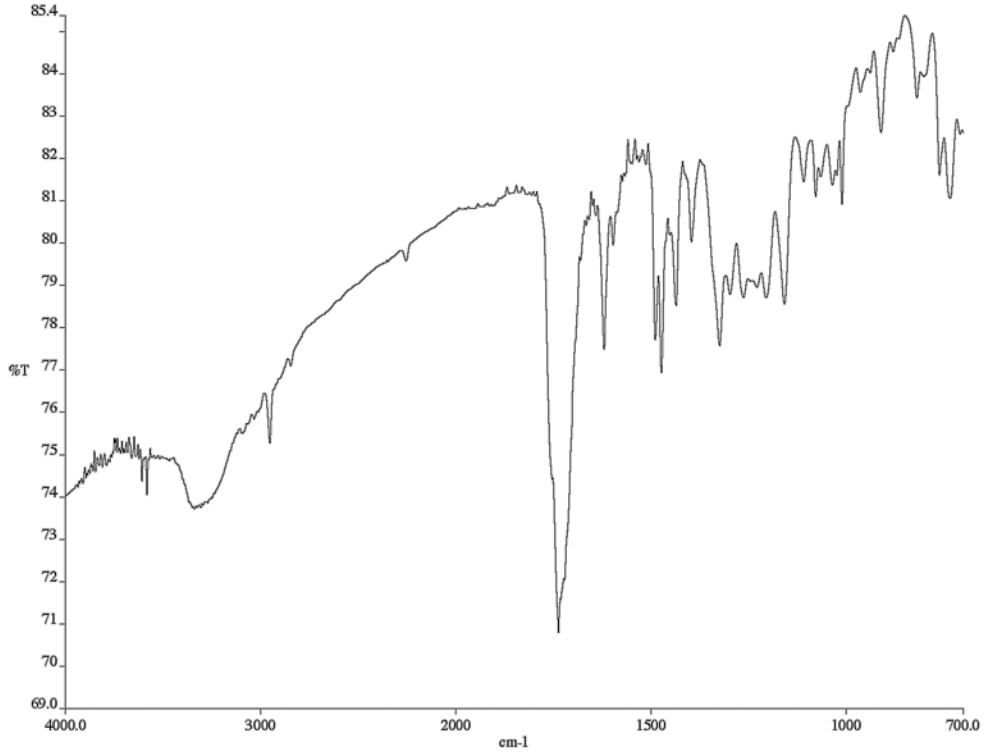


Figure A3.45.2 Infrared spectrum (thin film/NaCl) of compound **132** (Table 3.5, Entry 3).

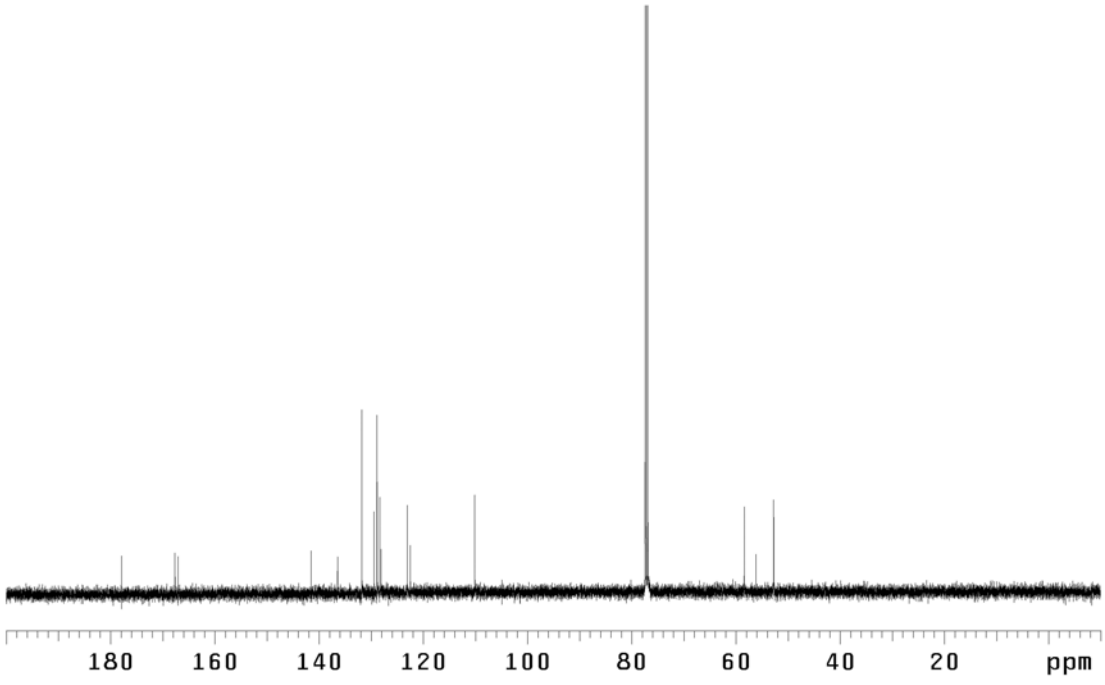
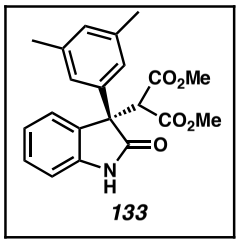


Figure A3.45.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **132** (Table 3.5, Entry 3).



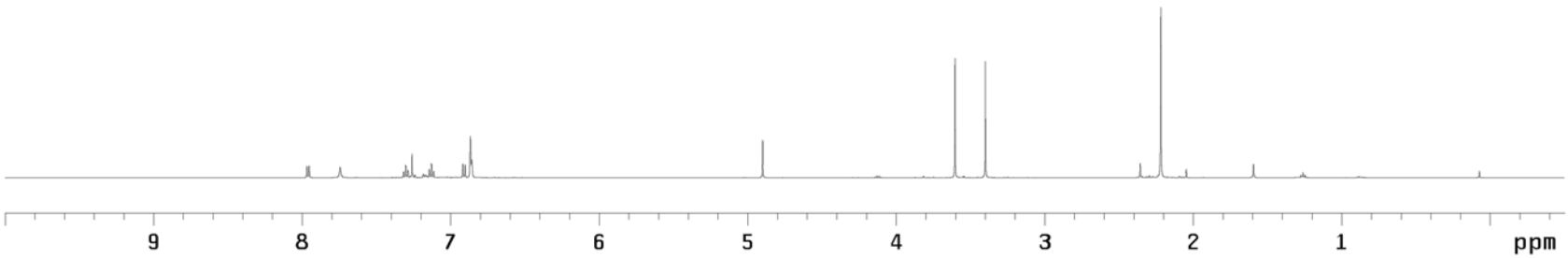


Figure A3.46.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **133** (Table 3.5, Entry 4).

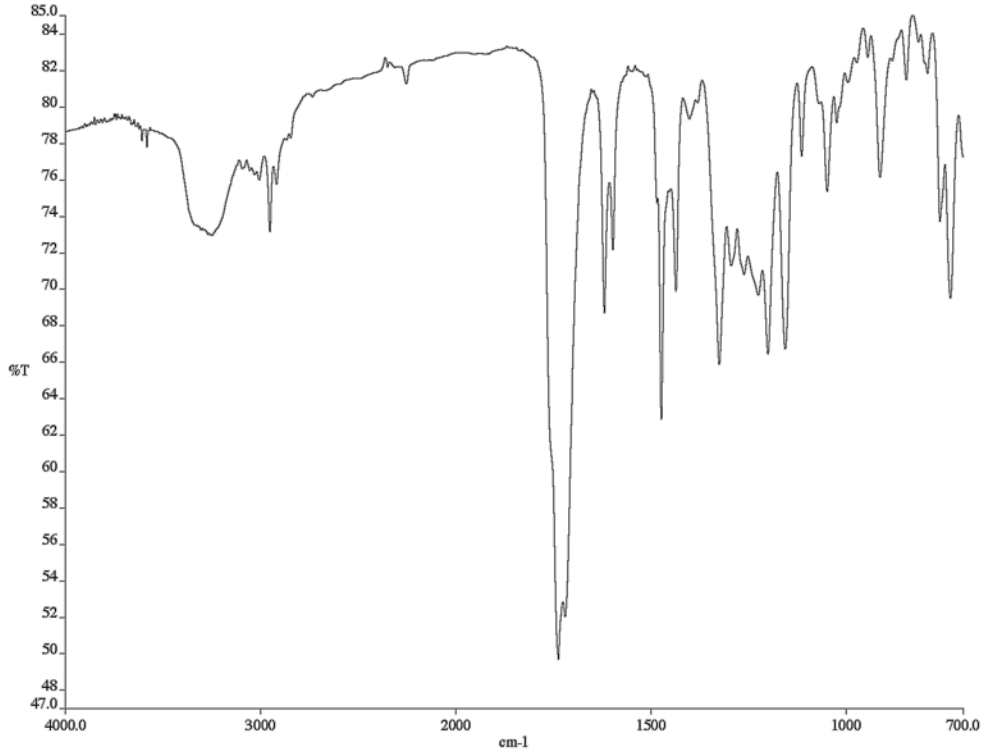


Figure A3.46.2 Infrared spectrum (thin film/NaCl) of compound **133** (Table 3.5, Entry 4).

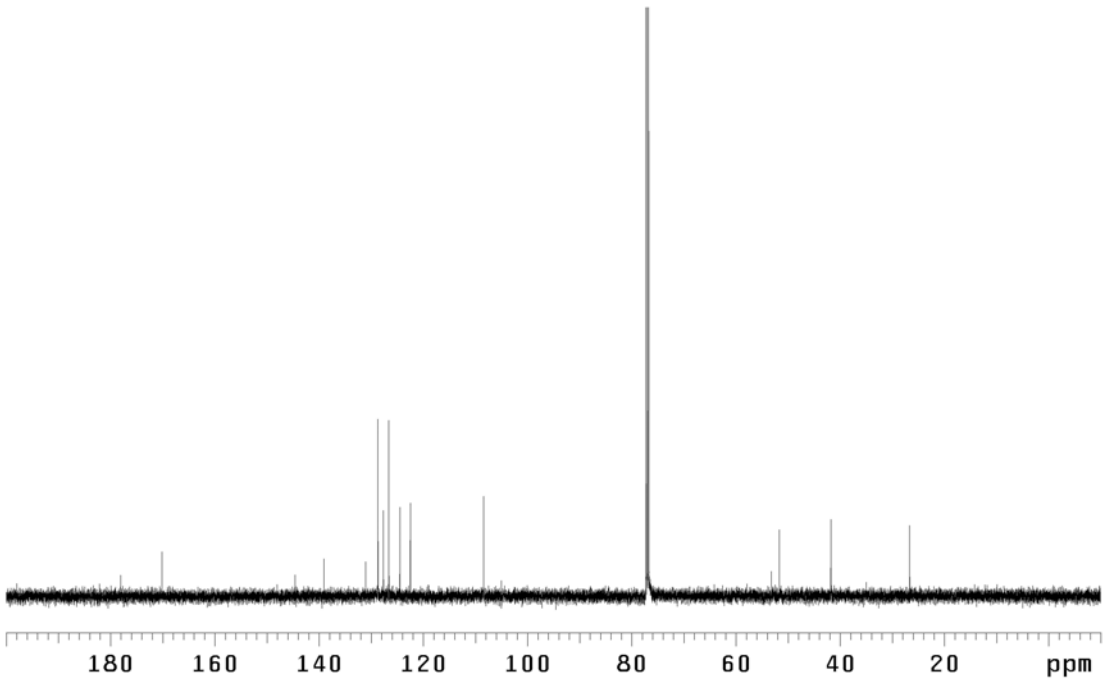
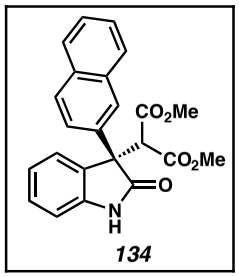


Figure A3.46.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **133** (Entry 3.5, Entry 4).



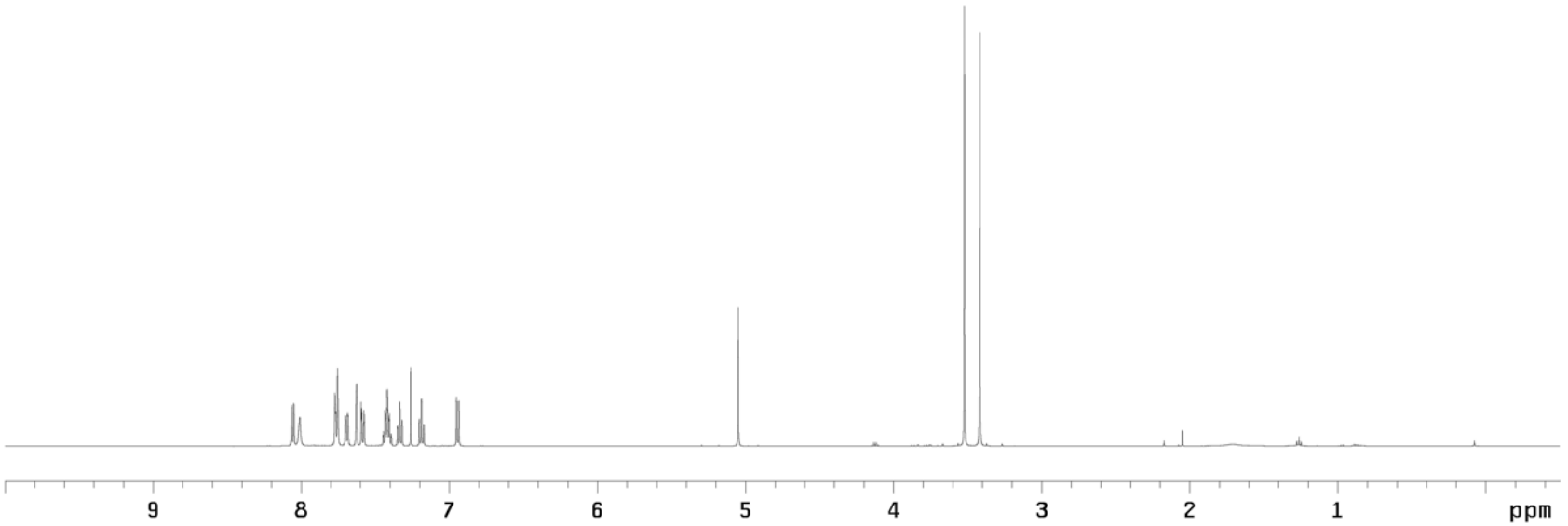


Figure A3.47.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **134** (Table 3.5, Entry 5).

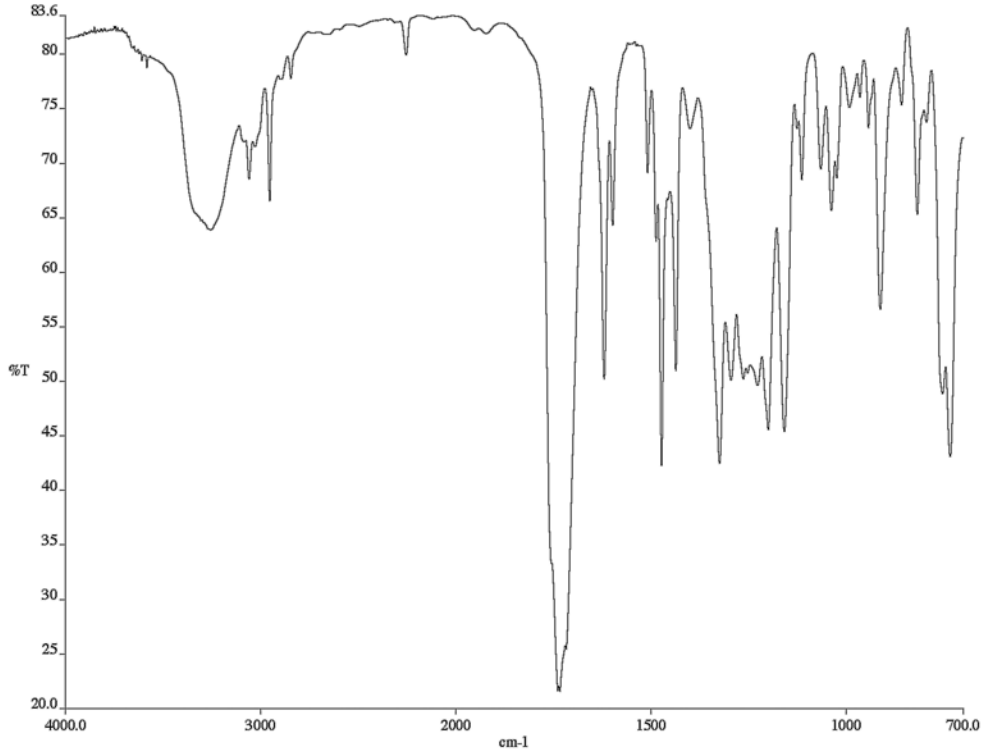


Figure A3.47.2 Infrared spectrum (thin film/NaCl) of compound **134** (Table 3.5, Entry 5).

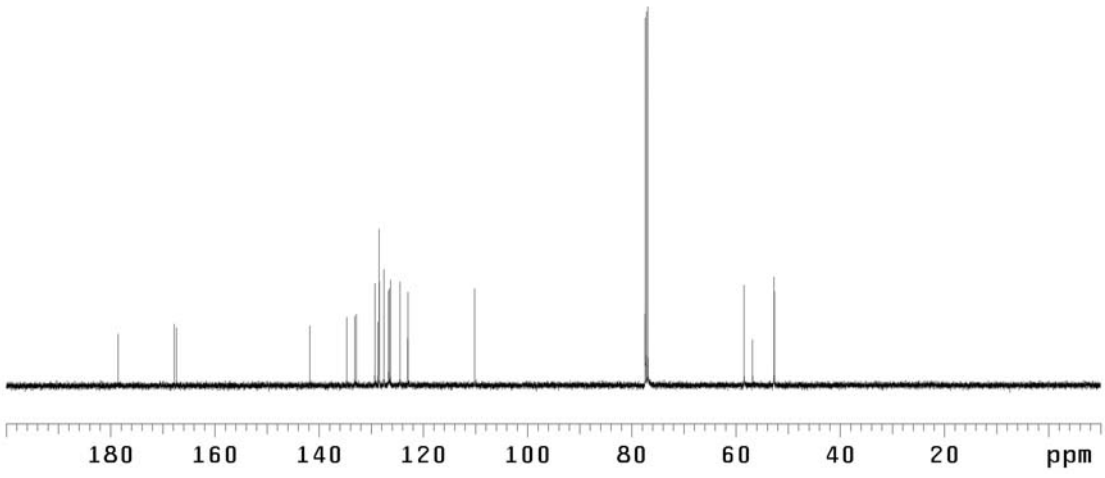
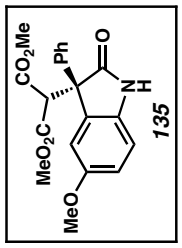


Figure A3.47.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **134** (Table, 3.5, Entry 5).



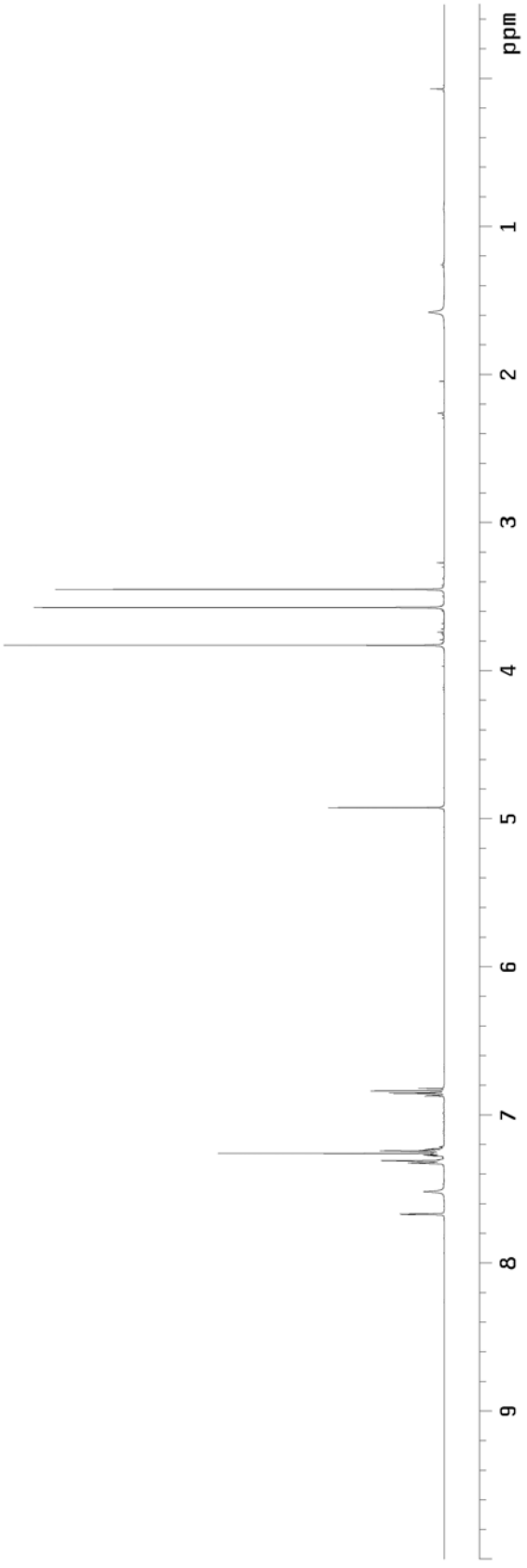


Figure A3.48.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **135** (Table 3.5, Entry 2).

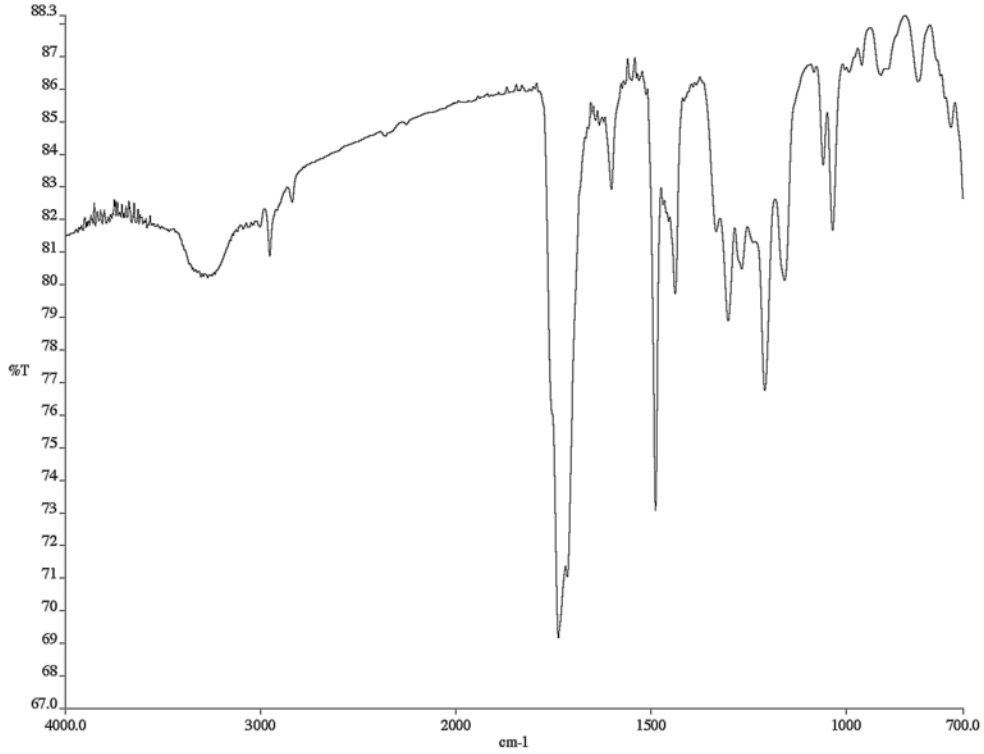


Figure A3.48.2 Infrared spectrum (thin film/NaCl) of compound **135** (Table 3.5, Entry 2).

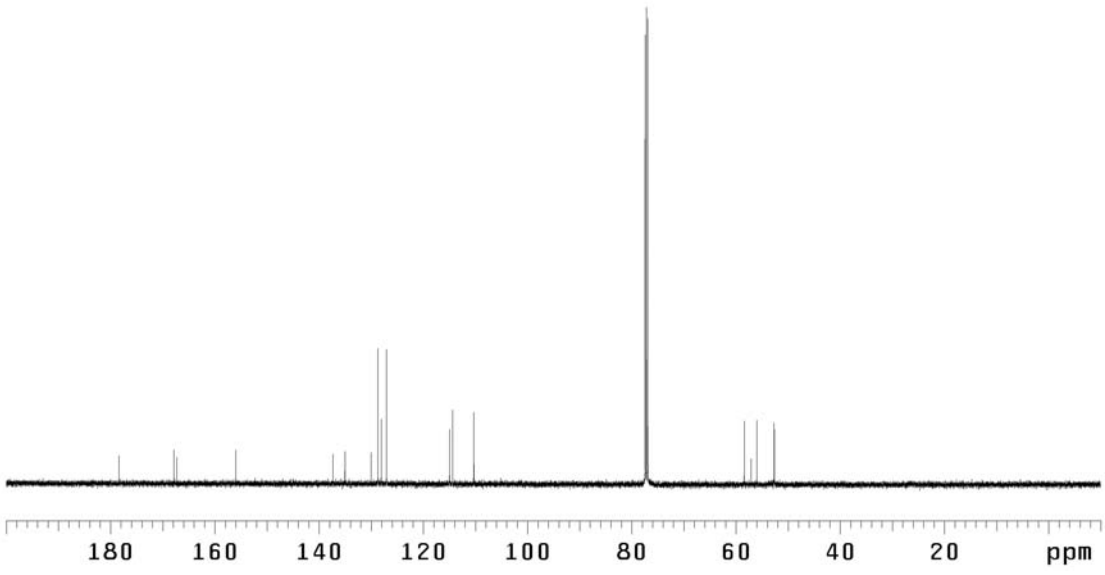
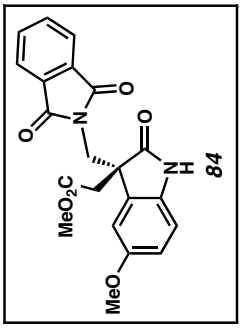


Figure A3.48.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **135** (Table 3.5, Entry 2).



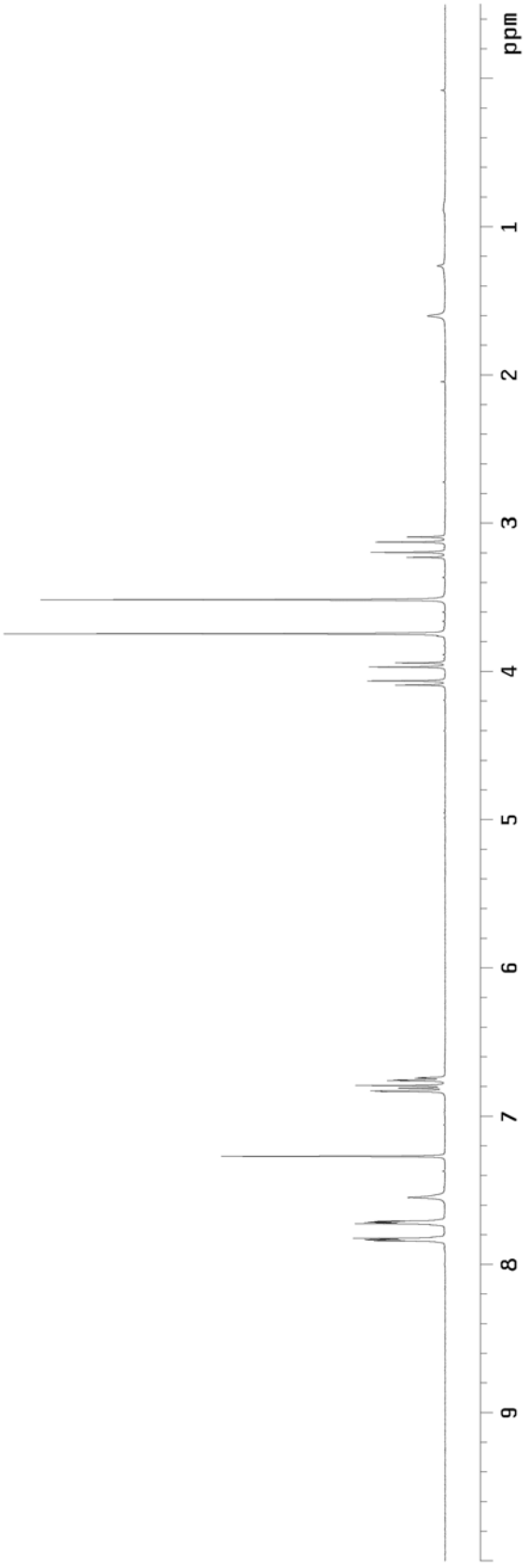


Figure A3.49.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **84**.

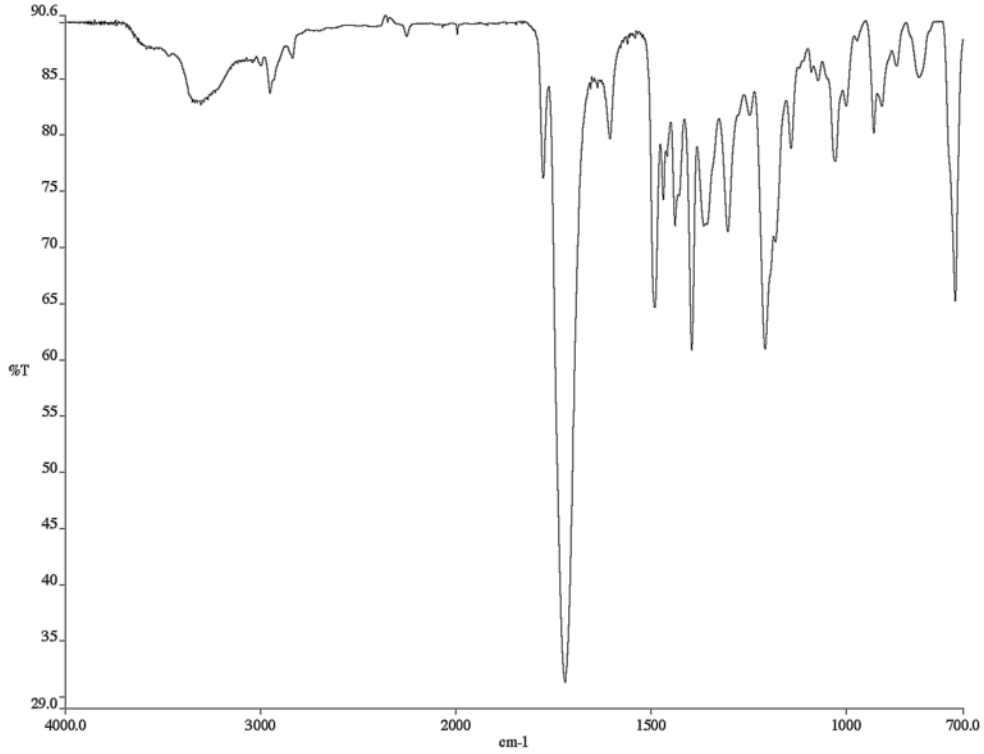


Figure A3.49.2 Infrared spectrum (thin film/NaCl) of compound **84**.

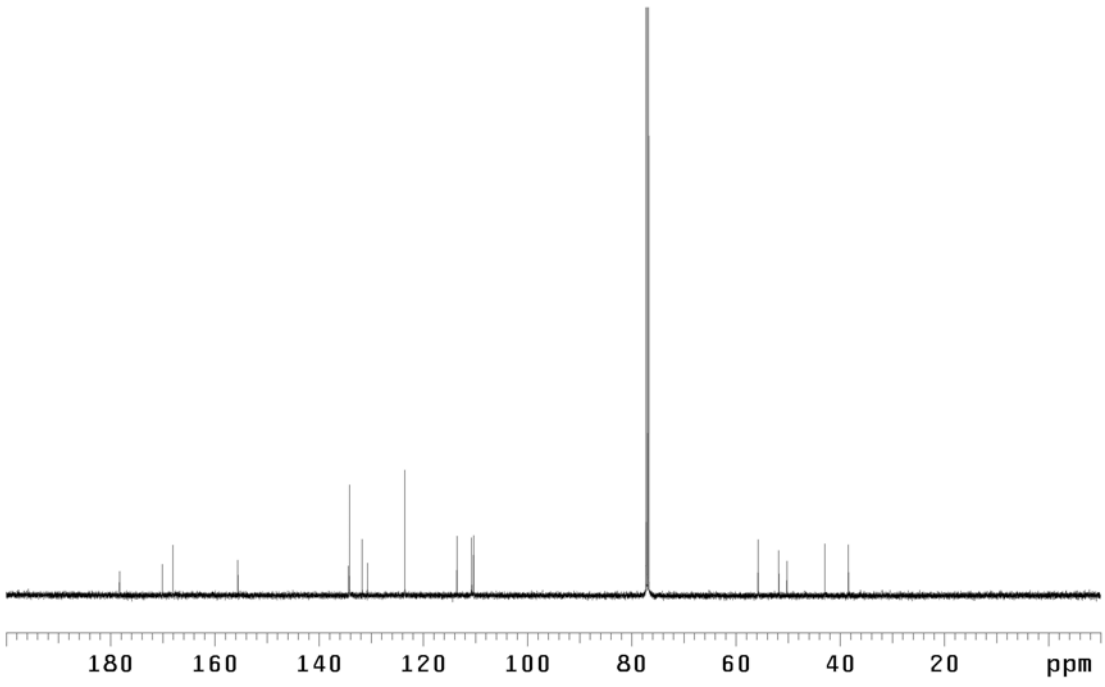


Figure A3.49.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **84**.

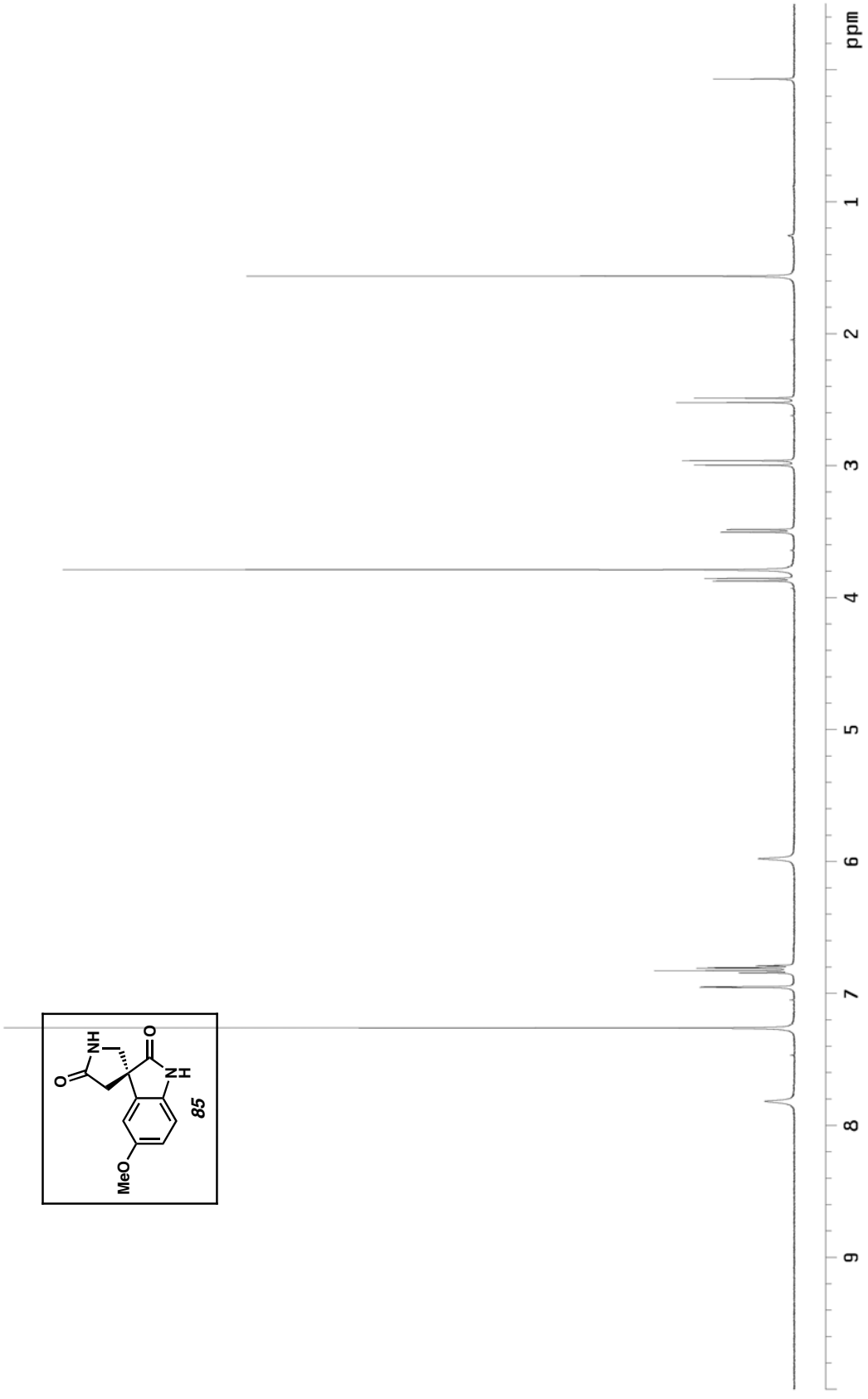


Figure A3.50.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **85**.

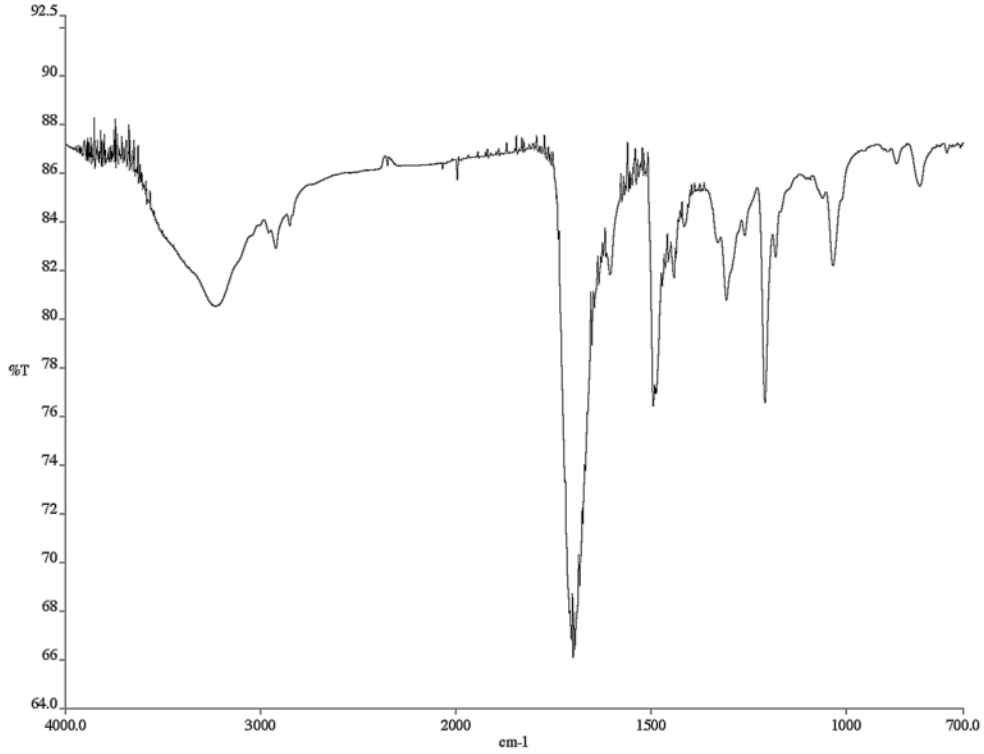


Figure A3.50.2 Infrared spectrum (thin film/NaCl) of compound **85**.

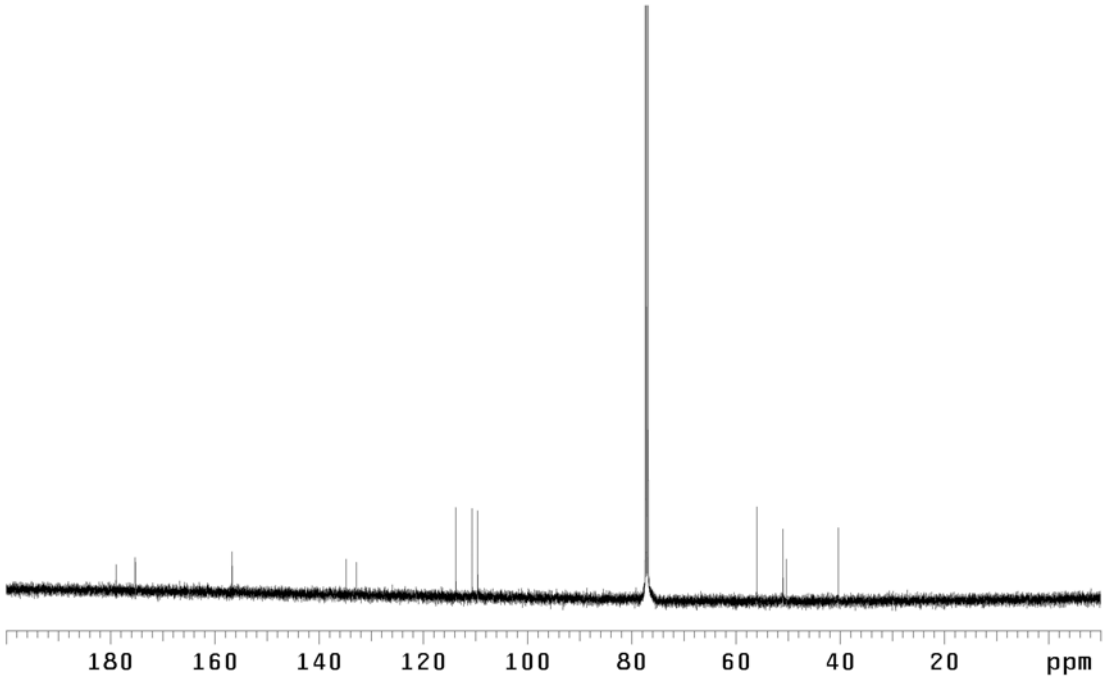
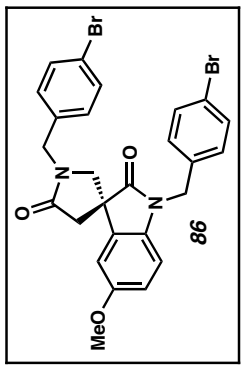


Figure A3.50.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **85**.



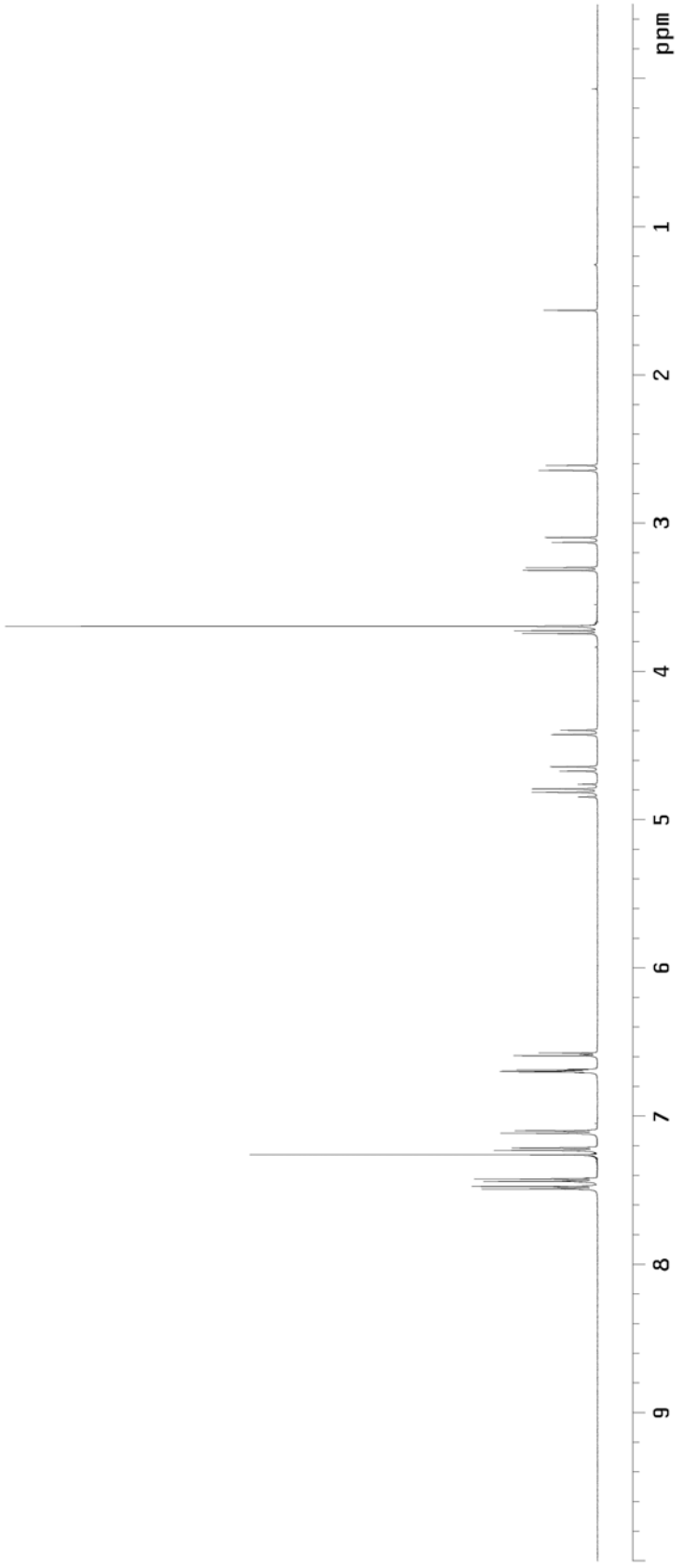


Figure A3.51.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **86**.

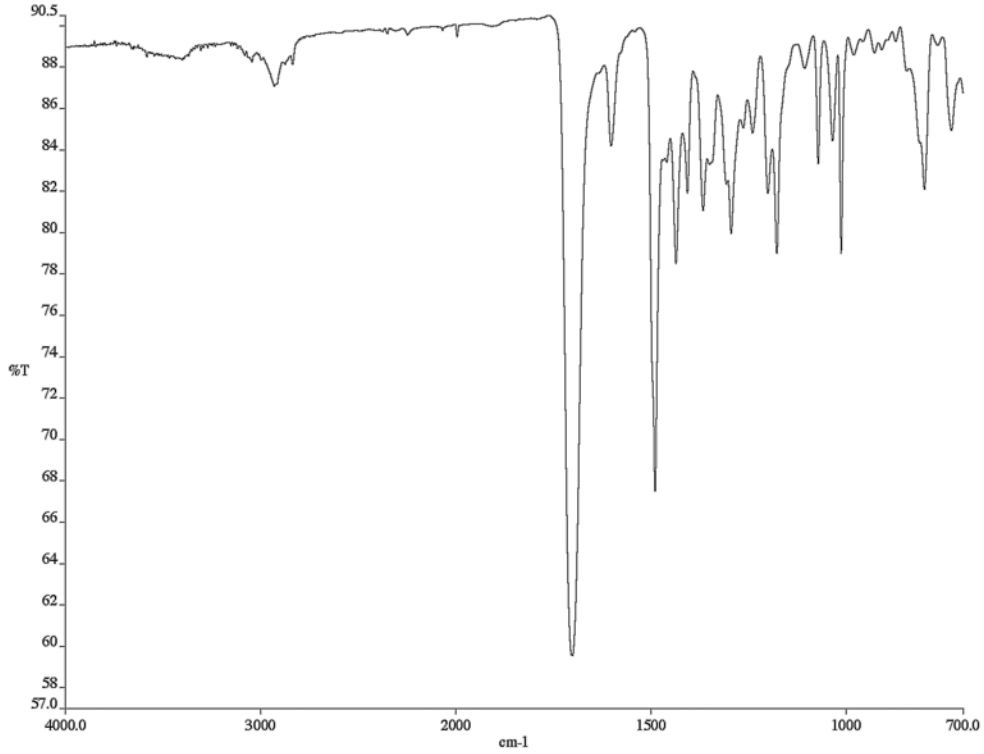


Figure A3.51.2 Infrared spectrum (thin film/NaCl) of compound **86**.

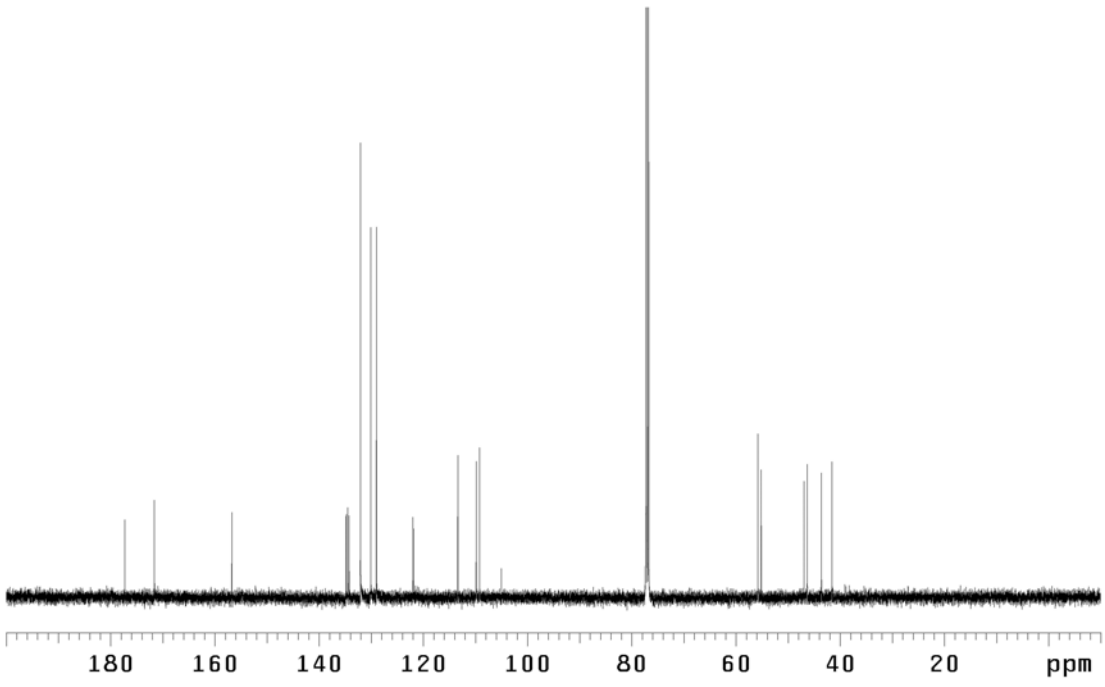


Figure A3.51.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **86**.

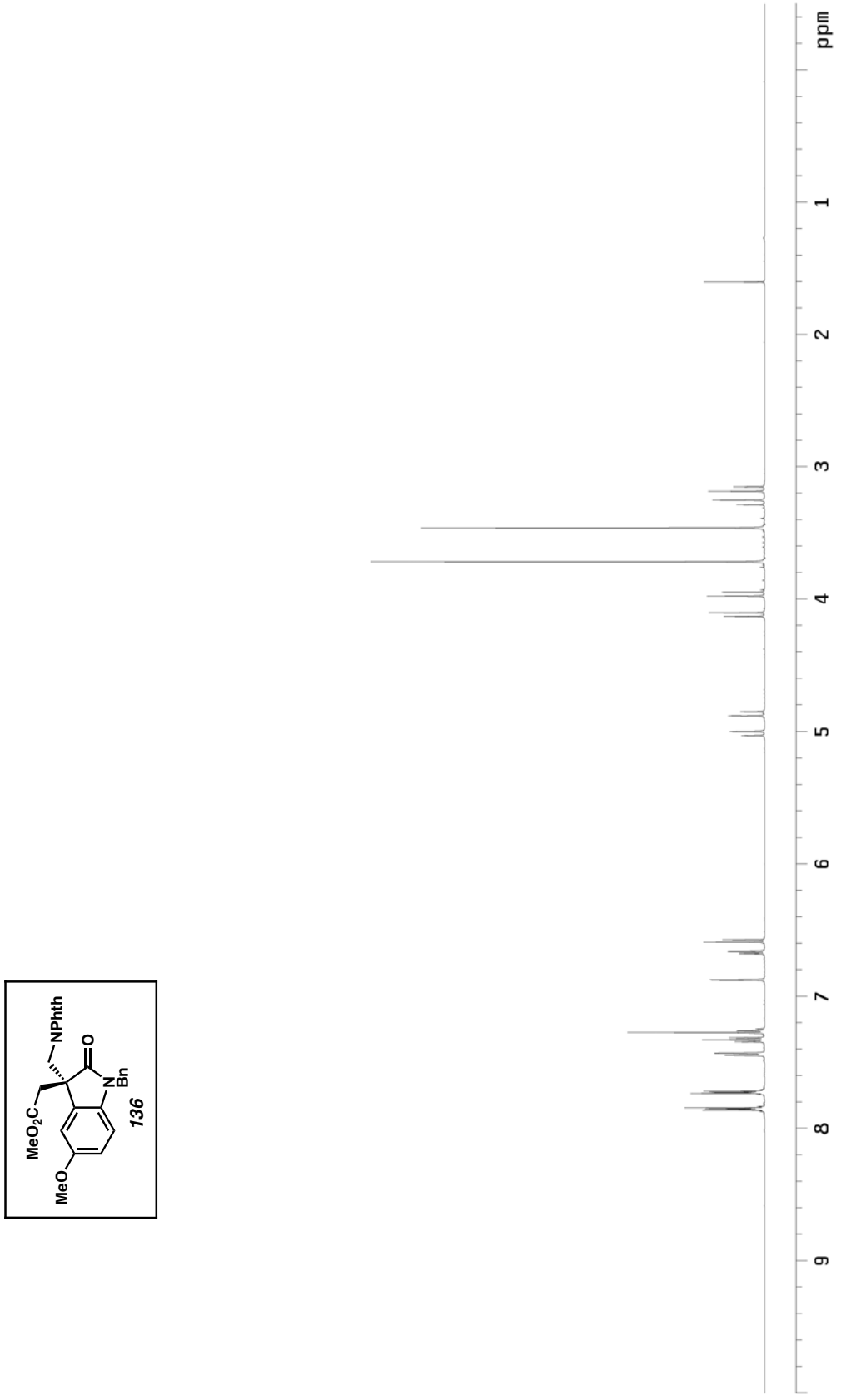


Figure A3.52.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **136**.

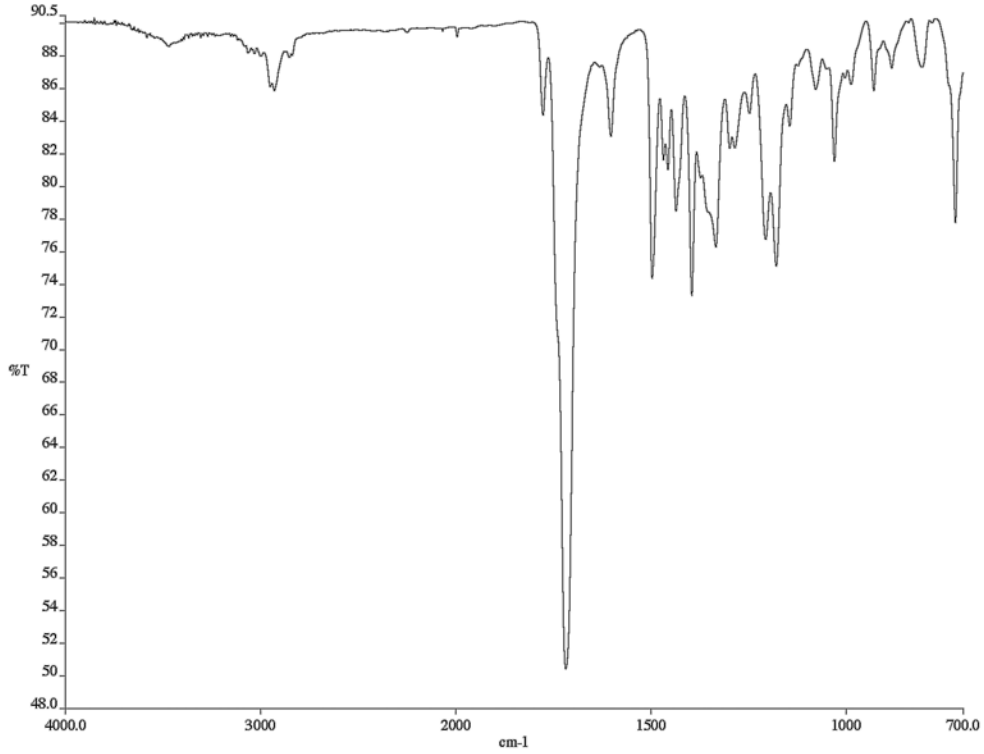


Figure A3.52.2 Infrared spectrum (thin film/NaCl) of compound **136**.

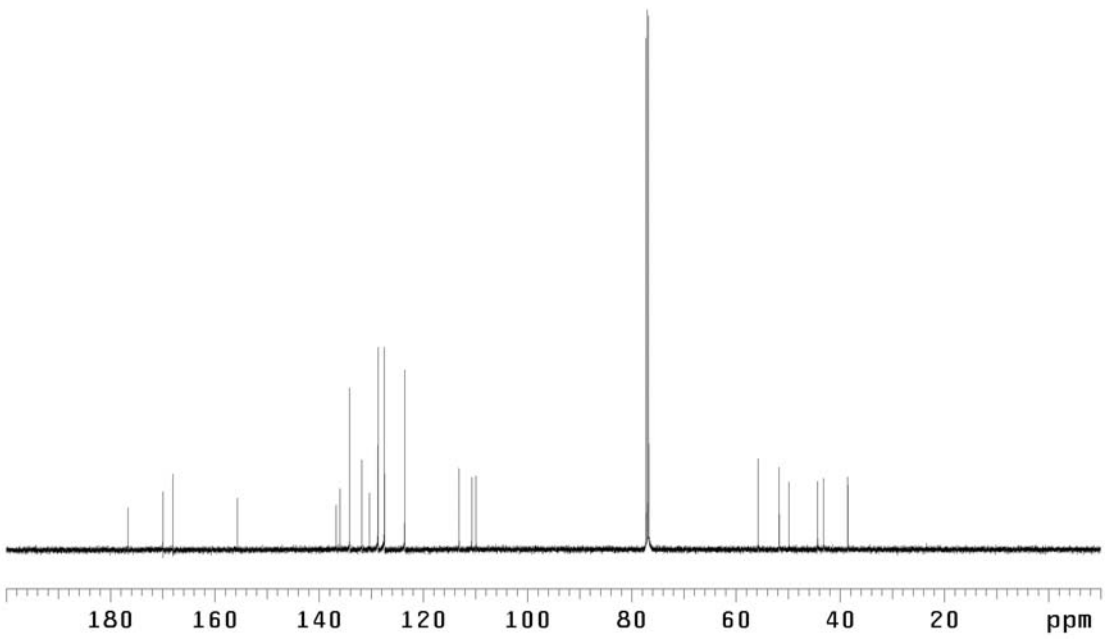


Figure A3.52.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **136**.

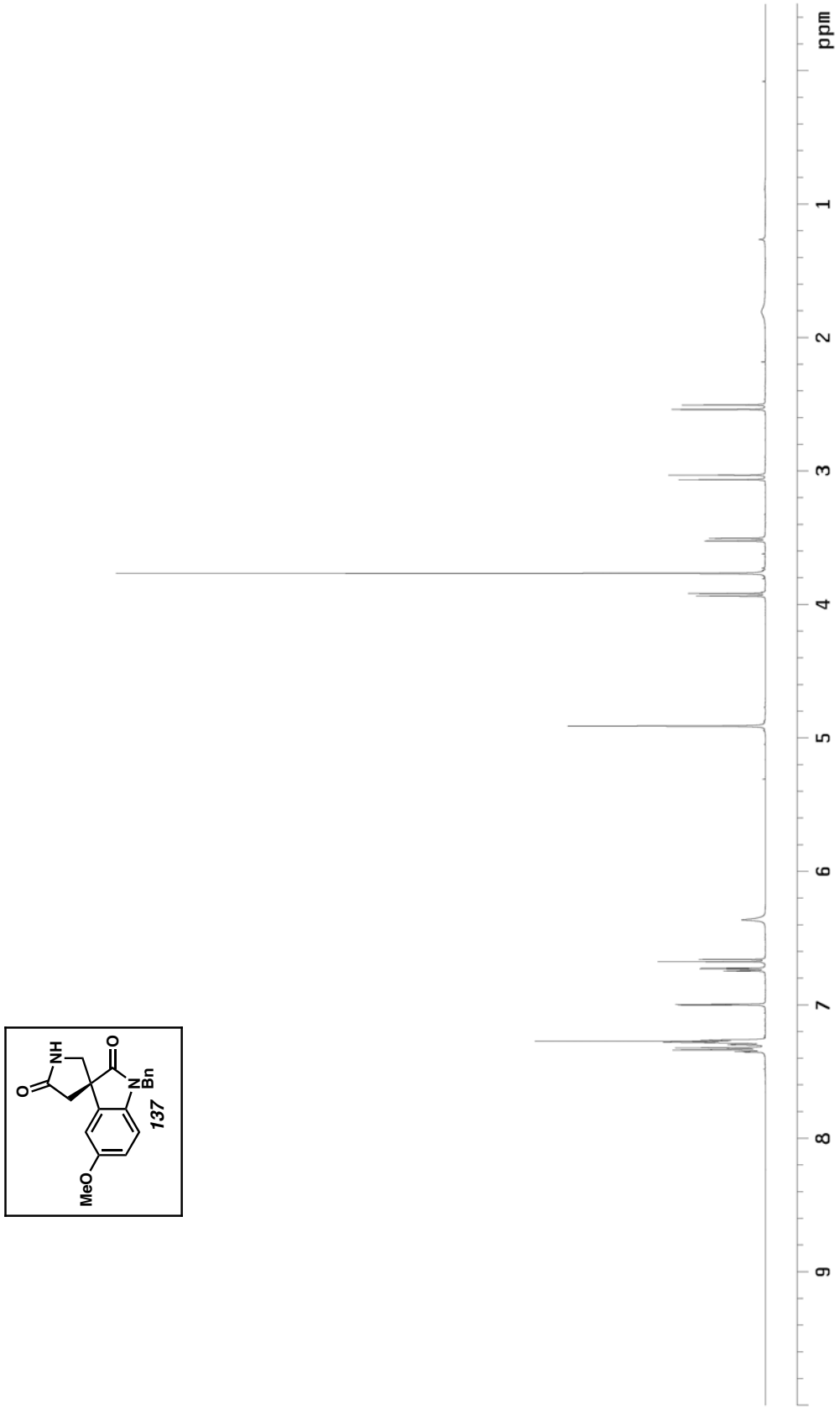


Figure A3.53.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **137**.

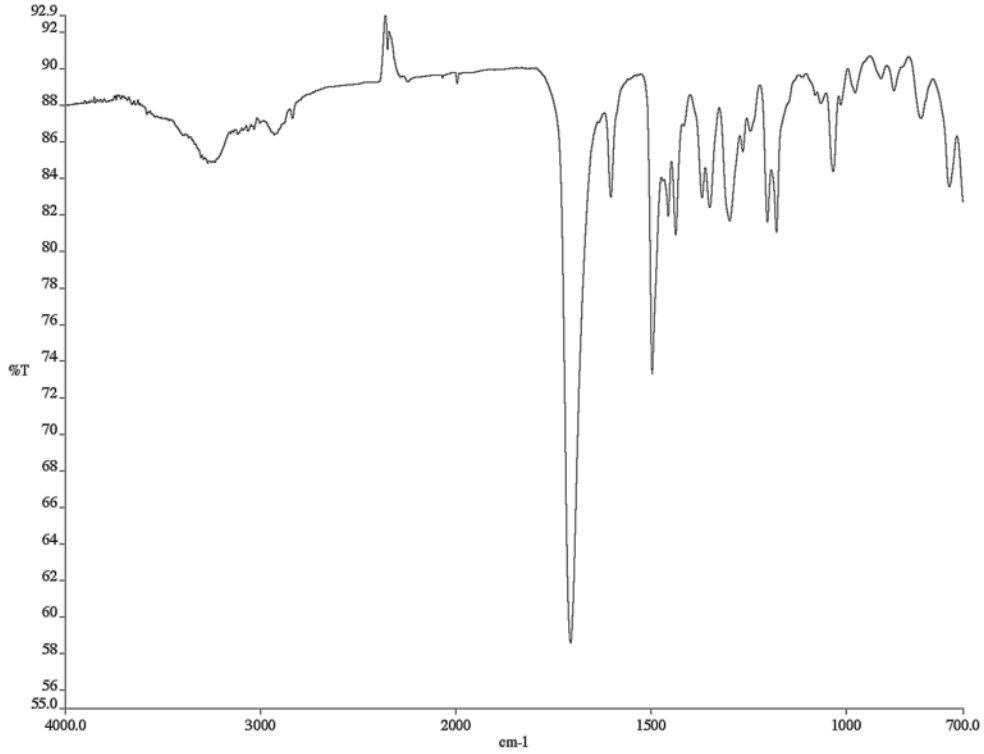


Figure A3.53.2 Infrared spectrum (thin film/NaCl) of compound **137**.

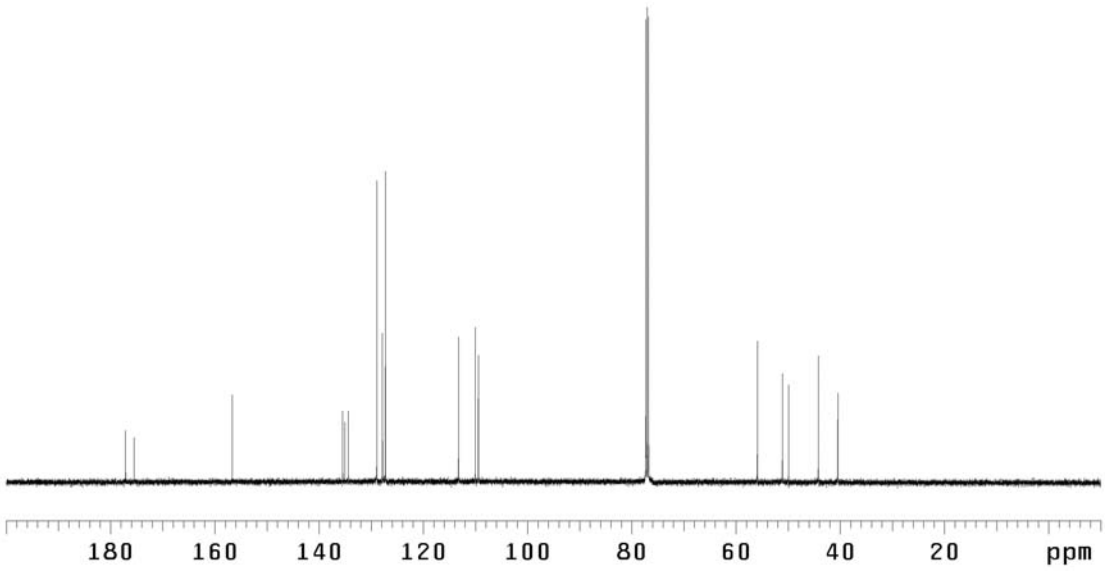


Figure A3.53.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **137**.

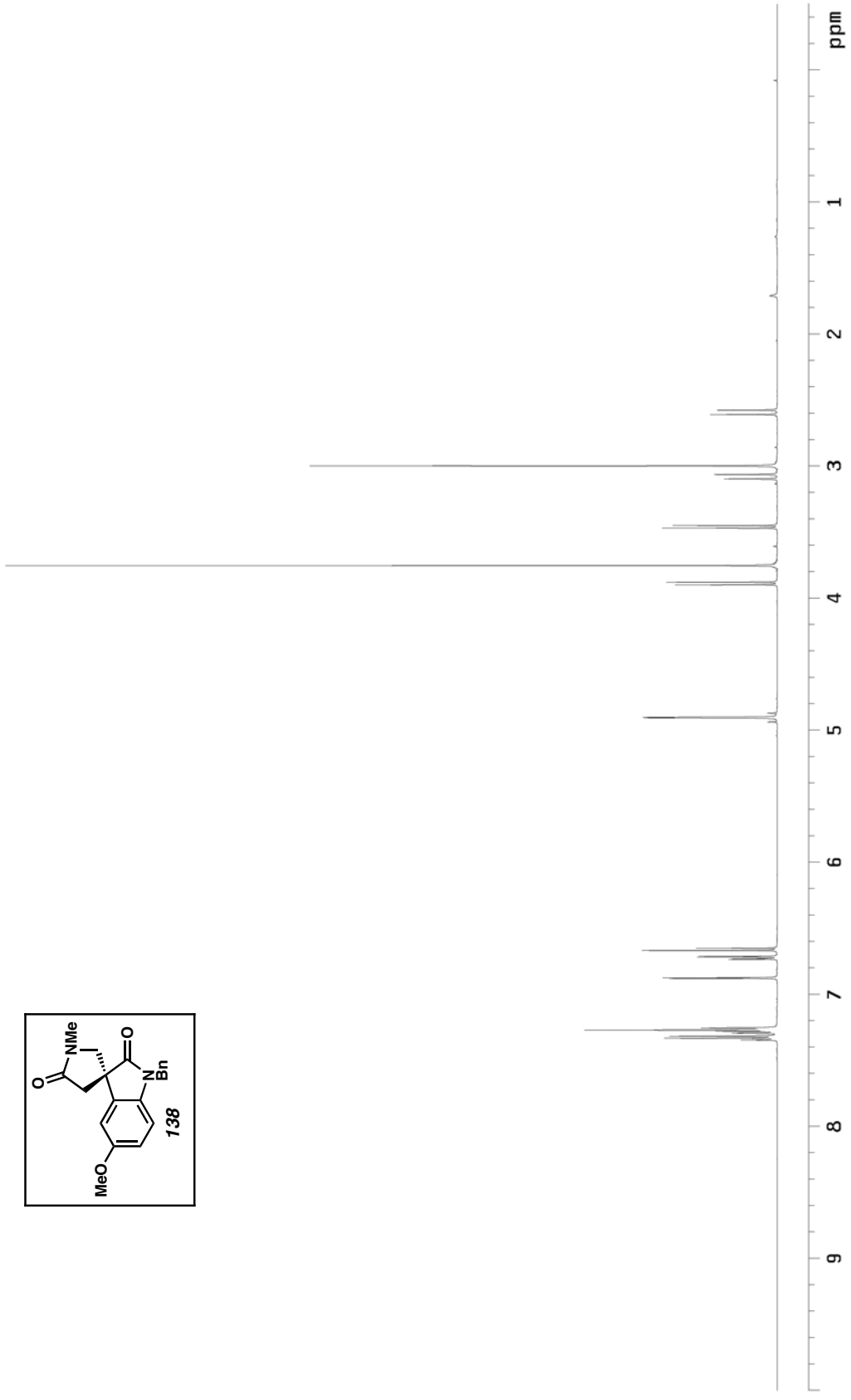


Figure A3.54.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **138**.

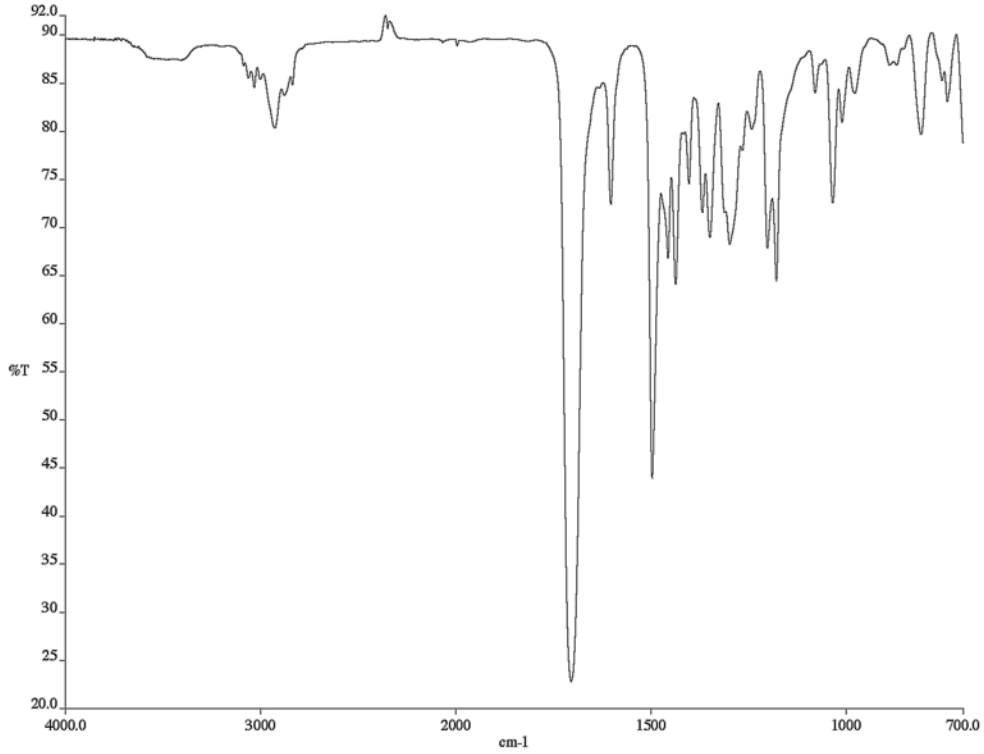


Figure A3.54.2 Infrared spectrum (thin film/NaCl) of compound **138**.

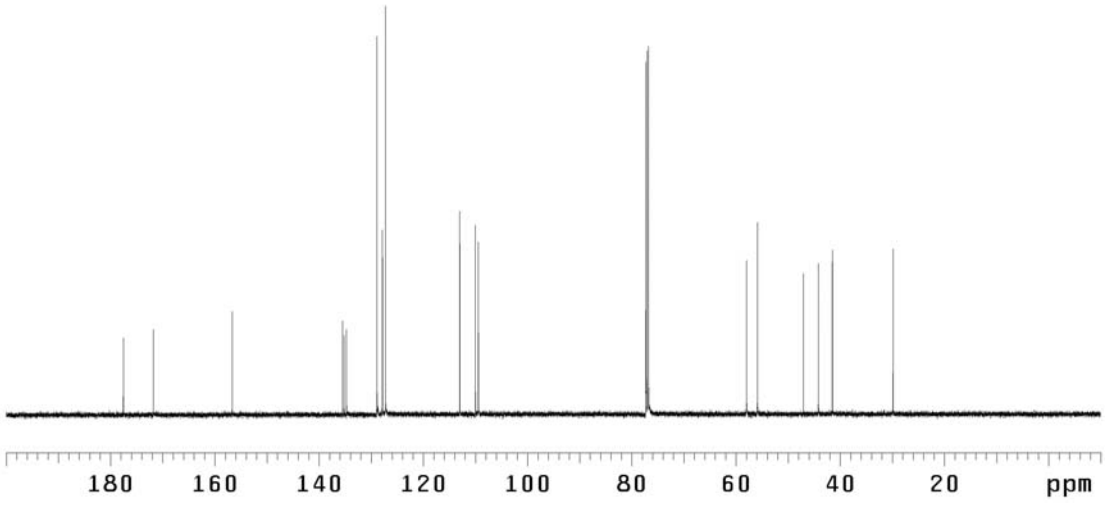
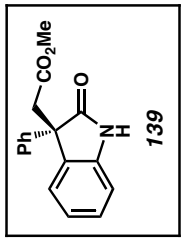


Figure A3.54.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **138**.



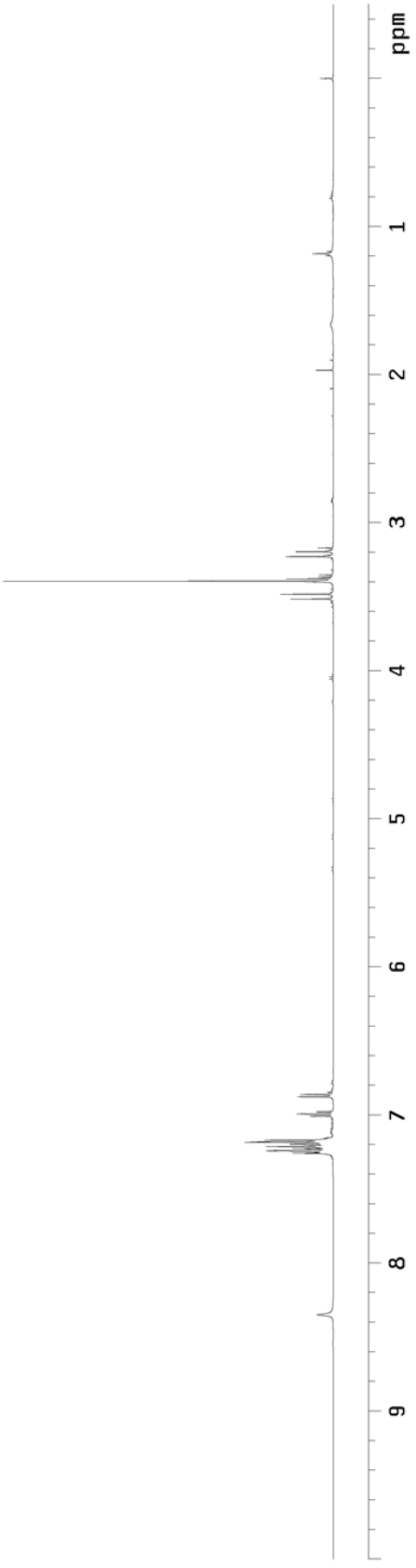


Figure A3.55.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **139**.

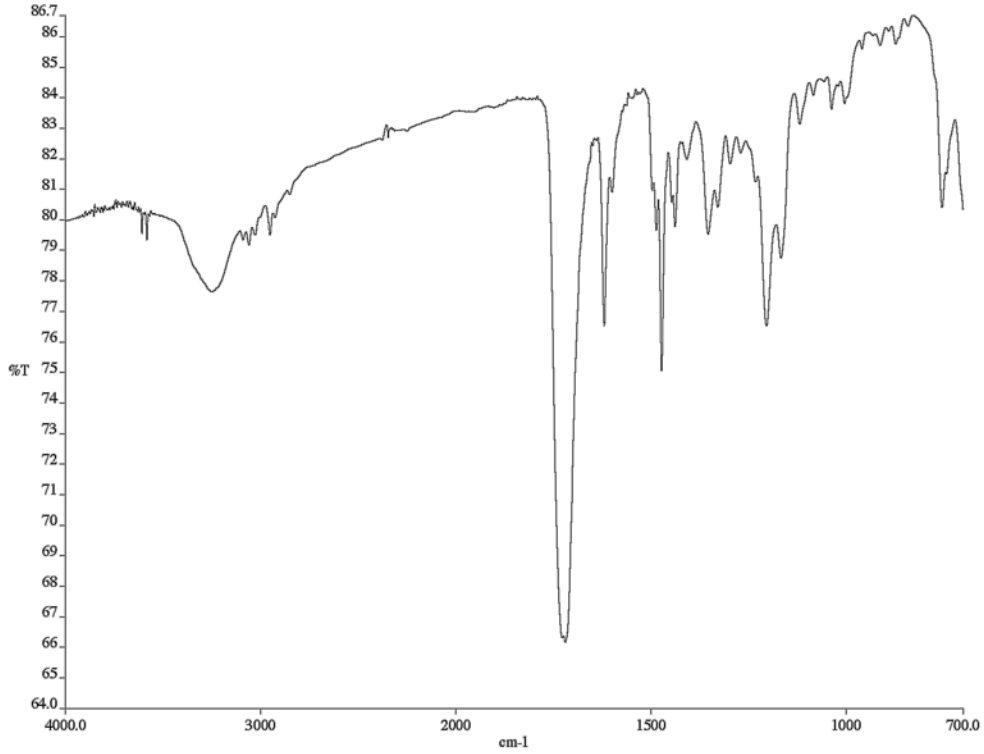


Figure A3.55.2 Infrared spectrum (thin film/NaCl) of compound **139**.

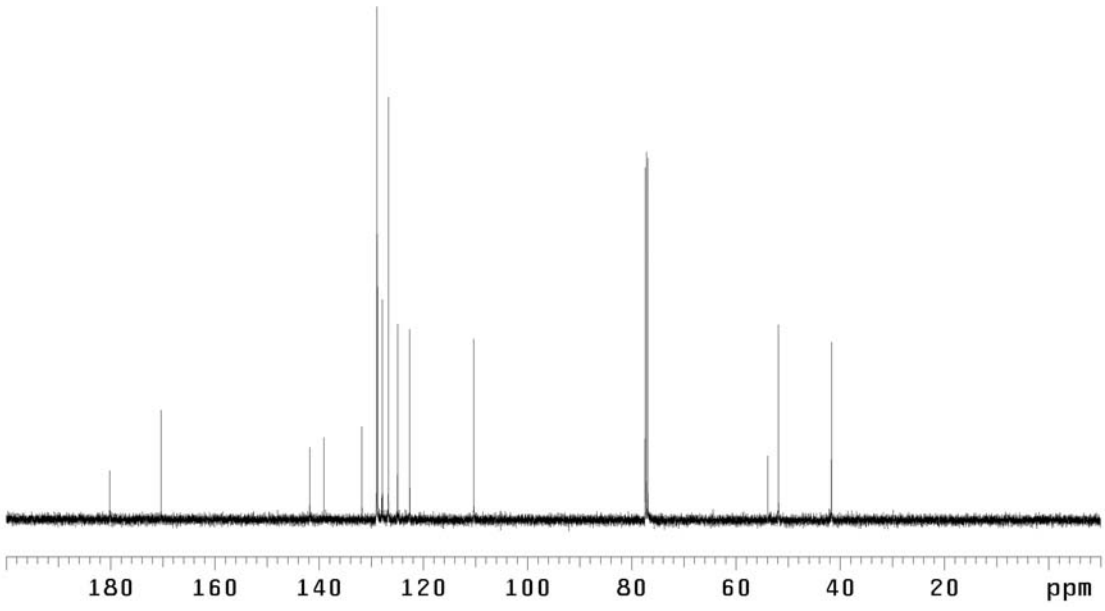
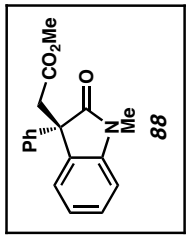


Figure A3.55.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **139**.



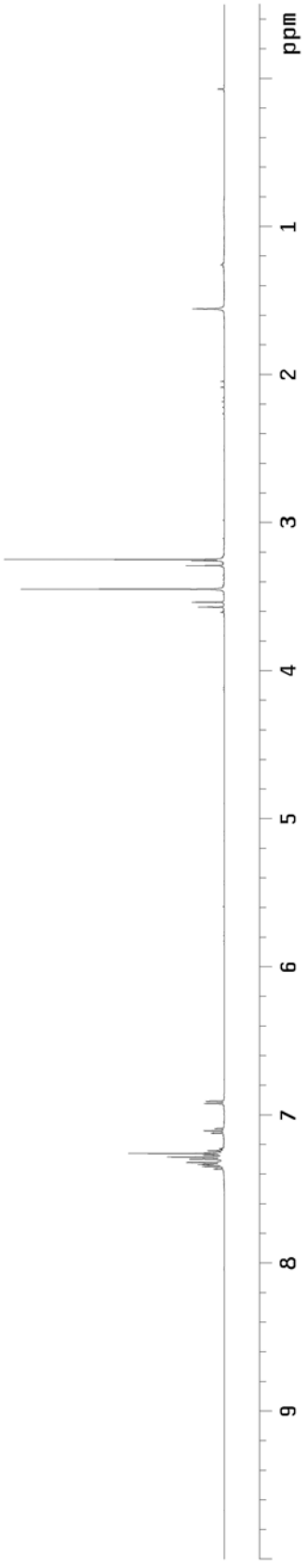


Figure A3.56.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **88**.

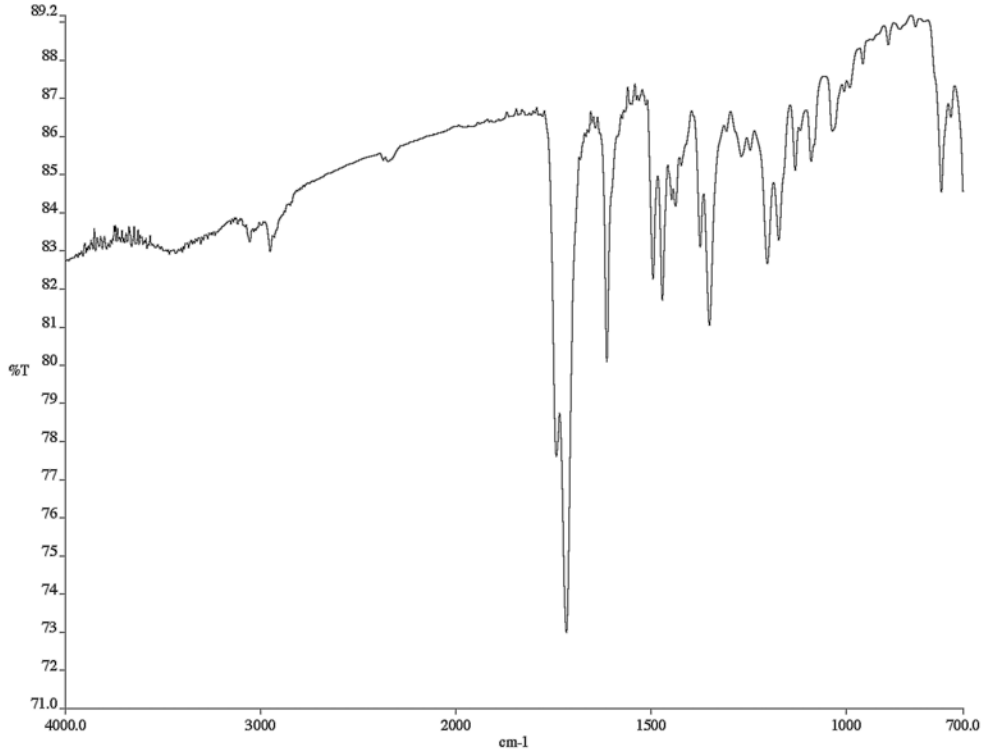


Figure A3.56.2 Infrared spectrum (thin film/NaCl) of compound **88**.

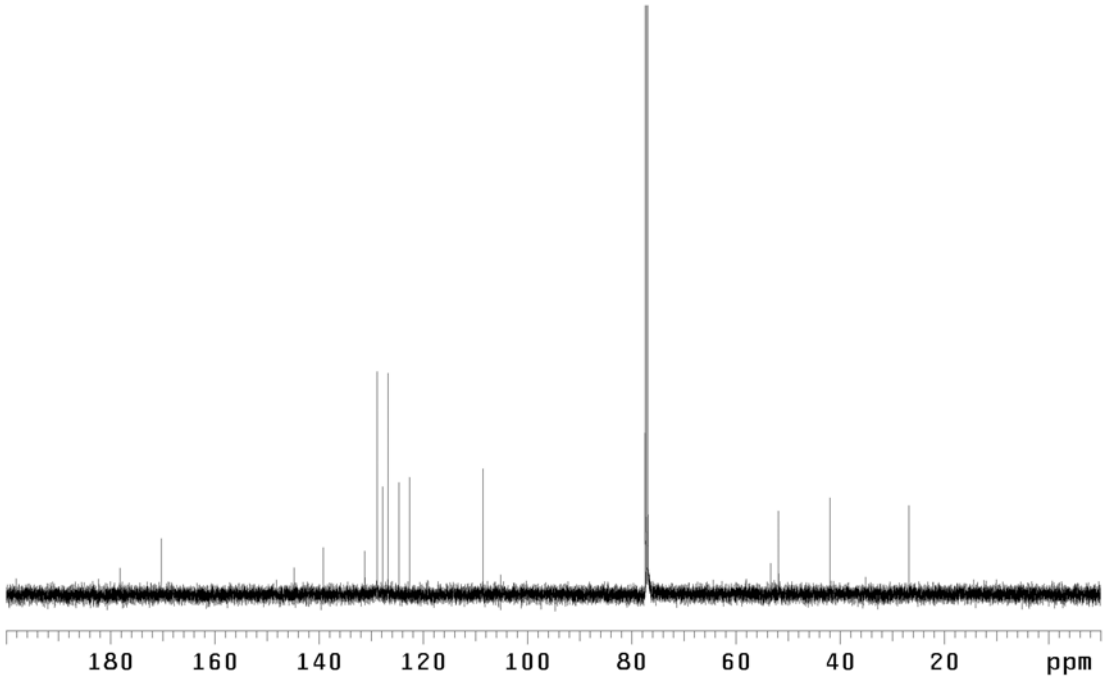
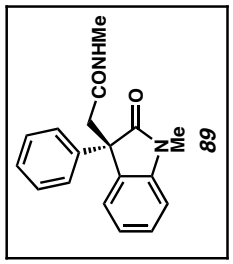


Figure A3.56.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **88**.



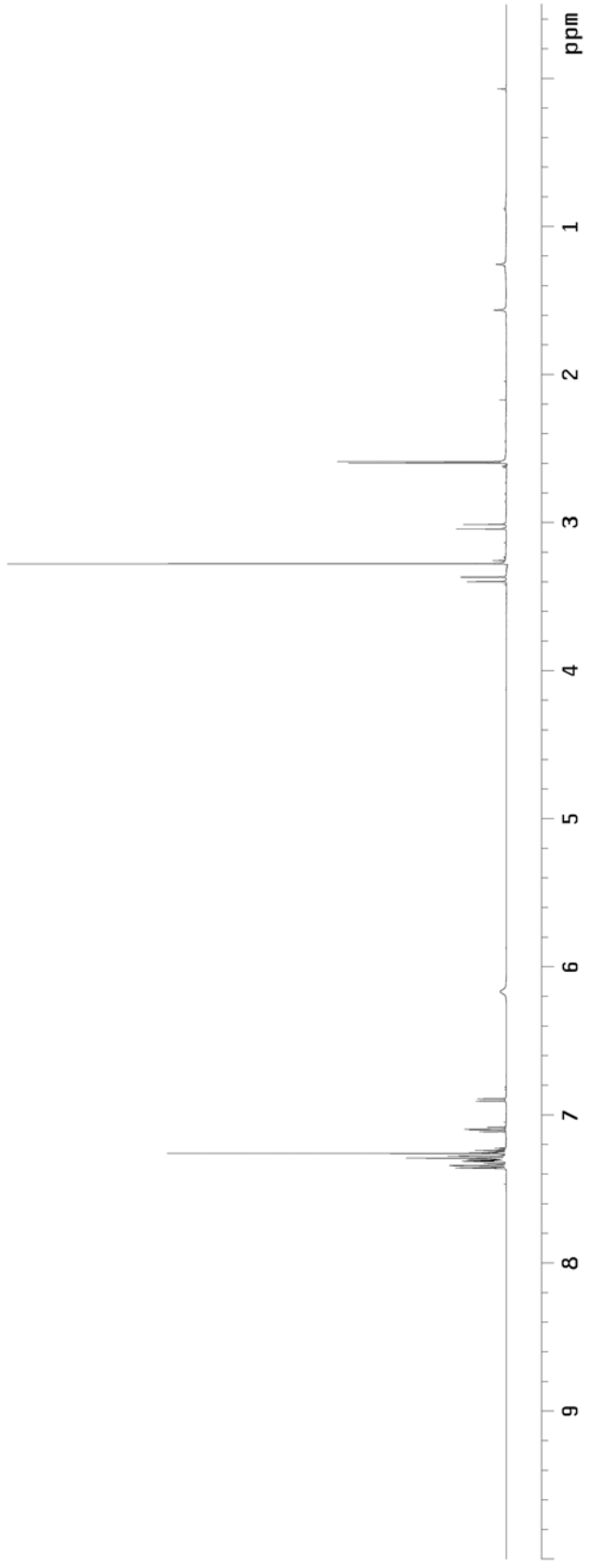


Figure A3.57.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **89**.

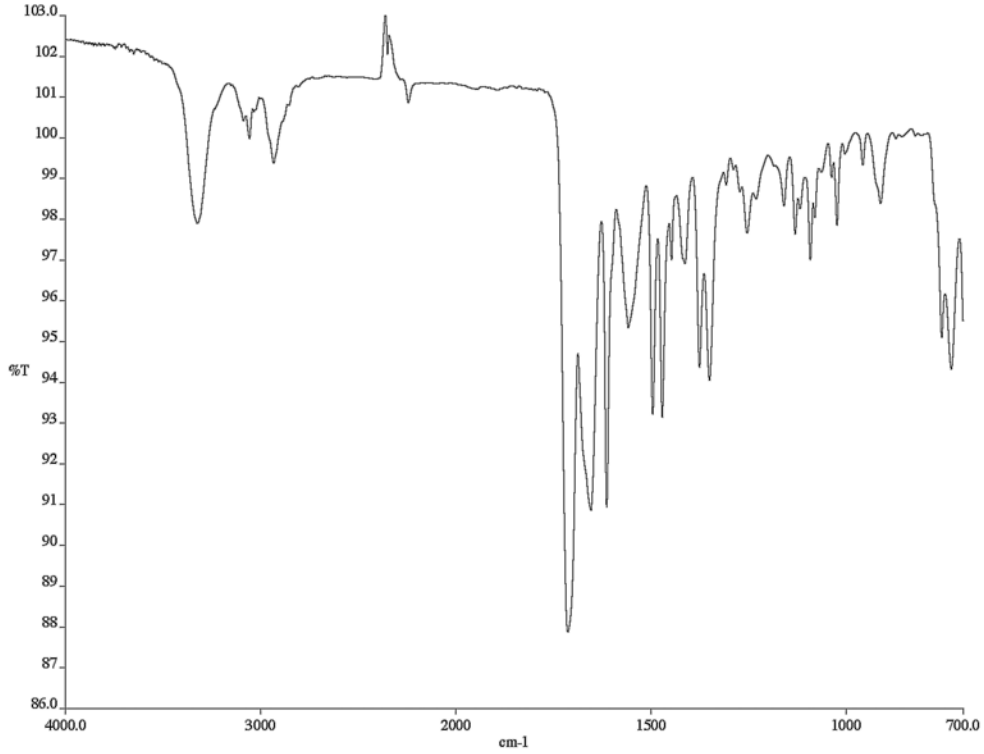


Figure A3.57.2 Infrared spectrum (thin film/NaCl) of compound **89**.

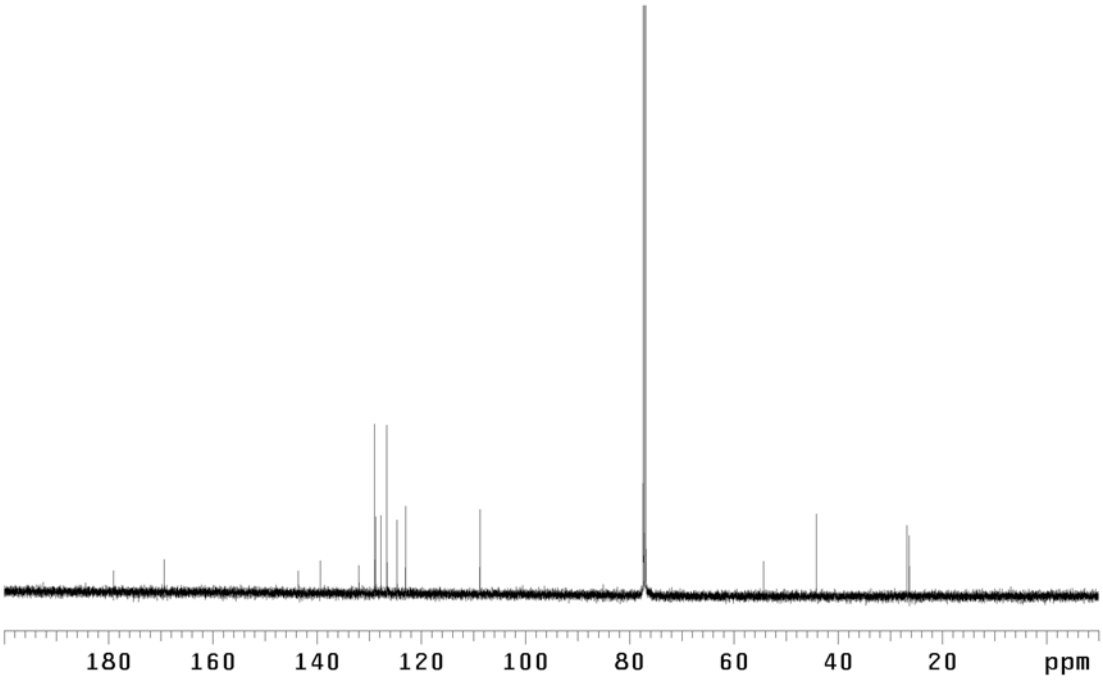
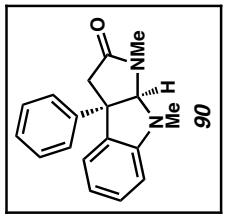


Figure A3.57.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **89**.



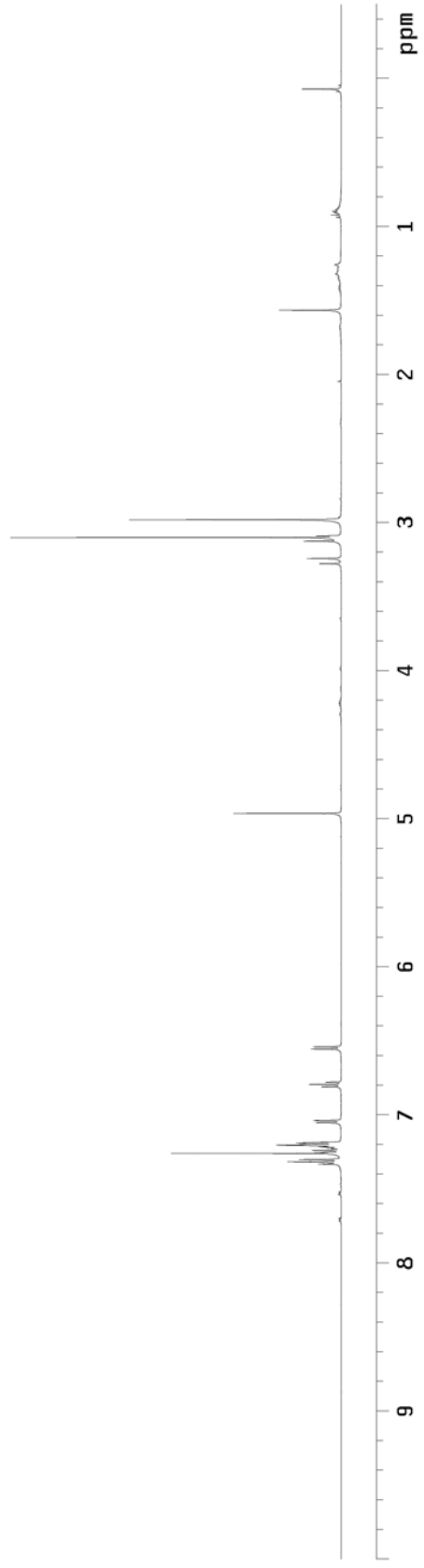


Figure A3.58.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **90**.

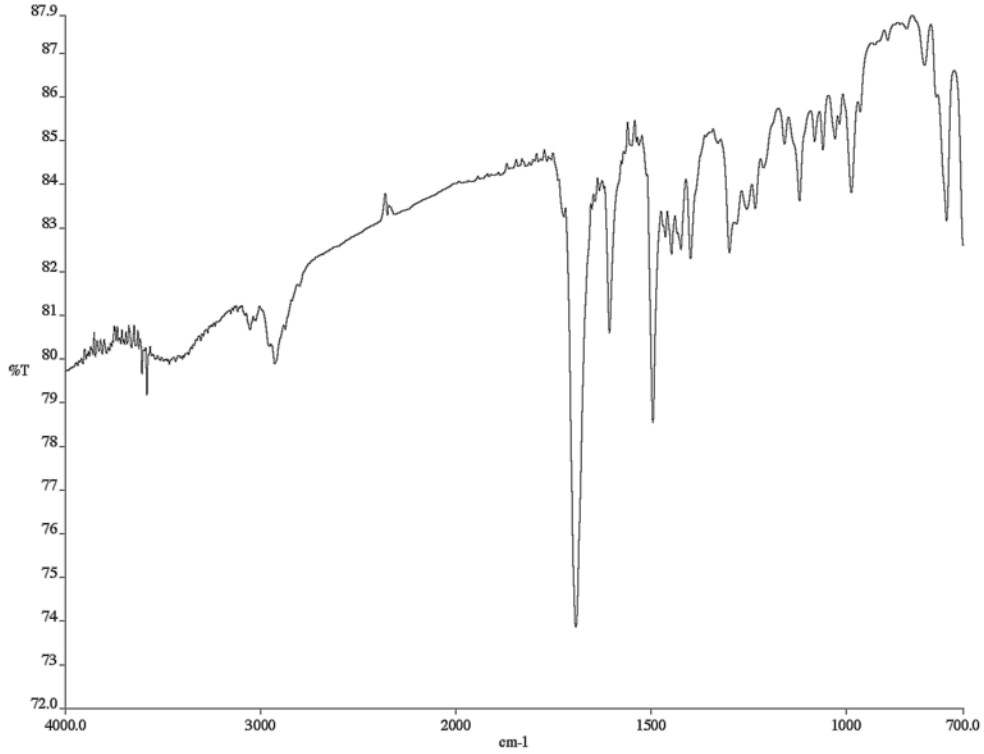


Figure A3.58.2 Infrared spectrum (thin film/NaCl) of compound **90**.

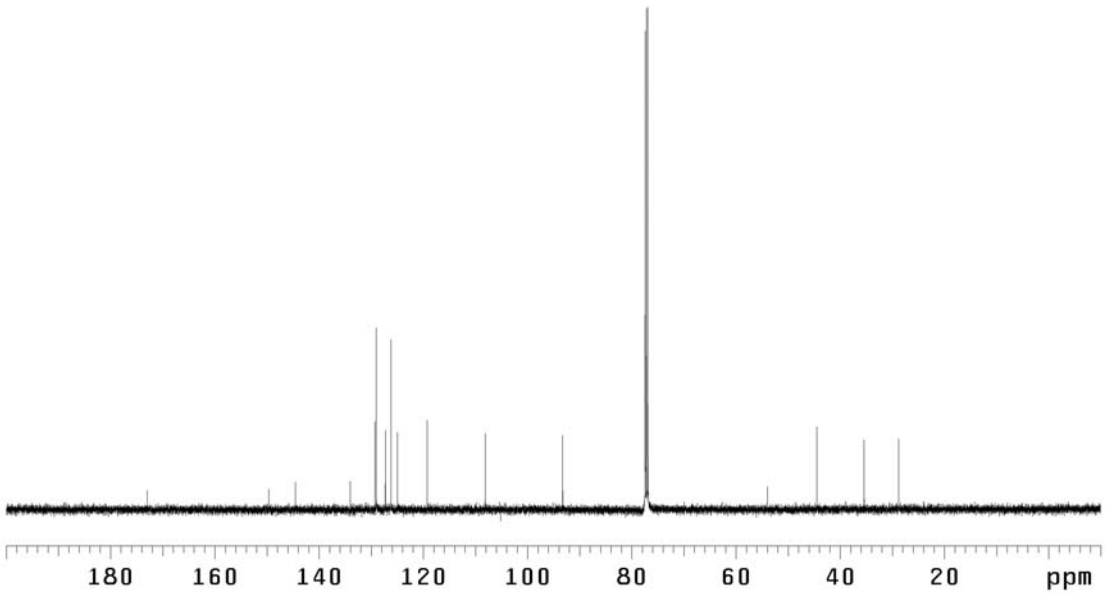


Figure A3.58.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **90**.

APPENDIX 4

X-Ray Crystallography Reports Relevant to Chapter 3

A4.1 CRYSTAL STRUCTURE OF COMPOUND 86

Figure A4.1 ORTEP drawing of ***86*** *(shown with 50% probability ellipsoids)*

NOTE: Crystallographic data have been deposited in the Cambridge Database (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 730732.

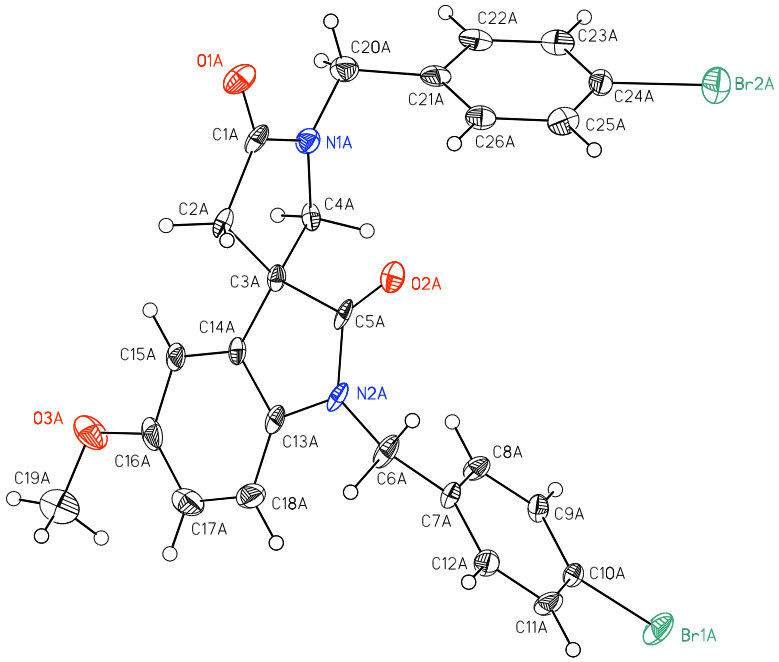


Table A4.1 Crystal data and structure refinement for compound ***86*** *(CCDC 730732)*

Empirical formula	$C_{26}H_{22}N_2O_3Br_2$
Formula weight	570.28
Crystallization Solvent	Dichloromethane/hexanes
Crystal Habit	Blade
Crystal size	0.31 x 0.15 x 0.04 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker KAPPA APEX II
Wavelength	0.71073 Å MoKα
Data Collection Temperature	100(2) K
θ range for 9806 reflections used in lattice determination	2.31 to 28.58°
Unit cell dimensions	a = 17.9356(10) Å b = 5.7243(3) Å β= 101.021(3)° c = 23.3899(14) Å
Volume	2357.1(2) $Å^3$
Z	4
Crystal system	Monoclinic
Space group	$P2_1$
Density (calculated)	1.607 Mg/m^3
F(000)	1144
Data collection program	Bruker APEX2 v2.1-0
θ range for data collection	1.59 to 28.84°
Completeness to θ = 28.84°	90.2 %
Index ranges	$-23 \le h \le 23, -7 \le k \le 7, -31 \le l \le 29$
Data collection scan type	ω scans; 9 settings
Data reduction program	Bruker SAINT-Plus v7.34A
Reflections collected	34011
Independent reflections	10814 [R_{int}= 0.0407]
Absorption coefficient	3.470 mm^{-1}
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7458 and 0.5386

Table A4.1 (cont.)

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 2008)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 2008)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	10814 / 1 / 597
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	2.111
Final R indices [I>2σ(I), 9564 reflections]	R1 = 0.0496, *w*R2 = 0.0966
R indices (all data)	R1 = 0.0583, *w*R2 = 0.0978
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.001
Average shift/error	0.000
Absolute structure determination	Anomalous differences
Absolute structure parameter	0.009(8)
Largest diff. peak and hole	2.847 and -0.755 e.Å^{-3}

Special Refinement Details

Crystals were mounted on a glass fiber using Paratone oil then placed on the diffractometer under a nitrogen stream at 100K.

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Table A4.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for compound ***86*** *(CCDC 730732). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor*

	x	y	z	U_{eq}
Br(1A)	6411(1)	2780(1)	8308(1)	29(1)
Br(2A)	8097(1)	4182(1)	4916(1)	33(1)
O(1A)	12421(2)	1951(6)	6948(1)	25(1)
O(2A)	10376(2)	281(6)	7431(1)	20(1)
O(3A)	11743(2)	8771(7)	9625(1)	31(1)
N(1A)	11400(2)	4312(8)	7006(1)	18(1)
N(2A)	10271(2)	1382(7)	8361(2)	17(1)
C(1A)	11958(2)	2785(9)	7218(2)	18(1)
C(2A)	11927(2)	2345(8)	7851(2)	16(1)
C(3A)	11155(2)	3428(7)	7935(2)	14(1)
C(4A)	10986(2)	5220(8)	7430(2)	16(1)
C(5A)	10557(2)	1508(9)	7858(2)	17(1)
C(6A)	9744(2)	-396(9)	8467(2)	23(1)
C(7A)	8938(2)	465(8)	8439(2)	16(1)
C(8A)	8681(2)	2519(9)	8168(2)	18(1)
C(9A)	7926(2)	3243(9)	8131(2)	17(1)
C(10A)	7439(2)	1833(9)	8367(2)	18(1)
C(11A)	7684(2)	-265(9)	8642(2)	21(1)
C(12A)	8437(2)	-903(10)	8676(2)	20(1)
C(13A)	10593(2)	3132(9)	8760(2)	17(1)
C(14A)	11120(2)	4401(9)	8526(2)	15(1)
C(15A)	11498(2)	6247(9)	8824(2)	18(1)
C(16A)	11341(2)	6784(10)	9370(2)	24(1)
C(17A)	10833(3)	5510(10)	9610(2)	27(1)
C(18A)	10446(2)	3638(9)	9304(2)	26(1)
C(19A)	11662(3)	9297(13)	10187(2)	45(2)
C(20A)	11306(3)	5406(9)	6431(2)	22(1)
C(21A)	10504(3)	5108(8)	6076(2)	19(1)
C(22A)	10186(3)	6841(9)	5691(2)	21(1)
C(23A)	9481(3)	6587(9)	5352(2)	23(1)
C(24A)	9080(2)	4582(9)	5399(2)	19(1)
C(25A)	9368(2)	2831(10)	5787(2)	22(1)
C(26A)	10081(2)	3084(10)	6124(2)	20(1)
Br(1B)	1104(1)	2958(1)	3114(1)	28(1)
Br(2B)	3076(1)	4135(1)	-196(1)	39(1)
O(1B)	7247(2)	2063(5)	2000(1)	20(1)
O(2B)	5178(2)	151(5)	2326(1)	18(1)
O(3B)	6124(2)	7947(8)	4777(1)	34(1)
N(1B)	6222(2)	4391(7)	2035(1)	15(1)
N(2B)	4931(2)	1065(7)	3223(2)	17(1)
C(1B)	6767(2)	2850(9)	2256(2)	15(1)
C(2B)	6684(2)	2272(8)	2874(2)	15(1)
C(3B)	5900(2)	3250(8)	2920(2)	13(1)

C(4B)	5767(2)	5166(8)	2442(2)	13(1)
C(5B)	5306(2)	1295(8)	2767(2)	16(1)
C(6B)	4364(2)	-719(9)	3256(2)	22(1)
C(7B)	3573(2)	228(9)	3239(2)	19(1)
C(8B)	3342(2)	2320(8)	2951(2)	22(1)
C(9B)	2611(2)	3124(10)	2926(2)	22(1)
C(10B)	2115(2)	1891(8)	3185(2)	18(1)
C(11B)	2330(3)	-221(9)	3469(2)	24(1)
C(12B)	3067(2)	-977(10)	3500(2)	22(1)
C(13B)	5183(2)	2750(10)	3654(2)	20(1)
C(14B)	5778(2)	4049(9)	3506(2)	17(1)
C(15B)	6123(2)	5828(9)	3860(2)	19(1)
C(16B)	5850(3)	6237(9)	4380(2)	25(1)
C(17B)	5248(3)	4923(9)	4512(2)	28(1)
C(18B)	4905(2)	3141(10)	4155(2)	25(1)
C(19B)	6686(3)	9372(10)	4644(2)	28(1)
C(20B)	6167(2)	5522(9)	1472(2)	18(1)
C(21B)	5395(2)	5191(8)	1084(2)	17(1)
C(22B)	5106(3)	6938(9)	686(2)	20(1)
C(23B)	4409(3)	6641(9)	300(2)	23(1)
C(24B)	4011(2)	4584(9)	335(2)	23(1)
C(25B)	4277(2)	2834(11)	726(2)	22(1)
C(26B)	4978(2)	3164(9)	1105(2)	19(1)

Table A4.3 Bond lengths [Å] and angles [°] for ***86*** *(CCDC 730732)*

Br(1A)-C(10A)	1.901(4)	C(13A)-C(14A)	1.384(6)
Br(2A)-C(24A)	1.917(4)	C(14A)-C(15A)	1.372(6)
O(1A)-C(1A)	1.233(5)	C(15A)-C(16A)	1.393(6)
O(2A)-C(5A)	1.213(5)	C(16A)-C(17A)	1.369(7)
O(3A)-C(19A)	1.383(6)	C(17A)-C(18A)	1.397(7)
O(3A)-C(16A)	1.416(6)	C(20A)-C(21A)	1.527(6)
N(1A)-C(1A)	1.350(6)	C(21A)-C(22A)	1.387(6)
N(1A)-C(4A)	1.443(5)	C(21A)-C(26A)	1.401(7)
N(1A)-C(20A)	1.464(6)	C(22A)-C(23A)	1.365(7)
N(2A)-C(5A)	1.373(5)	C(23A)-C(24A)	1.370(7)
N(2A)-C(13A)	1.414(6)	C(24A)-C(25A)	1.384(7)
N(2A)-C(6A)	1.443(6)	C(25A)-C(26A)	1.377(6)
C(1A)-C(2A)	1.511(6)	Br(1B)-C(10B)	1.890(4)
C(2A)-C(3A)	1.563(5)	Br(2B)-C(24B)	1.905(4)
C(3A)-C(14A)	1.502(6)	O(1B)-C(1B)	1.226(5)
C(3A)-C(5A)	1.522(6)	O(2B)-C(5B)	1.207(5)
C(3A)-C(4A)	1.550(6)	O(3B)-C(16B)	1.373(6)
C(6A)-C(7A)	1.517(6)	O(3B)-C(19B)	1.378(6)
C(7A)-C(8A)	1.373(6)	N(1B)-C(1B)	1.344(6)
C(7A)-C(12A)	1.384(6)	N(1B)-C(4B)	1.437(5)
C(8A)-C(9A)	1.402(6)	N(1B)-C(20B)	1.453(5)
C(9A)-C(10A)	1.379(6)	N(2B)-C(5B)	1.371(5)
C(10A)-C(11A)	1.393(6)	N(2B)-C(13B)	1.406(6)
C(11A)-C(12A)	1.385(6)	N(2B)-C(6B)	1.454(6)
C(13A)-C(18A)	1.381(6)	C(1B)-C(2B)	1.518(6)

C(2B)-C(3B)	1.537(5)
C(3B)-C(14B)	1.500(5)
C(3B)-C(5B)	1.539(6)
C(3B)-C(4B)	1.552(6)
C(6B)-C(7B)	1.513(6)
C(7B)-C(12B)	1.371(6)
C(7B)-C(8B)	1.397(6)
C(8B)-C(9B)	1.381(6)
C(9B)-C(10B)	1.364(6)
C(10B)-C(11B)	1.399(7)
C(11B)-C(12B)	1.380(6)
C(13B)-C(18B)	1.376(6)
C(13B)-C(14B)	1.397(6)
C(14B)-C(15B)	1.382(6)
C(15B)-C(16B)	1.415(6)
C(16B)-C(17B)	1.397(7)
C(17B)-C(18B)	1.386(7)
C(20B)-C(21B)	1.516(6)
C(21B)-C(26B)	1.386(7)
C(21B)-C(22B)	1.397(6)
C(22B)-C(23B)	1.406(7)
C(23B)-C(24B)	1.387(7)
C(24B)-C(25B)	1.379(7)
C(25B)-C(26B)	1.406(6)

C(19A)-O(3A)-C(16A)	116.0(4)
C(1A)-N(1A)-C(4A)	115.0(3)
C(1A)-N(1A)-C(20A)	124.2(4)
C(4A)-N(1A)-C(20A)	119.5(4)
C(5A)-N(2A)-C(13A)	110.8(4)
C(5A)-N(2A)-C(6A)	123.3(4)
C(13A)-N(2A)-C(6A)	125.8(4)
O(1A)-C(1A)-N(1A)	125.9(4)
O(1A)-C(1A)-C(2A)	126.3(4)
N(1A)-C(1A)-C(2A)	107.8(3)
C(1A)-C(2A)-C(3A)	104.8(3)
C(14A)-C(3A)-C(5A)	103.0(3)
C(14A)-C(3A)-C(4A)	114.8(4)
C(5A)-C(3A)-C(4A)	110.9(3)
C(14A)-C(3A)-C(2A)	117.2(3)
C(5A)-C(3A)-C(2A)	108.6(3)
C(4A)-C(3A)-C(2A)	102.4(3)
N(1A)-C(4A)-C(3A)	103.5(3)
O(2A)-C(5A)-N(2A)	126.1(4)
O(2A)-C(5A)-C(3A)	126.1(4)
N(2A)-C(5A)-C(3A)	107.8(4)
N(2A)-C(6A)-C(7A)	114.4(4)
C(8A)-C(7A)-C(12A)	118.8(4)
C(8A)-C(7A)-C(6A)	122.1(4)
C(12A)-C(7A)-C(6A)	119.0(4)
C(7A)-C(8A)-C(9A)	121.1(4)
C(10A)-C(9A)-C(8A)	118.6(4)
C(9A)-C(10A)-C(11A)	121.4(4)
C(9A)-C(10A)-Br(1A)	118.9(3)
C(11A)-C(10A)-Br(1A)	119.7(3)
C(12A)-C(11A)-C(10A)	118.1(4)
C(11A)-C(12A)-C(7A)	121.9(5)
C(18A)-C(13A)-C(14A)	121.3(5)
C(18A)-C(13A)-N(2A)	129.1(4)
C(14A)-C(13A)-N(2A)	109.6(4)
C(15A)-C(14A)-C(13A)	120.7(4)
C(15A)-C(14A)-C(3A)	130.5(4)
C(13A)-C(14A)-C(3A)	108.7(4)
C(14A)-C(15A)-C(16A)	118.0(4)
C(17A)-C(16A)-C(15A)	121.7(5)
C(17A)-C(16A)-O(3A)	125.4(4)
C(15A)-C(16A)-O(3A)	112.9(4)
C(16A)-C(17A)-C(18A)	120.2(4)
C(13A)-C(18A)-C(17A)	118.0(4)
N(1A)-C(20A)-C(21A)	112.5(4)
C(22A)-C(21A)-C(26A)	118.8(4)
C(22A)-C(21A)-C(20A)	120.1(4)
C(26A)-C(21A)-C(20A)	121.1(4)
C(23A)-C(22A)-C(21A)	121.4(5)
C(22A)-C(23A)-C(24A)	119.0(5)
C(23A)-C(24A)-C(25A)	121.6(4)
C(23A)-C(24A)-Br(2A)	119.4(4)
C(25A)-C(24A)-Br(2A)	119.0(4)
C(26A)-C(25A)-C(24A)	119.2(5)
C(25A)-C(26A)-C(21A)	119.9(5)
C(16B)-O(3B)-C(19B)	116.8(4)
C(1B)-N(1B)-C(4B)	114.3(3)
C(1B)-N(1B)-C(20B)	124.0(3)
C(4B)-N(1B)-C(20B)	120.9(4)
C(5B)-N(2B)-C(13B)	110.7(4)
C(5B)-N(2B)-C(6B)	124.1(4)
C(13B)-N(2B)-C(6B)	125.2(4)
O(1B)-C(1B)-N(1B)	125.5(4)
O(1B)-C(1B)-C(2B)	126.2(4)
N(1B)-C(1B)-C(2B)	108.3(3)
C(1B)-C(2B)-C(3B)	104.1(3)
C(14B)-C(3B)-C(2B)	118.0(3)
C(14B)-C(3B)-C(5B)	102.6(3)
C(2B)-C(3B)-C(5B)	108.7(4)
C(14B)-C(3B)-C(4B)	114.4(4)
C(2B)-C(3B)-C(4B)	102.9(3)
C(5B)-C(3B)-C(4B)	110.1(3)
N(1B)-C(4B)-C(3B)	103.3(3)
O(2B)-C(5B)-N(2B)	124.9(4)
O(2B)-C(5B)-C(3B)	127.0(4)
N(2B)-C(5B)-C(3B)	108.0(4)
N(2B)-C(6B)-C(7B)	114.2(4)
C(12B)-C(7B)-C(8B)	119.0(4)
C(12B)-C(7B)-C(6B)	120.3(4)
C(8B)-C(7B)-C(6B)	120.6(4)
C(9B)-C(8B)-C(7B)	119.8(4)

C(10B)-C(9B)-C(8B)	120.2(5)	C(17B)-C(16B)-C(15B)	120.5(5)
C(9B)-C(10B)-C(11B)	120.9(4)	C(18B)-C(17B)-C(16B)	122.5(4)
C(9B)-C(10B)-Br(1B)	119.3(4)	C(13B)-C(18B)-C(17B)	116.1(4)
C(11B)-C(10B)-Br(1B)	119.6(3)	N(1B)-C(20B)-C(21B)	112.5(4)
C(12B)-C(11B)-C(10B)	118.1(4)	C(26B)-C(21B)-C(22B)	119.2(4)
C(7B)-C(12B)-C(11B)	121.9(5)	C(26B)-C(21B)-C(20B)	121.4(4)
C(18B)-C(13B)-C(14B)	122.9(5)	C(22B)-C(21B)-C(20B)	119.4(4)
C(18B)-C(13B)-N(2B)	127.0(4)	C(21B)-C(22B)-C(23B)	120.9(5)
C(14B)-C(13B)-N(2B)	110.1(4)	C(24B)-C(23B)-C(22B)	117.9(4)
C(15B)-C(14B)-C(13B)	121.3(4)	C(25B)-C(24B)-C(23B)	122.7(4)
C(15B)-C(14B)-C(3B)	130.2(4)	C(25B)-C(24B)-Br(2B)	119.0(4)
C(13B)-C(14B)-C(3B)	108.5(4)	C(23B)-C(24B)-Br(2B)	118.3(3)
C(14B)-C(15B)-C(16B)	116.7(4)	C(24B)-C(25B)-C(26B)	118.3(5)
O(3B)-C(16B)-C(17B)	115.3(4)	C(21B)-C(26B)-C(25B)	120.9(5)
O(3B)-C(16B)-C(15B)	124.2(4)		

Table A4.4 Anisotropic displacement parameters ($Å^2$ x 10^4) for ***86*** *(CCDC 730732). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1A)	128(2)	360(3)	409(3)	30(3)	94(2)	53(3)
Br(2A)	238(2)	399(3)	346(3)	-7(3)	2(2)	-5(3)
O(1A)	196(16)	220(20)	360(20)	-52(16)	134(15)	40(14)
O(2A)	160(15)	167(19)	267(18)	-23(15)	13(14)	-6(14)
O(3A)	390(19)	320(20)	210(17)	-104(16)	27(15)	72(18)
N(1A)	144(16)	200(20)	195(18)	7(19)	36(14)	11(18)
N(2A)	60(16)	150(20)	290(20)	72(18)	21(15)	-8(15)
C(1A)	102(17)	110(20)	310(20)	60(20)	44(17)	-20(20)
C(2A)	84(17)	120(30)	270(20)	-28(19)	18(17)	0(17)
C(3A)	114(18)	110(30)	180(20)	25(17)	-18(17)	-26(16)
C(4A)	120(20)	160(30)	160(20)	-49(19)	-25(17)	24(18)
C(5A)	40(18)	170(30)	300(30)	50(20)	-2(18)	12(18)
C(6A)	90(19)	200(30)	400(30)	90(20)	39(19)	37(19)
C(7A)	101(19)	160(30)	210(20)	0(20)	16(18)	-31(18)
C(8A)	159(19)	160(30)	230(20)	60(20)	69(17)	-10(20)
C(9A)	147(18)	160(30)	190(20)	23(19)	-15(17)	-27(19)
C(10A)	91(19)	280(30)	170(20)	0(20)	19(17)	30(19)
C(11A)	180(20)	220(30)	240(20)	100(20)	83(19)	-20(20)
C(12A)	183(19)	210(30)	210(20)	50(20)	24(17)	-10(20)
C(13A)	64(16)	180(30)	250(20)	30(20)	-3(16)	49(19)
C(14A)	89(17)	160(30)	180(20)	0(20)	-27(16)	29(19)
C(15A)	90(19)	220(30)	200(20)	0(20)	-19(17)	47(19)
C(16A)	150(20)	330(30)	200(30)	-50(20)	-50(20)	100(20)
C(17A)	260(20)	360(30)	180(20)	0(20)	60(20)	160(20)
C(18A)	170(20)	380(40)	230(20)	100(20)	67(19)	60(20)
C(19A)	480(30)	560(40)	320(30)	0(30)	100(30)	-30(40)
C(20A)	240(20)	230(30)	200(20)	10(20)	60(20)	-30(20)
C(21A)	260(20)	180(30)	160(20)	-58(19)	112(19)	10(20)

C(22A)	330(30)	170(30)	170(20)	0(20)	110(20)	-10(20)
C(23A)	290(30)	200(30)	220(30)	40(20)	100(20)	60(20)
C(24A)	160(20)	230(30)	190(20)	-70(20)	34(18)	0(20)
C(25A)	280(20)	150(30)	270(20)	-70(30)	105(19)	-30(30)
C(26A)	250(20)	180(30)	190(20)	-20(20)	87(18)	20(20)
Br(1B)	132(2)	337(3)	363(3)	-22(3)	46(2)	44(3)
Br(2B)	193(2)	704(4)	240(3)	-31(3)	-56(2)	86(3)
O(1B)	190(15)	144(19)	299(18)	-31(14)	129(14)	-3(13)
O(2B)	174(15)	139(18)	228(17)	-23(14)	1(13)	24(13)
O(3B)	318(17)	380(20)	309(18)	-60(20)	78(15)	-90(20)
N(1B)	138(15)	150(20)	157(17)	37(18)	38(14)	34(17)
N(2B)	140(17)	190(20)	176(19)	2(17)	45(15)	-22(16)
C(1B)	129(17)	120(20)	210(20)	-50(20)	48(16)	-60(20)
C(2B)	83(18)	140(30)	210(20)	22(18)	8(17)	20(17)
C(3B)	135(18)	110(30)	150(20)	1(18)	42(16)	18(17)
C(4B)	120(20)	110(20)	140(20)	-8(18)	21(17)	25(17)
C(5B)	85(19)	120(30)	260(30)	30(20)	23(18)	24(18)
C(6B)	160(20)	150(30)	370(30)	120(20)	62(19)	0(20)
C(7B)	150(20)	230(30)	200(20)	30(20)	32(18)	20(20)
C(8B)	160(20)	190(30)	310(30)	70(20)	62(19)	8(19)
C(9B)	210(20)	160(30)	270(20)	20(20)	35(19)	50(20)
C(10B)	98(19)	240(30)	190(20)	-20(20)	18(18)	32(18)
C(11B)	190(20)	290(30)	270(30)	50(20)	80(20)	-30(20)
C(12B)	200(20)	190(30)	300(20)	90(20)	72(19)	-20(20)
C(13B)	172(19)	220(30)	210(20)	80(20)	49(17)	80(20)
C(14B)	116(18)	200(30)	190(20)	0(20)	-4(16)	80(20)
C(15B)	170(20)	200(30)	200(20)	10(20)	-6(19)	40(20)
C(16B)	210(20)	270(30)	250(30)	-30(20)	-20(20)	20(20)
C(17B)	280(30)	390(40)	160(20)	20(20)	50(20)	-10(20)
C(18B)	210(20)	310(30)	250(20)	40(20)	88(19)	20(20)
C(19B)	290(20)	270(30)	270(30)	-30(30)	60(20)	-90(30)
C(20B)	170(20)	230(30)	140(20)	10(20)	18(18)	-30(20)
C(21B)	210(20)	190(30)	140(20)	-24(19)	76(19)	30(20)
C(22B)	320(20)	190(30)	130(20)	54(19)	130(20)	90(20)
C(23B)	280(20)	280(30)	140(20)	50(20)	60(20)	140(20)
C(24B)	220(20)	320(30)	150(20)	-20(20)	27(18)	110(20)
C(25B)	220(20)	250(30)	190(20)	-50(20)	48(18)	10(30)
C(26B)	200(20)	170(30)	170(20)	-10(20)	3(18)	40(20)

A4.2 CRYSTAL STRUCTURE OF SPIROCYCLIC LACTAM 138

Figure A4.2. ORTEP drawing of spirocyclic lactam ***138*** *(shown with 50% probability ellipsoids)*

NOTE: Crystallographic data have been deposited in the Cambridge Database (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 725334.

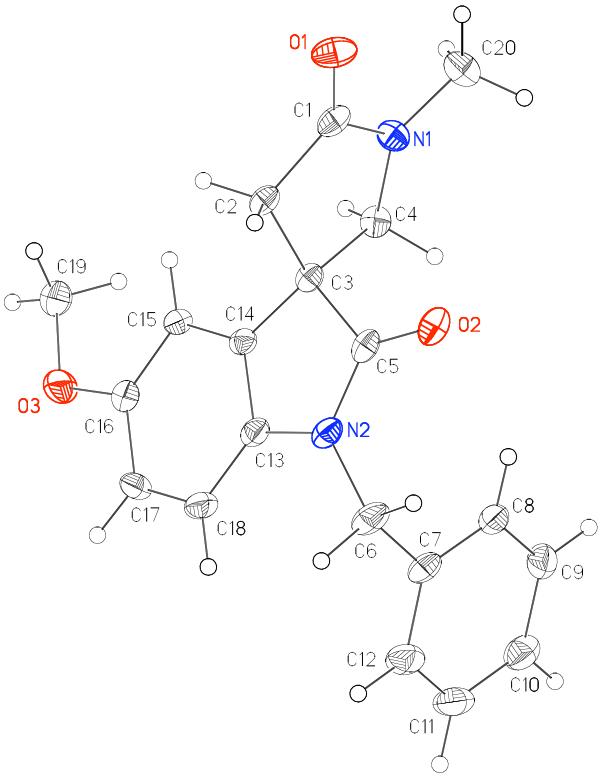


*Table A4.5 Crystal data and structure refinement for spirocyclic lactam **138** (CCDC 725334)*

Empirical formula	$C_{20}H_{20}N_2O_3$
Formula weight	336.38
Crystallization Solvent	Dichloromethane/ethylacetate/hexanes
Crystal Habit	Blade
Crystal size	0.33 x 0.14 x 0.07 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker SMART 1000
Wavelength	1.54178 Å CuKα
Data Collection Temperature	100(2) K
θ range for 11578 reflections used in lattice determination	3.58 to 69.41°
Unit cell dimensions	a = 5.50060(10) Å b = 15.6733(3) Å c = 19.9921(3) Å
Volume	1723.57(5) $Å^3$
Z	4
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Density (calculated)	1.296 Mg/m^3
F(000)	712
Data collection program	Bruker SMART v5.630
θ range for data collection	3.58 to 69.47°
Completeness to θ = 69.47°	98.8 %
Index ranges	$-5 \le h \le 6, -19 \le k \le 18, -23 \le l \le 24$
Data collection scan type	ω scans at 16 ϕ settings
Data reduction program	Bruker SAINT v6.45A
Reflections collected	23652
Independent reflections	3194 [R_{int}= 0.0979]
Absorption coefficient	0.712 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9518 and 0.7989

Table A4.5 (cont.)

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 2008)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 2008)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	3194 / 0 / 229
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	1.599
Final R indices [I>2σ(I), 2906 reflections]	R1 = 0.0349, *w*R2 = 0.0684
R indices (all data)	R1 = 0.0394, *w*R2 = 0.0697
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.000
Average shift/error	0.000
Absolute structure determination	Anomalous differences
Absolute structure parameter	-0.1(2)
Largest diff. peak and hole	0.148 and -0.215 e.Å^{-3}

Special Refinement Details

Crystals were mounted on a glass fiber using Paratone oil then placed on the diffractometer under a nitrogen stream at 100K.

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Table A4.6 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for spirocyclic lactam ***138*** *(CCDC 725334). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor*

	x	y	z	U_{eq}
O(1)	4099(2)	3561(1)	4909(1)	29(1)
O(2)	5712(2)	3042(1)	2912(1)	23(1)
O(3)	-1517(2)	-702(1)	3577(1)	28(1)
N(1)	1457(2)	3395(1)	4033(1)	20(1)
N(2)	5206(2)	1626(1)	2626(1)	20(1)
C(1)	3263(3)	3142(1)	4442(1)	20(1)
C(2)	3996(3)	2250(1)	4248(1)	18(1)
C(3)	2911(3)	2120(1)	3541(1)	16(1)
C(4)	798(3)	2766(1)	3531(1)	18(1)
C(5)	4779(3)	2342(1)	2999(1)	18(1)
C(6)	6585(3)	1623(1)	2000(1)	26(1)
C(7)	4892(3)	1665(1)	1403(1)	22(1)
C(8)	3225(3)	2328(1)	1358(1)	23(1)
C(9)	1587(3)	2363(1)	830(1)	26(1)
C(10)	1612(3)	1739(1)	340(1)	28(1)
C(11)	3264(4)	1079(1)	377(1)	30(1)
C(12)	4896(3)	1042(1)	907(1)	28(1)
C(13)	3623(3)	954(1)	2822(1)	19(1)
C(14)	2210(3)	1223(1)	3358(1)	16(1)
C(15)	459(3)	691(1)	3638(1)	18(1)
C(16)	171(3)	-122(1)	3359(1)	21(1)
C(17)	1664(3)	-394(1)	2837(1)	24(1)
C(18)	3413(3)	142(1)	2559(1)	24(1)
C(19)	-3252(3)	-409(1)	4053(1)	26(1)
C(20)	61(3)	4170(1)	4118(1)	27(1)

*Table A4.7 Bond lengths [Å] and angles [°] for spirocyclic lactam **138** (CCDC 725334)*

O(1)-C(1)	1.2309(19)	O(1)-C(1)-N(1)	125.42(16)
O(2)-C(5)	1.2240(19)	O(1)-C(1)-C(2)	126.27(15)
O(3)-C(16)	1.3704(19)	N(1)-C(1)-C(2)	108.26(13)
O(3)-C(19)	1.424(2)	C(1)-C(2)-C(3)	104.78(13)
N(1)-C(1)	1.347(2)	C(14)-C(3)-C(5)	102.24(13)
N(1)-C(20)	1.447(2)	C(14)-C(3)-C(4)	114.71(12)
N(1)-C(4)	1.452(2)	C(5)-C(3)-C(4)	110.24(13)
N(2)-C(5)	1.367(2)	C(14)-C(3)-C(2)	116.40(13)
N(2)-C(13)	1.422(2)	C(5)-C(3)-C(2)	110.92(12)
N(2)-C(6)	1.4640(19)	C(4)-C(3)-C(2)	102.51(12)
C(1)-C(2)	1.507(2)	N(1)-C(4)-C(3)	104.39(12)
C(2)-C(3)	1.546(2)	O(2)-C(5)-N(2)	125.90(15)
C(3)-C(14)	1.503(2)	O(2)-C(5)-C(3)	125.82(15)
C(3)-C(5)	1.535(2)	N(2)-C(5)-C(3)	108.28(13)
C(3)-C(4)	1.542(2)	N(2)-C(6)-C(7)	110.80(13)
C(6)-C(7)	1.514(2)	C(8)-C(7)-C(12)	118.60(16)
C(7)-C(8)	1.389(2)	C(8)-C(7)-C(6)	119.30(15)
C(7)-C(12)	1.392(2)	C(12)-C(7)-C(6)	122.07(16)
C(8)-C(9)	1.388(2)	C(9)-C(8)-C(7)	120.54(15)
C(9)-C(10)	1.385(2)	C(8)-C(9)-C(10)	120.19(17)
C(10)-C(11)	1.378(3)	C(11)-C(10)-C(9)	119.92(17)
C(11)-C(12)	1.390(3)	C(10)-C(11)-C(12)	119.88(17)
C(13)-C(18)	1.382(2)	C(11)-C(12)-C(7)	120.87(17)
C(13)-C(14)	1.390(2)	C(18)-C(13)-C(14)	121.77(15)
C(14)-C(15)	1.391(2)	C(18)-C(13)-N(2)	128.99(14)
C(15)-C(16)	1.399(2)	C(14)-C(13)-N(2)	109.24(14)
C(16)-C(17)	1.396(2)	C(13)-C(14)-C(15)	121.01(15)
C(17)-C(18)	1.393(2)	C(13)-C(14)-C(3)	109.17(14)
		C(15)-C(14)-C(3)	129.82(14)
C(16)-O(3)-C(19)	116.90(12)	C(14)-C(15)-C(16)	117.66(15)
C(1)-N(1)-C(20)	124.58(14)	O(3)-C(16)-C(17)	115.65(15)
C(1)-N(1)-C(4)	113.85(13)	O(3)-C(16)-C(15)	123.66(14)
C(20)-N(1)-C(4)	121.18(13)	C(17)-C(16)-C(15)	120.68(15)
C(5)-N(2)-C(13)	110.70(13)	C(18)-C(17)-C(16)	121.32(15)
C(5)-N(2)-C(6)	123.89(14)	C(13)-C(18)-C(17)	117.48(15)
C(13)-N(2)-C(6)	123.36(14)		

*Table A4.8 Anisotropic displacement parameters ($Å^2$ x 10^4) for spirocyclic lactam **138** (CCDC 725334). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	269(7)	394(8)	210(6)	-109(5)	-24(5)	-55(5)
O(2)	189(6)	298(7)	204(6)	67(5)	-26(5)	-51(5)

O(3)	359(7)	181(6)	294(6)	-18(5)	77(5)	-57(5)
N(1)	182(7)	189(7)	224(7)	-25(6)	-19(5)	-7(6)
N(2)	173(7)	263(8)	153(7)	33(6)	21(5)	22(6)
C(1)	161(8)	286(10)	154(8)	17(7)	20(6)	-67(7)
C(2)	153(8)	249(9)	139(8)	22(6)	-12(6)	-4(6)
C(3)	130(8)	201(8)	144(7)	19(6)	-17(6)	4(6)
C(4)	154(8)	207(9)	194(8)	-2(6)	-48(6)	-29(6)
C(5)	137(8)	261(9)	144(8)	53(7)	-63(6)	3(6)
C(6)	185(9)	398(10)	189(8)	31(8)	67(7)	32(7)
C(7)	191(8)	300(10)	165(8)	31(7)	75(6)	-26(7)
C(8)	304(10)	209(9)	168(8)	6(6)	22(7)	-29(7)
C(9)	314(10)	228(9)	229(9)	29(7)	-41(7)	19(8)
C(10)	317(10)	319(10)	197(8)	7(7)	-20(7)	-52(9)
C(11)	365(11)	326(11)	220(9)	-77(7)	68(8)	-31(9)
C(12)	264(9)	331(10)	248(9)	-26(8)	79(7)	57(8)
C(13)	179(8)	235(9)	143(7)	28(6)	5(6)	38(7)
C(14)	165(8)	193(8)	128(7)	3(6)	-21(6)	33(6)
C(15)	203(9)	190(8)	139(7)	-4(6)	14(6)	16(6)
C(16)	246(9)	194(9)	185(8)	30(6)	12(7)	-4(7)
C(17)	330(10)	176(8)	203(8)	-49(7)	-12(7)	54(7)
C(18)	288(10)	272(10)	171(8)	-10(7)	53(7)	75(7)
C(19)	280(10)	239(9)	252(9)	29(7)	33(8)	-27(7)
C(20)	243(9)	216(9)	346(9)	-33(8)	17(7)	-2(7)

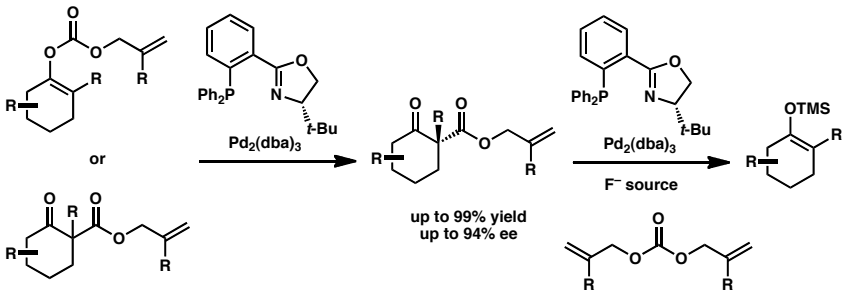
APPENDIX 5

Nonlinear Effect Experiment on Palladium-Catalyzed Decarboxylative Allylic Alkylation

A5.1 INTRODUCTION AND BACKGROUND

We have recently developed a series of palladium-catalyzed decarboxylative enantioselective allylic alkylation reactions of cyclic ketone enolates, such as allyl carbonates, β-ketoesters, and silyl enol ethers (Scheme A5.1).[1] These reactions proceed in the presence of steric hindrance, are compatible with a variety of functional groups, and demonstrate a high tolerance to water. These experimental observations support an inner-sphere mechanism, by which a palladium-bound enolate is operative. However, these studies do not discount the possibility of a bimetallic mechanism, wherein one palladium delivers the enolate to another palladium π-allyl complex. To probe the molecularity of the catalytically active species, we performed a nonlinear experiment.

Scheme A5.1 Palladium-catalyzed enantioselective decarboxylative allylic alkylation reactions of ketone enolates

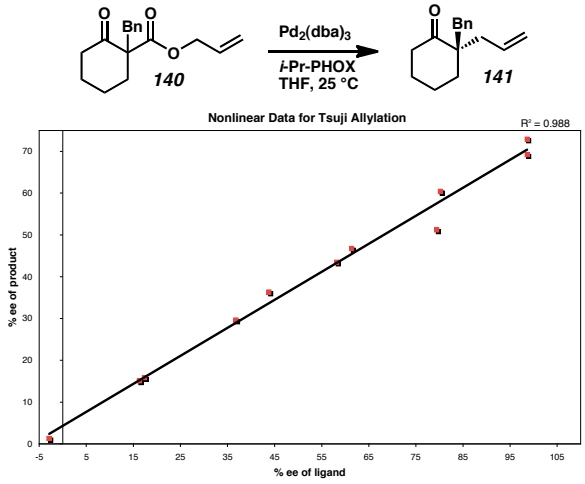


Pioneered by Kagan, the relationship between the enantiomeric excess of the chiral ligand and the enantiomeric excess of the product can provide mechanistic insight into the structure of the catalytically active species in asymmetric reactions.[2] When the relationship between the enantiomeric excess of the ligand and the enantiomeric excess of the product deviates from linearity, the phenomenon is described as a nonlinear effect. Nonlinear effects arise when the chiral catalyst undergoes aggregation at some stage of the reaction.

A5.2 NONLINEAR EFFECT EXPERIMENT

The decarboxylative asymmetric allylation of benzyl β-ketoester **140** was studied by using different enantiomeric purities of the *i*-Pr-PHOX ligand. Comparison of the enantiomeric excess of the product versus the enantiomeric excess of the *i*-Pr-PHOX ligand revealed a linear relationship (Scheme A5.2). The absence of a nonlinear effect suggests that the catalytically active species in our decarboxylative system involves one molecule of *i*-Pr-PHOX, thus one palladium metal center. Furthermore, the absence of a nonlinear effect does not support a mechanism that involves a bimetallic rate determining step where one palladium delivers the enolate to another palladium π-allyl complex.

Scheme A5.2 Nonlinear experiment on palladium-catalyzed decarboxylative allylic alkylation



A5.3 CONCLUSION

Probing the palladium-catalyzed decarboxylative allylic alkylation developed by our laboratories revealed a linear relationship between the enantiomeric excess of the ligand and the enantiomeric excess of the product, which suggests that the catalytically active species is a single ligand-bound palladium complex. The results of this study have contributed to the general understanding of the operative mechanism.[3]

A5.4 EXPERIMENTAL SECTION

A5.4.1 Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under argon atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) was purchased from Strem and stored in a desiccator under argon atmosphere prior to use. (*S*)-*t*-Bu-PHOX, (*S*)-*i*-Pr-PHOX, (*R*)-*i*-Pr-PHOX, and substrate were prepared by our previously reported methods.[1] Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed by using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching or anisaldehyde. ICN silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC, utilizing a Chiracel OJ column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 254 nm. Analytical achiral GC was performed with an Agilent 6850 GC utilizing a DB-WAX column (30 mm x 0.24 mm with 1.0 mL/min carrier gas flow).

A5.4.2. General Procedures for Nonlinear Experiments

THF stock solutions with the desired enantiomeric excess of *i*-Pr-PHOX were freshly prepared prior to each experiment. The enantiomeric excess of the *i*-Pr-PHOX delivered was confirmed by chiral HPLC analysis with a Chiracel OJ column using 1% ethanol in hexanes (1.0 mL/min) as eluent on the stock solution ((*S*)-*i*-Pr-PHOX: 13.16 min and (*R*)-*i*-Pr-PHOX: 7.60 min).

A 1-dram vial equipped with a stirbar was flame-dried twice under vacuum. After cooling under nitrogen, $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol) was added. The vial was evacuated for 5 minutes. THF (3 mL total) was added, and then *i*-Pr-PHOX (4.8 mg, 0.0125 mmol) in THF was added via syringe. The contents were allowed to stir for 30 minutes at 25 °C prior to addition of benzyl β-ketoester **140** (27.2 mg, 0.1 mmol) via syringe. The reaction progress was monitored by TLC. Upon completion, the reaction was concentrated and purified via column chromatography (20% ether in pentane). Subsequently, the enantiomeric excess of product **141** was determined by chiral HPLC analysis with a Chiracel OJ column using 1% ethanol in hexanes (1.0 mL/min) as eluent (**141**: 15.942 min and 24.345 min).

A5.5 NOTES AND REFERENCES FOR TEXT

(1) (a) Mohr, J. T.; Stoltz, B. M. *Chem. Asian. J.* **2007**, *2*, 1476–1491. (b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924–6927. (c) Behenna, D. C; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045. (d) Seto, M.; Roizen, J. L.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 6873–6876.

(2) (a) Kagan, H. B.; Girard, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2922–2959. (b) Satyanarayana, T.; Abraham, S.; Kagan, H. B. *Angew. Chem. Int. Ed.* **2009**, *48*, 456–494.

(3) (a) Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard III, W. A. *J. Am. Chem. Soc.* **2007**, *129*, 11876–11877. (b) Sherden, N. H.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6840–6843.

APPENDIX 6

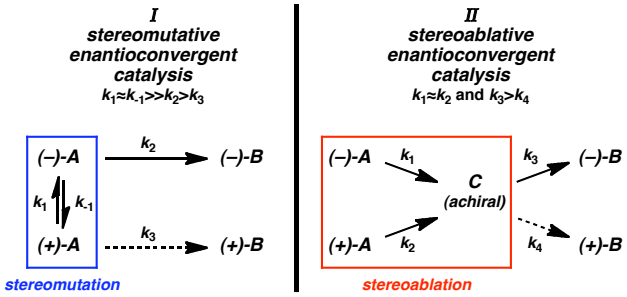
Palladium-Catalyzed Decarboxylative Allylic Alkylation of Diastereomeric β-Ketoesters

A6.1 INTRODUCTION AND BACKGROUND

We are interested in stereoablative enantioconvergent catalysis, a concept that is illustrated by the use of quaternary β-ketoesters in the palladium-catalyzed decarboxylative allylic alkylation reported by our laboratories.[1] Typical stereomutative enantioconvergent processes, such as dynamic kinetic resolution, require a pre-equilibration epimerization of starting material **A** followed by enantioselective conversion to product **B** (Pathway I, Scheme A6.1). Quaternary stereocenters are not typically epimerizable. Thus, we believe another pathway is operative, wherein both enantiomers of the starting material **A** convert irreversibly to prochiral intermediate **C**. This prochiral intermediate **C** can then preferentially form one enantiomer of product **B** under the influence of the chiral catalyst (Pathway II, Scheme A6.1). This alternate pathway has been termed stereoablative enantioconvergent catalysis. The lability of the

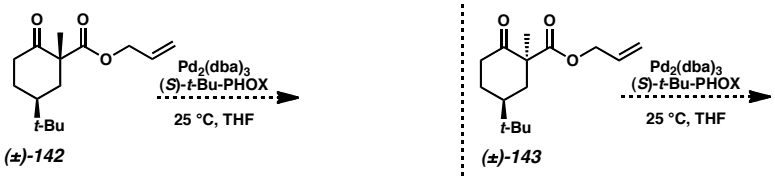
stereogenic center is illustrated with quaternary β-ketoesters, where enolate formation destroys the stereochemical information at the α-position.

Scheme A6.1 Stereomutative versus stereoablative enantioconvergent catalysis



To provide evidence for stereoablative enantioconvergent catalysis, we envisioned using diastereomeric β-ketoesters **142** and **143** as substrates for the palladium-catalyzed decarboxylative allylic alkylation (Scheme A6.2). The stereoablative hypothesis is supported if both β-ketoesters afford similar diastereomeric product ratios as the stereochemistry at α-position of the β-ketoester is not expected to influence the outcome of the reaction.

Scheme A6.2 Proposed experiment to test stereoablation hypothesis



A6.2 PALLADIUM-CATALYZED DECARBOXYLATIVE ALLYLIC ALKYLATION OF β-KETOESTERS

A6.2.1 Experimental Results

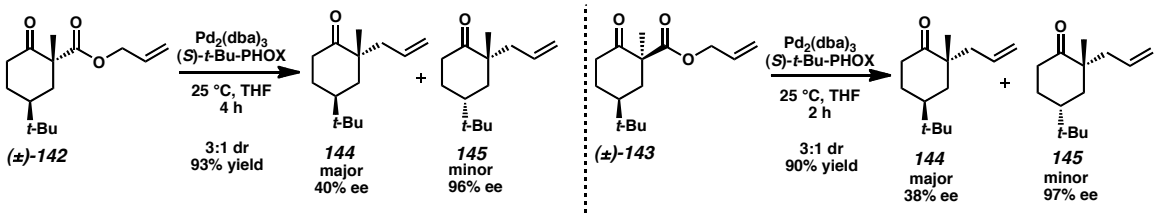
Once the synthesis and stereochemical verification of diastereomeric β-ketoesters **142** and **143** were completed,[2] we treated each β-ketoester with $Pd_2(dba)_3$ and (*S*)-*t*-Bu-PHOX. We observed similar product ratios and enantioselectivities for the asymmetric decarboxylative allylic alkylation of both **142** and **143** (Scheme A6.3). Thus, our results support the formation of an enolate wherein the stereochemistry at the α-position of the β-ketoester starting material does not influence the outcome of the reaction. The relative and absolute stereochemistry of the products **144** and **145** were determined by x-ray crystallography of their corresponding crystalline semicarbazone derivatives obtained from the asymmetric variant of the decarboxylative allylic alkylation (Scheme A6.4).[2]

However, two other interesting observations were made during this experiment. Minor product **145** had a significantly greater enantiomeric excess than that of major product **144** (97% ee versus 39% ee). Furthermore, decarboxylative allylation of **143** was 1.5 times faster than the decarboxylative allylation of **142**, which is surprising because stereoelectronic arguments would predict that **142** should be the faster reacting diastereomer as there is better orbital overlap between the carbonyl carbon and the α-carbon when the carboxyl is in the axial position.

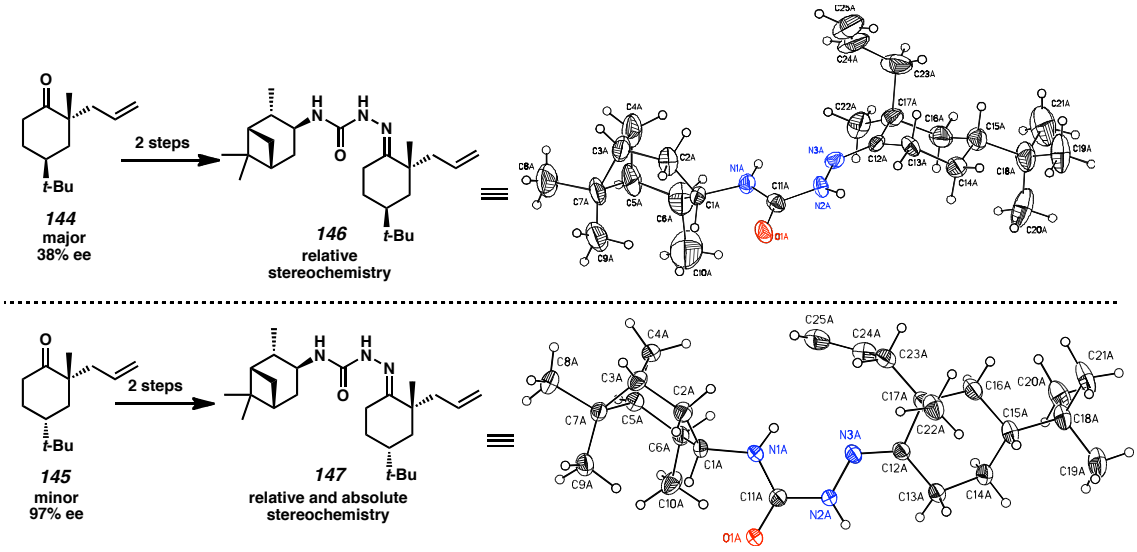
To confirm the observed difference in their relative rates of reaction, **142** and **143** were treated with an achiral catalyst (Scheme A6.5). Decarboxylative allylic alkylation of **142** and **143** using PPh_3 as the ligand gave the same major and minor products as those

observed in the enantioselective case. Furthermore, the difference in relative rate of reaction was more dramatic for the PPh_3 case; the decarboxylative allylic alkylation of **143** was 15.6 times faster than that observed for **142**.[3]

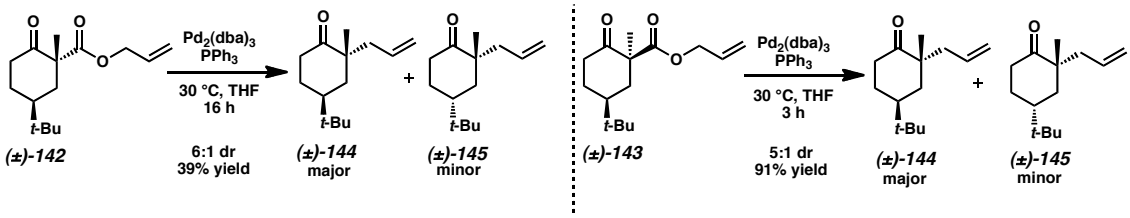
Scheme A6.3 Asymmetric palladium-catalyzed decarboxylative allylation of β-ketoesters



Scheme A6.4 Determination of relative and absolute stereochemistry



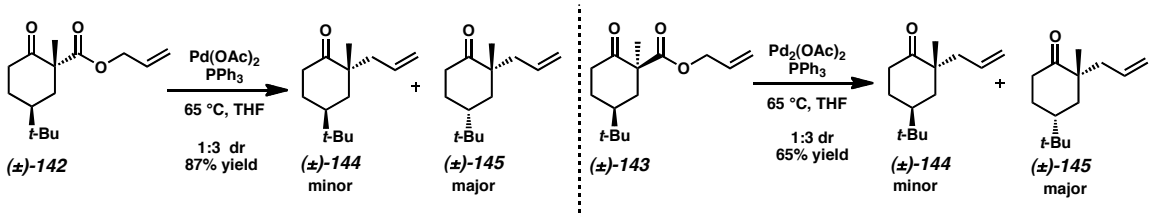
Scheme A6.5. Racemic palladium-catalyzed decarboxylative allylation of β-ketoesters



It is important to note that Tsuji has previously reported a nonenantioselective allylation reaction of diastereomeric β-ketoesters **142** and **143** (Scheme A6.6).[4] Tsuji's

assignment of the minor and major products are not in agreement with our results. In Tsuji's report, the yield and product ratios were determined by GC, and Tsuji does not offer any rationale for his assignment of **144** and **145**. Furthermore, Tsuji did not comment on the relative rate of reaction between the two diastereomers.

Scheme A6.6 Racemic palladium-catalyzed decarboxylative allylic alklylation as reported by Tsuji

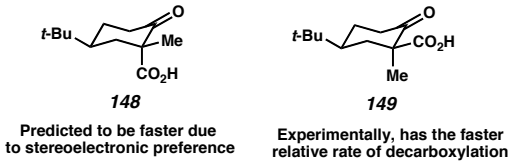


A6.2.2 Rationalization for Lack of Stereoelectronic Control in Decarboxylation of Diastereomeric β-Ketoacids

The surprising observation that β-ketoester **143**, which has the ester group in an equatorial position, is more reactive than β-ketoester **142**, which has the ester group in an axial position, contradicts stereoelectronic control arguments. However, this contradiction has also been observed in the decarboxylation of diastereomeric β-ketoacids.[5]

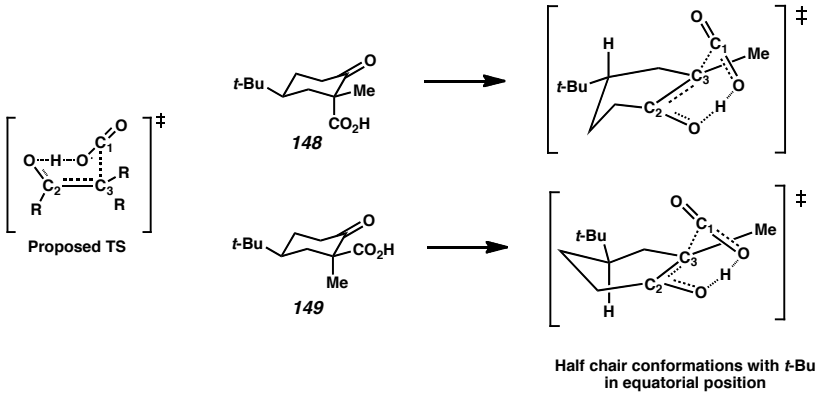
Based on stereoelectronic arguments, β-ketoacid **148** is predicted to be more reactive because having the carboxyl group in the axial position allows for continuous overlap of the incipient p-orbital with the p-orbital on the carbonyl carbon (Figure A6.1). However, Pollack has reported that β-ketoacid **149** decarboxylates 3-fold faster than **148** in acidic media.[5] Under basic conditions, the relative rate of reactions is more striking: β-ketoacid **149** decarboxylates 15- to 20-fold faster than **148**.

Figure A6.1 Kinetic experiments on rates of decarboxylation of β-ketoacids



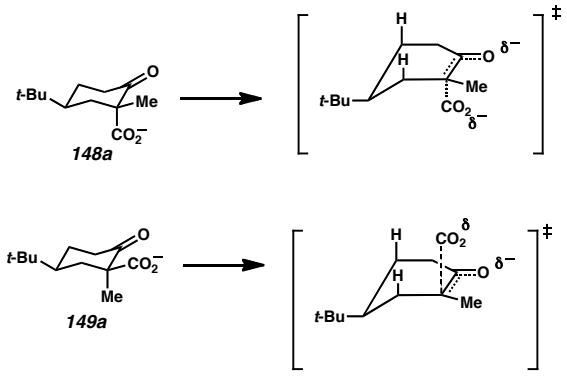
Under acidic conditions, Pollack has proposed that the transition state for decarboxylation is a six-membered intermediate, in which the O–H bond is in the same plane as the original C(3)–C(2)=O bond (Figure A6.2).[5] The C(1)–C(3) bond that is broken is perpendicular to this plane, which allows for the continuous overlap of the incipient p-orbital with the π^* of the carbonyl bond. The proposed transition states for β-ketoacids **148** and **149** are shown in Figure A6.2, where the cyclohexene is shown in a half chair conformation with the *tert*-butyl group in the equatorial position and the methyl group in the plane of the carbon–carbon double bond. If the energies of the transition states are similar, then the relative rate of decarboxylation is determined by the relative stabilities of β-ketoacids **148** and **149**. Based on A values derived from cyclohexanes (Me = 1.70 kcal/mol, COOH = 1.35 kcal/mol), β-ketoacid **149** is higher in energy; therefore, it should be more reactive.

Figure A6.2 Proposed transition states under acidic conditions



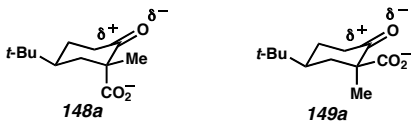
Rationalization of the relative rate of decarboxylation of β-ketoacids **148** and **149** under basic conditions is based on a similar argument. Decarboxylation of the carboxylate anions of β-ketoacids has not been investigated thoroughly, but studies on the decarboxylation of benzoylacetic acids have suggested that the transition state is late on the reaction coordinate; thus, the transition state resembles the enolate product (Figure A6.3).[6] We can apply this observation to the decarboxylation of carboxylates **148a** and **149a**. If steric interactions with the axial hydrogens are ignored in the transition states shown in Figure A6.3, these two transition states should have similar energies, and the relative rates of reaction reflect the differences in energy of carboxylates **148a** and **149a**.

Figure A6.3 Proposed transition states under basic conditions



To predict the relative energy of **148a** and **149a**, the dipole-dipole repulsions between the carboxylate and the carbonyl oxygen should be considered (Figure A6.4). For **149a**, the dipole-dipole repulsion is more significant; hence, **149a** is less stable and will decarboxylate more readily. Evidence that this dipole-dipole interaction is significant can be found in the pK_a values of **148** and **149**. Acid **149** has a higher pK_a than **148** (5.79 versus 5.29 in 70% MeOH in water at 0 °C).[6]

Figure A6.4 Dipole-dipole repulsions



A6.2.3 Rationalization for the Faster Relative Rate of Reaction for β-Ketoesters

A possible explanation for the increased reactivity of β-ketoester **143** relative to its diastereomer assumes that the palladium π-allyl complex is formed prior to decarboxylation, and that both of these events occur in a stepwise fashion. It is proposed that formation of a carboxylate intermediate occurs and that unfavorable dipole-dipole repulsion, such as those shown in Figure A6.4 for the carboxylate derived from **143** would make it the more reactive diastereomer. The formation of a palladium carboxylate intermediate in our decarboxylative allylic alkylation has been supported by subsequent mechanistic studies performed by our laboratories.[7]

A6.2.4 Rationale for Greater Enantioselectivity in Minor Product

The second interesting observation made in our asymmetric decarboxylative allylation of diastereomeric β-ketoesters is that the minor product **145** had a much greater enantiomeric excess than major product **144**. We believe that this observation can be attributed to competing modes of control. To help illustrate our point, we must consider all four possible products and their relative abundance for the asymmetric decarboxylative allylic alkylation of β-ketoester **142** (Scheme A6.3). The diastereomers and their enantiomers are shown in Figure A6.5, and the relative percentages of each of the products are shown in Figure A6.6.

Figure A6.5 All possible products from asymmetric decarboxylative allylic alkylation of β-ketoester ***142***

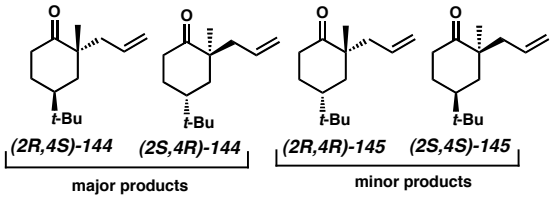
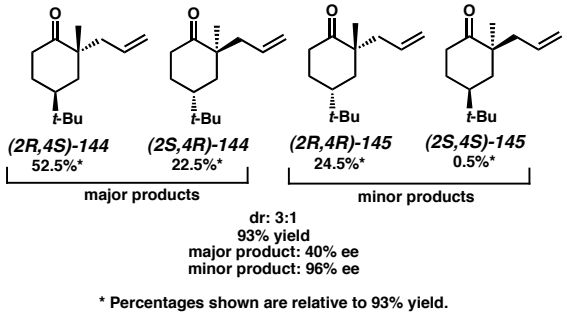


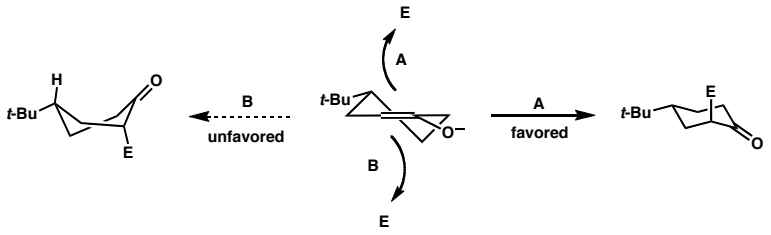
Figure A6.6 Product distribution asymmetric decarboxylative allylic alkylation of β-ketoester ***142***



One type of control believed to be operative is demonstrated in the non-enantioselective alkylation of 4-*tert*-butylcyclohexanone enolates, which are known to have an innate selectivity for one product. As shown in Scheme A6.7, the electrophile can be attacked by enolate from either its top face or bottom face. Studies by House and coworkers have shown that the electrophile and the *t*-butyl group have a trans relationship in the major product.[8] Approach from the bottom face will force the cyclohexane ring into a twist boat conformation and will install the electrophile on the same face as the *t*-butyl group. On the other hand, approach from the top face will install the electrophile trans to the *t*-butyl group and will lead directly to the product's chair conformation. The rationale for the favored trans relationship between the electrophile and the *t*-butyl group is that the chair-like transition state is lower in energy than the transition state in a twist boat conformation. Furthermore, although the cis relationship

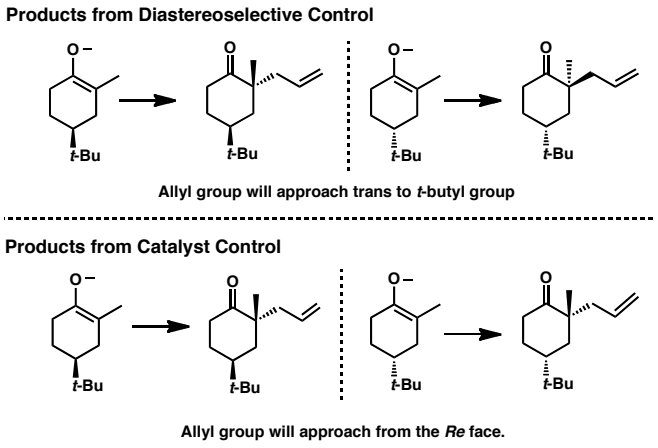
between the electrophile and *t*-butyl group affords a more thermodynamically stable product because both groups will be in equatorial positions, this reaction is under kinetic control. Thus, if we apply this diastereoselective model to β-ketoesters **142** and **143**, then the preferred products should have the allyl group trans to the *t*-butyl group (Scheme A6.8), a general trend that is observed for our decarboxylative allylic alkylation with PPh_3 (Scheme A6.5).

Scheme A6.7 Stereoselective alkylation of t-butylcyclohexanones



The other source of control is from our catalyst. From our experiments, we have found that (*S*)-*t*-Bu PHOX will incorporate the allyl group from the *Re* face;[1] the predicted products are shown in Scheme A6.8.

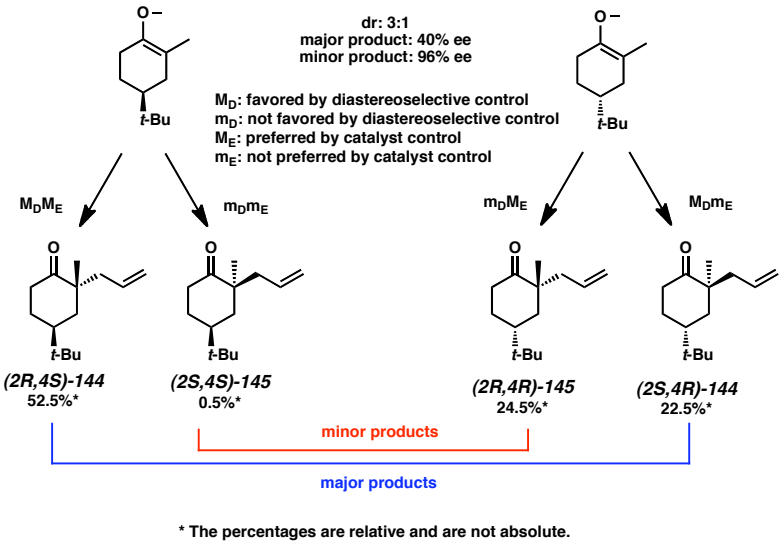
Scheme A6.8 Predicted products as dictated by mode of control



The high enantioselectivity observed for the minor product can be explained by considering the relative amount of each product and the competing modes of control

(Figure A6.7). Ketone (2*R*,4*S*)-**144** comprises half of the product mixture and is the product that is favored by both catalyst and diastereoselective controls. Ketone (2*S*,4*S*)-**145** is less than 1% of the product mixture and is favored neither by diastereoselective or by catalyst control. Ketone (2*R*,4*R*)-**145**, the major enantiomer of the minor product, is approximately 24% of the product mixture and is only favored by catalyst control. Ketone (2*S*,4*R*)-**144** is 22% of the product mixture and is only favored by diastereoselective control. Thus, the competition of these two types of control, one dictated by the catalyst and one dictated by the substrate, impart excellent enantioselectivity to the minor product but only moderate enantioselectivity to the major product.

Figure A6.7 Distribution of products as governed by two competing modes of control



From our studies of the asymmetric decarboxylative allylic alkylation of β-ketoesters derived 4-*tert*-butylcyclohexanone, we observe a case where the two types of control are closely matched. This conclusion is supported by the observation that the relative ratios of the products that are favored by only one type of control ((2*R*,4*R*)-**145** and (2*S*, 4*R*)-

144) are similar. It is because the substrate control and catalyst control are matched that we observed a situation where the major product has moderate ee while the minor product has high ee.

A6.3 CONCLUSION

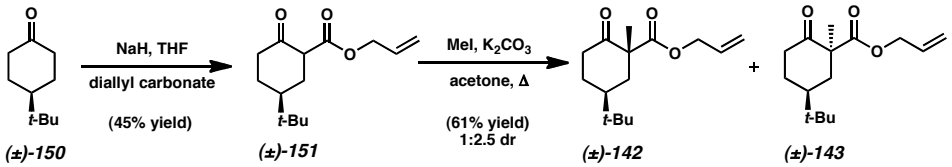
Our studies on the decarboxylative allylic alkylation of diastereomeric β-ketoesters derived from 4-*tert*-butylcyclohexanone support our theory of a stereoablative enantiovergent catalysis. These studies also reveal an interesting example of selectivity that is governed by competing modes of substrate and catalyst control.

A6.4 EXPERIMENTAL SECTION

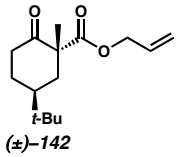
A6.4.1 Materials and Methods

Unless otherwise stated, reactions were performed at ambient temperature (typically 20 to 23 °C) in flame-dried glassware under a nitrogen or argon atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Brine solutions are saturated aqueous sodium chloride solutions. All commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV, anisaldehyde, permanganate, or CAM staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively) spectrometer and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility.

A6.4.2 Synthesis of β-Ketoesters

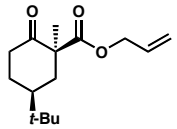


4-*t*-butylcyclohexanone (**150**) (1.094 g, 7.098 mmol) in THF (2.2 mL) was added dropwise to a cooled suspension of NaH (0.7098 g, 17.75 mmol, 60% dispersion in mineral oil) in THF (10 mL). Upon warming to room temperature, diallyl carbonate (1.5 mL, 10.65 mmol) was added. After 18 hours, the reaction was quenched with saturated aqueous NH_4Cl solution and 1 N HCl to give a pH of 4. The phases were separated and the aqueous phase was extracted with EtOAc (7 x 12 ml). The organic layers were combined, dried with sodium sulfate, and concentrated to afford a yellow oil. The resulting oil was purified by flash chromatography (5 cm by 11.5 cm SiO_2, 10 % ether in pentane) to afford the β-ketoester **151** as a yellow oil (0.770 g, 45.5%). The β-ketoester **151** was then added to K_2CO_3 (1.96 g, 14.20 mmol) in acetone (10 mL). Iodomethane (0.89 mL, 14.20 mmol) was added dropwise, and the reaction was heated at 50 °C for 14 hours. The reaction was filtered and the solids were rinsed with acetone. The resulting organics were collected and purified by column chromatography (10% → 50% ether in pentane), which allowed for the separation of **142** and **143** (494 mg, 60% yield, 1:2.5 dr (**142**:**143**)).



β-ketoester 142

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (m, *J* = 10.2 Hz, 16.2 H, 1H), 5.32 (m, *J* = 7.4 Hz, 1.2 Hz, 1H), 5.25 (m, *J* =10.2 Hz, 1.5 Hz), 4.62 (m, 2H), 2.49 (m, 3H), 2.02 (m,1H), 1.57-1.18 (comp. m, 6H), 1.29 (s, 3H), 0.90 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 173.2, 131.7, 119.2, 66.0, 56.5, 44.4, 40.6, 39.9, 32.5, 28.6, 27.7, 21.8; IR (Neat Film, NaCl) 2961, 2865, 1717, 1229, 1140 cm^{-1}; HRMS *m/z* calc'd for $C_{15}H_{24}O_3$ $[M]^+$: 252.1726, found 252.1714.

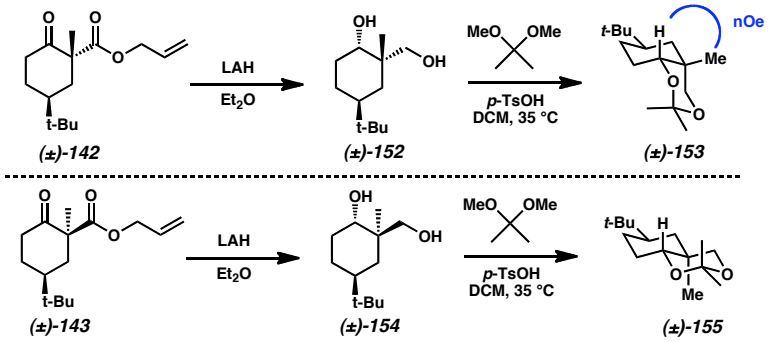


(±)–143

β-ketoester 143

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 (dddd, *J* = 17.4 Hz, 10.5 Hz, 5.7 Hz, 5.7 Hz, 1H), 5.33 (dq, *J* = 17.4 Hz, 1.2 Hz, 1H), 5.23 (dq, *J* = 10.5 Hz, 1.2 Hz, 1H), 4.65 (dt, *J* = 5.7 Hz, 1.2 Hz, 2H), 2.45 (m, 2H), 2.21 (t, *J* = 12.6, 1H), 2.02 (m, 1H), 1.84 (dt, *J* =13.5 Hz, 3.3 Hz, 1H), 1.59 (m, 1H), 1.46 (s, 3H), 0.93 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.5, 173.2, 132.2, 118.3, 66.0, 57.4, 41.9, 38.0, 37.0, 32.6, 27.6, 26.8, 21.0; IR (Neat Film, NaCl) 2958, 2876, 1740, 1712, 1459, 1367, 1249, 1227, 1165, 1112 cm^{-1}; HRMS *m/z* calc'd for $C_{15}H_{24}O_3$ $[M]^+$: 252.1726, found 252.1718.

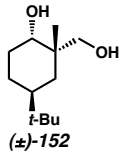
A6.4.3 Confirmation of Relative Stereochemistries of β-Ketoesters 142 and 143 via Acetonide Formation



General Procedure

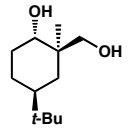
β-ketoester **143** (50 mg, 0.21 mmol) in ether (0.4 mL) was added slowly to LAH (23.9 mg, 0.63 mmol) in 0.5 mL ether at -78 °C. The reaction was allowed to warm to room temperature and was stirred for 20 minutes. The workup procedure was carried out as reported by Fieser and Fieser.[9] Water (24 μL), 15% aqueous NaOH (24 μL), and water (72 μL) were added to reaction at 0°C. A white precipitate was observed, and the reaction was allowed to stir for 30 minutes before filtration. The ether layer was washed with brine (2 x 2 mL) and saturated $NaHCO_3$ (2 x 2 ml). The ether layer was collected, dried with sodium sulfate, and concentrated to give a white solid.

Diol **154** (27.1 mg, 0.136 mmol) was dissolved in DCM (2 mL). *p*-TsOH monohydrate (~2 mg) and diomethoxypropane (33 μL, 0.2706 mmol) were added to the reaction. After 24 hours, the reaction mixture was concentrated and purified by column chromatography (2 cm x 20 cm SiO_2, 10% ether in hexanes) to afford a light yellow oil.



Diol 152.

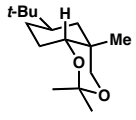
(29.8 mg, 70.9% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 (d, *J* =10.8 Hz, 1H), 3.46 (dd, *J* = 11.4 Hz, 4.2 Hz, 1H), 3.27 (d, *J* = 11.1 Hz, 1H), 2.74 (bs, 2H), 1.73 (m, 2H), 1.44 (dt, *J* = 13.5 Hz, 2.7 Hz, 1H), 1.30 (m, 2H), 1.19 (s, 3H), 0.81 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.0, 68.0, 42.3, 38.9, 37.9, 32.3, 31.7, 27.6, 26.3, 24.9; IR (KBr pellet) 3272, 2958, 2868, 1459, 1365, 1064, 1039, 1019, 999 cm^{-1}; HRMS *m/z* calc'd for $C_{12}H_{25}O_2$ $[M+H]^+$: 201.1855, found 201.1854.



(±)-154

Diol 154.

(36.5 mg, 85.7% yield): ^{1}H NMR (300 MHz) δ 3.58 (dd, *J* =11.4 Hz, 3.6 Hz, 1H), 3.50 (d, *J* = 9.3 Hz, 1H), 3.42 (dd, *J* = 10.5 Hz, 4.8 Hz), 2.84 (bs, 1H), 2.78 (bs, 1H), 1.74 (m, 1H), 1.41 (m, 2H), 1.23 (m, 2H), 0.99-0.78 (m, 2H), 0.99 (s, 3H), 0.82 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 77.5, 75.6, 41.7, 39.4, 34.7, 32.2, 31.0, 27.7, 25.6, 14.2; IR (KBr pellet) 3325, 2936, 2868, 1462, 1365, 1066, 1039, 991, 687 cm^{-1}; HRMS *m/z* calc'd for $C_{12}H_{25}O_2$ $[M+H]^+$: 201.1855, found 201.1847.

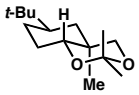


(±)-153

Acetonide 153.

(40 mg, 45% yield): ^{1}H NMR (300 MHz, C_6D_6) δ 3.64 (d, *J* = 11.1 Hz, 1H), 3.47 (dd, *J* = 4.5 Hz, 5.1 Hz, 1H), 3.05 (d, *J* = 11.1 Hz, 1H), 1.65 (comp. m, 3H), 1.48 (s, 1H), 1.37 (s, 3H), 1.36 (s, 3H), 1.14 (m, 1H), 0.94 (m, 1H), 0.89 (s, 3H), 0.78 (s, 9H), 0.69 (m, 1H),

^{13}C NMR (75 MHz, C_6D_6) δ 99.6, 74.0, 67.2, 40.3, 35.5, 33.8, 32.7, 27.6, 26.5, 26.3, 25.9, 25.1, 21.4; IR (Neat Film, NaCl) 2951, 2870, 1463, 1365, 1225, 1084, 1067 cm^{-1}; HRMS *m/z* calc'd for $C_{15}H_{28}O_2$ [M+H]$^+$: 241.2168, found 241.2173.

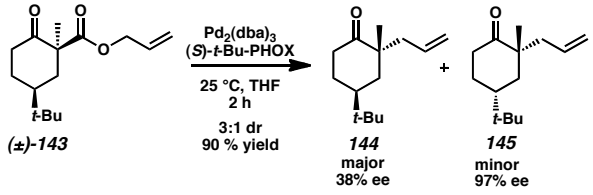


(±)-155

Acetonide 155.

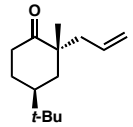
(40 mg, 71.8% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.57 (d, *J* = 10.5 Hz, 1H), 3.50 (dd, *J* = 11.4 Hz, 4.2 Hz, 1H), 3.33 (d, *J* = 10.8 Hz, 1H), 1.84 (m, 1H), 1.62-1.04 (m, 6H), 1.45 (s, 3H), 1.42 (s, 3H), 1.10 (s, 3H), 0.83 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 99.6, 76.0, 73.6, 41.5, 34.5, 33.8, 32.4, 30.2, 27.8, 27.2, 26.0, 19.4 15.9; IR (Neat Film, NaCl) 2992, 2944, 2870, 1462, 1384, 1366, 1270, 1235, 1204, 1104, 1084, 1040 cm^{-1}; HRMS *m/z* calc'd for $C_{15}H_{28}O_2$ [M+H]$^+$: 241.2168, found 241.2177.

A6.4.4 General Procedures for Pd-Catalyzed Decarboxylative Allylic Alkylation of Diastereomeric β-Ketoesters



$Pd_2(dba)_3$ (67 mg, 0.0733 mmol) and (*S*)-*t*-BuPHOX (73.8 mg, 0.19045 mmol) were combined in a round bottom flask. The vial was evacuated for 10 minutes prior to addition of THF (88 mL). The reaction was allowed to stir for 30 minutes prior to addition of β-ketoester **143** (739 mg, 2.93 mmol) via syringe. The reaction was monitored by TLC. Once the reaction was complete, the reaction was concentrated.

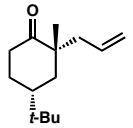
Isolation of products was accomplished by multiple flash chromatography (3 cm x 24 cm SiO_2, 10 % ether in pentane).



(±)-144

Major product 144.

^{1}H NMR (300 MHz) δ 5.64 (m, 1H), 5.04 (m, 2H), 2.38-2.23 (m, 4H), 2.03 (m, 1H), 1.84 (m, 1H), 1.70 (m, 1H), 1.42-1.13 (m, 2H), 1.00 (s, 3H), 0.89 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.0, 133.0, 118.5, 48.2, 42.0, 40.1, 38.5, 32.4, 28.3, 27.7, 22.7 ; IR (Neat Film, NaCl) 2962, 2870, 1709, 1366, 912 cm^{-1}; HRMS *m/z* calc'd for $C_{14}H_{24}O$ [M^+]: 208.1827, found 208.1825; $[\alpha]_D^{25.6}$ –30.00° (*c* 1.08, hexane).

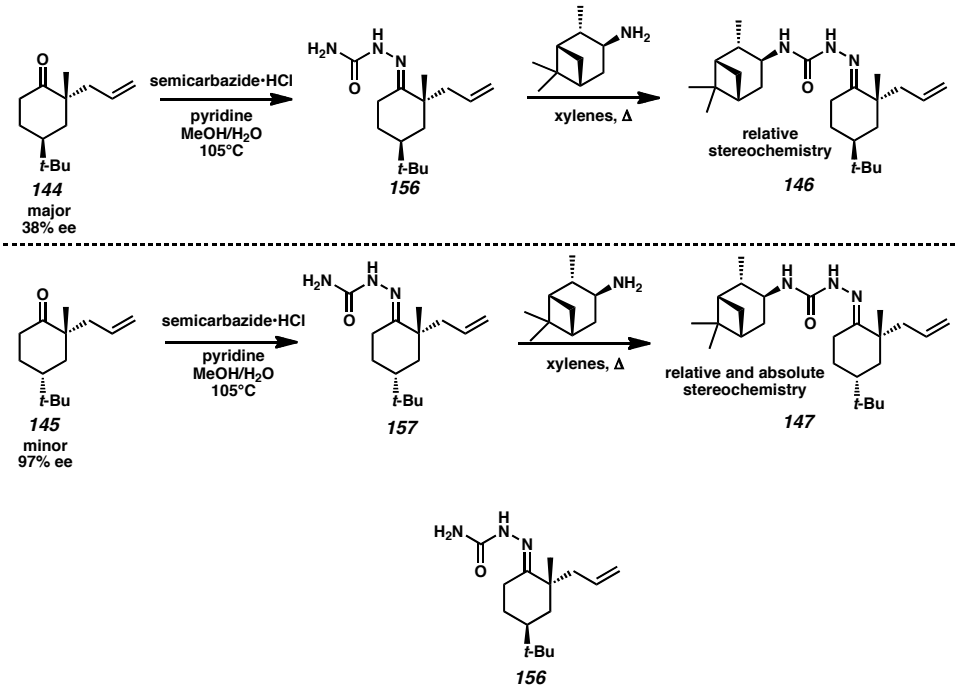


(±)-145

Minor product 145.

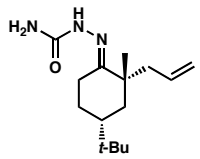
^{1}H NMR (300 MHz) δ 5.77 (m, 1H), 5.03 (m, 2H), 2.50 (m, 1H), 2.28 (m, 2H), 2.16 (m, 1H), 2.00 (m, 1H), 1.64 (m, 2H), 1.42 (m, 2H), 1.14 (s, 3H), 0.89 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.2, 135.0, 117.9, 47.3, 43.3, 42.3, 38.9, 38.5, 32.5, 27.8, 27.7, 24.2; IR (Neat Film, NaCl) 2963, 2870, 1709, 1366, 912 cm^{-1}; HRMS *m/z* calc'd for $C_{14}H_{24}O$ [M^+]: 208.1827, found 208.1836; $[\alpha]_D^{25.7}$ +77.81° (*c* 0.105, hexane).

A6.4.5 Determination of the Relative Stereochemistry for the Products from the Asymmetric Pd-Catalyzed Decarboxylative Allylic Alkylation



Major Semicarbazone 156.

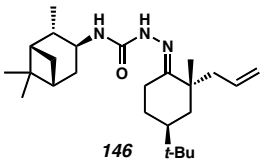
Prepared as reported by Behenna and Stoltz.[10] 131.7 mg, 69.1% yield; ^{1}H NMR (300 MHz) δ 7.66 (bs, 1H), 5.63 (m, 1H), 5.02 (m, 2H), 2.55 (m, 1H), 2.07 (m, 2H), 1.93 (m, 2H), 1.72 (m, 1H), 1.51-1.06 (m, 3H), 1.10 (s, 3H), 0.86 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 157.3, 134.0, 117.8, 42.8, 41.9, 41.9, 40.0, 32.5, 31.2, 27.0, 25.0, 22.8; IR (Neat Film, NaCl) 3470, 3194, 2963, 1689, 1583, 1475, 1366, 1078, 913, 770 cm^{-1}; HRMS *m/z* calc'd for $C_{15}H_{27}N_3O$ [M^+]: 265.2154, found 265.2149; $[\alpha]_D^{25.7}$ –8.23° (*c* 0.305, methanol).



157

Minor Semicarbazone 157.

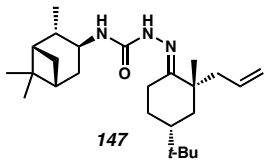
Prepared as reported by Behenna and Stoltz.[10] 103.7 mg, 81.4% yield; ^{1}H NMR (300 MHz) δ 7.96 (bs, 1H), 5.89 (m, 1H), 5.03 (app. d, 2H), 2.56 (m, 1H), 2.36 (m, 2H), 1.94 (m, 2H), 1.53 (m, 2H), 1.20-1.11 (m, 2H), 1.11 (s, 3H), 0.85 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 157.5, 136.0, 117.0, 45.2, 42.3, 41.3, 39.0, 32.5, 27.6, 26.8, 25.8, 23.1; IR (Neat Film, NaCl) 3473, 3199, 2963, 1694, 1578, 1473, 1366, 1101, 912 cm^{-1}; HRMS *m/z* calc'd for $C_{15}H_{27}N_3O$ [M^+]: 265.2154, found 265.2163; $[\alpha]_D^{25.9}$ –6.67° (*c* 0.995, methanol).



146

Major (isopinocampheylamine)-semicarbazone 146.

Prepared as reported by Behenna and Stoltz.[10] 40.1 mg, 66.2% yield; ^{1}H NMR (300 MHz) δ 7.83 (bs, 1H), 6.08 (d, *J* = 9 Hz, 1H), 5.65 (m, 1H), 5.05 (m, 2H), 4.17 (m, 1H), 2.68 – 1.46 (comp m., 13H), 1.22 (s, 3H), 1.08 (d, *J* = 7.2 Hz, 1H); 1.10 (s, 3H), 1.054 (s, 3H), 0.88 (d, 1H, *J* = 9.9 Hz), 0.85 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 156.0, 134.1, 117.8, 48.3, 48.2, 48.0, 47.1, 42.7, 41.9, 41.8, 39.8, 38.6, 38.1, 35.5, 32.5, 28.2, 27.6, 27.0, 25.0, 23.6, 22.6, 21.0; IR (Neat Film, NaCl) 3406, 3194, 3075, 2962, 1672, 1526 cm^{-1}, [M+H]$^+$: 402.3484, found 402.3487.



147

Minor (isopinocampheylamine)-semicarbazone 147.

Prepared as reported by Behenna and Stoltz.[10] 64.1 mg, 84.9% yield; ^{1}H NMR (300 MHz) δ 8.42 (bs, 1H), 6.08 (d, *J* = 9 Hz, 1H), 5.94 (m, 1H), 5.04 (m, 2H), 4.17 (m, 1H), 2.707 (m, 2H), 2.37 (m, 3H), 1.91 (m, 5H), 1.55 (m, 3H), 1.21 (s, 3H), 1.12 (d, *J* = 7.5, 3H), 1.10 (s, 3H), 1.04 (s, 3H), 0.87 (d, *J* = 9.9 Hz, 1H), 0.84 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 156.1, 136.4, 116.6, 48.2, 46.9, 45.1, 42.3, 41.9, 41.3, 39.4, 38.6, 38.0, 35.5, 32.5, 28.2, 27.6, 26.9, 25.6, 23.6, 22.9, 21.0; IR (Neat Film, NaCl) 3400, 3194, 2952, 2873, 1672, 1526 cm^{-1}; HRMS *m/z* calc'd for $C_{25}H_{43}N_3O$ $[M+H]^+$: 402.3484, found 402.3491; $[\alpha]_D^{25.1}$ +29.73° (*c* 0.2550, hexane).

A6.5 NOTES AND REFERENCES

(1) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924–6927.

(2) Please see Experimental Section for details.

(3) The relative rate of consumption of starting material was determined by comparing the negative slopes of ln[β-ketoester] versus time for β-ketoesters **142** and **143**.

(4) Tsuji, J.; Yamada, T.; Minami, L.; Yuhara, M.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1987**, *52*, 2988–2995.

(5) Kayser, R. H.; Brault, M.; Pollack, R. M.; Bantia, S.; Sadoff, S. F. *J. Org. Chem.* **1983**, *48*, 4497–4502.

(6) Pollack, R.M. In "Transition States of Biochemical Processes"; Gandour, R. D., Schowen, R. L., Eds.; Plenum: New York, 1978; p. 467.

(7) Please refer to Appendix 5 for references.

(8) House, H. O.; Tefertiller, B. A.; Olmstead, H. D. *J. Org. Chem.* **1968**, *33*, 935–942.

(9) Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis* **1967**, 581–595.

(10) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15055.

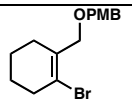
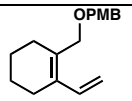
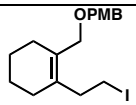
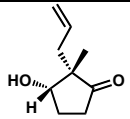
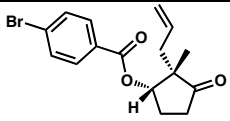
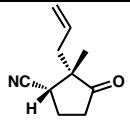
APPENDIX 7

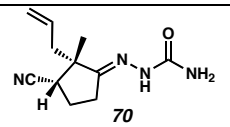
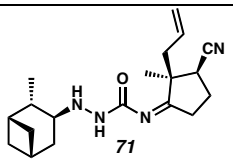
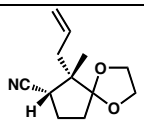
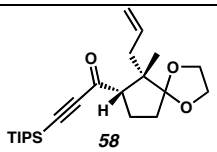
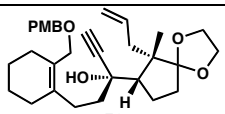
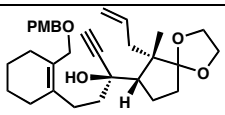
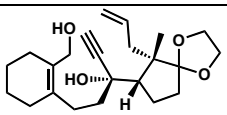
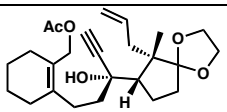
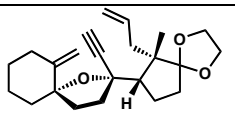
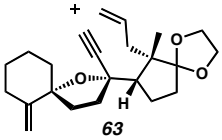
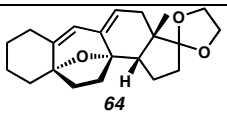
Notebook Cross-Reference

NOTEBOOK CROSS-REFERENCE

The following notebook cross-reference has been included to facilitate access to the original spectroscopic data obtained for the compounds presented in this thesis. For each compound, both hard copy and electronic characterization folders containing the original ^{1}H NMR, ^{13}C NMR, and IR spectra have been created. All notebooks and spectroscopic data are stored in the Stoltz research group archive.

Table A7.1. Compounds in Chapter 2 – Efforts toward the Rapid Construction of the Cortistatin A Carbocyclic Core

Compound	^{1}H NMR	^{13}C NMR	IR
 ***49***	SM-VII-77a	SM-VII-77a	SM-VII-77a
 ***50***	QL-V-95	QL-V-95	QL-V-95
 ***44***	CCB-2-227-1H	CCB-2-227-13C	CCB-2-227
 ***46 desired***	CCB-2-035-1H	CCB-2-035-13C	
 ***69***	SM-XII-55a	SM-XII-55a	SM-XII-55a
 ***54***	CCB-2-093-1H	CCB-2-093-13C	CCB-2-093

 *70*	SM-XII-75a	SM-XII-75a	SM-XII-75a
 *71*	SM-XII-137a	SM-XII-137a	SM-XII-137a
 *56*	CCB-2-101-IH	CCB-2-101-13C	CCB-2-101
 *58*	CCB-1-165a	CCB-1-165a	CCB-2-115a-2
 *59* *desired*	CCB-2-131d-1H	CCB-2-131d-13C	CCB-2-239c
 *60* *undesired*	CCB-2-131-2a-1H	CCB-2-131-2a-13C	CCB-2-239a
	CCB-2-245-1H	CCB-2-245-13C	CCB-2-245-2
 *61*	CCB-2-155-1H	CCB-2-155-13C	CCB-2-249-2
 *62* +  *63*	CCB-2-271a-1H	CCB-2-271-13C	CCB-2-271a
 *64*	CCB-2-241b-1H	CCB-2-241b-13C	CCB-2-241b

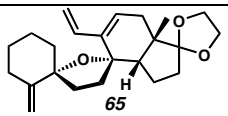
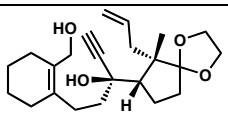
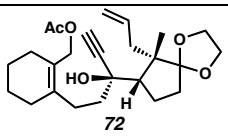
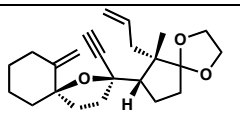
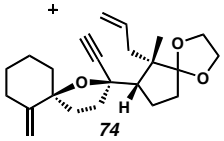
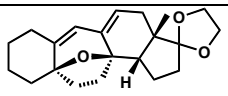
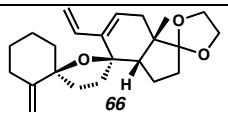
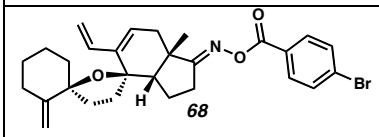
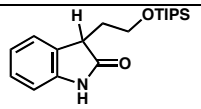
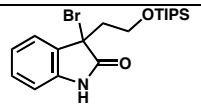
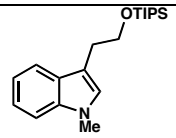
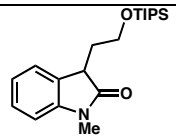
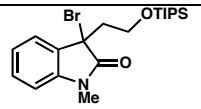
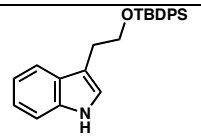
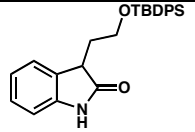
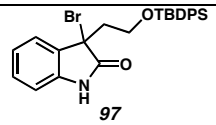
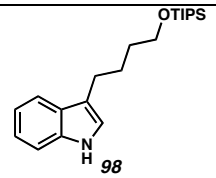
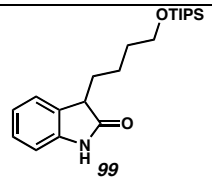
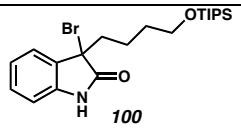
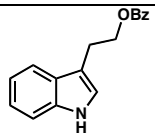
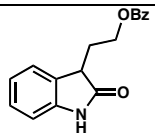
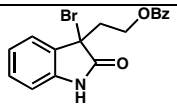
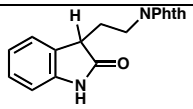
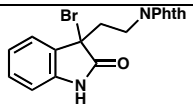
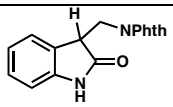
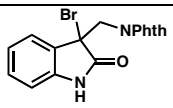
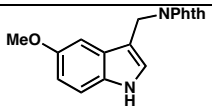
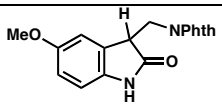
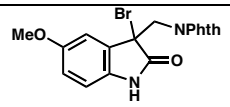
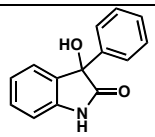
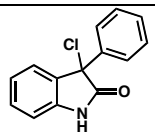
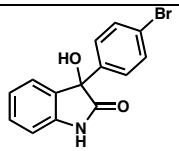
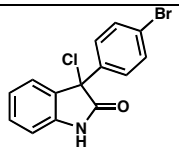
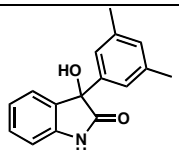
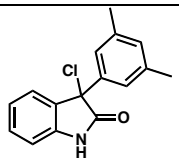
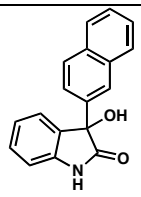
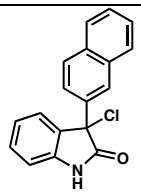
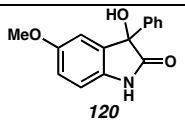
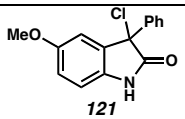
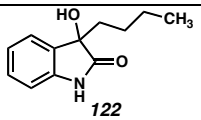
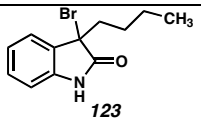
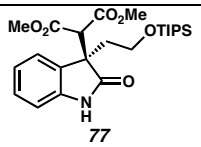
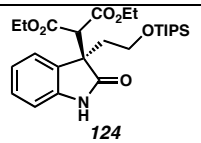
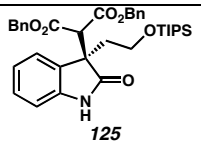
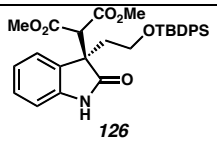
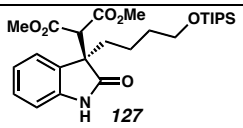
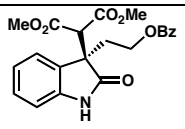
 ***65***	CCB-2-285a-1H	CCB-2-285a-13C	CCB-2-241-2a
	CCB-2-243-1H	CCB-2-243-13C	CCB-2-243-2
 ***72***	CCB-2-153-1H	CCB-2-153-13C	CCB-2-229b
 ***73*** +  ***74***	CCB-2-277a-1H	CCB-2-277-13C	CCB-2-277a
 ***75***	CCB-2-231 and 237-1H	CCB-2-231 and 237-13C	CCB-2-225b
 ***66***	CCB-2-237-1H	CCB-2-23713C	CCB-2-237a
 ***68***	CCB-3-219-1H	CCB-3-219-13C	CCB-3-219

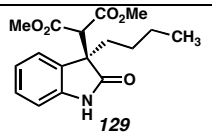
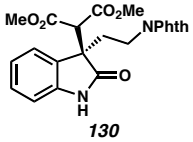
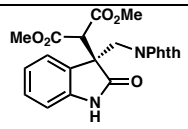
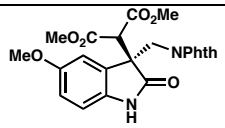
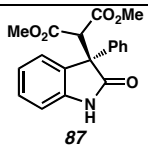
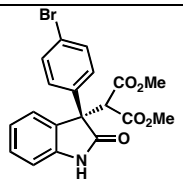
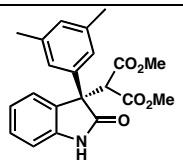
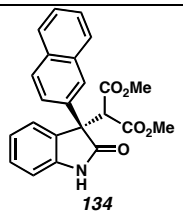
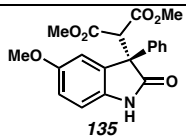
Table A7.2. Compounds in Chapter 3 – Catalytic Enantioselective Stereoablative Alkylation of 3-Halooxindoles

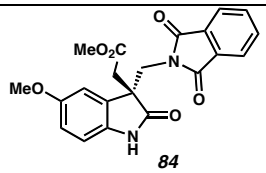
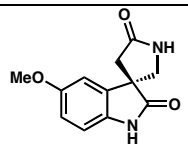
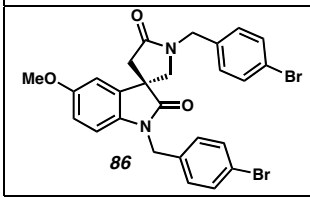
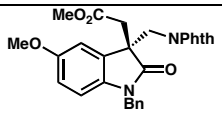
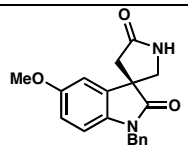
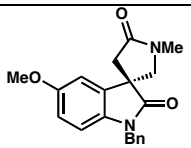
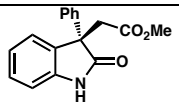
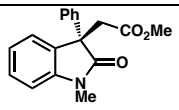
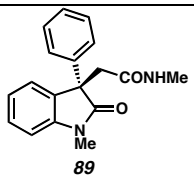
Compound	^{1}H NMR	^{13}C NMR	IR
 *91*	SK-7-167-2b	SK-7-167-2b	SK-7-167-2b-abc
 *76*	SK-7-59-2a	SK-7-59-2a	SK-7-145-2-abc
 *92*	XH-BMS-3-157	XH-BMS-3-157	XH-3-157
 *93*	XH-BMS-3-159c	XH-BMS-3-159c	XH-3-159c
 *94*	XH-BMS-3-159b	XH-BMS-3-159b	XH-3-159b
 *95*	XH-BMS-2-211	XH-BMS-2-211	
 *96*	XH-BMS-2-215c	XH-BMS-2-215c	XH-2-215c
 *97*	XH-BMS-2-215b	XH-BMS-2-251b	XH-2-215b
 *98*	XH-BMS-2-195	XH-BMS-2-195	XH-2-195

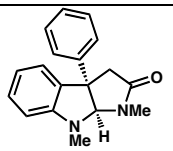
 ***99***	XH-BMS-2-197	XH-BMS-2-197	XH-2-197c
 ***100***	XH-BMS-2-197b	XH-BMS-2-197b	XH-2-197b
 ***101***	XH-BMS-1-131	XH-BMS-1-131	
 ***102***	XH-BMS-1-143C	XH-BMS-1-143C	XH-1-143c
 ***103***	XH-BMS-143B-1	XH-BMS-1-143B	XH-1-143b
 ***104***	SK-6-17-2D	SK-6-17-2D	SK-6-17-2D-abc
 ***105***	SK-6-17-2C	SK-6-17-2C	SK-6-17-2C-abc
 ***106***	XH-BMS-2-227d	XH-BMS-2-227d	
 ***107***	XH-BMS-2-227c	XH-BMS-2-227c	XH-2-227c
 ***108***	XH-BMS-2-251	XH-BMS-2-251	XH-2-251
 ***109***	XH-BMS-2-279c	XH-BMS-2-279c	

 ***110***	XH-BMS-2-265b	XH-BMS-2-265b	XH-2-279b
 ***112***	SK-VI-295	SK-VI-295	SK-VI-295
 ***113***	SM-XI-285b	SM-XI-285b	SM-XI-285b
 ***114***	SM-IX-171a	SM-IX-171a	SM-IX-199a
 ***115***	SM-IX-195	SM-IX-195	SM-IX-195
 ***116***	SM-IX-123a	SM-IX-123a	SM-XI-123a
 ***117***	SM-XI-139a	SM-XI-139a	SM-XI-139
 ***118***	SM-IX-251a	SM-IX-251a	SM-IX-251

 ***119***	SM-X-101a	SM-X-101a	SM-X-101a
 ***120***	SM-IX-153a	SM-IX-153a	SM-IX-153a
 ***121***	SM-IX-169	SM-IX-169	SM-IX-169
 ***122***	XH-BMS-1-135	XH-BMS-1-135	XH-1-135
 ***123***	XH-BMS-1-141	XH-BMS-1-141	XH-2-153
 ***77***	SK-7-225-2	SK-7-251-2a	SK-7-251-2a
 ***124***	XH-BMS-2-207	XH-BMS-2-207	SK-6-207-2b-abc2
 ***125***	XH-BMS-2-209	XH-BMS-2-209	SK-6-257-2abc
 ***126***	XH-BMS-2-217	XH-BMS-2-217	XH-2-217
 ***127***	XH-BMS-2-201	XH-BMS-2-201	XH-2-201
 ***128***	XH-BMS-1-151	XH-BMS-1-151	XH-1-151

 *129*	XH-BMS-1-145	XH-BMS-1-145	XH-1-145
 *130*	XH-BMS-2-203	XH-BMS-2-203	SM-XIII-93
 *131*	XH-BMS-2-229	XH-BMS-2-229	XH-2-229
 *83*	XH-BMS-2-297	XH-BMS-2-297	XH-2-267
 *87*	SM-XI-101a	SM-XI-101a	SM-XI-101a
 *132*	SM-IX-199a	SM-IX-199a	SM-IX-199a
 *133*	SM-XI-143b	SM-XI-143b	SM-XI-143b
 *134*	SM-IX-267a	SM-IX-267a	SM-IX-267a
 *135*	SM-IX-157a	SM-IX-157a	SM-IX-225a

 *84*	XH-BMS-2-301	XH-BMS-2-301	XH-2-301
 *85*	XH-BMS-3-271	XH-BMS-3-263	XH-3-45
 *86*	XH-BMS-3-273	XH-BMS-3-273	XH-3-273
 *136*	XH-BMS-3-213	XH-BMS-3-167	XH-3-167
 *137*	XH-BMS-3-187	XH-BMS-3-187	XH-3-187
 *138*	XH-BMS-3-145	XH-BMS-3-145	XH-3-145
 *139*	SM-X-67b	SM-X-67b	SM-X-67b
 *88*	SM-XI-149b	SM-XI-149b	SM-XI-149b
 *89*	SM-XI-49	SM-XI-49	SM-XI-49

 ***90***	SM-XI-189a	SM-XI-189a	SM-XI-189a

COMPREHENSIVE BIBLIOGRAPHY

Akai, S.; Tsujino, T.; Akiyama, E.; Tanimoto, K.; Naka, T.; Kita, Y. *J. Org. Chem.* **2004**, *69*, 2478–2486.

Akai, S.; Tsujino, T.; Naka, T.; Tanimoto, K.; Kita, Y. *Tetrahedron Lett.* **2001**, *42*, 7315–7317.

Aoki, S.; Watanabe, Y.; Sanagawa, M.; Setiawan, A.; Kotoku, N.; Kobayashi, M. *J. Am. Chem. Soc.* **2006**, *128*, 3148–3149.

Aoki, S.; Watanabe, Y.; Tanabe, D.; Arai, M.; Suna, H.; Miyamoto, K.; Tsujibo, H.; Tsujikawa, K.; Yamamoto, H.; Kobayashi, M. *Bioorg. Med. Chem.* **2007**, *15*, 6758–6762.

Aoki, S.; Watanabe, Y.; Tanabe, D.; Setiawan, A.; Arai, M.; Kobayashi, M. *Tetrahedron Lett.* **2007**, *48*, 4485–4488.

Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477–6487.

Ashimori, A.; Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Org. Chem.* **1993**, *58*, 6949–6951.

Atodiresei, I.; Schiffers, I.; Bolm, C. *Tetrahedron: Asymmetry* **2006**, *17*, 620–633.

Audis, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 3738–3740.

Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5482–5487.

Bagul, T. D.; Lakshmaiah, G.; Kawabata, T.; Fuji, K. *Org. Lett.* **2002**, *4*, 249–251.

Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Presekill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097–13105.

Bascop, S. I.; Sapi, J.; Laronze, J. Y.; Levy, J. *Heterocycles* **1994**, *38*, 725–732.

Baumgartner, C.; Ma, S.; Liu, Q.; Stoltz, B. M. *Org. Biomol. Chem.* **2010**, *8*, 2915–2917.

Beccalli, E. M.; Marchesini, A.; Pilati, T. *J. Chem. Soc. Perkin Trans. 1* **1994**, 579–587.

Behenna, D. C.; Stockdill, J. L.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 4077–4080.

Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15055.

Bella, M.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 3670–3671.

Brooks, D. W.; Mazdiyasni, H.; Grothaus, P. G. *J. Org. Chem.* **1987**, *52*, 3223–3232.

Busacca, C. A.; Grossbach, D.; So, R. C.; O'Brien, E. M.; Spinelli, E. M. *Org. Lett.* **2003**, *5*, 595–598.

Chavan, S. P.; Chavan, S. P.; Sonawane, H. R.; Kalkote, U. R.; Sudrik, S. G.; Gonnade, R. G.; Bhadbhade, M. M. *Eur. J. Org. Chem.* **2007**, 3277–3280.

Chen, J.-R.; Liu, X.-P.; Zhu, X.-Y.; Li, L.; Qiao, Y.-F.; Zhang, J.-M.; Xiao, W.-J. *Tetrahedron* **2007**, *63*, 10437–10444.

Cheung, C.-M.; Goldberg, F. W.; Magnus, P.; Russell, C. J.; Turnbull, R.; Lynch, V. *J. Am. Chem. Soc.* **2007**, *129*, 12320–12327.

Choi, T.-L.; Grubbs, R. H. *Chem. Comm.* **2001**, 2648–2649.

Christoffers, J.; Baro, A. *Adv. Synth. Catal*. **2005**, *347*, 1473–1482.

Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969–5994.

Craft, D. T.; Gung, B. W. *Tetrahedron Lett.* **2008**, *49*, 5931–5934.

Crawley, S. L.; Funk, R. L. *Org. Lett.* **2003**, *5*, 3169–3171.

Dai, M.; Danishefsky, S. J. *Heterocycles* **2009**, *77*, 157–161.

Dai, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**, *49*, 6610–6612.

Dai, M.; Wang, Z.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**, *49*, 6613–6616.

Denmark, S. D.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875–5878.

Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561–3651.

Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363–5367.

Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2964.

Edmonson, S. D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1138–1140.

Edmondson, S. D.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 2147–2155.

Edmondson, S.; Danishefsky, S. J.; Sepp-Lorenzino, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147–2155.

England, D. B.; Merey, G.; Padwa, A. *Org. Lett.* **2007**, *9*, 3805–3807.

Enquist, J. A. Jr.; Stoltz, B. M. *Nature* **2008**, *453*, 1228–1231.

Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635–1649.

Evans, D. A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*, 11583–11592.

Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 798–800.

Evans, D. A.; Rovis, T.; Johnson, J. S. *Pure Appl. Chem.* **1999**, *71*, 1407–1415.

Fejes, I.; Toke, L.; Nyerges, M.; Pak, C. S. *Tetrahedron* **2000**, *56*, 639–644.

Ferrara, N; Kerbel, R. S. *Nature* **2005**, *438*, 967–974.

Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis* **1967**, 581–595.

Folkman, J. *Nature Reviews Drug Discovery* **2007**, *6*, 273–286.

Frie, J. L.; Jeffrey, C. S.; Sorensen, E. J. *Org. Lett.* **2009**, *11*, 5394–5397.

Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 5068–5069.

Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2005**, *7*, 677–680.

Galliford, C.V.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8748–8758.

Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1–45.

Goldberg, F. W.; Magnus, P.; Turnbull, R. *Org. Lett.* **2005**, *7*, 4531–4534.

Hamashima, Y.; Sodeoka, M. *Synlett* **2006**, 1467–1478.

Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164–10165.

He, R.; Ding, C.; Maruoka, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 4559–4561.

Hills, I. D.; Fu, G. F. *Angew. Chem. Int. Ed.* **2003**, *42*, 3921–3924.

Hinman, R. L.; Bauman, C. P. *J. Org. Chem.* **1964**, *29*, 2431–2437.

House, H. O.; Tefertiller, B. A.; Olmstead, H. D. *J. Org. Chem.* **1968**, *33*, 935–942.

Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043–14053.

Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999–10003.

Imachi, M.; Ito, T.; Hasegawa, T. *Tetrahedron Lett.* **1993**, *34*, 2355–2358.

Ishimaru, T.; Shibata, N.; Horikawa, T.; Yasuda, N.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 4157–4161.

Ishimaru, T.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *J. Am. Chem. Soc.* **2006**, *128*, 16488–16489.

Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325–335.

Kagan, H. B.; Girard, C. *Angew. Chem. Int. Ed*. **1998**, *37*, 2922–2959.

Kawasaki, T.; Shinada, M.; Kamimura, D.; Ohzono, M.; Ogawa, A. *Chem. Commun.* **2006**, 420–422.

Kayser, R. H.; Brault, M.; Pollack, R. M.; Bantia, S.; Sadoff, S. F. *J. Org. Chem.* **1983**, *48*, 4497–4502.

Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard III, W. A. *J. Am. Chem. Soc.* **2007**, *129*, 11876–11877.

Kim, S.-H.; Bowden, N.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801–10802.

Kim, S.-H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073–1081.

Kim, Y. S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohsima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6506–6507.

Köhling, P.; Schmidt, A. M.; Eilbracht, P. *Org. Lett*. **2003**, *5*, 3213–3216.

Kornet, M. J.; Thio, A. P. *J. Med. Chem.* **1976**, *19*, 892–898.

Krapcho, A. P. *Synthesis* **1982**, 805–822.

Krapcho, A. P. *Synthesis* **1982**, 893–914.

Krishnan, S.; Stoltz, B. M. *Tetrahedron Lett.* **2007**, *48*, 7571–7573.

Kürti, L.; Czakó, B.; Corey, E. J. *Org. Lett.* **2008**, *10*, 5247–5250.

Kundig, E. P.; Seidel, T. M.; Jia, Y.-x.; Bernardinelli, G. *Angew. Chem. Int. Ed.* **2007**, *46*, 8484–8487.

Labroo, R. B.; Labroo, V. M.; King, M. M. Cohen, L. A. *J. Org. Chem.* **1991**, *56*, 3637–3642.

Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402–3415.

Lee, H. M.; Nieto-Oberhuber, C.; Shair, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 16864–16866.

Lee, T. B. K.; Wong, G. S. K. EP 438796A2, **1991** 19910731 US 90–46992.

Lee, T. B. K.; Wong, G. S. K. *J. Org. Chem.* **1991**, 56, 872–875.

Lerchner, A.; Carreira, E. M. *J. Am. Chem. Soc.* **2002**, *124*, 14826–14827.

Levine, S. R.; Krout, M. R.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 289–292.

Lin, H.; Danishesky, S. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 36–51.

Linton, E. C.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 16162–16163.

Liu, L.; Gao, Y.; Che, C.; Wu, N.; Wang, D. Z.; Li, C.-C.; Yang, Z. *Chem. Commun.* **2009**, 662–664.

Lo, M. M.-C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 16077–16086.

Lopez-Alvarado, P.; Caballero, E.; Avendano, C.; Menendez, J. C. *Org. Lett.* **2006**, *8*, 4303–4306.

Luppi, G.; Cozzi, P. G.; Monari, M.; Kaptein, B.; Broxterman, Q. B.; Tomasini, C. *J. Org. Chem.* **2005**, *70*, 7418–7421.

Ma, S.; Han, X.; Krishnan, S.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 8037–8041.

Magnus, P.; Littich, R. *Org. Lett.* **2009**, *11*, 3938–3941.

Magnus, P.; Turnbull, R. *Org. Lett.* **2006**, *8*, 3497–3499.

Majima, K.; Takita, R.; Okada, T.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 15837–15845.

Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143–11144.

Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505–11515.

Marti, C.; Carriera, E. M. *Eur. J. Org. Chem.* **2003**, 2209–2219.

Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500–6503.

May, J. A.; Stoltz, B. *Tetrahedron* **2006**, *62*, 15044–15045.

May, J. A; Zeidan, R. K.; Stoltz, B. M. *Tetrahedron Lett.* **2003**, *44*, 1203–1205.

McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738–7739.

McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151–4202.

Miyake, F. Y.; Yakshijin, K.; Horne, D. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 5357–5360.

Miyake, F. Y.; Yakushijin; K.; Horne, D. A. *Org. Lett.* **2004**, *6*, 4249–4251.

Mohr, J. T.; Behenna, D. C.; Harned, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924–6927.

Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924–6927.

Mohr, J. T.; Ebner, D. C.; Stoltz, B. M. *Org. Biomol. Chem.* **2007**, *5*, 3571–3576.

Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Nature* **2008**, *455*, 323–332.

Mohr, J. T.; Stoltz, B. M. *Chem. Asian. J.* **2007**, *2*, 1476–1491.

Nagata, K.; Sano, D.; Itoh, T. *Synlett* **2007**, 547–550.

Nakazawa, K.; Hayashi, M.; Tanaka, M.; Aso, M.; Suemune, H. *Tetrahedron Asymmetry* **2001**, *12*, 897–901.

Narayan, A. R. H.; Simmons, E. M.; Sarpong. R. *Eur. J. Org. Chem.* **2010**, 3553–3567.

Nicolaou, K. C.; Sun, Y.-P.; Peng, X.-S.; Polet, D.; Chen, D. Y.-K. *Angew. Chem. Int. Ed.* **2008**, *47*, 7310–7313.

Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsamura, E.; Nussbaum, F. v.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2000**, *39*, 2175–2178.

Ogawa, S.; Shibata, N.; Inagaki, J.; Nakamura, S. Toru, T.; Shiro, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 8666–8669.

Onishi, T.; Sebahar, P. R.; Williams, R. M. *Org. Lett.* **2003**, *5*, 3135–3137.

Overman, L. E.; Rosen, M. D. *Angew. Chem. Int. Ed.* **2000**, *39*, 4596–4599.

Pellegrini, C.; Strässlet, C.; Weber, M.; Borschberg, H.-J. *Tetrahedron: Asymmetry* **1994**, *5*, 1979–1992.

Petrova, K. V.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 293–295.

Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339–345.

Pinto, A.; Jia, Y.; Neuville, J.; Zhu, J. *Chem. Eur. J.* **2007**, *13*, 961–967.

Pollack, R.M. In "Transition States of Biochemical Processes"; Gandour, R. D., Schowen, R. L., Eds.; Plenum: New York, 1978; p. 467.

Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis; Christoffers, J.; Baro, A., Eds.; Wiley: Weinheim, 2005.

Rajamannar, T.; Balasubramanian, K. K. *Tetrahedron Lett.* **1988**, *29*, 5789–5792.

Rajeswaran, W. G.; Labroo, R. B.; Cohen, L. A. *J. Org. Chem.* **1999**, *64*, 1369–1371.

Ramon, D. J.; Yus, M. *Curr. Org. Chem.* **2004**, *8*, 149–183.

Sano, D.; Nagata, K.; Itoh, T. *Org. Lett.* **2008**, *10*, 1593–1595.

Satyanarayana, T.; Abraham, S.; Kagan, H. B. *Angew. Chem. Int. Ed.* **2009**, *48*, 456–494.

Seaton, J. C.; Nair, M. D.; Edwards, O. E.; Marion, L. *Can. J. Chem.* **1960**, *38*, 1035–1042.

Sehahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666–5667.

Seto, M.; Roizen, J. L.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 6873–6876.

Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. *J. Am. Chem. Soc.* **2006**, *128*, 925–934.

Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368–13369.

Shenvi, R. A.; Guerrero, C. A.; Shi, J.; Li, C.-C.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7241–7243.

Sherden, N. H.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6840–6843.

Shi, J.; Shigeshisa, H.; Guerrero, C. A.; Shenvi, R. A.; Li, C.-C.; Baran, P. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 4328–4331.

Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 3353–3356.

Siengalewicz, P.; Gaich, T., Mulzer, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 8170–8176.

Simmons, E. M.; Hardin, A. R.; Guo, X.; Sarpong, R. *Angew. Chem. Int. Ed.* **2008**, *47*, 6650–6653.

Simmons, E. M.; Hardin-Narayan, A. R.; Guo, X.; Sarpong, R. *Tetrahedron* **2010**, *66*, 4696–4700.

Takechi, H.; Machida, M.; Kanaoka, Y. *Chem. Pharm. Bull.* **1988**, *36*, 2853–2863.

Tan, G. H.; Zhu, X.; Ganesan, A. *Org. Lett.* **2003**, *5*, 1801–1803.

Tian, X.; Jiang, K.; Peng, J.; Du, W.; Chen, Y.-C. *Org. Lett.* **2008**, *10*, 3583–3586.

Toullec, P. Y.; Jagt, R. B. C.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Org. Lett.* **2006**, *8*, 2715–2718.

Trost, B. M.; Brennan, M. K. *Org. Lett.* **2006**, *8*, 2027–2030.

Trost, B. M. Stiles, D. T. *Org. Lett.* **2007**, *9*, 2763–2766.

Trost, B. M.; Cramer, N.; Silverman, S. M. *J. Am. Chem. Soc.* **2007**, *129*, 12396–12397.

Trost, B. M.; Frederiksen, M. U. *Angew. Chem. Int. Ed.* **2004**, *43*, 308–310.

Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369–396.

Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590–4591.

Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2007**, *129*, 14548–14549.

Tsuji, J.; Yamada, T.; Minami, L.; Yuhara, M.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1987**, *52*, 2988–2995.

Watanabe, M.; Ikagawa, A.; Wang, H.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* **2004**, *126*, 11148–11149.

Watanabe, Y.; Aoki, S.; Tanabe, D.; Setiawan, A.; Kobayashi, M. *Tetrahedron* **2007**, *63*, 4074–4079.

Wenkert, E.: Udelhofen, J. H.; Bhattacharayya, N. K. *J. Am. Chem. Soc.* **1959**, *81*, 3763–3768.

White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810–811.

Yamashita, S.; Iso, K.; Hirama, M. *Org. Lett.* **2008**, *10*, 3413–3415

Yasui, Y.; Kamisaki, H.; Takemoto, Y. *Org. Lett.* **2008**, *10*, 3303–3306.

Yu, P.; Cook, J. M. *Tetrahedron Lett.* **1997**, *38*, 8799–8802.

INDEX

A

B

C

D

E

F

H

I

K

L

M

N

O

P

Q

R

S

T

X

ABOUT THE AUTHOR

Sandy Ma was born on June 17th, 1982 in San Diego, California. She was the first child and only daughter of Wai Sit and Mei Ling Ma. Sandy spent the next 18 years of her life growing up in San Diego and graduated from Grossmont High School in 2000.

Sandy then moved up to Northern California to start her undergraduate studies at Stanford University. During her time at Stanford, Sandy pursued her undergraduate research in the laboratories of Prof. Robert Waymouth, where she had the opportunity to study organometallic and polymer chemistry. Sandy graduated in 2004 with a Bachelor of Science degree in both chemistry and biology.

She then moved to Pasadena, California to start her Ph.D. studies at the California Institute of Technology under the direction of Prof. Brian Stoltz. She received her degree for her work on the progress toward the cortistatin A carbocylic core and on the development of a catalytic enantioselective copper-catalyzed malonate addition of 3-halooxindoles. Sandy will be returning to San Diego to pursue her postdoctoral studies at The Scripps Research Institute in the laboratories of Prof. Jin-Quan Yu, where she will be studying C–H activation reactions.