I. SYNTHETIC STUDIES TOWARD THE TOTAL SYNTHESIS OF POLYCYCLIC NATURAL PRODUCTS – COMMUNESIN F, PEROPHORAMIDINE AND INELEGANOLIDE
II. NICKEL CATALYZED INTRAMOLECULAR C–O BOND FORMATION

Thesis by

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To my family,

for their unwavering support and dedication

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ABSTRACT

Expedient synthetic approaches to the highly functionalized polycyclic alkaloids communesin F and perophoramidine are described using a unified approach featuring a key decarboxylative allylic alkylation to access a crucial and highly congested 3,3-disubstituted oxindole. Described are two distinct, stereoselective alkylations that produce structures in divergent diastereomeric series possessing the critical vicinal all-carbon quaternary centers needed for each synthesis. Synthetic studies toward these challenging core structures have revealed a number of unanticipated modes of reactivity inherent to these complex alkaloid scaffolds. Finally, a previously unknown mild and efficient deprotection protocol for the *o*-nitrobenzyl group is disclosed – this serendipitous discovery permitted a concise endgame for the formal syntheses of both communesin F and perophoramidine.

In addition, the atroposelective synthesis of PINAP ligands has been accomplished via a palladium-catalyzed C–P coupling process through dynamic kinetic resolution. These catalytic conditions allow access to a wide variety of alkoxy- and benzyloxy-substituted PINAP ligands in high enantiomeric excess.

An efficient and exceptionally mild intramolecular nickel-catalyzed carbon–oxygen bond-forming reaction between vinyl halides and primary, secondary, and tertiary alcohols has been achieved. This operationally simple method allows direct access to cyclic vinyl ethers in high yields in a single step.

Finally, synthetic studies toward polycyclic ineleganolide are described. The entire fragmented carbon framework has been constructed from this work. Highly (Z)-selective olefination was achieved by the method by the Ando group.

PUBLISHED CONTENT AND CONTRIBUTIONS

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LIST OF ABBREVIATIONS

Å	Ångstrom
λ	wavelength
μ	micro
μwaves	microwave irradiation
$[\alpha]_D$	specific rotation at wavelength of sodium D line
[H]	reduction
[O]	oxidation
°C	degrees Celsius
Ac	acetyl
acac	acetylacetonate
AcOH	acetic acid
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl
atm	atmosphere
B3LYP	3-parameter hybrid Becke exchange/ Lee–Yang–Parr correlation functional
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOP	Bis(2-oxo-3-oxazolidinyl)phospinic
bp	boiling point
br	broad
Bu	butyl
Bz	benzoyl
c	concentration for specific rotation measurements

ca.	about (Latin circa)
calc'd	calculated
CAN	cerium ammonium nitrate
cat	catalytic
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
cf.	compare (Latin confer)
CI	chemical ionization
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
comp	complex
Cp	cyclopentadienyl
Cy	cyclohexyl
d	doublet
D	deuterium
DABCO	1,4-diazabicyclo[2,2,2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DEAD	diethyl azodicarboxylate
dec	decomposition
DFT	density functional theory
DIBAL	diisobutylaluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine
DKR	dynamic kinetic resolution
DMA	*N*,*N*-dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate

DMAP	4-dimethylaminopyridine
dmdba	bis(3,5-dimethoxybenzylidene)acetone
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
e.g.	for example (Latin exempli gratia)
E_A	activation energy
EC_{50}	median effective concentration (50%)
EDC	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide
ee	enantiomeric excess
EI+	electron impact
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
FAB	fast atom bombardment
FID	flame ionization detector
g	gram(s)
GC	gas chromatography
gCOSY	gradient-selected correlation spectroscopy
h	hour(s)
$h\nu$	light
HBPin	4,4,5,5-tetramethyl-1,3,2-dioxaborolane; pinacolborane
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol

HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HOBt	hydroxybenzotriazole
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
Hz	hertz
i.e.	that is (Latin id est)
IBX	2-iodoxybenzoic acid
IC_{50}	median inhibition concentration (50%)
IMDA	Intramolecular Diels–Alder reaction
IPA	isopropanol, 2-propanol
i-Pr	isopropyl
IR	infrared (spectroscopy)
IRC	intrinsic reaction coordinate
J	coupling constant
K	Kelvin(s) (absolute temperature)
kcal	kilocalorie
KHMDS	potassium hexamethyldisilazide
L	liter; ligand
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
lit.	literature value
m	multiplet; milli
m	meta
M	metal; molar; molecular ion
m/z	mass to charge ratio
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl

mg	milligram(s)
MHz	megahertz
min	minute(s)
MM	mixed method
MMPP	magnesium monoperoxyphthalate
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
MVK	methyl vinyl ketone
n	nano
N	normal
nbd	norbornadiene
NBS	*N*-bromosuccinimide
n-Bu	butyl
NHC	*N*-heterocyclic carbene
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nosyl	nitrobenzenesulfonyl
Nu	nucleophile
o	ortho
OKR	oxidative kinetic resolution
p	para
PCC	pyridinium chlorochromate
Pd/C	palladium on carbon
PDC	pyridinium dichromate

Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PHOX	phosphinooxazoline ligand
Piv	pivaloyl
p*Ka*	p*K* for association of an acid
PMB	*p*-methoxybenzyl
pmdba	bis(4-methoxybenzylidene)acetone
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
PTU	*n*-Propylthiouracil
Py	pyridine
q	quartet
R	generic for any atom or functional group
Ref.	reference
R_f	retention factor
s	singlet or strong or selectivity factor
sat.	saturated
Selectfluor	1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
SEM	2-(trimethylsilyl)ethoxymethyl
SFC	supercritical fluid chromatography
S_N2	second-order nucleophilic substitution
S_N2'	nucleophilic substitution with allylic rearrangement
sp	sparteine
sp.	species
t	triplet
TBAF	tetrabutylammonium fluoride

TBAI	tetrabutylammonium iodide
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBME	*tert*-butyl methyl ether
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
Tol	tolyl
t_R	retention time
Ts	*p*-toluenesulfonyl (tosyl)
UV	ultraviolet
v/v	volume to volume
$VO(acac)_2$	vanadyl acetoacetonate
w	weak
w/v	weight to volume
X	anionic ligand or halide

CHAPTER 1

The Evolution of a Unified, Stereodivergent Approach to the Synthesis of Communesin F and Perophoramidine[†]

1.1. Introduction

In 1993, communesin A (**1a**) was isolated along with communesin B (**1b**) from a strain of *Penicillium* sp. found growing on a marine alga by the Numata group (Figure 1.1.1).[1] Communesins A (**1a**) and B (**1b**) exhibit antiproliferative activity against P-388 lymphocytic leukemia cells (ED_{50} = 3.5 μg/mL and 0.45 μg/mL, respectively).[1] In addition, communesin B (**1b**) disrupts actin microfilaments in cultured mammalian cells and shows cytotoxic activity against LoVo and KB cells (MIC values of 2.0 μg/mL and 4.5 μg/mL, respectively).[2] Several other members of the comunesin family, communesins B–H (**1b**–**1h**), were disclosed from related marine fungal strains of

[†] This work was performed in collaboration with Dr. Florian Vogt, Dr. Jeremy A. May, Dr. Shyam Krishnan, Dr. Michele Gatti, and Dr. Scott C. Virgil. Additionally, this work has been published and adapted with permission from Han, S.-J.; Vogt, F.; May, J. A.; Krishnan, S.; Gatti, M.; Virgil, S. C.; Stoltz, B. M. *J. Org. Chem.* **2015**, *80*, 528–547. Copyright 2015 American Chemical Society. Related work has been published and adapted with permission from Han, S.-J.; Vogt, F.; Krishnan, S.; May, J. A.; Gatti, M.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2014**, *16*, 3316–3319. Copyright 2014 American Chemical Society.

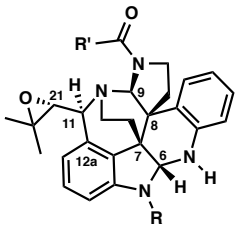
Penicillium sp. in the following years.[3] With the exception of communesins G (**1g**) and H (**1h**), the communesins show insecticidal activity and antiproliferative activity against a variety of cancer cells, with communesin B (**1b**) being the most potent.[1–3] These indole alkaloids contain several interesting structural features including vicinal all-carbon quaternary centers, bis-aminal functionalities, and a complex polycyclic core. The communesins are structurally unique when compared against other known microfilament-disrupting agents, which are primarily macrolides. Macrolide microfilament-disrupting agents show considerable structural similarity, and their interactions with actin have been crystallographically characterized, leading to hypotheses regarding their mechanism of action.[4] The unique structure of communesin B (**1b**) suggests that it may exhibit a novel mechanism of action on the cytoskeleton relative to other microfilament-disrupting agents.[5a] The development of a unified synthetic route to the communesins would enable the understanding of their effects on the cellular cytoskeleton, while addressing the scarcity of naturally occurring sources of the compounds.

In 2001, an intriguing natural product, nomofungin (**2**) was isolated from an unidentified fungus found on the bark of *Ficus microcarpa* by the Hemscheidt group.[2] Interestingly, the only structural difference between communesin B (**1b**) and nomofungin (**2**) is that communesin B has an aminal moiety instead of the *N,O*-acetal moiety present in nomofungin. A combination of experimental and theoretical exercises led to the independent discovery by our laboratory and the Funk group that the reported structure of nomofungin was incorrect, and that it is actually that of communesin B.[5a,b] Although the structure of nomofungin was erroneously assigned, its isolation and structural revision to that of an older structure can be viewed as the inception point for all synthetic efforts to

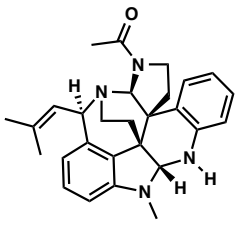
the communesin family members over the past decade. Interestingly, there were no reports of synthetic efforts toward the communesins from 1993 up to our initial report in 2003.[5i]

A structurally related compound, perophoramidine (**3**), was isolated in 2002 from the ascidian *Perophora namei*.[6] The core is comparable to the one found in the communesins, albeit in a higher oxidation state, with the alternate diastereomeric relationship between the vicinal quaternary carbons and without the azepine ring system. Perophoramidine (**3**) possesses modest cytotoxicity against the HCT 116 human colon carcinoma cell line (IC_{50} = 60 μM) and induces apoptosis.[7]

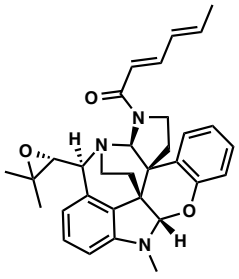
Figure 1.1.1. *Communesins (**1**), Nomofungin (**2**), and Perophoramidine (**3**)*



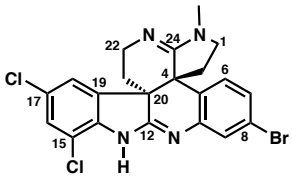
Communesin	R	R'
A (1a)	CH_3	CH_3
B (1b)	CH_3	pentadienyl
C (1c)	H	pentadienyl
D (1d)	CHO	pentadienyl
E (1e)	H	CH_3
G (1g)	CH_3	CH_2CH_3
H (1h)	CH_3	$CH_2CH_2CH_3$



Communesin F (1f)



Nomofungin (2)
(Original Structure)



Perophoramidine (3)

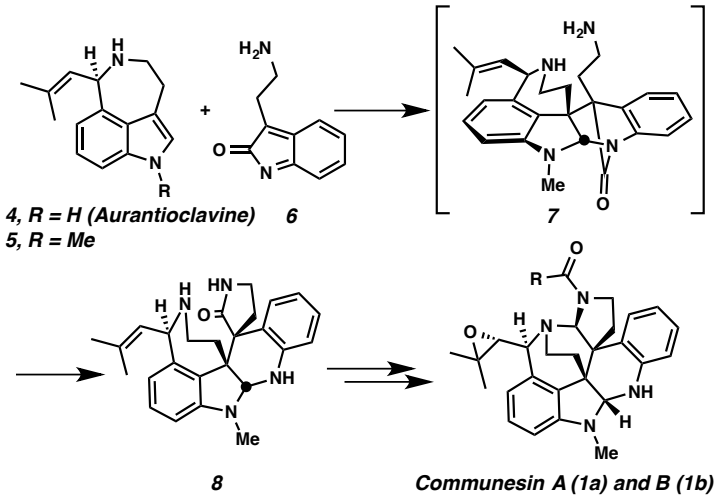
These complex, polycyclic, bioactive alkaloids have been the subject of intense synthetic efforts over the past decade.[5] Numerous approaches have been reported in the literature, including three from our laboratory.[5a,5c,5w] Herein, we report the evolution of an efficient, unified approach toward the synthesis of these unique alkaloids.

1.2. Results and Discussion

1.2.1. Biosynthesis-Inspired Diels–Alder Cycloaddition Strategy to Communesin F

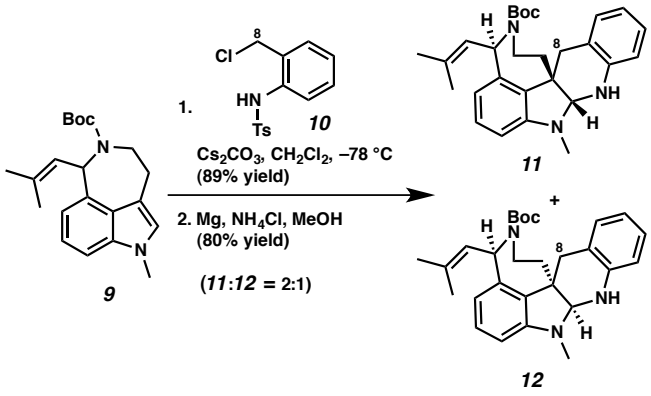
Our early efforts toward the communesin structure centered on the laboratory implementation of our proposed biosynthesis (Scheme 1.2.1).[5a,c,8] As the key step in the process, we envisioned a Diels–Alder cycloaddition to unite the two indole-based fragments by coupling of **5**, an *N*-methylated derivative of the ergot alkaloid aurantioclavine (**4**)[9,10] and an *o*-azaxylylene indolone **6** to generate the bridged lactam **7**. We anticipated that lactam **7** would be highly reactive due to the poor alignment of the nitrogen lone pair with the carbonyl.[11,12,13] As such, the pendant amino group would be expected to easily open the lactam, thus forming spirocycle **8**. Further tailoring would produce communesin A (**1a**) and B (**1b**).

Scheme 1.2.1. *Biosynthesis-Inspired Approach*



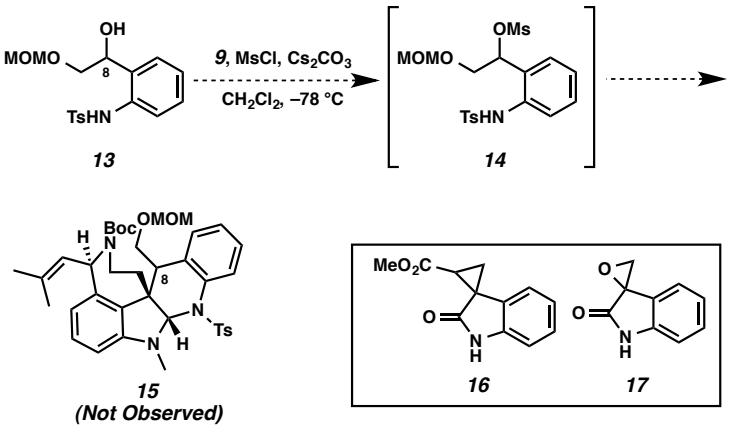
Toward this end, (±)-aurantioclavine was prepared using known methods[5a,14] and an enantioselective synthesis of (–)-aurantioclavine utilizing our oxidative kinetic resolution (OKR) technology was developed.[15] We proceeded to develop an efficient cycloaddition between (±)-indole **9** as a model coupling partner and chlorotoluamide **10** using conditions previously developed by Steinhagen and Corey[16] that resulted in a mixture of pentacyclic diastereomers (89% yield). Removal of the tosyl group with magnesium in methanol produced a 2:1 mixture of diastereomers **11** and **12** in 80% combined yield, with the desired relative stereochemistry evident in the major diastereomer (cf. **11** and **1a**) (Scheme 1.2.2).[5a]

Scheme 1.2.2. *Model Studies for a Diels–Alder Cycloaddtion Strategy To Construct the Pentacyclic Core Structure*



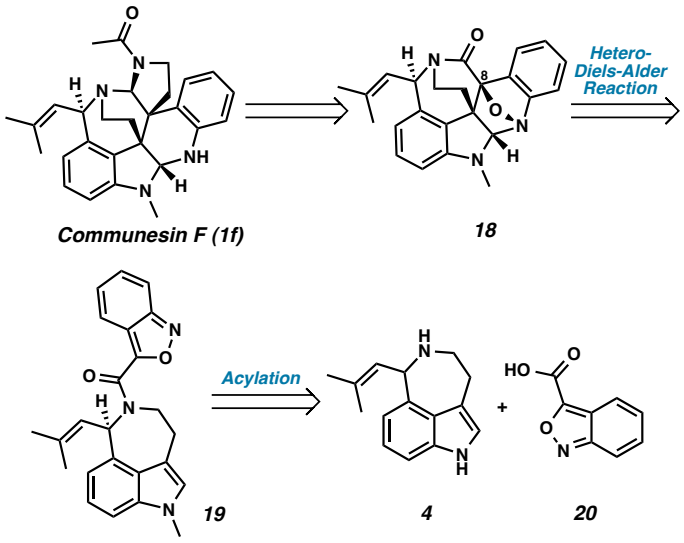
Despite the success of this model system, more advanced electrophiles (e.g., mesylate **14**, cyclopropane **16**, or epoxide **17**[17]) did not succumb to cycloaddition conditions (Scheme 1.2.3). Nor have we been successful in the oxidation of **11** and **12** at C(8), which would provide a functional handle for introduction of the second quaternary stereocenter.

Scheme 1.2.3. *Attempted Diels–Alder Cycloadditions with Advanced Electrophiles*



To obviate the difficulties encountered in our attempts to functionalize C(8), we next considered dienes possessing a functional handle at C(8) that could unite diene and dienophile, such as benzisoxazole **19**, thereby enabling an intramolecular Diels–Alder cycloaddition (Scheme 1.2.4). Thus, when coupled to aurantioclavine **4**, benzisoxazole **20** would offer a stable *o*-methide imine that could react with the indole moiety of compound **19** in a controlled and intramolecular manner.

Scheme 1.2.4. *Retrosynthetic Analysis of Communesin F by an Intramolecular Diels–Alder Cycloaddition*



Fischer esterification of commercially available carboxylic acid **21**, followed by heating in neat sulfuric acid provided the benzisoxazole acid **20** in 44% yield over 2 steps (Scheme 1.2.5).[18] Treatment of benzisoxazole acid **20** with oxalyl chloride provided the corresponding acid chloride, which was smoothly coupled with aurantioclavine **4** to furnish carboxamide **22** (91% yield, 2 steps). Similarly, 1-methylaurantioclavine **5**

reacted with the acid chloride to afford carboxamide **19** (77% yield, 2 steps). Substrates **22** and **19** were subjected to an intramolecular Diels–Alder cycloaddition under acidic conditions.[19] Unfortunately, the benzisoxazole reacted with the butenyl side chain of the aurantioclavine core to generate the bridged polycycles **23** and **24**. Nuclear Overhauser Effect NMR spectroscopy (NOESY) studies and X-ray analysis (Figure 1.2.1) demonstrated the relative stereochemistry shown for **24** and that of **23** was assigned by analogy.

Scheme 1.2.5. *Intramolecular Diels–Alder Cycloaddition*

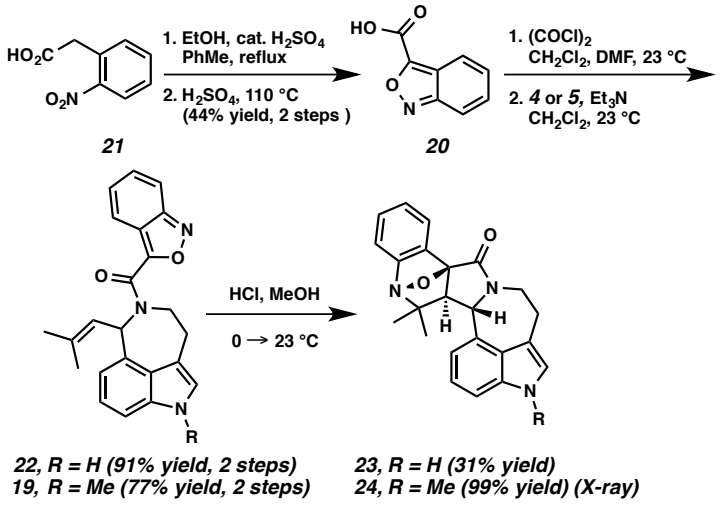
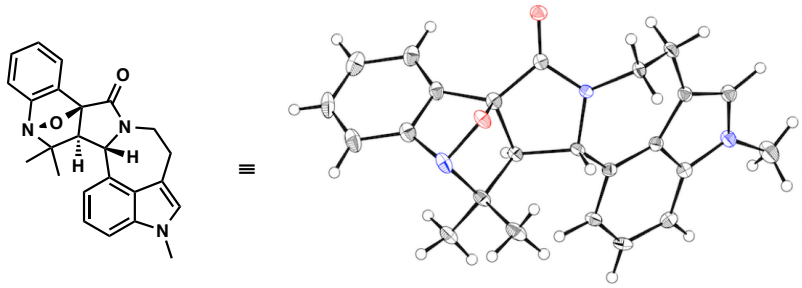


Figure 1.2.1. *X-ray Structure of Bridged Polycycle* ***24***



24 ***24***

At this point, we turned our attention to synthesizing 3-bromooxindole **26**, which would be a precursor to an *o*-methide imine such as reactive intermediate **6**, allowing for the construction of the communesin core according to our original biosynthesis-inspired model (Scheme 1.2.1). Aurantioclavine derivative **25** was reacted with bromooxindole **26** in an effort to produce adduct **27** (Scheme 1.2.6a). Interestingly, different reactivity was observed in coordinating and non-coordinating solvents. In THF or acetonitrile, the reaction afforded indole **28** in 69% yield, wherein the oxindole was introduced to position C(2) of the indole nucleus, presumably via rearrangement of the initially formed adduct **27** at C(3) (Scheme 1.2.6b). Sulfonylation of indole **28** with *o*-NsCl under basic conditions was accompanied by unexpected chlorination of the indole moiety to afford chloroindoline **29** (73% yield), the structure of which was unambiguously confirmed by X-ray crystallography (Figure 1.2.2). To the best of our knowledge, this constitutes the first use of *o*-NsCl for chlorination of an indole to provide the 3-chloroindolenine. On the other hand, the same coupling of derivatives **25** and **26** in benzene or dichloromethane furnished indole **28** (24% yield), and two additional undesired products **30** (32% yield) and **31** (24% yield) (Scheme 1.2.6c). Adduct **30** results from nucleophilic

attack at C(6) of the aurantioclavine indole core, while double adduct **31** is produced from both C(6) and C(2) functionalization. The structure of **30** was unambiguously determined following preparation of lactam **32** (Scheme 1.2.6d). Subjecting **30** to excess sodium hydride and *o*-NsCl conditions functionalized both the oxindole and indole nitrogens (66% yield) and subsequent reduction of the azide allowed for cyclization to lactam **32** in 66% yield. The structure of **32** was confirmed by single crystal X-ray diffraction (Figure 1.2.3).

Scheme 1.2.6. *Reaction of Aurantioclavine Derivative* ***25*** *with Bromooxindole* ***26***

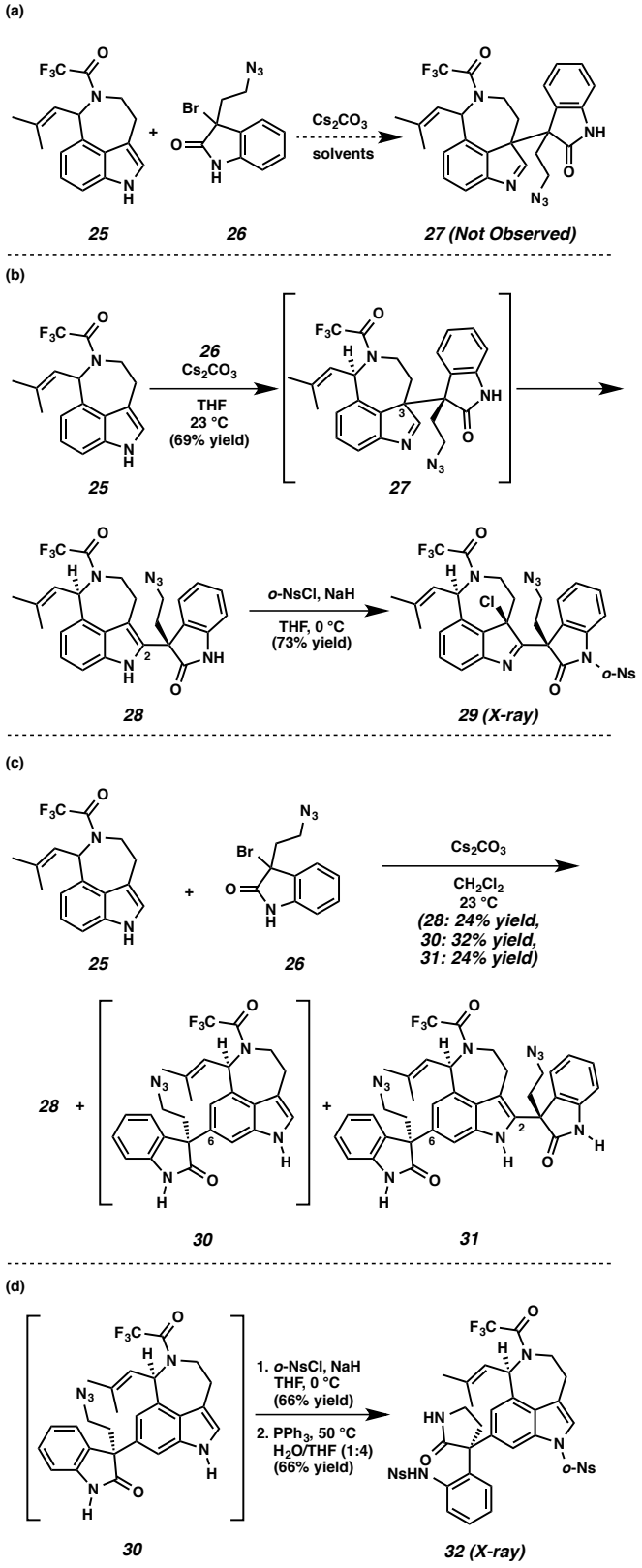
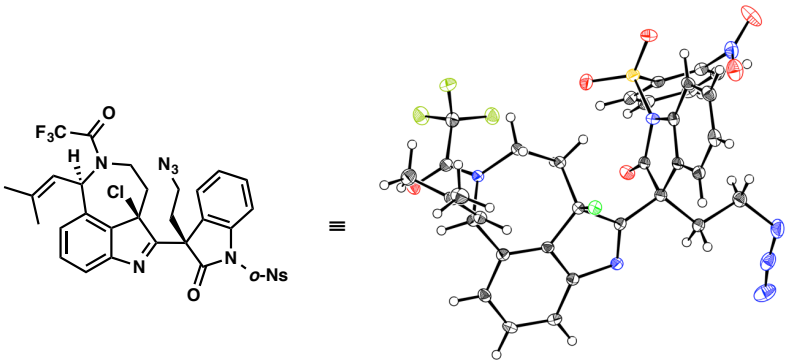
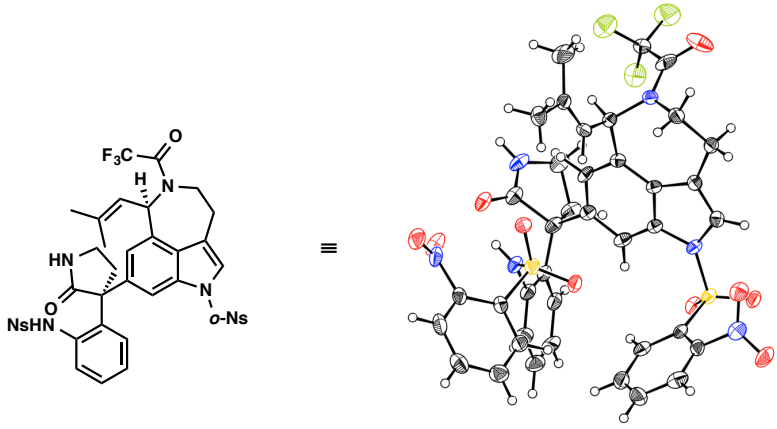


Figure 1.2.2. *X-ray Structure of Chloroindoline* ***29***



29 ***29***

Figure 1.2.3. *X-ray Structure of Lactam* ***32***



32 ***32***

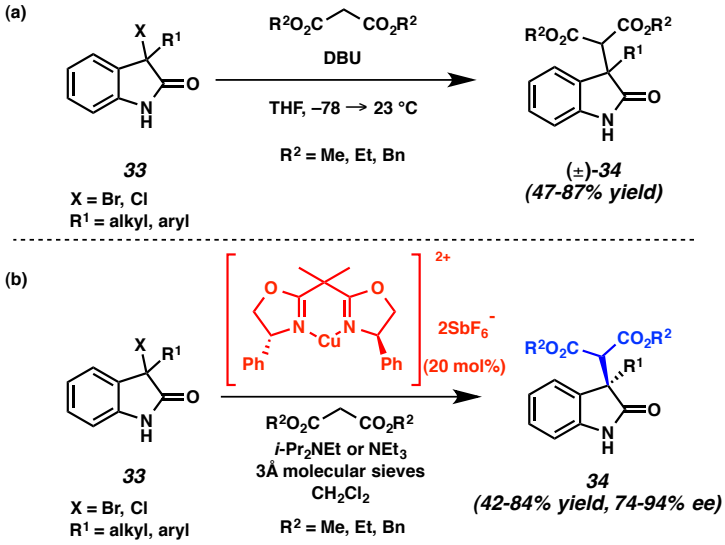
1.2.2. An Alkylation Route to Communesin F

Discouraged by the unsuccessful Diels–Alder cycloaddition-based approaches to communesin F (**1f**), we considered an alternative strategy toward the natural product. In 2007, as a direct result of our efforts toward the communesins and perophoramidine, we developed a method to generate 3,3-disubstituted oxindoles via the base-mediated coupling of oxindole electrophiles with malonate derived nuclophiles. (Scheme 1.2.7a).[20]

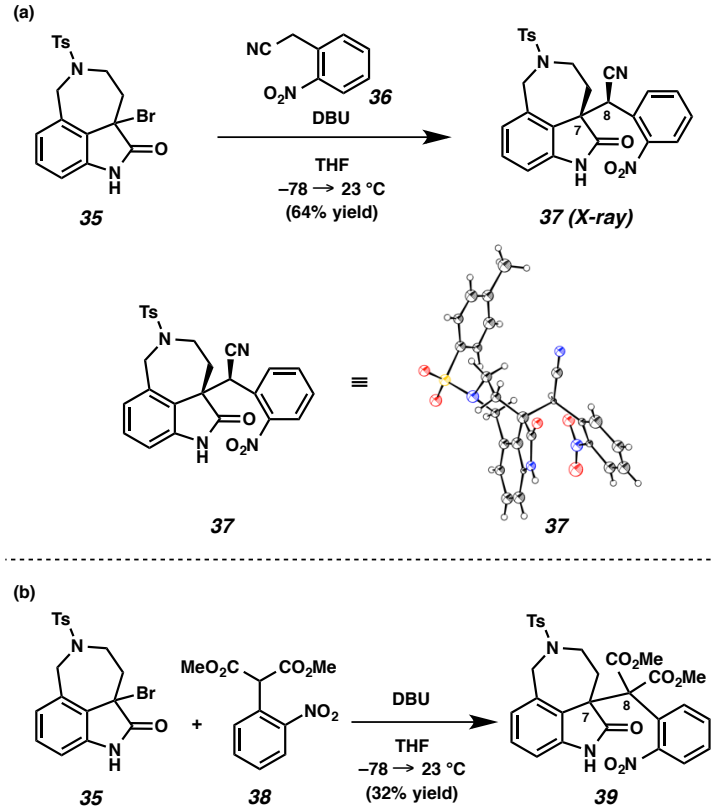
We also developed an asymmetric variant of this reaction utilizing copper bis(oxazoline) complexes (Scheme 1.2.7b).[21]

With the method shown in Scheme 1.2.7, we devised a new synthetic strategy that cast our coupling fragments in an *umpolung* manner, invoking an electrophilic aurantioclavine portion and a nucleophilic right hand fragment. We first pursued this notion in the context of the model azepine **35** (Scheme 1.2.8). Treatment of **35** with DBU and a pronucleophile (e.g., **36**[22] and **38**) produced oxindole adducts (i.e., **37** and **39**) possessing the key C(7)–C(8) linkage in modest but encouraging yields. Importantly, adduct **37** was crystalline, and we confirmed both the new C–C bond as well as the relative stereochemistry of the sole diastereomeric isolate via X-ray analysis.

Scheme 1.2.7. *Construction of 3,3-Disubstituted Oxindoles*



Scheme 1.2.8. *Construction of C(7)–C(8) Linkage by Alkylation Strategy*



Having produced the key C(7)–C(8) linkage via an *umpolung* strategy, we treated aurantioclavine-derived bromooxindole **40** with malonate **41** in the presence of DBU (Scheme 1.2.9). Smooth reactivity under our standard conditions led to the isolation of a single stereoisomeric adduct **42** in 74% yield. To our delight, oxindole adduct **42** was amenable to single crystal X-ray diffraction, however, the X-ray analysis surprisingly revealed that the alkylation occurs with high *syn* selectivity relative to the existing isobutenyl substituent (Figure 1.2.4). This result was intriguing, given that in the Diels–Alder cycloaddition of the corresponding indole **9** with the *o*-azaxylylene derived from chlorotoluamide **10**, the selectivity at C(7) favored the *anti* diastereomer **11** (cf. Schemes 1.2.9. and 1.2.2).[23]

Scheme 1.2.9. *Alkylation of Azepine Bromooxindole* ***40*** *with Malonate* ***41***

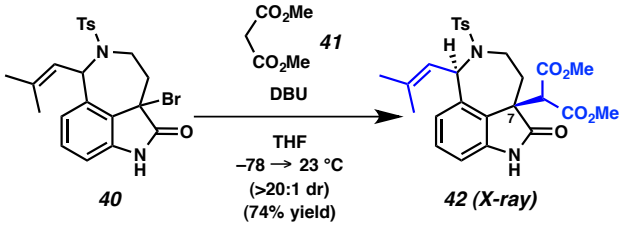
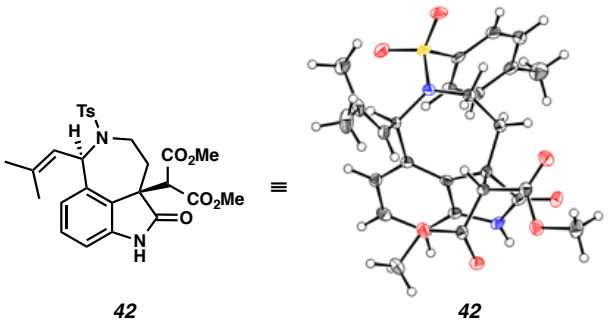
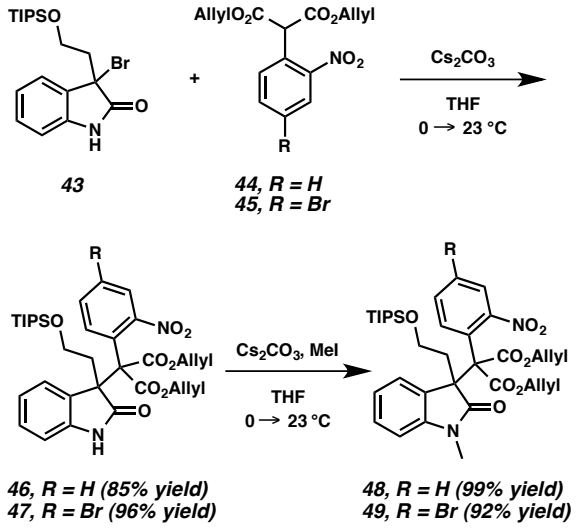


Figure 1.2.4. *X-ray Structure of Oxindole Adduct* ***42***



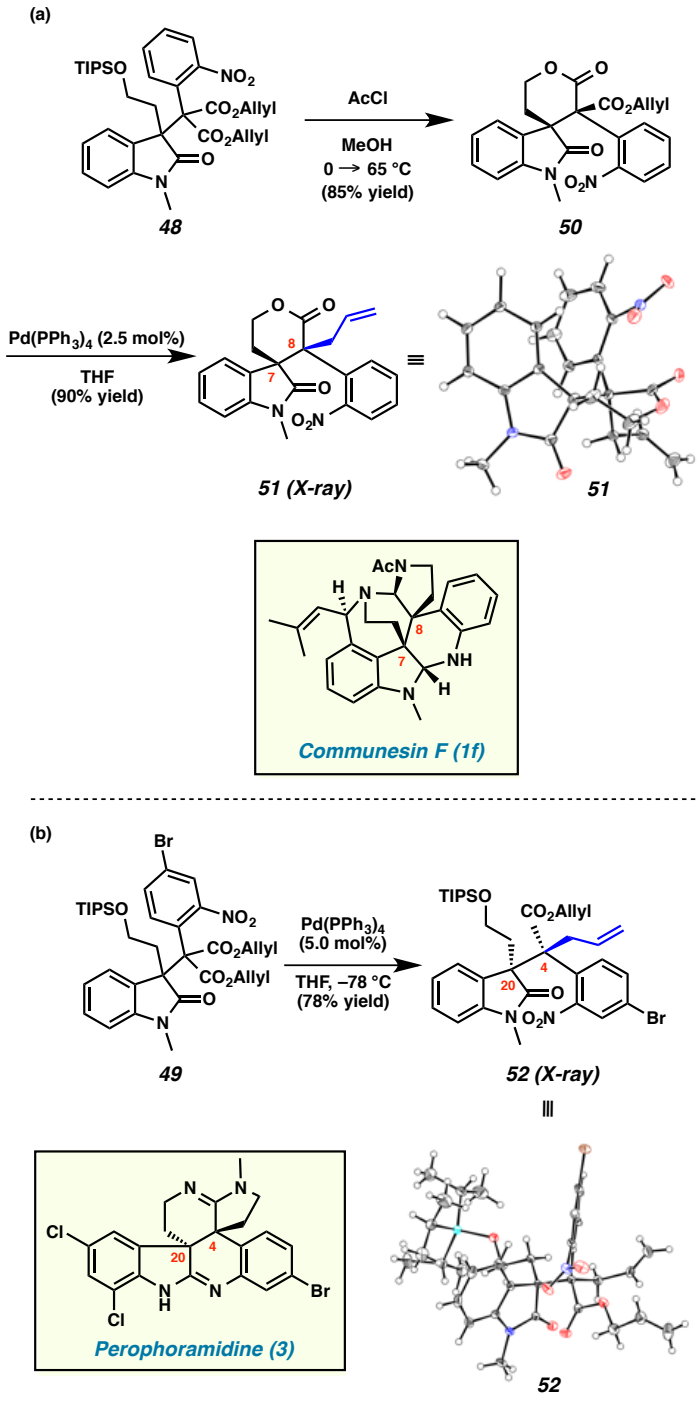
Since the undesired relative stereochemistry was obtained in adduct **42** from the alkylation of azepine **40** and malonate **41**, we explored our strategy in a model system lacking the azepine ring of the oxindole (Scheme 1.2.10). Known silyl ether **43**[21,22] was converted into malonate adducts **46** and **47** in 85% and 96% yield, respectively, under our previously reported conditions in Scheme 1.2.7. Importantly, in the non-azepine system, the efficiency of those alkylations is increased, even in these cases where vicinal quaternary centers are generated.[24] Methylation of oxindoles **46** and **47** produced **48** and **49** in 99% and 92% yield, respectively.

Scheme 1.2.10. *Alkylation of 3-Bromooxindole* ***43***



Acid-catalyzed desilylation and cyclization of diester **48** proceeded smoothly to furnish lactone **50** in 85% yield as a single diastereomer (Scheme 1.2.11a).[25] To our delight, lactone **50** underwent decarboxylative allylic alkylation when treated with $Pd(PPh_3)_4$, yielding **51** in 90% yield as a single diastereomer.[26,27] Single crystal X-ray analysis confirmed that lactone **51** possesses the relative stereochemistry at the vicinal quaternary carbon centers C(7) and C(8) that is needed for further elaboration to communesin F (**1f**). Interestingly, direct decarboxylative allylic alkylation of diester **49** again provided an alkylated product (i.e., **52**) as a single diastereomer in 78% yield (Scheme 1.2.11b). Through X-ray analysis, we discovered that the relative stereochemistry at the vicinal quaternary stereocenters C(20) and C(4) of **52** was complementary to that of the lactone **51**, and thus ideal for elaboration to perophoramidine (**3**).

Scheme 1.2.11. *Model Studies for Construction of the Vicinal Quaternary Centers*

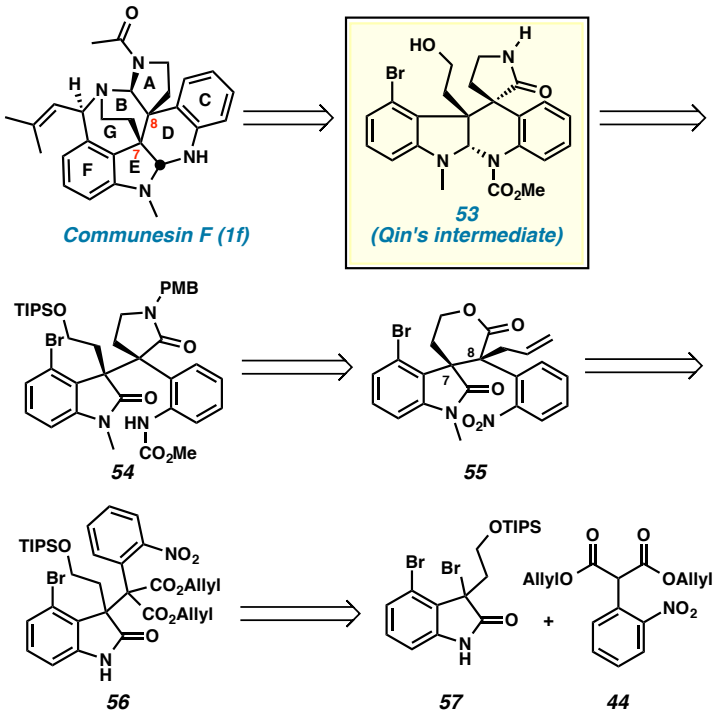


At this time, the underlying reasons for the stereochemical relationships observed in these two alkylation reactions are unclear. The fact that the reactions proceed stereodivergently with high diastereocontrol is quite remarkable. Work toward building reasonable models for stereoinduction of β-quaternary tetrasubstituted enolates in both cyclic and acyclic settings as well as the development of these interesting processes in more general cases is ongoing. Nevertheless, with the promising model systems **51** and **52** completed, we next applied our findings to expedient formal syntheses of communesin F (**1f**) and perophoramidine (**3**).

1.2.3. Formal Synthesis of Communesin F (1f)

As depicted in our retrosynthetic strategy (Scheme 1.2.12), communesin F could be completed from advanced intermediate **53** in Qin's synthesis.[5g] We anticipated the initial disconnection of the aminal linkage in **53**, thereby revealing oxindole and aniline moieties in **54**. Then, the lactam ring in **54** would be excised, affording lactone **55**. We envisioned that the relative stereochemical relationship at C(7) and C(8) of lactone **55** could be established by employing our decarboxylative allylic alkylation. The quaternary center on oxindole **56** was disassembled into 3-bromooxindole **57** and diallyl malonate **44**.

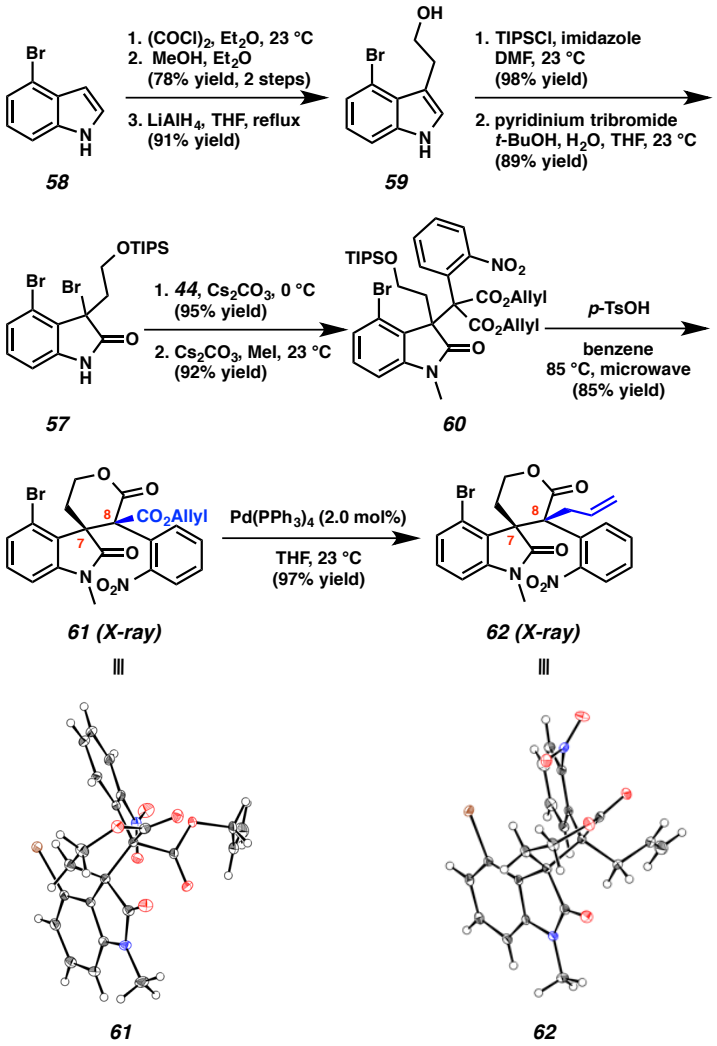
Scheme 1.2.12. *Retrosynthesis of Communesin F (**1f**)*



In the forward synthetic sense, our efforts toward communesin F commenced with the elaboration of 4-bromoindole **58** to diallyl malonate **60** (Scheme 1.2.13). Treatment of 4-bromoindole **58** with oxalyl chloride and methanol provided an oxoacetate (78% yield, 2 steps), which was reduced to the corresponding primary alcohol **59** with $LiAlH_4$ in 91% yield.[5g] Silylation of the primary alcohol with TIPSCl (98% yield) and subsequent oxidation with pyridinium tribromide afforded dibromooxindole **57** in 89% yield.[28] Despite the extra steric encumbrance of C(4) substitution, we were delighted to find that smooth coupling of dibromooxindole **57** with malonate **44** produced a 3,3-disubstituted oxindole in 95% yield. Protection of the oxindole with MeI delivered adduct **60** in 92% yield. Microwave assisted lactonization of diester **60** with *p*-TsOH proceeded smoothly to furnish lactone **61** as a single diastereomer (85% yield).

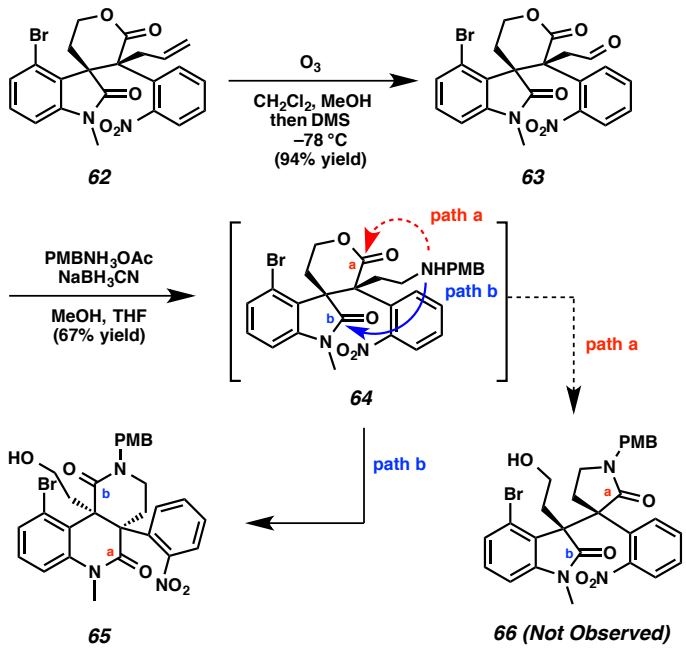
Gratifyingly, decarboxylative allylic alkylation constructed the quaternary center at C(8) of compound **62** as a single diastereomer in 97% yield under $Pd(PPh_3)_4$ catalysis. The relative stereochemistry at C(7) and C(8) of **61** and **62** was unambiguously confirmed by X-ray analysis.

Scheme 1.2.13. *Development of the Vicinal Quaternary Center*



Although ozonolysis of alkene **62** delivered aldehyde **63** in 94% yield, attempted reductive amination of aldehyde **63** did not produce the desired γ-lactam **66** (Scheme 1.2.14). Upon treatment of aldehyde **63** with *p*-methoxybenzylammonium acetate and sodium cyanoborohydride, amine intermediate **64** was likely produced.[29] Instead of opening the lactone directly (path a), nucleophilic attack by the newly generated amine at the oxindole moiety (path b), and subsequent ring-shift tautomerization delivered dihydroquinolinone **65** in 67% yield.

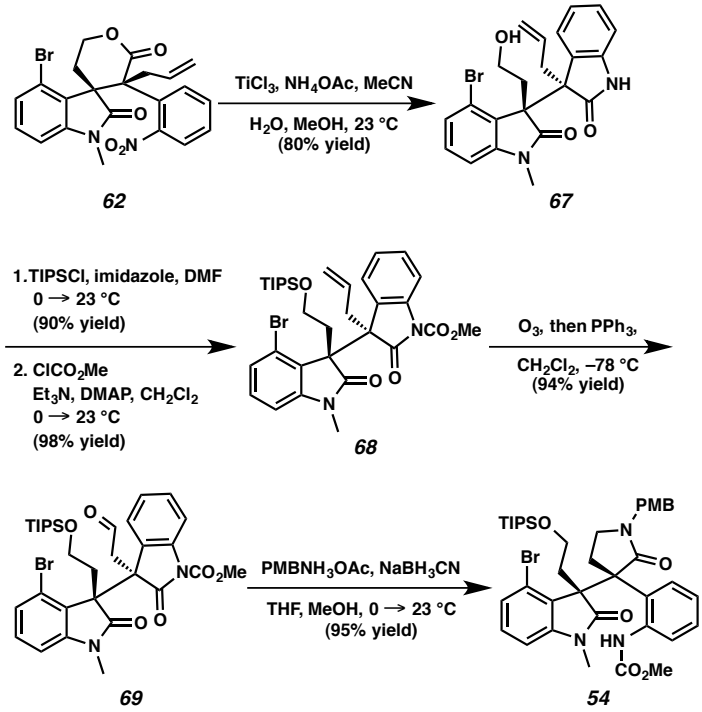
Scheme 1.2.14. *Ozonolysis and Reductive Amination of Lactone* ***62***



Alternatively, we found that lactam **54** (an analogue of **66**) could be obtained via the reaction sequence summarized in Scheme 1.2.15. The nitro group on compound **62** was reduced to the aniline, which resulted in concomitant lactone ring opening to furnish a bis-oxindole **67** in 80% yield. Protection of the primary alcohol with TIPSCl (90%

yield) and protection of the oxindole nitrogen with methyl chloroformate afforded carbamate **68** in 98% yield. Ozonolysis of alkene **68** generated aldehyde **69** (94% yield),[30] which underwent subsequent reductive amination and selective lactamization with the electron deficient oxindole to afford γ-lactam **54** in 95% yield.

Scheme 1.2.15. *Synthesis of Lactam* ***54***



With lactam **54** in hand, we envisioned that the piperidine D ring of **70** would be prepared by AlH_3-Me_2NEt mediated reductive cyclization (Scheme 1.2.16).[21,31] To our disappointment, treatment of lactam **54** with AlH_3-Me_2NEt produced undesired pyrrolidinoindoline derivative **71** as a single diastereomer in 61% yield, resulting from chemoselective reduction of the *N*-PMB-lactam in the presence of the oxindole. After cleavage of the TIPS group by TBAF (98% yield),[32] the PMB group was removed with

DDQ[33] to provide alcohol **72**. The structure of the pentacyclic heterocycle **72** was confirmed by X-ray analysis (Figure 1.2.5).

Scheme 1.2.16. *Reductive Cyclization of Lactam* ***54*** *with* AlH_3-Me_2NEt

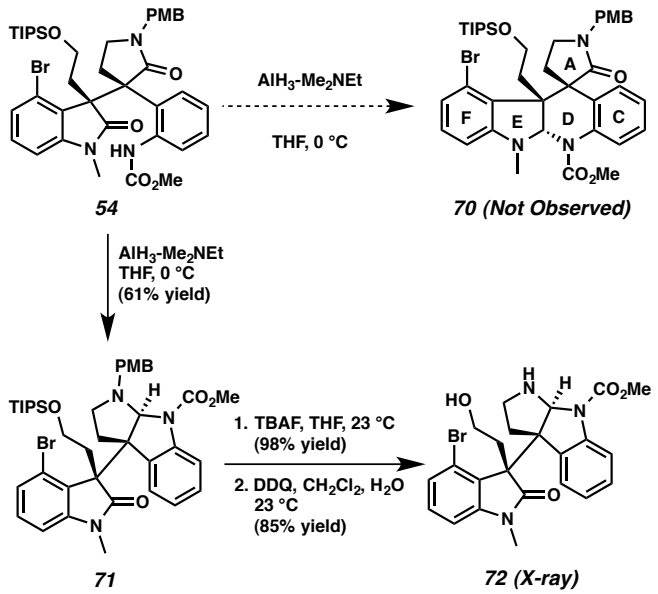
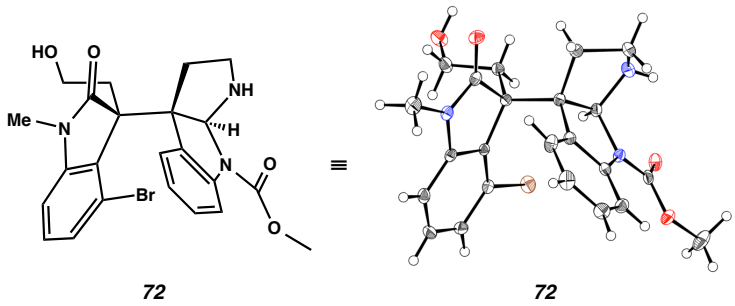


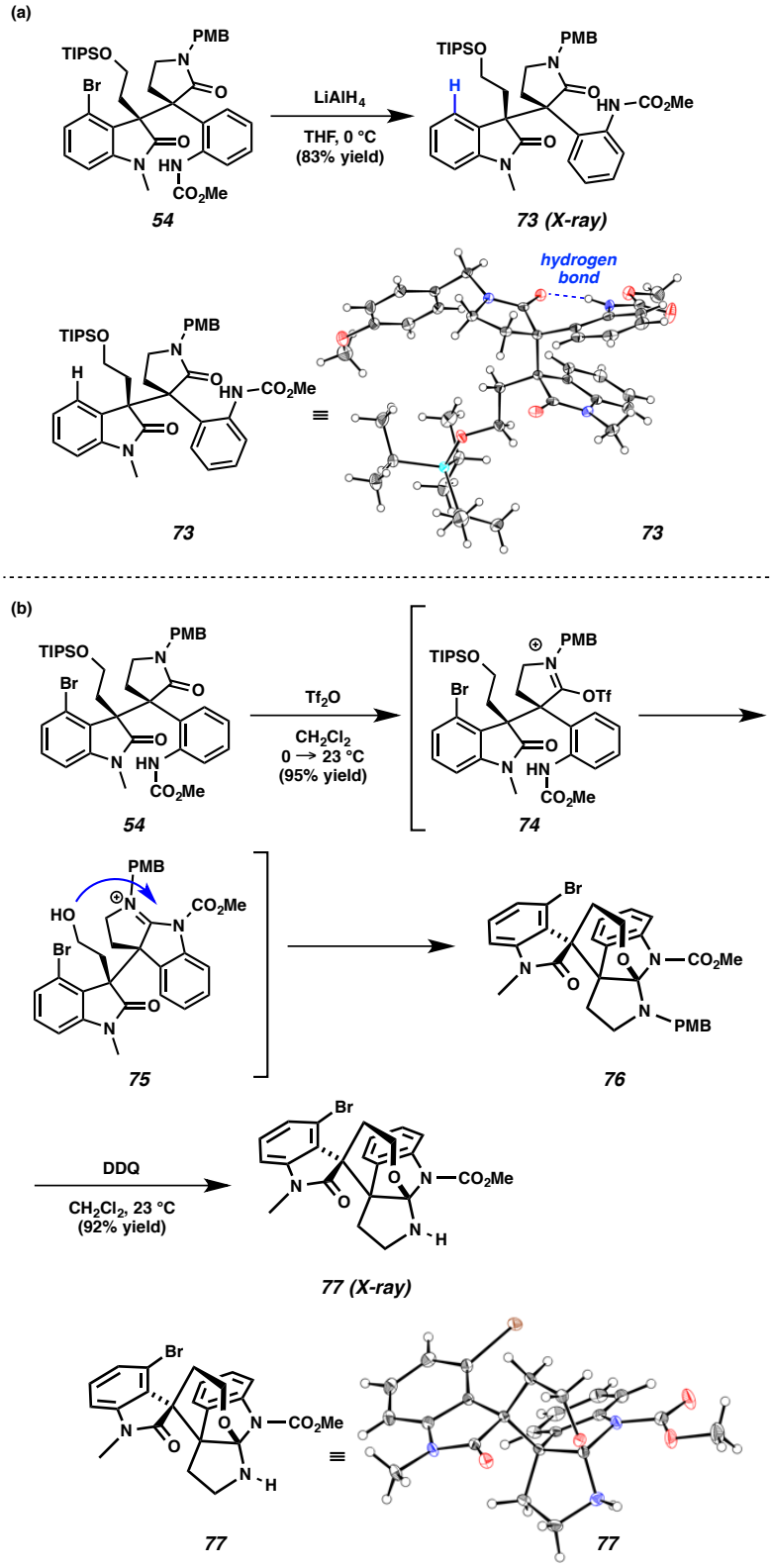
Figure 1.2.5. *X-ray Structure of Pyrrolidinoindoline* ***72***



Having failed on our initial exploration, alternative conditions for construction of the piperidine D ring were next explored. Treatment of the lactam **54** with $LiAlH_4$[34] produced debrominated compound **73** in 83% yield (Scheme 1.2.17a). X-ray analysis of

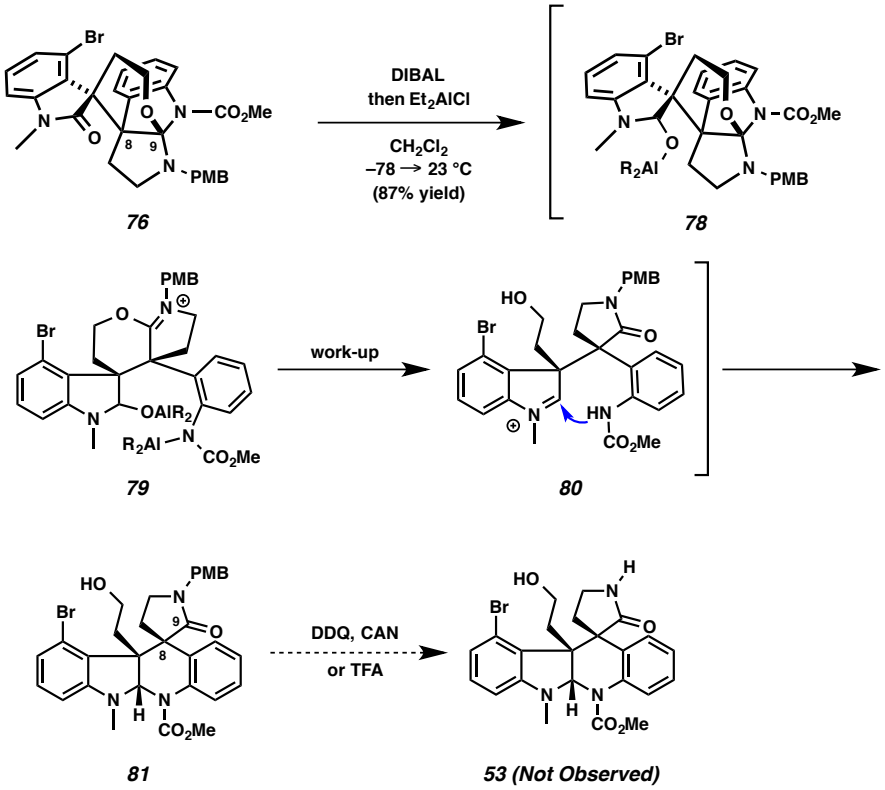
compound **73** showed a hydrogen bonding interaction between the carbonyl group of the PMB protected amide and the NH group of the carbamate. We reasoned that the undesired pyrrolidine was formed preferentially to the piperidine due to the close proximity of the carbamate NH and the carbonyl group of the PMB-protected amide. Next, a reductive cyclization reaction was attempted by treatment of **54** with Tf_2O and $NaBH_4$ to construct the piperidine ring. To our surprise, treatment of lactam **54** with Tf_2O provided the PMB-protected hexacyclic oxindole **76** in 95% yield (Scheme 1.2.17b). The PMB-protected amide of **54** was activated by Tf_2O to provide **74**, and nucleophilic attack by the aniline functionality furnished pyrrolidinoindoline derivative **75**. After the TIPS group was removed under the reaction conditions, the resultant hydroxyl group attacked the amidinium to generate the propellane structure of hexacyclic oxindole **76**. After cleavage of the PMB group using DDQ, the propellane structure of hexacyclic oxindole **77** was confirmed using X-ray analysis.

Scheme 1.2.17. *Attempted Reductive Cyclization of Lactam* ***54***



Despite this unexpected turn of events, we envisaged that the desired aminal **81** could be accessed from the propellane compound **76** using suitable conditions, since the oxidation state at C(9) of **76** is identical to that of the desired aminal **81** (Scheme 1.2.18). Moreover, the reactive *N*-PMB-pyrrolidinone in **54** is now protected by the propellane structure of **76**, thus leaving the oxindole as the only reducible carbonyl group. Fortunately, after extensive experimentation, we were pleased to find that reductive cyclization of hexacyclic oxindole **76** could be accomplished with DIBAL and Et_2AlCl to furnish aminal **81** in 87% yield (Scheme 1.2.18). Presumably, the oxindole of **76** was reduced by DIBAL to provide **78**, and rearrangement of the propellane structure generated iminium **79**. After the work-up, water attacked the iminium moiety of **79** to afford aniline **80**, and the resultant aniline group attacked the iminium of **80** to construct aminal **81**. In the last stage of the synthesis, we screened a variety of reaction conditions to remove the PMB group on the lactam **81** (e.g., DDQ, CAN, TFA, etc.) but, surprisingly, removal of the PMB group failed under all conditions attempted. This unexpected turn was particularly insidious since the PMB group was easily removed from hexacyclic oxindole **76** by DDQ (Scheme 1.2.17). The cleavage of allyl or benzyl groups were also examined, but disappointingly, cleavage of these groups on the lactam were similarly unsuccessful under several conditions.[35]

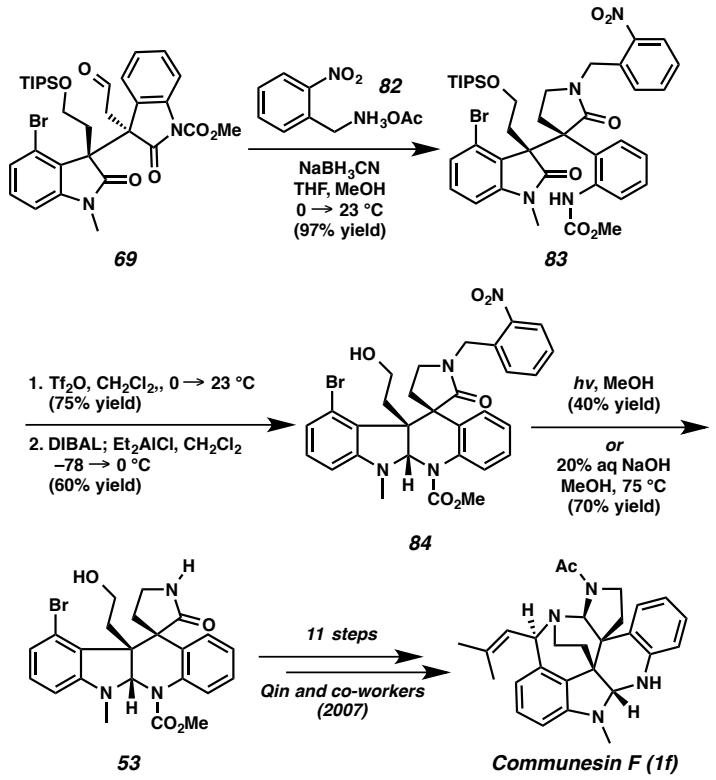
Scheme 1.2.18. *Synthesis of Aminal* ***81***



Given the difficulty of removal of PMB, allyl, and benzyl groups, our attention turned to exploring the *o*-nitrobenzyl group as a protecting group. However, subjecting the hexacyclic oxindole **77** to *o*-nitrobenzyl bromide under basic conditions to produce the *o*-nitrobenzyl protected propellane hexacyclic oxindole turned out to be challenging. Thus, we next investigated reductive amination of aldehyde **69** and were pleased to find that treatment of **69** with *o*-nitrobenzylammonium acetate **82** furnished lactam **83** in 97% yield (Scheme 1.2.19). Formation of the *o*-nitrobenzyl protected propellane hexacyclic oxindole using Tf_2O (75% yield) was followed by reductive cyclization with DIBAL and Et_2AlCl to furnish aminal **84** in 60% yield. To our delight, we found that removal of the *o*-nitrobenzyl group could be achieved by photolysis/irradiation at 350nm in 40% yield.[36]

Surprisingly, we discovered that removal of the *o*-nitrobenzyl group to produce compound **53** was also accomplished using 20% aq NaOH in methanol at 75 °C in 70% yield – a previously unknown deprotection protocol.[37] Aminal **53** has been advanced by the Qin group to communesin F,[5g] thus completing our formal synthesis of the natural product.

Scheme 1.2.19. *Completion of Formal Synthesis of Communesin F*

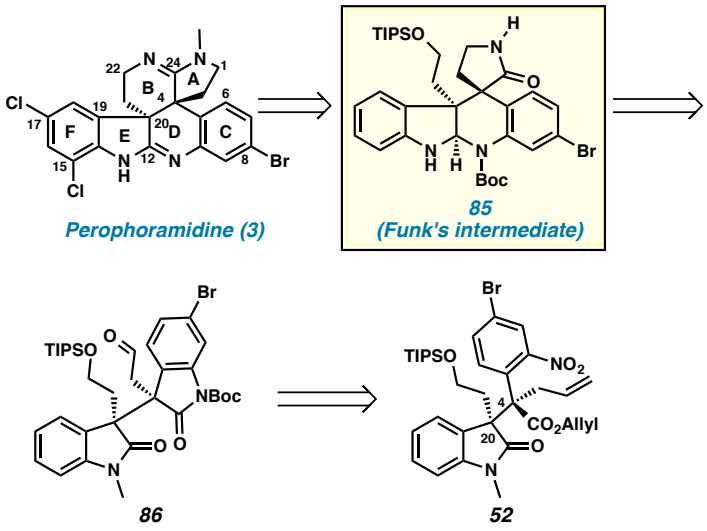


1.2.4. Formal Synthesis of Perophoramidine (3)

Our retrosynthetic analysis of perophoramidine (**3**) was based on our previously established expedient synthesis of oxindole derivative **52** (Scheme 1.2.20). We speculated that the aminal and lactam ring functionalities of pentacycle **85**, an

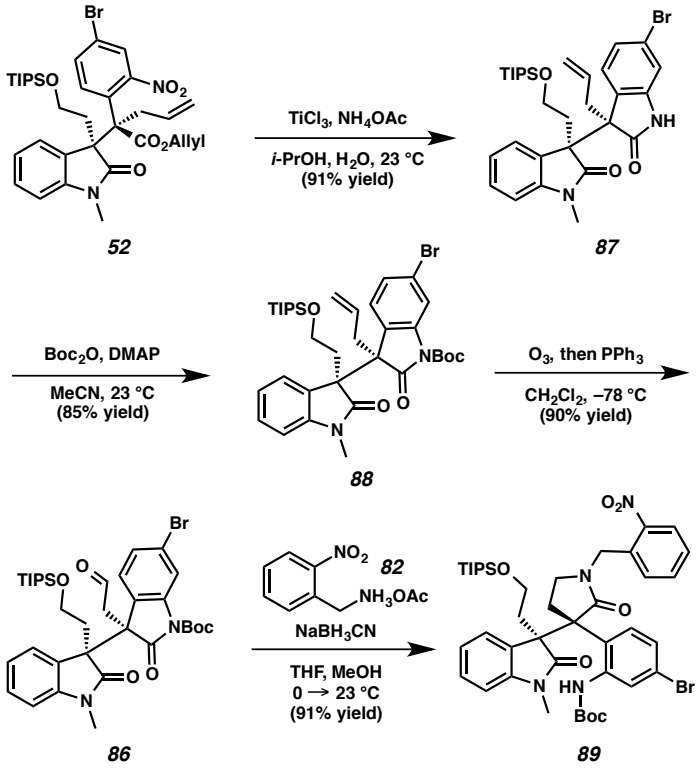
intermediate in Funk's synthesis,[5o] could be cleaved, thereby leading to aldehyde **86**. The *N–C* bond of the 6-bromooxindole moiety in **86** was excised to arrive at nitroarene **52**. The construction of the contiguous quaternary centers at C(20) and C(4) of allyl ester **52** with the proper relative stereochemistry was accessed by decarboxylative allylic alkylation as previously described (Scheme 1.2.11b).

Scheme 1.2.20. *Retrosynthesis of Perophoramidine (**3**)*



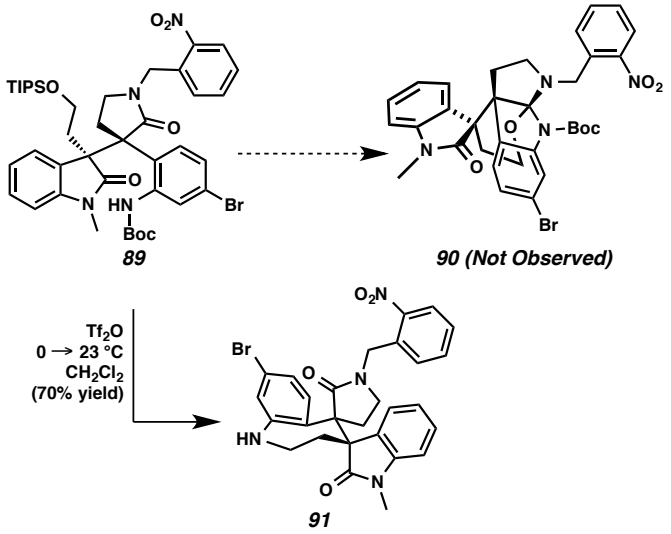
Carbamate **88** was obtained by reduction of nitroarene **52** with titanium chloride and simultaneous oxindole formation[38] to furnish the bis-oxindole moiety **87** in 91% yield followed by protection with Boc anhydride in 85% yield (Scheme 1.2.21). Ozonolysis of olefin **88** produced aldehyde **86** in 90% yield. Reductive amination of aldehyde **86** with *o*-nitrobenzylammonium acetate **82** resulted in an amine that underwent *in situ* lactam formation to afford oxindole lactam **89** in 91% yield.

Scheme 1.2.21. *Synthesis of Amide* ***89***



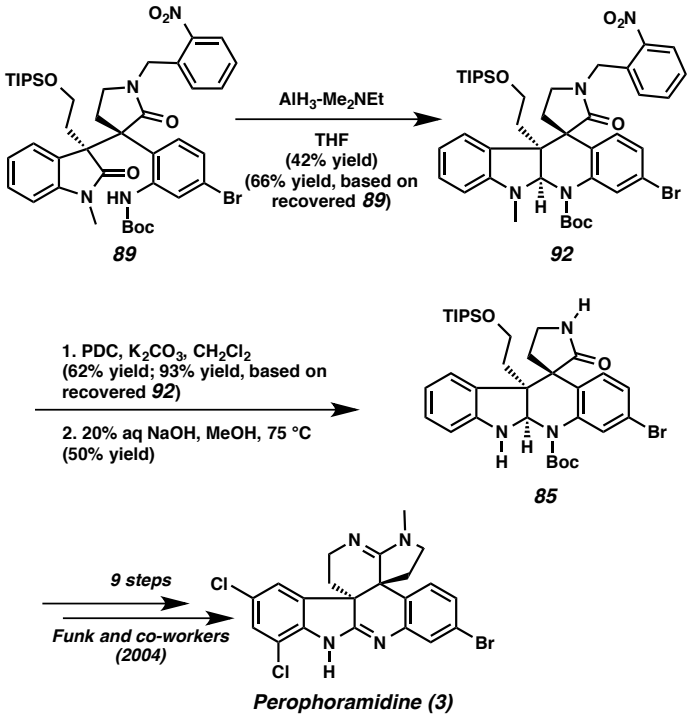
Initially, we attempted to generate the *o*-nitrobenzyl protected propellane hexacyclic oxindole **90** under analogous conditions to those used in our formal synthesis of communesin F on the pseudo diastereomeric series (vide supra). However, treatment of lactam **89** with Tf_2O yielded an unexpected azepine **91** in 70% yield (Scheme 1.2.22). Both the Boc and the TIPS groups on amide **89** were removed under the reaction conditions, and the resulting primary alcohol was presumably converted to the corresponding triflate. Finally, the aniline likely attacked the newly formed triflate to form azepine **91**.

Scheme 1.2.22. *Formation of Azepine* ***91*** *using* Tf_2O



After extensive experimentation, we discovered that in contrast to the communesin system, the desired reductive cyclization in the perophoramidine diastereomer occurred directly with AlH_3-Me_2NEt[31] to furnish cyclization product **92** in 42% yield (66% yield based on recovered starting material) (Scheme 1.2.23). The indoline methyl group was converted to a formyl group using PDC oxidation in 62% yield (93% yield based on recovered starting material).[39] To our delight, an attempt to remove the formyl group with 20% aq NaOH at 75 °C resulted in removal of both the formyl group and the *o*-nitrobenzyl group to produce aminal **85** in 50% yield.[37,40] This molecule was previously advanced by the Funk group to perophoramidine,[5o] and constitutes an expedient formal synthesis of the natural product.

Scheme 1.2.23. *Completion of Formal Synthesis of Perophoramidine*



1.3. Conclusion

In conclusion, we have conducted synthetic studies toward unique polycyclic alkaloids, and completed formal syntheses of communesin F (**1f**) in 9% overall yield over 17 steps and perophoramidine (**3**) in 6% overall yield (13% overall yield, based on recovered starting material) over 10 steps using a unified stereodivergent alkylation approach. The all-carbon quaternary center on the oxindole was established via stabilized enolate alkylation of 3-bromooxindoles, a method previously developed by our laboratory and now shown to be quite versatile even in particularly sterically challenging situations. The complementary relative stereochemistry of the two contiguous quaternary stereogenic centers found in communesin F (**1f**) and perophoramidine (**3**) respectively, was established by substrate controlled diastereoselective decarboxylative allylic

alkylation. A reductive amination approach furnished the A ring, and reductive cyclization produced the D ring for both communesin F (**1f**) and perophoramidine (**3**). En route to the evolution of our eventual successful strategy, we have discovered a method to convert an indole to a 3-chloroindolenine using a mild reagent such as *o*-NsCl during the synthesis. In addition, previously unknown, mild and efficient deprotection conditions for the *o*-nitrobenzyl group on the lactam were discovered. Further studies to rationalize unprecedented complementary selectivity by Pd-catalyzed allylic alkylation reactions are currently in progress.

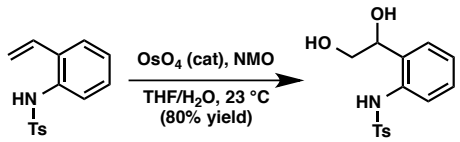
1.4. Experimental Methods and Analytical Data

1.4.1. Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Reaction progress was monitored by thin-layer chromatography (TLC). THF, Et_2O, CH_2Cl_2, toluene, benzene, CH_3CN, and dioxane were dried by passage through an activated alumina column under argon. Triethylamine was distilled over CaH_2 prior to use. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. Brine solutions are saturated aqueous solutions of sodium chloride. Commercially available reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulator unless otherwise indicated. Microwave-assisted reactions were performed in a Biotage Initiator 2.5 microwave reactor. Glove box manipulations were performed under a N_2 atmosphere. TLC was performed using E. Merck silica gel 60

F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or PMA (phosphomolybdic acid) staining. Silicycle Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.064 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on a Varian Inova 500 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm), or $(CD_3)_2CO$ (δ 2.05 ppm). ^{13}C NMR spectra are recorded on a Varian Inova 500 MHz spectrometer (125MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm), or $(CD_3)_2CO$ (δ 29.84 ppm). Data for ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d= broad doublet, app = apparent. Data for ^{13}C are reported in terms of chemical shifts (ppm). IR spectra were obtained using a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+). X-ray crystallography reports for compounds **29** and **32** can be found in ref 41.[41]

1.4.2. Experimental Procedures

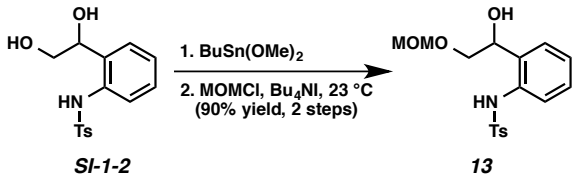


SI-1-1 *SI-1-2*

Diol SI-1-2. To a solution of styrene **SI-1-1** (6.11 g, 22.4 mmol, 1.0 equiv) in THF (140 mL) and water (70 mL) were added *N*-methylmorpholine *N*-oxide (5.96 g, 50.8 mmol,

2.3 equiv) and osmium tetroxide (11.6 mg, 43.9 μmol, 0.002 equiv). After addition, reaction was stirred for three days. The reaction was then concentrated to approximately 50 mL under reduced pressure, then extracted with a mixture of ether and THF (1:1) (3 x 45 mL). The organic layers were dried over sodium sulfate, and the solvent was removed under reduced pressure. Impurities were removed by washing solid with dichloromethane to afford diol **SI-1-2** (5.43 g, 80% yield) as a white solid. For spectrum, see ref 41.

R_f = 0.13 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.78–7.65 (m, 2H), 7.39 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.25–7.16 (m, 2H), 7.15–7.03 (m, 2H), 4.86–4.79 (m, 1H), 3.66–3.57 (m, 2H), 2.97 (s, 1H), 2.39 (s, 3H), 1.98 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 137.1, 136.3, 129.9, 129.8, 129.2, 128.5, 127.4, 127.0, 122.2, 74.78, 66.0, 21.8; IR (Neat Film NaCl) 3271, 1318, 1150 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{18}NO_4S$ $[M+H]^+$: 308.0951; found 308.0967.

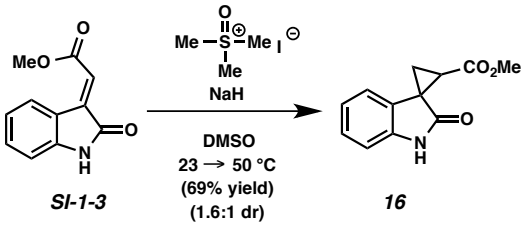


SI-1-2 *13*

Alcohol 13. To a solution of diol **SI-1-2** (500 mg, 1.63 mmol, 1.0 equiv) in toluene (70 mL) was added dibutyltin dimethoxide (410 μL, 1.79 mmol, 1.1 equiv). The flask was fitted with a short path distillation apparatus, and approximately half of the solvent was removed by distillation. To this solution was added MOMCl (136 μL, 1.79 mmol, 1.1 equiv) and tetrabutylammonium iodide (900 mg, 2.44 mmol, 1.5 equiv). After addition, the reaction was stirred for 12 h. Then, brine was added to this solution. The reaction

mixture was extracted with EtOAc (3 x 50 mL). The combined organic phases were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (3:1 → 1:1 hexanes:EtOAc) to afford alcohol **13** (513 mg, 90% yield, 2 steps) as a white solid. For spectrum, see ref 41.

R_f = 0.27 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.27–7.20 (m, 3H), 7.11–7.02 (m, 2H), 4.83–4.78 (m, 1H), 4.64 (s, 2H), 3.60 (dd, *J* = 10.5, 3.5 Hz, 1H), 3.48–3.41 (m, 2H), 3.39 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 137.1, 136.3, 129.7, 129.5, 128.9, 128.2, 127.2, 124.7, 122.0, 97.0, 73.3, 72.4, 55.6, 21.6; IR (Neat Film NaCl) 3233, 2932, 1598, 1497, 1335, 1161 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{22}NO_5S$ $[M+H]^+$: 352.1213; found 352.1219.



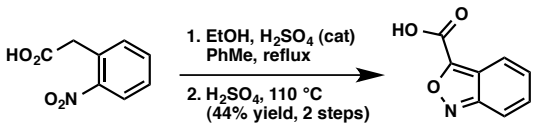
SI-1-3 *16*

Cyclopropane 16. A flame-dried flask (25 mL) equipped with a teflon stirbar was charged with sodium hydride (60% dispersion in mineral oil, 22 mg, 0.55 mmol, 1.1 equiv), which was washed 3 times with dry hexanes. Then, DMSO (5.5 mL) and trimethyl sulfoxonium iodide (119 mg, 0.58 mmol, 1.2 equiv) were added. To this solution was added oxindole **SI-1-3** (100 mg, 0.49 mmol, 1.0 equiv) in a solution of DMSO (2.5 mL). After addition, the reaction was stirred for 2 h, and then the temperature was raised to 50 °C. The reaction was complete after another hour. Brine

was added and then the mixture was extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (3:1 → 1:1 hexanes:EtOAc) to afford oxindole **16** as two diastereomers. Diastereomer 1: (44.7 mg, 42% yield); Diastereomer 2: (28.6 mg, 27% yield). For spectrum, see ref 41.

Diastereomer 1: R_f = 0.52 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.04–6.97 (m, 2H), 3.70 (s, 3H), 2.74 (t, *J* = 8.0 Hz, 1H), 2.18 (dd, *J* = 4.5, 7.5 Hz, 1H), 2.05 (dd, *J* = 4.5, 8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 169.3, 141.8, 127.9, 126.4, 123.0, 122.4, 110.3, 52.4, 34.3, 32.9, 21.1; IR (Neat Film NaCl) 3214, 1712, 1622, 1470, 1209 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{12}NO_3$ $[M+H]^+$: 218.0812; found 218.0825.

Diastereomer 2: R_f = 0.45 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.06 (s, 1H), 7.27–7.20 (m, 1H), 7.04–6.97 (m, 2H), 6.83 (d, *J* = 7.5 Hz, 1H), 3.75 (s, 3H), 2.68 (t, *J* = 8.0 Hz, 1H), 2.40 (dd, *J* = 5.0, 8.0 Hz, 1H), 1.84 (dd, *J* = 5.0, 8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 167.7, 141.1, 129.5, 188.0, 122.4, 118.9, 110.3, 52.6, 33.5, 32.9, 21.3; IR (Neat Film NaCl) 3256, 1739, 1710 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{12}NO_3$ $[M+H]^+$: 218.0812; found 218.0828.

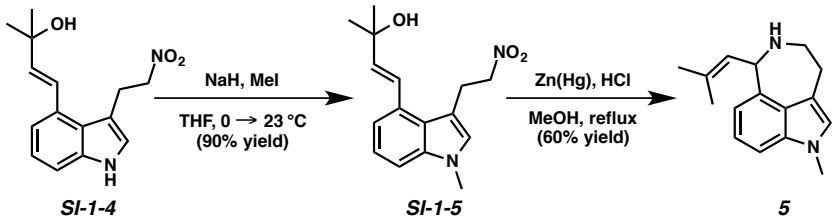


21 ***20***

Acid 20. A flame-dried flask (500 mL) equipped with a teflon stirbar was charged with acid **21** (10.0 g, 55.2 mmol, 1.0 equiv), ethanol (60 mL), sulfuric acid (200 μL), and

toluene (280 mL). The flask was fitted with a condenser, and the solution was refluxed for 14 h. The solvent was removed under reduced pressure and sulfuric acid (280 mL) was added. After addition, the reaction was heated to 110 °C and stirred for 90 min. The solution was then poured onto ice (600 g), the mixture was extracted with ether (3 x 200 mL). The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. Purification was performed via crystallization from water to afford acid **20** (3.94 g, 44% yield, 2 steps) as an off-white solid. For spectrum, see ref 41.

^{1}H NMR (300 MHz, acetone-d_6) δ 10.82 (br, s, 1H), 7.94 (d, J = 9.0 Hz, 1H), 7.75 (d, J = 10.0 Hz, 1H), 7.50 (dd, J = 6.5, 9.5 Hz, 1H), 7.34 (dd, J = 7.0, 8.5 Hz, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 158.5, 158.1, 155.3, 132.4, 128.8, 121.4, 121.0, 116.7; IR (Neat Film NaCl) 2360, 1731, 1301, 1231, 1189, 753 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_8H_6NO_3$ $[M+H]^+$: 164.0342; found 164.0341.

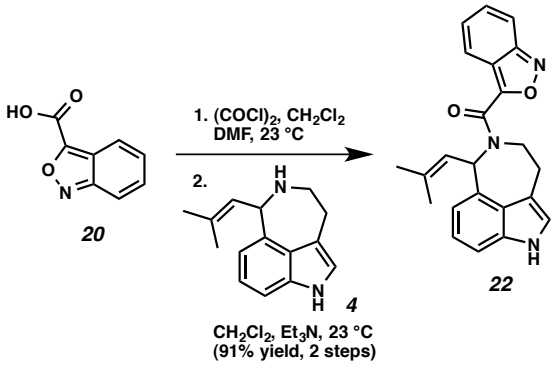


1-methylaurantioclavine 5. To a solution of indole **SI-1-4** (386 mg, 1.41 mmol, 1.0 equiv) in THF (14 mL) was added methyl iodide (875 μL, 14.1 mmol, 10 equiv) at 0 °C. Sodium hydride (60% dispersion in mineral oil, 562 mg, 14.5 mmol, 10.3 equiv) was then added to the solution, and the mixture was stirred for 25 min at 23 °C. The reaction was quenched with saturated ammonium hydroxide solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, and concentrated *in*

vacuo. The residue was purified by flash column chromatography (3:1 → 2:1 hexanes:EtOAc) to afford nitro compound **SI-1-5** (363.5 mg, 90% yield) as a yellow solid.

To a solution of nitro compound **SI-1-5** (512 mg, 1.78 mmol, 1.0 equiv) in MeOH (125 mL) and 2N HCl (40 mL) was added amalgamated zinc, which had been formed from zinc dust (6.5 g, 98.3 mmol, 55 equiv) and mercuric chloride (1.10 g, 3.55 mmol, 2.0 equiv) in 2N HCl and subsequently rinsed with MeOH. The mixture was stirred at reflux for 3 h. The reaction was then decanted from the remaining amalgam and then basified to pH >10. The solid was removed by filtration, and the resulting solution was extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (18:1 CH_2Cl_2:MeOH) to afford 1-methylaurantioclavine **5** (258 mg, 60% yield) as a yellow oil. For spectrum, see ref 41.

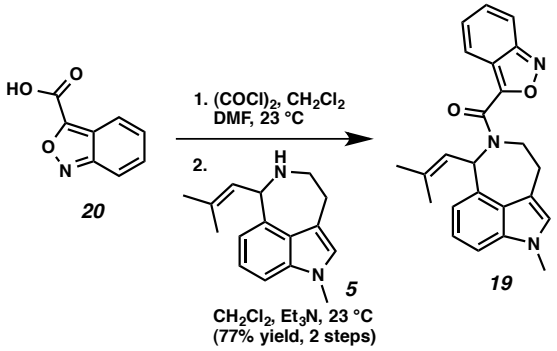
R_f = 0.30 (18:1 CH_2Cl_2:MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19–7.12 (m, 2H), 6.89–6.83 (m, 2H), 5.48 (d, *J* = 9.0 Hz, 1H), 4.92 (d, *J* = 9.0 Hz, 1H), 3.76 (s, 3H), 3.62–3.54 (m, 1H), 3.13–3.02 (m, 3H), 2.26 (br, s, 1H), 1.86 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 137.8, 133.3, 127.7, 125.9, 121.1, 117.4, 114.2, 107.3, 62.6, 48.9, 32.7, 30.8, 25.9, 18.4; IR (Neat Film NaCl) 3332, 2910, 1554, 1455 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{21}N_2$ $[M+H]^+$: 241.1699; found 241.1712.



Amide 22. To a solution of acid **20** (262 mg, 1.60 mmol, 1.25 equiv) in dichloromethane (5 mL) was added oxalyl chloride (420 μL, 4.81 mmol, 3.8 equiv) and then a small amount of DMF (~20 μL). The reaction was stirred for 1 h then the solvent was removed under reduced pressure; the residue was evaporated from benzene (2 mL) to remove excess reagent. Dichloromethane (10 mL) and triethylamine (537 μL, 3.85 mmol, 3.0 equiv) were added, and to this solution was added aurantioclavine **4** (290 mg, 1.28 mmol, 1.0 equiv). After addition, the reaction was stirred for 60 min, and then brine was added. The resulting solution was extracted with EtOAc (3 x 7 mL). The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (3:1 → 1:1 hexanes:EtOAc) to afford amide **22** (435 mg, 91% yield, 2 steps) as a white solid. For spectrum, see ref 41.

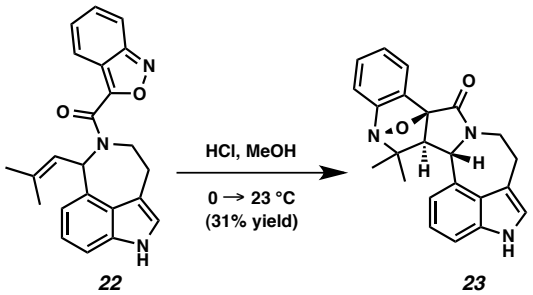
R_f = 0.72 (1:2 hexanes:EtOAc); (Due to the distinct presence of rotameric isomers, the ^{1}H NMR and ^{13}C NMR contained extra peaks. See the attached spectrum), ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00–8.86 (m, 2H), 7.98 (dq, *J* = 8.9, 0.9 Hz, 1H), 7.71–7.57 (m, 3H), 7.35–7.27 (m, 2H), 7.25–7.22 (m, 1H), 7.22–7.16 (m, 3H), 7.15–7.07 (m, 2H), 7.07–7.01 (m, 2H), 7.01–6.94 (m, 2H), 6.90–6.83 (m, 2H), 6.70 (d, *J* = 7.5 Hz, 1H), 5.48 (ddq, *J* = 7.9, 2.8, 1.6 Hz, 2H), 4.82–4.66 (m, 2H), 4.07 (ddd, *J* = 15.4, 10.0, 5.8 Hz, 1H), 3.82 (td,

J = 13.0, 2.6 Hz, 1H), 3.60–3.46 (m, 1H), 3.23–3.12 (m, 3H), 1.96 (d, *J* = 1.3 Hz, 3H), 1.79 (d, *J* = 1.5 Hz, 3H), 1.73 (d, *J* = 1.6 Hz, 3H), 1.64 (d, *J* = 1.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 158.4, 157.9, 157.8, 156.9, 156.8, 137.7, 137.4, 137.2, 136.9, 135.2, 135.1, 131.5, 131.4, 126.4, 126.1, 124.7, 124.3, 123.9, 123.8, 122.1, 121.9, 121.8, 121.7, 121.1, 121.0, 119.9, 118.3, 117.5, 114.9, 113.3, 112.6, 110.1, 109.9, 61.0, 57.5, 44.5, 43.1, 29.1, 25.9, 25.8, 25.7, 18.9, 18.2; IR (Neat Film NaCl) 3325, 2914, 2246, 1730, 1616, 1447 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{22}N_3O_2$ $[M+H]^+$: 372.1707; found: 372.1637.



Amide 19. To a solution of acid **20** (37.5 mg, 0.229 mmol, 1.1 equiv) in dichloromethane (500 μL) was added oxalyl chloride (59 μL, 0.676 mmol, 3.3 equiv) and then a small amount of DMF (~1 μL). The reaction was stirred for 1 h, and then the solvent was removed under reduced pressure. The residue was evaporated from benzene (1 mL) to remove excess reagent. Dichloromethane (1.1 mL) and triethylamine (30 μL, 0.215 mmol, 1.03 equiv) were added, and to this solution was added 1-methylaurantioclavine **5** (50.0 mg, 0.208 mmol, 1.0 equiv). After addition, the reaction was stirred for 60 min, and then brine was added. The resulting solution was extracted with EtOAc (3 x 1.5 mL). The combined organic layers were dried over $MgSO_4$, and

concentrated *in vacuo*. The residue was purified by flash column chromatography (3:1 → 2:1 hexanes:EtOAc) to afford amide **19** (61.6 mg, 77% yield, 2 steps) as a white solid. R_f = 0.79 (1:2 hexanes:EtOAc); (due to the distinct presence of rotameric isomers, the ^{1}H NMR and ^{13}C NMR contained extra peaks. For spectrum, see ref 41), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 9.0 Hz, 1H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.62 (t, *J* = 10.0 Hz, 1H), 7.37–7.30 (m, 1.5H), 7.22–7.18 (m, 2H), 7.13–7.08 (m, 2H), 7.04–6.99 (m, 1H), 6.95 (s, 1H), 6.86–6.84 (m, 2H), 6.67 (d, *J* = 7.5 Hz, 1H), 5.46 (d, *J* = 7.5 Hz, 1H), 4.69 (dd, *J* = 15.0, 38.0 Hz, 1H), 4.04 (dt, *J* = 4.5, 15.5 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.48 (t, *J* = 18.0 Hz, 1H), 3.25 (3.11, m, 2H), 1.92 (s, 3H), 1.78 (s, 3H), 1.72 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 158.5, 157.7, 157.6, 156.9, 156.8, 137.8, 137.7, 137.6, 136.8, 135.7, 135.6, 131.3, 131.2, 126.5, 126.3, 125.9, 124.8, 124.4, 124.3, 124.2, 122.1, 121.6, 121.5, 121.2, 121.1, 120.0, 118.1, 117.3, 115.0, 114.9, 112.3, 111.7, 107.9, 107.7, 60.9, 57.3, 44.5, 43.1, 32.6, 29.0, 25.9, 25.7, 18.9, 18.2; IR (Neat Film NaCl) 2913, 2245, 1615, 1455, 1410 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{24}H_{24}N_3O_2$ $[M+H]^+$: 386.1863; found 386.1775.

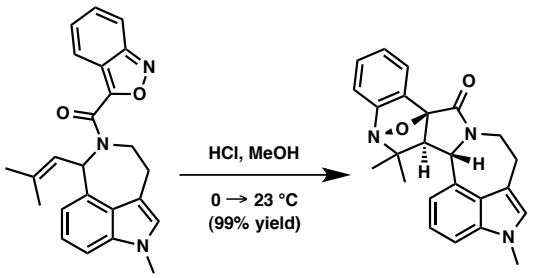


22 ***23***

Indole 23. A flame-dried vial (20 mL) equipped with a teflon stirbar was charged with amide **22** (100 mg, 0.269 mmol, 1.0 equiv) and cooled to 0 °C. To this reaction mixture

was added a 0.5 M solution of HCl in MeOH (2.7 mL, generated from addition of acetyl chloride to methanol at 0 ºC) at 0 °C. The mixture was stirred for 1 h and then warmed to 23 ºC over 30 min. The solvent was then removed under reduced pressure. Purification was performed by washing the solid with dichloromethane to afford indole **23** (31.1 mg, 31% yield) as a white solid. For spectrum, see ref 41.

R_f = 0.22 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, acetone-d_6) δ 11.05 (s, 1H), 7.34–7.17 (m, 6H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.61 (d, *J* = 7.5 Hz, 1H), 5.47 (d, *J* = 6.5 Hz, 1H), 4.21 (d, *J* = 13.0 Hz, 1H), 3.44 (t, *J* = 11.0 Hz, 1H), 3.18–2.98 (m, 2H), 2.37 (d, *J* = 6.5 Hz, 1H), 1.77 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 164.3, 153.0, 139.6, 137.0, 134.6, 127.3, 126.6, 123.7, 122.6, 121.4, 118.6, 118.0, 115.2, 112.7, 110.2, 96.4, 70.1, 63.1, 61.2, 44.4, 26.9, 26.6, 26.0; IR (Neat Film NaCl) 3314, 1681, 753 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{22}N_3O_2$ $[M+H]^+$: 372.1707; found 372.1710.

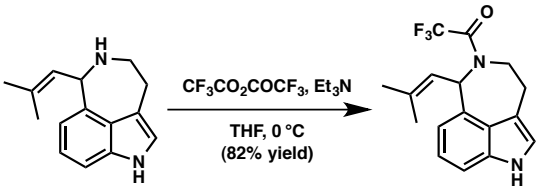


19 ***24***

Indole 24. A flame-dried vial (20 mL) equipped with a teflon stirbar was charged with amide **19** (100 mg, 0.259 mmol, 1.0 equiv) and cooled to 0 °C. To this solution was added a 0.5 M solution of HCl in MeOH (2.6 mL, generated from addition of acetyl chloride to methanol at 0 °C) at 0 °C. The mixture was stirred for 1 h and then warmed

to 23 °C over 30 min. The solvent was then removed under reduced pressure. Purification was performed via flash column chromatography (3:1 → 1:1 hexanes:EtOAc) to afford indole **24** (101 mg, 99% yield) as a white solid. For spectrum, see ref 41.

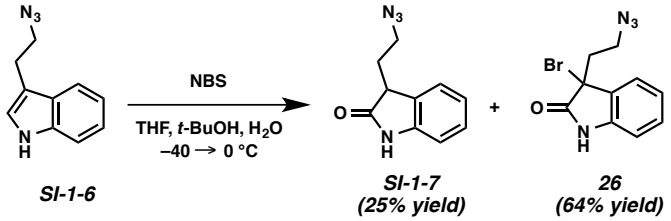
R_f = 0.29 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.17 (m, 6H), 7.00 (s, 1H), 6.76–6.73 (m, 1H), 5.51 (d, *J* = 6.5 Hz, 1H), 4.57–4.50 (m, 1H), 3.80 (s, 3H), 3.50–3.15 (m, 3H), 2.57 (d, *J* = 6.5 Hz, 1H), 1.95 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 153.5, 139.8, 137.9, 135.6, 127.5, 127.0, 126.9, 124.6, 121.9, 119.1, 118.4, 115.9, 113.4, 108.4, 97.2, 70.9, 64.1, 61.9, 45.2, 33.0, 27.5, 27.2, 26.6; IR (Neat Film NaCl) 3315, 2932, 1699, 1456, 1317, 754 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{24}H_{24}N_3O_2$ $[M+H]^+$: 386.1863; found 386.1809.



4 ***25***

***N*-trifluoroacetate-aurantioclavine 25.** To a solution of aurantioclavine **4** (882 mg, 3.90 mmol, 1.0 equiv) in THF (14 mL) were added triethylamine (820 μL, 5.88 mmol, 1.5 equiv) and trifluoroacetic anhydride (606 μL, 4.29 mmol, 1.1 equiv) at 0 °C. The reaction was complete immediately, so it was quenched with methanol. The solvent was then removed under reduced pressure. Purification was performed via flash column chromatography (9:1 → 3:1 hexanes:EtOAc) to afford the *N*-trifluoroacetate-aurantioclavine **25** (1.03 g, 82% yield) as a yellow foam. For spectrum, see ref 41.

R_f = 0.30 (3:1 hexanes:EtOAc); (Due to the distinct presence of rotameric isomers, the ^{1}H NMR and ^{13}C NMR contained extra peaks. See the attached spectrum), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (br, s, 1H), 7.29–7.26 (m, 1H), 7.02–6.97 (m, 2H), 6.90 (t, *J* = 7.0 Hz, 1H), 6.23 (d, *J* = 8.0 Hz, 1H), 5.40 (dd, *J* = 7.5, 19.5 Hz, 1H), 4.40 (d, *J* = 13.0 Hz, 1H), 4.16–4.10 (m, 1H), 4.04–3.94 (m, 2H), 3.83 (t, *J* = 13.0 Hz, 1H), 3.43 (t, *J* = 16.5 Hz, 1H), 3.27–3.23 (m, 1H), 3.09 (d, *J* = 16.5 Hz, 1H), 1.91 (s, 3H), 1.86 (s, 3H), 1.78 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 157.0, 156.8, 156.3, 138.5, 137.4, 137.2, 137.2, 135.1, 134.4, 124.3, 123.9, 123.5, 123.3, 122.1, 121.9, 121.8, 119.0, 118.8, 118.5, 117.1, 115.2, 115.0, 113.1, 112.6, 110.3, 110.1, 60.7, 60.6, 58.6, 43.7, 43.7, 28.4, 26.2, 25.7, 25.0, 18.9, 18.2; IR (Neat Film NaCl) 3361, 2917, 1667, 1441, 1205 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{18}N_2OF_3$ $[M+H]^+$: 323.1366; found 323.1308.



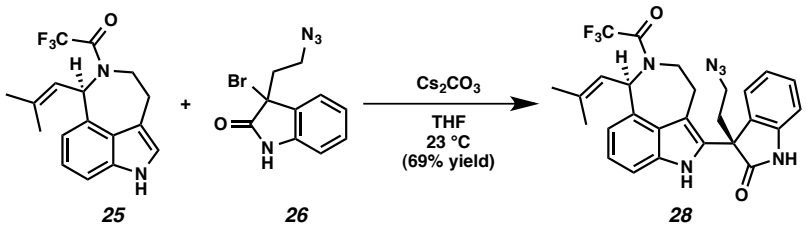
Bromooxindole 26. A flame-dried flask (1000 mL) equipped with a teflon stirbar was charged with azide **SI-1-6**[1] (5.03 g, 30.3 mmol, 1.0 equiv), to which was subsequently added THF (150 mL), *t*-BuOH (150 mL), and water (3.75 mL) and cooled to –40 °C. A 0 °C solution of NBS (8.03 g, 45.1 mmol, 1.5 equiv) in THF (450 mL) was then added via cannula over 30 min, and the resulting solution was allowed to warm to –10 °C over 2 h. Warming continued slowly over 30 min to 0 °C. After 20 min at 0 °C, the solvent was

[1] Suzuki, T.; Ota, Y.; Ri, M.; Bando, M.; Gotoh, A.; Itoh, Y.; Tsumoto, H.; Tatum, P. R.; Mizukami, T.; Nakagawa, H.; Iida, S.; Ueda, R.; Shirahige, K.; Miyata, N. *J. Med. Chem.* **2012**, *55*, 9562.

removed under reduced pressure. Purification was performed via flash column chromatography (9:1→1:2 pentanes:ether) to afford bromooxindole **26** (5.46 g, 64% yield) as a yellow solid. Oxindole **SI-1-7** (1.50 g, 25% yield) was also isolated as a light yellow solid. For spectrum, see ref 41.

Bromooxindole **26**: R_f = 0.46 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (br, s, 1H), 7.28–7.23 (m, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 3.61–3.44 (m, 2H), 2.32–2.17 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.5, 141.7, 128.4, 128.1, 123.8, 122.3, 110.2, 48.0, 43.3, 29.5; IR (Neat Film NaCl) 3228, 2100, 1693, 1620, 1470 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{10}H_{10}N_4OBr$ $[M+H]^+$: 281.0033; found 281.0040.

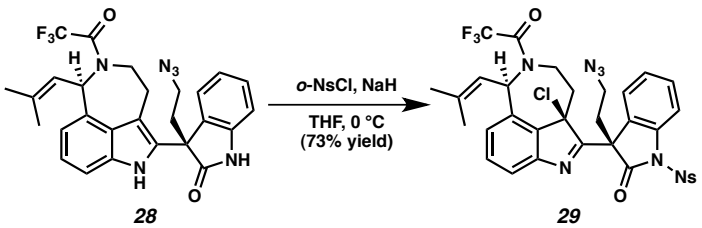
Oxindole **SI-1-7**: R_f = 0.37 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (br, s, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 3.41–3.20 (m, 3H), 2.84–2.57 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 139.8, 130.6, 129.1, 124.6, 123.5, 111.4, 54.5, 47.6, 38.0; IR (Neat Film NaCl) 3252, 2102, 1732, 1619, 1471 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{10}H_{11}N_4O[M+H]^+$: 203.0927; found 203.0933.



Adduct 28. A flame-dried vial (20 mL) equipped with a teflon stirbar was charged with indole **25** (120 mg, 0.372 mmol, 1.0 equiv) and bromooxindole **26** (157 mg, 0.559 mmol,

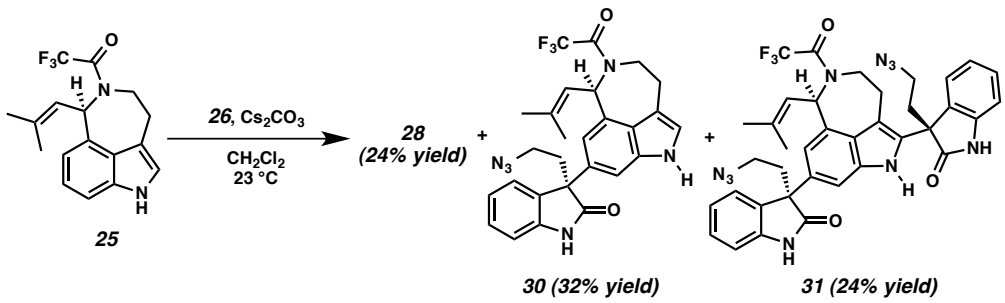
1.5 equiv), which were subsequently dissolved in THF (4 mL). Cesium carbonate (243 mg, 0.746 mmol, 2.0 equiv) was then added. After addition, the reaction was stirred for 12 h, and then water was added. The resulting solution was extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (9:1 → 2:1 hexanes:EtOAc) to afford adduct **28** (134 mg, 69% yield) as a yellow foam. For spectrum, see ref 41.

R_f = 0.34 (2:1 hexanes:EtOAc x2 elutions); (Due to the distinct presence of rotameric isomers, the ^{1}H NMR and ^{13}C NMR contained extra peaks. See the attached spectrum), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (br, s, 2H), 8.59 (br, s, 1H), 8.97 (br, s, 1H), 7.34–6.86 (m, 12H), 6.78 (t, *J* = 7.0 Hz, 1H), 6.11 (d, *J* = 8.0 Hz, 1H), 5.33 (dd, *J* = 7.5, 20.5 Hz, 2H), 4.16 (d, *J* = 13.5 Hz, 1H), 3.96–3.90 (m, 1H), 3.80 (t, *J* = 16.0 Hz, 1H), 3.63 (t, *J* = 13.5 Hz, 1H), 3.25–3.12 (m, 5H), 3.09–2.86 (m, 3H), 2.65–2.53 (m, 3H), 1.84 (s, 3H), 1.80 (s, 3H), 1.71 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8, 178.7, 157.1, 156.7, 156.5, 156.0, 141.4, 141.3, 138.4, 137.0, 136.0, 135.6, 135.1, 134.4, 130.1, 129.9, 129.8, 129.5, 129.5, 125.5, 125.0, 124.9, 124.8, 124.4, 123.7, 123.3, 122.4, 122.2, 119.5, 119.0, 118.7, 118.1, 114.9, 111.8, 111.5, 111.2, 111.2, 110.1, 109.8, 60.5, 58.3, 52.7, 52.6, 47.3, 47.3, 43.5, 43.4, 35.0, 34.8, 28.1, 26.3, 25.8, 24.5, 19.0, 18.3; IR (Neat Film NaCl) 3335, 2102, 1713, 1674 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{27}H_{26}N_6O_2F_3$ $[M+H]^+$: 523.2064; found 523.1982.



Chloride 29. To a solution of adduct **28** (183 mg, 0.350 mmol, 1.0 equiv) in THF (4 mL) was added sodium hydride (60% dispersion in mineral oil, 42 mg, 1.05 mmol, 3.0 equiv) at 0 °C. The reaction mixture was stirred for 5 min and *o*-nitrobenzylsulfonyl chloride (116 mg, 0.523 mmol, 1.5 equiv) was added at 0 ºC. The reaction was stirred for 10 min, and then a saturated solution of ammonium chloride was added. The resulting solution was extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (15:1 → 2:1 hexanes:EtOAc) to afford alkyl chloride **29** (142 mg, 73% yield) as a white crystalline solid. For spectrum, see ref 41.

R_f = 0.26 (2:1 hexanes:EtOAc); (Due to the distinct presence of rotameric isomers, the ^{1}H NMR and ^{13}C NMR contained extra peaks. See the attached spectrum), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64–8.59 (m, 2H), 7.95–7.84 (m, 8H), 7.55–7.47 (m, 6H), 7.37–7.26 (m, 5H), 7.15 (d, *J* = 7.0 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.31 (d, *J* = 7.5 Hz, 2H), 5.76–5.72 (m, 2H), 5.61 (d, *J* = 7.5 Hz, 1H), 4.20–4.08 (m, 2H), 3.94–3.67 (m, 3H), 3.31–3.19 (m, 2H), 2.99–2.74 (m, 6H), 2.29 (dd, *J* = 3.0, 10.5 Hz, 1H), 1.75 (s, 6H), 1.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 175.8, 173.8, 173.6, 156.3, 155.9, 151.7, 151.6, 148.2, 147.9, 141.6, 140.7, 139.9, 139.7, 139.2, 138.2, 137.4, 136.9, 136.4, 136.0, 135.3, 135.2, 132.6, 130.9, 130.8, 130.4, 130.4, 128.3, 126.8, 126.6, 126.4, 126.3, 125.8, 125.4, 125.3, 125.2, 124.9, 121.7, 121.6, 120.6, 119.8, 118.6, 115.4, 115.3, 114.8, 77.7, 77.4, 77.2, 76.8, 75.7, 75.5, 60.1, 57.6, 55.7, 55.6, 46.5, 46.4, 40.0, 39.1, 37.8, 37.6, 36.1, 32.6, 26.5, 26.0, 18.6, 18.1; IR (Neat Film NaCl) 2102, 1755, 1686, 1544, 1146 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{33}H_{28}O_7N_7F_3SCl$ $[M+H]^+$: 758.1406; found 758.1442.

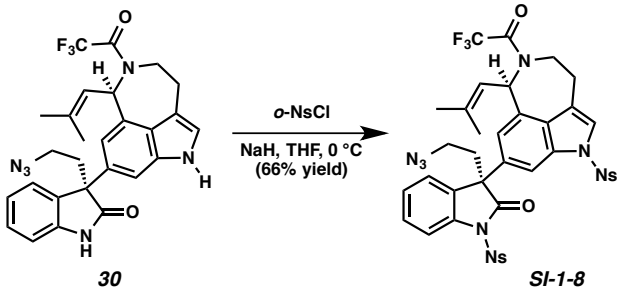


Adducts 28, 30, and 31. A flame-dried flask (100 mL) equipped with a teflon stirbar was charged with indole **25** (1.03 g, 3.21 mmol, 1.0 equiv) and bromooxindole **26** (2.25 mg, 8.02 mmol, 2.5 equiv), which were subsequently dissolved in dichloromethane (32 mL). Cesium carbonate (3.14 g, 9.62 mmol, 3.0 equiv) was then added. After addition, the reaction was stirred for 3 h, and then water was added. The resulting solution was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (18:1 → 1:2 hexanes:EtOAc) to afford adduct **28** (404 mg, 24% yield), adduct **30** (538 mg, 32% yield), and adduct **31** (548 mg, 24% yield). For spectrum, see ref 41.

Adduct **30**: R_f = 0.18 (2:1 hexanes:EtOAc x2 elutions); (due to the distinct presence of rotameric isomers, the ^{1}H NMR and ^{13}C NMR contained extra peaks), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (d, *J* = 13.0 Hz, 2H), 8.33 (d, *J* = 6.0 Hz, 2H), 7.28–6.86 (m, 9H), 6.75 (d, *J* = 7.5 Hz, 1H), 6.11 (d, *J* = 7.5 Hz, 1H), 5.31 (dd, *J* = 7.5, 29.5 Hz, 2H), 4.30 (d, *J* = 13.5 Hz, 1H), 4.06–4.01 (m, 1H), 3.94–3.84 (m, 1H), 3.71 (t, *J* = 13.0 Hz, 1H), 3.29 (t, *J* = 13.0 Hz, 1H), 3.17–3.13 (m, 4H), 2.98 (d, *J* = 16.5 Hz, 1H), 2.89–2.75 (m, 2H), 2.53–2.44 (m, 2H), 1.76 (s, 3H), 1.72 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.1, 180.9, 157.4, 157.0, 156.7, 156.2, 141.1, 138.5, 137.5, 137.3, 137.1, 135.5, 134.8, 133.4,

133.2, 132.2, 132.1, 128.8, 128.7, 125.1, 124.0, 123.6, 123.2, 123.1, 122.8, 122.5, 119.0, 118.7, 117.0, 115.7, 115.1, 114.9, 113.3, 112.6, 110.7, 108.6, 108.5, 60.6, 58.6, 55.5, 55.4, 47.9, 43.8, 43.7, 36.6, 36.3, 28.4, 26.3, 25.8, 25.0, 18.9, 18.3; IR (Neat Film NaCl) 3328, 2100, 1712, 1682 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{27}H_{26}N_6O_2F_3$ $[M+H]^+$: 523.2064, found 523.2002.

Adduct **31**: R_f = 0.09 (2:1 hexanes:EtOAc x2 elutions); (due to the distinct presence of rotameric isomers, the ^1H NMR and ^{13}C NMR contained extra peaks), ^1H NMR (300 MHz, acetone-d_6) δ 10.43 (d, *J* = 11.5 Hz, 1H), 9.80 (d, *J* = 8.0 Hz, 1H), 9.59 (s, 1H), 7.36–7.23 (m, 7H), 7.19–6.97 (m, 8H), 5.36 (dd, *J* = 7.0, 40.0 Hz, 2H), 4.02–3.50 (m, 6H), 3.25–3.10 (m, 8H), 3.04 (s, 2H), 3.01–2.44 (m, 8H), 1.76 (s, 3H), 1.73 (s, 3H), 1.68 (s, 6H); ^{13}C NMR (75 MHz, acetone-d_6) δ 180.2, 180.1, 177.9, 177.8, 143.1, 143.0, 142.9, 138.3, 137.4, 137.2, 136.8, 135.3, 134.8, 134.6, 134.4, 133.6, 133.3, 133.2, 133.0, 131.3, 129.9, 129.3, 129.2, 126.1, 125.3, 125.2, 125.0, 124.8, 123.9, 123.6, 122.9, 118.0, 147.1, 111.0, 110.9, 110.3, 109.9, 109.4, 109.2, 61.2, 59.2, 55.8, 55.7, 52.7, 52.7, 48.6, 47.6, 44.0, 37.0, 36.9, 35.4, 28.2, 26.1, 25.7, 24.8, 18.8, 18.3; IR (Neat Film NaCl) 3305, 2101, 1713, 1472 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{37}H_{34}N_{10}F_3O_3$ $[M+H]^+$: 723.2762; found 723.2689.

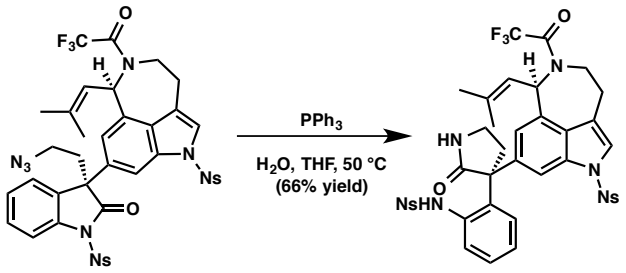


30 ***SI-1-8***

Nosylate SI-1-8. A flame-dried vial (4 mL) equipped with a teflon stirbar was charged with adduct **30** (43.7 mg, 0.0836 mmol), which was subsequently dissolved in THF (800 μL). The solution was cooled to 0 °C, and then sodium hydride (60% dispersion in mineral oil, 17 mg, 0.425 mmol) was added. 5 min after the sodium hydride addition, *o*-nitrobenzylsulfonyl chloride (93 mg, 0.420 mmol) was added. The reaction was stirred for 10 min, and then a saturated solution of ammonium chloride was added. The resulting solution was extracted 3 times with ether, the organic layers were combined and dried over magnesium sulfate, and the solvent was removed under reduced pressure. Purification was performed via flash column chromatography (9:1 →1:1 hexanes:EtOAc) to afford the bisnosylate **SI-1-8** (49.0 mg, 66% yield) as a yellow solid. For spectrum, see ref 41.

R_f = 0.42 (1:1 hexanes:EtOAc); (Due to the distinct presence of rotameric isomers, the ^{1}H NMR and ^{13}C NMR contained extra peaks), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54–8.51 (m, 2H), 8.03–8.00 (m, 2H), 7.88–7.56 (m, 10H), 7.50 (s, 1H), 7.42–7.35 (m, 5H), 7.18–7.12 (m, 3H), 6.95 (s, 1H), 6.61 (d, *J* = 7.5 Hz, 1H), 5.97 (d, *J* = 7.5 Hz, 1H), 5.23–5.16 (m, 2H), 4.27 (d, *J* = 13.5 Hz, 1H), 4.02 (d, *J* = 15.0 Hz, 1H), 3.89–3.79 (m, 1H), 3.64 (t, *J* = 11.0 Hz, 1H), 3.32–2.80 (m, 10H), 2.48–2.33 (m, 2H), 1.73 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 176.0, 157.3, 156.9, 156.5, 148.0, 148.0, 140.2, 140.1, 140.0, 138.6, 137.2, 136.6, 136.2, 136.0, 135.7, 135.5, 134.8, 134.7, 132.8, 132.8, 132.4, 131.2, 131.2, 131.1, 130.9, 130.6, 129.9, 129.8, 129.5, 129.2, 127.4, 127.0, 125.7, 125.7, 125.4, 125.4, 125.2, 125.1, 124.9, 122.8, 121.9, 121.1, 120.0, 118.8, 118.5, 117.9, 115.5, 114.9, 110.6, 60.2, 58.1, 55.0, 55.0, 47.5, 42.8, 42.7, 36.6, 36.6, 39.9, 28.0, 26.3, 25.8, 25.0,

18.9, 18.3; IR (Neat Film NaCl) 2930, 2101, 1754, 1684, 1544 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{39}H_{32}N_8O_{12}F_3S_2$ $[M+H]^+$: 925.1528, found 925.1613.

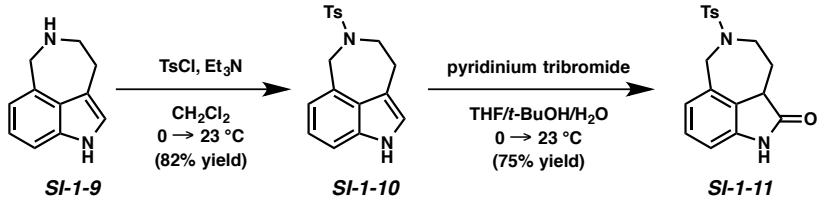


SI-1-8 ***32***

Lactam 32. To a solution of nosylate **SI-1-8** (43.1 mg, 0.0483 mmol, 1.0 equiv) in THF (1 mL) and water (250 μL) was added triphenylphosphine (25 mg, 0.0953 mmol, 2.0 equiv). The reaction was stirred for 3 h at 50 °C, and then the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (3:1 → 1:1 hexanes:EtOAc) to afford the lactam **32** (49.0 mg, 66% yield) as a yellow crystalline solid. For spectrum, see ref 41.

R_f = 0.14 (1:1 hexanes:EtOAc); (due to the distinct presence of rotameric isomers, the ^1H NMR and ^{13}C NMR contained extra peaks), ^1H NMR (300 MHz, $CDCl_3$) δ 7.75–7.50 (m, 6H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.34–7.22 (m, 4H), 7.14 (d, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 7.5 Hz, 2H), 6.55 (d, *J* = 6.5 Hz, 2H), 6.01 (d, *J* = 7.5 Hz, 1H), 5.32 (d, *J* = 8.0 Hz, 1H), 5.20 (d, *J* = 8.0 Hz, 1H), 4.26 (d, *J* = 13.5 Hz, 1H), 4.02 (d, *J* = 15.5 Hz, 1H), 3.81 (t, *J* = 11.5 Hz, 1H), 3.30–3.00 (m, 3H), 2.35–2.28 (m, 2H), 1.67 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.0, 157.3, 156.8, 156.7, 156.2, 147.9, 147.8, 147.7, 139.5, 139.4, 137.8, 137.5, 137.4, 136.9, 136.5, 136.4, 136.2, 136.1, 135.6, 135.3, 135.1, 133.6, 132.9, 132.5, 132.2, 132.0, 131.0, 130.9, 130.5, 129.0, 127.9, 127.8, 126.3, 126.2, 125.2, 125.1,

125.0, 124.9, 124.8, 124.5, 124.4, 124.3, 123.3, 122.4, 121.4, 120.5, 119.2, 118.9, 118.5, 118.4, 115.1, 110.2, 109.7, 77.7, 77.4, 77.2, 76.8, 60.1, 58.2, 57.7, 43.0, 42.8, 39.8, 38.8, 28.5, 26.1, 25.7, 25.3, 18.9, 18.3; IR (Neat Film NaCl) 3098, 2916, 1682, 1545, 1368, 1170, 732 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{39}H_{34}N_6O_{12}F_3S_2$ $[M+H]^+$: 899.1623, found 899.1731.

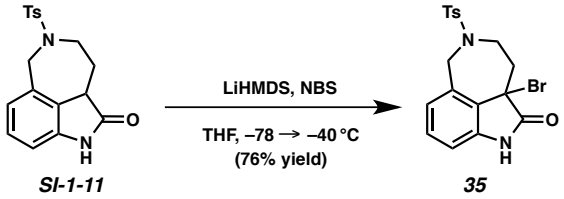


Oxindole SI-1-11. To a solution of indole **SI-1-9** (106 mg, 0.614 mmol, 1.0 equiv) and Et_3N (0.17 mL, 1.23 mmol, 2.0 equiv) in CH_2Cl_2 (4 mL) cooled to 0 ºC was added a solution of TsCl (117 mg, 0.614 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) dropwise. The ice bath was removed and the reaction mixture was stirred for 5 h, then diluted with EtOAc (160 mL) and washed with 0.5 N HCl (2 x 30 mL) and brine. The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (2:1 hexanes:EtOAc) to afford indole **SI-1-10** (164 mg, 82% yield).

Indole **SI-1-10** was dissolved in THF (10 mL), *t*-BuOH (10 mL) and water (1 mL). The solution was cooled to 0 ºC and pyridinium tribromide (504 mg, 1.54 mmol, 1.02 equiv) was added. The reaction mixture was stirred at 0 ºC for 45 min and then allowed to warm to ambient temperature. The reaction was quenched by addition of 10 mL of 1:1 v/v 1M $Na_2S_2O_3$:sat. $NaHCO_3$. The reaction mixture was diluted with brine (50 mL) and

extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (2:1 hexanes:acetone) to afford oxindole **SI-1-11** (397 mg, 75% yield) of as a white solid.

R_f = 0.15 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (br, s, 1H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.21–7.14 (m, 3H), 6.94 (d, *J* = 7.7 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 4.80 (d, *J* = 15.5 Hz, 1H), 4.30 (d, *J* = 13.6 Hz, 1H), 4.15 (d, *J* = 15.5 Hz, 1H), 3.52 (dd, *J* = 12.5, 3.5 Hz, 1H), 3.24 (t, *J* = 12.6 Hz, 1H), 2.38 (s, 3H), 2.30 (m, 1H), 1.53 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 178.4, 143.3, 140.5, 137.1, 135.9, 129.6, 128.4, 128.3, 127.0, 121.5, 109.1, 53.3, 51.6, 46.2, 28.6, 21.5; IR (Neat Film NaCl) 3276, 2925, 2853, 1698, 1618, 1463, 1326, 1153 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{19}N_2O_3S$ [M+H]+ : 343.1111; found: 343.1025.

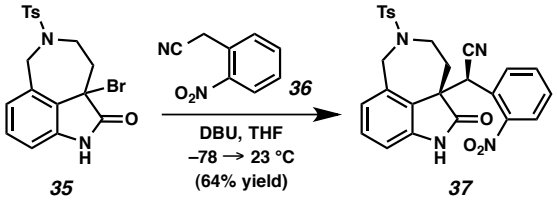


SI-1-11 *35*

Bromooxindole 35. LiHMDS (429 mg, 2.57 mmol, 2.5 equiv) was dissolved in THF (5 mL). The solution was cooled to –78 ºC and a solution of oxindole **SI-1-11** (352 mg, 1.03 mmol, 1.0 equiv) in THF (20 mL) was added dropwise over 20 min. The reaction mixture was stirred at –78 ºC for 20 min and transferred to a pre-cooled solution of *N*-bromosuccinimide (457 mg, 2.57 mmol, 2.5 equiv) in THF (10 mL) that was protected from light. The resulting reaction mixture was placed in a –40 ºC bath for 1h, while being protected from light, and then quenched with sat. NH_4Cl. The reaction mixture was

allowed to warm to ambient temperature, diluted with brine (100 mL) and extracted with EtOAc (3 x 70 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to afford a yellow oil, which was purified by silica gel chromatography (2:1 hexanes:EtOAc) to afford bromooxindole **35** (334 mg, 76% yield) as a yellow solid.

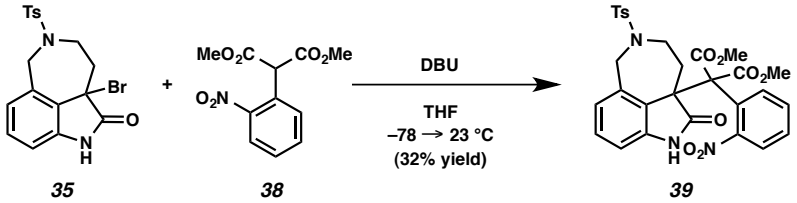
R_f = 0.40 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (br, s, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.24–7.19 (m, 3H), 6.96 (d, *J* = 7.7 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 4.76 (d, *J* = 15.4 Hz, 1H), 4.32 (m, 2H), 3.80 (t, *J* = 13.2 Hz, 1H), 2.39 (s, 3H), 2.33 (m, 1H), 1.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 143.5, 139.0, 137.7, 136.9, 130.7, 129.7, 128.7, 126.9, 122.6, 110.1, 59.2, 51.6, 48.3, 35.2, 21.5; IR (Neat Film NaCl) 3313, 2930, 1734, 1615, 1460, 1334, 1155, 1096, 727 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{18}BrN_2O_3S$ $[M+H]^+$: 421.0216; found: 421.0213.



Nitrile 37. A solution of bromooxindole **35** (44.9 mg, 0.107 mmol, 1.0 equiv) and 2-nitrophenylacetonitrile **36** (34.6 mg, 0.213 mmol, 2.0 equiv) in THF (3 mL) was cooled to –78 ºC. DBU (64 μL, 0.426 mmol, 4.0 equiv) was added dropwise. The reaction mixture was then allowed to gradually warm to ambient temperature. After 8 h, the reaction mixture was quenched with sat. NH_4Cl (10 mL) and the mixture was extracted with EtOAc (4 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and

concentrated under reduced pressure to afford a brown oil, which was purified by preparatory thin layer chromatography on silica gel (1:1 hexane:EtOAc x2 elutions) to afford nitrile **37** (34.8 mg, 64% yield) as an orange-yellow solid.

R_f = 0.28 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (m, 1H), 7.63 (m, 2H), 7.55 (m, 2H), 7.43 (m, 2H), 7.29 (d, *J* = 8.0 H, 2H), 7.18 (t, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 7.7 Hz, 1H), 6.48 (d, *J* = 7.4 Hz, 1H), 6.07 (s, 1H), 4.80 (d, *J* = 16.2 Hz, 1H), 4.29 (m, 2H), 3.45 (app. t, *J* = 13.2 Hz, 1H), 2.74 (app. dd, *J* = 15.0, 2.6 Hz, 1H), 2.43 (s, 3H), 1.94 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 147.9, 143.8, 140.3, 137.9, 136.5, 133.5, 132.5, 131.0, 130.3, 130.0, 127.0, 124.8, 124.5, 124.5, 123.7, 116.2, 109.4, 54.4, 52.6, 46.8, 34.2, 32.1, 21.6; IR (Neat Film NaCl) 3302, 2920, 1724, 1527, 1155, 724 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{26}H_{23}N_4O_5S$ $[M+H]^+$: 503.1384; found: 503.1411.

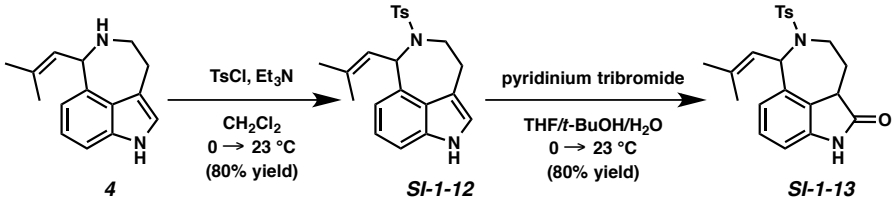


35 ***38*** ***39***

Aryl malonate 39. To a solution of bromooxindole **35** (50.0 mg, 0.119 mmol, 1.0 equiv) and malonate **38** (90.1 mg, 0.356 mmol, 3.0 equiv) in THF (0.6 mL) was added DBU (54.2 mg, 0.356 mmol, 3.0 equiv) at –78 ºC. The reaction solution was slowly warmed to 23 ºC. The reaction solution was stirred for 12 h, and quenched with sat. NH_4Cl. The mixture was extracted with EtOAc (3 x 1 mL) and brine. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure and then the residue

was purified by preparatory thin layer chromatography on silica gel (1:1 hexane:EtOAc) to afford nitrile **39** (23 mg, 32% yield).

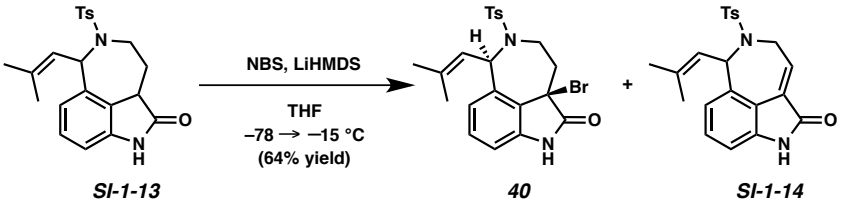
R_f = 0.15 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (br, s, 1H), 8.23 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.58–7.51 (m, 5H), 7.24 (d, *J* = 8.0 Hz, 2H), 6.96 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.76 (d, *J* = 1.5 Hz, 1H), 6.66 (d, *J* = 1.0 Hz, 1H), 4.44 (d, *J* = 15.4 Hz, 1H), 4.15 (d, *J* = 15.4 Hz, 1H), 3.95 (d, *J* = 14.6 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.69 (m, 1H), 2.40 (s, 3H), 1.95 (d, *J* = 14.6 Hz, 1H), 1.66 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 168.8, 148.1, 143.4, 141.2, 138.7, 137.0, 134.7, 133.9, 132.0, 129.7, 129.1, 128.3, 126.8, 125.7, 122.8, 110.7, 74.8, 68.7, 53.7, 53.5, 51.3, 46.0, 33.4, 21.5; IR (Neat Film NaCl) 3313, 1737, 1623, 1530, 1450, 1347, 1241, 1153, 1091, 895, 729 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{29}H_{26}N_3O_9S$ $[M-H]^-$: 592.1395; found: 592.1382.



Oxindole SI-1-13. To a solution of aurantioclavine **4** (300 mg, 0.00133 mol, 1.0 equiv) and Et_3N (0.37 mL, 0.00265 mol, 2.0 equiv) in CH_2Cl_2 (4 mL) cooled to 0 ºC was added a solution of TsCl (254 mg, 0.00133 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) dropwise. The ice bath was removed and the reaction mixture was stirred for 5 h, then diluted with EtOAc (200 mL) and washed with 0.5 N HCl (2 x 35 mL) and brine. The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (2:1 hexanes:EtOAc) to afford indole **SI-1-12** (405 mg, 80% yield).

A solution of indole **SI-1-12** (902.2 mg, 2.371 mmol, 1.0 equiv) in THF/*t*-BuOH/H_2O (10:10:1 v/v/v, 52.5 mL) was cooled to 0 ºC and pyridinium tribromide (834.2 mg, 2.608 mmol, 1.1 equiv) was added in small portions over 5 min. The reaction mixture was stirred at 0 ºC for 15 min, and then allowed to warm to ambient temperature. After 5 min at ambient temperature, the reaction mixture was quenched by addition of 1:1 v/v sat. $NaHCO_3$:1M aq $Na_2S_2O_3$ (15 mL), poured into brine (150 mL) and extracted with EtOAc (3 x 100 mL). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure to afford a brown solid, which was purified by silica gel chromatography (2:1 → 1:1 hexanes:EtOAc) to afford oxindole **SI-1-13** (747.5 mg, 80% yield).

R_f = 0.22 (5:1 benzene:MeCN); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (br, s, 1H), 7.33 (dd, *J* = 8.5, 2.1 Hz, 2H), 7.03 (m, 1H), 6.96 (d, *J* = 7.2 Hz, 2H), 6.82 (d, *J* = 7.7 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 5.76 (d, *J* = 8.0 Hz, 1H), 5.31 (m, 1H), 4.00 (dt, *J* = 15.7, 2.8 Hz, 1H), 3.64–3.50 (m, 2H), 2.22 (s, 3H), 2.00 (m, 1H), 1.67 (s, 3H), 1.65 (s, 3H), 1.25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 142.9, 140.9, 140.5, 138.2, 129.2, 128.3, 128.3, 127.0, 126.7, 121.3, 119.0, 108.7, 59.0, 46.0, 43.8, 27.8, 26.0, 21.4, 18.5; IR (Neat Film NaCl) 3246, 2925, 1713, 1615, 1460, 1326, 1155, 732 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{22}H_{25}N_2O_3S$ $[M+H]^+$: 397.1580; found: 397.1586.

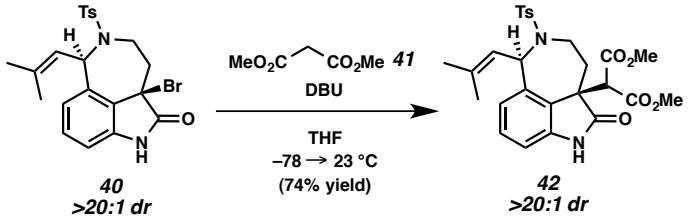


SI-1-13 *40* *SI-1-14*

Bromooxindole 40. A solution of oxindole **SI-1-13** (172.0 mg, 0.434 mmol, 1.0 equiv) in THF (5 mL) was added dropwise to a freshly prepared solution of LiHMDS (217.8 mg, 1.301 mmol, 3.0 equiv) in THF (5 mL) that had been pre-cooled to –78 ºC. After 20 min at –78 ºC, the resulting solution was transferred via cannula to a solution of *N*-bromosuccinimide (231.6 mg, 1.301 mmol, 3.0 equiv) in THF (5 mL) that had been pre-cooled to –78 ºC. The resulting yellow reaction mixture was allowed to warm to –15 ºC (the reaction flask was transferred to a bath composed of ethylene glycol and dry ice) and maintained at this temperature for 2 h. The reaction mixture was then cooled to –78 ºC and quenched by addition of sat. NH_4Cl (5 mL). The yellow reaction mixture was allowed to warm to ambient temperature and diluted with H_2O (80 mL), then extracted with EtOAc (3 x 70 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford a yellow oil, which was purified immediately by silica gel chromatography (2:1 hexanes:EtOAc) to afford a 3:1 mixture of bromooxindole **40** (>20:1 dr) and dehydrobromination product **SI-1-14** (131.1 mg, 64% combined yield, 50% yield of bromooxindole **40**). Bromooxindole **40** was stored frozen in benzene and used without further purification. The relative configuration of this bromooxindole was assigned based on the stereochemistry of the malonate adduct obtained (see below). Quenching the reaction prior to completion afforded the bromooxindole **40** as a single diastereomer, which showed greater stability, and could be fully characterized.

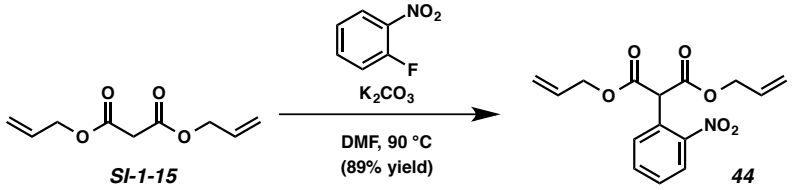
R_f = 0.50 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (br, s, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.21 (t, *J* = 8.0, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 7.5 Hz, 1H), 6.79 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.96 (td, *J* = 8.5, 1.5 Hz, 1H), 5.88 (d, *J* = 8.5 Hz, 1H),

4.18–4.02 (m, 2H), 2.35 (s, 3H), 2.27 (m, 1H), 1.97 (m, 1H), 1.76 (d, J = 1.0 Hz, 3H), 1.75 (d, J = 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 143.2, 142.4, 140.2, 139.2, 137.8, 130.8, 129.4, 126.9, 126.1, 122.7, 120.1, 109.7, 66.8, 59.5, 39.8, 34.4, 26.1, 21.4, 18.4; IR (Neat Film NaCl) 3291, 1734, 1617, 1602, 1457, 1326, 1156, 1092, 738 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{22}H_{23}BrN_2O_3S$ $[M+H]^+$: 475.0686; found: 475.0668.



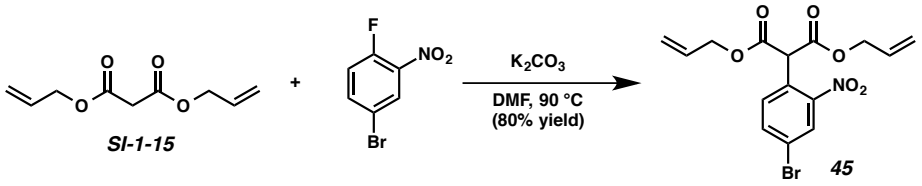
Malonate 42. Bromooxindole **40** (>20:1 dr, 51.3 mg, 0.108 mmol, 1.0 equiv) was dissolved in THF (2 mL). Dimethyl malonate **41** (37 μL, 0.324 mmol, 3.0 equiv) was added and the reaction mixture was cooled to –78 °C. DBU (48 μL, 0.324 mmol, 3.0 equiv) was added dropwise. The reaction mixture was stirred at –78 °C for 15 min and then warmed to 23 °C. After maintaining the reaction mixture at 23 °C for 6 h, sat. NH_4Cl (2 mL) was added and the reaction mixture was warmed to ambient temperature. The reaction mixture was diluted with EtOAc (50 mL) and sat. NH_4Cl (50 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to afford colorless oil. Analysis of the crude oil by ^{1}H NMR indicated >20:1 dr of the malonate adduct **42**. The residue was purified by silica gel chromatography (1:1 hexane:EtOAc) to afford malonate **42** (42 mg, 74% yield).

R_f = 0.20 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (br, s, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.91, (d, *J* = 7.5 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 5.92 (d, *J* = 4.5 Hz, 1H), 5.38 (d, *J* = 4.5 Hz, 1H), 4.62 (s, 1H), 4.06 (m, 1H), 3.89 (m, 1H), 3.78 (s, 3H), 3.46 (s, 3H), 2.40 (m, 1H), 2.30 (s, 3H), 1.82 (s, 3H), 1.79 (s, 3H), 1.07 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 166.8, 166.8, 143.0, 141.9, 141.4, 141.0, 137.9, 129.2, 128.9, 127.6, 127.0, 123.0, 124.0, 109.0, 59.6, 53.9, 52.9, 52.3, 51.3, 39.8, 28.9, 26.4, 21.4, 18.6; IR (Neat Film NaCl) 3338, 2953, 1733, 1618, 1597, 1458, 1327, 1158 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{27}H_{31}N_2O_7S$ $[M+H]^+$: 527.1846; found: 527.1848.



Diallyl 2-(2-nitrophenyl)malonate 44. A 500 mL round-bottom flask with a magnetic stir bar was charged with diallyl malonate **SI-1-15** (22.0 g, 118 mmol, 1.0 equiv), 1-fluoro-2-nitrobenzene (13.7 mL, 129 mmol, 1.1 equiv), and K_2CO_3 (48.9 g, 354 mmol, 3.0 equiv). DMF (120 mL) was added and the brown suspension was heated to 90 ºC for 16 h. The reaction mixture was cooled to ambient temperature and diluted with ice water (250 mL) and Et_2O (300 mL). The aqueous phase was extracted with Et_2O (3 x 300 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (9:1 hexanes:EtOAc) on silica gel to give arylated malonate **44** (32.1 g, 89% yield).

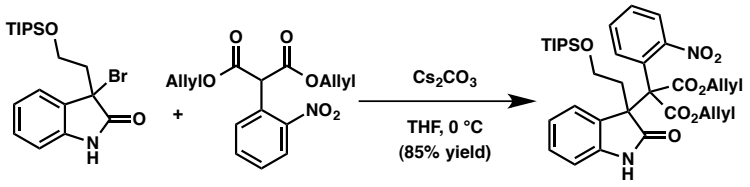
R_f = 0.51 (1:1 hexane:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.66 (td, *J* = 7.6, 1.4 Hz, 1H), 7.55–7.51 (m, 2H), 5.90 (ddt, *J* = 17.3, 10.4, 5.7 Hz, 2H), 5.39-5.23 (m, 5H), 4.70 (dt, *J* = 5.8, 1.4 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 148.7, 133.6, 131.4, 131.1, 129.3, 127.9, 125.3, 119.1, 66.8, 54.3; IR (Neat Film NaCl) 3086, 2950, 1738, 1611, 1530, 1447, 1350, 1154, 991, 937, 852, 787, 722 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{16}NO_6$ $[M+H]^+$: 306.0972; found: 306.0930.



Diallyl 2-(4-bromo-2-nitrophenyl)malonate 45. A 500 mL round-bottom flask with a magnetic stir bar was charged with diallyl malonate **SI-1-15** (15.0 g, 81.5 mmol, 1.0 equiv), 4-bromo-1-fluoro-2-nitrobenzene (11.0 mL, 89.7 mmol, 1.1 equiv), and K_2CO_3 (33.8 g, 245 mmol, 3.0 equiv). DMF (163 mL) was added and the brown suspension was heated to 90 ºC for 16 h. The reaction mixture was cooled to ambient temperature and diluted with ice water (250 mL) and Et_2O (300 mL). The aqueous phase was extracted with Et_2O (3 x 300 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (9:1 hexanes:EtOAc) on silica gel to give arylated malonate **45** (32.1 g, 80% yield).

R_f = 0.69 (1:1 hexane:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 2.1 Hz, 1H), 7.77 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 5.94–5.84 (m, 2H), 5.37–5.24 (m, 5H), 4.70 (dt, *J* = 5.9, 1.3 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 149.1, 136.5,

132.8, 131.0, 128.2, 126.8, 122.8, 119.3, 66.9, 53.8; IR (Neat Film NaCl) 3085, 2986, 2951, 1733, 1649, 1538, 1348, 1283, 1218, 1148, 989, 936 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{15}BrNO_6$ $[M+H]^+$: 384.0077; found: 384.0072.

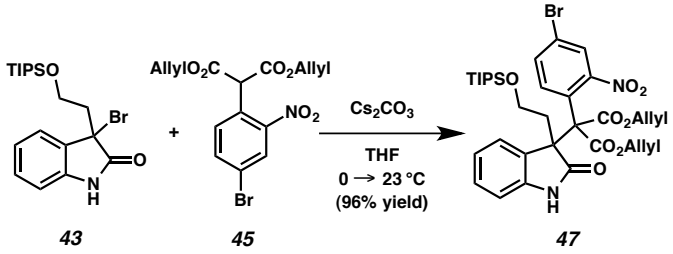


43 *44* *46*

Oxindole 46. To a suspension of Cs_2CO_3 (5.37 g, 16.5 mmol, 3.0 equiv) and bromooxindole **43** (2.27 g, 5.50 mmol, 1.0 equiv) in THF (100 mL) was added malonate **44** (5.04 g, 16.5 mmol, 3.0 equiv) at 0 °C. The reaction mixture was then allowed to slowly warm to 23 °C and stirred for 16 h. Solids were removed via a filtration through a celite plug (rinsed with EtOAc) and the resulting purple solution was concentrated under reduced pressure. The residue was purified by column chromatography using a Teledyne Isco CombiFlash (SiO_2, 120 g column, 100:0 → 3:1 hexanes:EtOAc) to provide alkylation product **46** (8.9 g, 85% yield) as a colorless oil.

R_f = 0.18 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.0 Hz, 1H), 7.94 (s, 1H), 7.73 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.41 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.38– 7.33 (m, 2H), 7.13 (dt, *J* = 7.7, 1.1 Hz, 1H), 6.89 (dt, *J* = 7.7, 1.0 Hz, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 5.88–5.73 (m, 2H), 5.25 (ddd, *J* = 17.2, 2.8, 1.4 Hz, 1H), 5.19–5.11 (m, 3H), 4.69 (tdd, *J* = 13.3, 5.7, 1.4 Hz, 1H), 4.64 (tdd, *J* = 13.3, 5.7, 1.3 Hz, 1H), 4.57 (tdd, *J* = 13.4, 5.9, 1.4 Hz, 1H), 4.48 (tdd, *J* = 13.1, 5.9, 1.1 Hz, 1H), 3.35 (ddd, *J* = 9.5, 8.5, 6.9 Hz, 1H), 3.07 (dt, *J* = 9.5, 4.5 Hz, 1H), 2.95 (ddd, *J* = 12.9, 8.7, 7.0 Hz, 1H), 2.63 (ddd, *J* =

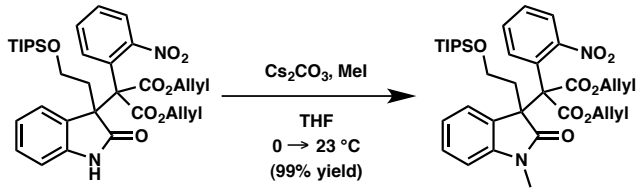
12.9, 8.5, 4.5 Hz, 1H), 0.97–0.77 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 166.7, 166.3, 150.2, 140.7, 132.4, 131.3, 131.0, 130.8, 129.5, 129.2, 128.5, 126.9, 125.3, 122.4, 119.2, 118.4, 109.1, 66.8, 66.7, 59.5, 56.7, 38.3, 17.8, 11.8; IR (Neat Film NaCl) 3332, 2942, 1714, 1649, 1618, 1538, 1471, 1356, 1230, 1114, 995, 933, 885, 850, 752, 683 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{34}H_{45}N_2O_8Si$ $[M+H]^+$: 637.2940; found: 637.2945.



Oxindole 47. To a solution of 3-bromooxindole **43** (2.0 g, 4.85 mmol, 1.0 equiv) and malonate **45** (3.7 g, 9.70 mmol, 2.0 equiv) in THF (49 mL) was added Cs_2CO_3 (3.2 g, 9.70 mmol, 2.0 equiv) at 0 °C. The reaction mixture was warmed to 23 °C and stirred overnight. Solids were removed via a filtration through a celite plug and the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (9:1 → 4:1 hexanes:EtOAc) on silica gel to give desired alkylated product **47** (3.3g, 96% yield).

R_f = 0.33 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (br, s, 1H), 7.95 (d, *J* = 8.9 Hz, 1H), 7.86 (d, *J* = 2.3 Hz, 1H), 7.53 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.43–7.39 (m, 1H), 7.16 (td, *J* = 7.7, 1.2 Hz, 1H), 6.92 (td, *J* = 7.7, 1.1 Hz, 1H), 6.75–6.72 (m, 1H), 5.79 (dddt, *J* = 33.6, 17.2, 10.4, 5.9 Hz, 2H), 5.26–5.18 (m, 2H), 5.19–5.14 (m, 2H), 4.66 (qdt, *J* = 13.2, 5.9, 1.4 Hz, 2H), 4.55–4.42 (m, 2H), 3.32 (dt, *J* = 9.7, 7.5 Hz, 1H), 3.09 (ddd, *J*

= 9.8, 8.5, 4.5 Hz, 1H), 2.89–2.82 (m, 1H), 2.63 (ddd, *J* = 12.7, 8.1, 4.5 Hz, 1H), 0.89 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 166.6, 166.2, 150.9, 140.9, 134.3, 134.1, 131.3, 130.8, 129.0, 129.0, 128.6, 128.3, 127.2, 122.7, 122.2, 119.6, 119.0, 109.5, 67.2, 67.1, 66.9, 59.7, 57.0, 38.4, 18.0, 11.9; IR (Neat Film NaCl) 3203, 2943, 2865, 1716, 1619, 1538, 1471, 1357, 1229, 1111, 992, 935, 753, 735 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{34}H_{44}BrN_2O_8Si$ $[M+H]^+$: 715.2045; found: 715.2090.

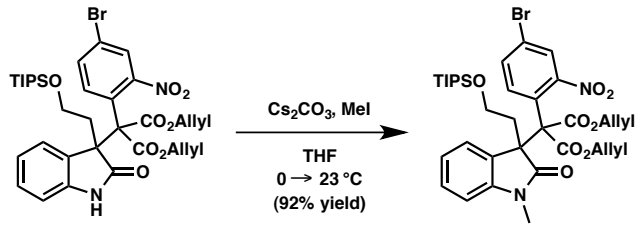


46 ***48***

Methyloxindole 48. To a suspension of oxindole **46** (0.50 g, 0.79 mmol, 1.0 equiv) and Cs_2CO_3 (0.77 g, 2.37 mmol, 3.0 equiv) in THF (4.0 mL) was added methyl iodide (0.3 mL, 4.7 mmol, 6.0 equiv) at 0 °C. The reaction mixture was stirred for 12 h at 23 °C. After the reaction was done, sat. NH_4Cl was added. The aqueous phase was extracted with EtOAc (3 x 3 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (3:1 hexanes:EtOAc) to give methylated oxindole **48** (0.51g, 99% yield).

R_f = 0.33 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 1H), 7.54 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.31 (dt, *J* = 7.7, 1.6 Hz, 1H), 7.25 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.10 (dt, *J* = 7.7, 0.9 Hz, 1H), 6.85 (dt, *J* = 7.8, 0.8 Hz, 1H), 6.57 (d, *J* = 7.7 Hz, 1H), 5.80 (tdd, *J* = 16.3, 10.7, 5.8 Hz, 1H), 5.71 (tdd, *J* = 16.4,

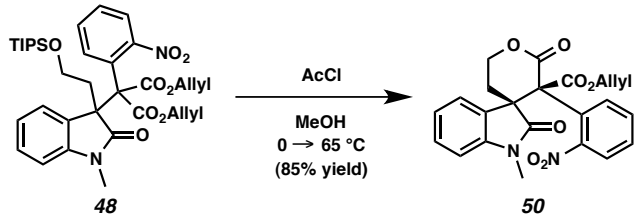
10.5, 5.9 Hz, 1H), 5.22–5.02 (m, 4H), 4.69–4.56 (m, 2H), 4.52 (tdd, *J* = 13.1, 5.8, 1.3 Hz, 1H), 4.36 (tdd, *J* = 13.3, 5.9, 1.3 Hz, 1H), 3.15–3.02 (m, 4H), 2.96 (ddd, *J* = 9.7, 8.3, 4.7 Hz, 1H), 2.85 (td, *J* = 13.2, 7.4 Hz, 1H), 2.67 (ddd, *J* = 12.8, 8.0, 4.7 Hz, 1H), 0.86–0.71 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.3, 166.5, 166.5, 150.3, 143.6, 132.7, 131.3, 130.9, 130.3, 128.8, 128.5, 128.5, 128.3, 126.9, 125.1, 122.3, 119.1, 118.5, 107.3, 66.7, 66.7, 59.6, 56.8, 37.9, 26.1, 17.8, 11.7; IR (Neat Film NaCl) 3421, 3054, 2944, 2866, 1723, 1613, 1539, 1473, 1356, 1253, 1180, 1104, 1068, 935, 862, 840, 752, 690 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{35}H_{47}N_2O_8Si$ $[M+H]^+$: 651.3096; found: 651.3184.



47 ***49***

Methyloxindole 49. To a solution of oxindole **47** (14.1 g, 0.0197 mol, 1.0 equiv) in THF (106 mL) was added Cs_2CO_3 (19.3 g, 0.0591 mol, 3.0 equiv) and MeI (7.40 mL, 0.118 mol, 6.0 equiv) at 0 ºC. Then, the reaction mixture was stirred for 12 h at 23 ºC. After the reaction was done, sat. NH_4Cl was added. The aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (7:1 hexanes:EtOAc) on silica gel to give methylated oxindole **49** (13.2 g, 92% yield).

R_f = 0.40 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.9 Hz, 1H), 7.76 (d, *J* = 2.3 Hz, 1H), 7.53–7.48 (m, 2H), 7.21 (td, *J* = 7.7, 1.2 Hz, 1H), 6.95 (td, *J* = 7.6, 1.1 Hz, 1H), 6.69–6.66 (m, 1H), 5.85 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.74 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.26–5.20 (m, 2H), 5.18 (ddt, *J* = 10.4, 2.2, 1.2 Hz, 2H), 4.72–4.63 (m, 2H), 4.54 (ddt, *J* = 13.1, 6.0, 1.4 Hz, 1H), 4.40 (ddt, *J* = 13.0, 6.0, 1.3 Hz, 1H), 3.18–3.13 (m, 1H), 3.13 (s, 3H), 3.05 (ddd, *J* = 9.9, 7.9, 4.7 Hz, 1H), 2.82 (dt, *J* = 13.0, 7.6 Hz, 1H), 2.71 (ddd, *J* = 12.8, 7.6, 4.7 Hz, 1H), 0.90–0.84 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.3, 166.3, 166.2, 150.8, 143.7, 134.4, 133.4, 131.1, 130.8, 128.8, 128.1, 128.0, 127.0, 122.5, 122.1, 119.4, 119.0, 107.6, 67.0, 66.9, 66.9, 59.6, 56.8, 37.9, 26.3, 17.8, 17.8, 11.8; IR (Neat Film NaCl) 2943, 2865, 1747, 1713, 1611, 1538, 1471, 1357, 1223, 1103, 993, 935, 882, 752 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{35}H_{46}BrN_2O_8Si$ $[M+H]^+$: 729.2201; found: 729.2253.

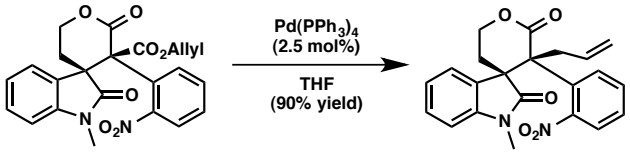


48 *50*

Lactone 50. Acetyl chloride (46.0 μL, 650 μmol, 10.0 equiv) was added to MeOH (1.0 mL) and cooled to 0 °C. The resulting mixture was stirred for 30 min and then the solution of oxindole **48** (21.0 mg, 32.0 μmol, 1.0 equiv) in MeOH (2.0 mL) was added. The reaction was stirred for 2 h at 23 ºC and then heated to 65 °C. The reaction mixture was stirred for 16 h at that temperature. The colorless solution was cooled to ambient temperature, concentrated under reduced pressure and subjected to column

chromatography (4:1 hexanes:EtOAc) to afford the desired lactone **50** (12 mg, 85% yield) as a colorless solid.

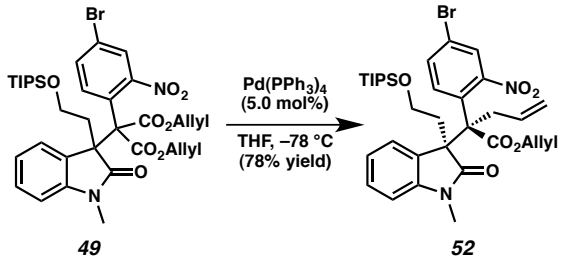
R_f = 0.29 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.4 Hz, 1H), 7.39–7.31 (m, 3H), 7.23–7.15 (m, 2H), 6.82–6.75 (m, 2H), 5.92 (tdd, *J* = 17.1, 10.6, 5.8 Hz, 1H), 5.30 (ddd, *J* = 17.2, 2.7, 1.3 Hz, 1H), 5.21 (ddd, *J* = 10.4, 2.4, 1.2 Hz, 1H), 4.98–4.90 (m, 2H), 4.74 (tdd, *J* = 13.1, 5.8, 1.3 Hz, 1H), 4.71–4.64 (m, 2H), 3.32 (s, 3H), 2.84–2.70 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 166.5, 165.7, 149.2, 142.2, 131.7, 131.4, 131.1, 128.8, 129.7, 129.3, 129.0, 128.9, 125.6, 124.8, 122.5, 118.9, 108.5, 67.5, 65.4, 53.7, 30.2, 26.7; IR (Neat Film NaCl) 2096, 1718, 1637, 1533, 1475, 1358, 1232, 1184, 760 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{21}N_2O_7$ $[M+H]^+$: 437.1343; found: 437.1298.



50 ***51***

Lactone 51. An oven dried flask was charged with ester **50** (1.3 g, 3.05 mmol, 1.0 equiv), sealed with a rubber stopper and evacuated. The flask was brought in a glove box and $Pd(PPh_3)_4$ (84 mg, 75.0 μmol, 0.025 equiv) was added. The flask was brought out of the dry box and THF (60 mL) was added. The reaction mixture was stirred for 5 min and concentrated under reduced pressure. Column chromatography using a Teledyne Isco CombiFlash R_f (SiO_2, 80 g column, 25→50% EtOAc in hexanes) afforded the desired protected alkylation product **51** (1.1 g, 90% yield) as a colorless solid.

R_f = 0.40 (1:1 hexane:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.18 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.12 (dt, *J* = 7.5, 1.7 Hz, 1H), 7.07 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.00 (d, *J* = 7.7 Hz, 1H), 6.85 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.68 (d, *J* = 7.7 Hz, 1H), 6.64 (dt, *J* = 7.7, 1.0 Hz, 1H), 5.55 (tdd, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.33 (ddd, *J* = 11.6, 10.0, 3.4 Hz, 1H), 5.01 (ddd, *J* = 17.1, 3.0, 1.5 Hz, 1H), 4.93 (ddd, *J* = 10.3, 2.7, 1.2 Hz, 1H), 4.68 (td, *J* = 11.6, 4.7 Hz, 1H), 3.45 (tdd, *J* = 15.6, 6.6, 1.3 Hz, 1H), 3.26 (s, 3H), 2.99 (tdd, *J* = 9.0, 6.9, 1.3 Hz, 1H), 2.87 (ddd, *J* = 14.6, 10.0, 4.6 Hz, 1H), 2.21 (ddd, *J* = 14.7, 4.8, 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 168.5, 149.8, 142.1, 133.9, 133.1, 131.1, 130.6, 130.4, 128.6, 127.8, 125.7, 124.8, 122.2, 119.0, 107.6, 64.8, 54.2, 54.0, 43.7, 30.7, 26.5; IR (Neat Film NaCl) 1701, 1614, 1531, 1473, 1356, 1300, 1259, 1202, 1105, 929, 739 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{22}H_{21}N_2O_5$ $[M+H]^+$: 393.1445; found: 393.1458.

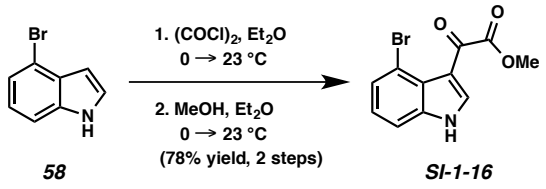


49 ***52***

Allyl 52. To a 500 mL round-bottom flask with a magnetic stir bar was added malonate **49** (11.1 g, 15.2 mmol, 1.0 equiv). The flask was brought into a N_2-filled glove box and then $Pd(PPh_3)_4$ (0.88 g, 0.761 mol, 0.05 equiv) was added. The reaction mixture was brought out from the glove box and treated with THF (152 mL). After 1 h stirring, the solvent was evaporated under reduced pressure. The residue was purified by column

chromatography (1:1 hexane:EtOAc) on silica gel to afford allylated product **52** (8.1 g, 78% yield).

R_f = 0.45 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.7 Hz, 1H), 7.97 (d, *J* = 2.3 Hz, 1H), 7.80 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.22 (td, *J* = 7.7, 1.1 Hz, 1H), 6.83–6.77 (m, 2H), 6.33 (d, *J* = 7.5 Hz, 1H), 5.66 (ddt, *J* = 16.9, 10.3, 6.2 Hz, 1H), 5.56 (ddt, *J* = 17.0, 10.1, 6.9 Hz, 1H), 5.16–5.09 (m, 2H), 4.91 (dq, *J* = 17.1, 1.5 Hz, 1H), 4.84 (ddd, *J* = 10.2, 1.9, 1.1 Hz, 1H), 4.38–4.26 (m, 2H), 3.37 (dd, *J* = 15.3, 7.0 Hz, 1H), 3.23 (s, 3H), 3.21–3.10 (m, 2H), 2.90 (ddd, *J* = 9.5, 8.5, 4.2 Hz, 1H), 2.59–2.51 (m, 1H), 2.16 (ddd, *J* = 12.5, 8.1, 4.3 Hz, 1H), 0.92–0.80 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7, 169.6, 152.1, 144.3, 134.8, 134.5, 133.7, 131.3, 131.1, 128.9, 128.8, 128.70, 125.13, 121.9, 121.8, 119.5, 118.2, 108.1, 65.7, 60.7, 59.5, 55.5, 39.0, 36.6, 26.5, 18.0, 11.9; IR (Neat Film NaCl) 2942, 2865, 1713, 1610, 1538, 1495, 1471, 1353, 1106, 995, 918, 882, 750, 732 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{34}H_{46}BrN_2O_6Si$ $[M+H]^+$: 685.2303; found: 685.2294.

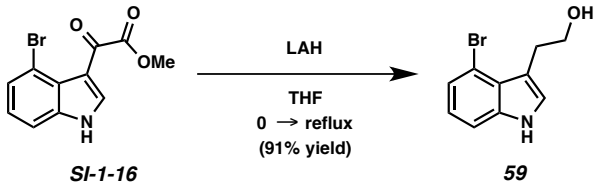


58 ***SI-1-16***

Oxoacetate SI-1-16. To a solution of 4-bromoindole **58** (8.0 g, 40.8 mmol, 1.0 equiv) in Et_2O (204 mL) was added oxalyl chloride (9.25 mL, 102 mmol, 2.5 equiv) dropwise at 0 °C. The reaction mixture was stirred for 16 h at 23 °C. The resulting suspension was filtered and washed with cold ether. The filter cake was dried *in vacuo* to afford the oxoacetyl chloride, which was used without further purification.

To a solution of oxoacetyl chloride in Et_2O (204 mL) was added MeOH (10 mL) at 0 ºC, and stirred for 2 h. The resulting mixture was concentrated *in vacuo* and purified by flash column chromatography (4:1 hexanes:EtOAc) on silica gel to give oxoacetate **SI-1-16** (9.0 g, 78% yield, 2 steps).

R_f = 0.23 (1:1 hexane:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (br, s, 1H), 8.27 (d, J = 3.2 Hz, 1H), 7.52 (dd, J = 7.6, 0.8 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.16 (t, J = 7.8Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, 164.0, 137.8, 136.2, 128.3, 125.3, 125.2, 115.3, 115.0, 111.0, 53.0; IR (Neat Film NaCl) 3206, 1656, 1500, 1410, 1306, 1252, 1196, 1139, 1104, 789, 770, 731 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{11}H_9BrNO_3$ $[M+H]^+$: 281.9760; found: 281.9760.



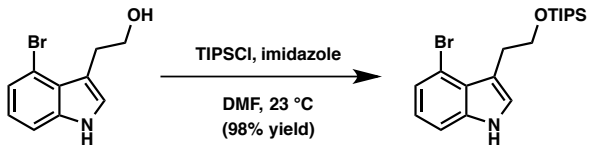
SI-1-16 *59*

Alcohol 59. To a solution of oxoacetate **SI-1-16** (6.8 g, 24.1 mmol, 1.0 equiv) in THF (120 mL) was added LAH (2.8 g, 72.3 mmol, 3.0 equiv) in portions at 0 ºC. The reaction mixture was refluxed for 4 h. When the reaction was done, the solution was cooled to 0 ºC, and quenched by Fieser work-up[2]. The suspension was filtered and the filter cake was washed with EtOAc. The combined organic phases were concentrated *in vacuo*, and extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with brine,

[2] Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis* **1967**, 581-595.

dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 hexane:EtOAc) on silica gel to give alcohol **59** (5.3 g, 91% yield).

R_f = 0.27 (1:1 hexane:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (br, s, 1H), 7.31 (dd, J = 7.6, 0.8 Hz, 1H), 7.28 (dd, J = 7.6, 0.8 Hz, 1H), 7.12 (dd, J = 2.8Hz, 1H), 7.01 (t, J = 7.8 Hz, 1H), 3.97 (t, J = 6.4 Hz, 2H), 3.28 (dt, J = 6.4, 0.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 125.4, 124.1, 123.0, 114.4, 113.1, 110.6, 63.6, 29.5 ; IR (Neat Film NaCl) 3369, 2929, 1899, 1613, 1478, 1425, 1335, 1185, 1029, 913, 815, 770, 736 cm $^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{10}H_{11}BrNO$ $[M+H]^+$: 240.0019; found: 240.0021.

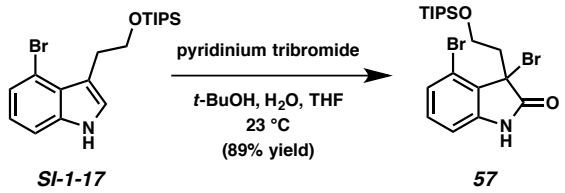


59 ***SI-1-17***

TIPS-ether SI-1-17. To a solution of alcohol **59** (8.1 g, 33.7 mmol, 1.0 equiv) in DMF (112 mL) was added imidazole (5.0 g, 74.2 mmol, 2.2 equiv) and TIPSCl (10.7 mL, 50.6 mmol, 1.5 equiv). After stirring for 3 h at 23 ºC, water (10 mL) was added. The aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (9:1 hexanes:EtOAc) on silica gel to give TIPS-ether **SI-1-17** (13.1 g, 98% yield).

R_f = 0.56 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (br, s, 1H), 7.30–7.25 (m, 2H), 7.12 (d, *J* = 2.4 Hz, 1H), 6.99 (t, *J* = 7.8 Hz, 1H), 4.00 (t, *J* = 7.1 Hz, 2H), 3.27 (t, *J* = 7.1 Hz, 2H), 1.05-1.07 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4, 125.7, 124.4, 123.9, 122.6, 114.3, 114.1, 110.4, 64.9, 29.9, 18.1, 12.0; IR (Neat Film NaCl)

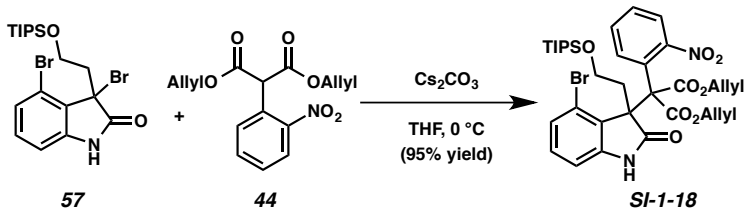
3425, 3286, 2942, 1614, 1561, 1549, 1463, 1425, 1382, 1336, 1246, 1184, 1102, 1064, 1013, 913, 883, 826, 772, 738 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{31}BrNOSi$ $[M+H]^+$: 396.1353; found: 396.1357.



SI-1-17 *57*

3-Bromooxindole 57. To a solution of indole **SI-1-17** (5.0 g, 12.6 mmol, 1.0 equiv) in *t*-BuOH (100 mL), THF (25 mL), and water (1.1 mL) was added pyridinium tribromide (7.9 g, 24.6 mmol, 1.95 equiv). The reaction mixture was stirred for 30 min and then diluted with EtOAc (50 mL) and water (80 mL). The aqueous phase was extracted with EtOAc (3 x 150 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (4:1 hexanes:EtOAc) on silica gel to give 3-bromooxindole **57** (5.5 g, 89% yield).

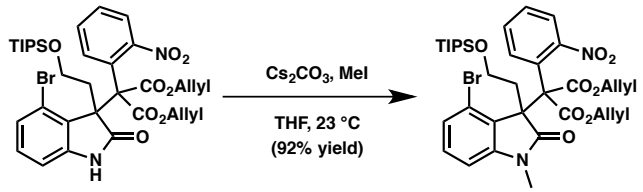
R_f = 0.31 (4:1 hexanes:EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 8.64 (br, s, 1H), 7.19 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.13 (t, *J* = 7.9 Hz, 1H), 6.86 (dd, *J* = 7.6, 1.0 Hz, 1H), 3.66 (ddd, *J* = 10.4, 5.5, 3.3 Hz, 1H), 3.46 (td, *J* = 10.5, 3.8 Hz, 1H), 3.08 (dt, *J* = 13.9, 3.5 Hz, 1H), 2.90 (ddd, *J* = 13.9, 10.6, 5.4 Hz, 1H), 0.87 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 142.3, 131.2, 127.5, 127.0, 120.8, 109.5, 60.6, 56.1, 39.6, 17.8, 11.8; IR (Neat Film NaCl) 2941, 2864, 2109, 1728, 1613, 1583, 1312, 1102, 882, 744 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{30}Br_2NO_2Si$ $[M+H]^+$: 490.0407; found: 490.0340.



57 ***44*** ***SI-1-18***

Oxindole SI-1-18. To a solution of 3-bromooxindole **57** (5.6 g, 11.4 mmol, 1.0 equiv) and malonate **44** (5.2 g, 17.1 mmol, 1.5 equiv) in THF was added Cs_2CO_3 (7.4 g, 22.8 mmol, 2.0 equiv) at 0 ºC. The reaction mixture was stirred for 1 h at 0 ºC. Solids were removed via a filtration through a celite plug and the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (9:1 → 4:1 hexanes:EtOAc) on silica gel to give desired alkylated product **SI-1-18** (5.4 g, 95% yield).

R_f = 0.18 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.90 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.68 (ddd, *J* = 8.5, 7.4, 1.6 Hz, 1H), 7.55 (d, *J* = 5.3 Hz, 1H), 7.51 (td, *J* = 7.7, 1.2 Hz, 1H), 7.02 (d, *J* = 7.9 Hz, 1H), 6.93 (dd, *J* = 8.1, 1.0 Hz, 1H), 6.78 (dd, *J* = 7.6, 1.0 Hz, 1H), 5.92–5.81 (m, 2H), 5.76–5.68 (m, 1H), 5.26–5.18 (m, 2H), 5.17–5.10 (m, 2H), 4.76-4.69 (m, 1H), 4.68-4.63 (m, 1H), 4.51–4.47 (m, 1H), 4.25–4.20 (m, 1H), 3.33–3.26 (m, 1H), 3.23–3.13 (m, 2H), 2.97-2.90 (m, 1H), 0.91 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4, 167.0, 166.0, 144.4, 133.8, 131.8, 131.3, 131.1, 129.8, 129.3, 128.3, 127.5, 126.9, 126.5, 121.82, 119.6, 119.0, 118.9, 108.5, 67.6, 66.6, 66.5, 59.5, 58.3, 32.9, 17.9, 11.9; IR (Neat Film NaCl) 3350, 3086, 2943, 1732, 1612, 1574, 1531, 1446, 1354, 1228, 1169, 1104, 992, 931, 789 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{34}H_{44}BrN_2O_8Si$ $[M+H]^+$: 715.2045; found 715.2055.

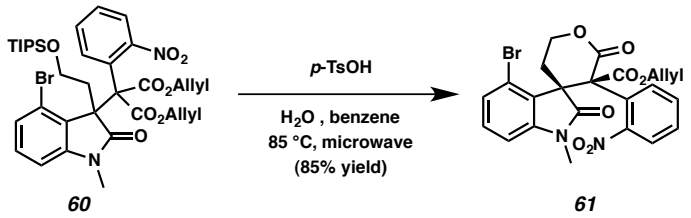


SI-1-18 ***60***

Methyloxindole 60. To a solution of oxindole **SI-1-18** (5.6 g, 11.2 mmol, 1.0 equiv) in THF (56 mL) was added Cs_2CO_3 (10.9 g, 33.6 mmol, 3.0 equiv) and MeI (4.3 mL, 67.2 mmol, 6.0 equiv) at 0 °C. Then, the reaction mixture was stirred for 12 h at 23 °C. After the reaction was done, sat. NH_4Cl was added. The aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (7:1 hexanes:EtOAc) on silica gel to give methylated oxindole **60** (7.5 g, 92% yield).

R_f = 0.38 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.91 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.69 (ddd, *J* = 8.5, 7.3, 1.6 Hz, 1H), 7.54–7.50 (m, 1H), 7.10 (t, *J* = 8.0 Hz, 1H), 6.95 (dd, *J* = 8.1, 1.0 Hz, 1H), 6.78 (dd, *J* = 7.8, 1.0 Hz, 1H), 5.88 (ddt, *J* = 16.5, 10.4, 5.8 Hz, 1H), 5.71 (ddt, *J* = 16.7, 10.2, 6.3 Hz, 1H), 5.27–5.11 (m, 4H), 4.78 (ddt, *J* = 13.1, 6.0, 1.4 Hz, 1H), 4.68 (ddt, *J* = 13.1, 5.6, 1.5 Hz, 1H), 4.47 (ddt, *J* = 12.7, 6.3, 1.2 Hz, 1H), 4.21 (ddt, *J* = 12.8, 6.4, 1.2 Hz, 1H), 3.24 (s, 3H), 3.20–3.15 (m, 3H), 3.00–2.93 (m, 1H), 0.91 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.14, 167.03, 165.81, 152.74, 147.67, 147.67, 133.81, 131.78, 131.42, 131.19, 129.73, 129.21, 128.45, 126.99, 126.85, 126.54, 121.57, 119.44, 106.83, 67.43, 66.37, 65.91, 59.57, 57.96, 32.75, 26.77, 17.90, 11.85; IR (Neat Film NaCl) 2917, 2863, 1721, 1600,

1529, 1450, 1350, 1231, 1088, 923, 883, 852 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{35}H_{46}BrN_2O_8Si$ $[M+H]^+$: 729.2201; found: 729.2240.

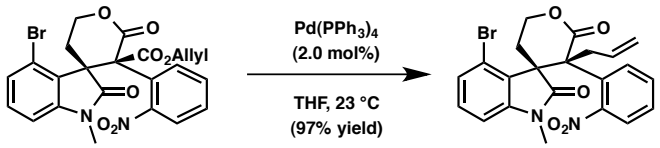


60 *61*

Lactone 61. To a 20 mL microwave vial with a magnetic stir bar were added oxindole **60** (500 mg, 0.69 mmol, 1.0 equiv), *p*-TsOH (520 mg, 2.7 mmol, 4.0 equiv), and benzene (20 mL). The reaction was sealed with a microwave crimp cap and subjected to microwave irradiation in a Biotage Initiator microwave reactor (temperature: 85 ºC, sensitivity: low) with a gradual temperature increase over 10 min (10 ºC increments). After 20 min of stirring, the vial was cooled to ambient temperature and uncapped. The reaction was diluted with EtOAc (10 mL) and quenched by addition of sat. $NaHCO_3$. The phases were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (1:1 hexane:EtOAc) on silica gel to afford lactone **61** (300 mg, 85% yield).

R_f = 0.23 (1:1 hexane:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 8.2, 1.5 Hz, 1H), 8.00–7.98 (m, 1H), 7.71 (dd, *J* = 9.1, 7.6 Hz, 1H), 7.61–7.57 (m, 1H), 7.11 (t, *J* = 8.0 Hz, 1H), 6.96 (dd, *J* = 8.1, 1.0 Hz, 1H), 6.87 (dd, *J* = 7.8, 1.0 Hz, 1H), 5.75–5.66 (m, 1H), 5.18–5.07 (m, 3H), 4.71 (td, *J* = 11.0, 10.4, 7.4 Hz, 1H), 4.55 (ddt, *J* = 12.9, 5.9, 1.3 Hz, 1H), 4.26 (ddt, *J* = 12.9, 6.2, 1.3 Hz, 1H), 3.63 (ddd, *J* = 15.2, 13.1, 7.3 Hz, 1H), 3.34

(s, 3H), 1.69–1.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 165.3, 152.1, 145.9, 136.8, 133.5, 131.9, 130.9, 130.2, 130.2, 127.7, 127.5, 119.3, 107.9, 70.5, 67.1, 64.9, 60.4, 54.5, 27.0, 24.1, 21.1, 14.2; IR (Neat Film NaCl) 2929, 1742, 1713, 1601, 1532, 1456, 1353, 1192, 1112, 1058, 1033, 993, 936, 856, 767 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{20}BrN_2O_7$ $[M+H]^+$: 515.0448; found: 515.0450.

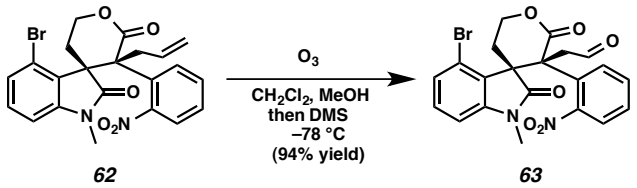


61 ***62***

Allyl 62. To a 250 mL round-bottom flask with a magnetic stir bar was added lactone **61** (2.5 g, 4.9 mmol, 1.0 equiv). The flask was brought into a N_2-filled glove box, and then $Pd(PPh_3)_4$ (0.1 g, 0.097 mmol, 0.02 equiv) was added. The reaction mixture was brought out from the glove box and treated with THF (97 mL). After 5 min stirring, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (1:1 hexane:EtOAc) on silica gel to afford allylated product **62** (2.0 g, 97% yield).

R_f = 0.24 (1:1 hexane:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.20 (dd, *J* = 9.6, 6.5 Hz, 2H), 7.01 (d, *J* = 8.1 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.48 (d, *J* = 8.1 Hz, 1H), 5.52 (ddt, *J* = 16.6, 12.0, 6.4 Hz, 1H), 5.43–5.35 (m, 1H), 4.79–4.72 (m, 3H), 4.32 (td, *J* = 13.7, 7.2 Hz, 1H), 3.31 (s, 3H), 3.13 (dd, *J* = 15.6, 5.0 Hz, 1H), 2.43–2.36 (m, 1H), 1.73 (dd, *J* = 14.7, 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 169.8, 152.4, 146.0, 134.7, 134.3, 130.9, 130.7, 130.4, 128.5, 128.3, 126.0, 125.2, 124.0, 117.8, 107.6, 64.7, 56.7, 54.2, 42.9, 26.4, 23.8; IR (Neat Film

NaCl) 3418, 2923, 1709, 1601, 1532, 1455, 1361, 1292, 1201, 1113, 1069, 986, 917, 777, 736 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{22}H_{20}BrN_2O_5$ $[M+H]^+$: 471.0550; found: 471.0552.

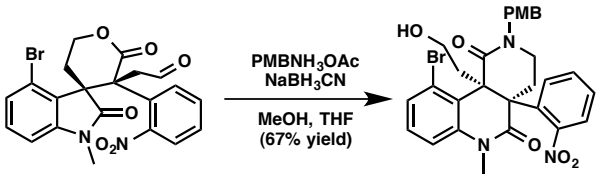


62 *63*

Aldehyde 63. A solution of alkene **62** (47.1 mg, 100 μmol, 1.0 equiv) in a mixture of CH_2Cl_2 (2.5 mL) and MeOH (2.5 mL) in a Schlenk flask hooked up to an ozone generator was purged with oxygen gas at –78 °C (5 min, flow 0.25). Then the ozone generator was turned on (low–medium setting) and an ozone/oxygen gas mixture was bubbled through the reaction. The progress of the reaction was checked via TLC (9:1 hexanes:CH_2Cl_2) in short time intervals (1-2 min). Upon completion of the reaction, the mixture was purged with oxygen gas for 5 min and DMS (36.0 μg, 500 μmol, 5.00 equiv) was added. The reaction mixture was slowly warmed to ambient temperature, and stirred for 16 h. The residue was purified by column chromatography (9:1 CH_2Cl_2:EtOAc) on silica gel to afford aldehyde **63** (44 mg, 94% yield).

R_f = 0.28 (9:1 CH_2Cl_2:EtOAc); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.64 (d, *J* = 3.4 Hz, 1H), 7.83–7.79 (m, 1H), 7.65–7.59 (m, 1H), 7.43–7.39 (m, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 5.15 (ddd, *J* = 12.5, 10.8, 4.7 Hz, 1H), 4.59 (dd, *J* = 11.1, 6.9 Hz, 1H), 3.94 (ddd, *J* = 14.5, 12.6, 7.1 Hz, 1H), 3.22 (s, 3H), 3.08 (d, *J* = 17.0 Hz, 1H), 2.67 (dd, *J* = 17.0, 3.5 Hz, 1H), 1.96 (dd, *J* = 14.7, 4.6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO) δ 198.0, 174.8, 171.0, 151.5, 146.3,

133.3, 131.9, 131.3, 129.9, 129.7, 127.6, 125.5, 124.6, 122.4, 109.3, 65.4, 55.6, 52.6, 49.8, 26.4, 22.3; IR (Neat Film NaCl) 1695, 1600, 1528, 1458, 1354, 1294, 1222, 1118, 850, 787 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{18}BrN_2O_6$ $[M+H]^+$: 473.0343 found:473.0346.

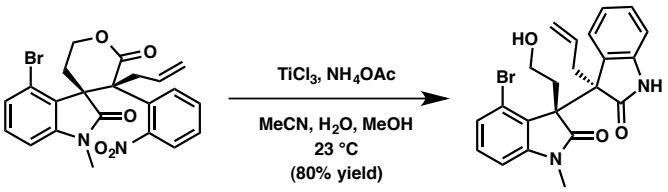


63 *65*

Amide 65. To a suspension of aldehyde **63** (47.3 mg, 100 μmol, 1.0 equiv) and the acetic acid ammonium salt of *para*-methoxybenzylamine (59.2 mg, 300 μmol, 3.0 equiv) in MeOH (4 mL) was added $NaBH_3CN$ (2.60 mg, 300 μmol, 3.0 equiv) in THF (2 mL). The reaction mixture was stirred at ambient temperature for 16 h (conversion of the suspension to a clear, colorless solution usually indicated the completion of the reaction) and then concentrated under reduced pressure. Column chromatography using a Teledyne Isco CombiFlash R_f (SiO_2, 12 g column, 1. 1:1 → 1:4 hexanes:EtOAc) yielded lactam **65** (39.7 mg, 67% yield) as a colorless solid.

R_f = 0.12 (19:1 CH_2Cl_2:MeOH); ^1H NMR (500 MHz, $CDCl_3$) δ 9.10 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.59–7.55 (m, 1H), 7.43 (ddd, *J* = 8.4, 7.3, 1.3 Hz, 1H), 7.36 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.17 (t, *J* = 7.9 Hz, 1H), 7.10 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.06–7.02 (m, 2H), 6.81–6.76 (m, 3H), 4.71 (d, *J* = 14.6 Hz, 1H), 3.98 (d, *J* = 14.6 Hz, 1H), 3.76 (s, 3H), 3.53–3.49 (m, 1H), 3.18 (s, 3H), 3.16–3.08 (m, 3H), 2.90 (ddd, *J* = 9.6, 8.5, 3.2 Hz, 1H), 2.78 (dt, *J* = 9.6, 7.3 Hz, 1H), 2.25 (ddd, *J* = 14.1, 7.1, 3.1 Hz, 1H), 2.14 (ddd, *J* = 14.0, 8.6,

7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7, 171.7, 159.2, 152.6, 147.2, 134.4, 130.9, 130.4, 130.3, 129.9, 129.0, 128.0, 127.9, 126.3, 125.5, 122.4, 114.1, 107.3, 60.1, 58.5, 55.7, 55.4, 47.4, 44.0, 32.1, 27.5, 26.8; IR (Neat Film NaCl) 3459, 2931, 1682, 1601, 1574, 1530, 1457, 1360, 1249, 1176, 1037, 910, 849, 783, 731 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{29}H_{29}BrN_3O_6$ $[M+H]^+$: 594.1234; found: 594.1230.

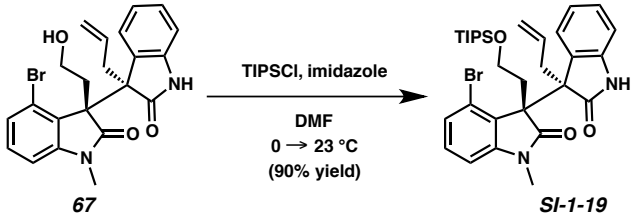


62 ***67***

Bis-oxindole 67. To a solution of lactone **62** (2.4 g, 5.6 mmol, 1.0 equiv) in H_2O (282 mL) and MeOH (565 mL) were added NH_4OAc (43.5 g, 564 mmol, 100.0 equiv) and $TiCl_3$ (10% w/w, 70.3 mL, 56.4 mmol, 10.0 equiv). Then, the reaction was stirred for 12 h at 23 °C. The reaction mixture was diluted with EtOAc (500 mL) and then the phases were separated and the aqueous phase was extracted with EtOAc (3 x 300 mL). The combined organic phases were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (1:1 hexane:EtOAc) on silica gel to afford bis-oxindole **67** (1.99 g, 80% yield).

R_f = 0.10 (1:1 hexane:EtOAc); ^{1}H NMR (500 MHz, DMSO) δ 10.33 (s, 1H), 6.98 (dd, *J* = 8.1, 1.0 Hz, 1H), 6.96–6.87 (m, 2H), 6.77–6.67 (m, 2H), 6.58 (dd, *J* = 7.8, 1.0 Hz, 1H), 6.45 (d, *J* = 7.6 Hz, 1H), 4.96 (ddt, *J* = 16.7, 9.7, 6.9 Hz, 1H), 4.86 (dd, *J* = 17.0, 2.5 Hz, 1H), 4.74 (dd, *J* = 9.9, 2.6 Hz, 1H), 4.39 (t, *J* = 5.0 Hz, 1H), 3.41–3.32 (m, 2H), 3.22–3.13 (m, 1H), 3.03 (s, 3H), 2.86 (dtd, *J* = 10.3, 7.9, 5.5 Hz, 1H), 2.76 (dd, *J* = 13.5, 6.8

Hz, 1H), 2.24 (dt, *J* = 13.2, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, DMSO) δ 177.5, 175.8, 146.5, 142.8, 133.4, 130.2, 128.5, 128.1, 126.9, 126.8, 123.5, 120.4, 119.3, 118.9, 108.9, 107.4, 58.4, 57.2, 56.0, 33.5, 28.9, 26.3; IR (Neat Film NaCl) 2917, 2356, 1697, 1599, 1574, 1455, 1349, 1184, 910, 752 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{22}H_{22}BrN_2O_3$ $[M+H]^+$: 441.0808; found 441.0812.

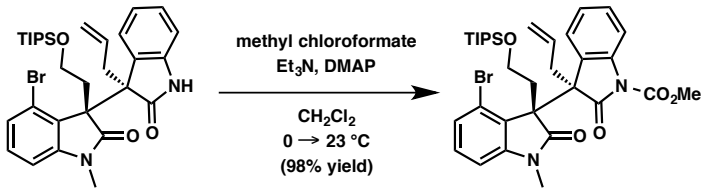


67 ***SI-1-19***

TIPS-ether SI-1-19. Bis-oxindole **67** (1.66 g, 3.76 mmol, 1.0 equiv) was dissolved in DMF (18.8 mL) to which TIPSCl (1.61 mL, 7.52 mmol, 2.0 equiv) and imidazole (1.02 g, 15.0 mmol, 4.0 equiv) were added at 0 °C. The reaction was slowly warmed to 23 °C, and stirred for 12 h. The reaction mixture was extracted with EtOAc (3 x 40 mL), and washed with brine. The combined organic phases were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 hexanes:EtOAc) on silica gel to afford TIPS protected compound **SI-1-19** (2.02 g, 90% yield).

R_f = 0.20 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 1H), 6.99–6.92 (m, 2H), 6.87–6.80 (m, 2H), 6.76 (t, *J* = 7.5 Hz, 1H), 6.49 (d, *J* = 7.8 Hz, 1H), 6.28 (d, *J* = 7.7 Hz, 1H), 5.10 (ddt, *J* = 16.9, 9.9, 7.1 Hz, 1H), 4.97 (dd, *J* = 17.1, 2.1 Hz, 1H), 4.77 (dd, *J* = 9.9, 2.2 Hz, 1H), 3.73 (ddd, *J* = 8.7, 5.7, 2.6 Hz, 1H), 3.57 (dd, *J* = 13.6, 7.1 Hz, 1H), 3.47–3.41 (m, 2H), 3.05 (s, 3H), 2.97 (dd, *J* = 13.6, 7.1 Hz, 1H), 2.60 (ddd, *J* = 15.0,

11.5, 5.6 Hz, 1H), 0.87–0.82 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 175.8, 146.3, 140.9, 132.6, 129.3, 128.2, 127.0, 126.8, 123.7, 120.6, 119.4, 119.1, 108.5, 106.2, 60.9, 57.7, 56.8, 33.0, 28.8, 25.9, 17.8, 17.8, 11.8; IR (Neat Film NaCl) 3191, 3081, 2942, 2865, 2251, 2699, 1602, 1471, 1337, 1236, 1108, 995, 920, 736 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{31}H_{42}BrN_2O_3Si$ $[M+H]^+$: 597.2143; found 597.2141.

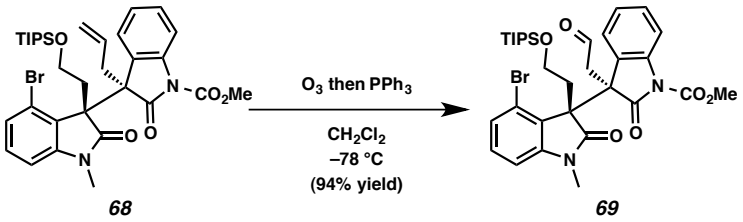


SI-1-19 ***68***

Carbamate 68. To a stirred solution of bis-oxindole **SI-1-19** (350 mg, 0.59 mmol, 1.0 equiv) in CH_2Cl_2 (5.86 mL) were added DMAP (7 mg, 0.059 mmol, 0.1 equiv), Et_3N (0.812 mL, 5.9 mmol, 10.0 equiv), and methyl chloroformate (0.16 mL, 1.76 mmol, 3.0 equiv) at 0 ºC. The reaction was slowly warmed to 23 ºC, and stirred for 12 h. The solvent was concentrated *in vacuo*, and then the residue was purified by column chromatography (4:1 hexanes:EtOAc) to afford carbamate **68** (377 mg, 98% yield).

R_f = 0.61 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (dt, *J* = 8.2, 0.8 Hz, 1H), 7.05 (ddd, *J* = 8.1, 6.1, 2.9 Hz, 1H), 6.96 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.92–6.91 (m, 2H), 6.82 (t, *J* = 7.9 Hz, 1H), 6.25 (dd, *J* = 7.8, 1.0 Hz, 1H), 5.06 (ddt, *J* = 16.6, 9.6, 6.9 Hz, 1H), 5.00 – 4.95 (m, 1H), 4.81–4.78 (m, 1H), 4.00 (s, 3H), 3.72 (ddd, *J* = 10.2, 5.7, 3.1 Hz, 1H), 3.61 (ddt, *J* = 13.8, 6.9, 1.0 Hz, 1H), 3.43 (td, *J* = 10.4, 3.9 Hz, 1H), 3.33–3.28 (m, 1H), 3.04–2.99 (m, 1H), 3.02 (s, 3H), 2.62 (ddd, *J* = 14.0, 10.6, 5.7 Hz, 1H), 0.87–0.81 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 174.2, 151.3, 146.1, 139.5,

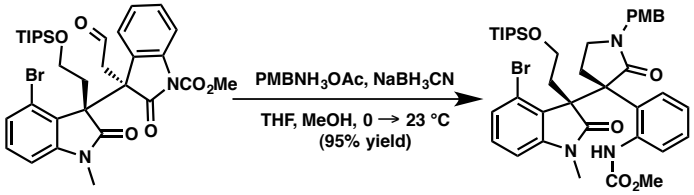
132.0, 129.6, 128.6, 127.1, 126.5, 126.2, 123.2, 122.7, 119.9, 119.0, 113.9, 106.3, 60.7, 58.4, 57.3, 53.7, 33.4, 28.9, 26.0, 17.7, 11.8; IR (Neat Film NaCl) 2942, 2865, 2089, 1722, 1602, 1463, 1348, 1201, 1243, 1166, 1104, 1026, 920, 883, 736, 772 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{33}H_{44}BrN_2O_5Si$ $[M+H]^+$: 655.2197; found 655.2199.



Aldehyde 69. To a 25 mL round bottom flask with magnetic stir bar was added alkene **68** (260 mg, 0.40 mmol, 1.0 equiv) and CH_2Cl_2 (2.0 mL). The flask was connected to an ozone generator, and purged with oxygen gas (flow: 0.5), for 5 min at –78 ºC and then ozone gas (flow: 0.5) was bubbled through into the reaction solution for 10 min at –78 ºC. After the reaction was done, oxygen gas was bubbled into the reaction mixture for 20 min and PPh_3 (313mg, 1.19 mmol, 3.0 equiv) was added. The reaction mixture was slowly warmed to ambient temperature, stirred for 16 h, and then concentrated under reduced pressure. The residue was purified by column chromatography (4:1 hexanes:EtOAc) to afford aldehyde **69** (245 mg, 94% yield).

R_f = 0.13 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.46 (d, *J*=1.0 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.06–7.01 (m, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.88–6.82 (m, 2H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.23 (d, *J* = 7.8 Hz, 1H), 4.33 (d, *J* = 19.4 Hz, 1H), 4.02 (s, 3H), 3.72 (ddd, *J* = 9.3, 5.6, 2.7 Hz, 1H), 3.58 (dd, *J* = 19.3, 1.2 Hz, 1H), 3.42 (td, *J* = 10.3, 3.4 Hz, 1H), 3.23 (dt, *J* = 14.0, 3.4 Hz, 1H), 2.99 (s, 3H), 2.56–2.48 (m, 1H), 0.86–0.79 (m,

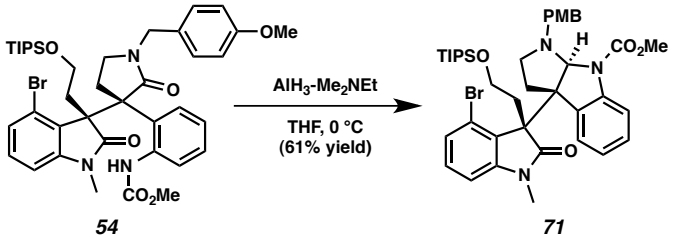
21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 175.4, 174.4, 151.3, 146.0, 140.0, 129.9, 128.8, 127.2, 126.5, 125.2, 122.6, 121.4, 119.3, 114.1, 106.5, 60.6, 58.2, 53.8, 52.8, 44.6, 28.9, 26.0, 17.7, 11.8; IR (Neat Film NaCl) 2942, 2865, 2255, 1773, 1718, 1603, 1576, 1459, 1351, 1295, 1245, 1163, 1108, 914, 883, 771, 732 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{32}H_{41}BrN_2O_6Si$ $[M+H]^+$: 657.1990; found: 657.1991.



Lactam 54. To a solution of aldehyde **69** (100 mg, 0.15 mmol, 1.0 equiv) and *p*-methoxybenzylammonium acetate (90 mg, 0.46 mmol, 3.0 equiv) in methanol (7.6 mL) was added $NaBH_3CN$ (21 mg, 0.30 mmol, 2.0 equiv) in THF (3.8 mL) at 0 °C. The reaction mixture was slowly warmed to 23 °C and stirred overnight. The reaction mixture was washed with EtOAc (3 x 10 mL), and brine. The combined organic phases were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 hexanes:EtOAc) on silica gel to afford lactam **54** (112 mg, 95% yield).

R_f = 0.20 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.14 (s, 1H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 2H), 7.15–7.10 (m, 2H), 7.05 (q, *J* = 8.5, 7.9 Hz, 2H), 6.88 (t, *J* = 7.7 Hz, 1H), 6.85–6.80 (m, 2H), 6.49 (d, *J* = 7.7 Hz, 1H), 4.80 (d, *J* = 14.4 Hz, 1H), 4.36 (d, *J* = 14.4 Hz, 1H), 3.78 (s, 3H), 3.70 (s, 1H), 3.63 (s, 3H), 3.52 (td, *J* = 6.9, 3.6 Hz, 1H), 3.43–3.36 (m, 1H), 3.27 (td, *J* = 9.3, 5.7 Hz, 1H), 3.17 (t, *J* = 9.6 Hz, 1H),

2.87 (ddd, *J* = 13.3, 6.1, 3.5 Hz, 1H), 2.66–2.60 (m, 1H), 2.56 (s, 3H), 2.54–2.49 (m, 1H), 0.85 (q, *J* = 3.8 Hz, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.94, 173.92, 159.34, 154.32, 146.89, 139.65, 132.30, 130.98, 130.07, 129.75, 128.88, 128.50, 127.57, 127.42, 126.71, 126.45, 121.74, 120.99, 120.75, 114.18, 107.15, 68.21, 61.31, 60.86, 60.43, 55.34, 51.42, 47.61, 44.98, 31.20, 25.78, 17.86, 11.88; IR (Neat Film NaCl) 2944, 2865, 2073, 1716, 1667, 1604, 1513, 1455, 1247, 1227, 1109, 1069, 1034, 883, 761 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{40}H_{53}BrN_3O_6Si$ $[M+H]^+$: 778.2882; found: 778.2879.

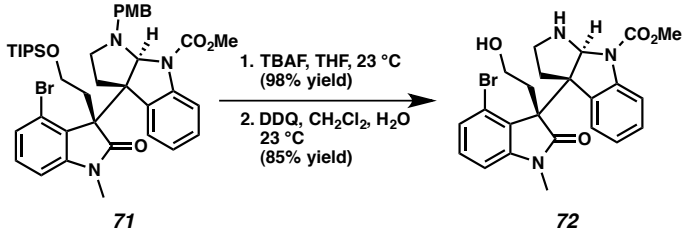


54 *71*

Aminal 71. To a solution of amide **54** (0.32 g, 0.41 mmol, 1.0 equiv) in THF (41.1 mL) was added AlH_3-Me_2NEt (0.5 M in toluene; 1.64 mL, 0.82 mmol, 2.0 equiv) dropwise at 0 ºC. The reaction was stirred for 2 h and quenched with MeOH. The reaction solution was concentrated *in vacuo* and purified by column chromatography (4:1 hexanes:EtOAc) to afford aminal **71** (0.19 g, 61% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.47 (m, 1H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.04–6.93 (m, 3H), 6.80 (dq, *J* = 14.8, 7.4 Hz, 4H), 6.39–6.24 (m, 2H), 4.00 (d, *J* = 13.7 Hz, 1H), 3.92–3.79 (m, 4H), 3.78 (s, 3H), 3.68 (dd, *J* = 10.2, 5.0 Hz, 1H), 3.57–3.43 (m, 1H), 3.03 (s, 3H), 2.65 (m, 4H), 2.26 (dt, *J* = 15.0, 7.2 Hz, 1H), 2.09 (dd, *J* = 11.9, 4.6 Hz, 1H), 0.87 (d, *J* = 3.2 Hz, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 175.7, 160.6, 146.3, 141.7, 133.9, 132.2, 130.3, 130.1, 126.8, 123.6, 123.2, 123.1, 115.1, 114.6, 113.9, 107.3, 107.1, 106.6,

82.4, 60.7, 60.1, 57.2, 55.3, 52.6, 51.0, 31.9, 31.1, 30.7, 29.7, 26.1, 17.7, 11.8; IR (Neat Film NaCl) 2943, 1722, 1604, 1464, 1386, 1344, 1254, 1107, 1033, 885, 760 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{40}H_{53}BrN_3O_5Si$ $[M+H]^+$: 762.2932; found: 762.2936.



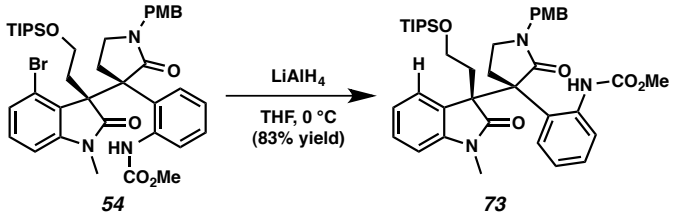
71 *72*

Aminal 72. To a solution of silyl ether **71** (98 mg, 0.13 mmol, 1.0 equiv) in THF (1.28 mL) was added TBAF (0.15 mL, 1.0 M solution in THF) at 0 ºC. The reaction mixture was stirred for 3 h at 23 ºC and quenched with sat. NH_4Cl. The reaction mixture was washed with EtOAc (3 x 1.5 mL), and brine. The combined organic phases were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (2:1 hexanes:EtOAc) on silica gel to afford PMB-protected aminal compound (78 mg, 98% yield).

To a solution of PMB-protected aminal compound (96 mg, 0.16 mmol, 1.0 equiv) in CH_2Cl_2 (3.1 mL) and H_2O (0.8 mL) was added DDQ (53 mg, 0.23 mmol, 1.5 equiv) in portions over 30 min at 0 ºC. The reaction mixture was stirred for 2 h at 23 ºC. The solution was diluted with CH_2Cl_2 and quenched with sat. $NaHCO_3$. The reaction mixture was washed with CH_2Cl_2 (3 x 2.5 mL), and brine. The combined organic phases were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column

chromatography (4:1 CH_2Cl_2:acetone) on silica gel to afford aminal **72** (64 mg, 85% yield).

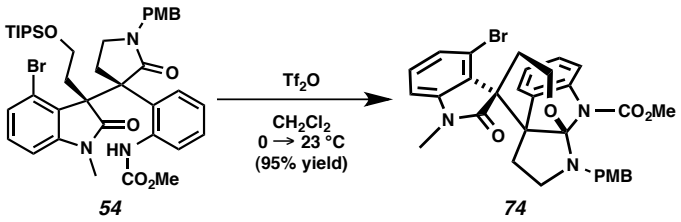
R_f = 0.31 (4:1 CH_2Cl_2:acetone); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.1 Hz, 1H), 7.01–6.96 (m, 2H), 6.84 (p, *J* = 8.6 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 6.73 (t, *J* = 7.5 Hz, 1H), 6.48 (s, 1H), 6.35 (d, *J* = 7.8 Hz, 1H), 3.87 (d, *J* = 17.2 Hz, 3H), 3.66 (ddd, *J* = 10.8, 6.8, 3.7 Hz, 1H), 3.35 (dt, *J* = 10.9, 5.3 Hz, 1H), 3.11 (s, 3H), 3.01 (dd, *J* = 10.0, 6.5 Hz, 1H), 2.8–2.76 (m, 1H), 2.76–2.62 (m, 2H), 2.50 (td, *J* = 10.3, 4.7 Hz, 1H), 2.24 (br, s, 1H), 2.20 (dd, *J* = 12.7, 4.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 152.8, 146.1, 142.7, 130.4, 129.7, 128.9, 127.4, 127.2, 122.8, 121.6, 118.5, 113.8, 106.8, 80.5, 63.4, 60.0, 57.2, 52.6, 44.6, 35.1, 31.5, 26.3; IR (Neat Film NaCl) 3417, 2925, 1710, 1604, 1487, 1458, 1392, 1362, 1272, 1093, 756 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{25}BrN_3O_4$ $[M+H]^+$: 486.1023; found: 486.1014.



54 ***73***

Oxindole 73. To a solution of lactam **54** (10.6 mg, 0.0136 mmol, 1.0 equiv) in THF (1.36 ml) was added $LiAlH_4$ (5.2 mg, 0.136 mmol, 10.0 equiv) in portions at 0 ºC. The reaction was stirred for 1 h and then quenched with sat. NaCl. The reaction mixture was washed with EtOAc (3 x 2 mL) and brine. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 hexanes:EtOAc) to afford oxindole **73** (7.9 mg, 83% yield).

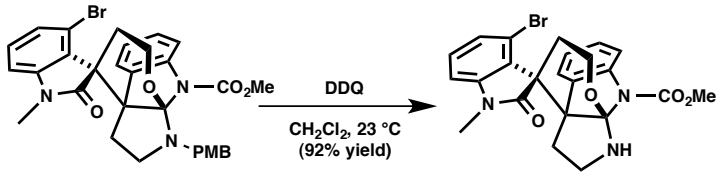
R_f = 0.25 (4:1 hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.64 (br, s, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 7.60 (s, 1H), 7.13 (d, *J* = 8.4 Hz, 3H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 7.7 Hz, 1H), 6.97 (s, 1H), 6.83 (d, *J* = 8.3 Hz, 3H), 6.38 (d, *J* = 7.7 Hz, 1H), 4.55 (d, *J* = 14.5 Hz, 1H), 4.44 (d, *J* = 14.5 Hz, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 3.31–3.27 (m, 1H), 3.24 (br, s, 2H), 3.14 (br, s, 1H), 3.05–3.00 (m, 1H), 2.85 (s, 3H), 2.72 (s, 1H), 2.52 (t, *J* = 9.9 Hz, 1H), 2.41 (br, s, 1H), 0.86 (q, *J* = 7.5, 6.2 Hz, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5, 159.4, 154.7, 143.7, 129.6, 129.4, 129.3, 129.2, 128.6, 128.4, 127.7, 127.5, 127.4, 122.2, 122.0, 121.8, 114.3, 107.3, 60.0, 56.6, 55.4, 52.1, 47.1, 44.0, 34.3, 29.9, 26.0, 18.0, 12.0; IR (Neat Film NaCl) 2941, 1732, 1711, 1610, 1515, 1442, 1375, 1248, 1225, 1105, 1070, 1036, 750 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{40}H_{54}N_3O_6Si$ $[M+H]^+$: 700.3776; found: 700.3776.



54 *74*

PMB-Propellane hexacycle 74. To a solution of lactam **54** (70 mg, 0.090 mmol, 1.0 equiv) in CH_2Cl_2 (9 mL) was added Tf_2O (45 μL, 0.27 mmol, 3.0 equiv) dropwise at 0 °C. The reaction mixture was slowly warmed to 23 °C and stirred for 2 h. The solution was neutralized by adding sat. $NaHCO_3$. The reaction mixture was washed with CH_2Cl_2 (3 x 5 mL) and brine. The combined organic phases were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (2:1 hexanes:EtOAc) on silica gel to afford propellane hexacycle **74** (52 mg, 95% yield).

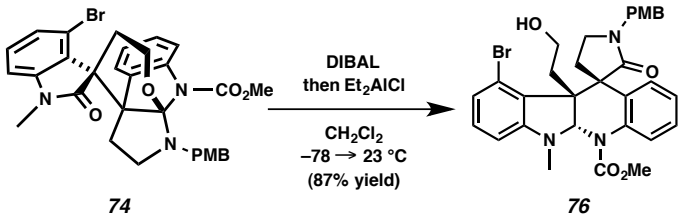
R_f = 0.25 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.16–7.11 (m, 3H), 6.95–6.93 (m, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 6.73 (td, *J* = 7.6, 1.1 Hz, 1H), 6.60 (t, *J* = 4.4 Hz, 1H), 6.36 (dd, *J* = 7.6, 1.5 Hz, 1H), 4.53 (dt, *J* = 11.5, 5.8 Hz, 1H), 4.47 (d, *J* = 14.9 Hz, 1H), 4.23–4.18 (m, 1H), 3.87 (s, 3H), 3.76 (s, 3H), 3.72 (d, *J* = 13.7 Hz, 1H), 3.21 (s, 3H), 3.01 (ddd, *J* = 14.4, 11.7, 8.4 Hz, 1H), 2.77–2.73 (m, 1H), 2.54 (q, *J* = 9.3 Hz, 1H), 2.13 (td, *J* = 8.8, 5.3 Hz, 1H), 1.93 (dd, *J* = 14.2, 6.3 Hz, 1H), 1.80–1.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 158.5, 153.7, 145.8, 142.5, 132.0, 130.9, 130.1, 129.5, 129.4, 128.9, 128.1, 124.6, 122.9, 121.5, 116.1, 113.6, 112.1, 106.6, 58.2, 57.0, 55.4, 54.4, 52.7, 50.2, 47.9, 33.7, 26.6, 23.2; IR (Neat Film NaCl) 1718, 1601, 1575, 1513, 1484, 1455, 1365, 1245, 1134, 1099, 1037, 912, 764, 731 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{31}H_{31}BrN_3O_5$ $[M+H]^+$: 604.1442; found: 604.1433.



74 *75*

Propellane hexacycle 75. To a solution of oxindole **74** (46 mg, 0.075 mmol, 1.0 equiv) in CH_2Cl_2 (3.8 mL) and H_2O (0.94 mL) was added DDQ (34 mg, 0.15 mmol, 2.0 equiv) at 0 ºC. The reaction mixture was slowly warmed to 23 ºC and stirred for 2 h. The solution was quenched with sat. $NaHCO_3$. The reaction mixture was washed with CH_2Cl_2 (3 x 3.0 mL) and brine. The combined organic phases were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 CH_2Cl_2:acetone) on silica gel to afford propellane hexacycle **75** (33 mg, 92% yield).

R_f = 0.1 (1:1 hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 1H), 7.16 (t, *J* = 7.9 Hz, 1H), 6.98 (dd, *J* = 21.2, 8.0 Hz, 2H), 6.71 (d, *J* = 7.7 Hz, 2H), 6.25 (d, *J* = 7.6 Hz, 1H), 4.45 (td, *J* = 11.1, 6.6 Hz, 1H), 4.10–4.02 (m, 1H), 3.92 (s, 3H), 3.23 (s, 3H), 3.14 (dd, *J* = 9.4, 6.0 Hz, 1H), 3.08–2.92 (m, 1H), 2.68–2.51 (m, 2H), 1.82 (td, *J* = 14.2, 12.6, 7.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 153.6, 145.8, 142.4, 133.3, 130.4, 129.7, 129.2, 128.1, 125.7, 123.2, 122.5, 114.3, 111.6, 106.9, 58.5, 55.7, 53.8, 53.0, 43.3, 36.5, 26.6, 23.5; IR (Neat Film NaCl) 2958, 1713, 1602, 1485, 1446, 1373, 1242, 1095, 754 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{23}BrN_3O_4$ $[M+H]^+$: 484.0866; found: 484.0874.

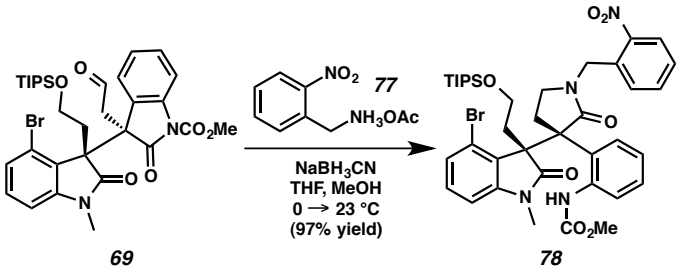


74 *76*

Aminal 76. To a solution of propellane hexacycle **74** (13 mg, 0.021 mmol, 1.0 equiv) in CH_2Cl_2 (2.14 mL) was added DIBAL (1.0 M in THF; 0.11 mL, 0.11 mmol, 5 equiv) dropwise at –78 ºC. The reaction mixture was stirred for 1 h and warmed to 0 ºC. DIBAL (1.0 M in THF; 21.4 μL, 21.4 μmol, 1 equiv) was added dropwise at 0 ºC and stirred for 1 h. Then, DIBAL (1.0 M in THF; 21.4 mL, 21.4 mmol, 1 equiv) was added one more time dropwise at 0 ºC and stirred for another 1 h. The reaction mixture was warmed to 23 ºC and Et_2AlCl (1.0 M in hexane; 42.8 mL, 42.8 mmol, 2 equiv) was added dropwise. The mixture was stirred for 30 min and quenched with sat. NH_4Cl and sat. potassium sodium tartrate. The reaction mixture was washed with CH_2Cl_2 (3 x 2.0 mL)

and brine. The combined organic phases were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (1:1 hexane:EtOAc) on silica gel to afford propellane aminal **76** (10.5 mg, 87% yield).

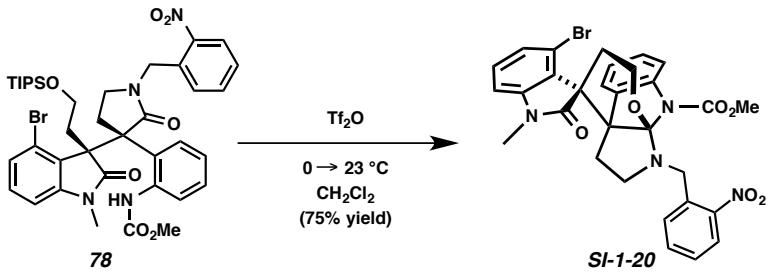
R_f = 0.25 (1:1 hexane:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.7 Hz, 1H), 7.24–7.22 (m, 2H), 7.17 (s, 1H), 7.08–7.03 (m, 1H), 6.87–6.84 (m, 2H), 6.82 (t, *J* = 7.9 Hz, 1H), 6.71 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.23 (br, s, 1H), 6.01 (dd, *J* = 7.9, 1.0 Hz, 1H), 5.15 (d, *J* = 14.5 Hz, 1H), 3.94 (d, *J* = 14.5 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.72–3.63 (m, 2H), 3.40 (dd, *J* = 9.5, 7.7 Hz, 1H), 3.12 (td, *J* = 9.7, 1.5 Hz, 1H), 3.10–3.04 (m, 1H), 2.89–2.82 (m, 1H), 2.48 (s, 3H), 2.32 (dt, *J* = 14.2, 7.2 Hz, 1H), 1.65 (dt, *J* = 14.7, 9.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 159.2, 152.7, 139.2, 136.3, 134.0, 130.4, 129.8, 128.8, 126.8, 126.7, 126.1, 125.2, 125.0, 122.9, 122.4, 114.2, 104.7, 83.3, 61.0, 60.5, 55.4, 53.6, 53.4, 47.1, 44.3, 35.3, 33.0, 31.1; IR (Neat Film NaCl) 2922, 1689, 1597, 1512, 1444, 1334, 1249, 1178, 1032, 754 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{31}H_{33}BrN_3O_5$ $[M+H]^+$: 606.1598; found: 606.1592.



Amide 78. To a solution of aldehyde **69** (100 mg, 0.13 mmol, 1.0 equiv) and *o*-nitrobenzylammonium acetate **77** (97 mg, 0.38 mmol, 3.0 equiv) in MeOH (7.6 mL) was added $NaBH_3CN$ (21 mg, 0.26 mmol, 2.0 equiv) in THF (3.8 mL) at 0 ºC. The reaction mixture was slowly warmed to ambient temperature and stirred for 12 h. Then, H_2O (5

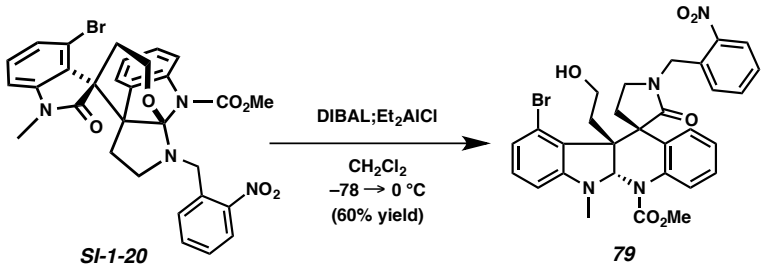
mL) was added and extracted with EtOAc (3 x 20 mL), and washed with brine. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 hexanes:EtOAc) on silica gel to afford *o*-nitrobenzyl protected amide **78** (116 mg, 97% yield).

R_f = 0.35 (2:1 hexanes:EtOAc); (Due to the distinct presence of rotameric isomers, the ^{1}H NMR and ^{13}C NMR contained extra peaks. See the attached spectrum), ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.63 (s, 1H), 8.06–7.97 (m, 2H), 7.51 (td, *J* = 7.6, 1.5 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.25–7.18 (m, 2H), 7.13 (dd, *J* = 14.1, 8.2 Hz, 2H), 7.05 (t, *J* = 7.9 Hz, 1H), 6.97–6.90 (m, 1H), 6.53 (d, *J* = 7.6 Hz, 1H), 5.32 (d, *J* = 16.5 Hz, 1H), 4.71 (dd, *J* = 16.4, 6.5 Hz, 1H), 3.70–3.63 (m, 2H), 3.57 (td, *J* = 6.3, 2.9 Hz, 1H), 3.55–3.51 (m, 1H), 3.35–3.26 (m, 2H), 2.92 (ddd, *J* = 13.1, 5.4, 3.3 Hz, 1H), 2.84 (s, 1H), 2.69 (ddd, *J* = 19.4, 8.7, 5.3 Hz, 2H), 2.63 (s, 3H), 0.85 (t, *J* = 4.1 Hz, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 175.4, 154.4, 148.7, 147.1, 139.7, 134.1, 132.1, 131.2, 130.0, 129.4, 128.8, 128.7, 127.6, 126.6, 126.0, 125.3, 122.1, 121.8, 121.3, 107.3, 60.9, 60.6, 60.4, 51.6, 46.0, 45.1, 31.8, 31.6, 25.9, 17.9, 11.9; IR (Neat Film NaCl) 3418, 2943, 2865, 2251, 1717, 1601, 1527, 1456, 1338, 1313, 1282, 1227, 1113, 1069, 911, 883, 857, 730 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{39}H_{50}BrN_4O_7Si$ $[M+H]^+$: 793.2627; found: 793.2658.



Propellane hexacycle SI-1-20. To a solution of amide **78** (54.1 mg, 0.087 mmol, 1.0 equiv) in CH_2Cl_2 (6.82 mL), was added Tf_2O (34 mL, 0.26 mmol, 3.0 equiv) dropwise at 0 ºC. The reaction mixture was slowly warmed to 23 ºC, and stirred for 2 h. After the reaction was done, the solution was brought to pH 10.5-11.0 by addition of sat. $NaHCO_3$. The reaction mixture was extracted with EtOAc (3 x 6 mL) and washed with brine. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (2:1 hexanes:EtOAc) on silica gel to afford propellane hexacycle **SI-1-20** (39.6 mg, 75% yield).

R_f = 0.46 (1:1 hexane:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.72–7.58 (m, 1H), 7.46–7.40 (m, 2H), 7.30 (ddd, *J* = 8.0, 6.7, 2.2 Hz, 1H), 7.21–7.14 (m, 1H), 6.99–6.93 (m, 2H), 6.81–6.76 (m, 1H), 6.64 (dd, *J* = 7.4, 1.4 Hz, 1H), 6.36 (dd, *J* = 7.7, 1.3 Hz, 1H), 4.61 (d, *J* = 16.6 Hz, 1H), 4.54 (d, *J* = 18.2 Hz, 1H), 4.45 (td, *J* = 11.4, 6.5 Hz, 1H), 4.18–4.11 (m, 1H), 3.72 (d, *J* = 9.4 Hz, 3H), 3.21 (s, 3H), 3.11–3.02 (m, 1H), 2.96–2.87 (m, 1H), 2.51 (dt, *J* = 14.4, 9.0 Hz, 2H), 1.94–1.81 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 153.5, 148.9, 145.8, 144.4, 142.1, 136.2, 132.9, 131.0, 130.0, 129.6, 129.1, 128.1, 127.3, 125.1, 124.3, 123.1, 116.1, 111.9, 106.8, 64.5, 58.4, 56.5, 54.5, 52.6, 50.0, 47.9, 33.9, 26.5, 22.8; IR (Neat Film NaCl) 2953, 2360, 1721, 1599, 1573, 1524, 1483, 1455, 1367, 1242, 1134, 1088, 1134, 1088, 947, 856, 761, 733 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{30}H_{28}BrN_4O_6$ $[M+H]^+$: 619.1187; found: 619.1188.

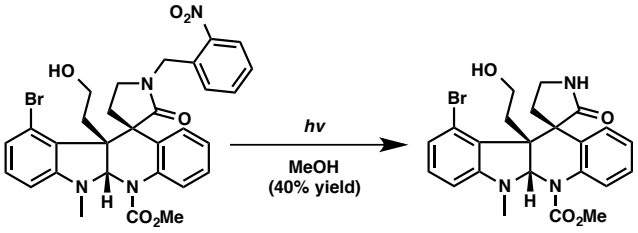


SI-1-20 *79*

Aminal 79. To a solution of propellane hexacyclic oxindole **SI-1-20** (14.6 mg, 0.024 mmol, 1.0 equiv) in CH_2Cl_2 (2.4 mL) was added DIBAL (1.0 M in THF; 0.12 mL, 0.12 mmol, 5 equiv) dropwise at –78 °C. After the reaction mixture was stirred for 1 h at –78 °C, the solution was warmed to 0 °C and DIBAL (1.0 M in THF; 24 mL, 0.024 mmol, 1.0 equiv) was added dropwise. The mixture was stirred for 1 h at 0 °C, and more DIBAL (1.0 M in THF; 24 mL, 0.024 mmol, 1.0 equiv) was added dropwise. The reaction mixture was stirred for 1 h at 0 °C, and warmed to 23 °C. To the reaction mixture was added Et_2AlCl (1.0 M in hexanes; 48 mL, 0.048 mmol, 2.0 equiv) dropwise. The reaction was stirred for 30 min and quenched with aq NH_4Cl (1 mL) and aq potassium sodium tartrate (1 mL). The reaction mixture was washed with EtOAc (3 x 3 mL), and brine. The combined organic phases were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (1:1 hexane:EtOAc) on silica gel to afford aminal **79** (8.9 mg, 60% yield).

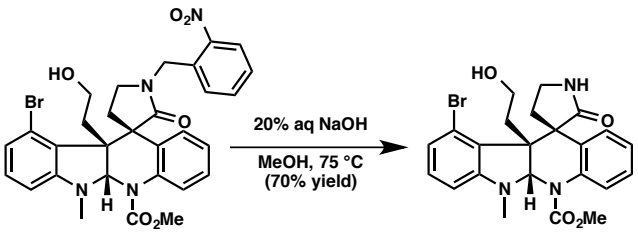
R_f = 0.12 (1:1 hexane:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.58 (td, *J* = 7.6, 1.3 Hz, 1H), 7.50–7.48 (m, 1H), 7.44 (ddd, *J* = 8.6, 7.4, 1.5 Hz, 1H), 7.37–7.34 (m, 1H), 7.23–7.19 (m, 1H), 7.09–7.05 (m, 1H), 6.81 (t, *J* = 7.9 Hz, 1H), 6.69 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.26 (s, 1H), 6.01 (dd, *J* = 7.9, 0.9 Hz, 1H), 5.41 (d, *J* = 16.3 Hz, 1H), 4.56 (d, *J* = 16.2 Hz, 1H), 3.86 (s, 3H), 3.73–3.64 (m, 2H), 3.56 (td, *J* = 9.5, 7.4 Hz, 1H), 3.24–3.18 (m, 1H), 3.09 (ddd, *J* = 13.6, 8.6, 5.3 Hz, 1H), 2.95 (ddd, *J* =

14.2, 7.4, 1.7 Hz, 1H), 2.48 (s, 3H), 2.35 (ddd, *J* = 13.2, 8.5, 6.2 Hz, 1H), 1.78 (dt, *J* = 14.2, 9.4 Hz, 1H), 1.74 (br, s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 171.3 152.6, 148.9, 138.8, 136.3, 133.7, 132.1, 130.4, 129.7, 128.4, 126.9, 126.2, 126.0, 125.0, 124.8, 122.7, 122.2, 104.6, 83.2, 64.4, 60.7, 60.4, 53.3, 53.1, 45.3, 44.5, 35.2, 33.0, 31.0; IR (Neat Film NaCl) 2955, 2357, 1694, 1595, 1524, 1444, 1335, 1281, 1073, 1032, 911, 857, 835, 730 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{30}H_{30}BrN_4O_6$ $[M+H]^+$: 621.1343; found: 621.1286.



79 ***53***

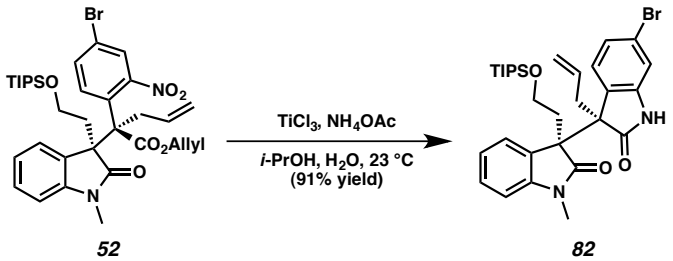
Amide 53. A solution of aminal **79** (21.5 mg, 0.035 mmol, 1.0 equiv) in anhydrous MeOH (3.5 mL) in a Pyrex flask was purged with N_2 for 5 min. The reaction mixture was irradiated in a cylindrical photoreactor with 254 nm lamps under N_2 for 3 h and concentrated. The residue was purified by column chromatography (4:1 CH_2Cl_2:acetone) on silica gel to afford aminal **53** (6.7 mg, 40% yield). See below for characterization data.



79 ***53***

Amide 53. To a solution of *o*-nitrobenzyl protected aminal **79** (10.8 mg, 0.017 mmol, 1.0 equiv) in MeOH (0.8 mL) was added 20% aq NaOH (0.2 mL) and the mixture was stirred for 4 h at 75 ºC. After the reaction mixture was cooled to 23 ºC, it was diluted with water and extracted with EtOAc (3 x 2 mL). The organic layer was washed with brine, dried over $MgSO_4$, concentrated *in vacuo*. The residue was purified by column chromatography (4:1 CH_2Cl_2:acetone) to afford compound **53** (5.9 mg, 70% yield).

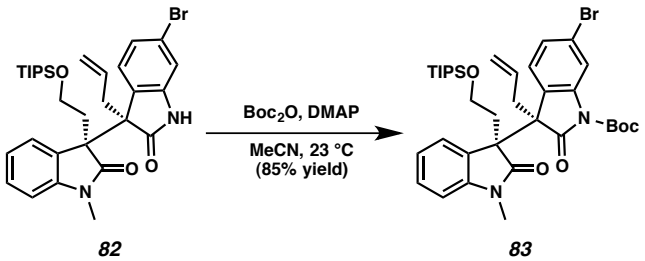
R_f = 0.18 (4:1 CH_2Cl_2:acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.45 (m, 1H), 7.19 (td, *J* = 7.6, 1.4 Hz, 1H), 7.05 (td, *J* = 7.7, 1.4 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 6.69 (dt, *J* = 8.0, 1.0 Hz, 1H), 6.60 (br, s, 1H), 6.25 (br, s, 1H), 5.99 (dd, *J* = 7.9, 0.9 Hz, 1H), 3.87 (s, 3H), 3.74–3.63 (m, 2H), 3.55 (td, *J* = 9.4, 7.3 Hz, 1H), 3.33 (ddd, *J* = 9.8, 8.8, 1.5 Hz, 1H), 3.17 (ddd, *J* = 13.6, 8.4, 5.6 Hz, 1H), 3.03–2.96 (m, 1H), 2.49 (s, 3H), 2.36 (ddd, *J* = 13.2, 8.2, 6.3 Hz, 1H), 1.92 (dt, *J* = 14.0, 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 155.4, 152.9, 138.6, 136.4, 130.4, 126.9, 126.6, 126.1, 125.0, 123.4, 122.5, 104.6, 83.2, 76.9, 60.9, 60.6, 53.5, 52.3, 40.4, 35.8, 35.2, 31.1; IR (Neat Film NaCl) 3418, 2955, 2357, 1693, 1593, 1446, 1335, 1282, 1032, 836, 754 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{25}BrN_3O_4$ $[M+H]^+$: 486.1023; found: 486.1004.



Bis-oxindole 82. To a solution of oxindole **52** (7.65 g, 11.2 mmol, 1.0 equiv) in H_2O (187 mL) and *i*-PrOH (373 mL) were added NH_4OAc (43.2 g, 0.560 mol, 50 equiv) and

$TiCl_3$ (20% w/w, 69.2 mL, 0.11 mol, 10 equiv). Then, the reaction was stirred for 12 h at 23 ºC. The reaction mixture was diluted with EtOAc (200 mL) and then the phases were separated and the aqueous phase was extracted with EtOAc (3 x 300 mL). The combined organic phases were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (2:1 hexanes:EtOAc) on silica gel to afford bis-oxindole **82** (6.10 g, 91% yield).

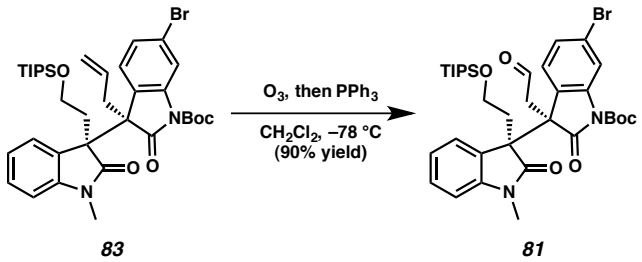
R_f = 0.68 (1:1 hexane:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (br, s, 1H), 7.31–7.26 (m, 1H), 6.98–6.90 (m, 2H), 6.88 (dd, *J* = 2.7, 1.5 Hz, 1H), 6.82 (s, 1H), 6.73–6.69 (m, 1H), 6.21 (br, s, 1H), 5.14 (ddt, *J* = 17.1, 10.0, 7.1 Hz, 1H), 4.96 (ddd, *J* = 17.1, 2.0, 0.9 Hz, 1H), 4.86–4.80 (m, 1H), 3.42–3.31 (m, 2H), 3.25 (ddd, *J* = 9.9, 7.5, 4.7 Hz, 1H), 3.05 (dt, *J* = 14.5, 7.4 Hz, 1H), 2.90 (s, 3H), 2.79 (dd, *J* = 13.0, 6.9 Hz, 1H), 2.34 (ddd, *J* = 13.4, 6.8, 4.7 Hz, 1H), 0.92–0.81 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.14, 176.05, 144.65, 142.73, 131.37, 128.80, 127.92, 127.73, 125.58, 124.41, 124.20, 121.97, 121.73, 119.88, 112.70, 108.15, 59.61, 56.86, 54.80, 35.16, 32.66, 25.91, 17.82, 11.77; IR (Neat Film NaCl) 3270, 2942, 2865, 1716, 1611, 1471, 1377, 1241, 1105, 916, 883, 791, 734 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{31}H_{42}BrN_2O_3Si$ $[M+H]^+$: 597.2143; found: 597.2187.



82 ***83***

Carbamate 83. To a stirred solution of bis-oxindole **82** (2.63 g, 4.40 mmol, 1.0 equiv) in CH_2Cl_2 (44 mL) were added DMAP (1.08 g, 8.80 mmol, 2.0 equiv) and Boc_2O (1.92 g, 8.80 mmol, 2.0 equiv) at 0 ºC. The reaction was slowly warmed to 23 ºC, and stirred for 12 h. The solvent was concentrated *in vacuo* and then the residue was purified by column chromatography (4:1 hexanes:EtOAc) to afford protected compound **83** (2.6 g, 85% yield).

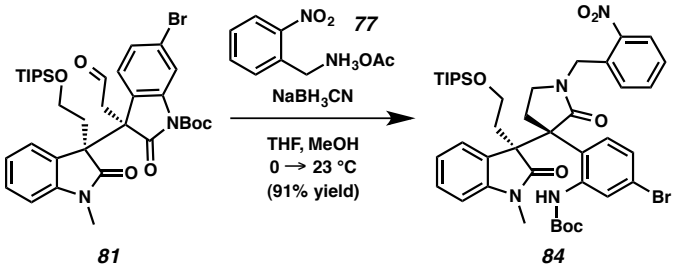
R_f = 0.52 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 1.9 Hz, 1H), 7.25 (td, *J* = 7.7, 1.3 Hz, 1H), 7.14–7.09 (m, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 6.71–6.67 (m, 1H), 6.62–6.53 (m, 1H), 6.47 (s, 1H), 5.10 (ddt, *J* = 17.0, 9.9, 7.1 Hz, 1H), 4.99–4.92 (m, 1H), 4.83 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.43 (dd, *J* = 13.3, 7.3 Hz, 1H), 3.35 (dt, *J* = 9.9, 7.2 Hz, 1H), 3.20 (ddd, *J* = 9.9, 7.7, 4.8 Hz, 1H), 2.94 (s, 3H), 2.90 (dd, *J* = 13.9, 8.0 Hz, 1H), 2.81–2.75 (m, 1H), 2.30 (ddd, *J* = 13.2, 7.2, 4.8 Hz, 1H), 1.51 (s, 9H), 0.89–0.84 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.60, 173.73, 148.46, 144.52, 141.67, 131.26, 128.95, 127.19, 126.28, 126.06, 125.32, 124.15, 122.43, 121.69, 120.23, 118.24, 108.06, 84.08, 59.56, 57.36, 55.29, 34.77, 32.70, 27.92, 25.97, 17.82, 11.76; IR (Neat Film NaCl) 2941, 2866, 1770, 1716, 1610, 1471, 1420, 1370, 1342, 1287, 1246, 1153, 1105, 1067, 1023, 919, 882, 845, 752, 733 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{31}H_{42}BrN_2O_3Si$ $[M+H\text{-}Boc]^+$: 597.2143 found: 597.2181.



83 ***81***

Aldehyde 81. To a 100 mL round bottom flask with magnetic stir bar was added alkene **83** (2.61 g, 0.00374 mol, 1.0 equiv). The flask was connected to an ozone generator and purged with oxygen gas (flow: 0.5) for 5 min at –78 ºC. Then, ozone gas (flow: 0.5) was bubbled through into the reaction solution for 30 min at –78 ºC. After the reaction was done, oxygen gas was bubbled into the reaction mixture for 20 min and PPh_3 (2.95 g, 0.0112 mol, 3.0 equiv) was added. The reaction mixture was slowly warmed to ambient temperature, stirred for 16 h, and then concentrated under reduced pressure. The residue was purified by column chromatography (4:1 hexanes:EtOAc) to afford aldehyde **81** (2.4 g, 90% yield).

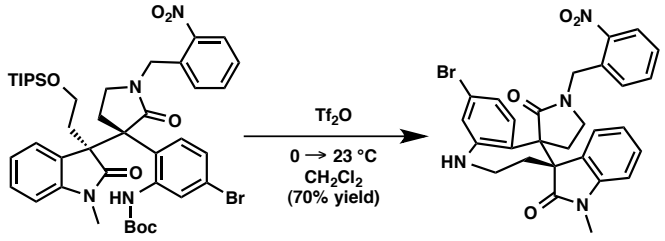
R_f = 0.23 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.45 (s, 1H), 8.00 (d, *J* = 1.8 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.21 (td, *J* = 7.8, 1.2 Hz, 1H), 6.93 (br, s, 1H), 6.77 (t, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 5.99 (br, s, 1H), 4.43 (d, *J* = 19.1 Hz, 1H), 3.39 (dd, *J* = 19.2, 1.1 Hz, 1H), 3.31 (dt, *J* = 9.9, 7.3 Hz, 1H), 3.15 (ddd, *J* = 9.9, 8.0, 4.7 Hz, 1H), 3.10 (s, 3H), 2.64 (dt, *J* = 12.8, 7.6 Hz, 1H), 2.20 (ddd, *J* = 12.6, 7.5, 4.7 Hz, 1H), 1.43 (s, 9H), 0.91–0.82 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.38, 175.36, 173.47, 148.07, 144.01, 142.38, 129.18, 126.57, 126.04, 125.73, 124.51, 123.59, 122.99, 121.72, 118.74, 108.14, 83.83, 59.25, 53.78, 53.64, 44.47, 33.42, 27.83, 26.20, 17.80, 11.74; IR (Neat Film NaCl) 1941, 2865, 1771, 1722, 1609, 1471, 1422, 1370, 1345, 1291, 1245, 1152, 1109, 1070, 1015, 882, 845, 793, 749 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{30}H_{40}BrN_2O_4Si$ $[M+H\text{-}Boc]^+$: 599.1935 found: 597.1971.



Amide 84. To a solution of aldehyde **81** (200 mg, 0.29 mmol, 1.0 equiv) and *o*-nitrobenzylammonium acetate **77** (182 mg, 0.86 mmol, 3.0 equiv) in MeOH (14.3 mL) was added $NaBH_3CN$ (39 mg, 0.57 mmol, 2.0 equiv) in THF (7.2 mL) at 0 °C. The reaction mixture was slowly warmed to ambient temperature, and stirred for 12 h. Then, H_2O (10 mL) was added. The mixture was extracted with EtOAc (3 x 20 mL) and washed with brine. The combined organic phases were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 hexanes:EtOAc) on silica gel to afford *o*-nitrobenzyl protected amide **84** (221 mg, 91% yield).

R_f = 0.22 (4:1 hexanes:EtOAc); (due to the distinct presence of rotameric isomers, the ^1H NMR and ^{13}C NMR contained extra peaks. See attached the spectrum behind); ^1H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.9 Hz, 1H), 8.36 (d, *J* = 2.3 Hz, 1H), 8.09 (s, 1H), 8.06–7.96 (m, 2H), 7.83 (s, 1H), 7.62 (d, *J* = 7.1 Hz, 2H), 7.46 (t, *J* = 8.5 Hz, 1H), 7.42–7.30 (m, 6H), 7.23 (d, *J* = 8.3 Hz, 3H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.93–6.86 (m, 2H), 6.81 (d, *J* = 7.5 Hz, 2H), 6.10 (d, *J* = 7.6 Hz, 1H), 5.00 (d, *J* = 16.9 Hz, 1H), 4.91 (d, *J* = 17.3 Hz, 1H), 4.58 (d, *J* = 17.3 Hz, 1H), 4.27 (s, 1H), 3.75 (s, 1H), 3.37 (t, *J* = 7.4 Hz, 1H), 3.28 (s, 3H), 3.23 (d, *J* = 4.9 Hz, 1H), 3.18 (d, *J* = 7.2 Hz, 4H), 3.14–3.06 (m, 3H), 2.99 (dt, *J* = 9.2, 4.7 Hz, 2H), 2.80 (dd, *J* = 13.3, 9.4 Hz, 3H), 2.43 (t, *J* = 7.8 Hz, 1H), 2.25–2.13 (m, 1H), 2.06 (d, *J* = 8.9 Hz, 2H), 0.87 (d, *J* = 1.9 Hz, 21H), 0.80 (d, *J* = 2.7 Hz,

21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, 176.9, 174.6, 152.9, 148.3, 148.1, 145.0, 144.7, 141.9, 134.5, 134.1, 131.8, 131.0, 129.1, 128.8, 128.8, 128.5, 128.4, 128.4, 128.2, 127.0, 125.3, 125.2, 125.1, 124.9, 123.2, 122.9, 122.1, 121.7, 108.4, 107.9, 79.9, 59.9, 59.2, 59.1, 52.9, 44.6, 44.2, 44.1, 36.4, 34.6, 31.3, 31.1, 28.6, 28.3, 26.5, 26.3, 18.2, 18.0, 17.9, 12.2, 12.1, 11.9; IR (Neat Film NaCl) 3329, 2941, 2866, 1701, 1612, 1531, 1496, 1473, 1344, 1280, 1159, 1103, 1072, 1024, 914, 885, 753, 731, 688 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{42}H_{56}BrN_4O_7Si$ $[M+H]^+$: 835.3096; found: 835.3105.

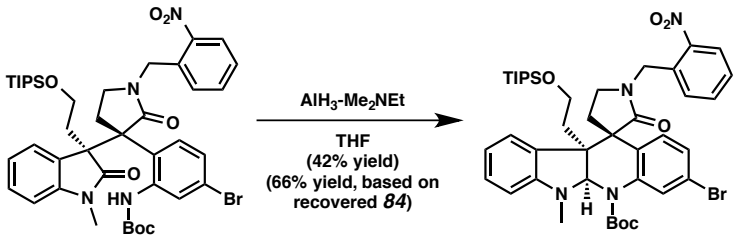


84 ***86***

Tetrahydroazepine 86. To a solution of amide **84** (20 mg, 0.0239 mmol, 1.0 equiv) in CH_2Cl_2 (2.39 mL), was added Tf_2O (0.0121 ml, 0.0718 mmol, 3.0 equiv) dropwise at 0 ºC. The reaction mixture was slowly warmed to 23 ºC, and stirred for 2 h. After the reaction was done, the solution was brought to pH 10.5-11.0 by addition of sat. $NaHCO_3$. The reaction mixture was extracted with EtOAc (3 x 3 mL) and washed with brine. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (2:1 hexanes:EtOAc) on silica gel to afford tetrahydroazepine **86** (9.4 mg, 70% yield).

R_f = 0.33 (2:1 hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.2 Hz, 1H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 6.98 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H),

6.73 (t, *J* = 7.7 Hz, 1H), 6.70 (dd, *J* = 8.4, 1.3 Hz, 1H), 6.18 (d, *J* = 7.6 Hz, 1H), 5.08 (d, *J* = 17.1 Hz, 1H), 4.47 (d, *J* = 17.1 Hz, 1H), 3.89 (s, br, 1H), 3.81–3.75 (m, 1H), 3.31–3.26 (m, 2H), 3.23 (td, *J* = 9.3, 8.5, 4.1 Hz, 1H), 3.18 (d, *J* = 1.5 Hz, 3H), 2.97–2.93 (m, 1H), 2.93–2.89 (m, 1H), 2.70 (dt, *J* = 13.7, 8.6 Hz, 1H), 1.45–1.39 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.4, 175.1, 150.3, 148.3, 143.8, 134.2, 132.5, 131.1, 131.1, 129.4, 129.2, 128.3, 127.7, 126.0, 125.3, 125.0, 124.6, 121.7, 121.3, 108.0, 58.8, 50.3, 44.6, 44.1, 43.4, 36.1, 27.6, 26.4; IR (Neat Film NaCl) 3343, 2942, 1703, 1611, 1588, 1524, 1471, 1357, 1285, 1137, 1106, 1065, 984, 858, 732 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{28}H_{26}BrN_4O_4$ $[M+H]^+$: 561.1132; found: 561.1165.

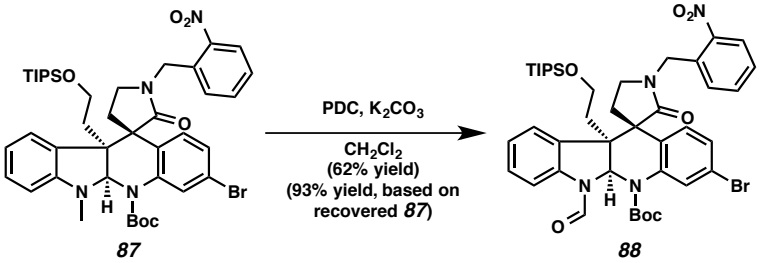


84 ***87***

Aminal 87. Oxindole **84** (20 mg, 0.0239 mmol, 1.0 equiv) was dissolved in THF (2.39 mL) and cooled to 0 ºC. AlH_3-Me_2NEt (0.5 M in toluene; 0.096 mL, 0.0478 mmol, 2.0 equiv) was added dropwise at 0 ºC. The solution was stirred for 2 h and quenched with MeOH. The solution was concentrated under reduced pressure and purified by column chromatography (4:1 hexanes:EtOAc) on silica gel to afford cyclized compound **87** (8.23 mg, 42% yield; 66% yield based on recovered starting material).

R_f = 0.33 (4:1 hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.9 Hz, 1H), 7.40 (s, 1H), 7.35 (dt, *J* = 19.0, 7.4 Hz, 2H), 7.06–7.03 (m, 1H), 6.96 (d, *J* = 7.6 Hz, 1H),

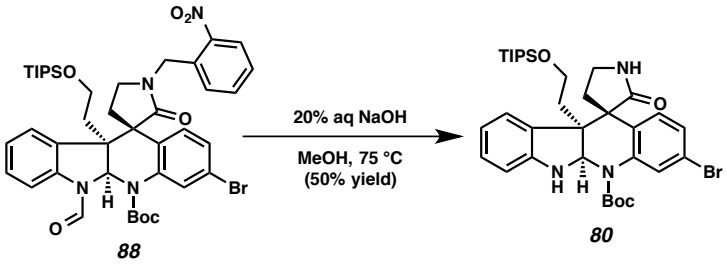
6.93–6.91 (m, 2H), 6.90–6.86 (m, 1H), 6.40 (t, *J* = 7.4 Hz, 1H), 6.20 (s, 1H), 6.12 (d, *J* = 7.8 Hz, 1H), 4.75 (q, *J* = 16.8, 16.1 Hz, 2H), 3.78 (td, *J* = 10.7, 10.3, 6.0 Hz, 1H), 3.53 (q, *J* = 8.8 Hz, 1H), 3.46 (t, *J* = 9.3 Hz, 1H), 3.16–3.07 (m, 2H), 2.84(s, 3H), 2.75 (dd, *J* = 13.4, 6.0 Hz, 1H), 2.50 (td, *J* = 11.4, 5.6 Hz, 1H), 2.23–2.16 (m, 1H), 1.47 (s, 9H), 0.95 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 153.6, 150.9, 148.7, 139.9, 133.5, 132.2, 131.0, 130.6, 128.9, 128.5, 128.2, 127.8, 125.2, 124.8, 123.2, 120.6, 116.2, 104.3, 80.9, 79.6, 59.9, 56.9, 54.12, 44.49, 43.5, 39.5, 31.0, 29.6, 28.2, 26.3, 17.9, 11.9; IR (Neat Film NaCl) 2941, 2865, 1697, 1603, 1528, 1491, 1333, 1302, 1168, 1100, 992, 882, 739 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{42}H_{56}BrN_4O_6Si$ $[M+H]^+$: 819.3147; found: 819.3153.



87 ***88***

Formyl 88. To a solution of methyl protected compound **87** (11 mg, 0.0161 mmol, 1.0 equiv) in CH_2Cl_2 (1.61 mL) was added PDC (9.1 mg, 0.0241 mmol, 1.5 equiv) at 23 ºC. After being stirred at 23 ºC for 12 h, the reaction mixture was quenched with water. The reaction mixture was washed with CH_2Cl_2 (3 x 2 mL), and brine. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 hexanes:EtOAc) on silica gel to afford aldehyde **88** (7.0 mg, 62% yield; 93% yield based on recovered starting material).

R_f = 0.55 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.96 (dd, *J* = 7.8, 2.5 Hz, 2H), 7.38 (q, *J* = 8.5, 8.0 Hz, 2H), 7.33 (s, br, 1H), 7.14–6.99 (m, 4H), 6.96–6.87 (m, 3H), 4.83 (s, br, 1H), 4.70 (d, 15Hz, 1H), 3.64–3.54 (m, 2H), 3.51 (t, *J* = 9.4 Hz, 1H), 3.26 (q, *J* = 10.0, 7.4 Hz, 1H), 3.11 (q, *J* = 10.9 Hz, 1H), 2.79 (dd, *J* = 13.2, 5.8 Hz, 1H), 2.58 (dt, *J* = 13.1, 7.8 Hz, 1H), 2.19 (ddd, *J* = 12.9, 7.9, 4.7 Hz, 1H), 1.44 (s, br, 9H), 0.98–0.76 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 161.4, 153.1, 148.7, 141.3, 138.3, 133.5, 131.8, 131.5, 131.2, 129.3, 128.7, 128.4, 125.1, 124.9, 124.2, 123.5, 121.1, 116.0, 81.9, 75.1, 59.4, 57.2, 54.1, 44.6, 43.6, 39.6, 29.7, 28.1, 26.3, 17.9, 17.9, 11.8; IR (Neat Film NaCl) 2942, 2866, 1683, 1591, 1527, 1489, 1393, 1323, 1280, 1155, 1096, 911, 733 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{42}H_{54}BrN_4O_7Si$ $[M+H]^+$: 833.2940; found: 833.2960.



Amide 80. To a solution of aldehyde **88** (14.8 mg, 0.0177 mmol, 1.0 equiv) in MeOH (0.4 mL) was added 20% aq NaOH (0.2 mL) and the reaction mixture was stirred for 4 h at 75 ºC. The reaction mixture was diluted with EtOAc (1 mL) and the aqueous phase was extracted with EtOAc (3 x 1 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 hexanes:EtOAc) on silica gel to afford desired amide **80** (5.9 mg, 50% yield).

R_f = 0.21 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.14 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.06 (dt, *J* = 7.7, 3.7 Hz, 3H), 6.70 (t, *J* = 7.4 Hz, 1H), 6.60 (d, *J* = 7.7 Hz, 1H), 6.17 (s, 1H), 5.72 (s, 1H), 3.69–3.61 (m, 1H), 3.48 (dt, *J* = 10.8, 5.6 Hz, 1H), 3.07 (m, 1H), 2.85 (m, 1H), 2.77 (m, 2H), 2.33 (d, *J* = 7.9 Hz, 1H), 1.59 (s, 9H), 0.91 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 153.9, 149.2, 138.2, 130.4, 128.9, 127.1, 126.8, 126.5, 124.4, 120.6, 119.5, 109.4, 82.5, 60.3, 55.6, 53.4, 38.9, 35.7, 31.2, 28.6, 18.4, 11.9; IR (Neat Film NaCl) 3401, 2941, 2865, 1696, 1487, 1465, 1314, 1163, 1094, 882, 740 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{34}H_{49}BrN_3O_4Si$ $[M+H]^+$: 670.2670; found: 670.2679.

1.5. References and Notes

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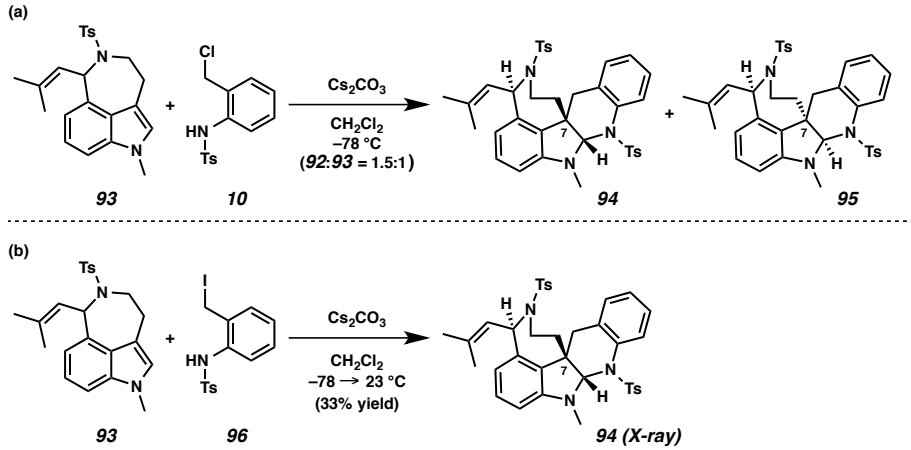
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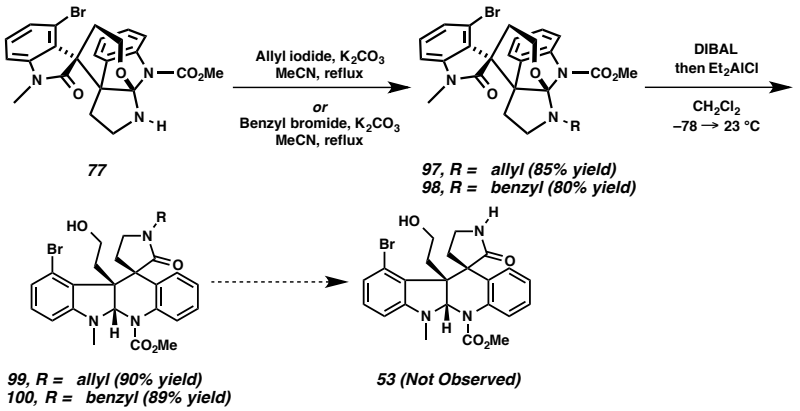
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APPENDIX 1

Spectra Relevant to Chapter 1:

The Evolution of a Unified, Stereodivergent Approach to the Synthesis of Communesin F and Perophoramidine

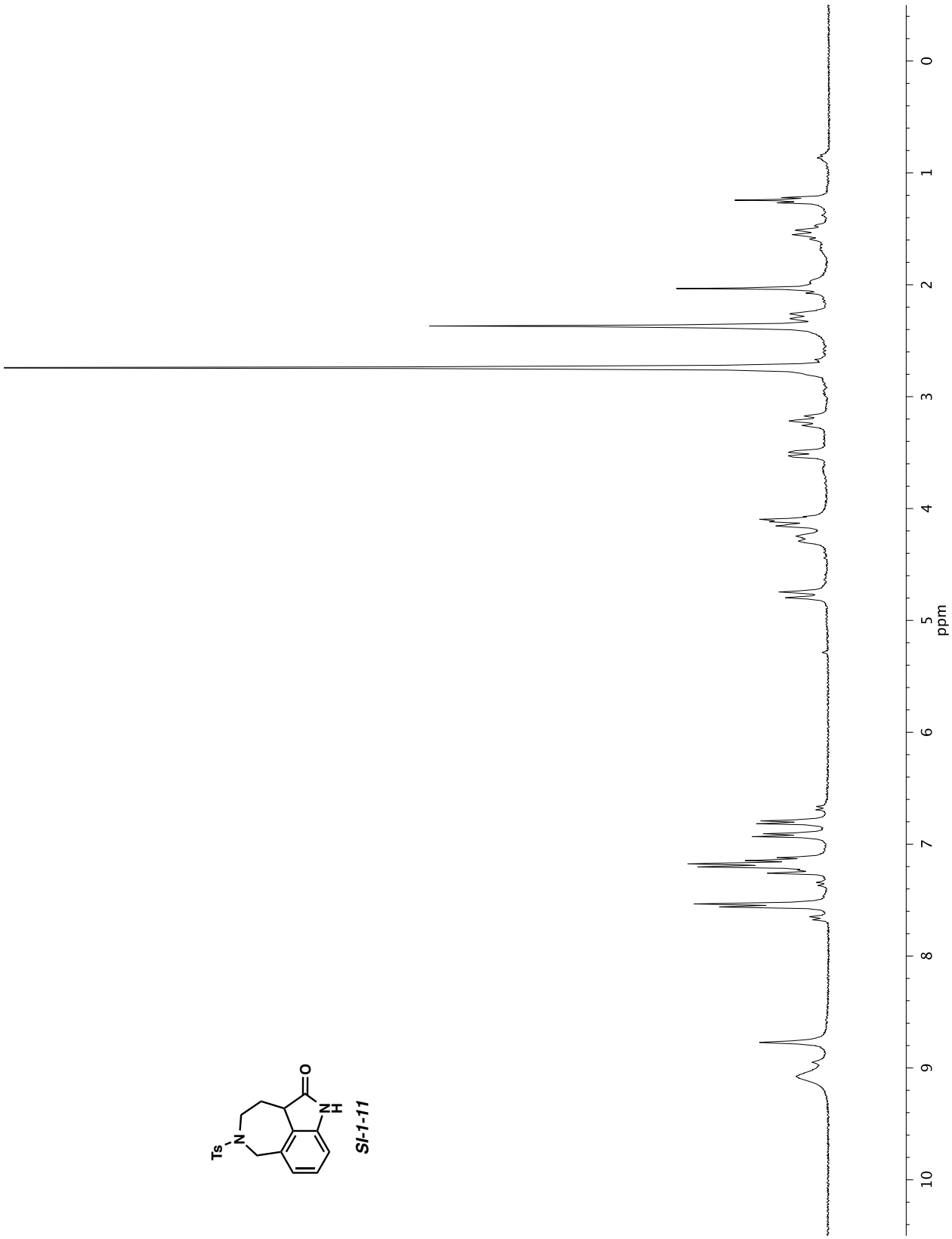


Figure A1.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **SI-1-11**.

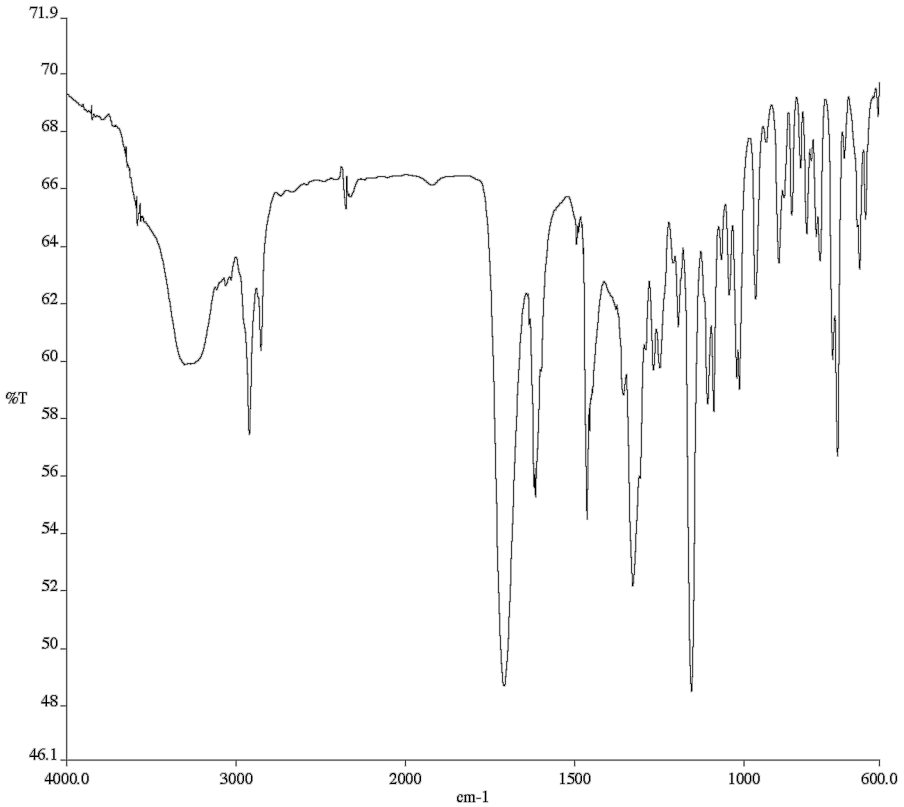


Figure A1.2. Infrared spectrum (Thin Film, NaCl) of compound **SI-1-11**.

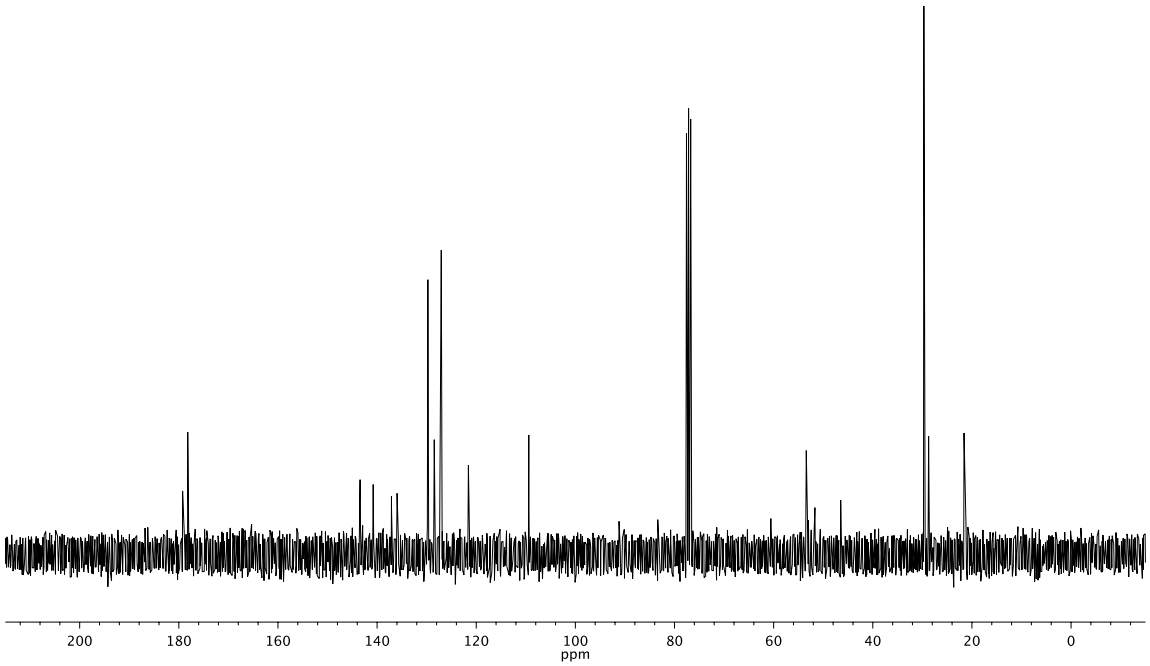


Figure A1.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **SI-1-11**.

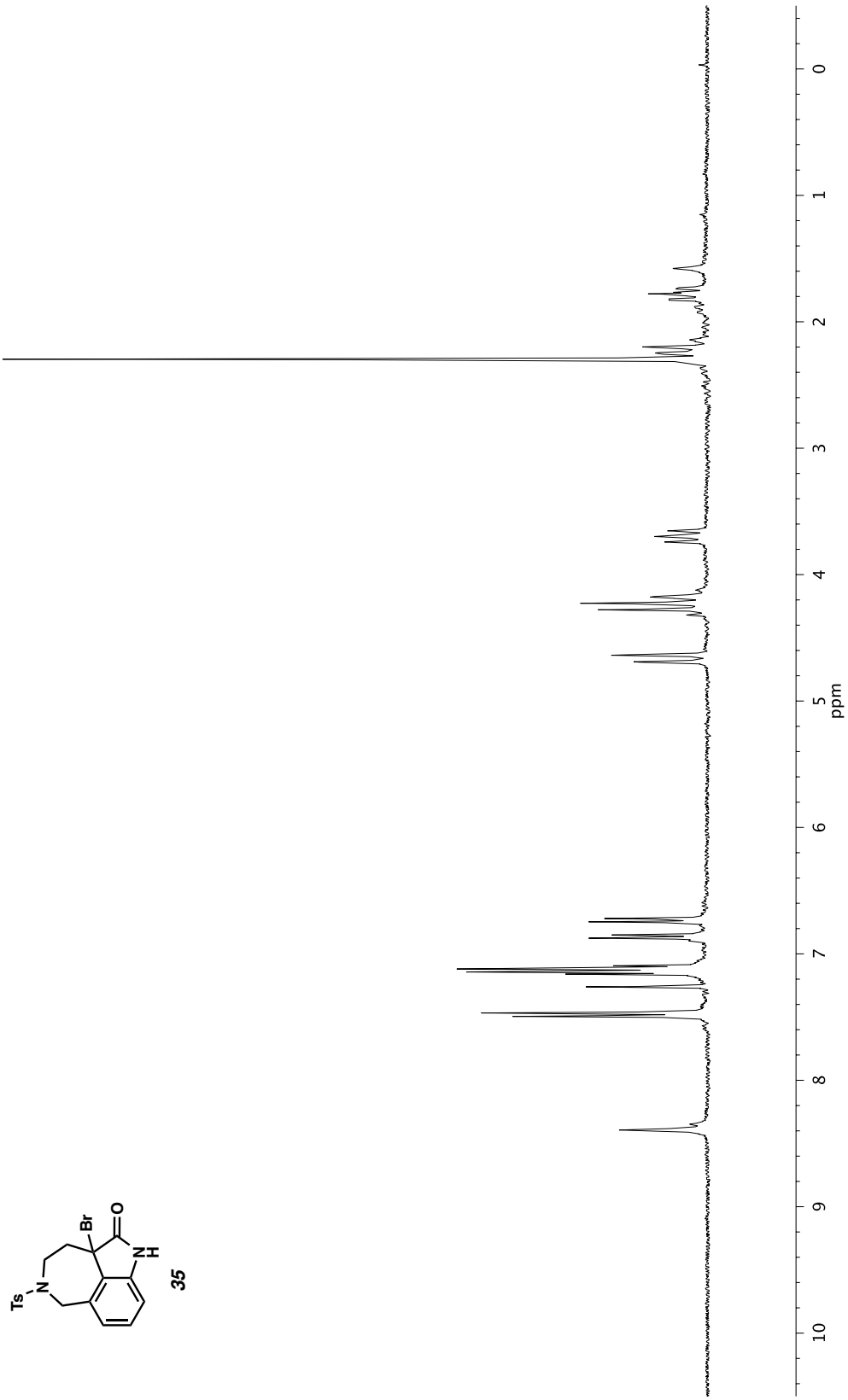


Figure A1.4. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **35**.

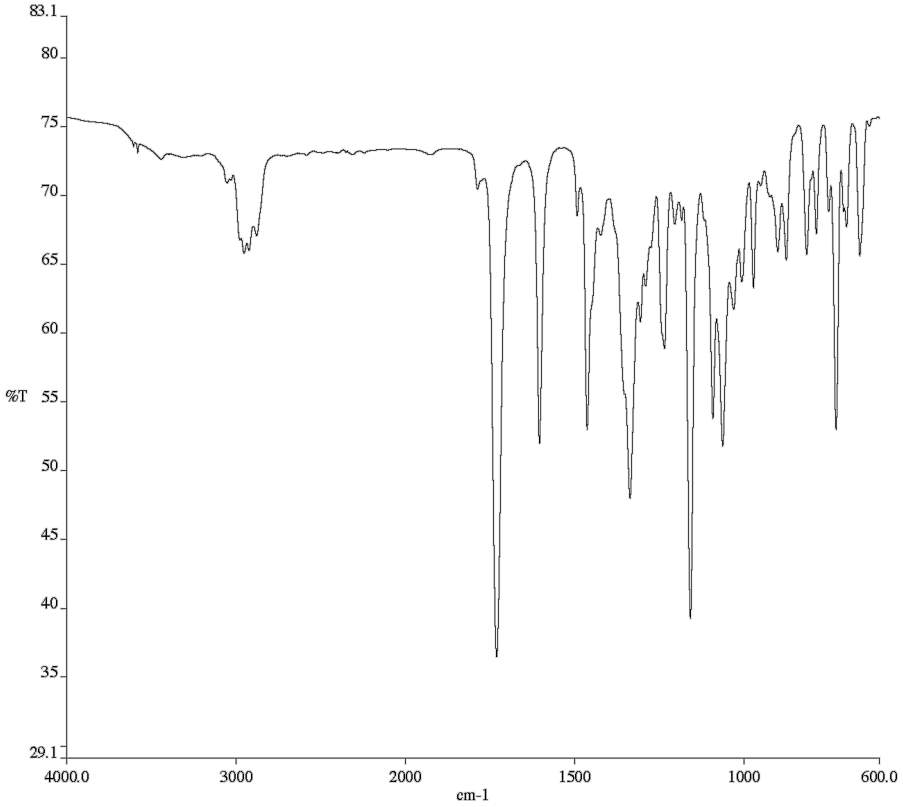


Figure A1.5. Infrared spectrum (Thin Film, NaCl) of compound **35**.

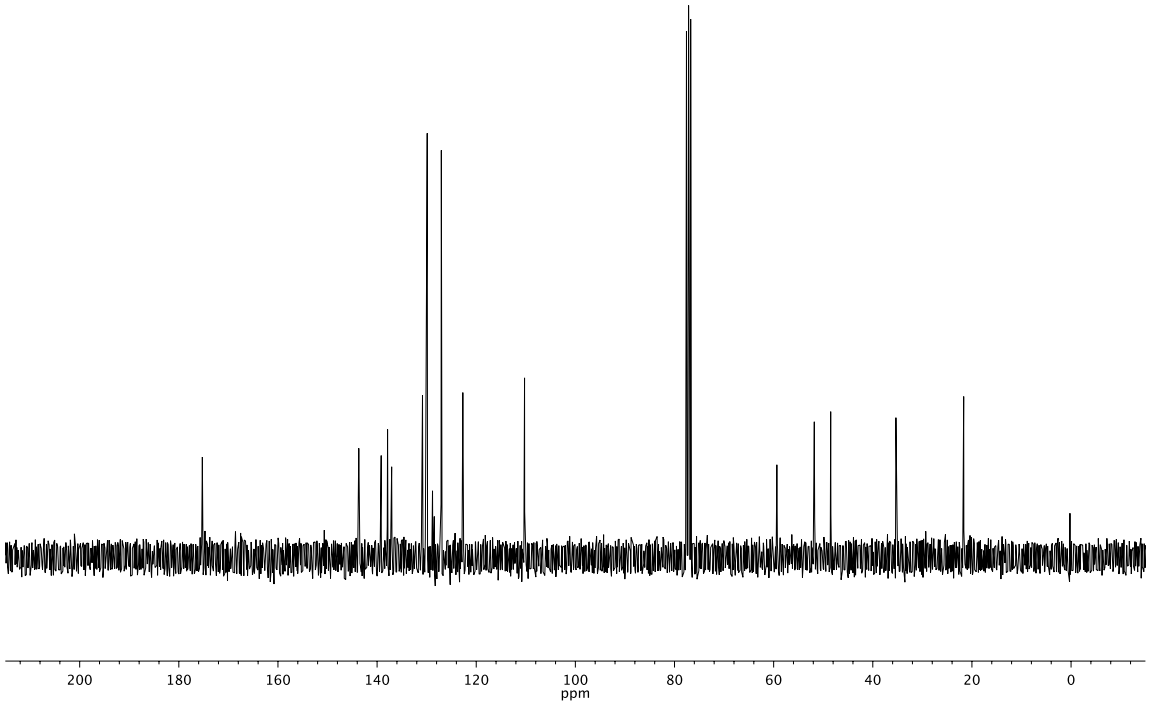


Figure A1.6. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **35**.

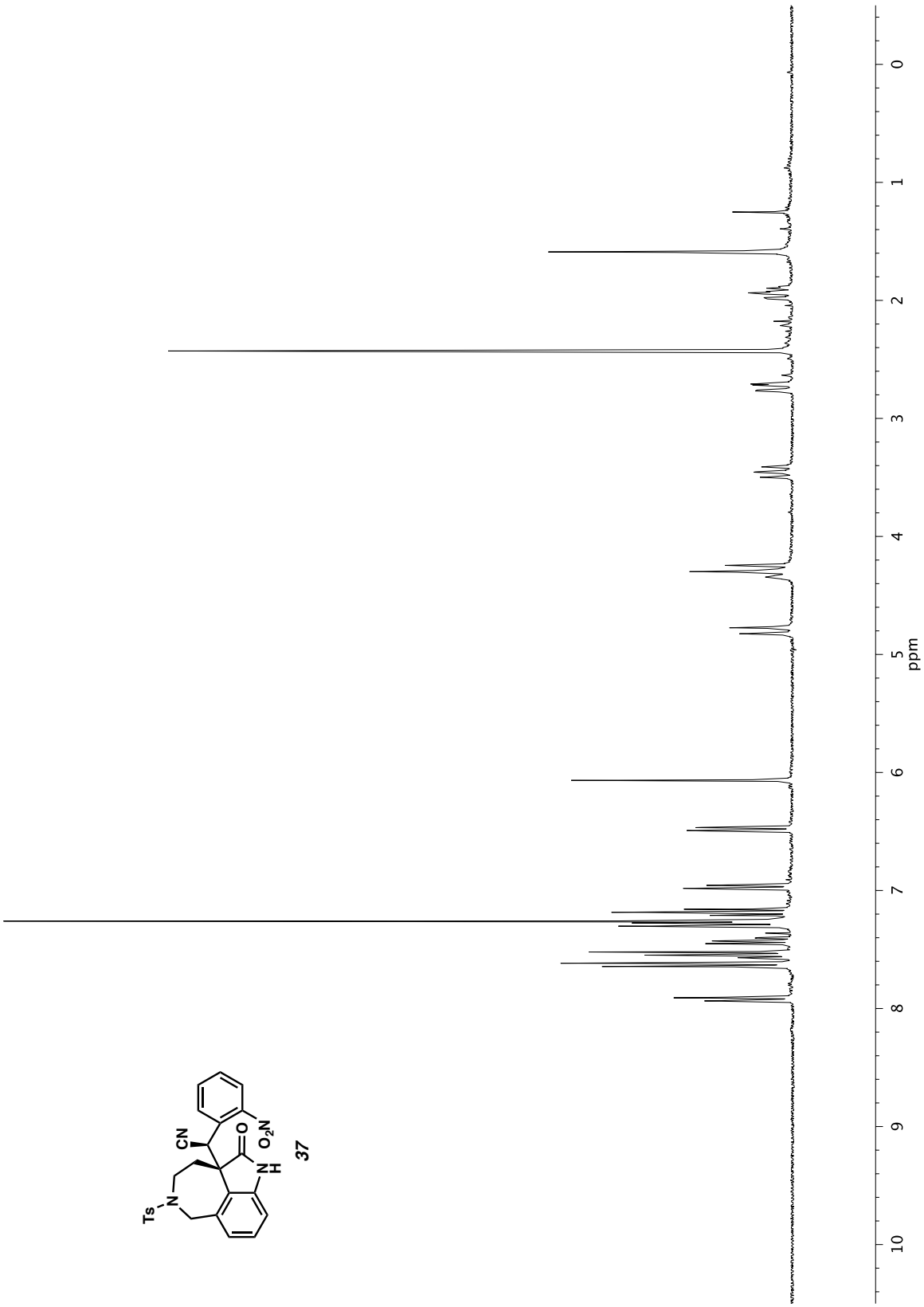


Figure A1.7. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **37**.

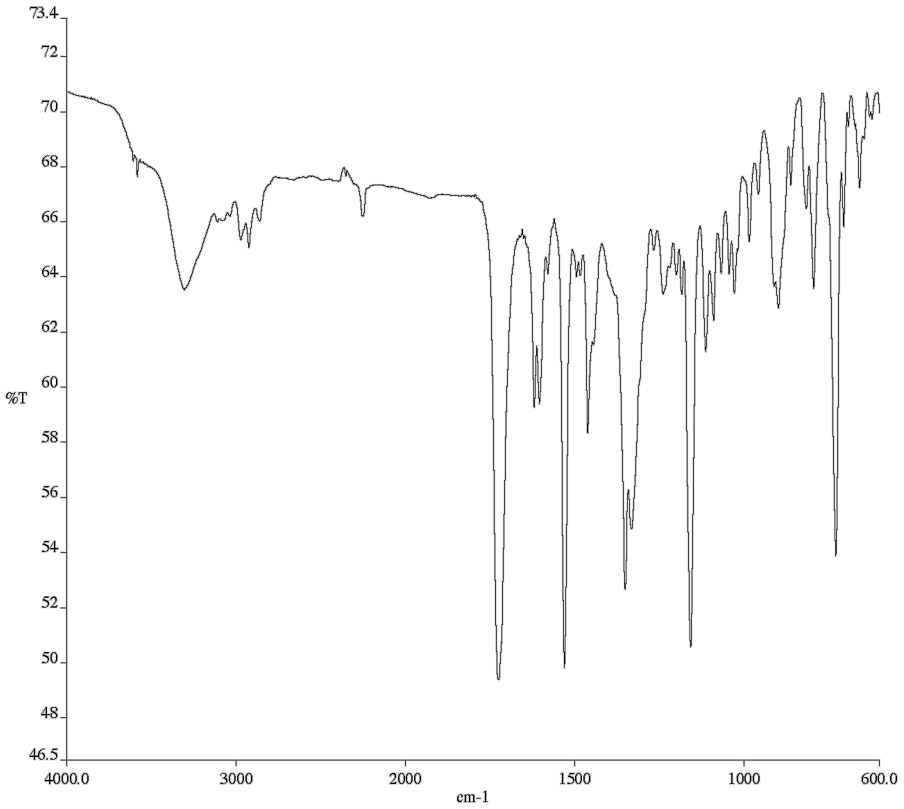


Figure A1.8. Infrared spectrum (Thin Film, NaCl) of compound **37**.

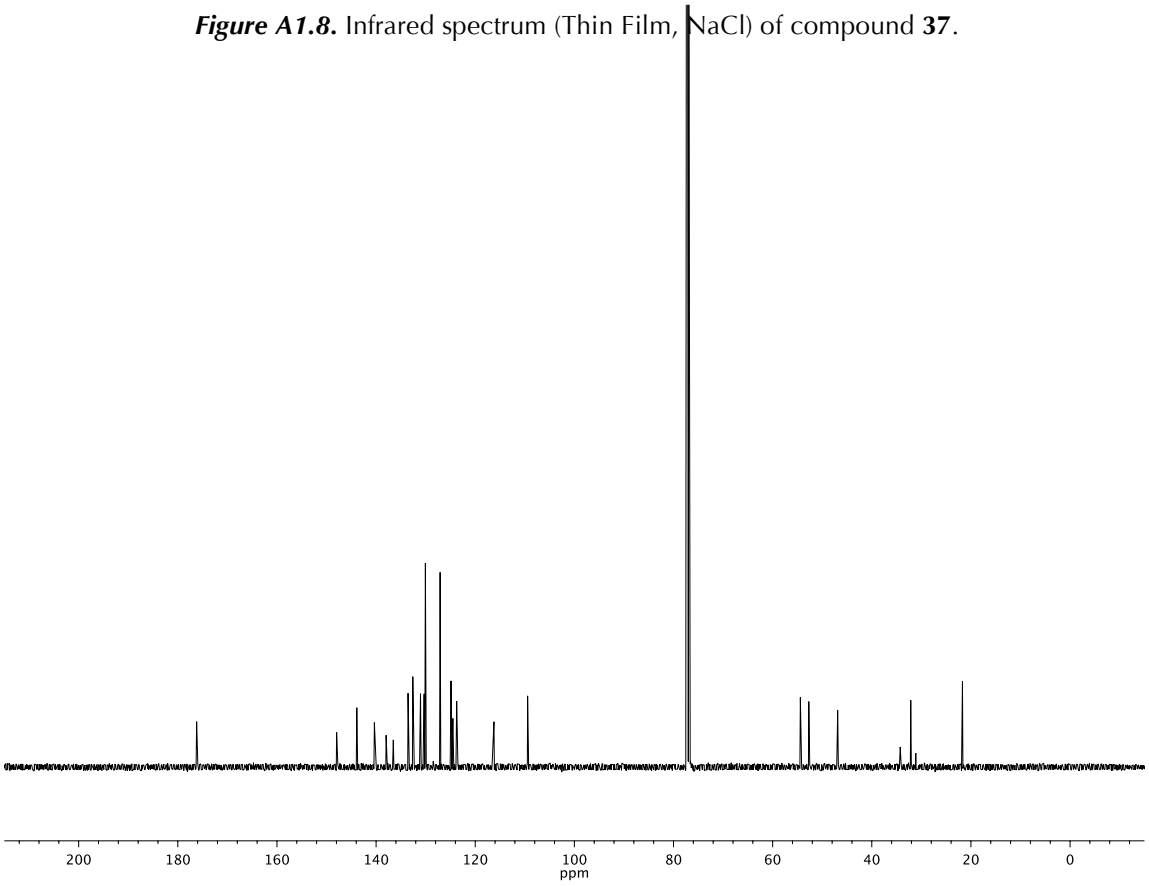


Figure A1.9. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **37**.

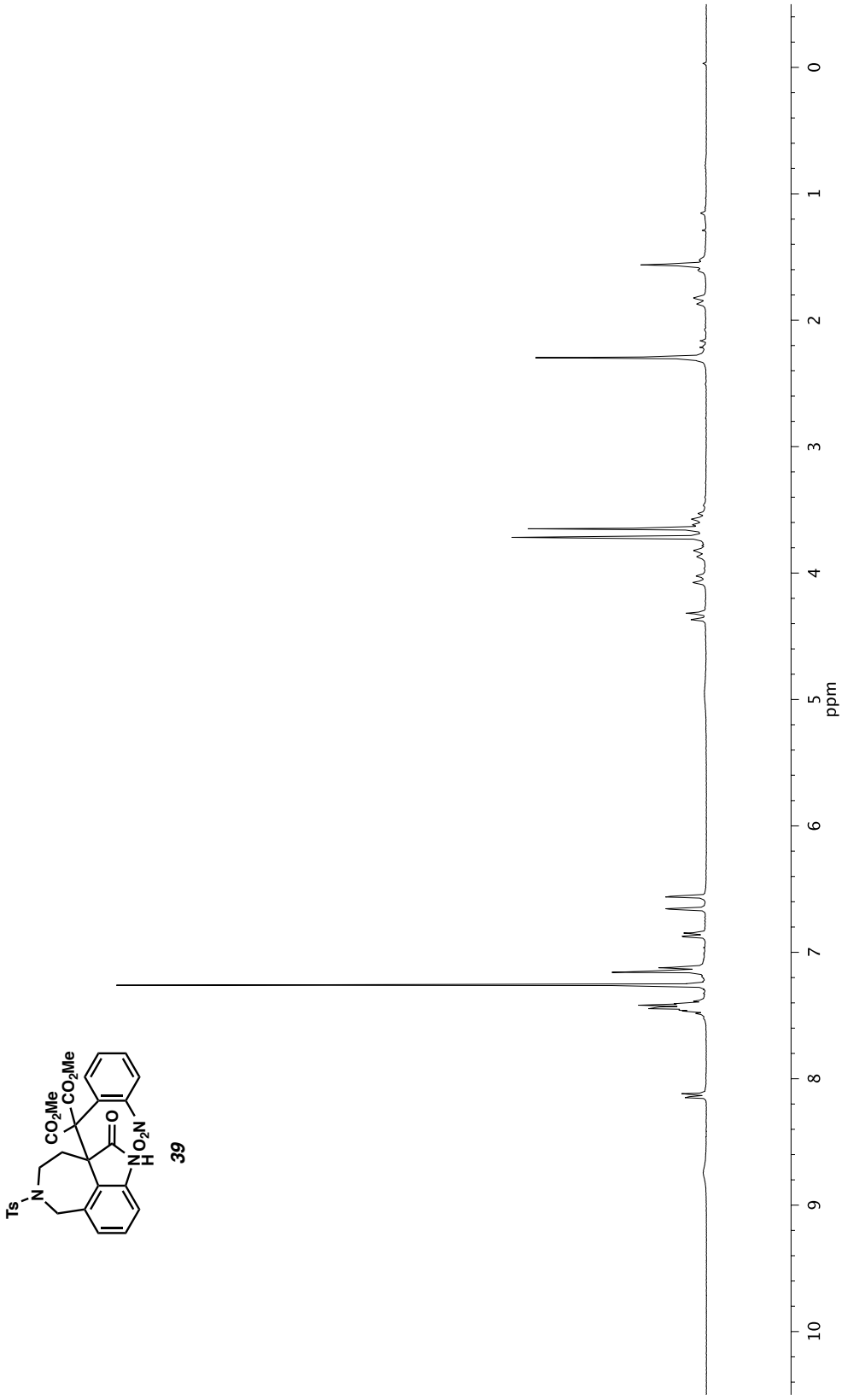


Figure A1.10. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **39**.

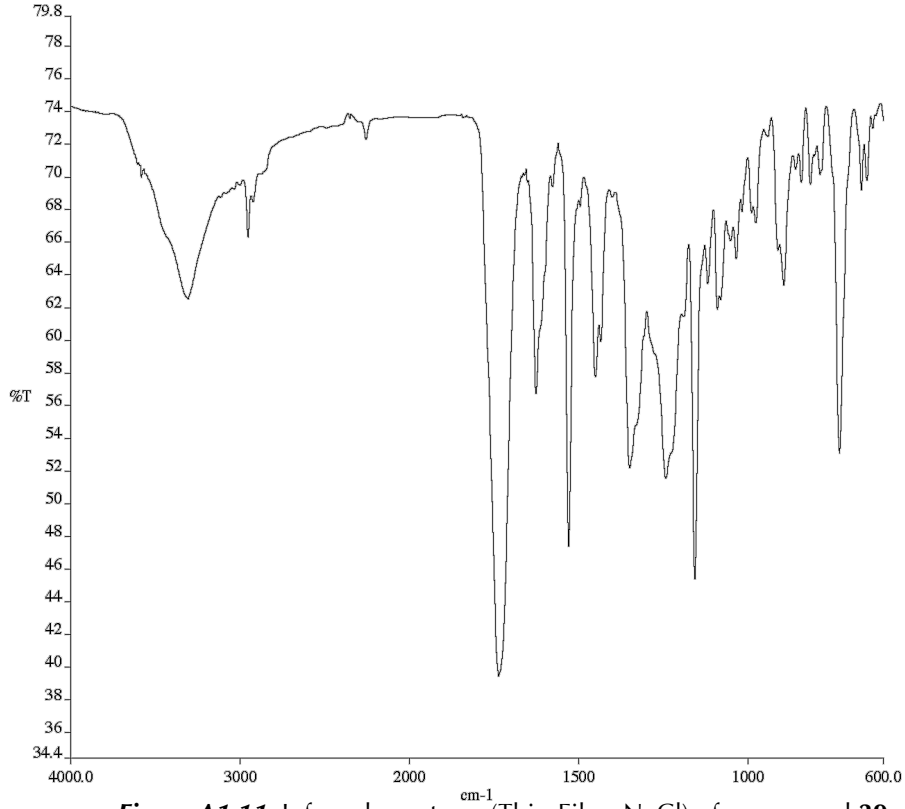


Figure A1.11. Infrared spectrum (Thin Film, NaCl) of compound **39**.

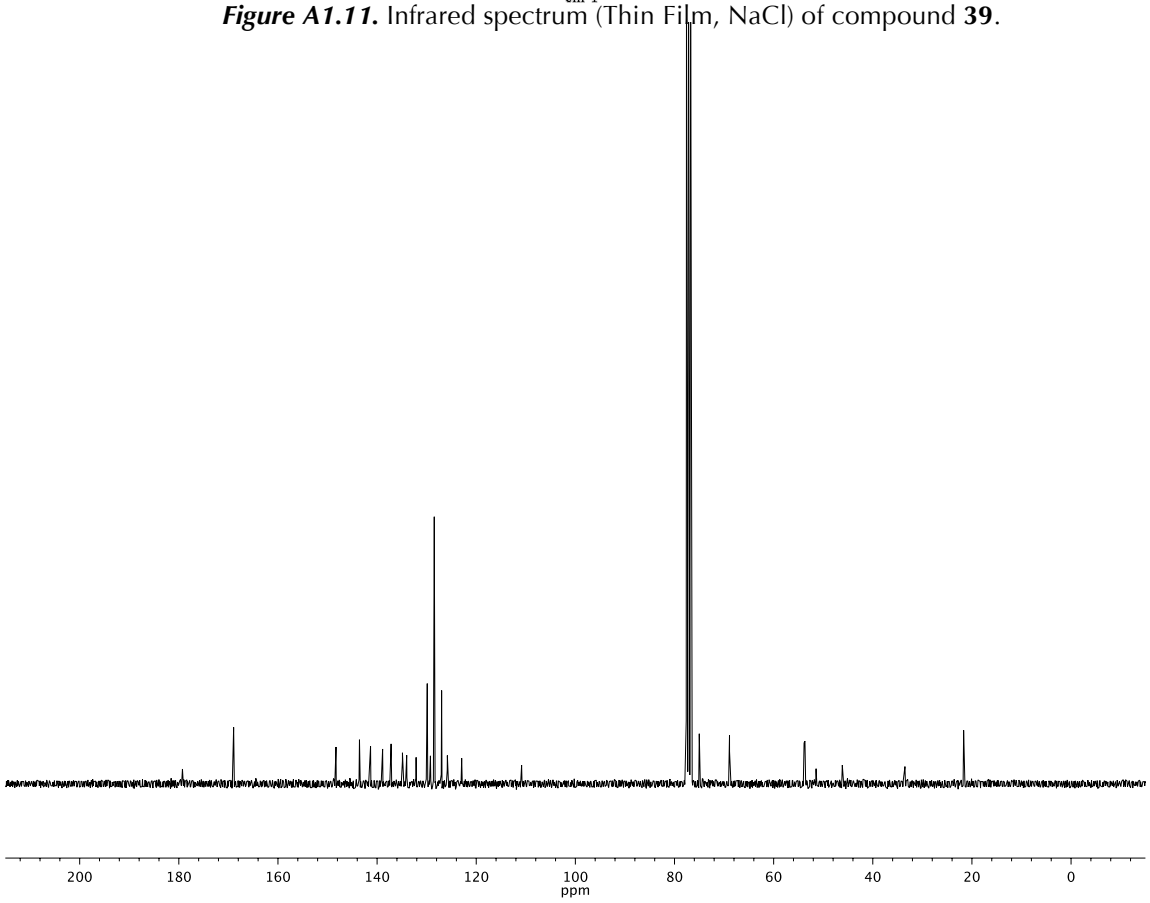


Figure A1.12. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **39**.

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

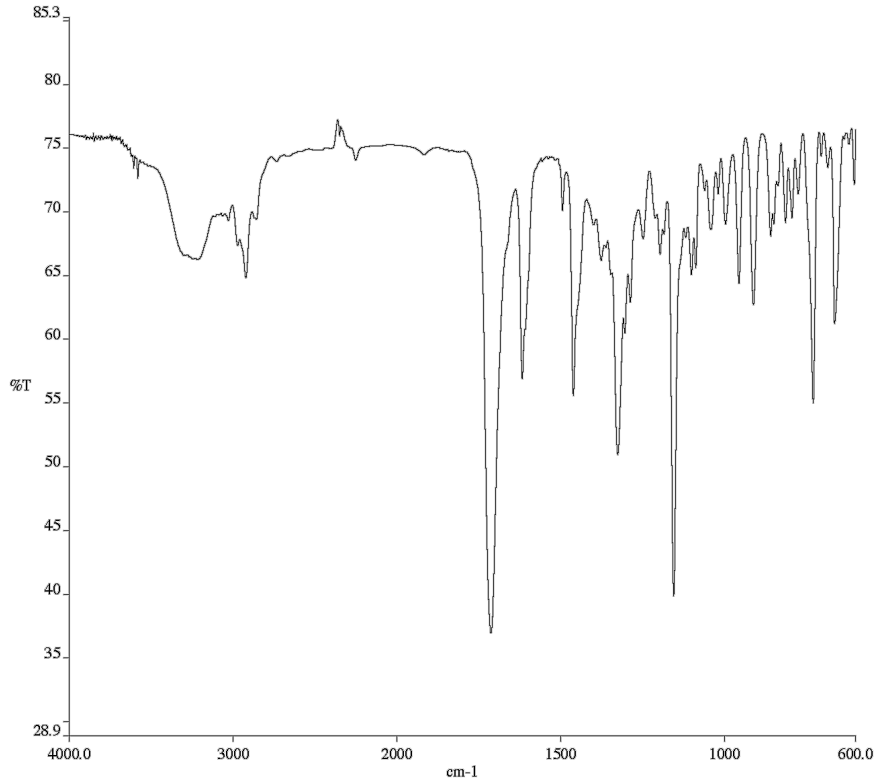


Figure A1.14. Infrared spectrum (Thin Film, NaCl) of compound **SI-1-13**.

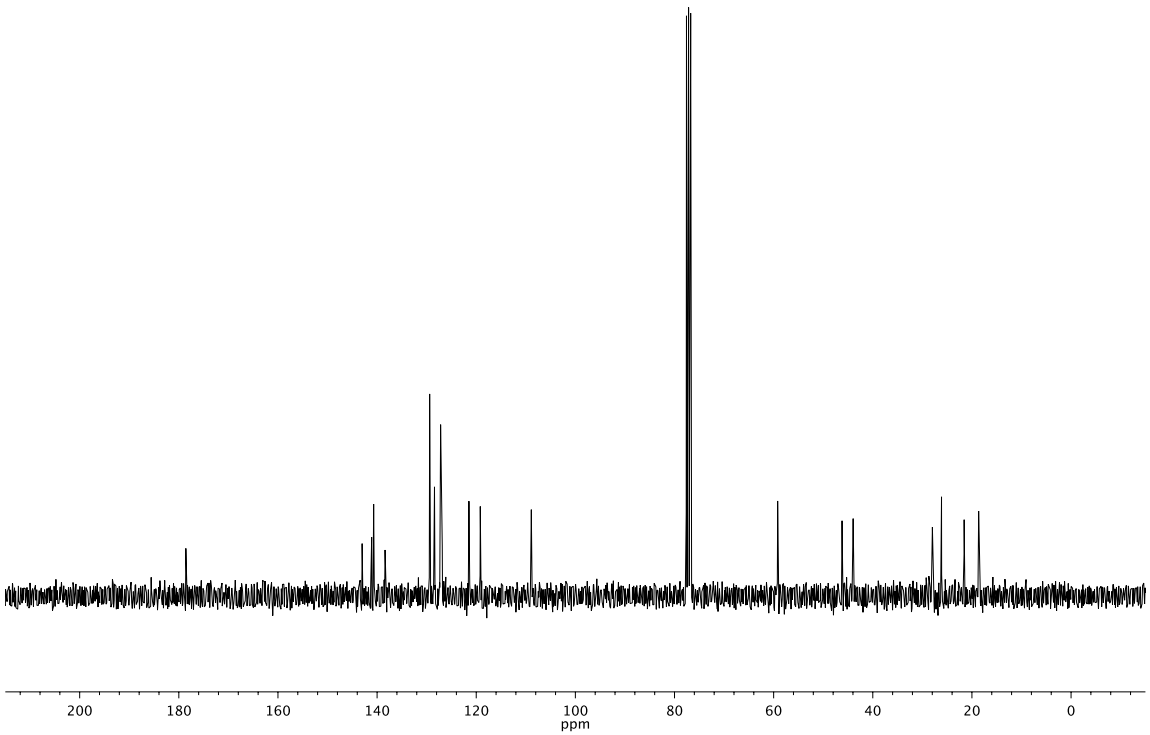


Figure A1.15. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **SI-1-13.**

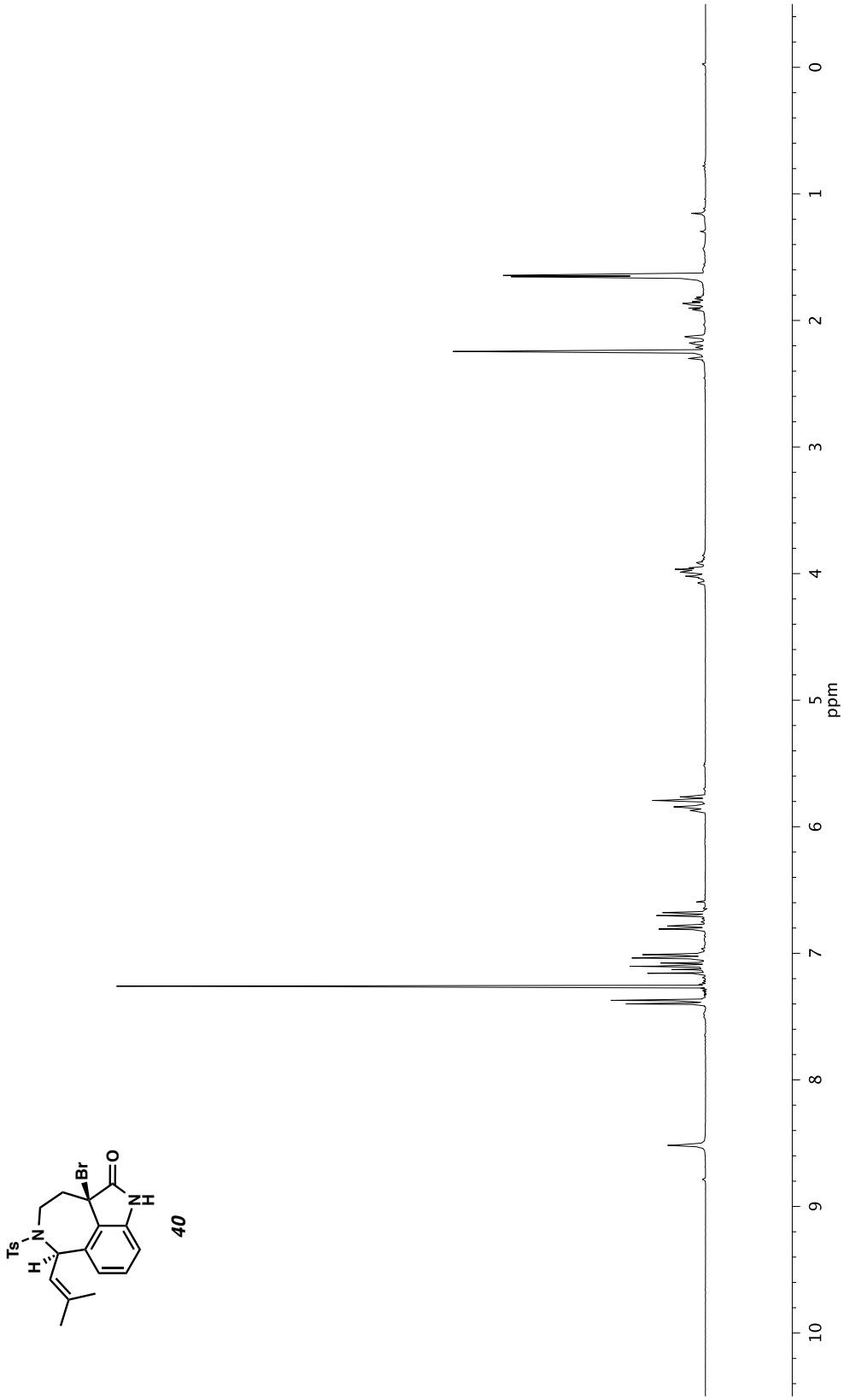


Figure A1.16. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **40**.

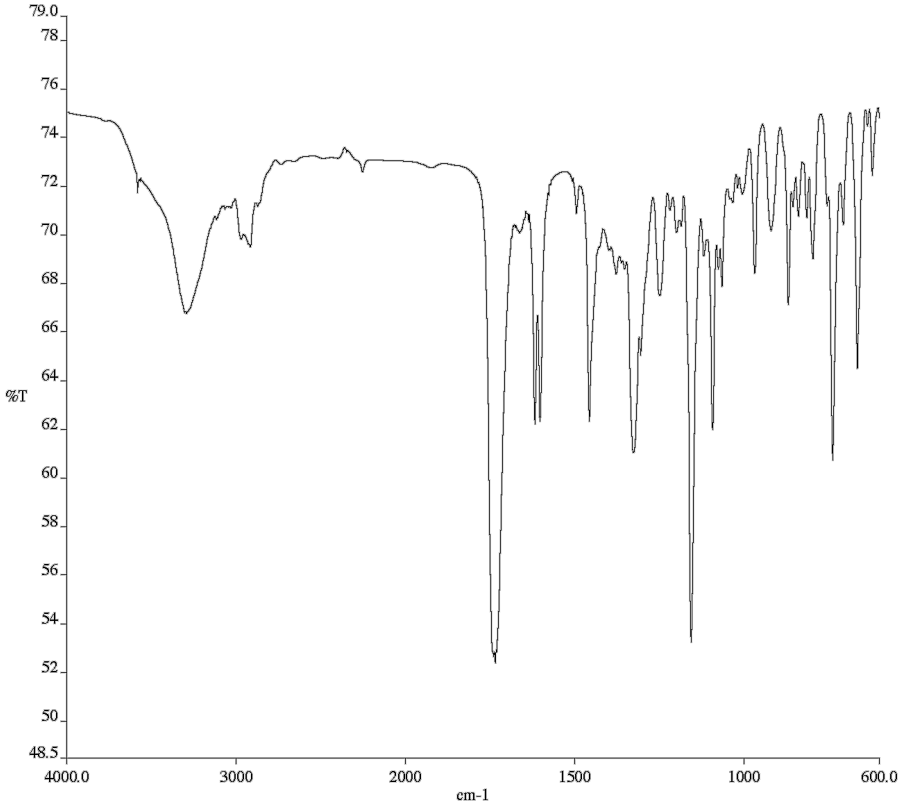


Figure A1.17. Infrared spectrum (Thin Film, NaCl) of compound **40**.

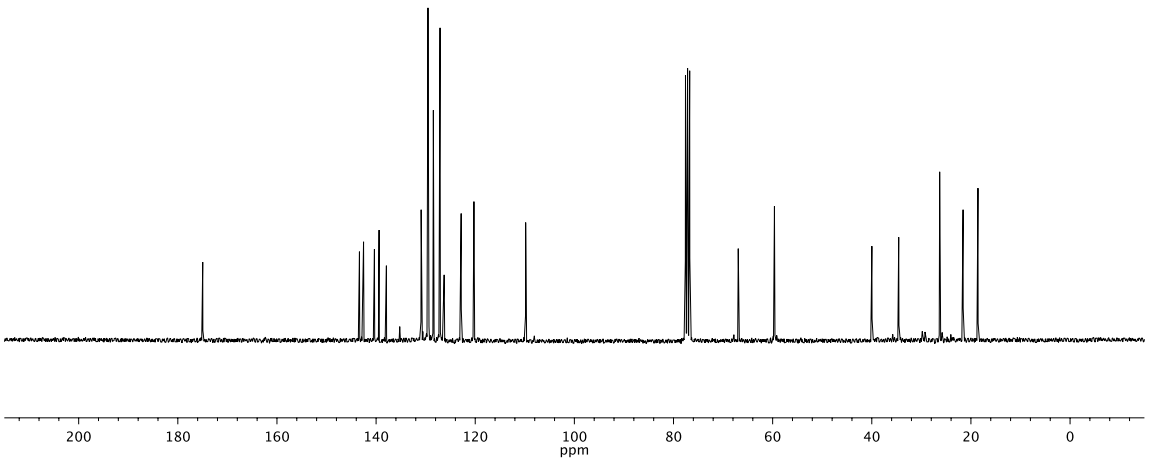


Figure A1.18. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **40.**

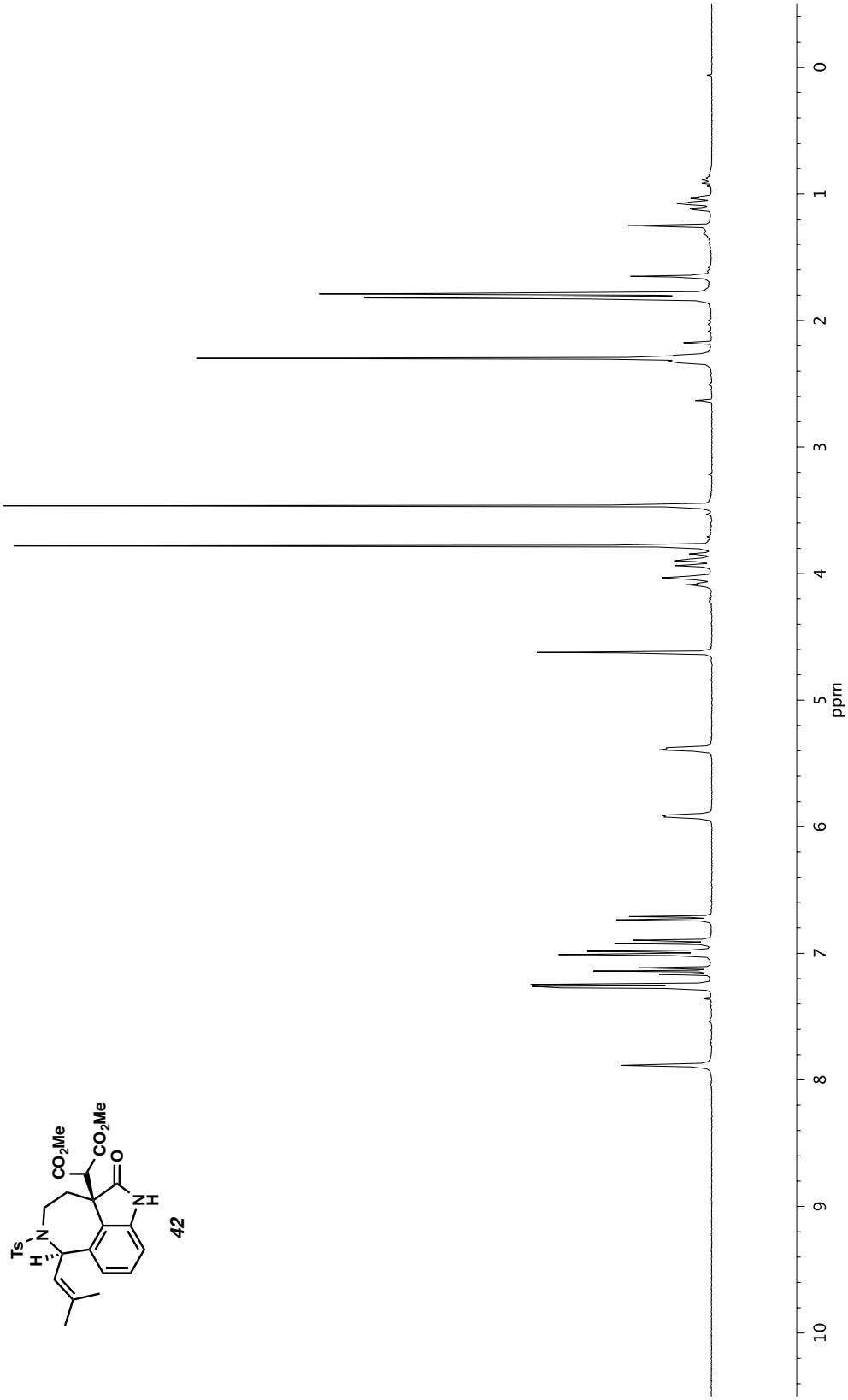


Figure A1.19. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **42**.

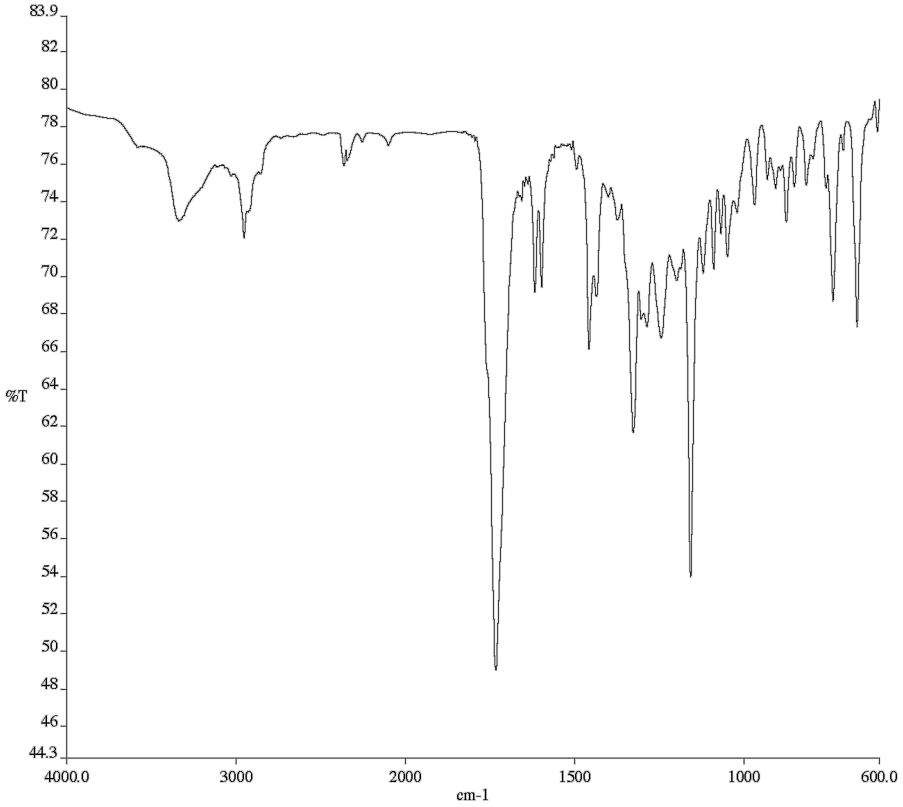


Figure A1.20. Infrared spectrum (Thin Film, NaCl) of compound **42**.

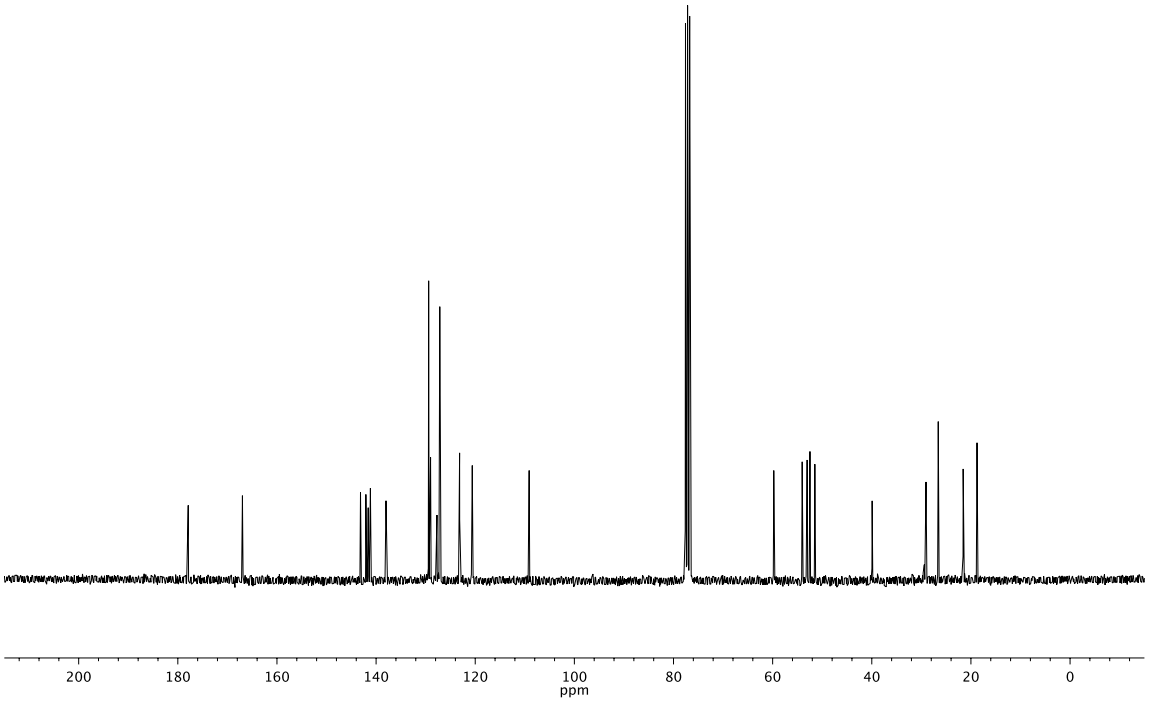


Figure A1.21. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **42.**

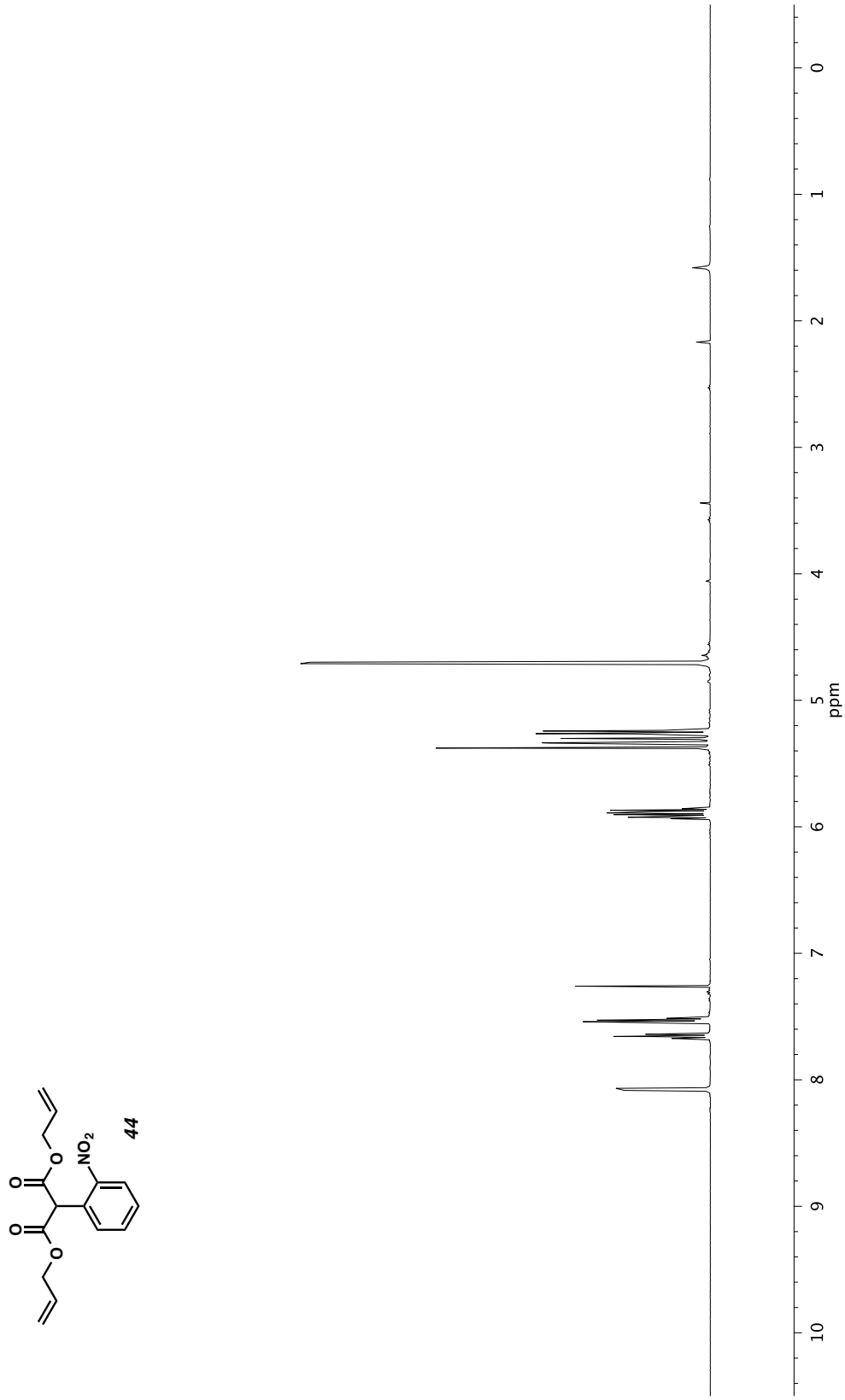


Figure A1.22. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **44**.

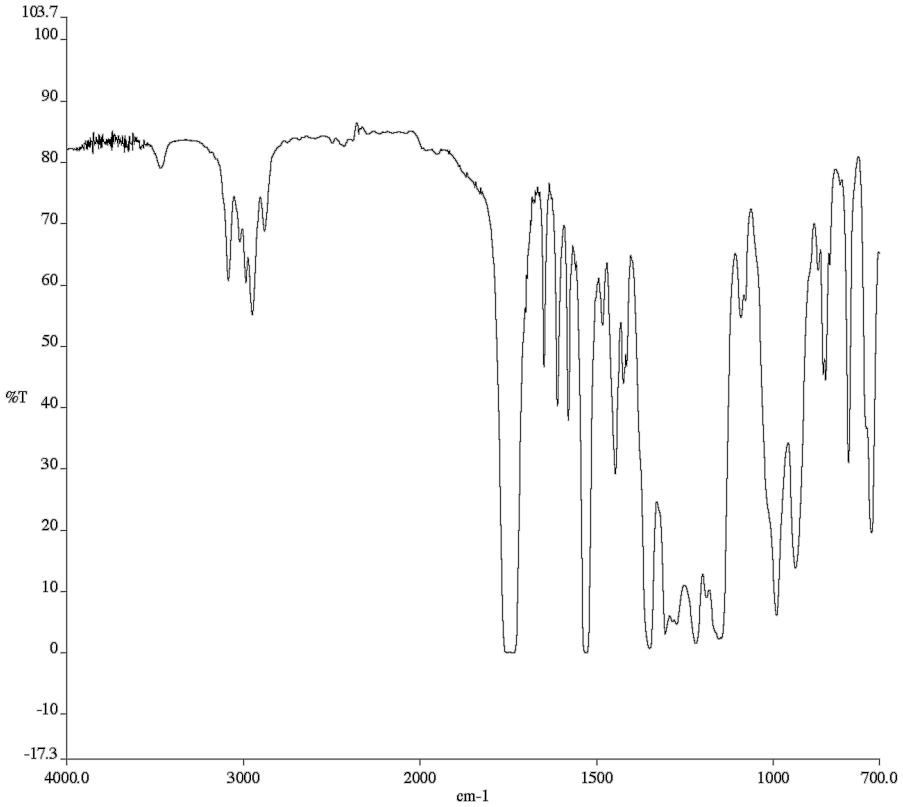


Figure A1.23. Infrared spectrum (Thin Film, NaCl) of compound **44**.

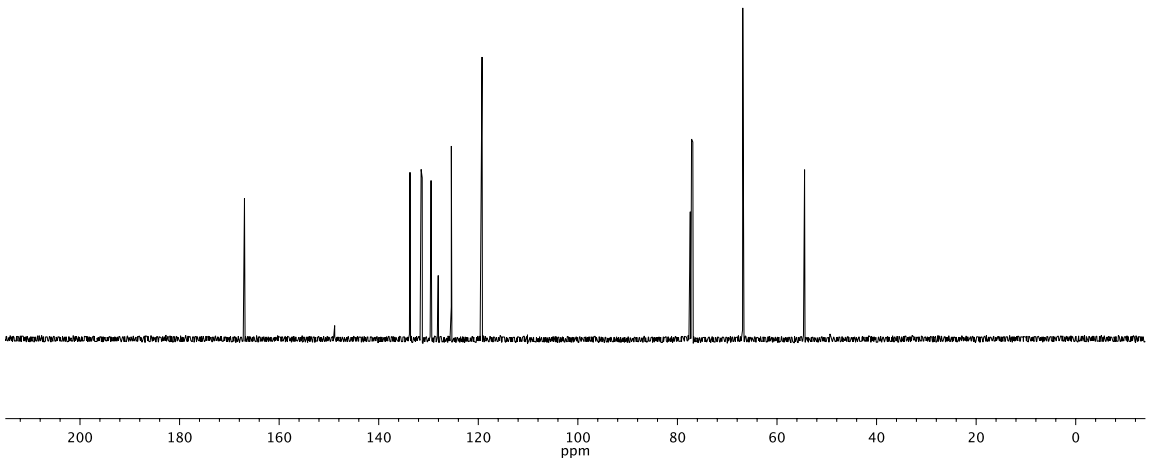


Figure A1.24. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **44**.

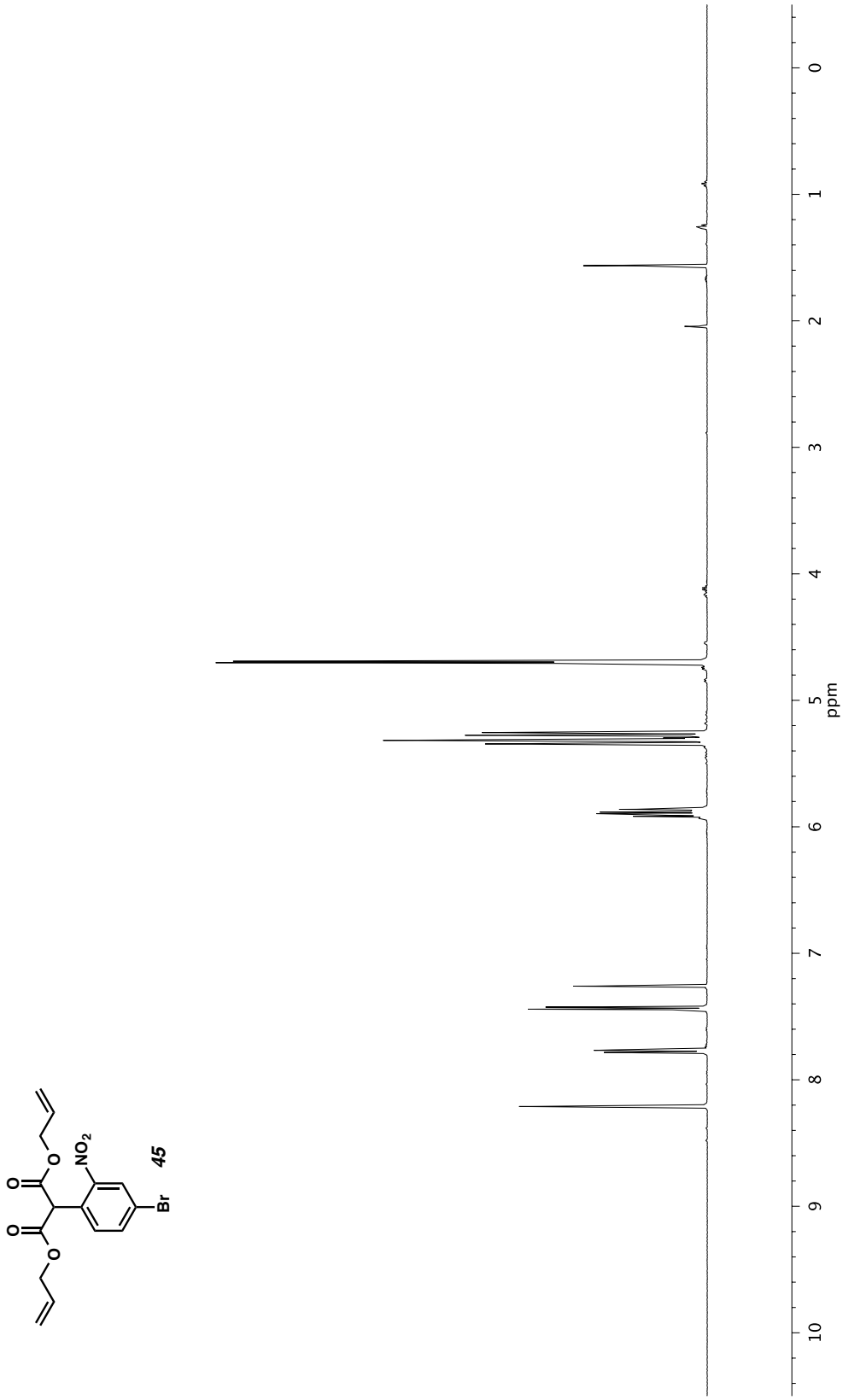


Figure A1.25. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **45**.

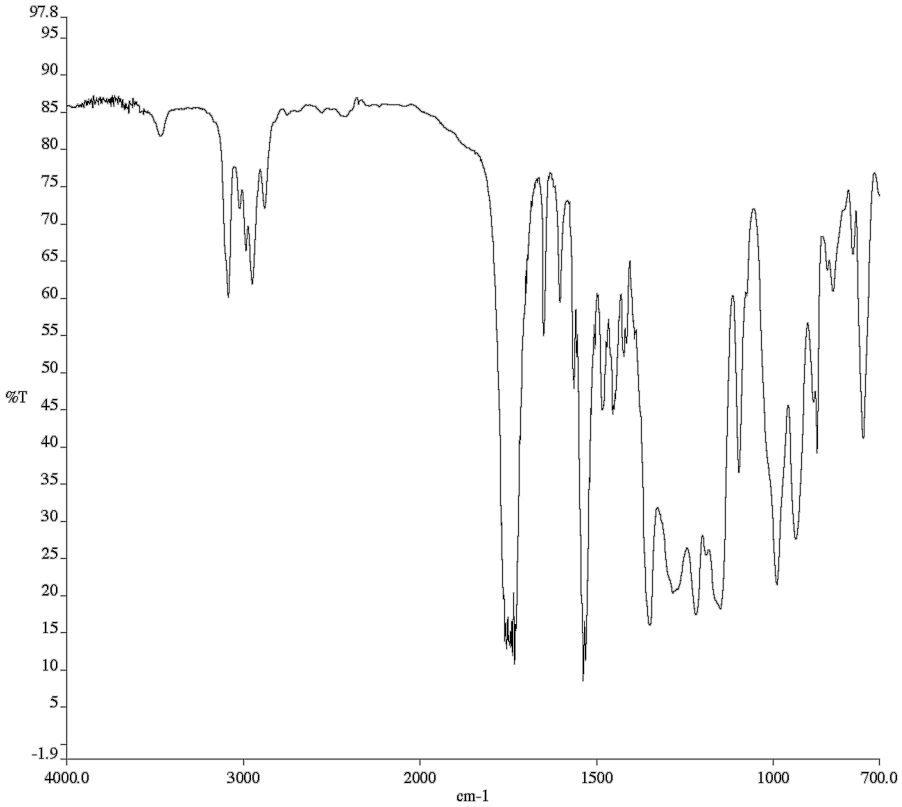


Figure A1.26. Infrared spectrum (Thin Film, NaCl) of compound **45**.

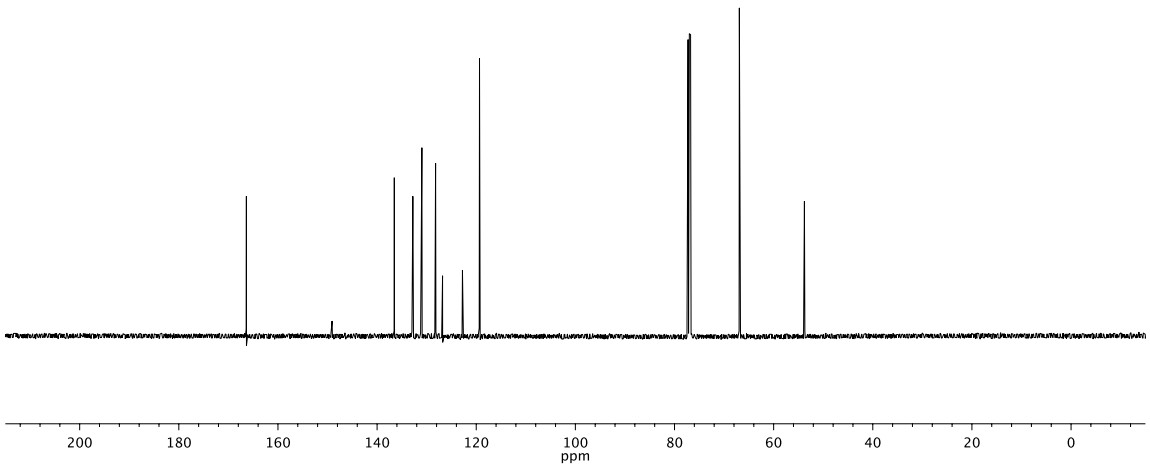


Figure A1.27. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **45**.

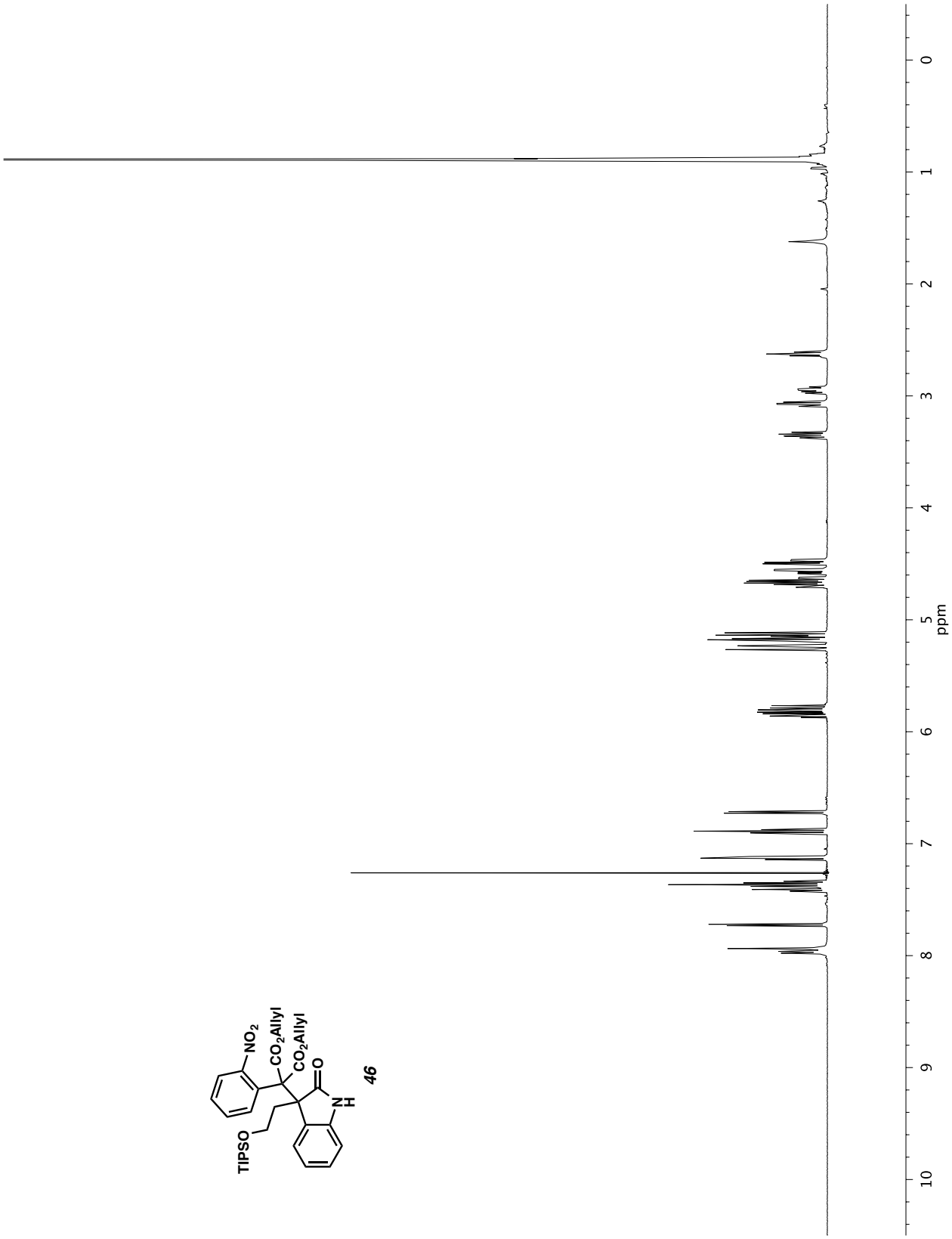


Figure A1.28. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **46**.

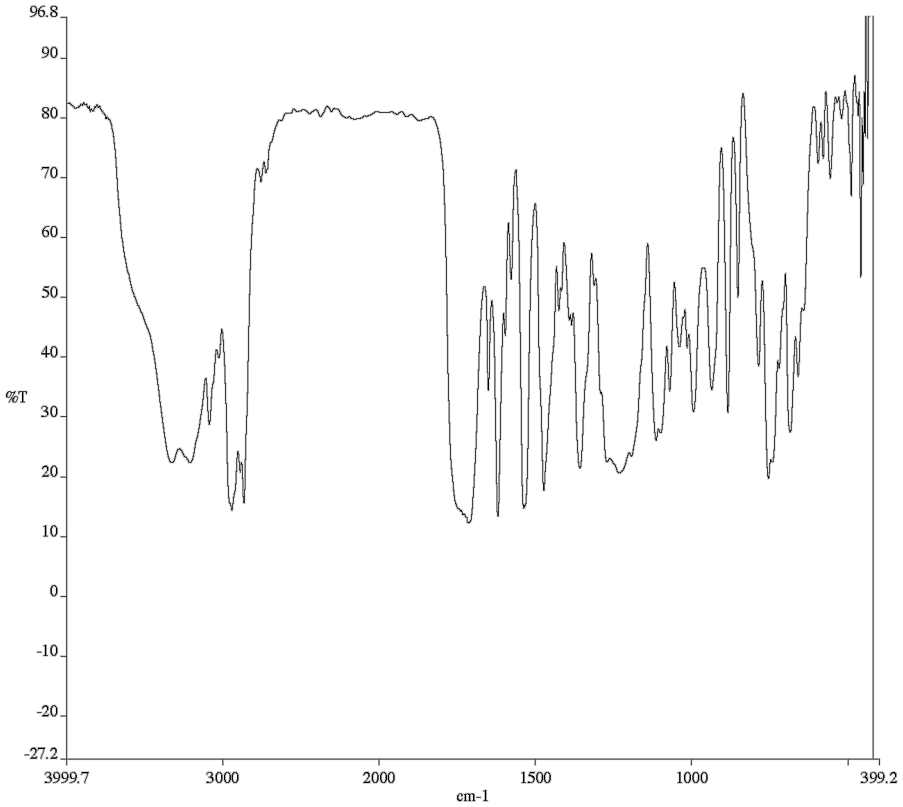


Figure A1.29. Infrared spectrum (Thin Film, NaCl) of compound **46**.

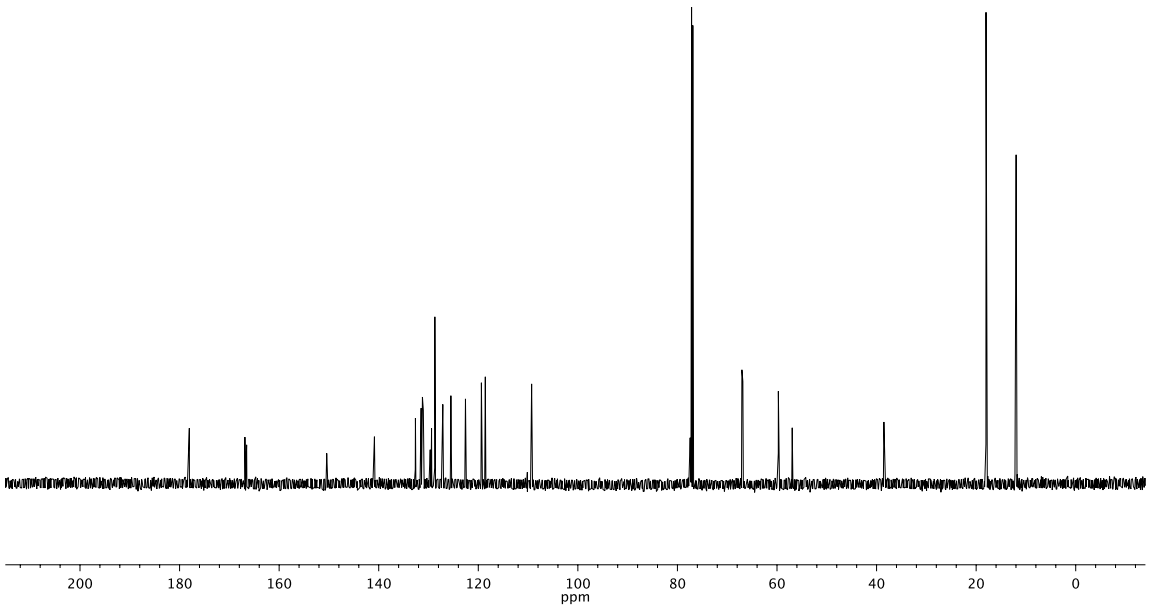


Figure A1.30. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **46**.

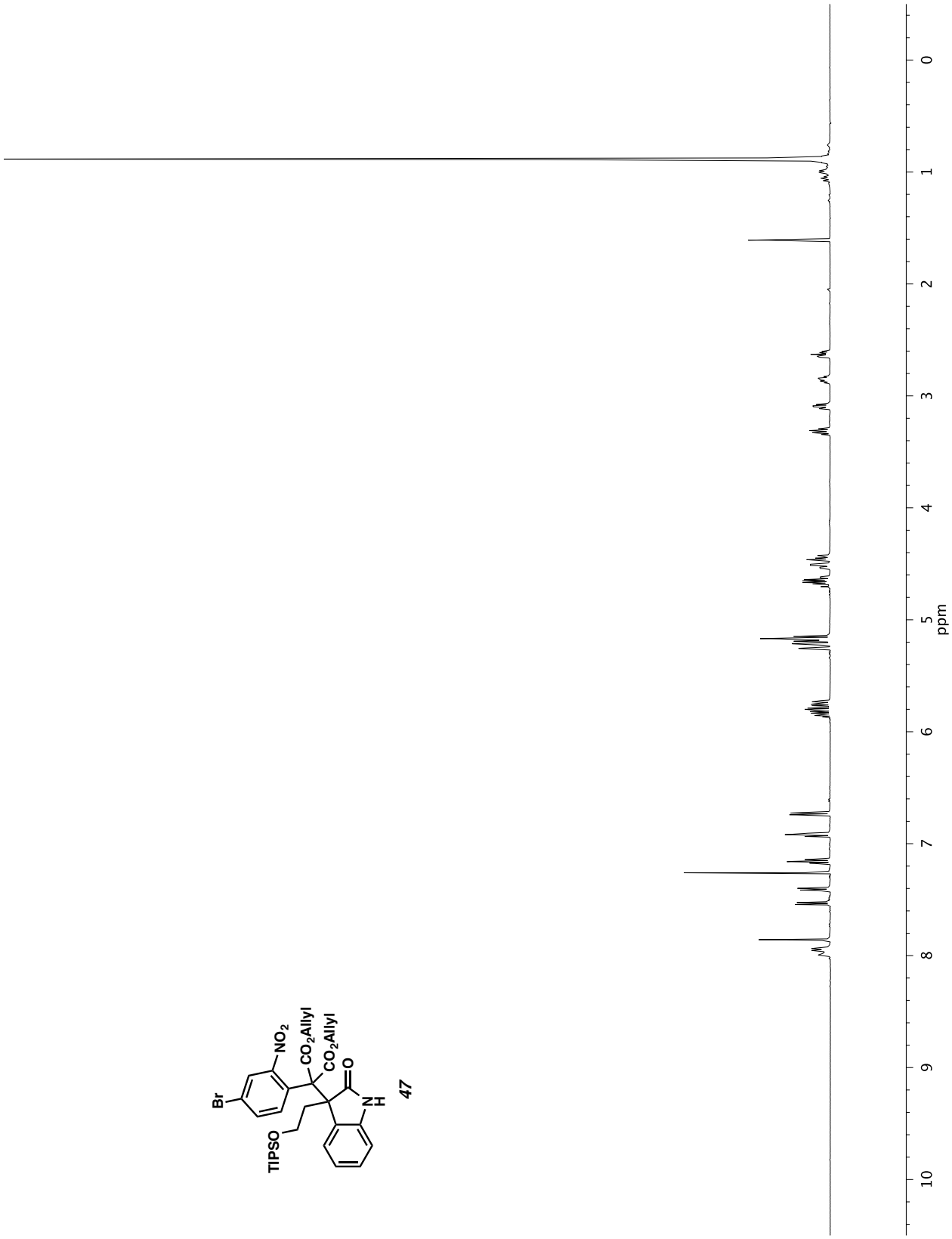


Figure A1.31. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **47**.

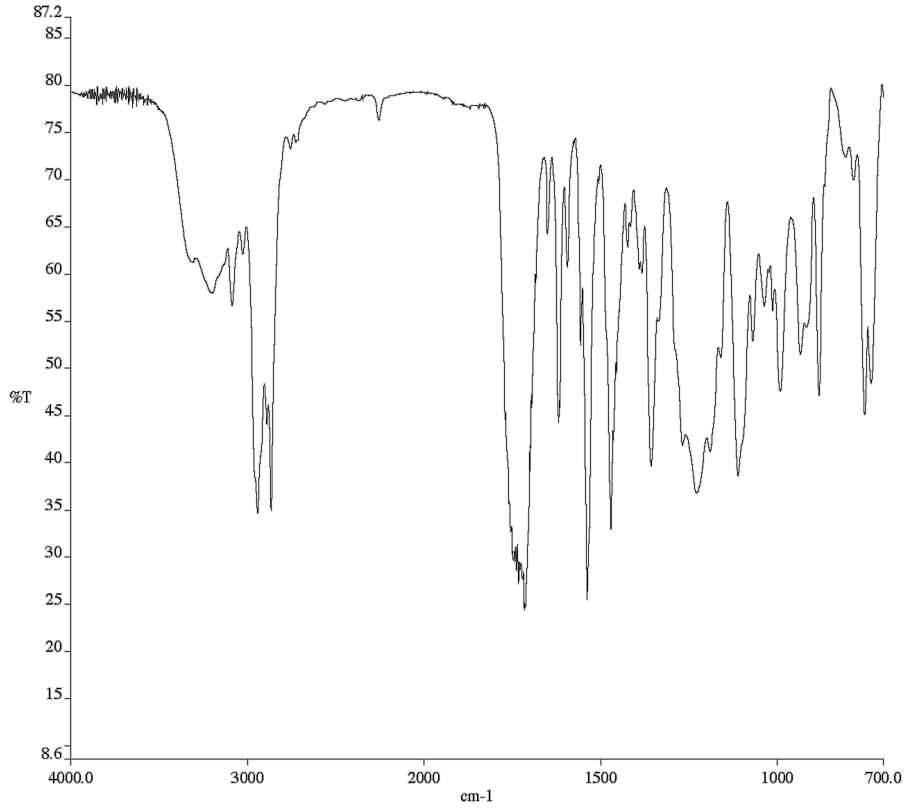


Figure A1.32. Infrared spectrum (Thin Film, NaCl) of compound **47**.

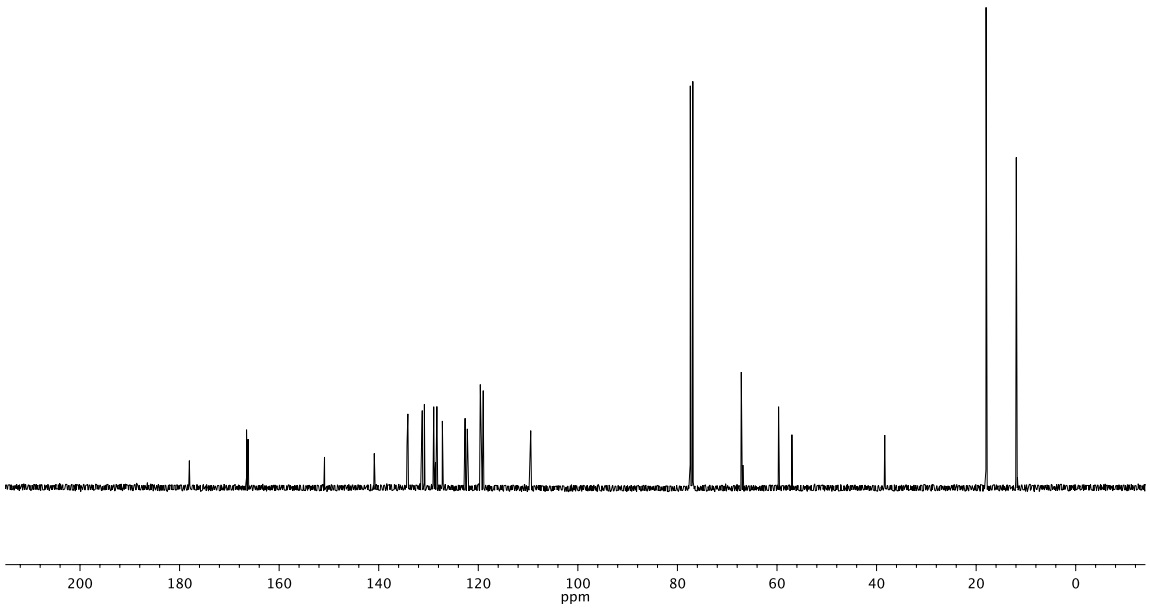


Figure A1.33. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **47**.

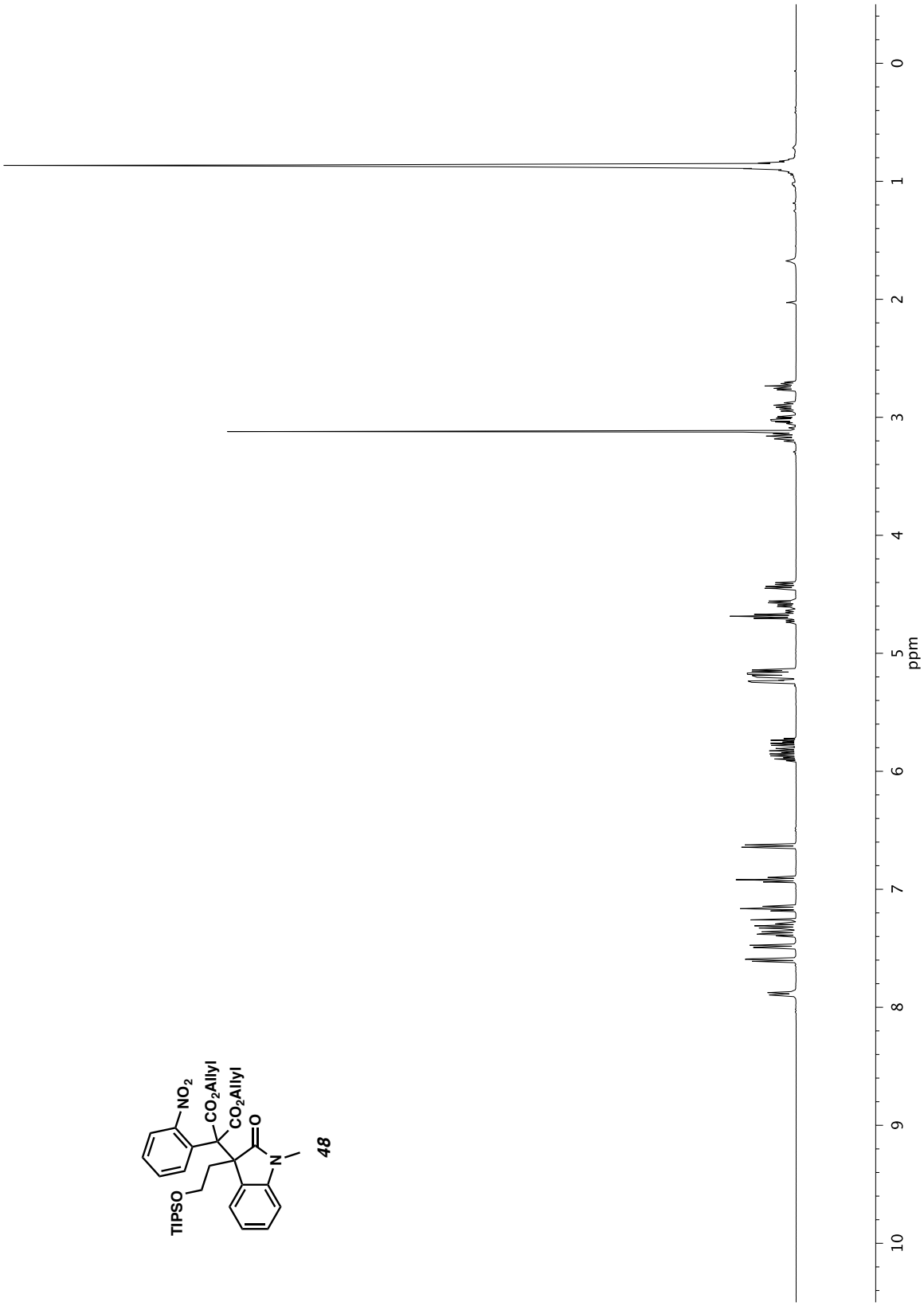


Figure A1.34. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **48**.

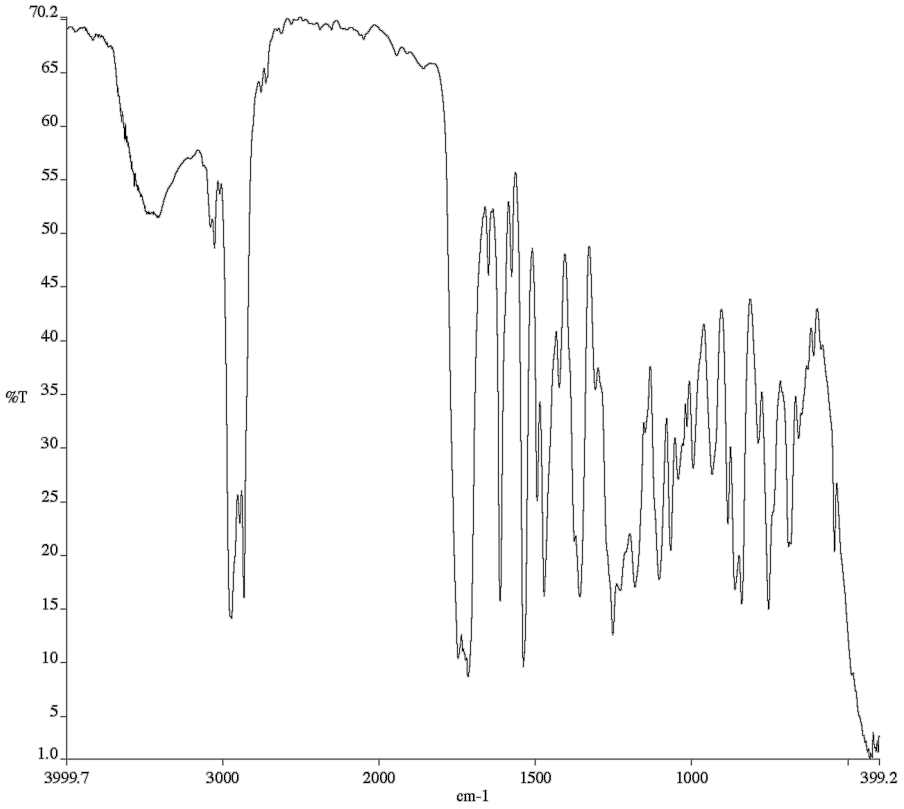


Figure A1.35. Infrared spectrum (Thin Film, NaCl) of compound **48**.

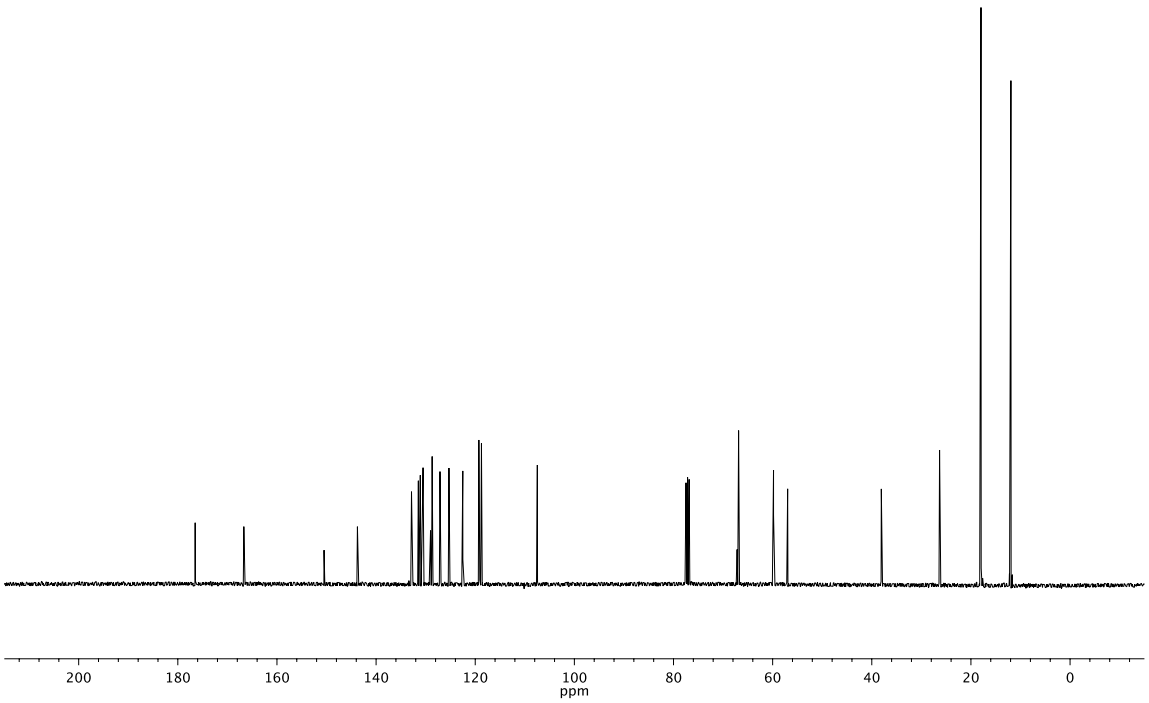


Figure A1.36. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **48**.

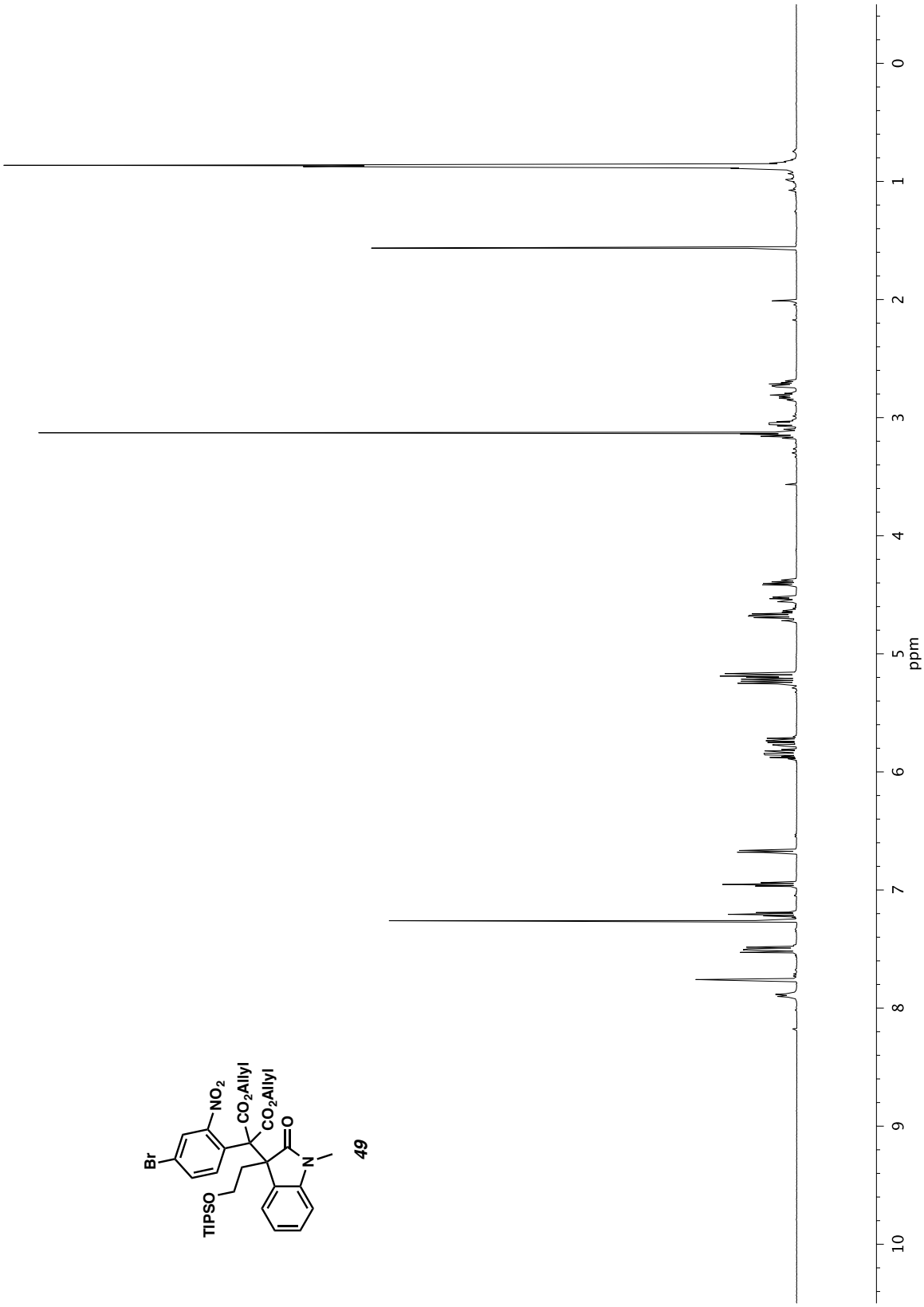


Figure A1.37. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **49**.

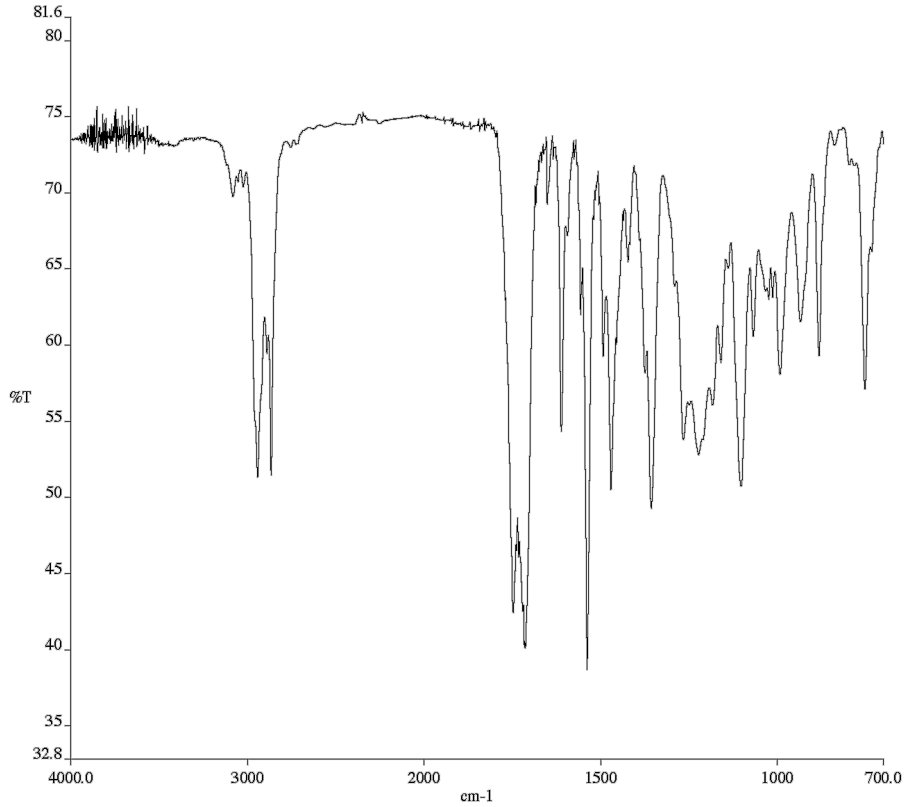


Figure A1.38. Infrared spectrum (Thin Film, NaCl) of compound **49**.

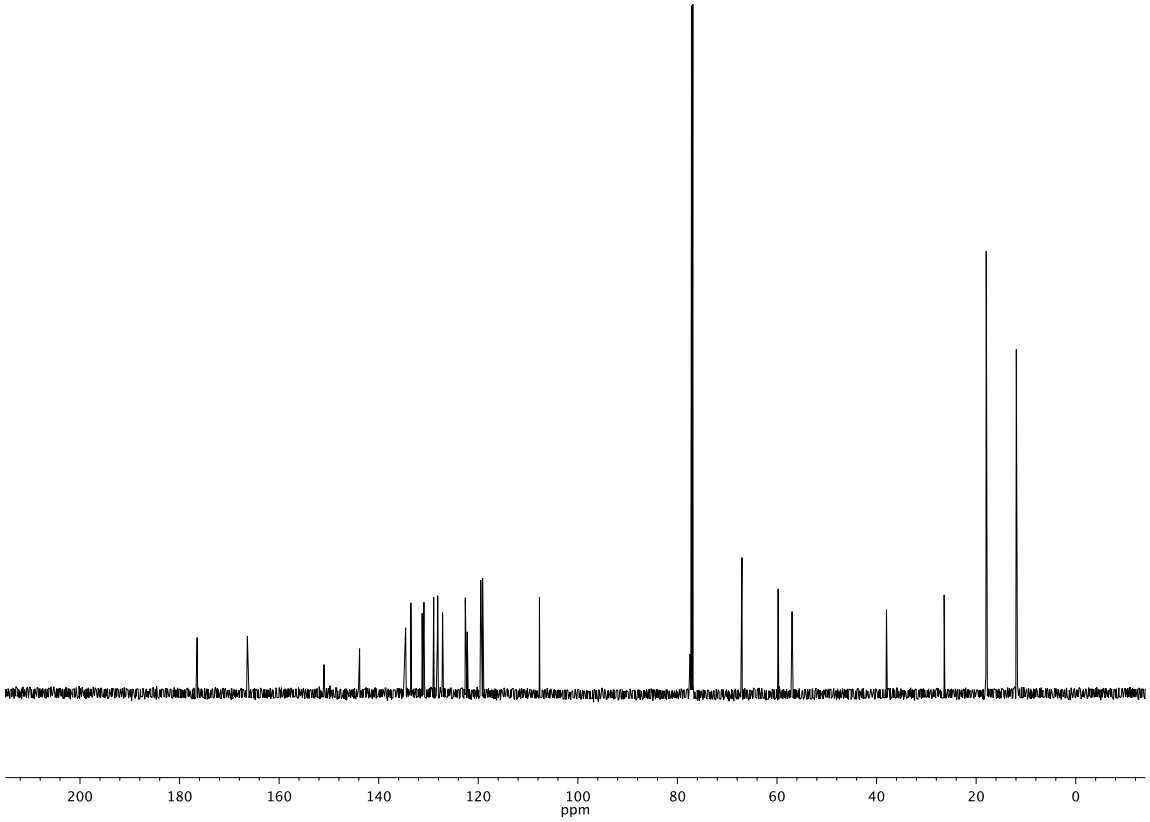
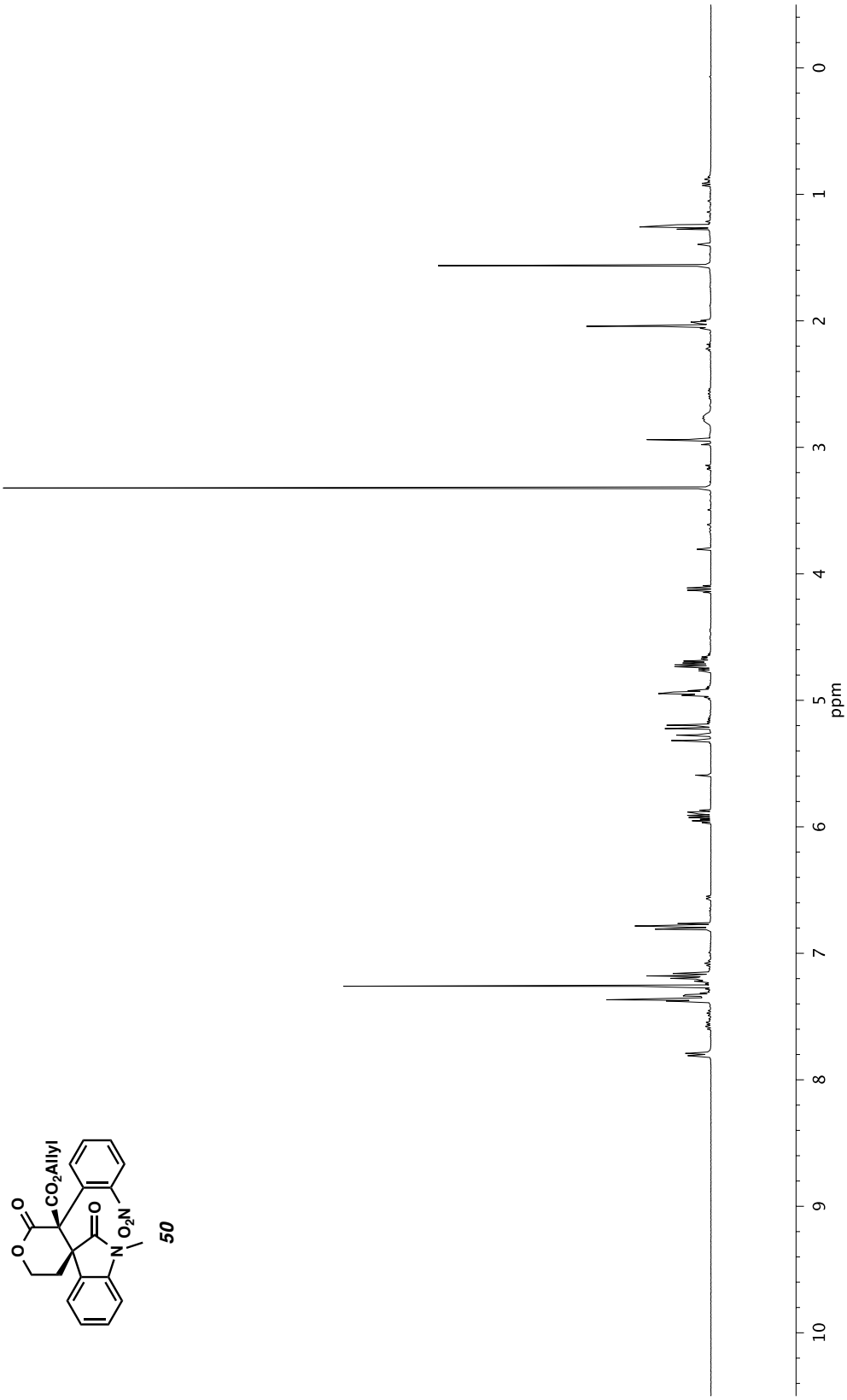


Figure A1.39. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **49**.



50

Figure A1.40. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **50**.

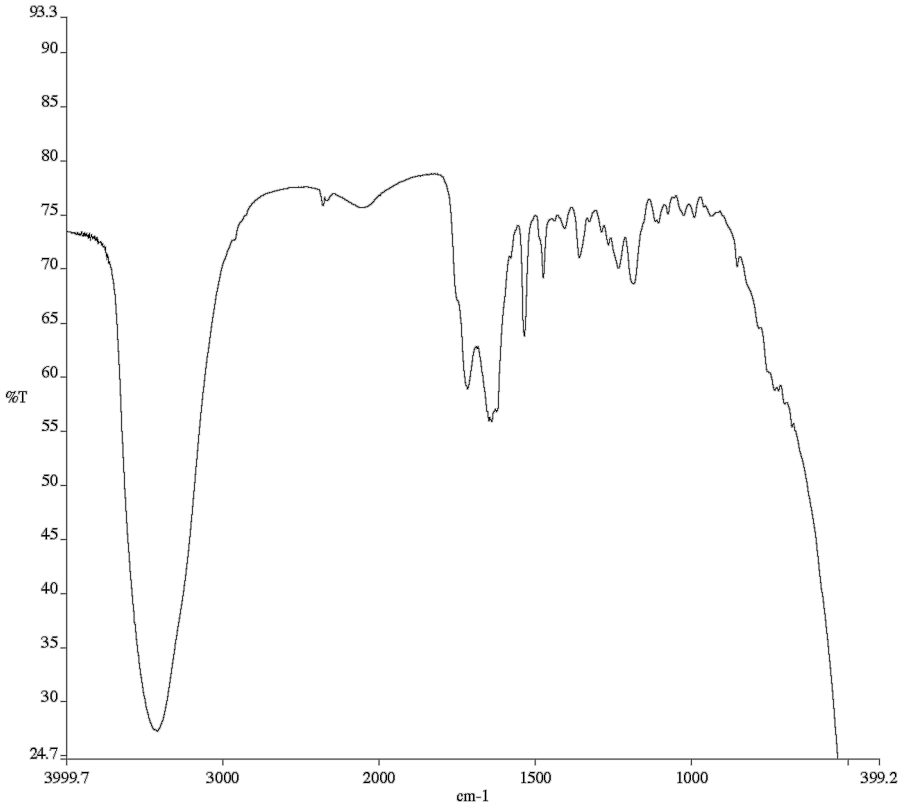


Figure A1.41. Infrared spectrum (Thin Film, NaCl) of compound **50**.

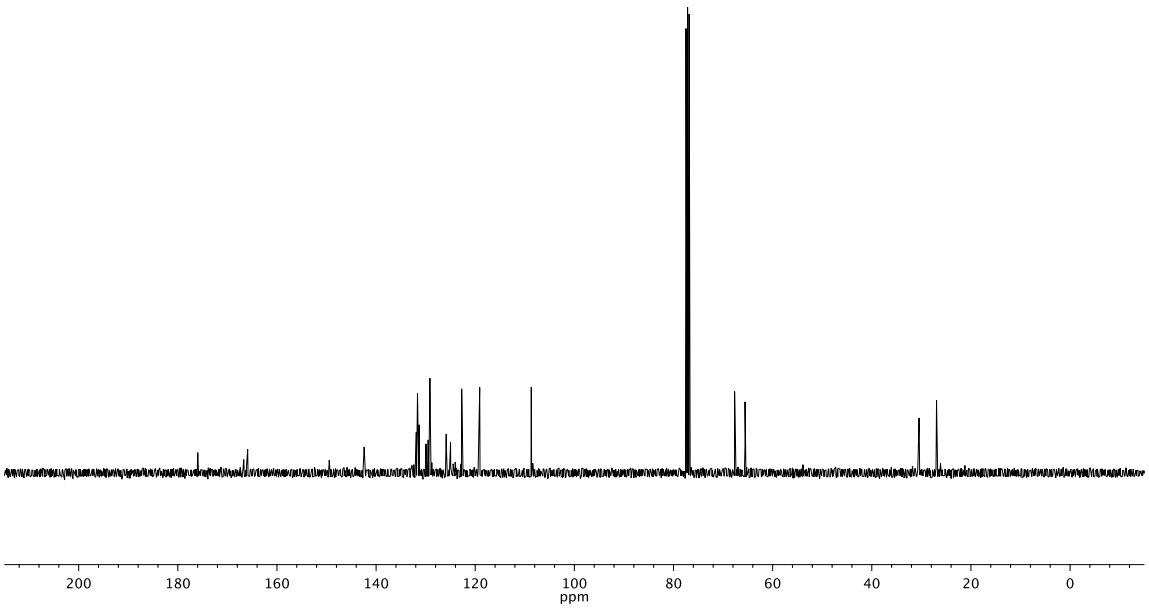


Figure A1.42. ^{13}C NMR (100 MHz, $CDCl_3$) of compound **50**.

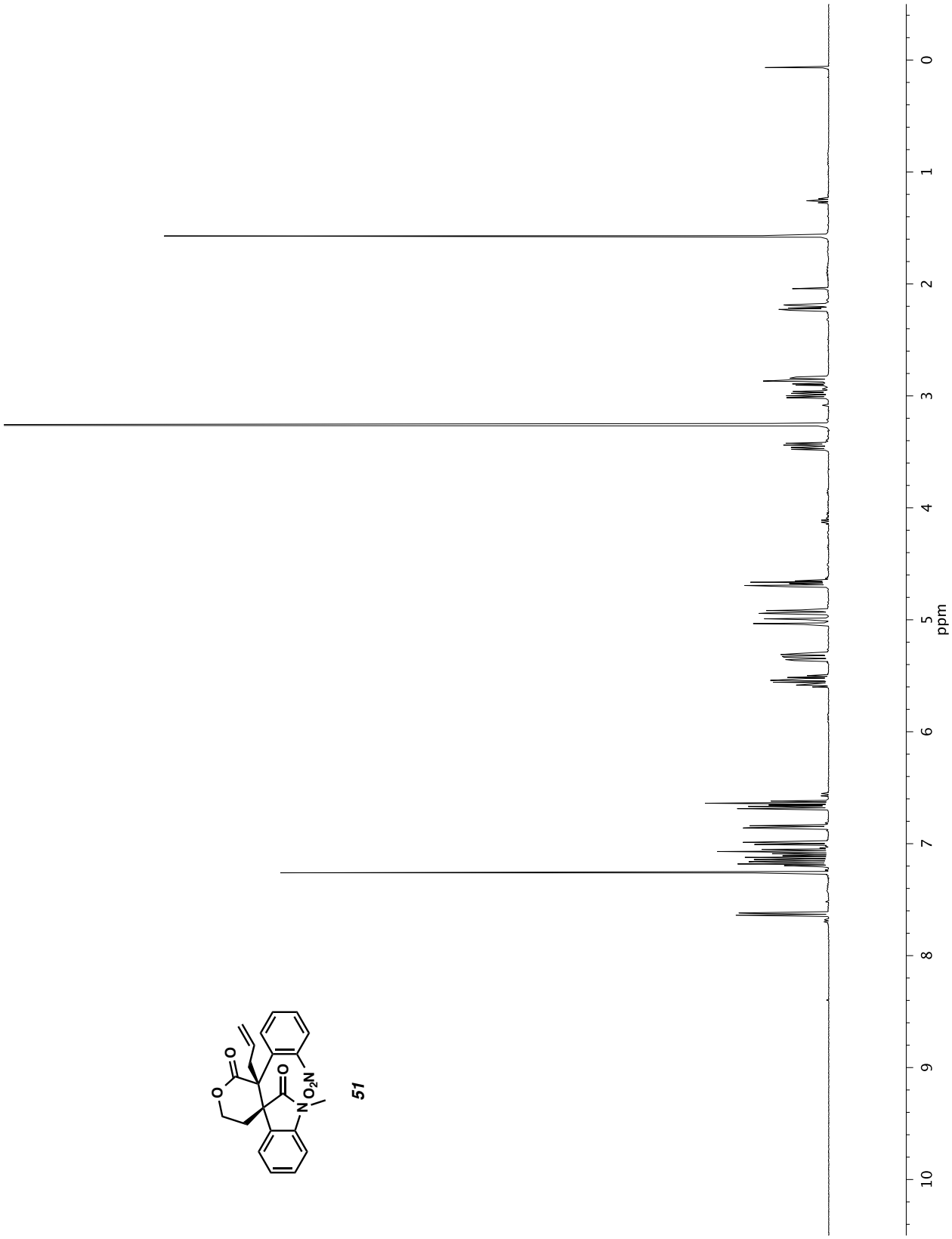


Figure A1.43. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **51**.

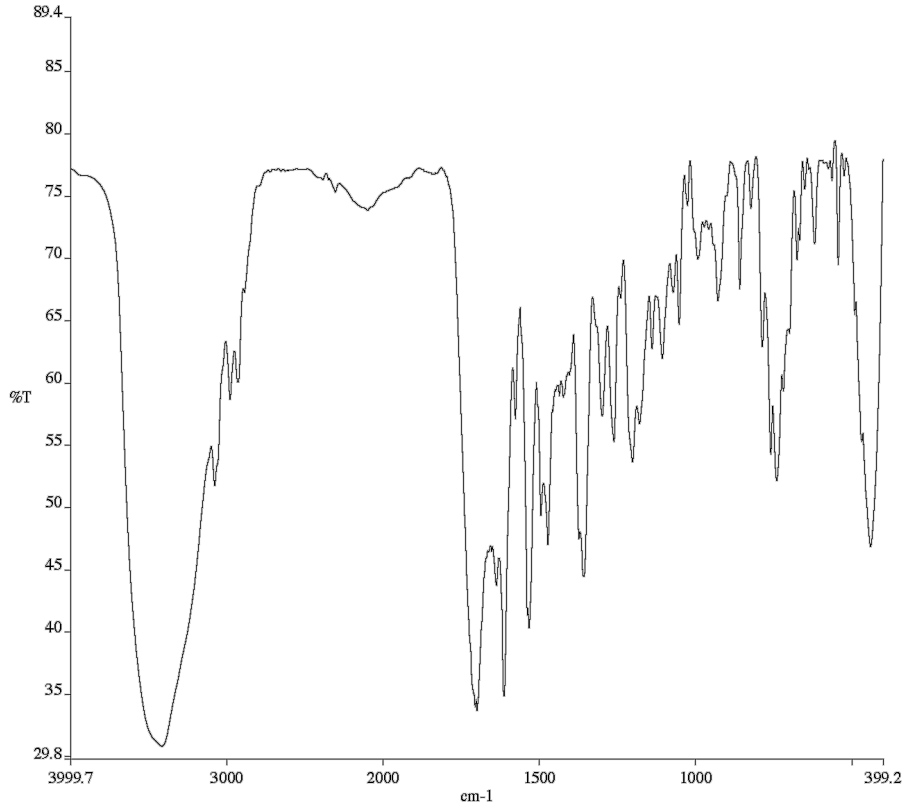


Figure A1.44. Infrared spectrum (Thin Film, NaCl) of compound **51**.

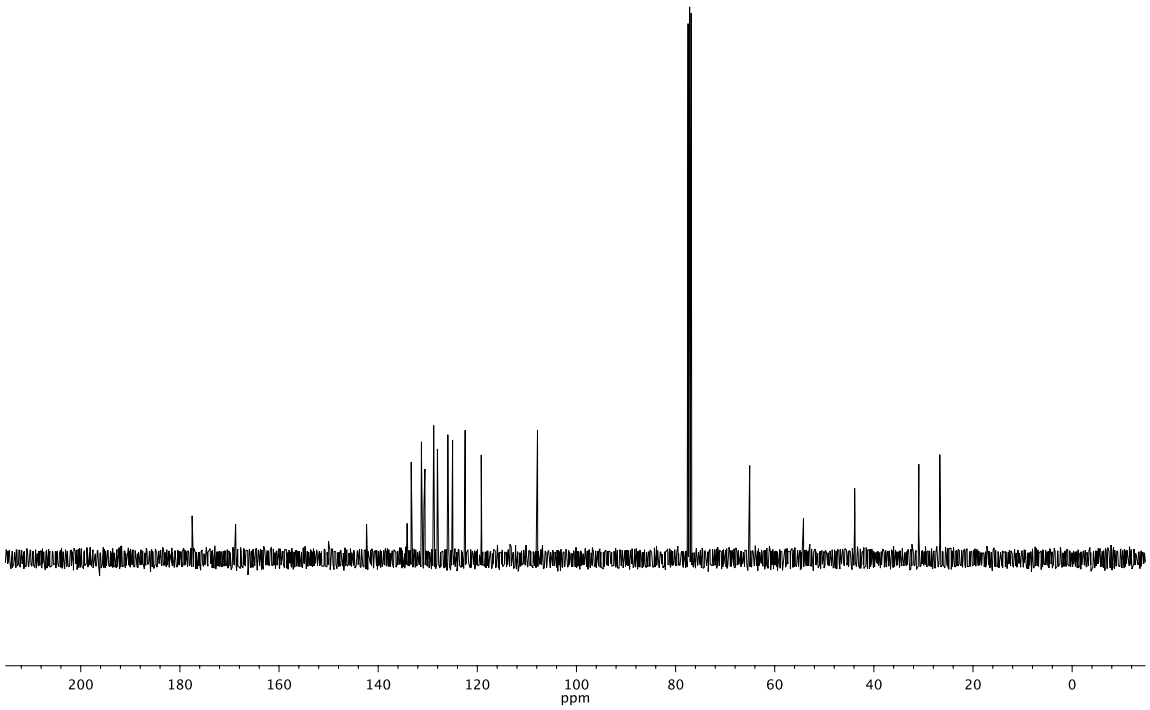


Figure A1.45. ^{13}C NMR (100 MHz, $CDCl_3$) of compound **51**.

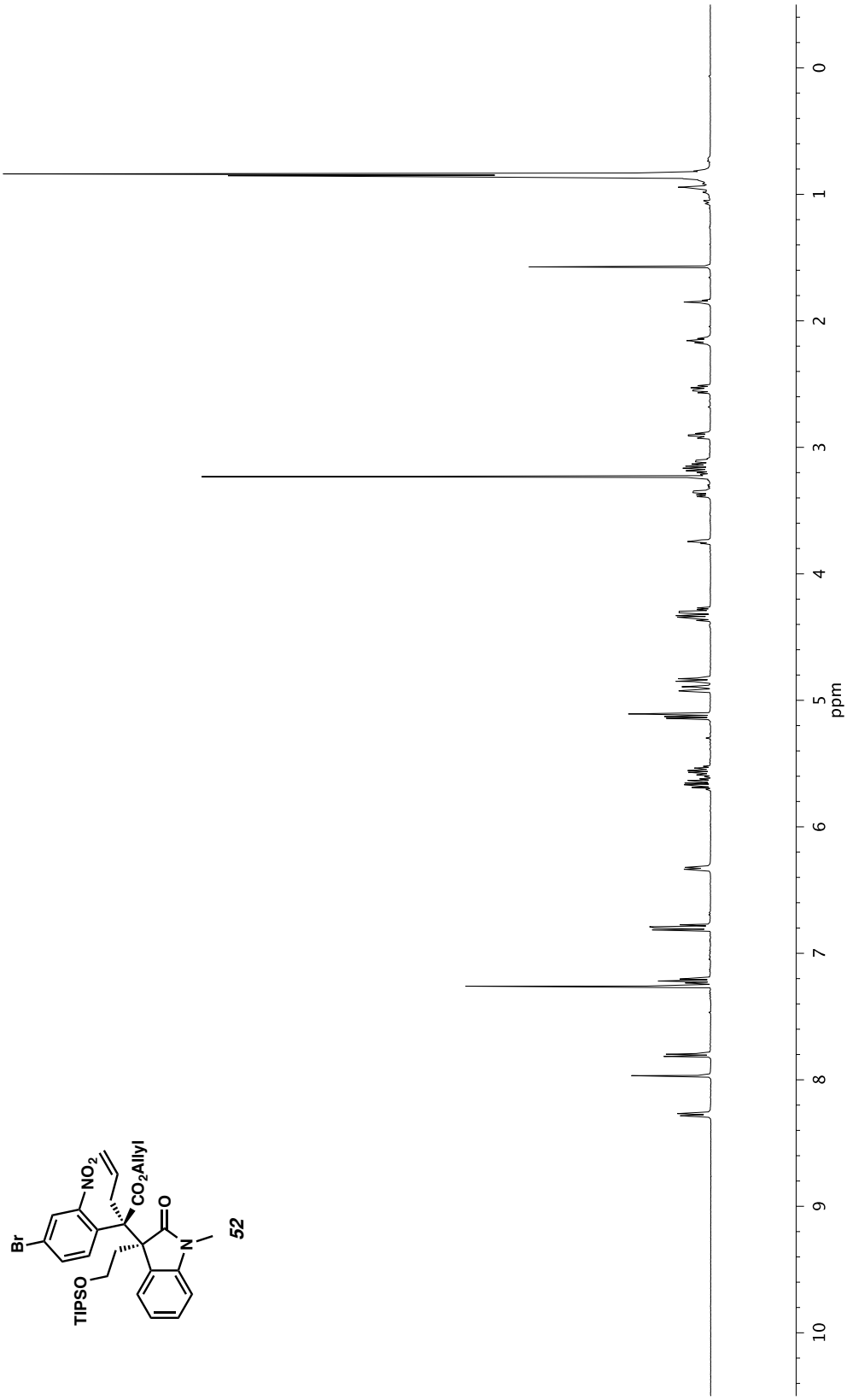


Figure A1.46. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **52**.

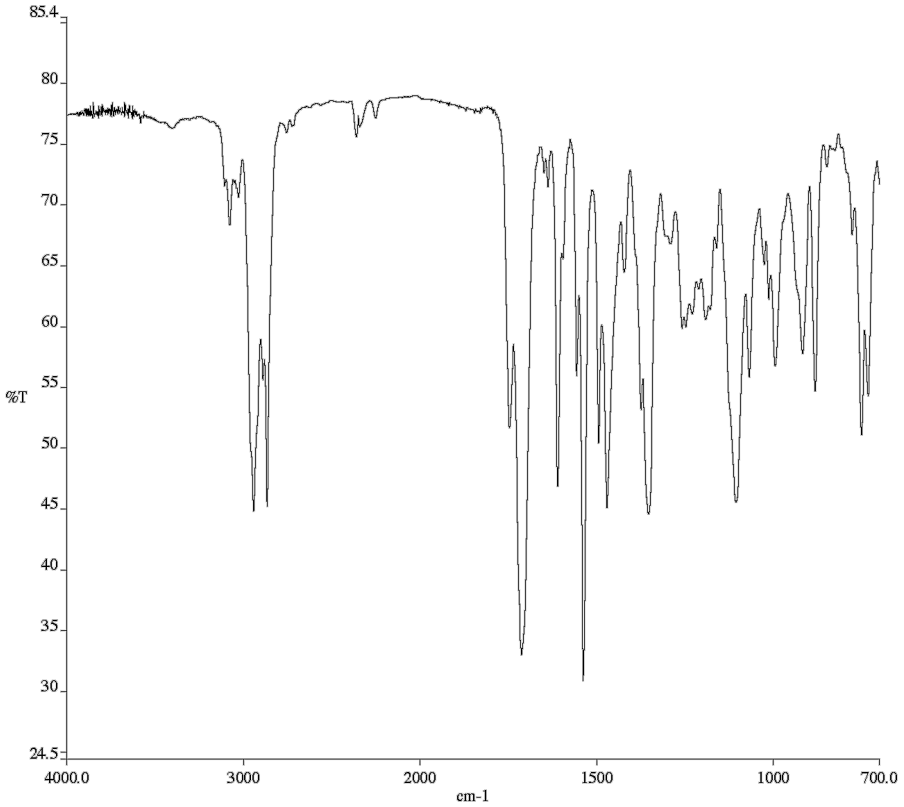


Figure A1.47. Infrared spectrum (Thin Film, NaCl) of compound **52**.

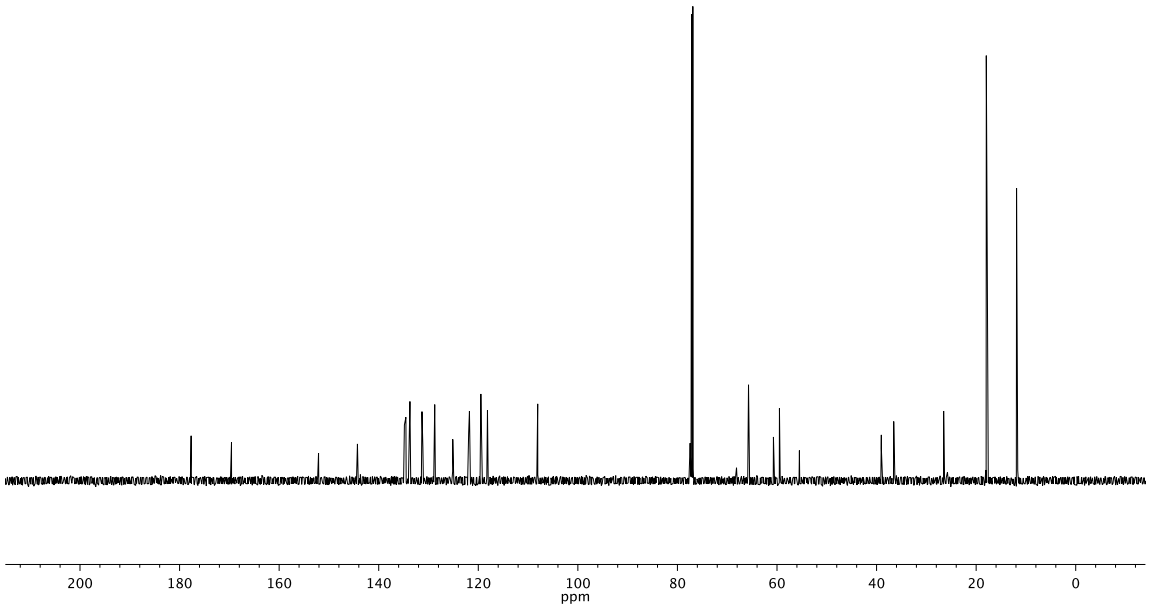


Figure A1.48. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **52**.

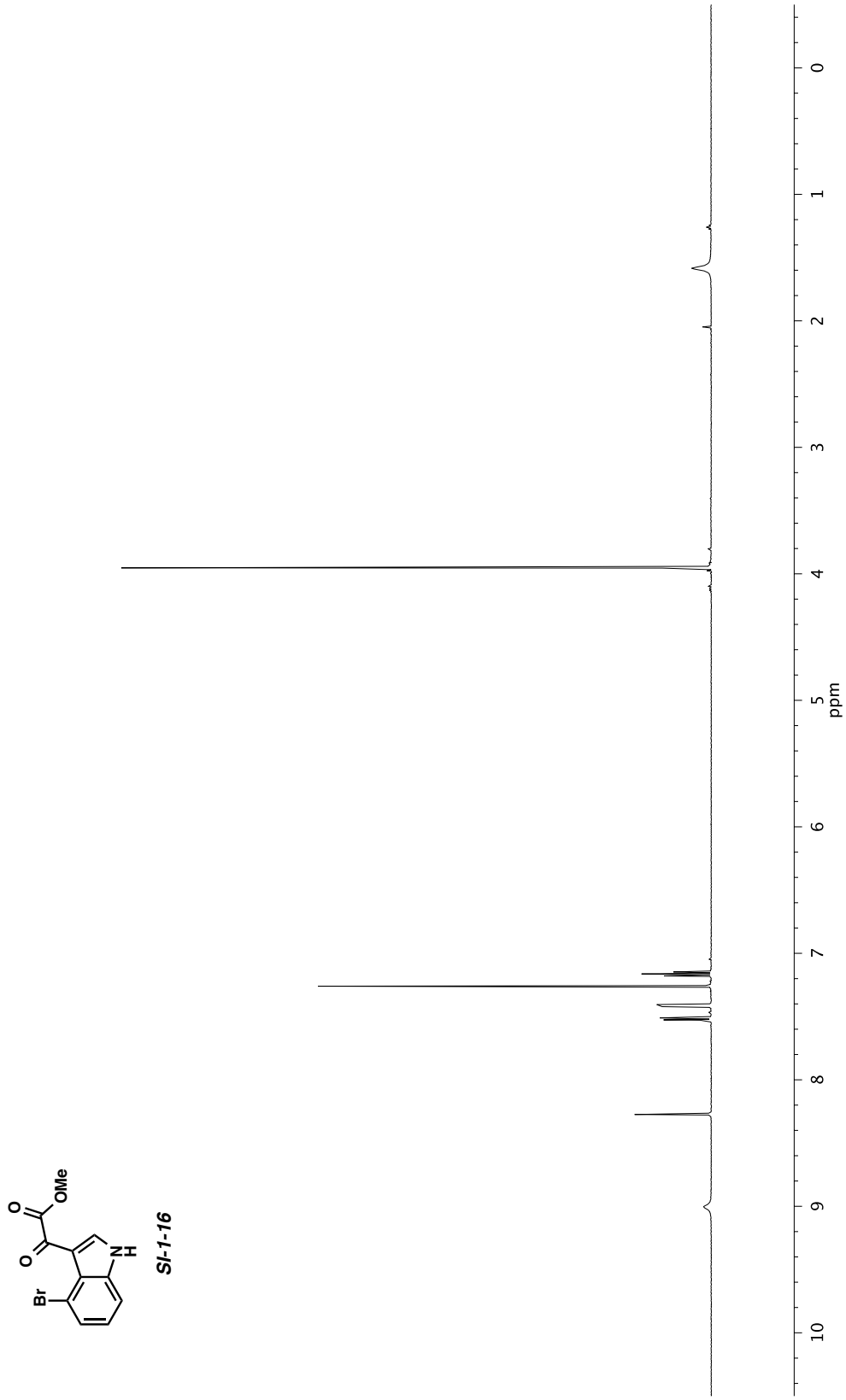


Figure A1.49. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **SI-1-16**.

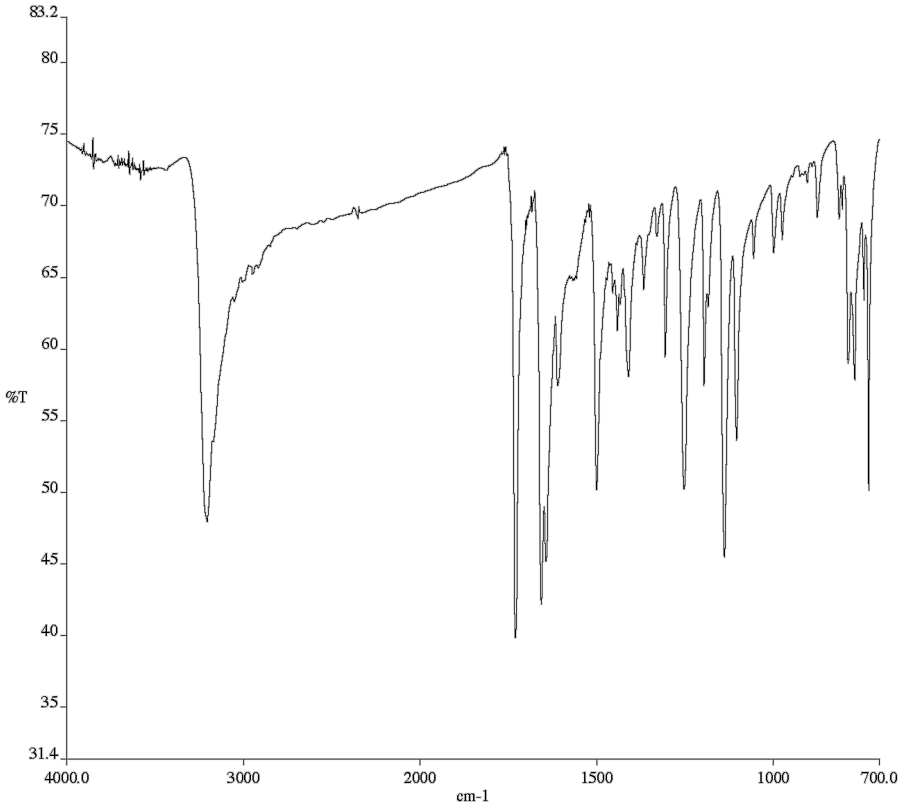


Figure A1.50. Infrared spectrum (Thin Film, NaCl) of compound **SI-1-16**.

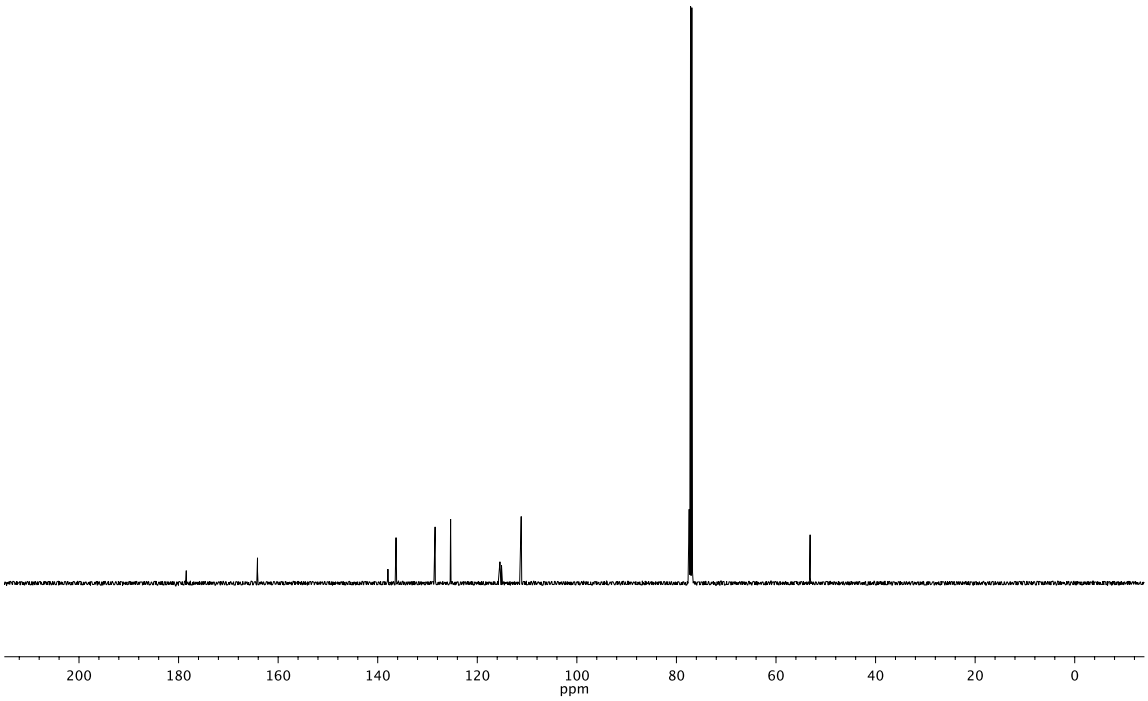


Figure A1.51. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **SI-1-16**.

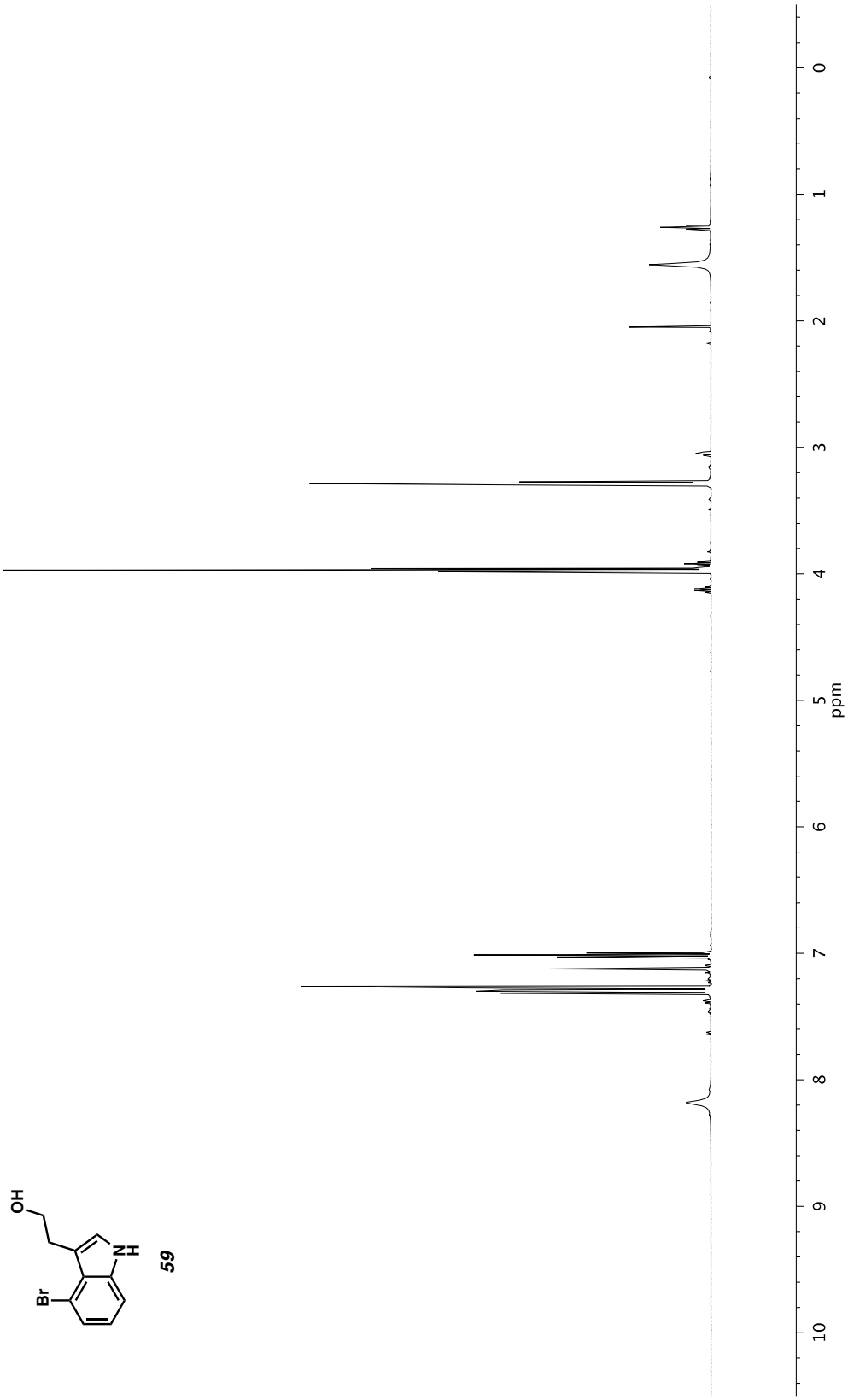


Figure A1.52. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **59**.

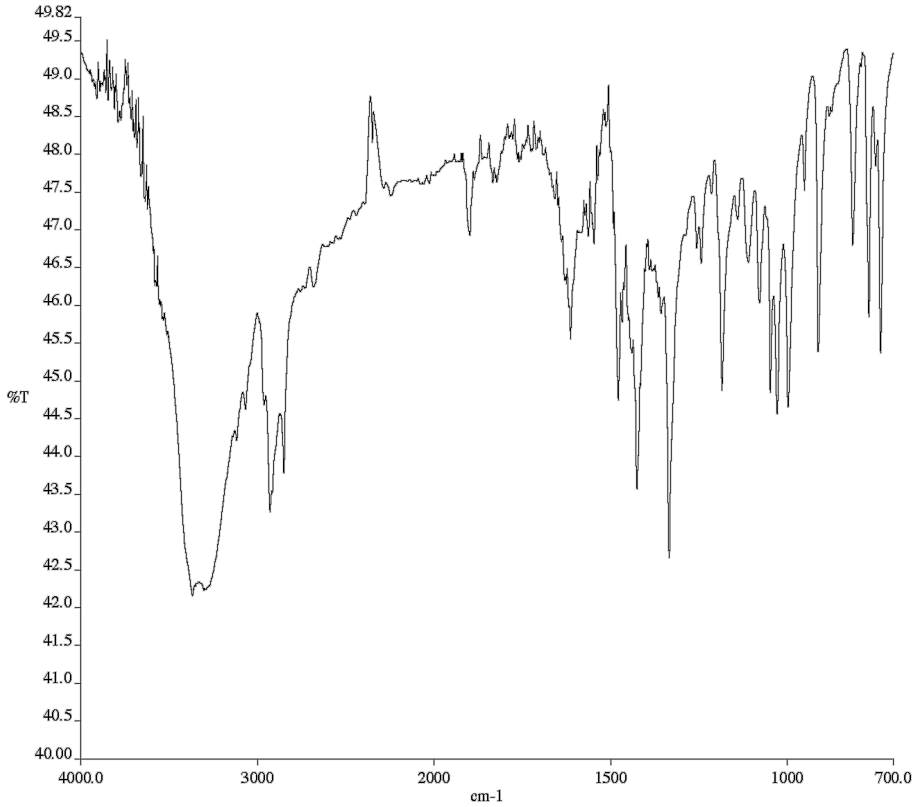


Figure A1.53. Infrared spectrum (Thin Film, NaCl) of compound **59**.

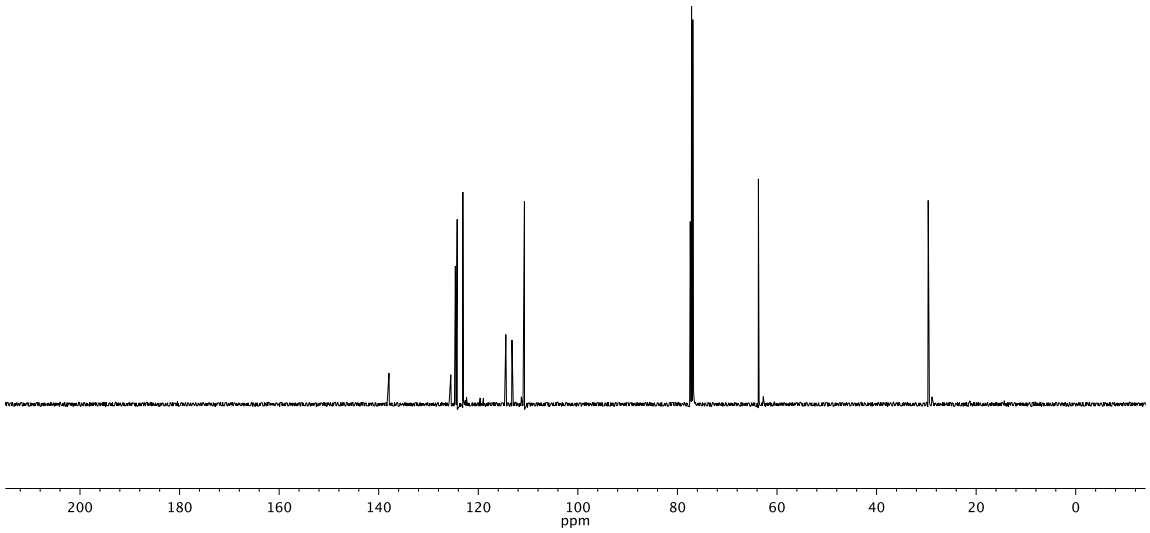


Figure A1.54. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **59**.

Figure A1.55. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **SI-1-17**.

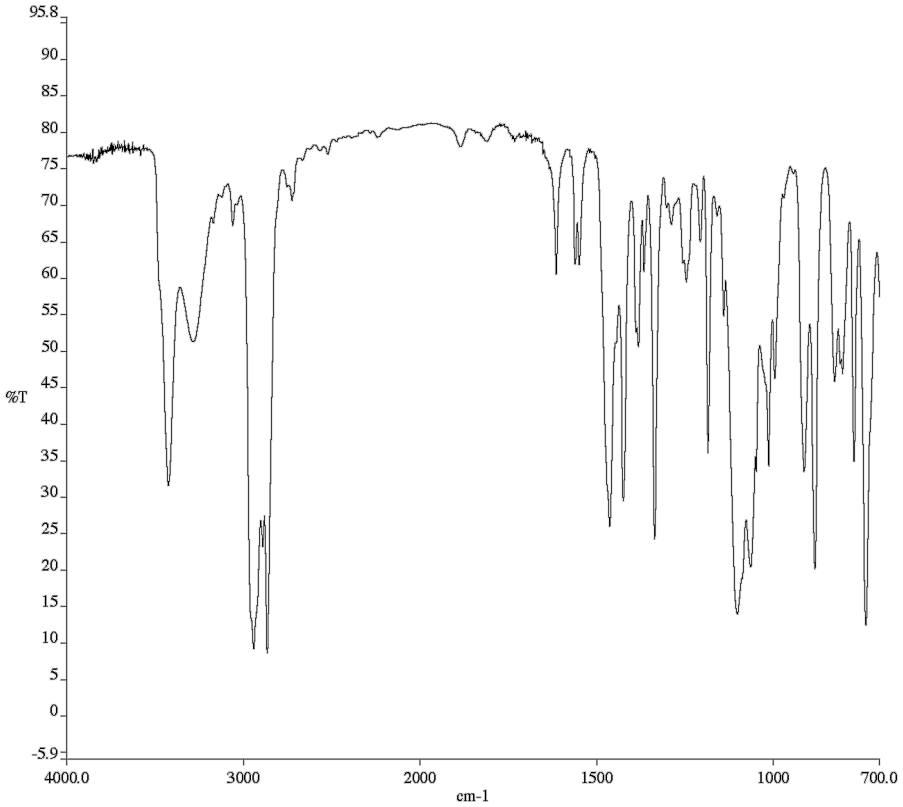


Figure A1.56. Infrared spectrum (Thin Film, NaCl) of compound **SI-1-17**.

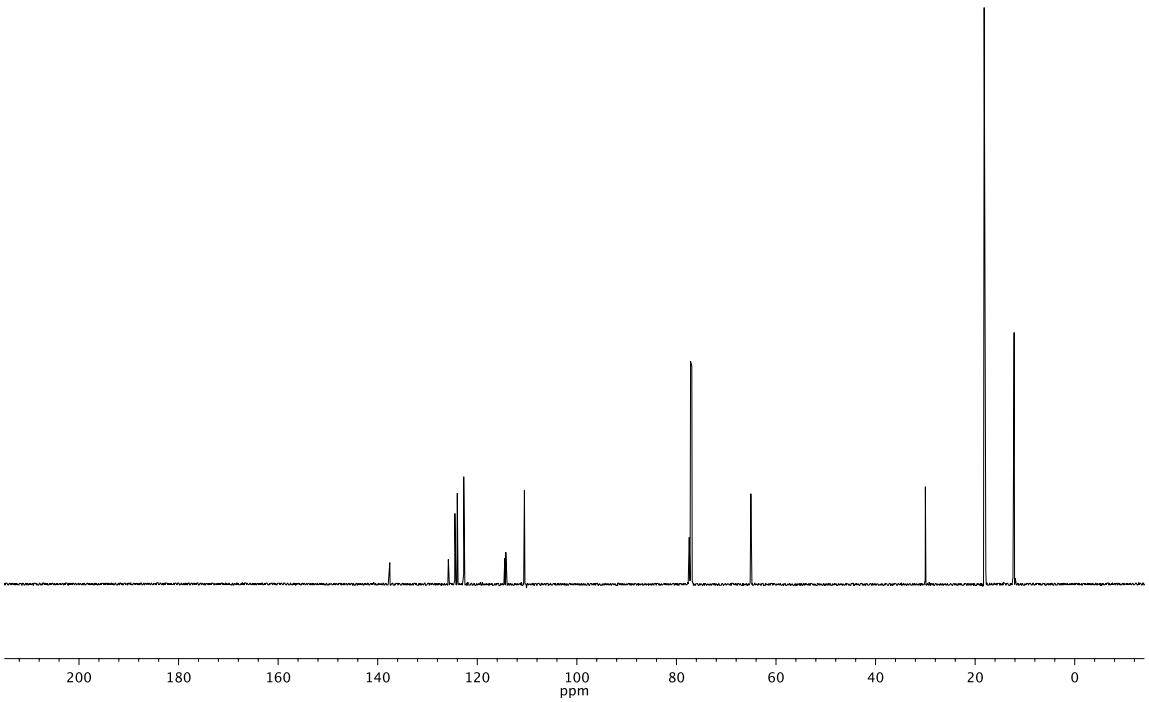


Figure A1.57. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **SI-1-17.**

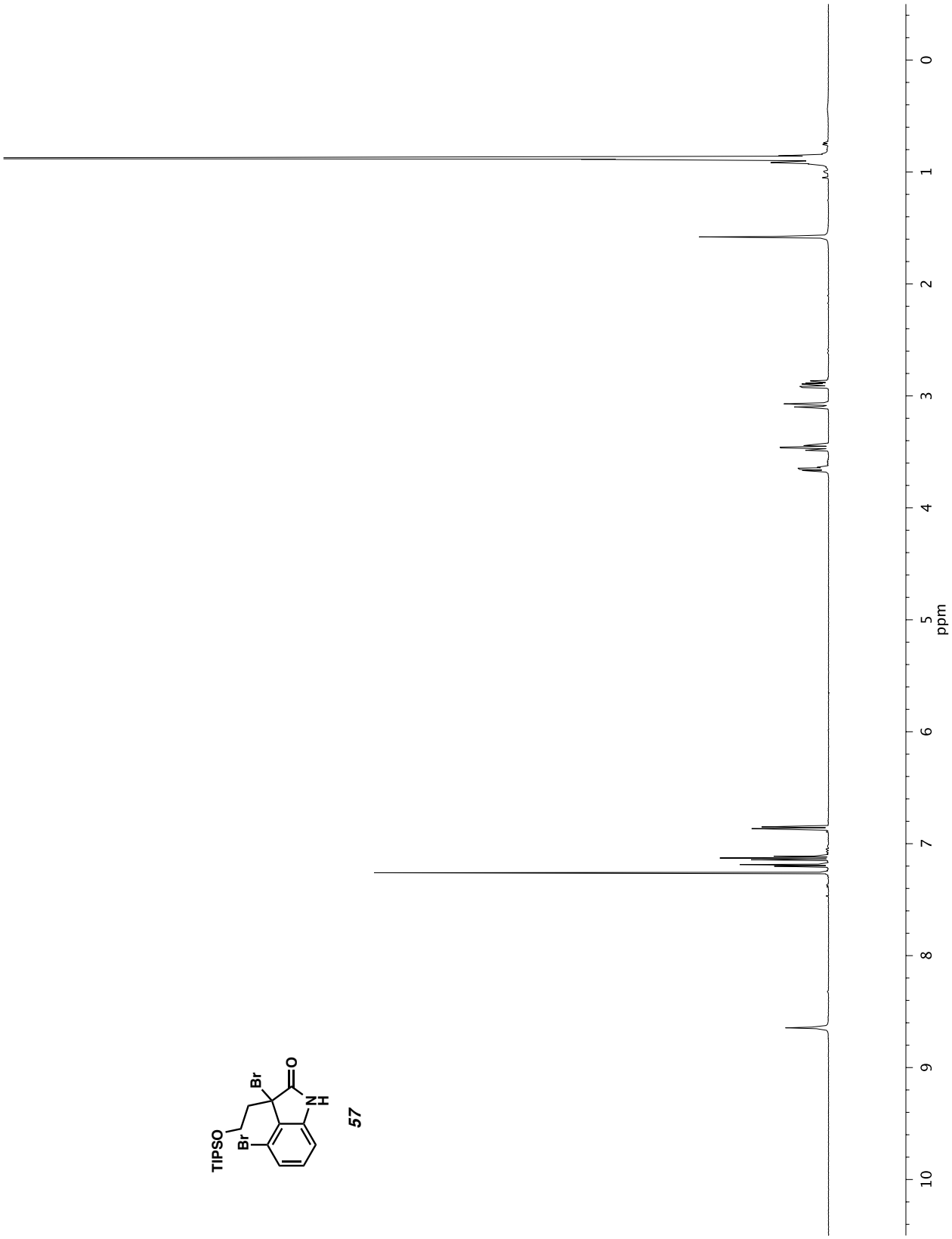


Figure A1.58. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **57**.

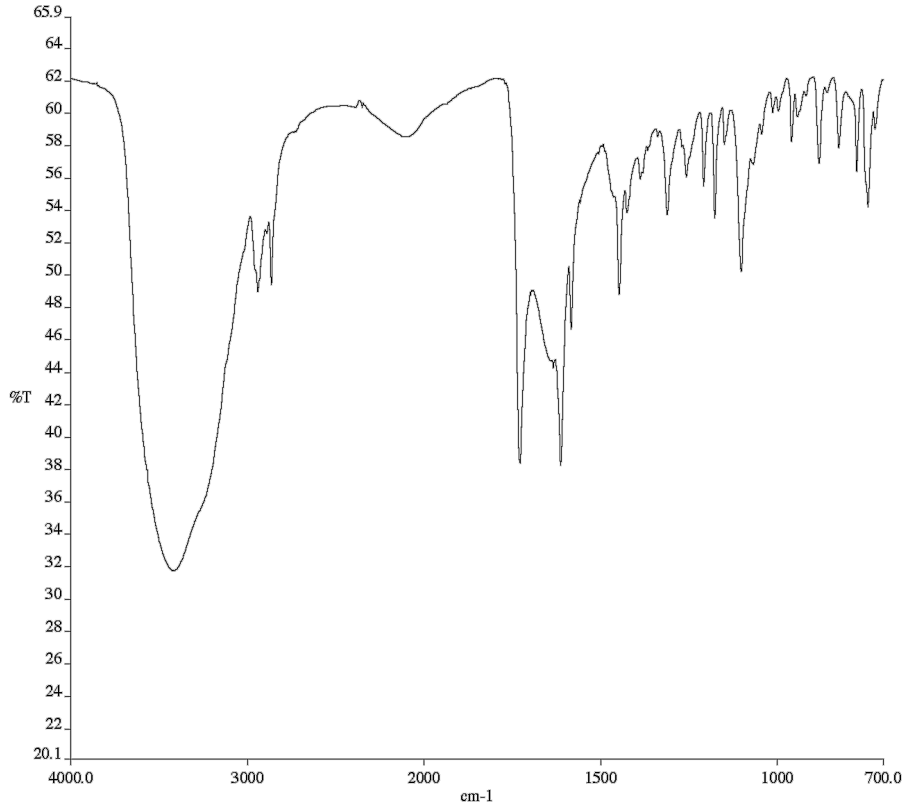


Figure A1.59. Infrared spectrum (Thin Film, NaCl) of compound **57**.

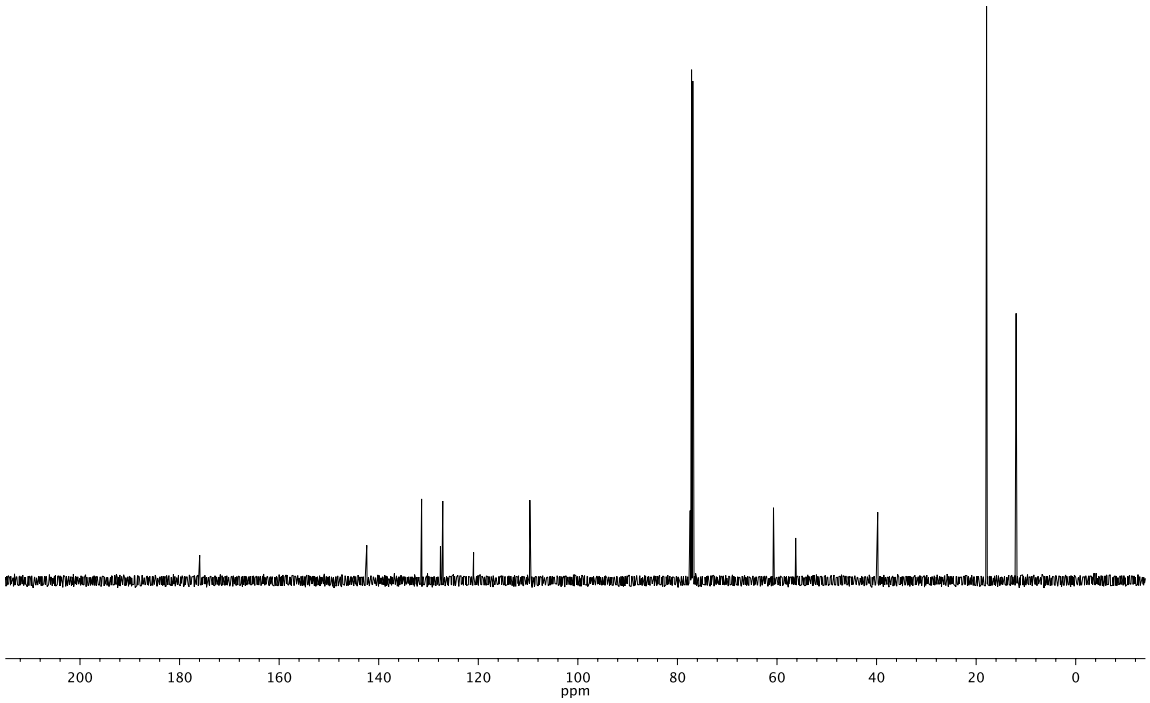


Figure A1.60. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **57.**

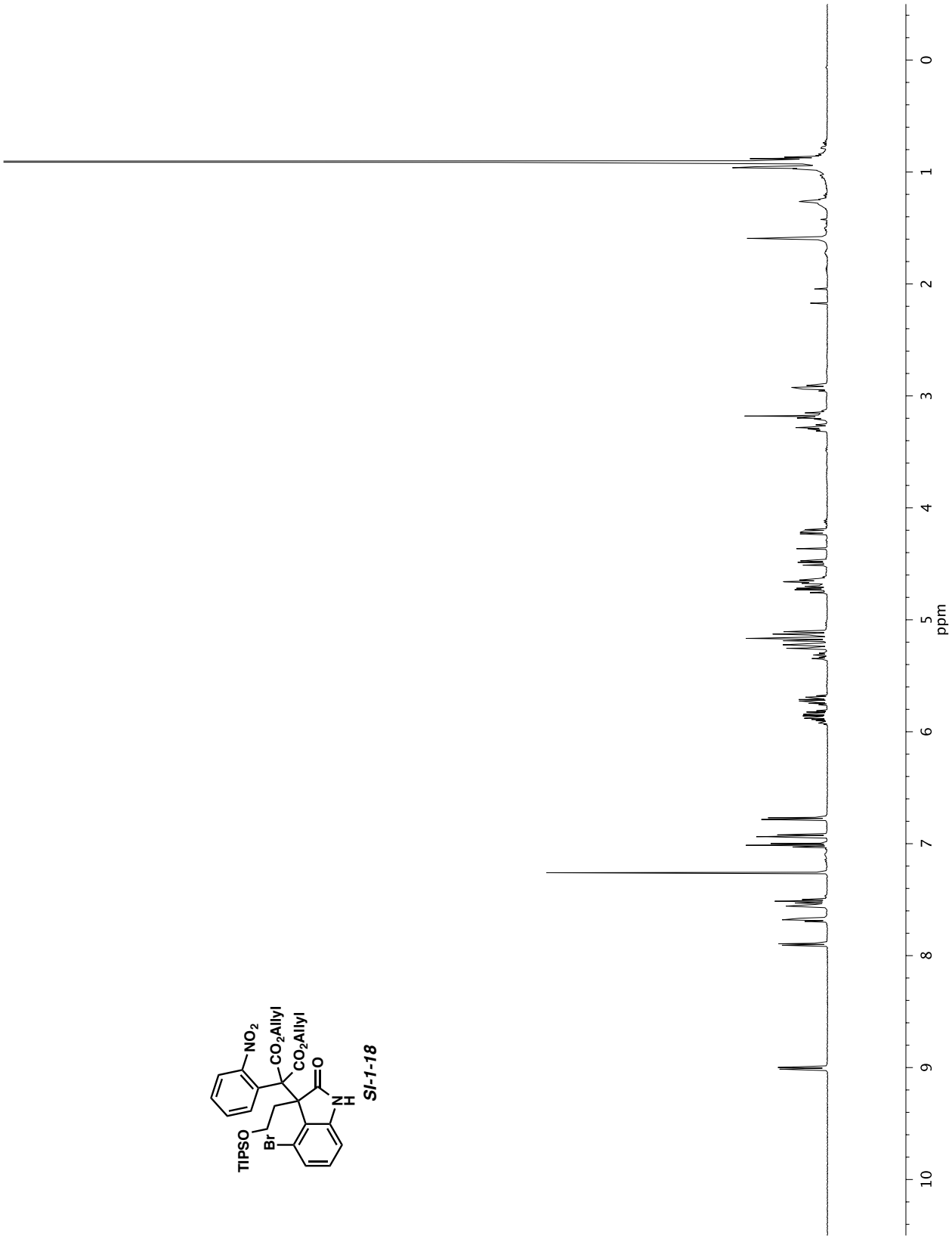


Figure A1.61. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **SI-1-18**.

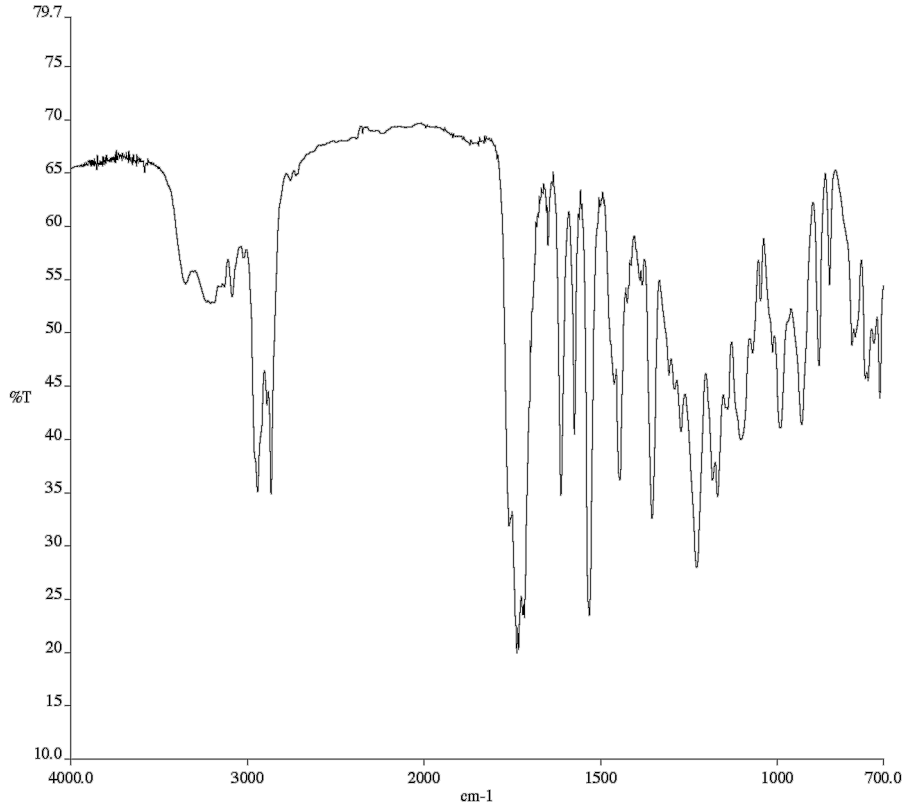


Figure A1.62. Infrared spectrum (Thin Film, NaCl) of compound **SI-1-18**.

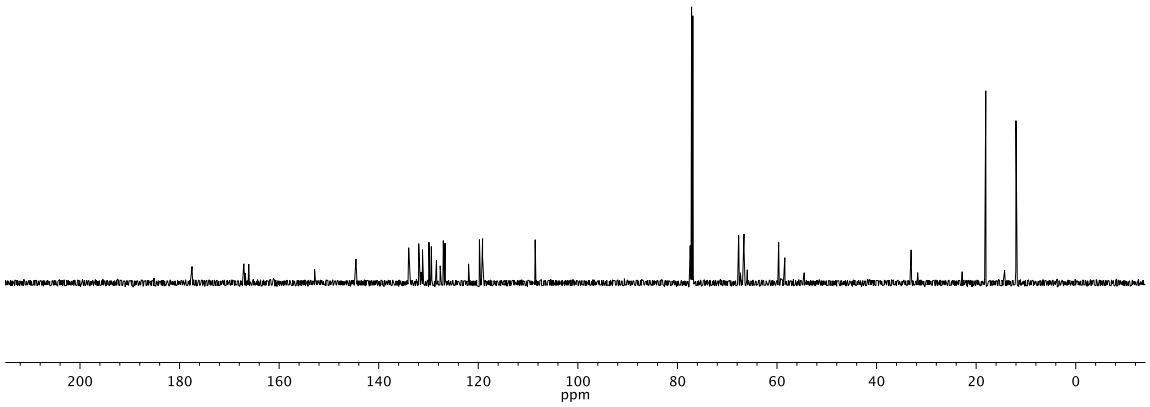


Figure A1.63. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **SI-1-18.**

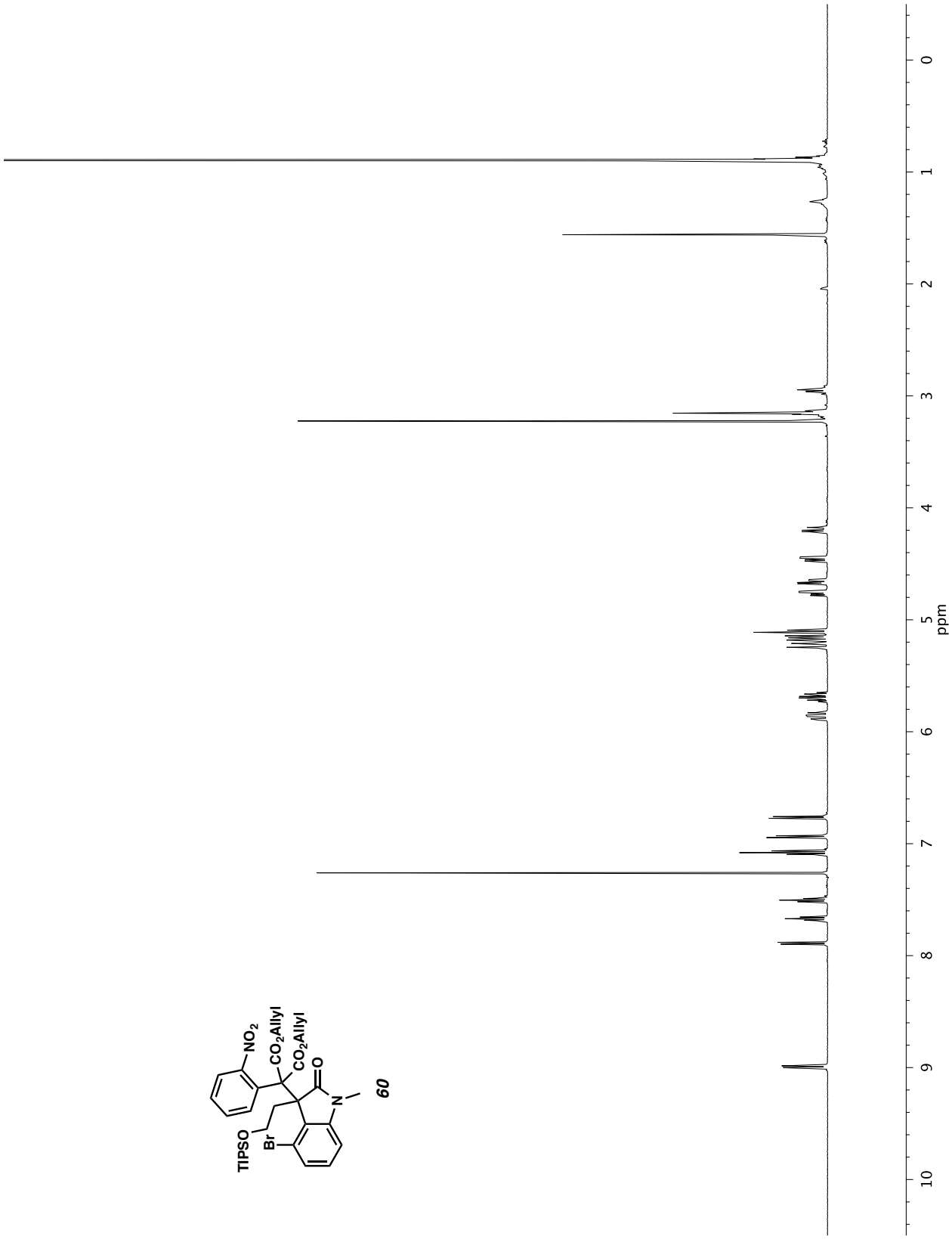


Figure A1.64. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **60**.

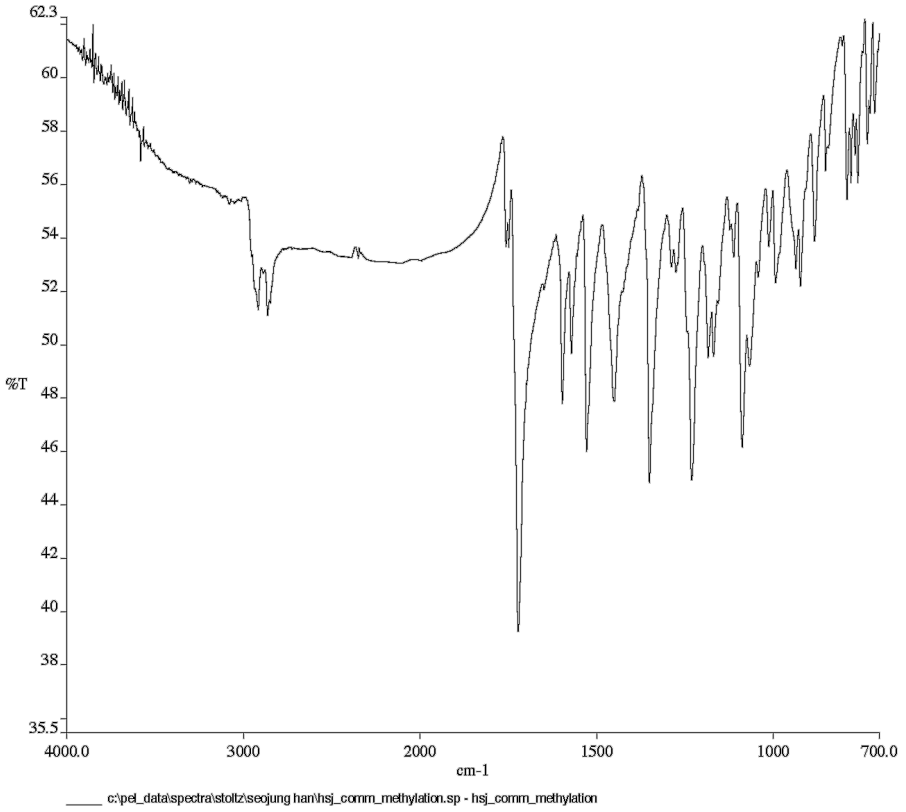


Figure A1.65. Infrared spectrum (Thin Film, NaCl) of compound **60**.

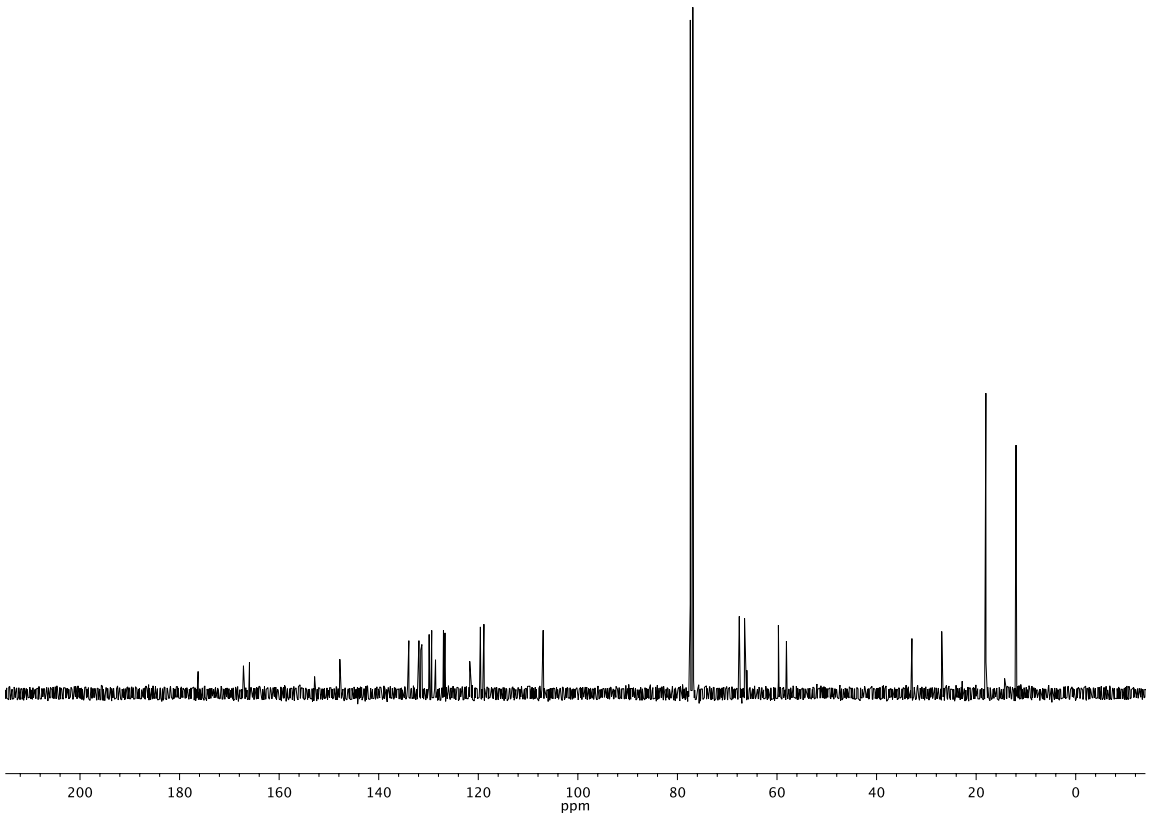


Figure A1.66. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **60**

61

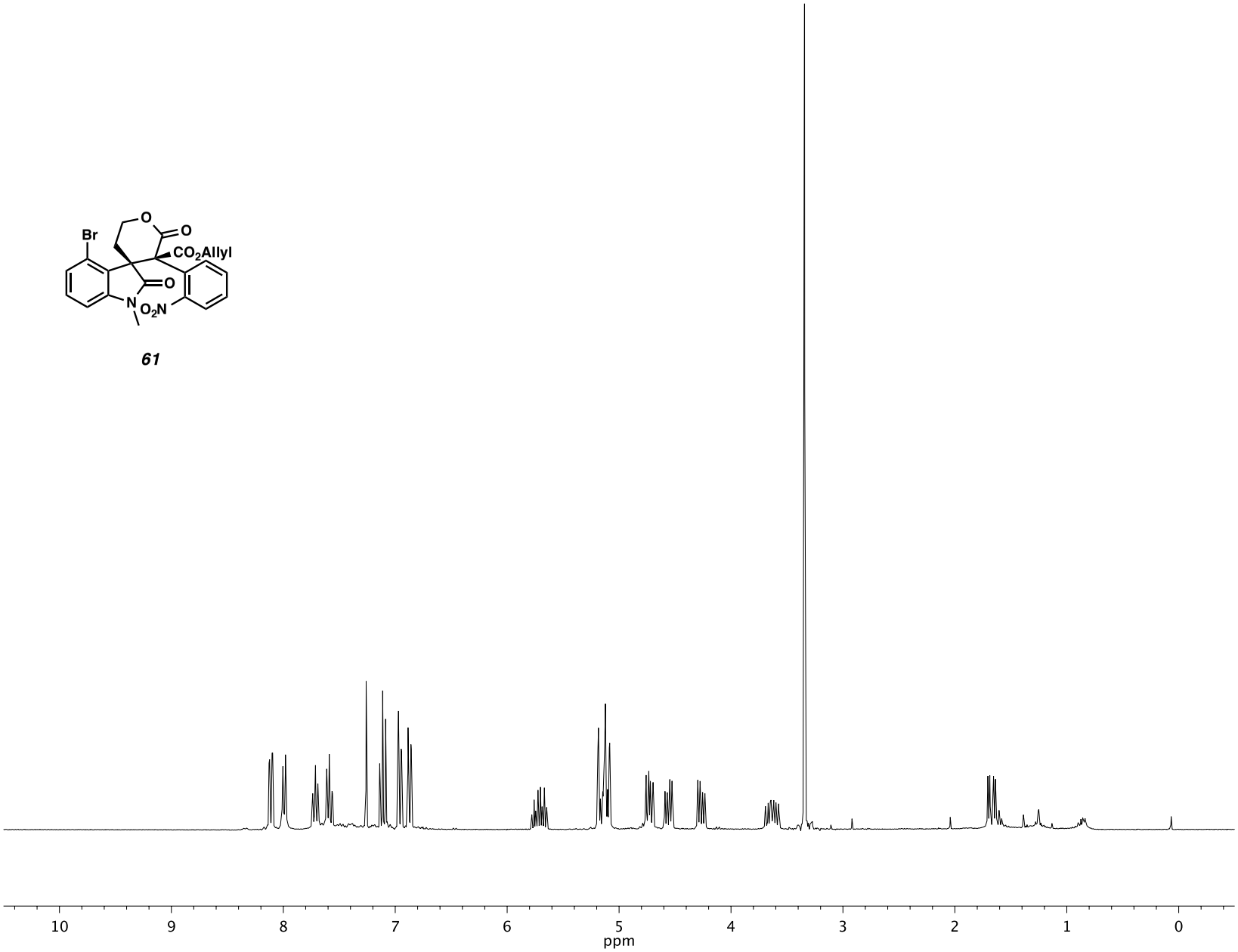


Figure A1.67. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **61**.

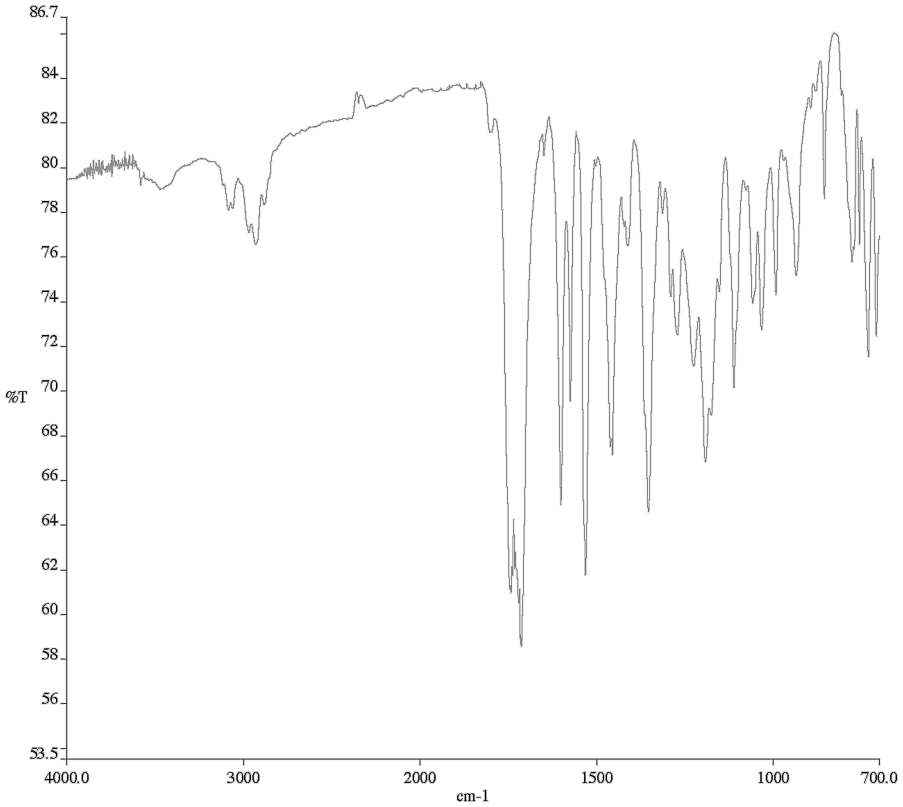


Figure A1.68. Infrared spectrum (Thin Film, NaCl) of compound **61**.

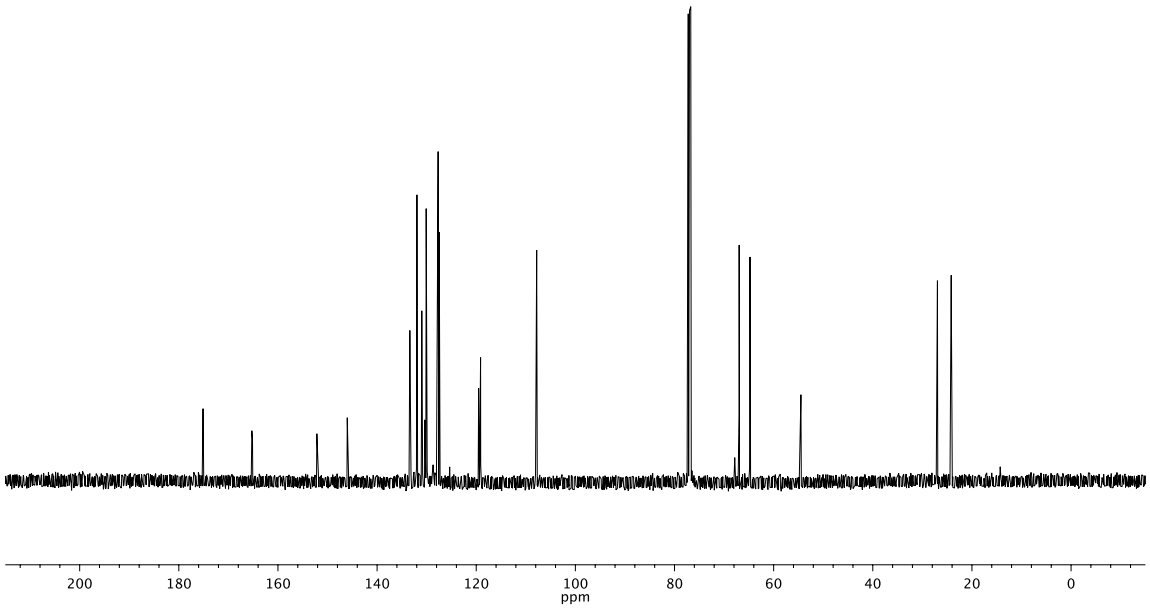
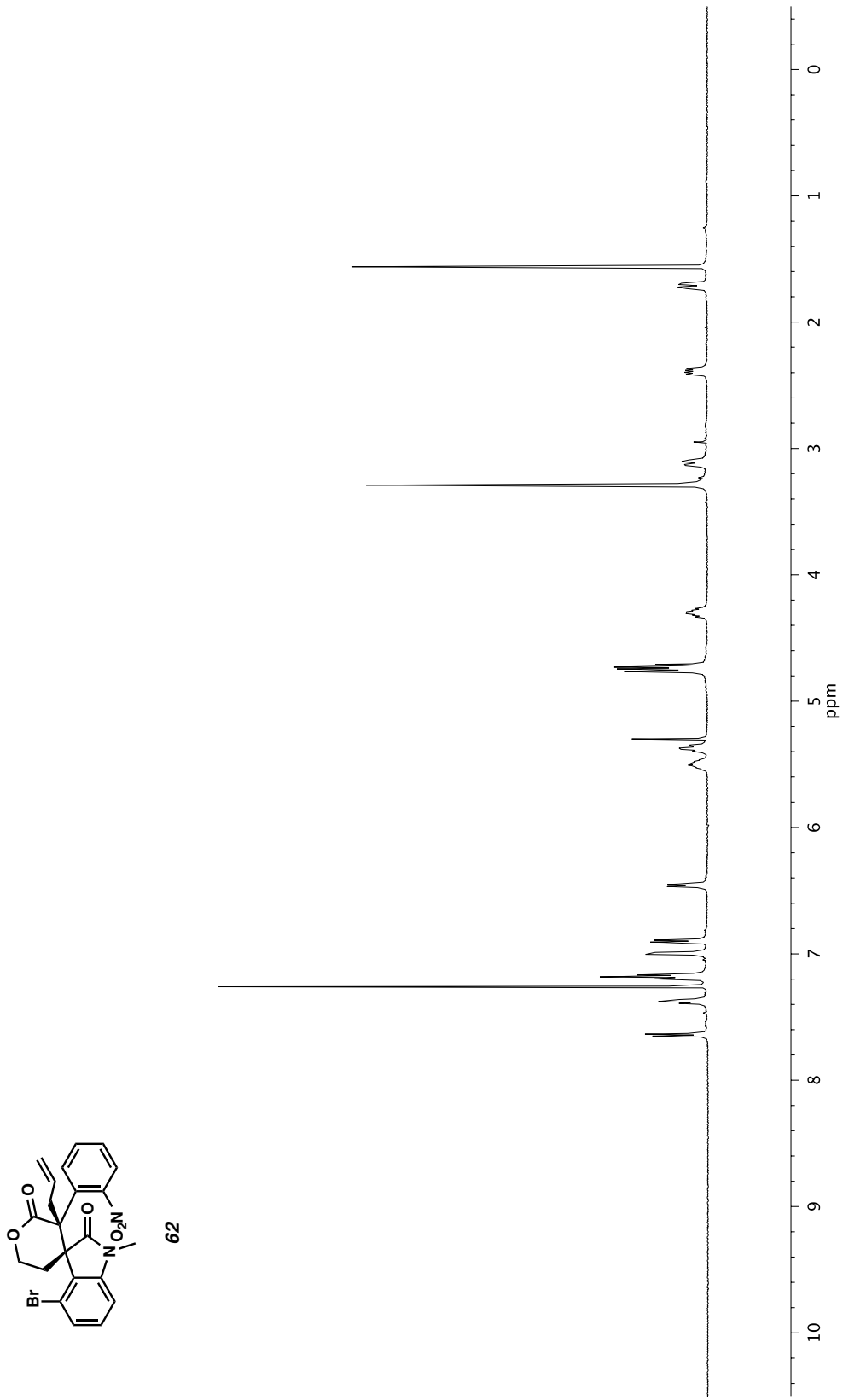


Figure A1.69. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **61.**



62

Figure A1.70. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **62**.

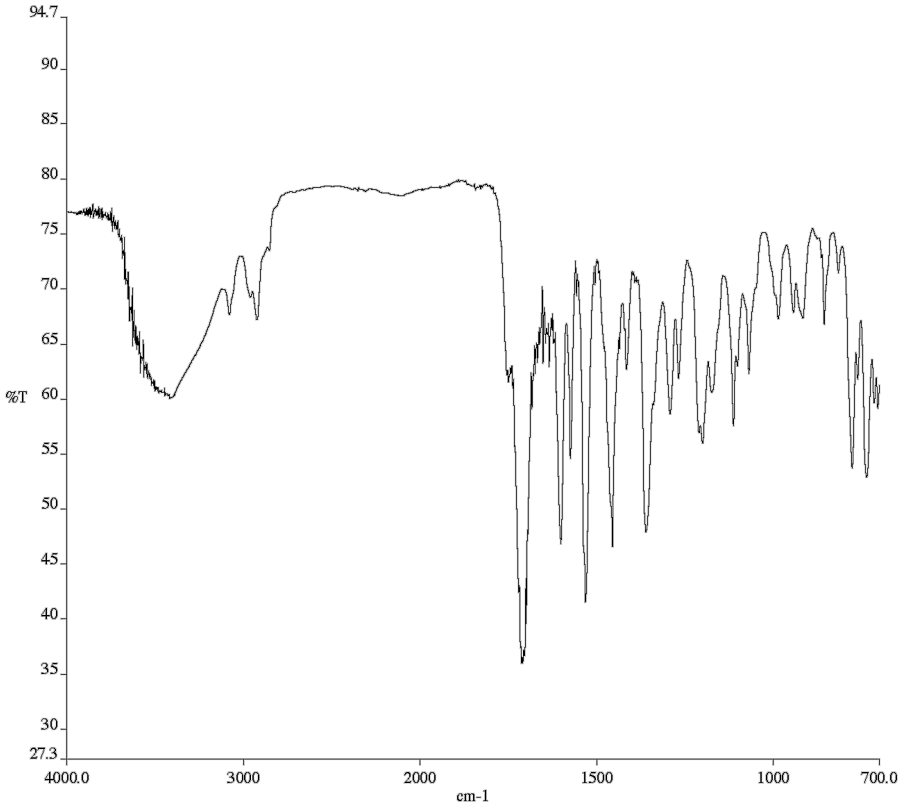


Figure A1.71. Infrared spectrum (Thin Film, NaCl) of compound **62**.

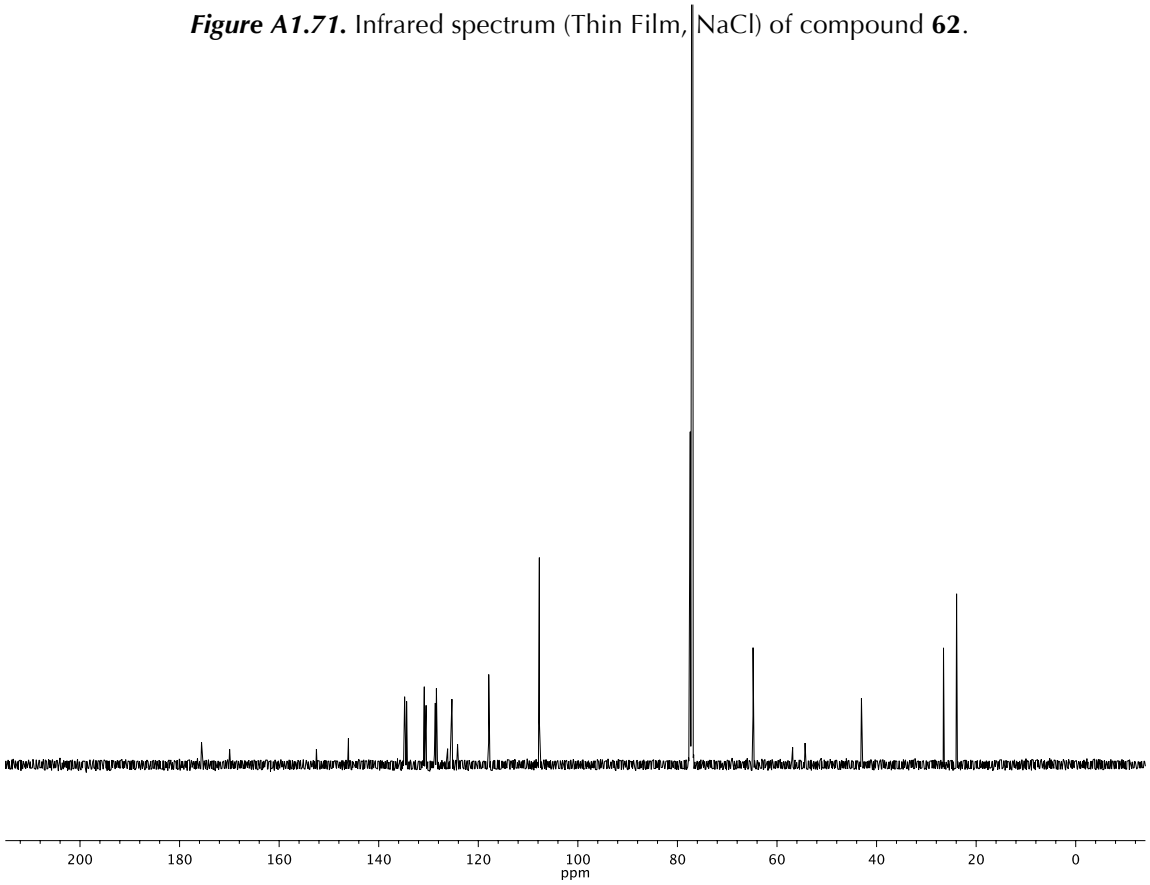
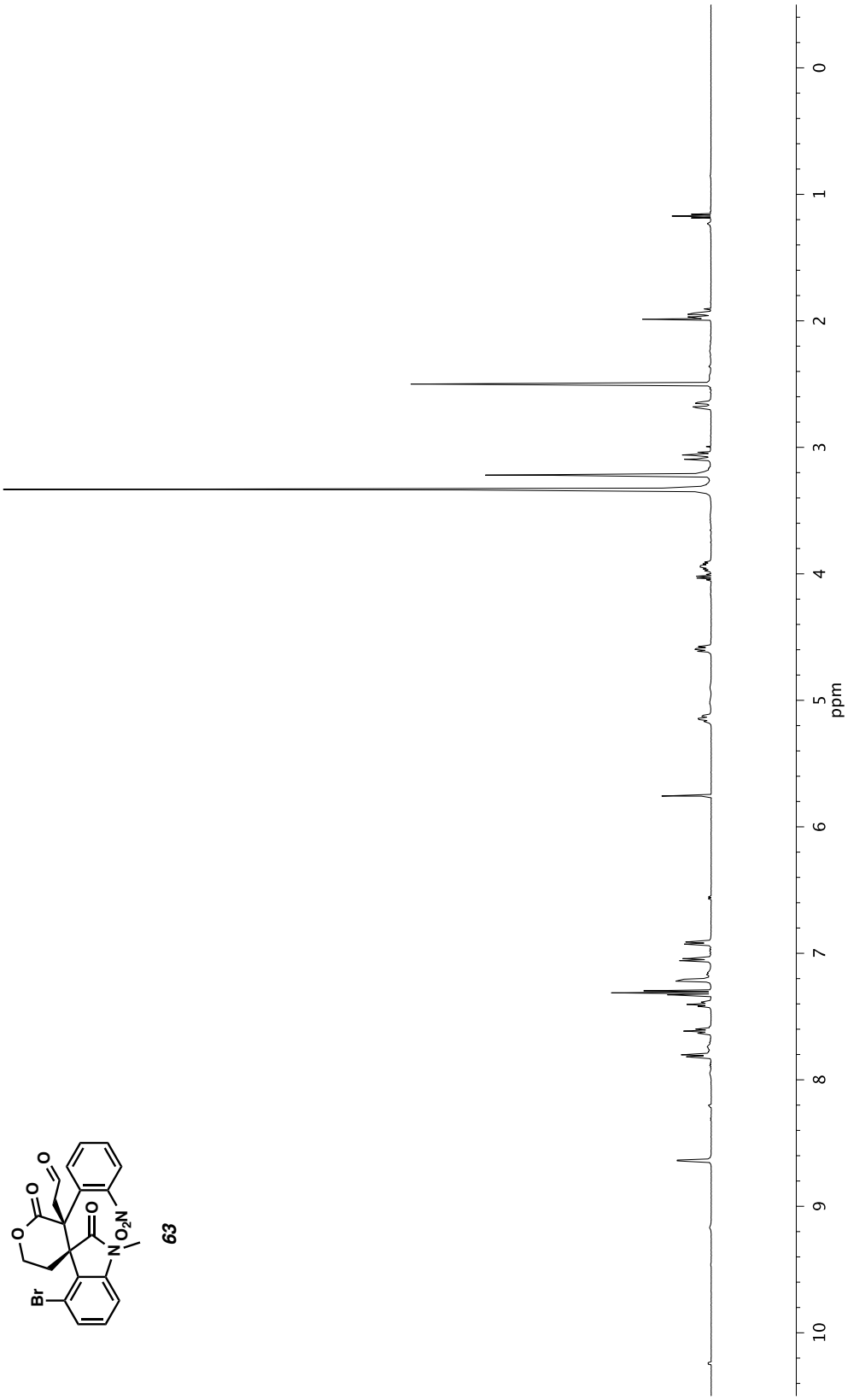


Figure A1.72. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **62.**



63

Figure A1.73. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **63**.

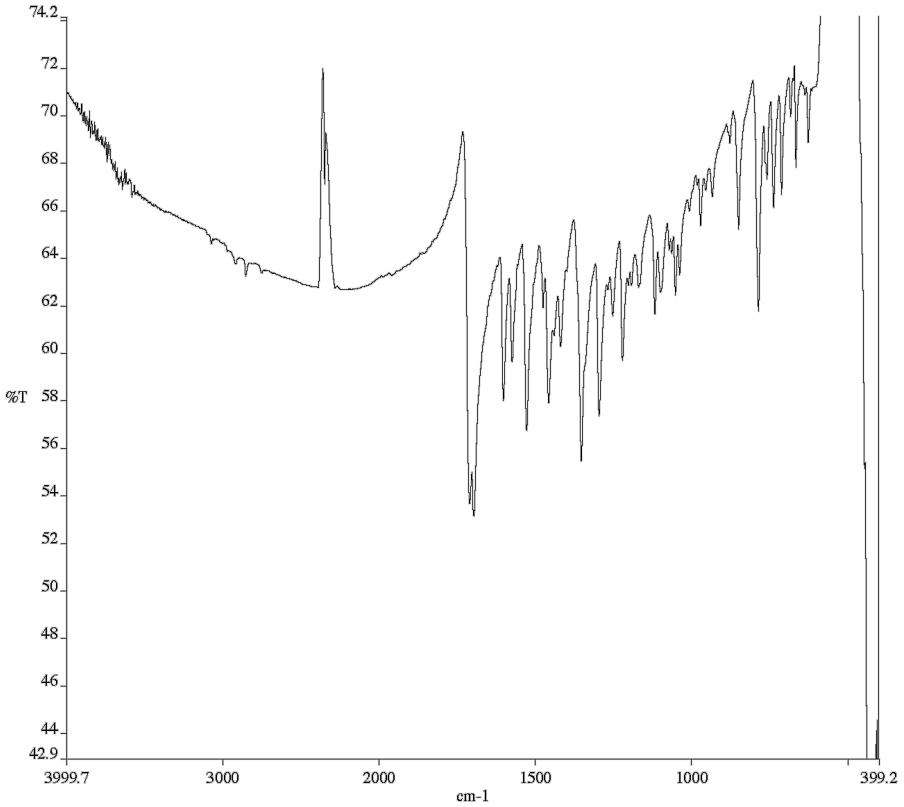


Figure A1.74. Infrared spectrum (Thin Film, NaCl) of compound **63**.

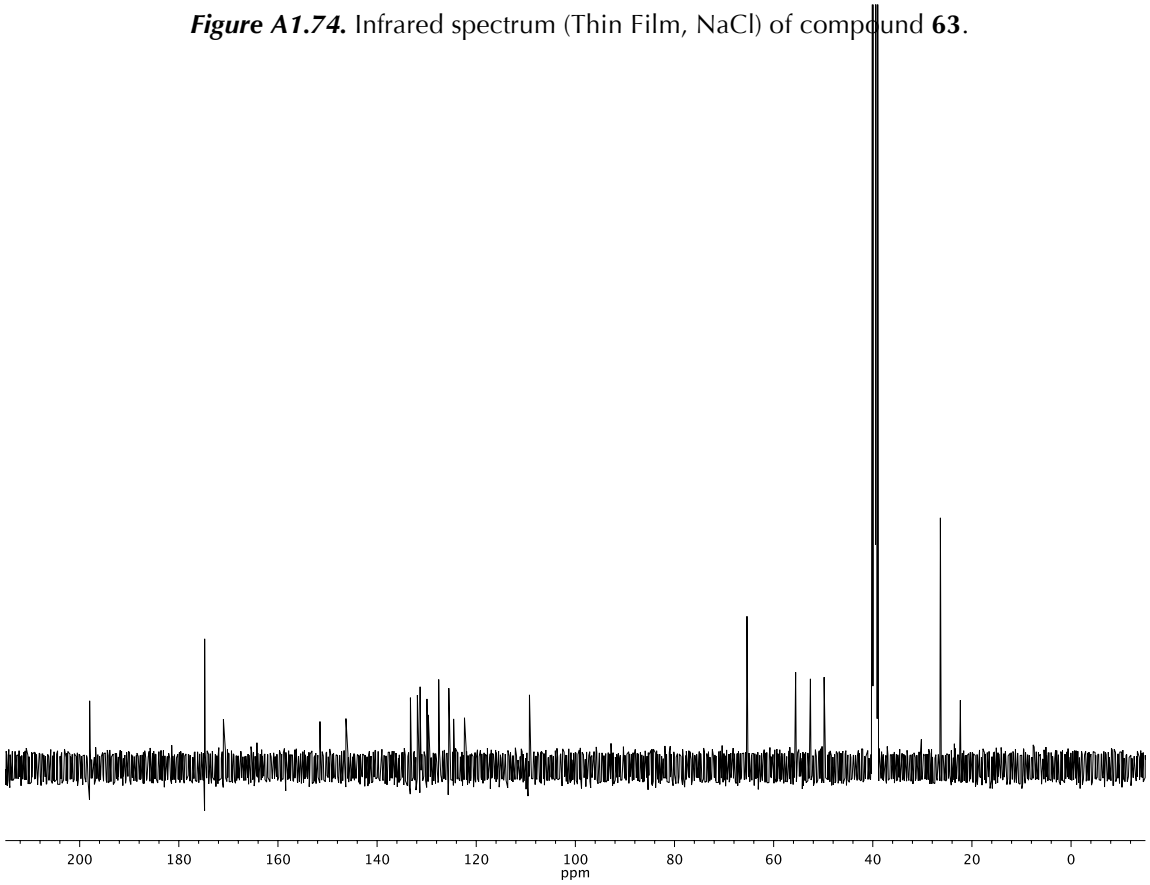
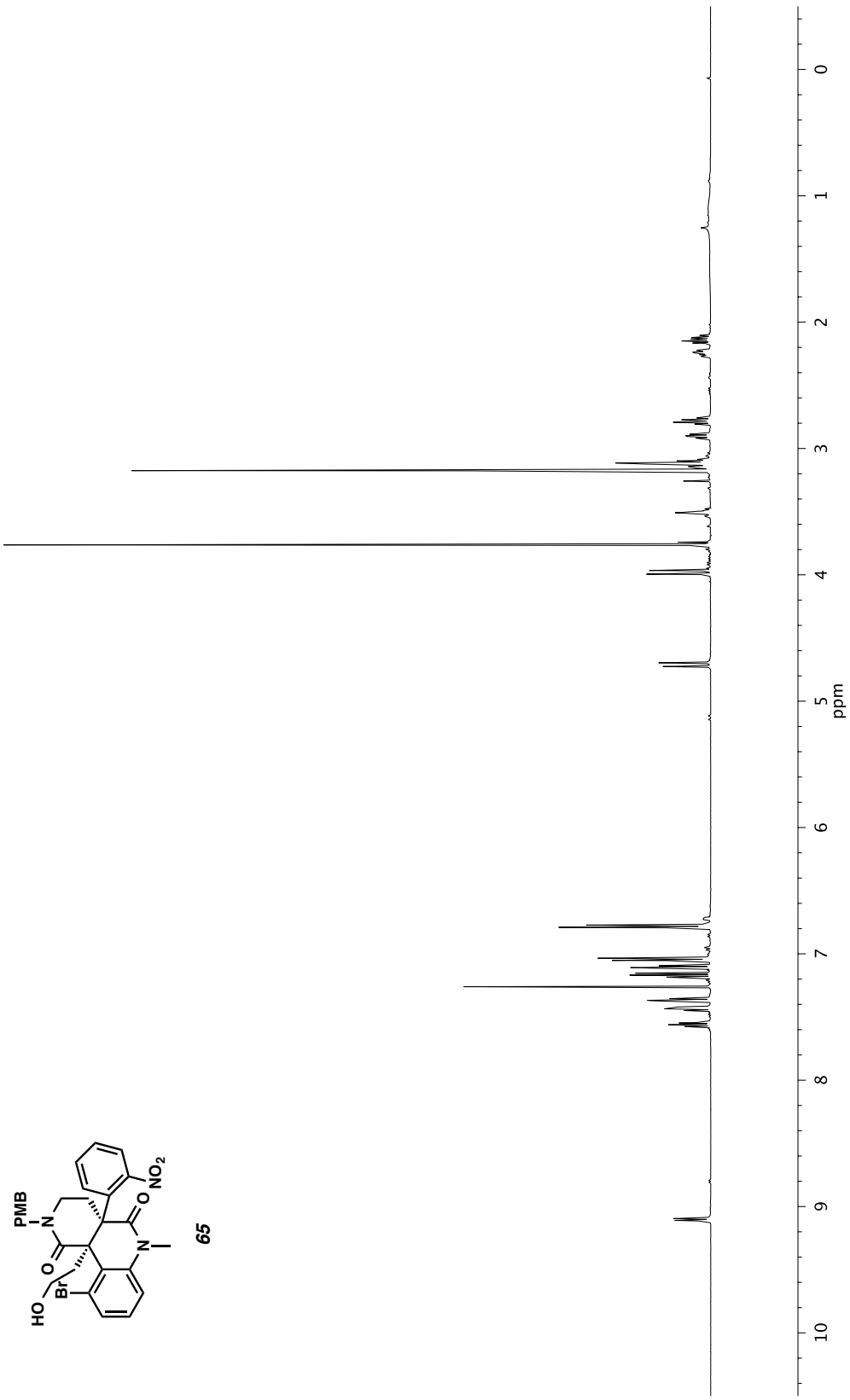


Figure A1.75. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **63.**



65

Figure A1.76. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **65**.

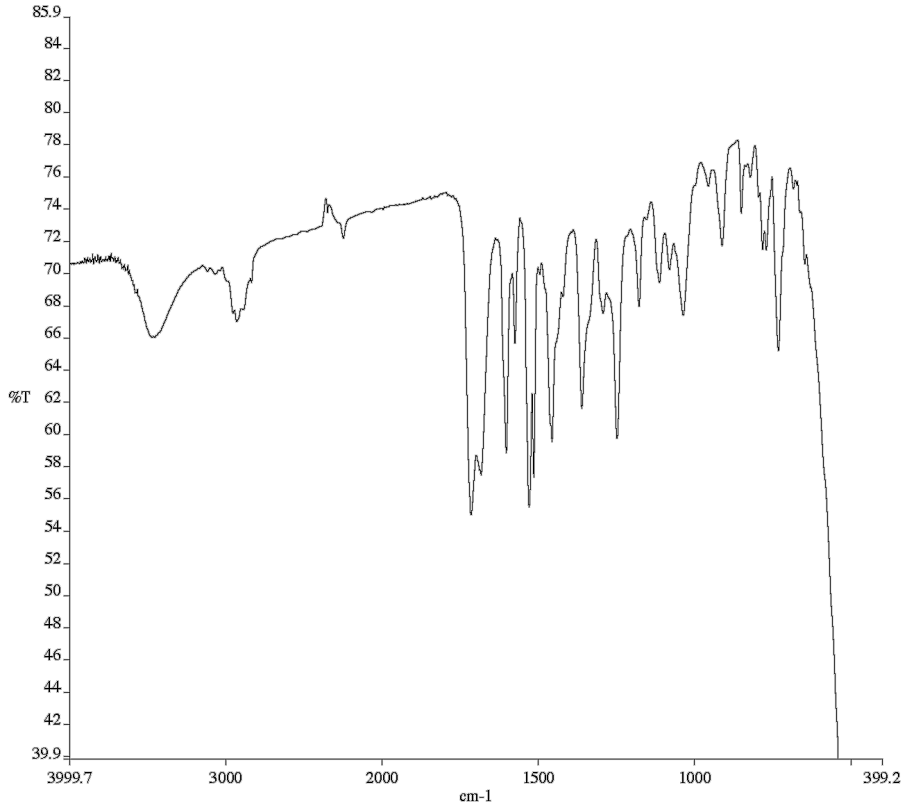


Figure A1.77. Infrared spectrum (Thin Film, NaCl) of compound **65**.

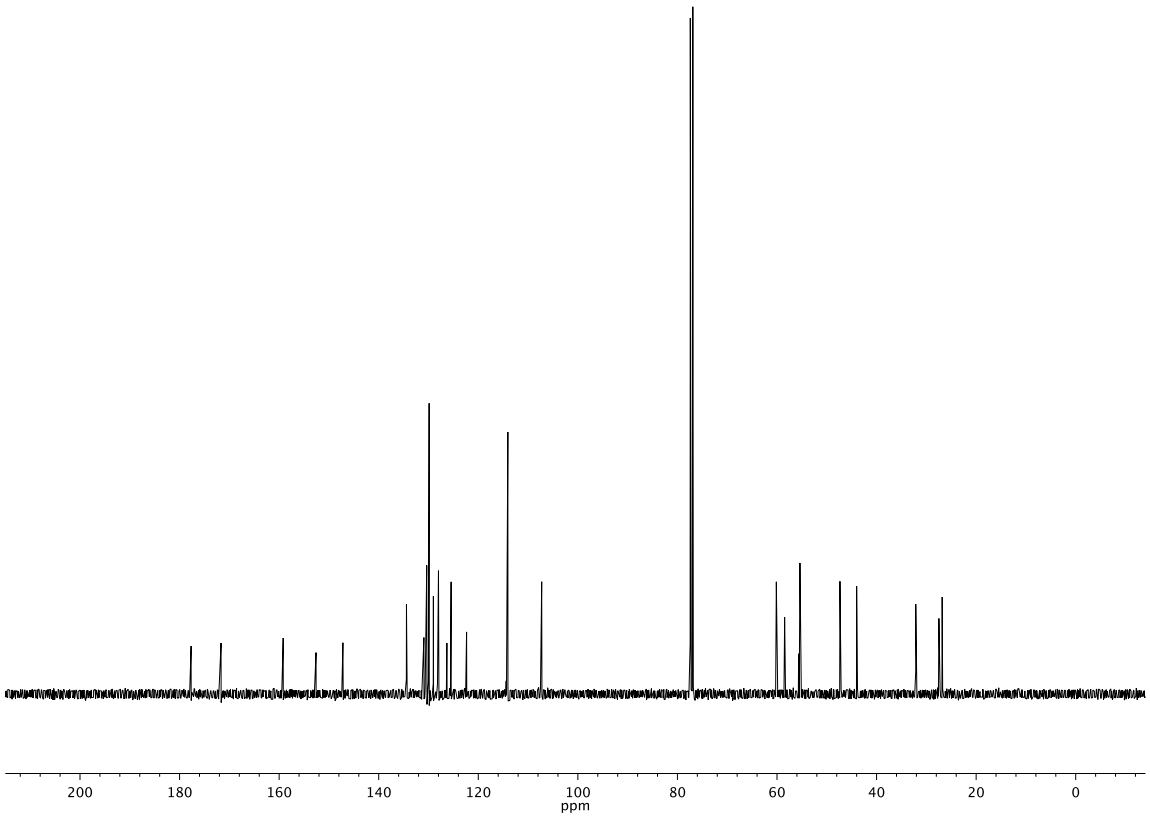


Figure A1.78. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **65.**

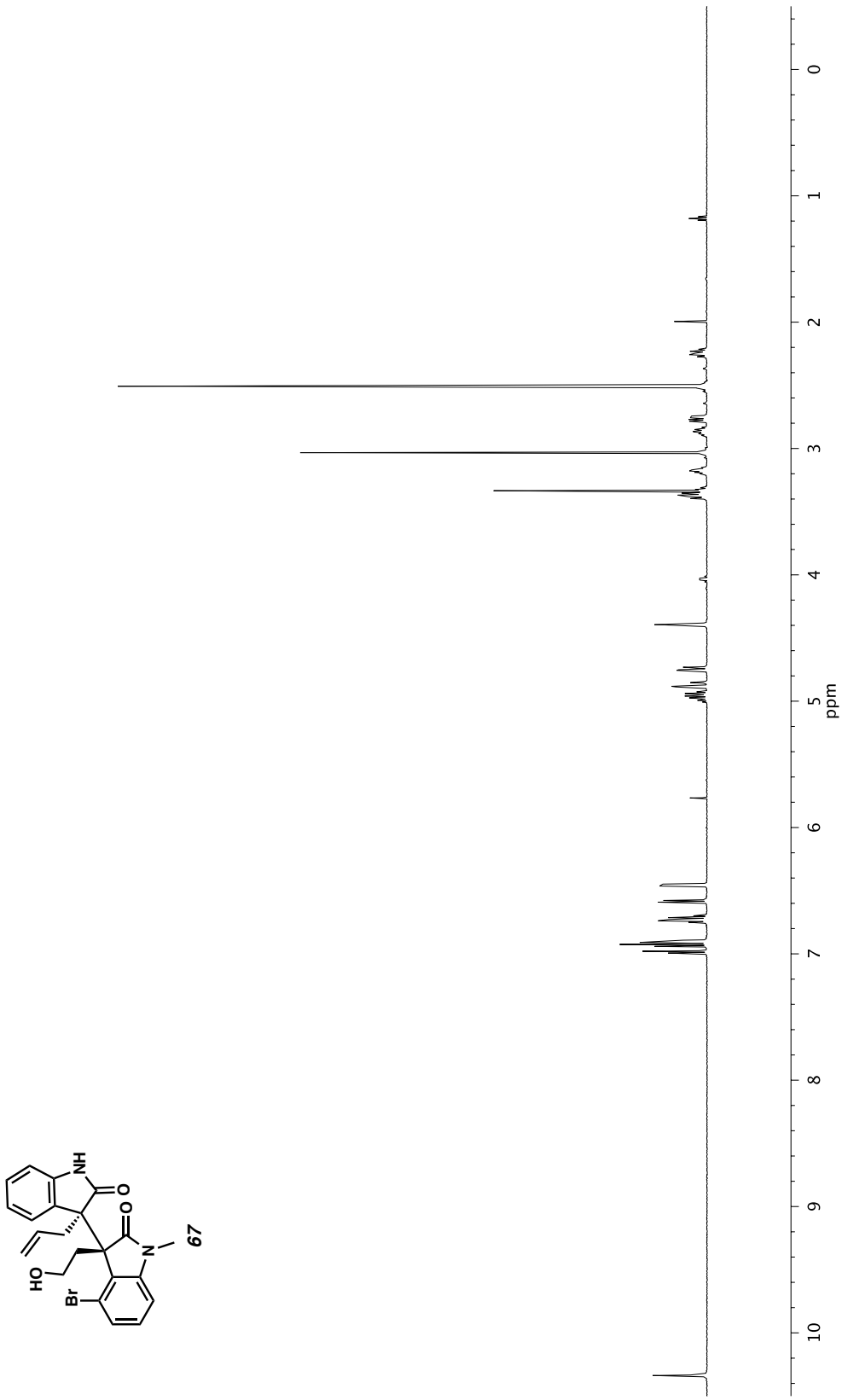


Figure A1.79. ^{1}H NMR (500 MHz, DMSO) of compound **67**.

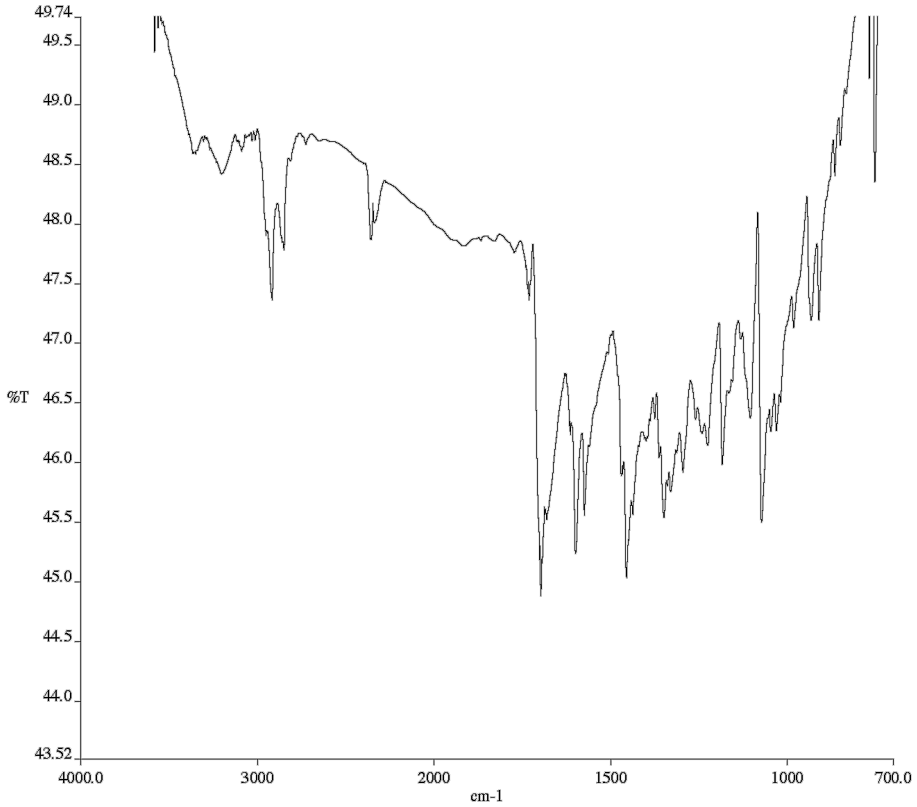


Figure A1.80. Infrared spectrum (Thin Film, NaCl) of compound **67**.

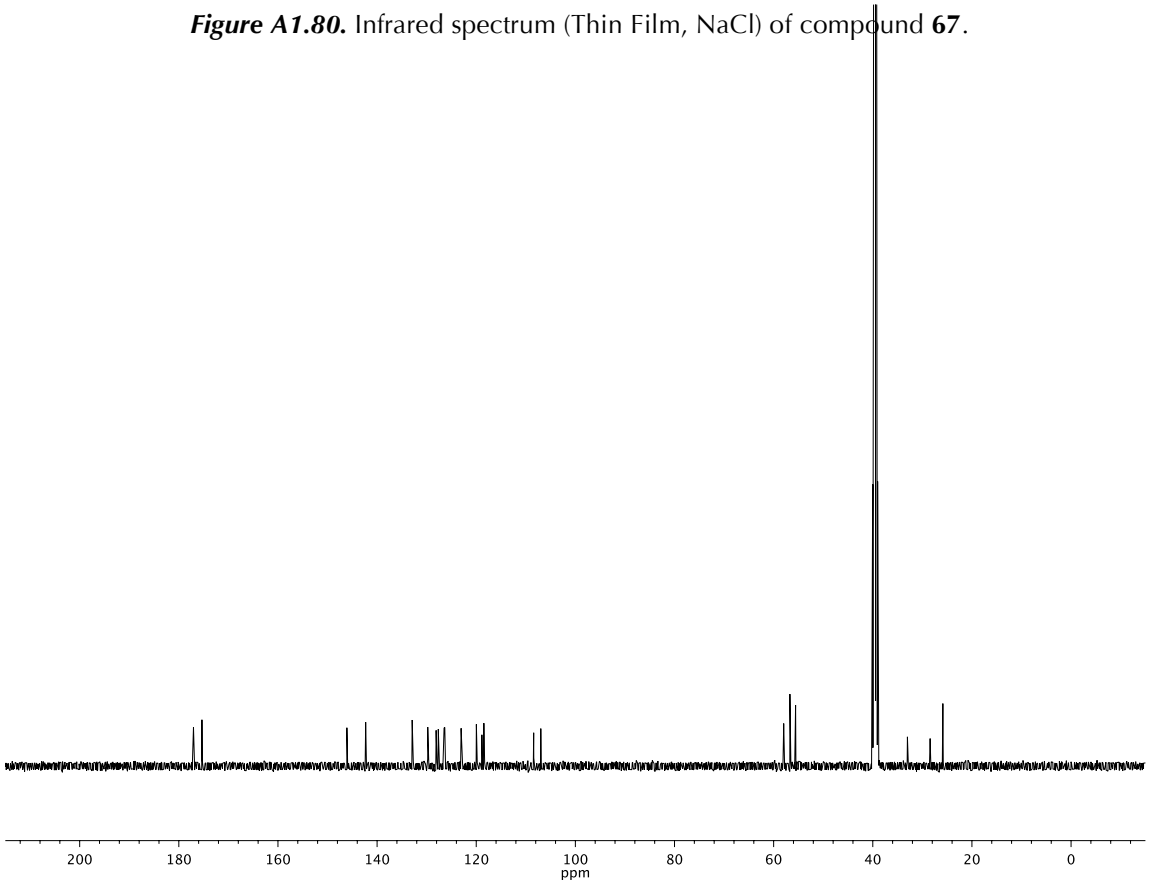


Figure A1.81. ^{13}C NMR (125 MHz, DMSO) of compound **67**.

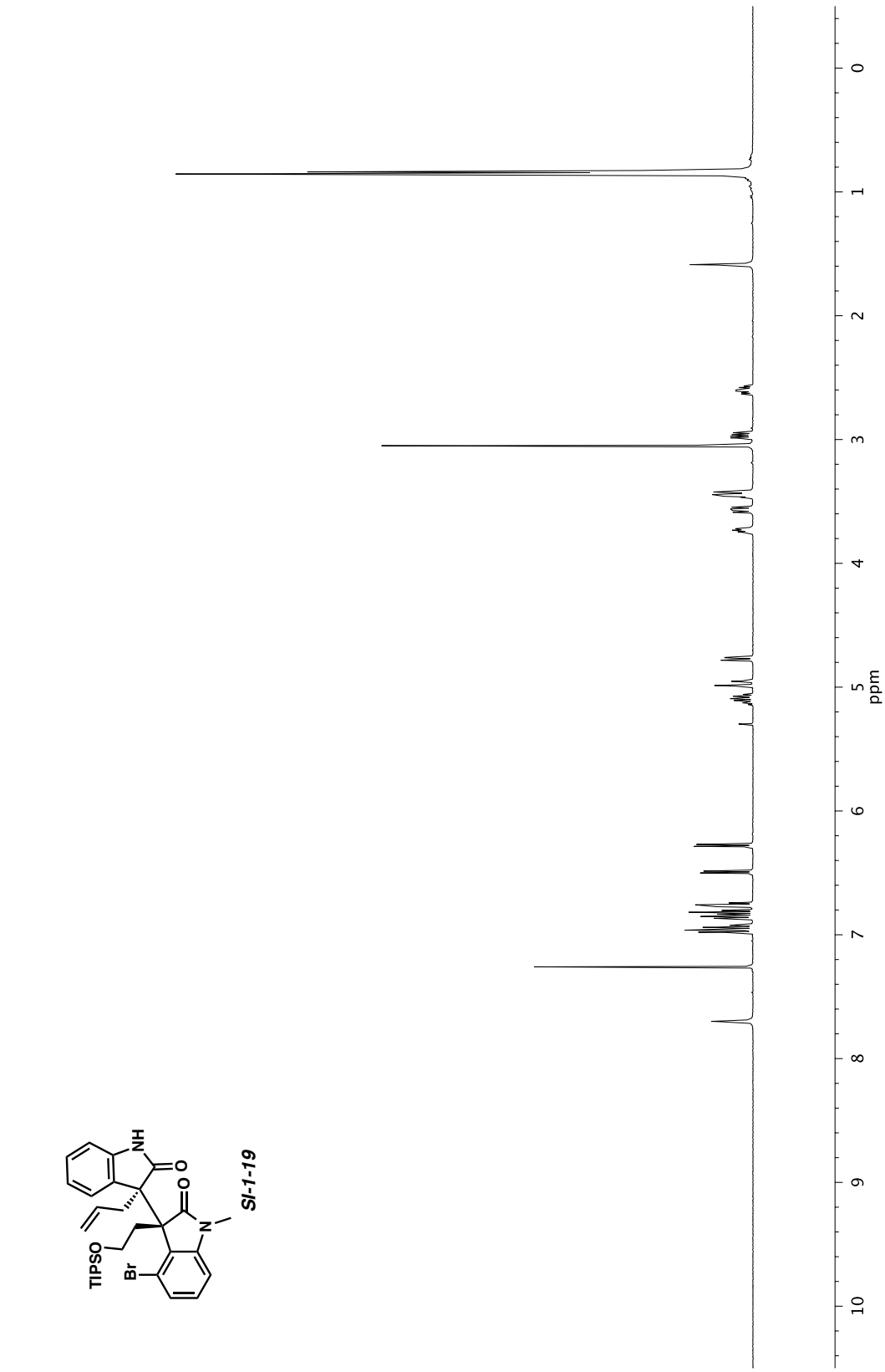


Figure A1.82. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **SI-1-19**.

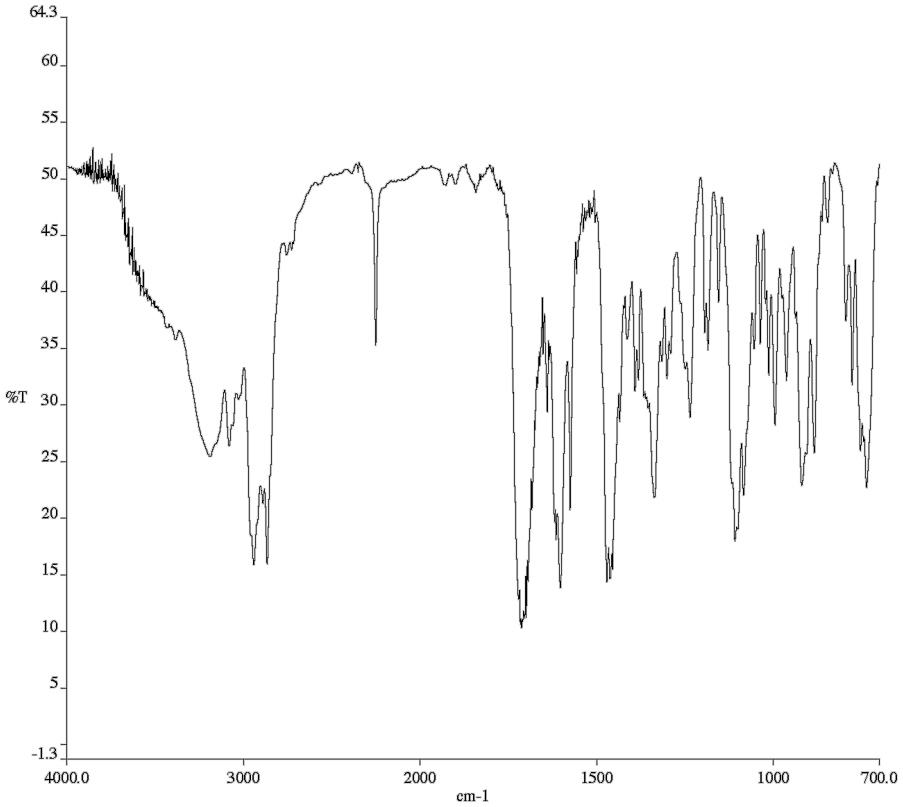


Figure A1.83. Infrared spectrum (Thin Film, NaCl) of compound **SI-1-19**.

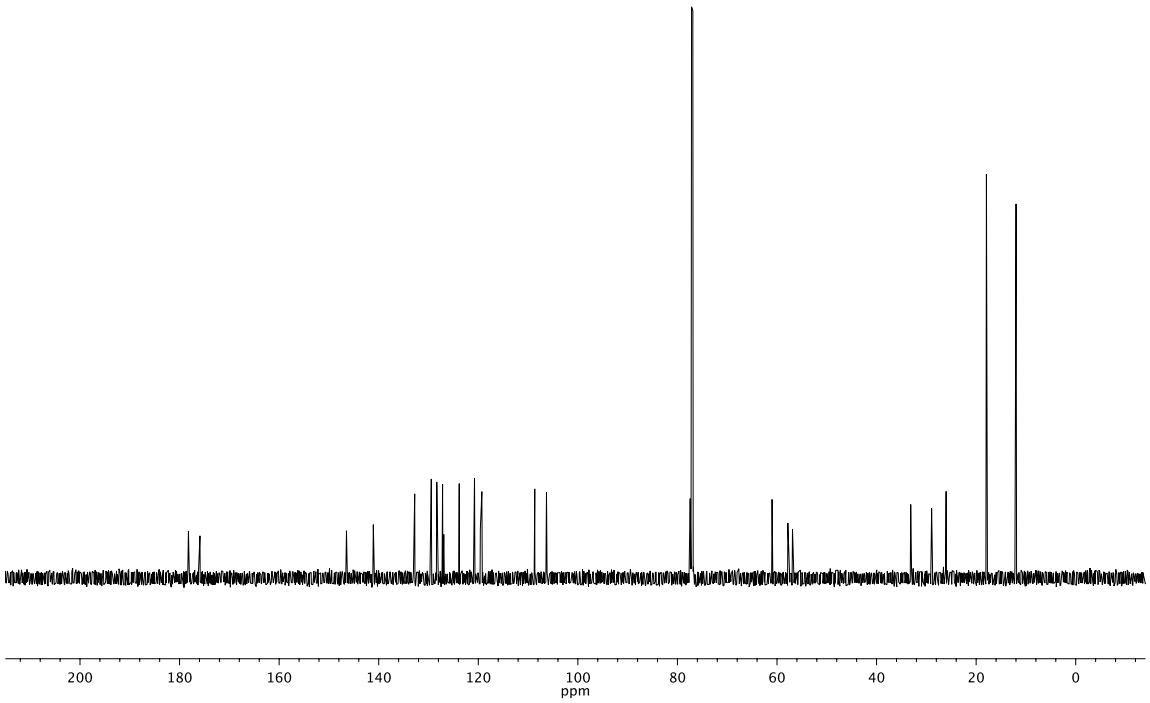


Figure A1.84. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **SI-1-19**.

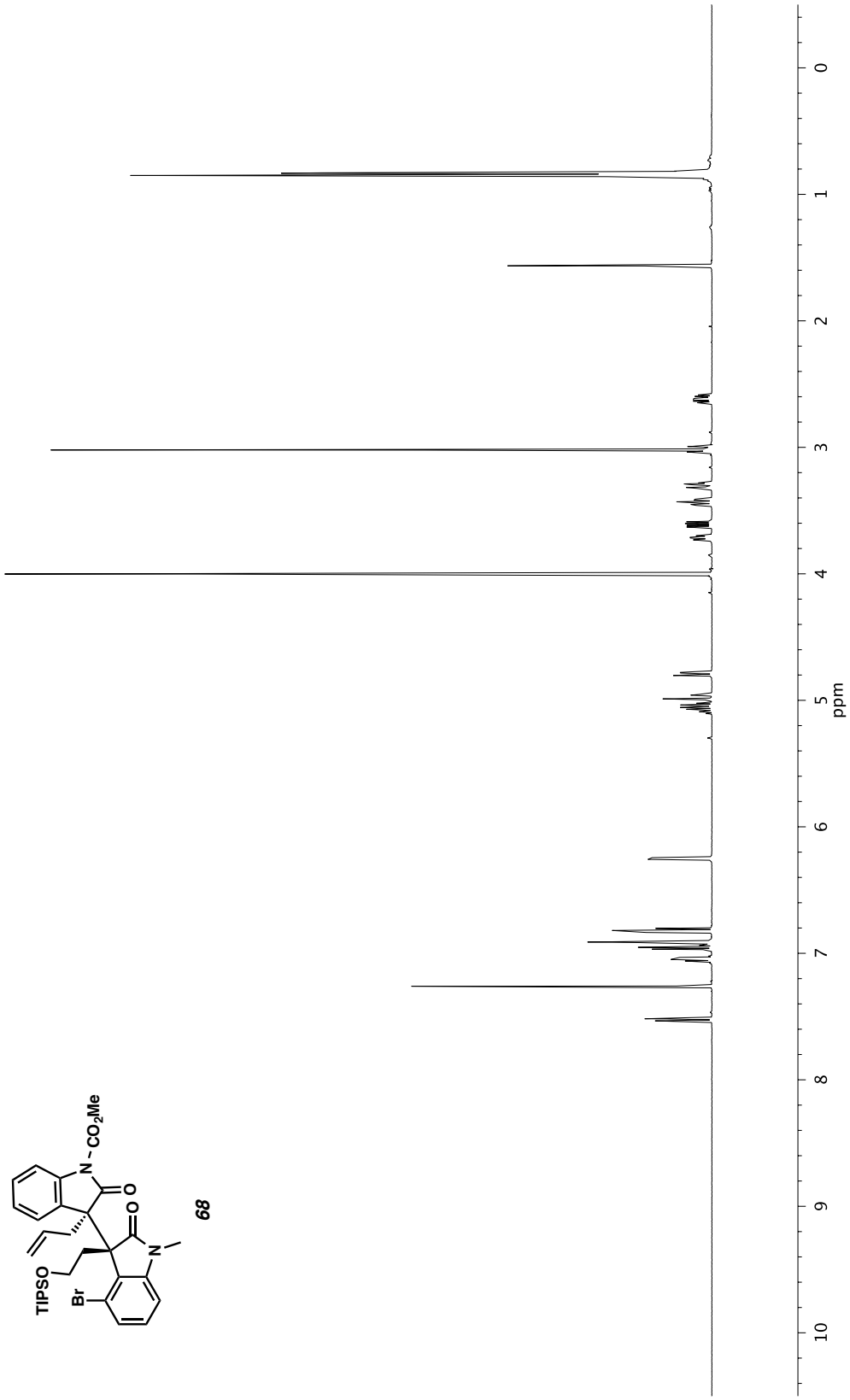


Figure A1.85. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **68**.

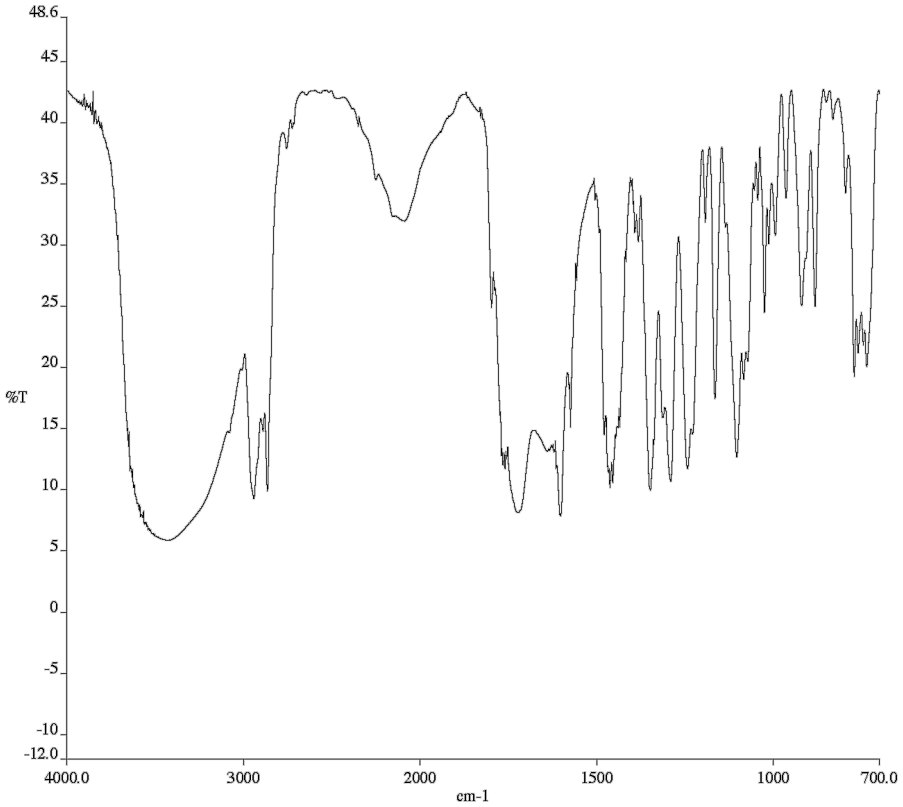


Figure A1.86. Infrared spectrum (Thin Film, NaCl) of compound **68**.

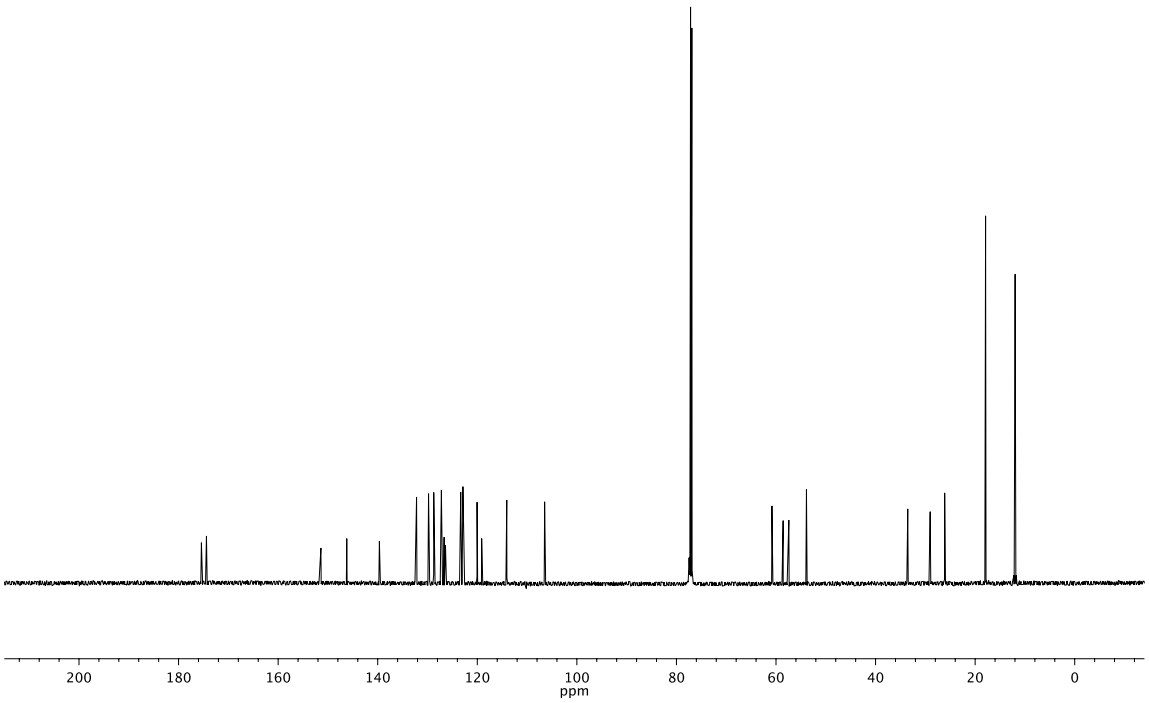


Figure A1.87. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **68**.

Figure A1.88. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **69**.

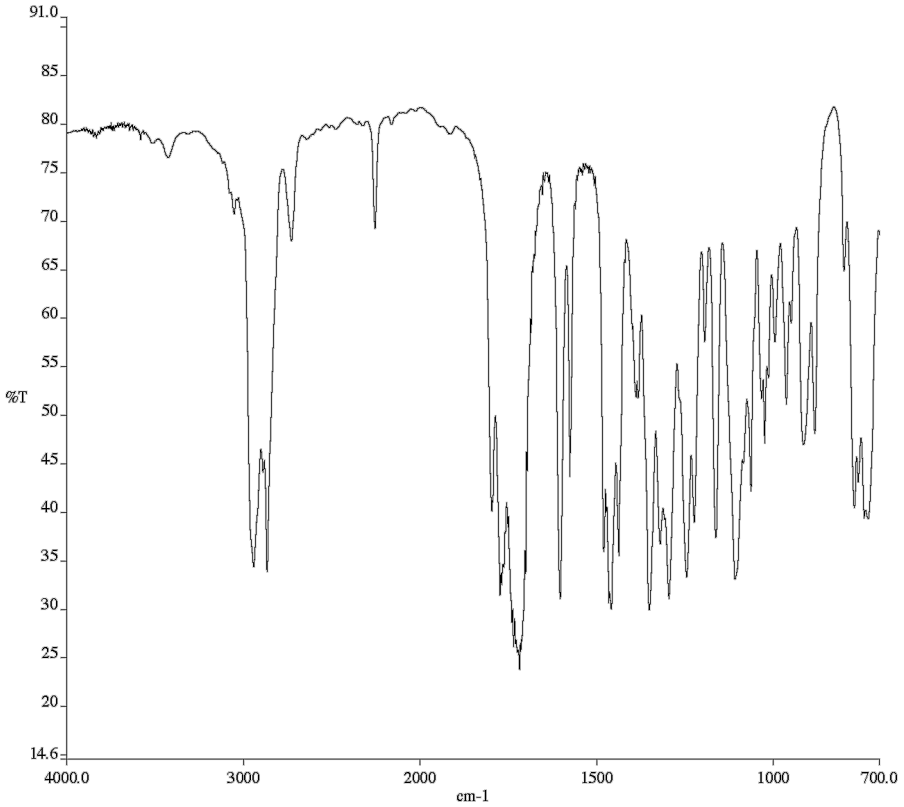


Figure A1.89. Infrared spectrum (Thin Film, NaCl) of compound **69**.

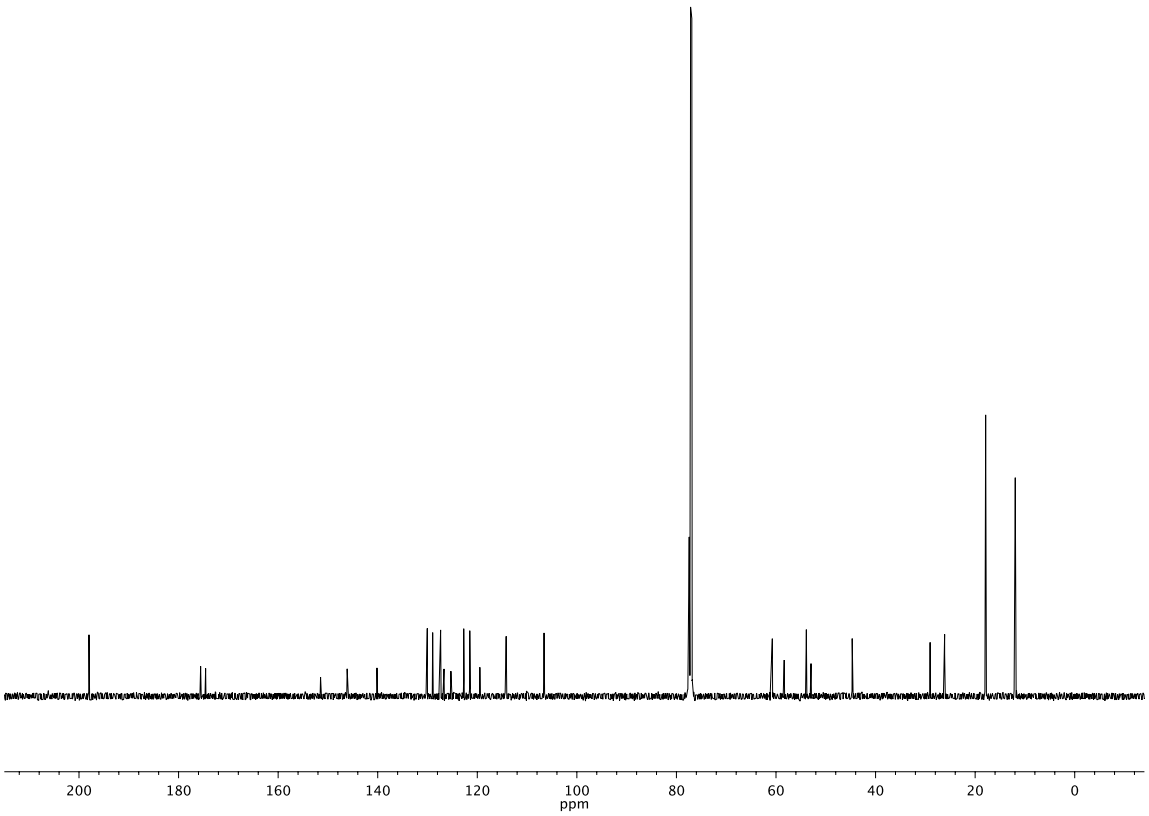


Figure A1.90. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **69**.

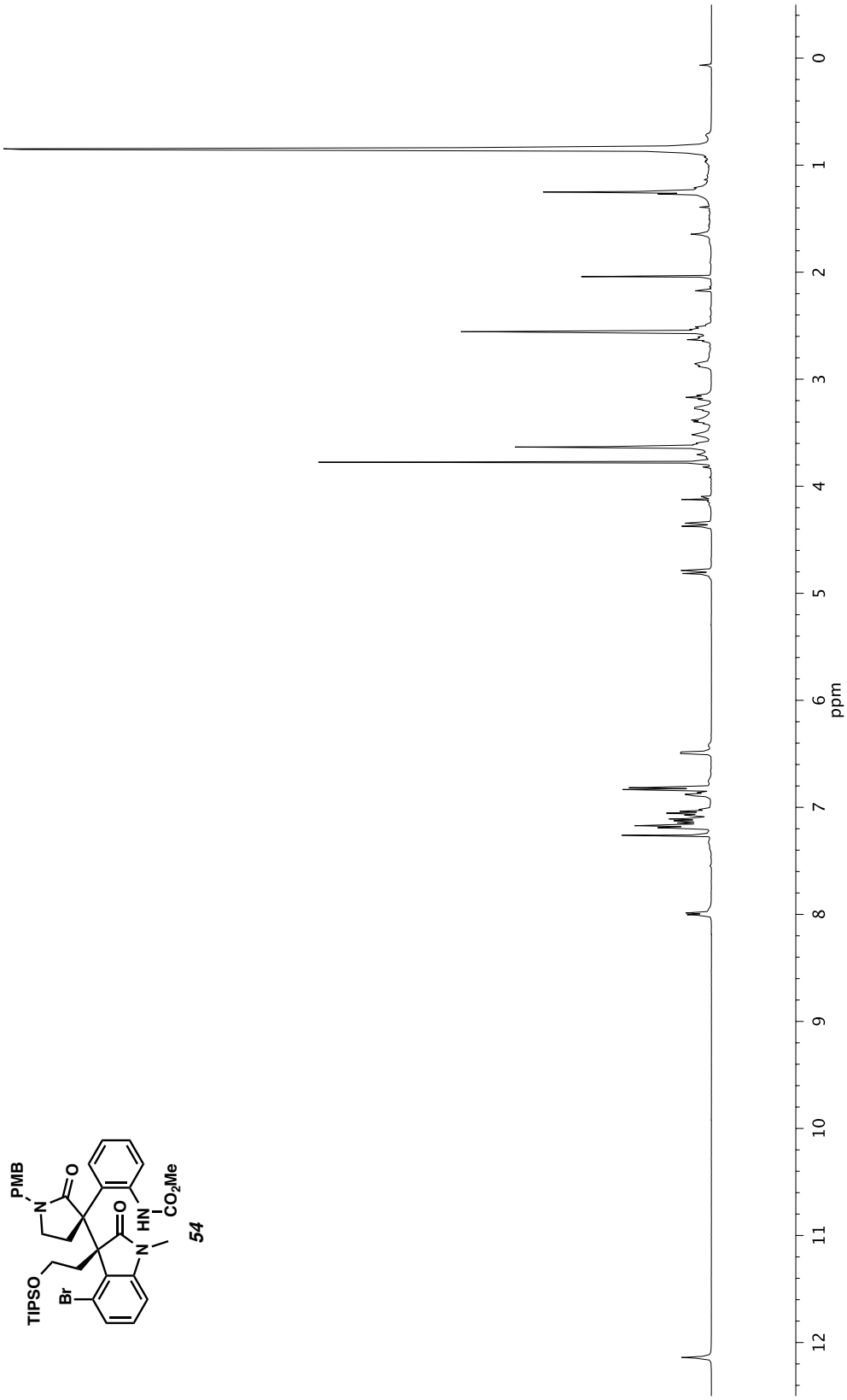


Figure A1.91. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **54**.

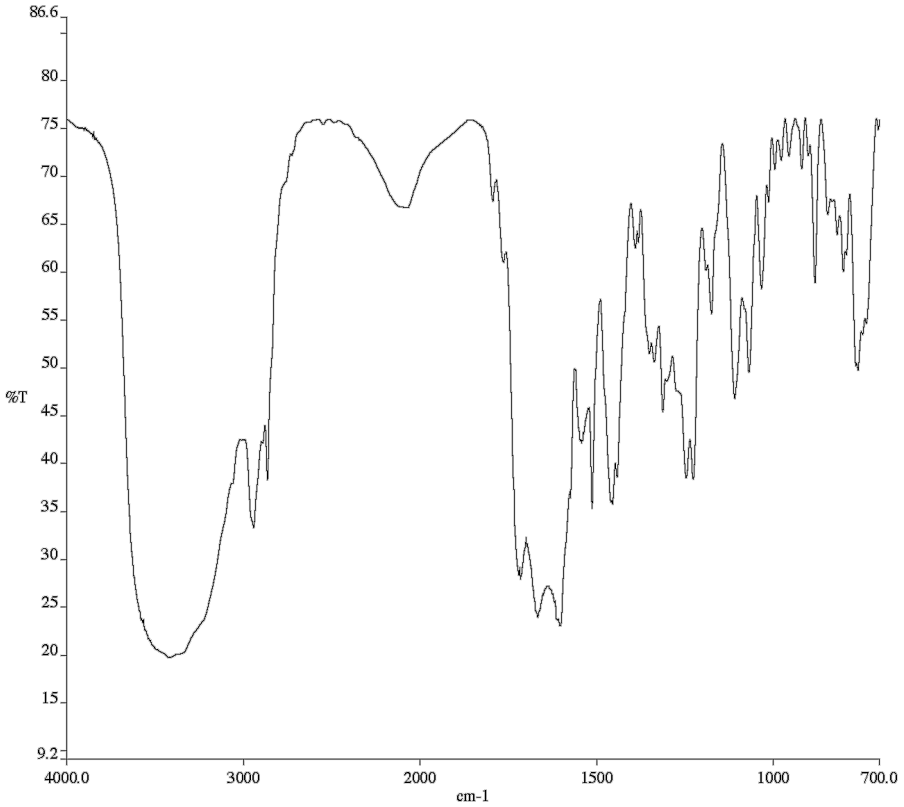


Figure A1.92. Infrared spectrum (Thin Film, NaCl) of compound **54**.

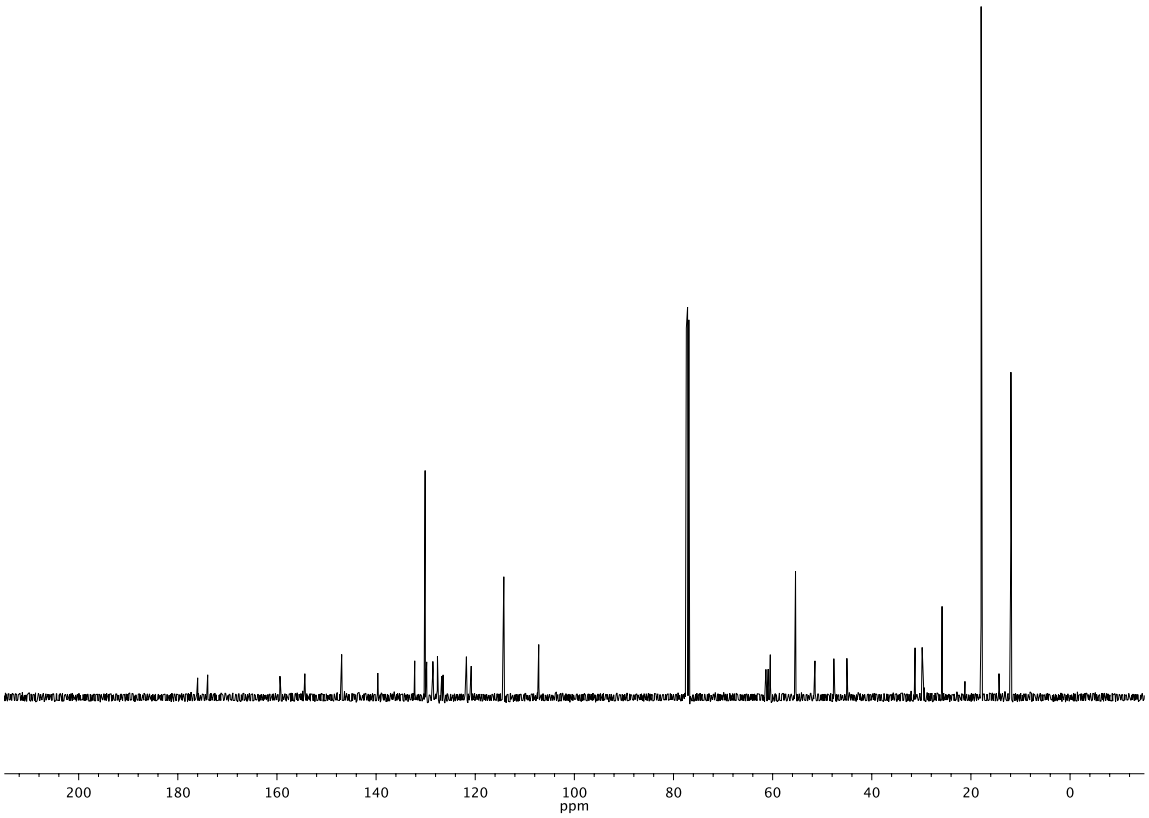


Figure A1.93. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **54**.

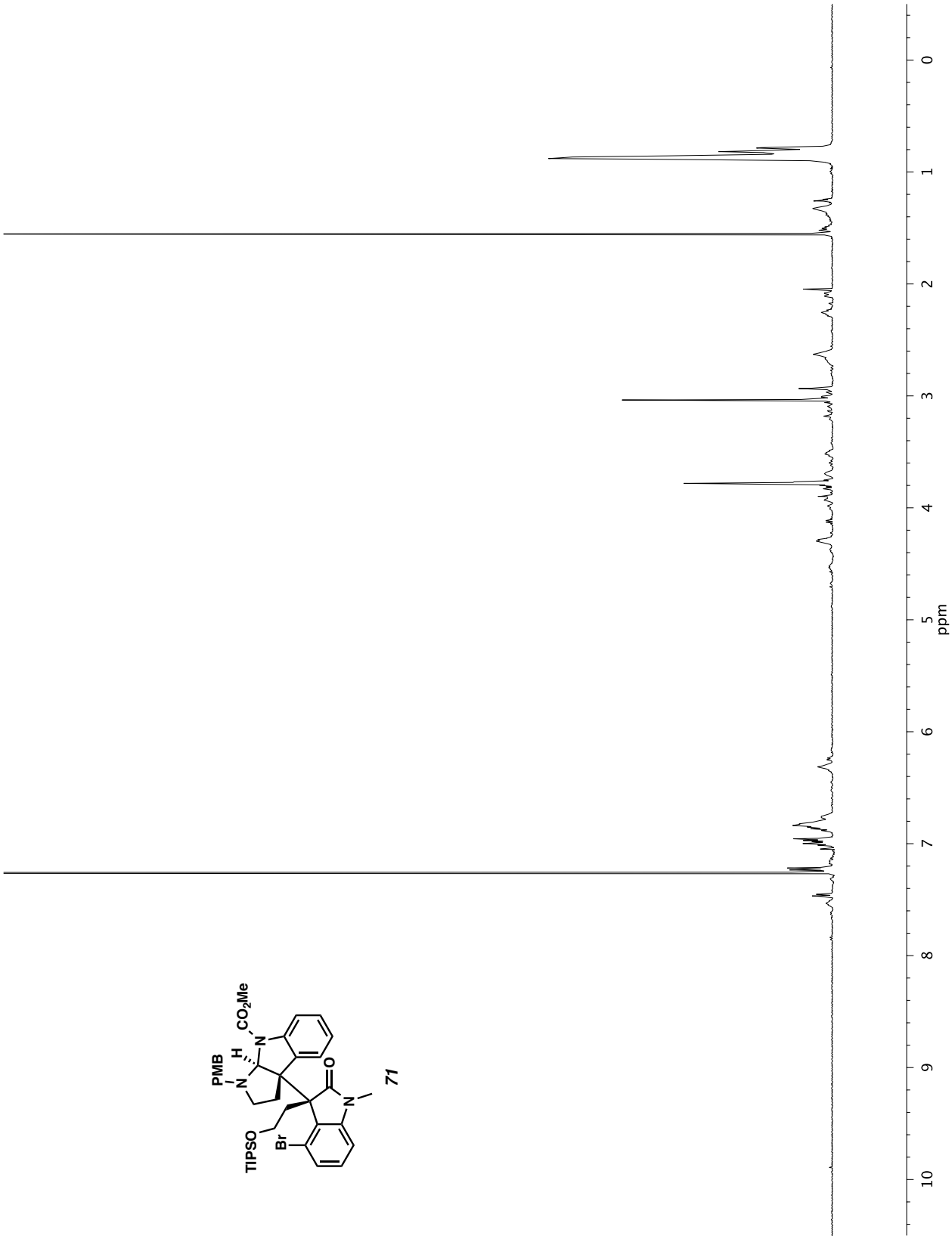


Figure A1.94. ^{1}H NMR (300 MHz, $CDCl_3$) of compound ***71***.

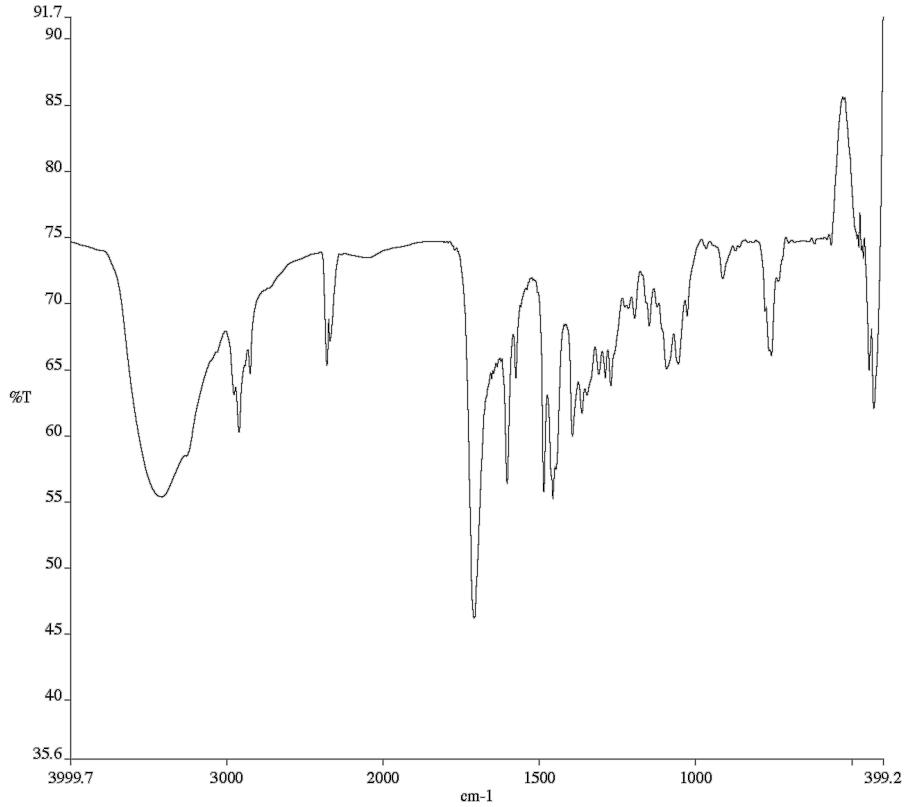


Figure A1.95. Infrared spectrum (Thin Film, NaCl) of compound **71**.

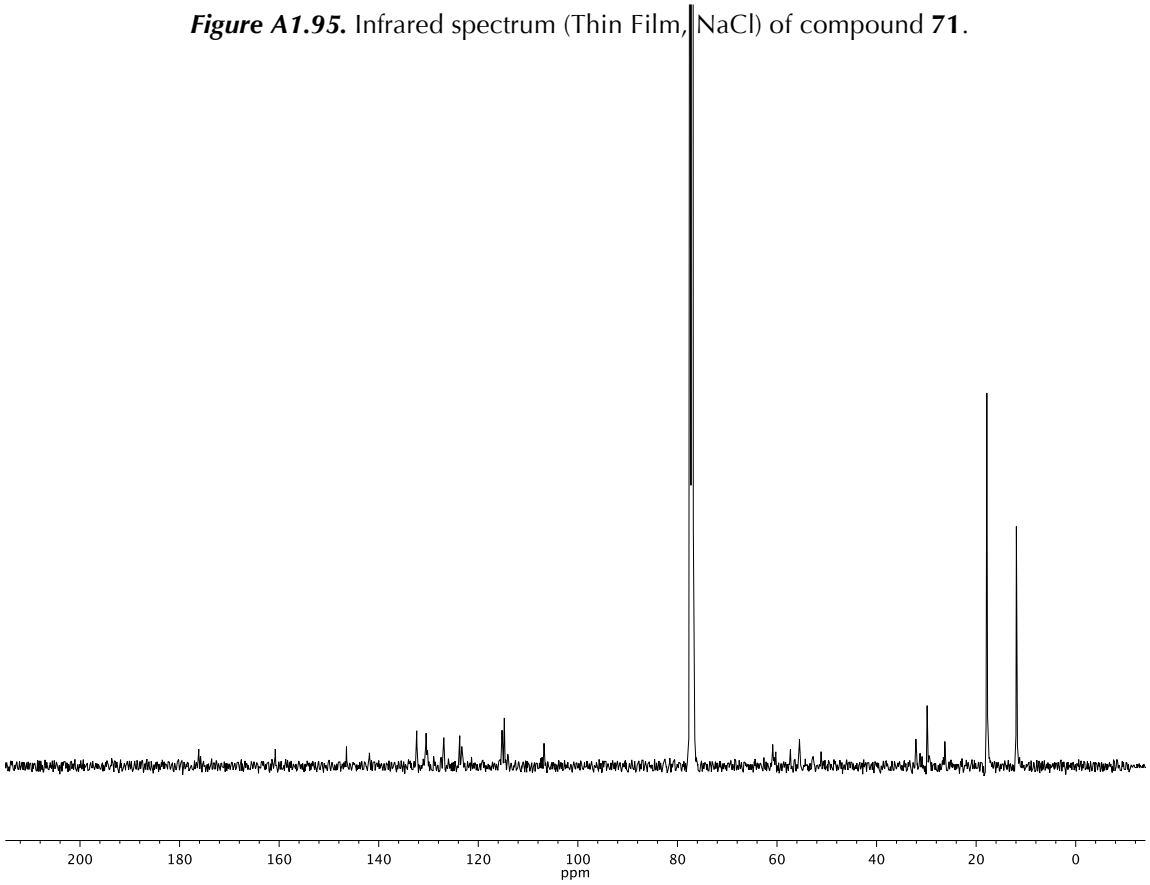


Figure A1.96. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **71**.

Figure A1.97. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **72**.

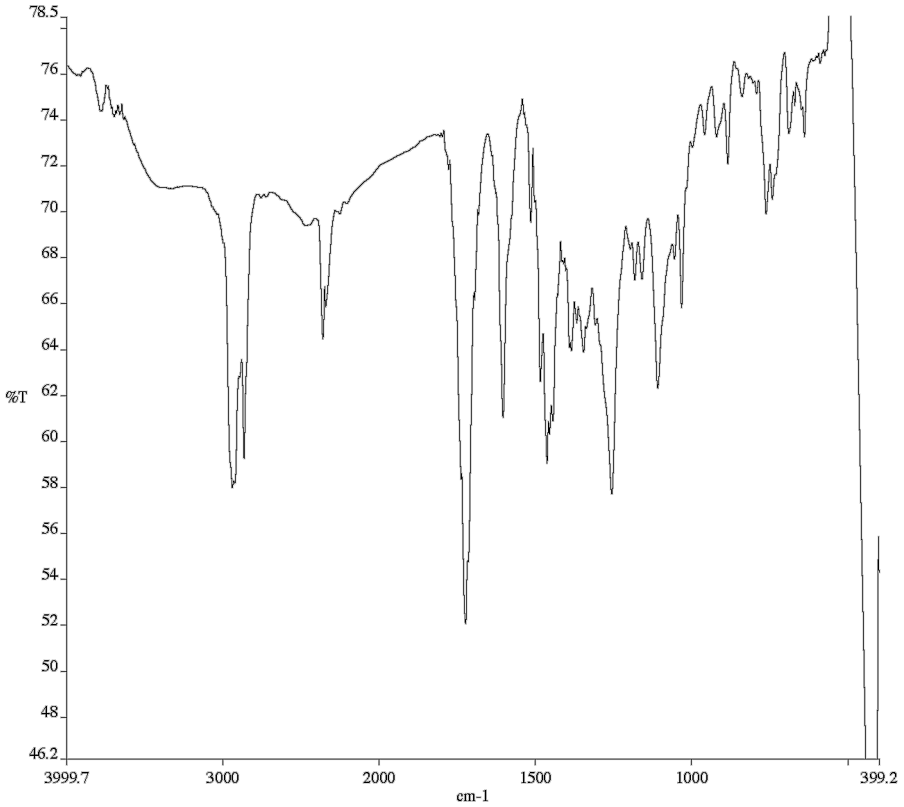


Figure A1.98. Infrared spectrum (Thin Film, NaCl) of compound **72**.

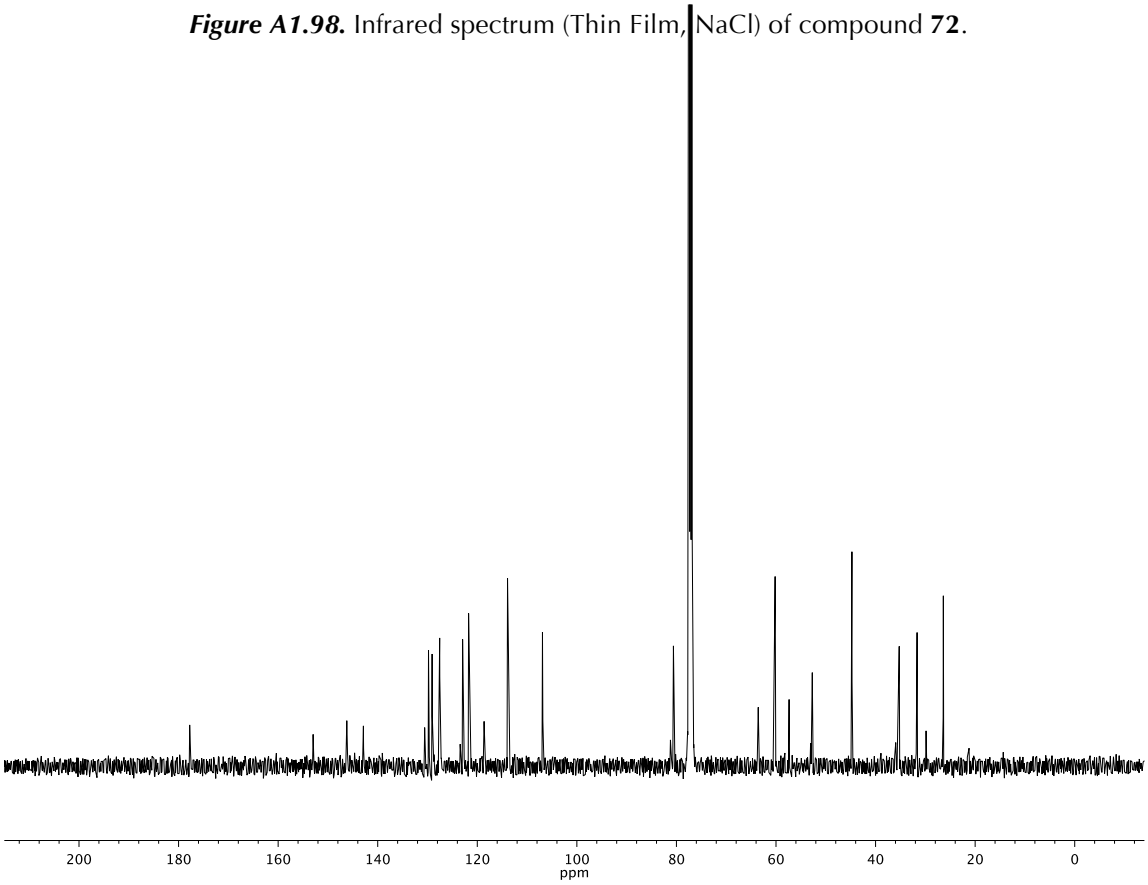


Figure A1.99. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **72**.

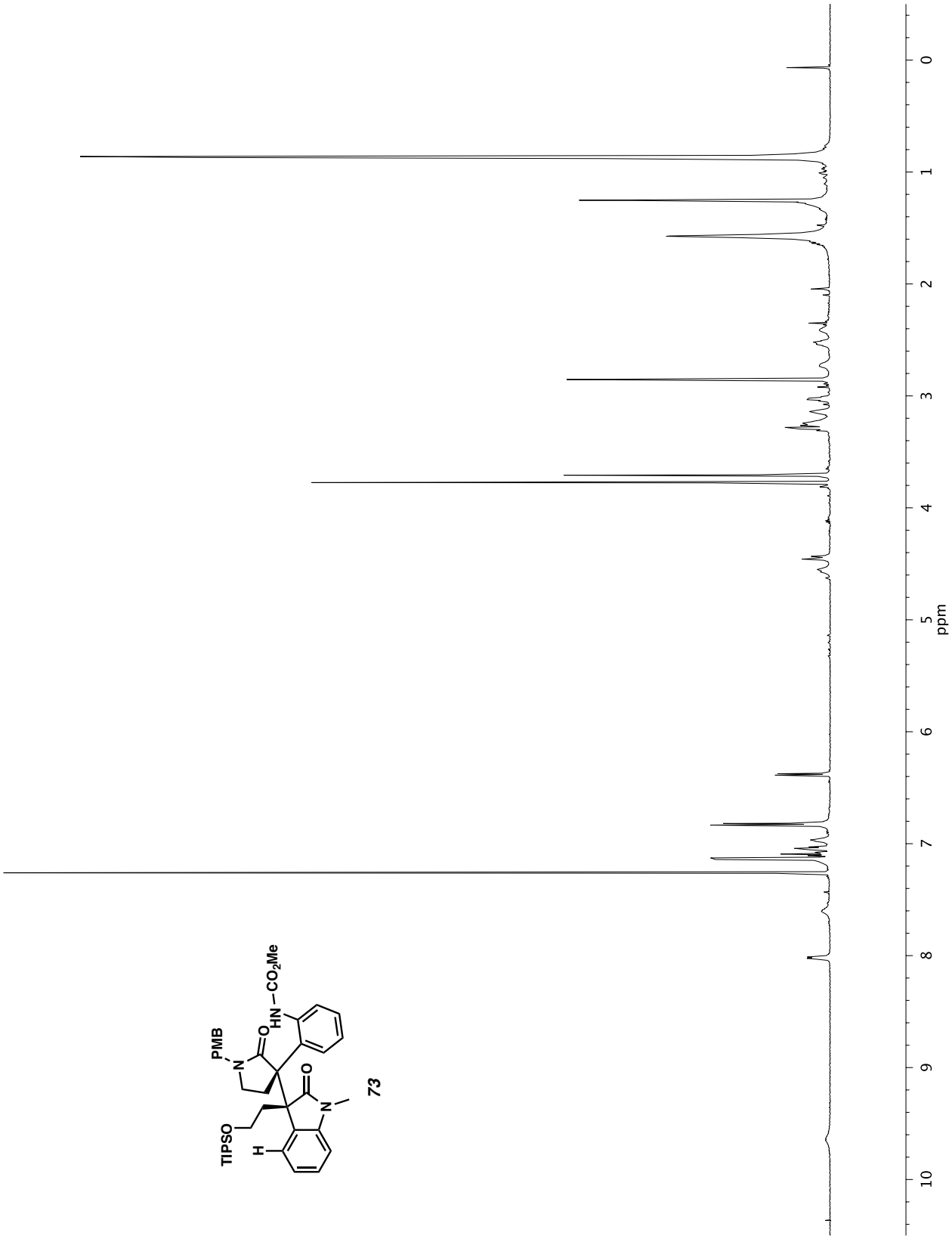


Figure A1.100. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **73**.

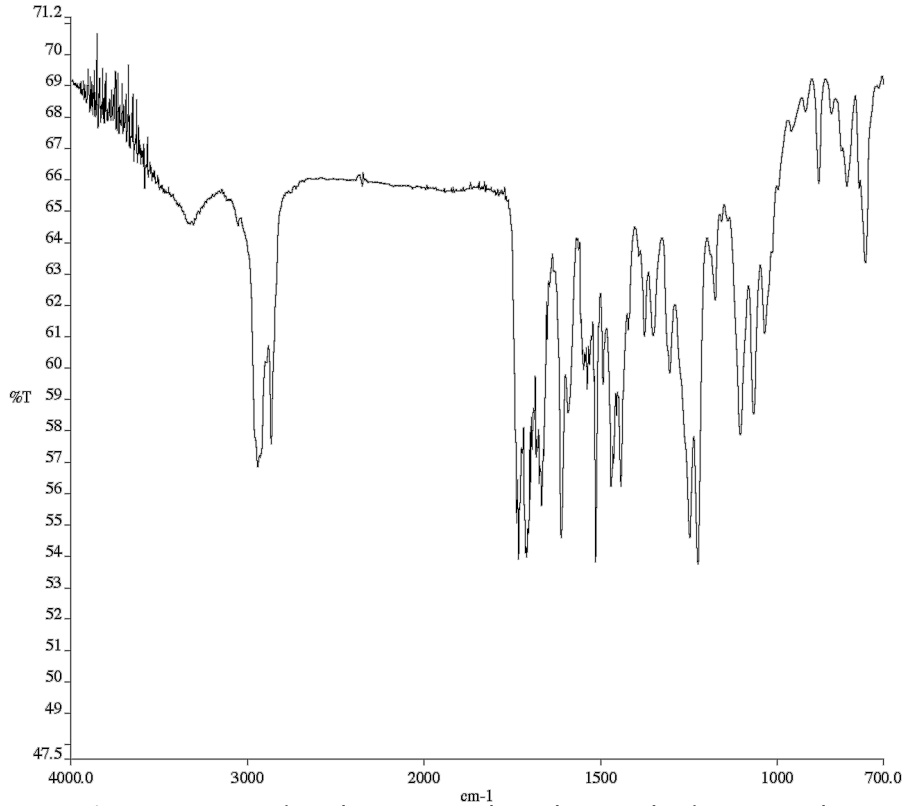


Figure A1.101. Infrared spectrum (Thin Film, NaCl) of compound **73**.

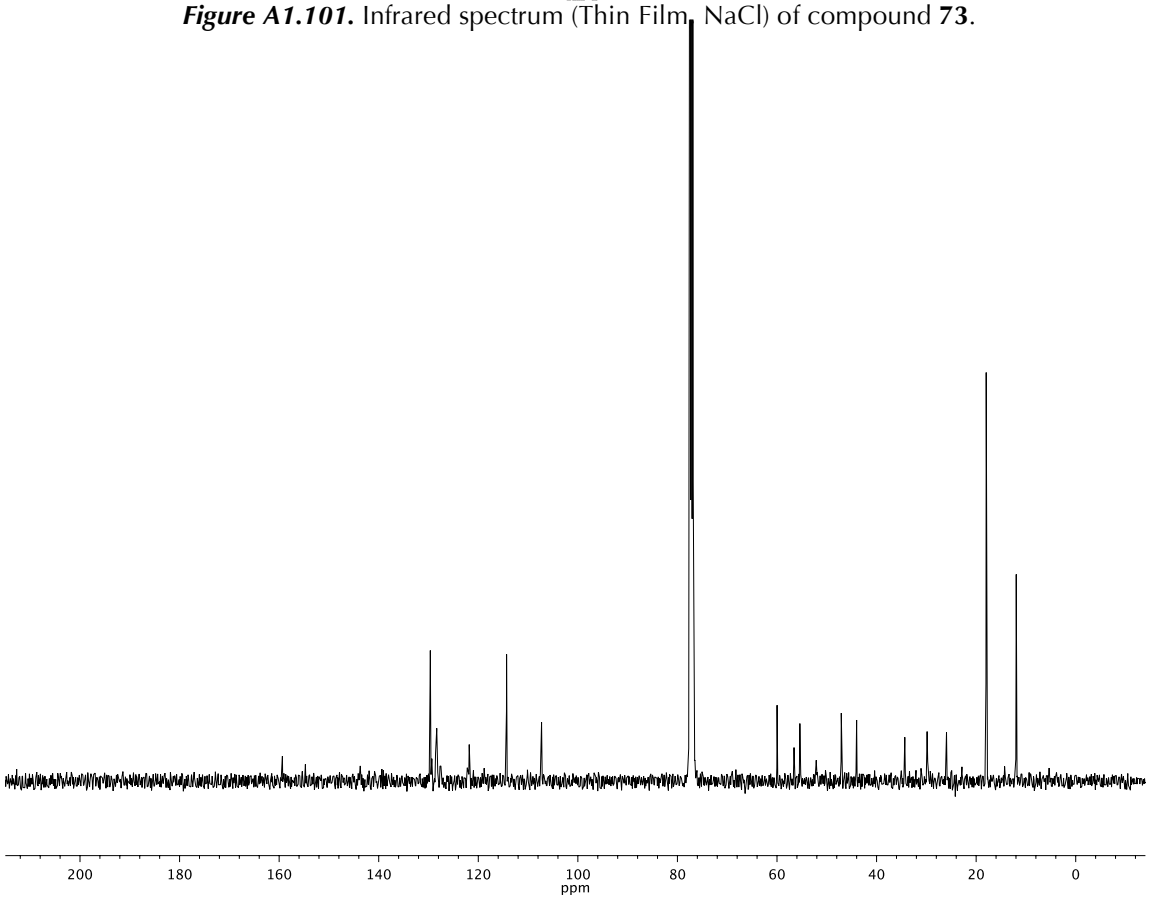


Figure A1.102. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **73**.

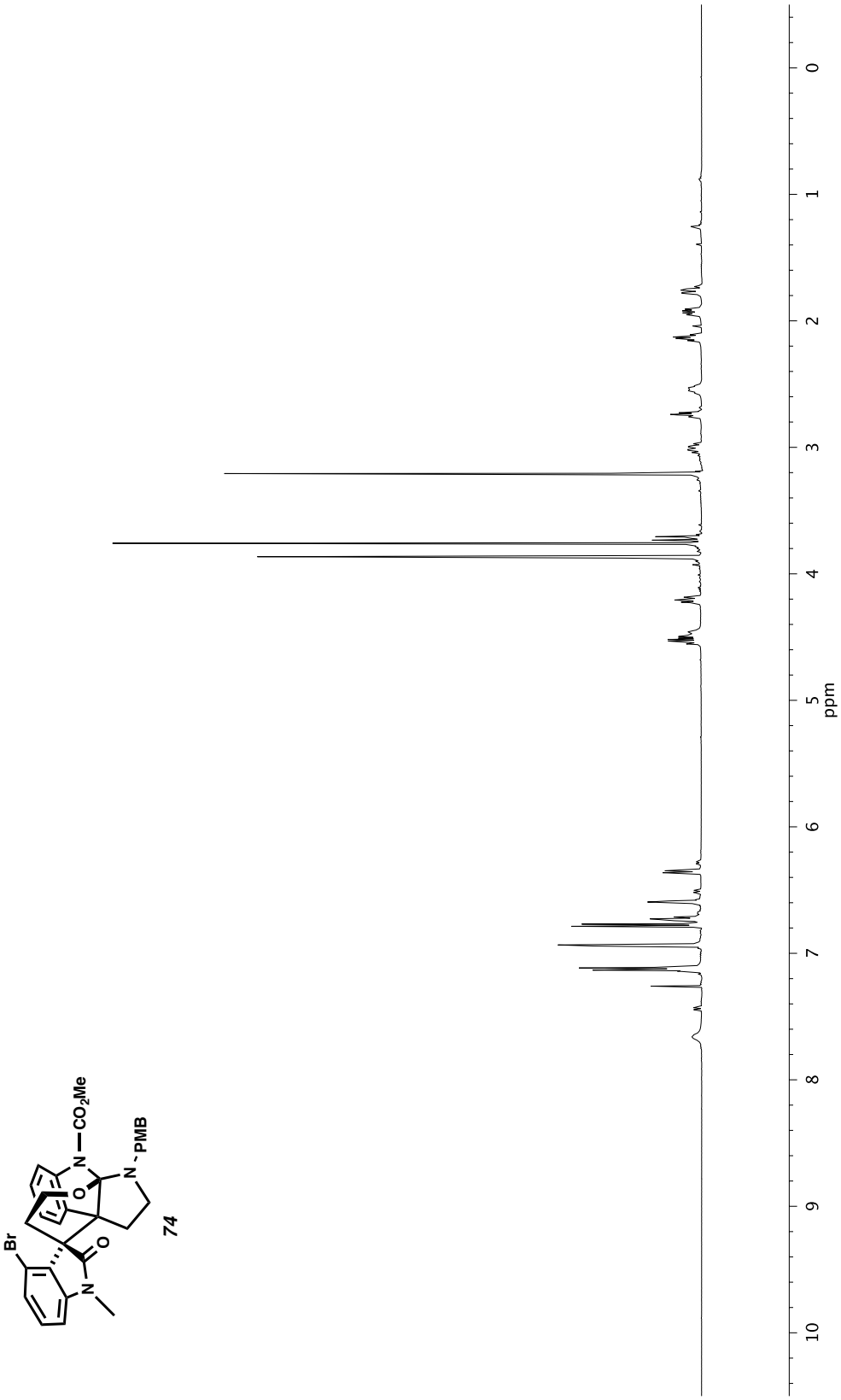


Figure A1.103. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **74**.

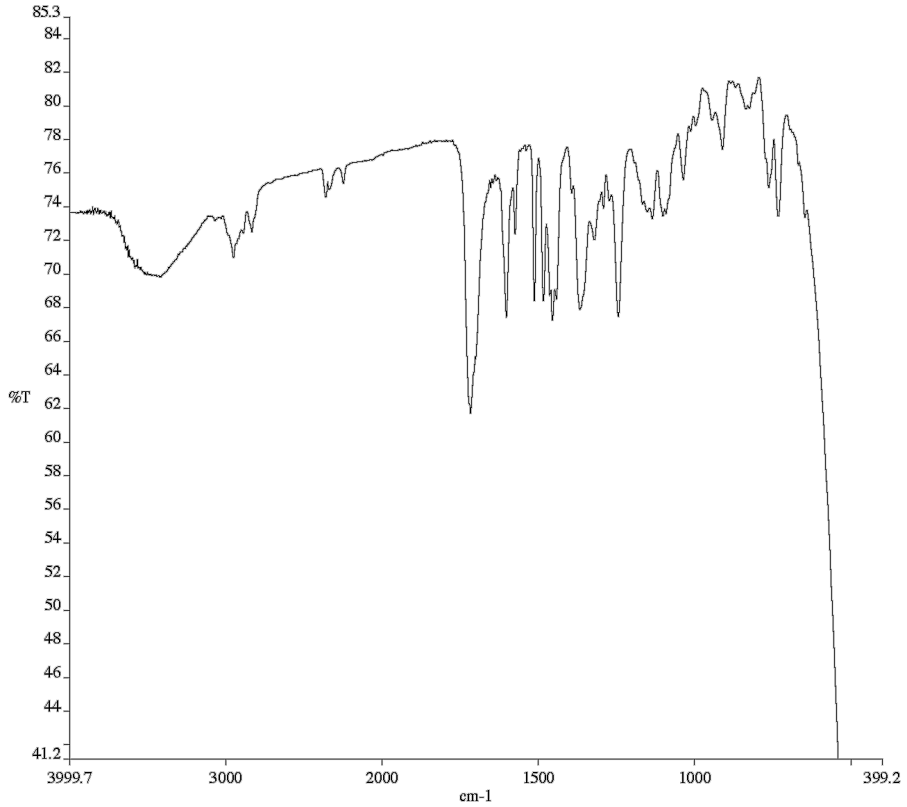


Figure A1.104. Infrared spectrum (Thin Film, NaCl) of compound **74**.

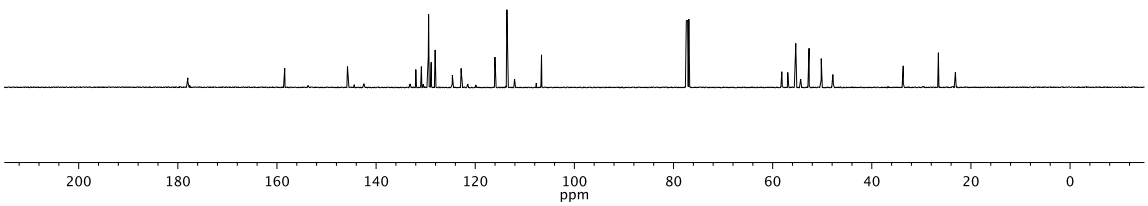


Figure A1.105. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **74**.

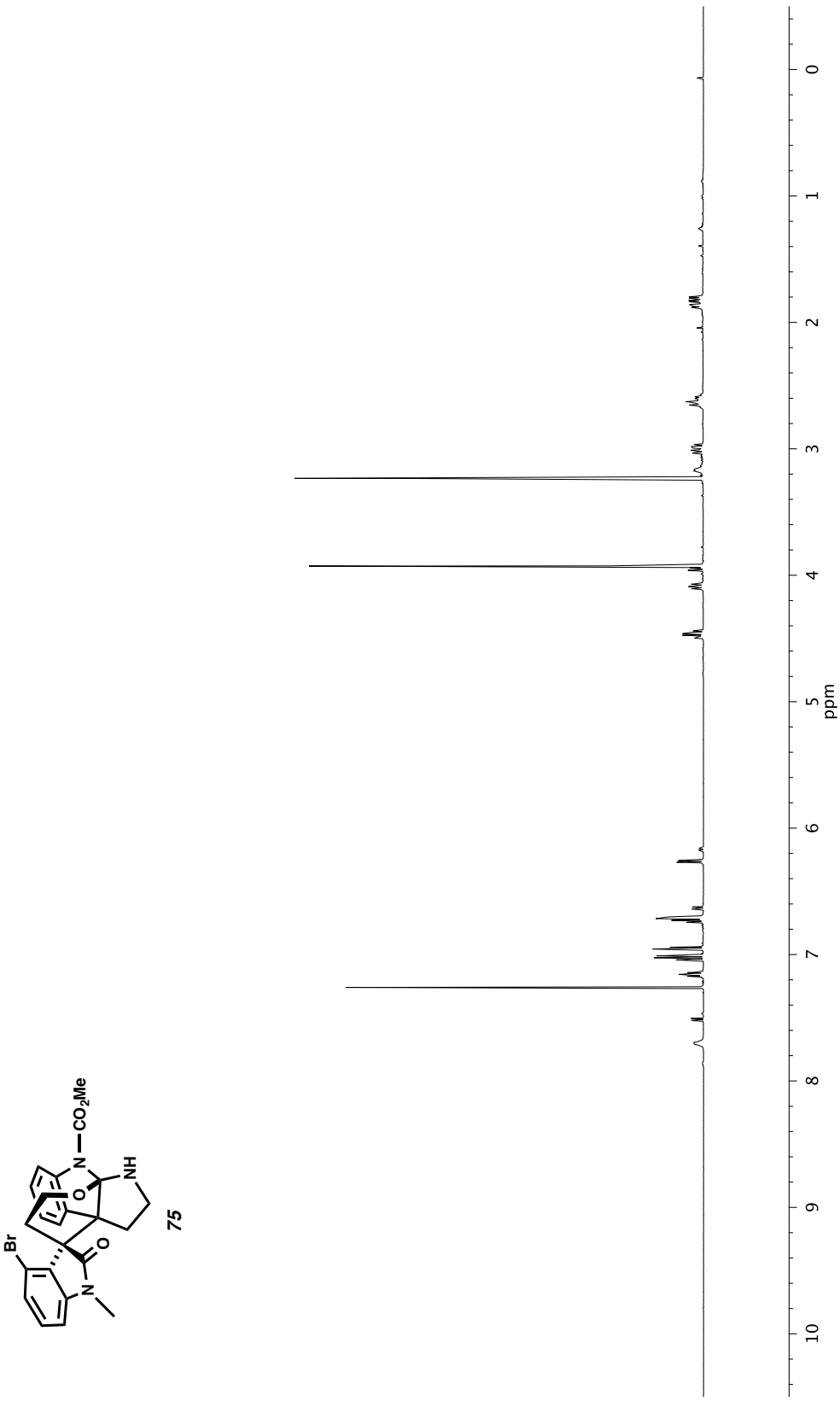


Figure A1.106. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **75**.

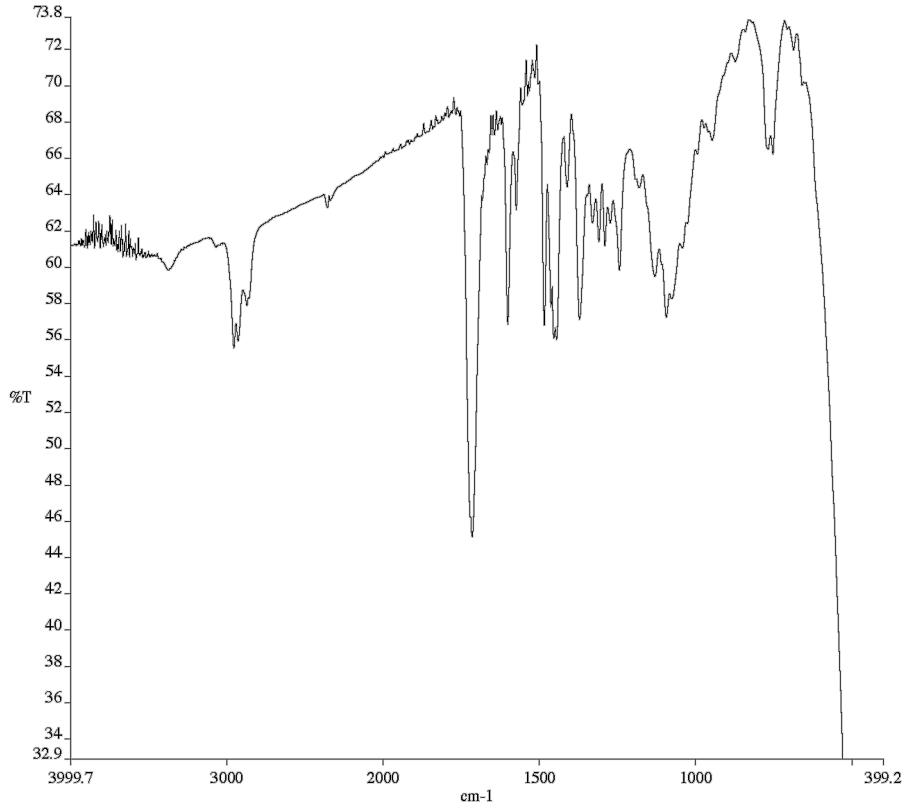


Figure A1.107. Infrared spectrum (Thin Film, NaCl) of compound **75**.

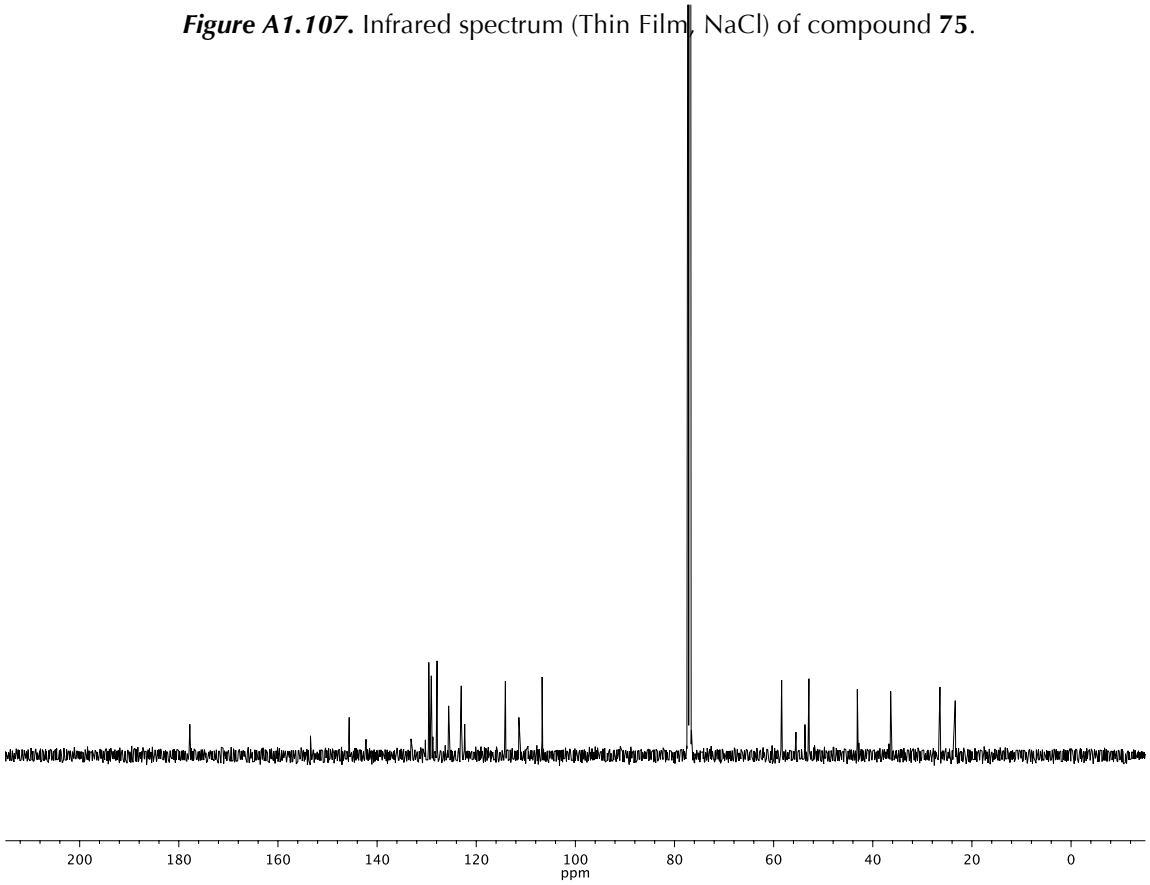


Figure A1.108. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **75**.

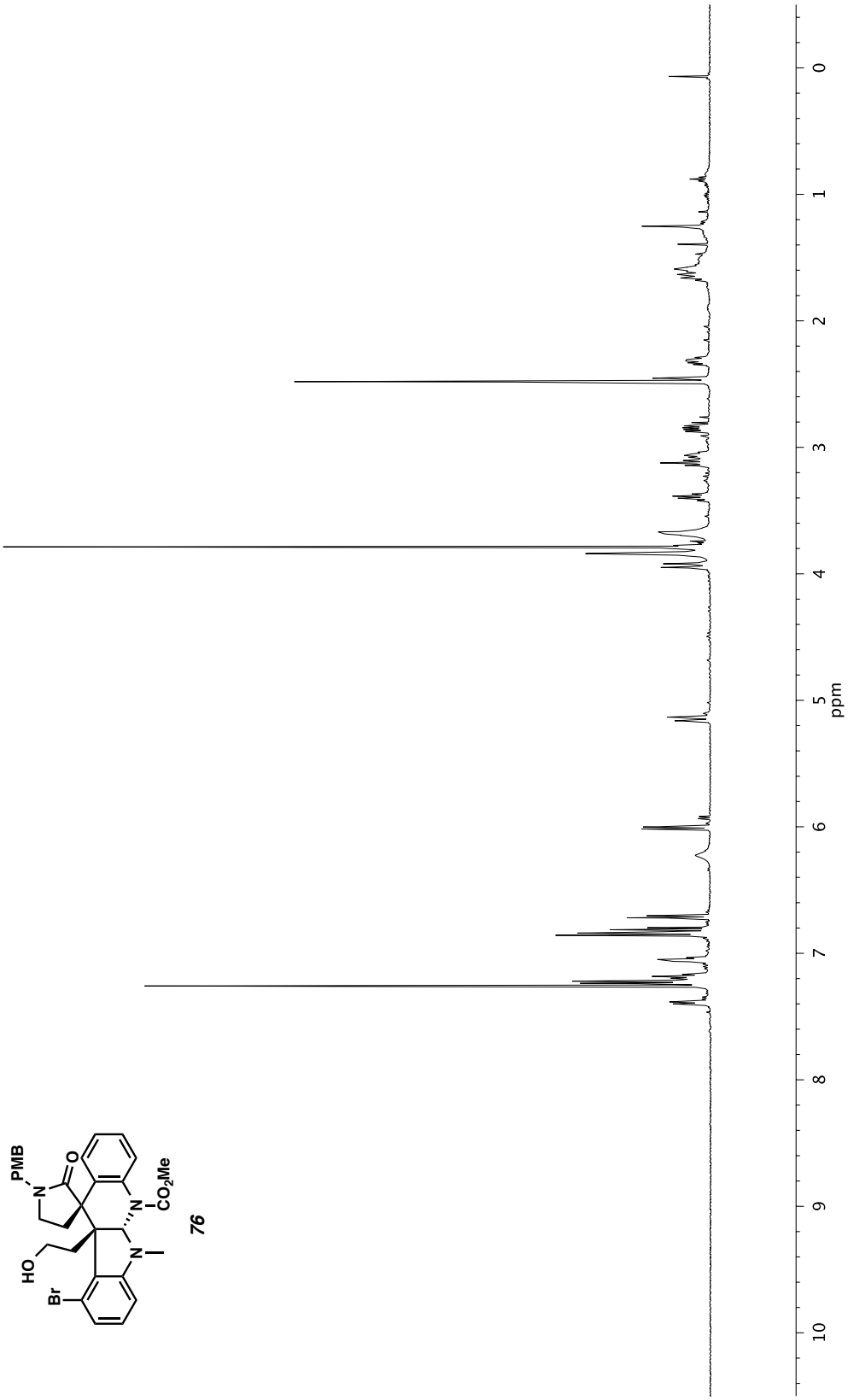


Figure A1.109. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **76**.

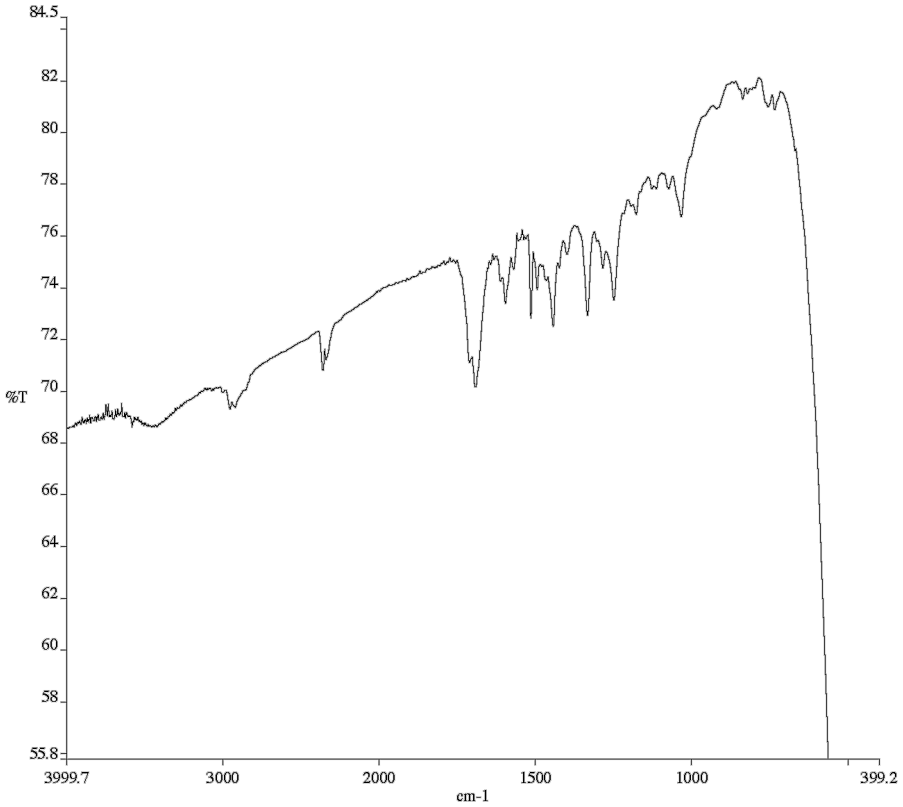


Figure A1.110. Infrared spectrum (Thin Film, NaCl) of compound **76**.

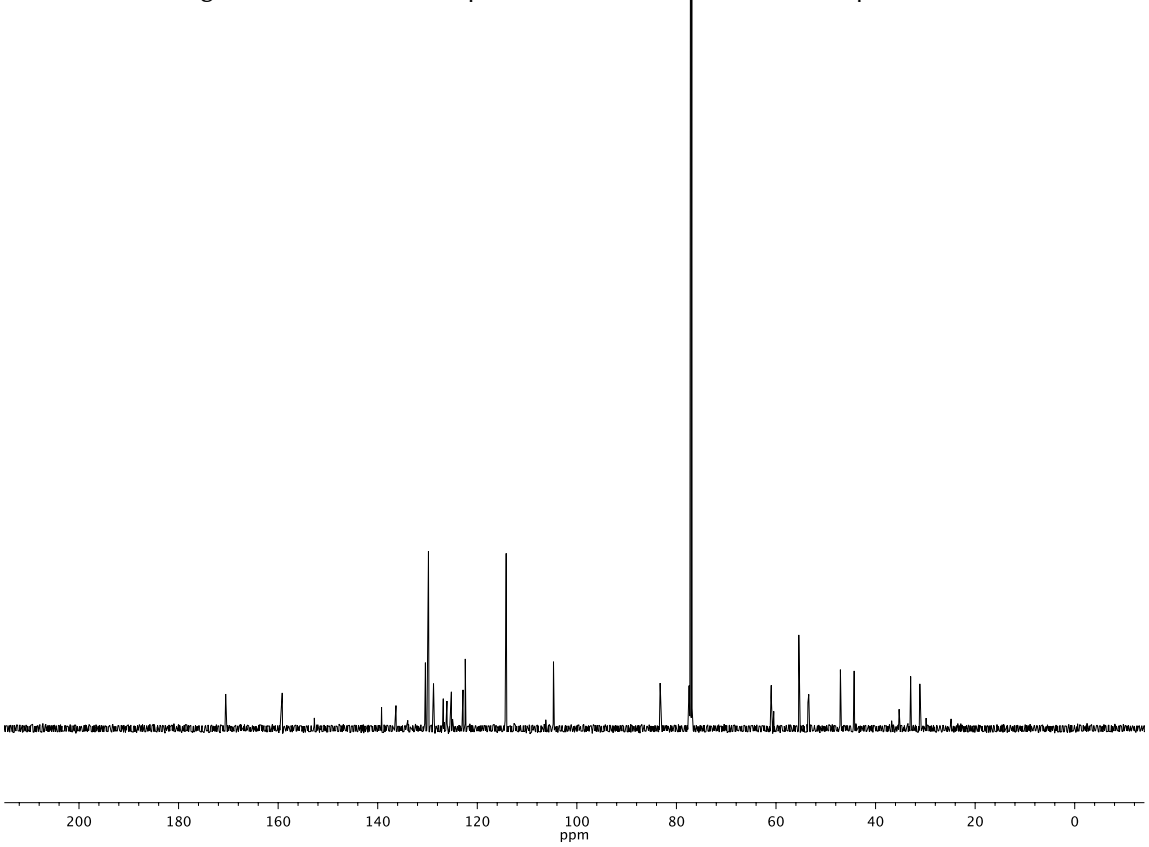


Figure A1.111. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **76**.

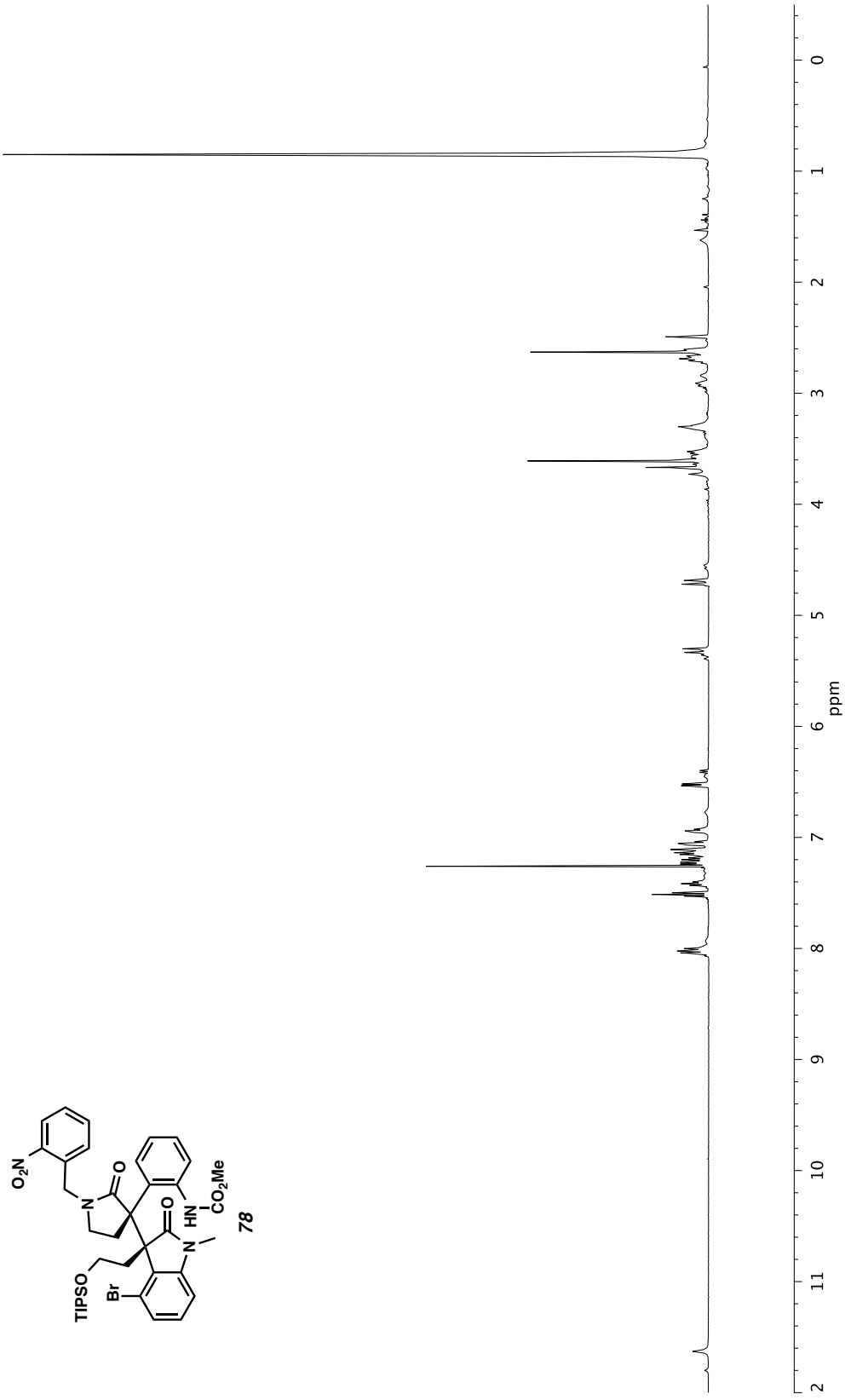


Figure A1.112. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **78**.

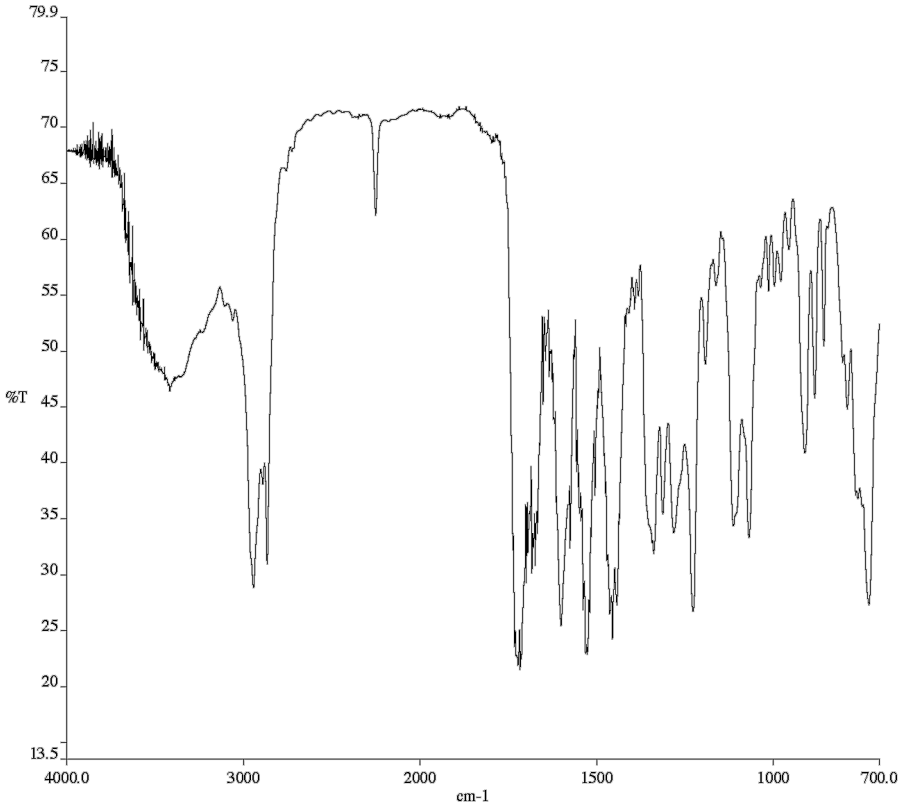


Figure A1.113. Infrared spectrum (Thin Film, NaCl) of compound **78**.

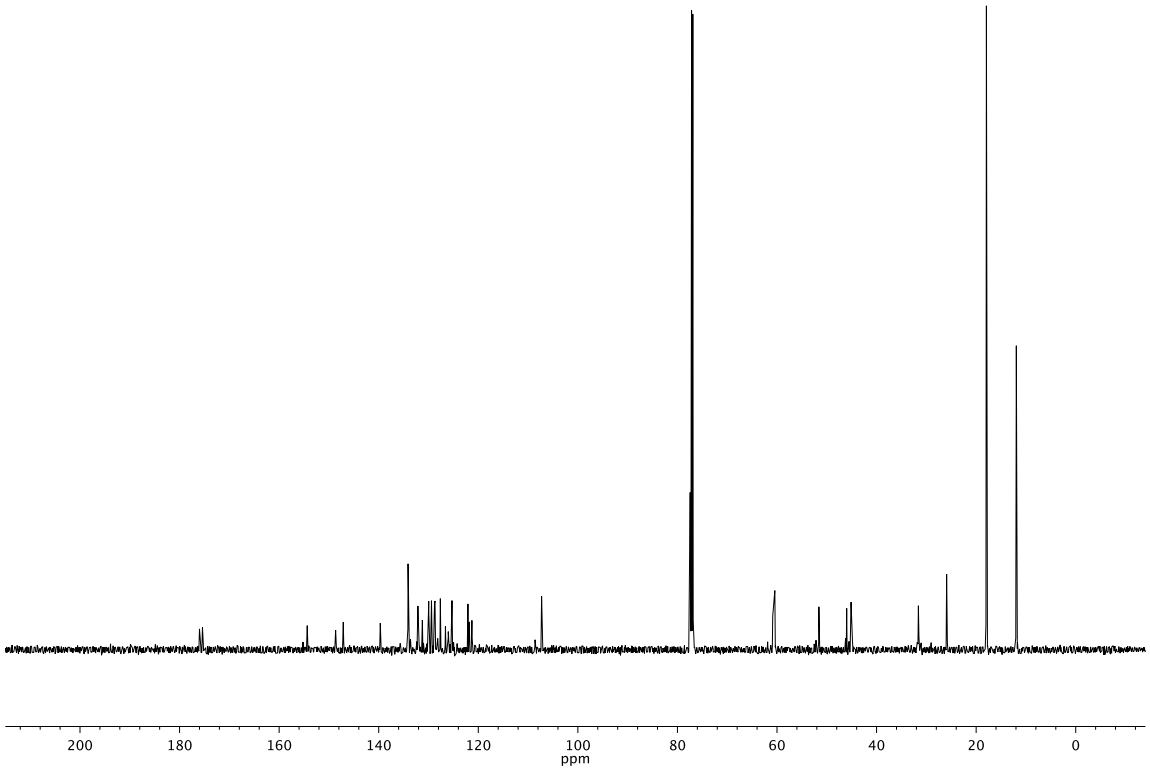


Figure A1.114. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **78**.

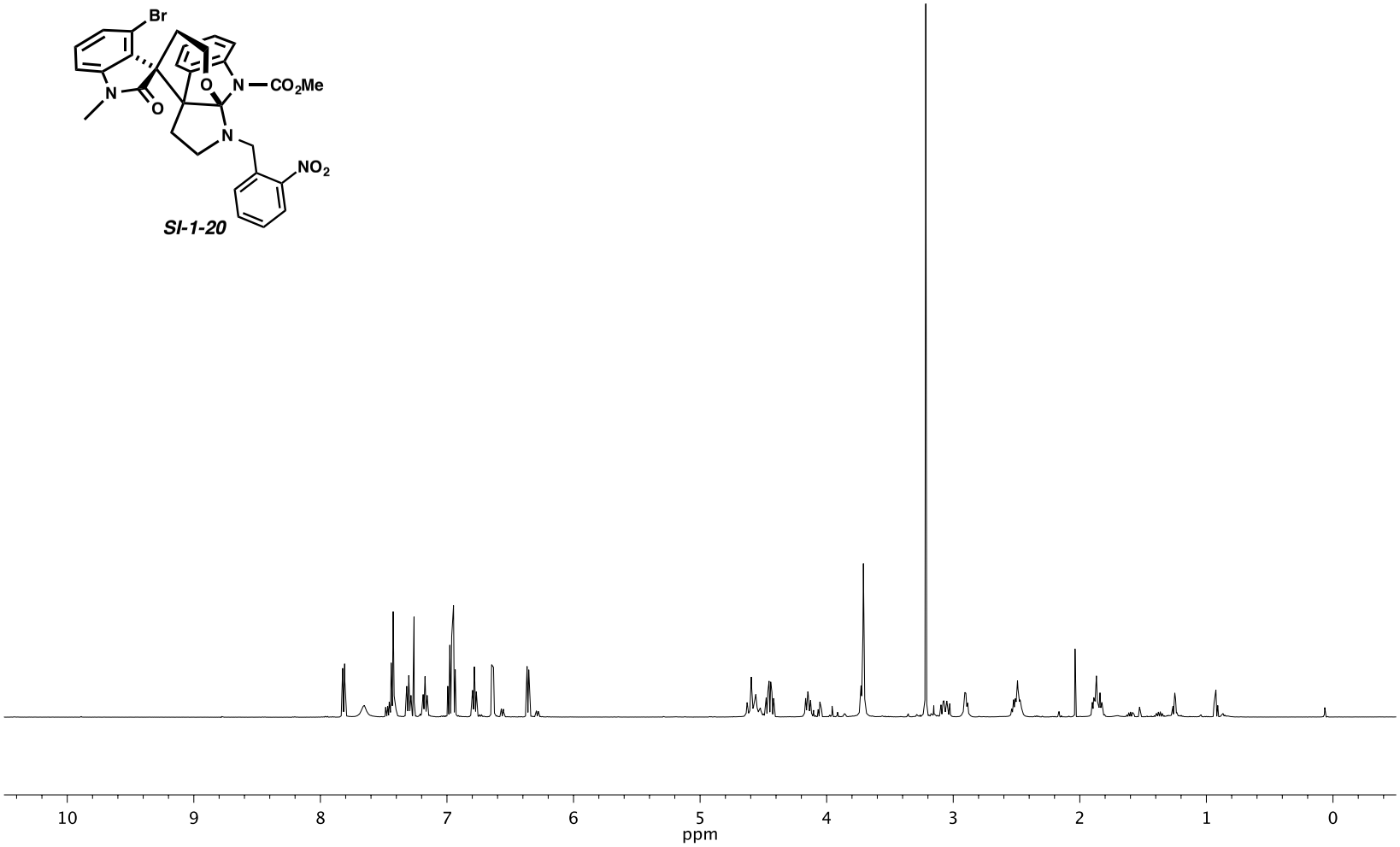


Figure A1.115. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **SI-1-20**.

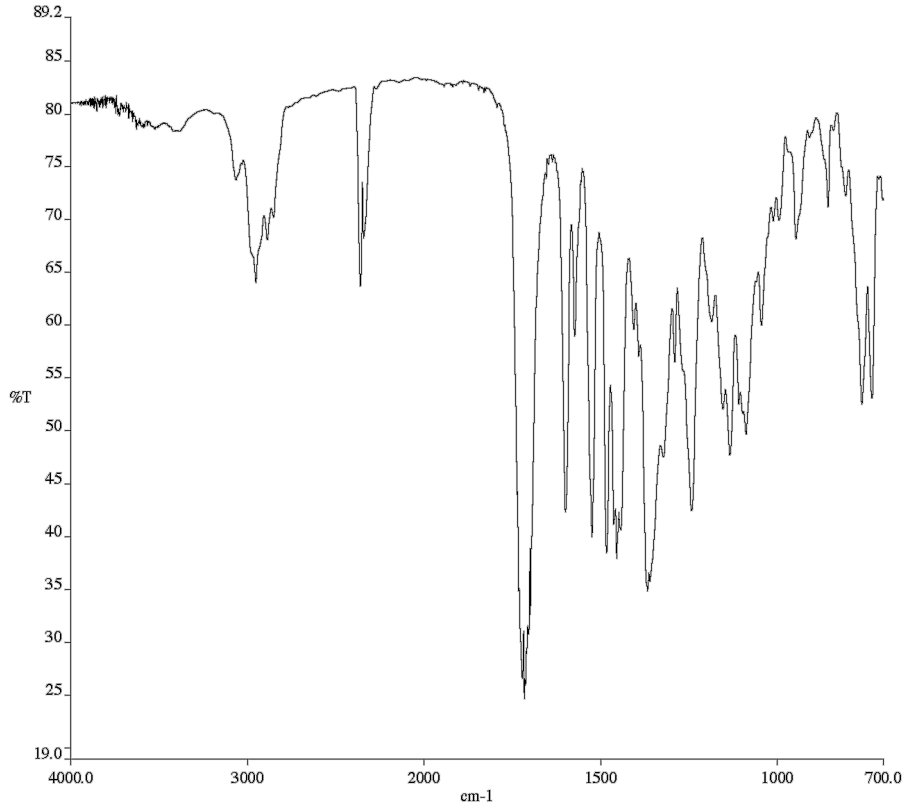


Figure A1.116. Infrared spectrum (Thin Film, NaCl) of compound **SI-1-20**.

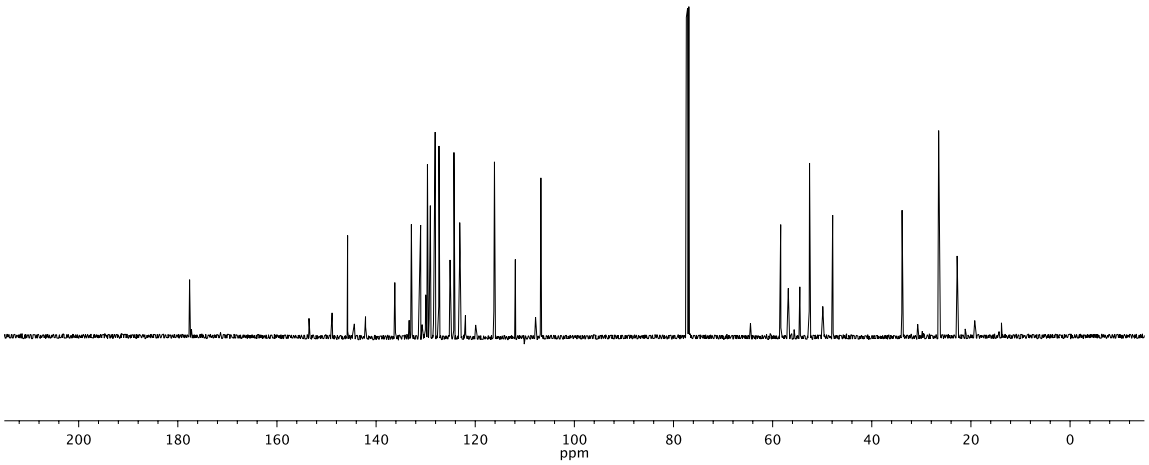


Figure A1.117. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **SI-1-20**.

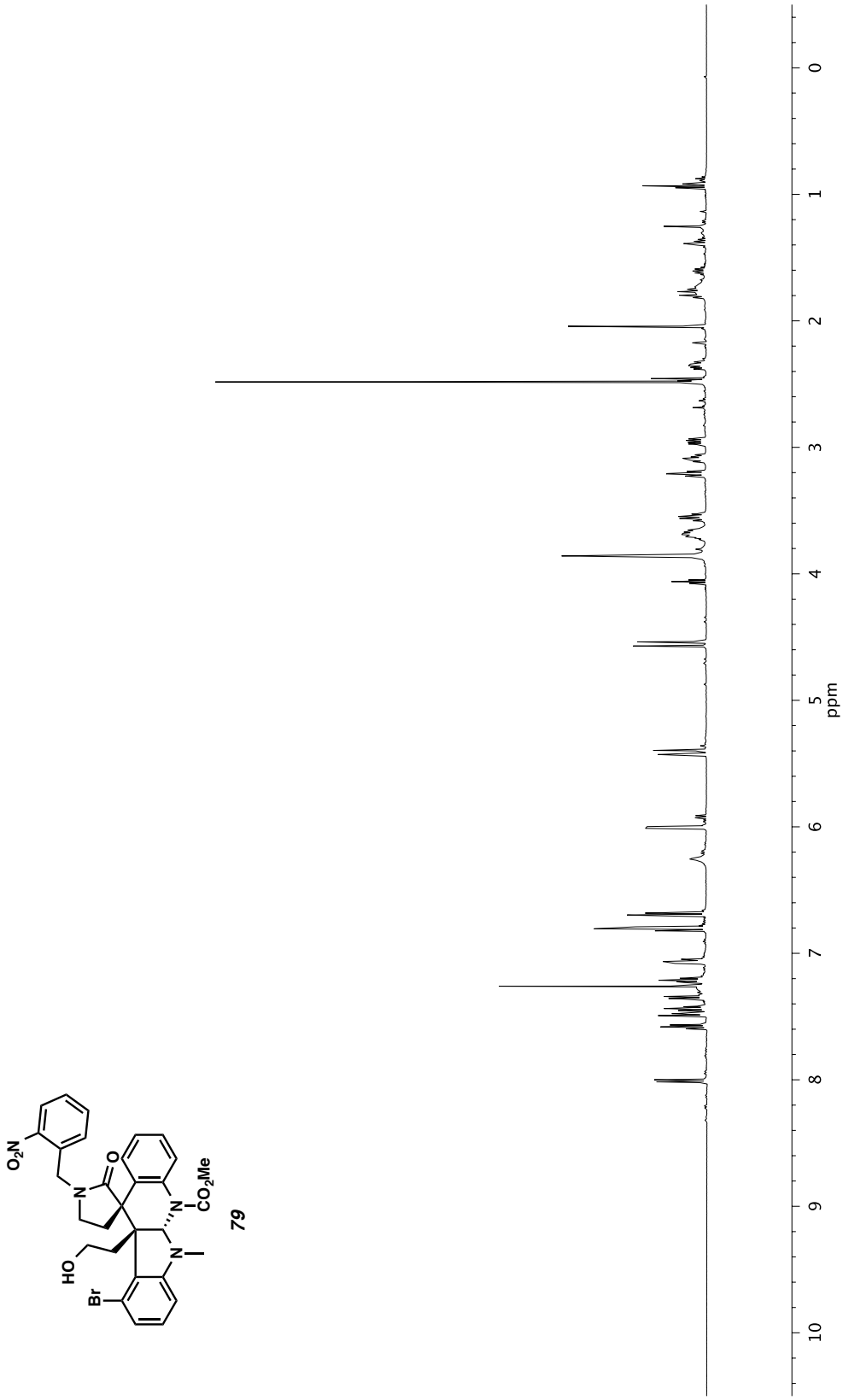


Figure A1.118. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **79**.

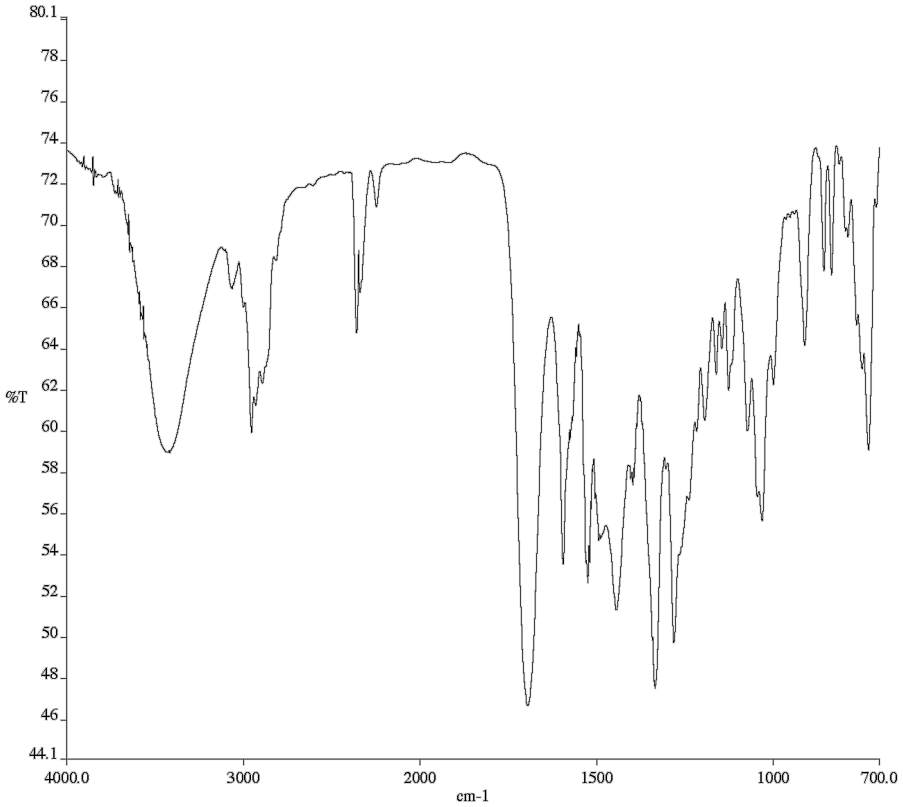


Figure A1.119. Infrared spectrum (Thin Film, NaCl) of compound **79**.

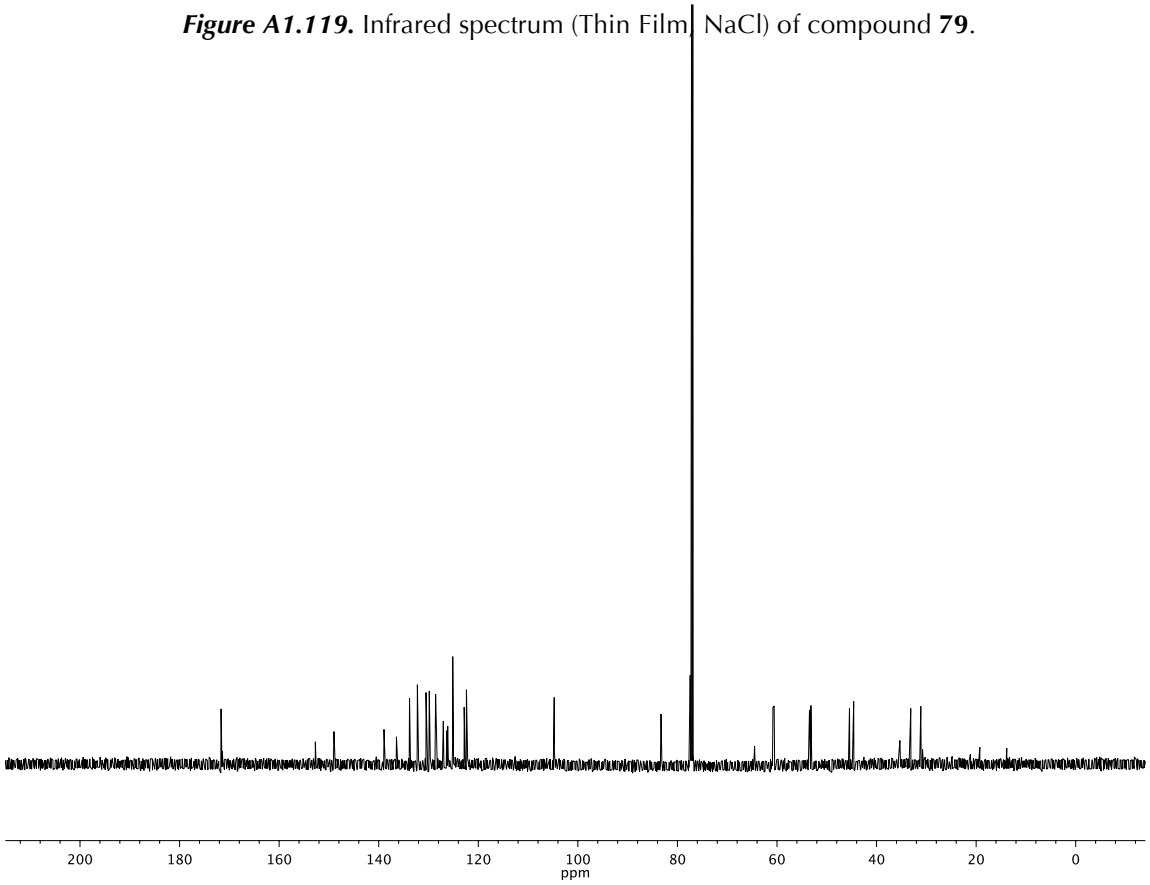
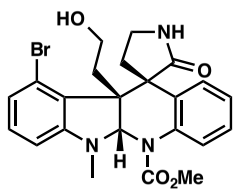


Figure A1.120. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **79**.



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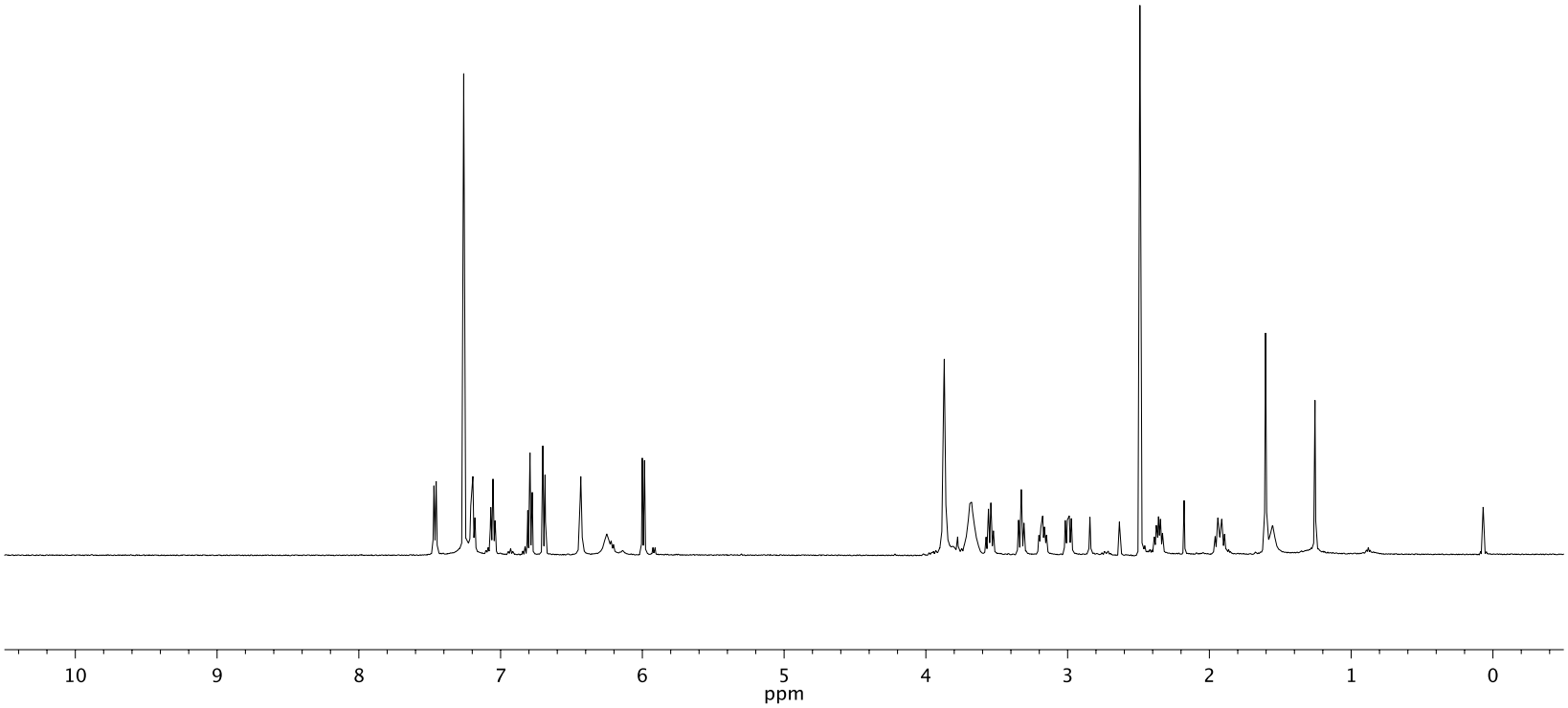


Figure A1.121. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **53**.

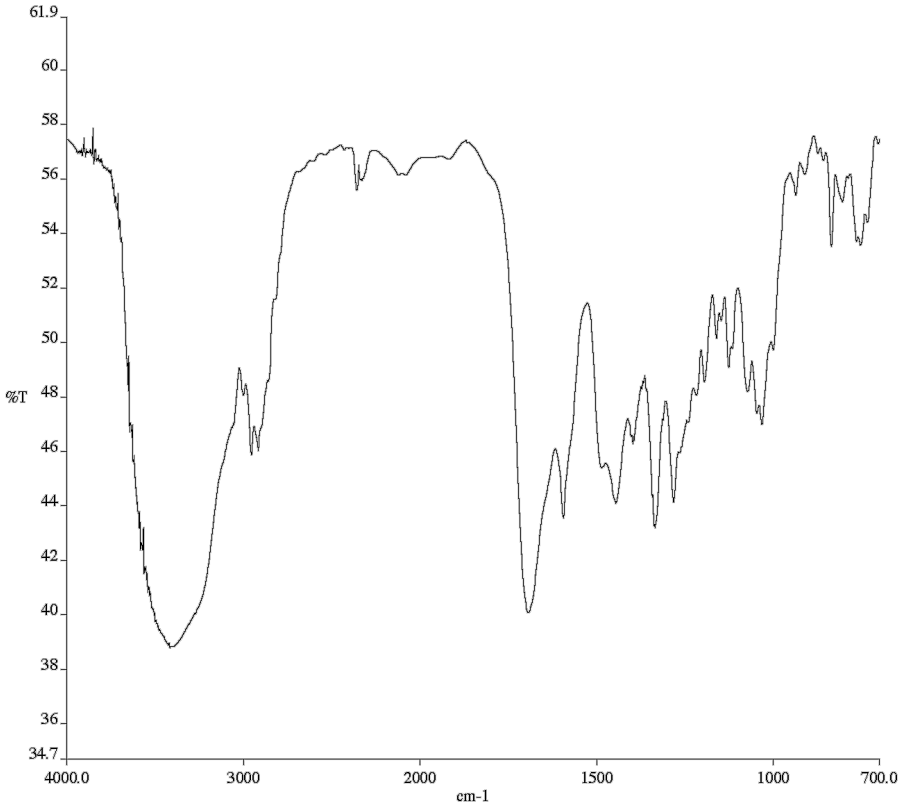


Figure A1.122. Infrared spectrum (Thin Film, NaCl) of compound **53**.

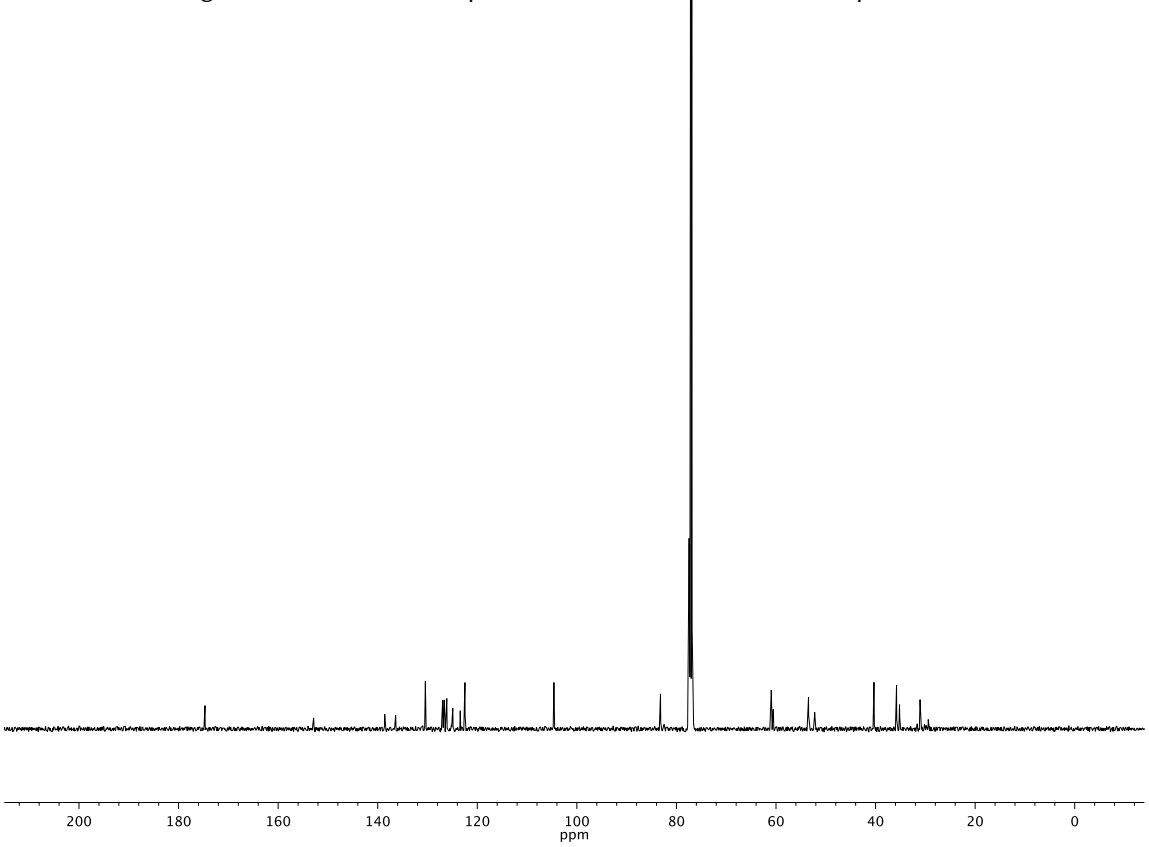


Figure A1.123. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **53**.

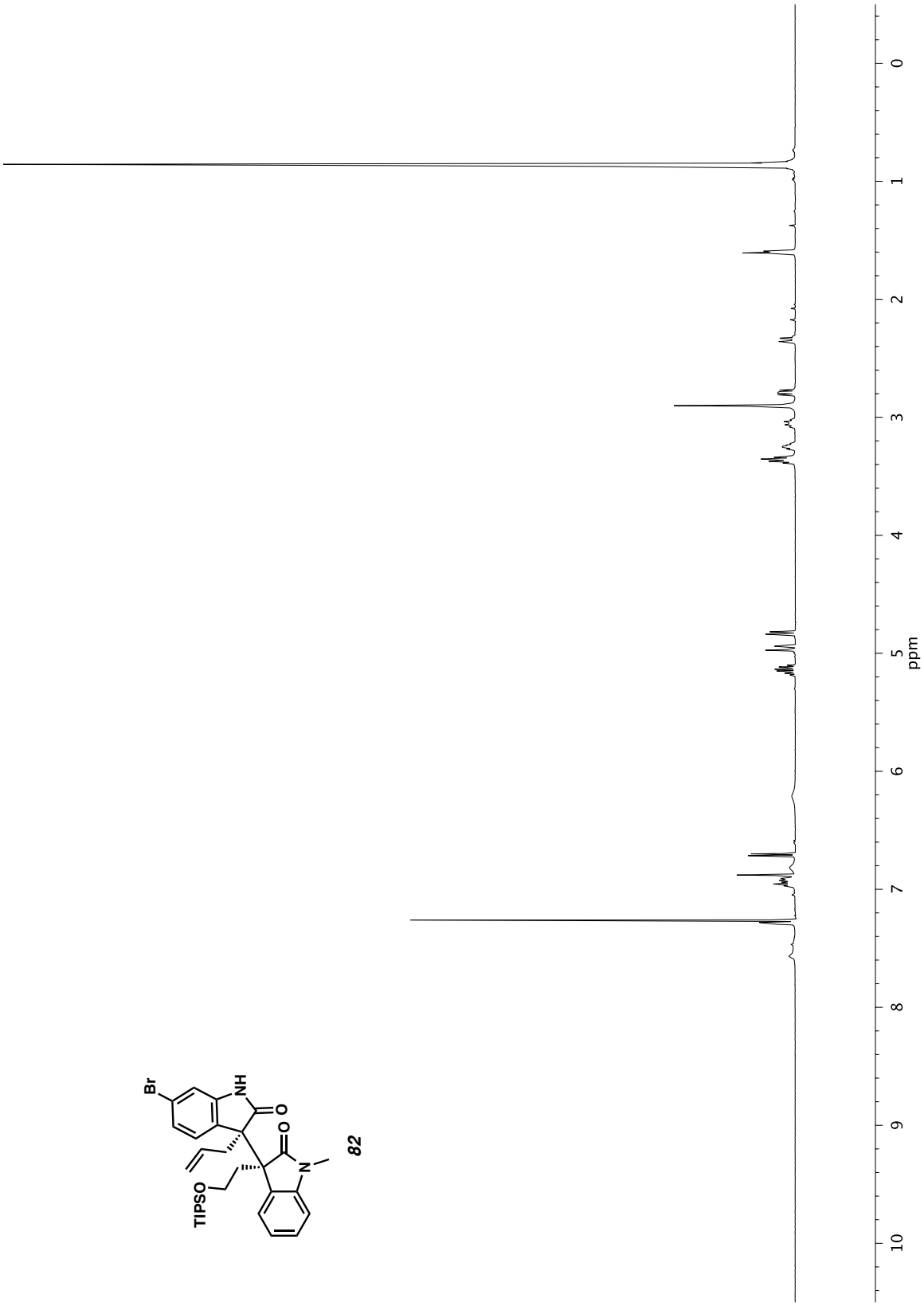


Figure A1.124. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **82**.

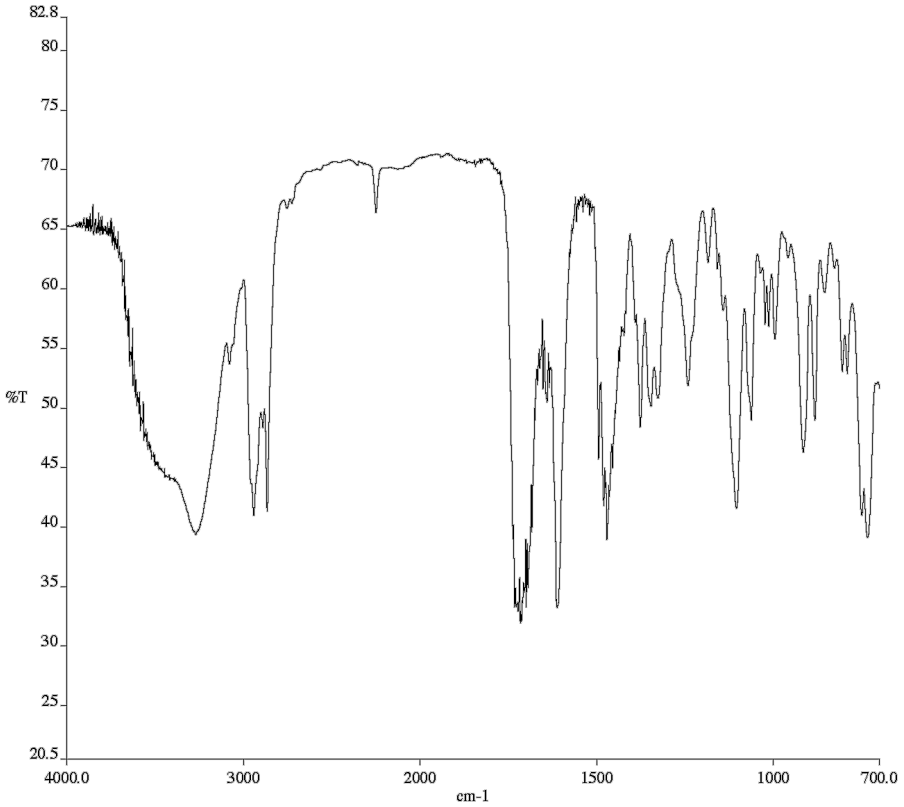


Figure A1.125. Infrared spectrum (Thin Film, NaCl) of compound **82**.

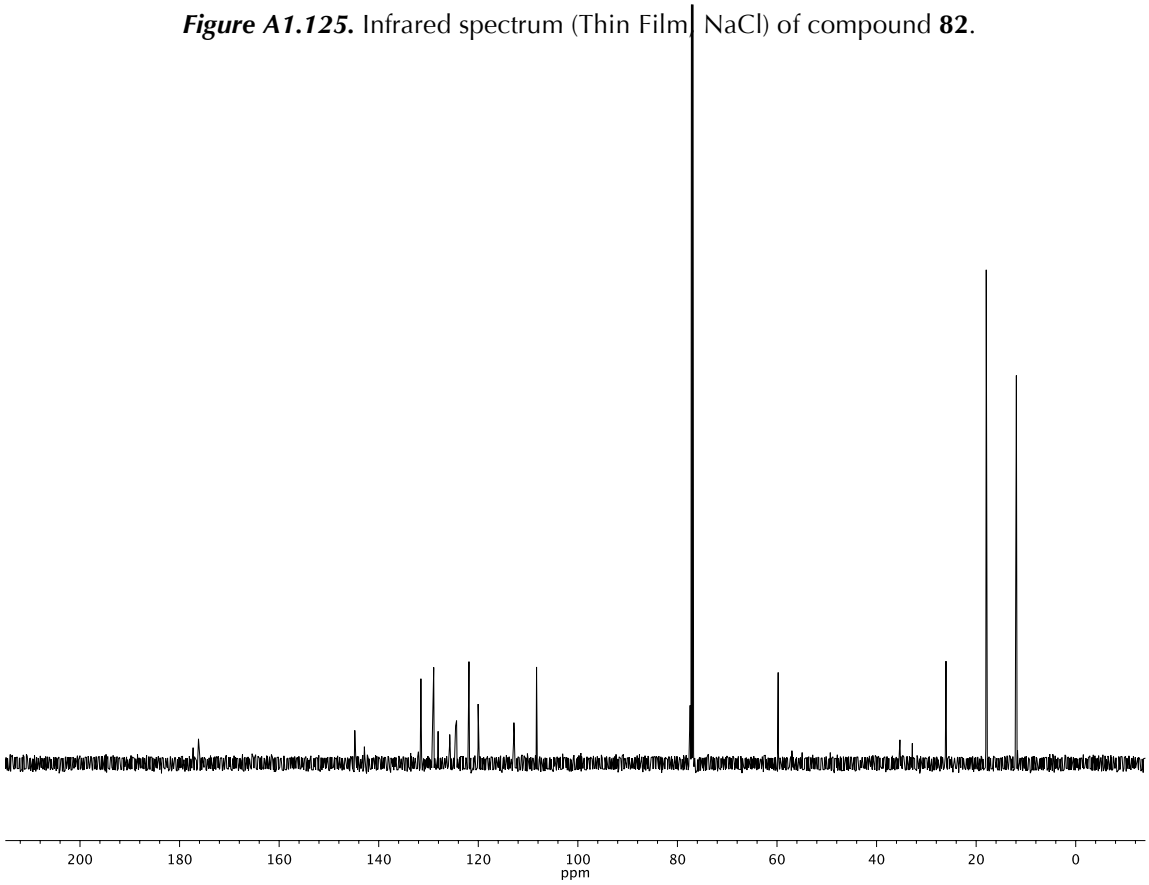


Figure A1.126. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **82**.

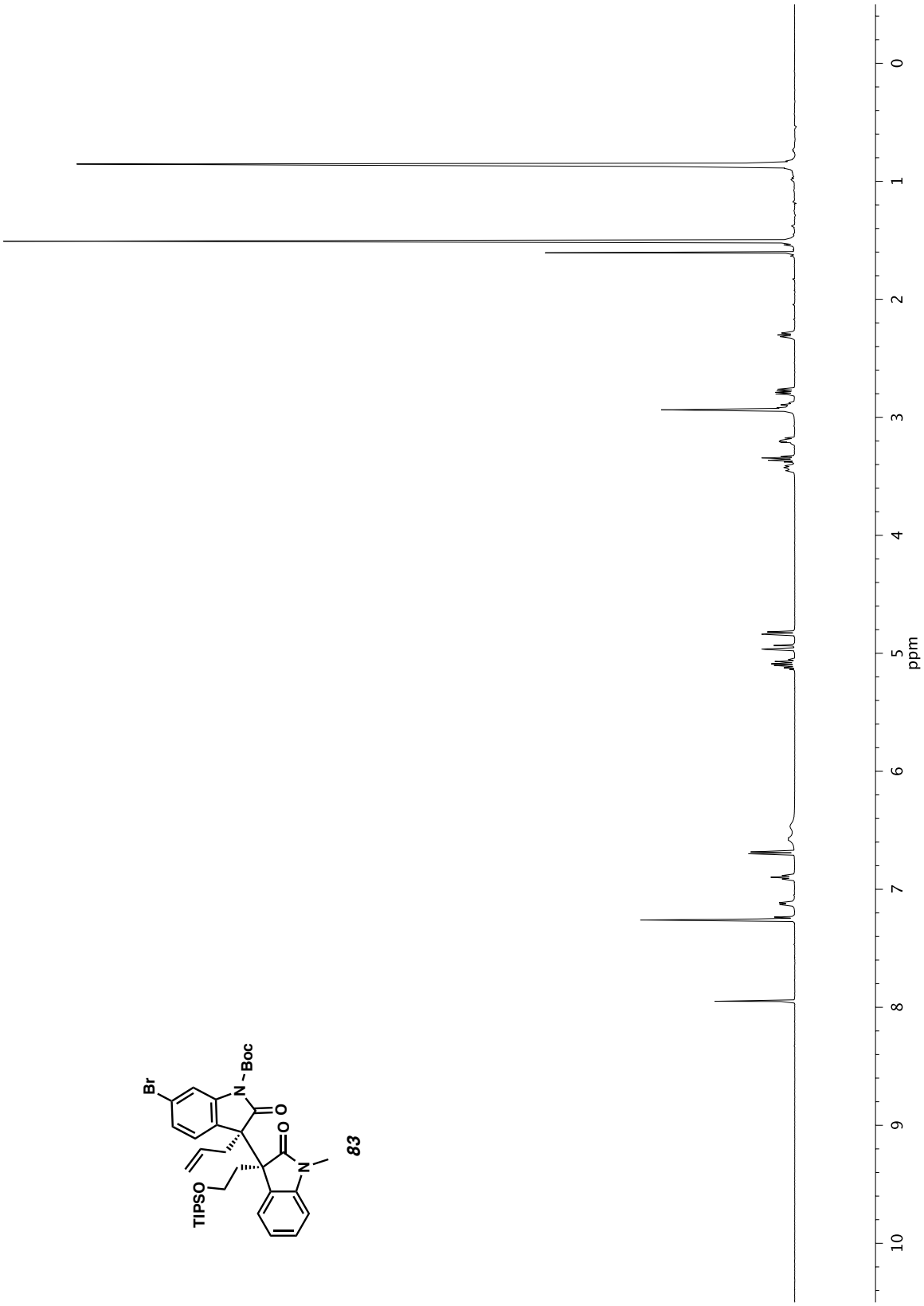


Figure A1.127. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **83**.

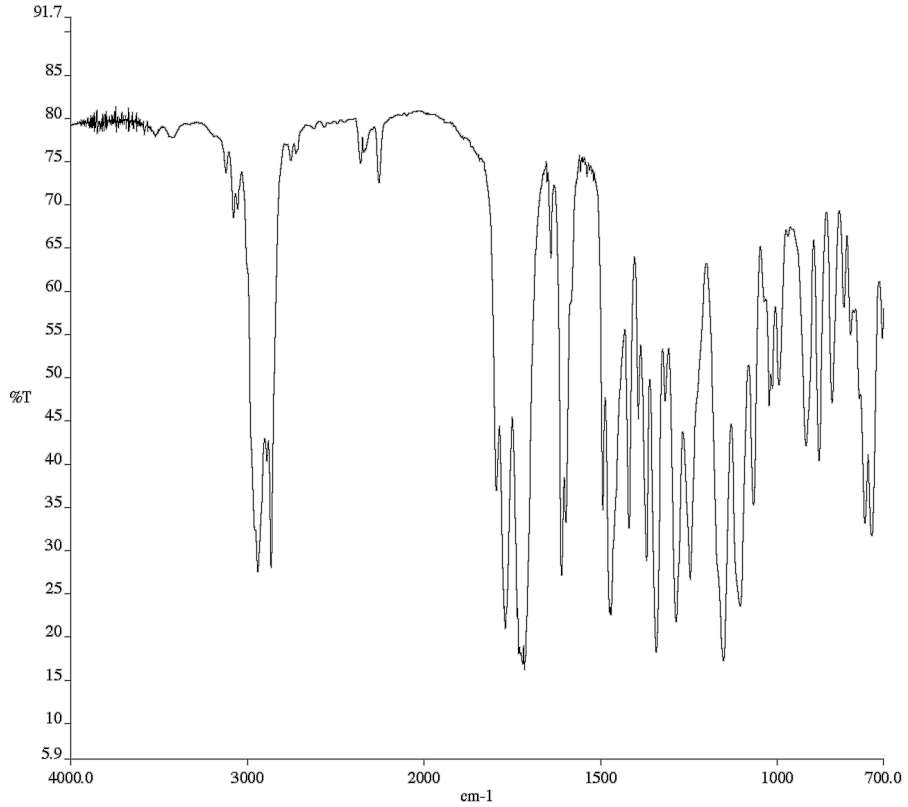


Figure A1.128. Infrared spectrum (Thin Film, NaCl) of compound **83**.

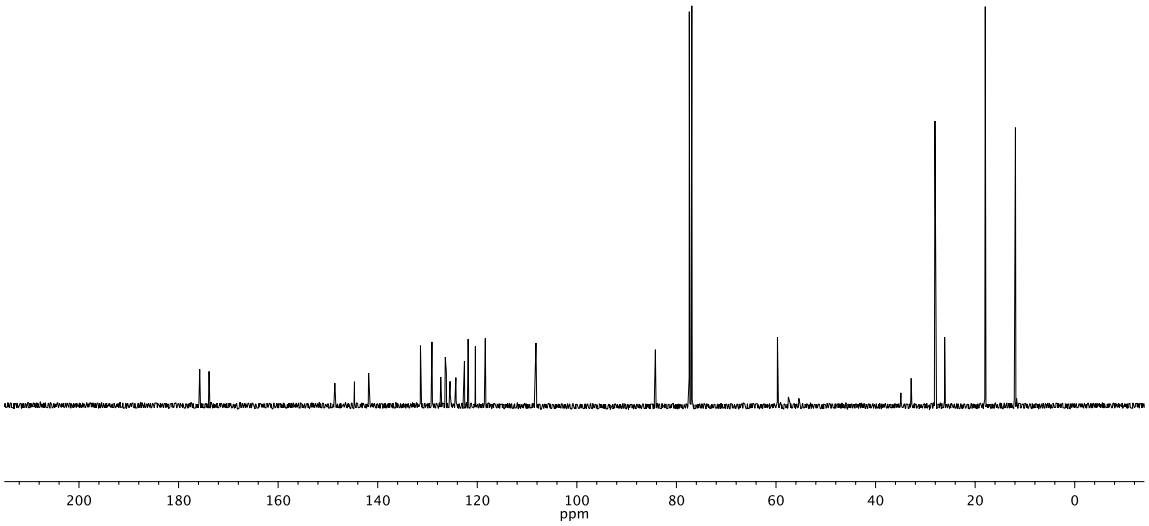


Figure A1.129. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **83**.

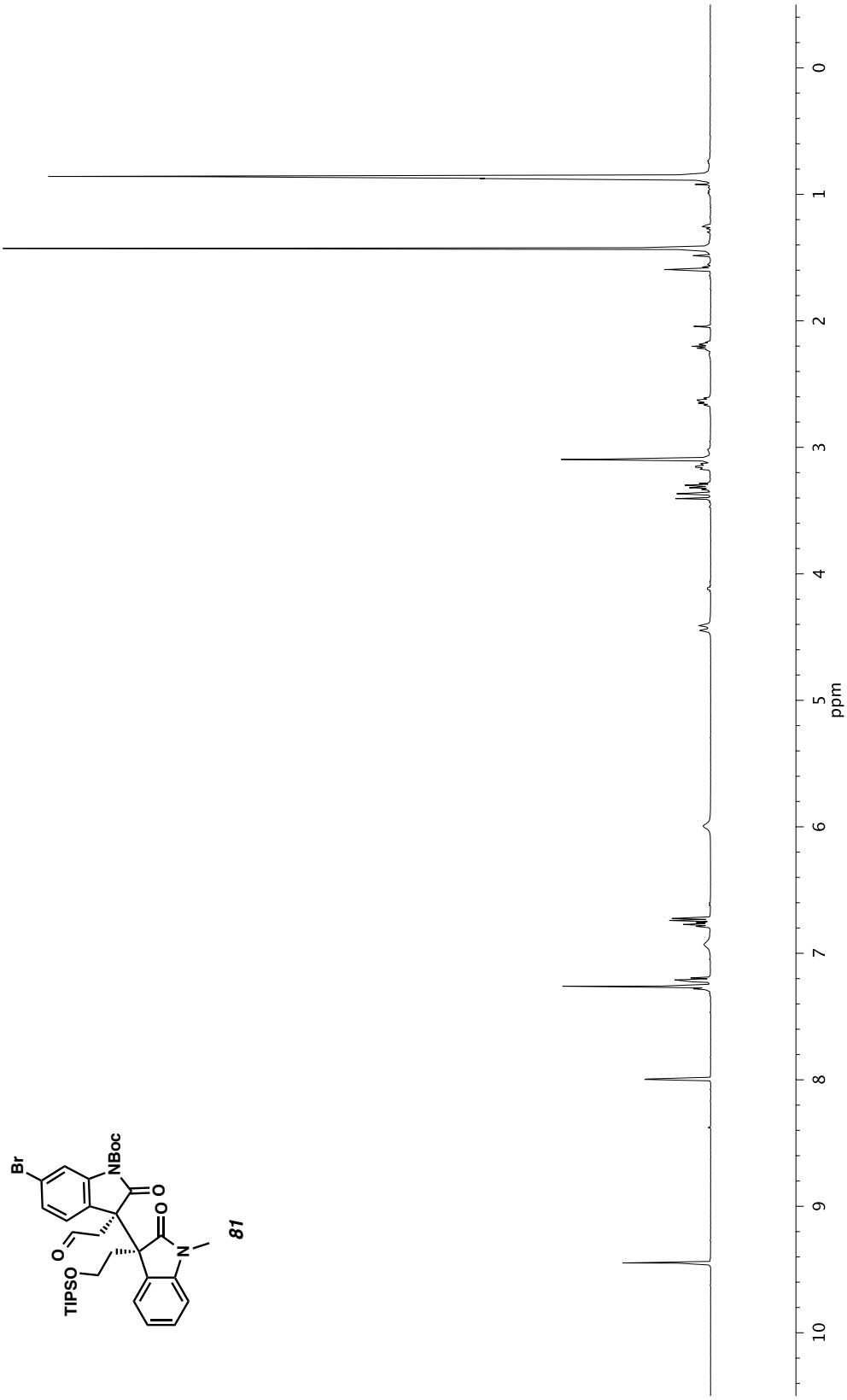


Figure A1.130. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **81**.

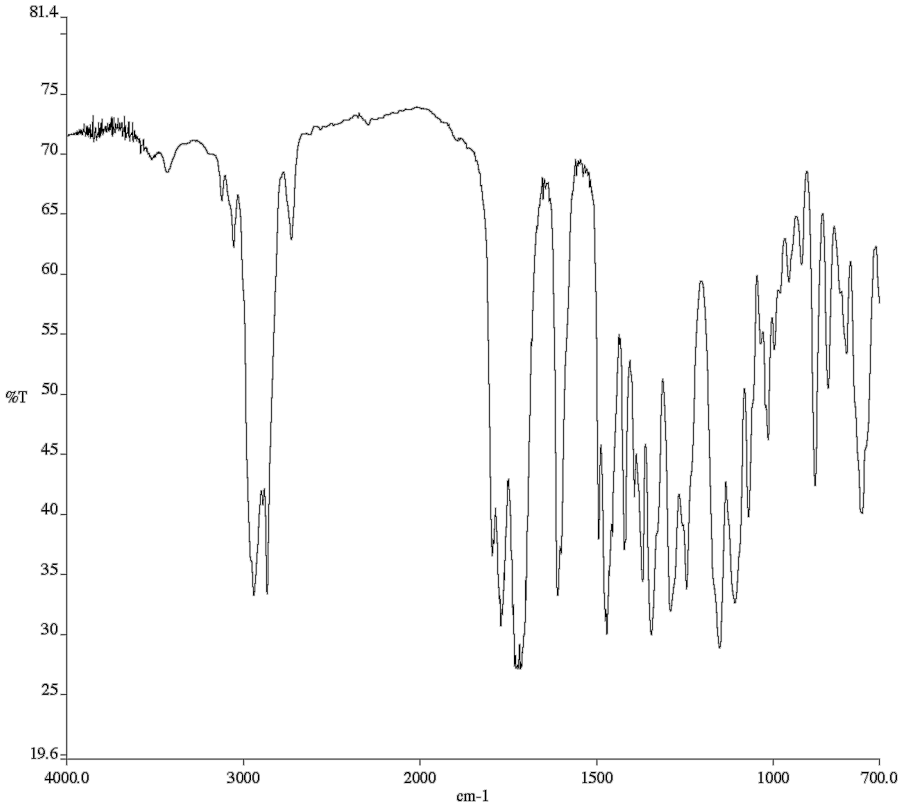


Figure A1.131. Infrared spectrum (Thin Film, NaCl) of compound **81**.

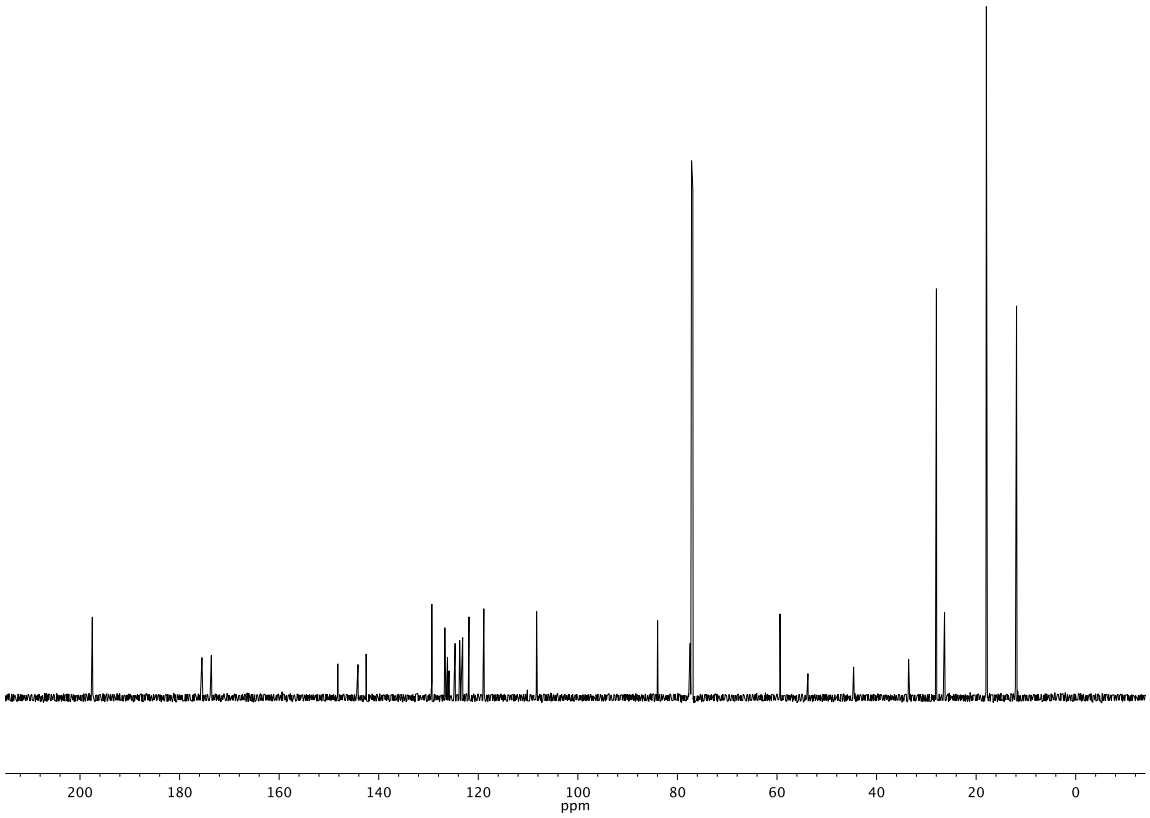


Figure A1.132. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **81**.

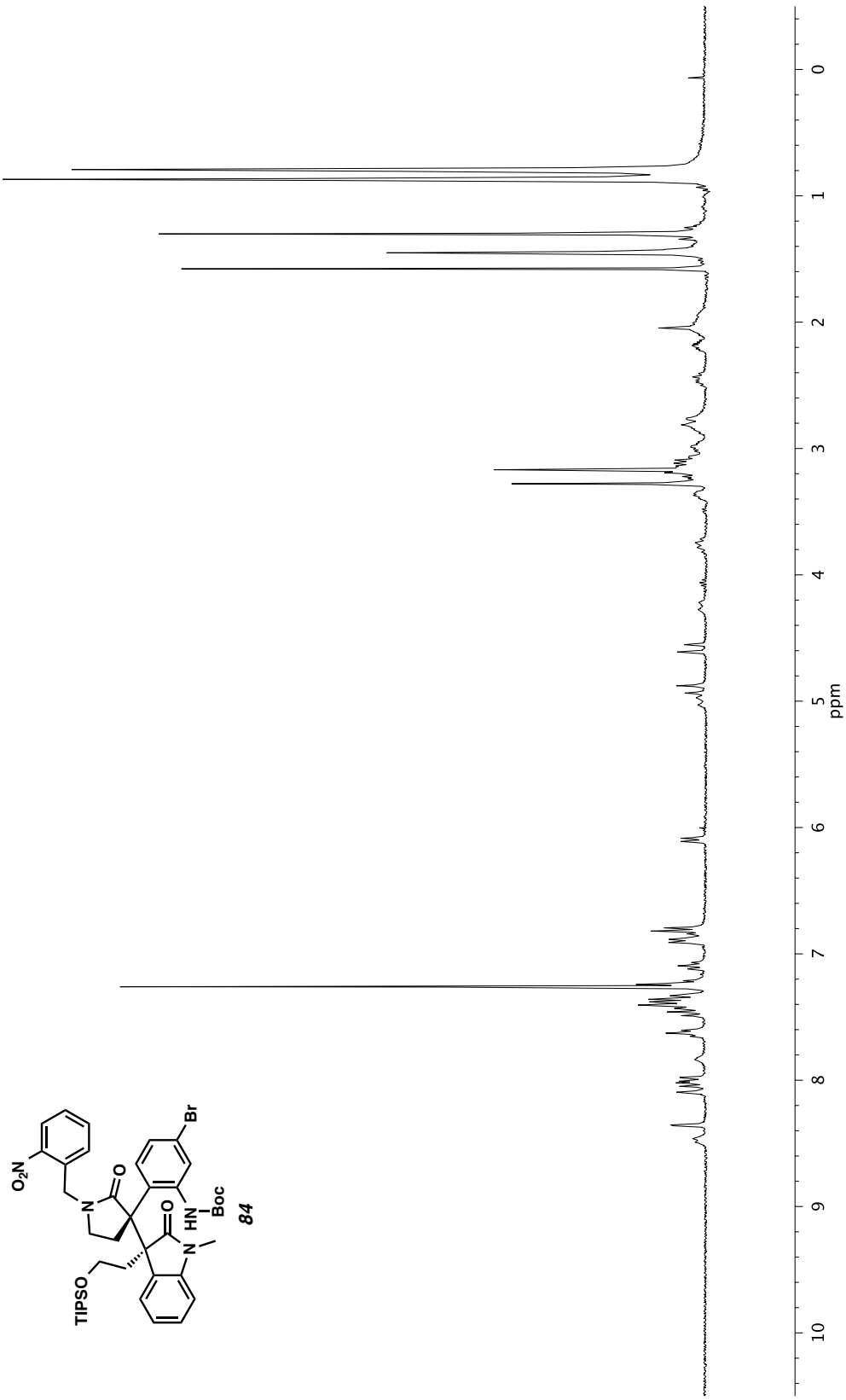


Figure A1.133. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **84**.

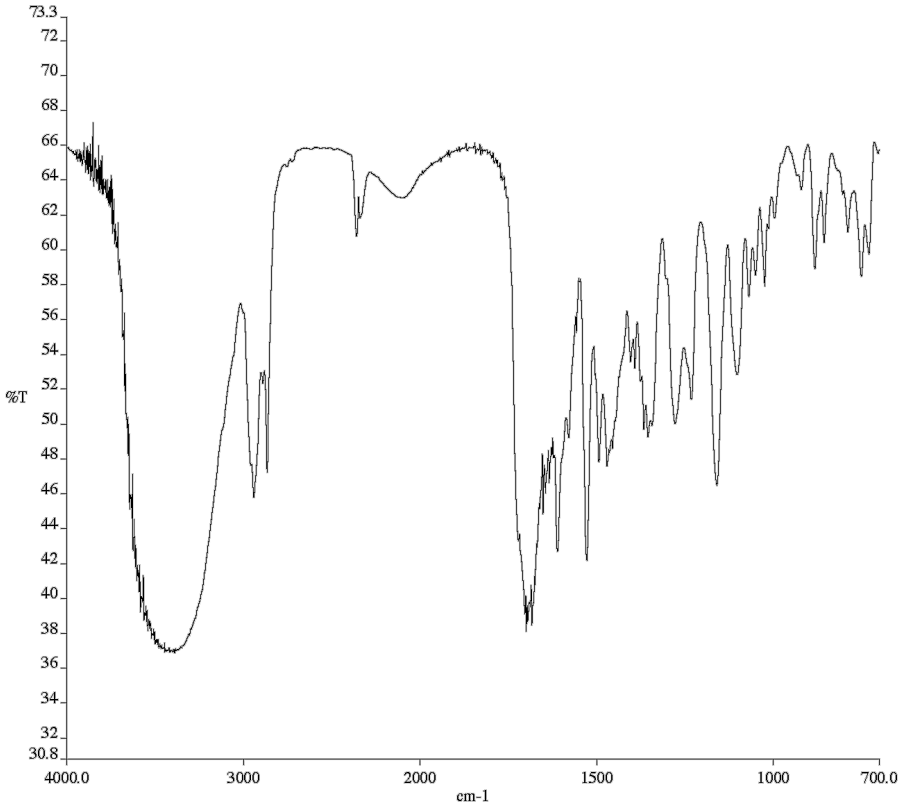


Figure A1.134. Infrared spectrum (Thin Film, NaCl) of compound **84**.

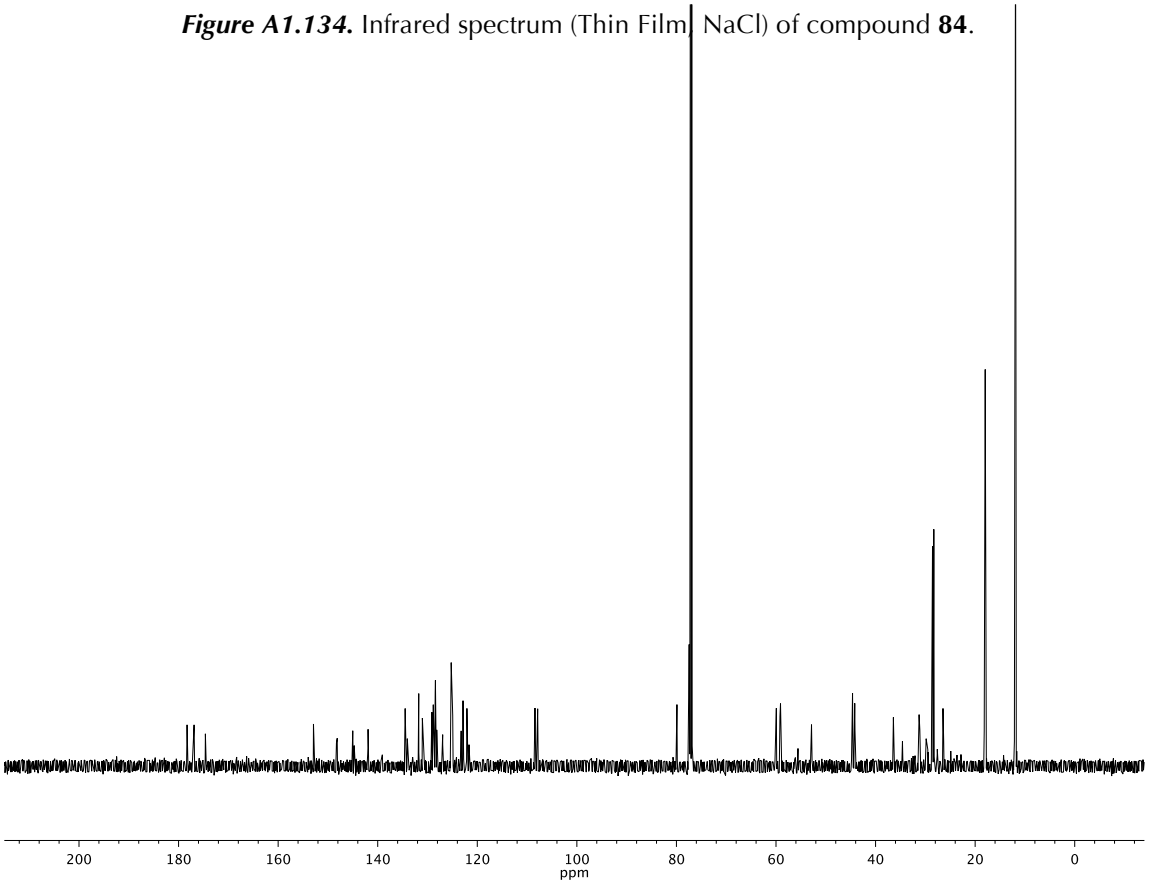


Figure A1.135. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **84**.

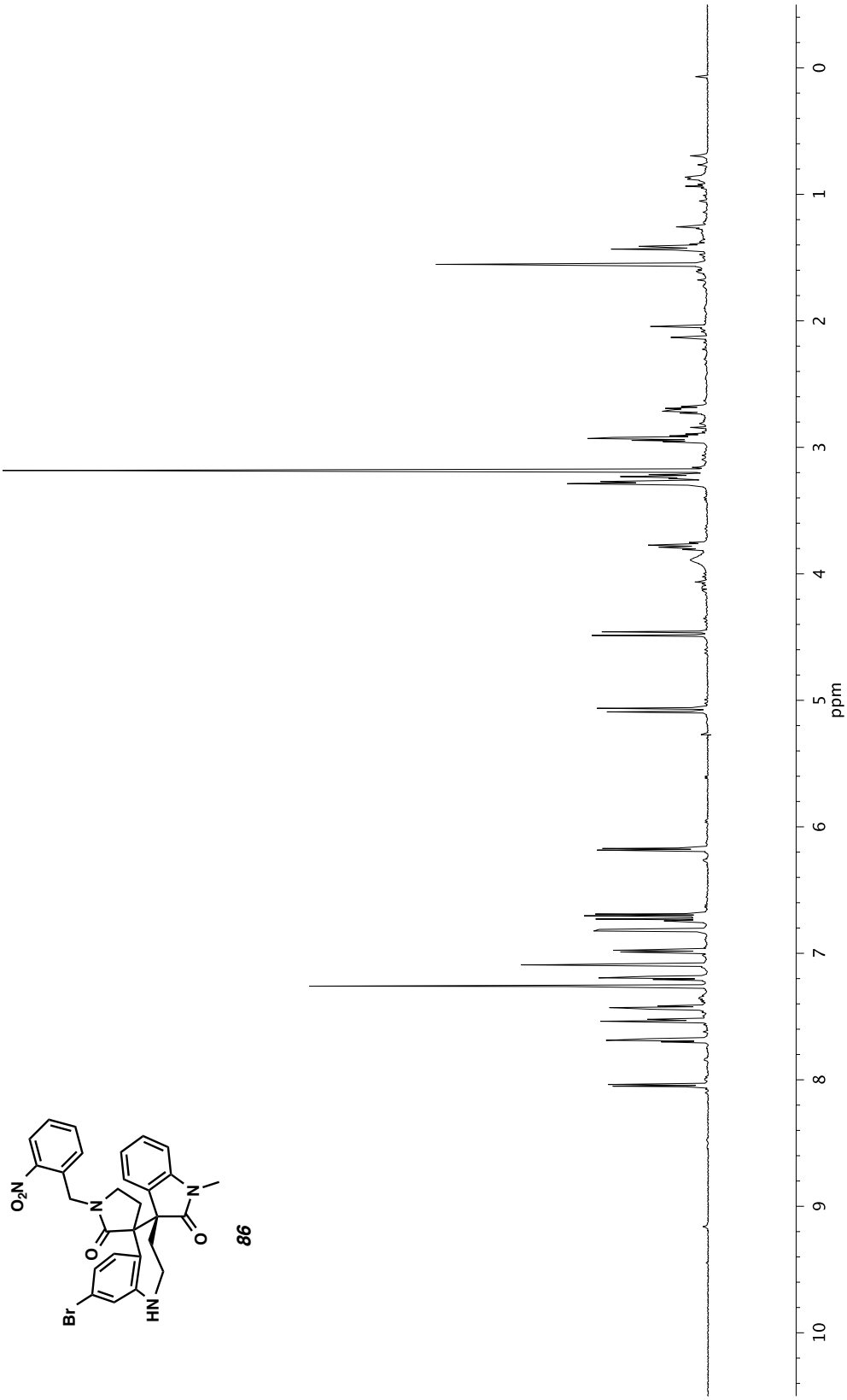


Figure A1.136. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **86**.

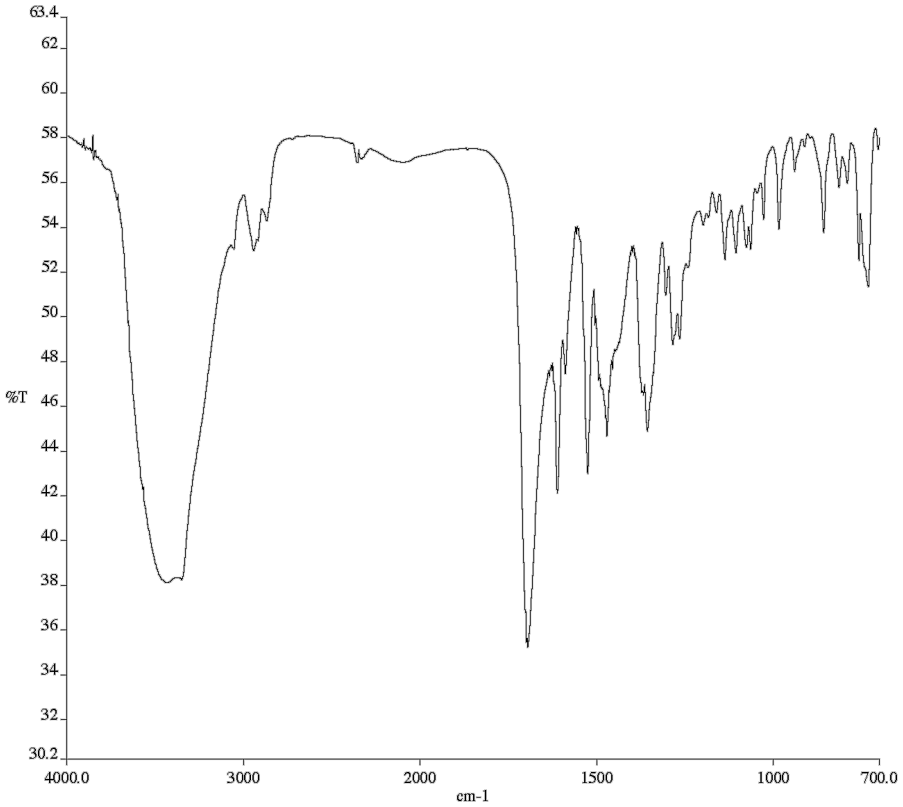


Figure A1.137. Infrared spectrum (Thin Film, NaCl) of compound **86**.

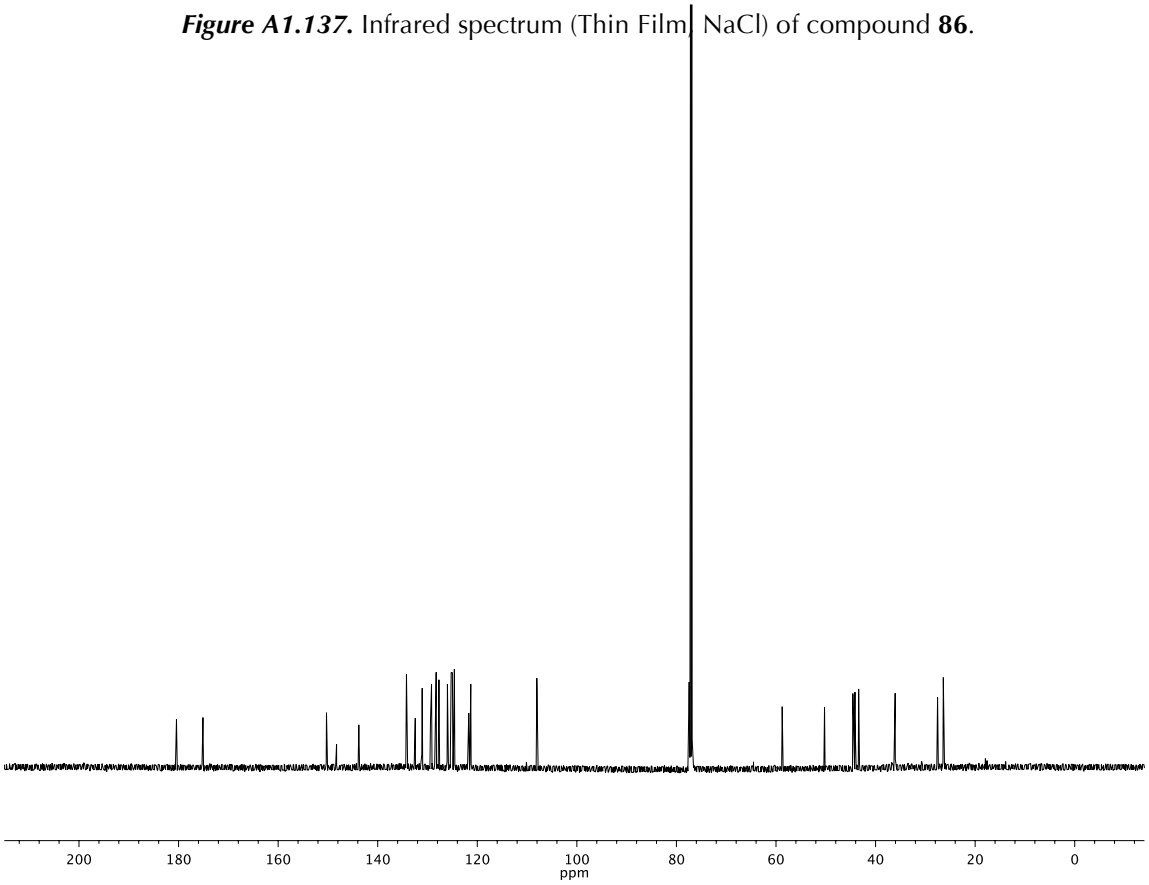


Figure A1.138. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **86**.

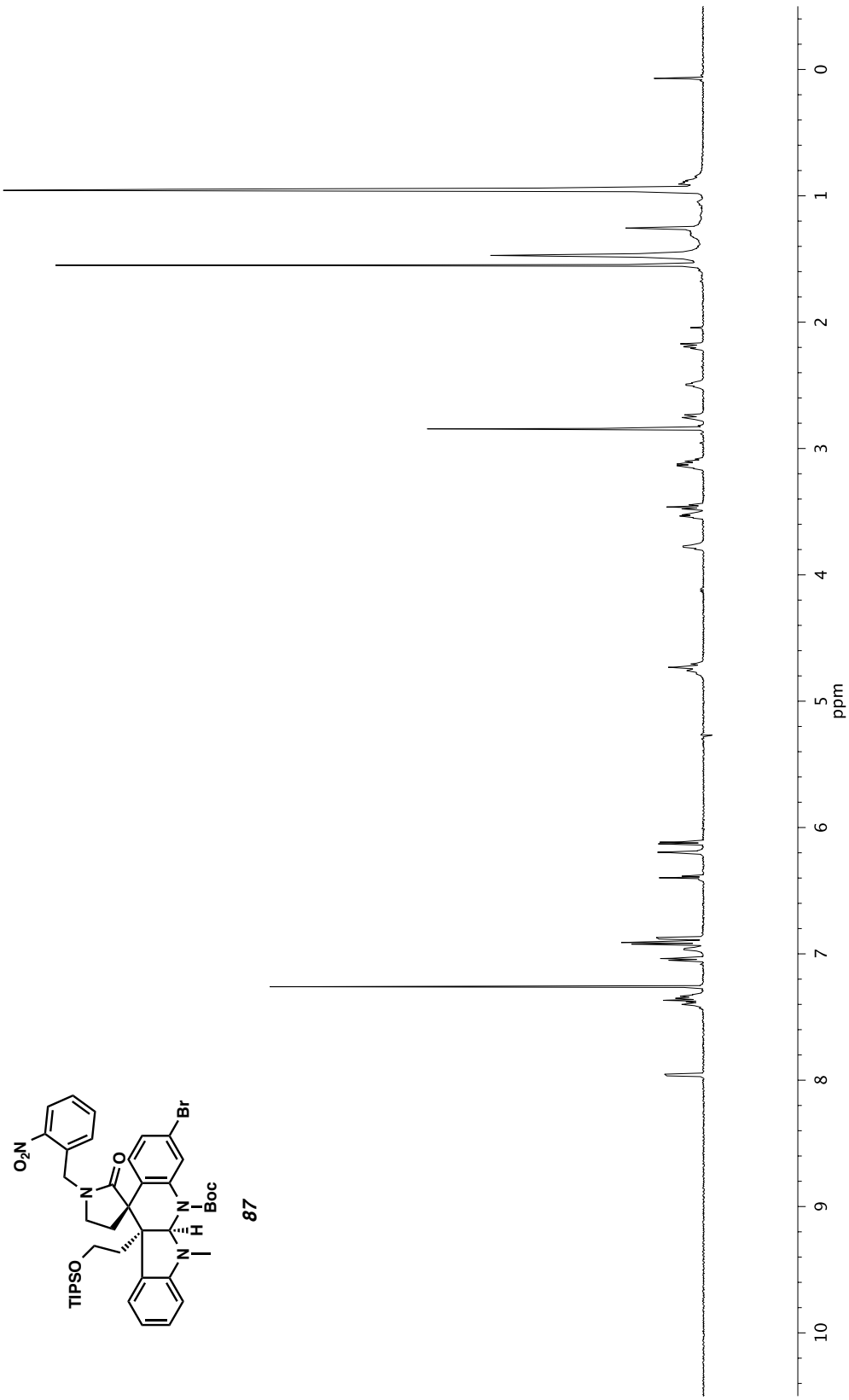


Figure A1.139. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **87**.

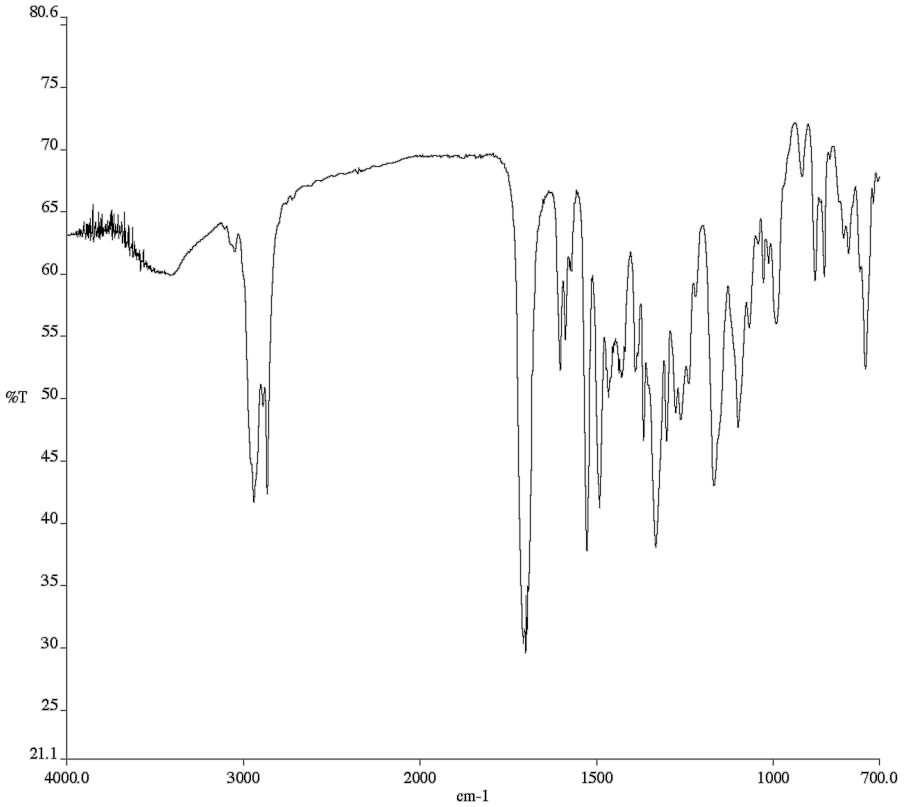


Figure A1.140. Infrared spectrum (Thin Film, NaCl) of compound **87**.

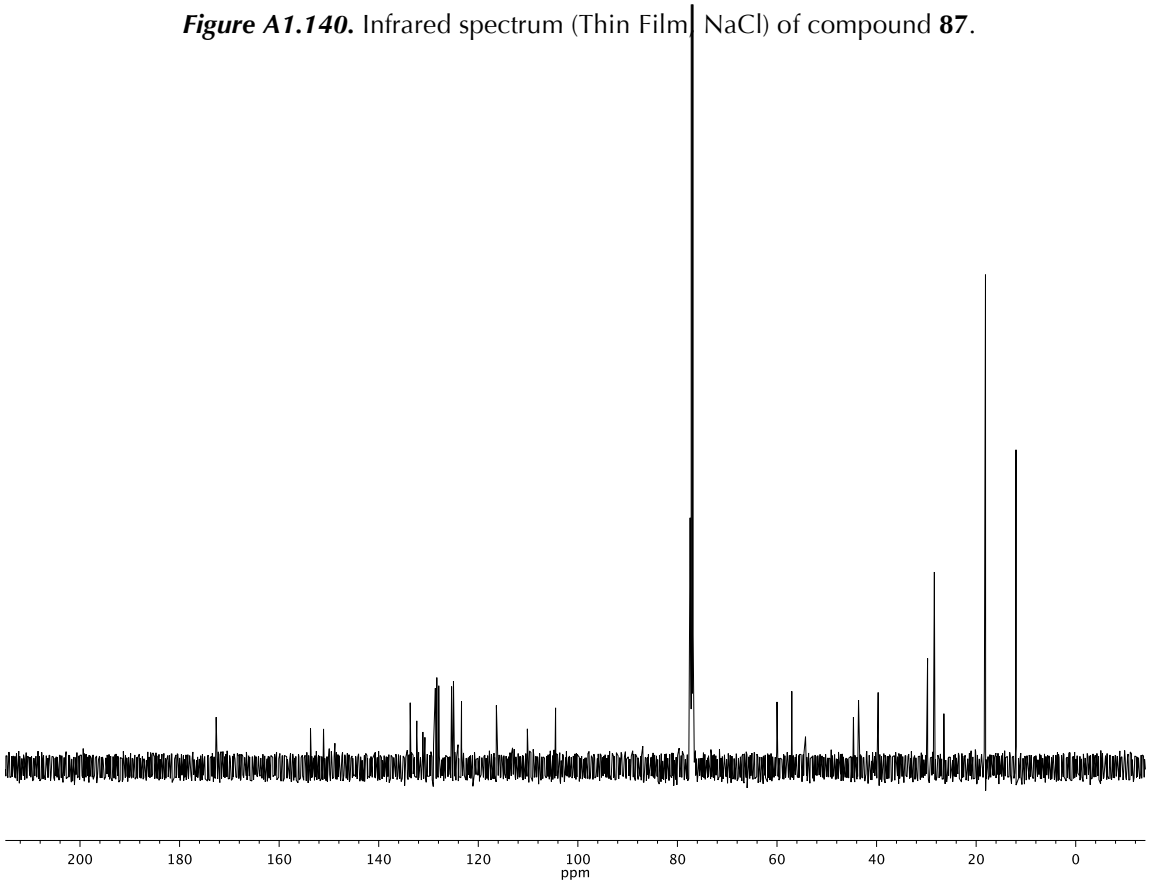


Figure A1.141. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **87**.

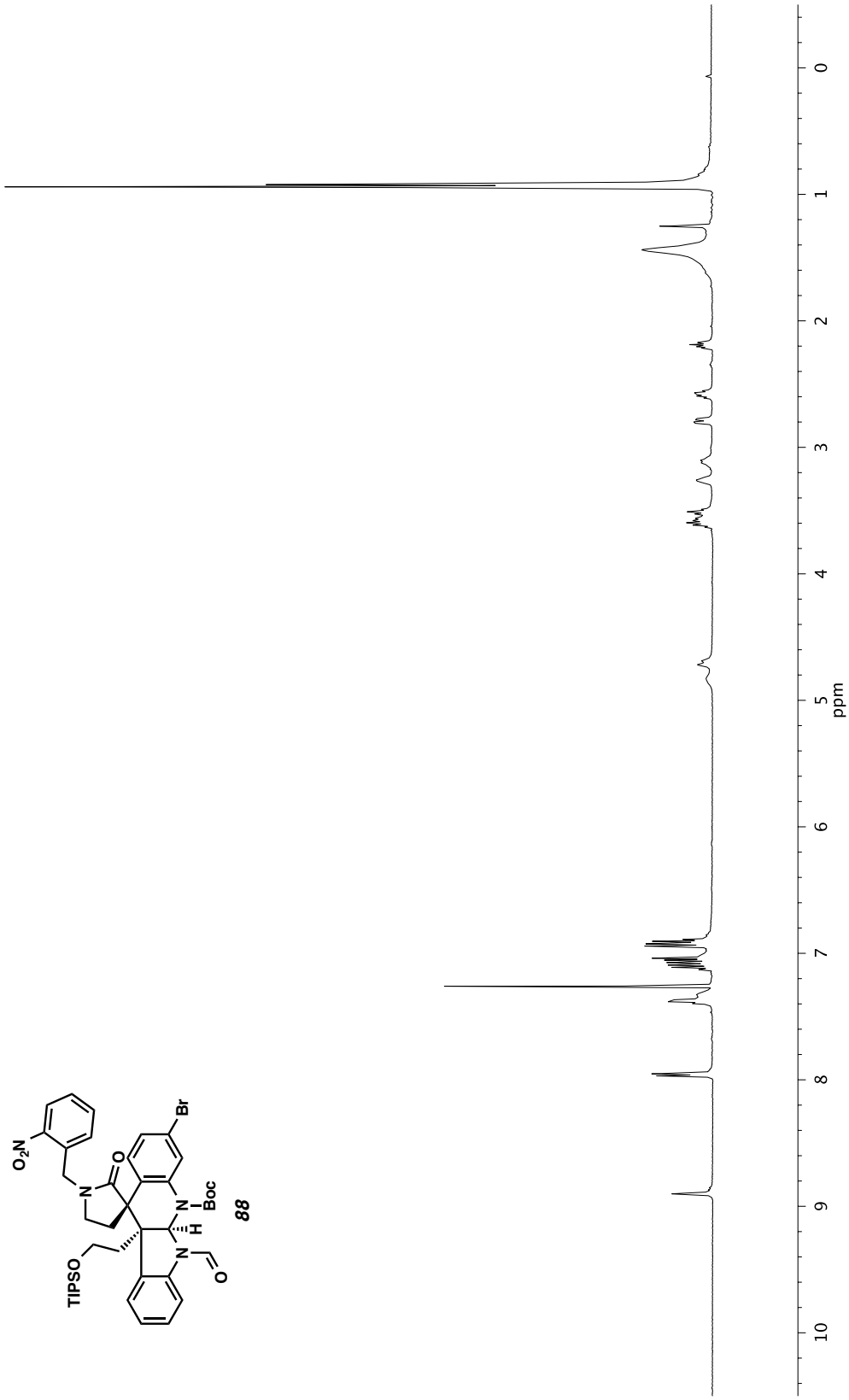


Figure A1.142. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **88**.

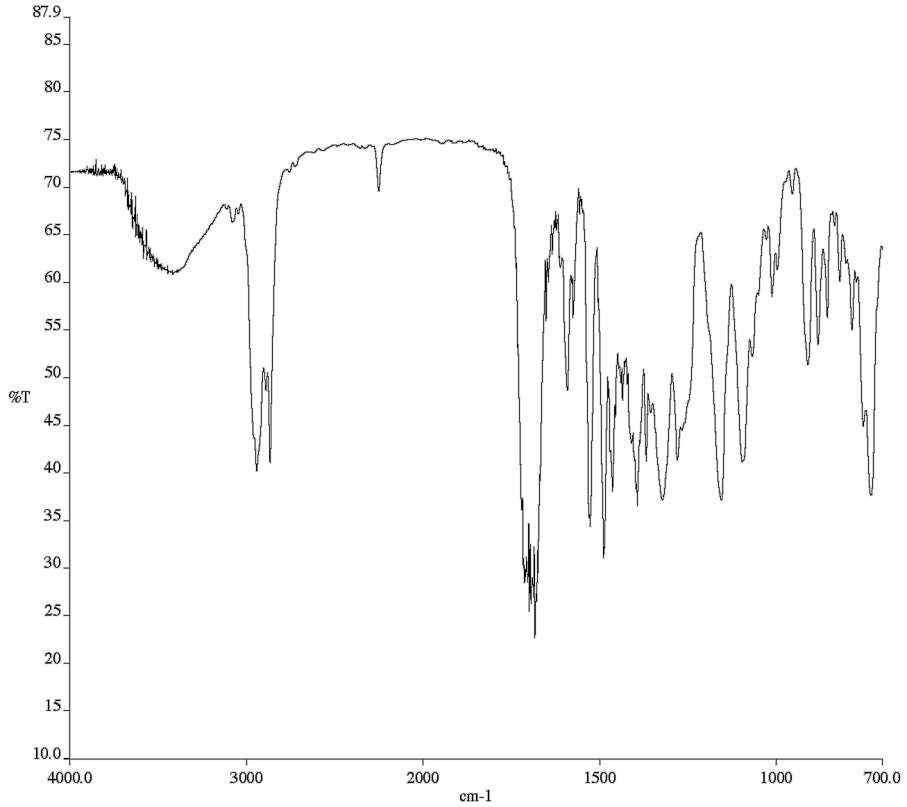


Figure A1.143. Infrared spectrum (Thin Film, NaCl) of compound **88**.

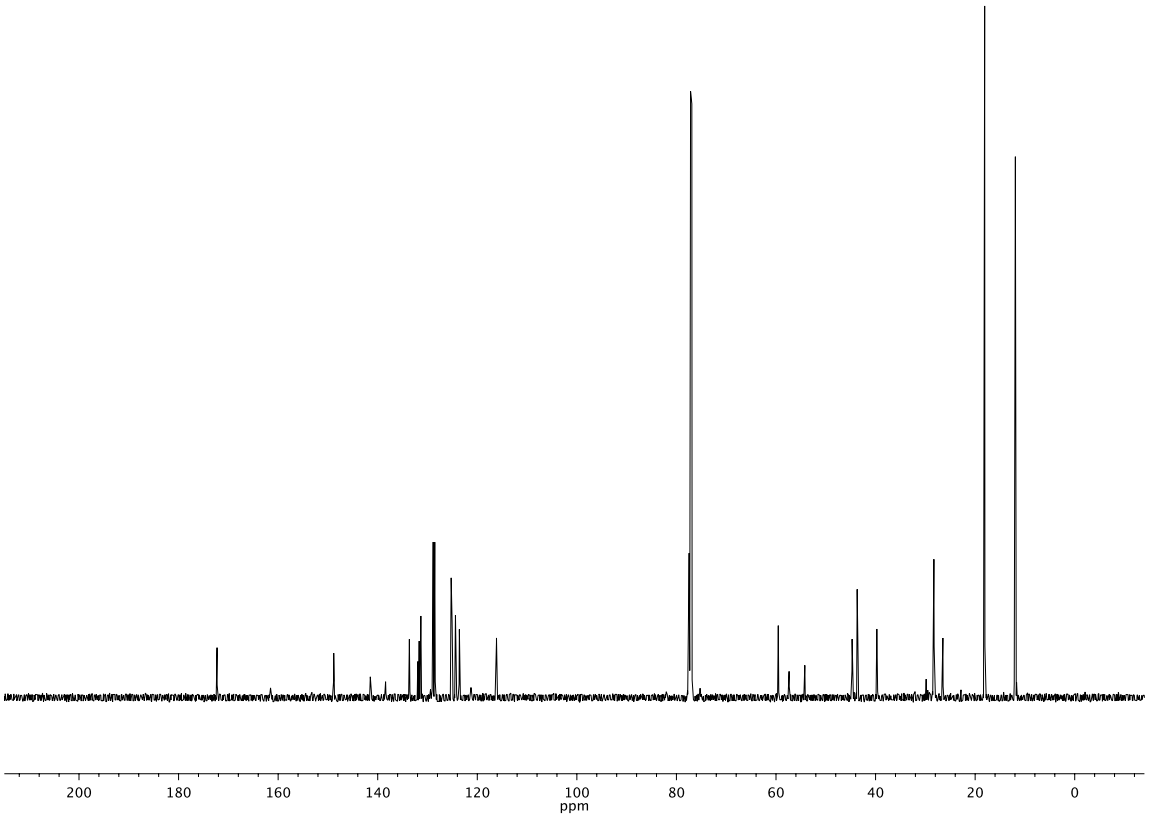


Figure A1.144. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **88**.

Figure A1.145. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **80**.

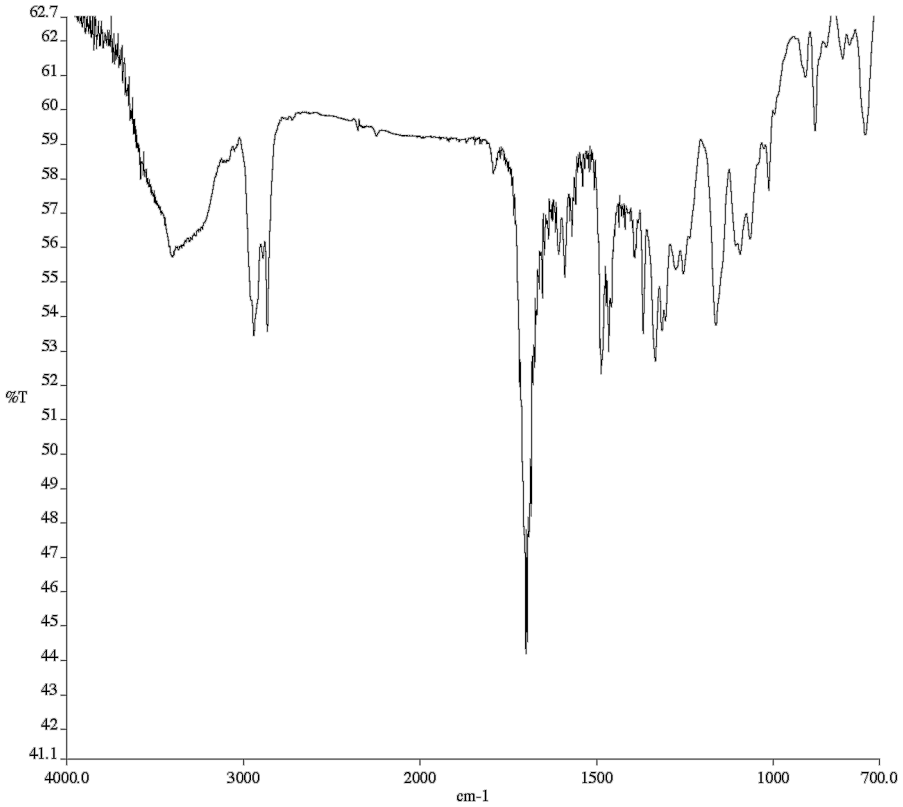


Figure A1.146. Infrared spectrum (Thin Film, NaCl) of compound **80**.

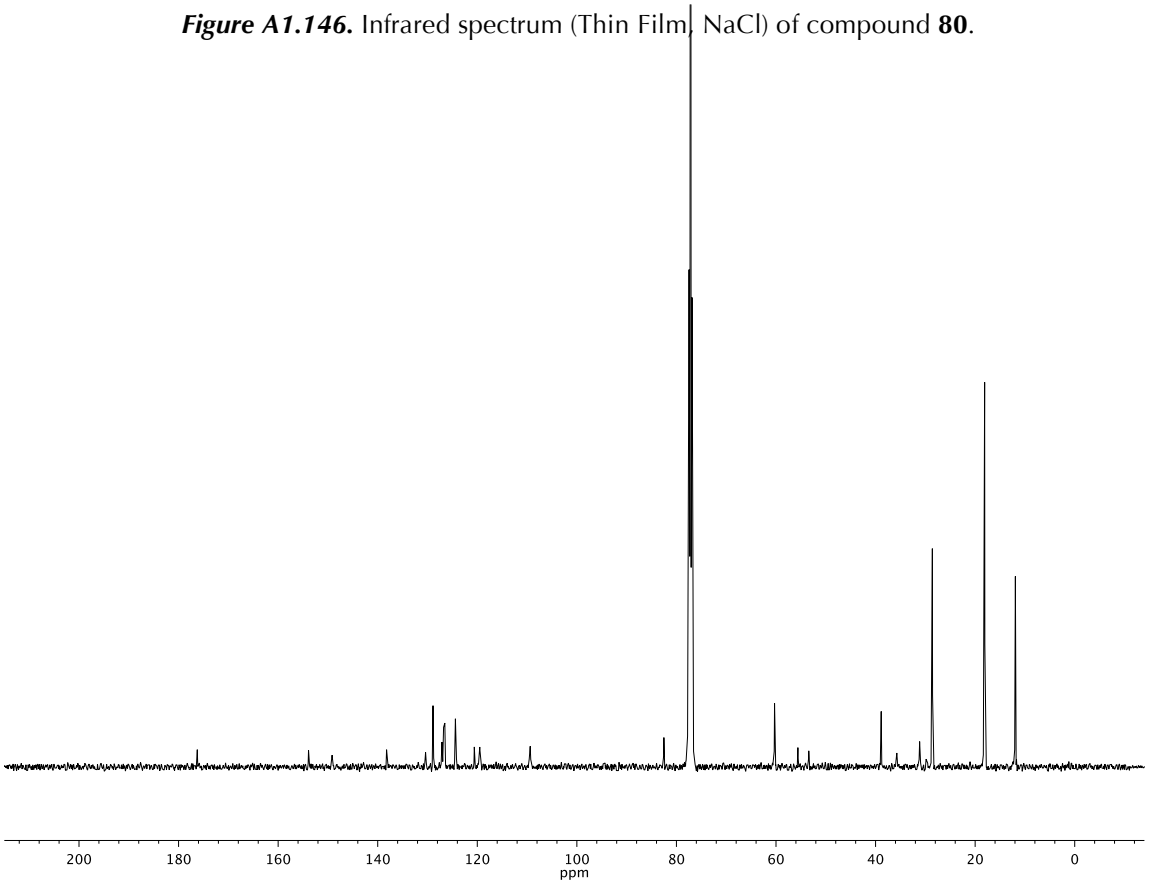


Figure A1.147. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **80**.

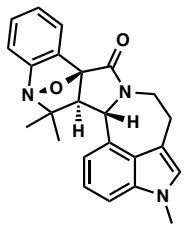
APPENDIX 2

X-Ray Crystallography Reports Relevant to Chapter 1:

The Evolution of a Unified, Stereodivergent Approach to the

Synthesis of Communesin F and Perophoramidine

A2.1. X-Ray Crystal Structure Analysis of 24



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Figure A2.1.1. *X-ray Crystal Structure of* ***24***

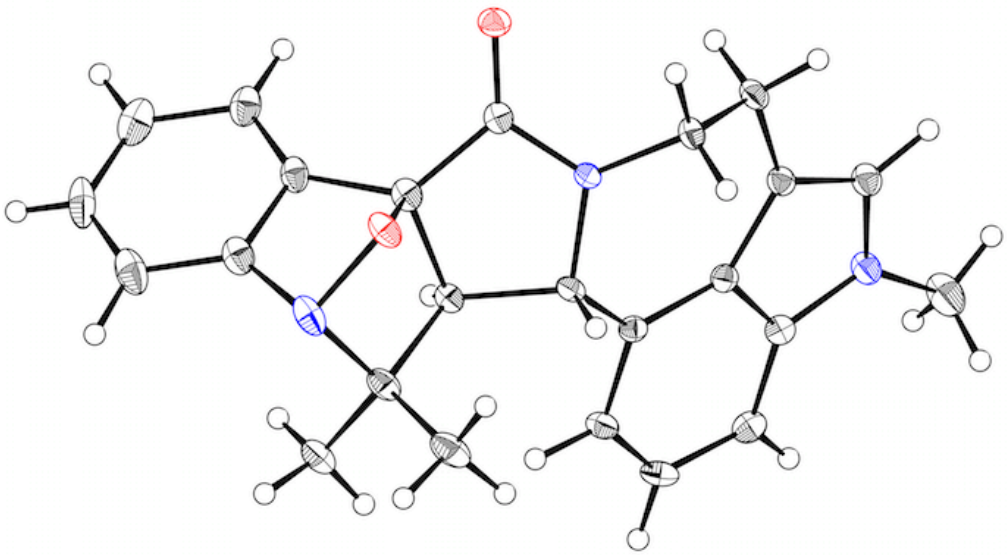


Table A2.1.1. *Crystal Data and Structure Analysis Details for* ***24***

Empirical formula	C25 H25 Cl2 N3 O2
Formula weight	470.38
Crystallization solvent	???Solvent???
Crystal shape	chunk
Crystal color	colourless
Crystal size	0.09 x 0.14 x 0.14 mm

Data Collection

Preliminary photograph(s)	rotation
Type of diffractometer	Bruker APEX-II CCD
Wavelength	0.71073 Å MoK
Data collection temperature	100 K

Theta range for 6076 reflections used in lattice determination	2.60 to 23.34°	
Unit cell dimensions	a = 8.2203(10) Å b = 26.018(3) Å c = 10.2431(12) Å	a= 90° b= 90° g = 90°
Volume	2190.8(5) $Å^3$	
Z	4	
Crystal system	orthorhombic	
Space group	P n a 21 (# 33)	
Density (calculated)	1.426 g/cm^3	
F(000)	984	
Theta range for data collection	1.6 to 32.9°	
Completeness to theta = 25.000°	100.0%	
Index ranges	-12 £ h £ 12, -39 £ k £ 39, -15 £ l £ 15	
Data collection scan type	and scans	
Reflections collected	54235	
Independent reflections	7838 [R_{int}= 0.0905]	
Reflections > 2s(I)	5779	
Average s(I)/(net I)	0.0696	
Absorption coefficient	0.33 mm^{-1}	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.9032	

Structure Solution and Refinement

Primary solution method	direct
Secondary solution method	?
Hydrogen placement	difmap
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7838 / 1 / 365
Treatment of hydrogen atoms	refxyz
Goodness-of-fit on F^2	1.13
Final R indices [I>2s(I), 5779 reflections]	R1 = 0.0490, wR2 = 0.0781
R indices (all data)	R1 = 0.0843, wR2 = 0.0857
Type of weighting scheme used	calc
Weighting scheme used	w=1/[^2^(Fo^2^)+(0.0300P)^2^] where P=(Fo^2^+2Fc^2^)/3
Max shift/error	0.000
Average shift/error	0.000
Absolute structure parameter	0.44(6)
Extinction coefficient	n/a

Largest diff. peak and hole	0.36 and -0.32 e·Å^{-3}

Programs Used

Cell refinement	SAINT V8.34A (Bruker-AXS, 2007)
Data collection	APEX2 2013.10-0 (Bruker-AXS, 2007)
Data reduction	SAINT V8.34A (Bruker-AXS, 2007)
Structure solution	XT (Sheldrick, 2012)
Structure refinement	SHELXL-2013/2 (Sheldrick, 2013)
Graphics	DIAMOND 3 (Crystal Impact, 1999)

References

Special Refinement Details

Table A2.1.2. *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for* ***24****. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor*

	x	y	z	U_{eq}
O(1)	4(2)	2120(1)	6508(2)	16(1)
O(2)	85(2)	911(1)	6456(2)	16(1)
N(1)	1141(2)	1782(1)	4648(2)	12(1)
N(2)	1982(3)	2496(1)	117(2)	16(1)
N(3)	-836(3)	449(1)	6069(2)	20(1)
C(1)	-798(3)	1282(1)	5638(2)	15(1)
C(2)	110(3)	1784(1)	5675(2)	13(1)
C(3)	2535(3)	2130(1)	4609(3)	14(1)
C(4)	2247(3)	2582(1)	3706(2)	16(1)
C(5)	2045(3)	2430(1)	2314(2)	14(1)
C(6)	2387(3)	2738(1)	1267(2)	16(1)
C(7)	2210(4)	2702(1)	-1189(3)	29(1)
C(8)	1399(3)	2015(1)	413(2)	14(1)
C(9)	862(3)	1636(1)	-448(2)	16(1)
C(10)	332(3)	1183(1)	92(3)	17(1)
C(11)	350(3)	1105(1)	1455(2)	16(1)
C(12)	898(3)	1479(1)	2324(2)	12(1)
C(13)	1425(3)	1954(1)	1793(2)	13(1)
C(14)	997(3)	1336(1)	3766(2)	13(1)
C(15)	-526(3)	1052(1)	4272(2)	13(1)
C(16)	-460(3)	459(1)	4594(3)	17(1)
C(17)	1216(4)	220(1)	4435(3)	22(1)
C(18)	-1727(4)	147(1)	3860(3)	20(1)
C(19)	-2483(3)	644(1)	6275(2)	19(1)
C(20)	-3860(4)	373(1)	6614(3)	26(1)
C(21)	-5287(4)	655(1)	6750(3)	27(1)
C(22)	-5336(4)	1177(1)	6574(3)	25(1)
C(23)	-3924(3)	1452(1)	6225(2)	20(1)
C(24)	-2515(3)	1175(1)	6080(2)	16(1)
Cl(1)	5159(1)	1123(1)	2694(1)	28(1)
Cl(2)	5970(1)	875(1)	1(1)	44(1)
C(25)	4688(4)	1234(1)	1034(3)	25(1)

Table A2.1.3. *Bond lengths [Å] and angles [°] for* ***24***

O(1)-C(2)	1.224(3)
O(2)-N(3)	1.475(3)
O(2)-C(1)	1.471(3)
N(1)-C(2)	1.352(3)
N(1)-C(3)	1.460(3)
N(1)-C(14)	1.475(3)
N(2)-C(6)	1.376(3)
N(2)-C(7)	1.453(4)
N(2)-C(8)	1.375(3)
N(3)-C(16)	1.542(3)
N(3)-C(19)	1.461(3)
C(1)-C(2)	1.504(3)
C(1)-C(15)	1.538(3)
C(1)-C(24)	1.508(3)
C(3)-H(3A)	0.96(3)
C(3)-H(3B)	0.99(3)
C(3)-C(4)	1.514(4)
C(4)-H(4A)	0.95(3)
C(4)-H(4B)	0.97(3)
C(4)-C(5)	1.490(3)
C(5)-C(6)	1.368(3)
C(5)-C(13)	1.440(3)
C(6)-H(6)	1.00(3)
C(7)-H(7A)	0.95(4)
C(7)-H(7B)	0.90(4)
C(7)-H(7C)	1.02(4)
C(8)-C(9)	1.393(3)
C(8)-C(13)	1.422(3)
C(9)-H(9)	0.95(3)
C(9)-C(10)	1.373(4)
C(10)-H(10)	0.95(3)
C(10)-C(11)	1.411(4)
C(11)-H(11)	1.03(3)
C(11)-C(12)	1.393(3)
C(12)-C(13)	1.419(3)
C(12)-C(14)	1.525(3)
C(14)-H(14)	0.96(3)
C(14)-C(15)	1.543(3)
C(15)-H(15)	0.95(3)
C(15)-C(16)	1.579(3)
C(16)-C(17)	1.520(4)
C(16)-C(18)	1.519(4)
C(17)-H(17A)	0.98(3)
C(17)-H(17B)	1.00(3)
C(17)-H(17C)	1.01(3)
C(18)-H(18A)	0.98(3)
C(18)-H(18B)	0.91(3)
C(18)-H(18C)	0.97(3)
C(19)-C(20)	1.378(4)
C(19)-C(24)	1.396(4)
C(20)-H(20)	0.98(3)
C(20)-C(21)	1.390(4)
C(21)-H(21)	0.86(3)
C(21)-C(22)	1.370(4)
C(22)-H(22)	0.95(3)

C(22)-C(23)	1.410(4)
C(23)-H(23)	0.99(3)
C(23)-C(24)	1.373(4)
Cl(1)-C(25)	1.768(3)
Cl(2)-C(25)	1.762(3)
C(25)-H(25A)	1.05(3)
C(25)-H(25B)	0.91(3)

C(1)-O(2)-N(3)	97.38(16)
C(2)-N(1)-C(3)	120.7(2)
C(2)-N(1)-C(14)	115.4(2)
C(3)-N(1)-C(14)	122.2(2)
C(6)-N(2)-C(7)	126.1(2)
C(8)-N(2)-C(6)	108.2(2)
C(8)-N(2)-C(7)	125.7(2)
O(2)-N(3)-C(16)	98.47(17)
C(19)-N(3)-O(2)	98.84(18)
C(19)-N(3)-C(16)	108.8(2)
O(2)-C(1)-C(2)	108.11(19)
O(2)-C(1)-C(15)	100.99(18)
O(2)-C(1)-C(24)	99.71(19)
C(2)-C(1)-C(15)	106.81(19)
C(2)-C(1)-C(24)	128.1(2)
C(24)-C(1)-C(15)	109.7(2)
O(1)-C(2)-N(1)	126.1(2)
O(1)-C(2)-C(1)	127.1(2)
N(1)-C(2)-C(1)	106.7(2)
N(1)-C(3)-H(3A)	105.4(16)
N(1)-C(3)-H(3B)	104.5(16)
N(1)-C(3)-C(4)	112.0(2)
H(3A)-C(3)-H(3B)	111(2)
C(4)-C(3)-H(3A)	112.9(17)
C(4)-C(3)-H(3B)	110.5(17)
C(3)-C(4)-H(4A)	109.4(17)
C(3)-C(4)-H(4B)	108.2(17)
H(4A)-C(4)-H(4B)	105(2)
C(5)-C(4)-C(3)	113.3(2)
C(5)-C(4)-H(4A)	109.6(18)
C(5)-C(4)-H(4B)	110.7(18)
C(6)-C(5)-C(4)	124.9(2)
C(6)-C(5)-C(13)	106.6(2)
C(13)-C(5)-C(4)	128.5(2)
N(2)-C(6)-H(6)	117.3(16)
C(5)-C(6)-N(2)	110.7(2)
C(5)-C(6)-H(6)	131.9(16)
N(2)-C(7)-H(7A)	110(2)
N(2)-C(7)-H(7B)	109(2)
N(2)-C(7)-H(7C)	101(2)
H(7A)-C(7)-H(7B)	116(3)
H(7A)-C(7)-H(7C)	116(3)
H(7B)-C(7)-H(7C)	103(3)
N(2)-C(8)-C(9)	127.9(2)
N(2)-C(8)-C(13)	108.3(2)
C(9)-C(8)-C(13)	123.7(2)
C(8)-C(9)-H(9)	120.8(17)
C(10)-C(9)-C(8)	116.9(2)
C(10)-C(9)-H(9)	122.3(17)
C(9)-C(10)-H(10)	116.5(18)

C(9)-C(10)-C(11)	121.3(2)
C(11)-C(10)-H(10)	122.2(18)
C(10)-C(11)-H(11)	122.5(17)
C(12)-C(11)-C(10)	122.3(2)
C(12)-C(11)-H(11)	115.2(17)
C(11)-C(12)-C(13)	117.6(2)
C(11)-C(12)-C(14)	117.8(2)
C(13)-C(12)-C(14)	124.5(2)
C(8)-C(13)-C(5)	106.2(2)
C(12)-C(13)-C(5)	135.6(2)
C(12)-C(13)-C(8)	118.2(2)
N(1)-C(14)-C(12)	113.95(19)
N(1)-C(14)-H(14)	106.4(16)
N(1)-C(14)-C(15)	103.67(18)
C(12)-C(14)-H(14)	107.2(17)
C(12)-C(14)-C(15)	113.51(19)
C(15)-C(14)-H(14)	111.9(15)
C(1)-C(15)-C(14)	103.71(19)
C(1)-C(15)-H(15)	106.3(17)
C(1)-C(15)-C(16)	101.28(18)
C(14)-C(15)-H(15)	110.2(16)
C(14)-C(15)-C(16)	120.7(2)
C(16)-C(15)-H(15)	112.7(15)
N(3)-C(16)-C(15)	102.36(19)
C(17)-C(16)-N(3)	106.3(2)
C(17)-C(16)-C(15)	114.1(2)
C(18)-C(16)-N(3)	109.8(2)
C(18)-C(16)-C(15)	113.2(2)
C(18)-C(16)-C(17)	110.5(2)
C(16)-C(17)-H(17A)	112.8(18)
C(16)-C(17)-H(17B)	111.4(19)
C(16)-C(17)-H(17C)	110.4(19)
H(17A)-C(17)-H(17B)	110(3)
H(17A)-C(17)-H(17C)	103(2)
H(17B)-C(17)-H(17C)	109(3)
C(16)-C(18)-H(18A)	109.3(18)
C(16)-C(18)-H(18B)	108(2)
C(16)-C(18)-H(18C)	113.1(19)
H(18A)-C(18)-H(18B)	111(3)
H(18A)-C(18)-H(18C)	105(3)
H(18B)-C(18)-H(18C)	111(3)
C(20)-C(19)-N(3)	128.3(2)
C(20)-C(19)-C(24)	121.8(3)
C(24)-C(19)-N(3)	109.9(2)
C(19)-C(20)-H(20)	121.3(19)
C(19)-C(20)-C(21)	116.7(3)
C(21)-C(20)-H(20)	121.3(19)
C(20)-C(21)-H(21)	121(2)
C(22)-C(21)-C(20)	122.3(3)
C(22)-C(21)-H(21)	117(2)
C(21)-C(22)-H(22)	120.7(19)
C(21)-C(22)-C(23)	120.8(3)
C(23)-C(22)-H(22)	118.5(19)
C(22)-C(23)-H(23)	118.4(17)
C(24)-C(23)-C(22)	117.1(3)
C(24)-C(23)-H(23)	124.4(17)
C(19)-C(24)-C(1)	102.0(2)
C(23)-C(24)-C(1)	136.5(2)

C(23)-C(24)-C(19)	121.3(2)
Cl(1)-C(25)-H(25A)	110.2(17)
Cl(1)-C(25)-H(25B)	107(2)
Cl(2)-C(25)-Cl(1)	111.07(16)
Cl(2)-C(25)-H(25A)	106.5(17)
Cl(2)-C(25)-H(25B)	108(2)
H(25A)-C(25)-H(25B)	113(3)

Symmetry transformations used to generate equivalent atoms:

Table A2.1.4. *Anisotropic displacement parameters ($Å^2 x\ 10^4$) for **24**. The anisotropic displacement factor exponent takes the form: $-2p^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	206(9)	155(8)	131(8)	-22(7)	-1(7)	-14(7)
O(2)	207(10)	124(8)	161(8)	51(7)	-61(7)	-31(7)
N(1)	126(10)	118(9)	127(9)	-25(8)	-2(8)	-24(8)
N(2)	203(11)	166(10)	125(9)	9(9)	-8(9)	-46(9)
N(3)	212(12)	166(11)	214(11)	57(9)	-55(9)	-61(9)
C(1)	171(12)	142(12)	126(11)	41(9)	-26(9)	3(10)
C(2)	146(12)	138(12)	117(10)	32(9)	-22(9)	3(9)
C(3)	126(12)	149(12)	159(11)	7(10)	-10(9)	-34(10)
C(4)	177(13)	139(12)	148(11)	-8(10)	-12(10)	-51(10)
C(5)	119(12)	133(12)	160(11)	-4(9)	-4(9)	-5(9)
C(6)	153(12)	172(12)	166(12)	1(10)	-11(10)	-24(9)
C(7)	420(20)	280(16)	154(13)	27(12)	-28(13)	-139(15)
C(8)	143(12)	150(12)	139(11)	0(9)	-5(9)	8(10)
C(9)	169(13)	201(13)	121(10)	-4(10)	-15(10)	24(10)
C(10)	212(13)	137(12)	167(11)	-54(10)	-42(10)	14(10)
C(11)	193(13)	109(11)	173(12)	-16(10)	-4(10)	-1(10)
C(12)	116(11)	119(11)	131(10)	-7(9)	-4(8)	17(9)
C(13)	102(12)	136(12)	141(11)	-3(9)	-3(9)	8(9)
C(14)	132(12)	97(11)	153(11)	-15(9)	-13(10)	-8(9)
C(15)	148(12)	118(12)	112(11)	17(9)	-27(9)	-10(9)
C(16)	191(13)	99(11)	221(12)	26(10)	-30(10)	1(9)
C(17)	227(15)	118(12)	329(16)	7(12)	-65(12)	5(11)
C(18)	215(14)	129(13)	264(14)	3(11)	-22(11)	-38(11)
C(19)	216(13)	199(12)	146(11)	44(10)	-28(10)	-40(10)
C(20)	297(17)	272(15)	199(13)	74(12)	-32(12)	-122(13)
C(21)	214(15)	394(17)	194(13)	80(12)	3(11)	-141(13)
C(22)	181(14)	404(17)	172(13)	48(12)	-9(11)	10(13)
C(23)	178(13)	276(14)	133(11)	30(11)	-6(10)	-30(11)
C(24)	169(12)	194(12)	123(11)	32(10)	-11(9)	-46(10)
Cl(1)	219(3)	371(4)	261(3)	-11(3)	-21(3)	63(3)
Cl(2)	350(5)	605(5)	360(4)	-126(4)	68(4)	131(4)
C(25)	205(14)	276(15)	265(14)	-15(12)	8(12)	51(12)

Table A2.1.5. *Hydrogen coordinates ($x\ 10^3$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for **24***

	x	y	z	U_{iso}

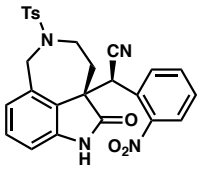
H(3A)	344(4)	192(1)	435(3)	17
H(3B)	266(3)	225(1)	552(3)	17
H(4A)	131(4)	277(1)	399(3)	19
H(4B)	315(3)	282(1)	380(3)	19
H(6)	291(3)	308(1)	120(3)	20
H(7A)	249(4)	305(1)	-114(4)	43
H(7B)	133(5)	262(1)	-168(3)	43
H(7C)	309(5)	246(1)	-155(3)	43
H(9)	86(4)	169(1)	-136(3)	20
H(10)	-5(3)	93(1)	-50(3)	21
H(11)	-4(3)	77(1)	188(3)	19
H(14)	197(3)	114(1)	388(3)	15
H(15)	-145(3)	114(1)	377(3)	15
H(17A)	204(4)	38(1)	500(3)	34
H(17B)	159(4)	23(1)	350(3)	34
H(17C)	121(4)	-15(1)	474(3)	34
H(18A)	-185(4)	-19(1)	428(3)	30
H(18B)	-138(4)	11(1)	302(3)	30
H(18C)	-280(4)	30(1)	389(3)	30
H(20)	-387(4)	0(1)	662(3)	31
H(21)	-620(4)	50(1)	691(3)	32
H(22)	-632(4)	136(1)	671(3)	30
H(23)	-402(4)	183(1)	605(3)	23
H(25A)	349(4)	112(1)	83(3)	30
H(25B)	486(4)	158(1)	87(3)	30

Table A2.1.6. *Hydrogen bonds for* ***24*** *[Å and °]*

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(7)-H(7B)...O(1)#1	0.90(4)	2.52(4)	3.338(4)	151(3)
C(7)-H(7C)...O(1)#2	1.02(4)	2.76(4)	3.325(4)	115(2)
C(9)-H(9)...O(1)#1	0.95(3)	2.55(3)	3.436(3)	156(2)

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

A2.2. X-Ray Crystal Structure Analysis of 37



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Figure A2.2.1. *X-ray Crystal Structure of* ***37***

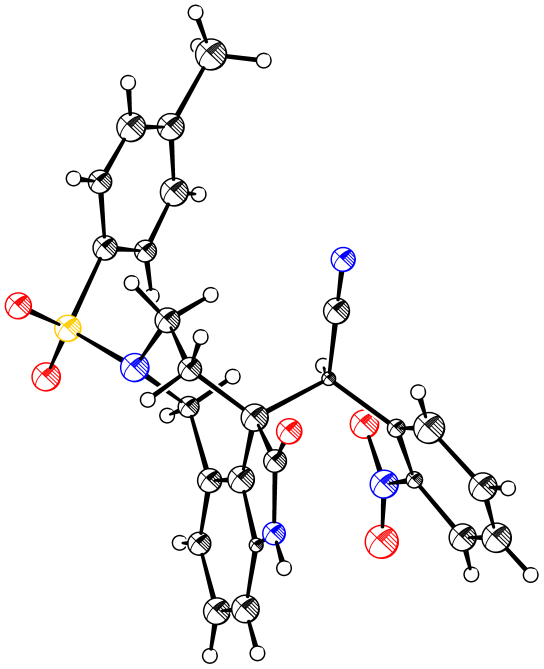


Table A2.2.1. *Crystal data and structure refinement for* ***37***

Empirical formula	C26 H22 N4 O5 S
Formula weight	502.54
Crystal Habit	Needle
Crystal size	0.30 x 0.07 x 0.07 mm^3
Crystal color	Colorless

Data Collection

Preliminary Photos	
Type of diffractometer	Bruker SMART 1000
Wavelength	0.71073 Å MoK⟨
Data Collection Temperature	100(2) K
\ range for 1342 reflections used	

in lattice determination	2.17 to 18.91°	
Unit cell dimensions	a = 13.243(2) Å b = 14.115(2) Å c = 25.059(4) Å	⟨= 90° ®= 90° © = 90°
Volume	4684.2(13) $Å^3$	
Z	8	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Density (calculated)	1.425 Mg/m^3	
F(000)	2096	
Data collection program	Bruker SMART v5.630	
\ range for data collection	1.63 to 22.98°	
Completeness to \ = 22.98°	83.9 %	
Index ranges	-12<=h<=13, -14<=k<=10, -27<=l<=21	
Data collection scan type	scans at 2 settings	
Data reduction program	Bruker SAINT v6.45A	
Reflections collected	10767	
Independent reflections	5122 [R_{int}= 0.1652]	
Absorption coefficient	0.185 mm^{-1}	
Absorption correction	None	
Max. and min. transmission	0.9871 and 0.9465	
Number of standards Variation of standards ?%.	? reflections measured every ?min.	

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	5122 / 0 / 291
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	1.294
Final R indices [I>2 ∫(I), 2377 reflections]	R1 = 0.1085, wR2 = 0.1814
R indices (all data)	R1 = 0.2168, wR2 = 0.2078
Type of weighting scheme used	Sigma
Weighting scheme used	w=1/s^2^(Fo^2^)
Max shift/error	0.015
Average shift/error	0.000

Absolute structure determination	?
Absolute structure parameter	0.5(3)
Largest diff. peak and hole	0.868 and -1.060 e.Å^{-3}

Special Refinement Details

Table A2.2.2. *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for* ***37****. U(eq) is defined asthe trace of the orthogonalized* U^{ij} *tensor*

	x	y	z	U_{eq}
S(1A)	2444(3)	6752(3)	3762(2)	24(1)
O(1A)	1847(8)	6830(7)	4221(4)	35(3)
O(2A)	2120(8)	7120(7)	3248(4)	25(3)
O(3A)	3062(8)	2592(7)	2393(4)	22(3)
O(4A)	4152(8)	3228(8)	4567(4)	26(3)
O(5A)	2979(9)	2243(8)	4804(4)	34(3)
N(1A)	2662(8)	5605(8)	3672(5)	10(3)
N(2A)	2007(9)	2282(9)	3084(5)	19(4)
N(3A)	3661(10)	2523(10)	4514(5)	27(4)
N(4A)	5462(11)	3745(9)	2693(6)	31(4)
C(1A)	3644(12)	7259(11)	3917(6)	19(4)
C(2A)	3980(11)	7265(11)	4429(6)	20(5)
C(3A)	4958(12)	7621(11)	4550(7)	31(5)
C(4A)	5605(14)	8037(13)	4166(7)	40(6)
C(5A)	5147(11)	8041(10)	3649(7)	21(5)
C(6A)	4202(11)	7655(10)	3519(6)	12(4)
C(7A)	6579(12)	8456(12)	4253(7)	36(5)
C(8A)	2748(12)	5013(10)	4169(6)	21(4)
C(9A)	2094(14)	4095(11)	4086(7)	36(5)
C(10A)	1349(11)	3803(11)	4439(6)	13(4)
C(11A)	810(12)	3025(11)	4359(6)	24(5)
C(12A)	966(12)	2434(12)	3927(6)	26(5)
C(13A)	1776(11)	2644(10)	3576(6)	19(4)
C(14A)	2313(11)	3475(10)	3645(6)	13(4)
C(15A)	3070(11)	3547(10)	3202(6)	17(4)
C(16A)	3010(11)	4510(10)	2925(6)	14(4)
C(17A)	3383(11)	5395(10)	3235(6)	15(4)
C(18A)	2703(12)	2749(11)	2827(6)	21(5)
C(19A)	4146(10)	3299(9)	3415(5)	3(4)
C(20A)	4911(12)	3517(11)	2992(6)	16(4)
C(21A)	4200(12)	2245(11)	3559(6)	23(5)
C(22A)	4506(10)	1615(10)	3185(6)	10(4)
C(23A)	4374(13)	614(12)	3276(7)	38(5)
C(24A)	4002(12)	326(12)	3754(7)	33(5)
C(25A)	3778(12)	949(11)	4169(7)	26(5)
C(26A)	3877(10)	1874(10)	4071(6)	8(4)
S(1B)	7184(3)	1177(3)	3593(2)	24(1)
O(1B)	6473(8)	1114(7)	4015(4)	28(3)
O(2B)	6953(8)	839(7)	3074(4)	24(3)
O(3B)	8347(8)	5377(7)	2346(4)	23(3)
O(4B)	9055(8)	4456(8)	4514(4)	28(3)
O(5B)	8036(9)	5576(8)	4787(5)	39(3)
N(1B)	7443(10)	2316(9)	3495(5)	28(4)

N(2B)	7154(9)	5718(9)	3014(5)	18(3)
N(3B)	8648(10)	5277(10)	4471(6)	28(4)
N(4B)	10569(10)	4005(9)	2678(5)	20(4)
C(1B)	8339(12)	633(11)	3783(7)	21(4)
C(2B)	8674(11)	682(11)	4310(6)	17(4)
C(3B)	9535(12)	304(11)	4441(7)	28(5)
C(4B)	10165(13)	-92(12)	4072(7)	26(5)
C(5B)	9804(12)	-94(11)	3538(7)	29(5)
C(6B)	8964(11)	227(10)	3393(7)	19(5)
C(7B)	11271(11)	-495(12)	4220(7)	34(5)
C(8B)	7549(12)	2872(9)	4003(6)	15(4)
C(9B)	7020(12)	3849(11)	3944(6)	20(4)
C(10B)	6276(11)	4107(10)	4280(6)	19(5)
C(11B)	5776(12)	4987(11)	4225(7)	25(5)
C(12B)	6092(12)	5574(12)	3800(6)	27(5)
C(13B)	6847(10)	5316(10)	3459(6)	7(4)
C(14B)	7352(12)	4461(11)	3542(7)	25(5)
C(15B)	8118(12)	4327(11)	3101(7)	26(5)
C(16B)	7989(12)	3429(10)	2779(6)	20(5)
C(17B)	8247(12)	2492(10)	3090(6)	22(5)
C(18B)	7896(12)	5207(11)	2769(6)	18(4)
C(19B)	9211(10)	4501(10)	3372(6)	7(4)
C(20B)	9978(12)	4216(11)	2978(7)	24(5)
C(21B)	9361(11)	5538(10)	3556(6)	11(4)
C(22B)	9696(13)	6156(11)	3175(7)	34(5)
C(23B)	9622(12)	7178(12)	3311(7)	28(5)
C(24B)	9228(12)	7468(12)	3774(7)	31(5)
C(25B)	8888(12)	6840(11)	4145(7)	26(5)
C(26B)	9000(11)	5871(10)	4031(6)	9(4)

Table A2.2.3. *Bond lengths [Å] and angles [°] for* ***37***

S(1A)-O(1A)	1.399(11)
S(1A)-O(2A)	1.455(11)
S(1A)-N(1A)	1.659(12)
S(1A)-C(1A)	1.786(16)
O(3A)-C(18A)	1.206(16)
O(4A)-N(3A)	1.196(14)
O(5A)-N(3A)	1.225(16)
N(1A)-C(17A)	1.484(17)
N(1A)-C(8A)	1.504(17)
N(2A)-C(18A)	1.305(17)
N(2A)-C(13A)	1.369(18)
N(3A)-C(26A)	1.469(18)
N(4A)-C(20A)	1.094(17)
C(1A)-C(2A)	1.357(19)
C(1A)-C(6A)	1.361(19)
C(2A)-C(3A)	1.42(2)
C(3A)-C(4A)	1.42(2)
C(4A)-C(5A)	1.43(2)
C(4A)-C(7A)	1.44(2)
C(5A)-C(6A)	1.403(19)
C(8A)-C(9A)	1.57(2)
C(9A)-C(10A)	1.39(2)
C(9A)-C(14A)	1.44(2)
C(10A)-C(11A)	1.32(2)

C(11A)-C(12A)	1.38(2)
C(12A)-C(13A)	1.42(2)
C(13A)-C(14A)	1.382(18)
C(14A)-C(15A)	1.50(2)
C(15A)-C(16A)	1.528(18)
C(15A)-C(18A)	1.55(2)
C(15A)-C(19A)	1.562(19)
C(16A)-C(17A)	1.552(18)
C(19A)-C(20A)	1.50(2)
C(19A)-C(21A)	1.532(19)
C(21A)-C(22A)	1.354(19)
C(21A)-C(26A)	1.45(2)
C(22A)-C(23A)	1.44(2)
C(23A)-C(24A)	1.36(2)
C(24A)-C(25A)	1.39(2)
C(25A)-C(26A)	1.336(19)
S(1B)-O(2B)	1.418(11)
S(1B)-O(1B)	1.418(11)
S(1B)-N(1B)	1.662(13)
S(1B)-C(1B)	1.776(16)
O(3B)-C(18B)	1.241(17)
O(4B)-N(3B)	1.282(14)
O(5B)-N(3B)	1.209(16)
N(1B)-C(17B)	1.493(18)
N(1B)-C(8B)	1.501(17)
N(2B)-C(13B)	1.316(17)
N(2B)-C(18B)	1.365(18)
N(3B)-C(26B)	1.463(18)
N(4B)-C(20B)	1.126(18)
C(1B)-C(2B)	1.40(2)
C(1B)-C(6B)	1.40(2)
C(2B)-C(3B)	1.301(19)
C(3B)-C(4B)	1.36(2)
C(4B)-C(5B)	1.42(2)
C(4B)-C(7B)	1.61(2)
C(5B)-C(6B)	1.254(19)
C(8B)-C(9B)	1.55(2)
C(9B)-C(10B)	1.35(2)
C(9B)-C(14B)	1.40(2)
C(10B)-C(11B)	1.41(2)
C(11B)-C(12B)	1.41(2)
C(12B)-C(13B)	1.36(2)
C(13B)-C(14B)	1.396(19)
C(14B)-C(15B)	1.51(2)
C(15B)-C(16B)	1.51(2)
C(15B)-C(18B)	1.52(2)
C(15B)-C(19B)	1.62(2)
C(16B)-C(17B)	1.572(19)
C(19B)-C(20B)	1.47(2)
C(19B)-C(21B)	1.547(19)
C(21B)-C(26B)	1.365(19)
C(21B)-C(22B)	1.37(2)
C(22B)-C(23B)	1.49(2)
C(23B)-C(24B)	1.34(2)
C(24B)-C(25B)	1.36(2)
C(25B)-C(26B)	1.41(2)

O(1A)-S(1A)-O(2A)	122.2(7)

O(1A)-S(1A)-N(1A)	106.7(7)
O(2A)-S(1A)-N(1A)	106.2(6)
O(1A)-S(1A)-C(1A)	107.0(7)
O(2A)-S(1A)-C(1A)	108.2(7)
N(1A)-S(1A)-C(1A)	105.4(7)
C(17A)-N(1A)-C(8A)	116.8(11)
C(17A)-N(1A)-S(1A)	114.1(9)
C(8A)-N(1A)-S(1A)	116.3(9)
C(18A)-N(2A)-C(13A)	114.5(13)
O(4A)-N(3A)-O(5A)	127.2(15)
O(4A)-N(3A)-C(26A)	119.8(14)
O(5A)-N(3A)-C(26A)	113.0(13)
C(2A)-C(1A)-C(6A)	120.8(16)
C(2A)-C(1A)-S(1A)	120.0(12)
C(6A)-C(1A)-S(1A)	119.2(12)
C(1A)-C(2A)-C(3A)	120.1(16)
C(4A)-C(3A)-C(2A)	123.5(17)
C(3A)-C(4A)-C(5A)	111.2(16)
C(3A)-C(4A)-C(7A)	127.6(17)
C(5A)-C(4A)-C(7A)	121.2(17)
C(6A)-C(5A)-C(4A)	125.9(16)
C(1A)-C(6A)-C(5A)	118.3(15)
N(1A)-C(8A)-C(9A)	107.8(12)
C(10A)-C(9A)-C(14A)	116.9(15)
C(10A)-C(9A)-C(8A)	123.5(16)
C(14A)-C(9A)-C(8A)	119.5(15)
C(11A)-C(10A)-C(9A)	122.1(16)
C(10A)-C(11A)-C(12A)	122.6(17)
C(11A)-C(12A)-C(13A)	118.2(16)
N(2A)-C(13A)-C(14A)	108.4(14)
N(2A)-C(13A)-C(12A)	130.5(15)
C(14A)-C(13A)-C(12A)	119.2(15)
C(13A)-C(14A)-C(9A)	120.6(14)
C(13A)-C(14A)-C(15A)	108.0(13)
C(9A)-C(14A)-C(15A)	131.4(13)
C(14A)-C(15A)-C(16A)	111.2(12)
C(14A)-C(15A)-C(18A)	101.0(12)
C(16A)-C(15A)-C(18A)	110.8(12)
C(14A)-C(15A)-C(19A)	110.0(12)
C(16A)-C(15A)-C(19A)	113.8(12)
C(18A)-C(15A)-C(19A)	109.4(11)
C(15A)-C(16A)-C(17A)	118.1(12)
N(1A)-C(17A)-C(16A)	109.0(12)
O(3A)-C(18A)-N(2A)	129.1(15)
O(3A)-C(18A)-C(15A)	123.9(15)
N(2A)-C(18A)-C(15A)	106.8(14)
C(20A)-C(19A)-C(21A)	109.5(13)
C(20A)-C(19A)-C(15A)	109.2(12)
C(21A)-C(19A)-C(15A)	109.9(12)
N(4A)-C(20A)-C(19A)	174.7(18)
C(22A)-C(21A)-C(26A)	117.6(14)
C(22A)-C(21A)-C(19A)	119.3(14)
C(26A)-C(21A)-C(19A)	123.0(14)
C(21A)-C(22A)-C(23A)	119.9(15)
C(24A)-C(23A)-C(22A)	118.5(17)
C(23A)-C(24A)-C(25A)	123.1(17)
C(26A)-C(25A)-C(24A)	117.4(17)
C(25A)-C(26A)-C(21A)	123.0(16)

C(25A)-C(26A)-N(3A)	116.9(14)
C(21A)-C(26A)-N(3A)	120.1(13)
O(2B)-S(1B)-O(1B)	121.3(7)
O(2B)-S(1B)-N(1B)	103.6(7)
O(1B)-S(1B)-N(1B)	107.9(7)
O(2B)-S(1B)-C(1B)	106.6(7)
O(1B)-S(1B)-C(1B)	110.2(7)
N(1B)-S(1B)-C(1B)	106.2(7)
C(17B)-N(1B)-C(8B)	115.0(12)
C(17B)-N(1B)-S(1B)	114.1(11)
C(8B)-N(1B)-S(1B)	113.6(10)
C(13B)-N(2B)-C(18B)	112.1(13)
O(5B)-N(3B)-O(4B)	122.8(14)
O(5B)-N(3B)-C(26B)	120.5(13)
O(4B)-N(3B)-C(26B)	116.6(13)
C(2B)-C(1B)-C(6B)	119.5(15)
C(2B)-C(1B)-S(1B)	120.4(13)
C(6B)-C(1B)-S(1B)	119.9(13)
C(3B)-C(2B)-C(1B)	119.8(16)
C(2B)-C(3B)-C(4B)	122.2(17)
C(3B)-C(4B)-C(5B)	115.7(16)
C(3B)-C(4B)-C(7B)	122.9(15)
C(5B)-C(4B)-C(7B)	121.4(15)
C(6B)-C(5B)-C(4B)	124.7(17)
C(5B)-C(6B)-C(1B)	118.0(17)
N(1B)-C(8B)-C(9B)	110.0(12)
C(10B)-C(9B)-C(14B)	120.9(15)
C(10B)-C(9B)-C(8B)	120.8(15)
C(14B)-C(9B)-C(8B)	118.3(14)
C(9B)-C(10B)-C(11B)	121.3(17)
C(12B)-C(11B)-C(10B)	116.8(16)
C(13B)-C(12B)-C(11B)	122.1(15)
N(2B)-C(13B)-C(12B)	130.0(15)
N(2B)-C(13B)-C(14B)	110.6(14)
C(12B)-C(13B)-C(14B)	119.2(15)
C(13B)-C(14B)-C(9B)	119.4(15)
C(13B)-C(14B)-C(15B)	108.7(15)
C(9B)-C(14B)-C(15B)	131.3(15)
C(16B)-C(15B)-C(14B)	114.8(14)
C(16B)-C(15B)-C(18B)	111.7(13)
C(14B)-C(15B)-C(18B)	99.6(13)
C(16B)-C(15B)-C(19B)	116.9(13)
C(14B)-C(15B)-C(19B)	105.9(13)
C(18B)-C(15B)-C(19B)	106.2(12)
C(15B)-C(16B)-C(17B)	114.6(12)
N(1B)-C(17B)-C(16B)	108.8(12)
O(3B)-C(18B)-N(2B)	128.9(14)
O(3B)-C(18B)-C(15B)	122.1(15)
N(2B)-C(18B)-C(15B)	108.9(13)
C(20B)-C(19B)-C(21B)	111.7(13)
C(20B)-C(19B)-C(15B)	107.0(13)
C(21B)-C(19B)-C(15B)	112.6(12)
N(4B)-C(20B)-C(19B)	179(2)
C(26B)-C(21B)-C(22B)	120.2(14)
C(26B)-C(21B)-C(19B)	122.6(14)
C(22B)-C(21B)-C(19B)	116.0(14)
C(21B)-C(22B)-C(23B)	115.9(16)
C(24B)-C(23B)-C(22B)	121.5(18)

C(23B)-C(24B)-C(25B)	121.5(17)
C(24B)-C(25B)-C(26B)	117.3(16)
C(21B)-C(26B)-C(25B)	123.3(15)
C(21B)-C(26B)-N(3B)	124.9(13)
C(25B)-C(26B)-N(3B)	111.7(13)

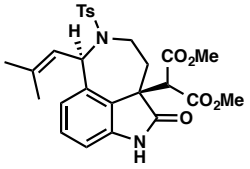
Symmetry transformations used to generate equivalent atoms:

Table A2.2.4. *Hydrogen bonds for* ***37*** *[Å and °]*

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2A)-H(2A)...O(3B)#1	0.88	2.11	2.933(16)	155.2
N(2B)-H(2B)...O(3A)#2	0.88	2.02	2.849(16)	157.3

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

A2.3. X-Ray Crystal Structure Analysis of 42



42

Figure A2.3.1. *X-ray Crystal Structure of* ***42***

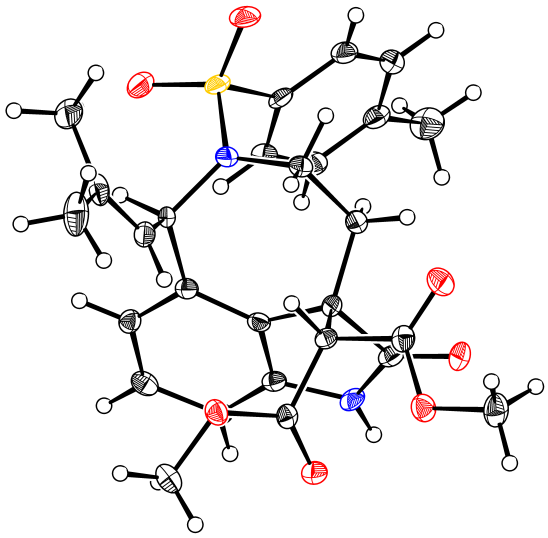


Table A2.3.1. *Crystal data and structure refinement for* ***42***

Empirical formula	C27 H30 N2 O7 S	
Formula weight	526.59	
Crystal Habit	Blade	
Crystal size	0.33 x 0.26 x 0.07 mm^3	
Crystal color	Colorless	

Data Collection

Preliminary Photos		
Type of diffractometer	Bruker SMART 1000	
Wavelength	0.71073 Å MoKa	
Data Collection Temperature	100(2) K	
q range for 9727 reflections used in lattice determination	2.40 to 33.11°	
Unit cell dimensions	a = 9.5308(8) Å b = 9.7901(9) Å c = 13.8253(12) Å	a= 90° b= 100.914(2)° g = 90°
Volume	1266.67(19) $Å^3$	
Z	2	
Crystal system	Monoclinic	

Space group	Pn
Density (calculated)	1.381 Mg/m^3
F(000)	556
Data collection program	Bruker SMART v5.630
q range for data collection	2.08 to 33.37°
Completeness to q = 33.37°	79.2 %
Index ranges	-12<=h<=12, -12<=k<=14, -20<=l<=18
Data collection scan type	scans at 5 settings
Data reduction program	Bruker SAINT v6.45A
Reflections collected	17354
Independent reflections	6630 [R_{int}= 0.0627]
Absorption coefficient	0.178 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9876 and 0.9436
Number of standards	? reflections measured every ?min.
Variation of standards	?%.

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	6630 / 2 / 339
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	1.413
Final R indices [I>2s(I), 5764 reflections]	R1 = 0.0412, wR2 = 0.0772
R indices (all data)	R1 = 0.0487, wR2 = 0.0785
Type of weighting scheme used	Sigma
Weighting scheme used	w=1/s^2^(Fo^2^)
Max shift/error	0.003
Average shift/error	0.000
Absolute structure determination	?
Absolute structure parameter	-0.06(5)
Largest diff. peak and hole	0.698 and -0.437 $e.Å^{-3}$

Special Refinement Details

Table A2.3.2. *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for* ***42****. U(eq) is defined as the trace of the orthogonalized U^{ij} tensor*

	x	y	z	U_{eq}
S(1)	2561(1)	4166(1)	5901(1)	20(1)
O(1)	1091(2)	3868(1)	5901(1)	28(1)
O(2)	3543(2)	3041(1)	5888(1)	26(1)
O(3)	5953(1)	9815(1)	6612(1)	23(1)
O(4)	7590(1)	7652(1)	8168(1)	25(1)
O(5)	7214(1)	9500(1)	9044(1)	22(1)
O(6)	4387(1)	10398(1)	8732(1)	21(1)
O(7)	3629(1)	8558(1)	9457(1)	19(1)
N(1)	3154(2)	5091(2)	6868(1)	18(1)
N(2)	3555(2)	10204(2)	6558(1)	18(1)
C(1)	2669(2)	5158(2)	4849(2)	17(1)
C(2)	3664(2)	4837(2)	4284(2)	21(1)
C(3)	3700(2)	5589(2)	3436(2)	23(1)
C(4)	2753(2)	6670(2)	3153(2)	21(1)
C(5)	1775(2)	6993(2)	3757(2)	24(1)
C(6)	1722(2)	6249(2)	4595(2)	22(1)
C(7)	2775(3)	7430(2)	2213(2)	33(1)
C(8)	4669(2)	5481(2)	7050(2)	19(1)
C(9)	4988(2)	6898(2)	6675(2)	17(1)
C(10)	4451(2)	8092(2)	7224(1)	15(1)
C(11)	2834(2)	8156(2)	7105(1)	15(1)
C(12)	1822(2)	7184(2)	7242(1)	15(1)
C(13)	2158(2)	5683(2)	7468(1)	16(1)
C(14)	2653(2)	5409(2)	8558(2)	18(1)
C(15)	2510(2)	4205(2)	8993(2)	23(1)
C(16)	1948(2)	2934(2)	8454(2)	32(1)
C(17)	2943(2)	4057(3)	10088(2)	37(1)
C(18)	404(2)	7610(2)	7130(1)	17(1)
C(19)	-10(2)	8938(2)	6853(1)	19(1)
C(20)	980(2)	9888(2)	6632(1)	18(1)
C(21)	2385(2)	9461(2)	6761(1)	15(1)
C(22)	4787(2)	9468(2)	6759(1)	18(1)
C(23)	5191(2)	8149(2)	8355(1)	16(1)
C(24)	6788(2)	8399(2)	8493(1)	18(1)
C(25)	8742(2)	9752(2)	9212(2)	27(1)
C(26)	4392(2)	9188(2)	8867(1)	15(1)
C(27)	2603(2)	9418(2)	9817(2)	25(1)

Table A2.3.3. *Bond lengths [Å] and angles [°] for* ***42***

S(1)-O(1)	1.4313(14)
S(1)-O(2)	1.4482(14)
S(1)-N(1)	1.6255(17)
S(1)-C(1)	1.767(2)
O(3)-C(22)	1.215(2)
O(4)-C(24)	1.204(2)
O(5)-C(24)	1.338(2)
O(5)-C(25)	1.451(2)

O(6)-C(26)	1.199(2)
O(7)-C(26)	1.341(2)
O(7)-C(27)	1.449(2)
N(1)-C(8)	1.469(2)
N(1)-C(13)	1.491(2)
N(2)-C(22)	1.361(2)
N(2)-C(21)	1.403(2)
C(1)-C(2)	1.374(3)
C(1)-C(6)	1.400(3)
C(2)-C(3)	1.390(3)
C(3)-C(4)	1.398(3)
C(4)-C(5)	1.401(3)
C(4)-C(7)	1.501(3)
C(5)-C(6)	1.377(3)
C(8)-C(9)	1.531(2)
C(9)-C(10)	1.532(2)
C(10)-C(11)	1.519(3)
C(10)-C(22)	1.551(2)
C(10)-C(23)	1.590(2)
C(11)-C(12)	1.393(2)
C(11)-C(21)	1.402(2)
C(12)-C(18)	1.395(2)
C(12)-C(13)	1.524(2)
C(13)-C(14)	1.515(3)
C(14)-C(15)	1.341(3)
C(15)-C(16)	1.496(3)
C(15)-C(17)	1.499(3)
C(18)-C(19)	1.392(3)
C(19)-C(20)	1.398(3)
C(20)-C(21)	1.382(3)
C(23)-C(24)	1.517(2)
C(23)-C(26)	1.524(3)

O(1)-S(1)-O(2)	118.70(9)
O(1)-S(1)-N(1)	107.55(8)
O(2)-S(1)-N(1)	107.99(8)
O(1)-S(1)-C(1)	108.78(9)
O(2)-S(1)-C(1)	105.60(9)
N(1)-S(1)-C(1)	107.79(8)
C(24)-O(5)-C(25)	114.58(15)
C(26)-O(7)-C(27)	114.87(15)
C(8)-N(1)-C(13)	120.84(15)
C(8)-N(1)-S(1)	117.58(12)
C(13)-N(1)-S(1)	121.04(13)
C(22)-N(2)-C(21)	111.90(15)
C(2)-C(1)-C(6)	120.90(18)
C(2)-C(1)-S(1)	119.74(14)
C(6)-C(1)-S(1)	119.35(16)
C(1)-C(2)-C(3)	119.21(17)
C(2)-C(3)-C(4)	121.30(19)
C(3)-C(4)-C(5)	118.11(18)
C(3)-C(4)-C(7)	120.25(18)
C(5)-C(4)-C(7)	121.62(17)
C(6)-C(5)-C(4)	121.13(18)
C(5)-C(6)-C(1)	119.32(19)
N(1)-C(8)-C(9)	115.42(15)
C(8)-C(9)-C(10)	114.69(15)
C(11)-C(10)-C(9)	113.86(15)

C(11)-C(10)-C(22)	101.80(14)
C(9)-C(10)-C(22)	110.06(14)
C(11)-C(10)-C(23)	110.93(14)
C(9)-C(10)-C(23)	112.65(14)
C(22)-C(10)-C(23)	106.77(14)
C(12)-C(11)-C(21)	119.60(16)
C(12)-C(11)-C(10)	132.16(16)
C(21)-C(11)-C(10)	108.20(15)
C(11)-C(12)-C(18)	117.54(16)
C(11)-C(12)-C(13)	124.25(16)
C(18)-C(12)-C(13)	118.17(15)
N(1)-C(13)-C(14)	111.94(14)
N(1)-C(13)-C(12)	113.07(14)
C(14)-C(13)-C(12)	112.87(15)
C(15)-C(14)-C(13)	124.25(18)
C(14)-C(15)-C(16)	124.3(2)
C(14)-C(15)-C(17)	120.4(2)
C(16)-C(15)-C(17)	115.24(18)
C(19)-C(18)-C(12)	121.84(17)
C(18)-C(19)-C(20)	120.92(17)
C(21)-C(20)-C(19)	116.63(16)
C(20)-C(21)-C(11)	123.04(17)
C(20)-C(21)-N(2)	127.26(16)
C(11)-C(21)-N(2)	109.68(16)
O(3)-C(22)-N(2)	126.81(16)
O(3)-C(22)-C(10)	125.37(16)
N(2)-C(22)-C(10)	107.82(15)
C(24)-C(23)-C(26)	114.28(15)
C(24)-C(23)-C(10)	112.17(14)
C(26)-C(23)-C(10)	108.22(14)
O(4)-C(24)-O(5)	123.72(18)
O(4)-C(24)-C(23)	123.19(17)
O(5)-C(24)-C(23)	113.04(15)
O(6)-C(26)-O(7)	124.28(17)
O(6)-C(26)-C(23)	125.06(17)
O(7)-C(26)-C(23)	110.58(15)

Symmetry transformations used to generate equivalent atoms:

Table A2.3.4. *Anisotropic displacement parameters ($Å^2 x\ 10^4$) for **42**. The anisotropic displacement factor exponent takes the form: $-2p^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	284(3)	91(2)	237(3)	-5(2)	94(2)	-26(2)
O(1)	333(8)	219(7)	297(9)	-67(6)	115(7)	-105(6)
O(2)	421(9)	99(6)	292(8)	25(6)	140(7)	25(6)
O(3)	230(7)	208(7)	267(8)	36(6)	97(6)	-55(6)
O(4)	187(7)	262(7)	301(9)	1(6)	61(6)	54(6)
O(5)	167(7)	267(7)	229(8)	-24(6)	36(6)	-9(5)
O(6)	212(7)	155(7)	276(8)	-7(6)	63(6)	11(5)
O(7)	199(7)	208(7)	180(7)	20(5)	78(5)	10(5)
N(1)	208(8)	126(8)	211(9)	-7(6)	88(6)	4(6)
N(2)	222(9)	96(7)	224(9)	48(6)	46(7)	-3(6)
C(1)	230(10)	101(8)	185(10)	-8(7)	38(8)	-49(7)
C(2)	201(10)	138(9)	284(12)	-18(8)	41(8)	15(7)
C(3)	239(11)	185(10)	280(12)	-13(8)	109(9)	0(7)

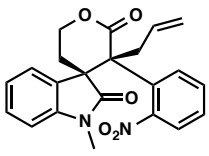
C(4)	235(10)	133(9)	252(11)	12(8)	34(8)	-12(7)
C(5)	241(10)	157(9)	309(12)	12(8)	25(8)	47(8)
C(6)	230(11)	164(10)	292(12)	-33(8)	84(9)	10(8)
C(7)	399(13)	255(11)	324(13)	85(10)	58(10)	33(10)
C(8)	196(10)	139(9)	246(11)	-4(7)	82(8)	25(7)
C(9)	172(10)	165(9)	189(10)	3(7)	60(7)	4(7)
C(10)	164(9)	124(8)	167(10)	21(7)	54(7)	-9(6)
C(11)	192(9)	133(9)	127(9)	-19(7)	52(7)	9(7)
C(12)	194(9)	132(9)	117(9)	9(7)	42(7)	9(7)
C(13)	139(9)	134(9)	213(10)	-13(7)	89(8)	-22(7)
C(14)	151(9)	169(9)	240(11)	33(8)	59(8)	1(7)
C(15)	146(9)	252(10)	302(12)	115(9)	93(8)	48(8)
C(16)	328(12)	154(10)	524(16)	127(10)	173(11)	49(8)
C(17)	283(12)	474(14)	361(14)	223(11)	103(10)	-17(10)
C(18)	185(10)	177(9)	151(10)	-8(7)	42(8)	-33(7)
C(19)	167(9)	221(10)	172(10)	-8(8)	10(8)	59(7)
C(20)	229(10)	141(9)	167(10)	25(7)	20(8)	50(7)
C(21)	225(10)	128(9)	107(9)	-1(7)	38(8)	-1(7)
C(22)	251(10)	130(9)	152(10)	1(7)	42(8)	-25(7)
C(23)	177(9)	105(8)	192(10)	30(7)	50(8)	12(7)
C(24)	186(10)	179(9)	179(10)	64(8)	37(8)	10(7)
C(25)	173(10)	374(12)	244(12)	-17(9)	12(8)	-73(8)
C(26)	97(8)	196(9)	151(10)	-6(7)	-8(7)	-9(7)
C(27)	231(10)	306(11)	241(11)	-9(9)	104(9)	37(8)

Table A2.3.5. *Hydrogen bonds for* ***42*** *[Å and °]*

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2)-H(2)...O(2)#1	0.88	2.05	2.928(2)	174.5

Symmetry transformations used to generate equivalent atoms:
#1 x,y+1,z

A2.4. X-Ray Crystal Structure Analysis of 51



51

Figure A2.4.1. *X-ray Crystal Structure of* ***51***

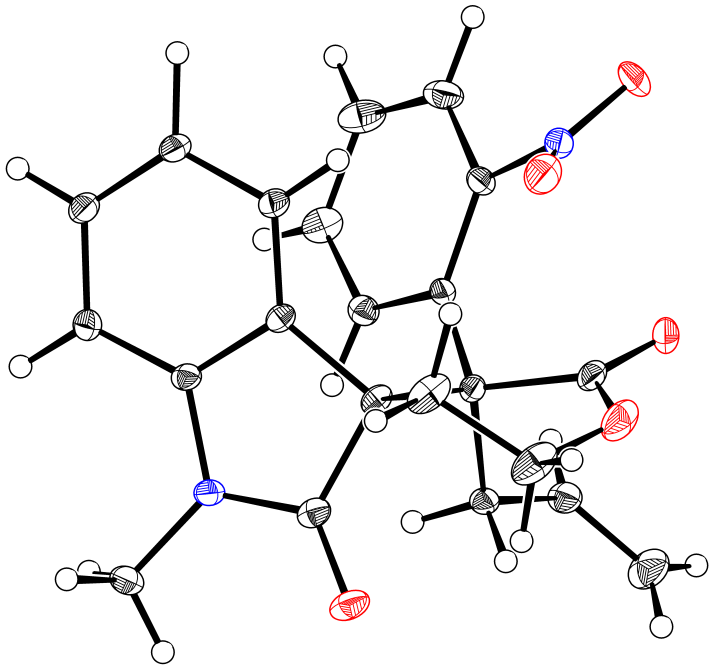


Table A2.4.1. *Crystal Data and Structure Analysis Details for* ***51***

Empirical formula	C22 H20 N2 O5
Formula weight	392.40
Crystal shape	plate
Crystal color	colourless
Crystal size	0.08 x 0.39 x 0.40 mm

Data Collection

Preliminary photograph(s)	rotation
Type of diffractometer	Bruker APEX-II CCD
Wavelength	0.71073 Å MoK

Data collection temperature	100 K	
Theta range for 9925 reflections used in lattice determination	2.59 to 33.53°	
Unit cell dimensions	a = 7.5798(3) Å b = 30.0522(12) Å c = 8.3663(3) Å	⟨= 90° ®= 103.6098(19)° © = 90°
Volume	1852.24(12) $Å^3$	
Z	4	
Crystal system	monoclinic	
Space group	P 1 21/c 1 (# 14)	
Density (calculated)	1.407 g/cm^3	
F(000)	824	
Theta range for data collection	2.6 to 36.7°	
Completeness to theta = 25.000°	99.9%	
Index ranges	-12 ″ h ″ 12, -48 ″ k ″ 48, -13 ″ l ″ 13	
Data collection scan type	and scans	
Reflections collected	90271	
Independent reflections	8678 [R_{int}= 0.0550]	
Reflections > 2 ∫(I)	6686	
Average ∫(I)/(net I)	0.0317	
Absorption coefficient	0.10 mm^{-1}	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.9172	

Structure Solution and Refinement

Primary solution method	?
Secondary solution method	?
Hydrogen placement	difmap
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8678 / 0 / 322
Treatment of hydrogen atoms	refxyz
Goodness-of-fit on F^2	1.63
Final R indices [I>2 ∫(I), 6686 reflections]	R1 = 0.0491, wR2 = 0.1139
R indices (all data)	R1 = 0.0700, wR2 = 0.1189
Type of weighting scheme used	calc
Weighting scheme used	w=1/[^2^(Fo^2^)+(0.0400P)^2^] where P=(Fo^2^+2Fc^2^)/3
Max shift/error	0.001
Average shift/error	0.000
Extinction coefficient	n/a

Largest diff. peak and hole	0.63 and -0.32 e·Å^{-3}

Programs Used

Cell refinement	SAINT V8.32B (Bruker-AXS, 2007)
Data collection	APEX2 2013.6-2 (Bruker-AXS, 2007)
Data reduction	SAINT V8.32B (Bruker-AXS, 2007)
Structure solution	SHELXT (Sheldrick, 2012)
Structure refinement	SHELXL-2013/2 (Sheldrick, 2013)
Graphics	DIAMOND 3 (Crystal Impact, 1999)

References

Special Refinement Details

Table A2.4.2. *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for* ***51****. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor*

	x	y	z	U_{eq}
O(1)	12316(1)	2035(1)	9127(1)	32(1)
O(2)	9477(1)	1887(1)	8963(1)	25(1)
O(3)	8678(1)	936(1)	10051(1)	25(1)
O(4)	11278(1)	1051(1)	9408(1)	24(1)
O(5)	5030(1)	428(1)	6376(1)	19(1)
N(1)	10836(1)	1886(1)	8401(1)	21(1)
N(2)	4779(1)	893(1)	4161(1)	15(1)
C(1)	8719(1)	1022(1)	7103(1)	12(1)
C(2)	9732(1)	1325(1)	6146(1)	12(1)
C(3)	9631(1)	1230(1)	4488(1)	14(1)
C(4)	10336(1)	1512(1)	3480(1)	19(1)
C(5)	11238(1)	1898(1)	4107(1)	22(1)
C(6)	11443(1)	1996(1)	5750(1)	20(1)
C(7)	10675(1)	1717(1)	6726(1)	15(1)
C(8)	8953(1)	519(1)	6658(1)	12(1)
C(9)	10876(1)	364(1)	6877(1)	17(1)
C(10)	11560(1)	15(1)	7771(2)	26(1)
C(11)	9646(1)	1021(1)	8938(1)	17(1)
C(12)	6715(2)	923(1)	9579(1)	25(1)
C(13)	5976(2)	1265(1)	8268(1)	21(1)
C(14)	6589(1)	1160(1)	6682(1)	13(1)
C(15)	6136(1)	1526(1)	5402(1)	12(1)
C(16)	6548(1)	1975(1)	5472(1)	14(1)
C(17)	6062(1)	2230(1)	4037(1)	15(1)
C(18)	5154(1)	2036(1)	2563(1)	15(1)
C(19)	4645(1)	1588(1)	2488(1)	14(1)
C(20)	5154(1)	1343(1)	3922(1)	13(1)
C(21)	5401(1)	776(1)	5771(1)	14(1)
C(22)	3576(1)	613(1)	2963(1)	21(1)

Table A2.4.3. *Bond lengths [Å] and angles [°] for* ***51***

O(1)-N(1)	1.2271(10)
O(2)-N(1)	1.2294(12)
O(3)-C(11)	1.3390(12)
O(3)-C(12)	1.4477(14)
O(4)-C(11)	1.2094(12)
O(5)-C(21)	1.2218(10)
N(1)-C(7)	1.4689(12)
N(2)-C(20)	1.4069(10)
N(2)-C(21)	1.3641(11)
N(2)-C(22)	1.4538(11)
C(1)-C(2)	1.5329(12)
C(1)-C(8)	1.5766(11)
C(1)-C(11)	1.5307(11)
C(1)-C(14)	1.6236(11)
C(2)-C(3)	1.4007(12)
C(2)-C(7)	1.4025(11)
C(3)-H(3)	0.978(12)
C(3)-C(4)	1.3876(13)
C(4)-H(4)	0.997(12)
C(4)-C(5)	1.3847(14)
C(5)-H(5)	0.971(13)
C(5)-C(6)	1.3777(15)
C(6)-H(6)	0.998(13)
C(6)-C(7)	1.3900(13)
C(8)-H(8A)	0.987(11)
C(8)-H(8B)	0.950(11)
C(8)-C(9)	1.4994(12)
C(9)-H(9)	0.991(12)
C(9)-C(10)	1.3224(13)
C(10)-H(10A)	0.966(14)
C(10)-H(10B)	0.964(14)
C(12)-H(12A)	0.995(13)
C(12)-H(12B)	0.963(14)
C(12)-C(13)	1.5109(14)
C(13)-H(13A)	1.014(13)
C(13)-H(13B)	1.006(13)
C(13)-C(14)	1.5372(12)
C(14)-C(15)	1.5167(11)
C(14)-C(21)	1.5506(12)
C(15)-C(16)	1.3832(11)
C(15)-C(20)	1.3979(11)
C(16)-H(16)	0.966(12)
C(16)-C(17)	1.3987(12)
C(17)-H(17)	1.136(12)
C(17)-C(18)	1.3904(12)
C(18)-H(18)	0.950(12)
C(18)-C(19)	1.3995(12)
C(19)-H(19)	0.987(12)
C(19)-C(20)	1.3821(11)
C(22)-H(22A)	0.984(13)
C(22)-H(22B)	0.962(13)
C(22)-H(22C)	0.999(13)
C(11)-O(3)-C(12)	120.79(7)
O(1)-N(1)-O(2)	124.15(9)

O(1)-N(1)-C(7)	117.31(9)
O(2)-N(1)-C(7)	118.48(7)
C(20)-N(2)-C(22)	124.99(7)
C(21)-N(2)-C(20)	110.73(7)
C(21)-N(2)-C(22)	123.14(7)
C(2)-C(1)-C(8)	110.41(7)
C(2)-C(1)-C(14)	109.21(6)
C(8)-C(1)-C(14)	110.84(6)
C(11)-C(1)-C(2)	110.91(7)
C(11)-C(1)-C(8)	100.61(6)
C(11)-C(1)-C(14)	114.61(7)
C(3)-C(2)-C(1)	118.59(7)
C(3)-C(2)-C(7)	114.70(8)
C(7)-C(2)-C(1)	126.55(7)
C(2)-C(3)-H(3)	120.3(7)
C(4)-C(3)-C(2)	122.62(8)
C(4)-C(3)-H(3)	117.0(7)
C(3)-C(4)-H(4)	121.5(7)
C(5)-C(4)-C(3)	120.40(9)
C(5)-C(4)-H(4)	118.1(7)
C(4)-C(5)-H(5)	121.2(8)
C(6)-C(5)-C(4)	119.15(9)
C(6)-C(5)-H(5)	119.6(8)
C(5)-C(6)-H(6)	119.9(7)
C(5)-C(6)-C(7)	119.50(8)
C(7)-C(6)-H(6)	120.5(7)
C(2)-C(7)-N(1)	122.81(8)
C(6)-C(7)-N(1)	113.54(8)
C(6)-C(7)-C(2)	123.53(8)
C(1)-C(8)-H(8A)	108.4(6)
C(1)-C(8)-H(8B)	108.6(7)
H(8A)-C(8)-H(8B)	105.1(10)
C(9)-C(8)-C(1)	115.38(7)
C(9)-C(8)-H(8A)	110.1(6)
C(9)-C(8)-H(8B)	108.7(7)
C(8)-C(9)-H(9)	116.9(7)
C(10)-C(9)-C(8)	123.80(9)
C(10)-C(9)-H(9)	119.2(7)
C(9)-C(10)-H(10A)	119.8(8)
C(9)-C(10)-H(10B)	120.9(8)
H(10A)-C(10)-H(10B)	119.2(12)
O(3)-C(11)-C(1)	120.03(8)
O(4)-C(11)-O(3)	118.26(8)
O(4)-C(11)-C(1)	121.28(8)
O(3)-C(12)-H(12A)	102.7(8)
O(3)-C(12)-H(12B)	108.1(8)
O(3)-C(12)-C(13)	111.22(8)
H(12A)-C(12)-H(12B)	108.5(11)
C(13)-C(12)-H(12A)	112.8(8)
C(13)-C(12)-H(12B)	112.9(8)
C(12)-C(13)-H(13A)	107.2(7)
C(12)-C(13)-H(13B)	108.4(7)
C(12)-C(13)-C(14)	110.64(8)
H(13A)-C(13)-H(13B)	107.4(10)
C(14)-C(13)-H(13A)	111.1(7)
C(14)-C(13)-H(13B)	111.9(7)
C(13)-C(14)-C(1)	110.64(7)
C(13)-C(14)-C(21)	108.51(7)

C(15)-C(14)-C(1)	112.77(7)
C(15)-C(14)-C(13)	113.42(7)
C(15)-C(14)-C(21)	100.57(6)
C(21)-C(14)-C(1)	110.42(6)
C(16)-C(15)-C(14)	131.73(8)
C(16)-C(15)-C(20)	119.23(7)
C(20)-C(15)-C(14)	109.02(7)
C(15)-C(16)-H(16)	121.0(7)
C(15)-C(16)-C(17)	119.14(8)
C(17)-C(16)-H(16)	119.8(7)
C(16)-C(17)-H(17)	115.2(6)
C(18)-C(17)-C(16)	120.51(8)
C(18)-C(17)-H(17)	124.2(6)
C(17)-C(18)-H(18)	119.0(7)
C(17)-C(18)-C(19)	121.07(8)
C(19)-C(18)-H(18)	119.9(7)
C(18)-C(19)-H(19)	120.2(7)
C(20)-C(19)-C(18)	117.12(8)
C(20)-C(19)-H(19)	122.7(7)
C(15)-C(20)-N(2)	109.59(7)
C(19)-C(20)-N(2)	127.61(8)
C(19)-C(20)-C(15)	122.79(7)
O(5)-C(21)-N(2)	124.73(8)
O(5)-C(21)-C(14)	126.63(8)
N(2)-C(21)-C(14)	108.62(7)
N(2)-C(22)-H(22A)	112.4(8)
N(2)-C(22)-H(22B)	110.5(8)
N(2)-C(22)-H(22C)	111.4(8)
H(22A)-C(22)-H(22B)	112.9(11)
H(22A)-C(22)-H(22C)	106.0(11)
H(22B)-C(22)-H(22C)	103.2(11)

Symmetry transformations used to generate equivalent atoms:

Table A2.4.4. *Anisotropic displacement parameters ($Å^2 x\ 10^4$) for **51**. The anisotropic displacement factor exponent takes the form: $-2\delta^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	343(4)	179(3)	323(4)	-43(3)	-181(3)	-49(3)
O(2)	381(4)	184(3)	153(3)	-24(2)	26(3)	42(3)
O(3)	415(4)	203(3)	116(3)	34(2)	60(3)	40(3)
O(4)	282(4)	167(3)	184(3)	7(2)	-95(3)	12(3)
O(5)	154(3)	142(3)	293(4)	70(2)	79(3)	1(2)
N(1)	276(4)	106(3)	178(3)	-16(3)	-71(3)	6(3)
N(2)	131(3)	102(3)	205(3)	17(2)	0(3)	-11(2)
C(1)	136(3)	101(3)	105(3)	0(2)	10(3)	10(3)
C(2)	105(3)	102(3)	128(3)	-4(3)	-1(3)	1(2)
C(3)	137(3)	137(3)	146(3)	-12(3)	30(3)	-2(3)
C(4)	213(4)	182(4)	211(4)	8(3)	106(3)	10(3)
C(5)	216(4)	171(4)	321(5)	22(4)	156(4)	-11(3)
C(6)	144(4)	134(4)	310(5)	-10(3)	39(3)	-25(3)
C(7)	137(3)	114(3)	169(4)	-19(3)	-18(3)	-1(3)
C(8)	121(3)	95(3)	153(3)	-9(3)	21(3)	7(3)

C(9)	136(3)	132(3)	222(4)	-2(3)	30(3)	14(3)
C(10)	192(4)	206(4)	367(6)	75(4)	47(4)	61(3)
C(11)	280(4)	98(3)	112(3)	0(3)	-5(3)	22(3)
C(12)	397(6)	217(5)	195(4)	55(4)	171(4)	69(4)
C(13)	310(5)	177(4)	201(4)	38(3)	147(4)	78(4)
C(14)	148(3)	108(3)	143(3)	18(3)	51(3)	31(3)
C(15)	126(3)	103(3)	136(3)	11(3)	38(3)	24(3)
C(16)	154(3)	108(3)	152(4)	1(3)	29(3)	18(3)
C(17)	158(4)	111(3)	176(4)	23(3)	28(3)	4(3)
C(18)	148(4)	133(3)	168(4)	34(3)	28(3)	9(3)
C(19)	126(3)	138(3)	157(4)	5(3)	8(3)	12(3)
C(20)	103(3)	98(3)	176(4)	8(3)	25(3)	9(2)
C(21)	101(3)	123(3)	210(4)	27(3)	53(3)	23(3)
C(22)	166(4)	128(4)	281(5)	-6(3)	-38(3)	-19(3)

Table A2.4.5. *Hydrogen coordinates (x 10^3) and isotropic displacement parameters (Å^{2}x 10^3) for* ***51***

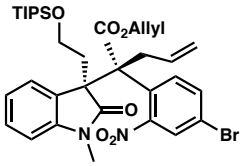
	x	y	z	U_{iso}
H(3)	900(2)	96(1)	398(1)	17
H(4)	1022(2)	144(1)	229(2)	23
H(5)	1177(2)	209(1)	342(2)	26
H(6)	1209(2)	227(1)	622(2)	24
H(8A)	832(2)	33(1)	732(1)	15
H(8B)	833(2)	47(1)	555(1)	15
H(9)	1164(2)	53(1)	626(2)	20
H(10A)	1081(2)	-15(1)	835(2)	31
H(10B)	1279(2)	-8(1)	784(2)	31
H(12A)	637(2)	98(1)	1064(2)	30
H(12B)	635(2)	62(1)	924(2)	30
H(13A)	644(2)	157(1)	873(2)	26
H(13B)	461(2)	127(1)	808(2)	26
H(16)	722(2)	211(1)	648(1)	17
H(17)	651(2)	259(1)	417(1)	18
H(18)	484(2)	222(1)	160(2)	18
H(19)	394(2)	146(1)	145(1)	17
H(22A)	232(2)	73(1)	268(2)	31
H(22B)	365(2)	31(1)	333(2)	31
H(22C)	398(2)	60(1)	191(2)	31

Table A2.4.6. *Hydrogen bonds for* ***51*** *[Å and °].*

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(12)-H(12B)...O(5)	0.963(14)	2.442(13)	3.0678(14)	122.4(10)
C(13)-H(13A)...O(2)	1.014(13)	2.460(13)	3.1858(14)	128.0(9)
C(19)-H(19)...O(4)#1	0.987(12)	2.622(12)	3.5589(11)	158.7(9)
C(22)-H(22B)...O(5)#2	0.962(13)	2.418(13)	3.3085(12)	153.8(10)

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

A2.5. X-Ray Crystal Structure Analysis of 52



52

Figure A2.5.1. *X-ray Crystal Structure of* ***52***

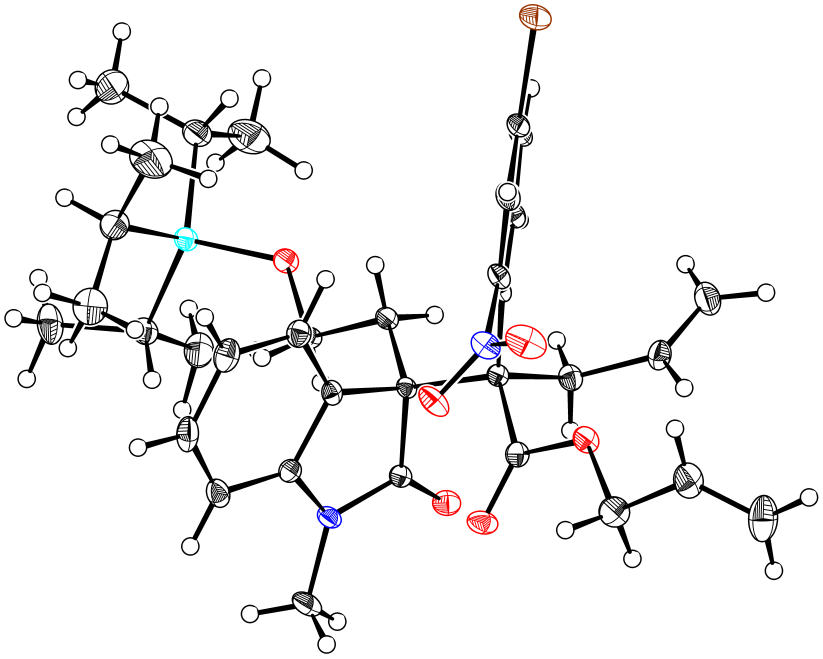


Table A2.5.1. *Crystal Data and Structure Analysis Details for* ***52***

Empirical formula	C34 H45 Br N2 O6 Si
Formula weight	685.72
Crystal shape	block
Crystal color	colourless
Crystal size	0.11 x 0.16 x 0.24 mm

Data Collection

Preliminary photograph(s)	rotation
Type of diffractometer	Bruker APEX-II CCD
Wavelength	0.71073 Å MoK
Data collection temperature	100 K

Theta range for 9950 reflections used in lattice determination	2.54 to 27.86°	
Unit cell dimensions	a = 8.0482(4) Å b = 14.1277(8) Å c = 15.3665(8) Å	⟨= 99.073(2)° ®= 94.101(3)° © = 91.448(2)°
Volume	1719.75(16) $Å^3$	
Z	2	
Crystal system	triclinic	
Space group	P -1 (# 2)	
Density (calculated)	1.324 g/cm^3	
F(000)	720	
Theta range for data collection	1.8 to 35.3°	
Completeness to theta = 25.000°	100.0%	
Index ranges	-13 ″ h ″ 11, -20 ″ k ″ 21, -22 ″ l ″ 23	
Data collection scan type	and scans	
Reflections collected	70933	
Independent reflections	11961 [R_{int}= 0.0565]	
Reflections > 2 ∫(I)	8549	
Average ∫(I)/(net I)	0.0555	
Absorption coefficient	1.27 mm^{-1}	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.8989	

Structure Solution and Refinement

Primary solution method	?
Secondary solution method	?
Hydrogen placement	difmap
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	11961 / 0 / 577
Treatment of hydrogen atoms	refall
Goodness-of-fit on F^2	1.12
Final R indices [I>2 ∫(I), 8549 reflections]	R1 = 0.0402, wR2 = 0.0805
R indices (all data)	R1 = 0.0754, wR2 = 0.0892
Type of weighting scheme used	calc
Weighting scheme used	w=1/[^2^(Fo^2^)+(0.0400P)^2^] where P=(Fo^2^+2Fc^2^)/3
Max shift/error	0.003
Average shift/error	0.000
Extinction coefficient	n/a
Largest diff. peak and hole	0.55 and -0.51 e·$Å^{-3}$

Programs Used

Cell refinement	SAINT V8.32B (Bruker-AXS, 2007)
Data collection	APEX2 2013.6-2 (Bruker-AXS, 2007)
Data reduction	SAINT V8.32B (Bruker-AXS, 2007)
Structure solution	SHELXT (Sheldrick, 2012)
Structure refinement	SHELXL-2013/2 (Sheldrick, 2013)
Graphics	DIAMOND 3 (Crystal Impact, 1999)

References

Refinement Details

Table A2.5.2. *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for* ***52****. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor*

	x	y	z	U_{eq}
Br(1)	3260(1)	-6095(1)	-8561(1)	25(1)
Si(1)	380(1)	-12429(1)	-8560(1)	14(1)
O(1)	-2560(1)	-5767(1)	-7181(1)	28(1)
O(2)	-3551(1)	-7223(1)	-7270(1)	22(1)
O(3)	-3839(1)	-8167(1)	-5718(1)	20(1)
O(4)	-2148(1)	-6852(1)	-5561(1)	17(1)
O(5)	-2199(1)	-10064(1)	-5391(1)	17(1)
O(6)	666(1)	-11489(1)	-7758(1)	16(1)
N(1)	-2394(2)	-6634(1)	-7234(1)	18(1)
N(2)	-4168(1)	-10184(1)	-6562(1)	15(1)
C(1)	-1041(2)	-8300(1)	-6228(1)	12(1)
C(2)	-118(2)	-7745(1)	-6847(1)	12(1)
C(3)	-688(2)	-6993(1)	-7276(1)	14(1)
C(4)	290(2)	-6508(1)	-7788(1)	17(1)
C(5)	1901(2)	-6790(1)	-7907(1)	16(1)
C(6)	2528(2)	-7532(1)	-7516(1)	17(1)
C(7)	1541(2)	-7977(1)	-6986(1)	14(1)
C(8)	-2544(2)	-7788(1)	-5839(1)	14(1)
C(9)	-3446(2)	-6292(1)	-5130(1)	24(1)
C(10)	-2758(2)	-5286(1)	-4906(1)	26(1)
C(11)	-2702(3)	-4786(1)	-4109(1)	34(1)
C(12)	142(2)	-8376(1)	-5382(1)	16(1)
C(13)	1021(2)	-7471(1)	-4906(1)	19(1)
C(14)	2624(2)	-7382(1)	-4698(1)	26(1)
C(15)	-1646(2)	-9346(1)	-6719(1)	11(1)
C(16)	-2895(2)	-9359(1)	-7511(1)	12(1)
C(17)	-2761(2)	-9042(1)	-8310(1)	17(1)
C(18)	-4123(2)	-9176(1)	-8938(1)	21(1)
C(19)	-5578(2)	-9640(1)	-8775(1)	22(1)
C(20)	-5714(2)	-9997(1)	-7988(1)	19(1)
C(21)	-4352(2)	-9853(1)	-7369(1)	14(1)
C(22)	-2666(2)	-9882(1)	-6111(1)	13(1)
C(23)	-5490(2)	-10648(1)	-6173(1)	26(1)
C(24)	-176(2)	-9986(1)	-7005(1)	13(1)
C(25)	-693(2)	-11038(1)	-7320(1)	16(1)

C(26)	-826(2)	-13397(1)	-8136(1)	18(1)
C(27)	28(2)	-13713(1)	-7308(1)	26(1)
C(28)	-1340(3)	-14267(1)	-8838(1)	27(1)
C(29)	2572(2)	-12703(1)	-8851(1)	24(1)
C(30)	3670(2)	-13040(2)	-8115(2)	36(1)
C(31)	2672(3)	-13392(2)	-9724(2)	47(1)
C(32)	-836(2)	-12104(1)	-9559(1)	21(1)
C(33)	-47(3)	-11230(2)	-9867(2)	40(1)
C(34)	-2704(2)	-11962(1)	-9483(1)	28(1)

Table A2.5.3. *Bond lengths [Å] and angles [°] for* ***52***

Br(1)-C(5)	1.8927(14)
Si(1)-O(6)	1.6623(10)
Si(1)-C(26)	1.8817(15)
Si(1)-C(29)	1.8856(16)
Si(1)-C(32)	1.8850(17)
O(1)-N(1)	1.2263(16)
O(2)-N(1)	1.2245(16)
O(3)-C(8)	1.1986(17)
O(4)-C(8)	1.3462(16)
O(4)-C(9)	1.4600(18)
O(5)-C(22)	1.2110(17)
O(6)-C(25)	1.4361(16)
N(1)-C(3)	1.4782(18)
N(2)-C(21)	1.3931(19)
N(2)-C(22)	1.3727(18)
N(2)-C(23)	1.4476(19)
C(1)-C(2)	1.5425(19)
C(1)-C(8)	1.5348(19)
C(1)-C(12)	1.576(2)
C(1)-C(15)	1.5971(18)
C(2)-C(3)	1.4053(19)
C(2)-C(7)	1.4058(19)
C(3)-C(4)	1.392(2)
C(4)-H(4)	0.929(17)
C(4)-C(5)	1.382(2)
C(5)-C(6)	1.377(2)
C(6)-H(6)	0.921(19)
C(6)-C(7)	1.386(2)
C(7)-H(7)	0.966(18)
C(9)-H(9A)	0.982(19)
C(9)-H(9B)	0.986(19)
C(9)-C(10)	1.491(2)
C(10)-H(10)	0.99(2)
C(10)-C(11)	1.311(3)
C(11)-H(11A)	0.97(2)
C(11)-H(11B)	0.95(2)
C(12)-H(12A)	0.889(18)
C(12)-H(12B)	0.979(17)
C(12)-C(13)	1.502(2)
C(13)-H(13)	0.945(19)
C(13)-C(14)	1.305(2)
C(14)-H(14A)	0.94(2)
C(14)-H(14B)	0.951(19)

C(15)-C(16)	1.5199(19)
C(15)-C(22)	1.5552(19)
C(15)-C(24)	1.5539(19)
C(16)-C(17)	1.382(2)
C(16)-C(21)	1.3977(19)
C(17)-H(17)	0.954(18)
C(17)-C(18)	1.397(2)
C(18)-H(18)	0.945(19)
C(18)-C(19)	1.385(2)
C(19)-H(19)	0.93(2)
C(19)-C(20)	1.391(2)
C(20)-H(20)	0.946(18)
C(20)-C(21)	1.388(2)
C(23)-H(23A)	1.01(2)
C(23)-H(23B)	0.93(2)
C(23)-H(23C)	0.91(2)
C(24)-H(24A)	0.964(17)
C(24)-H(24B)	0.946(17)
C(24)-C(25)	1.5258(19)
C(25)-H(25A)	0.962(17)
C(25)-H(25B)	0.974(17)
C(26)-H(26)	0.946(17)
C(26)-C(27)	1.536(2)
C(26)-C(28)	1.529(2)
C(27)-H(27A)	1.003(19)
C(27)-H(27B)	1.03(2)
C(27)-H(27C)	0.94(2)
C(28)-H(28A)	0.97(2)
C(28)-H(28B)	1.02(2)
C(28)-H(28C)	0.99(2)
C(29)-H(29)	0.972(19)
C(29)-C(30)	1.527(3)
C(29)-C(31)	1.537(3)
C(30)-H(30A)	1.01(2)
C(30)-H(30B)	0.98(3)
C(30)-H(30C)	1.00(2)
C(31)-H(31A)	0.88(3)
C(31)-H(31B)	0.96(2)
C(31)-H(31C)	0.99(3)
C(32)-H(32)	0.953(19)
C(32)-C(33)	1.529(2)
C(32)-C(34)	1.533(2)
C(33)-H(33A)	1.03(3)
C(33)-H(33B)	0.96(2)
C(33)-H(33C)	0.94(2)
C(34)-H(34A)	0.94(2)
C(34)-H(34B)	1.01(2)
C(34)-H(34C)	0.95(2)

O(6)-Si(1)-C(26)	108.45(6)
O(6)-Si(1)-C(29)	102.78(6)
O(6)-Si(1)-C(32)	111.24(6)
C(26)-Si(1)-C(29)	116.69(7)
C(26)-Si(1)-C(32)	108.76(7)
C(32)-Si(1)-C(29)	108.83(8)
C(8)-O(4)-C(9)	115.62(11)
C(25)-O(6)-Si(1)	122.38(9)
O(1)-N(1)-C(3)	117.69(12)

O(2)-N(1)-O(1)	124.37(12)
O(2)-N(1)-C(3)	117.93(12)
C(21)-N(2)-C(23)	124.40(13)
C(22)-N(2)-C(21)	111.59(11)
C(22)-N(2)-C(23)	123.24(13)
C(2)-C(1)-C(12)	109.54(11)
C(2)-C(1)-C(15)	111.12(11)
C(8)-C(1)-C(2)	114.19(11)
C(8)-C(1)-C(12)	102.89(11)
C(8)-C(1)-C(15)	108.71(11)
C(12)-C(1)-C(15)	110.07(11)
C(3)-C(2)-C(1)	128.63(12)
C(3)-C(2)-C(7)	113.94(12)
C(7)-C(2)-C(1)	117.37(12)
C(2)-C(3)-N(1)	123.50(12)
C(4)-C(3)-N(1)	112.78(12)
C(4)-C(3)-C(2)	123.72(13)
C(3)-C(4)-H(4)	119.1(10)
C(5)-C(4)-C(3)	118.92(14)
C(5)-C(4)-H(4)	121.9(10)
C(4)-C(5)-Br(1)	118.87(11)
C(6)-C(5)-Br(1)	120.73(11)
C(6)-C(5)-C(4)	120.31(13)
C(5)-C(6)-H(6)	121.7(12)
C(5)-C(6)-C(7)	119.26(13)
C(7)-C(6)-H(6)	118.9(12)
C(2)-C(7)-H(7)	118.4(10)
C(6)-C(7)-C(2)	123.79(13)
C(6)-C(7)-H(7)	117.8(10)
O(3)-C(8)-O(4)	123.79(13)
O(3)-C(8)-C(1)	125.80(12)
O(4)-C(8)-C(1)	110.08(11)
O(4)-C(9)-H(9A)	109.4(10)
O(4)-C(9)-H(9B)	107.4(10)
O(4)-C(9)-C(10)	106.28(13)
H(9A)-C(9)-H(9B)	110.0(15)
C(10)-C(9)-H(9A)	109.9(11)
C(10)-C(9)-H(9B)	113.6(11)
C(9)-C(10)-H(10)	113.0(12)
C(11)-C(10)-C(9)	123.47(19)
C(11)-C(10)-H(10)	123.5(12)
C(10)-C(11)-H(11A)	121.9(13)
C(10)-C(11)-H(11B)	121.7(14)
H(11A)-C(11)-H(11B)	116.4(19)
C(1)-C(12)-H(12A)	106.2(12)
C(1)-C(12)-H(12B)	111.1(10)
H(12A)-C(12)-H(12B)	105.2(15)
C(13)-C(12)-C(1)	117.48(12)
C(13)-C(12)-H(12A)	109.4(12)
C(13)-C(12)-H(12B)	106.9(10)
C(12)-C(13)-H(13)	117.6(12)
C(14)-C(13)-C(12)	124.11(15)
C(14)-C(13)-H(13)	118.0(12)
C(13)-C(14)-H(14A)	120.7(13)
C(13)-C(14)-H(14B)	120.4(11)
H(14A)-C(14)-H(14B)	118.9(17)
C(16)-C(15)-C(1)	114.67(11)
C(16)-C(15)-C(22)	101.34(11)

C(16)-C(15)-C(24)	108.87(11)
C(22)-C(15)-C(1)	110.99(11)
C(24)-C(15)-C(1)	112.86(11)
C(24)-C(15)-C(22)	107.29(11)
C(17)-C(16)-C(15)	131.56(13)
C(17)-C(16)-C(21)	119.36(13)
C(21)-C(16)-C(15)	108.89(12)
C(16)-C(17)-H(17)	119.5(11)
C(16)-C(17)-C(18)	119.06(15)
C(18)-C(17)-H(17)	121.4(11)
C(17)-C(18)-H(18)	120.6(12)
C(19)-C(18)-C(17)	120.73(15)
C(19)-C(18)-H(18)	118.7(12)
C(18)-C(19)-H(19)	120.8(12)
C(18)-C(19)-C(20)	121.03(15)
C(20)-C(19)-H(19)	118.1(12)
C(19)-C(20)-H(20)	121.0(11)
C(21)-C(20)-C(19)	117.51(14)
C(21)-C(20)-H(20)	121.4(11)
N(2)-C(21)-C(16)	110.02(12)
C(20)-C(21)-N(2)	127.73(13)
C(20)-C(21)-C(16)	122.21(14)
O(5)-C(22)-N(2)	124.97(13)
O(5)-C(22)-C(15)	126.91(12)
N(2)-C(22)-C(15)	107.94(12)
N(2)-C(23)-H(23A)	109.3(13)
N(2)-C(23)-H(23B)	110.9(14)
N(2)-C(23)-H(23C)	115.0(15)
H(23A)-C(23)-H(23B)	103.8(18)
H(23A)-C(23)-H(23C)	104.9(19)
H(23B)-C(23)-H(23C)	112(2)
C(15)-C(24)-H(24A)	108.7(10)
C(15)-C(24)-H(24B)	107.9(10)
H(24A)-C(24)-H(24B)	112.9(14)
C(25)-C(24)-C(15)	113.74(11)
C(25)-C(24)-H(24A)	106.1(10)
C(25)-C(24)-H(24B)	107.7(10)
O(6)-C(25)-C(24)	107.63(11)
O(6)-C(25)-H(25A)	109.7(10)
O(6)-C(25)-H(25B)	111.7(10)
C(24)-C(25)-H(25A)	110.4(10)
C(24)-C(25)-H(25B)	109.9(10)
H(25A)-C(25)-H(25B)	107.5(14)
Si(1)-C(26)-H(26)	104.7(11)
C(27)-C(26)-Si(1)	113.72(11)
C(27)-C(26)-H(26)	104.7(11)
C(28)-C(26)-Si(1)	114.04(11)
C(28)-C(26)-H(26)	108.3(11)
C(28)-C(26)-C(27)	110.66(13)
C(26)-C(27)-H(27A)	113.3(11)
C(26)-C(27)-H(27B)	108.8(11)
C(26)-C(27)-H(27C)	111.1(12)
H(27A)-C(27)-H(27B)	106.3(15)
H(27A)-C(27)-H(27C)	108.5(16)
H(27B)-C(27)-H(27C)	108.7(15)
C(26)-C(28)-H(28A)	112.5(12)
C(26)-C(28)-H(28B)	112.6(12)
C(26)-C(28)-H(28C)	112.8(12)

H(28A)-C(28)-H(28B)	100.8(16)
H(28A)-C(28)-H(28C)	110.9(16)
H(28B)-C(28)-H(28C)	106.5(16)
Si(1)-C(29)-H(29)	103.4(10)
C(30)-C(29)-Si(1)	114.40(13)
C(30)-C(29)-H(29)	107.0(11)
C(30)-C(29)-C(31)	110.15(17)
C(31)-C(29)-Si(1)	114.10(13)
C(31)-C(29)-H(29)	107.0(11)
C(29)-C(30)-H(30A)	114.8(13)
C(29)-C(30)-H(30B)	110.0(15)
C(29)-C(30)-H(30C)	111.3(13)
H(30A)-C(30)-H(30B)	109.4(19)
H(30A)-C(30)-H(30C)	106.0(18)
H(30B)-C(30)-H(30C)	104.8(19)
C(29)-C(31)-H(31A)	112.5(17)
C(29)-C(31)-H(31B)	110.3(14)
C(29)-C(31)-H(31C)	112.4(14)
H(31A)-C(31)-H(31B)	111(2)
H(31A)-C(31)-H(31C)	101(2)
H(31B)-C(31)-H(31C)	109(2)
Si(1)-C(32)-H(32)	105.3(11)
C(33)-C(32)-Si(1)	111.67(13)
C(33)-C(32)-H(32)	103.1(11)
C(33)-C(32)-C(34)	109.47(16)
C(34)-C(32)-Si(1)	116.52(12)
C(34)-C(32)-H(32)	109.8(11)
C(32)-C(33)-H(33A)	111.4(16)
C(32)-C(33)-H(33B)	111.6(14)
C(32)-C(33)-H(33C)	110.4(14)
H(33A)-C(33)-H(33B)	112(2)
H(33A)-C(33)-H(33C)	108(2)
H(33B)-C(33)-H(33C)	102.1(19)
C(32)-C(34)-H(34A)	111.1(13)
C(32)-C(34)-H(34B)	109.4(12)
C(32)-C(34)-H(34C)	114.4(13)
H(34A)-C(34)-H(34B)	105.6(18)
H(34A)-C(34)-H(34C)	110.8(18)
H(34B)-C(34)-H(34C)	104.9(17)

Symmetry transformations used to generate equivalent atoms:

Table A2.5.4. *Anisotropic displacement parameters ($Å^2 x\ 10^4$) for* ***52****. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	260(1)	269(1)	233(1)	77(1)	68(1)	-97(1)
Si(1)	147(2)	92(2)	183(2)	-2(2)	37(2)	-4(1)
O(1)	246(6)	146(5)	478(8)	137(5)	54(5)	60(4)
O(2)	126(5)	203(6)	324(6)	62(5)	-30(4)	-23(4)
O(3)	173(5)	134(5)	296(6)	8(4)	99(4)	3(4)
O(4)	150(5)	92(5)	260(6)	-20(4)	38(4)	19(4)
O(5)	189(5)	162(5)	179(5)	61(4)	30(4)	-3(4)
O(6)	137(5)	103(5)	237(6)	-30(4)	52(4)	19(4)

N(1)	146(6)	161(6)	228(7)	73(5)	-6(5)	15(5)
N(2)	124(5)	122(6)	189(6)	12(5)	34(5)	-27(4)
C(1)	119(6)	84(6)	141(6)	13(5)	17(5)	11(5)
C(2)	118(6)	90(6)	135(6)	0(5)	-8(5)	-26(5)
C(3)	115(6)	109(6)	184(7)	17(5)	-6(5)	-10(5)
C(4)	193(7)	130(7)	176(7)	44(6)	-14(6)	-27(5)
C(5)	178(7)	149(7)	156(7)	17(5)	29(6)	-69(5)
C(6)	121(7)	152(7)	211(7)	-11(6)	18(6)	-26(5)
C(7)	131(6)	105(6)	175(7)	7(5)	-5(5)	-7(5)
C(8)	163(7)	100(6)	164(7)	14(5)	17(5)	8(5)
C(9)	204(8)	150(7)	354(10)	-50(7)	71(7)	54(6)
C(10)	249(8)	145(7)	351(10)	-36(7)	14(7)	48(6)
C(11)	428(11)	201(9)	350(11)	-42(8)	-88(9)	60(8)
C(12)	171(7)	147(7)	154(7)	38(6)	-7(6)	-14(6)
C(13)	211(7)	156(7)	173(7)	-21(6)	1(6)	12(6)
C(14)	212(8)	230(8)	300(9)	-44(7)	-8(7)	-31(7)
C(15)	112(6)	76(6)	135(6)	10(5)	14(5)	-10(5)
C(16)	131(6)	83(6)	153(7)	-2(5)	-1(5)	13(5)
C(17)	193(7)	142(7)	169(7)	15(5)	8(6)	3(6)
C(18)	263(8)	207(8)	163(7)	16(6)	-30(6)	36(6)
C(19)	199(8)	222(8)	209(8)	-60(6)	-67(6)	44(6)
C(20)	139(7)	160(7)	251(8)	-51(6)	6(6)	6(6)
C(21)	139(6)	106(6)	170(7)	-22(5)	39(5)	17(5)
C(22)	133(6)	65(6)	174(7)	-8(5)	40(5)	7(5)
C(23)	201(8)	344(10)	239(9)	43(8)	41(7)	-137(7)
C(24)	112(6)	104(6)	175(7)	0(5)	22(5)	6(5)
C(25)	140(7)	104(6)	223(8)	-4(6)	68(6)	17(5)
C(26)	195(7)	115(7)	216(8)	23(6)	28(6)	-9(6)
C(27)	359(10)	214(8)	209(8)	59(7)	-3(7)	-47(7)
C(28)	409(10)	136(7)	254(9)	45(6)	-68(8)	-75(7)
C(29)	182(7)	175(8)	326(9)	-49(7)	84(7)	-9(6)
C(30)	214(9)	371(11)	519(13)	75(10)	60(8)	67(8)
C(31)	297(11)	476(14)	534(15)	-272(11)	171(10)	-23(10)
C(32)	273(8)	168(7)	207(8)	46(6)	35(6)	-14(6)
C(33)	459(13)	424(12)	378(12)	245(10)	12(10)	-117(10)
C(34)	300(9)	259(9)	283(9)	88(8)	-20(7)	56(7)

Table A2.5.5. *Hydrogen coordinates (x 10^3) and isotropic displacement parameters (Å^{2}x 10^3) for* ***52***

	x	y	z	U_{iso}
H(4)	-15(2)	-600(1)	-803(1)	15(4)
H(6)	362(2)	-770(1)	-756(1)	31(5)
H(7)	203(2)	-847(1)	-669(1)	22(4)
H(9A)	-369(2)	-654(1)	-459(1)	24(5)
H(9B)	-445(2)	-636(1)	-555(1)	24(5)
H(10)	-237(2)	-503(1)	-542(1)	35(5)
H(11A)	-313(3)	-504(2)	-362(2)	41(6)
H(11B)	-227(3)	-414(2)	-399(2)	51(7)
H(12A)	-48(2)	-862(1)	-501(1)	22(5)
H(12B)	100(2)	-884(1)	-552(1)	16(4)
H(13)	36(2)	-696(1)	-469(1)	34(5)
H(14A)	333(2)	-788(2)	-490(1)	37(6)
H(14B)	309(2)	-682(1)	-432(1)	28(5)

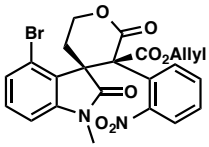
H(17)	-174(2)	-874(1)	-842(1)	20(4)
H(18)	-408(2)	-893(1)	-948(1)	28(5)
H(19)	-647(2)	-976(1)	-920(1)	32(5)
H(20)	-670(2)	-1033(1)	-788(1)	18(4)
H(23A)	-633(3)	-1016(2)	-596(2)	50(6)
H(23B)	-509(3)	-1086(2)	-566(2)	45(6)
H(23C)	-609(3)	-1111(2)	-655(2)	53(7)
H(24A)	29(2)	-976(1)	-750(1)	17(4)
H(24B)	60(2)	-996(1)	-651(1)	12(4)
H(25A)	-93(2)	-1135(1)	-682(1)	16(4)
H(25B)	-171(2)	-1108(1)	-771(1)	17(4)
H(26)	-180(2)	-1310(1)	-794(1)	21(4)
H(27A)	98(2)	-1415(1)	-744(1)	29(5)
H(27B)	-83(2)	-1410(1)	-702(1)	36(5)
H(27C)	42(2)	-1318(1)	-689(1)	28(5)
H(28A)	-199(2)	-1409(1)	-934(1)	33(5)
H(28B)	-216(3)	-1472(2)	-863(1)	39(6)
H(28C)	-38(3)	-1465(2)	-903(1)	37(6)
H(29)	304(2)	-1208(1)	-893(1)	24(5)
H(30A)	359(3)	-1266(2)	-751(2)	47(6)
H(30B)	483(3)	-1304(2)	-826(2)	65(8)
H(30C)	338(3)	-1372(2)	-806(2)	48(6)
H(31A)	218(3)	-1395(2)	-972(2)	57(8)
H(31B)	381(3)	-1347(2)	-986(2)	48(6)
H(31C)	203(3)	-1317(2)	-1023(2)	59(8)
H(32)	-67(2)	-1261(1)	-1003(1)	27(5)
H(33A)	-6(3)	-1063(2)	-940(2)	81(9)
H(33B)	-54(3)	-1113(2)	-1043(2)	48(6)
H(33C)	106(3)	-1134(2)	-999(2)	50(7)
H(34A)	-322(3)	-1249(2)	-929(1)	44(6)
H(34B)	-327(3)	-1193(2)	-1009(2)	45(6)
H(34C)	-296(3)	-1138(2)	-913(1)	41(6)

Table A2.5.6. *Hydrogen bonds for* ***52*** *[Å and °]*

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(6)-H(6)...O(2)#1	0.921(19)	2.353(19)	3.1624(18)	146.6(16)
C(23)-H(23A)...O(5)#2	1.01(2)	2.45(2)	3.197(2)	129.9(17)

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

A2.6. X-Ray Crystal Structure Analysis of 61



61

Figure A2.6.1. *X-ray Crystal Structure of* ***61***

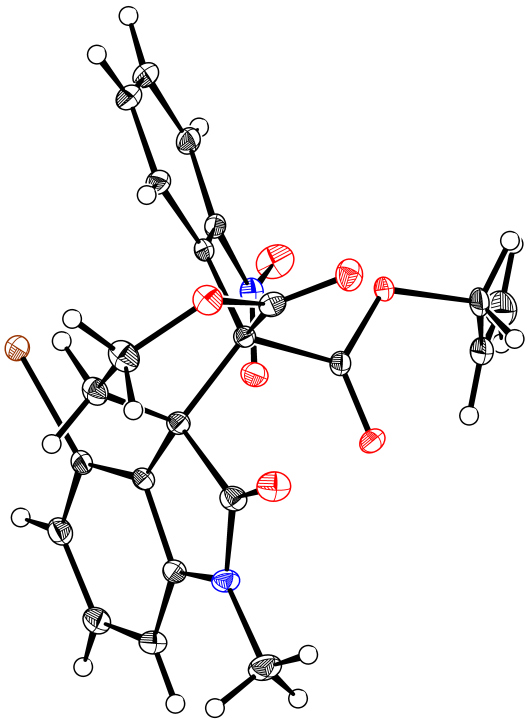


Table A2.6.1. *Crystal Data and Structure Analysis Details for* ***61***

Empirical formula	C23 H19 Br N2 O7.20
Formula weight	518.54
Crystallization solvent	???Solvent???
Crystal shape	plate
Crystal color	colourless
Crystal size	0.17 x 0.24 x 0.25 mm

Data Collection

Preliminary photograph(s)	rotation
Type of diffractometer	Bruker APEX-II CCD
Wavelength	0.71073 Å MoK

Data collection temperature	100 K	
Theta range for 9593 reflections used in lattice determination	2.62 to 36.54°	
Unit cell dimensions	a = 10.1321(5) Å b = 14.3644(6) Å c = 14.6551(6) Å	⟨= 90° ®= 104.647(3)° © = 90°
Volume	2063.61(16) $Å^3$	
Z	4	
Crystal system	monoclinic	
Space group	P 1 21/c 1 (# 14)	
Density (calculated)	1.669 g/cm^3	
F(000)	1054	
Theta range for data collection	2.0 to 42.9°	
Completeness to theta = 25.000°	100.0%	
Index ranges	-19 ″ h ″ 19, -27 ″ k ″ 27, -27 ″ l ″ 28	
Data collection scan type	and scans	
Reflections collected	166238	
Independent reflections	15005 [R_{int}= 0.0848]	
Reflections > 2 ∫(I)	9726	
Average ∫(I)/(net I)	0.0622	
Absorption coefficient	2.05 mm^{-1}	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.9002	

Structure Solution and Refinement

Primary solution method	?
Secondary solution method	?
Hydrogen placement	mixed
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	15005 / 0 / 309
Treatment of hydrogen atoms	constr
Goodness-of-fit on F^2	1.03
Final R indices [I>2 ∫(I), 9726 reflections]	R1 = 0.0534, wR2 = 0.1233
R indices (all data)	R1 = 0.1009, wR2 = 0.1398
Type of weighting scheme used	calc
Weighting scheme used	w=1/[^2^(Fo^2^)+(0.0618P)^2^+1.7296P] where P=(Fo^2^+2Fc^2^)/3
Max shift/error	0.000
Average shift/error	0.000
Extinction coefficient	n/a

Largest diff. peak and hole 5.40 and -1.57 e·Å^{-3}

Programs Used

Cell refinement	SAINT V8.32B (Bruker-AXS, 2007)
Data collection	APEX2 2012.10-0 (Bruker-AXS, 2007)
Data reduction	SAINT V8.32B (Bruker-AXS, 2007)
Structure solution	SHELXT (Sheldrick, 2012)
Structure refinement	SHELXL-2013/2 (Sheldrick, 2013)
Graphics	DIAMOND 3 (Crystal Impact, 1999)

References

Special Refinement Details

Table A2.6.2. *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for* ***61.*** *U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor*

	x	y	z	U_{eq}
Br(1)	2176(1)	3795(1)	4422(1)	16(1)
O(1)	4484(1)	6914(1)	2590(1)	19(1)
O(2)	4806(1)	5100(1)	1849(1)	17(1)
O(3)	3104(1)	5662(1)	752(1)	18(1)
O(4)	-1522(1)	4433(1)	2271(1)	22(1)
O(5)	142(1)	5360(1)	2886(1)	16(1)
O(6)	1437(1)	6845(1)	2016(1)	15(1)
O(7)	490(1)	5659(1)	1068(1)	13(1)
O(8)	1317(5)	4704(4)	5932(3)	13(1)
C(4)	1722(2)	5406(1)	5379(1)	15(1)
N(1)	3573(1)	7168(1)	3851(1)	14(1)
N(2)	-318(1)	4658(1)	2439(1)	13(1)
C(1)	3379(1)	5631(1)	3242(1)	11(1)
C(2)	2724(1)	5722(1)	4069(1)	12(1)
C(3)	2202(2)	5102(1)	4617(1)	12(1)
C(5)	1834(2)	6343(1)	5635(1)	17(1)
C(6)	2449(2)	6977(1)	5154(1)	16(1)
C(7)	2877(2)	6651(1)	4388(1)	12(1)
C(8)	3878(2)	6644(1)	3160(1)	14(1)
C(9)	3948(2)	8140(1)	4012(1)	20(1)
C(10)	4635(2)	4985(1)	3515(1)	15(1)
C(11)	5536(2)	5040(1)	2835(1)	19(1)
C(12)	3523(2)	5408(1)	1558(1)	14(1)
C(13)	2536(1)	5327(1)	2228(1)	10(1)
C(14)	1976(1)	4321(1)	2117(1)	10(1)
C(15)	2786(2)	3606(1)	1902(1)	14(1)
C(16)	2314(2)	2703(1)	1684(1)	16(1)
C(17)	985(2)	2474(1)	1652(1)	17(1)
C(18)	150(2)	3150(1)	1888(1)	15(1)
C(19)	644(2)	4040(1)	2126(1)	12(1)
C(20)	1417(2)	6040(1)	1779(1)	11(1)
C(21)	-565(2)	6275(1)	517(1)	15(1)
C(22)	-1606(2)	6519(1)	1041(1)	16(1)
C(23)	-2852(2)	6167(1)	839(1)	24(1)

Table A2.6.3. *Bond lengths [Å] and angles [°] for* ***61***

Br(1)-C(3)	1.8983(15)
O(1)-C(8)	1.2173(19)
O(2)-C(11)	1.450(2)
O(2)-C(12)	1.3369(19)
O(3)-C(12)	1.2057(19)
O(4)-N(2)	1.2258(18)
O(5)-N(2)	1.2285(17)
O(6)-C(20)	1.2060(18)
O(7)-C(20)	1.3313(18)
O(7)-C(21)	1.4626(18)
O(8)-C(4)	1.419(5)
O(8)-H(4)	0.5001
O(8)-H(8)	0.8315
C(4)-H(4)	0.9497
C(4)-C(3)	1.396(2)
C(4)-C(5)	1.394(2)
N(1)-C(7)	1.3965(19)
N(1)-C(8)	1.358(2)
N(1)-C(9)	1.451(2)
N(2)-C(19)	1.4738(19)
C(1)-C(2)	1.528(2)
C(1)-C(8)	1.555(2)
C(1)-C(10)	1.544(2)
C(1)-C(13)	1.5768(19)
C(2)-C(3)	1.389(2)
C(2)-C(7)	1.410(2)
C(5)-H(5)	0.9500
C(5)-C(6)	1.391(2)
C(6)-H(6)	0.9500
C(6)-C(7)	1.383(2)
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(10)-C(11)	1.514(2)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(13)	1.573(2)
C(13)-C(14)	1.5460(19)
C(13)-C(20)	1.5455(19)
C(14)-C(15)	1.400(2)
C(14)-C(19)	1.412(2)
C(15)-H(15)	0.9500
C(15)-C(16)	1.391(2)
C(16)-H(16)	0.9500
C(16)-C(17)	1.376(2)
C(17)-H(17)	0.9500
C(17)-C(18)	1.387(2)
C(18)-H(18)	0.9500
C(18)-C(19)	1.385(2)
C(21)-H(21A)	0.9900
C(21)-H(21B)	0.9900

C(21)-C(22)	1.494(2)
C(22)-H(22)	0.9500
C(22)-C(23)	1.322(3)
C(23)-H(23A)	0.9500
C(23)-H(23B)	0.9500

C(12)-O(2)-C(11)	123.19(13)
C(20)-O(7)-C(21)	117.17(12)
C(4)-O(8)-H(4)	16.4
C(4)-O(8)-H(8)	107.5
H(4)-O(8)-H(8)	113.1
O(8)-C(4)-H(4)	8.5
C(3)-C(4)-O(8)	116.4(3)
C(3)-C(4)-H(4)	120.1
C(5)-C(4)-O(8)	123.3(3)
C(5)-C(4)-H(4)	120.1
C(5)-C(4)-C(3)	119.77(14)
C(7)-N(1)-C(9)	124.62(13)
C(8)-N(1)-C(7)	111.67(12)
C(8)-N(1)-C(9)	123.70(14)
O(4)-N(2)-O(5)	123.20(14)
O(4)-N(2)-C(19)	118.81(13)
O(5)-N(2)-C(19)	117.95(12)
C(2)-C(1)-C(8)	101.37(11)
C(2)-C(1)-C(10)	109.88(12)
C(2)-C(1)-C(13)	122.06(12)
C(8)-C(1)-C(13)	107.22(11)
C(10)-C(1)-C(8)	108.64(12)
C(10)-C(1)-C(13)	106.98(11)
C(3)-C(2)-C(1)	135.18(13)
C(3)-C(2)-C(7)	116.15(13)
C(7)-C(2)-C(1)	108.06(12)
C(4)-C(3)-Br(1)	115.80(11)
C(2)-C(3)-Br(1)	122.67(11)
C(2)-C(3)-C(4)	121.47(14)
C(4)-C(5)-H(5)	119.6
C(6)-C(5)-C(4)	120.74(14)
C(6)-C(5)-H(5)	119.6
C(5)-C(6)-H(6)	121.2
C(7)-C(6)-C(5)	117.54(14)
C(7)-C(6)-H(6)	121.2
N(1)-C(7)-C(2)	110.18(12)
C(6)-C(7)-N(1)	125.78(13)
C(6)-C(7)-C(2)	123.98(14)
O(1)-C(8)-N(1)	125.78(14)
O(1)-C(8)-C(1)	125.49(14)
N(1)-C(8)-C(1)	108.69(12)
N(1)-C(9)-H(9A)	109.5
N(1)-C(9)-H(9B)	109.5
N(1)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(1)-C(10)-H(10A)	109.0
C(1)-C(10)-H(10B)	109.0
H(10A)-C(10)-H(10B)	107.8
C(11)-C(10)-C(1)	113.13(13)
C(11)-C(10)-H(10A)	109.0

C(11)-C(10)-H(10B)	109.0
O(2)-C(11)-C(10)	114.73(13)
O(2)-C(11)-H(11A)	108.6
O(2)-C(11)-H(11B)	108.6
C(10)-C(11)-H(11A)	108.6
C(10)-C(11)-H(11B)	108.6
H(11A)-C(11)-H(11B)	107.6
O(2)-C(12)-C(13)	119.80(13)
O(3)-C(12)-O(2)	119.04(14)
O(3)-C(12)-C(13)	120.80(14)
C(12)-C(13)-C(1)	106.83(11)
C(14)-C(13)-C(1)	117.09(11)
C(14)-C(13)-C(12)	106.13(11)
C(20)-C(13)-C(1)	112.41(11)
C(20)-C(13)-C(12)	101.50(11)
C(20)-C(13)-C(14)	111.34(11)
C(15)-C(14)-C(13)	119.25(13)
C(15)-C(14)-C(19)	114.17(13)
C(19)-C(14)-C(13)	126.32(12)
C(14)-C(15)-H(15)	118.4
C(16)-C(15)-C(14)	123.26(14)
C(16)-C(15)-H(15)	118.4
C(15)-C(16)-H(16)	119.8
C(17)-C(16)-C(15)	120.48(14)
C(17)-C(16)-H(16)	119.8
C(16)-C(17)-H(17)	120.7
C(16)-C(17)-C(18)	118.53(14)
C(18)-C(17)-H(17)	120.7
C(17)-C(18)-H(18)	119.8
C(19)-C(18)-C(17)	120.34(15)
C(19)-C(18)-H(18)	119.8
C(14)-C(19)-N(2)	122.70(12)
C(18)-C(19)-N(2)	114.14(13)
C(18)-C(19)-C(14)	123.08(14)
O(6)-C(20)-O(7)	125.14(13)
O(6)-C(20)-C(13)	123.77(13)
O(7)-C(20)-C(13)	110.96(12)
O(7)-C(21)-H(21A)	109.3
O(7)-C(21)-H(21B)	109.3
O(7)-C(21)-C(22)	111.77(12)
H(21A)-C(21)-H(21B)	107.9
C(22)-C(21)-H(21A)	109.3
C(22)-C(21)-H(21B)	109.3
C(21)-C(22)-H(22)	118.2
C(23)-C(22)-C(21)	123.59(16)
C(23)-C(22)-H(22)	118.2
C(22)-C(23)-H(23A)	120.0
C(22)-C(23)-H(23B)	120.0
H(23A)-C(23)-H(23B)	120.0

Symmetry transformations used to generate equivalent atoms:

Table A2.6.4. *Anisotropic displacement parameters ($Å^2 x\ 10^4$) for **61**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	228(1)	114(1)	135(1)	15(1)	21(1)	-20(1)
O(1)	183(5)	191(5)	217(5)	-12(4)	88(4)	-53(4)
O(2)	132(5)	207(5)	178(5)	-9(4)	52(4)	16(4)
O(3)	210(5)	193(5)	160(5)	40(4)	75(4)	13(4)
O(4)	116(5)	227(6)	338(7)	-22(5)	88(5)	-29(4)
O(5)	147(5)	162(5)	144(4)	-30(4)	14(4)	16(4)
O(6)	165(5)	101(4)	174(5)	-5(3)	25(4)	13(3)
O(7)	127(4)	124(4)	111(4)	5(3)	-16(3)	29(3)
O(8)	60(20)	270(30)	63(19)	92(17)	11(14)	-36(18)
C(4)	168(6)	170(6)	118(5)	11(5)	26(5)	-2(5)
N(1)	152(5)	112(5)	154(5)	-21(4)	37(4)	-42(4)
N(2)	117(5)	145(5)	130(5)	20(4)	28(4)	5(4)
C(1)	98(5)	112(5)	124(5)	-8(4)	11(4)	-8(4)
C(2)	107(5)	118(5)	105(5)	-9(4)	-2(4)	-3(4)
C(3)	129(6)	122(5)	107(5)	7(4)	-1(4)	-6(4)
C(5)	199(7)	183(6)	128(5)	-12(5)	44(5)	11(5)
C(6)	176(6)	140(6)	145(6)	-30(5)	29(5)	0(5)
C(7)	114(5)	120(5)	124(5)	-6(4)	5(4)	-7(4)
C(8)	116(5)	143(6)	150(5)	-13(4)	20(4)	-31(4)
C(9)	210(7)	129(6)	247(7)	-32(5)	39(6)	-55(5)
C(10)	101(5)	195(6)	149(6)	-8(5)	0(4)	22(5)
C(11)	107(6)	262(8)	188(6)	-20(6)	22(5)	12(5)
C(12)	130(6)	125(5)	157(6)	-9(4)	50(5)	-3(4)
C(13)	94(5)	101(5)	109(5)	-8(4)	12(4)	3(4)
C(14)	98(5)	105(5)	96(5)	4(4)	-1(4)	8(4)
C(15)	129(6)	121(5)	155(5)	-10(4)	19(4)	24(4)
C(16)	187(7)	114(5)	180(6)	-7(5)	22(5)	29(5)
C(17)	218(7)	99(5)	179(6)	7(5)	22(5)	-10(5)
C(18)	161(6)	115(5)	156(5)	24(4)	21(5)	-21(4)
C(19)	120(5)	107(5)	117(5)	16(4)	18(4)	5(4)
C(20)	111(5)	113(5)	113(5)	14(4)	17(4)	10(4)
C(21)	156(6)	164(6)	120(5)	31(4)	-3(4)	50(5)
C(22)	170(6)	154(6)	146(6)	10(5)	6(5)	39(5)
C(23)	183(7)	275(8)	256(8)	14(7)	26(6)	15(6)

Table A2.6.5. *Hydrogen coordinates ($x\ 10^3$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for **61***

	x	y	z	U_{iso}
H(4)	132	498	572	18
H(8)	171	481	649	23
H(5)	149	655	614	20
H(6)	257	761	534	19
H(9A)	316	850	409	30
H(9B)	425	838	347	30
H(9C)	469	820	459	30
H(10A)	518	515	415	18
H(10B)	432	434	354	18

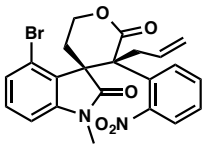
H(11A)	614	559	300	23
H(11B)	613	448	292	23
H(15)	370	374	191	17
H(16)	292	224	156	20
H(17)	65	187	147	20
H(18)	-76	300	189	18
H(21A)	-102	596	-8	18
H(21B)	-13	685	36	18
H(22)	-136	695	155	20
H(23A)	-313	573	34	29
H(23B)	-347	635	120	29

Table A2.6.6. *Hydrogen bonds for* ***61*** *[Å and °]*

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(8)-H(8)...O(4)#1	0.83	2.16	2.870(6)	143.3
O(8)-H(8)...N(2)#1	0.83	2.47	2.964(5)	118.6
C(5)-H(5)...O(6)#2	0.95	2.64	3.382(2)	135.3
C(6)-H(6)...O(3)#2	0.95	2.58	3.524(2)	173.5
C(9)-H(9A)...O(4)#3	0.98	2.62	3.270(2)	124.3
C(10)-H(10B)...Br(1)	0.99	2.90	3.5462(16)	123.5
C(18)-H(18)...O(6)#4	0.95	2.52	3.1613(19)	124.5

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

A2.7. X-Ray Crystal Structure Analysis of 62



62

Figure A2.7.1. *X-ray Crystal Structure of* ***62***

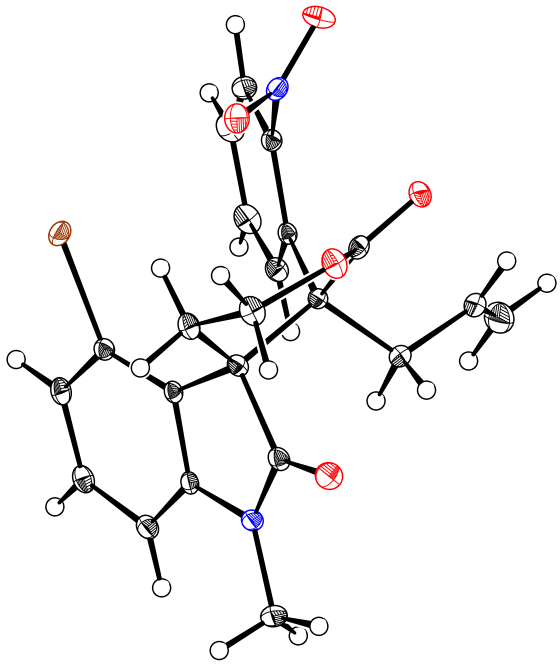


Table A2.7.1. *Crystal data and structure refinement for* ***62***

Empirical formula	C22 H19 Br N2 O5
Formula weight	471.30
Crystallization Solvent	???Solvent???
Crystal Habit	Block
Crystal size	0.25 x 0.25 x 0.22 mm^3
Crystal color	Light yellow

Data Collection

Preliminary Photos	
Type of diffractometer	Bruker SMART 1000
Wavelength	0.71073 Å MoKa
Data Collection Temperature	100(2) K

q range for 9803 reflections used in lattice determination	2.44 to 37.44°	
Unit cell dimensions	a = 9.1581(2) Å b = 12.6857(3) Å c = 16.7030(3) Å	a= 90° b= 90° g = 90°
Volume	1940.50(7) $Å^3$	
Z	4	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Density (calculated)	1.613 Mg/m^3	
F(000)	960	
Data collection program	Bruker SMART v5.630	
q range for data collection	2.02 to 38.73°	
Completeness to q = 38.73°	98.0 %	
Index ranges	-15<=h<=15, -22<=k<=22, -29<=l<=29	
Data collection scan type	scans at 9 settings	
Data reduction program	Bruker SAINT v6.45A	
Reflections collected	61657	
Independent reflections	10781 [R_{int}= 0.0854]	
Absorption coefficient	2.157 mm^{-1}	
Absorption correction	None	
Max. and min. transmission	0.6482 and 0.6146	

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	10781 / 0 / 272
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	1.035
Final R indices [I>2s(I), 9216 reflections]	R1 = 0.0252, wR2 = 0.0489
R indices (all data)	R1 = 0.0337, wR2 = 0.0500
Type of weighting scheme used	Sigma
Weighting scheme used	w=1/s^2^(Fo^2^)
Max shift/error	0.002
Average shift/error	0.000
Absolute structure determination	ad

Absolute structure parameter	-0.009(3)
Largest diff. peak and hole	0.506 and -0.302 e.Å^{-3}

Special Refinement Details

Table A2.7.2. *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for* ***62****. U(eq) is defined asthe trace of the orthogonalized U^{ij} tensor*

	x	y	z	U_{eq}
Br(1)	6172(1)	8240(1)	8167(1)	15(1)
O(1)	3907(1)	9672(1)	4985(1)	17(1)
O(2)	6918(1)	8349(1)	5024(1)	15(1)
O(3)	8739(1)	9434(1)	5191(1)	14(1)
O(4)	8625(1)	7737(1)	6394(1)	15(1)
O(5)	10809(1)	8399(1)	6452(1)	19(1)
N(1)	3093(1)	10408(1)	6153(1)	12(1)
N(2)	9490(1)	8431(1)	6587(1)	12(1)
C(1)	4851(1)	9334(1)	7882(1)	11(1)
C(2)	4150(1)	9836(1)	8519(1)	13(1)
C(3)	3074(1)	10582(1)	8369(1)	13(1)
C(4)	2660(1)	10820(1)	7588(1)	13(1)
C(5)	3393(1)	10316(1)	6972(1)	10(1)
C(6)	4553(1)	9605(1)	7092(1)	9(1)
C(7)	5158(1)	9288(1)	6276(1)	10(1)
C(8)	3998(1)	9786(1)	5710(1)	12(1)
C(9)	1825(1)	10950(1)	5827(1)	16(1)
C(10)	5199(1)	8087(1)	6152(1)	12(1)
C(11)	5626(1)	7790(1)	5306(1)	15(1)
C(12)	7535(1)	9152(1)	5408(1)	11(1)
C(13)	6734(1)	9783(1)	6067(1)	9(1)
C(14)	6523(1)	10915(1)	5677(1)	12(1)
C(15)	7876(1)	11577(1)	5570(1)	14(1)
C(16)	8070(1)	12508(1)	5908(1)	22(1)
C(17)	7685(1)	9912(1)	6823(1)	9(1)
C(18)	7318(1)	10731(1)	7352(1)	12(1)
C(19)	8056(1)	10912(1)	8064(1)	15(1)
C(20)	9254(1)	10302(1)	8269(1)	17(1)
C(21)	9707(1)	9521(1)	7747(1)	14(1)
C(22)	8925(1)	9334(1)	7045(1)	11(1)

Table A2.7.3. *Bond lengths [Å] and angles [°] for* ***62***

Br(1)-C(1)	1.9017(10)
O(1)-C(8)	1.2218(12)
O(2)-C(12)	1.3289(12)
O(2)-C(11)	1.4580(13)
O(3)-C(12)	1.2142(12)
O(4)-N(2)	1.2271(11)
O(5)-N(2)	1.2300(11)
N(1)-C(8)	1.3625(13)
N(1)-C(5)	1.3999(12)
N(1)-C(9)	1.4553(13)
N(2)-C(22)	1.4720(12)
C(1)-C(6)	1.3911(14)
C(1)-C(2)	1.3962(14)

C(2)-C(3)	1.3888(15)
C(3)-C(4)	1.3917(15)
C(4)-C(5)	1.3854(14)
C(5)-C(6)	1.4079(14)
C(6)-C(7)	1.5248(13)
C(7)-C(10)	1.5383(13)
C(7)-C(8)	1.5561(14)
C(7)-C(13)	1.6122(13)
C(10)-C(11)	1.5149(14)
C(12)-C(13)	1.5460(13)
C(13)-C(17)	1.5433(13)
C(13)-C(14)	1.5885(13)
C(14)-C(15)	1.5070(14)
C(15)-C(16)	1.3208(15)
C(17)-C(22)	1.4016(14)
C(17)-C(18)	1.4049(14)
C(18)-C(19)	1.3862(14)
C(19)-C(20)	1.3857(16)
C(20)-C(21)	1.3836(15)
C(21)-C(22)	1.3936(14)

C(12)-O(2)-C(11)	124.26(8)
C(8)-N(1)-C(5)	111.30(8)
C(8)-N(1)-C(9)	123.71(8)
C(5)-N(1)-C(9)	124.18(9)
O(4)-N(2)-O(5)	124.19(9)
O(4)-N(2)-C(22)	117.92(8)
O(5)-N(2)-C(22)	117.81(8)
C(6)-C(1)-C(2)	121.36(9)
C(6)-C(1)-Br(1)	122.86(7)
C(2)-C(1)-Br(1)	115.75(7)
C(3)-C(2)-C(1)	119.98(9)
C(2)-C(3)-C(4)	120.64(9)
C(5)-C(4)-C(3)	117.69(9)
C(4)-C(5)-N(1)	126.35(9)
C(4)-C(5)-C(6)	123.75(9)
N(1)-C(5)-C(6)	109.89(8)
C(1)-C(6)-C(5)	116.17(9)
C(1)-C(6)-C(7)	135.37(9)
C(5)-C(6)-C(7)	108.42(8)
C(6)-C(7)-C(10)	112.93(8)
C(6)-C(7)-C(8)	100.84(7)
C(10)-C(7)-C(8)	109.74(8)
C(6)-C(7)-C(13)	114.61(8)
C(10)-C(7)-C(13)	109.51(8)
C(8)-C(7)-C(13)	108.78(7)
O(1)-C(8)-N(1)	124.44(9)
O(1)-C(8)-C(7)	126.88(9)
N(1)-C(8)-C(7)	108.66(8)
C(11)-C(10)-C(7)	112.23(8)
O(2)-C(11)-C(10)	112.87(8)
O(3)-C(12)-O(2)	117.89(9)
O(3)-C(12)-C(13)	119.40(8)
O(2)-C(12)-C(13)	122.54(8)
C(17)-C(13)-C(12)	111.72(8)
C(17)-C(13)-C(14)	107.93(7)
C(12)-C(13)-C(14)	103.53(7)
C(17)-C(13)-C(7)	111.69(7)

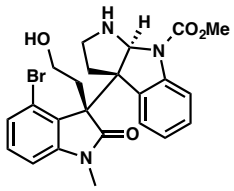
C(12)-C(13)-C(7)	112.19(7)
C(14)-C(13)-C(7)	109.36(7)
C(15)-C(14)-C(13)	116.88(8)
C(16)-C(15)-C(14)	123.95(11)
C(22)-C(17)-C(18)	114.45(9)
C(22)-C(17)-C(13)	128.21(8)
C(18)-C(17)-C(13)	117.30(8)
C(19)-C(18)-C(17)	123.03(10)
C(20)-C(19)-C(18)	120.40(10)
C(21)-C(20)-C(19)	118.74(10)
C(20)-C(21)-C(22)	119.86(10)
C(21)-C(22)-C(17)	123.37(9)
C(21)-C(22)-N(2)	112.90(9)
C(17)-C(22)-N(2)	123.65(8)

Symmetry transformations used to generate equivalent atoms:

Table A2.7.4. *Anisotropic displacement parameters ($Å^2 x\ 10^4$) for* ***62****. The anisotropic displacement factorexponent takes the form: $-2p^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	163(1)	167(1)	105(1)	41(1)	8(1)	33(1)
O(1)	154(3)	265(4)	81(3)	-9(3)	-27(3)	-9(3)
O(2)	166(3)	173(3)	96(3)	-45(3)	20(3)	-31(3)
O(3)	132(3)	170(3)	115(3)	6(2)	34(3)	1(3)
O(4)	182(4)	119(3)	161(3)	-8(2)	7(3)	-30(3)
O(5)	111(3)	226(4)	235(4)	-21(3)	9(3)	43(3)
N(1)	92(4)	177(4)	92(3)	20(3)	-10(3)	-1(3)
N(2)	135(4)	122(4)	108(3)	24(3)	-5(3)	14(3)
C(1)	99(4)	128(4)	92(4)	7(3)	0(3)	-8(3)
C(2)	148(5)	155(4)	88(4)	-3(3)	29(3)	-19(3)
C(3)	145(4)	134(4)	113(4)	-20(3)	41(3)	-17(3)
C(4)	115(4)	120(4)	141(4)	-1(3)	28(4)	-2(3)
C(5)	96(4)	118(4)	85(4)	12(3)	10(3)	-20(3)
C(6)	94(4)	120(4)	70(3)	1(3)	8(3)	-15(3)
C(7)	92(4)	138(4)	69(4)	-13(3)	2(3)	-7(3)
C(8)	96(4)	164(4)	102(4)	7(3)	-10(3)	-31(3)
C(9)	113(5)	217(5)	157(5)	36(4)	-33(4)	13(4)
C(10)	130(4)	137(4)	107(4)	-16(3)	13(3)	-34(3)
C(11)	160(5)	158(4)	120(4)	-43(3)	4(4)	-41(4)
C(12)	137(4)	119(4)	60(4)	2(3)	-3(3)	7(3)
C(13)	91(4)	105(4)	70(4)	-3(3)	-2(3)	-1(3)
C(14)	113(4)	134(4)	122(4)	26(3)	-8(3)	5(3)
C(15)	130(4)	142(5)	158(4)	45(3)	1(3)	0(3)
C(16)	203(6)	169(5)	299(6)	19(4)	21(5)	-23(4)
C(17)	91(4)	109(3)	75(3)	-1(3)	2(3)	-17(3)
C(18)	116(4)	137(4)	106(4)	-16(3)	9(3)	-9(3)
C(19)	159(4)	181(4)	114(5)	-54(3)	6(4)	-37(4)
C(20)	147(4)	262(5)	103(5)	-28(4)	-31(3)	-48(4)
C(21)	114(4)	189(5)	124(4)	21(3)	-30(3)	-10(4)
C(22)	104(4)	119(4)	93(3)	4(3)	2(3)	-3(3)

A2.8. X-Ray Crystal Structure Analysis of 72



72

Figure A2.8.1. *X-ray Crystal Structure of* ***72***

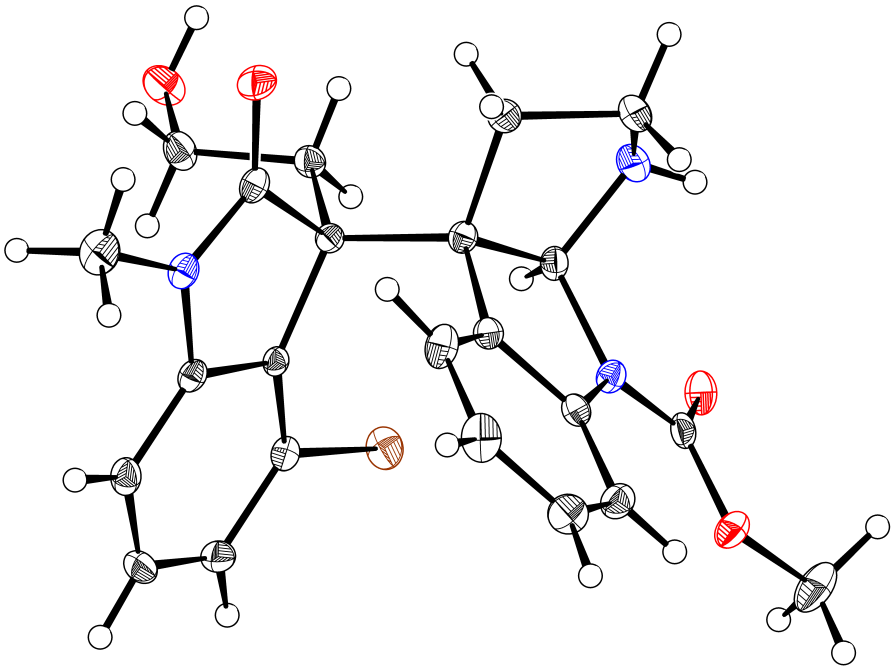


Table A2.8.1. *Crystal Data and Structure Analysis Details for* ***72***

Empirical formula	C23 H24 Br N3 O4
Formula weight	486.36
Crystal shape	plate
Crystal color	colourless
Crystal size	0.07 x 0.31 x 0.38 mm

Data Collection

Preliminary photograph(s)	rotation
Type of diffractometer	Bruker APEX-II CCD
Wavelength	0.71073 Å MoK
Data collection temperature	100 K
Theta range for 9871 reflections used	

in lattice determination	2.39 to 31.55°	
Unit cell dimensions	a = 8.9320(3) Å b = 27.1836(10) Å c = 9.0145(3) Å	a= 90° b= 107.683(2)° g = 90°
Volume	2085.34(13) $Å^3$	
Z	4	
Crystal system	monoclinic	
Space group	P 1 21/c 1 (# 14)	
Density (calculated)	1.549 g/cm^3	
F(000)	1000	
Theta range for data collection	2.4 to 37.5°	
Completeness to theta = 25.000°	99.9%	
Index ranges	-15 £ h £ 14, -46 £ k £ 45, -15 £ l £ 15	
Data collection scan type	and scans	
Reflections collected	104508	
Independent reflections	10606 [R_{int}= 0.0574]	
Reflections > 2s(I)	8291	
Average s(I)/(net I)	0.0362	
Absorption coefficient	2.01 mm^{-1}	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.8324	

Structure Solution and Refinement

Primary solution method	dual
Secondary solution method	?
Hydrogen placement	?
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	10606 / 0 / 376
Treatment of hydrogen atoms	refall
Goodness-of-fit on F^2	2.53
Final R indices [I>2s(I), 8291 reflections]	R1 = 0.0470, wR2 = 0.0646
R indices (all data)	R1 = 0.0694, wR2 = 0.0654
Type of weighting scheme used	calc
Weighting scheme used	
Max shift/error	0.001
Average shift/error	0.000
Extinction coefficient	0
Largest diff. peak and hole	1.86 and -1.09 $e·Å^{-3}$

Programs Used

Cell refinement	SAINT V8.27B (Bruker-AXS, 2007)
Data collection	APEX2 2012.4-3 (Bruker-AXS, 2007)
Data reduction	SAINT V8.27B (Bruker-AXS, 2007)
Structure solution	SHELXT (Sheldrick, 2012)
Structure refinement	SHELXL-2012/6 (Sheldrick, 2012)
Graphics	DIAMOND 3 (Crystal Impact, 1999)

References

Special Refinement Details

Table A2.8.2. *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for* ***72****. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor*

	x	y	z	U_{eq}
Br(1)	5616(1)	9528(1)	3588(1)	20(1)
O(1)	3320(1)	7660(1)	145(1)	19(1)
O(2)	2094(1)	8263(1)	4223(1)	22(1)
O(3)	10340(1)	9430(1)	2851(1)	18(1)
O(4)	9696(1)	9118(1)	4907(1)	18(1)
N(1)	2670(1)	8410(1)	-1033(1)	14(1)
N(2)	8487(1)	8844(1)	2459(1)	13(1)
N(3)	8419(2)	8060(1)	3813(1)	22(1)
C(1)	4542(1)	8418(1)	1464(1)	11(1)
C(2)	4040(1)	8938(1)	883(1)	11(1)
C(3)	4320(1)	9405(1)	1519(1)	14(1)
C(4)	3606(2)	9819(1)	682(2)	17(1)
C(5)	2602(2)	9765(1)	-815(2)	19(1)
C(6)	2257(2)	9306(1)	-1492(2)	16(1)
C(7)	2966(1)	8906(1)	-616(1)	12(1)
C(8)	3461(1)	8107(1)	138(1)	13(1)
C(9)	1534(2)	8243(1)	-2468(2)	21(1)
C(10)	4148(2)	8288(1)	2965(2)	14(1)
C(11)	2418(2)	8357(1)	2804(2)	19(1)
C(12)	6299(1)	8286(1)	1562(1)	12(1)
C(13)	6798(1)	8517(1)	248(1)	13(1)
C(14)	6207(2)	8430(1)	-1338(2)	18(1)
C(15)	6884(2)	8664(1)	-2346(2)	22(1)
C(16)	8156(2)	8973(1)	-1769(2)	20(1)
C(17)	8787(2)	9058(1)	-176(2)	17(1)
C(18)	8085(1)	8827(1)	816(1)	13(1)
C(19)	7546(1)	8484(1)	3051(1)	13(1)
C(20)	8360(2)	7697(1)	2606(2)	23(1)
C(21)	6642(2)	7726(1)	1632(2)	17(1)
C(22)	9528(1)	9132(1)	3521(2)	14(1)
C(23)	11536(2)	9722(1)	3929(2)	27(1)

Table A2.8.3. *Bond lengths [Å] and angles [°] for* ***72***

Br(1)-C(3)	1.9025(13)
O(1)-C(8)	1.2203(15)

O(2)-H(2)	0.856(18)
O(2)-C(11)	1.4180(16)
O(3)-C(22)	1.3461(15)
O(3)-C(23)	1.4446(17)
O(4)-C(22)	1.2132(15)
N(1)-C(7)	1.4020(16)
N(1)-C(8)	1.3567(16)
N(1)-C(9)	1.4531(16)
N(2)-C(18)	1.4145(15)
N(2)-C(19)	1.4905(16)
N(2)-C(22)	1.3609(16)
N(3)-H(3)	0.760(18)
N(3)-C(19)	1.4455(17)
N(3)-C(20)	1.457(2)
C(1)-C(2)	1.5279(16)
C(1)-C(8)	1.5399(17)
C(1)-C(10)	1.5387(17)
C(1)-C(12)	1.5856(17)
C(2)-C(3)	1.3835(17)
C(2)-C(7)	1.4026(16)
C(3)-C(4)	1.3978(18)
C(4)-H(4)	0.939(15)
C(4)-C(5)	1.3829(19)
C(5)-H(5)	0.921(16)
C(5)-C(6)	1.381(2)
C(6)-H(6)	0.925(14)
C(6)-C(7)	1.3800(18)
C(9)-H(9A)	0.960(17)
C(9)-H(9B)	0.961(16)
C(9)-H(9C)	0.996(17)
C(10)-H(10A)	0.897(13)
C(10)-H(10B)	0.984(15)
C(10)-C(11)	1.5195(18)
C(11)-H(11A)	0.946(16)
C(11)-H(11B)	0.983(15)
C(12)-C(13)	1.5211(17)
C(12)-C(19)	1.5569(17)
C(12)-C(21)	1.5515(17)
C(13)-C(14)	1.3857(17)
C(13)-C(18)	1.3912(17)
C(14)-H(14)	0.954(15)
C(14)-C(15)	1.3886(19)
C(15)-H(15)	0.888(15)
C(15)-C(16)	1.382(2)
C(16)-H(16)	0.952(13)
C(16)-C(17)	1.3941(19)
C(17)-H(17)	0.913(14)
C(17)-C(18)	1.3892(17)
C(19)-H(19)	0.943(12)
C(20)-H(20A)	0.974(15)
C(20)-H(20B)	0.997(14)
C(20)-C(21)	1.5206(19)
C(21)-H(21A)	0.939(13)
C(21)-H(21B)	0.956(14)
C(23)-H(23A)	0.931(16)
C(23)-H(23B)	0.962(15)
C(23)-H(23C)	1.013(16)

C(11)-O(2)-H(2)	108.4(11)
C(22)-O(3)-C(23)	114.73(11)
C(7)-N(1)-C(9)	124.25(11)
C(8)-N(1)-C(7)	111.34(10)
C(8)-N(1)-C(9)	124.10(11)
C(18)-N(2)-C(19)	111.20(10)
C(22)-N(2)-C(18)	131.13(11)
C(22)-N(2)-C(19)	117.66(10)
C(19)-N(3)-H(3)	110.4(14)
C(19)-N(3)-C(20)	107.07(11)
C(20)-N(3)-H(3)	110.6(14)
C(2)-C(1)-C(8)	101.12(9)
C(2)-C(1)-C(10)	113.01(10)
C(2)-C(1)-C(12)	114.20(10)
C(8)-C(1)-C(12)	107.26(9)
C(10)-C(1)-C(8)	107.47(10)
C(10)-C(1)-C(12)	112.73(10)
C(3)-C(2)-C(1)	135.27(11)
C(3)-C(2)-C(7)	116.19(11)
C(7)-C(2)-C(1)	108.38(10)
C(2)-C(3)-Br(1)	123.18(9)
C(2)-C(3)-C(4)	121.36(12)
C(4)-C(3)-Br(1)	115.42(9)
C(3)-C(4)-H(4)	117.3(9)
C(5)-C(4)-C(3)	119.63(13)
C(5)-C(4)-H(4)	123.1(9)
C(4)-C(5)-H(5)	117.6(10)
C(6)-C(5)-C(4)	121.31(12)
C(6)-C(5)-H(5)	121.0(10)
C(5)-C(6)-H(6)	123.9(9)
C(7)-C(6)-C(5)	117.20(12)
C(7)-C(6)-H(6)	118.9(9)
N(1)-C(7)-C(2)	109.69(10)
C(6)-C(7)-N(1)	126.00(11)
C(6)-C(7)-C(2)	124.23(12)
O(1)-C(8)-N(1)	125.30(12)
O(1)-C(8)-C(1)	125.66(11)
N(1)-C(8)-C(1)	109.04(10)
N(1)-C(9)-H(9A)	105.5(10)
N(1)-C(9)-H(9B)	108.1(10)
N(1)-C(9)-H(9C)	111.5(10)
H(9A)-C(9)-H(9B)	108.5(13)
H(9A)-C(9)-H(9C)	112.9(13)
H(9B)-C(9)-H(9C)	110.0(13)
C(1)-C(10)-H(10A)	110.7(8)
C(1)-C(10)-H(10B)	110.0(8)
H(10A)-C(10)-H(10B)	108.0(12)
C(11)-C(10)-C(1)	112.66(10)
C(11)-C(10)-H(10A)	108.2(8)
C(11)-C(10)-H(10B)	107.2(8)
O(2)-C(11)-C(10)	111.85(11)
O(2)-C(11)-H(11A)	104.6(9)
O(2)-C(11)-H(11B)	109.4(8)
C(10)-C(11)-H(11A)	110.7(9)
C(10)-C(11)-H(11B)	110.9(8)
H(11A)-C(11)-H(11B)	109.2(12)
C(13)-C(12)-C(1)	112.53(10)
C(13)-C(12)-C(19)	103.10(10)

C(13)-C(12)-C(21)	109.61(10)
C(19)-C(12)-C(1)	114.00(10)
C(21)-C(12)-C(1)	113.78(10)
C(21)-C(12)-C(19)	102.92(10)
C(14)-C(13)-C(12)	128.56(11)
C(14)-C(13)-C(18)	119.71(11)
C(18)-C(13)-C(12)	111.60(10)
C(13)-C(14)-H(14)	119.7(9)
C(13)-C(14)-C(15)	119.53(13)
C(15)-C(14)-H(14)	120.6(9)
C(14)-C(15)-H(15)	116.8(10)
C(16)-C(15)-C(14)	120.22(13)
C(16)-C(15)-H(15)	122.9(10)
C(15)-C(16)-H(16)	116.3(8)
C(15)-C(16)-C(17)	121.18(13)
C(17)-C(16)-H(16)	122.5(8)
C(16)-C(17)-H(17)	120.7(8)
C(18)-C(17)-C(16)	117.89(12)
C(18)-C(17)-H(17)	121.4(8)
C(13)-C(18)-N(2)	108.90(10)
C(17)-C(18)-N(2)	129.64(11)
C(17)-C(18)-C(13)	121.45(11)
N(2)-C(19)-C(12)	104.58(9)
N(2)-C(19)-H(19)	104.9(8)
N(3)-C(19)-N(2)	114.37(10)
N(3)-C(19)-C(12)	105.97(11)
N(3)-C(19)-H(19)	111.9(8)
C(12)-C(19)-H(19)	115.2(8)
N(3)-C(20)-H(20A)	109.9(9)
N(3)-C(20)-H(20B)	116.1(8)
N(3)-C(20)-C(21)	101.40(11)
H(20A)-C(20)-H(20B)	107.2(11)
C(21)-C(20)-H(20A)	113.9(9)
C(21)-C(20)-H(20B)	108.4(8)
C(12)-C(21)-H(21A)	110.3(8)
C(12)-C(21)-H(21B)	113.5(9)
C(20)-C(21)-C(12)	103.11(11)
C(20)-C(21)-H(21A)	108.7(8)
C(20)-C(21)-H(21B)	112.2(8)
H(21A)-C(21)-H(21B)	108.8(12)
O(3)-C(22)-N(2)	112.08(11)
O(4)-C(22)-O(3)	124.48(12)
O(4)-C(22)-N(2)	123.44(12)
O(3)-C(23)-H(23A)	112.0(11)
O(3)-C(23)-H(23B)	103.6(9)
O(3)-C(23)-H(23C)	107.6(9)
H(23A)-C(23)-H(23B)	106.2(13)
H(23A)-C(23)-H(23C)	112.2(13)
H(23B)-C(23)-H(23C)	115.1(12)

Symmetry transformations used to generate equivalent atoms:

Table A2.8.4. *Anisotropic displacement parameters ($Å^2 x\ 10^4$) for **72**. The anisotropic displacement factor exponent takes the form: $-2p^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$*

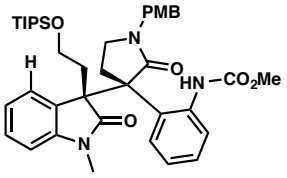
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	189(1)	189(1)	183(1)	-71(1)	-12(1)	-6(1)
O(1)	199(5)	132(5)	234(5)	-45(4)	54(4)	-35(4)
O(2)	251(5)	251(6)	230(5)	92(4)	159(4)	86(4)
O(3)	150(4)	180(5)	203(5)	-31(4)	41(4)	-51(3)
O(4)	139(4)	245(5)	136(4)	-30(4)	9(4)	8(4)
N(1)	123(5)	170(5)	100(5)	-24(4)	12(4)	-24(4)
N(2)	114(5)	152(5)	116(5)	-3(4)	26(4)	-17(4)
N(3)	163(6)	211(6)	235(6)	66(5)	-25(5)	12(5)
C(1)	110(5)	111(5)	115(5)	-8(4)	25(4)	-6(4)
C(2)	88(5)	125(6)	111(5)	6(4)	42(4)	0(4)
C(3)	108(5)	153(6)	143(6)	-18(5)	37(4)	-9(5)
C(4)	161(6)	126(6)	236(7)	6(5)	71(5)	-2(5)
C(5)	161(6)	181(7)	218(7)	86(5)	54(5)	38(5)
C(6)	124(6)	231(7)	134(6)	43(5)	30(5)	3(5)
C(7)	109(5)	158(6)	111(6)	-2(5)	49(4)	-19(4)
C(8)	114(6)	165(6)	126(6)	-23(5)	56(5)	-15(4)
C(9)	216(7)	265(8)	122(6)	-53(6)	-6(5)	-40(6)
C(10)	134(6)	151(6)	119(6)	20(5)	39(5)	9(5)
C(11)	160(6)	247(7)	188(7)	78(6)	91(5)	60(6)
C(12)	115(6)	135(6)	128(6)	-6(4)	45(5)	-1(4)
C(13)	121(6)	129(6)	142(6)	-3(5)	55(5)	11(4)
C(14)	144(6)	250(7)	165(6)	-53(5)	55(5)	-14(5)
C(15)	216(7)	320(8)	112(6)	-31(6)	57(5)	15(6)
C(16)	222(7)	242(7)	177(7)	32(6)	118(6)	20(6)
C(17)	153(6)	171(6)	191(7)	-5(5)	74(5)	-13(5)
C(18)	119(6)	128(6)	131(6)	-2(4)	40(5)	25(4)
C(19)	103(5)	172(6)	119(6)	19(5)	29(5)	4(5)
C(20)	158(7)	180(7)	362(9)	62(6)	77(6)	53(5)
C(21)	155(6)	137(6)	235(7)	-3(5)	78(5)	13(5)
C(22)	91(5)	142(6)	188(6)	-16(5)	28(5)	31(4)
C(23)	209(8)	299(8)	313(9)	-133(7)	93(7)	-119(6)

Table A2.8.5. *Hydrogen coordinates (x 10^3) and isotropic displacement parameters ($Å^2$ x 10^3) for* ***72***

	x	y	z	U_{iso}
H(2)	241(2)	797(1)	452(2)	42(5)
H(3)	926(2)	813(1)	424(2)	37(5)
H(4)	383(2)	1013(1)	119(2)	20(4)
H(5)	219(2)	1005(1)	-136(2)	30(4)
H(6)	159(2)	925(1)	-249(2)	18(4)
H(9A)	172(2)	790(1)	-252(2)	33(5)
H(9B)	176(2)	840(1)	-332(2)	32(5)
H(9C)	44(2)	832(1)	-248(2)	36(5)
H(10A)	441(1)	798(1)	324(2)	9(3)
H(10B)	475(2)	850(1)	382(2)	21(4)
H(11A)	211(2)	869(1)	257(2)	26(4)
H(11B)	176(2)	814(1)	198(2)	21(4)
H(14)	539(2)	819(1)	-172(2)	21(4)
H(15)	645(2)	861(1)	-336(2)	23(4)
H(16)	856(2)	913(1)	-252(2)	15(4)
H(17)	963(2)	926(1)	20(2)	12(3)

H(19)	714(1)	867(1)	373(1)	7(3)
H(20A)	868(2)	738(1)	308(2)	23(4)
H(20B)	902(2)	777(1)	192(2)	15(4)
H(21A)	603(2)	756(1)	216(2)	10(3)
H(21B)	646(2)	758(1)	63(2)	18(4)
H(23A)	1111(2)	996(1)	442(2)	35(5)
H(23B)	1202(2)	990(1)	327(2)	21(4)
H(23C)	1226(2)	949(1)	470(2)	30(4)

A2.9. X-Ray Crystal Structure Analysis of 73



73

Figure A2.9.1. *X-ray Crystal Structure of* ***73***

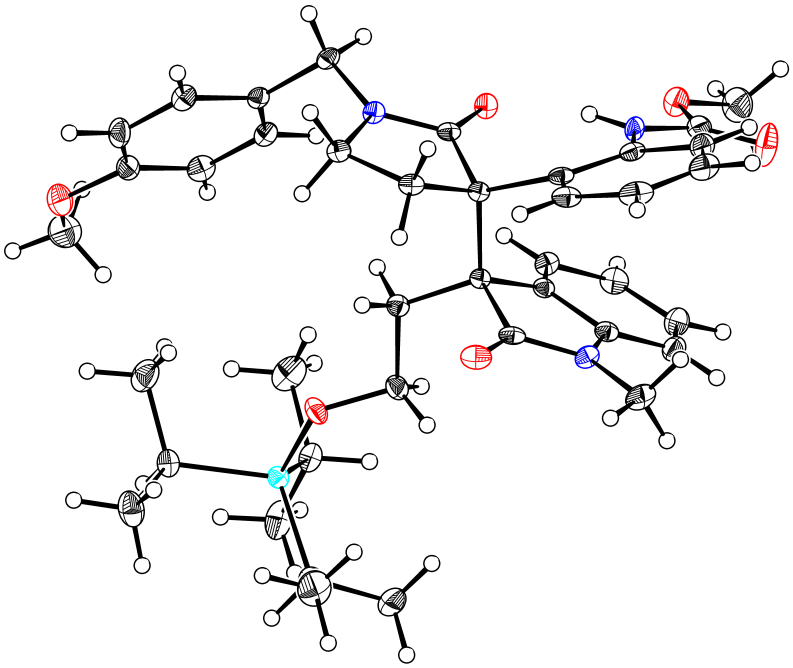


Table A2.9.1. *Crystal Data and Structure Analysis Details for* ***73***

Empirical formula	C40 H53 N3 O6 Si
Formula weight	699.94
Crystal shape	plate
Crystal color	colourless
Crystal size	0.04 x 0.20 x 0.20 mm

Data Collection

Preliminary photograph(s)	rotation
Type of diffractometer	Bruker APEX-II CCD
Wavelength	0.71073 Å MoK
Data collection temperature	100 K

Theta range for 9937 reflections used in lattice determination	2.40 to 30.23°	
Unit cell dimensions	a = 23.3177(12) Å b = 8.7021(4) Å c = 37.035(2) Å	a= 90° b= 94.394(3)° g = 90°
Volume	7492.8(7) $Å^3$	
Z	8	
Crystal system	monoclinic	
Space group	I 1 2/a 1 (# 15)	
Density (calculated)	1.241 g/cm^3	
F(000)	3008	
Theta range for data collection	2.4 to 35.0°	
Completeness to theta = 25.000°	99.9%	
Index ranges	-36 £ h £ 37, -13 £ k £ 13, -59 £ l £ 58	
Data collection scan type	and scans	
Reflections collected	146937	
Independent reflections	15890 [R_{int}= 0.1927]	
Reflections > 2s(I)	8277	
Average s(I)/(net I)	0.1381	
Absorption coefficient	0.11 mm^{-1}	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.9156	

Structure Solution and Refinement

Primary solution method	dual
Secondary solution method	?
Hydrogen placement	geom
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	15890 / 0 / 460
Treatment of hydrogen atoms	constr
Goodness-of-fit on F^2	1.25
Final R indices [I>2s(I), 8277 reflections]	R1 = 0.0718, wR2 = 0.1071
R indices (all data)	R1 = 0.1715, wR2 = 0.1233
Type of weighting scheme used	calc
Weighting scheme used	
Max shift/error	0.000
Average shift/error	0.000
Extinction coefficient	n/a
Largest diff. peak and hole	0.55 and -0.53 e·$Å^{-3}$

Programs Used

Cell refinement	SAINT V8.27B (Bruker-AXS, 2007)
Data collection	APEX2 2012.4-3 (Bruker-AXS, 2007)
Data reduction	SAINT V8.27B (Bruker-AXS, 2007)
Structure solution	SHELXT (Sheldrick, 2012)
Structure refinement	SHELXL-2013/2 (Sheldrick, 2013)
Graphics	DIAMOND 3 (Crystal Impact, 1999)

References

Special Refinement Details

Table A2.9.2. *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for* ***73****. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor*

	x	y	z	U_{eq}
Si(1)	3732(1)	673(1)	2268(1)	13(1)
O(1)	2790(1)	-3775(1)	1228(1)	19(1)
O(2)	3562(1)	-65(1)	1866(1)	18(1)
O(3)	793(1)	2007(1)	470(1)	20(1)
O(4)	337(1)	-285(1)	450(1)	34(1)
O(5)	2274(1)	1556(1)	486(1)	16(1)
O(6)	5052(1)	5085(1)	1358(1)	26(1)
N(1)	1864(1)	-2960(1)	1280(1)	14(1)
N(2)	1318(1)	-73(1)	418(1)	14(1)
N(3)	3199(1)	803(1)	470(1)	13(1)
C(1)	2509(1)	-1080(2)	1090(1)	12(1)
C(2)	1946(1)	-370(2)	1189(1)	12(1)
C(3)	1770(1)	1145(2)	1210(1)	15(1)
C(4)	1220(1)	1458(2)	1310(1)	19(1)
C(5)	854(1)	271(2)	1390(1)	20(1)
C(6)	1027(1)	-1258(2)	1380(1)	18(1)
C(7)	1575(1)	-1538(2)	1283(1)	14(1)
C(8)	2421(1)	-2773(2)	1207(1)	13(1)
C(9)	1600(1)	-4446(2)	1329(1)	21(1)
C(10)	3042(1)	-416(2)	1301(1)	14(1)
C(11)	2999(1)	-378(2)	1707(1)	18(1)
C(12)	2572(1)	-1120(2)	660(1)	11(1)
C(13)	2066(1)	-2081(2)	478(1)	13(1)
C(14)	2184(1)	-3655(2)	434(1)	18(1)
C(15)	1776(1)	-4714(2)	307(1)	23(1)
C(16)	1224(1)	-4227(2)	207(1)	24(1)
C(17)	1084(1)	-2692(2)	246(1)	20(1)
C(18)	1491(1)	-1618(2)	387(1)	14(1)
C(19)	2649(1)	553(2)	526(1)	12(1)
C(20)	3583(1)	-490(2)	547(1)	14(1)
C(21)	3161(1)	-1825(2)	574(1)	14(1)
C(22)	776(1)	440(2)	446(1)	19(1)
C(23)	254(1)	2706(2)	538(1)	31(1)
C(24)	3582(1)	-777(2)	2628(1)	21(1)
C(25)	3734(1)	-2424(2)	2519(1)	34(1)
C(26)	2957(1)	-746(2)	2726(1)	29(1)
C(27)	3303(1)	2471(2)	2331(1)	19(1)

C(28)	3433(1)	3174(2)	2709(1)	28(1)
C(29)	3380(1)	3672(2)	2034(1)	31(1)
C(30)	4519(1)	1125(2)	2262(1)	17(1)
C(31)	4674(1)	1762(2)	1896(1)	28(1)
C(32)	4920(1)	-219(2)	2369(1)	28(1)
C(33)	3412(1)	2292(2)	352(1)	14(1)
C(34)	3837(1)	3026(2)	627(1)	13(1)
C(35)	4426(1)	2770(2)	618(1)	18(1)
C(36)	4818(1)	3460(2)	866(1)	21(1)
C(37)	4626(1)	4444(2)	1127(1)	18(1)
C(38)	4044(1)	4715(2)	1142(1)	19(1)
C(39)	3654(1)	3996(2)	894(1)	16(1)
C(40)	4878(1)	6187(2)	1612(1)	32(1)

Table A2.9.3. *Bond lengths [Å] and angles [°] for* ***73***

Si(1)-O(2)	1.6433(11)
Si(1)-C(24)	1.8858(17)
Si(1)-C(27)	1.8806(17)
Si(1)-C(30)	1.8786(16)
O(1)-C(8)	1.2233(18)
O(2)-C(11)	1.4245(18)
O(3)-C(22)	1.367(2)
O(3)-C(23)	1.437(2)
O(4)-C(22)	1.2031(19)
O(5)-C(19)	1.2376(17)
O(6)-C(37)	1.3796(18)
O(6)-C(40)	1.425(2)
N(1)-C(7)	1.4092(19)
N(1)-C(8)	1.358(2)
N(1)-C(9)	1.4496(19)
N(2)-H(2)	0.8800
N(2)-C(18)	1.4106(19)
N(2)-C(22)	1.353(2)
N(3)-C(19)	1.3318(19)
N(3)-C(20)	1.4511(19)
N(3)-C(33)	1.4668(18)
C(1)-C(2)	1.519(2)
C(1)-C(8)	1.554(2)
C(1)-C(10)	1.530(2)
C(1)-C(12)	1.609(2)
C(2)-C(3)	1.385(2)
C(2)-C(7)	1.397(2)
C(3)-H(3)	0.9500
C(3)-C(4)	1.390(2)
C(4)-H(4)	0.9500
C(4)-C(5)	1.385(2)
C(5)-H(5)	0.9500
C(5)-C(6)	1.392(2)
C(6)-H(6)	0.9500
C(6)-C(7)	1.375(2)
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-H(10A)	0.9900

C(10)-H(10B)	0.9900
C(10)-C(11)	1.513(2)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(13)	1.558(2)
C(12)-C(19)	1.553(2)
C(12)-C(21)	1.560(2)
C(13)-C(14)	1.409(2)
C(13)-C(18)	1.416(2)
C(14)-H(14)	0.9500
C(14)-C(15)	1.381(2)
C(15)-H(15)	0.9500
C(15)-C(16)	1.377(2)
C(16)-H(16)	0.9500
C(16)-C(17)	1.386(2)
C(17)-H(17)	0.9500
C(17)-C(18)	1.404(2)
C(20)-H(20A)	0.9900
C(20)-H(20B)	0.9900
C(20)-C(21)	1.529(2)
C(21)-H(21A)	0.9900
C(21)-H(21B)	0.9900
C(23)-H(23A)	0.9800
C(23)-H(23B)	0.9800
C(23)-H(23C)	0.9800
C(24)-H(24)	1.0000
C(24)-C(25)	1.537(2)
C(24)-C(26)	1.529(2)
C(25)-H(25A)	0.9800
C(25)-H(25B)	0.9800
C(25)-H(25C)	0.9800
C(26)-H(26A)	0.9800
C(26)-H(26B)	0.9800
C(26)-H(26C)	0.9800
C(27)-H(27)	1.0000
C(27)-C(28)	1.536(2)
C(27)-C(29)	1.538(2)
C(28)-H(28A)	0.9800
C(28)-H(28B)	0.9800
C(28)-H(28C)	0.9800
C(29)-H(29A)	0.9800
C(29)-H(29B)	0.9800
C(29)-H(29C)	0.9800
C(30)-H(30)	1.0000
C(30)-C(31)	1.533(2)
C(30)-C(32)	1.531(2)
C(31)-H(31A)	0.9800
C(31)-H(31B)	0.9800
C(31)-H(31C)	0.9800
C(32)-H(32A)	0.9800
C(32)-H(32B)	0.9800
C(32)-H(32C)	0.9800
C(33)-H(33A)	0.9900
C(33)-H(33B)	0.9900
C(33)-C(34)	1.507(2)
C(34)-C(35)	1.394(2)
C(34)-C(39)	1.391(2)
C(35)-H(35)	0.9500

C(35)-C(36)	1.383(2)
C(36)-H(36)	0.9500
C(36)-C(37)	1.389(2)
C(37)-C(38)	1.382(2)
C(38)-H(38)	0.9500
C(38)-C(39)	1.388(2)
C(39)-H(39)	0.9500
C(40)-H(40A)	0.9800
C(40)-H(40B)	0.9800
C(40)-H(40C)	0.9800

O(2)-Si(1)-C(24)	109.49(7)
O(2)-Si(1)-C(27)	110.14(7)
O(2)-Si(1)-C(30)	103.79(7)
C(27)-Si(1)-C(24)	109.92(8)
C(30)-Si(1)-C(24)	112.46(7)
C(30)-Si(1)-C(27)	110.87(7)
C(11)-O(2)-Si(1)	126.94(10)
C(22)-O(3)-C(23)	114.30(13)
C(37)-O(6)-C(40)	116.98(14)
C(7)-N(1)-C(9)	125.13(13)
C(8)-N(1)-C(7)	111.14(12)
C(8)-N(1)-C(9)	123.66(13)
C(18)-N(2)-H(2)	116.7
C(22)-N(2)-H(2)	116.7
C(22)-N(2)-C(18)	126.52(13)
C(19)-N(3)-C(20)	115.41(12)
C(19)-N(3)-C(33)	122.84(12)
C(20)-N(3)-C(33)	121.72(12)
C(2)-C(1)-C(8)	100.58(12)
C(2)-C(1)-C(10)	113.97(12)
C(2)-C(1)-C(12)	113.17(11)
C(8)-C(1)-C(12)	106.16(11)
C(10)-C(1)-C(8)	109.56(12)
C(10)-C(1)-C(12)	112.38(12)
C(3)-C(2)-C(1)	131.70(14)
C(3)-C(2)-C(7)	119.12(14)
C(7)-C(2)-C(1)	109.13(13)
C(2)-C(3)-H(3)	120.5
C(2)-C(3)-C(4)	119.00(15)
C(4)-C(3)-H(3)	120.5
C(3)-C(4)-H(4)	119.8
C(5)-C(4)-C(3)	120.47(15)
C(5)-C(4)-H(4)	119.8
C(4)-C(5)-H(5)	119.2
C(4)-C(5)-C(6)	121.55(15)
C(6)-C(5)-H(5)	119.2
C(5)-C(6)-H(6)	121.6
C(7)-C(6)-C(5)	116.89(15)
C(7)-C(6)-H(6)	121.6
C(2)-C(7)-N(1)	109.37(13)
C(6)-C(7)-N(1)	127.66(14)
C(6)-C(7)-C(2)	122.89(14)
O(1)-C(8)-N(1)	125.48(14)
O(1)-C(8)-C(1)	125.94(14)
N(1)-C(8)-C(1)	108.58(13)
N(1)-C(9)-H(9A)	109.5
N(1)-C(9)-H(9B)	109.5

N(1)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(1)-C(10)-H(10A)	108.8
C(1)-C(10)-H(10B)	108.8
H(10A)-C(10)-H(10B)	107.7
C(11)-C(10)-C(1)	113.76(13)
C(11)-C(10)-H(10A)	108.8
C(11)-C(10)-H(10B)	108.8
O(2)-C(11)-C(10)	106.68(13)
O(2)-C(11)-H(11A)	110.4
O(2)-C(11)-H(11B)	110.4
C(10)-C(11)-H(11A)	110.4
C(10)-C(11)-H(11B)	110.4
H(11A)-C(11)-H(11B)	108.6
C(13)-C(12)-C(1)	108.45(12)
C(13)-C(12)-C(21)	110.47(12)
C(19)-C(12)-C(1)	108.49(11)
C(19)-C(12)-C(13)	117.86(12)
C(19)-C(12)-C(21)	100.20(12)
C(21)-C(12)-C(1)	111.17(11)
C(14)-C(13)-C(12)	115.09(13)
C(14)-C(13)-C(18)	116.05(14)
C(18)-C(13)-C(12)	128.49(13)
C(13)-C(14)-H(14)	118.2
C(15)-C(14)-C(13)	123.52(16)
C(15)-C(14)-H(14)	118.2
C(14)-C(15)-H(15)	120.3
C(16)-C(15)-C(14)	119.42(16)
C(16)-C(15)-H(15)	120.3
C(15)-C(16)-H(16)	120.3
C(15)-C(16)-C(17)	119.44(15)
C(17)-C(16)-H(16)	120.3
C(16)-C(17)-H(17)	119.2
C(16)-C(17)-C(18)	121.51(16)
C(18)-C(17)-H(17)	119.2
N(2)-C(18)-C(13)	121.55(13)
C(17)-C(18)-N(2)	118.41(14)
C(17)-C(18)-C(13)	119.97(14)
O(5)-C(19)-N(3)	123.16(14)
O(5)-C(19)-C(12)	126.97(14)
N(3)-C(19)-C(12)	109.83(12)
N(3)-C(20)-H(20A)	111.3
N(3)-C(20)-H(20B)	111.3
N(3)-C(20)-C(21)	102.24(12)
H(20A)-C(20)-H(20B)	109.2
C(21)-C(20)-H(20A)	111.3
C(21)-C(20)-H(20B)	111.3
C(12)-C(21)-H(21A)	110.3
C(12)-C(21)-H(21B)	110.3
C(20)-C(21)-C(12)	107.14(12)
C(20)-C(21)-H(21A)	110.3
C(20)-C(21)-H(21B)	110.3
H(21A)-C(21)-H(21B)	108.5
O(4)-C(22)-O(3)	122.93(16)
O(4)-C(22)-N(2)	128.98(16)
N(2)-C(22)-O(3)	108.09(13)

O(3)-C(23)-H(23A)	109.5
O(3)-C(23)-H(23B)	109.5
O(3)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
Si(1)-C(24)-H(24)	107.6
C(25)-C(24)-Si(1)	112.36(12)
C(25)-C(24)-H(24)	107.6
C(26)-C(24)-Si(1)	112.77(11)
C(26)-C(24)-H(24)	107.6
C(26)-C(24)-C(25)	108.78(14)
C(24)-C(25)-H(25A)	109.5
C(24)-C(25)-H(25B)	109.5
C(24)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25B)	109.5
H(25A)-C(25)-H(25C)	109.5
H(25B)-C(25)-H(25C)	109.5
C(24)-C(26)-H(26A)	109.5
C(24)-C(26)-H(26B)	109.5
C(24)-C(26)-H(26C)	109.5
H(26A)-C(26)-H(26B)	109.5
H(26A)-C(26)-H(26C)	109.5
H(26B)-C(26)-H(26C)	109.5
Si(1)-C(27)-H(27)	107.0
C(28)-C(27)-Si(1)	111.98(12)
C(28)-C(27)-H(27)	107.0
C(28)-C(27)-C(29)	110.83(14)
C(29)-C(27)-Si(1)	112.62(12)
C(29)-C(27)-H(27)	107.0
C(27)-C(28)-H(28A)	109.5
C(27)-C(28)-H(28B)	109.5
C(27)-C(28)-H(28C)	109.5
H(28A)-C(28)-H(28B)	109.5
H(28A)-C(28)-H(28C)	109.5
H(28B)-C(28)-H(28C)	109.5
C(27)-C(29)-H(29A)	109.5
C(27)-C(29)-H(29B)	109.5
C(27)-C(29)-H(29C)	109.5
H(29A)-C(29)-H(29B)	109.5
H(29A)-C(29)-H(29C)	109.5
H(29B)-C(29)-H(29C)	109.5
Si(1)-C(30)-H(30)	106.8
C(31)-C(30)-Si(1)	112.51(11)
C(31)-C(30)-H(30)	106.8
C(32)-C(30)-Si(1)	114.51(11)
C(32)-C(30)-H(30)	106.8
C(32)-C(30)-C(31)	108.92(14)
C(30)-C(31)-H(31A)	109.5
C(30)-C(31)-H(31B)	109.5
C(30)-C(31)-H(31C)	109.5
H(31A)-C(31)-H(31B)	109.5
H(31A)-C(31)-H(31C)	109.5
H(31B)-C(31)-H(31C)	109.5
C(30)-C(32)-H(32A)	109.5
C(30)-C(32)-H(32B)	109.5
C(30)-C(32)-H(32C)	109.5
H(32A)-C(32)-H(32B)	109.5

H(32A)-C(32)-H(32C)	109.5
H(32B)-C(32)-H(32C)	109.5
N(3)-C(33)-H(33A)	109.0
N(3)-C(33)-H(33B)	109.0
N(3)-C(33)-C(34)	113.08(12)
H(33A)-C(33)-H(33B)	107.8
C(34)-C(33)-H(33A)	109.0
C(34)-C(33)-H(33B)	109.0
C(35)-C(34)-C(33)	120.88(14)
C(39)-C(34)-C(33)	121.12(14)
C(39)-C(34)-C(35)	117.99(14)
C(34)-C(35)-H(35)	119.4
C(36)-C(35)-C(34)	121.12(15)
C(36)-C(35)-H(35)	119.4
C(35)-C(36)-H(36)	120.1
C(35)-C(36)-C(37)	119.81(15)
C(37)-C(36)-H(36)	120.1
O(6)-C(37)-C(36)	115.14(15)
O(6)-C(37)-C(38)	124.72(15)
C(38)-C(37)-C(36)	120.14(15)
C(37)-C(38)-H(38)	120.3
C(37)-C(38)-C(39)	119.46(15)
C(39)-C(38)-H(38)	120.3
C(34)-C(39)-H(39)	119.3
C(38)-C(39)-C(34)	121.46(15)
C(38)-C(39)-H(39)	119.3
O(6)-C(40)-H(40A)	109.5
O(6)-C(40)-H(40B)	109.5
O(6)-C(40)-H(40C)	109.5
H(40A)-C(40)-H(40B)	109.5
H(40A)-C(40)-H(40C)	109.5
H(40B)-C(40)-H(40C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table A2.9.4. *Anisotropic displacement parameters ($Å^2 x\ 10^4$) for **73**. The anisotropic displacement factor exponent takes the form: $-2p^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si(1)	140(2)	116(2)	135(2)	-12(2)	-3(2)	-6(2)
O(1)	266(6)	110(6)	194(6)	21(4)	21(5)	56(5)
O(2)	148(6)	238(6)	160(6)	-47(5)	-28(5)	6(5)
O(3)	166(6)	153(6)	292(7)	27(5)	31(5)	30(5)
O(4)	176(7)	275(7)	581(10)	-33(7)	54(6)	-87(6)
O(5)	154(6)	93(5)	220(6)	19(4)	7(5)	9(4)
O(6)	238(7)	285(7)	265(7)	-39(5)	-34(5)	-83(6)
N(1)	184(7)	74(6)	169(7)	7(5)	26(5)	-15(5)
N(2)	131(7)	104(6)	192(7)	9(5)	3(5)	-40(5)
N(3)	144(7)	68(6)	167(6)	14(5)	13(5)	5(5)
C(1)	132(7)	96(7)	117(7)	-3(6)	7(6)	0(6)
C(2)	142(8)	120(8)	102(7)	-10(6)	-1(6)	-8(6)
C(3)	181(8)	120(8)	151(8)	-15(6)	22(6)	-9(6)
C(4)	223(9)	149(8)	192(8)	-26(6)	29(7)	46(7)
C(5)	163(8)	221(9)	228(9)	-17(7)	53(7)	30(7)

C(6)	183(9)	184(9)	182(8)	0(6)	30(7)	-44(7)
C(7)	179(8)	117(8)	110(7)	-9(6)	-6(6)	-6(6)
C(8)	222(9)	92(7)	86(7)	-9(6)	2(6)	8(6)
C(9)	306(10)	103(8)	230(9)	16(7)	47(7)	-59(7)
C(10)	158(8)	136(8)	139(7)	-9(6)	4(6)	-4(6)
C(11)	164(8)	206(9)	153(8)	-24(6)	-15(6)	-19(7)
C(12)	143(8)	75(7)	117(7)	-6(5)	4(6)	4(6)
C(13)	215(8)	87(7)	94(7)	5(6)	13(6)	-23(6)
C(14)	279(9)	122(8)	123(8)	-3(6)	8(7)	-14(7)
C(15)	412(11)	106(8)	165(8)	-31(6)	36(8)	-64(8)
C(16)	362(11)	167(9)	189(9)	-36(7)	10(8)	-149(8)
C(17)	221(9)	201(9)	169(8)	-19(7)	5(7)	-78(7)
C(18)	219(8)	115(8)	103(7)	-1(6)	28(6)	-44(6)
C(19)	178(8)	90(7)	85(7)	-16(5)	6(6)	-11(6)
C(20)	151(8)	137(8)	150(7)	9(6)	31(6)	37(6)
C(21)	196(8)	84(7)	134(7)	-6(6)	18(6)	25(6)
C(22)	202(9)	208(9)	162(8)	10(7)	-8(7)	-47(7)
C(23)	218(10)	308(11)	402(12)	41(9)	43(8)	87(8)
C(24)	216(9)	186(9)	209(8)	36(7)	-21(7)	-49(7)
C(25)	378(12)	160(9)	488(13)	99(9)	-31(10)	-54(8)
C(26)	284(10)	310(10)	265(10)	55(8)	31(8)	-112(8)
C(27)	163(8)	170(9)	240(9)	-27(7)	47(7)	-15(7)
C(28)	233(10)	234(10)	378(11)	-146(8)	87(8)	-49(8)
C(29)	299(10)	205(10)	443(12)	72(8)	128(9)	89(8)
C(30)	147(8)	146(8)	211(8)	-31(6)	7(7)	2(6)
C(31)	200(9)	309(11)	341(11)	33(8)	94(8)	23(8)
C(32)	189(9)	215(9)	412(12)	4(8)	-35(8)	35(7)
C(33)	161(8)	92(7)	169(8)	30(6)	32(6)	-11(6)
C(34)	142(8)	91(7)	164(8)	29(6)	17(6)	0(6)
C(35)	170(8)	152(8)	211(8)	2(7)	50(7)	20(7)
C(36)	121(8)	237(9)	285(10)	19(7)	18(7)	16(7)
C(37)	185(8)	140(8)	206(8)	27(7)	-19(7)	-44(7)
C(38)	241(9)	117(8)	205(8)	-13(6)	34(7)	-7(7)
C(39)	146(8)	119(8)	207(8)	33(6)	43(6)	27(6)
C(40)	406(12)	303(11)	260(10)	-76(8)	-16(9)	-120(9)

Table A2.9.5. *Hydrogen coordinates (x 10^3) and isotropic displacement parameters (Å^{2}x 10^3) for* ***73***

	x	y	z	U_{iso}
H(2)	159	63	42	17
H(3)	202	196	116	18
H(4)	109	249	132	22
H(5)	48	51	145	24
H(6)	78	-207	144	22
H(9A)	135	-470	111	32
H(9B)	137	-441	154	32
H(9C)	190	-523	137	32
H(10A)	338	-104	125	17
H(10B)	311	64	122	17
H(11A)	273	44	177	21
H(11B)	286	-138	179	21
H(14)	256	-401	50	21
H(15)	187	-577	29	27

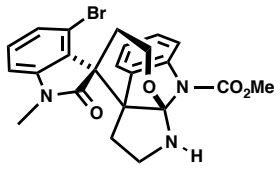
H(16)	94	-494	11	29
H(17)	70	-236	18	24
H(20A)	382	-34	78	17
H(20B)	384	-65	35	17
H(21A)	330	-254	77	17
H(21B)	312	-240	34	17
H(23A)	-3	250	33	46
H(23B)	31	382	57	46
H(23C)	12	228	76	46
H(24)	383	-51	285	25
H(25A)	367	-313	272	52
H(25B)	414	-246	246	52
H(25C)	349	-273	231	52
H(26A)	270	-96	251	43
H(26B)	287	27	282	43
H(26C)	290	-153	291	43
H(27)	289	217	231	23
H(28A)	384	351	274	42
H(28B)	337	240	289	42
H(28C)	318	406	274	42
H(29A)	311	451	206	47
H(29B)	331	319	180	47
H(29C)	377	408	206	47
H(30)	460	196	244	20
H(31A)	508	203	191	42
H(31B)	444	268	184	42
H(31C)	460	98	171	42
H(32A)	485	-106	220	41
H(32B)	484	-58	261	41
H(32C)	532	12	237	41
H(33A)	308	300	30	17
H(33B)	360	215	12	17
H(35)	456	211	44	21
H(36)	522	326	86	26
H(38)	391	539	132	22
H(39)	326	417	91	19
H(40A)	468	704	148	49
H(40B)	522	658	176	49
H(40C)	462	570	177	49

Table A2.9.6. *Hydrogen bonds for* ***73*** ***[Å and °]***

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2)-H(2)...O(5)	0.88	1.79	2.6356(16)	161.8
C(17)-H(17)...O(4)	0.95	2.27	2.862(2)	119.8
C(21)-H(21A)...O(1)	0.99	2.41	3.1343(19)	129.8

Symmetry transformations used to generate equivalent atoms:

A2.10. X-Ray Crystal Structure Analysis of 77



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Figure A2.10.1. *X-ray Crystal Structure of* ***77***

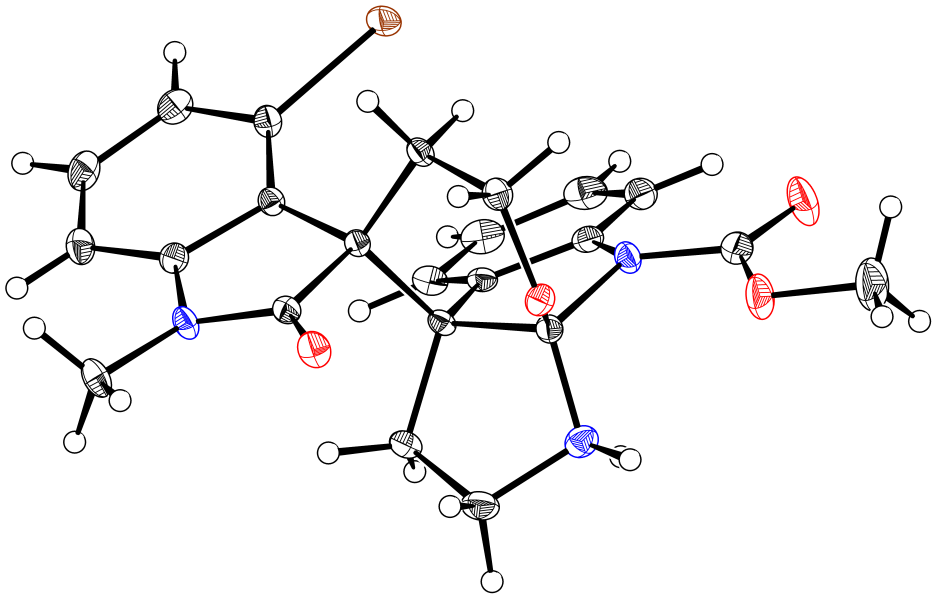


Table A2.10.1. *Crystal data and structure analysis details for* ***77***

Empirical formula	C46.40 H47.20 Br2 Cl0.80 N6 O8.20
Formula weight	1008.40
Crystallization solvent	isopropanol/hexane (dichloromethane)
Crystal shape	plate
Crystal color	colourless
Crystal size	0.05 x 0.20 x 0.46 mm

Data Collection

Preliminary photograph(s)	rotation
Type of diffractometer	Bruker APEX-II CCD
Wavelength	0.71073 Å MoK

Data collection temperature	100 K	
Theta range for 9880 reflections used in lattice determination	2.32 to 33.69°	
Unit cell dimensions	a = 17.6618(8) Å b = 17.4368(7) Å c = 13.5068(5) Å	⟨= 90° ®= 96.873(2)° © = 90°
Volume	4129.7(3) $Å^3$	
Z	4	
Crystal system	monoclinic	
Space group	P 1 21/c 1 (# 14)	
Density (calculated)	1.622 g/cm^3	
F(000)	2067	
Theta range for data collection	2.1 to 37.6°	
Completeness to theta = 25.000°	99.9%	
Index ranges	-29 ″ h ″ 30, -29 ″ k ″ 29, -23 ″ 1 ″ 22	
Data collection scan type	and scans	
Reflections collected	213592	
Independent reflections	21060 [R_{int}= 0.0668]	
Reflections > 2 ∫(I)	14742	
Average ∫(I)/(net I)	0.0422	
Absorption coefficient	2.08 mm^{-1}	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.8480	

Structure Solution and Refinement

Primary solution method	dual
Secondary solution method	?
Hydrogen placement	mixed
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	21060 / 3 / 592
Treatment of hydrogen atoms	mixed
Goodness-of-fit on F^2	3.31
Final R indices [I>2 ∫(I), 14742 reflections]	R1 = 0.0585, wR2 = 0.0955
R indices (all data)	R1 = 0.0953, wR2 = 0.0967
Type of weighting scheme used	calc
Weighting scheme used	
Max shift/error	0.002
Average shift/error	0.000
Extinction coefficient	0
Largest diff. peak and hole	3.94 and -2.05 e·$Å^{-3}$

Programs Used

Cell refinement	SAINT V8.27B (Bruker-AXS, 2007)
Data collection	APEX2 2012.4-3 (Bruker-AXS, 2007)
Data reduction	SAINT V8.27B (Bruker-AXS, 2007)
Structure solution	SHELXT (Sheldrick, 2012)
Structure refinement	SHELXL-2012/6 (Sheldrick, 2012)
Graphics	DIAMOND 3 (Crystal Impact, 1999)

References

Special Refinement Details

Table A2.10.2. *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for* ***77****. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor*

	x	y	z	U_{eq}
Br(1A)	4275(1)	4155(1)	4546(1)	17(1)
O(1A)	4849(1)	1093(1)	2821(1)	18(1)
O(2A)	3534(1)	1156(1)	3905(1)	14(1)
O(3A)	1677(1)	2261(1)	5024(1)	28(1)
O(4A)	2118(1)	1113(1)	4589(1)	24(1)
N(1A)	5279(1)	2188(1)	2142(1)	14(1)
N(2A)	2640(1)	2178(1)	4034(1)	14(1)
N(3A)	2591(1)	1331(1)	2600(1)	17(1)
C(1A)	4767(1)	3863(1)	3418(1)	14(1)
C(2A)	5155(1)	4451(1)	2990(1)	18(1)
C(3A)	5568(1)	4292(1)	2204(1)	20(1)
C(4A)	5638(1)	3544(1)	1865(1)	17(1)
C(5A)	5246(1)	2978(1)	2315(1)	14(1)
C(6A)	4769(1)	3120(1)	3055(1)	12(1)
C(7A)	4390(1)	2370(1)	3293(1)	11(1)
C(8A)	4859(1)	1789(1)	2758(1)	13(1)
C(9A)	5816(1)	1822(1)	1554(1)	19(1)
C(10A)	4427(1)	2208(1)	4414(1)	13(1)
C(11A)	4123(1)	1422(1)	4643(1)	16(1)
C(12A)	3085(1)	1712(1)	3373(1)	13(1)
C(13A)	3527(1)	2321(1)	2811(1)	11(1)
C(14A)	3397(1)	2045(1)	1702(1)	15(1)
C(15A)	3031(1)	1255(1)	1744(1)	20(1)
C(16A)	3091(1)	3045(1)	2962(1)	12(1)
C(17A)	2609(1)	2950(1)	3695(1)	14(1)
C(18A)	2158(1)	3551(1)	3966(1)	18(1)
C(19A)	2193(1)	4244(1)	3462(1)	21(1)
C(20A)	2647(1)	4337(1)	2706(1)	20(1)
C(21A)	3102(1)	3731(1)	2452(1)	16(1)
C(22A)	2101(1)	1885(1)	4585(1)	19(1)
C(23A)	1594(2)	770(1)	5202(2)	34(1)
Br(1B)	7671(1)	4207(1)	1850(1)	25(1)
O(1B)	9584(1)	1388(1)	2258(1)	28(1)
O(2B)	8160(1)	1198(1)	2987(1)	20(1)
O(3B)	6232(1)	1864(1)	4406(1)	29(1)

O(4B)	6979(1)	869(1)	4083(1)	23(1)
N(1B)	10134(1)	2569(1)	2268(1)	19(1)
N(2B)	7383(1)	2057(1)	3810(1)	18(1)
N(3B)	8495(1)	1439(1)	4657(1)	22(1)
C(1B)	8749(1)	4072(1)	2061(1)	21(1)
C(2B)	9187(2)	4725(1)	1973(2)	29(1)
C(3B)	9977(2)	4672(1)	2042(2)	32(1)
C(4B)	10341(1)	3971(1)	2150(2)	25(1)
C(5B)	9885(1)	3336(1)	2235(1)	20(1)
C(6B)	9091(1)	3365(1)	2251(1)	17(1)
C(7B)	8814(1)	2560(1)	2462(1)	16(1)
C(8B)	9533(1)	2080(1)	2309(1)	19(1)
C(9B)	10900(1)	2317(1)	2149(2)	29(1)
C(10B)	8104(1)	2283(1)	1797(1)	18(1)
C(11B)	7945(1)	1441(1)	1974(1)	21(1)
C(12B)	8160(1)	1753(1)	3723(1)	16(1)
C(13B)	8665(1)	2476(1)	3597(1)	16(1)
C(14B)	9393(1)	2339(1)	4357(1)	20(1)
C(15B)	9317(1)	1506(1)	4664(1)	22(1)
C(16B)	8167(1)	3112(1)	3924(1)	17(1)
C(17B)	7437(1)	2860(1)	4005(1)	17(1)
C(18B)	6878(1)	3355(1)	4264(1)	22(1)
C(19B)	7080(1)	4112(1)	4481(1)	24(1)
C(20B)	7819(2)	4353(1)	4474(1)	27(1)
C(21B)	8373(1)	3854(1)	4203(1)	22(1)
C(22B)	6812(1)	1614(1)	4130(1)	20(1)
C(23B)	6407(1)	360(1)	4393(2)	26(1)
Cl(1)	10468(1)	4314(1)	5067(1)	59(1)
C(1)	9892(3)	4837(3)	5573(4)	28(1)
O(1)	9448(4)	4184(4)	5213(5)	16(2)

Table A2.10.3. *Bond lengths [Å] and angles [°] for* ***77***

Br(1A)-C(1A)	1.9116(18)
O(1A)-C(8A)	1.217(2)
O(2A)-C(11A)	1.430(2)
O(2A)-C(12A)	1.396(2)
O(3A)-C(22A)	1.204(2)
O(4A)-C(22A)	1.345(2)
O(4A)-C(23A)	1.443(2)
N(1A)-C(5A)	1.398(2)
N(1A)-C(8A)	1.370(2)
N(1A)-C(9A)	1.455(2)
N(2A)-C(12A)	1.496(2)
N(2A)-C(17A)	1.421(2)
N(2A)-C(22A)	1.376(2)
N(3A)-H(3AA)	0.9200
N(3A)-H(3AB)	0.9200
N(3A)-C(12A)	1.440(2)
N(3A)-C(15A)	1.475(2)
C(1A)-C(2A)	1.397(3)
C(1A)-C(6A)	1.385(2)
C(2A)-H(2A)	0.9500
C(2A)-C(3A)	1.386(3)
C(3A)-H(3A)	0.9500

C(3A)-C(4A)	1.392(3)
C(4A)-H(4A)	0.9500
C(4A)-C(5A)	1.387(2)
C(5A)-C(6A)	1.405(2)
C(6A)-C(7A)	1.520(2)
C(7A)-C(8A)	1.543(2)
C(7A)-C(10A)	1.534(2)
C(7A)-C(13A)	1.586(3)
C(9A)-H(9AA)	0.9800
C(9A)-H(9AB)	0.9800
C(9A)-H(9AC)	0.9800
C(10A)-H(10A)	0.9900
C(10A)-H(10B)	0.9900
C(10A)-C(11A)	1.517(2)
C(11A)-H(11A)	0.9900
C(11A)-H(11B)	0.9900
C(12A)-C(13A)	1.567(2)
C(13A)-C(14A)	1.564(2)
C(13A)-C(16A)	1.504(2)
C(14A)-H(14A)	0.9900
C(14A)-H(14B)	0.9900
C(14A)-C(15A)	1.524(3)
C(15A)-H(15A)	0.9900
C(15A)-H(15B)	0.9900
C(16A)-C(17A)	1.392(3)
C(16A)-C(21A)	1.383(2)
C(17A)-C(18A)	1.391(3)
C(18A)-H(18A)	0.9500
C(18A)-C(19A)	1.392(3)
C(19A)-H(19A)	0.9500
C(19A)-C(20A)	1.381(3)
C(20A)-H(20A)	0.9500
C(20A)-C(21A)	1.394(3)
C(21A)-H(21A)	0.9500
C(23A)-H(23A)	0.9800
C(23A)-H(23B)	0.9800
C(23A)-H(23C)	0.9800
Br(1B)-C(1B)	1.906(2)
O(1B)-C(8B)	1.212(2)
O(2B)-C(11B)	1.439(2)
O(2B)-C(12B)	1.387(2)
O(3B)-C(22B)	1.212(2)
O(4B)-C(22B)	1.336(2)
O(4B)-C(23B)	1.444(2)
N(1B)-C(5B)	1.407(2)
N(1B)-C(8B)	1.368(3)
N(1B)-C(9B)	1.449(3)
N(2B)-C(12B)	1.489(3)
N(2B)-C(17B)	1.426(2)
N(2B)-C(22B)	1.379(3)
N(3B)-H(3BA)	0.9200
N(3B)-H(3BB)	0.9200
N(3B)-C(12B)	1.436(2)
N(3B)-C(15B)	1.456(3)
C(1B)-C(2B)	1.389(3)
C(1B)-C(6B)	1.383(3)
C(2B)-H(2B)	0.9500
C(2B)-C(3B)	1.390(3)

C(3B)-H(3B)	0.9500
C(3B)-C(4B)	1.380(3)
C(4B)-H(4B)	0.9500
C(4B)-C(5B)	1.381(3)
C(5B)-C(6B)	1.407(3)
C(6B)-C(7B)	1.524(3)
C(7B)-C(8B)	1.556(3)
C(7B)-C(10B)	1.532(3)
C(7B)-C(13B)	1.592(3)
C(9B)-H(9BA)	0.9800
C(9B)-H(9BB)	0.9800
C(9B)-H(9BC)	0.9800
C(10B)-H(10C)	0.9900
C(10B)-H(10D)	0.9900
C(10B)-C(11B)	1.519(3)
C(11B)-H(11C)	0.9900
C(11B)-H(11D)	0.9900
C(12B)-C(13B)	1.567(3)
C(13B)-C(14B)	1.565(3)
C(13B)-C(16B)	1.515(3)
C(14B)-H(14C)	0.9900
C(14B)-H(14D)	0.9900
C(14B)-C(15B)	1.521(3)
C(15B)-H(15C)	0.9900
C(15B)-H(15D)	0.9900
C(16B)-C(17B)	1.379(3)
C(16B)-C(21B)	1.384(3)
C(17B)-C(18B)	1.386(3)
C(18B)-H(18B)	0.9500
C(18B)-C(19B)	1.388(3)
C(19B)-H(19B)	0.9500
C(19B)-C(20B)	1.373(3)
C(20B)-H(20B)	0.9500
C(20B)-C(21B)	1.391(3)
C(21B)-H(21B)	0.9500
C(23B)-H(23D)	0.9800
C(23B)-H(23E)	0.9800
C(23B)-H(23F)	0.9800
Cl(1)-C(1)#1	1.794(6)
Cl(1)-C(1)	1.581(6)
C(1)-Cl(1)#1	1.794(6)
C(1)-C(1)#1	1.734(10)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
O(1)-H(1C)	0.848(10)
O(1)-H(1D)	0.855(10)

C(12A)-O(2A)-C(11A)	116.99(13)
C(22A)-O(4A)-C(23A)	113.72(16)
C(5A)-N(1A)-C(9A)	124.50(16)
C(8A)-N(1A)-C(5A)	111.22(14)
C(8A)-N(1A)-C(9A)	122.96(15)
C(17A)-N(2A)-C(12A)	108.96(13)
C(22A)-N(2A)-C(12A)	124.67(15)
C(22A)-N(2A)-C(17A)	121.53(16)
H(3AA)-N(3A)-H(3AB)	108.7
C(12A)-N(3A)-H(3AA)	110.5
C(12A)-N(3A)-H(3AB)	110.5

C(12A)-N(3A)-C(15A)	106.25(15)
C(15A)-N(3A)-H(3AA)	110.5
C(15A)-N(3A)-H(3AB)	110.5
C(2A)-C(1A)-Br(1A)	115.20(13)
C(6A)-C(1A)-Br(1A)	123.47(13)
C(6A)-C(1A)-C(2A)	121.29(17)
C(1A)-C(2A)-H(2A)	120.1
C(3A)-C(2A)-C(1A)	119.89(17)
C(3A)-C(2A)-H(2A)	120.1
C(2A)-C(3A)-H(3A)	119.5
C(2A)-C(3A)-C(4A)	120.96(17)
C(4A)-C(3A)-H(3A)	119.5
C(3A)-C(4A)-H(4A)	121.5
C(5A)-C(4A)-C(3A)	117.09(17)
C(5A)-C(4A)-H(4A)	121.5
N(1A)-C(5A)-C(6A)	109.47(15)
C(4A)-C(5A)-N(1A)	126.49(17)
C(4A)-C(5A)-C(6A)	123.99(16)
C(1A)-C(6A)-C(5A)	116.32(16)
C(1A)-C(6A)-C(7A)	135.22(16)
C(5A)-C(6A)-C(7A)	108.41(14)
C(6A)-C(7A)-C(8A)	101.00(14)
C(6A)-C(7A)-C(10A)	113.54(14)
C(6A)-C(7A)-C(13A)	112.66(14)
C(8A)-C(7A)-C(13A)	108.40(14)
C(10A)-C(7A)-C(8A)	112.28(14)
C(10A)-C(7A)-C(13A)	108.74(14)
O(1A)-C(8A)-N(1A)	124.26(16)
O(1A)-C(8A)-C(7A)	127.54(16)
N(1A)-C(8A)-C(7A)	108.13(14)
N(1A)-C(9A)-H(9AA)	109.5
N(1A)-C(9A)-H(9AB)	109.5
N(1A)-C(9A)-H(9AC)	109.5
H(9AA)-C(9A)-H(9AB)	109.5
H(9AA)-C(9A)-H(9AC)	109.5
H(9AB)-C(9A)-H(9AC)	109.5
C(7A)-C(10A)-H(10A)	109.0
C(7A)-C(10A)-H(10B)	109.0
H(10A)-C(10A)-H(10B)	107.8
C(11A)-C(10A)-C(7A)	113.14(14)
C(11A)-C(10A)-H(10A)	109.0
C(11A)-C(10A)-H(10B)	109.0
O(2A)-C(11A)-C(10A)	113.43(14)
O(2A)-C(11A)-H(11A)	108.9
O(2A)-C(11A)-H(11B)	108.9
C(10A)-C(11A)-H(11A)	108.9
C(10A)-C(11A)-H(11B)	108.9
H(11A)-C(11A)-H(11B)	107.7
O(2A)-C(12A)-N(2A)	112.12(14)
O(2A)-C(12A)-N(3A)	108.01(14)
O(2A)-C(12A)-C(13A)	115.79(15)
N(2A)-C(12A)-C(13A)	104.45(13)
N(3A)-C(12A)-N(2A)	111.50(16)
N(3A)-C(12A)-C(13A)	104.77(14)
C(12A)-C(13A)-C(7A)	110.33(14)
C(14A)-C(13A)-C(7A)	115.73(14)
C(14A)-C(13A)-C(12A)	103.34(13)
C(16A)-C(13A)-C(7A)	112.41(14)

C(16A)-C(13A)-C(12A)	102.11(14)
C(16A)-C(13A)-C(14A)	111.64(14)
C(13A)-C(14A)-H(14A)	110.8
C(13A)-C(14A)-H(14B)	110.8
H(14A)-C(14A)-H(14B)	108.8
C(15A)-C(14A)-C(13A)	104.90(14)
C(15A)-C(14A)-H(14A)	110.8
C(15A)-C(14A)-H(14B)	110.8
N(3A)-C(15A)-C(14A)	102.31(14)
N(3A)-C(15A)-H(15A)	111.3
N(3A)-C(15A)-H(15B)	111.3
C(14A)-C(15A)-H(15A)	111.3
C(14A)-C(15A)-H(15B)	111.3
H(15A)-C(15A)-H(15B)	109.2
C(17A)-C(16A)-C(13A)	111.31(15)
C(21A)-C(16A)-C(13A)	128.41(16)
C(21A)-C(16A)-C(17A)	120.22(17)
C(16A)-C(17A)-N(2A)	109.75(15)
C(18A)-C(17A)-N(2A)	129.11(17)
C(18A)-C(17A)-C(16A)	121.06(17)
C(17A)-C(18A)-H(18A)	121.1
C(17A)-C(18A)-C(19A)	117.73(18)
C(19A)-C(18A)-H(18A)	121.1
C(18A)-C(19A)-H(19A)	119.1
C(20A)-C(19A)-C(18A)	121.80(18)
C(20A)-C(19A)-H(19A)	119.1
C(19A)-C(20A)-H(20A)	120.1
C(19A)-C(20A)-C(21A)	119.74(18)
C(21A)-C(20A)-H(20A)	120.1
C(16A)-C(21A)-C(20A)	119.37(18)
C(16A)-C(21A)-H(21A)	120.3
C(20A)-C(21A)-H(21A)	120.3
O(3A)-C(22A)-O(4A)	123.93(18)
O(3A)-C(22A)-N(2A)	125.17(18)
O(4A)-C(22A)-N(2A)	110.89(17)
O(4A)-C(23A)-H(23A)	109.5
O(4A)-C(23A)-H(23B)	109.5
O(4A)-C(23A)-H(23C)	109.5
H(23A)-C(23A)-H(23B)	109.5
H(23A)-C(23A)-H(23C)	109.5
H(23B)-C(23A)-H(23C)	109.5
C(12B)-O(2B)-C(11B)	116.97(14)
C(22B)-O(4B)-C(23B)	114.79(16)
C(5B)-N(1B)-C(9B)	125.24(17)
C(8B)-N(1B)-C(5B)	110.68(17)
C(8B)-N(1B)-C(9B)	123.67(17)
C(17B)-N(2B)-C(12B)	108.85(16)
C(22B)-N(2B)-C(12B)	122.68(15)
C(22B)-N(2B)-C(17B)	121.78(16)
H(3BA)-N(3B)-H(3BB)	108.6
C(12B)-N(3B)-H(3BA)	110.5
C(12B)-N(3B)-H(3BB)	110.5
C(12B)-N(3B)-C(15B)	106.38(15)
C(15B)-N(3B)-H(3BA)	110.5
C(15B)-N(3B)-H(3BB)	110.5
C(2B)-C(1B)-Br(1B)	116.23(17)
C(6B)-C(1B)-Br(1B)	122.96(16)
C(6B)-C(1B)-C(2B)	120.8(2)

C(1B)-C(2B)-H(2B)	119.9
C(1B)-C(2B)-C(3B)	120.3(2)
C(3B)-C(2B)-H(2B)	119.9
C(2B)-C(3B)-H(3B)	119.5
C(4B)-C(3B)-C(2B)	121.1(2)
C(4B)-C(3B)-H(3B)	119.5
C(3B)-C(4B)-H(4B)	121.6
C(3B)-C(4B)-C(5B)	116.8(2)
C(5B)-C(4B)-H(4B)	121.6
C(4B)-C(5B)-N(1B)	125.6(2)
C(4B)-C(5B)-C(6B)	124.3(2)
C(6B)-C(5B)-N(1B)	110.01(17)
C(1B)-C(6B)-C(5B)	116.31(18)
C(1B)-C(6B)-C(7B)	135.46(19)
C(5B)-C(6B)-C(7B)	108.21(16)
C(6B)-C(7B)-C(8B)	100.70(15)
C(6B)-C(7B)-C(10B)	116.13(16)
C(6B)-C(7B)-C(13B)	110.98(15)
C(8B)-C(7B)-C(13B)	108.03(15)
C(10B)-C(7B)-C(8B)	112.10(15)
C(10B)-C(7B)-C(13B)	108.51(16)
O(1B)-C(8B)-N(1B)	123.69(19)
O(1B)-C(8B)-C(7B)	127.66(19)
N(1B)-C(8B)-C(7B)	108.63(16)
N(1B)-C(9B)-H(9BA)	109.5
N(1B)-C(9B)-H(9BB)	109.5
N(1B)-C(9B)-H(9BC)	109.5
H(9BA)-C(9B)-H(9BB)	109.5
H(9BA)-C(9B)-H(9BC)	109.5
H(9BB)-C(9B)-H(9BC)	109.5
C(7B)-C(10B)-H(10C)	109.3
C(7B)-C(10B)-H(10D)	109.3
H(10C)-C(10B)-H(10D)	108.0
C(11B)-C(10B)-C(7B)	111.50(16)
C(11B)-C(10B)-H(10C)	109.3
C(11B)-C(10B)-H(10D)	109.3
O(2B)-C(11B)-C(10B)	113.68(15)
O(2B)-C(11B)-H(11C)	108.8
O(2B)-C(11B)-H(11D)	108.8
C(10B)-C(11B)-H(11C)	108.8
C(10B)-C(11B)-H(11D)	108.8
H(11C)-C(11B)-H(11D)	107.7
O(2B)-C(12B)-N(2B)	112.64(16)
O(2B)-C(12B)-N(3B)	109.16(15)
O(2B)-C(12B)-C(13B)	115.73(15)
N(2B)-C(12B)-C(13B)	105.33(14)
N(3B)-C(12B)-N(2B)	110.71(15)
N(3B)-C(12B)-C(13B)	102.81(16)
C(12B)-C(13B)-C(7B)	109.92(15)
C(14B)-C(13B)-C(7B)	115.40(16)
C(14B)-C(13B)-C(12B)	103.86(15)
C(16B)-C(13B)-C(7B)	112.48(15)
C(16B)-C(13B)-C(12B)	101.45(16)
C(16B)-C(13B)-C(14B)	112.39(15)
C(13B)-C(14B)-H(14C)	111.1
C(13B)-C(14B)-H(14D)	111.1
H(14C)-C(14B)-H(14D)	109.0
C(15B)-C(14B)-C(13B)	103.47(16)

C(15B)-C(14B)-H(14C)	111.1
C(15B)-C(14B)-H(14D)	111.1
N(3B)-C(15B)-C(14B)	101.24(16)
N(3B)-C(15B)-H(15C)	111.5
N(3B)-C(15B)-H(15D)	111.5
C(14B)-C(15B)-H(15C)	111.5
C(14B)-C(15B)-H(15D)	111.5
H(15C)-C(15B)-H(15D)	109.3
C(17B)-C(16B)-C(13B)	111.82(16)
C(17B)-C(16B)-C(21B)	119.68(18)
C(21B)-C(16B)-C(13B)	128.31(19)
C(16B)-C(17B)-N(2B)	109.92(17)
C(16B)-C(17B)-C(18B)	121.42(18)
C(18B)-C(17B)-N(2B)	128.6(2)
C(17B)-C(18B)-H(18B)	120.9
C(17B)-C(18B)-C(19B)	118.2(2)
C(19B)-C(18B)-H(18B)	120.9
C(18B)-C(19B)-H(19B)	119.7
C(20B)-C(19B)-C(18B)	120.7(2)
C(20B)-C(19B)-H(19B)	119.7
C(19B)-C(20B)-H(20B)	119.7
C(19B)-C(20B)-C(21B)	120.6(2)
C(21B)-C(20B)-H(20B)	119.7
C(16B)-C(21B)-C(20B)	119.0(2)
C(16B)-C(21B)-H(21B)	120.5
C(20B)-C(21B)-H(21B)	120.5
O(3B)-C(22B)-O(4B)	124.24(19)
O(3B)-C(22B)-N(2B)	124.87(18)
O(4B)-C(22B)-N(2B)	110.89(17)
O(4B)-C(23B)-H(23D)	109.5
O(4B)-C(23B)-H(23E)	109.5
O(4B)-C(23B)-H(23F)	109.5
H(23D)-C(23B)-H(23E)	109.5
H(23D)-C(23B)-H(23F)	109.5
H(23E)-C(23B)-H(23F)	109.5
C(1)-Cl(1)-C(1)#1	61.5(3)
Cl(1)-C(1)-Cl(1)#1	118.5(3)
Cl(1)-C(1)-C(1)#1	65.3(3)
Cl(1)#1-C(1)-H(1A)	92.2
Cl(1)-C(1)-H(1A)	117.2
Cl(1)#1-C(1)-H(1B)	92.2
Cl(1)-C(1)-H(1B)	117.2
C(1)#1-C(1)-Cl(1)#1	53.2(3)
C(1)#1-C(1)-H(1A)	117.2
C(1)#1-C(1)-H(1B)	117.2
H(1A)-C(1)-H(1B)	114.2
H(1C)-O(1)-H(1D)	100(2)

Symmetry transformations used to generate equivalent atoms:
#1 +2

Table A2.10.4. *Anisotropic displacement parameters ($Å^2 x\ 10^4$) for **77**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}

Br(1A)	221(1)	127(1)	183(1)	-63(1)	55(1)	-12(1)
O(1A)	226(8)	99(6)	216(7)	-16(5)	81(6)	8(5)
O(2A)	139(7)	115(6)	164(6)	11(5)	19(5)	-6(5)
O(3A)	290(10)	282(8)	321(8)	-16(7)	201(7)	27(7)
O(4A)	256(9)	212(7)	285(8)	29(6)	150(7)	-49(6)
N(1A)	159(9)	123(7)	149(7)	-7(6)	77(6)	14(6)
N(2A)	144(9)	142(7)	154(7)	-18(6)	62(6)	2(6)
N(3A)	158(9)	142(7)	200(8)	-24(6)	14(7)	-6(6)
C(1A)	142(10)	127(8)	156(9)	4(7)	41(7)	3(7)
C(2A)	203(11)	111(8)	217(10)	13(7)	19(8)	-21(7)
C(3A)	203(11)	161(9)	228(10)	62(7)	36(8)	-51(8)
C(4A)	171(11)	184(9)	168(9)	36(7)	51(8)	-15(8)
C(5A)	139(10)	128(8)	145(8)	6(7)	19(7)	-5(7)
C(6A)	128(10)	105(7)	117(8)	8(6)	28(7)	2(7)
C(7A)	130(9)	72(7)	121(8)	-10(6)	38(7)	-4(6)
C(8A)	133(10)	128(8)	123(8)	-12(6)	24(7)	2(7)
C(9A)	182(11)	221(9)	193(9)	-12(8)	97(8)	53(8)
C(10A)	157(10)	124(8)	108(8)	1(6)	43(7)	-5(7)
C(11A)	175(11)	157(8)	138(8)	24(7)	28(7)	-15(7)
C(12A)	134(10)	115(8)	133(8)	-11(6)	34(7)	-10(7)
C(13A)	148(10)	93(7)	95(8)	-7(6)	29(7)	4(7)
C(14A)	183(11)	154(8)	111(8)	-14(7)	21(7)	2(7)
C(15A)	242(12)	181(9)	163(9)	-55(7)	21(8)	-19(8)
C(16A)	133(10)	112(8)	115(8)	-30(6)	4(7)	4(7)
C(17A)	122(10)	152(8)	145(8)	-37(7)	-6(7)	2(7)
C(18A)	139(10)	209(9)	200(9)	-67(8)	29(8)	22(8)
C(19A)	212(11)	161(9)	252(10)	-74(8)	-15(8)	65(8)
C(20A)	245(12)	132(9)	218(10)	-1(7)	-30(8)	31(8)
C(21A)	192(11)	156(8)	136(9)	-8(7)	5(7)	16(7)
C(22A)	184(11)	236(10)	159(9)	-2(8)	20(8)	-43(8)
C(23A)	339(15)	331(12)	380(13)	62(11)	178(11)	-93(11)
Br(1B)	308(1)	227(1)	224(1)	10(1)	22(1)	96(1)
O(1B)	288(10)	184(7)	394(9)	21(6)	144(7)	48(6)
O(2B)	263(9)	140(6)	210(7)	-28(5)	91(6)	7(6)
O(3B)	227(9)	276(8)	397(9)	-11(7)	150(7)	15(7)
O(4B)	265(9)	159(6)	294(8)	25(6)	131(6)	-22(6)
N(1B)	177(10)	212(8)	205(8)	5(7)	71(7)	0(7)
N(2B)	208(10)	138(7)	212(8)	9(6)	101(7)	7(7)
N(3B)	275(11)	186(8)	198(8)	31(7)	82(7)	36(7)
C(1B)	251(12)	227(10)	161(9)	-3(8)	43(8)	4(9)
C(2B)	490(17)	152(9)	240(11)	7(8)	77(10)	-23(10)
C(3B)	484(17)	207(10)	272(12)	-32(9)	97(11)	-143(10)
C(4B)	272(13)	276(11)	204(10)	-27(8)	56(9)	-99(9)
C(5B)	255(12)	200(9)	141(9)	5(7)	53(8)	-31(8)
C(6B)	201(11)	162(9)	144(9)	5(7)	36(8)	-17(8)
C(7B)	174(11)	140(8)	179(9)	0(7)	56(8)	6(7)
C(8B)	201(12)	211(10)	174(9)	19(8)	62(8)	7(8)
C(9B)	167(12)	343(12)	381(13)	2(10)	67(10)	-1(10)
C(10B)	209(12)	199(9)	137(9)	7(7)	51(8)	2(8)
C(11B)	239(12)	188(9)	199(10)	-38(8)	21(8)	-20(8)
C(12B)	180(11)	136(8)	181(9)	3(7)	51(8)	11(7)
C(13B)	181(11)	139(8)	179(9)	0(7)	40(8)	-6(7)
C(14B)	193(12)	226(10)	192(10)	-22(8)	29(8)	-2(8)
C(15B)	241(12)	227(10)	178(10)	31(8)	17(8)	70(9)
C(16B)	208(11)	161(9)	150(9)	4(7)	26(8)	22(8)
C(17B)	262(12)	146(8)	111(8)	13(7)	35(8)	46(8)
C(18B)	279(13)	227(10)	166(9)	1(8)	78(9)	72(9)

C(19B)	342(14)	211(10)	178(9)	-17(8)	36(9)	85(9)
C(20B)	470(16)	174(9)	162(10)	-35(8)	25(10)	54(9)
C(21B)	305(14)	189(9)	178(10)	-7(8)	42(9)	3(9)
C(22B)	228(12)	216(10)	176(9)	2(8)	63(8)	-3(8)
C(23B)	267(13)	225(10)	294(11)	39(9)	105(9)	-90(9)
Cl(1)	275(5)	605(6)	881(8)	237(5)	39(5)	-52(4)
C(1)	240(30)	410(30)	190(20)	-110(20)	40(20)	-110(30)

Table A2.10.5. *Hydrogen coordinates (x 10^3) and isotropic displacement parameters ($Å^2$x 10^3) for* ***77***

	x	y	z	U_{iso}
H(3AA)	216	162	243	20
H(3AB)	245	86	281	20
H(2A)	514	496	324	21
H(3A)	581	470	189	24
H(4A)	594	343	135	21
H(9AA)	632	204	173	29
H(9AB)	565	191	84	29
H(9AC)	583	127	169	29
H(10A)	496	225	472	15
H(10B)	413	260	472	15
H(11A)	455	105	470	19
H(11B)	392	144	530	19
H(14A)	306	240	129	18
H(14B)	389	201	142	18
H(15A)	269	114	112	23
H(15B)	342	85	186	23
H(18A)	184	349	448	22
H(19A)	190	466	364	25
H(20A)	265	481	236	24
H(21A)	342	379	193	19
H(23A)	170	97	588	51
H(23B)	166	21	521	51
H(23C)	107	89	493	51
H(3BA)	836	93	471	26
H(3BB)	834	171	518	26
H(2B)	895	521	186	35
H(3B)	1027	513	202	38
H(4B)	1088	393	216	30
H(9BA)	1094	176	225	44
H(9BB)	1127	258	264	44
H(9BC)	1101	244	147	44
H(10C)	766	259	194	22
H(10D)	818	236	109	22
H(11C)	739	134	179	25
H(11D)	823	113	153	25
H(14C)	986	242	404	24
H(14D)	940	269	494	24
H(15C)	951	115	418	26
H(15D)	959	141	534	26
H(18B)	637	318	429	26
H(19B)	670	447	464	29
H(20B)	795	487	466	32

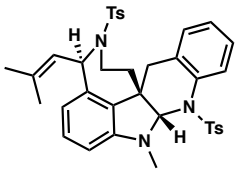
H(21B)	889	402	421	27
H(23D)	627	53	504	38
H(23E)	661	-16	446	38
H(23F)	596	37	390	38
H(1A)	1010	513	617	33
H(1B)	937	463	560	33
H(1C)	993(1)	423(6)	536(7)	24
H(1D)	929(5)	441(5)	572(5)	24

Table A2.10.6. *Hydrogen bonds for* ***77*** *[Å and °]*

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(3A)-H(3AB)...Br(1B)#2	0.92	2.92	3.8165(15)	164.2
N(3B)-H(3BB)...Br(1B)#3	0.92	3.11	3.6325(16)	118.2
C(9B)-H(9BC)...O(3A)#4	0.98	2.46	3.406(3)	163.4
C(15B)-H(15C)...O(1B)	0.99	2.65	3.346(2)	127.8
C(23B)-H(23F)...O(1A)	0.98	2.62	3.510(3)	151.5

Symmetry transformations used to generate equivalent atoms:
#1 +2 #2 +1
#3 #4 +1

A2.11. X-Ray Crystal Structure Analysis of 94



94

Figure A2.11.1. *X-ray Crystal Structure of* ***94***

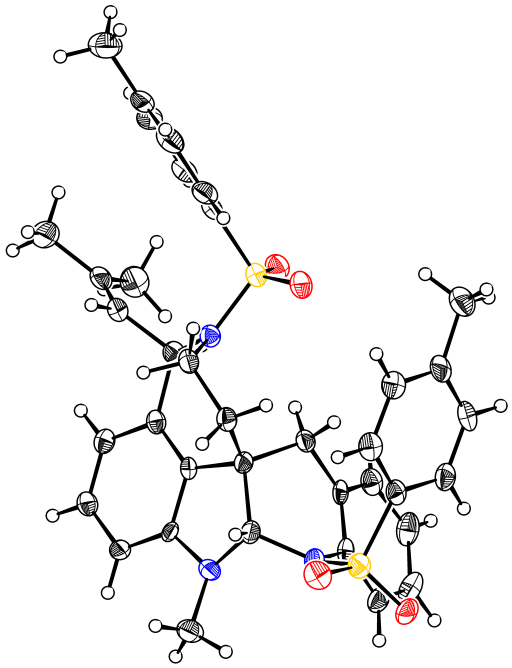


Table A2.11.1. *Crystal data and structure refinement for* ***94***

Empirical formula	C37 H39 N3 O4 S2
Formula weight	653.83
Crystallization Solvent	???Solvent???
Crystal Habit	Fragment
Crystal size	0.25 x 0.24 x 0.17 mm^3
Crystal color	Colorless

Data Collection

Preliminary Photos	
Type of diffractometer	Bruker SMART 1000
Wavelength	0.71073 Å MoK⟨
Data Collection Temperature	100(2) K

\ range for 8943 reflections used in lattice determination	2.22 to 27.43°	
Unit cell dimensions	a = 15.5078(13) Å b = 11.2221(10) Å c = 18.4268(16) Å	⟨= 90° ®= 94.7250(10)° © = 90°
Volume	3195.9(5) $Å^3$	
Z	4	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Density (calculated)	1.359 Mg/m^3	
F(000)	1384	
Data collection program	Bruker SMART v5.630	
\ range for data collection	1.65 to 28.34°	
Completeness to \ = 28.34°	94.1 %	
Index ranges	-20<=h<=20, -14<=k<=14, -24<=l<=24	
Data collection scan type	scans at 5 settings	
Data reduction program	Bruker SAINT v6.45A	
Reflections collected	44083	
Independent reflections	7500 [R_{int}= 0.1020]	
Absorption coefficient	0.213 mm^{-1}	
Absorption correction	None	
Max. and min. transmission	0.9647 and 0.9487	
Number of standards	? reflections measured every ?min.	
Variation of standards	?%.	

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	7500 / 0 / 420
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	1.394
Final R indices [I>2 ∫(I), 4434 reflections]	R1 = 0.0531, wR2 = 0.0888
R indices (all data)	R1 = 0.0982, wR2 = 0.0932
Type of weighting scheme used	Sigma
Weighting scheme used	w=1/s^2^(Fo^2^)
Max shift/error	0.001

Average shift/error	0.000
Absolute structure determination	?
Largest diff. peak and hole	0.629 and -0.498 e.Å^{-3}

Special Refinement Details

Table A2.11.2. *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for* ***94****. U(eq) is defined as the trace of the orthogonalized U^{ij} tensor*

	x	y	z	U_{eq}
S(1)	7430(1)	6065(1)	847(1)	26(1)
S(2)	7110(1)	2404(1)	-2197(1)	26(1)
O(1)	7087(1)	5440(1)	1441(1)	30(1)
O(2)	6897(1)	6283(1)	191(1)	31(1)
O(3)	7723(1)	2951(1)	-2627(1)	31(1)
O(4)	6624(1)	1390(1)	-2471(1)	30(1)
N(1)	8248(1)	5286(2)	622(1)	21(1)
N(2)	7649(1)	1964(2)	-1428(1)	20(1)
N(3)	9053(1)	1794(2)	-836(1)	25(1)
C(1)	7803(1)	7460(2)	1173(1)	24(1)
C(2)	7883(2)	8387(2)	687(1)	29(1)
C(3)	8173(2)	9490(2)	943(1)	33(1)
C(4)	8386(2)	9698(2)	1672(1)	31(1)
C(5)	8312(2)	8744(2)	2161(1)	29(1)
C(6)	8016(1)	7645(2)	1910(1)	27(1)
C(7)	8701(2)	10883(2)	1936(2)	46(1)
C(8)	8655(1)	5616(2)	-41(1)	24(1)
C(9)	8357(2)	4792(2)	-673(1)	22(1)
C(10)	8247(1)	3487(2)	-452(1)	20(1)
C(11)	8970(1)	3097(2)	114(1)	18(1)
C(12)	9226(1)	3566(2)	796(1)	21(1)
C(13)	8757(1)	4558(2)	1172(1)	22(1)
C(14)	9352(1)	5326(2)	1652(1)	25(1)
C(15)	9436(2)	5322(2)	2377(1)	28(1)
C(16)	10029(2)	6186(2)	2792(1)	40(1)
C(17)	8968(2)	4500(2)	2843(1)	39(1)
C(18)	9956(1)	3058(2)	1182(1)	24(1)
C(19)	10392(1)	2119(2)	898(1)	23(1)
C(20)	10133(1)	1653(2)	218(1)	22(1)
C(21)	9429(1)	2138(2)	-162(1)	17(1)
C(22)	8404(1)	2657(2)	-1116(1)	22(1)
C(23)	7170(1)	1365(2)	-902(1)	22(1)
C(24)	6883(2)	213(2)	-1018(1)	27(1)
C(25)	6385(2)	-308(2)	-509(1)	35(1)
C(26)	6207(2)	313(2)	108(1)	33(1)
C(27)	6542(2)	1444(2)	235(1)	26(1)
C(28)	7023(1)	1991(2)	-273(1)	20(1)
C(29)	7332(1)	3253(2)	-188(1)	21(1)
C(30)	9532(2)	1163(2)	-1354(1)	31(1)
C(31)	6376(2)	3476(2)	-1938(1)	23(1)
C(32)	6582(2)	4681(2)	-1968(1)	27(1)
C(33)	6067(2)	5512(2)	-1643(1)	27(1)
C(34)	5362(2)	5159(2)	-1284(1)	29(1)
C(35)	5149(2)	3940(2)	-1281(1)	30(1)

C(36)	5649(2)	3115(2)	-1606(1)	29(1)
C(37)	4847(2)	6041(2)	-885(1)	37(1)

Table A2.11.3. *Bond lengths [Å] and angles [°] for* ***94***

S(1)-O(2)	1.4297(15)
S(1)-O(1)	1.4381(16)
S(1)-N(1)	1.6227(18)
S(1)-C(1)	1.757(2)
S(2)-O(3)	1.4257(16)
S(2)-O(4)	1.4330(16)
S(2)-N(2)	1.6596(18)
S(2)-C(31)	1.750(2)
N(1)-C(8)	1.468(3)
N(1)-C(13)	1.479(3)
N(2)-C(23)	1.437(3)
N(2)-C(22)	1.482(3)
N(3)-C(21)	1.383(3)
N(3)-C(30)	1.443(3)
N(3)-C(22)	1.460(3)
C(1)-C(2)	1.385(3)
C(1)-C(6)	1.387(3)
C(2)-C(3)	1.387(3)
C(3)-C(4)	1.376(3)
C(4)-C(5)	1.409(3)
C(4)-C(7)	1.485(3)
C(5)-C(6)	1.382(3)
C(8)-C(9)	1.527(3)
C(9)-C(10)	1.533(3)
C(10)-C(11)	1.531(3)
C(10)-C(29)	1.559(3)
C(10)-C(22)	1.573(3)
C(11)-C(12)	1.391(3)
C(11)-C(21)	1.407(3)
C(12)-C(18)	1.406(3)
C(12)-C(13)	1.527(3)
C(13)-C(14)	1.497(3)
C(14)-C(15)	1.331(3)
C(15)-C(17)	1.490(3)
C(15)-C(16)	1.501(3)
C(18)-C(19)	1.379(3)
C(19)-C(20)	1.386(3)
C(20)-C(21)	1.362(3)
C(23)-C(24)	1.378(3)
C(23)-C(28)	1.390(3)
C(24)-C(25)	1.391(3)
C(25)-C(26)	1.380(3)
C(26)-C(27)	1.384(3)
C(27)-C(28)	1.387(3)
C(28)-C(29)	1.498(3)
C(31)-C(36)	1.386(3)
C(31)-C(32)	1.391(3)
C(32)-C(33)	1.395(3)
C(33)-C(34)	1.381(3)
C(34)-C(35)	1.408(3)
C(34)-C(37)	1.501(3)
C(35)-C(36)	1.375(3)

O(2)-S(1)-O(1)	120.13(10)
O(2)-S(1)-N(1)	106.61(9)
O(1)-S(1)-N(1)	106.12(9)
O(2)-S(1)-C(1)	106.75(10)
O(1)-S(1)-C(1)	107.87(10)
N(1)-S(1)-C(1)	109.02(10)
O(3)-S(2)-O(4)	120.13(10)
O(3)-S(2)-N(2)	106.90(10)
O(4)-S(2)-N(2)	106.10(9)
O(3)-S(2)-C(31)	109.52(11)
O(4)-S(2)-C(31)	107.86(11)
N(2)-S(2)-C(31)	105.34(10)
C(8)-N(1)-C(13)	117.95(18)
C(8)-N(1)-S(1)	118.38(15)
C(13)-N(1)-S(1)	120.44(15)
C(23)-N(2)-C(22)	114.75(17)
C(23)-N(2)-S(2)	117.62(15)
C(22)-N(2)-S(2)	120.12(15)
C(21)-N(3)-C(30)	121.98(19)
C(21)-N(3)-C(22)	111.09(17)
C(30)-N(3)-C(22)	117.99(18)
C(2)-C(1)-C(6)	119.6(2)
C(2)-C(1)-S(1)	119.49(18)
C(6)-C(1)-S(1)	120.90(18)
C(1)-C(2)-C(3)	119.6(2)
C(4)-C(3)-C(2)	121.9(2)
C(3)-C(4)-C(5)	118.0(2)
C(3)-C(4)-C(7)	121.2(2)
C(5)-C(4)-C(7)	120.8(2)
C(6)-C(5)-C(4)	120.5(2)
C(5)-C(6)-C(1)	120.4(2)
N(1)-C(8)-C(9)	110.94(18)
C(8)-C(9)-C(10)	114.14(18)
C(11)-C(10)-C(9)	111.28(17)
C(11)-C(10)-C(29)	112.00(18)
C(9)-C(10)-C(29)	111.58(18)
C(11)-C(10)-C(22)	102.01(17)
C(9)-C(10)-C(22)	109.37(18)
C(29)-C(10)-C(22)	110.18(17)
C(12)-C(11)-C(21)	120.0(2)
C(12)-C(11)-C(10)	130.2(2)
C(21)-C(11)-C(10)	109.72(18)
C(11)-C(12)-C(18)	117.4(2)
C(11)-C(12)-C(13)	125.12(19)
C(18)-C(12)-C(13)	117.4(2)
N(1)-C(13)-C(14)	110.77(18)
N(1)-C(13)-C(12)	109.80(17)
C(14)-C(13)-C(12)	113.23(18)
C(15)-C(14)-C(13)	126.6(2)
C(14)-C(15)-C(17)	124.6(2)
C(14)-C(15)-C(16)	120.9(2)
C(17)-C(15)-C(16)	114.5(2)
C(19)-C(18)-C(12)	121.2(2)
C(18)-C(19)-C(20)	121.1(2)
C(21)-C(20)-C(19)	118.3(2)
C(20)-C(21)-N(3)	127.6(2)
C(20)-C(21)-C(11)	121.9(2)

N(3)-C(21)-C(11)	110.44(19)
N(3)-C(22)-N(2)	106.80(17)
N(3)-C(22)-C(10)	105.32(17)
N(2)-C(22)-C(10)	116.47(18)
C(24)-C(23)-C(28)	122.0(2)
C(24)-C(23)-N(2)	120.8(2)
C(28)-C(23)-N(2)	117.1(2)
C(23)-C(24)-C(25)	118.7(2)
C(26)-C(25)-C(24)	120.2(2)
C(25)-C(26)-C(27)	120.3(2)
C(26)-C(27)-C(28)	120.4(2)
C(27)-C(28)-C(23)	118.2(2)
C(27)-C(28)-C(29)	122.2(2)
C(23)-C(28)-C(29)	119.5(2)
C(28)-C(29)-C(10)	114.72(18)
C(36)-C(31)-C(32)	120.0(2)
C(36)-C(31)-S(2)	119.38(19)
C(32)-C(31)-S(2)	120.01(18)
C(31)-C(32)-C(33)	119.4(2)
C(34)-C(33)-C(32)	121.2(2)
C(33)-C(34)-C(35)	118.4(2)
C(33)-C(34)-C(37)	121.3(2)
C(35)-C(34)-C(37)	120.3(2)
C(36)-C(35)-C(34)	120.8(2)
C(35)-C(36)-C(31)	120.2(2)

Symmetry transformations used to generate equivalent atoms:

Table A2.11.4. *Anisotropic displacement parameters ($Å^2 x\ 10^4$) for* ***94****. The anisotropic displacement factor exponent takes the form: $-2\partial^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	189(3)	284(4)	294(4)	-20(3)	14(3)	21(3)
S(2)	246(3)	321(4)	197(3)	2(3)	-38(3)	18(3)
O(1)	246(10)	297(10)	350(10)	-9(8)	77(8)	-2(8)
O(2)	229(10)	365(11)	334(10)	-4(8)	-69(8)	60(8)
O(3)	337(11)	387(11)	202(9)	68(8)	65(8)	12(8)
O(4)	281(10)	335(10)	266(10)	-58(8)	-110(8)	-5(8)
N(1)	193(11)	241(11)	202(11)	-2(9)	2(9)	7(9)
N(2)	195(11)	252(11)	158(10)	20(8)	-18(8)	-7(9)
N(3)	203(11)	288(12)	255(12)	-58(9)	-4(9)	60(9)
C(1)	175(13)	266(14)	284(14)	12(12)	26(11)	57(11)
C(2)	272(15)	297(15)	290(15)	-13(12)	22(12)	94(12)
C(3)	293(15)	290(16)	409(17)	75(13)	106(13)	77(13)
C(4)	218(14)	308(15)	429(17)	-103(13)	133(12)	-2(12)
C(5)	299(15)	327(16)	252(14)	-62(12)	57(12)	6(12)
C(6)	253(14)	272(15)	285(14)	31(12)	75(11)	67(12)
C(7)	497(19)	324(17)	580(20)	-79(14)	231(16)	-43(14)
C(8)	179(13)	249(14)	281(14)	19(11)	8(11)	3(11)
C(9)	186(13)	272(14)	211(13)	14(11)	-2(10)	3(11)
C(10)	177(13)	242(14)	187(13)	-22(10)	-11(10)	-10(11)
C(11)	128(12)	221(13)	198(13)	13(10)	4(10)	-22(10)
C(12)	170(13)	222(13)	224(13)	47(11)	22(10)	-17(11)
C(13)	214(13)	235(13)	194(13)	6(11)	1(10)	10(11)
C(14)	187(13)	269(14)	294(15)	-11(12)	14(11)	18(11)
C(15)	207(14)	332(15)	300(15)	-54(12)	-47(12)	101(12)

C(16)	389(17)	484(18)	316(15)	-121(14)	-89(13)	67(14)
C(17)	384(17)	587(19)	206(14)	-17(13)	4(12)	30(15)
C(18)	224(14)	250(14)	223(13)	18(11)	-25(11)	-24(11)
C(19)	197(13)	253(14)	243(14)	30(11)	-17(11)	28(11)
C(20)	204(13)	175(13)	280(14)	-29(11)	41(11)	-15(11)
C(21)	152(12)	187(13)	181(12)	-39(10)	8(10)	-62(10)
C(22)	182(13)	276(14)	214(13)	-28(11)	8(10)	-33(11)
C(23)	146(13)	270(14)	228(14)	45(11)	-52(10)	-26(11)
C(24)	264(14)	283(15)	250(14)	-21(12)	-77(11)	-23(12)
C(25)	365(16)	307(15)	340(16)	57(13)	-107(13)	-127(13)
C(26)	277(15)	454(17)	268(15)	84(13)	-10(12)	-111(13)
C(27)	217(14)	366(16)	204(13)	34(12)	-9(11)	16(12)
C(28)	128(12)	245(14)	216(13)	33(11)	-66(10)	-4(10)
C(29)	163(13)	255(14)	220(13)	-6(11)	0(10)	21(11)
C(30)	312(15)	320(15)	287(15)	-39(12)	5(12)	88(12)
C(31)	189(13)	308(15)	185(13)	30(11)	-42(10)	26(11)
C(32)	269(15)	350(16)	178(13)	75(12)	-11(11)	1(13)
C(33)	279(15)	293(15)	213(13)	90(11)	-58(11)	28(12)
C(34)	198(14)	354(16)	286(14)	25(12)	-81(11)	83(12)
C(35)	148(13)	412(17)	345(15)	48(13)	11(11)	14(13)
C(36)	217(14)	303(15)	324(15)	21(12)	-69(12)	-12(12)
C(37)	281(15)	370(16)	443(17)	52(13)	17(13)	61(13)

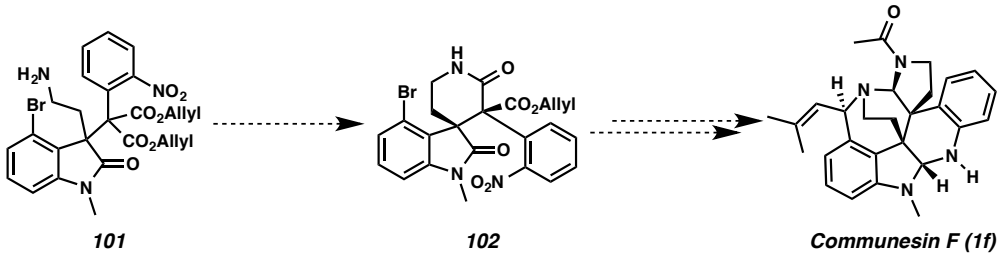
APPENDIX 3

Synthetic Studies Toward the Total Synthesis of Communesin F

A3.1. Direct Lactam-Forming Strategy

Having successfully completed our formal synthesis of communesin F (**1f**) and perophoramidine (**3**), our attention turned to a total synthesis of communesin F (**1f**). We envisioned that direct lactamization of malonate **101** would afford allyl ester **102**, which could be a potential precursor toward the efficient synthesis of communesin F (**1f**) (Scheme A3.1.1). Since lactonization of diester **60** afforded lactone **61** as a single diastereomer (Scheme 1.2.13, **60** → **61**), we believed that the diastereomer needed for elaboration to communesin F (**1f**) could be selectively formed by lactamization of malonate **101**.

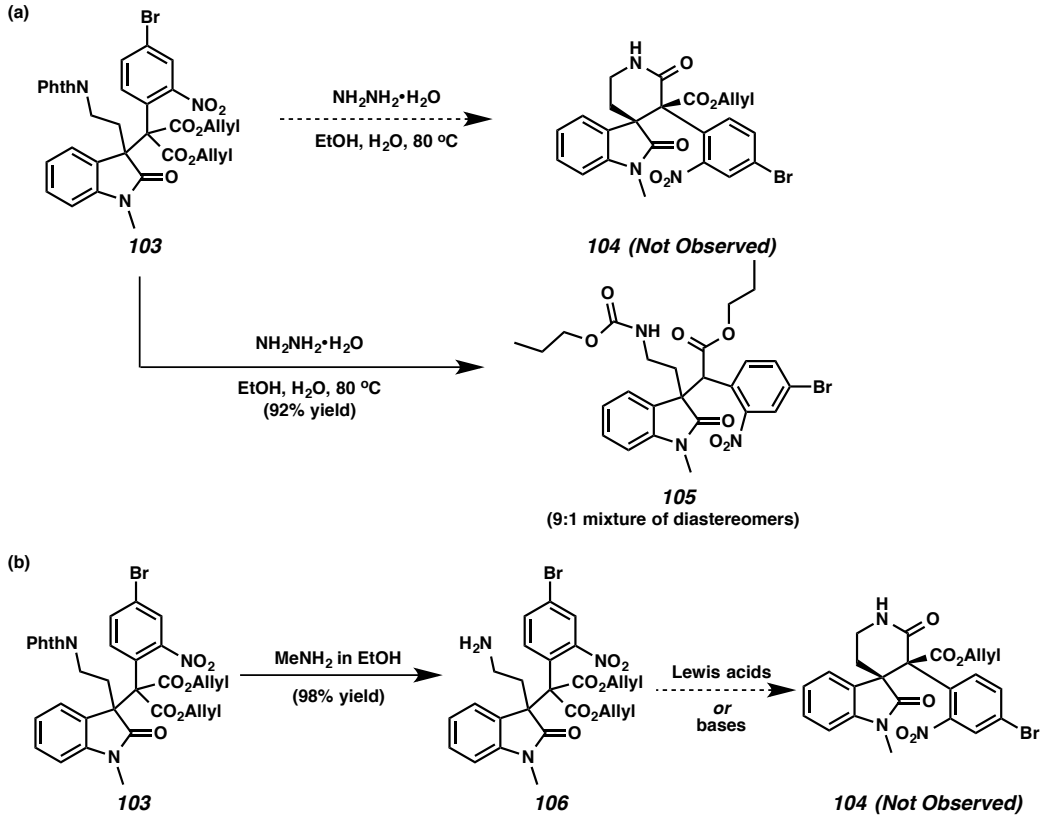
Scheme A3.1.1. *Direct Lactam-Forming Strategy Toward Communesin F (**1f**)*



101 ***102*** ***Communesin F (1f)***

To examine diastereoselective lactam formation, we chose phthalimide **103** as a model substrate. Interestingly, an attempt to remove the phthalyl protecting group and simultaneously construct lactam **104** from malonate **103** furnished a 9:1 diastereomeric mixture of **105** (Scheme A3.1.2a). The double bonds of the allyl groups were reduced and one of the resultant propyl esters was transferred to the amine. Treatment of phthalimide **103** with methylamine generated the desired amine **106** (Scheme A3.1.2b). Despite extensive screening of Lewis acids, acids, and bases (e.g., $AlMe_3$, KO*t*-Bu, *p*-TsOH), lactamization of malonate **106** proved to be challenging.

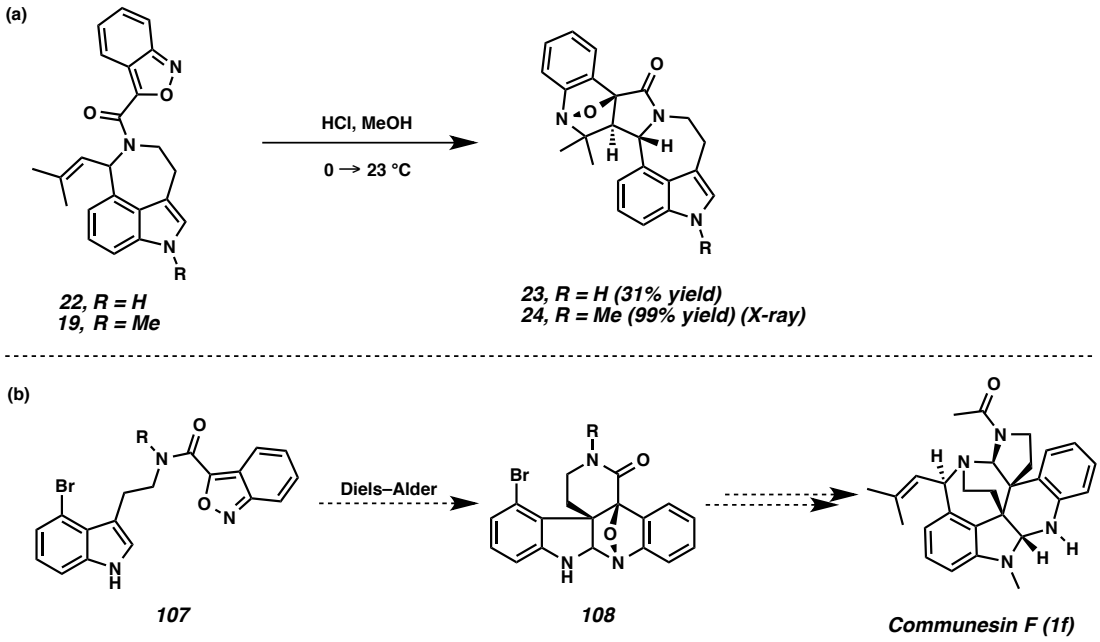
Scheme A3.1.2. *Attempted Lactam-Forming Reactions*



A3.2. Diels–Alder Strategy

Next, we investigated a Diels–Alder strategy toward the total synthesis of communesin F (**1f**). As described in Schemes A3.2.1a and 1.2.5, the benzisoxazole in **19** and **22** reacted with the butenyl side chain by an intramolecular Diels–Alder cycloaddtion to afford the undesired bridged polycycles **24** and **23**, respectively. We expected that the desired core structure could be constructed via an intramolecular Diels–Alder reaction with substrates, which possess no butenyl side chain (Scheme A3.2.1b).

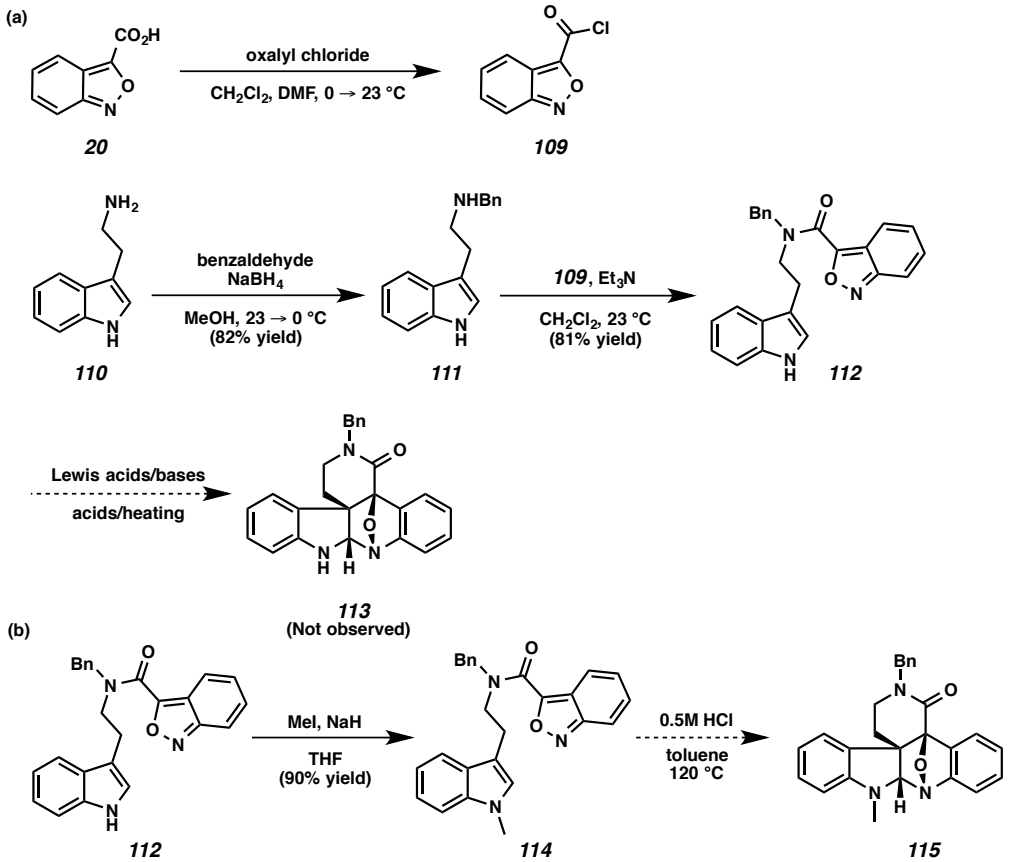
Scheme A3.2.1. *Diels–Alder Strategy Toward Communesin F (**1f**)*



Treatment of acid **20** with oxalyl chloride produced acyl chloride **109**, which was used directly without further purification (Scheme A3.2.2a). Tryptamine (**110**) was used as the model substrate to explore a Diels–Alder strategy. Reductive amination of tryptamine (**110**) with benzaldehyde furnished benzyl amine **111**, which was coupled

with acid chloride **109** to afford amide **112**. However, all attempts at intramolecular Diels–Alder reactions using a wide variety of conditions (e.g., HCl, $BF_3{\cdot}OEt_2$, Et_2AlCl, $SnCl_4$, KO*t*-Bu, SiO_2, MeMgBr, $AgClO_4$, heating) to provide the communesin F core structure were unsuccessful.[1] Indole **112** was protected with methyl iodide to produce **114**, but the desired Diels–Alder cycloaddition product was not observed (Scheme A3.2.2b).

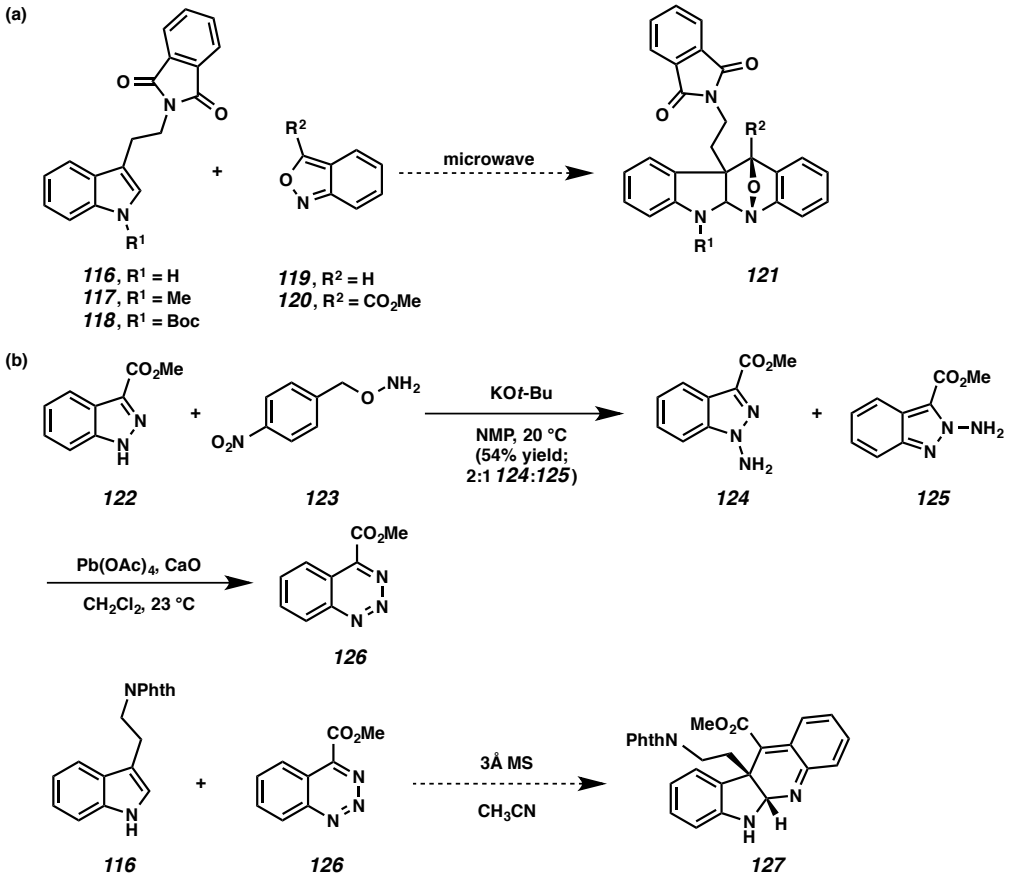
Scheme A3.2.2. *Intramolecular Diels–Alder Reactions*



Having failed to access the communesin F core by intramolecular Diels–Alder reactions, we chose to examine intermolecular Diels–Alder reactions (Scheme A3.2.3).

Intermolecular Diels–Alder reactions between phthalimide **116–118** and benzisoxazole **119–120** did not proceed below 150 °C and the anthranil fragment decomposed at a higher temperature (Scheme A3.2.3a). Addition of Lewis acids did not improve the reactivities. Alternatively, we envisioned that a Diels–Alder reaction of 1,2,3-benzotriazine with phthalimide **116** would afford **127** by loss of N_2 (Scheme A3.2.3b).[2] Amination of indazole **122** followed by oxidation with lead tetraacetate furnished 1,2,3-benzotriazine **126**. Disappointingly, the desired adduct (**127**) was not observed by intermolecular Diels–Alder reactions under several conditions.

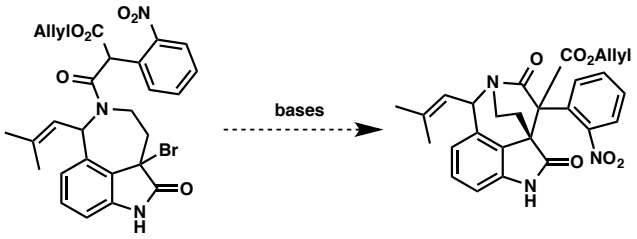
Scheme A3.2.3. *Intermolecular Diels–Alder Reactions*



A3.3. Intramolecular Alkylation of 3-Bromooxindole Strategy

A plausible rationale for forming *syn*-selective adduct **42** from alkylation of 3-bromooxindole **40** and malonate **41** is that the tosyl group would be located far from the isobutenyl group due to steric hindrance and thus, malonate **41** would approach *syn* to the isobutenyl group to reduce the steric interaction with the tosyl group (Scheme 1.2.9). We believed that intramolecular alkylation of the 3-bromooxindole with a tethered malonate derivative in **128** could deliver the stereochemistry needed for the synthesis of communesin F (**1f**).

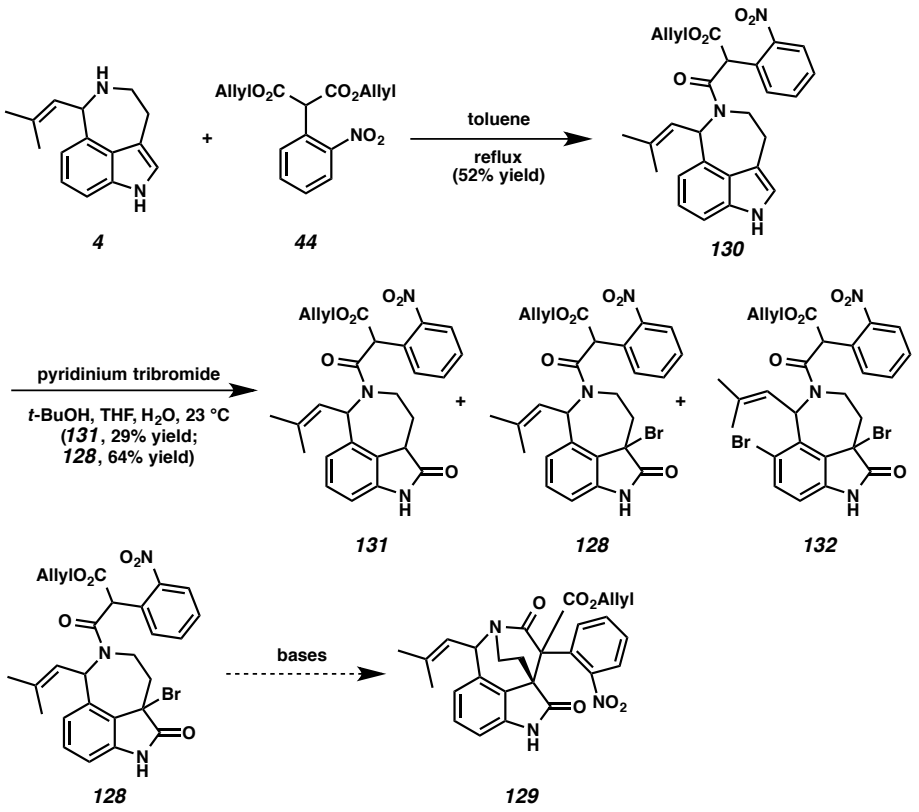
Scheme A3.3.1. *Intramolecular Alkylation Strategy*



128 *129*

Coupling of aurantioclavine (**4**) and malonate **44** afforded amide **130**, which was oxidized with pyridinium tribromide to furnish a mixture of **131**, **128**, and **132** (Scheme A3.3.2). Unfortunately, intramolecular alkylation of 3-bromooxindole **128** provided a complex mixture of the unisolable desired product and byproducts even after extensive screening of the reaction parameters.

Scheme A3.3.2. *Intramolecular Alkylation of 3-Bromooxindole*



Although our synthetic efforts toward the total synthesis of communesin F were unsuccessful, we believe that these routes are one of the most expedient routes to complex communesin F.

A3.4. Experimental Methods and Analytical Data

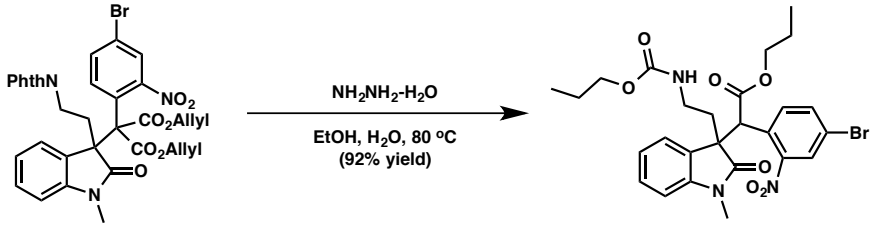
A3.4.1. Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Reaction progress was monitored by thin-layer chromatography (TLC). THF, Et_2O, CH_2Cl_2, toluene,

benzene, CH_3CN, and dioxane were dried by passage through an activated alumina column under argon. Triethylamine was distilled over CaH_2 prior to use. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. Brine solutions are saturated aqueous solutions of sodium chloride. Commercially available reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulator unless otherwise indicated. Microwave-assisted reactions were performed in a Biotage Initiator 2.5 microwave reactor. Glove box manipulations were performed under a N_2 atmosphere. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or PMA (phosphomolybdic acid) staining. Silicycle Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.064 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on a Varian Inova 500 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm), or $(CD_3)_2CO$ (δ 2.05 ppm). ^{13}C NMR spectra are recorded on a Varian Inova 500 MHz spectrometer (125MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm), or $(CD_3)_2CO$ (δ 29.84 ppm). Data for ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d= broad doublet, app = apparent. Data for ^{13}C are reported in terms of chemical shifts (ppm). IR spectra were obtained using a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from Agilent 6200 Series TOF with an Agilent G1978A

Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+).

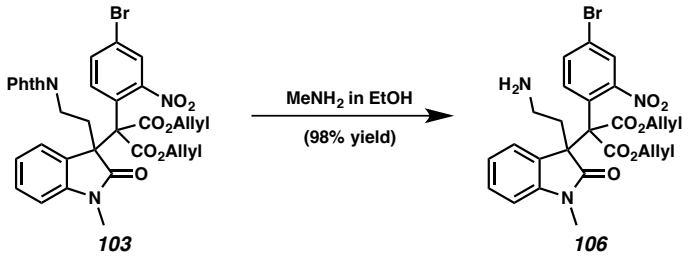
A3.4.2. Experimental Procedures



103 ***105***
(9:1 mixture of diastereomers)

To a solution of phthalimide **103** (20.0 mg, 0.0285 mmol, 1.00 equiv) in EtOH (3.00 mL) and H_2O (2.40 μL) was added hydrazine monohydrate (28.0 μL, 0.577 mmol, 20.0 equiv). The reaction mixture was heated to 80 °C for 1 h. The reaction mixture was then cooled to 23 °C and the resulting solid was filtered through a plug of celite. The residue was purified by column chromatography using mixtures of EtOAc and hexanes to provide oxindole **105** (15.1 mg, 92% yield).

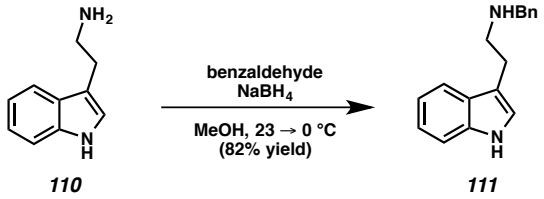
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (d, *J* = 2.1 Hz, 1H), 7.50 (d, *J* = 7.4 Hz, 1H), 7.47 – 7.42 (m, 1H), 7.35 (d, *J* = 8.6 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 5.07 (s, 1H), 4.35 (s, br, 1H), 3.96 (dt, *J* = 9.9, 6.7 Hz, 2H), 3.86 (t, *J* = 6.7 Hz, 2H), 3.02 (s, 3H), 2.81 – 2.70 (m, 2H), 2.29 (s, br, 1H), 2.08 – 2.03 (m, 1H), 1.55 – 1.47 (m, 4H), 0.88 (dd, *J* = 14.0, 7.0 Hz, 3H), 0.76 (t, *J* = 7.4 Hz, 3H).



103 *106*

To a solution of $MeNH_2$ (8M in EtOH; 9.5 mL) was added phthalimide **103** (20.0 mg, 0.0285 mmol). The solution was stirred for 12 h at 23 °C. Then, the solution was concentrated to afford amine **106** (16.0 mg, 98% yield).

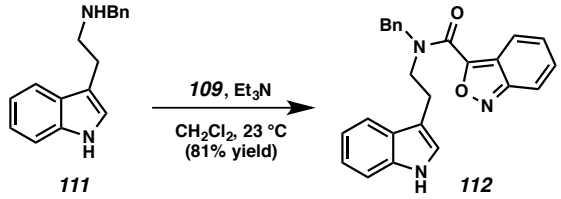
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (q, *J* = 2.2 Hz, 1H), 7.49 (dd, *J* = 7.5, 2.5 Hz, 1H), 7.41 (dt, *J* = 8.7, 2.4 Hz, 1H), 7.32 – 7.25 (m, 2H), 7.12 (ddd, *J* = 9.5, 7.6, 2.5 Hz, 1H), 6.70 (dd, *J* = 7.8, 2.5 Hz, 1H), 5.79 (ddq, *J* = 15.1, 9.3, 4.6, 4.2 Hz, 1H), 5.68 (ddtd, *J* = 16.9, 11.4, 5.7, 2.6 Hz, 1H), 5.19 (d, *J* = 17.1 Hz, 1H), 5.15 – 5.07 (m, 4H), 4.47 (pd, *J* = 12.2, 11.3, 4.9 Hz, 3H), 4.39 (d, *J* = 5.3 Hz, 2H), 2.97 (s, 3H), 2.75 (dp, *J* = 27.3, 6.8 Hz, 2H), 2.29 (dt, *J* = 12.6, 6.8 Hz, 1H), 2.09 – 2.01 (m, 1H).



110 *111*

To a solution of tryptamine (**110**) (500 mg, 3.12 mmol, 1.00 equiv) in MeOH (15.6 mL) at 23 °C was added benzaldehyde (0.350 mL, 3.43 mmol, 1.10 equiv). After 4 h, the reaction mixture was cooled to 0 °C. Then, $NaBH_4$ (177 mg, 4.68 mmol, 1.50 equiv) was added and the reaction mixture was stirred for an additional 1 h. The reaction was quenched with sat. aq $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (3 x 7.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and

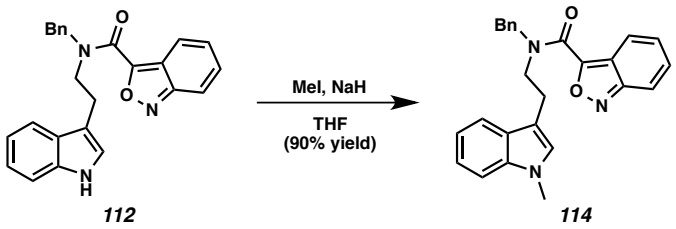
concentrated *in vacuo* to afford amine **111** (640 mg, 82% yield). Data for the compound matches reported data.[1]



To a solution of acid chloride **109** (0.613 mmol) and Et_3N (0.26 mL, 1.84 mmol, 3.00 equiv) in CH_2Cl_2 (3.10 mL) was added indole **111** (154 mg, 0.613 mmol, 1.00 equiv) at 23 °C. The reaction mixture was stirred for 6 h at 23 °C. After the reaction was done, water was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 3.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography with mixtures of EtOAc and hexanes to afford amide **112** (197 mg, 81% yield).

(Due to the distinct presence of rotameric isomers, the ^{1}H NMR contained extra peaks.) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.81 (d, *J* = 8.9 Hz, 1H), 7.64 – 7.53 (m, 3H), 7.47 – 7.41 (m, 1H), 7.38 – 7.35 (m, 4H), 7.33 – 7.28 (m, 5H), 7.23 – 7.14 (m, 4H), 7.13 – 7.02 (m, 5H), 6.94 (d, *J* = 2.4 Hz, 1H), 4.85 (s, 4H), 4.01 (t, *J* = 7.4 Hz, 2H), 3.82 (t, *J* = 7.6 Hz, 2H), 3.14 (dt, *J* = 14.5, 7.6 Hz, 4H).

[1] Martin, D. B. C.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 3472–3473.

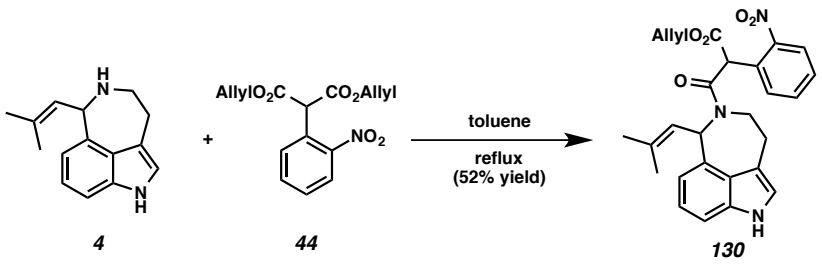


112 ***114***

To a solution of indole **112** (68.4 mg, 0.173 mmol, 1.00 equiv) in THF (0.900 mL) were added MeI (0.110 mL, 1.73 mmol, 10.0 equiv) and NaH (60%; 14.0 mg, 0.346 mmol, 2.00 equiv) at 0 °C. The reaction mixture was stirred at 23 °C for 4 h. The reaction was quenched with sat. aq NH_4Cl. The aqueous phase was extracted with EtOAc (3 x 1.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography with mixtures of EtOAc and hexanes to afford amide **114** (64.0 mg, 90% yield).

(Due to the distinct presence of rotameric isomers, the ^{1}H NMR contained extra peaks.)

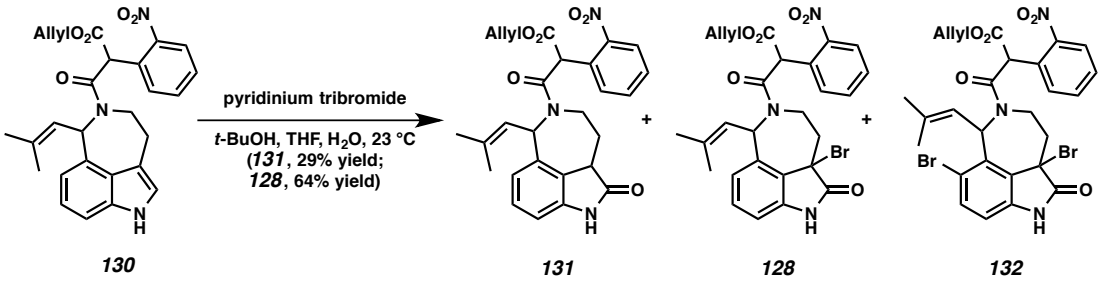
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.9 Hz, 0.5H), 7.69 (dt, *J* = 8.9, 1.1 Hz, 1H), 7.61 (dd, *J* = 12.1, 8.5 Hz, 1H), 7.54 (dt, *J* = 9.1, 1.0 Hz, 1H), 7.44 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.41 – 7.36 (m, 4H), 7.31 (tdd, *J* = 7.3, 4.0, 1.8 Hz, 5H), 7.12 – 7.05 (m, 4H), 6.91 (s, br, 0.5H), 6.76 (s, 1H), 4.88 (d, *J* = 2.3 Hz, 3.5H), 4.04 (t, *J* = 7.2 Hz, 2H), 3.86 – 3.78 (m, 1H), 3.74 (s, 1.5H), 3.57 (s, 3H), 3.16 (d, *J* = 8.2 Hz, 1H), 3.09 (t, *J* = 7.1 Hz, 2H).



4 ***44*** ***130***

To a solution of aurantioclavine (**4**) (10.0 mg, 0.0442 mmol, 1.00 equiv) in toluene (0.200

mL) was added malonate **44** (15.0 mg, 0.0486 mmol, 1.10 equiv). The reaction mixture was refluxed for 12 h. Then, the reaction was quenched with water. The aqueous phase was extracted with EtOAc (3 x 1.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography with mixtures of EtOAc and hexanes to afford indole **130** (10.8 mg, 52% yield). Due to the distinct presence of rotameric isomers and diastereomeric mixtures, the ^1H NMR contained extra peaks.



To a solution of indole **130** (10.9 mg, 0.0230 mmol, 1.00 equiv) in *t*-BuOH (0.230 mL) and THF (0.06 mL), H_2O (2.10 μL) was added. Then, pyridinium tribromide (14.3 mg, 0.0448 mmol, 1.95 equiv) was added at 23 °C. The reaction was stirred at 23 °C for 6 h. Then, the reaction was quenched with water. The aqueous phase was extracted with EtOAc (3 x 0.50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography with mixtures of EtOAc and hexanes to afford mixtures of **131** (3.30 mg, 29% yield), **128** (8.35 mg, 64% yield), and trace amounts of **132**. Due to the distinct presence of rotameric isomers and diastereomeric mixtures, the ^1H NMR contained extra peaks.

A3.5. References and Notes

(1) (a) Boger, D. L.; Cassidy, K. C.; Nakahara, S. *J. Am. Chem. Soc.* **1993**, *115*, 10733–10741. (b) Suzuki, T.; Kobayashi, S. *Org. Lett.* **2010**, *12*, 2920–2923. (c) Asao, N.; Sato, K.; Menggenbateer; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 3682–3685. (d) Martin, D. B. C.; Nguyen, L. Q.; Vanderwal, C. D. *J. Org. Chem.* **2012**, *77*, 17–46. (e) Chen, Y.; Wang, L.; Liu, Y.; Li, Y. *Chem. Eur. J.* **2011**, *17*, 12582–12586.

(2) Koyama, J.; Toyokuni, I.; Tagahara, K. *Chem. Pharm. Bull.* **1998**, *46*, 332–334.

APPENDIX 4

Stereochemical Evaluation of Bisphosphine Copper Catalysts for the Asymmetric Alkylation of 3-Bromooxindoles with α-Arylated Malonate Esters†

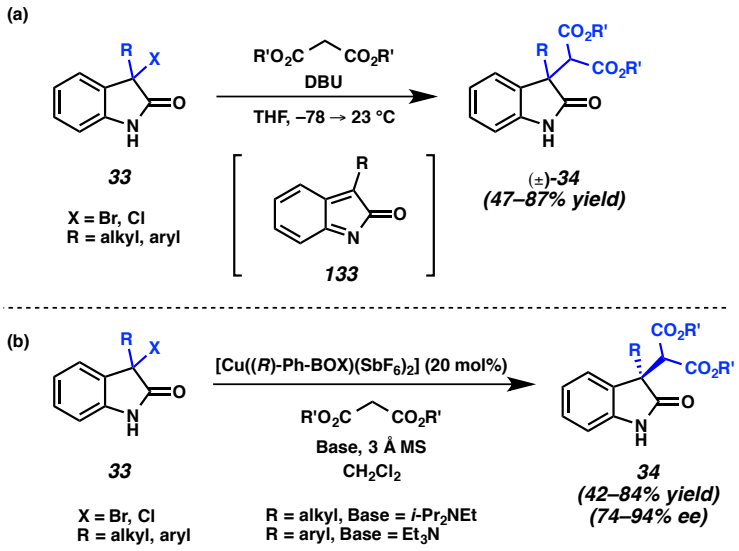
A4.1. Introduction

3,3-Disubstituted oxindole moieties are present in a wide variety of natural products and pharmaceutical agents.[1] Accordingly, methods for the asymmetric construction of 3,3-disubstituted oxindoles have attracted considerable attention from the synthetic community, and a number of catalytic stereoselective approaches to provide C3 quaternary stereocenters on oxindoles have been reported.[2,3] In 2007, we discovered that 3,3-disubstituted oxidoles **34** were furnished efficiently by base-mediated alkylation of reactive electrophilic *o*-azaxylyxene **133**, generated from 3-halooxindole **33**, with nucleophilic malonate esters (Scheme A4.1.1a).[3a] Additionally, we developed a method for the enantioselective alkylation of 3-bromooxindoles **33** by using a copper (*R*)-Ph-BOX ligand complex (Scheme A4.1.1b).[3b]

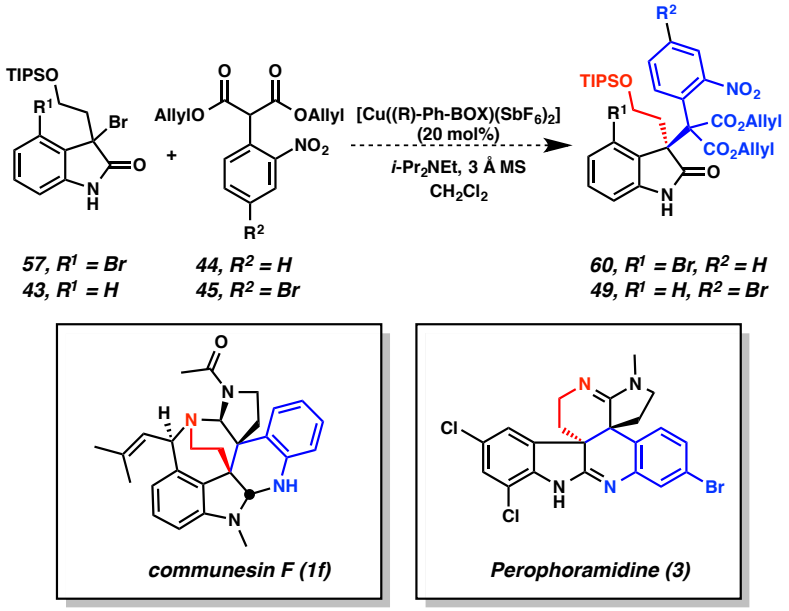
† This work was performed in collaboration with Dr. Chung Whan Lee and Dr. Scott C. Virgil. Additionally, this work has been published and adapted with permission from Lee, C. W.; Han, S.-J.; Virgil, S. C.; Stoltz, B. M. *Tetrahedron* **2014**, *71*, 3666–3670. Copyright 2014 Elsevier.

Following our development of these methods, our attention turned to the syntheses of the polycyclic alkaloids communesin F (**1f**) and perophoramidine (**3**).[4] We envisioned that the stereochemistry at the vicinal quaternary centers on communesin F and perophoramidine could be installed utilizing the conditions described in Scheme A4.1.1b. However, attempts to produce diesters **60** and **49** via copper catalyzed enantioselective alkylation of 3-bromooxindoles **57** and **43** with α-arylated malonate esters **44** and **45** were unsuccessful (Scheme A4.1.2). Therefore, we pursued the development of an alternative catalytic system.

Scheme A4.1.1. *Construction of 3,3-Disubstituted Oxindoles by Alkylation of 3-Halooxindoles*



Scheme A4.1.2. *Attempts for Alkylation of 3-Bromooxindoles with α-Arylated Malonate Esters*



In our previous studies, we tested a variety of metal catalysts (e.g. Cu^{II}, Mg^{II}, La^{III}, and Ni^{II}) and discovered that the combination of Cu^{II} and a chiral bisoxazoline ligand effectively promoted the catalytic reaction. Chiral Cu(II) bisphosphine complexes have also found use in stereoselective synthesis.[5] Since the catalytic system can be formed with a number of different chiral bisphosphine ligands, quite a few options would be available for developing a stereoselective reaction. Herein, we describe several screening studies designed and undertaken to optimize the reaction conditions for the alkylation of 3-bromooxindoles with α-arylated malonate esters using a copper(II) bisphosphine catalyst.

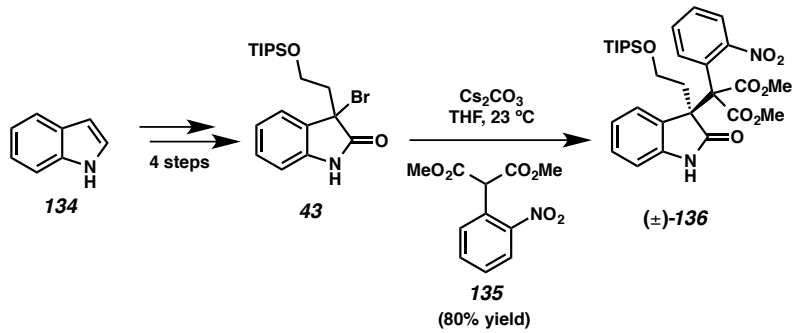
A4.2. Results and Discussion

A4.2.1. Initial Screening Results

To develop a stereoselective alkylation method, we chose simple substrates for optimization studies; specifically, we used bromooxindole **43** without a substituent on

the aromatic ring and *o*-nitrophenyl dimethylmalonate **135** as a coupling partner. Bromooxindole **43** was easily prepared from indole (**134**) in four steps by a known sequence,[4] which was then added to *o*-nitrophenyl dimethylmalonate **135** and cesium carbonate in THF solvent to afford a racemic product **136** in good yield. (Scheme A4.2.1).

Scheme A4.2.1. *Synthesis of the Racemic Product*



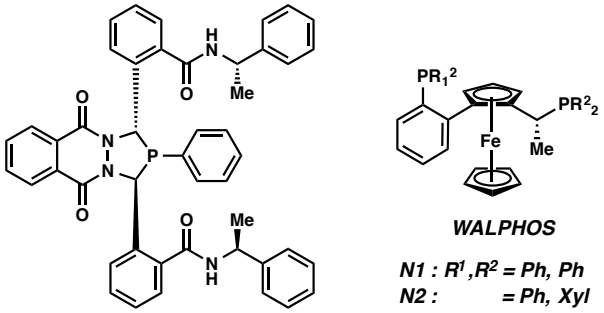
Choosing (*R*)-BINAP as a chiral ligand, we began our research by screening various copper sources, bases, and solvents. For instance we attempted the following variations of copper ions: Copper(II) triflate, copper(II) chloride with silver hexafluoroantimodate, copper(II) isobutyrate, copper(II) *tert*-butoxide (generated *in situ* by adding lithium *tert*-butoxide to copper(II) isobutyrate and ligand mixture), copper(II) ethylhexanoate, and copper(II) trifluoroacetylacetonate. We explored both organic and inorganic bases, including diisopropylethylamine, pyridine, tetramethylenediamine (TMEDA), triethylamine, diisopropylamine, 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU), sodium carbonate, potassium acetate, sodium ethylhexanoate and cesium carbonate. The various reactions combinations were attempted in the following solvents: dichloromethane, tetrahydrofuran, benzene, acetonitrile, and dioxane. Evaluating the 93 reactions that were explored,[6] we found

that copper(II) *tert*-butoxide and the ligand complex generated in THF, which was similar to Fandrick's conditions for asymmetric propargylation[5], exhibited the best reactivity without generation of side products for the coupling of the arylated malonate **135** and bromooxindole **43** in CH_2Cl_2 (high conversion, 20% ee).

A4.2.2. Ligand Screening and Optimization Studies

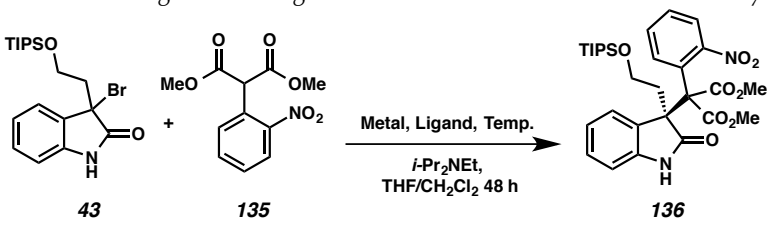
Based on previous studies, we selected copper(II) *iso*-butyrate, lithium *tert*-butoxide and THF solvent for generation of the catalytic species with chiral ligands, diisopropylamine as the base and CH_2Cl_2 as solvent. We have screened 69 chiral bisphosphine ligands[6] under similar condition, finding WALPHOS and DiazaPHOS to give the best enantioselectivities (Figure A4.2.1).

Figure A4.2.1. *Results with DiazaPHOS and WALPHOS*



Having identified the most effective ligands, we next screened several copper sources under lower temperatures. Although none of these sources exhibited better results than the combination of copper(II) isobutyrate and lithium *tert*-butoxide for WALPHOS (**N1** and **N2**), we were able to observe better stereoselectivity at low temperature (Table A4.2.1, entries 6 and 16). With DiazaPHOS (**W1**), copper(II) triflate showed better selectivity at 0 ºC (Table A4.2.1, entries 22 and 23).

Table A4.2.1. *Further investigations using WALPHOS and DiazaPHOS in the alkylation reaction*



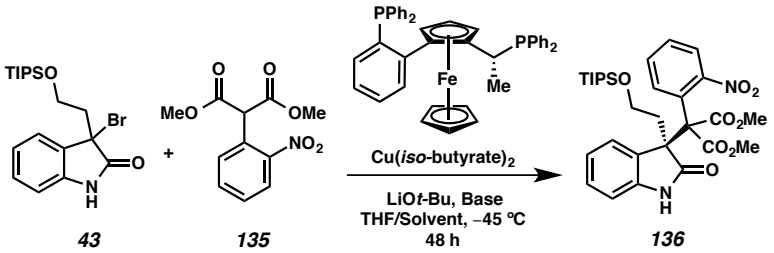
43 ***135*** ***136***

Entry	Metal Sources	Ligand	Additive	Temp.	ee[a]
1	$CuCl_2$	**N1**	$AgBF_4$	–45 ºC	–
2	$CuCl_2$	**N1**	$AgNTf_2$	–45 ºC	–
3	$CuCl_2$	**N1**	$AgPF_6$	–45 ºC	–
4	$CuCl_2$	**N1**	$AgSbF_6$	–45 ºC	–
5	$CuCl_2$	**N1**	LiO*t*-Bu	–45 ºC	–
6	Cu(*iso*-butyrate)$_2$	**N1**	LiO*t*-Bu	–45 ºC	44%
7	Cu(*iso*-butyrate)$_2$	**N1**	$AgSbF_6$	–45 ºC	–
8	Cu(hfacac)$_2$	**N1**		–45 ºC	trace
9	Cu(OTf)$_2$	**N1**		–45 ºC	trace
10	Cu(OTf)$_2$	**N1**	LiO*t*-Bu	–45 ºC	23%
11	Cu(EH)$_2$	**N1**		–45 ºC	trace
12	$CuCl_2$	**N2**	$AgBF_4$	–45 ºC	–
13	$CuCl_2$	**N2**	$AgNTf_2$	–45 ºC	–
14	$CuCl_2$	**N2**	$AgPF_6$	–45 ºC	–
15	$CuCl_2$	**N2**	$AgSbF_6$	–45 ºC	–
16	Cu(*iso*-butyrate)$_2$	**N2**	LiO*t*-Bu	–45 ºC	54%
17	Cu(hfacac)$_2$	**N2**		–45 ºC	30%
18	Cu(OTf)$_2$	**N2**		–45 ºC	45%
19	Cu(EH)$_2$	**N2**		–45 ºC	trace
20	Cu(*iso*-butyrate)$_2$	**W1**	LiO*t*-Bu	0 ºC	trace
21	Cu(*iso*-butyrate)$_2$	**W1**[b]	LiO*t*-Bu	0 ºC	trace
22	Cu(OTf)$_2$	**W1**		0 ºC	40%
23	Cu(OTf)$_2$	**W1**[b]		0 ºC	50%

Conditions: 0.0049 mmol **43**, 0.0145 mmol **135**, Cu (20 mol %), Ligand (22 mol %), Additive (20 mol %), *i*-Pr_2NEt (3 equiv.), 0.1 mL CH_2Cl_2 (0.049 M). Metal catalyst, ligand and additives were mixed in THF. THF was removed *in vacuo*, and the resultant was diluted with the reaction solvent. The reaction was initiated by addition of base. Cu(hfacac)$_2$: Copper(II) hexafluoroacetylacetonate, Cu(EH)$_2$: Copper(II) ethylhexanoate. [a] enantiomeric excess was measured by chiral SFC. [b] 44 mol % of ligand was used.

With a suitable bisphosphine ligand in hand (**N1**), we tested multiple solvents and bases. However, amine bases weaker than Hünig's base (Table A4.2.2, entries 1-12) could not initiate the reaction, whereas stronger bases (entries 13-18) decreased the stereoselectivity. The copper bisphosphine complex demonstrated similar selectivity in dichloromethane (entry 19), THF (entry 20), and chloroform (entry 22), however it showed worse selectivity in acetonitrile (entry 21) and failed to proceed at all in toluene and 1,2-dimethoxyethane (DME).

Table A4.2.2. *Investigation of reaction solvents and bases with WALPHOS in the alkylation reaction*



43 ***135*** ***136***

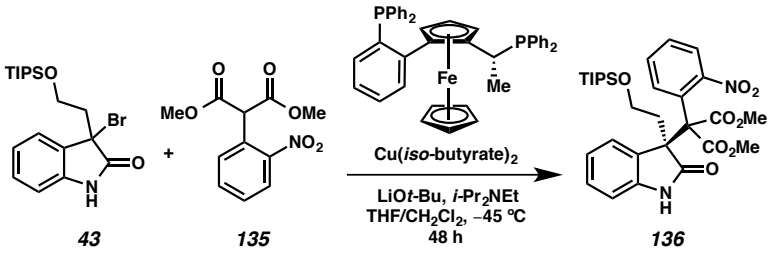
Entry	Solvent	Base	ee
1	CH_2Cl_2	DABCO	–
2	THF	DABCO	–
3	CH_3CN	DABCO	–
4	$CHCl_3$	DABCO	–
5	Toluene	DABCO	–
6	DME	DABCO	–
7	CH_2Cl_2	DMAP	–
8	THF	DMAP	–
9	CH_3CN	DMAP	–
10	$CHCl_3$	DMAP	–
11	Toluene	DMAP	–
12	DME	DMAP	–
13	CH_2Cl_2	Cs_2CO_3	35%
14	THF	Cs_2CO_3	15%
15	CH_3CN	Cs_2CO_3	20%
16	$CHCl_3$	Cs_2CO_3	20%
17	Toluene	Cs_2CO_3	–
18	DME	Cs_2CO_3	10%
19	CH_2Cl_2	*i*-Pr_2NEt	40%
20	THF	*i*-Pr_2NEt	50%
21	CH_3CN	*i*-Pr_2NEt	30%
22	$CHCl_3$	*i*-Pr_2NEt	40%
23	Toluene	*i*-Pr_2NEt	–
24	DME	*i*-Pr_2NEt	–

Conditions: 0.0024 mmol **43**, 0.0072 mmol **135**, Cu (20 mol %), Ligand (22 mol %), LiO*t*-Bu (20 mol %), Base (3 equiv), 0.06 mL CH_2Cl_2 (0.04 M).

In addition to these studies, we examined the effect of the catalyst and ligand loading on the stereoselectivity of our alkylation reaction. Unsatisfactory results were produced with low catalyst or ligand loading (Table A4.2.3, entries 1,2 and 4), but 20 mol % of copper(II) isobutyrate and 40 mol % of the ligand gave the product in 56% ee (Table A4.2.3, entry 3). Stoichiometric amounts of the copper presursor and ligand produced only a slight increase in ee (Table A4.2.3, entry 5). Additionally, we investigated the impact of the equivalents of Hünig's base on the selectivity of the reaction. Results showed the amount of Hünig's base had little effect on the

stereoselectivity of the product (Table A4.2.3, entries 6-13). Subsequent examination of concentration effects showed lowering the concentration of the reaction mixture from 0.05 M to 0.02 M resulted in increase stereoselectivity (Table A4.2.4).

Table A4.2.3. *Examination of the amount of catalyst and ligand loading in the alkylation reaction*

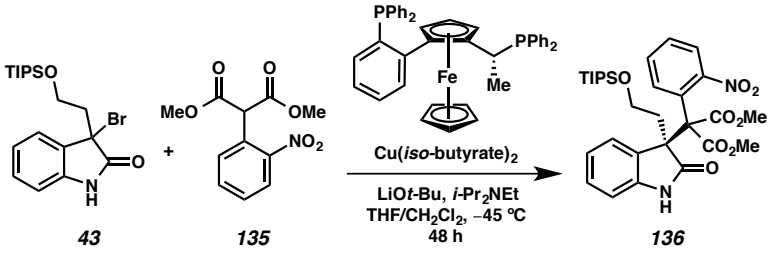


43 ***135*** ***136***

Entry	Cu(*iso*-butyrate)$_2$	Ligand	*i*-Pr$_2$NEt	ee
1	10 mol %	10 mol %	3.0 equiv	25%
2	10 mol %	20 mol %	3.0 equiv	28%
3	20 mol %	40 mol %	3.0 equiv	56%
4	20 mol %	10 mol %	3.0 equiv	35%
5	1 equiv	1 equiv	3.0 equiv	60%
6	20 mol %	20 mol %	1.0 equiv	33%
7	20 mol %	20 mol %	1.5 equiv	35%
8	20 mol %	20 mol %	2.0 equiv	38%
9	20 mol %	20 mol %	2.5 equiv	37%
10	20 mol %	20 mol %	4.0 equiv	36%
11	20 mol %	20 mol %	5.0 equiv	37%
12	20 mol %	20 mol %	6.0 equiv	36%
13	20 mol %	20 mol %	20 equiv	36%

Conditions: 0.0049 mmol **43**, 0.0145 mmol **135**, LiO*t*-Bu (10 mol %), 0.1 mL CH_2Cl_2 (0.049 M).

Table A4.2.4. *Examination of concentration in the malonate addition reaction*

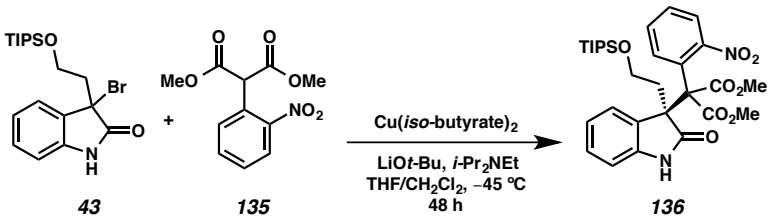


43 ***135*** ***136***

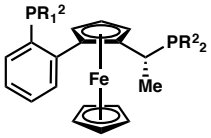
Entry	Concentration	ee
1	0.005 M	53%
2	0.01 M	63%
3	0.02 M	64%
4	0.05 M	55%
5	0.25 M	40%

Conditions: 0.0049 mmol **43**, 0.0145 mmol **135**, Cu (20 mol %), Ligand (40 mol %), LiO*t*-Bu (20 mol %), *i*-Pr$_2$NEt (3 equiv).

Table A4.2.5. *The effect of WALPHOS substituents under optimized conditions in the alkylation reaction*



43 ***135*** ***136***



WALPHOS

N1 : R^1,R^2 = Ph, Ph
N2 : = Ph, Xyl
N3 : = Ph, Xyl^F
N4 : = 3,5-Me_2-4-MeOPh, Xyl^F
N5 : = Ph, Cy
N6 : = Cy, Xyl^F
N7 : = Xyl, Xyl
N8 : = Ph, Norbornyl

Entry	Ligand	ee
1	**N1**	60%
2	**N2**	trace
3	**N3**	25%
4	**N4**	25%
5	**N5**	70%
6	**N6**	–
7	**N7**	–
8	**N8**	–

Conditions: 0.0049 mmol **43**, 0.0145 mmol **135**, Cu (20 mol %), Ligand (40 mol %), LiO*t*-Bu (20 mol %), *i*-Pr_2NEt (3 equiv), 0.25 mL CH_2Cl_2 (0.02 M).

Finally, we explored a set of WALPHOS ligands (**N1** – **N8**) under our optimized conditions. Gratifyingly, we observed improved ee by using (Ph,Cy)-WALPHOS (Table A4.2.5, entry 5), leading to product formation in 70% ee, whereas other ligands showed diminished selectivity. To date, this is the best result we have, which is a great improvement over the starting point.

A4.3. Conclusion

Asymmetric alkylation of 3-halooxindoles with malonate esters is an effective method to construct 3,3,-disubstituted oxindole moieties. Herein, we have reported that copper(II) chiral bisphosphine complex demonstrated reactivity with an α-arylated malonate ester, which was an unreactive substrate in previously developed

conditions. This method could be applied to the installation of vicinal quaternary centers on communesin F and perophoramidine and could be useful in the synthesis of a variety of other natural products.

A4.4. Selected Experiments

A4.4.1. Synthesis of (±)-136

To a flame-dried round-bottomed flask, equipped with a stirbar, was added bromooxindole **43** (20 mg, 0.045 mmol), *o*-nitrophenyl dimethylmalonate **135** (37 mg, 0.135 mmol) and THF (0.5 mL). To the mixture was added cesium carbonate (47.4 mg, 0.045 mmol) at ambient temperature and the reaction mixture was then stirred for 3 h. The reaction mixture was then treated with saturated NH_4Cl aqueous solution, extracted with EtOAc, washed with brine and dried over $MgSO_4$. After concentration *in vacuo*, the crude product was obtained. Chromatography (6:1 hexanes : ethyl acetate) on silica gel afforded the title compound **136** (23 mg, 80% yield) as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (d, *J* = 8.1 Hz, 1H), 7.85 (s, 1H), 7.74 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.40 (dtd, *J* = 26.6, 7.4, 1.5 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.14 (td, *J* = 7.7, 1.3 Hz, 1H), 6.90 (td, *J* = 7.7, 1.2 Hz ,1H), 6.75 (dd, *J* = 7.8, 1.1 Hz, 1H), 3.74 (s, 3H), 3.65 (s, 3H), 3.35 (ddd, *J* = 9.5, 8.4, 6.9 Hz, 1H), 3.06 (td, *J* = 9.3, 4.5, 1H), 2.93 (ddd, *J* = 12.6, 8.8, 6.7 Hz, 1H), 2.54 (ddd, *J* = 12.8, 8.4, 4.4 Hz, 1H), 0.89 (s, 21H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.86, 167.63, 167.27, 150.34, 140.67, 132.46, 131.12, 129.49, 129.23, 128.63, 128.61, 126.73, 125.39, 122.45, 109.98, 109.12, 59.52, 56.71, 52.81, 52.80, 38.34, 29.70, 17.85, 17,84, 11.80. IR (Neat Film, NaCl) 2923, 2852, 1722, 1617, 1532, 1463, 1353, 1259, 1097, 992,

799, 753 cm^{-1}; HRMS (MM) *m/z* calc'd for $C_{30}H_{40}N_2O_8Si$ $[M+H]^+$: 585.2627, found 585.2636.

A4.4.2. Ligand Screening Procedure

Every step was performed in a nitrogen-filled glove box. Solutions of Copper(II) isoburtyrate (8 mg, 0.034 mmol) in THF (3.5 mL), lithium *tert*-butoxide (2.72 mg, 0.034 mmol) in THF (3.5 mL), bromooxindole **43** (70 mg, 0.17 mmol) and malonate **135** (129 mg, 0.51 mmol) in CH_2Cl_2 (1.75 mL), *i*-Pr_2NEt (0.1 ml, 0.57 mmol) in CH_2Cl_2 (2 mL) were prepared in 2 dram vials prior to reaction setup. To a ligand (1.1 μmol, 22 mol %) in a 1 dram vial equipped with a stirbar was added copper(II) isobutyrate in THF (0.1 mL, 0.97 μmol, 20 mol %). The heterogeneous solution was agitated at room temperature for 10-20 min until a clear homogeneous solution was generated. The reaction mixtures were charged with lithium *tert*-butoxide in THF (0.1 mL, 0.97 μmol, 20 mol %). Reaction mixtures were allowed to stir for 5 min and concentrated under reduced pressure. A mixture of bromooxindole **43** and malonate **135** in CH_2Cl_2 (0.05 mL, 4.85 μmol, 14.55 μmol) was dispensed to each vial and allowed to stir for 10 min. After setting the reaction temperature, *i*-Pr_2NEt in CH_2Cl_2 (0.05 mL, 14.55 μmol, 3 equiv) was added to the reaction vials and allowed to stir for 48 h. Upon completion, sat. aq ammonium chloride solution (0.1 mL) was added, and the mixture was filtered through silica gel. Each filtrate was diluted by 1 mL of solvent (ethyl acetate or isopropanol) and analyzed by chiral SFC. The mixture was separated by an AD-H column with 20% isopropanol as eluent.

A4.5. References and Notes

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APPENDIX 5

Spectra Relevant to Appendix 4:

Stereochemical Evaluation of Bisphosphine Copper Catalysts for the Asymmetric Alkylation of 3-Bromooxindoles with α-Arylated Malonate Esters

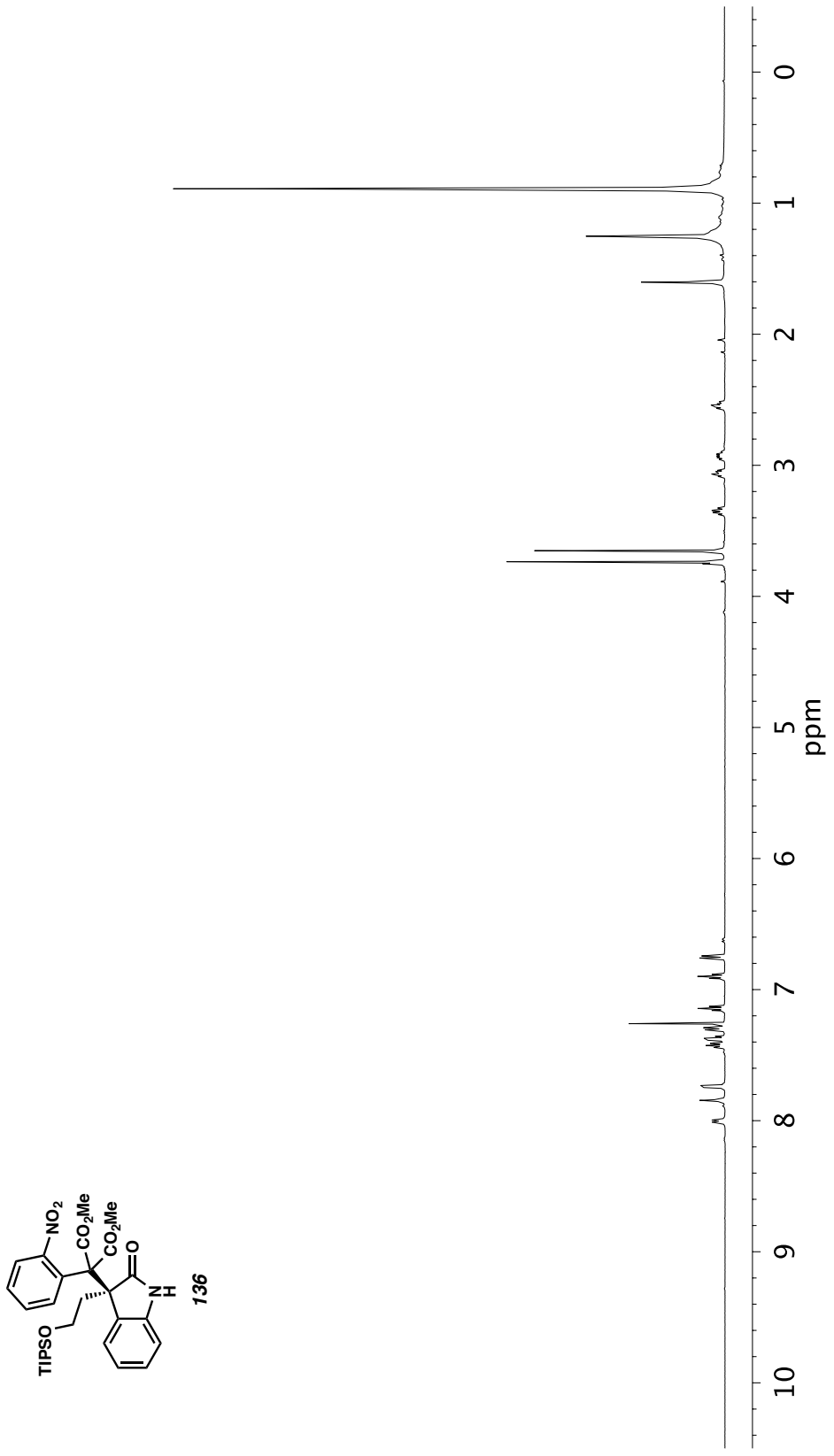


Figure A5.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **136**.

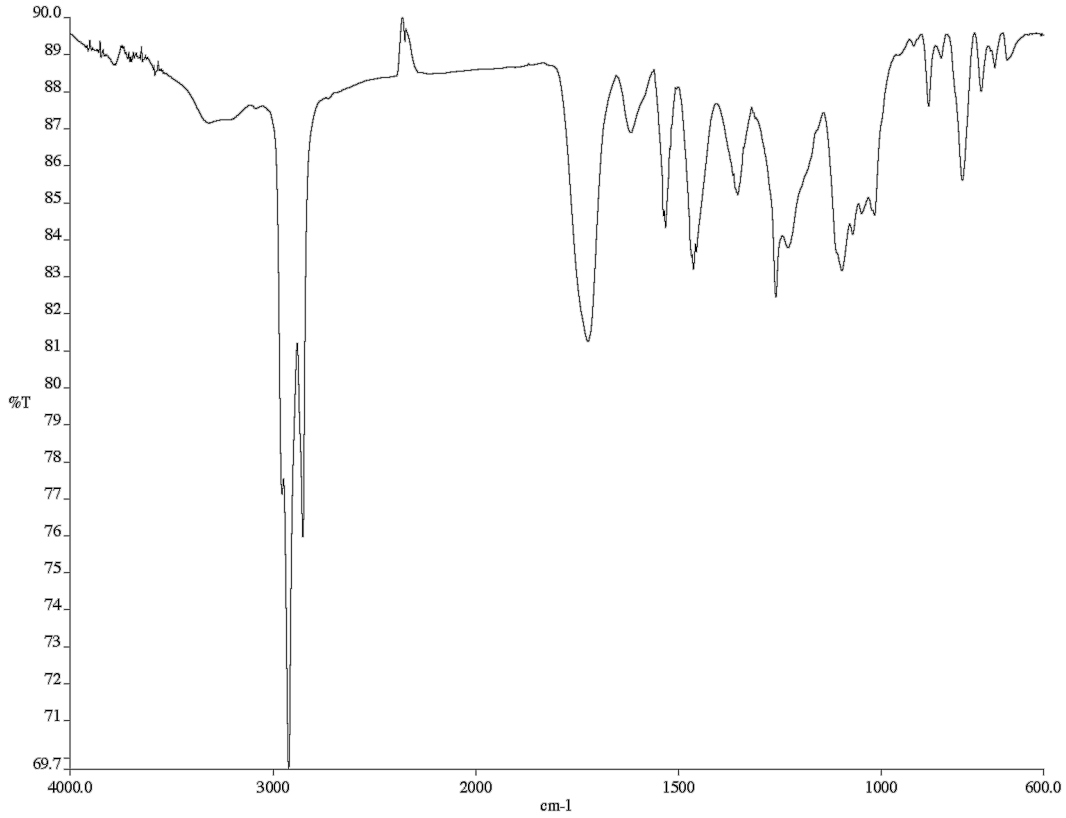


Figure A5.2. Infrared spectrum (Thin Film, NaCl) of compound **136**.

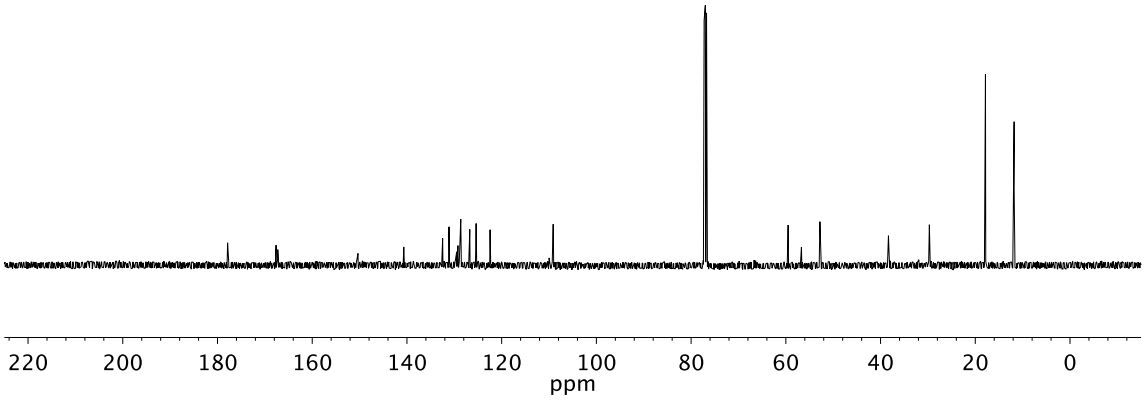


Figure A5.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **136**.

CHAPTER 2

A New Method for the Cleavage of Nitrobenzyl Amides and Ethers†

2.1. Introduction

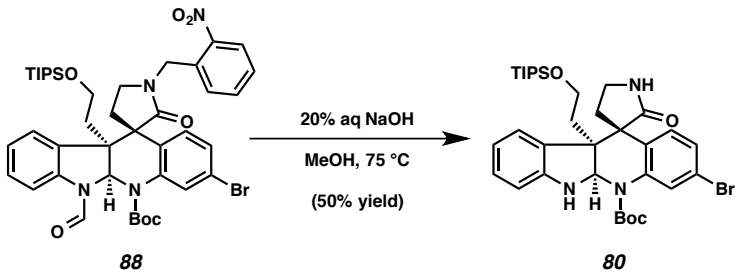
The selection of protection groups is critical to the synthesis of multifunctional complex molecules. Over the past decades, a wide variety of protecting groups have been developed to mask specific functional groups selectively.[1,2] However, despite considerable effort, relatively few protecting groups have been developed for the amide *N–H* (e.g., PMB, TBS, Benzyl, SEM, allyl, etc.).[3] Consequently, limitations associated with cleavage of amide protecting groups often arise.[4] Herein, we report *o*- and *p*-nitrobenzyl groups as easily introducible and removable protecting groups for both R_2N–*H* (including amides) and *RO–H* groups.

† This work was performed in collaboration with Gabriel Fernando de Melo. Additionally, this work has been published and adapted with permission from Han, S.-J.; Fernando de Melo, G.; Stoltz, B. M. *Tetrahedron Lett*. **2014**, *55*, 6467–6469. Copyright 2014 Elsevier.

2.2. Results and Discussion

In the course of our efforts toward the synthesis of the polycyclic, complex alkaloid perophoramidine, we serendipitously found that the *o*-nitrobenzyl group was easily removed by using 20% aqueous NaOH in methanol at 75 °C (Scheme 1).[5] *o*-Nitrobenzyl groups have been used as photocleavable protecting groups for amides and heterocycles such as indoles, benzimidazole, and 6-chlorouracil as well as the more common hydroxyl group.[6,7] In addition, a method for removing *p*-nitrobenzyl groups on hydroxyl groups in two steps by reduction to a *p*-aminobenzyl group followed by electrochemical oxidation was disclosed by the Kusumoto group.[8] To the best of our knowledge, ours was the first example of using simple aqueous NaOH to remove a nitrobenzyl group from a lactam.

Scheme 2.2.1. *o-Nitrobenzyl group cleavage on perophoramidine intermediate (**88**)*

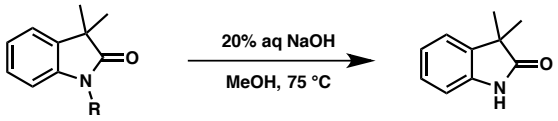


88 ***80***

To explore the general reactivity of nitrobenzyl group cleavage reactions by using simple aqueous NaOH, we initially chose 3,3-dimethyl oxindole as a test substrate (Table 2.2.1). We found that both *ortho*- and *para*-nitrobenzyl groups on oxindoles **137a** and **137c** were smoothly cleaved under our standard conditions (entries 1 and 3). However, a *meta*-nitrobenzyl group as well as a simple benzyl group on the oxindole

nitrogen (**137b** and **137d)** were both unreactive (entries 2 and 4). Notably, the *o*-nitrobenzyl group was also successfully removed even in the absence of light (entry 5). Interestingly, only trace amounts of product were observed when degassed water and methanol were used (entry 6). Furthermore, we discovered that cleavage of the *o*-nitrobenzyl group was successful when the degassed water and methanol were purged with oxygen gas (entry 7). We therefore concluded that oxygen was necessary for the reaction, but light was not.

Table 2.2.1. *Cleavage of nitrobenzyl groups on 3,3-dimethyloxindole*



137 ***138***

Entry	Substrate	R	Time (h)	Yield (%)
1	***137a***	-*o*-nitrobenzyl	5	69
2	***137b***	-*m*-nitrobenzyl	24	0
3	***137c***	-*p*-nitrobenzyl	1.5	63
4	***137d***	-benzyl	24	0
5[a]	***137a***	-*o*-nitrobenzyl	6.5	72
6[b]	***137a***	-*o*-nitrobenzyl	12	trace
7[b,c]	***137a***	-*o*-nitrobenzyl	6.5	66

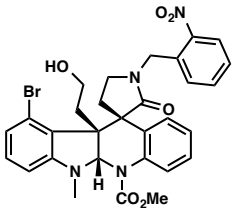
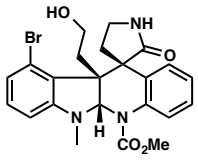
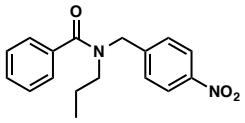
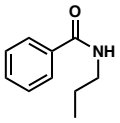
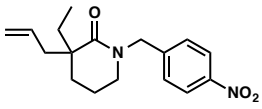
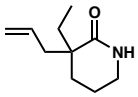
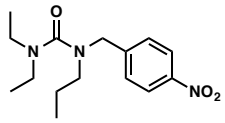
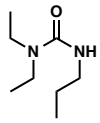
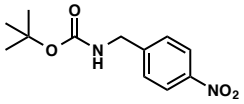
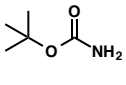
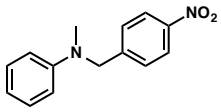
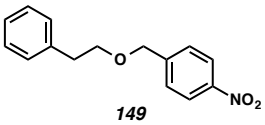
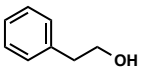
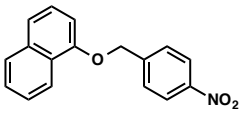
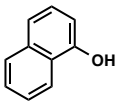
[a] The reaction was performed in the dark.
[b] Degassed water and methanol were used.
[c] Purged with O_2.

With the standard conditions in hand, we explored the scope of the *o*- and *p*-nitrobenzyl group cleavage reactions with various substrates (Table 2.2.2). *o*- and *p*-Nitrobenzyl protected substrates were easily prepared by a variety of methods, including reductive amination, simple alkylation, EDCI coupling, and acylation. The *o*-nitrobenzyl group on a highly functionalized communesin F intermediate **79** was smoothly cleaved

under our standard conditions in good yield (entry 1).[5] *p*-Nitrobenzyl groups on amide **139** and lactam **141** were also cleaved in moderate yields (entries 2 and 3). The *p*-nitrobenzyl group on urea **143** was also successfully cleaved and methyl 4-nitrobenzoate was isolated as a by-product (entry 4). An attempt to remove the *p*-nitrobenzyl group on secondary carbamate **145** proved unsuccessful (entry 5). Additionally, removal of the *p*-nitrobenzyl group on amine **147** was facile, furnishing aniline **148** in 65% yield (entry 6). Interestingly, 4-nitrobenzaldehyde was isolated as a by-product in this reaction, presumably resulting from the oxidation reaction at the benzylic position by oxygen dissolved in the solution. Furthermore, we successfully removed the *p*-nitrobenzyl groups from ethers **149** and **151** in moderate yields (entries 7 and 8). This work offers a one-step alternative to previous work by the Kusumoto group.[8] In the cases of deprotection reactions from urea **143** and ether **149**, the corresponding hemiaminal ether and acetal intermediates were observed (see ref. 9). It is important to note that these deprotection conditions are compatible with free hydroxyl groups, aminals, aryl bromides, methyl carbamates, silyl ethers, and Boc groups present on the substrates.

A representative procedure is as follows: To a 20 mL scintillation vial with a magnetic stir bar were added *p*-nitrobenzyl protected oxindole **137c** (30 mg, 0.10 mmol, 1.0 equiv), MeOH (1.0 mL), and 20% aq NaOH (1.0 mL). The reaction mixture was stirred for 1.5 h at 75 °C. The reaction mixture was then cooled to 23 °C, and extracted with EtOAc (3 x 2 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography to afford 3,3-dimethyloxindole **138** (10.3 mg, 63% yield).

Table 2.2.2. *Scope of the o- and p-nitrobenzyl deprotecion reactions*

Entry	Substrate	Product	Time (h)	Yield (%)
1	 ***79***	 ***53***	4	70
2	 ***139***	 ***140***	12	42
3	 ***141***	 ***142***	1	55
4	 ***143***	 ***144***	10.5	94[a,b]
5	 ***145***	 ***146***	6	0
6	 ***147***	 ***148***	2	65[c]
7	 ***149***	 ***150***	32	59[b] (74)[d]
8	 ***151***	 ***152***	48	48

[a] Methyl 4-nitrobenzoate was isolated as a by-product.
[b] See Ref. 9 for detail.
[c] 4-Nitrobenzaldehyde was isolated as a by-product.
[d] Yield based on recovered starting material.

2.3. Conclusion

In summary, a mild and efficient deprotection protocol was discovered for the cleavage of *o*- and *p*-nitrobenzyl ethers, amides, ureas, and anilines. Since relatively few options for protection of the amide *N–H* functionality exist, easily introducible and removable *o*- and *p*-nitrobenzyl groups could prove useful in the synthesis of alkaloids and biologically active molecules, which possess amide functionalities. In our laboratory, this has already been proven to be the case in our formal syntheses of communesin F and perophoramidine. In addition, *p*-nitrobenzyl-protected anilines, ureas, and alcohols were also competent substrates for this transformation, which may further its utility as a mild deprotection method in cases where other conditions fail.

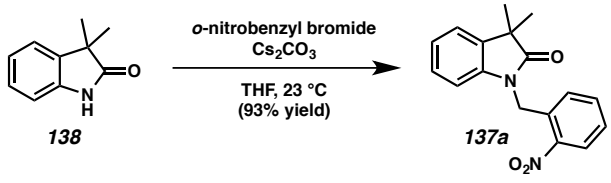
2.4. Experimental Methods and Analytical Data

2.4.1. Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Reaction progress was monitored by thin-layer chromatography (TLC). THF, Et_2O, CH_2Cl_2, toluene, benzene, CH_3CN, and dioxane were dried by passage through an activated alumina column under argon. Triethylamine was distilled over CaH_2 prior to use. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. Brine solutions are saturated aqueous solutions of sodium chloride. Commercially available reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulator unless otherwise indicated. Microwave-assisted reactions were

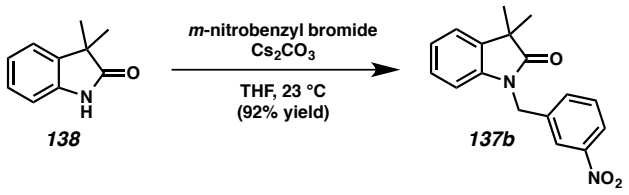
performed in a Biotage Initiator 2.5 microwave reactor. Glove box manipulations were performed under a N_2 atmosphere. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or PMA (phosphomolybdic acid) staining. Silicycle Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.064 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on a Varian Inova 500 MHz spectrometer and were reported relative to residual $CHCl_3$ (δ 7.26 ppm), or $(CD_3)_2CO$ (δ 2.05 ppm). ^{13}C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm), or $(CD_3)_2CO$ (δ 29.84 ppm). Data for ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d= broad doublet, app = apparent. Data for ^{13}C are reported in terms of chemical shifts (δ ppm). IR spectra were obtained using a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+).

2.4.2. Experimental Procedures



***N*–2-nitrobenzyloxindole 137a.** To a mixture of 3,3-dimethyloxindole **138**[1] (150 mg, 0.93 mmol, 1.00 equiv) and Cs_2CO_3 (606 mg, 1.86 mmol, 2.00 equiv) in THF (4.70 mL) was added *o*-nitrobenzyl bromide (302 mg, 1.40 mmol, 1.50 equiv). The reaction mixture was stirred overnight. Then, the reaction mixture was extracted with EtOAc (3 x 6 mL) and washed with brine. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:4 → 1:2 EtOAc:hexanes) on silica gel to afford *N*–2-nitrobenzyl-3,3-dimethyloxindole **137a** (258 mg, 93% yield).

R_f = 0.35 (1:2 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.51 (td, *J* = 7.6, 1.4 Hz, 1H), 7.44 (dddt, *J* = 8.1, 7.4, 1.4, 0.7 Hz, 1H), 7.28 (ddd, *J* = 7.3, 1.3, 0.6 Hz, 1H), 7.17 (td, *J* = 7.7, 1.3 Hz, 1H), 7.12 (dq, J = 7.8, 1.0 Hz, 1H), 7.09 (td, *J* = 7.5, 1.1 Hz, 1H), 6.61 (dt, *J* = 7.8, 0.8 Hz, 1H), 5.33 (d, *J* = 0.8 Hz, 2H), 1.48 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.8, 148.2, 141.4, 135.8, 134.2, 132.0, 128.5, 128.0, 127.6, 125.7, 123.2, 122.8, 108.8, 77.2, 44.5, 41.2, 24.8; IR (Neat Film NaCl) 2968, 1721, 1615, 1524, 1489, 1385, 1338, 1177, 1008, 858, 761 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{17}N_2O_3$ $[M+H]^+$: 297.1234; found: 297.1236.

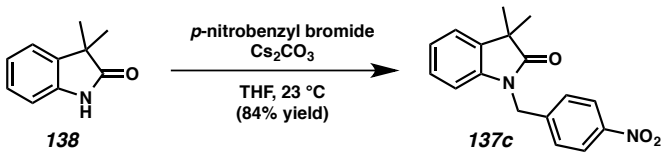


***N*–3-nitrobenzyloxindole 137b.** To a mixture of 3,3-dimethyloxindole **138**[1] (100 mg, 0.62 mmol, 1.00 equiv) and Cs_2CO_3 (403 mg, 1.24 mmol, 2.00 equiv) in THF (3.10 mL)

[1] Vu, A. T.; Cohn, S. T.; Zhang, P.; Kim, C. Y. Mahaney, P. E.; Bray, J. A.; Johnston, G. H.; Koury, E. J.; Cosmi, S. A.; Deecher, D. C.; Smith, V. A.; Harrison, J. E.; Leventhal, L.; Whiteside, G. T.; Kennedy, J. D.; Trybulski, E. J. *J. Med. Chem.* **2010**, *53*, 2051–2062.

was added *m*-nitrobenzyl bromide (335 mg, 1.55 mmol, 2.50 equiv). The reaction mixture was stirred overnight. Then, the reaction mixture was extracted with EtOAc (3 x 4 mL) and washed with brine. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:4 → 1:2 EtOAc:hexanes) on silica gel to afford *N*–3-nitrobenzyl-3,3-dimethyloxindole **137b** (170 mg, 92% yield).

R_f = 0.35 (1:2 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 – 8.11 (m, 2H), 7.60 (ddt, *J* = 7.7, 1.8, 0.9 Hz, 1H), 7.53 – 7.48 (m, 1H), 7.26 – 7.24 (m, 1H), 7.17 (td, *J* = 7.7, 1.3 Hz, 1H), 7.07 (td, *J* = 7.5, 1.0 Hz, 1H), 5.01 (s, 2H), 1.46 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.7, 148.6, 141.1, 138.5, 135.9, 133.3, 130.1, 127.9, 123.2, 122.9, 122.8, 122.2, 108.7, 77.2, 44.4, 43.0, 24.7; IR (Neat Film NaCl) 2969, 1652, 1538, 1348, 1011, 933, 761; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{17}N_2O_3$ $[M+H]^+$: 297.1234; found: 297.1241.

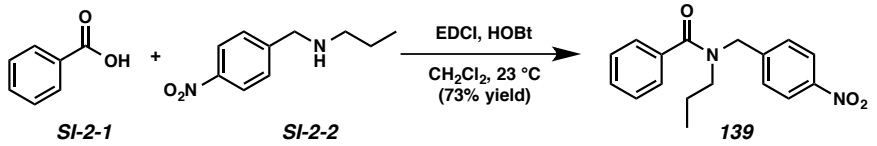


138 *137c*

***N*–4-nitrobenzyloxindole 137c.** To a mixture of 3,3-dimethyloxindole **138**[1] (50 mg, 0.31 mmol, 1.00 equiv) and Cs_2CO_3 (202 mg, 0.62 mmol, 2.00 equiv) in THF (1.60 mL) was added *p*-nitrobenzyl bromide (101 mg, 0.47 mmol, 1.50 equiv). The reaction mixture was stirred overnight. Then, the reaction mixture was extracted with EtOAc (3 x 3 mL) and washed with brine. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:4 → 1:2

EtOAc:hexanes) on silica gel to afford *N*–4-nitrobenzyl-3,3-dimethyloxindole **137c** (77.5 mg, 84% yield).

R_f = 0.35 (1:2 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 10.0 Hz, 2H), 7.25 (ddd, *J* = 7.3, 1.5, 0.7 Hz, 1H), 7.16 (td, *J* = 7.7, 1.3 Hz, 1H), 7.07 (td, *J* = 7.5, 1.1 Hz, 1H), 6.65 (dt, *J* = 7.7, 0.7 Hz, 1H), 5.01 (s, 2H), 1.45 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.6, 147.6, 143.7, 141.1, 135.8, 128.0, 127.9, 124.2, 123.2, 122.8, 108.7, 77.2, 44.4, 43.1, 24.7; IR (Neat Film NaCl) 2968, 1707, 1613, 1522, 1343, 1173, 1111, 1009, 760; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{17}N_2O_3$ $[M+H]^+$: 297.1234; found: 297.1239.

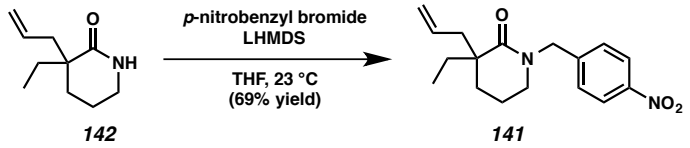


Benzamide 139. To a solution of benzoic acid **SI-2-1** (57.0 mg, 0.463 mmol, 1.00 equiv) and propylamine **SI-2-2**[2] (90.0 mg, 0.463 mmol, 1.00 equiv) in CH_2Cl_2 (2.30 mL) were added EDCI (90.0 mg, 0.579 mmol, 1.25 equiv) and HOBt (78.0 mg, 0.579, 1.25 equiv). The reaction mixture was stirred overnight at 23 °C. Then, the reaction mixture was extracted with CH_2Cl_2 (3 x 3 mL) and washed with brine. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:8 → 1:2 EtOAc:hexanes) on silica gel to afford *N*–3-nitrobenzyl-3,3-dimethyloxindole **139** (101 mg, 73% yield).

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[2] Hajipour, A. R.; Fontanilla, D.; Chu, U. B.; Arbabian, M.; Ruoho, A. E. *Bioorg. Med. Chem.* **2010**, *18*, 4397–4404.

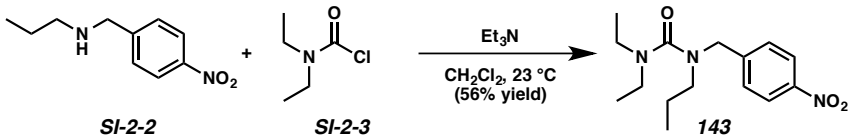
R_f = 0.32 (1:2 EtOAc:hexanes); (due to the distinct presence of rotameric isomers, the ^{1}H NMR and ^{13}C NMR contained extra peaks. See the attached spectrum); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 10 Hz 2H), 7.53 – 7.35 (m, br, 7H), 4.84 – 4.61 (m, br, 2H), 3.43 – 3.18 (m, br, 2H), 1.68 –1.53 (m, br, 2H), 0.95 – 0.73 (m, br, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.47, 147.44, 145.42, 136.17, 129.84, 128.71, 127.49, 126.61, 124.06, 77.16, 52.29, 50.82, 47.59, 46.85, 21.87, 20.34, 11.07; IR (Neat Film NaCl) 3060, 2963, 2874, 1633, 1519, 1461, 1412, 1344, 1258, 1098, 859, 791, 736; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{19}N_2O_3$ $[M+H]^+$: 299.1390; found: 299.1396.



***N*–4-nitrobenzylpiperidin-2-one 141.** To a solution of lactam **142** (34.0 mg, 0.203 mmol, 1.00 equiv) in THF (1.40 mL) was added LHMDS (41.0 mg, 0.244 mmol, 1.20 equiv) at 0 °C. The reaction mixture was stirred for 1 h, and then, *p*-nitrobenzyl bromide (66.0 mg, 0.305 mmol, 1.50 equiv) was added. The reaction mixture was stirred overnight at 23 °C. Then, the reaction mixture was extracted with EtOAc (3 x 3 mL) and washed with brine. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:2 EtOAc:hexanes) on silica gel to afford *N*–4-nitrobenzylpiperidin-2-one **141** (42.0 mg, 69% yield).

R_f = 0.25 (1:2 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.7 Hz, 2H), 7.41 (d, *J* = 8.7 Hz, 2H), 5.80 – 5.71 (m, 1H), 5.11 – 5.04 (m, 2H), 4.65 (d, *J* = 3.8 Hz, 2H), 3.22 (td, *J* = 6.1, 1.3 Hz, 2H), 2.54 (ddt, *J* = 13.5, 6.9, 1.3 Hz, 1H), 2.21 (ddt, *J* =

13.4, 8.0, 1.1 Hz, 1H), 1.81 (dddd, *J* = 11.9, 6.8, 2.9, 1.4 Hz, 3H), 1.76 – 1.72 (m, 2H), 1.55 (dq, *J* = 13.5, 7.4 Hz, 1H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 147.4, 145.6, 134.7, 128.7, 124.0, 118.3, 77.2, 50.5, 48.6, 45.5, 43.3, 31.6, 28.9, 19.9, 8.9; IR (Neat Film NaCl) 2939, 1633, 1519, 1344, 1196, 1109; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{23}N_2O_3$ $[M+H]^+$: 303.1703; found: 303.1707.



Urea 11. To a solution of propylamine **SI-2-2**[2] (100 mg, 0.515 mmol, 1.00 equiv) and Et_3N (0.18 mL, 1.29 mmol, 2.50 equiv) in CH_2Cl_2 (2.60 mL) was added diethylcarbamoyl chloride **SI-2-3** (72.0 mL, 0.566 mmol, 1.10 equiv) at 0 °C. The solution was warmed to 23 °C and stirred overnight. Then, the reaction mixture was extracted with CH_2Cl_2 (3 x 3.5 mL) and washed with brine. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:8 → 1:4 EtOAc:hexanes) on silica gel to afford urea **143** (85 mg, 56% yield).

R_f = 0.32 (1:4 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 4.42 (s, 2H), 3.22 (q, *J* = 7.1 Hz, 4H), 3.06 – 3.01 (m, 2H), 1.61 – 1.52 (m, 2H), 1.11 (t, *J* = 7.1 Hz, 6H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.9, 147.2, 146.9, 128.4, 123.8, 51.4, 51.2, 42.5, 21.1, 13.4, 11.4; IR (Neat Film NaCl) 2967, 1644, 1520, 1410, 1344, 1251, 1132, 1108; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{24}N_3O_3$ $[M+H]^+$: 294.1812; found: 294.1863.

2.5. References and Notes

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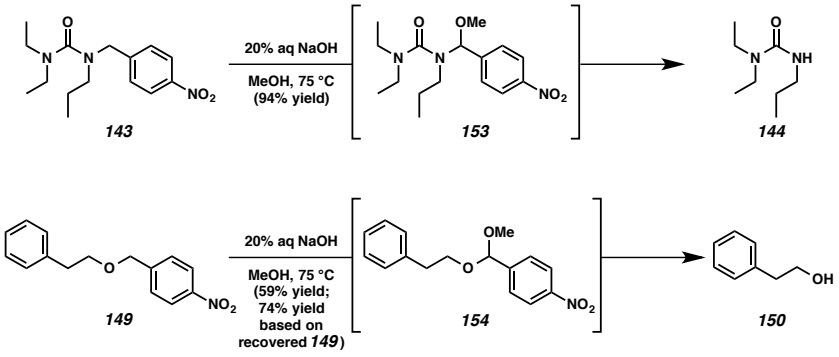
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(9) From the deprotection reaction of urea **143**, hemiaminal ether intermediate **153** was observed in 1 hour under the standard reaction conditions and intermediate **153** was converted to propyl urea **144** after 10.5 hours. In addition, acetal **154** was observed in 2 hours during the deprotection reaction of ether **149**, and the desired phenylethyl alcohol **150** was isolated after 32 hours.



APPENDIX 6

Spectra Relevant to Chapter 2:

A New Method for the Cleavage of Nitrobenzyl Amides and Ethers

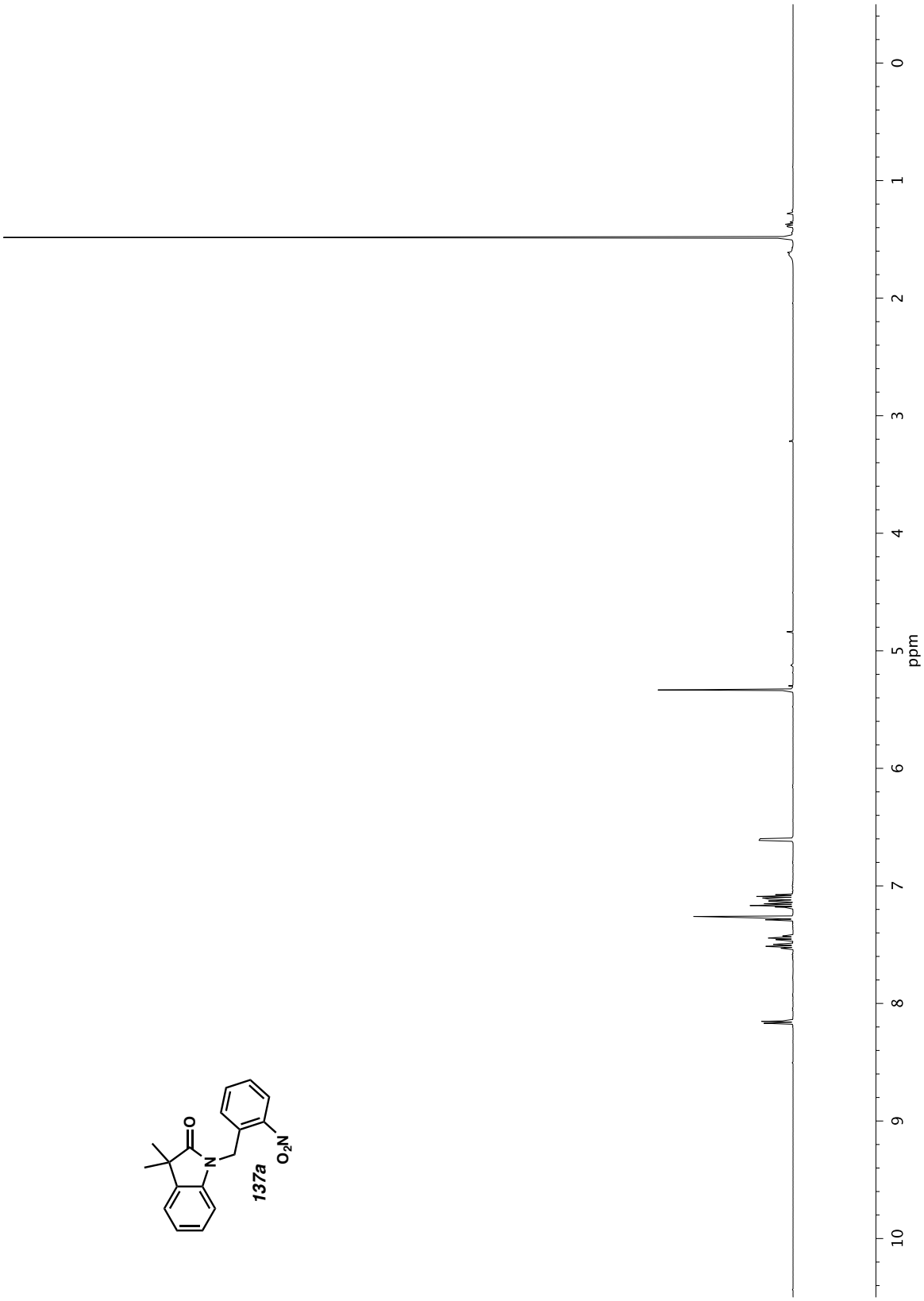


Figure A6.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **137a**.

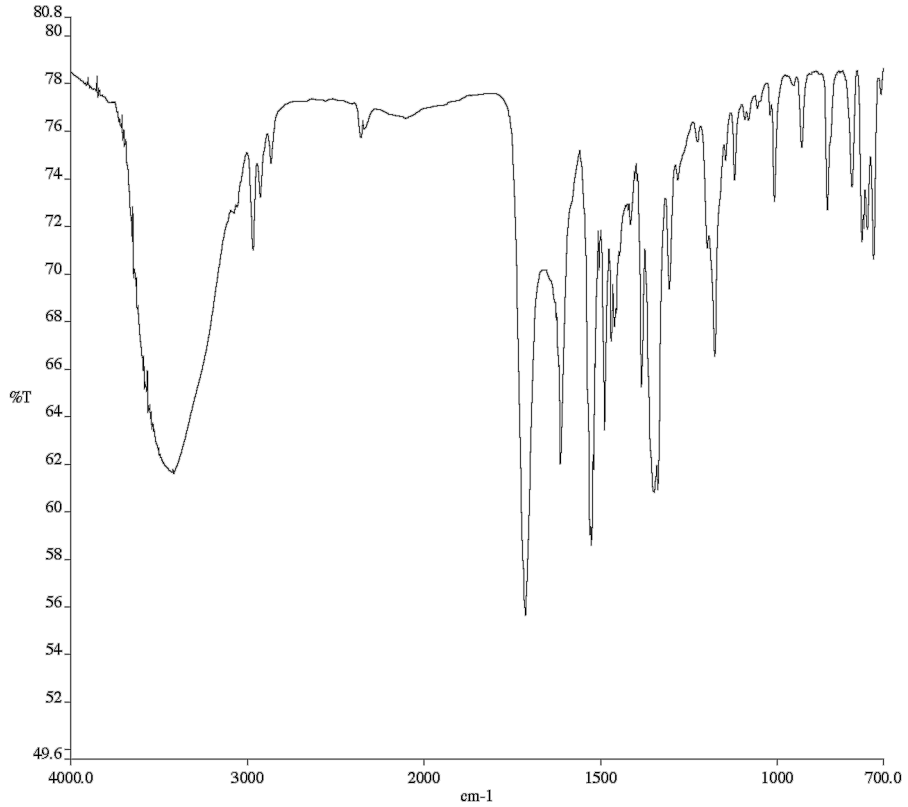


Figure A6.2. Infrared spectrum (Thin Film, NaCl) of compound **137a**.

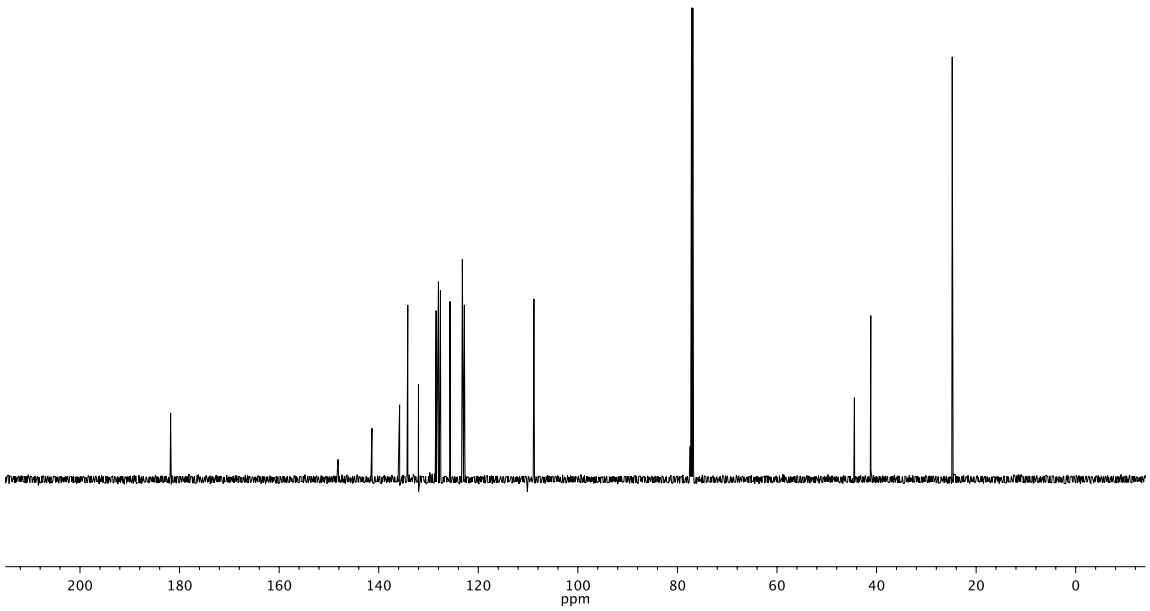


Figure A6.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **137a**.

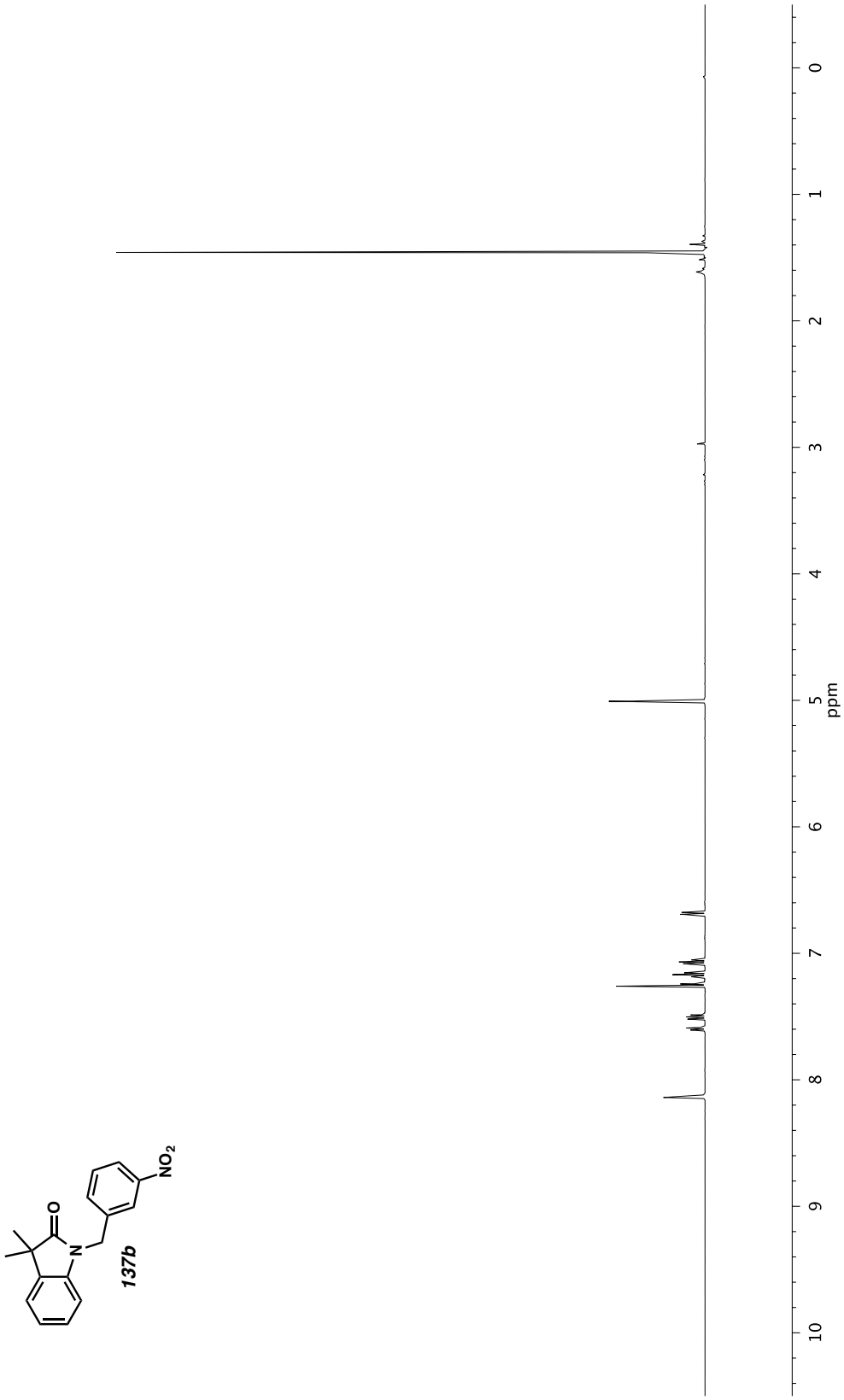


Figure A6.4. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **137b**.

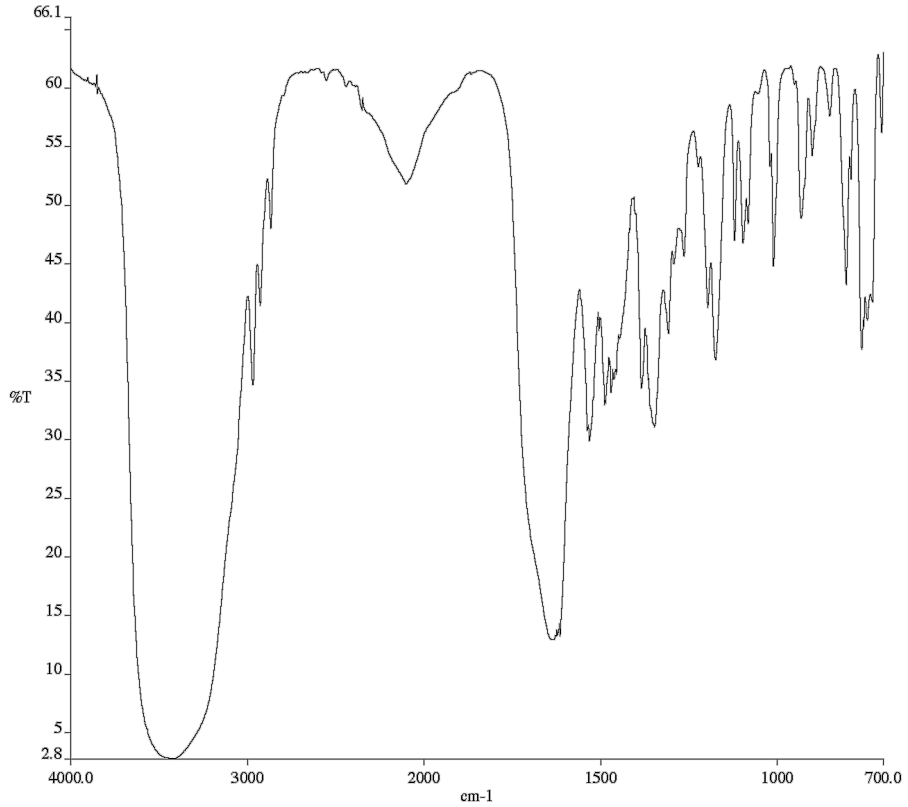


Figure A6.5. Infrared spectrum (Thin Film, NaCl) of compound **137b**.

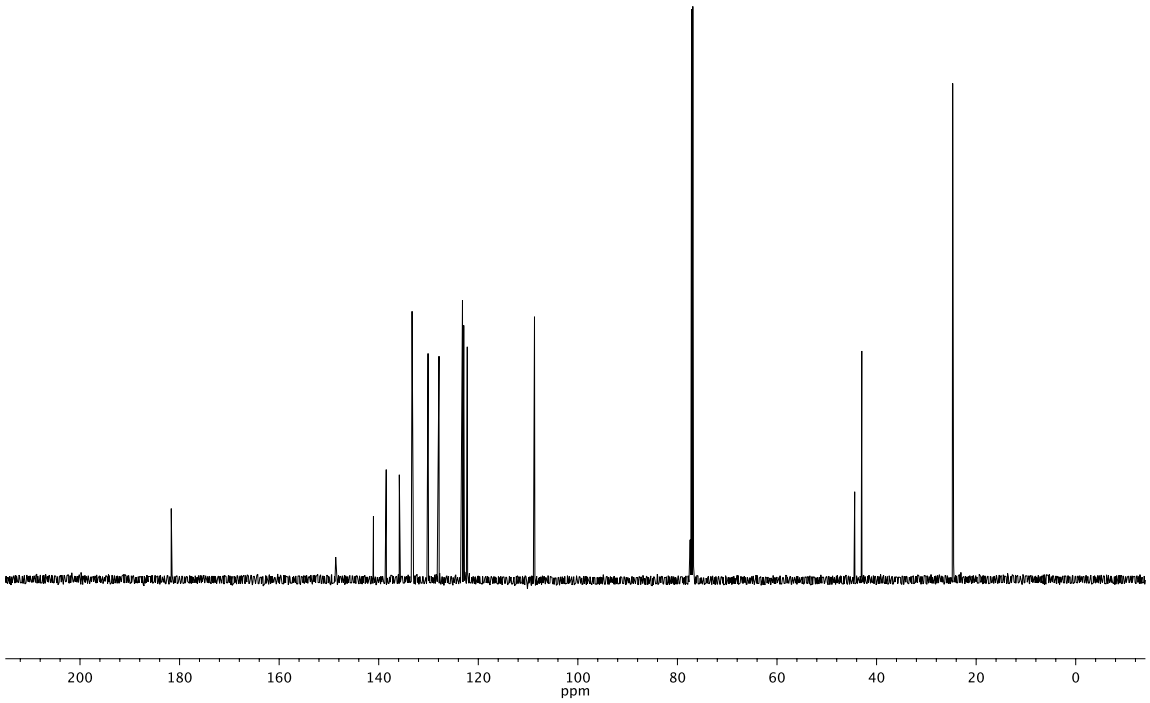


Figure A6.6. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **137b**.

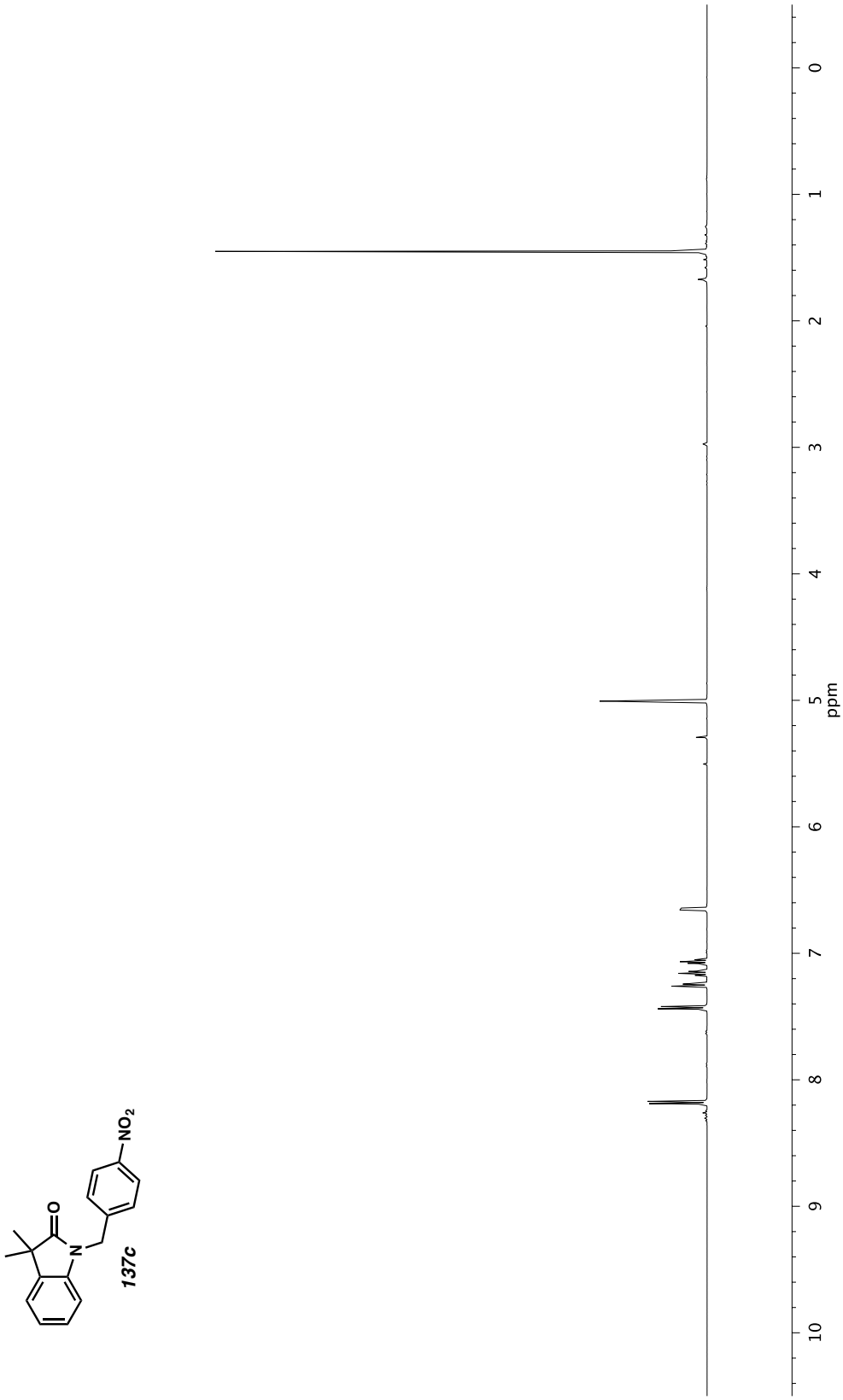


Figure A6.7. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **137c**.

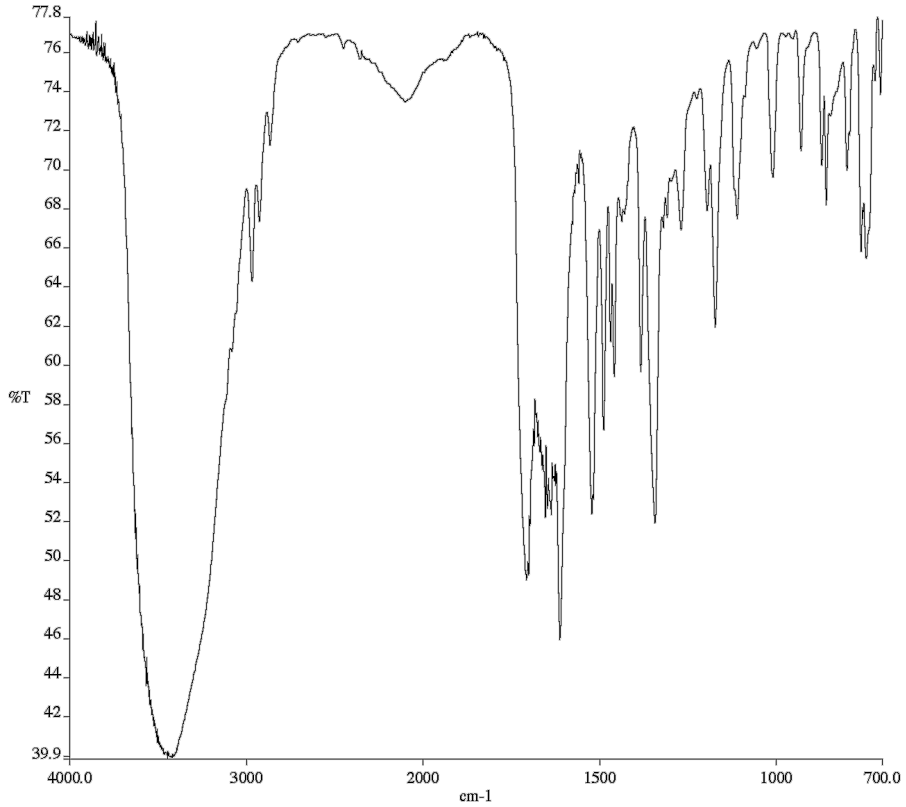


Figure A6.8. Infrared spectrum (Thin Film, NaCl) of compound **137c**.

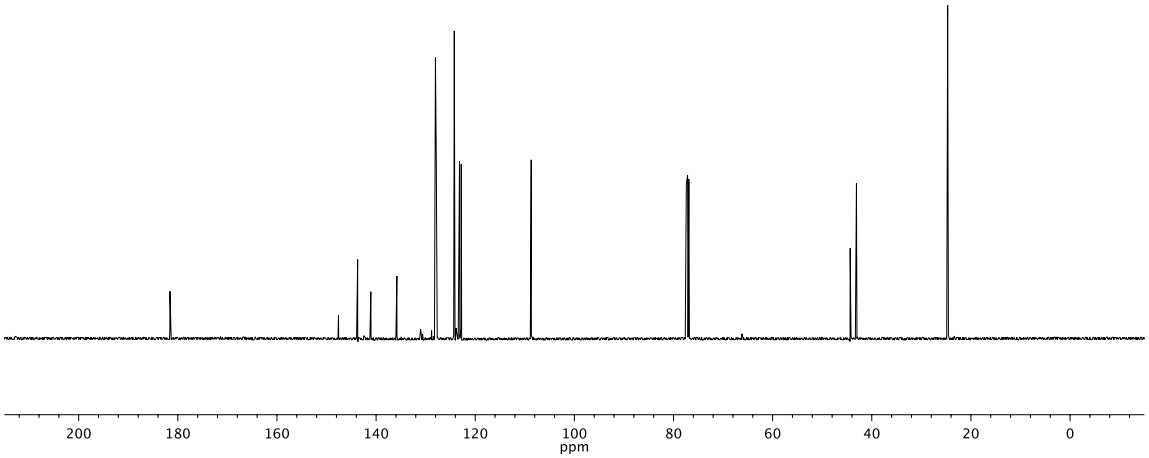


Figure A6.9. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **137c**.

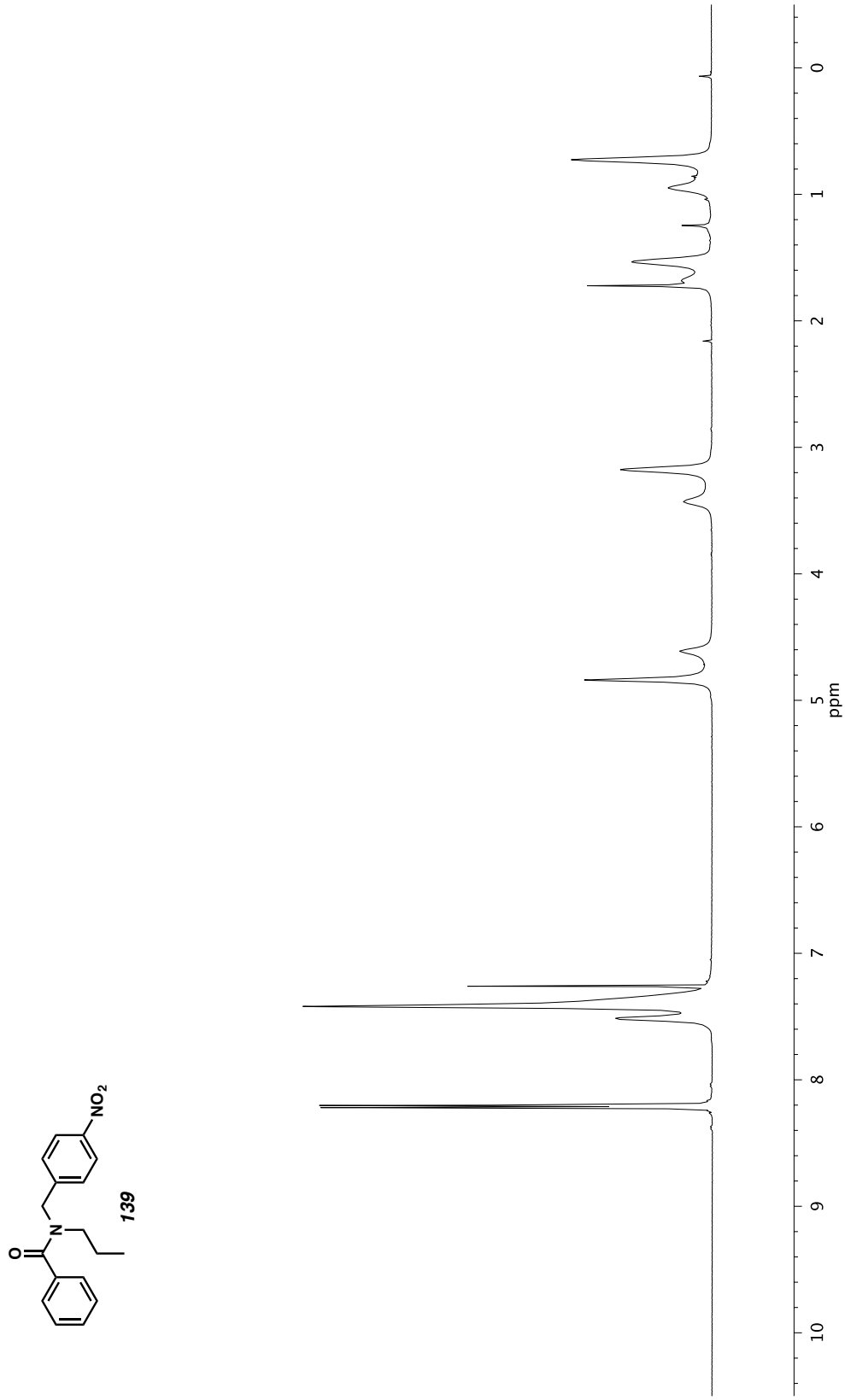


Figure A6.10. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **139**.

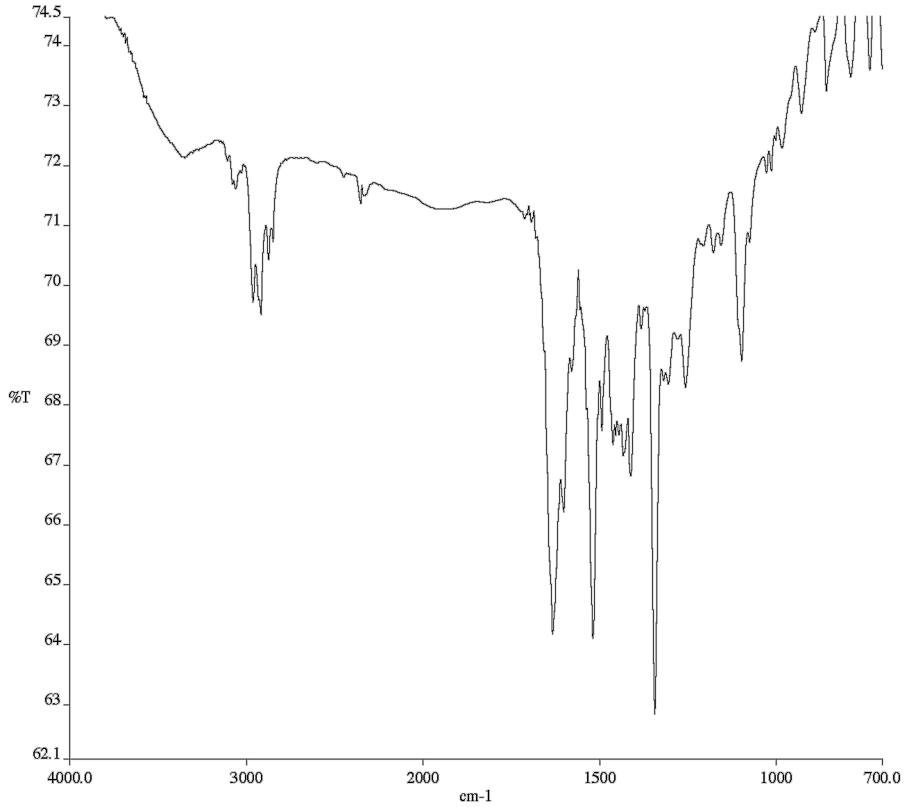


Figure A6.11. Infrared spectrum (Thin Film, NaCl) of compound **139**.

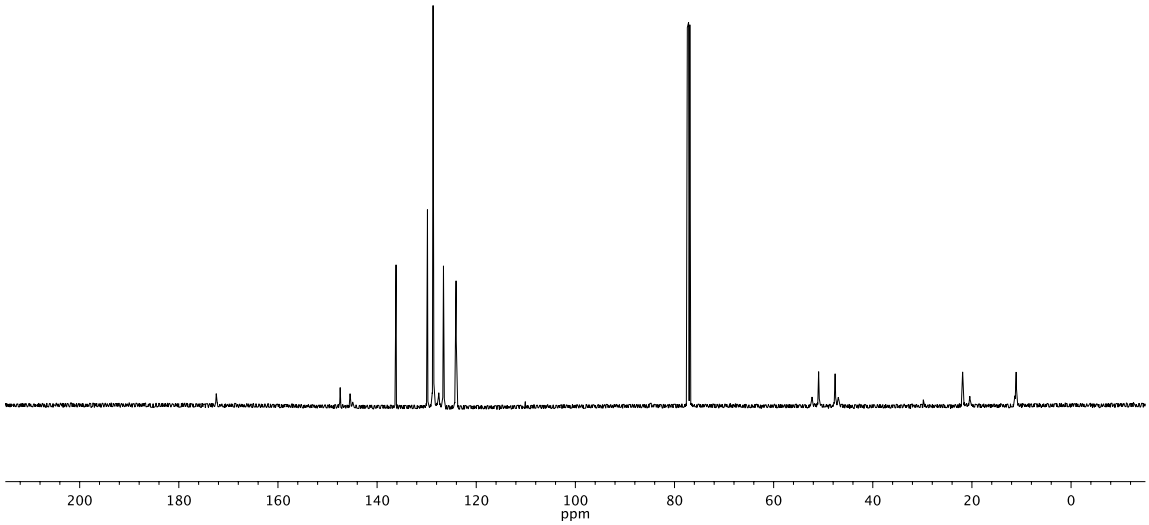


Figure A6.12. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **139**.

Figure A6.13. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **141**.

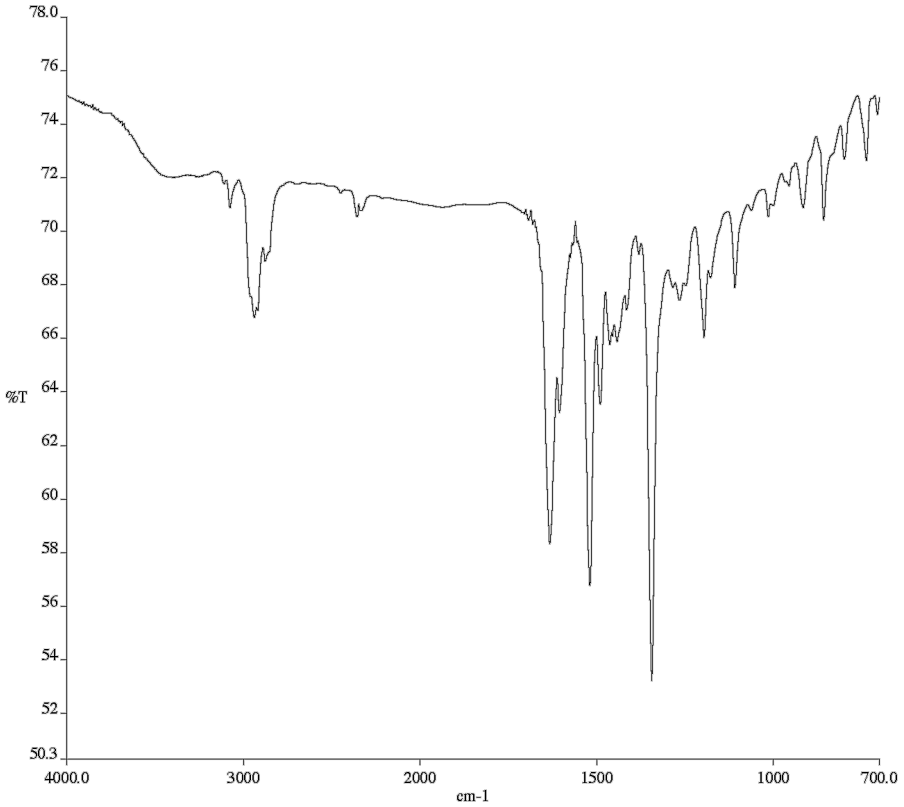


Figure A6.14. Infrared spectrum (Thin Film, NaCl) of compound **141**.

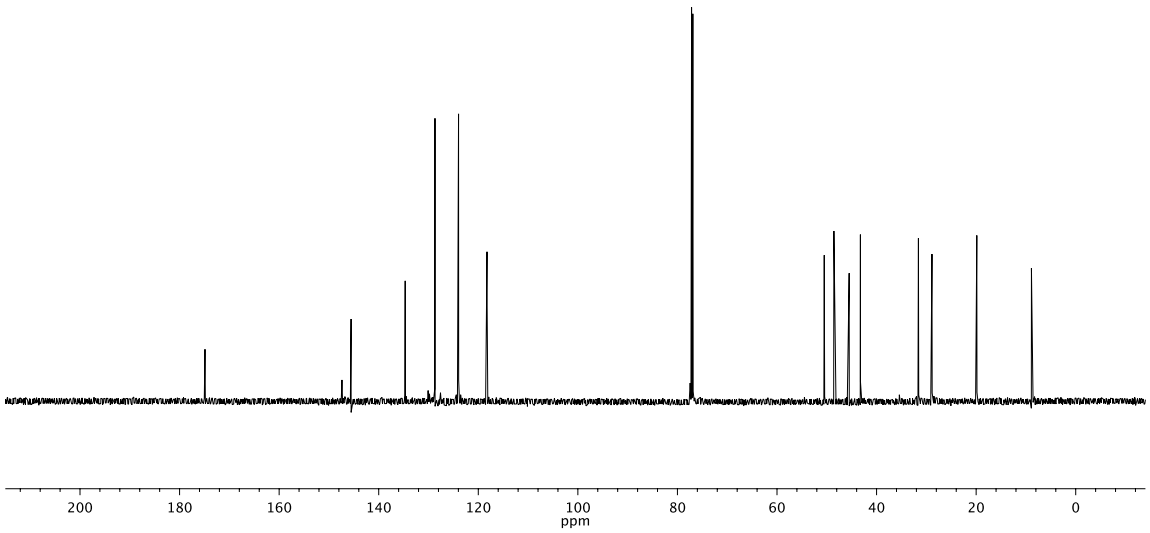


Figure A6.15. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **141**.

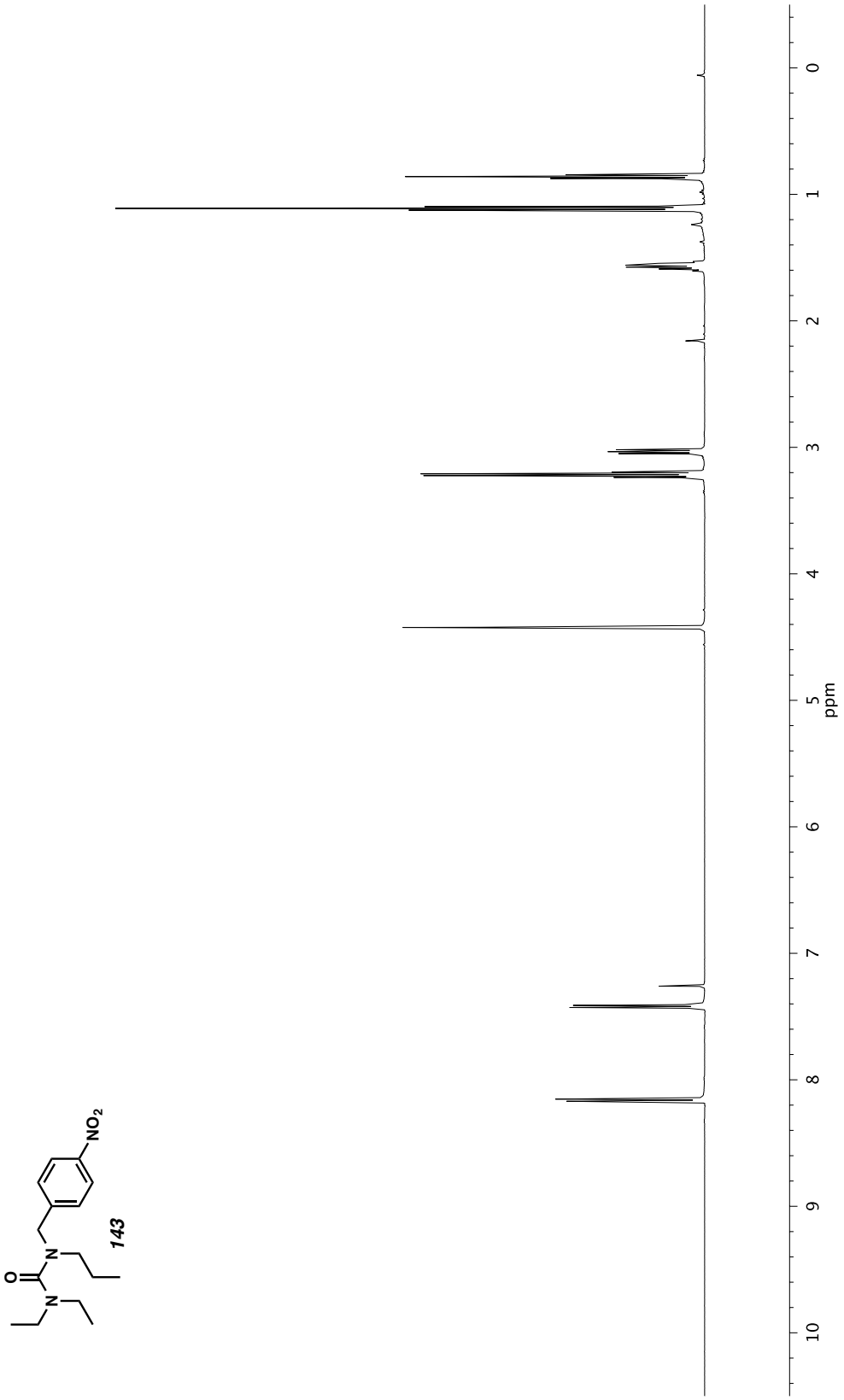


Figure A6.16. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **143**.

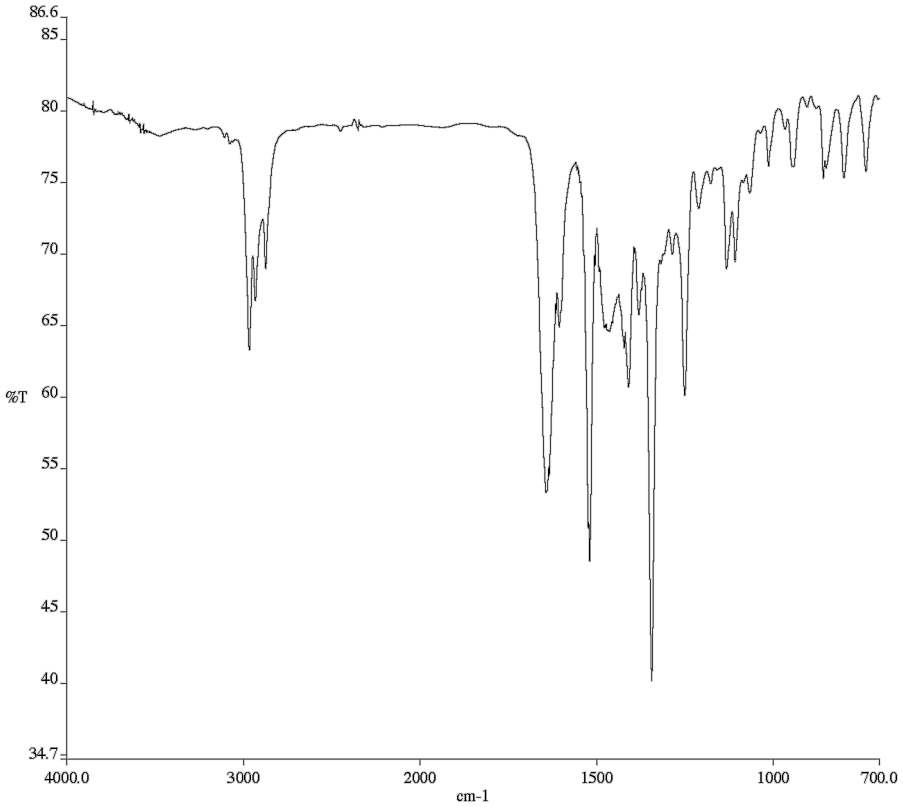


Figure A6.17. Infrared spectrum (Thin Film, NaCl) of compound **143**.

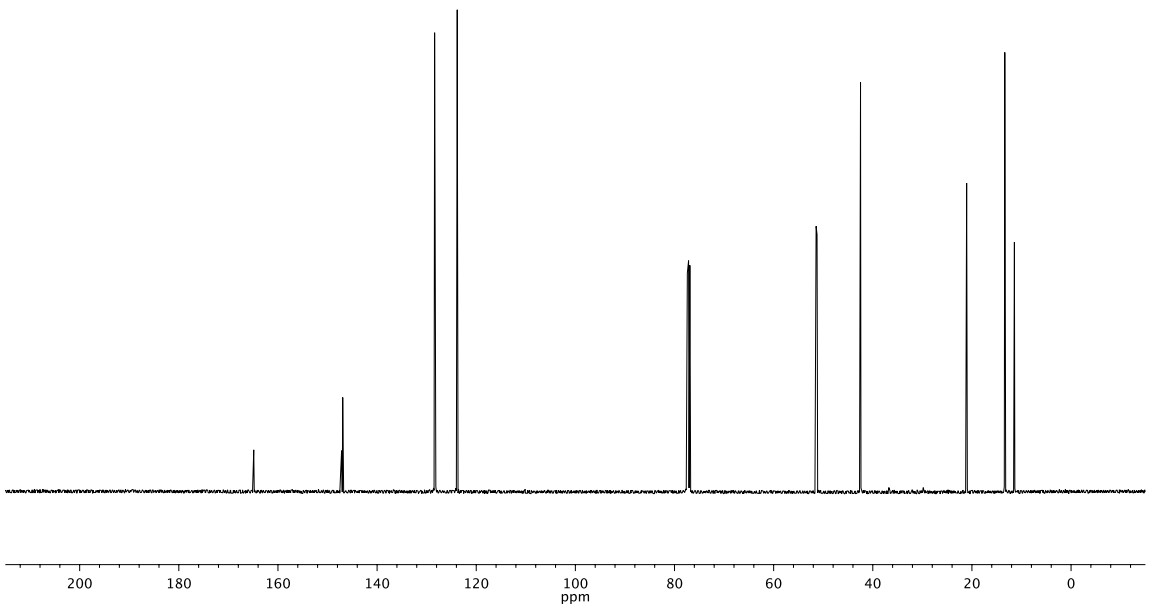


Figure A6.18. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **143**.

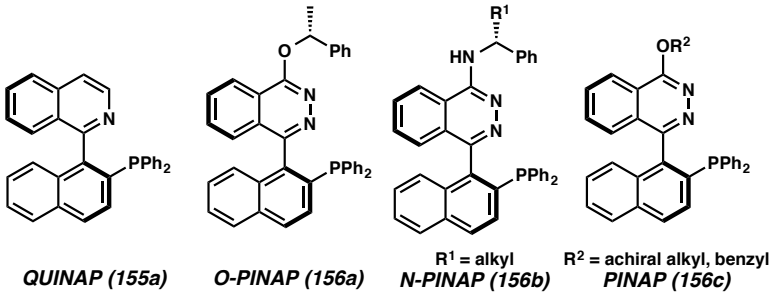
CHAPTER 3

Enantioselective Synthesis of PINAP via Dynamic Kinetic Resolution

3.1. Introduction

The unique properties of the axially chiral P,N ligand QUINAP (**155a**) have been employed widely for various transition metal catalyzed asymmetric reactions.[1] However, approaches to the synthesis of QUINAP ligands in high enantiomeric purity are limited.[2] In 2013, our laboratories explored the palladium-catalyzed atroposelective synthesis of QUINAP and its derivatives via kinetic resolution and dynamic kinetic resolution.[3] With a robust method for the synthesis of chiral QUINAP in hand, we turned our attention to the architecturally related PINAP ligands (**156**). PINAP ligands (**156a** and **156b**), which possess analogous ligation reactivity to QUINAP, were first developed by the Carreira group in 2004.[4] Carreira and co-workers separated the two atropoisomeric diastereomers through column chromatography by preparing chiral ether- or amine-substituted PINAP scaffolds. Herein, we disclose synthetic methods for accessing enantiomerically enriched PINAP ligands via dynamic kinetic resolution (**156a**, **156c**).

Figure 3.1.1. *QUINAP (**155**) and PINAP (**156**)*

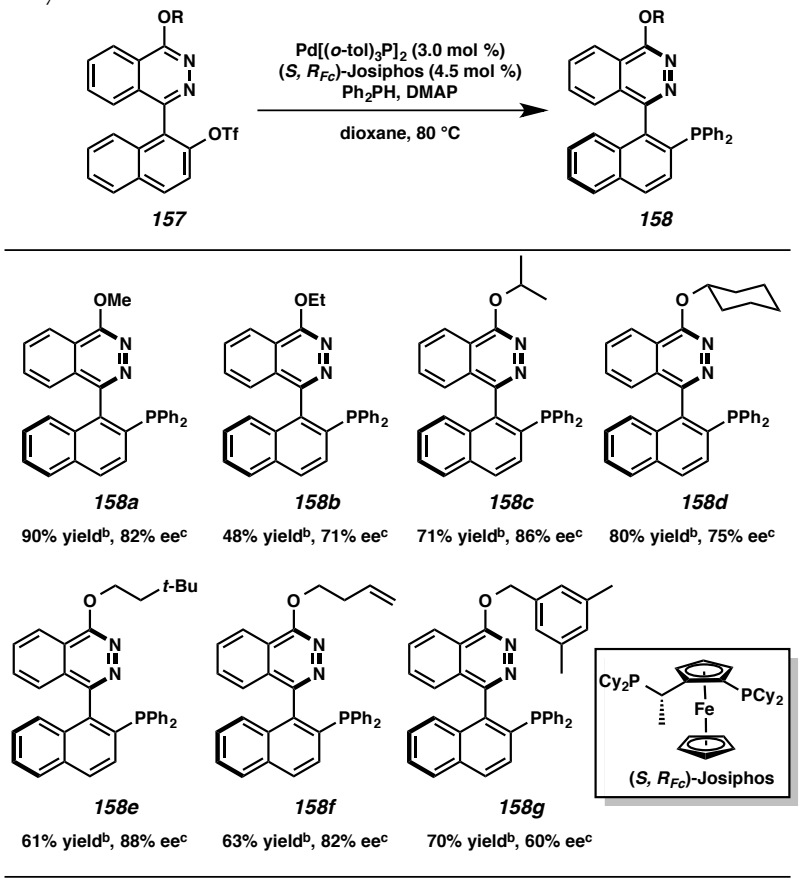


QUINAP (155a) ***O-PINAP (156a)*** ***N-PINAP (156b)*** ***PINAP (156c)***

3.2. Results and Discussion

Our initial attempts to apply the standard QUINAP dynamic kinetic resolution conditions,[3] 3.0 mol % of $Pd[(o\text{-tol})_3P]_2$ and 4.5 mol % of (S, R_{Fc})-Josiphos at 80 °C, to aryl triflate **157** afforded various alkyl- or benzyl-substituted PINAP ligands (Table 3.2.1). Asymmetric C–P couplings via dynamic kinetic resolution on substrates incorporating methoxy, ethoxy, and isopropoxy groups furnished the corresponding PINAP ligands in good yields and selectivities (**158a,b,c**). Cyclohexyl, 3,3-dimethyl-1-butyl, and homoallyl ether groups were also well tolerated under the reaction conditions to give the desired products. (**158d,e,f**). Additionally, 3,5-dimethyl benzyloxy-substituted PINAP was obtained in good yield and moderate selectivity (**158g**). Although these initial results were exciting, it was clear that additional optimization was needed to improve the enantioselectivities in the synthesis of these PINAP ligands.

Table 3.2.1. *Scope of dynamic kinetic resolution under initial standard conditions*

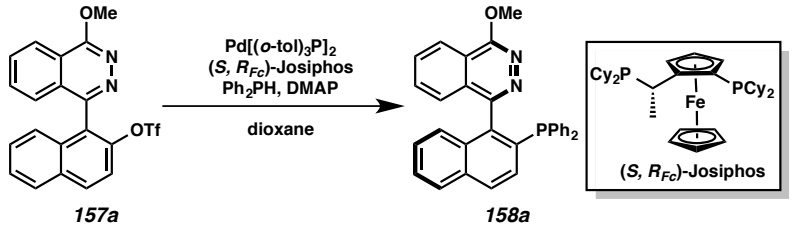


[a]Reactions performed with 1.0 equiv of triflate **157**, 4.0 equiv of DMAP, 3.0 mol % of Pd[(*o*-tol)$_3$P]$_2$, 4.5 mol % of (*S*, R_{Fc})-Josiphos, 1.05 equiv of Ph_2PH (1.0 M in dioxane) at 0.20 M in dioxane at 80 °C in a glovebox. Ph_2PH (1.0 M in dioxane) was added over 4 h.

In order to allow more time for the isomerization of the presumed arylpalladium complex before its subsequent phosphination, diphenylphosphine (1.0 M solution in dioxane) was added slowly.[5] In addition, we used pre-stirred 1.0 mol % of Pd[(*o*-tol)$_3$P]$_2$ and 1.5 mol % of (*S*, R_{Fc})-Josiphos solutions in dioxane. Interestingly, improved enantioselectivity was observed with reduced palladium and Josiphos ligand loadings (1.0 mol % and 1.5 mol %, respectively) (Table 3.2.2, entries 1 and 2). We were pleased to find that higher enantioselectivities were obtained at lower temperatures (Table 3.2.2,

entries 3 and 4). However, the conversion rate was dramatically diminished at 50 °C (Table 3.2.2, entry 5).

Table 3.2.2. *Optimization of reaction parameters*[a]



157a ***158a***

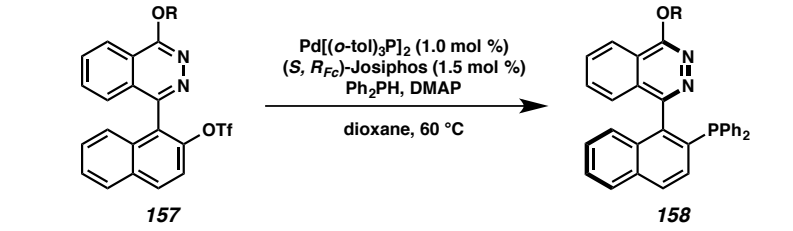
entry	$Pd[(o\text{-tol})_3P]_2$	(S, R_{Fc})-Josiphos	T (°C)	yield (%)[b]	ee (%)
1	3.0 mol %	4.5 mol %	80	90	82[c]
2	1.0 mol %	1.5 mol %	80	95	88[c]
3	1.0 mol %	1.5 mol %	70	75	92[c]
4	1.0 mol %	1.5 mol %	60	80	96[c]
5	1.0 mol %	1.5 mol %	50	–[d]	94[c]

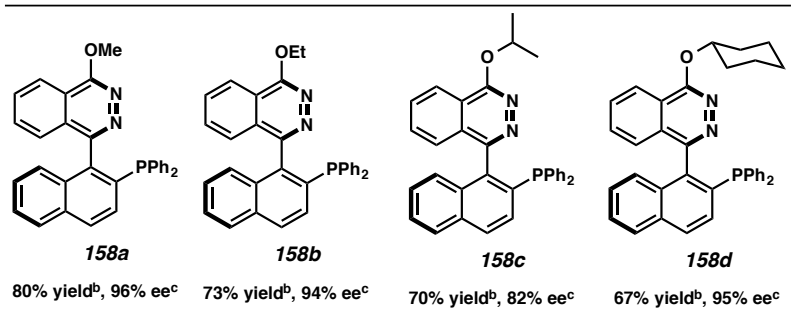
[a]Reactions performed with 1.0 equiv of **157a**, 4.0 equiv of DMAP, 1.0 mol % of $Pd[(o\text{-tol})_3P]_2$, 1.5 mol % of (S, R_{Fc})-Josiphos, 1.05 equiv of Ph_2PH (1.0 M in dioxane) at 0.20 M in dioxane in a glovebox. $Pd[(o\text{-tol})_3P]_2$ and (S, R_{Fc})-Josiphos in dioxane were pre-stirred before use. Ph_2PH (1.0 M in dioxane) was added over 8 h. [b]All yields are isolated yields. [c]Determined by chiral SFC analysis. [d]~50% conversion.

With the optimized conditions in hand, we investigated the substrate scope of the reaction (Table 3.2.3). Several alkoxy- and benzyloxy-substituted PINAP ligands were furnished in improved enantioselectivities under the optimized conditions (**158a**–**158h**, 57–80% yields and 82–96% ee). Applying our optimized conditions to a (*R*)-phenylethoxy-substituted substrate, which was previously prepared by the Carreira group by chromatographic separation, generated the corresponding PINAP product in 95% de (**158i**). Interestingly, diastereomeric PINAP **158j** was produced by our method with lower selectivity using the (R, S_{Fc})-Josiphos ligand indicating some balance between substitute and catalyst in the progress (e.g., mismatched pair). Thankfully, nearly enantiopure PINAP **158j** was obtained after recrystallization. Unfortunately, in the case of (*R*)-α-phenethylamine-substituted PINAP, only moderate selectivity was observed

(**158k**). Additionally, application of our conditions to the reaction of triflate **157a** with diphenylphosphine oxide or $(p\text{-}CF_3\text{-}C_6H_4)_2PH$ proved unsuccessful, and only low yield and selectivities were observed.[6,7]

Table 3.2.3. *Scope of dynamic kinetic resolution under optimized conditions*[a]



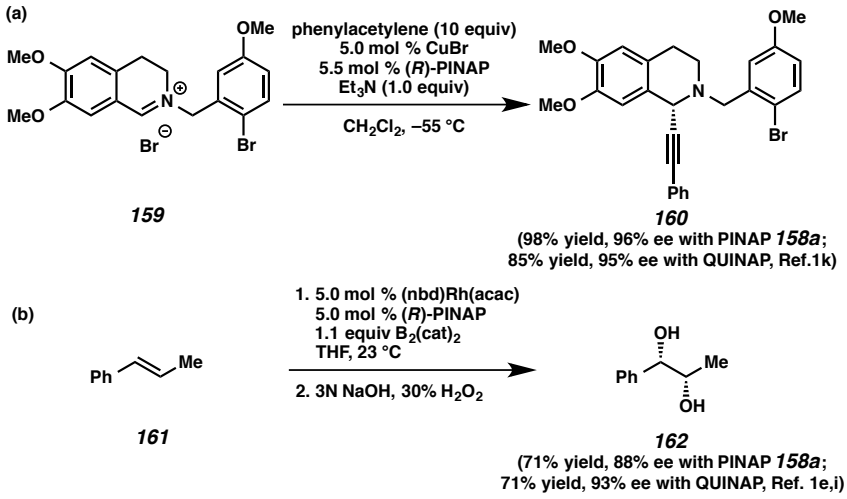


[a]Reactions performed with 1.0 equiv of **157a**, 4.0 equiv of DMAP, 1.0 mol % of $Pd[(o\text{-tol})_3P]_2$, 1.5 mol % of (S, R_{Fc})-Josiphos, 1.05 equiv of Ph_2PH (1.0 M in dioxane) at 0.20 M in dioxane at 60 °C in a glovebox. $Pd[(o\text{-tol})_3P]_2$ and (S, R_{Fc})-Josiphos in dioxane were pre-stirred before use. Ph_2PH (1.0 M in dioxane) was added over 8 h. [b]All yields are isolated yields. [c]Determined by chiral SFC analysis. [d]Determined by chiral

SFC analysis; SFC conditions: 40% IPA, 2.5 mL/min, Chiralpak OD-H column, t_R (min): major = 2.81, minor = 3.18. [e]Determined by chiral HPLC. [f](R, S_{Fc})-Josiphos was used. [g]Determined by ^{1}H NMR.

We applied PINAP ligand **158a** (96% ee) to two different reactions (Scheme 3.2.1).[8] Copper catalyzed asymmetric phenylacetylene addition to isoquinoline iminium **159** with PINAP ligand **158a** afforded propargylamine **160** in 98% yield and 96% ee (Scheme 3.2.1a).[1k,9] In addition, rhodium-catalyzed enantioselective diboration and oxidation of *trans*-b-methylstyrene **161** with PINAP **158a** produced diol **162** in 71% yield and 88% ee (Scheme 3.2.1b).[1e,i,10] The enantioselectivities and yields with PINAP **158a** ligand are parallel to those with QUINAP **155a**.

Scheme 3.2.1. *Applications*



3.3. Conclusion

In conclusion, the atroposelective synthesis of various achiral alkyl- or benzyloxy-substituted PINAP ligands via dynamic kinetic resolution has been developed. The asymmetric PINAP ligands formed in this communication are envisioned to be useful in several important asymmetric transformations.[4]

3.4. Experimental Methods and Analytical Data

3.4.1. Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Reaction progress was monitored by thin-layer chromatography (TLC). THF, Et_2O, CH_2Cl_2, toluene, benzene, CH_3CN, and dioxane were dried by passage through an activated alumina column under argon. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. Brine solutions are saturated aqueous solutions of sodium chloride. Commercially available reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulator unless otherwise indicated. Glove box manipulations were performed under a N_2 atmosphere. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or PMA (phosphomolybdic acid) staining. Silicycle Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.064 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on a Varian Inova 500 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra are recorded on a Varian Inova 500 MHz spectrometer (125MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm). Data for ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d= broad doublet, app = apparent. Data for ^{13}C are reported in terms of chemical shifts (δ ppm). IR spectra were obtained using a

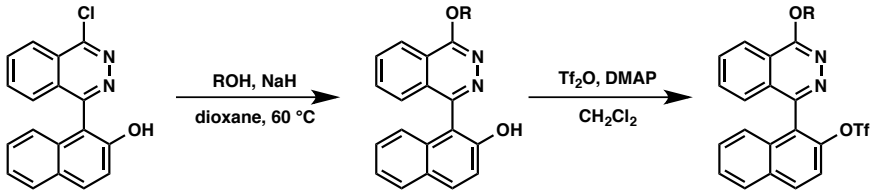
Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[a]_D^T$ (concentration in g/100 mL, solvent). Analytical HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralpak (AD-H or AS) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing Chiralpak (AD-H, AS-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.5 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode, or Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+).

Triflate substrates **157i–157k** were prepared by known methods.[11] All the data from pinap **158i**–**158k** were confirmed by reported data.[1]

(1) (a) Knöpfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem. Int., Ed.* **2004**, *43*, 5971–5973. (b) Fujimori, S.; Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Boyall, D.; Carreira, E. M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1635–1657.

3.4.2. Experimental Procedures

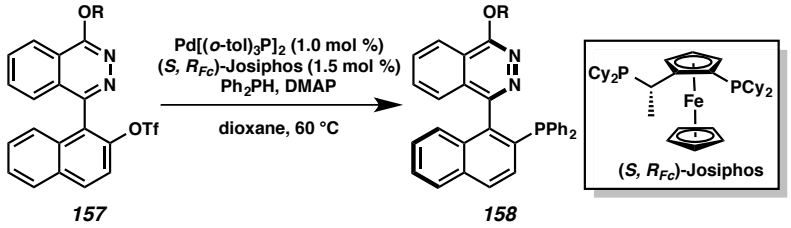
General Procedure for Synthesis of Triflate Substrates



SI-3-1 ***SI-3-2*** ***157***

To a solution of NaH (2.64 mmol, 2.00 equiv) in dioxane (5.60 mL) was added alcohol (1.39 mmol, 1.05 equiv) in dioxane (1.00 mL) dropwise. The reaction mixture was stirred for 15 min at 23 °C and then **SI-3-1** (1.32 mmol, 1.00 equiv) was added portionwise. The solution was stirred for 18 h at 60 °C then diluted with EtOAc (5.00 mL) and water (10.0 mL). The aqueous phase was extracted with EtOAc (3 x 5.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was used in the next step without further purification. To a solution of crude mixture of **SI-3-2** (1.32 mmol, 1.00 equiv) and DMAP (2.64 mmol, 2.00 equiv) in CH_2Cl_2 (13.2 mL) was added Tf_2O (1.32 mmol, 1.00 equiv) dropwise at 0 °C. The reaction mixture was stirred at 23 °C until **SI-3-2** was fully consumed by TLC analysis. The reaction mixture was diluted with CH_2Cl_2 (5.00 mL) and water (5.00 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 3.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:4 EtOAc:hexanes) on silica gel to give the corresponding triflate substrates.

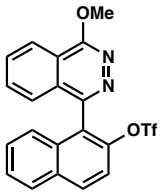
General Procedure of PINAP from Triflates via Dynamic Kinetic Resolution



157 ***158***

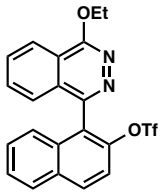
This reaction was performed in a nitrogen-filled glovebox. $Pd[(o\text{-tol})_3P]_2$ (10.8 mg, 0.0151 mmol) and (*S, R_{Fc}*)-Josiphos (13.7 mg, 0.0226 mmol) in dioxane (0.302 mL) were pre-stirred in a vial until all the solids were dissolved. To a solution of triflates **157** (0.211 mmol, 1.00 equiv) in dioxane (1.06 mL) was added DMAP (0.844 mmol, 4.00 equiv) and pre-stirred $Pd[(o\text{-tol})_3P]_2$ and (*S, R_{Fc}*)-Josiphos (0.05 M in dioxane; 0.00211 mmol, 0.01 equiv) at 23 °C. The mixture was placed in a reaction well preheated to 60 °C. A solution of Ph_2PH (1.00 M in dioxane; 0.317 mmol, 1.50 equiv) was added to the reaction mixture in 20 uL portions every 30 minutes manually. After completion of the addition (8 hours), the reaction was stirred for further 7 hours at which point complete consumption of the starting material was observed. The reaction was cooled, removed from the glovebox and dilulted with EtOAc (1.50 mL) and water (2.00 mL). The aqueous phase was extracted with EtOAc (3 x 1.50 mL). The combined organic phases were washed with brine, dried with $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography on silica gel to afford the corresponding PINAP **158**.

3.4.3. Spectroscopic Data



157a

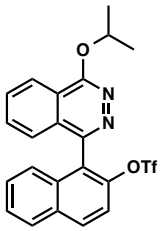
52% (2-step yield); R_f = 0.29 (1:4 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 8.2, 1.0 Hz, 1H), 8.12 (d, *J* = 9.1 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.87 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.70 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.62 (d, *J* = 9.1 Hz, 1H), 7.58 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.42 (ddd, *J* = 8.2, 6.7, 1.3 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.31 (dt, *J* = 8.4, 1.0 Hz, 1H), 4.41 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.9, 151.1, 145.6, 133.6, 132.7, 132.6, 132.4, 131.9, 129.2, 128.4, 128.1, 127.4, 126.7, 126.6, 125.7, 123.5, 119.9, 119.6, 117.1, 55.3; IR (Neat Film NaCl) 3063, 2945, 1668, 1581, 1541, 1496, 1457, 1420, 1364, 1247, 1213, 1139, 952, 834 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{14}F_3N_2O_4S$ $[M+H]^+$: 435.0621; found: 435.0625.



157b

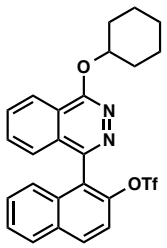
48% (2-step yield); R_f = 0.33 (1:4 EtOAc:hexanes); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.38 (dd, *J* = 8.2, 1.2 Hz, 1H), 8.12 (d, *J* = 9.1 Hz, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.87 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.69 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.61 (d, *J* = 9.0 Hz, 1H), 7.57 (ddd, *J* = 8.2, 6.7, 1.4 Hz, 1H), 7.42 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.29 (dd, *J* = 8.3, 1.0 Hz, 1H), 4.88 (qd, *J* = 7.0, 3.9 Hz, 2H), 1.62 (td, *J* =

7.1, 1.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.6, 150.7, 145.6, 133.6, 132.7, 132.5, 132.3, 131.8, 129.2, 128.4, 128.1, 127.4, 126.7, 126.6, 125.6, 123.6, 120.0, 119.6, 117.1, 63.9, 14.7; IR (Neat Film NaCl) 3066, 2984, 1582, 1540, 1495, 1422, 1381, 1342, 1214, 1140, 1073, 1024, 956, 941, 834 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{16}F_3N_2O_4S$ $[M+H]^+$: 449.0777; found: 449.0780.



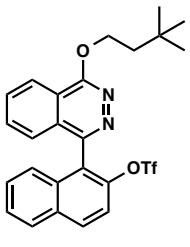
157c

37% (2-step yield); R_f = 0.35 (1:4 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (dd, *J* = 8.2, 1.0 Hz, 1H), 8.13 (d, *J* = 9.1 Hz, 1H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.87 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.69 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.62 (d, *J* = 9.1 Hz, 1H), 7.58 (ddd, *J* = 8.2, 6.7, 1.3 Hz, 1H), 7.43 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.30 (dt, *J* = 8.3, 0.9 Hz, 1H), 5.94 (hept, *J* = 6.2 Hz, 1H), 1.60 (d, *J* = 6.1 Hz, 3H), 1.58 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.3, 150.2, 145.7, 133.5, 132.7, 132.5, 132.4, 132.0, 129.3, 128.5, 128.2, 127.4, 126.6, 126.4, 125.7, 123.7, 120.4, 119.7, 71.1, 22.3, 22.1; IR (Neat Film NaCl) 2981, 1582, 1493, 1417, 1322, 1212, 1140, 1106, 958, 942, 833, 748 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{22}H_{17}F_3N_2O_4S$ $[M+H]^+$: 463.0934; found: 463.0964.



157d

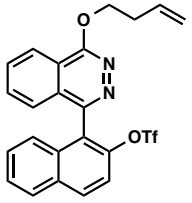
36% (2-step yield); R_f = 0.43 (1:4 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.2 Hz, 1H), 8.11 (dd, *J* = 9.1, 1.6 Hz, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.85 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.67 (td, *J* = 7.7, 7.0, 1.4 Hz, 1H), 7.61 (dd, *J* = 9.1, 2.0 Hz, 1H), 7.57 (ddd, *J* = 8.2, 6.2, 1.9 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.27 (d, *J* = 8.3 Hz, 1H), 5.72 (tt, *J* = 8.7, 3.7 Hz, 1H), 2.25 (d, *J* = 12.3 Hz, 2H), 1.90 (ddt, *J* = 13.9, 8.9, 4.5 Hz, 2H), 1.85 – 1.74 (m, 2H), 1.66 (td, *J* = 8.5, 7.7, 4.2 Hz, 1H), 1.57 (dtt, *J* = 13.5, 10.2, 3.4 Hz, 2H), 1.45 (ddt, *J* = 13.3, 10.1, 3.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.2, 150.3, 145.6, 133.6, 132.7, 132.3, 132.1, 131.7, 129.3, 128.4, 128.1, 127.3, 126.9, 126.7, 125.5, 123.7, 120.3, 119.7, 75.4, 32.0, 31.8, 25.9, 24.1; IR (Neat Film NaCl) 2937, 2858, 1582, 1537, 1493, 1418, 1362, 1342, 1214, 1140, 959, 944, 834 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{22}F_3N_2O_4S$ $[M+H]^+$: 503.1247; found: 503.1248.



157e

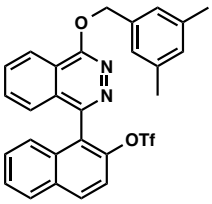
49% (2-step yield); R_f = 0.33 (1:4 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.2 Hz, 1H), 8.12 (d, *J* = 9.1 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.86 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.69 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H), 7.62 (d, *J* = 9.1 Hz, 1H), 7.57 (ddd,

J = 8.2, 6.6, 1.3 Hz, 1H), 7.42 (ddd, *J* = 8.1, 6.6, 1.2 Hz, 1H), 7.39 – 7.35 (m, 1H), 7.29 (d, *J* = 8.3 Hz, 1H), 4.88 (t, *J* = 7.2 Hz, 2H), 1.96 (t, *J* = 7.2 Hz, 2H), 1.10 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.7, 150.7, 145.6, 133.6, 132.7, 132.4, 132.3, 131.8, 129.2, 128.4, 128.1, 127.4, 126.6, 125.6, 123.5, 120.0, 119.6, 117.1, 110.2, 65.8, 42.5, 30.0; IR (Neat Film NaCl) 2958, 1582, 1538, 1495, 1422, 1360, 1214, 1141, 1073, 953, 834, 620 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{23}F_3N_2O_4S$ $[M+H]^+$: 505.1403; found: 505.1436.



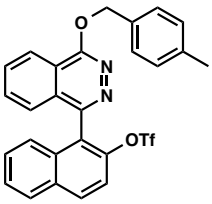
157f

52% (2-step yield); R_f = 0.33 (1:4 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 – 8.34 (m, 1H), 8.12 (d, *J* = 9.1 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.87 (ddd, *J* = 8.3, 7.0, 1.1 Hz, 1H), 7.69 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1H), 7.61 (d, *J* = 9.1 Hz, 1H), 7.57 (ddd, *J* = 8.2, 6.7, 1.3 Hz, 1H), 7.42 (ddd, *J* = 8.1, 6.7, 1.2 Hz, 1H), 7.38 – 7.35 (m, 1H), 7.30 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.04 (ddt, *J* = 17.1, 10.3, 6.7 Hz, 1H), 5.28 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.17 (dq, *J* = 10.3, 1.4 Hz, 1H), 4.94 – 4.83 (m, 2H), 2.78 (dddd, *J* = 8.1, 6.6, 5.2, 1.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.6, 150.9, 145.6, 134.6, 133.6, 132.7, 132.5, 132.3, 131.8, 129.2, 128.4, 128.1, 127.4, 126.7, 126.6, 125.6, 123.5, 119.9, 119.6, 117.3, 117.1, 67.0, 33.6; IR (Neat Film NaCl) 1581, 1538, 1494, 1421, 1349, 1213, 1139, 954, 833 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{18}F_3N_2O_4S$ $[M+H]^+$: 475.0934; found: 475.0956.



157g

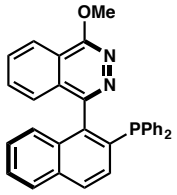
35% (2-step yield); R_f = 0.38 (1:4 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (dt, *J* = 8.2, 1.0 Hz, 1H), 8.13 (d, *J* = 9.1 Hz, 1H), 8.00 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.86 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H), 7.70 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H), 7.63 (d, *J* = 9.1 Hz, 1H), 7.58 (ddd, *J* = 8.2, 6.6, 1.3 Hz, 1H), 7.43 (ddd, *J* = 7.9, 6.6, 1.3 Hz, 1H), 7.39 (dd, *J* = 8.6, 1.2 Hz, 1H), 7.31 (dt, *J* = 8.4, 1.0 Hz, 1H), 7.04 (s, 1H), 5.80 (d, *J* = 2.3 Hz, 2H), 2.39 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.6, 151.1, 145.6, 138.3, 136.7, 133.6, 132.7, 132.6, 132.3, 131.8, 130.1, 129.3, 128.4, 128.1, 127.4, 126.7, 126.6, 126.6, 125.6, 123.7, 119.9, 119.7, 117.1, 69.8, 21.4; IR (Neat Film NaCl) 2917, 1581, 1494, 1418, 1343, 1213, 1140, 956, 835 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{28}H_{22}F_3N_2O_4S$ $[M+H]^+$: 539.1247; found: 539.1252.



157h

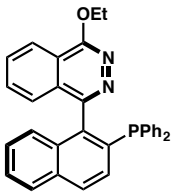
68% (2-step yield); R_f = 0.37 (1:4 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (dt, *J* = 8.2, 1.0 Hz, 1H), 8.13 (d, *J* = 9.1 Hz, 1H), 8.01 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.85 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 7.70 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.62 (dd, *J* = 9.1, 1.1 Hz, 1H), 7.58 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.43 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 7.37 (dt, J = 8.6, 1.0 Hz, 1H), 7.31 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.27 (d, *J* = 7.2

Hz, 2H), 5.81 (d, *J* = 7.1 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.5, 151.1, 145.5, 138.3, 133.7, 133.5, 132.6, 132.3, 131.9, 129.4, 129.2, 128.90, 128.4, 128.1, 127.4, 126.7, 126.6, 125.6, 123.6, 119.8, 119.6, 119.6, 117.0, 69.6, 21.4; IR (Neat Film NaCl) 3058, 1581, 1538, 1494, 1422, 1342, 1248, 1266, 1140, 1072, 953, 834, 776 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{27}H_{19}F_3N_2O_4S$ $[M+H]^+$: 525.1090; found: 525.1096.



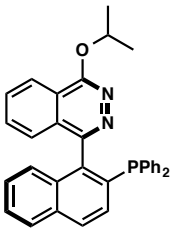
158a

$[a]_D^{25}$ +124.5 (*c* 0.51, $CHCl_3$); R_f = 0.42 (1:2 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.91 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.90 – 7.87 (m, 1H), 7.74 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.49 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.46 – 7.42 (m, 2H), 7.29 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.27 – 7.14 (m, 11H), 7.07 (dt, *J* = 8.2, 0.9 Hz, 1H), 4.36 (s, 3H); (due to the C–P coupling, the ^{13}C NMR contained extra peaks. See the attached spectrum); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.4, 156.8, 156.8, 141.5, 141.3, 137.5, 137.4, 137.3, 137.2, 136.0, 135.9, 134.0, 133.9, 133.7, 133.3, 133.2, 133.1, 131.8, 131.7, 130.3, 130.0, 129.9, 129.3, 128.7, 128.4, 128.4, 128.2, 128.1, 127.1, 126.9, 126.7, 126.7, 126.1, 123.2, 119.6, 55.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ -14.3; IR (Neat Film NaCl) 3053, 1582, 1538, 1495, 1456, 1362, 1112, 1018, 744 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{31}H_{23}N_2OP$ $[M+H]^+$: 471.1621; found: 471.1674; SFC conditions: 35% IPA, 2.5mL/min, Chiralcel OD-H column, t_R (min): major = 5.81, minor = 5.16.



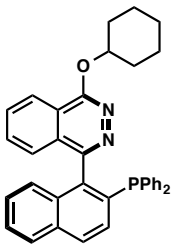
158b

$[a]_D^{25}$ +150.3 (*c* 0.47, $CHCl_3$); R_f = 0.54 (1:2 EtOAc:hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.91 (d, *J* = 8.6 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.74 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.49 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.29 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.27 – 7.13 (m, 11H), 7.07 (d, *J* = 8.2 Hz, 1H), 4.83 (qt, *J* = 7.1, 2.1 Hz, 2H), 1.60 (t, *J* = 7.1 Hz, 3H); (due to the C–P coupling, the ^{13}C NMR contained extra peaks. See the attached spectrum); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.2, 156.5, 156.5, 141.6, 141.3, 137.6, 137.5, 137.3, 137.2, 136.0, 135.9, 134.0, 133.8, 133.7, 133.3, 133.2, 133.1, 131.8, 131.5, 130.3, 130.0, 129.9, 129.2, 128.6, 128.4, 128.4, 128.2, 128.1, 127.1, 126.8, 126.8, 126.7, 126.1, 123.3, 119.6, 63.5, 14.9; ^{31}P NMR (121 MHz, $CDCl_3$) δ -14.2; IR (Neat Film NaCl) 3053, 2980, 1583, 1538, 1494, 1418, 1378, 1342, 1165, 1110, 1023, 818, 744 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{32}H_{25}N_2OP$ $[M+H]^+$: 485.1777; found: 485.1800; SFC conditions: 30% MeOH, 2.5mL/min, Chiralpak AD-H column, t_R (min): major = 2.60, minor = 3.09.



158c

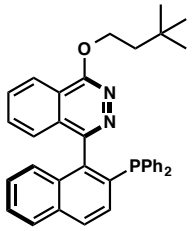
$[a]_D^{25}$ +131.7 (*c* 0.57, $CHCl_3$); R_f = 0.54 (1:2 EtOAc:hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.29 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.90 (t, *J* = 9.0 Hz, 2H), 7.73 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.52 – 7.42 (m, 3H), 7.30 (ddd, *J* = 8.4, 6.6, 1.2 Hz, 1H), 7.28 – 7.15 (m, 11H), 7.08 (dt, *J* = 8.1, 0.9 Hz, 1H), 5.88 (p, *J* = 6.2 Hz, 1H), 1.58 (d, *J* = 5.7 Hz, 3H), 1.56 (d, *J* = 5.7 Hz, 3H); (due to the C–P coupling, the ^{13}C NMR contained extra peaks. See the attached spectrum); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 156.0, 156.0, 141.6, 141.3, 137.6, 137.5, 137.3, 137.2, 136.0, 135.9, 134.0, 133.8, 133.7, 133.4, 133.2, 133.2, 133.1, 131.7, 131.4, 130.2, 130.0, 129.2, 128.6, 128.4, 128.4, 128.4, 128.4, 128.2, 128.1, 127.0, 126.8, 126.0, 123.4, 120.0, 70.1, 22.4, 22.3; ^{31}P NMR (121 MHz, $CDCl_3$) δ -13.9; IR (Neat Film NaCl) 3053, 2978, 1584, 1489, 1413, 1383, 1315, 1106, 744 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{33}H_{27}N_2OP$ $[M+H]^+$: 499.1934; found: 499.1960; SFC conditions: 40% MeOH, 2.5mL/min, Chiralpak AD-H column, t_R (min): major = 1.94, minor = 2.22.



158d

$[a]_D^{25}$ +91.0 (*c* 0.57, $CHCl_3$); R_f = 0.61 (1:2 EtOAc:hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.29 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.89 (ddd, *J* = 9.4, 8.2, 0.8 Hz, 2H), 7.73 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 7.49 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.29 (ddd, *J* = 8.2, 6.7, 1.3 Hz, 1H), 7.26 – 7.14 (m, 11H), 7.07 (dt, *J* = 8.3, 0.9 Hz, 1H), 5.67 (tt, *J* = 8.9, 3.8 Hz, 1H), 2.30 – 2.18 (m, 2H), 1.88 (ddtd, *J* = 9.3, 7.9, 5.4, 4.0 Hz, 2H), 1.76 (qdt,

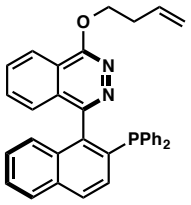
J = 9.9, 6.1, 3.7 Hz, 2H), 1.64 (tt, *J* = 9.1, 4.9 Hz, 1H), 1.54 (qq, *J* = 10.2, 3.5 Hz, 2H), 1.42 (ddt, *J* = 13.4, 10.2, 3.5 Hz, 1H); (due to the C–P coupling, the ^{13}C NMR contained extra peaks. See the attached spectrum); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 156.0, 155.9, 141.6, 141.4, 137.6, 137.5, 137.3, 137.2, 136.0, 135.9, 134.0, 133.9, 133.7, 133.4, 133.2, 131.7, 131.4, 130.3, 130.0, 129.2, 128.6, 128.4, 128.4, 128.4, 128.4, 128.2, 128.1, 127.0, 126.8, 126.8, 126.8, 126.0, 123.4, 120.0, 74.8, 32.0, 31.9, 25.9, 24.1, 24.0; ^{31}P NMR (121 MHz, $CDCl_3$) δ -13.9; IR (Neat Film NaCl) 3051, 2933, 2856, 1582, 1538, 1490, 1432, 1413, 1361, 1341, 1311, 1263, 1215, 1165, 1113, 1068, 1046, 1019, 744 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{36}H_{31}N_2OP$ $[M+H]^+$: 539.2247; found: 539.2268; SFC conditions: 25% MeOH, 2.5mL/min, Chiralcel OD-H column, t_R (min): major = 7.58, minor = 8.13.



158e

$[a]_D^{25}$ +101.2 (*c* 0.42, $CHCl_3$); R_f = 0.62 (1:2 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.73 (ddt, *J* = 8.7, 7.1, 1.4 Hz, 1H), 7.49 (ddt, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.29 (ddd, *J* = 8.2, 6.7, 1.3 Hz, 1H), 7.27 – 7.14 (m, 11H), 7.06 (d, *J* = 8.2 Hz, 1H), 4.87 – 4.77 (m, 2H), 1.94 (td, *J* = 7.1, 1.9 Hz, 2H), 1.09 (s, 9H); (due to the C–P coupling, the ^{13}C NMR contained extra peaks. See the attached spectrum); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.3, 156.5, 156.4, 141.6, 141.3, 137.6, 137.5, 137.3, 137.2, 136.0,

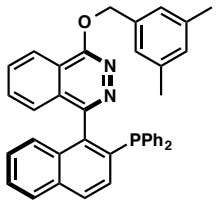
135.9, 134.0, 133.9, 133.7, 133.3, 133.2, 133.1, 131.7, 131.6, 130.3, 129.9, 129.2, 128.7, 128.4, 128.4, 128.2, 128.1, 127.1, 126.8, 126.8, 126.7, 126.1, 123.2, 119.7, 77.2, 65.4, 42.5, 30.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ -14.2; IR (Neat Film NaCl) 3051, 2956, 1418, 1386, 1114, 743 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{36}H_{33}N_2OP$ $[M+H]^+$: 541.2403; found: 541.2409; SFC conditions: 35% IPA, 2.5mL/min, Chiralcel OD-H column, t_R (min): major = 4.33, minor = 4.84.



158f

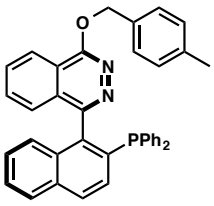
$[a]_D^{25}$ +117.9 (*c* 0.52, $CHCl_3$); R_f = 0.62 (1:2 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 8.6 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.75 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H), 7.52 – 7.41 (m, 3H), 7.30 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.26 – 7.14 (m, 11H), 7.08 (dt, *J* = 8.4, 0.9 Hz, 1H), 6.04 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.28 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.17 (dt, *J* = 10.5, 1.6 Hz, 1H), 4.88 – 4.77 (m, 2H), 2.75 (qt, *J* = 6.8, 1.3 Hz, 2H); (due to the C–P coupling, the ^{13}C NMR contained extra peaks. See the attached spectrum); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.1, 156.7, 156.6, 141.5, 141.2, 137.6, 137.5, 137.2, 137.2, 136.0, 135.9, 134.9, 134.0, 133.8, 133.7, 133.3, 133.2, 133.2, 133.1, 131.9, 131.6, 130.3, 130.0, 130.0, 129.3, 128.7, 128.4, 128.4, 128.2, 128.1, 127.1, 126.9, 126.7, 126.7, 126.1, 123.2, 119.6, 117.2, 77.2, 66.7, 33.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ -14.2; IR (Neat Film NaCl) 2096, 1642, 1417, 1348, 1113, 1020, 818, 744 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{34}H_{27}N_2OP$ $[M+H]^+$: 511.1934;

found: 511.1954; SFC conditions: 35% MeOH, 2.5mL/min, Chiralpak AD-H column, t_R (min): major = 3.00, minor = 3.66.



158g

$[a]_D^{25}$ +40.1 (*c* 0.31, $CHCl_3$); R_f = 0.56 (1:2 EtOAc:hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.2 Hz, 1H), 7.91 (t, *J* = 7.8 Hz, 2H), 7.73 (ddd, *J* = 8.3, 7.1, 1.3 Hz, 1H), 7.54 – 7.41 (m, 3H), 7.35 – 7.13 (m, 14H), 7.12 – 7.03 (m, 2H), 5.74 (d, *J* = 5.4 Hz, 2H), 2.39 (s, 6H); (due to the C–P coupling, the ^{13}C NMR contained extra peaks. See the attached spectrum); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 156.9, 156.8, 141.5, 141.1, 138.3, 137.5, 137.4, 137.3, 137.1, 136.9, 136.0, 135.9, 134.1, 133.8, 133.7, 133.4, 133.2, 133.1, 133.1, 131.9, 131.6, 130.3, 130.0, 130.0, 129.3, 128.7, 128.5, 128.4, 128.4, 128.2, 128.1, 127.1, 126.9, 126.7, 126.7, 126.6, 126.6, 126.1, 123.4, 119.6, 69.5, 21.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ -14.2; IR (Neat Film NaCl) 3052, 2917, 1608, 1582, 1538, 1492, 1480, 1432, 1414, 1386, 1345, 1264, 1165, 1113, 1019, 962, 851, 818, 777, 743 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{39}H_{31}N_2OP$ $[M+H]^+$: 575.2247; found: 575.2293; SFC conditions: 40% MeOH, 2.5mL/min, Chiralcel OD-H column, t_R (min): major = 5.77, minor = 6.82.



158h

$[a]_D^{25}$ +118.5 (*c* 0.33, $CHCl_3$); R_f = 0.61 (1:2 EtOAc:hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.29 (dt, *J* = 8.2, 1.7 Hz, 1H), 7.91 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.88 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.71 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.52 (dd, *J* = 8.2, 2.6 Hz, 2H), 7.48 (ddd, *J* = 8.2, 6.7, 1.3 Hz, 1H), 7.43 (dddd, *J* = 9.2, 6.0, 3.4, 1.8 Hz, 2H), 7.32 – 7.13 (m, 14H), 7.10 – 7.06 (m, 1H), 5.76 (q, *J* = 12.1 Hz, 2H), 2.40 (s, 3H); (due to the C–P coupling, the ^{13}C NMR contained extra peaks. See the attached spectrum); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.1, 156.9, 156.8, 141.4, 141.2, 138.1, 137.5, 137.4, 137.2, 137.1, 136.0, 135.9, 134.0, 133.9, 133.7, 133.4, 133.2, 133.1, 131.9, 131.6, 130.3, 130.0, 130.0, 129.4, 129.4, 129.3, 128.9, 128.7, 128.4, 128.4, 128.4, 128.4, 128.3, 128.1, 127.1, 126.9, 126.7, 126.7, 126.1, 123.3, 119.6, 69.3, 21.4; ^{31}P NMR (121 MHz, $CDCl_3$) δ -14.2; IR (Neat Film NaCl) 3051, 1583, 1492, 1416, 1345, 1163, 1112, 1019, 744 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{38}H_{29}N_2OP$ $[M+H]^+$: 561.2090; found: 561.2090; SFC conditions: 40% MeOH, 2.5mL/min, Chiralpak AD-H column, t_R (min): major = 3.43, minor = 5.21.

3.5. References and Notes

(1) (a) Doucet, H.; Fernandez, E.; Layzell, T. P.; Brown, J. M. *Chem. Eur. J.* **1999**, *5*, 1320–1330. (b) Faller, J. W.; Grimmond, B. J. *Organometallics* **2001**, *20*, 2454–2458. (c) Maeda, K.; Brown, J. M. *Chem. Commun.* **2002**, 310–311. (d) Gommermann, N.;

Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763–5766. (e) Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702–8703. (f) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174–10175. (g) Daura-Oller, E.; Segarra, A. M.; Poblet, J. M.; Claver, C.; Fernández, E.; Bo, C. *J. Org. Chem.* **2004**, *69*, 2669–2680. (h) Black, A.; Brown, J. M.; Pichon, C. *Chem. Commun.* **2005**, 5284–5286. (i) Trudeau, S.; Morgan, J. B.; Shrestha, M.; Morken, J. P. *J. Org. Chem.* **2005**, *70*, 9538–9544. (j) Gommermann, N.; Knochel, P. *Chem.–Eur. J.* **2006**, *12*, 4380–4392. (k) Taylor, A. M.; Schreiber, S. L. *Org. Lett.* **2006**, *8*, 143–146. (l) Li, X.; Kong, L.; Gao, Y.; Wang, X. *Tetrahedron Lett.* **2007**, *48*, 3915–3917. (m) Miura, T.; Yamauchi, M.; Kosaka, A.; Murakami, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4955–4957. (n) Lim, A. D.; Codelli, J. A.; Reisman, S. E. *Chem. Sci.* **2013**, *4*, 650–654. (o) Fernández, E. Guiry, P. J.; Connole, K. P. T.; Brown, J. M. *J. Org. Chem.* **2014**, *79*, 5391–5400.

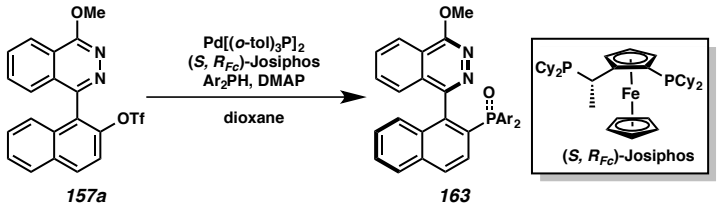
(2) (a) Alcock, N. W.; Brown, J. M.; Hulmes, D. I. *Tetrahedron: Asymmetry* **1993**, *4*, 743–756. (b) Lim, C. W.; Tissot, O.; Mattison, A. Hooper, M. W.; Brown, J. M.; Cowley, A. R.; Hulmes, D. I.; Blacker, A. J. *Org. Process Res. Dev.* **2003**, *7*, 379–384. (c) Thaler, T.; Geittner, F.; Knochel, P. *Synlett* **2007**, 2655–2658. (d) Clayden, J.; Fletcher, S. P.; McDouall, J. J. W.; Rowbottom, S. J. M. *J. Am. Chem. Soc.* **2009**, *131*, 5331–5343.

(3) Bhat, V.; Wang, S.; Stoltz, B. M.; Virgil, S. C. *J. Am. Chem. Soc.* **2013**, *135*, 16829–16832.

(4) (a) Knöpfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971–5973. (b) Fujimori, S.; Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Boyall, D.; Carreira, E. M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1635–1657.

(5) See Ref. 3 for a plausible mechanism of this dynamic kinetic resolution.

(6) Attempts to produce PINAP derivatives with diphenylphosphine oxide and (p-CF_3-$C_6H_4)_2PH$ in high enantioselectivities under our dynamic kinetic resolution conditions were unsuccessful.

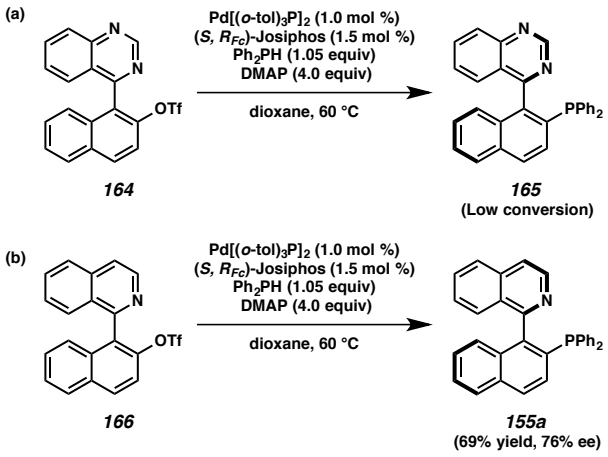


157a *163*

entry	$Ar_2\overset{O}{\overset{\|}{P}}H$	T (°C)	ee (%)
1	diphenylphosphine oxide	60	–[b]
2	(p-CF_3-$C_6H_4)_2PH$	60	–[c]
3	(p-CF_3-$C_6H_4)_2PH$	70	38[d]
4	(p-CF_3-$C_6H_4)_2PH$	80	50[d]

[a] Reactions performed with 1.0 equiv of **157a**, 4.0 equiv of DMAP, 1.0 mol % of $Pd[(o\text{-tol})_3P]_2$, 1.5 mol % of (S, R_{Fc})-Josiphos, 1.05 equiv of Ar_2PH (1.0 M in dioxane) at 0.20 M in dioxane in a glovebox. Ar_2PH (1.0 M in dioxane) was added over 8 h. [b] No reaction. [c] ~50% conversion. [d] Determined by chiral SFC analysis; SFC conditions: 35% IPA, 2.5 mL/min, Chiralpak IC column, t_R (min): major = 3.06, minor = 3.98.

(7) To demonstrate the scope of our methodology, the enantioselective synthesis of Quinazolinap from triflate **164** was attempted, but our reaction conditions led to poor conversion. Moreover, treatment of triflate **166** with the optimized conditions for PINAP provided the QUINAP ligand in diminished selectivity compared to that with the original reaction conditions[3].



(8) 96% ee (*R*)-PINAP **158a** was used for both applications.

(9) Determined by chiral HPLC analysis: conditions: 10% IPA 45 min, AD column, t_R: (min): minor = 10.5 min, major = 18.2 min. All the other spectra data were identical to the reported data. (ref. 1k)

(10) Determined by chiral SFC analysis: conditions: 20% MeOH, 2.5 mL/min, AD-H column, t_R (min): major = 2.46 min, minor = 2.92 min; $[a]_D^{25}$ +38.6 (*c* 0.19, $CHCl_3$)

APPENDIX 7

Spectra Relevant to Chapter 3:

Enantioselective Synthesis of PINAP via Dynamic Kinetic Resolution

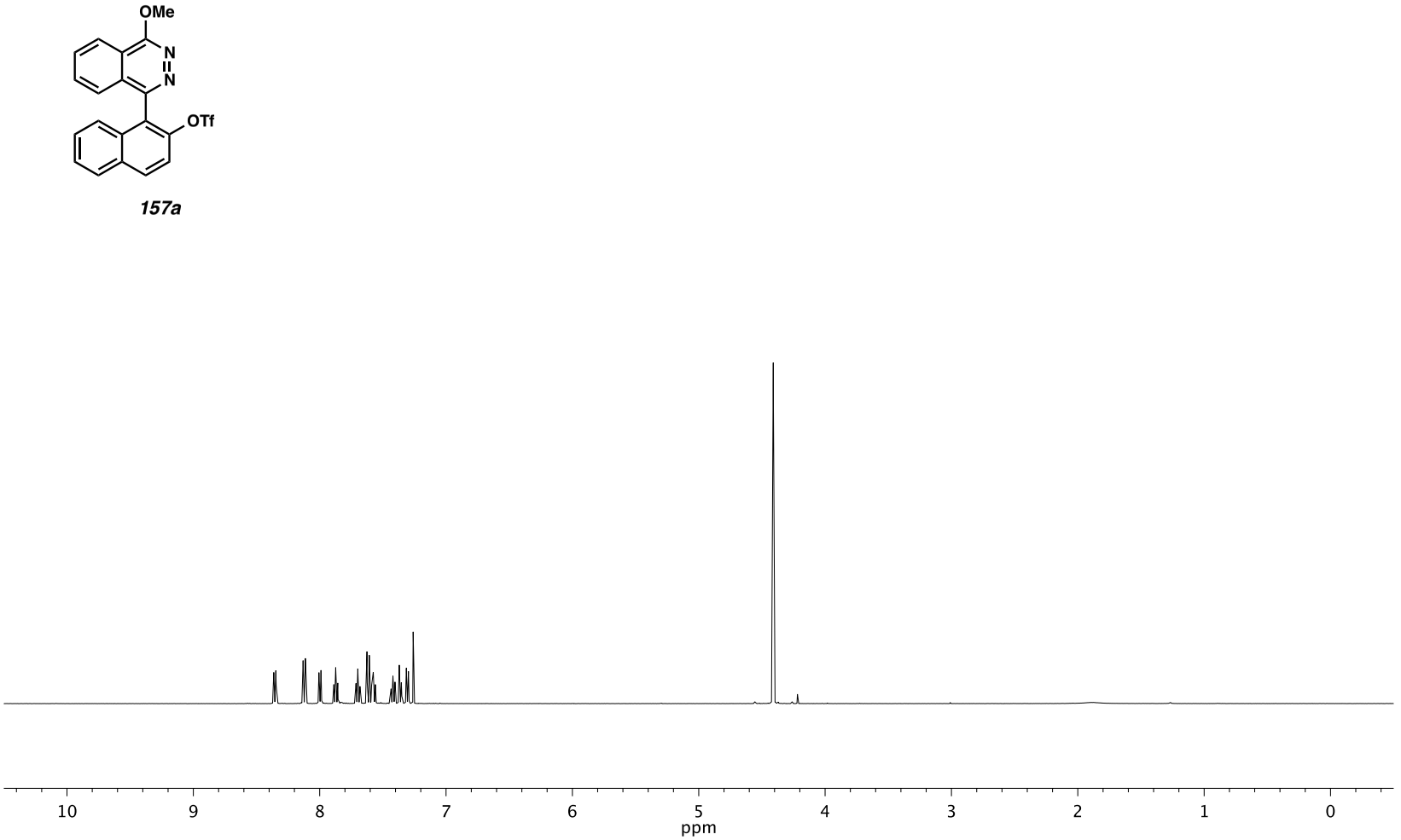


Figure A7.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **157a**.

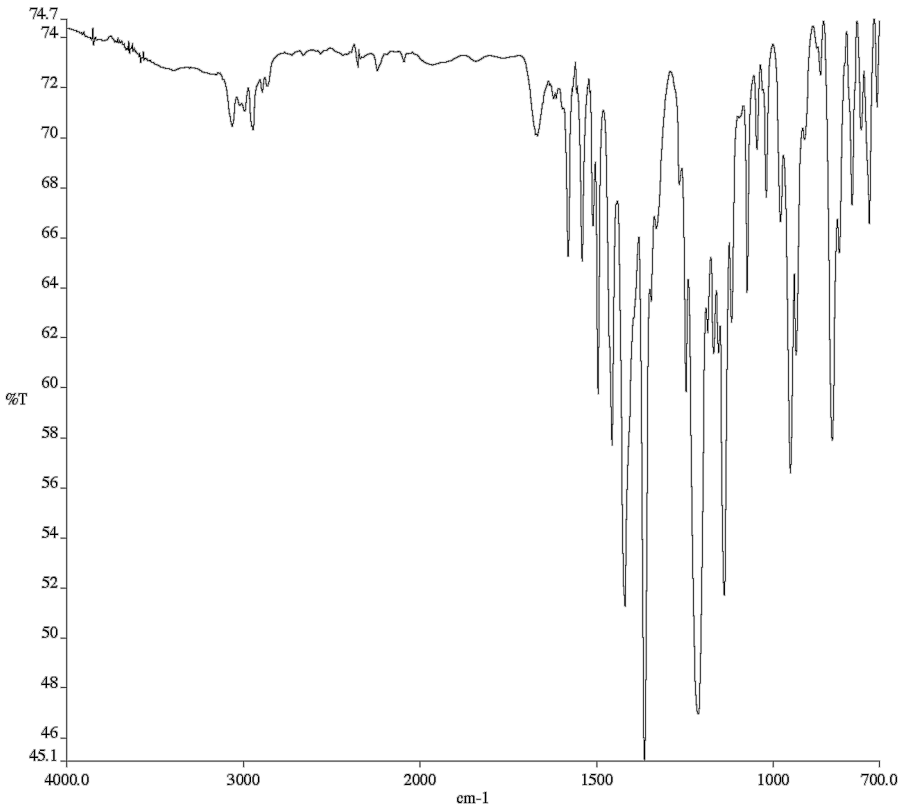


Figure A7.2. Infrared spectrum (Thin Film, NaCl) of compound **157a**.

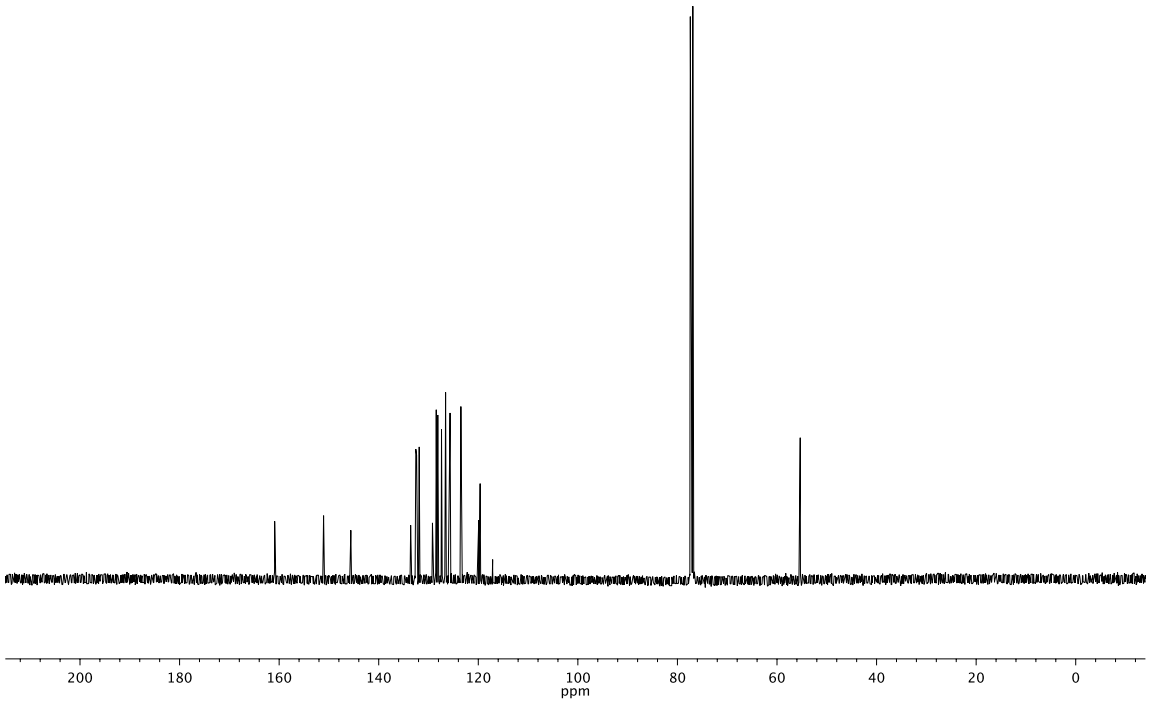


Figure A7.3. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **157a**.

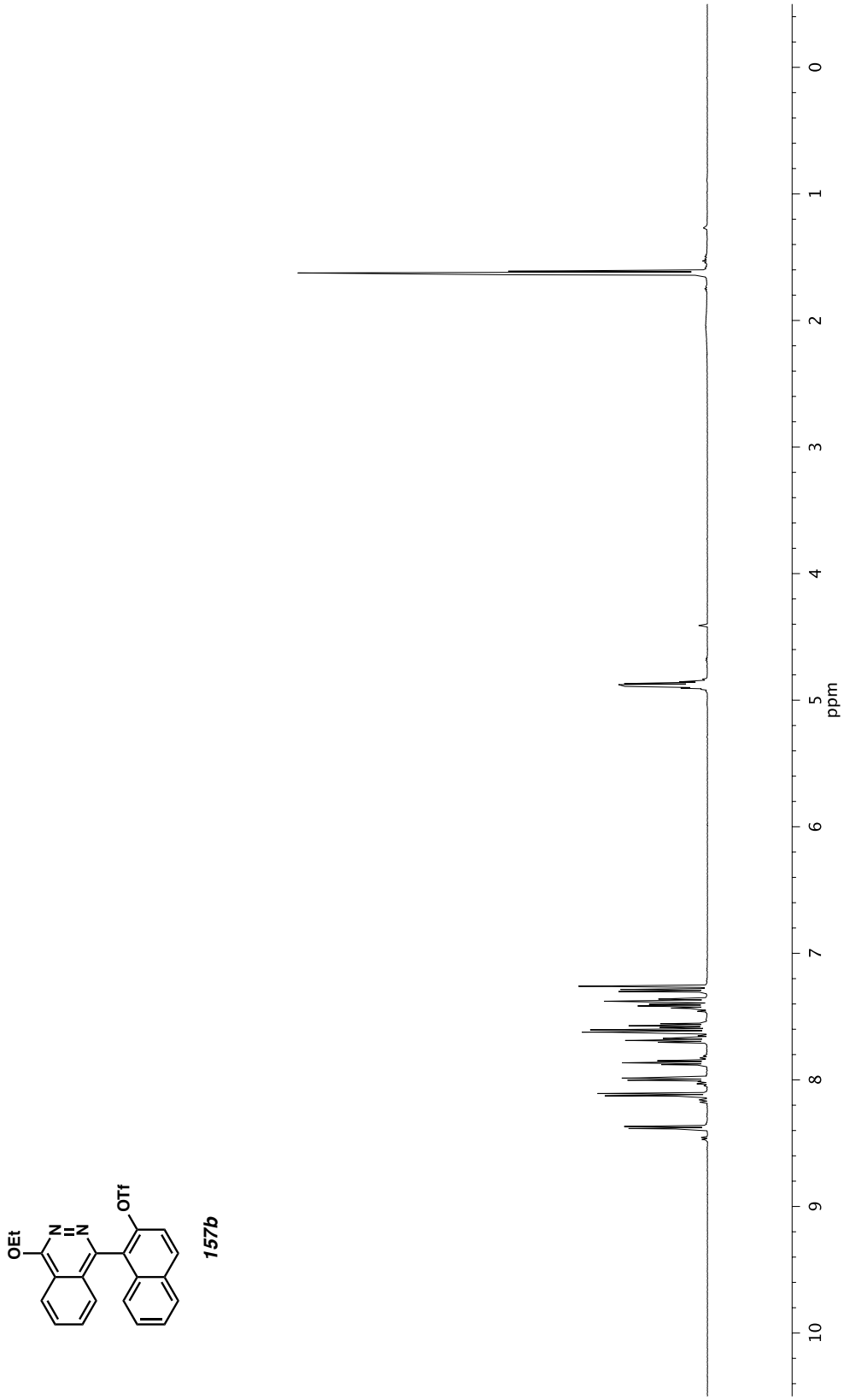


Figure A7.4. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **157b**.

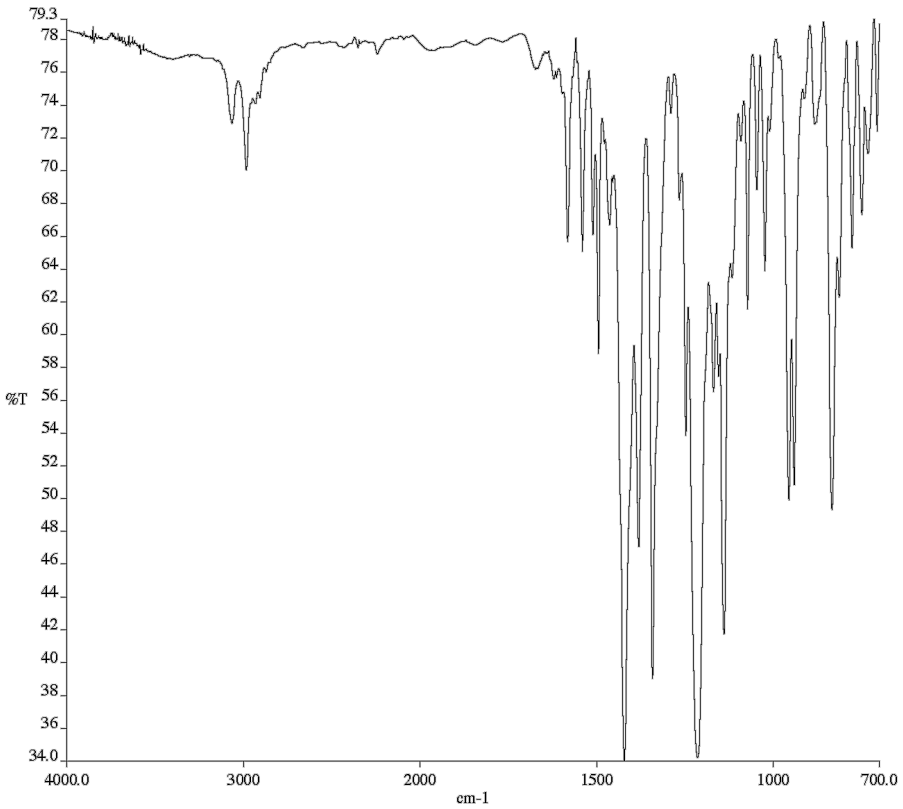


Figure A7.5. Infrared spectrum (Thin Film, NaCl) of compound **157b**.

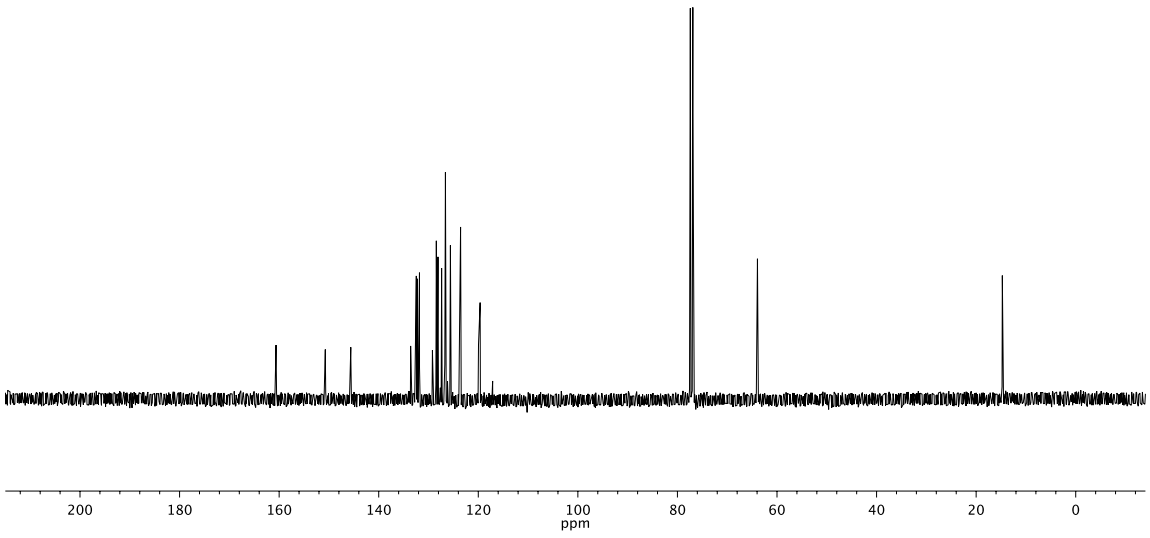


Figure A7.6. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **157b**.

Figure A7.7. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **157c**.

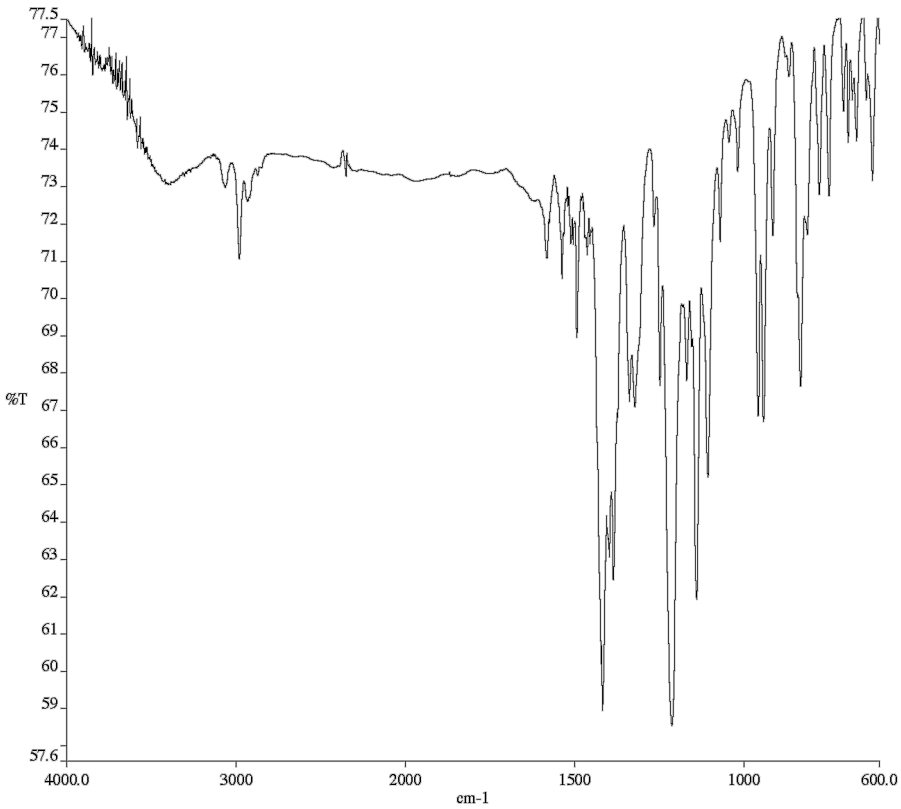


Figure A7.8. Infrared spectrum (Thin Film, NaCl) of compound **157c**.

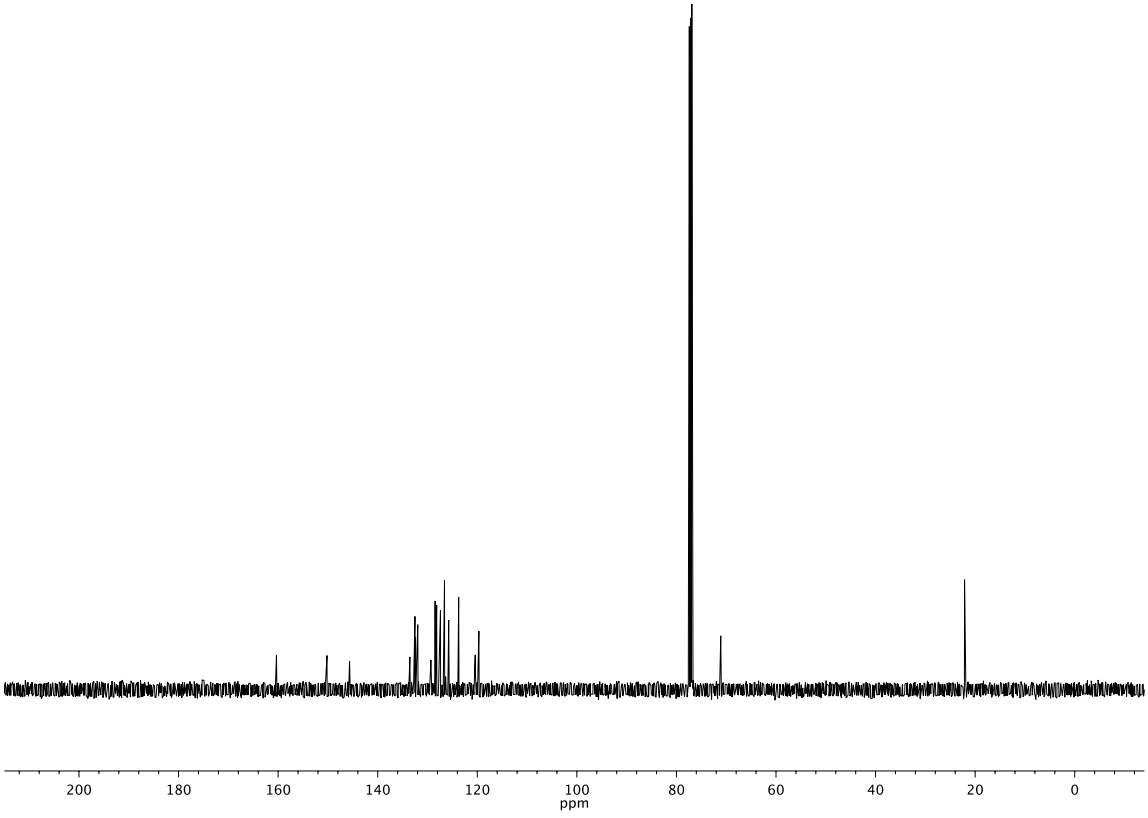


Figure A7.9. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **157c**.

Figure A7.10. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **157d**.

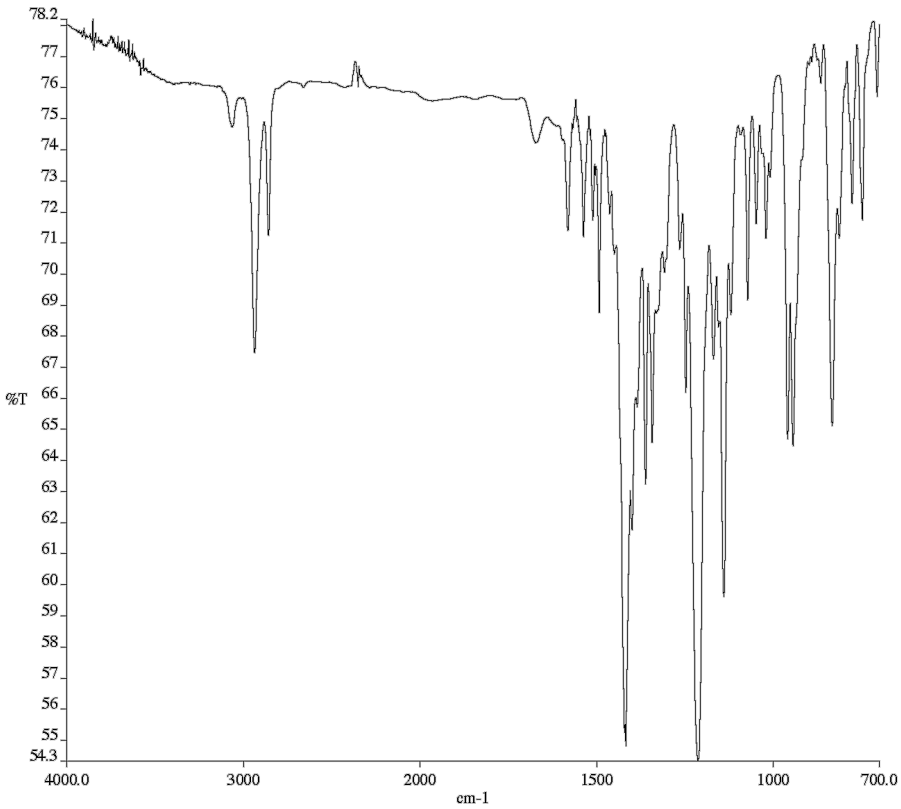


Figure A7.11. Infrared spectrum (Thin Film, NaCl) of compound **157d**.

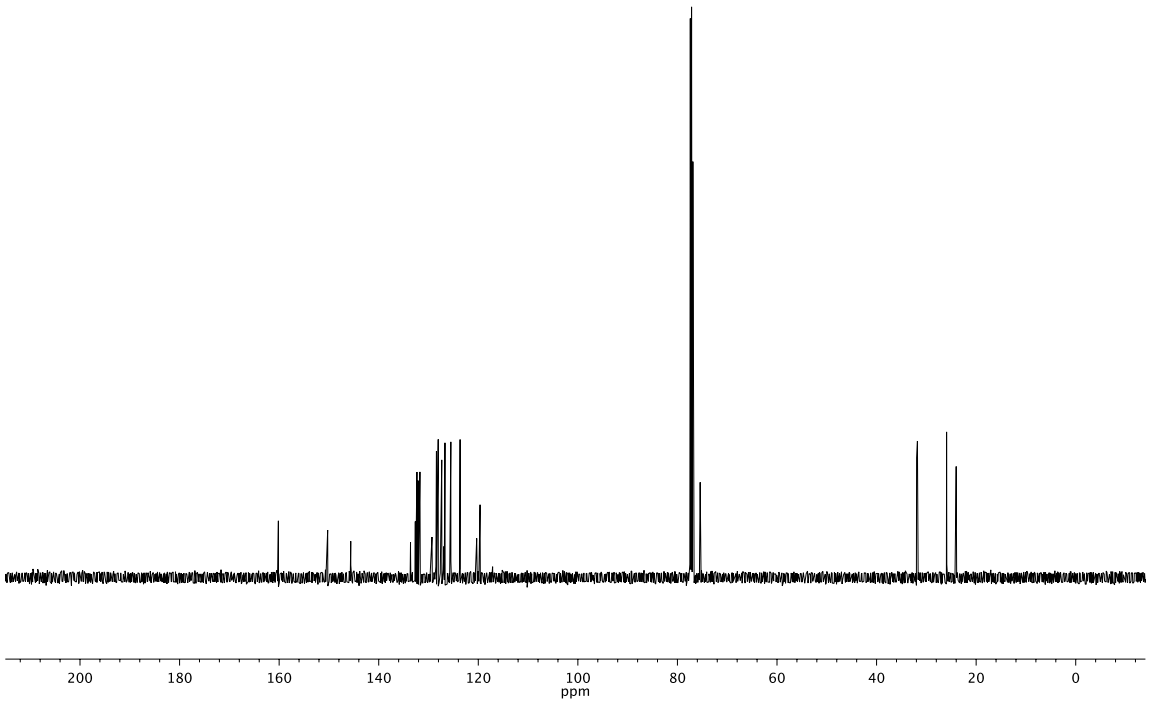


Figure A7.12. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **157d**.

Figure A7.13. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **157e**.

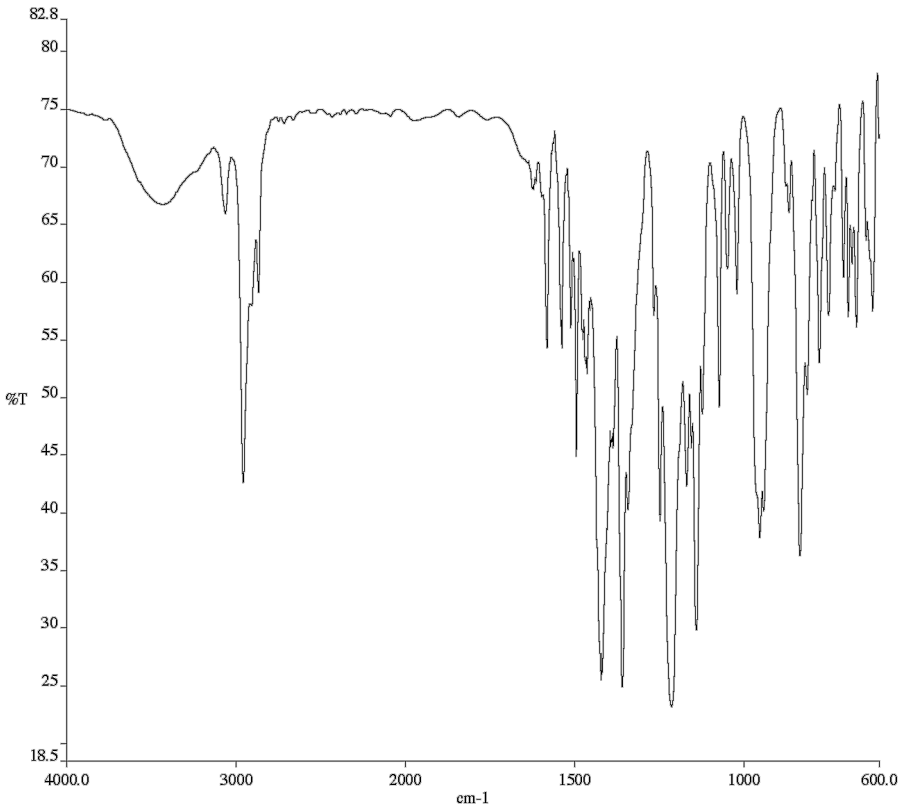


Figure A7.14. Infrared spectrum (Thin Film, NaCl) of compound **157e**.

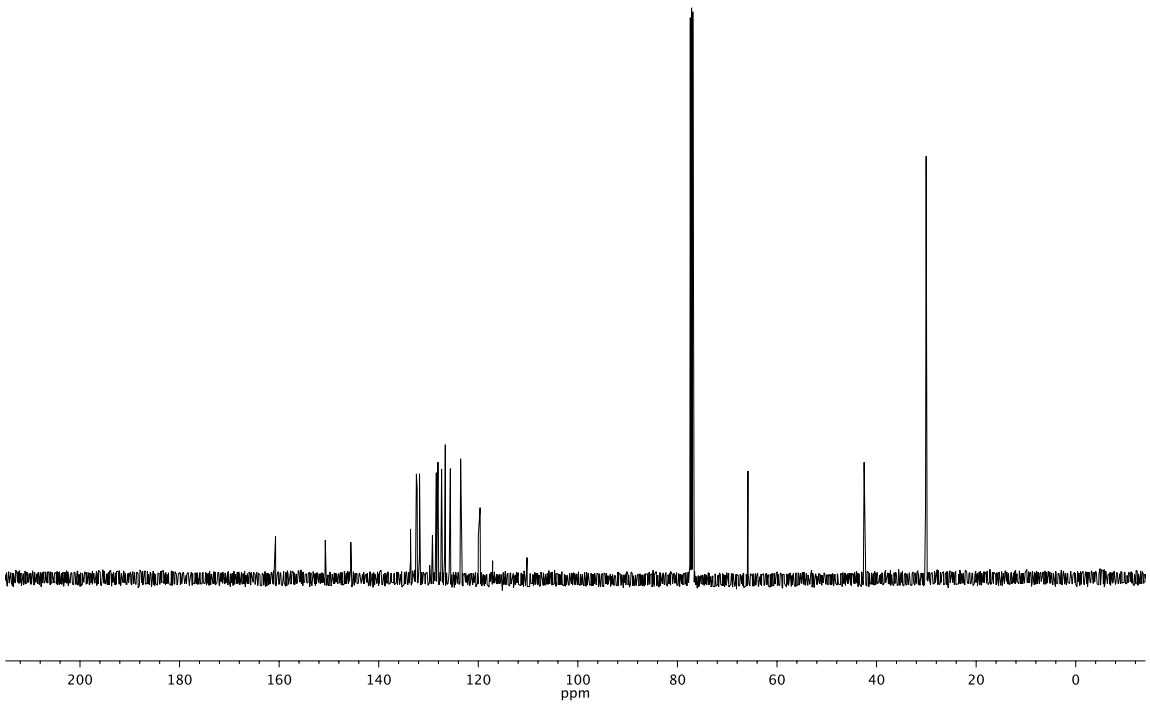


Figure A7.15. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **157e**.

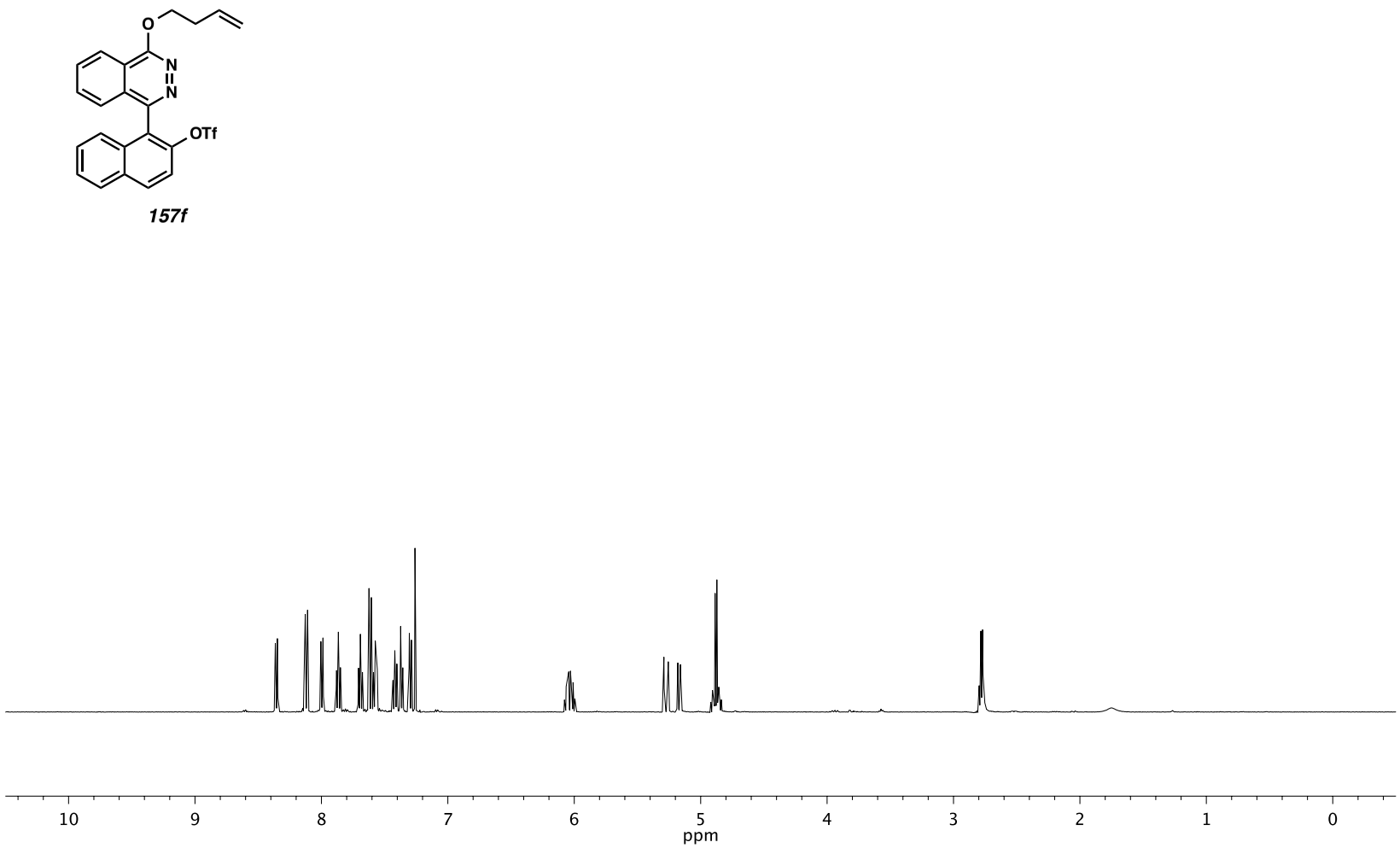


Figure A7.16. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **157f**.

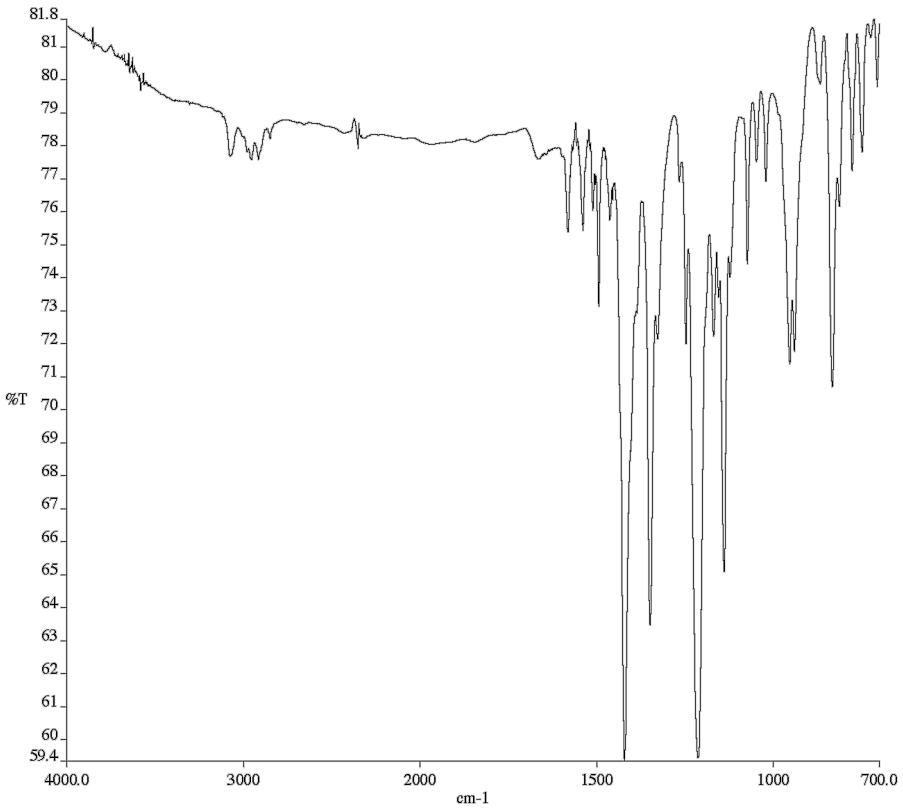


Figure A7.17. Infrared spectrum (Thin Film, NaCl) of compound **157f**.

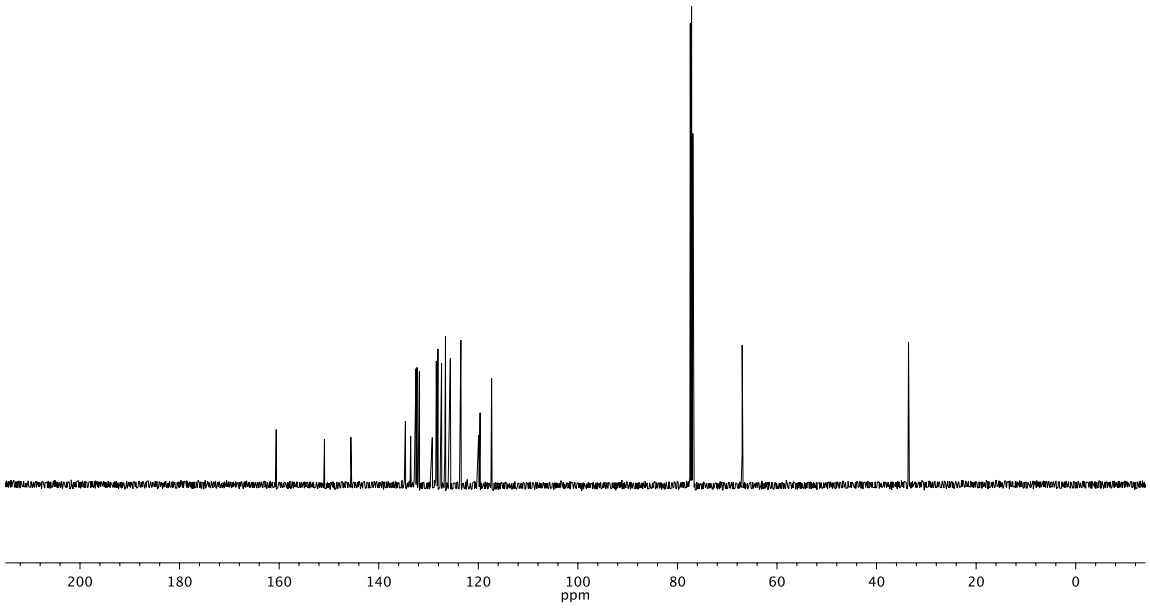


Figure A7.18. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **157f**.

Figure A7.19. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **157g**.

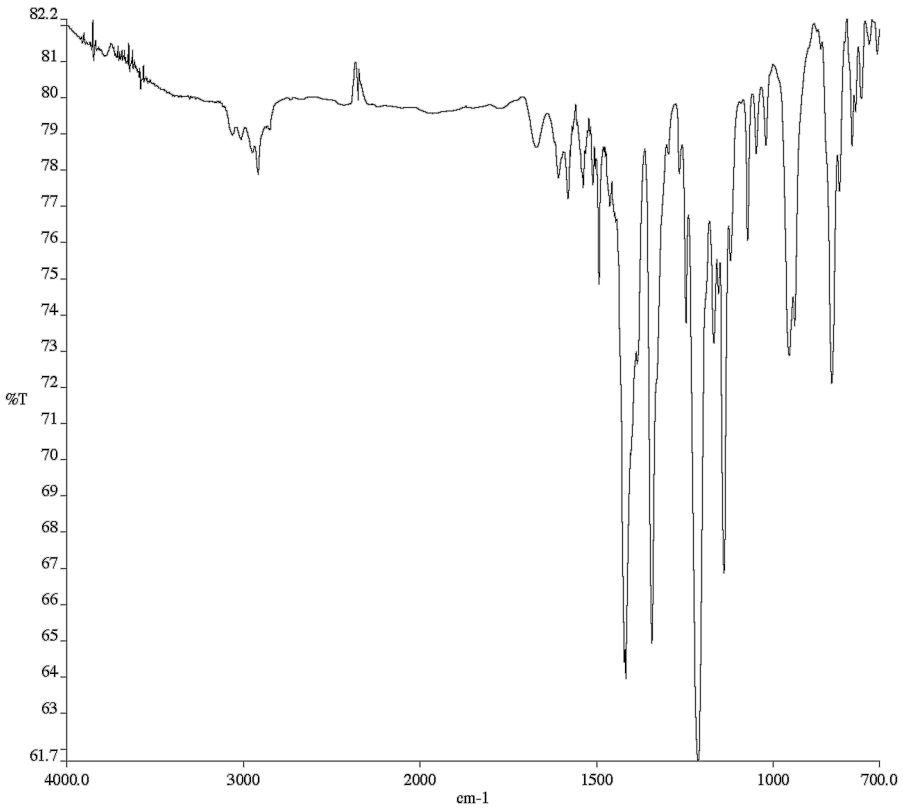


Figure A7.20. Infrared spectrum (Thin Film, NaCl) of compound **157g.**

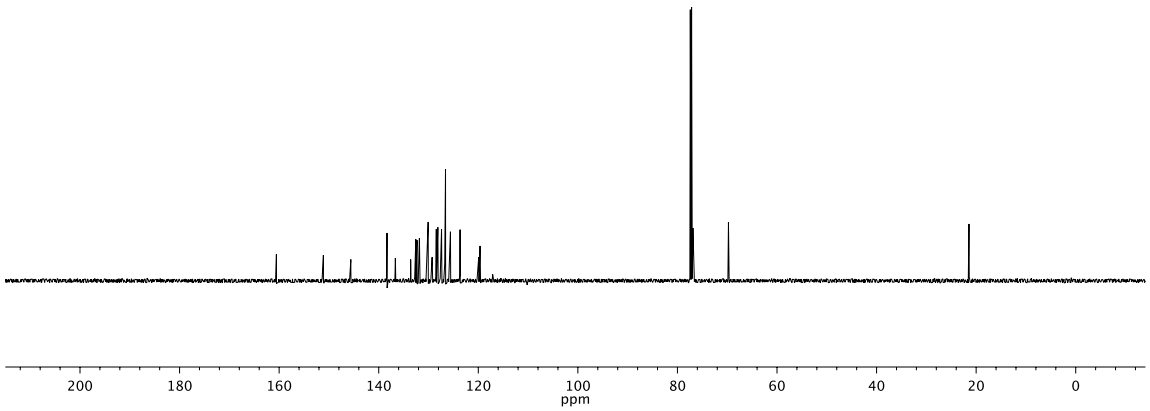


Figure A7.21. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **157g**.

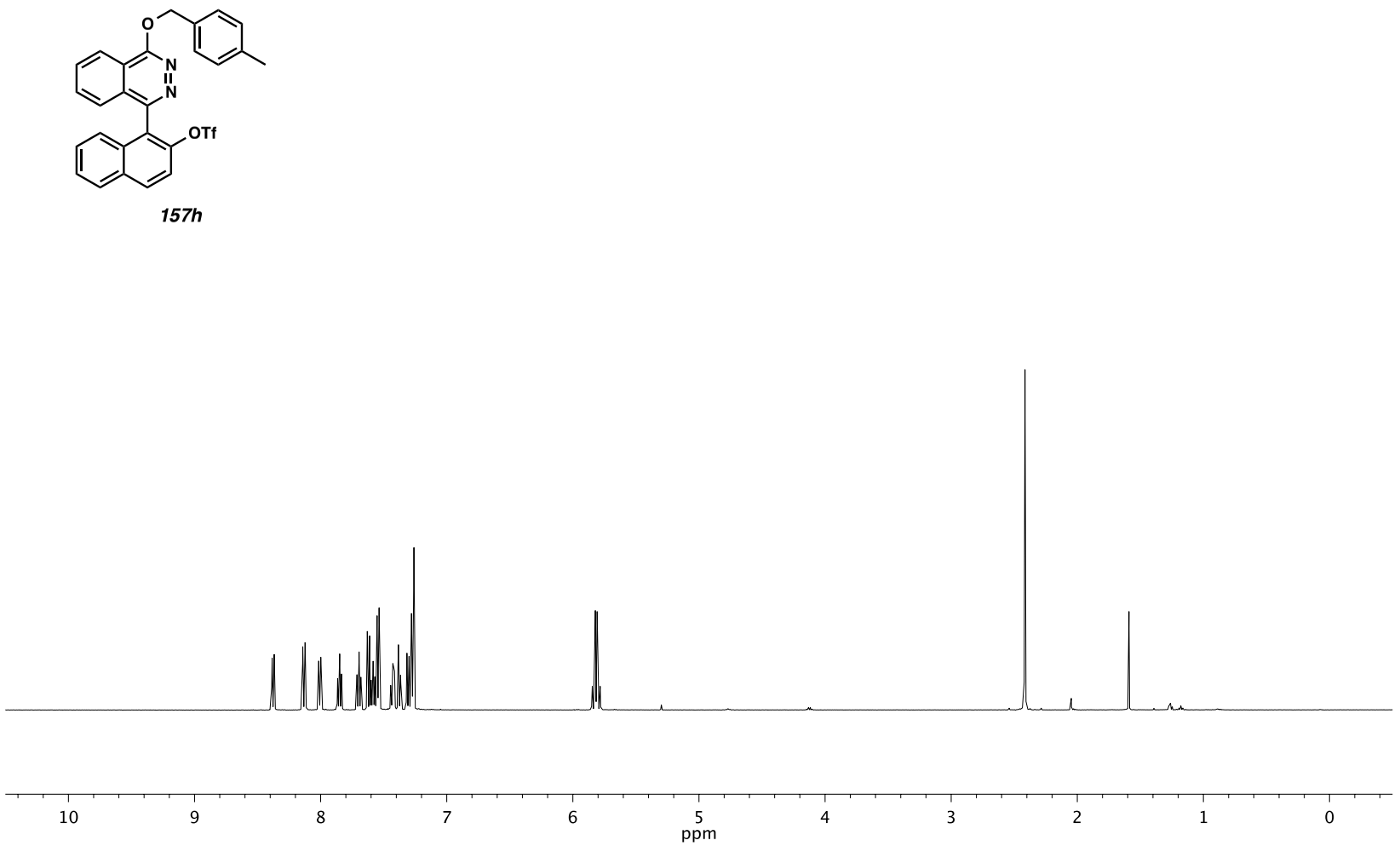


Figure A7.22. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **157h**.

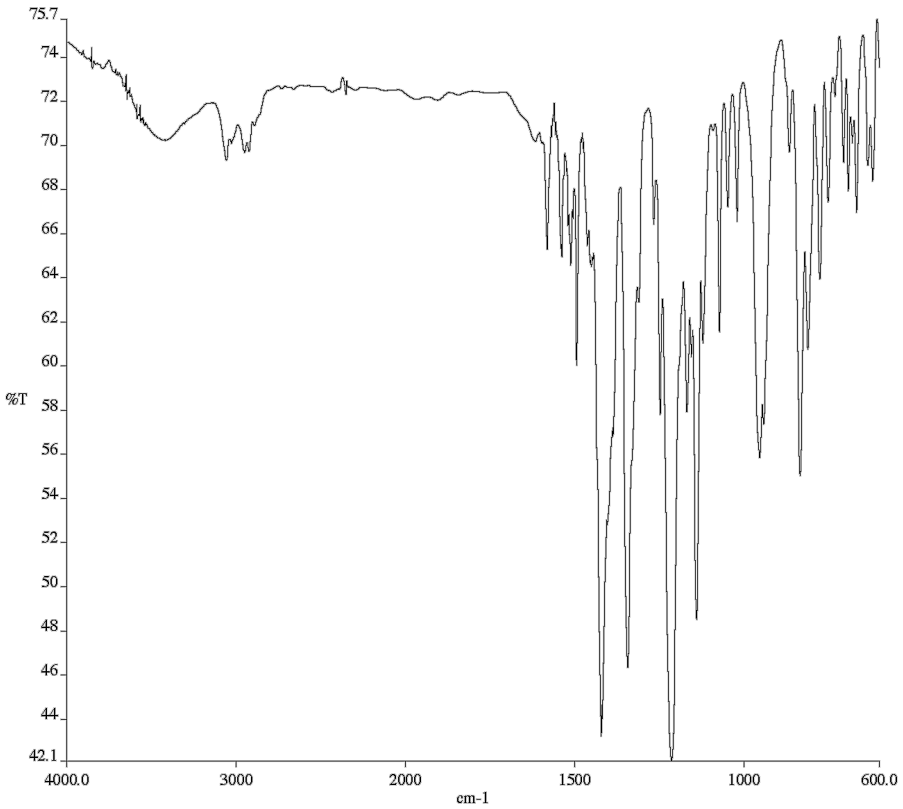


Figure A7.23. Infrared spectrum (Thin Film, NaCl) of compound **157h.**

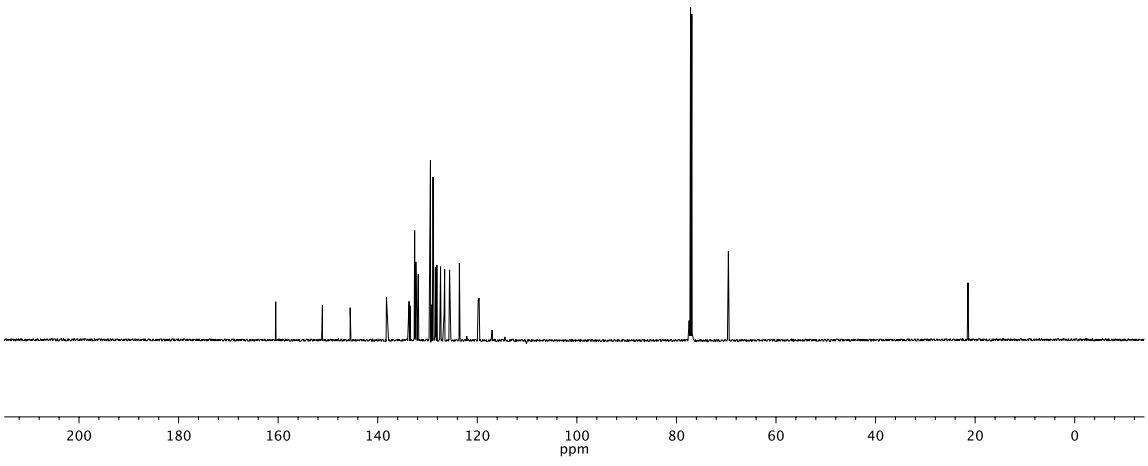


Figure A7.24. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **157h**.

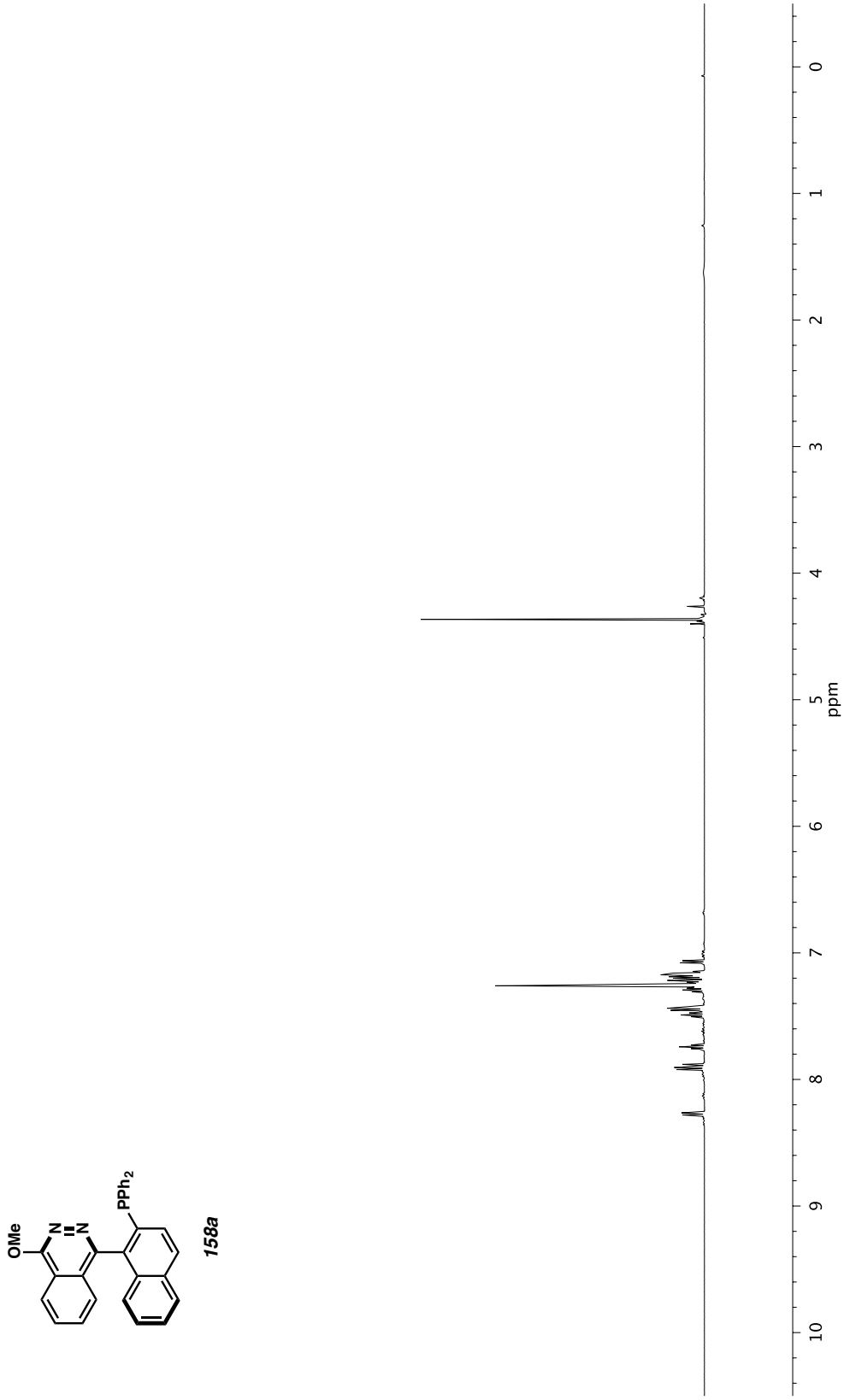


Figure A7.25. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **158a**.

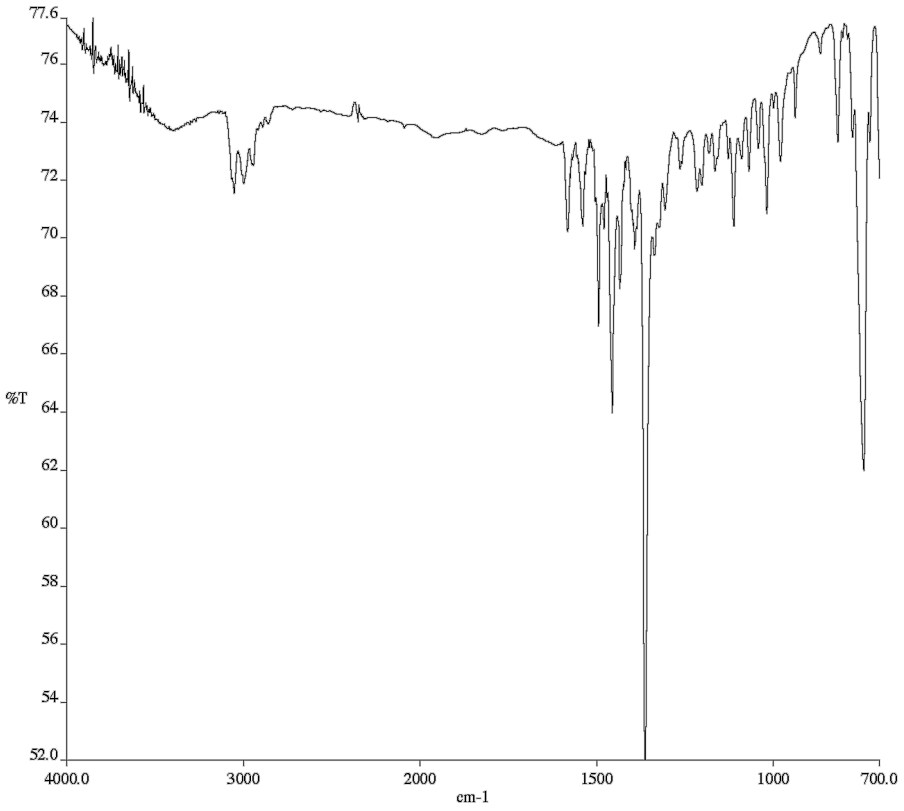


Figure A7.26. Infrared spectrum (Thin Film, NaCl) of compound **158a**.

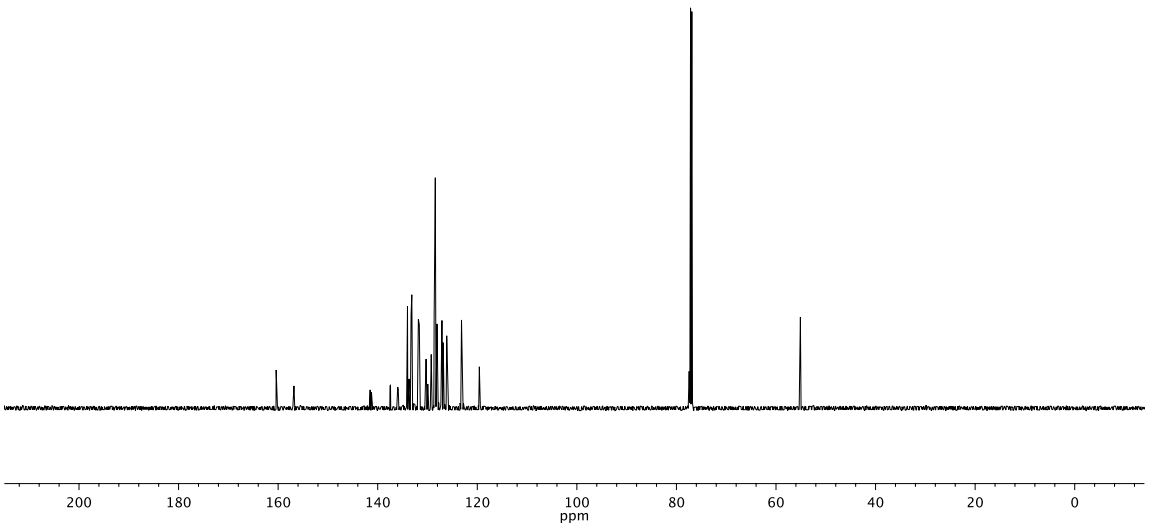


Figure A7.27. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **158a**.

Figure A7.28. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **158b**.

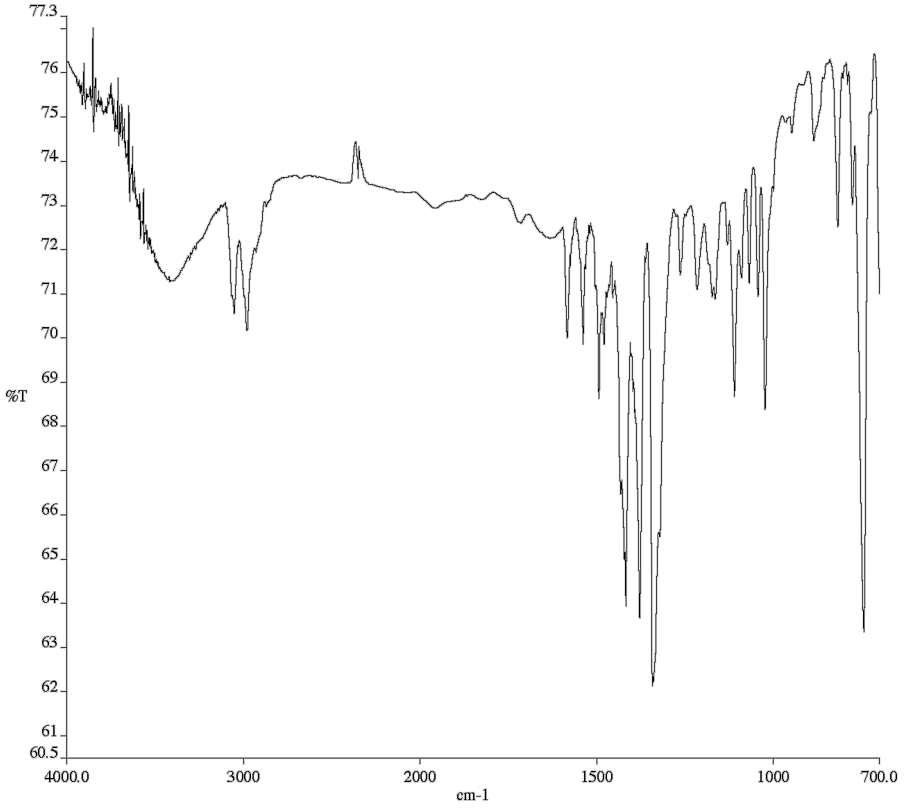


Figure A7.29. Infrared spectrum (Thin Film, NaCl) of compound **158b**.

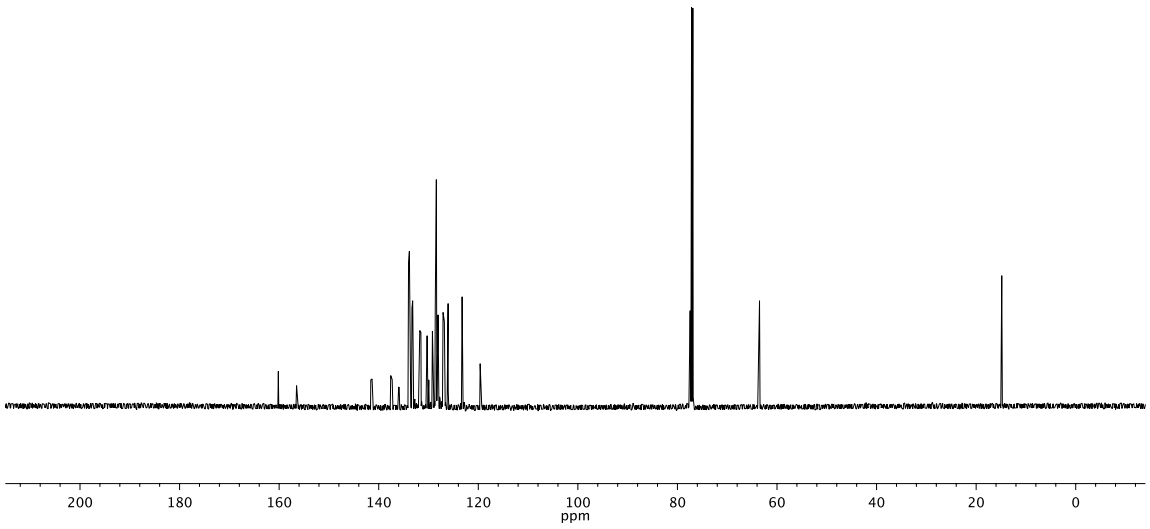


Figure A7.30. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **158b**.

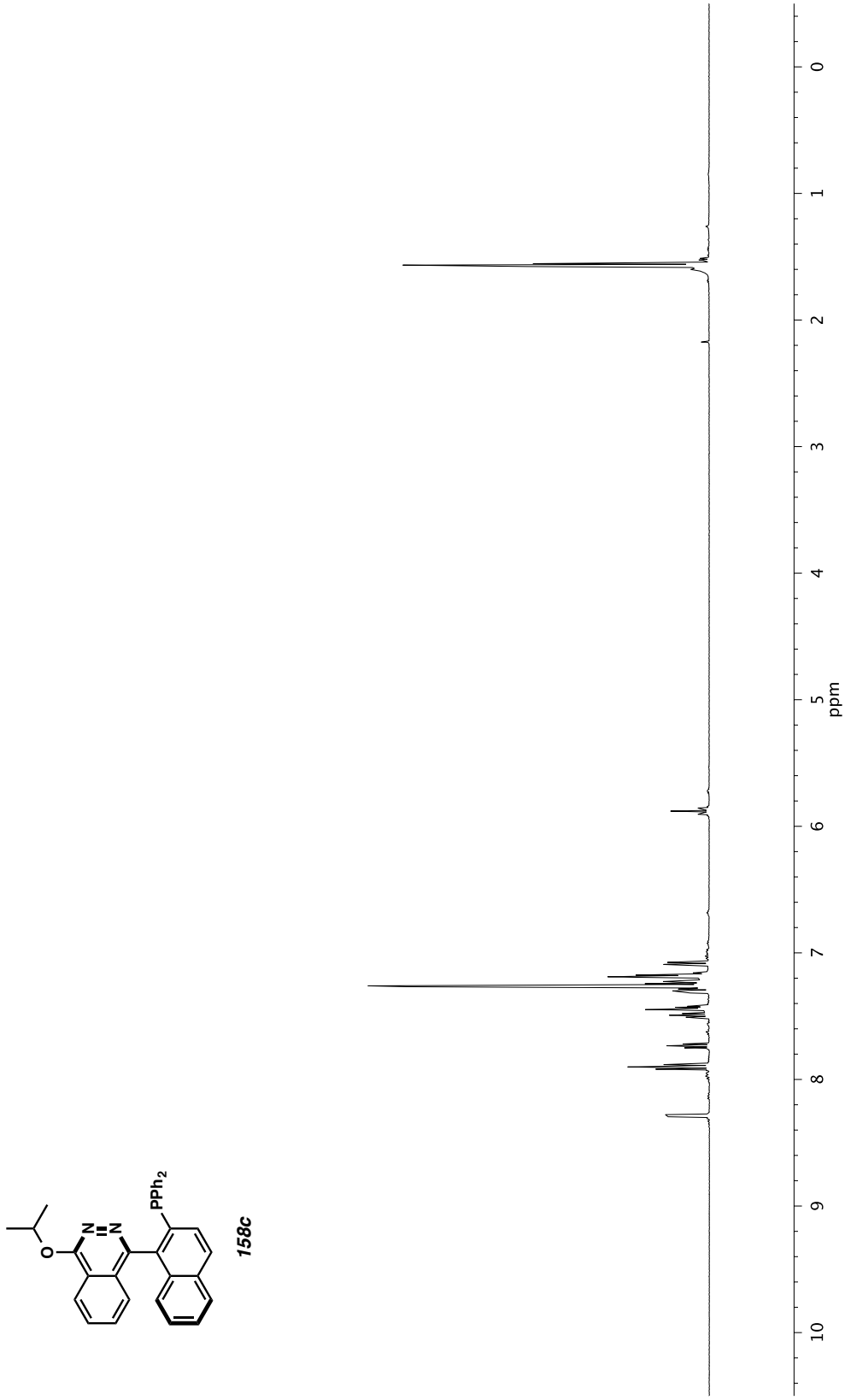


Figure A7.31. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **158c.**

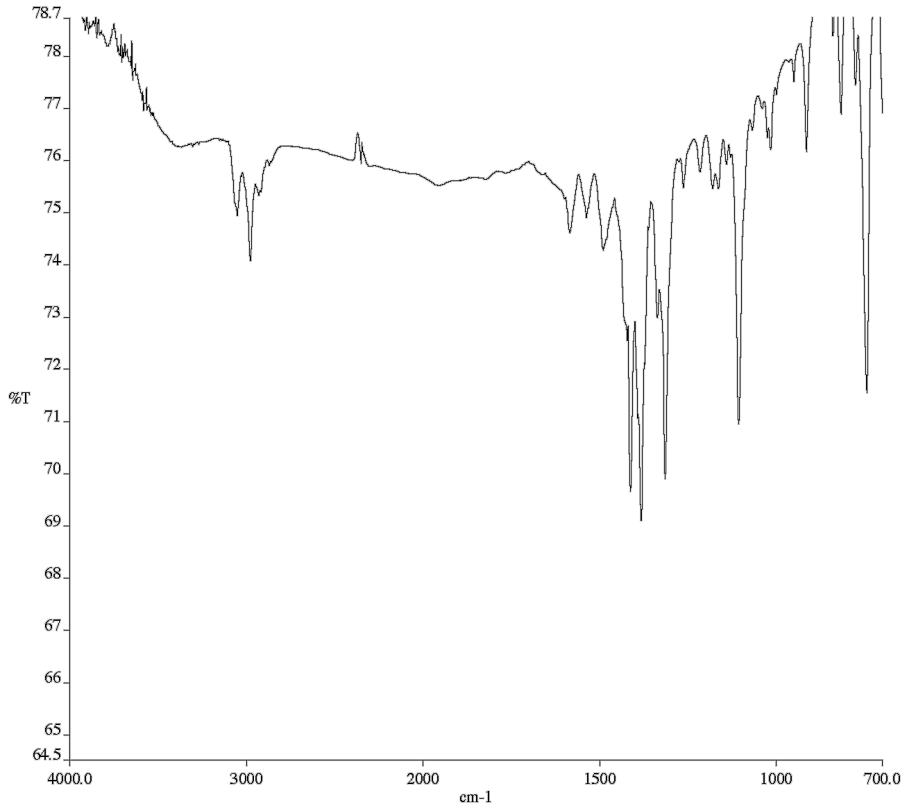


Figure A7.32. Infrared spectrum (Thin Film, NaCl) of compound **158c**.

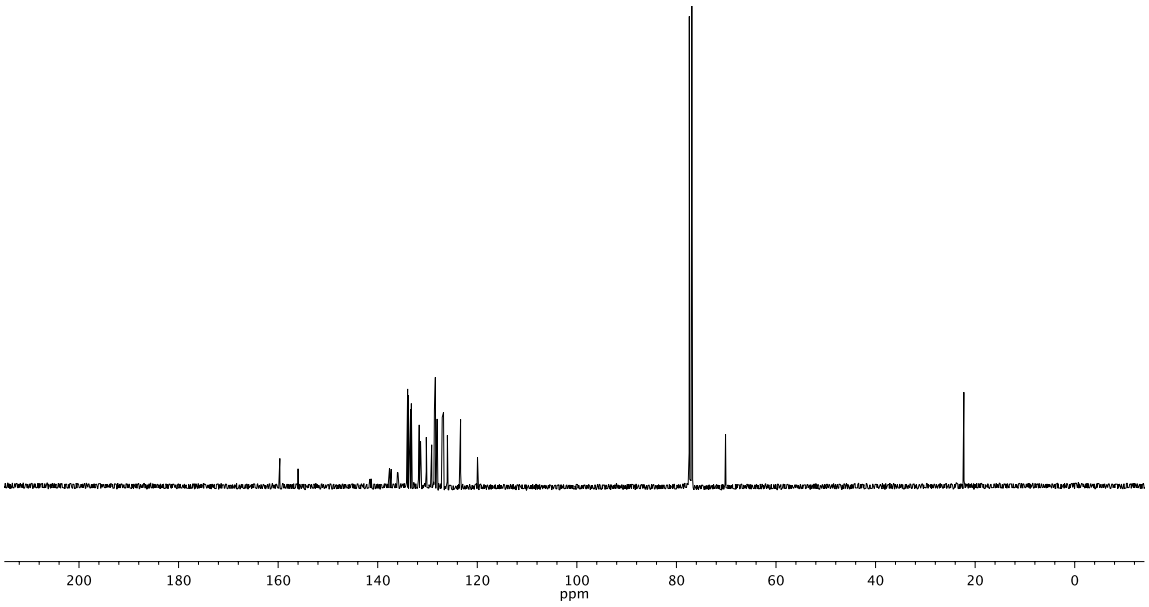


Figure A7.33. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **158c**.

Figure A7.34. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **158d.**

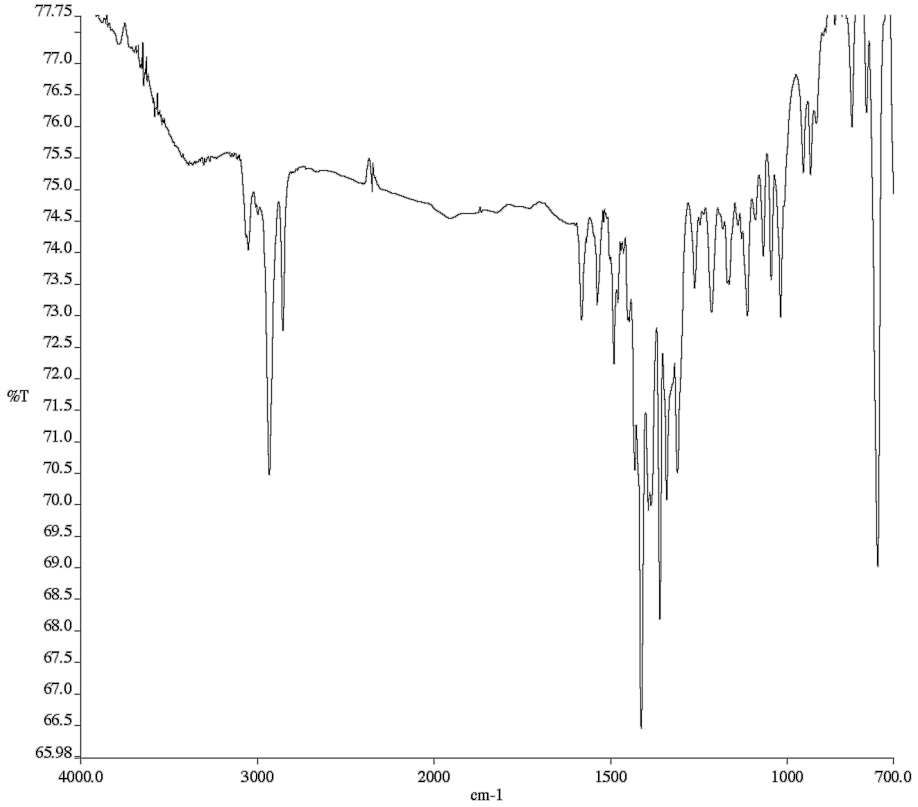


Figure A7.35. Infrared spectrum (Thin Film, NaCl) of compound **158d**.

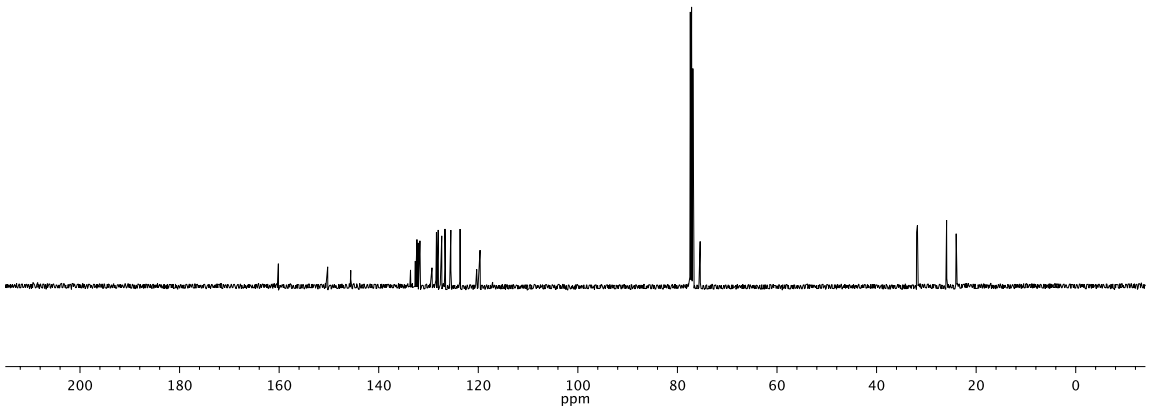


Figure A7.36. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **158d**.

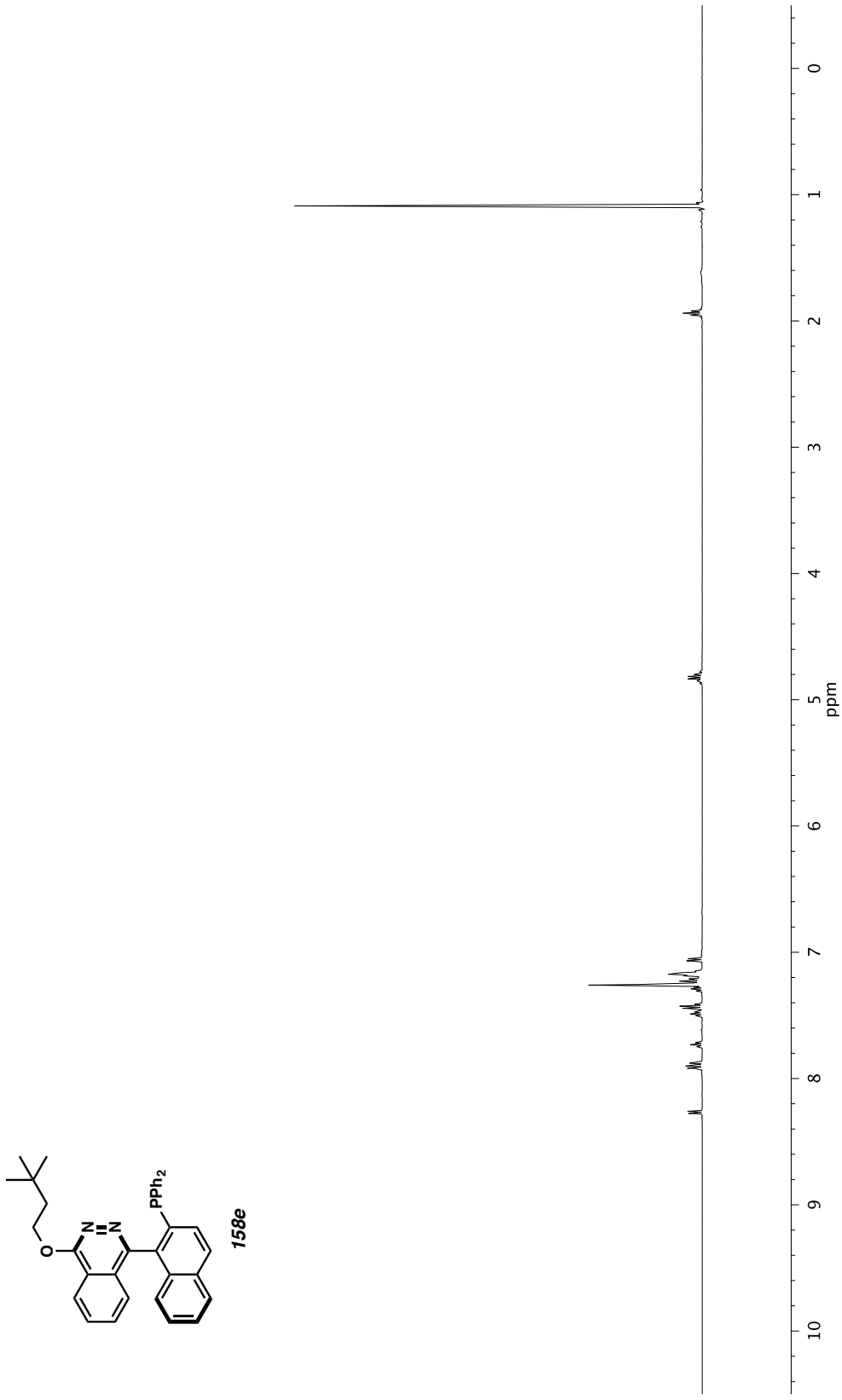


Figure A7.37. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **158e**.

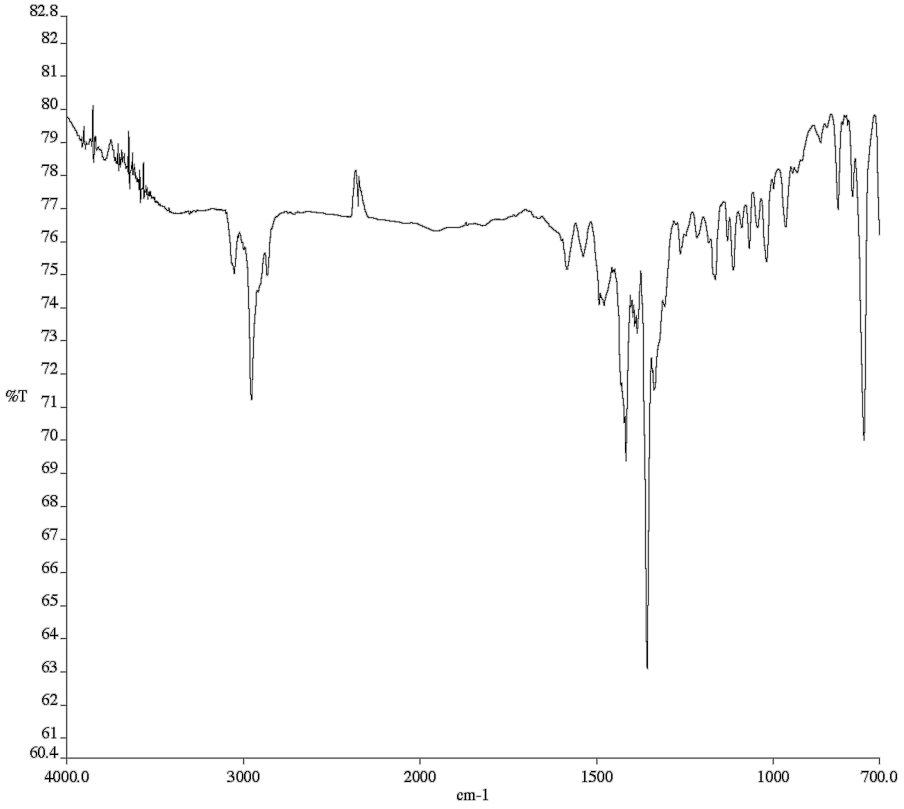


Figure A7.38. Infrared spectrum (Thin Film, NaCl) of compound **158e.**

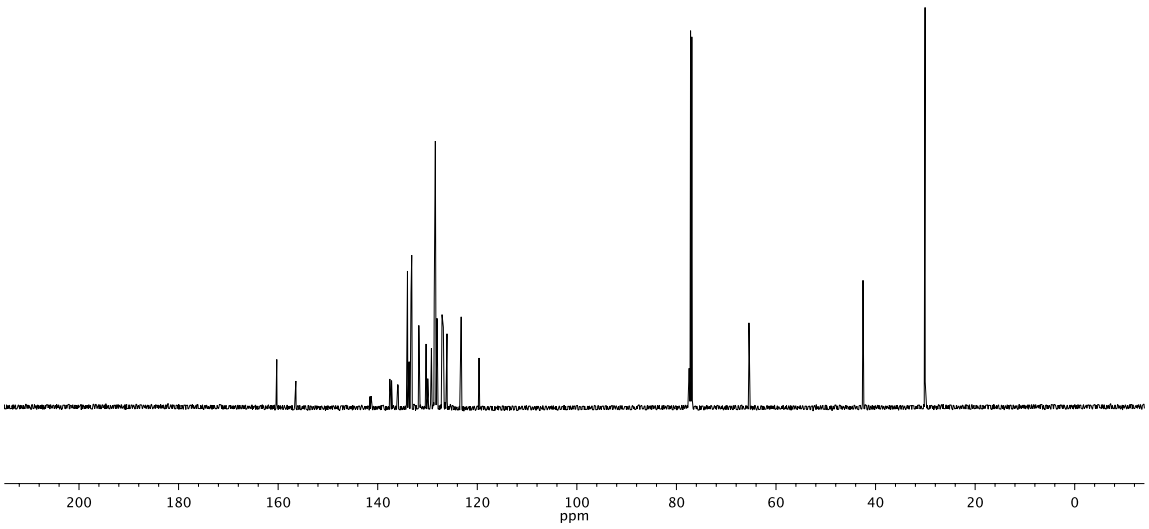


Figure A7.39. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **158e**.

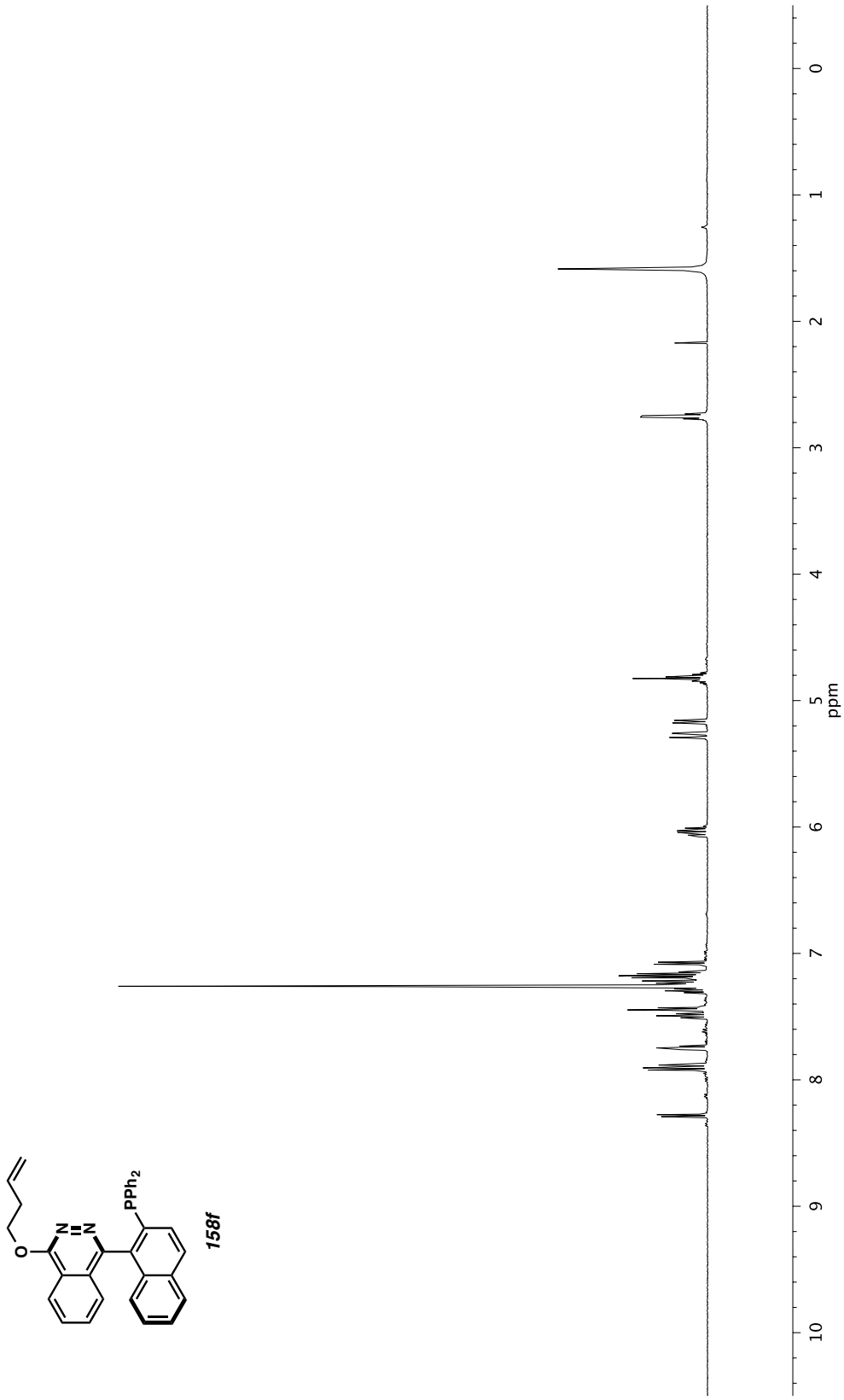


Figure A7.40. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **158f.**

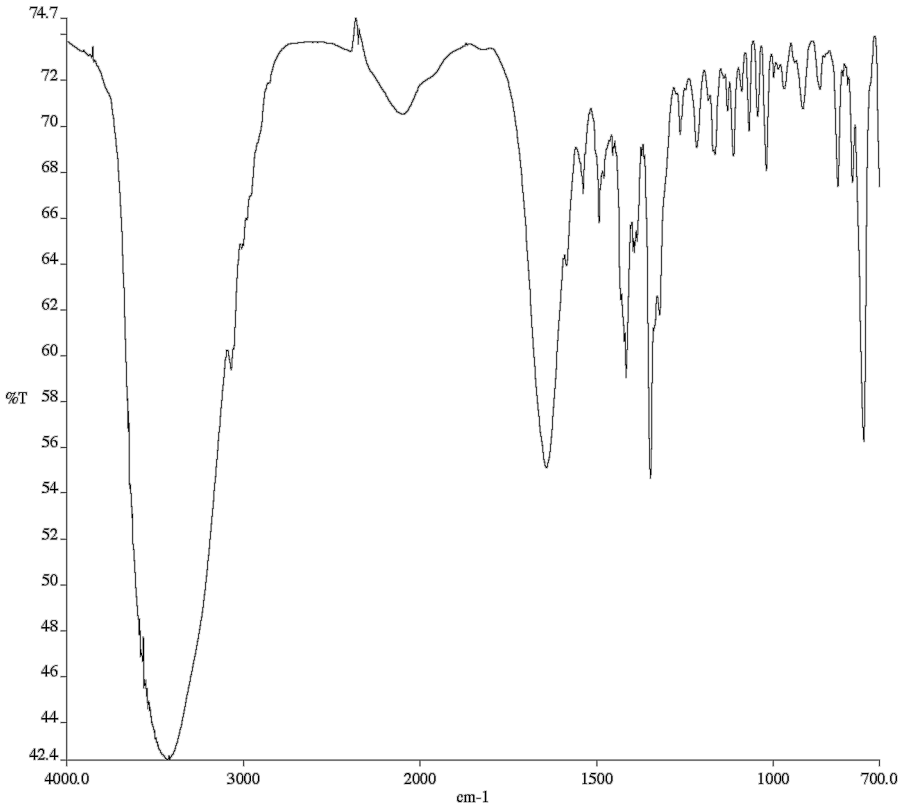


Figure A7.41. Infrared spectrum (Thin Film, NaCl) of compound **158f.**

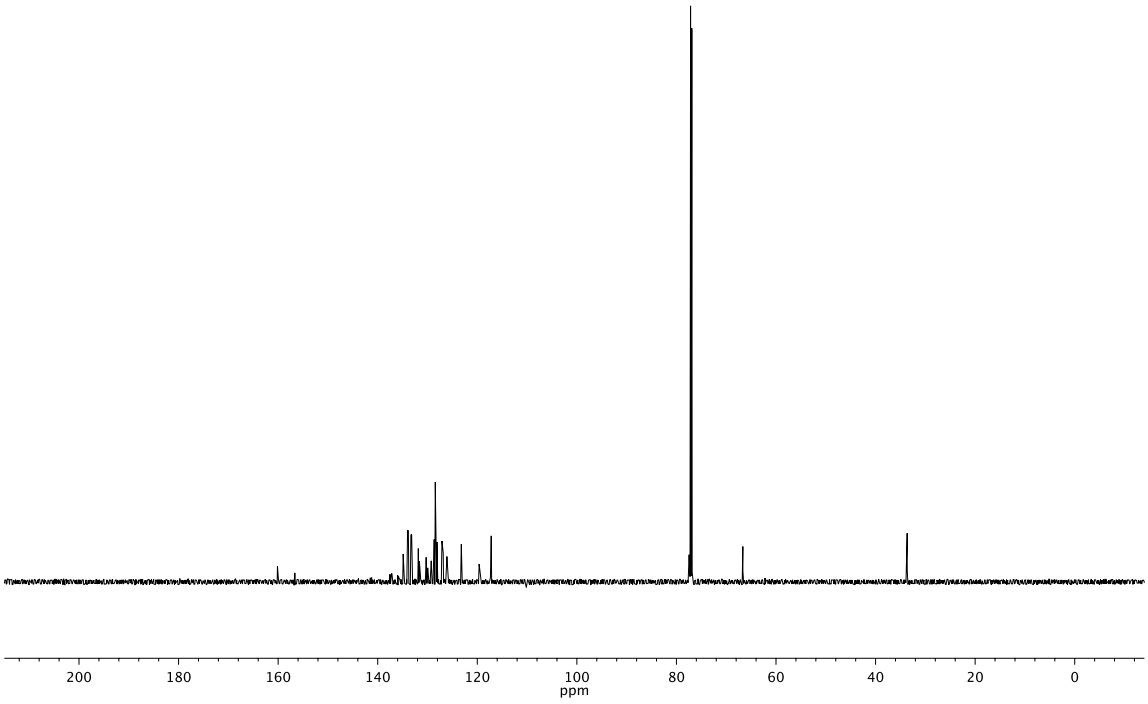


Figure A7.42. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **158f**.

Figure A7.43. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **158g**.

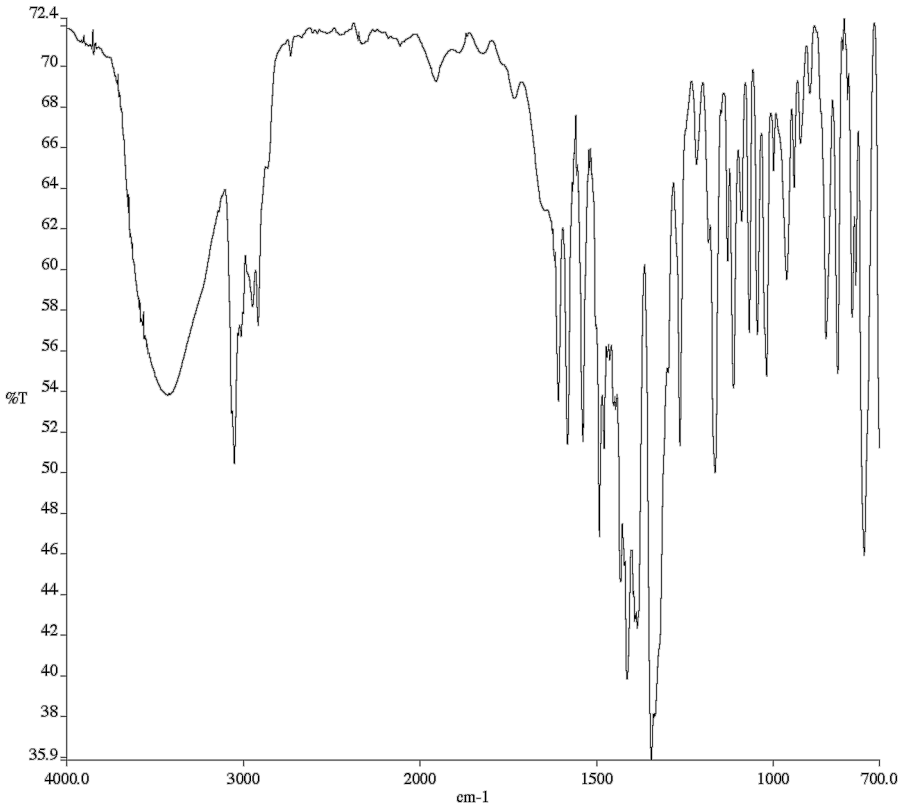


Figure A7.44. Infrared spectrum (Thin Film, NaCl) of compound **158g.**

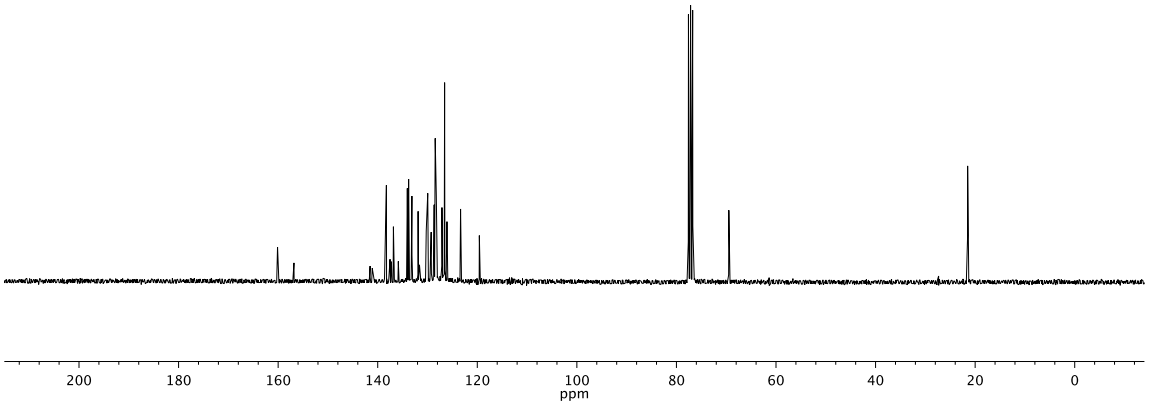


Figure A7.45. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **158g**.

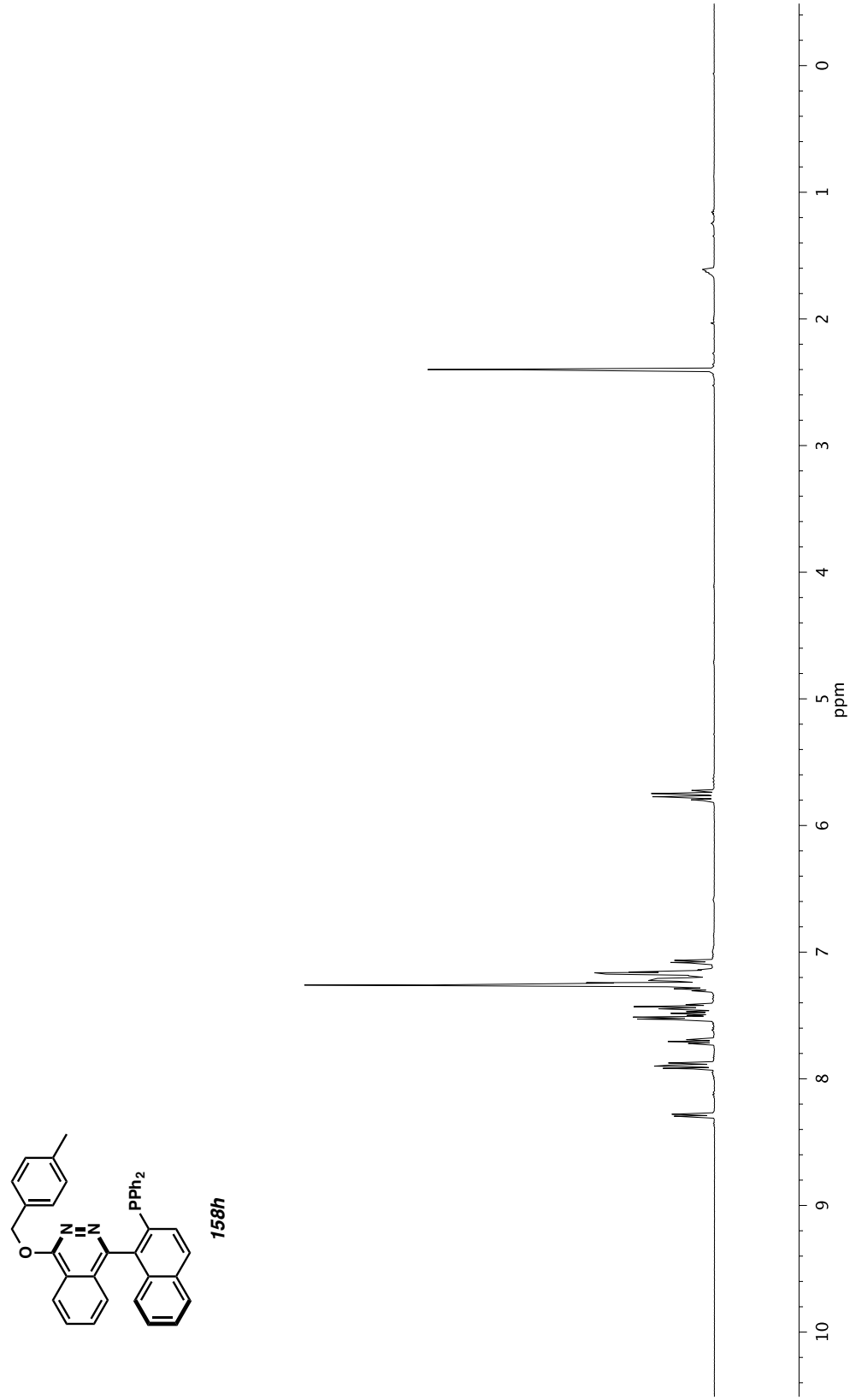


Figure A7.46. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **158h.**

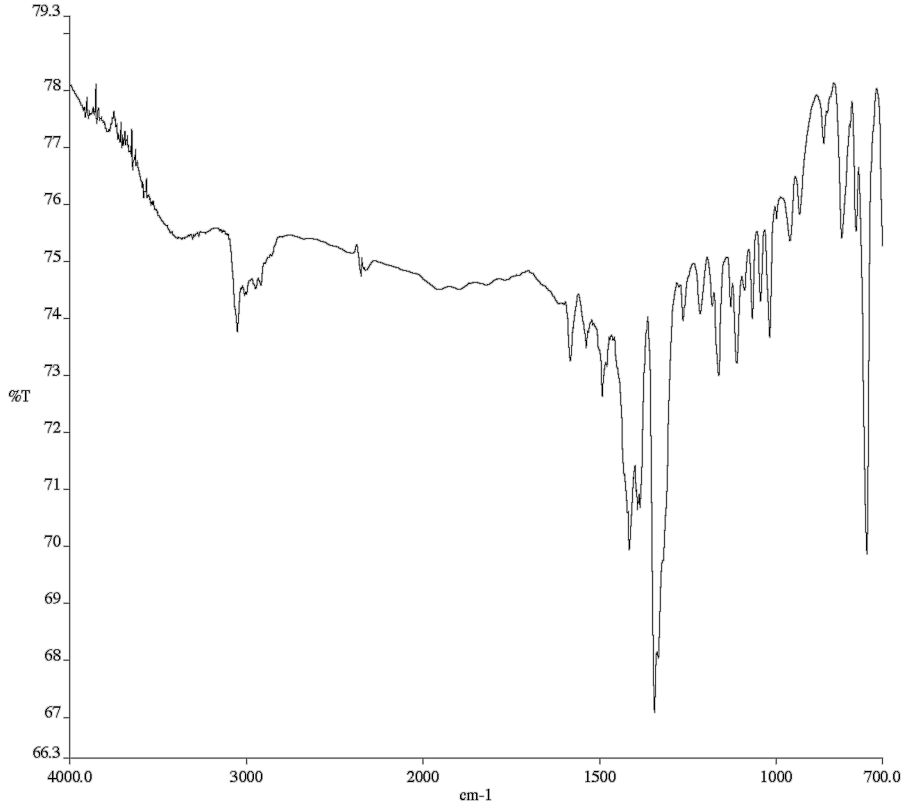


Figure A7.47. Infrared spectrum (Thin Film, NaCl) of compound **158h.**

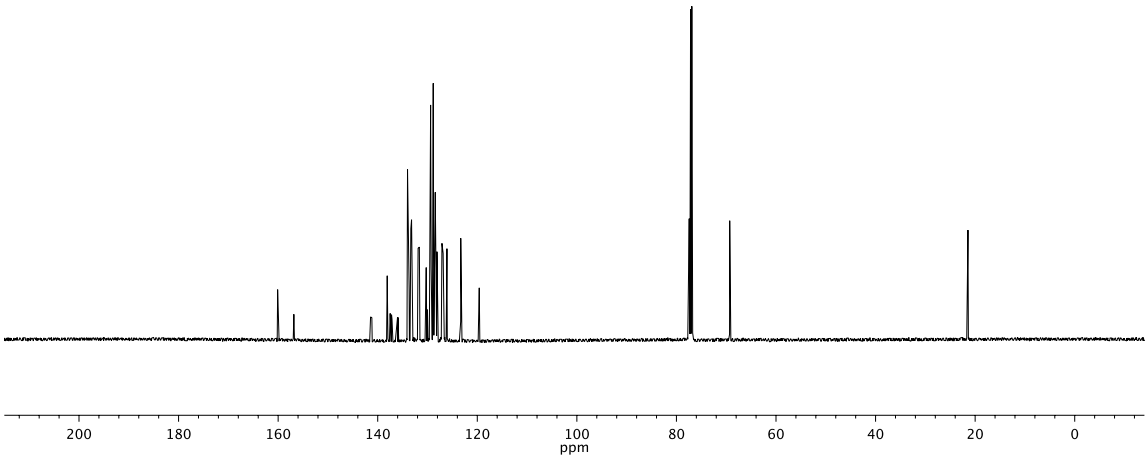


Figure A7.48. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **158h**.

CHAPTER 4

Ni-Catalyzed Intramolecular C–O Bond Formation: Synthesis of Cyclic Enol Ethers†

4.1. Introduction

Transition metal-catalyzed cross-coupling reactions have served a powerful tool for efficient carbon–carbon and carbon–heteroatom bond formations over the past several decades.[1] Recently, nickel catalysis has emerged in the synthetic community as an exceptionally useful strategy for cross-coupling.[2] Although tremendous advances in nickel-catalyzed carbon–carbon bond formation have been achieved (e.g., Negishi, Suzuki, Stille, Kumada, Hiyama couplings),[3] nickel-catalyzed carbon–oxygen bond forming processes have proven significantly more challenging. The rationale behind this is that reductive elimination of Ni(II) alkoxide complexes is often cited as being significantly challenging even at elevated temperatures.[4] To circumvent this challenge, stoichiometric oxidation of Ni(II) to the less stable Ni(III) analogs has been required. Additionally, reductive elimination of Ni(II) alkoxides is

† This work was performed in collaboration with Dr. Ryohei Doi. Additionally, this work has been published and adapted with permission from Han, S.-J.; Doi, R.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2016**, DOI: 10.1002/anie.201601991; Han, S.-J.; Doi, R.; Stoltz, B. M. *Angew. Chem.* **2016**, DOI: 10.1002/ange.201601991. Copyright 2016 Elsevier.

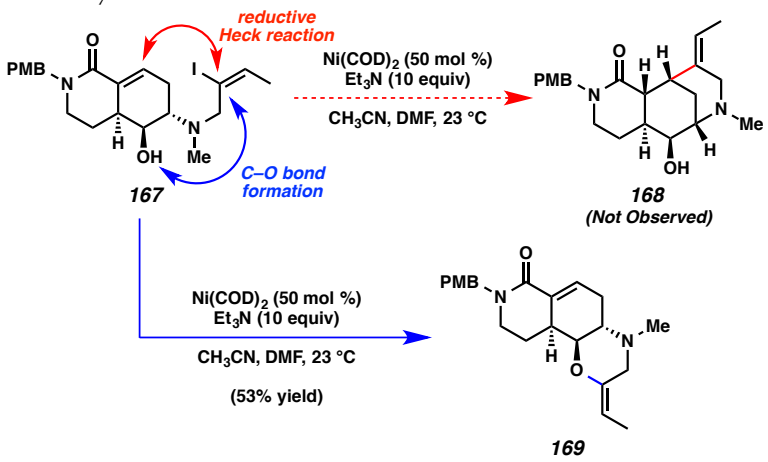
reported to be endothermic via computational analysis. This is in contrast to that of Pd(II) alkoxides, which are exothermic.[5] In 1997, Hartwig and co-workers developed the first nickel-catalyzed cross-coupling between electron-deficient aryl halides and pre-formed sodium alkoxides or sodium siloxides.[6] In 2014, the Ranu group reported a copper-assisted nickel-catalyzed coupling of phenol derivatives and vinyl halides.[7] However, both of these reactions require high temperatures, and the scope of the nucleophiles is limited to pre-formed alkoxides or phenols. Most recently, MacMillan and co-workers developed the nickel-catalyzed intermolecular cross-coupling of aryl bromides and aliphatic alcohols in the presence of light and a photoredox catalyst.[8] Importantly, MacMillan and co-workers could not observe their desired C–O coupling products in the absence of either the photocatalyst or light. Although Pd- or Cu-catalyzed C–O bond forming reactions have been significantly developed, most of these reactions require high temperature that can limit their utility in the synthesis of multifunctional complex molecules. Moreover, the vast majority of these examples are for aryl ether synthesis, not enol ether synthesis.[9,10,11] To our knowledge, a mild and efficient nickel-catalyzed intramolecular cross-coupling cyclization between aliphatic hydroxyl nucleophiles and tethered vinyl halides is unprecedented.

4.2. Results and Discussion

In the course of an alkaloid synthesis effort, we attempted a nickel-catalyzed reductive Heck reaction of vinyl iodide **167** with the aim of producing tricycle **168** (Scheme 4.2.1, red arrows).[12] Surprisingly, instead of the desired intramolecular C–C bond-forming reaction, a C–O bond-forming cyclization between the vinyl iodide and the free hydroxyl group furnished morpholine derivative **169** (Scheme 4.2.1, blue arrows). Given the lack of precedent in the literature for such a transformation with

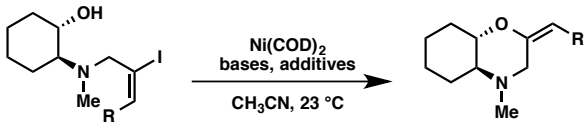
nickel catalysis, we set out to explore the generality of this reaction. Herein, we describe the first nickel-catalyzed cycloetherification of aliphatic alcohols with pendant vinyl halides.

Scheme 4.2.1. *Ni-Catalyzed C–O Bond Formation*



Given this interesting preliminary data, we chose aminocyclohexanols **170a** and **170b** as simplified substrates for reaction optimization studies (Table 4.2.1). Our initial reaction conditions afforded the corresponding morpholines **171a** and **171b** in 53% and 42% yield, respectively (entries 1 and 2). A wide variety of bases and additives were investigated to improve the yield and catalytic efficiency (entries 3–10). We found triethylamine to be superior to others examined (entries 3–5). The use of a 1:1 mixture of triethylamine and DABCO allowed etherification in 69% yield with reduced catalyst loading (i.e., 20 mol % $Ni(COD)_2$, entry 6). Gratifyingly, the use of 2 equiv of zinc powder as an additive resulted in a significant improvement in yield (84%) with only 5 mol % of $Ni(COD)_2$ (entry 10).[13,14,15,16,17]

Table 4.2.1. *Optimization of reaction parameters*[a]



R = Me (*170a*)
R = H (*170b*)

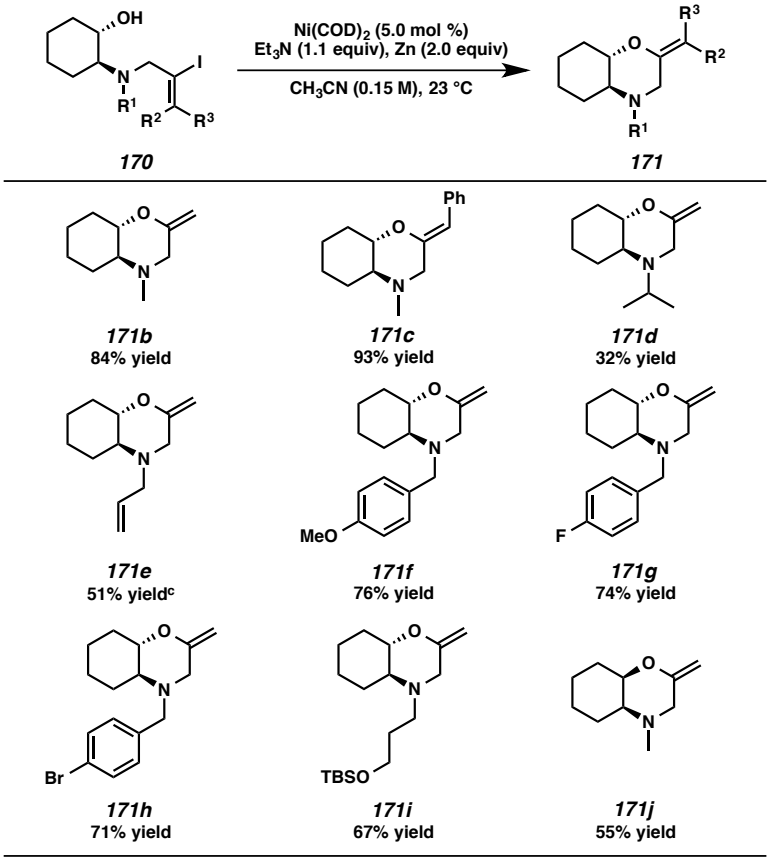
R = Me (*171a*)
R = H (*171b*)

entry	substrate	conc (M)	Ni mol %	base	additive	yield (%)[b]
1[c]	*170a*	0.02	50	Et_3N (10 equiv)	–	53
2[c]	*170b*	0.02	50	Et_3N (10 equiv)	–	42
3[c]	*170a*	0.02	35	Et_3N (10 equiv)	–	42[d]
4[c]	*170a*	0.02	35	Cs_2CO_3 (3.0 equiv)	–	30[d]
5[c]	*170a*	0.02	35	K_3PO_4 (3.0 equiv)	–	34[d]
6	*170b*	0.10	20	Et_3N (1.0 equiv)	DABCO (1.0 equiv)	69
7	*170b*	0.10	20	Et_3N (1.0 equiv)	CsF (1.0 equiv)	51
8	*170a*	0.04	20	DABCO (1.0 equiv)	–	24
9	*170a*	0.04	20	DABCO (2.0 equiv)	–	50[d]
10	*170b*	0.15	5	Et_3N (1.1 equiv)	Zn (2.0 equiv)	84

[a]Reactions were performed in a N_2-filled glove box. [b]Yield of isolated product. [c]DMF (0.04 M) was used as a co-solvent. [d]The reaction proceeded with incomplete conversion of starting material.

With optimized conditions in hand, we investigated the substrate scope of the transformation (Table 4.2.2). In addition to simple vinyl iodides (e.g., **170b**, R^1 = Me, R^2 = H, R^3 = H),[18] a (*Z*)-styrenyl iodide (i.e., **170c**, R^1 = Me, R^2 = H, R^3 = Ph)[19] furnished vinyl ether **171c** in high yield and without loss of olefin stereochemical fidelity. Aminocyclohexanols bearing isopropyl and allyl substituents on nitrogen afforded the corresponding products in reduced yields (**171d** and **171e**). Electronically variable benzyl groups were compatible under the reaction conditions, and even an aryl bromide was well tolerated (**171f–171h**). Additionally, a silyl ether group remained intact, generating substituted morpholine **171i** in good yield. Moreover, we discovered that a *cis*-aminocyclohexanol derived substrate was competent in the reaction, providing the *cis*-fused bicyclic product **171j**.[20,21]

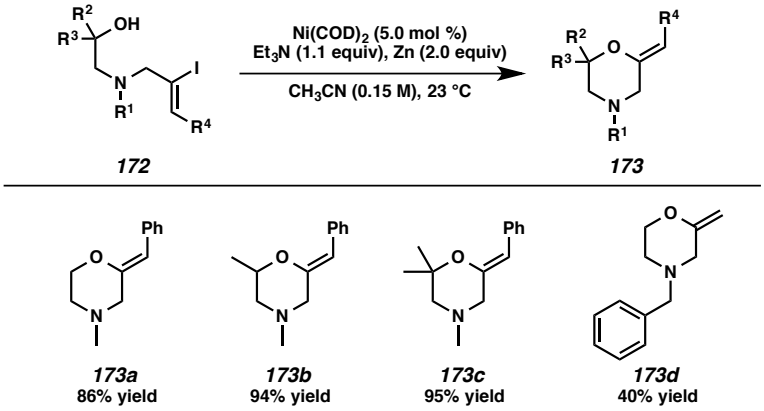
Table 4.2.2. *Intramolecular cross-coupling of amino-cyclohexanols*[a,b]



[a] Reactions were performed in a N_2-filled glove box. [b] Yield of isolated product. [c] 96 h.

To our delight, we found that the nickel-catalyzed intramolecular etherification reactions also proceeded with linear aminoalcohol substrates to generate monocyclic morpholine derivatives in moderate to high yields (Table 4.2.3). The steric environment of the alcohol fragment did not hinder the performance, as substrates containing primary, secondary, or highly congested tertiary hydroxyl nucleophiles furnished the corresponding cyclic vinyl ethers in excellent yields (**173a**–**173c**). Finally, a benzyl-substituted linear aminoalcohol substrate was transformed to the desired vinyl ether in modest yield (**173d**).

Table 4.2.3. *Intramolecular cross-coupling of linear aminoalcohols*[a,b]

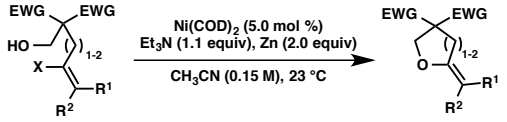


[a] Reactions were performed in a N_2-filled glove box. [b] Yield of isolated product.

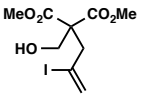
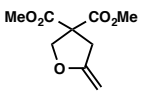
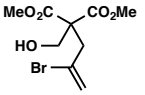
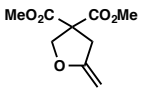
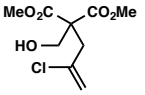
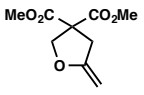
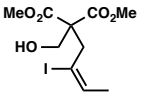
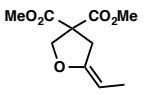
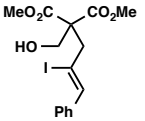
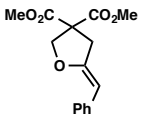
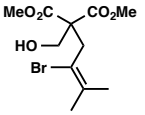
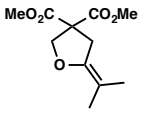
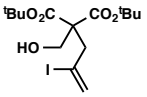
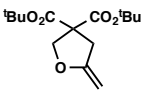
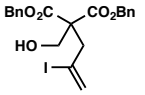
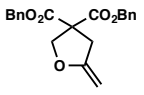
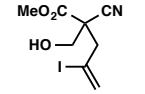
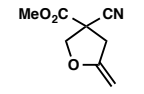
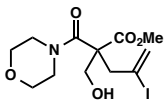
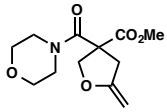
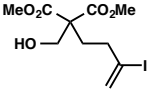
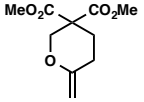
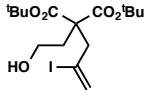
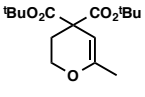
We were pleased to discover that additional acyclic substrates undergo the nickel-catalyzed carbon–oxygen cross-coupling to furnish alkylidene tetrahydrofurans and dihydropyrans (Table 4.2.4). Intramolecular etherification of vinyl iodide **174a** furnished the cyclic ether **175a** in good yield in only 1 h (entry 1). Although less reactive, a vinyl bromide also fared well in the reaction, affording the corresponding product in 52% yield after 12 h (entry 2). Unfortunately, attempts to employ a vinyl chloride as the coupling partner led predominantly to recovery of starting material (entry 3). Mono-methyl and mono-phenyl substituted vinyl iodides (**174d** and **174e**)[22] afforded the desired ethers (**175d** and **175e**) in good yields with retention of olefin stereochemistry (entries 4 and 5). Gratifyingly, tetrasubstituted vinyl bromide **174f**[23] furnished the corresponding tetrahydrofuran product **175f** in excellent yield (entry 6). Di-*tert*-butyl and dibenzyl malonates (**174g** and **174h**) were tolerated under the standard reaction conditions to afford the desired ethers (**175g** and **175h**) in good yields (entries 7 and 8). Additionally, carbon–oxygen bond formations were achieved with nitrile- and amide-containing substituents in 61% and 70% yield, respectively (entries 9 and 10). Formation of a six-membered cyclic vinyl ether (**175k**) from substrate **174k** was found to be challenging with only low levels of conversion (entry

11). Interestingly, cycloetherification of **174l** did indeed produce a pyran derivative in good yield, but only isomerized product **175l** was isolated (entry 12).[24,25,26]

Table 4.2.4. *Synthesis of substituted tetrahydrofuran and dihydropyran rings*[a]



174 *175*

entry	substrate	product	time (h)	yield (%)[b]
1	 *174a*	 *175a*	1	87
2	 *174b*	 *175a*	12	52
3	 *174c*	 *175a*	60	–[c]
4	 *174d*	 *175d*	2	87
5	 *174e*	 *175e*	12	91
6	 *174f*	 *175f*	48	98
7	 *174g*	 *175g*	1	87
8	 *174h*	 *175h*	1	66
9	 *174i*	 *175i*	12	61
10	 *174j*	 *175j*	1	70
11	 *174k*	 *175k*	72	–[c]
12	 *174l*	 *175l*	12	76

[a] Reactions were performed in a N_2-filled glove box. [b] Yield of isolated product. [c] Low conversion.

4.3. Conclusion

In conclusion, a highly efficient, mild, and operationally simple nickel-catalyzed intramolecular carbon–oxygen bond-forming reaction between vinyl halides and aliphatic alcohols has been developed. We discovered that zinc powder plays an important role in improving catalyst turnover and isolated yields. The reaction is tolerant of many functional groups, affording various cyclic vinyl ethers in good to excellent yields. This work further expands the capability of nickel catalysis in the context of small molecule chemical synthesis. Additional studies are ongoing to expand the scope of the reaction, to understand the mechanism, and to deploy the cyclization in the context of a complex molecular target.[27] These efforts will be reported in due course.

4.4. Experimental Methods and Analytical Data

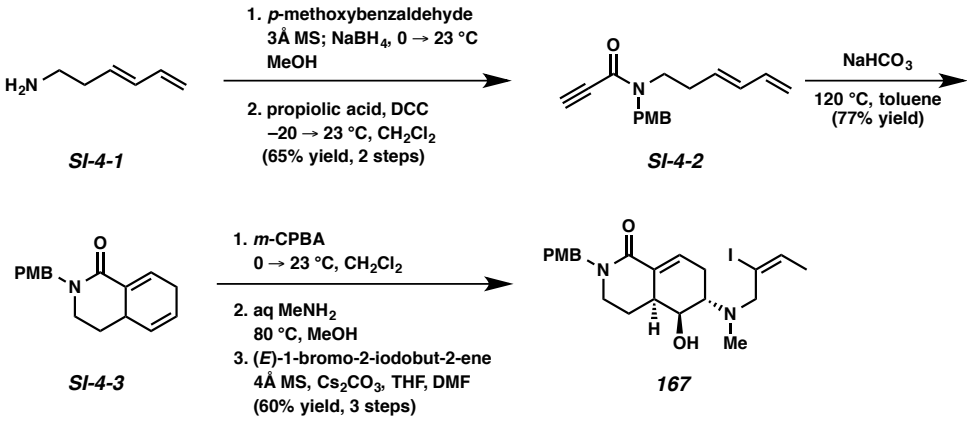
4.4.1. Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. THF, Et_2O, CH_2Cl_2, toluene, benzene, CH_3CN, and dioxane were dried by passage through an activated alumina column under argon. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. Brine solutions are saturated aqueous solutions of sodium chloride. Commercially available reagents were purchased from Sigma-Aldrich, Acros Organics, TCI, Oakwood chemicals, Strem, or Alfa Aesar and used as received unless otherwise stated. $Ni(COD)_2$ and NiI_2 were purchased from Strem. $NiBr_2$(dme) was purchased from Aldrich. Zinc dust

or powder purchased from Aldrich worked well for the reaction but zinc powder (99.999%) purchased from Strem gave poor conversion. Reaction temperatures were controlled by an IKAmag temperature modulator unless otherwise indicated. Glove box manipulations were performed under a N_2 atmosphere. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, $KMnO_4$ or PMA (phosphomolybdic acid) staining. Silicycle Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.064 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on a Varian Mercury 300 MHz, a Bruker AV III HD 400 MHz spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe, Varian Inova 500 MHz, and 600 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm), $CHDCl_2$ (δ 5.32) or C_6HD_6 (δ 7.16 ppm). ^{13}C NMR spectra are recorded on a Varian Mercury 300 MHz, a Bruker AV III HD 400 MHz spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe, Varian Inova 500 MHz, and 600 MHz spectrometers (75 MHz, 126 MHz, and 151 MHz, respectively) and are reported relative to $CHCl_3$ (δ 77.16 ppm), $CHDCl_2$ (δ 53.84) or C_6HD_5 (δ 128.06 ppm). ^{19}F NMR spectra are recorded on a Varian Mercury 300 MHz (at 282 MHz). ^{19}F NMR spectra are reported relative to $CFCl_3$(δ 0.0 ppm). Data for ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d= broad doublet, app = apparent. Data for ^{13}C are reported in terms of chemical shifts (δ ppm). IR spectra were obtained using a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron

ionization (EI+) mode, or Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+).

4.4.2. Experimental Procedures



To a solution of amine **SI-4-1** (6.66 g, 68.5 mmol, 1.00 equiv), which was prepared according to the literature procedure[1], in MeOH (171 mL) were added *p*-methoxybenzaldehyde (10.0 mL, 82.3 mmol, 1.20 equiv) and 3Å MS (18.8 g). The reaction mixture was stirred at 23 °C for 17 h. Then, $NaBH_4$ (5.20g, 0.137 mol, 2.00 equiv) was added to the solution at 0 °C. The solution was stirred at 23 °C for 12 h. After the reaction was done, water (40 mL) was added at 0 °C. The aqueous phase was extracted with EtOAc (3 x 80.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the PMB-amine, which was used without further purification.

A solution of propiolic acid (4.64 mL, 75.4 mmol, 1.10 equiv) in CH_2Cl_2 (343 mL) was cooled to 0 °C. DCC (15.6g, 75.4 mmol, 1.10 equiv) and the PMB-amine (68.5

[1] (a) Miller, C. A.; Batey, R. A. *Org. Lett*. **2004**, *6*, 699–702. (b) Grieco, P. A.; Galatsis, P.; Spohn, R. F. *Tetrahedron* **1986**, *42*, 2847–2853. (c) Nieto-García, O.; Alonso, R. *J. Org. Chem*. **2013**, *78*, 2564–2570.

mmol, 1.00 equiv) were added to the reaction mixture sequentially. The mixture was warmed to 23 °C and stirred for 30 min. The solvent was evaporated and the residue was purified by flash column chromatography (1:4 EtOAc:hexanes) on silica gel to give amide **SI-4-2** (12.0g, 65% yield, 2 steps).

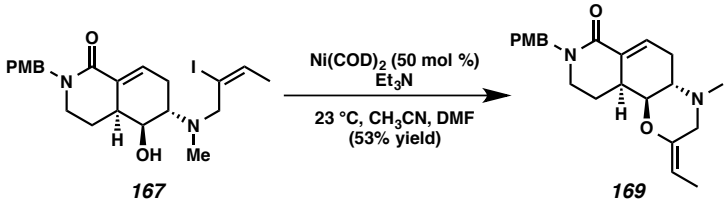
To a stirred solution of amide **SI-4-2** (12.0 g, 44.6 mmol, 1.00 equiv) in toluene (558 mL) was added solid $NaHCO_3$ (4.50g, 53.5 mmol, 1.20 equiv). The reaction mixture was heated to 120 °C for 48 h. After the reaction was done, water (200 mL) was added. The aqueous phase was extracted with EtOAc (3 x 120 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:4 EtOAc:hexanes) on silica gel to give lactam **SI-4-3** (9.25g, 77% yield).

To a stirred solution of lactam **SI-4-3** (339 mg, 1.26 mmol, 1.00 equiv) in CH_2Cl_2 (6.30 mL) at 0 °C was added *m*-CPBA (≤77%, 1.89 mmol, 424 mg, 1.50 equiv), and the mixture was stirred for 3 h at 23 °C. The reaction mixture was quenched with sat. $NaHSO_3$ and sat. $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (3 x 6.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to furnish the epoxide, which was used without further purification.

To a solution of epoxide (1.26 mmol, 1.00 equiv) in MeOH (6.30 mL) was added aq $MeNH_2$ (40 wt.% in H_2O, 12.6 mmol, 10.9 mL, 10.0 equiv). The reaction mixture was stirred at 80 °C for 12 h. After the reaction was done, water (6.00 mL) was added. The aqueous phase was extracted with EtOAc (3 x 8.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford the aminoalcohol, which was used without further purification.

To a solution of the aminoalcohol (1.26 mmol, 1.00 equiv) in THF (3.15 mL) and DMF (3.15 mL) were added 4Å MS (443 mg), (*E*)-1-bromo-2-iodobut-2-ene (411 mg, 1.58 mmol, 1.25 equiv) and Cs_2CO_3 (415 mg, 1.27 mmol, 1.01 equiv) at 23 °C. The reaction mixture was stirred at 23 °C for 24 h. The resulting suspension was filtered and washed with EtOAc (5.00 mL). The combined organic phases were extracted with EtOAc (3 x 6.00 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (2:1 EtOAc:hexane) on silica gel to give vinyl iodide **167** (375 mg, 60% yield, 3 steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.75 (dt, *J* = 6.7, 2.1 Hz, 1H), 6.47 – 6.41 (m, 1H), 4.71 (d, *J* = 14.4 Hz, 1H), 4.41 (d, *J* = 14.4 Hz, 1H), 3.96 – 3.89 (m, 2H), 3.80 (s, 3H), 3.35 – 3.27 (m, 2H), 3.20 (d, *J* = 13.6 Hz, 1H), 3.11 (d, *J* = 13.6 Hz, 1H), 2.99 – 2.91 (m, 1H), 2.61 (td, *J* = 10.7, 4.4 Hz, 1H), 2.39 – 2.26 (m, 2H), 2.22 (s, 3H), 2.20 – 2.14 (m, 1H), 1.74 (d, *J* = 7.1 Hz, 3H), 1.56 – 1.45 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3, 159.1, 139.0, 133.7, 130.3, 129.6, 129.5, 114.1, 103.3, 66.8, 60.1, 57.3, 55.4, 49.7, 46.9, 39.3, 35.6, 23.8, 22.3, 17.1; IR (Neat Film NaCl) 3416, 2927, 1663, 1613, 1512, 1454, 1246, 1175, 1034, 817, 732 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{22}H_{30}IN_2O_3$ $[M+H]^+$: 497.1296; found: 497.1296.



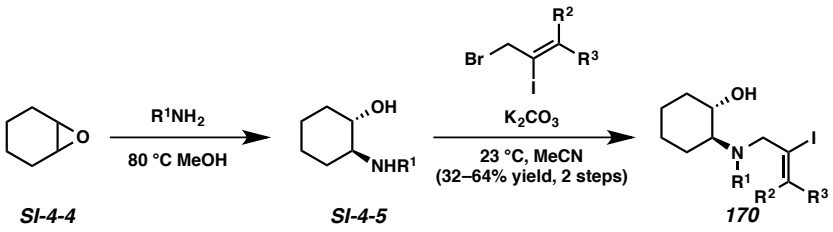
167 *169*

To a solution of vinyl iodide **167** (20.0 mg, 0.0402 mmol, 1.00 equiv) and Et_3N (56.0 μL, 0.402 mmol, 10.0 equiv) in CH_3CN (2.01 mL) and DMF (1.01 mL) in a

scintillation vial at 23 °C was added $Ni(COD)_2$ (6.00 mg, 0.0201 mmol, 0.50 equiv) in a nitrogen-filled glove box. The reaction mixture was stirred at 23 °C for 120 min, and then BHT (18.0 mg, 0.0804 mmol, 2.00 equiv) was added. After being stirred for 20 min, the vial was removed from the glovebox and uncapped. Saturated $NaHCO_3$ aqueous solution was added and the mixture was extracted with Et_2O (3 x 2.00 mL), the combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (1:20 MeOH:CH_2Cl_2) to give morpholine derivative **169** (7.85 mg, 53% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.66 (dt, *J* = 6.8, 1.9 Hz, 1H), 5.03 (qd, *J* = 7.1, 1.4 Hz, 1H), 4.63 (d, *J* = 14.4 Hz, 1H), 4.48 (d, *J* = 14.4 Hz, 1H), 3.78 (s, 3H), 3.76 (d, *J* = 7.1 Hz, 1H), 3.54 (d, *J* = 12.5 Hz, 1H), 3.29 – 3.24 (m, 2H), 2.86 – 2.74 (m, 1H), 2.68 – 2.60 (m, 2H), 2.32 (s, 3H), 2.30 – 2.24 (m, 1H), 2.12 – 1.96 (m, 2H), 1.58 (dd, *J* = 7.1, 1.3 Hz, 3H), 1.55 – 1.49 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 158.9, 148.5, 133.5, 129.5, 129.0, 113.9, 103.5, 77.8, 58.4, 52.2, 49.5, 46.6, 42.4, 37.9, 28.9, 24.3, 11.0; IR (Neat Film NaCl) 3416, 2927, 1663, 1613, 1512, 1454, 1246, 1175, 1034, 817, 732 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{22}H_{29}N_2O_3$ $[M+H]^+$: 369.2173; found: 369.2212.

Typical procedure for aminocyclohexanols 170



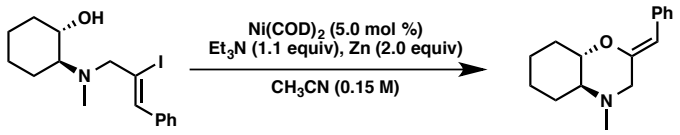
SI-4-4 *SI-4-5* *170*

To a scintillation vial were added cyclohexene oxide **SI-4-4** (5.09 mmol, 1.00 equiv), R^1NH_2 (5.09 mmol, 1.00 equiv), and MeOH (2.50 mL). The reaction mixture was

heated to 80 °C for 12 h. The solvent was evaporated to give the corresponding aminocyclohexanols **SI-4-5**, which were used without further purification.

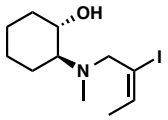
To a solution of aminocyclohexanols **SI-4-5** (5.09 mmol, 1.00 equiv) in MeCN (25.0 mL) were added K_2CO_3 (25.5 mmol, 5.00 equiv) and allyl bromides (5.60 mmol, 1.10 equiv). The reaction mixture was stirred for 12 h at 23 °C. Solids were removed via a filtration through a celite plug and the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography, using mixture of hexanes and ethyl acetate as eluent to furnish the product **170**.

Representative procedure for cross-coupling of aminocyclohexanols 170



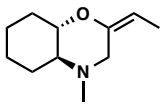
170c ***171c***

Ni-Catalyzed C–O bond formation experiments were performed in a nitrogen-filled glove box. To a solution of aminocyclohexanol **170c** (50.0 mg, 0.135 mmol, 1.00 equiv) in MeCN (0.900 mL) in a scintillation vial were added Et_3N (21.0 μL, 0.149 mmol, 1.10 equiv), Zn powder (17.7 mg, 0.270 mmol, 2.00 equiv), and $Ni(COD)_2$ (1.90 mg, 0.00673 mmol, 0.05 equiv). The reaction mixture was stirred at 23 °C for 24 h. After the reaction was done, the vial was removed from the glove box and uncapped. Solids were removed via a filtration through a celite plug and the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give **171c** (30.7 mg, 93% yield).



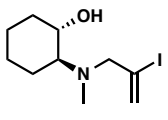
170a

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.41 (q, *J* = 7.1 Hz, 1H), 4.03 (s, 1H), 3.40 (td, *J* = 9.8, 4.5 Hz, 1H), 3.15 (d, *J* = 13.7 Hz, 1H), 3.08 (d, *J* = 13.9 Hz, 1H), 2.26 (ddd, *J* = 14.0, 10.2, 3.6 Hz, 1H), 2.18 (s, 3H), 2.15 – 2.11 (m, 1H), 1.79 (dt, *J* = 8.9, 2.0 Hz, 2H), 1.73 (d, *J* = 7.2 Hz, 3H), 1.31 – 1.17 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.3, 104.4, 69.3, 68.7, 57.3, 35.7, 33.3, 25.6, 24.2, 22.8, 17.0; IR (Neat Film NaCl) 3467, 2930, 2855, 1449, 1282, 1080, 1037 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{11}H_{21}NOI$ $[M+H]^+$: 310.0668; found: 310.0654.



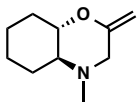
171a

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (qd, *J* = 7.1, 1.6 Hz, 1H), 3.58 (d, *J* = 12.6 Hz, 1H), 3.35 – 3.23 (m, 1H), 2.62 (d, *J* = 12.6 Hz, 1H), 2.29 (s, 3H), 2.09 (dtd, *J* = 12.9, 3.7, 2.0 Hz, 1H), 1.94 (ddt, *J* = 11.9, 4.5, 2.6 Hz, 1H), 1.85 (s, br, 1H), 1.77 – 1.71 (m, 2H), 1.56 (dd, *J* = 7.1, 1.5 Hz, 3H), 1.42 – 1.33 (m, 1H), 1.33 – 1.22 (m, 2H), 1.14 – 1.02 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 103.3, 81.1, 67.4, 53.0, 42.0, 31.4, 28.1, 24.8, 24.4, 11.1; IR (Neat Film NaCl) 2934, 2861, 2779, 1682, 1451, 1192, 1108, 841 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{11}H_{20}NO$ $[M+H]^+$: 182.1545; found: 182.1538.



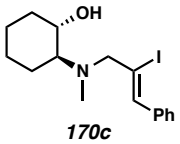
170b

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (q, *J* = 1.4 Hz, 1H), 5.86 (dt, *J* = 0.8, 1.6 Hz, 1H), 3.97 (s, 1H), 3.40 (m, 1H), 3.17 (d, *J* = 13.7 Hz, 1H), 2.96 (d, *J* = 13.7 Hz, 1H), 2.28 (m, 1H), 2.18 (s, 3H), 2.13 (m, 1H), 1.75 (m, 3H), 1.20 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 126.8, 113.7, 69.3, 69.1, 64.8, 35.8, 33.1, 25.4, 24.0, 22.6; IR (neat film NaCl) 3470, 2930, 2855, 2796, 1616, 1448, 1079, 1036 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{10}H_{19}INO$, $[M+H]^+$: 296.0506; found: 296.0499.



171b

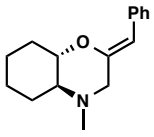
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40 (s, 1H), 4.16 (s, 1H), 3.36 (ddd, *J* = 2.5, 5.4, 6.7 Hz, 1H), 3.25 (d, *J* = 7.5 Hz, 1H), 2.81 (7.5 Hz, 1H), 2.24 (s, 3H), 2.09 (m, 1H), 1.98 (m, 1H), 1.84 – 1.73 (m, 3H), 1.43 – 1.07 (m, m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 91.9, 81.1, 66.8, 57.9, 41.7, 31.3, 28.1, 24.3, 24.3; IR (neat film NaCl) 2929, 2858, 2770, 1747, 1653, 1277, 1229, 1074 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{10}H_{18}NO$, $[M+H]^+$: 168.1383; found: 168.1385.



170c

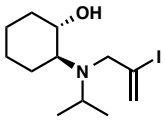
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.50 (m, 2H), 7.40 – 7.29 (m, 3H), 6.97 (s, 1H), 4.04 (s, 1H), 3.52 – 3.41 (m, 2H), 3.27 (dd, *J* = 13.5, 1.1 Hz, 1H), 2.42 – 2.29 (m, 1H), 2.24 (s, 3H), 2.19 – 2.11 (m, 1H), 1.79 (dd, *J* = 6.9, 3.9 Hz, 2H), 1.75 – 1.64 (m, 1H), 1.35 – 1.15 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4, 135.7, 128.8, 128.3, 128.2, 109.0, 69.5, 69.3, 66.8, 35.8, 33.3, 25.6, 24.2, 22.9; IR (neat film NaCl) 3467,

2930, 2855, 1446, 1079, 1058, 1033, 750, 695 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{16}H_{23}INO$, $[M+H]^+$: 372.0819; found: 372.0859.



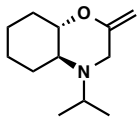
171c

^1H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.53 (m, 2H), 7.32 – 7.25 (m, 2H), 7.17 – 7.11 (m, 1H), 5.44 (d, *J* = 1.7 Hz, 1H), 3.53 (ddd, *J* = 11.5, 9.1, 4.3 Hz, 1H), 3.32 (d, *J* = 12.8 Hz, 1H), 3.00 (dd, *J* = 12.8, 1.6 Hz, 1H), 2.29 (s, 3H), 2.13 (ddtd, *J* = 12.5, 6.2, 4.3, 3.8, 2.1 Hz, 2H), 1.93 (td, *J* = 10.2, 9.1, 3.9 Hz, 1H), 1.79 (ddt, *J* = 13.0, 10.3, 2.9 Hz, 2H), 1.60 – 1.49 (m, 1H), 1.41 – 1.24 (m, 2H), 1.20 – 1.07 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4, 136.0, 128.5, 128.2, 126.0, 107.5, 80.8, 67.0, 59.2, 41.7, 31.4, 28.3, 24.7, 24.4; IR (neat film NaCl) 2935, 2860, 2774, 1664, 1449, 1342, 1179, 1060, 1032, 694 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{16}H_{22}NO$, $[M+H]^+$: 244.1696; found: 244.1716.



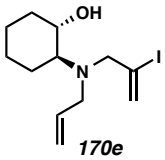
170d

^1H NMR (400 MHz, $CDCl_3$) δ 6.29 (s, 1H), 5.87 (s, 1H), 3.90 (s, 1H), 3.36 – 3.21 (m, 2H), 3.02 (td, *J* = 13.7, 6.6 Hz, 2H), 2.39 (d, *J* = 10.5 Hz, 1H), 2.19 – 2.09 (m, 1H), 1.73 (q, *J* = 10.1 Hz, 3H), 1.35 – 1.17 (m, 4H), 1.14 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 127.2, 116.0, 69.3, 61.7, 57.4, 48.1, 33.2, 28.0, 26.1, 24.4, 22.9, 18.0; IR (neat film NaCl) 2930, 1614, 1173, 1080, 896 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{12}H_{23}NOI$, $[M+H]^+$: 324.0819; found: 324.0845.



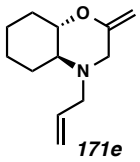
171d

^{1}H NMR (400 MHz, C_6D_6) δ 4.64 (d, *J* = 1.1 Hz, 1H), 4.12 (d, *J* = 1.5 Hz, 1H), 3.48 (ddd, *J* = 11.1, 8.9, 4.3 Hz, 1H), 3.23 (d, *J* = 12.7 Hz, 1H), 3.07 (p, *J* = 6.6 Hz, 1H), 2.89 (dt, *J* = 12.7, 1.4 Hz, 1H), 2.14 (ddd, *J* = 10.8, 8.9, 3.9 Hz, 1H), 2.02 – 1.93 (m, 1H), 1.75 (dq, *J* = 13.6, 2.9, 2.4 Hz, 1H), 1.48 – 1.33 (m, 4H), 0.99 (s, 3H), 0.96 – 0.79 (m, 2H), 0.65 (s, 3H). ^{13}C NMR (101 MHz, C_6D_6) δ 158.4, 89.6, 81.0, 62.1, 46.7, 45.8, 31.8, 28.1, 25.0, 24.4, 21.4, 12.4; IR (neat film NaCl) 2933, 1657, 1450, 1280, 1175, 1075, 800 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{12}H_{22}NO$, $[M+H]^+$: 196.1696; found: 196.1697.



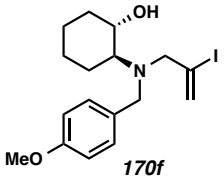
170e

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.29 (d, *J* = 1.8 Hz, 1H), 5.92 – 5.81 (m, 2H), 5.23 – 5.10 (m, 2H), 3.83 (s, 1H), 3.41 (td, *J* = 9.9, 4.5 Hz, 1H), 3.34 (d, *J* = 14.2 Hz, 1H), 3.31 – 3.23 (m, 1H), 2.94 (dd, *J* = 14.1, 8.4 Hz, 1H), 2.88 (d, *J* = 14.2 Hz, 1H), 2.41 (ddd, *J* = 12.7, 9.9, 3.4 Hz, 1H), 2.13 (ddq, *J* = 12.2, 4.6, 2.0 Hz, 1H), 1.85 – 1.74 (m, 2H), 1.71 – 1.68 (m, 1H), 1.32 – 1.16 (m, 3H), 1.15 – 1.03 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.4, 127.6, 117.9, 113.9, 69.1, 64.9, 60.4, 52.4, 33.2, 25.7, 24.2, 23.5; IR (neat film NaCl) 2930, 2856, 1615, 1450, 1157, 1078, 917 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{12}H_{21}NIO$, $[M+H]^+$: 322.0662; found: 322.0668.



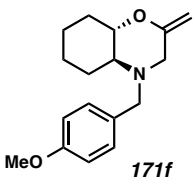
171e

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dddd, *J* = 17.1, 10.2, 8.0, 5.4 Hz, 1H), 5.24 – 5.16 (m, 2H), 4.38 (dt, *J* = 1.3, 0.7 Hz, 1H), 4.13 (dd, *J* = 1.6, 0.7 Hz, 1H), 3.48 (ddt, *J* = 13.6, 5.4, 1.6 Hz, 1H), 3.45 – 3.40 (m, 1H), 3.35 (d, *J* = 12.9 Hz, 1H), 2.88 – 2.79 (m, 2H), 2.17 – 2.04 (m, 2H), 1.99 (dddd, *J* = 10.2, 4.8, 3.9, 2.4 Hz, 1H), 1.79 – 1.69 (m, 2H), 1.46 – 1.37 (m, 1H), 1.35 – 1.21 (m, 2H), 1.12 (q, *J* = 12.3, 11.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.4, 134.3, 118.8, 91.6, 80.8, 64.6, 56.0, 53.7, 31.5, 28.2, 24.8, 24.3; IR (neat film NaCl) 2935, 2862, 1657, 1280, 1075, 839 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{12}H_{20}NO$, $[M+H]^+$: 194.1539; found: 194.1542.



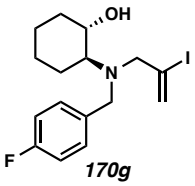
170f

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.32 (d, *J* = 1.7 Hz, 1H), 5.90 (t, *J* = 1.4 Hz, 1H), 3.80 (s, 3H), 3.81 – 3.74 (m, 2H), 3.44 (td, *J* = 9.8, 4.6 Hz, 1H), 3.36 (d, *J* = 13.9 Hz, 1H), 3.28 (d, *J* = 13.2 Hz, 1H), 2.92 (d, *J* = 14.0 Hz, 1H), 2.42 – 2.29 (m, 1H), 2.13 – 2.04 (m, 1H), 1.90 – 1.81 (m, 1H), 1.75 (ddd, *J* = 6.7, 4.4, 2.3 Hz, 1H), 1.70 – 1.63 (m, 1H), 1.25 – 1.04 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 130.6, 130.5, 128.1, 113.9, 113.5, 68.9, 63.6, 60.5, 55.4, 52.8, 33.3, 25.6, 24.2, 22.6; IR (neat film NaCl) 3483, 2931, 2855, 1612, 1511, 1247, 1036, 813 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{17}H_{25}INO_2$, $[M+H]^+$: 402.0924; found: 402.0934.



171f

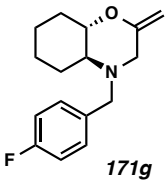
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.33 (s, 1H), 4.09 – 3.96 (m, 2H), 3.81 (s, 3H), 3.51 (s, br, 1H), 3.19 (d, *J* = 13.0 Hz, 1H), 3.09 (d, *J* = 12.9 Hz, 1H), 2.71 (d, *J* = 13.0 Hz, 1H), 2.21 (d, *J* = 12.9 Hz, 1H), 2.13 (s, br, 1H), 2.06 – 1.96 (m, 1H), 1.84 – 1.72 (m, 2H), 1.50 – 1.36 (m, 1H), 1.32 (qd, *J* = 11.1, 9.7, 5.6 Hz, 2H), 1.22 (d, *J* = 22.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 156.5, 130.4, 130.2, 113.8, 91.1, 80.4, 65.2, 56.5, 55.4, 53.4, 31.6, 28.7, 24.8, 24.4; IR (neat film NaCl) 2935, 2861, 1733, 1674, 1611, 1511, 1246, 1036, 843 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{17}H_{24}NO_2$, $[M+H]^+$: 274.1802; found: 274.1820.



170g

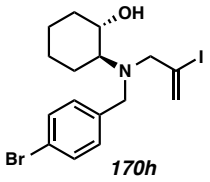
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 8.4, 5.6 Hz, 2H), 7.01 (t, *J* = 8.7 Hz, 2H), 6.33 (s, 1H), 5.91 (t, *J* = 1.4 Hz, 1H), 3.80 (d, *J* = 13.3 Hz, 1H), 3.73 (s, br, 1H), 3.45 (td, *J* = 9.7, 4.6 Hz, 1H), 3.35 (t, *J* = 12.6 Hz, 2H), 2.95 (d, *J* = 13.9 Hz, 1H), 2.33 (d, *J* = 10.4 Hz, 1H), 2.14 – 2.04 (m, 1H), 1.92 – 1.83 (m, 1H), 1.81 – 1.72 (m, 1H), 1.67 (dt, *J* = 7.8, 2.8 Hz, 1H), 1.25 – 1.06 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3 (d, *J* = 245.2 Hz), 134.2, 131.1 (d, *J* = 8.0 Hz), 128.4, 115.5 (d, *J* = 21.3 Hz), 113.1, 68.9, 63.8, 60.6, 52.7, 33.3, 25.5, 24.2, 22.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ -115.5; IR (neat film NaCl) 3485, 2930, 2856, 1602, 1508, 1221, 1152, 1073, 818 cm^{-1};

HRMS (MM: ESI-APCI+) m/z calc'd for $C_{16}H_{22}FNOI$, $[M+H]^+$: 390.0725; found: 390.0732.



171g

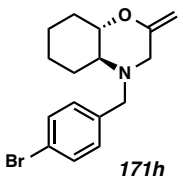
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 2H), 7.08 – 6.93 (m, 2H), 4.34 (s, 1H), 4.04 (d, *J* = 13.1 Hz, 1H), 3.99 (d, *J* = 1.5 Hz, 1H), 3.50 (tt, *J* = 11.8, 10.9, 4.1 Hz, 2H), 3.16 (d, *J* = 13.0 Hz, 1H), 3.08 (d, *J* = 13.2 Hz, 1H), 2.72 (d, *J* = 12.9 Hz, 1H), 2.24 – 2.05 (m, 2H), 2.07 – 1.94 (m, 1H), 1.87 – 1.66 (m, 2H), 1.53 – 1.35 (m, 1H), 1.38 – 1.24 (m, 1H), 1.24 – 1.13 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1 (d, *J* = 244.7 Hz), 156.3, 134.3, 130.1 (d, *J* = 6.1 Hz), 115.3 (d, *J* = 20.9 Hz), 91.2, 80.5, 65.3, 56.4, 53.6, 31.6, 28.8, 24.8, 24.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ -116.0; IR (neat film NaCl) 2936, 2862, 1736, 1673, 1604, 1508, 1222, 1075, 821 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{16}H_{21}FNO$, $[M+H]^+$: 262.1602; found: 262.1629.



170h

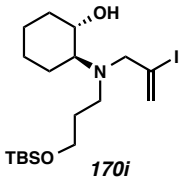
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.7 Hz, 2H), 7.27 (d, *J* = 7.7 Hz, 2H), 6.33 (s, br, 1H), 5.91 (t, *J* = 1.6 Hz, 1H), 3.78 (d, *J* = 13.3 Hz, 1H), 3.71 (s, br, 1H), 3.53 – 3.41 (m, 1H), 3.42 – 3.26 (m, 2H), 2.95 (d, *J* = 14.0 Hz, 1H), 2.33 (s, br, 1H), 2.08 (dd, *J* = 9.6, 4.3 Hz, 1H), 1.94 – 1.54 (m, 3H), 1.27 – 1.03 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 131.7, 131.2, 128.6, 121.4, 112.9, 69.0, 63.9, 60.6, 52.9, 33.3, 25.5, 24.2, 22.6; IR (neat film NaCl) 3486, 2930, 2855, 1615, 1486, 1450, 1403, 1152,

1071, 1011, 799 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{16}H_{22}BrNOI$, $[M+H]^+$: 449.9924; found: 449.9937.



171h

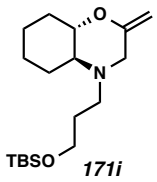
^1H NMR (500 MHz, CD_2Cl_2) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 4.24 (d, *J* = 1.1 Hz, 1H), 4.02 (d, *J* = 13.4 Hz, 1H), 3.93 (d, *J* = 1.5 Hz, 1H), 3.44 (ddd, *J* = 11.2, 8.7, 4.2 Hz, 1H), 3.13 (d, *J* = 12.9 Hz, 1H), 3.02 (d, *J* = 13.5 Hz, 1H), 2.69 (dt, *J* = 12.9, 1.5 Hz, 1H), 2.18 – 2.07 (m, 2H), 2.02 – 1.91 (m, 1H), 1.75 (tdd, *J* = 10.4, 5.5, 2.5 Hz, 2H), 1.47 – 1.34 (m, 1H), 1.36 – 1.22 (m, 2H), 1.19 – 1.06 (m, 1H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 157.1, 138.9, 131.8, 131.2, 121.0, 90.7, 81.0, 65.8, 56.9, 54.2, 31.9, 29.1, 25.2, 24.7; IR (neat film NaCl) 2935, 2861, 1654, 1486, 1280, 1074, 1012, 843, 802 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{16}H_{21}BrNO$, $[M+H]^+$: 322.0801; found: 322.0817.



170i

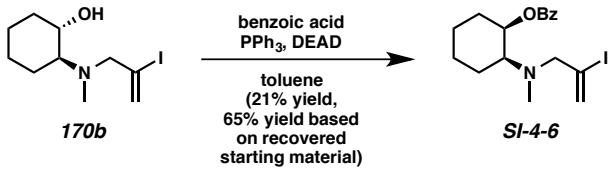
^1H NMR (500 MHz, $CDCl_3$) δ 6.28 (s, 1H), 5.84 (s, 1H), 3.83 (s, 1H), 3.66 (td, *J* = 6.2, 2.2 Hz, 2H), 3.38 (td, *J* = 9.9, 4.4 Hz, 1H), 3.29 (d, *J* = 14.1 Hz, 1H), 2.91 (d, *J* = 14.2 Hz, 1H), 2.65 (dt, *J* = 13.0, 8.0 Hz, 1H), 2.43 (ddd, *J* = 13.1, 7.4, 5.8 Hz, 1H), 2.34 (ddd, *J* = 12.6, 9.8, 3.3 Hz, 1H), 2.17 – 2.08 (m, 1H), 1.82 – 1.72 (m, 2H), 1.71 (dt, *J* = 8.4, 6.0 Hz, 3H), 1.32 – 1.14 (m, 3H), 1.10 (tt, *J* = 12.2, 5.9 Hz, 1H), 0.89 (d,

J = 0.9 Hz, 9H), 0.05 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 127.3, 114.2, 69.1, 65.6, 61.6, 61.4, 46.1, 33.3, 31.9, 26.1, 25.7, 24.3, 23.1, 18.4, -5.11, -5.13; IR (neat film NaCl) 3489, 2929, 2856, 1255, 1097, 835, 775 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{18}H_{37}INO_2Si$, $[M+H]^+$: 454.1633; found: 454.1658.



171i

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (s, 1H), 4.13 (s, 1H), 3.63 (td, *J* = 6.2, 2.2 Hz, 2H), 3.47 – 3.31 (m, 2H), 2.94 – 2.79 (m, 2H), 2.34 (s, br, 1H), 2.15 – 2.04 (m, 2H), 1.98 (ddq, *J* = 11.8, 4.4, 2.4, 1.9 Hz, 1H), 1.79 – 1.59 (m, 5H), 1.46 – 1.21 (m, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5, 91.4, 80.9, 64.6, 61.4, 53.8, 49.3, 31.5, 28.9, 28.3, 26.1, 24.8, 24.3, 18.4, -5.15, -5.17; IR (neat film NaCl) 2931, 2857, 1739, 1674, 1463, 1256, 1094, 838, 776 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{18}H_{36}NO_2Si$, $[M+H]^+$: 326.2510; found: 326.2544.

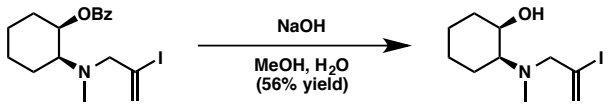


170b ***SI-4-6***

A solution of cyclohexanol **170b** (500 mg, 1.69 mmol, 1.00 equiv) in toluene (1.20 mL) was added to a cooled solution of PPh_3 (532 mg, 2.03 mmol, 1.20 equiv) and benzoic acid (248 mg, 2.03 mmol, 1.20 equiv) in toluene (8.45 mL) at –40 °C. Then, DEAD in toluene (40 wt% in toluene, 0.92 mL, 1.20 equiv) was added dropwise to a solution over 20 min at –40 °C. After stirring for 1.5 h at –40 °C, the solution was warmed to 23 °C. After being stirred for 18 h, saturated $NaHCO_3$ aqueous solution

was added and the mixture was extracted with EtOAc (3 x 7.00 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (1:20 EtOAc:hexanes) to give benzoate **SI-4-6** (142 mg, 21% yield, 65% yield based on recovered starting material).

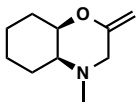
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.1 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 6.25 (s, 1H), 5.73 (s, 1H), 5.10 (td, *J* = 10.4, 4.6 Hz, 1H), 3.29 (d, *J* = 15.1 Hz, 1H), 3.22 (d, *J* = 15.1 Hz, 1H), 2.79 – 2.69 (m, 1H), 2.25 (s, 3H), 2.19 – 2.11 (m, 1H), 1.92 (d, *J* = 13.1 Hz, 1H), 1.83 – 1.72 (m, 2H), 1.40 (dddd, *J* = 17.5, 10.7, 8.0, 3.7 Hz, 2H), 1.35 – 1.23 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 132.9, 131.0, 129.9, 128.4, 125.5, 113.4, 73.5, 67.3, 65.8, 36.2, 32.2, 27.4, 25.3, 24.5; IR (Neat Film NaCl) 2934, 2858, 1714, 1450, 1317, 1273, 1175, 1106, 710 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{23}INO_2$ $[M+H]^+$: 400.0768; found: 400.0769.



SI-4-6 *170j*

A solution of benzoate **SI-4-6** (140 mg, 0.351 mmol, 1.00 equiv) in MeOH (1.80 mL) and H_2O (0.20 mL) was treated with NaOH (28 mg, 0.701 mmol, 2.00 equiv) at 60 °C. After 1 h and 45 min, the solution was poured into H_2O and the mixture was extracted with CH_2Cl_2 (3 x 3.00 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (1:8 EtOAc:hexanes) to give cyclohexanol **170j** (58 mg, 56% yield).

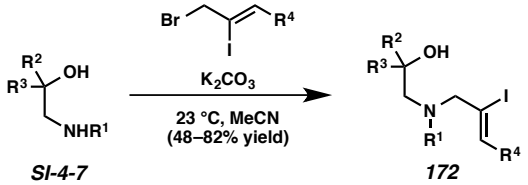
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (q, *J* = 1.4 Hz, 1H), 5.86 (dt, *J* = 1.6, 0.8 Hz, 1H), 3.96 (s, 1H), 3.40 (td, *J* = 9.9, 4.5 Hz, 1H), 3.17 (d, *J* = 13.8 Hz, 1H), 2.95 (d, *J* = 13.8 Hz, 1H), 2.28 (ddd, *J* = 11.4, 9.7, 3.5 Hz, 1H), 2.18 (s, 3H), 2.18 – 2.09 (m, 1H), 1.83 – 1.65 (m, 3H), 1.35 – 1.07 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 127.0, 113.8, 69.4, 69.3, 65.0, 35.9, 33.3, 25.6, 24.2, 22.8; IR (Neat Film NaCl) 3468, 2930, 2855, 2796, 1615, 1449, 1282, 1080, 1036, 901 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{10}H_{19}INO$ $[M+H]^+$: 296.0506; found: 296.0528.



171j

^{1}H NMR (400 MHz, CD_2Cl_2) δ 4.28 (dd, *J* = 1.4, 0.7 Hz, 1H), 4.09 (dd, *J* = 1.7, 0.5 Hz, 1H), 3.31 (ddd, *J* = 11.2, 9.0, 4.2 Hz, 1H), 3.21 (d, *J* = 12.7 Hz, 1H), 2.75 (dt, *J* = 12.7, 1.6 Hz, 1H), 2.18 (s, 3H), 2.12 – 2.01 (m, 1H), 1.90 (dtd, *J* = 13.3, 4.7, 2.7 Hz, 1H), 1.81 – 1.66 (m, 3H), 1.43 – 1.23 (m, 3H), 1.03 (tdd, *J* = 13.0, 11.2, 3.7 Hz, 1H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 157.3, 91.0, 81.4, 67.2, 58.2, 41.9, 31.7, 28.5, 25.1, 24.8; IR (Neat Film NaCl) 2937, 2862, 2770, 1654, 1451, 1339, 1278, 1161, 1075, 1042, 900, 836 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{10}H_{18}NO$ $[M+H]^+$: 168.1383; found: 168.1396.

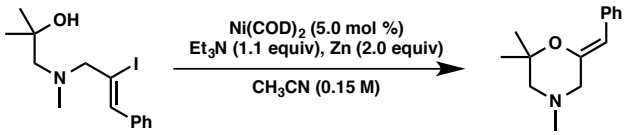
Typical procedure for linear aminoalcohols 172



SI-4-7 ***172***

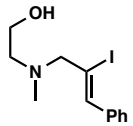
To a solution of aminoalcohols **SI-4-7** (1.12 mmol, 1.00 equiv) in MeCN (5.60 mL) were added K_2CO_3 (11.2 mmol, 10.0 equiv) and allyl bromides (1.23 mmol, 1.10 equiv). The reaction mixture was stirred for 12 h at 23 °C. Solids were removed via a filtration through a celite plug and the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography, using mixture of hexanes and ethyl acetate as eluent to give the product **172**.

Representative procedure for cross-coupling of linear aminoalcohols 172



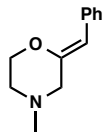
172c ***173c***

Ni-Catalyzed C–O bond formation experiments were performed in a nitrogen-filled glove box. To a solution of aminoalcohol **172c** (50.0 mg, 0.145 mmol, 1.00 equiv) in MeCN (0.97 mL) in a scintillation vial were added Et_3N (22.0 μL, 0.160 mmol, 1.10 equiv), Zn powder (19.0 mg, 0.290 mmol, 2.00 equiv), and $Ni(COD)_2$ (2.00 mg, 0.00724 mmol, 0.05 equiv). The reaction mixture was stirred at 23 °C for 24 h. After the reaction was done, the vial was removed from the glovebox and uncapped. Solids were removed via a filtration through a celite plug and the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography, using a mixture of hexanes and ethyl acetate as eluent to furnish the product **173c** (30.0 mg, 95% yield).



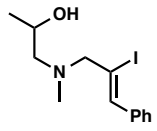
172a

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.36 (m, 3H), 6.98 (s, 1H), 3.65 (t, *J* = 5.4 Hz, 2H), 3.36 (s, 2H), 2.95 (br, 1H), 2.66 (t, *J* = 5.5 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 136.1, 128.7, 128.1, 128.0, 107.1, 70.4, 58.5, 57.8, 40.7; IR (neat film NaCl) 3442, 2946, 2840, 2792, 1490, 1445, 1083, 1066, 1046, 748, 694 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{12}H_{17}INO$, $[M+H]^+$: 318.0349; found: 318.0344.



173a

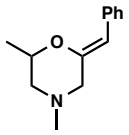
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.28 (m, 2H), 7.14 (m, 1H), 5.45 (s, 1H), 4.06 (m, 2H), 3.03 (s, 2H), 2.59 (m, 2H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 135.6, 128.4, 128.1, 125.9, 107.9, 67.4, 58.3, 54.1, 46.1; IR (neat film NaCl) 2939. 2790, 1738, 1668, 1452, 1339, 1170, 1051, 695; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{12}H_{16}NO$, $[M+H]^+$: 190.1226; found: 190.1228.



172b

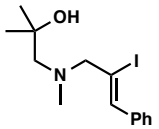
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.50 (m, 2H), 7.41 – 7.30 (m, 3H), 6.98 (s, 1H), 3.90 (dqd, *J* = 9.4, 6.1, 3.0 Hz, 1H), 3.75 – 3.53 (m, 1H), 3.47 (d, *J* = 13.5 Hz, 1H), 3.29 (d, *J* = 13.5 Hz, 1H), 2.45 (dd, *J* = 12.3, 3.1 Hz, 1H), 2.41 – 2.36 (m, 1H), 2.32 (s, 3H), 1.16 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4, 136.4, 128.8, 128.3, 128.3, 128.2, 107.1, 70.8, 64.6, 63.3, 41.3, 19.9; IR (neat film NaCl) 3459, 3054, 3023, 2968, 2930, 2843, 2795, 1598, 1491, 1446, 1408, 1361, 1324, 1291,

1209, 1161, 1135, 1065, 1029, 935, 841, 750, 695 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{13}H_{19}NIO$, $[M+H]^+$: 332.0506; found: 332.0519.



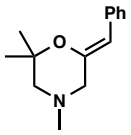
173b

^1H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.56 (m, 2H), 7.33 – 7.26 (m, 2H), 7.19 – 7.10 (m, 1H), 5.46 (d, *J* = 1.4 Hz, 1H), 4.06 (dqd, *J* = 9.9, 6.3, 2.6 Hz, 1H), 3.20 (dd, *J* = 12.5, 1.7 Hz, 1H), 2.85 – 2.72 (m, 2H), 2.31 (s, 3H), 2.06 (dd, *J* = 11.7, 9.8 Hz, 1H), 1.36 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.2, 136.0, 128.6, 128.2, 126.0, 107.8, 73.4, 60.9, 58.0, 46.1, 19.2; IR (neat film NaCl) 2973, 2936, 2788, 1666, 1448, 1328, 1154, 1070, 975, 755, 694 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{13}H_{18}NO$, $[M+H]^+$: 204.1383; found: 204.1386.



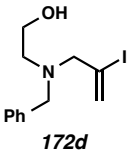
172c

^1H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.48 (m, 2H), 7.33 (s, 3H), 6.99 (s, 1H), 3.46 (s, 2H), 3.26 (s, br, 1H), 2.51 (s, 2H), 2.37 (s, 3H), 1.23 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 135.8, 129.2, 128.9, 128.2, 108.3, 73.0, 70.9, 68.1, 44.0, 28.0; IR (neat film NaCl) 2969, 2786, 2360, 1446, 1356, 1121, 1031, 970, 749, 695 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{14}H_{21}NIO$, $[M+H]^+$: 346.0662; found: 346.0664.



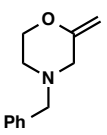
173c

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.59 (m, 2H), 7.29 – 7.25 (m, 2H), 7.17 – 7.09 (m, 1H), 5.47 (s, 1H), 2.94 (s, 2H), 2.38 (s, 2H), 2.28 (s, 3H), 1.39 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.2, 136.3, 128.3, 128.2, 125.8, 108.7, 76.8, 64.7, 58.3, 46.4, 26.3; IR (neat film NaCl) 2974, 2766, 1663, 1449, 1368, 1346, 1254, 1207, 1152, 1110, 968, 754, 694 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{14}H_{20}NO$, $[M+H]^+$: 218.1539; found: 218.1577.



172d

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 5H), 6.33 (q, *J* = 1.4 Hz, 1H), 5.92 (m, 1H), 3.63 (s, 2H), 3.56 (q, *J* = 5.4 Hz, 2H), 3.16 (s, 2H), 2.70 (t, *J* = 5.7 Hz, 1H), 2.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 129.3, 128.4, 127.9, 127.4, 111.9, 64.8, 58.5, 57.5, 54.1; IR (neat film NaCl) 3435, 3024, 2808, 1616, 1493, 1452, 1257, 1151, 1027, 904, 739, 698 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{12}H_{17}INO$, $[M+H]^+$: 318.0349; found: 318.0356.

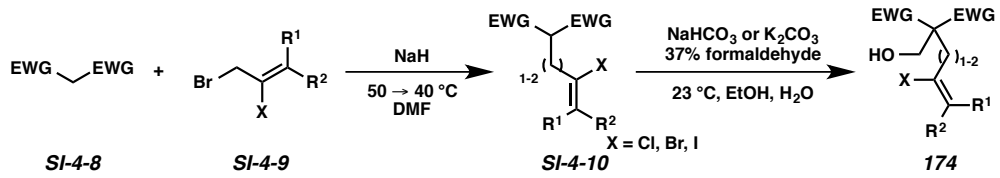


173d

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 5H), 4.39 (s, 1H), 4.11 (s, 1H), 3.90 (m, 2H), 3.50 (s, 2H), 2.98 (s, 2H), 2.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 137.4, 129.3, 128.5, 127.4, 92.2, 67.9, 63.2, 55.3, 52.1; IR (neat film NaCl)

2875, 2807, 1653, 1453, 1313, 1278, 1125, 1079, 1067, 851, 699 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{12}H_{16}NO$, $[M+H]^+$: 190.1226; found: 190.1229.

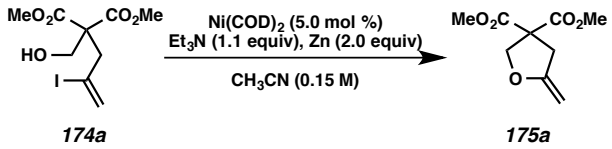
Typical procedure for malonate substrates 174



To a suspension of NaH (60% dispersion in mineral oil, 4.16 mmol, 1.10 equiv) in DMF (19.0 mL) at 0 °C was added malonate **SI-4-8** (3.78 mmol, 1.00 equiv) in portions. The reaction mixture was stirred at 50 °C for 1 h. The solution was cooled to 0 °C and allyl bromide (3.78 mmol, 1.00 equiv) in DMF (2 mL) was added in portions over 5 min. Then, the mixture was stirred at 40 °C for 1 h. The reaction was quenched by sat. NH_4Cl and the aqueous phase was extracted with Et_2O (3 x 10.0 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:20 EtOAc:hexanes) on silica gel to give vinyl halide **SI-4-10**.

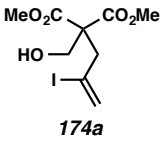
To a solution of vinyl halide **SI-4-10** (0.74 mmol, 1.00 equiv) in EtOH (0.50 mL) and H_2O (0.25 mL) were added solid $NaHCO_3$ or K_2CO_3 (0.15 mmol, 0.20 equiv) and formaldehyde (37wt.% in H_2O, 0.89 mmol, 1.20 equiv). The reaction mixture was stirred at 23 °C for 24 h. Then, water (0.40 mL) was added and the aqueous phase was extracted with EtOAc (3 x 1.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography, using a mixture of hexanes and ethyl acetate as eluent to furnish the product **174**.

Representative procedure for cross-coupling of malonates 174



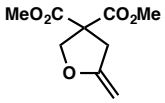
174a *175a*

Ni-Catalyzed C–O bond formation experiments were performed in a nitrogen-filled glove box. To a solution of vinyl iodide **174a** (83.9 mg, 0.256 mmol, 1.00 equiv) in MeCN (1.71 mL) in a scintillation vial were added Et_3N (39.0 μL, 0.282 mmol, 1.10 equiv), Zn powder (33.0 mg, 0.512 mmol, 2.00 equiv), and $Ni(COD)_2$ (3.50 mg, 0.013 mmol, 0.05 equiv). The reaction mixture was stirred at 23 °C for 1 h. After the reaction was done, the vial was removed from the glovebox and uncapped. Solids were removed via a filtration through a celite plug and the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (1:4 EtOAc:hexanes) to furnish the product **175a** (44.5 mg, 87% yield).



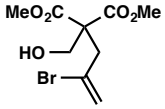
174a

^{1}H NMR (500 MHz, C_6D_6) δ 5.79 (q, *J* = 1.2 Hz, 1H), 5.61 (d, *J* = 1.4 Hz, 1H), 4.09 (d, *J* = 5.8 Hz, 2H), 3.33 (s, 6H), 3.32 (d, *J* = 1.1 Hz, 2H); ^{13}C NMR (126 MHz, C_6D_6) δ 169.9, 131.5, 101.2, 63.3, 59.3, 52.4, 45.4; IR (Neat Film NaCl) 3520, 2952, 1731, 1435, 1210, 1033 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_9H_{14}IO_5$ $[M+H]^+$: 328.9886; found: 328.9891.



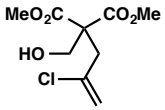
175a

^{1}H NMR (500 MHz, C_6D_6) δ 4.53 (q, *J* = 1.9 Hz, 1H), 4.44 (s, 2H), 3.91 (q, *J* = 1.7 Hz, 1H), 3.16 (s, 6H), 3.09 (t, *J* = 1.7 Hz, 2H); ^{13}C NMR (126 MHz, C_6D_6) δ 169.2, 160.2, 81.8, 74.3, 59.8, 52.6, 37.0; IR (Neat Film NaCl) 2957, 2358, 2340, 1737, 1436, 1280, 1046 cm^{-1}; HRMS (MM: ESI-APCI +) *m/z* calc'd for $C_9H_{13}O_5$ $[M+H]^+$: 201.0757; found: 201.0765.



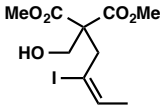
174b

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (dt, *J* = 1.7, 0.9 Hz, 1H), 5.59 (d, *J* = 1.7 Hz, 1H), 4.09 (s, 2H), 3.79 (s, 6H), 3.25 (d, *J* = 0.9 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 126.6, 122.4, 63.7, 59.0, 53.1, 42.4; IR (Neat Film NaCl) 2953, 1728, 1626, 1435, 1299, 1208, 1032, 902, 857 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_9H_{14}BrO_5$ $[M+H]^+$: 281.0024; found: 281.0036.



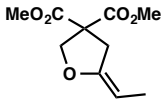
174c

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (d, *J* = 1.3 Hz, 1H), 5.30 – 5.28 (m, 1H), 4.07 (s, 2H), 3.78 (s, 6H), 3.13 (d, *J* = 0.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 136.6, 117.7, 63.8, 58.7, 53.0, 40.6; IR (Neat Film NaCl) 2955, 1735, 1632, 1437, 1212, 1035, 898 cm^{-1}; HRMS (MM: FAB +) *m/z* calc'd for $C_9H_{14}O_5Cl$ $[M+H]^+$: 237.0530; found: 237.0540.



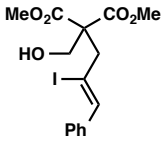
174d

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.50 (qt, *J* = 7.2, 0.8 Hz, 1H), 4.04 (d, *J* = 6.6 Hz, 2H), 3.80 (s, 6H), 3.30 (s, br, 2H), 2.36 (t, *J* = 6.7 Hz, 1H), 1.70 (dt, *J* = 7.2, 0.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 142.1, 91.5, 63.6, 59.2, 53.1, 38.7, 17.2; IR (Neat Film NaCl) 2952, 1733, 1436, 1299, 1223, 1040 cm^{-1}; HRMS (MM: FAB +) *m/z* calc'd for $C_{10}H_{16}O_5I$ $[M+H]^+$: 343.0043; found: 343.0048.



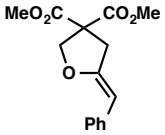
175d

^{1}H NMR (400 MHz, C_6D_6) δ 4.97 (qt, *J* = 7.0, 2.2 Hz, 1H), 4.44 (s, 2H), 3.18 (s, 6H), 3.11 (dq, *J* = 2.8, 1.5 Hz, 2H), 1.40 (dt, *J* = 7.1, 1.4 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 169.6, 153.8, 92.2, 73.6, 59.7, 52.6, 34.2, 12.2; IR (Neat Film NaCl) 2956, 1740, 1437, 1275, 1169, 1070, 803 cm^{-1}; HRMS (MM: FAB +) *m/z* calc'd for $C_{10}H_{14}O_5$ $[M]^{+\bullet}$: 214.0841; found: 214.0836.



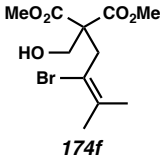
174e

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H), 6.88 (s, 1H), 4.15 (s, 2H), 3.81 (s, 6H), 3.57 (d, *J* = 0.9 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 140.1, 138.2, 128.7, 128.3, 128.3, 96.5, 63.6, 59.9, 53.1, 46.9; IR (Neat Film NaCl) 2951, 1727, 1437, 1215, 1032, 696 cm^{-1}; HRMS (MM: ESI-APCI +) *m/z* calc'd for $C_{15}H_{18}O_5I$ $[M+H]^+$: 405.0193; found: 405.0195.



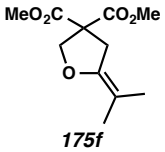
175e

^{1}H NMR (400 MHz, C_6D_6) δ 7.75 – 7.70 (m, 2H), 7.25 (t, *J* = 7.8 Hz, 2H), 7.05 (ddt, *J* = 8.6, 7.2, 1.2 Hz, 1H), 5.21 – 5.18 (m, 1H), 4.54 (s, 2H), 3.20 (d, *J* = 1.6 Hz, 2H), 3.16 (s, 6H); ^{13}C NMR (101 MHz, C_6D_6) δ 168.8, 153.7, 136.4, 128.2, 127.8, 125.3, 99.4, 75.2, 58.5, 52.3, 38.3; IR (Neat Film NaCl) 2953, 1738, 1678, 1435, 1279, 1210, 1028, 695 cm^{-1}; HRMS (MM: EI +) *m/z* calc'd for $C_{15}H_{16}O_5$ $[M]^{+\bullet}$: 276.0998; found: 276.1012.



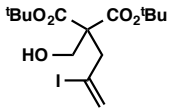
174f

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (s, 2H), 3.78 (s, 6H), 3.37 (s, 2H), 1.88 (d, *J* = 0.9 Hz, 3H), 1.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 136.4, 114.1, 63.7, 59.3, 53.0, 38.8, 25.9, 21.2; IR (Neat Film NaCl) 2952, 1734, 1437, 1209, 1043 cm^{-1}; HRMS (MM: FAB +) *m/z* calc'd for $C_{11}H_{18}O_5Br$ $[M+H]^+$: 309.0338; found: 309.0325.



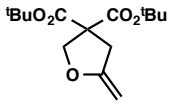
175f

^{1}H NMR (500 MHz, C_6D_6) δ 4.12 (d, *J* = 6.0 Hz, 2H), 3.57 (s, 2H), 3.38 (s, 6H), 1.66 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 170.6, 136.2, 115.0, 63.6, 59.5, 52.3, 39.0, 25.6, 20.8; IR (Neat Film NaCl) 2952, 1731, 1437, 1301, 1209, 1043 cm^{-1}; HRMS (MM: FAB +) *m/z* calc'd for $C_{11}H_{17}O_5$ $[M+H]^+$: 229.1076; found: 229.1074.



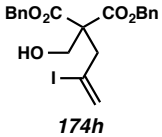
174g

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18 (q, *J* = 1.3 Hz, 1H), 5.91 (d, *J* = 1.5 Hz, 1H), 4.06 (d, *J* = 3.6 Hz, 2H), 3.20 (d, *J* = 1.1 Hz, 2H), 2.32 (s, 1H), 1.50 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 130.9, 101.6, 82.8, 63.9, 60.7, 45.4, 28.1; IR (Neat Film NaCl) 2978, 1728, 1369, 1256, 1148, 1020, 842 cm^{-1}; HRMS (MM: FAB +) *m/z* calc'd for $C_{15}H_{26}O_5I$ $[M+H]^+$: 413.0825; found: 413.0821.



175g

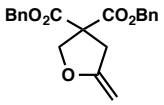
^{1}H NMR (500 MHz, C_6D_6) δ 4.54 (q, *J* = 1.8 Hz, 1H), 4.51 (s, 2H), 3.94 (q, *J* = 1.6 Hz, 1H), 3.14 (t, *J* = 1.7 Hz, 2H), 1.27 (s, 18H); ^{13}C NMR (126 MHz, C_6D_6) δ 168.3, 160.9, 81.8, 81.3, 74.5, 61.2, 37.0, 27.7; IR (Neat Film NaCl) 2979, 1732, 1370, 1146, 1050, 844 cm^{-1}; HRMS (MM: FAB +) *m/z* calc'd for $C_{15}H_{25}O_5$ $[M+H]^+$: 285.1702; found: 285.1693.



174h

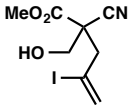
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 6H), 7.29 – 7.26 (m, 4H), 6.12 (q, *J* = 1.1 Hz, 1H), 5.87 (d, *J* = 1.6 Hz, 1H), 5.17 (d, *J* = 3.2 Hz, 4H), 4.13 (s, 2H), 3.29 (d, *J* = 1.1 Hz, 2H), 2.27 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 135.1, 131.8, 128.7, 128.6, 128.4, 100.3, 67.8, 63.6, 59.5, 45.4; IR (Neat Film NaCl) 2952, 1725, 1455,

1214, 695 cm^{-1}; HRMS (MM: ESI-APCI +) *m/z* calc'd for $C_{21}H_{22}O_5I$ $[M+H]^+$: 481.0506; found: 481.0509.



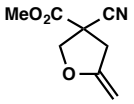
175h

^1H NMR (600 MHz, C_6D_6) δ 7.10 – 6.90 (m, 10H), 4.83 (d, *J* = 8.0 Hz, 4H), 4.50 (q, *J* = 1.8 Hz, 1H), 4.46 (s, 2H), 3.87 (q, *J* = 1.7 Hz, 1H), 3.11 (t, *J* = 1.7 Hz, 2H); ^{13}C NMR (151 MHz, C_6D_6) δ 168.7, 148.2, 135.6, 128.7, 128.5, 128.3, 81.9, 74.3, 67.7, 55.8, 37.0; IR (Neat Film NaCl) 2915, 1732, 1455, 1243, 1045, 901, 695 cm^{-1}; HRMS (MM: ESI-APCI +) *m/z* calc'd for $C_{21}H_{21}O_5$ $[M+H]^+$: 353.1384; found: 353.1394.



174i

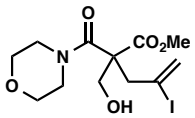
^1H NMR (500 MHz, $CDCl_3$) δ 6.35 (dt, *J* = 2.2, 1.1 Hz, 1H), 6.05 (d, *J* = 2.1 Hz, 1H), 4.04 (dd, *J* = 11.1, 7.6 Hz, 1H), 3.98 (dd, *J* = 11.1, 6.5 Hz, 1H), 3.90 (s, 3H), 3.13 (dd, *J* = 14.9, 1.1 Hz, 1H), 3.05 (dd, *J* = 14.9, 1.1 Hz, 1H), 2.45 (dd, *J* = 7.6, 6.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.6, 132.6, 117.2, 97.2, 66.0, 54.2, 52.1, 46.9; IR (Neat Film NaCl) 2952, 2359, 1738, 1611, 1434, 1224, 1144, 1060, 910 cm^{-1}; HRMS (MM: FAB +) *m/z* calc'd for $C_8H_{11}O_3NI$ $[M+H]^+$: 295.9784; found: 295.9775.



175i

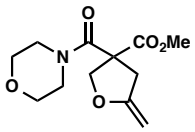
^1H NMR (500 MHz, C_6D_6) δ 4.44 (q, *J* = 2.0 Hz, 1H), 3.84 (d, *J* = 8.9 Hz, 1H), 3.79 – 3.75 (m, 2H), 3.02 (d, *J* = 0.7 Hz, 3H), 2.69 (dt, *J* = 15.9, 1.9 Hz, 1H), 2.42 (dt, *J* =

15.9, 1.6 Hz, 1H); ^{13}C NMR (126 MHz, C_6D_6) δ 166.1, 158.0, 117.3, 83.6, 75.1, 53.3, 46.9, 38.7; IR (Neat Film NaCl) 2959, 2249, 1747, 1682, 1435, 1231, 1046, 819 cm^{-1}; HRMS (MM: FAB +) *m/z* calc'd for $C_8H_{10}O_3N$ $[M+H]^+$: 168.0661; found: 168.0666.



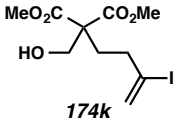
174j

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (q, *J* = 1.2 Hz, 1H), 5.97 (d, *J* = 1.6 Hz, 1H), 4.25 (d, *J* = 11.2 Hz, 1H), 3.88 (d, *J* = 11.2 Hz, 1H), 3.81 (s, 3H), 3.79 – 3.55 (m, 6H), 3.39 (s, br, 2H), 3.30 (dd, *J* = 15.5, 1.0 Hz, 1H), 3.06 (dd, *J* = 15.4, 1.1 Hz, 1H), 2.60 (s, br, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 167.7, 132.2, 99.9, 66.3, 66.1, 57.4, 53.1, 45.6, 37.2; IR (Neat Film NaCl) 2955, 2859, 1733, 1627, 1436, 1272, 1228, 1115, 1064, 999, 851 cm^{-1}; HRMS (MM: ESI-APCI +) *m/z* calc'd for $C_{12}H_{19}NO_5I$ $[M+H]^+$: 384.0302; found: 384.0315.



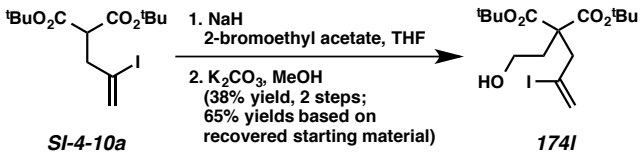
175j

^{1}H NMR (500 MHz, C_6D_6) δ 4.60 (d, *J* = 9.0 Hz, 1H), 4.55 (q, *J* = 1.8 Hz, 1H), 4.41 (d, *J* = 9.0 Hz, 1H), 3.94 (q, *J* = 1.7 Hz, 1H), 3.22 (s, br, 2H), 3.15 – 2.97 (m, 9H), 2.71 (s, br, 2H); ^{13}C NMR (101 MHz, C_6D_6) δ 171.6, 165.8, 160.7, 81.4, 75.2, 66.4, 66.0, 58.8, 52.5, 46.0, 43.5, 37.5; IR (Neat Film NaCl) 2857, 1733, 1651, 1435, 1274, 1115, 1018, 804 cm^{-1}; HRMS (MM: ESI-APCI +) *m/z* calc'd for $C_{12}H_{18}NO_5$ $[M+H]^+$: 256.1179; found: 256.1196.



174k

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 (q, *J* = 1.4 Hz, 1H), 5.72 (d, *J* = 1.7 Hz, 1H), 3.96 (s, 2H), 3.79 (d, *J* = 0.6 Hz, 6H), 2.49 – 2.43 (m, 2H), 2.20 – 2.13 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 126.4, 109.9, 64.9, 59.0, 52.9, 40.8, 31.5; IR (Neat Film NaCl) 2952, 1729, 1617, 1436, 1205, 1043, 898 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{10}H_{16}IO_5$ $[M+H]^+$: 343.0043; found: 343.0031.

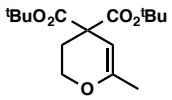


SI-4-10a ***174l***

To a solution of NaH (60% dispersion in mineral oil, 78.0 mg, 1.95 mmol, 2.00 equiv) in THF (3.26 mL) was added vinyl iodide **SI-4-10a** (374 mg, 0.977 mmol, 1.00 equiv), and the solution was stirred until gas evolution was complete. 2-Bromoethyl acetate (0.27 mL, 2.44 mmol, 2.50 equiv) was added to the reaction mixture at 0 °C and then, the solution was stirred at 23 °C for 24 h. The reaction was quenched with sat. NH_4Cl at 0 °C and the mixture was extracted with EtOAc (3 x 3.00 mL), the combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (1:20 EtOAc:hexanes) to give dialkylated malonate and recovered **SI-4-10a**.

To a solution of dialkylated malonate intermediate (344 mg, 0.735 mmol, 1.00 equiv) in MeOH (2.50 mL) was added K_2CO_3 (203 mg, 1.47 mmol, 2.00 equiv) and the solution was stirred at 23 °C for 24 h. The reaction mixture was diluted with CH_2Cl_2 (3.00 mL) and the mixture was extracted with CH_2Cl_2 (3 x 2.00 mL), the combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated *in*

vacuo. The residue was purified by silica gel flash chromatography (1:20 → 1:8 → 1:4 EtOAc:hexanes) to give malonate **174l** (159 mg, 38% yield, 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.14 (q, *J* = 1.4 Hz, 1H), 5.91 (d, *J* = 1.7 Hz, 1H), 3.72 (t, *J* = 6.7 Hz, 2H), 3.17 (d, *J* = 1.2 Hz, 2H), 2.28 (t, *J* = 6.7 Hz, 2H), 1.65 (s, br, 1H), 1.47 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 130.5, 102.2, 82.5, 59.2, 57.7, 46.9, 34.7, 28.1; IR (Neat Film NaCl) 3447, 2977, 1726, 1368, 1250, 1145, 843 cm^{-1}; HRMS (MM: FAB +) *m/z* calc'd for $C_{16}H_{28}IO_5$ $[M+H]^+$: 427.0982; found: 427.0985.



175l

^{1}H NMR (500 MHz, CD_2Cl_2) δ 4.68 (h, *J* = 0.9 Hz, 1H), 4.02 – 3.96 (m, 2H), 2.10 – 2.04 (m, 2H), 1.76 (d, *J* = 1.0 Hz, 3H), 1.43 (s, 18H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 170.6, 153.8, 94.6, 81.7, 64.1, 52.5, 28.7, 28.1, 20.6; IR (Neat Film NaCl) 2977, 2933, 1728, 1369, 1266, 1146, 1108, 1088, 847 cm^{-1}; HRMS (MM: FAB +) *m/z* calc'd for $C_{16}H_{27}O_5$ $[M+H]^+$: 299.1858; found: 299.1835.

4.5. References and Notes

(1) Selected recent reviews: (a) Han, F.-S. *Chem. Soc. Rev.* **2013**, *42*, 5270–5298. (b) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417–1492. (c) Hartwig, J. F. *Nature* **2008**, *455*, 314–322. (d) Terao, J.; Kambe, N. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 663–672.

(2) (a) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299–309. (b) Ananikov, V. P. *ACS Catal.* **2015**, *5*, 1964–1971.

(3) Selected recent reviews: (a) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525–1532. (b) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346–1416. (c) Hu, X. *Chem. Sci.* **2011**, *2*, 1867–1886. (d) Standley, E. A.; Tasker, S. Z.; Jensen, K. L.; Jamison, T. F. *Acc. Chem. Res.* **2015**, *48*, 1503–1514.

(4) For fundamental studies involving stoichiometric nickel-alkoxides, see: (a) Matsunaga, P. T.; Hillhouse, G. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 2075–2077. (b) Han, R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **1997**, *119*, 8135–8136.

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(8) Terrett, J. A.; Cuthbertson, J. D.; Shurtleff, V. W.; MacMillan, D. W. C. *Nature* **2015**, *524*, 330–334.

(9) For examples of intramolecular C–O cyclization using non-nickel catalysis, see: (a) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333–10334. (b) Torraca, K. E.; Kuwabe, S.-I.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12907–12908. (c) Kuwabe, S.-i.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem.*

Soc. **2001**, *123*, 12202–12206. . (d) Sun, C.; Fang, Y.; Li, S.; Zhang, Y.; Zhao, Q.; Zhu, S.; Li, C. *Org Lett*. **2009**, *11*, 4084–4087. (e) Fang, Y.; Li, C. *J. Am .Chem. Soc*. **2007**, *129*, 8092–8093. (f) Fang, Y.; Li, C. *Chem. Commun*. **2005**, 3574–3576.

(10) For examples of intermolecular C–O cyclization using non-nickel catalysis, see: (a) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc*. **1999**, *121*, 3224–3225. (b) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc*. **1999**, *121*, 4369–4378. (c) Burgos, C.; Barder, T. E.; Huang, X.; Buchwald, S. L. *Angew. Chem., Int. Ed*. **2006**, *45*, 4321–4326. (d) Parrish, C. A.; Buchwald, S. L. *J. Org. Chem*. **2001**, *66*, 2498–2500. (e) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. *J. Am. Chem. Soc*. **2000**, *122*, 10718–10719. (f) Wu, X.; Fors, B. P.; Buchwald, S. L. *Angew. Chem., Int. Ed*. **2011**, *50*, 9943–9947. (g) Surasani, R.; Kalita, D.; Rao, A. V. D.; Chandrasekhar, K. B. *Beilstein J. Org. Chem*. **2012**, *8*, 2004–2018. (h) Maiti, D.; Buchwald, S. L. *J. Org. Chem*. **2010**, *75*, 1791–1794. (i) Niu, J.; Guo, P.; Kang, J.; Li, Z.; Xu, J.; Hu, S. *J. Org. Chem*. **2009**, *74*, 5075–5078. (j) Nordmann, G.; Buchwald, S. L. *J. Am. Chem. Soc*. **2003**, *125*, 4978–4979. (k) Shade, R. E.; Hyde, A. M.; Olsen, J.-C.; Merlic, C. A. *J. Am. Chem. Soc*. **2010**, *132*, 1202–1203.

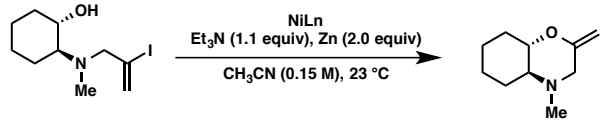
(11) For an example of a base-mediated intramolecular synthesis of an alkylidene morpholine by C–O bond formation, see: Bottini, A. T.; Mullikin, J. A.; Morris, C. J. *J. Org. Chem*. **1964**, *29*, 373–379.

(12) Teng, M.; Zi, W.; Ma, D. *Angew. Chem., Int. Ed*. **2014**, *53*, 1814–1817.

(13) Lebedev, S. A.; Lopatina, V. S.; Petrov, E. S.; Beletskaya, I. P. *J. Organomet. Chem*. **1988**, *344*, 253–259.

(14) Importantly, if the $Ni(COD)_2$ catalyst was omitted, no carbon–oxygen bond formation was observed. Addition of other additives such as Mg and CuI decreased the yields (36% and 0% yield, respectively).

(15) Intramolecular etherification of vinyl iodide **170b** proceeded with 5 mol % of NiI_2 or $NiBr_2$(dme) to furnish vinyl ether **171b** (entries 1 and 2). An increased rate of cycloetherification was observed with 10 mol % of $NiBr_2$(dme) (entries 2 and 3). Unfortunately, attempts to convert vinyl iodide **170b** to enol ether **171b** outside a N_2-filled glove box were unsuccessful (entries 4 and 5).



170b *171b*

entry	NiLn	Ni mol %	time	yield (%)[a]
1[b]	NiI_2	5	16 h	60
2[b]	$NiBr_2$(dme)	5	48 h	53
3[b]	$NiBr_2$(dme)	10	16 h	51
4[c]	NiI_2	5	24 h	0
5[c]	$NiBr_2$(dme)	5	24 h	0

[a] Yield of isolated product. [b] Reactions were performed in a N_2-filled glove box. [c] Reactions were performed under argon outside a N_2-filled glove box.

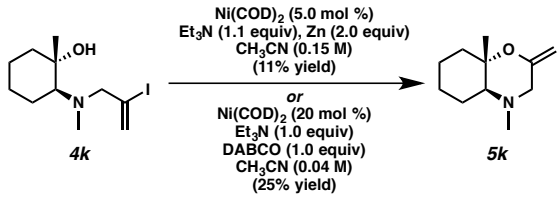
(16) No significant improvement in yield or catalyst turnover was observed when various ligands (e.g., various NHC, PYBOX, BOX, diamine, BiOX ligands) were employed.

(17) Since intramolecular etherifications of aminocyclohexanols **170a** or **170b** proceeded even without Zn powder despite low yields and catalyst turnover (Table 1), we envision that Zn powder likely plays an important role as a scavenger of the forming HI.

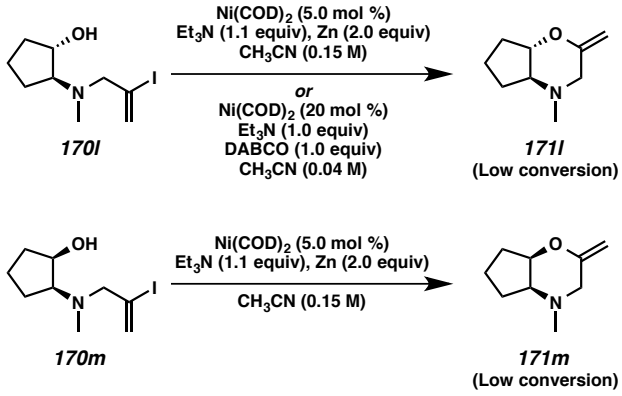
(18) Kurosu, M.; Lin, M.-H.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 12248–12249.

(19) Bowman, W. R.; Bridge, C. F.; Brookes, P.; Cloonan, M. O.; Leach, D. C. *J. Chem. Soc. Perkin. Trans. 1* **2002**, 58–68.

(20) An intramolecular cross-coupling of **170k** afforded the desired product **171k** in low yield under our standard reaction conditions.



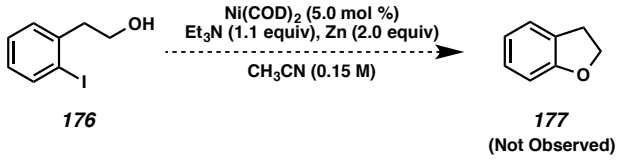
(21) Surprisingly, the cycloetherification of *trans*- and *cis*-aminocyclopentanol derived substrates resulted in very low conversion.



(22) Cao, H.; Yu, J.; Wearing, X. Z.; Zhang, C.; Liu, X.; Deschamps, J.; Cook, J. M. *Tetrahedron Lett.* **2003**, *44*, 8013–8017.

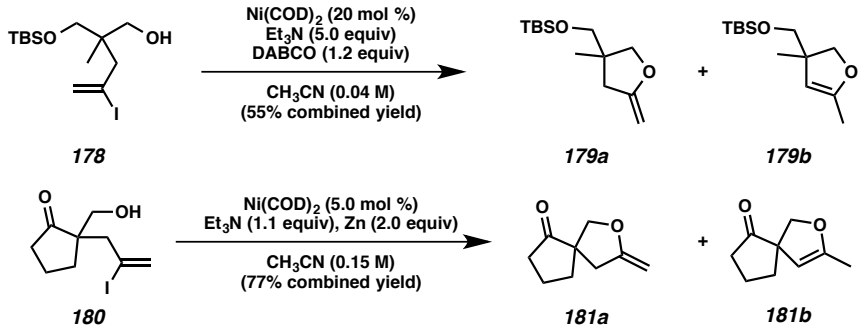
(23) Gatti, M.; Drinkel, E.; Wu, L.; Pusterla, I.; Gaggia, F.; Dorta, R. *J. Am. Chem. Soc.* **2010**, *132*, 15179–15181.

(24) Although we attempted to construct 2,3-dihydrobenzofuran **177** from aryl iodide **176** under our standard reaction conditions, only unreacted starting material was recovered.



176 ***177*** (Not Observed)

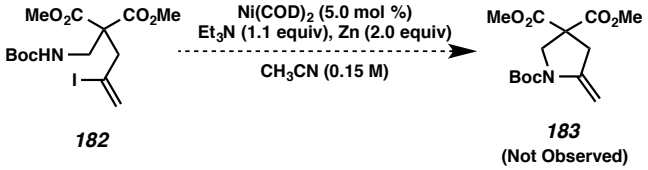
(25) Substrates containing alkyl- or mono-ketone substituents instead of a malonate provided a mixture of isomers upon subjection to carbon–oxygen cross-coupling conditions.



178 ***179a*** ***179b***

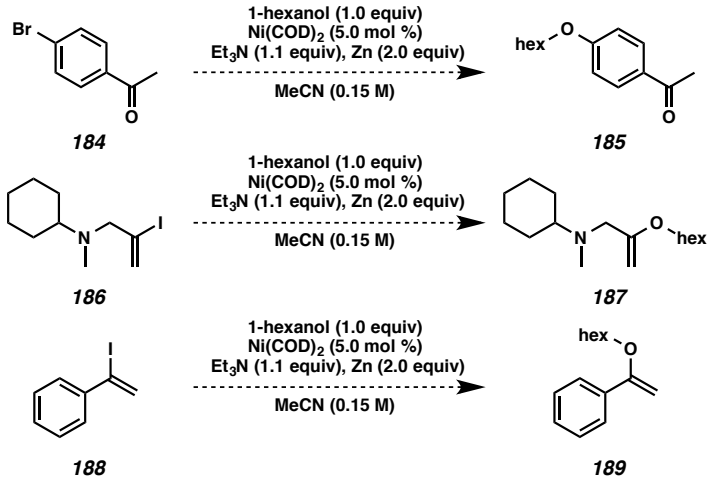
180 ***181a*** ***181b***

(26) Unfortunately, the cyclization reaction of a malonate substrate bearing a nitrogen nucleophile (**182**) was unsuccessful.



182 ***183*** (Not Observed)

(27) An intermolecular etherification of MacMillan's substrate **184** (ref. 8) with 1-hexanol under our reaction conditions was not successful. Additionally, attempted intermolecular cross-coupling processes of **186** and **188** with 1-hexanol under our standard reaction conditions resulted in no reaction.

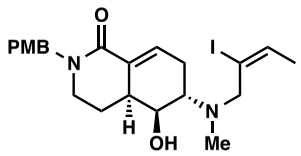

Br
O
1-hexanol (1.0 equiv)
Ni(COD)2 (5.0 mol %)
Et3N (1.1 equiv), Zn (2.0 equiv)
MeCN (0.15 M)
hex
O
O
184
185
1-hexanol (1.0 equiv)
Ni(COD)2 (5.0 mol %)
Et3N (1.1 equiv), Zn (2.0 equiv)
MeCN (0.15 M)
N
I
N
O
hex
186
187
1-hexanol (1.0 equiv)
Ni(COD)2 (5.0 mol %)
Et3N (1.1 equiv), Zn (2.0 equiv)
MeCN (0.15 M)
I
hex
O
188
189

APPENDIX 8

Spectra Relevant to Chapter 4:

Ni-Catalyzed Intramolecular C–O Bond Formation:

Synthesis of Cyclic Enol Ethers



167

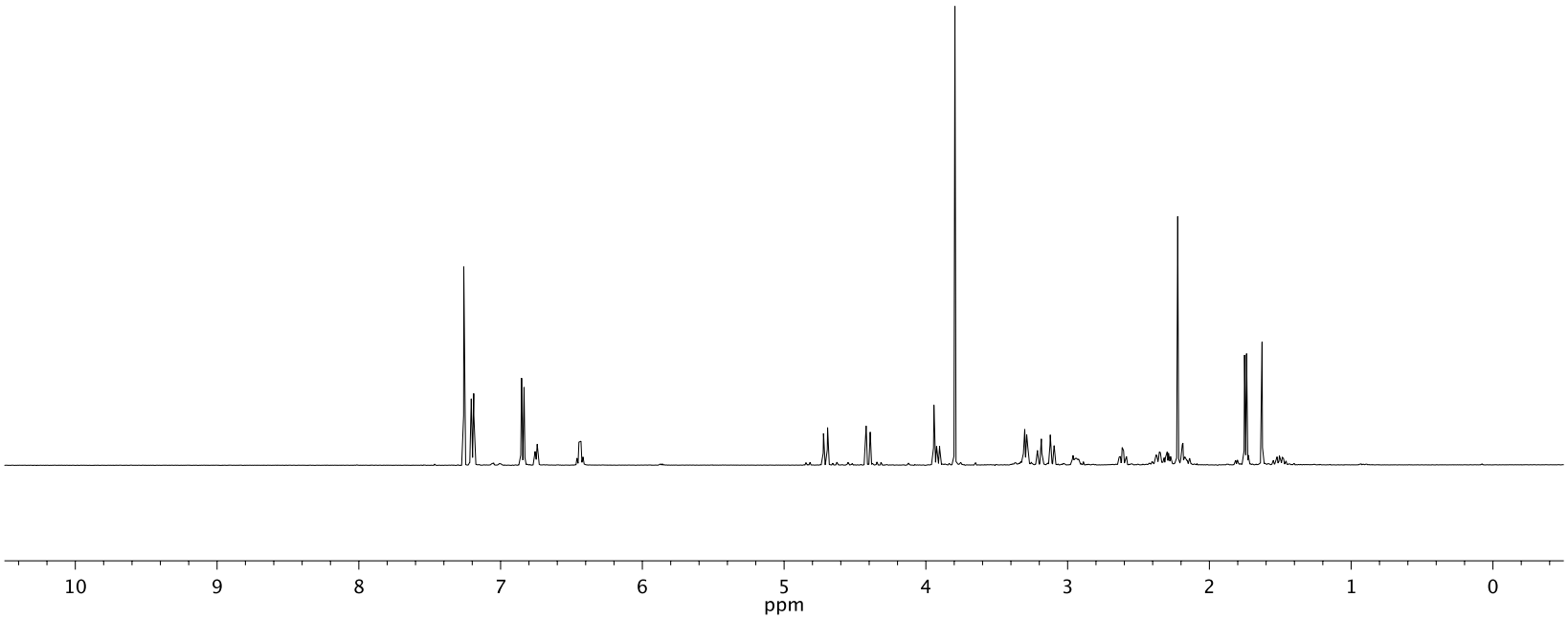


Figure A8.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **167**.

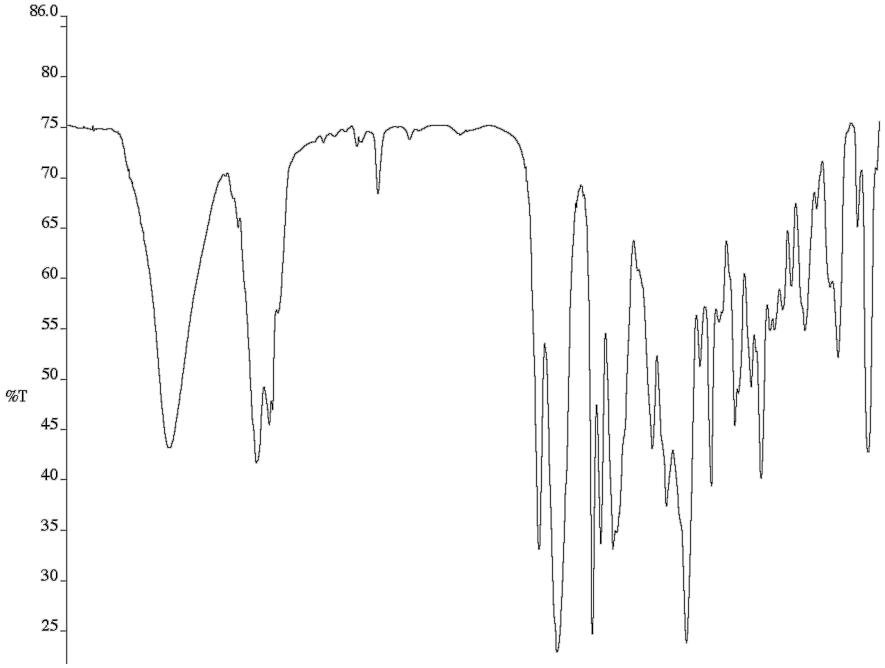


Figure A8.2. Infrared spectrum (Thin Film, NaCl) of compound **167**.

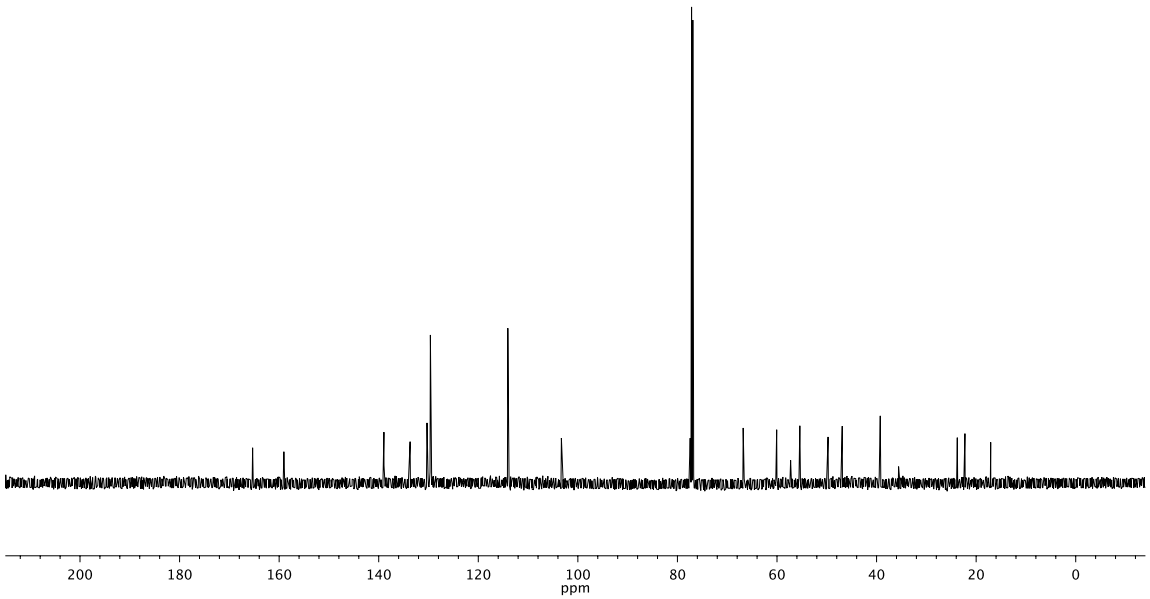


Figure A8.3. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **167**.

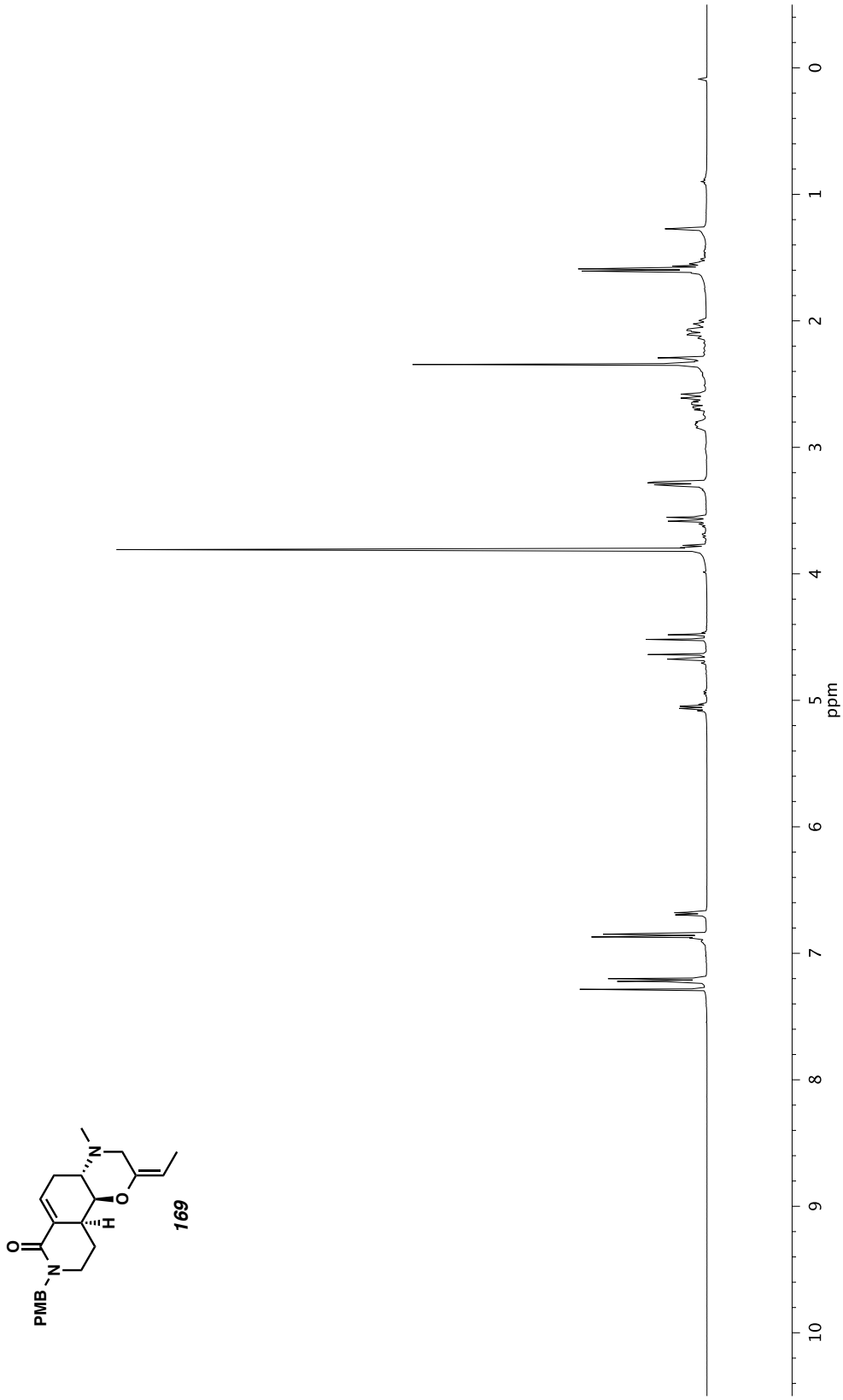


Figure A8.4. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **169**.

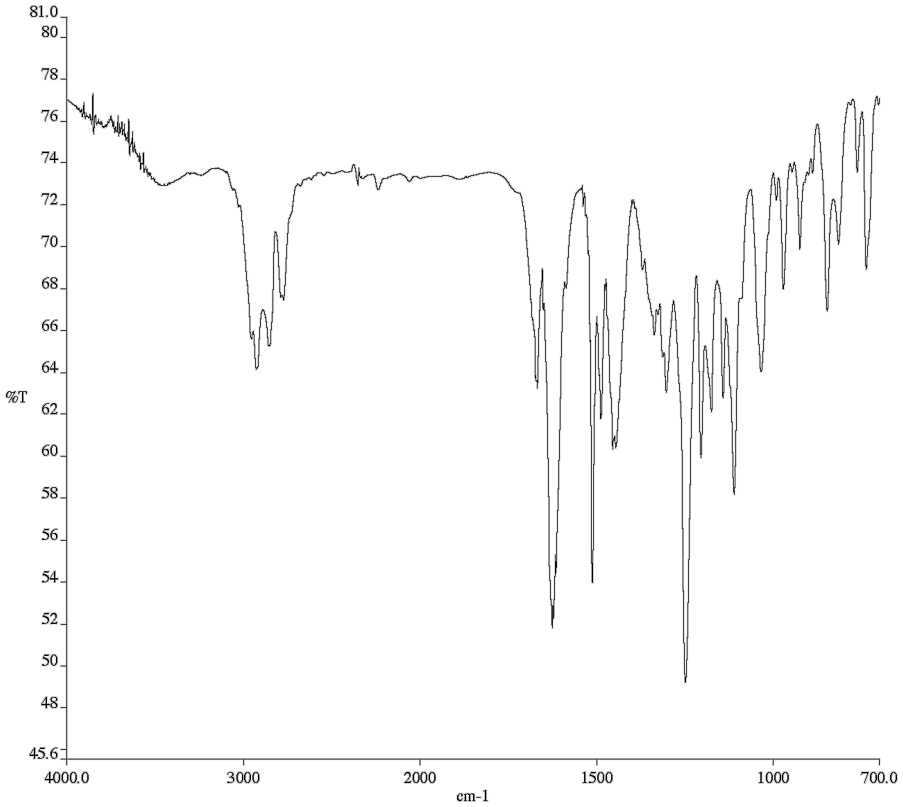


Figure A8.5. Infrared spectrum (Thin Film, NaCl) of compound **169**.

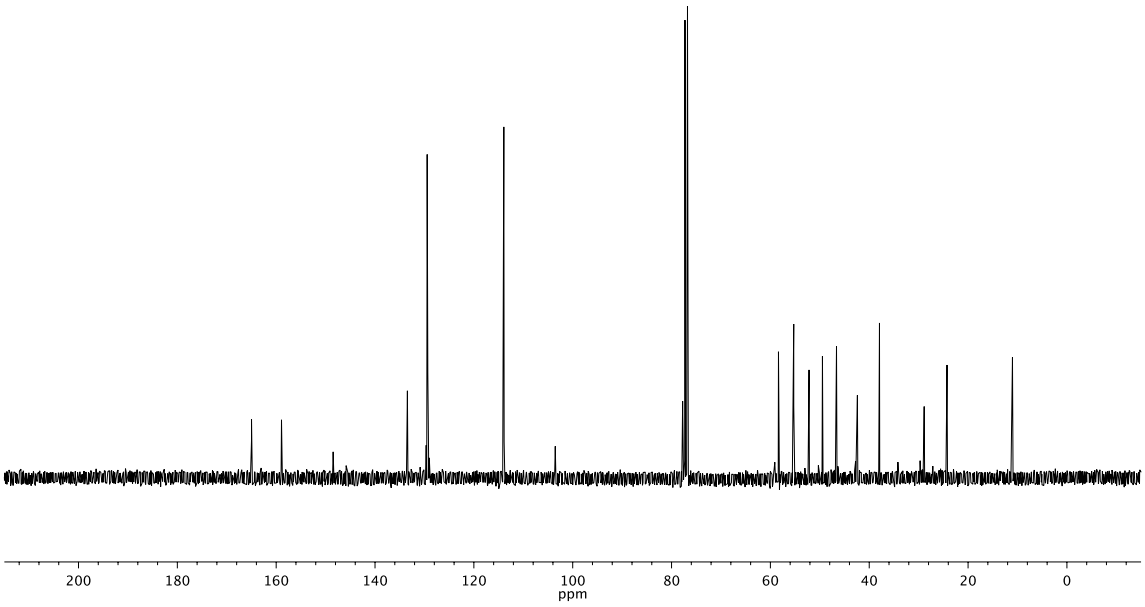


Figure A8.6. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **169**.

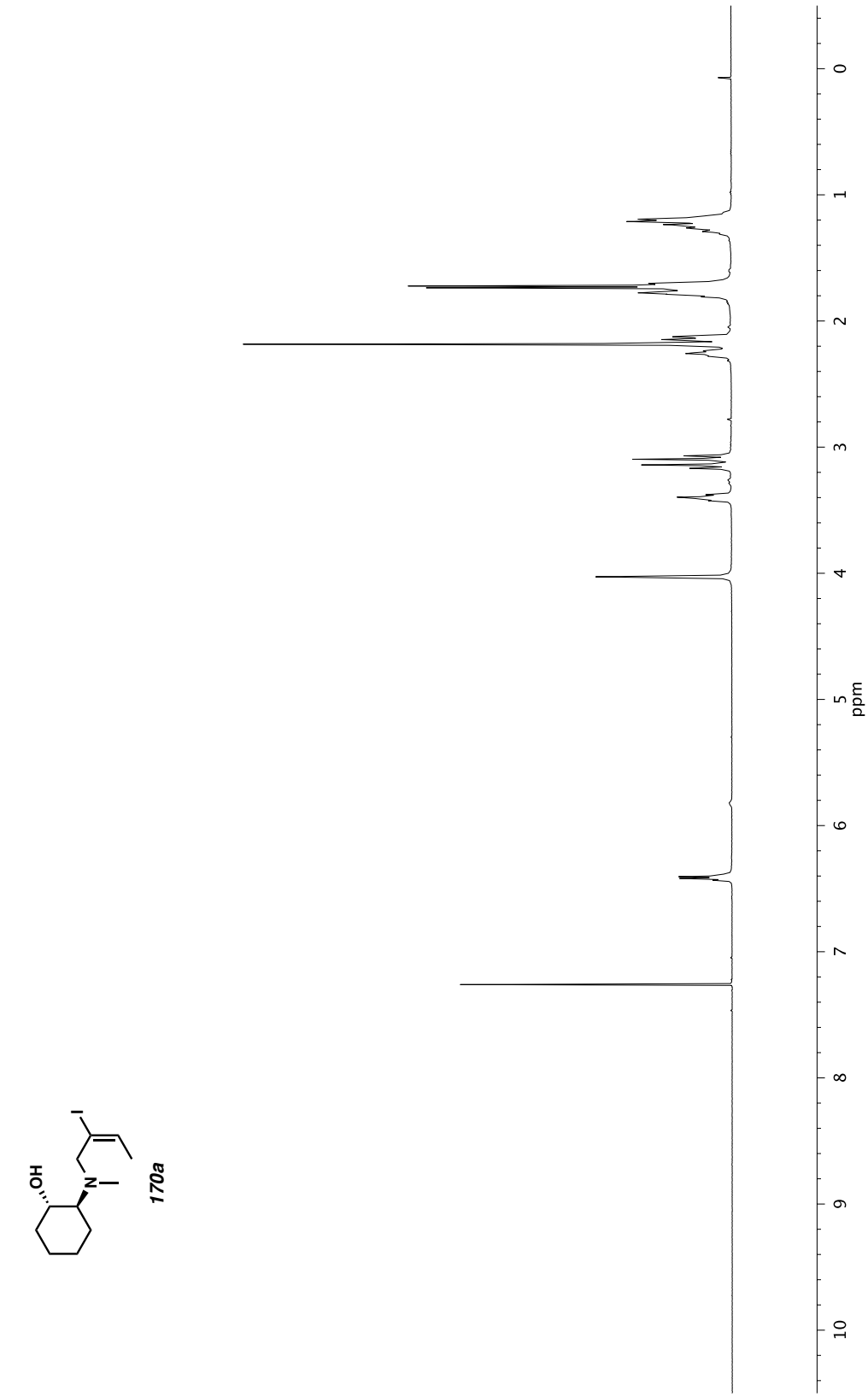


Figure A8.7. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **170a**.

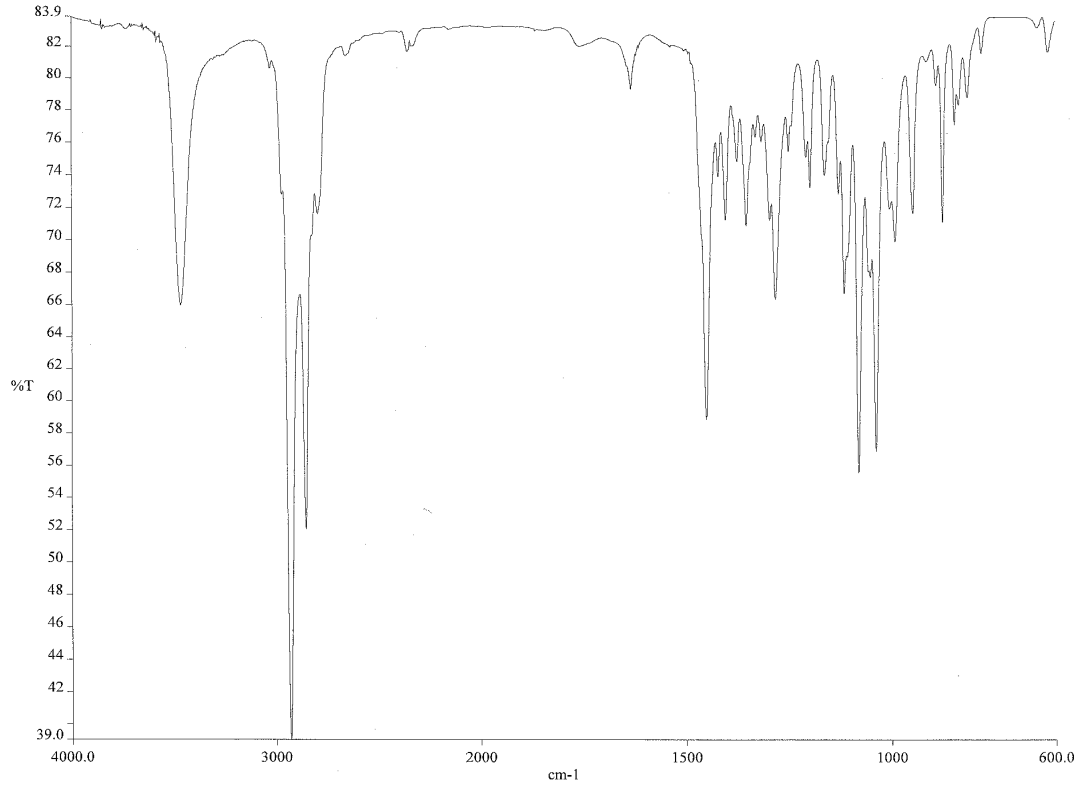


Figure A8.8. Infrared spectrum (Thin Film, NaCl) of compound **170a**.

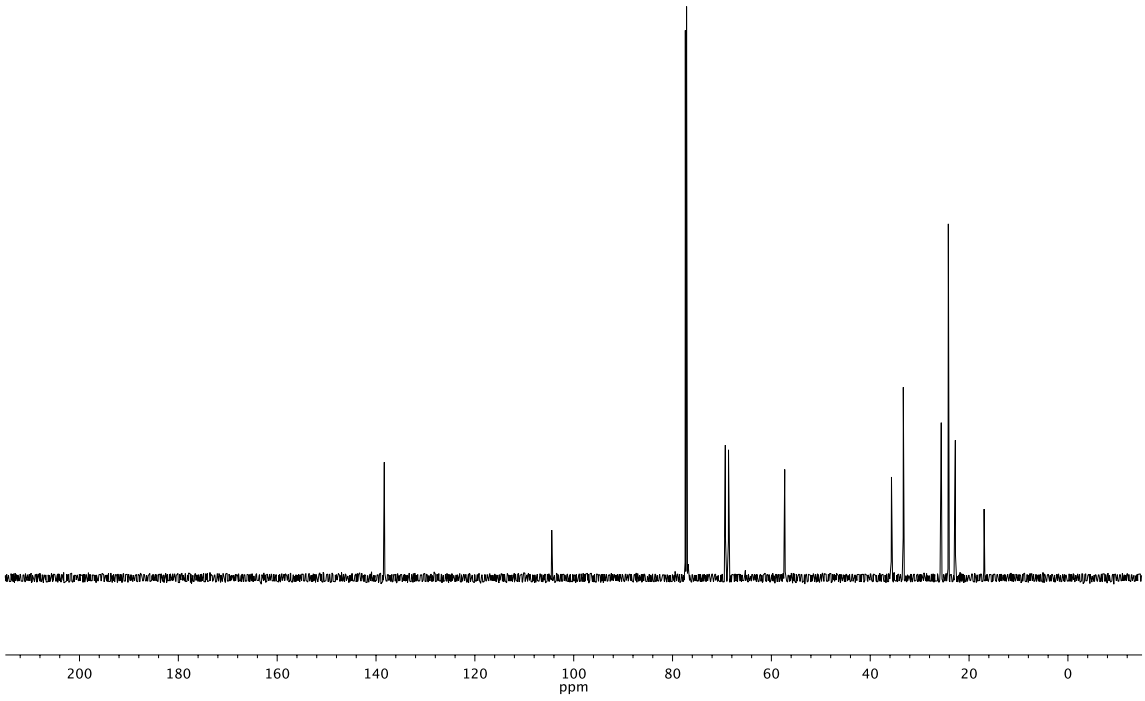


Figure A8.9. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **170a**.

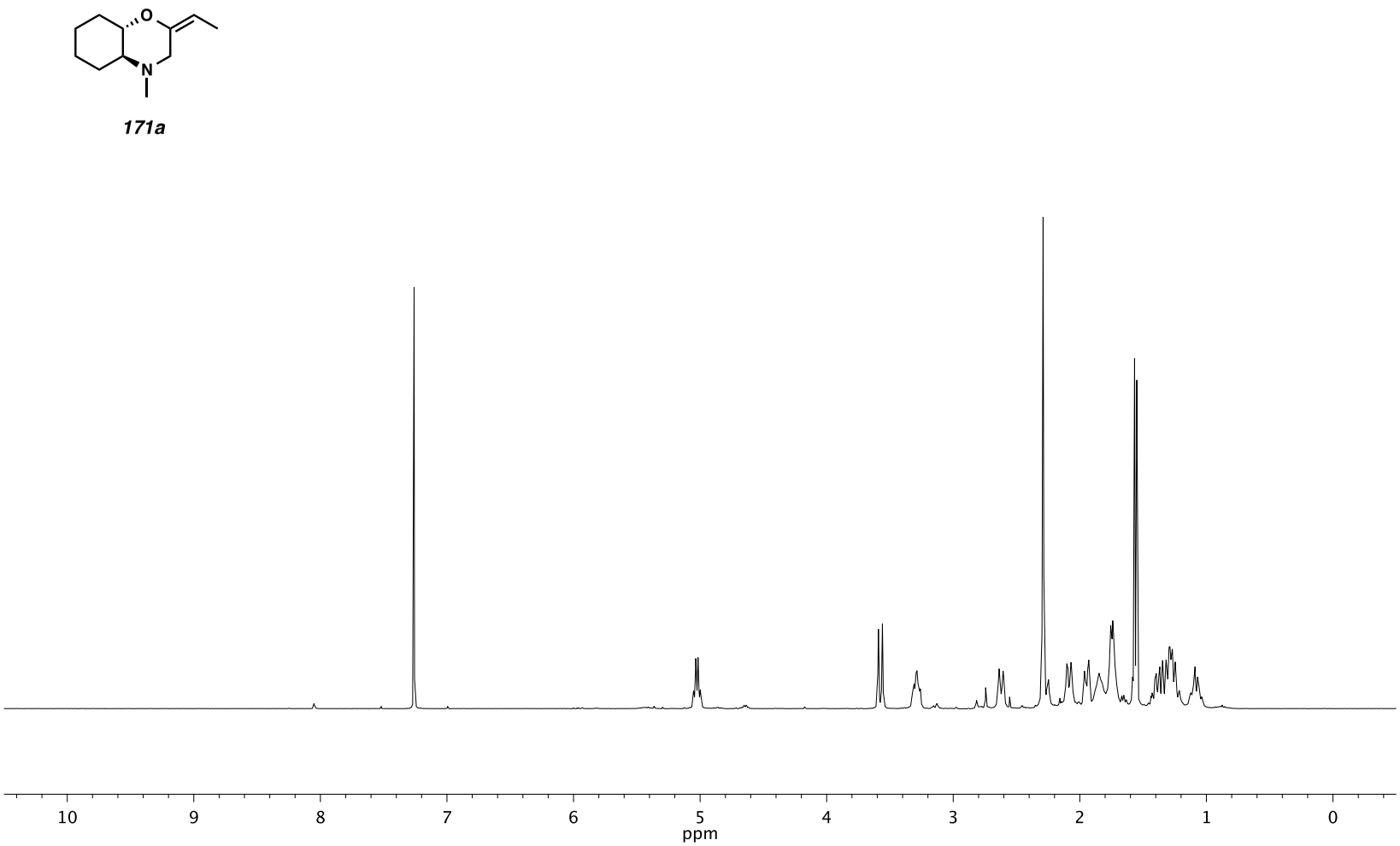


Figure A8.10. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **171a**.

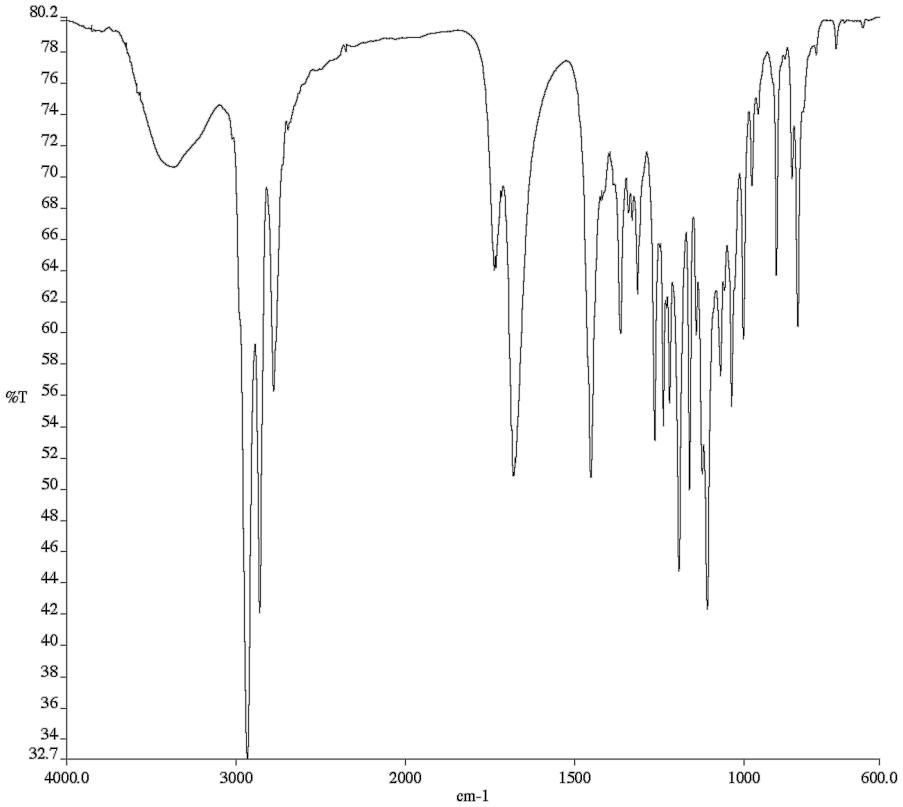


Figure A8.11. Infrared spectrum (Thin Film, NaCl) of compound **171a**.

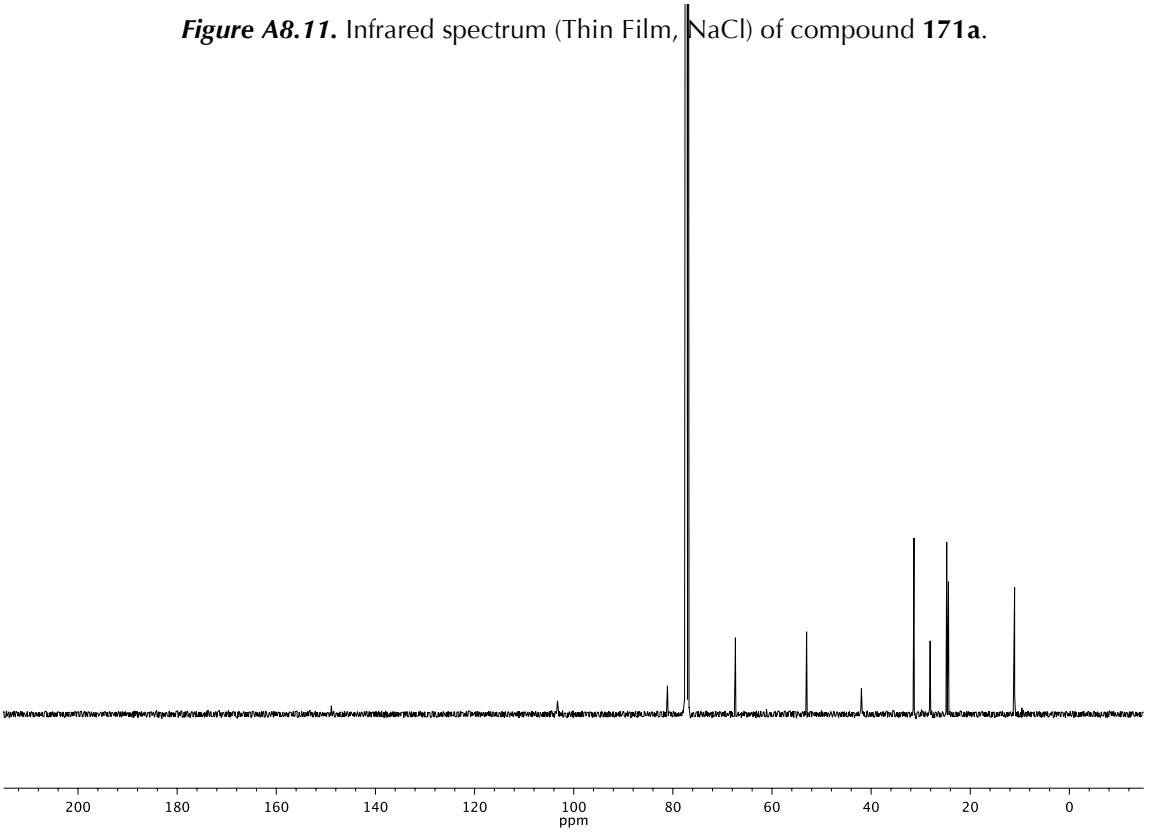


Figure A8.12. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **171a**.

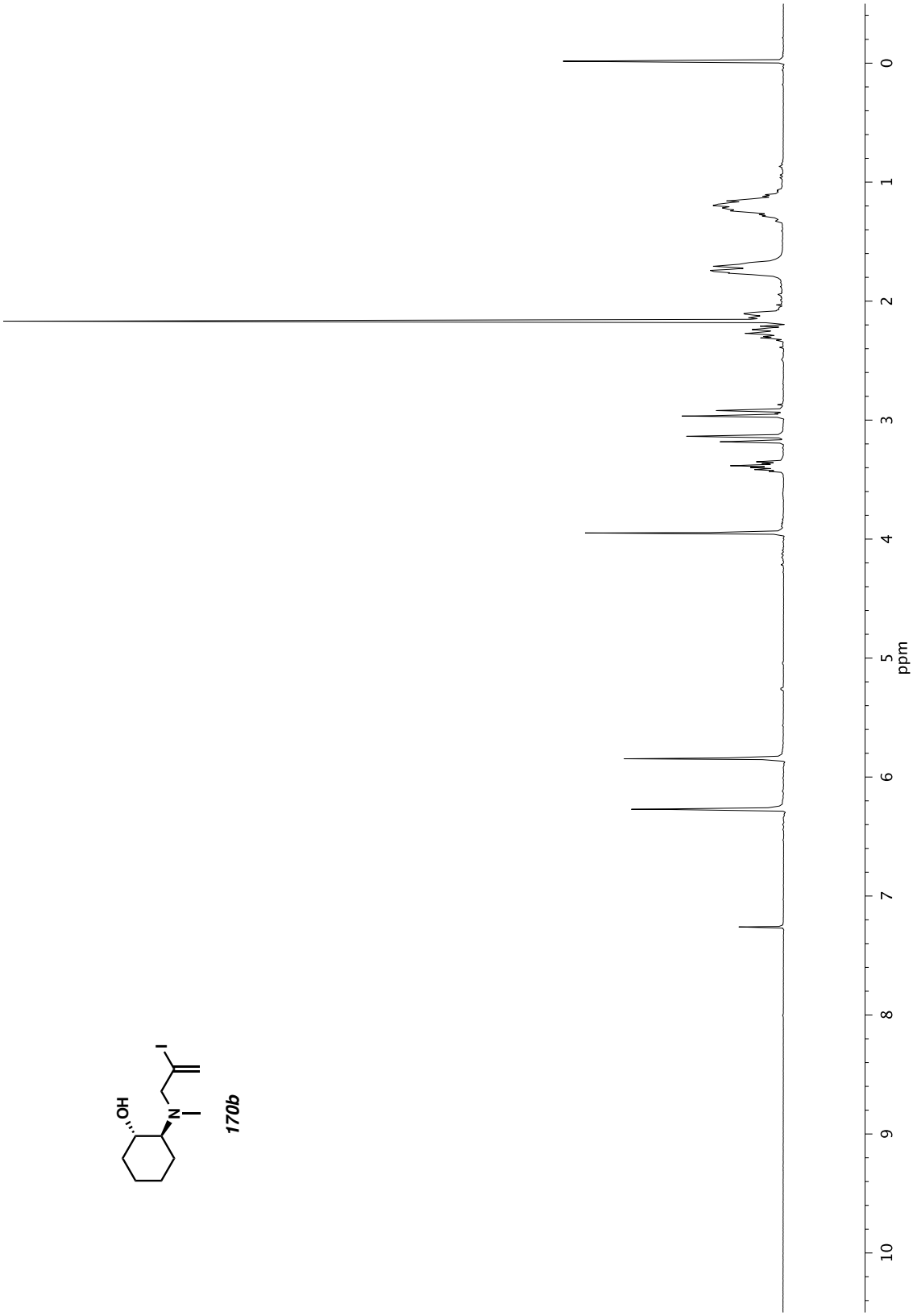


Figure A8.13. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **170b**.

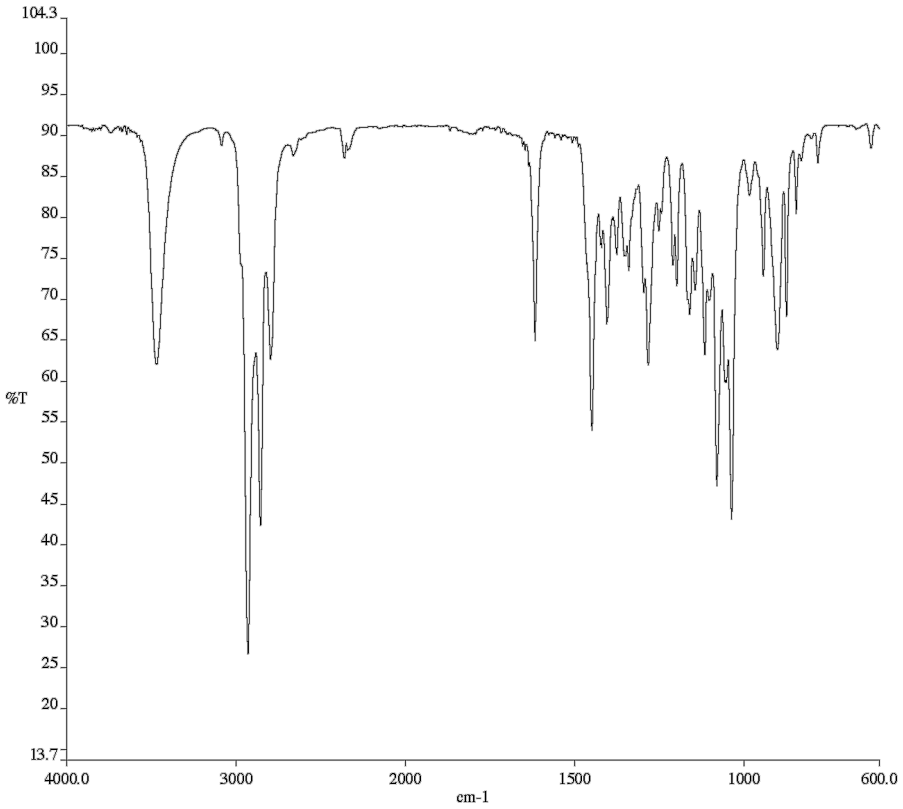


Figure A8.14. Infrared spectrum (Thin Film, NaCl) of compound **170b**.

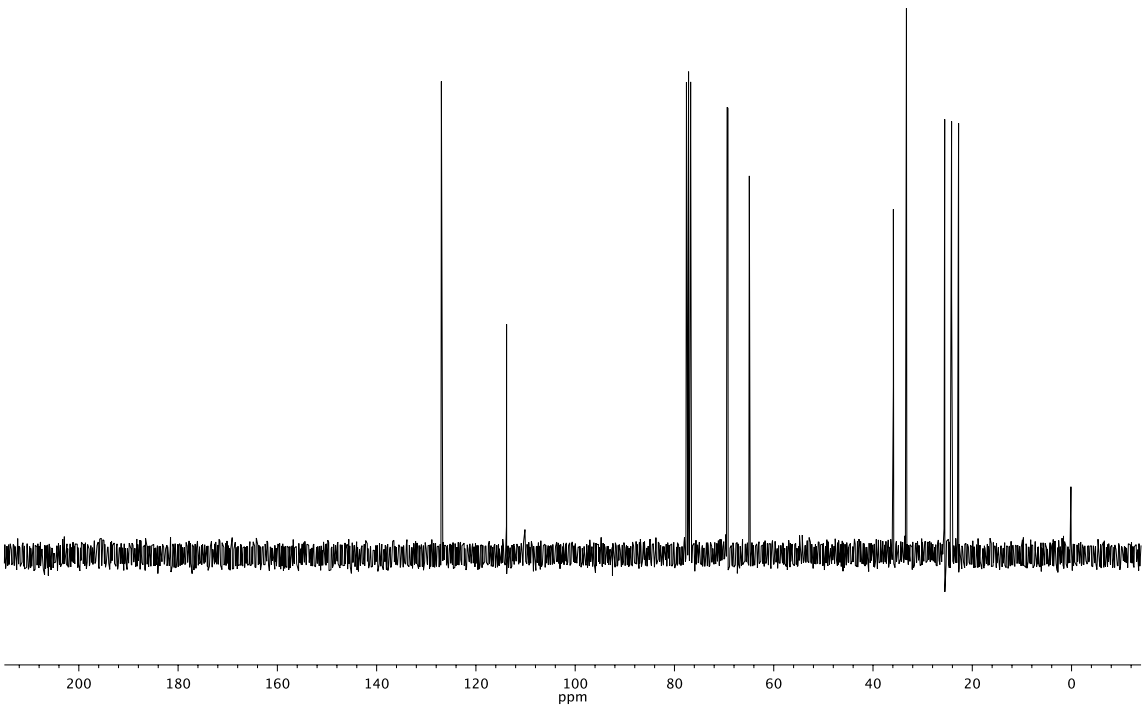
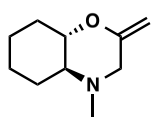


Figure A8.15. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **170b**.



171b

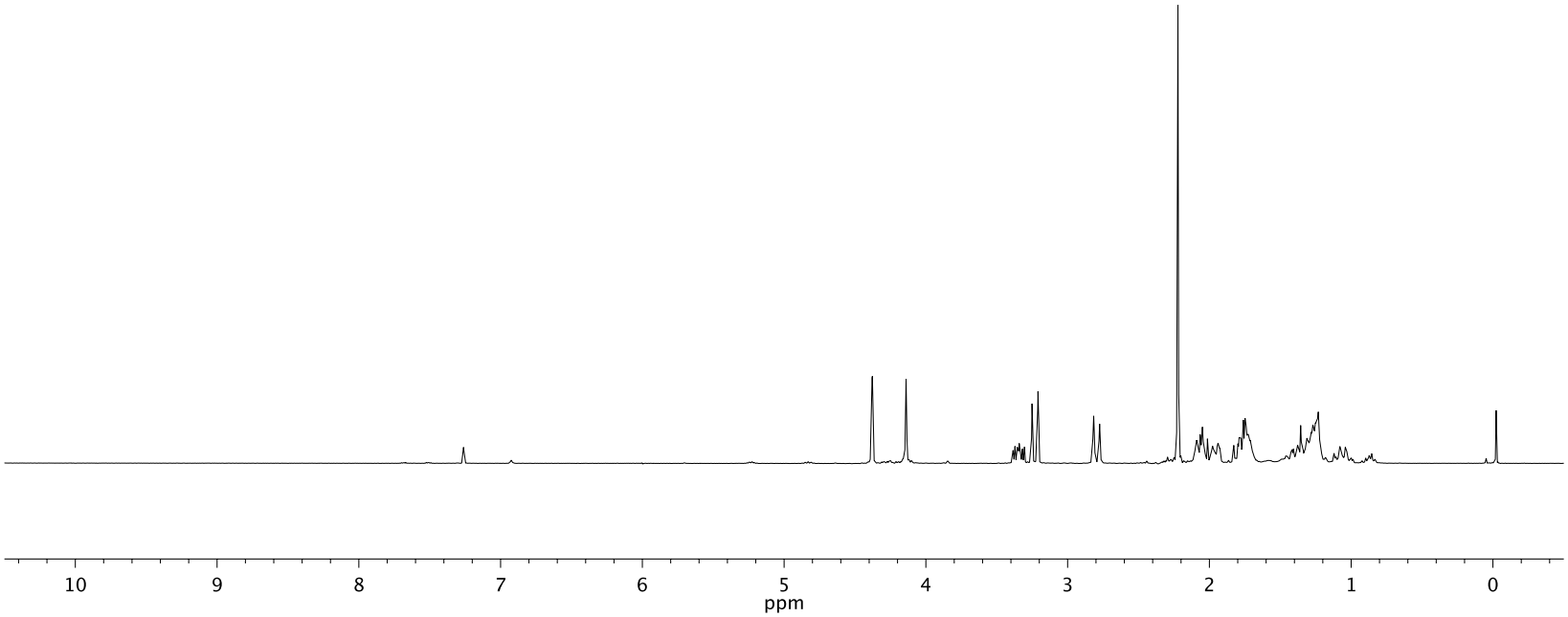


Figure A8.16. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **171b**.

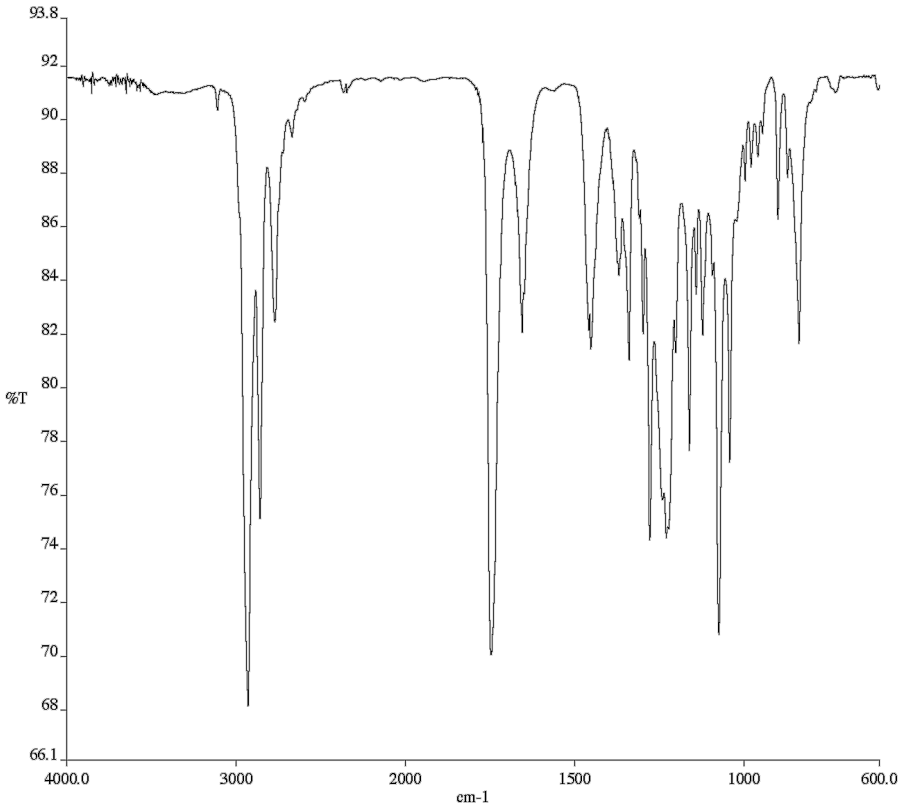


Figure A8.17. Infrared spectrum (Thin Film, NaCl) of compound **171b**.

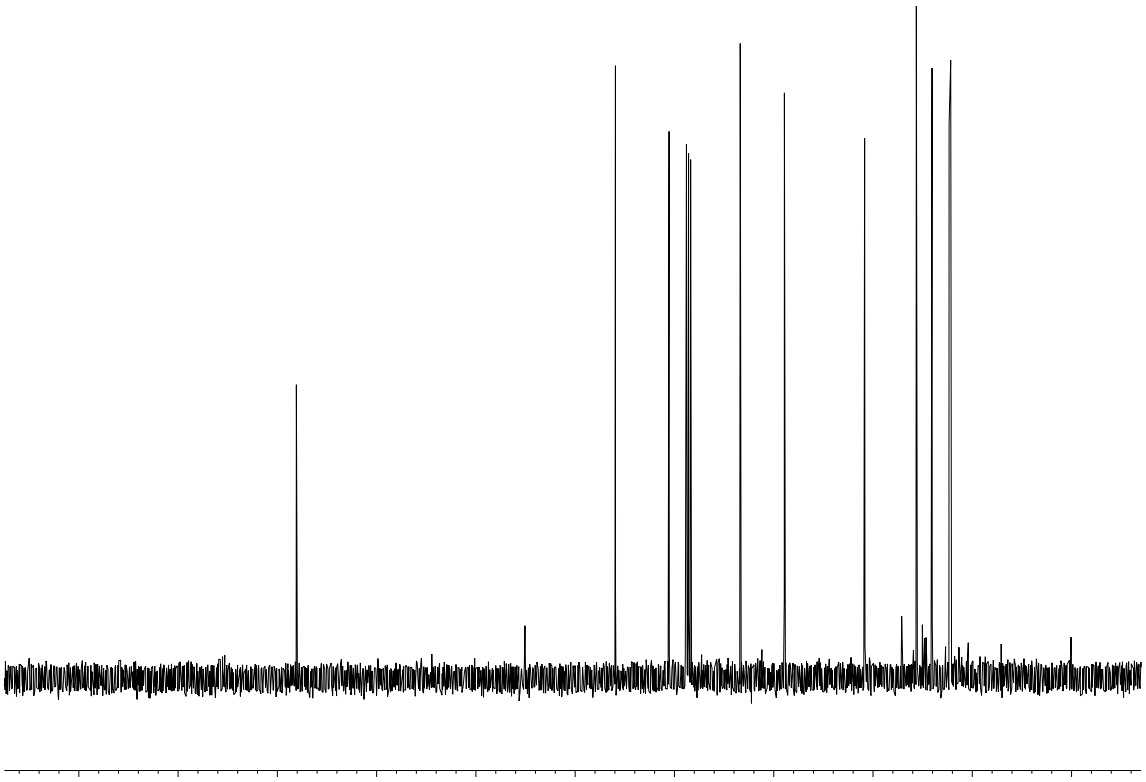


Figure A8.18. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **171b**.

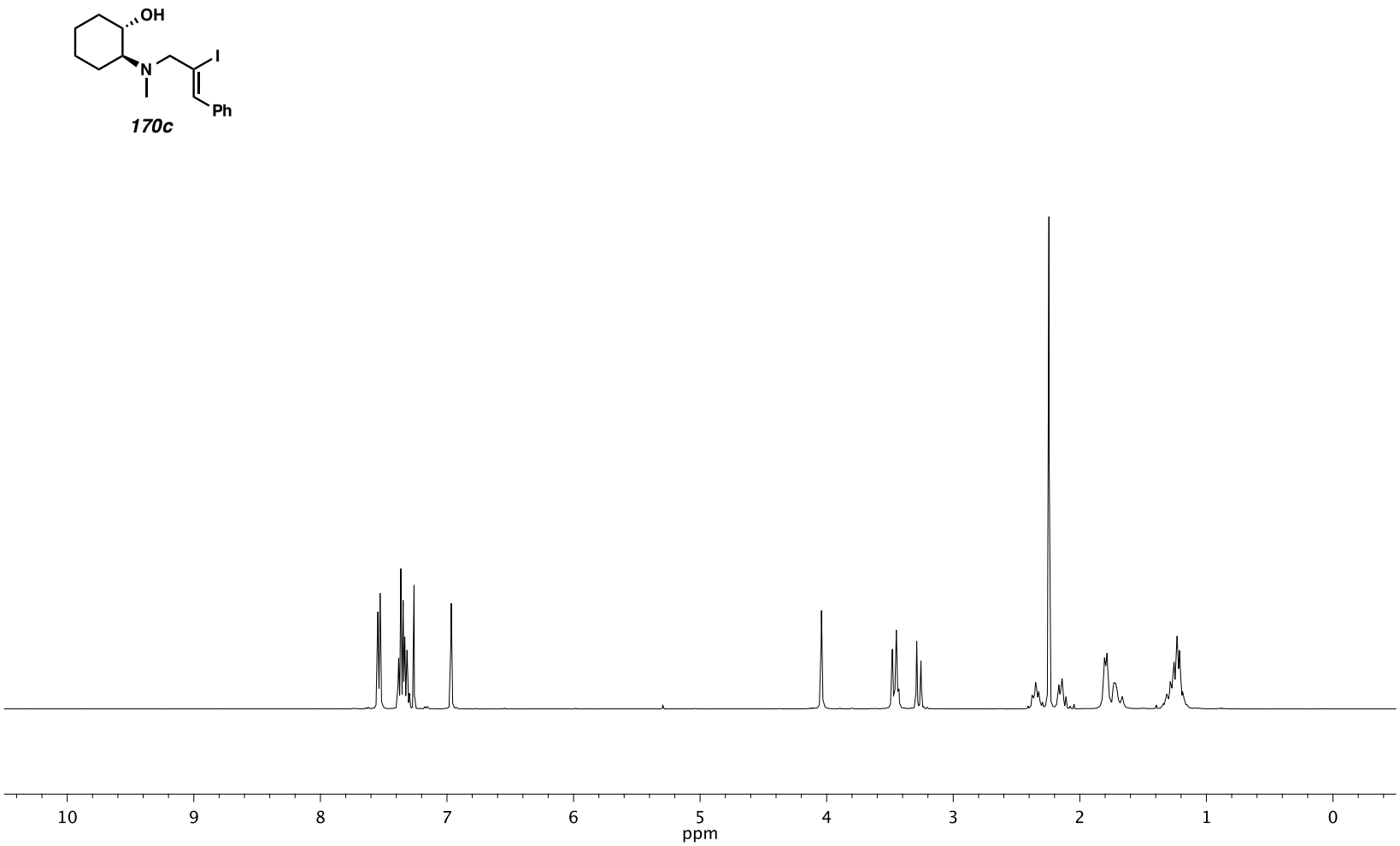


Figure A8.19. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **170c**.

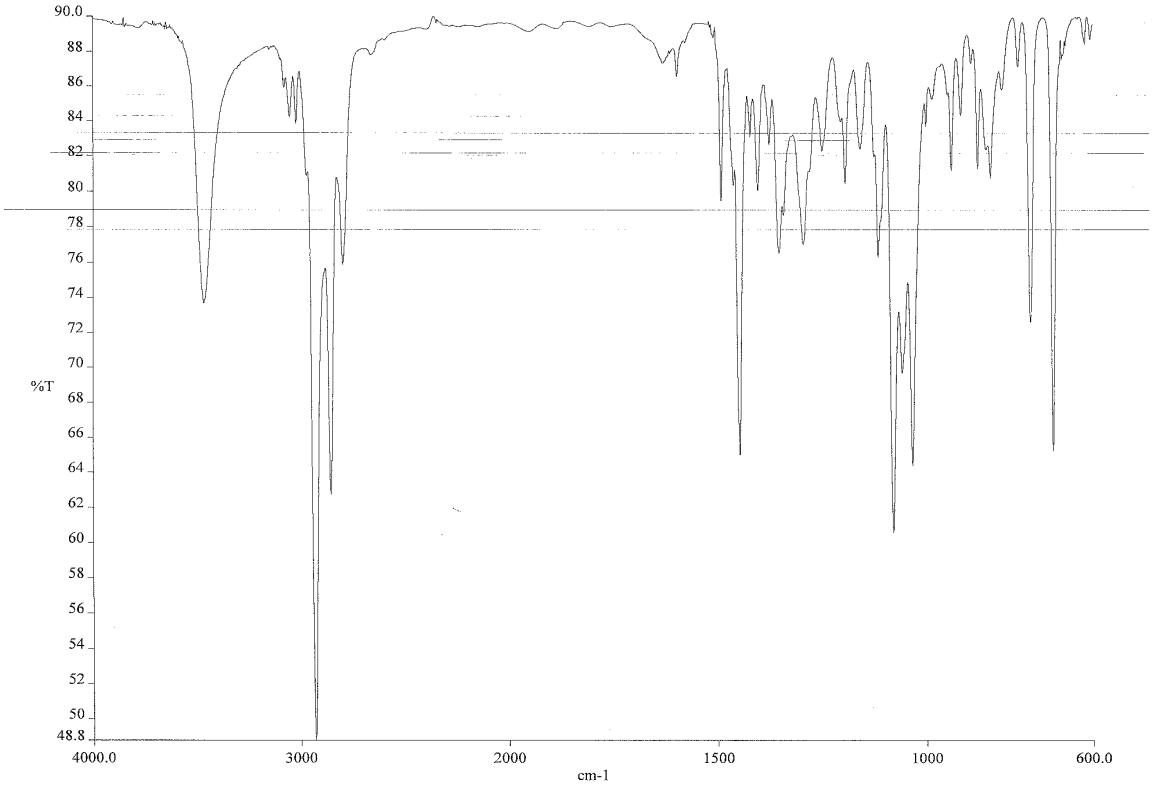


Figure A8.20. Infrared spectrum (Thin Film, NaCl) of compound **170c**.

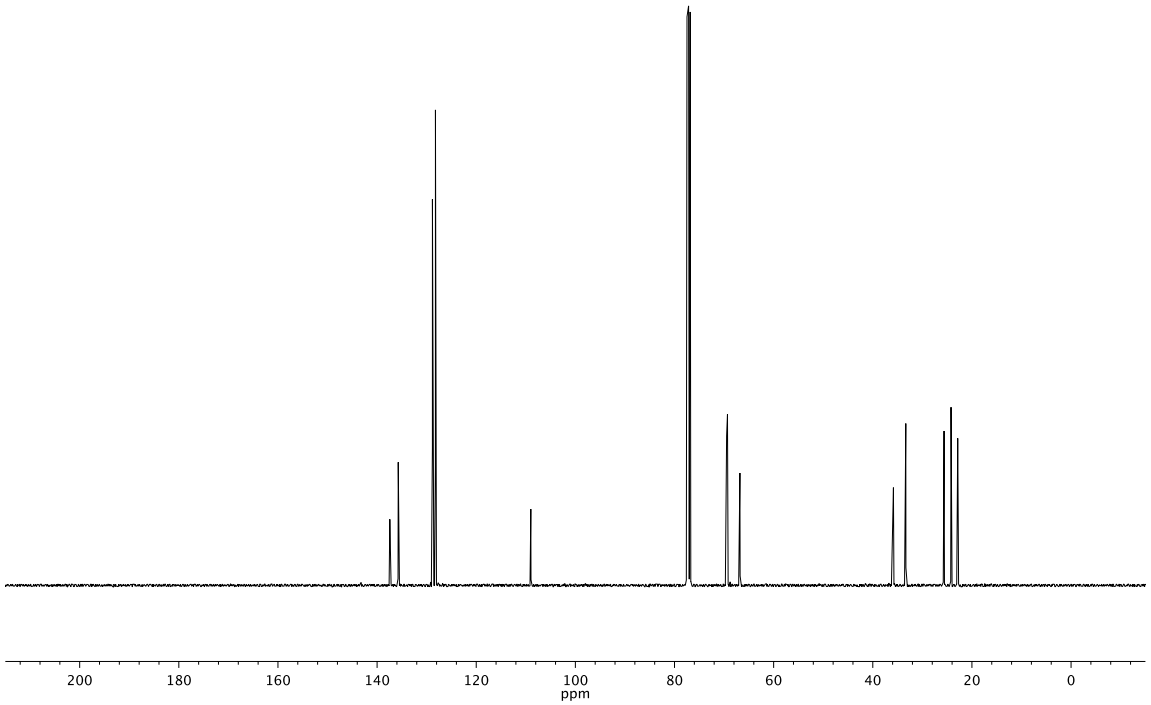


Figure A8.21. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **170c**.

Figure A8.22. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **171c**.

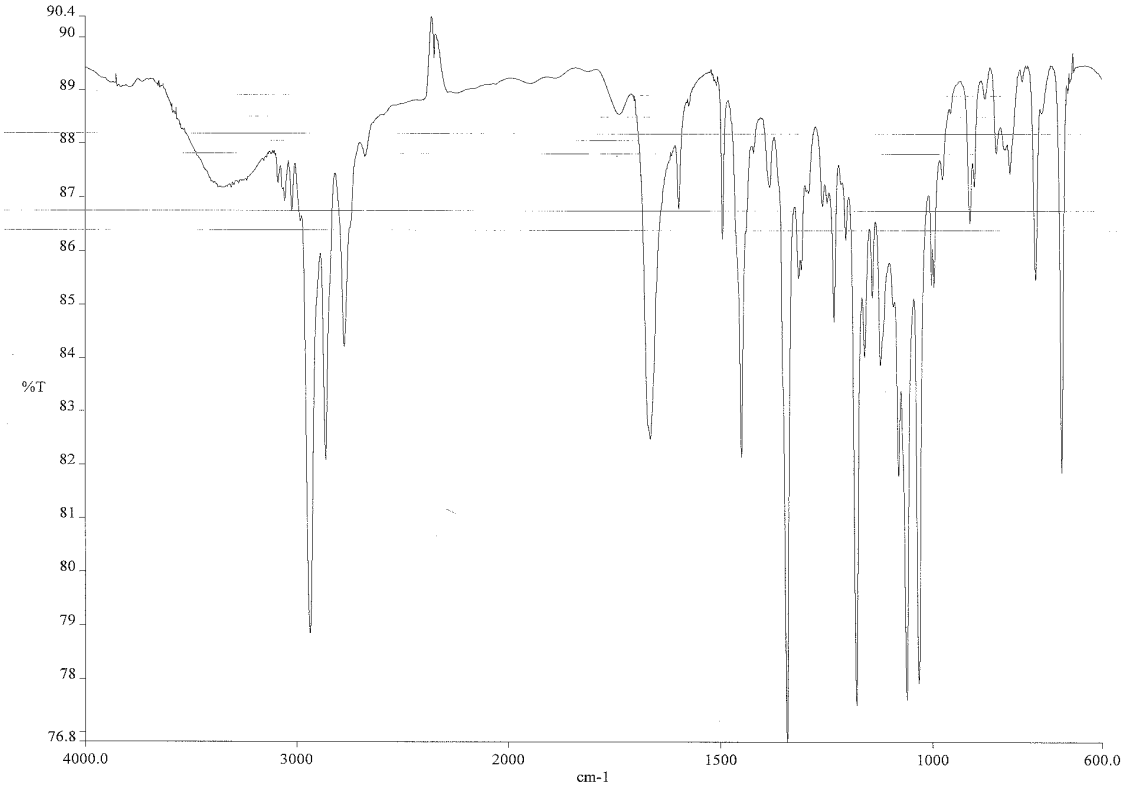


Figure A8.23. Infrared spectrum (Thin Film, NaCl) of compound **171c**.

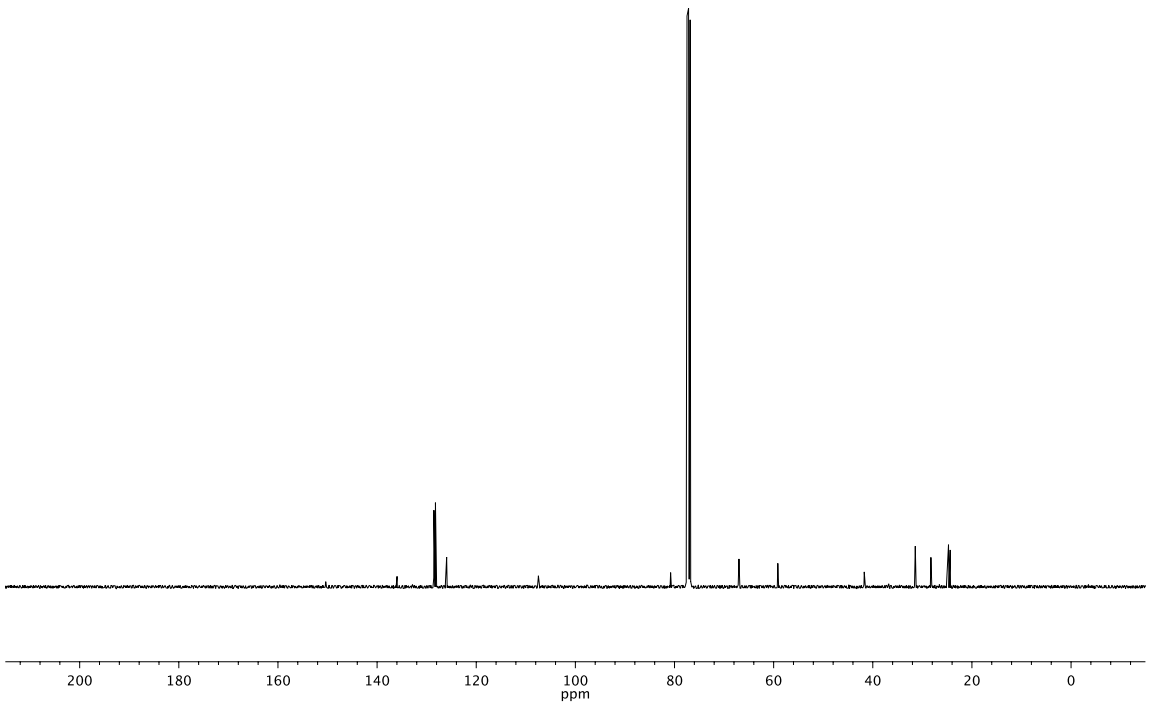


Figure A8.24. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **171c**.

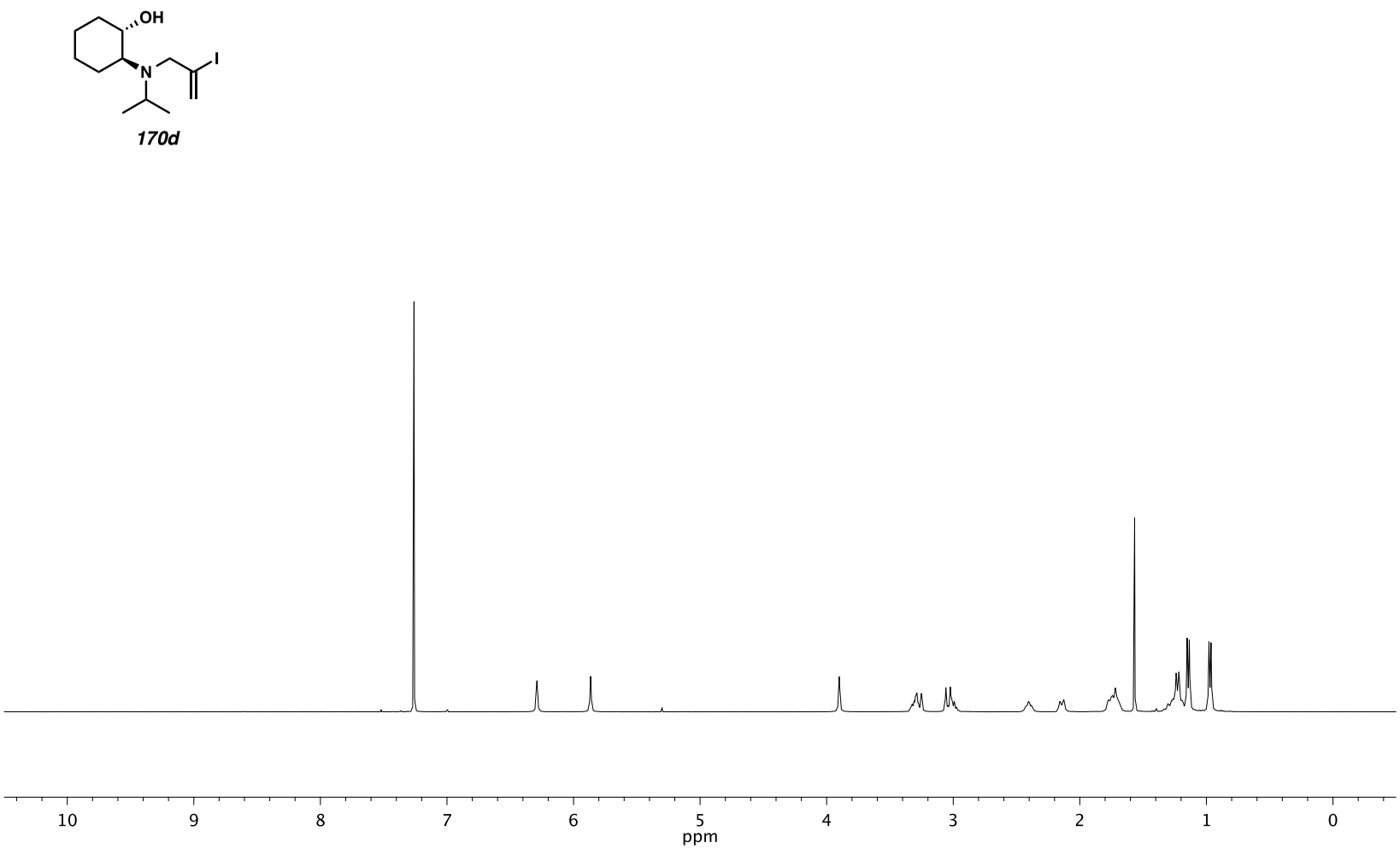


Figure A8.25. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **170d**.

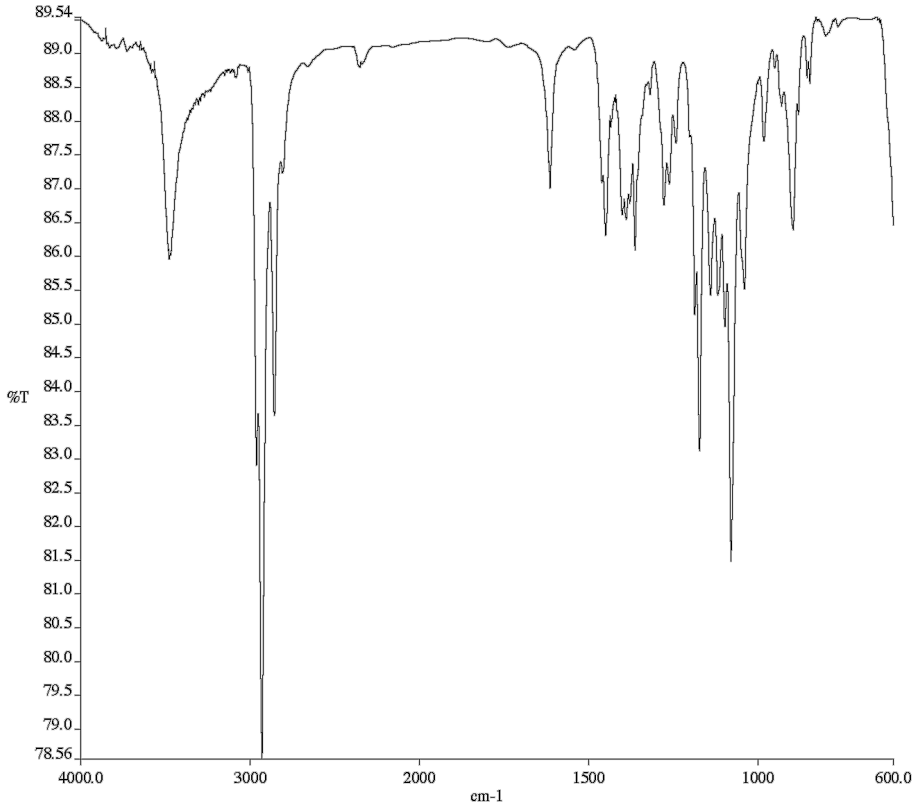


Figure A8.26. Infrared spectrum (Thin Film, NaCl) of compound **170d**.

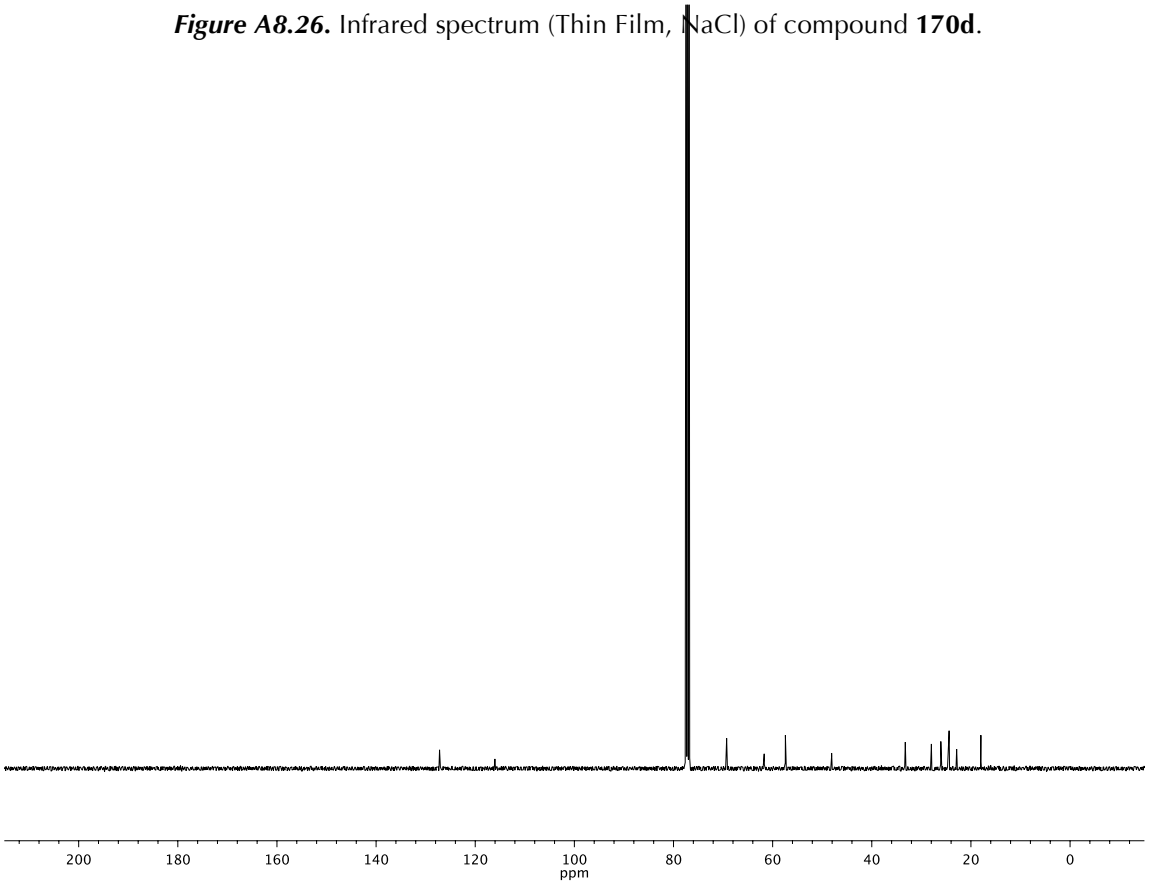


Figure A8.27. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **170d**.

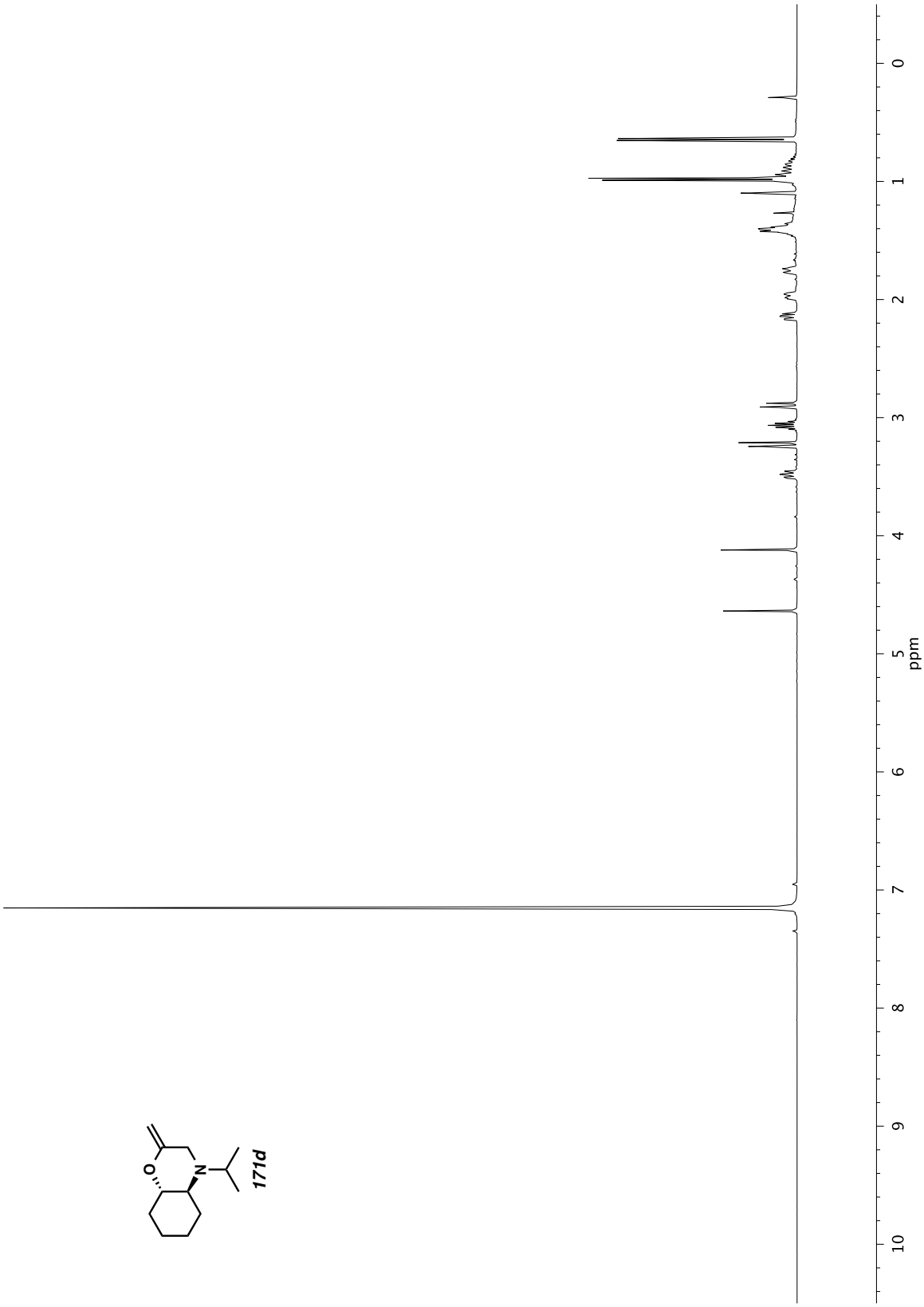


Figure A8.28. ^{1}H NMR (400 MHz, C_6D_6) of compound **171d**.

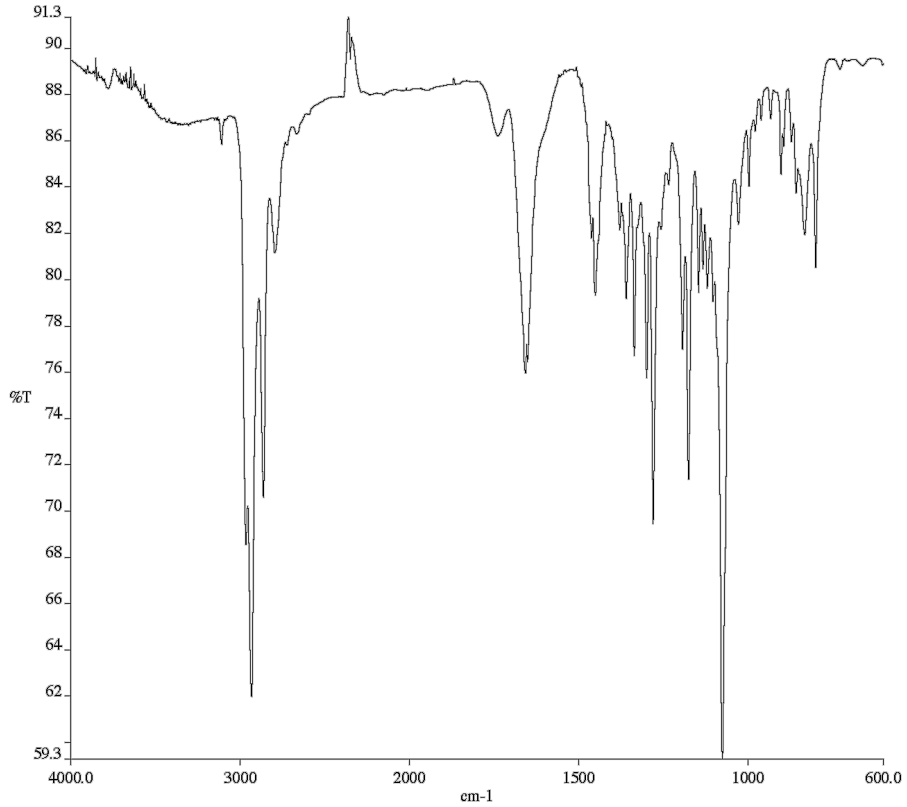


Figure A8.29. Infrared spectrum (Thin Film, NaCl) of compound **171d**.

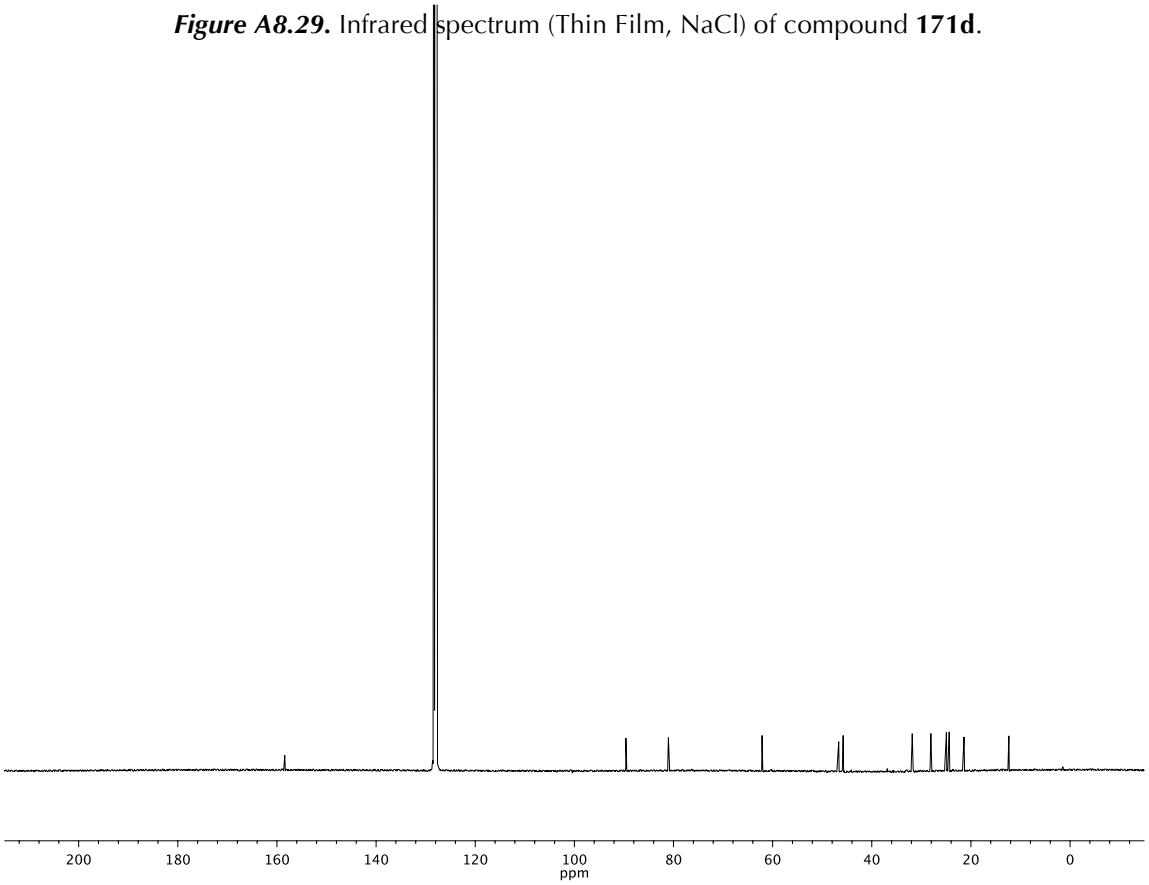


Figure A8.30. ^{13}C NMR (101 MHz, C_6D_6) of compound **171d**.

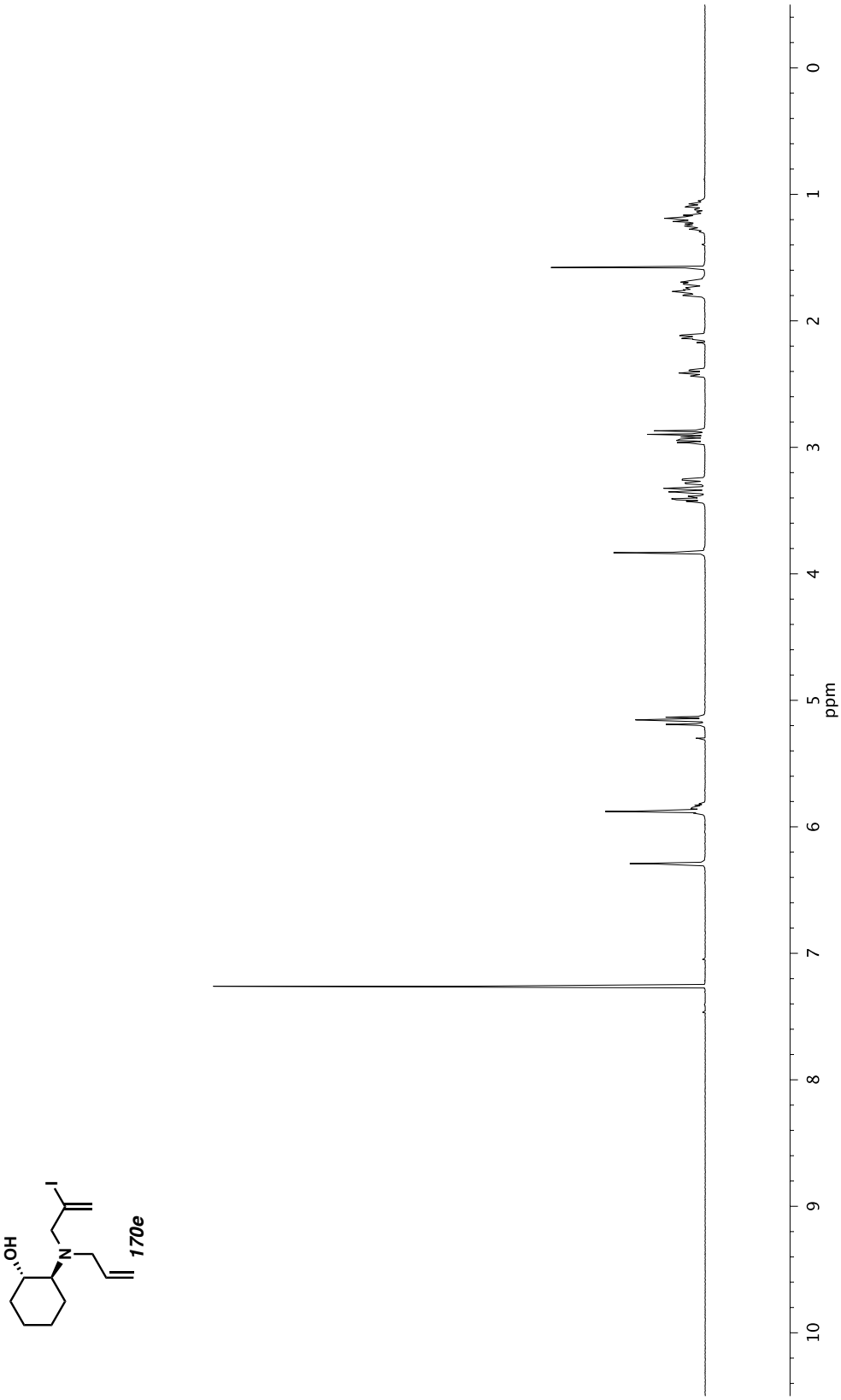


Figure A8.31. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **170e**.

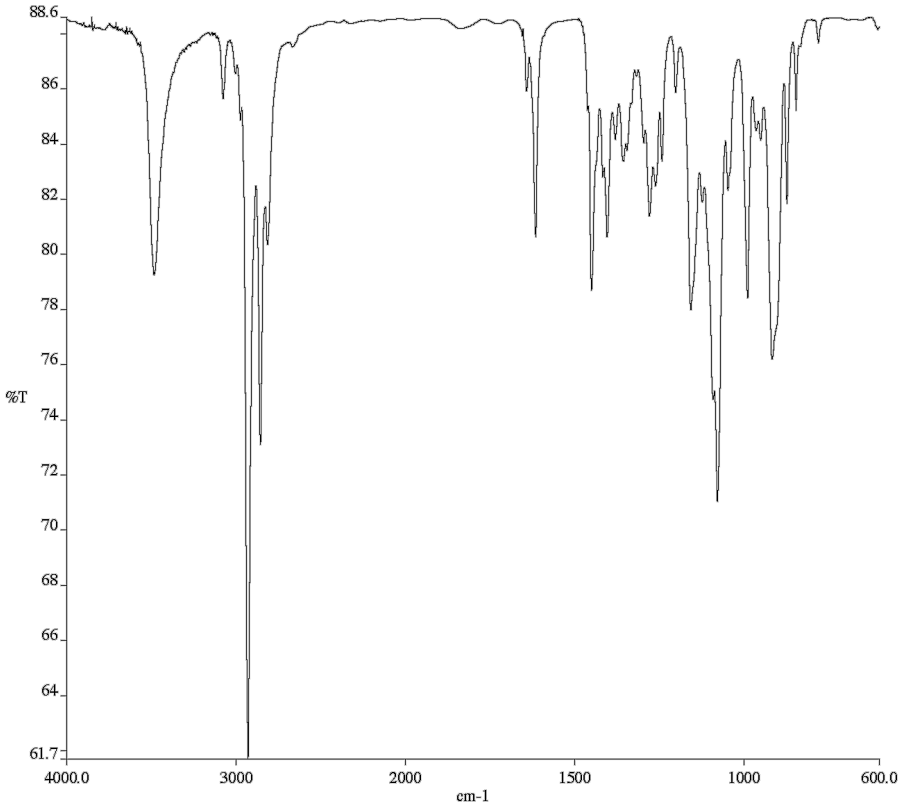


Figure A8.32. Infrared spectrum (Thin Film, NaCl) of compound **170e**.

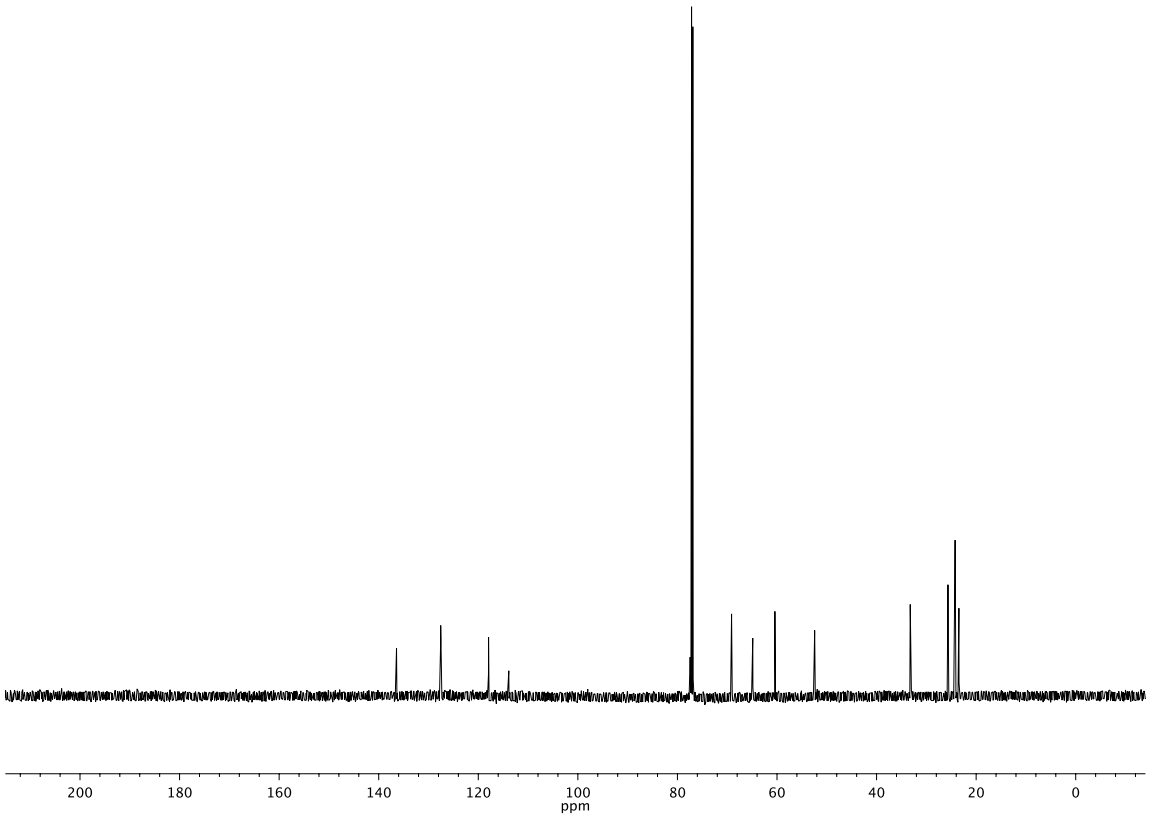


Figure A8.33. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **170e**.

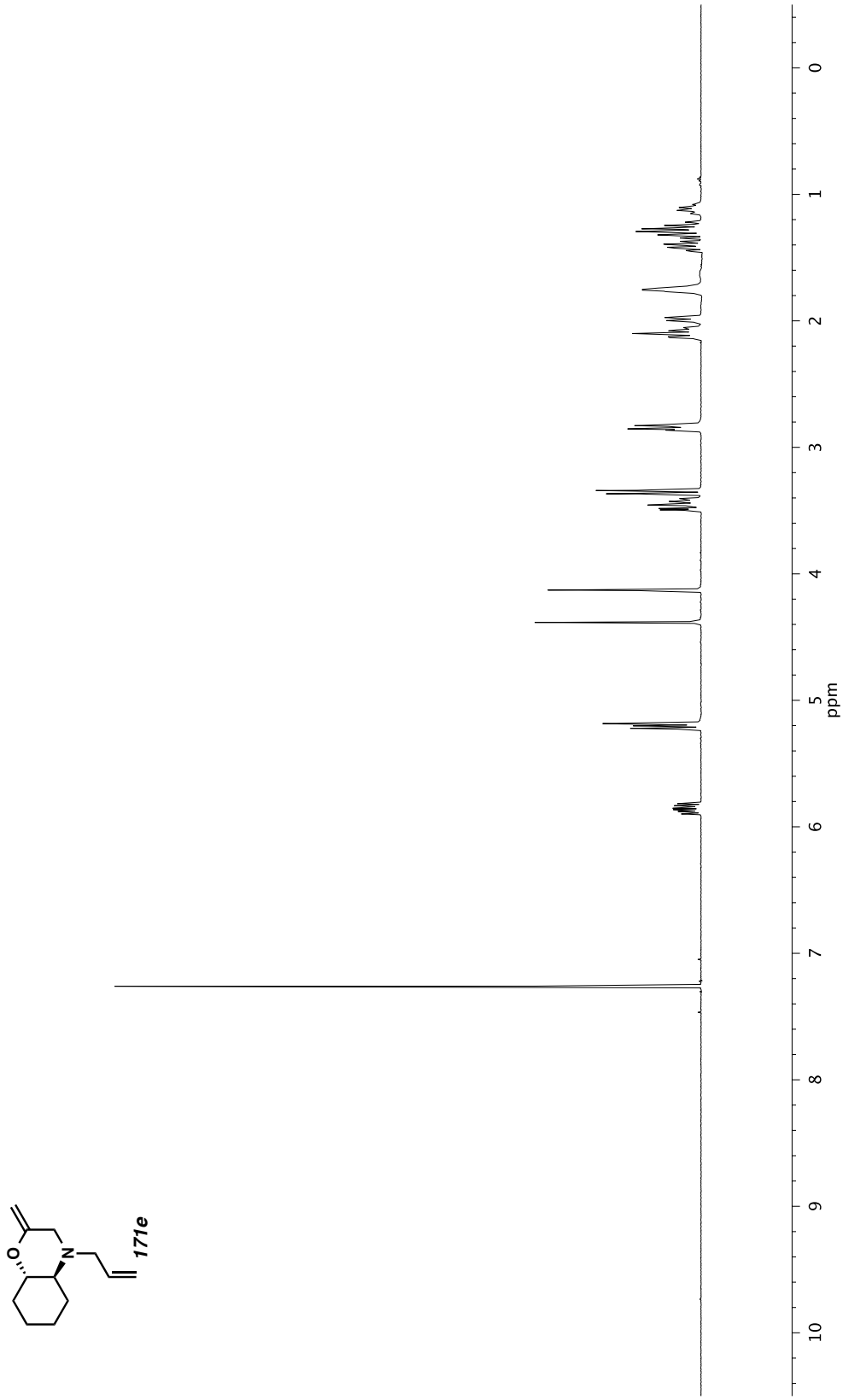


Figure A8.34. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **171e**.

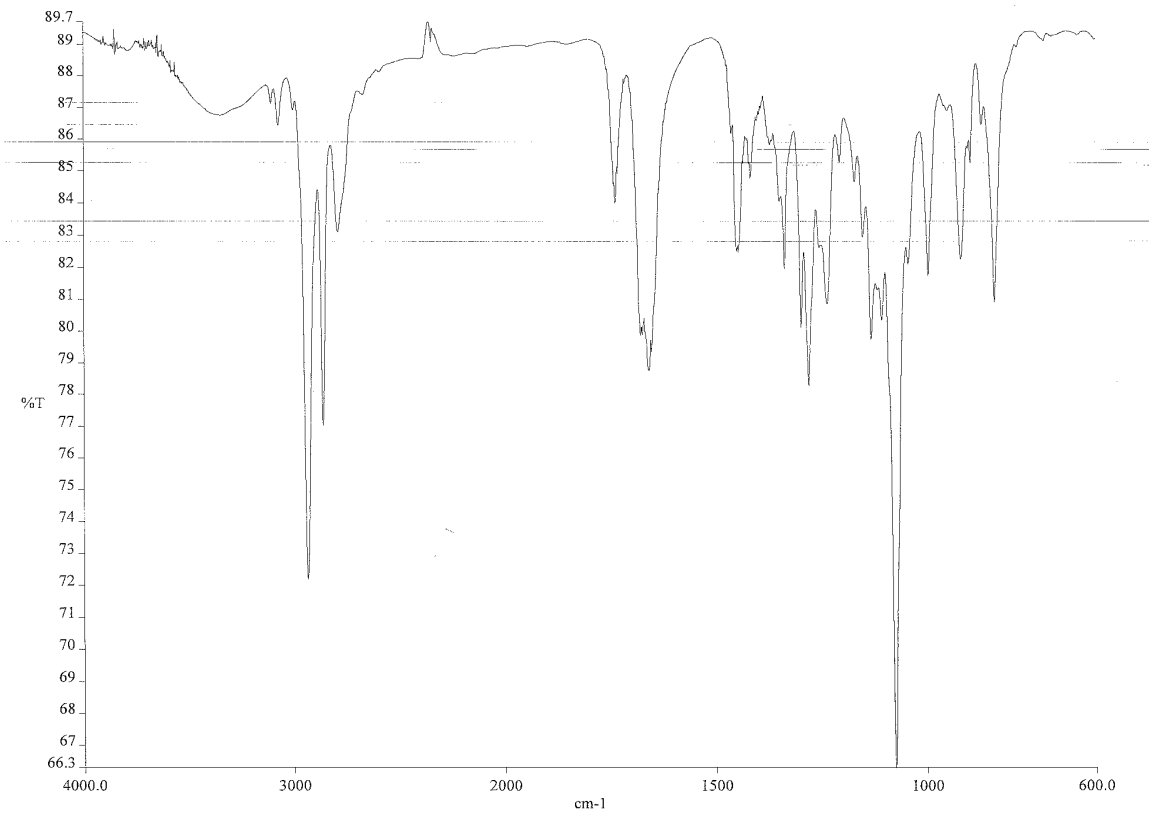


Figure A8.35. Infrared spectrum (Thin Film, NaCl) of compound **171e**.

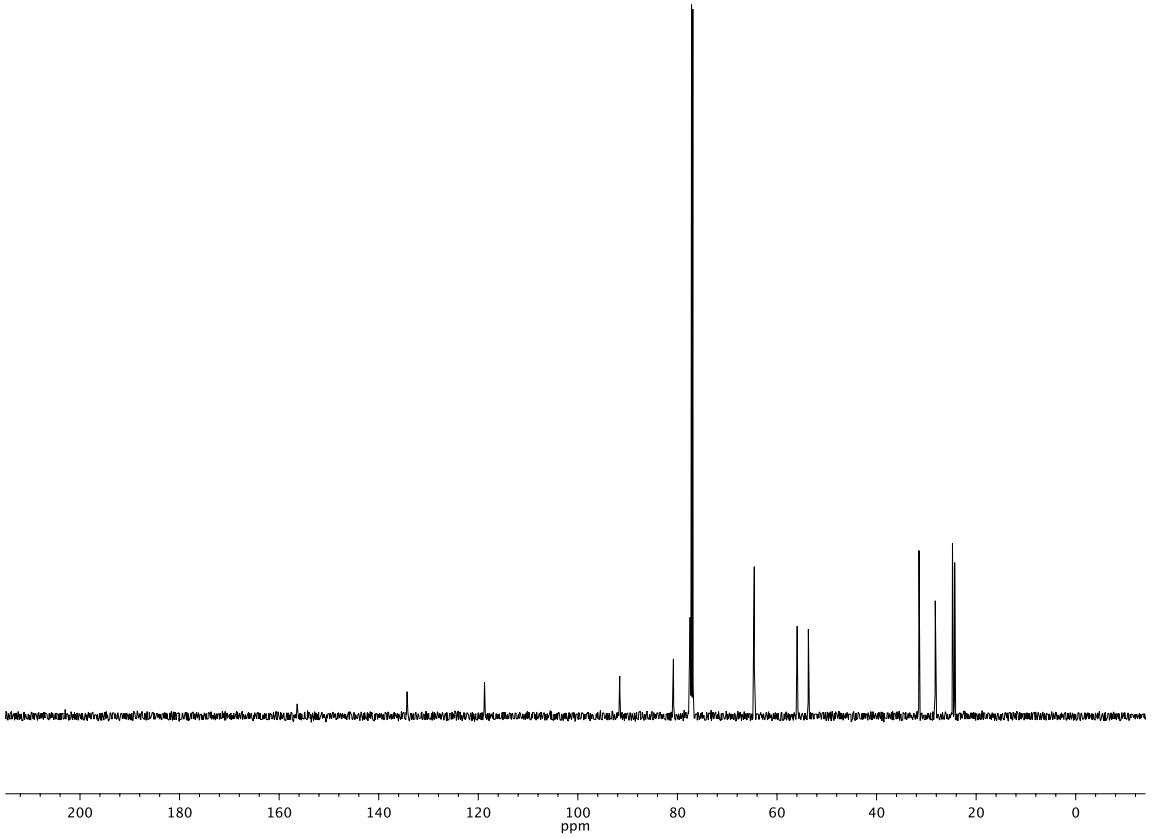


Figure A8.36. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **171e**.

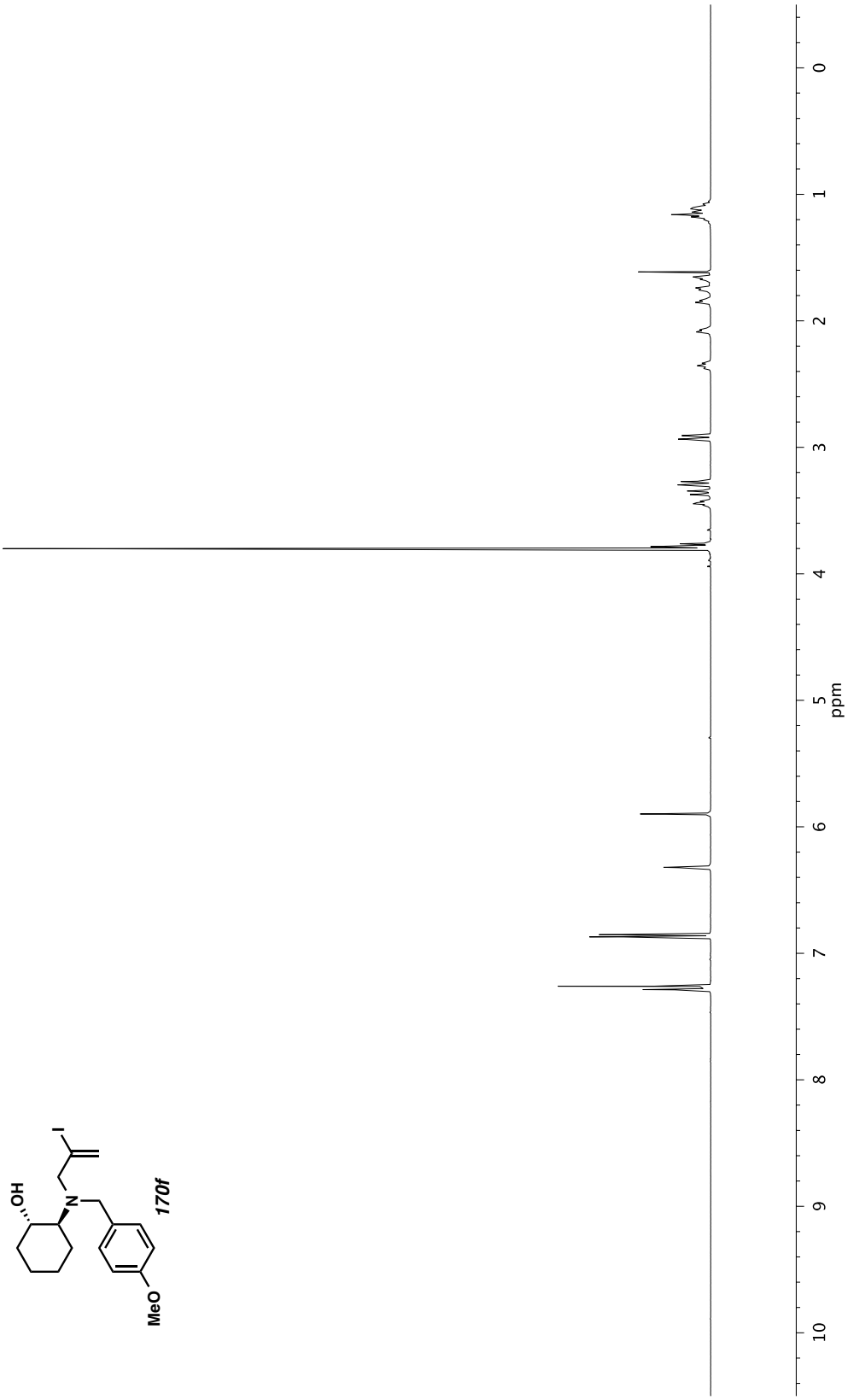


Figure A8.37. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **170f**.

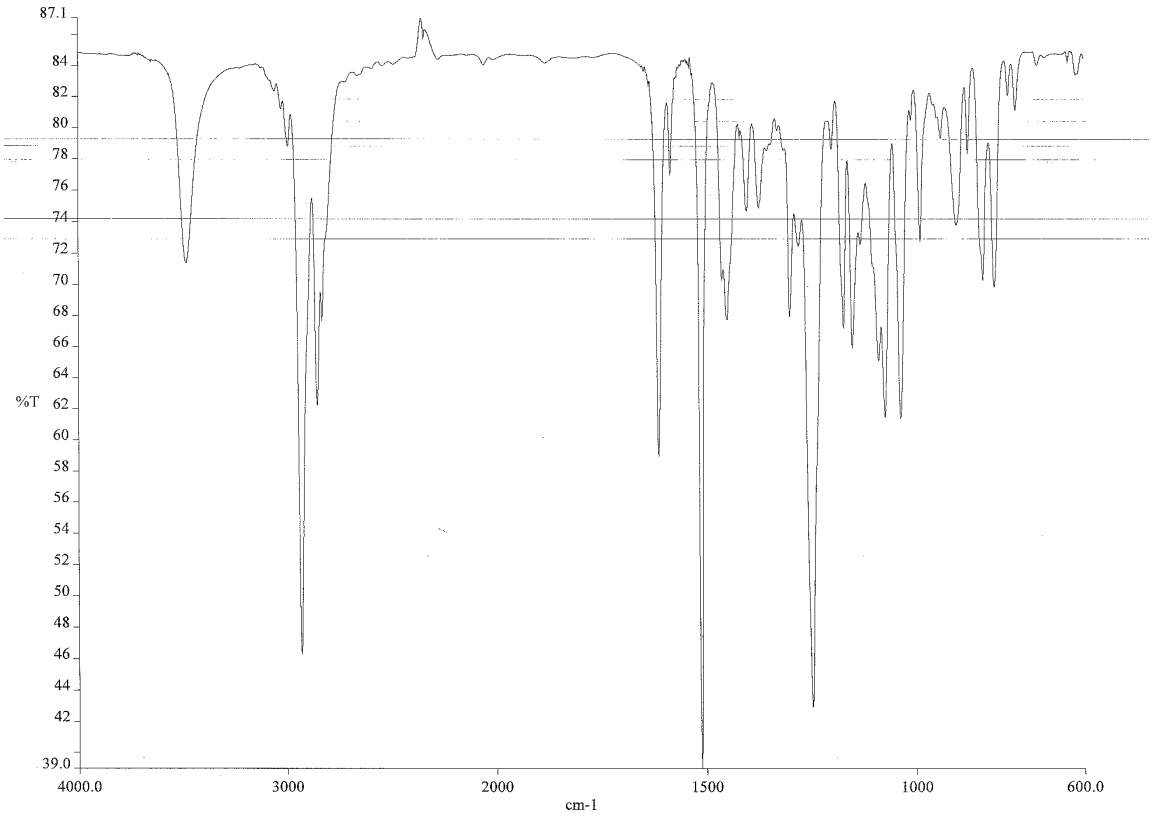


Figure A8.38. Infrared spectrum (Thin Film, NaCl) of compound **170f**.

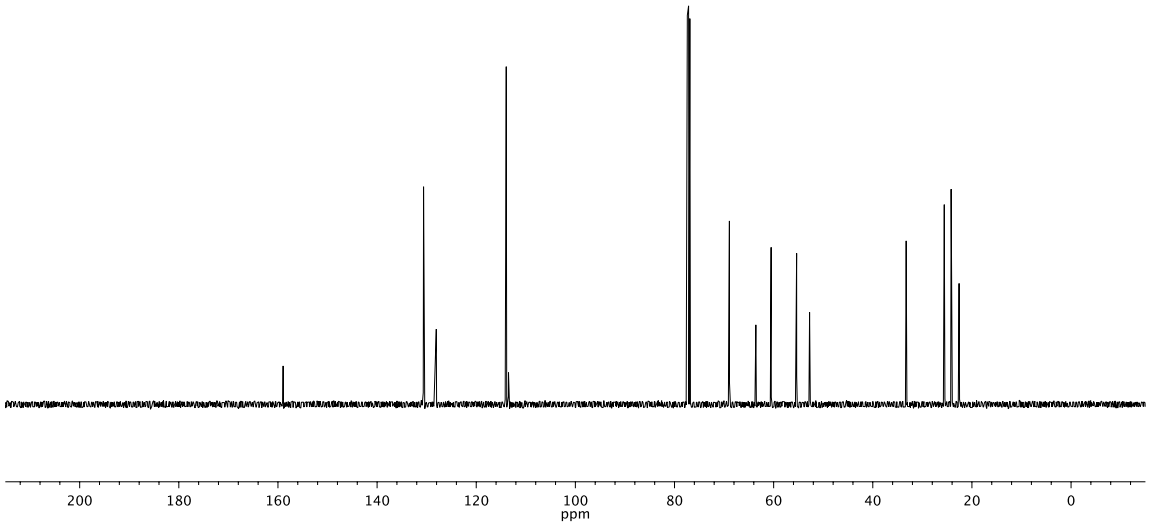


Figure A8.39. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **170f**.

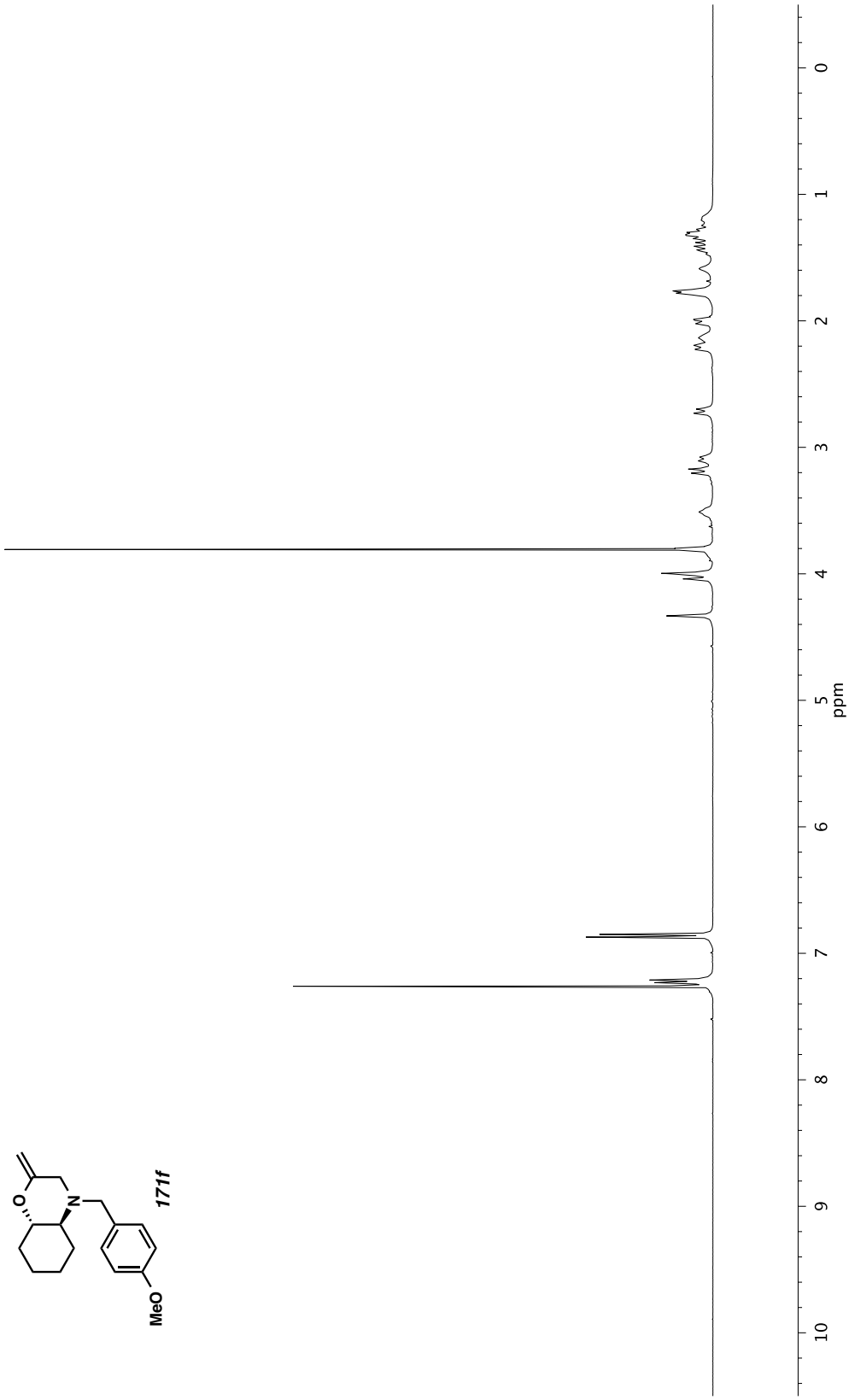


Figure A8.40. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **171f**.

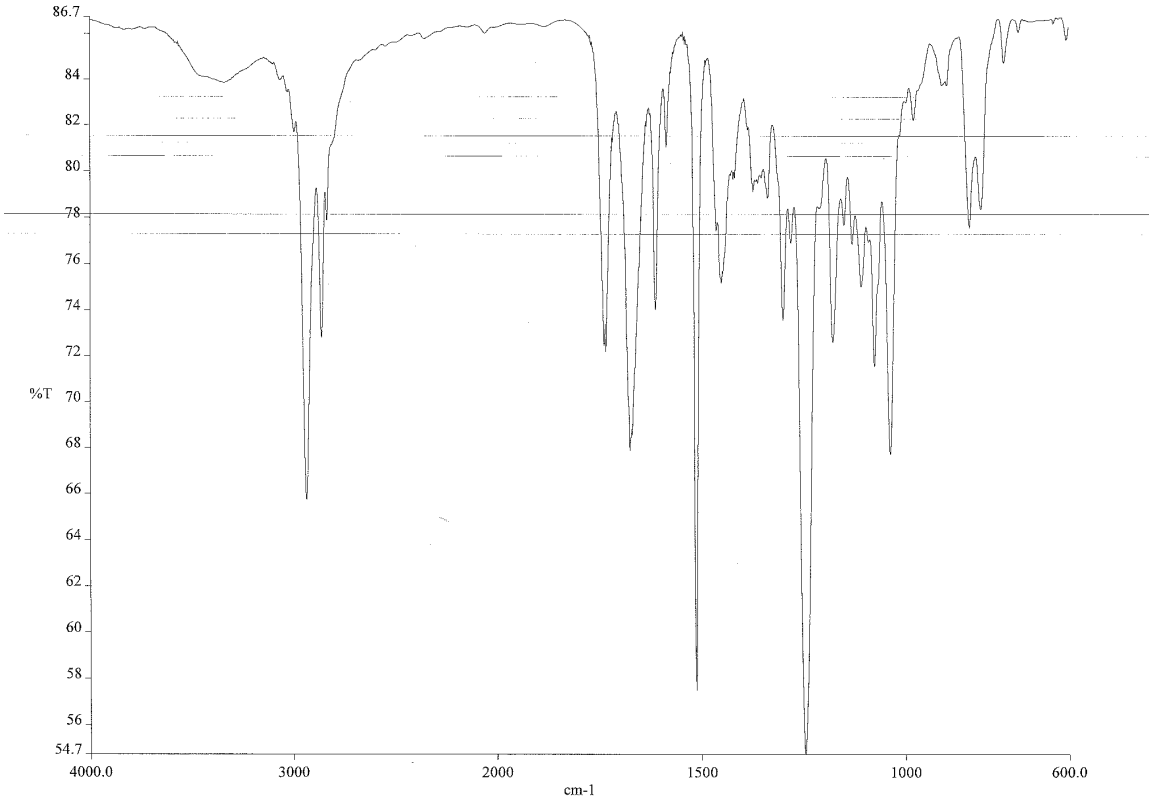


Figure A8.41. Infrared spectrum (Thin Film, NaCl) of compound **171f**.

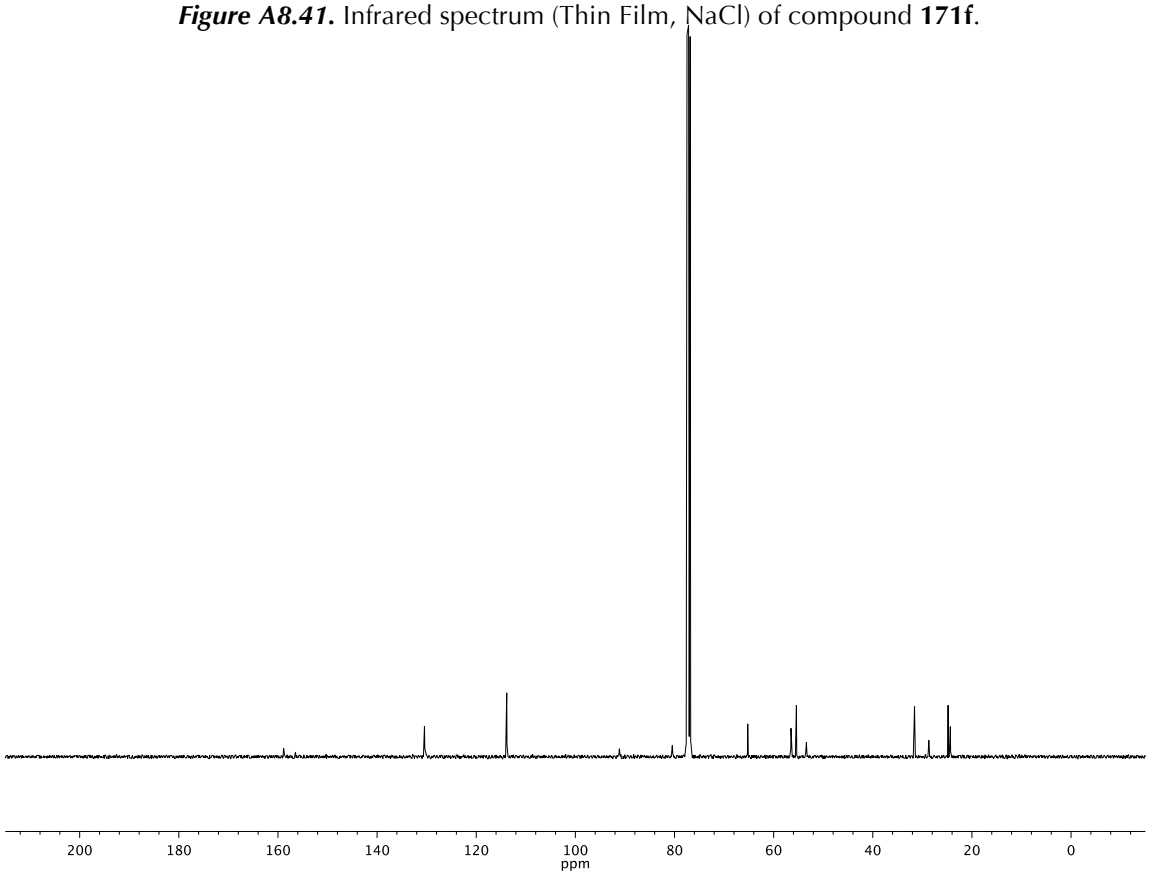


Figure A8.42. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **171f**.

Figure A8.43. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **170g**.

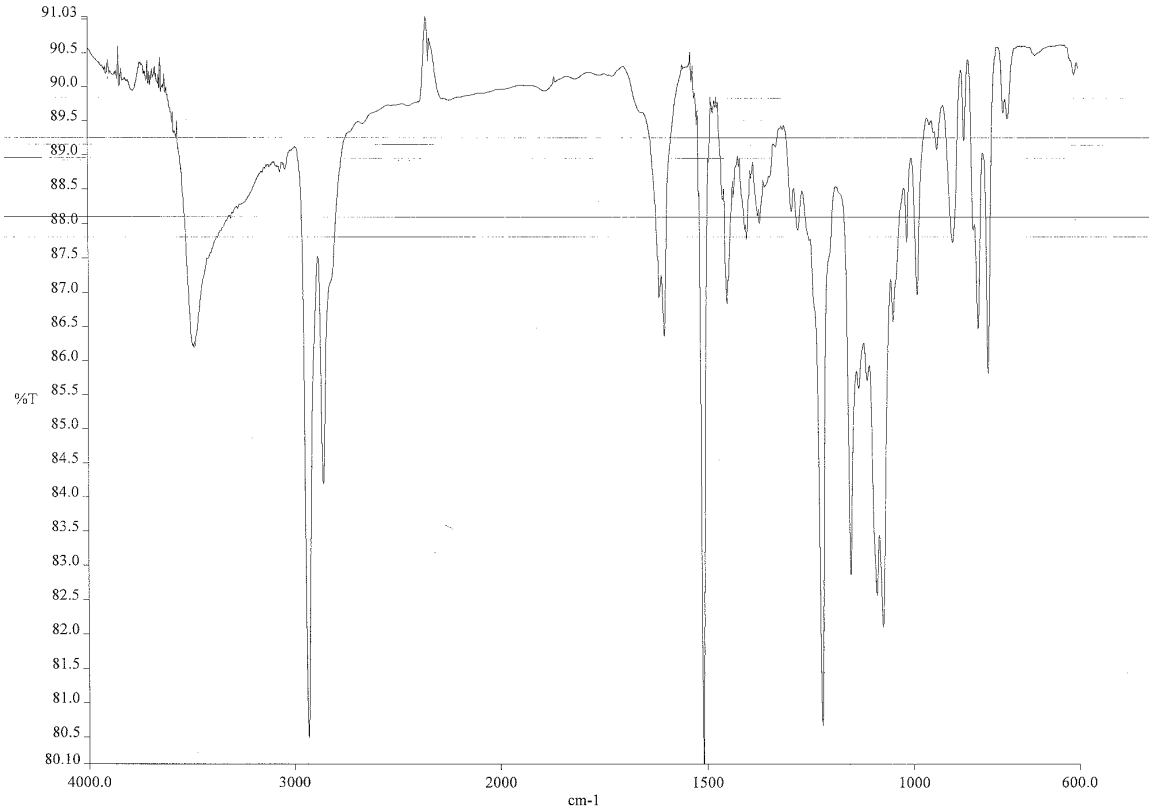


Figure A8.44. Infrared spectrum (Thin Film, NaCl) of compound **170g**.

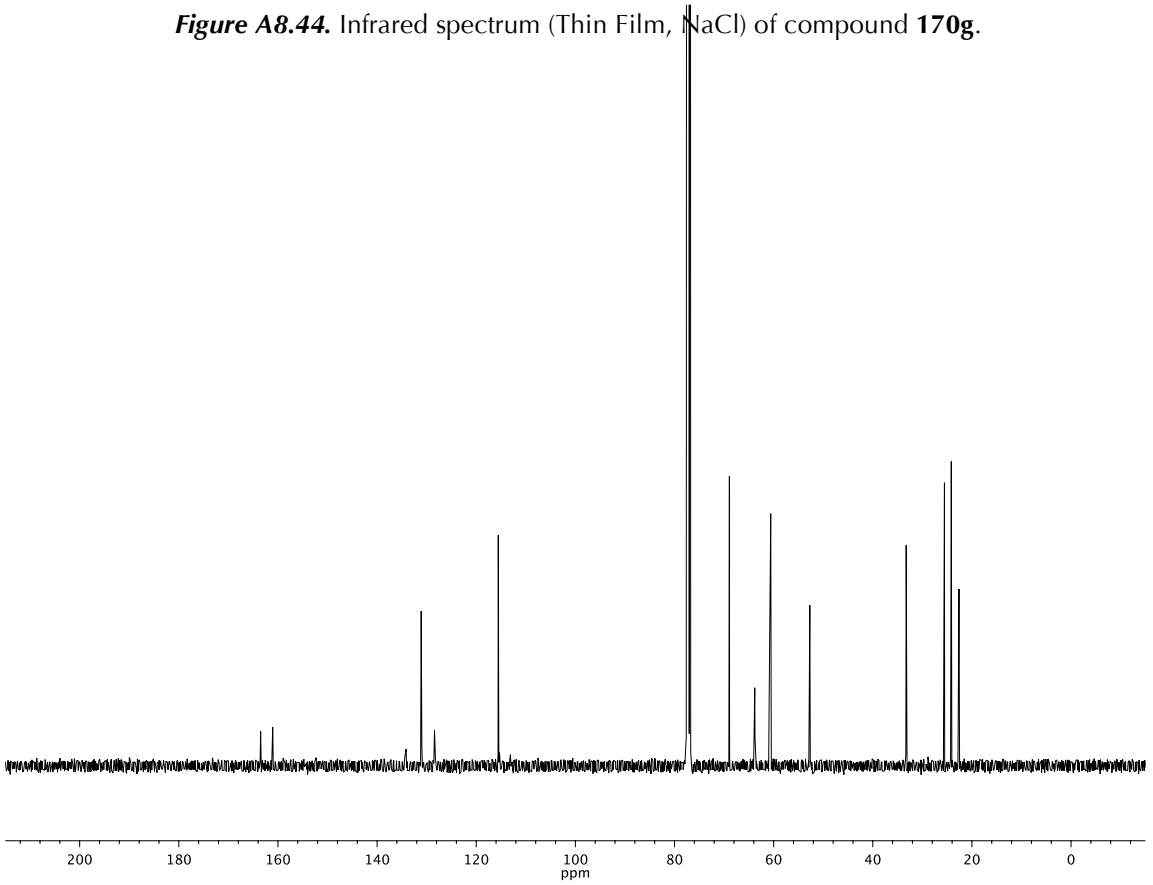


Figure A8.45. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **170g**.

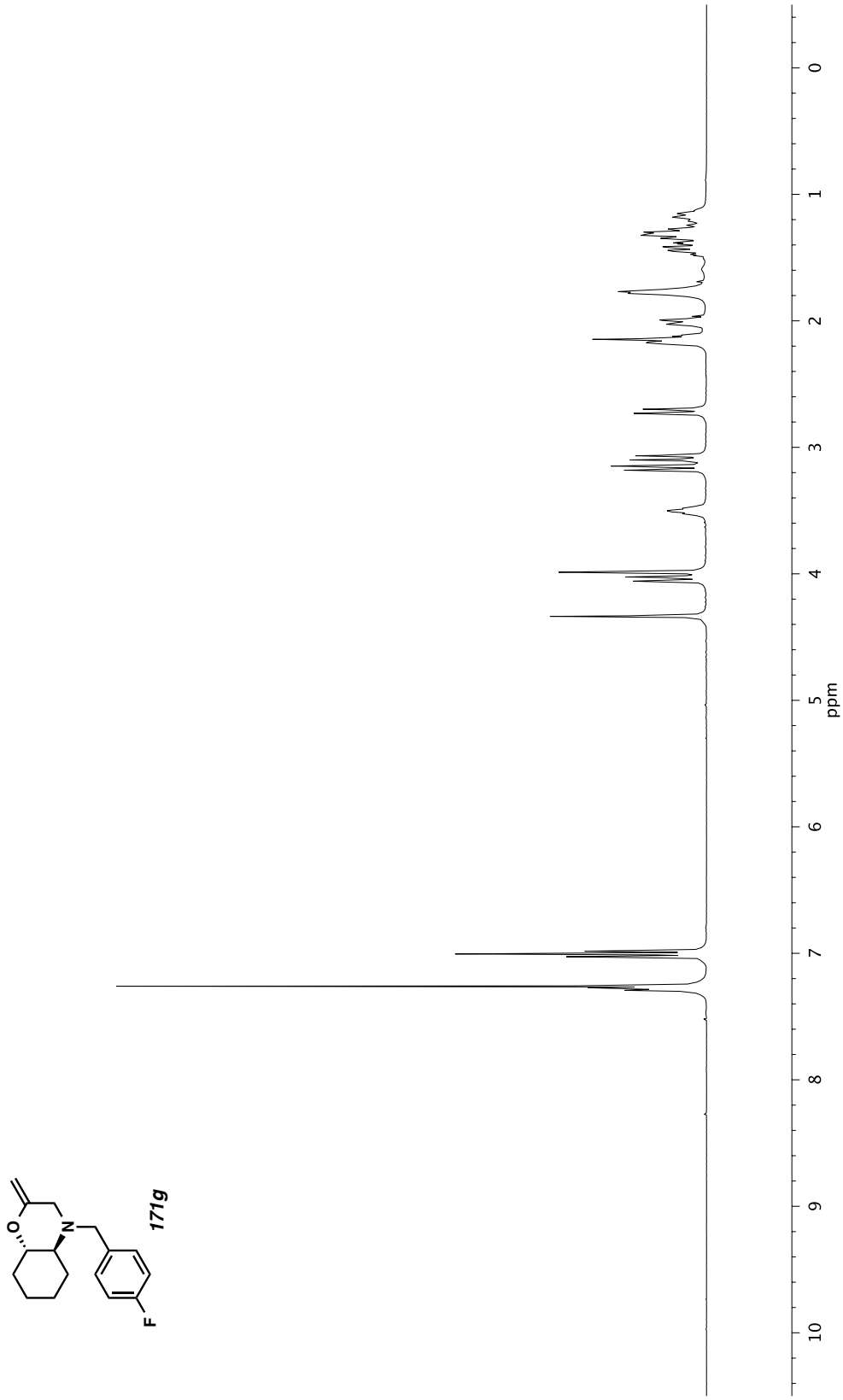


Figure A8.46. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **171g**.

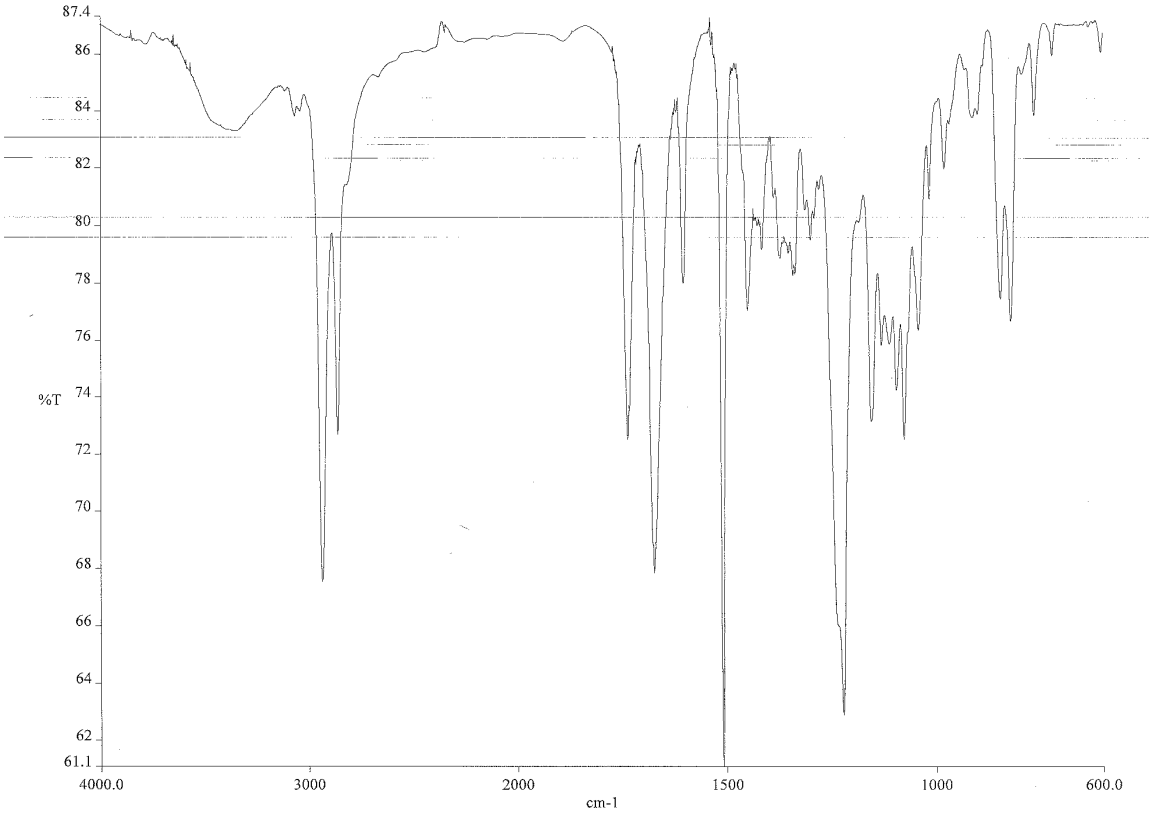


Figure A8.47. Infrared spectrum (Thin Film, NaCl) of compound **171g**.

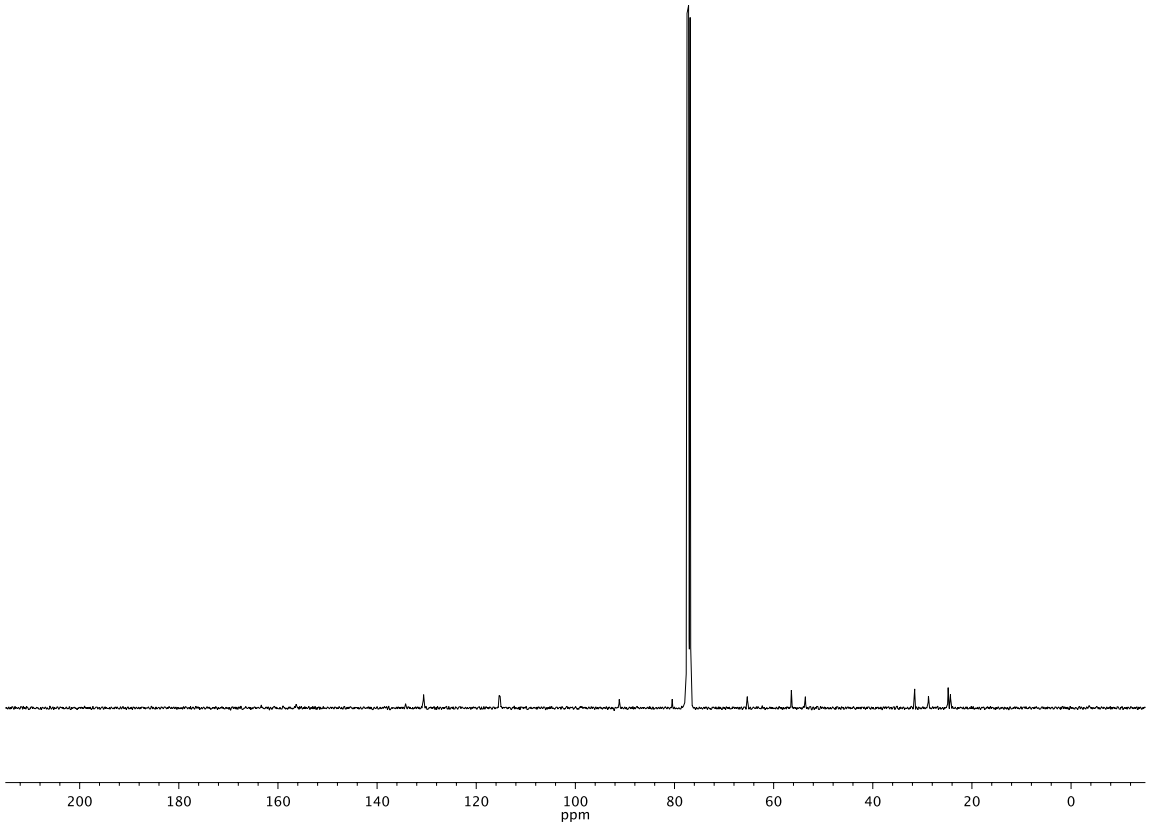


Figure A8.48. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **171g**.

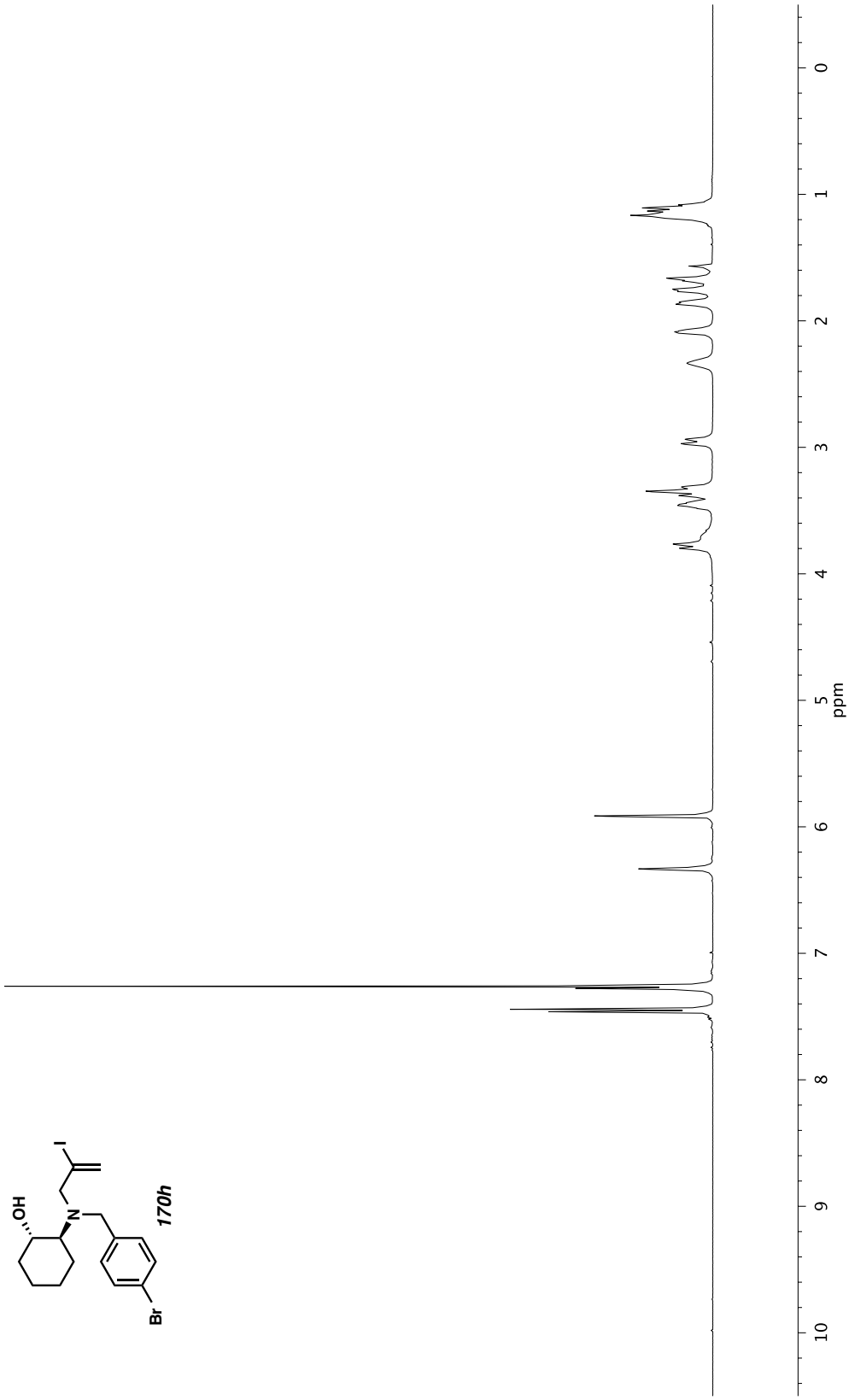


Figure A8.49. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **170h**.

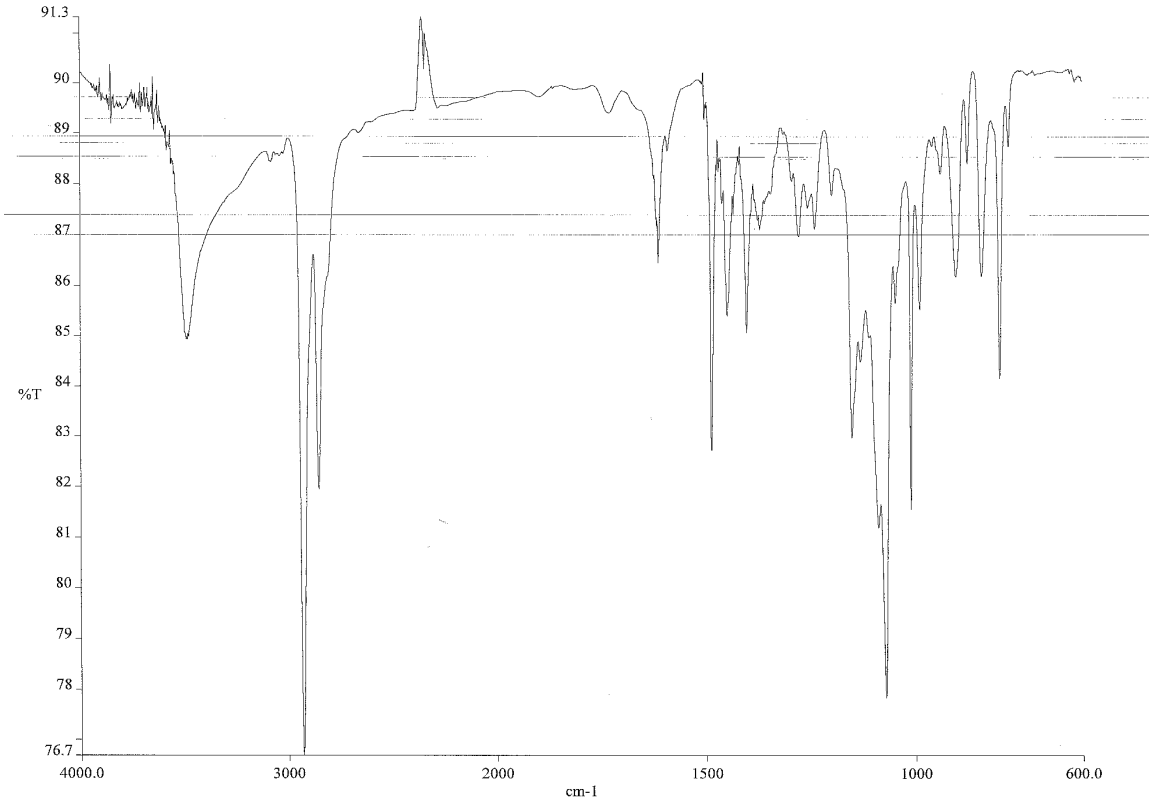


Figure A8.50. Infrared spectrum (Thin Film, NaCl) of compound **170h**.

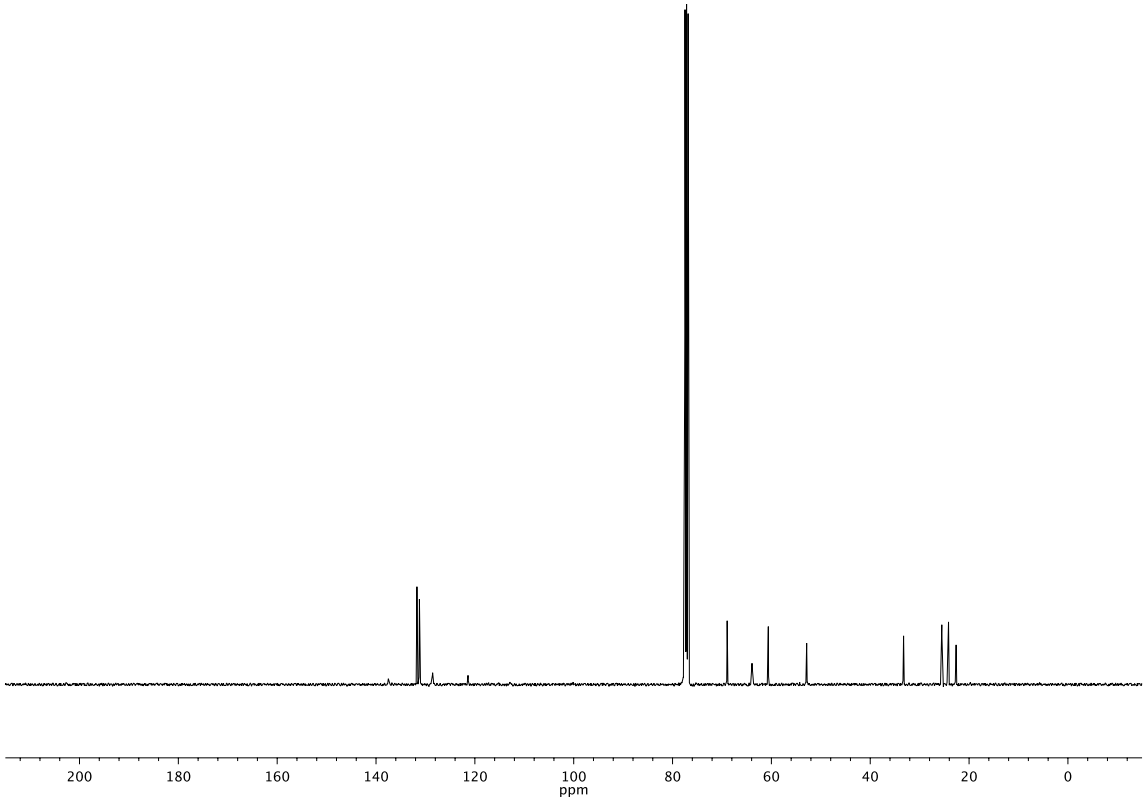


Figure A8.51. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **170h**.

Figure A8.52. ^{1}H NMR (500 MHz, CD_2Cl_2) of compound **171h**.

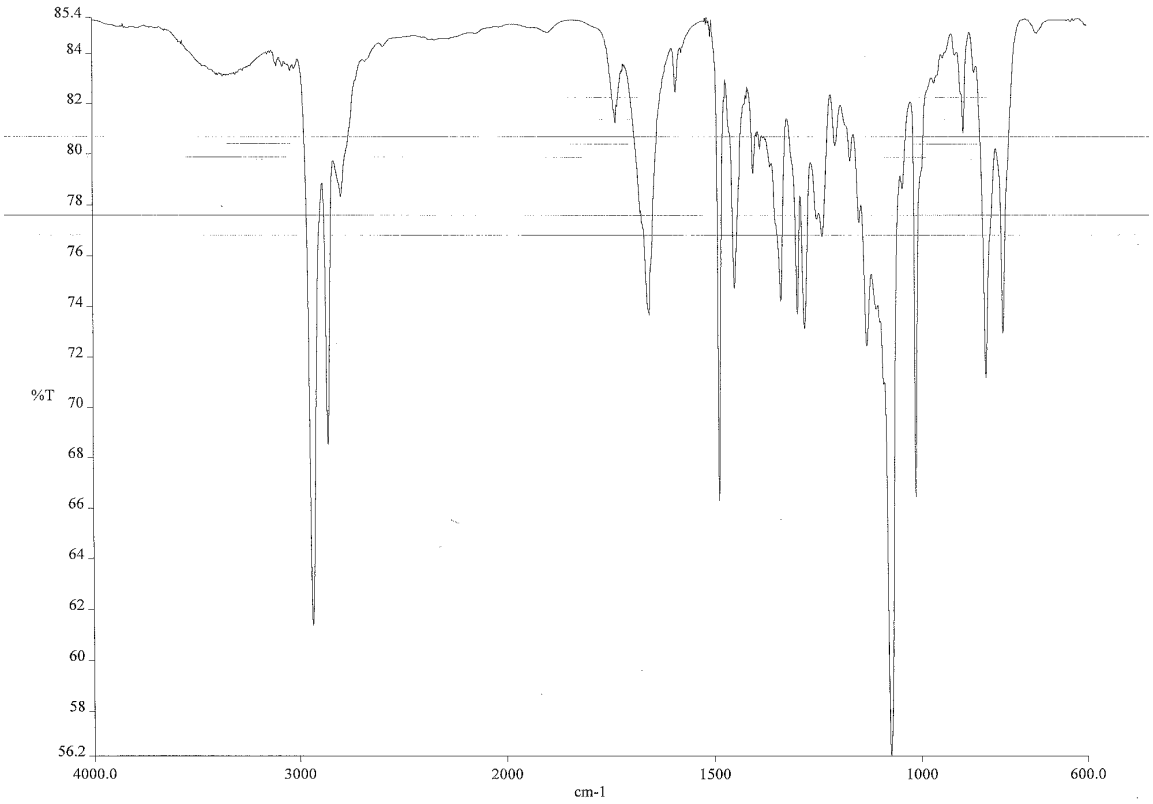


Figure A8.53. Infrared spectrum (Thin Film, NaCl) of compound **171h**.

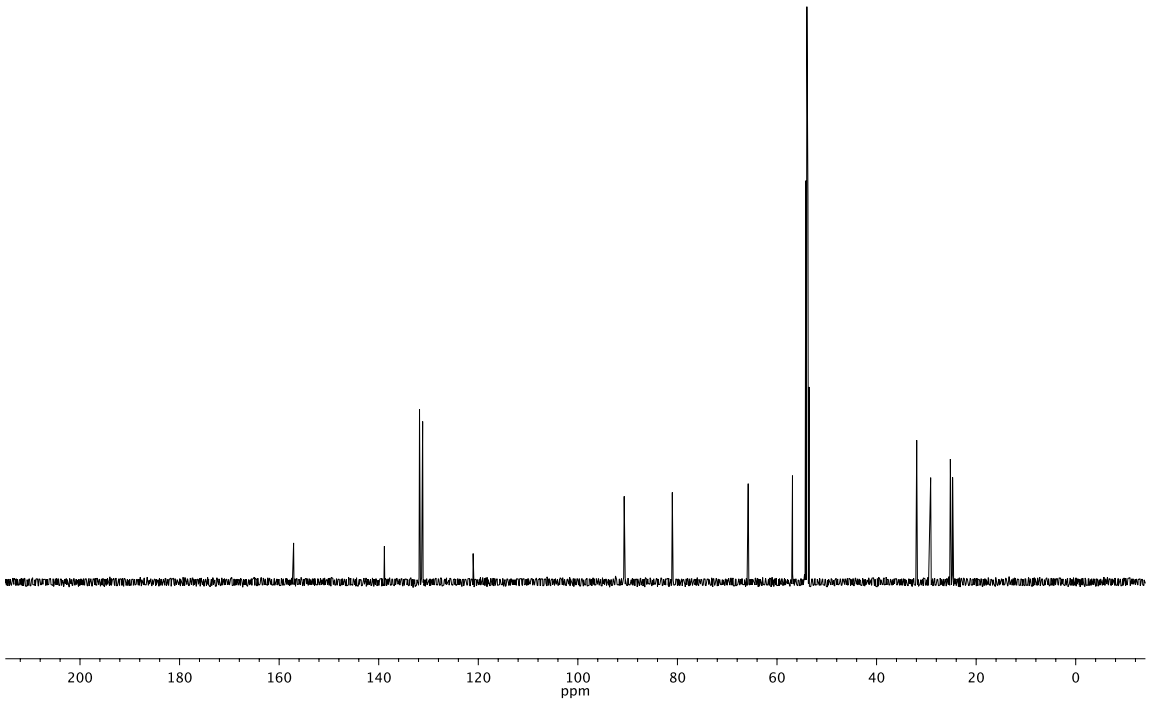


Figure A8.54. ^{13}C NMR (126 MHz, CD_2Cl_2) of compound **171h**.

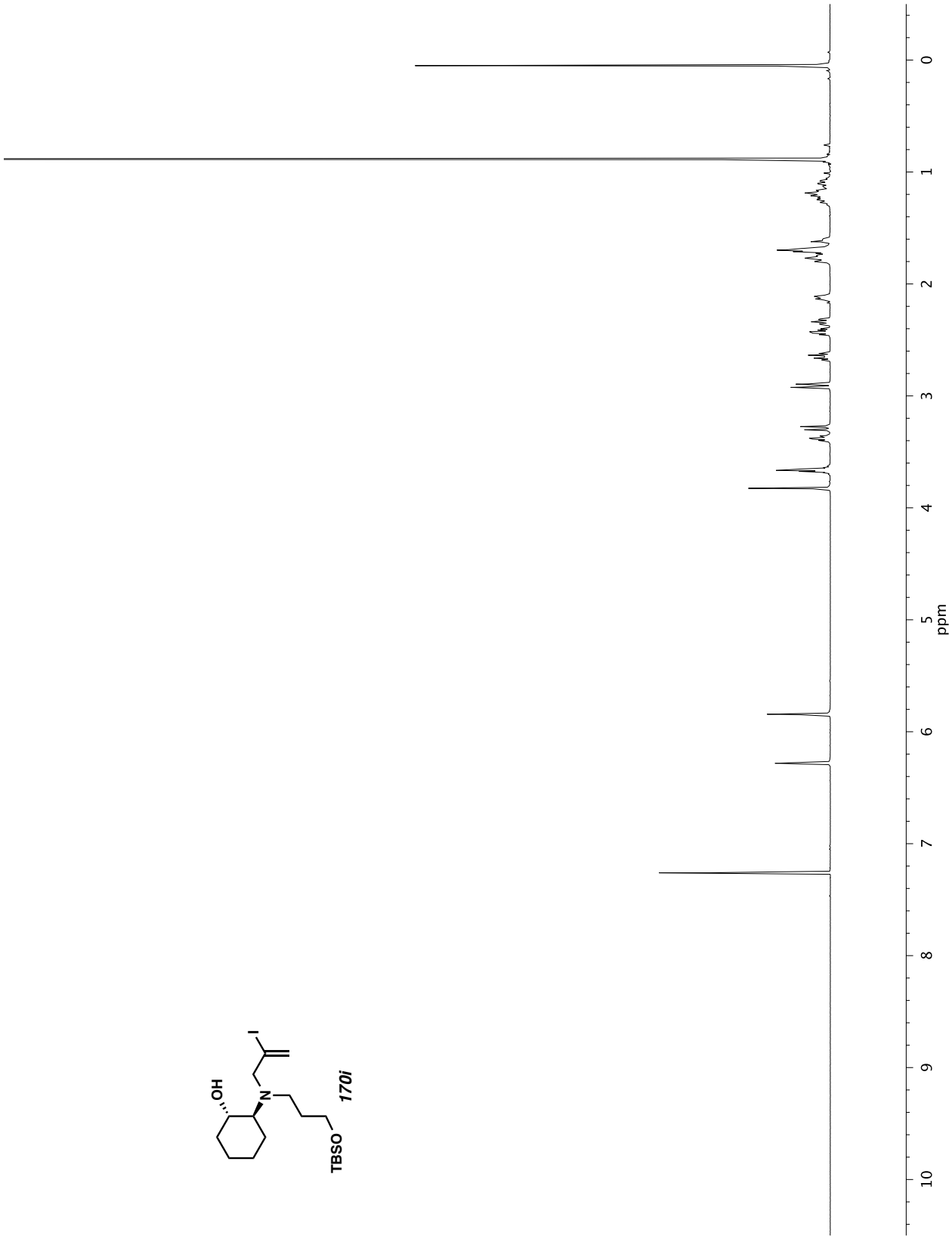


Figure A8.55. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **170i**.

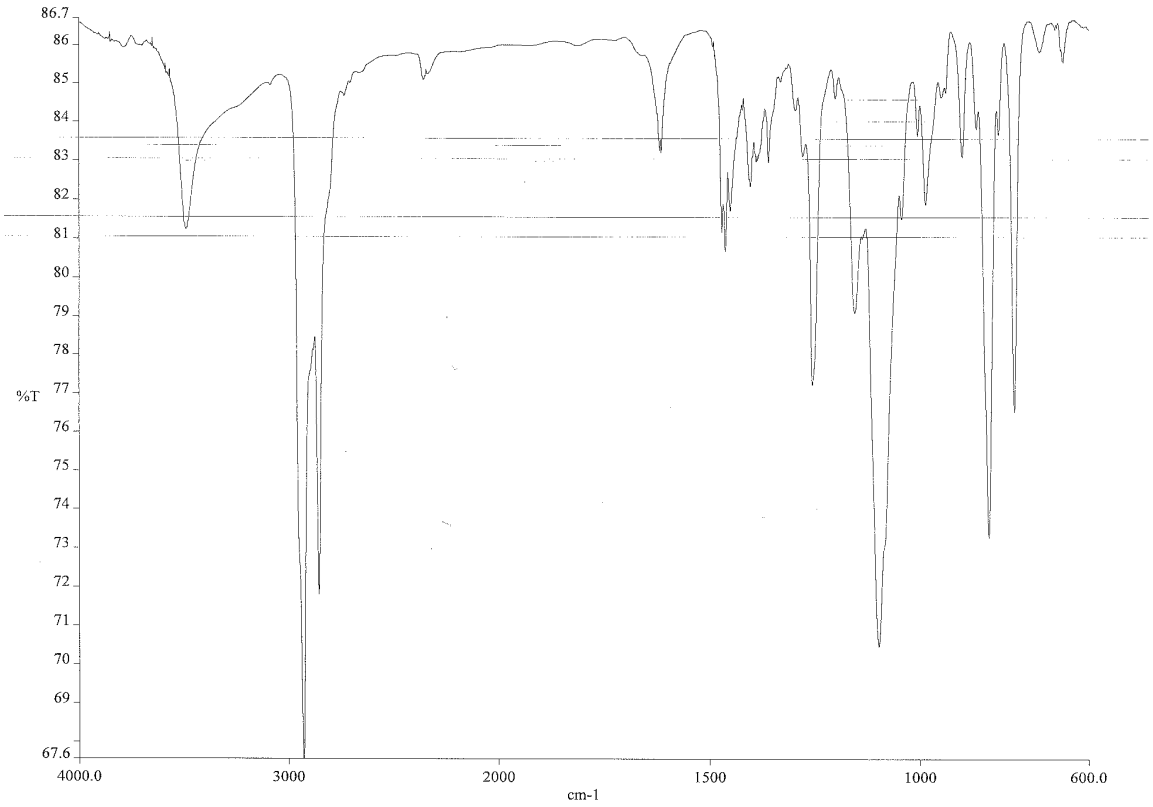


Figure A8.56. Infrared spectrum (Thin Film, NaCl) of compound **170i**.

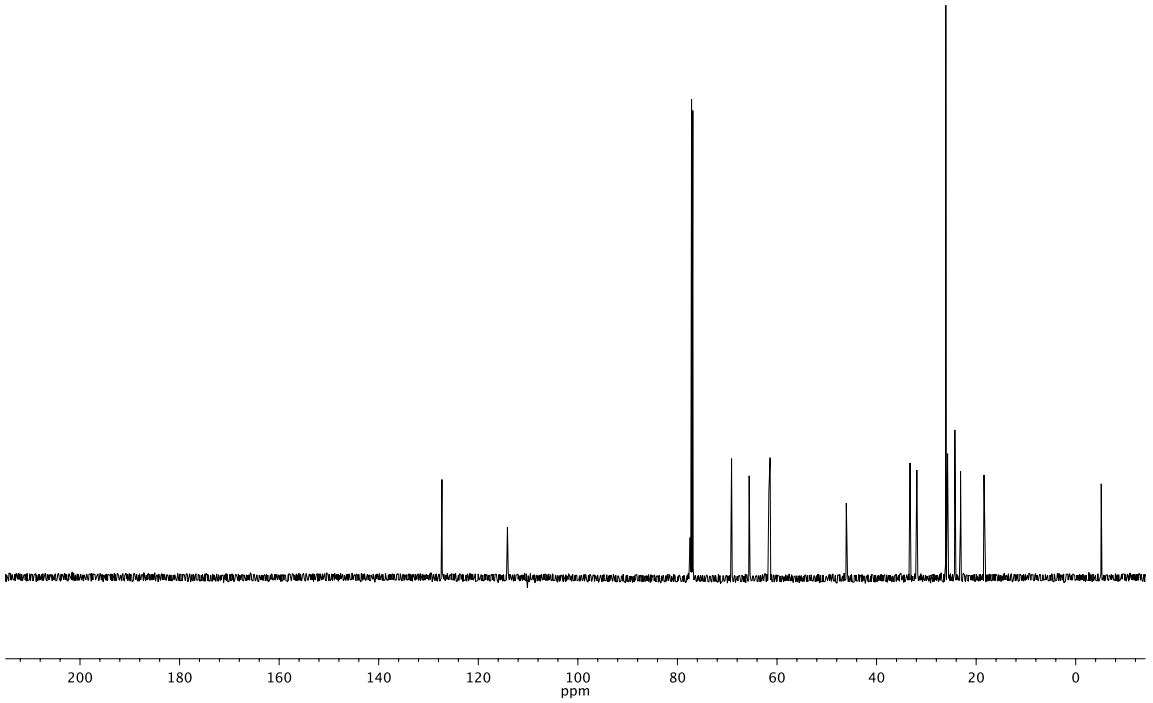


Figure A8.57. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **170i**.

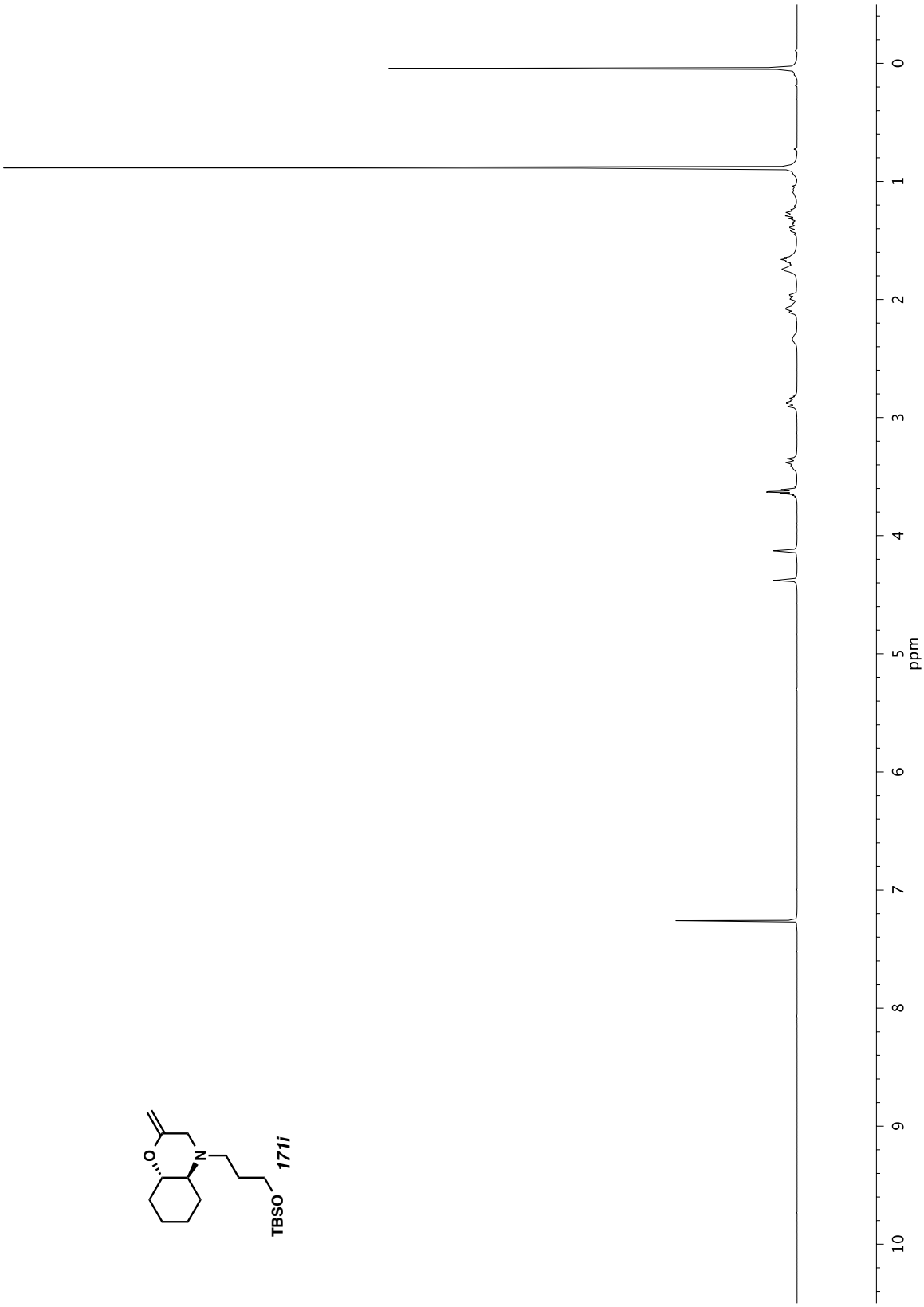


Figure A8.58. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **171i**.

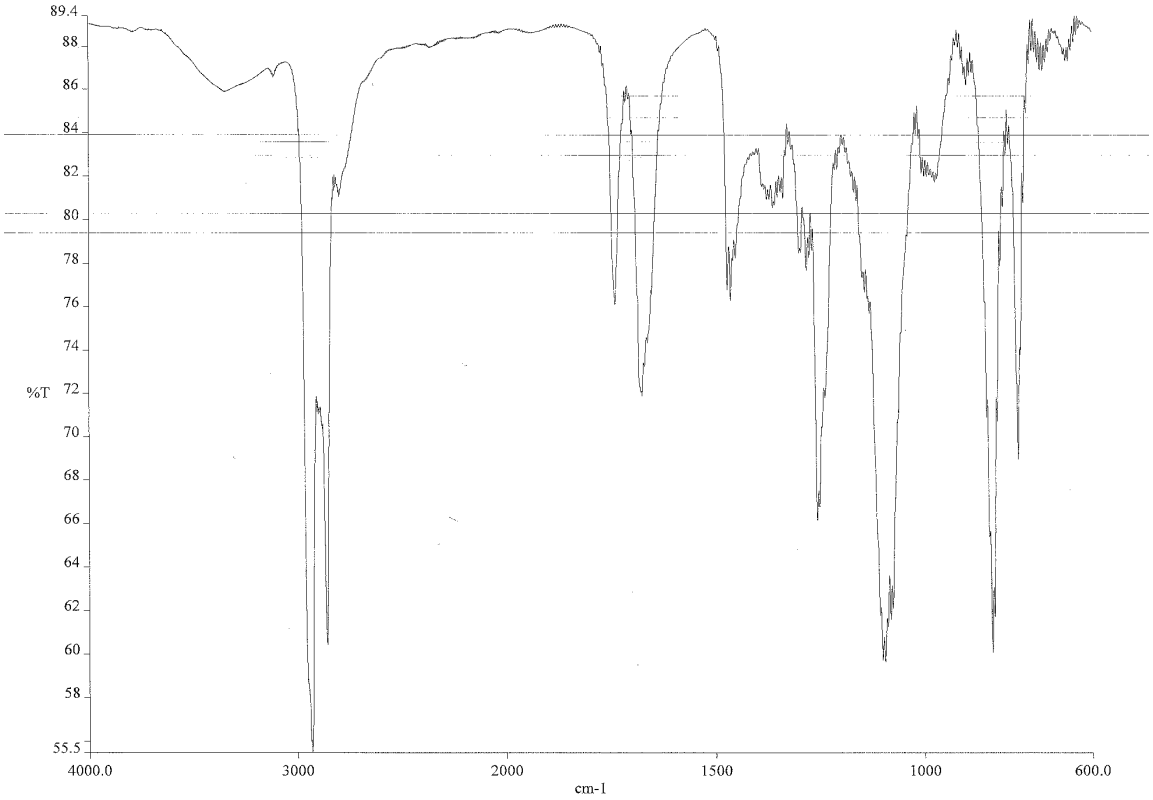


Figure A8.59. Infrared spectrum (Thin Film, NaCl) of compound **171i**.

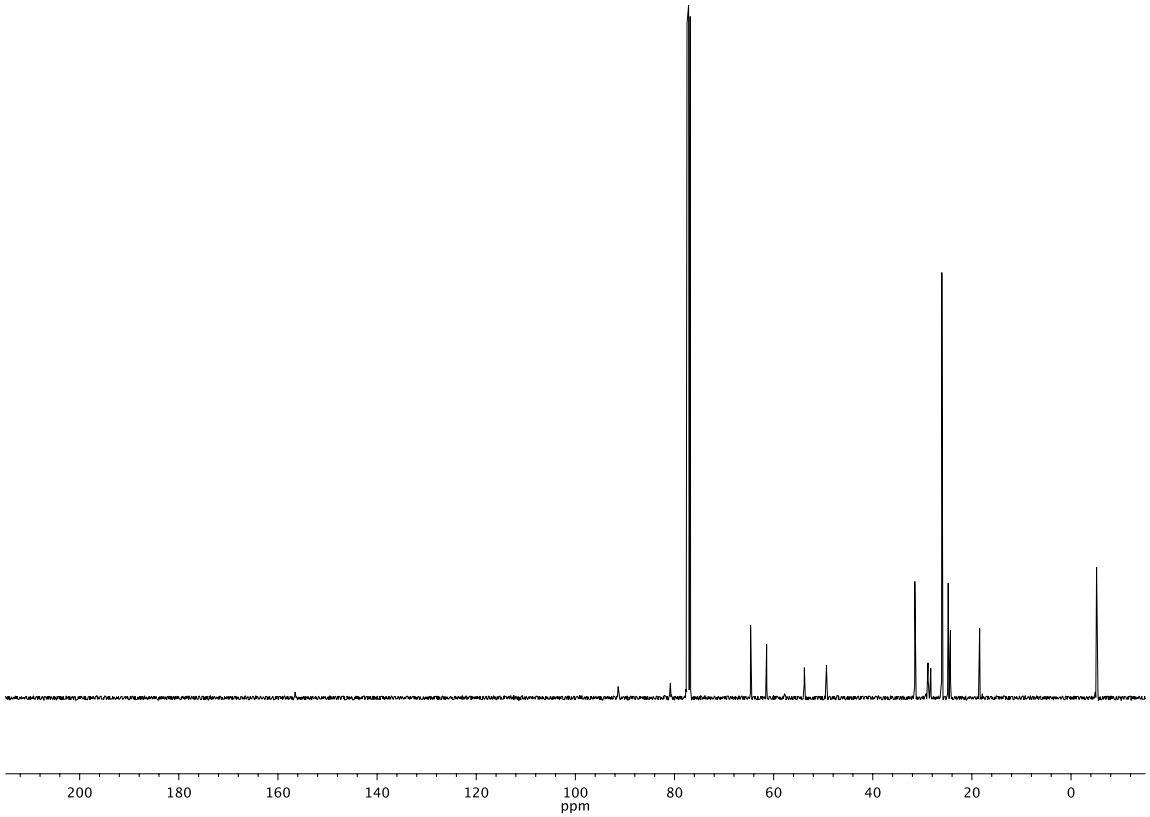


Figure A8.60. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **171i**.

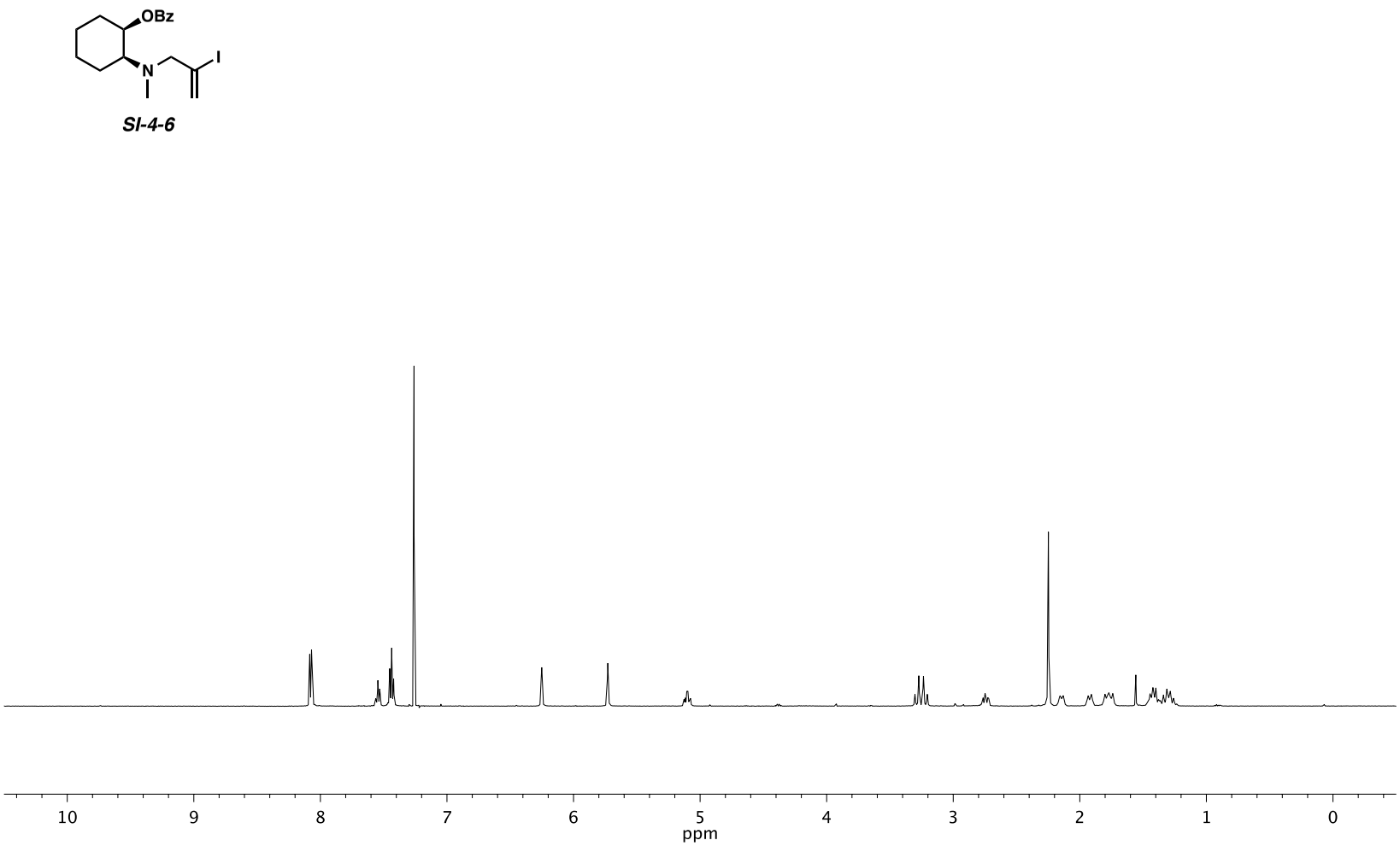


Figure A8.61. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **SI-4-6**.

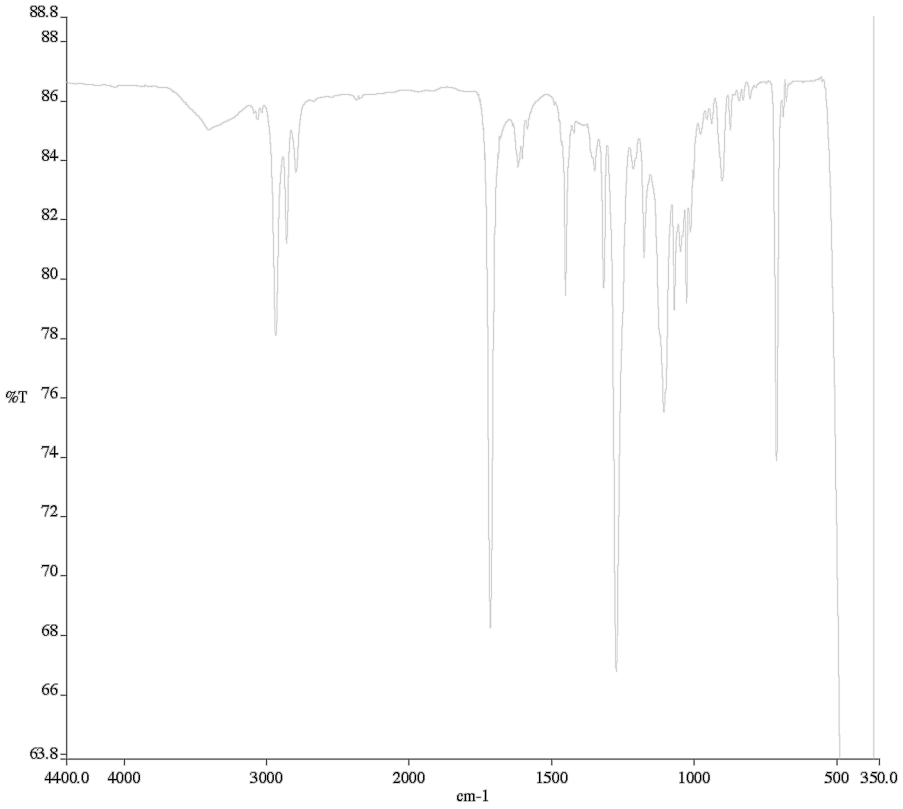


Figure A8.62. Infrared spectrum (Thin Film, NaCl) of compound **SI-4-6**.

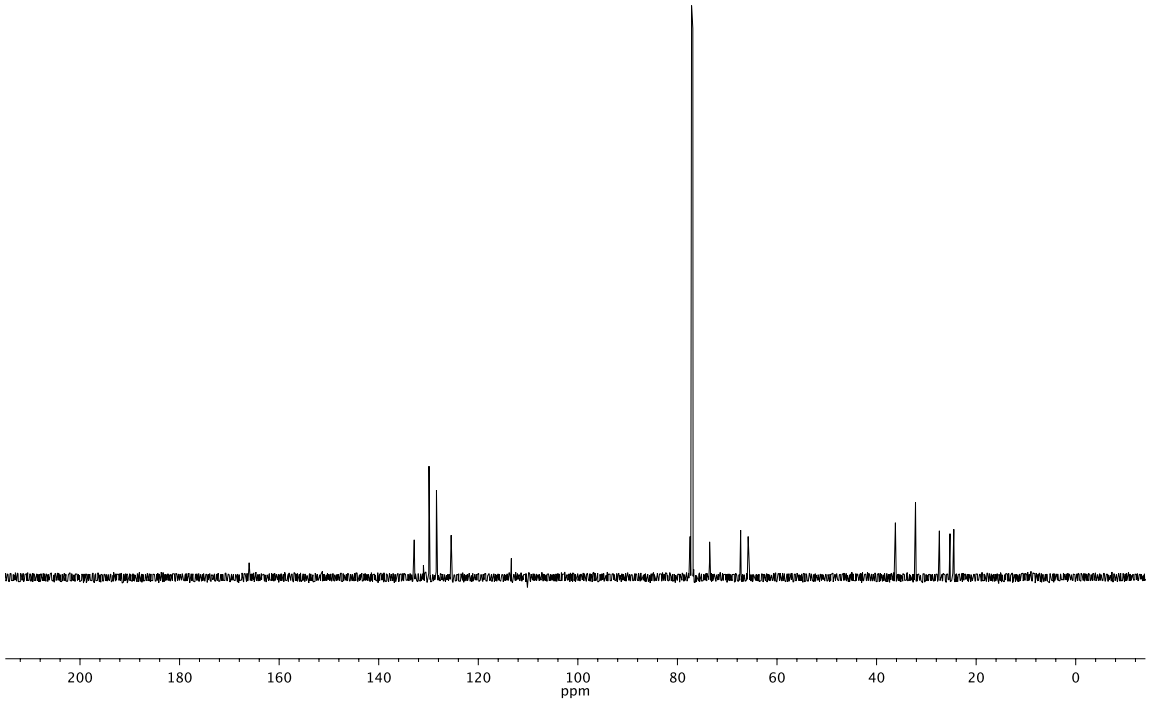


Figure A8.63. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **SI-4-6**.

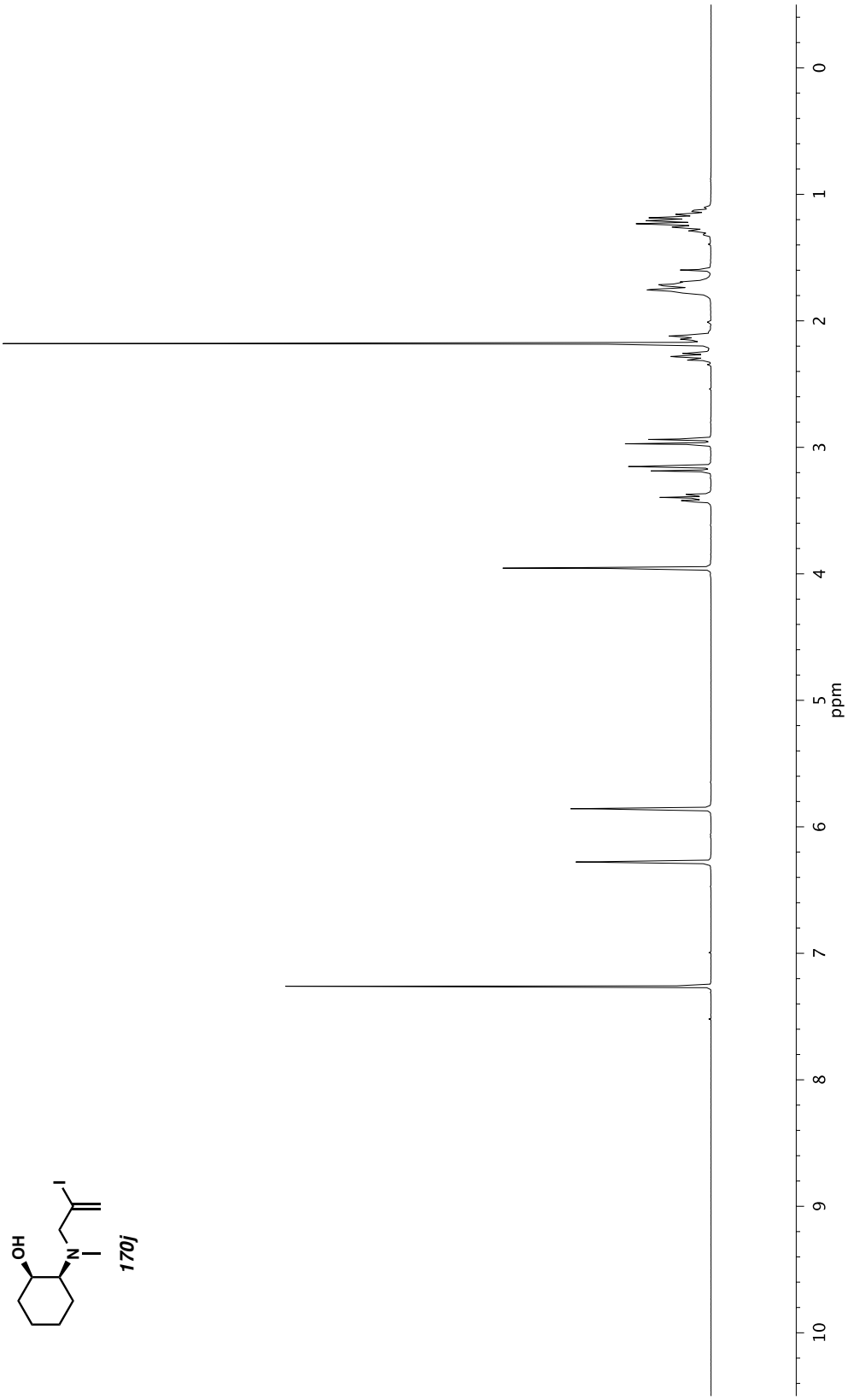


Figure A8.64. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **170j**.

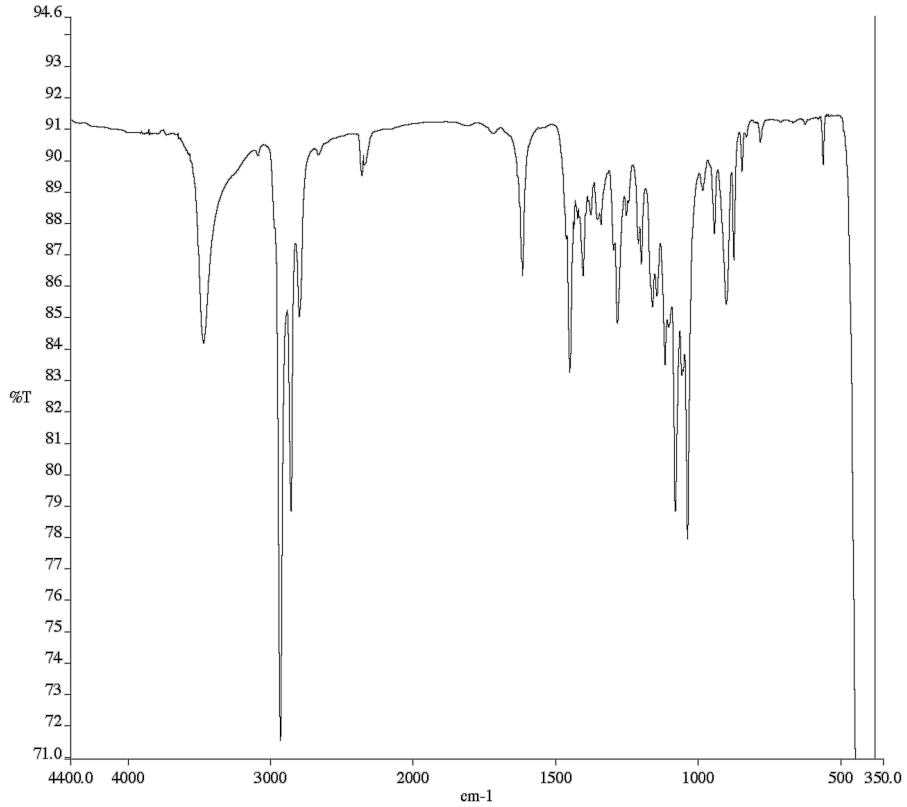


Figure A8.65. Infrared spectrum (Thin Film, NaCl) of compound **170j**.

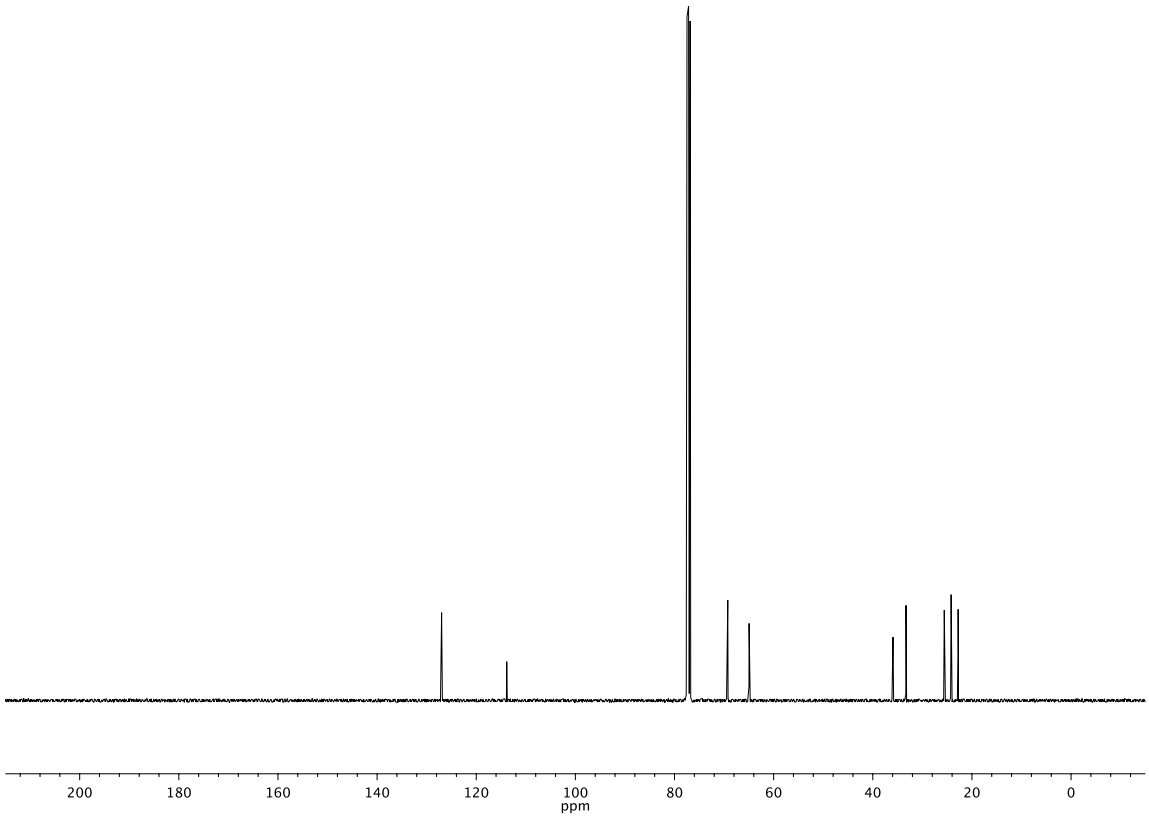
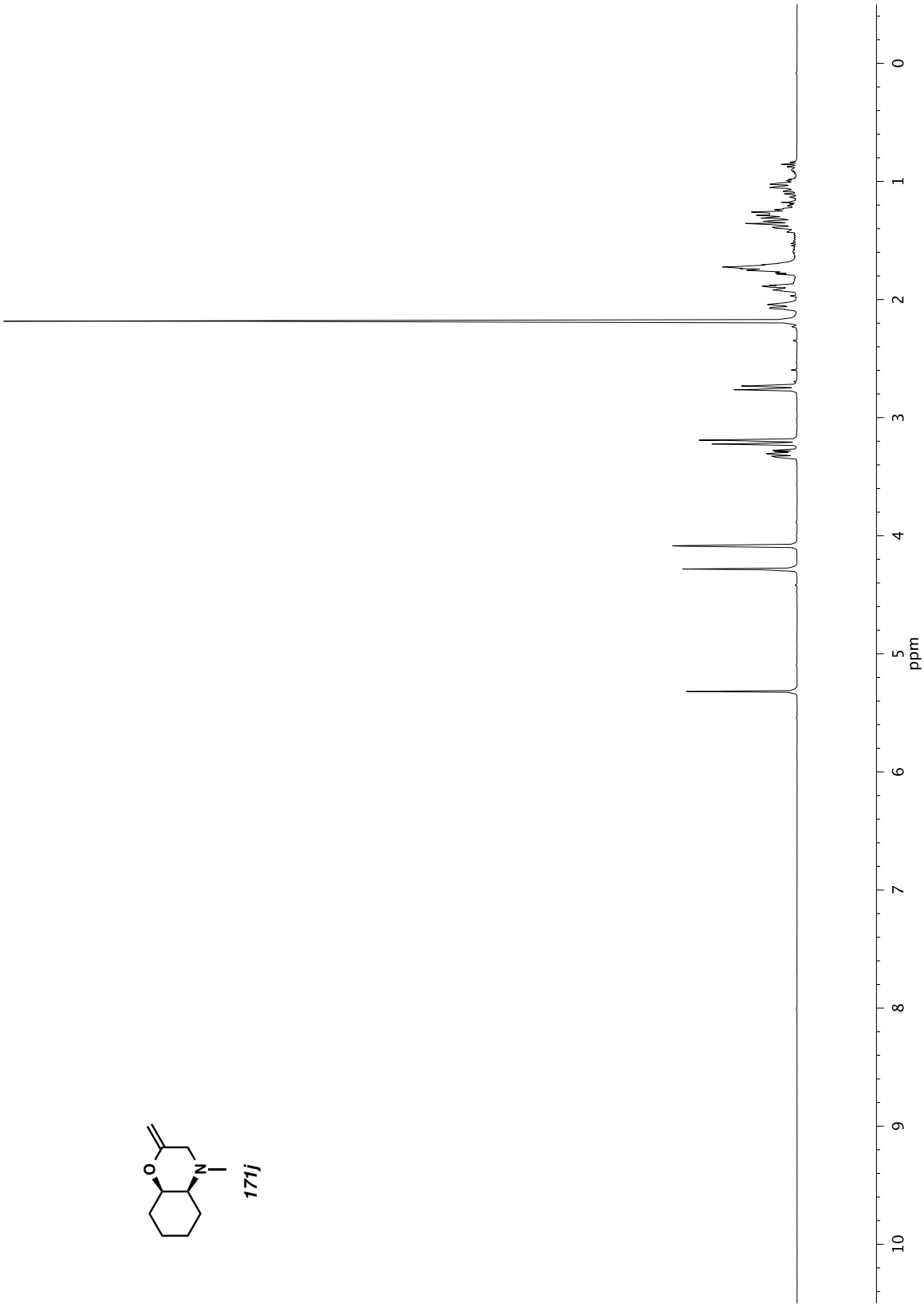


Figure A8.66. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **170j**.



171j

Figure A8.67. ^{1}H NMR (400 MHz, CD_2Cl_2) of compound **171j**.

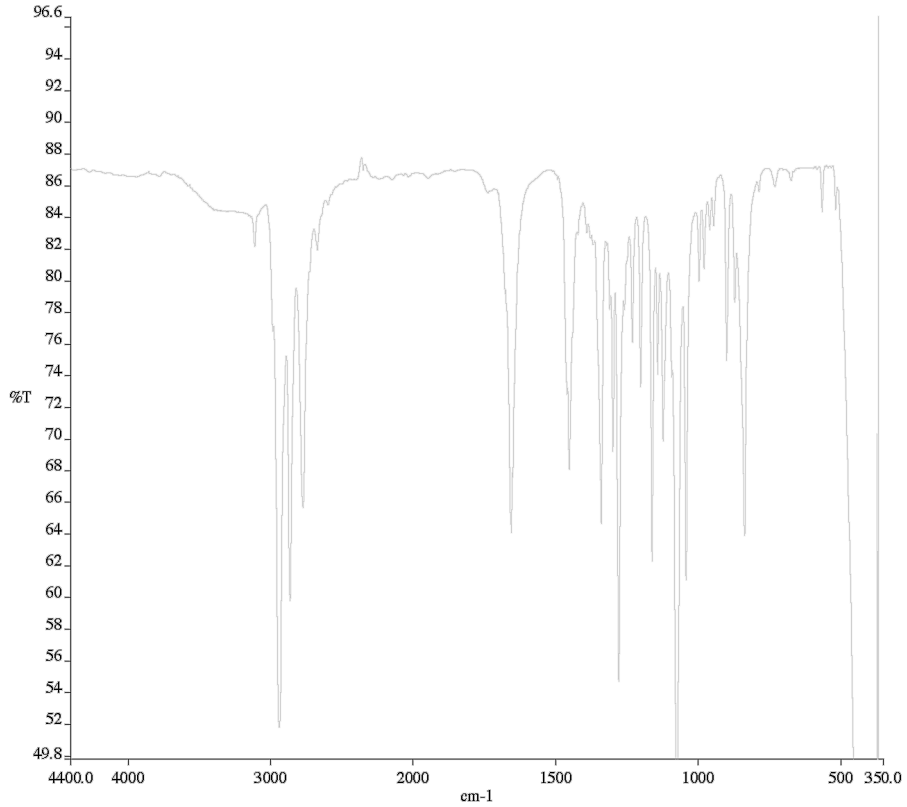


Figure A8.68. Infrared spectrum (Thin Film, NaCl) of compound **171j**.

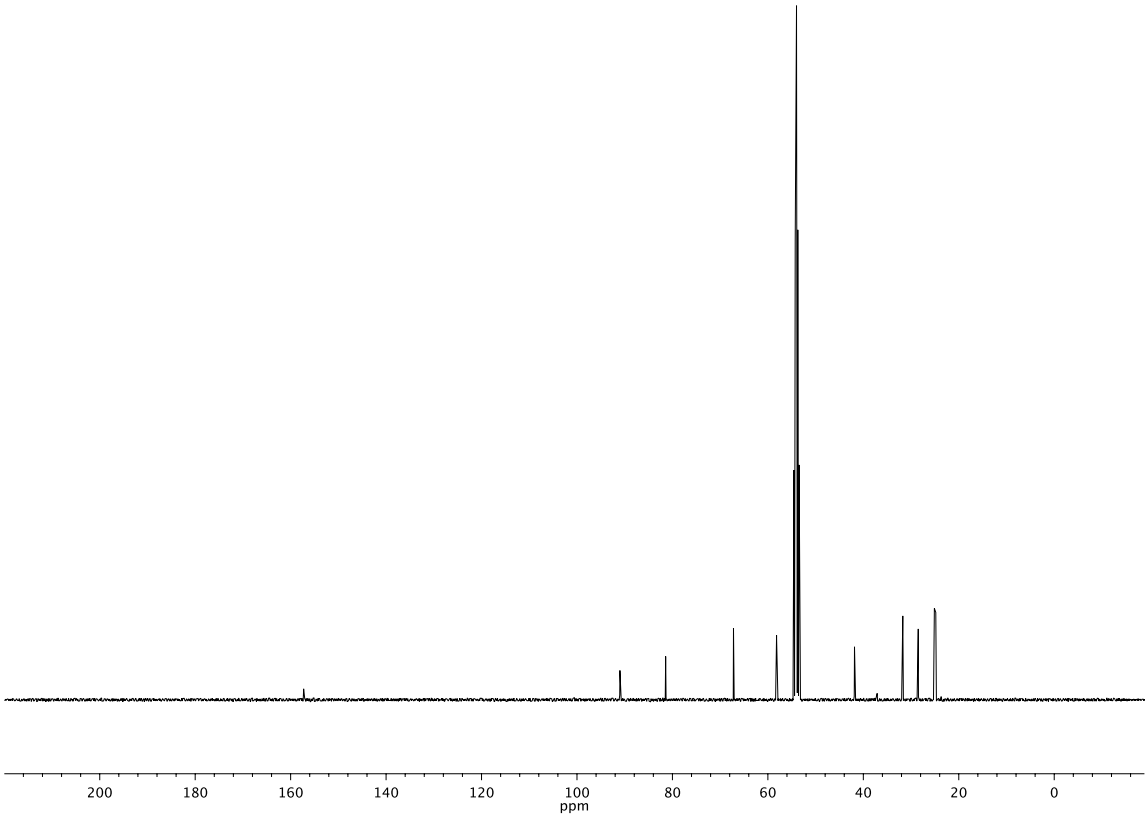


Figure A8.69. ^{13}C NMR (101 MHz, CD_2Cl_2) of compound **171j**.

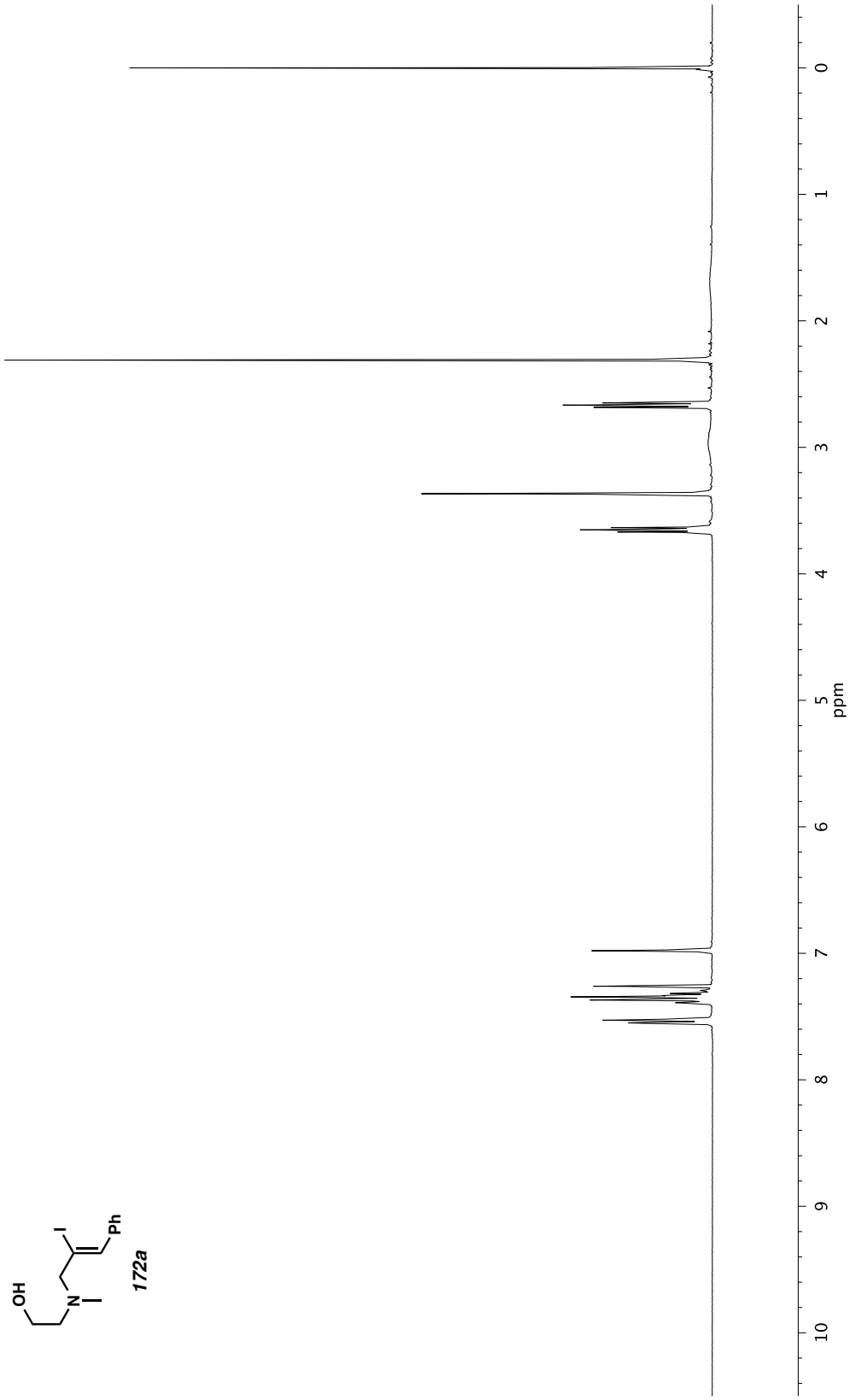


Figure A8.70. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **172a**.

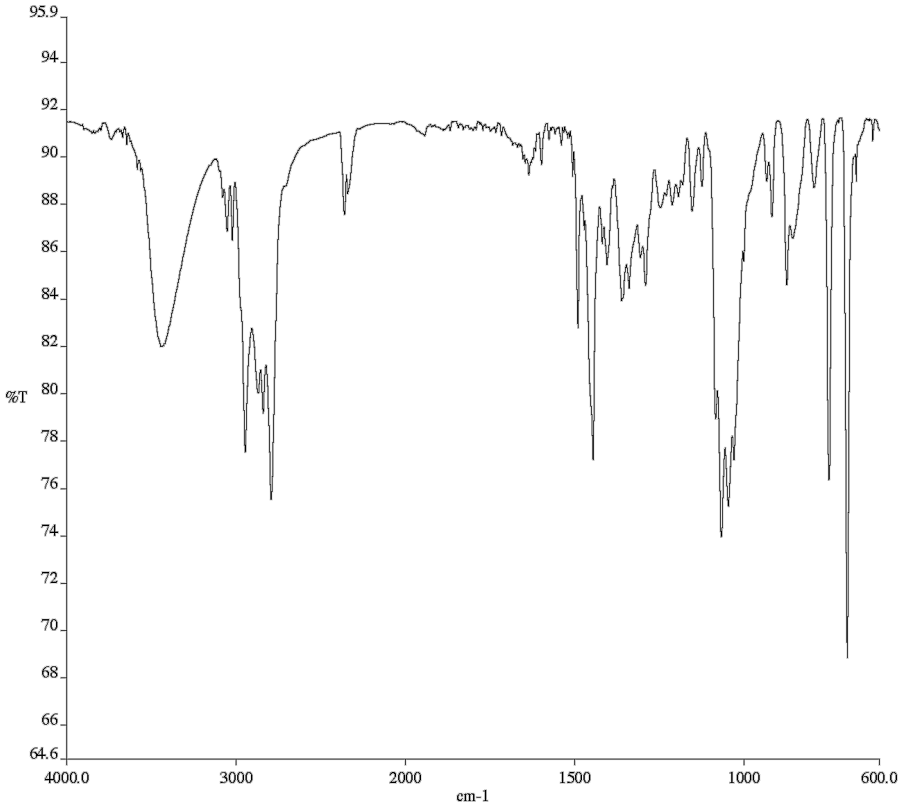


Figure A8.71. Infrared spectrum (Thin Film, NaCl) of compound **172a**.

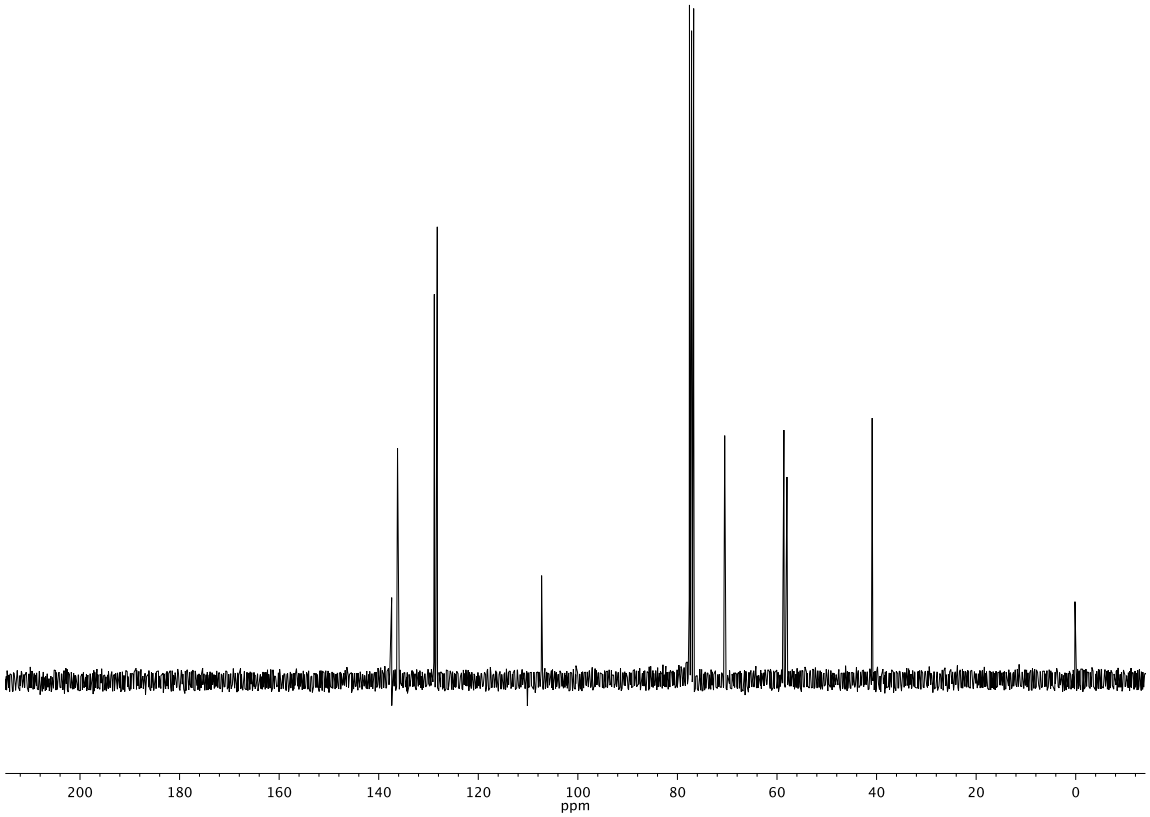


Figure A8.72. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **172a**.

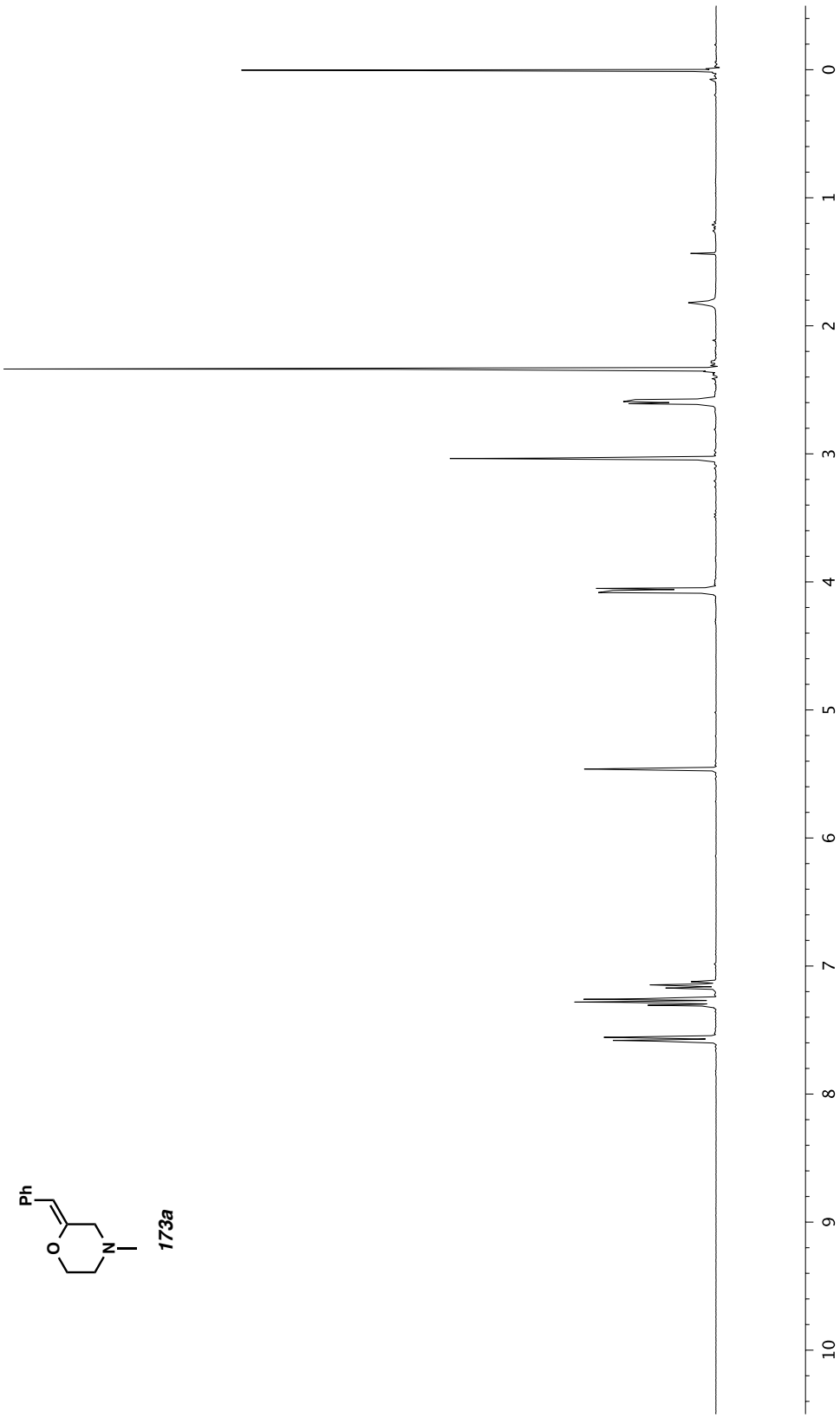


Figure A8.73. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **173a**.

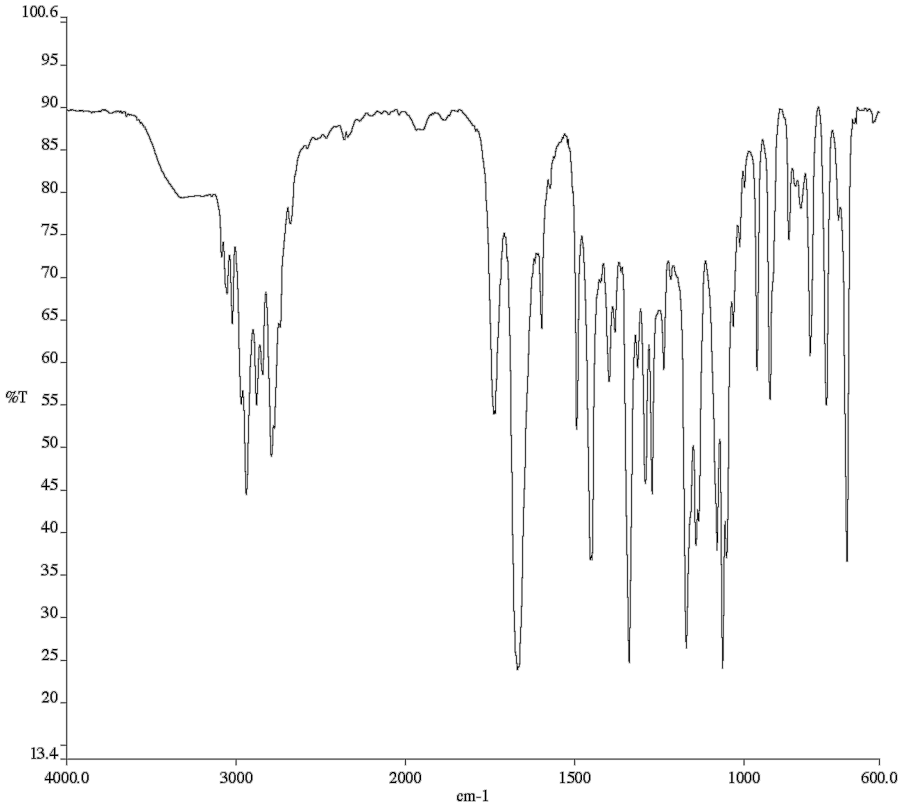


Figure A8.74. Infrared spectrum (Thin Film, NaCl) of compound **173a**.

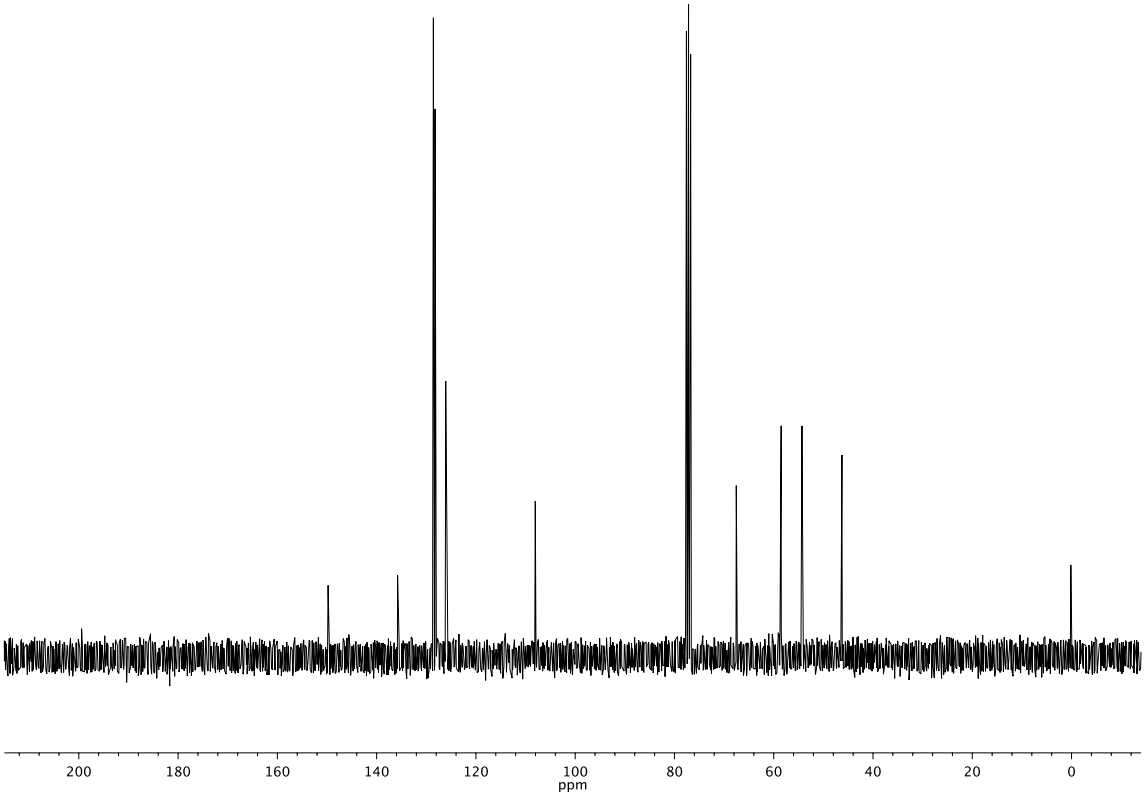


Figure A8.75. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **173a**.

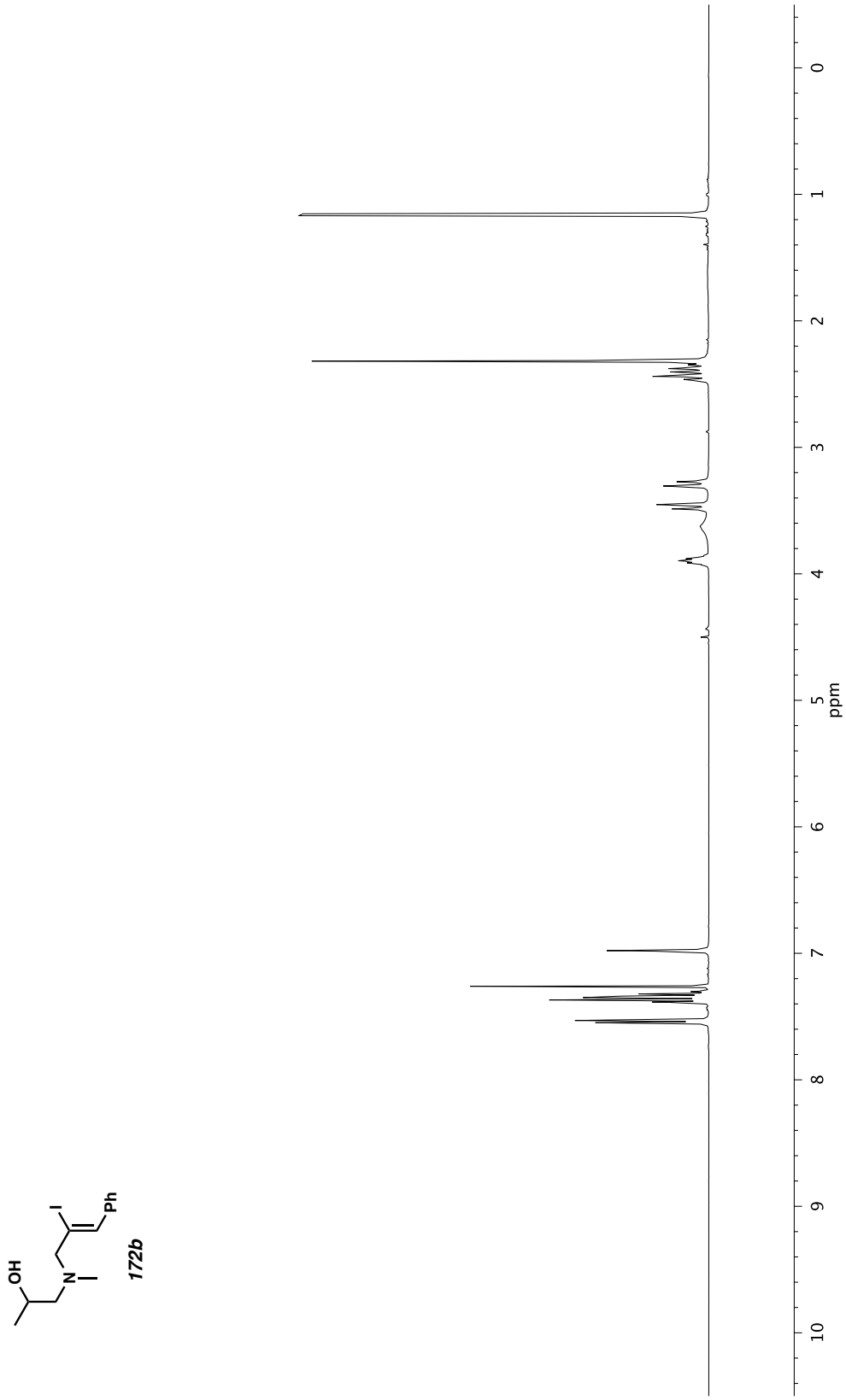


Figure A8.76. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **172b**.

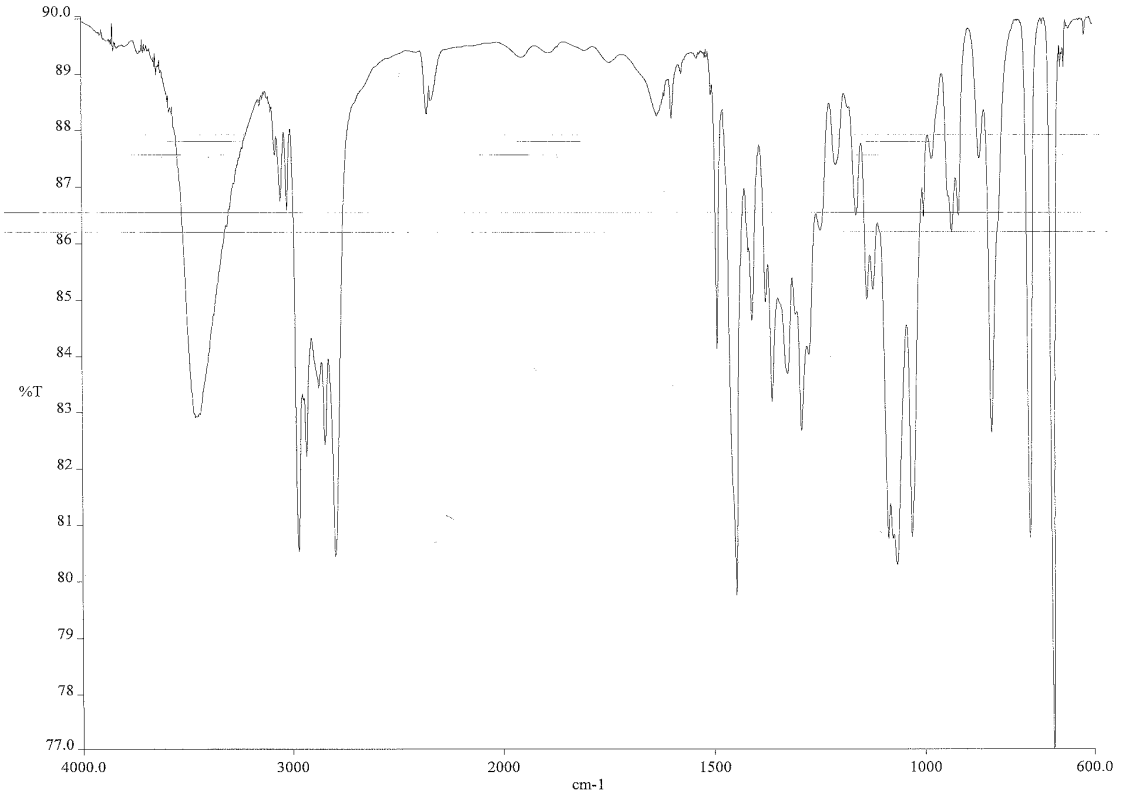


Figure A8.77. Infrared spectrum (Thin Film, NaCl) of compound **172b**.

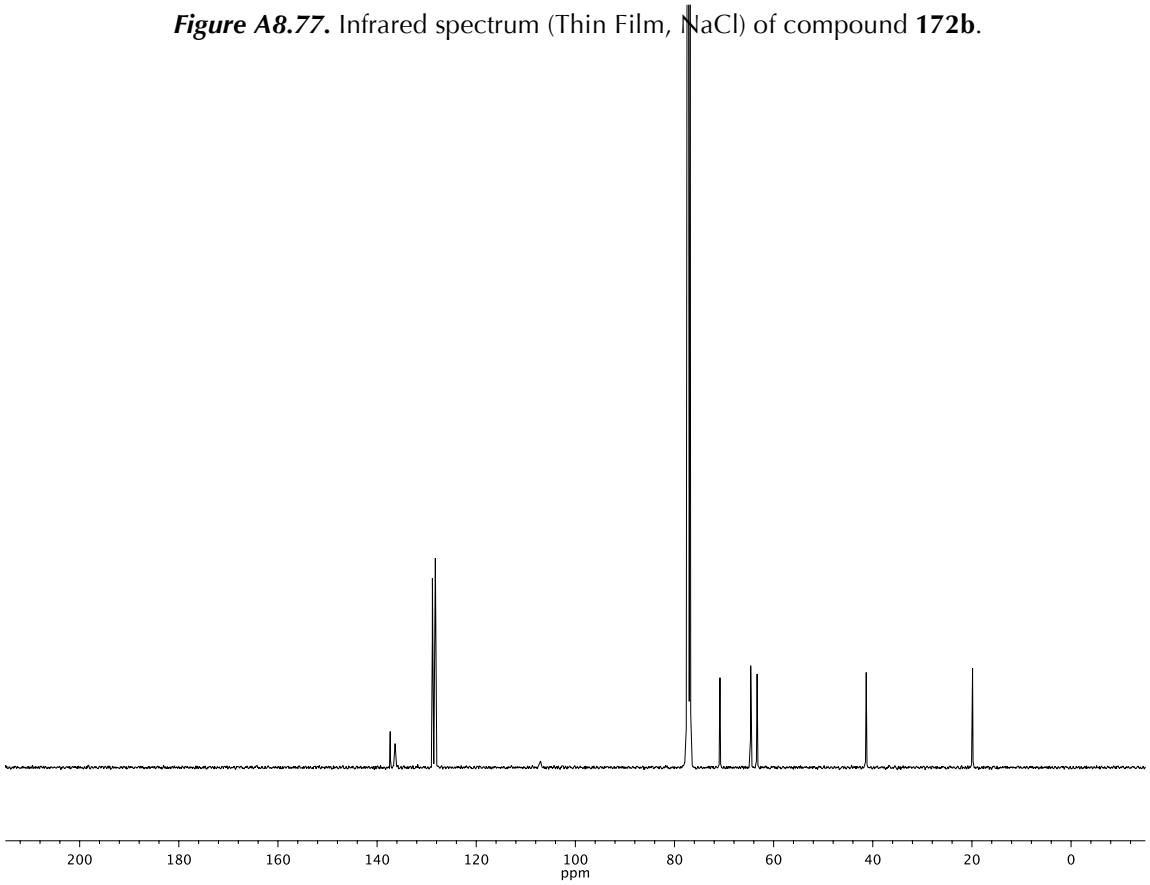


Figure A8.78. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **172b**.

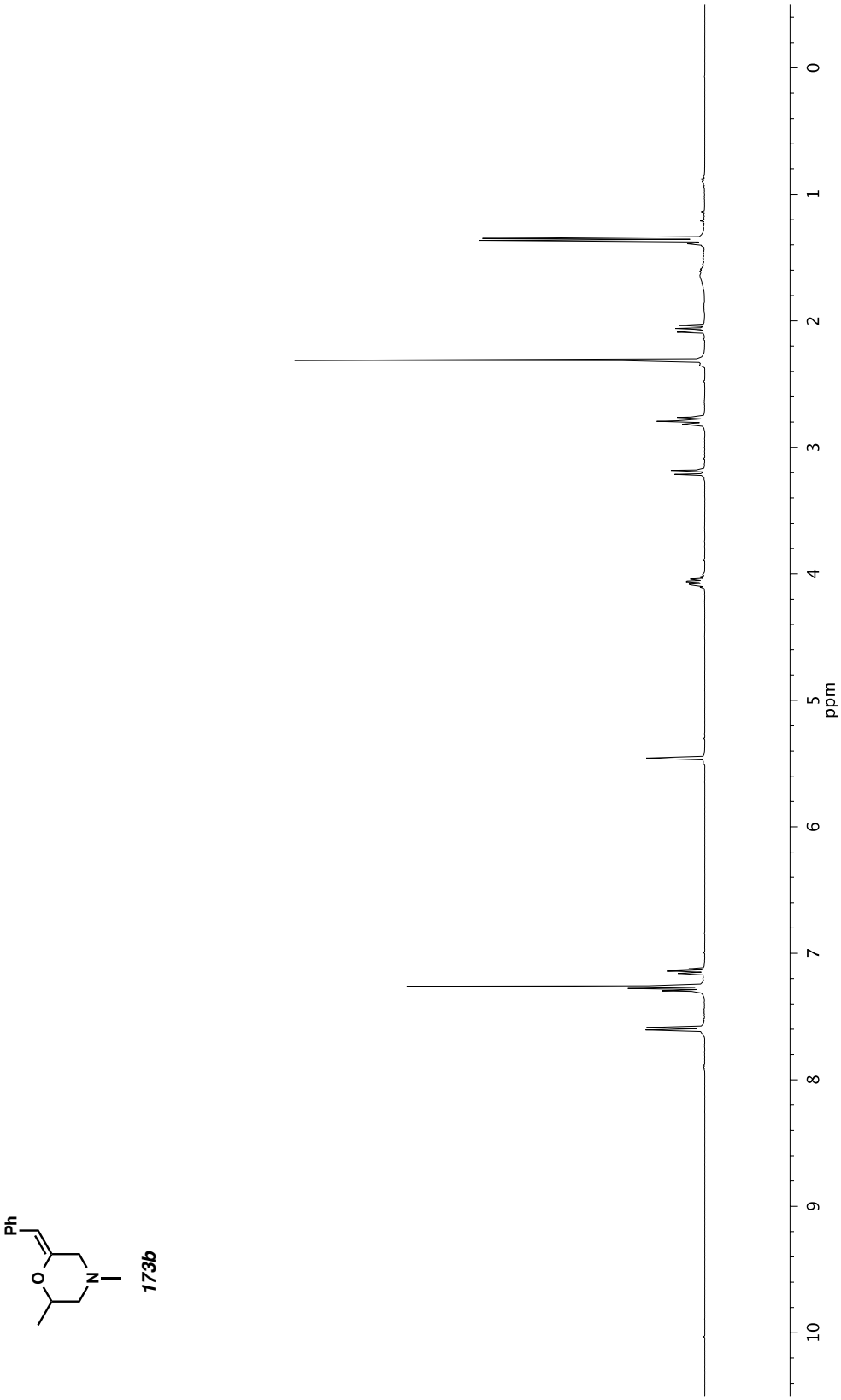


Figure A8.79. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **173b**.

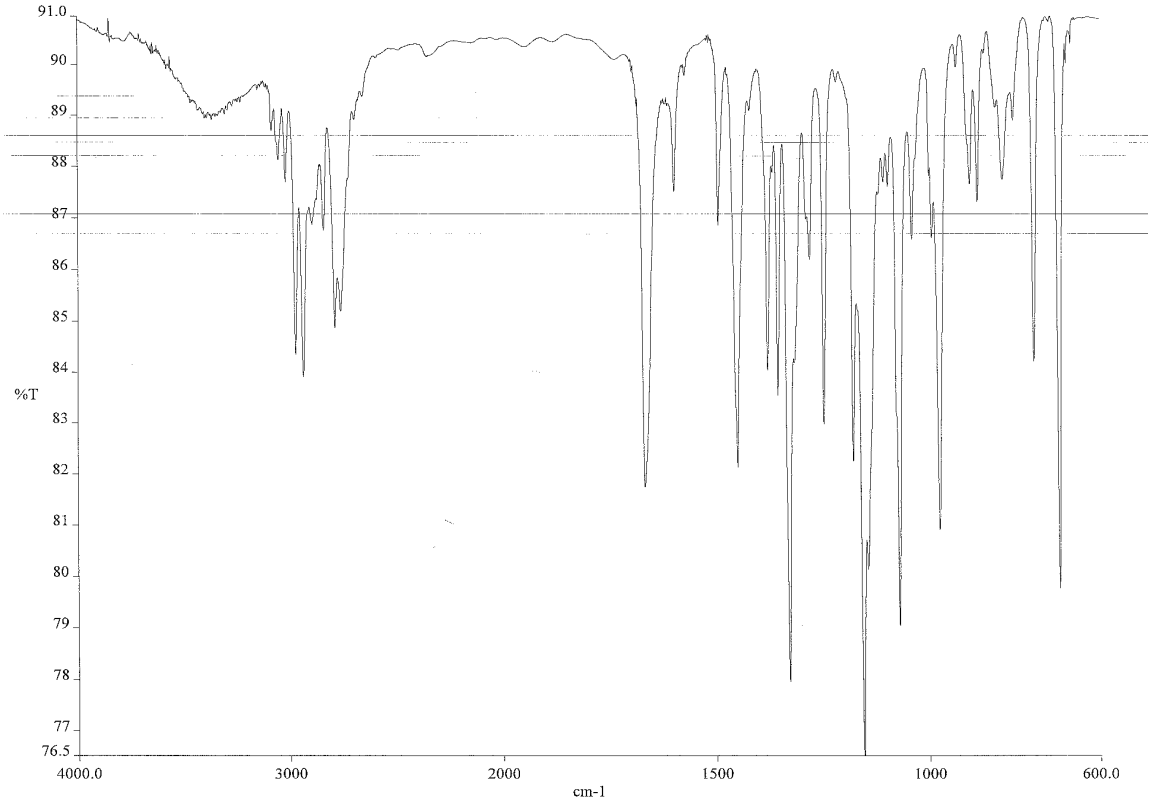


Figure A8.80. Infrared spectrum (Thin Film, NaCl) of compound **173b**.

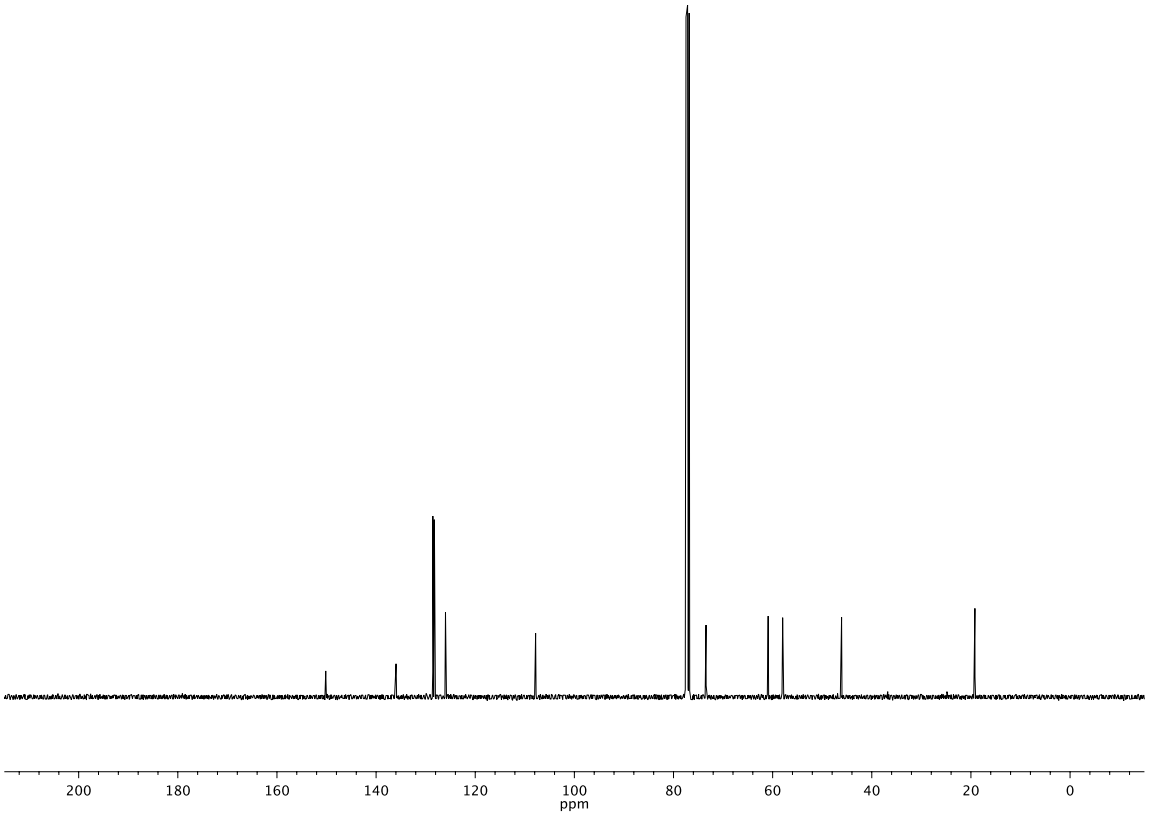


Figure A8.81. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **173b**.

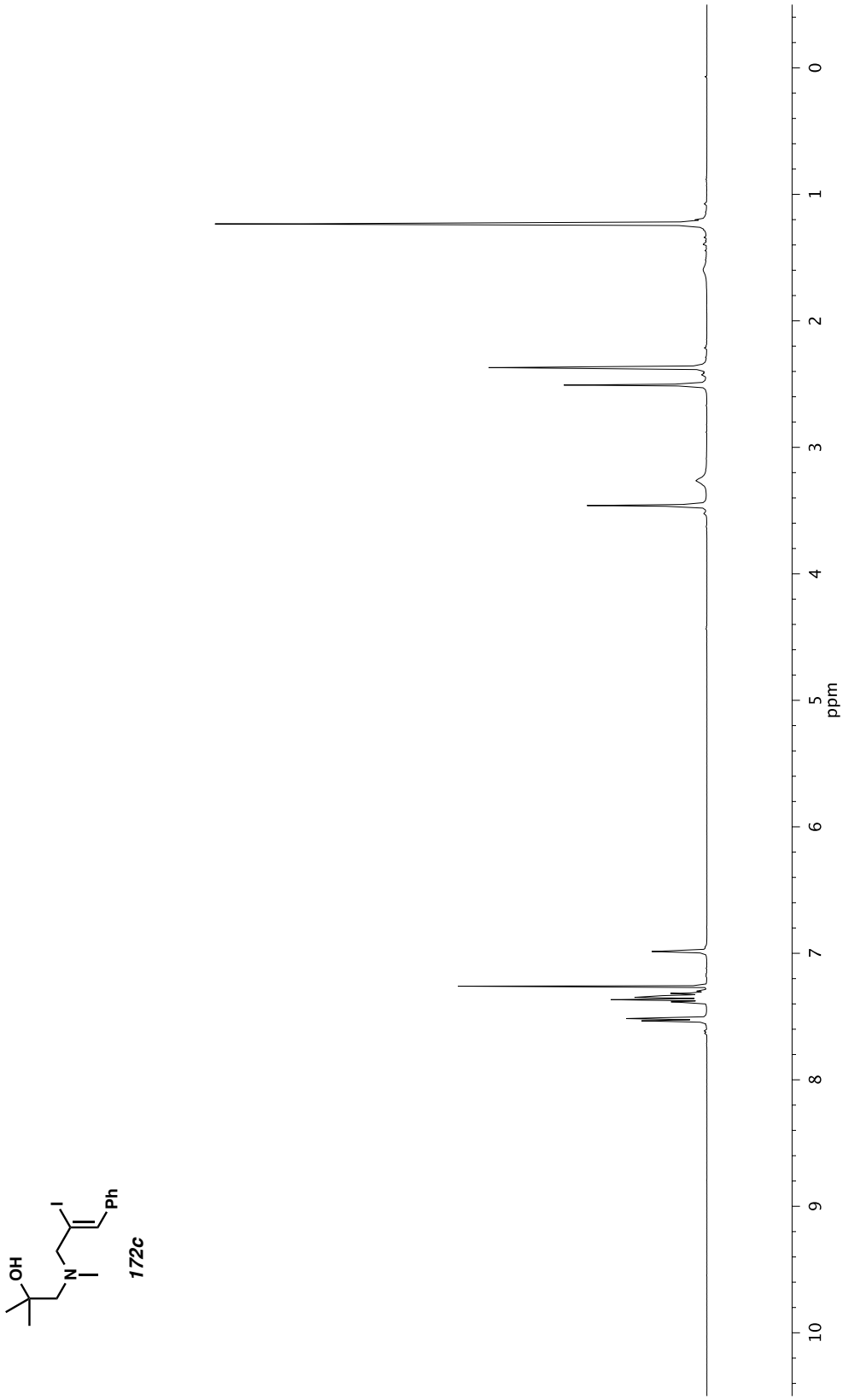


Figure A8.82. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **172c**.

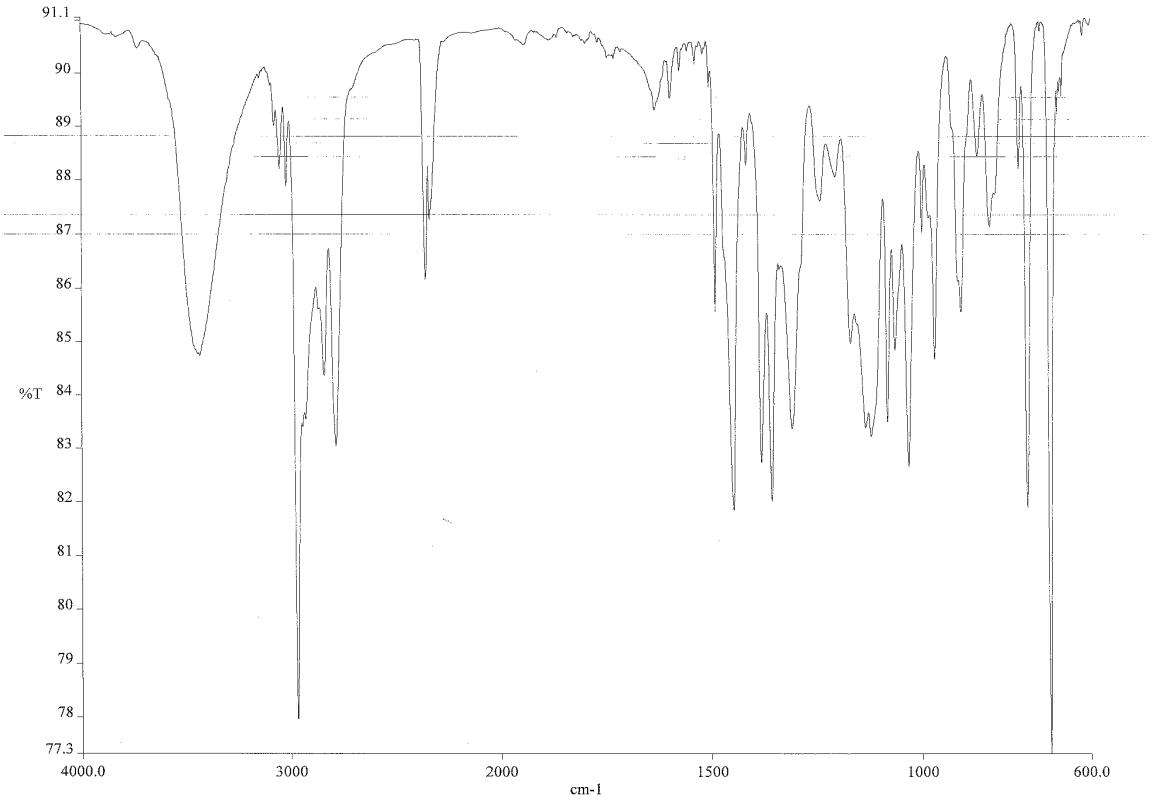


Figure A8.83. Infrared spectrum (Thin Film, NaCl) of compound **172c**.

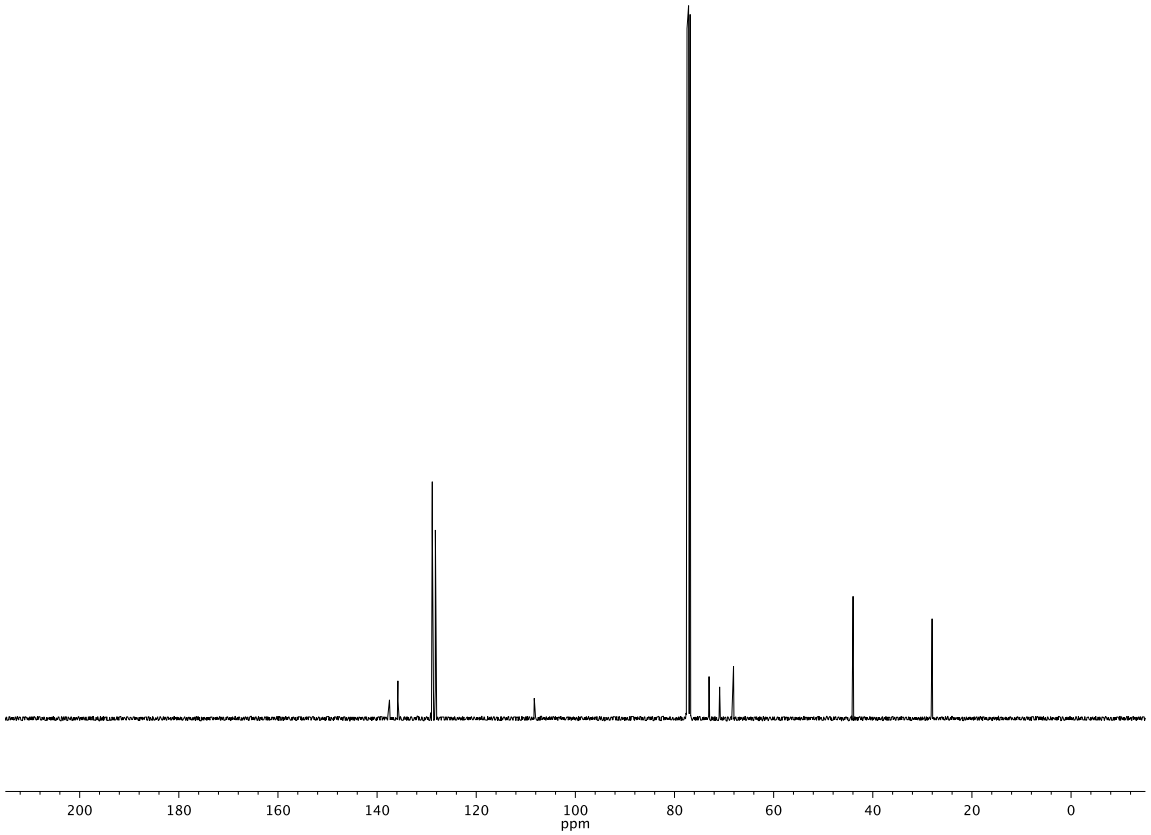


Figure A8.84. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **172c**.

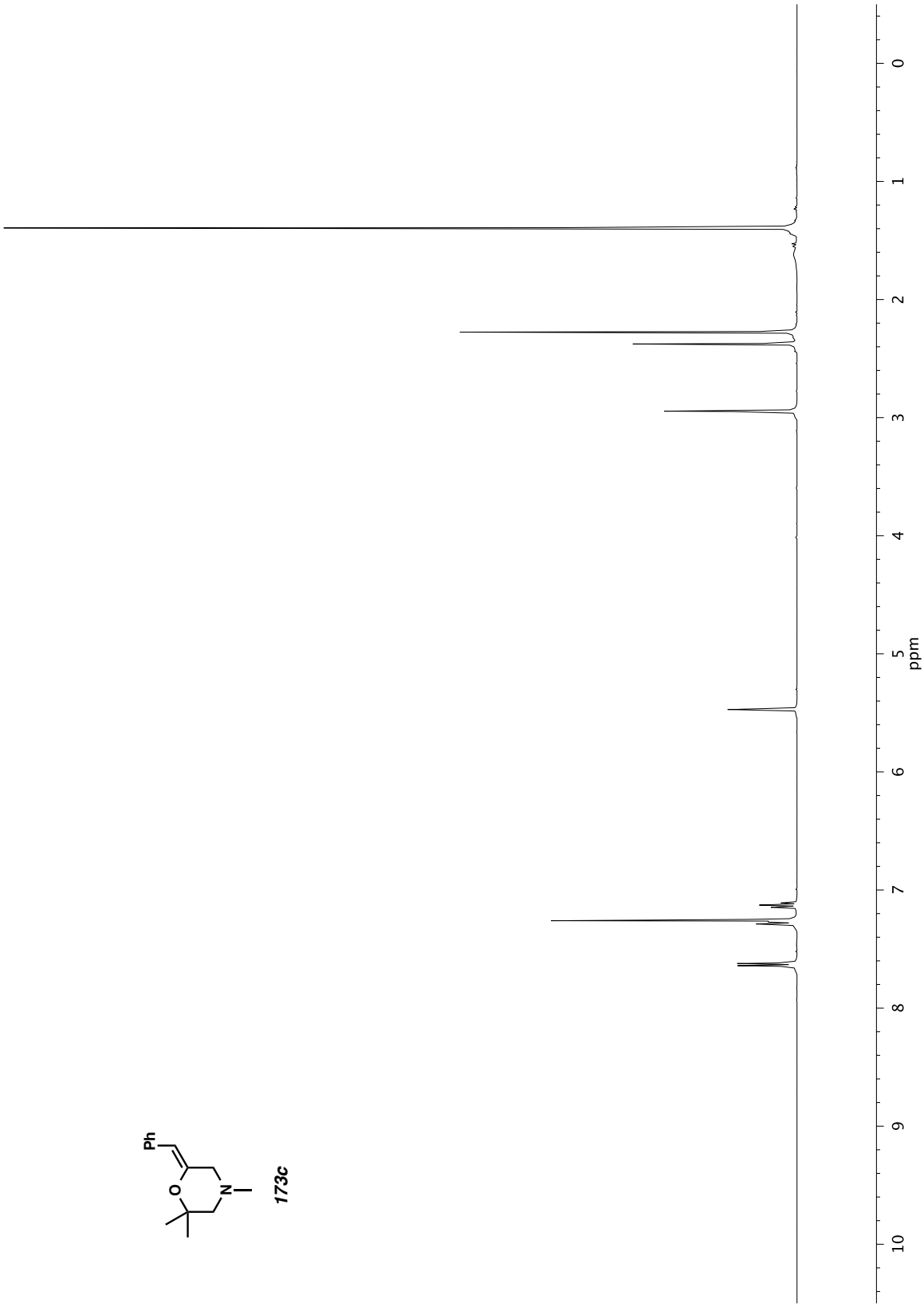


Figure A8.85. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **173c**.

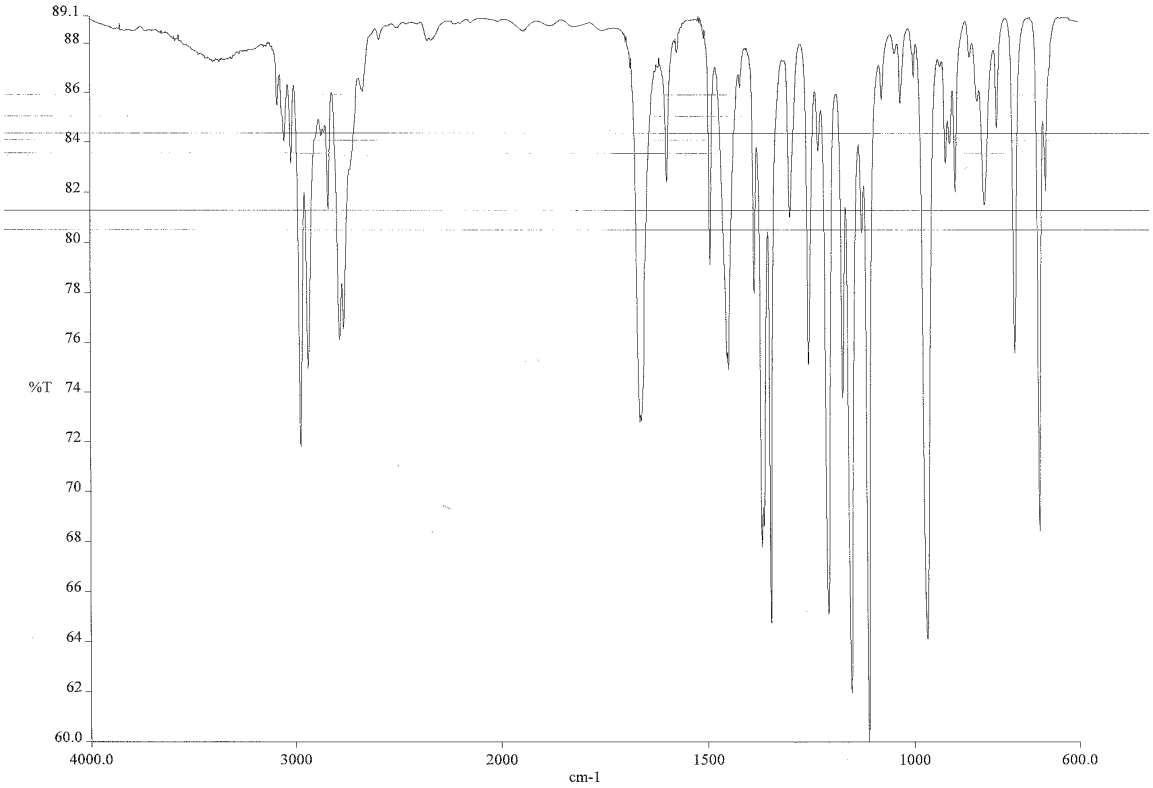


Figure A8.86. Infrared spectrum (Thin Film, NaCl) of compound **173c**.

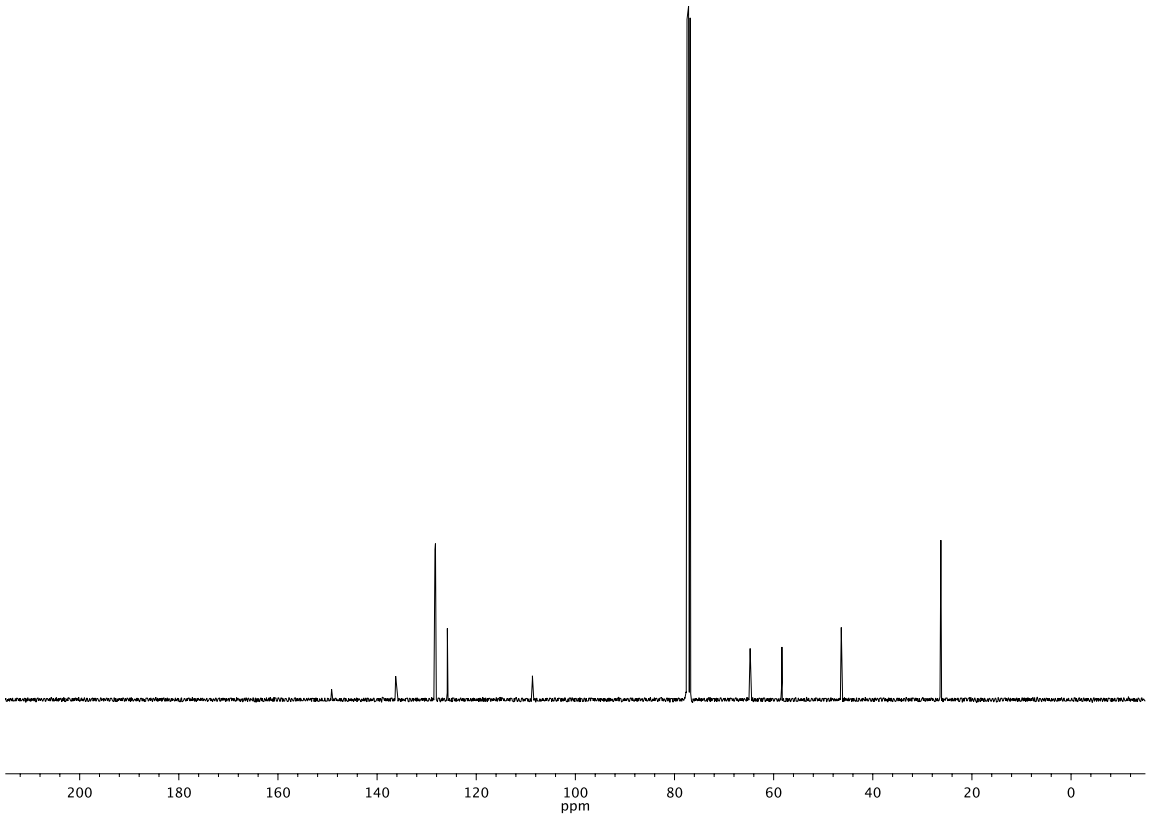


Figure A8.87. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **173c**.

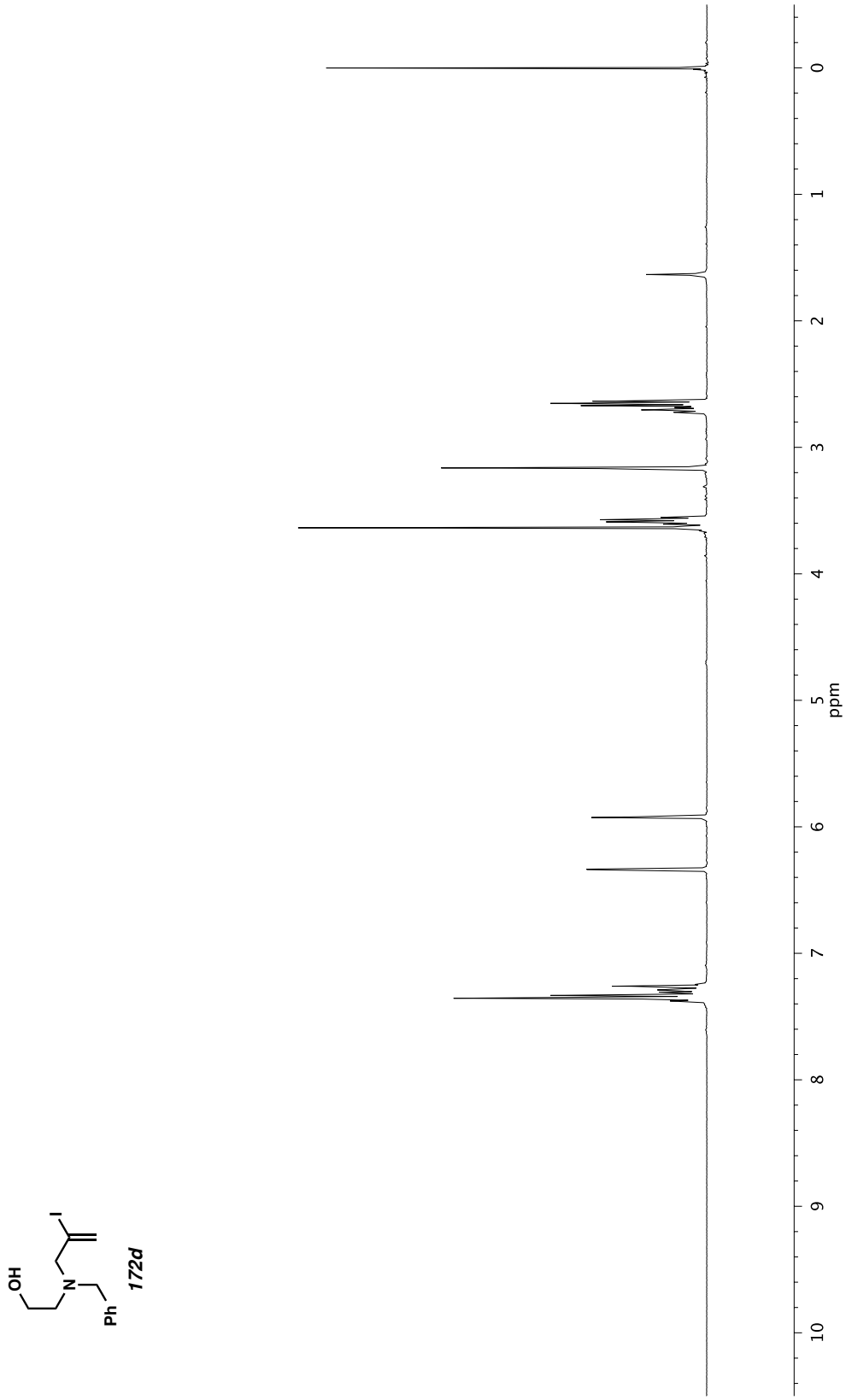


Figure A8.88. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **172d**.

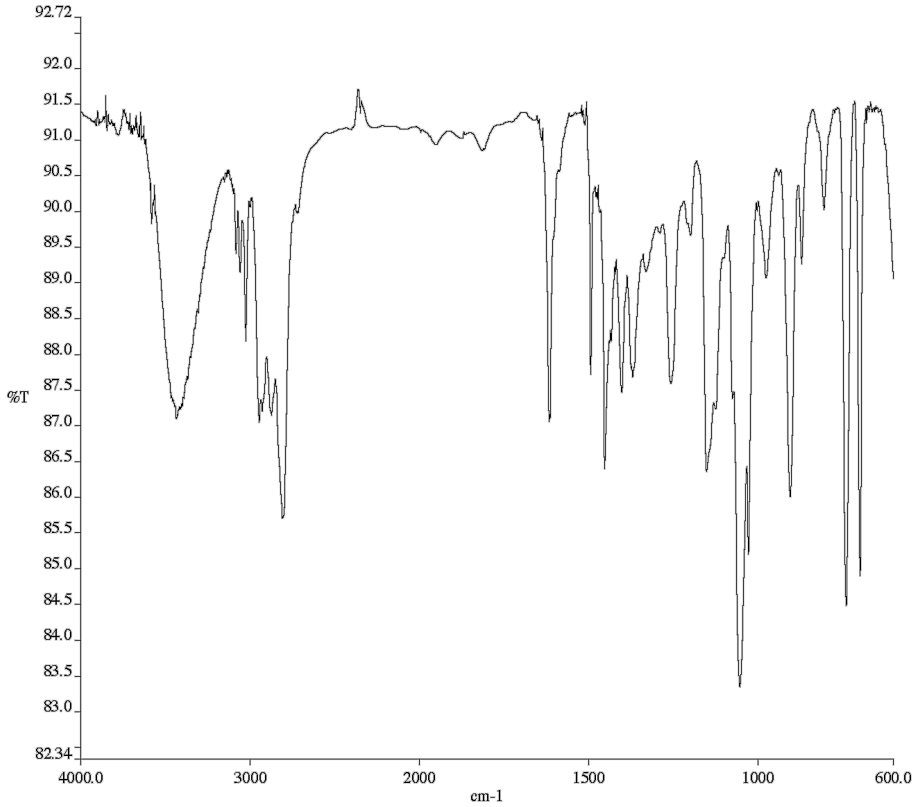


Figure A8.89. Infrared spectrum (Thin Film, NaCl) of compound **172d**.

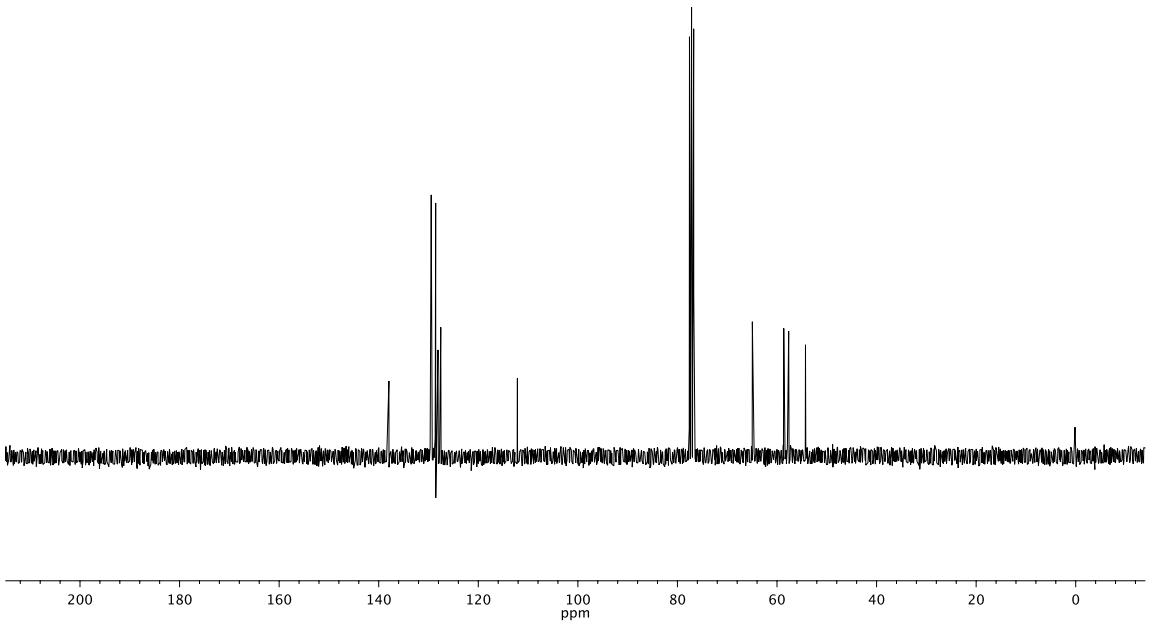


Figure A8.90. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **172d**.

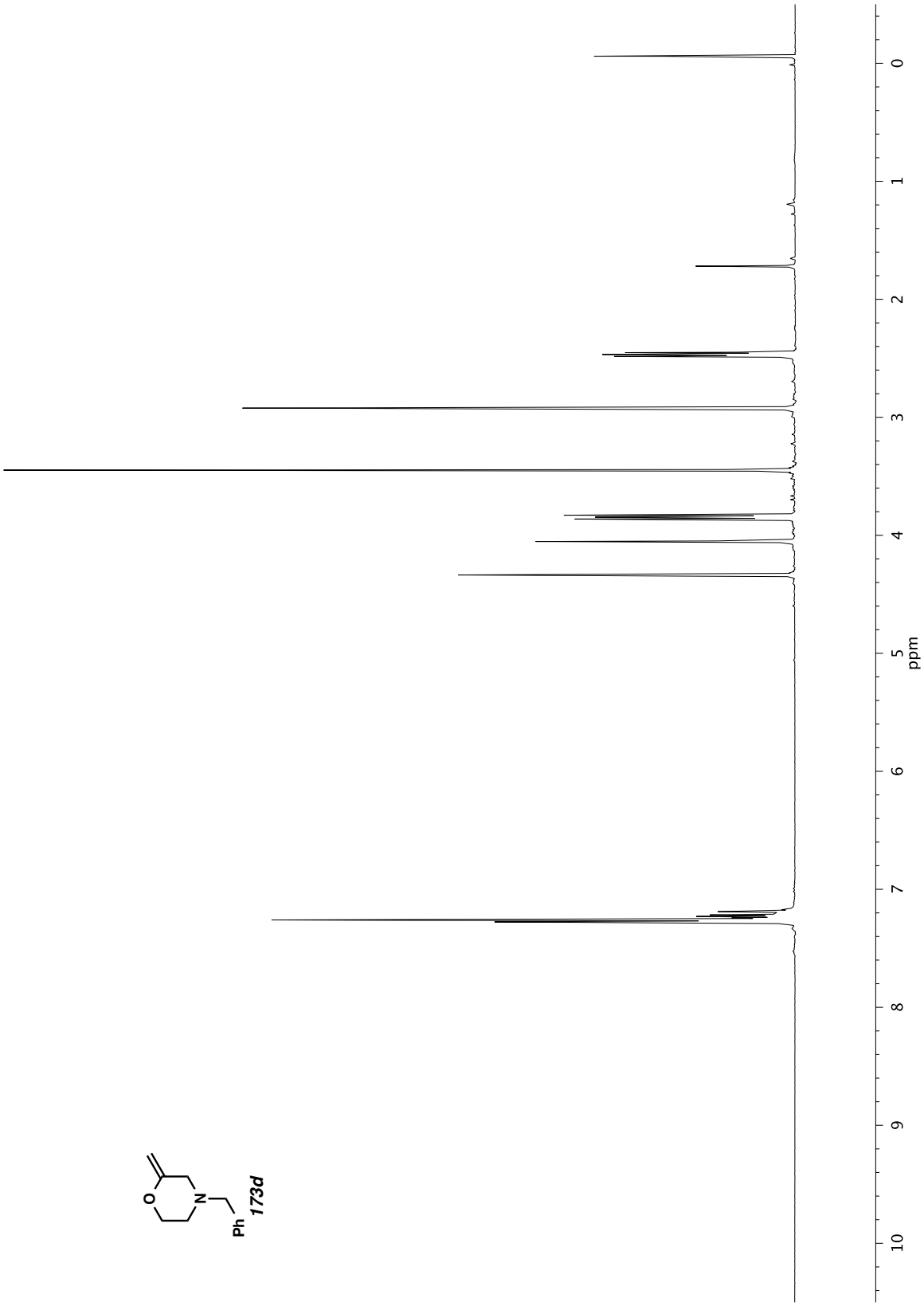


Figure A8.91. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **173d**.

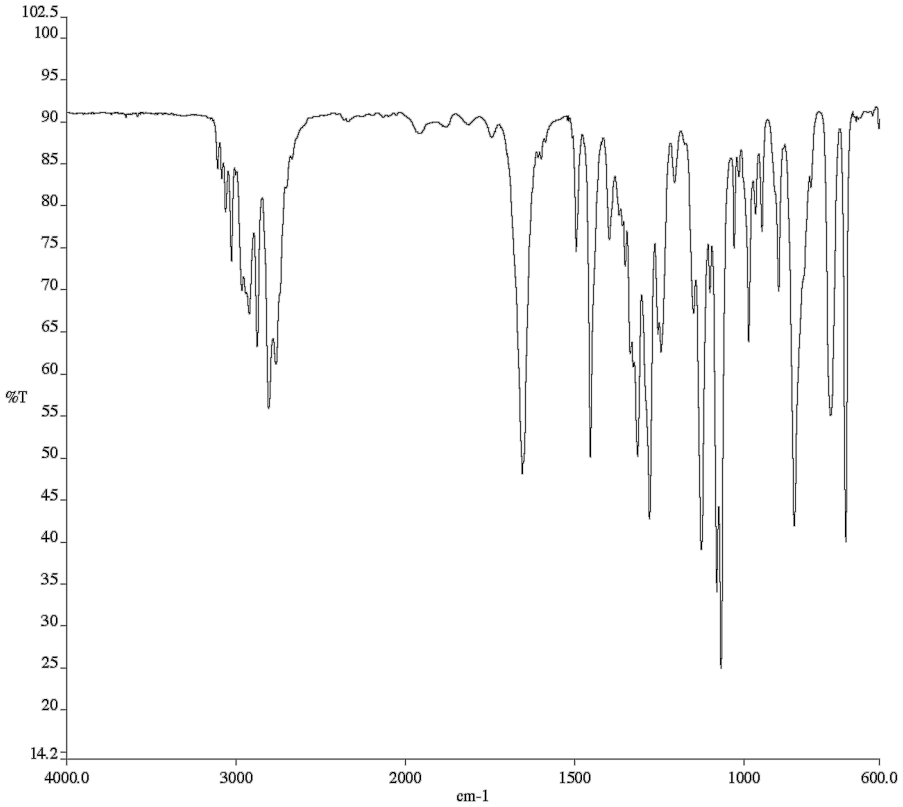


Figure A8.92. Infrared spectrum (Thin Film, NaCl) of compound **173d**.

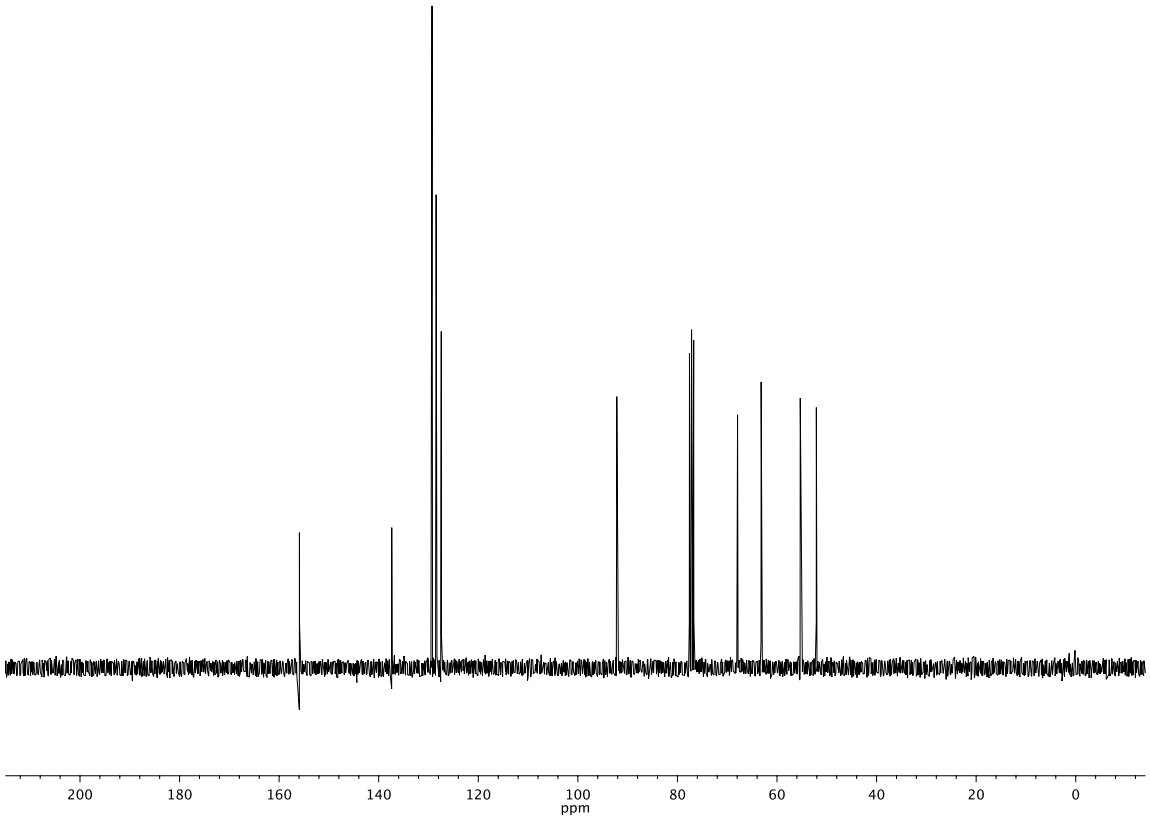


Figure A8.93. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **173d**.

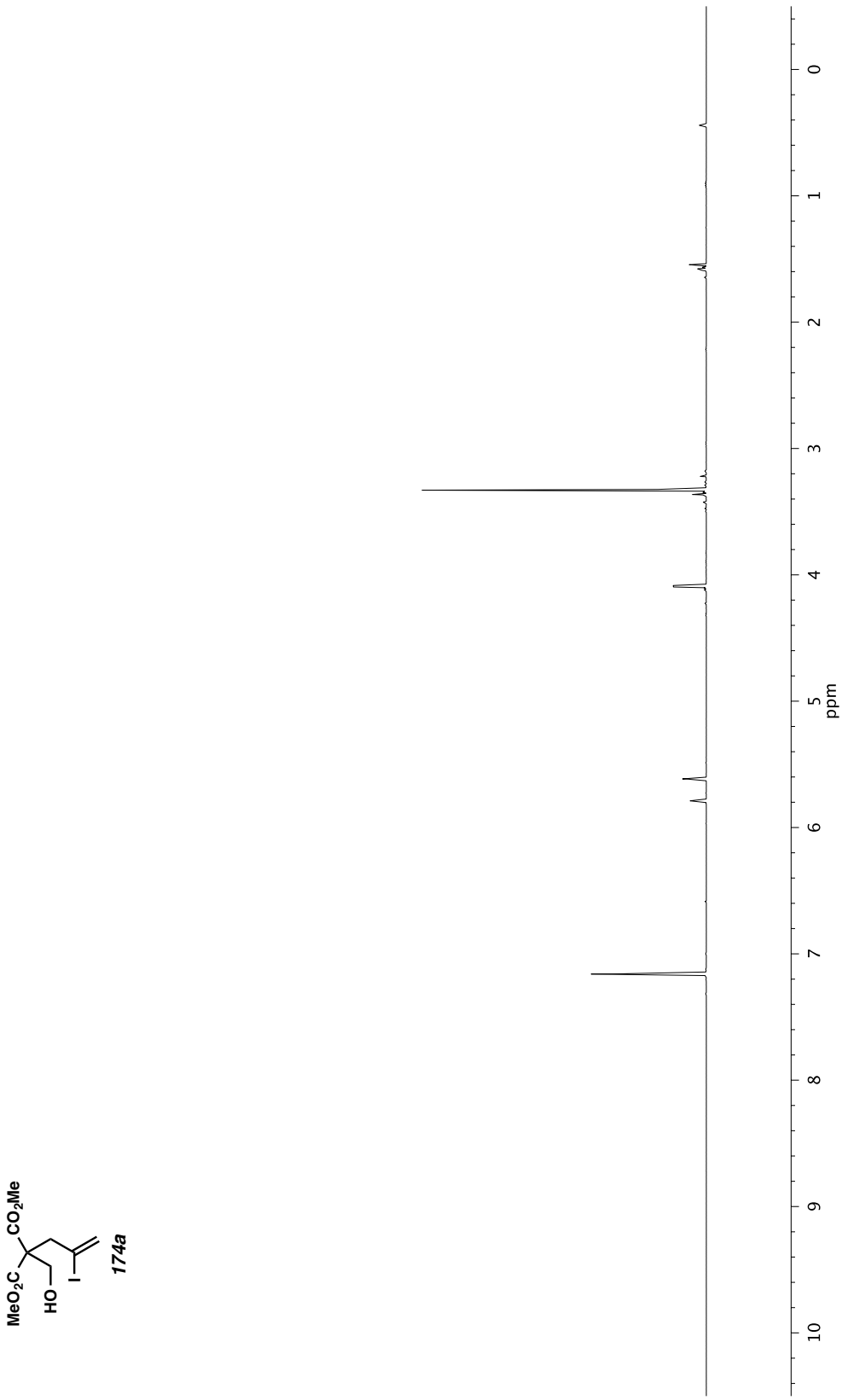


Figure A8.94. ^{1}H NMR (500 MHz, C_6D_6) of compound **174a**.

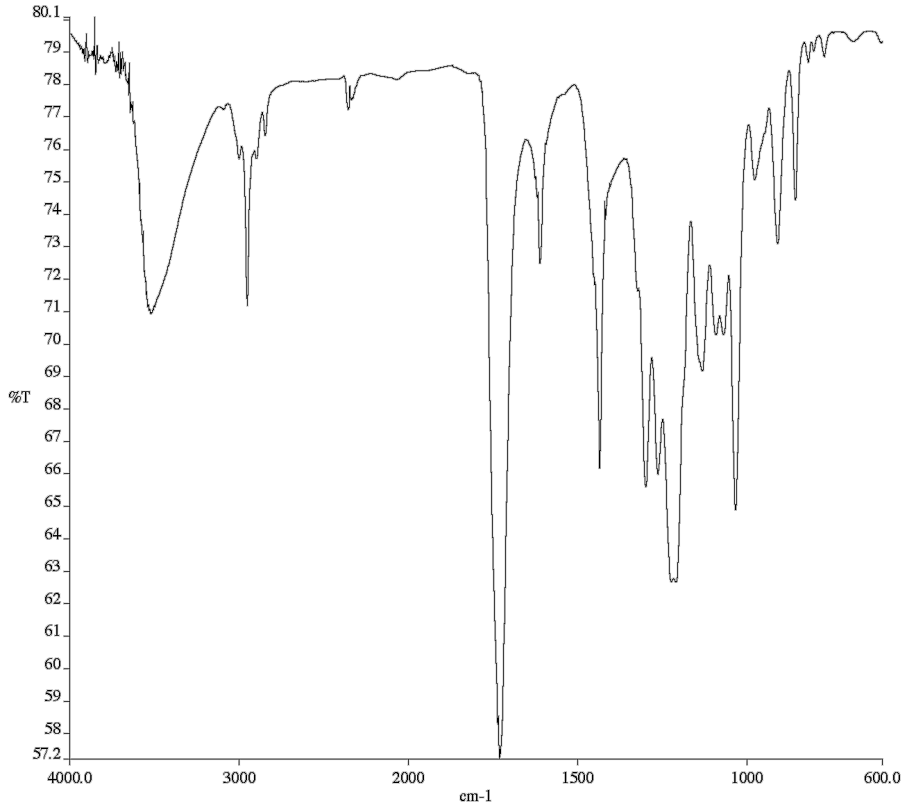


Figure A8.95. Infrared spectrum (Thin Film, NaCl) of compound **174a**.

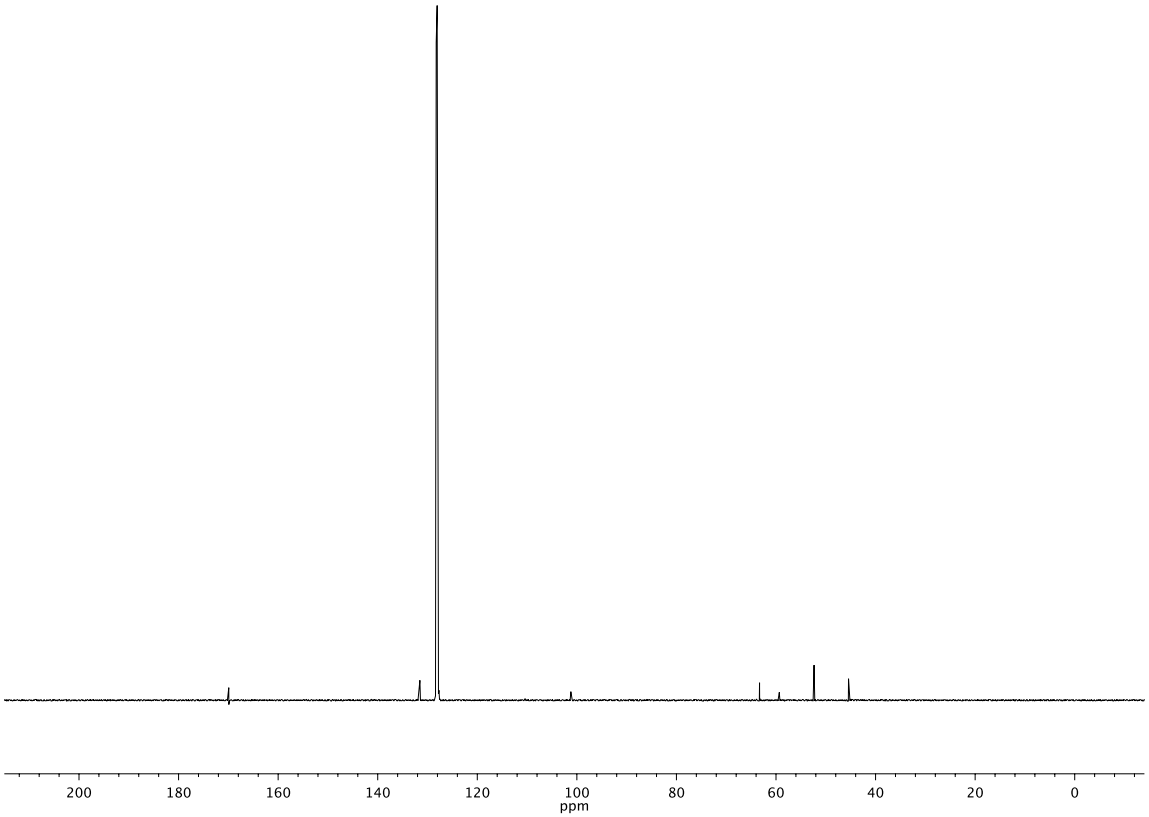


Figure A8.96. ^{13}C NMR (126 MHz, C_6D_6) of compound **174a**.

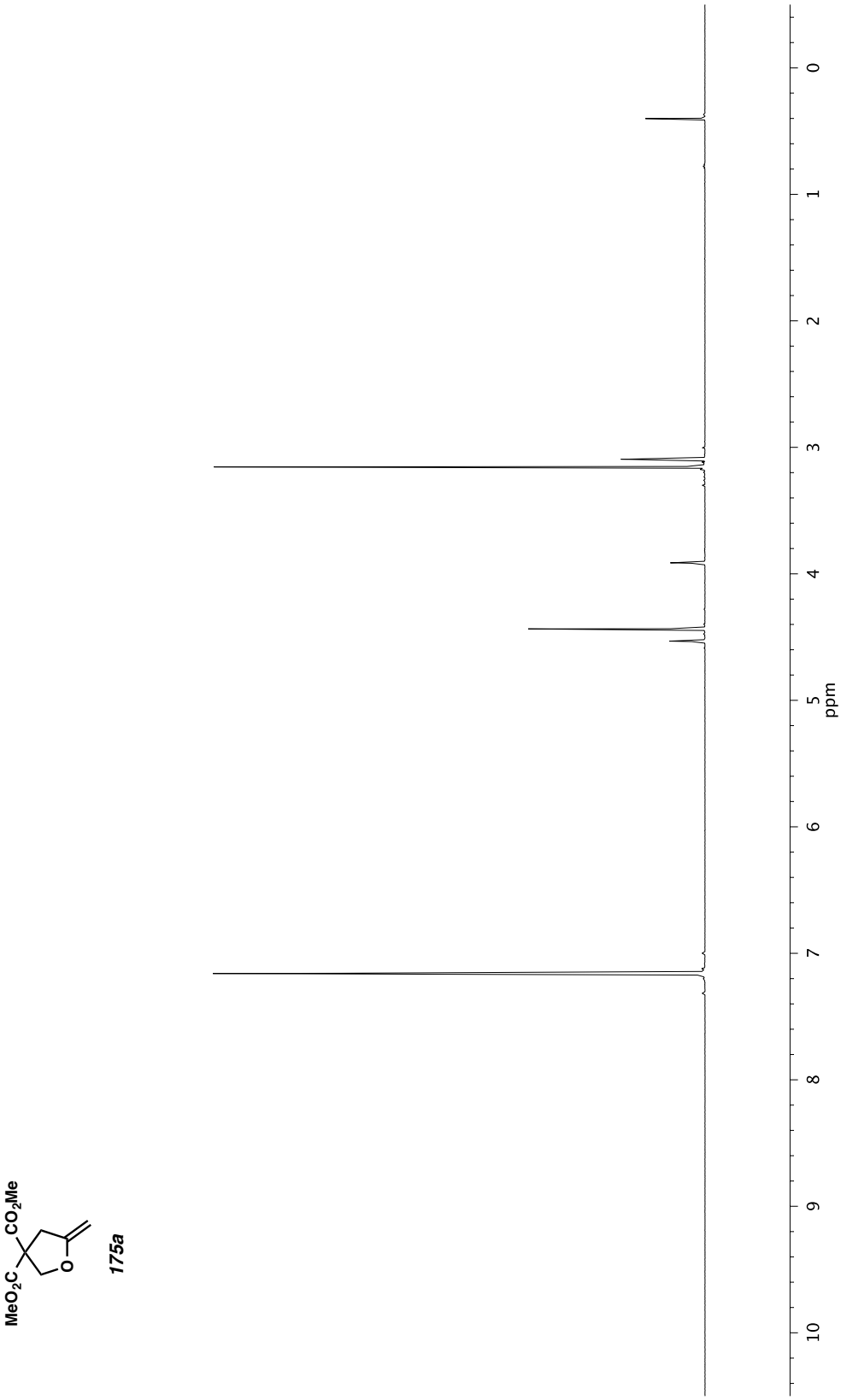


Figure A8.97. ^{1}H NMR (500 MHz, C_6D_6) of compound **175a**.

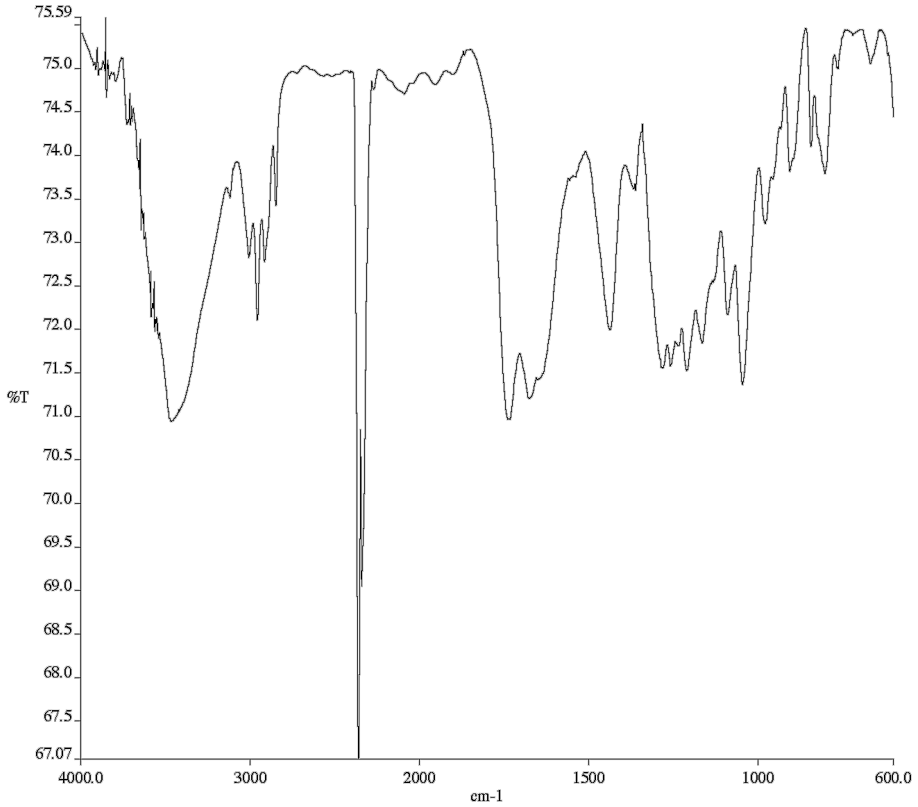


Figure A8.98. Infrared spectrum (Thin Film, NaCl) of compound **175a**.

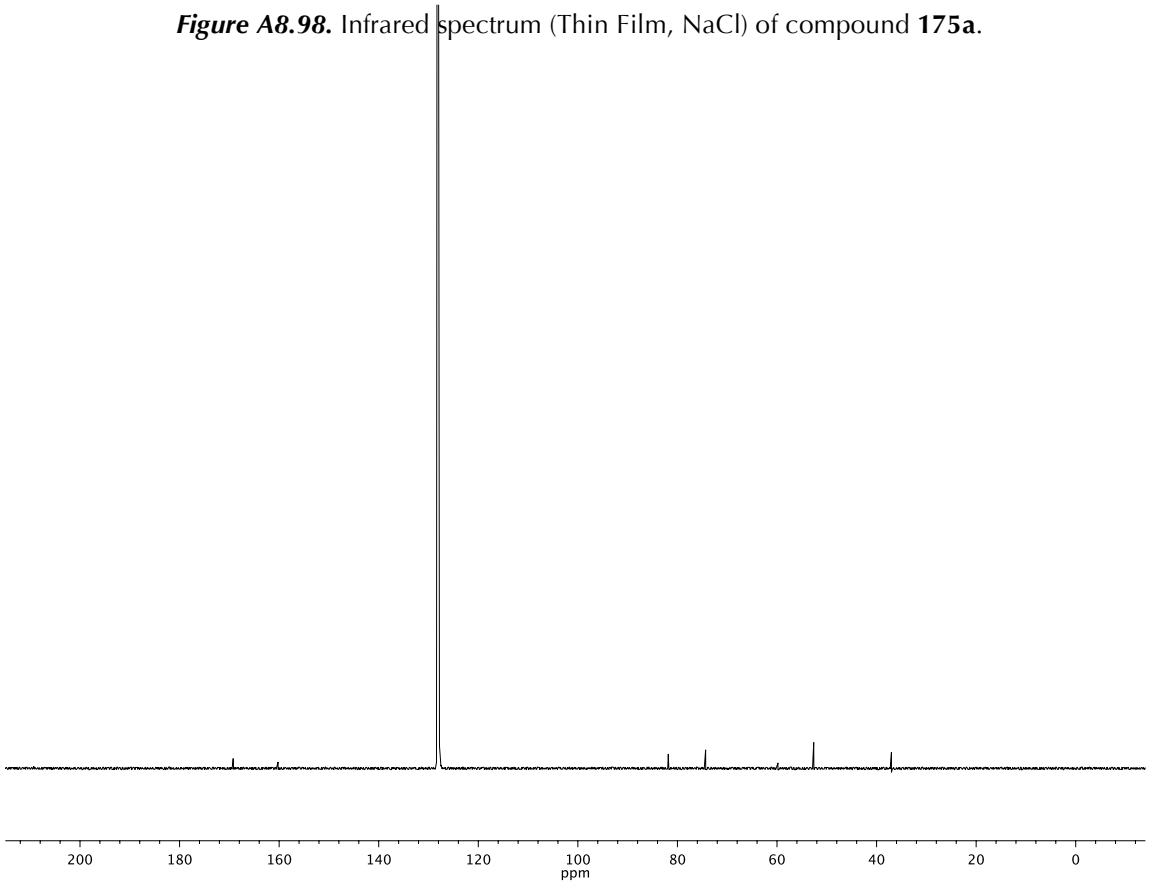


Figure A8.99. ^{13}C NMR (126 MHz, C_6D_6) of compound **175a**.

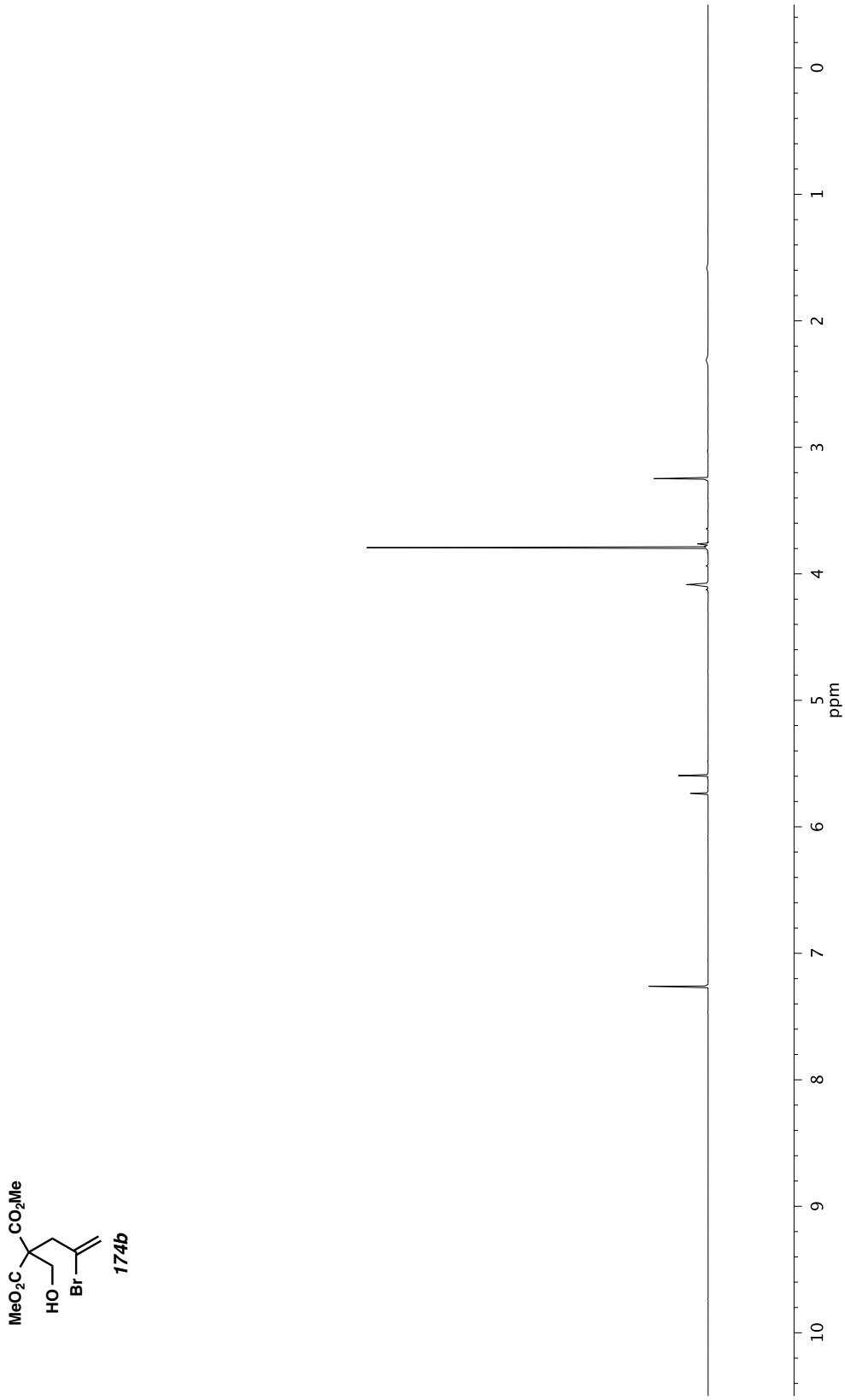


Figure A8.100. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **174b**.

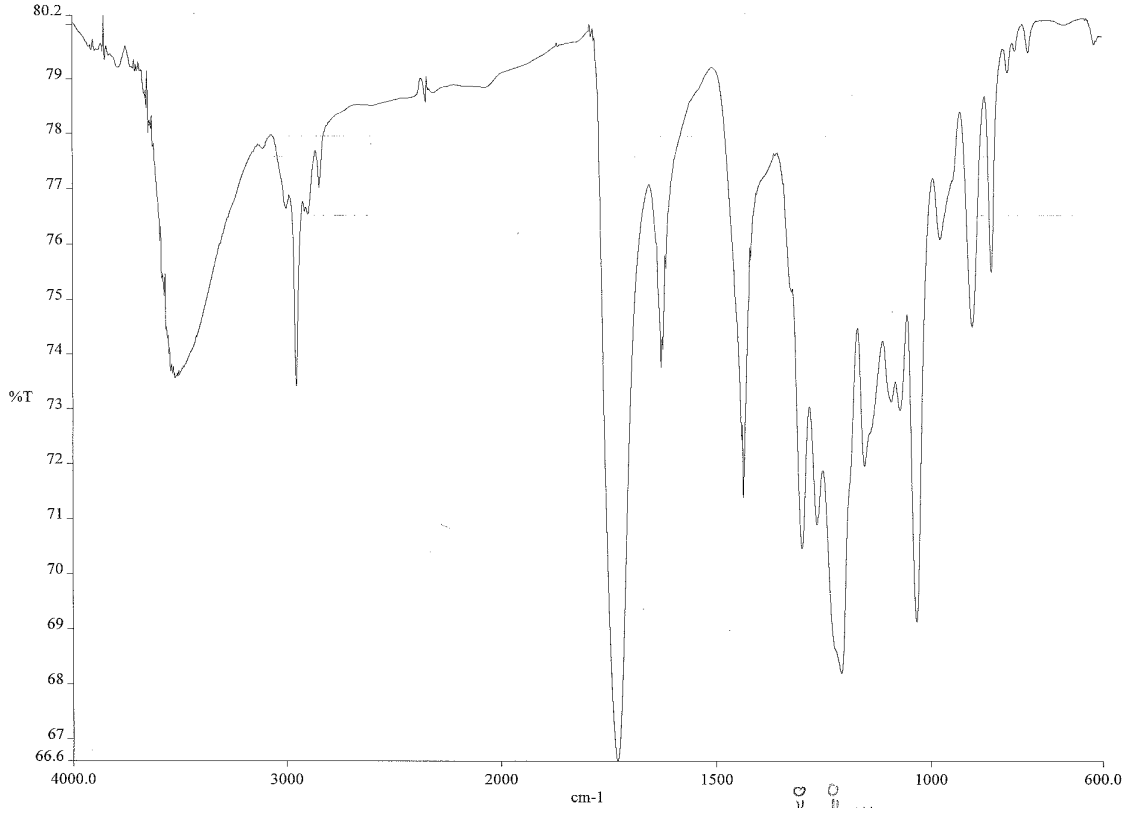


Figure A8.101. Infrared spectrum (Thin Film, NaCl) of compound **174b**.

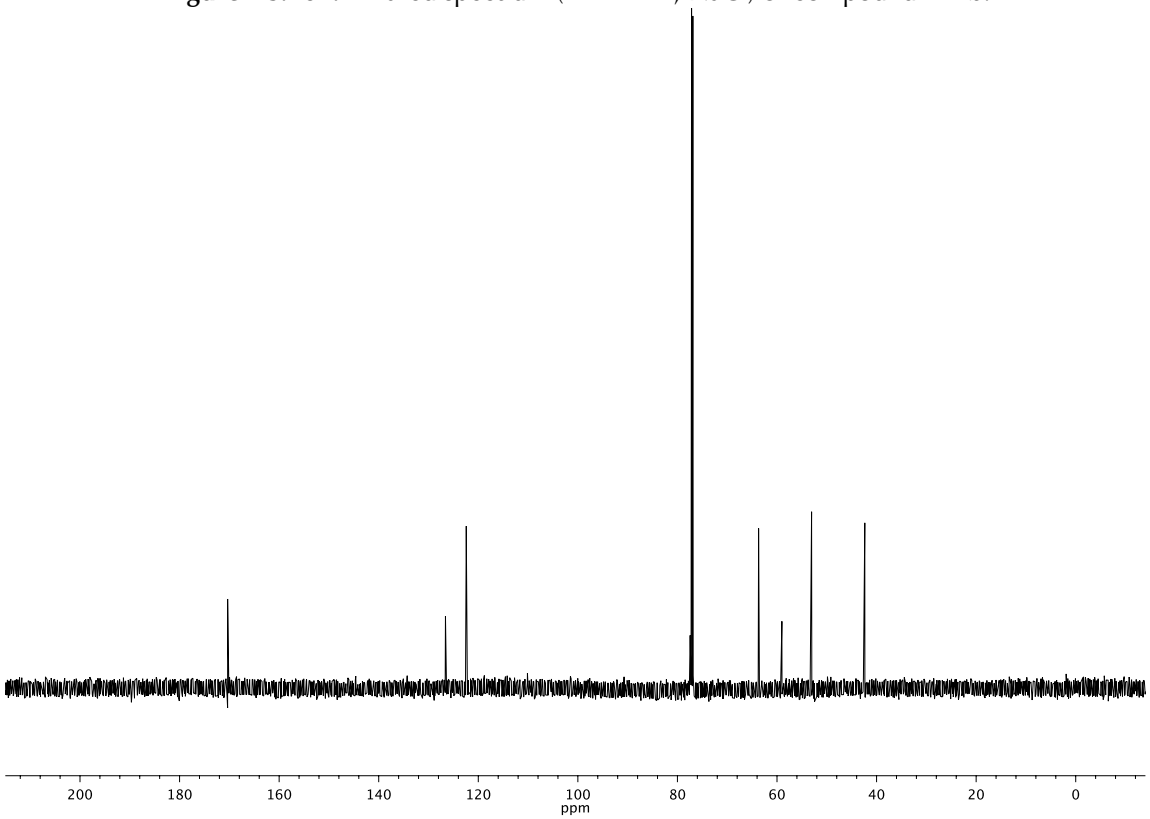


Figure A8.102. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **174b**.

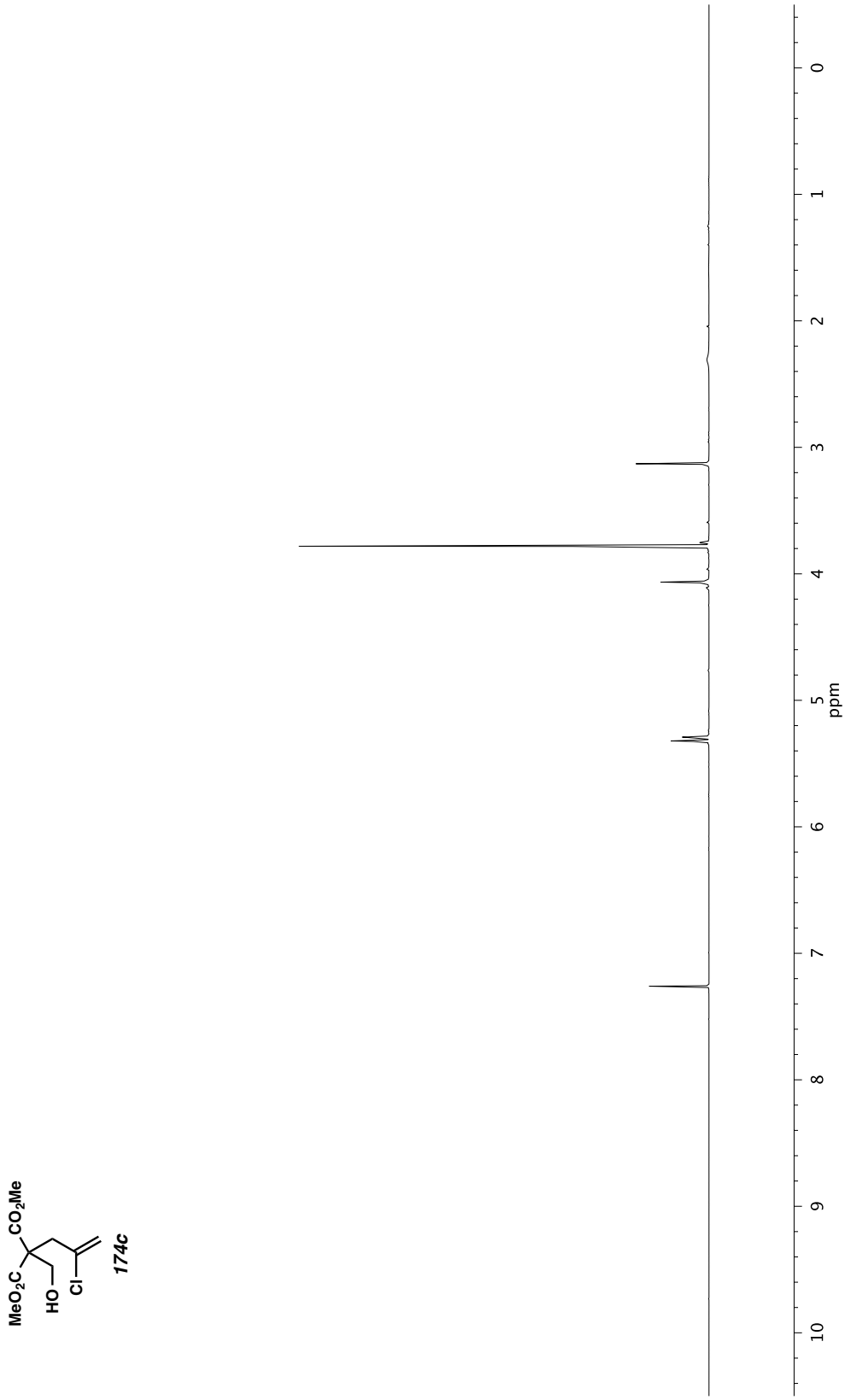


Figure A8.103. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **174c**.

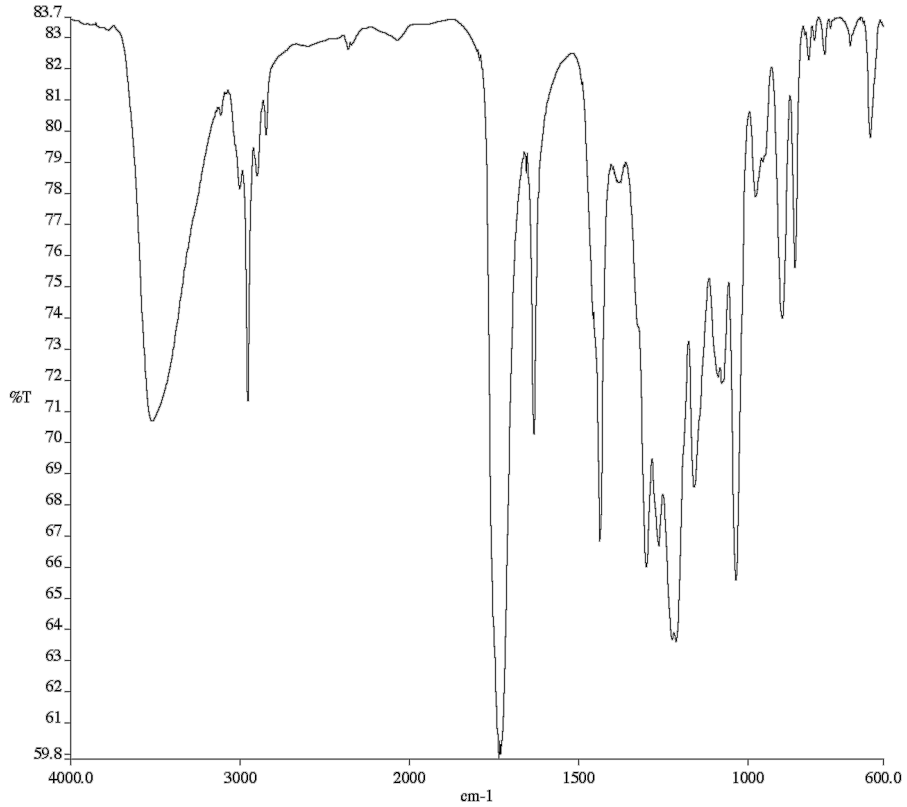


Figure A8.104. Infrared spectrum (Thin Film, NaCl) of compound **174c**.

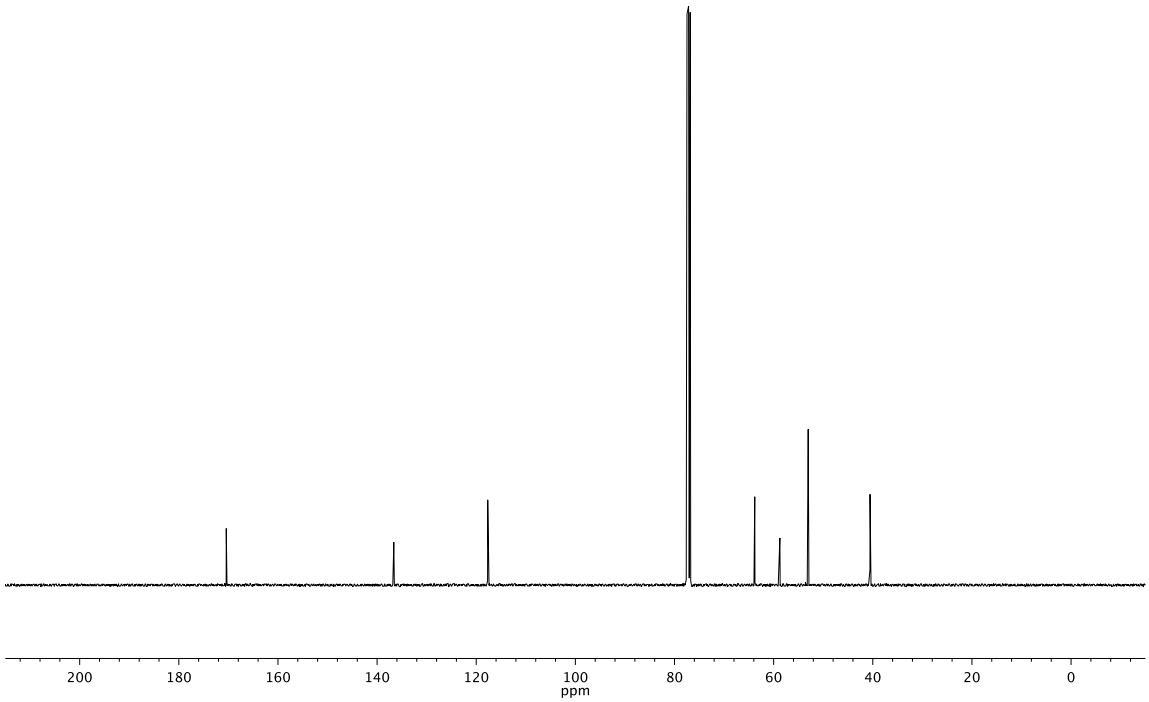


Figure A8.105. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **174c**.

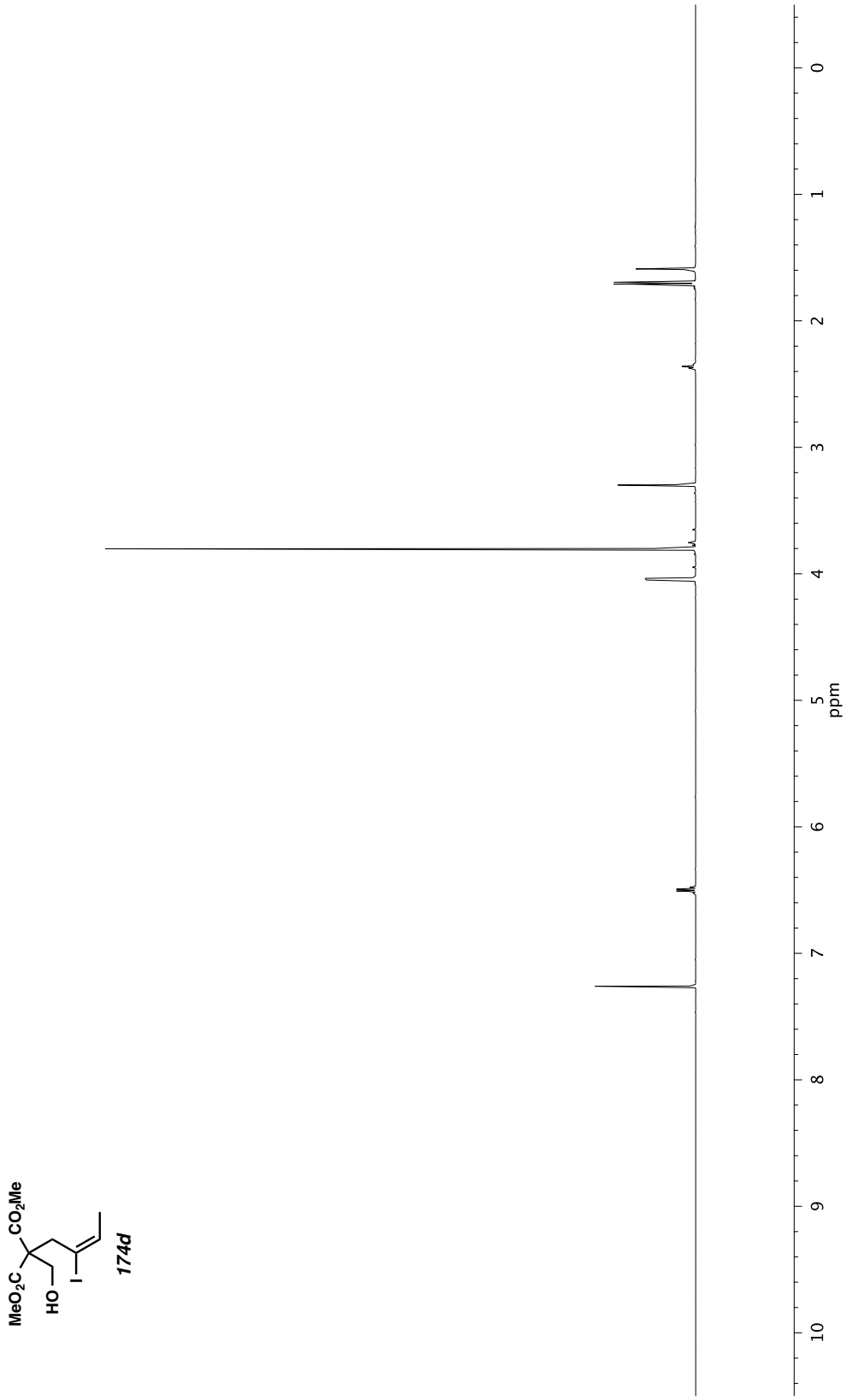


Figure A8.106. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **174d**.

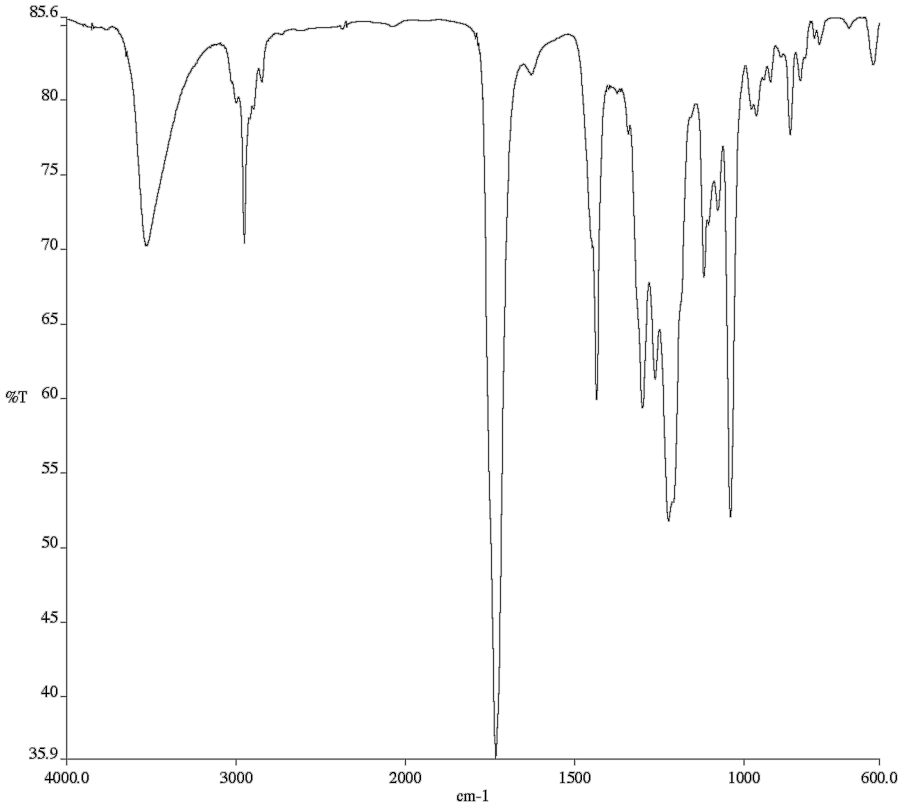


Figure A8.107. Infrared spectrum (Thin Film, NaCl) of compound **174d**.

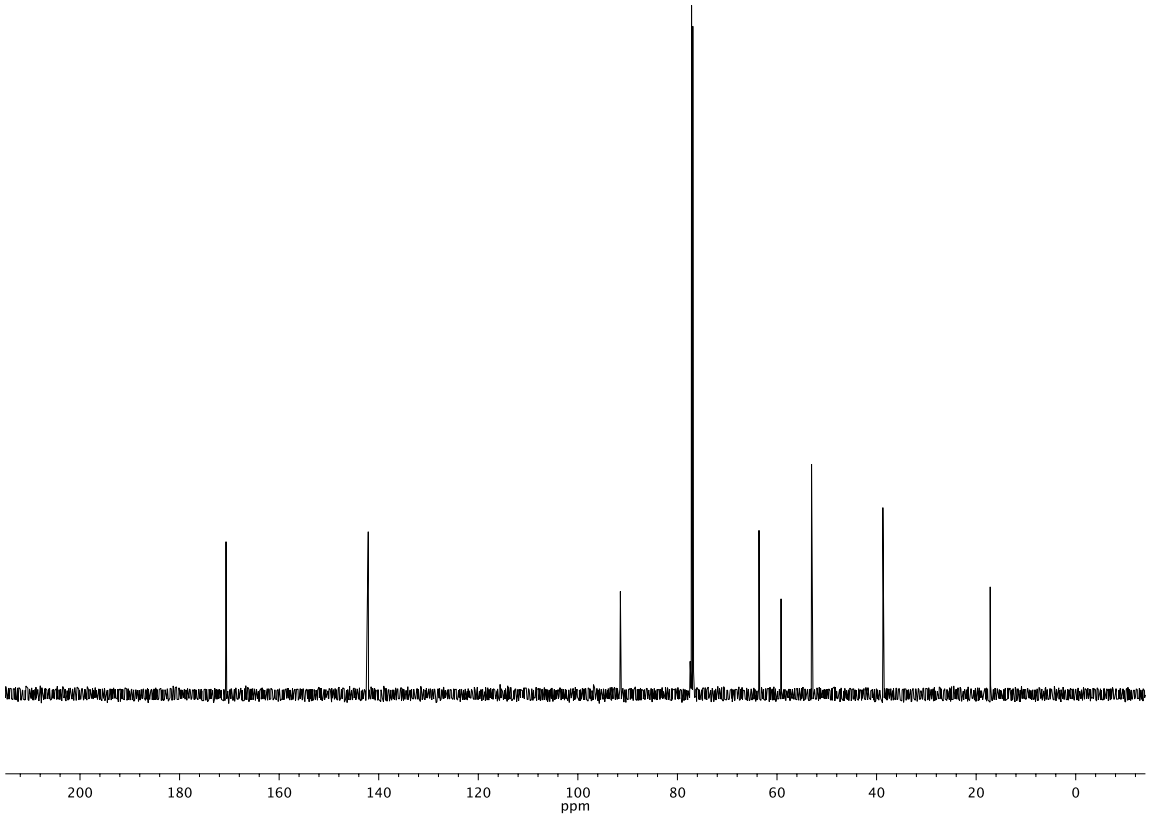


Figure A8.108. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **174d**.

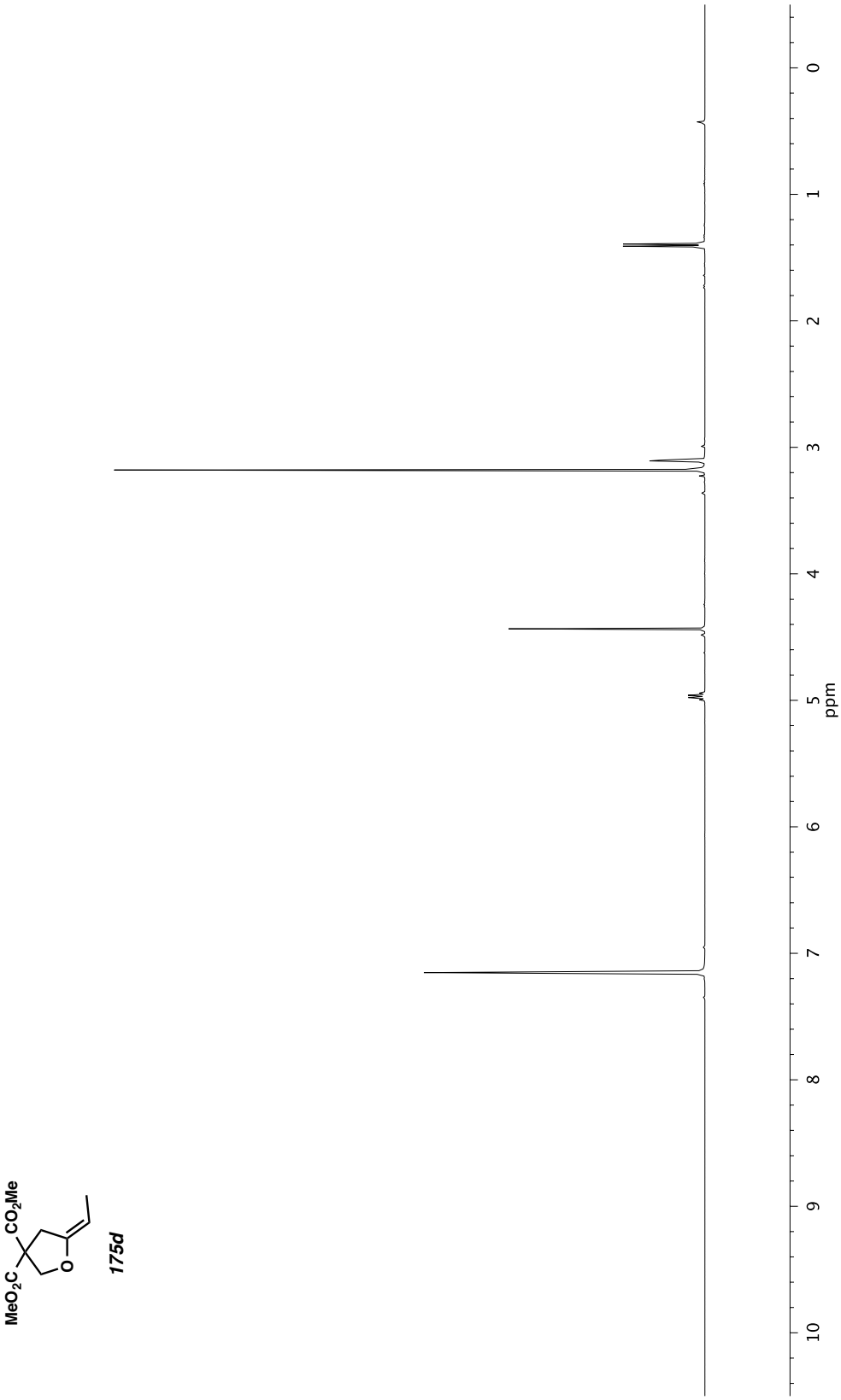


Figure A8.109. ^{1}H NMR (400 MHz, C_6D_6) of compound **175d**.

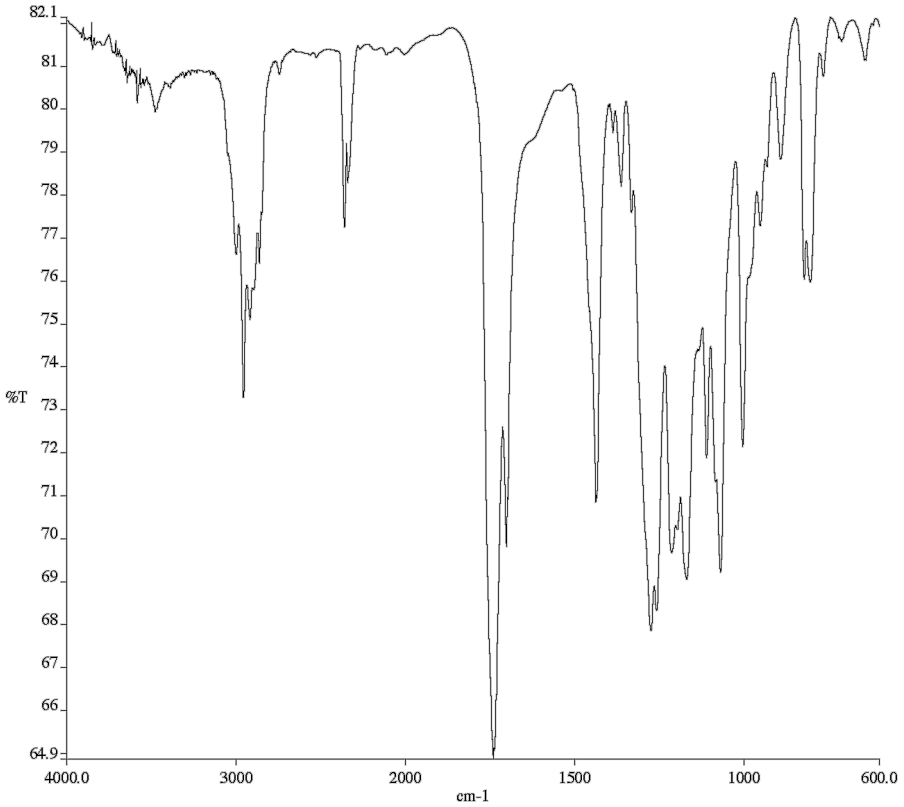


Figure A8.110. Infrared spectrum (Thin Film, NaCl) of compound **175d**.

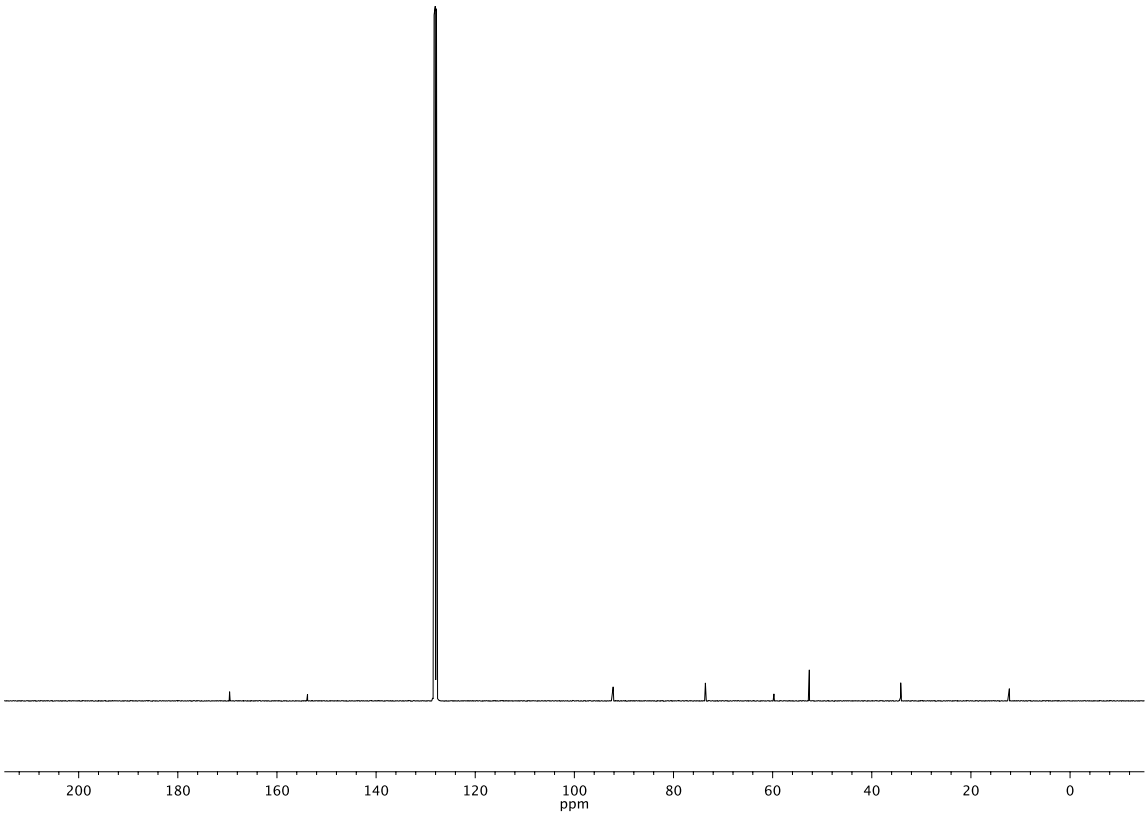


Figure A8.111. ^{13}C NMR (101 MHz, C_6D_6) of compound **175d**.

Figure A8.112. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **174e**.

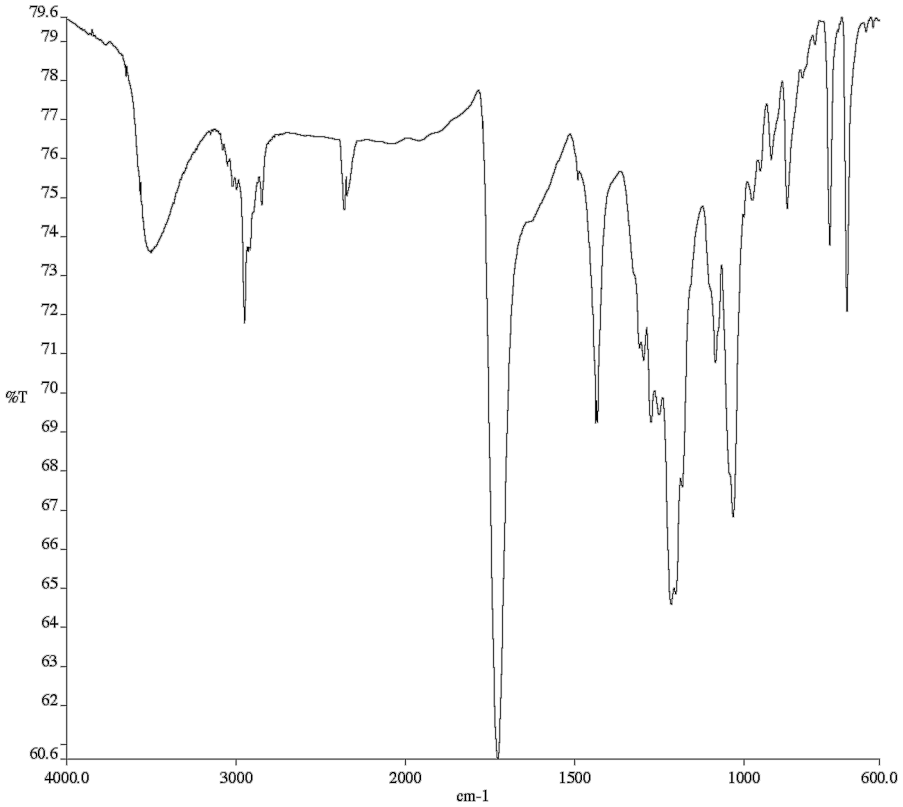


Figure A8.113. Infrared spectrum (Thin Film, NaCl) of compound **174e**.

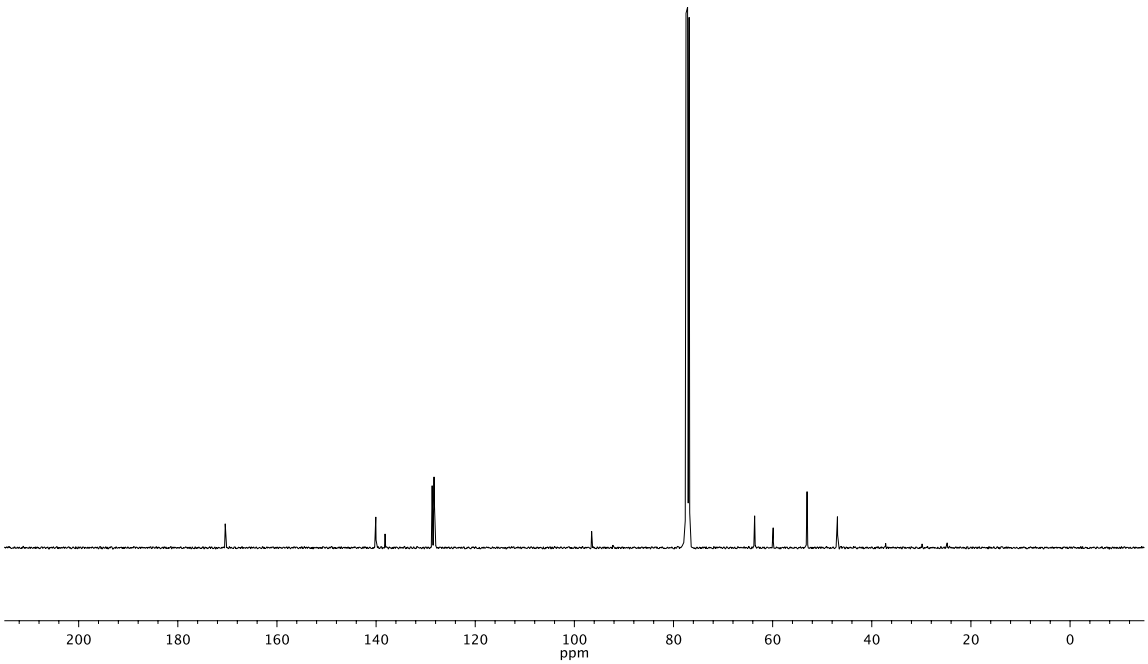


Figure A8.114. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **174e**.

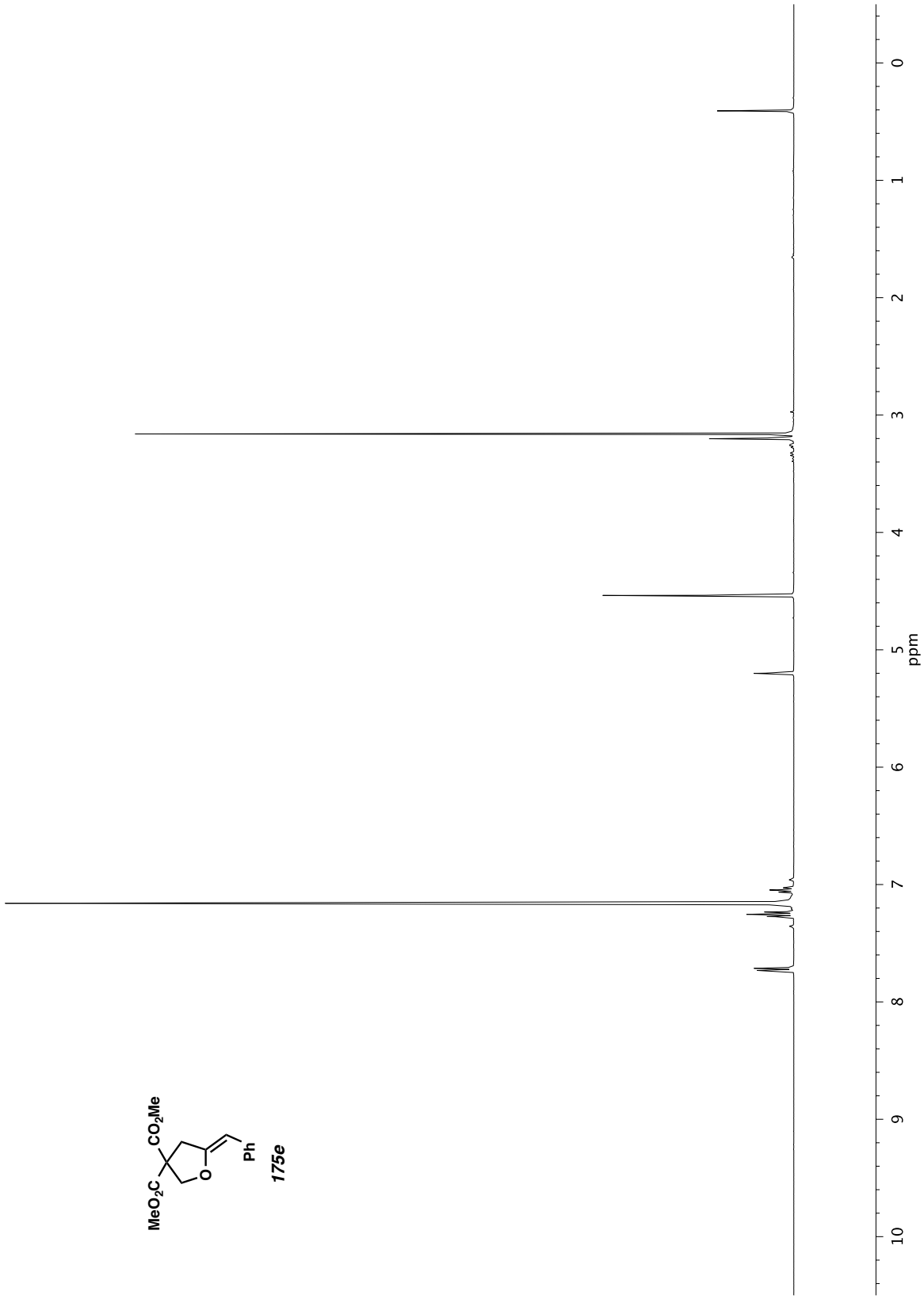


Figure A8.115. ^{1}H NMR (400 MHz, C_6D_6) of compound **175e**.

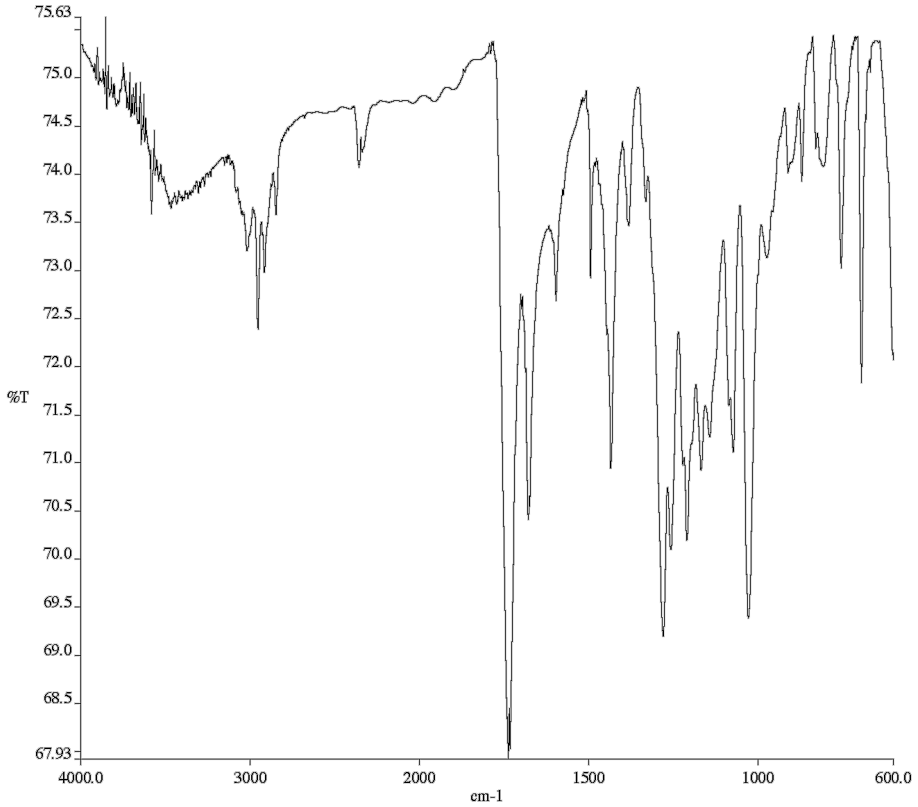


Figure A8.116. Infrared spectrum (Thin Film, NaCl) of compound **175e**.

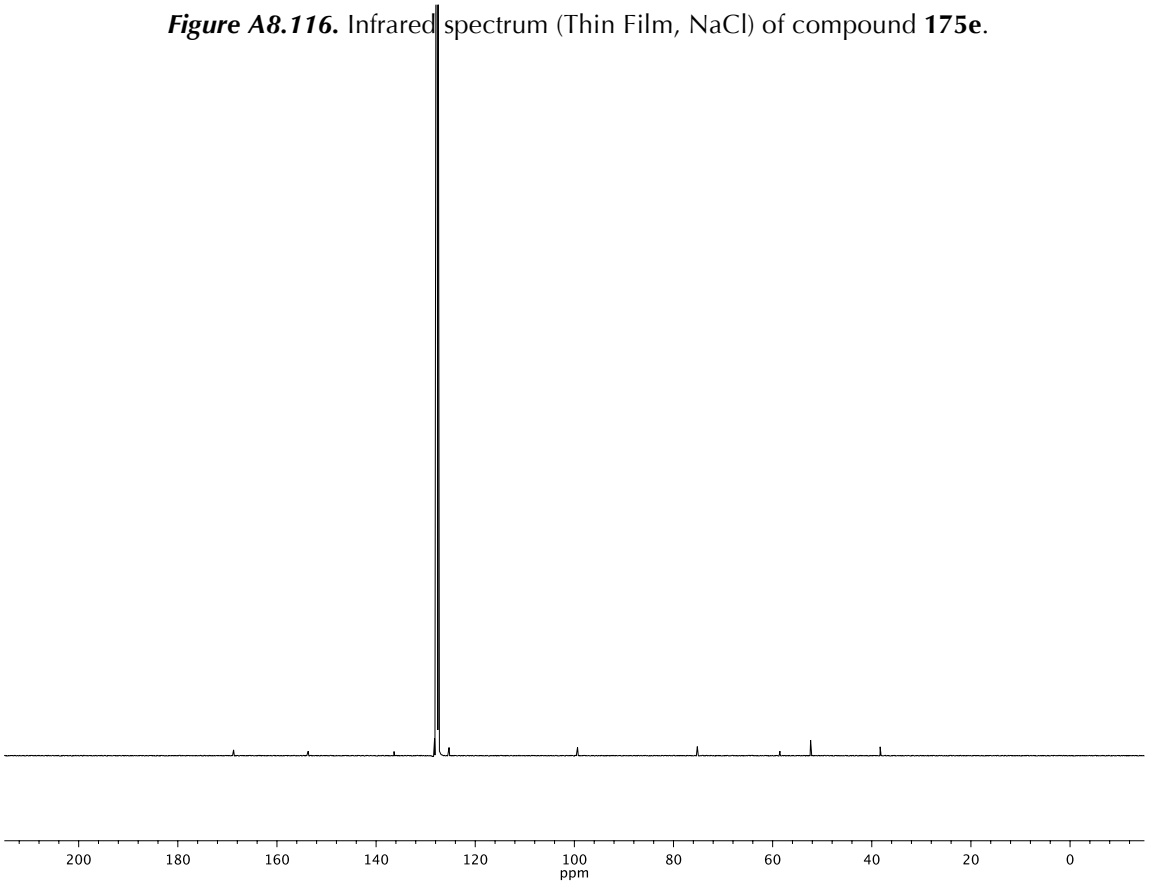


Figure A8.117. ^{13}C NMR (101 MHz, C_6D_6) of compound **175e**.

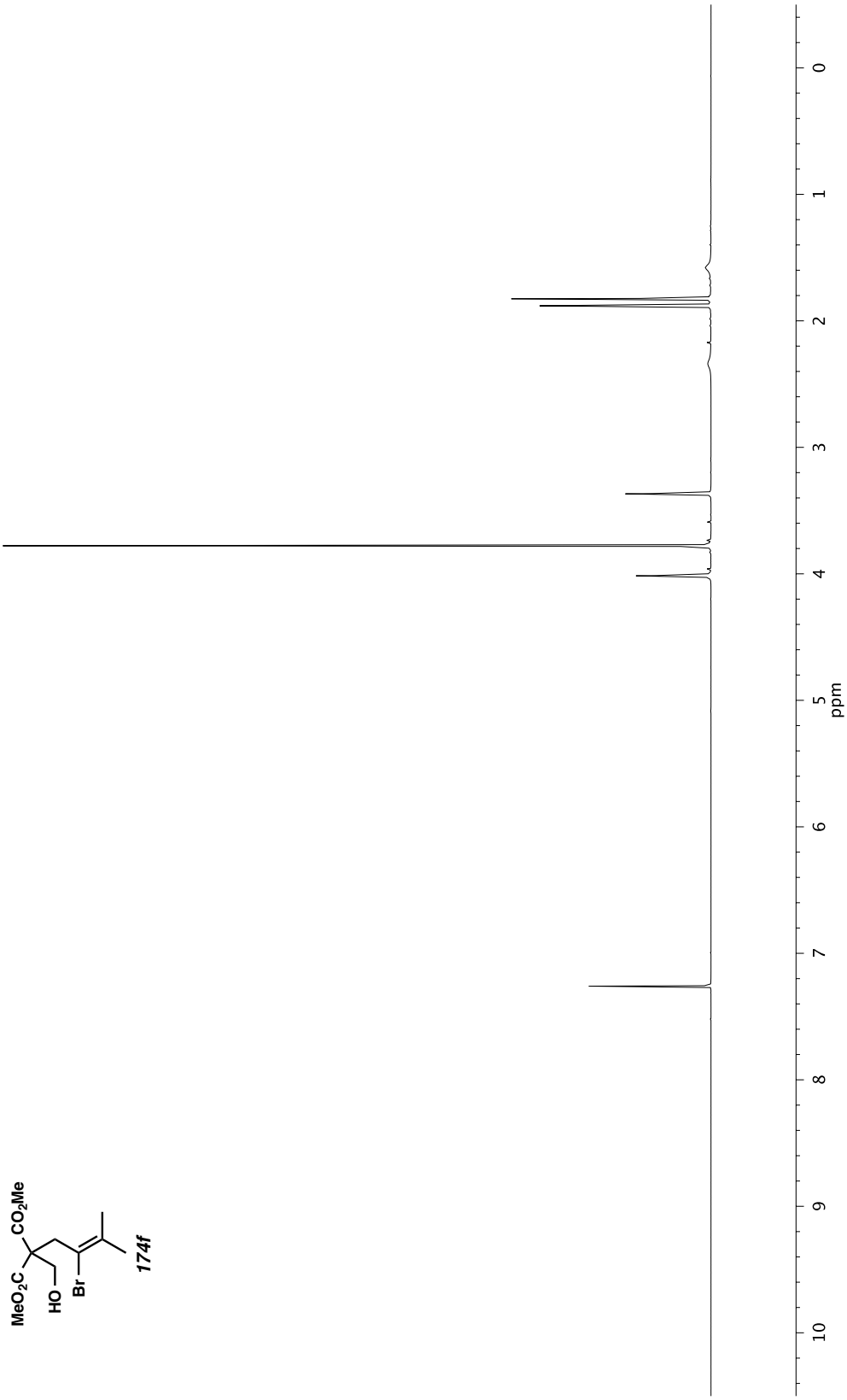


Figure A8.118. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **174f**.

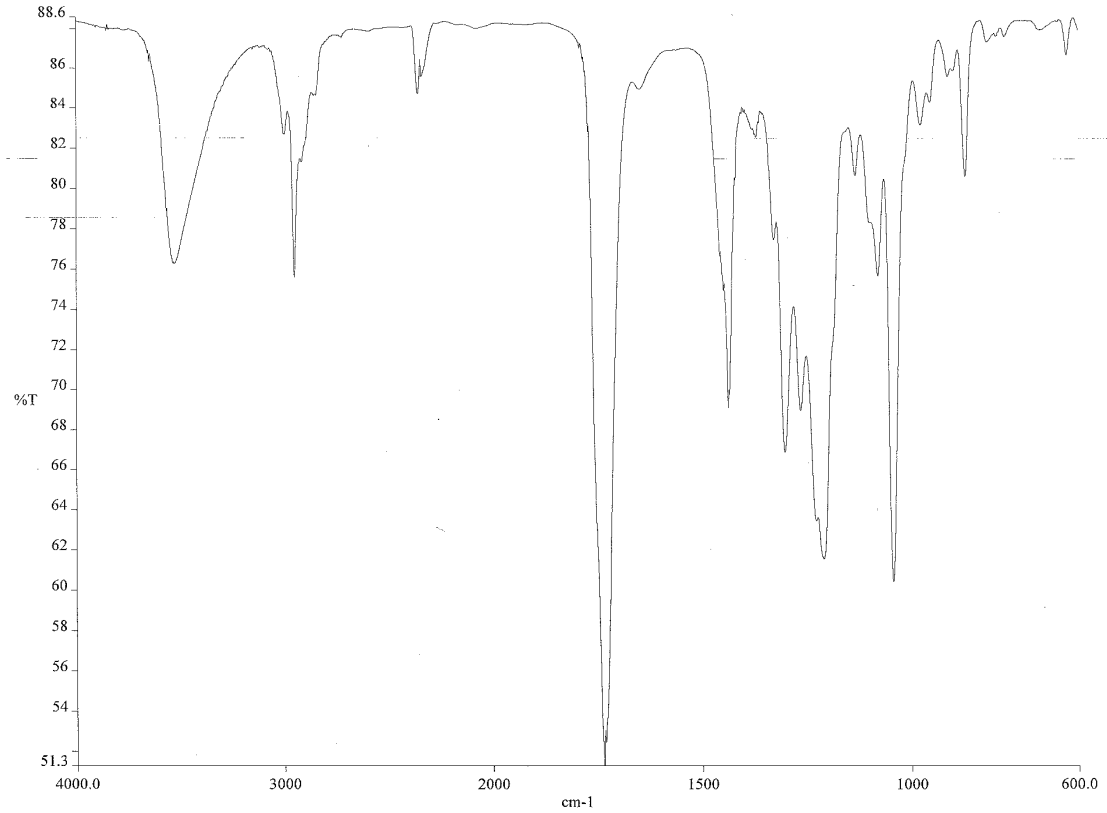


Figure A8.119. Infrared spectrum (Thin Film, NaCl) of compound **174f**.

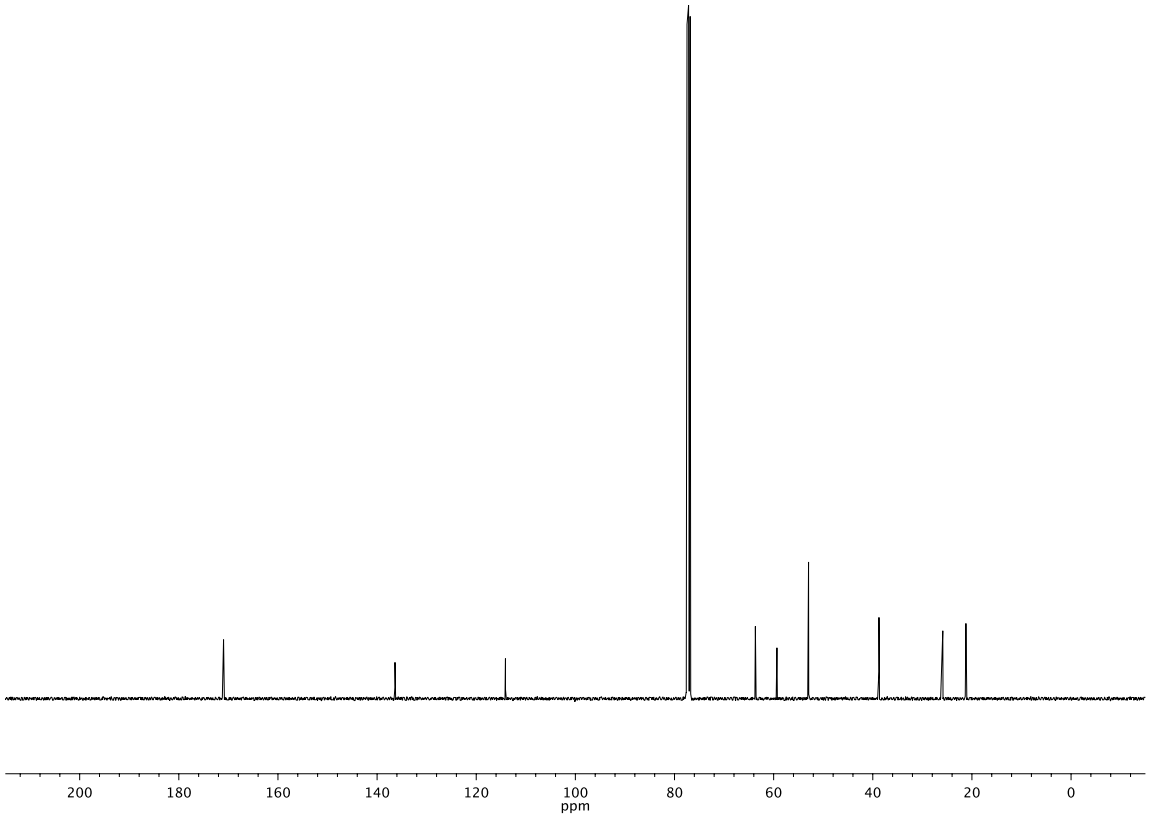


Figure A8.120. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **174f**.

Figure A8.121. ^{1}H NMR (500 MHz, C_6D_6) of compound **175f**.

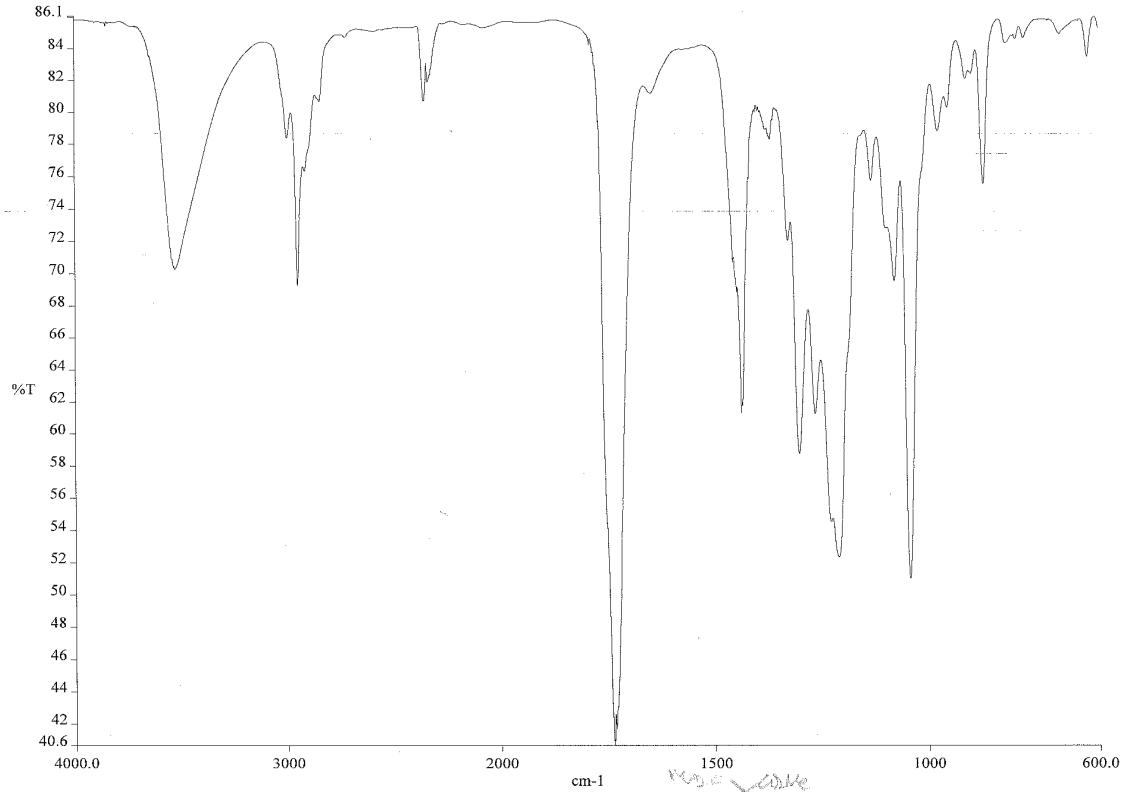


Figure A8.122. Infrared spectrum (Thin Film, NaCl) of compound **175f**.

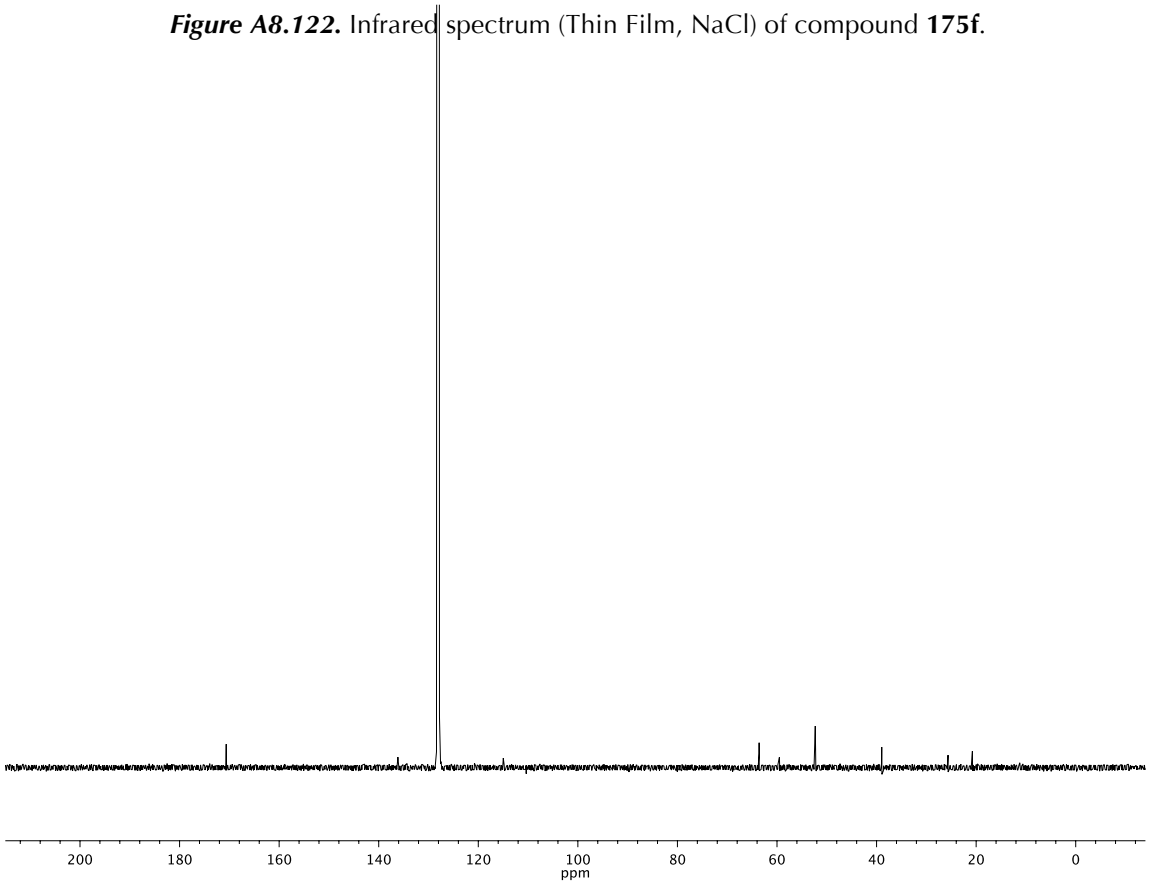


Figure A8.123. ^{13}C NMR (126 MHz, C_6D_6) of compound **175f**.

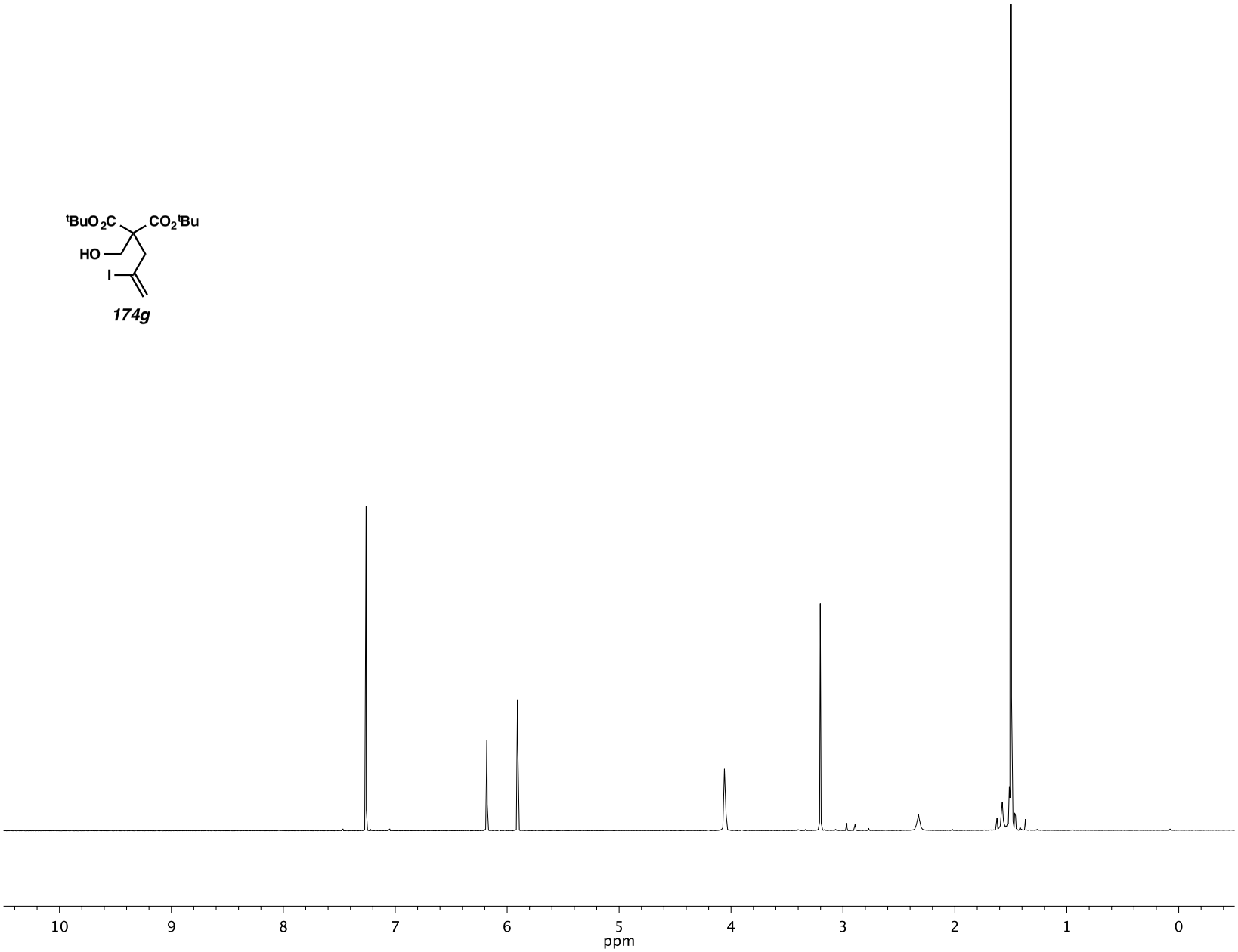


Figure A8.124. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **174g**.

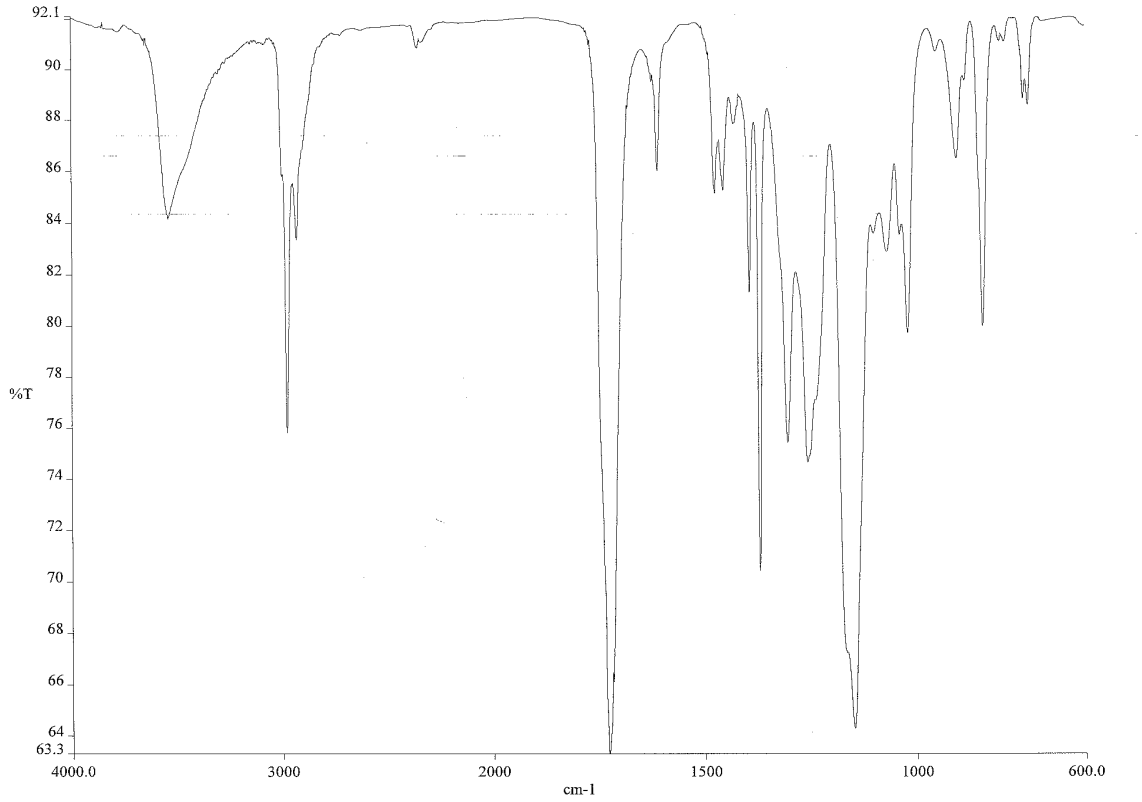


Figure A8.125. Infrared spectrum (Thin Film, NaCl) of compound **174g**.

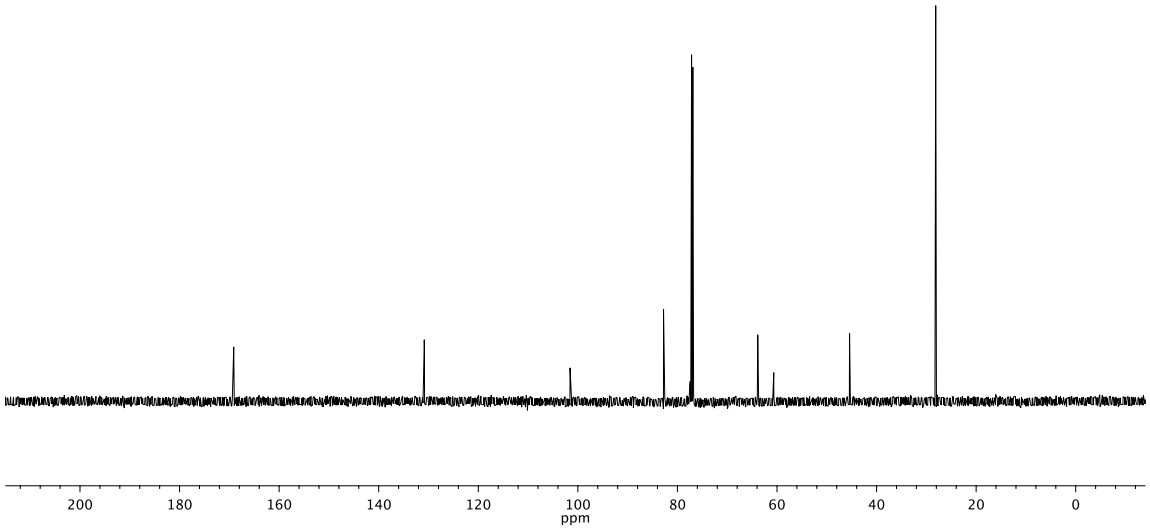


Figure A8.126. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **174g**.

Figure A8.127. ^{1}H NMR (500 MHz, C_6D_6) of compound **175g**.

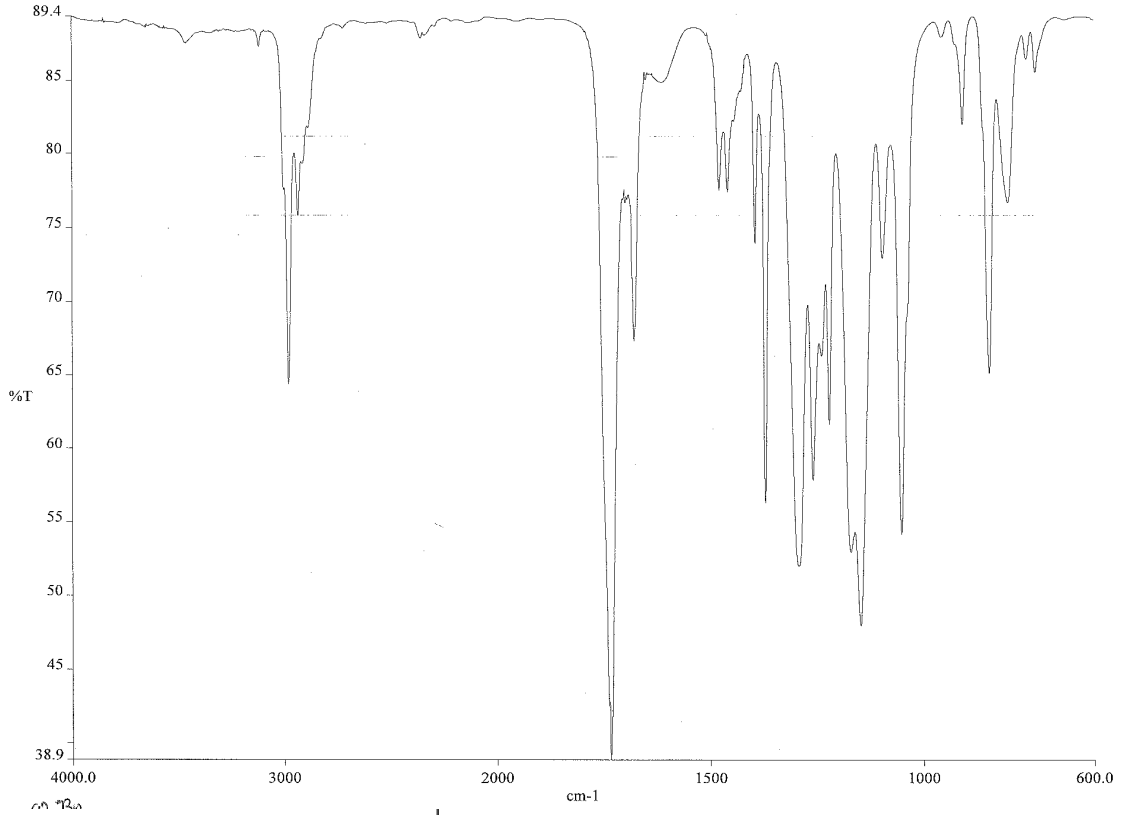


Figure A8.128. Infrared spectrum (Thin Film, NaCl) of compound **175g**.

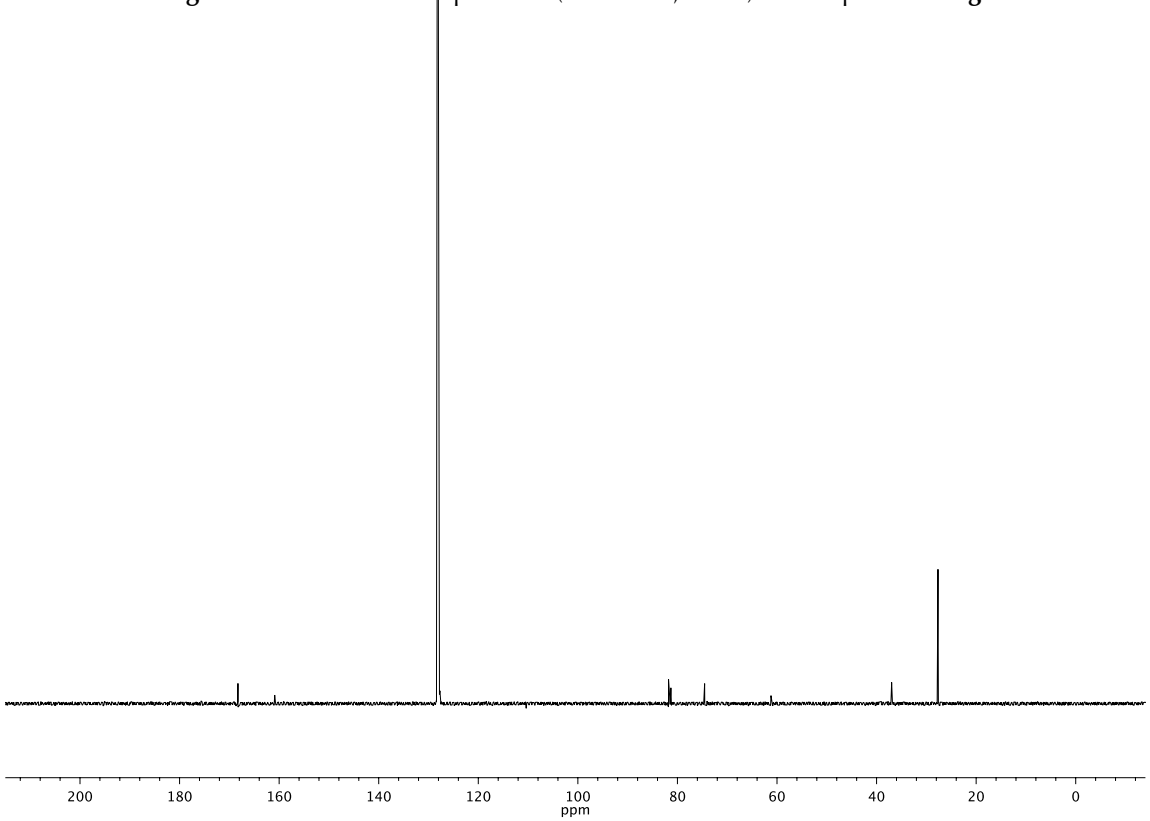


Figure A8.129. ^{13}C NMR (126 MHz, C_6D_6) of compound **175g**.

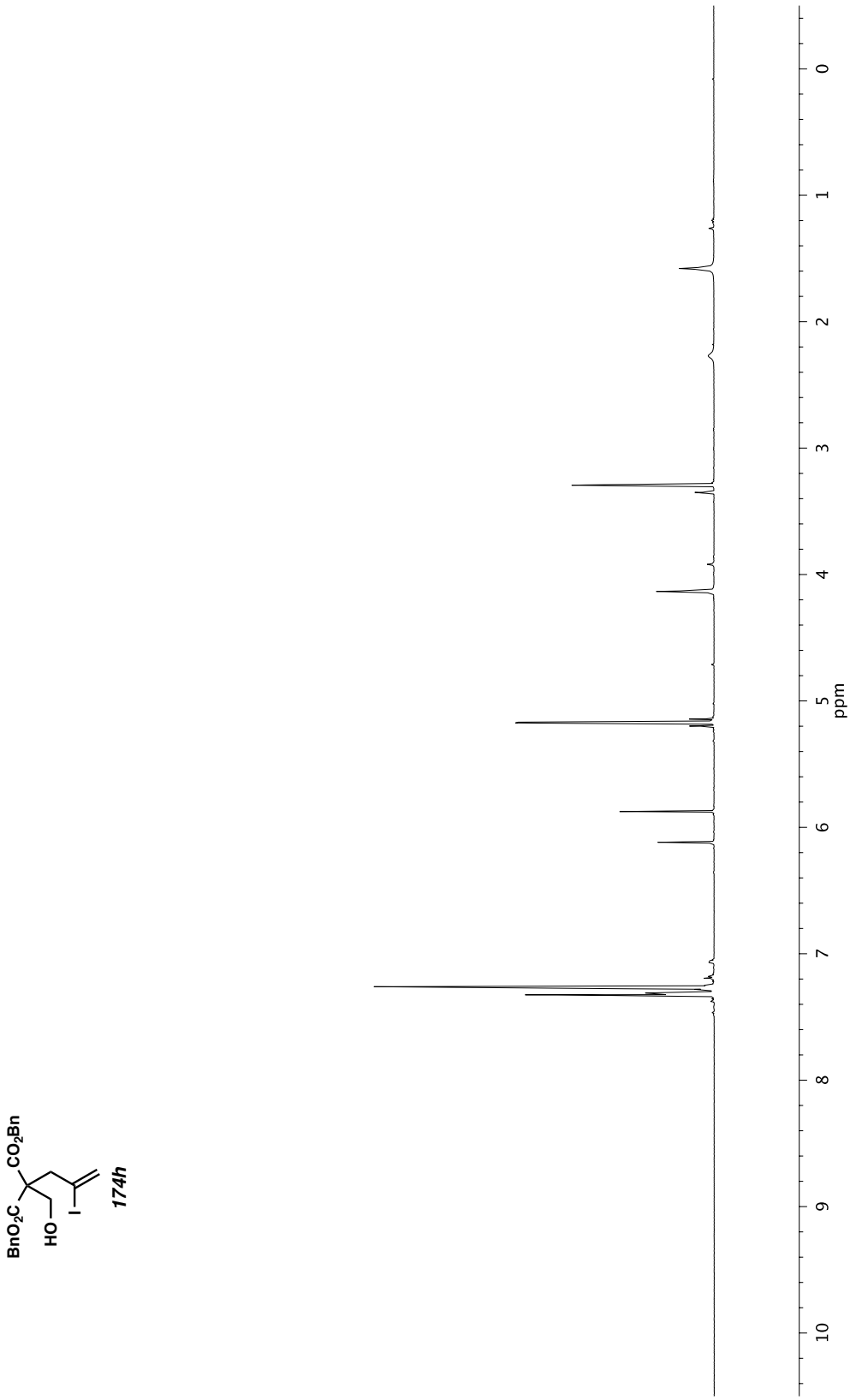


Figure A8.130. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **174h**.

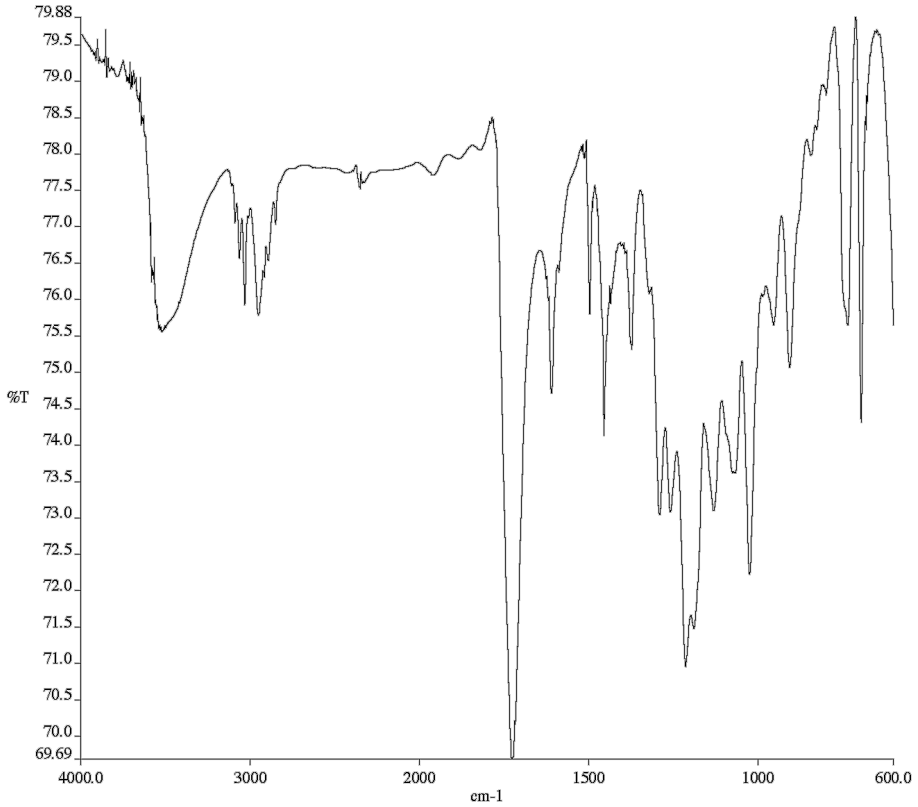


Figure A8.131. Infrared spectrum (Thin Film, NaCl) of compound **174h**.

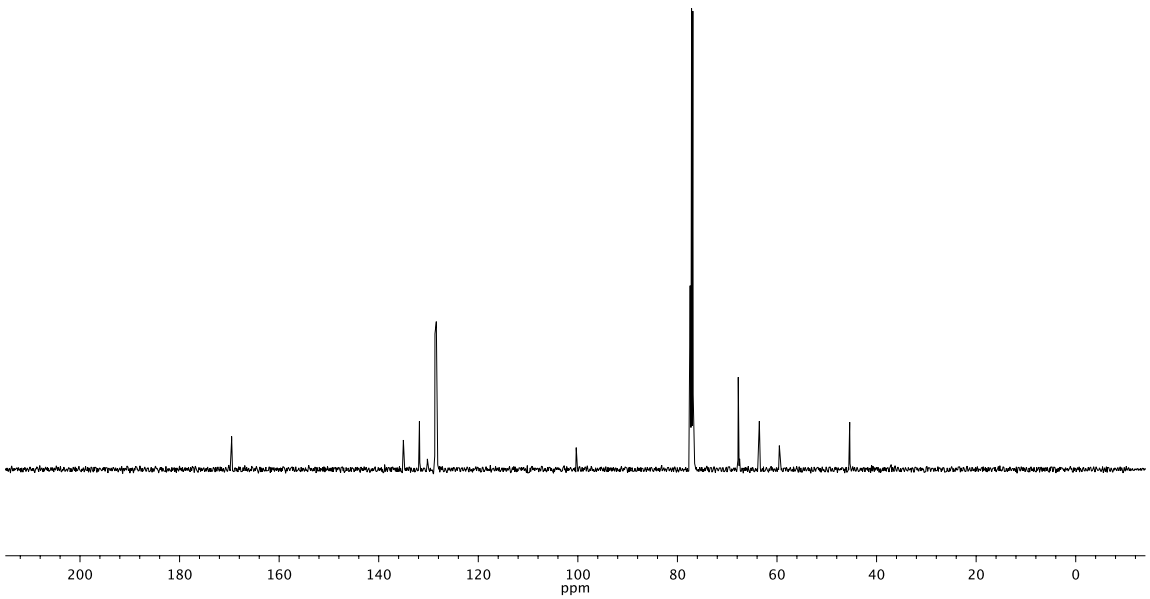


Figure A8.132. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **174h**.

Figure A8.133. ^{1}H NMR (600 MHz, C_6D_6) of compound **175h**.

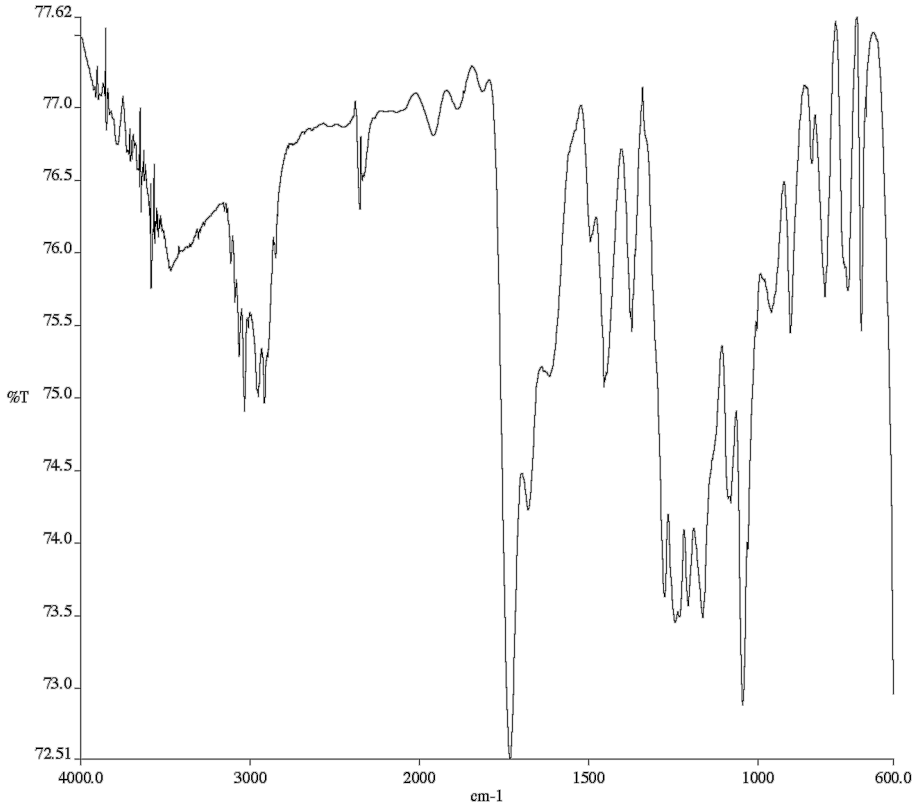


Figure A8.134. Infrared spectrum (Thin Film, NaCl) of compound **175h**.

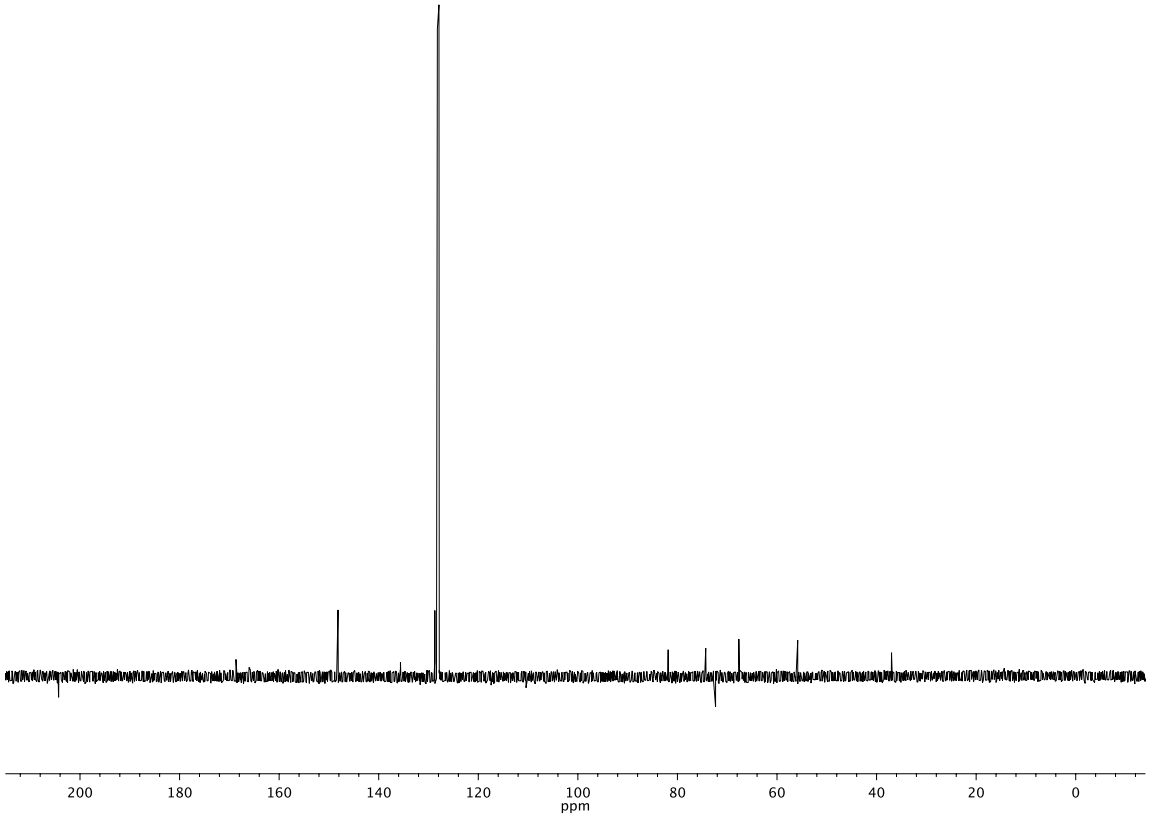


Figure A8.135. ^{13}C NMR (151 MHz, C_6D_6) of compound **175h**.

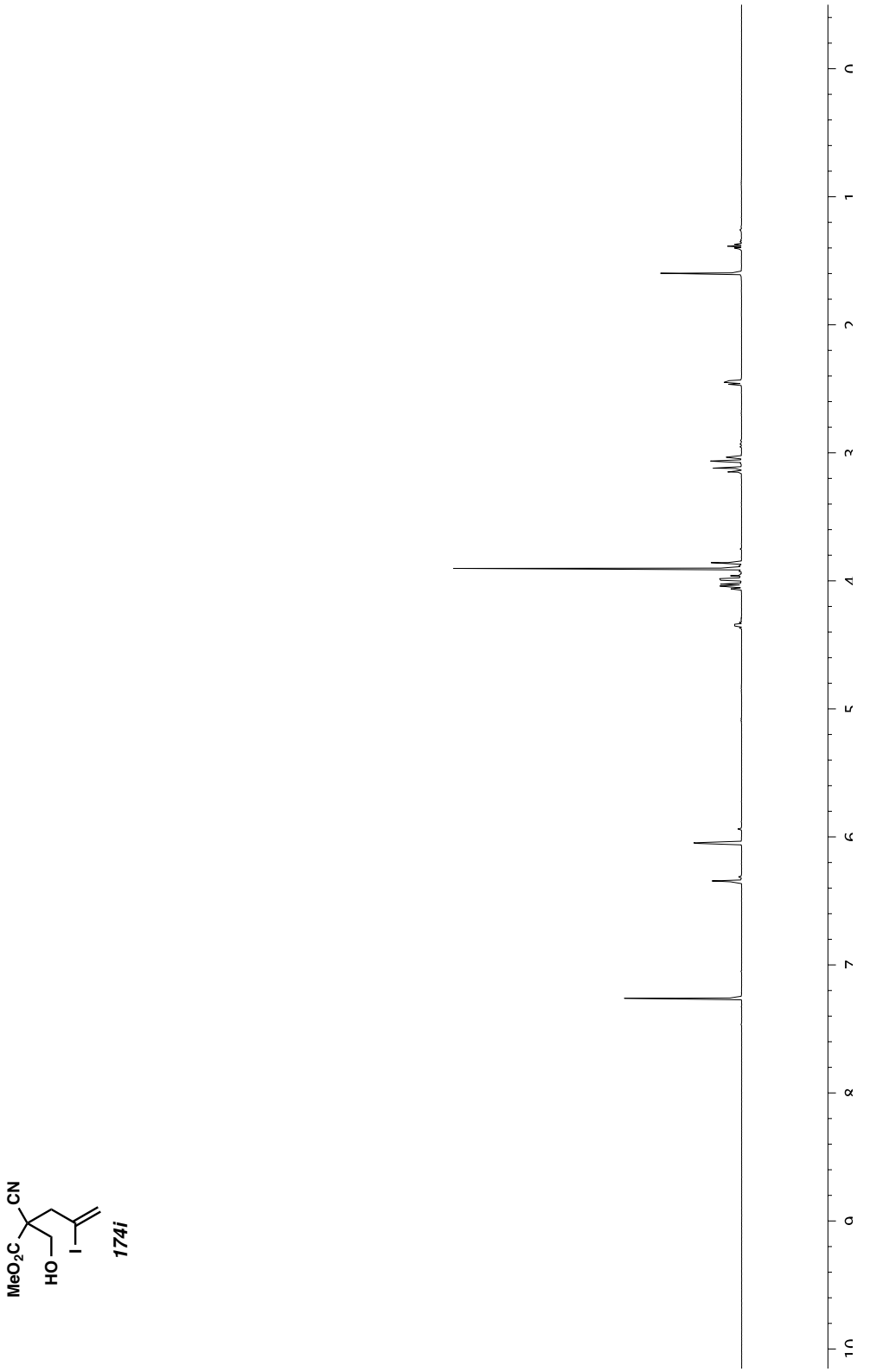


Figure A8.136. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **174i**.

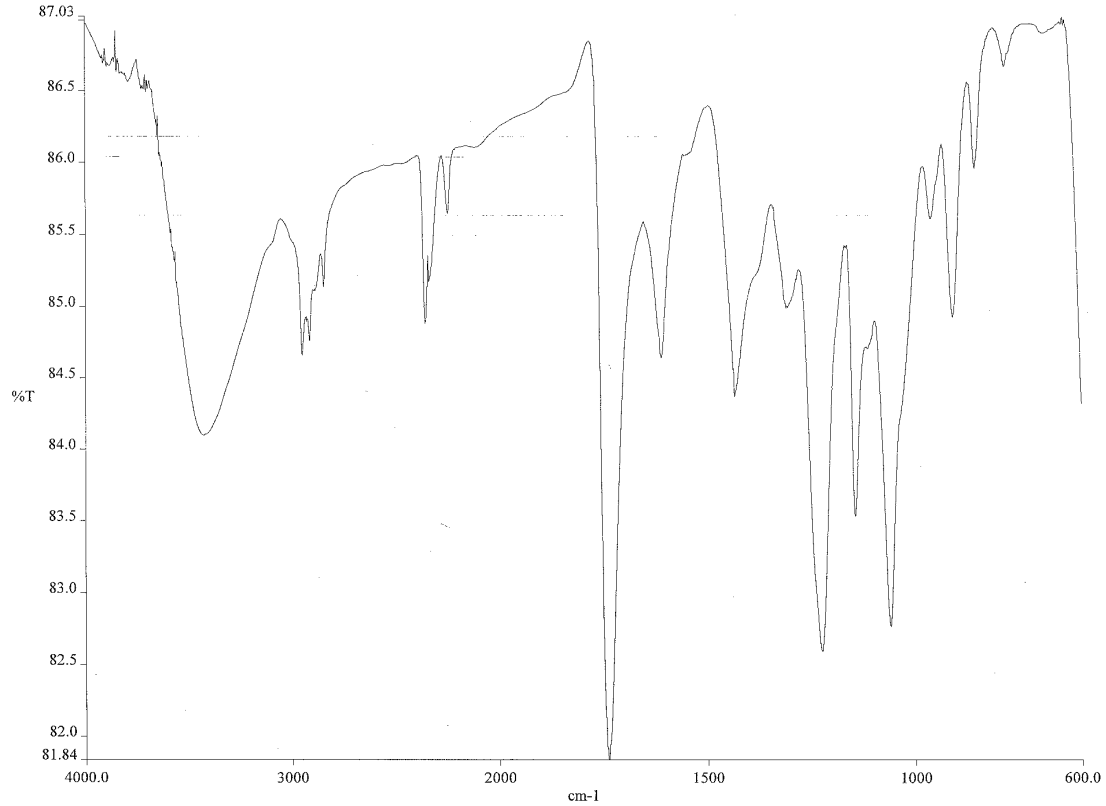


Figure A8.137. Infrared spectrum (Thin Film, NaCl) of compound **174i**.

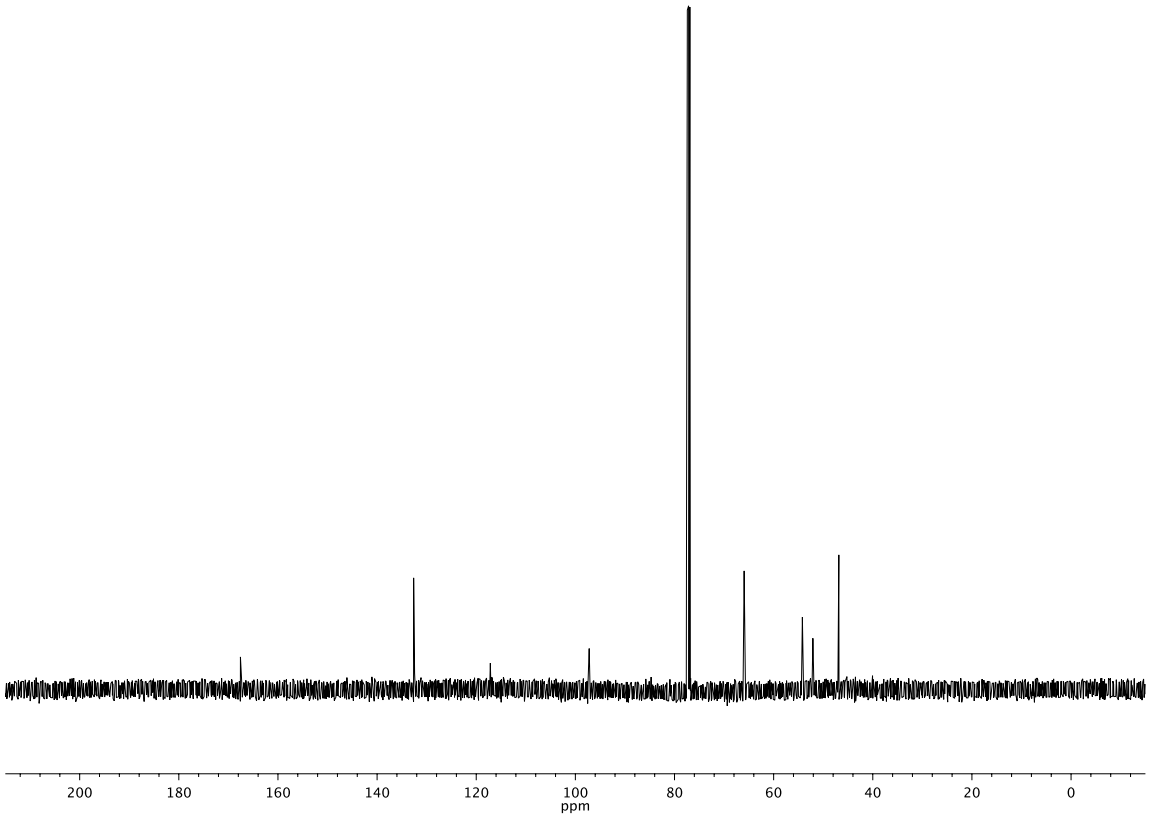


Figure A8.138. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **174i**.

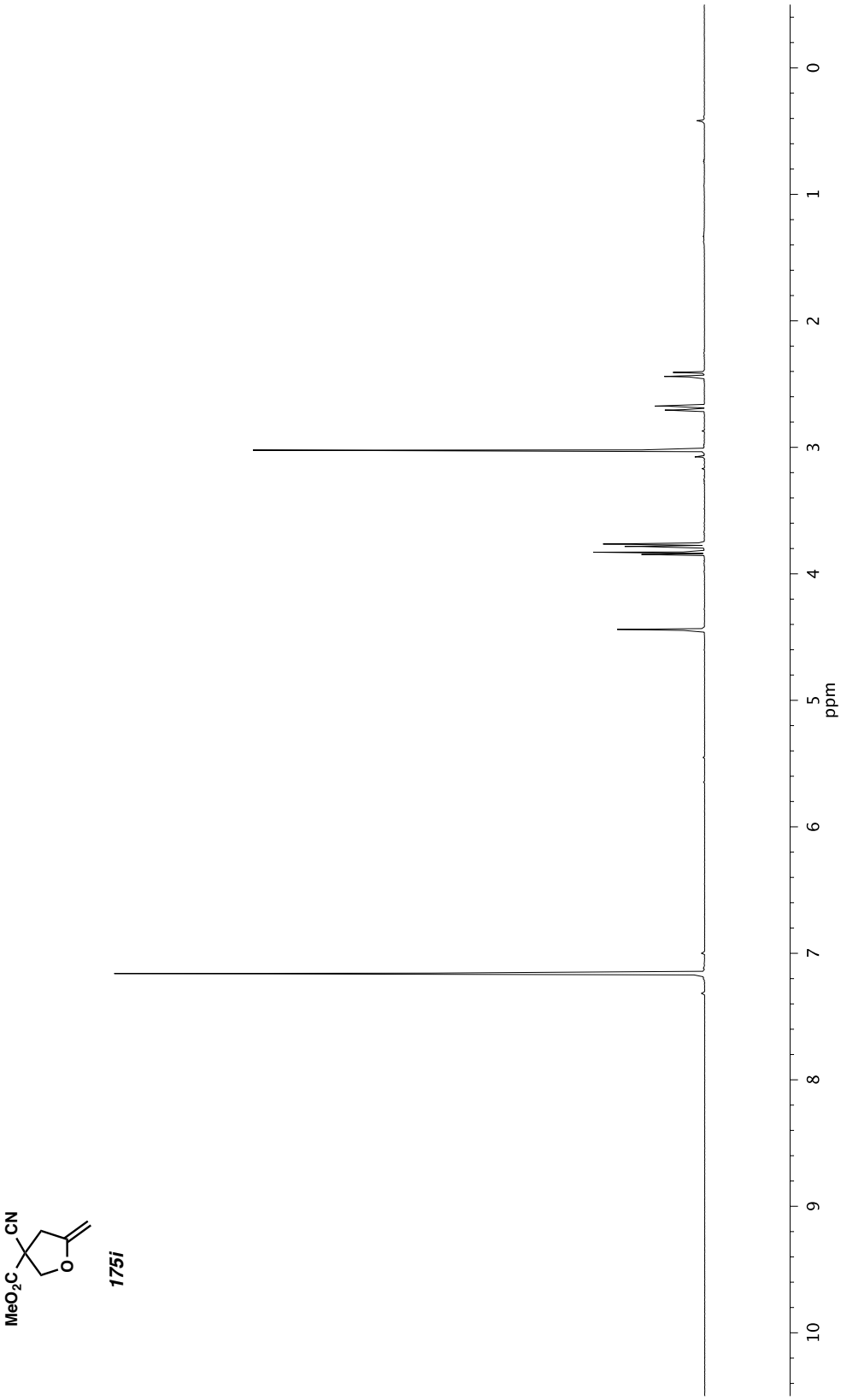


Figure A8.139. ^{1}H NMR (500 MHz, C_6D_6) of compound **175i**.

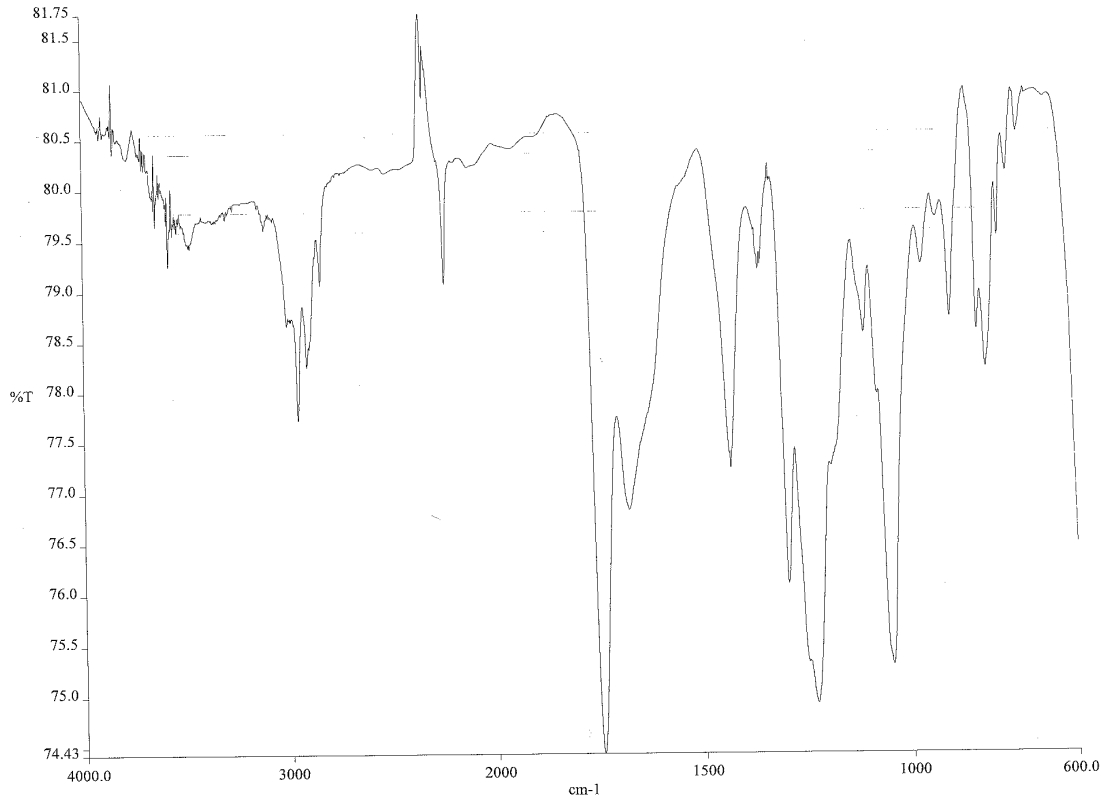


Figure A8.140. Infrared spectrum (Thin Film, NaCl) of compound **175i**.

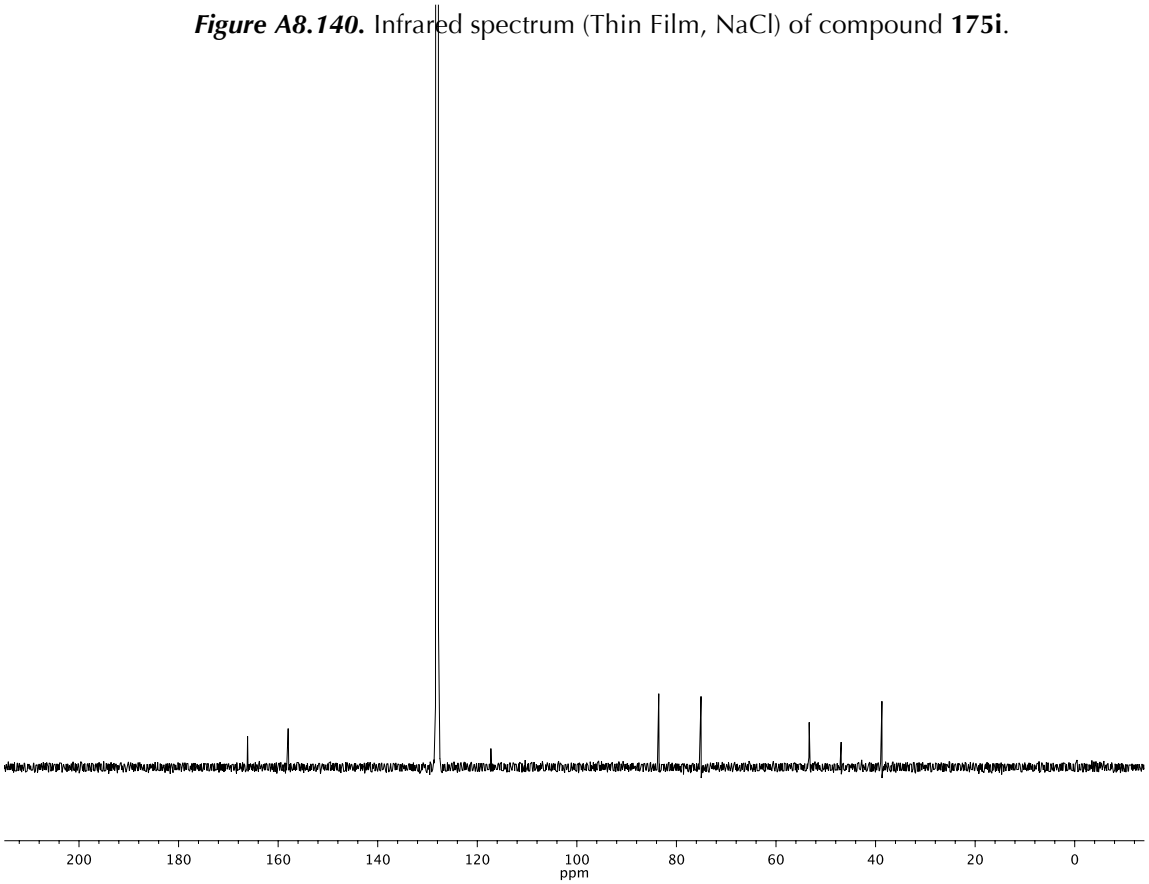
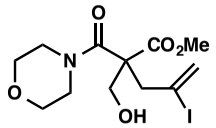


Figure A8.141. ^{13}C NMR (126 MHz, C_6D_6) of compound **175i**.



174j

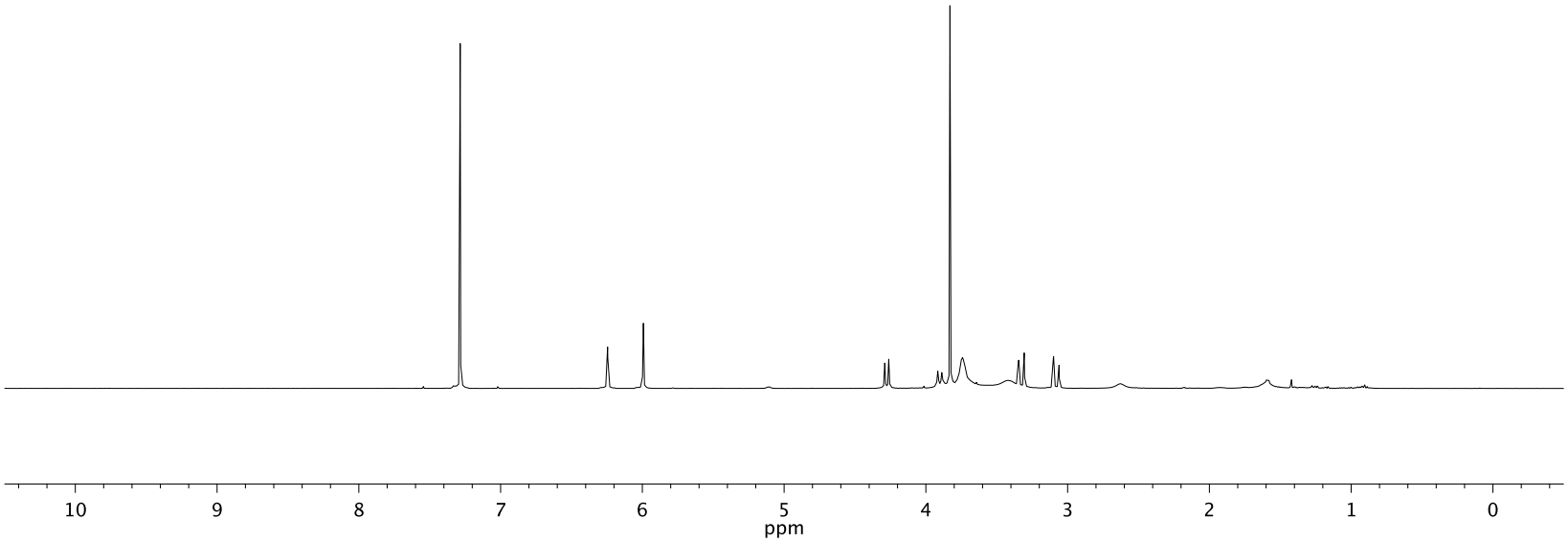


Figure A8.142. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **174j**.

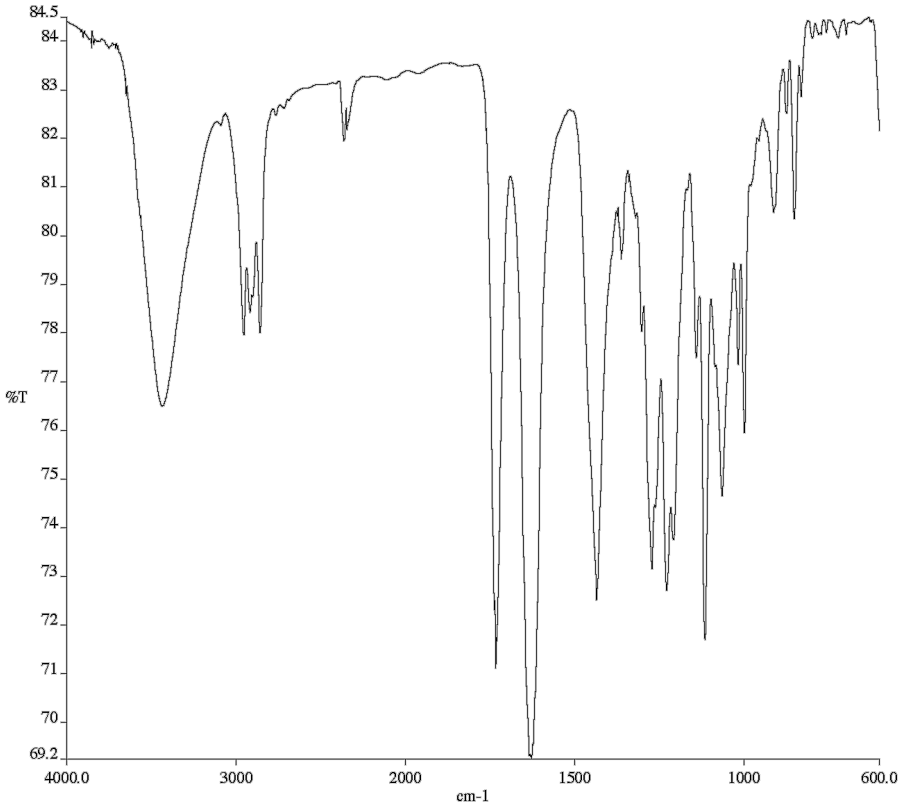


Figure A8.143. Infrared spectrum (Thin Film, NaCl) of compound **174j**

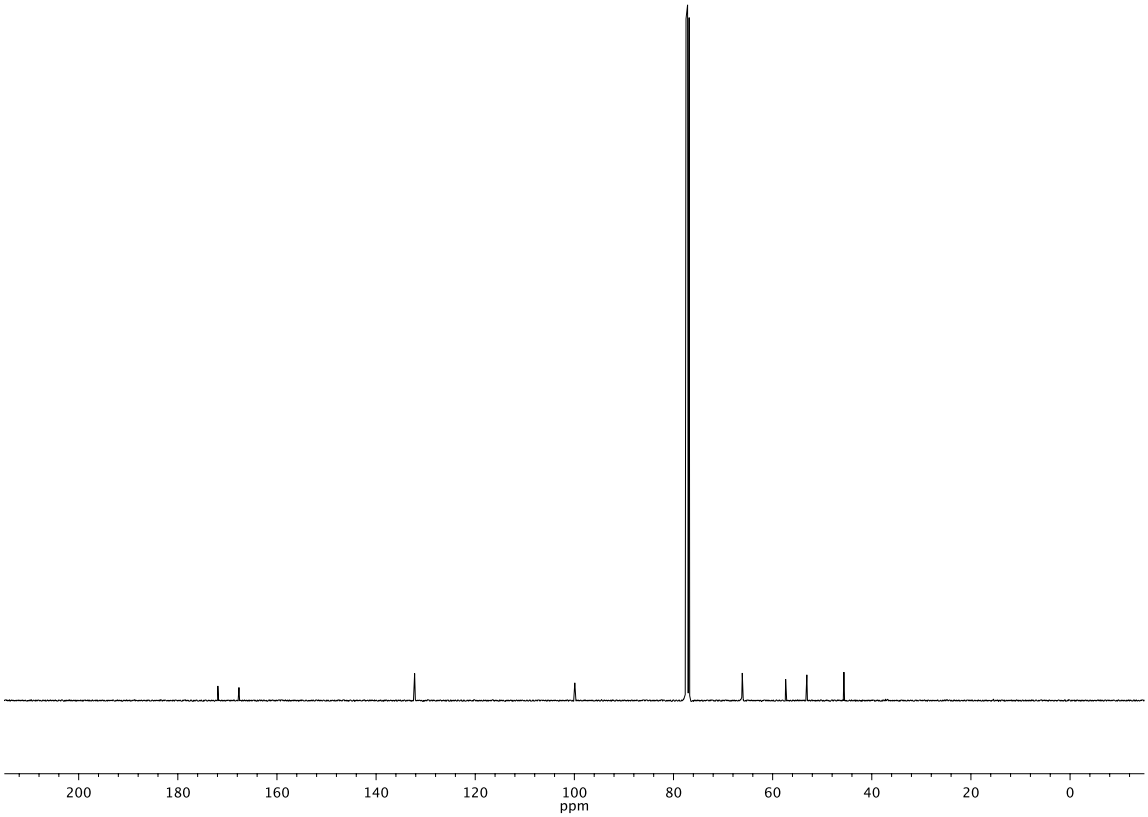
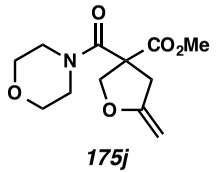


Figure A8.144. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **174j**.



175j

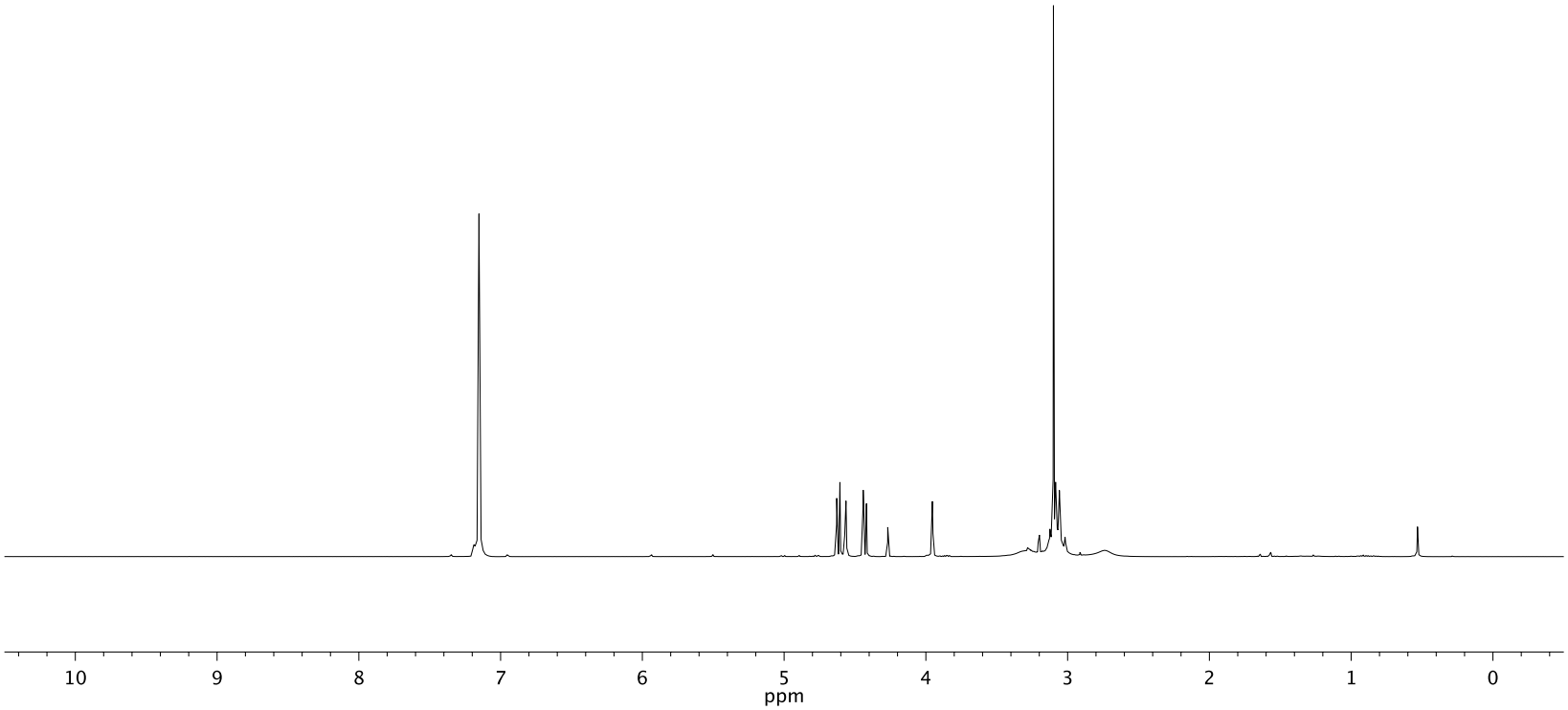


Figure A8.145. ^{1}H NMR (500 MHz, C_6D_6) of compound **175j**.

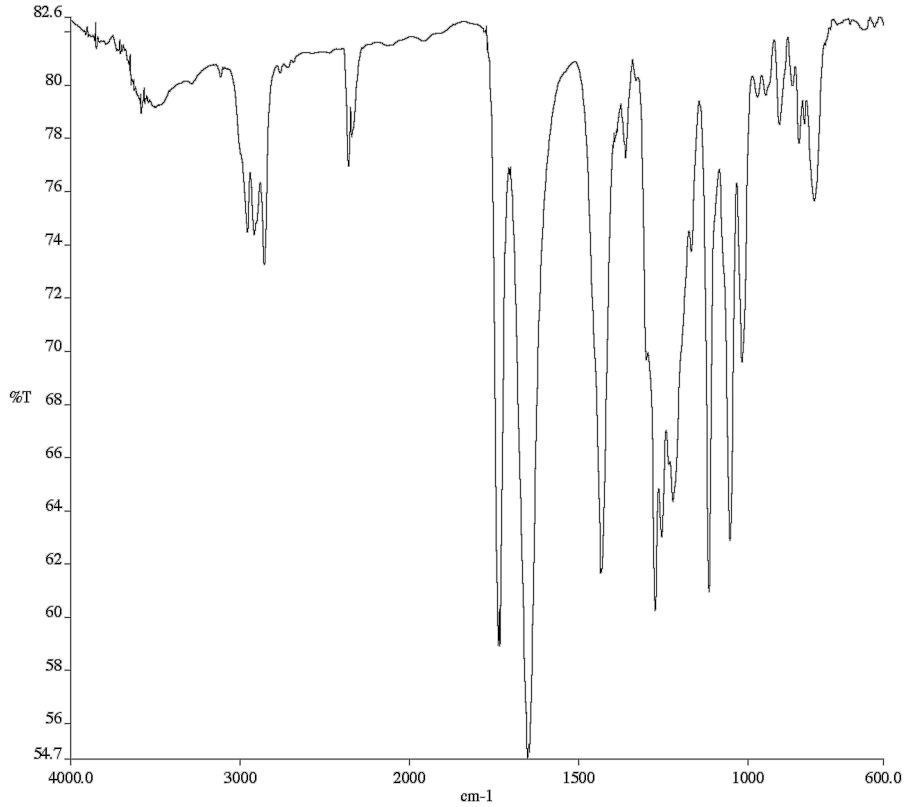


Figure A8.146. Infrared spectrum (Thin Film, NaCl) of compound **175j**

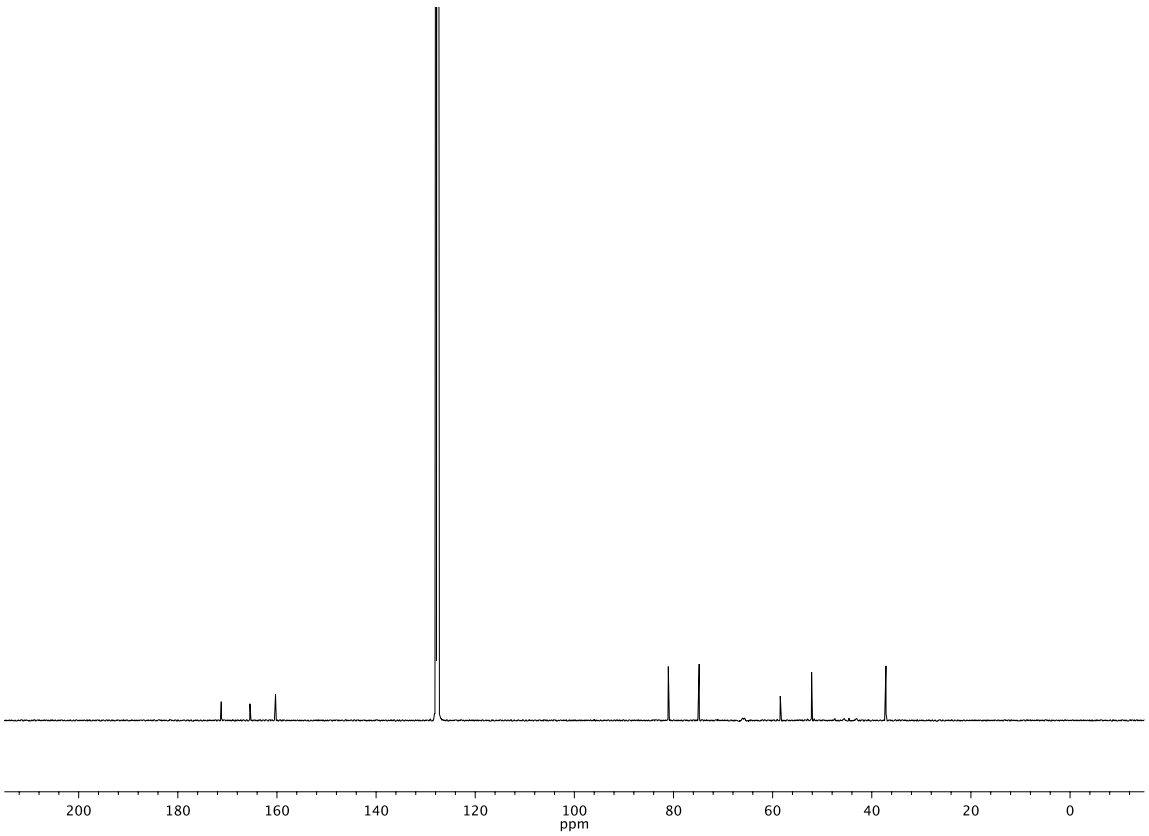


Figure A8.147. ^{13}C NMR (101 MHz, C_6D_6) of compound **175j**.

Figure A8.148. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **174k**.

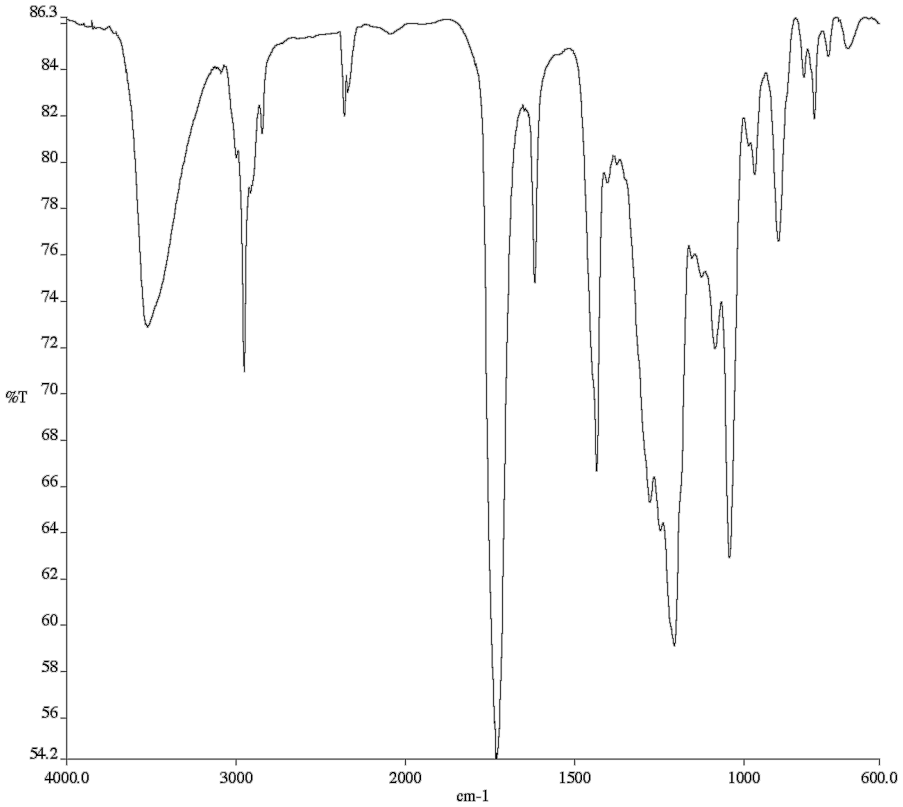


Figure A8.149. Infrared spectrum (Thin Film, NaCl) of compound **174k.**

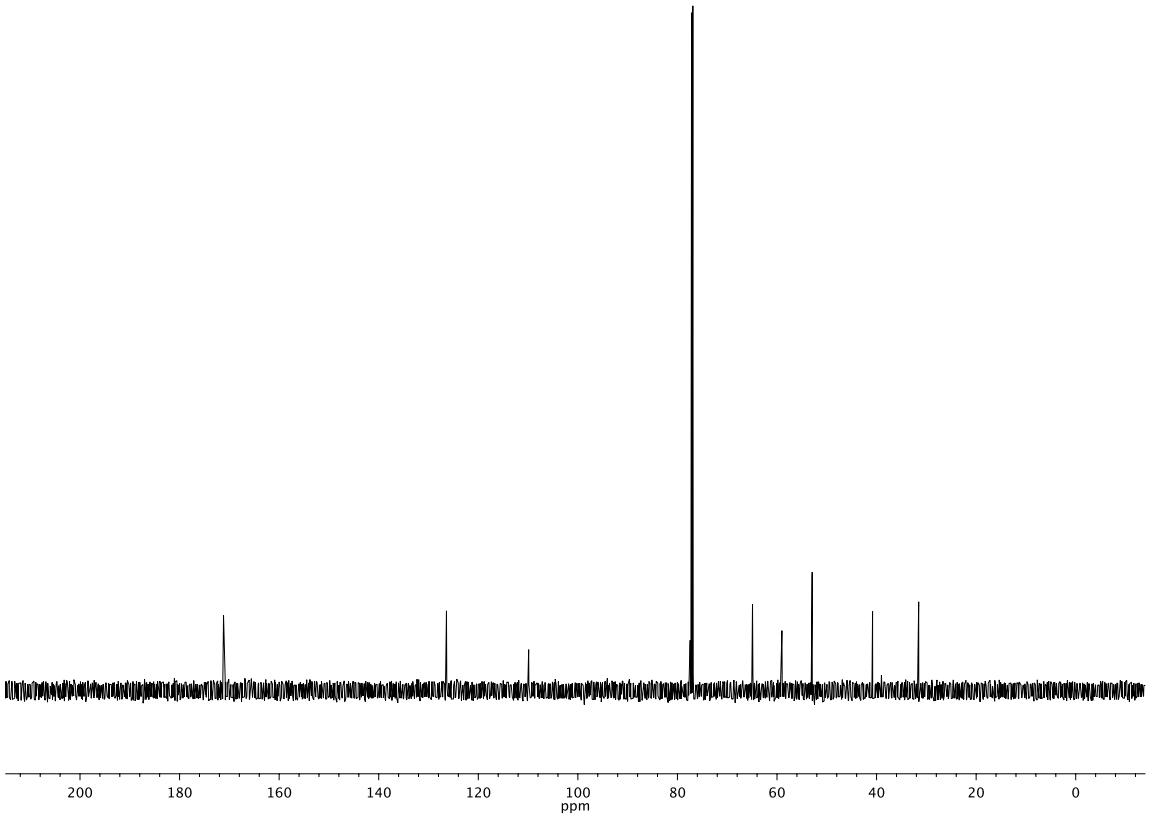


Figure A8.150. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **174k**.

174l

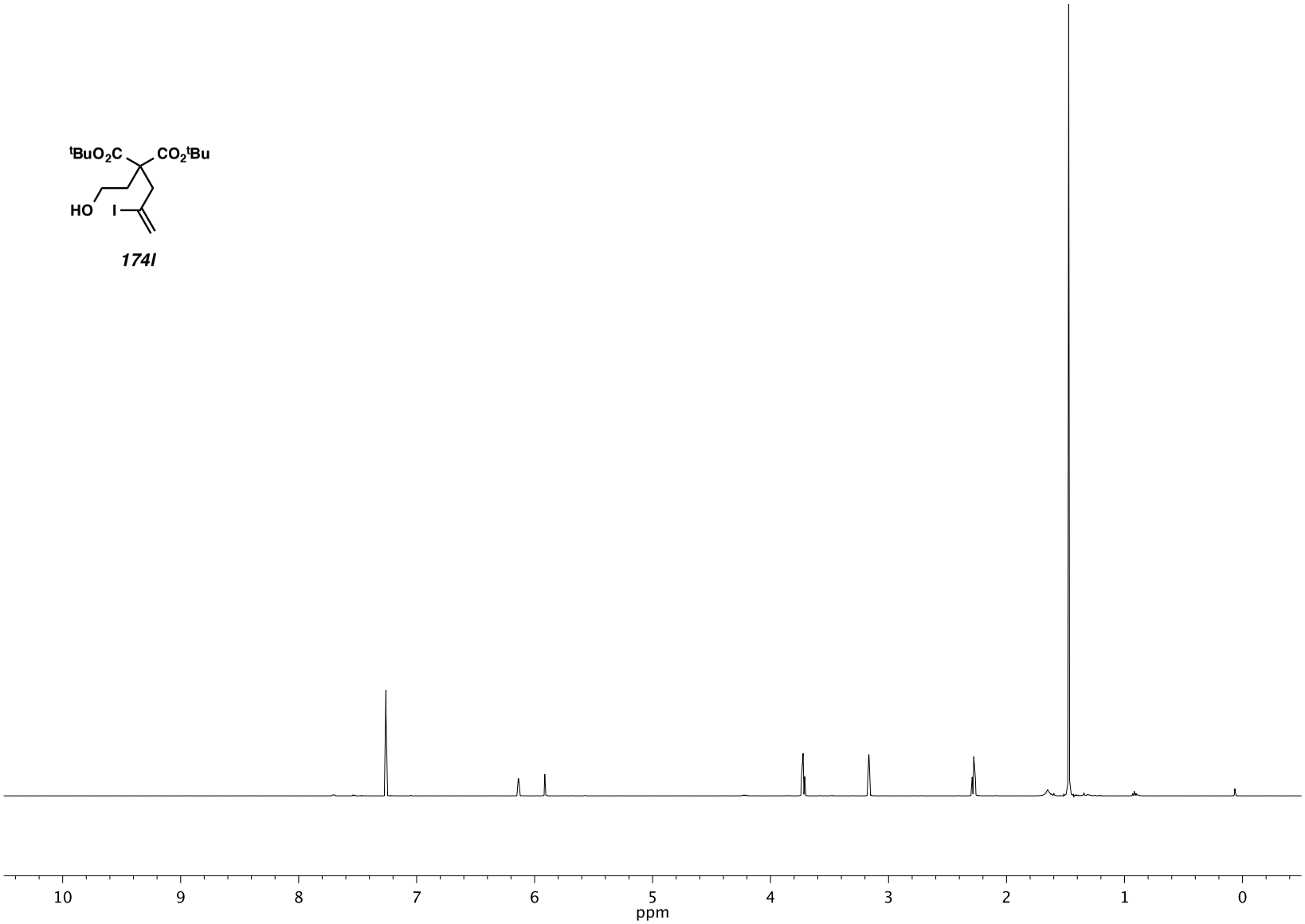


Figure A8.151. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **174l**.

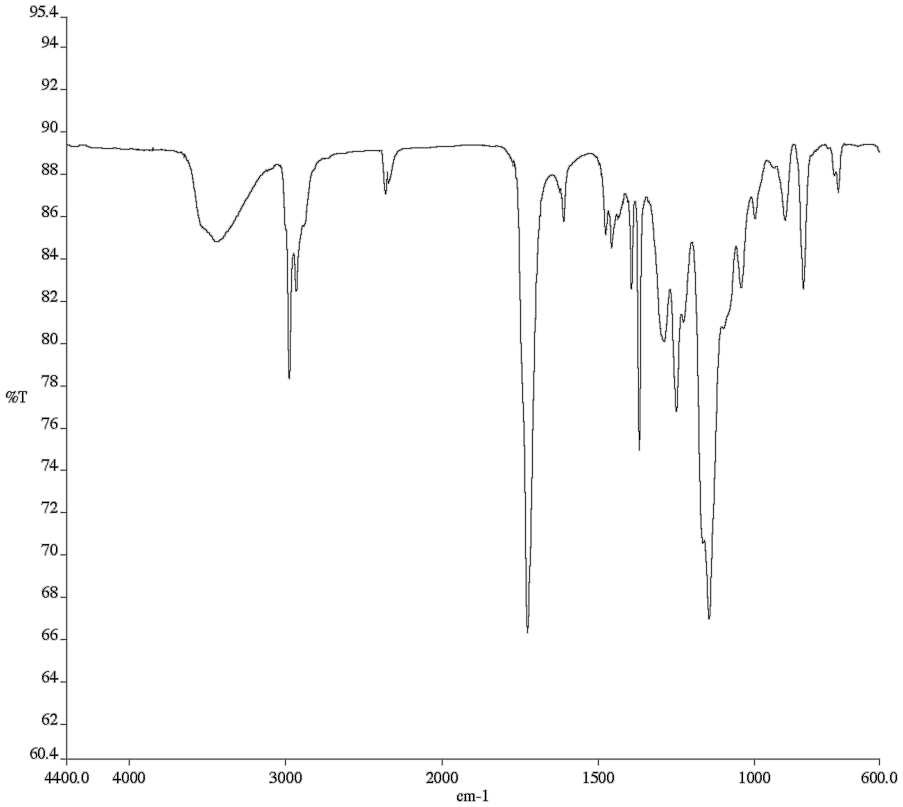


Figure A8.152. Infrared spectrum (Thin Film, NaCl) of compound **174l.**

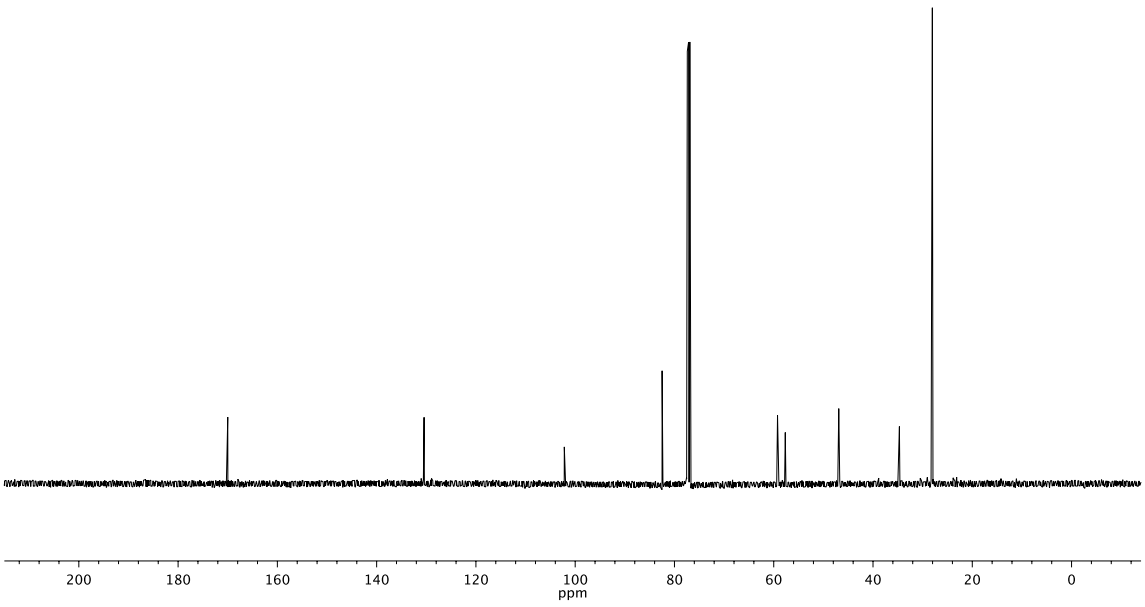


Figure A8.153. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **174l**.

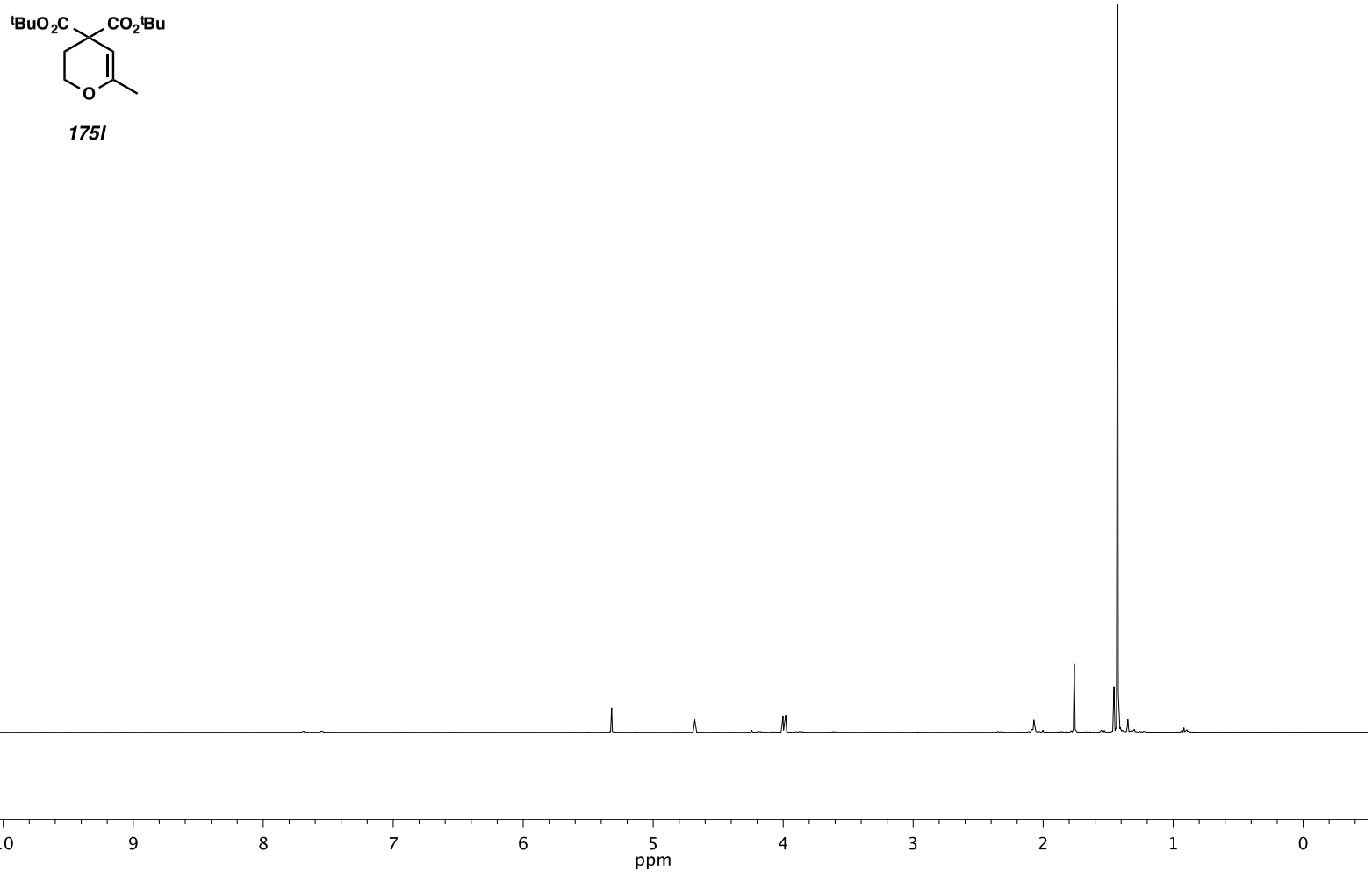


Figure A8.154. ^{1}H NMR (500 MHz, CD_2Cl_2) of compound **175l**.

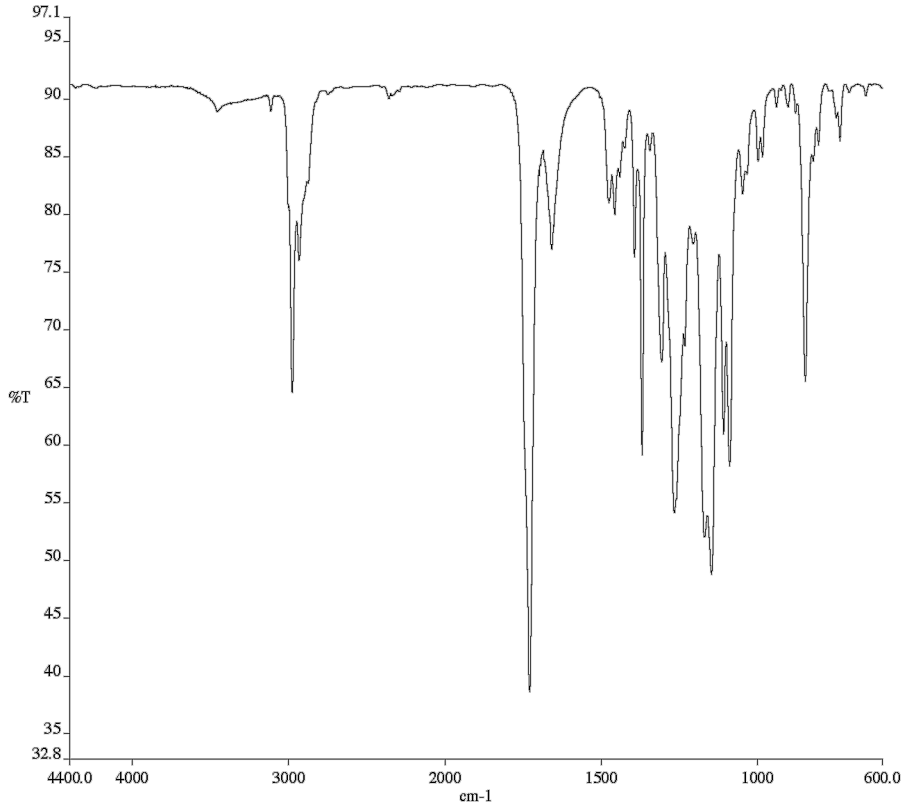


Figure A8.155. Infrared spectrum (Thin Film, NaCl) of compound **175l.**

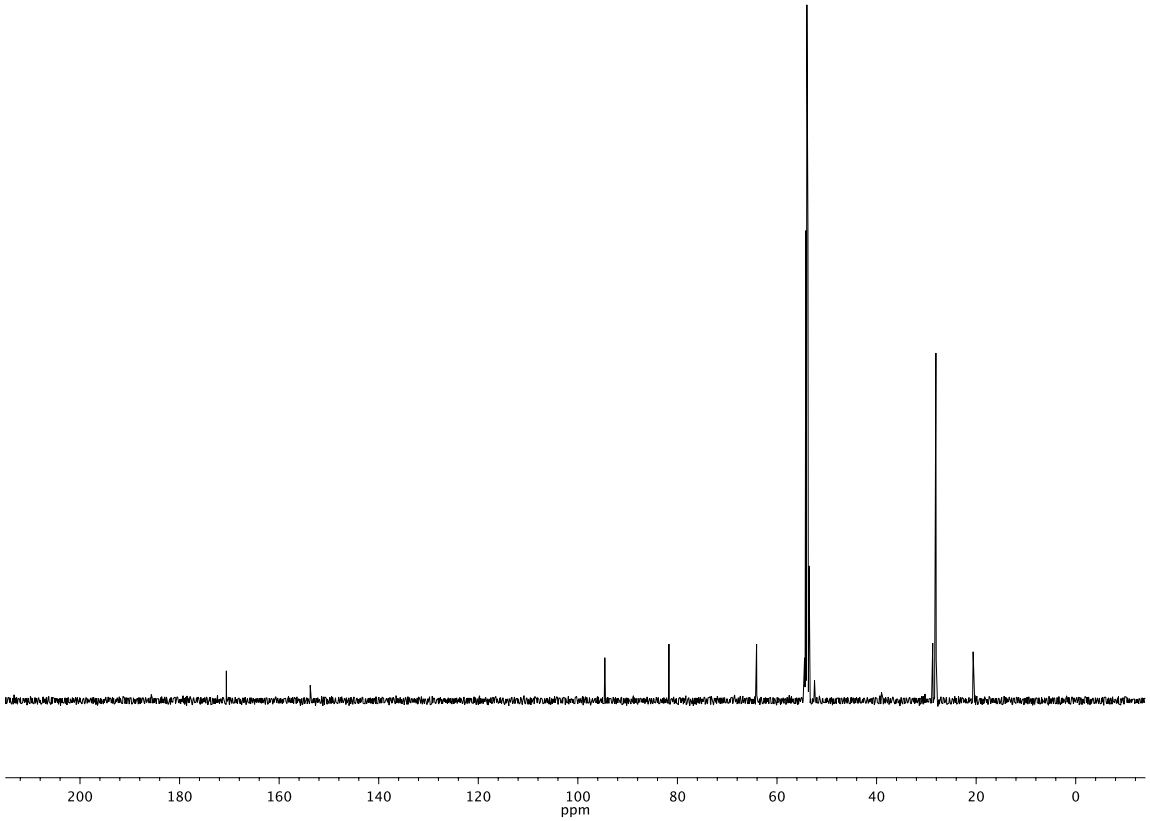


Figure A8.156. ^{13}C NMR (126 MHz, CD_2Cl_2) of compound **175l**.

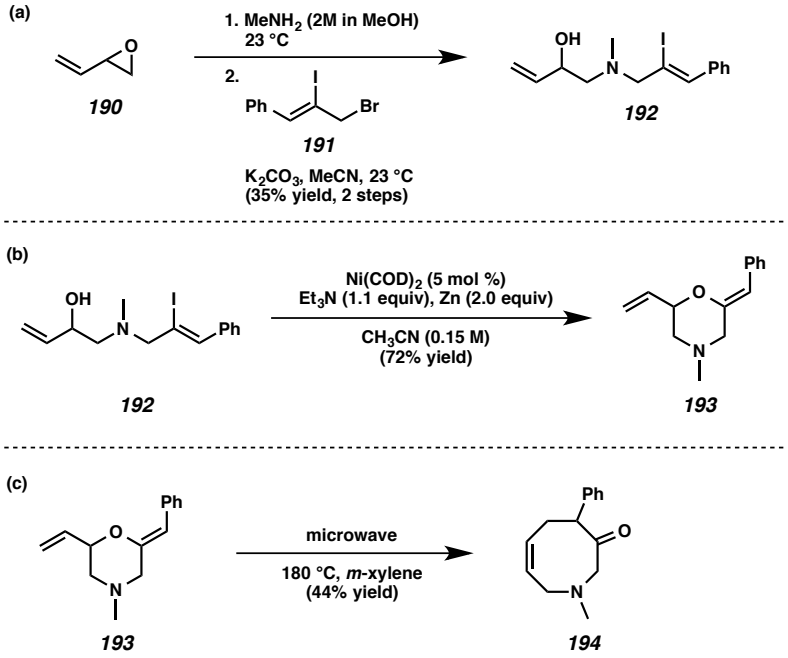
APPENDIX 9

Ni-Catalyzed C–O Bond Formation and Subsequent Claisen Rearrangement

A9.1. Claisen Rearrangement

Having successfully investigated Ni-catalyzed intramolecular C–O bond-forming reactions, we envisaged that allyl vinyl ethers prepared under our conditions could be substrates for subsequent Claisen rearrangement. Treatment of epoxide **190** with methylamine followed by alkylation with allyl bromide **191** afforded aminoalcohol **192** (Scheme A9.1.1a). Intramolecular etherification of aminoalcohol **192** furnished the desired allyl vinyl ether **193** (Scheme A9.1.1b). To our delight, microwave-assisted Claisen rearrangement of vinyl ether **193** in *m*-xylene at 180 °C produced **194** (Scheme A9.1.1c). Further investigation of the substrate scope for Claisen rearrangement is ongoing in our laboratory.

Scheme A9.1.1. *Ni-Catalyzed C–O Bond Formation and subsequent Claisen Rearrangement*



A9.2. Experimental Methods and Analytical Data

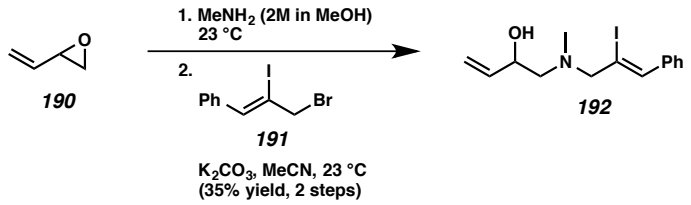
A9.2.1. Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. THF, Et_2O, CH_2Cl_2, toluene, benzene, CH_3CN, and dioxane were dried by passage through an activated alumina column under argon. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. Brine solutions are saturated aqueous solutions of sodium chloride. Commercially available reagents were purchased from Sigma-Aldrich, Acros Organics, TCI, Oakwood chemicals, Strem, or Alfa Aesar and used as received unless otherwise stated. $Ni(COD)_2$ and NiI_2 were purchased from Strem. $NiBr_2$(dme) was purchased from Aldrich. Zinc dust or powder purchased from Aldrich worked well for the reaction but zinc powder (99.999%) purchased from Strem gave poor conversion. Reaction temperatures were

controlled by an IKAmag temperature modulator unless otherwise indicated. Glove box manipulations were performed under a N_2 atmosphere. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, $KMnO_4$ or PMA (phosphomolybdic acid) staining. Silicycle Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.064 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on a Varian Mercury 300 MHz, a Bruker AV III HD 400 MHz spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe, Varian Inova 500 MHz, and 600 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm), $CHDCl_2$ (δ 5.32) or C_6HD_6 (δ 7.16 ppm). ^{13}C NMR spectra are recorded on a Varian Mercury 300 MHz, a Bruker AV III HD 400 MHz spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe, Varian Inova 500 MHz, and 600 MHz spectrometers (75 MHz, 126 MHz, and 151 MHz, respectively) and are reported relative to $CHCl_3$ (δ 77.16 ppm), $CHDCl_2$ (δ 53.84) or C_6HD_5 (δ 128.06 ppm). ^{19}F NMR spectra are recorded on a Varian Mercury 300 MHz (at 282 MHz). ^{19}F NMR spectra are reported relative to $CFCl_3$(δ 0.0 ppm). Data for ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d= broad doublet, app = apparent. Data for ^{13}C are reported in terms of chemical shifts (δ ppm). IR spectra were obtained using a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode, or Agilent 6200 Series TOF with an Agilent G1978A

Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+).

A9.2.2. Experimental Procedures

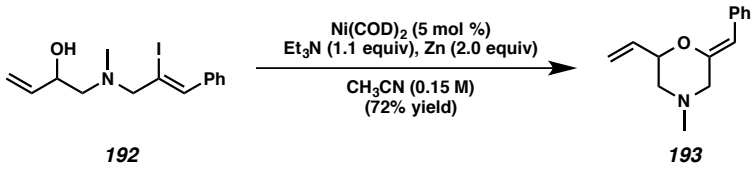


To epoxide **190** (300 mg, 4.28 mmol, 1.00 equiv) was added $MeNH_2$ (2M solution in MeOH; 3.71 mL, 42.8 mmol, 10.0 equiv). The solution was stirred for 12 h at 23 °C. The volatile was evaporated and the residue was used without further purification.

To a solution of the amine (4.28 mmol, 1.00 equiv) in MeCN (11.0 mL) were added K_2CO_3 (2.96 g, 21.4 mmol, 5.00 equiv) and allyl bromide **191** (691 mg, 2.14 mmol, 0.50 equiv). The solution was stirred for 12 h at 23 °C. After the reaction was done, water was added. The aqueous phase was extracted with EtOAc (3 x 7.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:4 EtOAc:hexanes) on silica gel to give aminoalcohol **192** (257 mg, 35% yield based on equivalent of allyl bromide **191**, 2 steps).

R_f = 0.65 (1:2 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.55 (m, 2H), 7.43 – 7.34 (m, 3H), 7.10 – 6.98 (s, br, 1H), 5.84 (ddd, *J* = 17.2, 10.5, 5.8 Hz, 1H), 5.45 – 5.37 (m, 1H), 5.21 (dt, *J* = 10.5, 1.5 Hz, 1H), 4.29 (s, br, 1H), 3.54 (s, br, 1H), 3.41 (s, br, 1H), 2.58 (s, br, 2H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0, 137.2, 136.9, 128.8, 128.4, 128.3, 116.3, 70.7, 68.7, 62.8, 61.1, 41.2; IR (Neat Film

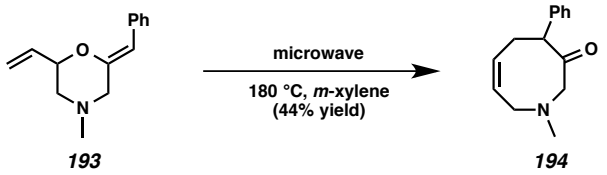
NaCl) 3435, 2795, 1491, 1446, 1083, 1029, 921, 750, 695 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{14}H_{19}NOI$ $[M+H]^+$: 344.0506; found: 344.0523.



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Ni-Catalyzed C–O bond formation experiments were performed in a nitrogen-filled glove box. To a solution of aminoalcohol **192** (100 mg, 0.291 mmol, 1.00 equiv) in MeCN (1.94 mL) in a scintillation vial were added Et_3N (45 μL, 0.320 mmol, 1.10 equiv), Zn powder (38.0 mg, 0.582 mmol, 2.00 equiv), and $Ni(COD)_2$ (4.00 mg, 0.0146 mmol, 0.05 equiv). The reaction mixture was stirred at 23 °C for 24 h. After the reaction was done, the vial was removed from the glovebox and uncapped. Solids were removed via a filtration through a celite plug and the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to furnish the product **193** (45.3 mg, 72% yield).

R_f = 0.23 (1:2 EtOAc:hexanes); ^1H NMR (400 MHz, CD_2Cl_2) δ 7.51 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.18 (dd, *J* = 8.4, 7.0 Hz, 2H), 7.08 – 7.01 (m, 1H), 5.89 (ddd, *J* = 17.3, 10.7, 5.6 Hz, 1H), 5.40 – 5.32 (m, 2H), 5.19 – 5.16 (m, 1H), 4.35 (dddt, *J* = 9.8, 5.7, 2.9, 1.5 Hz, 1H), 3.09 (dd, *J* = 12.6, 1.6 Hz, 1H), 2.78 – 2.69 (m, 2H), 2.21 (s, 3H), 2.08 (dd, *J* = 11.7, 9.5 Hz, 1H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 150.5, 136.4, 136.2, 128.9, 128.6, 126.4, 117.1, 107.9, 78.0, 59.5, 58.3, 46.2; IR (Neat Film NaCl) 2939, 2784, 2360, 1666, 1448, 1328, 1239, 1176, 1133, 1047, 985, 937, 755, 694 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{14}H_{18}NO$ $[M+H]^+$: 216.1383; found: 216.1399.



193 *194*

A solution of allyl vinyl ether **193** (11.0 mg, 0.0511 mmol, 1.00 equiv) in *m*-xylene (1.02 mL) was heated to 180 °C (power: 300 W) by microwave for 6 h. The resultant solution was then allowed to cool to ambient temperature, filtered through a pad of SiO_2 using hexanes as the eluent to remove *m*-xylene, at which time separate fractions were collected, eluting with EtOAc, to isolate reaction products. The filtrate was concentrated *in vacuo* and the residue was subsequently purified by flash chromatography (1:2 EtOAc:hexanes) to afford the Claisen product, **194** (4.80 mg, 44% yield).

R_f = 0.39 (1:2 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 2H), 7.35 (ddd, *J* = 7.7, 6.8, 1.2 Hz, 2H), 7.30 – 7.27 (m, 1H), 5.94 (m, 1H), 5.61 (dt, *J* = 10.8, 5.1 Hz, 1H), 3.87 (d, *J* = 13.9 Hz, 2H), 3.55 (d, *J* = 15.7 Hz, 1H), 3.42 (d, *J* = 15.3 Hz, 1H), 3.04 (t, *J* = 15.5 Hz, 1H), 2.84 (d, *J* = 15.4 Hz, 1H), 2.47 – 2.42 (m, 1H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.7, 138.3, 130.9, 129.0, 128.7, 128.1, 127.6, 66.1, 61.3, 58.1, 45.9, 29.1; IR (Neat Film NaCl) 2928, 2791, 1696, 1493, 1451, 1268, 1126, 699 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{14}H_{18}NO$ $[M+H]^+$: 216.1383; found: 216.1398.

APPENDIX 10

Spectra Relevant to Appendix 9:

Ni-Catalyzed C–O Bond Formation and Subsequent Claisen Rearrangement

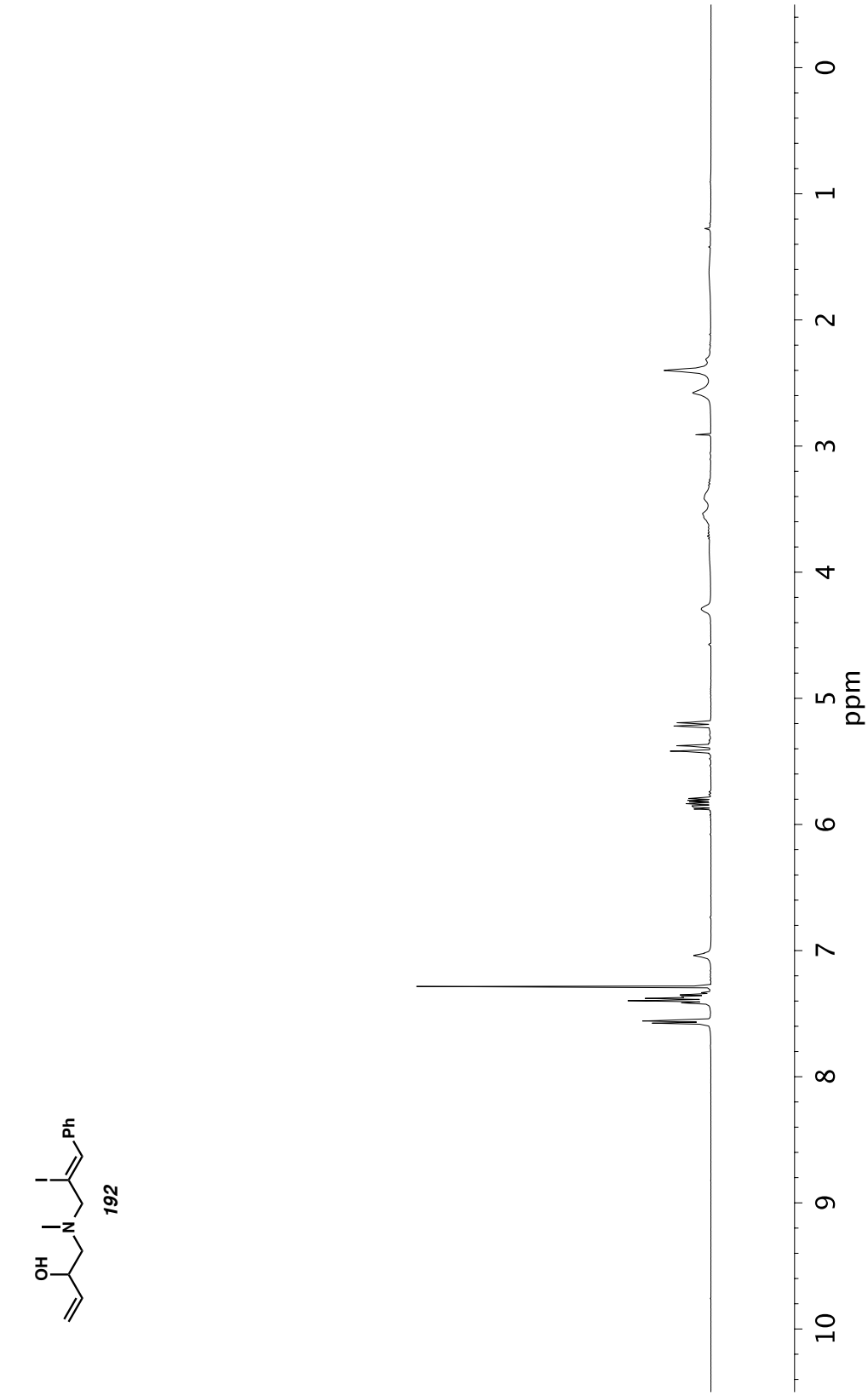


Figure A10.1. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **192**.

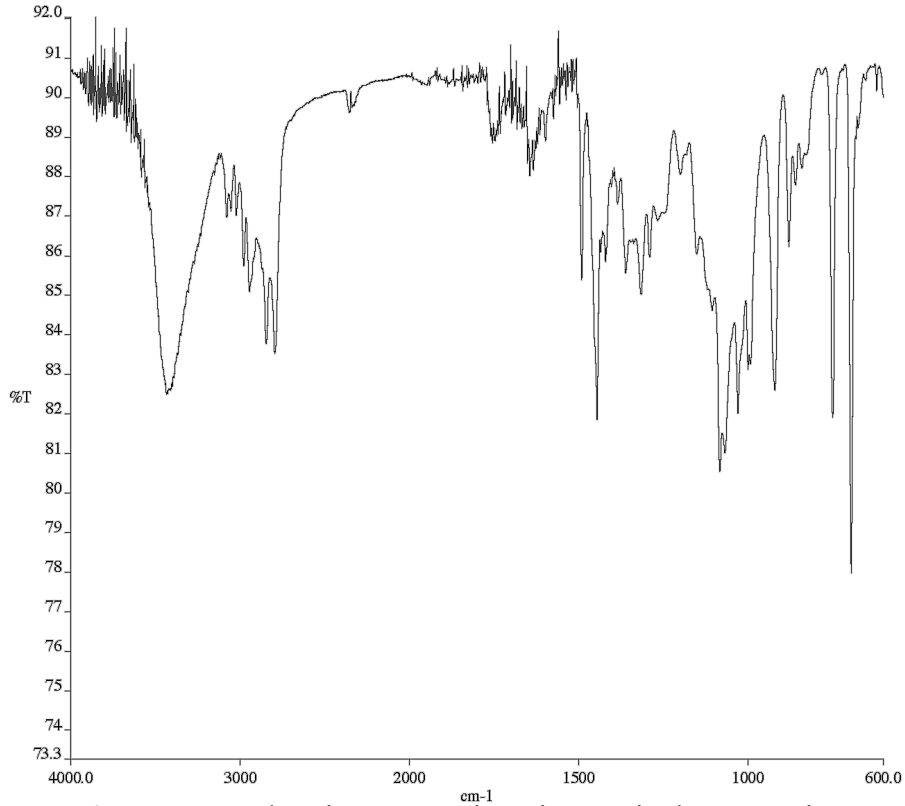


Figure A10.2. Infrared spectrum (Thin Film, NaCl) of compound **192**.

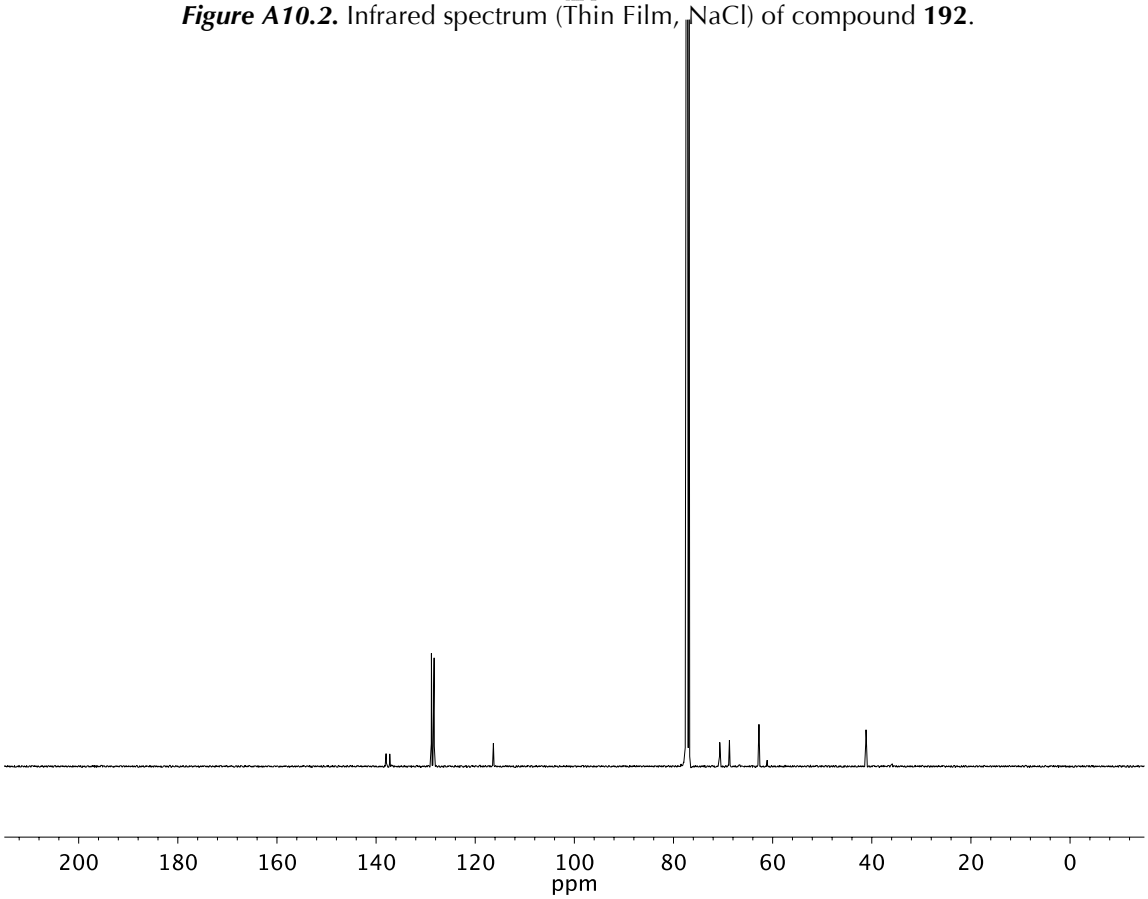


Figure A10.3. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **192**.

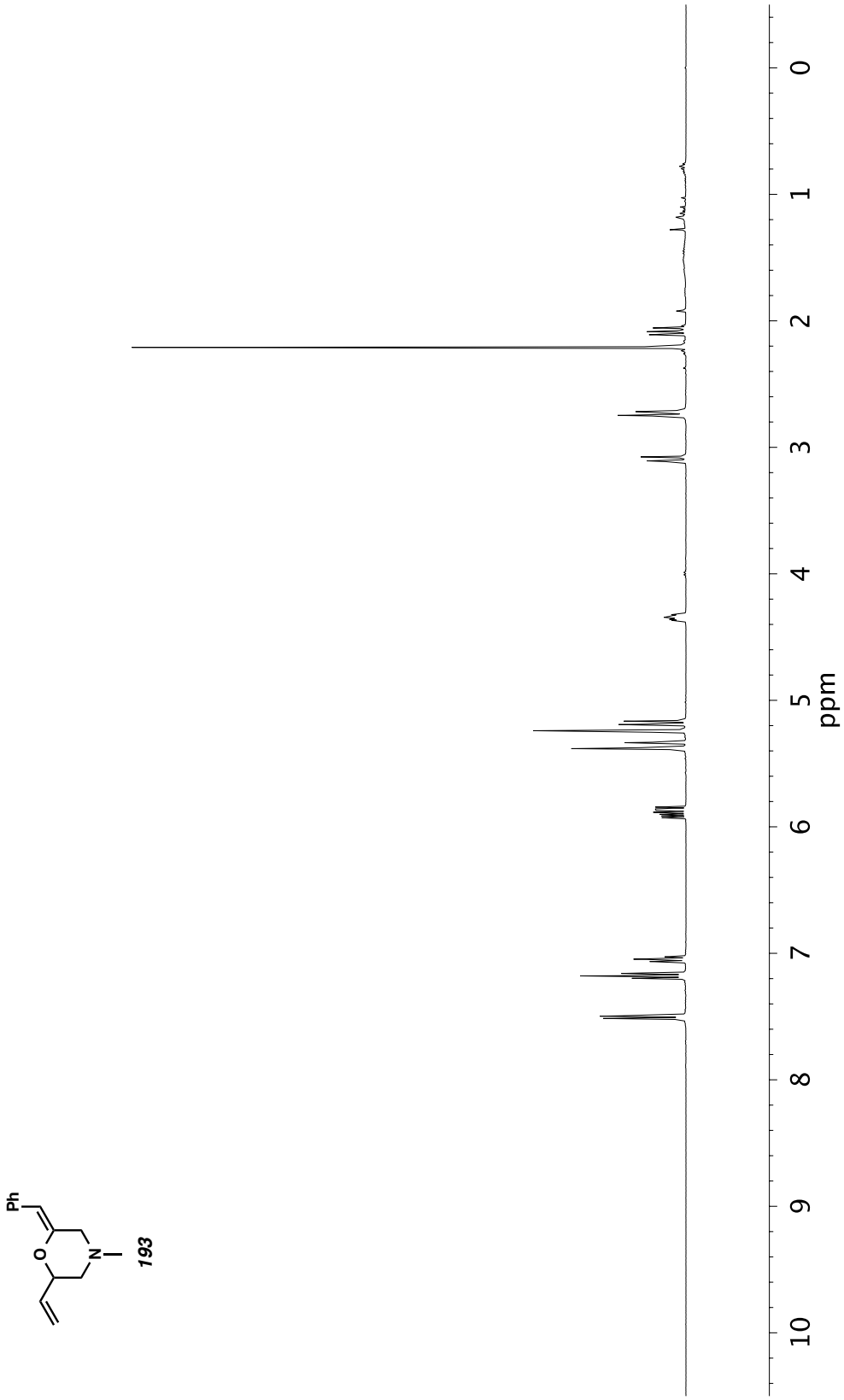


Figure A10.4. ^{1}H NMR (400 MHz, CD_2Cl_2) of compound **193**.

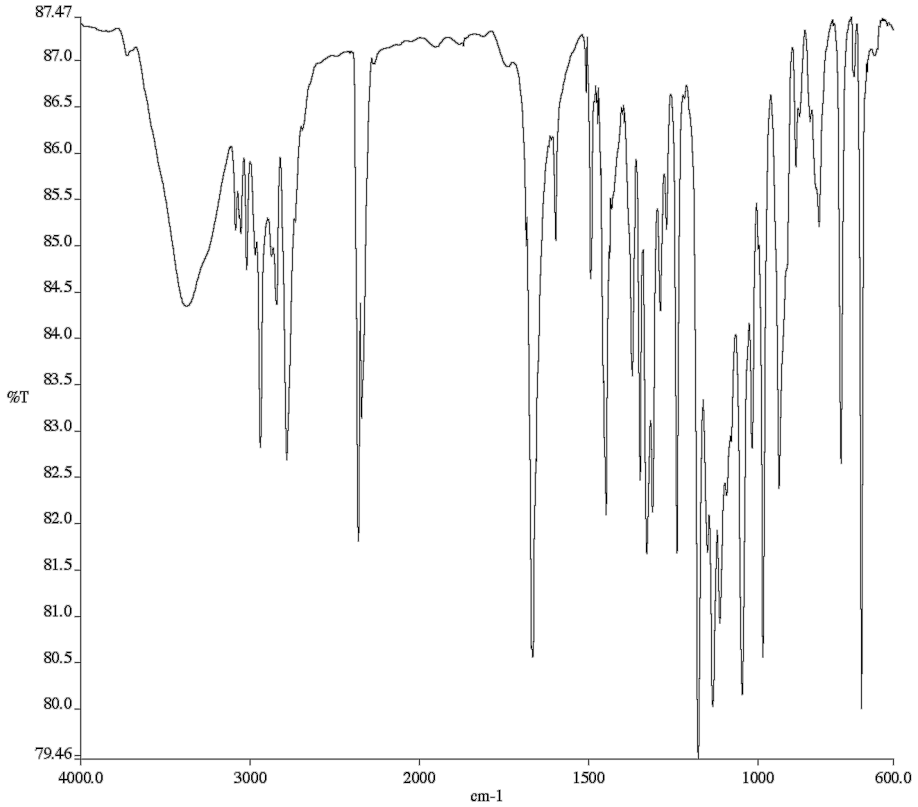


Figure A10.5. Infrared spectrum (Thin Film, NaCl) of compound **193**.

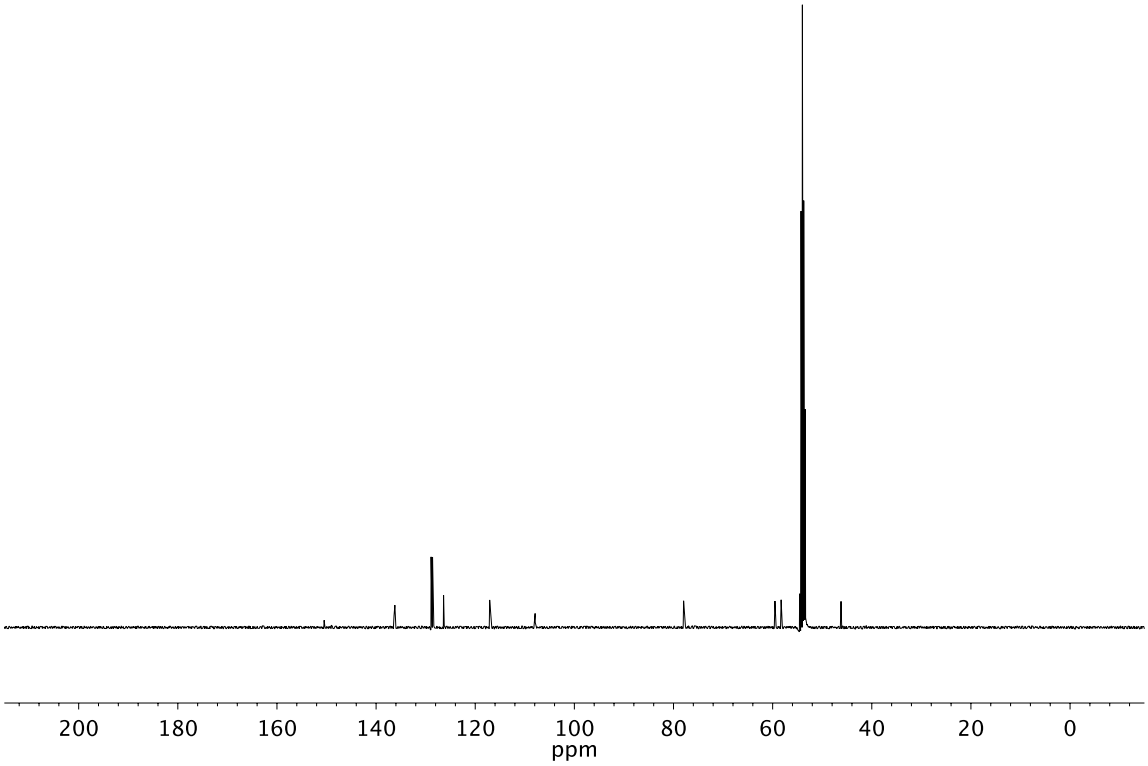


Figure A10.6. ^{13}C NMR (101 MHz, CD_2Cl_2) of compound **193**.

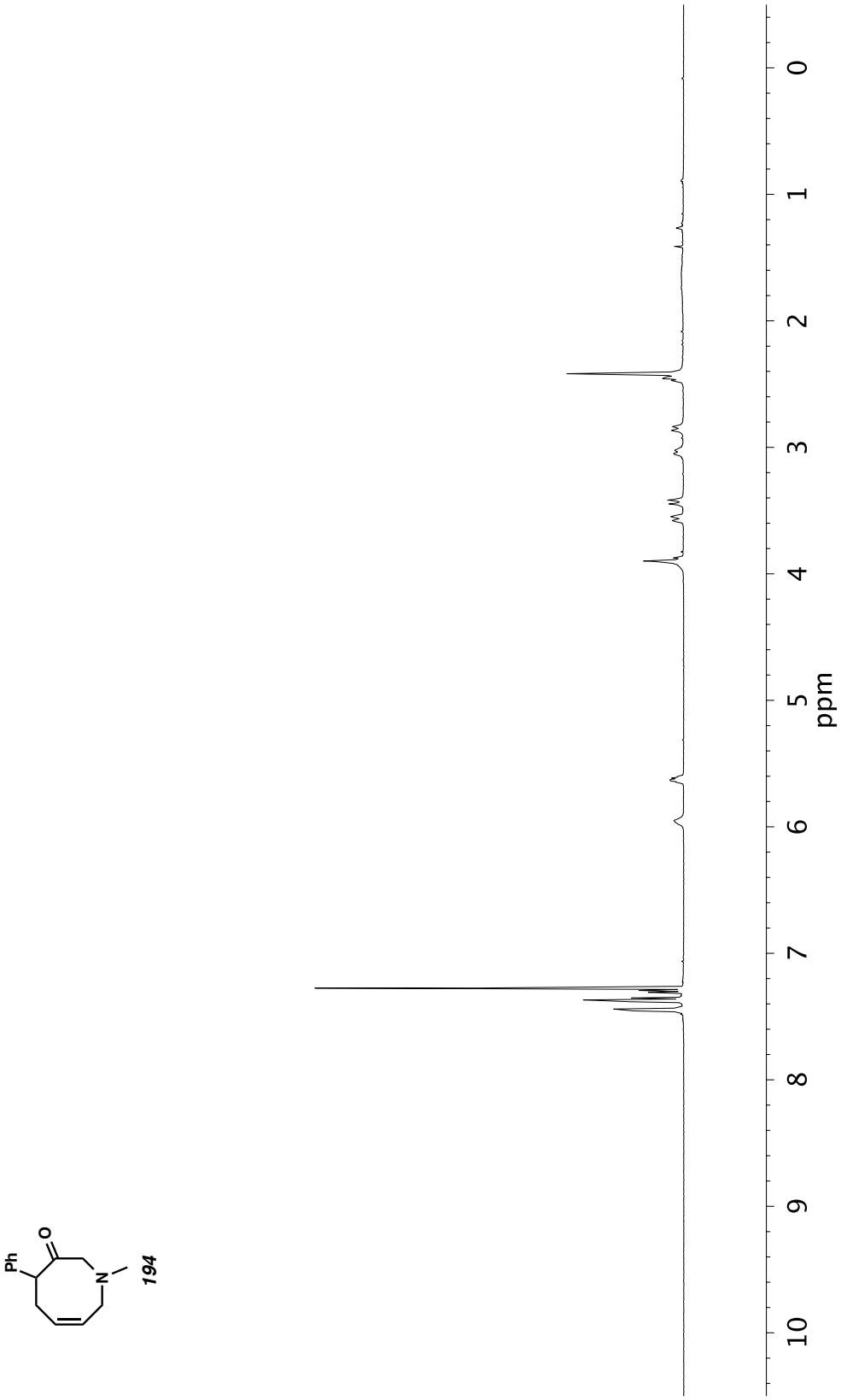


Figure A10.7. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **194**.

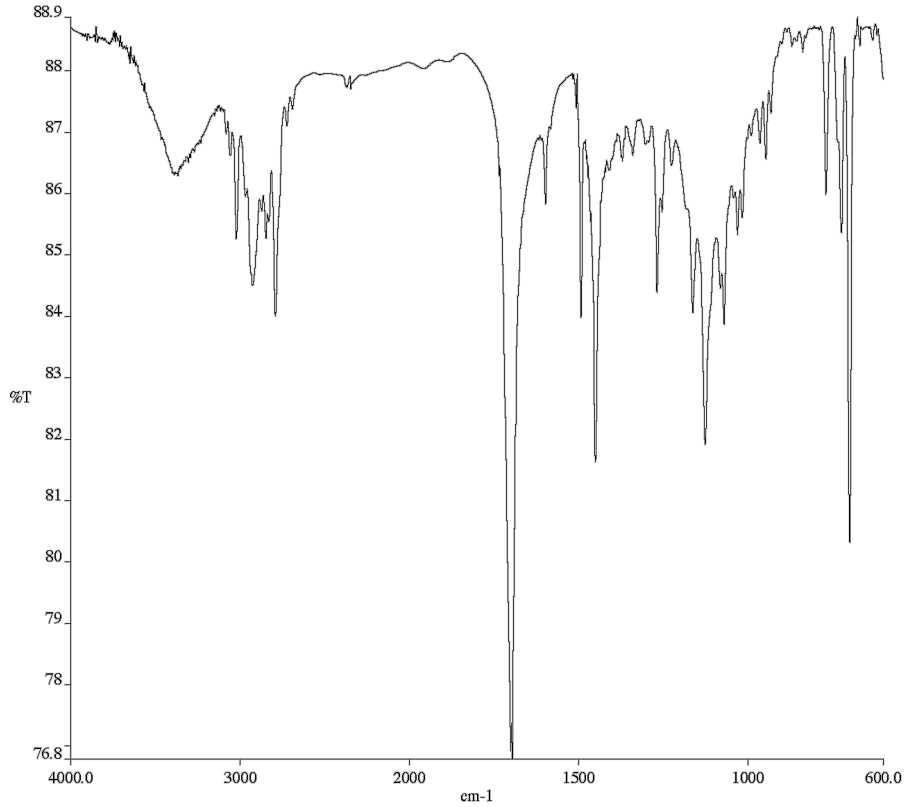


Figure A10.8. Infrared spectrum (Thin Film, NaCl) of compound **194**.

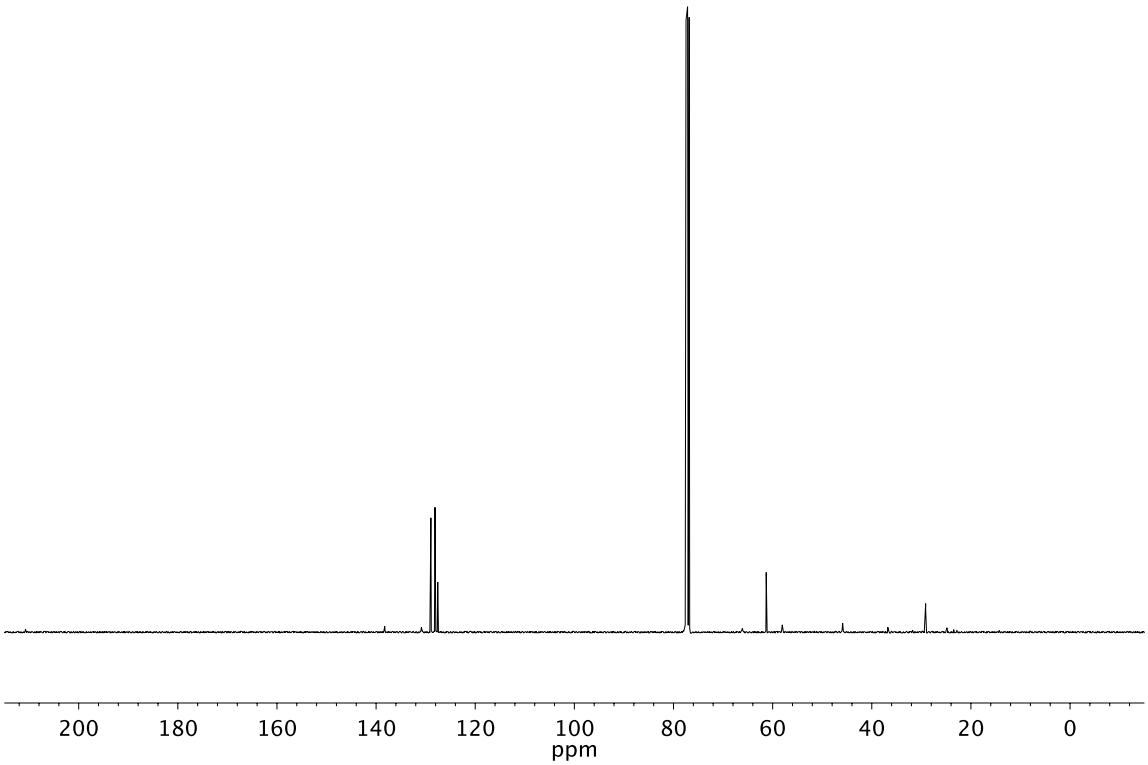


Figure A10.9. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **194**.

APPENDIX 11

Synthetic Studies Toward Alistonitrine A[†]

A11.1. Introduction

The polycyclic monoterpene alkaloid alistonitrine A (**195**) was isolated from the leaves of *Alstonia scholaris* in 2014 by the Bai and Jiang groups (Figure A11.1.1).[1] The alkaloids extracted from *Alstonia scholaris* possess interesting biological properties such as anticancer, antibacterial, anti-inflammatory, antiasthmatic, expectorant, analgesic, and antitussive activities.[2] Alistonitrine A (**195**) possesses intriguing structural features including an unprecedented caged skeleton, consecutive aminals, an epoxide, and a polycyclic system. Synthetic studies toward alistonitrine A have not been reported to date. Herein, we describe our synthetic efforts toward alistonitrine A (**195**).

Figure A11.1.1. *Structure of Alistonitrine A (**195**)*



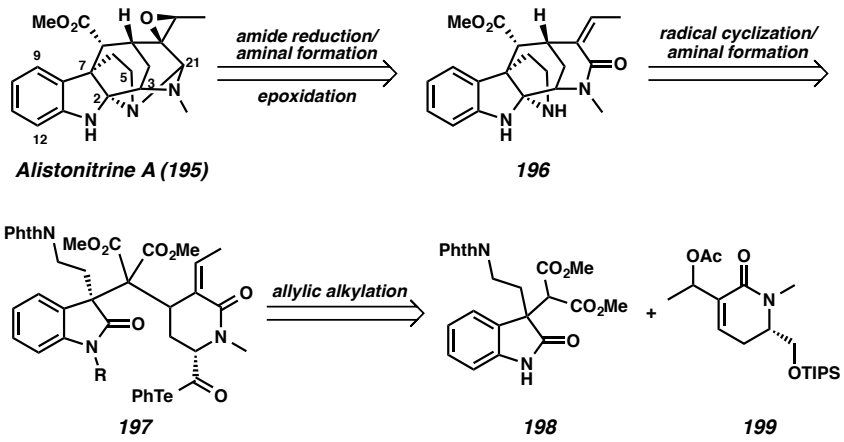
Alistonitrine A (195)

[†] Portions of this work have been published. Han, S.-J.; Stoltz, B. M. *Tetrahedron Lett*. **2016**, DOI: 10.1016/j.tetlet.2016.04.022

A11.2. Results and Discussion

Our initial retrosynthetic analysis of alistonitrine A is outlined in Scheme A11.2.1. Disconnection of the aminal at the C21 and epoxide functions in alistonitrine A (**195**) would afford amide **196**. Further cleavage of the C2–C3 bond and the second aminal functional group would provide intermediate **197**, in which the acyl telluride would serve as a handle for a decarbonylative radical cyclization.[3] We envisioned that the vicinal quaternary centers of intermediate **197** could be constructed by coupling of oxindole **198** and amide **199**.

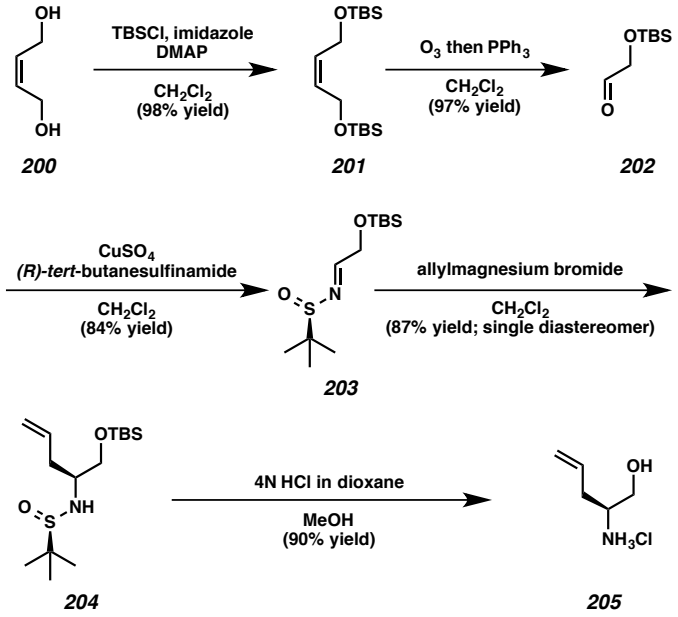
Scheme A11.2.1. *Retrosynthetic Analysis of Alistonitrine A (**195**)*



The synthesis commenced with the construction of amine **205**, which was adapted from Ellman and Nelson protocols (Scheme A11.2.2). Protection of diol **200** with TBSCl furnished bis-silyl ether **201**, which was converted to aldehyde **202** by ozonolysis. Condensation with (*R*)-*tert*-butanesulfinamide auxiliary produced *tert*-butylsulfinyl imine **203**.[4,5] 1,2-addition of allylmagnesium bromide to *tert*-butylsulfinyl imine **203** generated

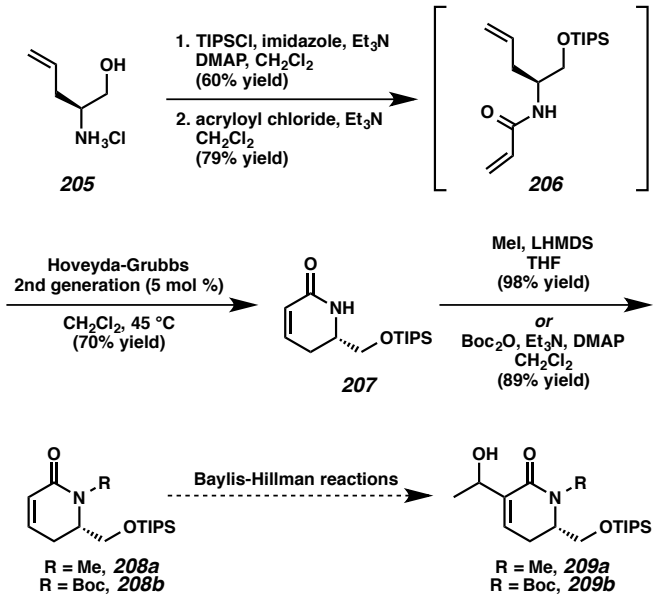
adduct **204** in high diastereoselectivity. Cleavage of the silyl and *tert*-butanesulfinyl groups under acidic conditions afforded chiral amine **205**.

Scheme A11.2.2. *Synthesis of Chiral Amine* ***205***



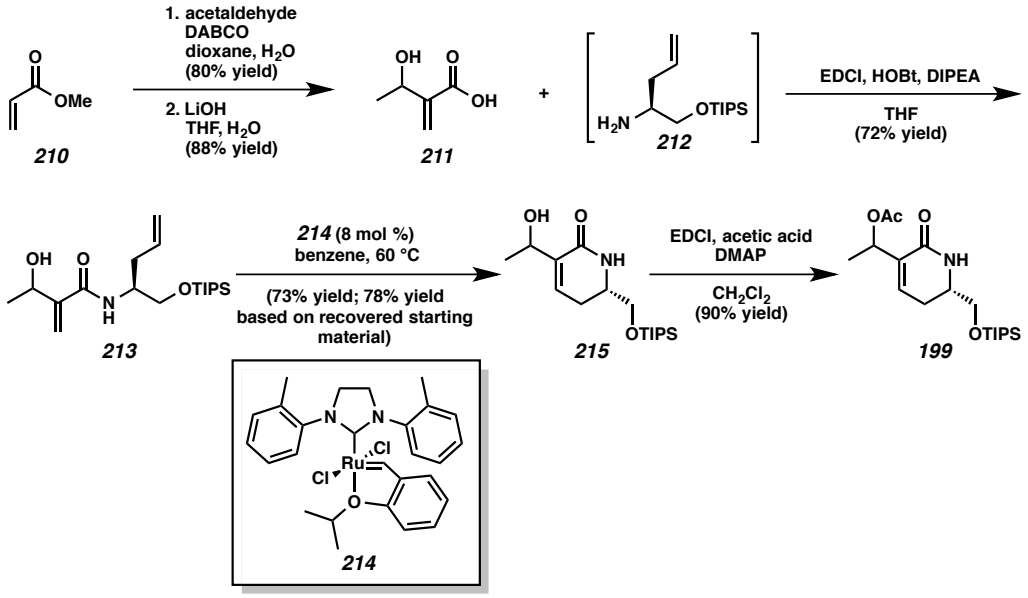
With chiral amine **205** in hand, α,β-unsaturated lactam formation was explored (Scheme A11.2.3). Silylation of amine **205** followed by acylation generated metathesis precursor **206**. We were delighted to find that ring-closing metathesis of **206** with Hoveyda-Grubbs 2nd generation catalyst smoothly produced lactam **207**.[6,7] Protection of the nitrogen of amide **207** with MeI or Boc_2O afforded the corresponding intermediates **208a** and **208b**. Unfortunately, attempted Baylis-Hillman reactions to furnish alcohol **209a** or **209b**, respectively, were unsuccessful.[8,9]

Scheme A11.2.3. *Synthesis of α,β-Unsaturated Lactams* ***208***



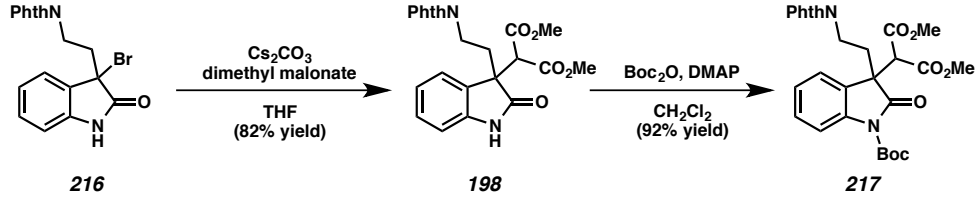
Alternatively, we decided to employ the Baylis-Hillman reaction at an earlier stage (Scheme A11.2.4). Reaction of methyl acrylate (**210**) with acetaldehyde and subsequent hydrolysis furnished acid **211**. Coupling of acid **211** and amine **212** with EDCI and HOBt proceeded smoothly to provide amide **213**. To our delight, ring-closing metathesis of **213** occurred with catalyst **214**, delivering the desired 2:3 mixture of two diastereomers of lactam **215**.[10] Coupling of alcohol **215** and acetic acid with EDCI and HOBt generated acetate **199**.

Scheme A11.2.4. *Synthesis of α,β-Unsaturated Lactam* ***199***



Having successfully prepared the amide fragment, we began the synthesis of the oxindole fragment **217** (Scheme A11.2.5). The quaternary center of oxindole **198** was constructed by the base-promoted alkylation of 3-bromooxindole **216** with dimethyl malonate, which proceeded via *in situ* formation of an *o*-azaxylylene intermediate.[11] Boc protection of the oxindole nitrogen generated oxindole fragment **217**.

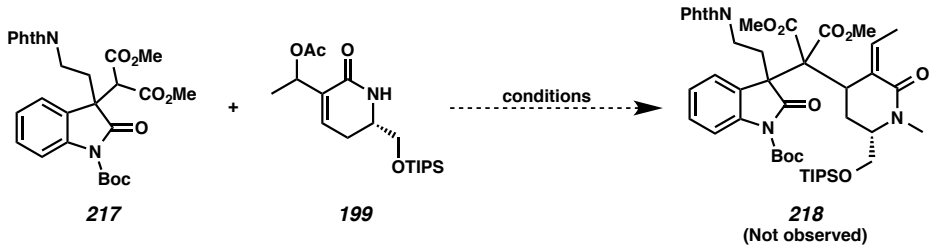
Scheme A11.2.5. *Synthesis of Oxindole Fragment* ***217***



With fragments **199** and **217** in hand, we investigated various alkylation reactions of malonate **217** with acetate **199** (Scheme A11.2.6). Unfortunately, only trace amounts

of the desired product and some byproducts were observed with palladium catalysts. Additionally, we attempted to form **218** under basic conditions, but only unreacted oxindole **217** and a byproduct were obtained.

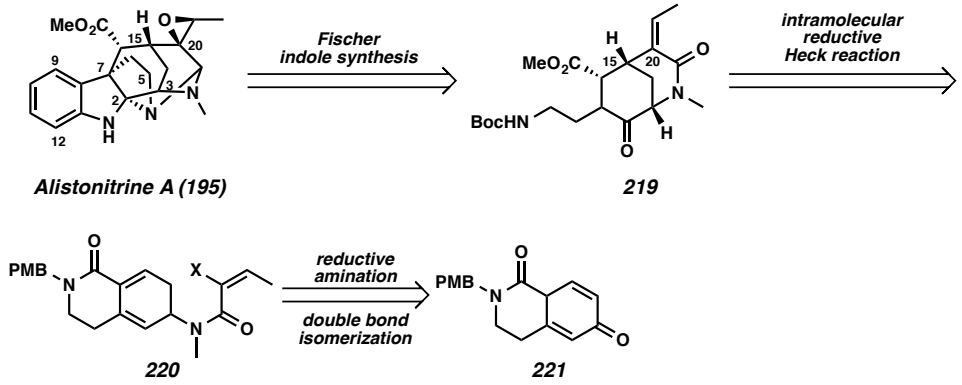
Scheme A11.2.6. *Attempted Coupling of Malonate **217** and Amide **199***



217 ***199*** ***218*** **(Not observed)**

Having failed in coupling of oxindole **217** and amide **199**, a revised retrosynthesis was devised (Scheme A11.2.7). We envisioned that a late stage Fischer indole synthesis of intermediate **219** would afford the core structure of alistonitrine A. Disconnection of the C15–C20 bond in intermediate **219** provided Heck reaction precursor **220**. Vinyl halide **220** was expected to be formed from ketone **221** by reductive amination and subsequent double bond isomerization.

Scheme A11.2.7. *A Revised Retrosynthesis Toward Alistonitrine A*

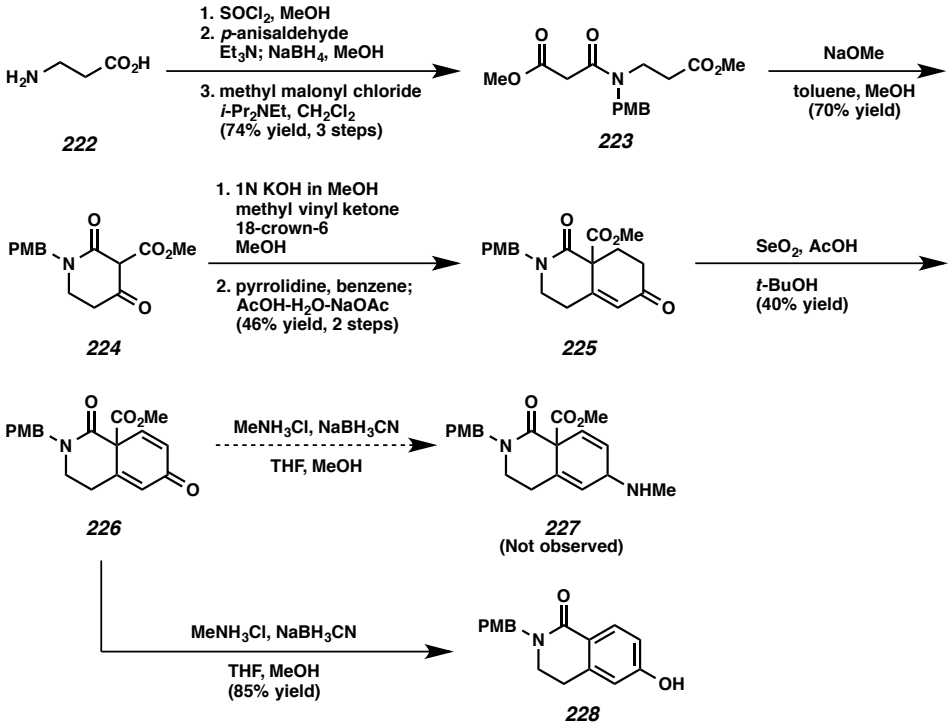


Alistonitrine A (195) ***219*** ***220*** ***221***

Esterification of acid **222** followed by subsequent reductive amination and acylation produced amide **223** (Scheme A11.2.8). Treatment of **223** with NaOMe afforded lactam **224**, and a subsequent Robinson annulation furnished bicycle **225**.[12] Oxidation of enone **225** was accomplished with SeO_2 to deliver dienone **226**.[13] However, an attempted reductive amination of dienone **226** to provide amine **227** resulted in the removal of the ester group and subsequent aromatization, affording phenol **228**.

Although our synthetic efforts toward alistonitrine A were unsuccessful, we were able to serendipitously discover a novel nickel-catalyzed C–O bond forming reaction (Chapter 4).

Scheme A11.2.8. *Synthesis of Bicycle* ***226***



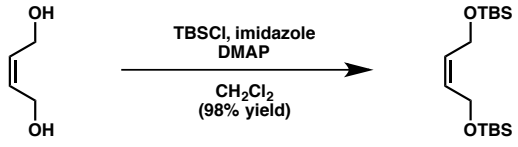
A11.3. Experimental Methods and Analytical Data

A11.3.1. Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Reaction progress was monitored by thin-layer chromatography (TLC). THF, Et_2O, CH_2Cl_2, toluene, benzene, CH_3CN, and dioxane were dried by passage through an activated alumina column under argon. Triethylamine was distilled over CaH_2 prior to use. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. Brine solutions are saturated aqueous solutions of sodium chloride. Commercially available reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulator unless otherwise indicated. Microwave-assisted reactions were performed in a Biotage Initiator 2.5 microwave reactor. Glove box manipulations were performed under a N_2 atmosphere. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or PMA (phosphomolybdic acid) staining. Silicycle Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.064 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on a Varian Inova 500 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm), or $(CD_3)_2CO$ (δ 2.05 ppm). ^{13}C NMR spectra are recorded on a Varian Inova 500 MHz spectrometer (125MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm), or $(CD_3)_2CO$ (δ 29.84 ppm). Data for ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d= broad doublet, app

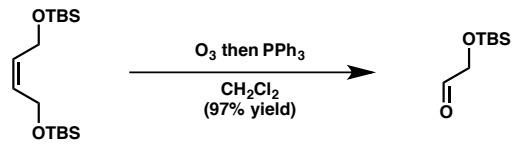
= apparent. Data for ^{13}C are reported in terms of chemical shifts (ppm). IR spectra were obtained using a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+).

A11.3.2. Experimental Procedures



200 ***201***

To a solution of diol **200** (0.930 mL, 11.3 mmol, 1.00 equiv) in CH_2Cl_2 (28.3 mL) were added imidazole (7.69 g, 113 mmol, 10.0 equiv) and TBSCl (5.11 g, 33.9 mmol, 3.00 equiv) at 23 °C. The reaction mixture was stirred for 12 h and quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3 x 10.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1:8 EtOAc:hexanes) to afford bis-silyl ether **201** (3.51 g, 98% yield). The spectroscopic data were identical to those previously reported.[1]

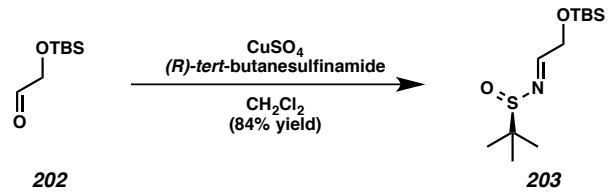


201 ***202***

[1] Tran, V. T.; Woerpel, K. A. *J. Org. Chem.* **2013**, *78*, 6609–6621.

A solution of bis-silyl ether **201** (1.00 g, 3.16 mmol, 1.00 equiv) in CH_2Cl_2 (21.1 mL) was cooled to –78 °C and ozone was bubbled through until the solution turned blue. N_2 gas was then bubbled through the solution until the reaction mixture turned colorless. PPh_3 (0.99 g, 3.79 mmol, 1.20 equiv) was then added and the mixture was warmed to 23 °C slowly. The reaction mixture was stirred under N_2 for 1.5 h and the solvent was evaporated *in vacuo*. The residue was purified by silica gel chromatography (1:8 EtOAc:hexanes) to afford aldehyde **202** (1.07 g, 97% yield).

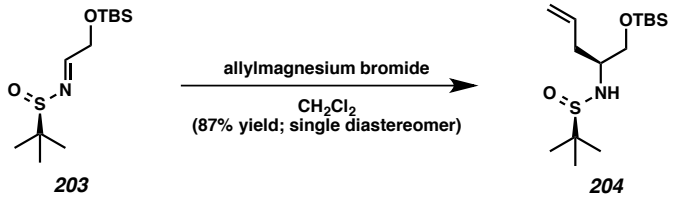
R_f = 0.25 (1:8 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (t, J = 0.8 Hz, 1H), 4.22 (d, J = 0.8 Hz, 2H), 0.93 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.5, 69.8, 25.9, 18.5, -5.3; IR (Neat Film NaCl) 2955, 2931, 2858, 1740, 1473, 1256, 1128, 838, 779 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_8H_{19}O_2Si$ $[M+H]^+$: 175.1154; found: 175.1067.



202 *203*

To a solution of aldehyde **202** (100 mg, 0.574 mmol, 1.00 equiv) in CH_2Cl_2 (1.91 mL) was added $CuSO_4$ (275 mg, 1.72 mmol, 3.00 equiv) followed by the addition of *tert*-butanesulfinamide (104 mg, 0.861 mmol, 1.50 equiv). The reaction mixture was stirred at 23 °C for 12 h. Solids were removed via a filtration through a celite plug and the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (1:8 EtOAc:hexanes) to furnish the *tert*-butylsulfinyl imine **203** (133 mg, 84% yield).

$[a]_D^{25}$ –127.8 (*c* 0.19, $CHCl_3$); R_f = 0.20 (1:8 EtOAc:hexanes); ^1H NMR (400 MHz, CD_2Cl_2) δ 7.99 (t, J = 3.1 Hz, 1H), 4.53 (d, J = 3.1 Hz, 2H), 1.17 (s, 9H), 0.92 (s, 9H), 0.10 (d, J = 0.6 Hz, 6H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 169.1, 66.1, 57.1, 26.1, 22.6, 18.8, -5.1; IR (Neat Film NaCl) 2956, 2930, 2858, 1628, 1473, 1364, 1255, 1089, 838, 779 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{28}NO_2SSi$ $[M+H]^+$: 278.1605; found: 278.1606.

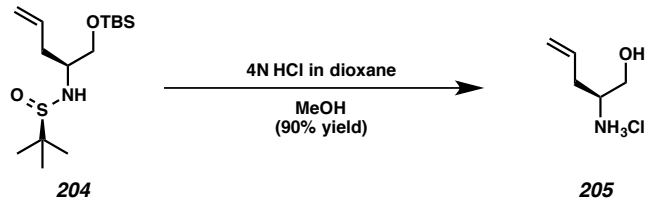


203 ***204***

To a solution of *tert*-butylsulfinyl imine **203** (800 mg, 2.88 mmol, 1.00 equiv) in CH_2Cl_2 (14.4 mL) was added allylmagnesium bromide (1M in diethyl ether; 6.05 mL, 6.05 mmol, 2.10 equiv) dropwise at –78 °C. The reaction mixture was stirred for 5 h at –78 °C and slowly warmed to 23 °C. The reaction was quenched with sat. aq NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (3 x 10.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1:4 EtOAc:hexanes) to afford silyl ether **204** (797 mg, 87% yield).

$[a]_D^{25}$ –53.7 (*c* 0.26, $CHCl_3$); R_f = 0.25 (1:4 EtOAc:hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddt, J = 17.3, 10.2, 7.2 Hz, 1H), 5.18 – 5.11 (m, 2H), 3.66 (dd, J = 9.9, 4.2 Hz, 1H), 3.54 – 3.51 (m, 1H), 3.48 (s, 1H), 3.34 (t, J = 5.8 Hz, 1H), 2.55 – 2.48 (m, 1H), 2.39 (dtt, J = 13.9, 6.7, 1.3 Hz, 1H), 1.19 (s, 9H), 0.89 (s, 9H), 0.05 (d, J = 0.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.5, 118.6, 77.2, 65.1, 56.5, 56.0, 37.2, 26.0, 22.7, 18.4, -

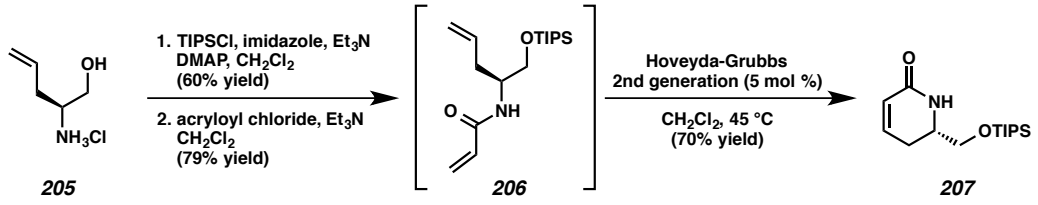
5.3, -5.3; IR (Neat Film NaCl) 2955, 2929, 2858, 1472, 1253, 1113, 1072, 836, 777 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{15}H_{34}NO_2SSi$ $[M+H]^+$: 320.2001; found: 320.2084.



204 ***205***

To a solution of silyl ether **204** (126 mg, 0.394 mmol, 1.00 equiv) in MeOH (1.97 mL) was added 4N HCl in dioxane (1.97 mL, 1.97 mmol, 5.00 equiv) at 0 °C. The reaction mixture was warmed to 23 °C and stirred for 2 h. The volatile was evaporated under reduced pressure. The resulting oil was washed with ether revealing a yellow solid. The solid was filtered to give amine hydrochloride **205** (49.0 mg, 90% yield).

$[a]_D^{25}$ +9.52 (*c* 0.06, MeOH); R_f = 0.10 (2:1 EtOAc:hexane); ^1H NMR (500 MHz, CD_3OD) δ 5.81 (ddt, J = 17.3, 10.2, 7.2 Hz, 1H), 5.29 – 5.19 (m, 2H), 3.76 (dd, J = 11.6, 3.7 Hz, 1H), 3.55 (dd, J = 11.6, 6.7 Hz, 1H), 3.29 – 3.20 (m, 1H), 2.47 – 2.32 (m, 2H); ^{13}C NMR (126 MHz, CD_3OD) δ 133.28, 120.24, 61.92, 53.96, 34.90; IR (Neat Film NaCl) 3369, 2929, 1618, 1508, 1053, 928 cm^{-1}.



205 ***206*** ***207***

To a solution of amine hydrochloride **205** (188 mg, 1.37 mmol, 1.00 equiv) in CH_2Cl_2 (7.00 mL) were added Et_3N (0.38 mL, 2.74 mmol, 2.00 equiv), imidazole (930 mg, 13.7 mmol, 10.0 equiv), DMAP (8.40 mg, 0.0685 mmol, 0.05 equiv), and TIPSCl (0.59 mL,

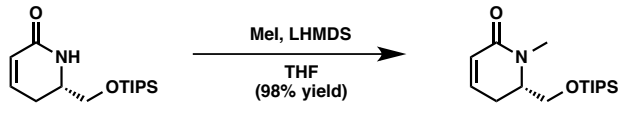
2.74 mmol, 2.00 equiv). The reaction mixture was stirred for 12 h at 23 °C and quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3 x 8.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (2:1 EtOAc:hexane) to afford the silyl ether (212 mg, 60% yield).

To a solution of the resultant silyl ether (100 mg, 0.388 mmol, 1.00 equiv) and Et_3N (0.160 mL, 1.16 mmol, 3.00 equiv) in CH_2Cl_2 (1.94 mL) was added acryloyl chloride (35.0 μL, 0.427 mmol, 1.10 equiv) at 23 °C. The reaction was stirred for 12 h at 23 °C and quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3 x 2.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1:4 EtOAc:hexanes) to afford amide **206** (95.0 mg, 79% yield).

To a stirred solution of amide **206** (1.08 g, 3.47 mmol, 1.00 equiv) in CH_2Cl_2 (116 mL) was added Hoveyda-Grubbs 2nd generation catalyst (0.109 g, 0.173 mmol, 0.05 equiv) at 23 °C. Then, the solution was stirred at 45 °C for 12 h. After the reaction was done, the solution was cooled to 23 °C and water was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 30.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1:2 EtOAc:hexanes) to afford lactam **207** (688 mg, 70% yield).

$[a]_D^{25}$ –15.6 (*c* 0.22, $CHCl_3$); R_f = 0.20 (1:2 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (ddd, *J* = 9.9, 5.4, 3.0 Hz, 1H), 5.92 (dtd, *J* = 9.9, 2.4, 1.3 Hz, 1H), 5.87 (s, br, 1H), 3.80 – 3.72 (m, 2H), 3.66 – 3.58 (m, 1H), 2.31 (dtt, *J* = 17.6, 5.4, 1.2 Hz, 1H), 2.16 (ddt, *J* = 17.7, 10.9, 2.8 Hz, 1H), 1.21 – 1.00 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ

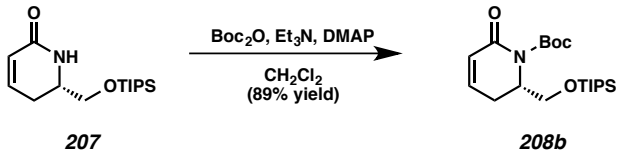
166.0, 140.0, 124.8, 66.0, 52.6, 26.0, 18.1, 12.0; IR (Neat Film NaCl) 2943, 2866, 1682, 1615, 1463, 1114, 813 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{30}NO_2Si$ $[M+H]^+$: 284.2040; found: 284.2045.



207 ***208a***

To a solution of lactam **207** (100 mg, 0.353 mmol, 1.00 equiv) in THF (1.80 mL) was added LHMDS (89.0 mg, 0.530 mmol, 1.50 equiv) at 0 °C. The reaction was stirred for 1 h and then MeI (66.0 μL, 1.06 mmol, 3.00 equiv) was added. The solution was stirred for 4 h at 23 °C and quenched with sat. aq NH_4Cl. The aqueous phase was extracted with EtOAc (3 x 2.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1:2 EtOAc:hexanes) to afford amide **208a** (103 mg, 98% yield).

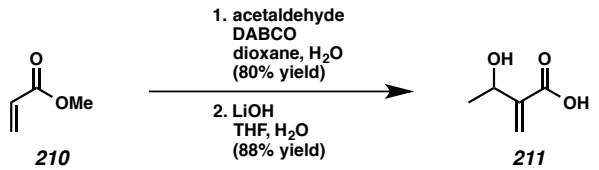
$[a]_D^{25}$ +46.9 (*c* 0.12, $CHCl_3$); R_f = 0.27 (1:2 EtOAc:hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 6.42 – 6.35 (m, 1H), 5.91 (ddd, J = 9.8, 2.7, 1.1 Hz, 1H), 3.74 (dd, J = 9.6, 5.2 Hz, 1H), 3.66 (dd, J = 9.6, 8.6 Hz, 1H), 3.55 – 3.48 (m, 1H), 3.05 (s, 3H), 2.58 (ddt, J = 6.8, 5.0, 2.0 Hz, 2H), 1.15 – 1.00 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.1, 137.3, 125.0, 61.6, 59.2, 34.3, 25.0, 18.1, 12.0; IR (Neat Film NaCl) 2942, 2866, 1670, 1618, 1464, 1111, 882 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{32}NO_2Si$ $[M+H]^+$: 298.2197; found: 298.2199.



207 ***208b***

To a solution of amide **207** (50.0 mg, 0.176 mmol, 1.00 equiv) and DMAP (32.2 mg, 0.264 mmol, 1.50 equiv) in CH_2Cl_2 (0.90 mL) at 0 °C were added Et_3N (49.1 μL, 0.352 mmol, 2.00 equiv) and Boc anhydride (77.0 mg, 0.353 mmol, 2.00 equiv). The reaction mixture was warmed to 23 °C and stirred for 12 h. The reaction was quenched with sat. aq NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (3 x 1.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1:8 EtOAc:hexanes) to afford carbamate **208b** (60.0 mg, 89% yield).

$[a]_D^{25}$ +11.5 (*c* 0.07, $CHCl_3$); R_f = 0.85 (1:2 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 (ddt, J = 9.8, 6.3, 1.9 Hz, 1H), 5.94 (ddd, J = 9.8, 3.1, 0.8 Hz, 1H), 4.45 (ddt, J = 9.6, 4.8, 3.1 Hz, 1H), 3.74 (dd, J = 9.3, 4.8 Hz, 1H), 3.67 (t, J = 9.5 Hz, 1H), 2.76 (dd, J = 18.8, 6.3 Hz, 1H), 2.62 – 2.54 (m, 1H), 1.53 (s, 9H), 1.20 – 0.96 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.3, 152.3, 140.9, 126.0, 83.1, 77.2, 61.8, 54.6, 28.2, 24.8, 18.1, 12.0; IR (Neat Film NaCl) 2944, 2867, 1717, 1368, 1297, 1239, 1160, 1114, 810 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{30}NO_2Si$ $[M+H–Boc]^+$: 284.2040; found: 284.2046.



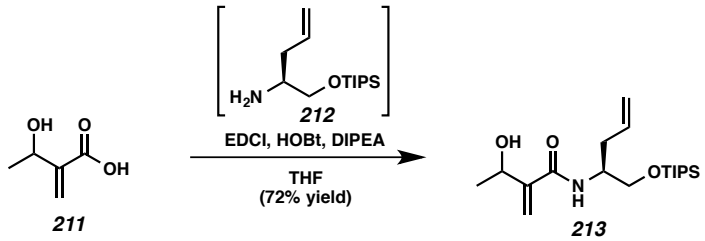
210 ***211***

To a solution of acetaldehyde (1.27 mL, 22.7 mmol, 1.00 equiv) in dioxane/water (1.10 mL/1.10 mL) was added methyl acrylate **210** (6.13 mL, 68.1 mmol, 3.00 equiv) and

DABCO (2.55 g, 22.7 mmol, 1.00 equiv). The reaction was stirred at 23 °C for 48 h. After the reaction was done, water was added. The aqueous phase was extracted with EtOAc (3 x 10.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1:4 EtOAc:hexanes) to afford the ester (2.36 g, 80% yield). The spectroscopic data were identical to those previously reported.[2]

To a solution of the resultant ester (300 mg, 2.31 mmol, 1.00 equiv) in THF (12.0 mL) and H_2O (5.00 mL) at 23 °C was added LiOH (88.0 mg, 3.69 mmol, 1.60 equiv). The reaction was stirred at 23 °C for 1 h and then water was added. The aqueous phase was separated and acidified until pH = 1 with 1N HCl. Then, the aqueous phase was extracted with EtOAc (3 x 10.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford acid **211** (236 mg, 88% yield).

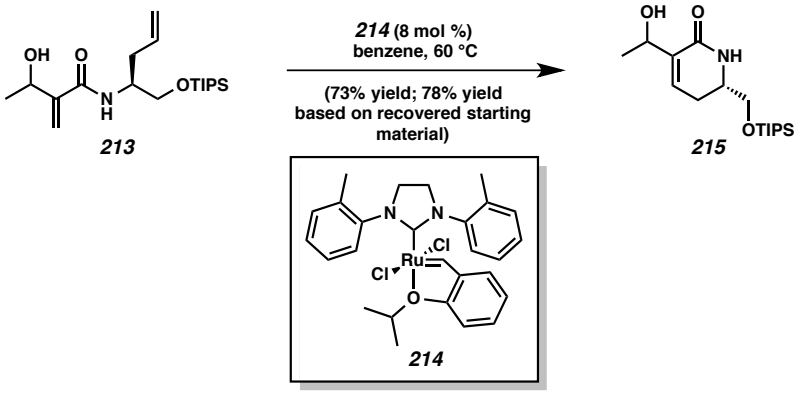
R_f = 0.15 (1:1 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (t, *J* = 0.8 Hz, 1H), 5.96 (t, *J* = 1.1 Hz, 1H), 4.65 (q, J = 6.5 Hz, 1H), 1.42 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 142.8, 127.0, 67.1, 22.2; IR (Neat Film NaCl) 3390, 1694, 1633, 1416, 1277, 1176, 1093, 962, 928 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_5H_9O_3$ $[M+H]^+$: 117.0552; found: 117.0521.



[2] Latorre, A.; Sáez, J. A.; Rodríguez, S.; González, F. V. *Tetrahedron* **2014**, *70*, 97–102.

To a solution of amine **212** (50.0 mg, 0.194 mmol, 1.00 equiv) in THF (1.00 mL) were added acid **211** (24.0 mg, 0.204 mmol, 1.05 equiv), HOBt (39.3 mg, 0.291 mmol, 1.50 equiv), EDCI (45.2 mg, 0.291 mmol, 1.50 equiv), and DIPEA (41.0 μL. 0.233 mmol, 1.2 equiv). The reaction was stirred for 12 h at 23 °C and then quenched with sat. aq NH_4Cl. The aqueous phase was extracted with EtOAc (3 x 1.50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1:4 → 1:2 EtOAc:hexanes) to afford amide **213** (49.7 mg, 72% yield).

$[a]_D^{25}$ –29.5 (*c* 0.07, $CHCl_3$); R_f = 0.35 (1:2 EtOAc:hexanes); (due to the distinct presence of rotameric isomers, the ^{13}C NMR contained extra peaks. See the attached spectrum), ^1H NMR (400 MHz, $CDCl_3$) δ 6.65 (dd, *J* = 18.7, 8.7 Hz, 1H), 5.81 (ddtd, *J* = 17.2, 10.2, 7.1, 1.5 Hz, 1H), 5.65 (d, *J* = 6.5 Hz, 1H), 5.45 (s, br, 1H), 5.19 – 5.00 (m, 2H), 4.57 (qt, *J* = 6.5, 1.2 Hz, 1H), 4.10 (dddddd, *J* = 8.2, 6.9, 5.1, 3.9, 2.8, 1.2 Hz, 1H), 3.85 – 3.68 (m, 2H), 2.48 – 2.29 (m, 2H), 1.38 (d, *J* = 6.5 Hz, 3H), 1.16 – 1.02 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 167.6, 147.24, 147.17, 134.80, 134.77, 118.0, 117.9, 117.9, 117.7, 69.2, 69.1, 64.12, 64.11, 50.13, 50.12, 36.09, 36.07, 21.94, 21.86, 18.1, 12.0; IR (Neat Film NaCl) 3305, 2943, 2866, 1655, 1618, 1542, 1534, 1460, 1118, 882, 788, 682 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{38}NO_3Si$ $[M+H]^+$: 356.2615; found: 356.2624.

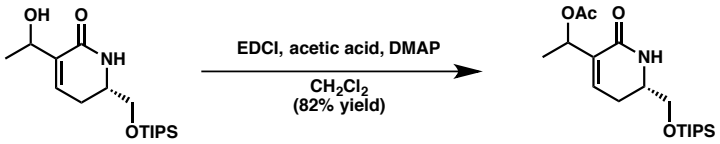


To a solution of amide **213** (740 mg, 2.08 mmol, 1.00 equiv) in benzene (104 mL) was added Ru catalyst **214** (95.0 mg, 0.17 mmol, 0.08 equiv). The solution was stirred at 60 °C for 12 h. The solvent was concentrated under reduced pressure. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to furnish two diastereomers of lactam **215** (499 mg, 73% yield; 2:3 **215a**:**215b**; 78% yield based on recovered starting material).

Diastereomer **215a**: $[a]_D^{25}$ –1.54 (*c* 0.78, $CHCl_3$); R_f = 0.35 (1:1 EtOAc:hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 6.44 (ddd, *J* = 5.7, 3.0, 1.2 Hz, 1H), 5.93 (s, br, 1H), 4.62 – 4.55 (m, 1H), 3.75 (dd, *J* = 9.2, 4.3 Hz, 1H), 3.61 (dd, *J* = 9.2, 8.5 Hz, 1H), 2.38 – 2.31 (m, 1H), 2.22 – 2.15 (m, 1H), 1.38 (d, *J* = 6.5 Hz, 3H), 1.13 – 1.03 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 137.0, 132.9, 66.7, 66.0, 52.3, 25.8, 21.1, 18.1, 12.0; IR (Neat Film NaCl) 3408, 2943, 2866, 1678, 1627, 1461, 1117, 1070, 882, 789, 683 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{34}NO_3Si$ $[M+H]^+$: 328.2302; found: 328.2306.

Diastereomer **215b**: $[a]_D^{25}$ –1.77 (*c* 0.43, $CHCl_3$); R_f = 0.30 (1:1 EtOAc:hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 6.40 (dd, J = 5.8, 3.0 Hz, 1H), 5.92 (s, br, 1H), 4.54 (q, J = 6.5 Hz, 1H), 3.78 – 3.74 (m, 1H), 3.74 – 3.69 (m, 1H), 3.60 (t, J = 8.8 Hz, 1H), 2.31 (dt, J = 17.5, 5.5 Hz, 1H), 2.22 – 2.15 (m, 1H), 1.40 (d, J = 6.4 Hz, 3H), 1.13 – 1.04 (m, 21H);

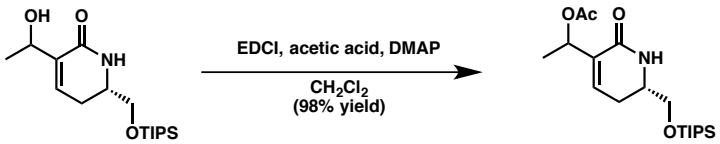
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 137.1, 133.2, 67.7, 66.0, 52.2, 25.8, 21.7, 18.1, 12.0; IR (Neat Film NaCl) 3294, 2943, 2866, 1678, 1627, 1463, 1115, 882 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{34}NO_3Si$ $[M+H]^+$: 328.2302; found: 328.2303.



215a ***199a***

To a solution of EDCI (960 mg, 6.18 mmol, 10.0 equiv) and DMAP (38.0 mg, 0.309 mmol, 0.50 equiv) in CH_2Cl_2 (6.18 mL) was added acetic acid (0.354 mL, 6.18 mmol, 10.0 equiv). The solution was stirred for 5 min at 0 °C and then lactam **215a** (202 mg, 0.618 mmol, 1.00 equiv) in CH_2Cl_2 (0.5 mL) was added. The reaction mixture was stirred 12 h at 23 °C and then quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3 x 4.50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography with mixtures of EtOAc and hexanes to afford acetate **199a** (187 mg, 82% yield).

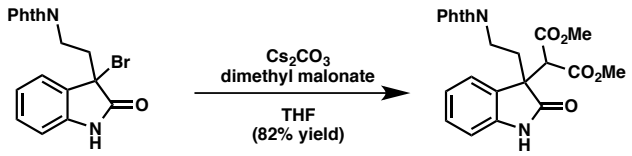
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.48 (ddd, *J* = 5.4, 3.3, 1.3 Hz, 1H), 6.06 (s, br, 1H), 5.78 (q, *J* = 6.6 Hz, 1H), 3.76 – 3.68 (m, 2H), 3.65 – 3.58 (m, 1H), 2.34 (dt, *J* = 17.5, 5.4 Hz, 1H), 2.26 – 2.15 (m, 1H), 2.07 (s, 3H), 1.40 (d, *J* = 6.5 Hz, 3H), 1.15 – 0.99 (m, 21H).



215b ***199b***

To a solution of EDCI (1.41 g, 9.07 mmol, 10.0 equiv) and DMAP (55.4 mg, 0.454 mmol, 0.50 equiv) in CH_2Cl_2 (9.07 mL) was added acetic acid (0.520 mL, 9.07 mmol, 10.0 equiv). The solution was stirred for 5 min at 0 °C and then lactam **215b** (297 mg, 0.907 mmol, 1.00 equiv) in CH_2Cl_2 (1.0 mL) was added. The reaction mixture was stirred 12 h at 23 °C and then quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3 x 6.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography with mixtures of EtOAc and hexanes to afford acetate **199b** (328 mg, 98% yield).

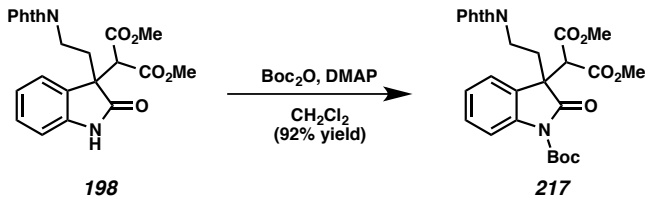
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52 (ddd, *J* = 5.6, 3.2, 1.2 Hz, 1H), 6.07 (s, br, 1H), 5.77 – 5.69 (m, 1H), 3.72 (qd, *J* = 4.5, 2.0 Hz, 2H), 3.65 – 3.56 (m, 1H), 2.41 – 2.27 (m, 1H), 2.25 – 2.17 (m, 1H), 2.06 (s, 3H), 1.41 (d, *J* = 6.4 Hz, 3H), 1.14 – 1.00 (m, 21H).



216 ***198***

To a solution of bromooxindole **216** (3.60 g, 9.34 mmol, 1.00 equiv) and dimethyl malonate (2.62 mL, 28.0 mmol, 3.00 equiv) in THF (47.0 mL) was added Cs_2CO_3 (9.13 g, 28.0 mmol, 3.00 equiv). The reaction mixture was stirred for 12 h at 23 °C. After the reaction was done, water was added. The aqueous phase was extracted with EtOAc (3 x 15.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography with

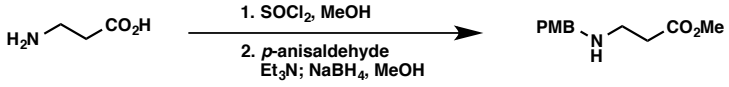
mixtures of EtOAc and hexanes to afford oxindole **198** (3.34 g, 82% yield). Data for the compound matches reported data.[3]



198 ***217***

To a solution of oxindole **198** (4.08 g, 9.34 mmol, 1.00 equiv) in CH_2Cl_2 (47.0 mL) were added DMAP (0.114 g, 0.934 mmol, 0.10 equiv) and Boc_2O (3.06 g, 14.0 mmol, 1.50 equiv). The reaction mixture was stirred for 12 h at 23 °C. Then, the reaction was quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3 x 15.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography with mixtures of EtOAc and hexanes to afford carbamate **217** (4.61 g, 92% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 – 7.76 (m, 1H), 7.74 – 7.68 (m, 2H), 7.68 – 7.62 (m, 2H), 7.61 – 7.56 (m, 1H), 7.18 – 7.11 (m, 1H), 7.01 (td, *J* = 7.6, 1.2 Hz, 1H), 4.21 (s, 1H), 3.80 (s, 3H), 3.53 (t, *J* = 7.1 Hz, 2H), 3.49 (s, 3H), 2.51 (dt, *J* = 14.8, 7.5 Hz, 1H), 2.40 (dt, *J* = 13.8, 6.8 Hz, 1H), 1.65 (s, 9H).



222 ***SI-A11-1***

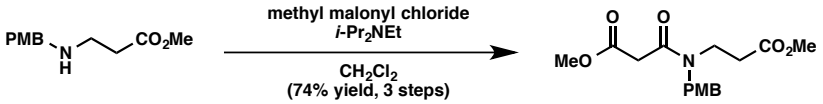
β-Alanine (**222**) (5.00 g, 56.1 mmol, 1.00 equiv) was added to MeOH (94.0 mL) and cooled to 0 °C before dropwise addition of $SOCl_2$ (8.19 mL, 0.112 mol, 2.00 equiv).

[3] Krishnan, S.; Stoltz, B. M. *Tetrahedron* **2007**, *48*, 7571–7573.

Then, the reaction was stirred for 2 h at 90 °C. The solution was concentrated under reduced pressure and treated with ether. The resulting crystals were removed by filtration to afford the ester, which was used without further purification.

To a solution of the resultant ester-HCl salt (2.00 g, 14.4 mmol, 1.00 equiv) and Et_3N (4.02 mL, 28.9 mmol, 2.00 equiv) in MeOH (40.0 mL) was added anisaldehyde (1.83 mL, 15.1 mmol, 1.05 equiv) and the reaction mixture was stirred for 1.5 h. Then, $NaBH_4$ (1.09 g, 28.8 mmol, 2.00 equiv) was added in portions in 1 h at 0 °C. The reaction was stirred at 23 °C for 8 h and then quenched with water. The aqueous phase was extracted with EtOAc (3 x 25.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford amine **SI-A11-1**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.20 (m, 2H), 6.89 – 6.82 (m, 2H), 3.79 (s, 3H), 3.74 (s, 2H), 3.68 (s, 3H), 2.89 (t, *J* = 6.5 Hz, 2H), 2.54 (t, *J* = 6.5 Hz, 2H), 1.87 (s, br, 1H).

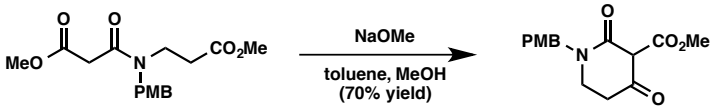


SI-A11-1 ***223***

To a solution of amine **SI-A11-1** (2.64 g, 11.8 mmol, 1.00 equiv) and *i*-Pr_2NEt (4.22 mL, 24.2 mmol, 2.05 equiv) in CH_2Cl_2 (59.0 mL) was added methyl malonyl chloride (2.02 mL, 18.9 mmol, 1.60 equiv) at °C. The solution was warmed to 23 °C and stirred for 1 h. Then, the reaction was quenched with sat. aq NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (3 x 25.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel

chromatography with mixtures of EtOAc and hexanes to afford amide **223** (2.82 g, 74% yield, 3 steps).

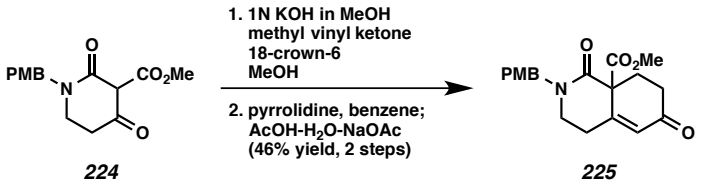
(Due to the distinct presence of rotameric isomers, the ^{1}H NMR contained extra peaks.) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.6 Hz, 1H), 7.14 – 7.06 (m, 1H), 6.93 – 6.87 (m, 1H), 6.87 – 6.82 (m, 1H), 4.57 (s, 1H), 4.52 (s, 1H), 3.80 (s, 2H), 3.79 (s, 1H), 3.76 (s, 1H), 3.72 (s, 2H), 3.68 – 3.58 (m, 5H), 3.52 (t, *J* = 7.1 Hz, 1H), 3.47 (s, 1H), 2.63 (t, *J* = 6.9 Hz, 1H), 2.54 (t, *J* = 7.1 Hz, 1H).



223 ***224***

To a solution of NaOMe (95%; 0.87 g, 15.2 mmol, 1.10 equiv) in toluene (69.0 mL) and MeOH (11.0 mL) was added amide **223** (2.81 g, 8.69 mmol, 1.00 equiv) in toluene (1.00 mL) dropwise. The solution was stirred at 90 °C for 6 h. The solution was cooled to 23 °C and water was added. The aqueous phase was extracted with EtOAc (3 x 25.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography with mixtures of EtOAc and hexanes to afford lactam **224** (1.78 g, 70% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 13.91 (s, 1H), 7.24 – 7.17 (m, 2H), 6.87 – 6.81 (m, 2H), 4.57 (s, 2H), 3.93 (s, 3H), 3.79 (s, 3H), 3.31 (t, *J* = 6.8 Hz, 2H), 2.57 (t, *J* = 6.8 Hz, 2H).



224 ***225***

To a stirred solution of lactam **224** (600 mg, 2.06 mmol, 1.00 equiv) in MeOH (1.60 mL) at 23 °C were added 1N KOH solution in MeOH (0.21 mL, 0.206 mmol, 0.10 equiv) and 18-crown-6 (54.0 mg, 0.206 mmol, 0.10 equiv) under N_2. After stirring for 10 min, methyl vinyl ketone (0.55 mL, 6.80 mmol, 3.30 equiv) was added dropwise at 23 °C and stirred for 22 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was treated with sat. aq KCl solution. The aqueous phase was extracted with EtOAc (3 x 3.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford the ketone, which was used without further purification.

To a stirred solution of the resultant ketone (2.06 mmol, 1.00 equiv) in benzene (20.6 mL) was added pyrrolidine (0.43 mL, 5.15 mmol, 2.50 equiv) and the mixture was stirred at 90 °C for 6 h using Dean-Stark apparatus. The solution was cooled to 23 °C. The reaction mixture was treated with a mixture of AcOH/H_2O/NaOAc (2/2/1) (7.92 mL) and stirred at 100 °C for 3 h. The solution was cooled to 23 °C and treated with H_2O. The aqueous phase was extracted with EtOAc (3 x 25.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography with mixtures of EtOAc and hexanes to afford bicycle **225** (325 mg, 46% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 – 7.08 (m, 2H), 6.94 – 6.77 (m, 2H), 4.73 (d, *J* = 14.5 Hz, 1H), 4.41 (d, *J* = 14.5 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.38 (ddd, *J* = 12.1, 6.3, 3.9 Hz, 1H), 3.24 (ddd, *J* = 12.2, 9.9, 4.6 Hz, 1H), 3.04 – 2.96 (m, 1H), 2.90 – 2.77 (m, 1H), 2.59 – 2.43 (m, 2H), 2.18 – 2.10 (m, 1H), 2.08 – 2.04 (m, 1H).



225 ***226***

To a solution bicycle **225** (28.0 mg, 0.0815 mmol, 1.00 equiv) in *t*-BuOH (2.04 mL) were added AcOH (0.2 mL) and SeO_2 (18.1 mg, 16.3 mmol, 2.00 equiv). The reaction was stirred for 12 h at 100 °C. Solids were removed via a filtration through a celite plug and the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography, using mixture of hexanes and ethyl acetate as eluent to furnish dienone **226** (11.1 mg, 40% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 10.1, 0.5 Hz, 1H), 7.24 – 7.19 (m, 2H), 6.90 – 6.85 (m, 2H), 6.45 (ddd, *J* = 10.1, 1.7, 0.6 Hz, 1H), 6.26 (td, *J* = 1.7, 0.7 Hz, 1H), 4.89 (d, *J* = 14.6 Hz, 1H), 4.28 (d, *J* = 14.6 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.42 (ddd, *J* = 12.1, 7.0, 3.6 Hz, 1H), 3.26 (ddd, *J* = 12.2, 9.5, 5.6 Hz, 1H), 2.96 (dddd, *J* = 14.6, 9.3, 7.0, 1.9 Hz, 1H), 2.63 (ddd, *J* = 14.5, 5.6, 3.6 Hz, 1H).

A11.4. References and Notes

(1) Zhu, G.-Y.; Yao, X.-J.; Liu, L.; Bai, L.-P.; Jiang, Z.-H. *Org. Lett.* **2014**, *16*, 1080–1083.

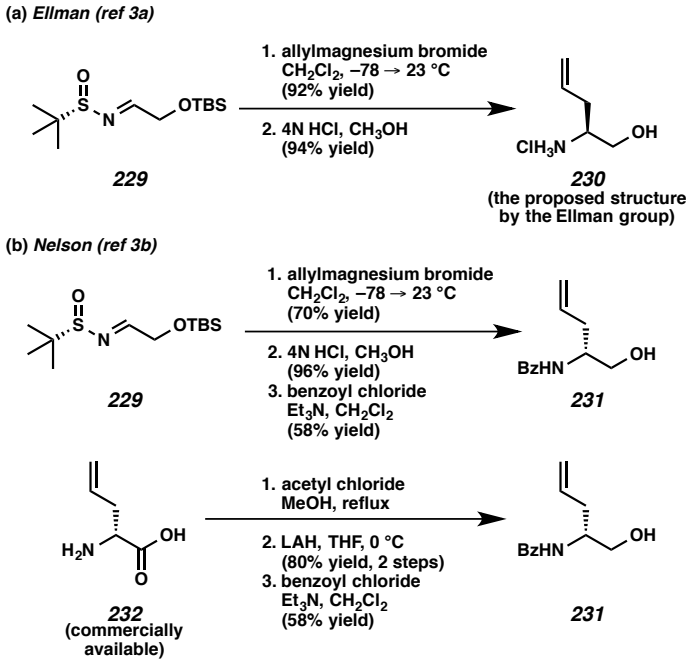
(2) (a) Shang, J. H.; Cai, X. H.; Feng, T.; Zhao, Y. L.; Wang, J. K.; Zhang, L. Y.; Yan, M.; Luo, X. D. *J. Ethnopharmacol.* **2010**, *129*, 174–181. (b) Shang, J.; H.; Cai, X. H.; Zhao, Y. L.; Feng, T.; Luo, X. D. *J. Ethnopharmacol.* **2010**, *129*, 293–298. (c) Baliga, M. S. *Integr. Cancer Ther.* **2010**, *9*, 261–269. (d) Lee, S. J.; Cho, S. A.; An, S. S.; Na, Y. J.;

Park, N. H.; Kim, H. S.; Lee, C. W.; Kim, H. K.; Kim, E. K.; Jang, Y. P.; Kim, J. W. *Evid. Based Complement Alternat. Med.* **2012**, *2012*, 190370.

(3) Horning, B. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 6442–6445.

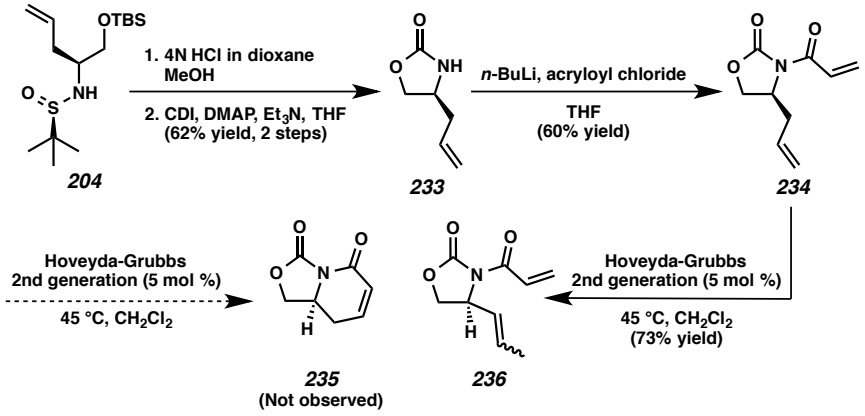
(4) (a) Rech, J. C.; Yato, M.; Duckett, D.; Ember, B.; LoGrasso, P. V.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 490–491. (b) Maurya, S. K.; Dow, M.; Warriner, S.; Nelson, A. *Beilstein J. Org. Chem.* **2013**, *9*, 775–785. (c) Koriyama, Y.; Nozawa, A.; Hayakawa, R.; Shimizu, M. *Tetrahedron* **2002**, *58*, 9621–9628.

(5) Although the Ellman group reported that allylmagnesium bromide was added from the *Si*-face of (*S*)-*tert*-butylsulfinyl imine **229** to deliver **230** (ref 3a), the opposite configuration was later confirmed by the Nelson group (ref 3b). The Nelson group prepared (*R*)-benzamide **231** from both the commercially available (*R*)-2-amino-4-pentenoic acid (**232**) and using Ellman's method with (*S*)-*tert*-butanesulfinamide. Then they discovered that the retention time of both benzamides (**231**) was identical on chiral HPLC.



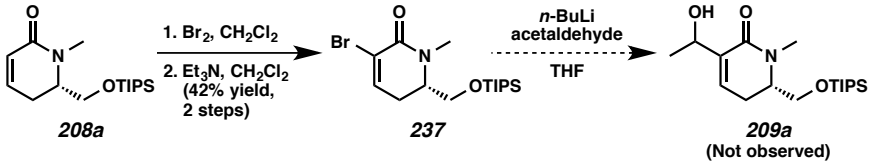
(6) (a) Donohoe, T. J.; Fishlock, L. P.; Procopiou, P. A. *Org. Lett.* **2008**, *10*, 285–288. (b) Hoffmann, T.; Lanig, H.; Waibel, R.; Gmeiner, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 3361–3364. (c) Huwe, C. M.; Kiehl, O. C.; Blechert, S. Synlett 1996, 65–66.

(7) Acidic removal of the silyl and *tert*-butanesulfinyl groups of **204** followed by carbamate formation with CDI afforded **233**. Although acylation of **233** generated metathesis precursor **234**, attempted ring-closing metathesis with Hoveyda-Grubbs 2nd generation catalyst to form bicycle **235** led only to double bond isomerization, generating **236**.



(8) (a) Latorre, A.; Sáez, J. A.; Rodríguez, S.; González, F. V. *Tetrahedron* **2014**, *70*, 97–102. (b) Rao, V. R.; Muthenna, P.; Shankaraiah, G.; Akileshwari, C.; Babu, K. H.; Suresh, G.; Babu, K. S.; Kumar, R. S. C.; Prasad, K. R.; Yadav, P. A.; Petrash, J. M.; Reddy, G. B.; Rao, J. M. *Eur. J. Med. Chem.* **2012**, *57*, 344–361. (c) Lee, K. C.; Loh, T. P. *Chem. Commun.* **2006**, *40*, 4209–4211.

(9) Although a-bromination of lactam **208a** produced bromide **237**, attempts to prepare the desired alcohol **209a** from bromide **237** were unsuccessful.



(10) The same result of the ring-closing metathesis of amide **213** was obtained with Hoveyda-Grubbs 2nd generation catalyst.

(11) (a) Krishnan, S.; Stoltz, B. M. *Tetrahedron Lett.* **2007**, *48*, 7571–7573. (b) Ma, S.; Han, X.; Krishnan, S.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8037–8041.

(12) Schultz, A. G.; Lucci, R. D.; Napier, J. J.; Kinoshita, H.; Ravichandran, R.; Shannon, P.; Yee, Y. K. *J. Org. Chem.* **1985**, *50*, 217–231.

(13) Pereira, J.; Barlier, M.; Guillou, C. *Org. Lett.* **2007**, *9*, 3101–3103.

APPENDIX 12

Spectra Relevant to Appendix 11:

Synthetic Studies Toward Alistonitrine A

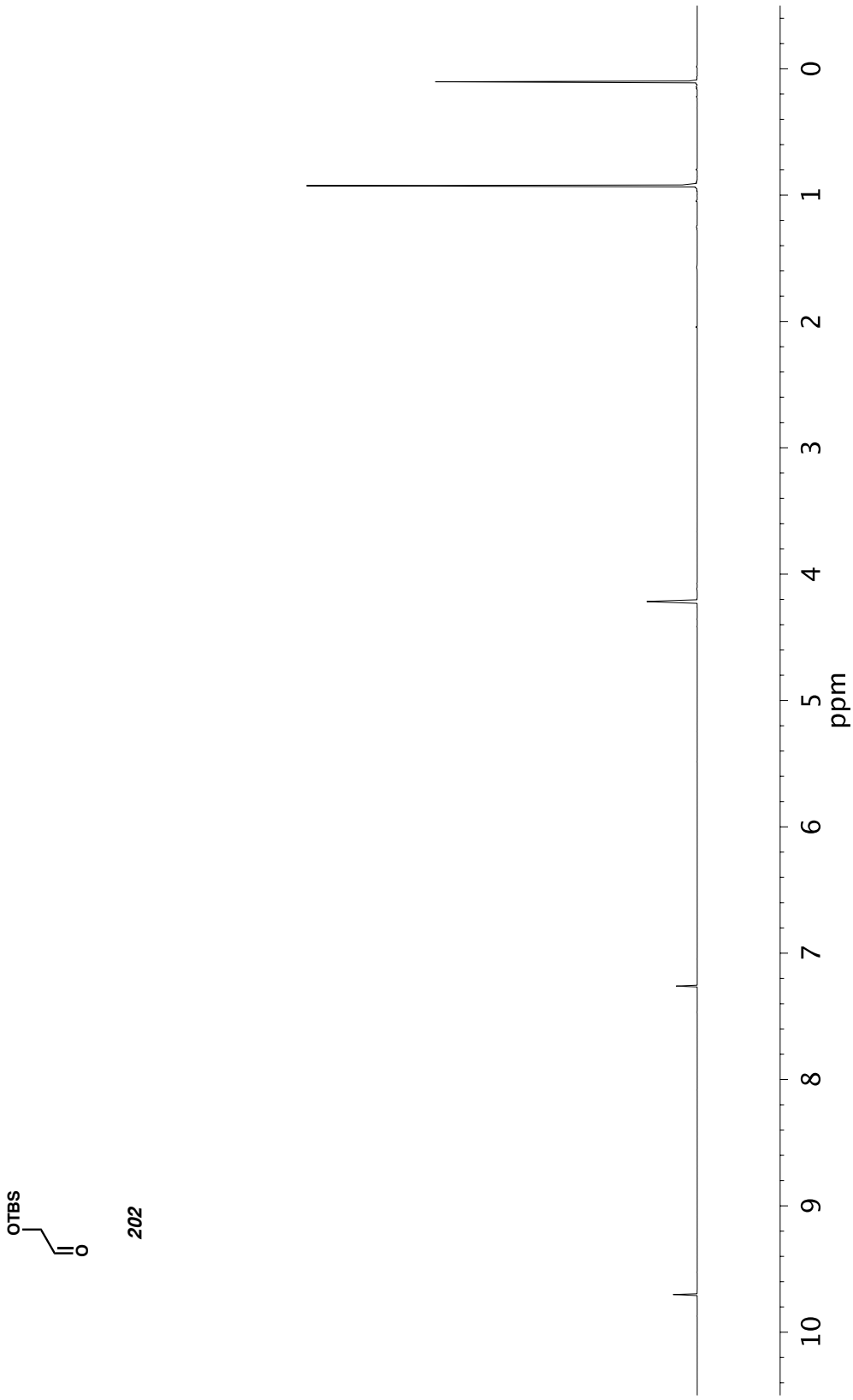


Figure A12.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **202**.

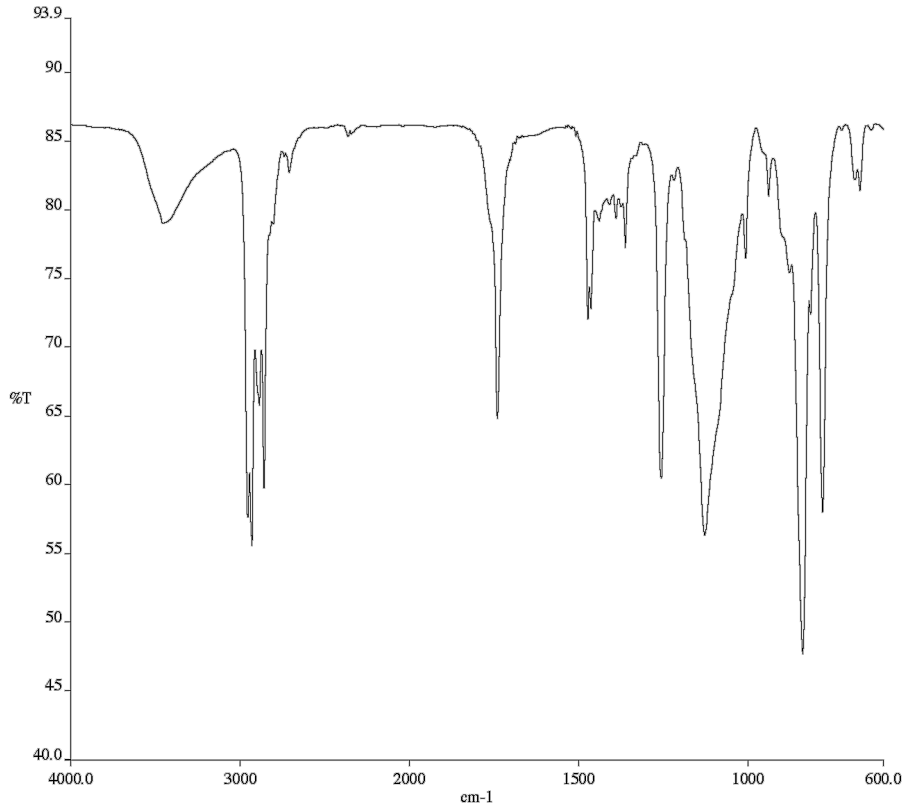


Figure A12.2. Infrared spectrum (Thin Film, NaCl) of compound **202**.

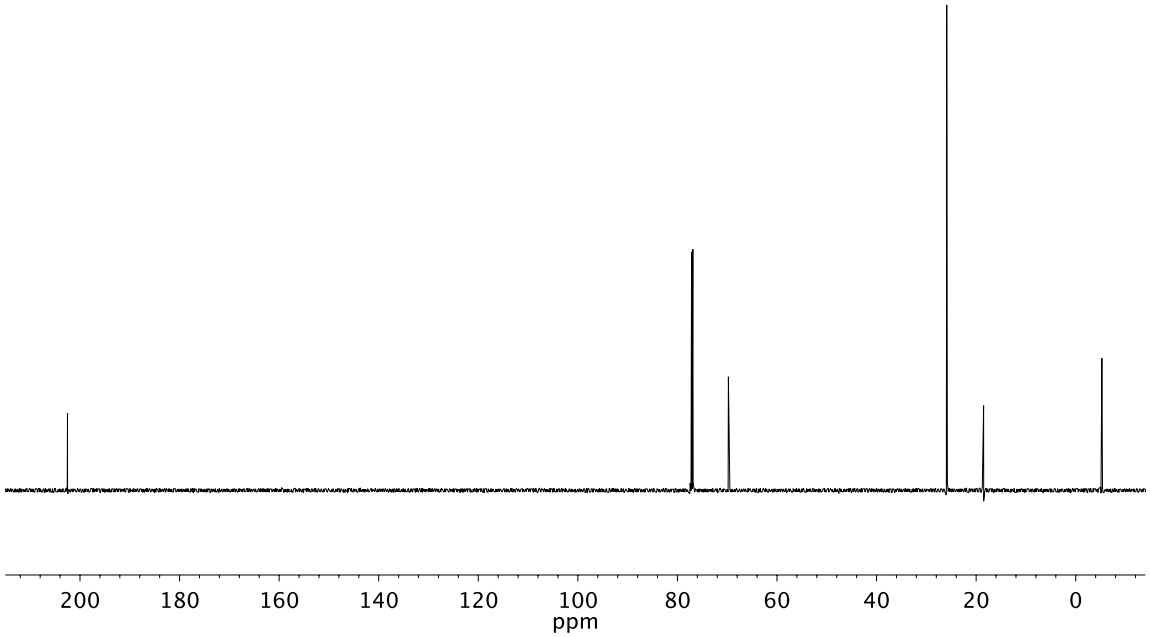


Figure A12.3. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **202**.

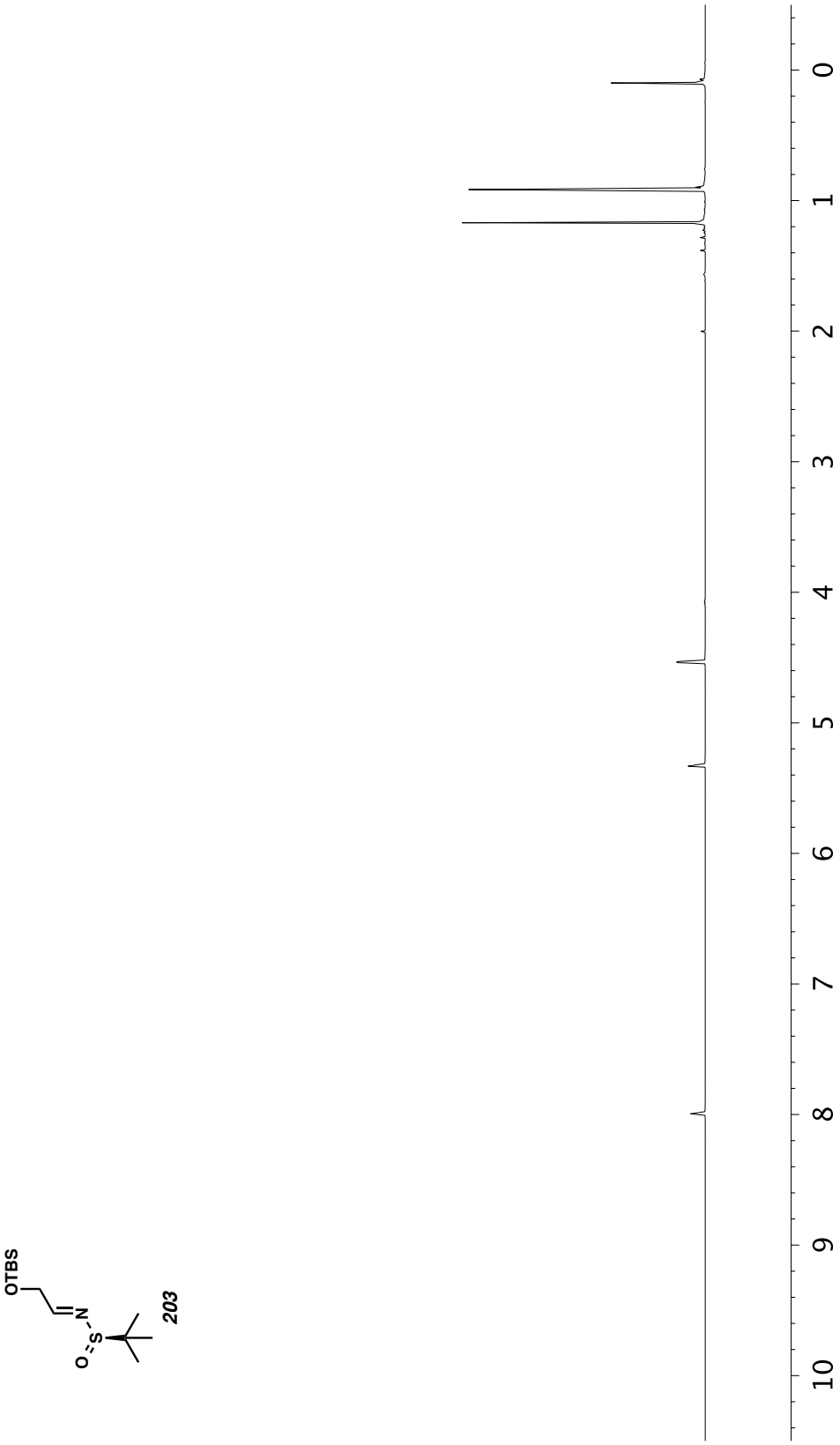


Figure A12.4. ^{1}H NMR (400 MHz, CD_2Cl_2) of compound **203**.

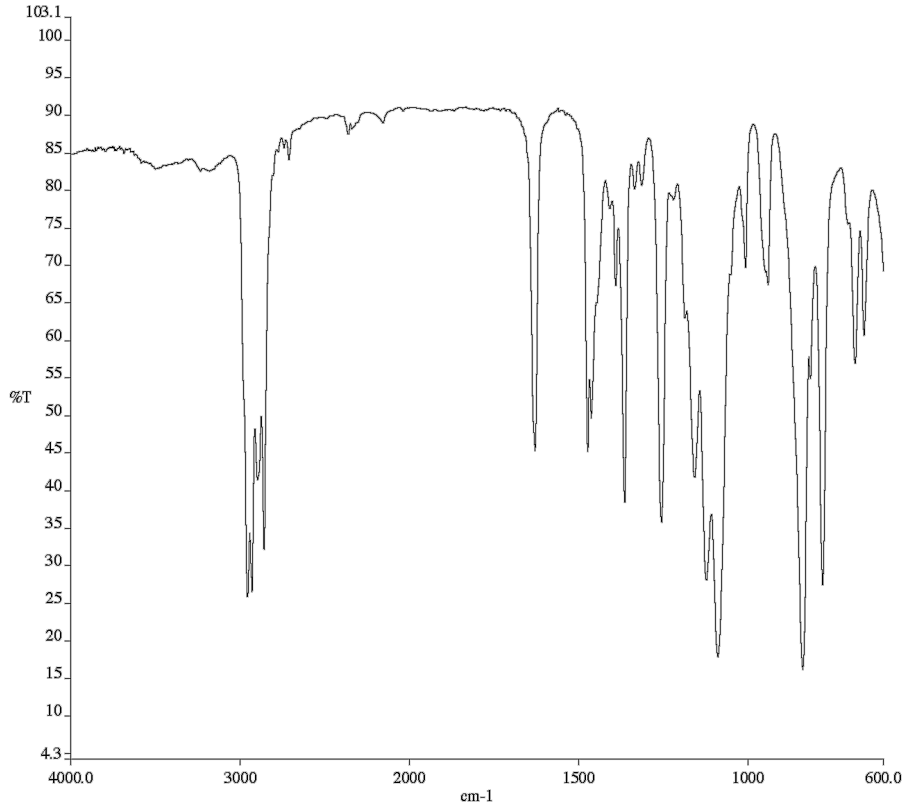


Figure A12.5. Infrared spectrum (Thin Film, NaCl) of compound **203**.

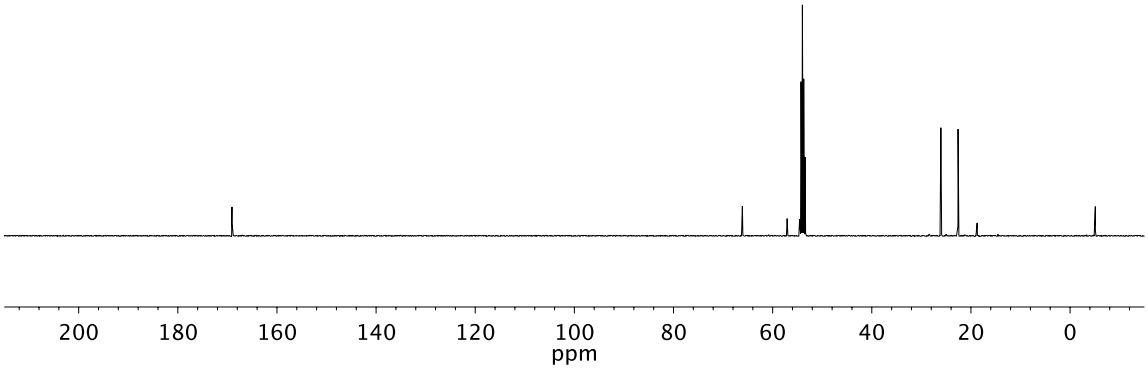


Figure A12.6. ^{13}C NMR (101 MHz, CD_2Cl_2) of compound **203**.

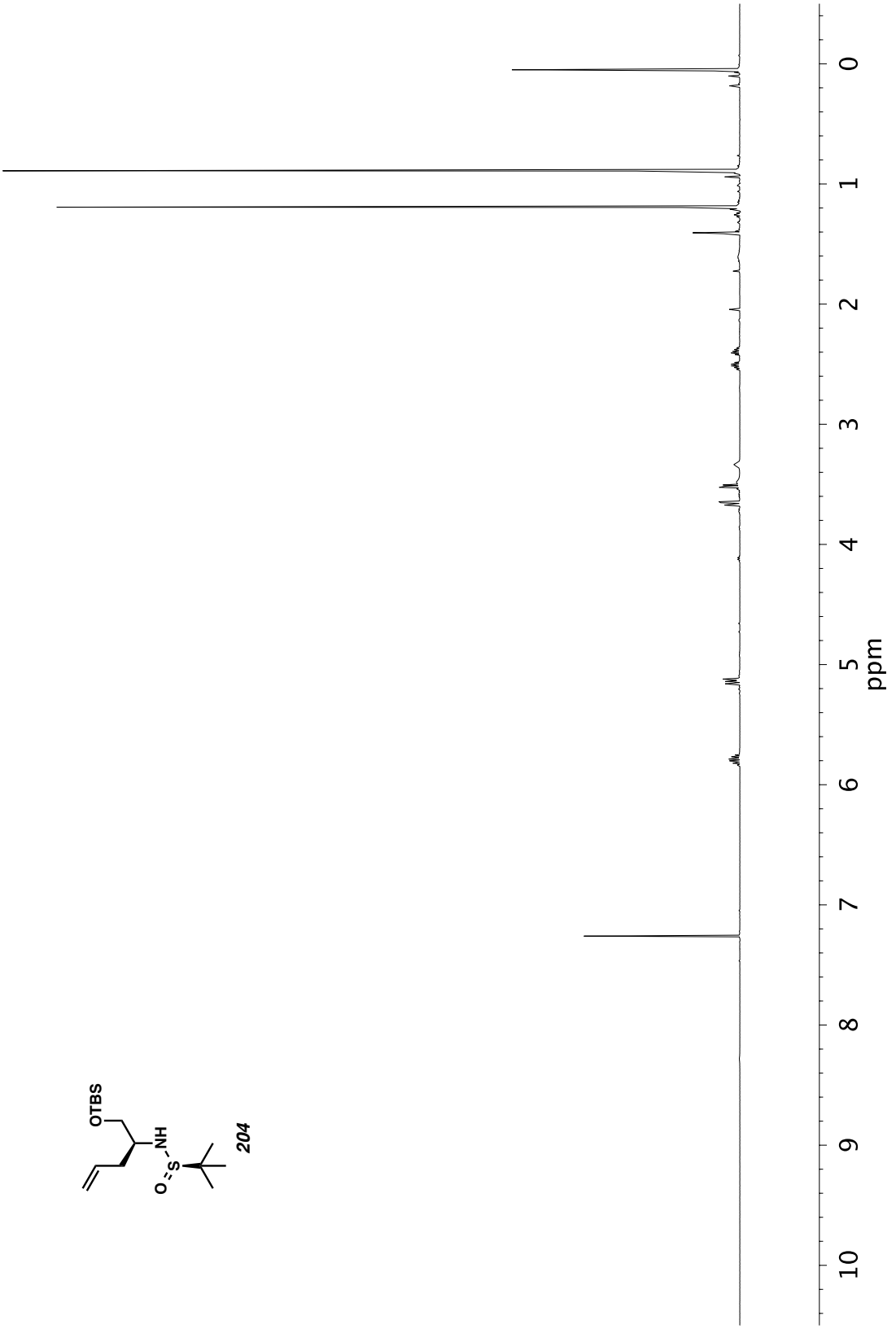


Figure A12.7. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **204**.

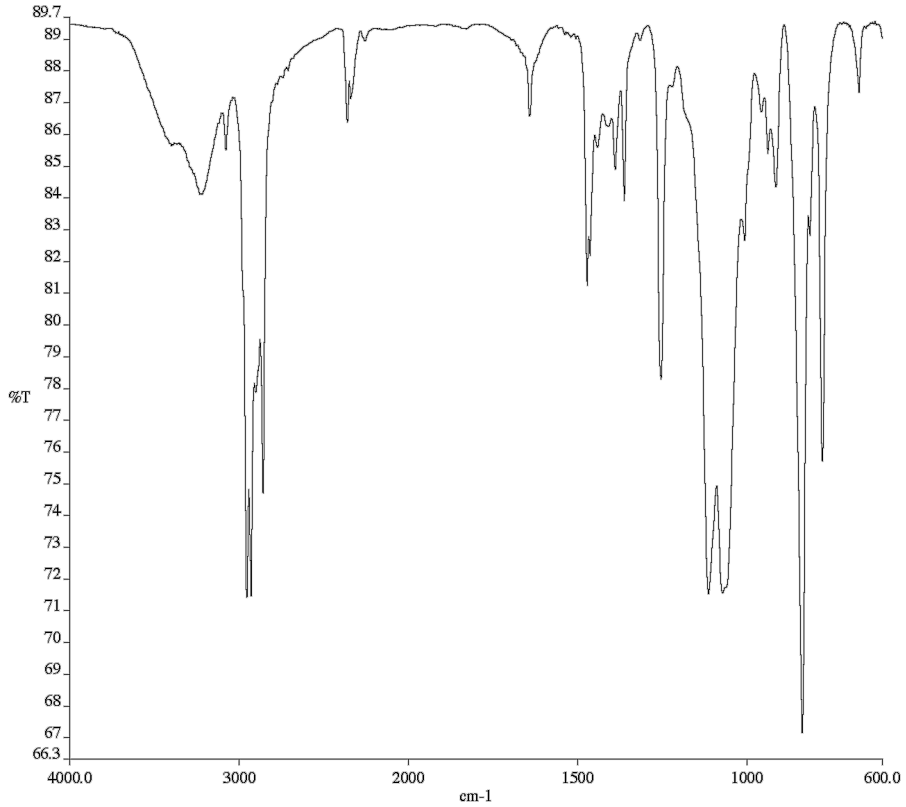


Figure A12.8. Infrared spectrum (Thin Film, NaCl) of compound **204**.

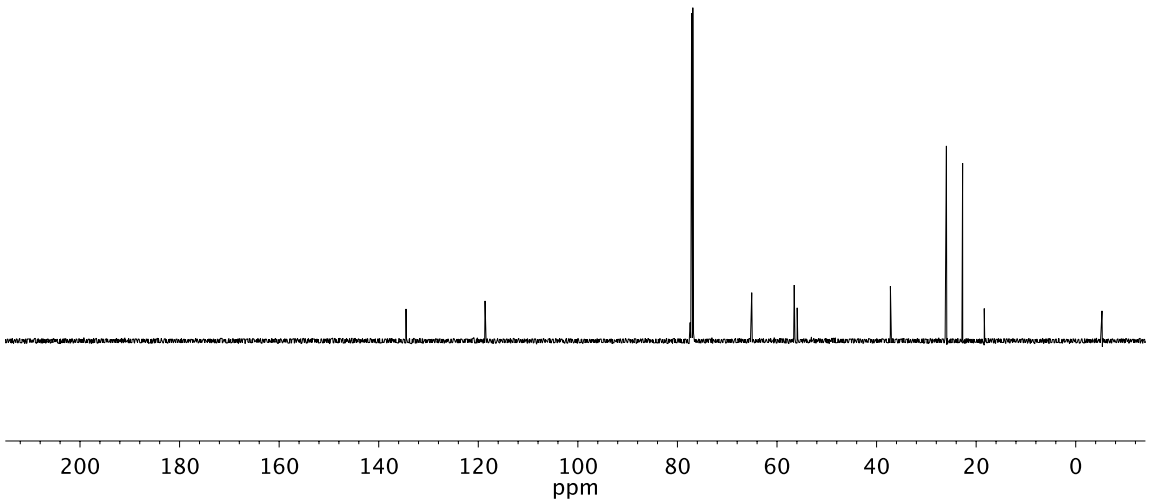


Figure A12.9. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **204**.

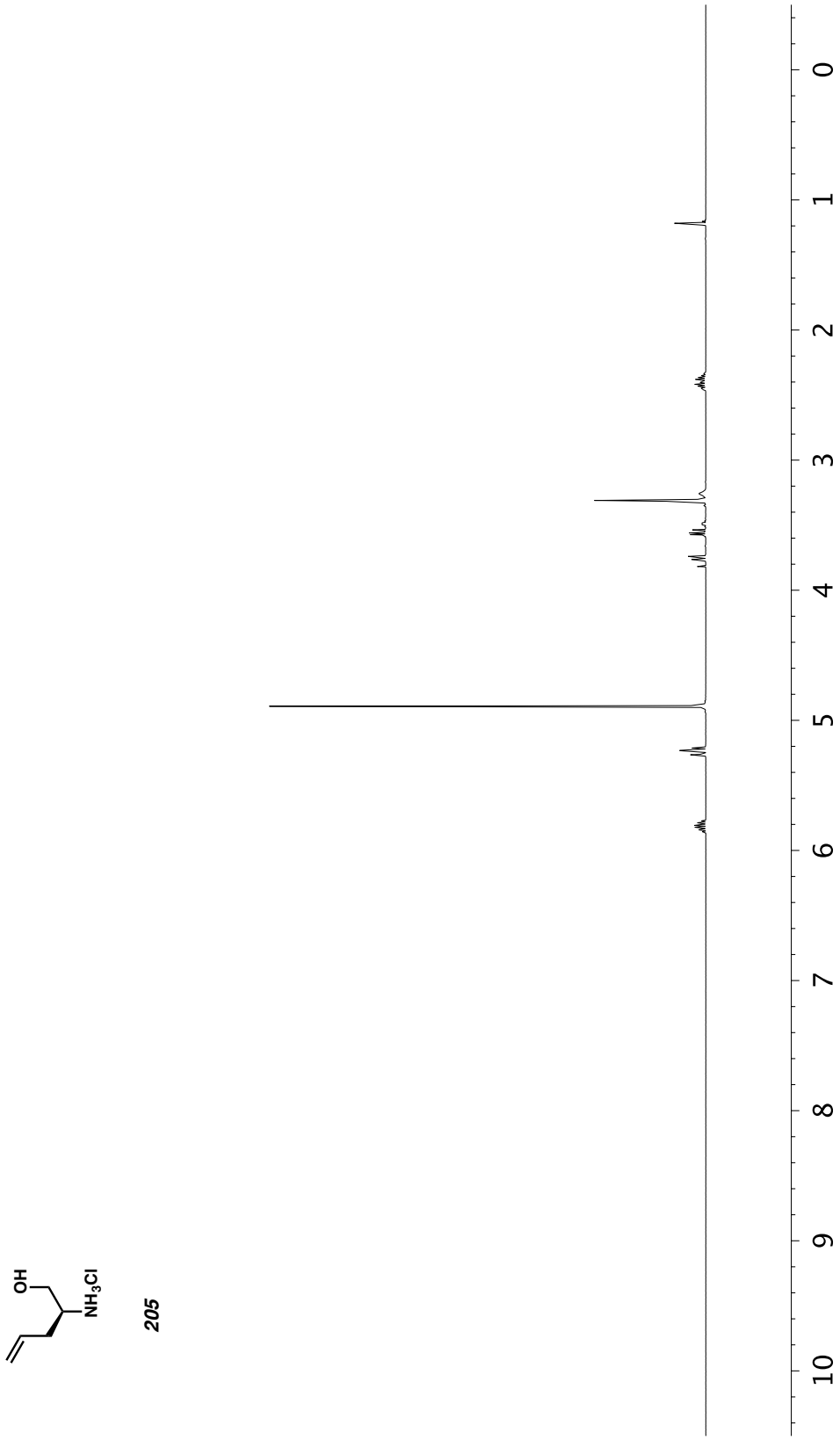


Figure A12.10. ^{1}H NMR (500 MHz, CD_3OD) of compound **205**.

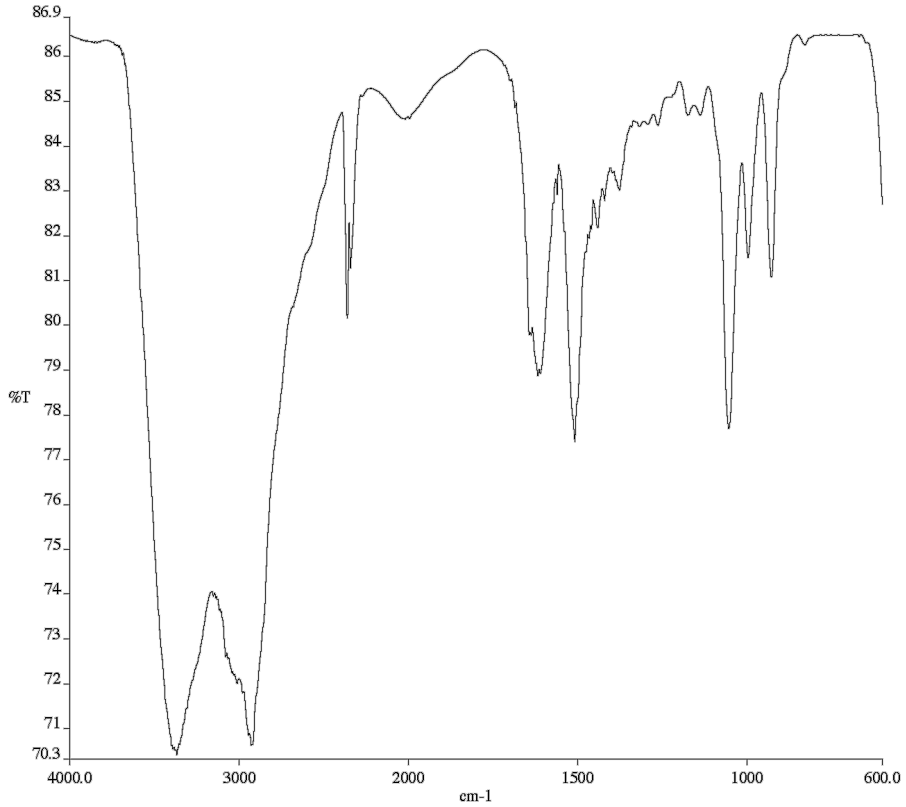


Figure A12.11. Infrared spectrum (Thin Film, NaCl) of compound **205**.

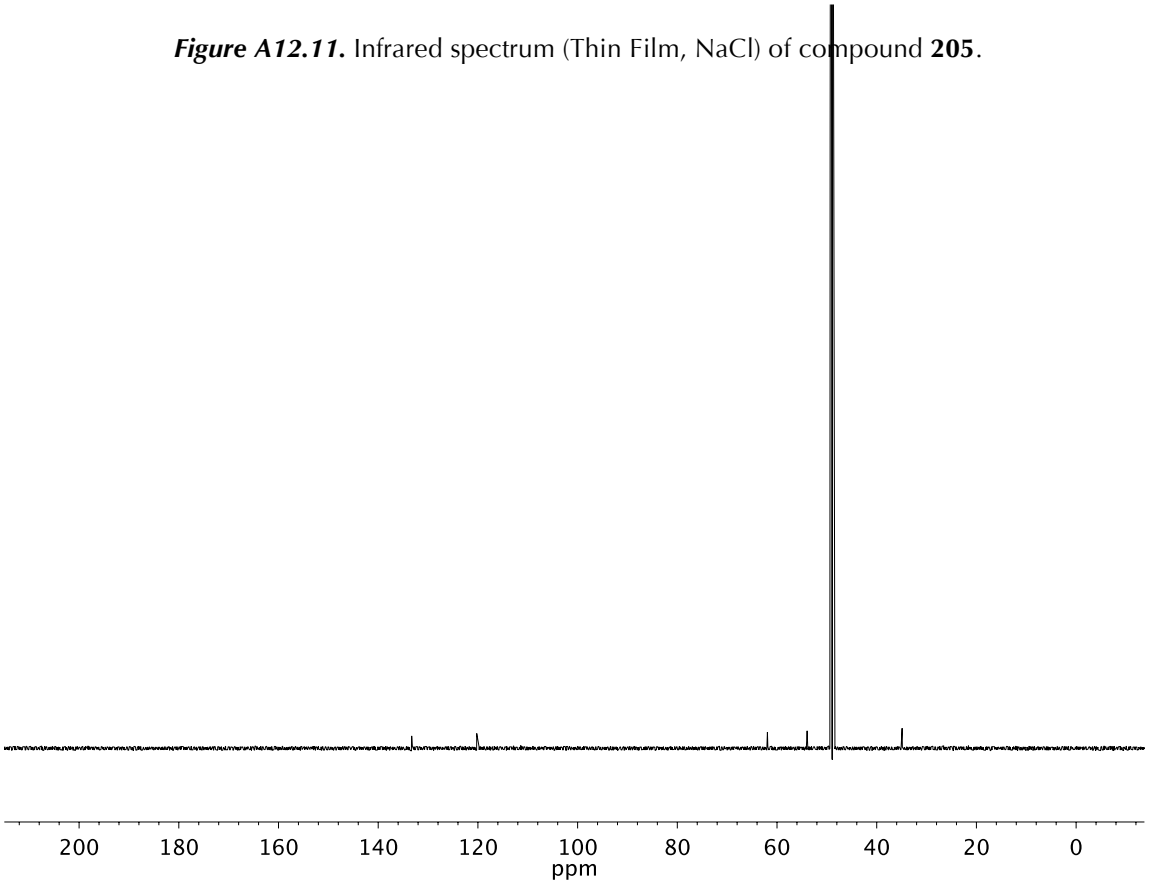


Figure A12.12. ^{13}C NMR (126 MHz, CD_3OD) of compound **205**.

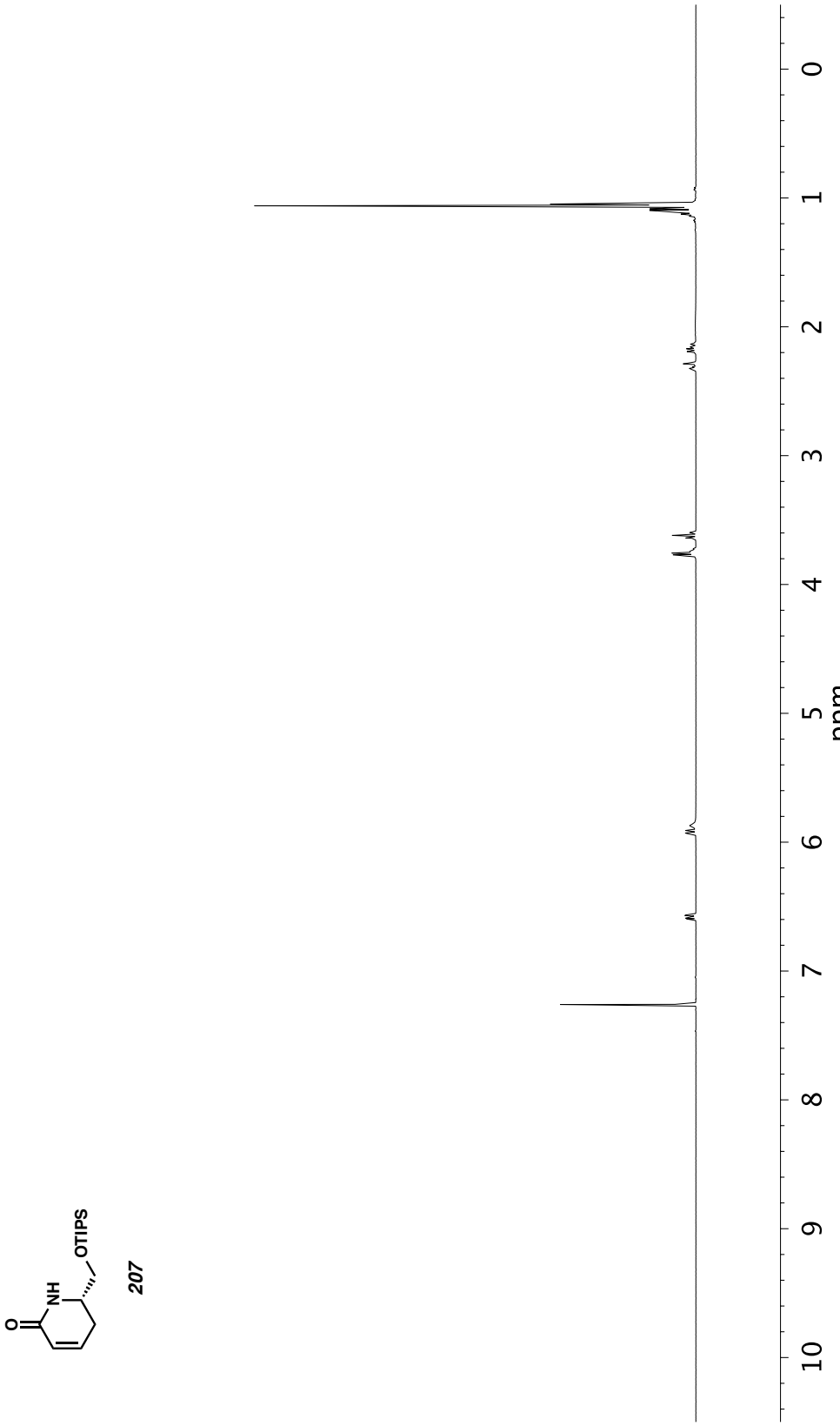


Figure A12.13. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **207**.

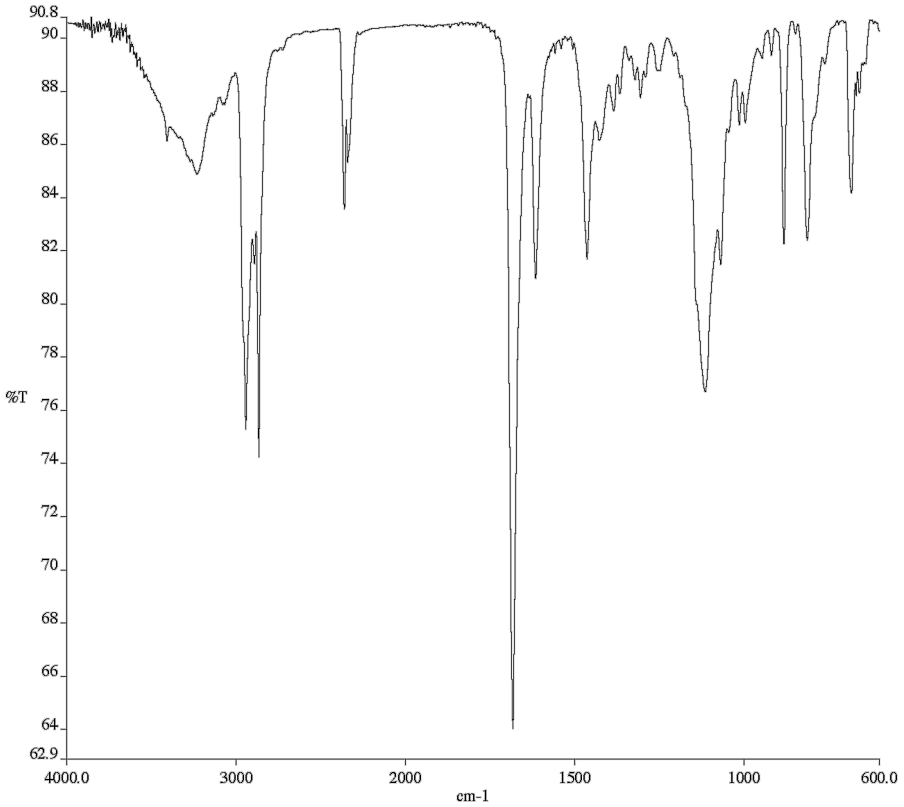


Figure A12.14. Infrared spectrum (Thin Film, NaCl) of compound **207**.

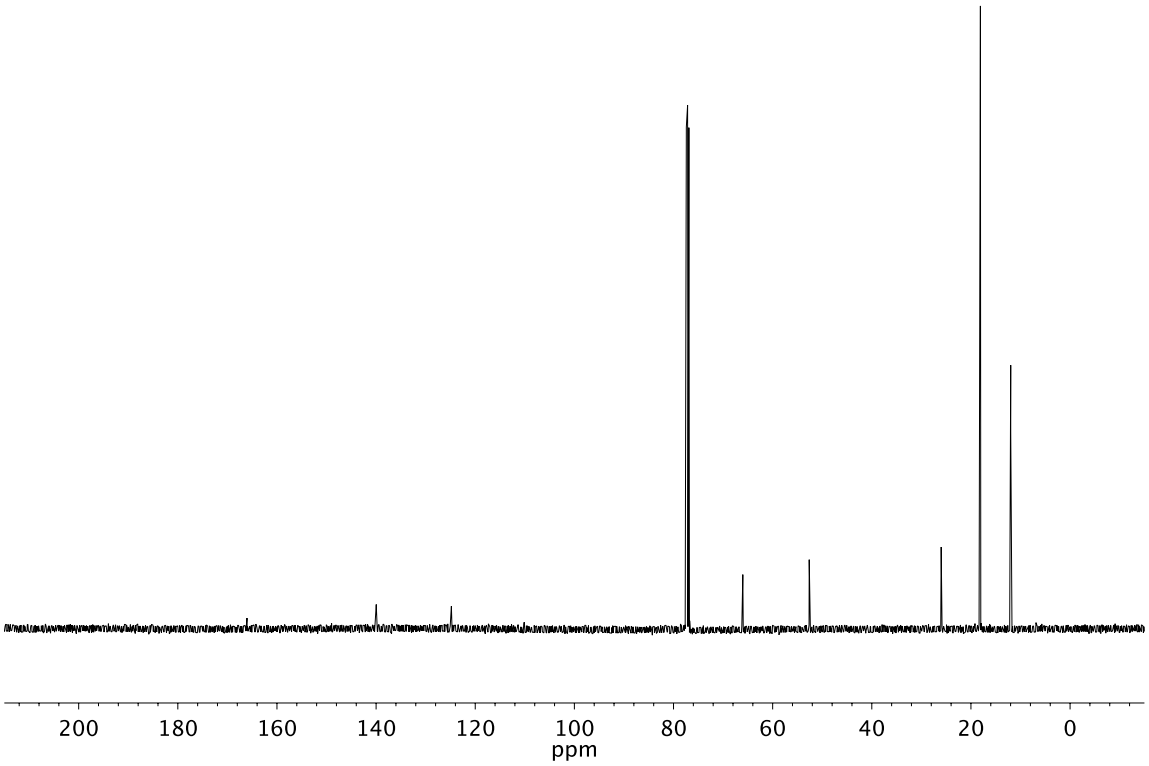


Figure A12.15. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **207**.

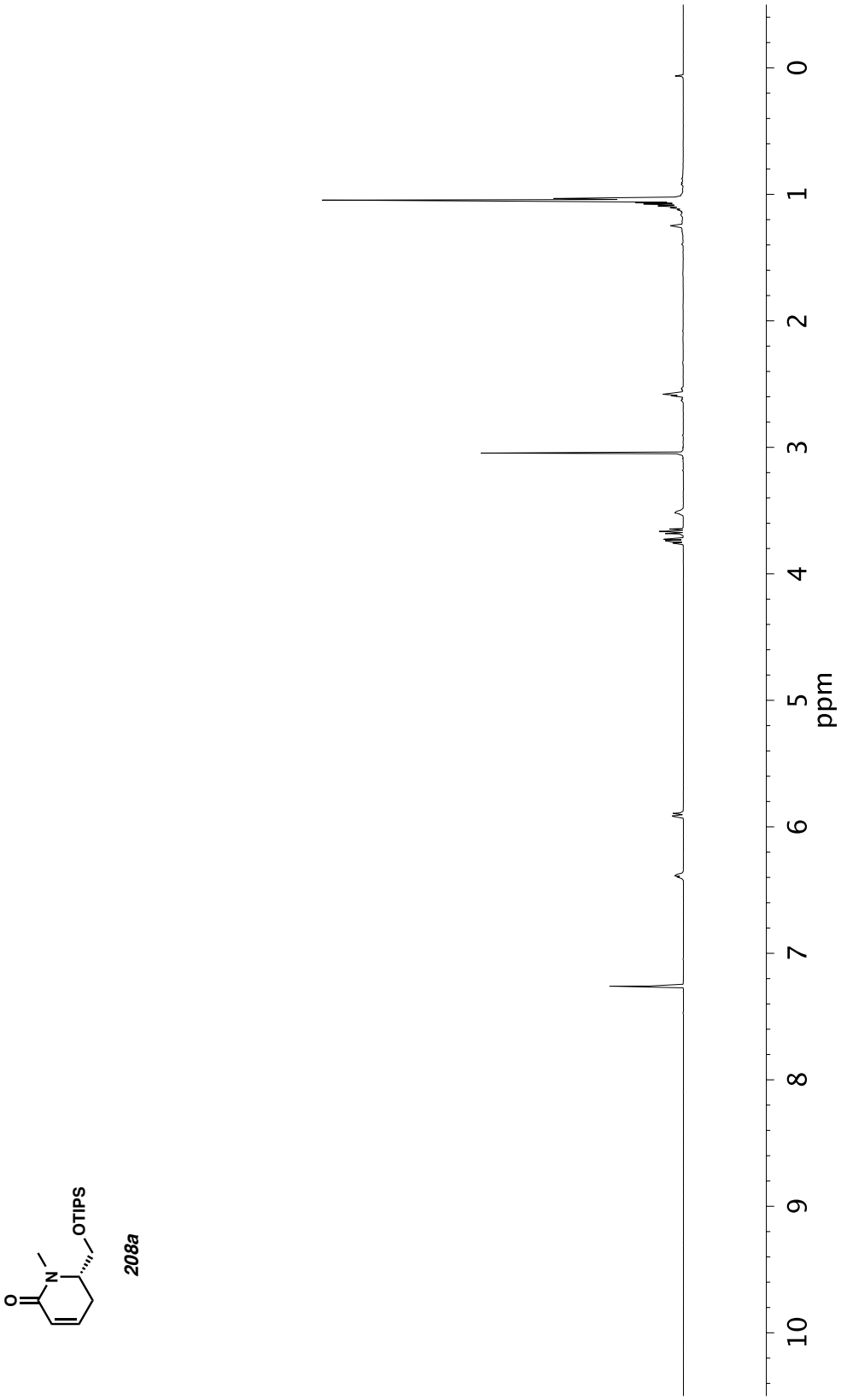


Figure A12.16. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **208a**.

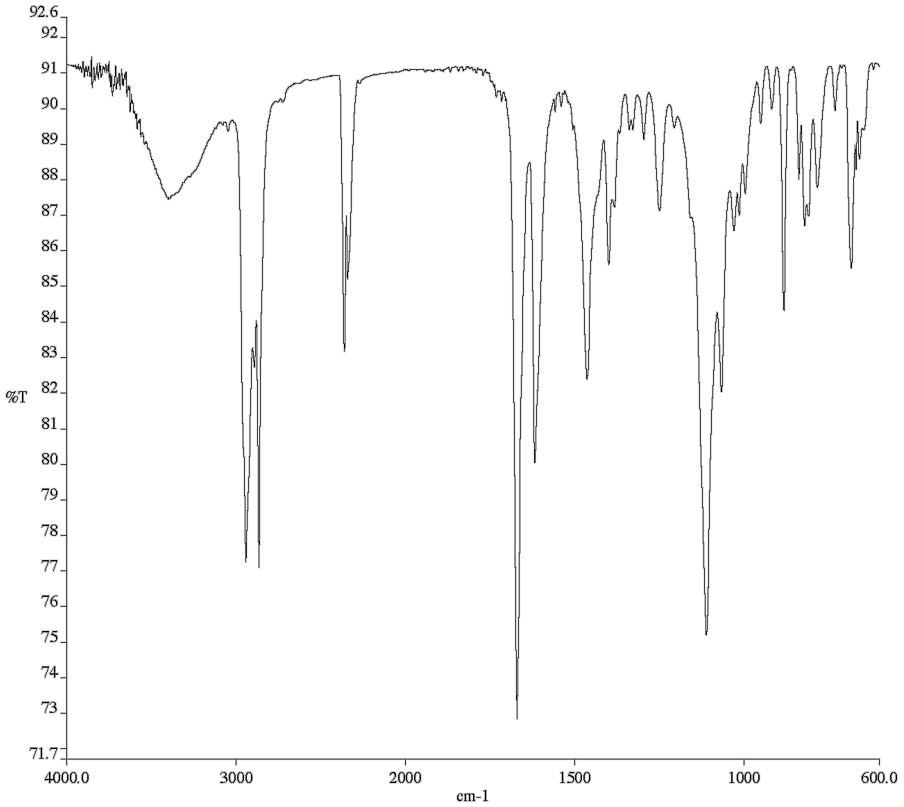


Figure A12.17. Infrared spectrum (Thin Film, NaCl) of compound **208a**.

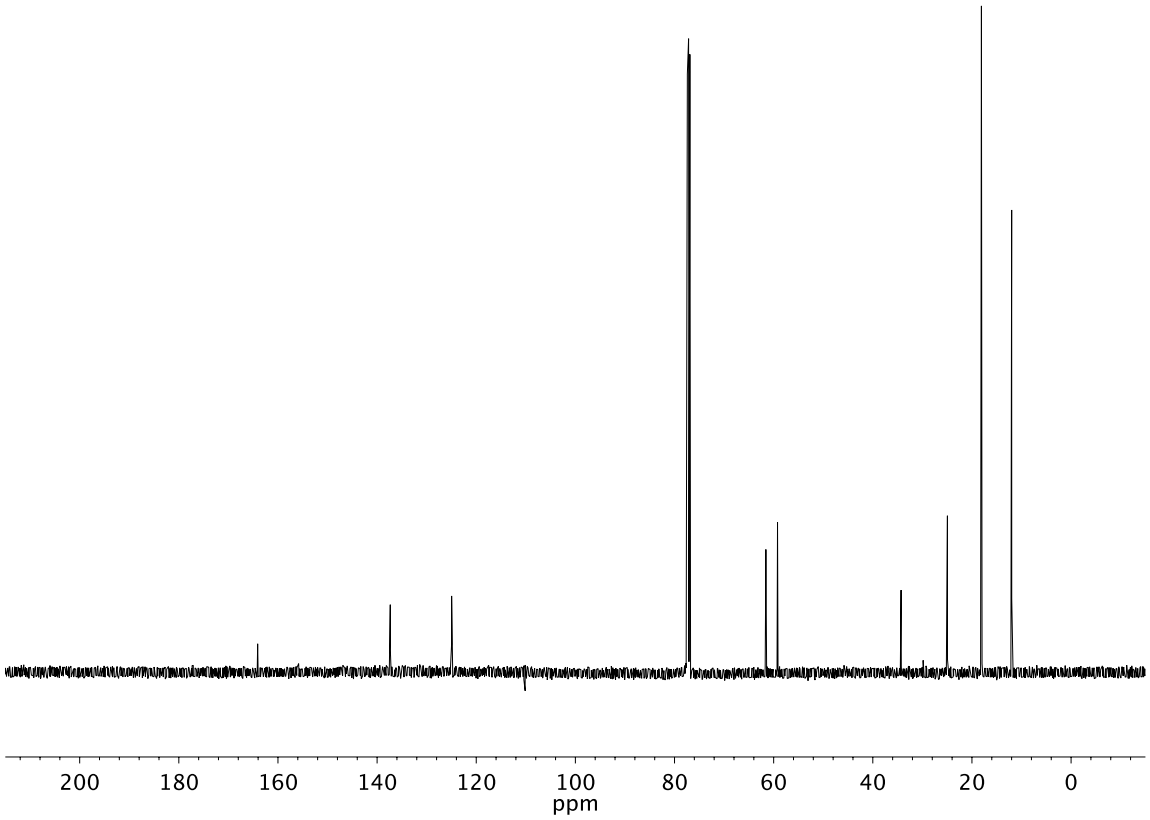


Figure A12.18. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **208a**.

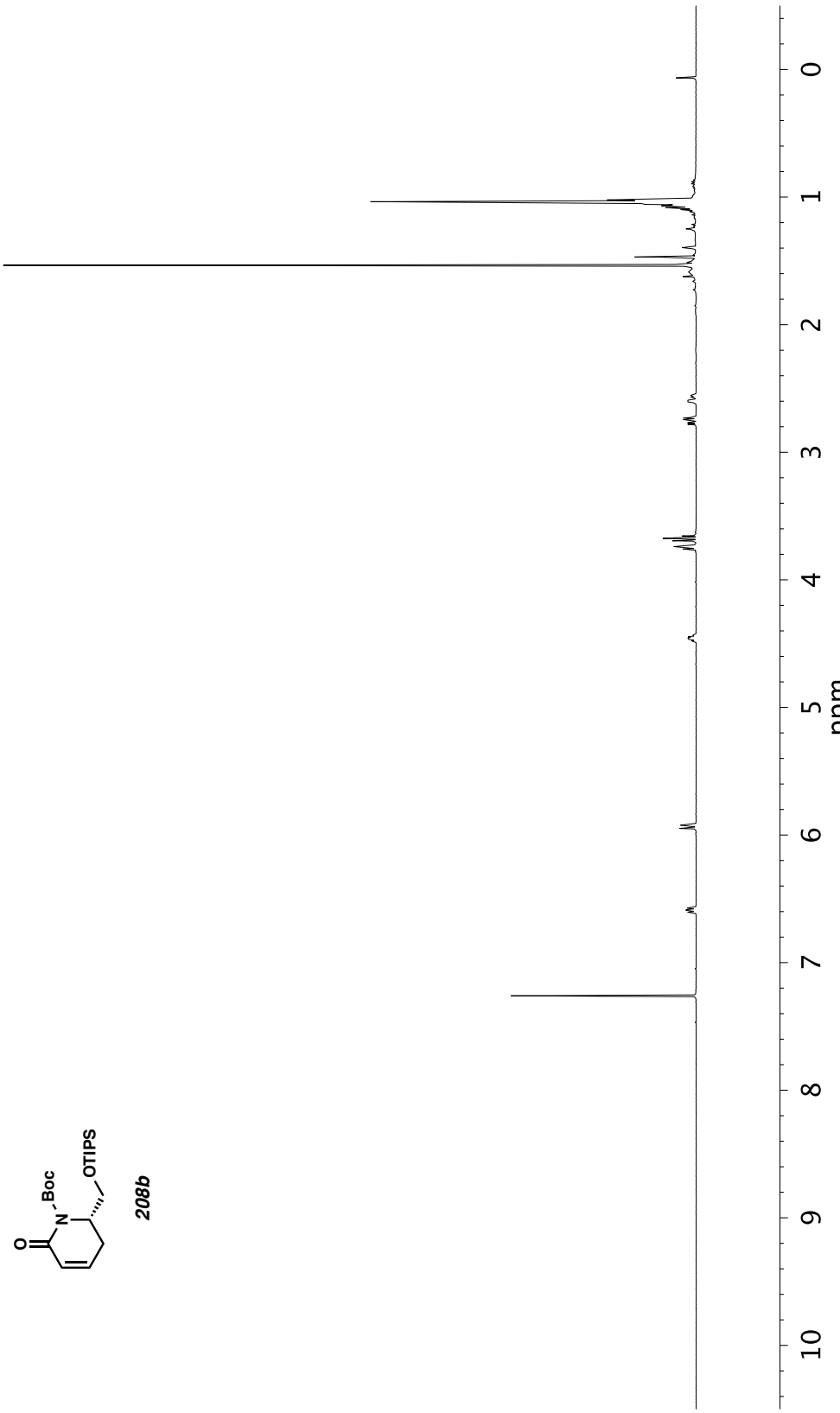


Figure A12.19. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **208b**.

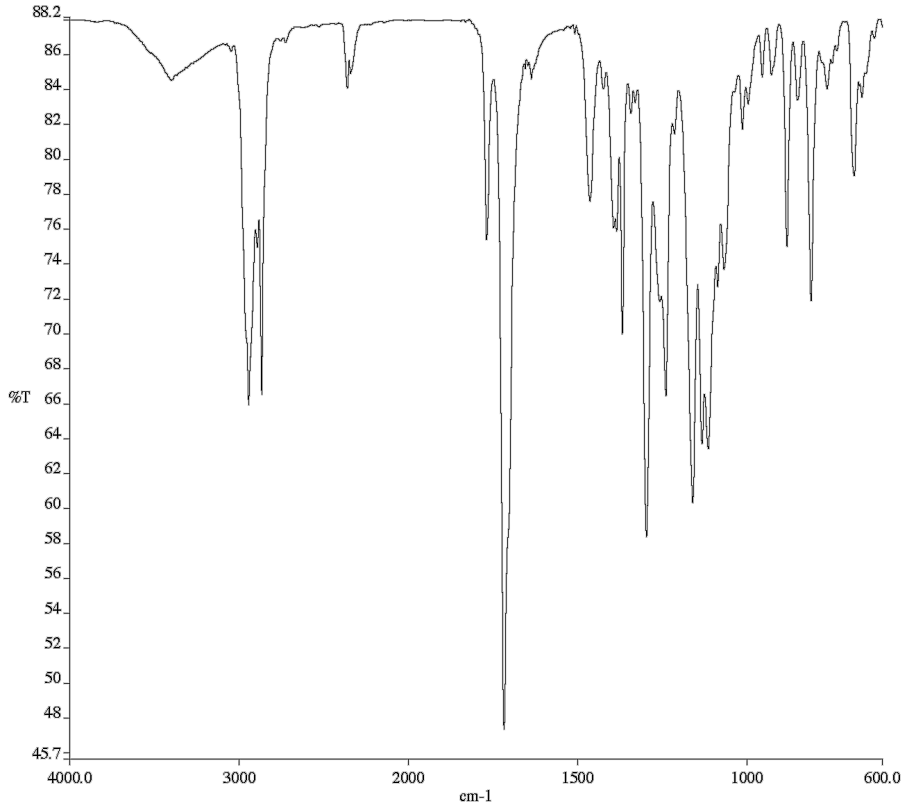


Figure A12.20. Infrared spectrum (Thin Film, NaCl) of compound **208b**.

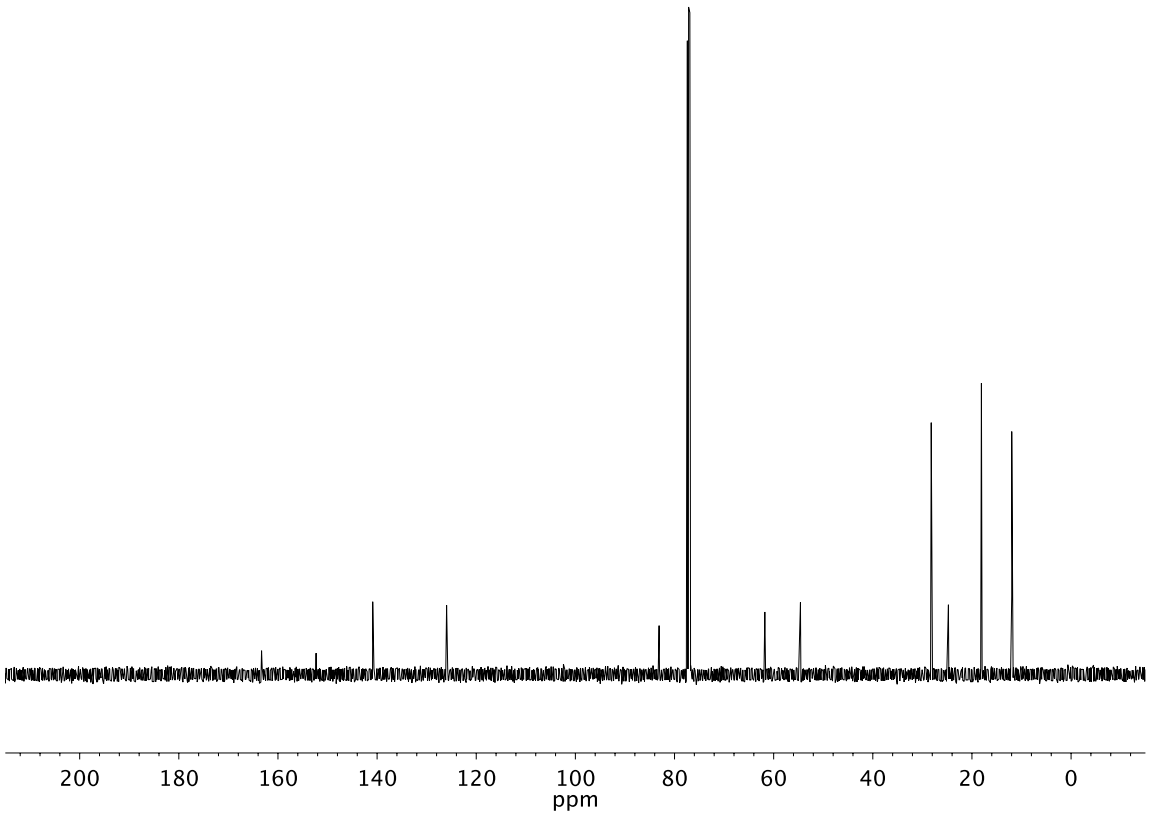


Figure A12.21. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **208b**.

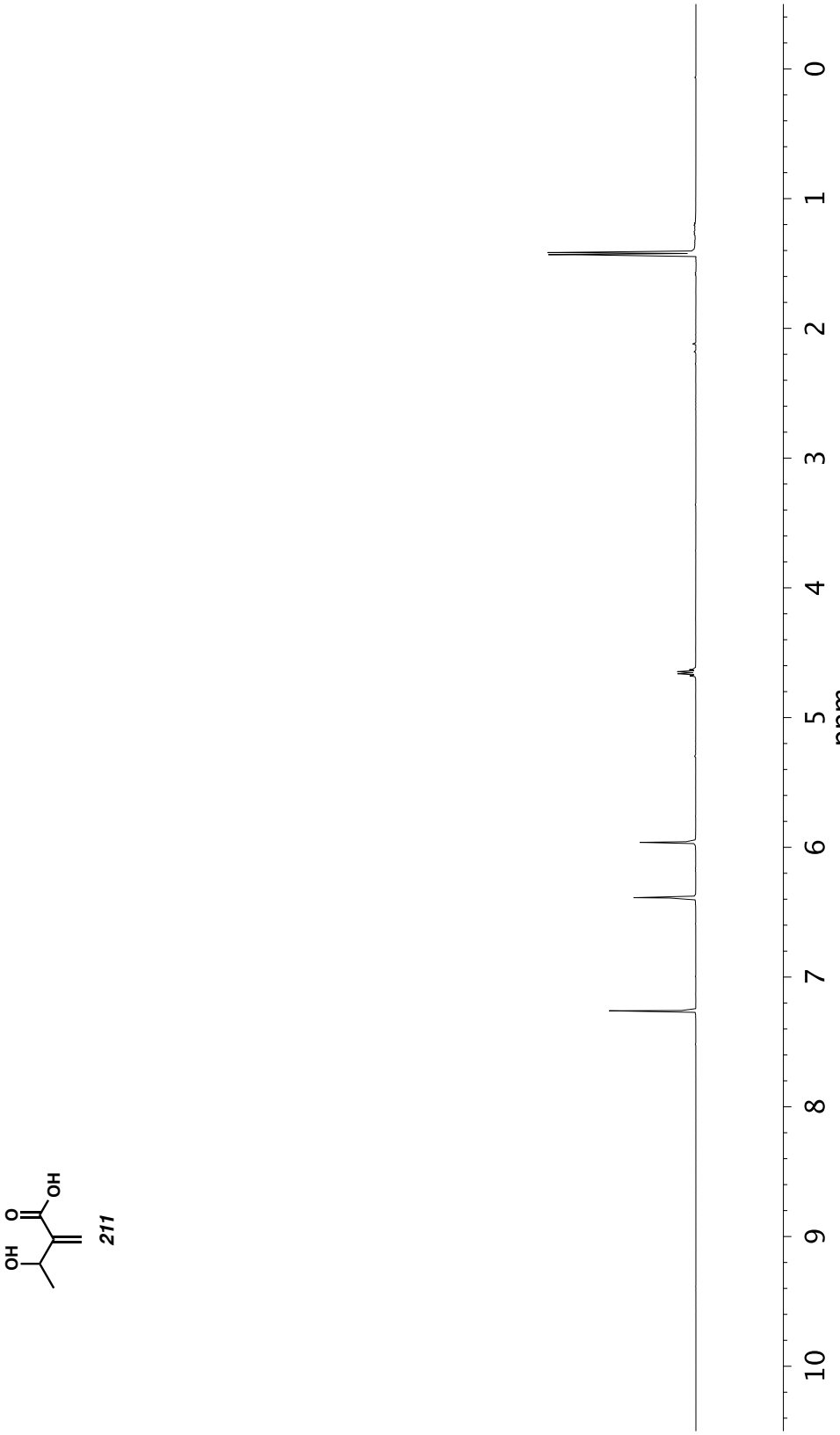


Figure A12.22. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **211**.

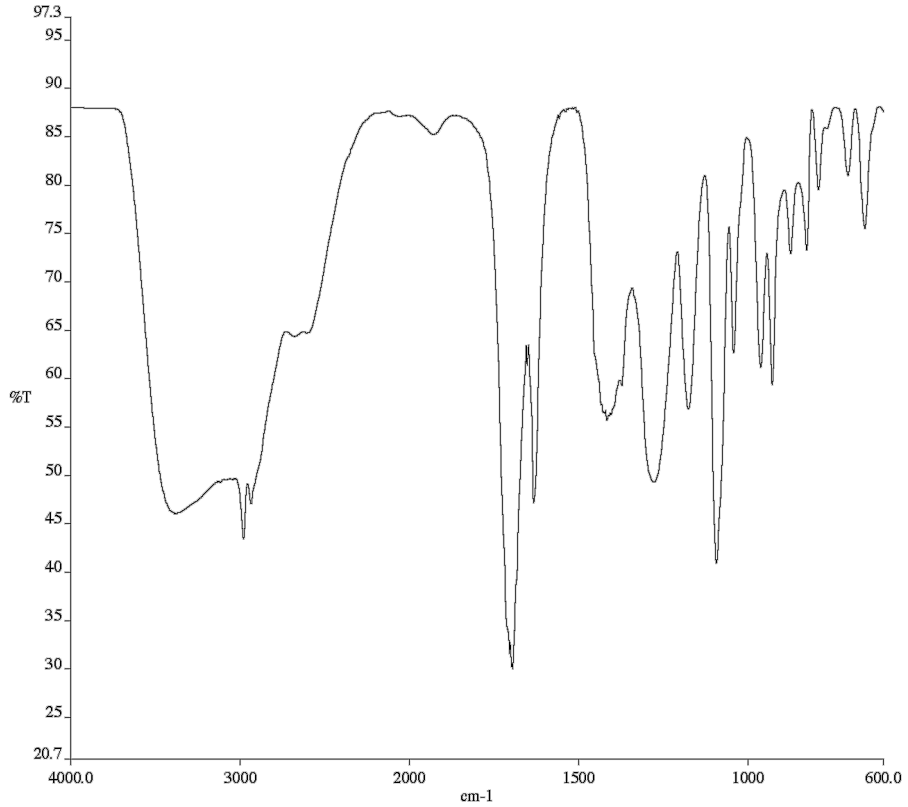


Figure A12.23. Infrared spectrum (Thin Film, NaCl) of compound **211**.

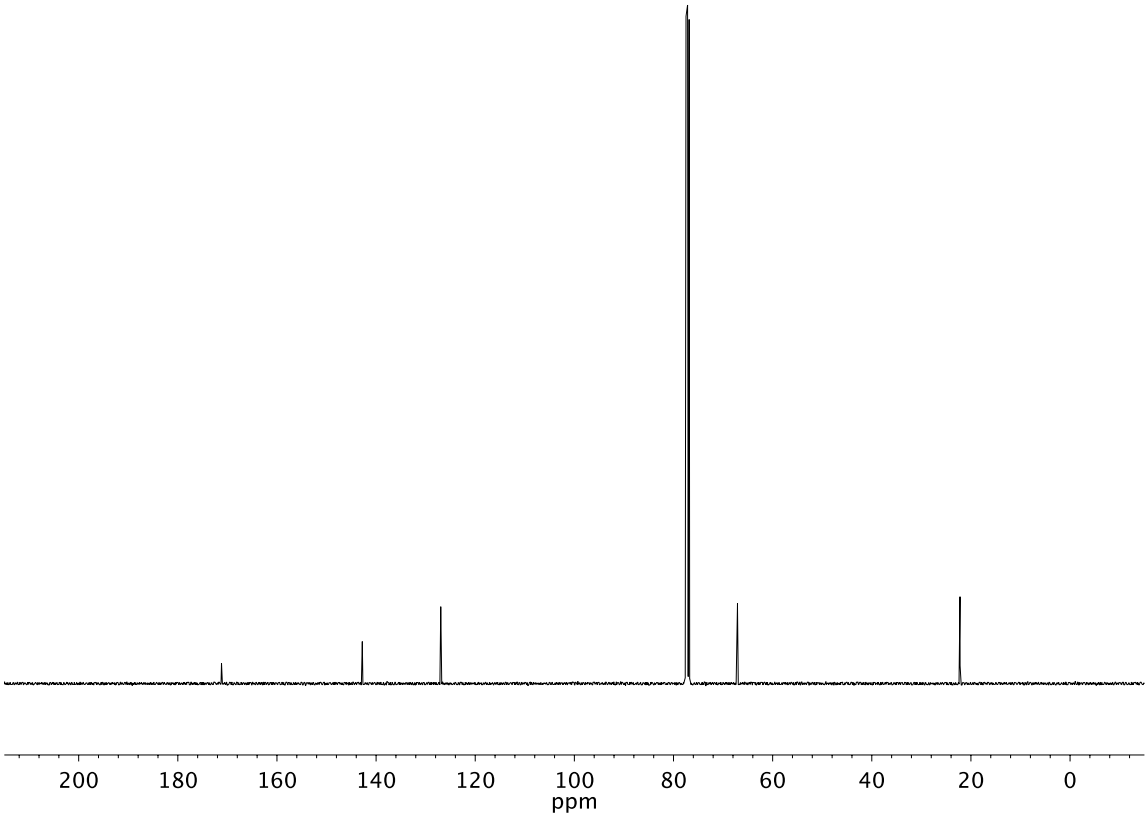


Figure A12.24. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **211**.

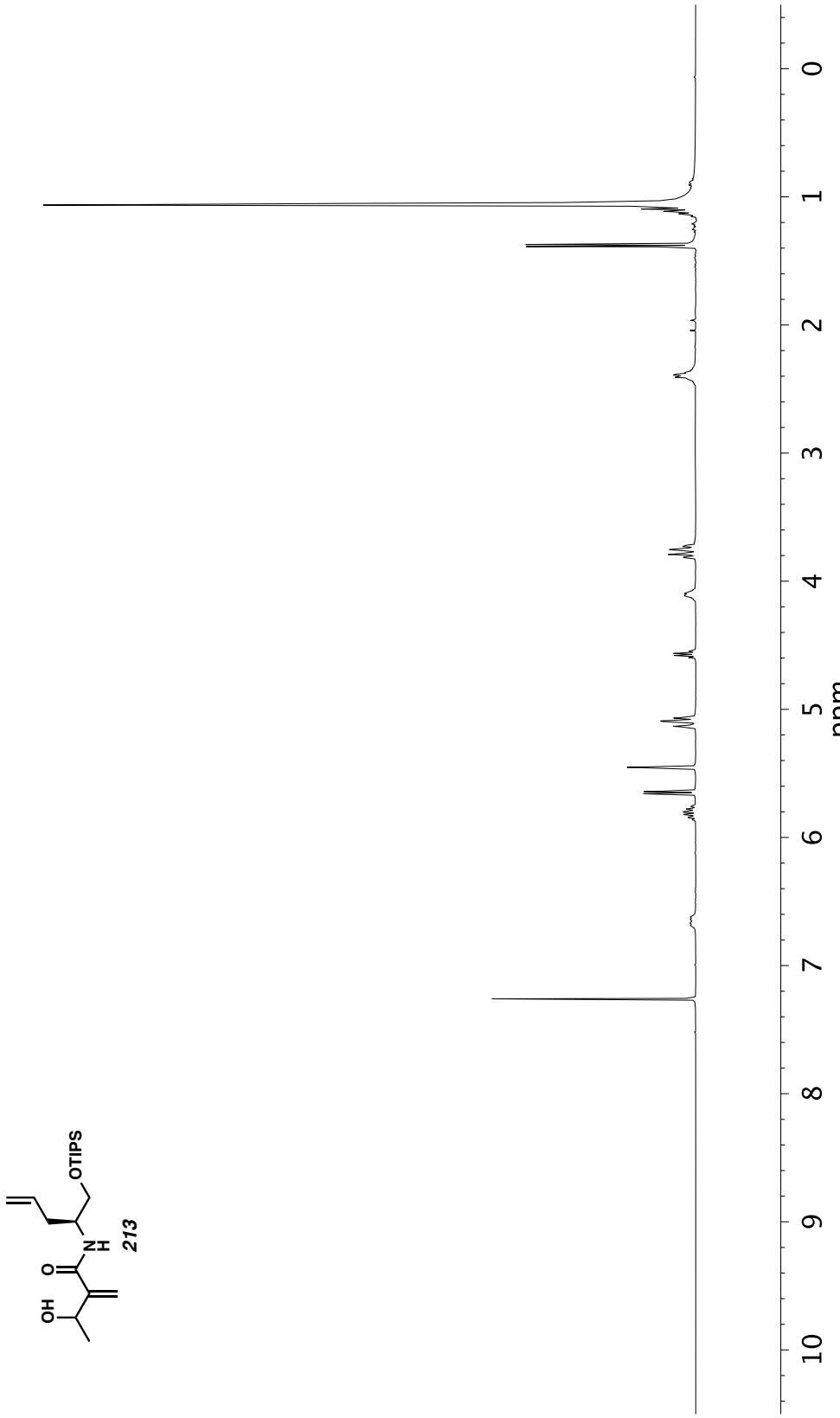


Figure A12.25. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **213**.

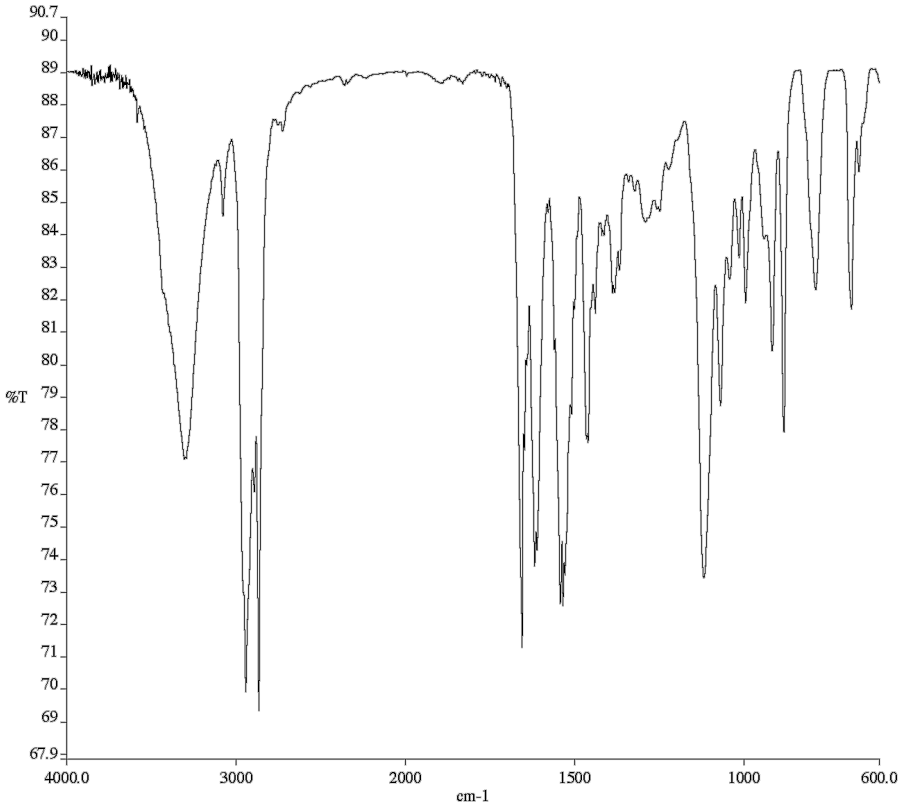


Figure A12.26. Infrared spectrum (Thin Film, NaCl) of compound **213**.

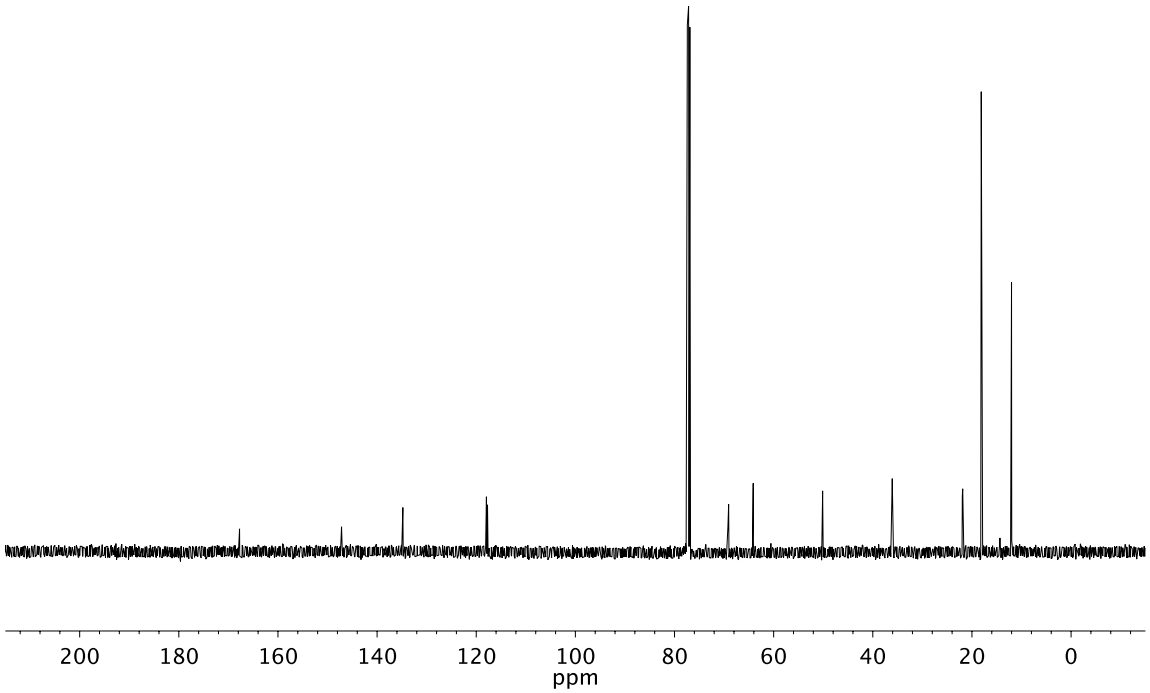


Figure A12.27. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **213**.

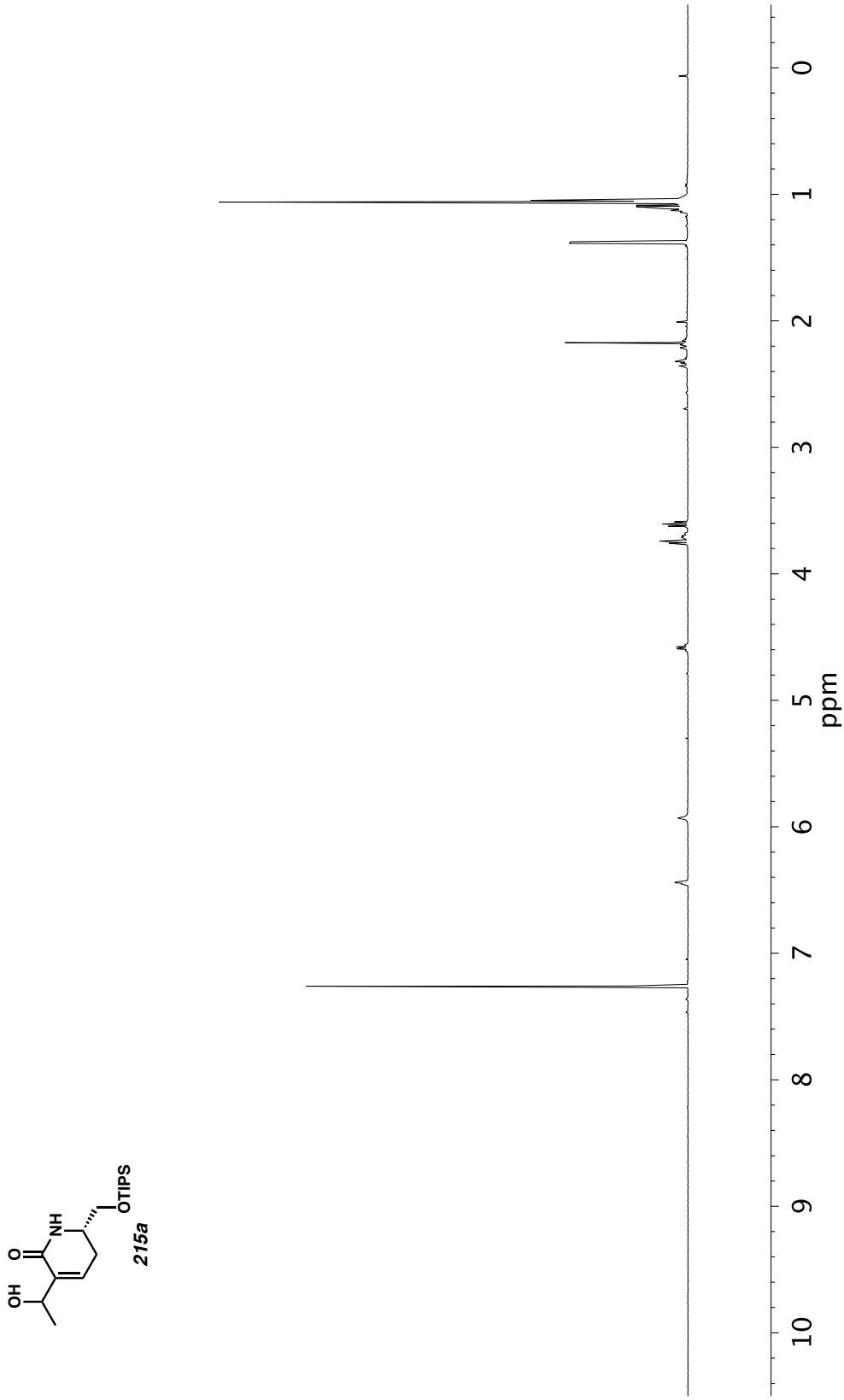


Figure A12.28. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **215a**.

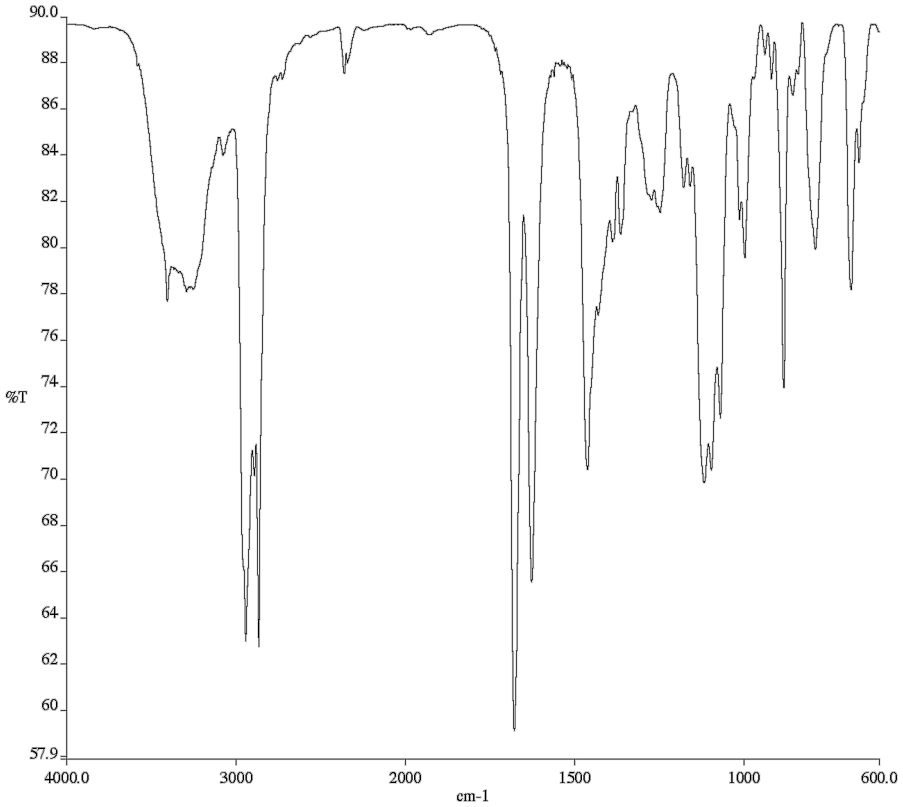


Figure A12.29. Infrared spectrum (Thin Film, NaCl) of compound **215a**.

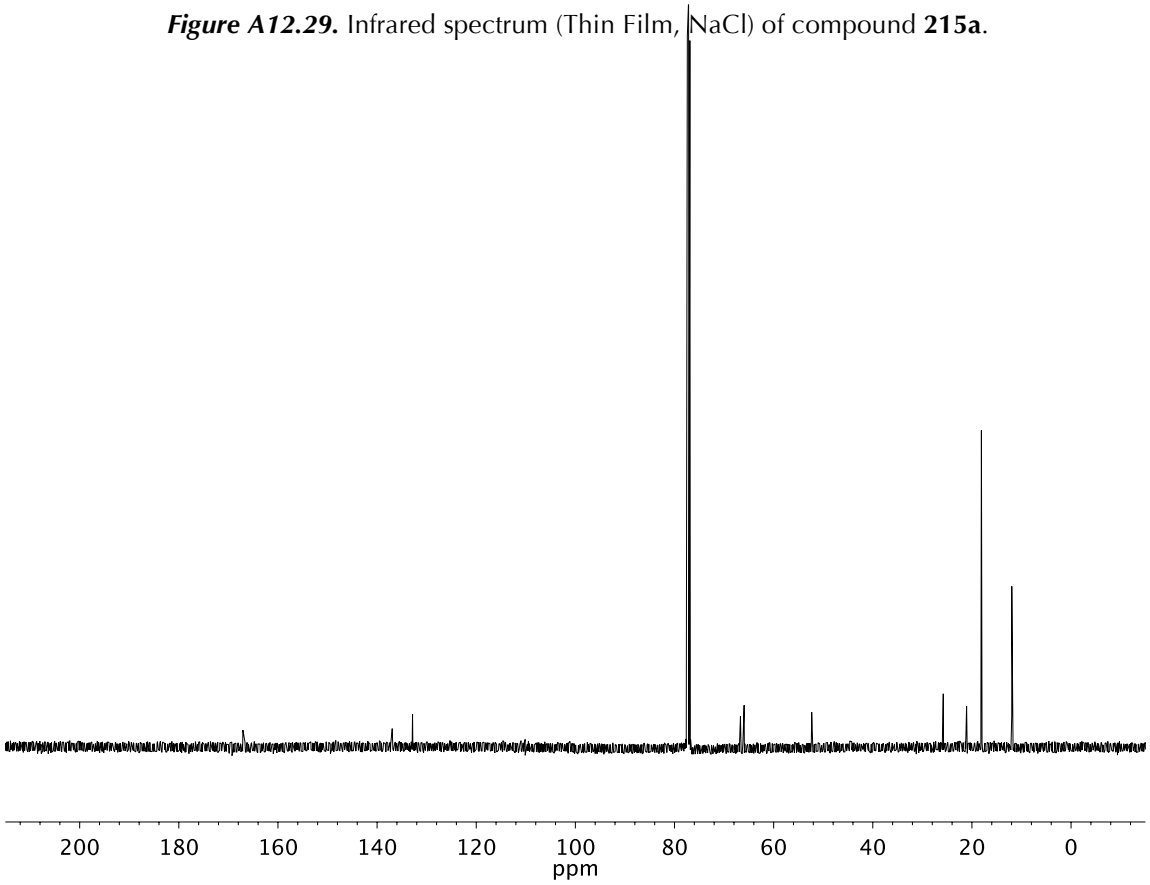


Figure A12.30. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **215a**.

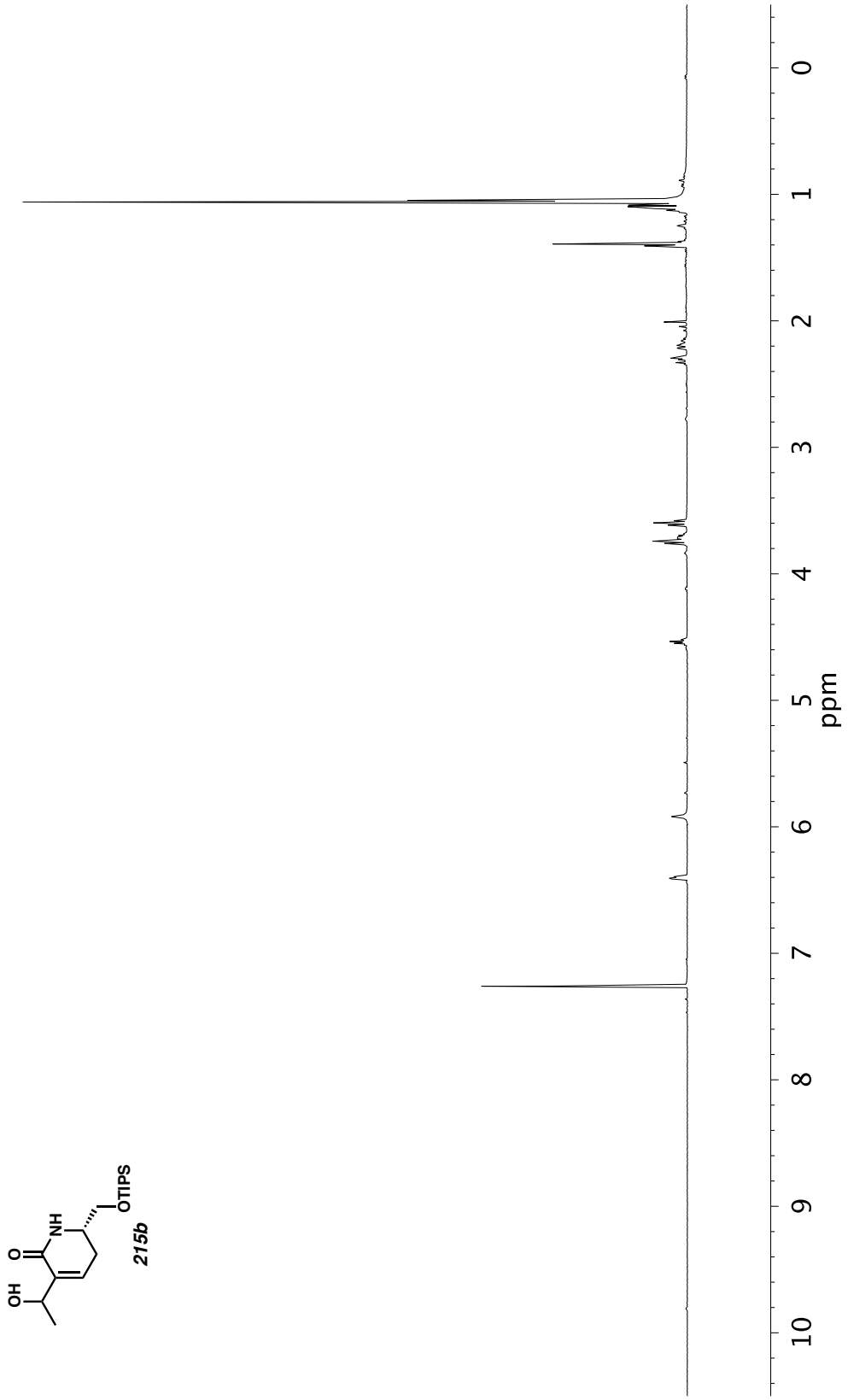


Figure A12.31. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **215b**.

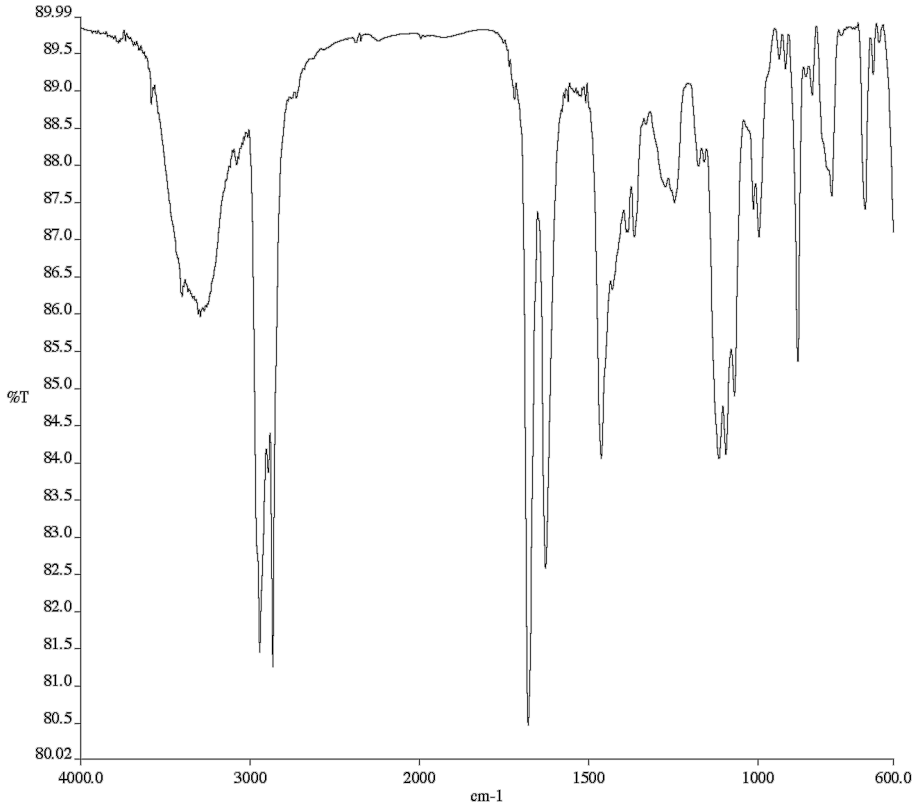


Figure A12.32. Infrared spectrum (Thin Film, NaCl) of compound **215b**.

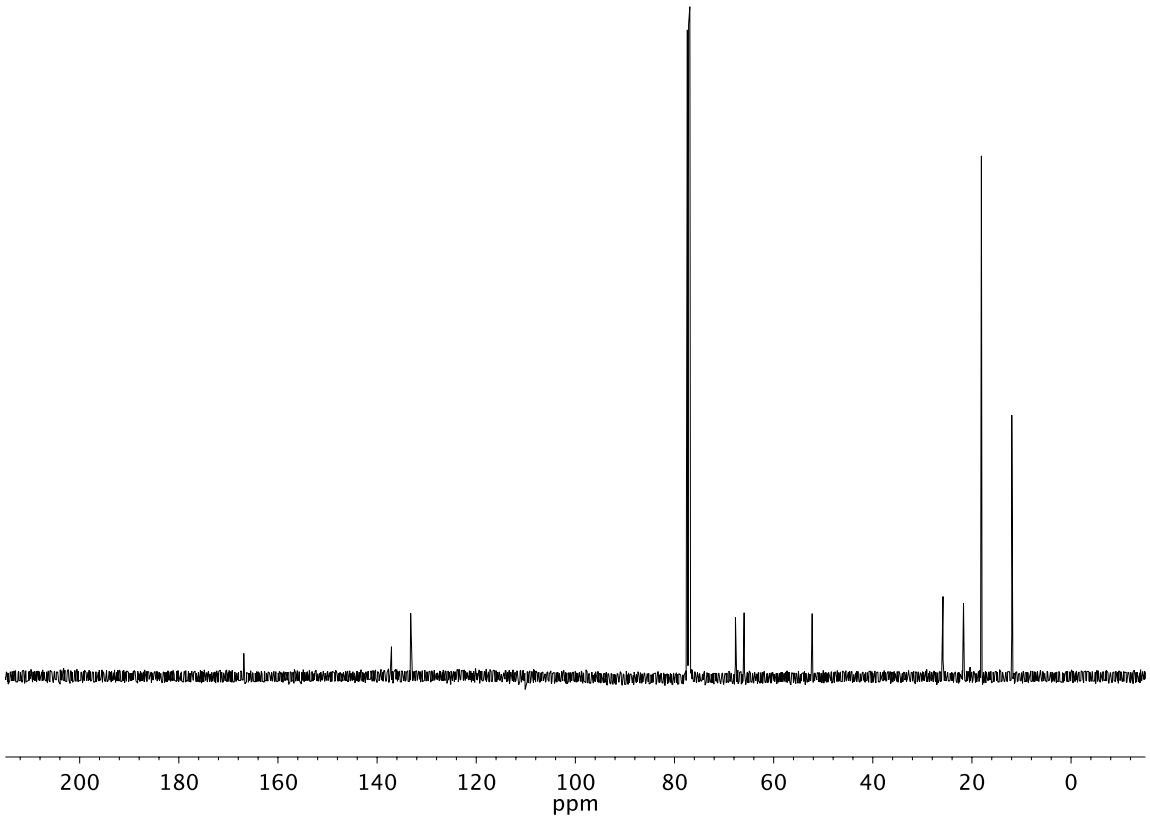


Figure A12.33. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **215b**.

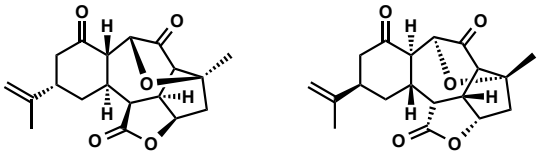
CHAPTER 5

Synthetic Studies Toward Polycyclic Ineleganolide

5.1. Introduction

The complex polycyclic norcembranoid ineleganolide (**238**) was first isolated from the Taiwanese coral *Sinularia inelegans* in 1999 by the Duh group (Figure 5.1.1).[1,2] The relative stereochemistry of ineleganolide (**238**) was unambiguously confirmed by X-ray analysis and spectroscopic method. This complex polycyclic norditerpenoid possesses intriguing architectural features including an ether bridge, which connects two carbocyclic rings and an angular fusion of five-, seven,- and six-membered carbocyclic rings linked with a five-membered lactone ring. Ineleganolide exhibits cytotoxic activity against P-388 murine leukemia cells (ED_{50} = 3.82 μg/mL).[1]

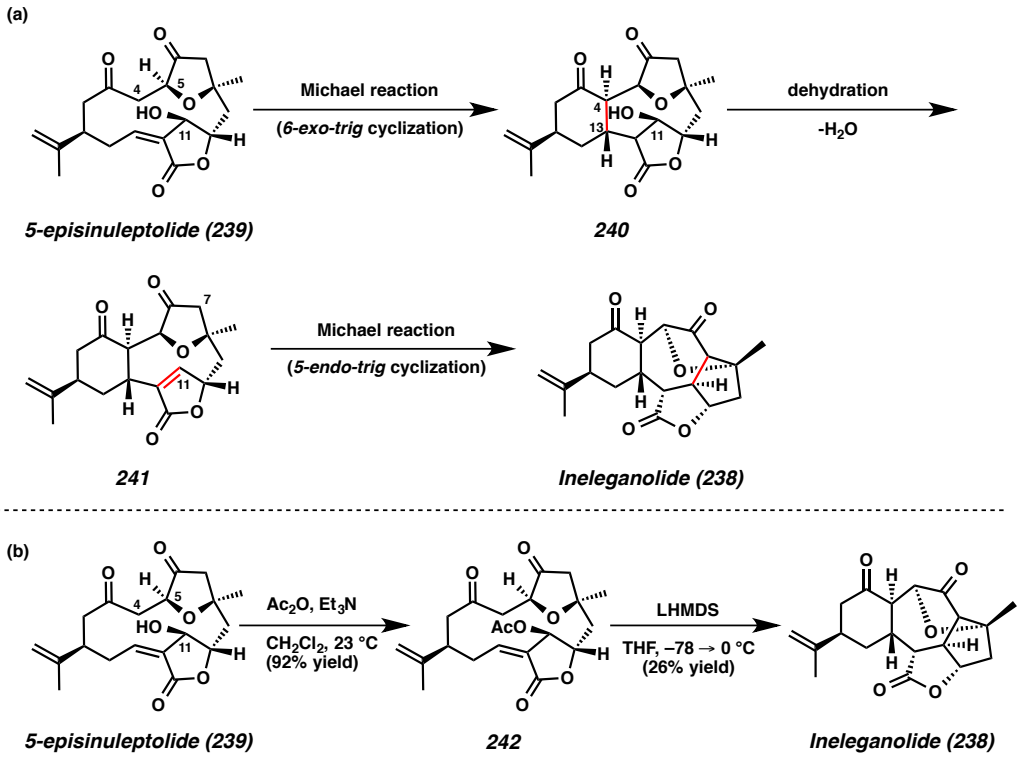
Figure 5.1.1. *Structure of Ineleganolide (**238**). (Originally depicted structure shown on the left-hand side; the proposed actual structure from biosynthetic studies shown on the right-hand side.)*[3]



Ineleganolide (238)

A biosynthetic pathway of ineleganolide was proposed by Pattenden and co-workers (Scheme 5.1.1a).[4] It is hypothesized that ineleganolide (**238**) is biosynthetically constructed by successive transannular Michael reactions of macrocyclic 5-episinuleptolide (**239**). An initial intramolecular Michael reaction of 5-episinuleptolide (**239**) establishes the C4–C13 bond to furnish cyclohexanone **240**. Dehydration of **240** at C11 and subsequent bond formation between C7 and C11 by a second Michael reaction affords ineleganolide (**238**). The Pattenden group proved this biosynthetic route experimentally by a semisynthesis of ineleganolide (**238**) from 5-episinuleptolide (**239**), which was isolated from *Sinularia scabra* species (Scheme 5.1.1b).[5] Acetylation of the hydroxyl group at C11 position of 5-episinuleptolide (**239**) furnished acetate **242**. Ineleganolide (**238**) was obtained in 26% yield by treatment of acetate **242** with LHMDS.

Scheme 5.1.1. *Proposed Biosynthesis of Ineleganolide (**238**)*

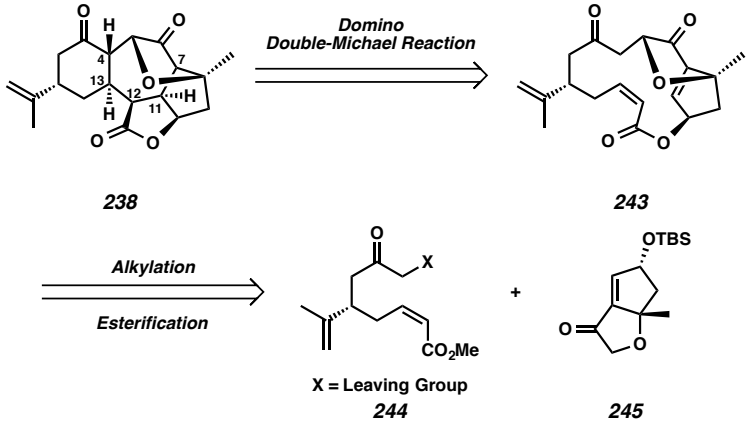


Although this intriguing polycyclic norditerpenoid ineleganolide (**238**) has attracted much attention from the synthetic community over the past decade including extensive efforts from my lab at Caltech,[6] a total synthesis of ineleganolide has not been reported. Herein, we describe new synthetic strategies toward an enantioselective synthesis of ineleganolide (**238**). We chose to pursue the synthesis of the enantiomer of ineleganolide (**238**), which was depicted in the original isolation paper.

5.2. Results and Discussion

We envisioned that a total synthesis of ineleganolide (**238**) could be achieved by successive transannular Michael reactions (Scheme 5.2.1). Disconnections of the C4–C13 and C11–C12 bonds affords domino double-Michael reaction precursor **243**. The 1,4-diketone and ester functional groups of macrocycle **243** can be disassembled into α,β-unsaturated ester **244** and bicycle **245**.

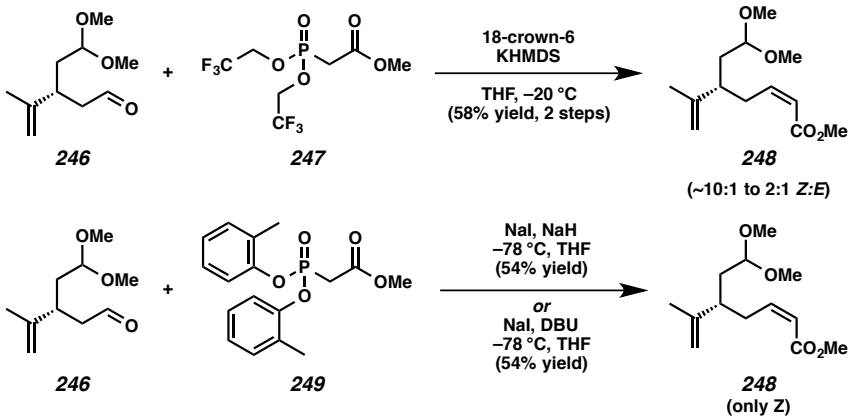
Scheme 5.2.1. *Retrosynthesis of Ineleganolide (**238**)*



Our synthesis began with the known acetal **246**[7] to prepare the α,β-unsaturated ester fragment **248** (Scheme 5.2.2). Subjection of acetal **246** to Still-Gennari

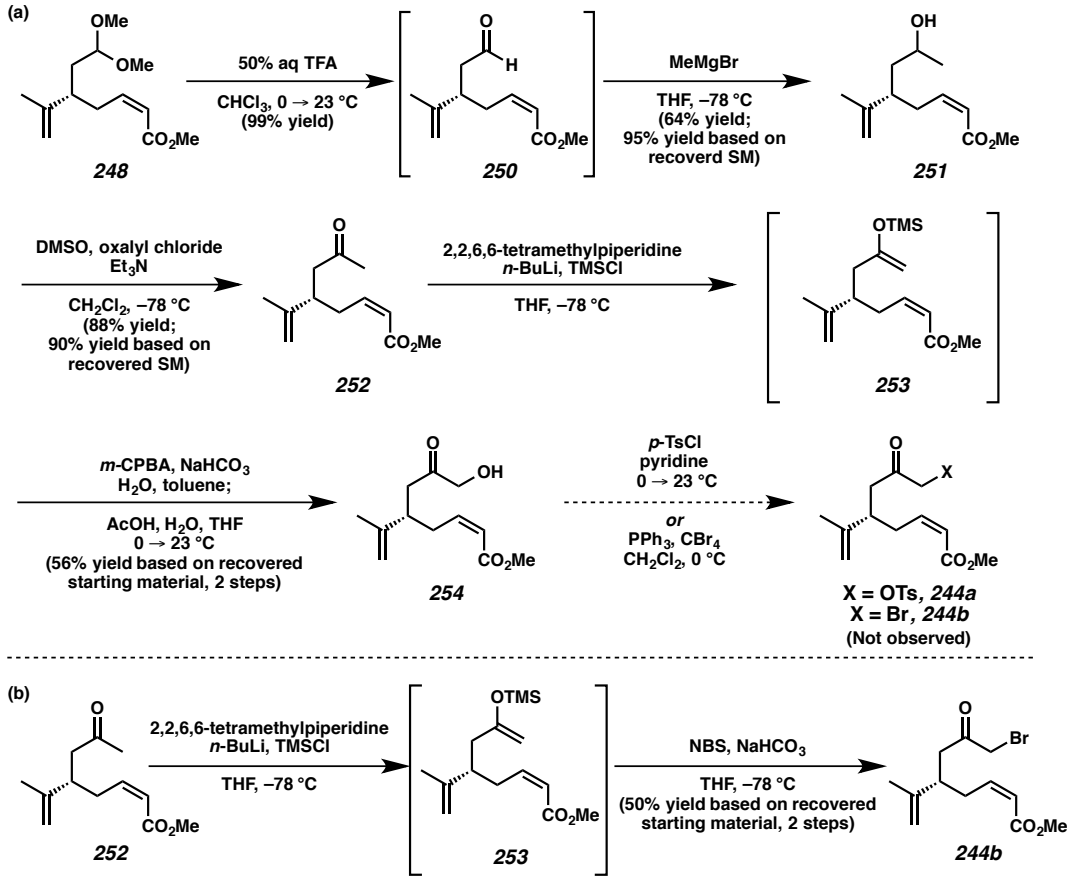
olefination conditions[8,9] afforded the (*Z*)- and (*E*)-isomers of enoate **248** in ratios ranging from 10:1 to 2:1, respectively. We were delighted to find that highly (*Z*)-selective olefination occurred to furnish enoate **248** in 54% yield using conditions developed by the Ando group.[10]

Scheme 5.2.2. *Synthesis of (Z)-Selective Enoate* ***248***



Acid-mediated acetal hydrolysis of **248** furnished aldehyde **250** in quantitative yield (Scheme 5.2.3a). Methyl Grignard addition to aldehyde **250** produced diastereomeric mixtures of alcohol **251**, which was converted to ketone **252** by Swern oxidation. After extensive experimentation, it was found that employing LiTMP (TMP = 2,2,6,6-tetramethylpiperidine) and TMSCl afforded kinetically favored silyl enol ether **253** selectively.[11] Silyl enol ether **253** was subsequently transformed to α-hydroxyketone **254** by Rubottom oxidation.[12] Surprisingly, tosylation and bromination of α-hydroxyketone **254** proved to be challenging. However, we were delighted to find that treatment of silyl enol ether **253** with NBS furnished α-bromoketone **244b** (Scheme 5.2.3b).

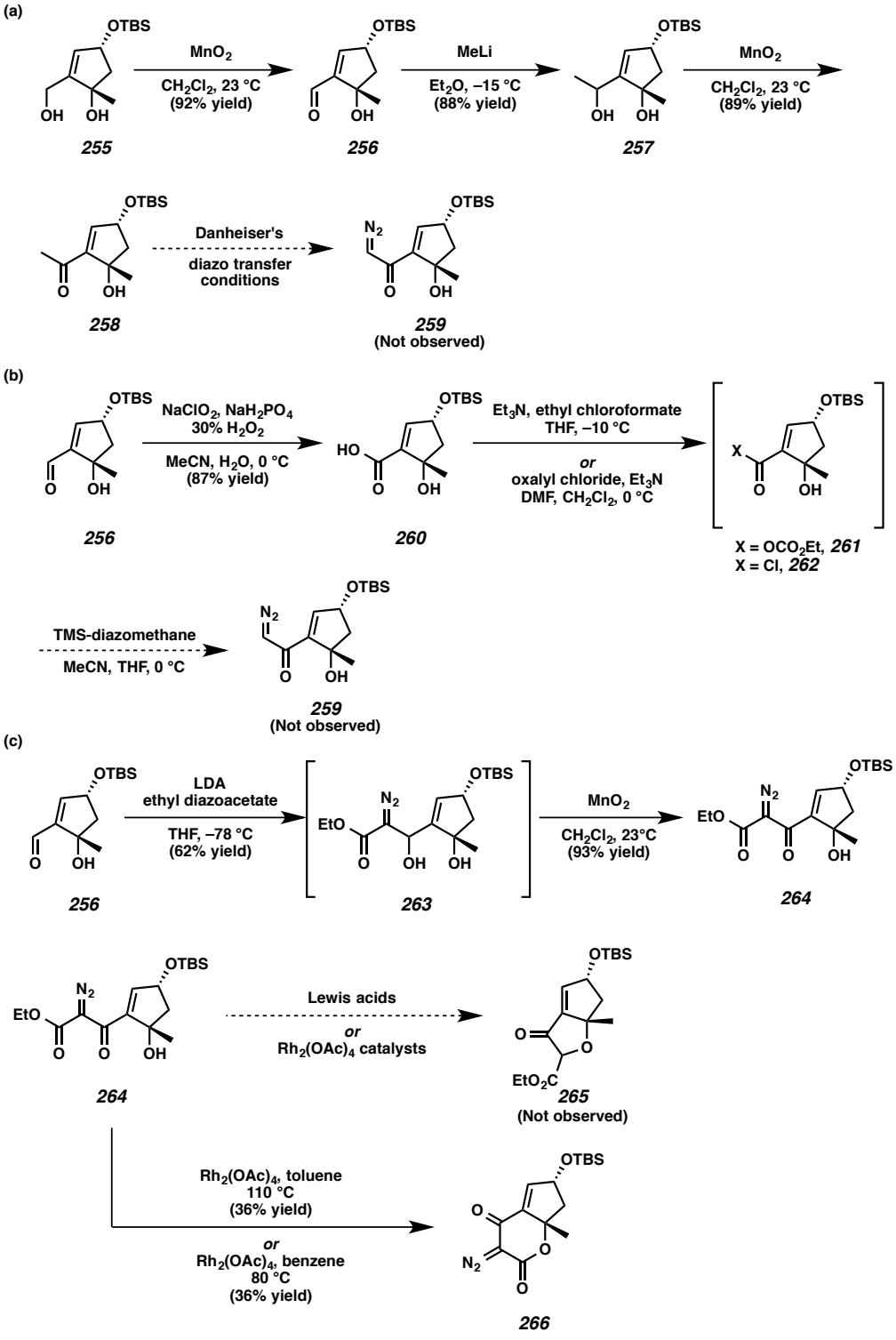
Scheme 5.2.3. *Synthesis of α-Bromoketone* ***244b***



With α,β-unsaturated ester fragment **244b** in hand, we turned our attention to preparing bicyclic fragment **245**. Oxidation of known diol **255**[6a,13] with MnO_2 delivered aldehyde **256** (Scheme 5.2.4a). Methyllithium addition to aldehyde **256** provided secondary alcohol **257**, which was oxidized with MnO_2 to afford ketone **258**. Unfortunately, we explored diazo transfer reactions extensively with various diazo sources (e.g., *p*-ABSA, 4-dodecylbenzenesulfonyl azide) under Danheiser's conditions,[14] but the desired diazo **259** was not observed. Another strategy was devised to obtain diazo ketone **259** by using Pinnick oxidation of aldehyde **256** to furnish acid **260** (Scheme 5.2.4b). Treatment of acid **260** with ethyl chloroformate or oxalyl chloride generated the corresponding intermediates **261** or **262**, respectively. However, attempts to obtain the desired diazo ketone **259** from intermediate **261** or

262 with TMS-diazomethane were unsuccessful.[15,16,17] Alternatively, we envisioned that the diazo functional group could be inserted by addition of ethyl diazoacetate to aldehyde **256** (Scheme 5.2.4c). Deprotonation of ethyl diazoacetate by LDA followed by addition to aldehyde **256** resulted in an alcohol (**263**) that could be oxidized to diazo compound **264**. Disappointingly, intramolecular O–H insertion of the tertiary alcohol to the diazo in **264** was found to be challenging under Lewis acid conditions. Despite screening numerous rhodium catalysts, solvents, and temperature, only undesired lactonization occurred to form **266**.[18]

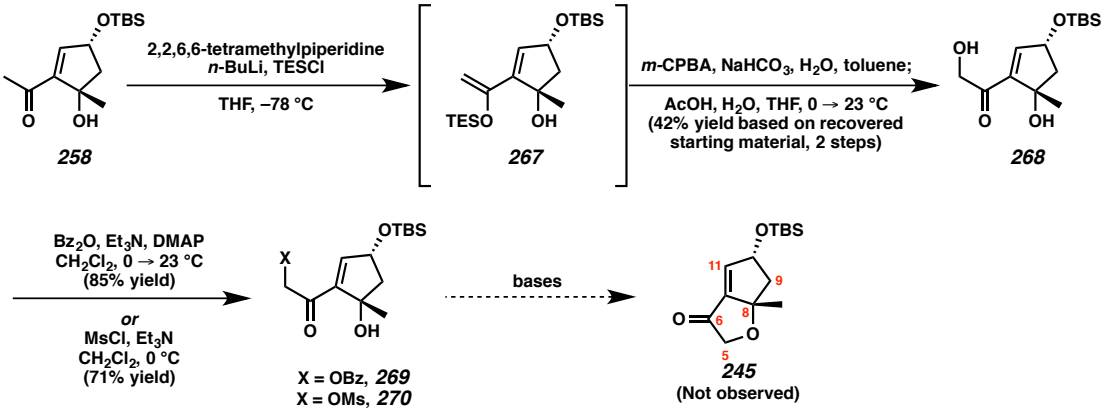
Scheme 5.2.4. *Attempts to Synthesize Bicyclic Fragment via Diazo Compounds*



Having failed to access the bicyclic fragment using diazo strategies, a revised approach was put forward (Scheme 5.2.5). Treatment of methyl ketone **258** with

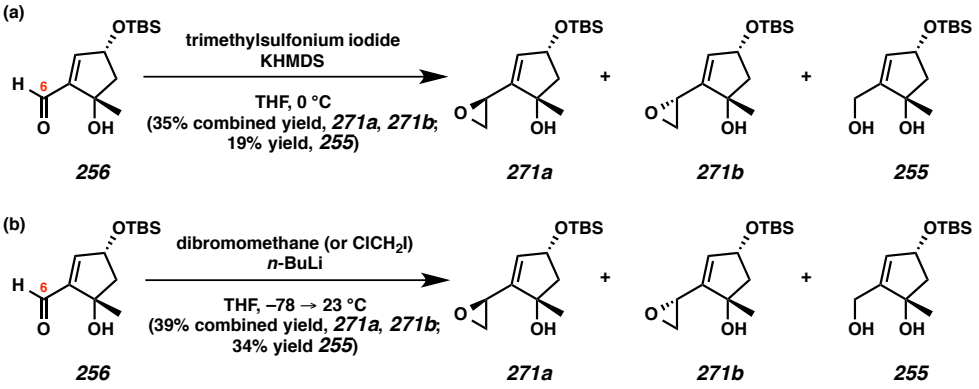
LiTMP (TMP = 2,2,6,6,-tetramethylpiperidine) and TESCl provided silyl ether **267**, which was transformed to α-hydroxyketone **268** by Rubottom oxidation. However, the desired bicycle **245** was not observed under various basic conditions (e.g., NaOH, KO^{t}Bu, NaH, LHMDS, LDA) from benzoate **269** and mesylate **270**, which were prepared from α-hydroxyketone **268**.[19,20]

Scheme 5.2.5. *Attempted Williamson Etherifications*



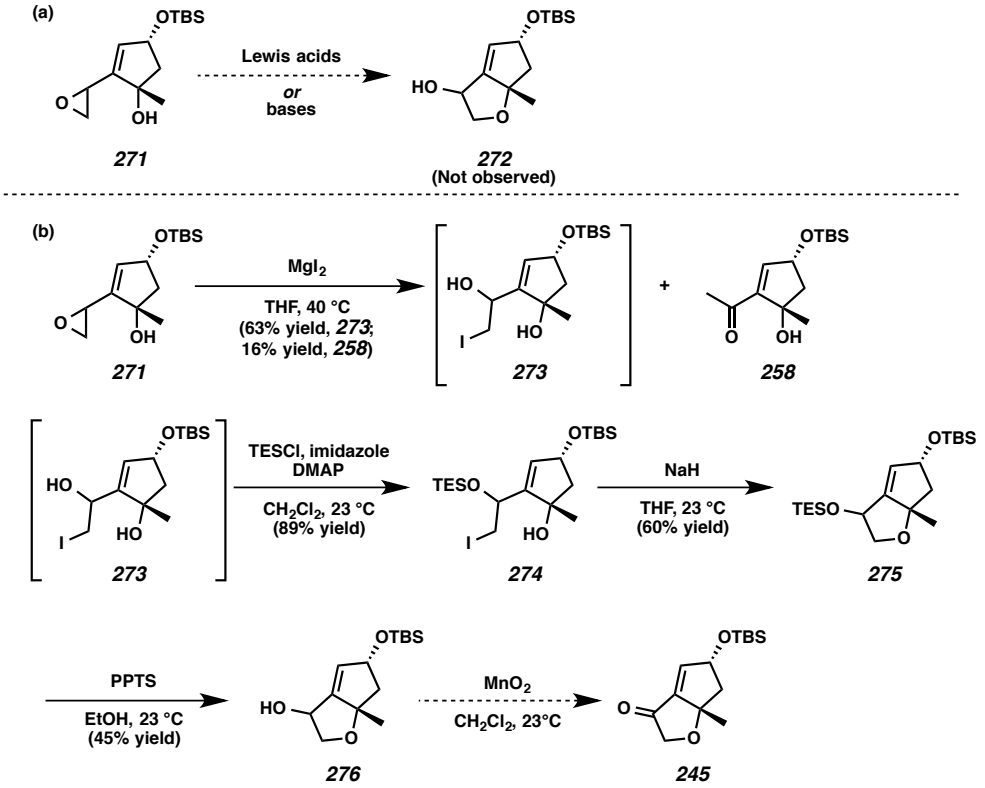
The desired bicycle **245** seemed highly angularly strained due to the α,β-unsaturated ketone at the junction of the bicycle. We envisaged that the strain would be reduced by converting the sp^2-hybridized carbon to the sp^3-hybridized carbon at C6. After considerable experimentation, we found that diastereomeric mixtures of epoxides **271a** and **271b** could be obtained by a Corey-Chaykovsky reaction (Scheme 5.2.6a).[21] Surprisingly, diol **255** was furnished as a major byproduct under these reaction conditions. Treatment of aldehyde **256** with dibromomethane (or chloroiodomethane) and *n*-BuLi also produced diastereomeric mixtures of epoxides **271a** and **271b** along with diol **255** (Scheme 5.2.6b).[22]

Scheme 5.2.6. *Synthesis Epoxides* ***271a*** *and* ***271b***



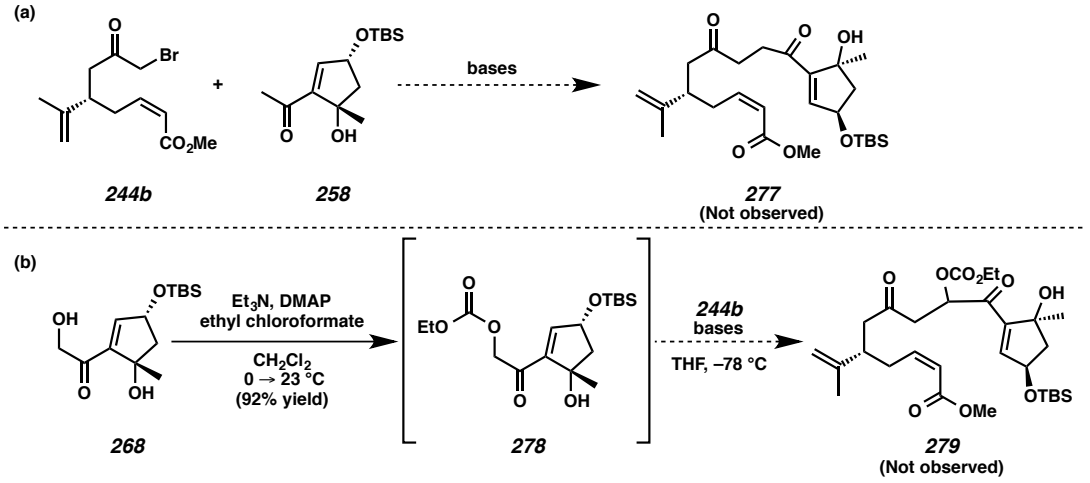
With epoxide **271** in hand, direct epoxide ring opening reactions were conducted to deliver **272** (Scheme 5.2.7a). Unfortunately, 5-membered ring formation to generate **272** was not observed with various Lewis acids (e.g., $CeCl_3$, TMSOTf, $In(OTf)_3$, PPTS) or bases (e.g., KHMDS, NaH).[23] Interestingly, treatment of epoxide **271** with MgI_2 at 40 °C generated iodohydrin **273** along with methyl ketone **258** (Scheme 5.2.7b).[24,25] Protection of secondary alcohol **273** with TESCl and subsequent intramolecular etherification of iodide **274** with NaH afforded bicyclc **275**.[26] Selective removal of TES group in **275** with PPTS furnished mono-silyl ether **276**. An attempt to oxidize secondary alcohol **276** to ketone **245** shows promise by TLC analysis but to date we have not successfully isolated and characterized **245**.[27]

Scheme 5.2.7. *Formation of Bicyclic Fragment*



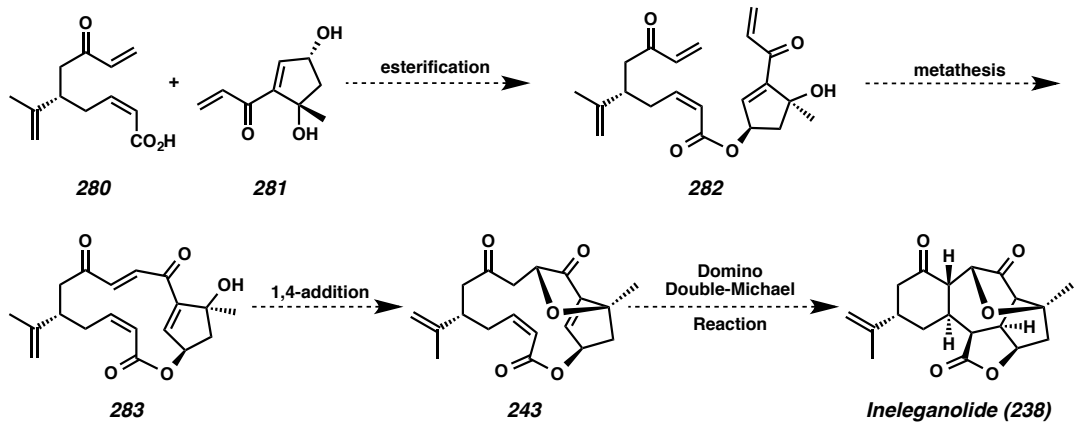
We next investigated coupling reactions of α-bromoketone **244b** and methylketone **258**, which could be easily prepared (Scheme 5.2.8a). Despite extensive experimentation, alkylation of methylketone **258** with α-bromoketone **244b** failed under basic conditions.[28] Treatment of hydroxyketone **268** with ethyl chloroformate afforded the carbonate intermediate, which was subjected to α-bromoketone **244b** to generate 1,4-diketone **279** under basic conditions. However, α-bromoketone **244b** appeared to decompose under the basic conditions and only the unreacted cyclopentene fragment was recovered.

Scheme 5.2.8. *Coupling of the Fragments*



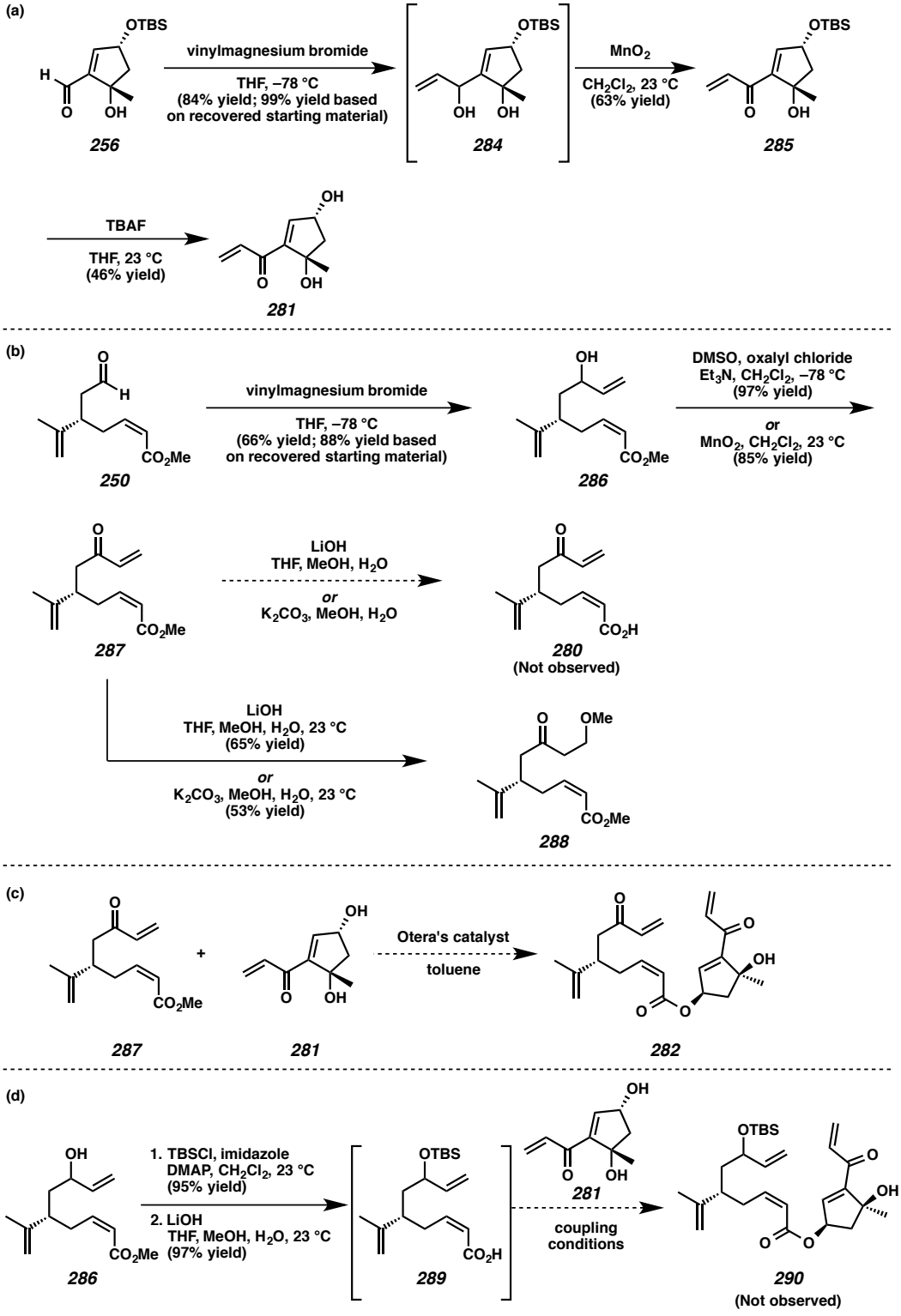
Since coupling reactions of α-bromoketone **244b** and the cyclopentene fragment by alkylation did not proceed, we next chose to focus on metathesis strategies to combine these two fragments (Scheme 5.2.9). We believed that esterification of acid **280** and secondary alcohol **281** would afford metathesis precursor diene **282**. Intramolecular metathesis reaction between the vinyl groups of **282** was expected to produce macrocycle **283**. 1,4-Addition of tertiary alcohol to the α,β-unsaturated ketone could deliver 5-membered ether **243**, which would proceed domino double-Michael reaction to afford ineleganolide (**238**).

Scheme 5.2.9. *Synthetic Plan by Using Metathesis Strategies*



1,2-Addition of vinylmagnesium bromide to aldehyde **256** furnished allyl alcohol **284**, which was oxidized by MnO_2 to deliver vinyl ketone **285** (Scheme 5.2.10a). Removal of silyl group on **285** with TBAF afforded diol **281**. Vinyl Grignard addition to aldehyde **250** and subsequent oxidation of the resultant alcohol **286** produced ketone **287** (Scheme 5.2.10b). However, an attempted hydrolysis of methyl ester **287** afforded Michael adduct **288** instead of the desired acid **280**. Additionally, transesterifications of ester **287** with alcohol **281** were unsuccessful with Otera's catalyst (Scheme 5.2.10c).[29] Therefore, we decided to explore esterification reactions with silyl ether **289** (Scheme 5.2.10d). Silylation of secondary alcohol **286** with TBSCl and subsequent hydrolysis produced acid intermediate **289**. Disappointingly, esterification of acid **289** and alcohol **281** was found to be challenging under several coupling conditions (e.g., EDCI, DCC, BOPCl).[30]

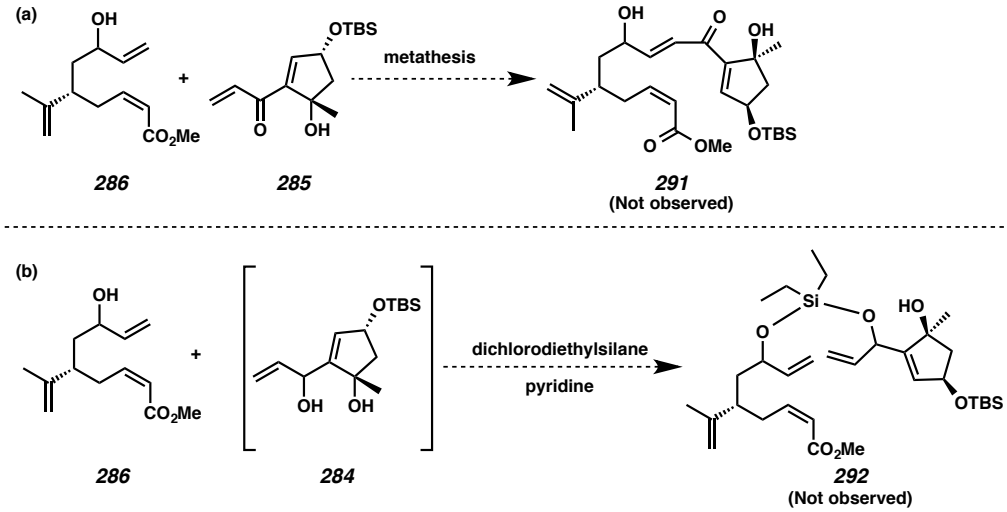
Scheme 5.2.10. *Coupling of the Fragments by Esterification*



At this stage, we began to investigate intermolecular metathesis between allyl alcohol **286** and vinyl ketone **285** with Grubbs' catalysts (Scheme 5.2.11a).[31]

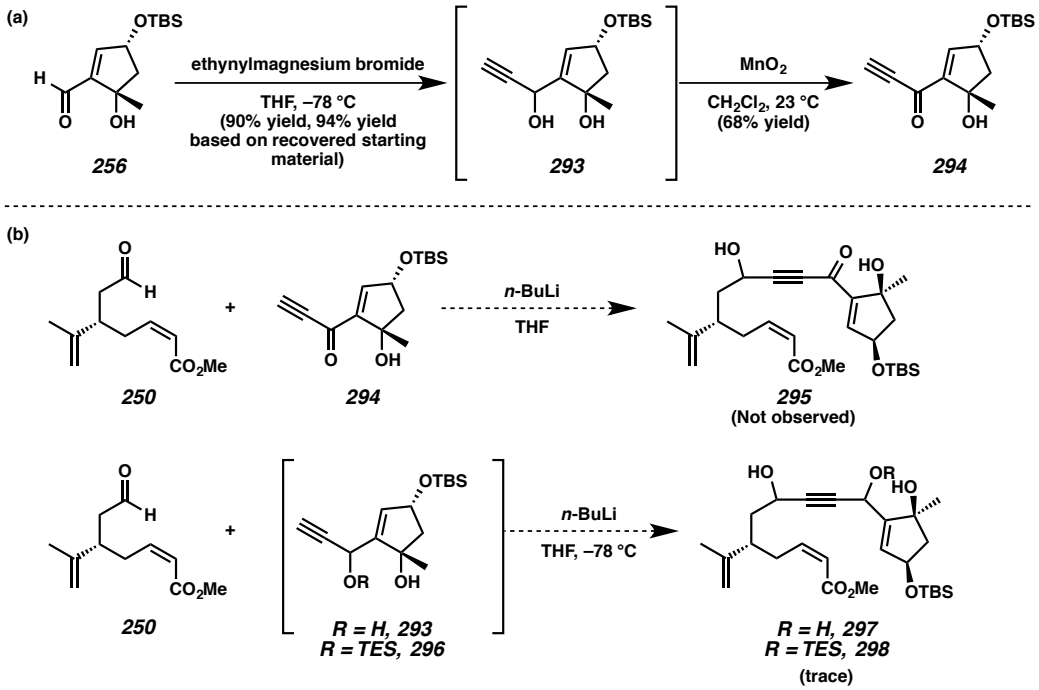
However, intermolecular metathesis of **286** and **285** to deliver **291** proved to be difficult. Alternatively, we attempted to connect allyl alcohol **286** and diol **284** via a silyl tether, but the yield was unsatisfactory (Scheme 5.2.11b).

Scheme 5.2.11. *Intermolecular Metathesis*



Since combining the two fragments appeared to be challenging, we devised a new synthetic strategy that utilized an alkyne functionality (Scheme 5.2.12). Addition of ethynylmagnesium bromide to aldehyde **256** provided intermediate **293**, which was oxidized by MnO_2 to generate ynone **294** (Scheme 5.2.12a). Although *n*-BuLi was subjected to alkyne **294** to form lithium acetylide, which was added to aldehyde **250**, little or no conversion was observed (Scheme 5.2.11b). We also attempted the lithium acetylide addition reaction with alcohol **293** or silyl ether **296**,[32] but only trace amounts of the respective coupling products **297** or **298** were observed.

Scheme 5.2.12. *Alkyne Addition*



5.3. Conclusion

We have described our efforts toward the synthesis of ineleganolide. Highly (*Z*)-selective olefination at C12–C13 was achieved by a method developed by the Ando group. The C–O bond formation at C5, which proved to be challenging in the other strategy investigated in our group,[6a] was accomplished. Although the entire fragmented carbon framework was constructed from this work, unfortunately, coupling of the two fragments was unsuccessful. We will further investigate a total synthesis of ineleganolide using modified strategies.

5.4. Experimental Methods and Analytical Data

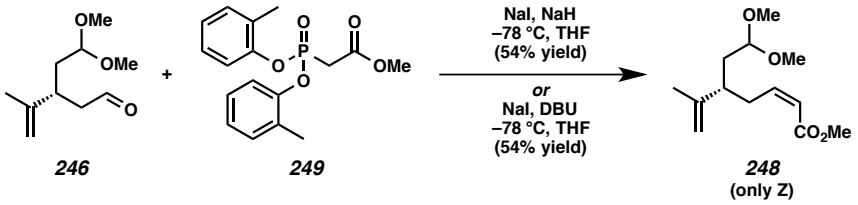
5.4.1. Materials and Methods

Unless stated otherwise, reactions were performed at ambient temperature (23 °C) in flame-dried glassware under an argon atmosphere using dry, deoxygentated solvents

(distilled or passed over a column of activated alumina) using a Teflon®-coated magnetic stirring bar. Commercially available reagents were used as received unless otherwise noted. Et_3N was distilled from calcium hydride immediately prior to use. MeOH was distilled from magnesium methoxide immediately prior to use. Reactions requiring external heat were modulated to the specified temperatures using an IKAmag temperature controller. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (250 nm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. Silicycle SiliaFlash P60 Academic Silica gel (particle size 40-63 nm) was used for flash chromatography. ^{1}H NMR spectra were recorded on a Varian Mercury 300 MHz, a Bruker AV III HD 400 MHz spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe, Varian Inova 500 MHz, and 600 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm), $CHDCl_2$ (δ 5.32) or C_6HD_6 (δ 7.16 ppm). ^{13}C NMR spectra are recorded on a Varian Mercury 300 MHz, a Bruker AV III HD 400 MHz spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe, Varian Inova 500 MHz, and 600 MHz spectrometers (75 MHz, 126 MHz, and 151 MHz, respectively) and are reported relative to $CHCl_3$ (δ 77.16 ppm), $CHDCl_2$ (δ 53.84) or C_6HD_5 (δ 128.06 ppm). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode or acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in atmospheric pressure

chemical ionization (APCI) or mixed (MultiMode ESI/APCI) ionization mode. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path length cell at 589 nm.

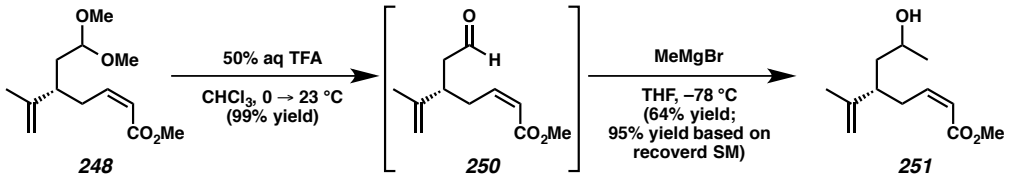
5.4.2. Experimental Procedures



246 ***249*** ***248*** (only Z)

A solution of phosphate **249** (108 mg, 0.322 mmol, 1.20 equiv) in THF (2.68 mL) was treated with NaI (52.0 mg, 0.349 mmol, 1.30 equiv) and DBU (53.0 mg, 0.348 mmol, 1.30 equiv) at 0 °C and stirred for 10 min. After the mixture was cooled to –78 °C, aldehyde **246** was added. The reaction was done in 3 min, and quenched with sat. aq NH_4Cl. The aqueous phase was extracted with EtOAc (3 x 3.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:8 EtOAc:hexanes) on silica gel to afford α,β-unsaturated ester **248** (35.5 mg, 54% yield). (The same result was obtained by using 1.05 equiv NaH instead of DBU.)

R_f = 0.62 (1:4 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (dt, *J* = 11.5, 7.2 Hz, 1H), 5.79 (dt, *J* = 11.5, 1.9 Hz, 1H), 4.79 (ddt, *J* = 13.6, 2.1, 1.1 Hz, 2H), 4.35 (dd, *J* = 7.0, 4.7 Hz, 1H), 3.70 (s, 3H), 3.31 (s, 3H), 3.30 (s, 3H), 2.80 – 2.71 (m, 2H), 2.37 (tt, *J* = 8.5, 6.5 Hz, 1H), 1.76 – 1.64 (m, 2H), 1.65 (dd, *J* = 1.5, 0.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 148.9, 146.3, 120.0, 112.7, 103.0, 53.2, 52.7, 51.2, 43.2, 35.9, 32.6, 18.4; IR (Neat Film NaCl) 2949, 2830, 1723, 1646, 1437, 1408, 1203, 1127, 1053, 892, 819 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{13}H_{21}O_4$ $[M+H]^+$-H_2 : 241.1440; found: 241.1431; $[\alpha]_D^{25.0}$ 3.04° (*c* 0.30, $CHCl_3$).

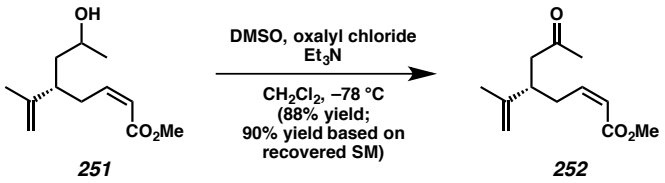


To a solution of acetal **248** (129 mg, 0.494 mmol, 1.00 equiv) in $CHCl_3$ (2.47 mL) was added 50% aq TFA (1.23 mL) at 0 °C. The reaction mixture was stirred for 3 h at 23 °C before it was quenched by the addition of sat. aq $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (3 x 4.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford aldehyde **250** (95.0 mg, 99% yield), which was used without further purification.

To a solution of aldehyde **250** (95.0 mg, 0.484 mmol, 1.00 equiv) in THF (5.00 mL) was added MeMgBr (3.0 M solution in diethyl ether; 0.21 mL, 0.629 mmol, 1.30 equiv) at –78 °C. The mixture was stirred for 1 h at –78 °C. Then, the solution was quenched by the addition of sat. aq $NaHCO_3$. The aqueous phase was extracted with EtOAc (3 x 5.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:4 EtOAc:hexanes) on silica gel to afford secondary alcohol **251** (65.5 mg, 64% yield).

R_f = 0.22 (1:4 EtOAc:hexanes); (due to the presence of diastereomeric mixtures, the ^1H NMR and ^{13}C NMR contained extra peaks. See the attached spectrum) ^1H NMR (400 MHz, $CDCl_3$) δ 6.18 (ddt, *J* = 11.5, 9.8, 7.4 Hz, 2H), 5.82 – 5.76 (m, 2H), 4.86 – 4.76 (m, 4H), 3.92 – 3.83 (m, 1H), 3.77 (ddt, *J* = 9.4, 6.3, 3.1 Hz, 1H), 3.70 (s, 6H), 2.87 (dddd, *J* = 15.1, 7.3, 5.0, 1.8 Hz, 1H), 2.74 (dddd, *J* = 8.3, 7.3, 5.1, 1.8 Hz, 2H), 2.64 – 2.55 (m, 1H), 2.49 (dddd, *J* = 10.0, 8.6, 6.5, 4.9 Hz, 1H), 2.37 (dddd, *J* = 9.8, 8.1, 6.7, 5.0 Hz, 1H), 1.68 (t, *J* = 1.2 Hz, 3H), 1.63 (dd, *J* = 1.5, 0.8 Hz, 3H), 1.55 – 1.42 (m, 4H), 1.19 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 149.2,

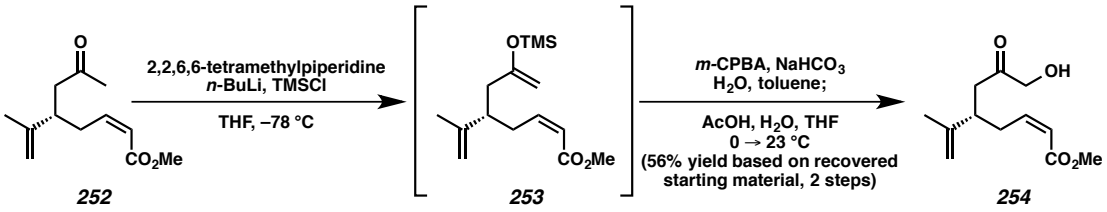
149.1, 147.7, 146.8, 119.9, 112.9, 112.4, 66.6, 65.9, 51.3, 51.2, 45.1, 44.1, 43.1, 42.4, 33.0, 32.0, 24.2, 23.5, 18.5, 18.1; IR (Neat Film NaCl) 3421, 2966, 2928, 1724, 1646, 1438, 1408, 1203, 1170, 892, 819 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{12}H_{21}O_3$ $[M+H]^+$: 213.1491; found 213.1489; $[\alpha]_D^{25.0}$ –9.52° (*c* 0.11, $CHCl_3$).



251 ***252***

To a stirred solution of oxalyl chloride (0.21 mL, 2.40 mmol, 1.50 equiv) in CH_2Cl_2 (8.00 mL) was added DMSO (0.34 mL, 4.79 mmol, 3.00 equiv) dropwise at –78 °C. The reaction mixture was stirred for 15 min, and alcohol **251** (339 mg, 1.60 mmol, 1.00 equiv) in CH_2Cl_2 (1.00 mL) was added dropwise. The solution was stirred for 2 h and 30 min at –78 °C, then Et_3N (1.56 mL, 7.00 equiv) was added. After 90 min at –78 °C, the solution was warmed to 23 °C over 30 min and quenched with H_2O. The aqueous phase was extracted with CH_2Cl_2 (3 x 10.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:4 EtOAc:hexanes) on silica gel to afford ketone **252** (295 mg, 88% yield).

R_f = 0.35 (1:4 EtOAc:hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 6.19 – 6.10 (m, 1H), 5.81 (dt, *J* = 11.6, 1.7 Hz, 1H), 4.79 (p, *J* = 1.5 Hz, 1H), 4.74 (dt, *J* = 1.7, 0.8 Hz, 1H), 3.70 (s, 3H), 2.84 – 2.73 (m, 3H), 2.61 – 2.46 (m, 2H), 2.12 (d, *J* = 0.5 Hz, 3H), 1.68 (dd, *J* = 1.5, 0.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.8, 166.9, 148.3, 146.2, 120.4, 112.3, 51.3, 47.6, 42.1, 32.4, 30.6, 19.5; IR (Neat Film NaCl) 2951, 1718, 1647, 1437, 1204, 1272, 821 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{19}O_3$ $[M+H]^+$: 211.1329; found: 211.1327; $[\alpha]_D^{25.0}$ –9.42° (*c* 0.15, $CHCl_3$).



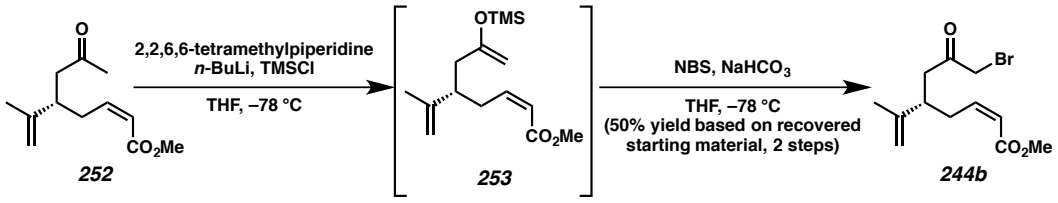
252 ***253*** ***254***

To a solution of 2,2,6,6-tetramethylpiperidine (50 μL, 0.296 mmol, 1.50 equiv) in THF (2.00 mL) was added *n*-BuLi (2.5 M in hexane; 0.12 mL, 0.296 mmol, 1.50 equiv) at 0 °C. The reaction mixture was stirred for 15 min at 0 °C, and TMSCl (0.13 mL, 0.990 mmol, 5.00 equiv) was added at –78 °C. Then, methyl ketone **252** (42.0 mg, 0.198 mmol, 1.00 equiv) in THF (1.00 mL) was added dropwise at –78 °C. The solution was stirred for 1 h and quenched with Et_3N, followed by sat. aq $NaHCO_3$. The aqueous phase was extracted with EtOAc (3 x 2.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was quickly filtered by column chromatography (1:8 EtOAc:hexanes) on silica gel to afford silyl ether **253**, which was used without further purification.

To a solution of *m*-CPBA (75%; 41.0 mg, 0.178 mmol, 0.90 equiv) in toluene (2.74 mL) was added solid $NaHCO_3$ (35.0 mg, 0.411 mmol, 2.08 equiv). The heterogeneous mixture was stirred for 15 min at 23 °C, then H_2O (0.40 mL) was added. Silyl ether **253** in toluene (0.50 mL) was added dropwise to the reaction mixture at 0 °C. After the solution was stirred for 30 min at 0 °C, sat. aq $NaHCO_3$ was added and stirred for 10 min at 0 °C. The aqueous phase was extracted with EtOAc (3 x 3.00 mL). The combined organic phases were washed with $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. To the residue dissolved in THF (0.30 mL) and H_2O (0.17 mL) was added AcOH (0.17 mL). The mixture was stirred for 2 h at 23 °C. Then, the solution was diluted with EtOAc and H_2O, and solid $NaHCO_3$ was added until the gas evolution ceased. The aqueous phase was extracted with EtOAc (3 x 1.00 mL). The combined organic phases were washed with brine,

dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:4 EtOAc:hexanes) on silica gel to afford α-hydoxyketone **254** (12.0 mg, 56% yield based on recovered starting material, 2 steps).

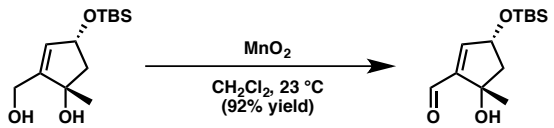
R_f = 0.35 (1:4 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (dt, *J* = 11.5, 7.1 Hz, 1H), 5.83 (ddd, *J* = 11.6, 2.0, 1.3 Hz, 1H), 4.82 (p, *J* = 1.5 Hz, 1H), 4.75 (dt, *J* = 1.6, 0.8 Hz, 1H), 4.20 (d, *J* = 3.0 Hz, 2H), 3.71 (s, 3H), 3.05 (s, br, 1H), 2.91 – 2.71 (m, 3H), 2.62 – 2.43 (m, 2H), 1.69 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.6, 166.8, 147.6, 145.5, 120.8, 112.8, 68.8, 51.3, 42.3, 42.1, 32.4, 19.5; IR (Neat Film NaCl) 2917, 1716, 1440, 1205, 1172 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{12}H_{19}O_4$ $[M+H]^+$: 227.1283; found: 227.1288; $[\alpha]_D^{25.0}$ –4.11° (*c* 0.09, $CHCl_3$).



To a solution of 2,2,6,6-tetramethylpiperidine (0.23 mL, 1.39 mmol, 1.60 equiv) in THF (8.70 mL) was added *n*-BuLi (1.98 M in hexane; 0.70 mL, 1.39 mmol, 1.60 equiv) at 0 °C. The reaction mixture was stirred for 15 min at 0 °C, and TMSCl (0.55 mL, 4.35 mmol, 5.00 equiv) was added at –78 °C. Then, methyl ketone **252** (183 mg, 0.870 mmol, 1.00 equiv) in THF (1.00 mL) was added dropwise at –78 °C. The solution was stirred for 1 h and quenched with Et_3N, followed by sat. aq $NaHCO_3$. The aqueous phase was extracted with EtOAc (3 x 10.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was quickly filtered by column chromatography (1:8 EtOAc:hexanes) on silica gel to afford silyl ether **253**, which was used without further purification.

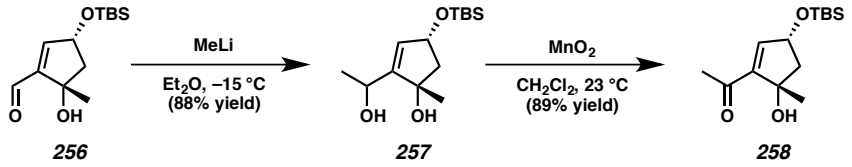
A solution of silyl ether **253** in THF (8.70 mL) at –78 °C was treated with solid $NaHCO_3$ (132 mg, 1.57 mmol, 1.80 equiv) and stirred for 10 min at –78 °C. NBS (248 mg, 1.39 mmol, 1.60 equiv) was then added portionwise and stirred for 15 min at –78 °C. The solvent was evaporated and the residue was purified by column chromatography (1:8 EtOAc:hexanes) on silica gel to afford α-bromoketone **244b** (55.0 mg, 50% yield based on recovered starting material, 2 steps).

R_f = 0.65 (1:4 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (dt, *J* = 11.5, 7.2 Hz, 1H), 5.83 (dt, *J* = 11.6, 1.6 Hz, 1H), 4.82 (p, *J* = 1.5 Hz, 1H), 4.77 (dt, *J* = 1.5, 0.8 Hz, 1H), 3.87 (d, *J* = 1.0 Hz, 2H), 3.71 (s, 3H), 2.89 – 2.68 (m, 6H), 1.72 – 1.69 (m, 3H), 1.56 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9, 166.9, 147.8, 145.7, 120.7, 112.7, 51.3, 43.7, 42.1, 34.8, 32.2, 19.7; IR (Neat Film NaCl) 2949, 2360, 1716, 1645, 1439, 1203, 1172 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{11}H_{14}O_2Br$ [M-OMe]$^+$: 257.0177; found: 257.0170; $[\alpha]_D^{25.0}$ –4.06° (*c* 0.09, $CHCl_3$).



255 ***256***

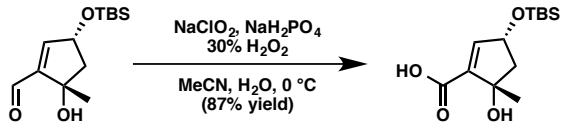
To a stirred solution of diol **255** (20.0 mg, 0.0774 mmol, 1.00 equiv) in CH_2Cl_2 (0.80 mL) was added MnO_2 (85%; 119 mg, 1.16 mmol, 15.0 equiv). The solution was stirred for 12 h at 23 °C. Solids were removed via a filtration through a celite plug (rinsed with CH_2Cl_2) and the resulting solution was concentrated under reduced pressure. The residue was purified by column chromatography (1:4 EtOAc:hexanes) on silica gel to afford aldehyde **256** (18.3 mg, 92% yield). All the spectrum data matched with those reported in ref 6a.



256 ***257*** ***258***

To a solution of aldehyde **256** (100 mg, 0.390 mmol, 1.00 equiv) in Et_2O (2.00 mL) was added MeLi (1.6 M in diethyl ether; 1.95 mL, 3.12 mmol, 8.00 equiv) at –10 °C. The solution was stirred for 2 h and quenched with sat. aq NH_4Cl. The solution was poured into H_2O. The aqueous phase was extracted with EtOAc (3 x 3.00 mL), washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:2 EtOAc:hexanes) on silica gel to afford alcohol **257** (93.4 mg, 88% yield).

To a stirred solution of alcohol **257** (162 mg, 0.594 mmol, 1.00 equiv) in CH_2Cl_2 (6.00 mL) was added MnO_2 (85%; 1.20 g, 11.9 mmol, 20.0 equiv). The solution was stirred for 12 h at 23 °C. Solids were removed via a filtration through a celite plug (rinsed with CH_2Cl_2) and the resulting solution was concentrated under reduced pressure. The residue was purified by column chromatography (1:4 EtOAc:hexanes) on silica gel to afford ketone **258** (143 mg, 89% yield). All the spectrum data matched with those reported in ref 6a.

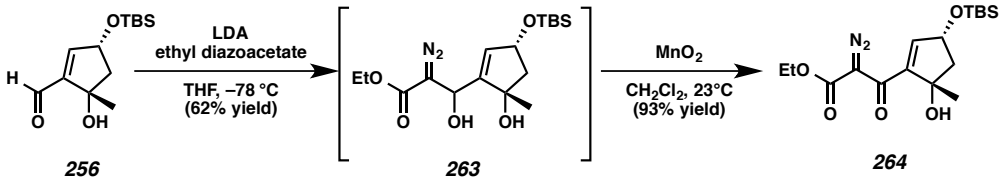


256 ***260***

To a stirred solution of aldehyde **256** (18.3 mg, 0.0714 mmol, 1.00 equiv) in MeCN (0.70 mL) were added NaH_2PO_4 (30.0 mg, 0.25 mmol, 3.50 equiv) in H_2O (0.50 mL) and 30% H_2O_2 (10 μL) at 0 °C. Then, a solution of $NaClO_2$ (23.0 mg, 0.25 mmol, 3.50 equiv) in H_2O (0.70 mL) was added dropwise in 1 h at 0 °C. The reaction

mixture was stirred for 10 min and quenched with sat. aq Na_2SO_3. The aqueous phase was extracted with EtOAc (2.00 mL). The combined aqueous phases were acidified with 2N HCl to make the solution pH 5–6. The aqueous phase was extracted with EtOAc (3 x 4.00 mL) washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford acid **260** (17.0 mg, 87% yield).

R_f = 0.15 (1:1 EtOAc:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (d, *J* = 1.8 Hz, 1H), 4.75 (td, *J* = 6.7, 1.9 Hz, 1H), 2.50 (dd, *J* = 12.9, 6.9 Hz, 1H), 2.09 – 2.03 (m, 1H), 1.48 (d, *J* = 0.7 Hz, 3H), 0.90 (s, 9H), 0.10 (d, *J* = 3.0 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 147.9, 139.6, 79.5, 72.7, 51.3, 27.7, 25.9, 18.2, -4.5, -4.6; IR (Neat Film NaCl) 2929, 2857, 1701, 1362, 1258, 1097, 898, 837, 778 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{12}H_{19}O_4$ $[M+H]^+$-H_2: 271.1366; found: 271.1357; $[\alpha]_D^{25.0}$ 185.9° (*c* 0.31, $CHCl_3$).



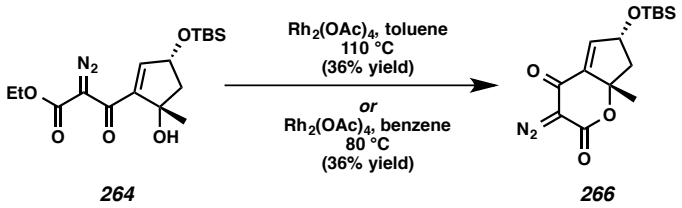
256 ***263*** ***264***

To a solution of aldehyde **256** (15.0 mg, 0.0585 mmol, 1.00 equiv) and ethyl diazoacetate (22 μL, 0.205 mmol, 3.50 equiv) in THF (0.60 mL) was added LDA (0.20 M solution in THF; 0.44 mL, 0.088 mmol, 1.50 equiv) at –78 °C. The reaction mixture was stirred for 10 min and quenched with sat. aq NH_4Cl. The aqueous phase was extracted with EtOAc (3 x 1.00 mL) washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford alcohol **263**, which was used without further purification (13.5 mg, 62% yield).

To a solution of alcohol **263** (13.0 mg, 0.0351 mmol, 1.00 equiv) in CH_2Cl_2 (0.40 mL) was added MnO_2 (85%; 72.0 mg, 0.702 mmol, 20.0 equiv) at 23 °C. The reaction

mixture was stirred overnight. Solids were removed via a filtration through a celite plug (rinsed with CH_2Cl_2) and the resulting solution was concentrated under reduced pressure. The residue was purified by column chromatography (1:4 EtOAc:hexanes) on silica gel to afford diazo **264** (12.0 mg, 93% yield).

R_f = 0.56 (1:2 EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.27 (d, *J* = 2.0 Hz, 1H), 4.79 (ddd, *J* = 6.9, 5.6, 2.0 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 2.45 (dd, *J* = 13.0, 6.9 Hz, 1H), 2.01 (dd, *J* = 13.0, 5.7 Hz, 1H), 1.39 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.4, 161.4, 145.4, 141.0, 82.3, 73.8, 62.0, 51.7, 27.3, 26.0, 25.8, 18.3, 14.4, -4.5, -4.6; IR (Neat Film NaCl) 3499, 2930, 2857, 2141, 1728, 1471, 1370, 1300, 1259, 1094, 906, 837 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{17}H_{29}O_5N_2Si$ $[M+H]^+$: 369.1846; found 369.1845; $[\alpha]_D^{25.0}$ 14.2° (*c* 0.25, $CHCl_3$).

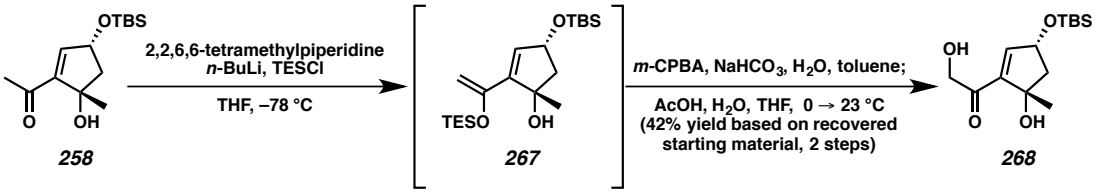


264 ***266***

To a solution of diazo **264** (12.0 mg, 0.0326 mmol, 1.00 equiv) in toluene (0.30 mL), was added dirhodium tetraacetate (0.70 mg, 0.00163 mmol, 0.05 equiv). The solution was refluxed under argon for 10 min. Solids were removed via a filtration through a celite plug (rinsed with EtOAc) and the resulting solution was concentrated under reduced pressure. The residue was purified by column chromatography (1:4 EtOAc:hexanes) on silica gel to afford lactone **266** (4.0 mg, 36% yield). (Similar result was obtained with benzene solvent at 80 °C.)

R_f = 0.30 (1:2 EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (d, *J* = 1.6 Hz, 1H), 4.85 (ddd, *J* = 7.1, 6.4, 1.7 Hz, 1H), 2.72 (dd, *J* = 12.6, 6.4 Hz, 1H), 2.40 – 2.30

(m, 1H), 1.58 (s, 3H), 0.90 (s, 9H), 0.11 (d, J = 4.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.7, 175.1, 142.6, 138.1, 87.6, 73.5, 51.1, 26.9, 25.8, 18.2, 14.3, -4.6, -4.7; IR (Neat Film NaCl) 2953, 2856, 2146, 1713, 1661, 1330, 1302, 1097, 1066, 837 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{15}H_{23}O_4N_2Si$ $[M+H]^+$: 323.1427; found 323.1417; $[\alpha]_D^{25.0}$ 7.77° (*c* 0.20, $CHCl_3$).

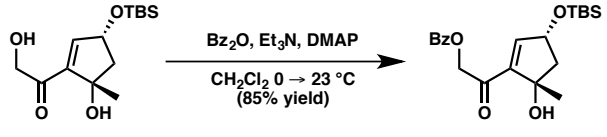


To a solution of 2,2,6,6-tetramethylpiperidine (0.20 mL, 1.19 mmol, 5.00 equiv) in THF (2.40 mL) was added *n*-BuLi (1.96 M in hexane; 0.61 mL, 1.19 mmol, 5.00 equiv) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, and TMSCl (0.20 mL, 1.19 mmol, 5.00 equiv) was added at –78 °C. Methyl ketone **258** (50.0 mg, 0.238 mmol, 1.00 equiv) in THF (0.60 mL) was added dropwise at –78 °C. The solution was stirred for 30 min and quenched with Et_3N, followed by sat. aq $NaHCO_3$. The aqueous phase was extracted with EtOAc (3 x 3.50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was quickly filtered by column chromatography (1:8 EtOAc:hexanes) on silica gel to afford silyl ether **267**, which was used without further purification.

To a solution of *m*-CPBA (75%; 50.0 mg, 0.217 mmol, 0.91 equiv) in toluene (3.34 mL) was added $NaHCO_3$ (55.0 mg, 0.651 mmol, 2.74 equiv). The heterogeneous mixture was stirred for 15 min at 23 °C, then H_2O (0.56 mL) was added. Silyl ether **267** in toluene (0.50 mL) was added dropwise to the reaction mixture at 0 °C. After the solution was stirred for 45 min at 0 °C, sat. aq $NaHCO_3$ was added and stirred for 10 min at 0 °C. The aqueous phase was extracted with EtOAc (3 x 3.00 mL). The

combined organic phases were washed with $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. To the residue dissolved in THF (0.42 mL) and H_2O (0.21 mL) was added AcOH (0.21 mL). The mixture was stirred for 2 h at 23 °C. After the solution was diluted with EtOAc and H_2O, solid $NaHCO_3$ was added until the gas evolution ceased. The aqueous phase was extracted with EtOAc (3 x 2.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:4 EtOAc:hexanes) on silica gel to afford α-hydoxyketone **268** (12.0 mg, 42% yield based on recovered starting material, 2 steps).

R_f = 0.30 (1:2 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (d, *J* = 1.9 Hz, 1H), 4.79 (td, *J* = 6.9, 1.9 Hz, 1H), 4.59 (d, *J* = 18.6 Hz, 1H), 4.51 (d, *J* = 18.6 Hz, 1H), 3.12 (s, br, 1H), 2.44 (dd, *J* = 12.8, 7.0 Hz, 1H), 2.05 – 1.99 (m, 1H), 1.47 (s, 3H), 0.90 (s, 9H), 0.10 (d, *J* = 4.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4, 145.8, 143.8, 80.5, 73.4, 65.8, 50.9, 28.0, 25.9, 18.2, -4.5, -4.6; IR (Neat Film NaCl) 3418, 2929, 2857, 1682, 1361, 1259, 1093, 912, 835 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{14}H_{27}O_4Si$ $[M+H]^+$:287.1679; found: 287.1677; $[\alpha]_D^{25.0}$ 78.9° (*c* 0.10, $CHCl_3$).

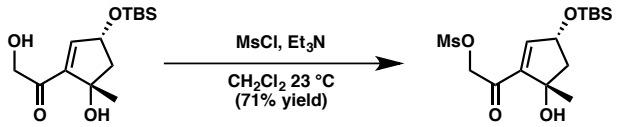


268 ***269***

To a solution of α-hydroxyketone **268** (9.80 mg, 0.0342 mmol, 1.00 equiv) in CH_2Cl_2 (0.30 mL) were added DMAP (8.40 mg, 0.0684 mmol, 2.00 equiv) and Et_3N (38 μL, 0.274 mmol, 8.00 equiv). The solution was cooled to 0 °C and benzoic anhydride (15.0 mg, 0.0684 mmol, 2.00 equiv) was added in one portion. After 30 min, the

solution was warmed to 23 °C and stirred for 2 h. After the reaction was done, water was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 1.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:4 EtOAc:hexanes) on silica gel to afford benzoate **269** (11.4 mg, 85% yield).

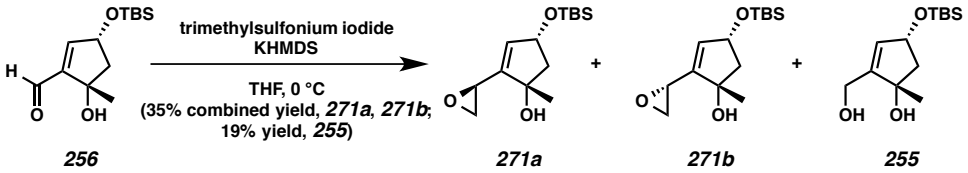
R_f = 0.75 (1:2 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.07 (m, 2H), 7.65 – 7.55 (m, 1H), 7.51 – 7.42 (m, 2H), 6.65 (d, *J* = 1.9 Hz, 1H), 5.30 (d, *J* = 16.4 Hz, 1H), 5.18 (d, *J* = 16.4 Hz, 1H), 4.81 (td, *J* = 7.1, 1.9 Hz, 1H), 2.44 (dd, *J* = 12.7, 7.0 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.47 (s, 3H), 0.91 (s, 9H), 0.11 (d, *J* = 4.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6, 166.0, 145.5, 144.2, 133.6, 130.1, 129.3, 128.7, 80.6, 73.4, 66.3, 50.7, 28.1, 25.9, 18.3, -4.5, -4.6; IR (Neat Film NaCl) 2928, 1728, 1691, 1259, 1098, 836 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{21}H_{29}O_5Si$ $[M+H]^+$-H_2: 389.1784; found: 389.1783; $[\alpha]_D^{25.0}$ 40.9° (*c* 0.16, $CHCl_3$).



268 ***270***

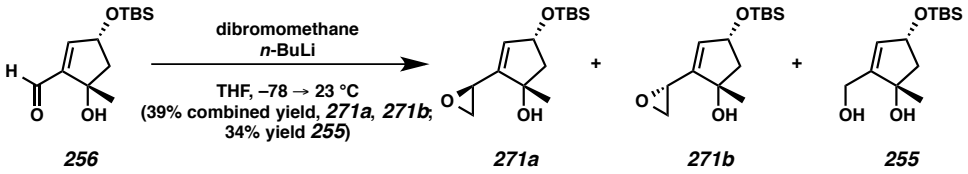
To a stirred solution of α-hydroxyketone **268** (49.0 mg, 0.171 mmol, 1.00 equiv) in CH_2Cl_2 (1.71 mL) were added Et_3N (72 μL, 0.513 mmol, 3.00 equiv) and MsCl (20 μL, 0.257 mmol, 1.50 equiv) at 0 °C. The solution was stirred at 0 °C for 2 h and quenched with H_2O. The aqueous phase was extracted with CH_2Cl_2 (3 x 2.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:4 EtOAc:hexanes) on silica gel to afford mesylate **270** (44.0 mg, 71% yield).

R_f = 0.43 (1:4 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (d, *J* = 1.9 Hz, 1H), 5.15 (s, 2H), 4.78 (td, *J* = 7.0, 1.9 Hz, 1H), 3.23 (s, 3H), 2.44 (dd, *J* = 12.8, 7.0 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.95 (s, br, 1H), 1.46 (s, 3H), 0.90 (s, 9H), 0.11 (d, *J* = 4.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.2, 146.5, 143.8, 80.6, 73.3, 69.8, 50.7, 39.3, 27.9, 25.9, 18.2, -4.5, -4.7; IR (Neat Film NaCl) 2930, 2856, 1693, 1354, 1259, 1173, 1091, 1042, 959, 912, 835, 777 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{15}H_{27}O_5SiS$ [M-OH]$^•$: 347.1348; found: 347.1357; $[\alpha]_D^{25.0}$ 36.3° (*c* 0.12, $CHCl_3$).



256 ***271a*** ***271b*** ***255***

To a solution of trimethylsulfonium iodide (18.0 mg, 0.0877 mmol, 1.50 equiv) in THF (0.60 mL) was added dry KHMDS (17.0 mg, 0.0877 mmol, 1.50 equiv) in portions over 30 min at 0 °C. The mixture was stirred for 1 h. Then, a solution of aldehyde **256** in THF (0.30 mL) was added to a reaction vessel. The solution was stirred for 30 min and quenched with H_2O. The aqueous phase was extracted with EtOAc (3 x 1.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:4 EtOAc:hexanes) on silica gel to afford epoxide **271a** and **271b** (5.50 mg, 35% yield). See below for characterization data.

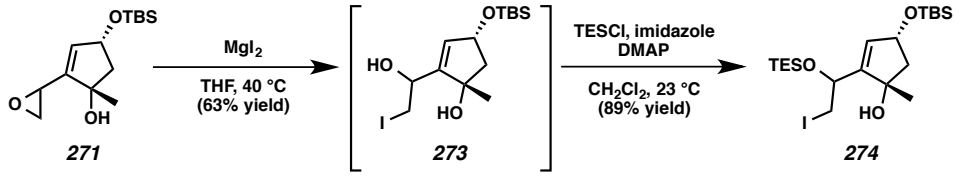


256 ***271a*** ***271b*** ***255***

To a solution of aldehyde **256** (155 mg, 0.604 mmol, 1.00 equiv) and dibromomethane (51.0 μL, 0.725 mmol, 1.20 equiv) in THF (3.02 mL) was added *n*-BuLi (2.4 M solution in hexane; 0.28 mL, 0.665 mmol, 1.10 equiv) dropwise over 30 min at –78 °C. The reaction mixture was slowly warmed to 23 °C and stirred overnight. Then, the reaction was quenched with sat. aq NH_4Cl. The aqueous phase was extracted with EtOAc (3 x 3.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:4 EtOAc:hexanes) on silica gel to afford epoxide **271a** and **271b** (64.0 mg, 39% yield).

R_f = 0.56 (1:2 EtOAc:hexanes); Diastereomer 1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (dd, *J* = 2.2, 1.0 Hz, 1H), 4.61 (ddd, *J* = 6.5, 3.8, 2.3 Hz, 1H), 3.55 (ddt, *J* = 4.3, 2.7, 0.8 Hz, 1H), 2.97 (dd, *J* = 6.0, 4.2 Hz, 1H), 2.74 (dd, *J* = 6.0, 2.7 Hz, 1H), 2.36 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.06 (d, *J* = 15.5 Hz, 1H), 1.89 (dd, *J* = 13.5, 3.8 Hz, 1H), 1.37 (s, 3H), 0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4, 131.1, 81.3, 73.3, 52.6, 49.7, 48.2, 26.1, 26.0, 18.3, -4.6; IR (Neat Film NaCl) 3408, 2929, 2856, 1361, 1252, 1085, 835 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{14}H_{25}O_3Si$ $[M+H]^+$-H_2: 269.1573; found: 269.1568; $[\alpha]_D^{25.0}$ 44.7° (*c* 0.08, $CHCl_3$).

Diastereomer 2: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (dd, *J* = 2.1, 1.0 Hz, 1H), 4.65 (dddd, *J* = 6.4, 4.4, 2.1, 1.1 Hz, 1H), 3.50 (ddt, *J* = 3.7, 2.7, 1.0 Hz, 1H), 3.04 (dd, *J* = 5.7, 4.2 Hz, 1H), 2.88 (dd, *J* = 5.7, 2.7 Hz, 1H), 2.44 (dd, *J* = 13.3, 6.5 Hz, 1H), 2.15 (s, 1H), 1.90 (dd, *J* = 13.3, 4.4 Hz, 1H), 1.44 (s, 3H), 0.90 (s, 9H), 0.09 (d, *J* = 1.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2, 131.1, 81.1, 73.2, 52.8, 49.5, 47.5, 26.1, 26.0, 18.3, -4.6; IR (Neat Film NaCl) 2956, 2929, 2856, 1361, 1253, 1086, 836, 776 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{14}H_{25}O_3Si$ $[M+H]^+$-H_2: 269.1573; found: 269.1577; $[\alpha]_D^{25.0}$ 11.5° (*c* 0.15, $CHCl_3$).



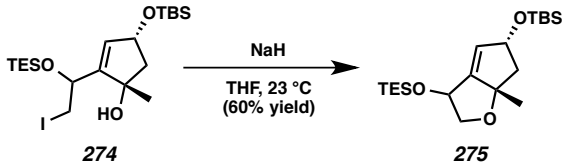
271 *273* *274*

To a solution of epoxide **271** (64.0 mg, 0.237 mmol, 1.00 equiv) in THF (1.19 mL) was added MgI_2 (69.0 mg, 0.248 mmol, 1.05 equiv). The reaction mixture was stirred overnight at 40 °C and then quenched with H_2O. The aqueous phase was extracted with EtOAc (3 x 2.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:4 EtOAc:hexanes) on silica gel to afford iodohydrin **273** (59.0 mg, 63% yield).

To a solution of iodohydrin **273** (13.5 mg, 0.0338 mmol, 1.00 equiv) in CH_2Cl_2 (0.20 mL) were added imidazole (11.5 mg, 0.169 mmol, 5.00 equiv), DMAP (0.20 mg, 0.0016 mmol, 0.05 equiv), and TESCl (6.20 μL, 0.0371 mmol, 1.10 equiv). The reaction mixture was stirred overnight at 23 °C and then H_2O was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 0.50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:8 EtOAc:hexanes) on silica gel to afford silyl ether **274** (11.5 mg, 89% yield).

R_f = 0.80 (1:4 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (ddd, *J* = 2.1, 1.3, 0.5 Hz, 1H), 4.57 (dtd, *J* = 5.4, 3.0, 1.4 Hz, 1H), 4.30 (ddt, *J* = 6.5, 3.9, 1.3 Hz, 1H), 3.59 (dd, *J* = 10.2, 3.8 Hz, 1H), 3.35 (dd, *J* = 10.2, 6.4 Hz, 1H), 2.26 – 2.20 (m, 1H), 1.91 – 1.84 (m, 1H), 1.33 (s, 3H), 0.99 – 0.95 (m, 9H), 0.88 (s, 9H), 0.65 – 0.60 (m, 6H), 0.08 (d, *J* = 0.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.8, 132.3, 80.6, 72.8, 69.2, 52.5, 26.0, 25.4, 18.2, 15.4, 7.1, 5.0, -4.4, -4.6; IR (Neat Film NaCl) 2955, 1256,

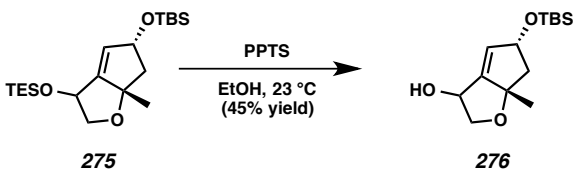
1088, 836, 740 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{20}H_{40}O_3Si_2I$ $[M+H]^+-H_2$: 511.1561; found: 511.1573; $[\alpha]_D^{25.0}$ 4.31° (*c* 0.20, $CHCl_3$).



274 ***275***

To a solution of NaH (60%, 1.00 mg, 0.0246 mmol, 1.10 equiv) in THF (1.12 mL) was added silyl ether **274** (11.5 mg, 0.0224 mmol, 1.00 equiv) in THF (0.50 mL) at 23 °C. The solution was stirred overnight and then H_2O was added. The aqueous phase was extracted with EtOAc (3 x 1.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:8 EtOAc:hexanes) on silica gel to afford ether **275** (5.20 mg, 60% yield).

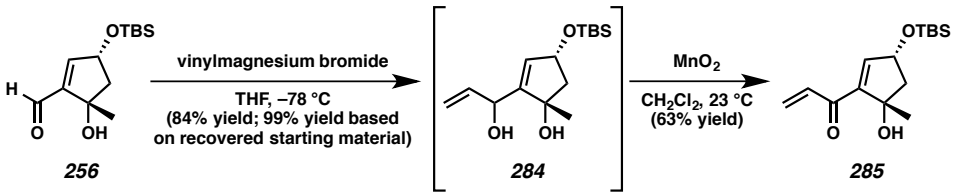
R_f = 0.23 (1:8 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (dd, *J* = 2.2, 1.1 Hz, 1H), 4.99 (dddd, *J* = 7.4, 5.4, 3.2, 1.1 Hz, 1H), 4.84 (tdd, *J* = 7.5, 3.2, 2.2 Hz, 1H), 4.16 (t, *J* = 7.9 Hz, 1H), 3.56 (dd, *J* = 8.2, 7.2 Hz, 1H), 2.40 (dd, *J* = 11.5, 5.4 Hz, 1H), 2.00 (ddd, *J* = 11.5, 7.3, 1.0 Hz, 1H), 1.21 (d, *J* = 0.9 Hz, 3H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.90 (s, 9H), 0.68 – 0.52 (m, 6H), 0.10 – 0.06 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1, 126.0, 89.1, 79.3, 73.6, 68.2, 54.4, 26.0, 6.9, 4.8, -4.5; IR (Neat Film NaCl) 2955, 2927, 2875, 2360, 1459, 1256, 1089, 835 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{20}H_{39}O_3Si_2$ $[M+H]^+-H_2$: 383.2438; found: 383.2409; $[\alpha]_D^{25.0}$ 12.7° (*c* 0.15, $CHCl_3$).



275 ***276***

To a solution of ether **275** (5.10 mg, 0.0132 mmol, 1.00 equiv) in EtOH (0.13 mL) was added PPTS (0.30 mg, 0.00132 mmol, 0.10 equiv) and stirred at 23 °C for 30 min. The reaction was quenched with sat. aq $NaHCO_3$ and the aqueous phase was extracted with EtOAc (3 x 0.70 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:4 EtOAc:hexanes) on silica gel to afford alcohol **276** (1.61 mg, 45% yield).

R_f = 0.23 (1:8 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (dd, *J* = 2.2, 1.2 Hz, 1H), 5.14 – 5.03 (m, 1H), 4.86 (m, br, 1H), 4.35 (dd, *J* = 9.4, 7.5 Hz, 1H), 3.69 (dd, *J* = 9.4, 5.5 Hz, 1H), 2.43 (dd, *J* = 11.7, 5.5 Hz, 1H), 2.02 (ddd, *J* = 11.7, 7.3, 1.0 Hz, 1H), 1.22 (s, 3H), 0.90 (s, 9H), 0.09 (d, *J* = 5.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 126.3, 90.2, 79.9, 75.1, 68.6, 54.0, 26.0, 24.1, -4.5, -4.6; IR (Neat Film NaCl) 2929, 2857, 1361, 1256, 1084, 835, 776 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{14}H_{27}O_3Si$ $[M+H]^+$: 271.1730; found: 271.1734; $[\alpha]_D^{25.0}$ 33.7° (*c* 0.06, $CHCl_3$).

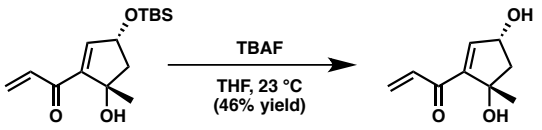


A flame-dried flask was charged with aldehyde **256** (399 mg, 1.56 mmol, 1.00 equiv) and THF (7.80 mL). Then, vinylmagnesium bromide (1.0 M solution in THF; 20.5 mL, 20.3 mmol, 13.0 equiv) was added to the solution at –78 °C and stirred for 3 h. The reaction was quenched with sat. aq NH_4Cl and the aqueous phase was extracted with EtOAc (3 x 10.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column

chromatography (1:2 EtOAc:hexanes) on silica gel to afford allyl alcohol **284** (371 mg, 84% yield).

To a solution of allyl alcohol **284** (371 mg, 1.30 mmol, 1.00 equiv) in CH_2Cl_2 (13.0 mL) was added MnO_2 (85%; 4.00 g, 39.1 mmol, 30.0 equiv). The mixture was stirred for 12 h. Solids were removed via a filtration through a celite plug (rinsed with CH_2Cl_2) and the resulting solution was concentrated under reduced pressure. The residue was purified by column chromatography (1:4 EtOAc:hexanes) on silica gel to afford vinyl ketone **285** (230 mg, 63% yield).

R_f = 0.55 (1:2 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (dd, *J* = 17.1, 10.5 Hz, 1H), 6.60 (d, *J* = 1.9 Hz, 1H), 6.35 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.80 (dd, *J* = 10.5, 1.6 Hz, 1H), 4.79 (td, *J* = 7.1, 1.9 Hz, 1H), 3.67 (s, 1H), 2.44 (dd, *J* = 12.7, 7.0 Hz, 1H), 2.04 (ddd, *J* = 12.6, 7.1, 0.9 Hz, 1H), 1.46 (s, 3H), 0.91 (s, 9H), 0.11 (d, *J* = 4.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.7, 147.0, 145.9, 132.3, 129.4, 80.4, 73.2, 51.0, 28.2, 25.9, 18.3, -4.4, -4.6; IR (Neat Film NaCl) 2955, 2929, 2856, 1658, 1605, 1361, 1259, 1091, 911, 837, 777 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{15}H_{25}O_3Si$ $[M+H]^+$-H_2: 281.1573; found: 281.1569; $[\alpha]_D^{25.0}$ 33.3° (*c* 0.06, $CHCl_3$).

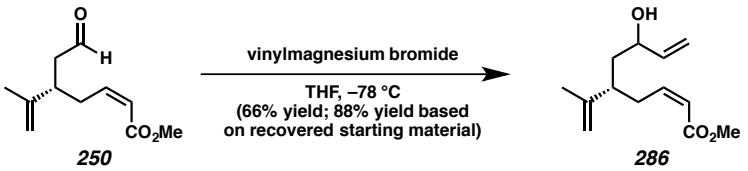


285 ***281***

To a solution of ketone **285** (22.1 mg, 0.0782 mmol, 1.00 equiv) in THF (0.80 mL) was added TBAF (1.0 M solution in THF; 0.16 mL, 0.156 mmol, 2.00 equiv) at 23 °C and stirred for 30 min. The reaction was quenched with sat. aq NH_4Cl. The aqueous phase was extracted with EtOAc (3 x 1.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was

purified by column chromatography (1:1 EtOAc:hexanes) on silica gel to afford diol **281** (6.00 mg, 46% yield).

R_f = 0.15 (1:1 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (dd, *J* = 17.1, 10.5 Hz, 1H), 6.68 (d, *J* = 2.1 Hz, 1H), 6.36 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.85 (dd, *J* = 10.5, 1.6 Hz, 1H), 4.82 (ddd, *J* = 7.4, 5.8, 2.1 Hz, 1H), 3.62 (s, br, 1H), 2.51 (dd, *J* = 13.4, 7.1 Hz, 1H), 2.01 (dd, *J* = 13.4, 5.7 Hz, 1H), 1.48 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.3, 148.2, 144.3, 132.6, 130.0, 81.2, 73.5, 50.2, 27.7; IR (Neat Film NaCl) 2922, 1657, 1605, 1407, 1264, 1223, 1148, 1067, 961, 796 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_9H_{13}O_3$ $[M+H]^+$: 169.0865; found: 169.0864; $[\alpha]_D^{25.0}$ 25.8° (*c* 0.10, $CHCl_3$).

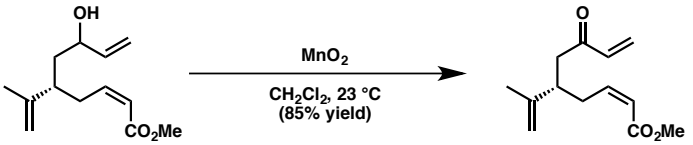


250 ***286***

To a stirred solution of aldehyde **250** (300 mg, 1.53 mmol, 1.00 equiv) in THF (15.3 mL) was added vinylmagnesium bromide (1.0 M solution in THF; 2.29 mmol, 1.50 equiv) at –78 °C. The reaction was stirred for 1 h at –78 °C and quenched with sat. aq NH_4Cl. The aqueous phase was extracted with EtOAc (3 x 6.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:4 EtOAc:hexanes) on silica gel to afford allyl alcohol **286** (227 mg, 66% yield).

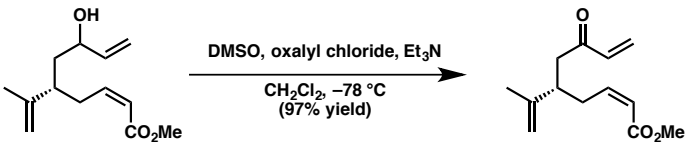
R_f = 0.32 (1:4 EtOAc:hexanes); (due to the presence of diastereomeric mixtures, the ^{1}H NMR and ^{13}C NMR contained extra peaks. See the attached spectrum) ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23 – 6.14 (m, 2H), 5.92 – 5.82 (m, 2H), 5.82 – 5.77 (m, 2H), 5.23 (ddt, *J* = 17.2, 5.0, 1.5 Hz, 2H), 5.10 (ddt, *J* = 13.4, 10.4, 1.4 Hz, 2H), 4.86 –

4.74 (m, 4H), 4.17 (q, *J* = 6.7 Hz, 1H), 4.13 – 4.07 (m, 1H), 3.71 – 3.68 (m, 6H), 2.91 – 2.81 (m, 1H), 2.76 (ddd, *J* = 7.3, 6.2, 1.8 Hz, 2H), 2.69 – 2.62 (m, 1H), 2.54 (dtd, *J* = 9.8, 7.6, 4.6 Hz, 2H), 2.37 (ddd, *J* = 15.1, 9.2, 5.8 Hz, 1H), 1.65 (dq, *J* = 1.5, 0.8 Hz, 3H), 1.63 – 1.51 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 149.1, 149.0, 147.1, 146.5, 141.5, 140.9, 119.9, 115.2, 114.3, 113.2, 112.6, 71.6, 70.9, 51.3, 51.2, 44.2, 40.7, 40.2, 32.9, 32.1, 18.6, 18.2; IR (Neat Film NaCl) 2929, 1722, 1644, 1439, 1202, 1168, 1124, 993 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{13}H_{21}O_3$ $[M+H]^+$: 225.1491; found: 225.1491.



286 ***287***

To a solution of allyl alcohol **286** (10.0 mg, 0.0446 mmol, 1.00 equiv) in CH_2Cl_2 (0.45 mL) was added MnO_2 (85%; 182 mg, 1.78 mmol, 40.0 equiv). The mixture was stirred for 12 h at 23 °C. Solids were removed via a filtration through a celite plug (rinsed with CH_2Cl_2) and the resulting solution was concentrated under reduced pressure. The residue was purified by column chromatography (1:6 EtOAc:hexanes) on silica gel to afford ketone **287** (8.41 mg, 85% yield). See below for characterization data.

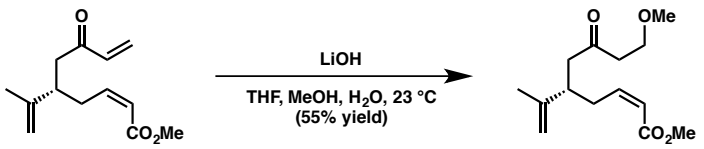


286 ***287***

To a stirred solution of oxalyl chloride (29 μL, 0.335 mmol, 1.50 equiv) in CH_2Cl_2 (1.10 mL) was added DMSO (47 μL, 0.669 mmol, 3.00 equiv) at –78 °C. The

solution was stirred for 15 min, then alcohol **286** (50.0 mg, 0.223 mmol, 1.00 equiv) in CH_2Cl_2 (0.6 mL) was added at –78 °C. The mixture was stirred for 3 h and 30 min at –78 °C, and then Et_3N (0.22 mL, 1.56 mmol, 7.00 equiv) was added. After 90 min at –78 °C, the solution was slowly warmed to 23 °C over 30 min and H_2O was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 2.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:6 EtOAc:hexanes) on silica gel to afford ketone **287** (47.9 mg, 97% yield).

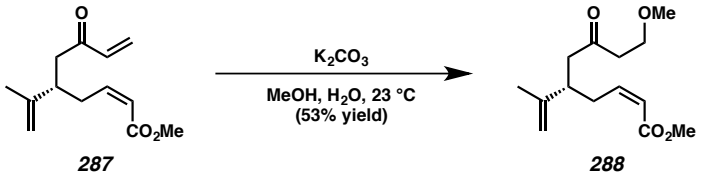
R_f = 0.55 (1:4 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (dd, *J* = 17.7, 10.4 Hz, 1H), 6.23 – 6.12 (m, 2H), 5.84 – 5.78 (m, 2H), 4.78 (p, *J* = 1.5 Hz, 1H), 4.74 (dt, *J* = 1.7, 0.8 Hz, 1H), 3.70 (s, 3H), 2.88 – 2.77 (m, 3H), 2.73 – 2.61 (m, 2H), 1.69 (dd, *J* = 1.5, 0.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.6, 166.9, 148.4, 146.1, 136.8, 128.4, 120.4, 112.3, 51.2, 43.5, 42.2, 32.4, 19.6; IR (Neat Film NaCl) 2950, 1716, 1645, 1439, 1407, 1204, 1173, 992, 895, 818 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{13}H_{19}O_3$ $[M+H]^+$: 223.1334; found: 223.1325; $[\alpha]_D^{25.0}$ –0.98° (*c* 0.28, $CHCl_3$).



287 ***288***

To a solution of ester **287** (10.0 mg, 0.0449 mmol, 1.00 equiv) in THF (0.50 mL) was added a solution of LiOH (2.20 mg, 0.0898 mmol, 2.00 equiv) in H_2O (0.20 mL). After 2 h at 23 °C, the aqueous phase was extracted with EtOAc (3 x 1.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:4

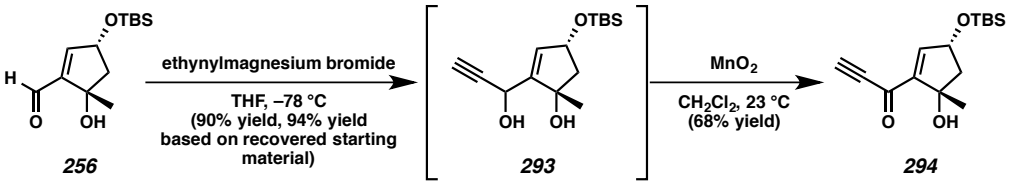
EtOAc:hexanes) on silica gel to afford Michael adduct **288** (6.28 mg, 55% yield). See below for characterization data.



287 ***288***

To a stirred solution of ester **287** (6.80 mg, 0.00306 mmol, 1.00 equiv) in MeOH (0.10 mL) and H_2O (0.10 mL) was added K_2CO_3 (17.0 mg, 0.122 mmol, 4.00 equiv). After 7 h, the aqueous phase was extracted with EtOAc (3 x 0.50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:4 EtOAc:hexanes) on silica gel to afford Michael adduct **288** (4.11 mg, 53% yield).

R_f = 0.25 (1:4 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (dt, *J* = 11.6, 7.1 Hz, 1H), 5.80 (dt, *J* = 11.6, 1.7 Hz, 1H), 4.78 (p, *J* = 1.5 Hz, 1H), 4.77 – 4.70 (m, 1H), 3.70 (s, 3H), 3.61 (t, *J* = 6.3 Hz, 2H), 3.31 (s, 3H), 2.88 – 2.71 (m, 3H), 2.63 (t, *J* = 6.3 Hz, 2H), 2.61 – 2.45 (m, 2H), 1.68 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0, 166.9, 148.4, 146.2, 120.3, 112.2, 67.6, 59.0, 51.2, 47.3, 43.3, 41.8, 32.3, 19.6; IR (Neat Film NaCl) 2922, 1719, 1646, 1438, 1203, 1172, 1117, 894, 820 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{14}H_{23}O_4$ $[M+H]^+$: 255.1596; found: 255.1604; $[\alpha]_D^{25.0}$ – 3.01° (*c* 0.36, $CHCl_3$).



256 ***293*** ***294***

A flame-dried flask was charged with aldehyde **256** (53.4 mg, 0.208 mmol, 1.00 equiv) and THF (1.04 mL). Then, ethynylmagnesium bromide (0.4M solution in THF; 5.20 mL, 2.08 mmol, 10.0 equiv) was added at –78 °C and stirred for 3 h. The reaction mixture was slowly warmed to 23 °C and stirred for 5 h. The reaction was quenched by adding sat. aq NH_4Cl. The aqueous phase was extracted with EtOAc (3 x 1.50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:2 EtOAc:hexanes) on silica gel to afford diol **293** (53.0 mg, 90% yield).

To a solution of diol **293** (11.1 mg, 0.0392 mmol, 1.00 equiv) in CH_2Cl_2 (0.40 mL) was added MnO_2 (85%; 52.0 mg, 0.510 mmol, 13.0 equiv). The mixture was stirred for 12 h. Solids were removed via a filtration through a celite plug (rinsed with CH_2Cl_2) and the resulting solution was concentrated under reduced pressure. The residue was purified by column chromatography (1:4 EtOAc:hexanes) on silica gel to afford ketone **294** (7.50 mg, 68% yield).

R_f = 0.56 (1:2 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (d, *J* = 1.9 Hz, 1H), 4.79 (tdd, *J* = 7.2, 1.9, 0.7 Hz, 1H), 3.29 (s, 1H), 3.09 (s, 1H), 2.47 (dd, *J* = 12.8, 7.0 Hz, 1H), 2.07 (ddt, *J* = 12.8, 7.1, 0.8 Hz, 1H), 1.58 (s, br, 1H), 1.46 (s, 3H), 0.91 (s, 9H), 0.11 (d, *J* = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 151.9, 147.9, 79.9, 79.5, 79.3, 72.9, 51.5, 27.8, 25.9, 18.2, -4.6; IR (Neat Film NaCl) 2929, 2955, 2857, 2097, 1638, 1361, 1272, 1259, 1209, 1093, 837, 777 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{25}O_3Si$ $[M+H]^+$: 281.1567; found: 281.1569; $[\alpha]_D^{25.0}$ 13.3° (*c* 0.06, $CHCl_3$).

5.5. References and Notes

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(3) The absolute stereochemistry has yet to be confirmed.

(4) (a) Li, Y.; Pattenden, G. *Nat. Prod. Rep*. **2011**, *28*, 429–440. (b) Li, Y.; Pattenden, G. *Nat. Prod. Rep*. **2011**, *28*, 1269–1310. (c) Chen, W.; Li, Y.; Guo, Y. *Acta Pharm. Sin. B* **2012**, *2*, 227–237.

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(6) (a) Craig, R. A., II Ph.D. Thesis, California Institute of Technology, Pasadena, CA, May 2015. (b) Roizen, J. L. Ph.D. Thesis, California Institute of Technology, Pasadena, CA, Nov 2009. (c) Tang, F. Thesis, Washington University, St. Louis, MO, May 2009. (d) Liu, G.; Romo, D. *Abstracts of Papers*, 237th ACS National Meeting, Salt Lake City, UT, Mar 22–26, 2009; American Chemical Society, 2009; ORGN-083. (e) O'Connell, C. E.; Frontier, A. J. *Abstracts of Papers*, 32nd Northeast Regional Meeting of the American Chemical Society, Rochester, NY, Oct 31–Nov 3, 2004; American Chemical Society, 2004, GEN-088. (f) Horn, E. J.; Silverston, J. S.; Vanderwal, C. D. *J. Org. Chem*. **2016**, DOI: 10.1021/acs.joc.5b02550.

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(8) For a synthetic procedure of phosphonates, see: Messik, F.; Oberthür, M. *Synthesis* **2013**, *45*, 167–170.

(9) (a) Moura-Letts, G.; Curran, D. P. *Org. Lett.* **2007**, *9*, 5–8. (b) Danishefsky, S. J.; DeNinno, M. P.; Chen, S.-h. *J. Am. Chem. Soc.* **1988**, *110*, 3929–3940. (c) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942–10953. (d) Panek, J. S.; Xu, F.; Rondón, A. C. *J. Am. Chem. Soc.* **1998**, *120*, 4113–4122.

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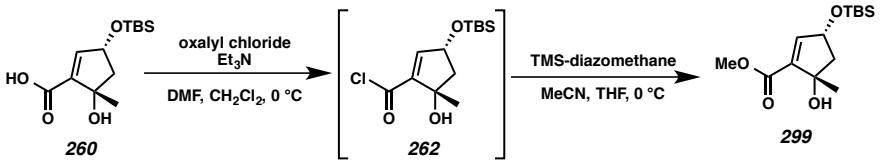
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(12) (a) Frontier, A. J.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 6151–6159. (b) Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2000**, *122*, 10482–10483.

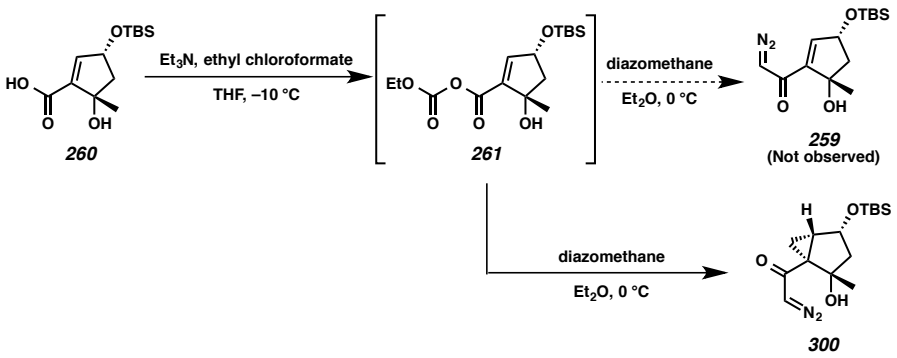
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(14) (a) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959–1964. (b) Arthuis, M.; Beaud, R.; Gandon, V.; Roulland, E. *Angew. Chem., Int. Ed.* **2012**, *51*, 10510–10514. (c) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 9279–9282.

(15) Treatment of TMS-diazomethane to acid chloride **262** afforded only methyl ester **299**.



(16) Addition of diazomethane to intermediate **261** furnished cyclopropane **300**.

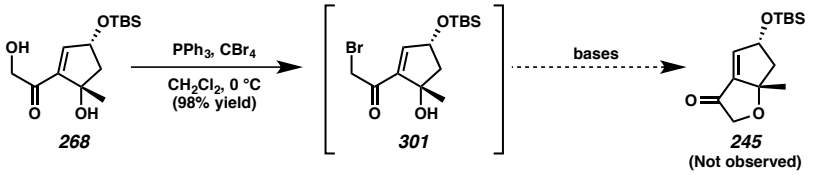


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(20) Attempted etherifications of α-bromoketone **301**, which was prepared from α-hydroxyketone **268**, was also unsuccessful.



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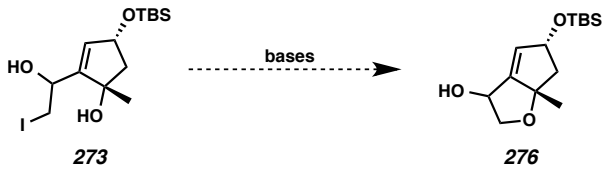
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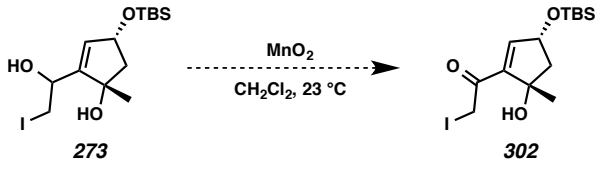
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(25) Only ketone **258** was observed when the reaction was conducted at 80 °C.

(26) Attempts on direct intramolecular etherification of iodohydrin **273** under basic conditions failed to produce **276**. In addition, oxidation of iodohydrin **273** with MnO_2 produced complex mixtures of byproducts.



273 ***276***



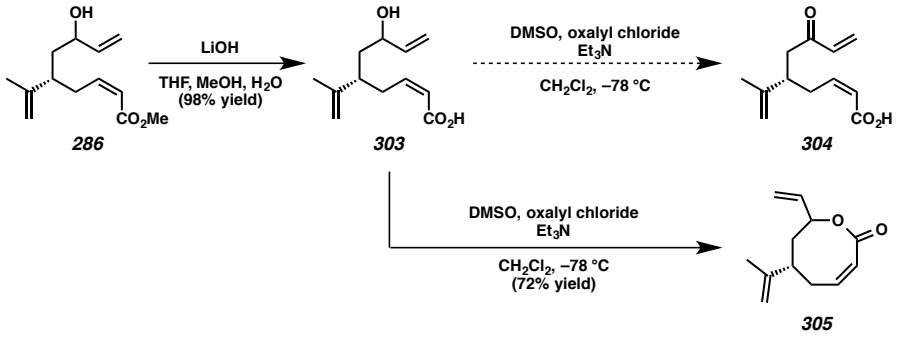
273 ***302***

(27) Because oxidation of secondary alcohol **276** with MnO_2 was conducted on small scale, the amount of the obtained ketone **245** was too little to be characterized by NMR analysis.

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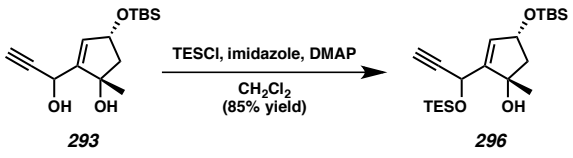
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(30) An attempt to oxidize secondary alcohol **303**, which was prepared by hydrolysis of ester **286** using Swern oxidation conditions, caused lactonization to give **305** instead of the desired **304**.



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(32) Silyl ether **296** was prepared from diol **293** with TESCl.



APPENDIX 13

Spectra Relevant to Chapter 5:

Synthetic Studies Toward Polycyclic Ineleganolide

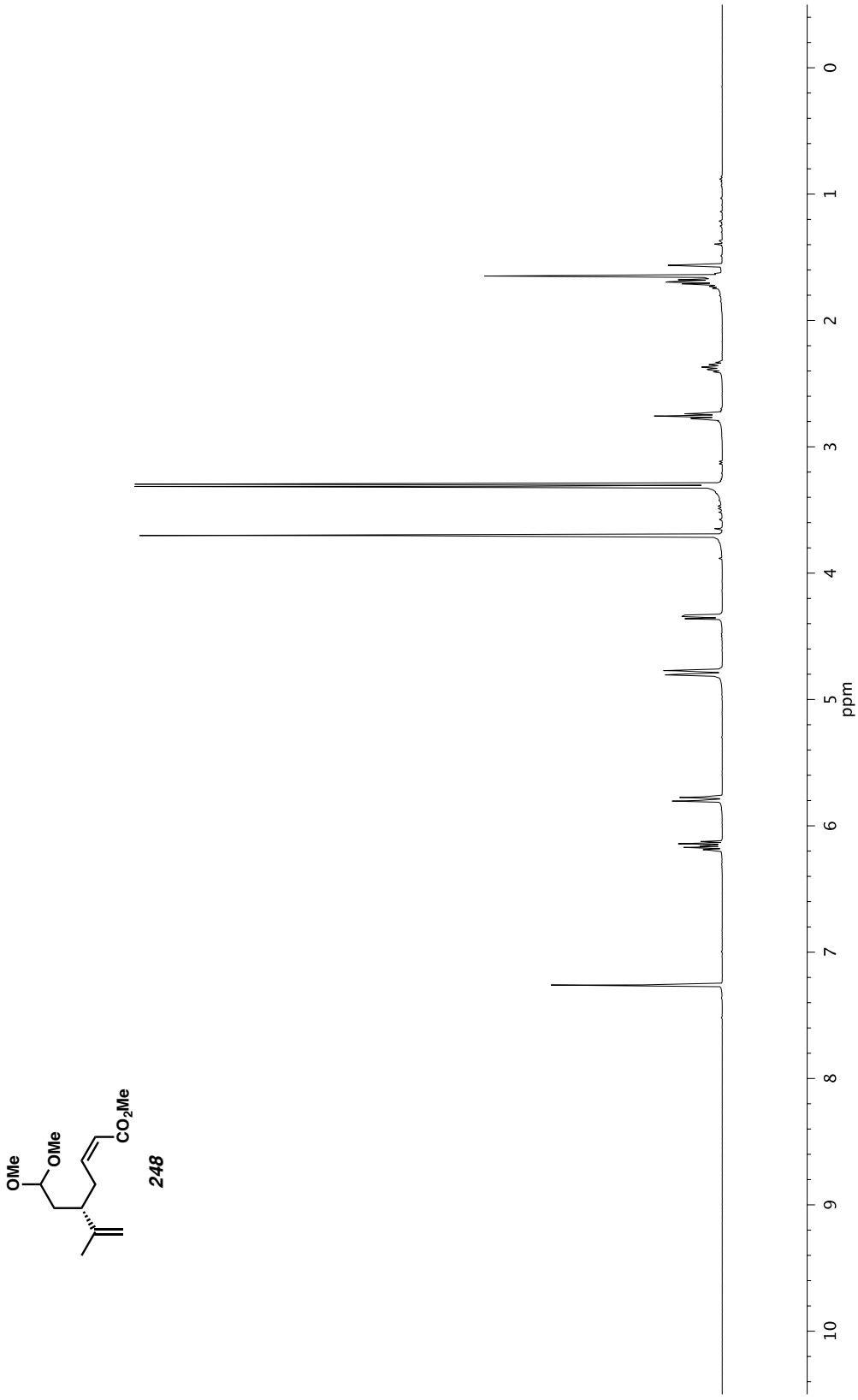


Figure A13.1. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **248**.

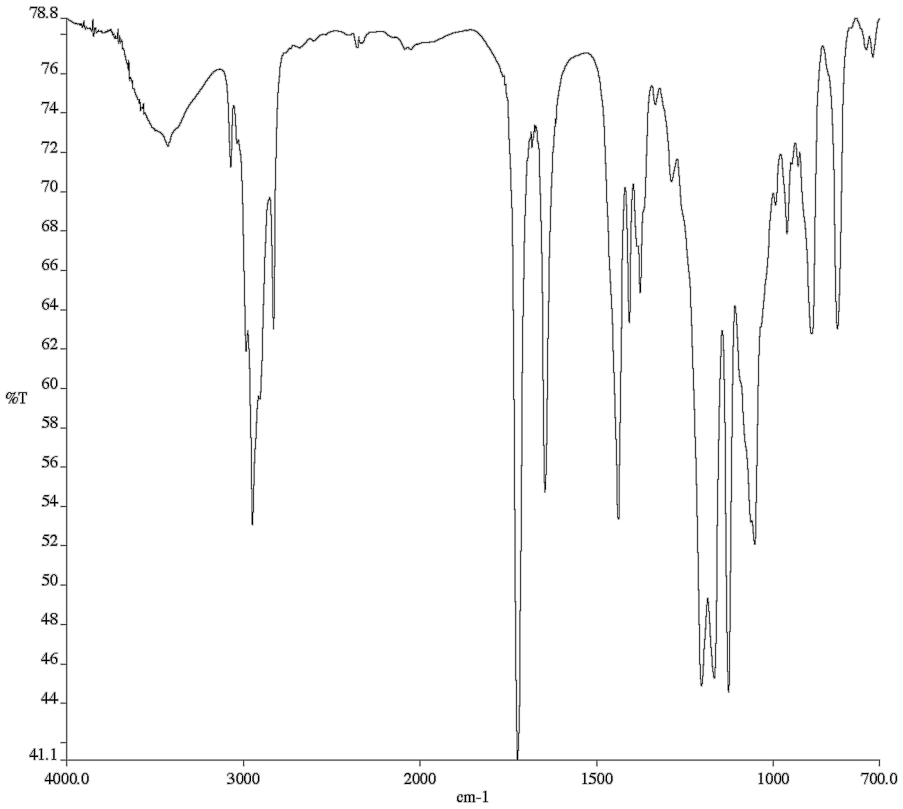


Figure A13.2. Infrared spectrum (Thin Film, NaCl) of compound **248**.

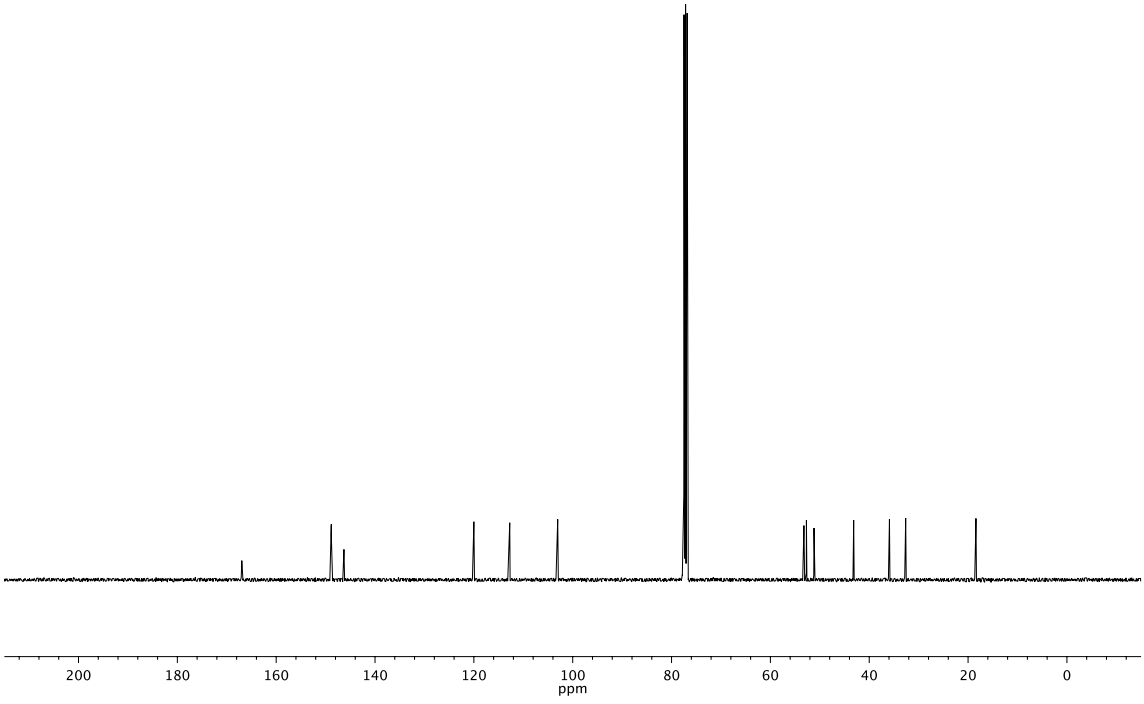


Figure A13.3. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **248**.

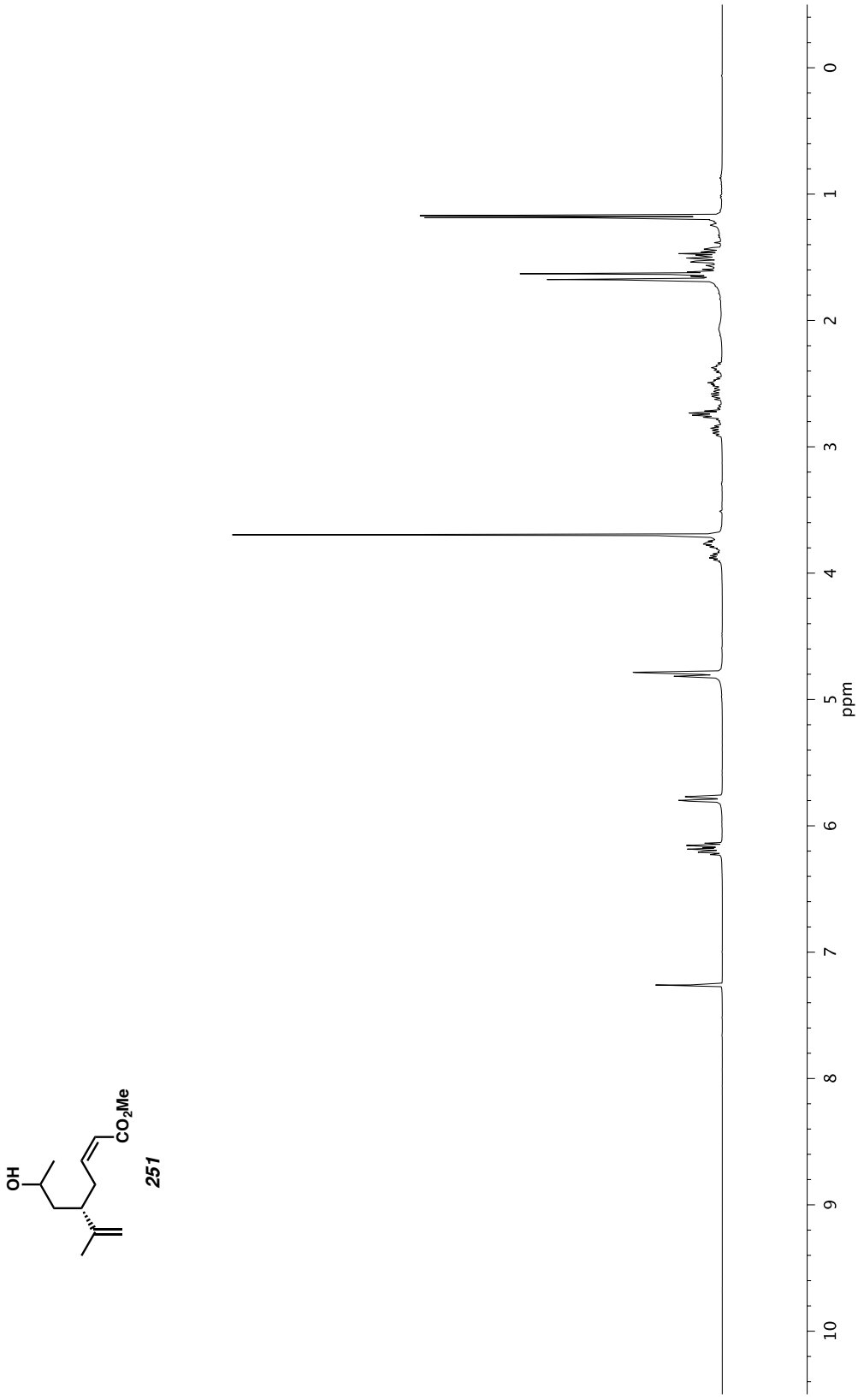


Figure A13.4. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **251**.

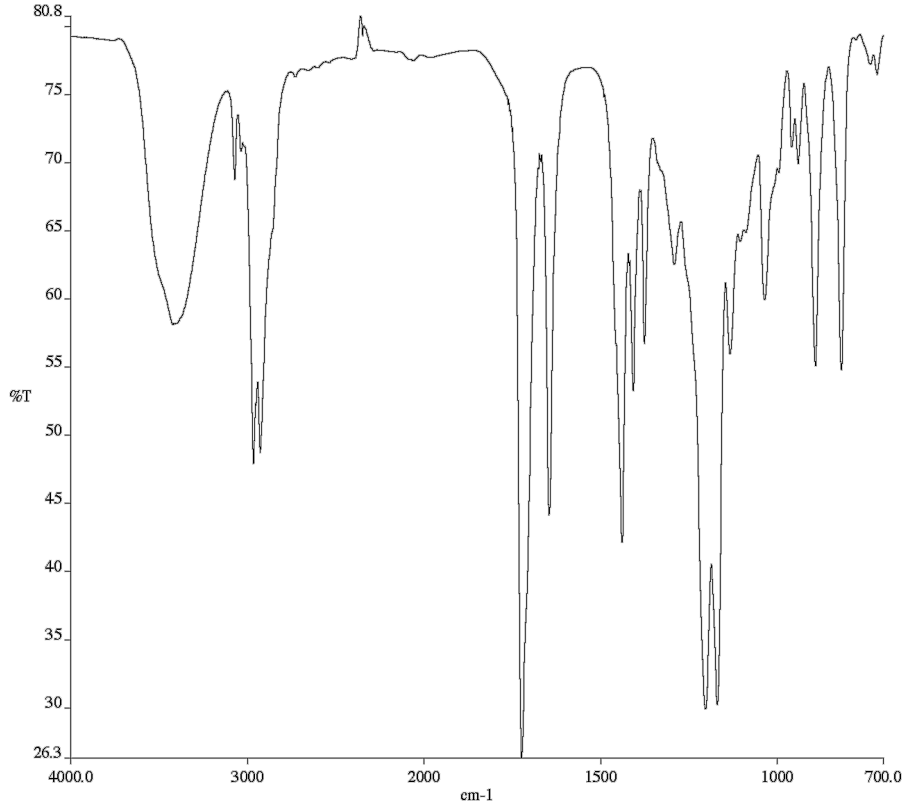


Figure A13.5. Infrared spectrum (Thin Film, NaCl) of compound **251**.

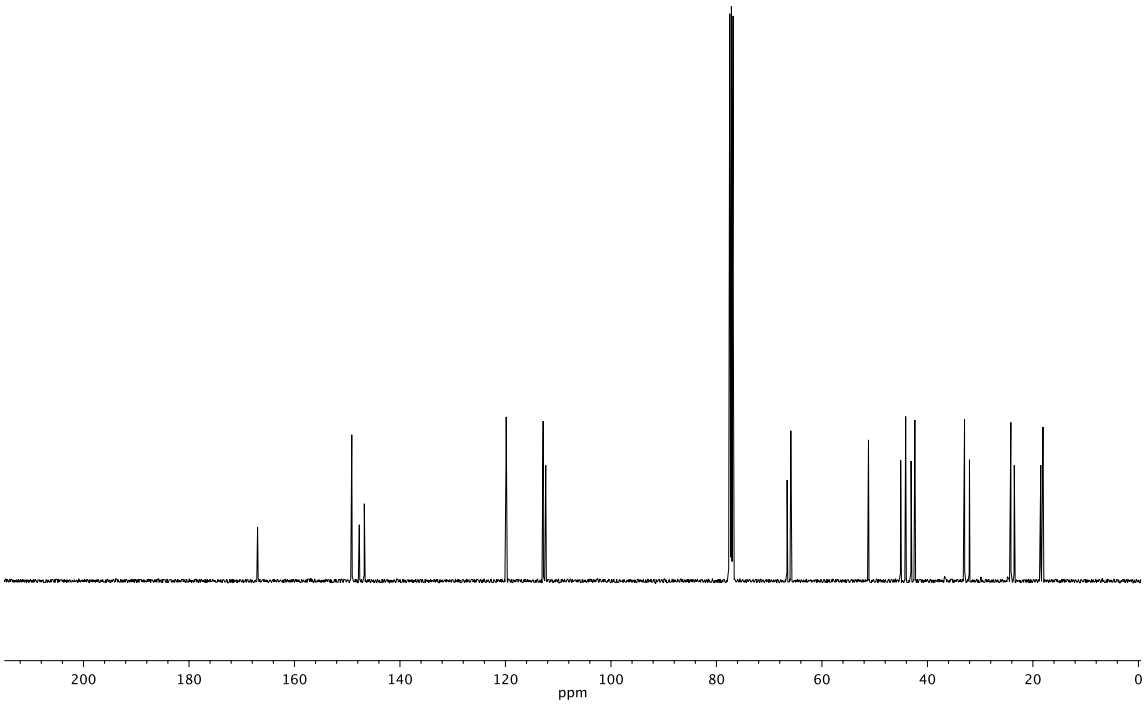


Figure A13.6. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **251**.

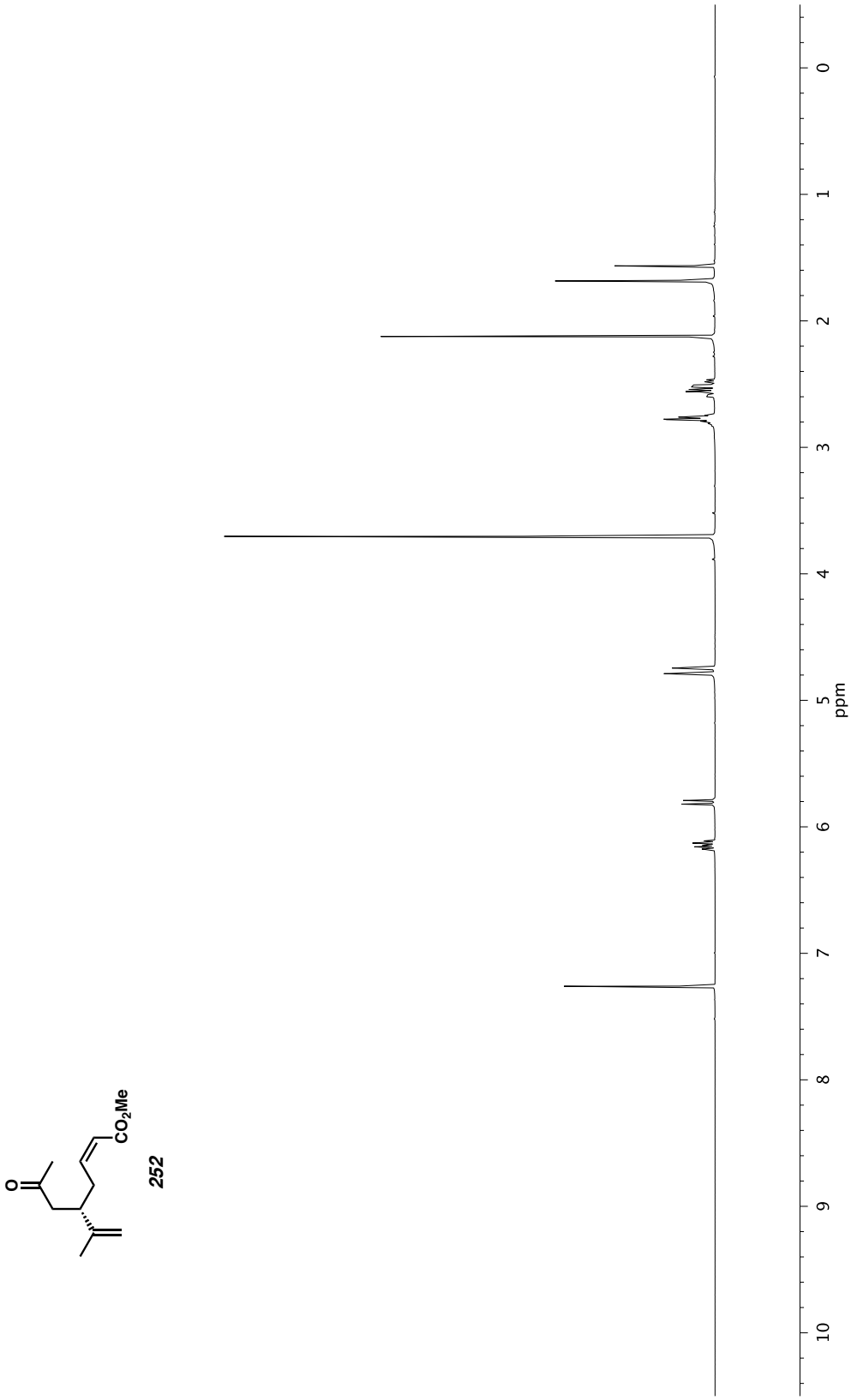


Figure A13.7. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **252**.

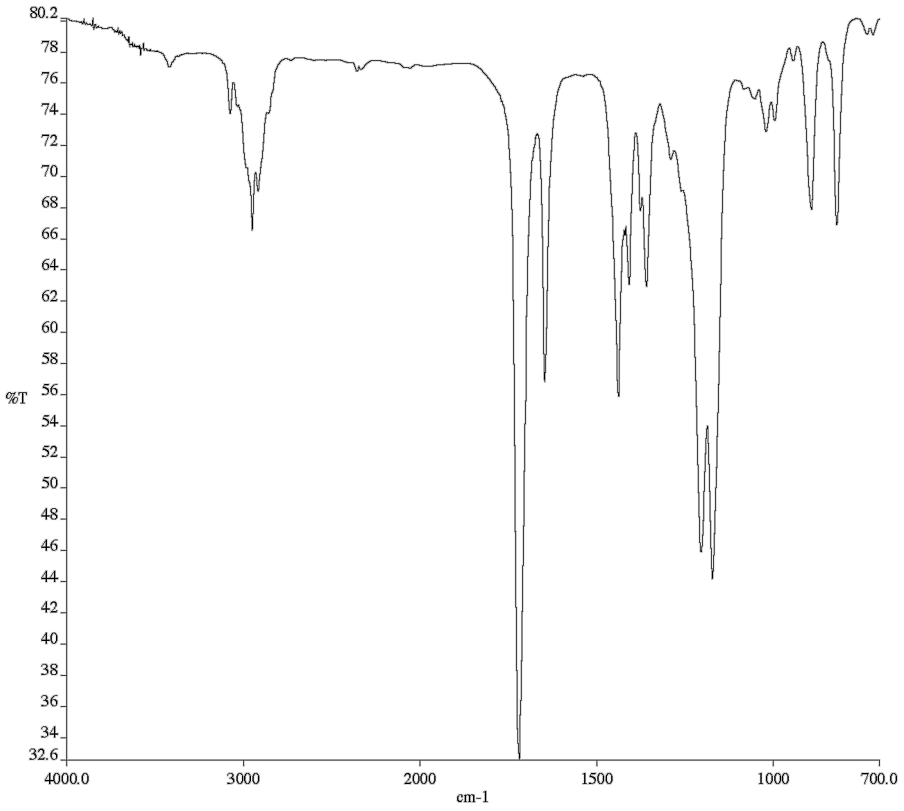


Figure A13.8. Infrared spectrum (Thin Film, NaCl) of compound **252**.

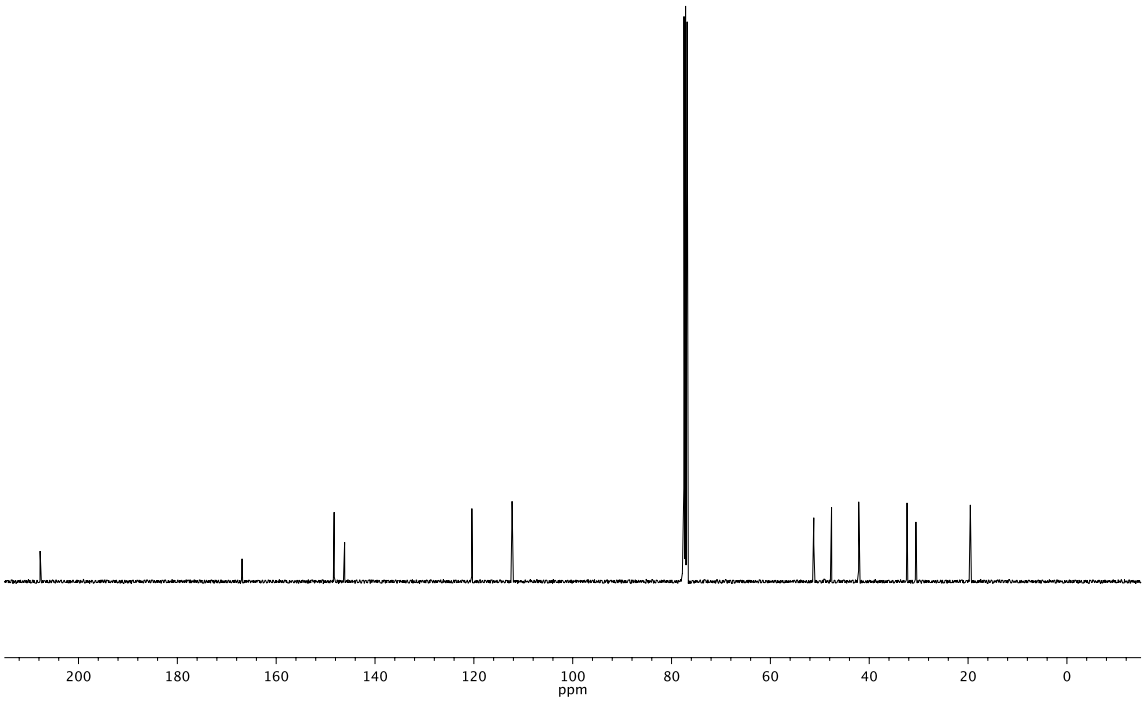


Figure A13.9. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **252**.

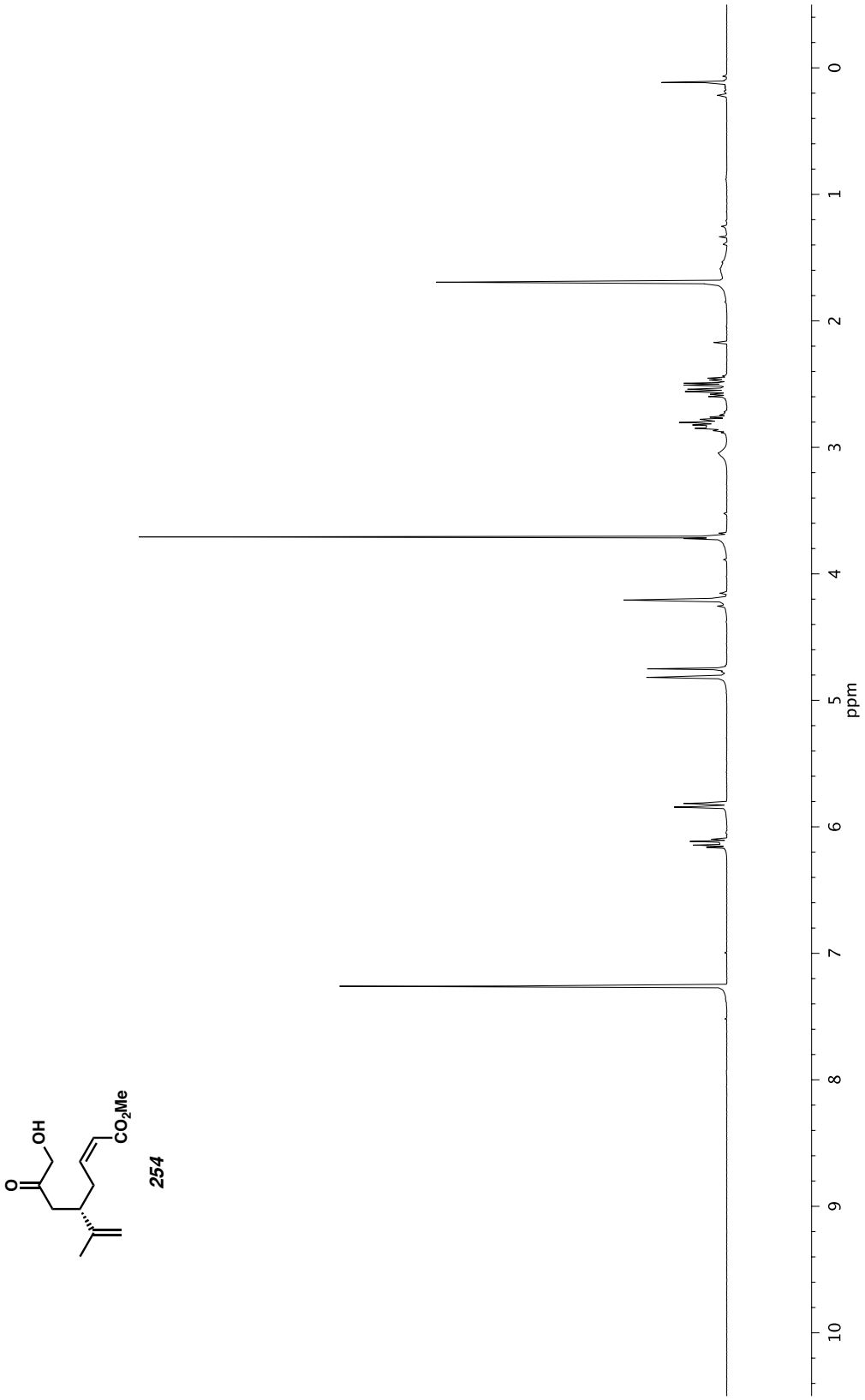


Figure A13.10. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **254**.

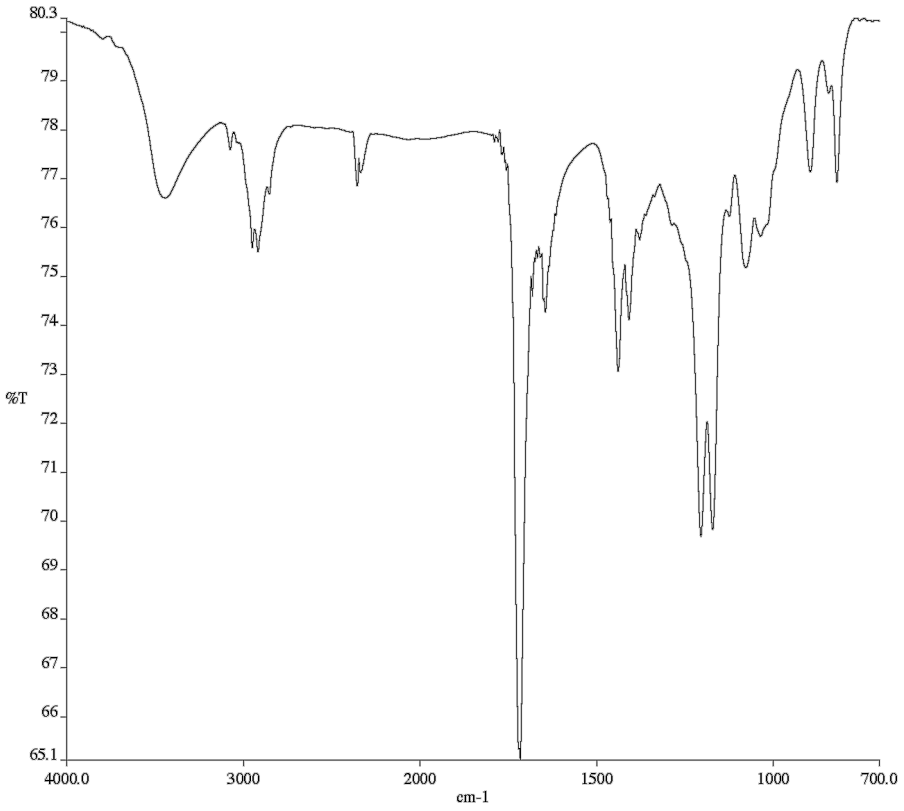


Figure A13.11. Infrared spectrum (Thin Film, NaCl) of compound **254**.

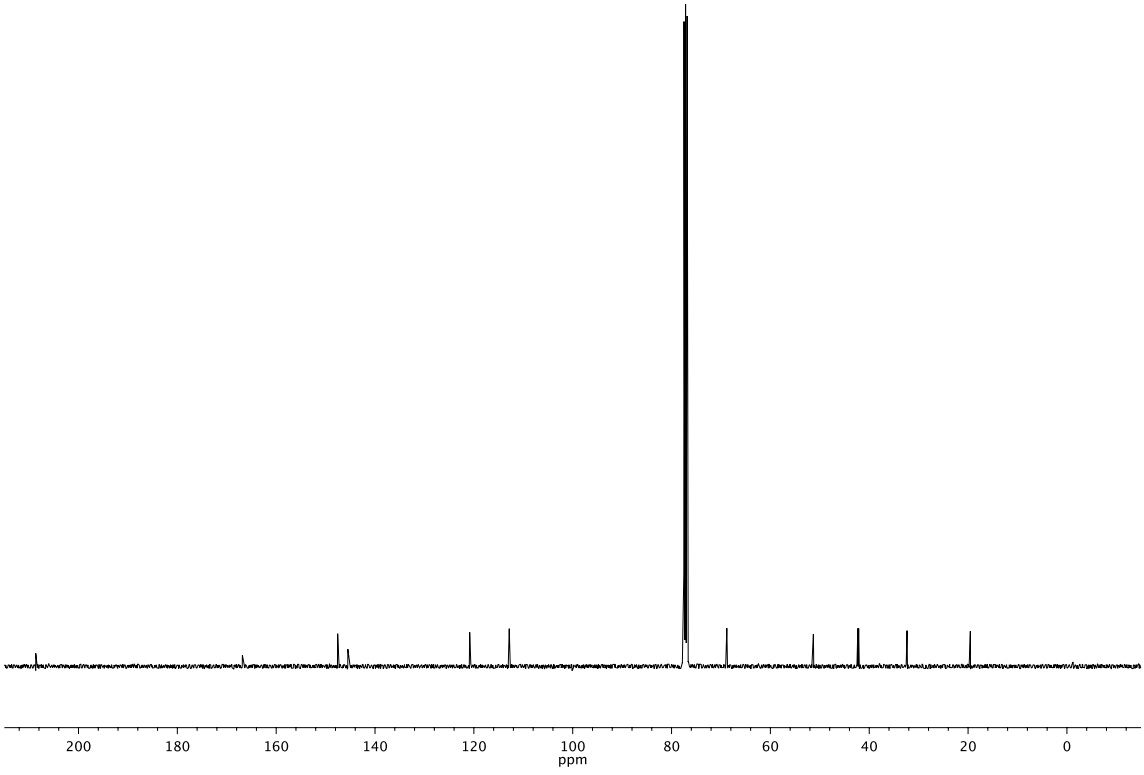


Figure A13.12. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **254**.

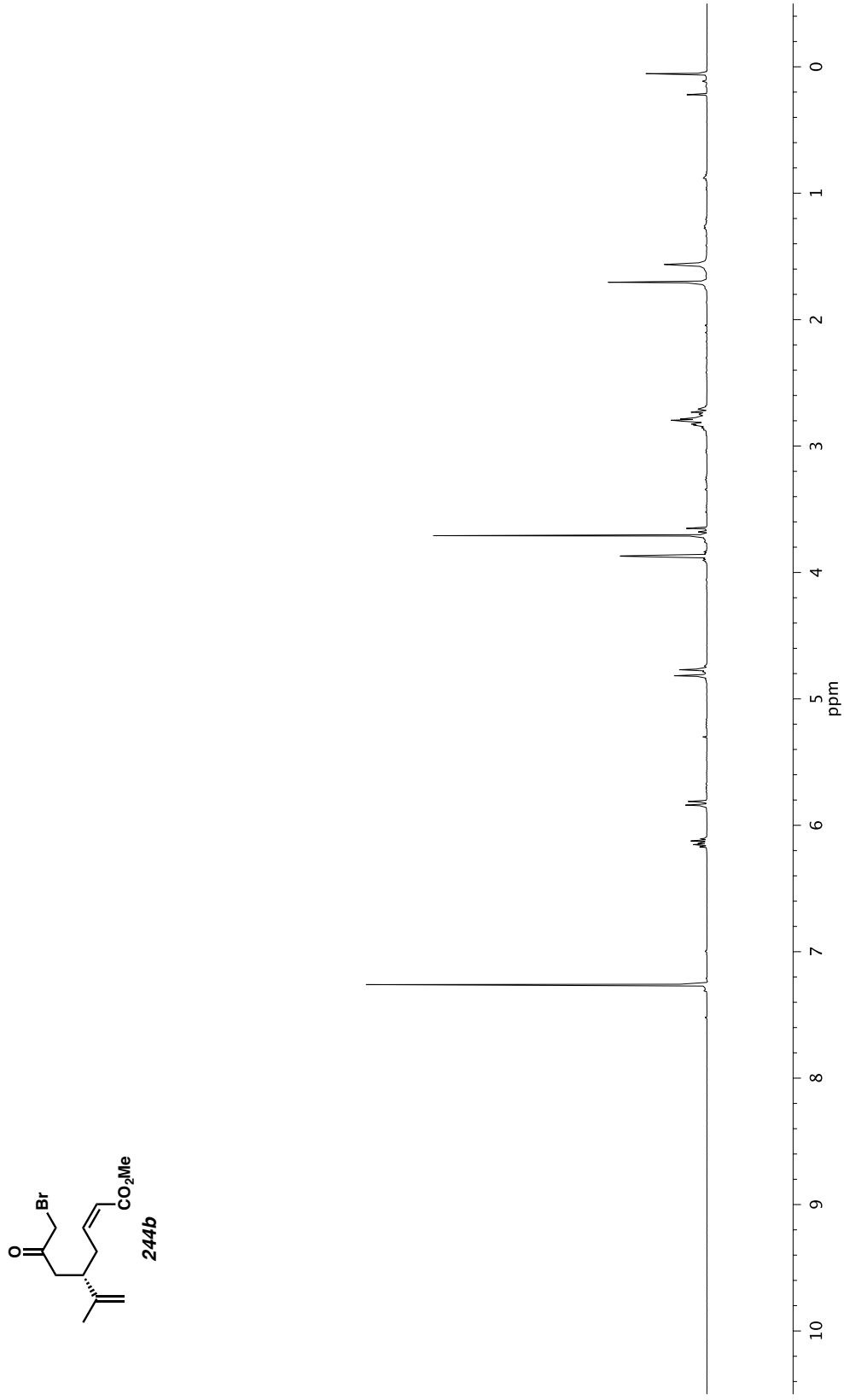


Figure A13.13. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **244b**.

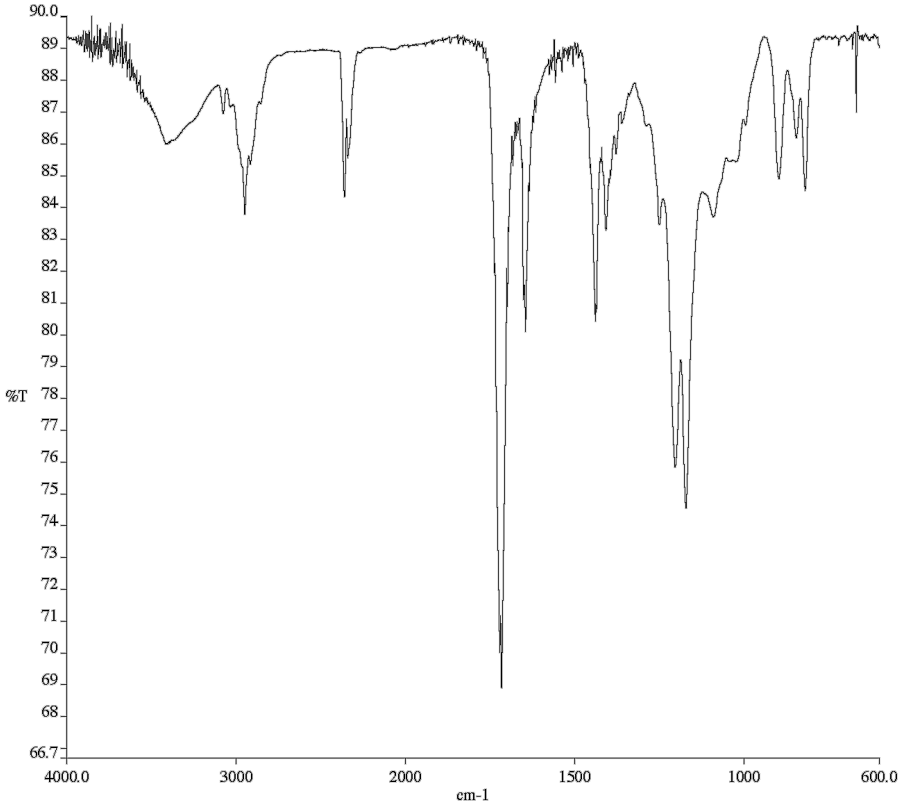


Figure A13.14. Infrared spectrum (Thin Film, NaCl) of compound **244b**.

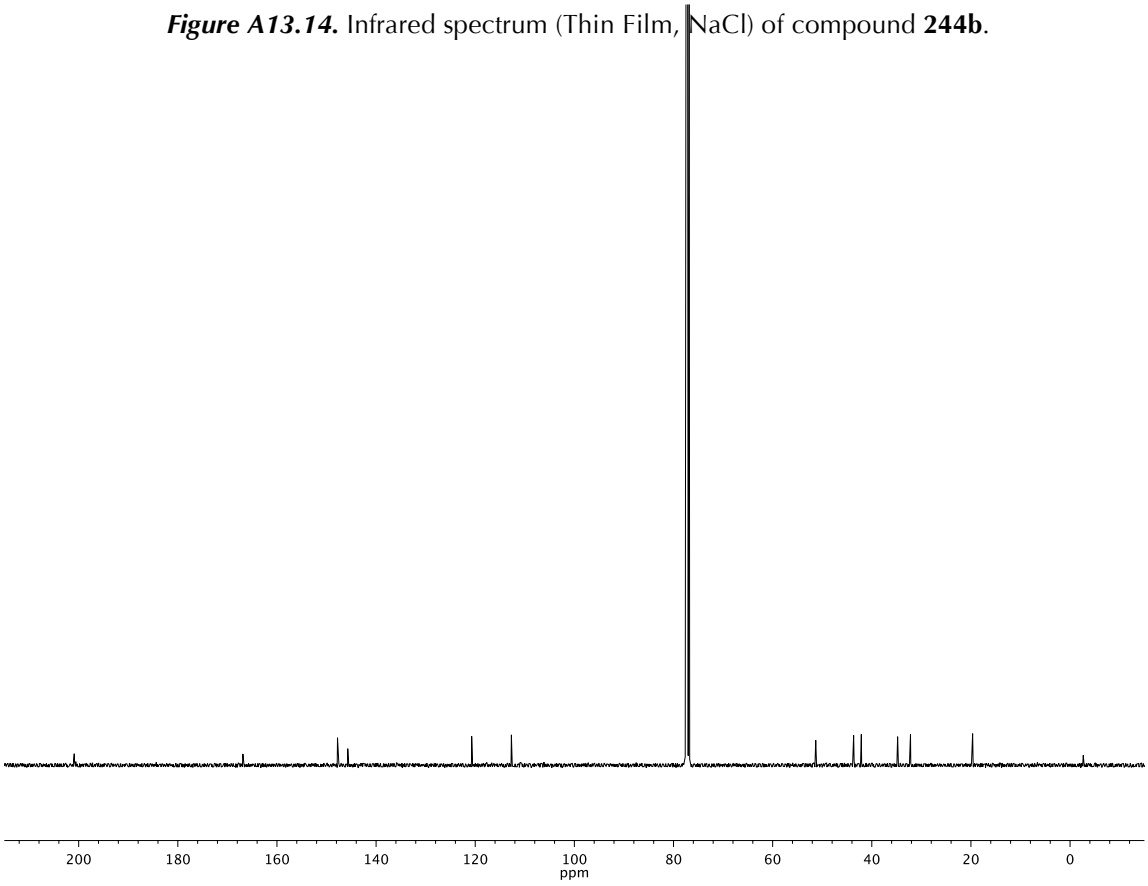


Figure A13.15. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **244b**.

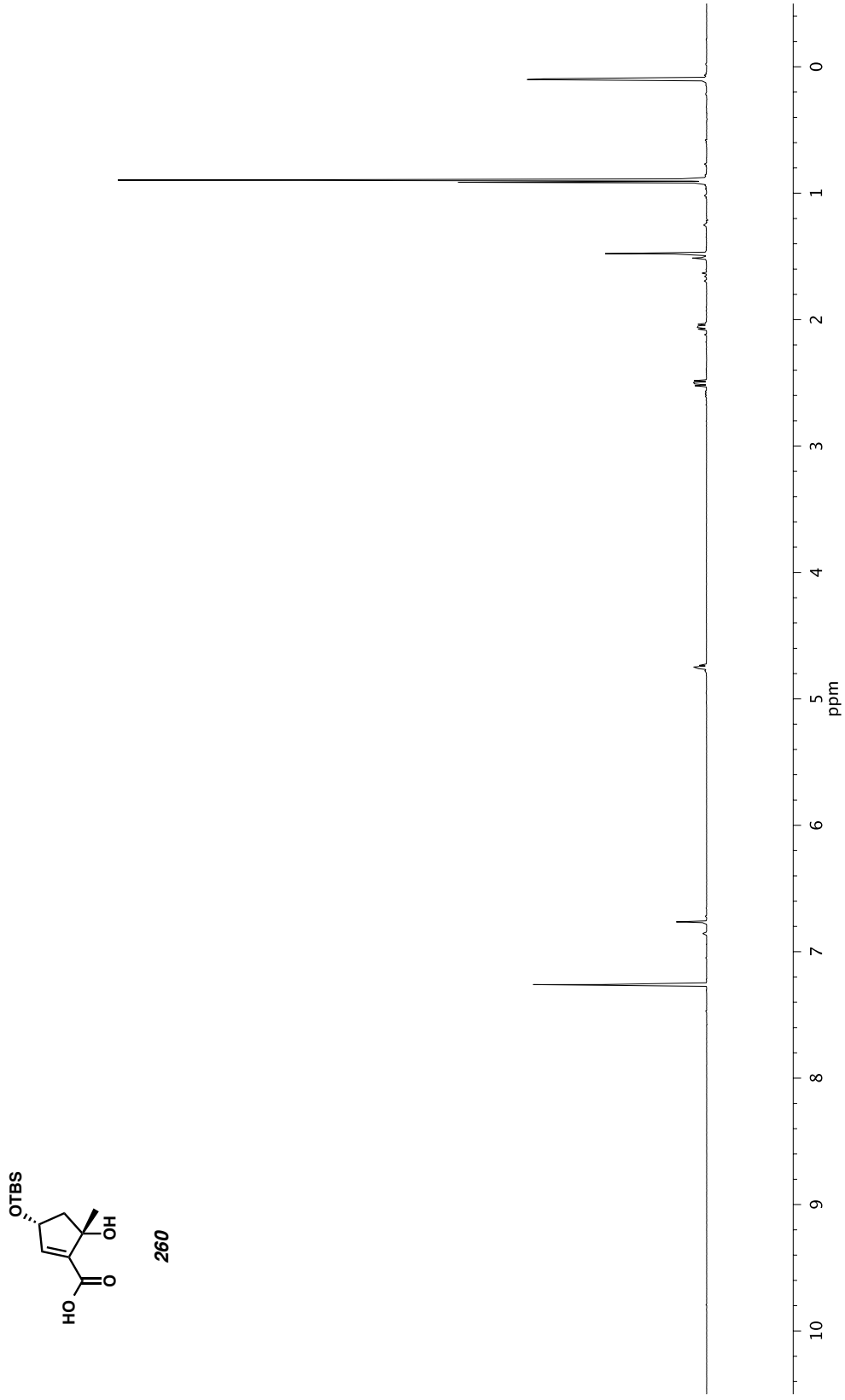


Figure A13.16. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **260**.

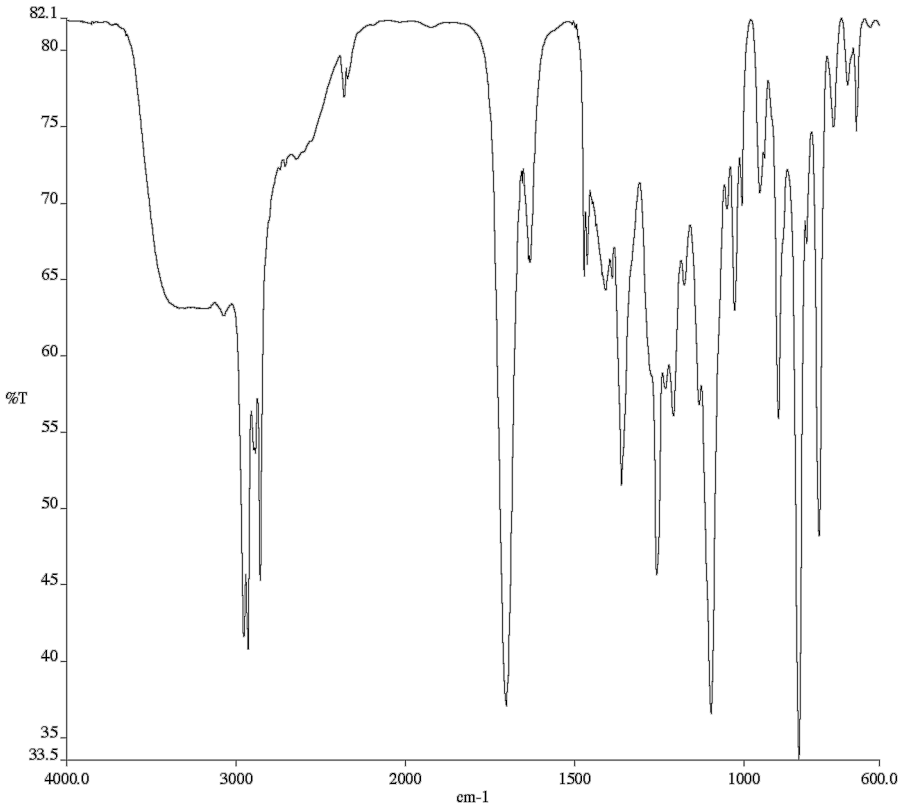


Figure A13.17. Infrared spectrum (Thin Film, NaCl) of compound **260**.

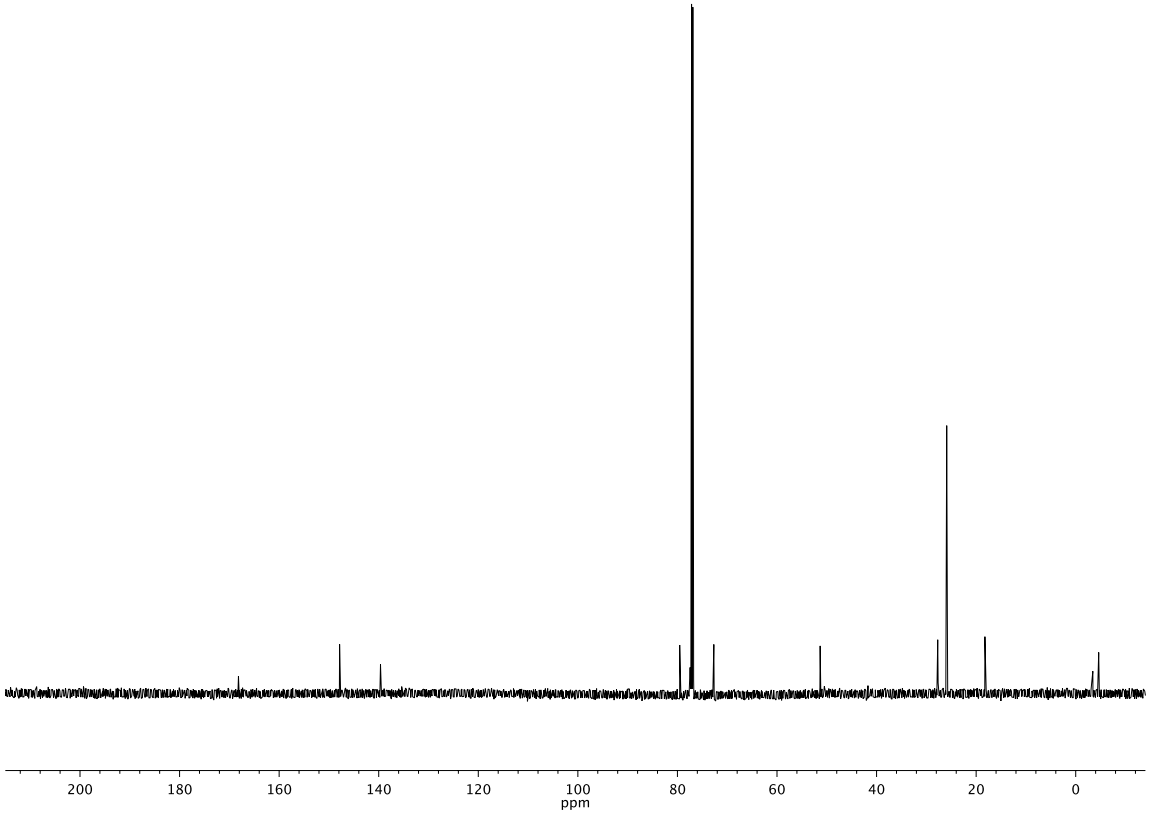
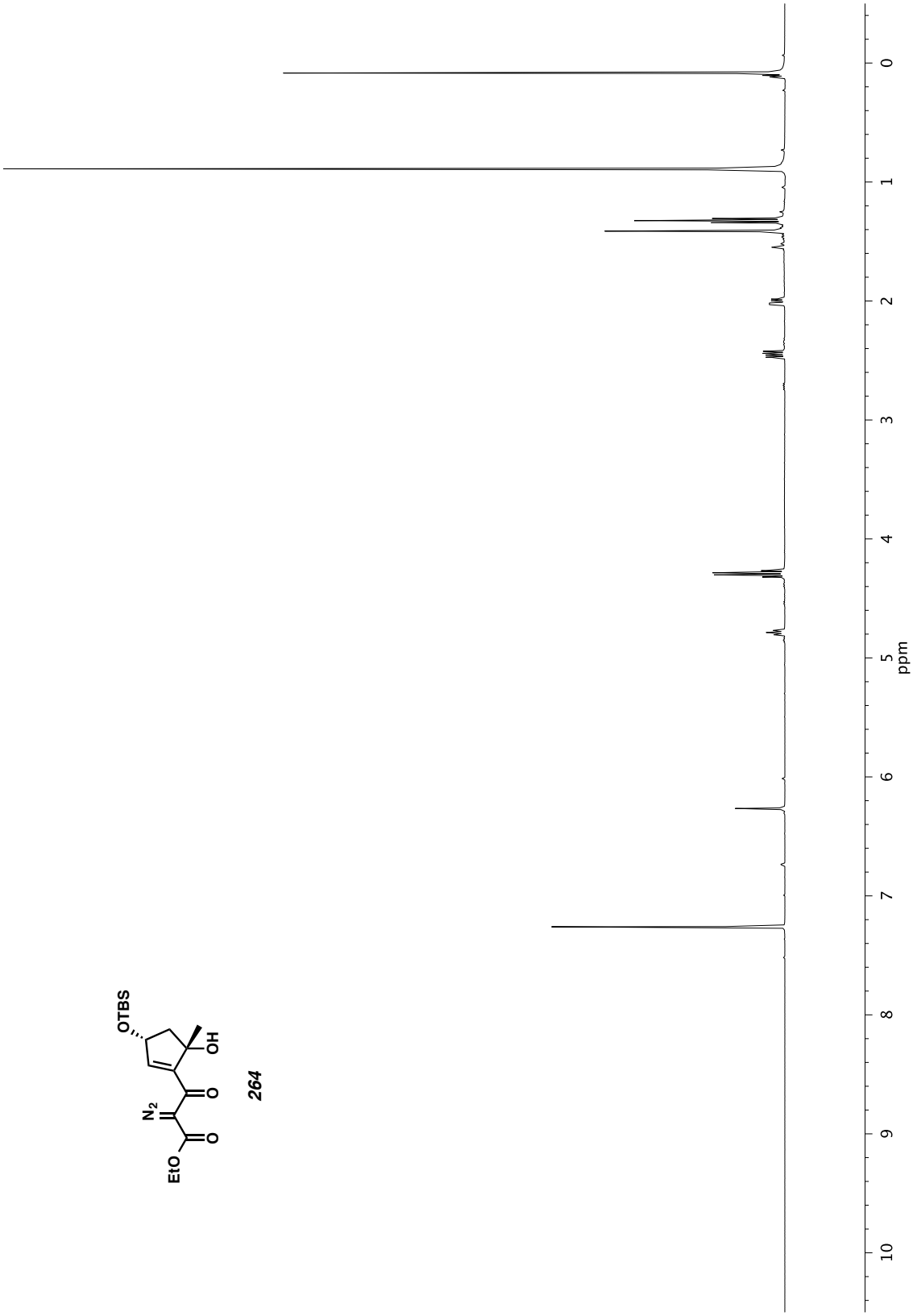


Figure A13.18. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **260**.



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Figure A13.19. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **264**.

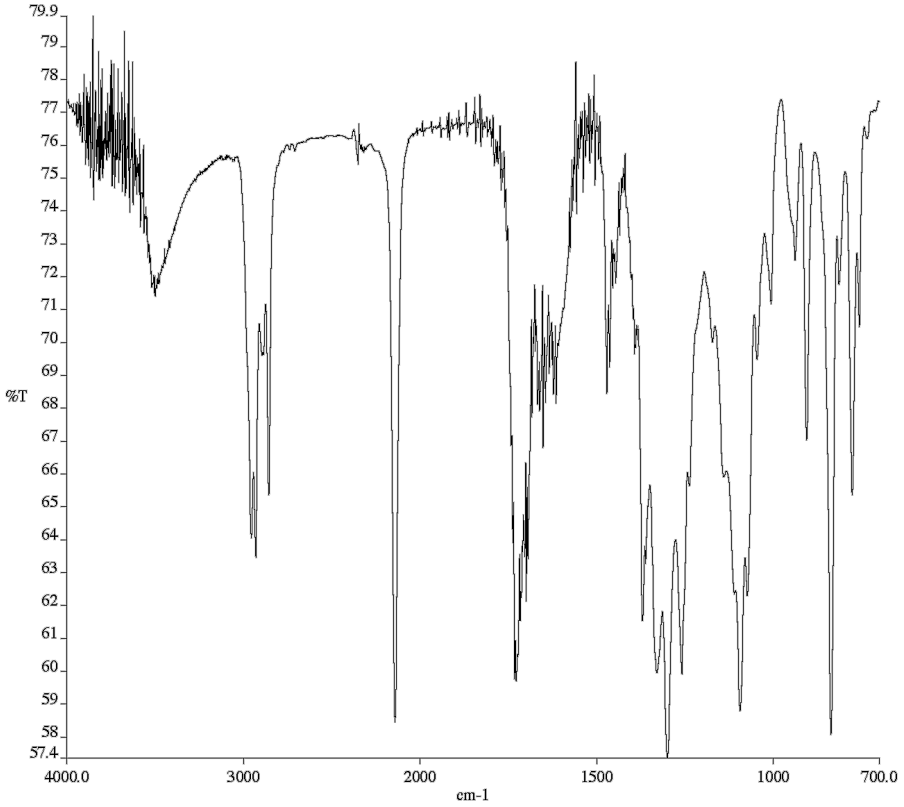


Figure A13.20. Infrared spectrum (Thin Film, NaCl) of compound **264**.

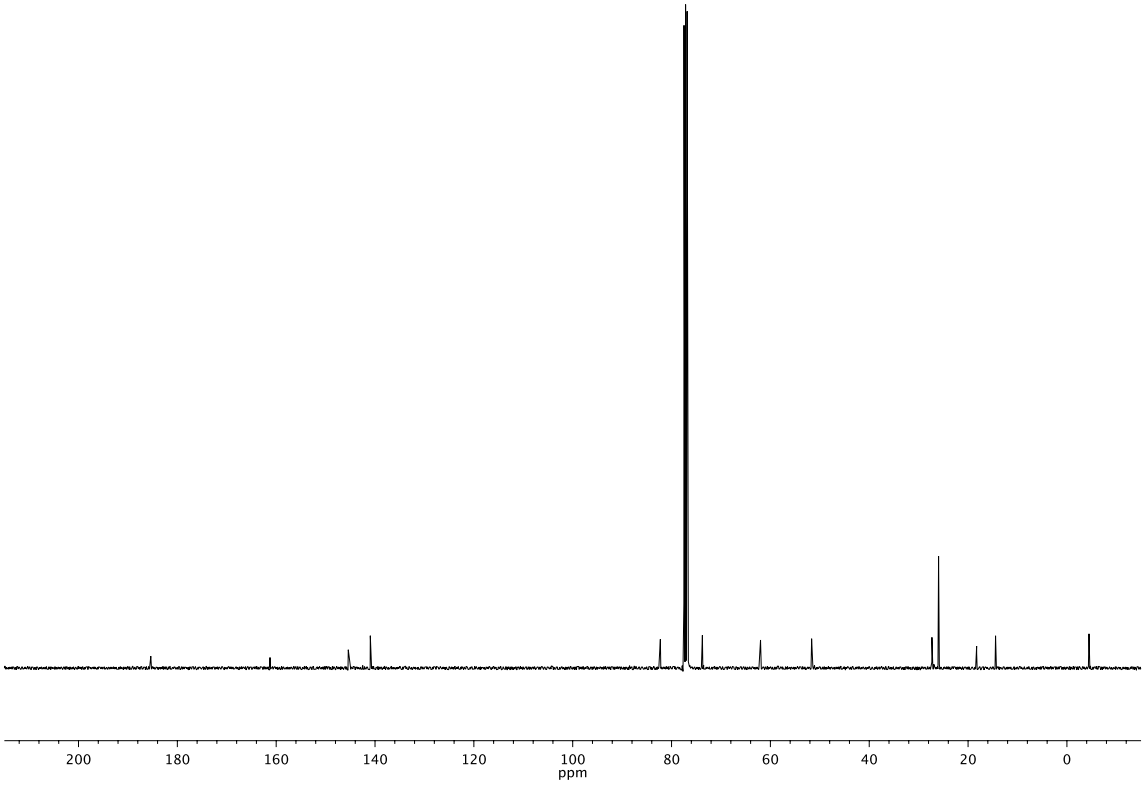


Figure A13.21. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **264**.

Figure A13.22. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **266**.

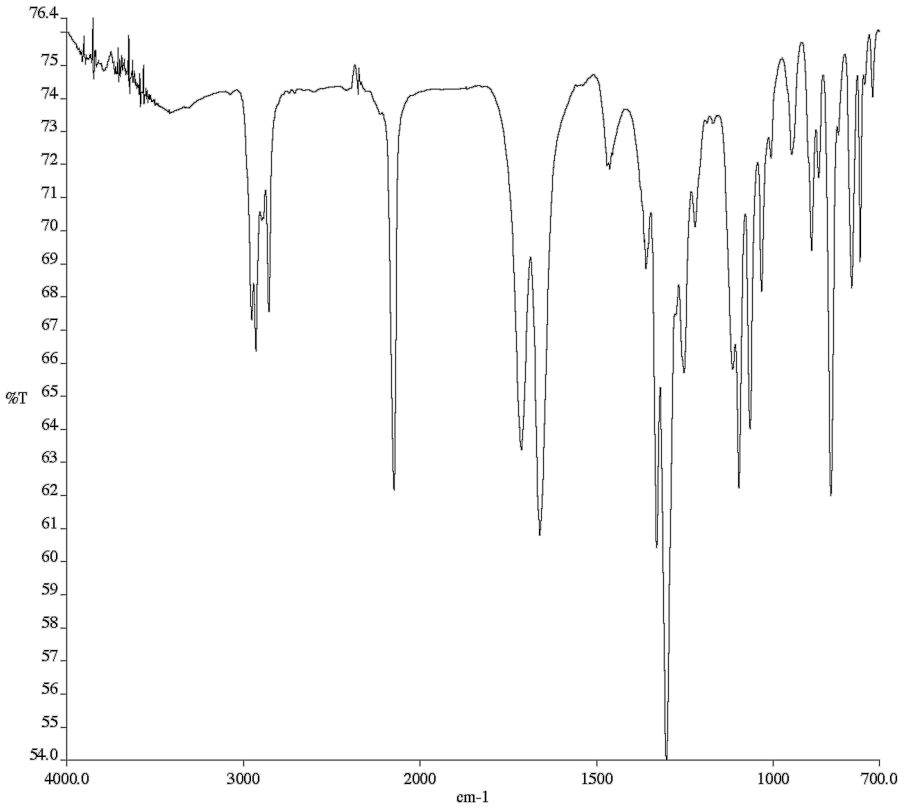


Figure A13.23. Infrared spectrum (Thin Film, NaCl) of compound **266**.

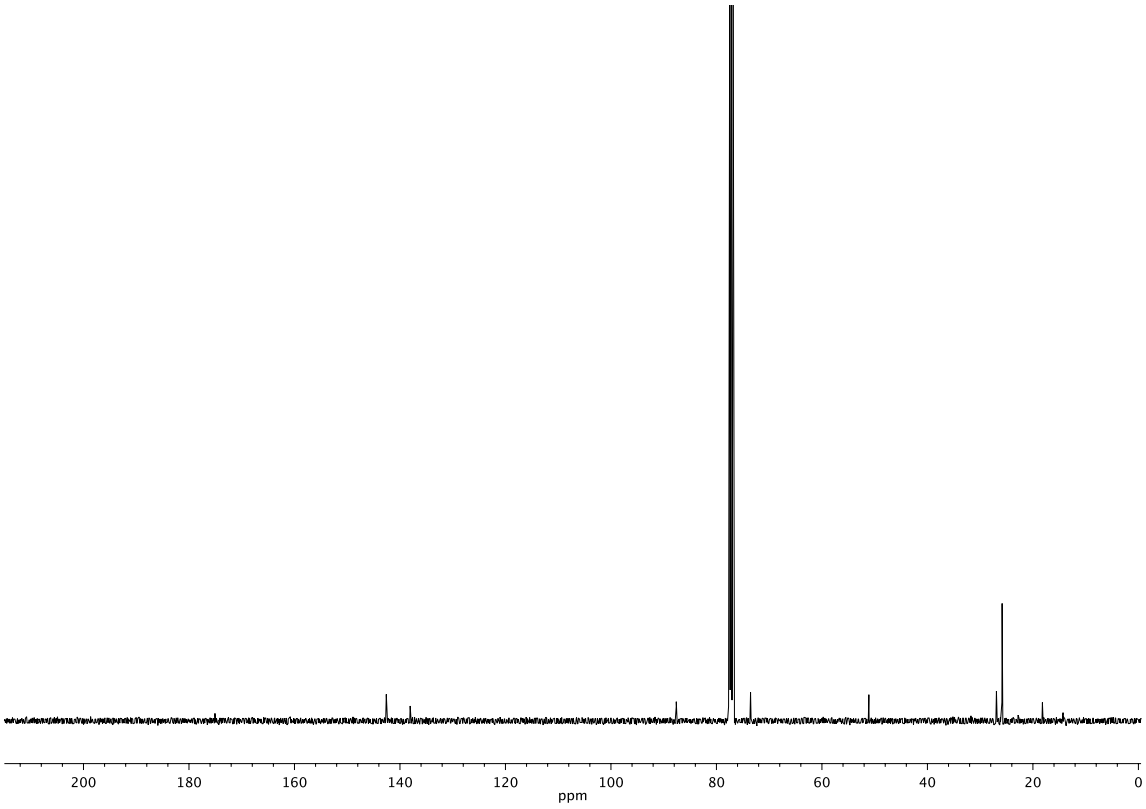


Figure A13.24. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **266**.

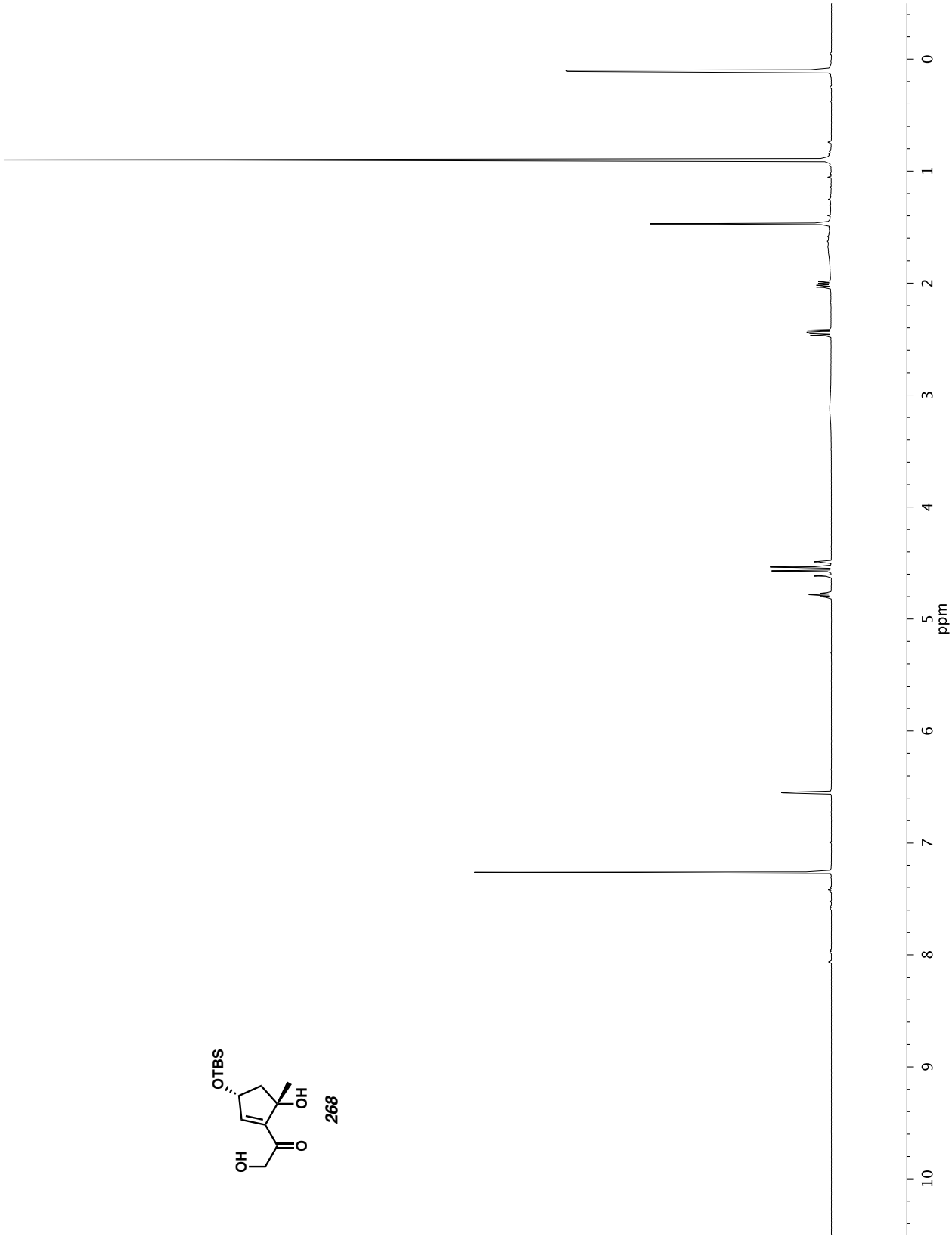


Figure A13.25. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **268**.

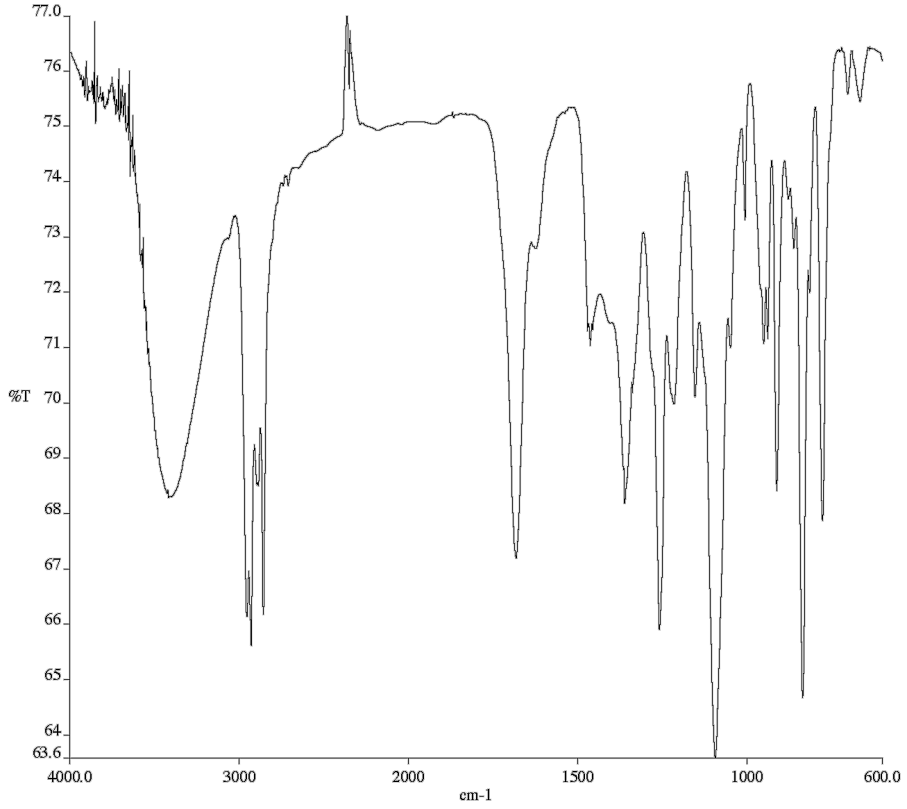


Figure A13.26. Infrared spectrum (Thin Film, NaCl) of compound **268**.

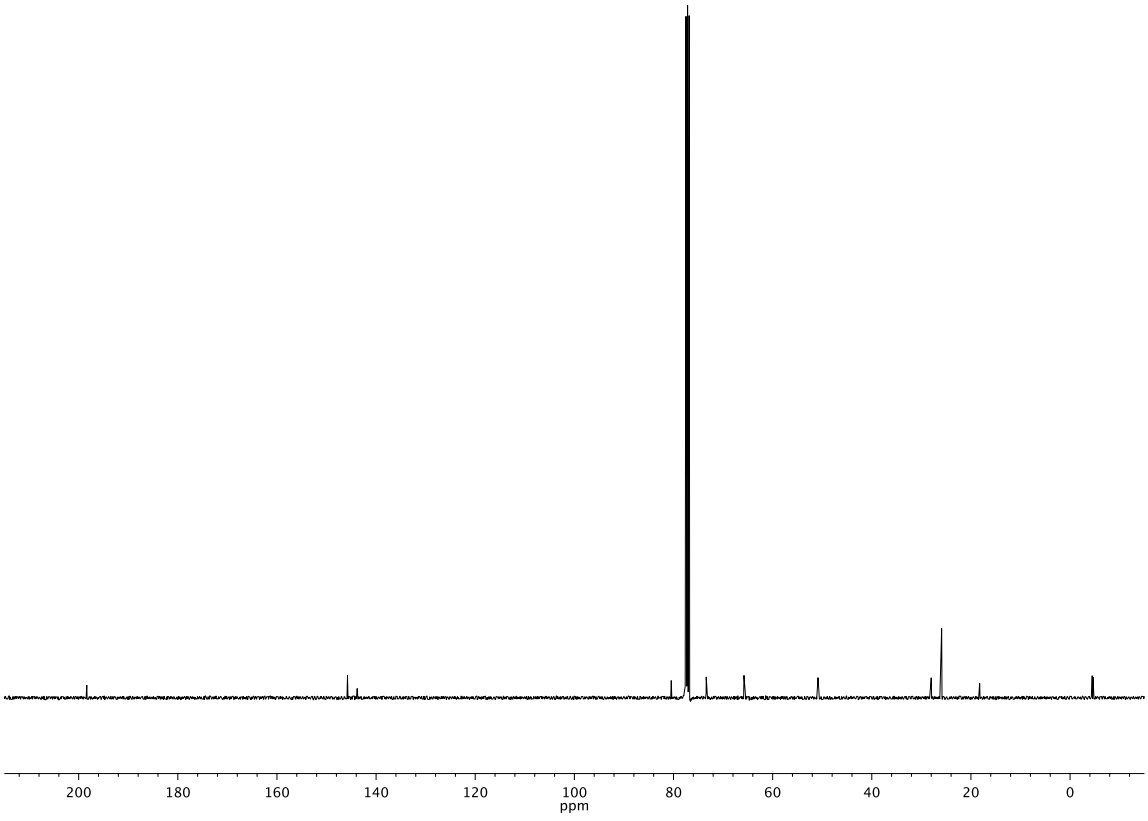


Figure A13.27. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **268**.

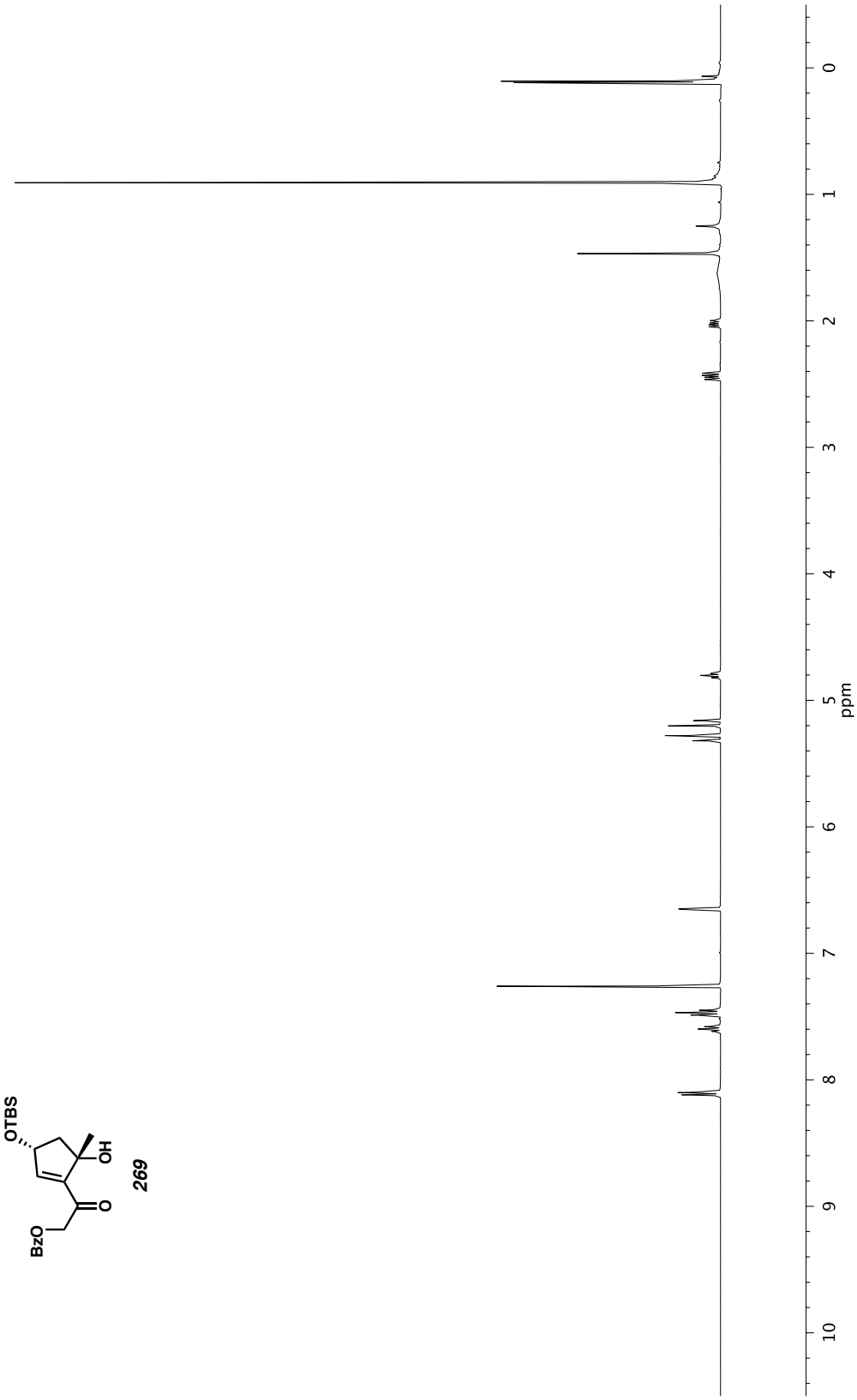


Figure A13.28. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **269**.

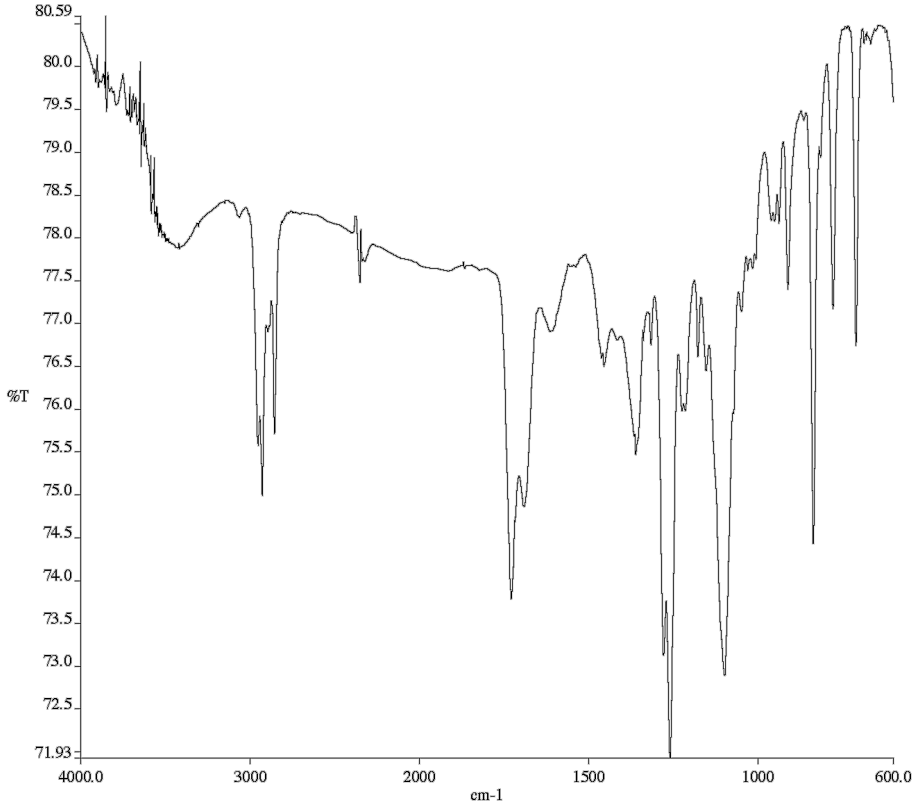


Figure A13.29. Infrared spectrum (Thin Film, NaCl) of compound **269**.

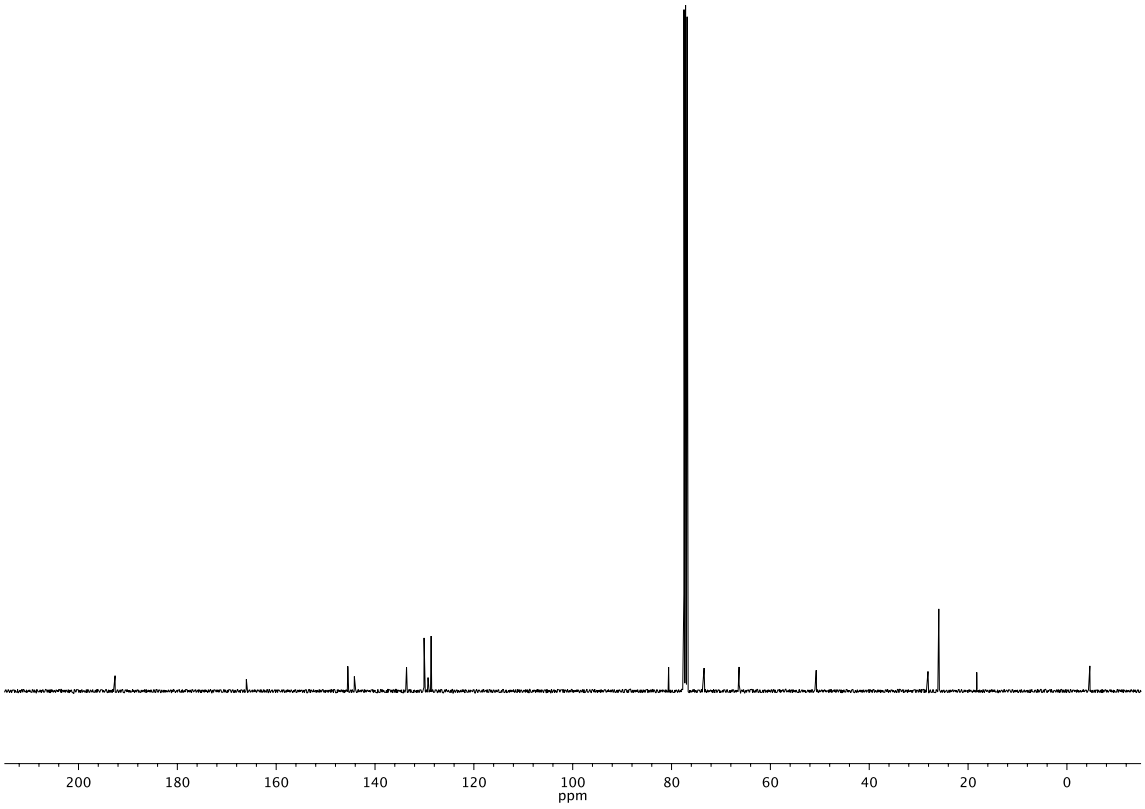


Figure A13.30. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **269**.

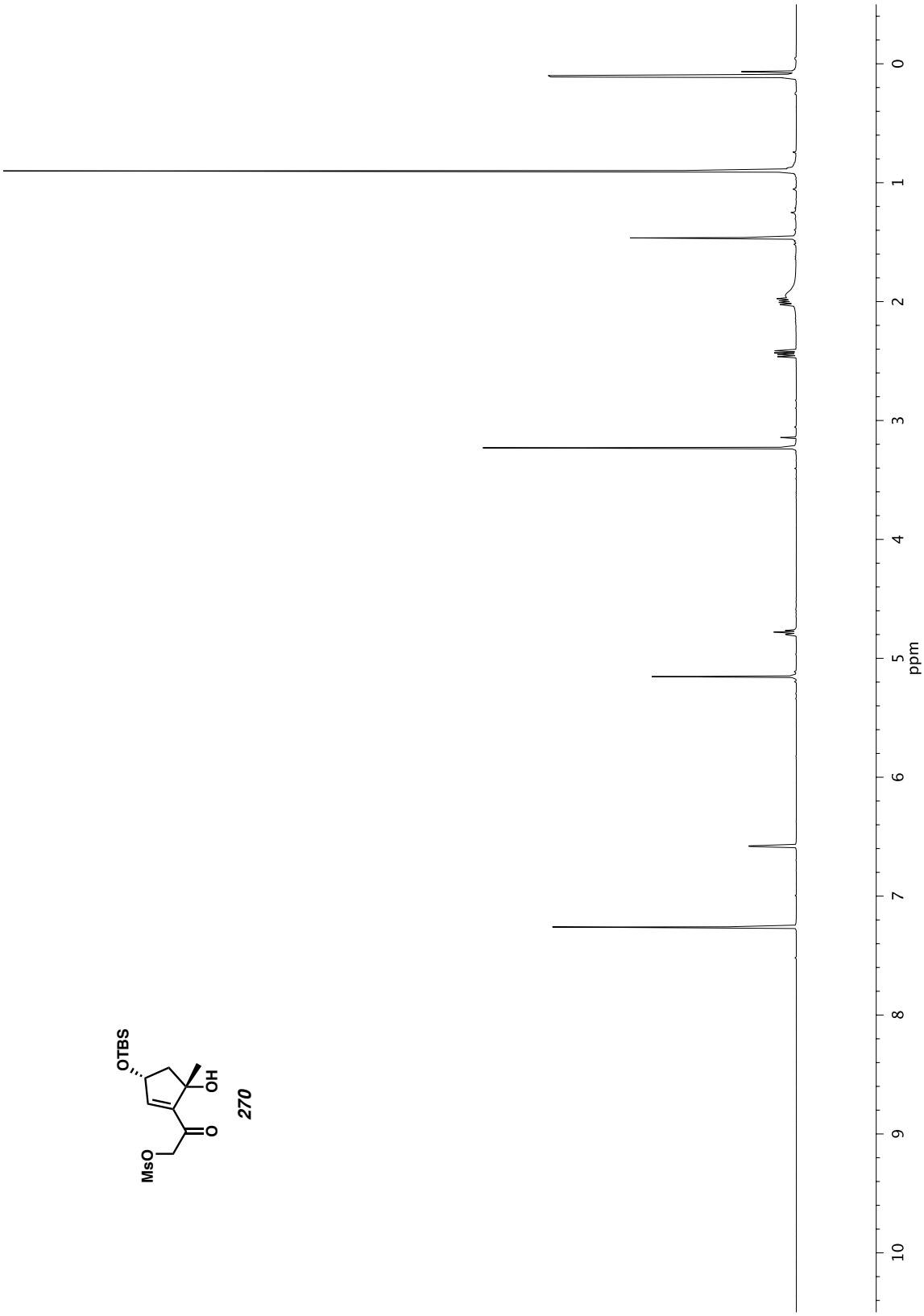


Figure A13.31. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **270**.

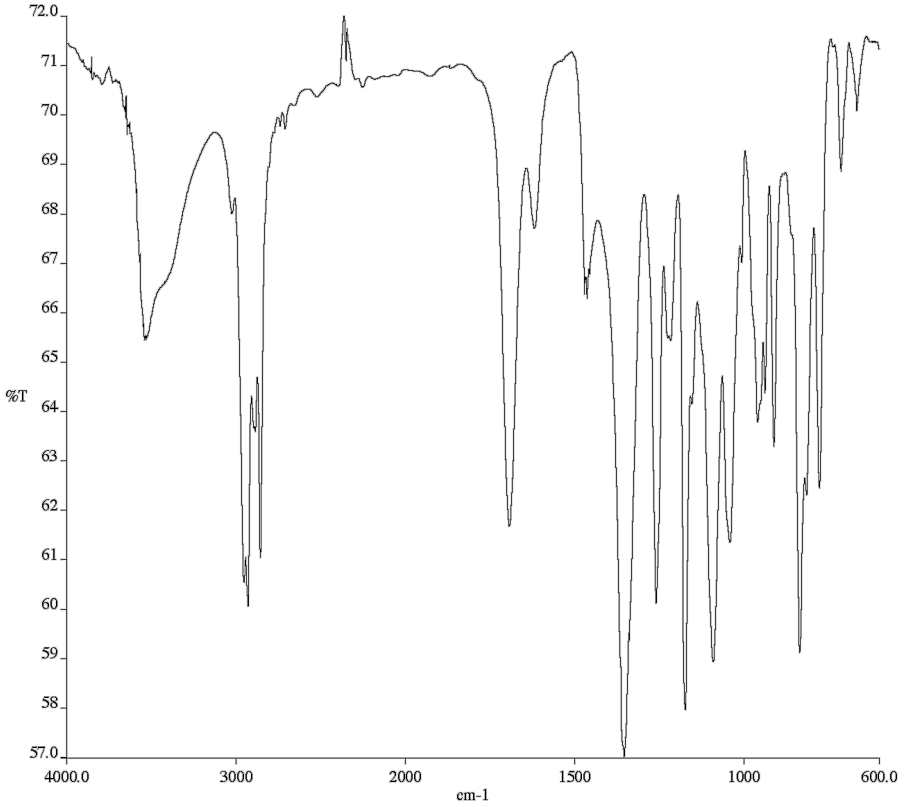


Figure A13.32. Infrared spectrum (Thin Film, NaCl) of compound **270**.

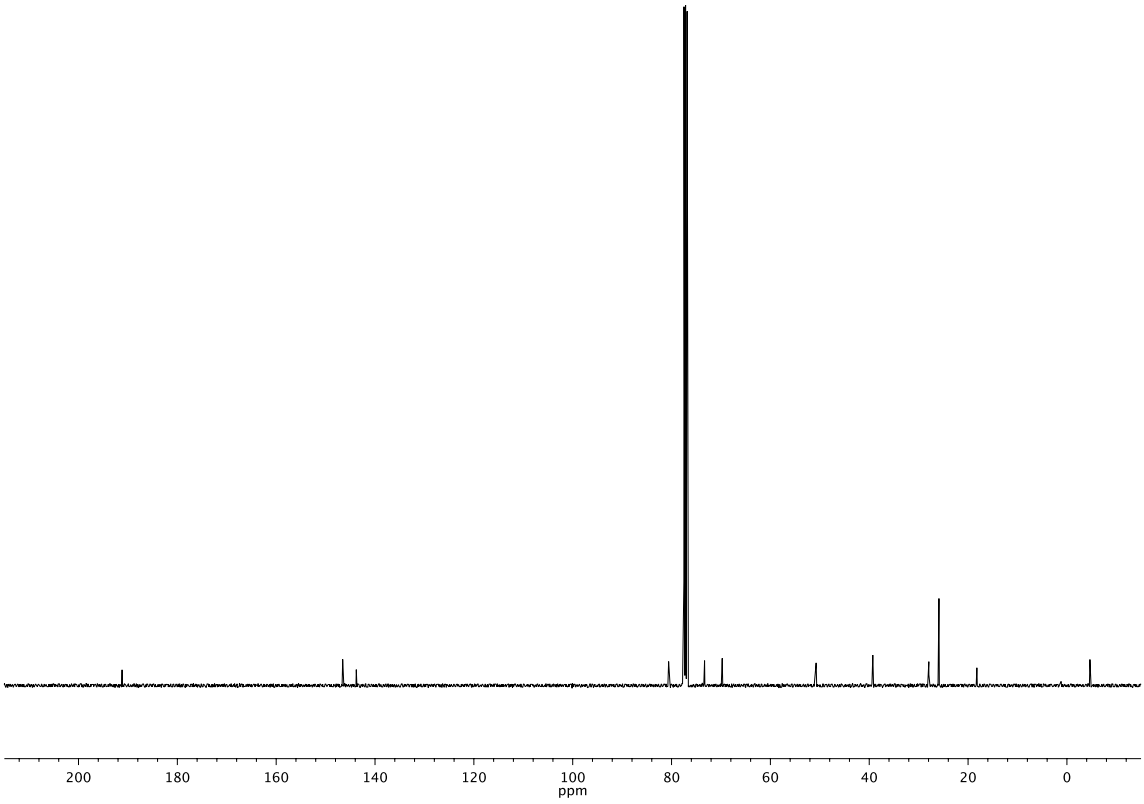


Figure A13.33. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **270**.

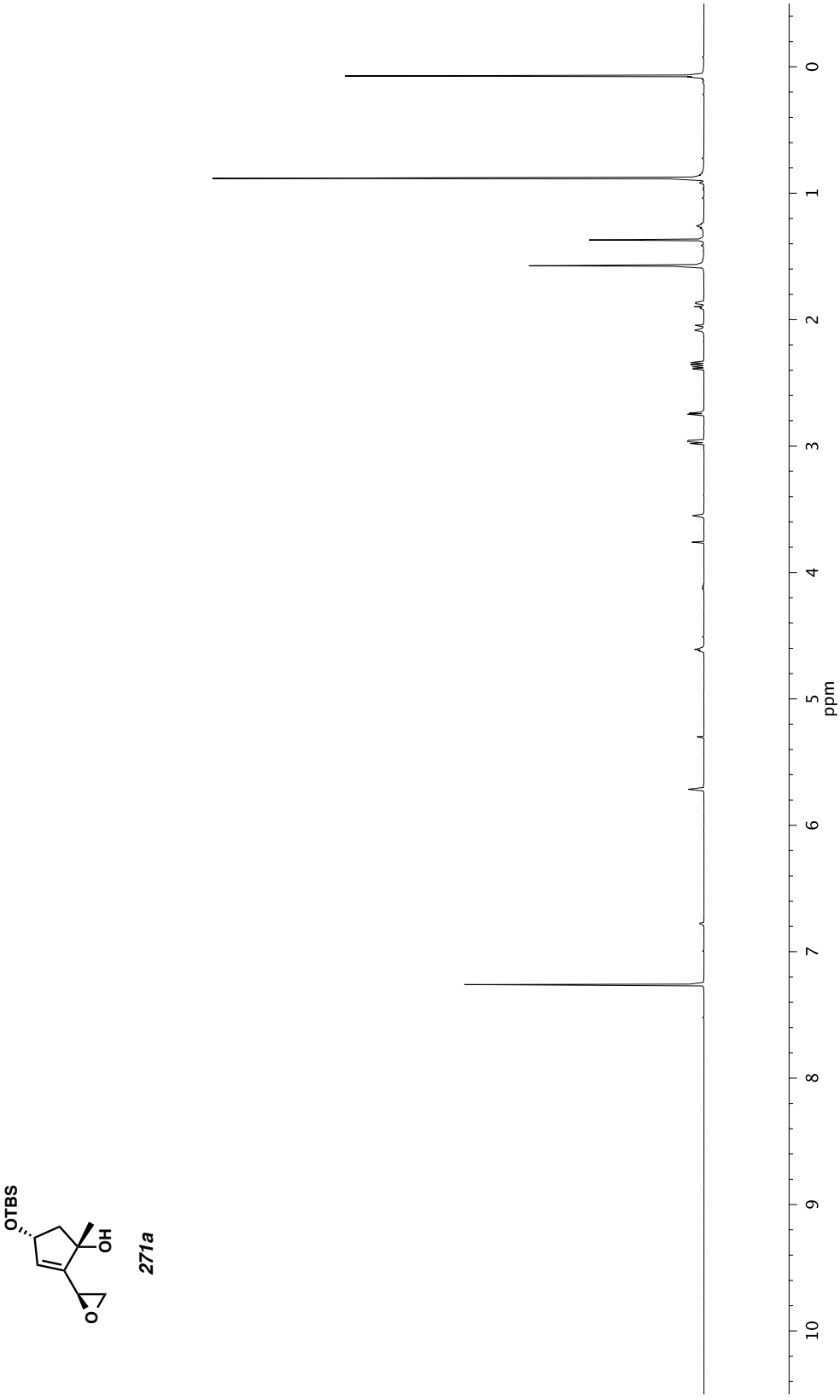


Figure A13.34. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **271a**.

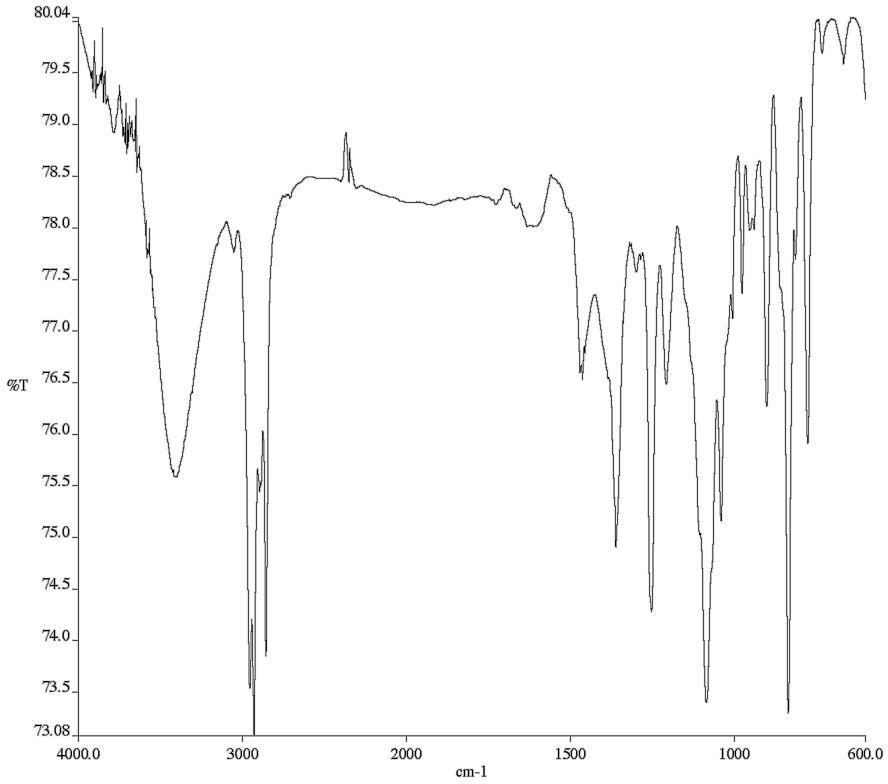


Figure A13.35. Infrared spectrum (Thin Film, NaCl) of compound **271a**.

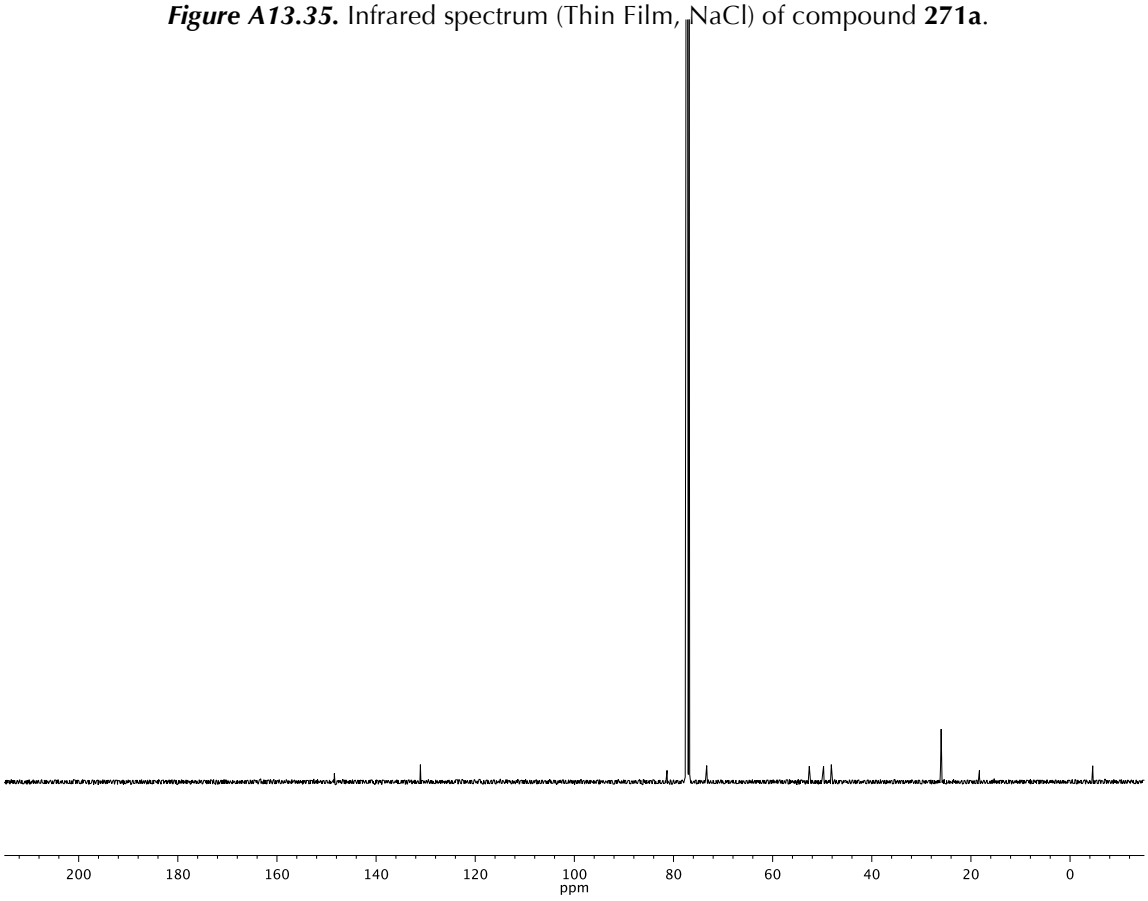


Figure A13.36. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **271a**.

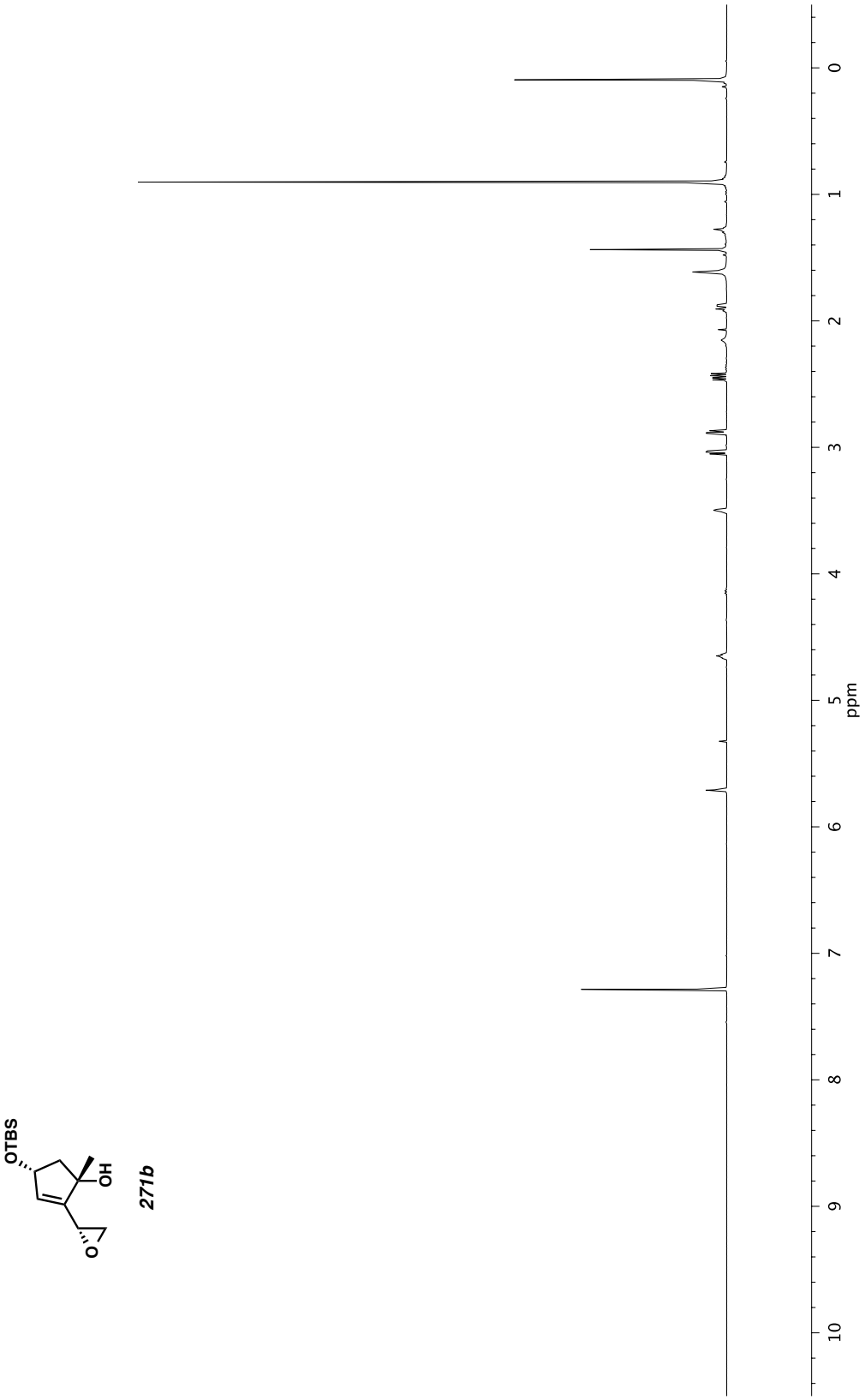


Figure A13.37. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **271b**.

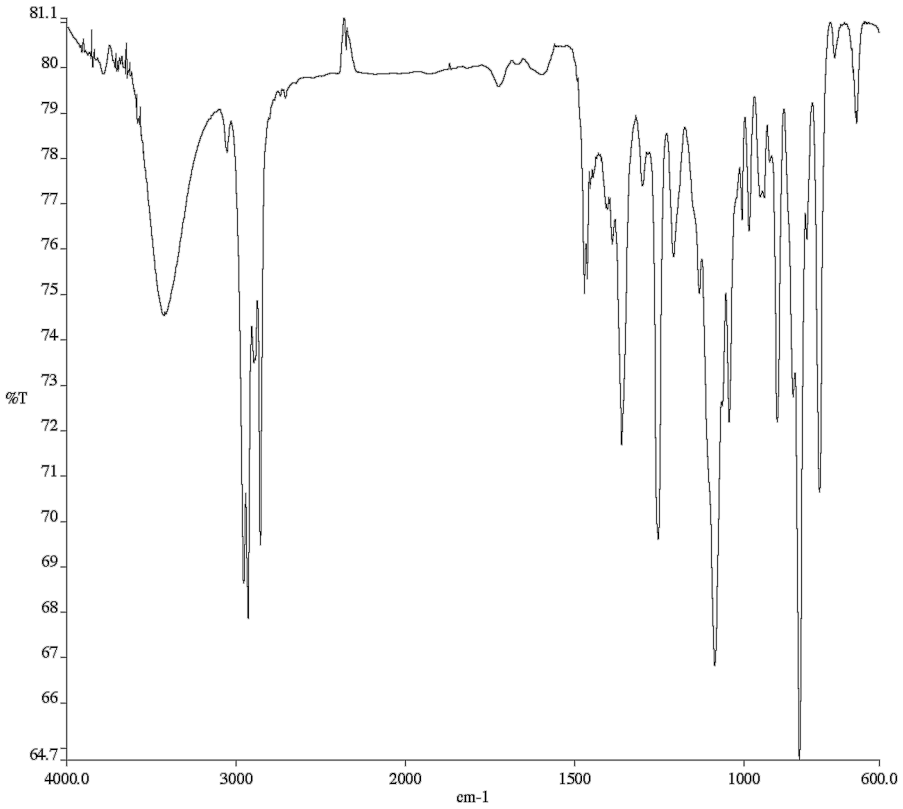


Figure A13.38. Infrared spectrum (Thin Film, NaCl) of compound **271b**.

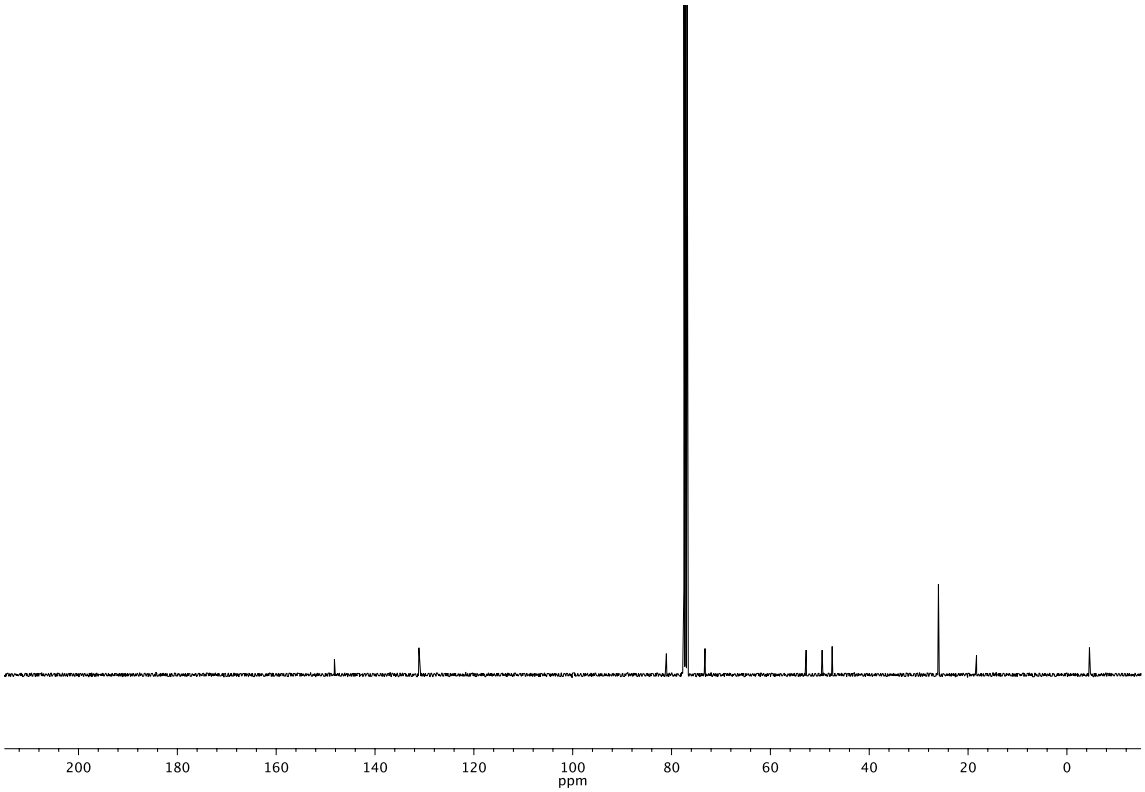


Figure A13.39. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **271b**.

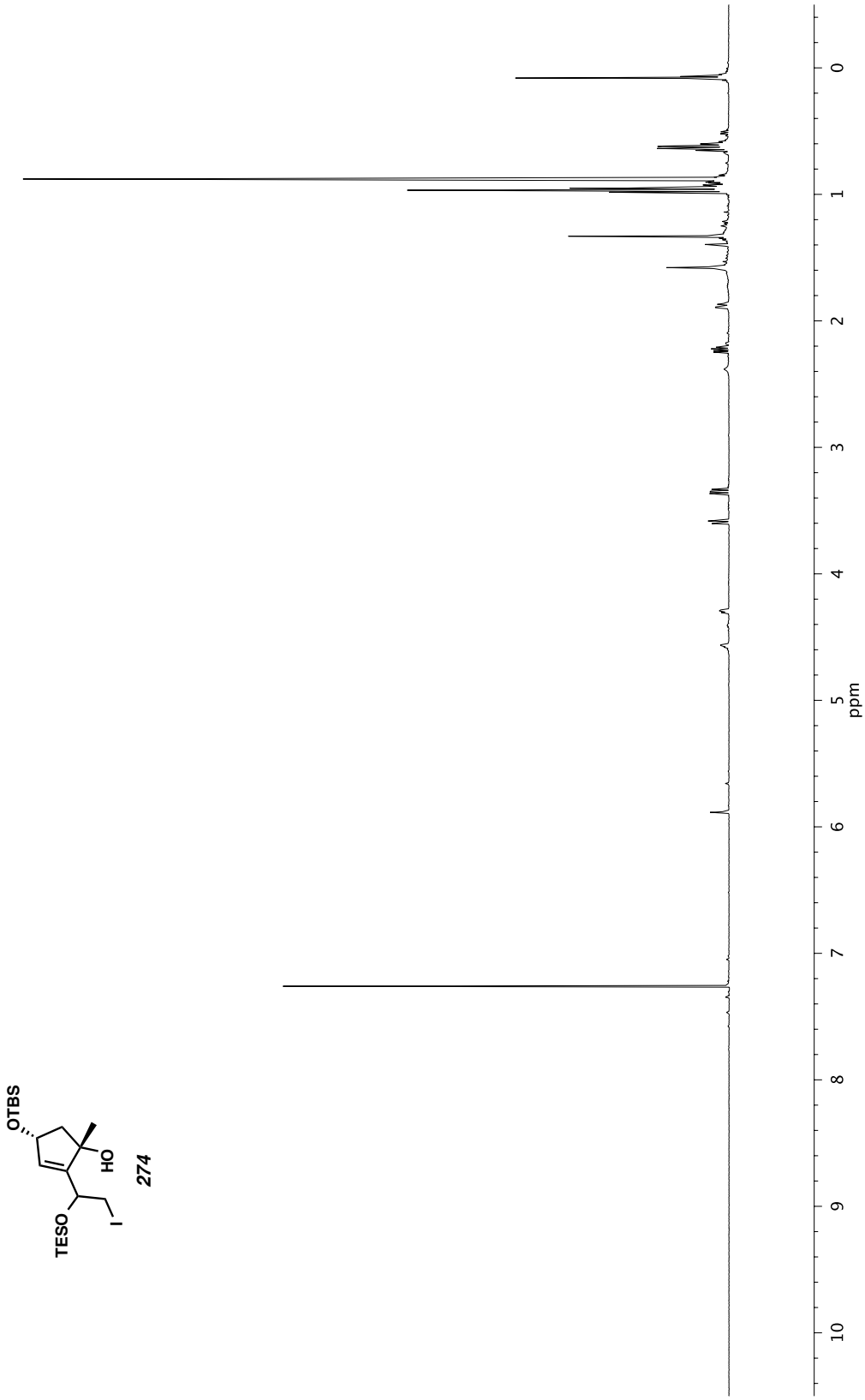


Figure A13.40. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **274**.

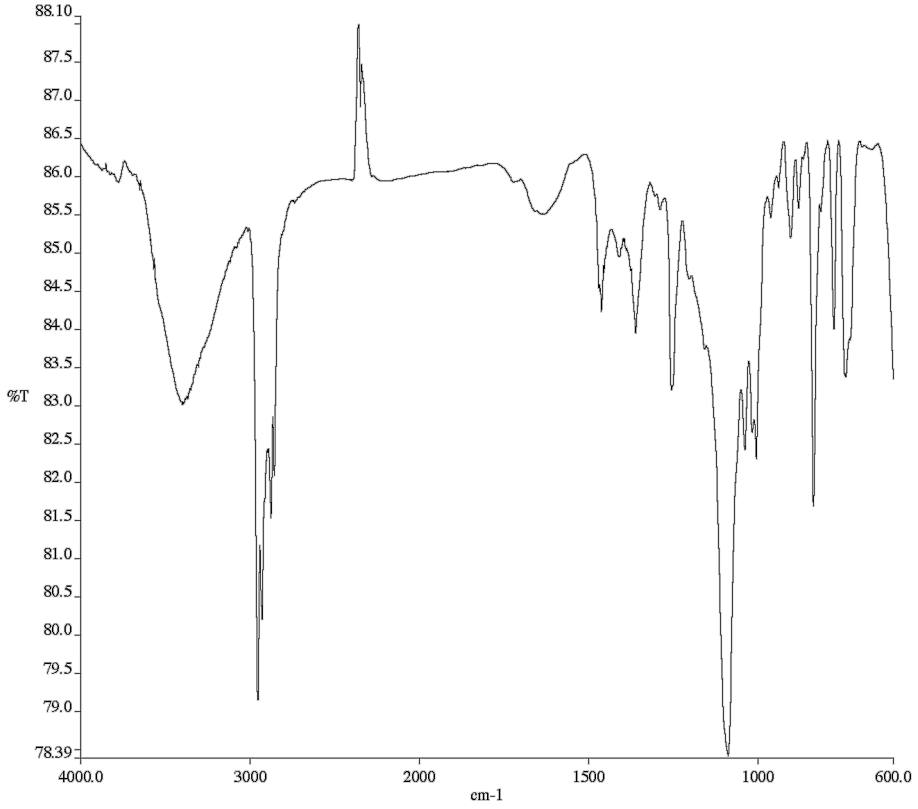


Figure A13.41. Infrared spectrum (Thin Film, NaCl) of compound **274**.

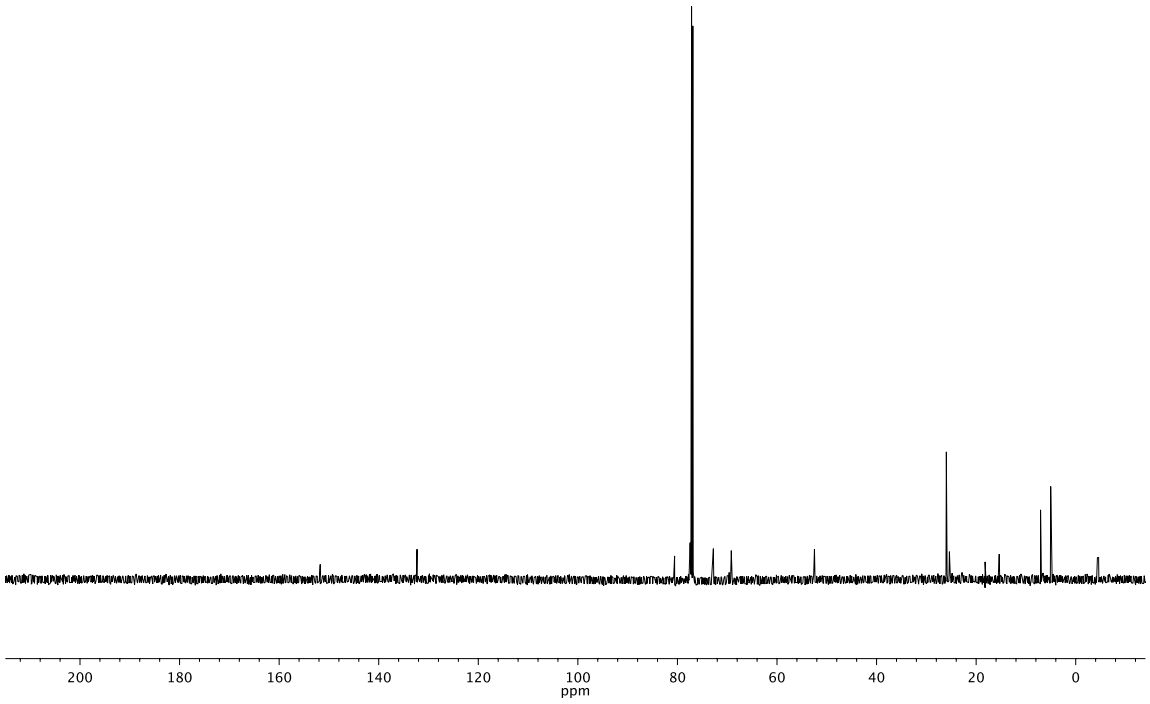


Figure A13.42. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **274**.

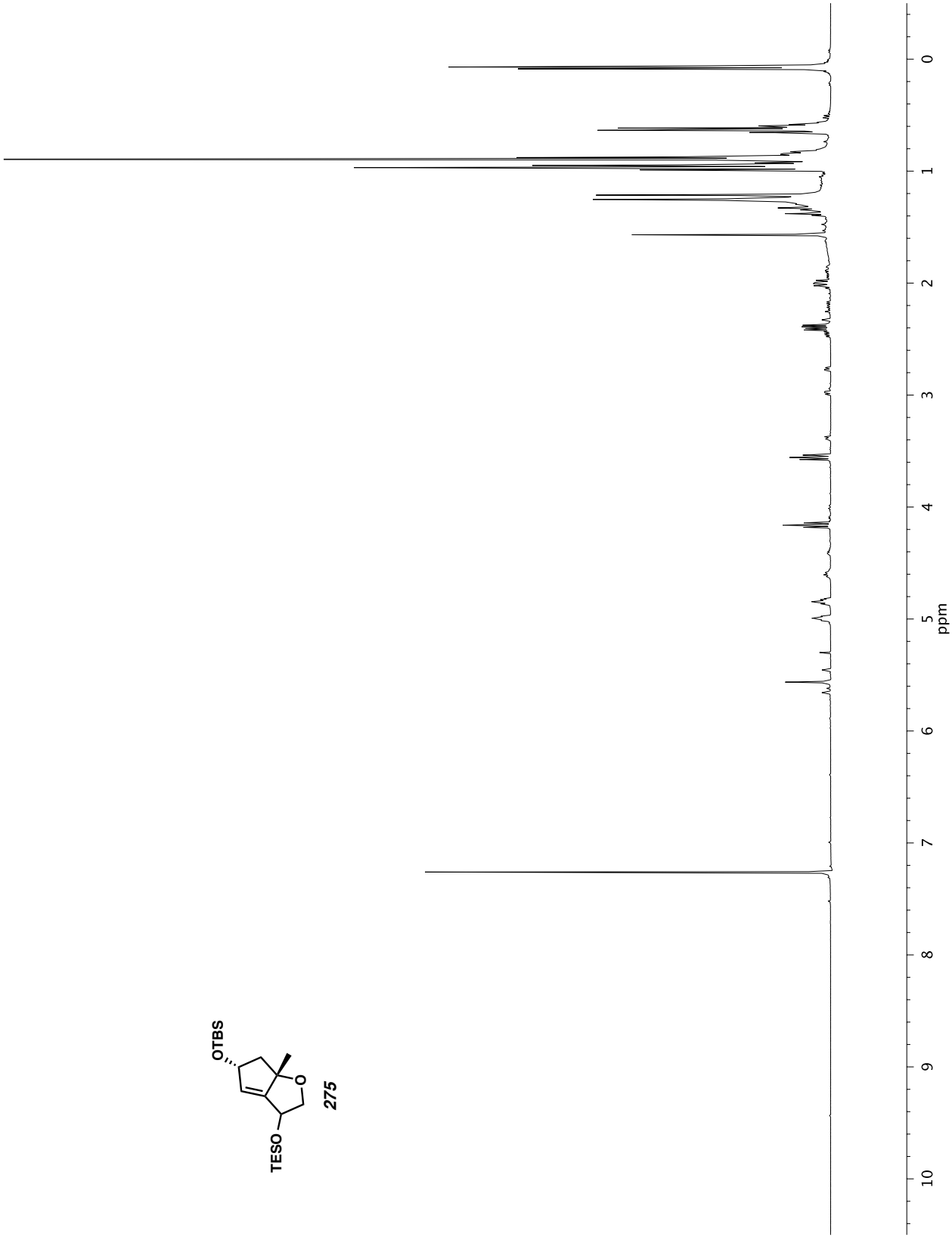


Figure A13.43. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **275**.

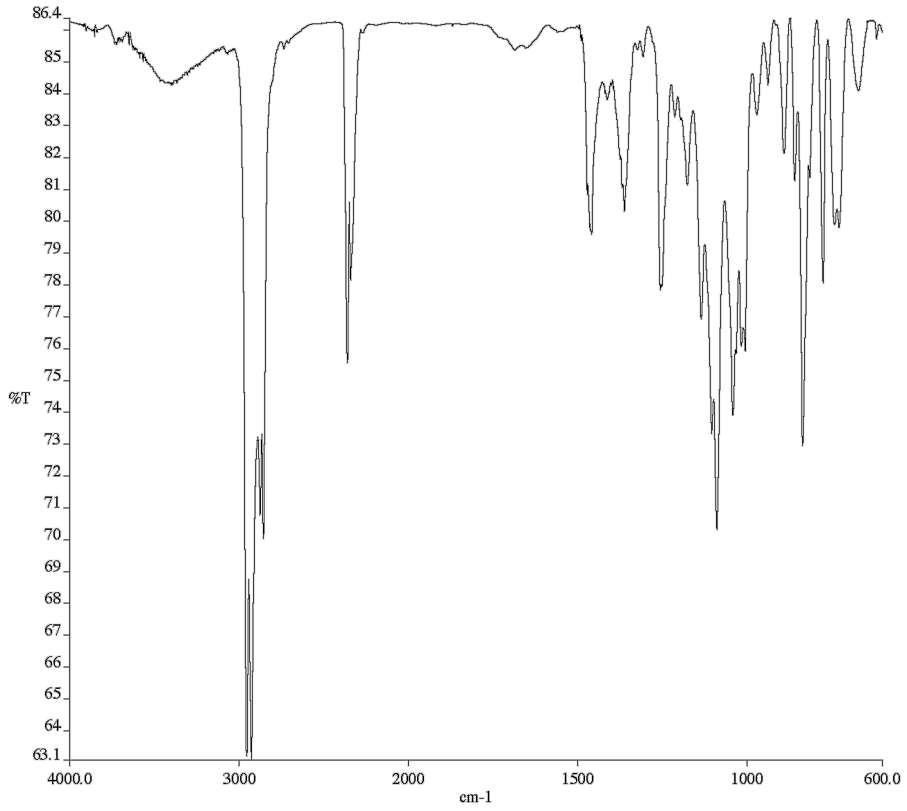


Figure A13.44. Infrared spectrum (Thin Film, NaCl) of compound **275.**

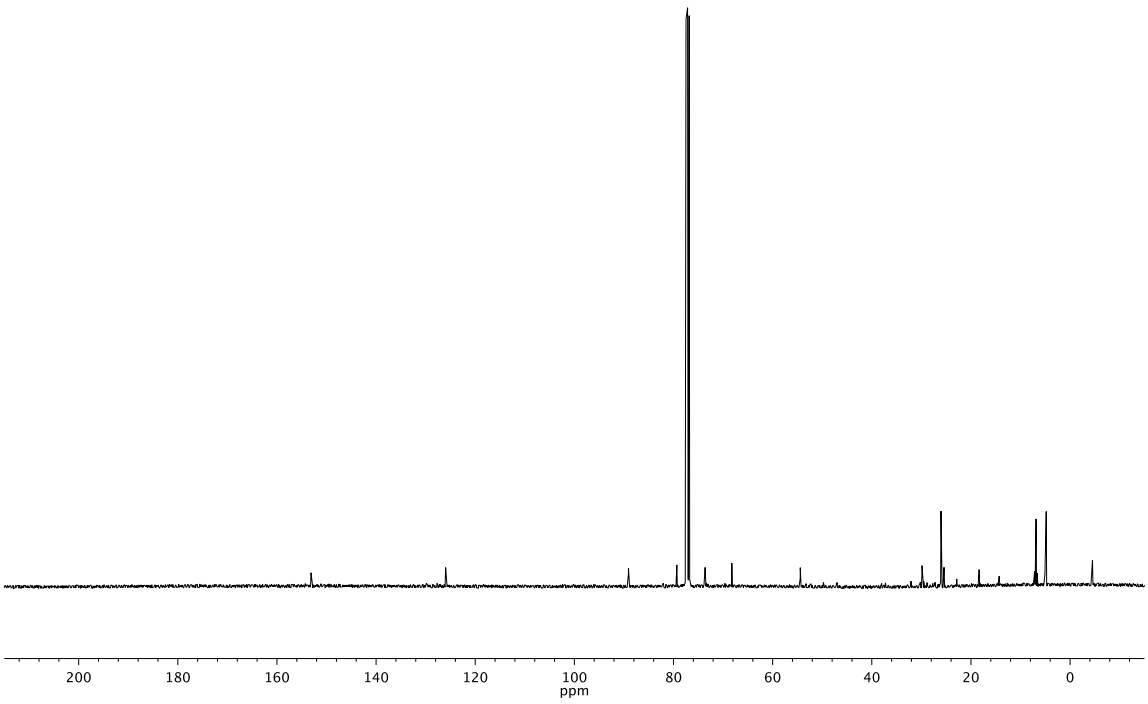


Figure A13.45. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **275**.

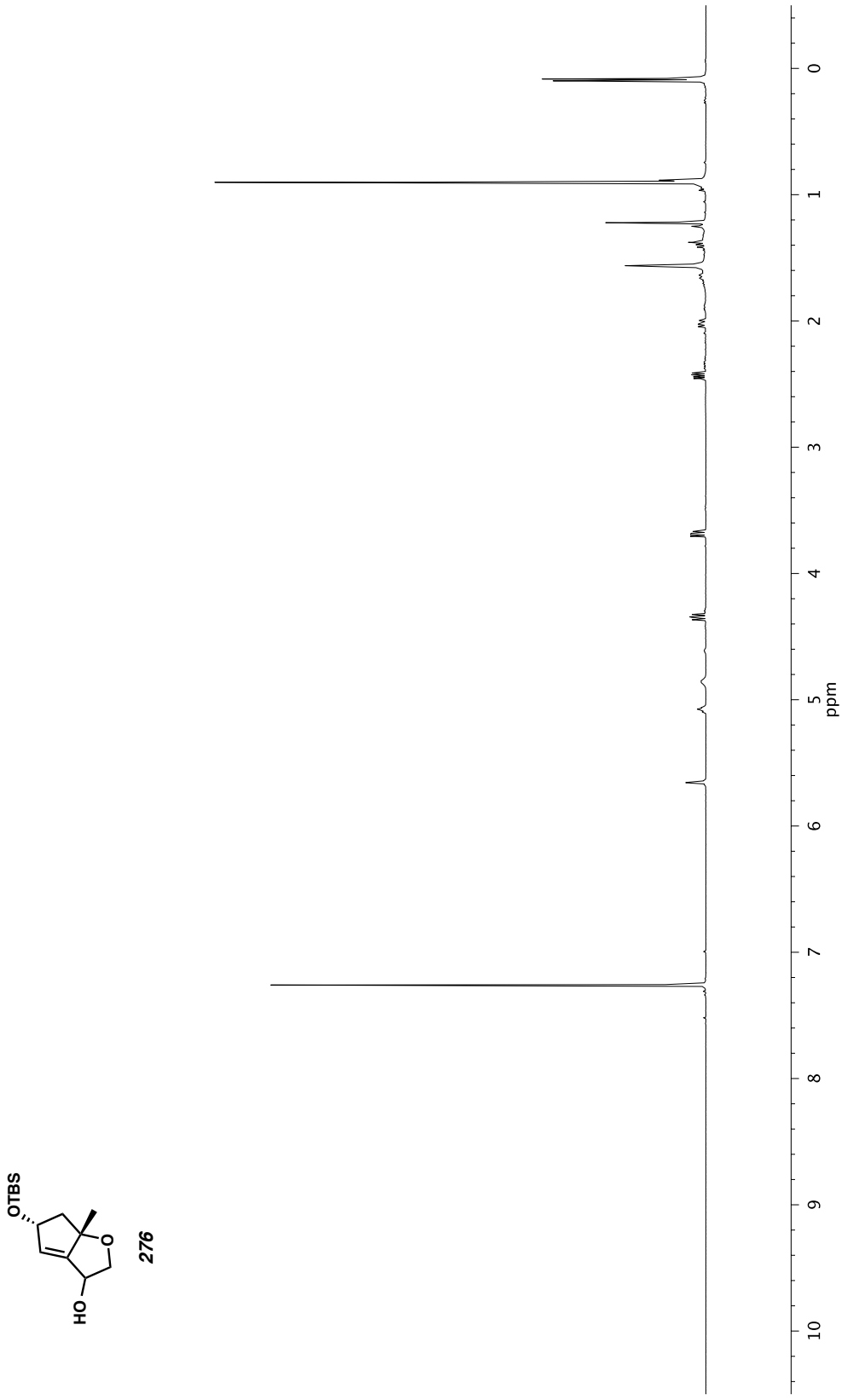


Figure A13.46. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **276**.

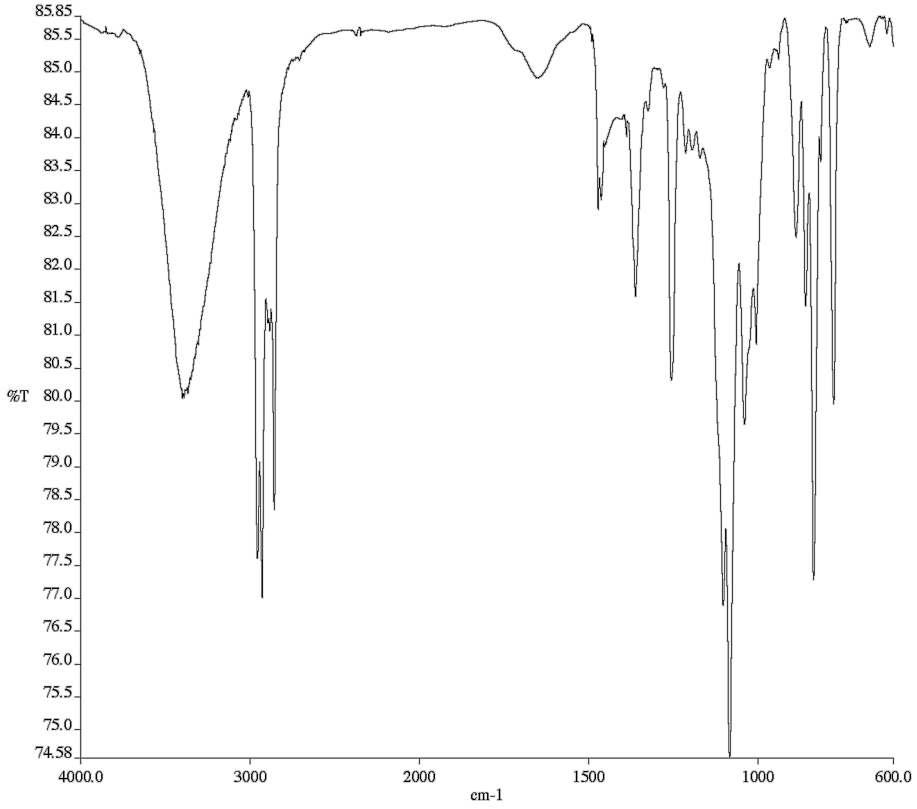


Figure A13.47. Infrared spectrum (Thin Film, NaCl) of compound **276**.

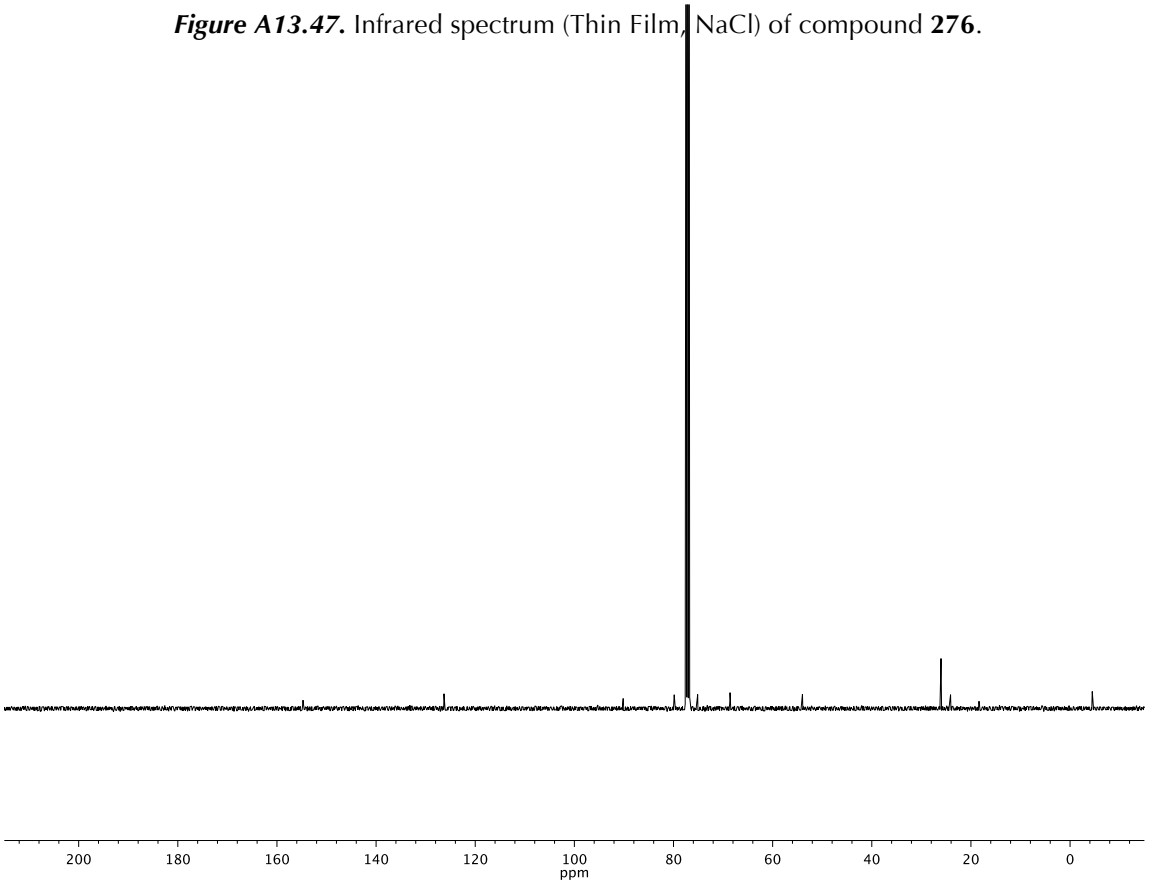


Figure A13.48. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **276**.

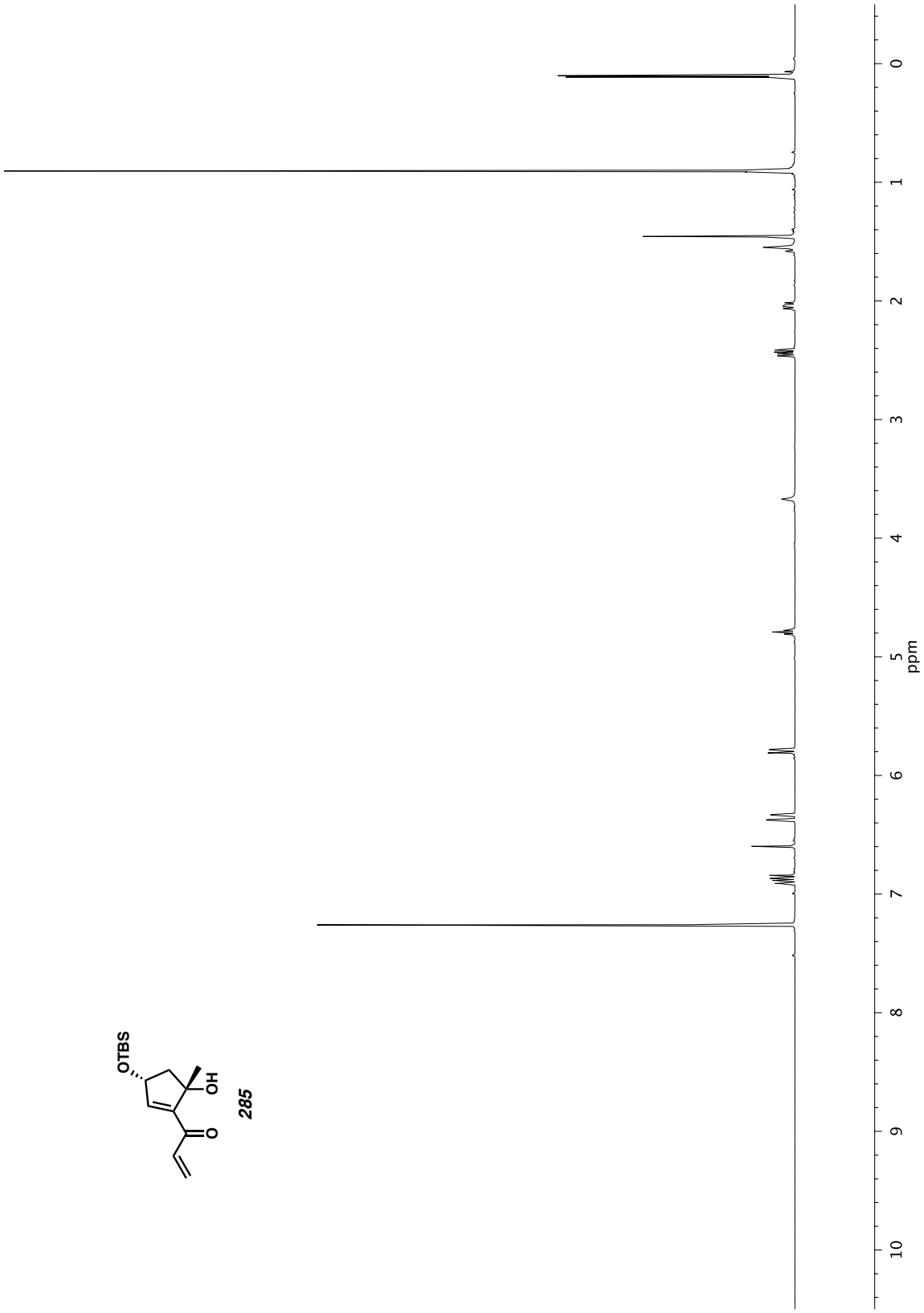


Figure A13.49. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **285**.

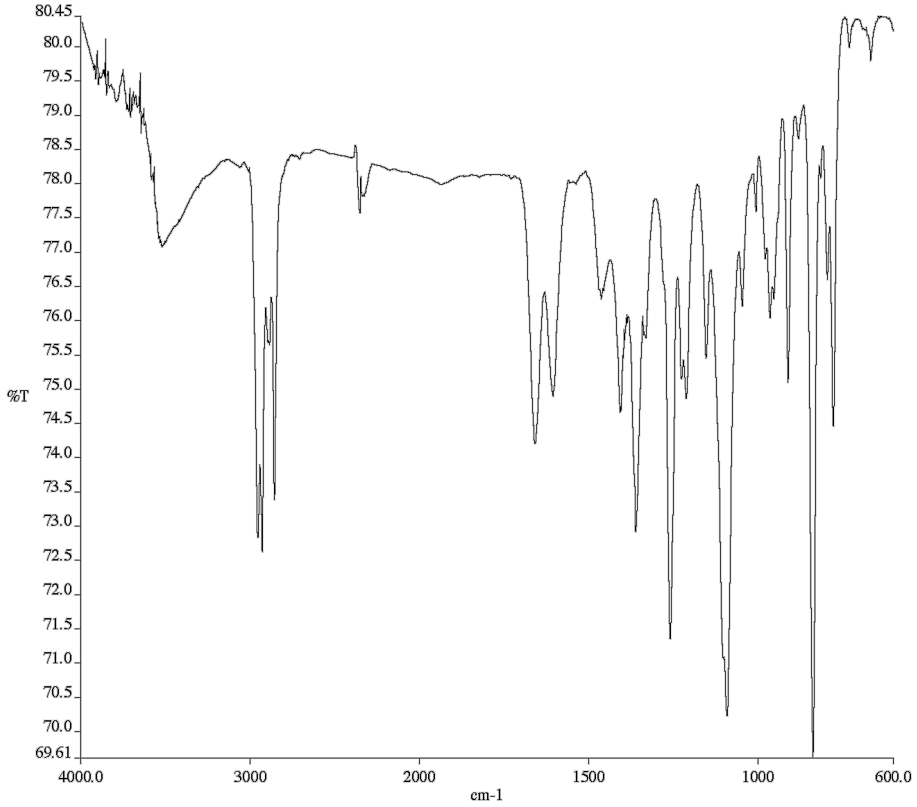


Figure A13.50. Infrared spectrum (Thin Film, NaCl) of compound **285**.

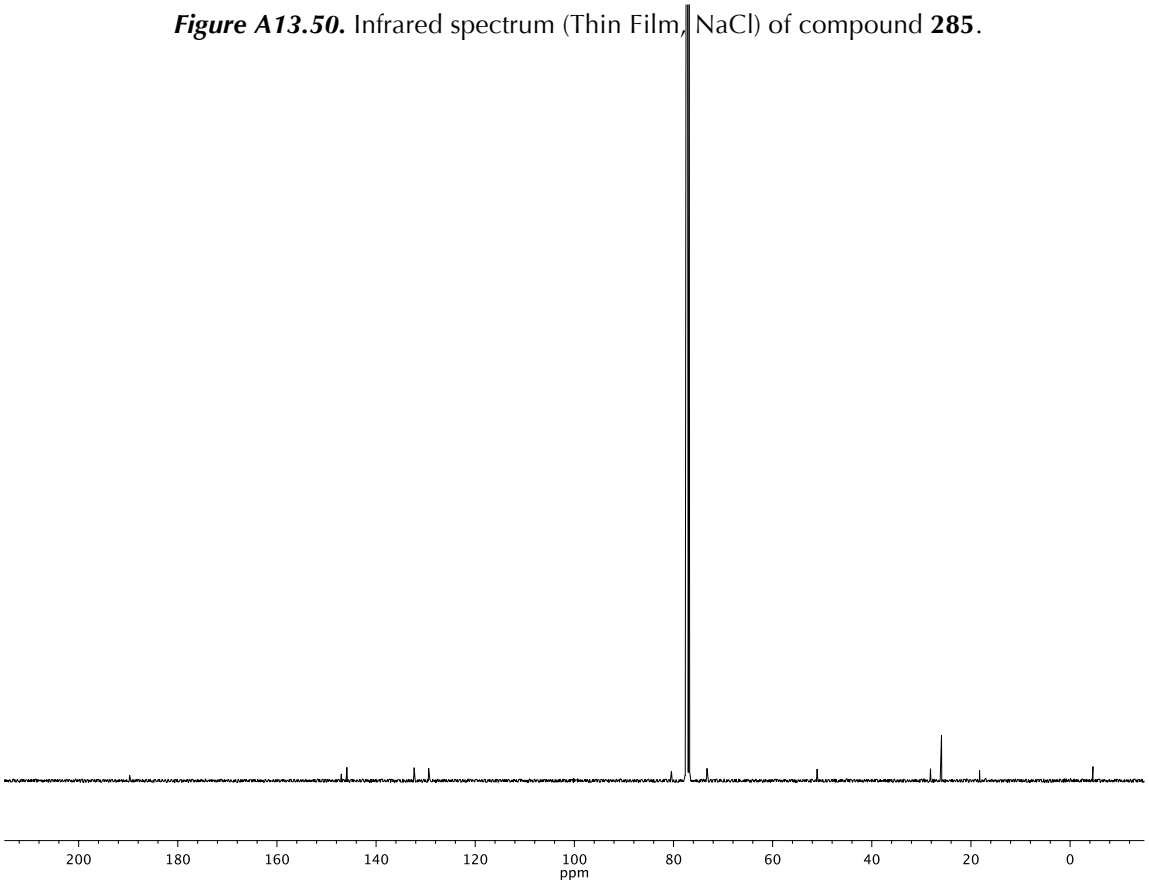


Figure A13.51. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **285**.

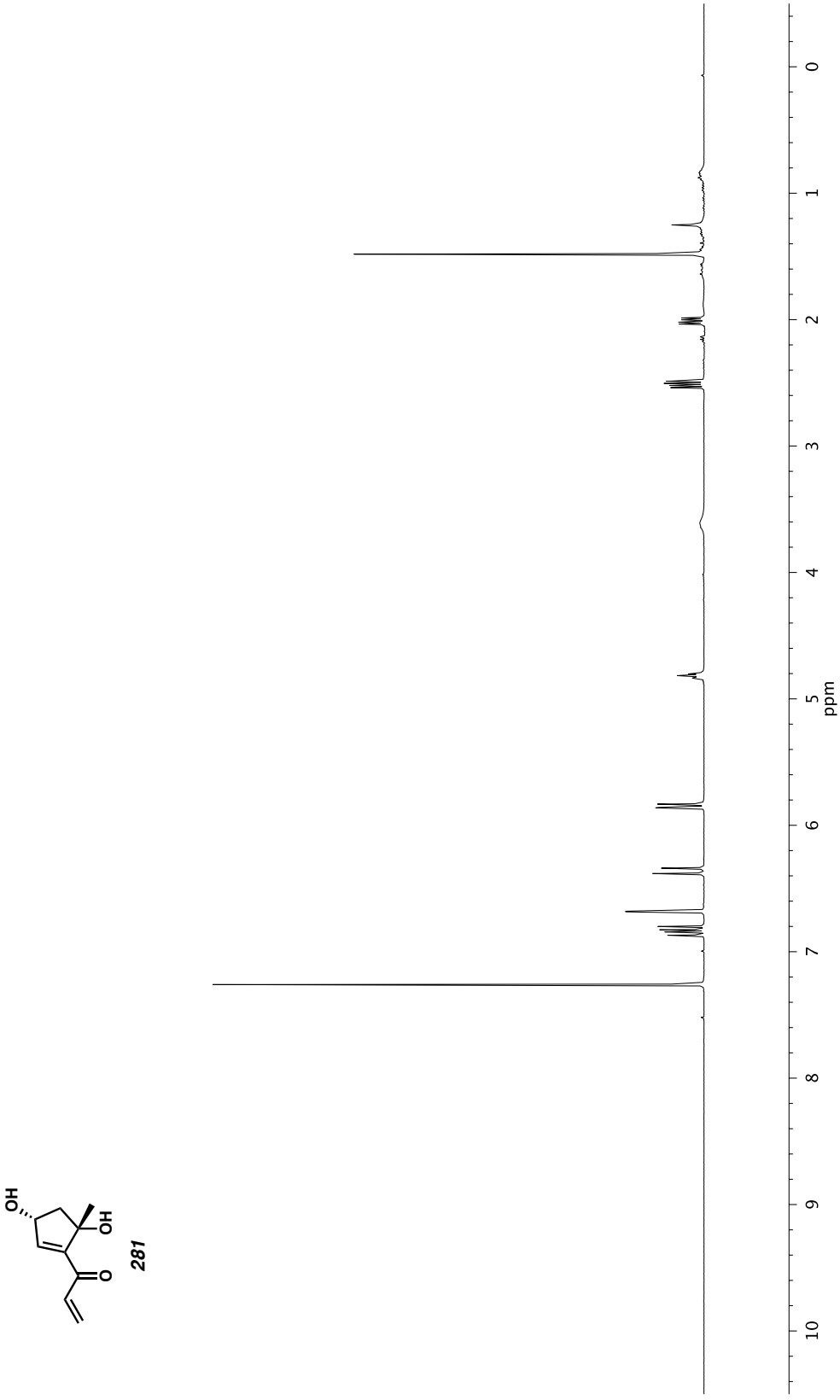


Figure A13.52. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **281**.

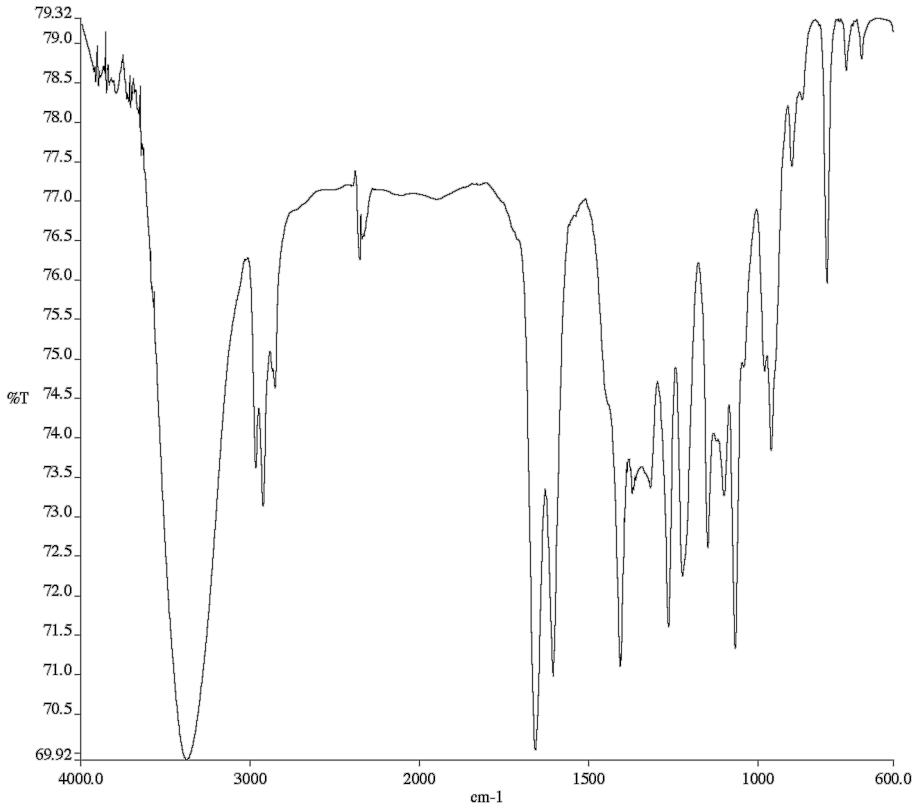


Figure A13.53. Infrared spectrum (Thin Film, NaCl) of compound **281**.

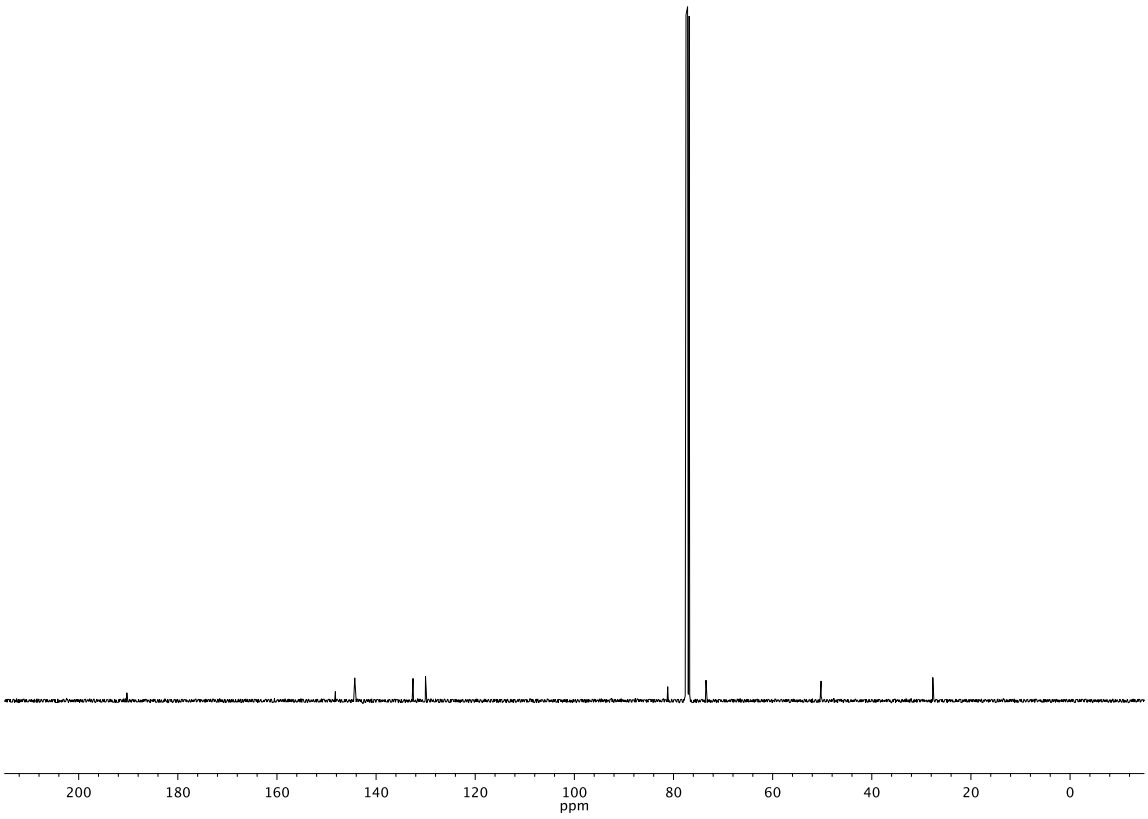


Figure A13.54. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **281**.

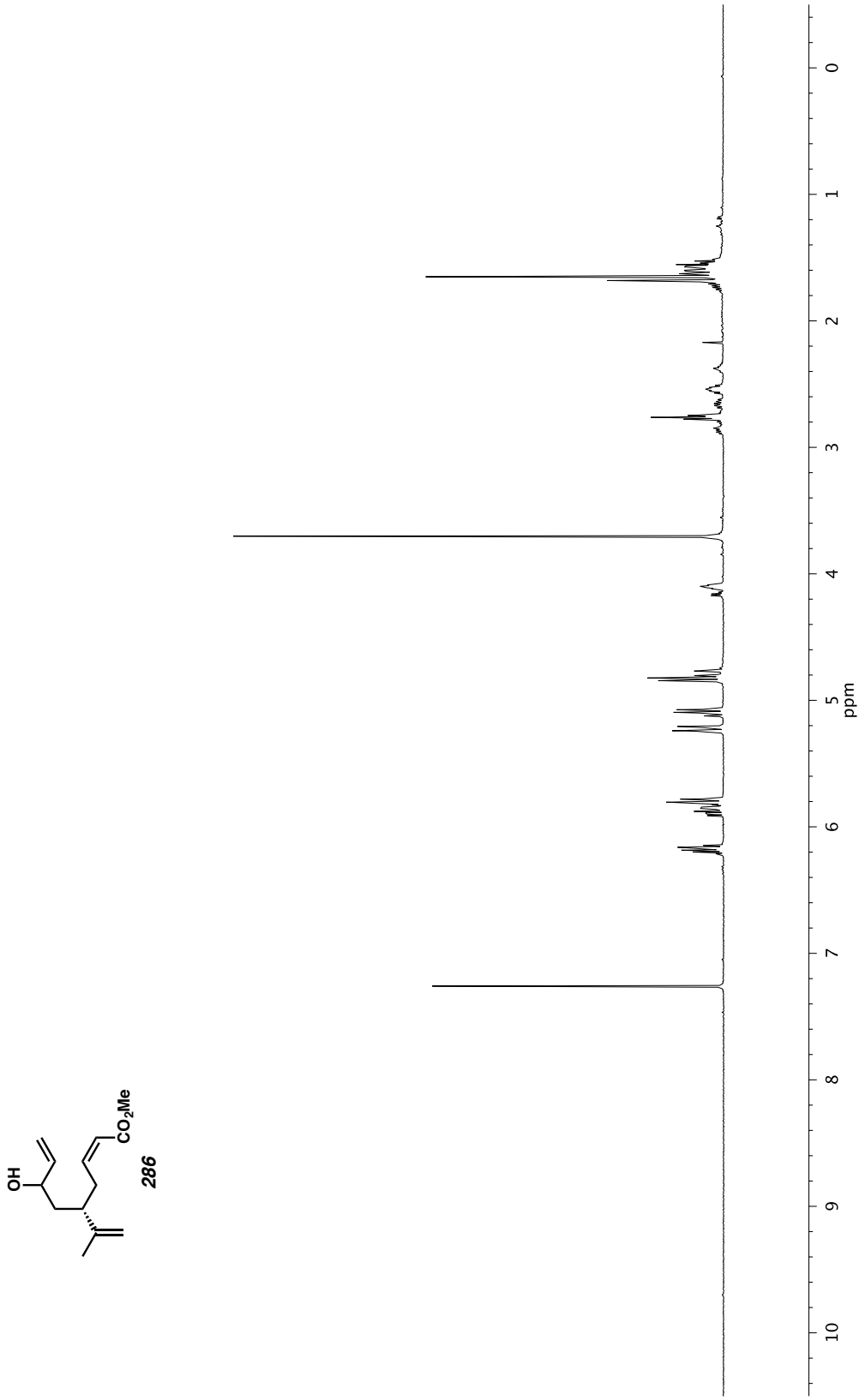


Figure A13.55. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **286**.

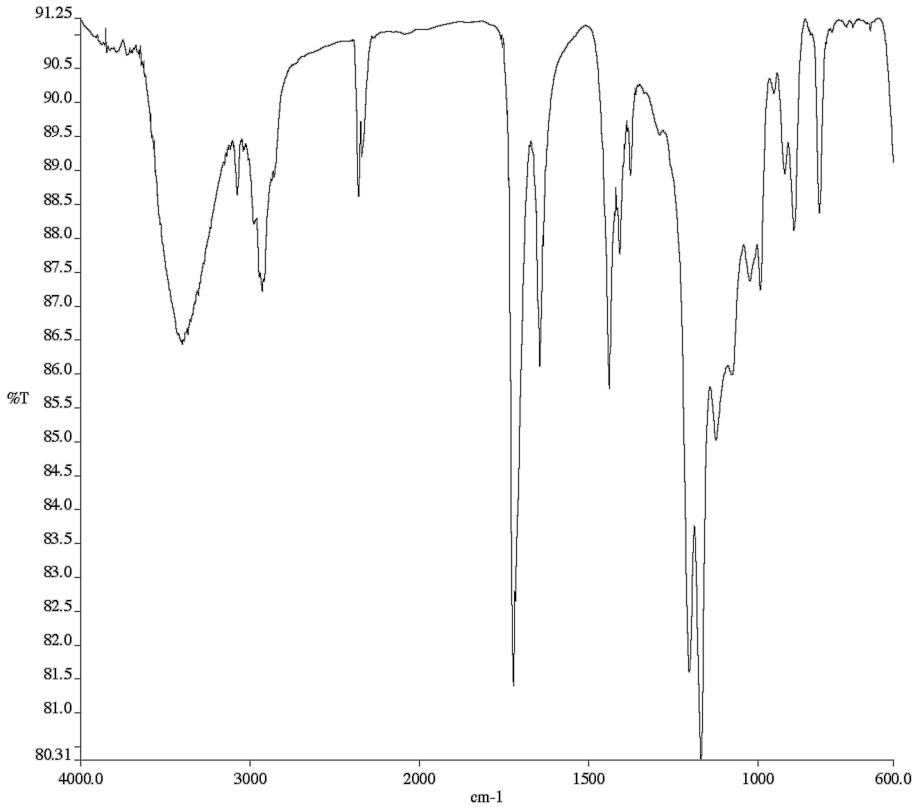


Figure A13.56. Infrared spectrum (Thin Film, NaCl) of compound **286**.

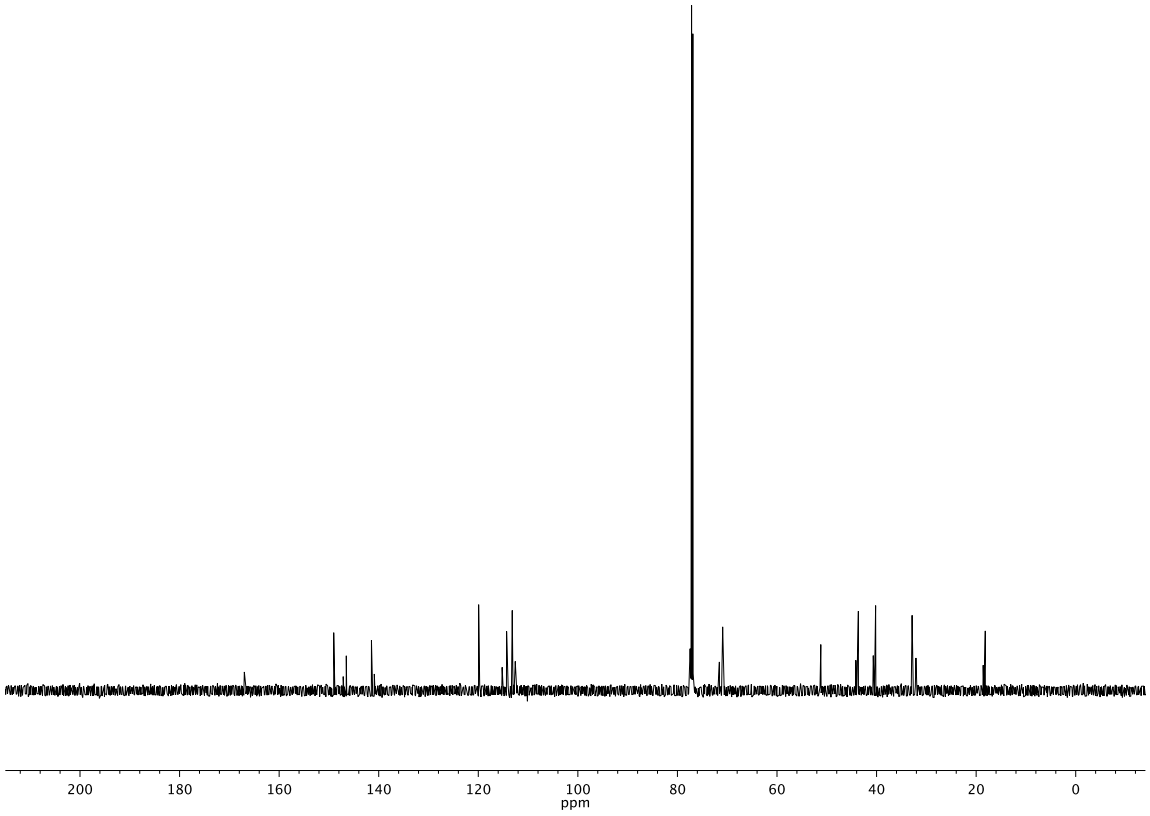


Figure A13.57. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **286**.

Figure A13.58. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **287**.

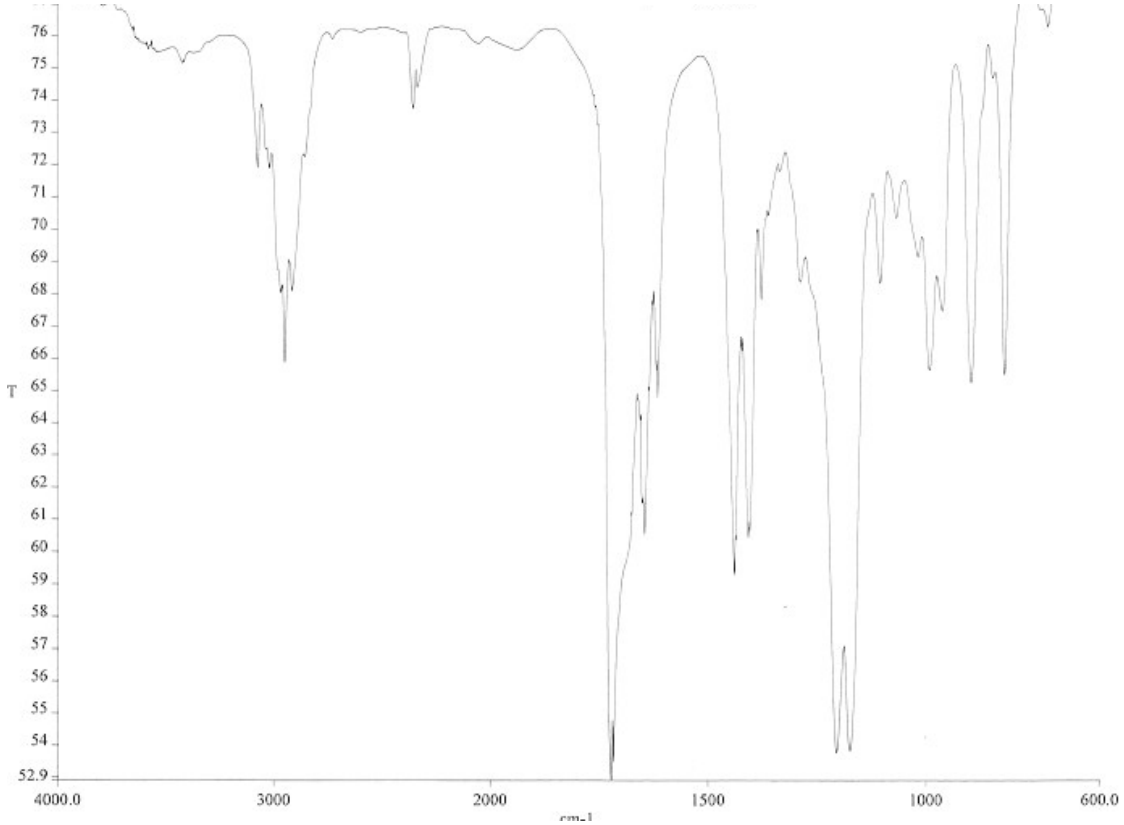


Figure A13.59. Infrared spectrum (Thin Film, NaCl) of compound **287**.

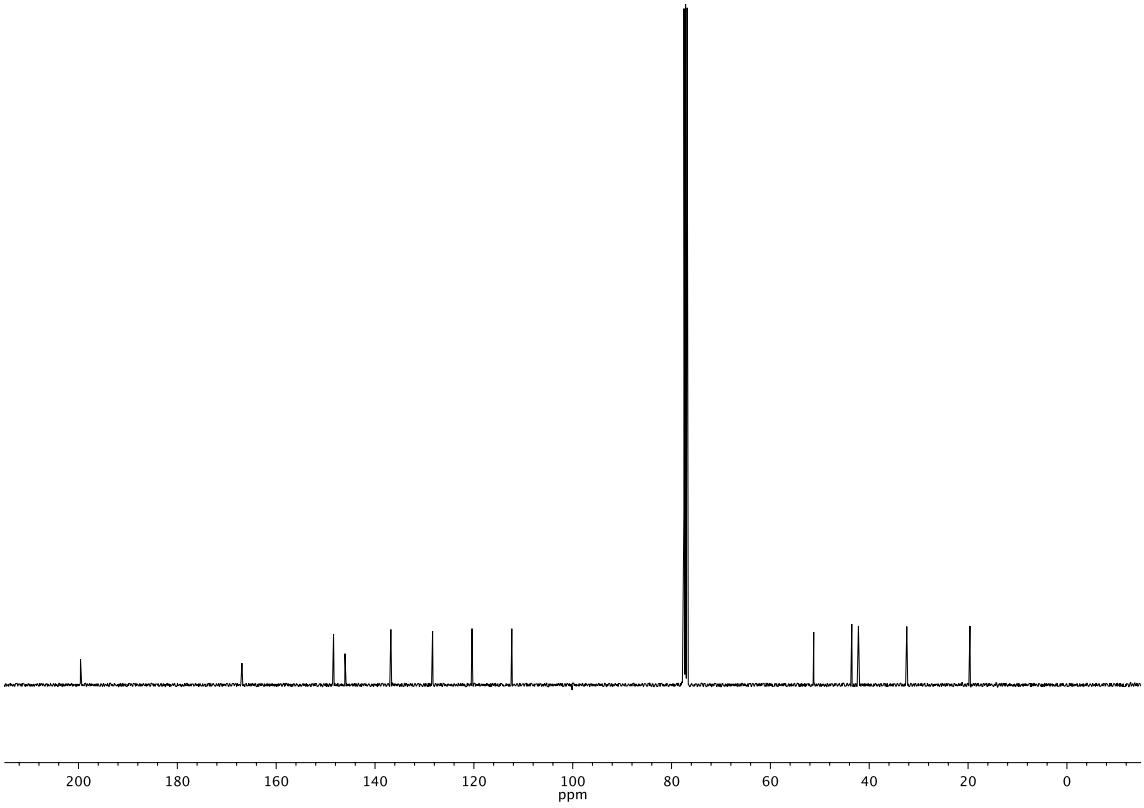


Figure A13.60. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **287**.

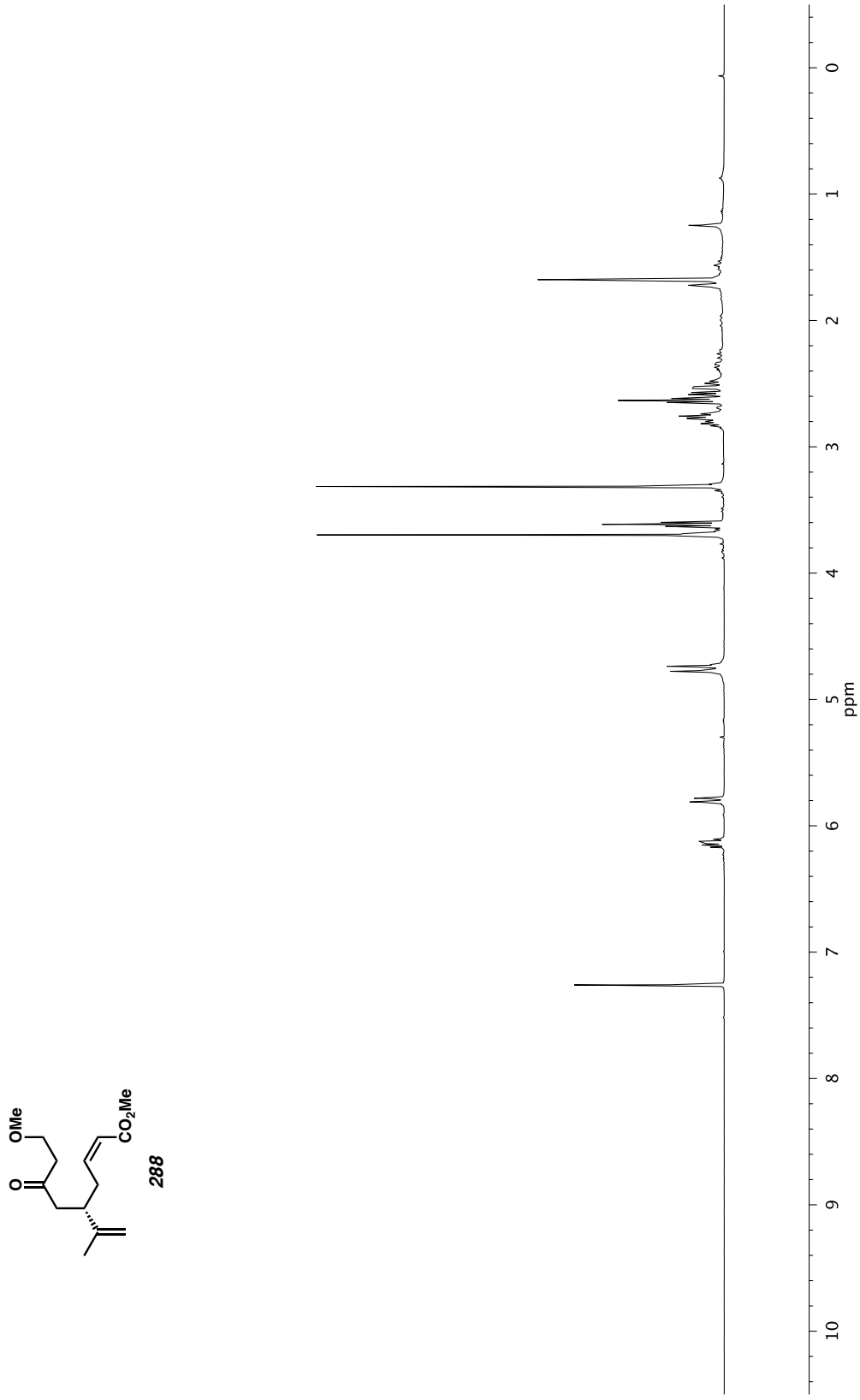


Figure A13.61. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **288**.

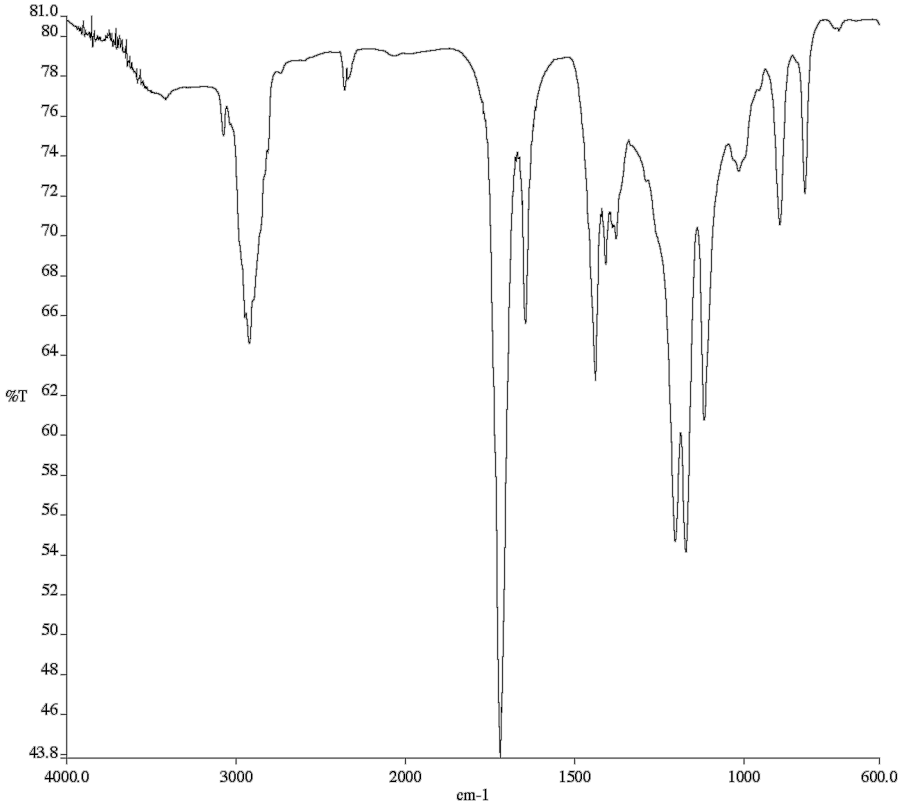


Figure A13.62. Infrared spectrum (Thin Film, NaCl) of compound **288**.

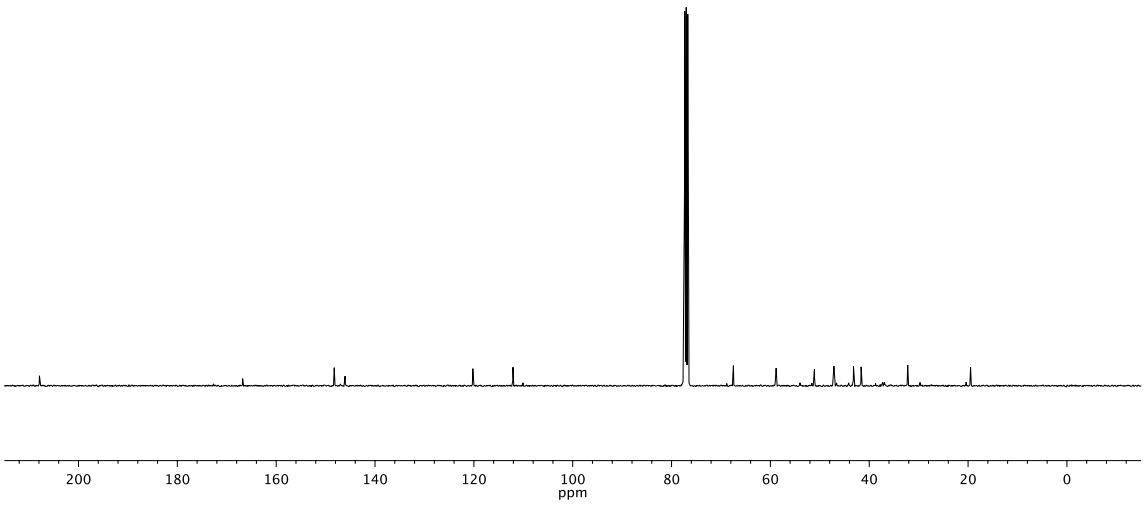


Figure A13.63. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **288**.

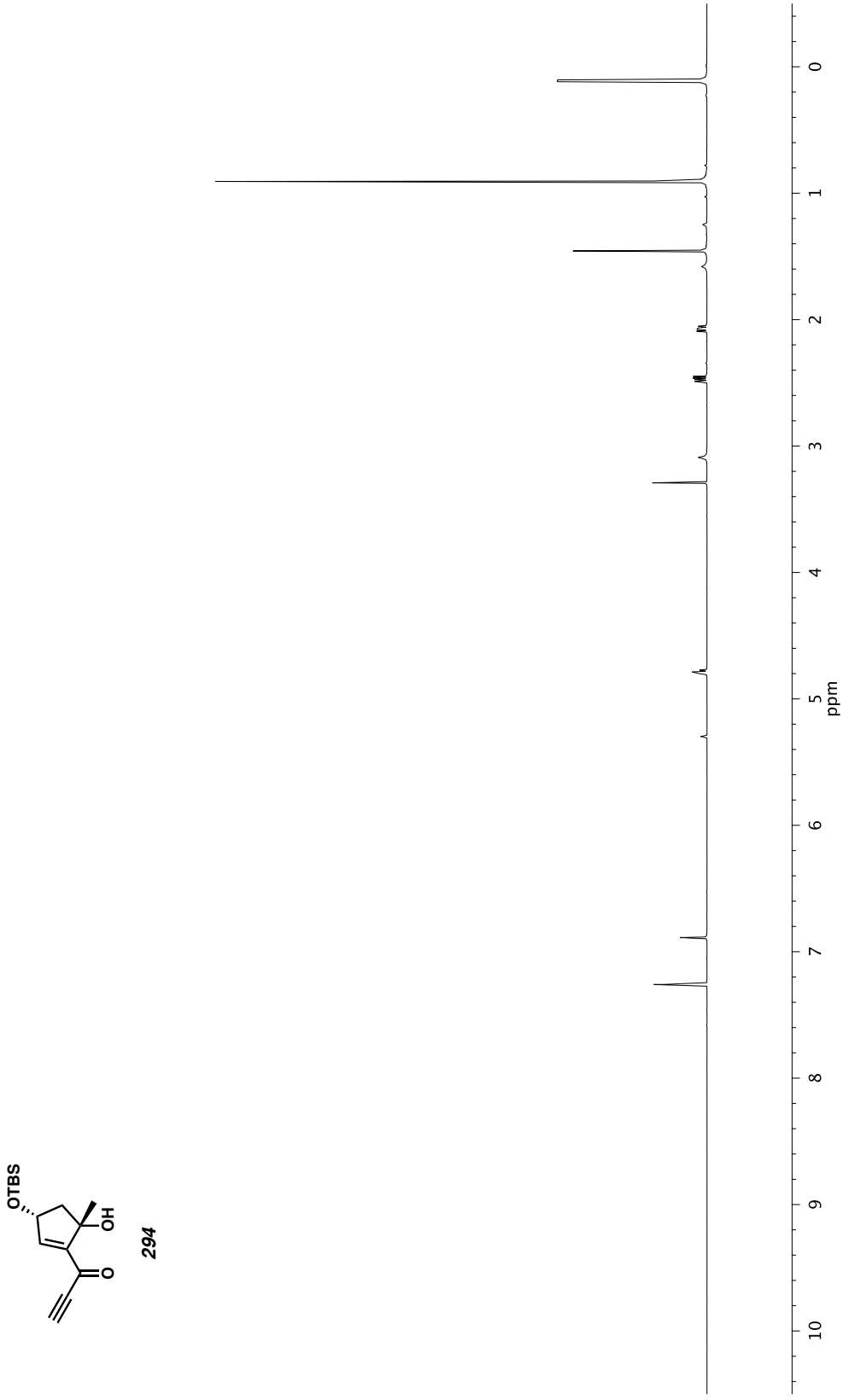


Figure A13.64. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **294**.

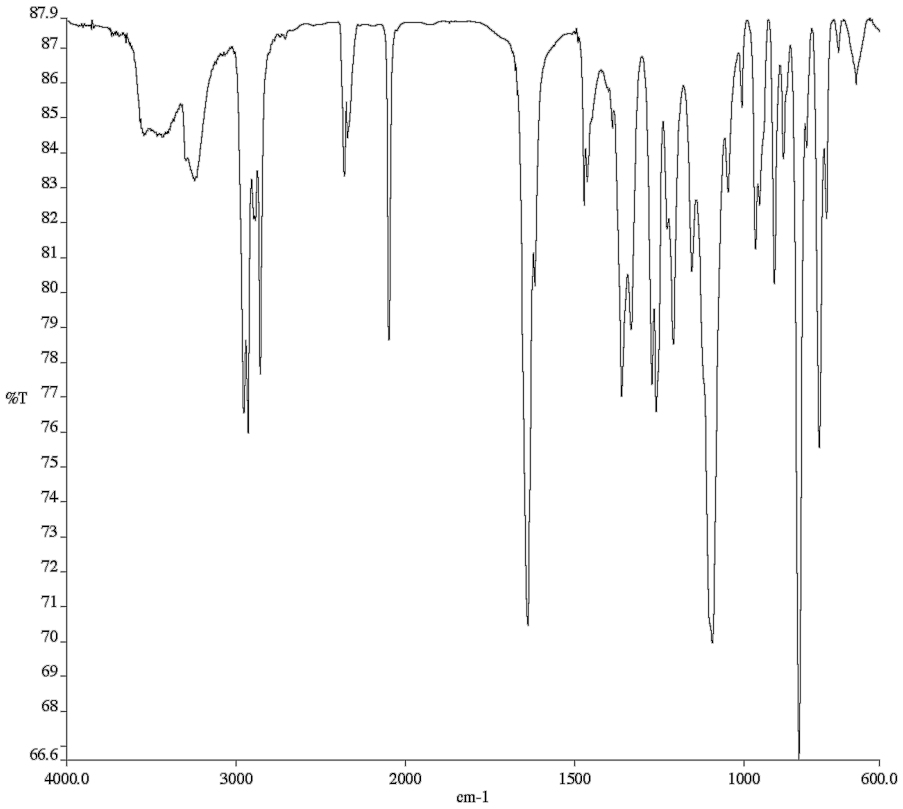


Figure A13.65. Infrared spectrum (Thin Film, NaCl) of compound **294**.

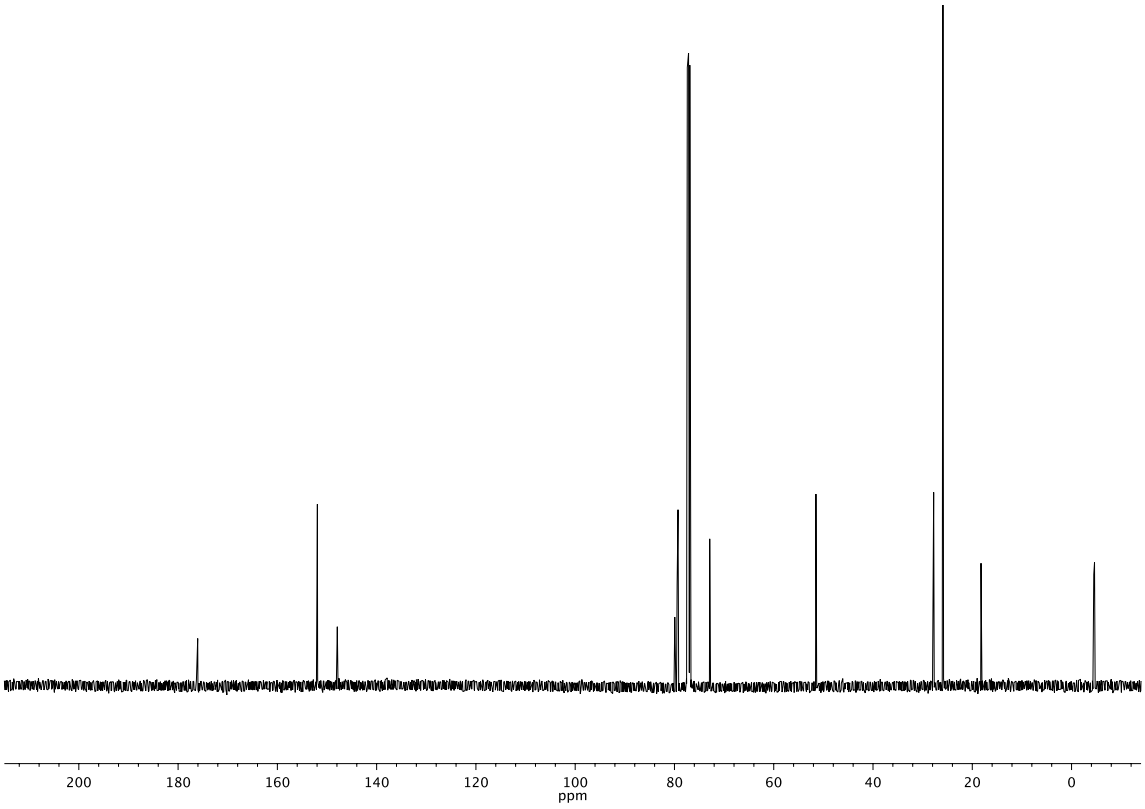


Figure A13.66. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **294**.

APPENDIX 14

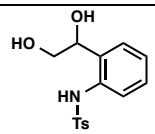
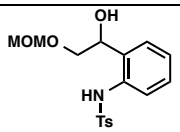
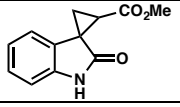
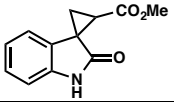
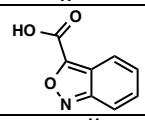
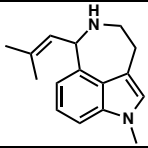
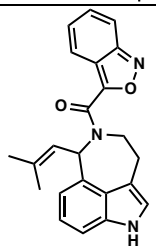
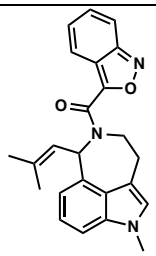
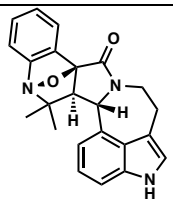
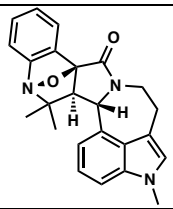
Notebook Cross-Reference for New Compounds

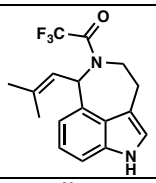
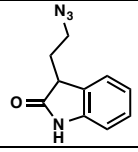
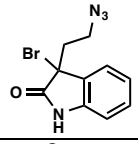
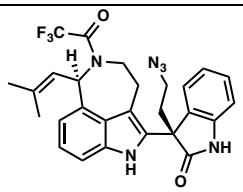
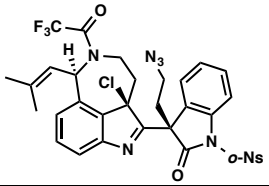
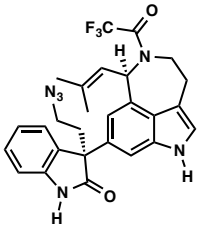
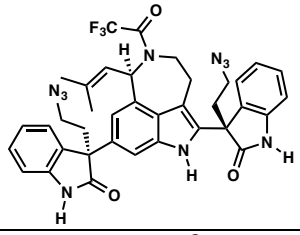
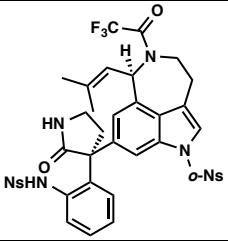
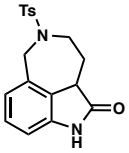
A14.1. Contents

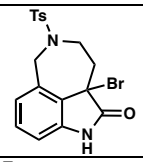
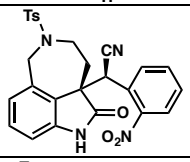
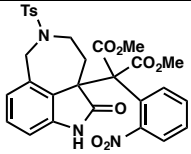
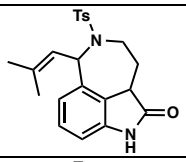
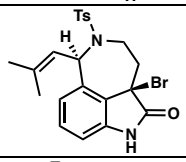
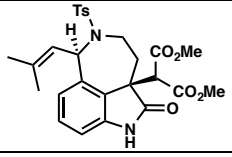
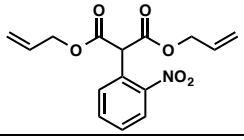
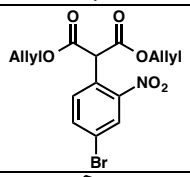
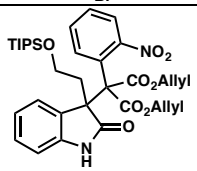
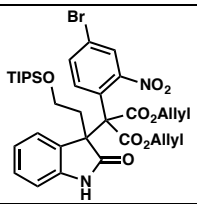
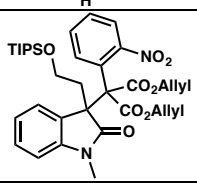
The following notebook cross-reference has been included to facilitate access to the original spectroscopic data obtained for the compounds presented within this thesis. The information is organized by chapter and sequentially by compound number, noting the instrument on which the primary NMR data was collected. All ^{1}H NMR, ^{13}C NMR, and any two-dimensional NMR data available as well as ^{19}F NMF and ^{31}P NMR, if applicable, are electronically stored on the NMR laboratory server (mangia.caltech.edu, most typically under the username 'shan') and on the Stoltz group server. All IR spectra were taken on the Stoltz group IR and an electronic copy of each spectrum as a postscript file can be found on the Stoltz group server. A hard copy of each spectrum has been provided with this text, as well. All laboratory notebooks are stored in the Stoltz group archive.

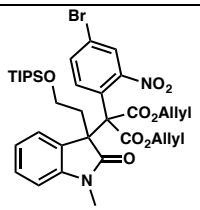
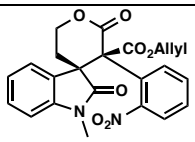
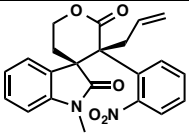
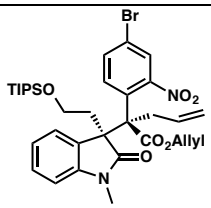
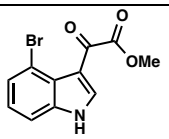
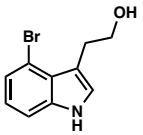
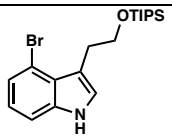
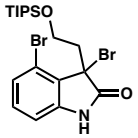
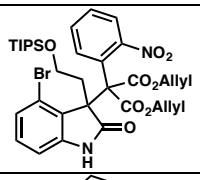
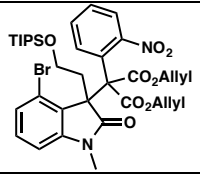
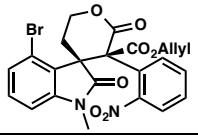
A14.2. Notebook Cross-Reference Tables

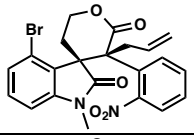
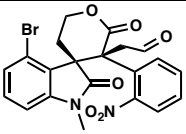
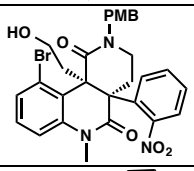
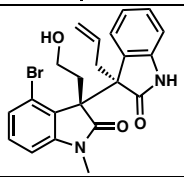
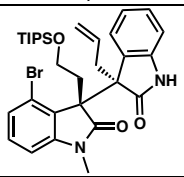
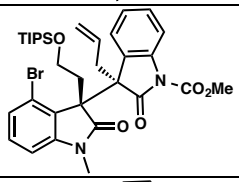
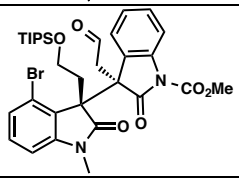
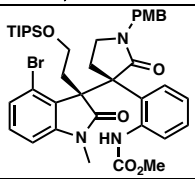
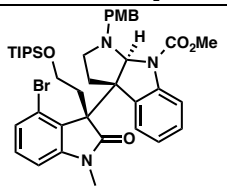
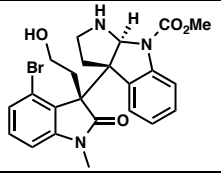
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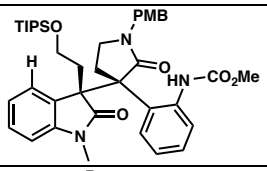
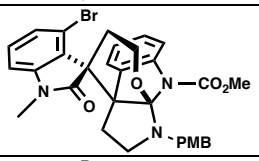
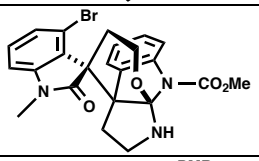
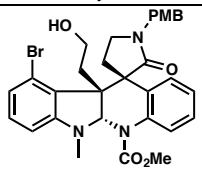
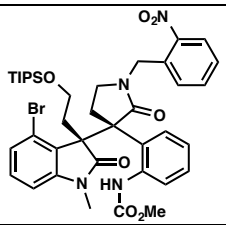
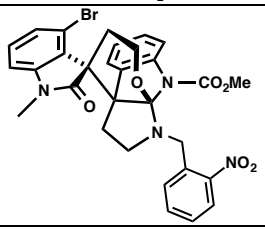
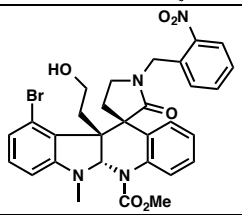
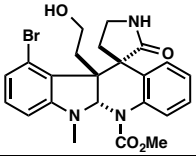
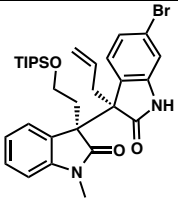
compound	chemical structure	^{1}H NMR	^{13}C NMR	IR
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13		JAMX-75ii	JAMX-75ii	JAMX-75ii
16a		JAMXII-75ii	JAMXII-75ii	JAMXII-75ii
16b		JAMXII-75iii	JAMXII-75iii	JAMXII-75iii
20		JAMXVI-201	JAMXVI-201	JAMXVI-201
5		JAMXIII-45i	JAMXIII-45i	JAMXIII-45i
22		JAMXVI-157	JAMXVI-157	JAMXVI-157
19		JAMXVI-155	JAMXVI-155	JAMXVI-155
23		JAMXVI-161	JAMXVI-161	JAMXVI-161
24		JAMXVI-159	JAMXVI-159	JAMXVI-159

25		JAMXVI-41i	JAMXVI-41i	JAMXVI-41i
SI-1-7		JAMXV-243iii	JAMXV-243iii	JAMXV-243iii
26		JAMXV-243i	JAMXV-243i	JAMXV-243i
28		JAMXVI-85iib	JAMXVI-35iib	JAMXVI-35iib
29		JAMXV-233	JAMXV-233	JAMXV-233
30		JAMXVI-47iib	JAMXVI-47iib	JAMXVI-47iib
31		JAMXVI-85iv	JAMXVI-85iv	JAMXVI-85iv
32		JAMXVI-93	JAMXVI-93	JAMXVI-93
SI-1-11		SK-IV-27-2B	SK-IV-27-2B-c13	Communesin_SI_11_sk-3-281_SI-11

35		SK-5-201-2A	SK-5-201-2A_C13	Communesin_35_SK-5-125-35
37		SK-7-183-f6+7	SK-7-183-C13	37_SK-183-37
39		SK-4-219-2	SK-4-219-2_C13	39_SK-4-219-39
SI-1-13		SK-5-93-2B	SK-5-93-2B_C13	SI-13_SK-5_93_SI-13
40		SK-6-99-2A	SK-6-99-2A-C13	40_SK-6-99-40
42		SK-6-203-3-1H	SK-6-203-3-13C	42_SK-6-203-42
44		hsj_ch_comm_nas	hsj_ch_comm_nas	44_Comm_NAS
45		20130328_pero_ch_coupling_precursor	20130328_pero_ch_coupling_precursor	45_pero_coupling_precursor
46		FV-I-091	FV-I-091	46_coupling_MS
47		20130403_pero_ch_coupling	20130403_pero_ch_coupling	47_pero_coupling
48		FV-I-097-1	FV-I-097-1	48_MeI_MS

49		pero_ch_ methylation	pero_ch_ methylation	49_pero_ methylation
50		FV-I-179	FV-I-179	50_ lactonization
51		FV-I-189-1	FV-I-189-1	51_Tsuji_ model study
52		20130404_ pero_ch_ Tsuji	20130404_ pero_ch_ Tsuji	52_pero_tsuji
SI-1-16		03272012_ Oxyalyl_ column	03272012_ Oxyalyl_ column	SI-16_Com_ oxalyl
59		03282012_ Comm_ LAH	03282012_ Comm_ LAH_ reduction_C	59_Com_LAH reduc
SI-1-17		Comm_TIPS _protection	Comm_TIPS _protection	SI-17_Com _tips_protec
57		HSJ_ch_ communesin_ oxidative_ bromination	HSJ_ch_ communesin_ oxidative_ bromination	57_3-bromo oxindole
SI-1-18		ch_commune _coupling	hsj_comm_ coupling	SI-18_comm_ coupling
60		hsj_ch_ comm_ methylation	hsj_ch_ comm_ methylation	60_com_ Methylation
61		hsj_ch_TIPS _depro_cycle	hsj_ch_TIPS _depro_cycle	61_Tips_ depro_cycle

62		hsj_Tsuji	Tsuji_C	62_tsuji
63		20131003_ aldehyde_fl _ch	20131003_ aldehyde_fl _ch	63_Floh_ aldehyde
65		20131001_ Floh_RA	20131001_ Floh_RA	65_FL_ reductive_ amination
67		1_comm_ nitro reduction_ 02_17	1_comm_ nitro reduction_ 02_17	67_nitro recution
SI-1-19		TIPS_ protection	TIPS_ protection	SI-19_ TIPS Protection
68		20121017_ CO2Me_ Chara	20121017_ CO2Me_ Chara	68_ CO2Me_ protection
69		1_comm_ aldehyde_ 500	1_comm_ aldehyde_ 500	69_ aldehyde
54		Comm_ PMB_ cycle	Comm_ PMB_ cycle	54_PMB_ cycle
71		1_53_ final_ cyclization_ comm	1_53_ final_ cyclization_ comm	71_5,5_ fused_ AlH3
72		Comm_final_ 2nd_last	Communesin _final_C	72_5,5_ fused_depro

73		20120621_ LAH_new	20120621_ LAH_C	73_LAH_ Debro
74		20130920_ Tf2O_PMB _char	20130920_ Tf2O_PMB _char	74_Tf2O_ PMB
75		20130926_ pmb_depro	20130926_ PMB_ depro_cage_ C	75_PMB_ depro_cage
76		20130922_ Dibal_ PMB_ch	20130922_ Dibal_ PMB_ch	76_dibal_ PMB
78		20130507_ comm_ch_ reductive_ amination	20130507_ comm_ch_ reductive_ amination	78_comm_ nitro_ reductive amination
SI-1-20		20130507_ Comm_ Tf2O	20130507_ comm_ Tf2O_C	SI-20_ch_ caged nitro
79		20130322_ dibal_nitro_ rearr	20130322_ dibal_nitro_ rearr	79_dibal_ nitro
53		20130325-final-communesin-CDCl3	20130325-final-communesin-CDCl3	53_comm_ final
82		20130405_ pero_Ti_NO2 _reduction	20130405_ pero_Ti_NO2 _reduction	82_pero_Ti_ cyclization

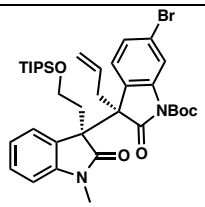
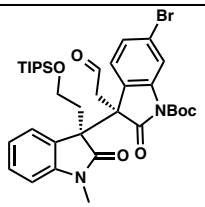
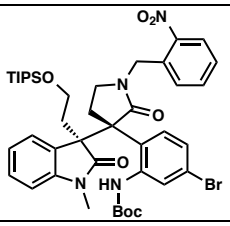
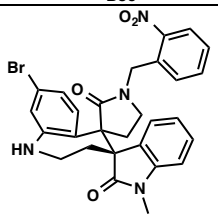
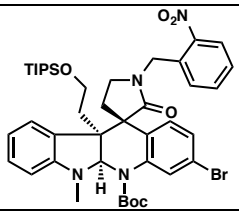
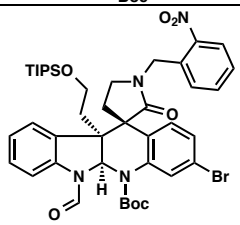
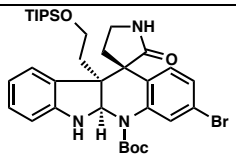
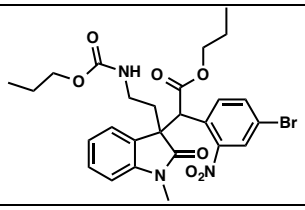
83		20130407_ pero_Boc_ protection	20130407_ pero_Boc_ protection_ch	83_pero_Boc _protection
81		20130408_ pero_ch_ aldehyde	20130408_ pero_ch_ aldehyde	81_pero_ aldehyde
84		20130409_ pero_ nitrobenzyl_ reductive_ amin	20130508_ pero_ reductive_ amination	84_pero_ nitro_ reductive_ amination
86		20130410_ pero_Tf2O	20130409_ pero_cage_C	86_pero_Tf2O
87		20130415_ pero_AlH3	20130414_ AlH3_C_ pero	87_pero_AlH3
88		20130502_ pero_PDC	20130503_ pero_PDC_C	88_pero_pdc
80		20130521_ pero_final_2	20130521_ pero_final_C	80_pero_final

Table A14.2. *Notebook cross-reference for compounds in Appendix 3*

compound	chemical structure	^{1}H NMR	^{13}C NMR	IR
105		20131031_ hydrazine	—	—

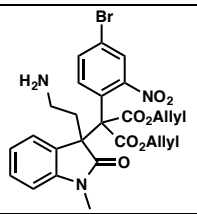
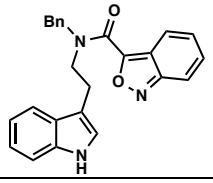
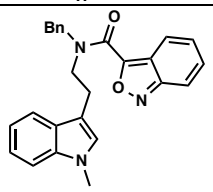
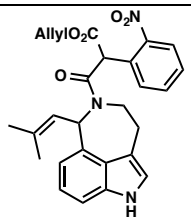
106		20131108_MeNH2 -major	—	—
112		20131125_ coupling	—	—
114		20131202_ methylation	—	—
130		20131217_ coupling	—	—

Table A14.3. *Notebook cross-reference for compounds in Appendix 4*

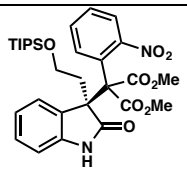
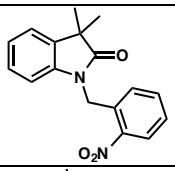
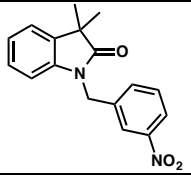
compound	chemical structure	^{1}H NMR	^{13}C NMR	IR
136		CWL-VI-141	CWL-VI-141	CWL-VI-141-oxindole

Table A14.4. *Notebook cross-reference for compounds in Chapter 2*

compound	chemical structure	^{1}H NMR	^{13}C NMR	IR
137a		20130830_ o-nitro_ch	20130830_ o-nitro_ch	3a_depro_ o-nitro
137b		20130830_ m-nitro	20130830_ m-nitro	3b_depro_ m-nitro

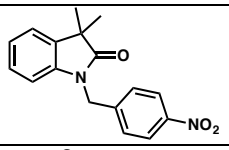
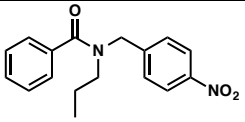
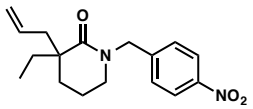
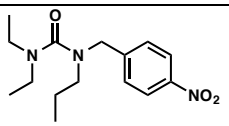
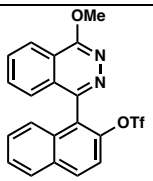
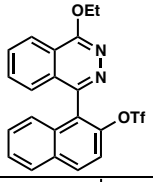
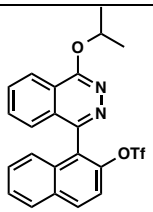
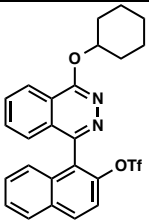
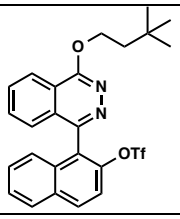
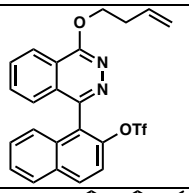
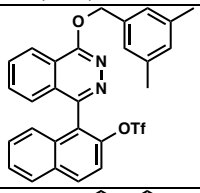
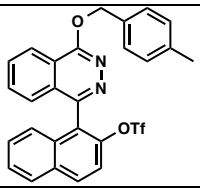
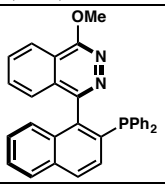
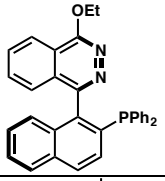
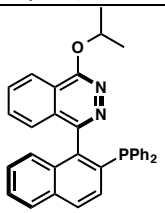
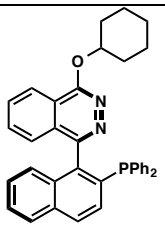
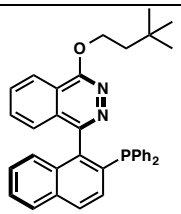
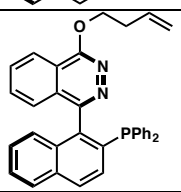
137c		20130830_ p-nitro_ch	20130830_ p-nitro_ch	3c_depro_ p-nitro
139		CH-EDCI	CH-EDCI	7_depro_ propylbenzamide _pt
141		20131024_ Boger_ substrate_ protection_ ch(C/H)	20131024_ Boger_ substrate_ protection_ ch(C/H)	9_depro_ r-lactam_pt
143		GFMI-CARBA MOYL	GFMI-CARBA MOYL	11_deprotection _urea

Table A14.5. *Notebook cross-reference for compounds in Chapter 3*

compound	**chemical structure**	**^{1}H NMR**	**^{13}C NMR**	**IR**
157a		PINAP_ OMe_OTf	PINAP_ OMe_OTf	PINAP_ sjh_OMe
157b		PINAP_Et_OTf _ch_H_C	PINAP_Et_OTf _ch_H_C	PINAP_ sjh_Et
157c		PINAP_iPr_OTf	PINAP_iPr_OTf	PINAP_ OTf_iPr_2
157d		SJHXII_127_ A_ch_H_C	SJHXII_127_ A_ch_H_C	PINAP_ sjh_A_ cyclohexyl
157e		PINAP_L_ again_tBu	PINAP_L_ again_tBu	PINAP_ OTf_L_tBu

157f		PINAP_H_ OTf	PINAP_H_ OTf	PINAP_ sjh_H_ homoallyl
157g		PINAP_N_ OTf	PINAP_N_ OTf	PINAP_ sjh_ 3,5-dimethyl phenyl
157h		PINAP_ 4-methylbenzyl _OTf_C_H_	PINAP_ 4-methylbenzyl _OTf_C_H_	PINAP_ OTf_ 4-MeBn
158a		PINAP_OMe character_P_ cdcl3_ 20140626_	PINAP_OMe character_P_ cdcl3_ 20140626_	PINAP_ P_OMe
158b		PINAP_Et_P _cdcl3_ 20140626_	PINAP_Et_P _cdcl3_ 20140626_	PINAP_P _Et
158c		PINAP_iPr_P _cdcl3_ 20140626_	PINAP_iPr_P _cdcl3_ 20140626_	PINAP_P_ iPr
158d		PINAP_P_ char_H_c	PINAP_P_ char_H_c	PINAP_P_ A
158e		PINAP_L_ P_HC	PINAP_L_ P_HC	PINAP_P_ L
158f		PINAP_H_P Ch(H,C)	PINAP_H_P Ch(H,C)	PINAP_P_ H

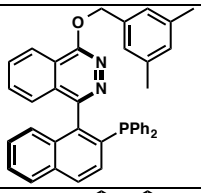
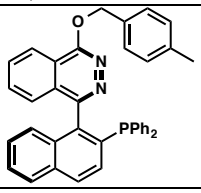
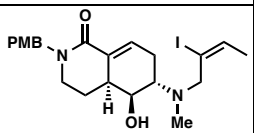
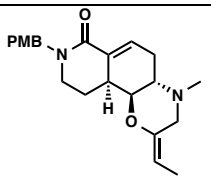
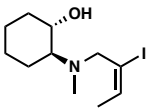
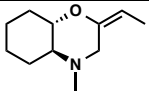
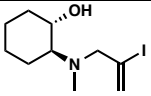
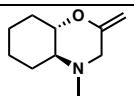
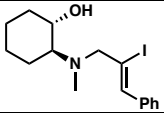
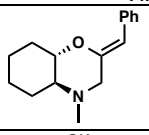
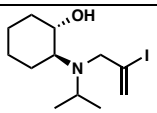
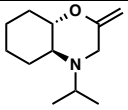
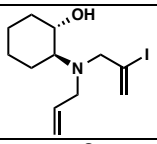
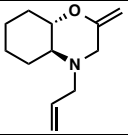
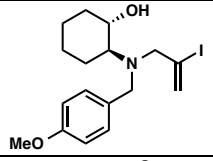
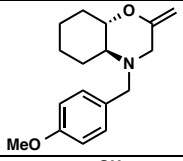
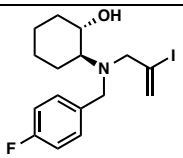
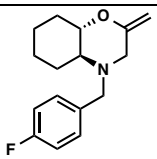
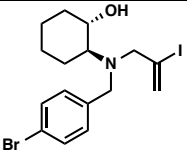
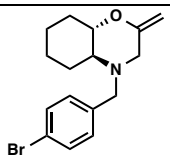
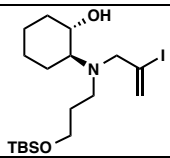
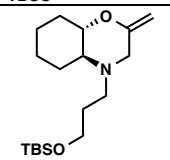
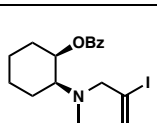
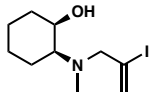
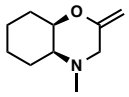
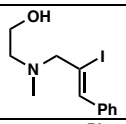
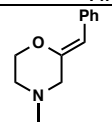
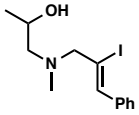
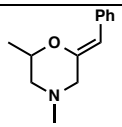
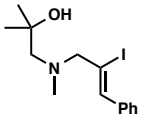
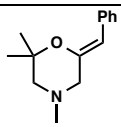
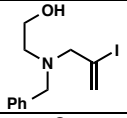
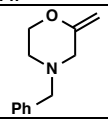
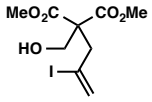
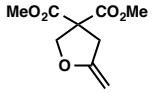
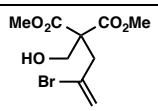
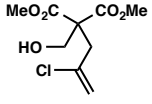
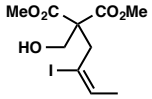
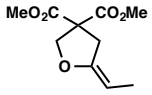
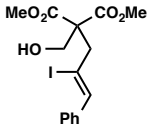
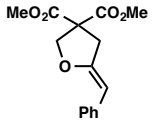
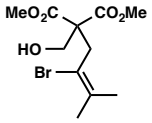
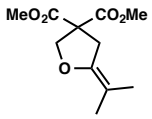
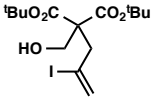
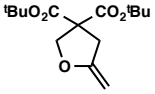
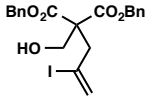
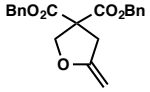
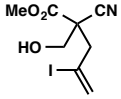
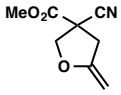
158g		PINAP_N_ PPh2_Ch(C,H)	PINAP_N_ PPh2_Ch(C,H)	PINAP_P_ N
158h		PINAP_ 4-methylbenzyl _P(H,C)	PINAP_ 4-methylbenzyl _P(H,C)	PINAP_P_ 4-methylBn

Table A14.6. *Notebook cross-reference for compounds in Chapter 4*

compound	chemical structure	^{1}H NMR	^{13}C NMR	IR
167		SJHXI_Alisto_ Ni_SM	SJHXI_Alisto_ Ni_SM	Alistonitrine _iodo_NiSM
169		SJHXI_ Alistonitrine_ Ni	SJHXI_195_ Alisto_Ni_C_ 15	Alistonitrine _Ni_SJHXI_ 195
170a		SJHXIII_ model substrate_ ch_H_C	SJHXIII_ model substrate_ ch_H_C	Ni_C_O_ Ni_catalyzed SJHXIII_ model substrate
171a		SJHXIII_Ni_ C–O_ch_H	SJHXIII_Ni_ C–O_ch_C	Ni_C_O_ SJHXIII_Ni_ C_O_
170b		RD1-76column	RD1-76carbon	RD1-76
171b		RD1-212column	RD1-212column	RD1-212
170c		SJHXV_19_Ph _ch_2	SJHXV_19_Ph _ch_2	Ni_C_O_ SJHXV_19_Ph _substrate
171c		SJHXV_Ph_ PDT	SJHXV_Ph_ PDT	Ni_C_O_ SJHXV_27_ Ph_PDT
170d		SJHXIV_281_ isopropyl	SJHXIV_281_ isopropyl	Ni_C_O_ SJHXIV_281_ iPr

171d		SJHXIV_297_ iPr_PDT	SJHXIV_297_ iPr_PDT	Ni_C_O_ SJHXIV_297_ iPr_PDT
170e		SJHXIV_281_ allyl	SJHXIV_281_ allyl	Ni_C_O_ SJHXIV_281_ allyl
171e		SJHXIV_245 _allyl_PDT	SJHXIV_245 _allyl_PDT	Ni_C_O_ SJHXIV_297_ allyl
170f		SJHXV_15_ PMB_ch_ H_C_2	SJHXV_15_ PMB_ch_ H_C_2	Ni_C_O_ SJHXV_15_ PMB_substrate
171f		SJHXV_25_ PMB_PDT	SJHXV_25_ PMB_PDT	Ni_C_O_ SJHXV_25_ PMB_PDT
170g		SJHXV_29_ 4-fluoro_ substrate	SJHXV_29_ 4-fluoro_ substrate	Ni_C_O_ SJHXV_29_ 4_F_ substrate
171g		SJHXV_37_ 4-Fluoro_ PDT	SJHXV_37_ 4-Fluoro_ PDT	Ni_C_O_ SJHXV_37_ 4_F-PDT
170h		SJHXV_61_ p-Br_ substrate	SJHXV_61_ p-Br_ substrate	Ni_C_O_ SJHXV_61_ pBr_ substrate
171h		SJHXV_65_ 4-Br_char_ inDCM	SJHXV_65_ 4-Br_char_ inDCM	Ni_C_O_ SJHXV_65_ p-Br_PDT
170i		SJHXV_31_ TBS_ substrate	SJHXV_31_ TBS_ substrate	Ni_C_O_ SJHXV_31_ TBS_substrate
171i		SJHXV_37_ TBS_ PDT	SJHXV_37_ TBS_ PDT	Ni_C_O_ SJHXV_37_ TBS_PDT
SI-4-6		SJHXV_77_ Mitsunobu_ 6membered	SJHXV_77_ Mitsunobu_ 6membered	Ni_C_O_ SJHXV_79_ Mitsunobu_ 6_membered

170j		SJHXV_87_ hydrolysis_ 6_membered	SJHXV_87_ hydrolysis_ 6_membered	Ni_C_O_ SJHXV_87_ hydrolysis_ 6-membered
171j		SJHXV_89_6_ membered_cis _cyclization	SJHXV_89_6_ membered_cis _cyclization	Ni_C_O_ SJHXV_89_cis _6-membered_ cyclization
172a		RD1-140column	RD1-140column	RD1-230
173a		RD1-168column	RD1-168column	RD1-168
172b		SJHXIV_301_ monomethyl_ H	SJHXIV_301_ monomethyl_C	Ni_C_O_ SJHXIV_301_ monomethyl_ substrate
173b		SJHXV_13_ monomethyl_ PDT	SJHXV_13_ monomethyl_ PDT	Ni_C_O_ SJHXV_13_ mono_PDT
172c		SJHXIV_299_ dimethyl_ch_ H	SJHXIV_299_ dimethyl_ch_C	Ni_C_O_ SJHXIV_299_ dimethyl_ substrate
173c		SJHXV_11_ dimethyl_PDT	SJHXV_11_ dimethyl_PDT	Ni_C_O_ SJHXV_11_ dimethyl_PDT
172d		RD1-194column	RD1-194column	RD1-194
173d		RD1-206column	RD1-206carbon	RD1-206
174a		SJHXIII_289_ SM_ch	SJHXIII_289_ SM_ch	Ni_C_O_ SJHXIII_289_ cyclization_ SM
175a		SJHXIII_289_ benzene	SJHXIII_289_ benzene	Ni_C-O_ SJHXIII_289_ cyclization
174b		SJHXIV_31_ bromide_ substrate	SJHXIV_31_ bromide_ substrate	Ni_C-O_ SJHXIV_31_ vinylbromide
174c		SJHXIV_177_ vinyl_chloride _H	SJHXIV_177_ vinyl_chloride _C	Ni_C_O_ SJHXIV_177_ vinyl_chloride

				_substrate
174d		SJHXIV_151_ methyl_vinyl_ iodide_H_C	SJHXIV_151_ methyl_vinyl_ iodide_H_C	Ni_C_O_ SJHXIV_151_ methylsub_ vinyliodide_ substrate
175d		SJHXIV_157_ methylsub_ cyclization	SJHXIV_157_ methylsub_ cyclization	Ni_C_O_ SJHXIV_147_ methylsub_ vinyliodide_ cyclization
174e		SJHXIV_167_ Ph_substituted _substrate	SJHXIV_167_ Ph_substituted _substrate	Ni_C_O_ SJHXIV_167_ Ph_substituted _substrate
175e		SJHXIV_169_ ph_sub_ cyclization	SJHXIV_169_ ph_sub_ cyclization	Ni_C_O_ SJHXIV_169_ Ph_sub_ cyclization
174f		SJHXIV_77_ gemdimethyl_ substrate	SJHXIV_77_ gemdimethyl_ substrate_C	Ni_C_O_ SJHXIV_77_ gemdimethyl_ substrate
175f		SJHXIV_85_ gemdimethyl_ PDT	SJHXIV_85_ gemdimethyl_ PDT	Ni_C_O_ SJHXIV_83_ gemdimethyl_ PDT
174g		SJHXIV_47_ tbutyl_ substrate	SJHXIV_47_ tbutyl_ substrate	Ni_C_O_SJHX IV_47_tbutyl_ substrate
175g		SJHXIV_47_ tbu_cyclization	SJHXIV_47_ tbu_cyclization	Ni_C_O_ SJHXIV_57_ tbutyl_ cyclization
174h		SJHXIV_113_ Bn_substrate_ ch	SJHXIV_113_ Bn_substrate_ ch	Ni_C_O_ SJHXIV_113_ Bn_substrate
175h		SJHXIV_117_ Bn_cyclization	SJHXIV_117_ Bn_cyclization	Ni_C_O_ SJHXIV_117_ cyclization
174i		SJHXIV_67_ cyanatesubstrat e_down	SJHXIV_67_ cyanatesubstrat e_down	Ni_C_O_ SJHXIV_67_ cyanate_ substrate
175i		SJHXIV_71_ cha_proton_2	SJHXIV_71_ cyanate_ cyclization	Ni_C_O_ SJHXIV_71_ cyanate_ cyclization

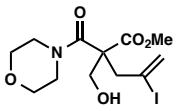
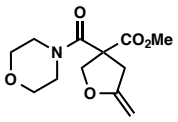
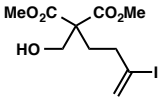
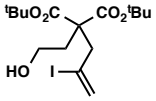
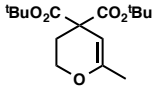
174j		SJHXIV_191_ morpholine_ substrate_H	SJHXIV_191_ morpholine_ substrate	Ni_C_O_ SJHXIV_191_ morpholine_ substrate
175j		SJHXIV_195_ cyclization_H	SJHXIV_195_ cyclization_C	Ni_C_O_ SJHXIV_195_ morpholine_ cyclization
174k		SJHXIV_37_ CH2CH2_ substrate	SJHXIV_37_ CH2CH2_ substrate	Ni_C_O_ SJHXIV_37_C H2CH2vinylio dide_substrate
174l		SJHXV_179_h ydrolysis_H_c h	SJHXV_179_c h_hydrolysis_ H_C	Ni_C_O_ SJHXV_179_ hydrolysis
175l		SJHXV_183_ cyclization_ch _H_C	SJHXV_183_ cyclization_ch _H_C	Ni_C_O_ SJHXV_183_ cyclization

Table A14.7. *Notebook cross-reference for compounds in Appendix 9*

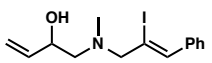
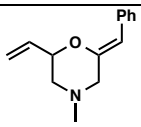
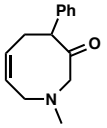
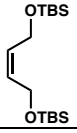
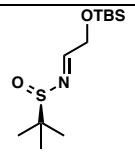
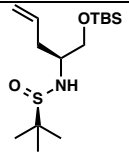
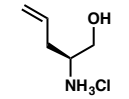
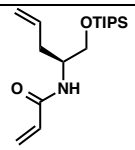
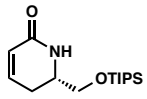
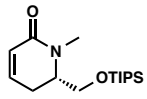
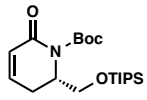
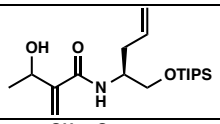
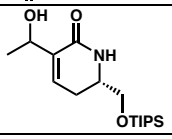
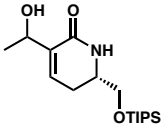
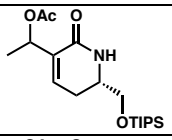
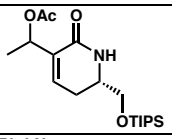
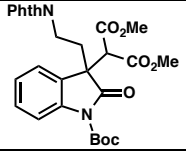
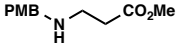
compound	chemical structure	^{1}H NMR	^{13}C NMR	IR
192		SJHXV_241_ alkylation_ch	SJHXV_241_ C_moretime	Ni_Claisen_ SJHXV_241_ alkylation
193		SJHXV_243_Ni _cyclization_ bottom_major	SJHXV_243_Ni_ cyclization_C	Ni_Claisen_ SJHXV_245_ Claisen_sub
194		SJHXV_261_ Claisen_H	SJHXV_269_ Claisen_C	Ni_Claisen_ SJHXV_261_ Claisen PDT

Table A14.8. *Notebook cross-reference for compounds in Appendix 11*

compound	chemical structure	^{1}H NMR	^{13}C NMR	IR
201		SJHVII_77_ TBS_protection	—	—
202		SJHXVI_19_ ozonolysis	SJHXVI_19_ ozonolysis	Alistonitrine_ SJHXVI_19_ ozonolysis

203		SJHXVI_21_ sulfinamide_H	SJHXVI_21_ sulfinamide_C	Alistonitrine_ SJHXVI_21_ sulfinamide
204		SJHXVI_23_ allyladdn_ major	SJHXVI_23_ allyladdn_ major	Alistonitrine_ SJHXVI_23_ allyl_addn-major
205		SJHXVI_25_ amine_MeOD	SJHXVI_25_ amine_MeOD	Alistonitrine_ SJHXVI_25_ amine2
206		SJHVII_167_ acylation	—	Alistonitrine_ SJHXVI_27_ amine_TIPS
207		SJHXVI_ Grubbs_ pdt	SJHXVI_ Grubbs_ pdt	Alistonitrine_ SJHXVI_ Grubbs_PDT
208a		SJHXVI_15_ Me_ characterization	SJHXVI_15_ Me_ characterization	Alistonitrine_ SJHXVI_ 15_Me
208b		SJHXVI_17_ Boc	SJHXVI_17_ Boc	Alistonitrine_ SJHXVI_ 17_Boc
213		SJHXVI_29_ amide_2	SJHXVI_29_ amide_2	Alistonitrine_ SJHXVI_ 29_amide
215a		SJHXVI_31_ Grubbs_up	SJHXVI_31_ Grubbs_up	Alistonitrine_ SJHXVI_ 31_Grubbs_up
215b		SJHXVI_31_ Grubbs_down	SJHXVI_31_ Grubbs_down	Alistonitrine_ SJHXVI_ 31_Grubbs_ down
199a		SJHVIII_29_ up_acetate	—	—
199b		SJHVIII_29_ down_acetate	—	—
217		SJHVIII_33_ Boc_protection	—	—
SI-A11-1		SJHIX_211_ RA_PMB	—	—

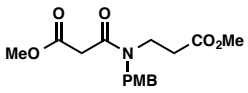
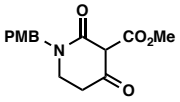
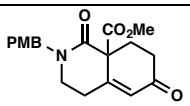
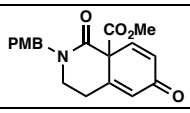
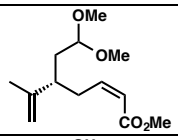
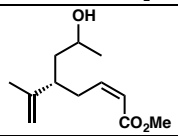
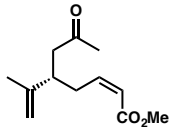
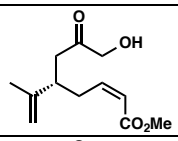
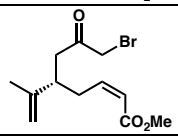
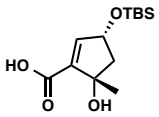
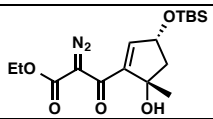
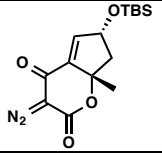
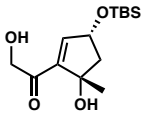
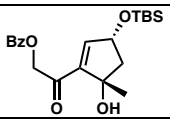
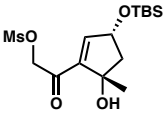
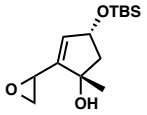
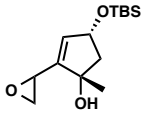
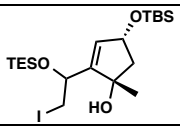
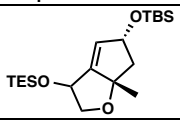
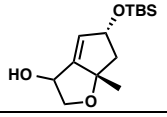
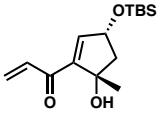
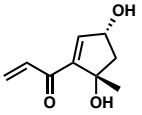
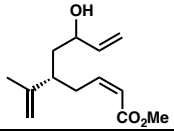
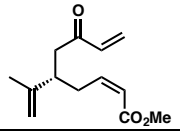
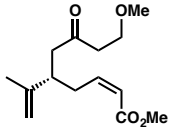
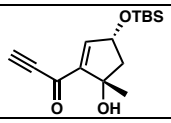
223		SJHIX-213-Acylation_ PMB	—	—
224		SJHIX-215-Dieckmann-pmb	—	—
225		SJHIX_221_ Robinson	—	—
226		SJHIX_239_ SeO2	—	—

Table A14.9. *Notebook cross-reference for compounds in Chapter 5*

compound	**chemical structure**	**^{1}H NMR**	**^{13}C NMR**	**IR**
248		SJHXI_201_PDT	SJHXI_201_ Still_Gennari _C	Ineleganolide _SJHXI_201_ Still_Gennari
251		SJHXI_INELE_ MeAddn_ch	SJHXI_INELE_ MeAddn_ch	Inele_SJHXI _211_Me_ Addn_PDt
252		SJHXI_211_ swern_H	SJHXI_211_ swern_C	Ineleganolide_ SJHXI_211_ Swern
254		SJHXI_ Ineleganolide_ mcpba_H	SJHXI_ Ineleganolide_ mcpba_C	Ineleganolide_ SJHXI_Inele_ mcpba
244b		SJHXV_217_ 7_bromide	SJHXV_217_ 7_bromide_C	Ineleganolide_ SJHXV_217_ NBS
260		SJH_ ineleganolide _acid_ characterization	SJH_ ineleganolide _acid_ characterization	Ineleganolide_ SJH_ acid
264		SJHXII_235_ MnO2	SJHXII_235_ MnO2_C	Ineleganolide_ SJHXII_Rh_ SM_diazo
266		SJHXII_201_H	SJHXII_201_C	Ineleganolide_ SJHXII_Rh_ TLC_prep

268		SJHXIII_25_ Rubottom_ characterization _H	SJHXIII_25_ Rubottom_ characterization _C	Ineleganolide_ SJHXIII_25_ rubottom_ RobFrag
269		SJHXIII_39_ Benzoylation_H	SJHXIII_39_ Benzoylation_C	Ineleganolide_ SJHXIII_39_ benzoyl
270		SJHXIII_27_ Mesyl_ characterization _H	SJHXIII_27_ Mesyl_ characterization _C	Ineleganolide_ SJHXIII_27_ Mesylate
271a		SJHXIII_215_ 1_H	SJHXIII_215_ 1_C	Ineleganolide_ SJHXIII_231 _epoxide_1_ cosy
271b		SJHXIII_215_ 2_H	SJHXIII_215_ 2_C	Ineleganolide_ SJHXIII_231 _epoxide2_ corey
274		SJHXV_201_ TES	SJHXV_201_ TES	Ineleganolide_ SJHXV_201 _TES
275		SJHXV_221_ cyclization_H	SJHXV_221_ cyclization_C	Ineleganolide_ SJHXV_221 _cyclization
276		SJHXV_239_ TES_depro_H	SJHXV_239_ TES_depro_C	Ineleganolide_ SJHXV_239 _TES_depro
285		SJHXIII_MnO2 _ch_H	SJHXIII_MnO2 _ch_C	Ineleganolide_ SJHXIII_ MnO2_after vinyladdn
281		SJHXIII_107_ TBAF_H	SJHXIII_107_ TBAF_C	Ineleganolide_ SJHXIII_105 _TBAF_ desilylation
286		SJH_vinyl_ addn_ characterization	SJH_vinyl_ addn_ characterization	Ineleganolide_ SJH_vinyl_ addn_left part
287		SJHXIII_41_ swern_H-ch	SJHXIII_41_ swern_C-ch	Ineleganolide_ SJHXIII_ 81_Swern
288		SJHXIII_85_ OMe_addn_H	SJHXIII_85_ OMe_addn_c	Ineleganolide_ SJHXIII_ 89_OMe_addn _unexpected

294		SJHXV_271_ MnO2_ oxidation	SJHXV_271_ MnO2_ oxidation	Ineleganolide_ SJHXV_271_ MnO2

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About the Author

Seojung Han was born on March 2nd, 1985 in Gumi, Gyeongsang buk-do Province, South Korea. She spent her early life in the company of her parents and her younger brother Sangjun in Gumi. Seojung attended Gyeongbuk Foreign Language High School, where she learned foreign languages such as English, Japanese and Chinese and developed interest in science.

In 2004, she began her undergraduate studies at Sogang University in Seoul, Korea. Seojung became attracted to organic chemistry because any of the desired new compounds could be prepared by organic synthesis. Eager to apply the knowledge from her studies, Seojung joined Prof. Duck-Hyung Lee's laboratory as an undergraduate research assistant and practiced multi-step reactions and synthesized heterocycles related to medicinal chemistry. Seojung received bachelor's degree in chemistry *summa cum laude* from Sogang University in 2008.

Upon graduation, Seojung joined the research group of Prof. Duck-Hyung Lee for an M.S. degree in organic chemistry at Sogang University and completed the enantioselective synthesis of a C9–C17 fragment of (–)-amphidinolide O and P. In addition, she synthesized fragments of ascospiroketal B and arenicolide A. Upon obtaining an M.S. degree in 2010 *summa cum laude*, she worked at the Korea Research Institute of Chemical Technology in the medicinal chemistry department to contribute to the development of novel drug candidates for treatment of metabolic diseases and new fluorescent small molecule probes for staining blood vessels.

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