METHODOLOGICAL DEVELOPMENTS AND SYNTHETIC APPLICATIONS OF STRAINED RINGS

AND

ALLYLIC C–H FUNCTIONALIZATION OF HINDERED SUBSTRATES

Thesis by

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ABSTRACT

Formal dipolar cycloadditions of cyclopropanes and aziridines are useful methods for the formation of carbo- and heterocycles. Given our group's previous interest in this area, we sought to expand the scope of strained ring cycloadditions by employing heterocumulenes as dipolarophiles. This thesis describes our development of Lewis acid catalyzed formal (3 + 2) cycloadditions between donor–acceptor cyclopropanes and isocyanates, isothiocyanates, and carbodiimides to furnish various five-membered heterocycles. Enantioenriched cycloadducts can be accessed through a stereospecific reaction if enantiopure substrates are employed. We also present a method to access more highly nitrogenated heterocycles by replacing donor–acceptor cyclopropanes with activated aziridines. These aziridines react smoothly with isothiocyanates and carbodiimides in the presence of zinc Lewis acids to afford iminothiazolidine and iminoimidazolidine products in good yields. Our efforts to apply a cyclopropane cycloaddition toward the total synthesis of the indole alkaloid calophyline A are also described

In addition, a method for the activation of sterically hindered allylic C–H bonds is presented. Despite numerous recent advances in the functionalization of allylic C–H bonds and the general utility of these transformations, reactions of sterically hindered substrates remain challenging. In this thesis we describe the development of a novel system for the palladium(II)-catalyzed allylic C–H acetoxylation of α-allyl lactams. We believe the lactam moiety may act as a directing group to aid in the palladation of these generally unreactive substrates. During optimization, we also discovered enal products were formed if water was added. These conditions represent the first example of a transition metal catalyzed C–H oxidation system with tunable selectivity over the extent of oxidation.

PUBLISHED CONTENT AND CONTRIBUTIONS

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N.R.O. discussed the contents of this perspective review with the other authors and wrote the manuscript with their input.

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LIST OF ABBREVIATIONS

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
Ac	acetyl
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl group
atm	atmosphere(s)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	butyl or *norm*-butyl
t-Bu	*tert*-butyl
Bn	benzyl
Bz	benzoyl
c	concentration of sample for measurement of optical rotation
^{13}C	carbon-13 isotope
/C	supported on activated carbon charcoal
°C	degrees Celsius

calc'd	calculated
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
cf.	consult or compare to (Latin: *confer*)
cm^{-1}	wavenumber(s)
COD	1,5-cyclooctadiene
comp	complex
conc.	concentrated
d	doublet
D	dextrorotatory
dba	dibenzylideneacetone
pmdba	bis(4-methoxybenzylidene)acetone
dmdba	bis(3,5-dimethoxybenzylidene)acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
de	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane

DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
ee	enantiomeric excess
E	trans (entgegen) olefin geometry
EC_{50}	median effective concentration (50%)
e.g.	for example (Latin: *exempli gratia*)
EI	electron impact
ESI	electrospray ionization
Et	ethyl
et al.	and others (Latin: *et alii*)
FAB	fast atom bombardment
g	gram(s)
h	hour(s)
^1H	proton
HMDS	hexamethyldisilamide or hexamethyldisilazide
$h\nu$	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IC_{50}	half maximal inhibitory concentration (50%)
i.e.	that is (Latin: *id est*)

IR	infrared spectroscopy
J	coupling constant
k	rate constant
kcal	kilocalorie(s)
kg	kilogram(s)
L	liter or neutral ligand
L	levorotatory
LA	Lewis acid
LD_{50}	median lethal dose (50%)
LDA	lithium diisopropylamide
m	multiplet
M	molar or molecular ion
m	meta
μ	micro
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
Mes	mesityl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mol	mole(s)
MOM	methoxymethyl

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

n-Pr	propyl or *norm*-propyl
psi	pounds per square inch
py	pyridine
q	quartet
R	alkyl group
R	rectus
r	selectivity = [major stereoisomer – minor stereoisomer]/[major stereoisomer + minor stereoisomer]
ref	reference
R_f	retention factor
s	singlet or seconds
S	sinister
sat.	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBAT	tetra-*n*-butylammonium difluorotriphenylsilicate
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
temp	temperature
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran

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

CHAPTER 1[†]

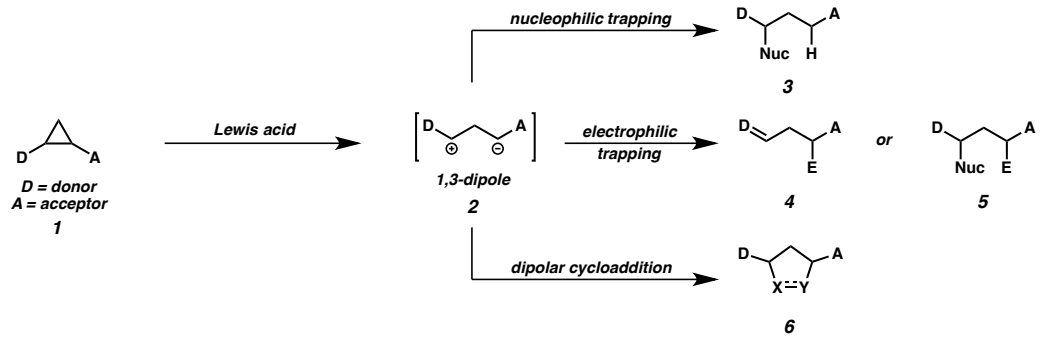
Synthetic Applications and Methodological Developments of Donor–Acceptor Cyclopropanes and Related Compounds in the Stoltz Laboratory

1.1 INTRODUCTION

Donor–acceptor cyclopropanes (**1**, Scheme 1.1), or those possessing one or more electron-donating groups and electron-withdrawing groups on adjacent carbons, are useful building blocks in organic synthesis.[1] Due to the presence of these vicinal charge-stabilizing groups and the strain inherent to the cyclopropane core, ring opening can occur under mild conditions. Typically, treatment with a Lewis acid at room temperature is sufficient to induce carbon–carbon bond cleavage, leading to an all-carbon 1,3-dipole (**2**). These dipoles are quite versatile, having been shown to undergo nucleophilic trapping, electrophilic trapping, or dipolar cycloadditions to form a wide array of products (**3**–**6**, Scheme 1.1).

[†] Portions of this chapter have been adapted with permission from O'Connor, N. R.; Wood, J. L.; Stoltz, B. M. *Isr. J. Chem.* **2016**, *56*, 431–444.

Scheme 1.1 Basic reactivity modes of donor–acceptor cyclopropanes



The acceptor groups are often carbonyl derivatives (with esters, ketones, and nitriles most common), although other electron-withdrawing groups, including sulfonyl, sulfinyl, and phosphoryl, are occasionally used. Traditional donor groups are alkoxy, silyloxy, and amino substituents. Over the past decade, however, the use of aryl donor groups has become widespread, pioneered by the work of Kerr[2] and Johnson.[3] Aryl-substituted cyclopropanes are readily available in one or two steps from styrenes or benzaldehydes using straightforward methods.[1a] These compounds are typically more stable than cyclopropanes with heteroatom-based donors, and in some circumstances are capable of undergoing stereospecific reactions.[4]

The Stoltz laboratory's interest in donor–acceptor cyclopropanes was sparked during Brian M. Stoltz's use of cyclopropane fragmentations (classified as electrophilic trapping in Scheme 1.1) as a method of ring expansion in the synthesis of K252a and the welwitindolinone C isothiocyanate core during his graduate studies in the John L. Wood research laboratory at Yale University. This chapter describes Stoltz and Wood's work in more detail below, and proceeds to examine

the independent Stoltz laboratory's continued use of donor–acceptor cyclopropane fragmentations and cycloadditions toward the total synthesis of natural products. Our endeavours in natural products synthesis have also resulted in the development of several novel synthetic methodologies involving strained ring intermediates. Two examples of such methods are summarized in this chapter, and two others are described in detail in the following chapters of this thesis.

1.2 USE OF DONOR–ACCEPTOR CYCLOPROPANES AS INTERMEDIATES IN NATURAL PRODUCTS SYNTHESIS

The following sections describe the use of donor–acceptor cyclopropanes as intermediates in natural products synthesis from the Wood research laboratory in the 1990s and the Stoltz research laboratory over the past 16 years. The donor–acceptor cyclopropanes featured in the examples below include both isolable intermediates and transient, highly reactive transient species.

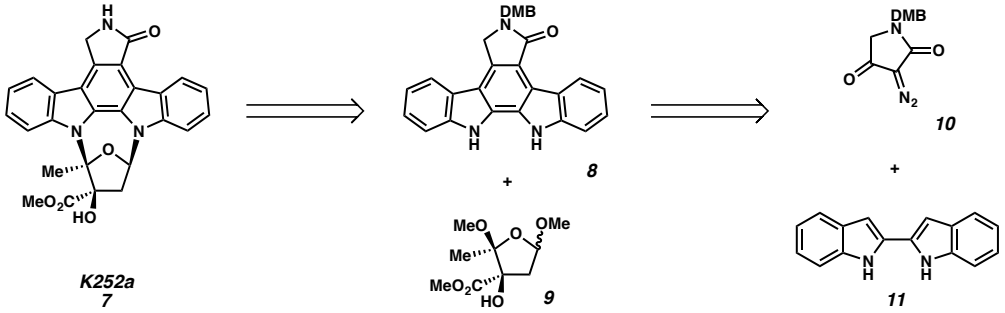
1.2.1 TOTAL SYNTHESIS OF K252a

Our interest in the use of donor–acceptor cyclopropanes as intermediates in natural products total synthesis began with the synthesis of K252a (**7**, Scheme 1.2) by Brian M. Stoltz while a graduate student in the Wood laboratory at Yale.[5] Isolated in 1985 by Sezaki and co-workers from a culture of the soil bacterium *Actinomadura* sp. SF-2370,[6] (+)-K252a was found to possess nanomolar inhibitory activity against protein kinase C.[7] Subsequent studies showed that structurally related compounds possess similar activity,

and suggested these indolocarbazole alkaloids may have potential in the treatment of cancers[8] and neurodegenerative diseases.[9]

Stoltz, Wood, and co-workers envisioned accessing K252a (**7**) by late stage glycosylation of an indolocarbazole precursor **8**, itself constructed by coupling of diazolactam **10**[10] and 2,2'-biindole[11] (**11**, Scheme 1.2). Rationale for this disconnection was provided by several reports of indole C3-functionalization through reactions with carbenes or metal carbenoids.[12] These functionalizations were proposed to occur by cyclopropanation of the indole C2–C3 bond and subsequent cyclopropane fragmentation.

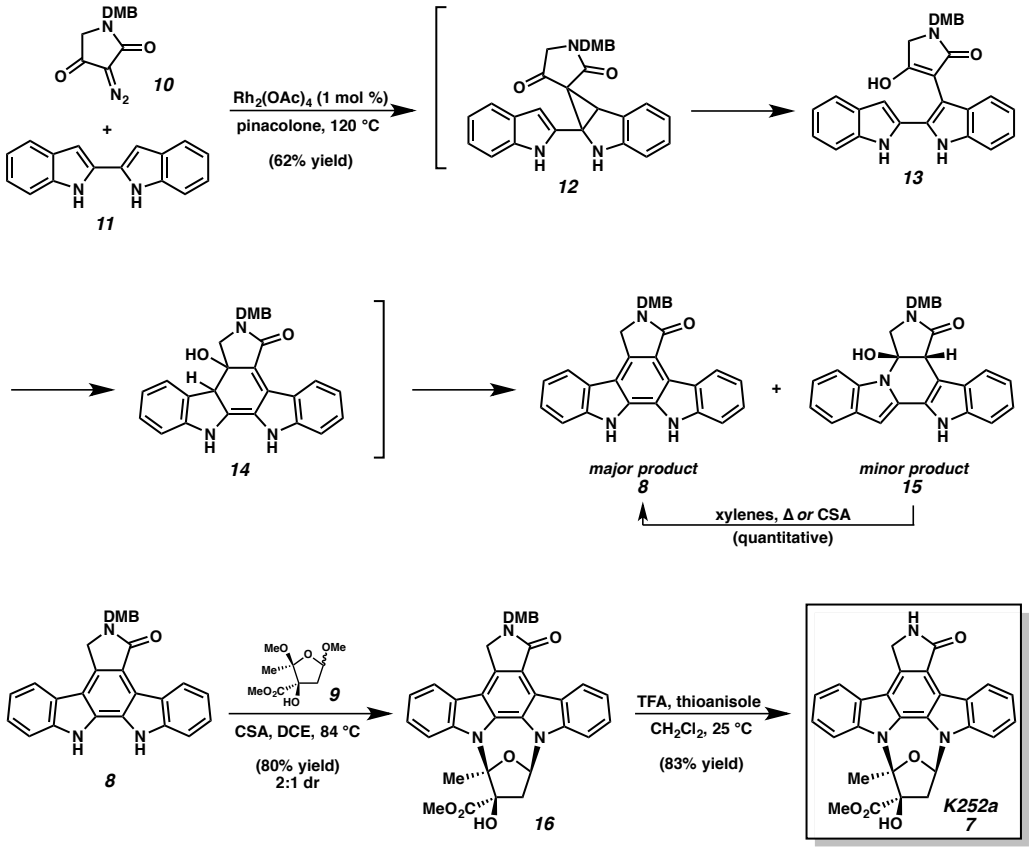
Scheme 1.2 Retrosynthetic analysis of K252a



Extensive experimentation revealed that treatment of a mixture of **10** and **11** with 1 mol % rhodium(II) acetate in pinacolone at 120 °C furnished the desired indolocarbazole **8** in 62% yield.[13] Although no intermediates could be observed by TLC or NMR, the reaction is presumed to proceed via the transient donor–acceptor cyclopropane **12**, produced by cyclopropanation of the rhodium carbenoid onto an indole C2–C3 bond (Scheme 1.3). This cyclopropane is expected to rapidly fragment to form the more stable enol biindole **13**, which can undergo a 6π electrocyclic ring closure, followed by dehydrative aromatization to form **8**. Small

amounts of hemiaminal **15** were also obtained in the reaction, and subjection of this material to xylenes at reflux or CSA resulted in quantitative conversion to **8**. It was postulated that this byproduct was formed from adduct **13**, supporting the proposed mechanism outlined in Scheme 1.3.

Scheme 1.3 Total synthesis of K252a

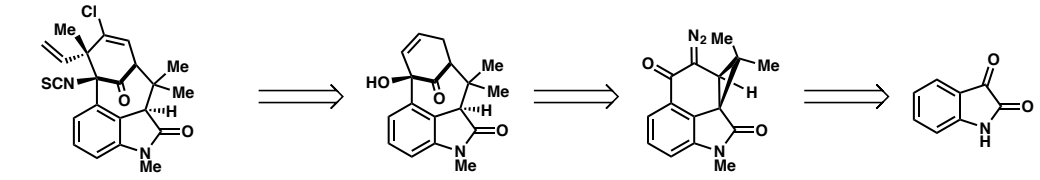


Indolocarbazole **8** was advanced to K252a by coupling with furanose **9** (synthesized in four steps from methyl diazoacetoacetate) using conditions inspired by McCombie.[14] The desired isomer of the two glycosylated indolocarbazoles (**16**) was then deprotected using TFA and thioanisole to provide the target with a longest linear sequence of seven steps.

1.2.2 SYNTHESIS OF THE WELWITINDOLINONE CARBON SKELETON

Stoltz, Wood, and co-workers continued to pursue their interest in donor–acceptor cyclopropane intermediates in their efforts toward the carbon skeleton of the welwitindolinone alkaloids.[15] Isolated in the 1990s from various cyanobacteria, some welwitindolinone alkaloids act as P-glycoprotein P-170 inhibitors with multidrug-resistance reversing activity.[16] Stoltz and Wood planned to form the carbon skeleton of the most potent member of the family, *N*-methylwelwitindolinone C isothiocyanate (**17**, Scheme 1.4) by elaboration of oxindole **18**, itself formed by ring opening and further functionalization of a donor–acceptor cyclopropane derived from compound **19**. Diazo **19** was to be synthesized from isatin (**20**).

Scheme 1.4 Retrosynthetic analysis of N*-methylwelwitindolinone C isothiocyanate*



N-*Methylwelwitindolinone C Isothiocyanate* *17*

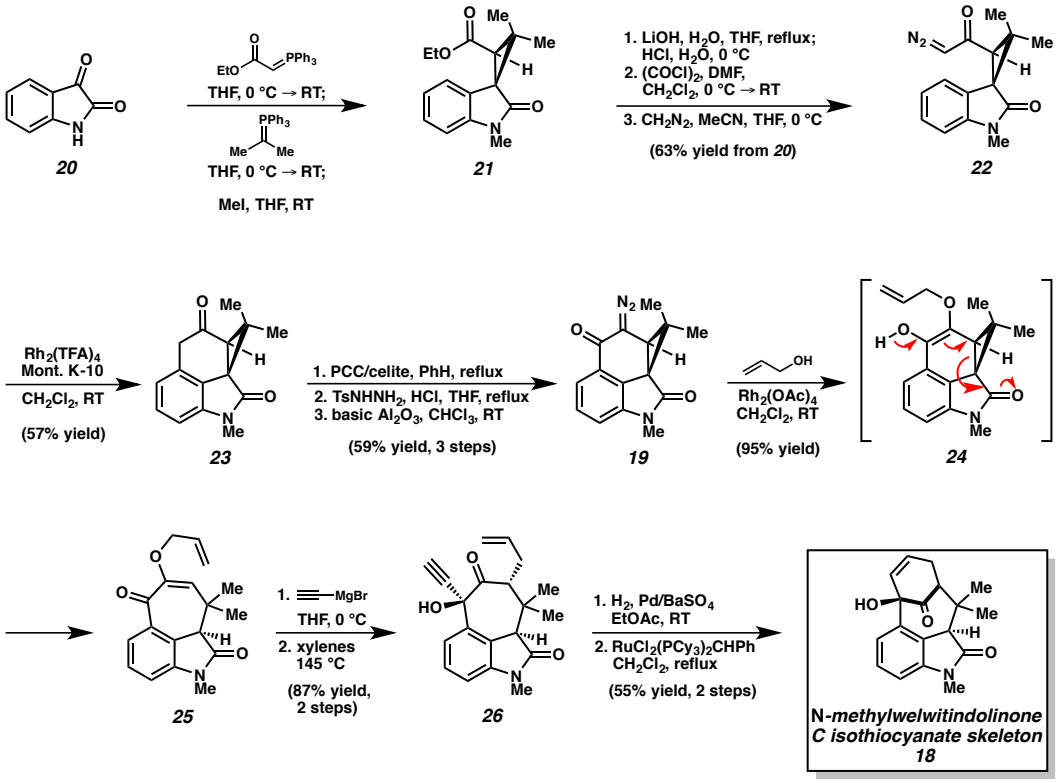
18

19

20

In the forward direction, Wittig homologation of isatin (**20**) and cyclopropanation of the resulting olefin using a phosphorus ylide, followed by *N*-methylation produced stable cyclopropane **21**, containing one aryl donor group and two vicinal carbonyl acceptor groups (Scheme 1.5). The ethyl ester was converted to α-diazo ketone **22**, which upon treatment with rhodium(II) trifluoroacetate and Montmorillonite K-10 clay underwent an aryl C–H insertion step to afford tetracycle **23** in good yield.

Scheme 1.5 Synthesis of the carbon skeleton of N*-methylwelwitindolinone C isothiocyanate*



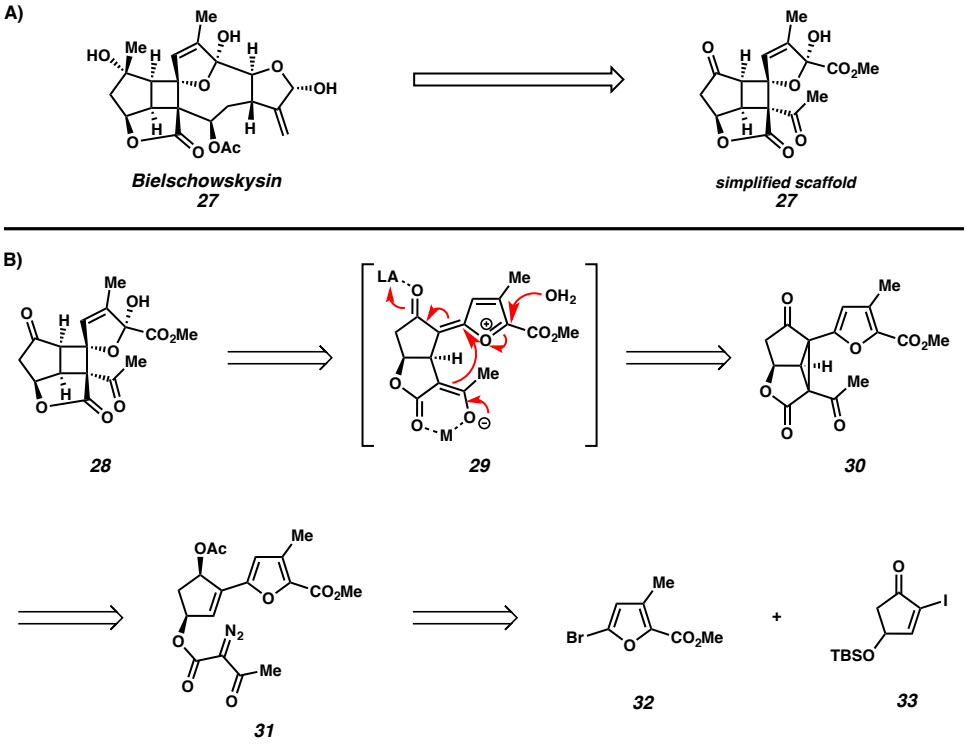
Benzylic oxidation, tosylhydrazone formation, and elimination selectively formed the desired α-diazo ketone (**19**). Exposure of the corresponding rhodium carbenoid to allyl alcohol furnished cycloheptenone **25** in nearly quantitative yield. This reaction proceeds by initial insertion of the rhodium carbenoid into the O–H bond of allyl alcohol to form transient cyclopropane **24**, which features a strong enol donor substituent at one position and a carbonyl acceptor group at a vicinal position. This unstable intermediate undergoes fragmentation to produce cycloheptenone **25**. Addition of ethynylmagnesium bromide and Claisen rearrangement gave enyne **26**, which was advanced to the welwitindolinone carbon skeleton (**18**) by Lindlar hydrogenation and ring closing metathesis.

1.2.3 APPROACH TOWARD THE SYNTHESIS OF BIELSCHOWSKYSIN

The independent Stoltz laboratory continued to investigate the strategy of cyclopropane fragmentation en route to larger carbocyclic rings in their approach toward the total synthesis of bielschowskysin (**27**, Scheme 1.6A).[17] Isolated in 2004 from a Caribbean coral, **27** was found to possesses potent anticancer activity.[18] The simplified scaffold of **28** was chosen as a model system.

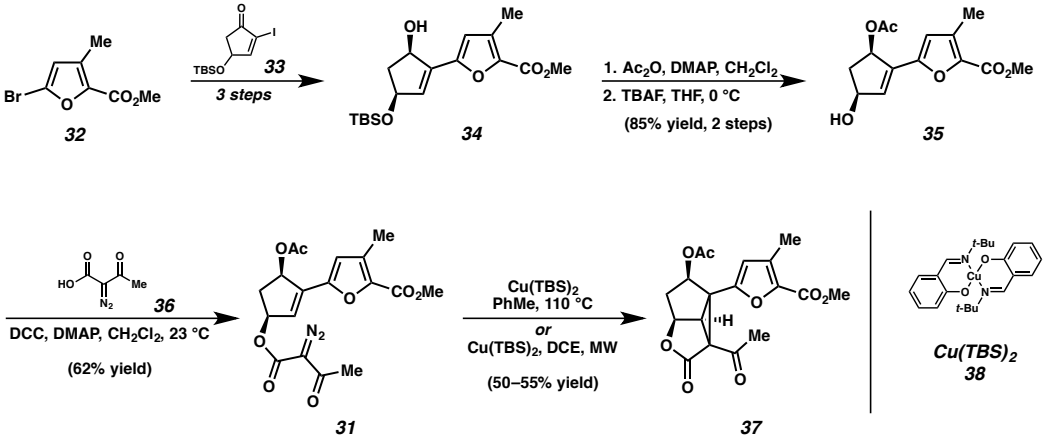
Stoltz and co-workers planned to construct the highly functionalized core cyclobutane ring of **28** from donor–acceptor cyclopropane **30** by a ring opening-Michael addition cascade sequence proceeding through intermediate **29** (Scheme 1.6B). Cyclopropane **30** would be synthesized from diazoacetoacetate **31**, which in turn would be accessed from simple aryl bromide (**32**)[19] and enone (**33**)[20] building blocks.

Scheme 1.6 A) Bielschowskysin and a simplified scaffold and B) Retrosynthetic analysis of bielschowskysin



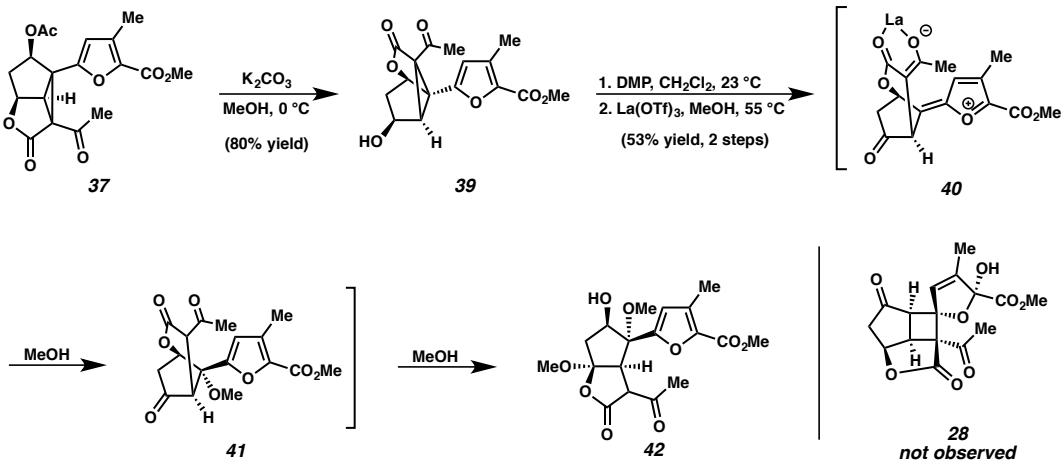
In the forward direction, alcohol **34** was synthesized from **32** using a three-step sequence consisting of borylation,[21] Suzuki cross-coupling with vinyl iodide **33**,[22] and diastereoselective Luche reduction (Scheme 1.7). At this stage, optically pure material could be optained by the oxidative kinetic resolution protocol previously developed in the Stoltz laboratory.[23] Advancement to diazoacetoacetate **31** was achieved through another three step sequence.[24] The key donor–acceptor cyclopropane **37** was obtained in moderate yield upon heating **30** with $Cu(TBS)_2$ (**38**) in toluene or DCE.

*Scheme 1.7 Synthesis of donor–acceptor cyclopropane **37***



At this point, it was envisioned that acetate cleavage and oxidation of the resulting hydroxyl group would afford cyclopropane **30**, which would undergo the fragmentation-Michael addition cascade upon exposure to a Lewis acid. Unfortunately, acetate cleavage, oxidation, and treatment with lanthanum triflate in methanol produced cyclopentanol **42** (Scheme 1.8) rather than desired cyclobutane **28**. This occurs as the result of an undesired translactonization following acetate hydrolysis to give **39**. Oxidation and exposure to Lewis acid induces fragmentation of the cyclopropane to form a stabilized enolate and an extended oxocarbenium cation (**40**). Addition of one equivalent of methanol provides presumed intermediate **41**, which proceeds through two transesterifications and hemiketal formation to provide the observed cyclopentanol (**42**). Unfortunately, all attempts to avoid this undesired translactonization were unsuccessful, and synthetic efforts concluded at this point. This effort highlights the tenuous nature of such reactive, strained, and sterically constrained donor–acceptor cyclopropane systems.

Scheme 1.8 Cyclopropane fragmentation

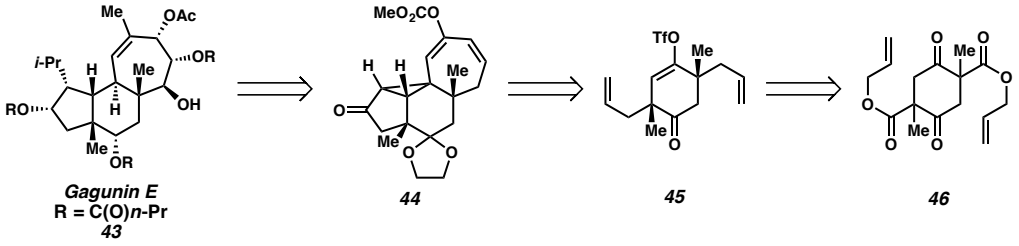


1.2.4 SYNTHESIS OF THE CORE OF THE GAGUNIN DITERPENOIDS

Stoltz and co-workers again chose to investigate a donor–acceptor cyclopropane fragmentation strategy in their construction of the carbocyclic core structure of the gagunin diterpenoids.[25] The gagunin family of natural products, isolated in 2002 from the sea sponge *Phorbas* sp., are characterized by a highly oxygenated 5–6–7 tricyclic core containing two all-carbon quaternary stereocenters. Depending on the extent of core oxygenation, these diterpenoids exhibit varying levels of cytotoxicity.[26]

Retrosynthetically, access to these natural products (exemplified by gagunin E, **43**, Scheme 1.9) would proceed via fragmentation of donor–acceptor cyclopropane **44**. This compound would be reached from triflate **45**, itself accessed from symmetrical precursor **46**, a key intermediate in our previously reported total synthesis of the related cyathane diterpenoids.[27]

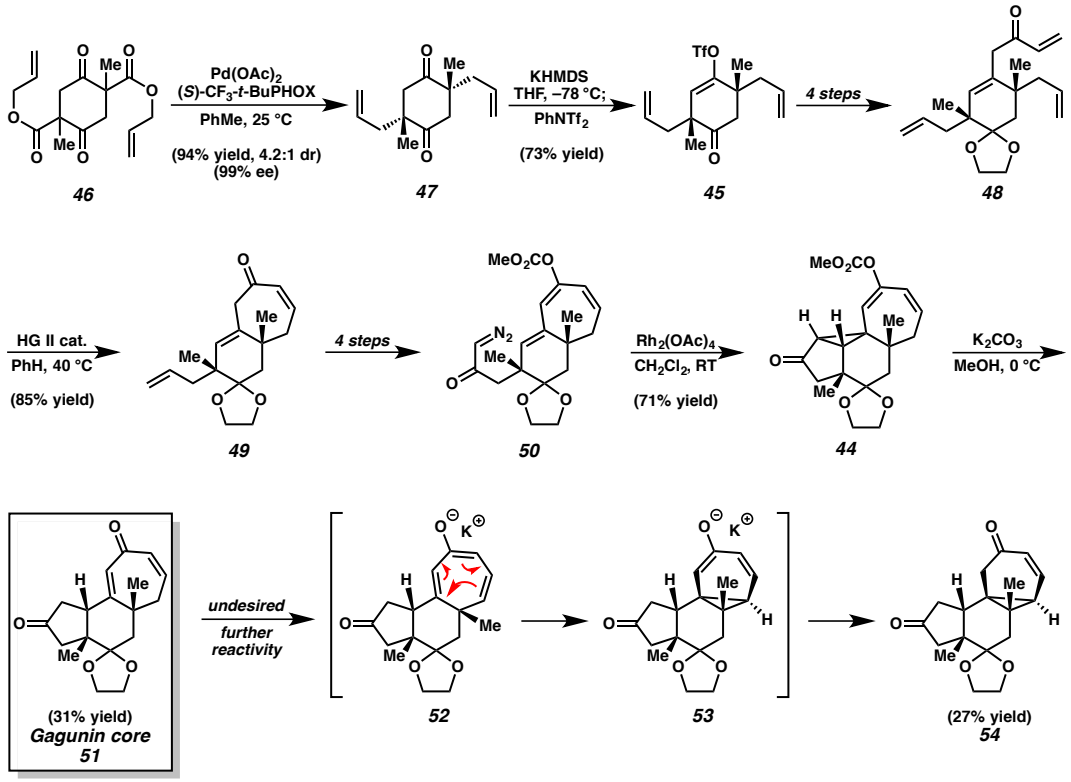
Scheme 1.9 Retrosynthetic analysis of gagunin E



In the forward direction (Scheme 1.10), compound **46** was synthesized from diallyl succinate in two steps as a mixture of diastereomers.[27a] Subjection of this material to a double enantioselective decarboxylative allylic alkylation reaction[28] using conditions developed in the Stoltz laboratory gave bis-allylated cyclohexane-1,4-dione **47** in excellent yield, good diastereoselectivity, and excellent enantioselectivity. Enol triflate formation afforded **45**, which was converted to tetraene **48** over four steps. Ring-closing metathesis produced **49**, containing the seven-membered ring of the gagunin core. A four-step sequence consisting of enone carbonate protection and allyl functional group interconversions delivered α-diazo ketone **50**.

Treatment of **50** with rhodium(II) acetate in dichloromethane gave cyclopropane **44** in good yield, and ring fragmentation with potassium carbonate in methanol furnished **51**, which contains the 5–6–7 tricyclic core of the gagunin diterpenoids, in 31% yield. This appears to be an uncommon example of the reactivity of a donor–acceptor cyclopropane with a transiently formed enolate acting as the donor.[29] Interestingly, cyclopropane **54** was also isolated from the fragmentation step in 27% yield. This unexpected compound is presumed to arise from deprotonation of **51** and subsequent retro-norcaradiene rearrangement.[30]

Scheme 1.10 Synthesis of the gagunin core



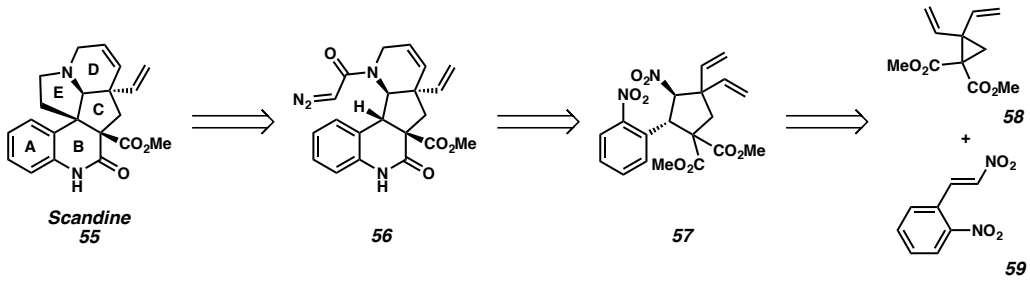
1.2.5 SYNTHESIS OF THE ABCD RING SYSTEM OF SCANDINE

Having gained an appreciation for the utility of donor–acceptor cyclopropanes in synthesis, Stoltz and co-workers planned to use a cyclopropane-olefin cycloaddition to construct the central C ring of scandine (**55**, Scheme 1.11), the parent compound of the *Melodinus* alkaloids.[31,32] Although they possess no known biological activity, these compounds are of interest due to their structural complexity, specifically in regard to the highly congested cyclopentane (C) ring.

The original retrosynthesis is shown in Scheme 1.11. Incorporation of a late-stage E ring formation by carbenoid C–H insertion simplifies the target to tetracycle

56, which could arise from cyclopentane **57** by nitro reduction, lactam ring closure, allylation, and diastereoselective ring-closing metathesis.[33] This cyclopentane could be formed by a palladium-catalyzed formal (3 + 2) cycloaddition between donor–acceptor cyclopropane **58** and nitroolefin **59**.[34]

Scheme 1.11 Retrosynthetic analysis of scandine

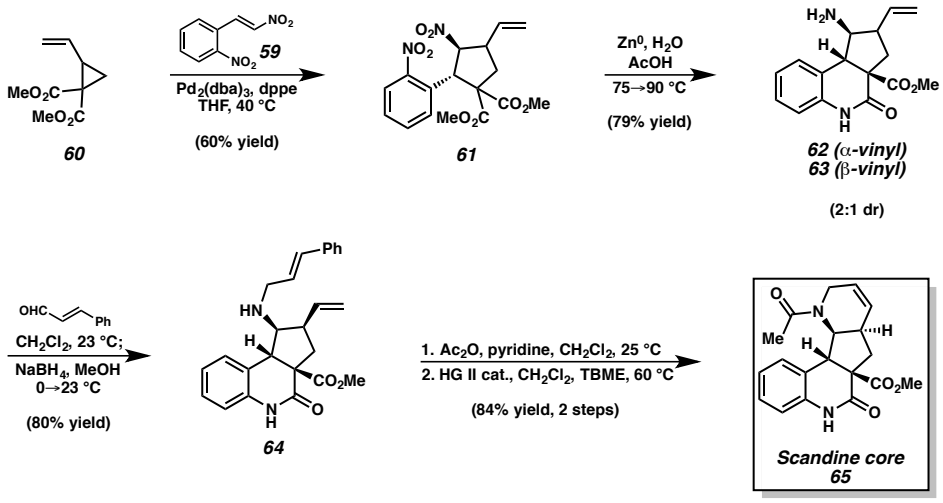


Unfortunately, despite significant effort, the synthesis of divinyl cyclopropane **58** proved elusive.[35] A revised retrosynthesis was developed, beginning with a monovinyl cyclopropane in the (3 + 2) reaction, and relying on a late-stage C–H vinylation to install the second vinyl group. The use of stable vinylcyclopropane **60** (Scheme 1.12) relied upon the known reactivity of such compounds to unveil their donor–acceptor reactivity upon treatment with palladium(0) complexes.[34]

In the forward sense, exposure of monovinyl cyclopropane **60**[36] and commercially available dinitrostyrene **59** to a palladium(0) phosphine complex afforded nitrocyclopentane **61** in good yield as a mixture of diastereomers (Scheme 1.12). Treatment of the mixture with zinc dust in acetic acid resulted in reduction of both nitro groups and subsequent lactamization (with exclusive *cis* ring fusion) to afford the quinolone products as a 2:1 mixture of vinyl diastereomers. The desired minor diastereomer (**63**) was allylated under reductive amination conditions affording **64**.

Amine protection and ring-closing metathesis furnished tetracycle **65** in good yield. Although **65** does not contain the vinyl group present in the natural product, Stoltz's route assembled four out of the five rings in only six steps from commercial sources.

Scheme 1.12 Synthesis of the ABCD ring system of scandine



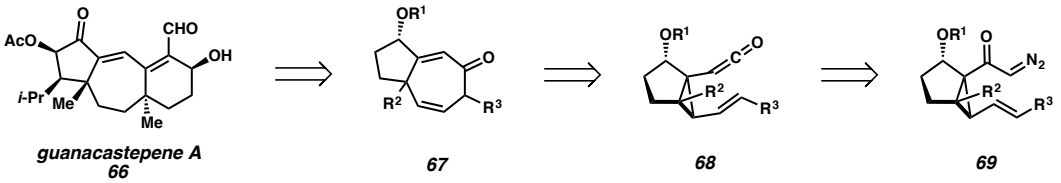
1.3 DEVELOPMENT OF NOVEL REACTIONS OF TRANSIENT DONOR–ACCEPTOR CYCLOPROPANES AND CYCLOBUTANES

The following sections describe methodologies developed in the Stoltz research laboratory inspired by their efforts in the total synthesis of natural products. These methods are believed to proceed through transient donor–acceptor cyclopropane or cyclobutane intermediates.

1.3.1 SYNTHESIS OF FUSED CARBOCYCLES BY A TANDEM WOLFF–COPE REARRANGEMENT

Natural products containing fused 5–7 and 6–7 ring systems are of considerable interest to the synthetic community due to their biological potential.[37] Inspired by complex seven-membered-ring-containing natural products like guanacastepene A (**66**, Scheme 1.13),[38] Stoltz and co-workers devised a novel approach to the fused cycloheptadienone scaffold **67**, which could be viewed as a synthetic intermediate en route to these targets. This scaffold could conceivably arise through a ketene-Cope rearrangement of a divinyl cyclopropane such as **68**. While compounds like **68** do not fit the typical structural motif of a donor–acceptor cyclopropane, they are nevertheless quite reactive. For any asynchronous reactions of these compounds, it is possible to envision the transition state featuring vicinal positive and negative charge stabilization, as is the case for most reactions of traditional donor–acceptor cyclopropanes. If the ketene moiety of **87** were to be accessed from an α-diazo ketone (**69**), it may be possible to form the desired cycloheptadienones in a single pot through a tandem Wolff–Cope rearrangement.[39]

Scheme 1.13 Synthetic inspiration for the tandem Wolff–Cope rearrangement

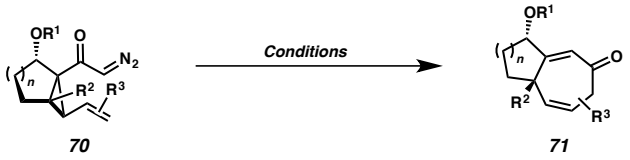


***guanacastepene A* 66** **67** **68** **69**

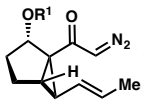
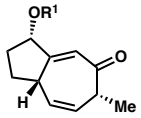
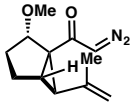
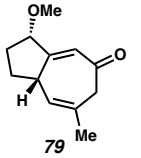
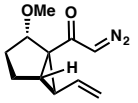
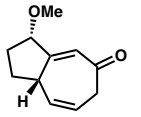
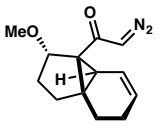
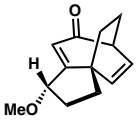
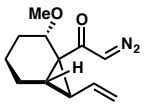
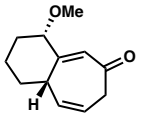
Donor–acceptor cyclopropane **72** was synthesized from methyl acetoacetate and sorbyl alcohol, and was treated with a variety of conditions known to effect Wolff

rearrangements. Extensive optimization revealed that the use of silver benzoate and triethylamine with sonication in THF at 45 °C resulted in nearly quantitative yield of the desired fused cycloheptadienone product **75** as a single diastereomer (Scheme 1.14).

Scheme 1.14 Selected scope of the tandem Wolff–Cope rearrangement



70 ***71***

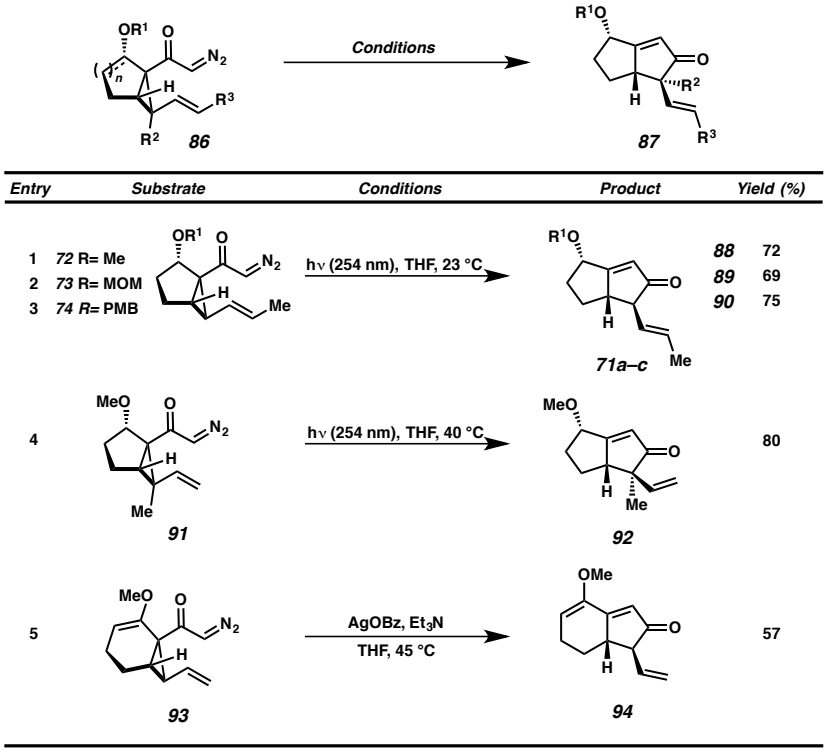
Entry	*Substrate*	*Conditions*[a]	*Product*	*Yield (%)*
1 *72* R^1 = Me 2 *73* R^1 = MOM 3 *74* R^1 = PMB		Conditions (A)		*75* 95 *76* 88 *77* 92
			70a–c	
4		Conditions (A)		98
	78		***79***	
5		Conditions (B)		80
	80		***81***	
6		Conditions (A) Conditions (B)		76 94
	82		***83***	
7		Conditions (B)		88
	84		***85***	

[a] Conditions A: AgOBz, Et_3N, THF, 45 °C. Conditions B: hν (310 nm), PhH, 23 °C.

The substrate scope of the reaction is shown in Scheme 1.14. A range of hydroxyl protecting groups were tolerated (**72–74**). Compounds containing a 1,1-disubstituted olefin (**78**) or a monosubstituted olefin (**80** and **84**) were also competent substrates. Finally, a tricyclic product (**83**) and a 6–7 ring system (**85**) could be formed in excellent yields. Interestingly, photochemical conditions were necessary to achieve high yields with the substrates containing monosubstituted olefins (**80** and **84**).

Treatment of substrate **72** with the photochemical conditions shown in Scheme 1.15 resulted in the isolation of the fused cyclopentenone product **88** in good yield after a prolonged reaction time. This product is proposed to arise from a Norrish type I fragmentation of cycloheptadienone **75**, followed by intramolecular radical recombination, resulting in a net 1,3-acyl migration process.[40]

Scheme 1.15 Selected scope of the tandem Wolff–Cope–1,3-acyl shift reaction



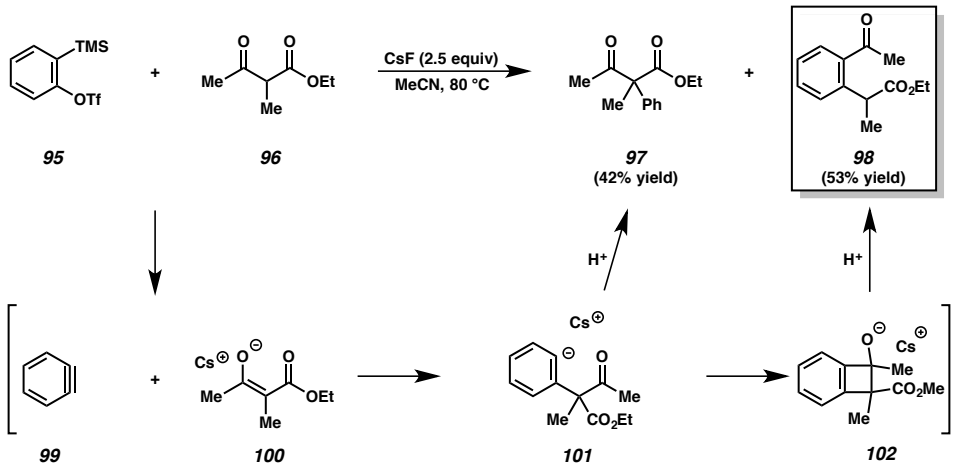
The substrate scope of the tandem Wolff–Cope–1,3-acyl shift process is shown in Scheme 1.15. As with the simpler Wolff–Cope rearrangement, this reaction is successful on substrates incorporating a variety of hydroxyl protecting groups (**72–74**) and olefin substitutions (**91** and **93**). This method is able to deliver α-quaternary cyclopentenone **92** in excellent diastereoselectivity. Finally, access to both the 5–5 (**88–90**, **92**) and 5–6 (**94**) fused ring systems is possible in good yields and diastereoselectivities.

1.3.2 THE ACYL-ALKYLATION OF ARYNES WITH β-KETOESTERS

During efforts directed toward the arylation of enolates with benzyne to form all-carbon quaternary stereocenters (e.g. **97**), we found that treatment of β-ketoester **96** with benzyne (**99**, generated in situ from **95** and fluoride) unexpectedly resulted

in the formation of disubstituted arene **98** in moderate yield (Scheme 1.16).[41] This represented the first mild and direct example of the insertion of benzyne into a β-ketoester carbon–carbon bond,[42] and is likely produced by fragmentation of transiently generated donor–acceptor cyclobutane **102**.

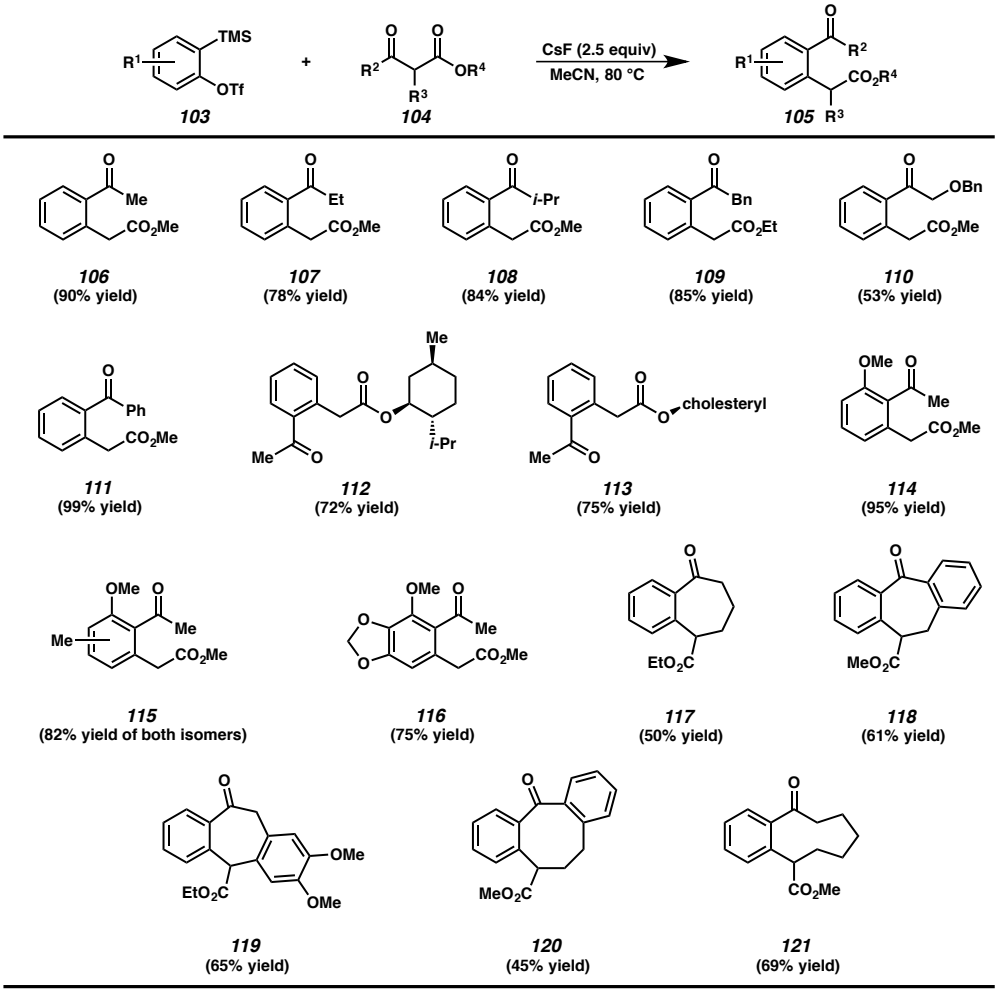
Scheme 1.16 Unexpected aryne C–C insertion and mechanistic proposal



This reactivity of benzyne with β-ketoesters proved to be quite general, and the scope of acyl-alkylation products produced is shown in Scheme 1.17. A variety of β-ketoesters were tolerated, including those with branching or heteroatom-containing groups at the γ-position (providing products **107–111**). β-Ketoesters derived from bulky and complex alcohols also afforded the acyl-alkylation products in good yield (**112** and **113**). Substituted arynes could also be used, furnishing **114–116** in good to excellent yields. Finally, cyclic β-ketoesters were also capable substrates, reacting to give ring expansion products **117–121**, in moderate yields, representing a novel route to medium-sized rings. The Stoltz laboratory has demonstrated the utility of this transformation as well as related aryne insertion reactions in several total syntheses.[43] Furthermore, their mechanistic

hypothesis has been invoked by numerous groups in recent disclosures of aryne insertion reactions.[44]

Scheme 1.17 Scope of the acyl-alkylation of arynes



1.4 SUMMARY

Donor–acceptor cyclopropanes have been used for decades to rapidly transform simple starting materials to complex products. Recent developments in the use of aryl donor groups have led to a resurgence of interest in these useful building blocks.

This chapter has described the Stoltz laboratory's use of donor–acceptor cyclopropanes and related compounds in both natural products synthesis and methodological developments over the past 15 years with inspiration dating into the early 1990s. As is the case in many laboratories, endeavors in total synthesis often inspire the development of new methods.[45] In this case, application of a donor–acceptor cyclopropane (3 + 2) cycloaddition toward the synthesis of scandine initiated further investigations into related reactivity, culminating the development of novel cycloadditions of cyclopropanes and aziridines described in Chapters 2 and 3 of this thesis. Additionally, the laboratory's interest in cyclopropane cycloadditions inspired the initial approach to the total synthesis of calophyline A, which is described in Chapter 4.

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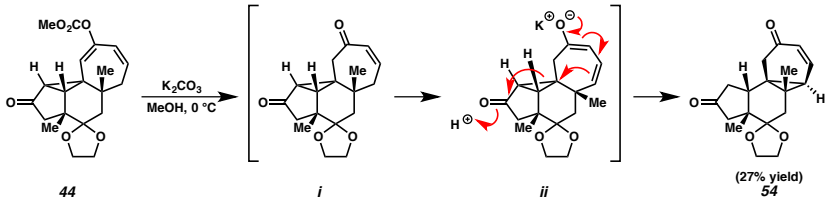

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CHAPTER 2[†]

Lewis Acid Mediated (3 + 2) Cycloadditions of

Donor–Acceptor Cyclopropanes with Heterocumulenes

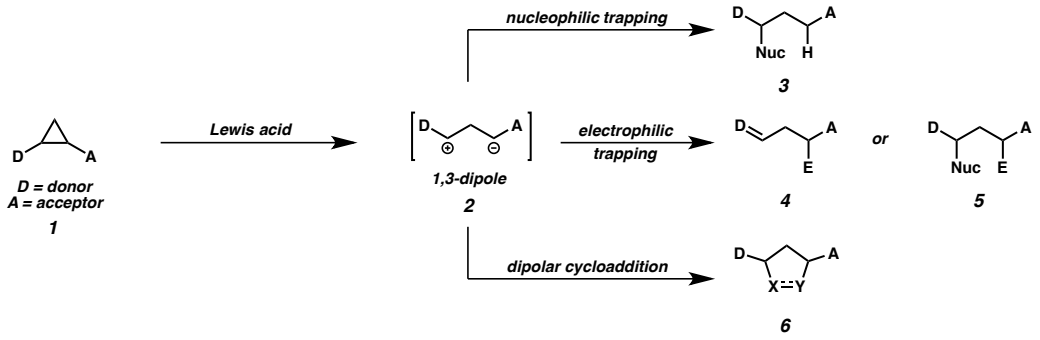
2.1 INTRODUCTION

Donor–acceptor cyclopropanes (**1**), or those possessing one or more electron-donating groups and electron-withdrawing groups on vicinal carbons, have found utility in organic synthesis due to their ease of construction and unique reactivity profiles.[1] Upon treatment with a Lewis acid, these cyclopropanes are converted to reactive 1,3-dipoles (**2**), which can undergo nucleophilic trapping, electrophilic trapping, or dipolar cycloadditions to give a wide array of useful products (**3**–**6**, Scheme 2.1). Dipolar cycloadditions of donor–acceptor cyclopropanes (i.e. **1**→**6**) are a particularly powerful

[†] This work was performed in collaboration with Dr. Alexander F. G. Goldberg and Dr. Robert A. Craig, II, alumni of the Stoltz group. This work has been published, with portions of this chapter adapted with permission from Goldberg, A. F. G.; O'Connor, N. R.; Craig, R. A., II; Stoltz, B. M. *Org. Lett.* **2012**, *14*, 5314–5317. Copyright 2012 American Chemical Society.

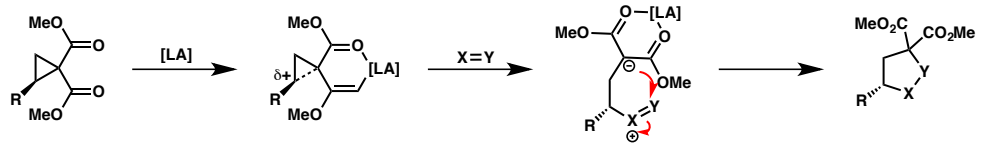
method for the construction of five- and six-membered rings, and this approach has been used in several recent total syntheses of natural products.[2]

Scheme 2.1 Basic reactivity modes of donor–acceptor cyclopropanes



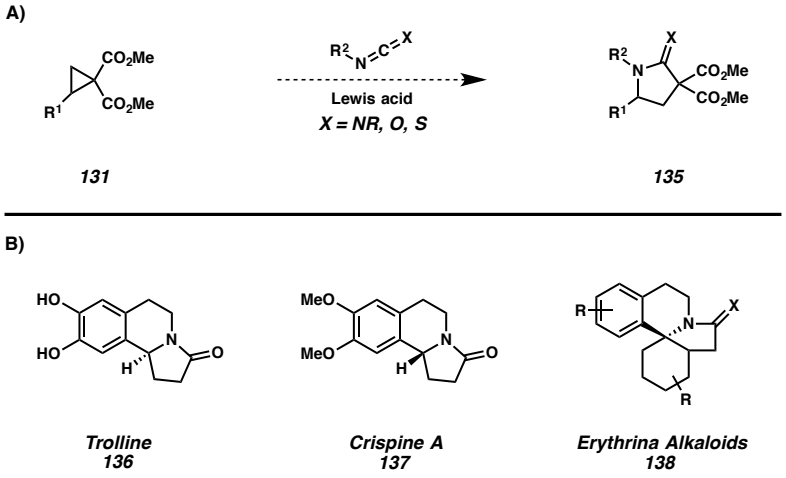
The first reports of dipolar cycloadditions of donor–acceptor cyclopropanes were limited to cyclopropanes with alkoxy and silyloxy donor groups. In recent years, however, several groups have been investigating the use of aryl donor groups. Work by Kerr, Johnson, and others have shown that aryl-substituted cyclopropane 1,1-diesters are capable of undergoing formal cycloadditions with a variety of dipolarophiles, including nitrones,[3] aldehydes,[4] imines,[5] and silyl enol ethers.[6] Unlike with alkoxy and silyloxy donor groups, cyclopropanes with aryl donor groups can undergo enantiospecific reactions with proper choice of Lewis acid. It is believed that a correctly tuned Lewis acid can activate these aryl-substituted cyclopropanes (**131**, Scheme 2.2) toward nucleophilic attack by a dipolarophile without complete cleavage of the carbon–carbon bond, allowing the stereochemical information of the starting material to be transferred to the product through an S_N2-like nucleophilic attack of the dipolarophile upon activated intermediate **132**. The resulting zwitterion (**133**) then undergoes ring closure to give the cyclic product **134** (Scheme 2.2).[4c]

Scheme 2.2 Mechanistic rationale for the stereospecific cycloadditions of donor–acceptor cyclopropanes with aryl donor groups



Our research group has had a longstanding interest in the application of donor–acceptor cyclopropanes toward the construction of complex natural products.[7] Our recent use of a cyclopropane-olefin cycloaddition in the construction of the core of the *Melodinus* alkaloids furthered our interest in this area.[2e] We were interested in extending Kerr and Johnson's methodolgies for the cycloadditions of aryl-substituted donor–acceptor cyclopropanes to include heterocumulene dipolarophiles. Specifically, we hoped to use isocyanates as electrophiles to access 5-aryl γ-lactam derivatives (**135**, Scheme 2.3), as they form part of the core of many natural products such as trolline (**136**),[8] crispine A (**137**),[9] and many of the *Erythrina* alkaloids (**138**).[10] Although isocyanates and isothiocyanates have been shown to undergo (3 + 2) cycloadditions with alkoxy-substituted donor–acceptor cyclopropanes, yields were low and the reaction stereochemistry was controlled by existing stereocenters in the reactants, rather than through an enantioselective or enantiospecific mechanism.[11]

Scheme 2.3 A) Proposed reactions of donor–acceptor cyclopropanes with heterocumulenes and B) Potential synthetic targets containing the 5-aryl γ-lactam motif



2.2 INITIAL EFFORTS: REACTIONS OF DONOR–ACCEPTOR CYCLOPROPANES WITH ISOCYANATES

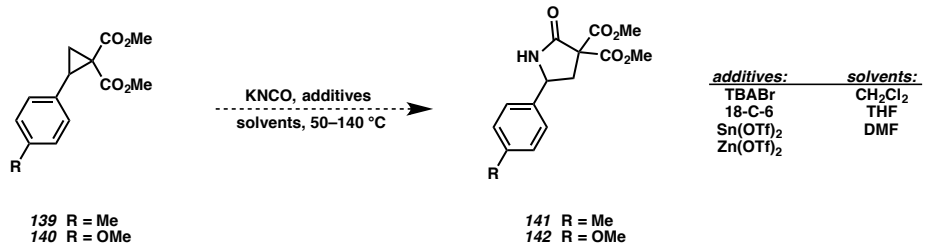
We chose to focus our initial efforts on the reactions of donor–acceptor cyclopropanes with isocyanates, as the product lactams could be most directly applied toward the synthesis of alkaloids such as those shown in Scheme 2.3.

2.2.1 CYCLOADDITIONS OF DONOR–ACCEPTOR CYCLOPROPANES WITH POTASSIUM CYANATE AND TRIMETHYLSILYL ISOCYANATE

We began our studies by investigating the reactivity of potassium cyanate with aryl-substituted donor–acceptor cyclopropane **139** (Scheme 2.4). Although the reactivity of inorganic cyanates with cyclopropanes was not known, the analogous reactivity with epoxides had been demonstrated by Swern in 1968.[12] We hoped to apply Swern's

methodology to the synthesis of secondary γ-lactams, and use of an inorganic cyanate would allow for direct and economical access to the desired heterocycles.

Scheme 2.4 Initial screening of cyclopropane reactivity with potassium cyanate



139 R = Me
140 R = OMe

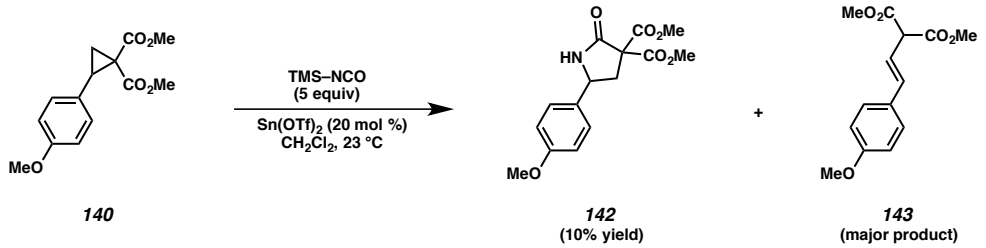
141 R = Me
142 R = OMe

We screened for reactivity of cyclopropane **139** with potassium cyanate in DMF, THF, and dichloromethane, at temperatures ranging from 50 to 140 °C, but detected no product by LCMS analysis (Scheme 2.4). Use of additives such as tetra(*n*-butyl)ammonium bromide and 18-crown-6 also failed to produce the desired reactivity. In all cases, the results were either a lack of reactivity or isomerization of the starting material to styrene **143** (see Scheme 2.5). In order to increase the reactivity of the cyclopropane, we attempted the use of a stronger donating group (**140**), but this was also unsuccessful. We hypothesized that a Lewis acid might assist in the reaction by further activating the cyclopropane, but addition of tin(II) triflate and zinc(II) triflate made no difference, possibly due to cyanate coordination to and deactivation of the Lewis acids.

We investigated the use of trimethylsilyl isocyanate as an alternative that may be less likely to coordinate to and deactivate the Lewis acid, and we were able to observe the desired lactam product in 10% yield when 20 mol % tin(II) triflate was used in dichloromethane (Scheme 2.5). A screen of various Lewis acids, solvents, and relative stoichiometries was unable to identify conditions to reliably afford the lactam product in high yield. We then proceeded to investigate the reactivity of other isocyanates in the

reaction, but phenyl and tosyl isocyanate were not successful, and isopropyl isocyanate gave only a trace of the desired product.

Scheme 2.5 Initial observation of desired reactivity with trimethylsilylisocyanate



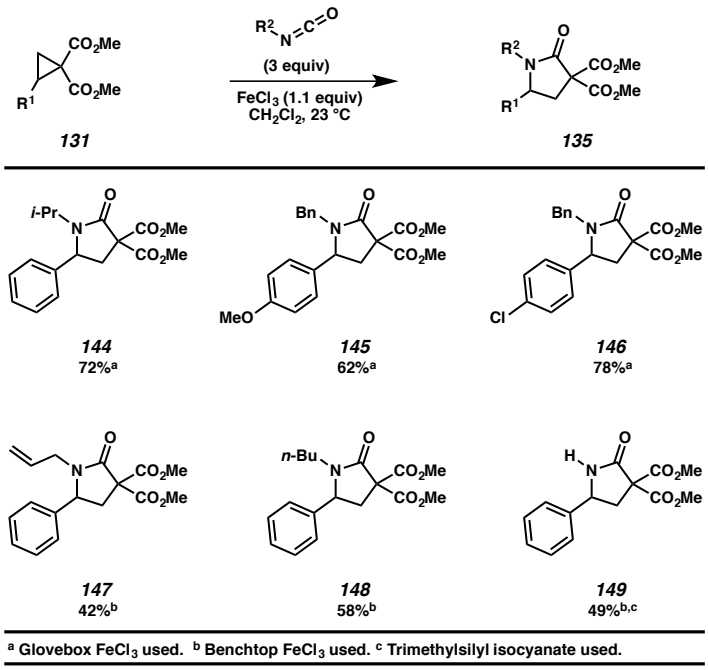
140 ***142*** **(10% yield)** ***143*** **(major product)**

2.2.2 CYCLOADDITIONS OF DONOR–ACCEPTOR CYCLOPROPANES WITH ALKYL ISOCYANATES

After our lack of success with potassium cyanate, trimethylsilyl isocyanate, tosyl isocyanate, and phenyl isocyanate, we proceeded to study more robust and reactive alkyl isocyanates, such as benzyl- and isopropyl isocyanate. These alkyl dipolarophiles displayed sluggish reactivity with tin(II) triflate, but a study of stronger Lewis acids and a reinvestigation of the other reaction parameters found that the tertiary lactam products could be obtained in good to moderate yields using stoichiometric iron(III) chloride in dichloromethane. The scope of the reaction is shown in Scheme 2.6. Lactams arising from cyclopropanes with both electron-rich (**145**) and electron-poor (**146**) donor groups are easily accessed, as is the product arising from use of the sterically bulky dipolarophile isopropyl isocyanate (**144**).

Notably, secondary lactam **149** can be accessed if trimethylsilyl isocyanate is used, with the trimethylsilyl group being lost during reaction workup.

Scheme 2.6 Scope of the iron-mediated cycloadditions of donor–acceptor cyclopropanes with isocyanates



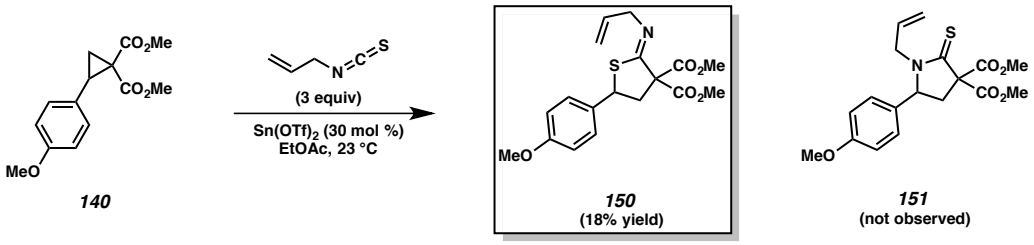
2.3 REACTIONS OF DONOR–ACCEPTOR CYCLOPROPANES WITH ISOTHIOCYANATES

Having established the desired reactivity with isocyanate dipolarophiles, we subsequently investigated the reactions of isothiocyanates in order to furnish analogous thioamide products.

2.3.1 INITIAL REACTIVITY AND STRUCTURAL REASSIGNMENT

When cyclopropane **140** was subjected to an excess of allyl isothiocyanate in the presence of 30 mol % tin(II) triflate in wet ethyl acetate, we isolated 18% yield of a product with the formula and mass of our expected thioamide product (Scheme 2.7). Upon closer examination of the ^{13}C NMR and infrared spectra, we were surprised to find that our isolated product was in fact thioimidate **150**, rather than thioamide **151**.

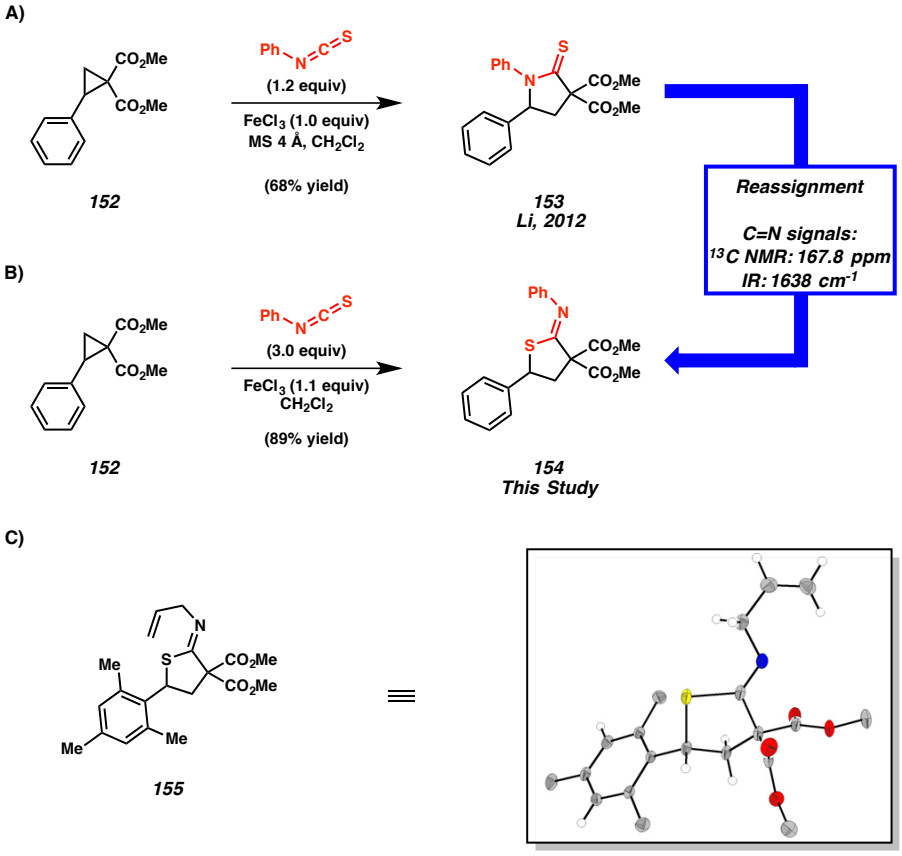
Scheme 2.7 Initial observation of desired reactivity with allyl isothiocyanate



During this time, Li and coworkers reported an iron(III) chloride mediated (3 + 2) cycloaddition of aryl-substituted donor–acceptor cyclopropanes and aryl isothiocyanates giving thioamide products (Scheme 2.8A).[13] We suspected Li's products may have been misassigned due to the close similarities between the proton NMR spectra of the two compounds and Li's lack of inclusion of IR spectra in their characterization data. We treated cyclopropane **152** with phenyl isothiocyanate under Li's conditions with slight modifications (Scheme 2.8B), and obtained a product with identical proton and ^{13}C NMR spectra as those reported by Li for compound **153**. The ^{13}C NMR showed a peak consistent with a thioimidate carbon (approximately 160 ppm), rather than a thioamide (approximately 200 ppm). Additionally, the IR spectrum showed a C=N stretch (approximately 1640 cm^{-1}), rather than a C=S stretch (approximately 1160 cm^{-1}).[14] We

believe these data, in combination with a crystal structure of one of our other thioimidate products (**155**, Scheme 2.8C) provide sufficient support for our reassignment of Li's products as thioimidates rather than thioamides.

Scheme 2.8 Structural reassignment of Li's products[15]

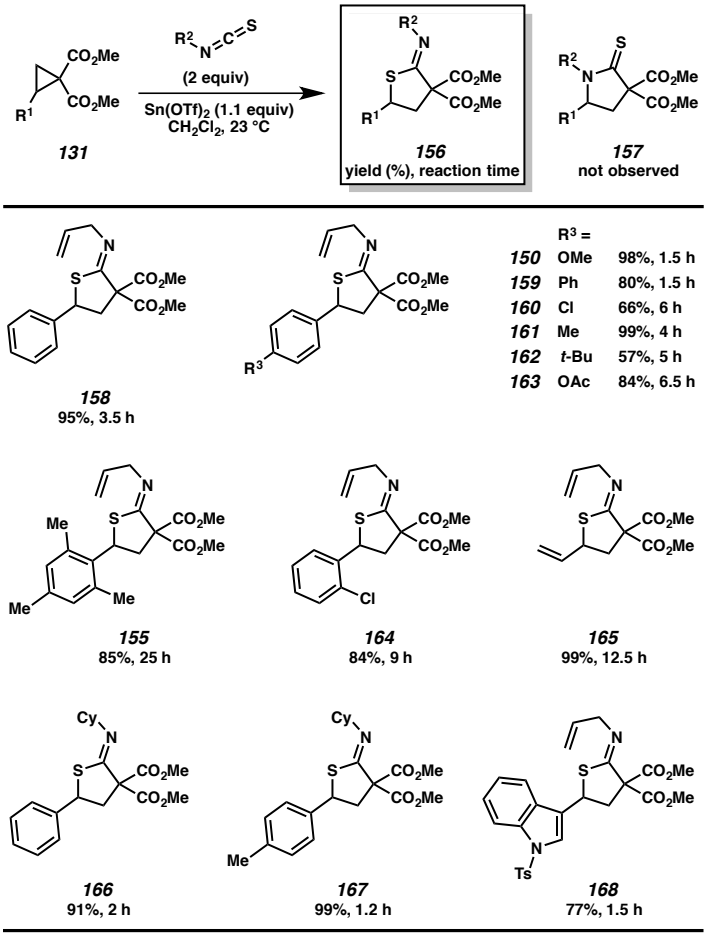


2.3.2 OPTIMIZATION AND SCOPE OF CYCLOADDITIONS WITH ISOTHIOCYANATES

Upon further optimization of our initial isothiocyanate hit, we found that use of stoichiometric tin(II) triflate and 2 equivalents of the dipolarophile in dry

dichloromethane gave the best yields. Furthermore, the products slowly decompose under the reaction conditions so prompt workup and purification was necessary. The substrate scope of the reaction is displayed in Scheme 2.9. Cyclopropanes bearing electron-rich aryl rings were the most reactive, whereas those with electron-withdrawing or *ortho* substituents were less reactive. A vinyl group could replace the aryl group as a donor, giving vinyl thioimidate **165** in quantitative yield. Finally, cyclohexyl isothiocyanate also worked well in the reaction. Crystallographic analysis of compound **155** confirmed our assignments of these products as thioimidates (other products assigned by analogy).

Scheme 2.9 Scope of the tin-mediated cycloadditions of donor–acceptor cyclopropanes with isothiocyanates

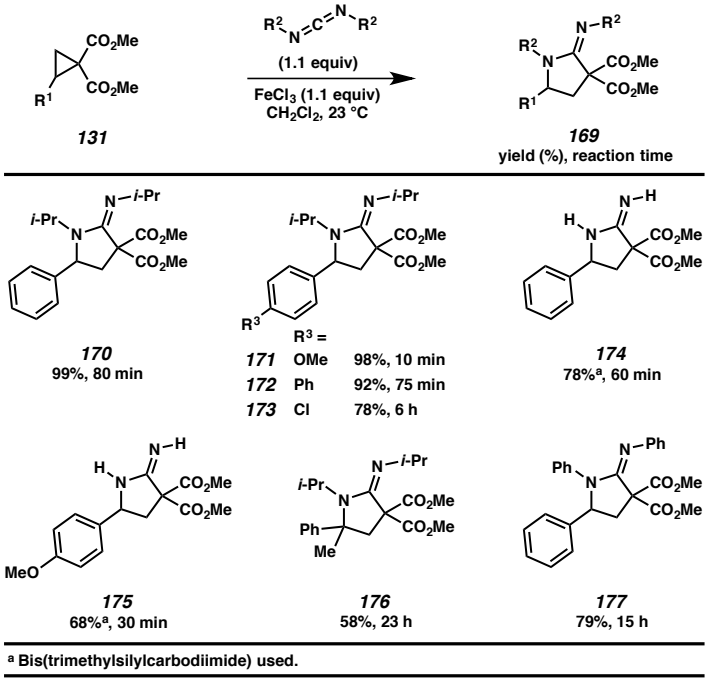


2.4 REACTIONS OF DONOR–ACCEPTOR CYCLOPROPANES WITH CARBODIIMIDES

We next examined carbodiimides as dipolarophiles in the (3 + 2) cycloaddition reaction. Our initial attempt in benchtop ethyl acetate formed the desired product in 22% yield but suffered from the formation of a large amount of urea byproduct due to hydrolysis of the carbodiimide in the wet solvent. Further optimization studies resulted in near quantitative yields when slight excesses of Lewis acid and dipolarophile were

used in dry dichloromethane. The scope of the reaction is shown in Scheme 2.10. In general, these reactions were faster than the reactions with isothiocyanates, forming the amidine products in as little as 10 minutes. The primary amidines **174** and **175** could be formed in good yields using bis(trimethylsilyl)carbodiimide. Highly substituted amidine **176** could be prepared in moderate yield, and an aryl carbodiimide also underwent the reaction to give amidine **177** in good yield.

Scheme 2.10 Scope of the tin-mediated cycloadditions of donor–acceptor cyclopropanes with carbodiimides



2.5 INVESTIGATIONS INTO THE REACTION STEREOCHEMISTRY

After concluding our study of the reaction scope, we investigated the possible transfer of stereochemical information from the cyclopropane starting material to the heterocyclic

products. Although treatment of enantioenriched cyclopropane **(*S*)-152** with an isocyanate in the presence of iron(III) chloride resulted in complete racemization of the benzylic stereocenter (Scheme 2.11A),[16] we observed transfer of chirality in the case of the tin(II) triflate mediated cycloadditions (Scheme 2.11B,C). Notably, substrates that required longer reaction times resulted in increased erosion of enantiomeric excess.[17] The absolute configuration of an amidine product was confirmed by crystallographic analysis of the hydrobromide salt (Figure 2.1), which revealed an inversion of configuration at the benzylic position during the course of the reaction.

*Scheme 2.11 Stereochemical investigations of the reaction of enantioenriched cyclopropane **(S)-152** with A) isocyanates, B) isothiocyanates, and C) carbodiimides*

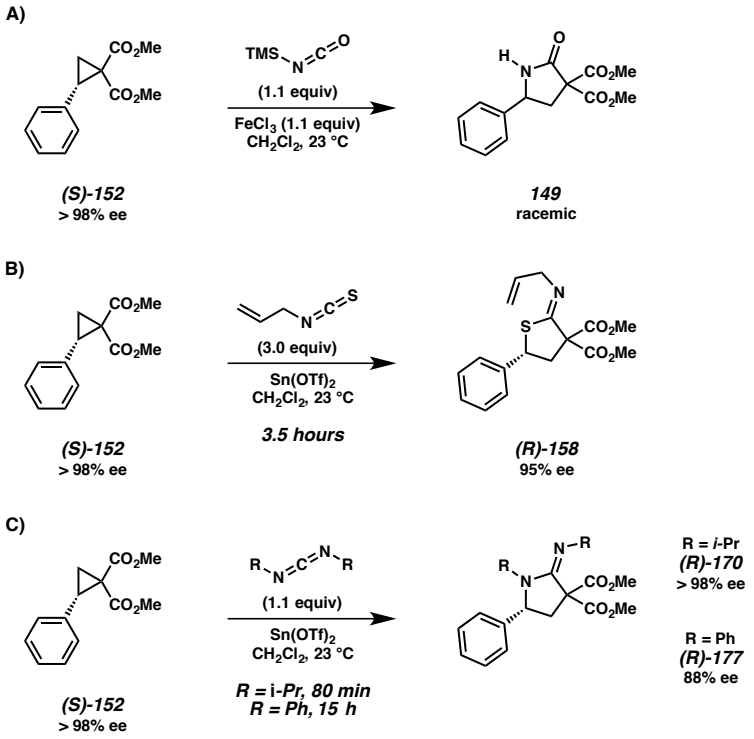
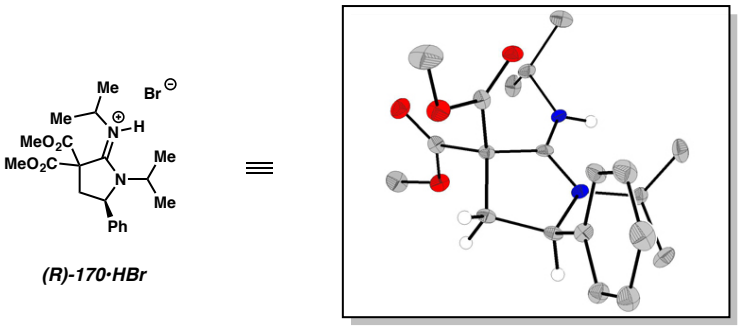


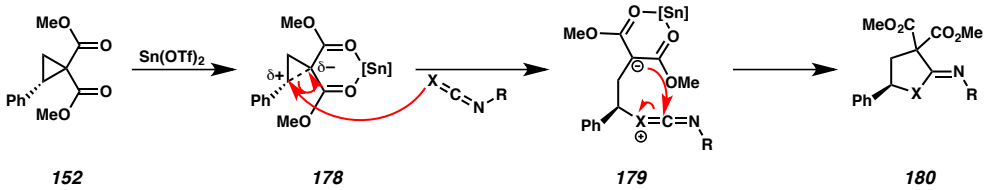
Figure 2.1 Absolute configuration of an amidine product determined by X-ray crystallography[18]



2.6 PROPOSED MECHANISM

We propose the mechanism of the isothiocyanate and carbodiimide reactions involves coordination of the Lewis acid to the cyclopropane to weaken the polarized C–C bond, forming intermediate **178**. Attack of the nucleophilic dipolarophile in an S_N2-like fashion followed by ring closure affords heterocyclic product **180** (Scheme 2.12). This mechanism is supported by our observations of the reaction stereochemistry and the greater reactivity of electron-rich dipolarophiles and of cyclopropanes with electron-rich aryl donor groups. Our mechanism is analogous to that proposed by Johnson and Kerr for the (3 + 2) cycloadditions of donor–acceptor cyclopropanes with aldehydes and nitrones, respectively.[3d,4c,19] We propose a similar mechanism for the reactions of isocyanates, however the stronger Lewis acid iron(III) chloride likely promotes the formation of a zwitterionic intermediate, preventing the transfer of stereochemical information from the starting material to the product in these reactions.

Scheme 2.12 Proposed mechanism of reactions of donor–acceptor cyclopropanes with isothiocyanates and carbodiimides



2.7 CONCLUSIONS AND FUTURE DIRECTIONS

In conclusion, we have developed a novel method for the formation of five-membered heterocycles from simple and readily accessible precursors. Our studies suggest that carbodiimides are more reactive than isothiocyanates, which in turn are more reactive than isocyanates. Furthermore, with tin(II) triflate as a Lewis acid, a highly stereselective reaction is possible, allowing for the synthesis of enantioenriched heterocycles from enantioenriched cyclopropanes. Investigations to apply this methodology toward the total synthesis of natural products are described in Appendix 2.

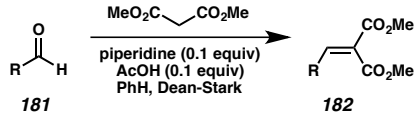
2.8 EXPERIMENTAL SECTION

2.8.1 MATERIALS AND METHODS

Unless stated otherwise, reactions were performed in flame-dried or oven-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina).[20] Diazodimethylmalonate was prepared according to the method of Davies and coworkers.[21] Potassium cyanate and all heterocumulenes were obtained from commercial suppliers. Commercially obtained

reagents were used as received with the exception of tin(II) triflate and iron(III) chloride, which were stored in a nitrogen-filled glovebox. A separate bottle of iron(III) chloride was stored in a calcium sulfate desiccator on the benchtop. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040–0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 (at 400 MHz and 100 MHz, respectively) or on a Varian Mercury 500 (at 500 MHz and 126 MHz, respectively) and are reported relative to $CHCl_3$ (δ 7.26 & 77.16 ppm, respectively) or tetramethylsilane (0.00 ppm). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Abbreviations are used as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, hept = heptet, m = complex multiplet, app = apparent br = broad. IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode; HRMS were also acquired using a JEOL JMS-600H with fast atom bombardment (FAB). Optical rotations were recorded on a JASCO P-2000 Polarimeter. Enantiomeric excesses were determined by chiral HPLC (Agilent 1100 Series) or chiral SFC (Thar).

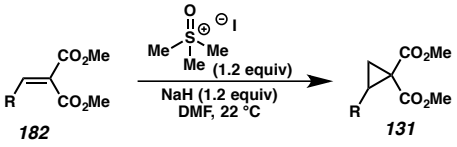
2.8.2 GENERAL AND MISCELLANEOUS EXPERIMENTAL PROCEDURES



181 *182*

General Procedure A. *Knoevenagel condensation*.

A round-bottom flask was charged with the appropriate aldehyde (**181**, 14.4 mmol), followed by benzene (85 mL), dimethyl malonate (15.8 mmol), piperidine (1.44 mmol), and acetic acid (1.44 mmol). The flask was equipped with a Dean-Stark trap and condenser and the solution heated to reflux. Upon completion (as determined by TLC analysis), evaporation of the solvent gave the crude product, which was purified by silica gel column chromatography.

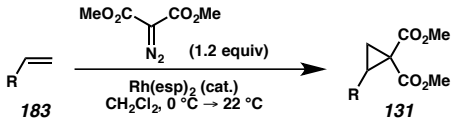


182 *131*

General Procedure B. *Corey–Chaykovsky cyclopropanation*.

Sodium hydride (2.56 mmol, 60% dispersion in mineral oil) was suspended in anhydrous DMF (4 mL) in a flame-dried round-bottom flask under nitrogen. Trimethylsulfoxonium iodide (2.56 mmol) was added, and the solution stirred at ambient temperature for 1 hour. A solution of the appropriate benzylidene malonate (**182**, 2.13 mmol) in anhydrous DMF (2 mL) was added, and the reaction mixture allowed to stir at room temperature. Upon completion (as determined by TLC analysis), the solution was poured onto a mixture of ice and aqueous 2 M HCl (10 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed once with brine, dried over

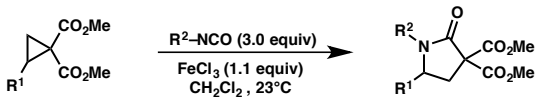
magnesium sulfate, filtered, and concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography.



183 ***131***

General Procedure C. *Styrene cyclopropanation.*

$Rh_2(esp)_2$ (0.3 mg) was added to a flame-dried round-bottom flask, which was then evacuated and backfilled with nitrogen three times. The appropriate styrene (**183**, 5.0 mmol) and anhydrous dichloromethane (5 mL) were then added and the solution was stirred under nitrogen and cooled in an ice bath. A solution of diazodimethylmalonate (6.0 mmol) in anhydrous dichloromethane (5 mL) was added dropwise over 20 minutes. The reaction solution was then allowed to warm to ambient temperature. Upon completion (as determined by TLC analysis), the crude product was adsorbed onto silica gel and purified by column chromatography. When traces of the rhodium catalyst remained after chromatography (as determined by a blue discoloration), the product was dissolved in anhydrous benzene (1.5 mL) in a flame-dried round-bottom flask. A solution of tetrakis(hydroxymethyl)phosphonium hydroxide (10 mL, 1 M in isopropanol) was added,[22] and the mixture was stirred at 60 °C for 12 hours. The solution was then cooled to room temperature, diluted with diethyl ether (20 mL), washed once with water and once with brine, dried over magnesium sulfate, filtered, and concentrated to give the purified product.



131 ***135***

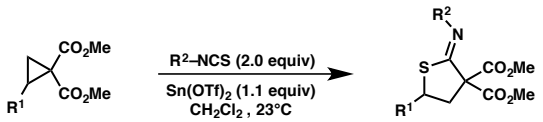
General Procedure D. *Isocyanate (3 + 2) reaction with D-A cyclopropanes, Method A.*

To a flame-dried 10 mL flask equipped with a magnetic stir bar was added iron(III) chloride (0.44 mmol) in an inert atmosphere glovebox. The flask was sealed with a Teflon septum, removed from the glovebox, and placed under a nitrogen atmosphere. To an oven-dried 1 dram vial were added the appropriate cyclopropane (**131**, 0.4 mmol) and isocyanate (1.2 mmol). The vial was sealed with a screw cap fitted with a Teflon septum, and this mixture was transferred to the reaction flask as a solution in anhydrous dichloromethane (1 mL + 0.33 mL rinse). The solution was then allowed to stir at ambient temperature under nitrogen. Upon consumption of the cyclopropane (as determined by TLC analysis), the reaction solution was diluted with dichloromethane, adsorbed onto Celite, and purified by silica gel column chromatography.

General Procedure E. *Isocyanate (3 + 2) reaction with D-A cyclopropanes, Method B.*

To an oven-dried 1 dram vial equipped with a magnetic stir bar was added iron (III) chloride (0.44 mmol) and oven-dried 4Å molecular sieves (50 mg). The vial was sealed with a screw cap fitted with a rubber septum, and was placed under a nitrogen atmosphere. To a second oven-dried 1 dram vial was added the appropriate cyclopropane (**131**, 0.4 mmol) and isocyanate (1.2 mmol). The vial was sealed with a screw cap fitted with a Teflon septum and this mixture was transferred to the first vial as a solution in anhydrous dichloromethane (1 mL + 0.33 mL rinse). The mixture was then allowed to stir at ambient temperature under nitrogen. Upon consumption of the cyclopropane (as

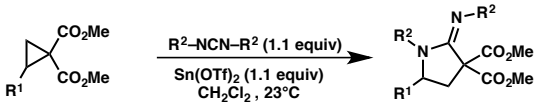
determined by TLC analysis), the reaction mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The layers were separated and the aqueous phase was washed twice with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography.



131 *156*

General Procedure F. *Isothiocyanate (3 + 2) reaction with D-A cyclopropanes.*

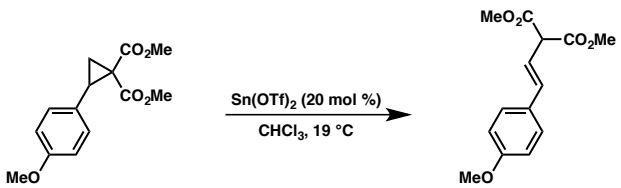
To an oven-dried 1 dram vial equipped with a magnetic stir bar was added tin(II) trifluoromethanesulfonate (0.44 mmol) in an inert atmosphere glovebox. The vial was sealed with a screw cap fitted with a Teflon® septum, removed from the glovebox, and placed under a nitrogen atmosphere. To a separate, oven-dried 1 dram vial were added the appropriate cyclopropane (**131**, 0.4 mmol) and isothiocyanate (0.8 mmol). The vial was sealed with a screw cap fitted with a Teflon® septum, and the mixture was transferred to the first vial as a solution in anhydrous dichloromethane (1 mL + 0.33 mL rinse). The heterogeneous reaction mixture was then allowed to stir at ambient temperature under nitrogen. Upon consumption of the cyclopropane (as determined by TLC analysis), the reaction solution was diluted with dichloromethane (3 mL) and methanol (1 mL), adsorbed onto Celite, and purified by silica gel column chromatography. The products of this reaction were often found to be unstable during prolonged storage (~1 week) at ambient temperature; the decomposition products have not been identified.



131 ***169***

General Procedure G. *Carbodiimide (3 + 2) reaction with D-A cyclopropanes*.

To an oven-dried 1 dram vial equipped with a magnetic stir bar was added tin(II) trifluoromethanesulfonate (0.44 mmol) in an inert atmosphere glovebox. The vial was sealed with a screw cap fitted with a Teflon® septum, removed from the glovebox and placed under a nitrogen atmosphere. To a separate, oven-dried 1 dram vial were added the appropriate cyclopropane (**131**, 0.4 mmol) and carbodiimide (0.44 mmol). The vial was sealed with a screw cap fitted with a Teflon® septum, and the mixture was transferred to the first vial as a solution in anhydrous dichloromethane (1 mL + 0.33 mL rinse). The heterogeneous reaction mixture was then allowed to stir at ambient temperature under nitrogen. Upon consumption of the cyclopropane (as determined by TLC analysis), the reaction solution was diluted with dichloromethane (3 mL) and methanol (1 mL), adsorbed onto Celite, and purified by silica gel column chromatography. The product obtained after column chromatography is an amidinium salt, which is dissolved in DCM, and washed with aqueous sodium hydroxide (0.1 M) and brine, then dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield the free amidine base.

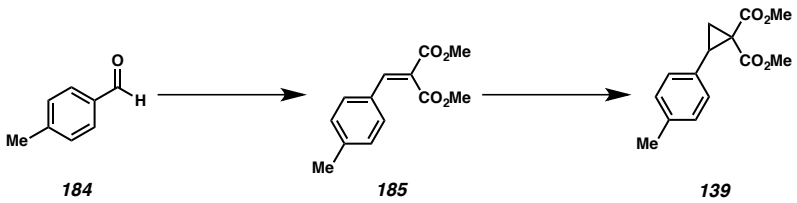


140 ***143***

Preparation of Styrene 143.

A 1 dram vial, equipped with a magnetic stir bar, was charged with tin(II) triflate (16.7 mg, 0.04 mmol, 0.2 equiv), then cyclopropane **140** (54.1 mg, 0.2 mmol, 1 equiv) was added as a solution in chloroform (1 mL). Stirring was initiated and a heterogeneous mixture with a yellow supernatant resulted. Consumption of starting material was observed by LCMS after 35 minutes. The reaction mixture was dry-loaded onto SiO_2 (~1 mL) and purified by silica gel column chromatography (3:1 hexanes:EtOAc) to afford styrene **143** as a colorless solid. Characterization data match those reported in the literature.[23]

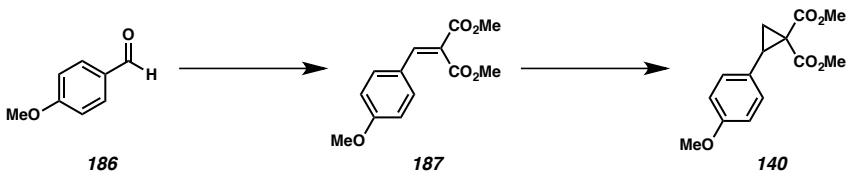
2.8.3 CYCLOPROPANE CHARACTERIZATION DATA



184 *185* *139*

dimethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate (139):

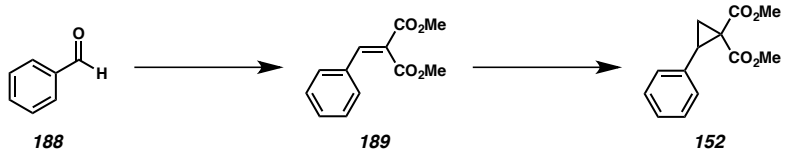
Benzylidene dimethylmalonate **185** was prepared according to General Method A: 30% yield. R_f = 0.19 (3:1 Heaxanes:EtOAc eluent). Characterization data matches those reported in the literature.[24] Cyclopropane **139** was prepared according to General Method B: 77% yield. R_f = 0.60 (3:1 Hexanes:EtOAc). Characterization data match those reported in the literature.[25]



186 *187* *140*

dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (140):

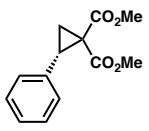
Benzylidene dimethylmalonate **187** was prepared according to General Method A: 92% yield. R_f = 0.27 (3:1 Hexanes:EtOAc eluent). Characterization data match those reported in the literature.[26] Cyclopropane **140** was prepared according to General Method B: 95% yield. R_f = 0.40 (3:1 Hexanes:EtOAc eluent). Characterization data match those reported in the literature.[27]



188 *189* *152*

dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (152):

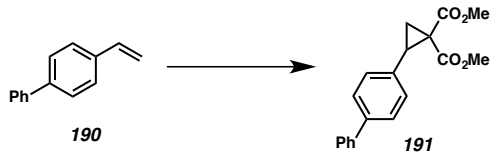
Benzylidene dimethylmalonate **189** was prepared according to General Method A: 99% yield. R_f = 0.60 (3:1 Hexanes:EtOAc eluent). Characterization data match those reported in the literature.[28] Cyclopropane **152** was prepared according to General Method B: 66% yield. R_f = 0.60 (3:1 Hexanes:EtOAc eluent). Characterization data match those reported in the literature.[29]



(S)-152

(*S*)-dimethyl 2-phenylcyclopropane-1,1-dicarboxylate ((*S*)-152):

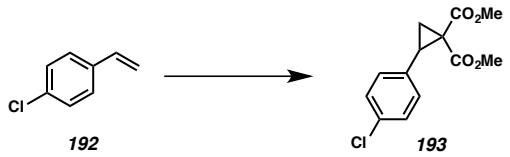
Cyclopropane **(*S*)-152** was prepared according to literature methods.[30] $[\alpha]_D^{25.0}$ – 133.17° (*c* 0.99, $CHCl_3$, >98% *ee*).



190 *191*

dimethyl 2-([1,1'-biphenyl]-4-yl)cyclopropane-1,1-dicarboxylate (191):

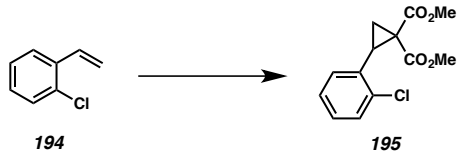
Cyclopropane **191** was prepared according to General Method C: 99% yield. R_f = 0.48 (3:1 Hexanes:EtOAc eluent). Characterization data match those reported in the literature.[31]



192 *193*

dimethyl 2-(4-chlorophenyl)cyclopropane-1,1-dicarboxylate (193):

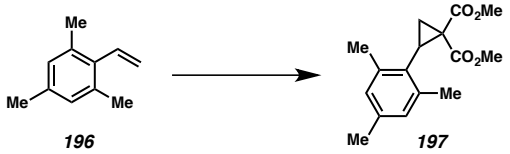
Cyclopropane **193** was prepared according to General Method C: 99% yield. R_f = 0.53 (3:1 Hexanes:EtOAc eluent). Characterization data match those reported in the literature.[26]



194 *195*

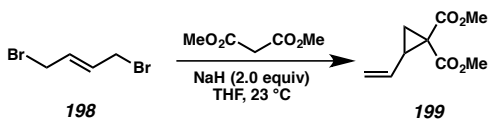
dimethyl 2-(2-chlorophenyl)cyclopropane-1,1-dicarboxylate (195):

Cyclopropane **195** was prepared according to General Method C: 60% yield. R_f = 0.50 (3:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.33 (m, 1H), 7.22–7.15 (m, 2H), 7.11–7.07 (m, 1H), 3.81 (s, 3H), 3.36 (s, 4H), 2.26 (dd, *J* = 8.3, 5.2 Hz, 1H), 1.79 (dd, *J* = 9.1, 5.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 167.1, 136.6, 132.8, 129.3, 129.0, 128.9, 126.5, 53.0, 52.4, 36.5, 31.3, 19.0; IR (Neat Film, NaCl) 3001, 2953, 1732, 1483, 1435, 1377, 1331, 1288, 1219, 1131, 1055, 894, 785, 754 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{13}H_{14}{}^{35}ClO_4$ $[M+H]^+$: 269.0575, found 269.0573.



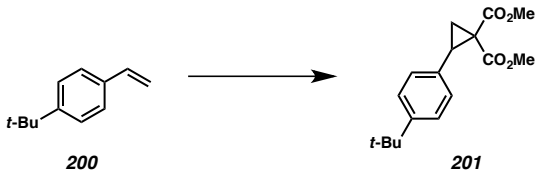
dimethyl 2-mesitylcyclopropane-1,1-dicarboxylate (197):

Cyclopropane **197** was prepared according to General Method C: 71% yield. R_f = 0.40 (3:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (s, 2H), 3.83 (s, 3H), 3.34 (s, 3H), 3.10–3.02 (app t, *J* = 9.3 Hz, 1H), 2.42–2.36 (dd, *J* = 8.9, 4.9 Hz, 1H), 2.32 (s, 6H), 2.22 (s, 3H), 1.97–1.89 (dd, *J* = 9.6, 4.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 168.0, 136.6, 129.2, 128.5, 52.9, 52.2, 35.3, 32.0, 24.0, 21.0; IR (Neat Film, NaCl) 2953, 2921, 1728, 1612, 1437, 1372, 1328, 1287, 1224, 1196, 1128, 1096, 1032, 1015, 992, 894, 852, 782, 718 cm^{-1}; HRMS (Low Voltage MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{21}O_4$ $[M+H]^+$: 277.1434, found 277.1420.



dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (199):

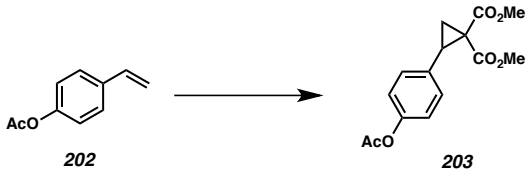
Cyclopropane **199** was prepared according to the method of Johnson and coworkers.[32]



200 *201*

dimethyl 2-(4-(*tert*-butyl)phenyl)cyclopropane-1,1-dicarboxylate (201):

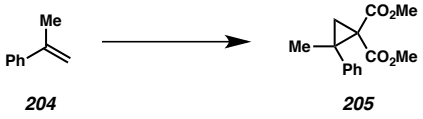
Cyclopropane **201** was prepared according to General Method C: 89% yield. R_f = 0.50 (3:1 Hexanes:EtOAc eluent). Characterization data match those reported in the literature.[33]



202 *203*

dimethyl 2-(4-acetoxyphenyl)cyclopropane-1,1-dicarboxylate (203):

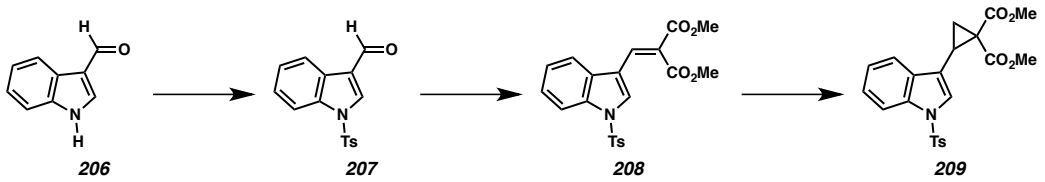
Cyclopropane **203** was prepared according to General Method C: 67% yield. R_f = 0.30 (3:1 Hexanes:EtOAc eluent). Characterization data match those reported in the literature.[4c]



204 *205*

dimethyl 2-methyl-2-phenylcyclopropane-1,1-dicarboxylate (205):

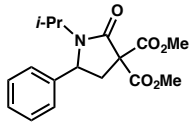
Cyclopropane **205** was prepared according to General Method C: 41% yield. R_f = 0.53 (3:1 Hexanes:EtOAc eluent). Characterization data match those reported in the literature.[34]



dimethyl 2-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1,1-dicarboxylate (209):

N-Tosylindole-3-carboxaldehyde (**207**) was prepared according to literature methods from indole-3-carbodaldehyde (**206**).[35] Benzylidene dimethylmalonate **208** was prepared according to General Method A: 75% yield. R_f = 0.20 (3:1 Hexanes:EtOAc eluent). Characterization data match those reported in the literature.[36] Cyclopropane **209** was prepared according to General Method B: 95% yield. R_f = 0.30 (3:1 Hexanes:EtOAc eluent). Characterization data match those reported in the literature.[35]

2.8.4 LACTAM CHARACTERIZATION DATA

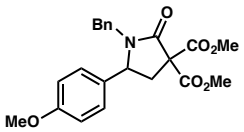


144

dimethyl 1-isopropyl-2-oxo-5-phenylpyrrolidine-3,3-dicarboxylate (144):

Prepared according to General Method F. 72% yield. R_f = 0.46 (1:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H), 4.64 (t, *J* = 7.3 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.80–3.71 (m, 1H), 3.02 (dd, *J* = 13.8, 7.7 Hz, 1H), 2.59 (dd, *J* =

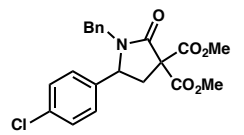
13.8, 6.9 Hz, 1H), 1.25 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 168.1, 167.2, 141.0, 129.0, 128.6, 127.2, 63.4, 59.7, 53.7, 53.5, 47.1, 38.4, 19.8, 19.7; IR (Neat Film, NaCl) 2954, 1735, 1703, 1495, 1457, 1434, 1367, 1342, 1259, 1218, 1130, 1090, 1065, 998, 966, 919, 894, 774 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{22}NO_5$ $[M+H]^+$: 320.1492, found 320.1490.



145

dimethyl 1-butyl-2-oxo-5-(4-methoxyphenyl)pyrrolidine-3,3-dicarboxylate (145):

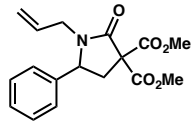
Prepared according to General Method F. 62% yield. R_f = 0.39 (1:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.23 (m, 3H), 7.08–7.02 (m, 4H), 6.94–6.87 (m, 2H), 5.11 (d, *J* = 14.5 Hz, 1H), 4.31 (t, *J* = 7.6 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.46 (d, *J* = 14.6 Hz, 1H), 2.94 (dd, *J* = 13.8, 7.2 Hz, 1H), 2.65 (dd, *J* = 13.8, 8.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 167.9, 167.1, 160.0, 135.5, 130.4, 128.8, 128.7, 128.6, 127.9, 114.6, 63.4, 58.3, 55.5, 53.7, 53.6, 45.2, 38.1; IR (Neat Film, NaCl) 2953, 1735, 1705, 1513, 1434, 1281, 1247 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{22}H_{24}NO_6$ $[M+H]^+$: 398.1598, found 398.1581.



146

dimethyl 1-butyl-2-oxo-5-(4-chlorophenyl)pyrrolidine-3,3-dicarboxylate (146):

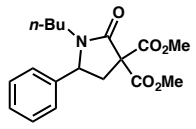
Prepared according to General Method F. 78% yield. R_f = 0.41 (1:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.33 (m, 2H), 7.29–7.24 (m, 3H), 7.10–7.05 (m, 2H), 7.04–7.00 (m, 2H), 5.13 (d, *J* = 14.6 Hz, 1H), 4.33 (t, *J* = 7.6 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.46 (d, *J* = 14.6 Hz, 1H), 2.97 (dd, *J* = 13.9, 7.4 Hz, 1H), 2.60 (dd, *J* = 13.9, 7.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 167.7, 167.2, 137.3, 135.1, 134.7, 129.5, 128.8, 128.7, 128.6, 128.0, 63.2, 58.1, 53.8, 53.7, 45.3, 37.9; IR (Neat Film, NaCl) 2953, 1736, 1708, 1435, 1242, 1204, 1090 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{21}{}^{35}ClNO_5$ $[M+H]^+$: 402.1103, found 402.1084.



147

dimethyl 1-allyl-2-oxo-5-phenylpyrrolidine-3,3-dicarboxylate (147):

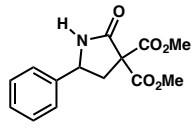
Prepared according to General Method G. 42% yield. R_f = 0.52 (1:1 Hexanes:EtOAc eluent);^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.29 (m, 3H), 7.24–7.18 (m, 2H), 5.71–5.52 (m, 1H), 5.12 (ddt, *J* = 10.1, 1.3, 0.7 Hz, 1H), 4.99–4.91 (m, 1H), 4.64 (t, *J* = 7.5 Hz, 1H), 4.40 (m, 1H), 3.90–3.84 (m, 3H), 3.82 (d, *J* = 0.9 Hz, 3H), 3.15–3.02 (m, 2H), 2.62 (dd, *J* = 13.8, 7.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 167.9, 166.8, 138.9, 131.0, 129.2, 128.8, 127.3, 118.9, 63.1, 59.1, 53.8, 53.6, 44.1, 38.0; IR (Neat Film, NaCl) 2953, 1735, 1707, 1433, 1245, 1214, 1070 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{20}NO_5$ $[M+H]^+$: 318.1341, found 318.1356.



148

dimethyl 1-butyl-2-oxo-5-phenylpyrrolidine-3,3-dicarboxylate (148):

Prepared according to General Method G. 58% yield. R_f = 0.10 (4:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.31 (m, 3H), 7.25–7.20 (m, 2H), 4.63 (t, *J* = 7.5 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.70 (dt, *J* = 13.7, 7.9 Hz, 1H), 3.06 (dd, *J* = 13.7, 7.3 Hz, 1H), 2.57–2.53 (m, 2H), 1.43–1.30 (m, 2H), 1.29–1.10 (m, 2H), 0.82 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 168.0, 166.9, 139.1, 129.2, 128.7, 127.1, 63.2, 59.5, 53.7, 53.6, 41.1, 38.3, 28.6, 19.8, 13.7; IR (Neat Film, NaCl) 2957, 2873, 1732, 1708, 1495, 1456, 1435, 1370, 1278, 1242, 1202, 1108, 1090, 1070, 893, 771 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{24}NO_5$ $[M+H]^+$: 334.1654, found 334.1646.



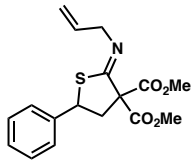
149

dimethyl 2-oxo-5-phenylpyrrolidine-3,3-dicarboxylate (149):

Prepared according to General Method G. 49% yield. R_f = 0.48 (1:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.33 (m, 2H), 7.33–7.28 (m, 3H), 6.93–6.69 (br s, 1H), 4.75 (t, *J* = 7.4 Hz, 1H), 3.85 (d, *J* = 1.6 Hz, 3H), 3.77 (dd, *J* = 2.1, 0.9 Hz, 3H), 3.18 (ddt, *J* = 13.6, 7.2, 0.8 Hz, 1H), 2.63 (ddd, *J* = 13.5, 7.8, 1.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 167.5, 167.4, 140.3, 129.0, 128.4, 126.0, 63.2, 55.4, 53.7, 53.6, 40.4; IR (Neat Film, NaCl) 3251, 2955, 1729, 1435, 1250, 1208, 1060 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{14}H_{16}NO_5$ $[M+H]^+$: 278.1028, found 278.1042.

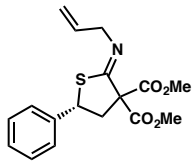
2.8.5 THIOIMIDATE CHARACTERIZATION DATA

Unless stated otherwise, all thioimidates were prepared according to General Method F.



158

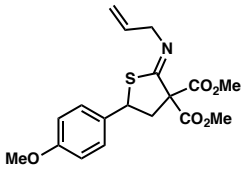
(*Z*)-dimethyl 2-(allylimino)-5-phenyldihydrothiophene-3,3(2*H*)-dicarboxylate (158): 92% yield. R_f = 0.45 (7:3 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.40 (m, 2H), 7.39–7.34 (m, 2H), 7.33–7.29 (m, 1H), 5.99 (ddt, *J* = 17.1, 10.4, 5.2 Hz, 1H), 5.26 (dq, *J* = 17.2, 1.8 Hz, 1H), 5.13 (dq, *J* = 10.4, 1.7 Hz, 1H), 4.73 (dd, *J* = 11.7, 4.9 Hz, 1H), 4.00 (dtd, *J* = 5.5, 1.8, 0.7 Hz, 2H), 3.88 (s, 3H), 3.81 (s, 3H), 3.12 (dd, *J* = 13.0, 4.9 Hz, 1H), 2.90 (dd, *J* = 13.0, 11.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 168.1, 166.0, 138.2, 134.0, 129.0, 128.5, 127.8, 116.0, 71.0, 59.8, 53.8, 53.6, 50.9, 44.3; IR (Neat Film, NaCl) 3010, 2952, 1738, 1652, 1495, 1435, 1269, 1227, 1169, 1098, 1064, 977, 921, 862, 842, 799, 765 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{20}NO_4S$ $[M+H]^+$: 334.1108, found 334.1113.



(R)-158

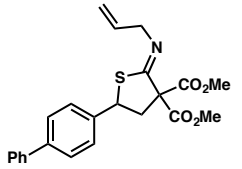
(*R*,*Z*)-dimethyl 2-(allylimino)-5-phenyldihydrothiophene-3,3(2H)-dicarboxylate ((*R*)-158):

Characterization data are same as above; $[\alpha]_D^{25.0}$ +8.8° (*c* 0.445, $CHCl_3$, 95% *ee*).



150

dimethyl 1-allyl-5-(4-methoxyphenyl)-2-thioxopyrrolidine-3,3-dicarboxylate (150): 98% yield. R_f = 0.49 (7:3 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.32 (m, 2H), 6.90–6.85 (m, 2H), 6.03–5.92 (m, 1H), 5.24 (dq, *J* = 17.2, 1.8 Hz, 1H), 5.12 (dq, *J* = 10.4, 1.7 Hz, 1H), 4.71 (dd, *J* = 11.8, 4.8 Hz, 1H), 3.99 (dt, *J* = 5.2, 1.8 Hz, 2H), 3.87 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.07 (dd, *J* = 13.0, 4.9 Hz, 1H), 2.87 (dd, *J* = 13.0, 11.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 168.1, 166.5, 159.7, 134.0, 130.0, 129.0, 116.0, 114.3, 71.1, 59.7, 55.5, 53.8, 53.6, 50.6, 44.5; IR (Neat Film, NaCl) 3003, 2953, 2837, 1736, 1638, 1610, 1513, 1435, 1305, 1250, 1175, 1098, 1070, 1032, 922, 831, 792 cm^{-1}; HRMS (Low Voltage MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{22}NO_5S$ $[M+H]^+$: 364.1213, found 364.1193.

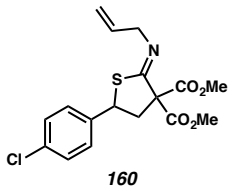


159

(*Z*)-dimethyl 5-([1,1'-biphenyl]-4-yl)-2-(allylimino)dihydrothiophene-3,3(2*H*)-dicarboxylate (159):

80% yield. R_f = 0.53 (7:3 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62–7.56 (m, 4H), 7.53–7.49 (m, 2H), 7.48–7.42 (m, 2H), 7.39–7.33 (m, 1H), 6.00 (ddt, *J* =

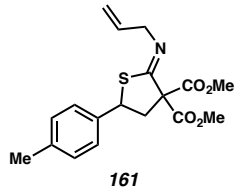
17.2, 10.4, 5.2 Hz, 1H), 5.27 (dq, *J* = 17.1, 1.8 Hz, 1H), 5.14 (dq, *J* = 10.3, 1.7 Hz, 1H), 4.79 (dd, *J* = 11.7, 4.9 Hz, 1H), 4.02 (dt, *J* = 5.2, 1.8 Hz, 2H), 3.89 (s, 3H), 3.83 (s, 3H), 3.16 (dd, *J* = 13.0, 4.9 Hz, 1H), 2.94 (dd, *J* = 13.0, 11.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 168.0, 166.2, 141.4, 140.4, 137.0, 133.8, 128.9, 128.2, 127.6, 127.1, 116.0, 71.0, 59.6, 53.7, 53.5, 50.6, 44.2; IR (Neat Film, NaCl) 3029, 2952, 1736, 1651, 1639, 1487, 1435, 1412, 1279, 1263, 1226, 1168, 1099, 1070, 1008, 977, 920, 836, 799, 767, 738 cm^{-1}; HRMS (Low Voltage MM: ESI-APCI) *m/z* calc'd for $C_{23}H_{24}NO_4S$ $[M+H]^+$: 410.1421, found 410.1408.



160

(*Z*)-dimethyl 2-(allylimino)-5-(4-chlorophenyl)dihydrothiophene-3,3(2*H*)-dicarboxylate (160):

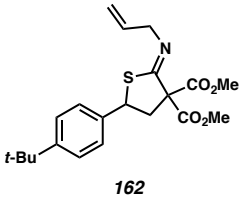
66% yield. R_f = 0.49 (7:3 Hexanes:EtOAc eluent); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.19 (m, 4H), 5.97 (ddt, *J* = 17.1, 10.4, 5.1 Hz, 1H), 5.23 (dq, *J* = 17.2, 1.9 Hz, 1H), 5.12 (dq, *J* = 10.4, 1.7 Hz, 1H), 4.69 (dd, *J* = 11.6, 4.9 Hz, 1H), 3.98 (dt, *J* = 5.1, 1.8 Hz, 2H), 3.86 (s, 3H), 3.79 (s, 3H), 3.09 (dd, *J* = 13.0, 5.0 Hz, 1H), 2.82 (dd, *J* = 13.0, 11.6 Hz, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 167.8, 165.3, 136.7, 134.2, 133.8, 129.0, 129.0, 115.9, 70.8, 59.7, 53.7, 53.4, 50.0, 44.1; IR (Neat Film, NaCl) 2953, 1733, 1652, 1637, 1491, 1434, 1266, 1221, 1167, 1090, 1068, 1011 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{19}{}^{35}ClNO_4S$ $[M+H]^+$: 368.0718, found 368.0729.



161

(Z)-dimethyl 2-(allylimino)-5-(p-tolyl)dihydrothiophene-3,3(2H)-dicarboxylate (161):

99% yield. R_f = 0.47 (7:3 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2H), 7.19–7.15 (m, 2H), 5.98 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.25 (dq, *J* = 17.2, 1.8 Hz, 1H), 5.14 (dq, *J* = 10.4, 1.7 Hz, 1H), 4.72 (dd, *J* = 11.8, 4.8 Hz, 1H), 4.01 (dt, *J* = 5.2, 1.8 Hz, 2H), 3.88 (s, 3H), 3.82 (s, 3H), 3.10 (dd, *J* = 13.1, 4.9 Hz, 1H), 2.88 (dd, *J* = 13.0, 11.8 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 168.0, 138.5, 134.9, 133.7, 129.7, 127.7, 116.3, 71.1, 59.5, 53.9, 53.7, 51.1, 44.5, 21.3; IR (Neat Film, NaCl) 3011, 2952, 1737, 1652, 1639, 1515, 1435, 1278, 1269, 1257, 1228, 1169, 1071, 1018, 978, 921, 864, 848, 818, 790 cm^{-1}; HRMS (Low Voltage MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{22}NO_4S$ $[M+H]^+$: 348.1264, found 348.1254.

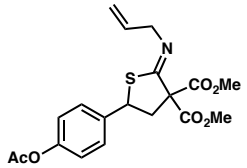


162

(Z)-dimethyl 2-(allylimino)-5-(4-(*tert*-butyl)phenyl)dihydrothiophene-3,3(2*H*)-dicarboxylate (162):

41% yield. R_f = 0.30 (3:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.32 (m, 4H), 5.98 (ddt, *J* = 17.1, 10.4, 5.2 Hz, 1H), 5.25 (dq, *J* = 17.2, 1.8 Hz, 1H), 5.13 (dq, *J* = 10.4, 1.7 Hz, 1H), 4.71 (dd, *J* = 11.8, 4.9 Hz, 1H), 3.99 (dt, *J* = 5.1, 1.7 Hz, 2H), 3.88 (s, 3H), 3.81 (s, 3H), 3.07 (dd, J = 13.0, 4.9 Hz, 1H), 2.90 (dd, J = 13.0, 11.8 Hz,

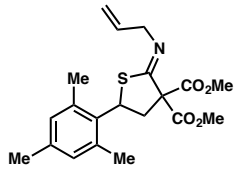
1H) 1.31 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 168.2, 166.3, 151.6, 135.1, 134.1, 127.5, 125.9, 116.0, 71.1, 59.8, 53.8, 53.6, 50.7, 44.3, 34.8, 31.4; IR (Neat Film, NaCl) 2955, 2904, 2868, 1737, 1652, 1639, 1509, 1435, 1363, 1280, 1267, 1227, 1168, 1111, 1070, 1016, 978, 920, 828 cm^{-1}; HRMS (Low Voltage MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{28}NO_4S$ $[M+H]^+$: 390.1734, found 390.1726.



163

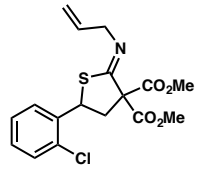
(*Z*)-dimethyl 5-(4-acetoxyphenyl)-2-(allylimino)dihydrothiophene-3,3(2*H*)-dicarboxylate (163):

84% yield. R_f = 0.20 (3:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.41 (m, 2H), 7.12–7.05 (m, 2H), 5.97 (ddt, *J* = 17.2, 10.3, 5.2 Hz, 1H), 5.25 (dq, *J* = 17.2, 1.8 Hz, 1H), 5.13 (dq, *J* = 10.4, 1.7 Hz, 1H), 4.72 (dd, *J* = 11.6, 4.9 Hz, 1H), 3.99 (ddd, *J* = 7.0, 1.7, 1.0 Hz, 2H), 3.87 (s, 3H), 3.80 (s, 3H), 3.11 (dd, *J* = 13.1, 4.9 Hz, 1H), 2.85 (dd, *J* = 13.1, 11.6 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 168.4, 168.0, 165.8, 150.6, 135.8, 134.0, 129.0, 122.2, 116.0, 71.0, 59.8, 53.8, 53.6, 50.3, 44.5, 21.3; IR (Neat Film, NaCl) 2953, 1736, 1649, 1639, 1507, 1436, 1370, 1280, 1257, 1194, 1167, 1099, 1016, 911, 851 cm^{-1}; HRMS (Low Voltage MM: ESI-APCI) *m/z* calc'd for $C_{19}H_{22}NO_6S$ $[M+H]^+$: 392.1162, found 392.1159.



155

(*Z*)-dimethyl 2-(allylimino)-5-mesityldihydrothiophene-3,3(2*H*)-dicarboxylate (155): 85% yield. White, translucent crystals were obtained by slow diffusion of 1% benzene in heptane into a solution of thioimidate **155** in EtOAc, M.P.: 89–91 °C; R_f = 0.52 (7:3 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87–6.84 (m, 2H), 5.99 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.32 (dd, *J* = 12.5, 5.3 Hz, 1H), 5.24 (dq, *J* = 17.2, 1.8 Hz, 1H), 5.13 (dq, *J* = 10.4, 1.7 Hz, 1H), 4.02 (dtd, *J* = 5.2, 1.8, 0.8 Hz, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 3.24 (dd, *J* = 13.3, 12.5 Hz, 1H), 2.93 (dd, *J* = 13.3, 5.3 Hz, 1H), 2.46 (s, 6H), 2.25 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 168.3, 166.8, 137.9, 134.0, 130.9, 129.2, 116.0, 71.1, 59.8, 53.8, 53.6, 46.2, 40.0, 21.3, 20.9; IR (Neat Film, NaCl) 3010, 2952, 2918, 1737, 1649, 1638, 1611, 1435, 1267, 1230, 1203, 1167, 1097, 1073, 1015, 976, 921, 954, 822, 799, 774, 739 cm^{-1}; HRMS (Low Voltage MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{26}NO_4S$ $[M+H]^+$: 376.1577, found 376.1563.

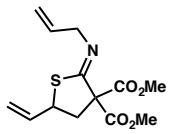


164

(*Z*)-dimethyl 2-(allylimino)-5-(2-chlorophenyl)dihydrothiophene-3,3(2*H*)-dicarboxylate (164):

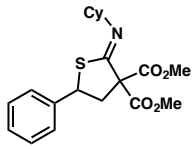
84% yield. R_f = 0.48 (7:3 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.38 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.31 (td, *J* = 7.6, 1.4 Hz, 1H),

7.23 (td, *J* = 7.6, 1.7, 1H), 5.98 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.30–5.22 (m, 2H), 5.14 (dq, *J* = 10.4, 1.7 Hz, 1H), 4.03 (td, *J* = 4.4, 2.0 Hz, 2H), 3.88 (s, 3H), 3.77 (s, 3H), 3.19 (dd, *J* = 13.0, 5.1 Hz, 1H), 2.84 (dd, *J* = 13.0, 11.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 168.0, 165.7, 135.8, 134.0, 133.9, 130.0, 129.5, 128.5, 127.5, 116.1, 70.6, 59.7, 53.8, 53.6, 47.0, 42.6; IR (Neat Film, NaCl) 3011, 2953, 1737, 1651, 1639, 1435, 1279, 1256, 1228, 1171, 1130, 1100, 1069, 1051, 1038, 977, 921, 760 cm^{-1}; HRMS (Low Voltage MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{19}{}^{35}ClNO_4S$ $[M+H]^+$: 368.0718, found 368.0700.



165

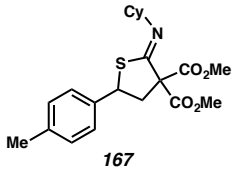
(*Z*)-dimethyl 2-(allylimino)-5-vinyldihydrothiophene-3,3(2*H*)-dicarboxylate (165): 99% yield. R_f = 0.45 (7:3 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.80 (ddd, *J* = 16.9, 10.0, 8.4 Hz, 1H), 5.33 (dq, *J* = 16.9, 0.8 Hz, 1H), 5.23 (ddd, *J* = 17.3, 1.8, 0.6 Hz, 1H), 5.19 (d, *J* = 10.1. 1H), 5.13 (ddd, *J* = 10.4, 1.7, 0.7 Hz, 1H), 4.22 (m, 1H), 3.98 (dd, *J* = 5.2, 2.0 Hz, 2H), 3.84 (s, 3H), 3.81 (d, *J* = 0.6 Hz, 3H), 2.97 (ddd, *J* = 13.1, 5.1, 0.8 Hz, 1H), 2.61 (dd, *J* = 13.1, 10.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 168.0, 135.7, 133.6, 118.9, 116.3, 70.5, 59.4, 53.8, 53.7, 50.3, 42.2; IR (Neat Film, NaCl) 2952, 1735, 1649, 1638, 1434, 1328, 1272, 1254, 1169, 1139, 1097, 1068, 987, 923, 859, 787, 728 cm^{-1}; HRMS (Low Voltage MM: ESI-APCI) *m/z* calc'd for $C_{13}H_{18}NO_4S$ $[M+H]^+$: 284.0951, found 284.0962.



166

(*Z*)-dimethyl 2-(cyclohexylimino)-5-phenyldihydrothiophene-3,3(2*H*)-dicarboxylate (166):

91% yield. R_f = 0.40 (3:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.42 (m, 2H), 7.36 (ddd, *J* = 8.2, 7.1, 0.9 Hz, 2H), 7.30 (m, 1H), 4.69 (dd, *J* = 11.7, 4.9 Hz, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.08 (dd, *J* = 13.0, 4.9 Hz, 1H), 2.98 (tt, *J* = 10.1, 3.6 Hz, 1H), 2.85 (dd, *J* = 13.0, 11.7 Hz, 1H), 1.85–1.72 (m, 4H), 1.65–1.57 (m, 1H), 1.57–1.44 (m, 2H), 1.37–1.20 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 168.3, 161.5, 138.6, 128.9, 128.4, 127.8, 70.8, 67.1, 53.7, 53.4, 50.6, 44.0, 32.8, 31.7, 25.8, 24.7, 24.6; IR (Neat Film, NaCl) 2930, 2854, 1738, 1651, 1435, 1168, 1067, 973, 912, 764 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{20}H_{26}NO_4S$ $[M+H]^+$: 376.1577, found 356.1589.

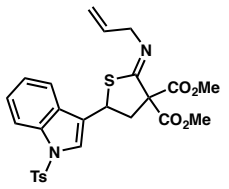


167

(*Z*)-dimethyl 2-(cyclohexylimino)-5-(*p*-tolyl)dihydrothiophene-3,3(2*H*)-dicarboxylate (167):

99% yield. R_f = 0.63 (2:1 Hexanes: EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.29 (m, 2H), 7.18–7.14 (m, 2H), 4.67 (dd, *J* = 11.8, 4.8 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.05 (dd, *J* = 13.0, 4.9 Hz, 1H), 2.98 (tt, *J* = 10.1, 3.6 Hz, 1H), 2.83 (dd, *J* = 13.0, 11.8 Hz, 1H), 2.35 (s, 3H), 1.83–1.72 (m, 4H), 1.65–1.57 (m, 1H), 1.56–1.44 (m, 2H),

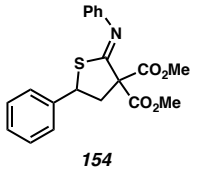
1.38–1.21 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.7, 168.3, 161.5, 138.2, 135.5, 129.6, 127.6, 70.9, 67.0, 53.6, 53.4, 50.4, 44.0, 32.8, 31.7, 25.8, 24.7, 24.5, 21.2; IR (Neat Film, NaCl) 2929, 2853, 1735, 1648, 1434, 1255, 1167, 1071, 973, 818 cm^{-1}; HRMS (APCI) *m/z* calc'd for $C_{21}H_{28}NO_4S$ $[M+H]^+$: 390.1734, found 390.1738.



168

(*Z*)-dimethyl 2-(allylimino)-5-(1-tosyl-1*H*-indol-3-yl)dihydrothiophene-3,3(2*H*)-dicarboxylate (168):

77% yield. R_f = 0.80 (1:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 168.1, 167.9, 166.2, 145.4, 135.5, 135.1, 133.6, 130.2, 128.9, 127.1, 125.5, 123.9, 123.5, 119.9, 116.3, 114.0, 77.4, 70.5, 59.7, 53.9, 53.7, 42.7, 41.7, 21.7; ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 167.9, 166.2, 145.4, 135.5, 135.1, 133.6, 130.2, 128.9, 127.1, 125.5, 123.9, 123.5, 119.9, 116.3, 114.0, 77.4, 70.5, 59.7, 53.9, 53.7, 42.7, 41.7, 21.7; IR (Neat Film, NaCl) 2953, 1738, 1639, 1447, 1372, 1275, 1175, 1126, 1095, 974, 912, 733 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{26}H_{27}N_2O_6S_2$ $[M+H]^+$: 527.1305, found 527.1298.



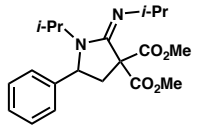
154

(*Z*)-dimethyl 5-phenyl-2-(phenylimino)dihydrothiophene-3,3(2*H*)-dicarboxylate (154):

Prepared using General Procedure D, using phenylisothiocyanate. 89% yield. R_f = 0.60 (3:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.37 (m, 2H), 7.36–7.31 (m, 4H), 7.30–7.27 (m, 1H), 7.16–7.11 (m, 1H), 7.05–7.01 (m, 2H), 4.76 (dd, *J* = 11.7, 4.9 Hz, 1H), 3.97 (s, 3H), 3.87 (s, 3H), 3.19 (dd, *J* = 13.1, 4.9 Hz, 1H), 2.99 (dd, *J* = 13.1, 11.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 167.9, 167.8, 151.0, 137.8, 129.1, 129.0, 128.5, 127.8, 125.3, 120.2, 71.4, 54.0, 53.8, 51.2, 43.9; IR (Neat Film, NaCl) 3030, 2952, 1735, 1638, 1593, 1486, 1434, 1268, 1224, 1170, 1063, 973, 763 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{20}H_{20}NO_4S$ $[M+H]^+$: 370.1108, found 370.1098.

2.8.6 AMIDINE CHARACTERIZATION DATA

All amidines were synthesized according to General Method E.

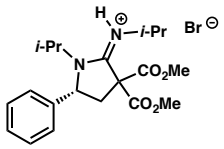


170

(*E*)-dimethyl 1-isopropyl-2-(isopropylimino)-5-phenylpyrrolidine-3,3-dicarboxylate (170):

98% yield. R_f = 0.39 (9:1 CH_2Cl_2:MeOH eluent); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.18 (m, 5H), 4.52 (t, *J* = 7.1 Hz, 1H), 3.99 (p, *J* = 6.8 Hz, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.50 (hept, *J* = 6.0 Hz, 1H), 2.95 (dd, *J* = 12.8, 7.0 Hz, 1H), 2.33 (dd, *J* = 12.8, 7.2 Hz, 1H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.11 (d, *J* = 6.0 Hz, 3H), 1.05 (d, *J* = 5.9 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 169.2, 151.3, 143.8, 128.5, 127.8, 127.0, 60.5, 59.8, 53.1, 52.9, 51.4, 47.3, 43.4, 24.7, 24.3, 19.6, 19.2; IR (Neat Film,

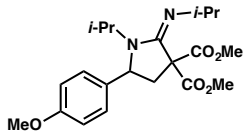
NaCl) 2963, 1731, 1659, 1436, 1261, 1212, 1063, 969 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{29}N_2O_4$ $[M+H]^+$: 361.2122, found 361.2018.



(R)-170•HBr

(*R*,*E*)-dimethyl 1-isopropyl-2-(isopropylimino)-5-phenylpyrrolidine-3,3-dicarboxylate ((*R*)-170•HBr):

Acetyl bromide (22 mL, 0.3 mmol) was dissolved in dichloromethane (3 mL) in a 10 mL round bottom flask. Methanol (41 mL, 1 mmol) was added to the solution and this mixture was transferred into a second flask containing a solution of amidine **(*R*)-170** (72 mg, 0.2 mmol). The mixture was concentrated in vacuo and crystallized by vapor diffusion of diethyl ether into dichloromethane to produce fine colorless needles suitable for X-ray crystallography. $[\alpha]_D^{25.0}$ +8.8° (*c* 0.445, $CHCl_3$, >98% *ee*).

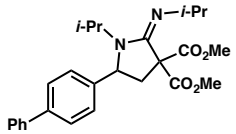


171

(*E*)-dimethyl 1-isopropyl-2-(isopropylimino)-5-(4-methoxyphenyl)pyrrolidine-3,3-dicarboxylate (171):

98% yield. R_f = 0.42 (9:1 CH_2Cl_2:MeOH eluent); ^1H NMR (400 MHz, $CDCl_3$) δ 7.25–7.16 (m, 2H), 6.89–6.79 (m, 2H), 4.50 (br t, *J* = 6.9 Hz, 1H), 4.07–3.95 (br m, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.72 (s, 3H), 3.49 (p, *J* = 6.0 Hz, 1H), 2.93 (br dd, *J* = 12.8, 6.9 Hz, 1H), 2.30 (br dd, *J* = 12.9, 7.3 Hz, 1H), 1.14 (br d, *J* = 6.9 Hz, 4H), 1.11 (d, *J* = 4.3 Hz,

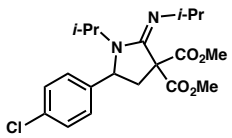
2H), 1.05 (d, *J* = 6.0 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 169.0, 159.3, 151.6, 135.2, 128.2, 113.9, 60.7, 59.6, 55.3, 53.2, 53.0, 51.4, 47.4, 43.4, 24.5, 24.1, 19.7, 19.2.; IR (Neat Film, NaCl) 2963, 2928, 1736, 1654, 1612, 1513, 1249, 1214, 1172, 1081 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{31}N_2O_5$ $[M+H]^+$: 391.2227, found 391.2208.



172

(*E*)-dimethyl 5-([1,1'-biphenyl]-4-yl)-1-isopropyl-2-(isopropylimino)pyrrolidine-3,3-dicarboxylate (172):

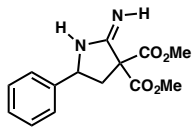
92% yield. R_f = 0.42 (9:1 CH_2Cl_2:MeOH eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63–7.53 (m, 4H), 7.47–7.38 (m, 4H), 7.37–7.32 (m, 1H), 4.59 (t, *J* = 7.1 Hz, 1H), 4.04 (hept, *J* = 6.9 Hz, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 3.53 (hept, *J* = 5.9 Hz, 1H), 3.00 (dd, *J* = 12.8, 7.0 Hz, 1H), 2.37 (dd, *J* = 12.8, 7.3 Hz, 1H), 1.20 (d, *J* = 6.8 Hz, 3H), 1.15 (d, *J* = 6.0 Hz, 3H), 1.08 (d, *J* = 5.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.7, 169.2, 151.4, 142.9, 140.8, 140.7, 128.9, 127.5, 127.4, 127.2, 127.1, 60.6, 59.6, 53.2, 53.0, 51.5, 47.4, 43.4, 24.7, 24.4, 19.8, 19.2; IR (Neat Film, NaCl) 2964, 1733, 1658, 1486, 1435, 1375, 1358, 1264, 1216, 1165, 1126, 1076, 1008, 973, 841, 767, 733 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{26}H_{33}N_2O_4$ $[M+H]^+$: 437.2435, found 437.2411.



173

(*E*)-dimethyl 5-(4-chlorophenyl)-1-isopropyl-2-(isopropylimino)pyrrolidine-3,3-dicarboxylate (173):

78% yield. R_f = 0.40 (9:1 CH_2Cl_2:MeOH eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.23 (m, 4H), 4.50 (t, *J* = 7.1 Hz, 1H), 4.00 (hept, *J* = 6.9 Hz, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.48 (hept, *J* = 5.9 Hz, 1H), 2.95 (dd, *J* = 12.8, 7.1 Hz, 1H), 2.27 (dd, *J* = 12.9, 7.1 Hz, 1H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.09 (d, *J* = 6.0 Hz, 3H), 1.04 (d, *J* = 5.9 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 169.1, 151.2, 142.6, 133.4, 128.7, 128.3, 60.4, 59.1, 53.2, 53.0, 51.5, 47.3, 43.3, 24.7, 24.3, 19.9, 19.1; IR (Neat Film, NaCl) 2965, 1733, 1658, 1489, 1435, 1376, 1359, 1269, 1214, 1165, 1126, 1088, 1014, 974, 831 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{28}{}^{35}ClN_2O_4$ $[M+H]^+$: 395.1732, found 395.1755.

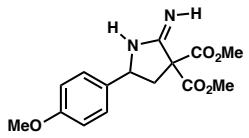


174

dimethyl 2-imino-5-phenylpyrrolidine-3,3-dicarboxylate (174):

78% yield. R_f = 0.45 (9:1 CH_2Cl_2:MeOH eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ7.34–7.27 (m, 3H), 7.25–7.21 (m, 2H), 4.99 (dd, *J* = 8.2, 6.9 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.10 (dd, *J* = 13.6, 7.0 Hz, 1H), 2.37 (dd, *J* = 13.6, 8.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 168.3, 160.2, 144.2, 128.6, 127.1, 126.4, 68.4, 67.4, 53.6, 53.4, 42.8; IR (Neat Film, NaCl) 3449, 3028, 1729, 1665, 1600, 1435, 1386, 1354, 1279, 1243,

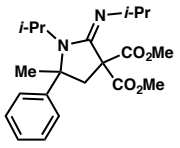
1201, 1154, 1114, 1075, 765 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{14}H_{17}N_2O_4$ $[M+H]^+$: 277.1188, found 277.1176.



175

dimethyl 2-imino-5-(4-methoxyphenyl)pyrrolidine-3,3-dicarboxylate (175):

68% yield. R_f = 0.47 (9:1 CH_2Cl_2:MeOH eluent); ^1H NMR (500 MHz, $CDCl_3$) δ 7.23–7.16 (m, 2H), 6.84 (dd, *J* = 6.8, 1.9 Hz, 2H), 4.97–4.88 (m, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.06 (dd, *J* = 13.6, 6.9 Hz, 1H) 2.34 (dd, *J* = 13.6, 8.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 168.3, 160.1, 158.7, 136.3, 127.5, 113.9, 113.9, 67.8, 67.4, 55.4, 53.6, 53.4, 42.9; IR (Neat Film, NaCl) 3464, 3374, 3102, 2955, 2838, 1738, 1662, 1612, 1514, 1439, 1351, 1247, 1213, 1175, 1105, 1077, 1034, 831, 733 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{19}N_2O_5$ $[M+H]^+$: 307.1294, found 307.1287.

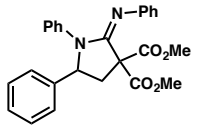


176

(*E*)-dimethyl 1-isopropyl-2-(isopropylimino)-5-methyl-5-phenylpyrrolidine-3,3-dicarboxylate (176):

58% yield. R_f =0.35 (10:1 $CHCl_3$:MeOH eluent); ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.44 (m, 2H), 7.38–7.33 (m, 2H), 7.29–7.24 (m, 1H), 3.85 (s, 3H), 3.71 (s, 3H), 3.44 (dt, *J* = 11.8, 5.9 Hz, 1H), 3.09–2.99 (hept, *J* = 6.7 Hz, 1H), 2.83–2.72 (m, 2H), 1.61 (s, 3H), 1.35 (dd, *J* = 17.2, 6.7 Hz, 6H), 1.10 (dd, *J* = 18.8, 5.9 Hz, 6H); ^{13}C NMR (126 MHz,

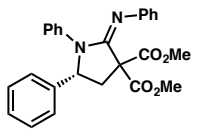
$CDCl_3$) δ 170.5, 170.2, 148.5, 146.8, 128.3, 127.2, 126.7, 64.8, 60.3, 53.2, 53.1, 51.4, 50.5, 47.1, 24.9, 24.8, 24.5, 19.9, 19.1; IR (Neat Film, NaCl) 2963, 1731, 1654, 1375, 1251, 1217, 1090 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{31}N_2O_4$ $[M+H]^+$: 375.2278, found 375.2297.



177

(*E*)-dimethyl 1,5-diphenyl-2-(phenylimino)pyrrolidine-3,3-dicarboxylate (177):

79% yield. R_f =0.32 (10:1 CH_2Cl_2:MeOH eluent); ^1H NMR (400 MHz, DMSO-d_6, 80 °C) δ 7.34–7.16 (m, 8H), 7.10 (dt, *J* = 15.2, 7.6 Hz, 5H), 6.95 (t, *J* = 7.4 Hz, 1H), 6.80 (t, *J* = 7.3 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 2H), 5.28 (t, *J* = 7.0 Hz, 1H), 3.66 (s, 3H) 3.45 (s, 3H), 3.17 (dd, *J* = 13.0, 7.2 Hz, 1H), 3.05 (s, 1H), 2.71 (dd, *J* = 13.0, 6.9 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, 100 °C) δ 168.5, 168.2, 152.0, 148.4, 148.3, 140.9, 129.6, 129.5, 129.4, 129.3, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.2, 128.2, 128.1, 128.0, 127.7, 127.5, 127.4, 127.3, 127.2, 126.6, 125.9, 124.6, 122.0, 121.9, 120.9, 64.1, 63.1, 62.7, 55.3, 54.5, 54.3, 53.4, 52.6, 52.4, 51.9, 43.0; IR (Neat Film, NaCl) 3062, 3027, 2948, 1730, 1661, 1592, 1493, 1372, 1263, 1051 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{26}H_{25}N_2O_4$ $[M+H]^+$: 429.1809, found 429.1825.



(R)-177

(*R*,*E*)-dimethyl 1,5-diphenyl-2-(phenylimino)pyrrolidine-3,3-dicarboxylate ((*R*)-177):

Characterization data same as above; $[\alpha]_D^{25.0}$ +36.7° (*c* 0.805, $CHCl_3$, 88% *ee*).

2.9 NOTES AND REFERENCES

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(7) See Chapter 1 of this thesis.

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(15) Methyl hydrogen atoms have been omitted from the crystal structure for clarity.

(16) Treatment of cyclopropane **(*S*)-152** with stoichiometric iron(III) chloride in the absence of a dipolarophile results in complete racemization within one hour.

(17) Treatment of cyclopropane **(*S*)-152** with catalytic tin(II) triflate in the absence of a diplarophile results in slow racemization over 16 hours. See ref 5c.

(18) Methyl and phenyl hydrogen atoms and the bromide counterion are omitted for clarity.

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APPENDIX 1[†]

Supplementary Synthetic Information for Chapter 2

A1.1 INTRODUCTION

This appendix discusses cyclopropanes and heterocumulenes that did not successfully react to form the desired heterocycles. Efforts to use a tin-phenanthroline complex as the catalyst are also presented. Finally, two attempts at product derivitization are included.

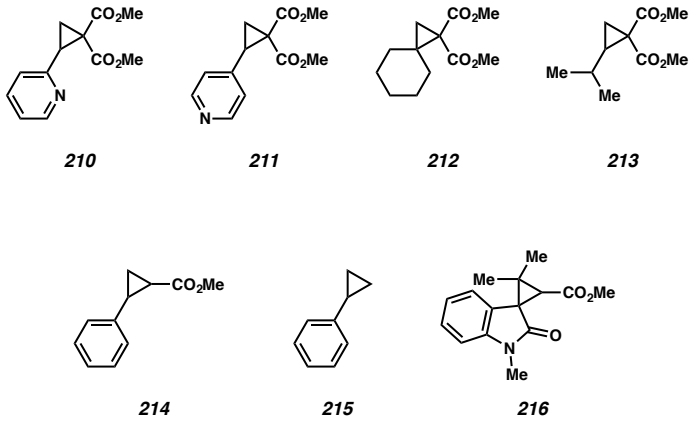
A1.2 UNREACTIVE CYCLOPROPANES

During our investigations of the substrate scope of these reactions, we encountered a number of cyclopropanes that did not undergo the desired reactivity (Figure A1.1). Cyclopropanes with aryl substitutents incorporating coordinating groups such as pyridine rings (**210** and **211**) failed to produce the desired heterocycles even in the presence of additional sacrificial Lewis acid to coordinate to the pyridine nitrogen atom. Attempts to replace the aryl or vinyl donor groups of successful substrates with alkyl groups (**212** and **213**) were also unsuccessful. An

[†] This work was performed in collaboration with Dr. Alexander F. G. Goldberg and Dr. Robert A. Craig, II, alumni of the Stoltz group.

examination of the acceptor groups revealed both ester functionalities to be critical, as cyclopropanes with one (**214**) or zero (**215**) carboxylate groups were completely unreactive under our conditions. Finally, highly functionalized cyclopropane **216** did not react under our carbodiimide conditions, likely due to its lack of a clearly polarized C–C bond.

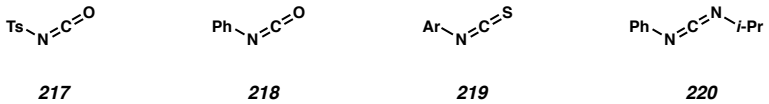
Figure A1.1 Unreactive cyclopropanes



A1.3 PROBLEMATIC HETEROCUMULENES

A variety of heterocumulenes were also found to lack the desired reactivity. Treatment of cyclopropanes with tosylisocyanate (**217**) or phenylisocyanate (**218**) resulted in no formation of the desired lactams (Figure A1.2). Aryl isothiocyanates (**219**) were also unreactive under our tin-mediated conditions, although we were able to obtain reactivity using conditions similar to those reported by Li (see Scheme 2.8).[1] Finally, the use of a mixed carbodiimide (**220**) afforded an inseparable mixture of isomeric products.

Figure A1.2 Problematic heterocumulenes

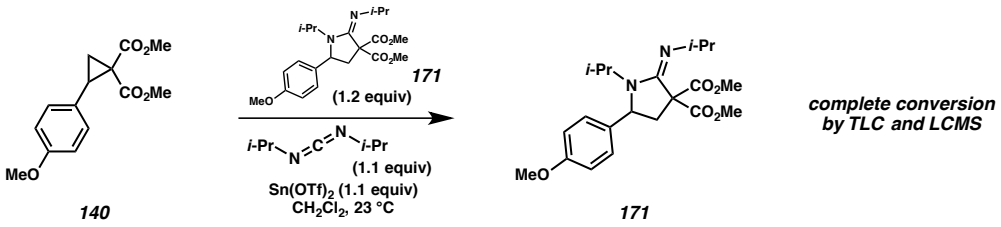


217 ***218*** ***219*** ***220***

A1.4 TESTING FOR PRODUCT INHIBITION

The requirement for stoichiometric Lewis acid in all reactions, regardless of dipolarophile identity is a practical drawback for which a solution has not yet been discovered. Product inhibition of the catalyst does not appear to play a role, as experiments showed the reaction to proceed smoothly in the presence of a slight excess of an amidine product (Scheme A1.1). Attempts to catalyze the reaction with phenanthroline-ligated tin complexes were also unsuccessful.

Scheme A1.1 Testing for product inhibition

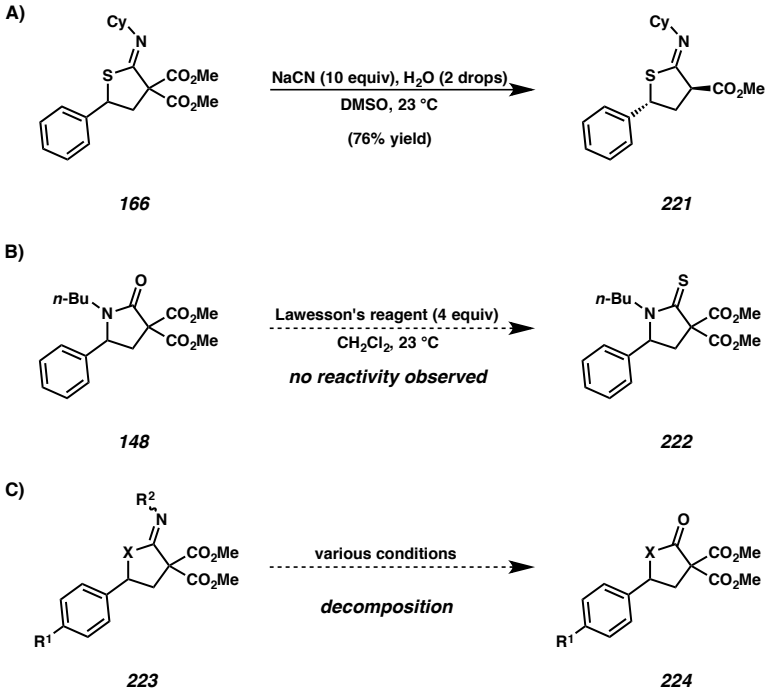


A1.5 PRODUCT DERIVATIZATIONS

To demonstrate the utility of the thioimidate products produced by our method, we attempted several derivatizations. Decarboxylation using Krapcho's protocol[2] was successful, delivering monocarboxylate **221** in good yield as a single diastereomer (Scheme A1.2A). Interestingly, while a single decarboxylation could be carried out

easily at room temperature, heating to achieve a double decarboxylation gave a complex mixture. Unfortunately, an attempt to form a thiolactam from lactam **148** using Lawesson's reagent was unsuccessful (Scheme A1.2B), as were several attempts to hydrolyze thioimidates or amidines to thioester or lactam products (Scheme A1.2C).

Scheme A1.2 Derivatization of the cycloadducts



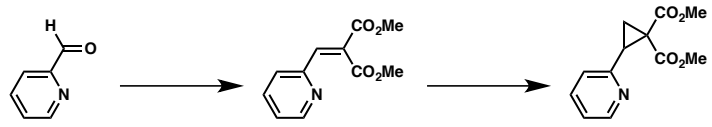
A1.6 EXPERIMENTAL SECTION

A1.6.1 MATERIALS AND METHODS

Unless stated otherwise, reactions were performed in flame-dried or oven-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina).[3] Diazodimethylmalonate was prepared according to the method of Davies and coworkers.[4] Cyclopropylbenzene,

potassium cyanate, and all organic heterocumulenes except phenylisopropylcarbodiimide were obtained from commercial suppliers. Cyclopropane **233** was obtained upon request from the research laboratories of Professor John L. Wood at Colorado State University (currently at Baylor University). Commercially obtained reagents were used as received with the exception of tin(II) triflate and iron(III) chloride, which were stored in a nitrogen-filled glovebox. A separate bottle of iron(III) chloride was stored in a calcium sulfate desiccator on the benchtop. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040-–0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 (at 400 MHz and 100 MHz, respectively) or on a Varian Mercury 500 (at 500 MHz and 126 MHz, respectively) and are reported relative to $CHCl_3$ (δ 7.26 & 77.16 ppm, respectively) or tetramethylsilane (0.00 ppm). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Abbreviations are used as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, hept = heptet, m = complex multiplet, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode.

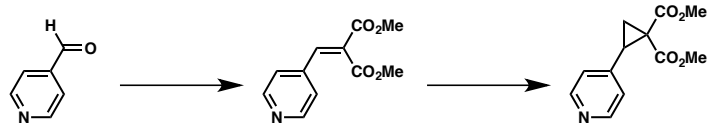
A1.6.2 SYNTHESIS OF UNREACTIVE CYCLOPROPANES



225 ***226*** ***210***

dimethyl 2-(pyridin-2-yl)cyclopropane-1,1-dicarboxylate (210):

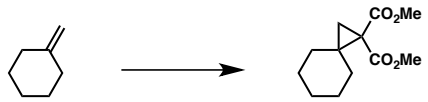
Benzylidene dimethylmalonate **226** was prepared according to the method described in General Procedure A, Experimental Section, Chapter 2: 97% yield. R_f = 0.81 (3:1 Hexanes:EtOAc eluent). Characterization data match those reported in the literature.[5] Cyclopropane **210** was prepared according to the method described in General Procedure B, Experimental Section, Chapter 2 using saturated aqueous ammonium chloride in the workup instead of 2 M HCl: 95% yield. R_f = 0.30 (3:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45–8.34 (ddd, *J* = 4.8, 1.9, 1.0 Hz, 1H), 7.62–7.53 (tdd, *J* = 7.3, 4.9, 1.1 Hz, 1H), 7.29–7.26 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.12–7.05 (ddt, *J* = 7.3, 4.9, 1.1 Hz, 1H), 3.82–3.68 (m, 3H), 3.53–3.43 (m, 3H), 3.12–3.06 (ddd, *J* = 8.8, 7.4, 1.1 Hz, 1H), 2.36–2.31 (ddd, *J* = 7.4, 4.5, 1.1 Hz, 1H), 1.84–1.78 (ddd, *J* = 9.0, 4.5, 1.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 167.3, 155.4, 149.0, 136.3, 124.0, 122.0, 53.0, 52.4, 38.0, 33.0, 20.5; IR (Neat Film, NaCl) 3011, 2952, 1734, 1593, 1570, 1477, 1437, 1379, 1334, 1301, 1275, 1210, 1132, 1085, 998, 970, 924, 878, 807, 759, 749 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{14}NO_4$ $[M+H]^+$: 236.0917, found 236.0911.



227 ***228*** ***211***

dimethyl 2-(pyridin-2-yl)cyclopropane-1,1-dicarboxylate (211):

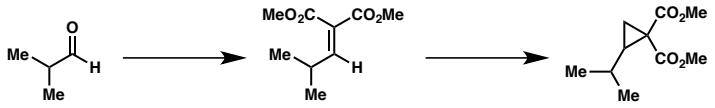
Benzylidene dimethylmalonate **228** was prepared according to the method described in General Procedure A, Experimental Section, Chapter 2: 76% yield. R_f = 0.58 (1:1 Hexanes:EtOAc eluent); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72–8.60 (m, 2H), 7.68 (s, 1H), 7.29–7.21 (m, 2H), 3.87 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 163.8, 150.7, 140.4, 140.0, 129.9, 122.8, 53.2, 53.1; IR (Neat Film, NaCl) 2954, 1732, 1638, 1596, 1437, 1374, 1269, 1225, 1067, 813 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{12}NO_4$ $[M+H]^+$: 222.0761, found 222.0750. Cyclopropane **211** was prepared according to the method described in General Procedure B, Experimental Section, Chapter 2: 81% yield. R_f = 0.13 (3:1 Hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 5.6 Hz, 2H), 7.02 (dd, *J* = 4.4, 1.7 Hz, 2H), 3.73 (s, 3H), 3.35 (s, 3H), 3.07 (dd, *J* = 9.1, 7.9, 1H), 2.11 (dd, *J* = 8.0, 5.4 Hz, 1H), 1.71 (dd, *J* = 9.1, 5.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 166.4, 149.6, 144.1, 123.3, 53.0, 52.5, 37.7, 30.9, 18.7; IR (Neat Film, NaCl) 3029, 2954, 1732, 1601, 1437, 1335, 1282, 1212, 1133, 991, 836 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{14}NO_4$ $[M+H]^+$: 236.0917, found 236.0908.



229 ***212***

dimethyl spiro[2.5]octane-1,1-dicarboxylate (212):

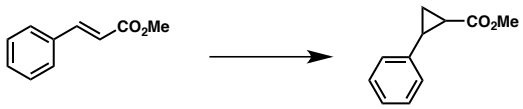
Cyclopropane **212** was prepared according to the method described in General Procedure C, Experimental Section, Chapter 2: 40% yield. R_f = 0.20 (9:1 Hexanes:EtOAc eluent). Characterization data match those reported in the literature.[6]



230 ***231*** ***213***

dimethyl 2-isopropylcyclopropane-1,1-dicarboxylate (213):

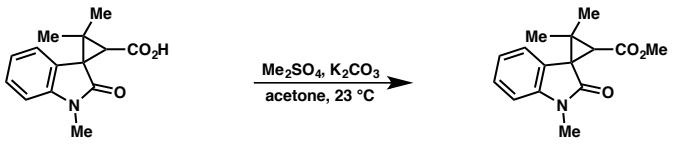
Isopropylidene dimethylmalonate **231** was prepared according to the method described in General Procedure A, Experimental Section, Chapter 2: 94% yield. R_f = 0.30 (9:1 Hexanes:EtOAc eluent). Characterization data match those reported in the literature.[7] Cyclopropane **213** was prepared according to the method described in General Procedure B, Experimental Section, Chapter 2: R_f = 0.40 (9:1 Hexanes:EtOAc eluent). Characterization data match those reported in the literature.[8]



232 ***214***

methyl 2-phenylcyclopropanecarboxylate (214):

Cyclopropane **214** was prepared according to the method described in General Procedure B, Experimental Section, Chapter 2: 24% yield. R_f = 0.60 (3:1 Hexanes:EtOAc eluent). Characterization data match those reported in the literature.[9]

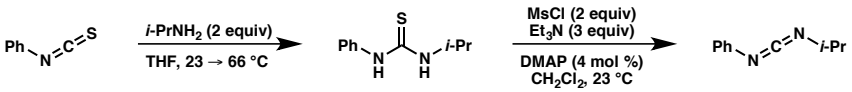


233 ***216***

methyl 1',2,2-trimethyl-2'-oxospiro[cyclopropane-1,3'-indoline]-3-carboxylate (216):

To a flame-dried round-bottomed flask equipped with a magnetic stir bar were added carboxylic acid **233** (200 mg, 0.77 mmol) and potassium carbonate (131 mg, 0.95 mmol). Acetone (8.75 mL) and dimethylsulfate (90 μL) were added and the heterogeneous mixture was stirred at ambient temperature for 1 hour. The mixture was poured into water (20 mL) and ether (20 mL). The ether layer was separated, dried over magnesium sulfate, and filtered and concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography (3:1 hexanes:EtOAc) to afford cyclopropane **216** as a colorless oil (179 mg, 84% yield). R_f = 0.60 (3:1 Hexanes:EtOAc eluent). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (ddd, *J* = 7.7, 1.2, 0.6 Hz, 1H), 7.30 (td, *J* = 7.7, 1.2 Hz, 1H), 7.06 (td, *J* = 7.7, 1.1 Hz, 1H), 6.90 (ddd, *J* = 7.8, 1.2, 0.5 Hz, 1H), 3.67 (s, 3H), 3.27 (s, 3H), 2.79 (s, 1H), 1.61 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 169.3, 144.3, 127.1, 125.6, 125.0, 121.6, 107.9, 51.7, 41.9, 40.8, 35.0, 26.6, 20.6, 17.0.

A1.6.3 SYNTHESIS OF MIXED CARBODIIMIDE 220



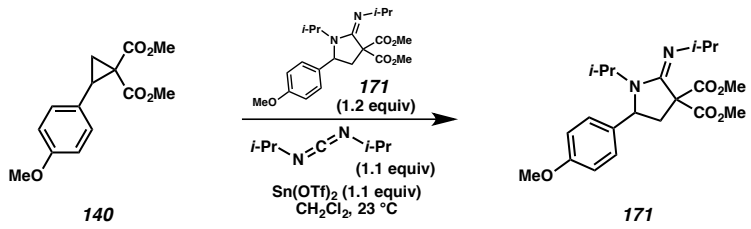
234 ***235*** ***220***

Thiourea 235. Prepared according to the method of Zhou and coworkers.[10] To a flame-dried round-bottom flask, equipped with a magnetic stir bar and fitted with a rubber septum was added phenyl isothiocyanate (1.2 mL, 10 mmol, 1 equiv) and anhydrous THF (32 mL) under an inert atmosphere. To the stirring solution was added isopropylamine (1.64 mL, 20 mmol, 2 equiv) dropwise. The rubber septum was quickly

replaced with a reflux condenser fitted with a hose adapter, connected to an inert atmosphere manifold. The resulting solution was heated to reflux with stirring for 40 minutes. The reaction mixture was then cooled to ambient temperature and the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (60 mL) and washed with aqueous hydrochloric acid (10 mL, 1 N) and brine (10 mL), and the organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford crude thiourea **235** (1.89 g, 97%) as a white solid which was carried forward directly to the next step in the synthesis.

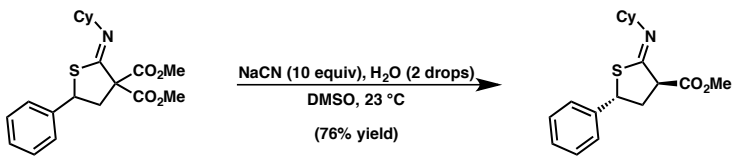
Carbodiimide 220. Prepared according to the method of Fell and Coppola.[11] To a flame-dried, round-bottom flask, equipped with a magnetic stir bar was added crude thiourea **235** (971 mg, 5 mmol, 1 equiv). The flask was sealed with a rubber septum and placed under an inert atmosphere. To the flask was added dry dichloromethane (50 mL, 0.1 M) and freshly distilled triethylamine (2.1 mL, 15 mmol, 3 equiv), followed by a dropwise addition of mesyl chloride (0.78 mL, 10 mmol, 2 equiv). Complete consumption of starting material was observed within 5 minutes, as determined by TLC. The volatiles were removed *in vacuo*, and a precipitate was observed. The mixture was filtered twice through silica gel (100 mL), eluting with dichloromethane, then purified by silica gel column chromatography (10:1 hexanes:EtOAc) to afford carbodiimide **220** (332.2 mg, 41% yield) as a yellow oil: R_f = 0.81 (3:1 Hexanes:EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.20 (m, 2H), 7.21–7.02 (m, 3H), 3.80 (hept, J = 6.4 Hz, 1H), 1.35 (d, J = 6.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.9, 136.6, 129.4, 124.7, 123.4, 50.3, 24.9; IR (Neat Film, NaCl) 3419, 3067, 2973, 2129, 1637, 1592, 1501, 1454, 1367, 1320 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{10}H_{13}N_2$ $[M+H]^+$: 161.1073, found 161.1077.

A1.6.4 INVESTIGATION OF PRODUCT INHIBITION

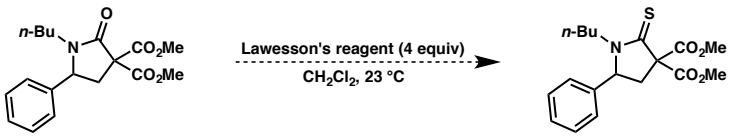


To an oven-dried 1 dram vial equipped with a magnetic stir bar was added tin(II) trifluoromethanesulfonate (0.44 mmol) in an inert atmosphere glovebox. The vial was sealed with a screw cap fitted with a Teflon® septum, removed from the glovebox, and placed under a nitrogen atmosphere. To a separate, oven-dried 1 dram vial were added cyclopropane **140** (106 mg, 0.4 mmol), carbodiimide (68 μL, 0.44 mmol), and amidine **171** (195 mg, 0.5 mmol). The vial was sealed with a screw cap fitted with a Teflon® septum, and the mixture was transferred to the first vial as a solution in anhydrous dichloromethane (1 mL + 0.33 mL rinse). The heterogeneous reaction mixture was then allowed to stir at ambient temperature under nitrogen for 10 minutes. TLC and LCMS analysis showed complete conversion of the starting material and an increase in concentration of product amidine **171**.

A1.6.5 PRODUCT DERIVATIZATIONS



Krapcho decarboxylation. To a 1 dram vial equipped with a magnetic stir bar were added thioimidate **166** (100 mg, 0.27 mmol) and sodium cyanide (132 mg, 2.7 mmol). DMSO (2.3 mL) and water (2 drops) were added, the vial was capped, and the mixture was stirred vigorously at ambient temperature for 48 hours. The reaction mixture was partitioned between ether (5 mL) and water (5 mL), and the aqueous layer was extracted with ether (3 x 10 mL). The organic layers were combined and washed with water (3 x 10 mL), brine (1 x 10 mL), dried over magnesium sulfate, and filtered and concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography (95:5 hexanes:EtOAc) to afford thioimidate **221** as a colorless oil (65 mg, 95% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.48–7.40 (m, 2H), 7.37–7.31 (m, 2H), 7.31 (m, 1H), 4.84 (t, *J* = 8.1 Hz, 1H), 3.69 (s, 3H), 3.39 (dd, *J* = 13.9, 8.5 Hz, 1H), 3.20 (dp, *J* = 9.3, 5.1 Hz, 1H), 3.14 (dd, *J* = 14.0, 7.7 Hz, 1H), 2.01 (m, 2H), 1.83–1.70 (m, 2H), 1.69–1.54 (m, 2H), 1.41–1.28 (m, 3H), 1.28–1.17 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 165.2, 141.7, 128.7, 127.7, 127.2, 86.5, 56.6, 51.6, 50.2, 40.8, 34.1, 33.9, 25.3, 24.6, 24.6.



140 ***222***

Attempted synthesis of a thiolactam. To an oven-dried 1 dram vial equipped with a magnetic stir bar were added lactam **140** (12 mg, 0.035 mmol), Lawesson's reagent (56 mg, 0.140 mmol), and dichloromethane (70 μL). The mixture was stirred at room temperature for 15 hours, but TLC, LCMS, and ^{1}H NMR analysis showed no conversion.

A1.7 NOTES AND REFERENCES

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APPENDIX 2[†]

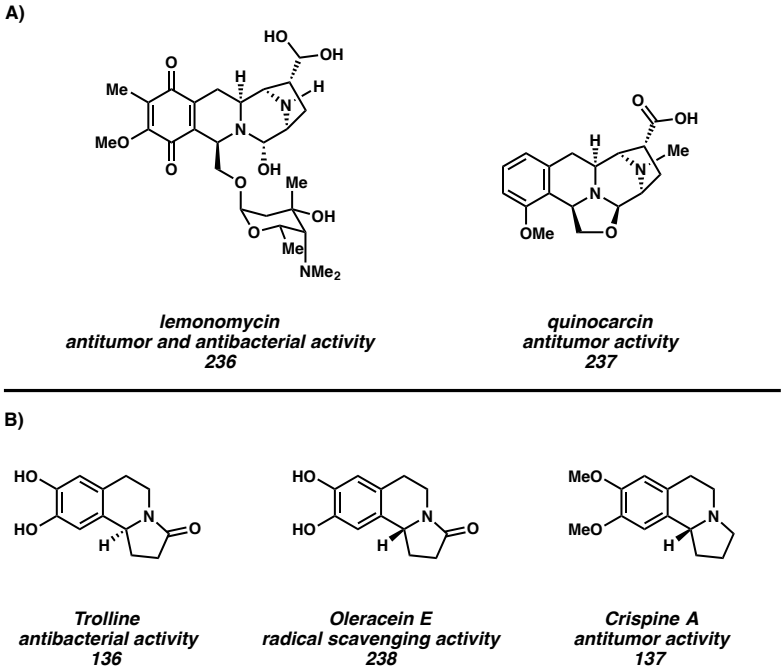
Application of Cyclopropane Cycloadditions toward the Synthesis of Tetrahydroisoquinoline Alkaloids and Discovery of a Novel Route to Isoindolones

A2.1 INTRODUCTION AND INITIAL RETROSYNTHETIC ANALYSIS

The tetrahydroisoquinoline (THIQ) alkaloids are a large class of natural products which have attracted attention from the synthetic community due to their potentially useful biological activities and structural diversity.[1] Our research laboratory has completed total syntheses of the antitumor bis-THIQ alkaloids lemonomycin (**236**)[2] and quinocarcin (**237**)[3] using Pictet–Spengler and aryne annulation strategies, respectively (Figure A2.1A). Simpler THIQ alkaloids, such as those shown in Figure A2.1B,[4] also possess notable bioactivities, and our ability to rapidly access 5-aryl γ-lactams by cycloadditions of donor–acceptor cyclopropanes and isocyanates inspired us to work toward a concise route to these targets.

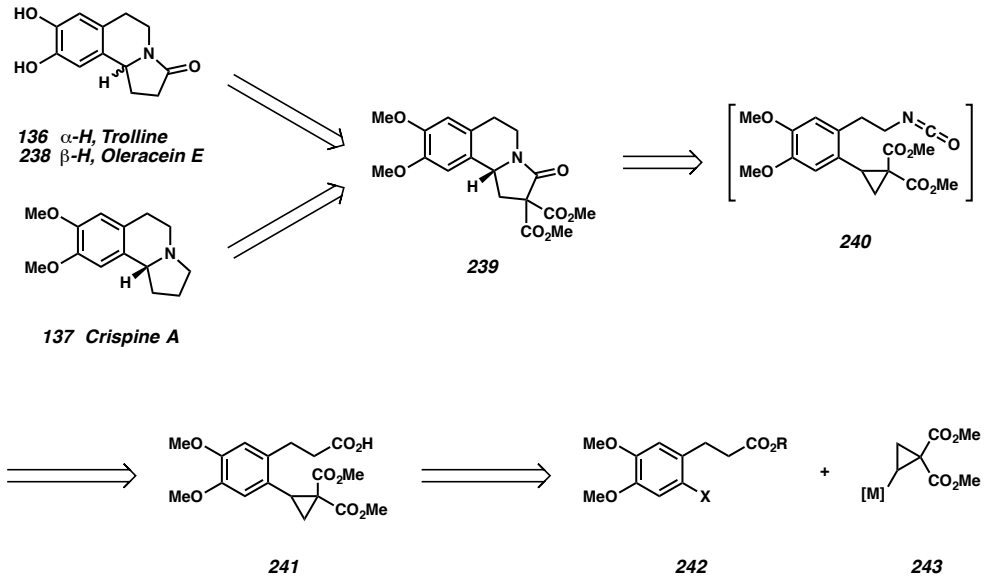
[†] This work was performed in collaboration with Dr. Alexander F. G. Goldberg and Moriam Masha, alumni of the Stoltz group.

Figure A2.1 A) Tetrahydroisoquioline alkaloids previously synthesized in our laboratory. B) Tetrahydroisoquinoline alkaloids targeted for application of a cyclopropane-isocyanate cycloaddition.



We envisioned these alkaloids could be accessed from common intermediate **239** by double Krapcho decarboxylation and either demethylation (to afford trolline and oleracein E) or lactam reduction (to afford crispine A). Lactam **239** was to be constructed using an intramolecular cycloaddition of isocyanate **240**, which in turn would be accessed from acid **241**. This carboxylic acid would be assembled by a cross coupling between aryl halide (**242**) and cyclopropylmetal (**243**) components (Scheme A2.1).

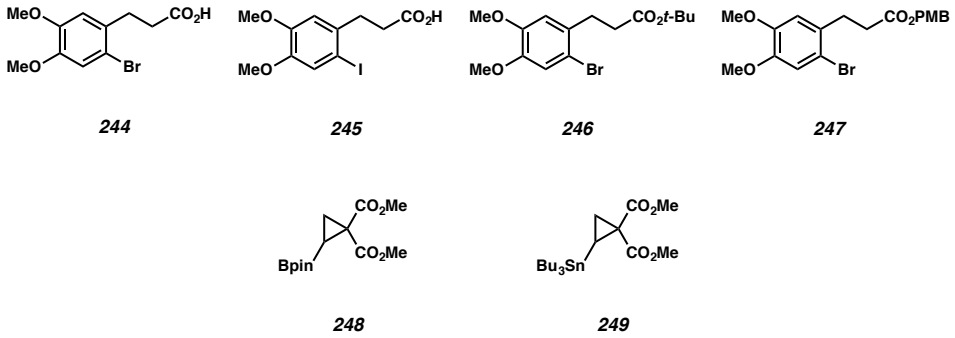
*Scheme A2.1 Retrosynthetic analysis of **136**, **238**, and **137***



A2.2 TOWARD THE SYNTHESIS OF AN INTRAMOLECULAR CYCLOADDITION SUBSTRATE

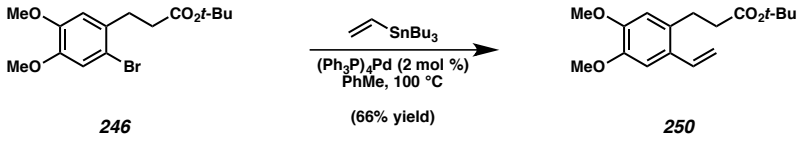
In the forward direction, aryl halides **244**–**247** were synthesized according to reported methods or standard procedures. Cyclopropylboronate ester **248** was synthesized using the method developed by Gevorgyan.[5] Although the enantioenriched product is known, we chose to probe initial reactivity using the racemic compound, which would also allow access to both trolline and oleracein E through a divergent synthesis. Unfortunately, various attempts to hydrolyze the boronate ester of **248** were unsuccessful, leaving us unable to evaluate the presumably more reactive boronic acid in the coupling reaction. However, we were able to synthesize cyclopropylstannane **249** using conditions reported by Gevorgyan,[6] which allowed for an alternative organometallic coupling partner to be studied.

Figure A2.2 Cross-coupling partners prepared



Unfortunately, despite extensive screening of conditions using the coupling partners shown above, we were unable to achieve the desired transformation, with all attempts displaying either significant protodehalogenation or a total lack of reactivity. However, we were able to couple bromide **246** with vinyltributylstannane to afford styrene **250** in moderate yield. Although not pursued due to concerns about step count, a conceivable route forward would involve styrene cyclopropanation, cleavage of the *tert*-butyl ester group, formation of the isocyanate by Curtius rearrangement, and subsequent cycloaddition to afford the desired lactam **239**.

*Scheme A2.2 Successful cross-coupling of aryl bromide **246** with vinyltributylstannane*

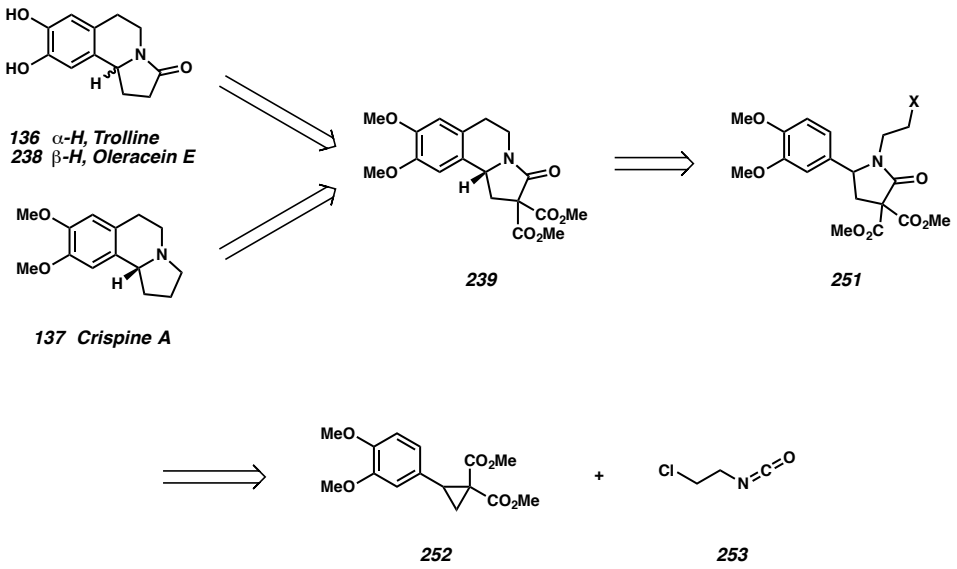


A2.3 REVISED RETROSYNTHETIC ANALYSIS

Given our inability to construct cyclopropane **241** in a concise fashion, we turned our attention to the use of an intermolecular cycloaddition, which would allow for the joining of simpler fragments. Specifically, the targeted alkaloids would still be accessed from

common intermediate **239**, but this tricycle would be formed by an intramolecular Friedel–Crafts alkylation of lactam **251**. The Friedel–Crafts substrate would be constructed by an intermolecular cycloaddition between known cyclopropane **252**[7] and commercially available isocyanate **253**.

Scheme A2.3 Revised retrosynthetic analysis

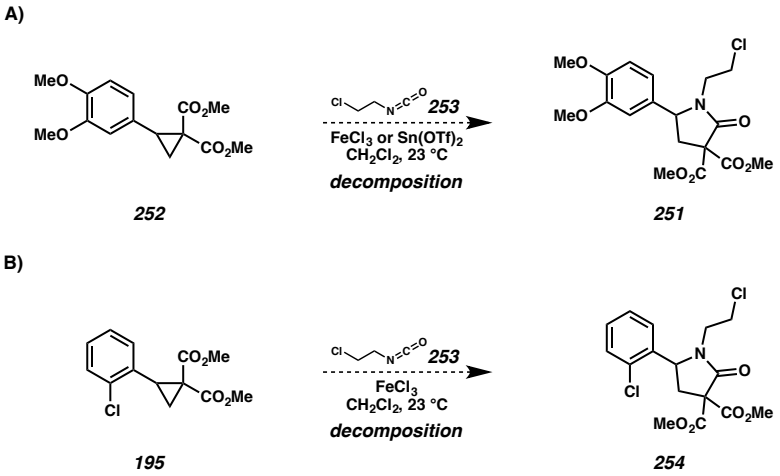


A2.4 ATTEMPTED INTERMOLECULAR CYCLOADDITION

Cyclopropane **252** was prepared using known methods and exposed to isocyanate **253** in the presence of either iron(III) chloride or tin(II) triflate. Unfortunately both cases resulted in decoposition (Scheme A2.4A). In order to determine the problematic component, we conducted control reactions between isocyanate **253** and a cyclopropane known to be competent in cycloadditions with isocyanates (**195**). These experiments resulted in decomposition, suggesting **253** is not compatible with the reaction conditions (Scheme A2.4B). However, given that reactions with 2-(benzyloxy)ethylisocyanate, 2-

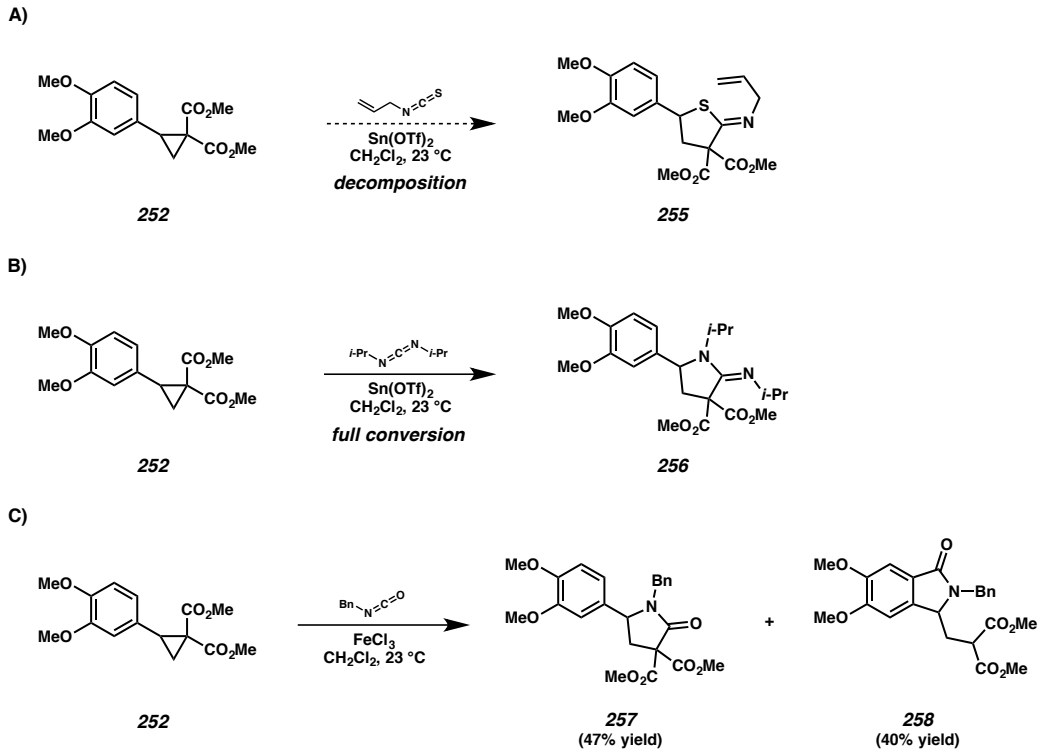
(*tert*-butyldimethysiloxy)ethylisocyanate, and trimethylsilylisocyanate (planning future lactam *N*-alkylation) were also unsuccessful, we suspected the cyclopropane partner (**252**) may also be problematic.

Scheme A2.4 A) Unsuccessful intramolecular cycloadditions. B) A control experiment with a competent cyclopropane.



To investigate the viability of cyclopropane **252** in cycloadditions with dipolarophiles known to be competent (Scheme A2.5). Reaction of **252** with allyl isothiocyanate afforded only decomposition products, but cycloaddition with diisopropylcarbodiimide smoothly provided amidine **256**. The use of benzyl isocyanate gave rise to a mixture of expected lactam **257** in 47% yield as well as isoindolone **258** in 40% yield. These results suggested cyclopropane **252** is a problematic substrate in the desired cycloaddition reaction, which combined with the uncooperative reactivity of isocyanate **253** significantly limits the feasibility of our revised synthetic plan.

Scheme A2.5 Control experiments with competent dipolarophiles

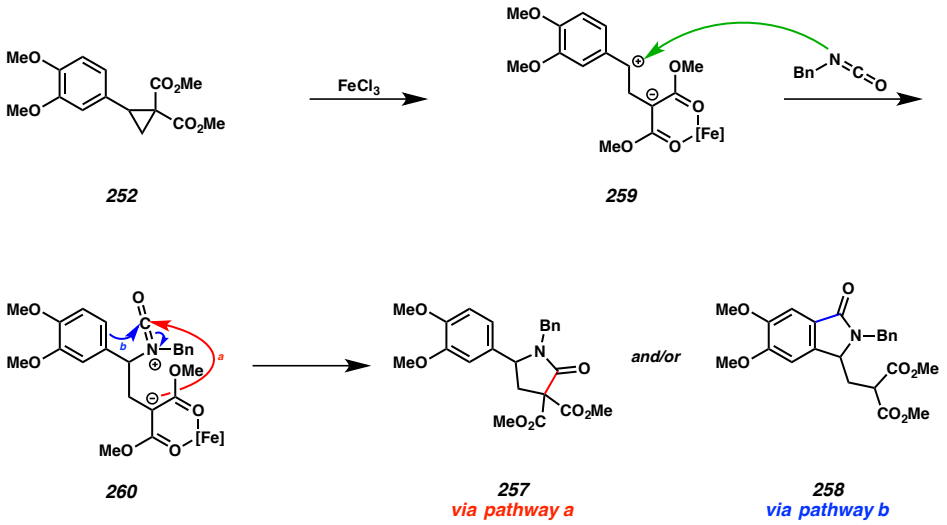


A2.5 INVESTIGATION OF THE ISOINDOLONE FORMATION

We did not observe the formation of isoindolone products or byproducts during our previous studies of cyclopropane cycloadditions with isocyanates (see Chapter 2). However, we believe this can be accounted for by considering the mechanisms by which the 5-aryl lactam and isoindolone products are formed, which are shown in Scheme A2.6. In both cases, coordination of the Lewis acid to the ester functional groups is thought to fully cleave the polarized C–C bond in the cyclopropane, giving rise to zwitterionic intermediate **259**.[8] Subsequent attack of the isocyanate at the benzylic carbocation produces **260**. At this stage, the highly electrophilic carbon atom is typically attacked by the malonate group to deliver 5-aryl lactam product **257** (pathway a, red). In substrates with very electron-rich aryl rings, however, a Pictet-Spengler-like attack of the arene on

the electrophilic carbon (and subsequent rearomatization) furnishes isoindolone **258** (pathway b, blue). The requirement for a highly electron-rich aryl ring accounts for the lack of isoindolone formation in our earlier studies, as only less electron-rich substrates were used. Indeed, similar reactivity between cyclopropanes and olefins[9] and alkynes,[10] as well as dimerization[7,11] and intramolecular rearrangement[12] reactions all require very electron-rich aryl groups.

*Scheme A2.6 Proposed mechanism for the formation of 5-aryl γ-lactam **257** and isoindolone **258***

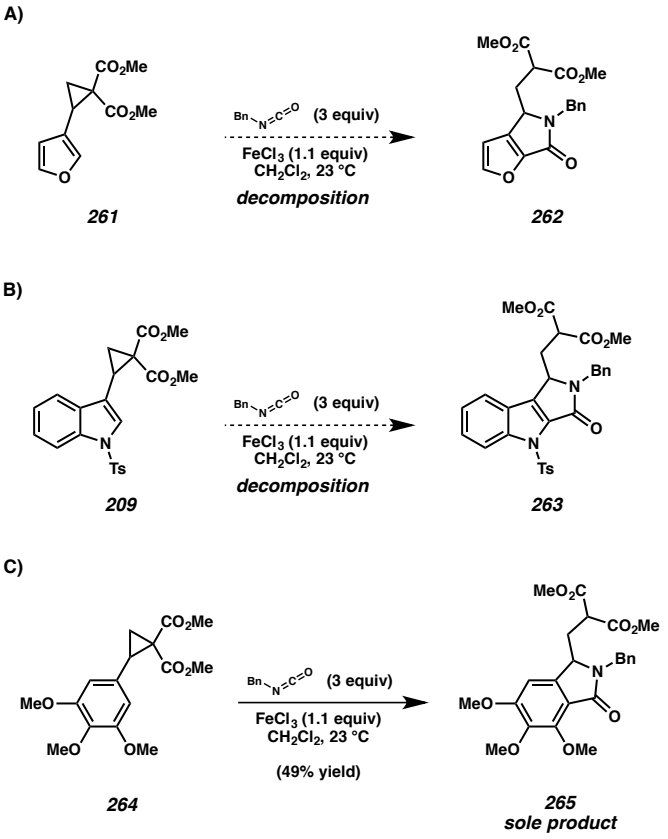


Despite the similar methods mentioned above,[7–10] isocyanates (or any other heteroatom-containg dipolarophiles) were not reported to undergo such reactions. Given the prevalence of isoindolones in biologically active compounds[13] and our discovery of a novel method for their synthesis, we attempted to optimize conditions for their formation. Unfortunately, screening a number of Lewis acids, solvents, and isocyanate equivalents provided no useful insights, with only low conversion or decomposition being observed.

We next investigated the influence of the aryl donor group on the cyclopropane, reasoning that a more strongly electron-donating group would allow the aryl group to

better compete with the malonate moiety in attacking the electrophilic carbon atom. While the use of heteroaryl donor groups such as furyl (**261**) and indolyl (**209**) cyclopropanes resulted in only decomposition, use of a 3,4,5-trimethoxyphenyl donor group (**264**) afforded the isoindolone product as the exclusive product in moderate yield.

Scheme A2.7 Attempts at isoindolone formation from cyclopropanes with strongly electron-donating groups



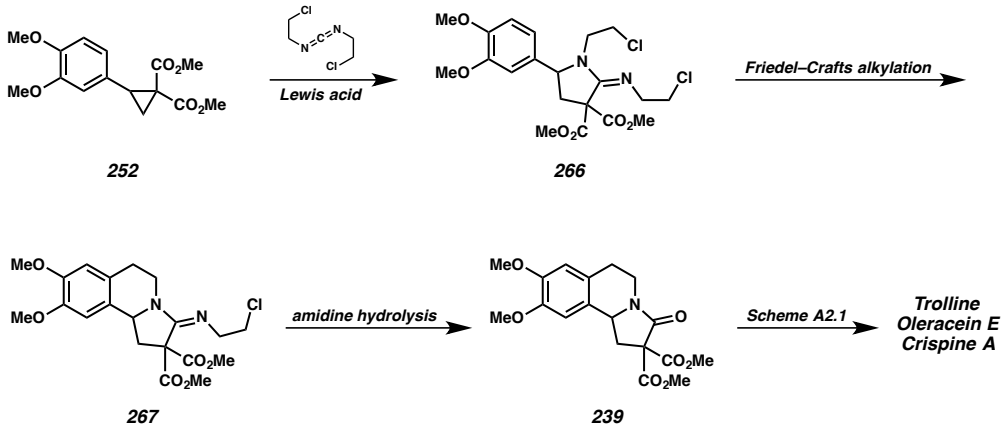
Similarly, more strongly electron-withdrawing acceptor groups on the cyclopropane should shift the product distribution to favor the isoindolones. Unfortunately attempts to synthesize cyclopropanes with acceptor groups derived from Meldrum's acid or 1,3-dimethylbarbituric acid were not successful.[14]

A2.6 FUTURE DIRECTIONS

A2.6.1 THIQ ALKALOID SYNTHESIS

Although the use of an intermolecular cyclopropane-isocyanate cycloaddition in the THIQ alkaloid synthesis does not appear promising, the success of a carbodiimide dipolarophile in the cycloaddition reaction (Scheme A2.5B) suggests a different approach may be feasible. Utilization of bis(2-chloroethyl)carbodiimide (or a more stable analogue) would enable the synthesis of amidine **266**, which could undergo a sequence of Fridel–Crafts alkylation and amidine hydrolysis[15] to afford lactam **239** (Scheme A2.8). This common intermediate could be advanced to the target molecules as described above.

Scheme A2.8 Proposed synthetic route utilizing a cyclopropane-carbodiimide cycloaddition

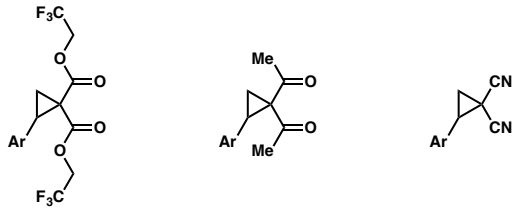


A2.6.2 SYNTHESIS OF ISOINDOLONES

Our newly discovered route to isoindolones requires further optimization, but the demonstrated ability of a 3,4,5-trimethoxyphenyl donor group to suppress formation of the typical dipolar cycloadduct is a promising starting point. Future studies may include slightly increasing the electron-withdrawing ability of the acceptor groups (**268**–**270**,

Figure A2.3) and re-screening of Lewis acids and solvents with the 3,4,5-trimethoxyphenyl cyclopropane substrate.

Figure A2.3 Cyclopropanes bearing slighly more electron-withdrawing acceptor groups



268 ***269*** ***270***

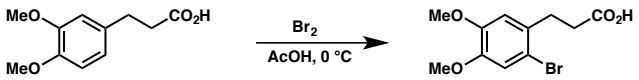
A2.7 EXPERIMENTAL SECTION

A2.7.1 MATERIALS AND METHODS

Unless stated otherwise, reactions were performed in flame-dried or oven-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina).[16] All heterocumulenes were obtained from commercial suppliers. Commercially obtained reagents were used as received with the exception of tetrakis(triphenylphospine)palladium(0), tin(II) triflate, and iron(III) chloride, which were stored in a nitrogen-filled glovebox. Diazodimethylmalonate was prepared according to the method of Davies and coworkers.[17] Cyclopropanes **195** and **209** were prepared as described in Chapter 2. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040–0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra

were recorded on a Varian 400 (at 400 MHz and 100 MHz, respectively) or on a Varian Mercury 500 (at 500 MHz and 126 MHz, respectively) and are reported relative to $CHCl_3$ (δ 7.26 & 77.16 ppm, respectively) or tetramethylsilane (0.00 ppm). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Abbreviations are used as follows: s = singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = complex multiplet, app = apparent.

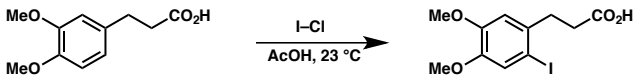
A2.7.2 PREPARATION OF ARYL HALIDES AND CYCLOPROPANES



271 ***244***

3-(2-bromo-3,4-dimethoxyphenyl)propionic acid (244):

Prepared according to the method of Lebel and coworkers[18] with minor modifications: pre-cooling the acetic acid solution in an ice-water bath resulted in a frozen mixture; therefore, the solution was cooled until it began to freeze, and bromine was added thereafter, with continued cooling in the ice-water bath. The characterization data matched those reported by Lebel and coworkers.[17]

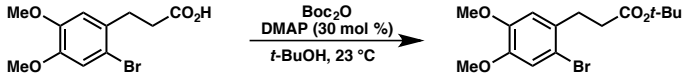


271 ***245***

3-(2-iodo-3,4-dimethoxyphenyl)propionic acid (245):

Carboxylic acid **271** (1.08 g, 5.14 mmol, 1 equiv) was dissolved in acetic acid (6 mL) in a round-bottom flask. Iodine monochloride (1.1370 g, 6.94 mmol, 1.35 equiv) was

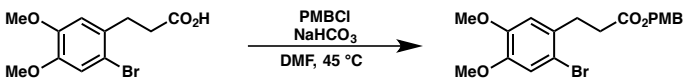
added in portions at ambient temperature to afford an orange solution. After at least 20 minutes, a precipitate was observed. After 85 minutes, the suspension was poured over water (10 mL) and a saturated solution of aqueous sodium thiosulfate was slowly added until the orange color disappeared. The suspension was filtered, washed with water, and air-dried to afford iodide **245** (1.5503 g, 90% yield) as a white amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (s, 1H), 6.80 (s, 1H), 3.85 (s, 6H), 3.00 (t, J = 7.8 Hz, 2H), 2.66 (t, J = 7.8 Hz, 2H).



244 ***246***

***tert*-butyl 3-(2-bromo-4,5-dimethoxyphenyl)propanoate (246):**

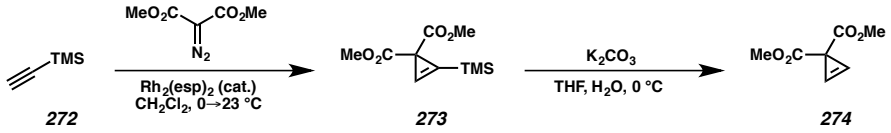
According to the procedure of Takeda and coworkers.[19] To a suspension of acid **244** (1.00 g, 3.4 mmol, 1 equiv) and di-*tert*-butyl dicarbonate (2.2544 g, 10.4 mmol, 3 equiv) in *tert*-butanol (8.5 mL, 0.4 M) was added 4-(*N*,*N*-dimethylamino)pyridine (127 mg, 1.02 mmol, 0.3 equiv). Vigorous bubbling was observed and the solution became yellow. After one hour, the reaction mixture was dry-loaded directly onto SiO_2 (~10 mL) and purified by silica gel column chromatography (20:1 → 10:1 hexanes:EtOAc) to afford *tert*-butyl ester **246** (581.6 mg, 49% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.77 (s, 1H), 3.85 (s, 6H), 2.95 (t, J = 7.7 Hz, 2H), 2.52 (t, J = 7.7 Hz, 2H), 1.43 (s, 9H).



244 ***247***

4-methoxybenzyl 3-(2-bromo-4,5-dimethoxyphenyl)propanoate (247):

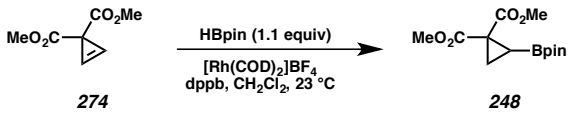
To a flame-dried round bottom flask equipped with a magnetic stir bar were added aryl bromide **244** (500 mg, 1.73 mmol), sodium bicarbonate (291 mg, 3.46 mmol), *para*-methoxybenzyl chloride (258 μL, 1.90 mmol), and DMF (1 mL). The mixture was stirred under nitrogen at 45 °C for 29 hours. Upon completion (as determined by TLC analysis), the mixture was cooled to room temperature, diluted with ethyl acetate (5 mL), washed with water (2 x 10 mL) and brine (1 x 10 mL), dried over sodium sulfate, and filtered and evaporated to give the crude product as a yellow oil. The oil was purified by silica gel column chromatography (9:1 hexanes:EtOAc) to give ester **247** (594 mg, 91% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.18 (m, 2H), 6.96 (s, 1H), 6.88–6.80 (m, 2H), 6.71 (s, 1H), 5.03 (s, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 3.76 (s, 3H), 2.98 (t, J = 8.2, 2H), 2.63 (t, J = 8.2, 2H).



dimethyl 2-(trimethylsilyl)cycloprop-2-ene-1,1-dicarboxylate (274):

Prepared by an improved procedure based on that reported by Gevorgyan and coworkers.[5] To a flame-dried round-bottom flask equipped with a magnetic stir bar was added bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)] (0.7 mg, 0.9 μmol, 0.016 mol %) and trimethylsilylacetylene (**272**, 0.82 mL, 5.75 mmol, 1 equiv). The flask was sealed with a rubber septum, then evacuated and backfilled with argon three times. Dichloromethane was then added (10 mL, 0.6 M) and the flask was cooled in an ice-water bath with stirring. Diazodimethylmalonate (0.9982 g, 6.3 mmol, 1.1 equiv) was added dropwise, then the flask was removed from the bath and allowed to

warm to ambient temperature, stirring overnight (13 h). Complete consumption of the starting material was observed (TLC), and the solvent was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (20:1 → 6:1 hexanes:EtOAc) to afford cyclopropene **273** as a blue oil which was carried forward directly to the next stage. Cyclopropene **273** was dissolved in tetrahydrofuran (30 mL) in a round-bottom flask, and the solution was cooled in an ice-water bath. To this solution was added K_2CO_3 (10 mL, 10% in water) with stirring. After 10 minutes, TLC indicated complete consumption of starting material (R_f: 3:1 hexanes:EtOAc, SM = 0.62, prod = 0.21). The phases were separated and the organic phase was concentrated to an approximate volume of 5 mL. The aqueous and organic phases were recombined and diluted with water (10 mL) and diethyl ether (25 mL). The phases were separated and the aqueous layer was extracted with additional diethyl ether (25 mL). The combined organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (9:1 hexanes:EtOAc) to afford cyclopropene **274** (634.1 mg, 70% yield) as an amorphous white solid. The characterization data matched those reported by Gevorgyan and coworkers.[5]

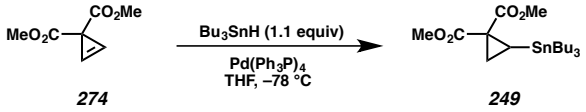


274 *248*

dimethyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropane-1,1-dicarboxylate (248):

In a nitrogen filled glove-box, an oven-dried scintillation vial was charged with bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate (5.2 mg, 0.013 mmol, 0.02 equiv)

and dppb (6.0 mg, 0.014 mmol, 0.022 equiv), and the solids were dissolved in dichloromethane, affording an orange solution. A separate one dram vial was charged with cyclopropene **274** (99.5 mg, 0.64 mmol, 1 equiv) and pinacolborane (100 μL, 0.7 mmol, 1.1 equiv). The mixture was dissolved in dichloromethane (0.5 mL) and transferred into the first vial; the second vial was then washed with additional dichloromethane (0.3 mL) and transferred into the first vial. The reaction was stirred for 17 hours and complete conversion of the starting material was observed (TLC: 3:1 hexanes:EtOAc, R_f: SM = 0.21, product: 0.46). The reaction mixture was dry-loaded onto SiO_2 (~1 mL) and purified by silica gel column chromatography (8:1 hexanes:EtOAc) to afford cyclopropane **248** (160.7 mg, 89% yield). The characterization data matched those reported by Gevorgyan.[5]

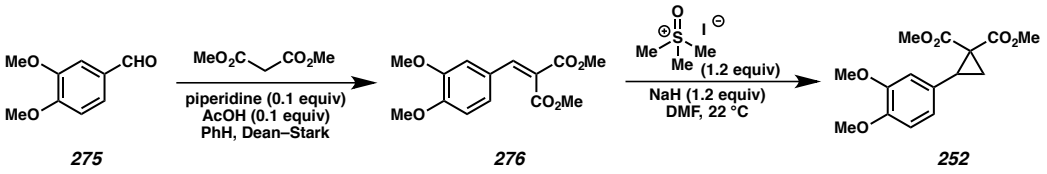


274 *249*

dimethyl 2-(tributylstannyl)cyclopropane-1,1-dicarboxylate (249):

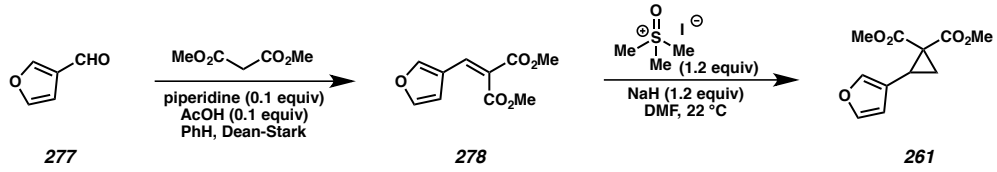
Prepared by a procedure reported by Gevorgyan and coworkers.[6] In a nitrogen filled glove-box, an oven-dried scintillation vial was charged with tetrakis(triphenylphosphine)palladium(0) (10 mg, 0.002 mmol). The vial was capped with a screw cap fitted with a Teflon septum and removed from the glovebox. THF (1.55 mL) was added and the mixture was stirred until the catalyst dissolved. The solution was then cooled to –78 °C under nitrogen and tributyltin hydride (460 μL, 0.34 mmol) was added. Finally, a solution of the starting material (**274**, 250 mg, 0.31 mmol) in THF (0.5 mL) was added and the reaction was stirred at –78 °C for five minutes. Upon completion

(as determined by TLC analysis), the mixture was concentrated and purified by silica gel column chromatography (hexanes) to afford cyclopropylstannane **249** (510 mg, 72% yield). The characterization data match those reported by Gevorgyan.[6]



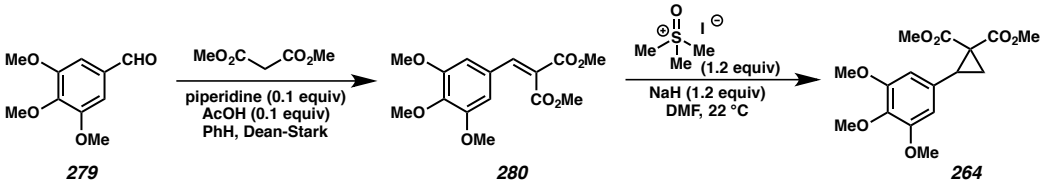
dimethyl 2-(3,4-dimethoxyphenyl)cyclopropane-1,1-dicarboxylate (252):

Cyclopropane **252** was synthesized following our standard procedures. See General Proceedures A and B, Experimental Section, Chapter 2. The characterization data match those reported by Müller.[20]



dimethyl 2-(furan-3-yl)cyclopropane-1,1-dicarboxylate (261)

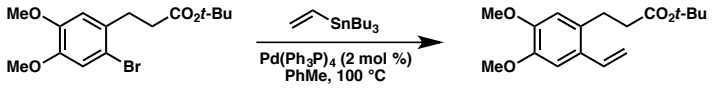
Cyclopropane **261** was synthesized following our standard procedures. See General Proceedures A and B, Experimental Section, Chapter 2. The characterization data match those reported by Skvorcova.[21]



dimethyl 2-(3,4,5-trimethoxyphenyl)cyclopropane-1,1-dicarboxylate (264):

Cyclopropane **264** was synthesized following our standard procedures. See General Proceedures A and B, Experimental Section, Chapter 2. The characterization data match those reported by Melnikov.[7]

A2.7.3 SYNTHESIS OF STYRENE 250 VIA STILLE COUPLING



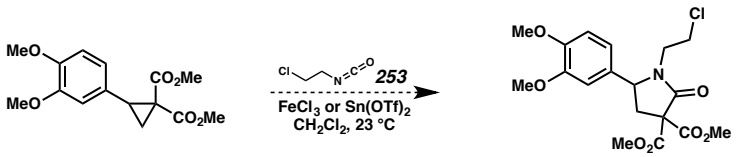
246 ***250***

***tert*-butyl 3-(4,5-dimethoxy-2-vinylphenyl)propanoate (250):**

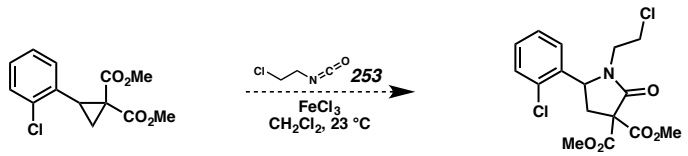
In a nitrogen-filled glovebox, a flame-dried Schlenk bomb was charged with tetrakis(triphenylphosphine)palladium(0) (30 mg, 0.03 mmol, 0.02 equiv). The bomb was sealed, removed from the glovebox, and placed under an atmosphere of argon. To a vial containing bromide **246** (455.1 mg, 1.30 mmol, 1 equiv) was added dry toluene, which was then removed *in vacuo*; this procedure was repeated twice to remove traces of water from the substrate. Under an atmosphere of argon, the bromide was dissolved in toluene (3 mL) and transferred to the Schlenk bomb under a high flow of argon. Finally, vinyl tributyltin (0.4 mL, 1.37 mmol, 1.05 equiv) was added as a neat oil to the Schlenk bomb under a high flow of argon. The bomb was sealed and lowered into an oil bath which was preheated to 100 °C. After 17 hours, the bomb was cooled to ambient temperature, and a crude product was obtained by a workup procedure that was not properly recorded. The crude product was purified by column chromatography to afford styrene **250** as a yellow solid (253.1 mg, 66% yield). ^{1}H NMR of the crude material showed complete consumption of the starting material and clean signals corresponding to

the vinyl group: 5.87 (dd, J = 17.2, 10.5 Hz, 1H), 5.09 (d, J = 10.5 Hz, 1H), 5.04 (d, J = 17.2 Hz, 1 H). ^{1}H NMR of the purified product was poorly shimmed or had paramagnetic impurities.

A2.7.4 PROCEDURE FOR ATTEMPTED REACTIONS WITH 2-(CHLOROETHYL)ISOCYANATE



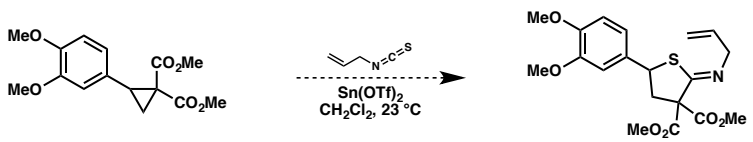
252 *251*



195 *254*

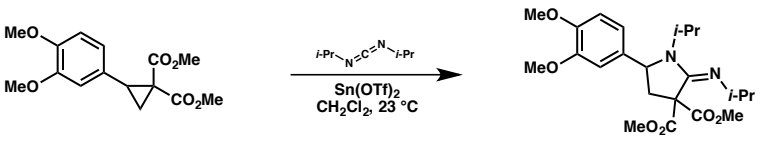
These reactions were carried out using our standard procedure. See General Procedure D, Experimental Section, Chapter 2. In no case did analysis of the reaction mixture and crude product by TLC, LCMS, and NMR show anything other than decomposition products.

A2.7.5 CONTROL REACTIONS WITH CYCLOPROPANE 252



252 *255*

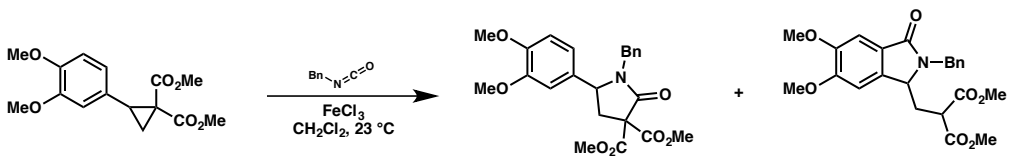
The reaction of cyclopropane **252** with allyl isothiocyanate was carried out using our standard procedure. See General Proceedure F, Experimental Section, Chapter 2. Analysis of the reaction mixture and crude product by TLC, LCMS, and NMR showed only decomposition.



252 *256*

dimethyl (*E*)-5-(3,4-dimethoxyphenyl)-1-isopropyl-2-(isopropylimino)pyrrolidine-3,3-dicarboxylate (256):

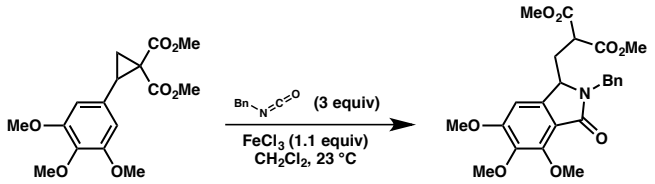
The reaction of cyclopropane **252** with diisopropylcarbodiimide was carried out using our standard procedure. See General Proceedure G, Experimental Section, Chapter 2. Analysis of the reaction mixture and crude product by TLC, LCMS, and NMR showed only decomposition. ^{1}H NMR analysis (300 MHz, $CDCl_3$) of the crude product (**256**) showed signals correponsing to the 5-arylamidine ring: δ 5.19 (dd, J = 8.4, 3.7, 1H), 3.23 (dd, J = 13.7, 8.5, 1H), 2.69 (dd, J = 13.7, 3.7, 1H). Further purification was not attempted.



252 ***257*** ***258***

The reaction of cyclopropane **252** with benzyl isocyanate was carried out using our standard procedure. See General Proceedure D, Experimental Section, Chapter 2. A mixture of **257** and **258** was obtained, and the following characterization data was collected. **257** (47% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.27 (m, 3H), 7.10–7.06 (m, 2H), 6.87 (d, *J* = 8.2, 1H), 6.72 (dd, *J* = 8.2, 2.1, 1H), 6.63 (d, *J* = 2.1, 1H), 5.11 (d, *J* = 14.5, 1H), 4.33 (t, *J* = 7.6, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.55 (d, *J* = 14.6, 1H), 2.97 (dd, *J* = 13.9, 7.3, 1H), 2.69 (dd, *J* = 13.9, 7.9, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 167.8, 167.0, 149.6, 149.2, 135.5, 130.7, 128.7, 128.5, 127.8, 120.1, 111.1, 109.7, 63.3, 58.6, 56.0, 55.9, 53.6, 53.5, 45.2, 37.8. **258** (40% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.35–7.24 (m, 5H), 6.80 (d, *J* = 0.6, 1H), 5.33 (d, *J* = 15.3, 1H), 4.42 (dd, *J* = 4.2, 3.3, 1H), 4.09 (d, *J* = 15.3, 1H), 3.98 (s, 3H), 3.94 (s, 3H), 3.72 (s, 3H), 3.49 (s, 3H), 2.88 (dd, *J* = 6.9, 6.3, 1H), 2.77 (ddd, *J* = 15.1, 7.0, 4.4, 1H), 2.60 (ddd, *J* = 15.0, 6.2, 3.2, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 169.5, 169.0, 152.7, 150.0, 137.0, 136.6, 128.8, 128.1, 127.6, 125.0, 105.4, 104.9, 56.4, 56.3, 56.3, 53.0, 52.6, 45.5, 43.8, 29.0.

A2.7.6 REACTION OF CYCLOPROPANE 264 WITH BENZYL ISOCYANATE



264 ***265***

The reaction of cyclopropane **264** with benzyl isocyanate was carried out using our standard procedure. See General Proceedure D, Experimental Section, Chapter 2. Isoindolone **265** was obtained in approximately 49% yield, although purification was difficult. ^{1}H NMR analysis (300 MHz, $CDCl_3$) of showed signals corresponding to the 5-malonyl-containing side chain off the isoindoline ring: δ 3.03–2.94 (m, 1H), 2.83–2.70 (m, 1H), 2.54 (dd, J = 9.9, 7.0, 1H). Further purification was not attempted.

A2.8 NOTES AND REFERENCES

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APPENDIX 3

Spectra Relevant to Chapter 2:

Lewis Acid Mediated (3 + 2) Cycloadditions of

Donor–Acceptor Cyclopropanes with Heterocumulenes

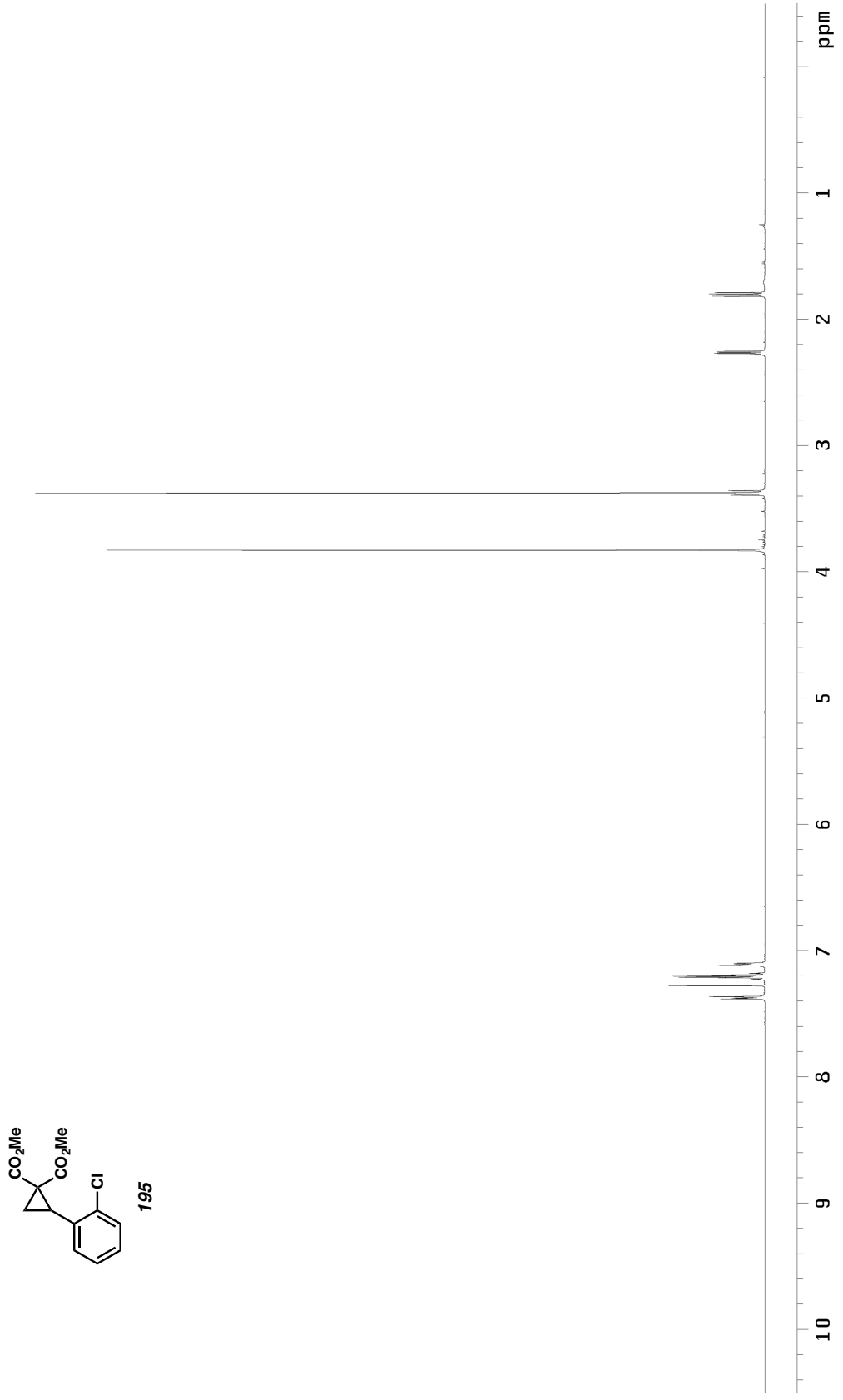


Figure A3.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **195**.

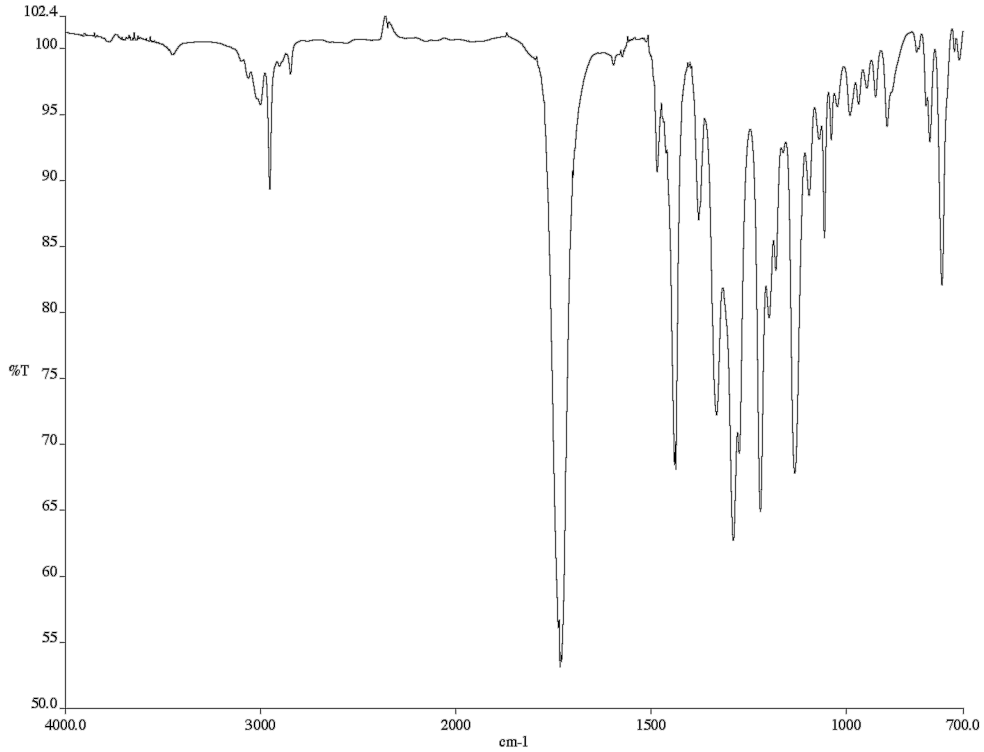


Figure A3.2 Infrared spectrum (thin film/NaCl) of compound **195**.

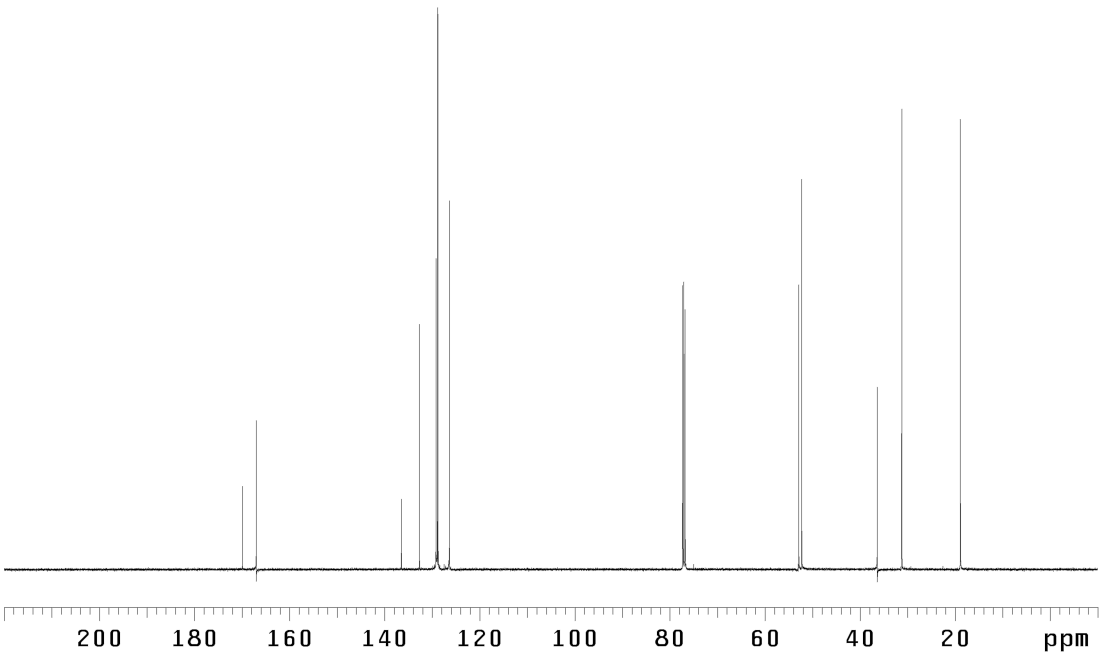


Figure A3.3 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **195**.

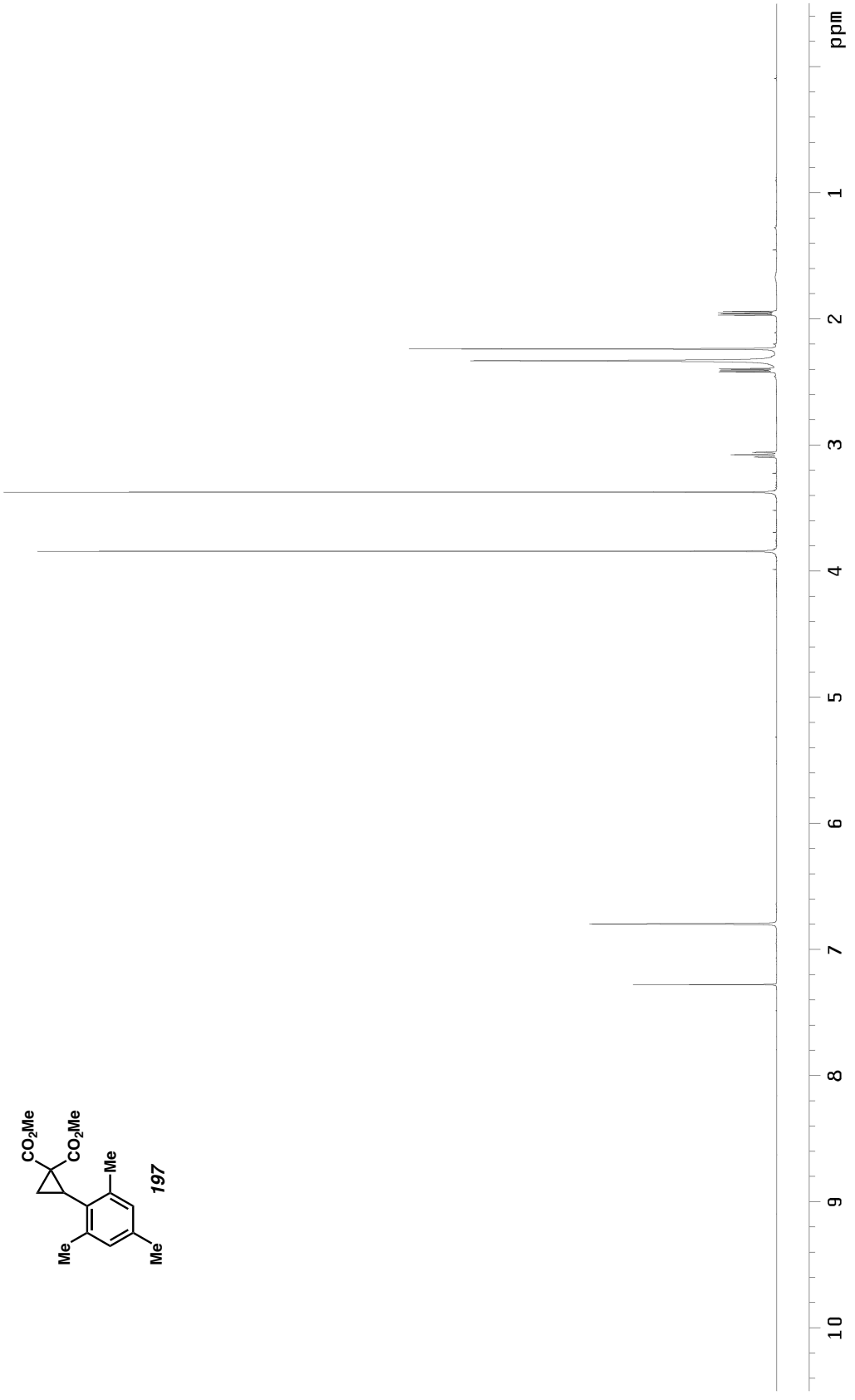


Figure A3.4 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **197**.

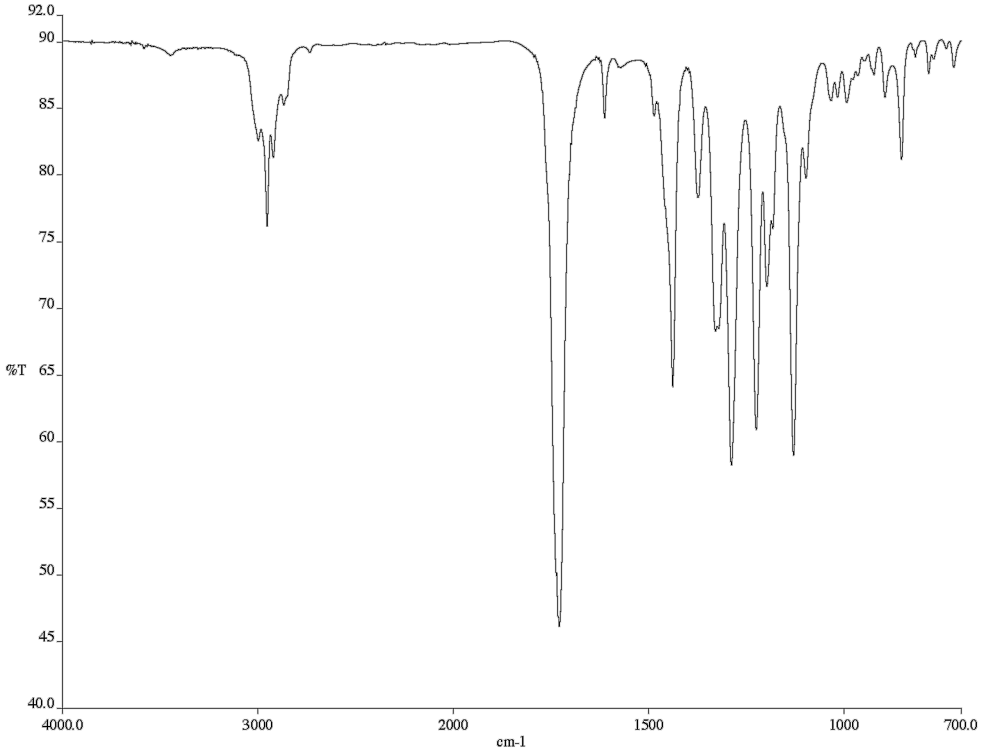


Figure A3.5 Infrared spectrum (thin film/NaCl) of compound **197**.

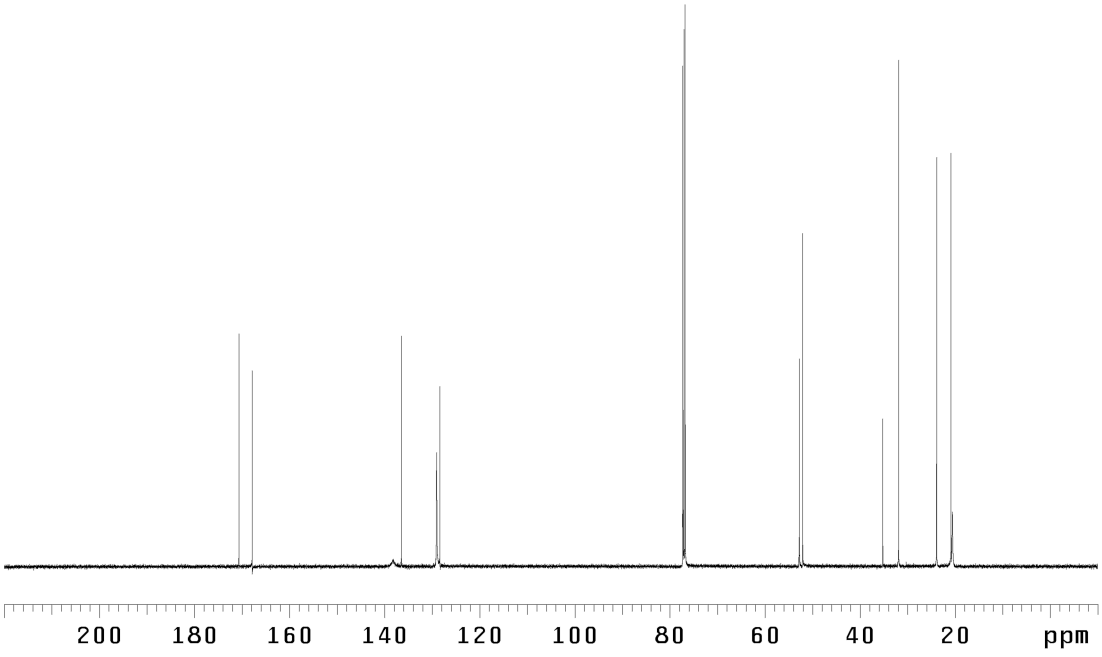


Figure A3.6 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **197**.

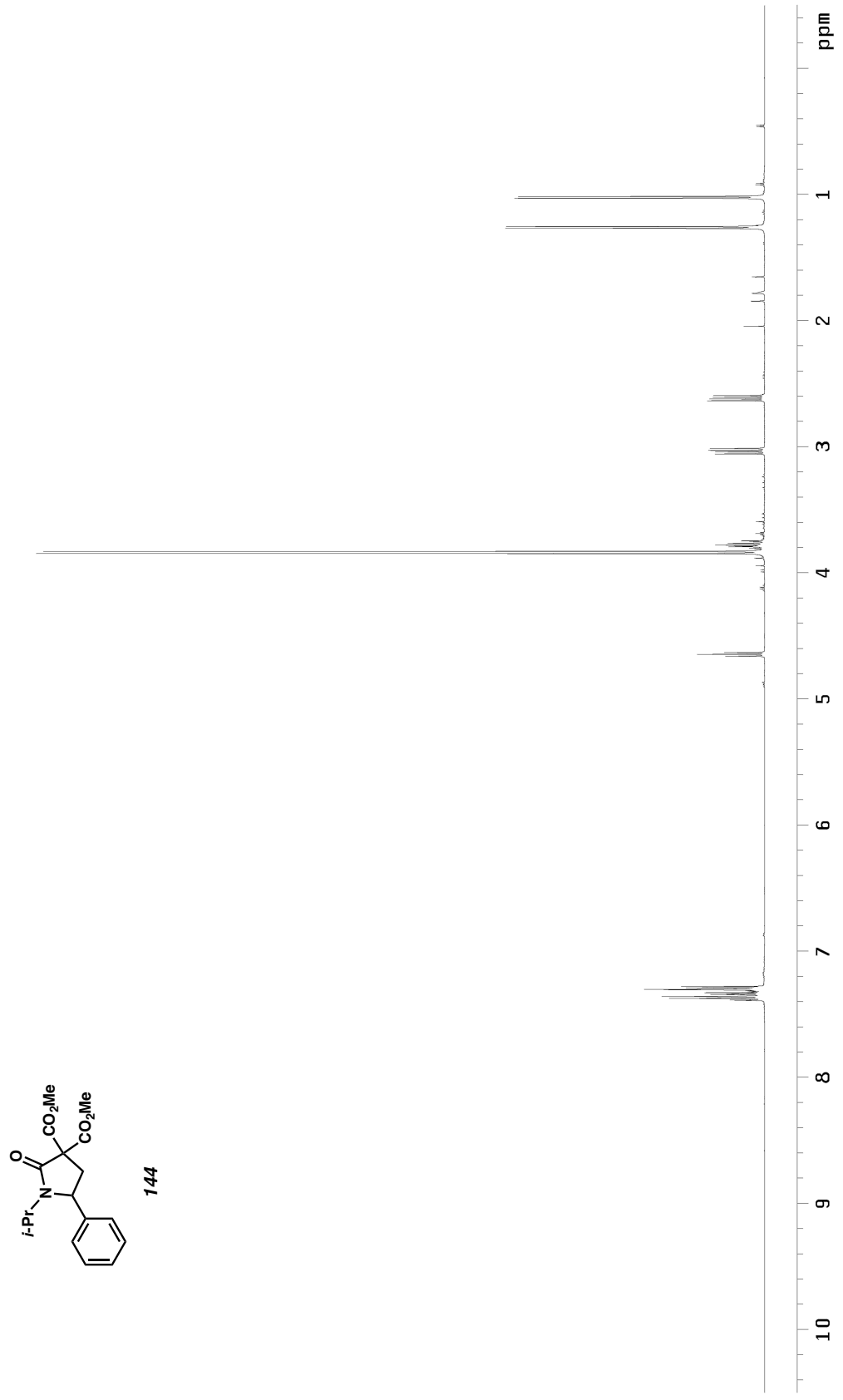


Figure A3.7 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **144**.

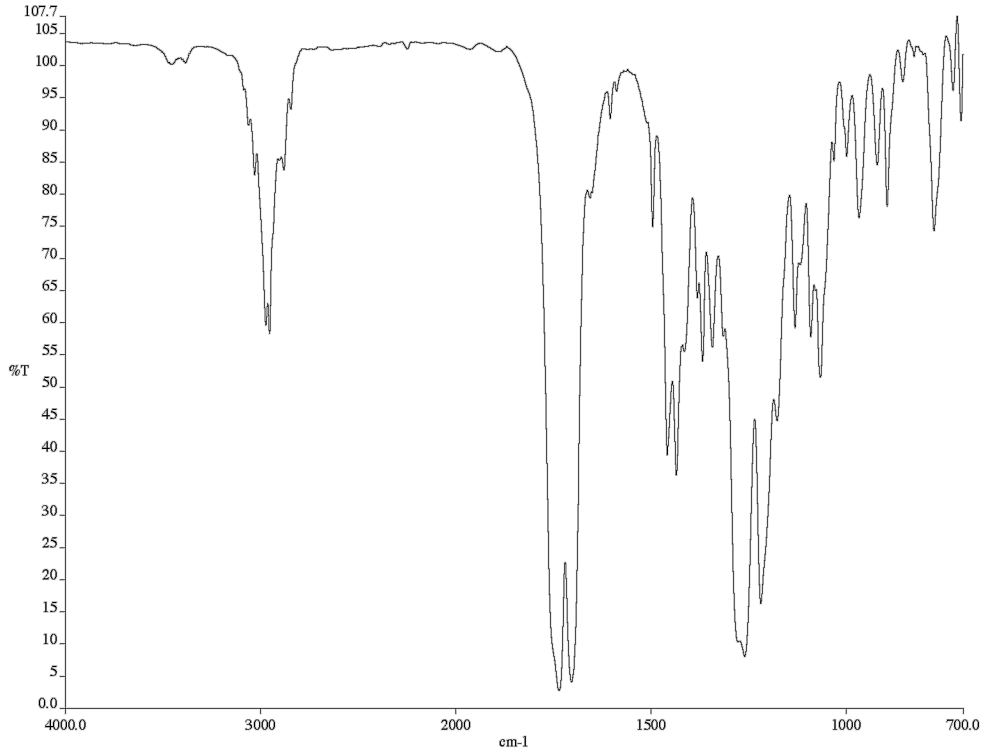


Figure A3.8 Infrared spectrum (thin film/NaCl) of compound **144**.

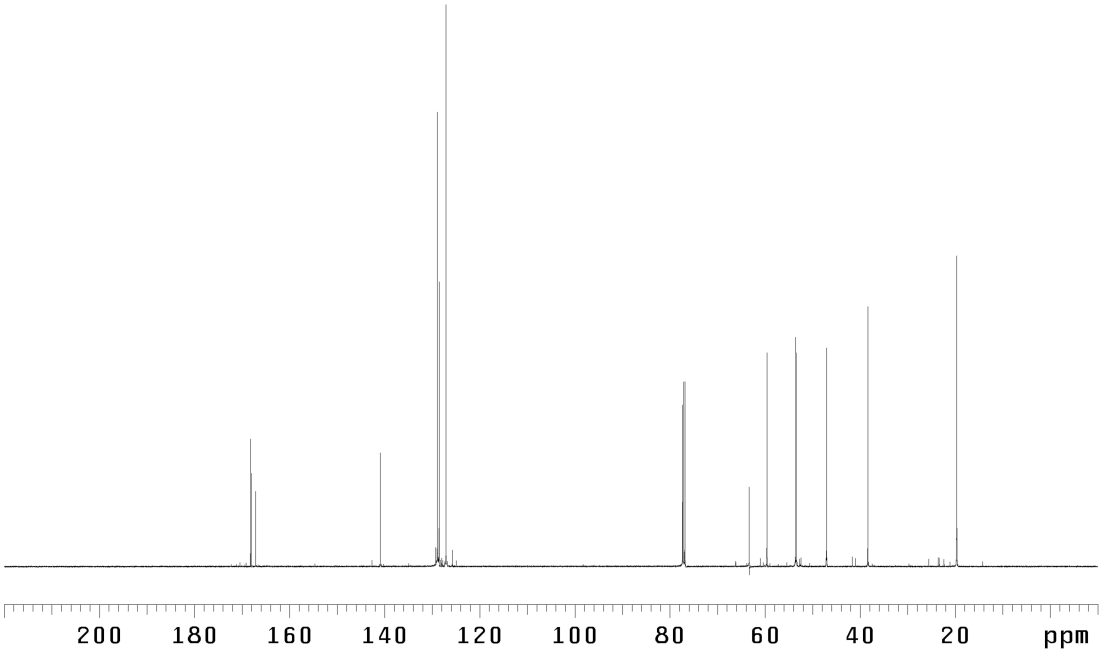


Figure A3.9 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **144**.

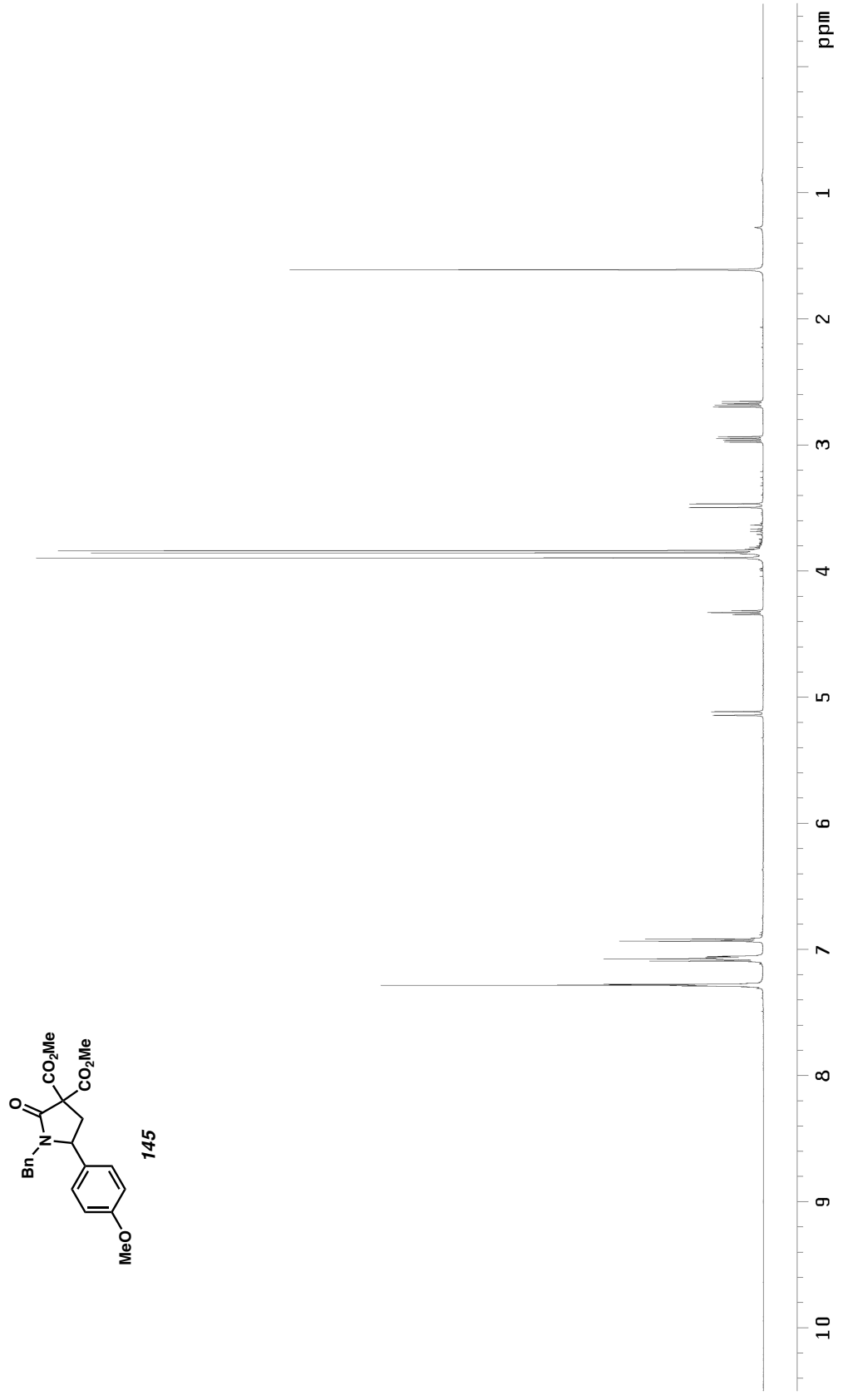


Figure A3.10 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **145**.

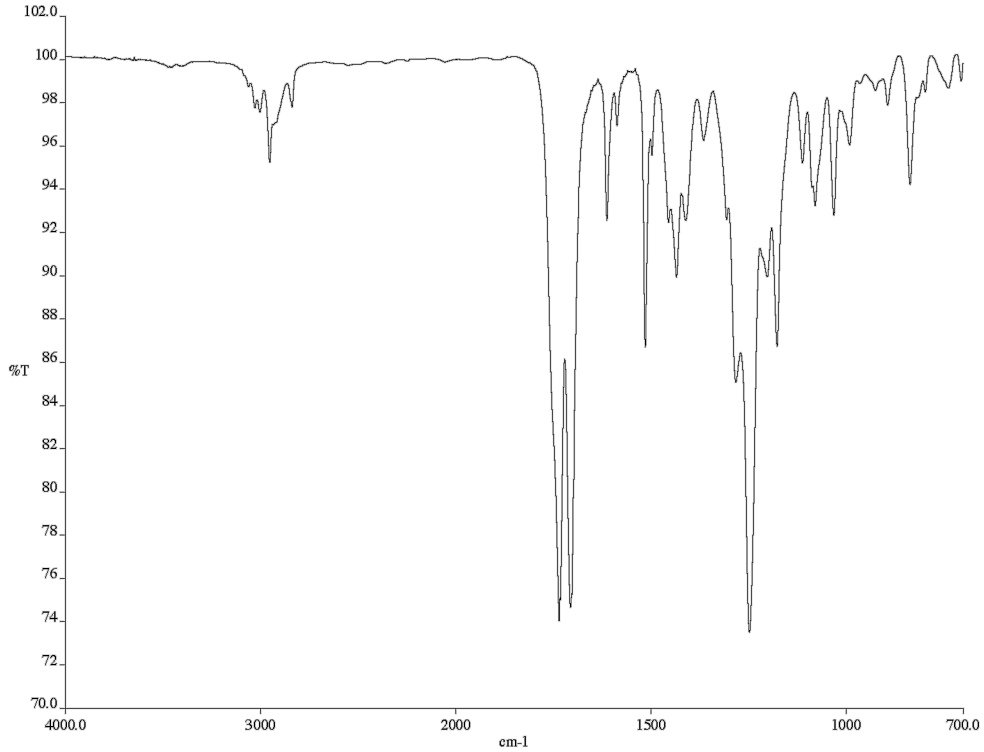


Figure A3.11 Infrared spectrum (thin film/NaCl) of compound **145**.

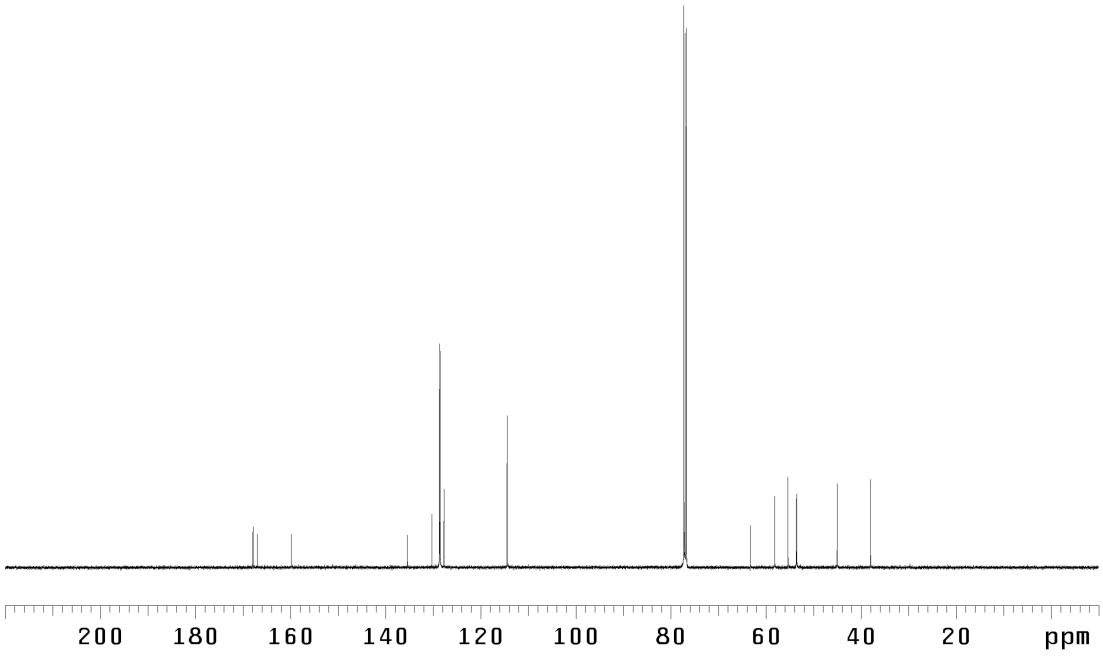


Figure A3.12 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **145**.

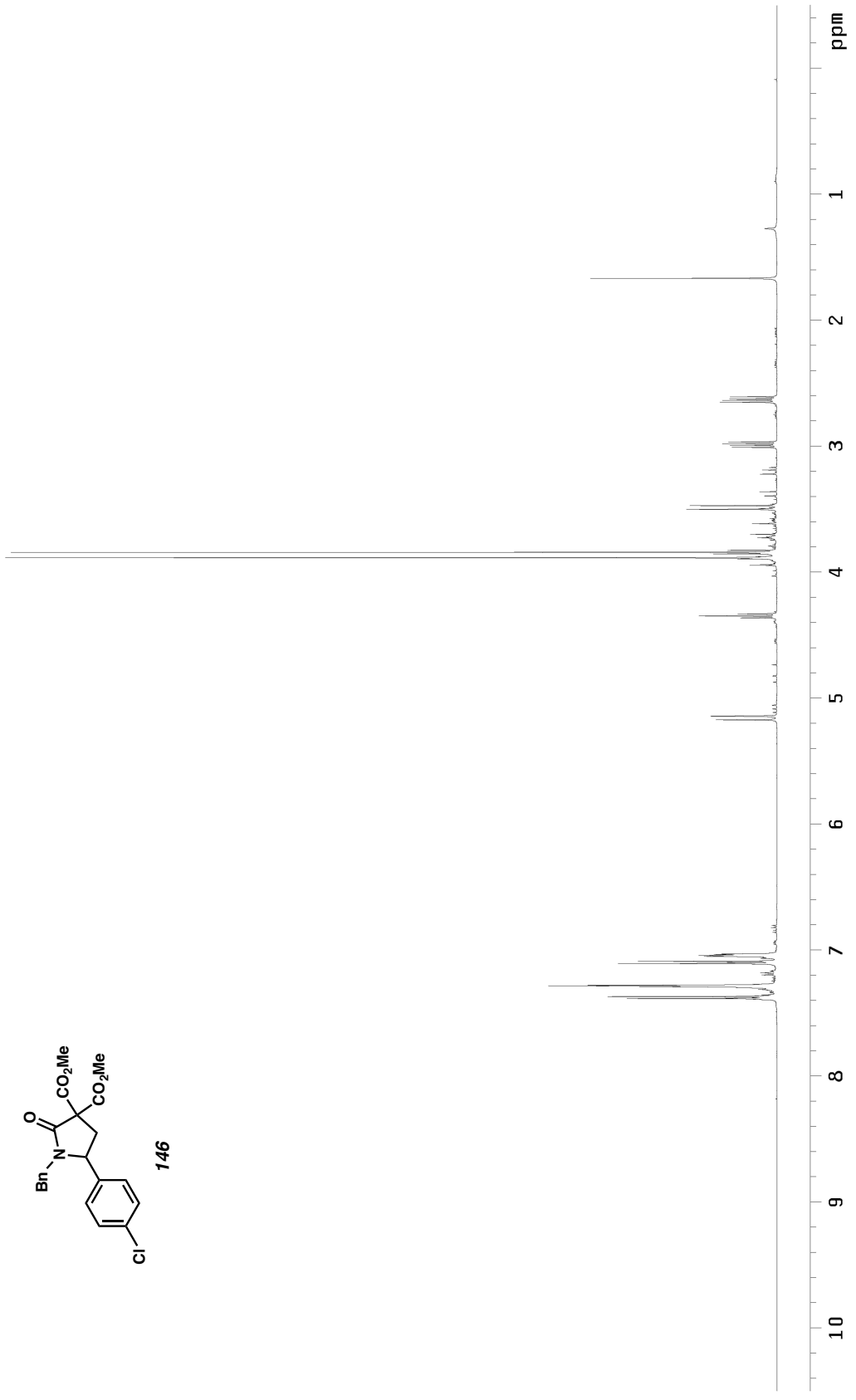


Figure A3.13 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **146**.

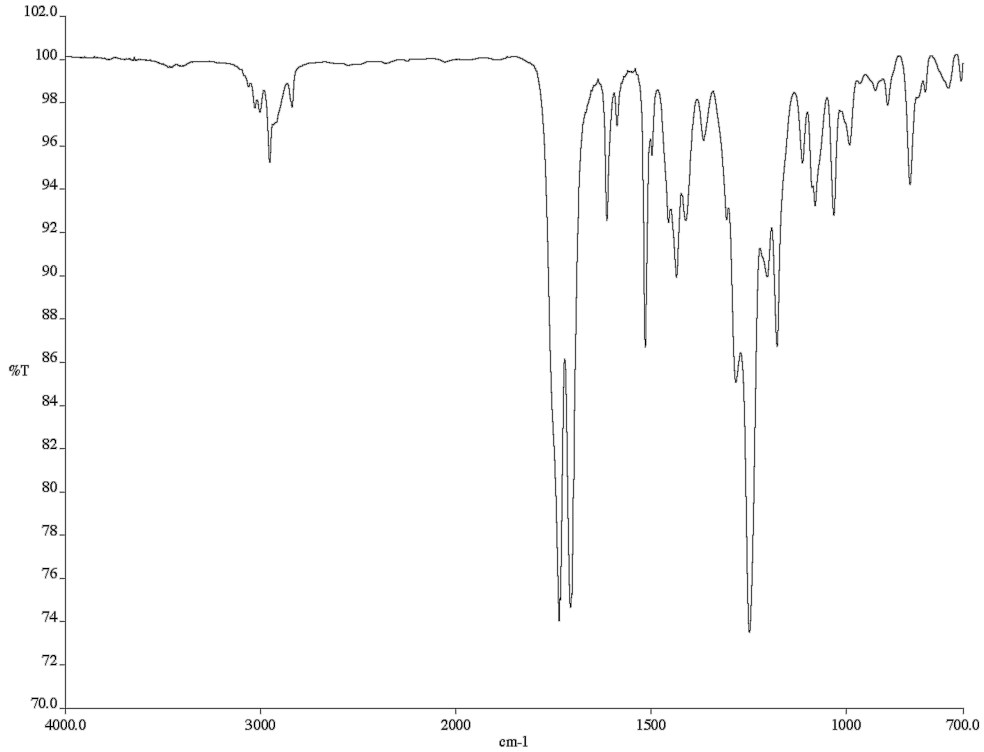


Figure A3.14 Infrared spectrum (thin film/NaCl) of compound **146**.

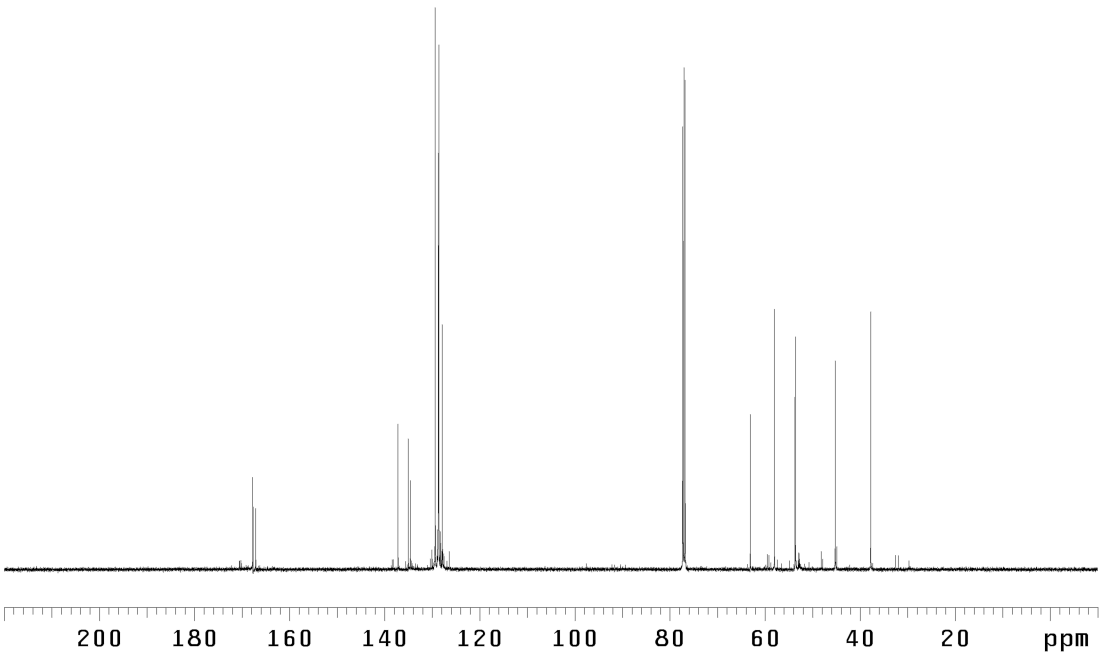


Figure A3.15 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **146**.

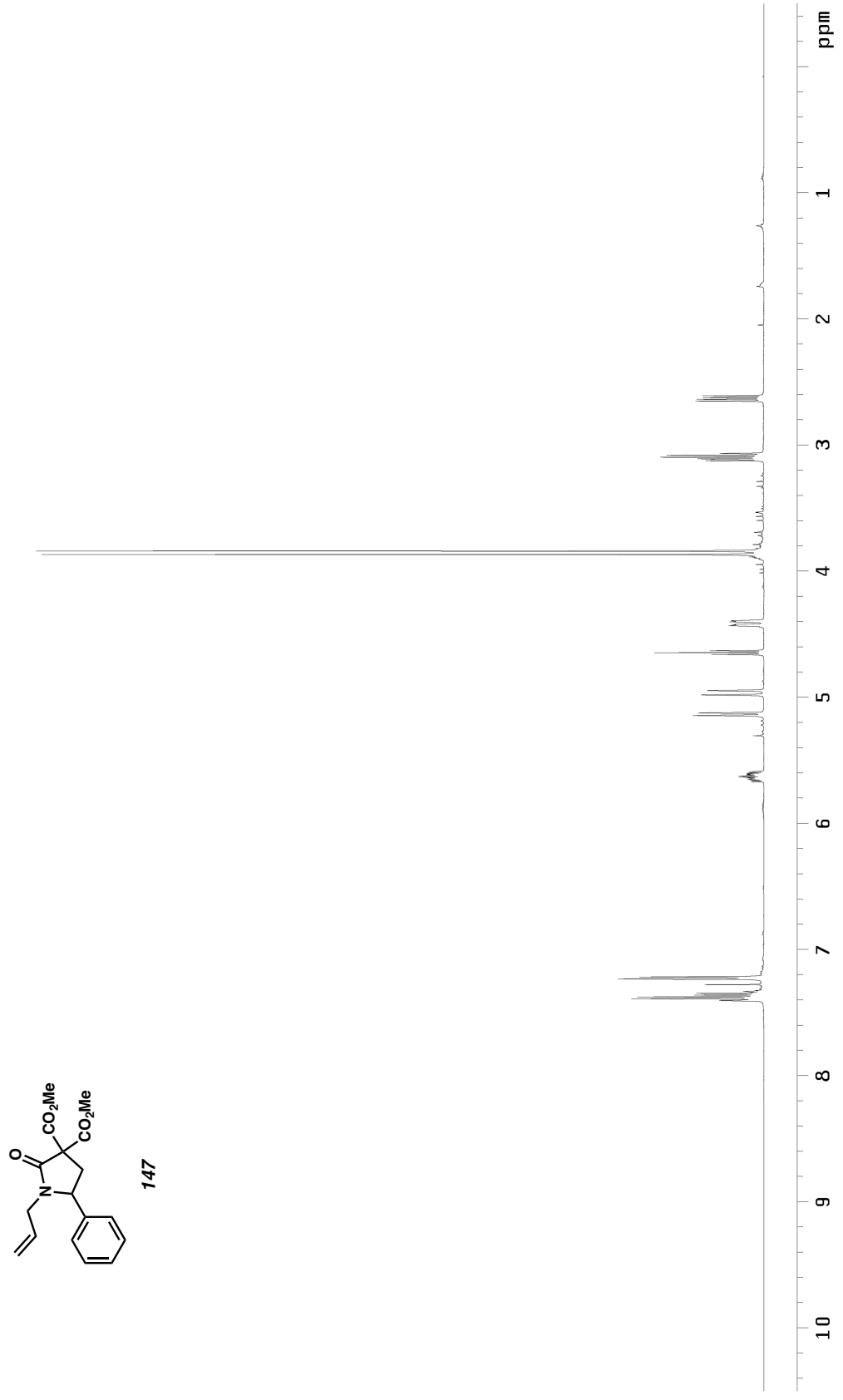


Figure A3.16 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **147**.

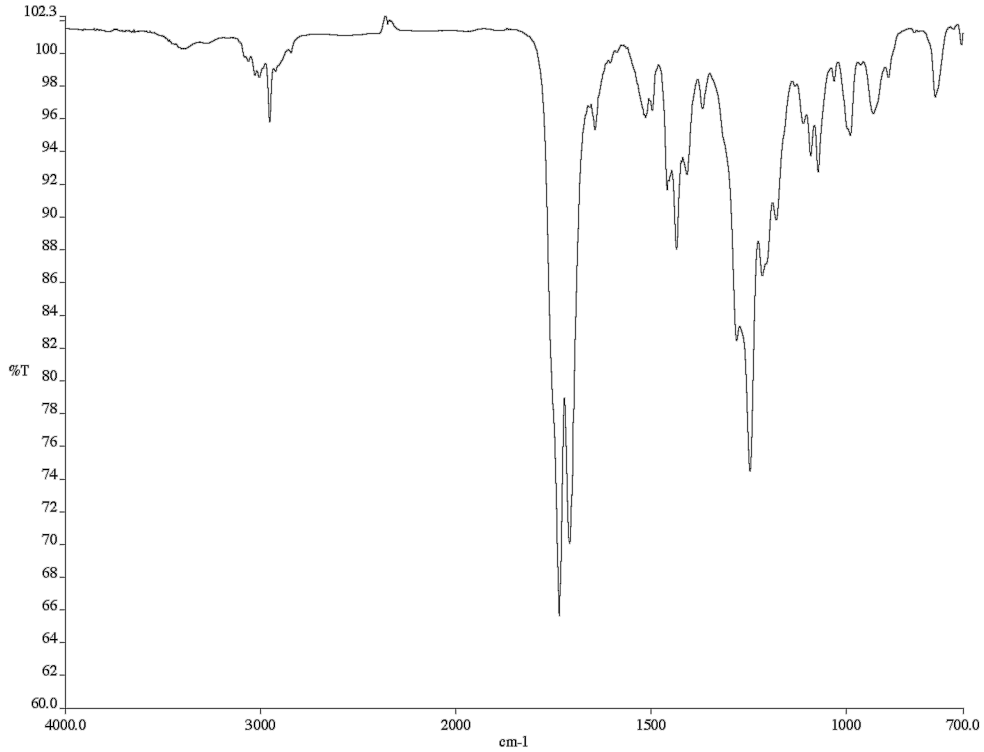


Figure A3.17 Infrared spectrum (thin film/NaCl) of compound **147**.

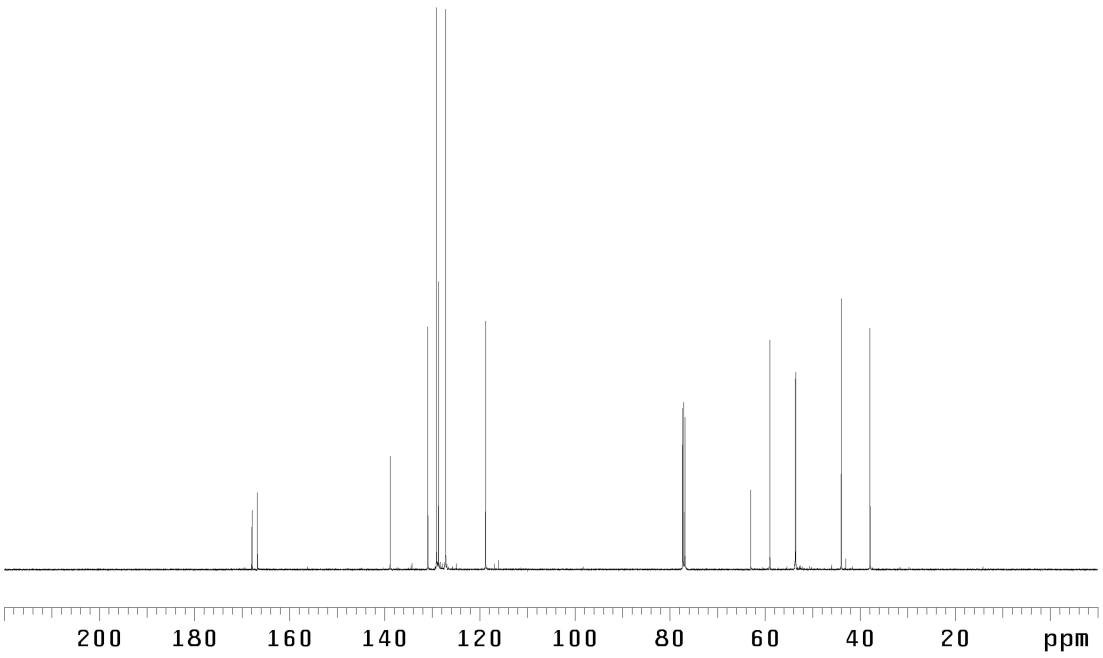


Figure A3.18. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **147**.

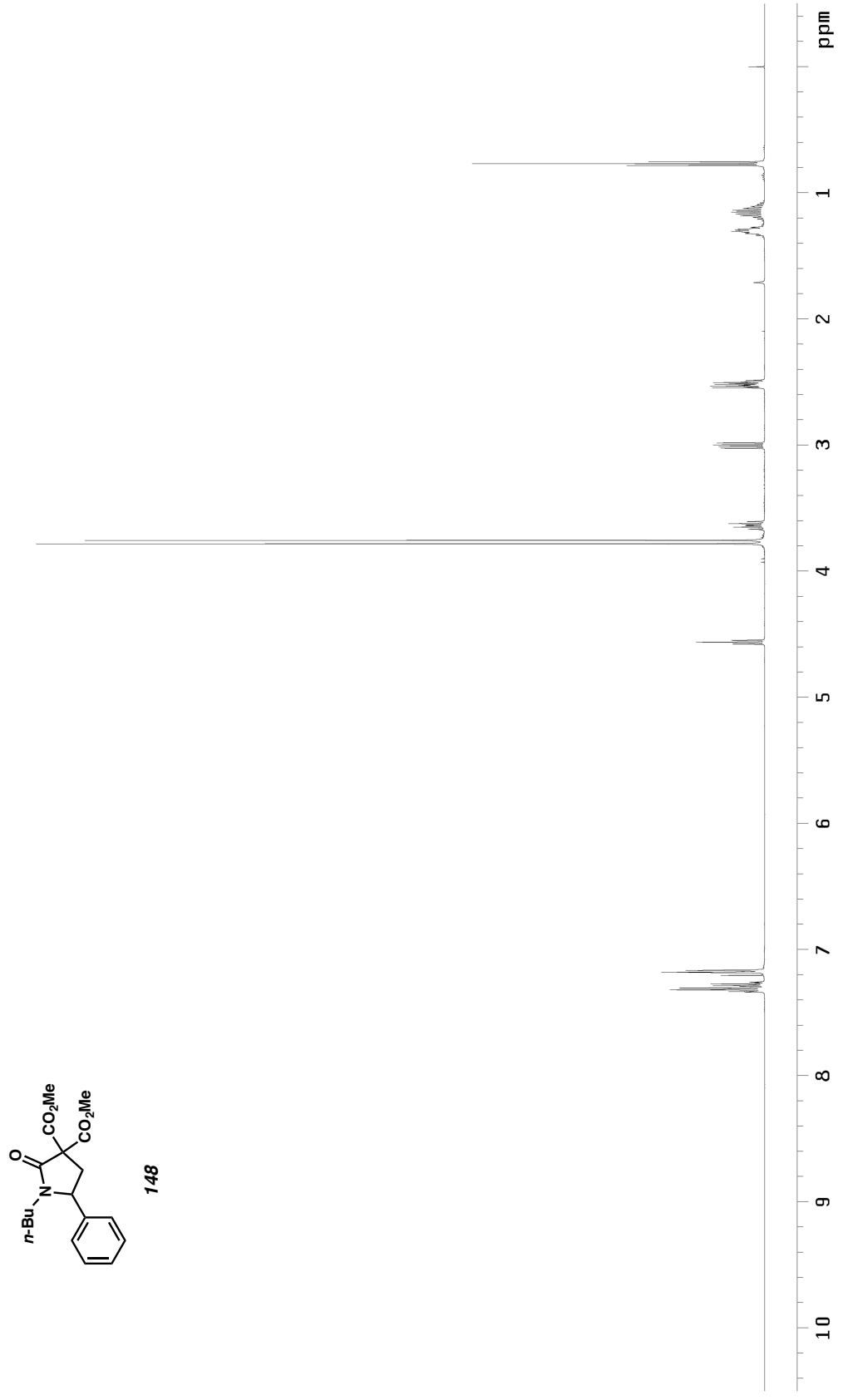


Figure A3.19 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **148**.

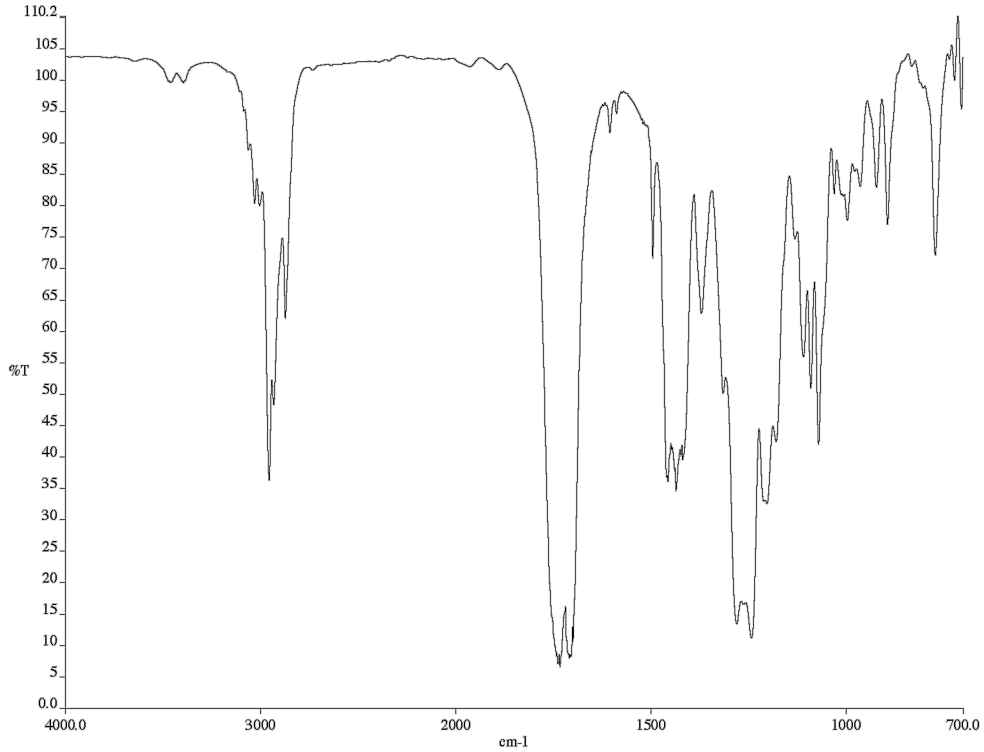


Figure A3.20 Infrared spectrum (thin film/NaCl) of compound **148**.

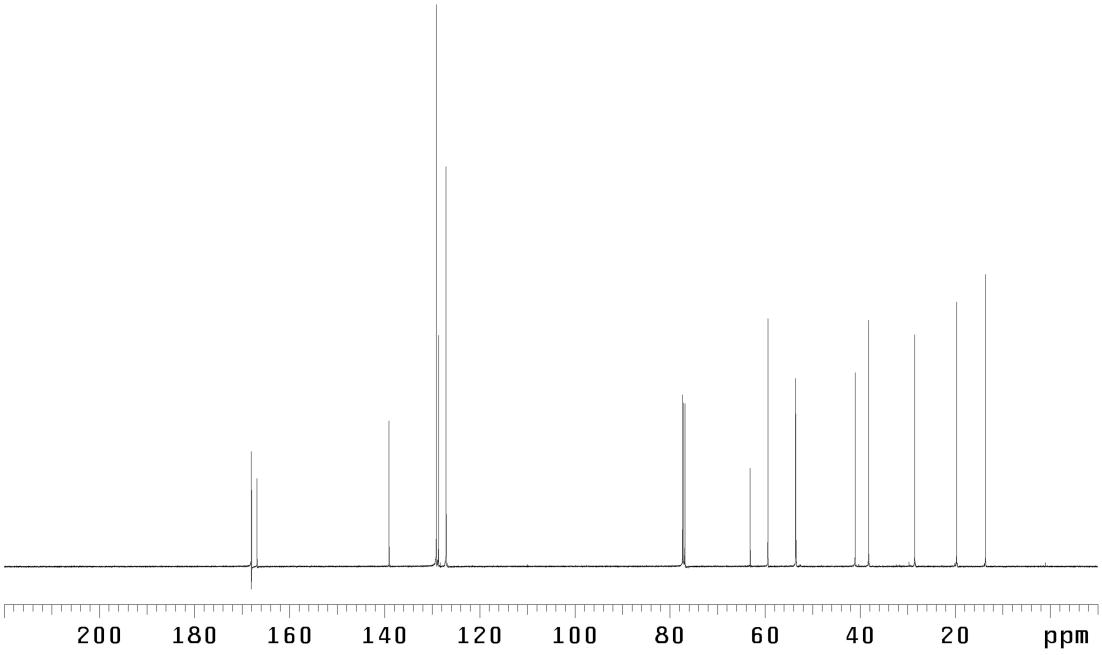


Figure A3.21 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **148**.

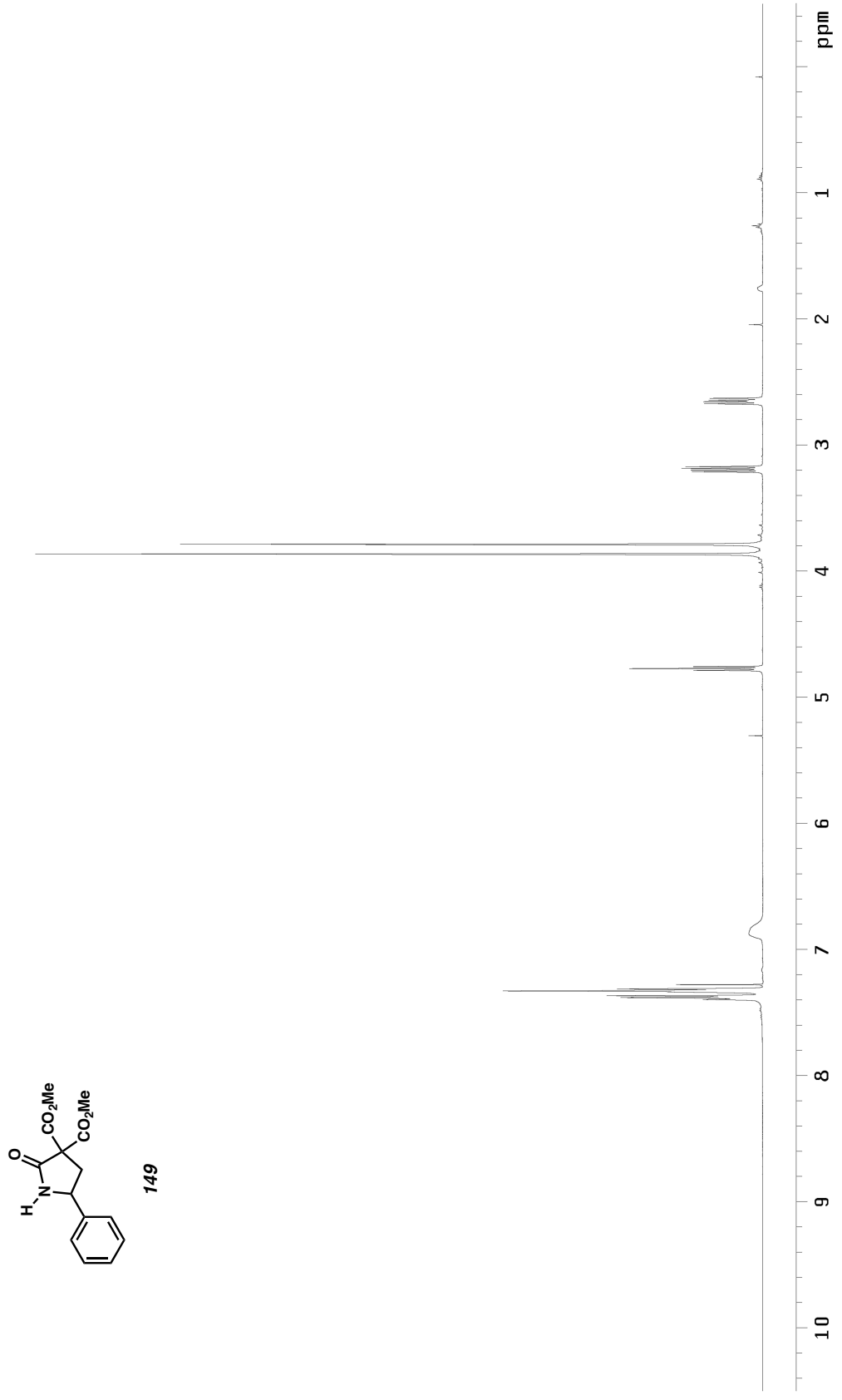


Figure A3.22 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **149**.

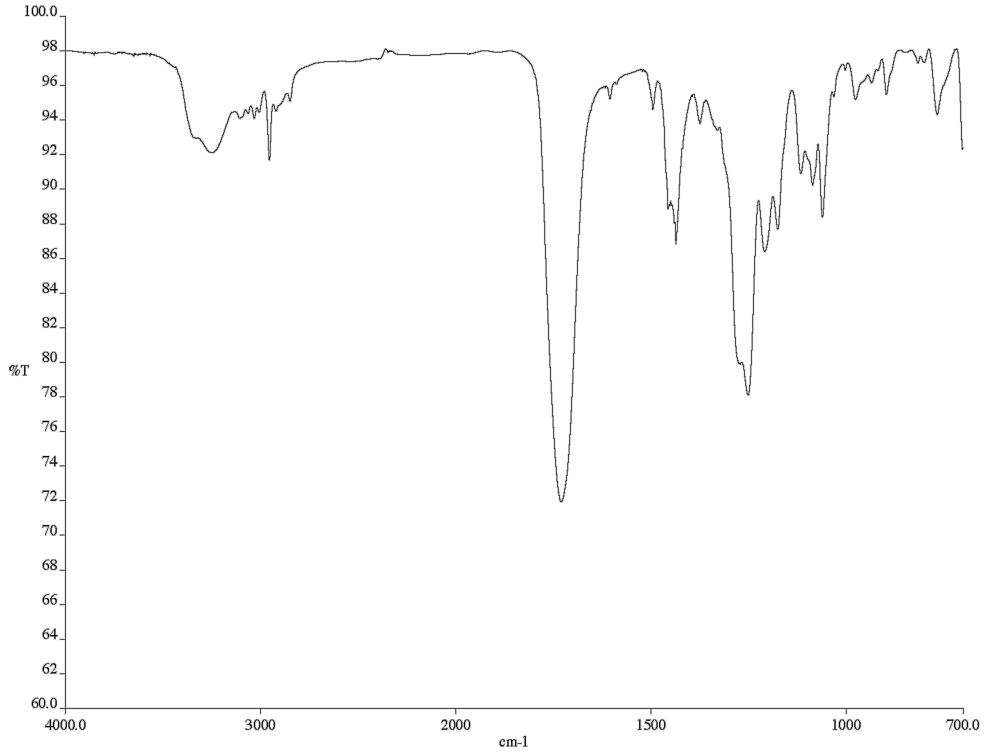


Figure A3.23 Infrared spectrum (thin film/NaCl) of compound **149**.

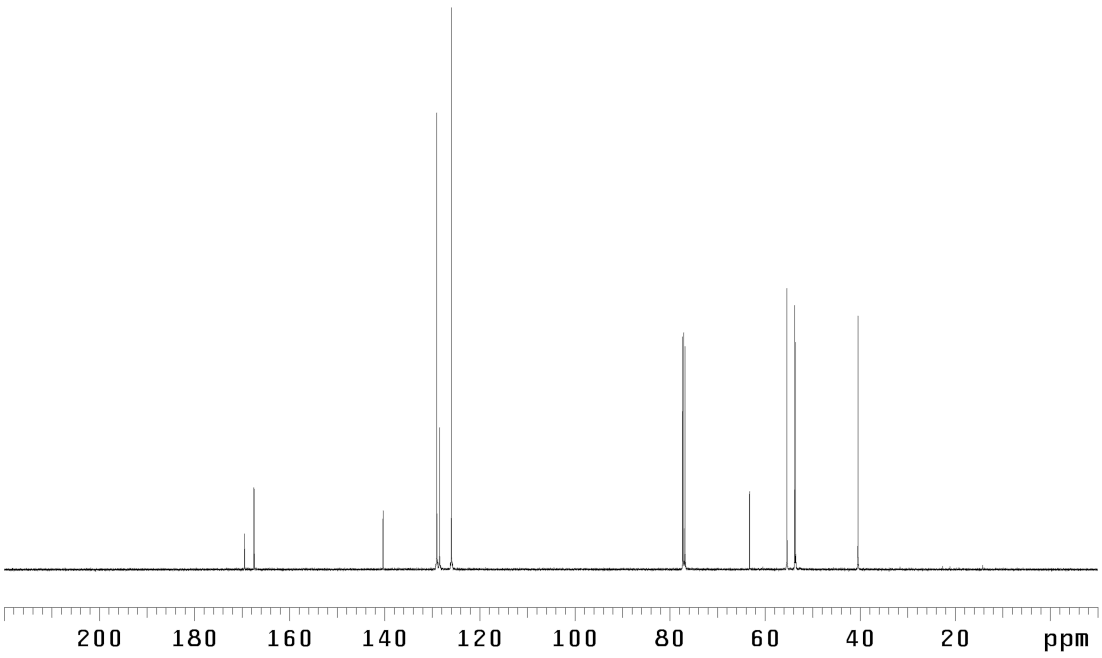


Figure A3.24 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **149**.

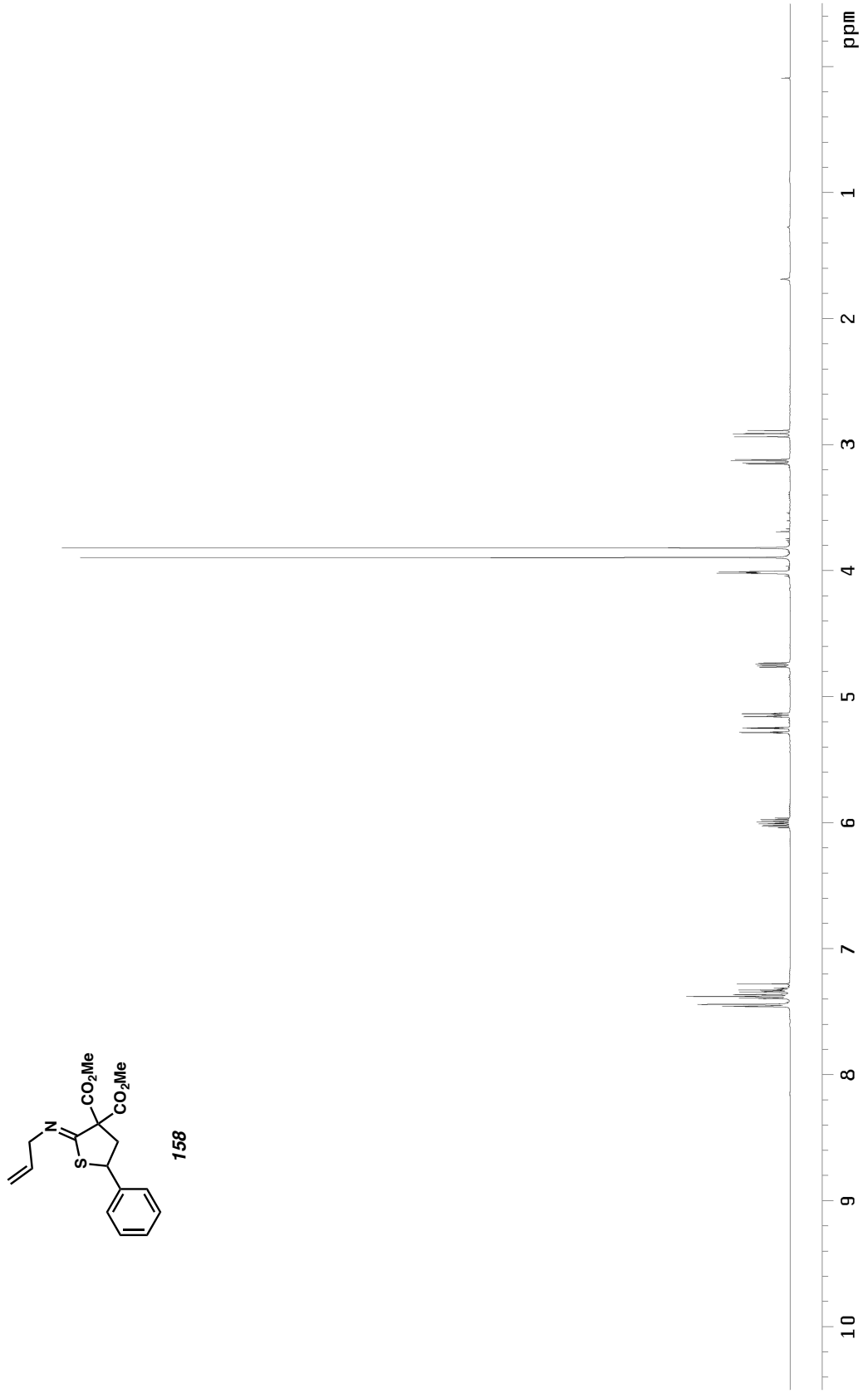


Figure A3.25 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **158**.

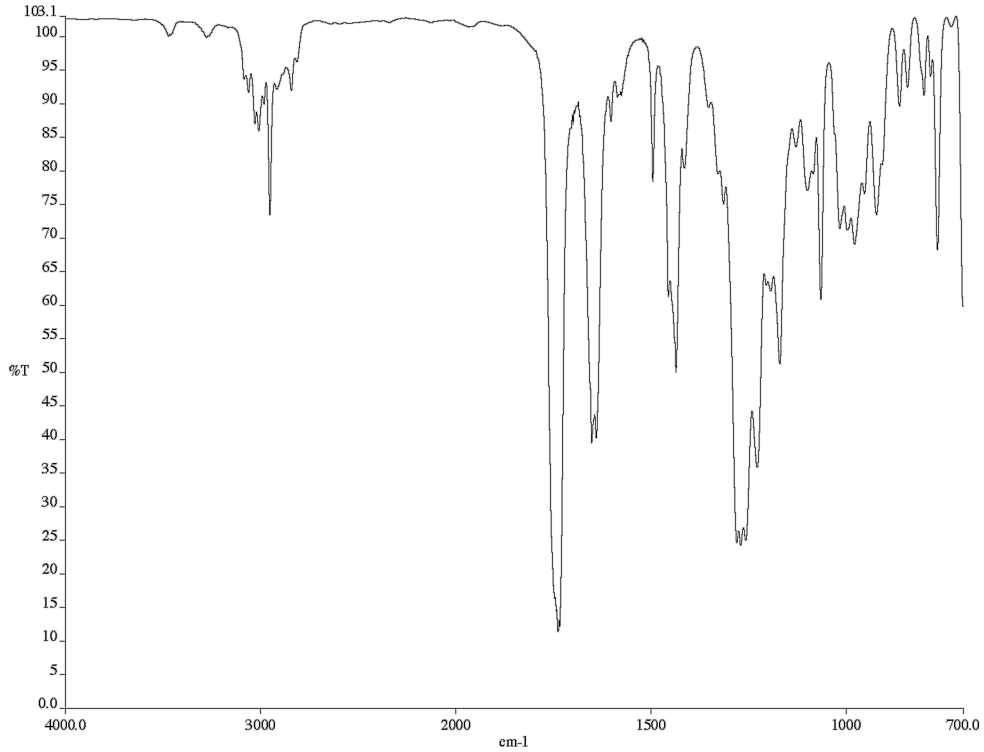


Figure A3.26 Infrared spectrum (thin film/NaCl) of compound **158**.

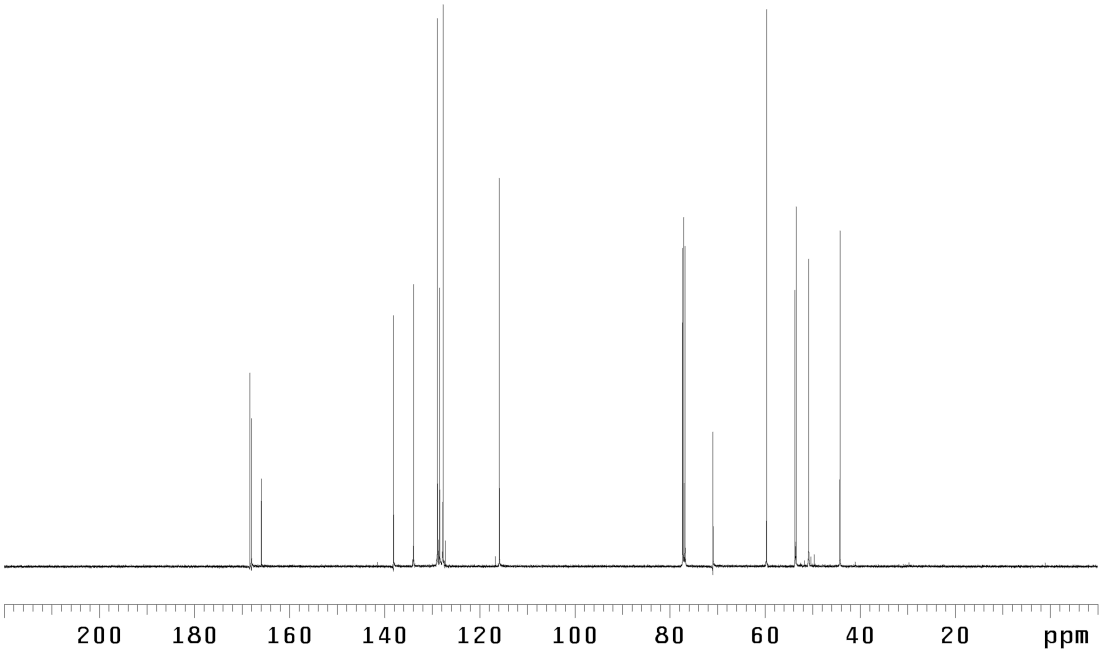


Figure A3.27 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **158**.

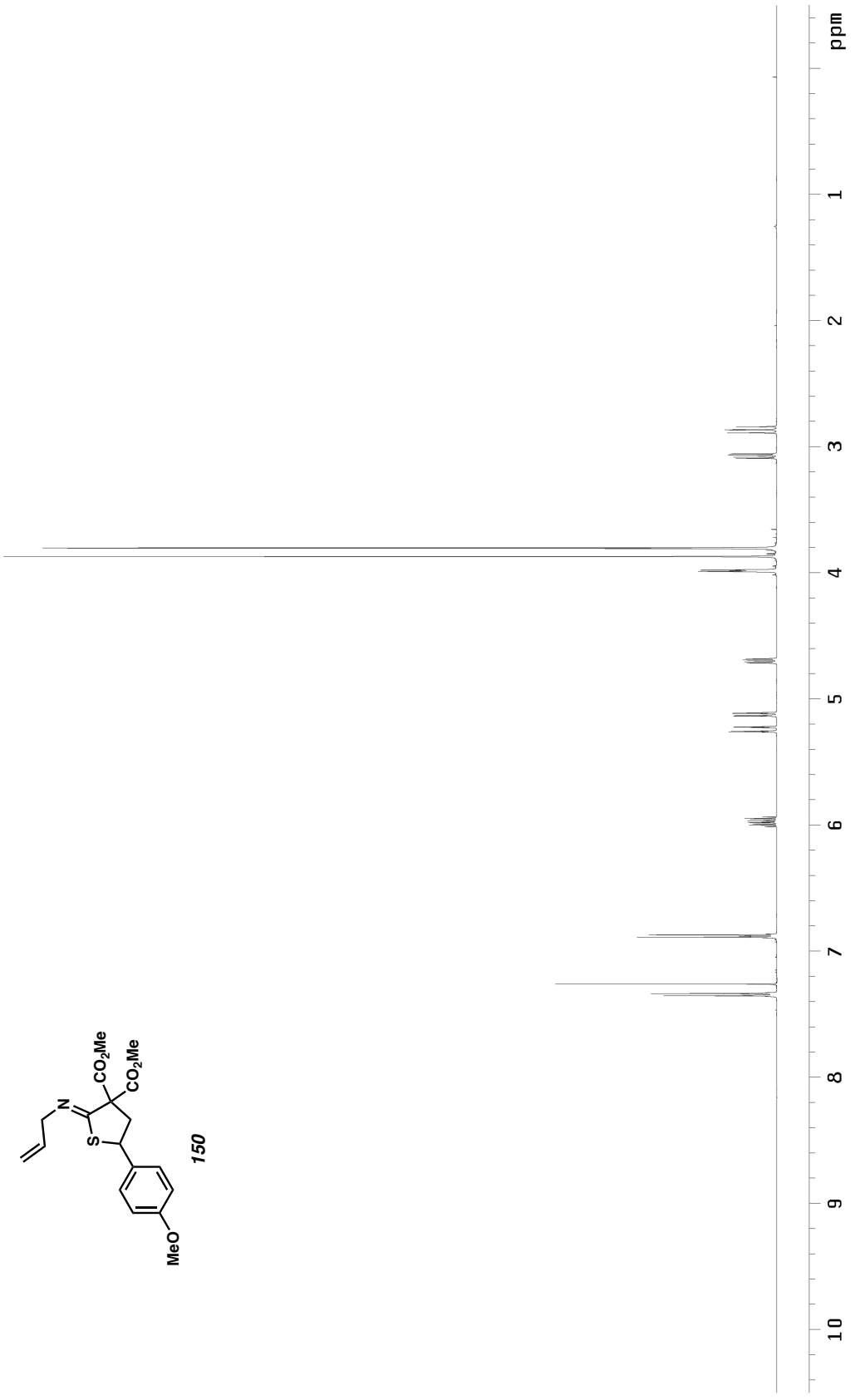


Figure A3.28 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **158**.

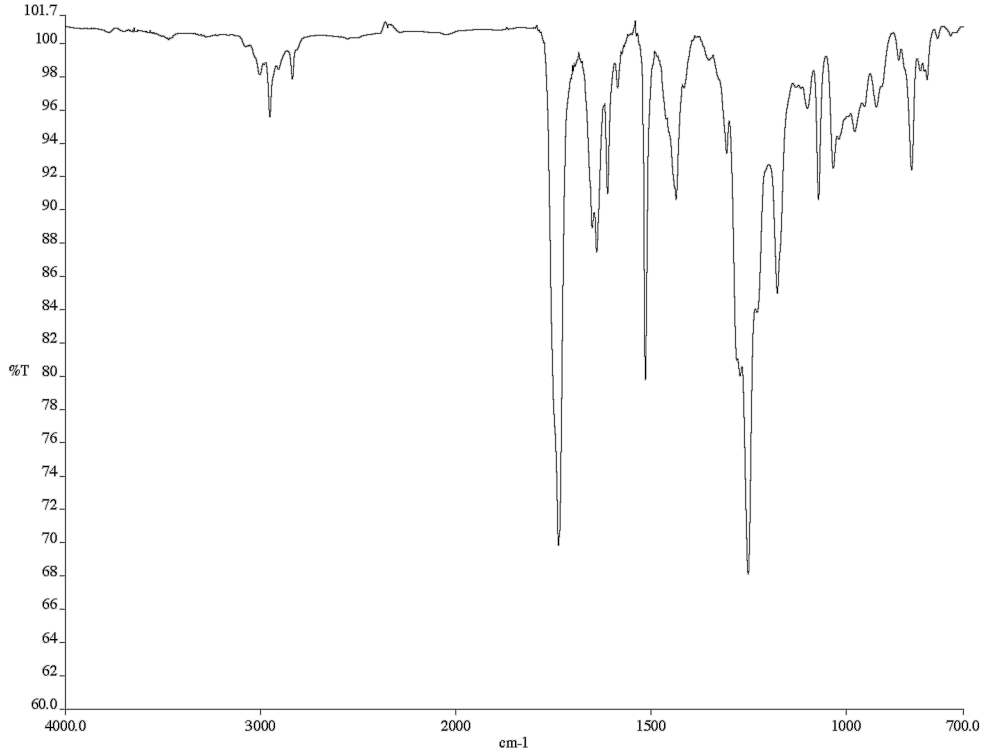


Figure A3.29 Infrared spectrum (thin film/NaCl) of compound **150**.

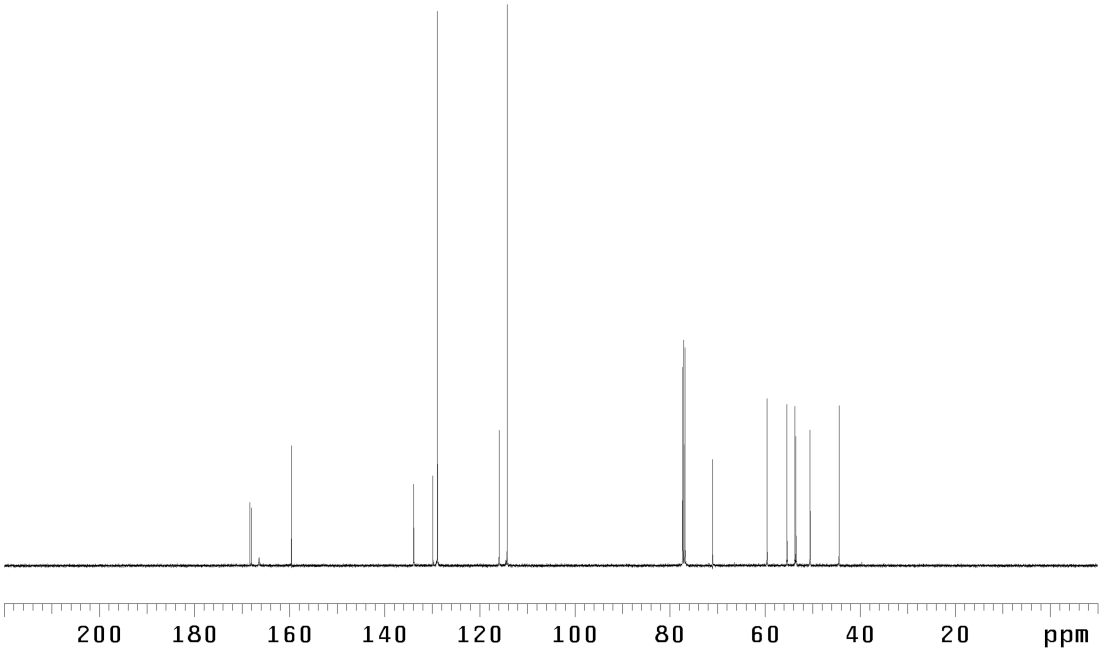


Figure A3.30 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **150**.

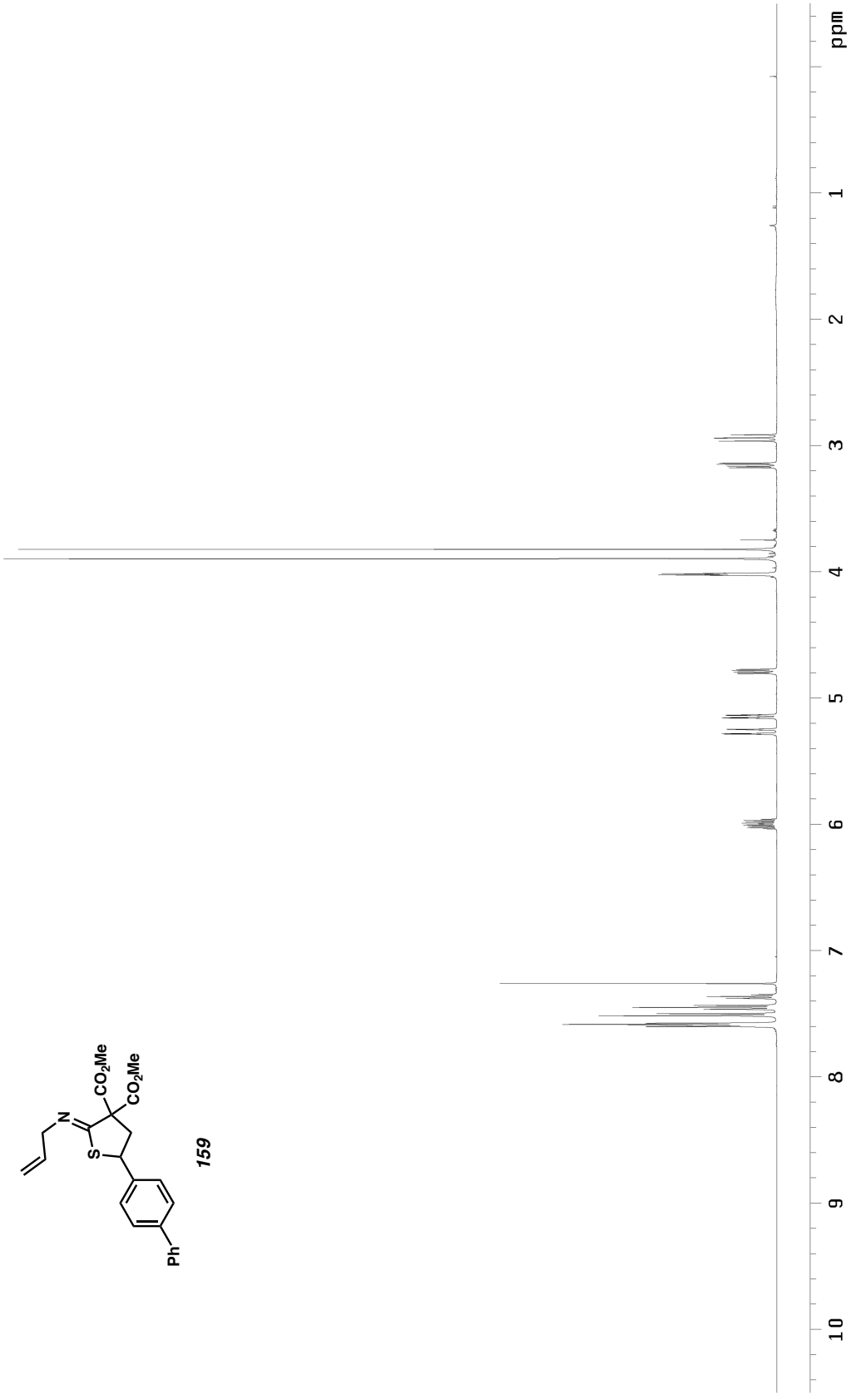


Figure A3.31 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **159**.

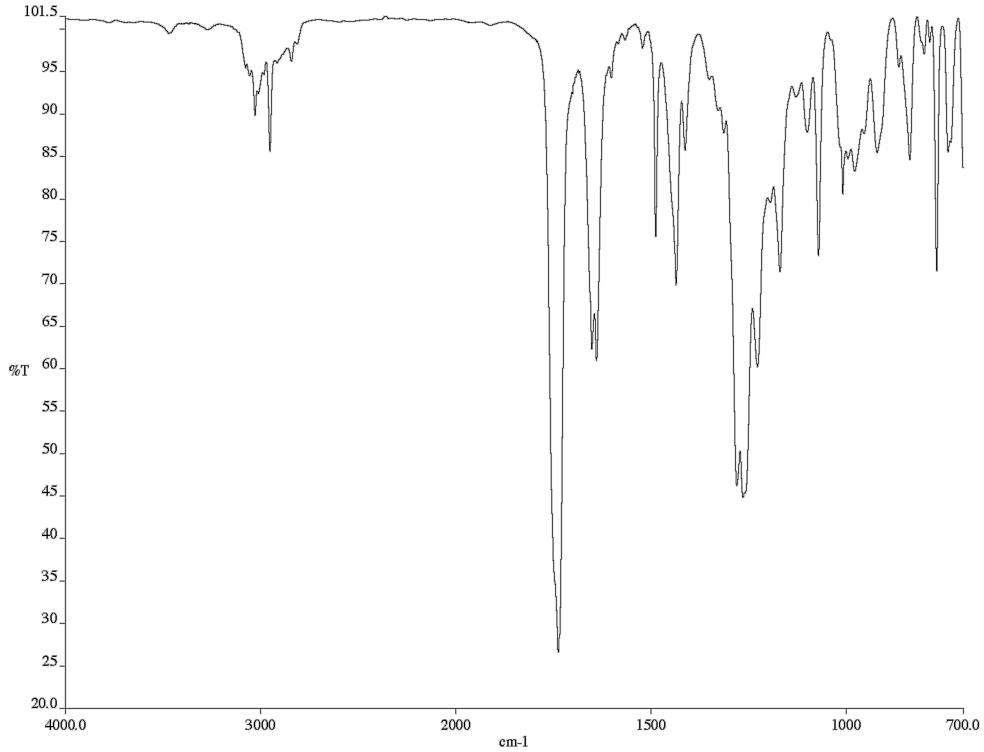


Figure A3.32 Infrared spectrum (thin film/NaCl) of compound **159**.

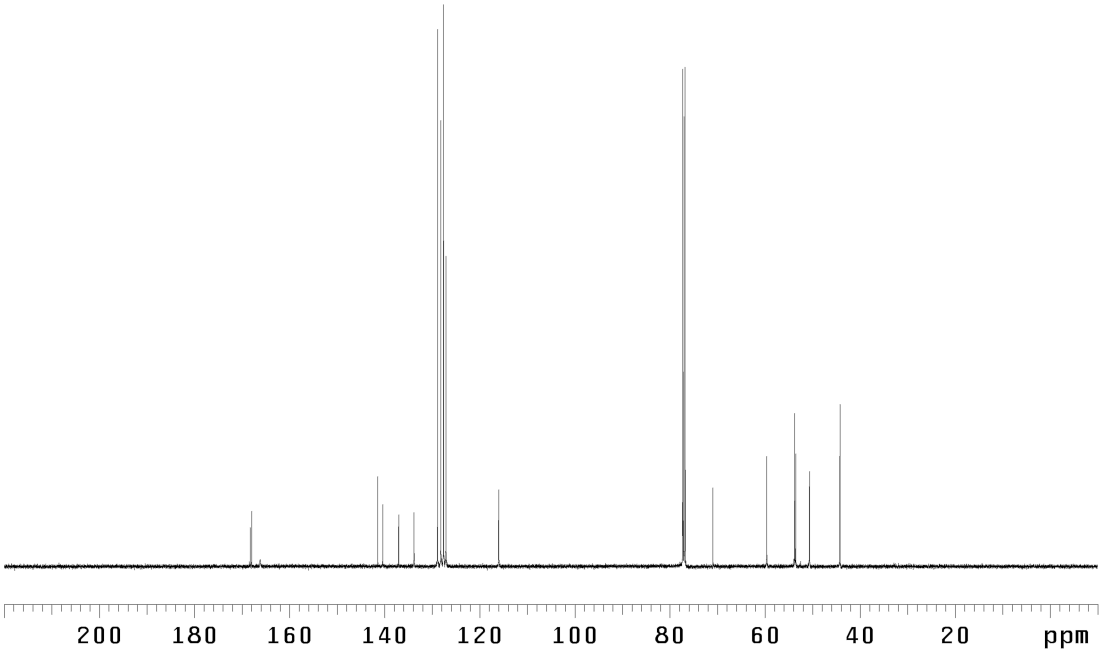


Figure A3.33 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **159**.

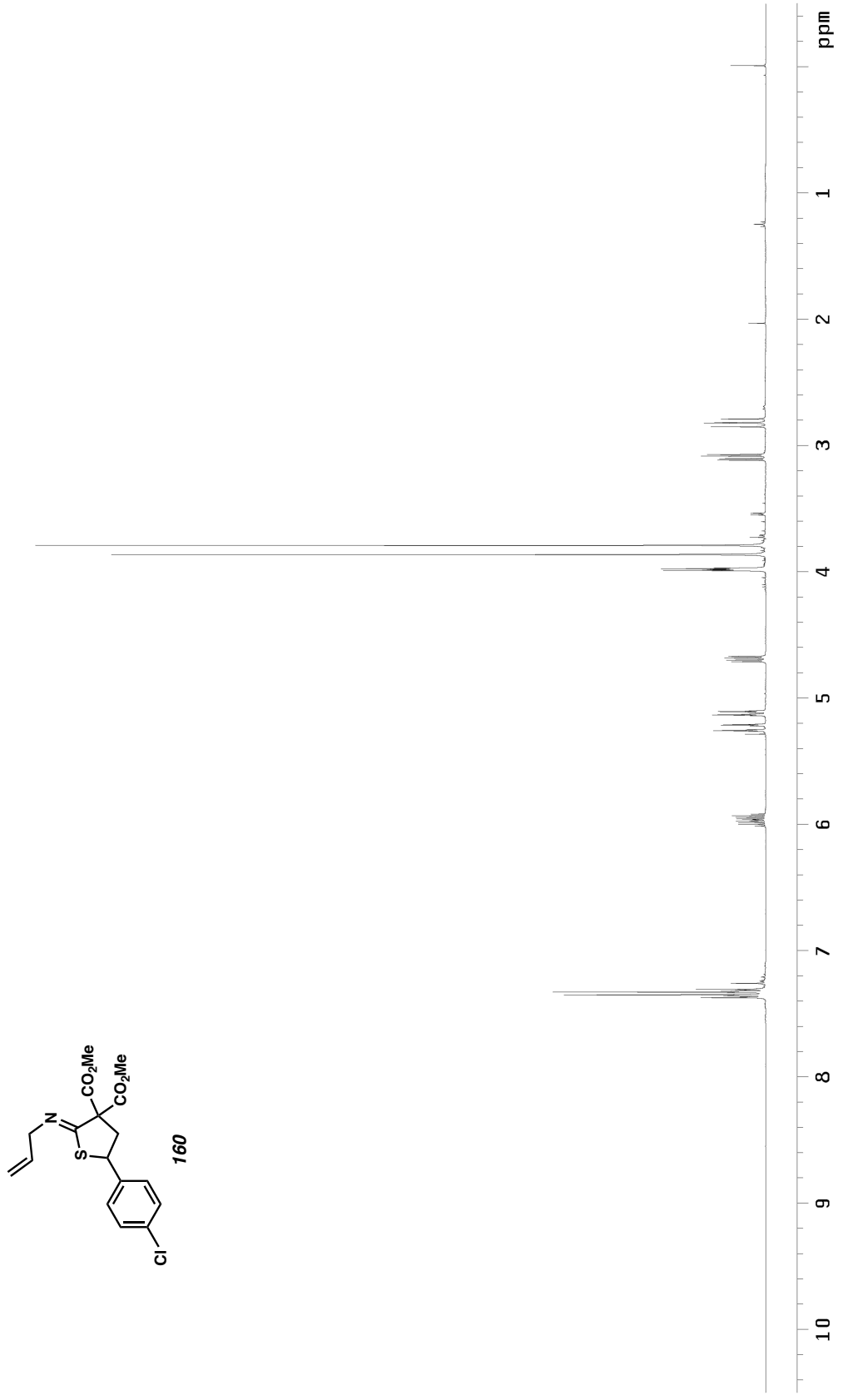


Figure A3.34 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **160**.

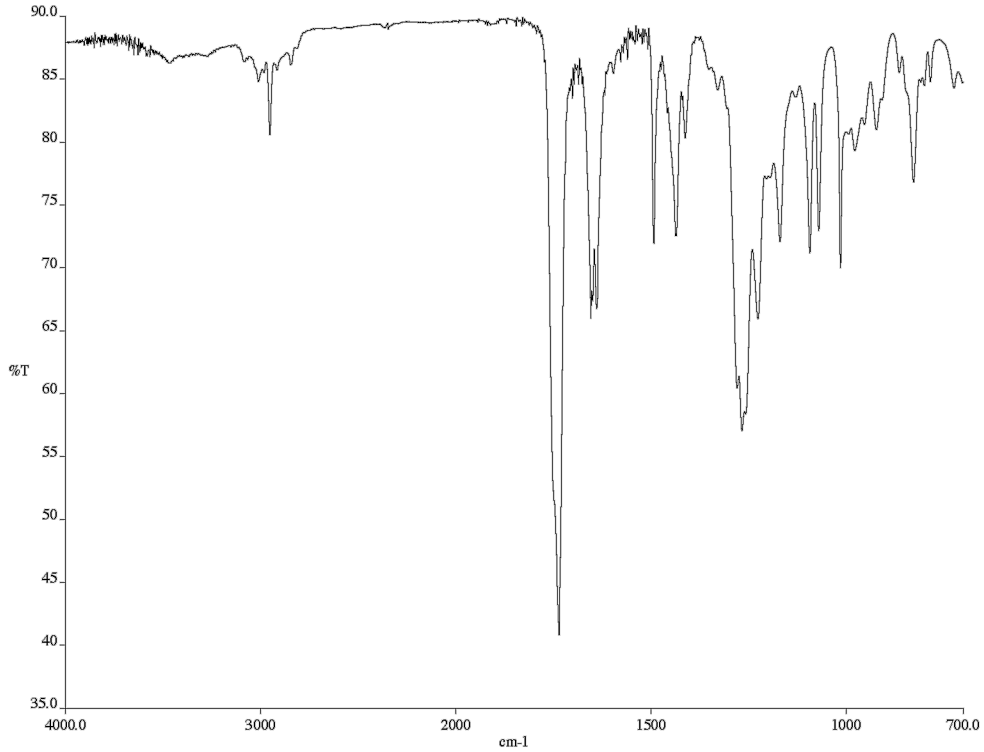


Figure A3.35 Infrared spectrum (thin film/NaCl) of compound **160**.

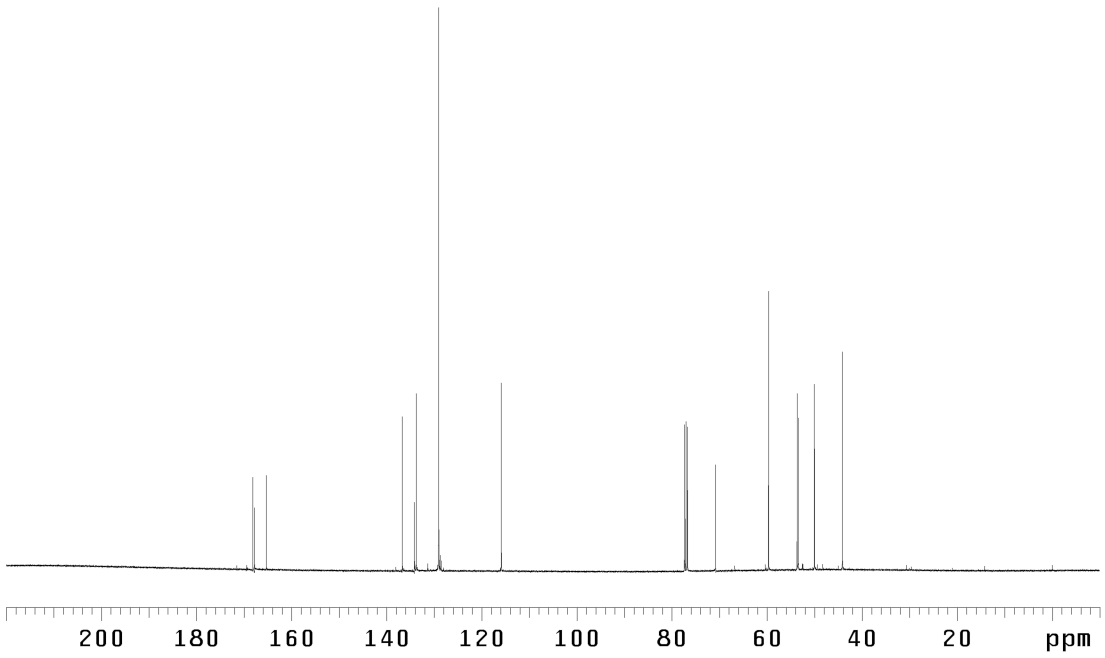


Figure A3.36 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **160**.

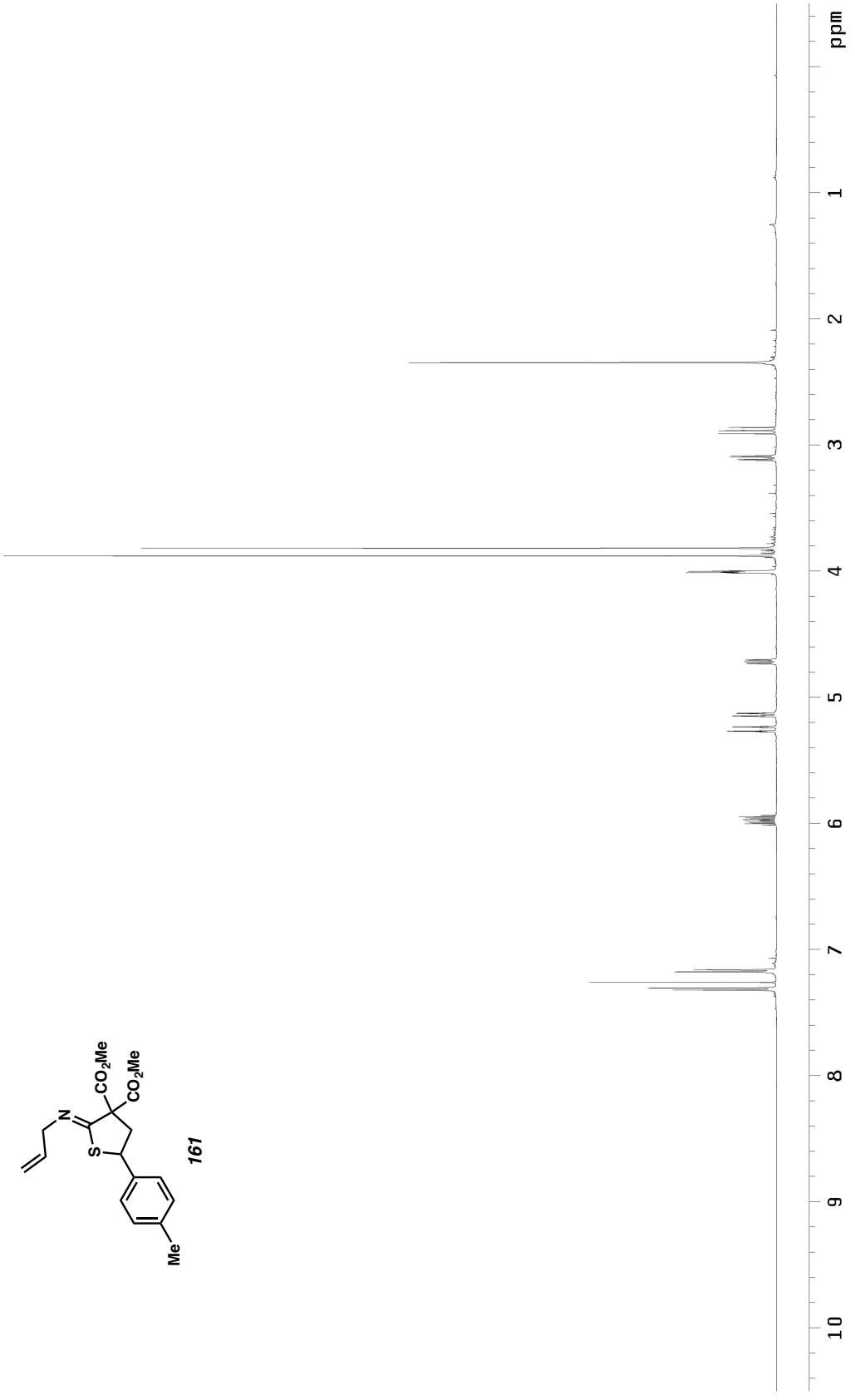


Figure A3.37 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **161**.

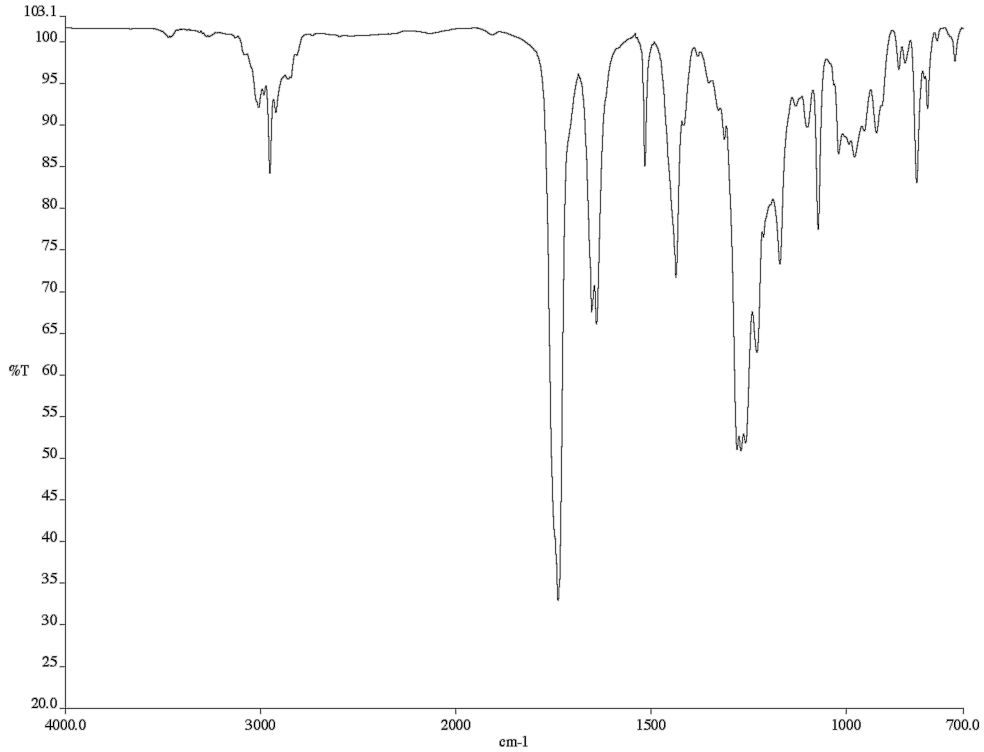


Figure A3.38 Infrared spectrum (thin film/NaCl) of compound **161**.

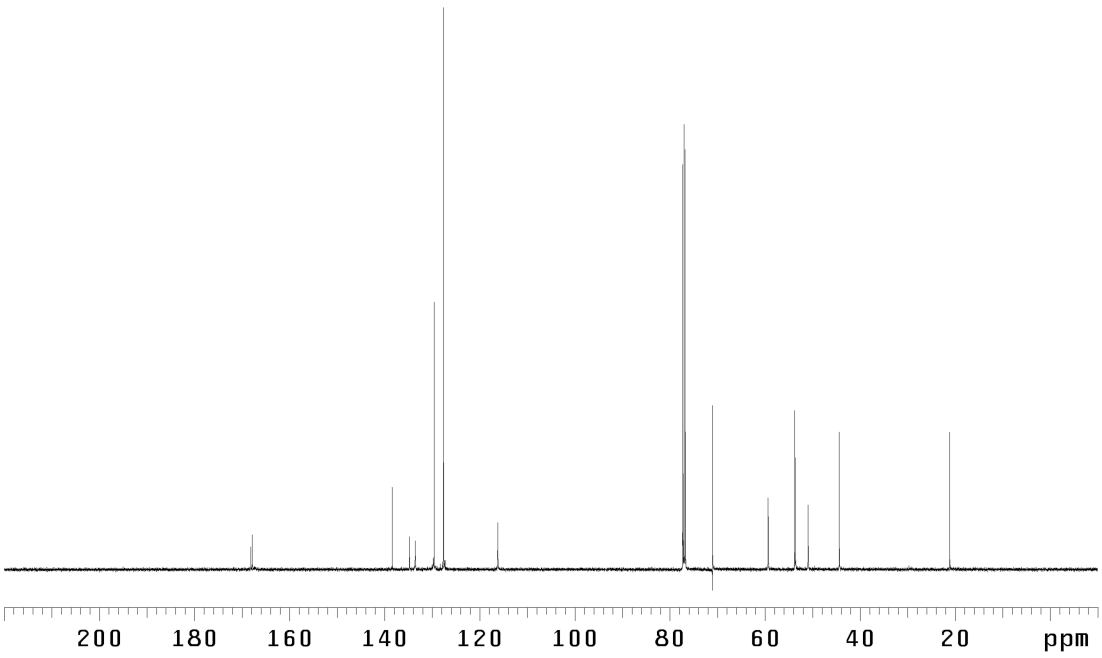


Figure A3.39 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **161**.

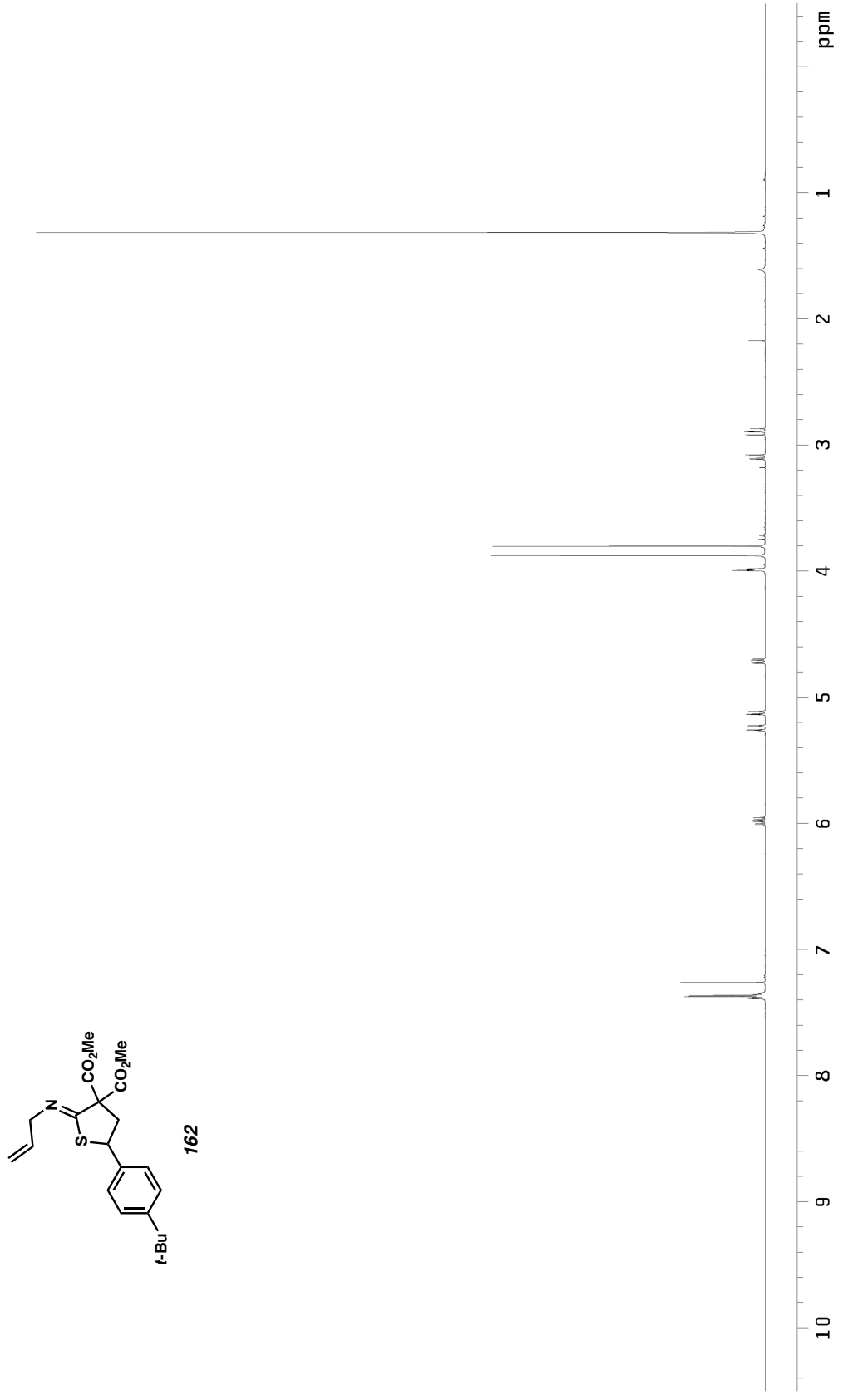


Figure A3.40 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **162**.

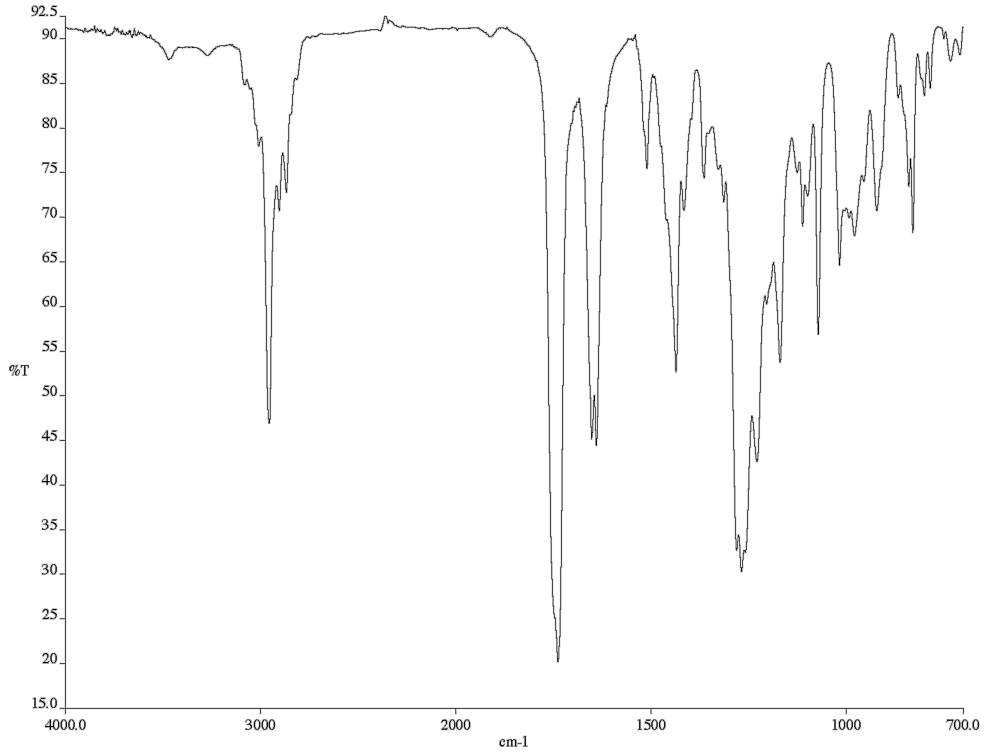


Figure A3.41 Infrared spectrum (thin film/NaCl) of compound **162**.

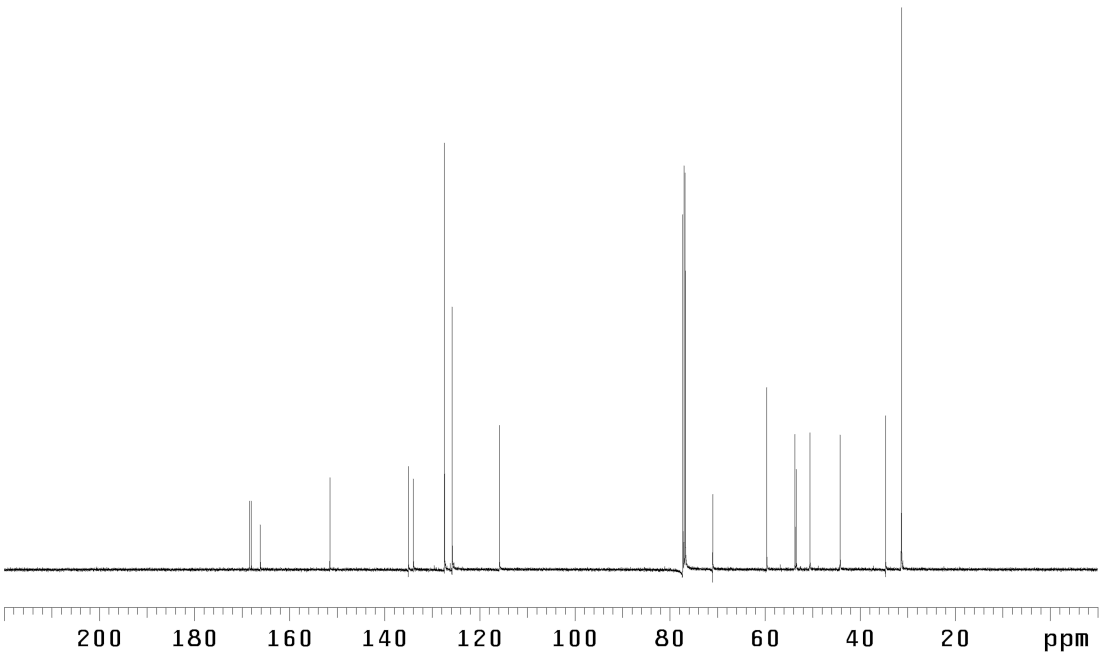


Figure A3.42 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **162**.

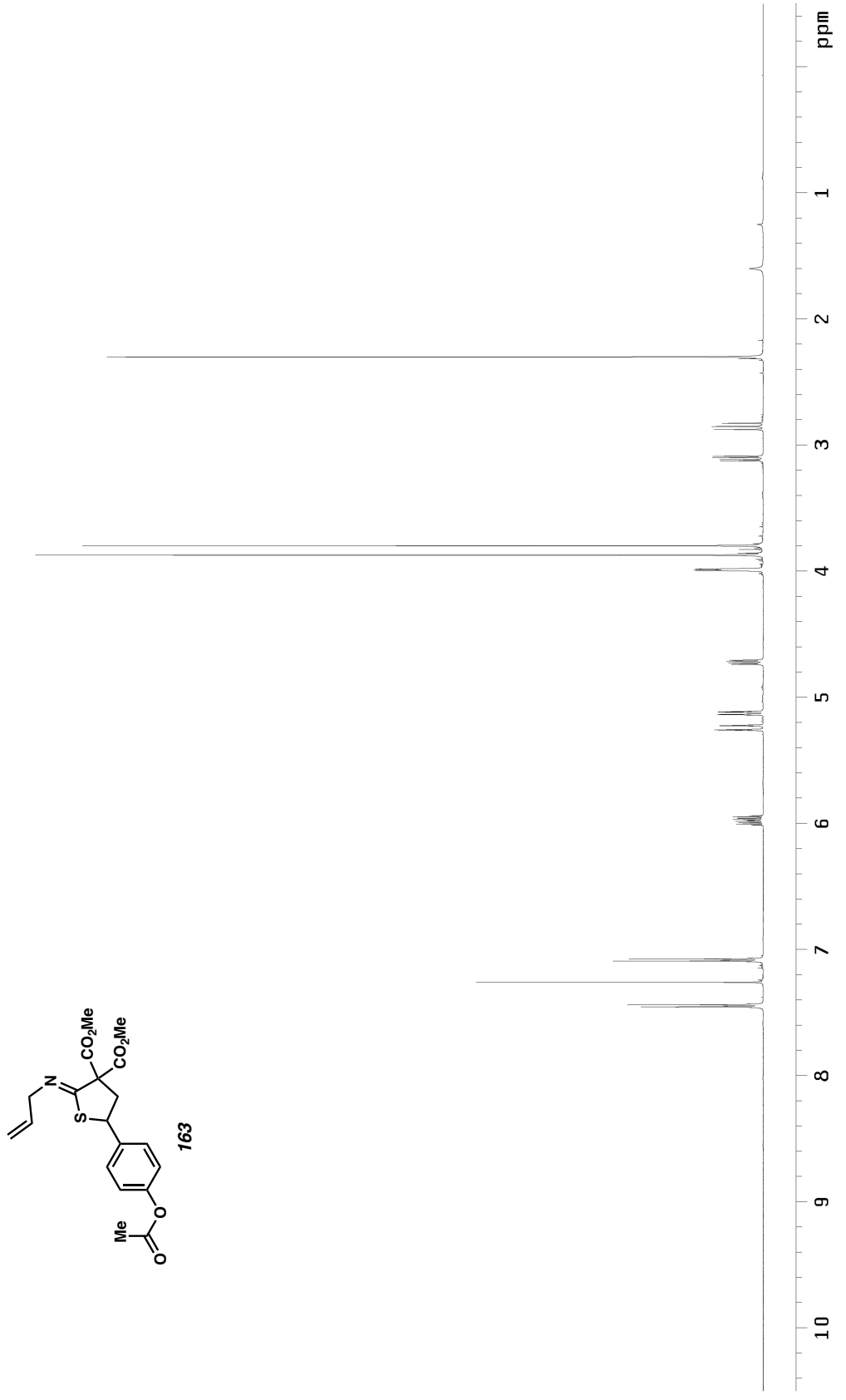


Figure A3.43 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **163**.

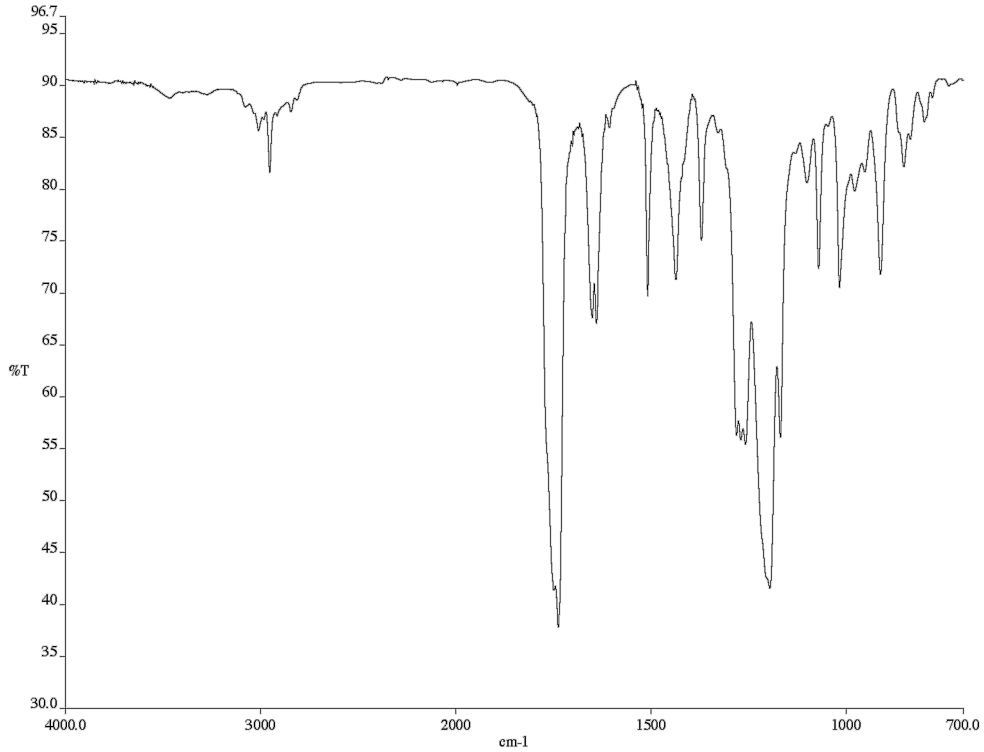


Figure A3.44 Infrared spectrum (thin film/NaCl) of compound **163**.

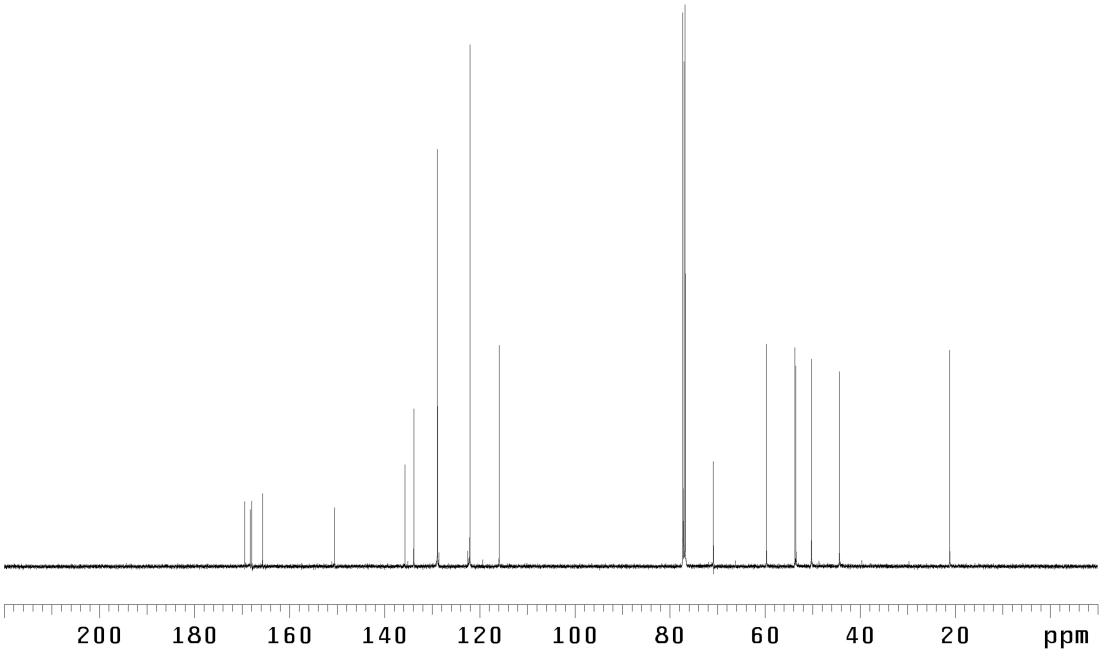


Figure A3.45 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **163**.

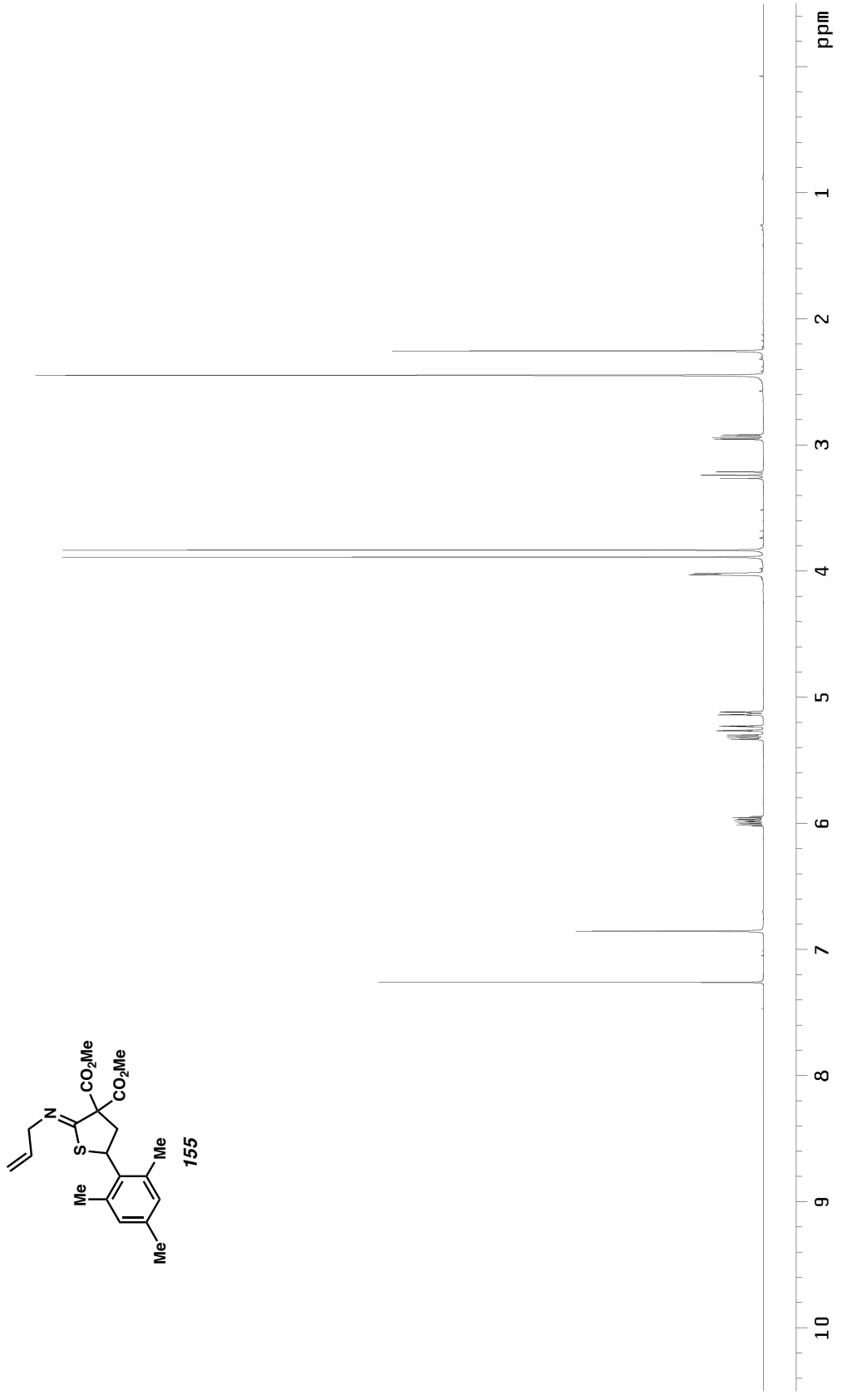


Figure A3.46 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **155**.

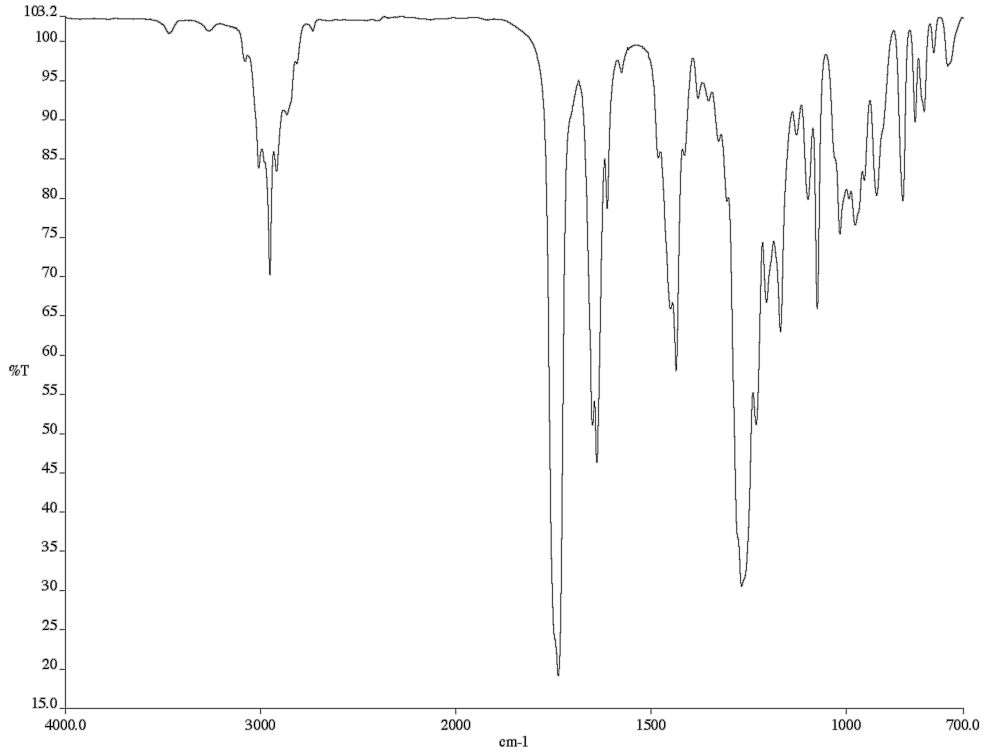


Figure A3.47 Infrared spectrum (thin film/NaCl) of compound **155**.

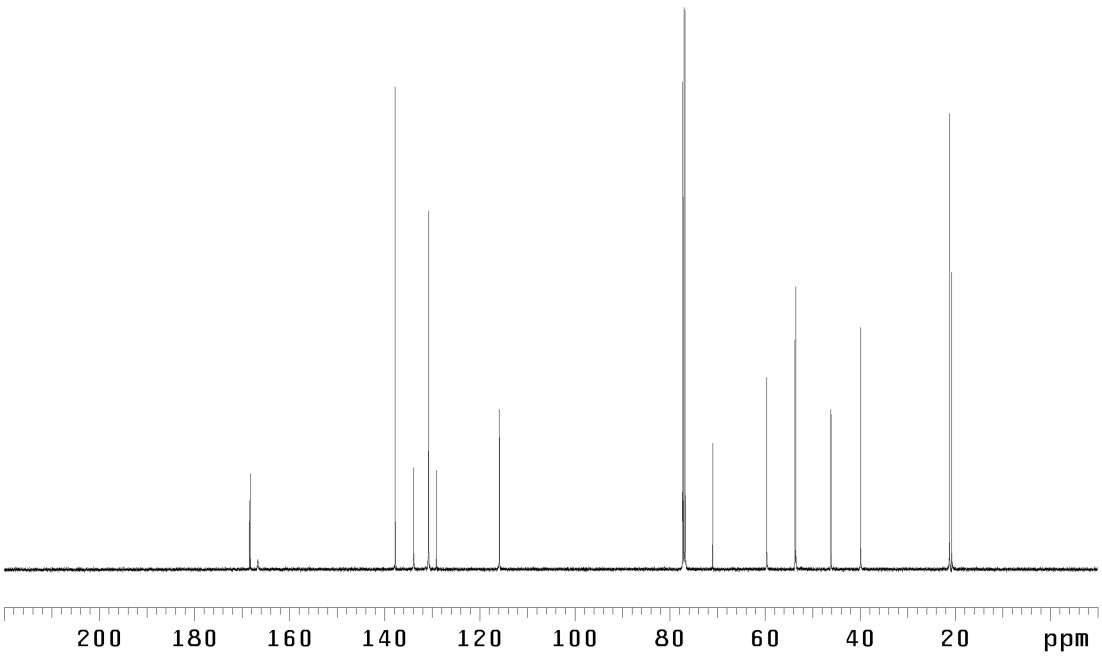


Figure A3.48 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **155**.

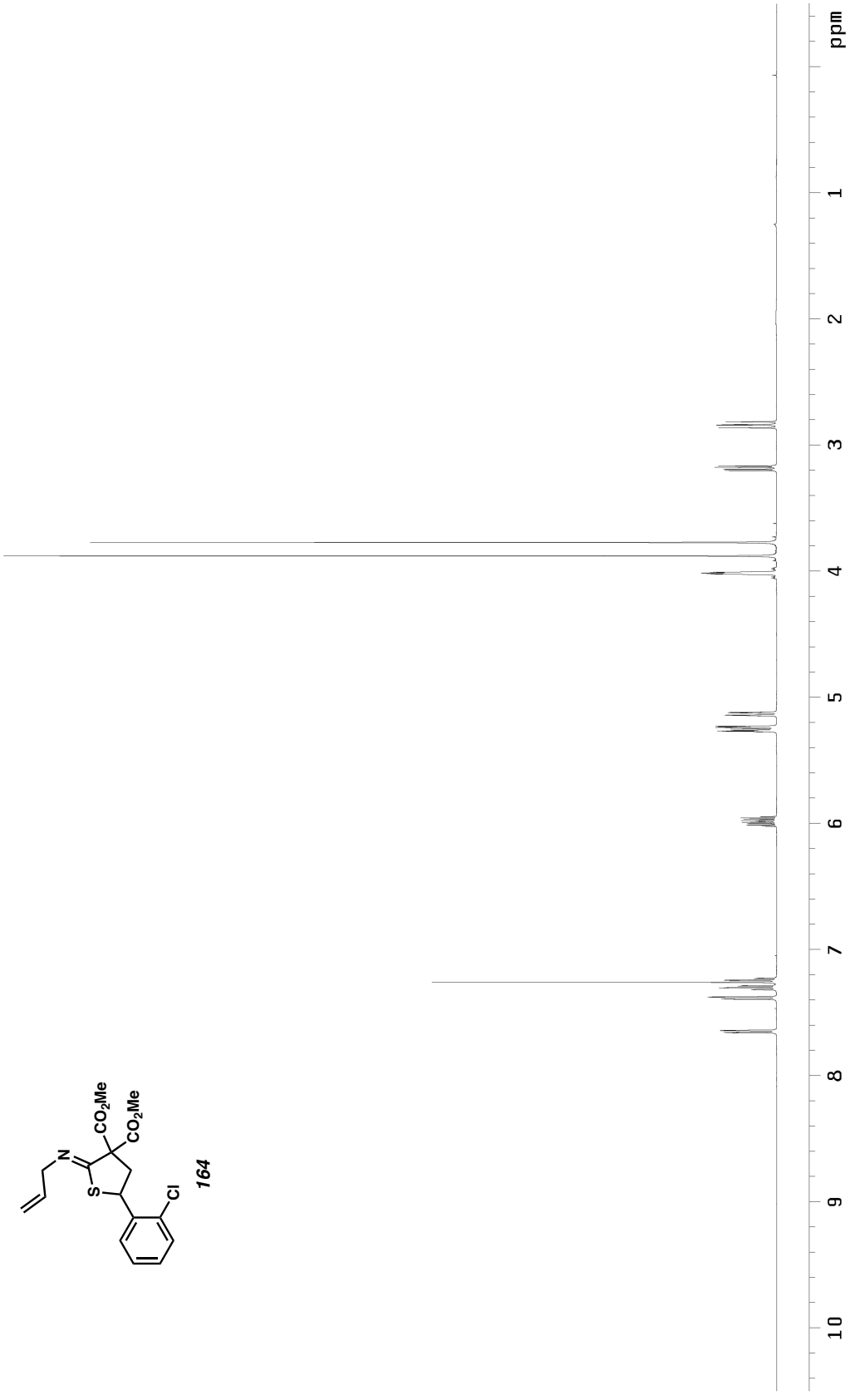


Figure A3.49 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **164**.

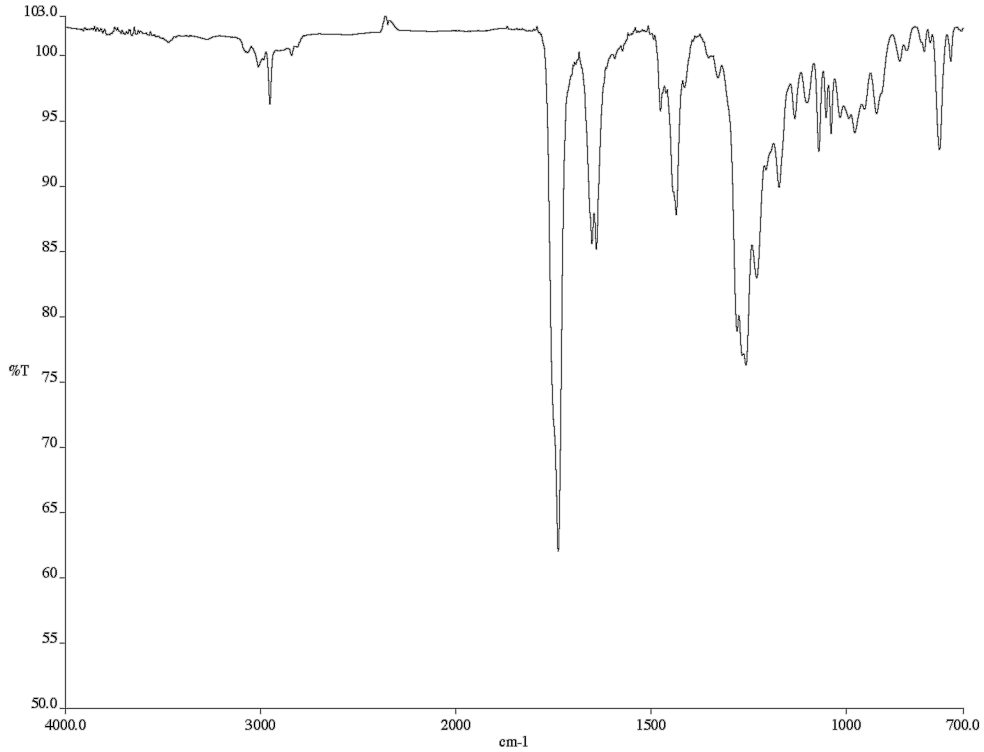


Figure A3.50 Infrared spectrum (thin film/NaCl) of compound **164**.

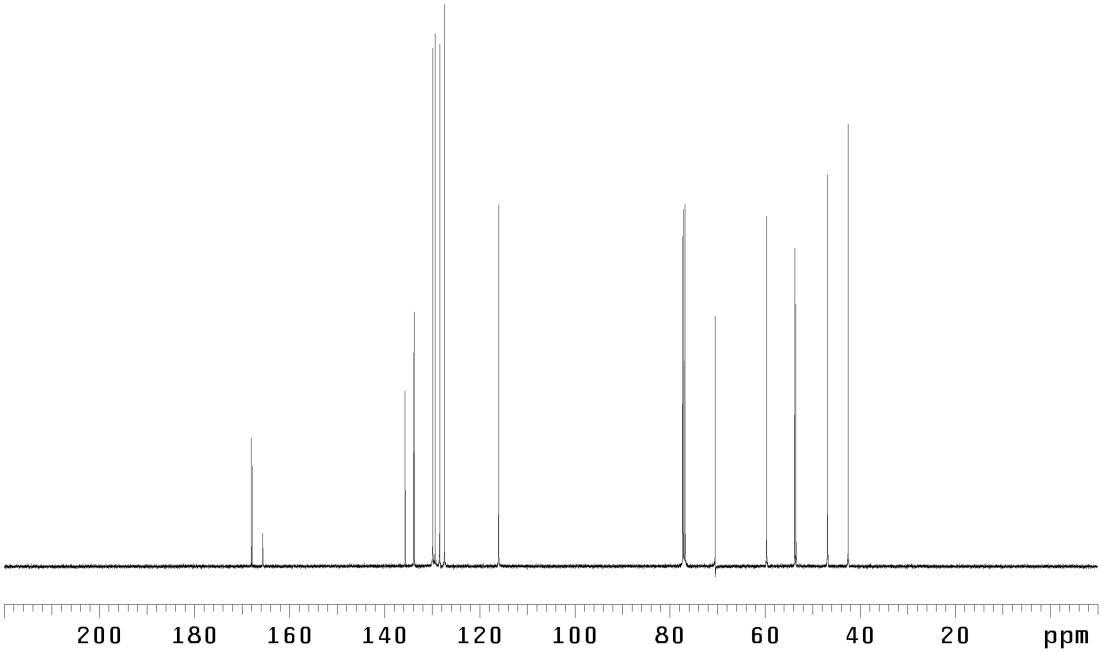


Figure A3.51 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **164**.

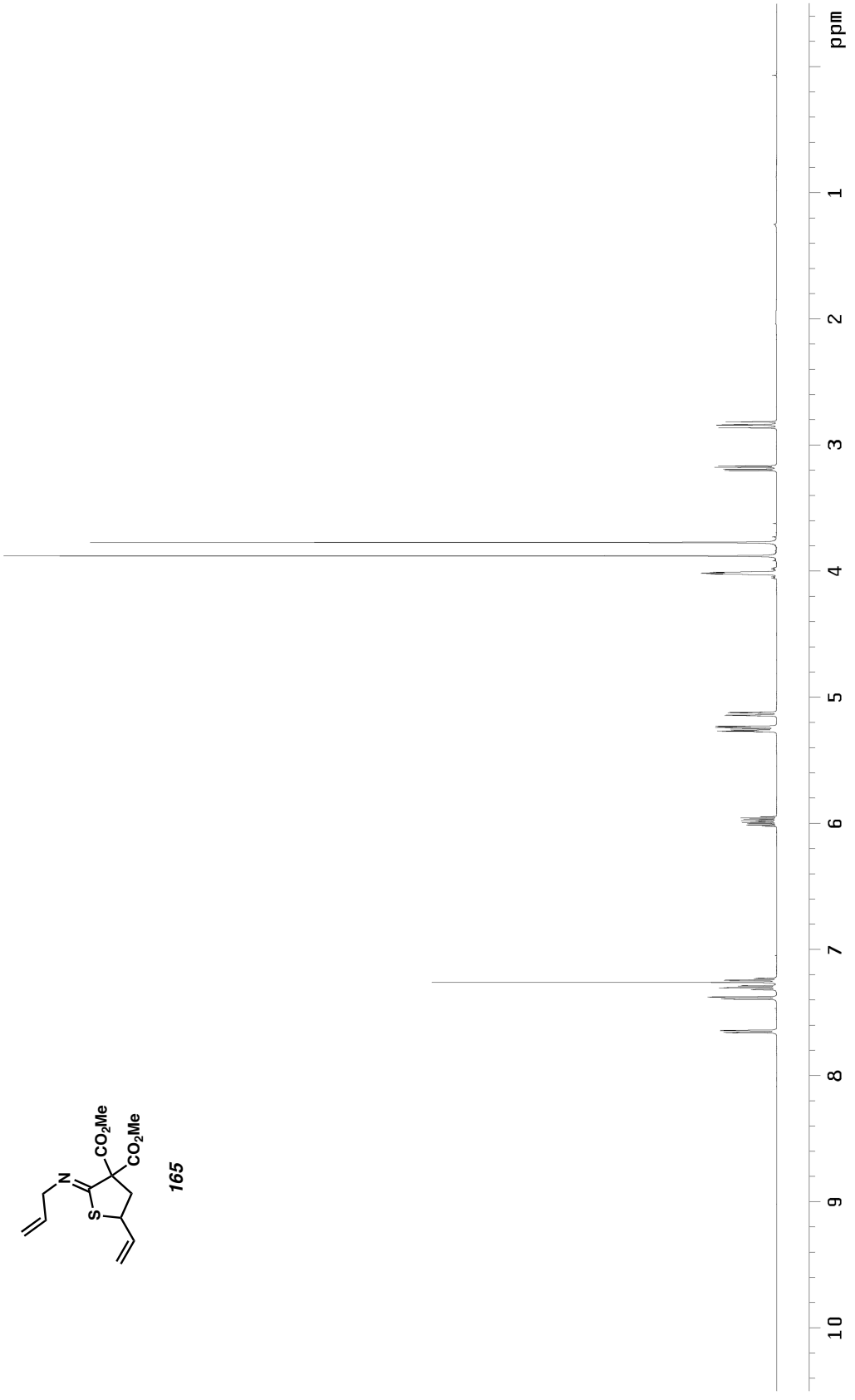


Figure A3.52 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **165**.

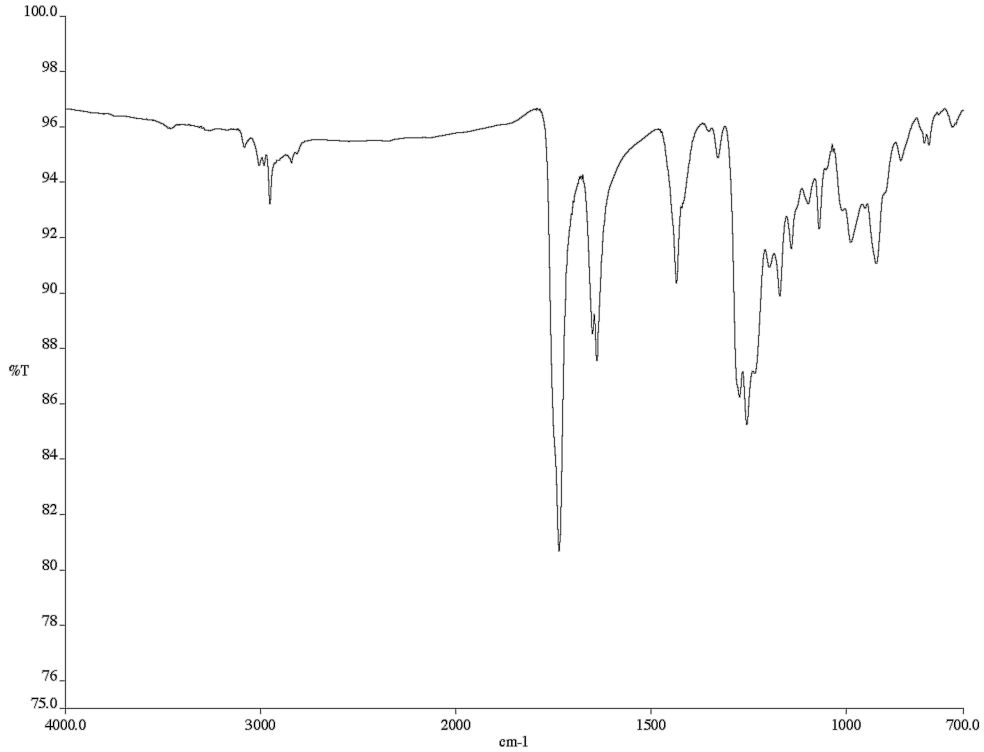


Figure A3.53 Infrared spectrum (thin film/NaCl) of compound **165**.

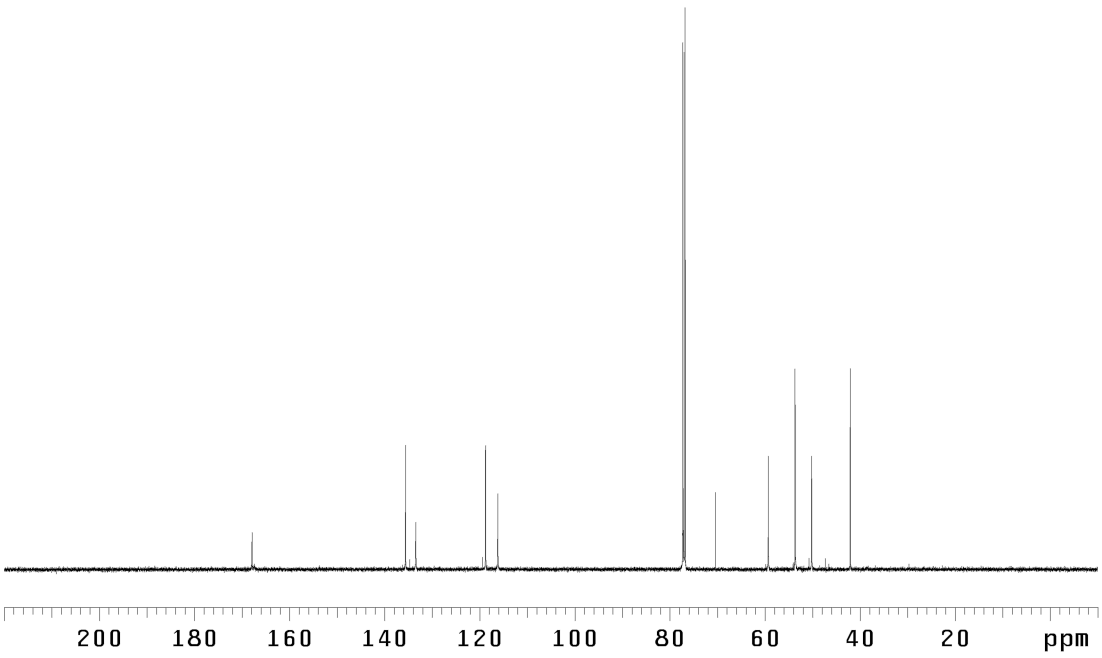


Figure A3.54 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **165**.

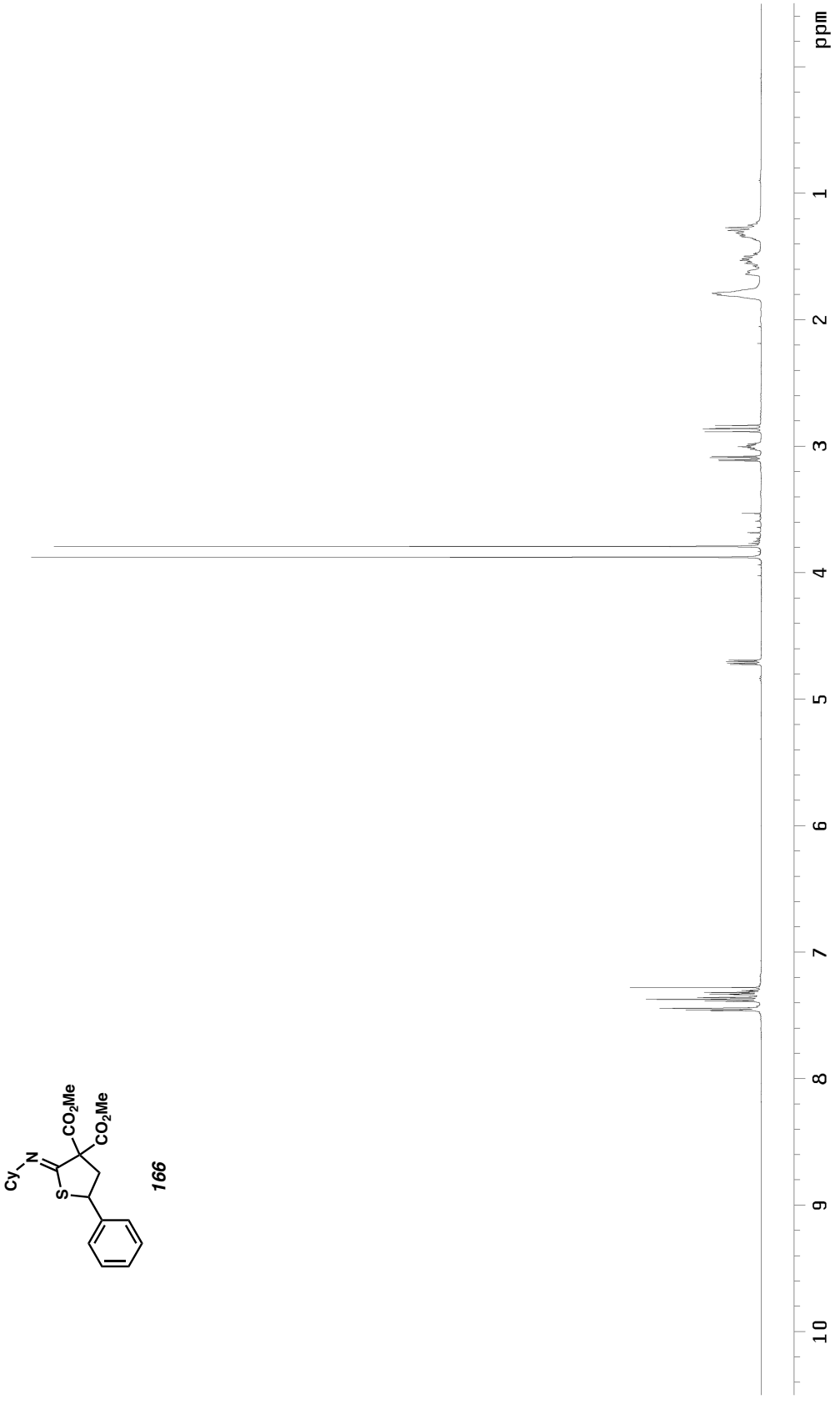


Figure A3.55 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **166**.

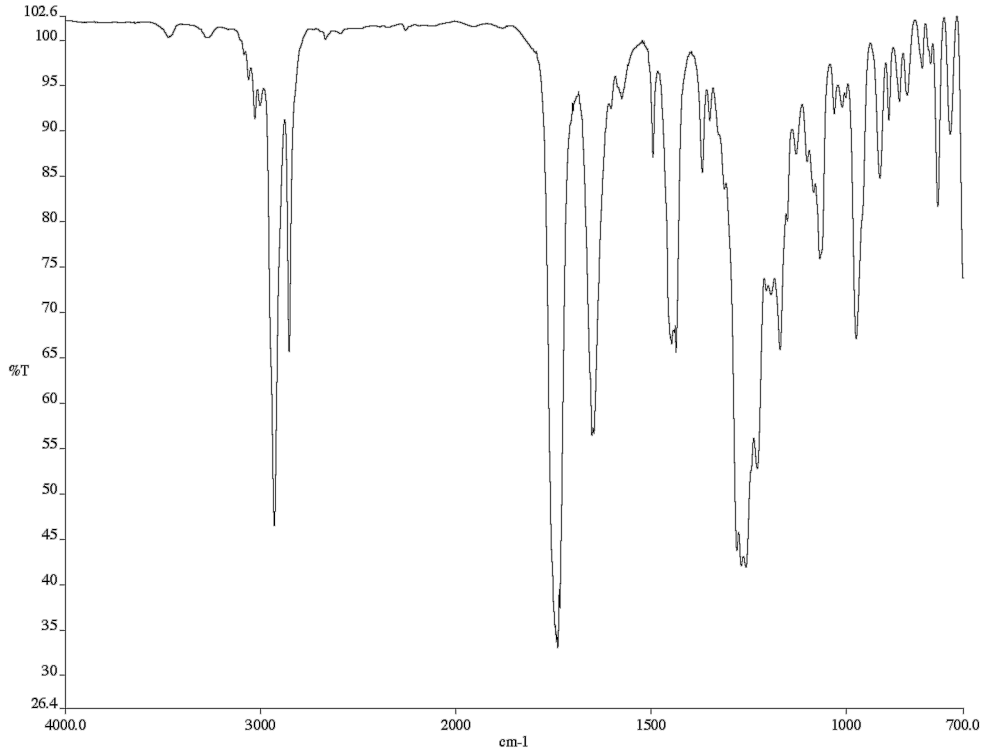


Figure A3.56 Infrared spectrum (thin film/NaCl) of compound **166**.

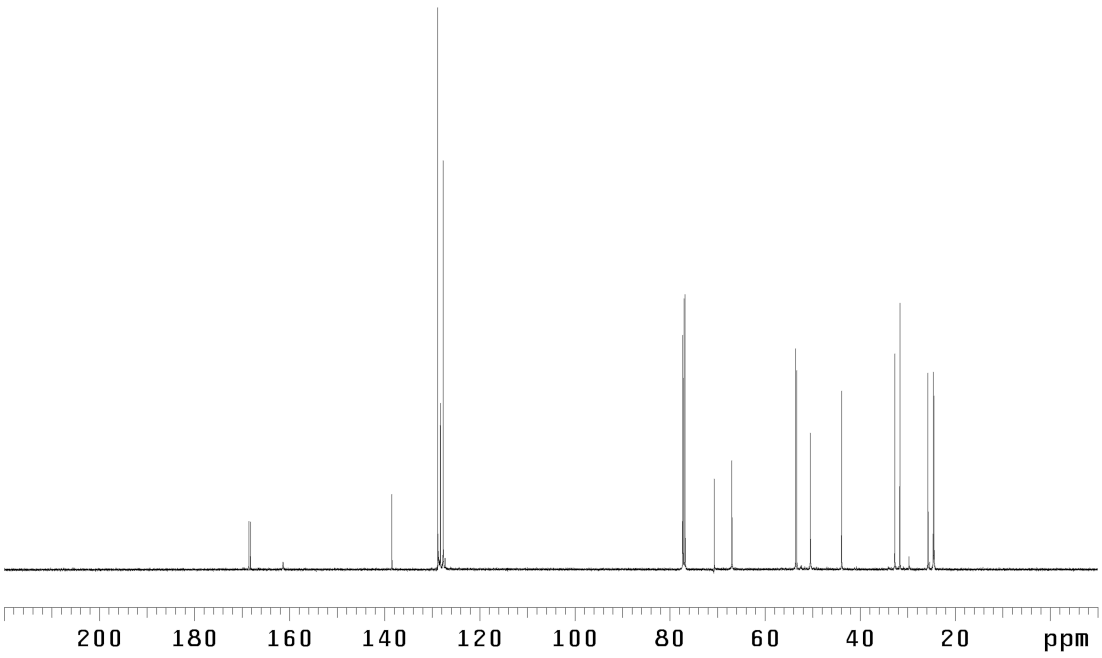


Figure A3.57 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **166**.

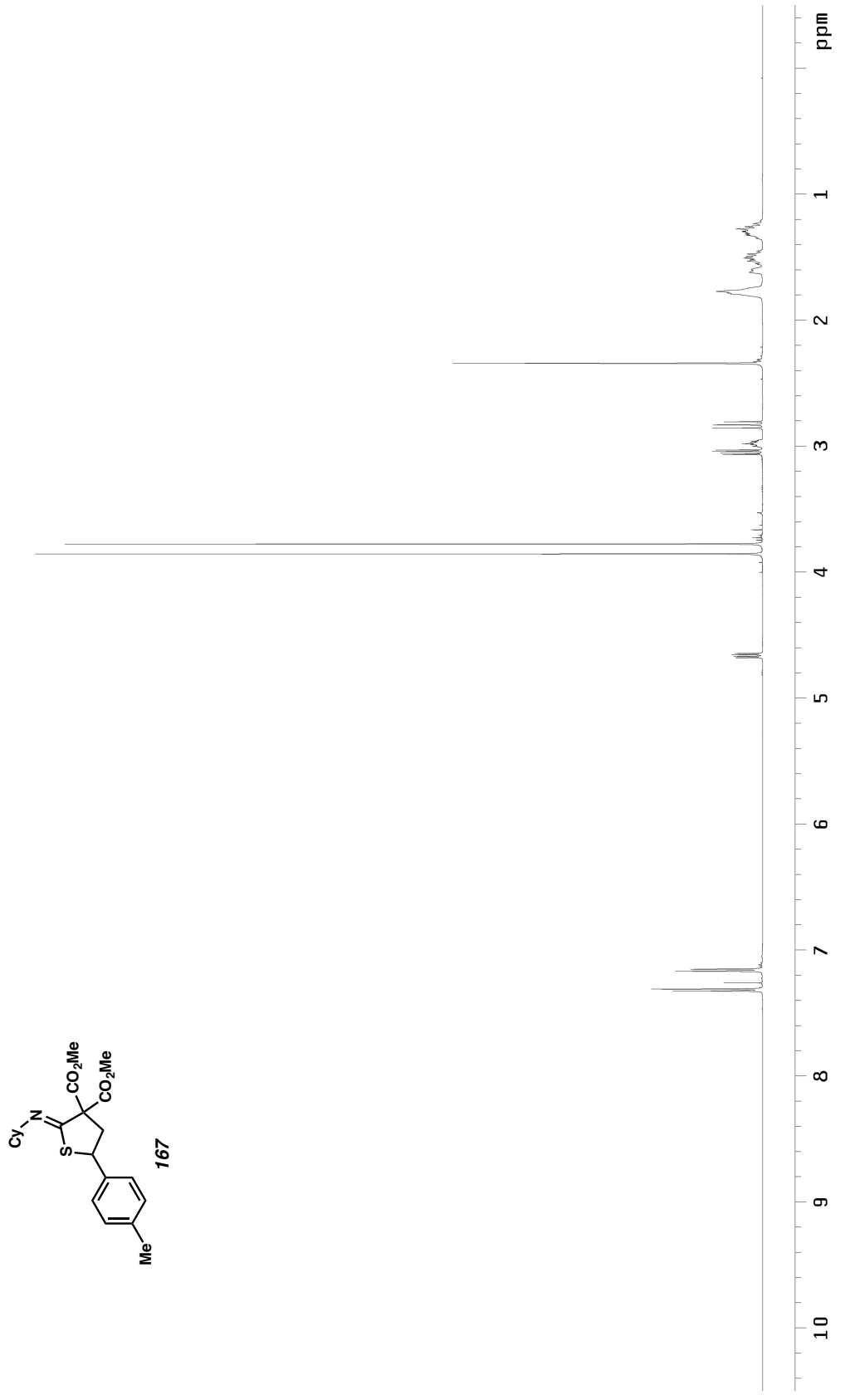


Figure A3.58 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **167**.

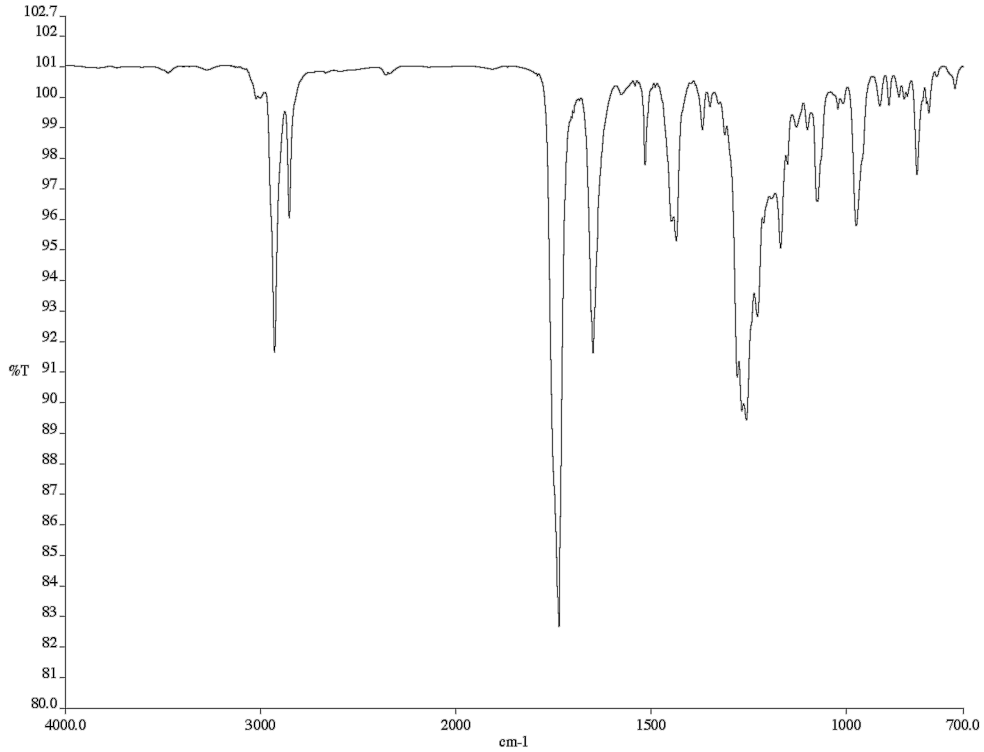


Figure A3.59 Infrared spectrum (thin film/NaCl) of compound **167**.

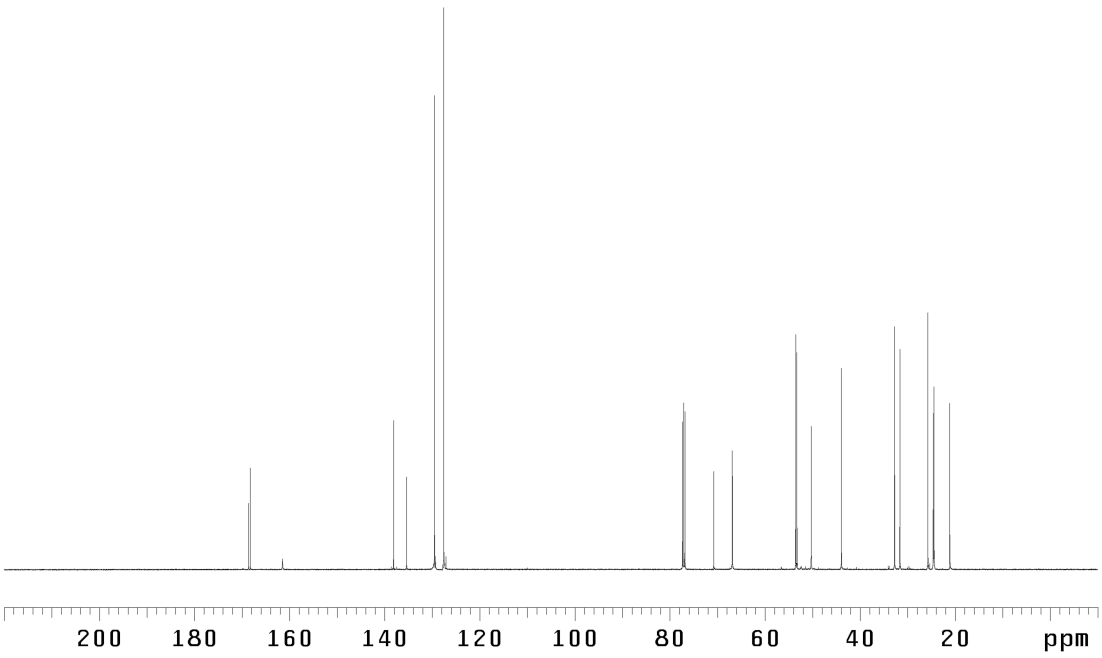


Figure A3.60 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **167**.

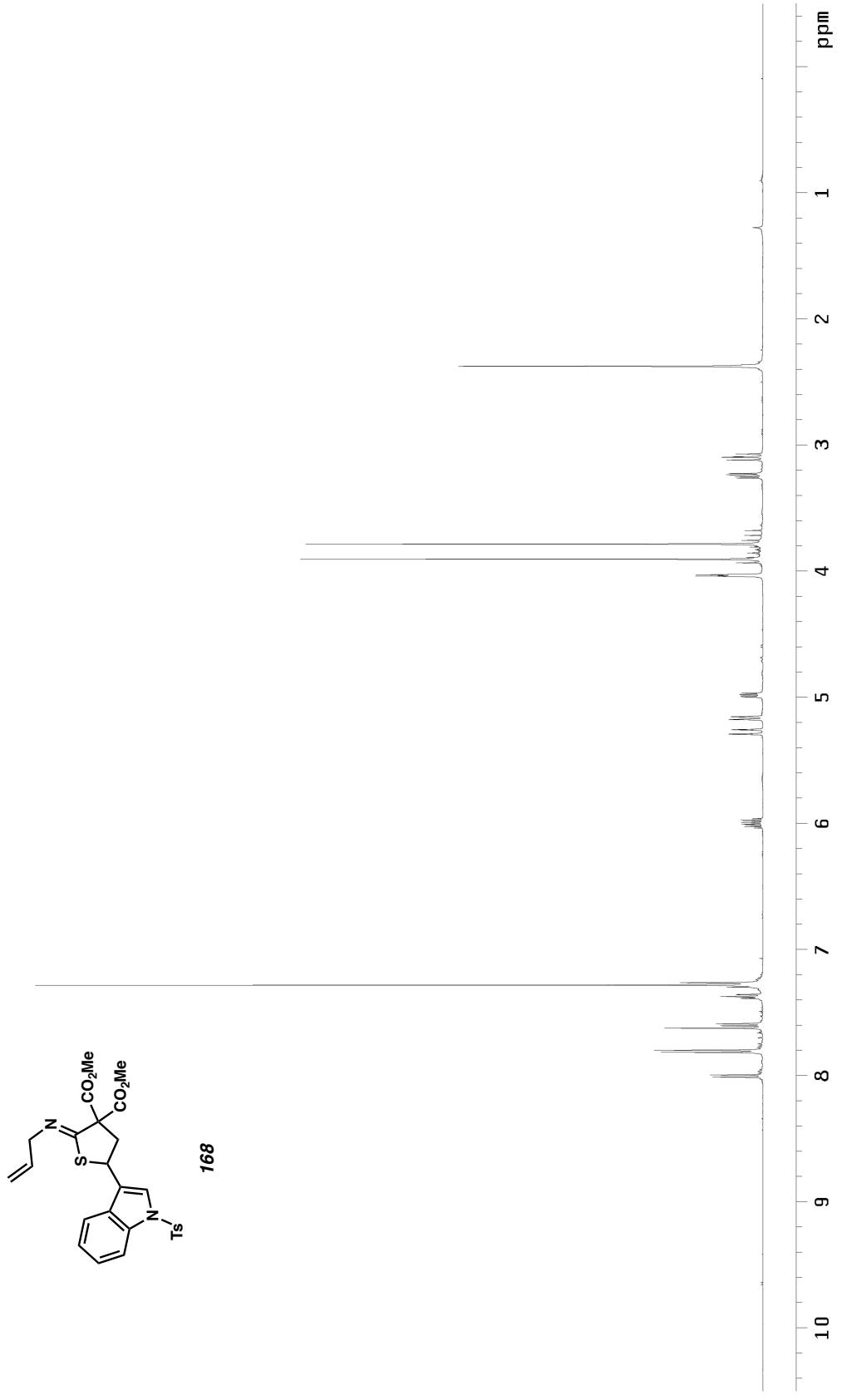


Figure A3.61 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **168**.

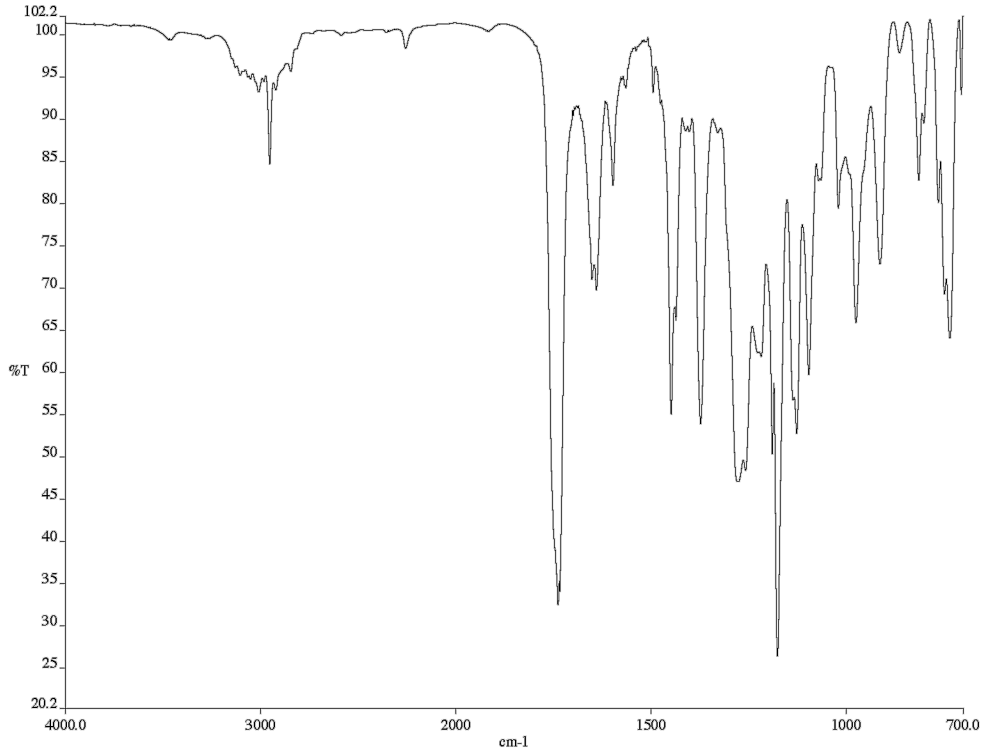


Figure A3.62 Infrared spectrum (thin film/NaCl) of compound **168**.

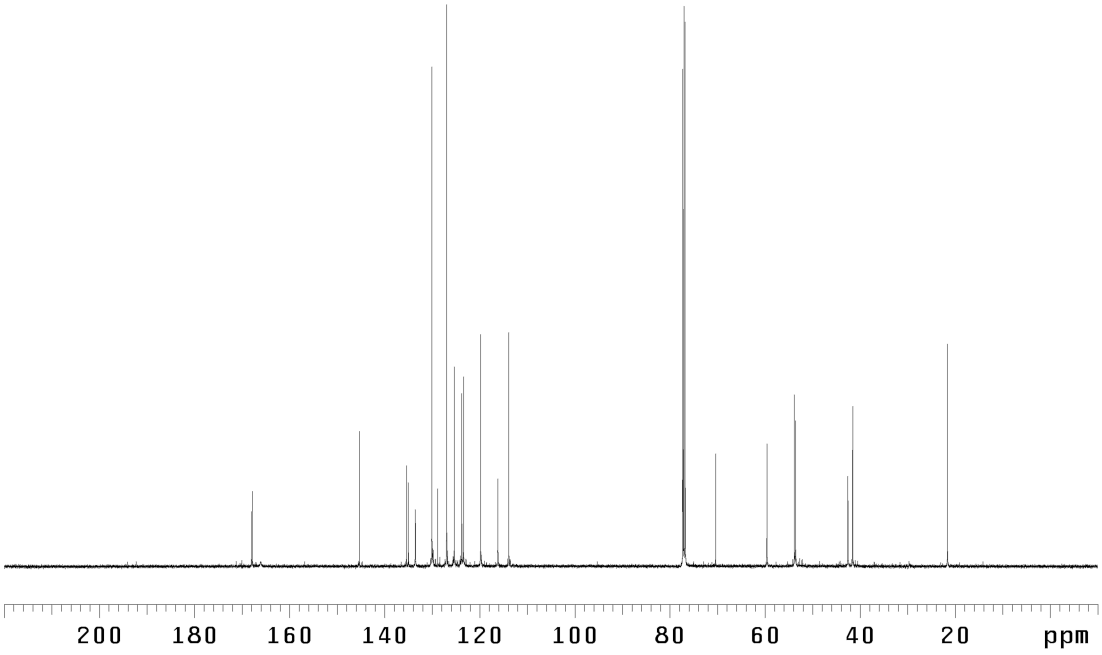


Figure A3.63 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **168**.

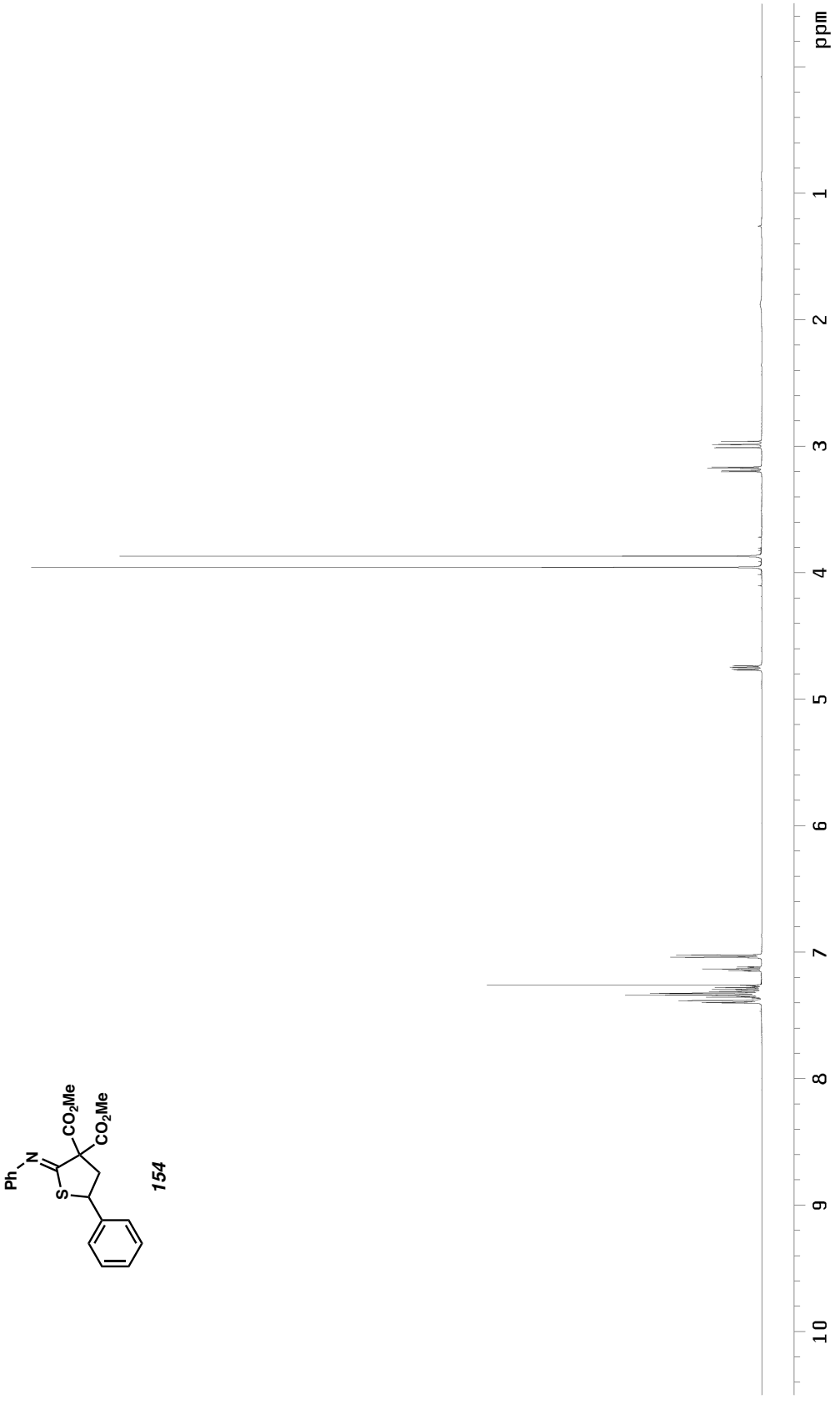


Figure A3.64 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **154**.

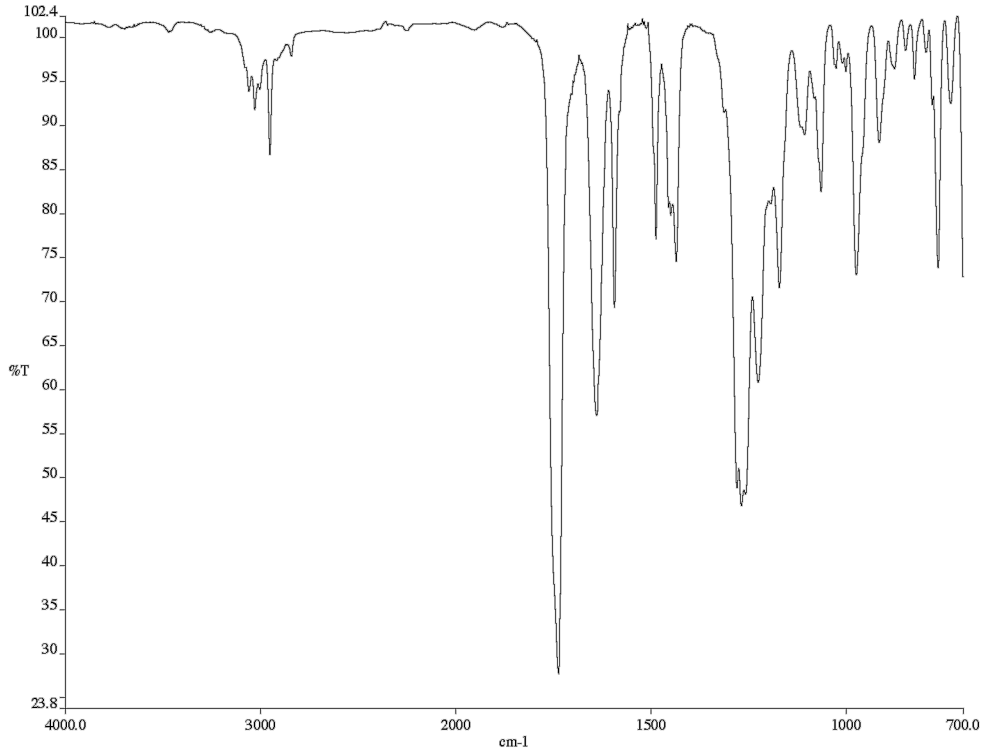


Figure A3.65 Infrared spectrum (thin film/NaCl) of compound **154**.

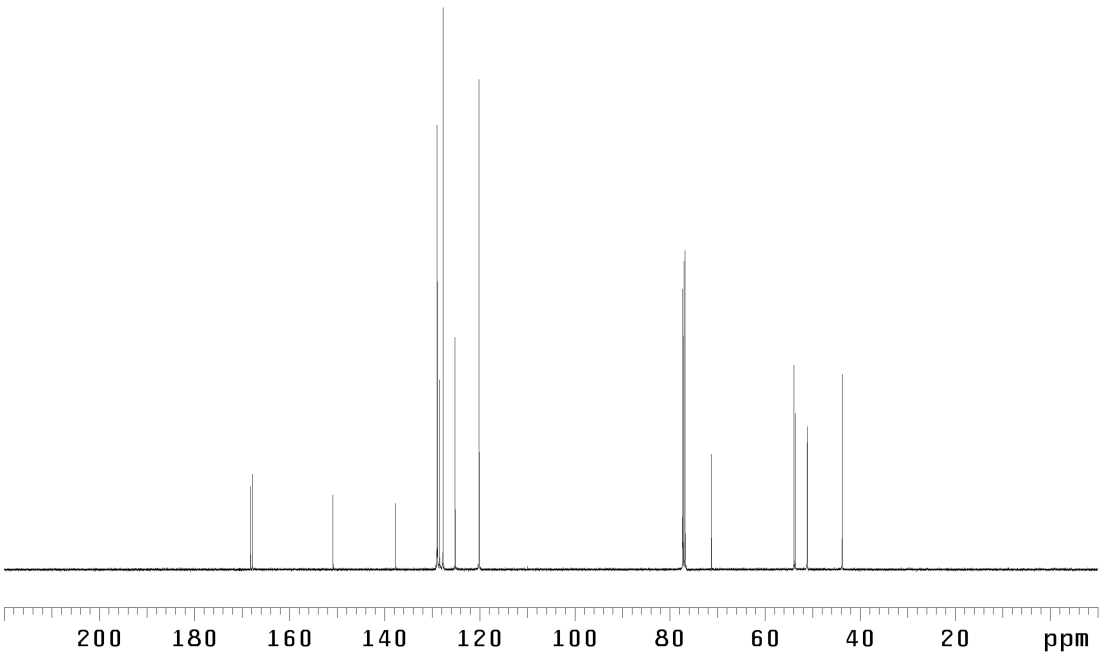


Figure A3.66 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **154**.

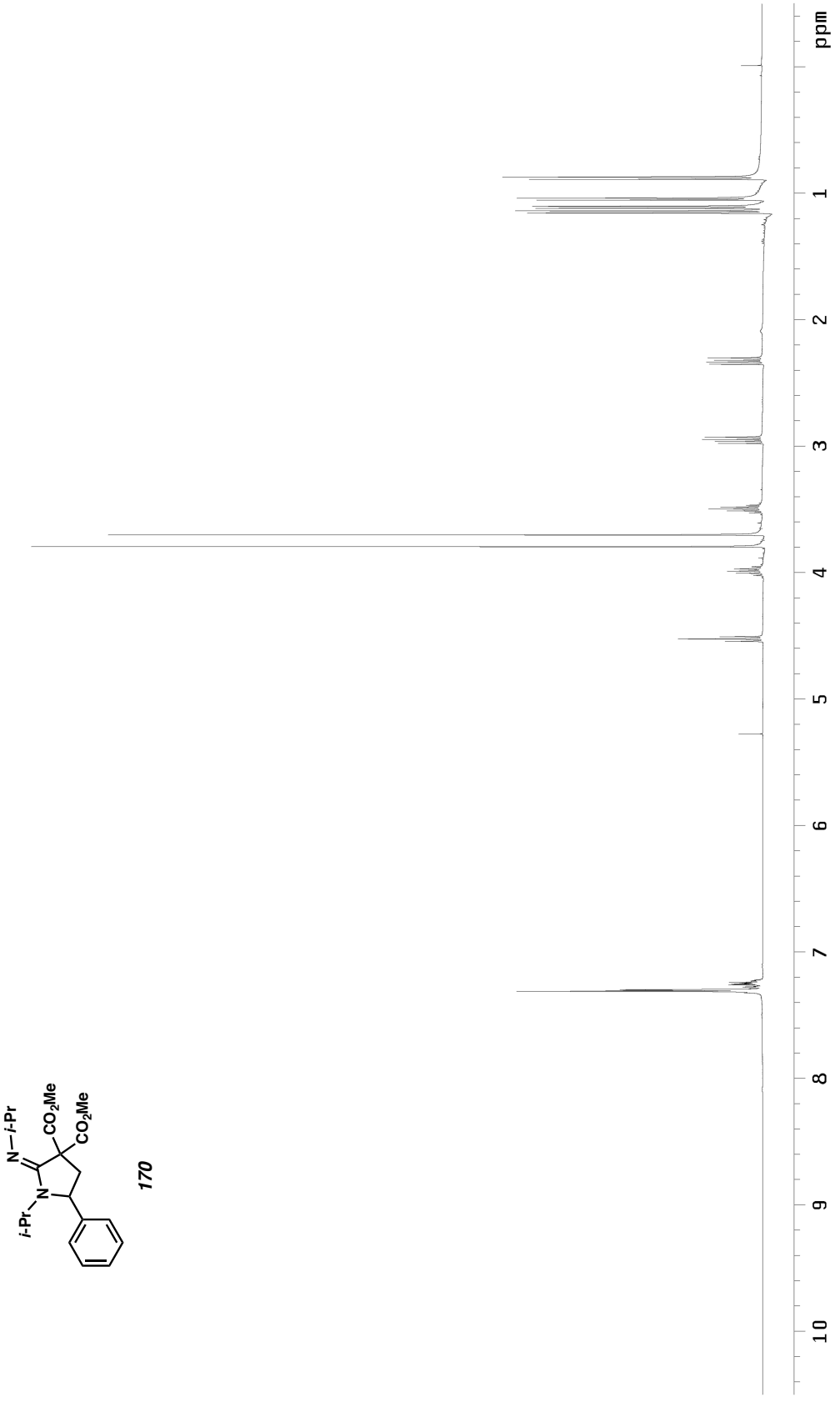


Figure A3.67 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **170**.

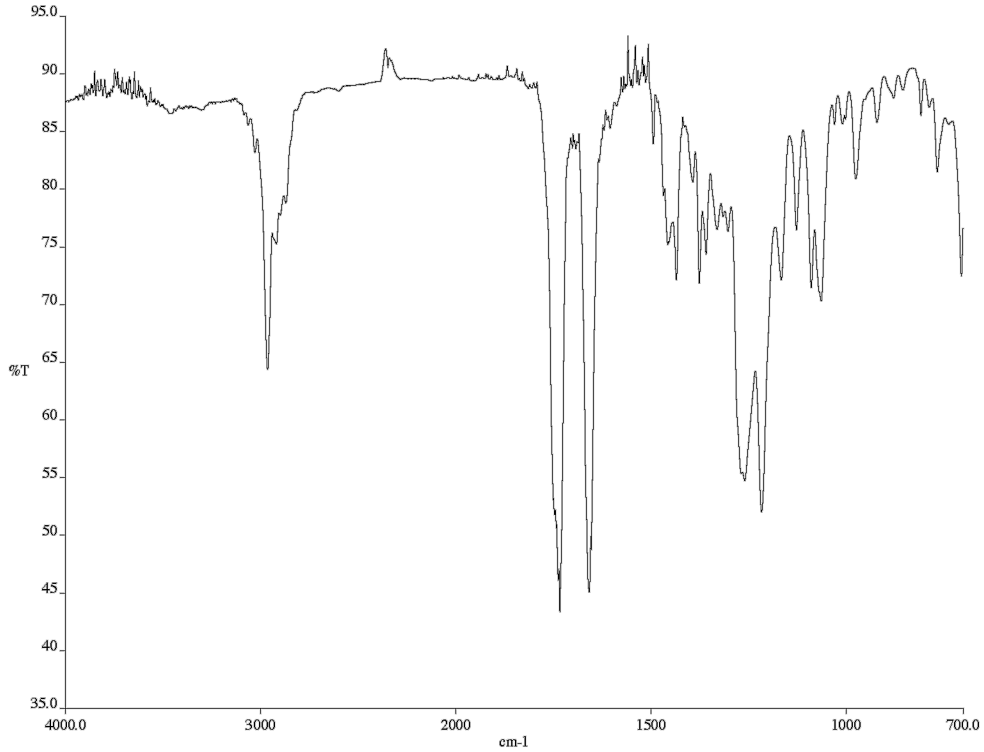


Figure A3.68 Infrared spectrum (thin film/NaCl) of compound **170**.

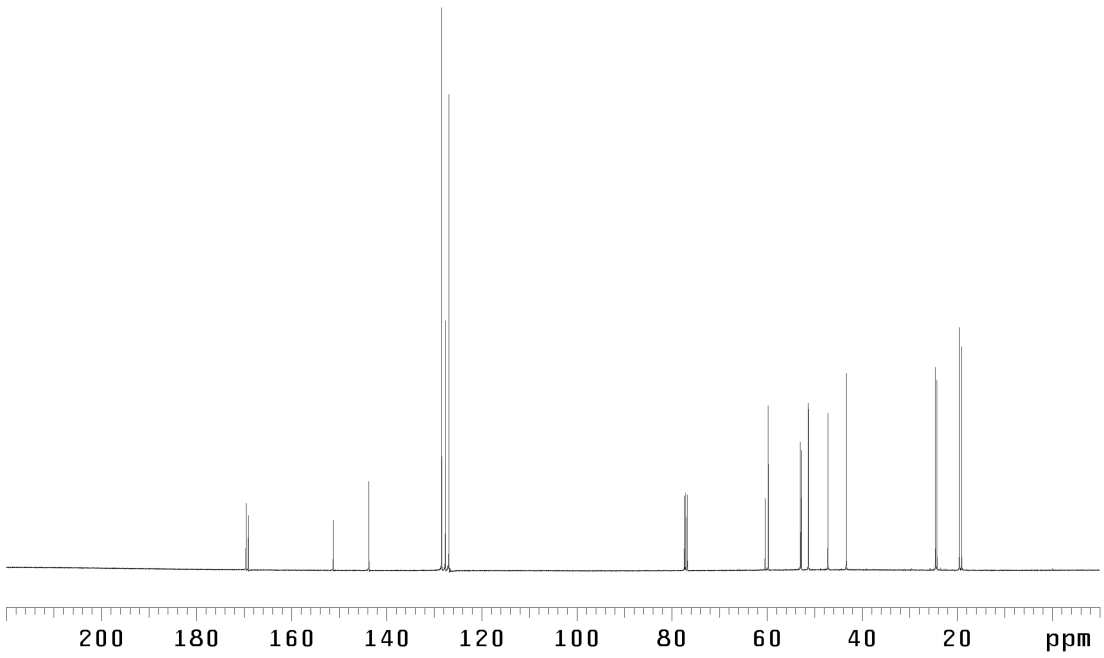


Figure A3.69 ^{13}C NMR (101 MHz, $CDCl_3$) of compound **170**.

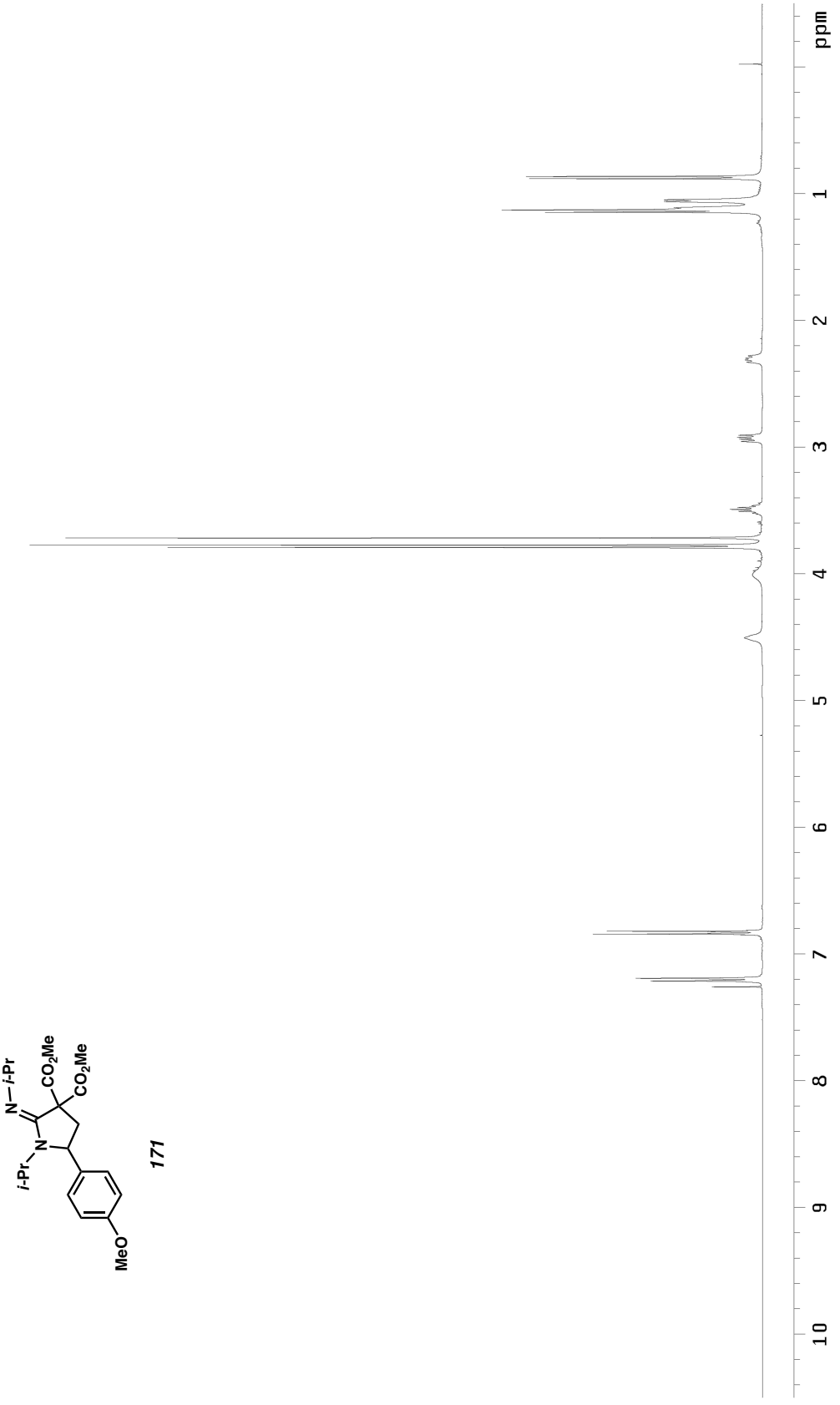


Figure A3.70 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **171**.

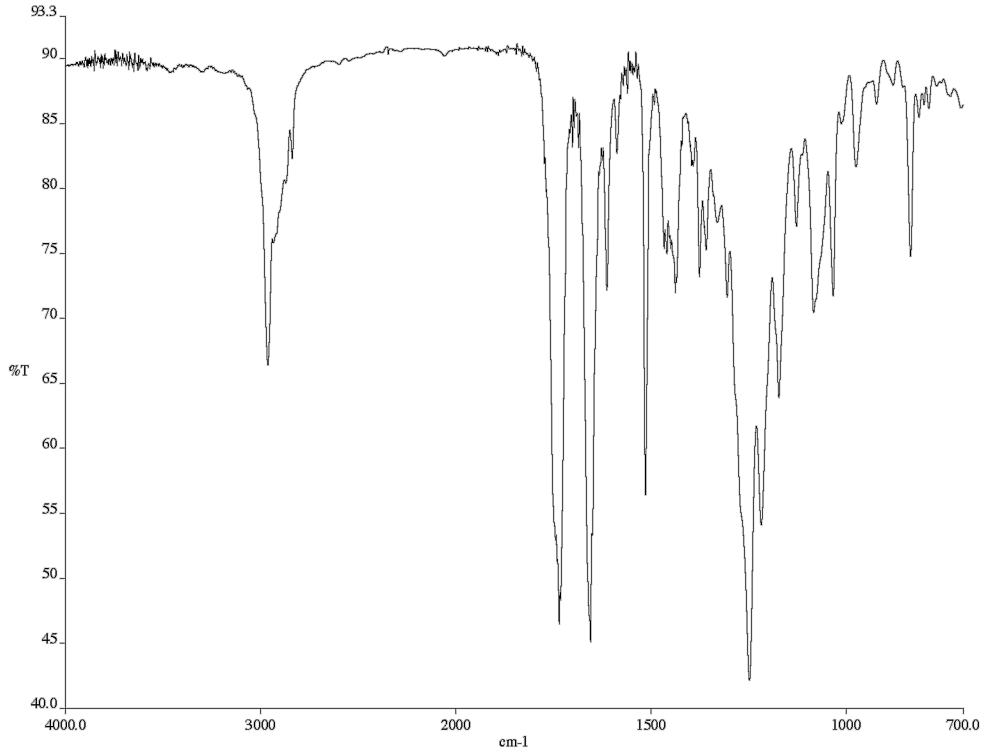


Figure A3.71 Infrared spectrum (thin film/NaCl) of compound **171**.

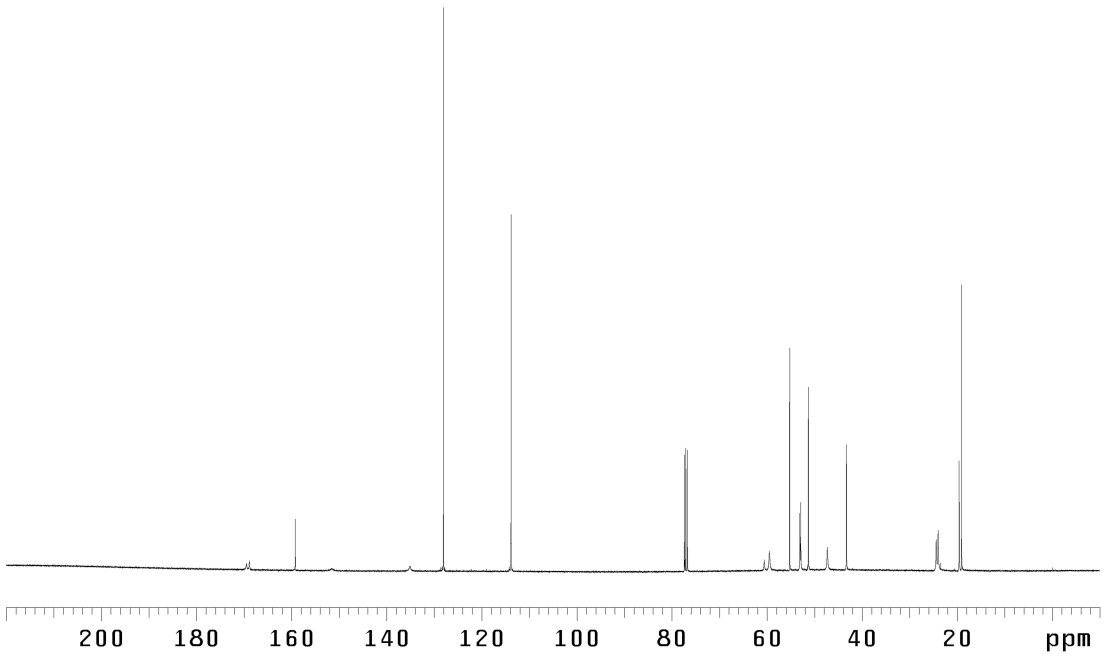


Figure A3.72 ^{13}C NMR (101 MHz, $CDCl_3$) of compound **171**.

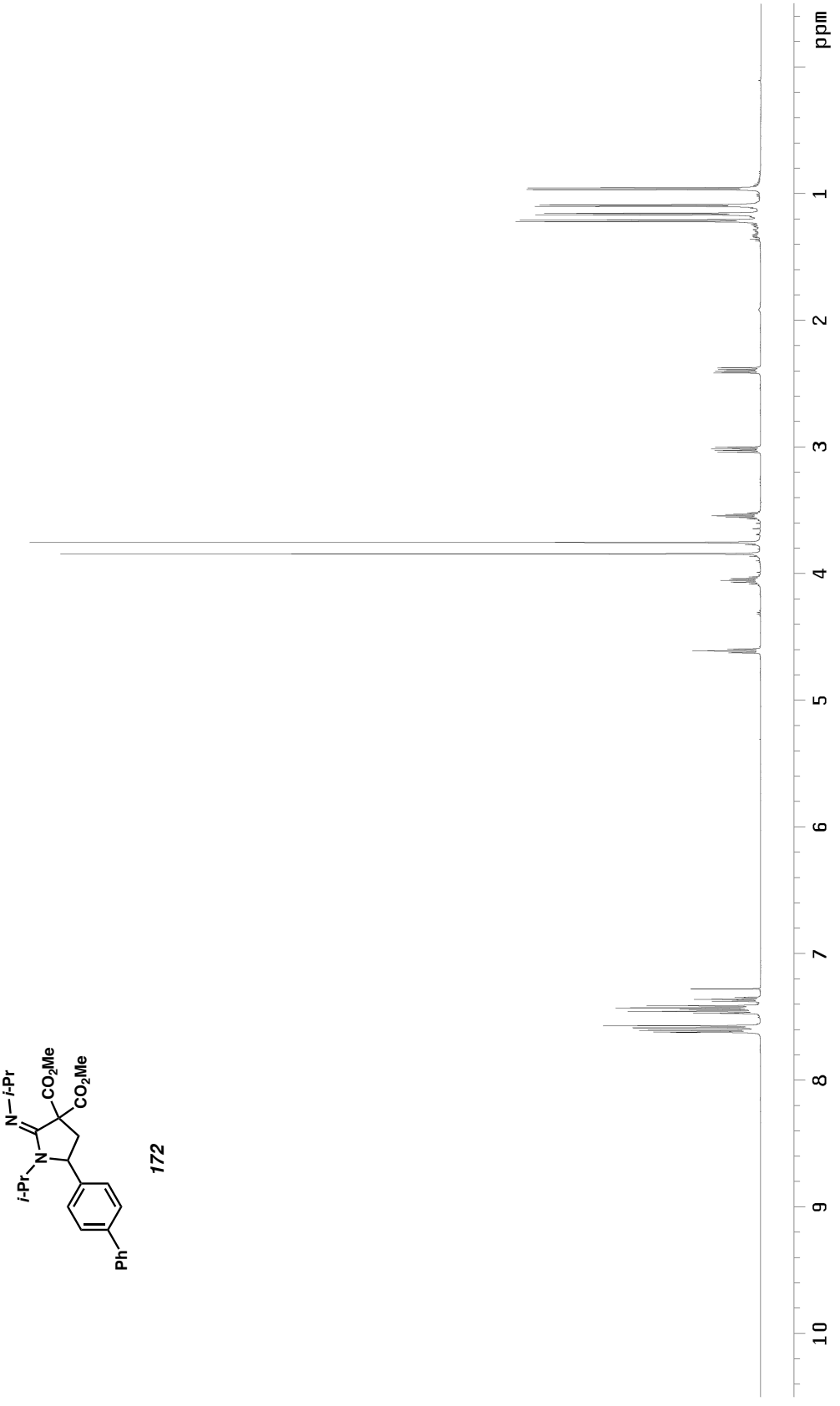


Figure A3.73 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **172**.

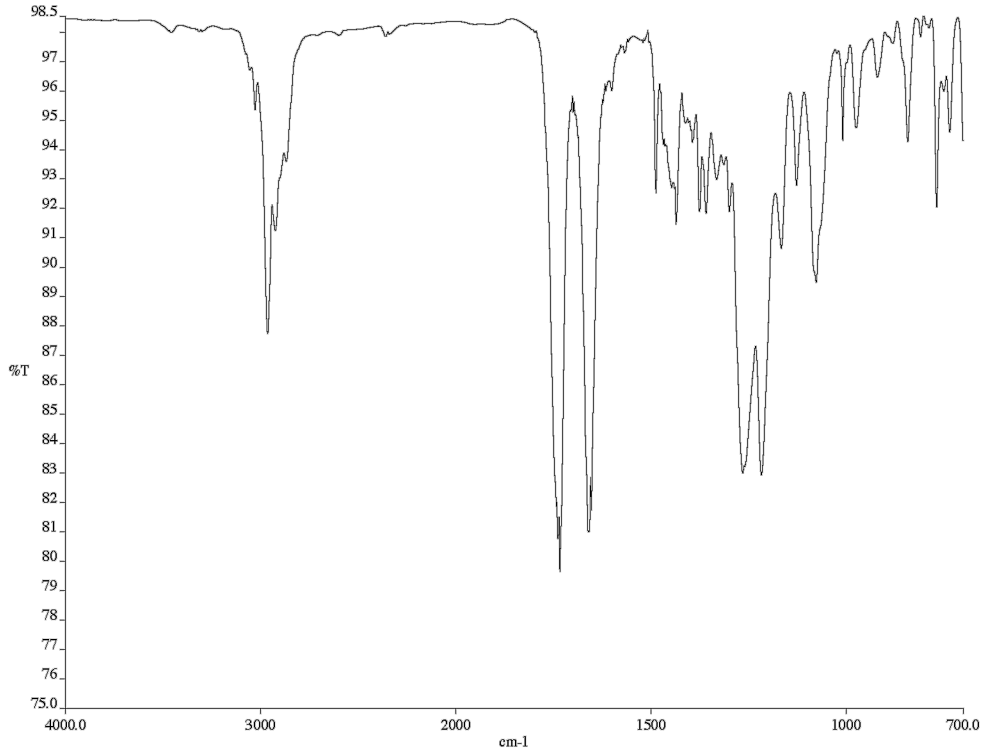


Figure A3.74 Infrared spectrum (thin film/NaCl) of compound **172**.

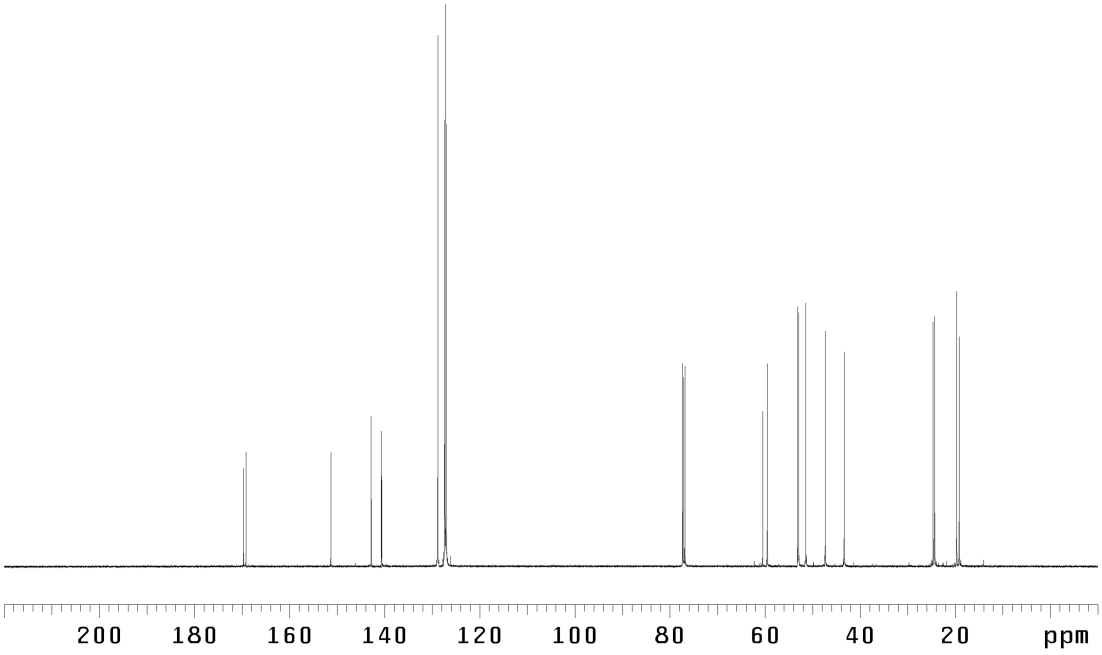


Figure A3.75 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **172**.

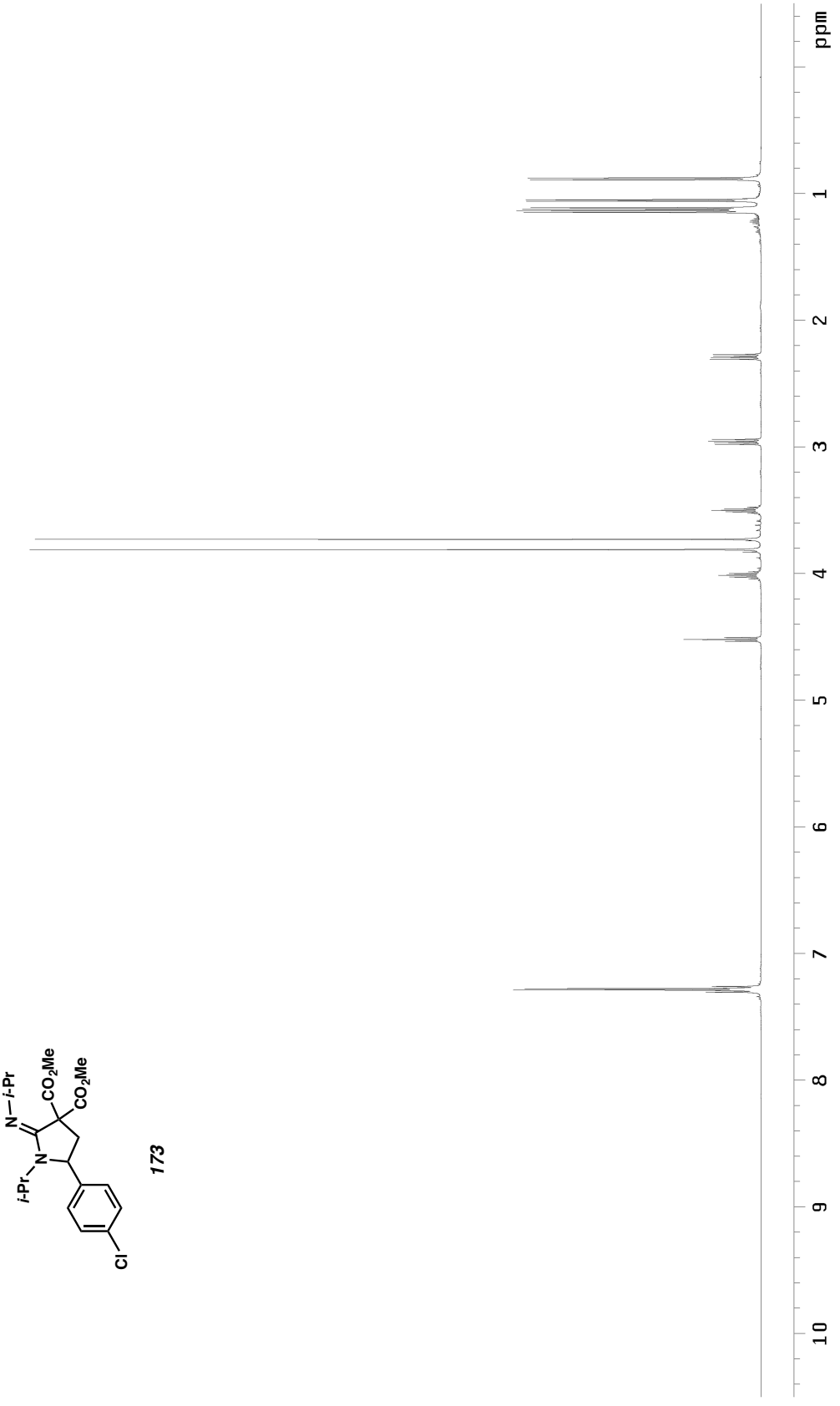


Figure A3.76 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **173**.

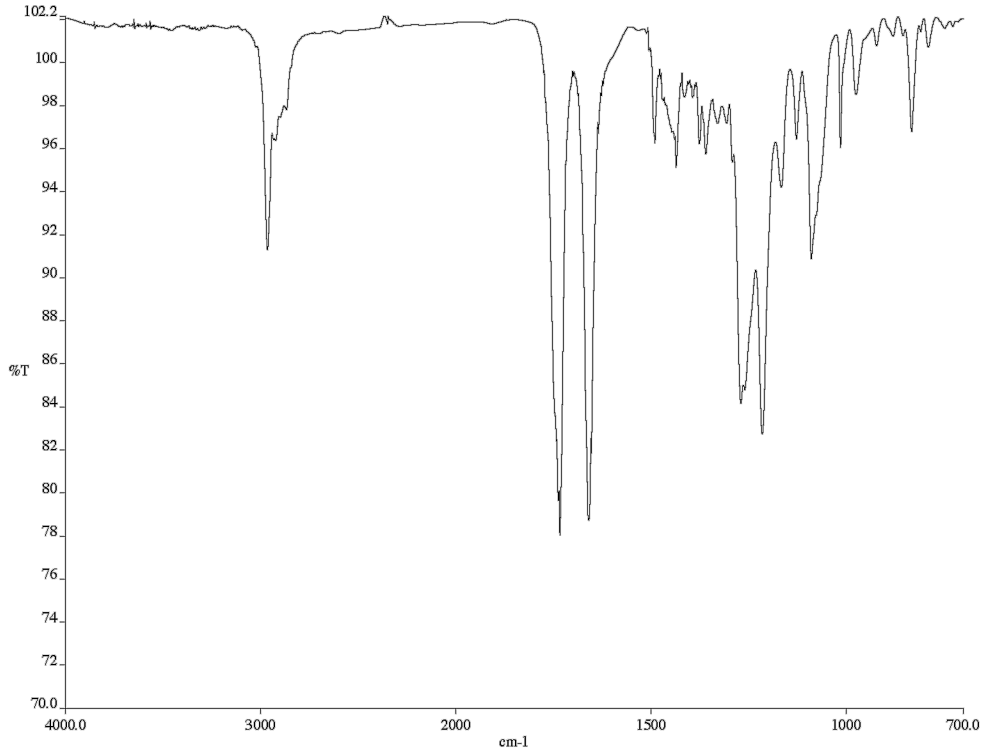


Figure A3.77 Infrared spectrum (thin film/NaCl) of compound **173**.

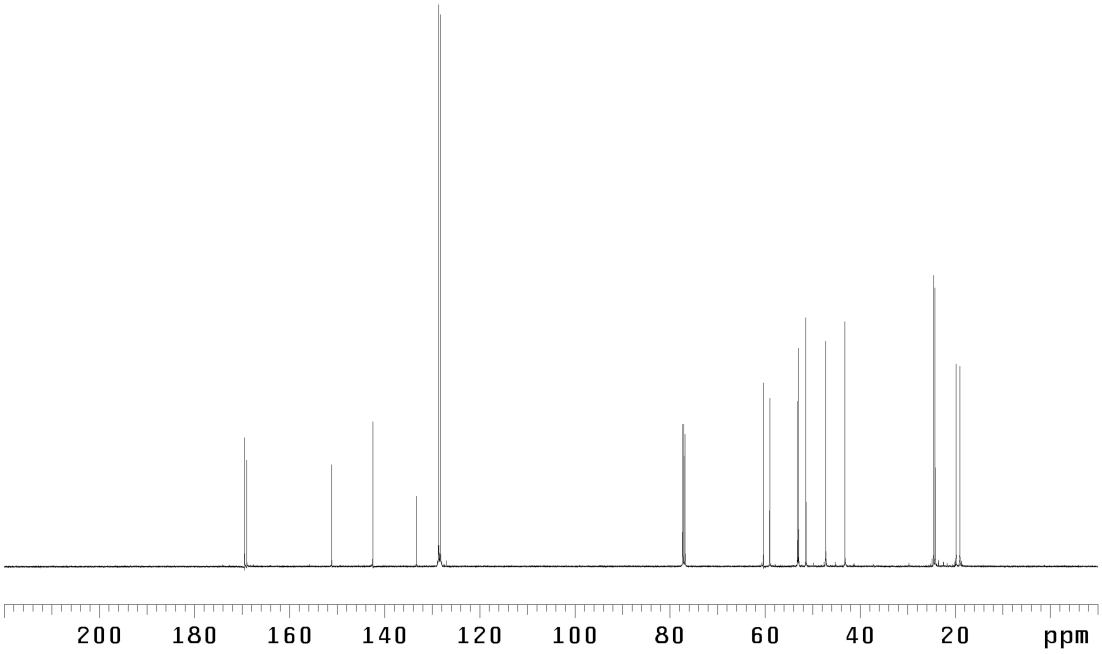


Figure A3.78 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **173**.

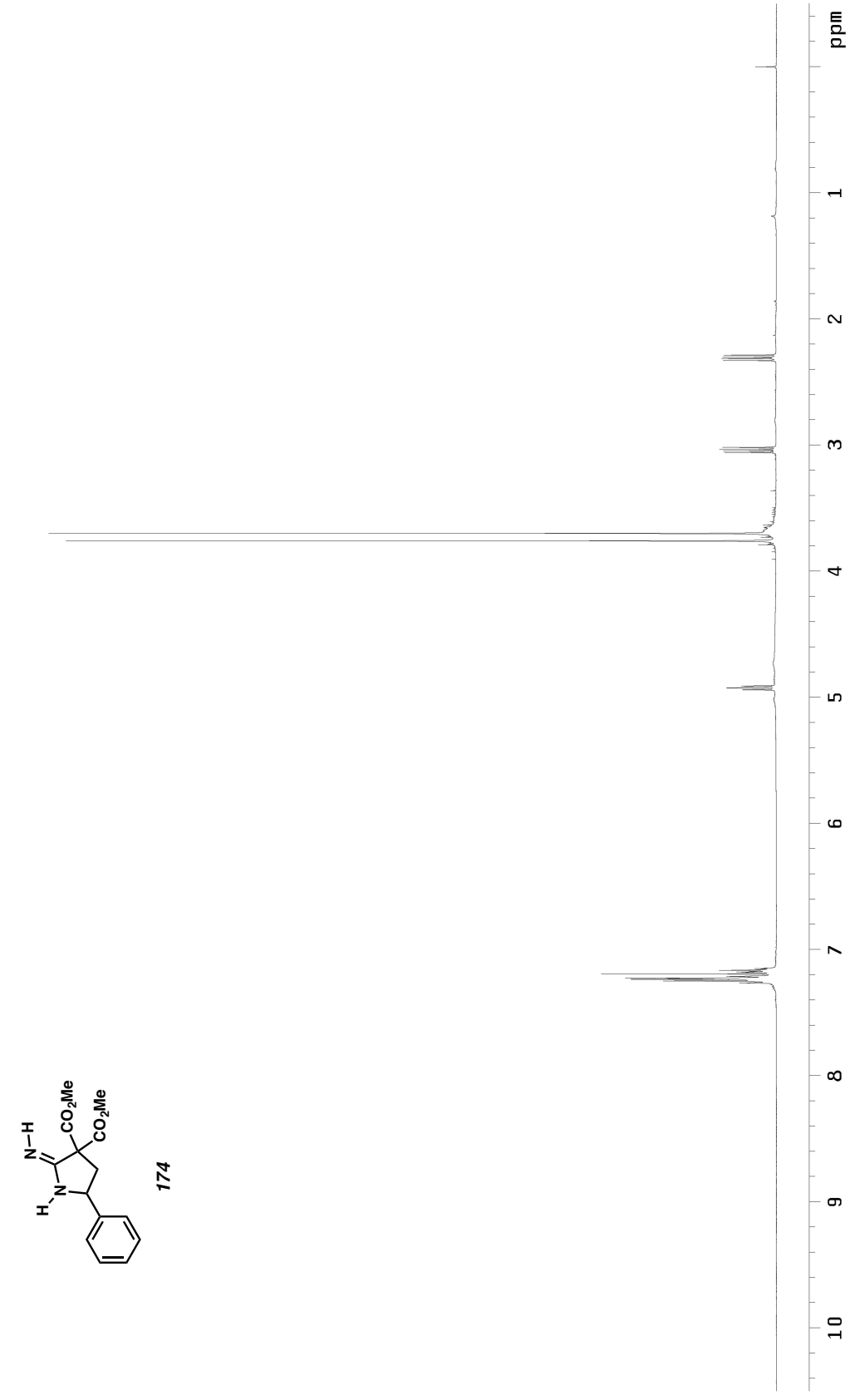


Figure A3.79 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **174**.

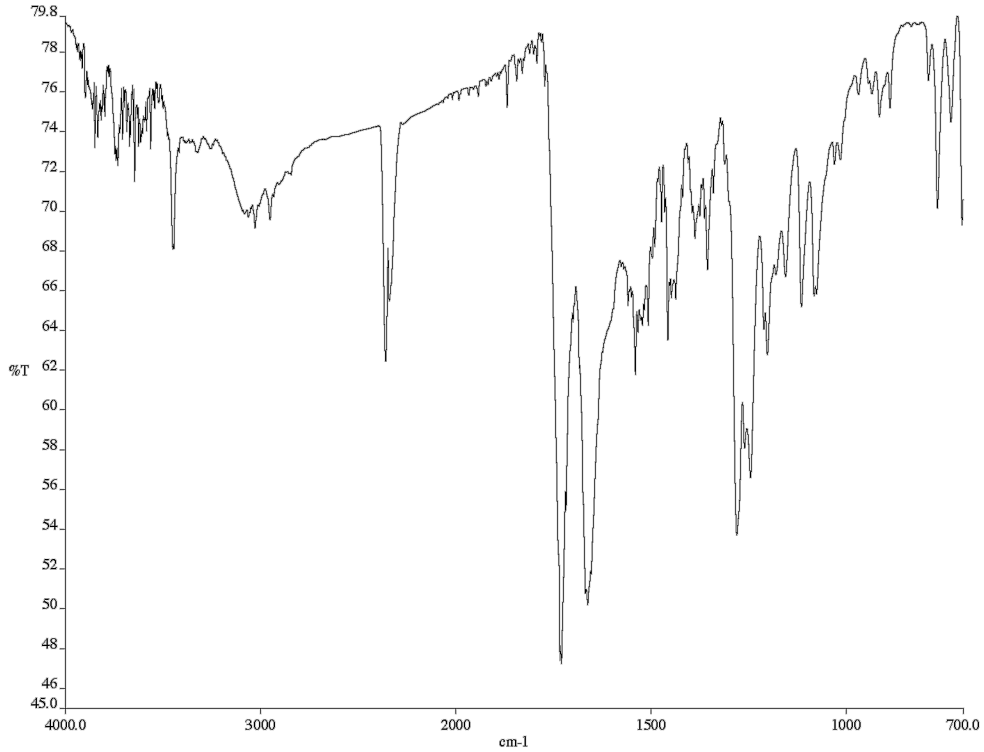


Figure A3.80 Infrared spectrum (thin film/NaCl) of compound **174**.

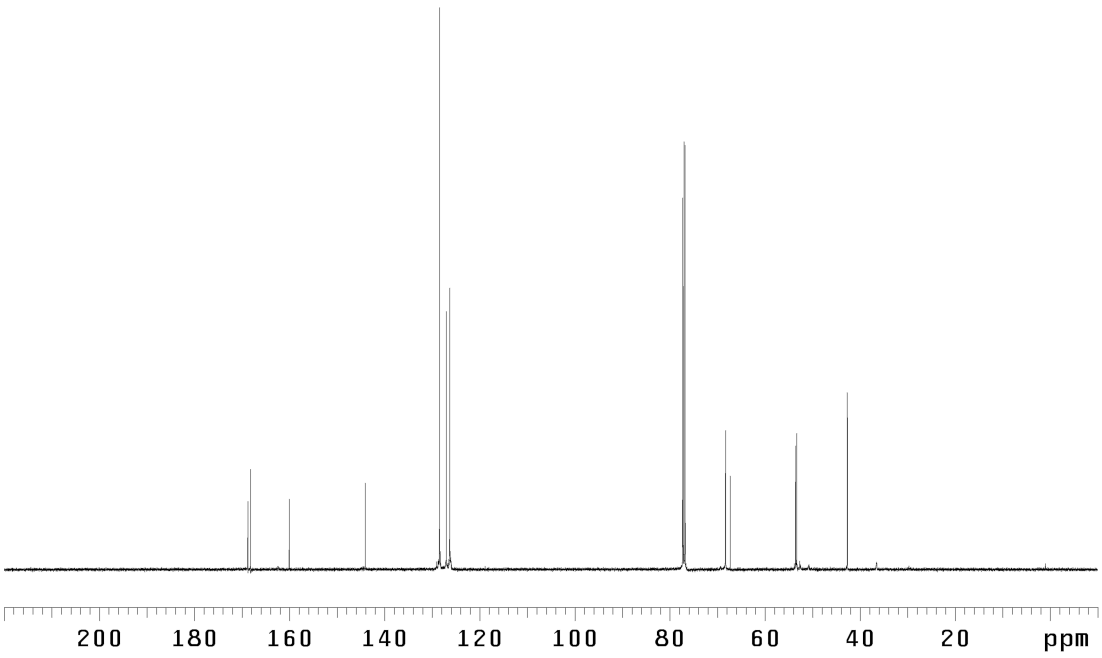


Figure A3.81 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **174**.

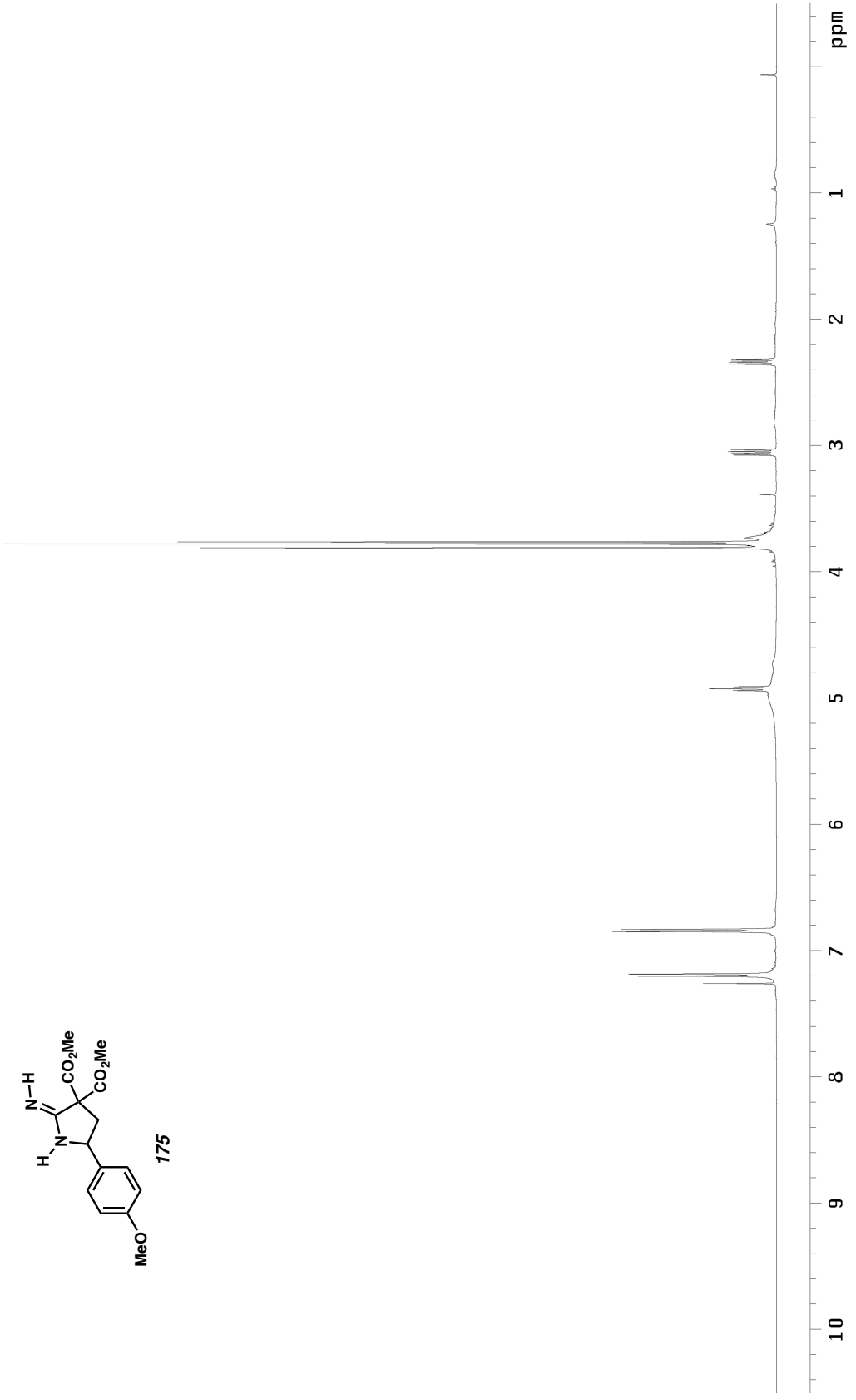


Figure A3.82 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **175**.

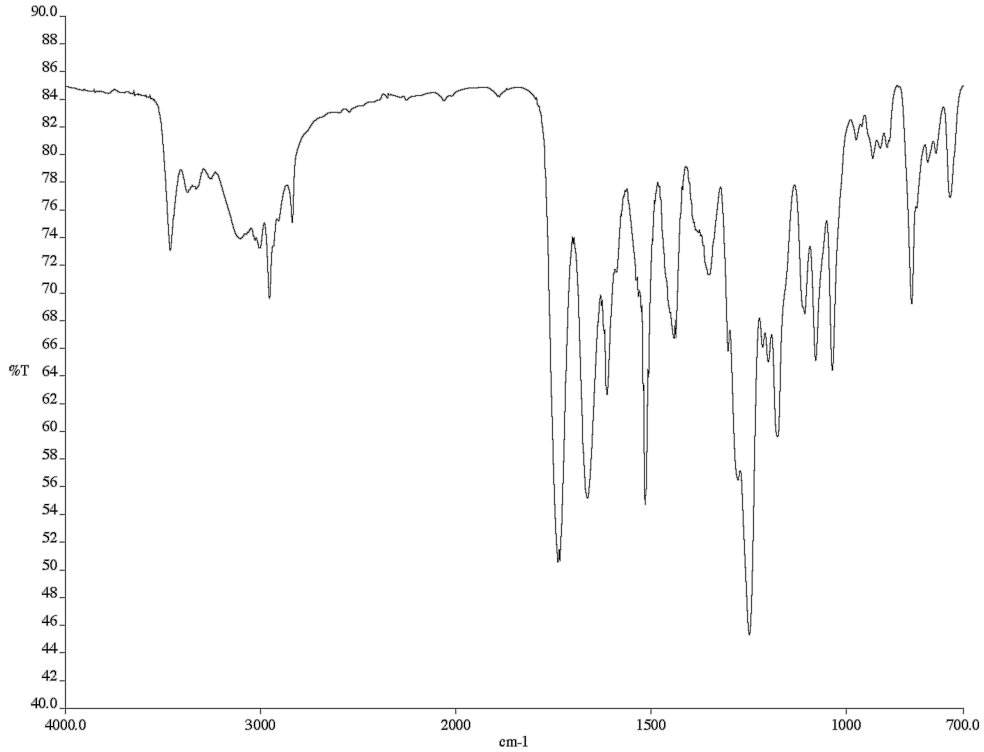


Figure A3.83 Infrared spectrum (thin film/NaCl) of compound **175**.

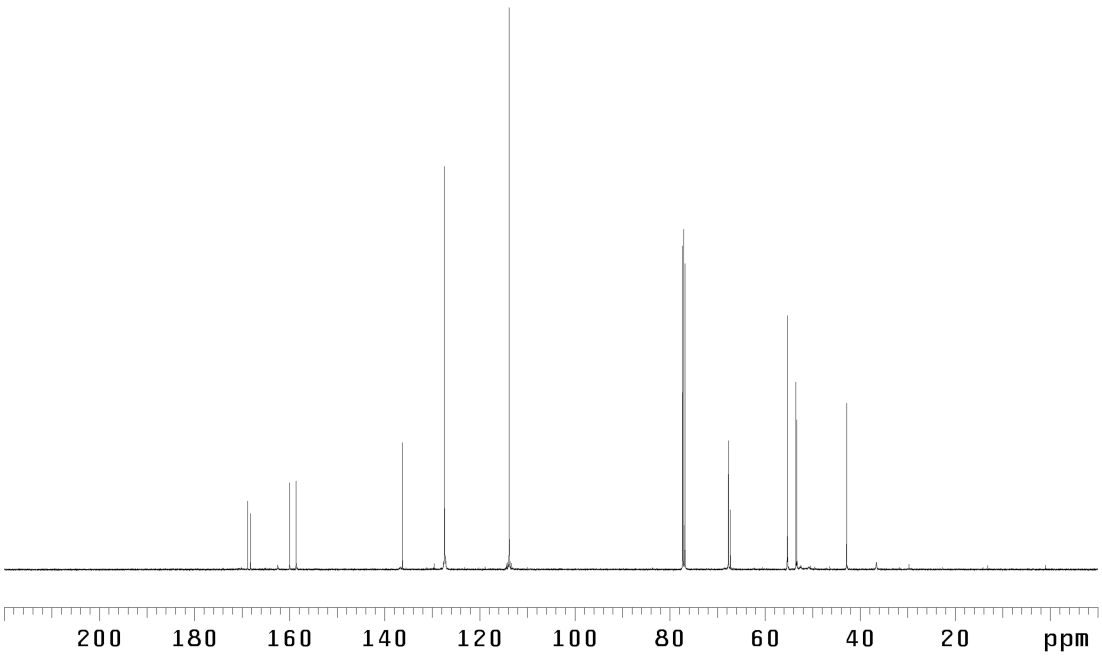


Figure A3.84 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **175**.

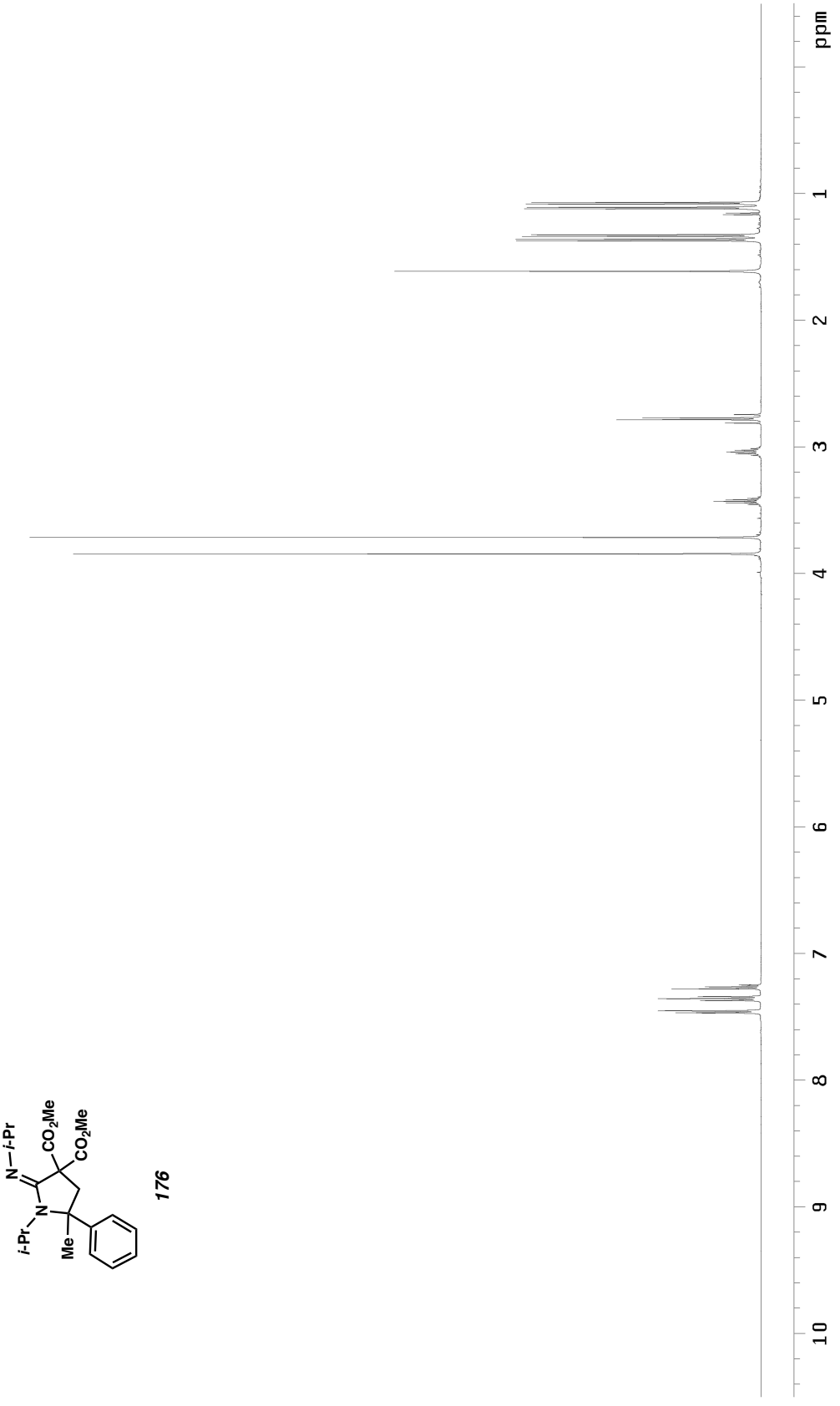


Figure A3.85 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **176**.

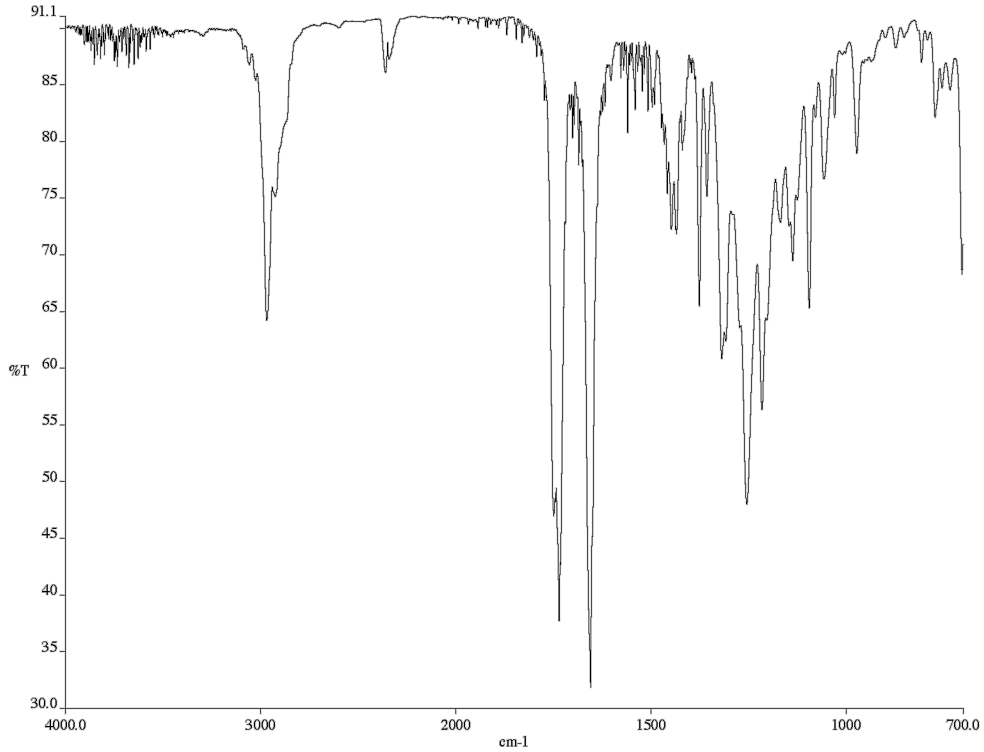


Figure A3.86 Infrared spectrum (thin film/NaCl) of compound **176**.

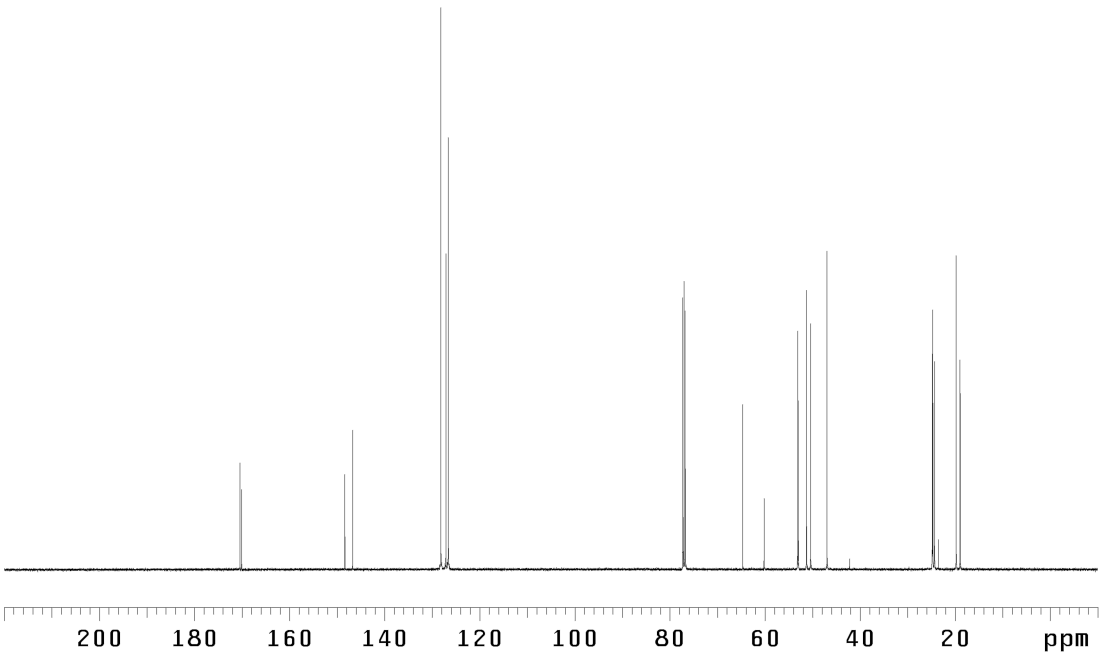


Figure A3.87 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **176**.

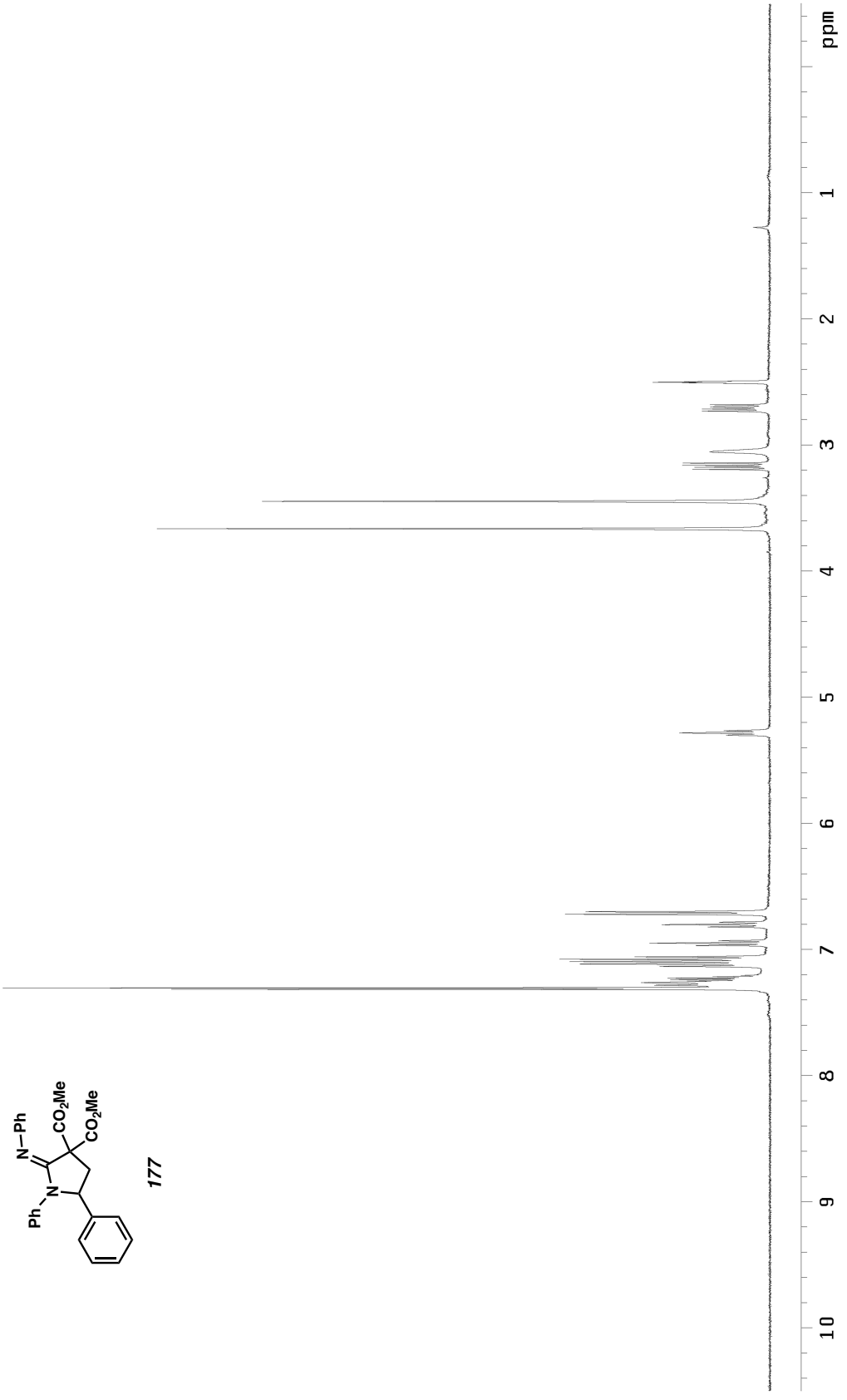


Figure A3.88 ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C) of compound **177**.

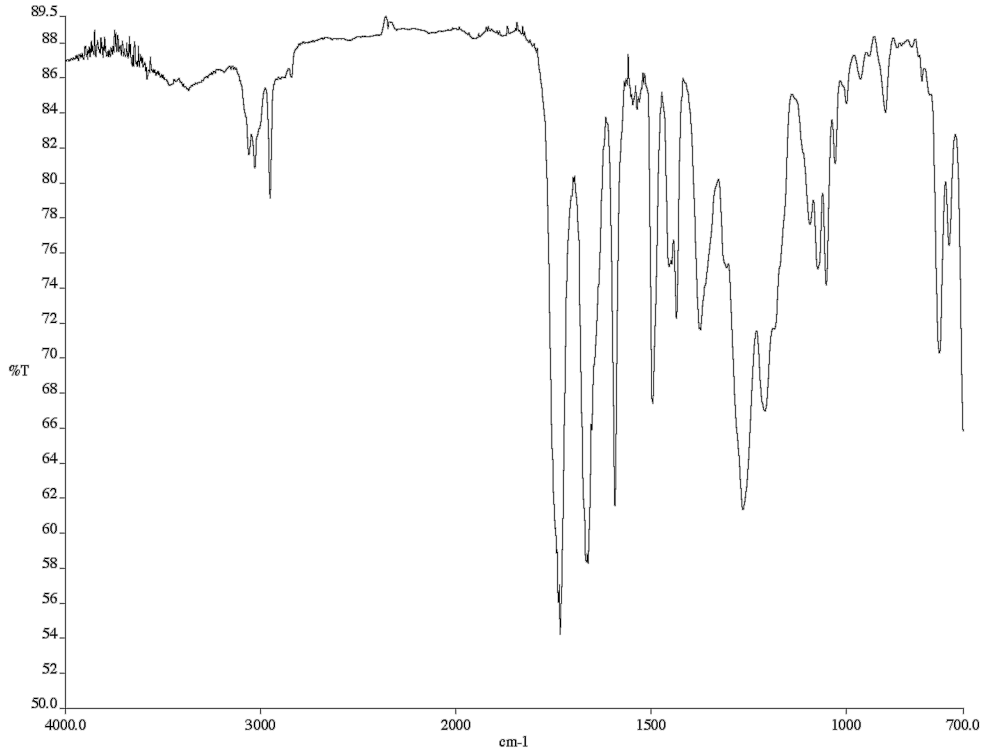


Figure A3.89 Infrared spectrum (thin film/NaCl) of compound **177**.

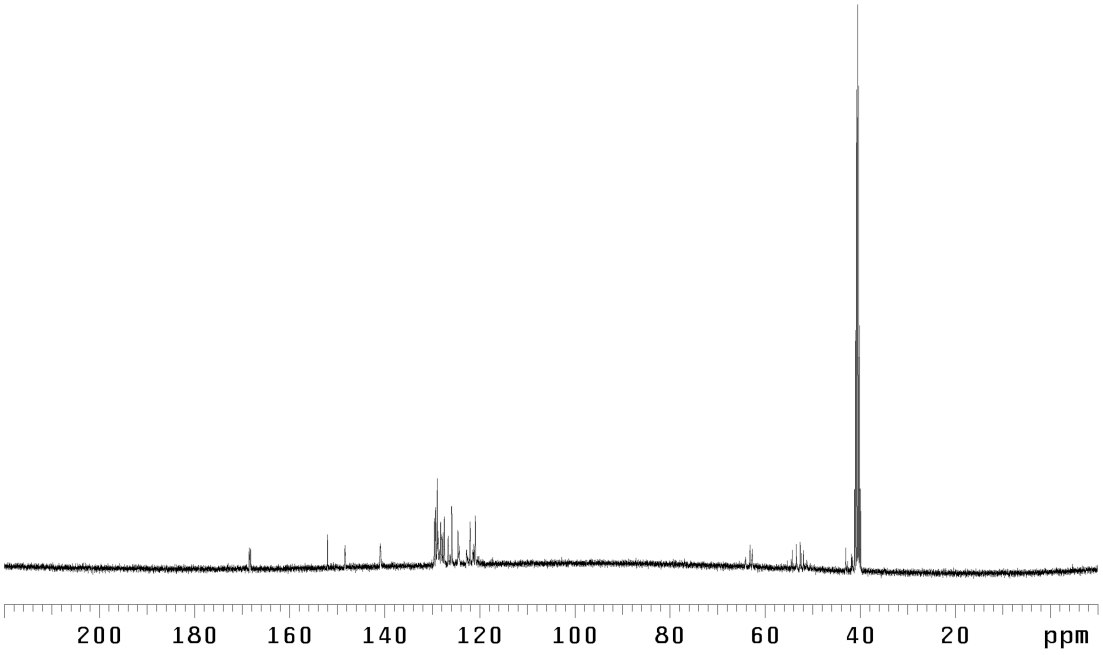


Figure A3.90 ^{13}C NMR (101 MHz, DMSO-d_6, 100 °C) of compound **177**.

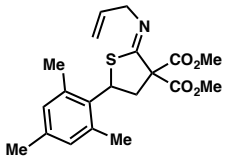
APPENDIX 4

X-Ray Crystallography Reports Relevant to Chapter 2:

Lewis Acid Mediated (3+2) Cycloadditions of

Donor–Acceptor Cyclopropanes with Heterocumulenes

A4.1 X-RAY CRYSTAL STRUCTURE ANALYSIS OF THIOIMIDATE 155



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Contents

Figure A4.1.1 X-ray crystal structure of thioimidate ***155***

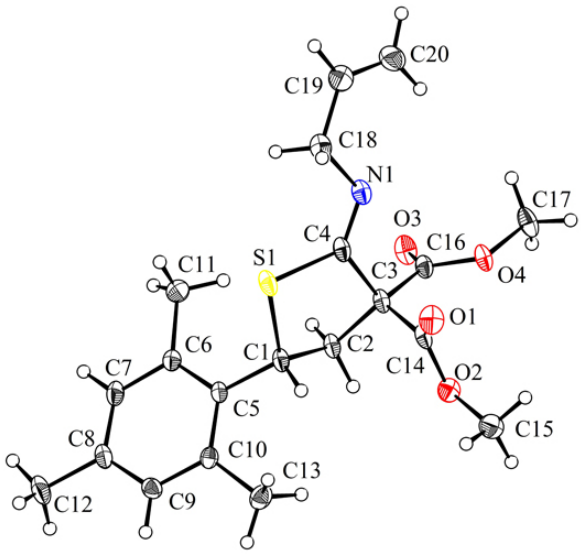


*Table A4.1.1 Crystal data and structure refinement for thioimidate **155***

Caltech Identification Number	rac13
CCDC Deposition Number	911991
Empirical formula	C20 H25 N O4 S
Formula weight	375.47
Crystallization solvent	Benzene/Heptane/Ethyl Acetate
Crystal color	colourless
Crystal size	0.08 x 0.19 x 0.46 mm

Data Collection

Preliminary photograph(s)	rotation	
Type of diffractometer	Bruker KAPPA APEX II	
Wavelength	0.71073 ≈ MO K	
Data collection temperature	100.15 K	
Theta range for 5787 reflections used in lattice determination	2.521 to 31.600°	
Unit cell dimensions	a = 14.5982(10) ≈ b = 16.1620(12) ≈ c = 8.2014(6) ≈	α= 90° β= 92.145(4)° γ = 90°
Volume	1933.7(2) $\approx^3$	
Z	4	
Crystal system	monoclinic	
Space group	P 1 21/c 1 (# 14)	
Density (calculated)	1.290 g/cm^3	
F(000)	800	
Theta range for data collection	1.4 to 37.4∞	
Completeness to theta = 25.00°	100.0%	
Index ranges	$-24 \le h \le 24, 0 \le k \le 27, 0 \le l \le 13$	
Data collection scan type	narrow and scans	
Reflections collected	15085	
Independent reflections	15085 [R_{int}= 0.0000]	
Reflections > 2s(I)	10418	
Average s(I)/(net I)	0.0676	
Absorption coefficient	0.19 mm^{-1}	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9848 and 0.9170	

Table A4.1.1 (cont'd)

Reflections monitored for decay	0
Decay of standards	0%

Structure Solution and Refinement

Primary solution method	direct
Secondary solution method	difmap
Hydrogen placement	geom
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	15085 / 0 / 241
Treatment of hydrogen atoms	constr
Goodness-of-fit on F^2	1.06
Final R indices [I>2s(I), 10418 reflections]	R1 = 0.0592, wR2 = 0.1221
R indices (all data)	R1 = 0.1034, wR2 = 0.1431
Type of weighting scheme used	calc
Weighting scheme used	calc w=1/[^2^(Fo^2^)+(0.0645P)^2^+0.3700P] where P=(Fo^2^+2Fc^2^)/3
Max shift/error	0.001
Average shift/error	0.000
Largest diff. peak and hole	0.49 and -0.37 e$\sum\approx^{-3}$

Programs Used

Cell refinement	SAINT V8.18C (Bruker-AXS, 2007)
Data collection	APEX2 2012.2-0 (Bruker-AXS, 2007)
Data reduction	SAINT V8.18C (Bruker-AXS, 2007)
Structure solution	SHELXS-97 (Sheldrick, 1990)
Structure refinement	SHELXL-97 (Sheldrick, 1997)
Graphics	DIAMOND 3 (Crystal Impact, 1999)

*Table A4.1.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for thioimidate **155**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U_{eq}
S(1)	7001(1)	6892(1)	2895(1)	22(1)
O(1)	8360(1)	6282(1)	6404(1)	27(1)
O(2)	7480(1)	5212(1)	7100(1)	22(1)
O(3)	7866(1)	4219(1)	2706(1)	26(1)
O(4)	8857(1)	4560(1)	4768(1)	22(1)
N(1)	8660(1)	6157(1)	2476(1)	20(1)
C(1)	6183(1)	6259(1)	4018(2)	18(1)
C(2)	6567(1)	5375(1)	4014(2)	18(1)
C(3)	7607(1)	5456(1)	4275(2)	17(1)
C(4)	7894(1)	6152(1)	3131(2)	18(1)
C(5)	5192(1)	6358(1)	3430(1)	15(1)
C(6)	4890(1)	6274(1)	1789(1)	18(1)
C(7)	3969(1)	6418(1)	1363(2)	20(1)
C(8)	3336(1)	6643(1)	2493(2)	20(1)
C(9)	3634(1)	6687(1)	4121(2)	19(1)
C(10)	4541(1)	6543(1)	4608(1)	17(1)
C(11)	5514(1)	6056(1)	420(2)	26(1)
C(12)	2354(1)	6831(1)	1995(2)	29(1)
C(13)	4795(1)	6554(1)	6414(1)	24(1)
C(14)	7874(1)	5710(1)	6034(2)	18(1)
C(15)	7719(1)	5383(1)	8800(2)	26(1)
C(16)	8111(1)	4667(1)	3805(2)	18(1)
C(17)	9433(1)	3862(1)	4390(2)	29(1)
C(18)	8876(1)	6851(1)	1424(2)	23(1)
C(19)	9690(1)	6694(1)	428(2)	27(1)
C(20)	10218(1)	6036(1)	521(2)	31(1)

*Table A4.1.3 Bond lengths [Å] and angles [°] for thioimidate **155***

S(1)-C(1)	1.8457(13)
S(1)-C(4)	1.7750(12)
O(1)-C(14)	1.1975(14)
O(2)-C(14)	1.3343(15)
O(2)-C(15)	1.4511(15)
O(3)-C(16)	1.1997(14)
O(4)-C(16)	1.3320(15)
O(4)-C(17)	1.4486(16)
N(1)-C(4)	1.2587(17)
N(1)-C(18)	1.4571(16)
C(1)-H(1)	1.0000
C(1)-C(2)	1.5343(16)
C(1)-C(5)	1.5167(17)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(2)-C(3)	1.5308(17)
C(3)-C(4)	1.5333(17)
C(3)-C(14)	1.5361(17)
C(3)-C(16)	1.5297(16)
C(5)-C(6)	1.4066(16)
C(5)-C(10)	1.4121(18)
C(6)-C(7)	1.3959(18)
C(6)-C(11)	1.5136(19)
C(7)-H(7)	0.9500
C(7)-C(8)	1.3812(19)
C(8)-C(9)	1.3904(17)
C(8)-C(12)	1.5075(18)
C(9)-H(9)	0.9500
C(9)-C(10)	1.3892(17)
C(10)-C(13)	1.5126(16)
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800

Table A4.1.3 (cont'd)

C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800
C(18)-H(18A)	0.9900
C(18)-H(18B)	0.9900
C(18)-C(19)	1.489(2)
C(19)-H(19)	0.9500
C(19)-C(20)	1.313(2)
C(20)-H(20A)	0.9500
C(20)-H(20B)	0.9500

C(4)-S(1)-C(1)	93.31(6)
C(14)-O(2)-C(15)	114.91(10)
C(16)-O(4)-C(17)	116.24(10)
C(4)-N(1)-C(18)	118.20(11)
S(1)-C(1)-H(1)	106.7
C(2)-C(1)-S(1)	105.80(9)
C(2)-C(1)-H(1)	106.7
C(5)-C(1)-S(1)	114.20(8)
C(5)-C(1)-H(1)	106.7
C(5)-C(1)-C(2)	116.22(10)
C(1)-C(2)-H(2A)	110.5
C(1)-C(2)-H(2B)	110.5
H(2A)-C(2)-H(2B)	108.7
C(3)-C(2)-C(1)	106.28(9)

Table A4.1.3 (cont'd)

C(3)-C(2)-H(2A)	110.5
C(3)-C(2)-H(2B)	110.5
C(2)-C(3)-C(4)	105.66(9)
C(2)-C(3)-C(14)	111.69(10)
C(4)-C(3)-C(14)	108.25(9)
C(16)-C(3)-C(2)	112.20(10)
C(16)-C(3)-C(4)	108.18(10)
C(16)-C(3)-C(14)	110.60(9)
N(1)-C(4)-S(1)	127.60(9)
N(1)-C(4)-C(3)	122.25(10)
C(3)-C(4)-S(1)	110.15(9)
C(6)-C(5)-C(1)	123.69(11)
C(6)-C(5)-C(10)	118.76(11)
C(10)-C(5)-C(1)	117.55(10)
C(5)-C(6)-C(11)	123.86(11)
C(7)-C(6)-C(5)	119.14(11)
C(7)-C(6)-C(11)	116.99(11)
C(6)-C(7)-H(7)	118.7
C(8)-C(7)-C(6)	122.59(11)
C(8)-C(7)-H(7)	118.7
C(7)-C(8)-C(9)	117.69(11)
C(7)-C(8)-C(12)	121.68(12)
C(9)-C(8)-C(12)	120.63(12)
C(8)-C(9)-H(9)	119.1
C(10)-C(9)-C(8)	121.88(11)
C(10)-C(9)-H(9)	119.1
C(5)-C(10)-C(13)	121.74(11)
C(9)-C(10)-C(5)	119.79(11)
C(9)-C(10)-C(13)	118.41(11)
C(6)-C(11)-H(11A)	109.5
C(6)-C(11)-H(11B)	109.5
C(6)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11C)	109.5

Table A4.1.3 (cont'd)

H(11B)-C(11)-H(11C)	109.5
C(8)-C(12)-H(12A)	109.5
C(8)-C(12)-H(12B)	109.5
C(8)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(10)-C(13)-H(13A)	109.5
C(10)-C(13)-H(13B)	109.5
C(10)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
O(1)-C(14)-O(2)	124.42(11)
O(1)-C(14)-C(3)	124.85(12)
O(2)-C(14)-C(3)	110.72(10)
O(2)-C(15)-H(15A)	109.5
O(2)-C(15)-H(15B)	109.5
O(2)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
O(3)-C(16)-O(4)	125.53(11)
O(3)-C(16)-C(3)	124.03(11)
O(4)-C(16)-C(3)	110.43(10)
O(4)-C(17)-H(17A)	109.5
O(4)-C(17)-H(17B)	109.5
O(4)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
N(1)-C(18)-H(18A)	109.0
N(1)-C(18)-H(18B)	109.0
N(1)-C(18)-C(19)	112.84(11)

Table A4.1.3. (cont'd)

H(18A)-C(18)-H(18B)	107.8
C(19)-C(18)-H(18A)	109.0
C(19)-C(18)-H(18B)	109.0
C(18)-C(19)-H(19)	117.1
C(20)-C(19)-C(18)	125.79(13)
C(20)-C(19)-H(19)	117.1
C(19)-C(20)-H(20A)	120.0
C(19)-C(20)-H(20B)	120.0
H(20A)-C(20)-H(20B)	120.0

Symmetry transformations used to generate equivalent atoms:

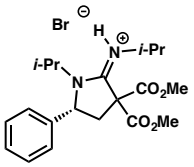
*Table A4.1.4 Anisotropic displacement parameters ($Å^2x10^3$) for thioimidate **155**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$.*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	146(1)	147(1)	372(2)	67(1)	-20(1)	19(1)
O(1)	275(6)	192(4)	326(5)	-16(4)	-66(4)	-65(4)
O(2)	204(5)	218(4)	232(4)	-6(3)	-28(3)	-45(3)
O(3)	261(5)	201(4)	313(5)	-57(4)	-71(4)	32(4)
O(4)	175(5)	176(4)	300(5)	-10(3)	-55(3)	60(3)
N(1)	170(5)	157(4)	275(5)	8(4)	-34(4)	-1(4)
C(1)	140(6)	152(5)	228(5)	21(4)	-52(4)	-1(4)
C(2)	142(6)	134(5)	259(6)	23(4)	-55(4)	-3(4)
C(3)	136(6)	125(5)	245(5)	10(4)	-47(4)	5(4)
C(4)	160(6)	127(5)	256(6)	6(4)	-50(5)	11(4)
C(5)	138(5)	139(5)	181(5)	20(4)	-28(4)	4(4)
C(6)	174(6)	184(5)	173(5)	13(4)	-19(4)	7(4)
C(7)	185(6)	211(6)	210(5)	35(4)	-70(5)	-12(5)
C(8)	145(6)	157(5)	286(6)	54(4)	-41(5)	-6(4)
C(9)	177(6)	168(5)	237(5)	19(4)	25(5)	20(4)
C(10)	192(6)	127(5)	180(5)	16(4)	-14(4)	13(4)
C(11)	258(7)	331(7)	186(5)	-2(5)	10(5)	35(6)
C(12)	152(6)	289(7)	436(8)	87(6)	-65(6)	12(5)
C(13)	311(8)	249(6)	171(5)	-12(5)	-13(5)	31(5)
C(14)	130(6)	132(5)	272(6)	0(4)	-39(4)	27(4)
C(15)	236(7)	302(7)	241(6)	-38(5)	-11(5)	-12(5)
C(16)	158(6)	137(5)	248(6)	31(4)	-22(5)	14(4)
C(17)	232(7)	237(7)	401(8)	-37(6)	-48(6)	116(5)
C(18)	207(7)	182(5)	301(6)	22(5)	-30(5)	-21(5)
C(19)	219(7)	292(7)	309(7)	32(5)	-34(5)	-87(5)
C(20)	211(7)	391(8)	323(7)	-5(6)	2(6)	-20(6)

Table A4.1.5 Hydrogen coordinates ($x10^3$) and isotropic displacement parameters ($Å^2x10^3$) for thioimidate ***155***

	x	y	z	U_{iso}
H(1)	622	645	518	21
H(2A)	631	504	490	22
H(2B)	641	510	296	22
H(7)	377	636	25	24
H(9)	320	682	492	23
H(11A)	516	576	-44	39
H(11B)	601	570	84	39
H(11C)	578	656	-2	39
H(12A)	227	677	81	44
H(12B)	221	740	230	44
H(12C)	195	645	255	44
H(13A)	424	663	704	37
H(13B)	522	701	665	37
H(13C)	509	603	672	37
H(15A)	839	538	896	39
H(15B)	745	496	949	39
H(15C)	748	593	910	39
H(17A)	907	335	441	44
H(17B)	994	382	520	44
H(17C)	968	394	330	44
H(18A)	899	735	211	28
H(18B)	834	697	68	28
H(19)	984	711	-34	33
H(20A)	1009	561	128	37
H(20B)	1072	599	-17	37

A4.2 X-RAY CRYSTAL STRUCTURE ANALYSIS OF AMIDINE (*R*)-170•HBr



(R)-170•HBr

Contents

Figure A4.2.1 X-ray crystal structure of amidine ***(R)-170•HBr***

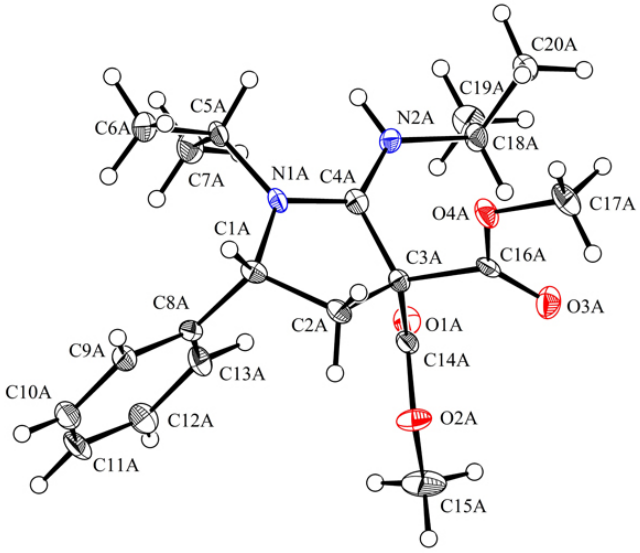


Table A4.2.1 Crystal data and structure refinement for amidine ***(R)-170•HBr***

Caltech Identification Number	afg04
CCDC Deposition Number	911990
Empirical formula	C20 H31 Br N2 O5
Formula weight	459.38
Crystallization solvent	diethyl ether / dichloromethane
Crystal shape	prism
Crystal color	colourless
Crystal size	0.17 x 0.18 x 0.47 mm

Data Collection

Preliminary photograph(s)	rotation	
Type of diffractometer	Bruker KAPPA APEX II	
Wavelength	0.71073 ≈ MO K	
Data collection temperature	100.15 K	
Theta range for 9397 reflections used in lattice determination	2.620 to 31.334∞	
Unit cell dimensions	a = 8.0748(6) ≈ b = 15.1323(12) ≈ c = 29.190(2) ≈	α= 98.815(5)∞ β= 92.189(5)∞ γ = 105.250(4)∞
Volume	3388.9(5) ≈^{3}	
Z	6	
Crystal system	triclinic	
Space group	P 1 (# 1)	
Density (calculated)	1.351 g/cm^3	
F(000)	1440	
Theta range for data collection	1.7 to 35.3∞	
Completeness to theta = 25.00∞	99.7%	
Index ranges	–12 ≤ h ≤ 12, –24 ≤ k ≤ 24, –46 ≤ l ≤ 45	
Data collection scan type	narrow and scans	
Reflections collected	161414	
Independent reflections	54469 [R_{int}= 0.0430]	
Reflections > 2σ(I)	44420	
Average σ(I)/(net I)	0.0781	
Absorption coefficient	1.85 mm^{-1}	
Absorption correction	Semi-empirical from equivalents	

Table A4.2.1 (cont'd)

Max. and min. transmission	1.0000 and 0.8047
Reflections monitored for decay	0
Decay of standards	0%

Structure Solution and Refinement

Primary solution method	direct
Secondary solution method	difmap
Hydrogen placement	geom
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	54469 / 21 / 1585
Treatment of hydrogen atoms	mixed
Goodness-of-fit on F^2	1.65
Final R indices [I>2σ(I), 44420 reflections]	R1 = 0.0568, wR2 = 0.1138
R indices (all data)	R1 = 0.0743, wR2 = 0.1159
Type of weighting scheme used	calc
Weighting scheme used	calc w=1/[^2^(Fo^2^)+(0.0000P)^2^+0.0000P] where P=(Fo^2^+2Fc^2^)/3
Max shift/error	0.001
Average shift/error	0.000
Absolute structure parameter	0.029(3)
Largest diff. peak and hole	3.05 and -1.34 e∑≈$^{-3}$

Programs Used

Cell refinement	SAINT V8.18C (Bruker-AXS, 2007)
Data collection	APEX2_2011.2-3 (Bruker-AXS, 2007)
Data reduction	SAINT V8.18C (Bruker-AXS, 2007)
Structure solution	SHELXS-97 (Sheldrick, 1990)
Structure refinement	
Graphics	

Table A4.2.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for amidine ***(R)-170•HBr****. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U_{eq}
O(1A)	5205(3)	3297(1)	8553(1)	18(1)
O(2A)	8042(3)	3464(1)	8523(1)	23(1)
O(3A)	7013(3)	1830(2)	9013(1)	23(1)
O(4A)	6394(3)	573(1)	8452(1)	19(1)
N(1A)	4511(3)	1542(2)	7520(1)	13(1)
N(2A)	2967(3)	1288(2)	8164(1)	14(1)
C(1A)	6285(4)	1836(2)	7379(1)	14(1)
C(2A)	7391(4)	1877(2)	7827(1)	14(1)
C(3A)	6203(4)	1976(2)	8227(1)	12(1)
C(4A)	4428(4)	1573(2)	7975(1)	14(1)
C(5A)	2951(4)	1256(2)	7188(1)	16(1)
C(6A)	3358(5)	925(2)	6694(1)	24(1)
C(7A)	2076(4)	2039(2)	7207(1)	23(1)
C(8A)	6672(4)	2728(2)	7175(1)	15(1)
C(9A)	7542(4)	2761(2)	6775(1)	18(1)
C(10A)	8003(4)	3575(2)	6590(1)	21(1)
C(11A)	7600(4)	4364(2)	6807(1)	23(1)
C(12A)	6731(4)	4340(2)	7206(1)	22(1)
C(13A)	6259(4)	3527(2)	7390(1)	18(1)
C(14A)	6408(4)	2992(2)	8455(1)	14(1)
C(15A)	8393(5)	4430(2)	8746(1)	34(1)
C(16A)	6583(4)	1461(2)	8621(1)	14(1)
C(17A)	6827(5)	27(2)	8784(1)	25(1)
C(18A)	2705(4)	1332(2)	8666(1)	18(1)
C(19A)	1333(5)	1853(2)	8773(1)	26(1)
C(20A)	2143(4)	350(2)	8781(1)	23(1)
O(1B)	2761(3)	3136(1)	5141(1)	17(1)
O(2B)	5580(3)	3478(1)	5045(1)	21(1)
O(3B)	5020(3)	2039(1)	5691(1)	20(1)

Table A4.2.2 (cont'd)

O(4B)	4388(3)	642(1)	5224(1)	15(1)
N(1B)	2497(3)	1144(2)	4168(1)	13(1)
N(2B)	861(3)	1029(2)	4810(1)	13(1)
C(1B)	4227(4)	1579(2)	4036(1)	12(1)
C(2B)	5323(4)	1771(2)	4507(1)	14(1)
C(3B)	4061(4)	1890(2)	4879(1)	11(1)
C(4B)	2345(4)	1315(2)	4624(1)	10(1)
C(5B)	1134(4)	495(2)	3828(1)	16(1)
C(6B)	1108(6)	-489(2)	3872(1)	34(1)
C(7B)	1377(5)	664(2)	3331(1)	25(1)
C(8B)	4279(4)	2426(2)	3819(1)	16(1)
C(9B)	5329(4)	2597(2)	3455(1)	20(1)
C(10B)	5427(5)	3384(2)	3252(1)	27(1)
C(11B)	4507(5)	4012(2)	3411(1)	27(1)
C(12B)	3444(5)	3838(2)	3769(1)	29(1)
C(13B)	3321(4)	3048(2)	3970(1)	21(1)
C(14B)	4016(4)	2910(2)	5039(1)	14(1)
C(15B)	5731(5)	4454(2)	5218(1)	35(1)
C(16B)	4545(4)	1538(2)	5321(1)	11(1)
C(17B)	4834(4)	217(2)	5610(1)	19(1)
C(18B)	562(4)	1128(2)	5308(1)	16(1)
C(19B)	-769(4)	1662(2)	5395(1)	24(1)
C(20B)	24(5)	159(2)	5438(1)	23(1)
O(1C)	7414(3)	3248(1)	1843(1)	18(1)
O(2C)	10170(3)	3462(1)	1676(1)	20(1)
O(3C)	9486(3)	1908(1)	2270(1)	18(1)
O(4C)	8375(3)	559(1)	1779(1)	17(1)
N(1C)	6577(3)	1420(2)	803(1)	12(1)
N(2C)	5107(3)	1248(2)	1469(1)	14(1)
C(1C)	8322(4)	1713(2)	645(1)	14(1)
C(2C)	9463(4)	1764(2)	1090(1)	14(1)
C(3C)	8351(4)	1926(2)	1498(1)	12(1)
C(4C)	6541(4)	1503(2)	1260(1)	12(1)
C(5C)	4995(4)	1095(2)	474(1)	16(1)

Table A4.2.2 (cont'd)

C(6C)	5401(5)	735(2)	-8(1)	25(1)
C(7C)	4090(4)	1873(2)	480(1)	23(1)
C(8C)	8674(4)	2610(2)	448(1)	14(1)
C(9C)	9607(4)	2662(2)	57(1)	17(1)
C(10C)	10051(4)	3492(2)	-124(1)	22(1)
C(11C)	9592(4)	4260(2)	85(1)	21(1)
C(12C)	8658(4)	4211(2)	475(1)	19(1)
C(13C)	8190(4)	3389(2)	650(1)	17(1)
C(14C)	8566(4)	2959(2)	1696(1)	15(1)
C(15C)	10528(5)	4459(2)	1838(1)	28(1)
C(16C)	8817(4)	1481(2)	1902(1)	13(1)
C(17C)	8809(5)	56(2)	2138(1)	24(1)
C(18C)	4905(4)	1339(2)	1975(1)	15(1)
C(19C)	3653(5)	1915(2)	2094(1)	24(1)
C(20C)	4316(4)	374(2)	2103(1)	20(1)
O(1D)	1240(3)	5108(1)	6240(1)	20(1)
O(2D)	3700(3)	4743(1)	6402(1)	20(1)
O(3D)	4660(3)	6149(1)	5724(1)	18(1)
O(4D)	5282(3)	7583(1)	6158(1)	16(1)
N(1D)	3160(3)	7177(2)	7194(1)	15(1)
N(2D)	1547(3)	7222(2)	6524(1)	14(1)
C(1D)	4426(4)	6735(2)	7354(1)	16(1)
C(2D)	5261(4)	6488(2)	6909(1)	15(1)
C(3D)	3823(4)	6343(2)	6516(1)	13(1)
C(4D)	2718(4)	6949(2)	6737(1)	12(1)
C(5D)	2529(5)	7876(2)	7495(1)	21(1)
C(6D)	3492(7)	8846(2)	7419(1)	44(1)
C(7D)	2737(6)	7782(3)	8001(1)	40(1)
C(8D)	3631(4)	5924(2)	7600(1)	16(1)
C(9D)	4577(4)	5780(2)	7978(1)	19(1)
C(10D)	3931(5)	5037(2)	8204(1)	24(1)
C(11D)	2319(5)	4419(2)	8048(1)	24(1)
C(12D)	1365(4)	4564(2)	7676(1)	24(1)
C(13D)	2023(4)	5321(2)	7453(1)	19(1)

Table A4.2.2 (cont'd)

C(14D)	2742(4)	5328(2)	6366(1)	14(1)
C(15D)	2805(5)	3759(2)	6283(1)	26(1)
C(16D)	4603(4)	6663(2)	6069(1)	18(1)
C(17D)	6055(4)	7985(2)	5766(1)	20(1)
C(18D)	1059(4)	7056(2)	6019(1)	16(1)
C(19D)	-850(4)	6519(2)	5928(1)	22(1)
C(20D)	1460(5)	7990(2)	5849(1)	23(1)
O(1E)	8189(3)	5002(1)	2884(1)	17(1)
O(2E)	10789(3)	4812(1)	3084(1)	20(1)
O(3E)	11510(3)	6349(1)	2459(1)	19(1)
O(4E)	11784(3)	7706(1)	2936(1)	16(1)
N(1E)	9306(3)	6863(2)	3901(1)	14(1)
N(2E)	7912(3)	7004(2)	3214(1)	13(1)
C(1E)	10840(4)	6612(2)	4078(1)	15(1)
C(2E)	11850(4)	6544(2)	3643(1)	16(1)
C(3E)	10485(4)	6346(2)	3224(1)	13(1)
C(4E)	9125(4)	6767(2)	3441(1)	12(1)
C(5E)	8093(4)	7202(2)	4207(1)	17(1)
C(6E)	8924(5)	7597(2)	4695(1)	24(1)
C(7E)	6434(4)	6429(2)	4205(1)	25(1)
C(8E)	10401(4)	5743(2)	4298(1)	14(1)
C(9E)	11448(4)	5716(2)	4684(1)	18(1)
C(10E)	11196(5)	4923(2)	4890(1)	24(1)
C(11E)	9887(4)	4130(2)	4696(1)	25(1)
C(12E)	8829(4)	4150(2)	4313(1)	22(1)
C(13E)	9087(4)	4951(2)	4113(1)	20(1)
C(14E)	9677(4)	5308(2)	3044(1)	13(1)
C(15E)	10098(5)	3806(2)	2945(1)	28(1)
C(16E)	11305(4)	6788(2)	2820(1)	13(1)
C(17E)	12685(5)	8211(2)	2588(1)	22(1)
C(18E)	7528(4)	6881(2)	2704(1)	14(1)
C(19E)	5668(4)	6298(2)	2585(1)	19(1)
C(20E)	7882(4)	7829(2)	2556(1)	20(1)
O(1F)	3235(3)	5134(1)	-412(1)	19(1)

Table A4.2.2 (cont'd)

O(2F)	5671(3)	4755(1)	-225(1)	18(1)
O(3F)	6672(3)	6143(1)	-899(1)	18(1)
O(4F)	7152(3)	7587(1)	-500(1)	16(1)
N(1F)	5150(3)	7135(2)	573(1)	13(1)
N(2F)	3519(3)	7236(2)	-81(1)	12(1)
C(1F)	6479(4)	6698(2)	719(1)	14(1)
C(2F)	7291(4)	6503(2)	261(1)	14(1)
C(3F)	5819(4)	6356(2)	-119(1)	12(1)
C(4F)	4727(4)	6948(2)	117(1)	12(1)
C(5F)	4508(5)	7803(2)	905(1)	21(1)
C(6F)	5459(6)	8792(2)	852(1)	36(1)
C(7F)	4692(5)	7654(2)	1401(1)	27(1)
C(8F)	5722(4)	5850(2)	939(1)	16(1)
C(9F)	6733(5)	5676(2)	1296(1)	21(1)
C(10F)	6146(5)	4885(2)	1498(1)	26(1)
C(11F)	4527(5)	4264(2)	1334(1)	32(1)
C(12F)	3517(5)	4448(2)	988(1)	30(1)
C(13F)	4112(4)	5250(2)	793(1)	22(1)
C(14F)	4735(4)	5344(2)	-269(1)	14(1)
C(15F)	4757(5)	3776(2)	-342(1)	23(1)
C(16F)	6572(4)	6673(2)	-552(1)	11(1)
C(17F)	7860(4)	7967(2)	-903(1)	20(1)
C(18F)	3033(4)	7127(2)	-582(1)	15(1)
C(19F)	1129(4)	6619(2)	-683(1)	21(1)
C(20F)	3407(5)	8094(2)	-714(1)	23(1)
Br(1A)	8079(1)	123(1)	6649(1)	21(1)
Br(1B)	6474(1)	134(1)	3290(1)	18(1)
Br(1C)	137(1)	-30(1)	-14(1)	21(1)
Br(1D)	8418(1)	8234(1)	7949(1)	23(1)
Br(1E)	4521(1)	8396(1)	4618(1)	20(1)
Br(1F)	358(1)	8210(1)	1391(1)	21(1)
O(5A)	9657(3)	349(1)	7734(1)	19(1)
O(5B)	7574(3)	112(2)	4381(1)	21(1)
O(5C)	1767(3)	255(2)	1077(1)	20(1)

Table A4.2.2 (cont'd)

O(5D)	9265(3)	8257(2)	6859(1)	25(1)
O(5E)	5655(3)	8046(1)	3544(1)	18(1)
O(5F)	1187(3)	8178(2)	296(1)	24(1)

Table A4.2.3 Bond lengths [Å] and angles [°] for amidine ***(R)-170•HBr***

O(1A)-C(14A)	1.207(4)
O(2A)-C(14A)	1.316(4)
O(2A)-C(15A)	1.456(3)
O(3A)-C(16A)	1.189(3)
O(4A)-C(16A)	1.326(3)
O(4A)-C(17A)	1.454(4)
N(1A)-C(1A)	1.479(4)
N(1A)-C(4A)	1.327(3)
N(1A)-C(5A)	1.483(4)
N(2A)-H(2A)	0.8800
N(2A)-C(4A)	1.319(4)
N(2A)-C(18A)	1.482(4)
C(1A)-H(1A)	1.0000
C(1A)-C(2A)	1.539(4)
C(1A)-C(8A)	1.521(4)
C(2A)-H(2AA)	0.9900
C(2A)-H(2AB)	0.9900
C(2A)-C(3A)	1.555(4)
C(3A)-C(4A)	1.513(4)
C(3A)-C(14A)	1.541(4)
C(3A)-C(16A)	1.548(4)
C(5A)-H(5A)	1.0000
C(5A)-C(6A)	1.531(4)
C(5A)-C(7A)	1.527(4)
C(6A)-H(6AA)	0.9800
C(6A)-H(6AB)	0.9800
C(6A)-H(6AC)	0.9800
C(7A)-H(7AA)	0.9800
C(7A)-H(7AB)	0.9800
C(7A)-H(7AC)	0.9800
C(8A)-C(9A)	1.386(4)
C(8A)-C(13A)	1.401(4)
C(9A)-H(9A)	0.9500

Table A4.2.3 (cont'd)

C(9A)-C(10A)	1.388(4)
C(10A)-H(10A)	0.9500
C(10A)-C(11A)	1.386(5)
C(11A)-H(11A)	0.9500
C(11A)-C(12A)	1.382(4)
C(12A)-H(12A)	0.9500
C(12A)-C(13A)	1.385(4)
C(13A)-H(13A)	0.9500
C(15A)-H(15G)	0.9800
C(15A)-H(15H)	0.9800
C(15A)-H(15I)	0.9800
C(17A)-H(17G)	0.9800
C(17A)-H(17H)	0.9800
C(17A)-H(17I)	0.9800
C(18A)-H(18A)	1.0000
C(18A)-C(19A)	1.535(5)
C(18A)-C(20A)	1.529(4)
C(19A)-H(19G)	0.9800
C(19A)-H(19H)	0.9800
C(19A)-H(19I)	0.9800
C(20A)-H(20G)	0.9800
C(20A)-H(20H)	0.9800
C(20A)-H(20I)	0.9800
O(1B)-C(14B)	1.186(4)
O(2B)-C(14B)	1.325(3)
O(2B)-C(15B)	1.456(4)
O(3B)-C(16B)	1.204(3)
O(4B)-C(16B)	1.314(3)
O(4B)-C(17B)	1.458(3)
N(1B)-C(1B)	1.473(4)
N(1B)-C(4B)	1.332(3)
N(1B)-C(5B)	1.485(3)
N(2B)-H(2B)	0.8800
N(2B)-C(4B)	1.330(4)

Table A4.2.3 (cont'd)

N(2B)-C(18B)	1.473(3)
C(1B)-H(1B)	1.0000
C(1B)-C(2B)	1.552(4)
C(1B)-C(8B)	1.505(4)
C(2B)-H(2BA)	0.9900
C(2B)-H(2BB)	0.9900
C(2B)-C(3B)	1.540(4)
C(3B)-C(4B)	1.524(4)
C(3B)-C(14B)	1.552(4)
C(3B)-C(16B)	1.544(4)
C(5B)-H(5B)	1.0000
C(5B)-C(6B)	1.509(5)
C(5B)-C(7B)	1.523(4)
C(6B)-H(6BA)	0.9800
C(6B)-H(6BB)	0.9800
C(6B)-H(6BC)	0.9800
C(7B)-H(7BA)	0.9800
C(7B)-H(7BB)	0.9800
C(7B)-H(7BC)	0.9800
C(8B)-C(9B)	1.398(4)
C(8B)-C(13B)	1.401(4)
C(9B)-H(9B)	0.9500
C(9B)-C(10B)	1.395(4)
C(10B)-H(10B)	0.9500
C(10B)-C(11B)	1.391(5)
C(11B)-H(11B)	0.9500
C(11B)-C(12B)	1.391(5)
C(12B)-H(12B)	0.9500
C(12B)-C(13B)	1.393(4)
C(13B)-H(13B)	0.9500
C(15B)-H(15D)	0.9800
C(15B)-H(15E)	0.9800
C(15B)-H(15F)	0.9800
C(17B)-H(17D)	0.9800

Table A4.2.3 (cont'd)

C(17B)-H(17E)	0.9800
C(17B)-H(17F)	0.9800
C(18B)-H(18B)	1.0000
C(18B)-C(19B)	1.513(5)
C(18B)-C(20B)	1.527(4)
C(19B)-H(19D)	0.9800
C(19B)-H(19E)	0.9800
C(19B)-H(19F)	0.9800
C(20B)-H(20D)	0.9800
C(20B)-H(20E)	0.9800
C(20B)-H(20F)	0.9800
O(1C)-C(14C)	1.194(4)
O(2C)-C(14C)	1.327(4)
O(2C)-C(15C)	1.457(3)
O(3C)-C(16C)	1.192(3)
O(4C)-C(16C)	1.334(3)
O(4C)-C(17C)	1.470(4)
N(1C)-C(1C)	1.476(4)
N(1C)-C(4C)	1.322(3)
N(1C)-C(5C)	1.492(4)
N(2C)-H(2C)	0.8800
N(2C)-C(4C)	1.324(4)
N(2C)-C(18C)	1.481(3)
C(1C)-H(1C)	1.0000
C(1C)-C(2C)	1.544(4)
C(1C)-C(8C)	1.517(4)
C(2C)-H(2CA)	0.9900
C(2C)-H(2CB)	0.9900
C(2C)-C(3C)	1.546(4)
C(3C)-C(4C)	1.524(4)
C(3C)-C(14C)	1.544(4)
C(3C)-C(16C)	1.525(4)
C(5C)-H(5C)	1.0000
C(5C)-C(6C)	1.510(4)

Table A4.2.3 (cont'd)

C(5C)-C(7C)	1.539(4)
C(6C)-H(6CA)	0.9800
C(6C)-H(6CB)	0.9800
C(6C)-H(6CC)	0.9800
C(7C)-H(7CA)	0.9800
C(7C)-H(7CB)	0.9800
C(7C)-H(7CC)	0.9800
C(8C)-C(9C)	1.392(4)
C(8C)-C(13C)	1.391(4)
C(9C)-H(9C)	0.9500
C(9C)-C(10C)	1.403(4)
C(10C)-H(10C)	0.9500
C(10C)-C(11C)	1.373(5)
C(11C)-H(11C)	0.9500
C(11C)-C(12C)	1.390(4)
C(12C)-H(12C)	0.9500
C(12C)-C(13C)	1.383(4)
C(13C)-H(13C)	0.9500
C(15C)-H(15A)	0.9800
C(15C)-H(15B)	0.9800
C(15C)-H(15C)	0.9800
C(17C)-H(17A)	0.9800
C(17C)-H(17B)	0.9800
C(17C)-H(17C)	0.9800
C(18C)-H(18C)	1.0000
C(18C)-C(19C)	1.516(5)
C(18C)-C(20C)	1.522(4)
C(19C)-H(19A)	0.9800
C(19C)-H(19B)	0.9800
C(19C)-H(19C)	0.9800
C(20C)-H(20A)	0.9800
C(20C)-H(20B)	0.9800
C(20C)-H(20C)	0.9800
O(1D)-C(14D)	1.197(4)

Table A4.2.3 (cont'd)

O(2D)-C(14D)	1.333(4)
O(2D)-C(15D)	1.454(3)
O(3D)-C(16D)	1.184(4)
O(4D)-C(16D)	1.335(3)
O(4D)-C(17D)	1.462(3)
N(1D)-C(1D)	1.460(4)
N(1D)-C(4D)	1.335(3)
N(1D)-C(5D)	1.478(4)
N(2D)-H(2D)	0.8800
N(2D)-C(4D)	1.300(4)
N(2D)-C(18D)	1.477(4)
C(1D)-H(1D)	1.0000
C(1D)-C(2D)	1.529(4)
C(1D)-C(8D)	1.525(4)
C(2D)-H(2DA)	0.9900
C(2D)-H(2DB)	0.9900
C(2D)-C(3D)	1.549(4)
C(3D)-C(4D)	1.531(4)
C(3D)-C(14D)	1.541(4)
C(3D)-C(16D)	1.559(4)
C(5D)-H(5D)	1.0000
C(5D)-C(6D)	1.523(5)
C(5D)-C(7D)	1.514(4)
C(6D)-H(6DA)	0.9800
C(6D)-H(6DB)	0.9800
C(6D)-H(6DC)	0.9800
C(7D)-H(7DA)	0.9800
C(7D)-H(7DB)	0.9800
C(7D)-H(7DC)	0.9800
C(8D)-C(9D)	1.394(4)
C(8D)-C(13D)	1.384(4)
C(9D)-H(9D)	0.9500
C(9D)-C(10D)	1.385(4)
C(10D)-H(10D)	0.9500

Table A4.2.3 (cont'd)

C(10D)-C(11D)	1.400(5)
C(11D)-H(11D)	0.9500
C(11D)-C(12D)	1.384(5)
C(12D)-H(12D)	0.9500
C(12D)-C(13D)	1.397(4)
C(13D)-H(13D)	0.9500
C(15D)-H(15P)	0.9800
C(15D)-H(15Q)	0.9800
C(15D)-H(15R)	0.9800
C(17D)-H(17P)	0.9800
C(17D)-H(17Q)	0.9800
C(17D)-H(17R)	0.9800
C(18D)-H(18D)	1.0000
C(18D)-C(19D)	1.533(4)
C(18D)-C(20D)	1.527(4)
C(19D)-H(19P)	0.9800
C(19D)-H(19Q)	0.9800
C(19D)-H(19R)	0.9800
C(20D)-H(20P)	0.9800
C(20D)-H(20Q)	0.9800
C(20D)-H(20R)	0.9800
O(1E)-C(14E)	1.215(4)
O(2E)-C(14E)	1.325(4)
O(2E)-C(15E)	1.462(3)
O(3E)-C(16E)	1.200(3)
O(4E)-C(16E)	1.325(3)
O(4E)-C(17E)	1.465(3)
N(1E)-C(1E)	1.485(4)
N(1E)-C(4E)	1.327(3)
N(1E)-C(5E)	1.486(4)
N(2E)-H(2E)	0.8800
N(2E)-C(4E)	1.317(4)
N(2E)-C(18E)	1.481(4)
C(1E)-H(1E)	1.0000

Table A4.2.3 (cont'd)

C(1E)-C(2E)	1.541(4)
C(1E)-C(8E)	1.515(4)
C(2E)-H(2EA)	0.9900
C(2E)-H(2EB)	0.9900
C(2E)-C(3E)	1.553(4)
C(3E)-C(4E)	1.520(4)
C(3E)-C(14E)	1.533(4)
C(3E)-C(16E)	1.532(4)
C(5E)-H(5E)	1.0000
C(5E)-C(6E)	1.514(4)
C(5E)-C(7E)	1.528(4)
C(6E)-H(6EA)	0.9800
C(6E)-H(6EB)	0.9800
C(6E)-H(6EC)	0.9800
C(7E)-H(7EA)	0.9800
C(7E)-H(7EB)	0.9800
C(7E)-H(7EC)	0.9800
C(8E)-C(9E)	1.394(4)
C(8E)-C(13E)	1.394(4)
C(9E)-H(9E)	0.9500
C(9E)-C(10E)	1.396(4)
C(10E)-H(10E)	0.9500
C(10E)-C(11E)	1.398(5)
C(11E)-H(11E)	0.9500
C(11E)-C(12E)	1.390(5)
C(12E)-H(12E)	0.9500
C(12E)-C(13E)	1.396(4)
C(13E)-H(13E)	0.9500
C(15E)-H(15M)	0.9800
C(15E)-H(15N)	0.9800
C(15E)-H(15O)	0.9800
C(17E)-H(17M)	0.9800
C(17E)-H(17N)	0.9800
C(17E)-H(17O)	0.9800

Table A4.2.3 (cont'd)

C(18E)-H(18E)	1.0000
C(18E)-C(19E)	1.525(4)
C(18E)-C(20E)	1.520(4)
C(19E)-H(19M)	0.9800
C(19E)-H(19N)	0.9800
C(19E)-H(19O)	0.9800
C(20E)-H(20M)	0.9800
C(20E)-H(20N)	0.9800
C(20E)-H(20O)	0.9800
O(1F)-C(14F)	1.209(4)
O(2F)-C(14F)	1.328(4)
O(2F)-C(15F)	1.451(3)
O(3F)-C(16F)	1.212(3)
O(4F)-C(16F)	1.321(3)
O(4F)-C(17F)	1.459(3)
N(1F)-C(1F)	1.481(4)
N(1F)-C(4F)	1.329(3)
N(1F)-C(5F)	1.497(4)
N(2F)-H(2F)	0.8800
N(2F)-C(4F)	1.316(4)
N(2F)-C(18F)	1.473(3)
C(1F)-H(1F)	1.0000
C(1F)-C(2F)	1.533(4)
C(1F)-C(8F)	1.517(4)
C(2F)-H(2FA)	0.9900
C(2F)-H(2FB)	0.9900
C(2F)-C(3F)	1.542(4)
C(3F)-C(4F)	1.526(4)
C(3F)-C(14F)	1.537(4)
C(3F)-C(16F)	1.513(4)
C(5F)-H(5F)	1.0000
C(5F)-C(6F)	1.526(5)
C(5F)-C(7F)	1.506(4)
C(6F)-H(6FA)	0.9800

Table A4.2.3 (cont'd)

C(6F)-H(6FB)	0.9800
C(6F)-H(6FC)	0.9800
C(7F)-H(7FA)	0.9800
C(7F)-H(7FB)	0.9800
C(7F)-H(7FC)	0.9800
C(8F)-C(9F)	1.398(4)
C(8F)-C(13F)	1.383(4)
C(9F)-H(9F)	0.9500
C(9F)-C(10F)	1.394(4)
C(10F)-H(10F)	0.9500
C(10F)-C(11F)	1.410(5)
C(11F)-H(11F)	0.9500
C(11F)-C(12F)	1.381(6)
C(12F)-H(12F)	0.9500
C(12F)-C(13F)	1.397(4)
C(13F)-H(13F)	0.9500
C(15F)-H(15J)	0.9800
C(15F)-H(15K)	0.9800
C(15F)-H(15L)	0.9800
C(17F)-H(17J)	0.9800
C(17F)-H(17K)	0.9800
C(17F)-H(17L)	0.9800
C(18F)-H(18F)	1.0000
C(18F)-C(19F)	1.521(4)
C(18F)-C(20F)	1.527(4)
C(19F)-H(19J)	0.9800
C(19F)-H(19K)	0.9800
C(19F)-H(19L)	0.9800
C(20F)-H(20J)	0.9800
C(20F)-H(20K)	0.9800
C(20F)-H(20L)	0.9800
O(5A)-H(5AA)	0.846(17)
O(5A)-H(5AB)	0.830(17)
O(5B)-H(5BA)	0.863(17)

Table A4.2.3 (cont'd)

O(5B)-H(5BB)	0.845(17)
O(5C)-H(5CA)	0.882(17)
O(5C)-H(5CB)	0.850(17)
O(5D)-H(5DA)	0.874(18)
O(5D)-H(5DB)	0.895(17)
O(5E)-H(5EA)	0.857(17)
O(5E)-H(5EB)	0.891(17)
O(5F)-H(5FA)	0.866(19)
O(5F)-H(5FB)	0.896(18)

C(14A)-O(2A)-C(15A)	115.9(3)
C(16A)-O(4A)-C(17A)	115.2(2)
C(1A)-N(1A)-C(5A)	123.7(2)
C(4A)-N(1A)-C(1A)	113.8(2)
C(4A)-N(1A)-C(5A)	122.5(2)
C(4A)-N(2A)-H(2A)	116.3
C(4A)-N(2A)-C(18A)	127.4(3)
C(18A)-N(2A)-H(2A)	116.3
N(1A)-C(1A)-H(1A)	108.2
N(1A)-C(1A)-C(2A)	102.6(2)
N(1A)-C(1A)-C(8A)	113.9(2)
C(2A)-C(1A)-H(1A)	108.2
C(8A)-C(1A)-H(1A)	108.2
C(8A)-C(1A)-C(2A)	115.3(2)
C(1A)-C(2A)-H(2AA)	110.7
C(1A)-C(2A)-H(2AB)	110.7
C(1A)-C(2A)-C(3A)	105.2(2)
H(2AA)-C(2A)-H(2AB)	108.8
C(3A)-C(2A)-H(2AA)	110.7
C(3A)-C(2A)-H(2AB)	110.7
C(4A)-C(3A)-C(2A)	101.9(2)
C(4A)-C(3A)-C(14A)	109.6(2)
C(4A)-C(3A)-C(16A)	114.3(2)
C(14A)-C(3A)-C(2A)	113.6(2)

Table A4.2.3 (cont'd)

C(14A)-C(3A)-C(16A)	106.5(2)
C(16A)-C(3A)-C(2A)	111.1(2)
N(1A)-C(4A)-C(3A)	110.6(2)
N(2A)-C(4A)-N(1A)	122.7(3)
N(2A)-C(4A)-C(3A)	126.8(2)
N(1A)-C(5A)-H(5A)	107.5
N(1A)-C(5A)-C(6A)	111.8(3)
N(1A)-C(5A)-C(7A)	110.5(2)
C(6A)-C(5A)-H(5A)	107.5
C(7A)-C(5A)-H(5A)	107.5
C(7A)-C(5A)-C(6A)	111.9(3)
C(5A)-C(6A)-H(6AA)	109.5
C(5A)-C(6A)-H(6AB)	109.5
C(5A)-C(6A)-H(6AC)	109.5
H(6AA)-C(6A)-H(6AB)	109.5
H(6AA)-C(6A)-H(6AC)	109.5
H(6AB)-C(6A)-H(6AC)	109.5
C(5A)-C(7A)-H(7AA)	109.5
C(5A)-C(7A)-H(7AB)	109.5
C(5A)-C(7A)-H(7AC)	109.5
H(7AA)-C(7A)-H(7AB)	109.5
H(7AA)-C(7A)-H(7AC)	109.5
H(7AB)-C(7A)-H(7AC)	109.5
C(9A)-C(8A)-C(1A)	118.4(3)
C(9A)-C(8A)-C(13A)	119.2(3)
C(13A)-C(8A)-C(1A)	122.3(3)
C(8A)-C(9A)-H(9A)	119.8
C(8A)-C(9A)-C(10A)	120.4(3)
C(10A)-C(9A)-H(9A)	119.8
C(9A)-C(10A)-H(10A)	120.0
C(11A)-C(10A)-C(9A)	120.0(3)
C(11A)-C(10A)-H(10A)	120.0
C(10A)-C(11A)-H(11A)	119.9
C(12A)-C(11A)-C(10A)	120.1(3)

Table A4.2.3 (cont'd)

C(12A)-C(11A)-H(11A)	119.9
C(11A)-C(12A)-H(12A)	119.9
C(11A)-C(12A)-C(13A)	120.1(3)
C(13A)-C(12A)-H(12A)	119.9
C(8A)-C(13A)-H(13A)	119.9
C(12A)-C(13A)-C(8A)	120.1(3)
C(12A)-C(13A)-H(13A)	119.9
O(1A)-C(14A)-O(2A)	125.7(3)
O(1A)-C(14A)-C(3A)	123.3(3)
O(2A)-C(14A)-C(3A)	111.1(2)
O(2A)-C(15A)-H(15G)	109.5
O(2A)-C(15A)-H(15H)	109.5
O(2A)-C(15A)-H(15I)	109.5
H(15G)-C(15A)-H(15H)	109.5
H(15G)-C(15A)-H(15I)	109.5
H(15H)-C(15A)-H(15I)	109.5
O(3A)-C(16A)-O(4A)	126.2(3)
O(3A)-C(16A)-C(3A)	123.8(2)
O(4A)-C(16A)-C(3A)	110.0(2)
O(4A)-C(17A)-H(17G)	109.5
O(4A)-C(17A)-H(17H)	109.5
O(4A)-C(17A)-H(17I)	109.5
H(17G)-C(17A)-H(17H)	109.5
H(17G)-C(17A)-H(17I)	109.5
H(17H)-C(17A)-H(17I)	109.5
N(2A)-C(18A)-H(18A)	109.3
N(2A)-C(18A)-C(19A)	107.7(3)
N(2A)-C(18A)-C(20A)	109.9(2)
C(19A)-C(18A)-H(18A)	109.3
C(20A)-C(18A)-H(18A)	109.3
C(20A)-C(18A)-C(19A)	111.3(3)
C(18A)-C(19A)-H(19G)	109.5
C(18A)-C(19A)-H(19H)	109.5
C(18A)-C(19A)-H(19I)	109.5

Table A4.2.3 (cont'd)

H(19G)-C(19A)-H(19H)	109.5
H(19G)-C(19A)-H(19I)	109.5
H(19H)-C(19A)-H(19I)	109.5
C(18A)-C(20A)-H(20G)	109.5
C(18A)-C(20A)-H(20H)	109.5
C(18A)-C(20A)-H(20I)	109.5
H(20G)-C(20A)-H(20H)	109.5
H(20G)-C(20A)-H(20I)	109.5
H(20H)-C(20A)-H(20I)	109.5
C(14B)-O(2B)-C(15B)	115.1(3)
C(16B)-O(4B)-C(17B)	115.6(2)
C(1B)-N(1B)-C(5B)	122.4(2)
C(4B)-N(1B)-C(1B)	113.4(2)
C(4B)-N(1B)-C(5B)	123.9(2)
C(4B)-N(2B)-H(2B)	116.3
C(4B)-N(2B)-C(18B)	127.4(2)
C(18B)-N(2B)-H(2B)	116.3
N(1B)-C(1B)-H(1B)	109.3
N(1B)-C(1B)-C(2B)	101.5(2)
N(1B)-C(1B)-C(8B)	112.3(2)
C(2B)-C(1B)-H(1B)	109.3
C(8B)-C(1B)-H(1B)	109.3
C(8B)-C(1B)-C(2B)	114.9(2)
C(1B)-C(2B)-H(2BA)	110.8
C(1B)-C(2B)-H(2BB)	110.8
H(2BA)-C(2B)-H(2BB)	108.9
C(3B)-C(2B)-C(1B)	104.9(2)
C(3B)-C(2B)-H(2BA)	110.8
C(3B)-C(2B)-H(2BB)	110.8
C(2B)-C(3B)-C(14B)	114.4(2)
C(2B)-C(3B)-C(16B)	110.6(2)
C(4B)-C(3B)-C(2B)	101.5(2)
C(4B)-C(3B)-C(14B)	110.4(2)
C(4B)-C(3B)-C(16B)	113.9(2)

Table A4.2.3 (cont'd)

C(16B)-C(3B)-C(14B)	106.2(2)
N(1B)-C(4B)-C(3B)	110.4(2)
N(2B)-C(4B)-N(1B)	122.7(2)
N(2B)-C(4B)-C(3B)	126.9(2)
N(1B)-C(5B)-H(5B)	108.1
N(1B)-C(5B)-C(6B)	108.7(3)
N(1B)-C(5B)-C(7B)	112.4(2)
C(6B)-C(5B)-H(5B)	108.1
C(6B)-C(5B)-C(7B)	111.1(3)
C(7B)-C(5B)-H(5B)	108.1
C(5B)-C(6B)-H(6BA)	109.5
C(5B)-C(6B)-H(6BB)	109.5
C(5B)-C(6B)-H(6BC)	109.5
H(6BA)-C(6B)-H(6BB)	109.5
H(6BA)-C(6B)-H(6BC)	109.5
H(6BB)-C(6B)-H(6BC)	109.5
C(5B)-C(7B)-H(7BA)	109.5
C(5B)-C(7B)-H(7BB)	109.5
C(5B)-C(7B)-H(7BC)	109.5
H(7BA)-C(7B)-H(7BB)	109.5
H(7BA)-C(7B)-H(7BC)	109.5
H(7BB)-C(7B)-H(7BC)	109.5
C(9B)-C(8B)-C(1B)	118.6(3)
C(9B)-C(8B)-C(13B)	118.9(3)
C(13B)-C(8B)-C(1B)	122.4(3)
C(8B)-C(9B)-H(9B)	120.0
C(10B)-C(9B)-C(8B)	120.0(3)
C(10B)-C(9B)-H(9B)	120.0
C(9B)-C(10B)-H(10B)	119.6
C(11B)-C(10B)-C(9B)	120.8(3)
C(11B)-C(10B)-H(10B)	119.6
C(10B)-C(11B)-H(11B)	120.3
C(10B)-C(11B)-C(12B)	119.3(3)
C(12B)-C(11B)-H(11B)	120.3

Table A4.2.3 (cont'd)

C(11B)-C(12B)-H(12B)	119.9
C(11B)-C(12B)-C(13B)	120.2(3)
C(13B)-C(12B)-H(12B)	119.9
C(8B)-C(13B)-H(13B)	119.7
C(12B)-C(13B)-C(8B)	120.6(3)
C(12B)-C(13B)-H(13B)	119.7
O(1B)-C(14B)-O(2B)	125.7(3)
O(1B)-C(14B)-C(3B)	124.5(2)
O(2B)-C(14B)-C(3B)	109.8(2)
O(2B)-C(15B)-H(15D)	109.5
O(2B)-C(15B)-H(15E)	109.5
O(2B)-C(15B)-H(15F)	109.5
H(15D)-C(15B)-H(15E)	109.5
H(15D)-C(15B)-H(15F)	109.5
H(15E)-C(15B)-H(15F)	109.5
O(3B)-C(16B)-O(4B)	127.1(3)
O(3B)-C(16B)-C(3B)	123.2(2)
O(4B)-C(16B)-C(3B)	109.7(2)
O(4B)-C(17B)-H(17D)	109.5
O(4B)-C(17B)-H(17E)	109.5
O(4B)-C(17B)-H(17F)	109.5
H(17D)-C(17B)-H(17E)	109.5
H(17D)-C(17B)-H(17F)	109.5
H(17E)-C(17B)-H(17F)	109.5
N(2B)-C(18B)-H(18B)	108.8
N(2B)-C(18B)-C(19B)	108.8(3)
N(2B)-C(18B)-C(20B)	108.3(2)
C(19B)-C(18B)-H(18B)	108.8
C(19B)-C(18B)-C(20B)	113.3(3)
C(20B)-C(18B)-H(18B)	108.8
C(18B)-C(19B)-H(19D)	109.5
C(18B)-C(19B)-H(19E)	109.5
C(18B)-C(19B)-H(19F)	109.5
H(19D)-C(19B)-H(19E)	109.5

Table A4.2.3 (cont'd)

H(19D)-C(19B)-H(19F)	109.5
H(19E)-C(19B)-H(19F)	109.5
C(18B)-C(20B)-H(20D)	109.5
C(18B)-C(20B)-H(20E)	109.5
C(18B)-C(20B)-H(20F)	109.5
H(20D)-C(20B)-H(20E)	109.5
H(20D)-C(20B)-H(20F)	109.5
H(20E)-C(20B)-H(20F)	109.5
C(14C)-O(2C)-C(15C)	116.4(2)
C(16C)-O(4C)-C(17C)	114.6(2)
C(1C)-N(1C)-C(5C)	122.5(2)
C(4C)-N(1C)-C(1C)	114.1(2)
C(4C)-N(1C)-C(5C)	123.3(2)
C(4C)-N(2C)-H(2C)	116.0
C(4C)-N(2C)-C(18C)	128.0(2)
C(18C)-N(2C)-H(2C)	116.0
N(1C)-C(1C)-H(1C)	108.9
N(1C)-C(1C)-C(2C)	101.6(2)
N(1C)-C(1C)-C(8C)	113.8(2)
C(2C)-C(1C)-H(1C)	108.9
C(8C)-C(1C)-H(1C)	108.9
C(8C)-C(1C)-C(2C)	114.5(2)
C(1C)-C(2C)-H(2CA)	110.6
C(1C)-C(2C)-H(2CB)	110.6
C(1C)-C(2C)-C(3C)	105.5(2)
H(2CA)-C(2C)-H(2CB)	108.8
C(3C)-C(2C)-H(2CA)	110.6
C(3C)-C(2C)-H(2CB)	110.6
C(4C)-C(3C)-C(2C)	101.2(2)
C(4C)-C(3C)-C(14C)	109.0(2)
C(4C)-C(3C)-C(16C)	115.9(2)
C(14C)-C(3C)-C(2C)	114.2(2)
C(16C)-C(3C)-C(2C)	110.4(2)
C(16C)-C(3C)-C(14C)	106.4(2)

Table A4.2.3 (cont'd)

N(1C)-C(4C)-N(2C)	123.3(3)
N(1C)-C(4C)-C(3C)	110.4(2)
N(2C)-C(4C)-C(3C)	126.3(2)
N(1C)-C(5C)-H(5C)	107.5
N(1C)-C(5C)-C(6C)	111.3(3)
N(1C)-C(5C)-C(7C)	110.1(2)
C(6C)-C(5C)-H(5C)	107.5
C(6C)-C(5C)-C(7C)	112.6(3)
C(7C)-C(5C)-H(5C)	107.5
C(5C)-C(6C)-H(6CA)	109.5
C(5C)-C(6C)-H(6CB)	109.5
C(5C)-C(6C)-H(6CC)	109.5
H(6CA)-C(6C)-H(6CB)	109.5
H(6CA)-C(6C)-H(6CC)	109.5
H(6CB)-C(6C)-H(6CC)	109.5
C(5C)-C(7C)-H(7CA)	109.5
C(5C)-C(7C)-H(7CB)	109.5
C(5C)-C(7C)-H(7CC)	109.5
H(7CA)-C(7C)-H(7CB)	109.5
H(7CA)-C(7C)-H(7CC)	109.5
H(7CB)-C(7C)-H(7CC)	109.5
C(9C)-C(8C)-C(1C)	117.5(2)
C(13C)-C(8C)-C(1C)	123.6(2)
C(13C)-C(8C)-C(9C)	118.8(3)
C(8C)-C(9C)-H(9C)	120.0
C(8C)-C(9C)-C(10C)	119.9(3)
C(10C)-C(9C)-H(9C)	120.0
C(9C)-C(10C)-H(10C)	119.8
C(11C)-C(10C)-C(9C)	120.4(3)
C(11C)-C(10C)-H(10C)	119.8
C(10C)-C(11C)-H(11C)	120.0
C(10C)-C(11C)-C(12C)	119.9(3)
C(12C)-C(11C)-H(11C)	120.0
C(11C)-C(12C)-H(12C)	120.1

Table A4.2.3 (cont'd)

C(13C)-C(12C)-C(11C)	119.8(3)
C(13C)-C(12C)-H(12C)	120.1
C(8C)-C(13C)-H(13C)	119.4
C(12C)-C(13C)-C(8C)	121.1(3)
C(12C)-C(13C)-H(13C)	119.4
O(1C)-C(14C)-O(2C)	125.9(3)
O(1C)-C(14C)-C(3C)	123.2(3)
O(2C)-C(14C)-C(3C)	110.9(2)
O(2C)-C(15C)-H(15A)	109.5
O(2C)-C(15C)-H(15B)	109.5
O(2C)-C(15C)-H(15C)	109.5
H(15A)-C(15C)-H(15B)	109.5
H(15A)-C(15C)-H(15C)	109.5
H(15B)-C(15C)-H(15C)	109.5
O(3C)-C(16C)-O(4C)	126.0(3)
O(3C)-C(16C)-C(3C)	124.1(2)
O(4C)-C(16C)-C(3C)	109.9(2)
O(4C)-C(17C)-H(17A)	109.5
O(4C)-C(17C)-H(17B)	109.5
O(4C)-C(17C)-H(17C)	109.5
H(17A)-C(17C)-H(17B)	109.5
H(17A)-C(17C)-H(17C)	109.5
H(17B)-C(17C)-H(17C)	109.5
N(2C)-C(18C)-H(18C)	108.7
N(2C)-C(18C)-C(19C)	109.0(2)
N(2C)-C(18C)-C(20C)	109.0(2)
C(19C)-C(18C)-H(18C)	108.7
C(19C)-C(18C)-C(20C)	112.7(3)
C(20C)-C(18C)-H(18C)	108.7
C(18C)-C(19C)-H(19A)	109.5
C(18C)-C(19C)-H(19B)	109.5
C(18C)-C(19C)-H(19C)	109.5
H(19A)-C(19C)-H(19B)	109.5
H(19A)-C(19C)-H(19C)	109.5

Table A4.2.3 (cont'd)

H(19B)-C(19C)-H(19C)	109.5
C(18C)-C(20C)-H(20A)	109.5
C(18C)-C(20C)-H(20B)	109.5
C(18C)-C(20C)-H(20C)	109.5
H(20A)-C(20C)-H(20B)	109.5
H(20A)-C(20C)-H(20C)	109.5
H(20B)-C(20C)-H(20C)	109.5
C(14D)-O(2D)-C(15D)	115.9(3)
C(16D)-O(4D)-C(17D)	114.6(2)
C(1D)-N(1D)-C(5D)	123.8(2)
C(4D)-N(1D)-C(1D)	113.7(2)
C(4D)-N(1D)-C(5D)	122.3(2)
C(4D)-N(2D)-H(2D)	116.2
C(4D)-N(2D)-C(18D)	127.6(3)
C(18D)-N(2D)-H(2D)	116.2
N(1D)-C(1D)-H(1D)	108.5
N(1D)-C(1D)-C(2D)	102.4(2)
N(1D)-C(1D)-C(8D)	112.9(2)
C(2D)-C(1D)-H(1D)	108.5
C(8D)-C(1D)-H(1D)	108.5
C(8D)-C(1D)-C(2D)	115.6(2)
C(1D)-C(2D)-H(2DA)	110.9
C(1D)-C(2D)-H(2DB)	110.9
C(1D)-C(2D)-C(3D)	104.1(2)
H(2DA)-C(2D)-H(2DB)	109.0
C(3D)-C(2D)-H(2DA)	110.9
C(3D)-C(2D)-H(2DB)	110.9
C(2D)-C(3D)-C(16D)	110.7(2)
C(4D)-C(3D)-C(2D)	102.1(2)
C(4D)-C(3D)-C(14D)	111.0(2)
C(4D)-C(3D)-C(16D)	112.7(2)
C(14D)-C(3D)-C(2D)	114.5(2)
C(14D)-C(3D)-C(16D)	106.1(2)
N(1D)-C(4D)-C(3D)	109.1(2)

Table A4.2.3 (cont'd)

N(2D)-C(4D)-N(1D)	124.0(3)
N(2D)-C(4D)-C(3D)	126.9(2)
N(1D)-C(5D)-H(5D)	108.5
N(1D)-C(5D)-C(6D)	109.5(3)
N(1D)-C(5D)-C(7D)	111.0(3)
C(6D)-C(5D)-H(5D)	108.5
C(7D)-C(5D)-H(5D)	108.5
C(7D)-C(5D)-C(6D)	110.9(3)
C(5D)-C(6D)-H(6DA)	109.5
C(5D)-C(6D)-H(6DB)	109.5
C(5D)-C(6D)-H(6DC)	109.5
H(6DA)-C(6D)-H(6DB)	109.5
H(6DA)-C(6D)-H(6DC)	109.5
H(6DB)-C(6D)-H(6DC)	109.5
C(5D)-C(7D)-H(7DA)	109.5
C(5D)-C(7D)-H(7DB)	109.5
C(5D)-C(7D)-H(7DC)	109.5
H(7DA)-C(7D)-H(7DB)	109.5
H(7DA)-C(7D)-H(7DC)	109.5
H(7DB)-C(7D)-H(7DC)	109.5
C(9D)-C(8D)-C(1D)	118.6(3)
C(13D)-C(8D)-C(1D)	121.9(3)
C(13D)-C(8D)-C(9D)	119.5(3)
C(8D)-C(9D)-H(9D)	119.7
C(10D)-C(9D)-C(8D)	120.7(3)
C(10D)-C(9D)-H(9D)	119.7
C(9D)-C(10D)-H(10D)	120.3
C(9D)-C(10D)-C(11D)	119.5(3)
C(11D)-C(10D)-H(10D)	120.3
C(10D)-C(11D)-H(11D)	119.9
C(12D)-C(11D)-C(10D)	120.1(3)
C(12D)-C(11D)-H(11D)	119.9
C(11D)-C(12D)-H(12D)	120.1
C(11D)-C(12D)-C(13D)	119.9(3)

Table A4.2.3 (cont'd)

C(13D)-C(12D)-H(12D)	120.1
C(8D)-C(13D)-C(12D)	120.3(3)
C(8D)-C(13D)-H(13D)	119.9
C(12D)-C(13D)-H(13D)	119.9
O(1D)-C(14D)-O(2D)	125.5(3)
O(1D)-C(14D)-C(3D)	123.7(3)
O(2D)-C(14D)-C(3D)	110.8(2)
O(2D)-C(15D)-H(15P)	109.5
O(2D)-C(15D)-H(15Q)	109.5
O(2D)-C(15D)-H(15R)	109.5
H(15P)-C(15D)-H(15Q)	109.5
H(15P)-C(15D)-H(15R)	109.5
H(15Q)-C(15D)-H(15R)	109.5
O(3D)-C(16D)-O(4D)	127.4(3)
O(3D)-C(16D)-C(3D)	124.0(3)
O(4D)-C(16D)-C(3D)	108.5(2)
O(4D)-C(17D)-H(17P)	109.5
O(4D)-C(17D)-H(17Q)	109.5
O(4D)-C(17D)-H(17R)	109.5
H(17P)-C(17D)-H(17Q)	109.5
H(17P)-C(17D)-H(17R)	109.5
H(17Q)-C(17D)-H(17R)	109.5
N(2D)-C(18D)-H(18D)	108.8
N(2D)-C(18D)-C(19D)	108.8(2)
N(2D)-C(18D)-C(20D)	108.8(2)
C(19D)-C(18D)-H(18D)	108.8
C(20D)-C(18D)-H(18D)	108.8
C(20D)-C(18D)-C(19D)	112.7(3)
C(18D)-C(19D)-H(19P)	109.5
C(18D)-C(19D)-H(19Q)	109.5
C(18D)-C(19D)-H(19R)	109.5
H(19P)-C(19D)-H(19Q)	109.5
H(19P)-C(19D)-H(19R)	109.5
H(19Q)-C(19D)-H(19R)	109.5

Table A4.2.3 (cont'd)

C(18D)-C(20D)-H(20P)	109.5
C(18D)-C(20D)-H(20Q)	109.5
C(18D)-C(20D)-H(20R)	109.5
H(20P)-C(20D)-H(20Q)	109.5
H(20P)-C(20D)-H(20R)	109.5
H(20Q)-C(20D)-H(20R)	109.5
C(14E)-O(2E)-C(15E)	115.7(2)
C(16E)-O(4E)-C(17E)	115.6(2)
C(1E)-N(1E)-C(5E)	123.7(2)
C(4E)-N(1E)-C(1E)	113.6(2)
C(4E)-N(1E)-C(5E)	122.7(3)
C(4E)-N(2E)-H(2E)	116.0
C(4E)-N(2E)-C(18E)	128.1(3)
C(18E)-N(2E)-H(2E)	116.0
N(1E)-C(1E)-H(1E)	108.6
N(1E)-C(1E)-C(2E)	102.3(2)
N(1E)-C(1E)-C(8E)	113.7(2)
C(2E)-C(1E)-H(1E)	108.6
C(8E)-C(1E)-H(1E)	108.6
C(8E)-C(1E)-C(2E)	114.8(2)
C(1E)-C(2E)-H(2EA)	110.7
C(1E)-C(2E)-H(2EB)	110.7
C(1E)-C(2E)-C(3E)	105.2(2)
H(2EA)-C(2E)-H(2EB)	108.8
C(3E)-C(2E)-H(2EA)	110.7
C(3E)-C(2E)-H(2EB)	110.7
C(4E)-C(3E)-C(2E)	101.4(2)
C(4E)-C(3E)-C(14E)	109.2(2)
C(4E)-C(3E)-C(16E)	114.9(2)
C(14E)-C(3E)-C(2E)	113.6(2)
C(16E)-C(3E)-C(2E)	109.9(2)
C(16E)-C(3E)-C(14E)	107.9(2)
N(1E)-C(4E)-C(3E)	110.5(2)
N(2E)-C(4E)-N(1E)	123.4(3)

Table A4.2.3 (cont'd)

N(2E)-C(4E)-C(3E)	126.1(2)
N(1E)-C(5E)-H(5E)	107.7
N(1E)-C(5E)-C(6E)	111.4(3)
N(1E)-C(5E)-C(7E)	110.5(2)
C(6E)-C(5E)-H(5E)	107.7
C(6E)-C(5E)-C(7E)	111.8(3)
C(7E)-C(5E)-H(5E)	107.7
C(5E)-C(6E)-H(6EA)	109.5
C(5E)-C(6E)-H(6EB)	109.5
C(5E)-C(6E)-H(6EC)	109.5
H(6EA)-C(6E)-H(6EB)	109.5
H(6EA)-C(6E)-H(6EC)	109.5
H(6EB)-C(6E)-H(6EC)	109.5
C(5E)-C(7E)-H(7EA)	109.5
C(5E)-C(7E)-H(7EB)	109.5
C(5E)-C(7E)-H(7EC)	109.5
H(7EA)-C(7E)-H(7EB)	109.5
H(7EA)-C(7E)-H(7EC)	109.5
H(7EB)-C(7E)-H(7EC)	109.5
C(9E)-C(8E)-C(1E)	117.9(2)
C(13E)-C(8E)-C(1E)	123.2(3)
C(13E)-C(8E)-C(9E)	118.8(3)
C(8E)-C(9E)-H(9E)	119.2
C(8E)-C(9E)-C(10E)	121.6(3)
C(10E)-C(9E)-H(9E)	119.2
C(9E)-C(10E)-H(10E)	120.6
C(9E)-C(10E)-C(11E)	118.8(3)
C(11E)-C(10E)-H(10E)	120.6
C(10E)-C(11E)-H(11E)	120.0
C(12E)-C(11E)-C(10E)	120.0(3)
C(12E)-C(11E)-H(11E)	120.0
C(11E)-C(12E)-H(12E)	119.8
C(11E)-C(12E)-C(13E)	120.5(3)
C(13E)-C(12E)-H(12E)	119.8

Table A4.2.3 (cont'd)

C(8E)-C(13E)-C(12E)	120.2(3)
C(8E)-C(13E)-H(13E)	119.9
C(12E)-C(13E)-H(13E)	119.9
O(1E)-C(14E)-O(2E)	125.6(2)
O(1E)-C(14E)-C(3E)	122.3(3)
O(2E)-C(14E)-C(3E)	112.1(2)
O(2E)-C(15E)-H(15M)	109.5
O(2E)-C(15E)-H(15N)	109.5
O(2E)-C(15E)-H(15O)	109.5
H(15M)-C(15E)-H(15N)	109.5
H(15M)-C(15E)-H(15O)	109.5
H(15N)-C(15E)-H(15O)	109.5
O(3E)-C(16E)-O(4E)	126.0(3)
O(3E)-C(16E)-C(3E)	123.6(2)
O(4E)-C(16E)-C(3E)	110.3(2)
O(4E)-C(17E)-H(17M)	109.5
O(4E)-C(17E)-H(17N)	109.5
O(4E)-C(17E)-H(17O)	109.5
H(17M)-C(17E)-H(17N)	109.5
H(17M)-C(17E)-H(17O)	109.5
H(17N)-C(17E)-H(17O)	109.5
N(2E)-C(18E)-H(18E)	108.7
N(2E)-C(18E)-C(19E)	108.1(2)
N(2E)-C(18E)-C(20E)	109.4(2)
C(19E)-C(18E)-H(18E)	108.7
C(20E)-C(18E)-H(18E)	108.7
C(20E)-C(18E)-C(19E)	113.2(3)
C(18E)-C(19E)-H(19M)	109.5
C(18E)-C(19E)-H(19N)	109.5
C(18E)-C(19E)-H(19O)	109.5
H(19M)-C(19E)-H(19N)	109.5
H(19M)-C(19E)-H(19O)	109.5
H(19N)-C(19E)-H(19O)	109.5
C(18E)-C(20E)-H(20M)	109.5

Table A4.2.3 (cont'd)

C(18E)-C(20E)-H(20N)	109.5
C(18E)-C(20E)-H(20O)	109.5
H(20M)-C(20E)-H(20N)	109.5
H(20M)-C(20E)-H(20O)	109.5
H(20N)-C(20E)-H(20O)	109.5
C(14F)-O(2F)-C(15F)	115.7(2)
C(16F)-O(4F)-C(17F)	116.4(2)
C(1F)-N(1F)-C(5F)	122.3(2)
C(4F)-N(1F)-C(1F)	113.4(2)
C(4F)-N(1F)-C(5F)	123.9(2)
C(4F)-N(2F)-H(2F)	116.3
C(4F)-N(2F)-C(18F)	127.5(2)
C(18F)-N(2F)-H(2F)	116.3
N(1F)-C(1F)-H(1F)	109.2
N(1F)-C(1F)-C(2F)	101.6(2)
N(1F)-C(1F)-C(8F)	112.3(2)
C(2F)-C(1F)-H(1F)	109.2
C(8F)-C(1F)-H(1F)	109.2
C(8F)-C(1F)-C(2F)	115.1(2)
C(1F)-C(2F)-H(2FA)	110.9
C(1F)-C(2F)-H(2FB)	110.9
C(1F)-C(2F)-C(3F)	104.4(2)
H(2FA)-C(2F)-H(2FB)	108.9
C(3F)-C(2F)-H(2FA)	110.9
C(3F)-C(2F)-H(2FB)	110.9
C(4F)-C(3F)-C(2F)	101.8(2)
C(4F)-C(3F)-C(14F)	110.5(2)
C(14F)-C(3F)-C(2F)	115.0(2)
C(16F)-C(3F)-C(2F)	109.2(2)
C(16F)-C(3F)-C(4F)	114.2(2)
C(16F)-C(3F)-C(14F)	106.4(2)
N(1F)-C(4F)-C(3F)	109.5(2)
N(2F)-C(4F)-N(1F)	123.0(3)
N(2F)-C(4F)-C(3F)	127.5(2)

Table A4.2.3 (cont'd)

N(1F)-C(5F)-H(5F)	108.0
N(1F)-C(5F)-C(6F)	108.8(3)
N(1F)-C(5F)-C(7F)	112.4(3)
C(6F)-C(5F)-H(5F)	108.0
C(7F)-C(5F)-H(5F)	108.0
C(7F)-C(5F)-C(6F)	111.4(3)
C(5F)-C(6F)-H(6FA)	109.5
C(5F)-C(6F)-H(6FB)	109.5
C(5F)-C(6F)-H(6FC)	109.5
H(6FA)-C(6F)-H(6FB)	109.5
H(6FA)-C(6F)-H(6FC)	109.5
H(6FB)-C(6F)-H(6FC)	109.5
C(5F)-C(7F)-H(7FA)	109.5
C(5F)-C(7F)-H(7FB)	109.5
C(5F)-C(7F)-H(7FC)	109.5
H(7FA)-C(7F)-H(7FB)	109.5
H(7FA)-C(7F)-H(7FC)	109.5
H(7FB)-C(7F)-H(7FC)	109.5
C(9F)-C(8F)-C(1F)	117.4(3)
C(13F)-C(8F)-C(1F)	122.6(3)
C(13F)-C(8F)-C(9F)	120.0(3)
C(8F)-C(9F)-H(9F)	119.9
C(10F)-C(9F)-C(8F)	120.3(3)
C(10F)-C(9F)-H(9F)	119.9
C(9F)-C(10F)-H(10F)	120.5
C(9F)-C(10F)-C(11F)	119.0(3)
C(11F)-C(10F)-H(10F)	120.5
C(10F)-C(11F)-H(11F)	119.7
C(12F)-C(11F)-C(10F)	120.6(3)
C(12F)-C(11F)-H(11F)	119.7
C(11F)-C(12F)-H(12F)	120.1
C(11F)-C(12F)-C(13F)	119.8(3)
C(13F)-C(12F)-H(12F)	120.1
C(8F)-C(13F)-C(12F)	120.3(3)

Table A4.2.3 (cont'd)

C(8F)-C(13F)-H(13F)	119.8
C(12F)-C(13F)-H(13F)	119.8
O(1F)-C(14F)-O(2F)	125.8(2)
O(1F)-C(14F)-C(3F)	123.1(3)
O(2F)-C(14F)-C(3F)	111.1(2)
O(2F)-C(15F)-H(15J)	109.5
O(2F)-C(15F)-H(15K)	109.5
O(2F)-C(15F)-H(15L)	109.5
H(15J)-C(15F)-H(15K)	109.5
H(15J)-C(15F)-H(15L)	109.5
H(15K)-C(15F)-H(15L)	109.5
O(3F)-C(16F)-O(4F)	124.5(2)
O(3F)-C(16F)-C(3F)	123.4(2)
O(4F)-C(16F)-C(3F)	112.0(2)
O(4F)-C(17F)-H(17J)	109.5
O(4F)-C(17F)-H(17K)	109.5
O(4F)-C(17F)-H(17L)	109.5
H(17J)-C(17F)-H(17K)	109.5
H(17J)-C(17F)-H(17L)	109.5
H(17K)-C(17F)-H(17L)	109.5
N(2F)-C(18F)-H(18F)	109.5
N(2F)-C(18F)-C(19F)	109.5(2)
N(2F)-C(18F)-C(20F)	108.1(2)
C(19F)-C(18F)-H(18F)	109.5
C(19F)-C(18F)-C(20F)	110.7(3)
C(20F)-C(18F)-H(18F)	109.5
C(18F)-C(19F)-H(19J)	109.5
C(18F)-C(19F)-H(19K)	109.5
C(18F)-C(19F)-H(19L)	109.5
H(19J)-C(19F)-H(19K)	109.5
H(19J)-C(19F)-H(19L)	109.5
H(19K)-C(19F)-H(19L)	109.5
C(18F)-C(20F)-H(20J)	109.5
C(18F)-C(20F)-H(20K)	109.5

Table A4.2.3 (cont'd)

C(18F)-C(20F)-H(20L)	109.5
H(20J)-C(20F)-H(20K)	109.5
H(20J)-C(20F)-H(20L)	109.5
H(20K)-C(20F)-H(20L)	109.5
H(5AA)-O(5A)-H(5AB)	117(3)
H(5BA)-O(5B)-H(5BB)	113(3)
H(5CA)-O(5C)-H(5CB)	109(2)
H(5DA)-O(5D)-H(5DB)	105(2)
H(5EA)-O(5E)-H(5EB)	107(2)
H(5FA)-O(5F)-H(5FB)	107(4)

Symmetry transformations used to generate equivalent atoms:

Table A4.2.4 Anisotropic displacement parameters ($Å^2x10^3$) for amidine ***(R)-170•HBr****. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$.*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1A)	246(12)	132(9)	182(10)	11(8)	35(9)	80(8)
O(2A)	202(12)	132(9)	284(12)	-45(8)	-6(10)	-9(8)
O(3A)	331(14)	195(10)	173(11)	39(8)	-26(9)	90(9)
O(4A)	285(12)	137(9)	176(10)	71(8)	42(9)	65(8)
N(1A)	177(13)	123(10)	105(10)	40(8)	46(9)	41(9)
N(2A)	155(12)	152(11)	102(10)	1(8)	21(9)	42(9)
C(1A)	149(14)	90(11)	175(13)	15(9)	50(11)	44(10)
C(2A)	140(14)	140(12)	166(13)	42(10)	68(11)	49(10)
C(3A)	147(14)	99(11)	127(12)	30(9)	28(10)	48(9)
C(4A)	192(15)	94(11)	134(12)	6(9)	48(11)	67(10)
C(5A)	163(15)	194(13)	128(13)	75(10)	35(11)	34(11)
C(6A)	268(18)	294(16)	135(14)	33(12)	30(13)	16(14)
C(7A)	220(17)	257(16)	255(16)	115(13)	-14(13)	95(13)
C(8A)	149(14)	127(12)	145(13)	25(10)	14(11)	4(10)
C(9A)	168(15)	212(14)	163(13)	51(11)	30(11)	29(11)
C(10A)	199(16)	235(15)	212(15)	95(12)	31(12)	45(12)
C(11A)	228(17)	202(14)	290(17)	162(12)	62(14)	43(12)
C(12A)	259(17)	168(13)	260(16)	73(11)	35(13)	94(12)
C(13A)	190(16)	203(13)	187(14)	96(11)	63(12)	100(11)
C(14A)	140(14)	141(12)	161(13)	67(10)	21(11)	28(10)
C(15A)	360(20)	110(13)	450(20)	-96(14)	49(18)	-22(13)
C(16A)	117(14)	129(12)	180(13)	69(10)	40(11)	3(10)
C(17A)	302(19)	203(14)	296(17)	153(13)	75(14)	93(13)
C(18A)	193(16)	232(14)	115(13)	25(11)	59(11)	65(12)
C(19A)	259(18)	254(16)	277(17)	30(13)	97(14)	104(14)
C(20A)	185(16)	288(16)	213(16)	120(12)	7(13)	4(13)
O(1B)	177(11)	139(9)	201(11)	-4(8)	21(9)	82(8)
O(2B)	154(11)	78(8)	366(13)	-25(8)	34(10)	-8(7)
O(3B)	257(12)	180(10)	138(10)	-21(8)	-66(9)	43(9)
O(4B)	246(12)	108(8)	107(9)	31(7)	-2(8)	55(8)
N(1B)	116(12)	124(10)	121(10)	30(8)	7(9)	-3(8)

Table A4.2.4 (cont'd)

N(2B)	113(12)	158(11)	100(10)	4(8)	13(9)	1(9)
C(1B)	119(13)	108(11)	130(12)	20(9)	38(10)	4(9)
C(2B)	114(13)	121(11)	168(13)	28(10)	7(11)	21(10)
C(3B)	104(13)	107(11)	104(11)	5(9)	-30(10)	13(9)
C(4B)	115(13)	72(10)	113(12)	21(9)	9(10)	35(9)
C(5B)	144(14)	199(13)	96(12)	-27(10)	6(10)	-10(11)
C(6B)	490(20)	151(14)	245(17)	-70(12)	-74(17)	-43(15)
C(7B)	207(17)	349(18)	140(14)	29(12)	38(12)	-12(14)
C(8B)	162(15)	128(12)	167(13)	19(10)	-22(11)	-9(10)
C(9B)	205(16)	190(14)	179(14)	59(11)	19(12)	-31(12)
C(10B)	277(19)	219(15)	241(16)	117(12)	7(14)	-80(13)
C(11B)	350(20)	161(14)	267(17)	92(12)	-67(15)	-32(13)
C(12B)	400(20)	211(15)	274(18)	68(13)	-41(15)	112(14)
C(13B)	270(18)	165(13)	208(15)	52(11)	16(13)	69(12)
C(14B)	155(14)	87(11)	158(13)	29(9)	11(11)	16(10)
C(15B)	340(20)	73(13)	550(20)	-81(14)	87(18)	-24(13)
C(16B)	122(13)	81(11)	116(12)	1(9)	15(10)	-4(9)
C(17B)	277(17)	193(13)	122(13)	67(10)	20(12)	100(12)
C(18B)	198(16)	172(13)	74(12)	-18(10)	23(11)	7(11)
C(19B)	122(15)	279(16)	282(17)	-48(13)	56(13)	44(12)
C(20B)	232(17)	285(16)	180(15)	103(12)	63(13)	32(13)
O(1C)	224(12)	106(9)	222(11)	35(8)	32(9)	54(8)
O(2C)	191(12)	114(9)	264(11)	14(8)	58(9)	-16(8)
O(3C)	211(12)	148(9)	152(10)	8(7)	-45(8)	31(8)
O(4C)	276(12)	117(9)	126(9)	37(7)	7(8)	61(8)
N(1C)	160(12)	110(10)	107(10)	28(8)	49(9)	39(9)
N(2C)	150(12)	162(11)	83(10)	17(8)	14(9)	30(9)
C(1C)	205(15)	133(12)	116(12)	57(10)	76(11)	71(11)
C(2C)	175(15)	139(12)	130(12)	40(9)	53(11)	63(10)
C(3C)	117(13)	100(11)	131(12)	9(9)	13(10)	27(9)
C(4C)	156(14)	80(11)	120(12)	33(9)	20(10)	37(10)
C(5C)	183(15)	176(13)	95(12)	27(10)	4(11)	27(11)
C(6C)	291(19)	258(16)	136(14)	-22(12)	0(13)	3(13)
C(7C)	197(17)	208(14)	280(17)	79(12)	-25(13)	51(12)

Table A4.2.4 (cont'd)

C(8C)	176(15)	122(12)	119(12)	32(9)	19(11)	39(10)
C(9C)	222(16)	183(13)	124(13)	54(10)	83(11)	51(11)
C(10C)	269(18)	221(14)	201(15)	137(12)	107(13)	49(13)
C(11C)	280(18)	154(13)	213(15)	108(11)	56(13)	43(12)
C(12C)	275(17)	124(12)	199(14)	51(10)	31(12)	73(11)
C(13C)	246(17)	155(13)	161(13)	49(10)	98(12)	102(11)
C(14C)	205(15)	111(12)	96(12)	29(9)	1(11)	-5(10)
C(15C)	320(20)	139(13)	348(19)	12(12)	154(16)	-19(13)
C(16C)	98(14)	131(12)	192(14)	64(10)	31(11)	54(10)
C(17C)	350(20)	200(14)	228(15)	150(12)	56(14)	115(13)
C(18C)	160(15)	214(13)	83(12)	53(10)	0(10)	29(11)
C(19C)	311(19)	283(16)	89(13)	-87(11)	12(12)	92(14)
C(20C)	206(16)	223(15)	157(14)	76(11)	13(12)	10(12)
O(1D)	206(12)	167(10)	223(11)	30(8)	2(9)	26(8)
O(2D)	223(12)	110(9)	280(12)	53(8)	49(9)	69(8)
O(3D)	225(12)	131(9)	181(10)	15(8)	12(9)	35(8)
O(4D)	216(11)	87(8)	170(10)	36(7)	16(8)	4(8)
N(1D)	224(14)	153(11)	80(10)	19(8)	-16(9)	79(9)
N(2D)	181(13)	132(10)	105(10)	19(8)	5(9)	63(9)
C(1D)	184(15)	166(13)	128(13)	35(10)	-17(11)	64(11)
C(2D)	134(14)	177(13)	175(13)	64(10)	-15(11)	77(11)
C(3D)	118(13)	113(11)	148(13)	17(9)	2(10)	22(10)
C(4D)	167(14)	70(10)	127(12)	23(9)	-21(10)	26(10)
C(5D)	310(18)	229(14)	132(13)	-30(11)	-18(12)	167(13)
C(6D)	750(30)	164(15)	360(20)	-54(14)	0(20)	124(18)
C(7D)	780(30)	490(20)	120(15)	39(14)	63(17)	510(20)
C(8D)	174(15)	148(12)	171(13)	43(10)	-12(11)	77(11)
C(9D)	209(16)	158(13)	192(14)	28(11)	-26(12)	59(11)
C(10D)	312(19)	235(15)	202(15)	74(12)	-17(14)	108(13)
C(11D)	308(19)	221(15)	211(15)	116(12)	57(14)	76(13)
C(12D)	223(17)	249(15)	206(15)	93(12)	-12(13)	-12(13)
C(13D)	159(15)	240(14)	152(14)	86(11)	-33(11)	2(12)
C(14D)	174(15)	132(12)	115(12)	57(9)	36(11)	20(10)
C(15D)	330(20)	115(13)	308(18)	33(12)	31(15)	43(12)

Table A4.2.4 (cont'd)

C(16D)	137(15)	141(13)	296(17)	48(12)	79(13)	57(11)
C(17D)	227(17)	170(13)	199(15)	86(11)	30(12)	31(12)
C(18D)	166(15)	187(13)	120(13)	29(10)	-25(11)	64(11)
C(19D)	229(17)	246(15)	180(15)	49(12)	-67(13)	67(13)
C(20D)	274(18)	202(14)	207(15)	74(12)	-23(13)	51(12)
O(1E)	127(11)	105(9)	242(11)	17(8)	-31(9)	-22(7)
O(2E)	186(11)	130(9)	271(12)	11(8)	-32(9)	54(8)
O(3E)	205(12)	141(9)	192(10)	5(8)	50(9)	13(8)
O(4E)	206(11)	121(9)	142(9)	41(7)	-18(8)	-3(8)
N(1E)	182(13)	111(10)	108(11)	17(8)	-20(9)	32(9)
N(2E)	147(12)	147(11)	117(11)	22(8)	4(9)	62(9)
C(1E)	146(14)	134(12)	139(13)	24(10)	-37(11)	-6(10)
C(2E)	113(14)	146(12)	192(14)	63(10)	-21(11)	-20(10)
C(3E)	118(13)	97(11)	149(12)	26(9)	-8(10)	-6(9)
C(4E)	113(13)	91(11)	131(12)	15(9)	-13(10)	-22(9)
C(5E)	233(16)	159(13)	131(13)	39(10)	28(11)	78(11)
C(6E)	330(20)	286(16)	104(13)	37(11)	-32(13)	89(14)
C(7E)	231(18)	286(17)	260(17)	79(13)	89(14)	70(13)
C(8E)	150(14)	136(12)	139(12)	34(10)	-17(10)	33(10)
C(9E)	159(15)	203(13)	176(14)	60(11)	-20(11)	35(11)
C(10E)	284(19)	223(15)	235(16)	93(12)	-43(13)	83(13)
C(11E)	278(18)	203(14)	275(17)	115(12)	-25(14)	54(13)
C(12E)	209(17)	175(13)	258(16)	114(12)	-28(13)	-8(12)
C(13E)	185(16)	198(14)	208(15)	85(11)	-32(12)	43(12)
C(14E)	168(14)	113(11)	108(12)	32(9)	3(10)	30(10)
C(15E)	330(20)	83(12)	420(20)	14(12)	-59(16)	79(12)
C(16E)	115(13)	116(11)	167(13)	44(10)	15(11)	15(10)
C(17E)	259(18)	179(14)	194(15)	105(11)	14(13)	-8(12)
C(18E)	173(15)	177(13)	87(12)	35(10)	-15(10)	75(11)
C(19E)	150(15)	196(14)	222(15)	-15(11)	-45(12)	65(11)
C(20E)	226(17)	224(14)	194(15)	100(12)	23(12)	93(12)
O(1F)	190(12)	151(10)	243(11)	61(8)	13(9)	47(8)
O(2F)	231(12)	101(9)	213(11)	20(8)	15(9)	35(8)
O(3F)	243(12)	163(9)	150(10)	-4(8)	55(9)	67(8)

Table A4.2.4 (cont'd)

O(4F)	257(12)	107(8)	99(9)	34(7)	29(8)	12(8)
N(1F)	168(13)	136(10)	110(10)	33(8)	-17(9)	80(9)
N(2F)	141(12)	133(10)	98(10)	20(8)	-12(9)	52(9)
C(1F)	147(14)	163(12)	135(12)	46(10)	1(11)	71(10)
C(2F)	167(14)	134(12)	121(12)	35(9)	7(11)	39(10)
C(3F)	126(13)	91(11)	132(12)	27(9)	-2(10)	16(9)
C(4F)	140(14)	81(11)	132(12)	26(9)	10(10)	17(9)
C(5F)	326(18)	192(14)	160(14)	0(11)	9(13)	160(13)
C(6F)	630(30)	219(16)	240(17)	2(13)	13(18)	172(17)
C(7F)	380(20)	330(17)	125(14)	-28(12)	-34(14)	192(15)
C(8F)	225(16)	146(12)	131(13)	35(10)	39(11)	85(11)
C(9F)	310(18)	229(15)	174(14)	68(11)	42(13)	174(13)
C(10F)	430(20)	278(16)	180(15)	111(12)	94(14)	237(15)
C(11F)	550(30)	199(15)	261(17)	104(13)	208(17)	145(15)
C(12F)	430(20)	203(15)	258(17)	91(13)	153(16)	59(15)
C(13F)	246(18)	229(15)	183(15)	69(12)	45(13)	60(13)
C(14F)	157(14)	123(12)	128(12)	21(9)	13(11)	24(10)
C(15F)	350(20)	72(11)	238(15)	8(10)	62(14)	23(12)
C(16F)	132(14)	155(12)	50(11)	17(9)	-21(10)	62(10)
C(17F)	238(17)	216(14)	155(14)	107(11)	27(12)	22(12)
C(18F)	177(15)	168(12)	99(12)	22(10)	-28(11)	61(11)
C(19F)	215(17)	139(13)	200(15)	-5(11)	-47(13)	-39(11)
C(20F)	351(19)	240(15)	129(13)	76(11)	-9(13)	130(13)
Br(1A)	265(2)	205(1)	172(1)	6(1)	-6(1)	118(1)
Br(1B)	212(2)	209(1)	143(1)	38(1)	18(1)	89(1)
Br(1C)	286(2)	173(1)	186(2)	-11(1)	-24(1)	92(1)
Br(1D)	242(2)	223(2)	175(2)	45(1)	22(1)	-12(1)
Br(1E)	225(2)	166(1)	142(1)	0(1)	31(1)	-40(1)
Br(1F)	212(2)	228(2)	157(1)	45(1)	-2(1)	10(1)
O(5A)	202(12)	160(10)	207(11)	8(8)	11(9)	47(8)
O(5B)	155(11)	210(10)	200(11)	29(8)	-5(9)	-74(9)
O(5C)	189(12)	159(10)	246(12)	43(8)	21(9)	55(9)
O(5D)	342(15)	272(12)	219(12)	50(9)	23(10)	202(11)
O(5E)	200(12)	176(10)	162(10)	29(8)	54(9)	63(8)

Table A4.2.4 (cont'd)

O(5F)	253(13)	291(12)	214(12)	35(9)	37(10)	159(10)

Table A4.2.5 Hydrogen coordinates (x10^3) and isotropic displacement parameters (Å^{2}x10^3) for amidine ***(R)-170•HBr***

	x	y	z	U_{iso}
H(2A)	204	104	797	17
H(1A)	646	133	714	16
H(2AA)	842	242	787	17
H(2AB)	776	130	782	17
H(5A)	213	72	729	19
H(6AA)	404	146	657	37
H(6AB)	228	64	650	37
H(6AC)	402	47	670	37
H(7AA)	186	224	753	35
H(7AB)	98	182	702	35
H(7AC)	282	256	709	35
H(9A)	782	222	663	22
H(10A)	859	359	632	25
H(11A)	792	492	668	27
H(12A)	646	488	735	26
H(13A)	565	351	766	21
H(15G)	784	477	855	51
H(15H)	964	472	878	51
H(15I)	794	446	905	51
H(17G)	691	-57	862	37
H(17H)	593	-8	900	37
H(17I)	793	36	896	37
H(18A)	381	168	885	21
H(19G)	173	248	870	38
H(19H)	114	190	910	38
H(19I)	25	151	859	38
H(20G)	99	3	863	35
H(20H)	211	38	912	35
H(20I)	296	1	867	35
H(2B)	-4	75	461	16
H(1B)	460	112	381	15

Table A4.2.5 (cont'd)

H(2BA)	580	124	454	16
H(2BB)	628	234	453	16
H(5B)	0	59	391	20
H(6BA)	226	-58	383	50
H(6BB)	27	-92	363	50
H(6BC)	78	-61	418	50
H(7BA)	134	130	331	37
H(7BB)	45	22	312	37
H(7BC)	249	58	324	37
H(9B)	598	218	334	25
H(10B)	613	349	300	32
H(11B)	460	456	328	33
H(12B)	280	426	388	35
H(13B)	258	293	421	25
H(15D)	494	467	503	53
H(15E)	692	482	520	53
H(15F)	543	453	554	53
H(17D)	488	-42	549	28
H(17E)	396	20	584	28
H(17F)	596	58	576	28
H(18B)	166	149	549	19
H(19D)	-33	229	532	36
H(19E)	-101	171	572	36
H(19F)	-183	134	520	36
H(20D)	-108	-19	527	35
H(20E)	-10	21	577	35
H(20F)	90	-16	536	35
H(2C)	416	99	128	16
H(1C)	849	121	40	17
H(2CA)	1052	228	112	17
H(2CB)	979	118	109	17
H(5C)	419	57	59	19
H(6CA)	606	125	-15	37
H(6CB)	432	43	-20	37

Table A4.2.5 (cont'd)

H(6CC)	608	29	1	37
H(7CA)	386	208	80	34
H(7CB)	300	164	28	34
H(7CC)	483	240	36	34
H(9C)	994	214	-9	21
H(10C)	1067	352	-39	26
H(11C)	991	482	-4	25
H(12C)	834	474	62	23
H(13C)	753	336	91	21
H(15A)	1026	476	158	42
H(15B)	1175	471	195	42
H(15C)	982	457	209	42
H(17A)	855	-61	201	36
H(17B)	813	14	240	36
H(17C)	1004	30	224	36
H(18C)	605	167	215	18
H(19A)	412	254	202	36
H(19B)	349	197	243	36
H(19C)	254	161	192	36
H(20A)	317	5	195	30
H(20B)	427	43	244	30
H(20C)	513	2	200	30
H(2D)	98	754	670	16
H(1D)	531	721	758	19
H(2DA)	563	591	691	18
H(2DB)	628	700	687	18
H(5D)	128	777	740	26
H(6DA)	471	898	753	65
H(6DB)	300	931	760	65
H(6DC)	339	888	709	65
H(7DA)	236	712	803	60
H(7DB)	204	812	818	60
H(7DC)	395	804	812	60
H(9D)	568	620	808	22

Table A4.2.5 (cont'd)

H(10D)	458	495	846	29
H(11D)	188	390	820	28
H(12D)	26	415	757	28
H(13D)	136	542	720	23
H(15P)	229	362	596	38
H(15Q)	190	360	649	38
H(15R)	363	339	631	38
H(17P)	515	793	552	30
H(17Q)	688	765	564	30
H(17R)	665	864	587	30
H(18D)	176	667	586	19
H(19P)	-101	589	600	33
H(19Q)	-123	649	560	33
H(19R)	-153	684	613	33
H(20P)	67	834	598	34
H(20Q)	132	788	551	34
H(20R)	265	834	596	34
H(2E)	725	727	339	16
H(1E)	1153	714	432	18
H(2EA)	1241	603	363	19
H(2EB)	1274	713	364	19
H(5E)	778	772	408	20
H(6EA)	909	709	485	36
H(6EB)	818	791	487	36
H(6EC)	1004	804	468	36
H(7EA)	600	615	388	38
H(7EB)	557	669	436	38
H(7EC)	667	595	437	38
H(9E)	1236	625	481	22
H(10E)	1190	492	516	29
H(11E)	972	358	483	30
H(12E)	792	362	419	26
H(13E)	836	496	385	23
H(15M)	935	367	266	42

Table A4.2.5 (cont'd)

H(15N)	943	355	319	42
H(15O)	1105	352	290	42
H(17M)	1192	808	230	32
H(17N)	1372	801	252	32
H(17O)	1302	888	271	32
H(18E)	830	654	255	17
H(19M)	557	566	263	29
H(19N)	533	629	226	29
H(19O)	491	656	279	29
H(20M)	708	816	269	30
H(20N)	772	775	222	30
H(20O)	907	819	266	30
H(2F)	294	753	11	15
H(1F)	736	716	95	17
H(2FA)	771	594	25	17
H(2FB)	827	704	23	17
H(5F)	326	770	82	25
H(6FA)	669	891	94	54
H(6FB)	499	923	105	54
H(6FC)	530	887	53	54
H(7FA)	413	700	142	40
H(7FB)	415	806	160	40
H(7FC)	592	780	150	40
H(9F)	782	610	140	26
H(10F)	683	477	174	31
H(11F)	413	372	146	38
H(12F)	242	403	88	35
H(13F)	341	538	56	26
H(15J)	426	364	-66	34
H(15K)	383	363	-14	34
H(15L)	556	340	-30	34
H(17J)	696	780	-116	30
H(17K)	882	771	-100	30
H(17L)	828	864	-82	30

Table A4.2.5 (cont'd)

H(18F)	373	676	-76	18
H(19J)	93	599	-62	31
H(19K)	78	660	-101	31
H(19L)	45	695	-49	31
H(20J)	267	844	-55	34
H(20K)	318	804	-105	34
H(20L)	462	843	-62	34
H(5AA)	998(5)	-14(2)	771(1)	29
H(5AB)	915(5)	48(2)	797(1)	29
H(5BA)	681(4)	-35(2)	445(1)	32
H(5BB)	758(5)	62(1)	454(1)	32
H(5CA)	145(5)	-29(1)	117(1)	29
H(5CB)	114(4)	59(2)	119(1)	29
H(5DA)	897(5)	875(2)	681(1)	38
H(5DB)	901(5)	820(2)	715(1)	38
H(5EA)	601(5)	860(2)	349(1)	26
H(5EB)	528(5)	808(2)	383(1)	26
H(5FA)	230(2)	832(3)	35(1)	35
H(5FB)	75(5)	820(3)	57(1)	35

CHAPTER 3[†]

Stereoselective Lewis Acid Mediated (3 + 2) Cycloadditions of N-H- and N-Sulfonylaziridines with Heterocumulenes

3.1 INTRODUCTION

Having studied the cycloadditions of donor–acceptor cyclopropanes with heterocumulenes, we sought to expand the reactivity by replacing cyclopropanes with activated aziridines in order to access more highly nitrogenated heterocycles. Aziridines are versatile intermediates and reaction partners for the preparation of a structurally diverse assortment of nitrogen-containing architectures.[1] These heterocycles are characterized by a unique reactivity profile, in part due to the large strain energy (27 kcal mol^{-1}) contained within their three-membered rings,[2] rendering them susceptible to nucleophilic ring opening,[3] carbonylation,[4] and ring expansion.[5] Previous work has shown the utility of 2-arylaziridines in transition-metal-mediated and -catalyzed (3 + 2) cycloadditions with heterocumulenes for the formation of imidazolines,[6 a–e]

[†] This work was performed in collaboration with Dr. Robert A. Craig, II, and Dr. Alexander F. G. Goldberg, alumni of the Stoltz group. This work has been published, with portions of this chapter adapted with permission from Craig, R. A., II; O'Connor, N. R.; Goldberg, A. F. G.; Stoltz, B. M. *Chem. Eur. J.* **2014**, *20*, 4806–4813.

oxazolidines,[6d–e] iminoazolidinones,[6f–i] iminothiazolidines,[6i–k] and iminoimidazolidines.[6f,l] Iminothiazolidines and iminoimidazolidines have seen use as effective organic catalysts in asymmetric transformations including Strecker reactions,[7a] *O*- and *N*-acylations,[7b–c] and Michael additions,[7d] and as highly active pharmacophores for the treatment of a wide range of medical conditions including obesity, diabetes, cancer, and arthritis.[8]

The critical limitation of the majority of existing (3 + 2) cycloaddition manifolds is the requirement that the aziridine starting materials bear either alkyl or aryl *N*-substitution. The harsh conditions necessary for the removal of such robust groups severely limits the potential for derivatization and, thus, the utility of the products. Despite this, the use of *N*-sulfonyl-protected aziridines in (3 + 2) cycloadditions has been explored minimally.[6a–e,k] Prior to our studies, the work of Nadir and co-workers stood as the only previous study of (3 + 2) cycloadditions of *N*-sulfonyl-2-arylaziridines with heterocumulenes.[6k,9] Their reaction system has a narrow scope and is only able to accommodate aryl isocyanates and aryl isothiocyanates, resulting in similarly limited product derivatization options. This transformation depends on the use of an alkali metal iodide as a noninnocent reaction partner; Nadir and co-workers explicitly demonstrate the formation of the ring-opened iodide intermediate prior to product formation.

Additionally, only a single example of the synthesis of enantioenriched iminothiazolidines by a stereoselective (3 + 2) cycloaddition is known[6i] despite readily available enantiopure aziridine starting materials.[1,2,6h] This method, however, has an extremely narrow substrate scope, requiring the use of *N*-alkyl- or *N*-arylaziridines and aryl heterocumulenes. There are no examples of this transformation with *N*-sulfonyl-protected aziridines or more synthetically versatile heterocumulenes.

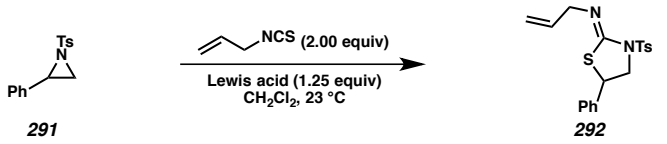
3.2 DEVELOPMENT OF THE RACEMIC (3 + 2) CYCLOADDITION

From this foundation, we sought to develop the first stereoselective Lewis acid mediated (3 + 2) cycloaddition reaction of *N*-sulfonyl-2-substituted aziridines and alkyl heterocumulenes. The Lewis acid mediated conditions would likely enable the use of a broad variety of heterocumulenes and consequently furnish readily derivatizable, highly enantioenriched heterocyclic building blocks.

3.2.1 OPTIMIZATION OF THE REACTION CONDITIONS

Initial reaction development focused on the cycloaddition of *N*-tosyl-2-phenylaziridine (**291**) with allyl isothiocyanate (Scheme 3.1). In contrast to our previous work on (3 + 2) cycloadditions of donor–acceptor cyclopropanes with heterocumulenes,[10] tin(II) triflate was found to be an ineffective Lewis acid mediator for the desired transformation (entry 1). Alternatively, zinc(II) salts proved competent for the formation of iminothiazolidine **292**. While zinc(II) triflate furnished the product in good yield, the reaction times were greatly reduced when zinc(II) halides were employed (entries 2–5). Lithium bromide mediated reaction conditions resulted in low conversion (entry 6). Attempts to develop a catalytic system with zinc(II) bromide proved unsuccessful, even in the presence of an additional bromide ion (entry 7). Ultimately, the use of 1.25 equivalents of zinc(II) bromide and 2.00 equivalents of allyl isothiocyanate in dichloromethane at ambient temperature proved optimal (entry 5).[11]

Scheme 3.1 Optimization of the reaction conditions



291 ***292***

Entry	*Lewis Acid*	*t (h)*	*Yield (%)[a]*
1	$Sn(OTf)_2$	1.0	0
2	$Zn(OTf)_2$	60.0	79
3	$ZnCl_2$	6.0	95
4	ZnI_2	3.0	95
5	$ZnBr_2$	1.3	99
6	$LiBr_2$[b]	72.0[c]	7
7	$ZnBr_2$[d]	72.0[c]	4

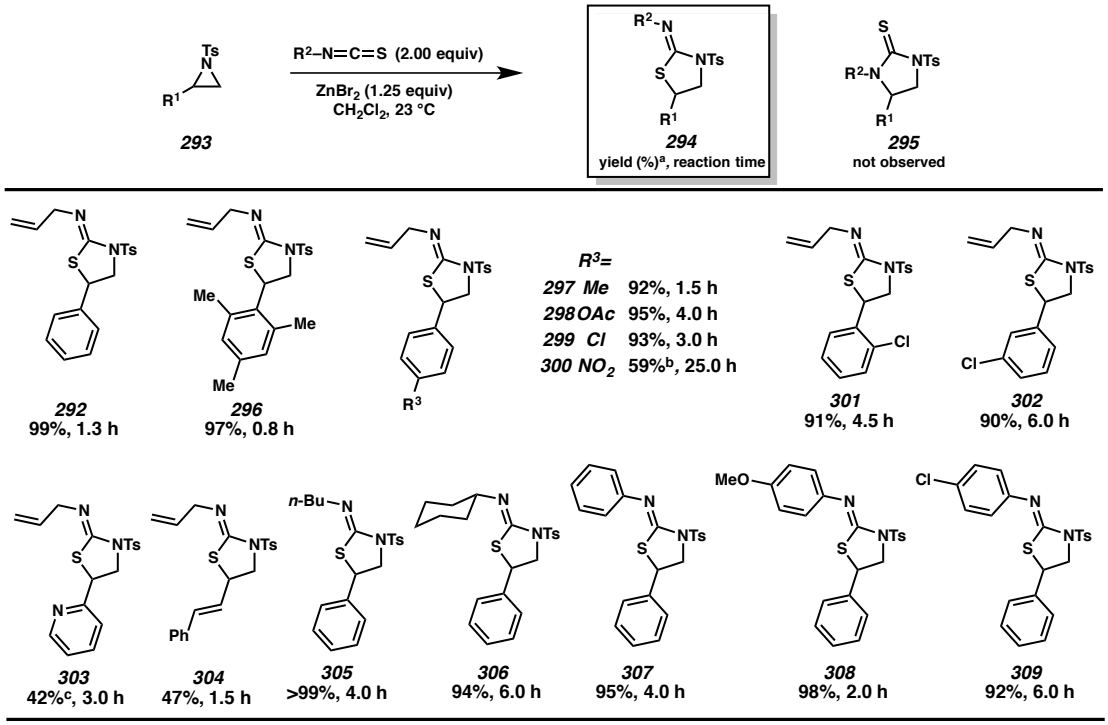
Conditions: aziridine 291 (0.40 mmol), isothiocyanate (0.80 mmol), Lewis acid (0.50 mmol), CH_2Cl_2 (0.80 mL). [a] Isolated yield. [b] 1.00 mmol of LiBr. [c] Starting material was not fully consumed. [d] 0.12 mmol of $ZnBr_2$ with 0.40 mmol of tetra(*n*-buty)lammonium bromide additive.

3.2.2 EXPLORATION OF 2-AZIRIDINE AND HETEROCUMULENE SUBSTITUTION

With optimized conditions identified, we examined the substrate scope of the reaction. We found that a variety of *N*-tosyl-2-aryl-substituted aziridines participated effectively in the zinc(II) bromide mediated (3 + 2) cycloaddition with allyl isothiocyanate to yield the corresponding iminothiazolidine products with complete chemo- and regioselectivity (Scheme 3.2).[12,13] Altering the *C*-aryl substitution from phenyl to mesityl allowed for the formation of the corresponding heterocycle (**296**) in a shorter reaction time despite the increased steric bulk.[14] Similarly, (*p*-tolyl)thiazolidine **297** was successfully furnished with a slightly decreased yield. Acetoxy substitution was compatible with the reaction conditions as well, generating **298** in excellent yield. Compared to the *p*-chlorophenyl- or *o*-chlorophenylthiazolidines (**299** and **301**, respectively), the more electronically deactivated *m*-chlorophenylthiazolidine **302** was produced more slowly, albeit without any significant reduction in yield.[15] The highly electron-deficient *p*-nitrophenyl-thiazolidine **300** was formed in modest yield, with a

significant portion of starting material lost to nucleophilic ring opening of the aziridine by the bromide counterion.[16] Substrates bearing coordinating *C*-aryl substituents served to slow the rate of reaction (e.g. **298** and **300**) or require additional $ZnBr_2$ to drive the reaction to completion (**303**). Styrenyl thiazolidine **304** could also be synthesized in approximately the same reaction time as phenyl product **292**. Additionally, primary and secondary alkyl isothiocyanates were found to be highly compatible under the reaction conditions as were electron-neutral, -rich, and -deficient aryl isothiocyanates, all furnishing the desired iminothiazolidines in excellent yields (**305–309**, respectively).

Scheme 3.2 Substrate scope of the isothiocyanate (3 + 2) cycloaddition

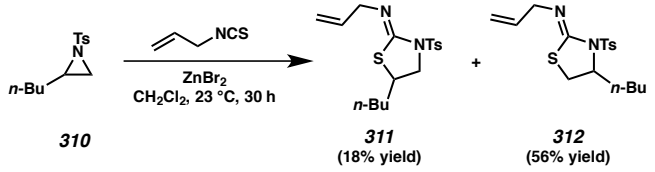


Conditions: aziridine 293 (0.40 mmol), isothiocyanate (0.80 mmol), $ZnBr_2$ (0.50 mmol), CH_2Cl_2 (0.80 mL). [a] Isolated yield. [b] The product of nucleophilic ring opening of the starting material by a bromide ion was isolated in 35% yield. [c] 0.90 mmol of $ZnBr_2$ were used.

In contrast to the *C*-aryl-substituted aziridines, *C*-alkyl-substituted aziridine **310** reacted with allyl isothiocyanate under the reaction conditions to furnish two isomeric

(3 + 2) adducts (Scheme 3.3). Formation of 5-alkyl-substituted iminothiazolidine **311** was accomplished in only 18% yield, whereas 4-alkyl-substituted product **312** was furnished in 56% yield. While *C*-alkyl-substituted aziridines are suitable reaction partners in the (3 + 2) cycloaddition and the heterocyclic products are formed with complete chemoselectivity, they are not formed with the regiofidelity exhibited by aziridines substituted at carbon with aryl groups or other conjugated systems.

*Scheme 3.3 (3 + 2) cycloaddition with 2-alkylaziridine **310***

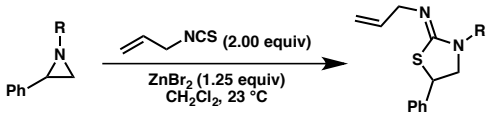


310 ***311*** (18% yield) ***312*** (56% yield)

3.2.3 EFFECT OF AZIRIDINE N-*SUBSTITUTION*

As an extension of the substrate scope, we investigated the effect of *N*-substitution on the aziridine (Scheme 3.4). Aziridines protected with *N*-sulfonyl groups provided the desired iminothiazolidines (**292**, **315**–**317**) in excellent yields, generally showing reaction times that were slightly shorter for electron-deficient sulfonyl groups (entry 2) and slightly longer for more electron-rich sulfonyl groups (entries 3–4) in comparison to the *N*-tosyl-substituted substrate (entry 1).

Scheme 3.4 Scope of N*-substitution in the isothiocyanate (3 + 2) cycloaddition reaction*



313 ***314***

Entry	*R*	*Product*	*t (h)*	*Yield (%)*[a]
1	tosyl	***292***	1.3	99
2	*p*-NO_2-C_6H_4-SO_2	***315***	1.2	94
3	mesyl	***316***	1.8	91
4	*p*-OMe-C_6H_4-SO_2	***317***	2.0	90
5	H	***318***	0.5	75
6	*n*-$C_{10}H_{21}$	***319***	96.0[b]	0
7	pivaloyl	***320***	96.0[b]	0
8	benzoyl	***321***	96.0[b]	0

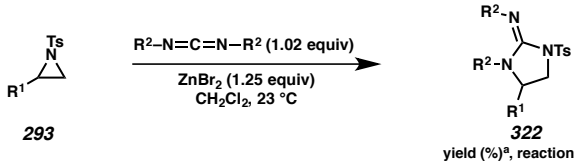
Conditions: aziridine 313 (0.40 mmol), isothiocyanate (0.80 mmol), $ZnBr_2$ (0.50 mmol), CH_2Cl_2 (0.80 mL). [a] Isolated yield. [b] Starting material was not fully consumed.

Interestingly, unprotected 2-phenylaziridine showed an improved reaction time yet a partially decreased yield of the heterocyclic product **318**, whereas *N*-(*n*-decyl)-substituted aziridine was unreactive under the reaction conditions (entries 5–6). *N*-Acyl aziridines also failed to furnish any of the desired heterocycles **320** and **321** (entries 7–8).

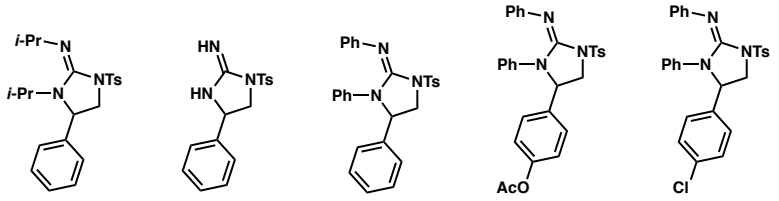
3.2.4 EXTENSION OF HETEROCUMULENE SCOPE

Subsequently, we turned our attention to broadening the scope of competent heterocumulenes. We found that isocyanates gave only trace yields of the (3 + 2) cycloaddition adducts,[17] but carbodiimides were compatible with the conditions, furnishing iminoimidazolidines (Scheme 3.5).[18] Unlike previously known systems,[6,9] our unique zinc-mediated conditions enabled the (3 + 2) cycloadditions of *N*-sulfonylaziridines with dialkyl- and disilylcarbodiimides systems, allowing access to diisopropyliminoimidazolidine **323** and secondary imidazolidine **324**. In accordance with our observations of the isothiocyanate (3 + 2) cycloadditions, a variety of 2-arylaziridines were suitable reaction partners with diphenylcarbodiimide (**325**–**327**).

Scheme 3.5 Substrate scope of carbodiimide (3 + 2) cycloaddition



yield (%)[a], reaction time



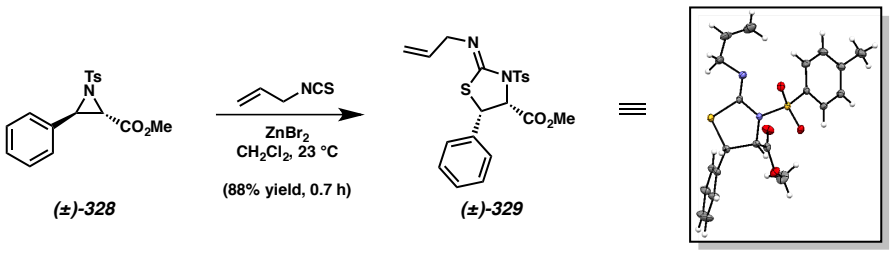
323	***324***	***325***	***326***	***327***
55%, 11.0 h	61%[b], 9.0 h	96%[b], 8.0 h	99%[b], 6.0 h	87%[b], 7.5 h

Conditions: aziridine 293 (0.40 mmol), carbodiimide (0.41 mmol), $ZnBr_2$ (0.50 mmol), CH_2Cl_2 (0.80 mL). [a] Isolated yield. [b] Bis(trimethylsilyl)carbodiimide was used.

3.2.5 CYCLOADDITION OF DISUBSTITUTED N-SULFONYLAZIRIDINES

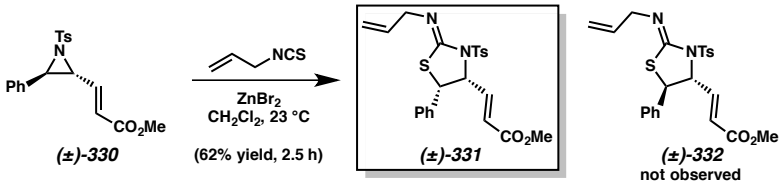
During our investigation of the substrate scope of the (3 + 2) cycloaddition of *N*-sulfonylaziridines with isothiocyanates, we discovered that *trans*-2,3-disubstituted aziridine **328** was an acceptable reaction partner, furnishing *cis*-thiazolidine **329** in high yield and with the shortest reaction time observed for any *N*-tosyl-substituted substrate (Scheme 3.6). Iminothiazolidine **329** was formed as a single diastereomer, and the relative stereochemistry was confirmed by single-crystal X-ray diffraction. The *cis* configuration of **329** led to the hypothesis that the mechanism of the reaction involves inversion at the benzylic position of the aziridine starting material.[19]

*Scheme 3.6 Diastereoselective (3 + 2) cycloaddition with aziridine **328***



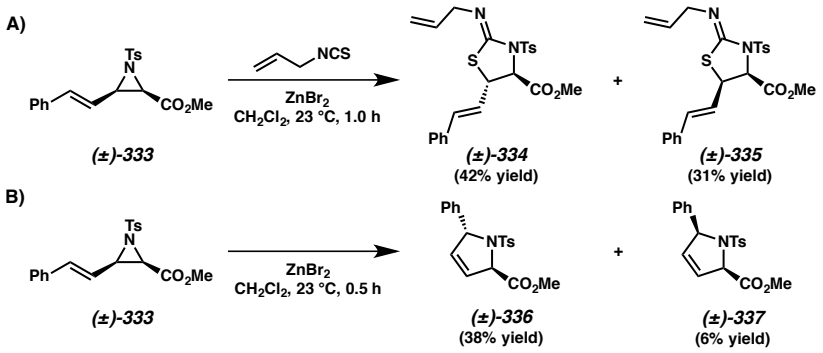
To confirm that the chemo-, regio-, and diastereoselective formation of *cis*-thiazolidine **329** was not substrate dependent, we exposed *trans*-2,3-disubstituted acroylaziridine **330** to identical reaction conditions and were pleased to find that *cis*-acroylthiazolidine **331** was formed as the sole product and as a single diastereomer (Scheme 3.7).

*Scheme 3.7 Diastereoselective (3 + 2) cycloaddition with aziridine **330***



In contrast, the (3 + 2) cycloaddition of allyl isothiocyanate with *cis*-2,3-disubstituted aziridine **333** resulted in the nondiastereoselective formation of both *trans*-thiazolidine **334** and the *cis* isomer **335** (Scheme 3.8A). Interestingly, exposure of *cis*-aziridine **333** to the reaction conditions in the absence of heterocumulene resulted in the rapid formation of pyrrolines **336** and **337** (Scheme 3.8B).[20] Finally, we found that geminally disubstituted *N*-tosyl-2-methyl-2-phenylaziridine failed to provide any (3 + 2) cycloaddition product.[21]

*Scheme 3.8 (3 + 2) Cycloaddition with aziridine **333***



3.3 DEVELOPMENT OF THE STEREOSELECTIVE (3 + 2) CYCLOADDITION

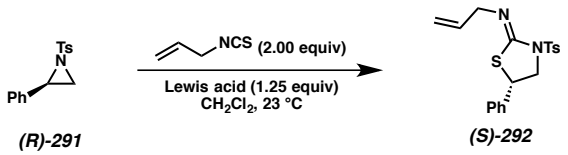
The formation of *cis*-thiazolidines **329** and **331** with excellent chemo-, regio-, and diastereoselectivity intimated the potential to develop a stereoselective reaction manifold.

3.3.1 DEVELOPMENT OF A STERESELECTIVE (3 + 2) CYCLOADDITION

Initial development focused on the (3 + 2) cycloaddition of (*R*)-*N*-tosyl-2-phenylaziridine ((***R*)-291**) with allyl isothiocyanate (Scheme 3.9).[22] The optimized zinc(II) bromide mediated reaction conditions furnished **(*S*)-292** in excellent yield and with 42% enantiomeric excess (*ee*) (entry 1). Other zinc(II) halide salts furnished the desired product in similar yield, with zinc(II) chloride giving the best *ee* (entries 2–3). Zinc(II) triflate provided no improvement in the *ee* of **(*S*)-292** (entry 4). Lithium bromide mediated and catalytic zinc(II) bromide conditions both exhibited incomplete conversion of **(*R*)-291** (entries 5–6). Interestingly, while the lithium bromide conditions furnished the opposite enantiomer **(*R*)-292**, the catalytic zinc(II) bromide conditions produced **(*S*)-292** with an improved 69% *ee*. Inspired by this result, we were pleased to

find that increasing the equivalents of isothiocyanate in the presence of stoichiometric zinc(II) bromide could provide a similar boost in *ee* while maintaining full conversion of the starting material (entry 7). Ultimately, the use of 1.25 equivalents of zinc(II) chloride and 10.0 equivalents of allyl isothiocyanate in dichloromethane at ambient temperature proved optimal, furnishing **(*S*)-292** in 99% yield and with 94% *ee* (entry 8).

Scheme 3.9 Optimization of the stereoselective reaction conditions



(R)-291
99% *ee*

(S)-292

Entry	*Lewis acid*	*t (h)*	*Yield (%)*[a]	*ee (%)*[b]
1	$ZnBr_2$	1.3	99	42
2	ZnI_2	3.0	95	32
3	$ZnCl_2$	6.0	95	63
4	$Zn(OTf)_2$	60.0	79	31
5	LiBr	96[c]	10	–76
6	$ZnBr_2$[d]	72[c]	67	69
7	$ZnBr_2$[e]	1.3	98	65
8	$ZnCl_2$[f]	2.0	99	94

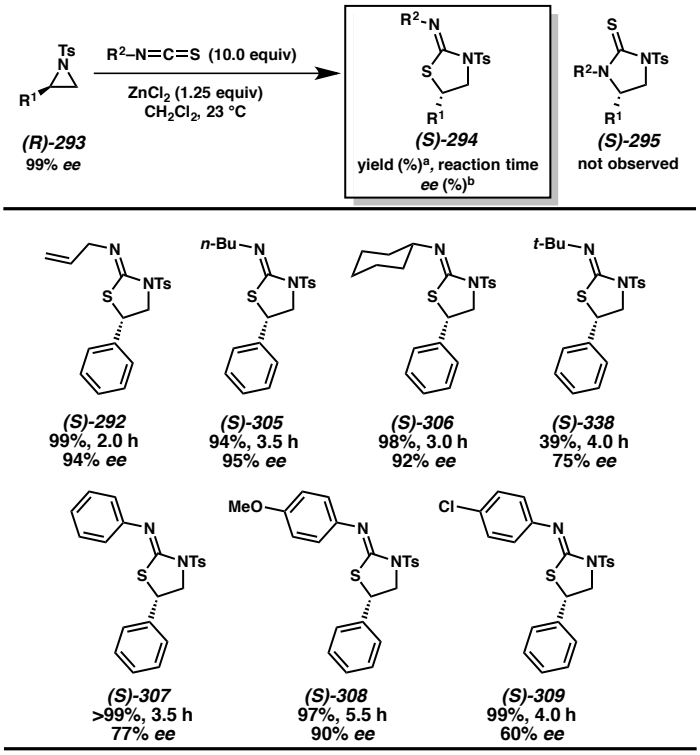
Conditions: aziridine (*R*)-291 (0.40 mmol, 99% *ee*), isothiocyanate (0.80 mmol), Lewis acid (0.50 mmol), CH_2Cl_2 (0.80 mL). [a] Isolated yield. [b] Determined by analytical chiral SFC. [c] Starting material was not fully consumed. [d] 0.12 mmol of $ZnBr_2$. [e] 6.00 equiv allyl isothiocyanate. [f] 10.0 equiv allyl isothiocyanate.

3.3.2 EXPLORATION OF ISOTHIOCYANATE SUBSTITUTION

With optimal conditions identified, we examined the scope of heterocumulene substitution in the reaction.[23] We found that, along with allyl isothiocyanate, primary and secondary alkyl isothiocyanates were all highly compatible under the reaction conditions, furnishing desired enantioenriched iminothiazolidines **(*S*)-292**, **(*S*)-305**, and **(*S*)-306** in uniformly excellent yields and *ee* (Scheme 3.10).[13] The use of a tertiary isothiocyanate, however, extended the reaction time and provided thiazolidine **(*S*)-338** in decreased yield and *ee*. Additionally, aryl isothiocyanates were competent cycloaddition reaction

partners under the zinc(II) chloride mediated conditions, providing thiazolidine products **(*S*)-307**, **(*S*)-308**, and **(*S*)-309** in excellent yields. While phenyliminothiazolidine **(*S*)-307** was isolated with good *ee*, the use of a more electron-rich isothiocyanate resulted in the formation of a thiazolidine product (**(*S*)-308**) with an excellent 90% *ee*, whereas the use of a more electron-deficient isothiocyanate provided a product with a significantly lower *ee* (**(*S*)-309**).

Scheme 3.10 Substrate scope of stereoselective isothiocyanate (3 + 2) cycloaddition

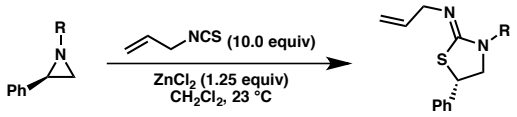


Conditions: aziridine (*R*)-293 (0.40 mmol, 99% *ee*), isothiocyanate (4.00 mmol), $ZnCl_2$ (0.50 mmol), CH_2Cl_2 (0.80 mL). [a] Isolated yield. [b] Determined by analytical chiral SFC.

3.3.3 EFFECT OF AZIRIDINE N-SUBSTITUTION ON THE TRANSFER OF CHIRAL INFORMATION

We subsequently investigated the effect of *N*-substitution on the aziridine in the stereoselective (3 + 2) cycloaddition. Aziridines with *N*-sulfonyl substitutions were extremely well tolerated under the reaction conditions, furnishing the desired thiazolidines ((***S*)-292**, (***S*)-315**–(***S*)-317**) in excellent yields and with uniformly high *ee*'s, and reaction times that increased slightly when moving from more electron-deficient (Scheme 3.11, entry 2) to more electron-rich (entry 4) sulfonyl groups. While unprotected 2-phenylaziridine showed an improved reaction time, unfortunately both the yield and *ee* of thiazolidine **(*S*)-318** were reduced (entry 5).

Scheme 3.11 Scope of N*-substitution in the stereoselective isothiocyanate (3 + 2)*



(R)-313 **99% *ee*** ***(S)-314***

Entry	*R*	*Product*	*t (h)*	*Yield (%)*[b]	*ee (%)*[c]
1	tosyl	*(S)-292*	2.0	99	94
2	*p*-NO_2-C_6H_4-SO_2	*(S)-315*	1.8	>99	95
3	mesyl	*(S)-316*	4.0	95	90
4	*p*-OMe-C_6H_4-SO_2	*(S)-317*	5.0	94	91
5	H	*(S)-318*	0.5	31	34

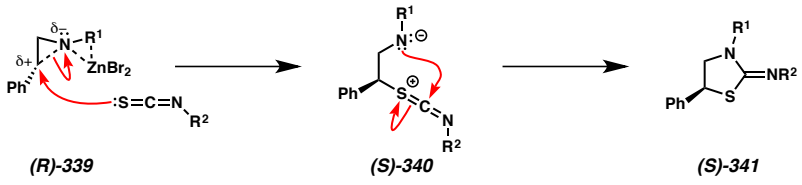
Conditions: aziridine (*R*)-313 (0.40 mmol, 99% *ee*), isothiocyanate (4.00 mmol), $ZnCl_2$ (0.50 mmol), CH_2Cl_2 (0.80 mL). [a] Isolated yield. [b] Determined by analytical chiral SFC.

3.3.4 PROPOSED MECHANISM OF STEREOSELECTIVE (3 + 2) CYCLOADDITION

We hypothesize that the mechanism of the (3 + 2) cycloadditions presented herein proceeds through a stereoselective intimate-ion-pair mechanism similar to that invoked in

our previous work[10] and by Johnson[24] and Kerr[25] in related work on the cycloadditions of donor–acceptor cyclopropanes (Scheme 3.12). Our observations including lack of reactivity in the absence of Lewis acid,[11,26] inversion at the benzylic position, greater reactivity of aziridines with electron-rich aryl substituents, and shorter reaction times of *N*-substituted aziridines with more electron-withdrawing groups are all consistent with this mechanistic hypothesis. The formation of **(*R*)-292** under lithium bromide mediated conditions strongly suggests we have developed a Lewis acid mediated process in contrast to the related alkali metal halide mediated system reported by Nadir and co-workers,[6k,9] who observe overall stereoretention as a result of a double inversion pathway, which proceeds through an iodinated intermediate. It also suggests a distinct mechanism from the palladium(II)-catalyzed reaction reported Alper and co-workers,[6i] who observe the stereoretentive product as the major enantiomer. Our hypothesis accounts for the observed nondiastereoselective formation of thiazolidines **334** and **335** and pyrrolines **336** and **337**, considering the fully separated ion-pair intermediate that likely results from destabilization of the polarized C–N bond by the steric interaction between the *cis* substituents on aziridine **333** (see Scheme 3.8).

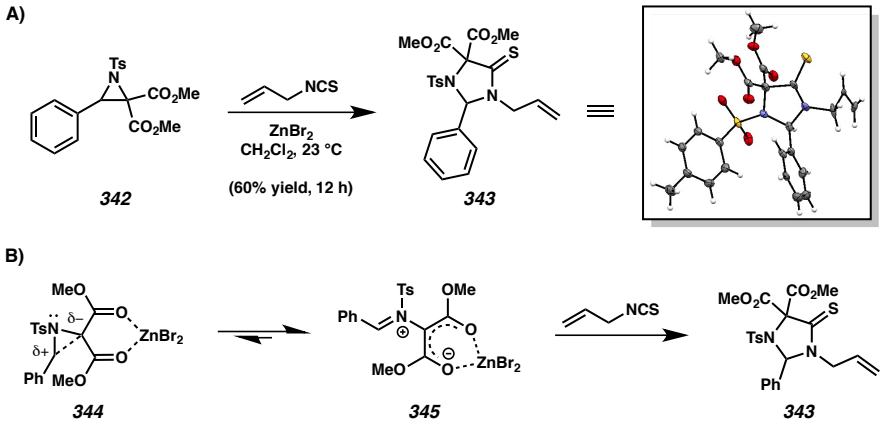
Scheme 3.12 Proposed general reaction mechanism for the stereoselective (3 + 2) cycloaddition



3.4 CYCLOADDITION OF AN AZIRIDINE DICARBOXYLATE

Noting the apparent mechanistic similarities with our previous work,[10] we synthesized aziridine dicarboxylate **342** to assess the potential for selective activation of the C–C or C–N bond under either our tin(II)- or zinc(II)-mediated conditions, respectively.[27] Unfortunately, $Sn(OTf)_2$ failed to provide any cycloaddition product.[28] Alternatively, use of $ZnBr_2$ provided thiolactam **343** as the sole (3 + 2) adduct (Scheme 3.13A).

*Scheme 3.13 (3 + 2) Cycloaddition with aziridine dicarboxylate **342***



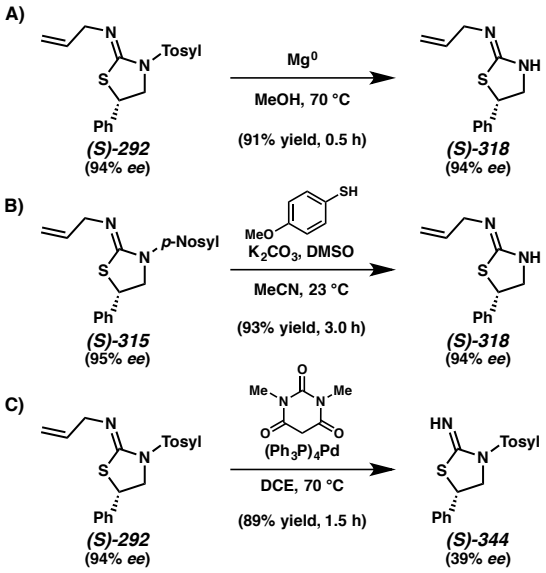
This is the only thiolactam (3 + 2) cycloaddition product observed during our studies.[13] The ability of the malonate group to stabilize the negative charge and the nitrogen to further stabilize the benzylic positive charge allows for the formation of zwitterion **345**, likely resulting in the observed divergent reactivity (Scheme 3.13B).[29]

3.5 DEPROTECTION OF IMINOTHIAZOLIDINE PRODUCTS

Having explored a range of substrates, heterocumulenes, and *N*-protecting groups, we next sought to assess the potential to derivatize our heterocyclic products. As expected, the *N*-sulfonyl protecting group removal was trivial. Secondary iminothiazolidine **(*S*)-**

318 could be accessed rapidly in an excellent 91% yield without any loss of enantiomeric excess through detosylation of thiazolidine **(*S*)-292** (Scheme 3.14A).[30] Alternatively, **(*S*)-318** could be reached by the desulfonylation of *p*-nosyl-protected thiazolidine **(*S*)-315** (Scheme 3.41B), furnishing thiazolidine **(*S*)-318** in 87% yield and with 94% *ee* over two steps from (*R*)-*N*-(*p*-nitrobenzenesulfonyl)-2-phenylaziridine.[31]

Scheme 3.14 Desulfonylation and deallylation of iminothiazolidine products



Alternatively, cleavage of the allyl imine C–N bond of heterocycle **(*S*)-292** in the presence of palladium(0) enabled access to secondary iminothiazolidine **(*S*)-344** with some loss of enantiomeric excess (Scheme 3.14C). While the deallylation of various nitrogen groups, including amines[32] and amides,[33] is known, this is the first example of imino *N*-allyl bond cleavage.

Iminothiazolidines **(*S*)-318** and **(*S*)-344** are extremely versatile heterocycles. Derivatization and synthetic manipulations of the imine, allyl group, and secondary nitrogen could be envisioned to provide rapid access to highly enantioenriched

oxothiazolidines, thiazoles, and a variety of polycyclic scaffolds.[34] Critically, access to the enantioenriched secondary thiazolidine and imidazolidine products enabled by our (3 + 2) cycloaddition allows for their use as asymmetric organic catalysts, as the free secondary nitrogen functions as a necessary hydrogen bond donor for the majority of these applications.[7a–d]

3.6 CONCLUSIONS

We have disclosed the first stereoselective Lewis acid mediated (3 + 2) cycloaddition of *N*-H- and *N*-sulfonylaziridines with alkyl heterocumulenes. These zinc(II)-mediated conditions offer broad tolerance of alkyl, silyl, and aryl heterocumulenes, as well as aziridine substitution, enabling the formation of iminoimidazolidines and enantioenriched iminothiazolidines in overall excellent yields from enantioenriched aziridines, which are easily accessible from their amino acid precursors. Combined with the exhibited ability to simply and orthogonally remove the sulfonyl and allyl protecting groups, this reaction system enables the installation of a broad number of functional group handles for further derivatization of these biologically and catalytically important heterocyclic scaffolds.

3.7 EXPERIMENTAL SECTION

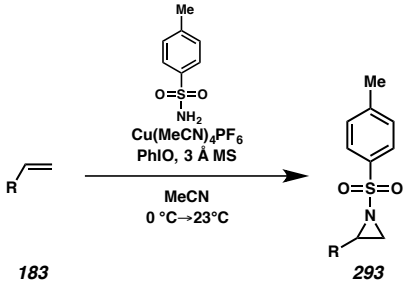
3.7.1 MATERIALS AND METHODS

Unless stated otherwise, reactions were performed at ambient temperature (23 °C) in flame-dried or oven-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina).[35] Commercially obtained reagents were used as received with the exception of tetra(*n*-

butyl)ammonium bromide (TBAB), zinc(II) chloride, zinc(II) bromide, zinc(II) iodide, zinc(II) triflate, tin(II) triflate, lithium bromide, tetrakis(acetonitrile)copper(I) hexafluorophosphate, and tetrakis(triphenylphosphine)palladium(0), which were stored in a nitrogen-filled glovebox. Triethylamine and pyridine were distilled from calcium hydride immediately prior to use. Methanol was distilled from magnesium methoxide immediately prior to use. Iodosobenzene[36] and diphenylcarbodiimide[37]were prepared by known methods. Reactions requiring external heat were modulated to the specified temperatures using an IKAmag temperature controller. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-LCMS. TLC was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 spectrometer (500 MHz and 126 MHz, respectively) and are reported in terms of chemical shift relative to residual $CHCl_3$ (δ 7.26 and δ 77.16 ppm, respectively), $D_3CS(O)CHD_2$ (δ 2.50 and δ 39.52 ppm, respectively), or $CHDCl_2$ (δ 5.32 and δ 53.84 ppm, respectively). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Abbreviations are used as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = complex multiplet, bs = broad singlet. 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 with fast atom bombardment (FAB+)

ionization mode or were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in atmospheric pressure chemical ionization (APCI+), electrospray ionization (ESI+), 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. Analytical supercritical fluid chromatography (SFC) was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing Chiralpak (AD-H or AS-H) or Chiralcel (OB-H or OD-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd.

3.7.2 GENERAL EXPERIMENTAL PROCEDURES

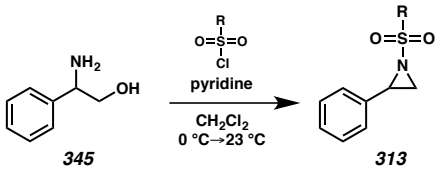


183 ***293***

General Procedure A. *Direct aziridination of olefins.*[38]

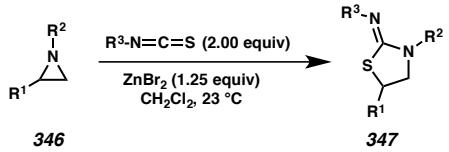
To a flame-dried round-bottom flask with a stir bar were added *p*-toluenesulfonamide (5.60 mmol, 1.40 equiv), tetrakis(acetonitrile)copper(I) hexafluorophosphate (0.40 mmol, 0.10 equiv), the appropriate olefin (**183**, 4.00 mmol, 1.00 equiv), activated 3 Å molecular sieves (2.40 g, 600 mg/mmol olefin), and acetonitrile (10 mL). The stirred suspension was cooled to 0 °C (ice/H_2O bath), and iodosobenzene (5.60 mmol, 1.40 equiv) was added as a solid in one portion. The bath was immediately removed and the reaction mixture was allowed to warm to ambient temperature. Upon consumption of starting material (determined by TLC or LCMS analysis, ca. 12–48 h), the mixture was filtered

through Celite, washing with acetonitrile (50 mL) and ethyl acetate (50 mL). The filtrate was concentrated in vacuo to give the crude product, which was purified by silica gel column chromatography (EtOAc in hexanes eluent).



General Procedure B. *Ring closure of amino alcohols.*[39]

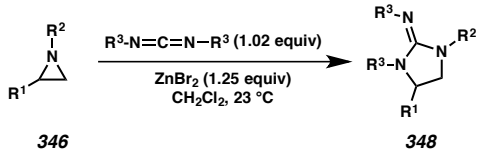
A flame-dried round-bottom flask with a stir bar was charged with 2-phenylglycinol (**345**, 0.73 mmol, 1.00 equiv), which was then suspended in CH_2Cl_2 (500 μL) and pyridine (250 μL). The stirred suspension was cooled to 0 °C (ice/H_2O bath) at which time the appropriate sulfonyl chloride (2.19 mmol, 3.00 equiv) was added in one portion. The bath was immediately removed and the reaction mixture was allowed to warm to ambient temperature. Upon completion (determined by TLC or LCMS analysis, ca. 1–5 h), the mixture was diluted with CH_2Cl_2 (12 mL), and washed with aqueous 2 N HCl (3 x 4 mL). The combined acidic aqueous layers were extracted with CH_2Cl_2 (1 x 4 mL). The organic layers were combined and carefully washed with aqueous 2 N KOH (6 x 8 mL). The combined basic aqueous layers were then extracted with CH_2Cl_2 (1 x 12 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (EtOAc in hexanes eluent).



346 ***347***

General Procedure C. *Isothiocyanate (3 + 2) cycloaddition with 2-subsituted aziridines.*

To an oven-dried 1-dram vial equipped with a magnetic stir bar was added zinc(II) bromide (113 mg, 0.50 mmol, 1.25 equiv), freshly powdered with a mortar and pestle, in an inert atmosphere glovebox. The vial was sealed with a screw cap fitted with a Teflon septum, removed from the glovebox, and placed under an inert atmosphere. To a separate, oven-dried 1-dram vial was added the appropriate aziridine (**346**, 0.40 mmol, 1.00 equiv). The vial was sealed with a screw cap fitted with a Teflon septum and anhydrous CH_2Cl_2 (0.60 mL) and isothiocyanate (0.80 mmol, 2.00 equiv) were added. The mixture was transferred to the first vial with a rinse of anhydrous CH_2Cl_2 (0.20 mL). The heterogeneous reaction mixture was then allowed to stir at ambient temperature. Upon consumption of the aziridine (determined by TLC or LCMS analysis), the reaction solution was diluted with CH_2Cl_2 (3 mL) and CH_3OH (1 mL), adsorbed onto Celite, and purified by silica gel column chromatography (acetone in hexanes eluent).

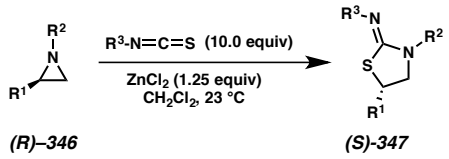


346 ***348***

General Procedure D. *Carbodiimide (3 + 2) cycloaddition with 2-subsituted aziridines.*

To an oven-dried 1-dram vial equipped with a magnetic stir bar was added zinc(II) bromide (113 mg, 0.50 mmol, 1.25 equiv), freshly powdered with a mortar and pestle, in

an inert atmosphere glovebox. The vial was sealed with a screw cap fitted with a Teflon septum, removed from the glovebox, and placed under an inert atmosphere. To a separate, oven-dried 1-dram vial was added the appropriate aziridine (**346**, 0.40 mmol, 1.00 equiv). The vial was sealed with a screw cap fitted with a Teflon septum and anhydrous CH_2Cl_2 (0.60 mL) and carbodiimide (0.41 mmol, 1.02 equiv) were added. The mixture was transferred to the first vial with a rinse of anhydrous CH_2Cl_2 (0.20 mL). The heterogeneous reaction mixture was then allowed to stir at ambient temperature. Upon consumption of the aziridine (determined by TLC or LCMS analysis), the reaction solution was diluted with CH_2Cl_2 (3 mL) and CH_3OH (1 mL), adsorbed onto Celite, and purified by silica gel column chromatography (acetone in hexanes or CH_3OH in CH_2Cl_2 eluent).



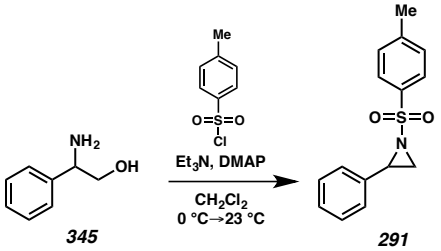
(R)–346 *(S)-347*

General Procedure E. *Stereoselective Isothiocyanate (3 + 2) cycloaddition with 2-subsituted aziridines.*

To an oven-dried 1-dram vial equipped with a magnetic stir bar was added powdered zinc(II) chloride (68 mg, 0.50 mmol, 1.25 equiv) in an inert atmosphere glovebox. The vial was sealed with a screw cap fitted with a Teflon septum, removed from the glovebox, and placed under an inert atmosphere. To a separate, oven-dried 1-dram vial was added the appropriate aziridine (**(*R*)-346**, 0.40 mmol, 1.00 equiv). The vial was sealed with a screw cap fitted with a Teflon septum and anhydrous CH_2Cl_2 (0.60 mL) and isothiocyanate (4.00 mmol, 10.0 equiv) were added. The mixture was transferred to the

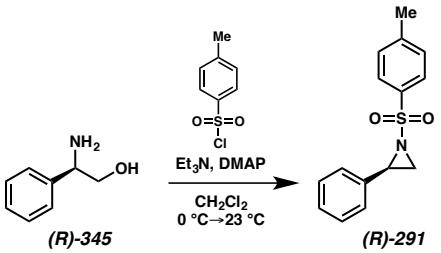
first vial with a rinse of anhydrous CH_2Cl_2 (0.20 mL). The heterogeneous reaction mixture was then allowed to stir at ambient temperature. Upon consumption of the aziridine (determined by TLC or LCMS analysis), the reaction solution was diluted with CH_2Cl_2 (3 mL) and CH_3OH (1 mL), adsorbed onto Celite, and purified by silica gel column chromatography (acetone in hexanes).

3.7.3 AZIRIDINE SYNTHESIS AND CHARACTERIZATION DATA



***N*-tosyl-2-phenylaziridine (291)**:

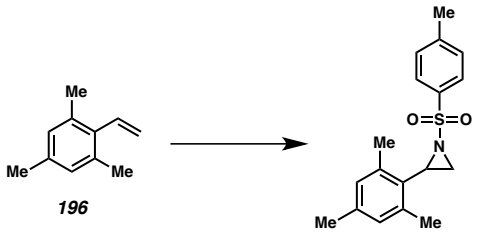
Aziridine **291** was prepared according to General Procedure B from 2-phenylglycinol (**345**): 85% yield; R_f = 0.25 (1:4 Acetone:Hexanes eluent); characterization data match those reported in the literature.[40]



(*R*)-*N*-tosyl-2-phenylaziridine ((*R*)-291):

Aziridine **(*R*)-291** was prepared according to a procedure modified from literature methods.[41] A flame-dried round-bottom flask with a stir bar was charged with (*R*)-(–)-2-

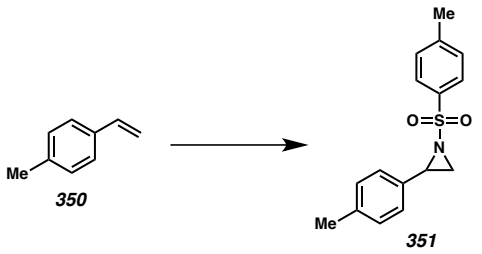
phenylglycinol (**(*R*)-345**, 5.00 g, 36.4 mmol, 1.00 equiv), *p*-toluenesulfonyl chloride (17.4 g, 91.1 mmol, 2.50 equiv), and 4-(dimethylamino)pyridine (DMAP, 445 mg, 3.64 mmol, 0.10 equiv). The solids were suspended in dichloromethane under nitrogen, and the flask was cooled in an ice-water bath. Triethylamine (Et_3N, 15.2 mL, 109 mmol, 3.00 equiv) was added dropwise, and the reaction mixture became clear and colorless. The flask was allowed to warm to room temperature and stir under nitrogen. Upon completion (as determined by LCMS analysis, ca. 8 h), the reaction was quenched by addition of saturated aqueous NH_4Cl (80 mL). The organic layer was removed and the aqueous layer extracted with dichloromethane (3 x 60 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. The crude solid was purified by silica gel column chromatography (10% EtOAc in hexanes eluent) to give aziridine **(*R*)-291** (6.34 g, 64% yield) as a fluffy white solid: characterization data are the same as above; $[\alpha]_D^{25.0}$ –108.6° (*c* 0.950, $CHCl_3$); enantiomeric excess was determined by analytical SFC (Chiralcel OB-H column, 10% isopropyl alcohol in CO_2, 2.5 mL/min, λ = 254 nm, major retention time: 7.5 minutes, minor retention time: 10.2 minutes, >99% ee).



196 ***349***

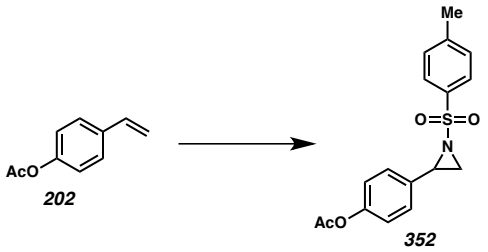
_N_-tosyl-2-mesitylaziridine (349):

Aziridine **349** was prepared according to General Procedure A: 40% yield; R_f = 0.29 (1:9 EtOAc:Hexanes eluent); characterization data match those reported in the literature.[42]



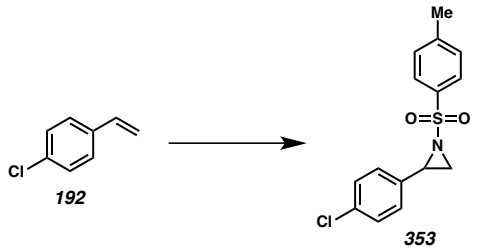
***N*-tosyl-2-(*p*-tolyl)aziridine (351)**:

Aziridine **351** was prepared according to General Procedure A: 75% yield; R_f = 0.34 (1:4 Acetone:Hexanes eluent); characterization data match those reported in the literature.[42]



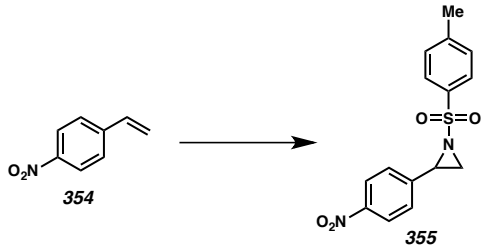
***N*-tosyl-2-(*p*-acetoxyphenyl)aziridine (352)**:

Aziridine **352** was prepared according to General Procedure A: 76% yield; R_f = 0.32 (3:7 EtOAc:Hexanes eluent); characterization data for ^{1}H NMR, ^{13}C NMR, and IR spectra match those reported in the literature;[42a] HRMS (ESI+) *m/z* calc'd for $C_{17}H_{18}NO_4S$ $[M+H]^+$: 332.0951, found 332.0958.



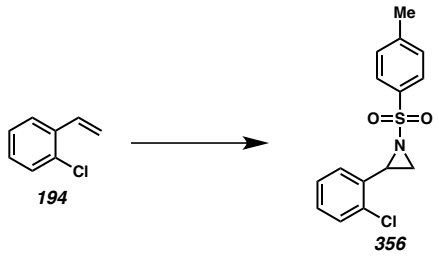
***N*-tosyl-2-(*p*-chlorophenyl)aziridine (353)**:

Aziridine **353** was prepared according to General Procedure A: 82% yield; R_f = 0.30 (3:17 EtOAc:Hexanes eluent); characterization data match those reported in the literature.[42]



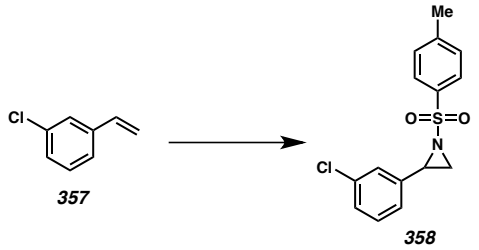
***N*-tosyl-2-(*p*-nitrophenyl)aziridine (355)**:

Aziridine **355** was prepared according to General Procedure A: 31% yield; R_f = 0.27 (1:4 Acetone:Hexanes eluent); characterization data match those reported in the literature.[42b]



***N*-tosyl-2-(*o*-chlorophenyl)aziridine (356)**:[43]

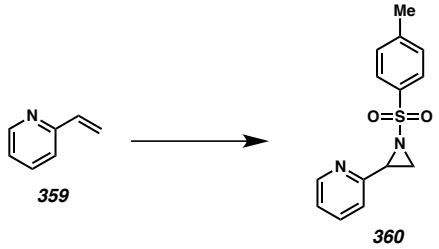
Aziridine **356** was prepared according to General Procedure A: 90% yield; R_f = 0.45 (1:3 EtOAc:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.93–7.87 (m, 2H), 7.37–7.34 (m, 2H), 7.34–7.31 (m, 1H), 7.23–7.14 (m, 3H), 4.04 (dd, *J* = 7.2, 4.4 Hz, 1H), 3.03 (d, *J* = 7.2 Hz, 1H), 2.45 (s, 3H), 2.29 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 145.0, 134.8, 133.9, 133.2, 129.9, 129.4, 129.3, 128.2, 127.6, 127.1, 39.1, 35.8, 21.8; IR (Neat Film, NaCl) 3065, 1596, 1444, 1328, 1163, 1093, 913, 815, 759, 732 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{15}{}^{35}ClNO_2S$ $[M+H]^+$: 308.0512, found 308.0520.



357 ***358***

***N*-tosyl-2-(*m*-chlorophenyl)aziridine (358)**:[43]

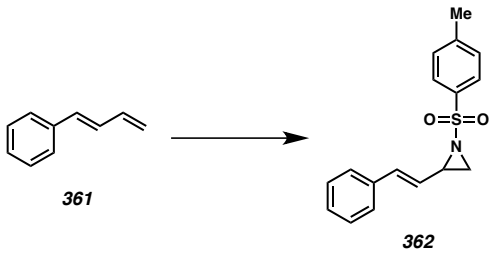
Aziridine **358** was prepared according to General Procedure A: 97% yield; R_f = 0.46 (1:3 EtOAc:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.89–7.84 (m, 2H), 7.37–7.32 (m, 2H), 7.26–7.17 (m, 3H), 7.12 (dtd, *J* = 7.1, 1.5, 0.5 Hz, 1H), 3.73 (dd, *J* = 7.1, 4.4 Hz, 1H), 2.97 (d, *J* = 7.2 Hz, 1H), 2.44 (s, 3H), 2.35 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 145.0, 137.4, 134.9, 134.7, 130.0, 129.9, 128.6, 128.1, 126.7, 125.0, 40.2, 36.3, 21.8; IR (Neat Film, NaCl) 3062, 1597, 1451, 1326, 1161, 1092, 919, 786, 723 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{15}{}^{35}ClNO_2S$ $[M+H]^+$: 308.0512, found 308.0515.



359 *360*

_N_-tosyl-2-(_o_-pyridyl)aziridine (360):[44]

Aziridine **360** was prepared according to General Procedure A: 68% yield; R_f = 0.34 (1:1 EtOAc:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.52 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.89–7.83 (m, 2H), 7.62 (td, *J* = 7.7, 1.8 Hz, 1H), 7.34–7.30 (m, 2H), 7.26 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.19 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 3.90 (dd, *J* = 7.2, 4.4 Hz, 1H), 2.97 (d, *J* = 7.2 Hz, 1H), 2.65 (d, *J* = 4.4 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 154.4, 149.7, 144.9, 136.9, 134.6, 129.9, 128.2, 123.4, 121.9, 41.4, 35.1, 21.8; IR (Neat Film, NaCl) 3064, 1594, 1477, 1437, 1326, 1204, 1161, 1092, 915, 804, 715 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{14}H_{15}N_2O_2S$ $[M+H]^+$: 275.0849, found 275.0835.

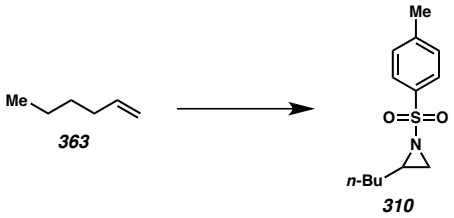


361 *362*

_N_-tosyl-2-((_E_)-styryl)aziridine (362):

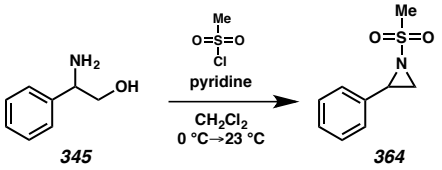
Aziridine **362** was prepared according to General Procedure A: 11% yield; R_f = 0.18 (1:9 EtOAc:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.90–7.82 (m, 2H), 7.36–7.23 (m, 7H), 6.73 (d, *J* = 15.9 Hz, 1H), 5.84 (dd, *J* = 15.9, 7.9 Hz, 1H), 3.46 (dddd, *J* = 7.8, 7.1, 4.5, 0.7 Hz, 1H), 2.87 (d, *J* = 7.1 Hz, 1H), 2.44 (s, 3H), 2.32 (d, *J* = 4.5 Hz, 1H); ^{13}C

NMR ($CDCl_3$, 126 MHz) δ 144.8, 135.9, 135.2, 129.9, 128.8, 128.4, 128.0, 126.6, 126.6, 124.2, 41.4, 34.8, 21.8; IR (Neat Film, NaCl) 3287, 3028, 2924, 1597, 1494, 1450, 1323, 1160, 1090, 964, 939, 884, 815, 753, 714 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{18}NO_2S$ $[M+H]^+$:300.1053, found 300.1057.



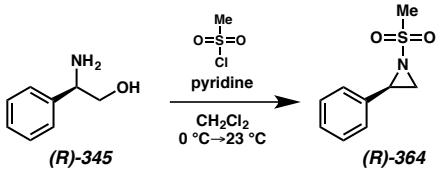
_N_-tosyl-2-(_n_-butyl)aziridine (310):

Aziridine **310** was prepared according to General Procedure A: 32% yield; R_f = 0.44 (1:3 EtOAc:Hexanes eluent); characterization data match those reported in the literature.[42b]



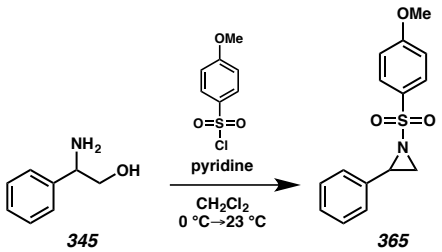
_N_-mesyl-2-phenylaziridine (364):

Aziridine **364** was prepared according to General Procedure B from 2-phenylglycinol (**345**); 88% yield; R_f = 0.29 (3:7 Acetone:Hexanes eluent); characterization data match those reported in the literature.[45]



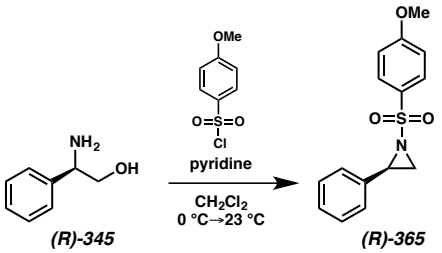
(*R*)-*N*-mesyl-2-phenylaziridine ((*R*)-364):

Aziridine **(*R*)-364** was prepared according to General Procedure B from (*R*)-(–)-2-phenylglycinol (**(*R*)-345**): characterization data are the same as above; $[\alpha]_D^{25.0}$ –194.5° (*c* 0.500, $CHCl_3$); enantiomeric excess was determined by analytical SFC (Chiralpak AS-H column, 10% isopropyl alcohol in CO_2, 2.5 mL/min, λ = 254 nm, major retention time: 3.0 minutes, minor retention time: 3.3 minutes, 99% ee).



***N*-(*p*-methoxybenzenesulfonyl)-2-phenylaziridine (365)**:

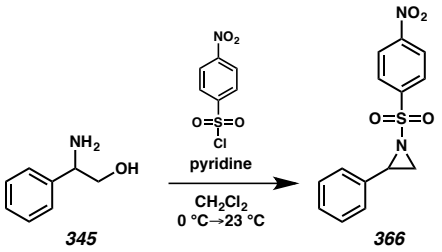
Aziridine **365** was prepared according to General Procedure B from 2-phenylglycinol (**345**): 81% yield; R_f = 0.39 (3:7 Acetone:Hexanes eluent); characterization data match those reported in the literature.[40]



(*R*)-*N*-(*p*-methoxybenzenesulfonyl)-2-phenylaziridine ((*R*)-365):

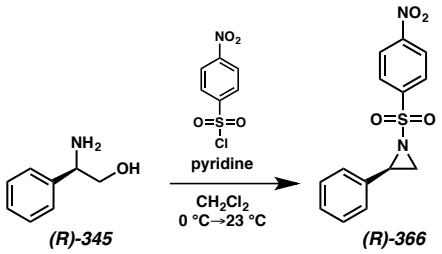
Aziridine **(*R*)-365** was prepared according to General Procedure B from (*R*)-(–)-2-phenylglycinol (**(*R*)-345**): characterization data are the same as above; $[\alpha]_D^{25.0}$ –78.0° (*c*

0.850, $CHCl_3$); enantiomeric excess was determined by analytical SFC (Chiralpak AS-H column, 10% isopropyl alcohol in CO_2, 2.5 mL/min, λ = 254 nm, major retention time: 10.0 minutes, minor retention time: 11.3 minutes, >99% ee).



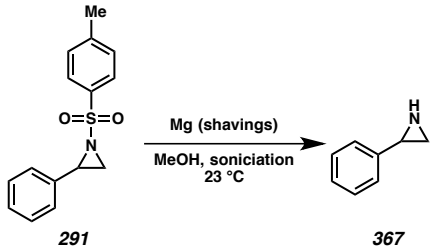
***N*-(*p*-nitrobenzenesulfonyl)-2-phenylaziridine (366)**:

Aziridine **366** was prepared according to General Procedure B from 2-phenylglycinol (**345**): 76% yield; R_f = 0.24 (1:4 Acetone:Hexanes eluent); characterization data match those reported in the literature.[40]



(*R*)-*N*-(*p*-nitrobenzenesulfonyl)-2-phenylaziridine ((*R*)-366):

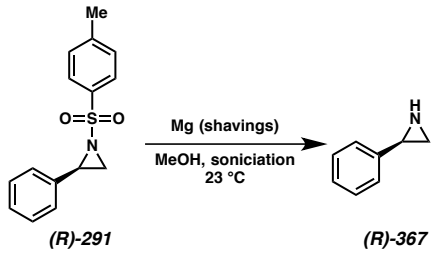
Aziridine **(*R*)-366** was prepared according to General Procedure B from (*R*)-(–)-2-phenylglycinol (**(*R*)-345**): characterization data are the same as above; $[\alpha]_D^{25.0}$ –58.4° (*c* 0.600, $CHCl_3$); enantiomeric excess was determined by analytical SFC (Chiralcel OD-H column, 10% isopropyl alcohol in CO_2, 2.5 mL/min, λ = 254 nm, major retention time: 8.9 minutes, minor retention time: 9.8 minutes, >99% ee).



291 ***367***

2-phenylaziridine (367):

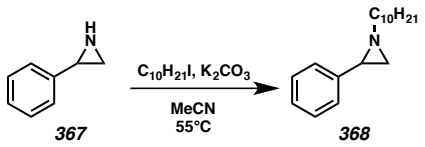
Aziridine **367** was prepared according to literature methods from *N*-tosyl-2-phenylaziridine (**291**).[30] To a suspension of magnesium metal shavings (474 mg, 19.5 mmol, 5.33 equiv) in CH_3OH (37 mL) was added a solution of aziridine **291** (1.00 g, 3.66 mmol, 1.00 equiv) in CH_3OH (24 mL) quickly dropwise. The reaction mixture was then sonicated at ambient temperature until consumption of the starting material was complete (determined by TLC analysis, ca. 30 min). The resulting white suspension was poured over brine (200 mL) and extracted with CH_2Cl_2 (4 x 150 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to generate a white solid. The crude residue was purified by column chromatography (85% EtOAc and 3% Et_3N in hexanes→3%Et_3N in EtOAc eluent) to afford aziridine **367** (342 mg, 78% yield) as a clear, colorless oil: R_f = 0.42 (EtOAc eluent); characterization data match those reported in the literature.[30]



(R)-291 ***(R)-367***

(*R*)-2-phenylaziridine ((*R*)-367):

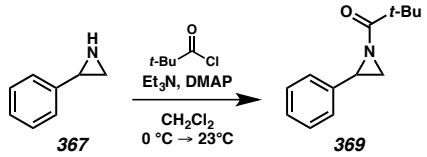
Aziridine **(*R*)-367** was prepared according to literature methods from (*R*)-*N*-tosyl-2-phenylaziridine (**(*R*)-291**) as described above: characterization data are the same as above; $[\alpha]_D^{25.0}$ –59.4° (*c* 0.750, $CHCl_3$); enantiomeric excess was determined by analytical SFC (Chiralcel OD-H column, 10% isopropyl alcohol in CO_2, 2.5 mL/min, λ = 254 nm, major retention time: 7.8 minutes, minor retention time: 4.4 minutes, >99% ee).



***N*-(*n*-decyl)-2-phenylaziridine (368)**:

Aziridine **368** was prepared according to a procedure modified from literature methods.[5c] To an oven-dried vial with a stir bar were added aziridine **367** (113 mg, 0.95 mmol, 1.20 equiv) and acetonitrile (1.2 mL). Potassium carbonate (130 mg, 0.95 mmol, 1.20 equiv) and decyl iodide (170 μL, 0.79 mmol, 1.00 equiv) were then added, and the vial was sealed and heated to 55 °C. Upon consumption of starting material (determined by LCMS analysis, ca. 17 h), the reaction mixture was allowed to cool to room temperature, concentrated in vacuo, and the residue partitioned between diethyl ether and brine. The organic layer was separated and concentrated in vacuo to afford a gold oil. The crude residue was purified by column chromatography (5% EtOAc in hexanes eluent) to furnish alkylated aziridine **368** (138 mg, 67% yield) as a clear, colorless oil: R_f = 0.33 (1:19 EtOAc:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33–7.18 (m, 5H), 2.52–2.44 (m, 1H), 2.36–2.26 (m, 2H), 1.89 (dd, *J* = 3.4, 0.7 Hz, 1H), 1.65 (dd, *J* = 6.5, 0.7 Hz, 1H), 1.64–1.56 (m, 2H), 1.41–1.18 (m, 14H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126

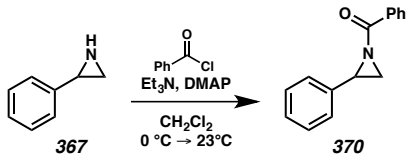
MHz) δ 140.7, 128.4, 126.9, 126.3, 62.1, 41.4, 37.9, 32.1, 30.0, 29.8, 29.7, 29.7, 29.5, 27.6, 22.8, 14.3; IR (Neat Film, NaCl) 3036, 2925, 2853, 1606, 1495, 1467, 1377, 1207, 1084, 746 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{30}N$ $[M+H]^+$: 260.2373, found 260.2378.



_N_-pivoyl-2-phenylaziridine (369):

To a stirred solution of 2-phenylaziridine (**367**, 568 mg, 4.77 mmol, 1.00 equiv) in CH_2Cl_2 (12 mL) were added triethylamine (Et_3N, 0.39 mL, 5.25 mmol, 1.10 equiv) and trimethylacetyl chloride (1.17 mL, 9.54 mmol, 2.00 equiv) dropwise. The reaction mixture was cooled to 0 °C (ice/H_2O bath) at which time 4-(dimethylamino)pyridine (DMAP, 59 mg, 0.49 mmol, 0.10 equiv) was added as a solid in one portion. The bath was immediately removed and the reaction mixture was allowed to warm to ambient temperature. Upon consumption of starting material (determined by TLC analysis, ca. 1 h), the reaction mixture was concentrated in vacuo to afford a gold oil. The crude residue was purified by column chromatography (20% EtOAc in hexanes eluent) to afford aziridine **369** (204 mg, 21% yield) as a clear, colorless oil: R_f = 0.31 (1:4 EtOAc:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.33 (m, 2H), 7.32–7.28 (m, 1H), 7.27–7.24 (m, 2H), 5.44 (dd, *J* = 10.3, 7.8 Hz, 1H), 4.24 (dd, *J* = 14.2, 10.3 Hz, 1H), 3.74 (dd, *J* = 14.2, 7.8 Hz, 1H), 1.30 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 174.2, 141.8, 128.8, 128.1, 125.6, 80.7, 63.0, 33.4, 27.9; IR (Neat Film, NaCl) 2971, 2873, 1661, 1480, 1455,

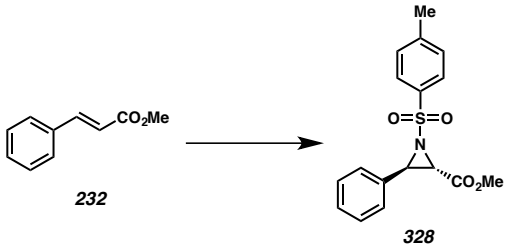
1265, 1132, 988, 954, 759 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{13}H_{18}NO$ $[M+H]^+$: 204.1388, found 204.1385.



367 *370*

***N*-benzoyl-2-phenylaziridine (370)**:

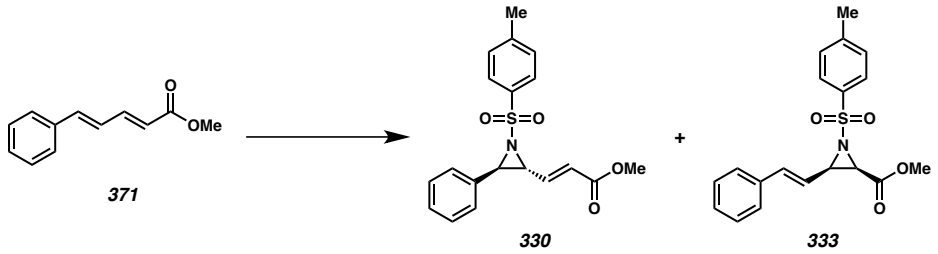
To a stirred solution of 2-phenylaziridine (**367**, 119 mg, 1.00 mmol, 1.00 equiv) in CH_2Cl_2 (2.5 mL) were added triethylamine (Et_3N, 0.16 mL, 1.10 mmol, 1.10 equiv) and benzoyl chloride (0.23 mL, 2.00 mmol, 2.00 equiv) dropwise. The reaction mixture was cooled to 0 °C (ice/H_2O bath) at which time 4-(dimethylamino)pyridine (12 mg, 0.10 mmol, 0.10 equiv) was added as a solid in one portion. The bath was immediately removed and the reaction mixture was allowed to warm to ambient temperature. Upon consumption of starting material (determined by TLC analysis, ca. 1 h), the reaction mixture was concentrated in vacuo to afford a gold oil. The crude residue was purified by column chromatography (10% EtOAc with 1% Et_3N in hexanes eluent) to afford aziridine **370** (222 mg, 99% yield) as a white amorphous solid: R_f = 0.40 (1:9 EtOAc:Hexanes eluent); characterization data match those reported in the literature.[46]



232 *328*

***trans*-methyl *N*-tosyl-3-phenylaziridine-2-carboxylate (328)**:

Aziridine **328** was prepared according to General Procedure A: 52% yield; R_f = 0.29 (3:7 Acetone:Hexanes eluent); characterization data match those reported in the literature.[42]



371 *330* *333*

***trans*-*N*-tosyl-2-((*E*)-2-(methoxycarbonyl)ethenyl)-3-phenylaziridine (330) and *cis*-methyl *N*-tosyl-3-((*E*)-styryl)aziridine-2-carboxylate (333)**:

Aziridines **330** and **333** were prepared according to General Procedure A:

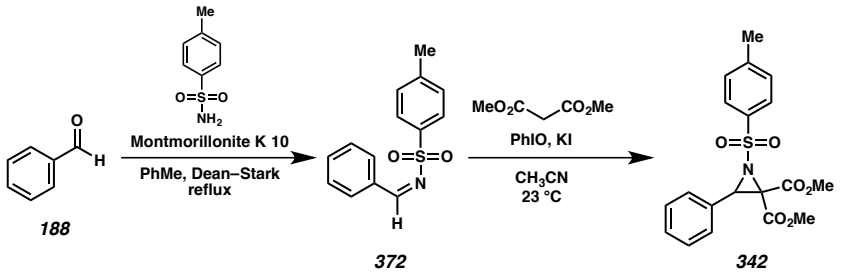
***trans*-*N*-tosyl-2-((*E*)-2-(methoxycarbonyl)ethenyl)-3-phenylaziridine (330)**:

20% yield; R_f = 0.42 (3:7 EtOAc:Hexanes eluent); characterization data for ^{1}H and ^{13}C NMR spectra match those reported in the literature;[47] IR (Neat Film, NaCl) 3032, 2952, 2256, 1722, 1651, 1597, 1495, 1435, 1407, 1329, 1268, 1162, 1089, 1034, 980, 900, 865, 815, 766, 733 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{19}H_{20}NO_4S$ $[M+H]^+$: 358.1108, found 358.1108.

***cis*-methyl *N*-tosyl-3-((*E*)-styryl)aziridine-2-carboxylate (333)**:

30% yield; R_f = 0.45 (3:7 EtOAc:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.90–7.83 (m, 2H), 7.37–7.24 (m, 7H), 6.81 (d, *J* = 16.0 Hz, 1H), 6.06 (dd, *J* = 16.0, 8.5 Hz, 1H), 3.74 (s, 3H), 3.72 (ddd, *J* = 8.5, 7.4, 0.6 Hz, 1H), 3.62 (d, *J* = 7.3 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.0, 145.3, 137.8, 135.7, 134.3, 130.1, 128.8, 128.7, 128.2, 126.8, 119.8, 52.9, 46.0, 42.0, 21.9; IR (Neat Film, NaCl) 3029, 2955,

2256, 1747, 1597, 1445, 1329, 1207, 1161, 1090, 1035, 969, 915, 802, 761, 734 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{19}H_{20}NO_4S$ $[M+H]^+$: 358.1108, found 358.1110.

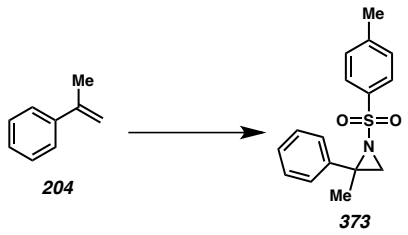


dimethyl *N*-tosyl-3-phenylaziridine-2,2-dicarboxylate (342):

Aziridine **342** was prepared according to literature methods from benzaldehyde over two steps. Procedure for the condensation of *p*-toluenesulfonamide onto benzaldehyde (**188**) was followed from the literature.[48] A stirred suspension of benzaldehyde (**188**, 1.02 mL, 10.0 mmol, 1.00 equiv), *p*-toluenesulfonamide (1.71 g, 10.0 mmol, 1.00 equiv), and montmorillonite K 10 (900 mg) in toluene (50 mL) was heated to reflux under a Dean-Stark apparatus. After 2.5 h, the consumption of starting material was complete (as determined by TLC analysis) and the reaction mixture was allowed to cool and filtered through Celite rinsing with toluene eluent (30 mL). The filtrate was concentrated in vacuo and the crude solids were purified by silica gel column chromatography (40% Et_2O in hexanes eluent), ensuring the product was eluted quickly,[49] to furnish imine **372** (2.13 g, 82% yield) as a white solid: R_f = 0.32 (2:3 Et_2O:Hexanes eluent); characterization data matches those reported in the literature.[50]

Procedure for the oxidative cycloaddition of dimethyl malonate with imine **372** was followed from the literature.[51] To a stirred solution of imine **372** (648 mg, 2.50 mmol,

1.00 equiv) and dimethyl malonate (0.32 mL, 2.75 mmol, 1.10 equiv) in acetonitrile (5 mL) were added iodosobenzene (1.10 g, 5.00 mmol, 2.00 equiv) and potassium iodide (85 mg, 0.50 mmol, 0.20 equiv) as solids, each in a single portion. After 10 minutes, the consumption of starting material was complete (as determined by TLC analysis) and the reaction mixture was diluted with dichloromethane (20 mL), dry loaded onto Celite (2.5 g), and purified by silica gel column chromatography (25% EtOAc in hexanes eluent) to afford aziridine **342** (658 mg, 68% yield) as a viscous clear, colorless oil; R_f = 0.17 (1:4 EtOAc:Hexanes eluent); characterization data for ^{1}H and ^{13}C NMR and HRMS spectra match those reported in the literature;[52] IR (Neat Film, NaCl) 3281, 2956, 1749, 1435, 1344, 1234, 1165, 1092, 816.



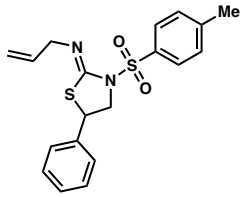
204 ***373***

***N*-tosyl-2-methyl-2-phenylaziridine (373)**:

Aziridine **373** was prepared according to General Procedure A: 32% yield; R_f = 0.44 (1:3 EtOAc:Hexanes eluent); characterization data match those reported in the literature.[42]

3.7.4 IMINOTHIAZOLIDINE SYNTHESIS AND CHARACTERIZATION DATA

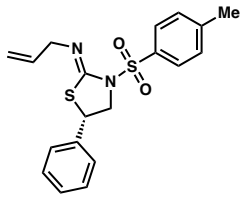
Unless otherwise stated, all iminothiazolidines were prepared according to General Procedure C and were isolated as amorphous white solids.



292

(*Z*)-5-phenyl-3-tosyl-2-(allylimino)thiazolidine (292):

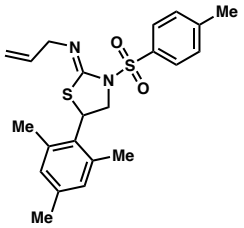
99% yield; R_f = 0.28 (1:4 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.94–7.89 (m, 2H), 7.40–7.32 (m, 5H), 7.32–7.28 (m, 2H), 5.84 (ddt, *J* = 17.1, 10.3, 5.1 Hz, 1H), 5.12–4.98 (m, 2H), 4.80 (dd, *J* = 8.4, 6.3 Hz, 1H), 4.50 (dd, *J* = 10.3, 6.3 Hz, 1H), 3.94 (dd, *J* = 10.3, 8.5 Hz, 1H), 3.86 (ddt, *J* = 15.9, 5.1, 1.8 Hz, 1H), 3.77 (ddt, *J* = 15.9, 5.2, 1.8 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 151.2, 144.6, 136.8, 135.0, 134.9, 129.2, 129.1, 129.0, 128.8, 127.6, 115.3, 58.0, 56.6, 47.1, 21.8; IR (Neat Film, NaCl) 2923, 1653, 1596, 1355, 1168, 1108, 810, 764 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{19}H_{21}N_2O_2S_2$ $[M+H]^+$: 373.1039, found 373.1049.



(S)-292

(*S*,*Z*)-5-phenyl-3-tosyl-2-(allylimino)thiazolidine ((*S*)-292):

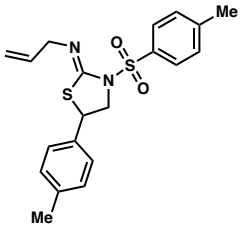
Thiazolidine **(*S*)-292** was prepared according to General Procedure E: 99% yield; R_f = 0.28 (1:4 Acetone:Hexanes eluent); characterization data match those above; $[\alpha]_D^{25.0}$ –13.1° (*c* 1.600, $CHCl_3$); enantiomeric excess was determined by analytical SFC (Chiralpak AD-H, 30% isopropyl alcohol in CO_2, 2.5 mL/min, λ = 254 nm, major retention time: 5.4 minutes, minor retention time: 3.8 minutes, 94% ee).



296

(*Z*)-5-mesityl-3-tosyl-2-(allylimino)thiazolidine (296):

97% yield; R_f = 0.23 (1:4 Et_2O:Hexanes eluent); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.99–7.91 (m, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.85 (s, 2H), 5.83 (ddt, *J* = 17.2, 10.3, 5.1 Hz, 1H), 5.43 (dd, *J* = 11.0, 7.6 Hz, 1H), 5.11–4.97 (m, 2H), 4.41 (dd, *J* = 10.4, 7.6 Hz, 1H), 4.14 (t, *J* = 10.7 Hz, 1H), 3.85 (ddt, *J* = 16.0, 5.1, 1.8 Hz, 1H), 3.73 (ddt, *J* = 16.0, 5.2, 1.7 Hz, 1H), 2.45 (s, 3H), 2.40 (s, 6H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 151.9, 144.6, 138.4, 138.0, 135.4, 135.2, 131.0, 129.3, 129.1, 127.3, 115.2, 58.0, 52.3, 42.4, 21.8, 21.6, 20.9; IR (Neat Film, NaCl) 2920, 1656, 1637, 1450, 1357, 1170, 1106, 1090, 858, 789 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{22}H_{27}N_2O_2S_2$ $[M+H]^+$: 415.1508, found 415.1519.

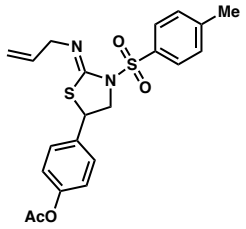


297

(*Z*)-5-(*p*-tolyl)-3-tosyl-2-(allylimino)thiazolidine (297):

92% yield; R_f = 0.38 (1:4 Acetone:Hexanes eluent); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.95–7.89 (m, 2H), 7.32–7.28 (m, 2H), 7.28–7.24 (m, 2H), 7.19–7.13 (m, 2H), 5.84 (ddt, *J* = 17.1, 10.3, 5.1 Hz, 1H), 5.06 (dq, *J* = 17.2, 1.9 Hz, 1H), 5.02 (dq, *J* = 10.3, 1.7 Hz, 1H),

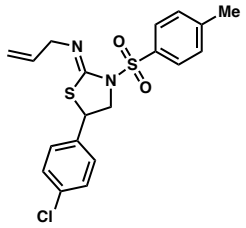
4.77 (dd, *J* = 8.6, 6.3 Hz, 1H), 4.48 (dd, *J* = 10.3, 6.3 Hz, 1H), 3.91 (dd, *J* = 10.3, 8.7 Hz, 1H), 3.85 (ddt, *J* = 15.9, 5.1, 1.8 Hz, 1H), 3.76 (ddt, *J* = 15.9, 5.2, 1.8 Hz, 1H), 2.44 (s, 3H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 151.4, 144.6, 138.7, 135.1, 135.0, 133.7, 129.8, 129.2, 129.1, 127.5, 115.2, 58.0, 56.6, 47.0, 21.8, 21.2; IR (Neat Film, NaCl) 3007, 2922, 1657, 1639, 1597, 1514, 1358, 1170, 1110, 915, 814, 774, 732 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{20}H_{23}N_2O_2S_2$ $[M+H]^+$: 387.1195, found 387.1202.



298

(*Z*)-5-(*p*-acetoxyphenyl)-3-tosyl-2-(allylimino)thiazolidine (298):

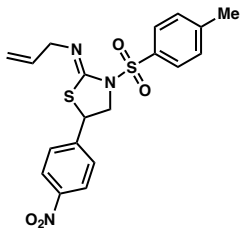
95% yield; R_f = 0.37 (3:7 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.93–7.87 (m, 2H), 7.42–7.34 (m, 2H), 7.32–7.27 (m, 2H), 7.10–7.04 (m, 2H), 5.83 (ddt, *J* = 17.1, 10.3, 5.1 Hz, 1H), 5.12–4.97 (m, 2H), 4.78 (dd, *J* = 8.3, 6.3 Hz, 1H), 4.47 (dd, *J* = 10.3, 6.3 Hz, 1H), 3.91 (dd, *J* = 10.3, 8.3 Hz, 1H), 3.84 (ddt, *J* = 15.9, 5.1, 1.8 Hz, 1H), 3.76 (ddt, *J* = 15.9, 5.2, 1.8 Hz, 1H), 2.43 (s, 3H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 169.4, 151.0, 150.8, 144.7, 135.0, 134.9, 134.5, 129.2, 129.1, 128.8, 122.3, 115.3, 58.0, 56.6, 46.5, 21.8, 21.2; IR (Neat Film, NaCl) 2922, 1760, 1657, 1505, 1360, 1202, 1169, 1107, 912, 811 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{21}H_{23}N_2O_4S_2$ $[M+H]^+$: 431.1094, found 431.1113.



299

(*Z*)-5-(*p*-chlorophenyl)-3-tosyl-2-(allylimino)thiazolidine (299):

93% yield; R_f = 0.29 (1:4 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.92–7.87 (m, 2H), 7.32–7.27 (m, 6H), 5.83 (ddt, *J* = 17.1, 10.3, 5.1 Hz, 1H), 5.10–4.99 (m, 2H), 4.75 (dd, *J* = 7.8, 6.3 Hz, 1H), 4.45 (dd, *J* = 10.3, 6.3 Hz, 1H), 3.93 (dd, *J* = 10.3, 7.8 Hz, 1H), 3.84 (ddt, *J* = 15.9, 5.1, 1.8 Hz, 1H), 3.77 (ddt, *J* = 15.9, 5.2, 1.8 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 150.7, 144.7, 135.7, 135.0, 134.9, 134.7, 129.3, 129.2, 129.1, 129.0, 115.4, 58.1, 56.4, 46.4, 21.8; IR (Neat Film, NaCl) 2924, 1651, 1597, 1493, 1354, 1168, 1090, 1014, 917, 809, 731 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{19}H_{20}{}^{35}ClN_2O_2S_2$ $[M+H]^+$: 407.0649, found 407.0665.

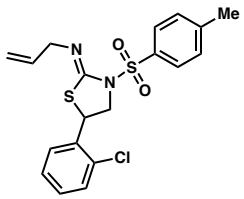


300

(*Z*)-5-(*p*-nitrophenyl)-3-tosyl-2-(allylimino)thiazolidine (300):

59% yield; R_f = 0.20 (1:4 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.25–8.19 (m, 2H), 7.93–7.87 (m, 2H), 7.59–7.53 (m, 2H), 7.34–7.28 (m, 2H), 5.84 (ddt, *J* = 17.1, 10.3, 5.1 Hz, 1H), 5.12–5.01 (m, 2H), 4.84 (t, *J* = 6.5 Hz, 1H), 4.47 (dd, *J* = 10.5, 6.3 Hz, 1H), 4.06 (dd, *J* = 10.5, 6.7 Hz, 1H), 3.88–3.77 (m, 2H), 2.45 (d, *J* = 0.8 Hz, 3H);

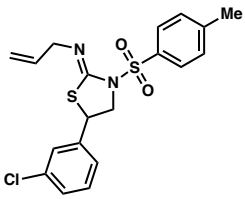
^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.8, 148.1, 145.0, 134.8, 134.7, 129.4, 129.1, 128.6, 124.4, 115.6, 58.3, 55.9, 46.0, 21.8; IR (Neat Film, NaCl) 1656, 1597, 1521, 1347, 1169, 1107, 857, 813 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{19}H_{20}N_3O_4S_2$ $[M+H]^+$: 418.0890, found 418.0907.



301

(*Z*)-5-(*o*-chlorophenyl)-3-tosyl-2-(allylimino)thiazolidine (301):

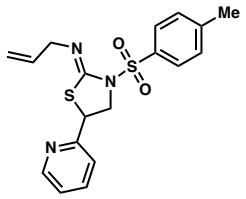
91% yield; R_f = 0.35 (1:4 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.92–7.87 (m, 2H), 7.60–7.56 (m, 1H), 7.43–7.38 (m, 1H), 7.31–7.26 (m, 4H), 5.83 (ddt, *J* = 17.1, 10.3, 5.1 Hz, 1H), 5.19 (dd, *J* = 6.3, 5.2 Hz, 1H), 5.09–5.00 (m, 2H), 4.39 (dd, *J* = 10.5, 6.3 Hz, 1H), 4.20 (dd, *J* = 10.5, 5.2 Hz, 1H), 3.85 (ddt, *J* = 15.9, 5.1, 1.8 Hz, 1H), 3.79 (ddt, *J* = 15.9, 5.2, 1.8 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 150.8, 144.7, 135.6, 135.0, 134.9, 133.6, 130.0, 129.7, 129.3, 129.1, 128.1, 127.7, 115.3, 58.1, 54.9, 42.8, 21.8; IR (Neat Film, NaCl) 3067, 2881, 1657, 1597, 1470, 1444, 1361, 1284, 1171, 1109, 919, 811, 750 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{19}H_{20}{}^{35}ClN_2O_2S_2$ $[M+H]^+$: 407.0649, found 407.0665.



302

(*Z*)-5-(*m*-chlorophenyl)-3-tosyl-2-(allylimino)thiazolidine (302):

90% yield; R_f = 0.35 (1:4 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.92–7.86 (m, 2H), 7.37–7.34 (m, 1H), 7.33–7.25 (m, 5H), 5.83 (ddt, *J* = 17.1, 10.3, 5.1 Hz, 1H), 5.09–5.00 (m, 2H), 4.74 (dd, *J* = 7.8, 6.3 Hz, 1H), 4.48 (dd, *J* = 10.4, 6.3 Hz, 1H), 3.94 (dd, *J* = 10.4, 7.8 Hz, 1H), 3.85 (ddt, *J* = 15.9, 5.1, 1.8 Hz, 1H), 3.77 (ddt, *J* = 15.9, 5.2, 1.8 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 150.6, 144.8, 139.3, 135.0, 134.9, 134.8, 130.5, 129.3, 129.1, 129.0, 127.8, 125.9, 115.4, 58.1, 56.4, 46.4, 21.8; IR (Neat Film, NaCl) 2923, 1656, 1596, 1479, 1360, 1169, 1110, 917, 812 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{19}H_{20}{}^{35}ClN_2O_2S_2$ $[M+H]^+$: 407.0649, found 407.0669.

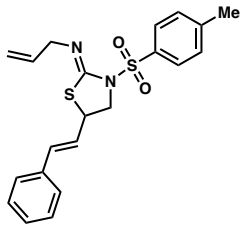


303

(*Z*)-5-(*o*-pyridyl)-3-tosyl-2-(allylimino)thiazolidine (303):

General Procedure C followed using 2.25 equivalents of zinc(II) bromide: 42% yield; R_f = 0.28 (1:1 EtOAc:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.58 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.86–7.79 (m, 2H), 7.64 (td, *J* = 7.7, 1.8 Hz, 1H), 7.38 (dq, *J* = 7.9, 0.9 Hz, 1H), 7.26–7.21 (m, 3H), 5.98–5.93 (m, 1H), 5.85 (ddt, *J* = 17.2, 10.3, 5.1 Hz, 1H), 5.10 (dq, *J* = 17.1, 1.8 Hz, 1H), 5.03 (dq, *J* = 10.3, 1.7 Hz, 1H), 3.88 (ddt, *J* = 15.9, 5.2, 1.8 Hz, 1H), 3.77 (ddt, *J* = 15.9, 5.1, 1.8 Hz, 1H), 3.69 (dd, *J* = 11.0, 7.2 Hz, 1H), 3.53 (dd, *J* = 11.0, 1.3 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.5, 152.2, 149.6, 144.6, 137.0, 136.1, 135.1, 129.2, 129.1, 123.1, 121.1, 115.3, 64.5, 58.4, 34.6,

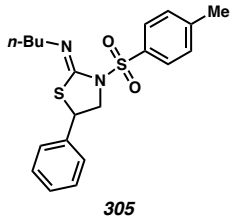
21.8; IR (Neat Film, NaCl) 2921, 1655, 1638, 1590, 1352, 1169, 1110, 1088, 792 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{18}H_{20}N_3O_2S_2$ $[M+H]^+$: 374.0991, found 374.1006.



304

(*Z*)-5-((*E*)-styryl)-3-tosyl-2-(allylimino)thiazolidine (304):

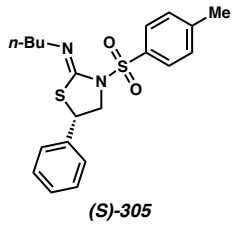
47% yield; R_f = 0.34 (1:4 Acetone:Hexanes eluent); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.94–7.90 (m, 2H), 7.38–7.26 (m, 7H), 6.64 (dd, *J* = 15.6, 0.8 Hz, 1H), 6.13 (dd, *J* = 15.6, 8.9 Hz, 1H), 5.82 (ddt, *J* = 17.1, 10.3, 5.1 Hz, 1H), 5.09–4.97 (m, 2H), 4.42 (dddd, *J* = 8.9, 7.4, 6.0, 0.8 Hz, 1H), 4.34 (dd, *J* = 10.2, 6.0 Hz, 1H), 3.87 (dd, *J* = 10.2, 7.5 Hz, 1H), 3.82 (ddt, *J* = 15.8, 5.1, 1.8 Hz, 1H), 3.75 (ddt, *J* = 15.9, 5.2, 1.8 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 151.2, 144.7, 135.6, 135.0, 134.9, 134.4, 129.3, 129.1, 128.9, 128.6, 126.8, 124.6, 115.3, 58.1, 54.9, 46.2, 21.8; IR (Neat Film, NaCl) 2925, 2254, 1645, 1452, 1353, 1259, 1168, 1090, 1019, 915, 811, 753 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{21}H_{23}N_2O_2S_2$ $[M+H]^+$: 399.1195, found 399.1201.



305

(*Z*)-5-phenyl-3-tosyl-2-((*n*-butyl)imino)thiazolidine (305):

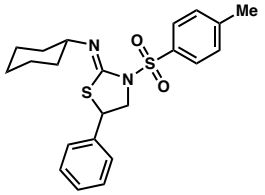
>99% yield; R_f = 0.36 (1:4 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.92–7.87 (m, 2H), 7.40–7.32 (m, 5H), 7.31–7.27 (m, 2H), 4.78 (dd, *J* = 8.4, 6.3 Hz, 1H), 4.48 (dd, *J* = 10.2, 6.3 Hz, 1H), 3.91 (dd, *J* = 10.2, 8.4 Hz, 1H), 3.20 (dt, *J* = 12.6, 6.7 Hz, 1H), 3.08 (dt, *J* = 12.7, 6.8 Hz, 1H), 2.44 (s, 3H), 1.50 (dddd, *J* = 13.5, 8.7, 6.7, 2.2 Hz, 2H), 1.23–1.13 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.4, 144.5, 137.1, 135.1, 129.1, 129.1, 129.1, 128.8, 127.7, 56.4, 56.1, 47.0, 32.9, 21.8, 20.5, 14.0; IR (Neat Film, NaCl) 2955, 2928, 2870, 1658, 1455, 1357, 1170, 1096, 811, 765 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{25}N_2O_2S_2$ $[M+H]^+$: 389.1352, found 389.1368.



(S)-305

(*S*,*Z*)-5-phenyl-3-tosyl-2-(*n*-butylimino)thiazolidine ((*S*)-305):

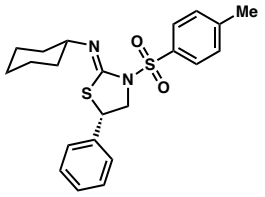
Thiazolidine **(*S*)-305** was prepared according to General Procedure E: 94% yield; R_f = 0.36 (1:4 Acetone:Hexanes eluent); characterization data match those above; $[\alpha]_D^{25.0}$ –6.45° (*c* 2.800, $CHCl_3$); enantiomeric excess was determined by analytical SFC (Chiralpak AD-H column, 30% isopropyl alcohol in CO_2, 2.5 mL/min, λ = 254 nm, major retention time: 4.7 minutes, minor retention time: 3.6 minutes, 95% ee).



306

(*Z*)-5-phenyl-3-tosyl-2-(cyclohexylimino)thiazolidine (306):

94% yield; R_f = 0.41 (1:4 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.95–7.89 (m, 2H), 7.41–7.31 (m, 5H), 7.31–7.27 (m, 2H), 4.76 (dd, *J* = 8.5, 6.3 Hz, 1H), 4.46 (dd, *J* = 10.3, 6.3 Hz, 1H), 3.87 (dd, *J* = 10.2, 8.5 Hz, 1H), 2.77 (tt, *J* = 9.5, 3.9 Hz, 1H), 2.44 (s, 3H), 1.79–1.62 (m, 3H), 1.58 (dddd, *J* = 12.8, 5.9, 3.6, 1.7 Hz, 2H), 1.40 (ddtd, *J* = 22.7, 16.6, 9.5, 4.6 Hz, 2H), 1.33–1.18 (m, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 147.2, 144.4, 137.2, 135.0, 129.3, 129.1, 129.0, 128.7, 127.6, 65.5, 56.1, 47.0, 33.6, 33.4, 25.8, 24.5, 24.5, 21.8; IR (Neat Film, NaCl) 2928, 2853, 1652, 1450, 1362, 1171, 1100, 812, 760 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{22}H_{27}N_2O_2S_2$ $[M+H]^+$: 415.1508, found 415.1493.

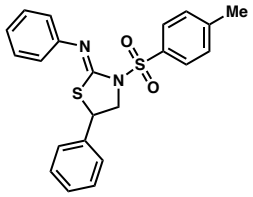


(S)-306

(*S*,*Z*)-5-phenyl-3-tosyl-2-(cyclohexylimino)thiazolidine ((*S*)-306):

Thiazolidine **(*S*)-306** was prepared according to General Procedure E: 98% yield; R_f = 0.41 (1:4 Acetone:Hexanes eluent); characterization data match those above; $[\alpha]_D^{25.0}$ 0.72° (*c* 4.200, $CHCl_3$); enantiomeric excess was determined by analytical SFC

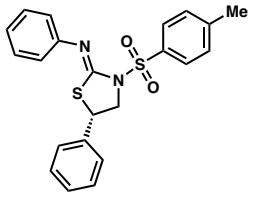
(Chiralpak AS-H column, 30% isopropyl alcohol in CO_2, 2.5 mL/min, λ = 254 nm, major retention time: 5.1 minutes, minor retention time: 4.0 minutes, 92% ee).



307

(*Z*)-5-phenyl-3-tosyl-2-(phenylimino)thiazolidine (307):

95% yield; R_f = 0.23 (1:4 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03–7.96 (m, 2H), 7.41–7.29 (m, 7H), 7.30–7.22 (m, 2H), 7.12–7.03 (m, 1H), 6.83–6.75 (m, 2H), 4.80 (dd, *J* = 8.5, 6.4 Hz, 1H), 4.60 (dd, *J* = 10.4, 6.4 Hz, 1H), 4.06 (dd, *J* = 10.4, 8.5 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 152.3, 150.1, 145.0, 136.6, 134.7, 129.3, 129.2, 129.1, 129.0, 128.9, 127.6, 124.4, 120.9, 56.9, 47.1, 21.9; IR (Neat Film, NaCl) 3030, 1640, 1591, 1487, 1360, 1171, 1135, 1100, 763 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{22}H_{21}N_2O_2S_2$ $[M+H]^+$: 409.1039, found 409.1051.

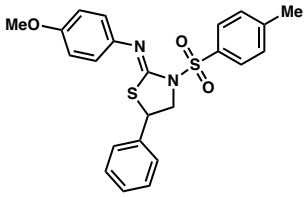


(S)-307

(*S*,*Z*)-5-phenyl-3-tosyl-2-(phenylimino)thiazolidine ((*S*)-307):

Thiazolidine **(*S*)-307** was prepared according to General Procedure E: >99% yield; R_f = 0.23 (1:4 Acetone:Hexanes eluent); characterization data match those above; $[\alpha]_D^{25.0}$ 49.9° (*c* 3.400, $CHCl_3$); enantiomeric excess was determined by analytical SFC

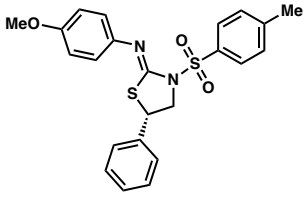
(Chiralpak AS-H column, 30% isopropyl alcohol in CO_2, 2.5 mL/min, λ = 254 nm, major retention time: 7.3 minutes, minor retention time: 5.7 minutes, 77% ee).



308

(*Z*)-5-phenyl-3-tosyl-2-((*p*-methoxyphenyl)imino)thiazolidine (308):

98% yield; R_f = 0.31 (3:7 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03–7.94 (m, 2H), 7.39–7.28 (m, 7H), 6.85–6.79 (m, 2H), 6.79–6.73 (m, 2H), 4.79 (dd, *J* = 8.4, 6.4 Hz, 1H), 4.59 (dd, *J* = 10.4, 6.4 Hz, 1H), 4.05 (dd, *J* = 10.4, 8.5 Hz, 1H), 3.76 (s, 3H), 2.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 156.6, 151.9, 144.9, 143.4, 136.7, 134.8, 129.3, 129.2, 129.1, 128.8, 127.6, 121.9, 114.2, 56.7, 55.5, 47.0, 21.8; IR (Neat Film, NaCl) 2949, 1640, 1505, 1455, 1360, 1290, 1242, 1168, 1101, 1033, 910, 832, 811, 768, 733 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{23}H_{23}N_2O_3S_2$ $[M+H]^+$: 439.1145, found 439.1161.

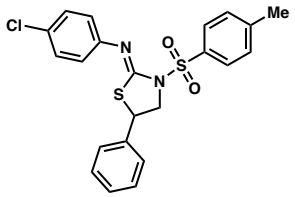


(S)-308

(*S*,*Z*)-5-phenyl-3-tosyl-2-(*p*-methoxyphenylimino)thiazolidine ((*S*)-308):

Thiazolidine **(*S*)-308** was prepared according to General Procedure E: 97% yield; R_f = 0.31 (3:7 Acetone:Hexanes eluent); characterization data match those above; $[\alpha]_D^{25.0}$

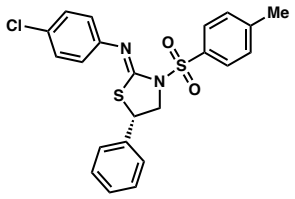
61.6° (*c* 2.800, $CHCl_3$); enantiomeric excess was determined by analytical SFC (Chiralpak AS-H column, 30% isopropyl alcohol in CO_2, 2.5 mL/min, λ = 254 nm, major retention time: 9.1 minutes, minor retention time: 6.9 minutes, 90% ee).



309

(*Z*)-5-phenyl-3-tosyl-2-((*p*-chlorophenyl)imino)thiazolidine (309):

92% yield; R_f = 0.29 (1:4 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.01–7.93 (m, 2H), 7.39–7.30 (m, 7H), 7.25–7.18 (m, 2H), 6.76–6.70 (m, 2H), 4.81 (dd, *J* = 8.4, 6.4 Hz, 1H), 4.60 (dd, *J* = 10.4, 6.5 Hz, 1H), 4.07 (dd, *J* = 10.4, 8.5 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 153.0, 148.5, 145.2, 136.4, 134.6, 129.7, 129.4, 129.2, 129.2, 129.1, 129.0, 127.6, 122.3, 56.9, 47.2, 21.9; IR (Neat Film, NaCl) 2924, 1634, 1588, 1486, 1360, 1172, 1139, 1088, 833, 812 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{22}H_{20}{}^{35}ClN_2O_2S_2$ $[M+H]^+$: 443.0649, found 443.0664.

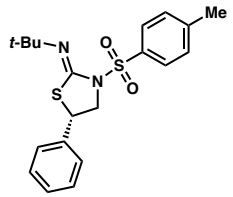


(S)-309

(*S*,*Z*)-5-phenyl-3-tosyl-2-(*p*-chlorophenylimino)thiazolidine ((*S*)-309):

Thiazolidine **(*S*)-309** was prepared according to General Procedure E: 99% yield; R_f = 0.29 (1:4 Acetone:Hexanes eluent); characterization data match those above; $[\alpha]_D{}^{25.0}$

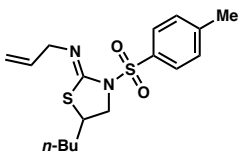
44.7° (*c* 4.950, $CHCl_3$); enantiomeric excess was determined by analytical SFC (Chiralpak AS-H column, 30% isopropyl alcohol in CO_2, 2.5 mL/min, λ = 254 nm, major retention time: 7.7 minutes, minor retention time: 6.1 minutes, 60% ee).



(S)-338

(*S*,*Z*)-5-phenyl-3-tosyl-2-(*t*-butylimino)thiazolidine ((*S*)-338):

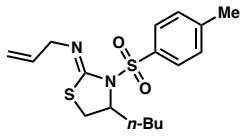
39% yield; R_f = 0.38 (1:4 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.88–7.83 (m, 2H), 7.42–7.31 (m, 5H), 7.30–7.26 (m, 2H), 4.79 (dd, *J* = 8.4, 6.2 Hz, 1H), 4.47 (dd, *J* = 10.3, 6.2 Hz, 1H), 3.88 (dd, *J* = 10.3, 8.4 Hz, 1H), 2.44 (s, 3H), 1.17 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 144.2, 142.9, 137.3, 135.7, 129.4, 129.1, 128.8, 128.7, 127.7, 55.0, 54.7, 48.3, 28.9, 21.8; IR (Neat Film, NaCl) 2971, 1653, 1600, 1496, 1454, 1360, 1167, 1092, 810, 771, 701 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{20}H_{25}N_2O_2S_2$ $[M+H]^+$: 389.1352, found 389.1362; $[\alpha]_D^{25.0}$ 3.33° (*c* 1.900, $CHCl_3$); enantiomeric excess was determined by analytical SFC (Chiralpak IC-3 column, 30% isopropyl alcohol in CO_2, 2.5 mL/min, λ = 254 nm, major retention time: 6.2 minutes, minor retention time: 7.0 minutes, 75% ee).



311

(*Z*)-5-(*n*-butyl)-3-tosyl-2-(allylimino)thiazolidine (311):[53]

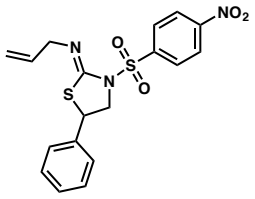
18% yield; R_f = 0.44 (1:4 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.94–7.86 (m, 2H), 7.30–7.26 (m, 2H), 5.80 (ddt, *J* = 17.1, 10.3, 5.1 Hz, 1H), 5.04–4.96 (m, 2H), 4.21 (dd, *J* = 10.0, 5.9 Hz, 1H), 3.81–3.73 (m, 2H), 3.70 (dd, *J* = 10.0, 7.1 Hz, 1H), 3.59 (ddt, *J* = 8.4, 7.0, 6.0 Hz, 1H), 2.42 (s, 3H), 1.82–1.70 (m, 1H), 1.71–1.60 (m, 1H), 1.42–1.27 (m, 4H), 0.90 (td, *J* = 7.4, 3.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 151.6, 144.5, 135.2, 130.0, 129.2, 129.0, 115.1, 58.0, 55.0, 44.0, 33.9, 30.1, 22.5, 21.8, 14.0; IR (Neat Film, NaCl) 2957, 2928, 2871, 1652, 1598, 1456, 1357, 1170, 1106, 918, 812 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{17}H_{25}N_2O_2S_2$ $[M+H]^+$: 353.1352, found 353.1364.



312

(*Z*)-4-(*n*-butyl)-3-tosyl-2-(allylimino)thiazolidine (312):[53]

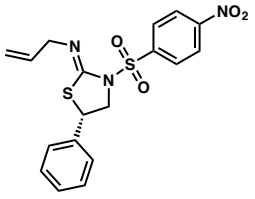
56% yield; R_f = 0.44 (1:4 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.95–7.85 (m, 2H), 7.29–7.24 (m, 2H), 5.80 (ddt, *J* = 17.1, 10.3, 5.2 Hz, 1H), 5.03 (dq, *J* = 17.2, 1.9 Hz, 1H), 4.99 (dq, *J* = 10.3, 1.8 Hz, 1H), 4.82–4.74 (m, 1H), 3.81 (ddt, *J* = 15.9, 5.2, 1.8 Hz, 1H), 3.70 (ddt, *J* = 15.9, 5.1, 1.8 Hz, 1H), 3.33 (dd, *J* = 11.0, 6.8 Hz, 1H), 2.94 (dd, *J* = 11.1, 0.8 Hz, 1H), 2.41 (s, 3H), 1.88–1.73 (m, 2H), 1.47–1.27 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 151.8, 144.2, 136.8, 135.1, 129.2, 128.9, 115.1, 61.2, 58.2, 33.1, 32.3, 28.7, 22.5, 21.7, 14.1; IR (Neat Film, NaCl) 2957, 2928, 2860, 1651, 1598, 1455, 1351, 1164, 1117, 1088, 918, 813 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{17}H_{25}N_2O_2S_2$ $[M+H]^+$: 353.1352, found 353.1358.



315

(*Z*)-5-phenyl-3-(*p*-nitrobenzenesulfonyl)-2-(allylimino)thiazolidine (315):

94% yield; R_f = 0.28 (1:4 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.37–8.28 (m, 2H), 8.26–8.16 (m, 2H), 7.42–7.31 (m, 5H), 5.82 (ddt, *J* = 17.1, 10.4, 5.2 Hz, 1H), 5.11–5.03 (m, 2H), 4.86 (dd, *J* = 8.3, 6.3 Hz, 1H), 4.54 (dd, *J* = 10.3, 6.3 Hz, 1H), 3.98 (dd, *J* = 10.3, 8.4 Hz, 1H), 3.83 (ddt, *J* = 15.9, 5.2, 1.8 Hz, 1H), 3.75 (ddt, *J* = 15.8, 5.3, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 151.1, 150.6, 143.6, 136.3, 134.6, 130.4, 129.2, 129.1, 127.6, 123.7, 115.7, 57.9, 56.5, 47.5; IR (Neat Film, NaCl) 3106, 1656, 1530, 1349, 1314, 1175, 1109, 854, 740 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{18}H_{18}N_3O_4S_2$ $[M+H]^+$: 404.0733, found 404.0742.

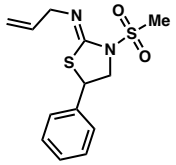


(S)-315

(*S*,*Z*)-5-phenyl-3-(*p*-nitrobenzenesulfonyl)-2-(allylimino)thiazolidine ((*S*)-315):

Thiazolidine **(*S*)-315** was prepared according to General Procedure E and was isolated as a white crystalline solid: 95% yield; R_f = 0.28 (1:4 Acetone:Hexanes eluent); characterization data match those above; colorless, translucent X-ray quality crystals were obtained by slow diffusion of 1% benzene in heptane into a solution of

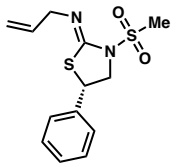
iminothiazolidine **(*S*)-315** in ethyl acetate, mp: 70–72 °C; $[\alpha]_D^{25.0}$ 1.7° (*c* 2.250, $CHCl_3$); enantiomeric excess was determined by analytical SFC (Chiralcel OD-H column, 30% isopropyl alcohol in CO_2, 2.5 mL/min, λ = 254 nm, major retention time: 6.6 minutes, minor retention time: 5.5 minutes, 95% ee).



316

(*Z*)-5-phenyl-3-mesyl-2-(allylimino)thiazolidine (316):

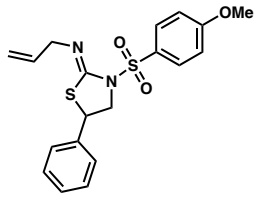
Thiazolidine **316** was isolated as a clear, colorless oil: 91% yield; R_f = 0.40 (3:7 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46–7.31 (m, 5H), 5.97 (ddt, *J* = 17.1, 10.3, 5.2 Hz, 1H), 5.27 (dq, *J* = 17.1, 1.8 Hz, 1H), 5.13 (dq, *J* = 10.3, 1.7 Hz, 1H), 4.84 (dd, *J* = 8.6, 6.3 Hz, 1H), 4.41 (dd, *J* = 10.4, 6.3 Hz, 1H), 3.99–3.90 (m, 3H), 3.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 153.0, 136.6, 134.9, 129.2, 129.0, 127.7, 115.8, 58.1, 55.6, 47.6, 40.5; IR (Neat Film, NaCl) 3011, 1656, 1651, 1346, 1163, 1113, 964, 764 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{13}H_{17}N_2O_2S_2$ $[M+H]^+$: 297.0726, found 297.0739.



(S)-316

(*S*,*Z*)-5-phenyl-3-mesyl-2-(allylimino)thiazolidine ((*S*)-316):

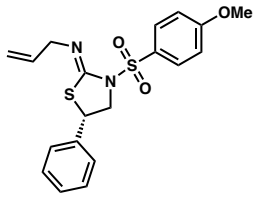
Thiazolidine **(*S*)-316** was prepared according to General Procedure E and was isolated as a clear, colorless oil: 95% yield; R_f = 0.40 (3:7 Acetone:Hexanes eluent); characterization data match those reported above; $[\alpha]_D^{25.0}$ –55.5° (*c* 2.200, $CHCl_3$); enantiomeric excess was determined by analytical SFC (Chiralpak AD-H column, 7% isopropyl alcohol in CO_2, 2.5 mL/min, λ = 254 nm, major retention time: 12.6 minutes, minor retention time: 11.3 minutes, 90% ee).



317

(*Z*)-5-phenyl-3-(*p*-methoxybenzenesulfonyl)-2-(allylimino)thiazolidine (317):

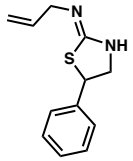
90% yield; R_f = 0.40 (3:7 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.01–7.93 (m, 2H), 7.42–7.29 (m, 5H), 6.98–6.93 (m, 2H), 5.85 (ddt, *J* = 17.1, 10.3, 5.2 Hz, 1H), 5.08 (dq, *J* = 17.1, 1.8 Hz, 1H), 5.03 (dq, *J* = 10.3, 1.7 Hz, 1H), 4.79 (dd, *J* = 8.4, 6.3 Hz, 1H), 4.49 (dd, *J* = 10.3, 6.3 Hz, 1H), 3.92 (dd, *J* = 10.3, 8.4 Hz, 1H), 3.88 (s, 3H), 3.88–3.83 (m, 1H), 3.77 (ddt, *J* = 15.9, 5.2, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 163.8, 151.3, 136.9, 135.1, 131.4, 129.5, 129.2, 128.8, 127.7, 115.3, 113.8, 58.1, 56.6, 55.8, 47.1; IR (Neat Film, NaCl) 2927, 1655, 1595, 1497, 1356, 1262, 1162, 1110, 1090, 1025, 833, 810 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{19}H_{21}N_2O_3S_2$ $[M+H]^+$: 389.0988, found 389.1004.



(S)-317

(*S*,*Z*)-5-phenyl-3-(*p*-methoxybenzenesulfonyl)-2-(allylimino)thiazolidine ((*S*)-317):

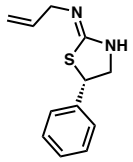
Thiazolidine **(*S*)-317** was prepared according to General Procedure E: 94% yield; R_f = 0.40 (3:7 Acetone:Hexanes eluent); characterization data match those reported above; $[\alpha]_D^{25.0}$ –6.6° (*c* 2.000, $CHCl_3$); enantiomeric excess was determined by analytical SFC (Chiralpak AD-H column, 30% isopropyl alcohol in CO_2, 2.5 mL/min, λ = 254 nm, major retention time: 4.4 minutes, minor retention time: 6.6 minutes, 91% ee).



318

(*Z*)-5-phenyl-2-(allylimino)thiazolidine (318):

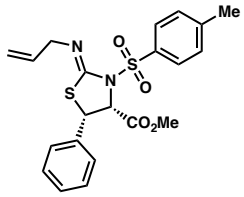
75% yield; R_f = 0.19 (3:7 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.36 (m, 2H), 7.35–7.30 (m, 2H), 7.29–7.26 (m, 1H), 5.94 (ddt, *J* = 17.2, 10.2, 5.5 Hz, 1H), 5.27 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.18 (dq, *J* = 10.3, 1.4 Hz, 1H), 5.02 (dd, *J* = 7.8, 6.3 Hz, 1H), 4.34 (dd, *J* = 13.4, 7.8 Hz, 1H), 4.10 (dd, *J* = 13.4, 6.3 Hz, 1H), 3.97 (dt, *J* = 5.5, 1.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 160.7, 141.3, 134.5, 128.9, 127.9, 127.4, 116.6, 68.4, 56.7, 47.3; IR (Neat Film, NaCl) 2924, 2853, 1612, 1454, 1260, 1023, 802, 758 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{12}H_{15}N_2S$ $[M+H]^+$: 219.0950, found 219.0950.



(S)-318

(*S*,*Z*)-5-phenyl-2-(allylimino)thiazolidine ((*S*)-318):

Thiazolidine **(*S*)-318** was prepared according to General Procedure E: 31% yield; R_f = 0.19 (3:7 Acetone:Hexanes eluent); characterization data match those reported above; $[\alpha]_D^{25.0}$ 26.4° (*c* 0.200, $CHCl_3$); enantiomeric excess was determined by analytical SFC (Chiralcel OB-H column, 10% methanol in CO_2, 2.5 mL/min, λ = 254 nm, major retention time: 3.9 minutes, minor retention time: 8.4 minutes, 34% ee).

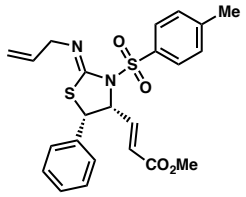


329

***cis*-methyl (*Z*)-5-phenyl-3-tosyl-2-(allylimino)thiazolidine-4-carboxylate (329)**:

Thiazolidine **329** was isolated as a white crystalline solid and colorless, translucent X-ray quality crystals were obtained by slow diffusion of 1% benzene in heptane into a solution of iminothiazolidine **329** in ethyl acetate, mp: 107–109 °C: 88% yield; R_f = 0.32 (3:7 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.96–7.90 (m, 2H), 7.38–7.31 (m, 5H), 7.30–7.25 (m, 2H), 5.86 (ddt, *J* = 17.1, 10.3, 4.9 Hz, 1H), 5.33 (d, *J* = 8.0 Hz, 1H), 5.26 (d, *J* = 8.0 Hz, 1H), 5.07 (dq, *J* = 17.1, 1.9 Hz, 1H), 5.03 (dq, *J* = 10.4, 1.8 Hz, 1H), 3.91 (ddt, *J* = 16.1, 4.9, 1.8 Hz, 1H), 3.83 (ddt, *J* = 16.1, 4.8, 1.9 Hz, 1H), 3.25 (s, 3H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 168.0, 150.2, 144.7, 135.4, 134.8,

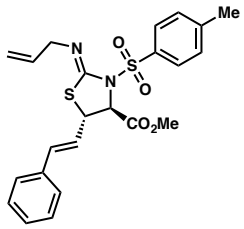
132.9, 129.7, 129.3, 128.9, 128.8, 128.4, 115.1, 65.7, 57.9, 52.1, 49.8, 21.8; IR (Neat Film, NaCl) 2952, 2253, 1748, 1660, 1595, 1444, 1353, 1166, 1107, 915, 811 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{21}H_{23}N_2O_4S_2$ $[M+H]^+$: 431.1094, found 431.1114.



331

***cis*-(*Z*)-4-((*E*)-2-(methoxycarbonyl)ethenyl)-5-phenyl-3-tosyl-2-(allylimino)thiazolidine (331)**:

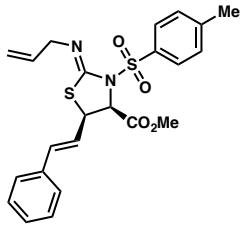
62% yield; R_f = 0.43 (3:7 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.93–7.87 (m, 2H), 7.36–7.27 (m, 5H), 7.26–7.23 (m, 2H), 6.60 (dd, *J* = 15.6, 7.4 Hz, 1H), 5.88 (ddt, *J* = 17.1, 10.2, 5.0 Hz, 1H), 5.80 (dd, *J* = 15.7, 1.1 Hz, 1H), 5.42 (ddd, *J* = 7.5, 6.5, 1.1 Hz, 1H), 5.22 (d, *J* = 6.5 Hz, 1H), 5.11 (dq, *J* = 17.1, 1.9 Hz, 1H), 5.06 (dq, *J* = 10.3, 1.7 Hz, 1H), 3.90 (ddt, *J* = 16.0, 4.9, 1.8 Hz, 1H), 3.84 (ddt, *J* = 16.0, 5.1, 1.8 Hz, 1H), 3.66 (s, 3H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 165.6, 149.6, 144.7, 140.3, 135.9, 134.9, 132.2, 129.6, 129.2, 129.1, 129.0, 128.7, 125.8, 115.4, 65.3, 58.1, 52.8, 51.9, 21.8; IR (Neat Film, NaCl) 2951, 1726, 1659, 1436, 1360, 1276, 1168, 1109, 917, 812 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{23}H_{25}N_2O_4S_2$ $[M+H]^+$: 457.1250, found 457.1268.



334

***trans*-methyl (*Z*)-5-((*E*)-styryl)-3-tosyl-2-(allylimino)thiazolidine-4-carboxylate (334)**:[54]

42% yield; R_f = 0.39 (3:7 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98–7.93 (m, 2H), 7.34 (m, 4H), 7.32–7.27 (m, 1H), 7.25–7.20 (m, 2H), 6.62 (dd, *J* = 15.7, 0.9 Hz, 1H), 6.22 (dd, *J* = 15.6, 8.5 Hz, 1H), 5.84 (ddt, *J* = 17.1, 10.1, 4.9 Hz, 1H), 5.20 (d, *J* = 1.7 Hz, 1H), 5.07–4.99 (m, 2H), 4.57 (ddd, *J* = 8.5, 1.8, 1.0 Hz, 1H), 3.82 (ddd, *J* = 5.1, 3.5, 1.8 Hz, 2H), 3.80 (s, 3H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 169.4, 149.2, 144.6, 135.7, 135.5, 134.8, 133.2, 129.7, 128.9, 128.8, 128.6, 126.9, 125.9, 115.2, 66.9, 58.0, 53.4, 48.3, 21.8; IR (Neat Film, NaCl) 2954, 1756, 1661, 1597, 1495, 1435, 1354, 1167, 1113, 1089, 916, 813, 781, 754 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{23}H_{25}N_2O_4S_2$ $[M+H]^+$: 457.1250, found 457.1252.



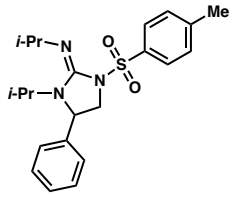
335

***cis*-methyl (*Z*)-5-((*E*)-styryl)-3-tosyl-2-(allylimino)thiazolidine-4-carboxylate (335)**:[54]

31% yield; R_f = 0.39 (3:7 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.97–7.92 (m, 2H), 7.36–7.27 (m, 7H), 6.66 (dd, *J* = 15.6, 0.9 Hz, 1H), 6.00 (dd, *J* = 15.5, 9.1 Hz, 1H), 5.84 (ddt, *J* = 17.1, 10.3, 4.9 Hz, 1H), 5.27 (d, *J* = 7.6 Hz, 1H), 5.09–4.98 (m, 2H), 4.80 (ddd, *J* = 9.1, 7.6, 0.9 Hz, 1H), 3.85 (ddt, *J* = 16.1, 4.9, 1.9 Hz, 1H), 3.80 (ddt, *J* = 16.1, 4.8, 1.9 Hz, 1H), 3.68 (s, 3H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 168.2, 150.2, 144.7, 135.7, 135.5, 135.5, 134.8, 129.7, 129.0, 128.9, 128.8, 126.9, 121.2, 115.2, 64.5, 58.0, 52.6, 48.3, 21.8; IR (Neat Film, NaCl) 2952, 1750, 1661, 1597, 1495, 1450, 1354, 1206, 1169, 1121, 1089, 966, 916, 841, 813, 751 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{23}H_{25}N_2O_4S_2$ $[M+H]^+$: 457.1250, found 457.1253.

3.7.5 IMINOIMIDAZOLIDINE SYNTHESIS AND CHARACTERIZATION DATA

Unless otherwise stated, all iminothiazolidines were prepared according to General Procedure D and were isolated as amorphous white solids.

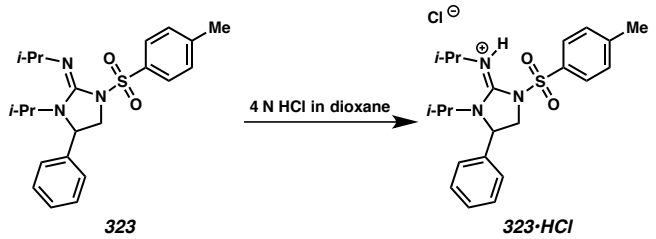


323

(*E*)-3-isopropyl-4-phenyl-1-tosyl-2-(isopropylimino)imidazolidine (323):

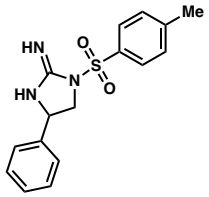
Product was initially prepared according to General Procedure D, isolating the product as a salt after column chromatography (2%→5% CH_3OH in CH_2Cl_2eluent). The resulting white foam was dissolved in 20 mL CH_2Cl_2 and washed with aqueous 0.1 N NaOH (3 x

10 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo to give imidazolidine **323** (88 mg, 55% yield) as a colorless oil.



323 ***323·HCl***

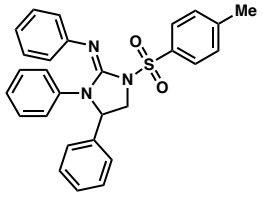
For the purpose of characterization, to a portion of iminoimidazolidine **323** (ca. 0.20 mmol) as a neat oil was added 4 N HCl in dioxane (3 mL) immediately followed by Et_2O (40 mL) causing a white precipitate to form. The supernatant was decanted and the residual white solid was washed with Et_2O (3 x 10 mL) and dried in vacuo furnishing iminoimidazolidinium hydrochloride **323•HCl** as a white solid: R_f = 0.39 (1:9 CH_3OH:CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.95 (bs, 1H), 7.69–7.59 (m, 2H), 7.30–7.24 (m, 3H), 7.18 (dd, *J* = 8.2, 6.9 Hz, 2H), 6.96–6.85 (m, 2H), 5.52–5.32 (m, 1H), 4.82–4.75 (m, 1H), 4.48–4.26 (m, 2H), 4.03 (dd, *J* = 12.0, 3.0 Hz, 1H), 2.46 (s, 3H), 1.70 (d, *J* = 6.4 Hz, 3H), 1.51 (d, *J* = 6.4 Hz, 3H), 1.28–1.21 (m, 3H), 0.95 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 154.7, 146.9, 137.9, 133.7, 130.8, 129.3, 128.8, 127.7, 125.9, 57.0, 56.1, 54.0, 51.3, 24.3, 22.2, 21.9, 21.3, 20.8; IR (Neat Film, NaCl) 2972, 1636, 1457, 1435, 1367, 1260, 1172, 1088, 1036, 907, 814, 729 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{22}H_{30}N_3O_2S$ $[M–Cl]^+$: 400.2053, found 400.2067



324

4-phenyl-1-tosyl-2-iminoimidazolidine (324):

Prepared according to General Procedure D followed by purification by column chromatography using deactivated silica gel (1% Me_2NEt and 1% MeOH in CH_2Cl_2 eluent): 61% yield; R_f = 0.41 (1:9 CH_3OH:CH_2Cl_2 eluent); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.86–7.79 (m, 2H), 7.46 (dd, *J* = 8.4, 0.9 Hz, 2H), 7.21–7.16 (m, 3H), 6.92 (dd, *J* = 6.7, 2.9 Hz, 2H), 4.77 (dd, *J* = 9.2, 6.5 Hz, 1H), 4.14 (t, *J* = 9.6 Hz, 1H), 3.35 (bs, 2H), 3.26 (dd, *J* = 9.9, 6.5 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (DMSO-d_6, 126 MHz) δ 151.2, 145.0, 143.6, 132.9, 130.1, 128.2, 127.5, 126.9, 125.9, 61.4, 55.2, 21.1; IR (Neat Film, NaCl) 3445, 2920, 1683, 1397, 1350, 1161, 1091, 1002 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{16}H_{18}N_3O_2S$ $[M+H]^+$: 316.1114, found 316.1126.

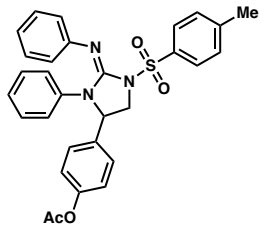


325

(*E*)-3,4-diphenyl-1-tosyl-2-(phenylimino)imidazolidine (325):

96% yield; R_f = 0.22 (1:4 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03–7.96 (m, 2H), 7.37–7.28 (m, 5H), 7.24–7.15 (m, 2H), 6.82–6.73 (m, 5H), 6.60–6.48 (m, 3H), 6.42–6.34 (m, 2H), 4.77 (dd, *J* = 8.2, 5.7 Hz, 1H), 4.45 (dd, *J* = 9.9, 8.2 Hz, 1H), 3.94 (dd, *J* = 9.9, 5.8 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 146.6, 144.6,

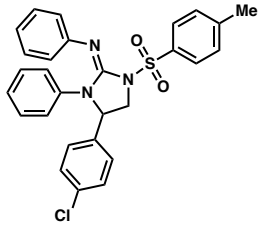
143.4, 139.9, 139.8, 135.0, 129.4, 129.3, 129.2, 128.8, 128.3, 127.8, 126.9, 125.8, 125.6, 121.9, 121.4, 64.9, 52.5, 21.9; IR (Neat Film, NaCl) 3027, 2924, 1667, 1593, 1488, 1354, 1166, 1089, 813, 759 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{28}H_{26}N_3O_2S$ $[M+H]^+$: 468.1740, found 468.1755.



326

(*E*)-4-(*p*-acetoxyphenyl)-3-phenyl-1-tosyl-2-(phenylimino)imidazolidine (326):

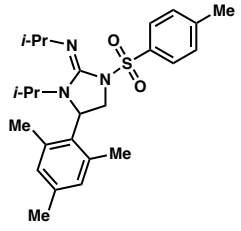
99% yield; R_f = 0.28 (3:7 Acetone:Hexanes eluent); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.03–7.96 (m, 2H), 7.37–7.29 (m, 2H), 7.22–7.18 (m, 2H), 7.08–7.02 (m, 2H), 6.82–6.75 (m, 5H), 6.61–6.55 (m, 1H), 6.55–6.52 (m, 2H), 6.41–6.36 (m, 2H), 4.80 (dd, *J* = 8.1, 5.7 Hz, 1H), 4.44 (dd, *J* = 9.9, 8.1 Hz, 1H), 3.92 (dd, *J* = 9.9, 5.7 Hz, 1H), 2.48 (s, 3H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 169.4, 150.9, 146.1, 144.8, 143.5, 139.6, 137.2, 134.7, 129.4, 129.3, 128.4, 128.0, 127.9, 126.0, 125.7, 122.5, 122.0, 121.6, 64.4, 52.4, 21.9, 21.3; IR (Neat Film, NaCl) 3057, 2928, 1760, 1670, 1591, 1495, 1367, 1211, 1167, 1113, 1090, 1017, 911, 813, 763, 734 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{30}H_{28}N_3O_4S$ $[M+H]^+$: 526.1795, found 526.1800.



327

(*E*)-4-(*p*-chlorophenyl)-3-phenyl-1-tosyl-2-(phenylimino)imidazolidine (327):

87% yield; R_f = 0.19 (1:4 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03–7.95 (m, 2H), 7.35–7.31 (m, 2H), 7.30–7.27 (m, 2H), 7.16–7.12 (m, 2H), 6.83–6.75 (m, 5H), 6.61–6.56 (m, 1H), 6.53 (dd, *J* = 6.8, 2.9 Hz, 2H), 6.42–6.35 (m, 2H), 4.79 (dd, *J* = 8.1, 5.6 Hz, 1H), 4.44 (dd, *J* = 9.9, 8.1 Hz, 1H), 3.90 (dd, *J* = 9.9, 5.6 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 146.0, 144.8, 143.4, 139.4, 138.2, 134.7, 134.6, 129.4, 129.4, 129.2, 128.4, 128.3, 127.9, 126.1, 125.7, 122.0, 121.7, 64.3, 52.3, 21.9; IR (Neat Film, NaCl) 3062, 1668, 1591, 1492, 1360, 1213, 1167, 1090, 1014, 910, 813, 761, 734 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{28}H_{25}{}^{35}ClN_3O_2S$ $[M+H]^+$: 502.1351, found 502.1355.

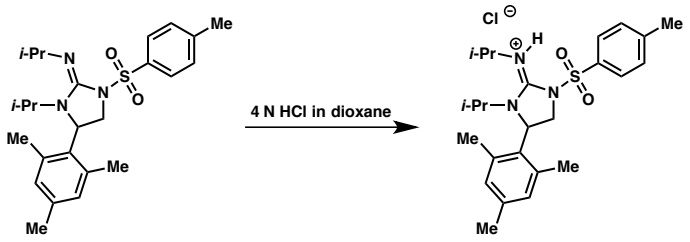


374

(*E*)-3-isopropyl-4-mesityl-1-tosyl-2-(isopropylimino)imidazolidine (374):

Product was initially prepared according to General Procedure D, isolating the product as the H($ZnBr_3$•MeOH) salt after column chromatography (2%→5% MeOH in CH_2Cl_2 eluent). A portion of this resulting white foam was crystallized, forming colorless,

translucent X-ray quality crystals after slow evaporation from a solution of **374** in MeOH, mp: 118–120 °C.

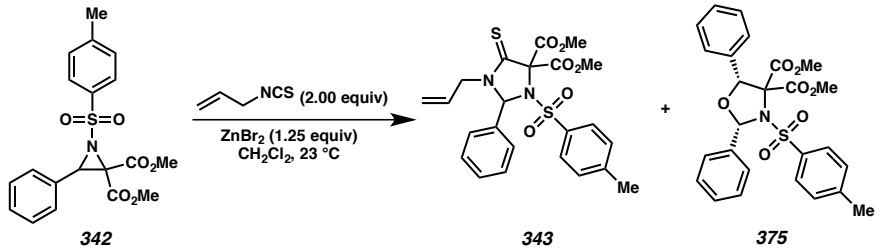


374 ***374·HCl***

The remaining portion of the white foam was dissolved in 20 mL CH_2Cl_2 and washed with aqueous 0.1 N NaOH (3 x 10 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo to give iminoimidazolidine **374** as a colorless oil.

To neat **374** was then added 4 N HCl in dioxane (3 mL) immediately followed by Et_2O (40 mL). The organics were then concentrated in vacuo to furnish iminoimidazolidinium hydrochloride **374•HCl** as a white foam: R_f = 0.41 (1:9 MeOH:CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.98 (bs, 1H), 7.88 (d, *J* = 7.2 Hz, 2H), 7.52 (d, *J* = 7.1 Hz, 2H), 6.83 (s, 1H), 6.79 (s, 1H), 5.16 (bs, 1H), 4.56 (bs, 2H), 4.28 (bs, 1H), 3.92–3.81 (m, 1H), 2.52 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H), 2.03 (s, 3H), 1.72 (d, *J* = 6.0 Hz, 3H), 1.54 (d, *J* = 6.0 Hz, 3H), 0.94–0.80 (m, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 155.1, 147.5, 139.7, 136.7, 136.2, 133.4, 132.6, 131.1, 130.5, 128.2, 127.8, 56.0, 54.9, 51.9, 50.9, 24.7, 22.0, 21.8, 20.9, 20.5, 20.5, 20.4, 19.7; IR (Neat Film, NaCl) 2925, 1640, 1441, 1366, 1276, 1171, 1089, 815 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{25}H_{36}N_3O_2S$ $[M–Cl]^+$: 442.2523, found 442.2514.

3.7.6 PREPARATION OF THIOXOIMIDAZOLIDINE 343

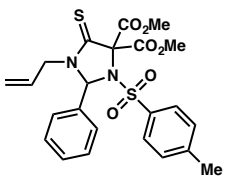


342 ***343*** ***375***

*Imidazolidine **343** was prepared from diester aziridine **342** according to two procedures:*

Initially, imidazolidine **343** was prepared according to General Procedure C. The reaction mixture was an intensely neon orange-red color throughout the duration of the reaction (ca. 11 h). Upon purification of the reaction mixture by silica gel column chromatography (20% acetone in hexanes eluent), imidazolidine **343** (70 mg, 36% yield) and *cis*-oxazolidine **375** (48 mg, 24% yield) were both isolated as white crystalline solids.

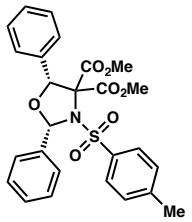
Suspecting the formation of *cis*-oxazolidine **375** was a result of partial hydrolysis of the ion-paired intermediate during the course of the reaction, imidazolidine **343** was subsequently prepared according to General Procedure C in the anhydrous environment of an inert atmosphere glovebox. The reaction mixture was an intensely neon orange-red color throughout the duration of the reaction (ca. 12 h) under these conditions as well. Upon purification of the reaction mixture by silica gel column chromatography (20% acetone in hexanes eluent), imidazolidine **343** (116 mg, 60% yield) was isolated in the absence of an isolable portion of *cis*-oxazolidine **375**.



343

dimethyl 3-allyl-2-phenyl-4-thioxo-1-tosyl-imidazolidine-5,5-dicarboxylate (343):

Colorless, translucent X-ray quality crystals of imidazolidine **343** were obtained by slow diffusion of 1% benzene in heptane into a solution of imidazolidine **343** in ethyl acetate, mp: 147–150 °C: R_f = 0.41 (3:7 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42–7.15 (m, 5H), 7.05–6.95 (m, 2H), 6.94–6.86 (m, 2H), 6.39 (s, 1H), 5.63 (dddd, *J* = 17.4, 10.3, 7.3, 4.3 Hz, 1H), 5.24 (ddt, *J* = 10.3, 1.8, 1.0 Hz, 1H), 5.10 (ddt, *J* = 17.2, 2.1, 1.2 Hz, 1H), 4.87–4.70 (m, 1H), 3.96 (s, 3H), 3.86 (s, 3H), 3.25 (ddt, *J* = 15.4, 7.4, 1.1 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 186.5, 164.9, 164.3, 143.9, 136.7, 133.3, 130.6, 129.5, 129.0, 128.8, 128.3, 127.8, 120.1, 82.4, 82.3, 54.1, 53.9, 47.6, 21.6; IR (Neat Film, NaCl) 2952, 1794, 1771, 1489, 1354, 1257, 1162, 1090, 1061, 913, 850, 810, 777, 731 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{23}H_{25}N_2O_6S_2$ $[M+H]^+$: 489.1149, found 489.1164.

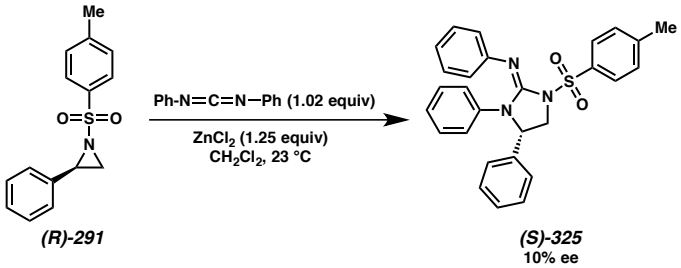


375

***cis*-dimethyl 2,5-diphenyl-3-tosyloxazolidine-4,4-dicarboxylate (375)**:

Colorless, translucent X-ray quality crystals of *cis*-oxazolidine **375** were obtained by slow evaporation of a solution of *cis*-oxazolidine **375** in ethyl acetate, mp: 145–147 °C: R_f = 0.50 (3:7 Acetone:Hexanes eluent); characterization data match those reported in the literature.[55]

3.7.7 STEREOSELECTIVE (3 + 2) CYCLOADDITION WITH DIPHENYLCARBODIIMIDE

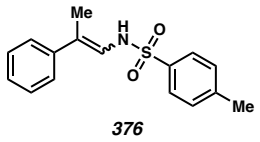


(R)-291 *(S)-325* 10% ee

(*S*,*E*)-3,4-diphenyl-1-tosyl-2-(phenylimino)imidazolidine ((*S*)-325):[56]

Imidazolidine **(*S*)-325** was prepared according to General Procedure E using diphenylcarbodiimide (79 mg, 0.41 mmol, 1.02 equiv) in place of isothiocyanate:[57] 96% yield; R_f = 0.22 (1:4 Acetone:Hexanes eluent); characterization data match those reported above; $[\alpha]_D^{25.0}$ 46.6° (*c* 0.550, $CHCl_3$); enantiomeric excess was determined by analytical SFC (Chiralpak AS-H column, 30% isopropyl alcohol in CO_2, 2.5 mL/min, λ = 254 nm, major retention time: 9.6 minutes, minor retention time: 7.0 minutes, 10% ee).

3.7.8 CHARACTERIZATION OF (3 + 2) CYCLOADDITION BYPRODUCTS

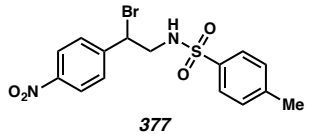


376

4-methyl-*N*-(2-phenylprop-1-en-1-yl)benzenesulfonamide (376):

Sulfonamide **376** was prepared by General Procedure C from aziridine **373**: 65% combined yield as a 2:1 *Z*:*E* ratio of products as an amorphous white solid; R_f = 0.15 (1:4 Acetone:Hexanes eluent); ^1H and ^{13}C NMR spectra match those reported in the literature;[58] IR (Neat Film, NaCl) 3357, 3260, 1721, 1683, 1598, 1448, 1337, 1301, 1269,

1161, 1096, 904, 817, 761 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{16}H_{18}NO_2S$ $[M+H]^+$: 288.1053, found 288.1044.

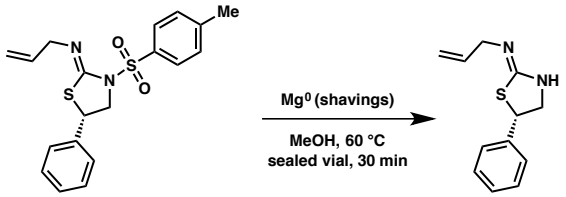


377

1-bromo-1-(4-nitrophenyl)-2-(p-toluenesulfonamido)ethane (377):[59]

Bromide **377** was isolated as a byproduct of the reaction of aziridine **355** under the reaction conditions specified in General Procedure C: 35% yield as an amorphous white solid; R_f = 0.15 (1:4 Acetone:Hexanes eluent); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.24–8.14 (m, 2H), 7.75–7.67 (m, 2H), 7.53–7.46 (m, 2H), 7.35–7.29 (m, 2H), 5.02 (t, *J* = 7.1 Hz, 1H), 4.83 (dd, *J* = 7.4, 5.9 Hz, 1H), 3.64–3.50 (m, 2H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 148.1, 145.3, 144.3, 136.8, 130.1, 129.0, 127.1, 124.3, 50.5, 50.1, 21.7; IR (Neat Film, NaCl) 3278, 1598, 1522, 1423, 1346, 1157, 1092, 855, 814 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{14}{}^{81}BrN_2O_4S$ $[(M–H_2)+H]^+$: 398.9837, found 398.9834.

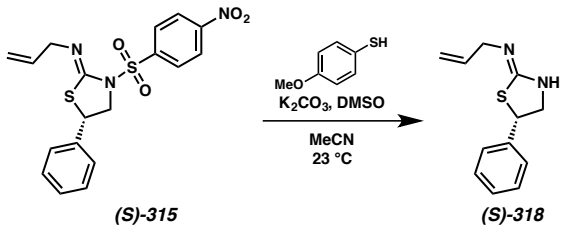
3.7.9 DEPROTECTION OF IMINOTHIAZOLIDINES (S)-292 and (S)-315



(S)-292 ***(S)-318***

Procedure for the desulfonylation of thiazolidine **(*S*)-292** was adapted from the literature.[30] Iminothiazolidine **(*S*)-292** (50 mg, 0.13 mmol, 1.00 equiv) was suspended in freshly distilled CH_3OH (2.2 mL) in an oven-dried vial with a stir bar and heated to 70 °C

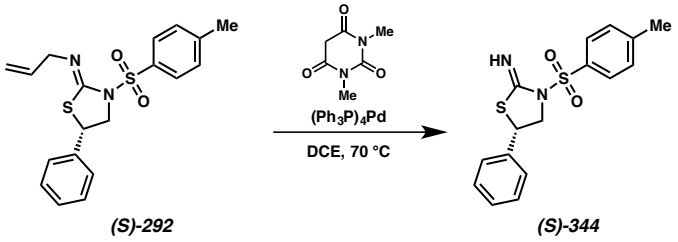
until a homogeneous solution was formed. Magnesium turnings (49 mg, 2.01 mmol, 15 equiv) were then added and the vial was sealed. The reaction mixture was stirred at 70 °C. Upon consumption of starting material (determined by LCMS analysis, ca. 30 min), the reaction mixture was allowed to cool to room temperature and filtered through Celite, washing with CH_2Cl_2 (20 mL) and CH_3OH (20 mL). The filtrate was adsorbed onto Celite and purified by silica gel column chromatography (30% acetone and 1% Et_3N in hexanes) to give iminothiazolidine **(*S*)-318** (26 mg, 91% yield) as a white amorphous solid; characterization data match those reported above; $[\alpha]_D^{25.0}$ –61.2° (*c* 0.23, $CHCl_3$); enantiomeric excess was determined by analytical SFC (Chiralcel OB-H column, 10% methanol in CO_2, 2.5 mL/min, λ = 254 nm, major retention time: 3.9 minutes, minor retention time: 8.4 minutes, 94% ee).



(S)-315 *(S)-318*

Procedure for the desulfonylation of thiazolidine **(*S*)-315** was adapted from the literature.[31a] To a solution of iminothiazolidine **(*S*)-315** (120 mg, 0.30 mmol, 1.00 equiv, 95% ee) and *p*-methoxythiophenol (110 μL, 0.89 mmol, 3.00 equiv) in acetonitrile (1.96 mL) was added DMSO (40 μL), followed by potassium carbonate (164 mg, 1.18 mmol, 4.00 equiv). The vial was loosely capped and the heterogeneous mixture was stirred at room temperature until the reaction was complete (determined by TLC analysis, ca. 3 h). The reaction mixture was concentrated and the residue partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over sodium

sulfate, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (30% acetone and 1% Et_3N in hexanes eluent) to give iminothiazolidine **(*S*)-318** (60 mg, 93% yield) as a white amorphous solid; characterization data match those reported above; $[\alpha]_D^{25.0}$ –61.2° (*c* 0.23, $CHCl_3$); enantiomeric excess was determined by analytical SFC (Chiralcel OB-H column, 10% methanol in CO_2, 2.5 mL/min, λ = 254 nm, major retention time: 3.9 minutes, minor retention time: 8.4 minutes, 94% ee).

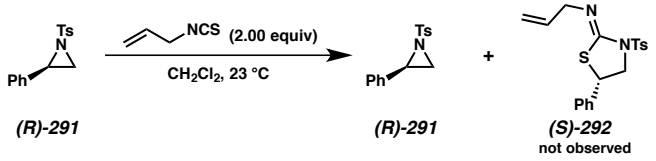


Procedure for the deallylation of thiazolidine **(*S*)-292** was adapted from the literature.[60] To a solution of iminothiazolidine **(*S*)-292** (25 mg, 0.067 mmol, 1.00 equiv) in dichloroethane (750 μL) in an oven dried vial with a stir bar were added tetrakis(triphenylphosphine)palladium(0) (39 mg, 0.034 mmol, 0.50 equiv) and 1,3-dimethylbarbituric acid (157 mg, 1.01 mmol, 15.0 equiv). The vial was sealed and stirred at 70 °C until the reaction was complete (determined by LCMS analysis, ca. 1.5 h). The reaction mixture was diluted with CH_2Cl_2, adsorbed onto Celite, and purified by silica gel column chromatography (10% acetone and 1% Et_3N in hexanes) to give iminothiazolidine **(*S*)-344** (20 mg, 89% yield) as a white amorphous solid; R_f = 0.30 (3:7 Acetone:Hexanes eluent); ^1H NMR (CD_2Cl_2, 500 MHz) δ 7.83–7.78 (m, 2H), 7.38–7.34 (m, 2H), 7.34–7.31 (m, 5H), 4.77 (t, *J* = 7.0 Hz, 1H), 4.46 (dd, *J* = 10.5, 6.4 Hz, 1H), 4.01

(dd, J = 10.5, 7.6 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (CD_2Cl_2, 126 MHz) δ 160.3, 145.9, 137.3, 130.4, 129.8, 129.4, 129.0, 128.1, 127.8, 58.8, 21.8; IR (Neat Film, NaCl) 3311, 3031, 2922, 1622, 1597, 1494, 1454, 1358, 1168, 1089, 1054, 814 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{17}N_2O_2S_2$ $[M+H]^+$: 333.0726, found 333.0736; $[\alpha]_D^{25.0}$ – 10.0° (*c* 0.1, $CHCl_3$); enantiomeric excess was determined by analytical SFC (Chiralpak AD-H column, 30% isopropyl alcohol in CO_2, 2.5 mL/min, λ = 254 nm, major retention time: 7.3 minutes, minor retention time: 8.4 minutes, 39% ee).

3.7.10 EXPERIMENTAL PROCEDURES FOR CONTROL REACTIONS[61]

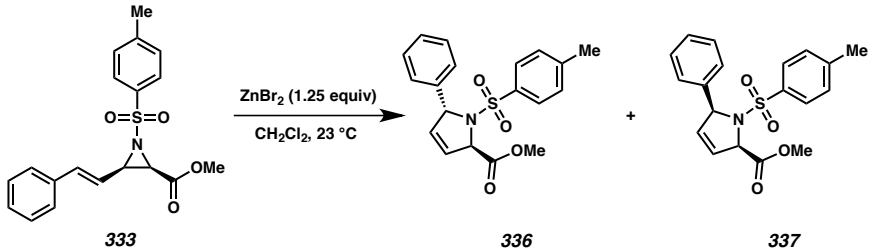
3.7.10.1 Reaction in the Absence of Lewis Acid



(R)-291 *(R)-291* *(S)-292* not observed

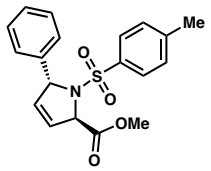
To an oven-dried 1-dram vial equipped with a magnetic stir bar were added (*R*)-*N*-tosyl-2-phenylaziridine (**(*R*)-291**, 109 mg, 0.40 mmol, 1.00 equiv, >99% ee) and allyl isothiocyanate (79 μL, 0.80 mmol, 2.00 equiv). The vial was sealed with a screw cap fitted with a Teflon septum, placed under an inert atmosphere, and dissolved in anhydrous dichloromethane (0.80 mL). The heterogeneous reaction mixture was then allowed to stir at ambient temperature. Over the course of 96 hours, no formation of thiazolidine **(*S*)-292** was observed. At 96 hours, the enantiomeric excess of the remaining aziridine **(*R*)-291** was determined by analytical SFC (Chiralcel OB-H column, 10% isopropyl alcohol in CO_2, 2.5 mL/min, λ = 254 nm, major retention time: 7.5 minutes, minor retention time: 10.2 minutes, >99% ee).

3.7.10.2 Isomerization of Disubstituted Aziridine 333



333 ***336*** ***337***

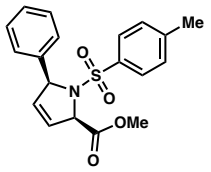
To an oven-dried 1-dram vial equipped with a magnetic stir bar was added zinc(II) bromide (25 mg, 0.113 mmol, 1.25 equiv), freshly powdered with a mortar and pestle, in an inert atmosphere glovebox. The vial was sealed with a screw cap fitted with a Teflon septum, removed from the glovebox and placed under an inert atmosphere. To a separate, oven-dried 1-dram vial was added *cis*-aziridine **333** (32 mg, 0.090 mmol, 1.00 equiv). The vial was sealed with a screw cap fitted with a Teflon septum, and the mixture was transferred to the first vial as a solution in anhydrous dichloromethane (0.15 mL + 0.05 mL rinse). The heterogeneous reaction mixture was then allowed to stir at ambient temperature. Upon consumption of starting material (determined by LCMS, ca. 30 min), the reaction mixture directly purified by silica gel column chromatography (20% acetone in hexanes eluent) to furnish *trans*-pyrroline **336** (12 mg, 38% yield) and *cis*-pyrroline **337** (2 mg, 6% yield) as white amorphous solids.



336

methyl *trans*-5-phenyl-1-tosyl-3-pyrroline-2-carboxylate (336):

R_f = 0.38 (3:7 EtOAc:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.21–7.16 (m, 1H), 7.12–7.05 (m, 4H), 7.00–6.96 (m, 2H), 6.95–6.90 (m, 2H), 5.87 (dt, *J* = 6.2, 1.6 Hz, 1H), 5.84 (dt, *J* = 6.2, 1.8 Hz, 1H), 5.76 (dt, *J* = 6.2, 1.6 Hz, 1H), 5.18 (dt, *J* = 5.7, 1.7 Hz, 1H), 3.86 (s, 3H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.2, 142.6, 137.9, 136.9, 134.7, 129.0, 128.9, 128.4, 128.3, 126.8, 124.0, 70.5, 69.3, 53.0, 21.5; IR (Neat Film, NaCl) 2953, 1747, 1598, 1456, 1343, 1262, 1200, 1158, 1100, 1018, 813, 763 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{19}H_{20}NO_4S$ $[M+H]^+$: 358.1108, found 358.1106.

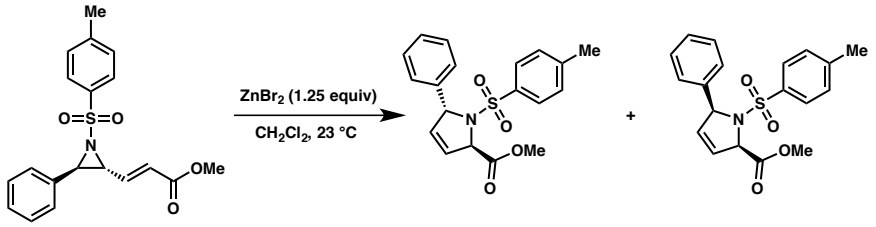


337

methyl *cis*-5-phenyl-1-tosyl-3-pyrroline-2-carboxylate (337):

R_f = 0.47 (3:7 EtOAc:Hexanes eluent); characterization data match those reported in the literature.[62]

3.7.10.3 Isomerization of Disubstituted Aziridine 330

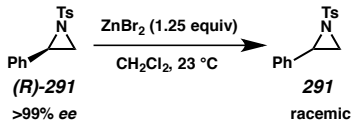


330 ***336*** not observed ***337*** not observed

To an oven-dried 1-dram vial equipped with a magnetic stir bar was added zinc(II) bromide (17 mg, 0.074 mmol, 1.25 equiv), freshly powdered with a mortar and pestle, in

an inert atmosphere glovebox. The vial was sealed with a screw cap fitted with a Teflon septum, removed from the glovebox and placed under an inert atmosphere. To a separate, oven-dried 1-dram vial was added *trans*-aziridine **330** (21 mg, 0.059 mmol, 1.00 equiv). The vial was sealed with a screw cap fitted with a Teflon septum, and the mixture was transferred to the first vial as a solution in anhydrous dichloromethane (0.15 mL + 0.05 mL rinse). The heterogeneous reaction mixture was then allowed to stir at ambient temperature. The slow decomposition of aziridine **330** was complete after 96 h (determined by LCMS) and was characterized by the formation of no major products including neither *trans*-pyrroline **336** nor *cis*-pyrroline **337**.[63]

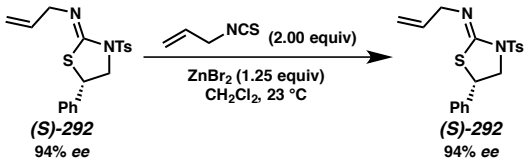
3.7.10.4 Racemization of Aziridine Starting Material (R)-291



To an oven-dried 1-dram vial equipped with a magnetic stir bar was added zinc(II) bromide (113 mg, 0.50 mmol, 1.25 equiv), freshly powdered with a mortar and pestle, in an inert atmosphere glovebox. The vial was sealed with a screw cap fitted with a Teflon septum, removed from the glovebox and placed under an inert atmosphere. To a separate, oven-dried 1-dram vial was added *N*-tosyl-2-phenylaziridine (**(*R*)-291**, 109 mg, 0.40 mmol, 1.00 equiv). The vial was sealed with a screw cap fitted with a Teflon septum, and the mixture was transferred to the first vial as a solution in anhydrous dichloromethane (0.60 mL + 0.20 mL rinse). The heterogeneous reaction mixture was then allowed to stir at ambient temperature. Racemization of the aziridine was complete after 10 minutes as determined by analytical SFC (Chiralcel OB-H column, 10% isopropyl alcohol in CO_2,

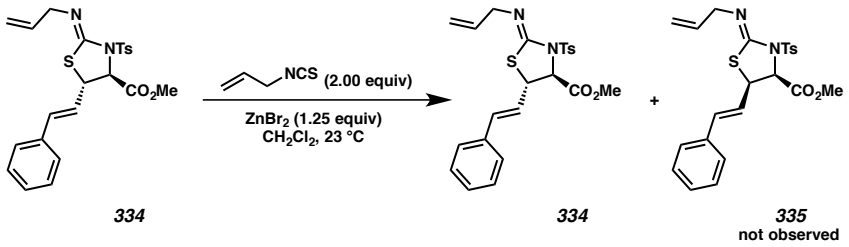
2.5 mL/min, λ = 254 nm, major retention time: 7.5 minutes, minor retention time: 10.2 minutes).

3.7.10.5 Racemization of Product (S)-292



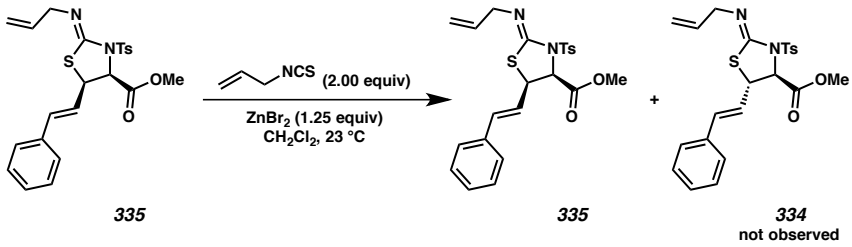
To an oven-dried 1-dram vial equipped with a magnetic stir bar was added zinc(II) bromide (31 mg, 0.14 mmol, 1.25 equiv), freshly powdered with a mortar and pestle, in an inert atmosphere glovebox. The vial was sealed with a screw cap fitted with a Teflon septum, removed from the glovebox and placed under an inert atmosphere. To a separate, oven-dried 1-dram vial were added the iminothiazolidine **(*S*)-292** (40 mg, 0.11 mmol, 1.00 equiv, 94% ee) and allyl isothiocyanate (22 μL, 0.22 mmol, 2.00 equiv). The vial was sealed with a screw cap fitted with a Teflon septum, and the mixture was transferred to the first vial as a solution in anhydrous dichloromethane (0.15 mL + 0.10 mL rinse). The heterogeneous reaction mixture was then allowed to stir at ambient temperature. After 96 hours, the enantiomeric excess of thiazolidine **(*S*)-292** was determined by analytical SFC (Chiralpak AD-H, 30% isopropyl alcohol in CO_2, 2.5 mL/min, λ = 254 nm, major retention time: 5.4 minutes, minor retention time: 3.8 minutes, 94% ee).

3.7.10.6 Isomerization of trans*-Disubstituted Thiazolidine 334*



To an oven-dried 1-dram vial equipped with a magnetic stir bar was added zinc(II) bromide (10 mg, 0.044 mmol, 1.25 equiv), freshly powdered with a mortar and pestle, in an inert atmosphere glovebox. The vial was sealed with a screw cap fitted with a Teflon septum, removed from the glovebox and placed under an inert atmosphere. To a separate, oven-dried 1-dram vial were added the *trans*-iminothiazolidine **334** (16 mg, 0.035 mmol, 1.00 equiv) and allyl isothiocyanate (7 μL, 0.070 mmol, 2.00 equiv). The vial was sealed with a screw cap fitted with a Teflon septum, and the mixture was transferred to the first vial as a solution in anhydrous dichloromethane (0.10 mL + 0.05 mL rinse). The heterogeneous reaction mixture was then allowed to stir at ambient temperature. Over the course of 96 hours, no decomposition of *trans*-iminothiazolidine **334** or isomerization of *trans*-iminothiazolidine **334** to *cis*-iminothiazolidine **335** was observed (determined by LCMS).

3.7.10.7 Isomerization of cis*-Disubstituted Thiazolidine 335*



To an oven-dried 1-dram vial equipped with a magnetic stir bar was added zinc(II) bromide (10 mg, 0.044 mmol, 1.25 equiv), freshly powdered with a mortar and pestle, in an inert atmosphere glovebox. The vial was sealed with a screw cap fitted with a Teflon septum, removed from the glovebox and placed under an inert atmosphere. To a separate, oven-dried 1-dram vial were added the *cis*-iminothiazolidine **335** (16 mg, 0.035 mmol, 1.00 equiv) and allyl isothiocyanate (7 μL, 0.070 mmol, 2.00 equiv). The vial was sealed with a screw cap fitted with a Teflon septum, and the mixture was transferred to the first vial as a solution in anhydrous dichloromethane (0.10 mL + 0.05 mL rinse). The heterogeneous reaction mixture was then allowed to stir at ambient temperature. Over the course of 96 hours, no decomposition of *cis*-iminothiazolidine **335** or isomerization of *cis*-iminothiazolidine **335** to *trans*-iminothiazolidine **334** was observed (determined by LCMS).

3.8 NOTES AND REFERENCES

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(11) No reaction was observed in the absence of Lewis acid. For full details, see Section 3.7.10.1.

(12) The *Z*-imino stereochemistry of the iminothiazolidine products was assigned by analogy to the structure of thiazolidine **329**, which was unambiguously established by single-crystal X-ray diffraction. For full details, see Appendix 6.

(13) Thiourea **295** was not observed in any case during this study. Similarly, the analogous thiolactam product was not observed during our previous studies of (3

+ 2) cycloadditions of donor–acceptor cyclopropanes with heterocumulenes, see reference 10.

(14) This observation is in stark contrast to our previous studies of (3 + 2) cycloadditions of donor–acceptor cyclopropanes with heterocumulenes, in which increased steric bulk on the ring caused a large increase in reaction time, see reference 10.

(15) a) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev*. **1991**, *91*, 165–195; b) Hammett, L. P. *J. Am. Chem. Soc*. **1937**, *59*, 96–103.

(16) This was the only substrate found to be susceptible to nucleophilic ring opening by the zinc(II) counterion during our studies. For full details, see Section 3.7.8.

(17) A variety of isocyanates were tested under zinc(II) bromide mediated conditions, including trimethylsilyl, phenyl, and allyl isocyanates.

(18) The assignment of the *E*-imino-stereochemistry of the iminoimidazolidine products was assigned by analogy to a structure related to imidazolidine **323**, which was unambiguously established by single-crystal X-ray diffraction of the corresponding imidazolidinium ion. For full details, see Appendix 6.

(19) Inversion at the benzylic position was observed in our previous studies of stereoselective (3 + 2) cycloadditions of donor–acceptor cyclopropanes with heterocumulenes, see reference 10.

(20) Alternatively, *trans*-aziridine **330** did not undergo this transformation under the same conditions, although both styryl- and acroylaziridines are known to isomerize to pyrrolines, see: a) Brichacek, M.; Villalobos, M. N.; Plichta, A.; Njardarson, J. T. *Org. Lett.* **2011**, *13*, 1110–1113; b) Li, A.-H.; Dai, L.-X.; Hou, X.-L. *J. Chem. Soc. Perkin Trans. 1* **1996**, 2725–2729; c) Atkinson, R. S.; Rees, C. W. *J. Chem. Soc. Chem. Commun. (London)* **1967**, 1232.

(21) *N*-Tosyl-2-methyl-2-phenylaziridine proved susceptible to isomerization under the reaction conditions, furnishing no (3 + 2) adduct, but rather a mixture of *E* and *Z* enamine isomers. For full details, see Section 3.7.8.

(22) Absolute stereochemistry of the iminothiazolidine products was assigned by analogy to the structure of thiazolidine **(*S*)-315**, which was unambiguously established by single-crystal X-ray diffraction. For full details, see appendix 6.

(23) As with the zinc(II) bromide mediated conditions, isocyanates were not suitable cycloaddition partners under our stereospecific reaction conditions. Diphenylcarbodiimide was compatible with the zinc(II) chloride mediated

conditions, furnishing the iminoimidazolidine product in excellent yield, but with comparatively reduced *ee*. For full details, see Section 3.7.7.

(24) a) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642–8650; b) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014–16015.

(25) a) Karadeolian, A.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 10251–10253; b) Sapeta, K.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 8597–8599; c) Wanapun, D.; Van Gorp, K. A.; Mosey, N. J.; Kerr, M. A.; Woo, T. K. *Can. J. Chem.* **2005**, *83*, 1752–1767.

(26) In the absence of heterocumulene, aziridine **(*R*)-291** was completely racemized in 10 minutes. Furthermore, no reduction in *ee* of **(*S*)-292** was observed upon reexposure to the reaction conditions. For full details, see Sections 3.7.10.4 and 3.7.10.5.

(27) The selective C–C bond cleavage of *N*-tosyl-3-arylaziridine-2,2-dicarboxylates has been explored previously in the literature, see: a) Li, L.; Zhang, J. *Org. Lett.* **2011**, *13*, 5940–5943; b) Jiang, Z.; Wang, J.; Lu, P.; Wang, Y. *Tetrahedron* **2011**, *67*, 9609–9617; c) Pohlhaus, P. D.; Bowman, R. K.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2294–2295.

(28) Conditions: aziridine **342** (0.40 mmol), allyl isothiocyanate (0.80 mmol), $Sn(OTf)_2$ (0.44 mmol), CH_2Cl_2 (1.3 mL). See reference 10 and general procedure F in Section 2.8.2.

(29) The same mode of reactivity has been previously observed in (3 + 2) cycloadditions with the *N*-alkylated and *N*-arylated derivatives of aziridine **342** under thermolysis conditions with isothiocyanates, see: Benhaoua, H.; Texier, F. *Tetrahedron* **1978**, *34*, 1153–1161.

(30) Alonso, D. A.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 9455–9461.

(31) a) Narayan, R. S.; VanNieuwenhze, M. S. *Org. Lett.* **2005**, *7*, 2655–2658; b) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353–359; c) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373–6374.

(32) a) Chandrasekhar, S.; Reddy, C. R.; Rao, R. J. *Tetrahedron* **2001**, *57*, 3435–3438; b) Honda, M.; Morita, H.; Nagakura, I. *J. Org. Chem.* **1997**, *62*, 8932–8936; c) Garro-Helion, F.; Merzouk, A.; Guibe, F. *J. Org. Chem.* **1993**, *58*, 6109–6113.

(33) a) Matsumura, T.; Akiba, M.; Arai, S.; Nakagawa, M.; Nishida, A. *Tetrahedron Lett.* **2007**, *48*, 1265–1268; b) Koch, T.; Hesse, M. *Synthesis* **1992**, 931–932.

(34) a) Jasinski, M.; Mloston, G.; Heimgartner, H.; *J. Heterocycl. Chem.* **2010**, *47*, 1287–1293; b) Keiji, K.; Takanobu, K.; Masaki, K.; Hiroki, S. Thiazoline Derivative and Use of the Same. Eur. Pat. Appl. 1669352, 2006; c) Pecorari, P.; Rinaldi, M.; Costantino, L.; Provvisionato, A; Cermelli, C.; Portolani, M. *Farmaco* **1991**, *46*, 899–911; d) Crossley, R. 2,3-Dihydro- Thiazolo- and Thiazino- Benzimidazoles as Anti-Hyper Secretion Agents. U. S. Patent 4,873,237, October 10, 1989; e) Skaric, V.; Skaric, D; Cizmek, A. *J. Chem. Soc. Perkin Trans. 1* **1984**, 2221–2225; f) Brown, G. R. *J. Chem. Soc. Perkin Trans. 1* **1973**, 2022–2024.

(35) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

(36) Huang, C.-Y.; Doyle, A. G. *J. Am. Chem. Soc.* **2012**, *134*, 9541–9544.

(37) Fell, J. B.; Coppola, G. M. *Synth. Commun.* **1995**, *25*, 43–47.

(38) Procedure adapted from the literature and typically run on 3.0–4.0 mmol scale; see reference 36.

(39) Procedure adapted from the literature and typically run on 1.0–4.0 mmol scale, see: Farràs, J.; Ginesta, X.; Sutton, P. W.; Taltavull, J.; Egeler, F.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron* **2001**, *57*, 7665–7674.

(40) Ruppel, J. V.; Jones, J. E.; Huff, C. A.; Kamble, R. M.; Chen, Y.; Zhang, X. P. *Org. Lett.* **2008**, *10*, 1995–1998.

(41) Procedure adapted from the literature, see: Vicario, J. L.; Badía, D.; Carrillo, L. *ARKIVOC* **2007**, 304–311.

(42) a) Gao, G.-Y.; Harden, J. D.; Zhang, X. P. *Org. Lett.* **2005**, *7*, 3191–3193; b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742–2753.

(43) Aziridines **356** and **358** are known in the literature, but characterization data were not provided, see: Nebra, N.; Lescot, C.; Dauban, P.; Mallet-Ladeira, S.; Martin-Vaca, B.; Bourissou, D. *Eur. J. Org. Chem.* **2013**, 984–990.

(44) Aziridine **360** is known in the literature, but not fully characterized; see reference 36.

(45) a) Nishimura, M.; Minakata, S.; Takahashi, T.; Oderaotoshi, Y.; Komatsu, M. *J. Org. Chem.* **2002**, *67*, 2101–2110; b) Müller, P.; Baud, C.; Jacquier, Y. *Can. J. Chem.* **1998**, *76*, 738–750.

(46) Stamm, H.; Sommer, A.; Woderer, A.; Wiesert, W.; Mall, T.; Assithianakis, P. *J. Org. Chem.* **1985**, *50*, 4946–4955.

(47) The IR and HRMS spectra for aziridine **330** are not reported in the literature. For ^{1}H and ^{13}C NMR spectra, see reference 20b).

(48) Jin, T.-S.; Yu, M.-J.; Liu, L.-B.; Zhao, Y.; Li, T.-S. *Synth. Commun.* **2006**, *36*, 2339–2344.

(49) Any delay during elution or prolonged exposure to silica gel can result in the partial hydrolysis of the desired imine.

(50) Hatano, M.; Hattori, Y.; Furuya, Y.; Ishihara, K. *Org. Lett.* **2009**, *11*, 2321–2324.

(51) Fan, R.; Wang, L.; Ye, Y.; Zhang, J. *Tetrahedron Lett.* **2009**, *50*, 3857–3859.

(52) The IR spectrum for aziridine **342** is not reported in the literature. For ^{1}H and ^{13}C NMR and HRMS spectra, see: Fan, R.; Ye, Y. *Adv. Synth. Catal.* **2008**, *350*, 1526–1530.

(53) For the purpose of characterization, thiazolidines **311** and **312** were purified using an Agilent 1200 series preparative HPLC (Agilent Prep-SIL column (5 mm, 30 x

250 mm), 6% EtOAc in hexane, 50.00 mL/min, l = 254 nm, compound **311**: 12.036 min, compound **312**: 11.372 min).

(54) For the purpose of characterization, *trans*-thiazolidine **334** and *cis*-thiazolidine **335** were purified using an Agilent 1200 series preparative HPLC (Agilent Prep-SIL column (5 mm, 30 x 250 mm), 15% EtOAc in hexane, 50.00 mL/min, l = 254 nm, *trans*-thiazolidine **334**: 12.218 min, *cis*-thiazolidine **335**: 8.845 min).

(55) Wu, X.; Li, L.; Zhang, J. *Chem. Commun.* **2011**, *47*, 7824–7826.

(56) The absolute stereochemistry of iminoimidazolidine **(*S*)-325** was assigned by analogy to the absolute stereochemistry of thiazolidine **(*S*)-323** that was unambiguously established by single crystal X-ray diffraction.

(57) The use of additional equivalents of carbodiimide greatly increased the reaction time.

(58) Lee, K. Y.; Lee, C. G.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 1231–1234.

(59) Compound **377** is known in the literature, but characterized as a mixture with 2-bromo-1-(4-nitrophenyl)-1-(*p*-toluenesulfonamido)ethane, see: Hayakawa, J.; Kuzuhara, M.; Minakata, S. *Org. Biomol. Chem.* **2010**, *8*, 1424–1430.

(60) For examples of palladium-catalyzed deallylation of amines, see reference 32. For examples of palladium-catalyzed deallylation of amides, see reference 33.

(61) Zinc(II) bromide was used as the Lewis acid for the control experiments as it was the most effective zinc(II) salt at preforming the (3 + 2) cycloaddition of aziridines with heterocumulenes.

(62) Jones, A. D.; Redfern, A. L.; Knight, D. W.; Morgan, I. R.; Williams, A. C. *Tetrahedron* **2006**, *62*, 9247–9257.

(63) Although the pyrroline products of the vinylaziridine-pyrroline rearrangement were not observed, aziridine **330** is known to readily undergo this transformation, see reference 20.

APPENDIX 5

Spectra Relevant to Chapter 3:

Stereoselective Lewis Acid Mediated (3 + 2) Cycloadditions of

N-*H- and* N-*Sulfonylaziridines with Heterocumulenes*

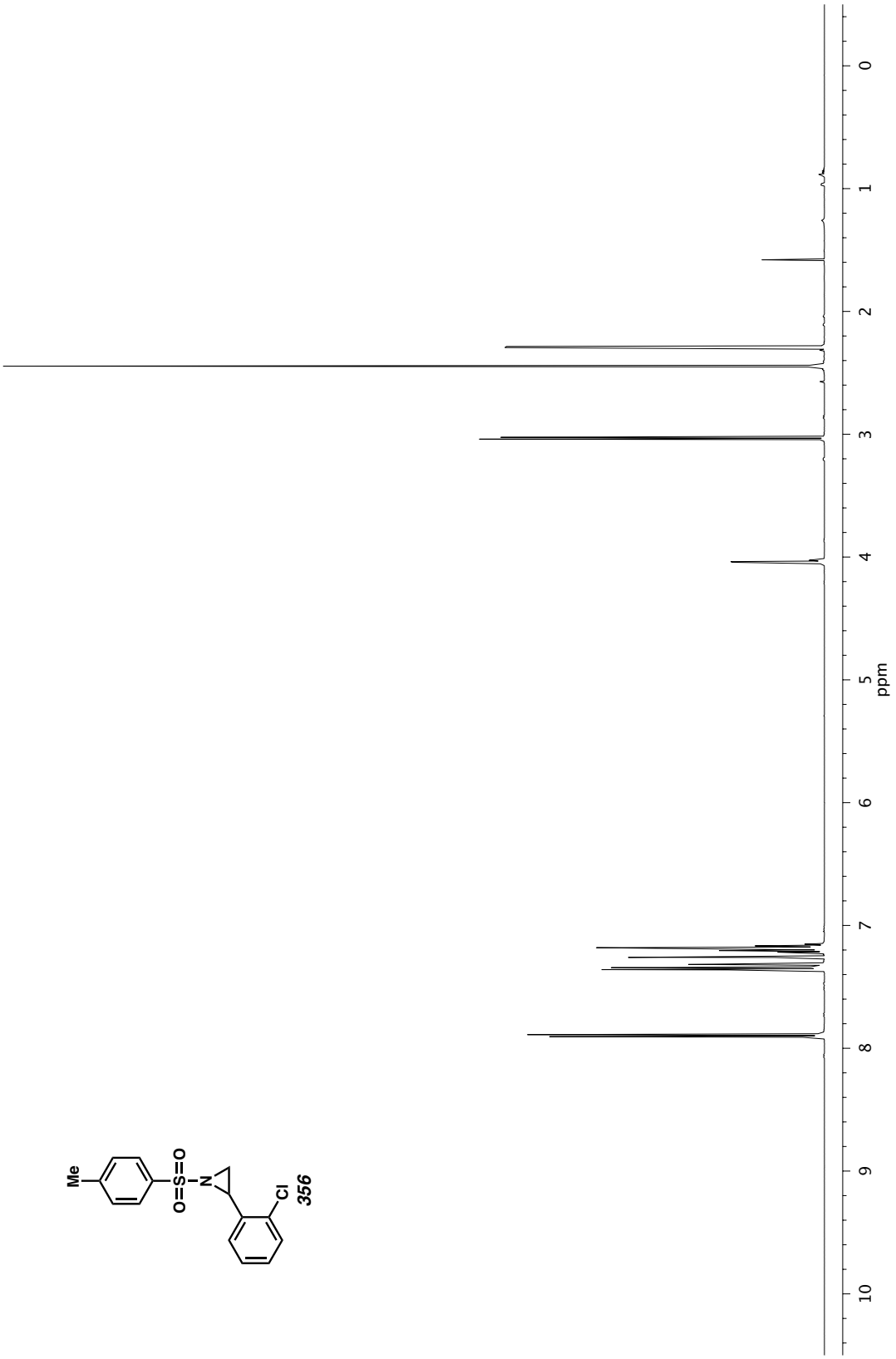


Figure A5.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **356**.

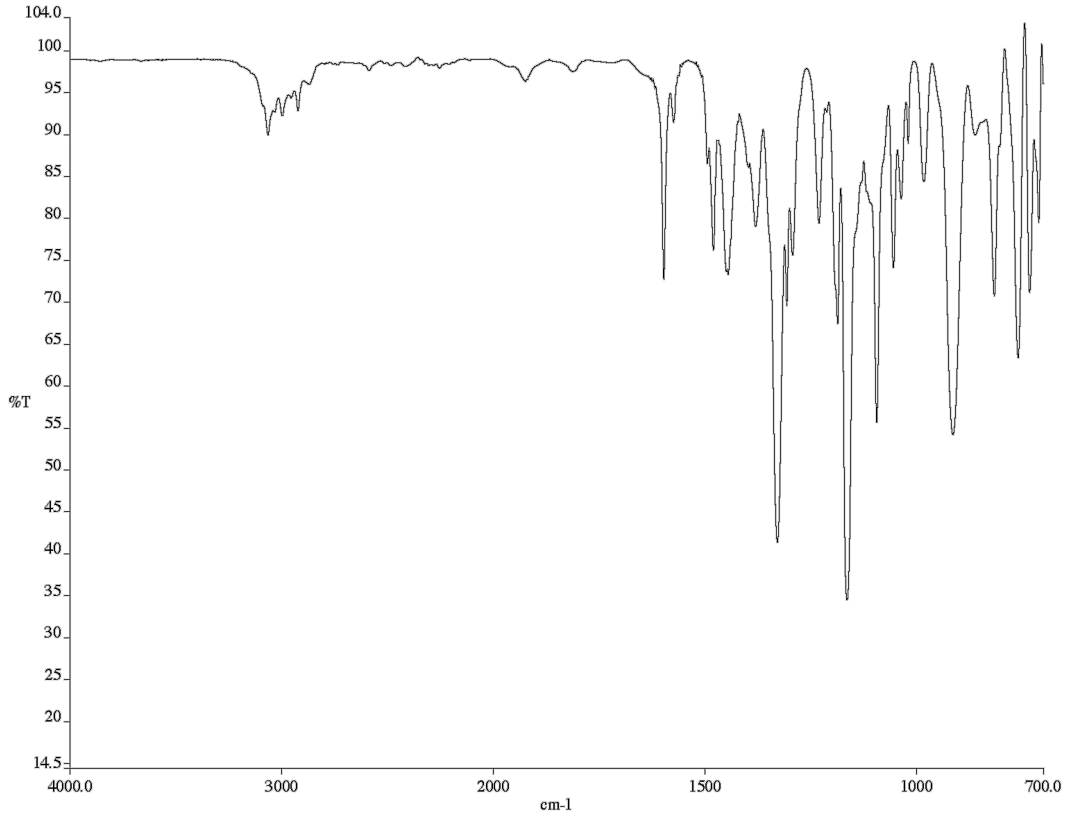


Figure A5.2 Infrared spectrum (thin film/NaCl) of compound **356**.

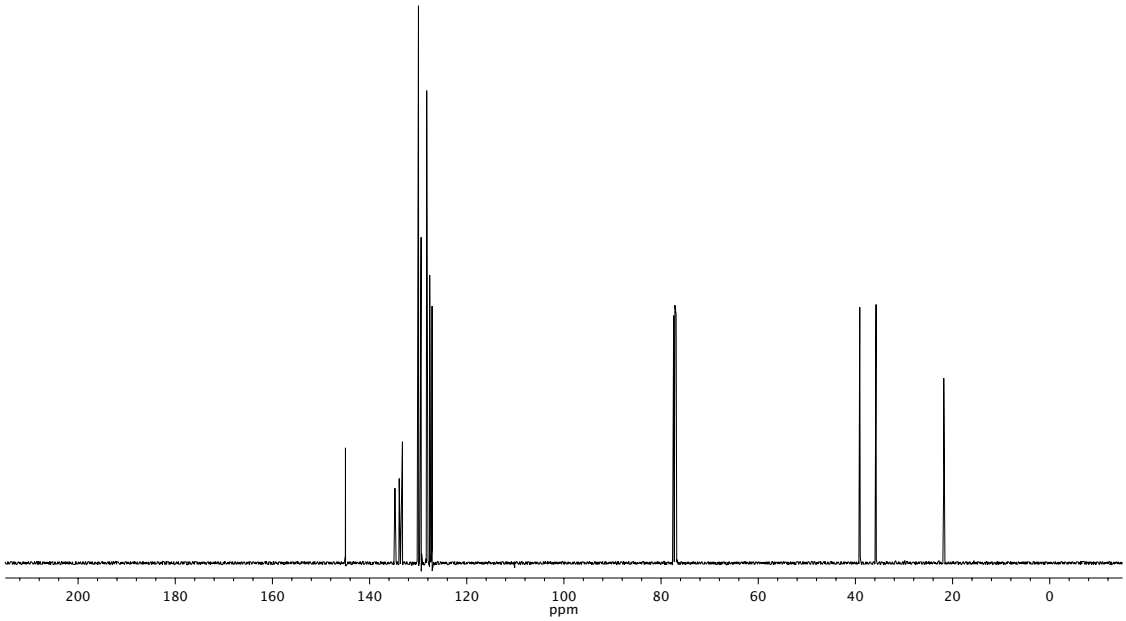


Figure A5.3 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **356**.

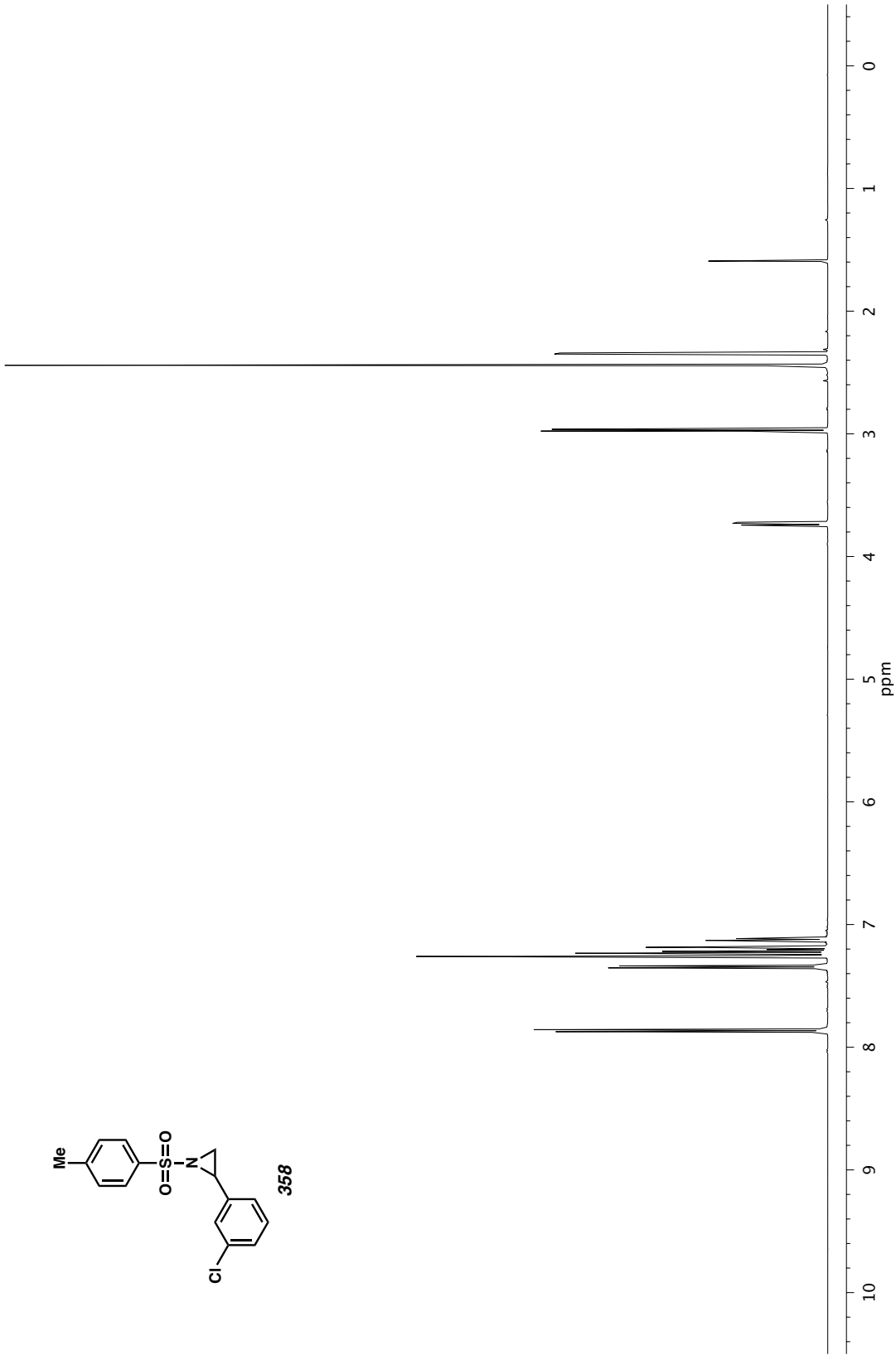


Figure A5.4 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **358**.

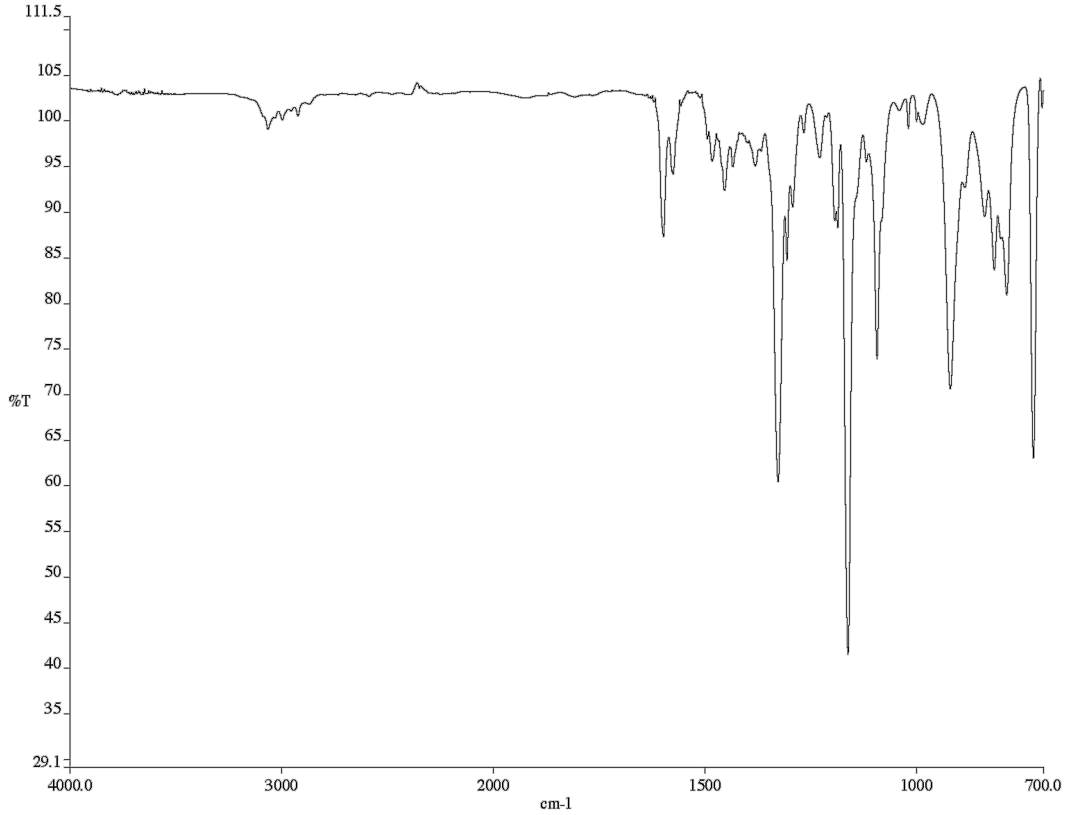


Figure A5.5 Infrared spectrum (thin film/NaCl) of compound **358**.

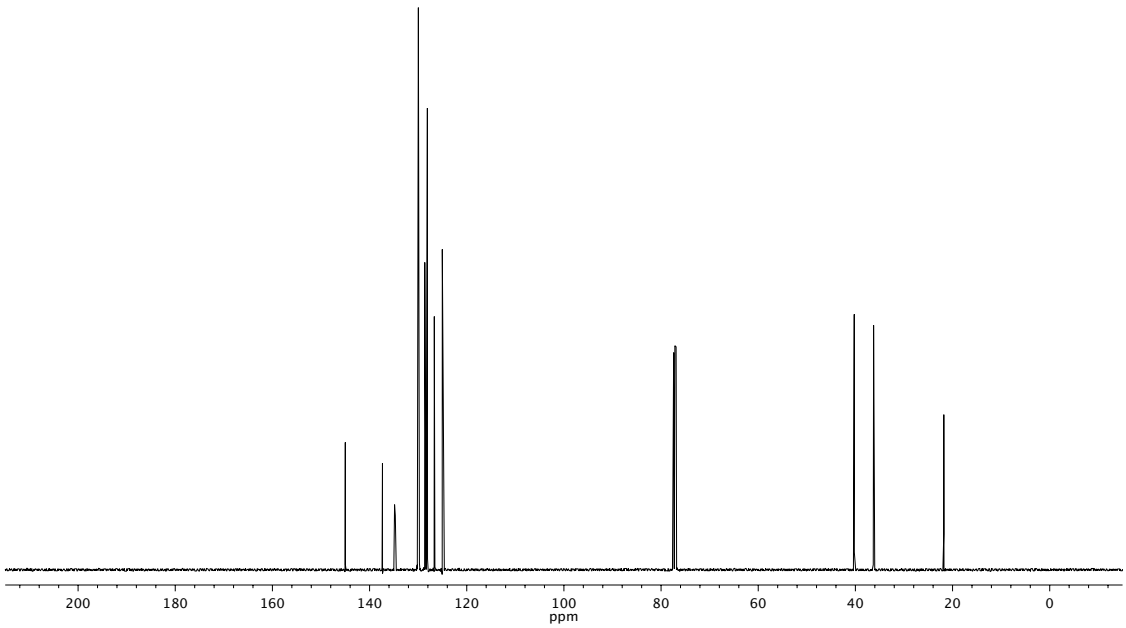


Figure A5.6 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **358**.

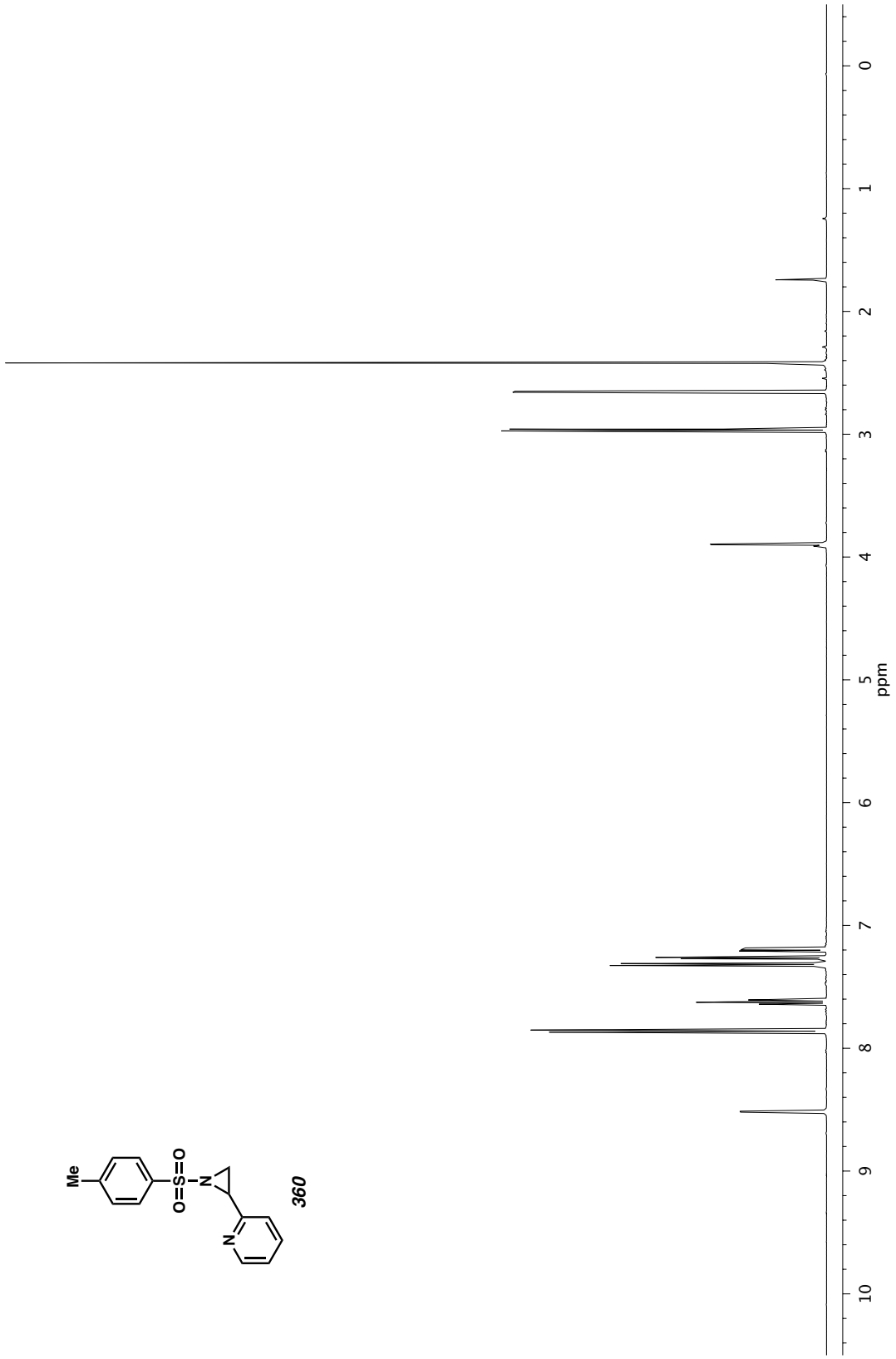


Figure A5.7 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **360**.

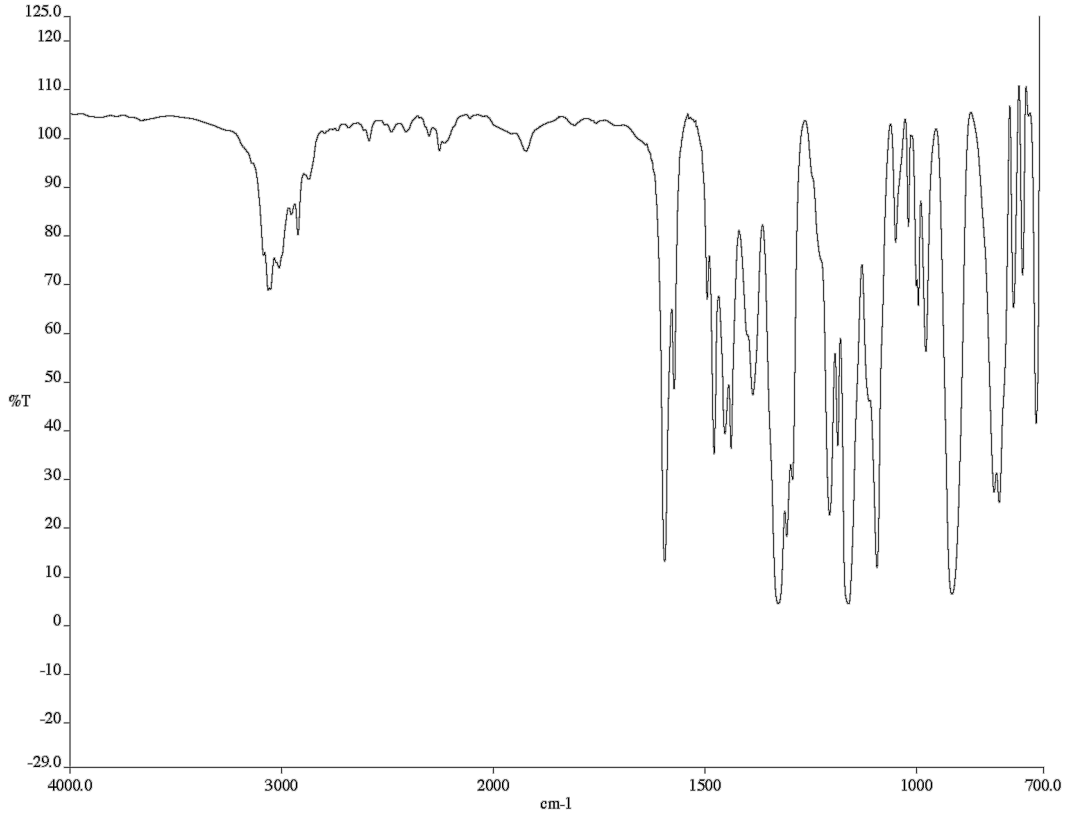


Figure A5.8 Infrared spectrum (thin film/NaCl) of compound **360**.

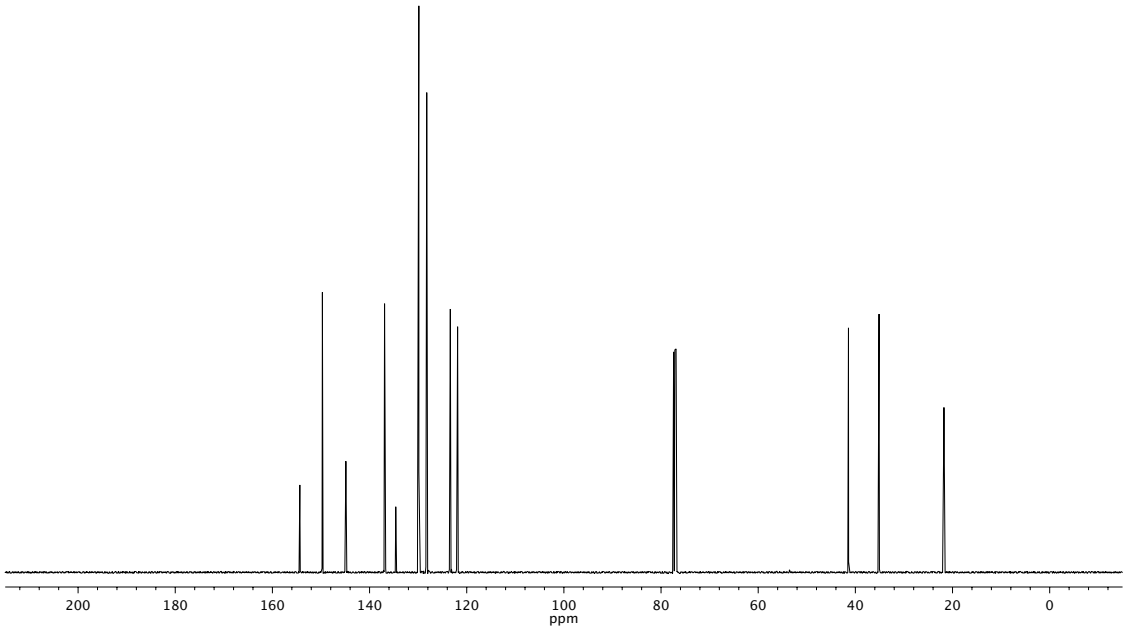


Figure A5.9 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **360**.

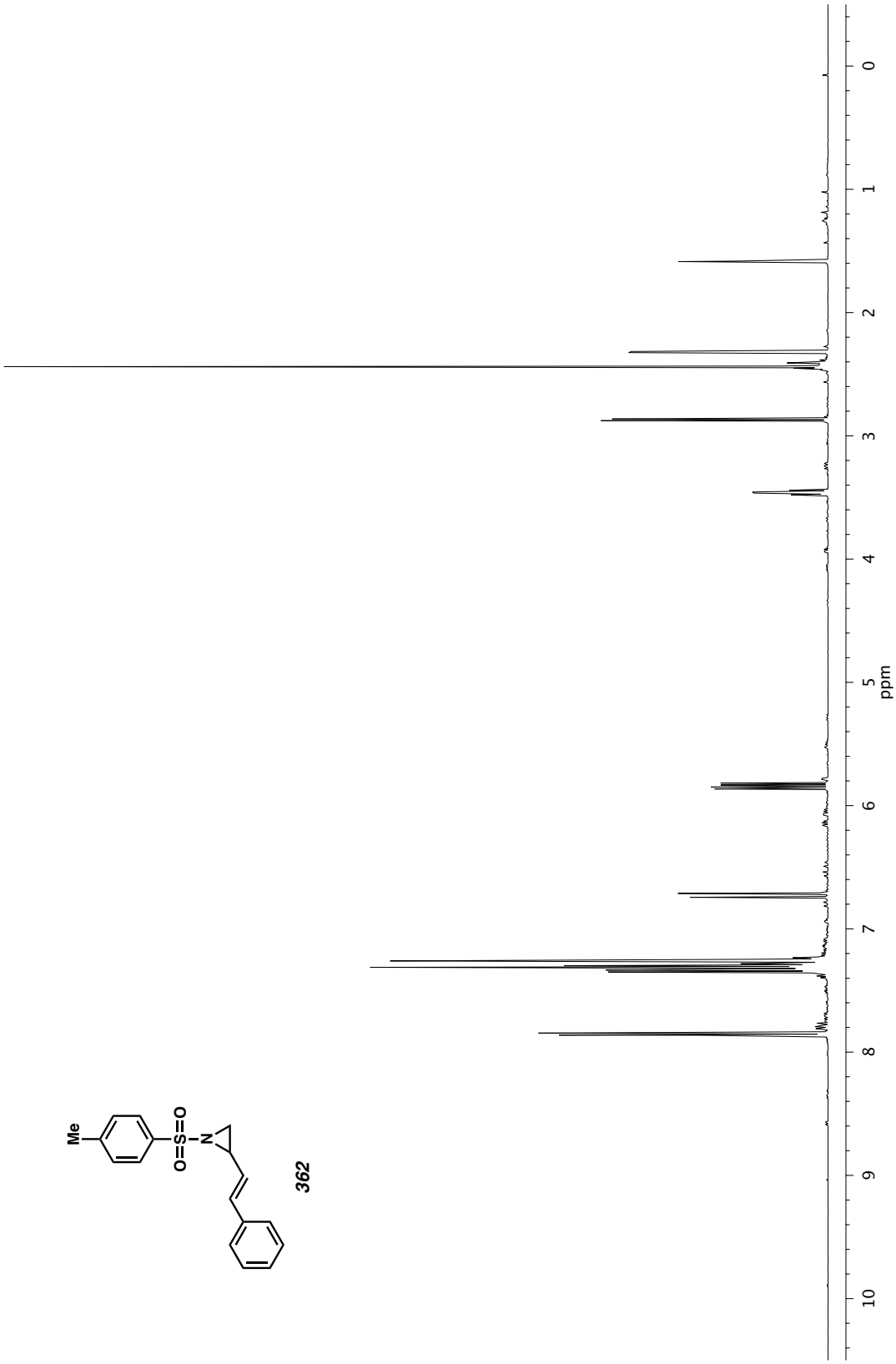


Figure A5.10 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **362**.

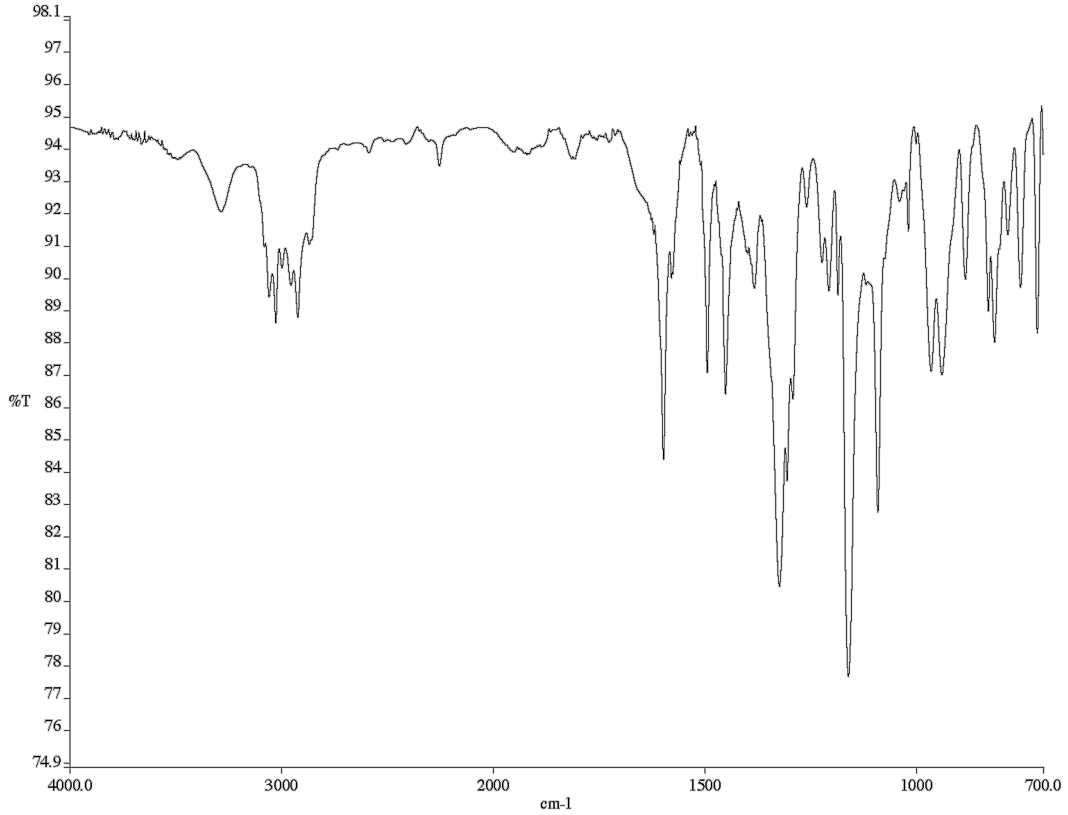


Figure A5.11 Infrared spectrum (thin film/NaCl) of compound **362**.

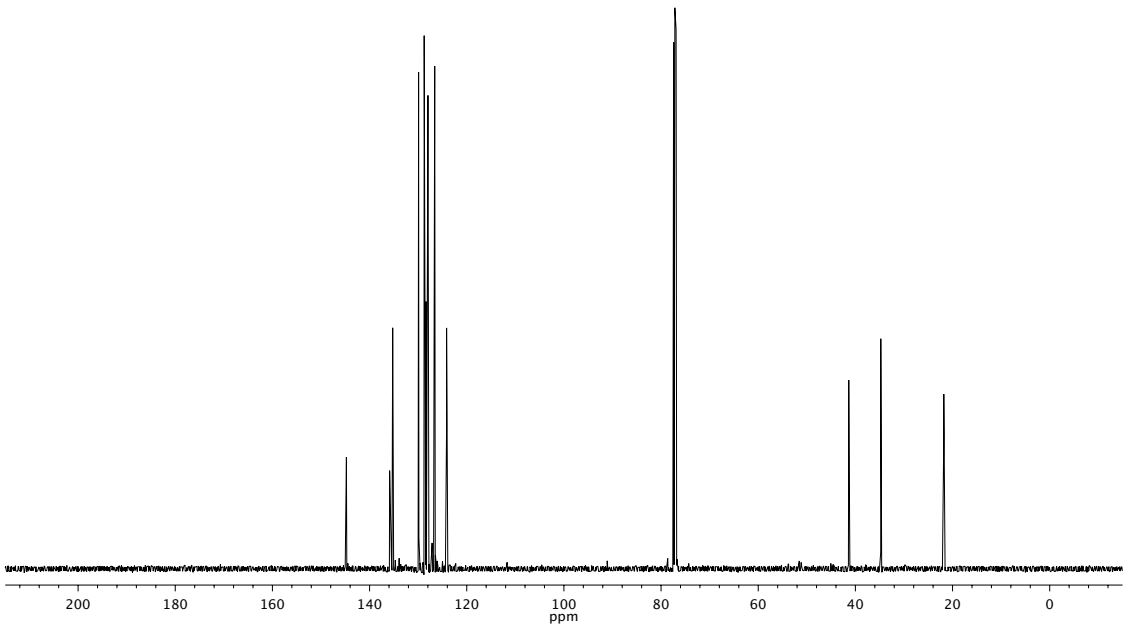
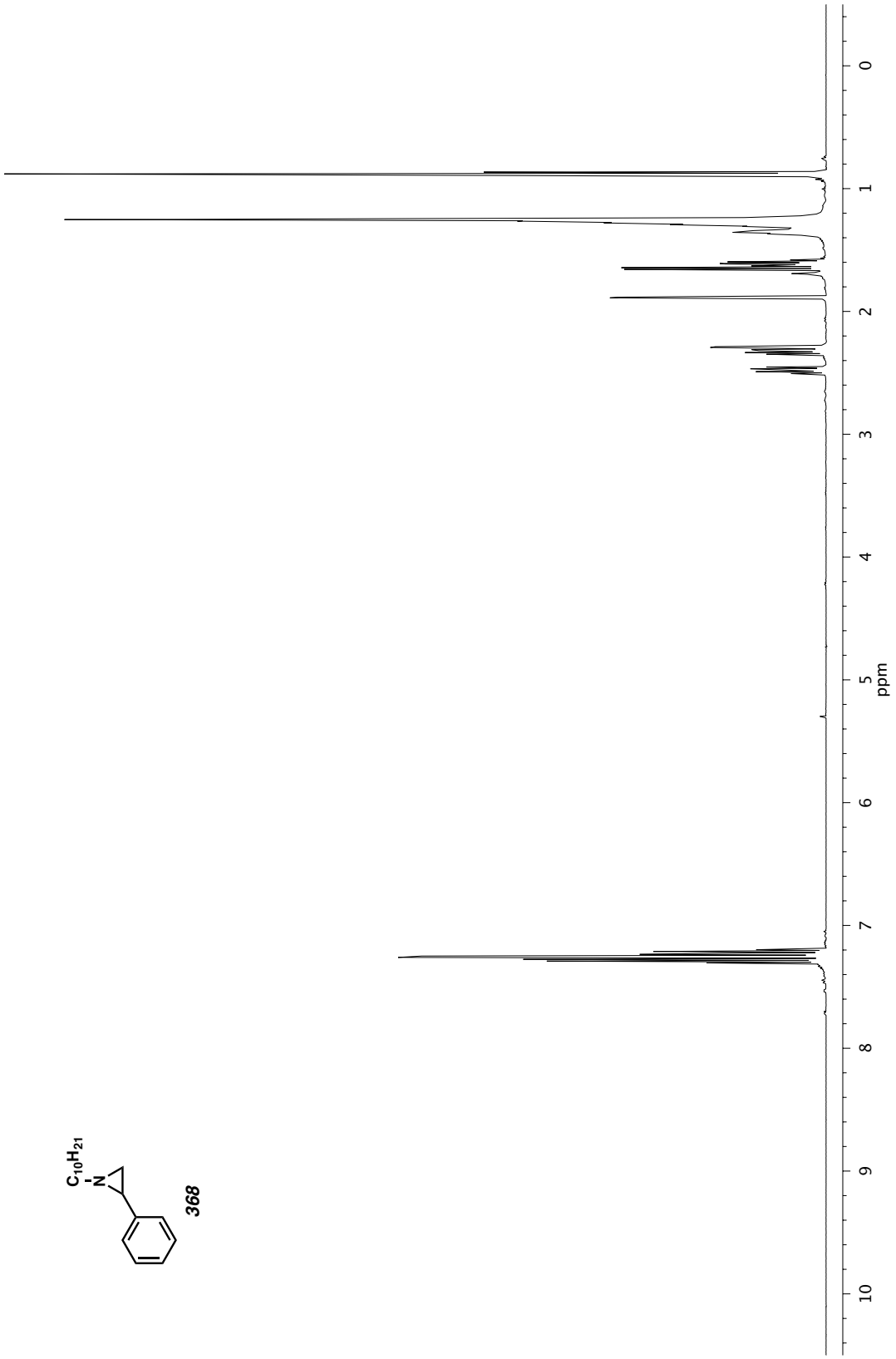


Figure A5.12 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **362**.



368

Figure A5.13 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **368**.

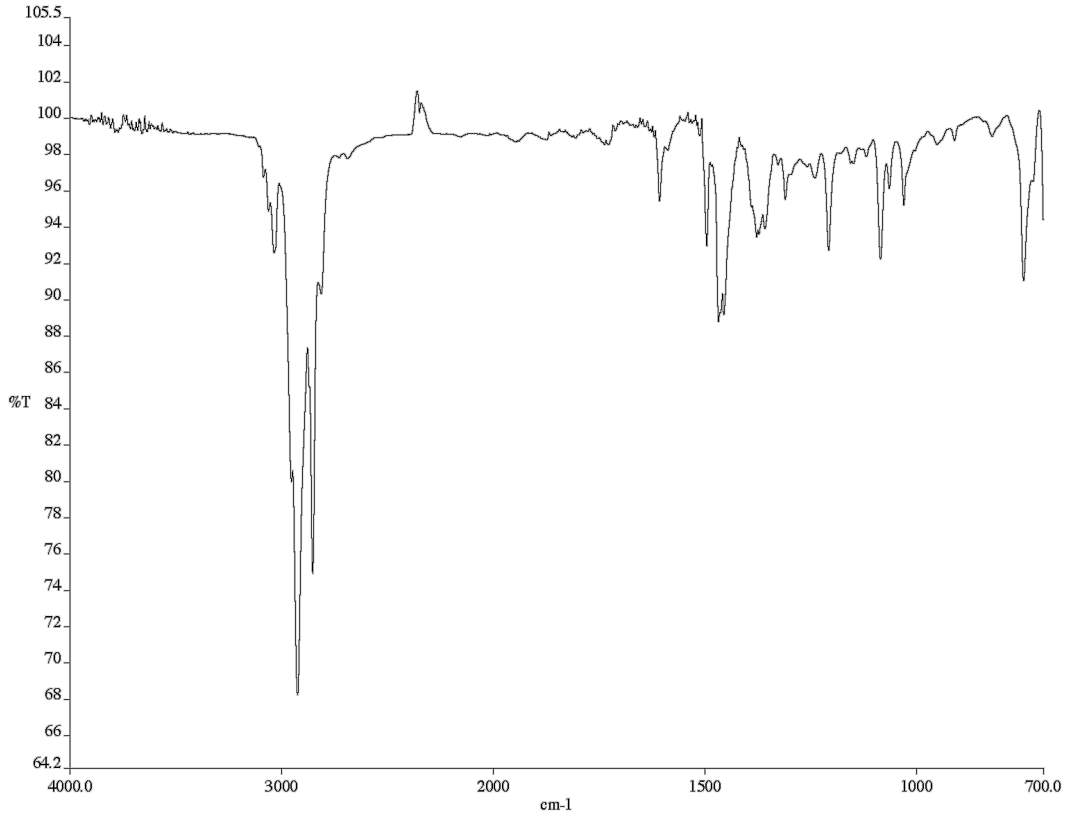


Figure A5.14 Infrared spectrum (thin film/NaCl) of compound **368**.

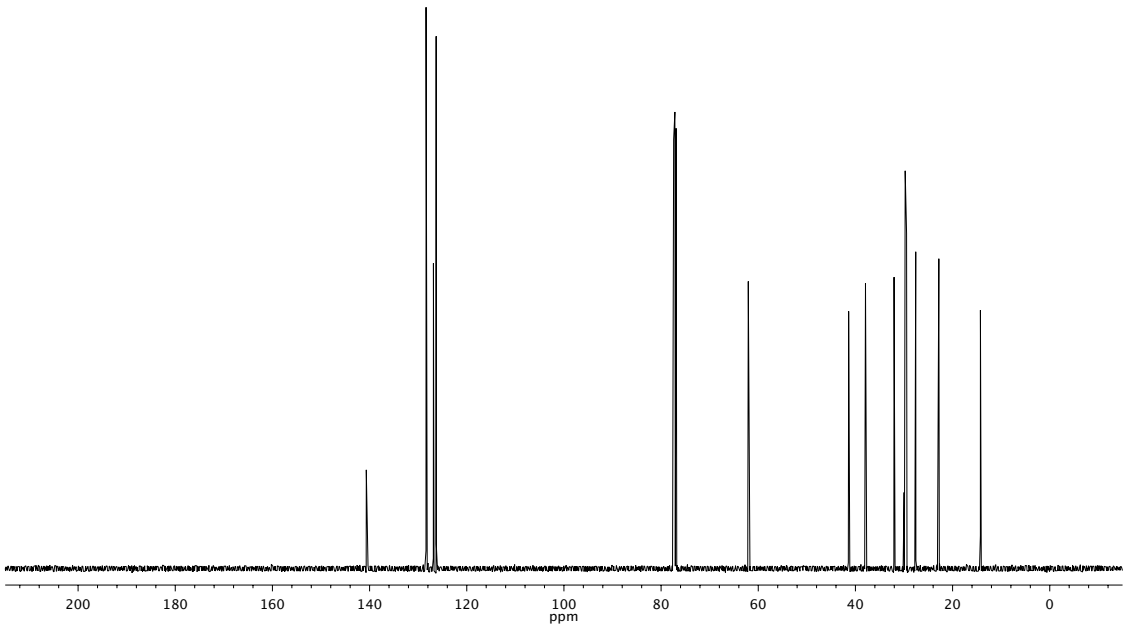


Figure A5.15 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **368**.

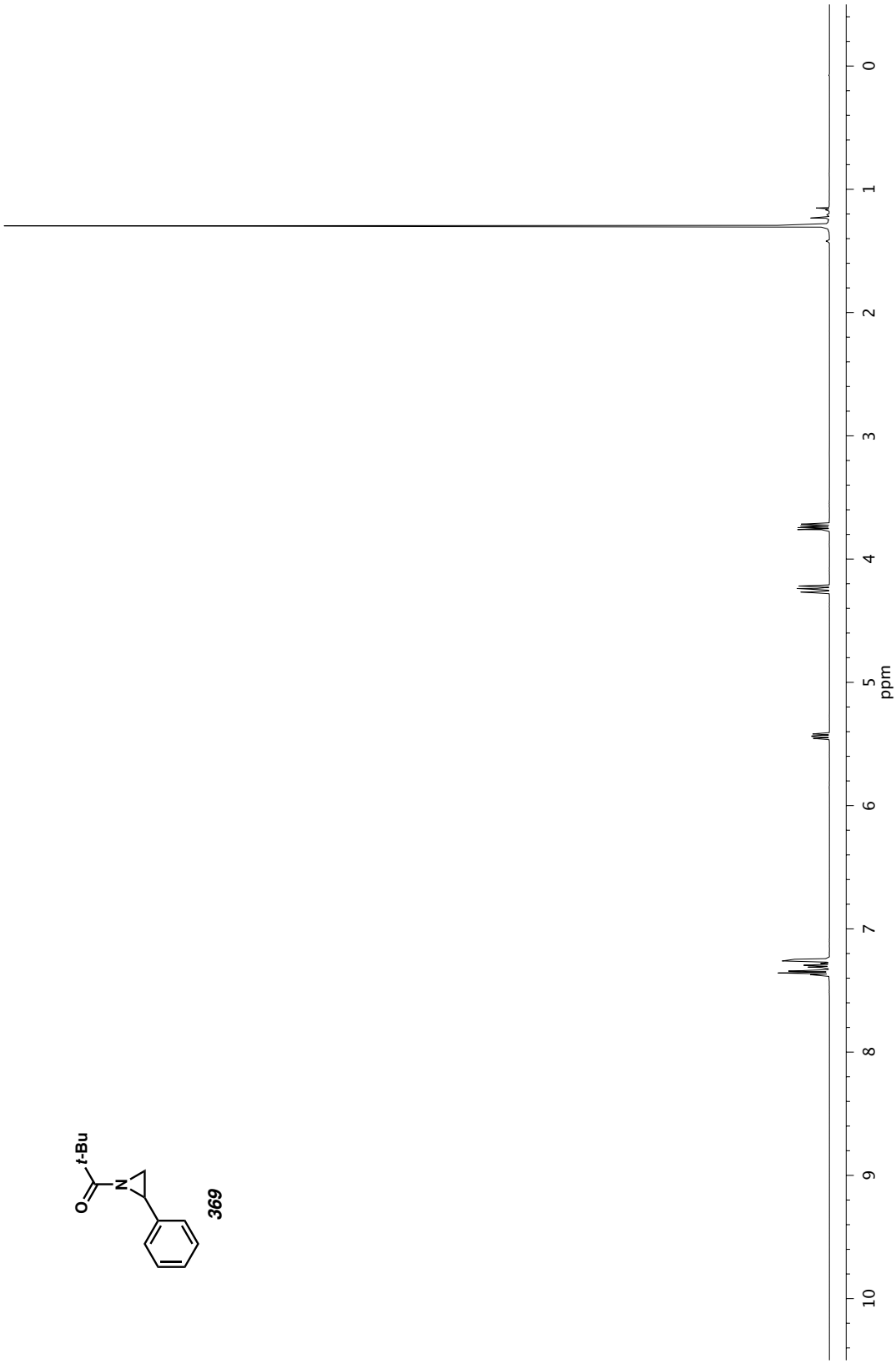


Figure A5.16 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **369**.

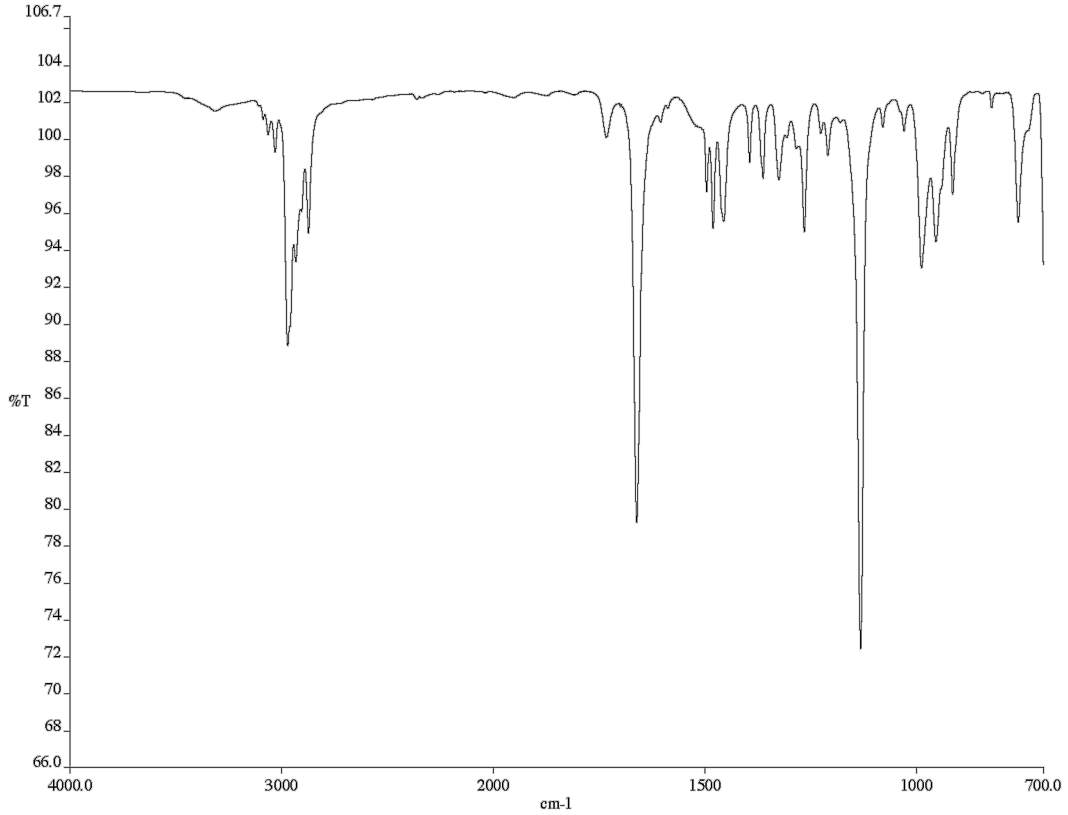


Figure A5.17 Infrared spectrum (thin film/NaCl) of compound **369**.

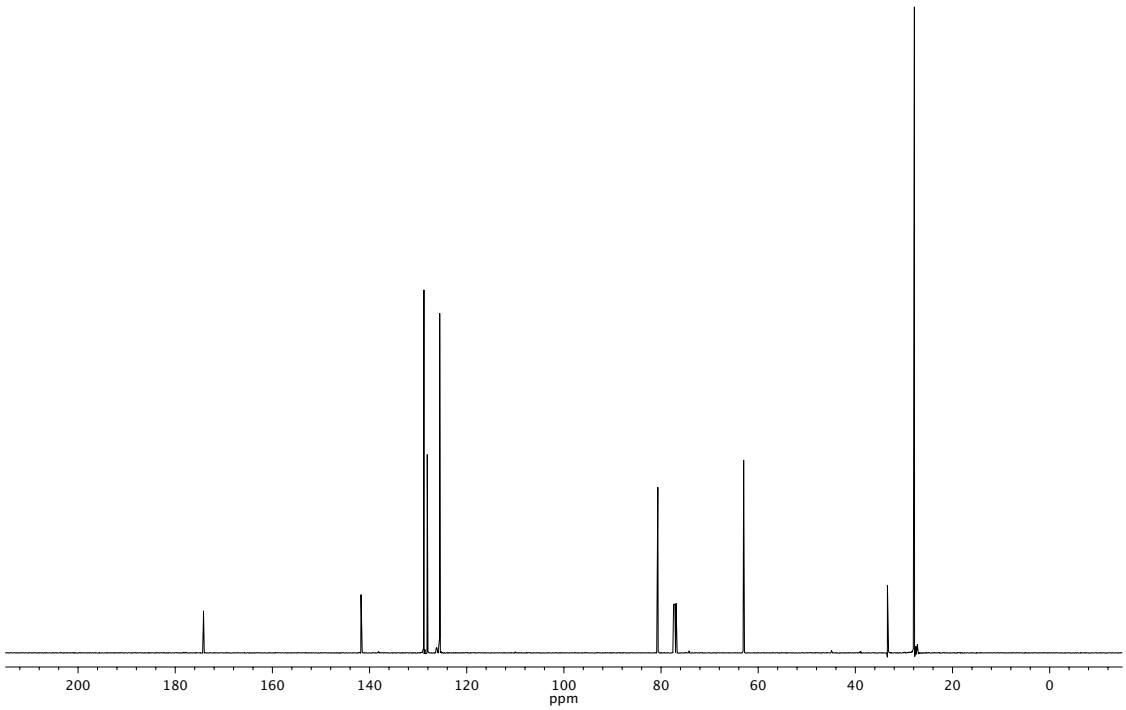


Figure A5.18 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **369**.

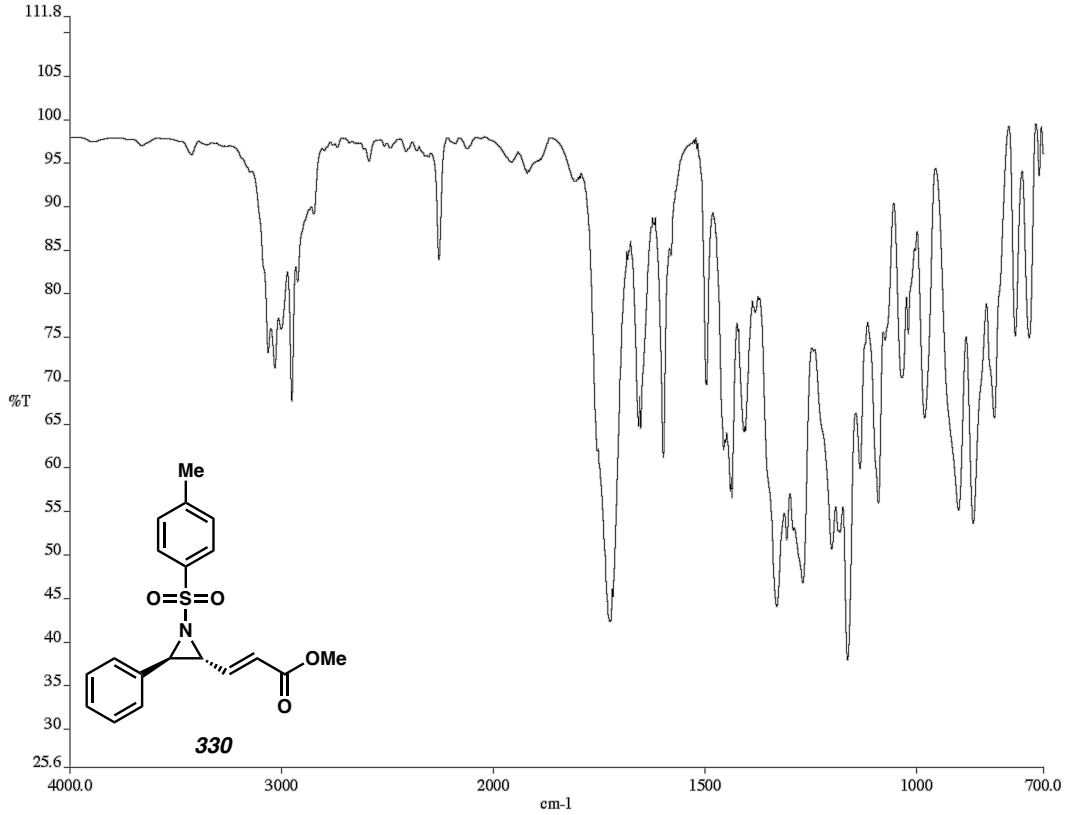


Figure A5.19 Infrared spectrum (thin film/NaCl) of compound **330**.

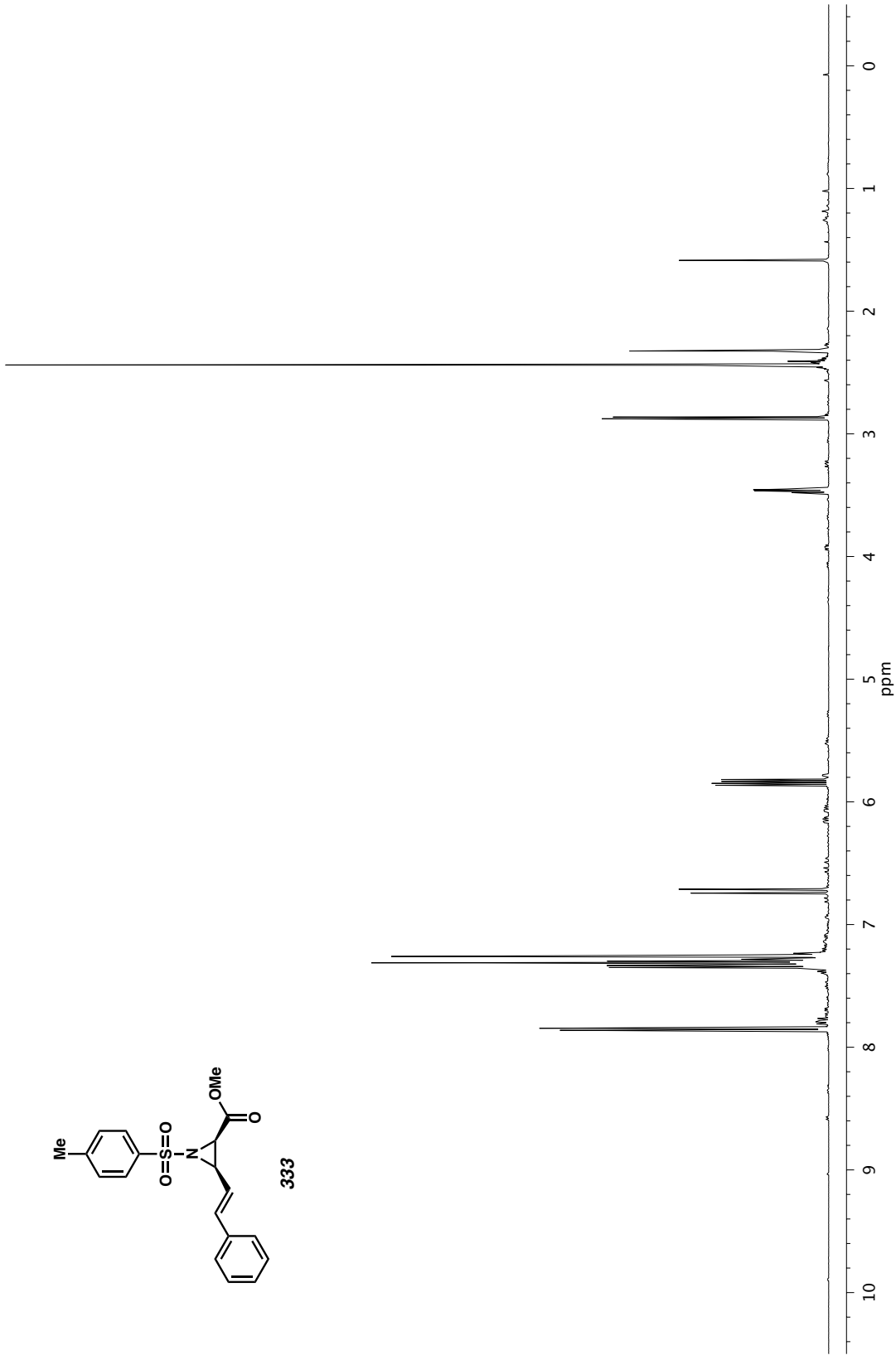


Figure A5.20 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **333**.

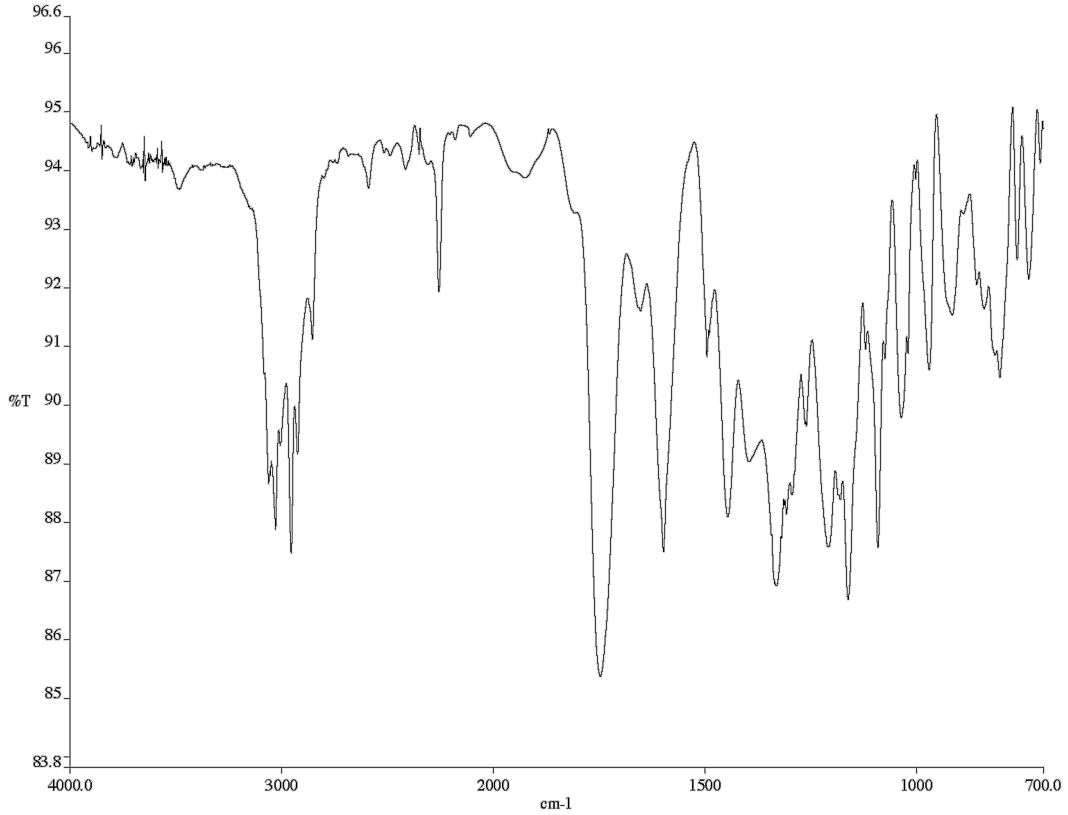


Figure A5.21 Infrared spectrum (thin film/NaCl) of compound **333**.

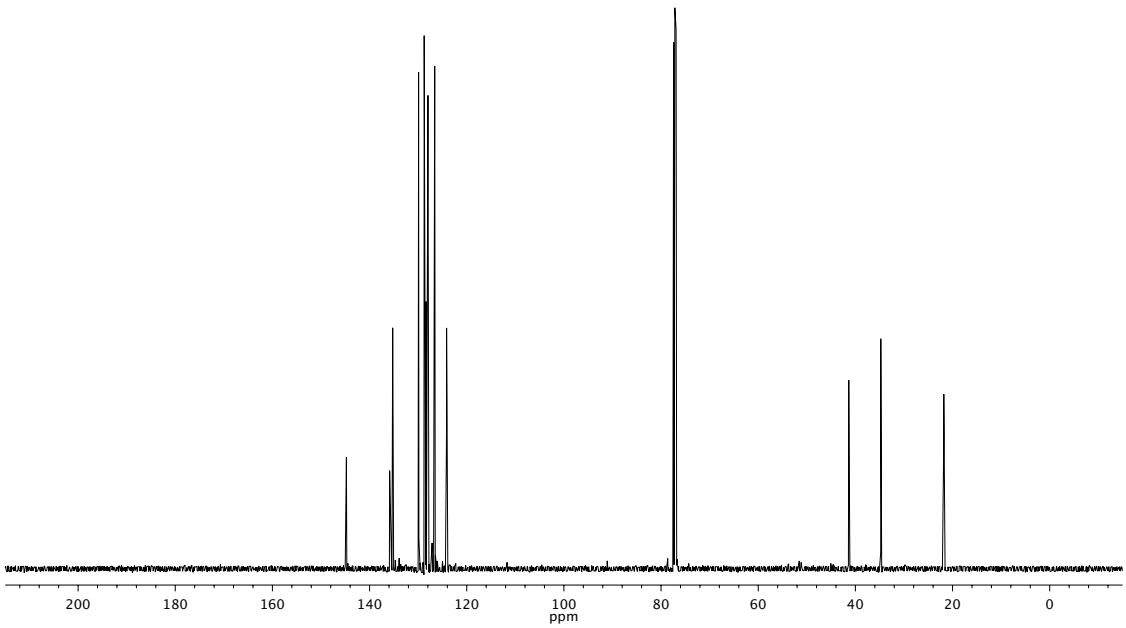


Figure A5.22 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **333**.

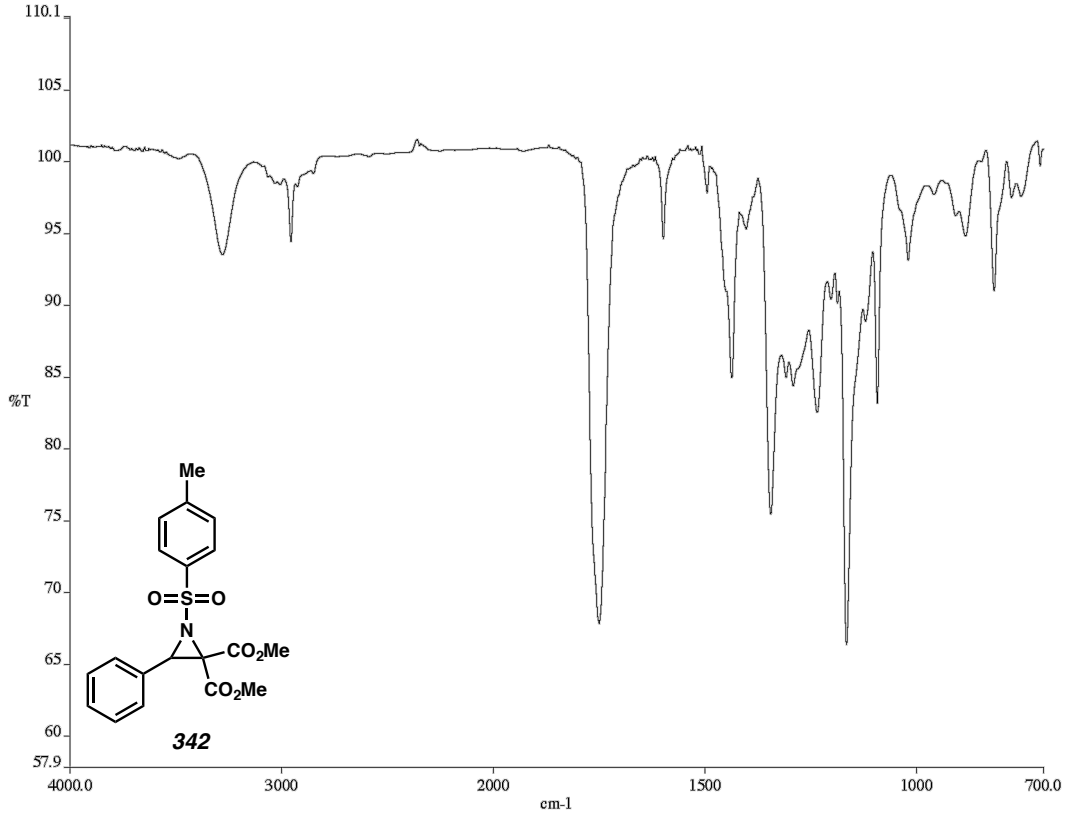


Figure A5.23 Infrared spectrum (thin film/NaCl) of compound **342**.

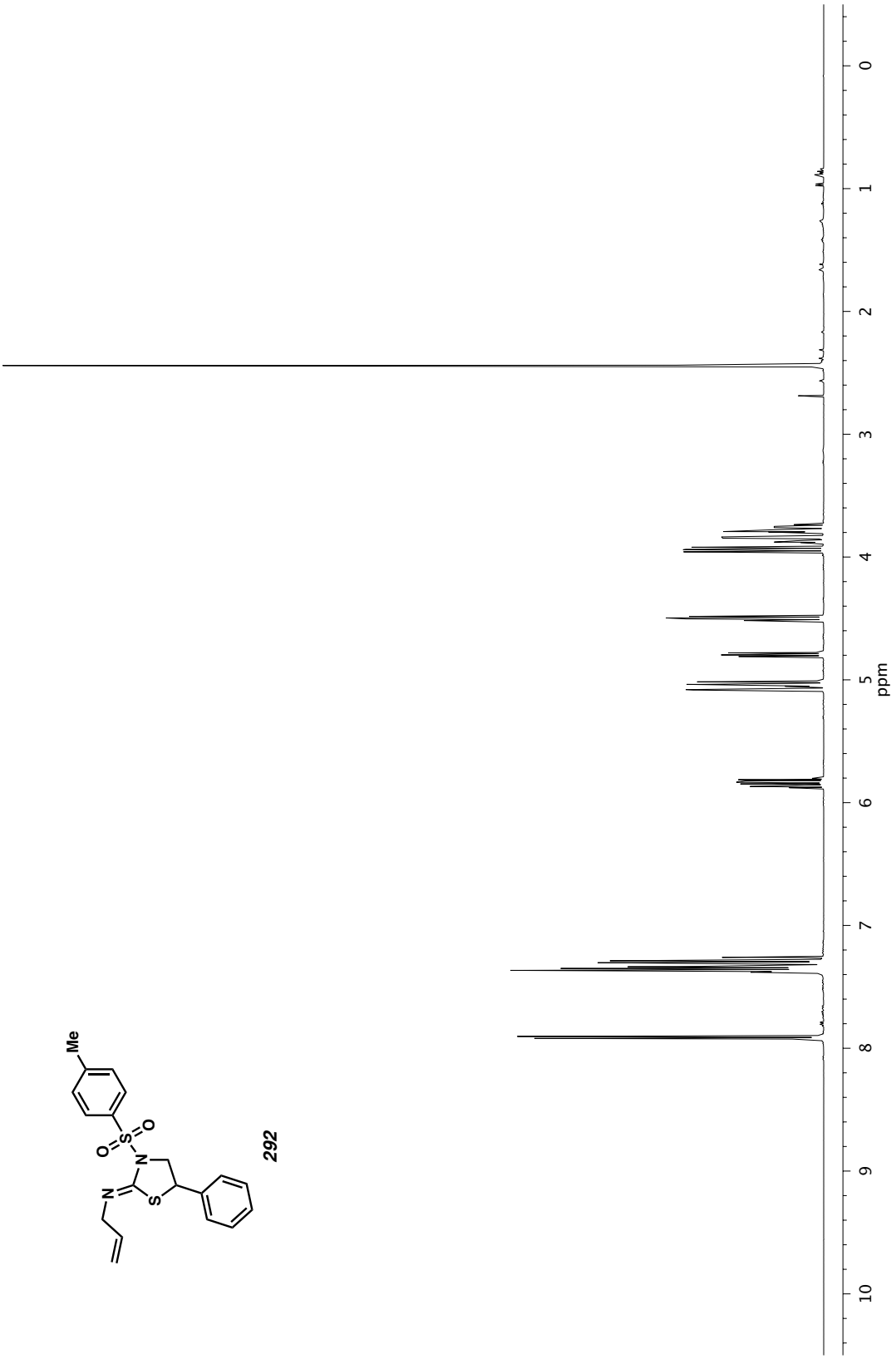


Figure A5.24 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **292**.

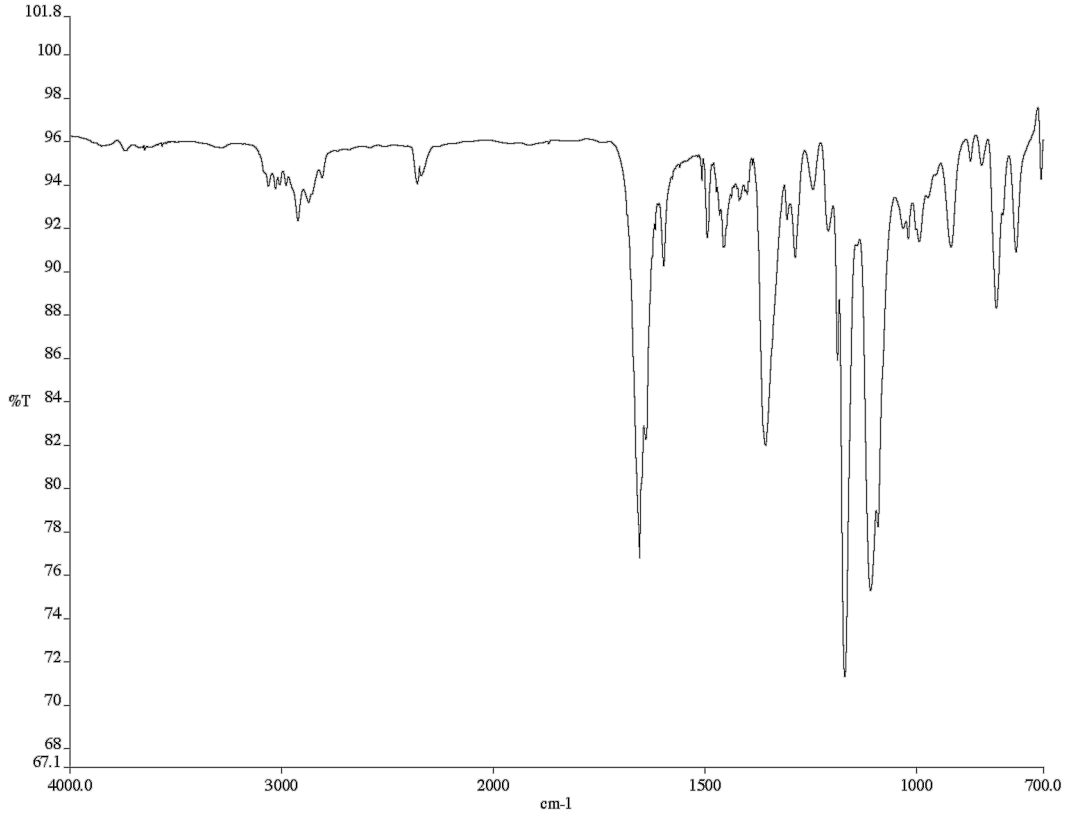


Figure A5.25 Infrared spectrum (thin film/NaCl) of compound **292**.

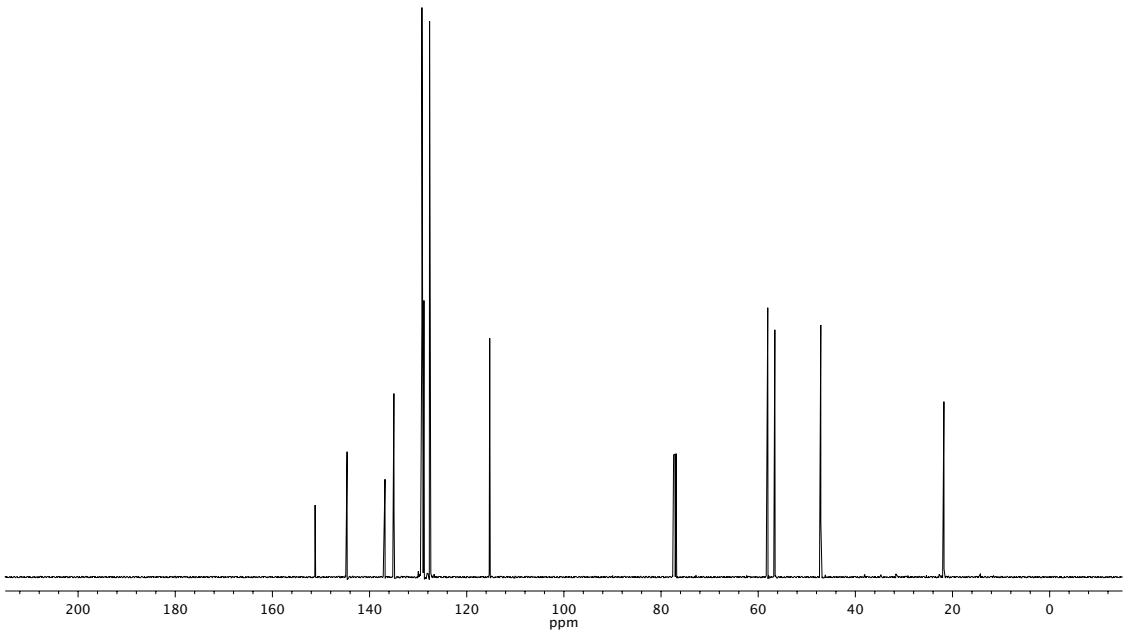


Figure A5.26 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **292**.

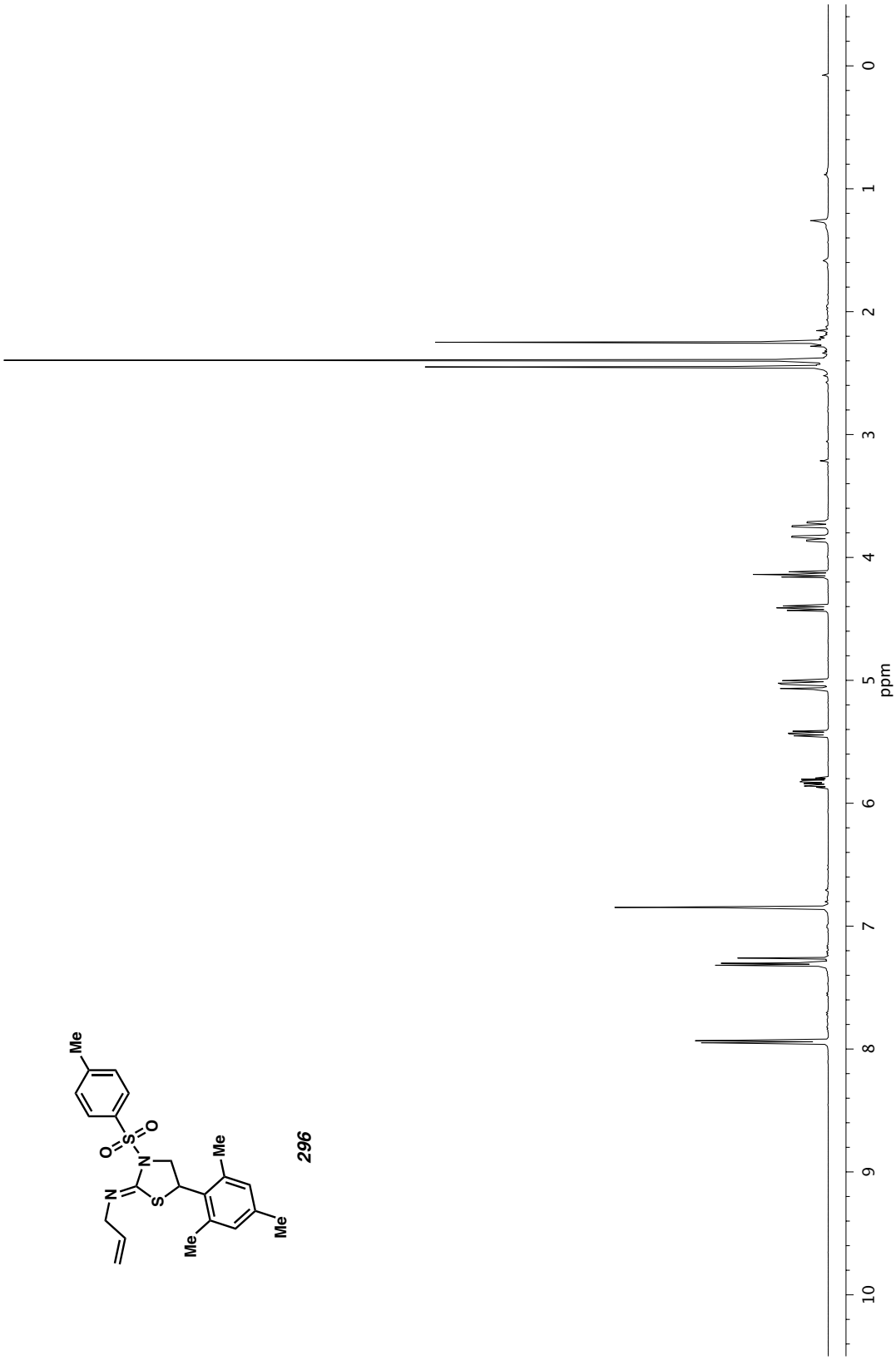


Figure A5.27 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **296**.

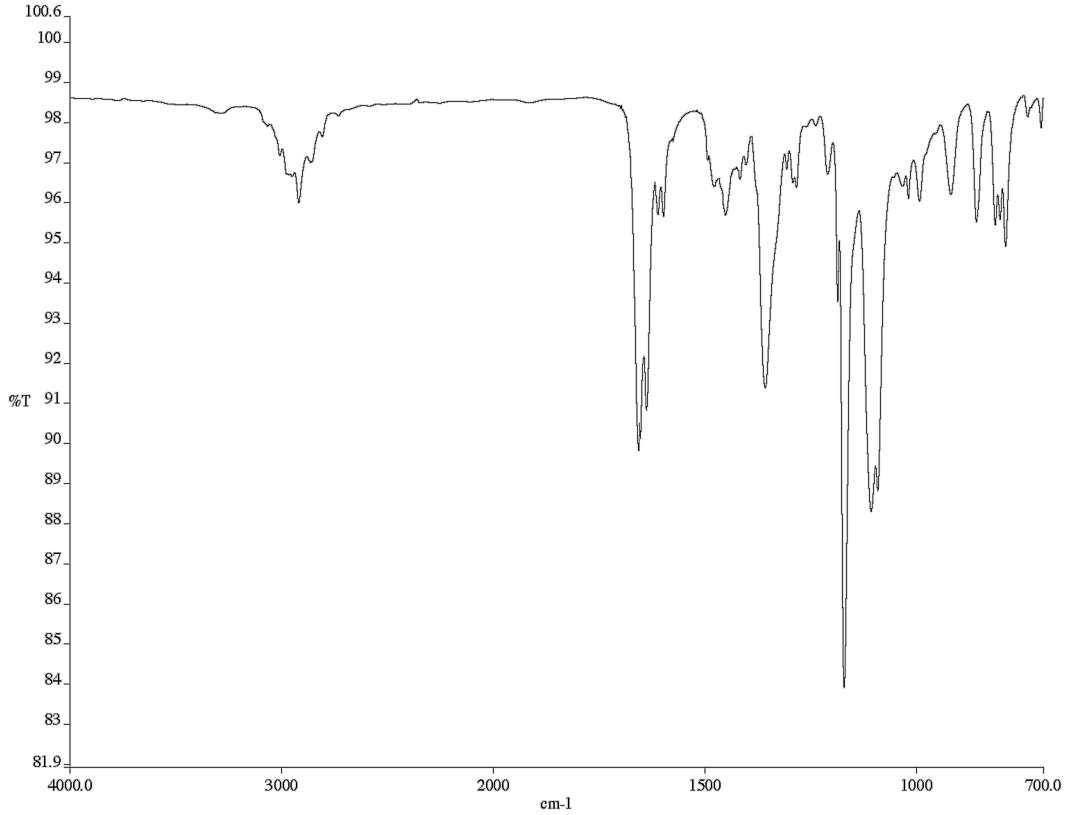


Figure A5.28 Infrared spectrum (thin film/NaCl) of compound **296**.

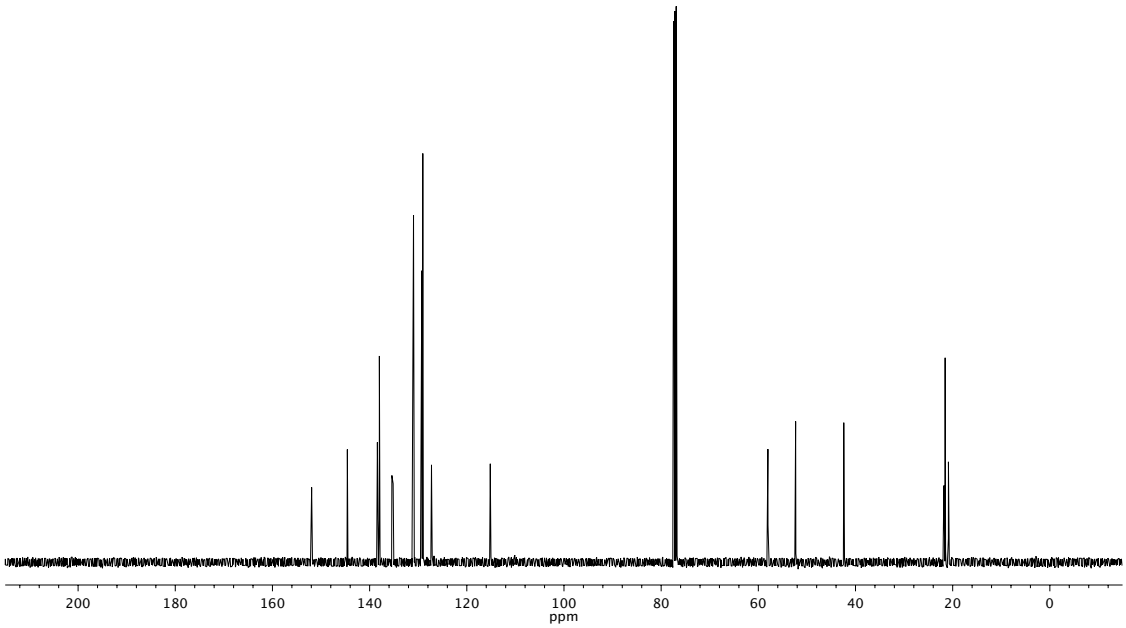


Figure A5.29 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **296**.

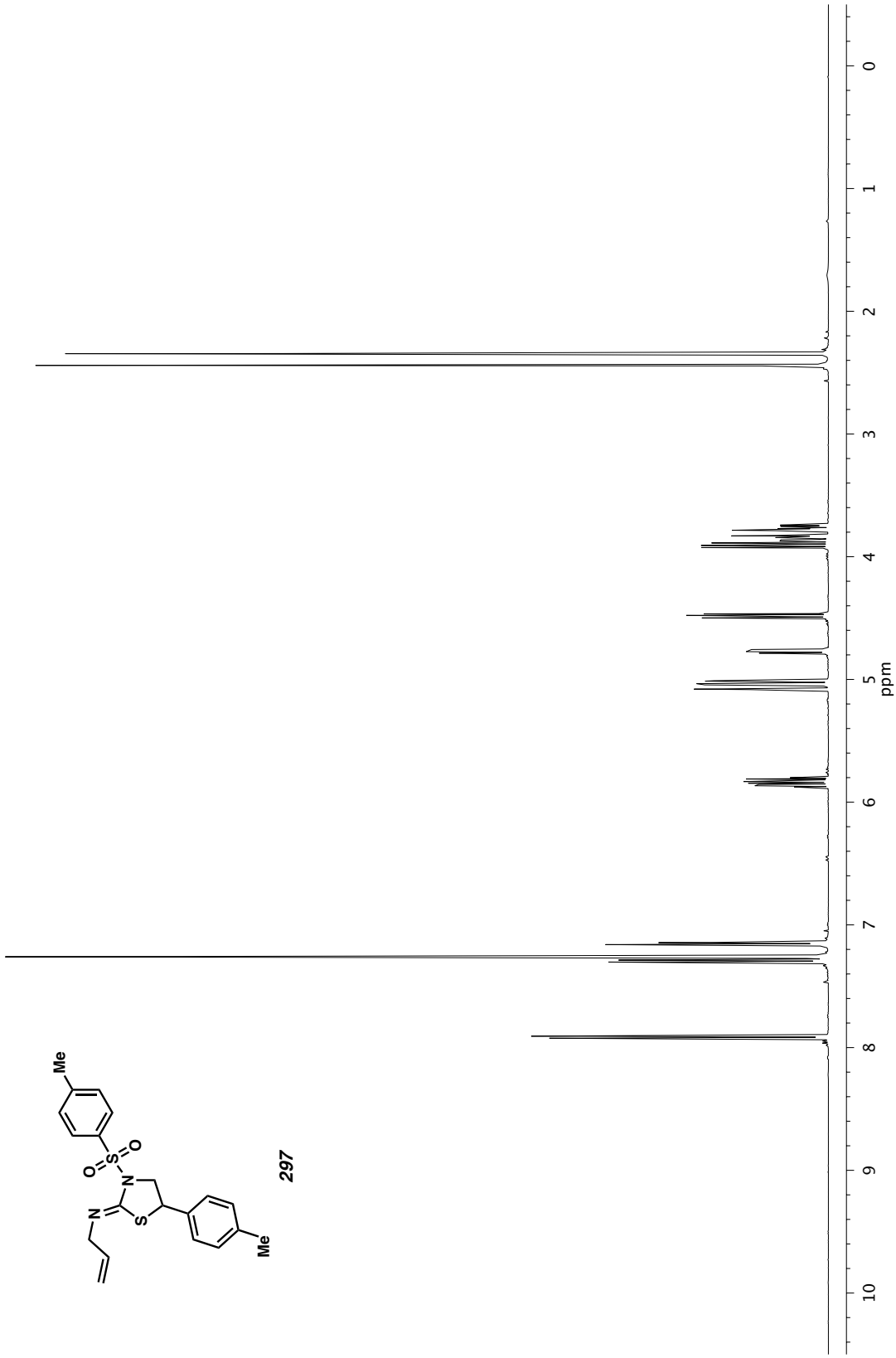


Figure A5.30 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **297**.

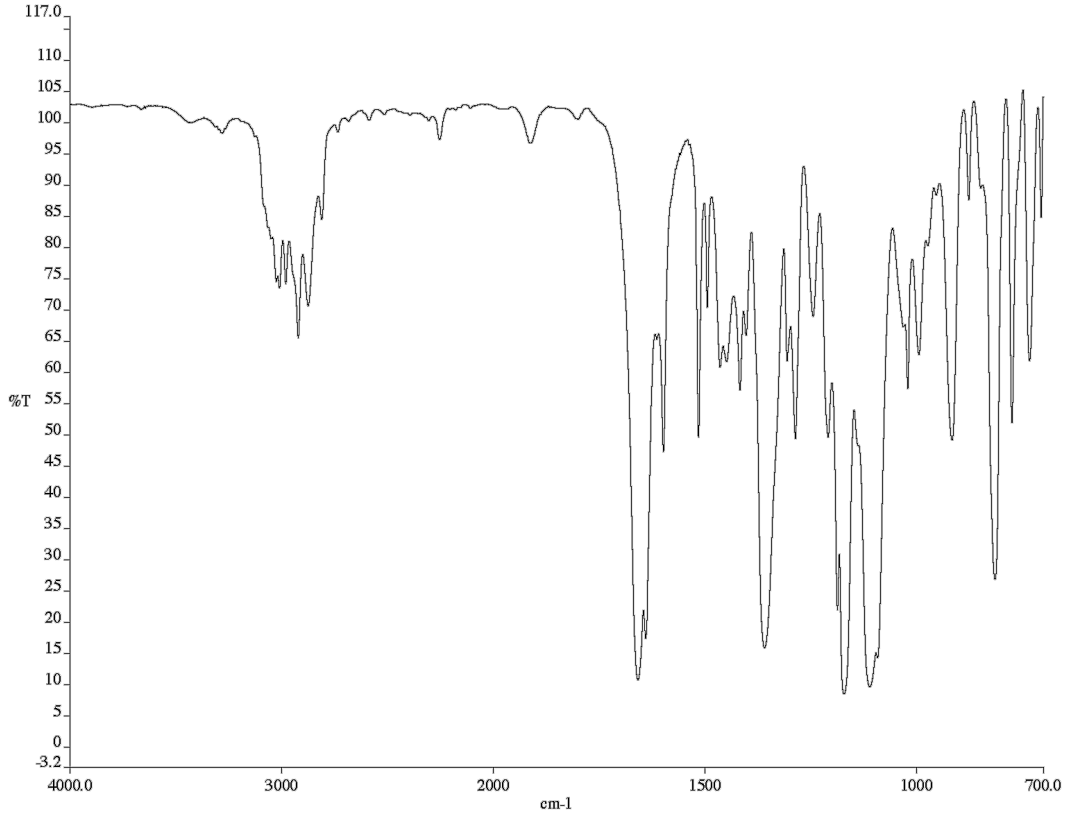


Figure A5.31 Infrared spectrum (thin film/NaCl) of compound **297**.

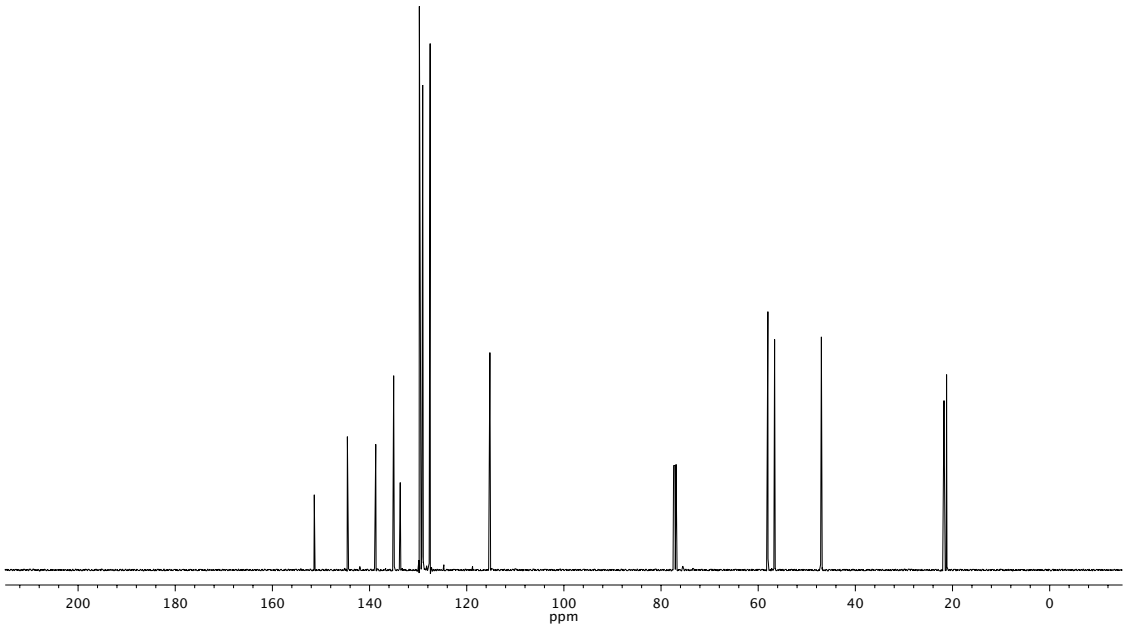


Figure A5.32 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **297**.

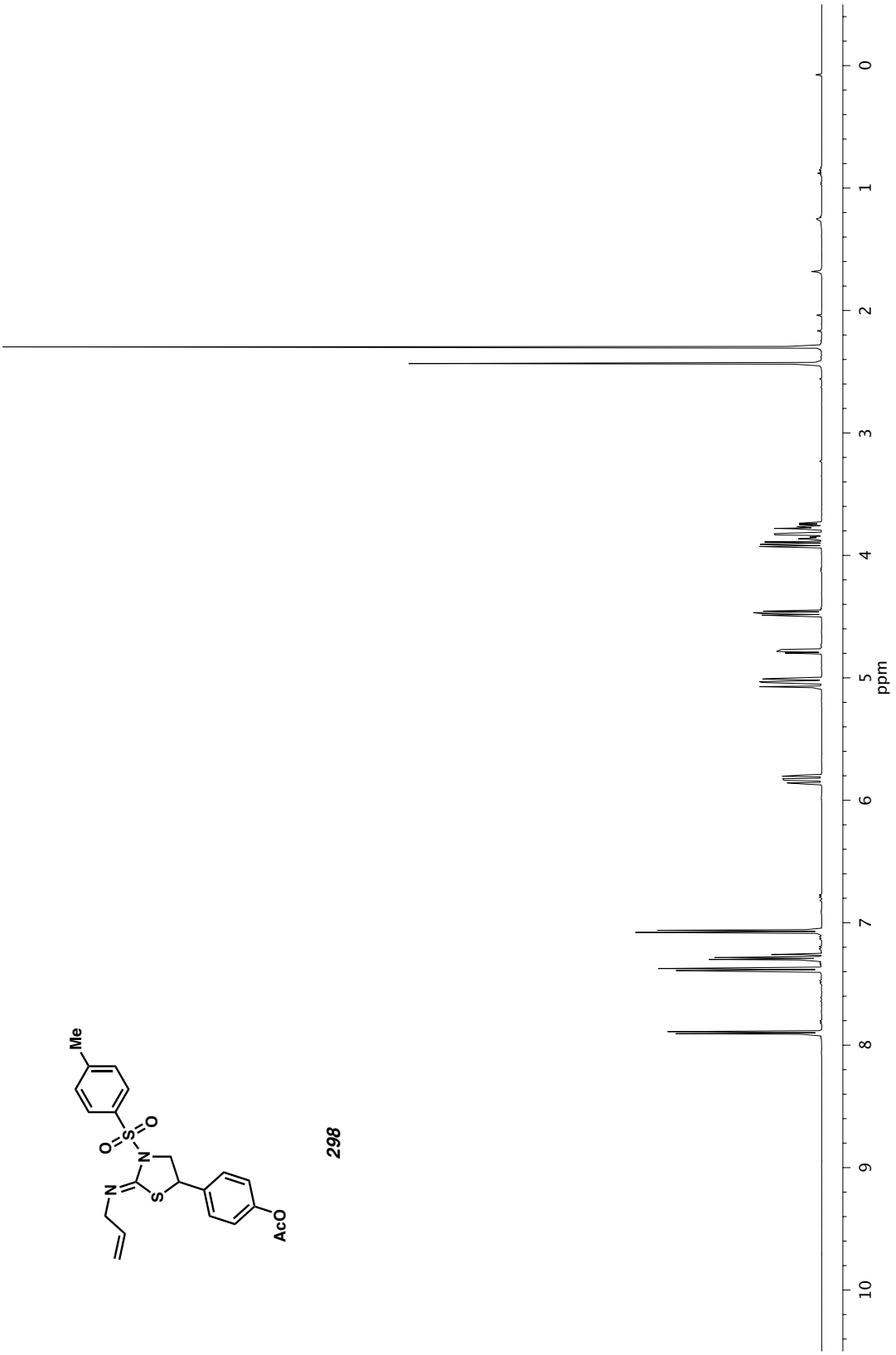


Figure A5.33 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **298**.

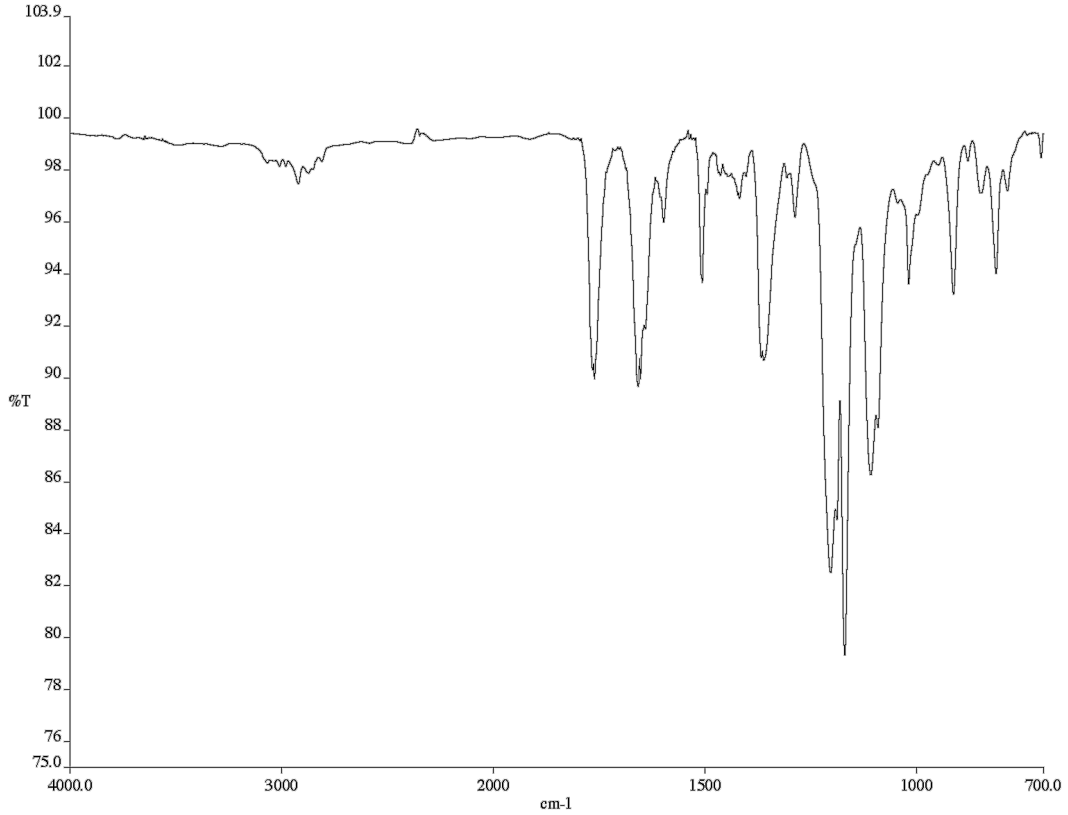


Figure A5.34 Infrared spectrum (thin film/NaCl) of compound **298**.

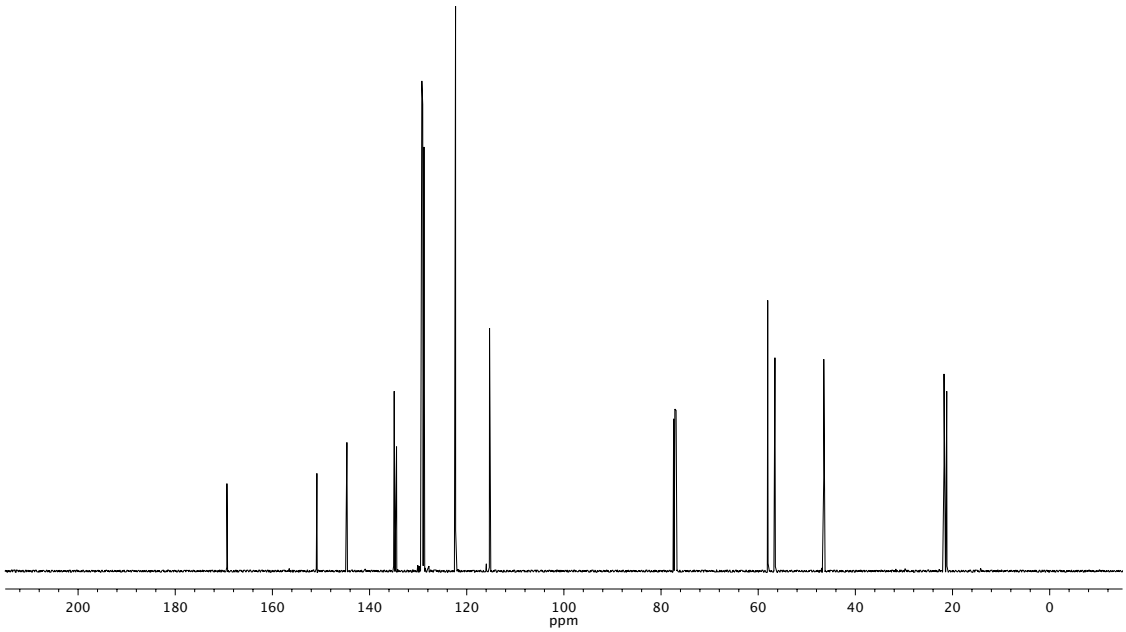


Figure A5.35 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **298**.

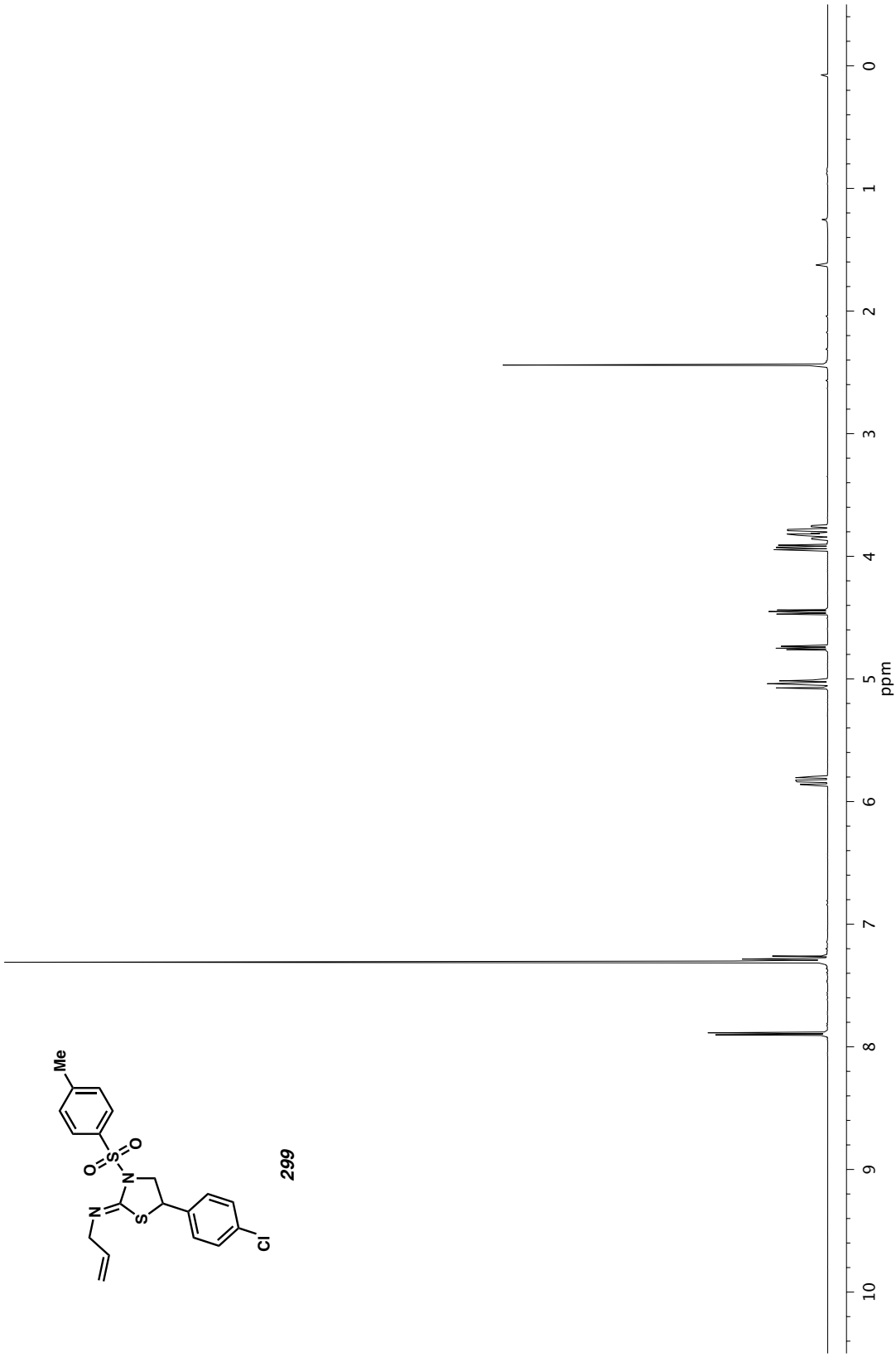


Figure A5.36 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **299**.

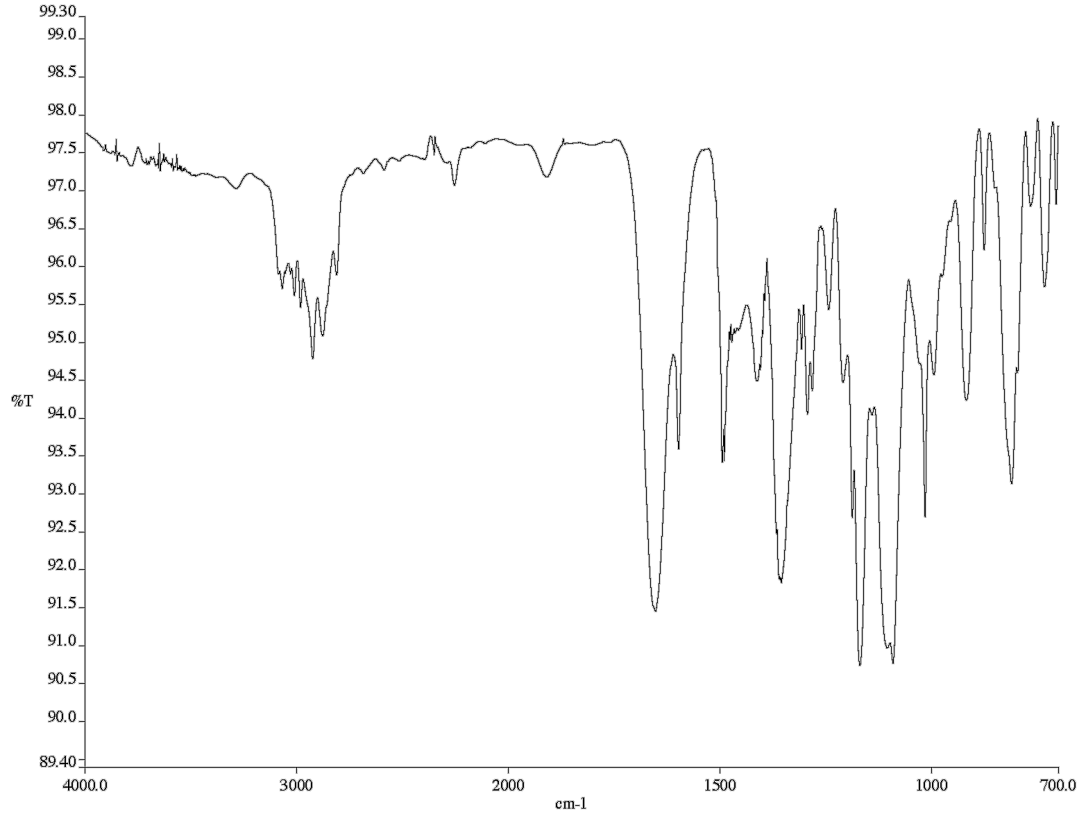


Figure A5.37 Infrared spectrum (thin film/NaCl) of compound **299**.

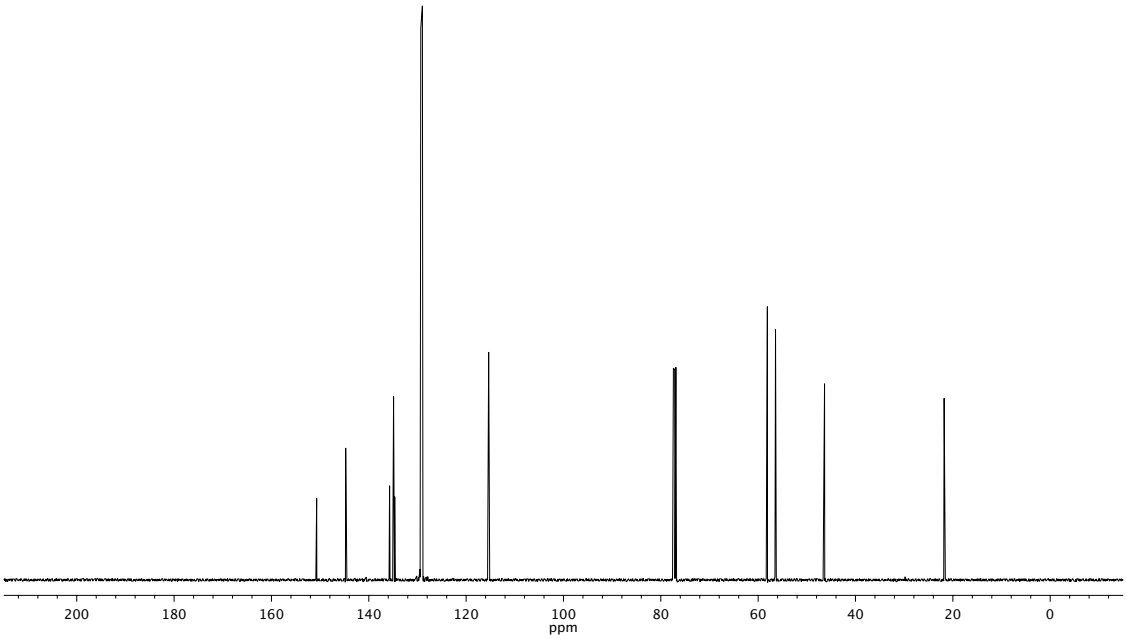


Figure A5.38 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **299**.

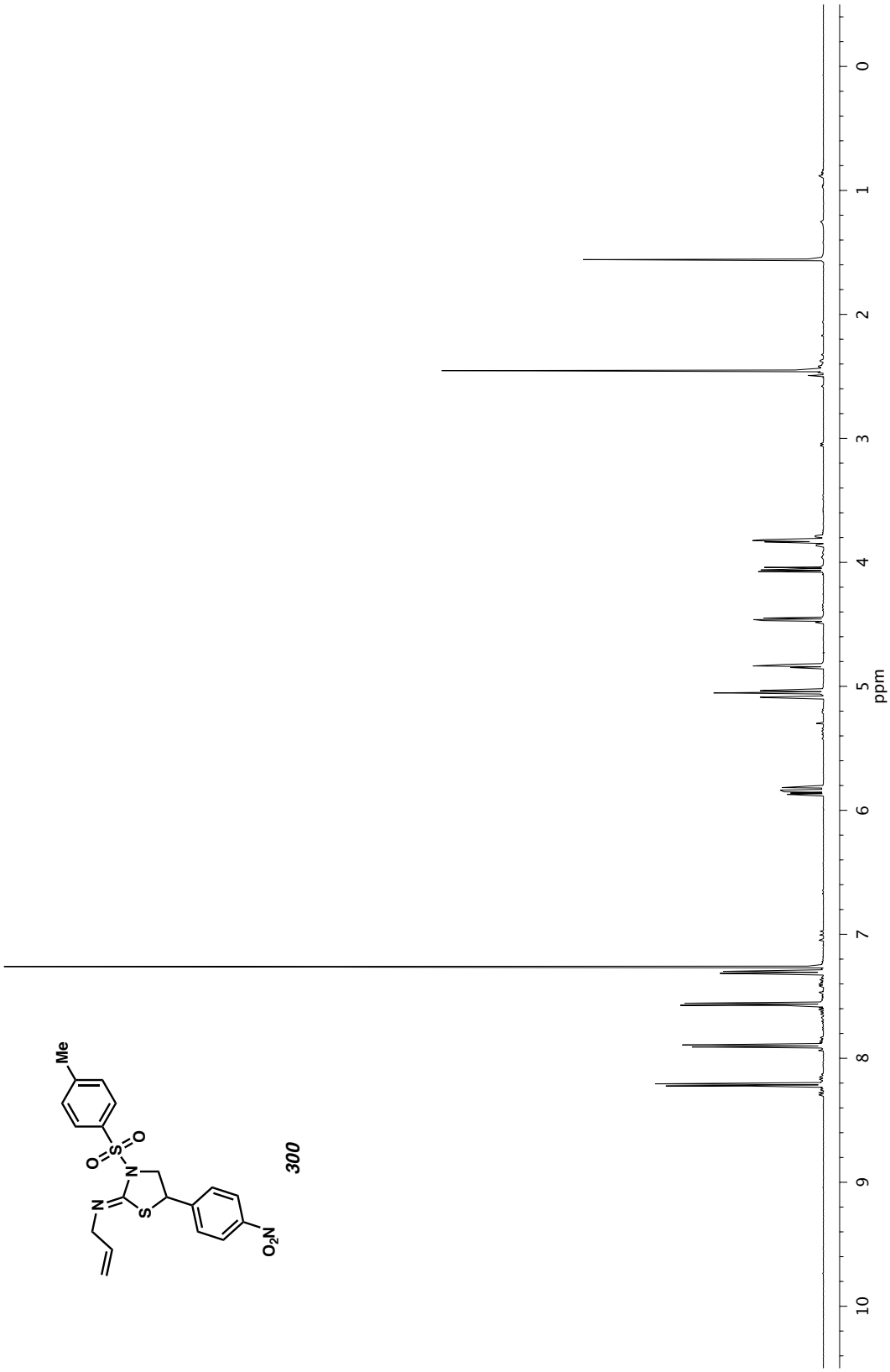


Figure A5.39 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **300**.

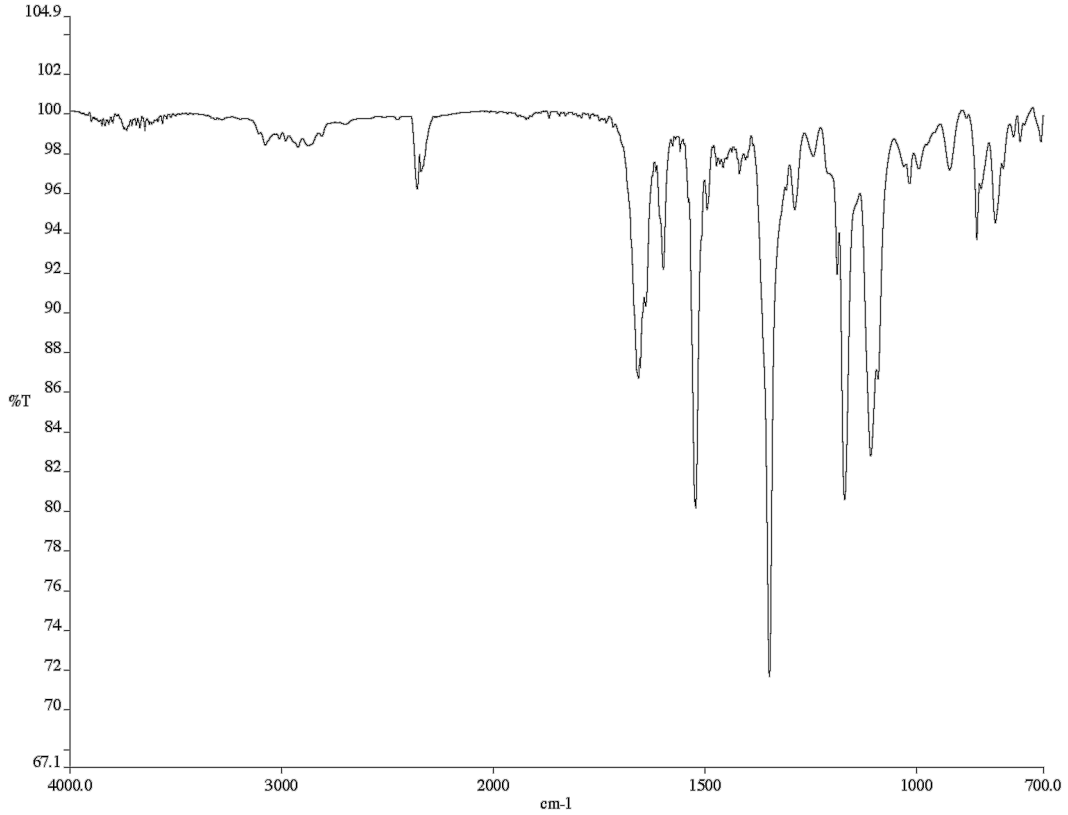


Figure A5.40 Infrared spectrum (thin film/NaCl) of compound **300**.

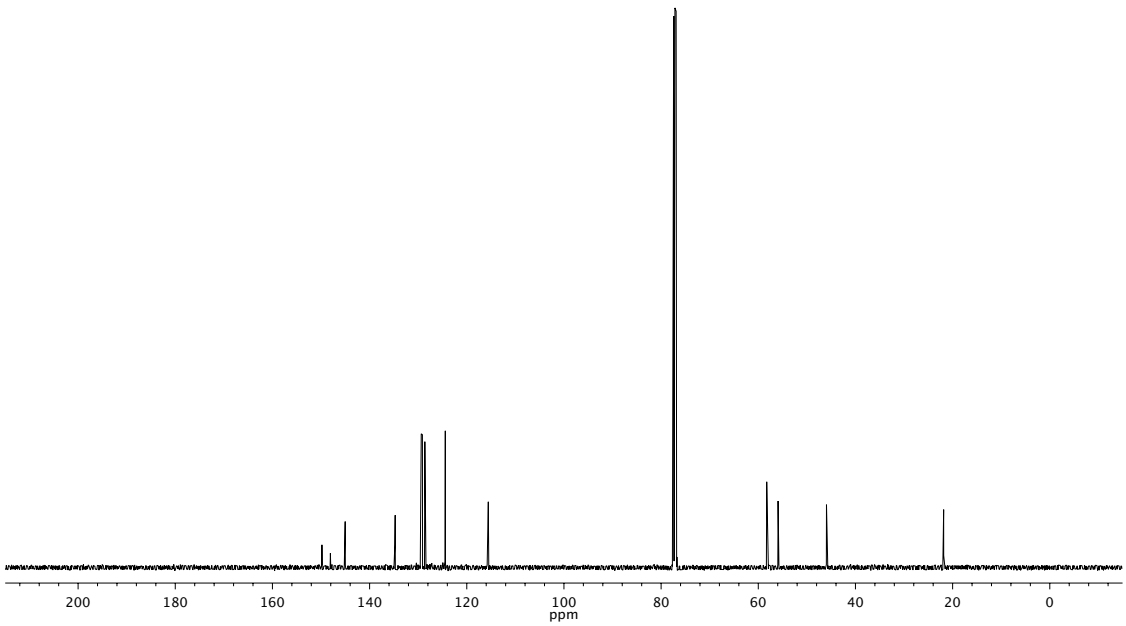


Figure A5.41 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **300**.

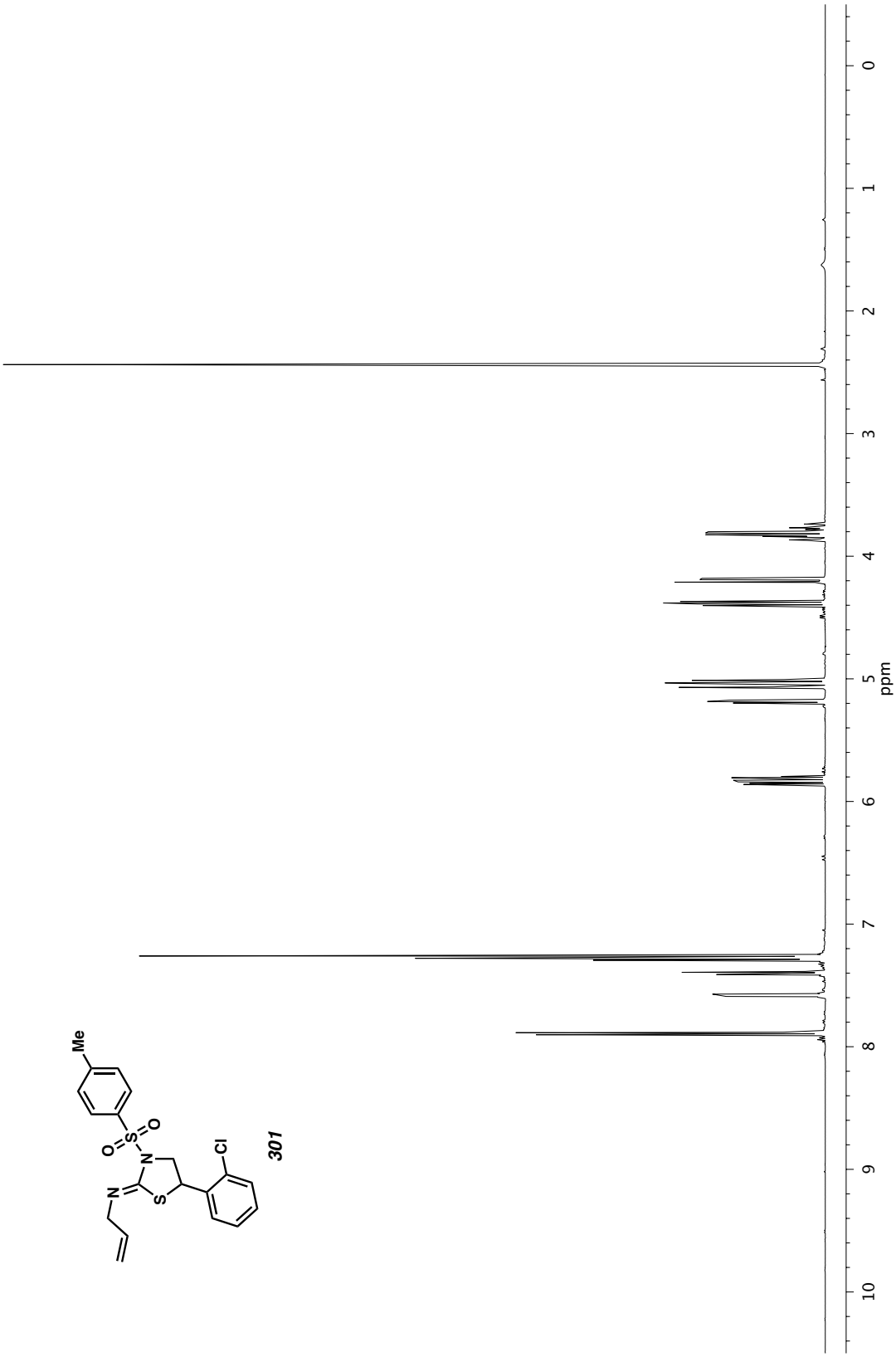


Figure A5.42 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **301**.

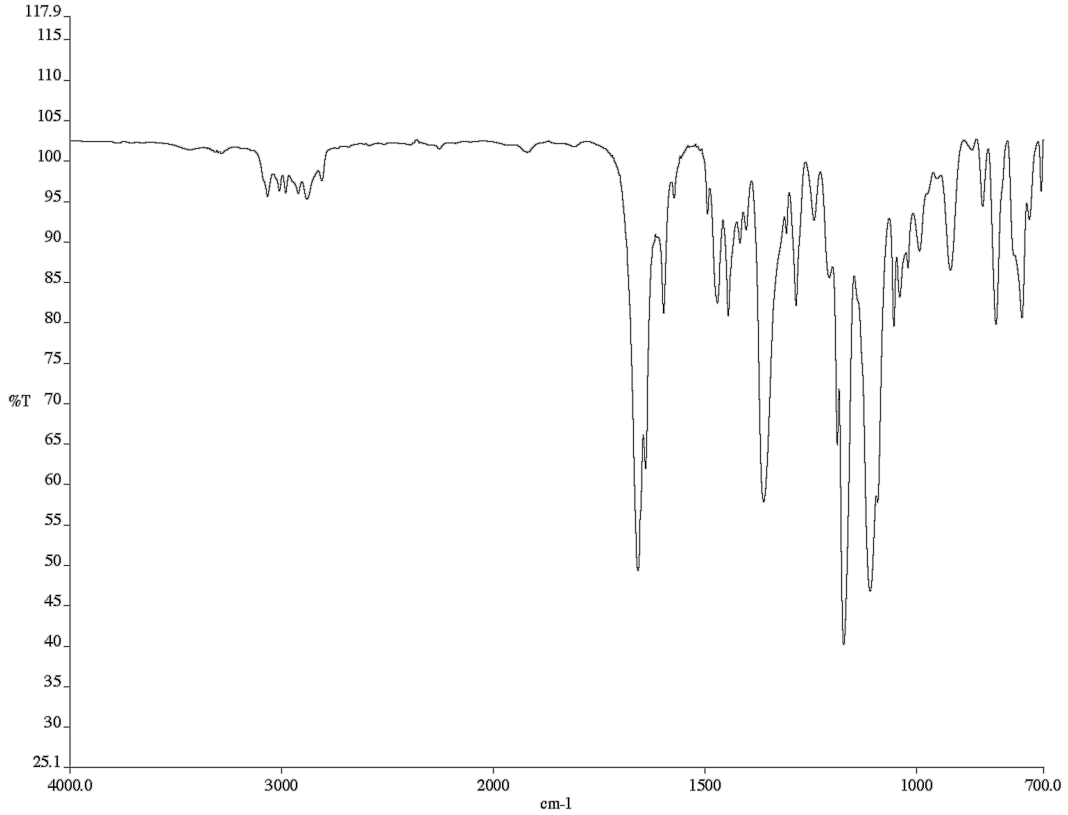


Figure A5.43 Infrared spectrum (thin film/NaCl) of compound **301**.

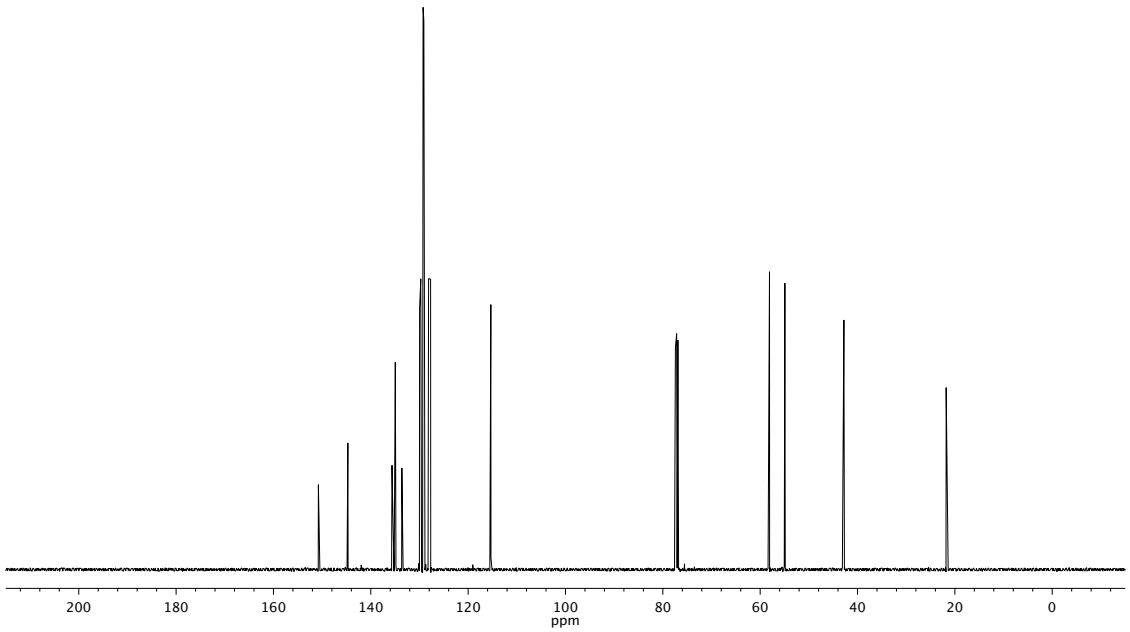


Figure A5.44 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **301**.

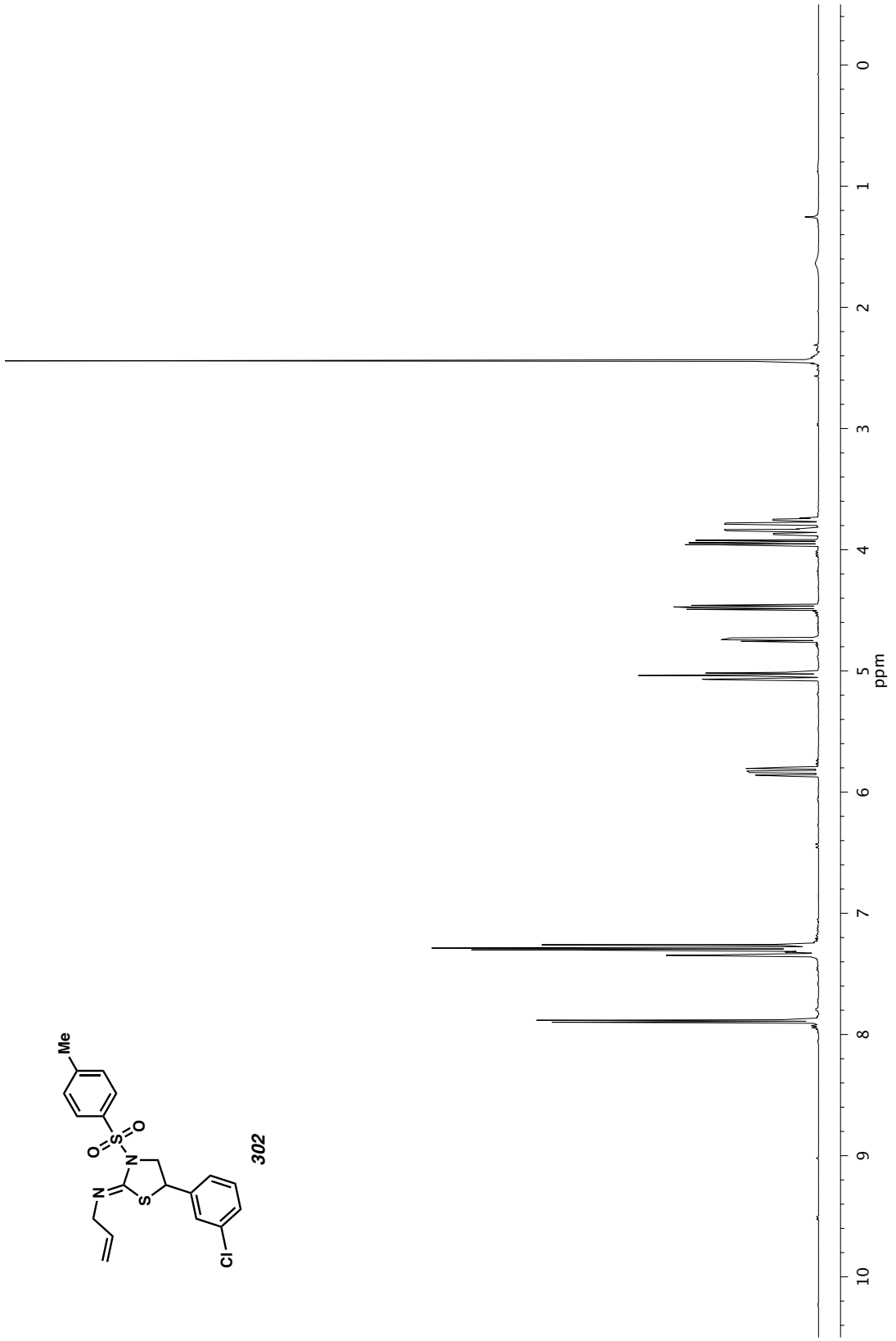


Figure A5.45 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **302**.

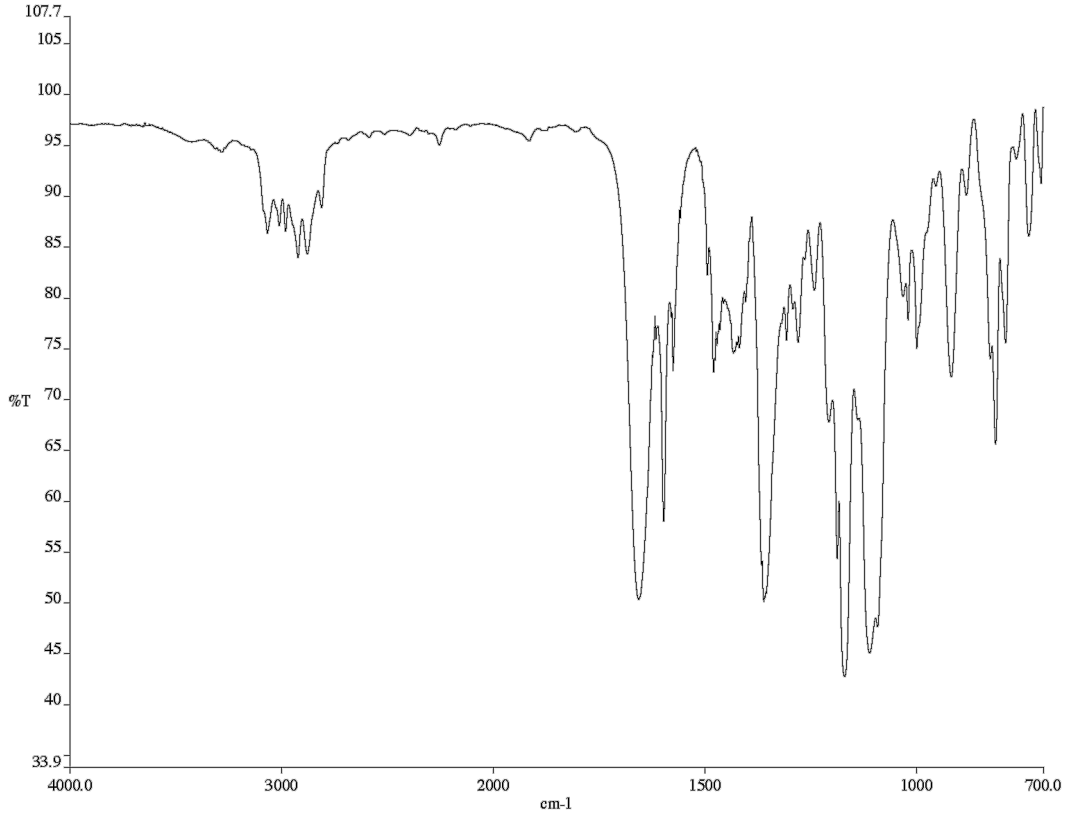


Figure A5.46 Infrared spectrum (thin film/NaCl) of compound **302**.

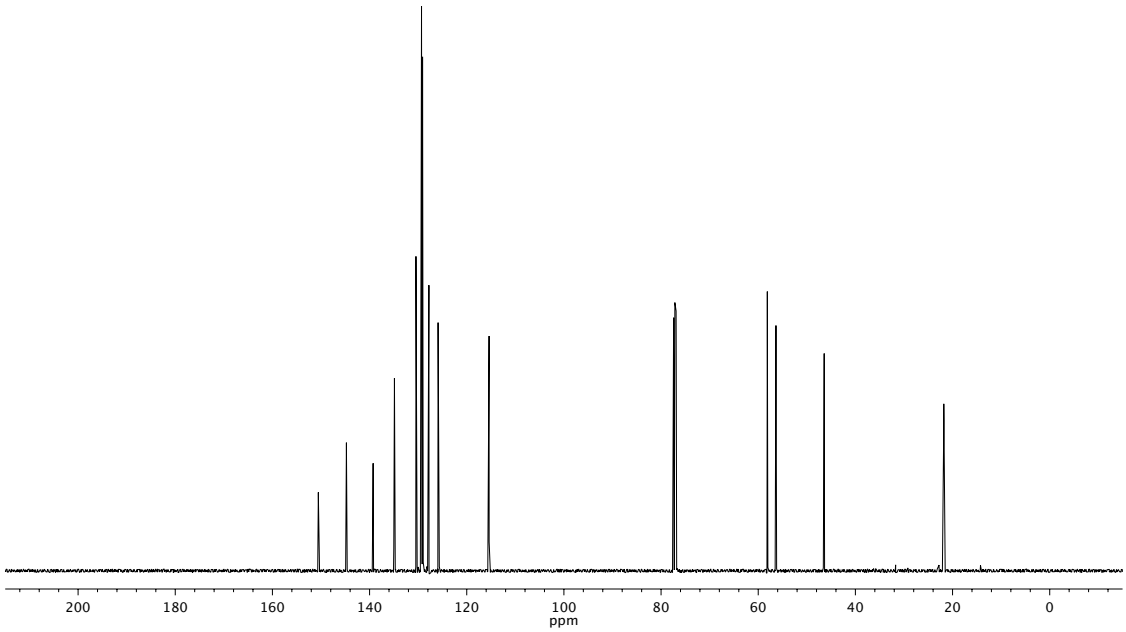


Figure A5.47 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **302**.

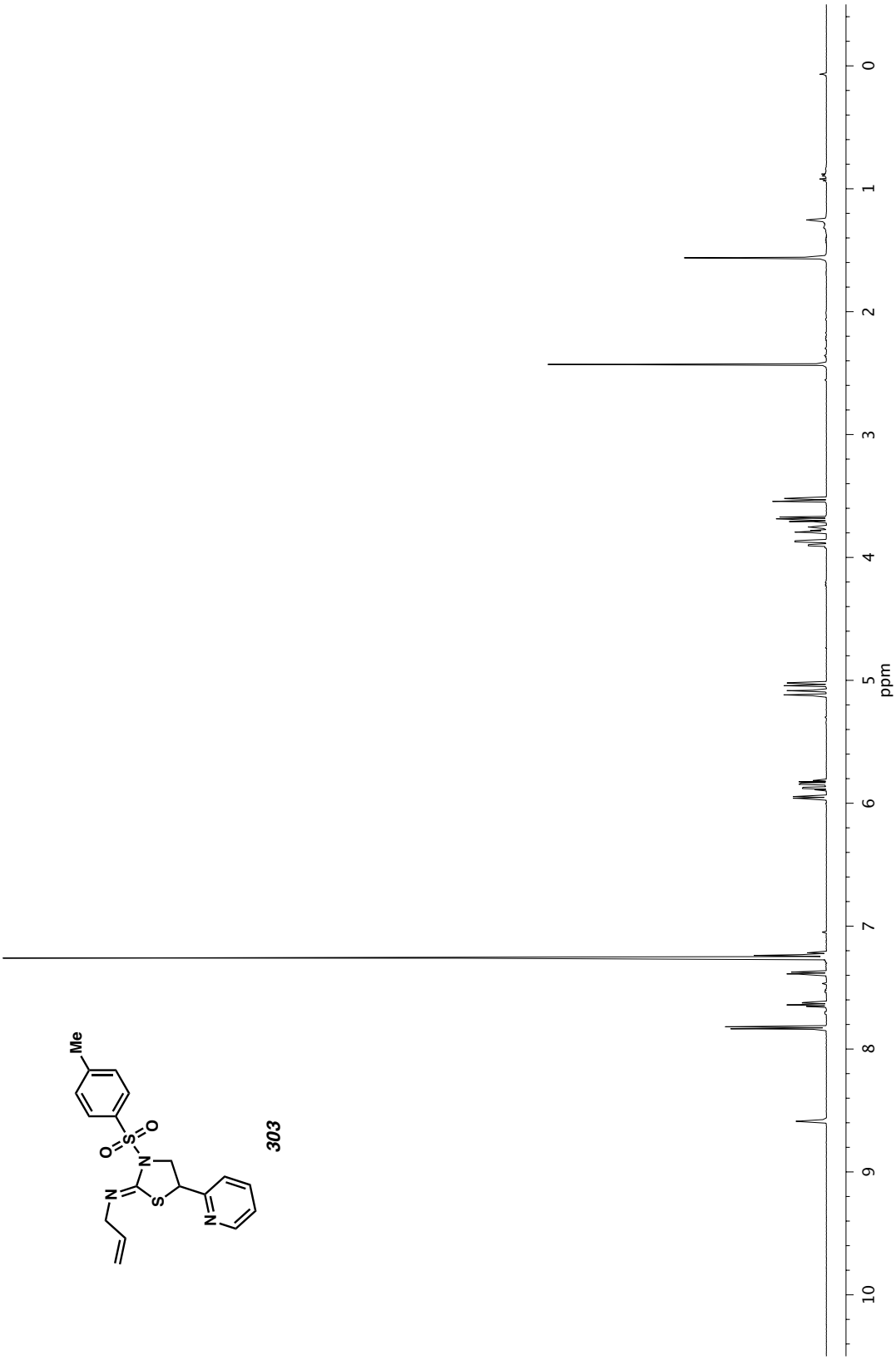


Figure A5.48 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **303**.

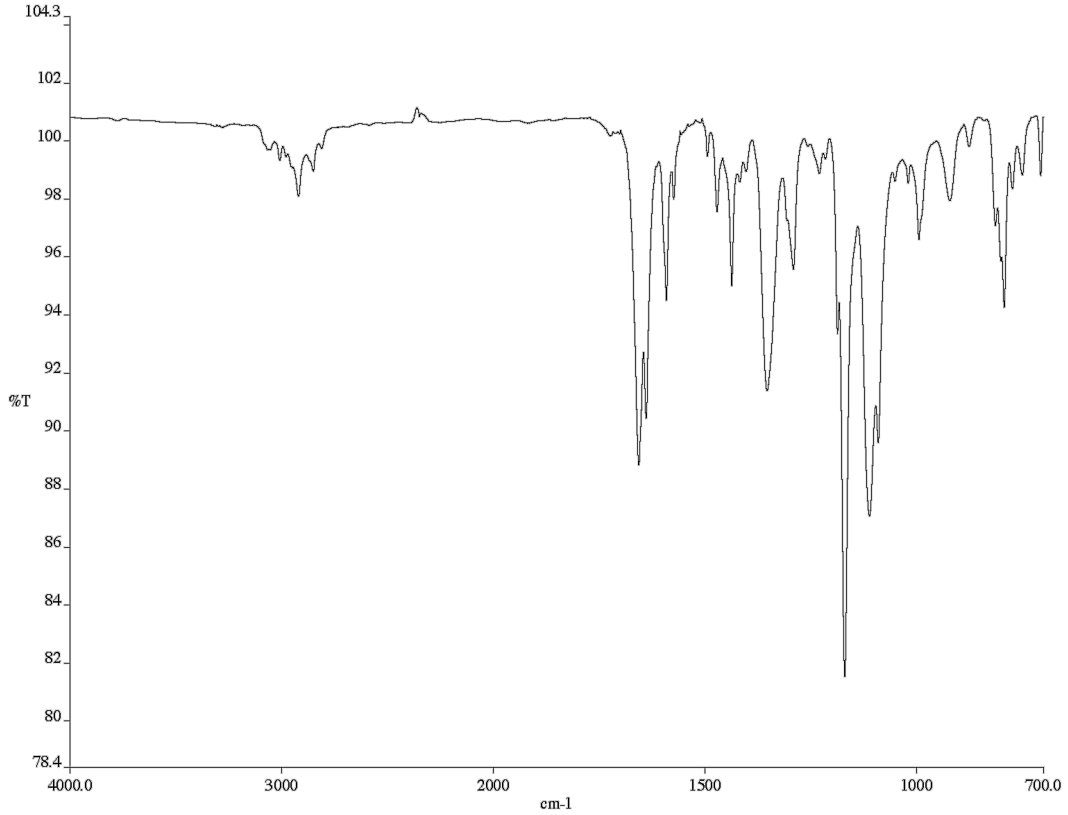


Figure A5.49 Infrared spectrum (thin film/NaCl) of compound **303**.

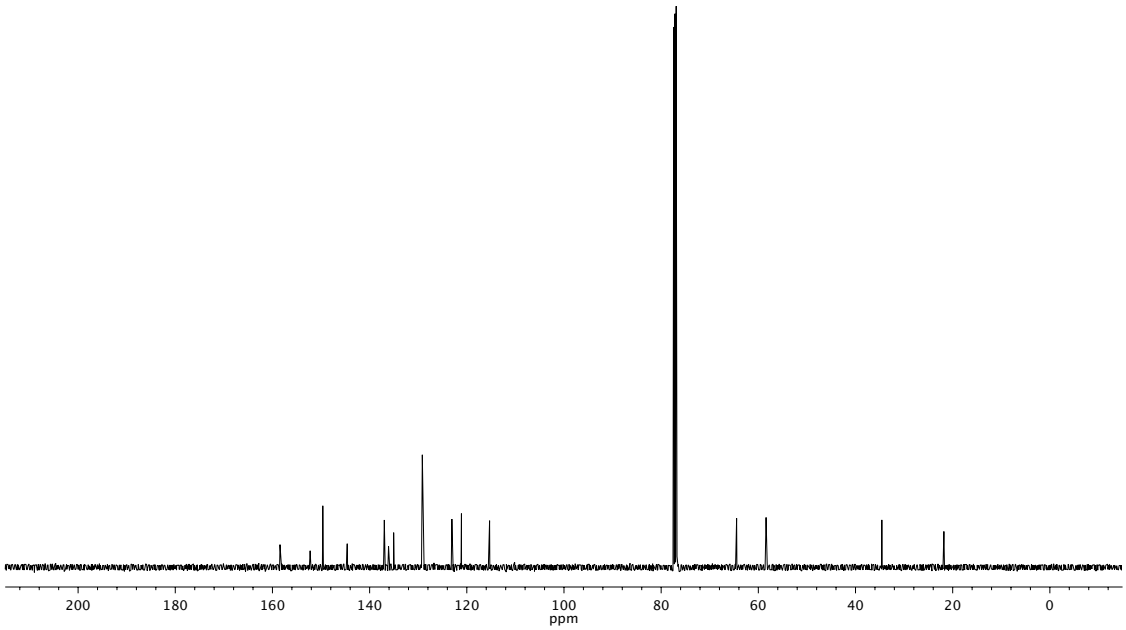


Figure A5.50 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **303**.

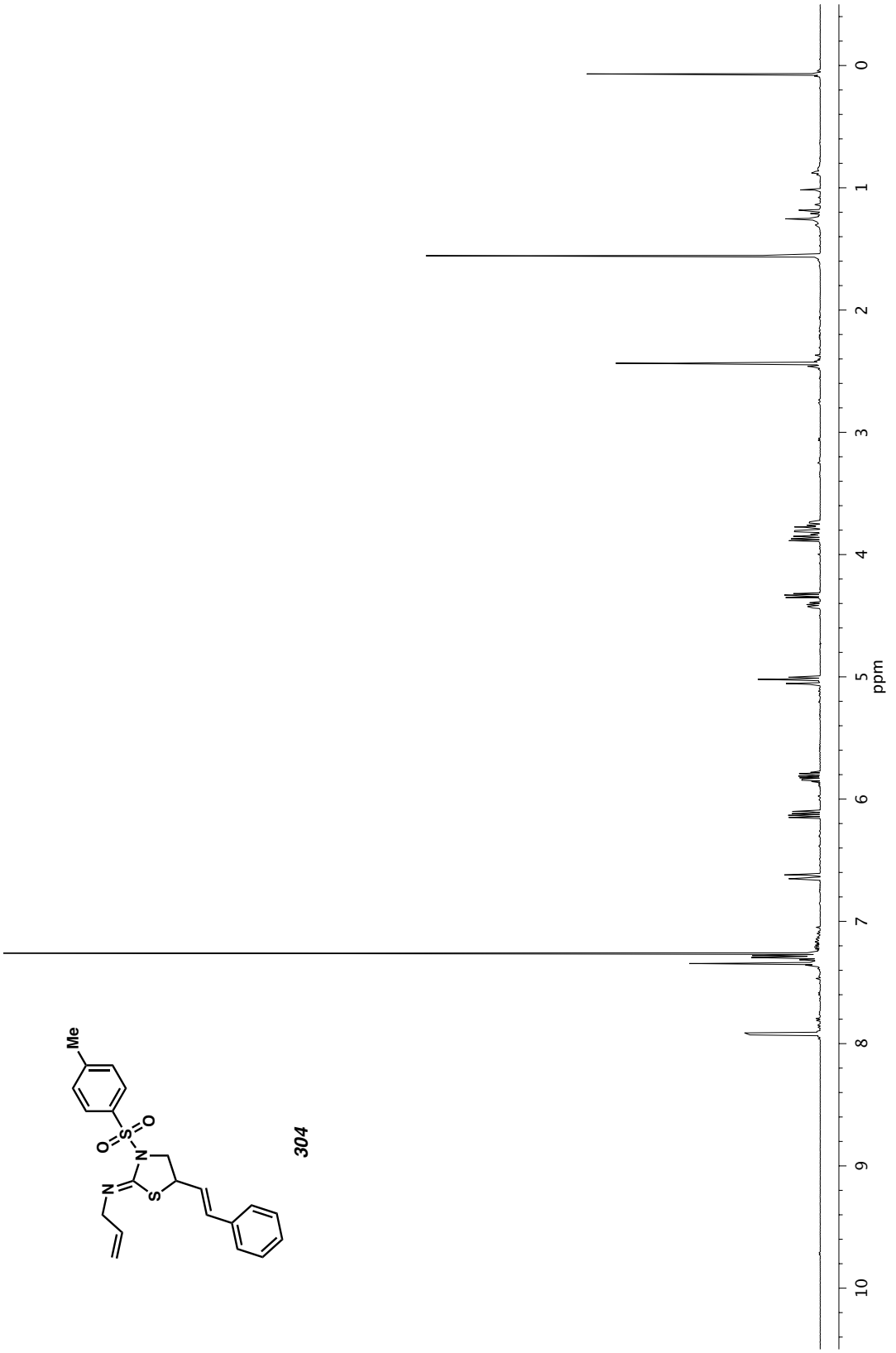


Figure A5.51 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **304**.

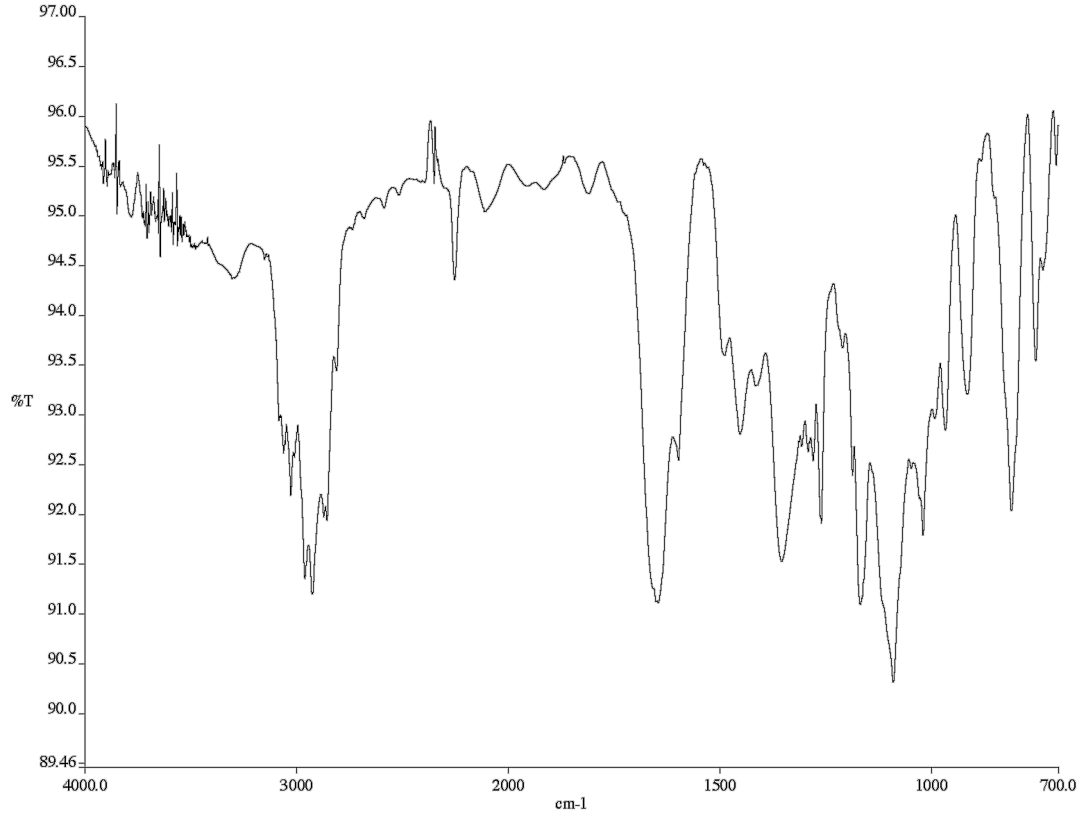


Figure A5.52 Infrared spectrum (thin film/NaCl) of compound **304**.

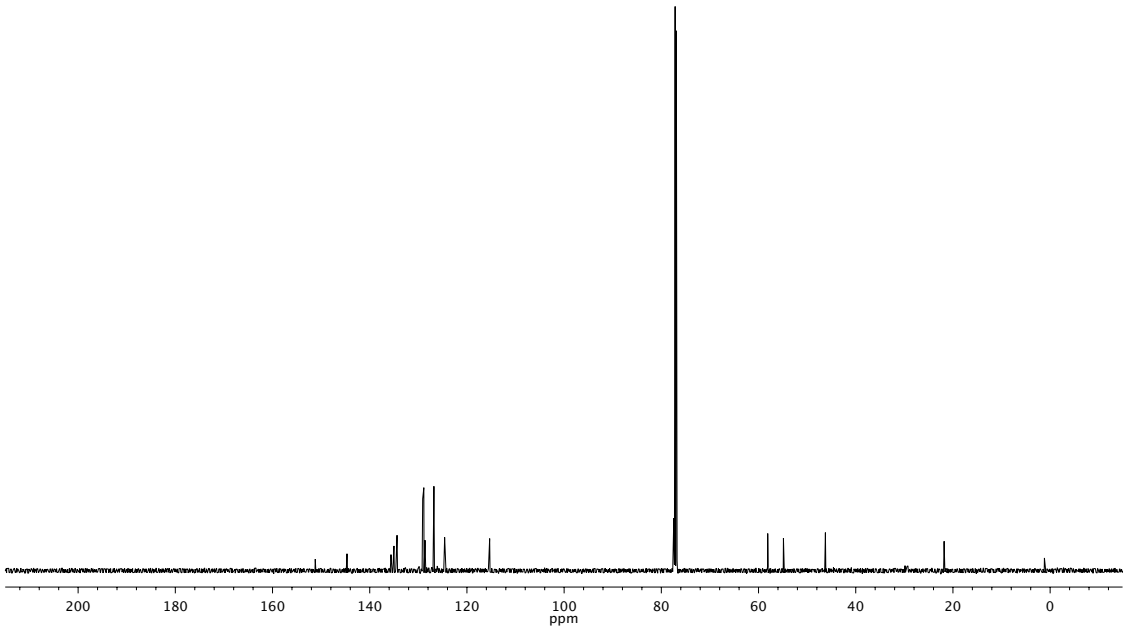


Figure A5.53 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **304**.

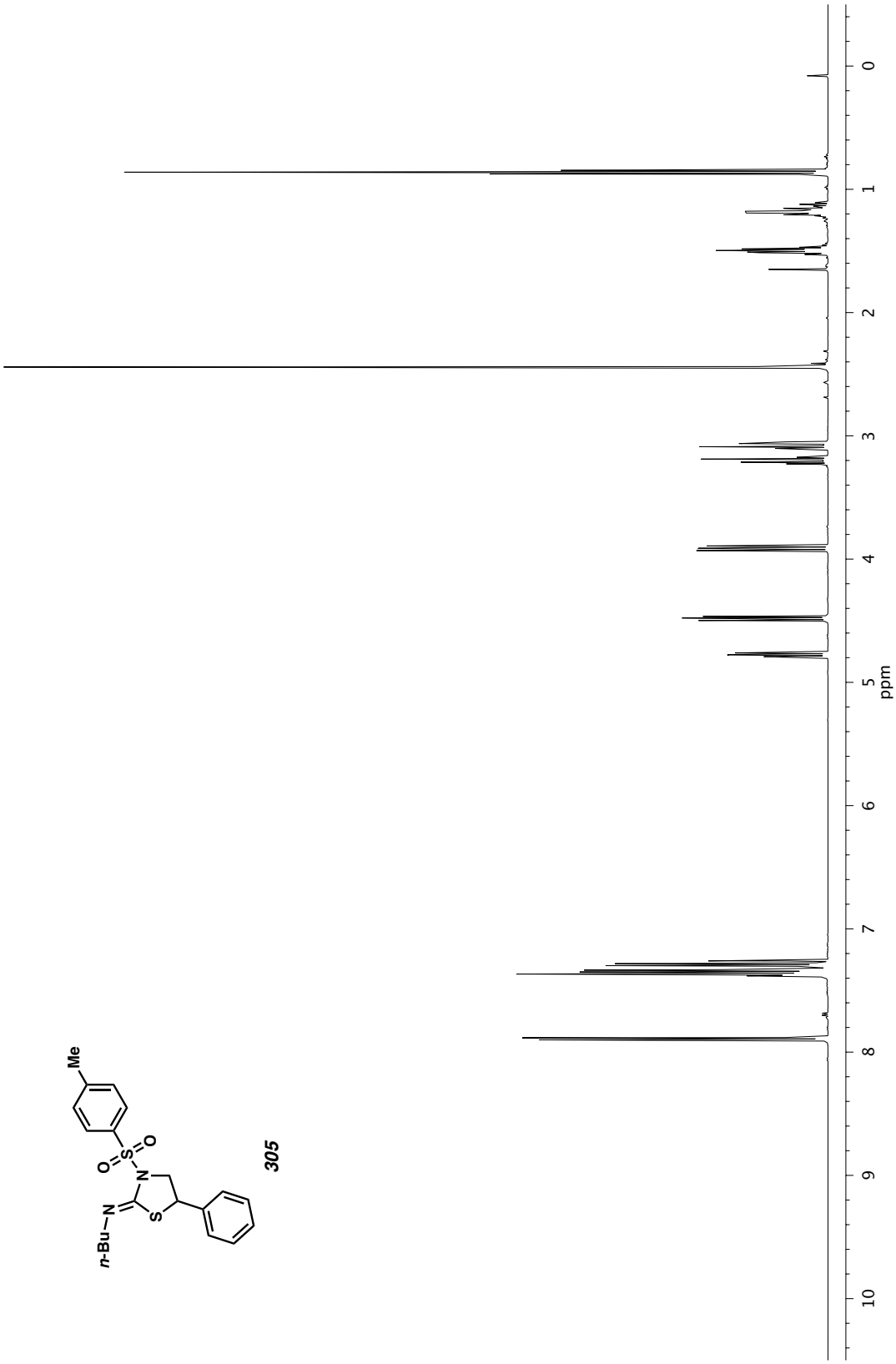


Figure A5.54 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **305**.

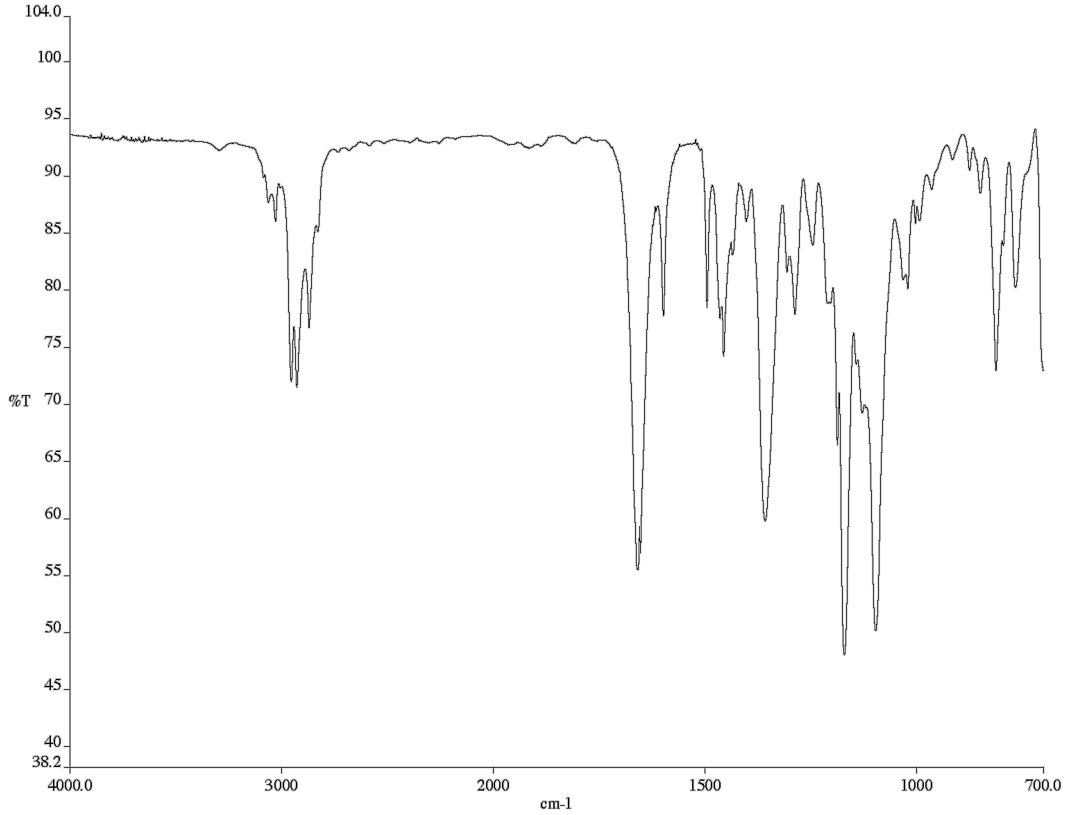


Figure A5.55 Infrared spectrum (thin film/NaCl) of compound **305**.

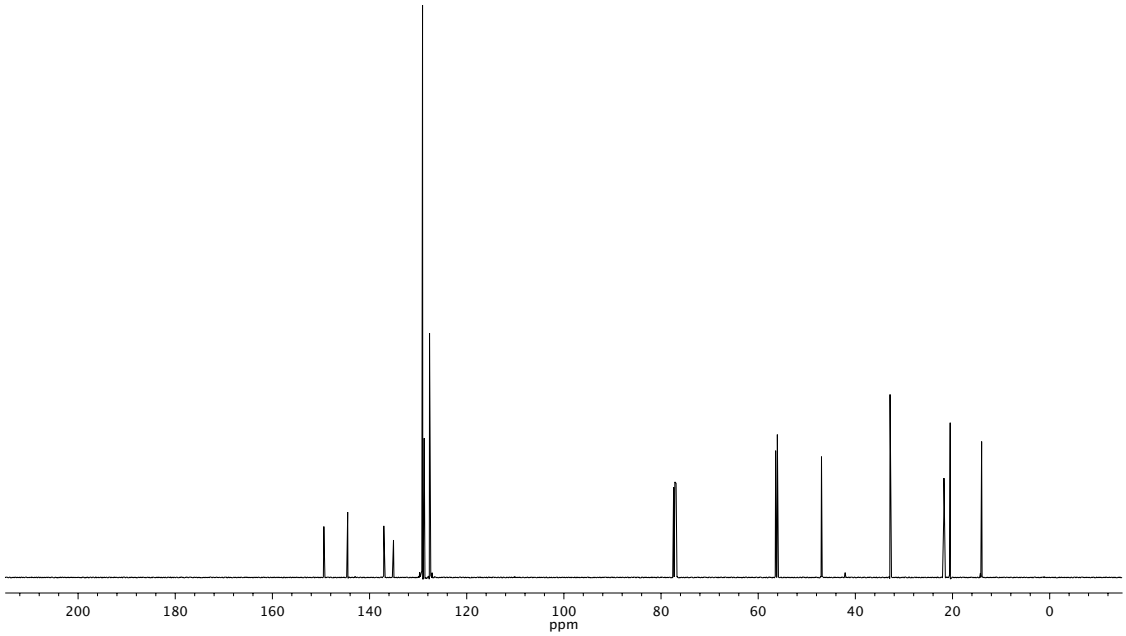


Figure A5.56 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **305**.

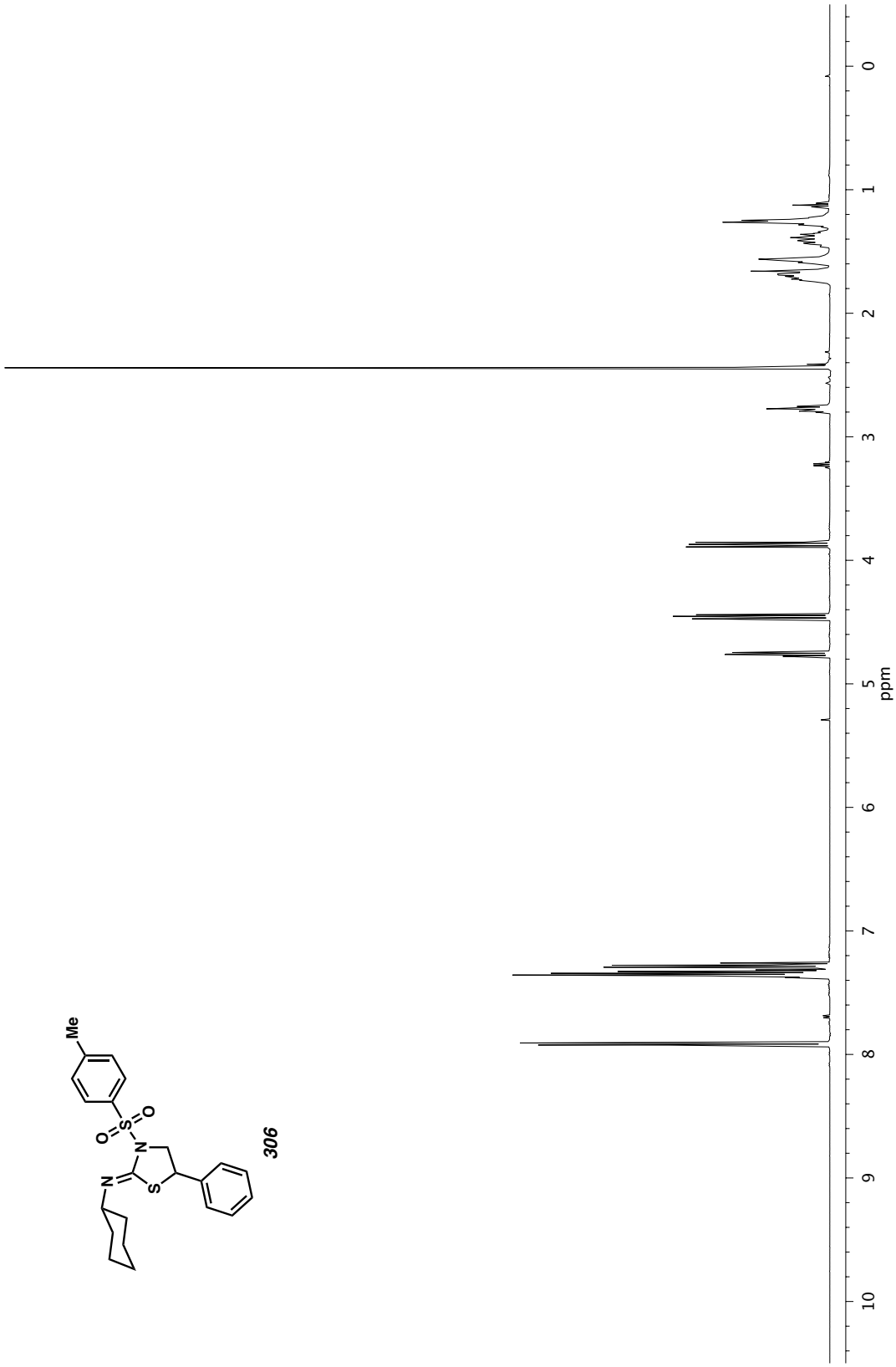


Figure A5.57 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **306**.

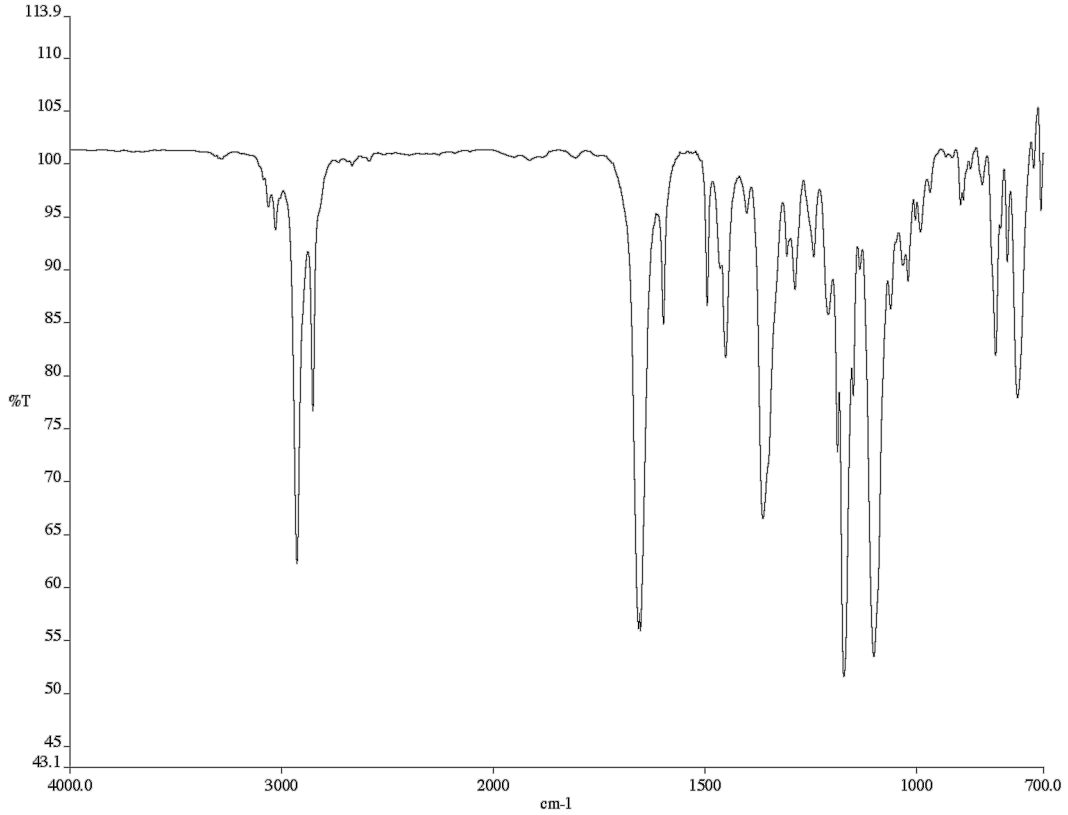


Figure A5.58 Infrared spectrum (thin film/NaCl) of compound **306**.

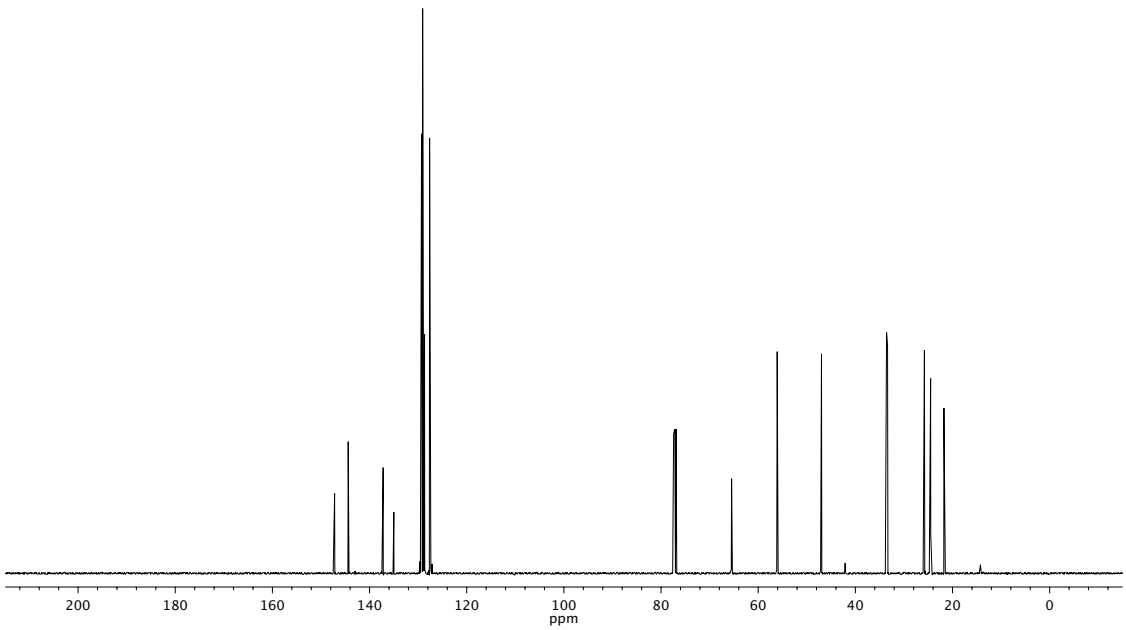


Figure A5.59 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **306**.

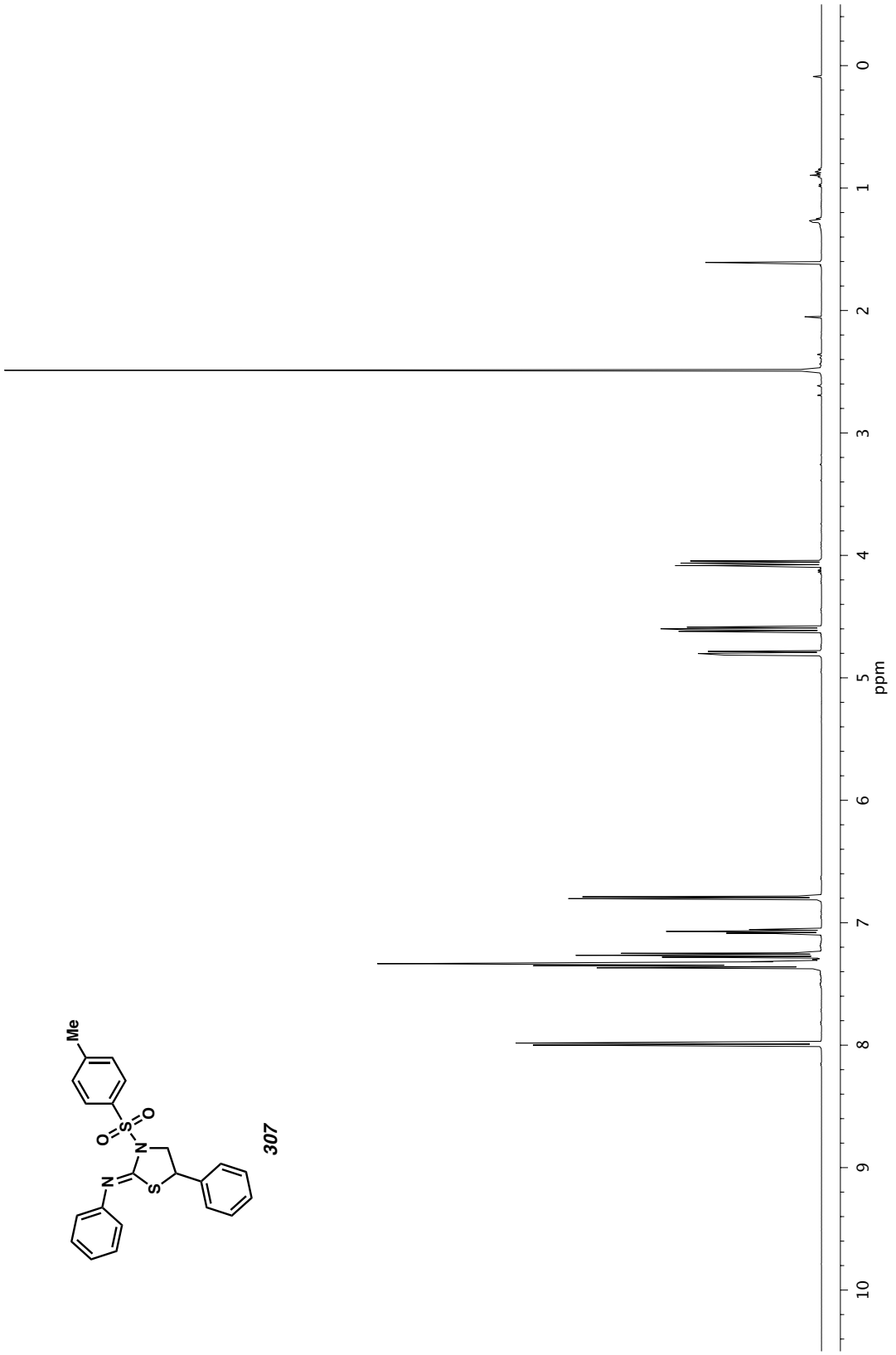


Figure A5.60 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **307**.

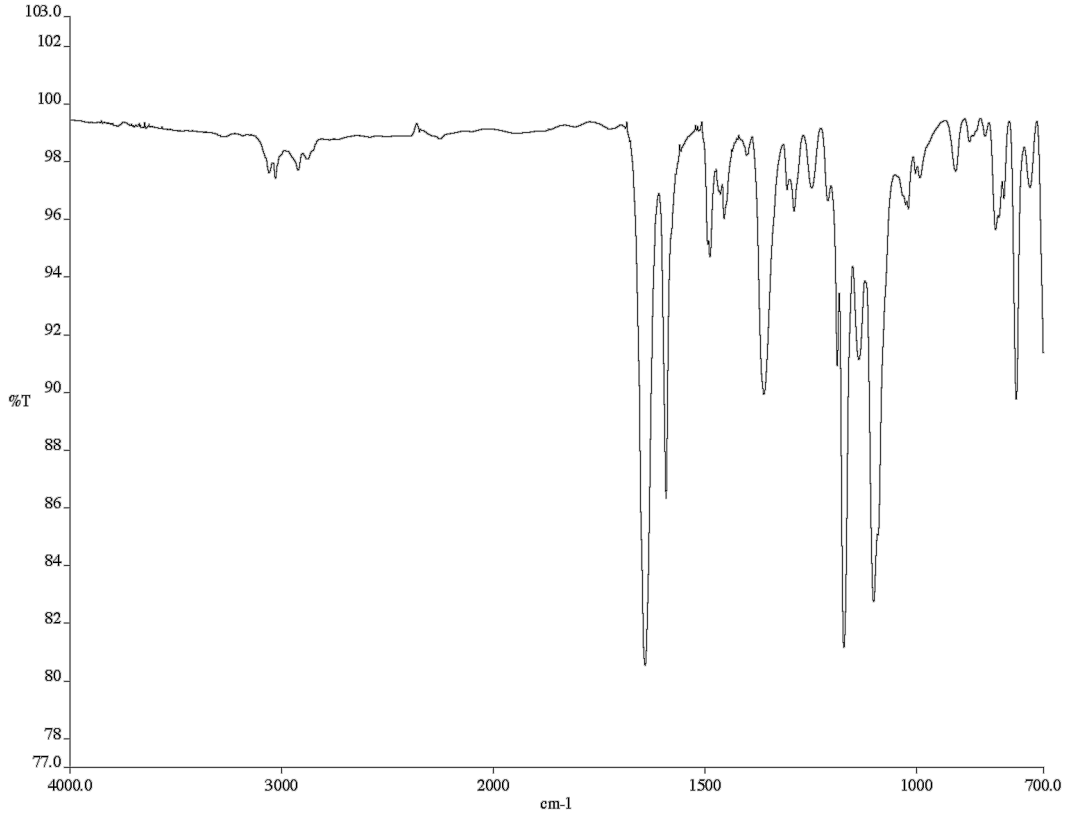


Figure A5.61 Infrared spectrum (thin film/NaCl) of compound **307**.

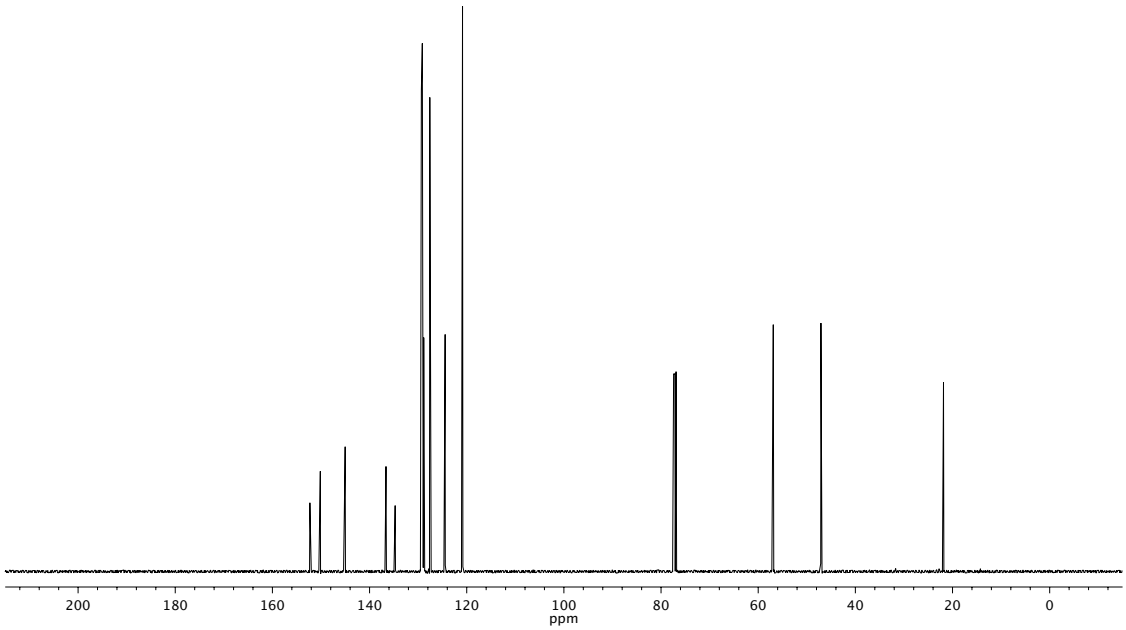


Figure A5.62 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **307**.

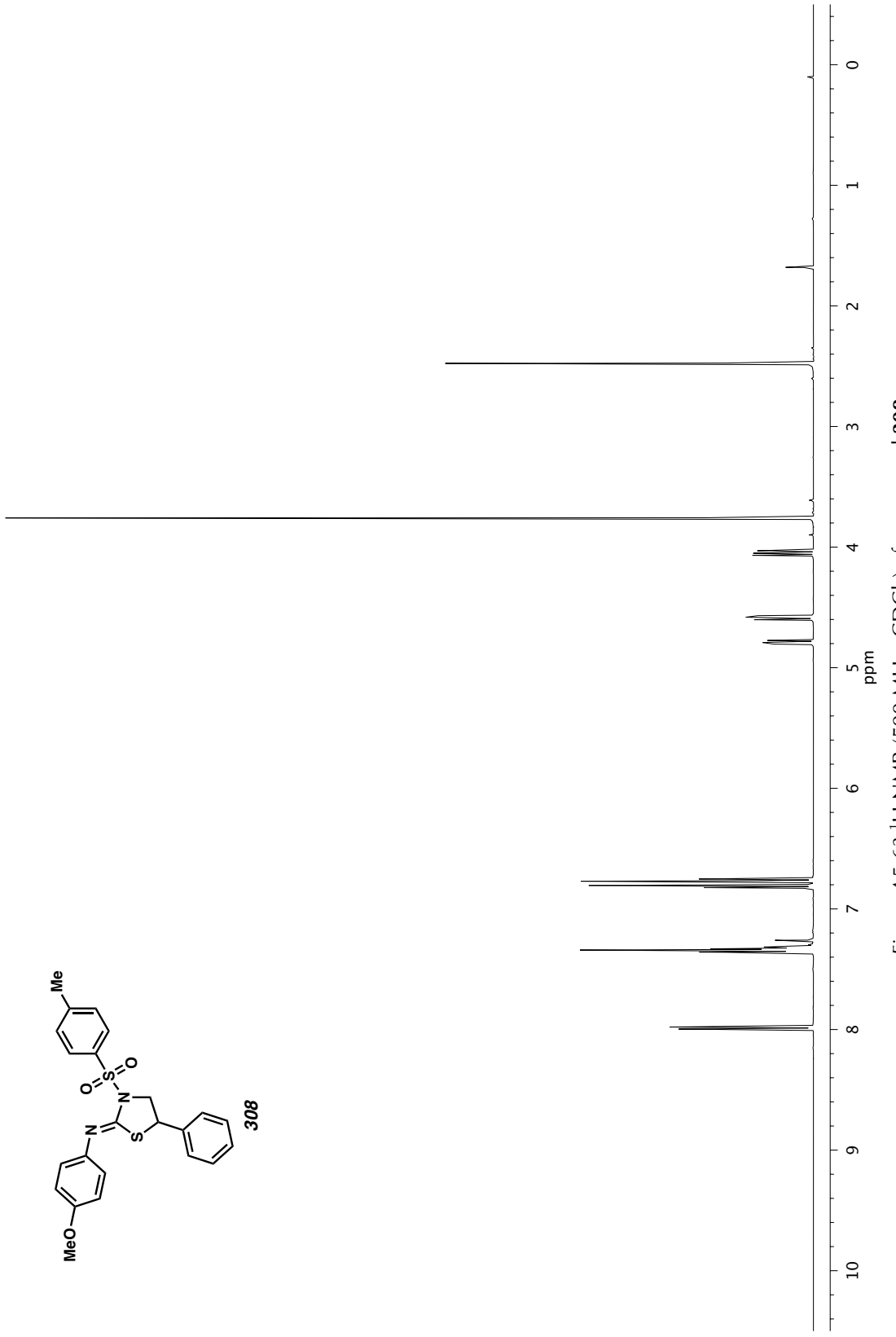


Figure A5.63 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **308**.

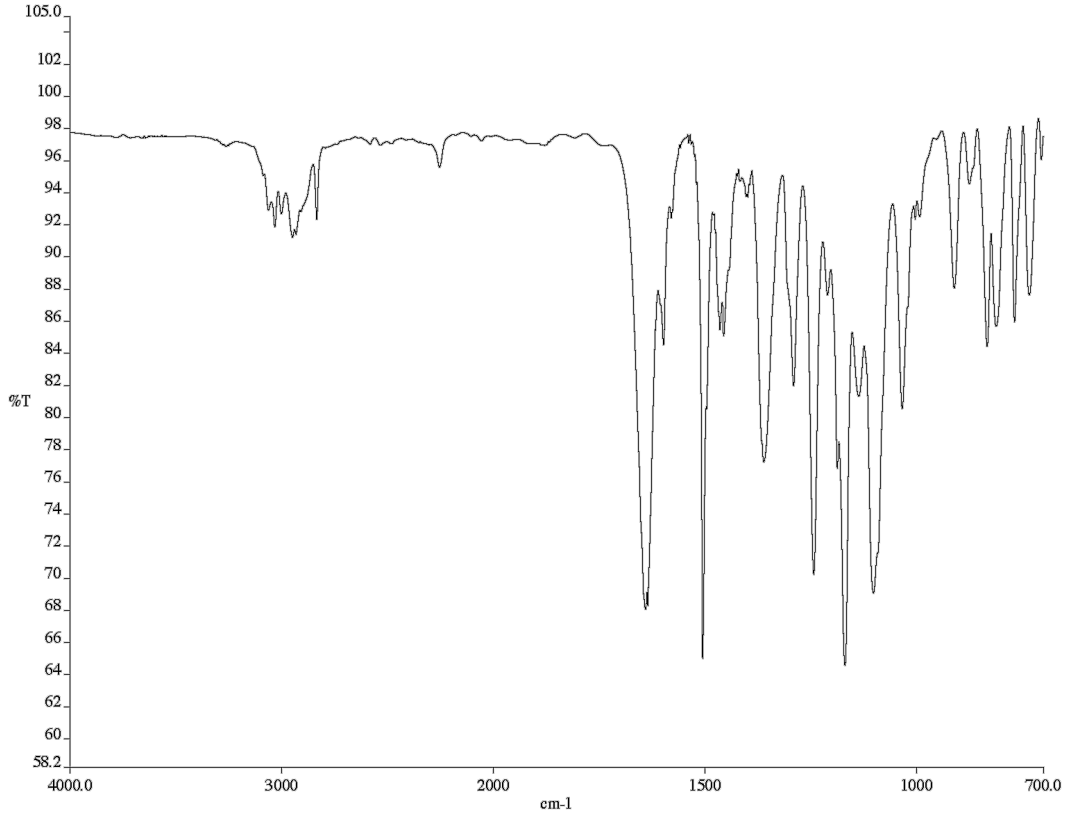


Figure A5.64 Infrared spectrum (thin film/NaCl) of compound **308**.

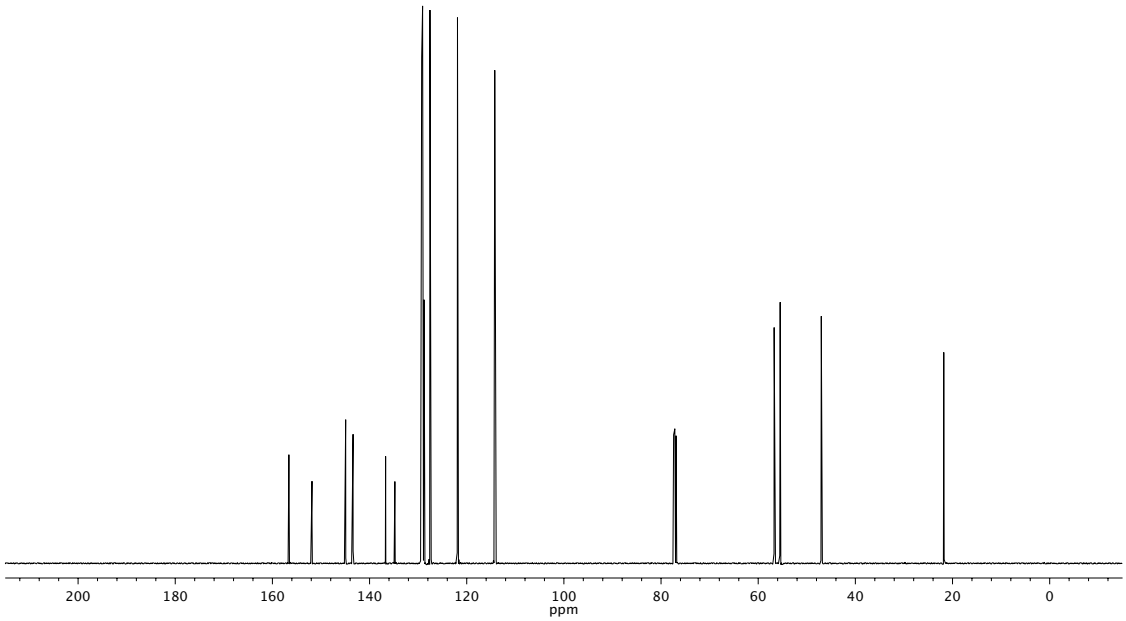


Figure A5.65 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **308**.

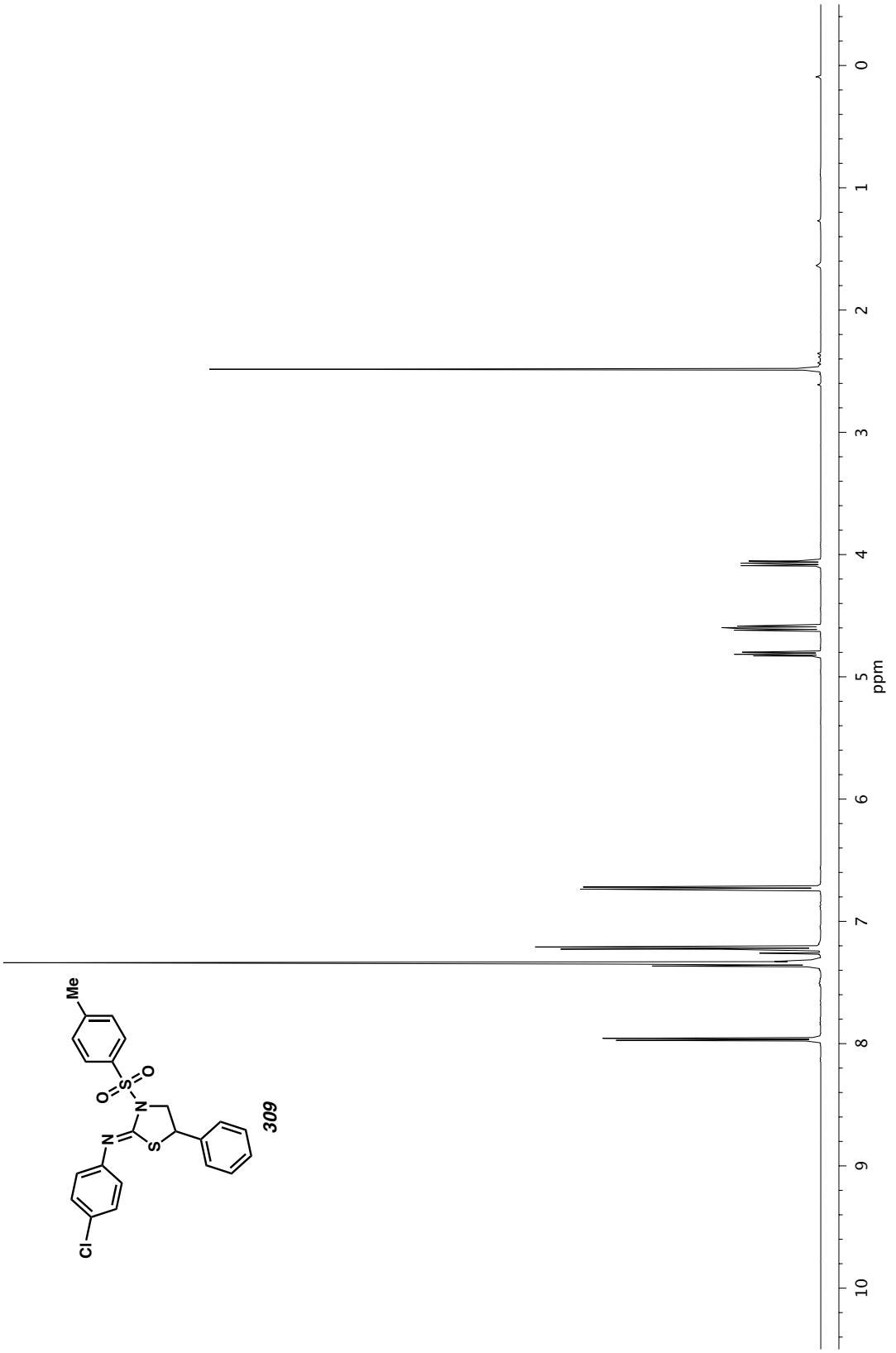


Figure A5.66 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **309**.

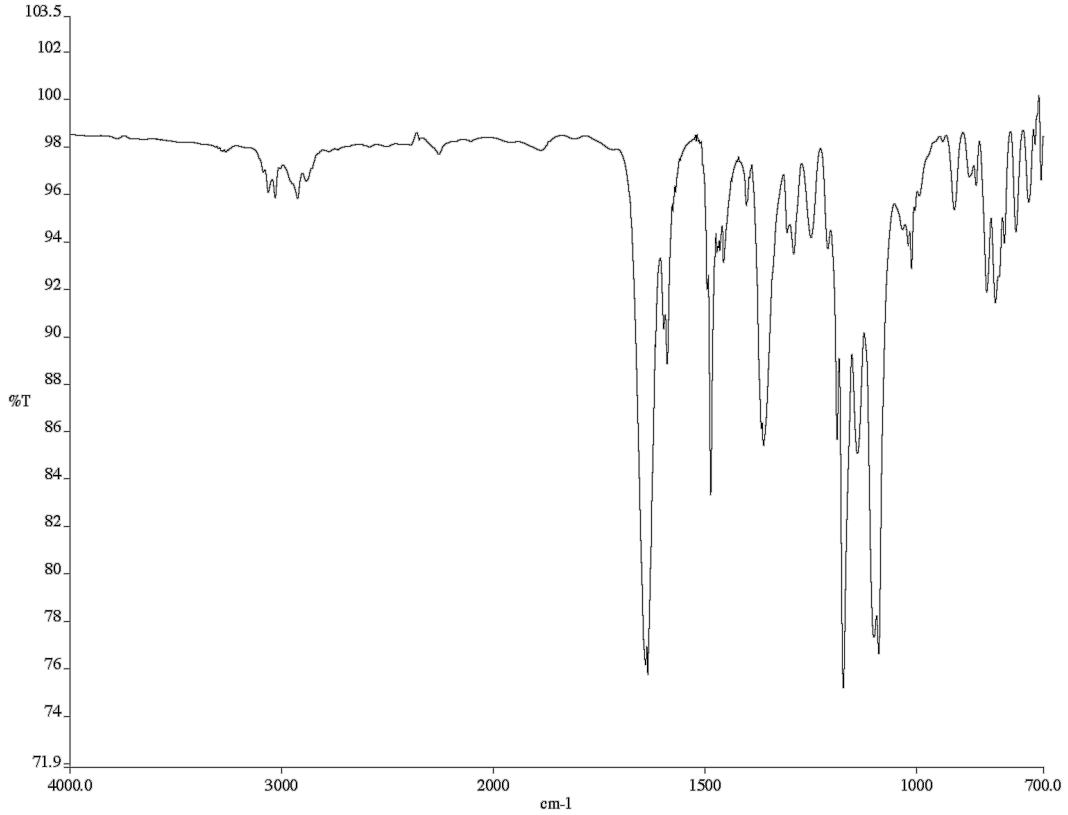


Figure A5.67 Infrared spectrum (thin film/NaCl) of compound **309**.

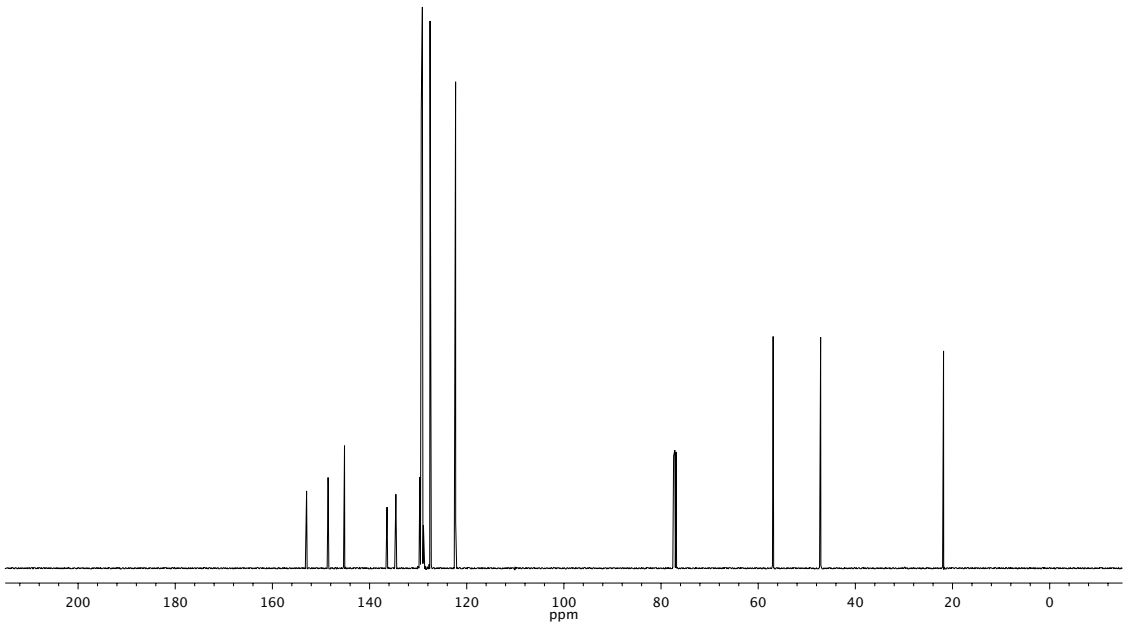


Figure A5.68 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **309**.

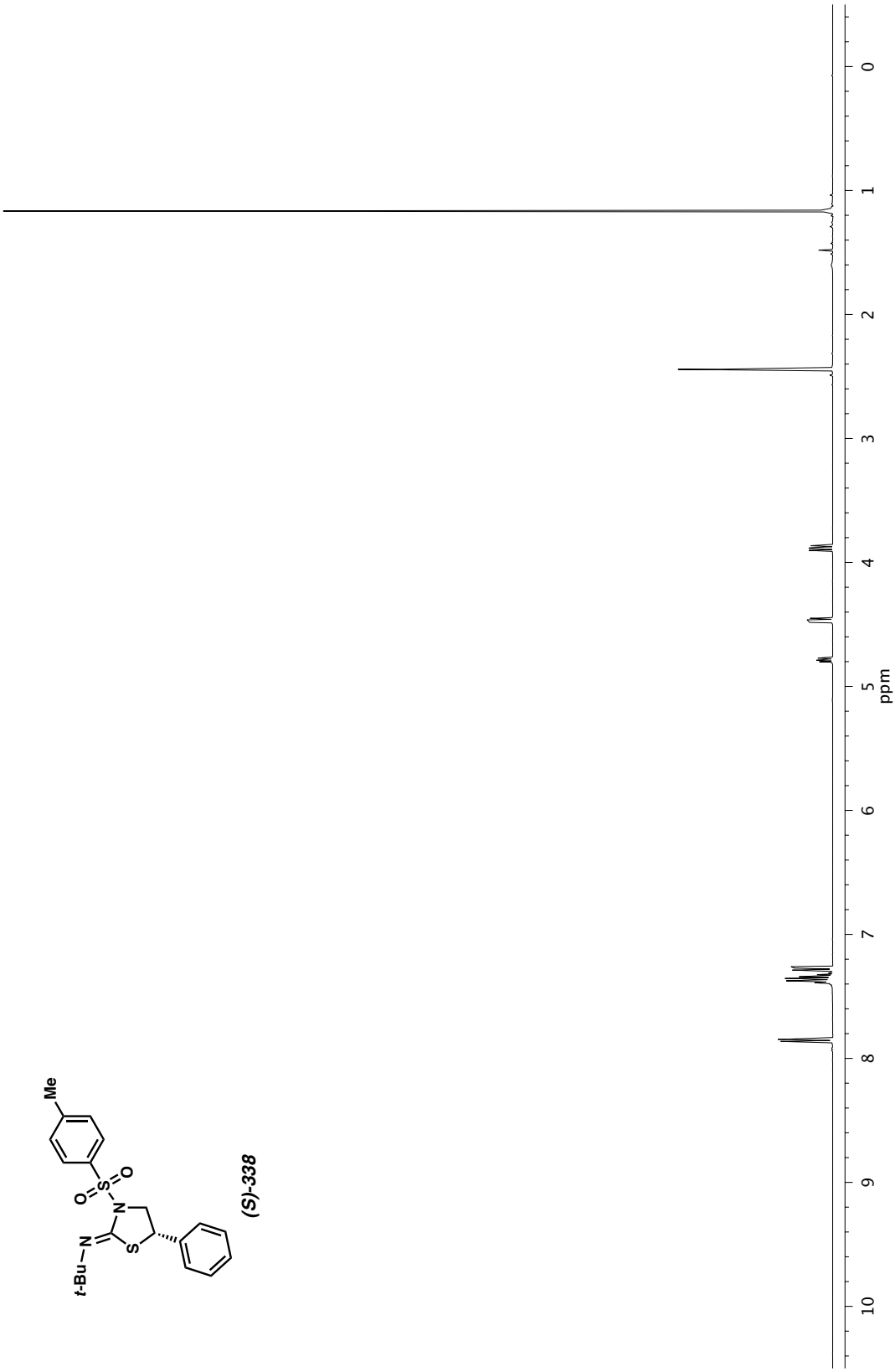


Figure A5.69 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **(*S*)-338**.

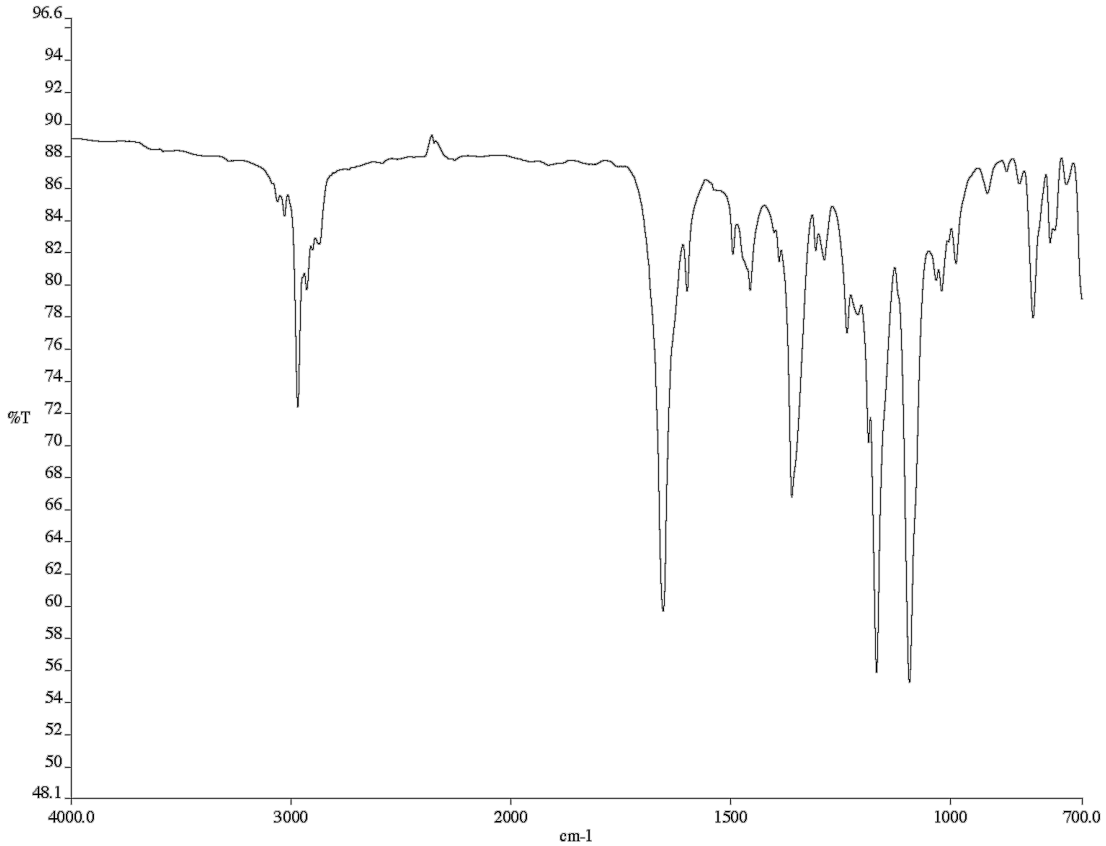


Figure A5.70 Infrared spectrum (Thin Film, NaCl) of compound **(*S*)-338**.

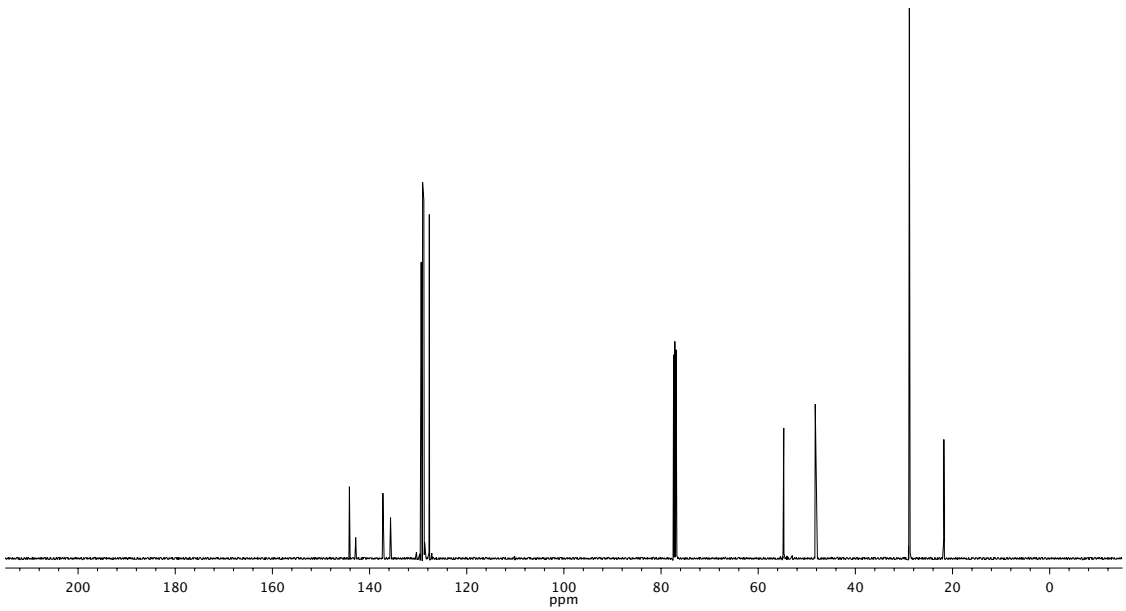


Figure A5.71 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **(*S*)-338**.

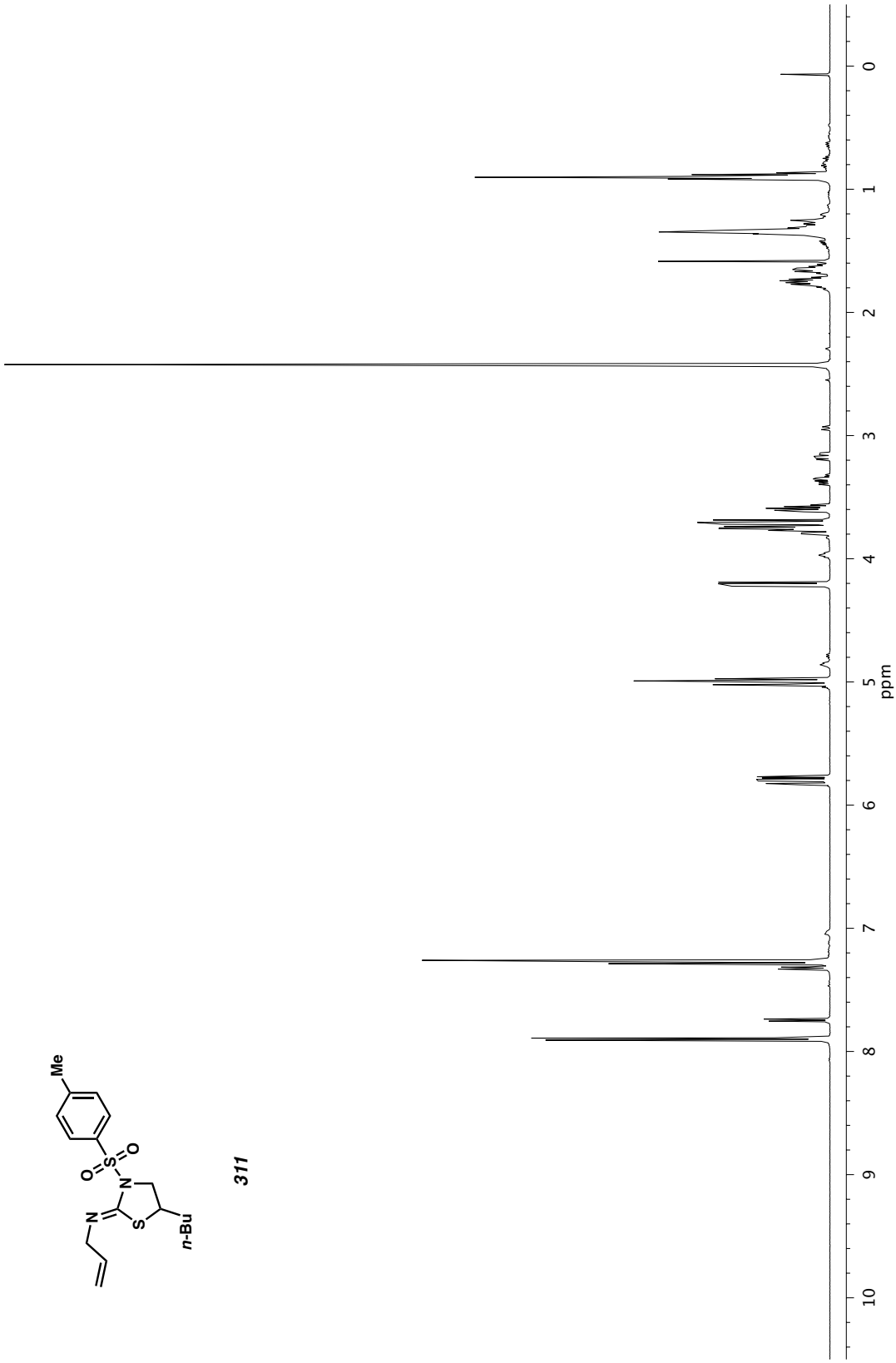


Figure A5.72 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **311**.

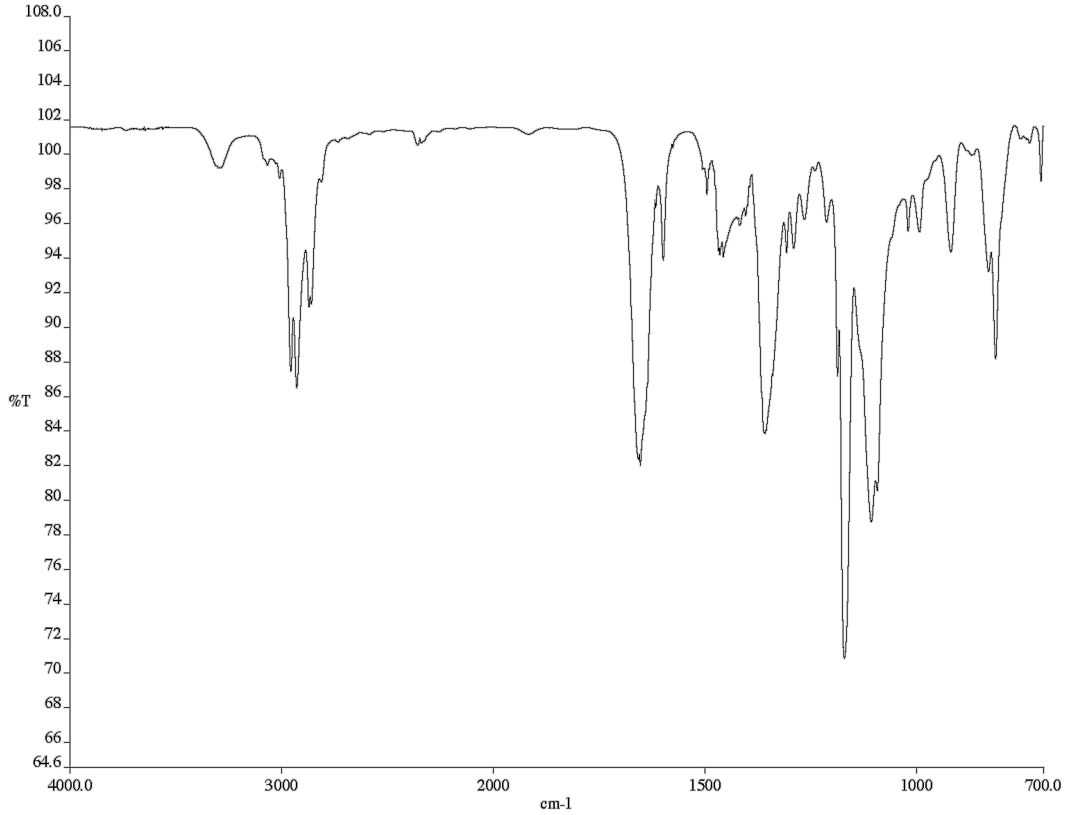


Figure A5.73 Infrared spectrum (thin film/NaCl) of compound **311**.

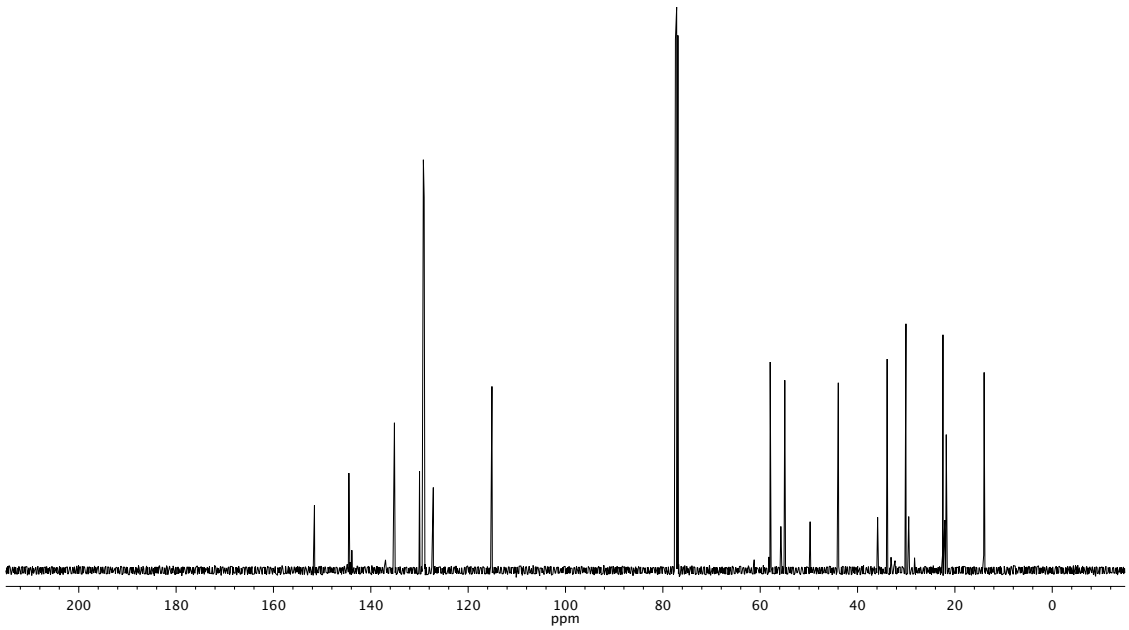


Figure A5.74 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **311**.

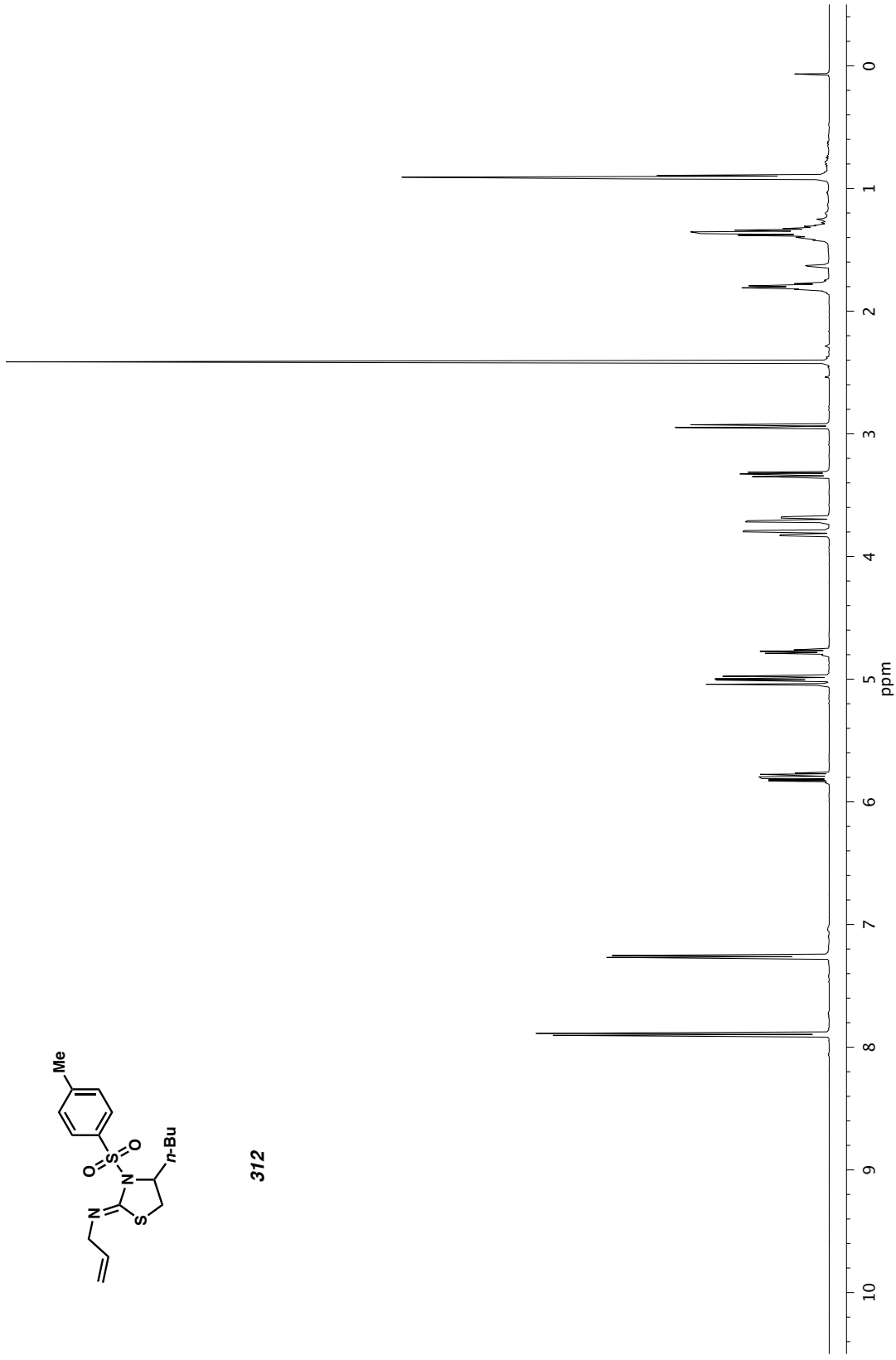


Figure A5.75 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **312**.

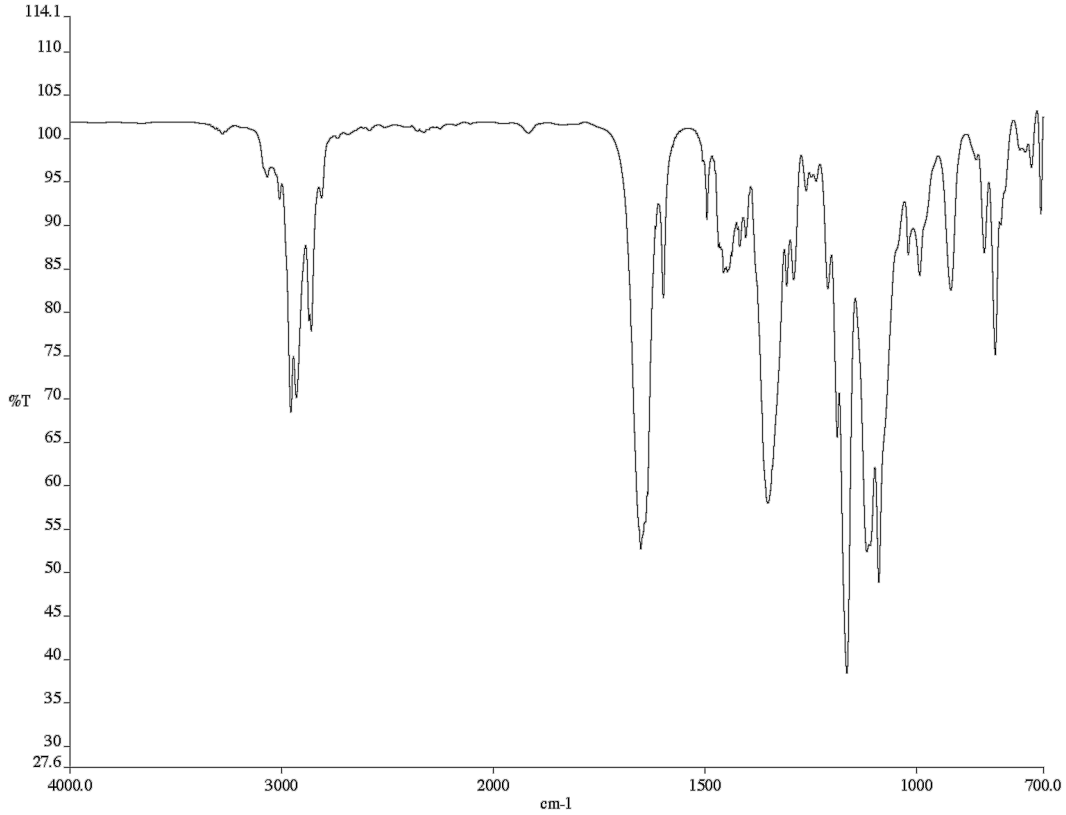


Figure A5.76 Infrared spectrum (thin film/NaCl) of compound **312**.

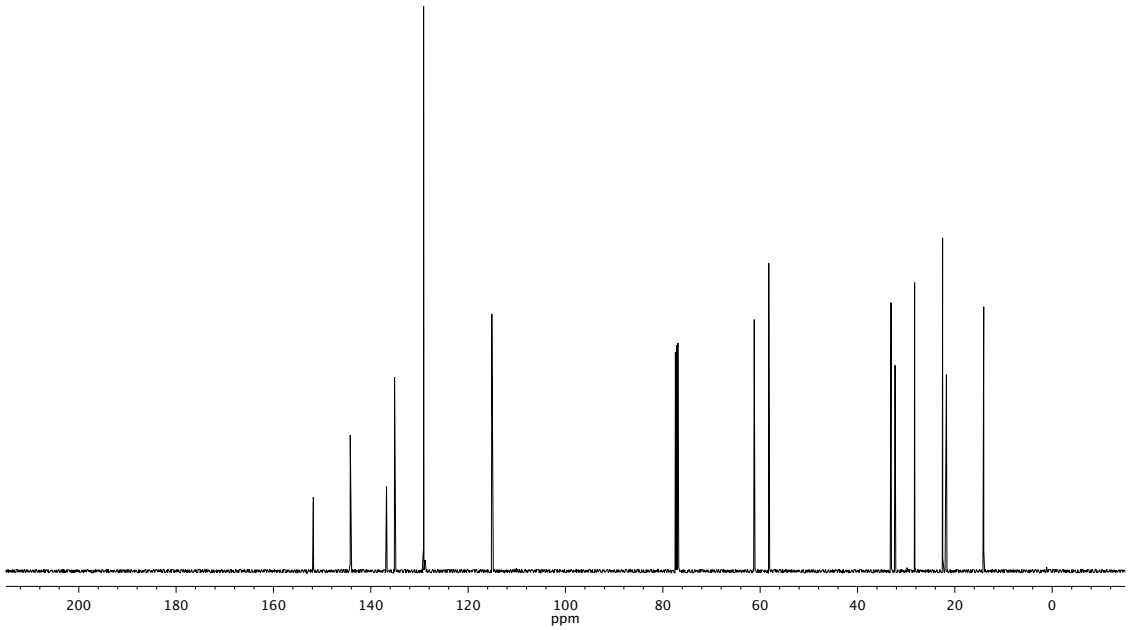


Figure A5.77 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **312**.

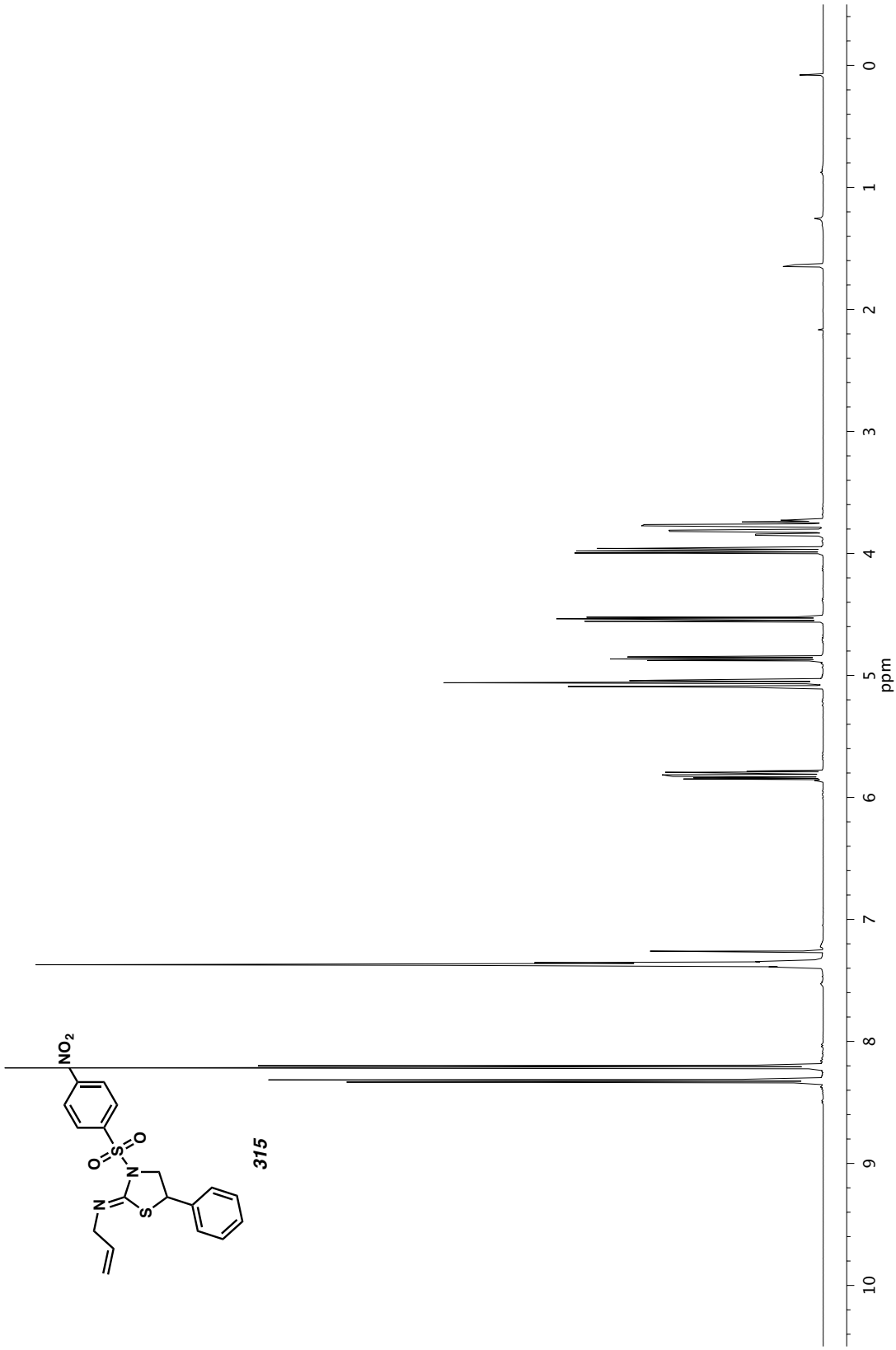


Figure A5.78 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **315**.

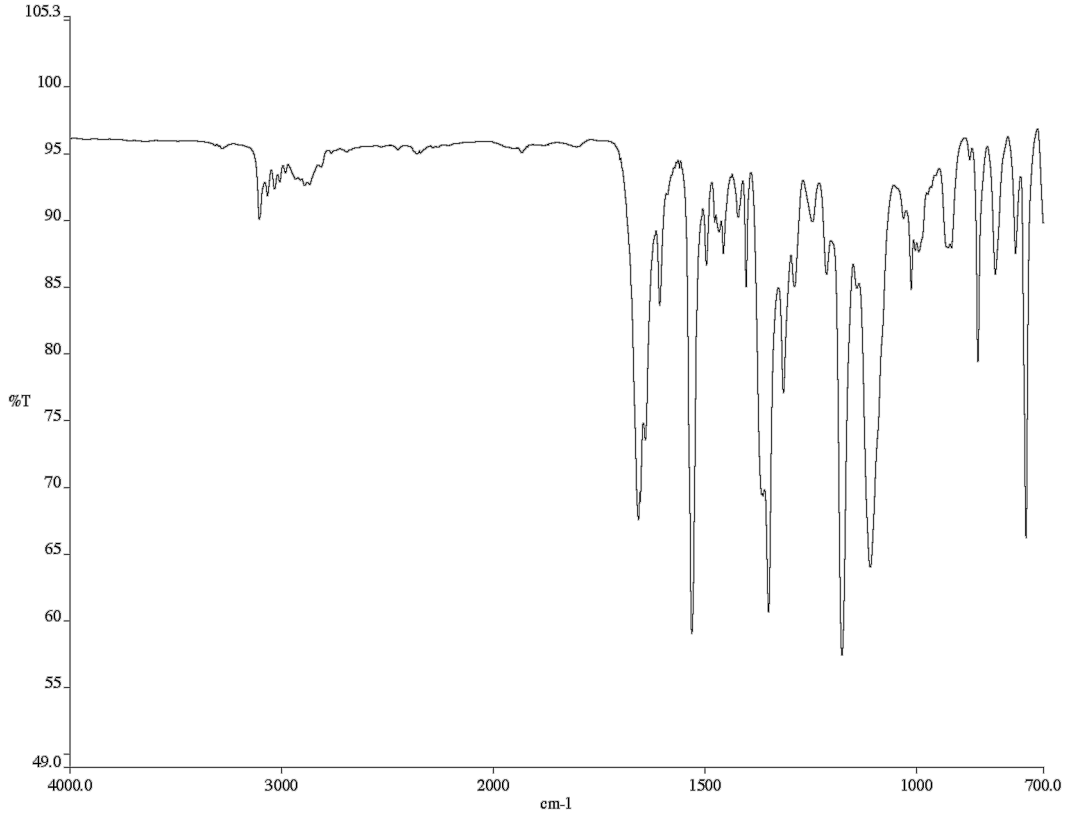


Figure A5.79 Infrared spectrum (thin film/NaCl) of compound **315**.

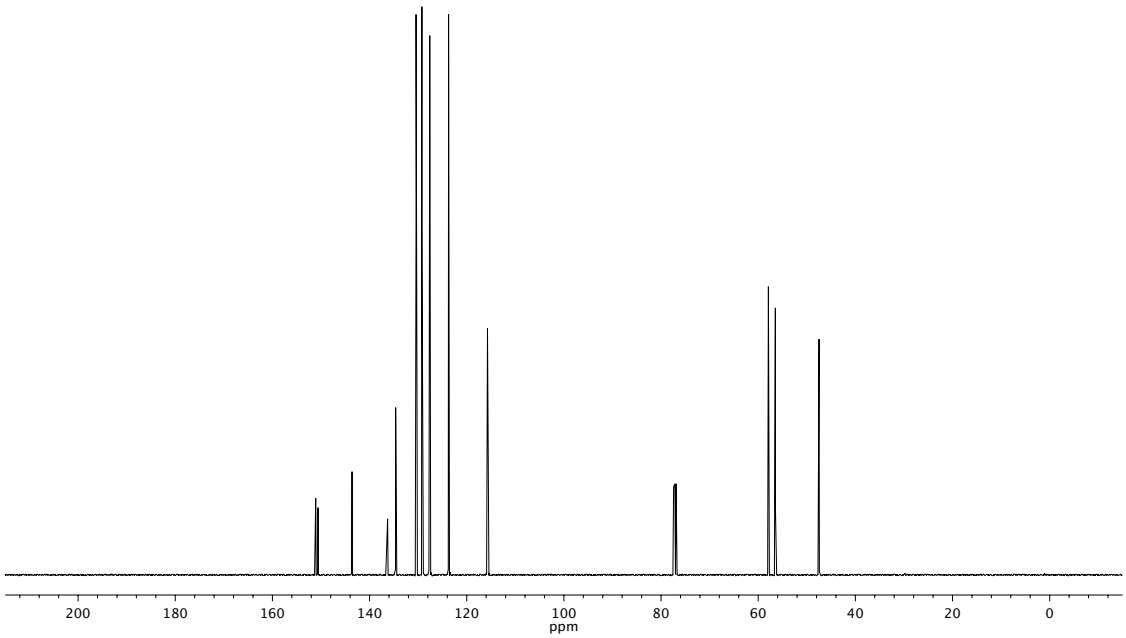


Figure A5.80 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **315**.

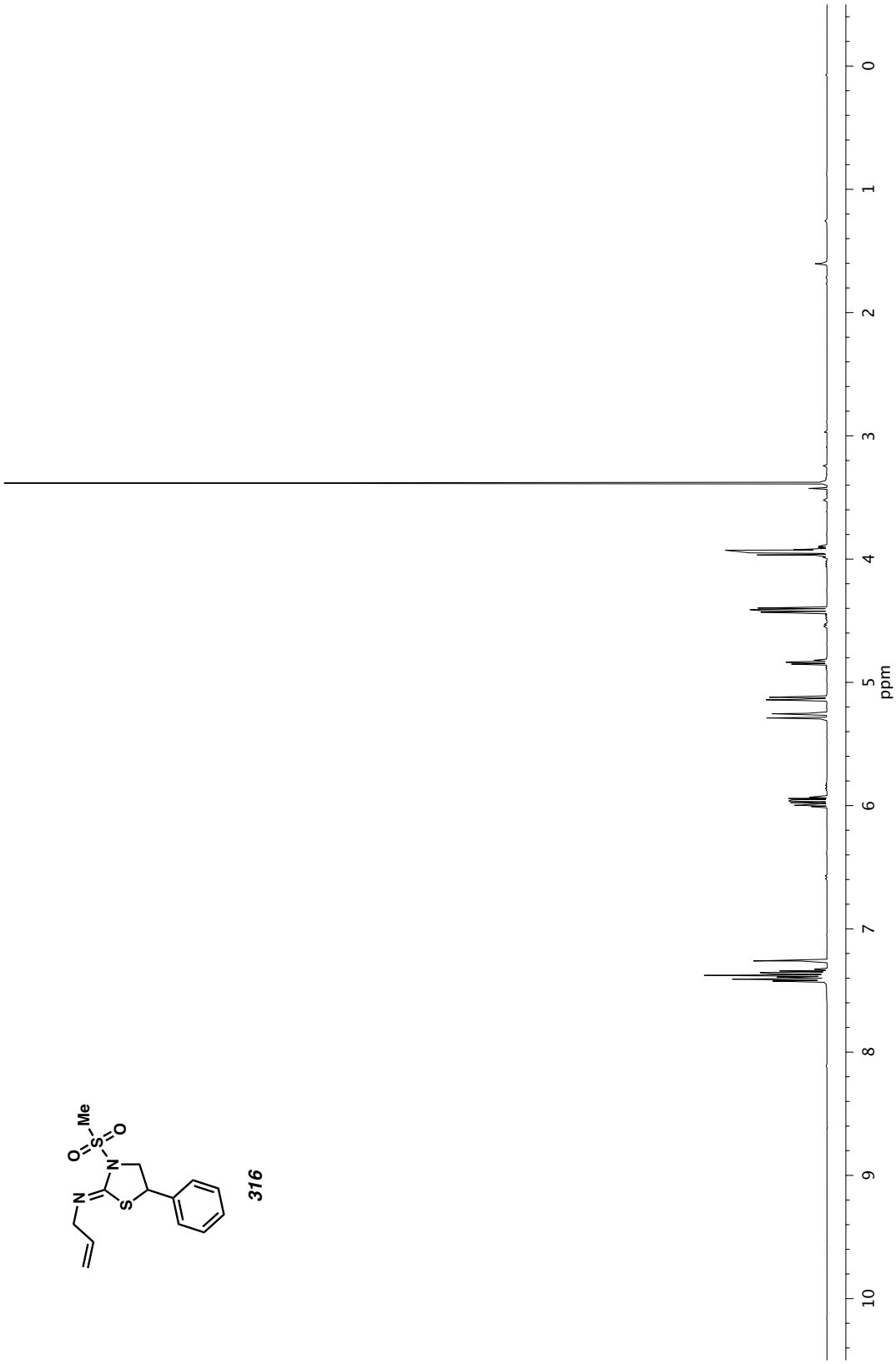


Figure A5.81 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **316**.

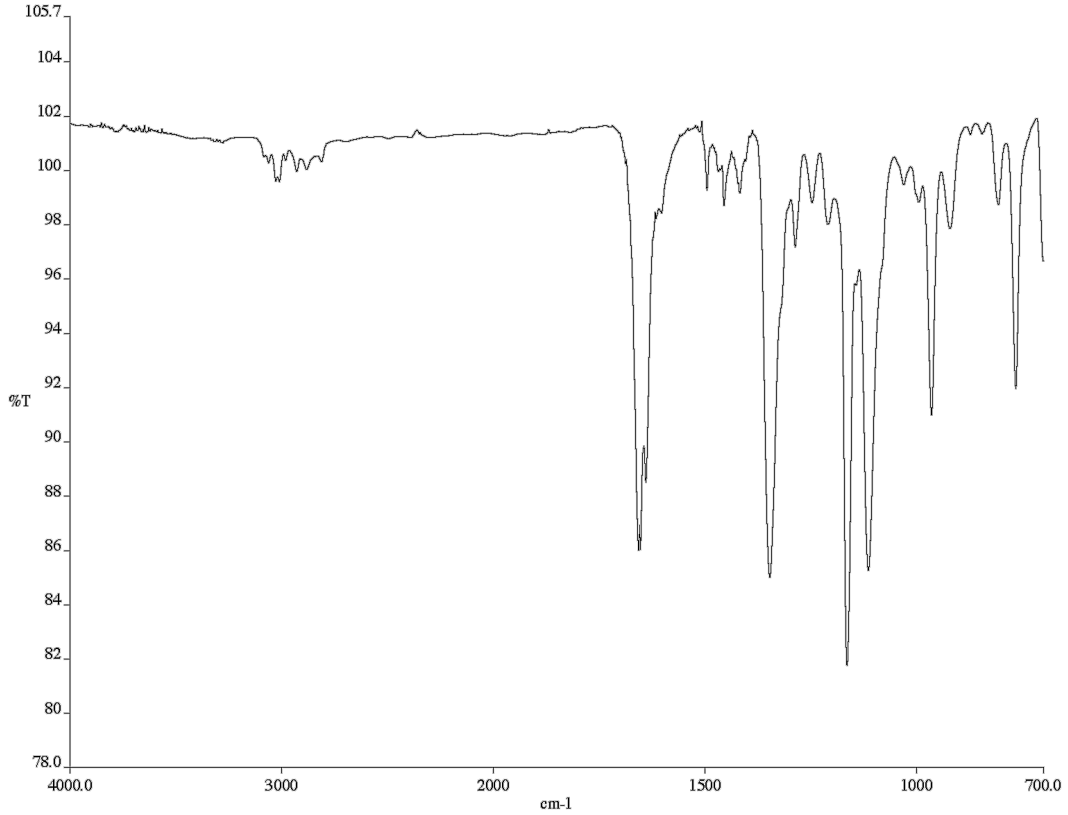


Figure A5.82 Infrared spectrum (thin film/NaCl) of compound **316**.

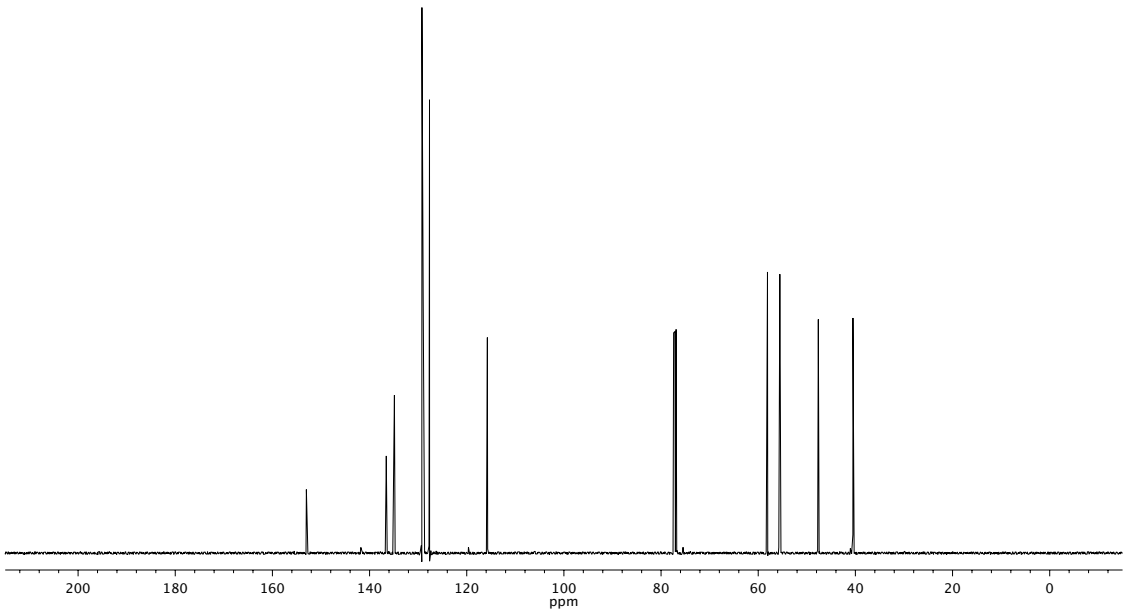


Figure A5.83 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **316**.

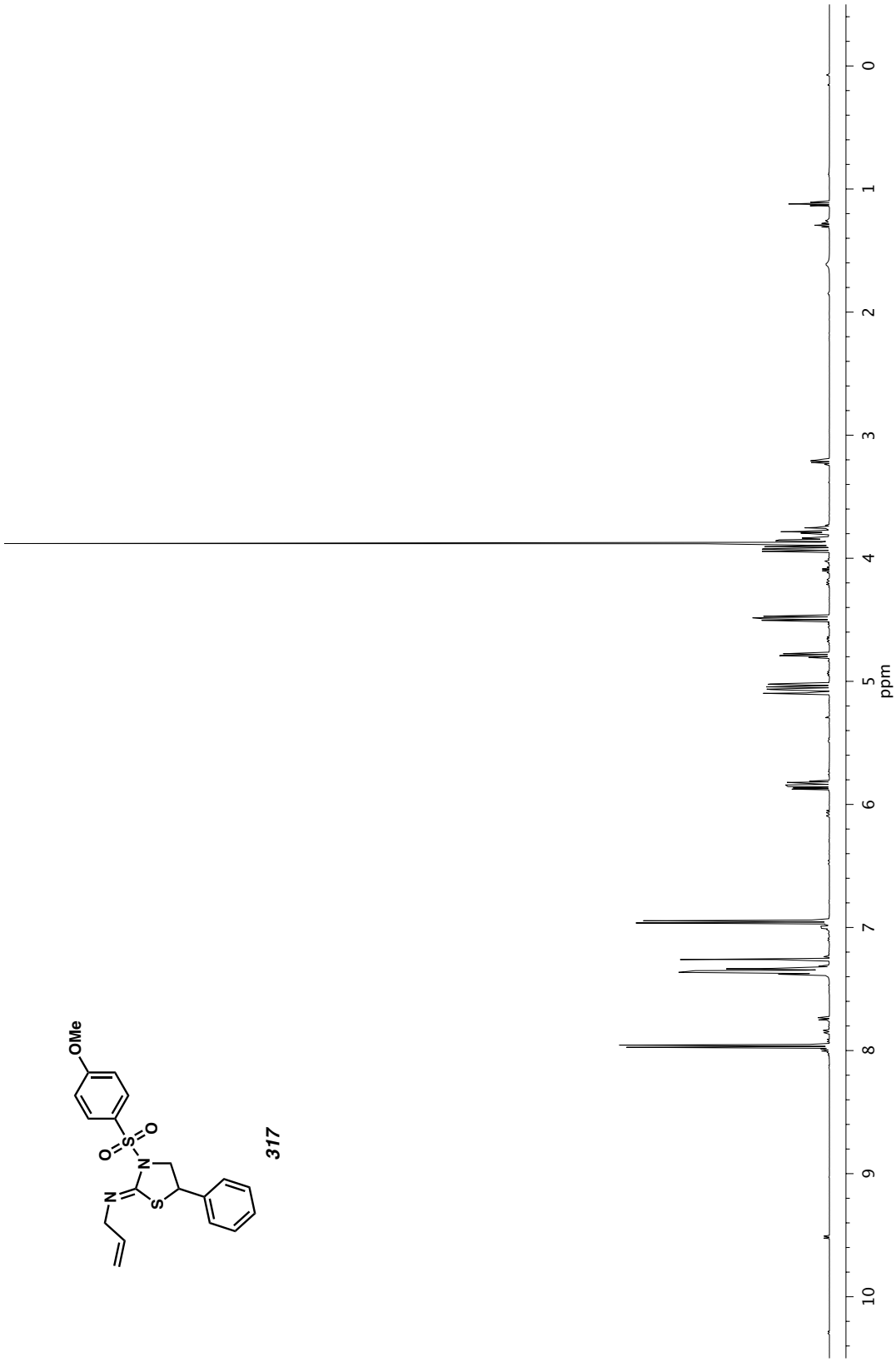


Figure A5.84 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **317**.

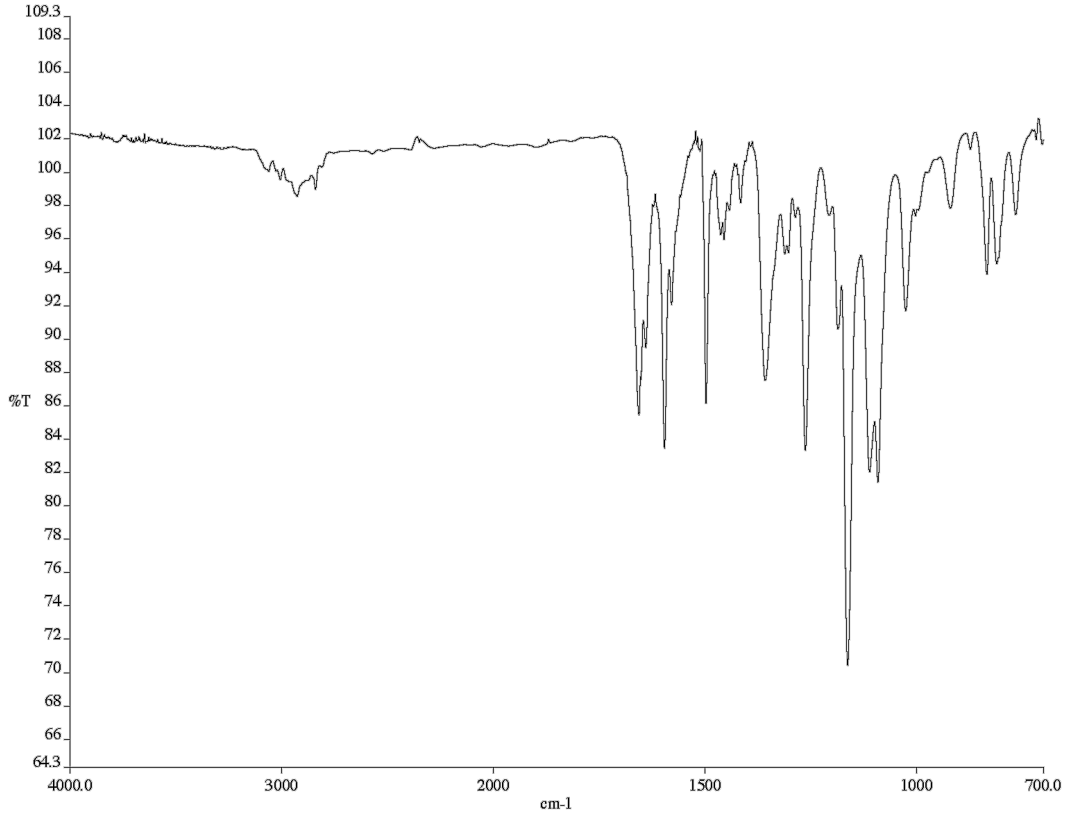


Figure A5.85 Infrared spectrum (thin film/NaCl) of compound **317**.

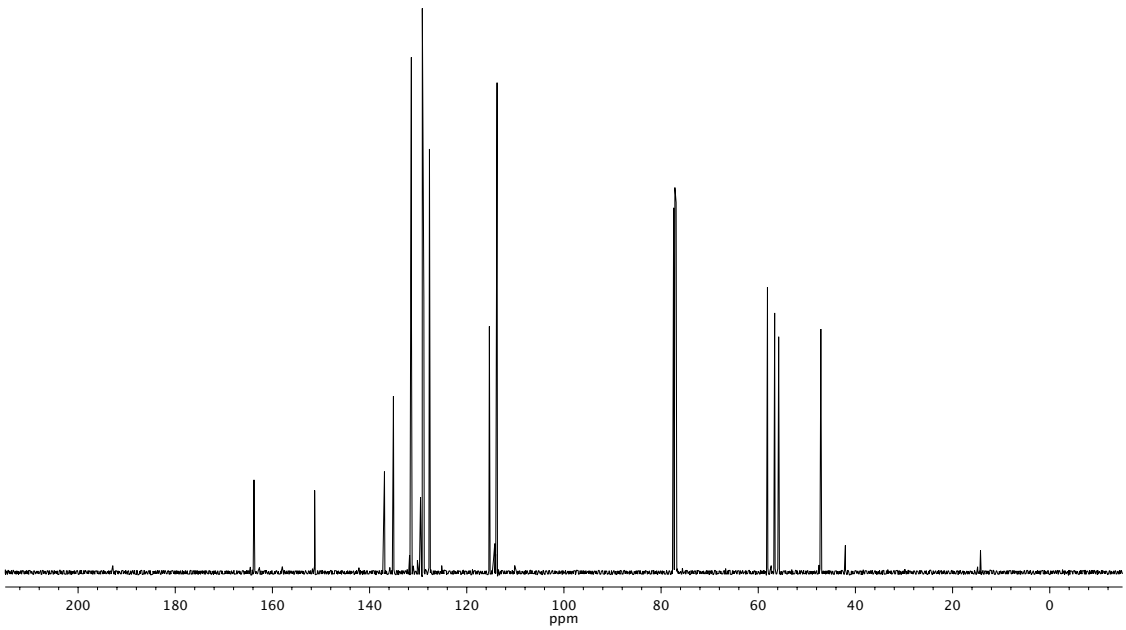


Figure A5.86 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **317**.

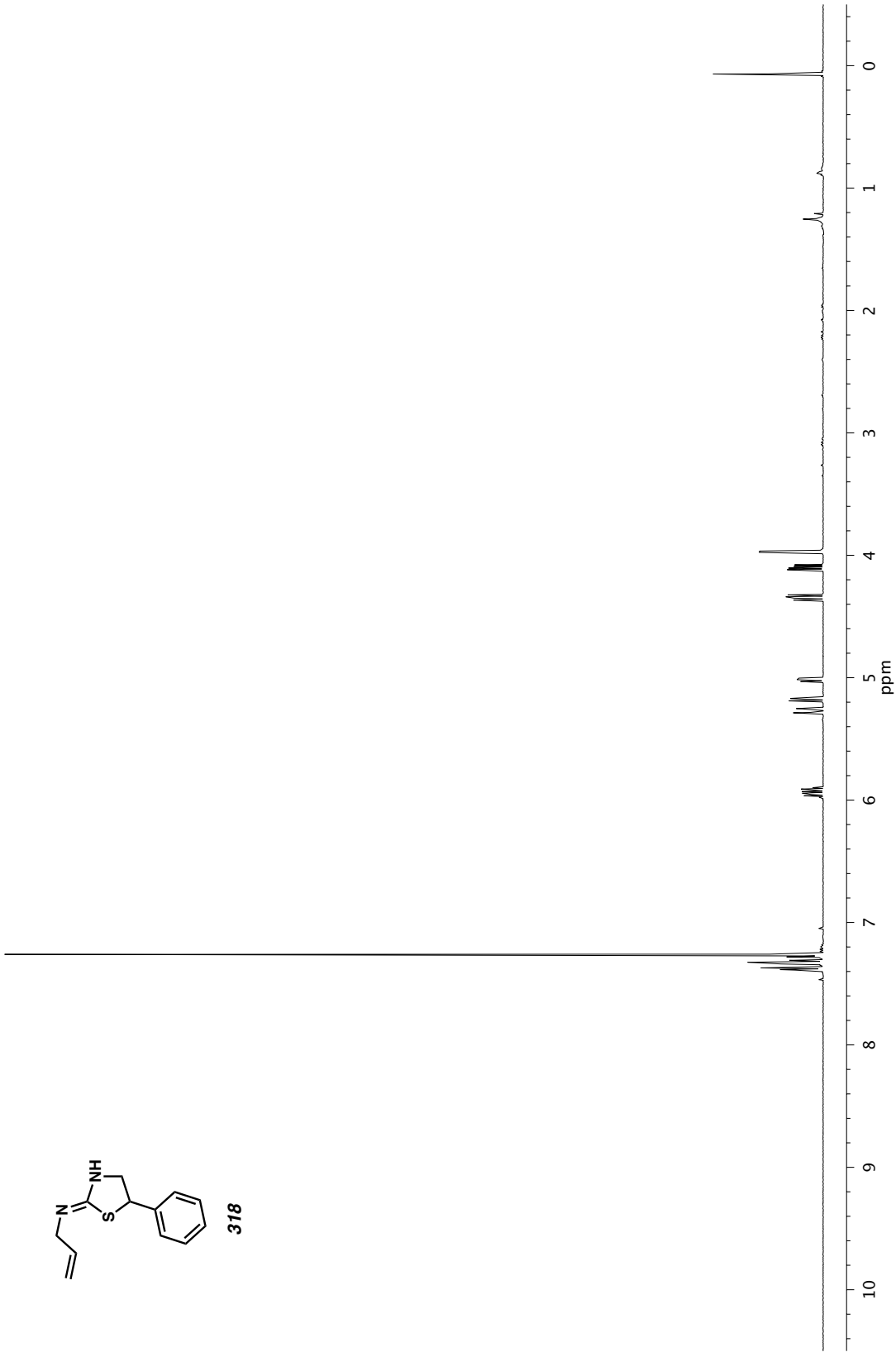


Figure A5.87 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **318**.

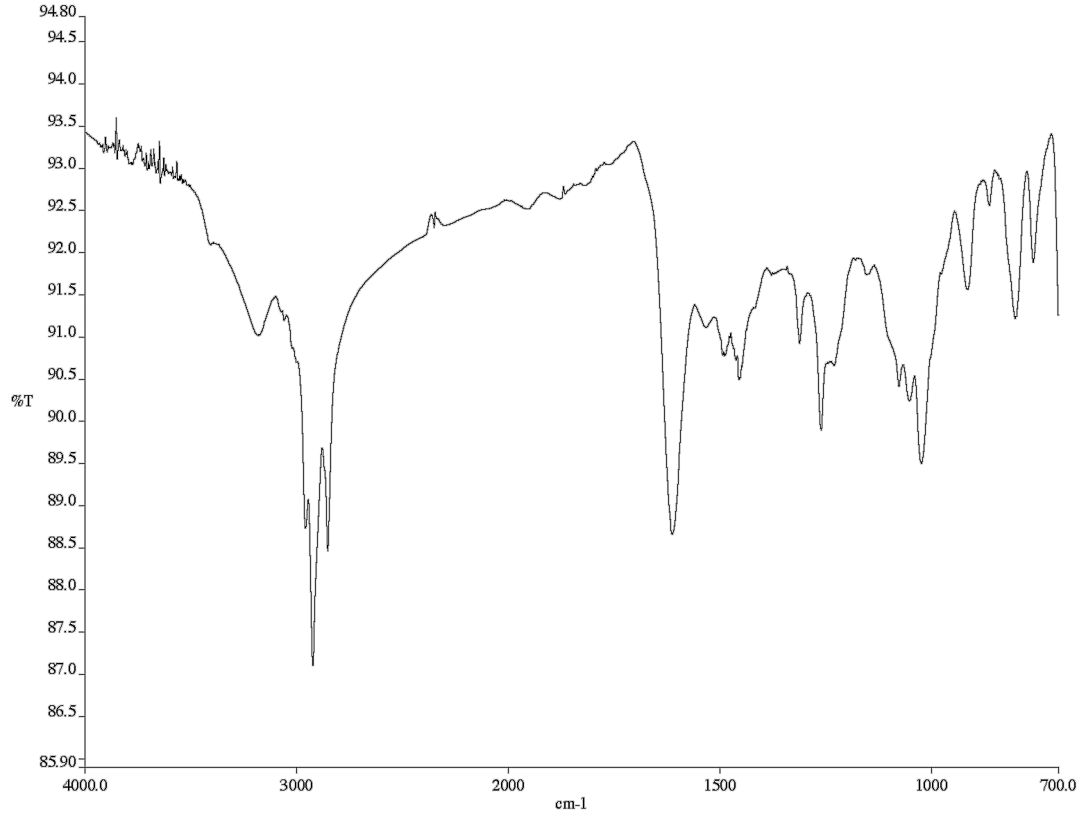


Figure A5.88 Infrared spectrum (thin film/NaCl) of compound **318**.

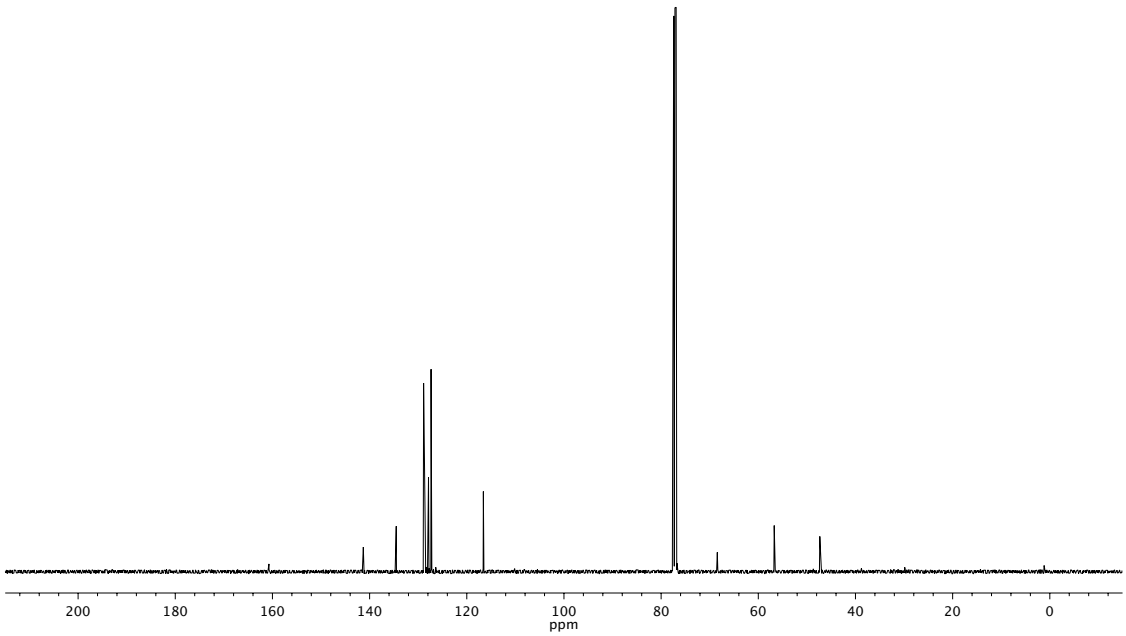


Figure A5.89 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **318**.

Figure A5.90 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **323•HCl**.

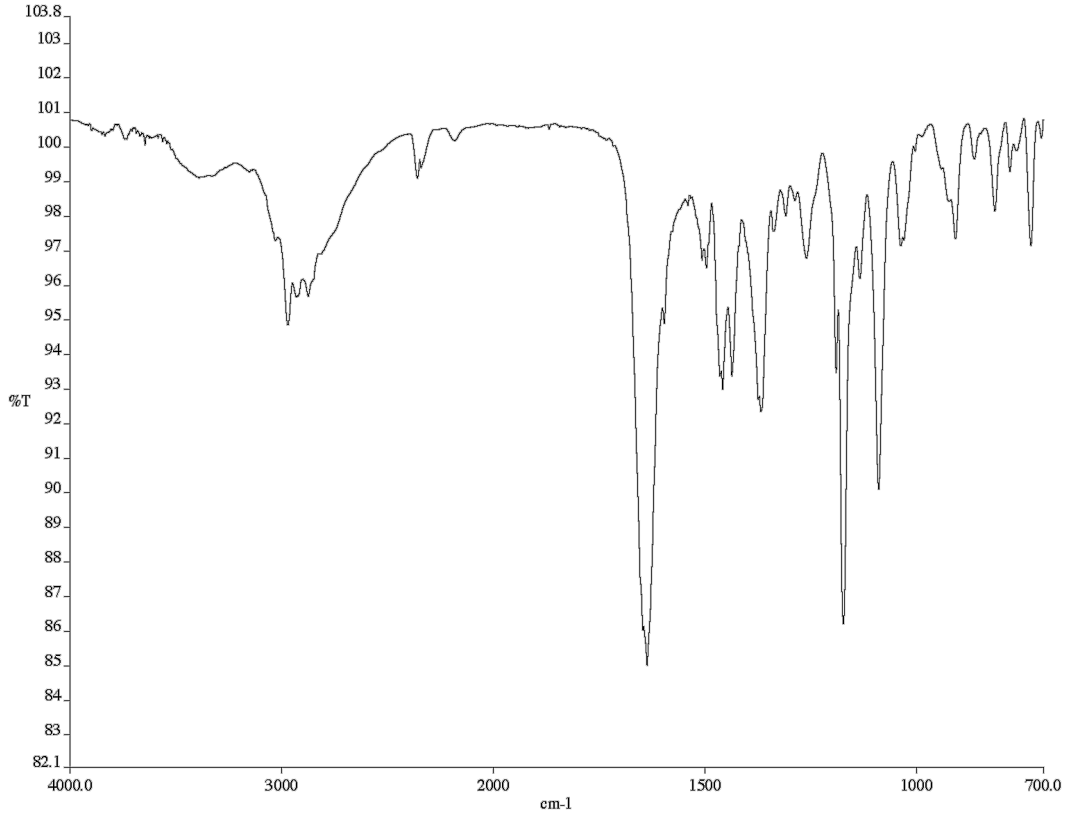


Figure A5.91 Infrared spectrum (Thin Film, NaCl) of compound **323•HCl**.

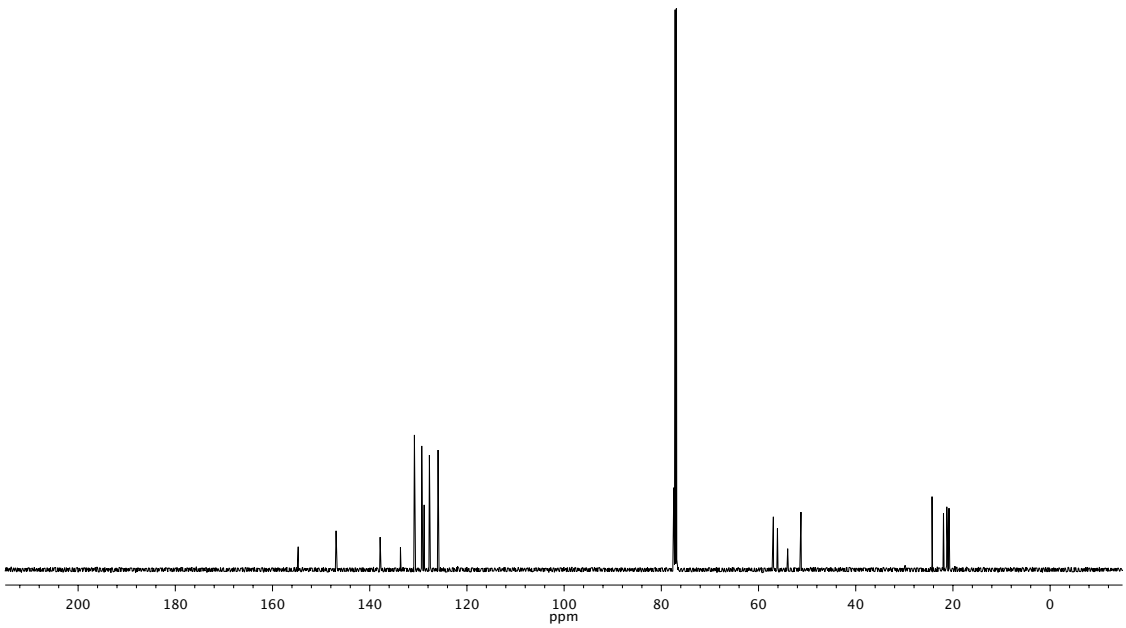


Figure A5.92 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **323•HCl**.

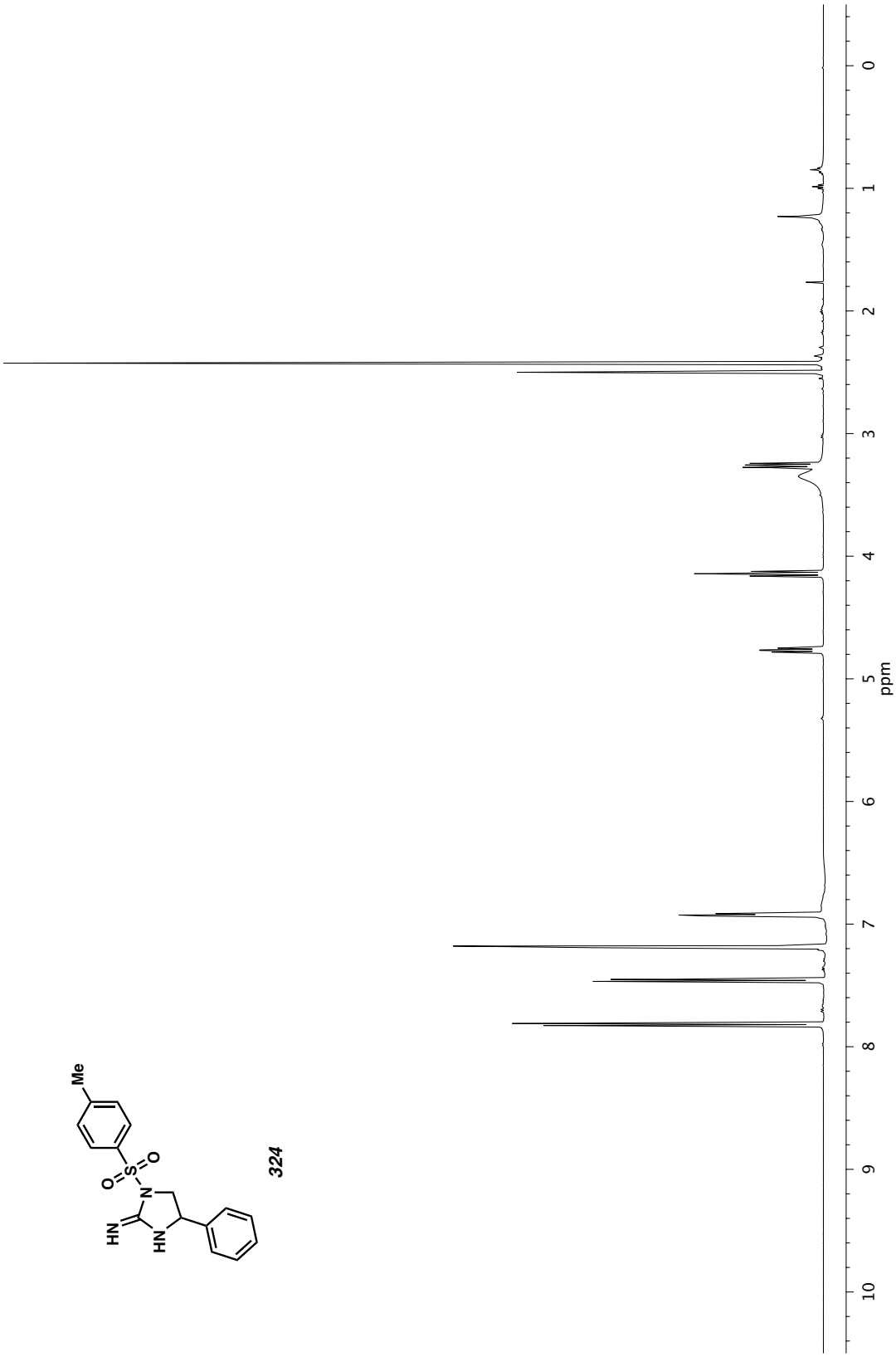


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Figure A5.93 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **324**.

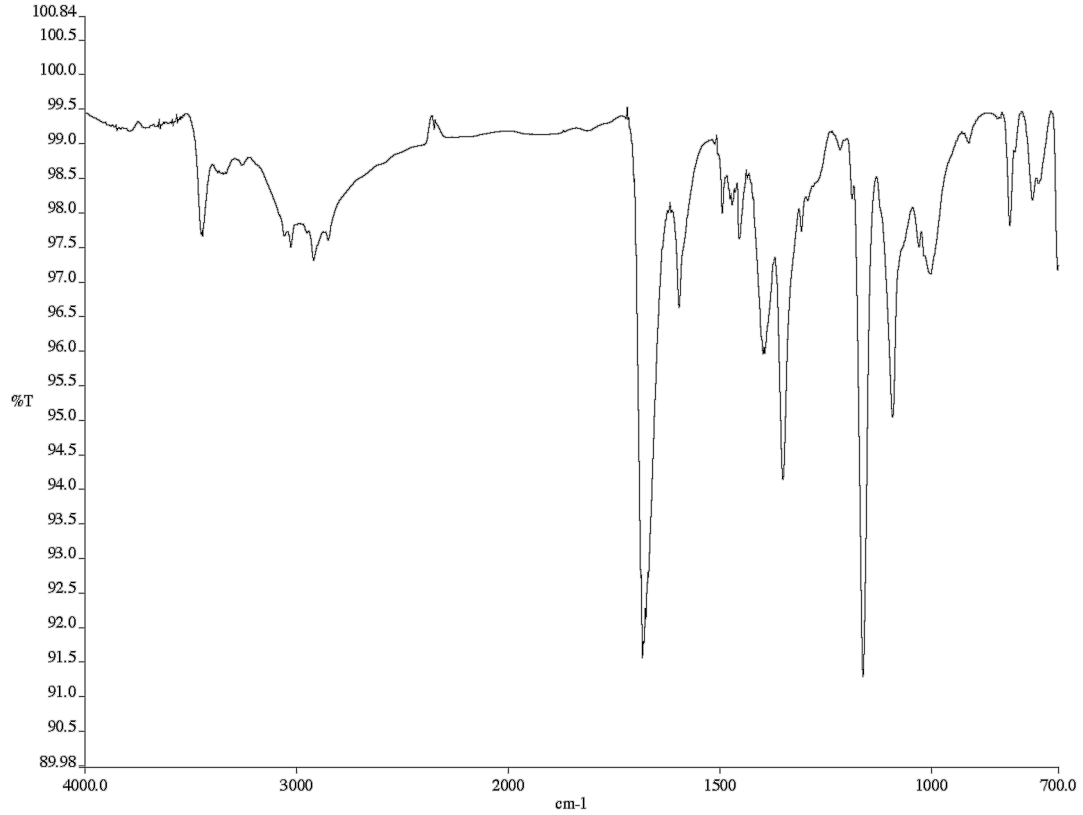


Figure A5.94 Infrared spectrum (thin film/NaCl) of compound **324**.

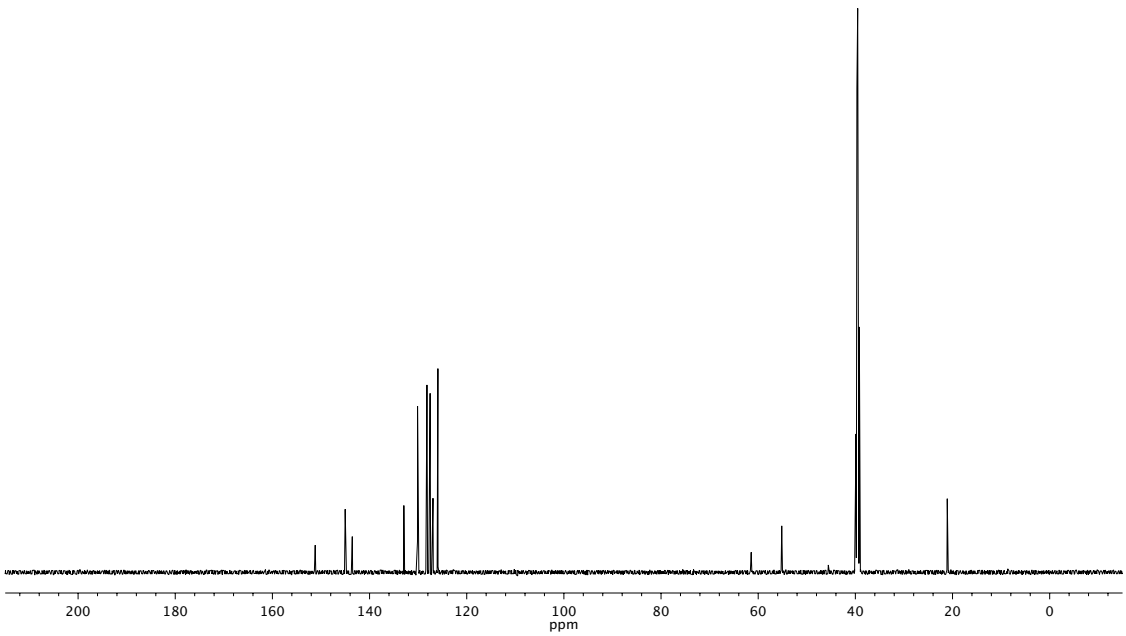


Figure A5.95 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **324**.

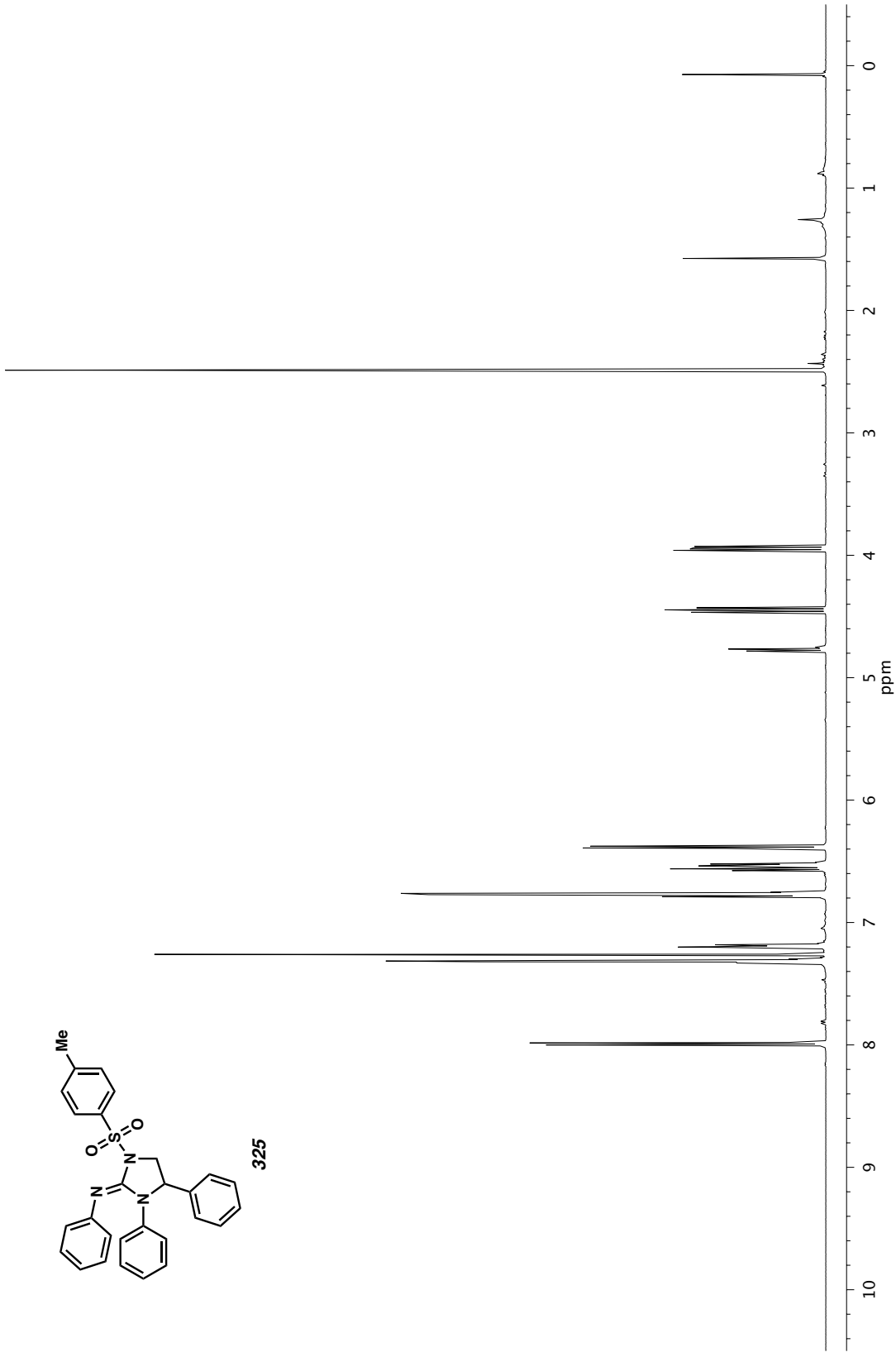


Figure A5.96 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **325**.

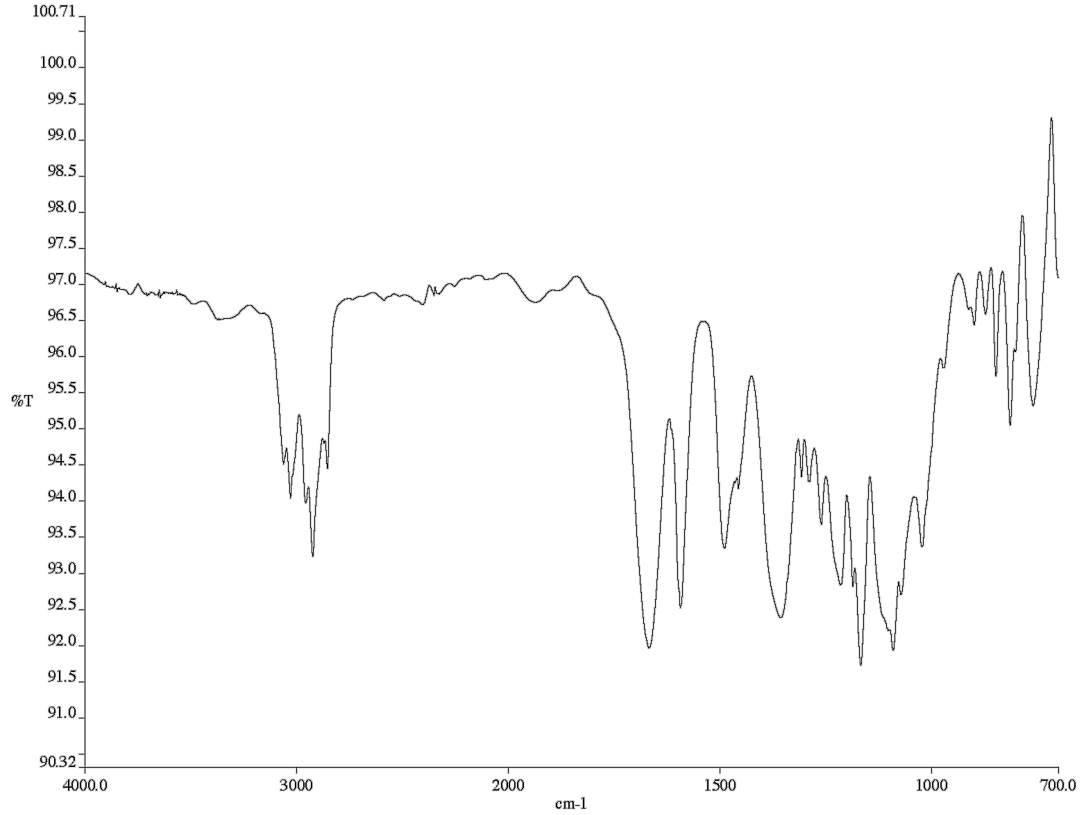


Figure A5.97 Infrared spectrum (thin film/NaCl) of compound **325**.

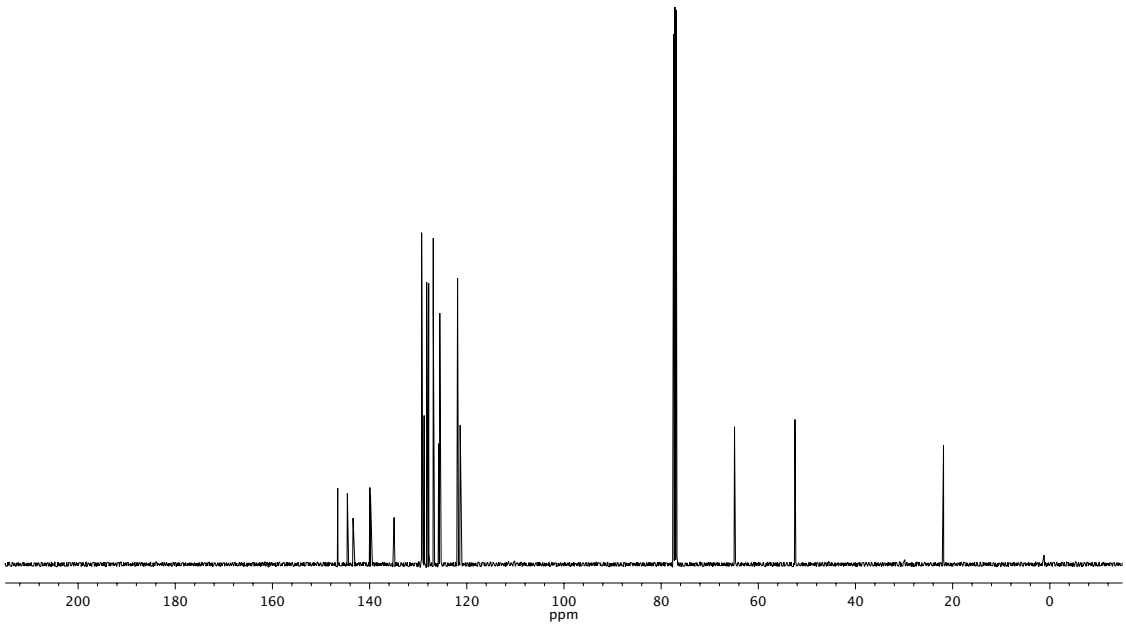


Figure A5.98 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **325**.

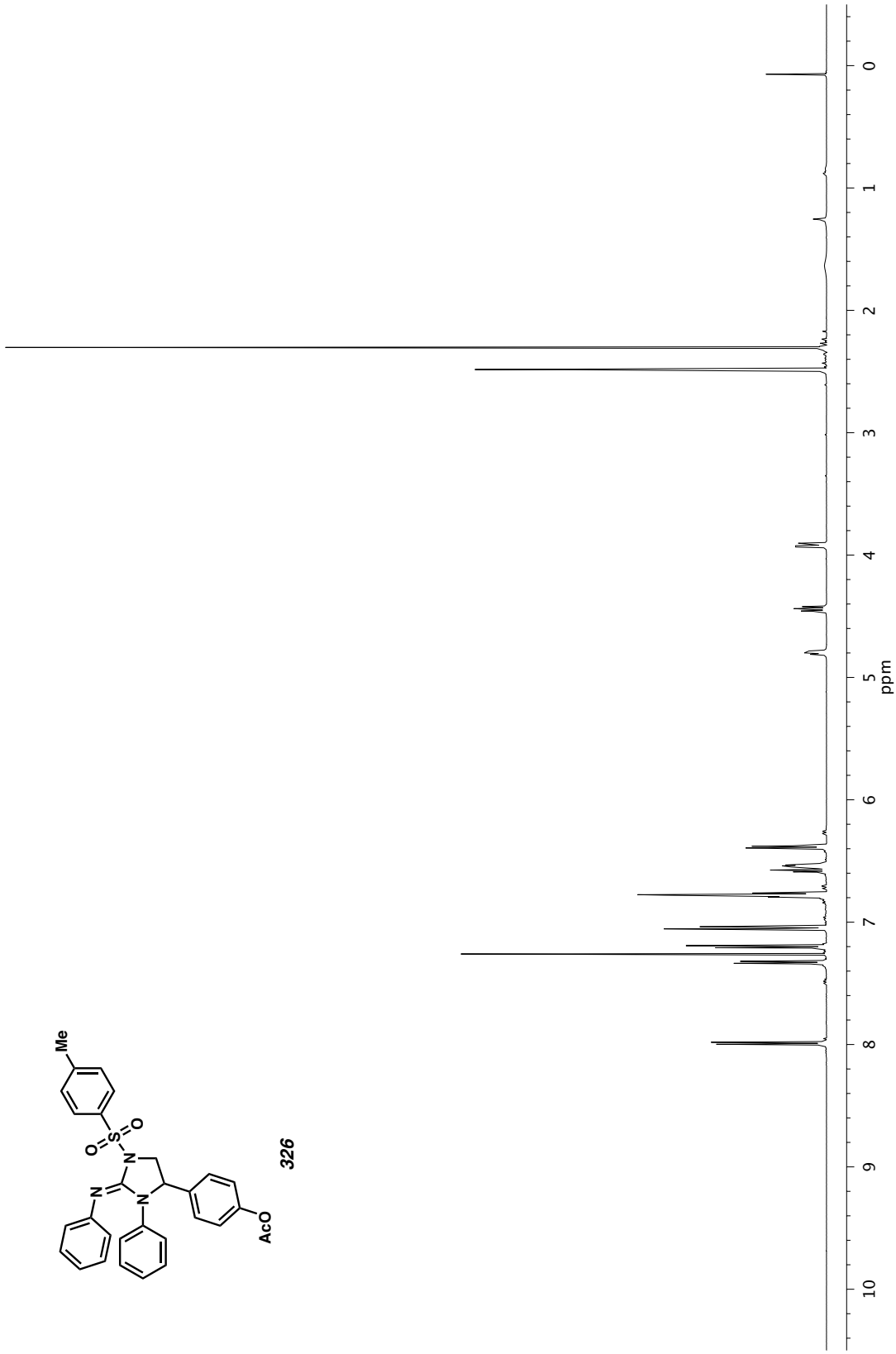


Figure A5.99 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **326**.

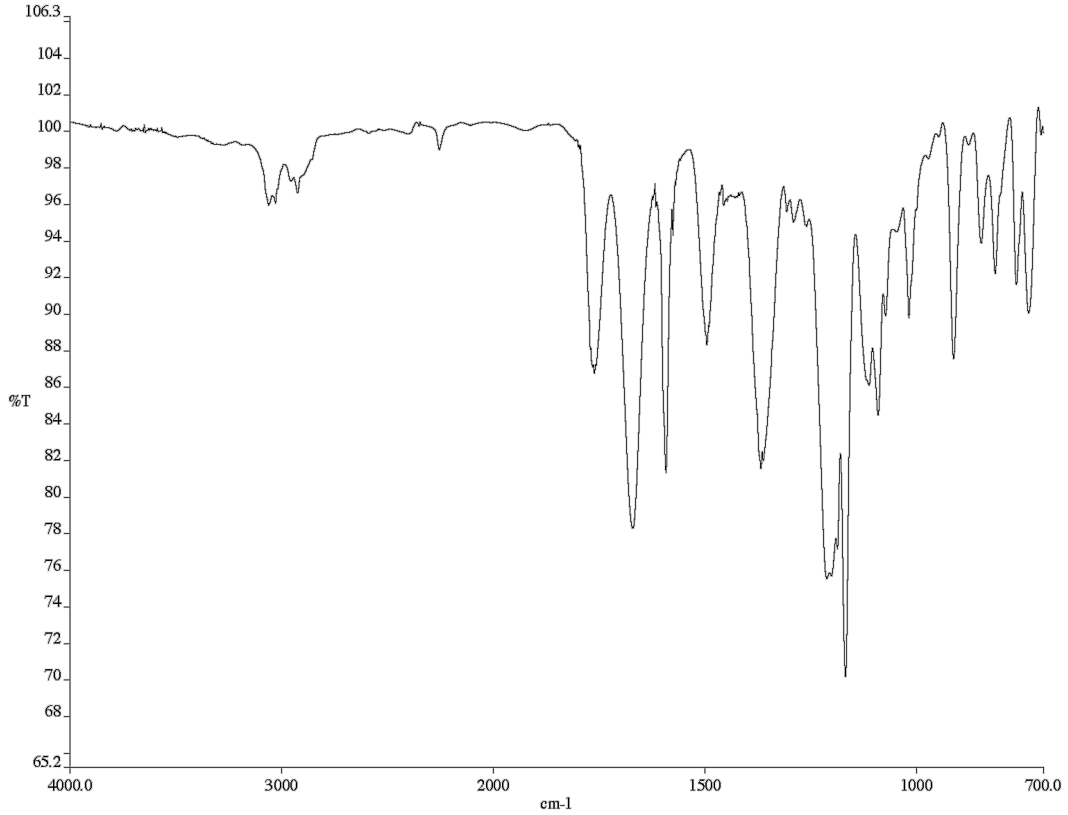


Figure A5.100 Infrared spectrum (thin film/NaCl) of compound **326**.

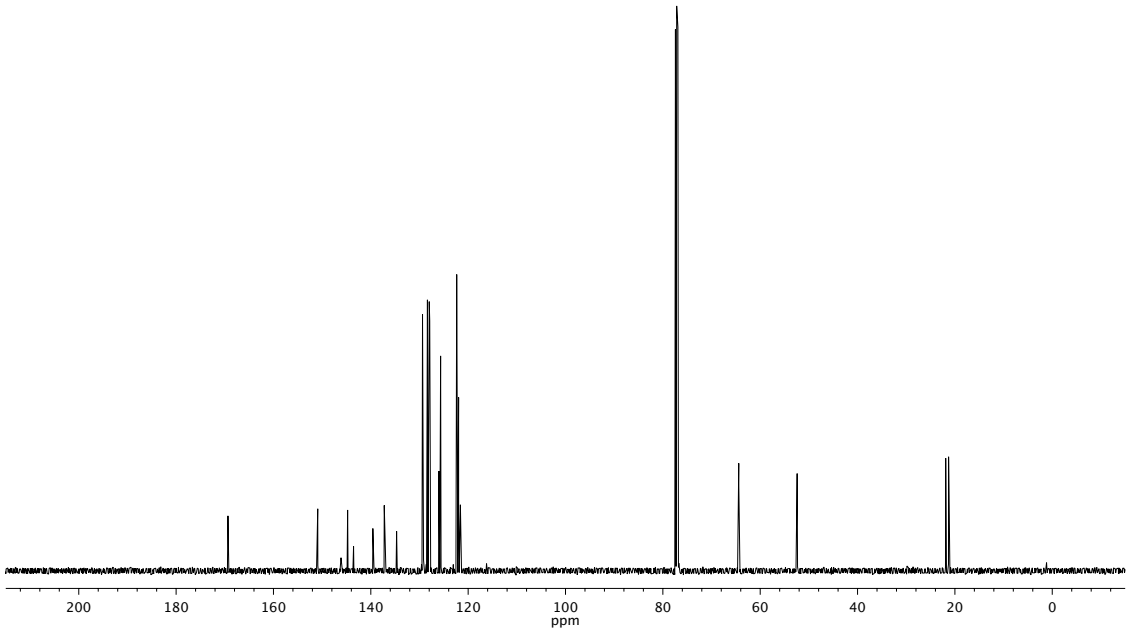


Figure A5.101 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **326**.

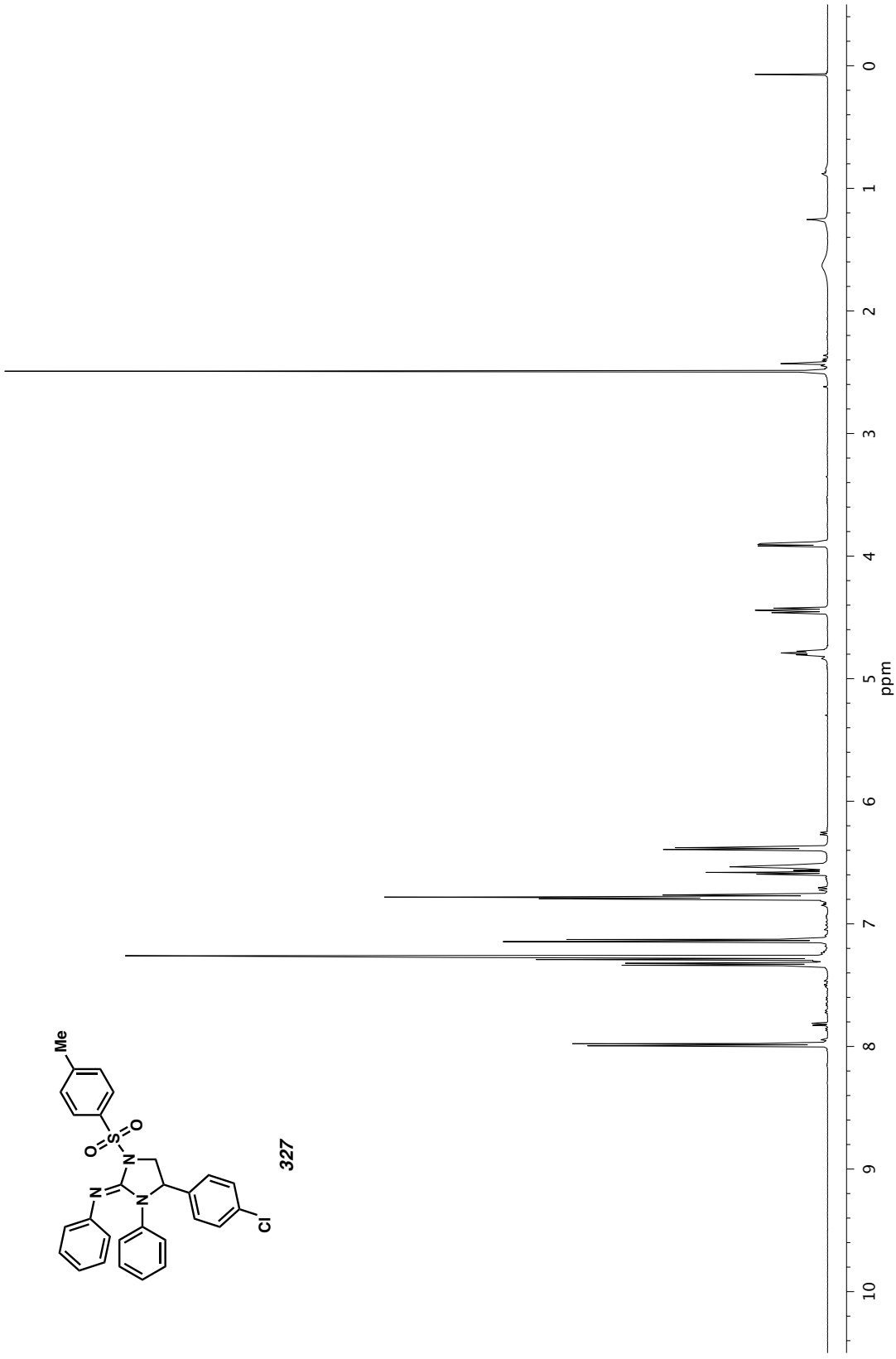


Figure A5.102 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **327**.

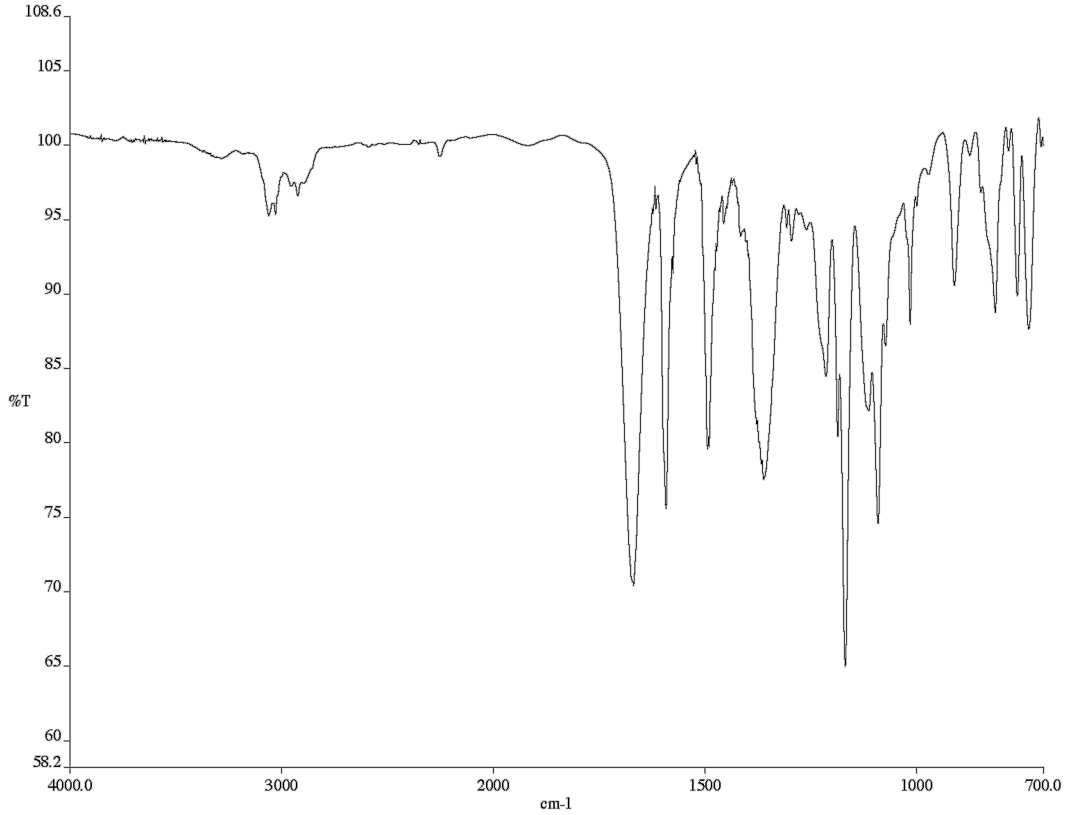


Figure A5.103 Infrared spectrum (thin film/NaCl) of compound **327**.

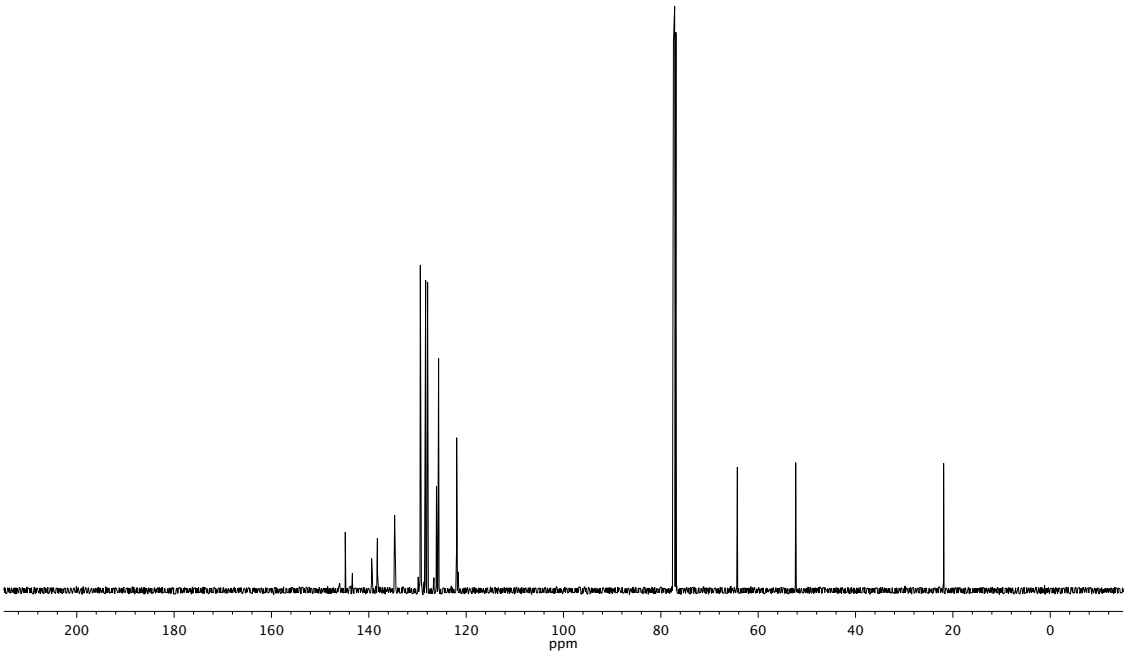


Figure A5.104 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **327**.

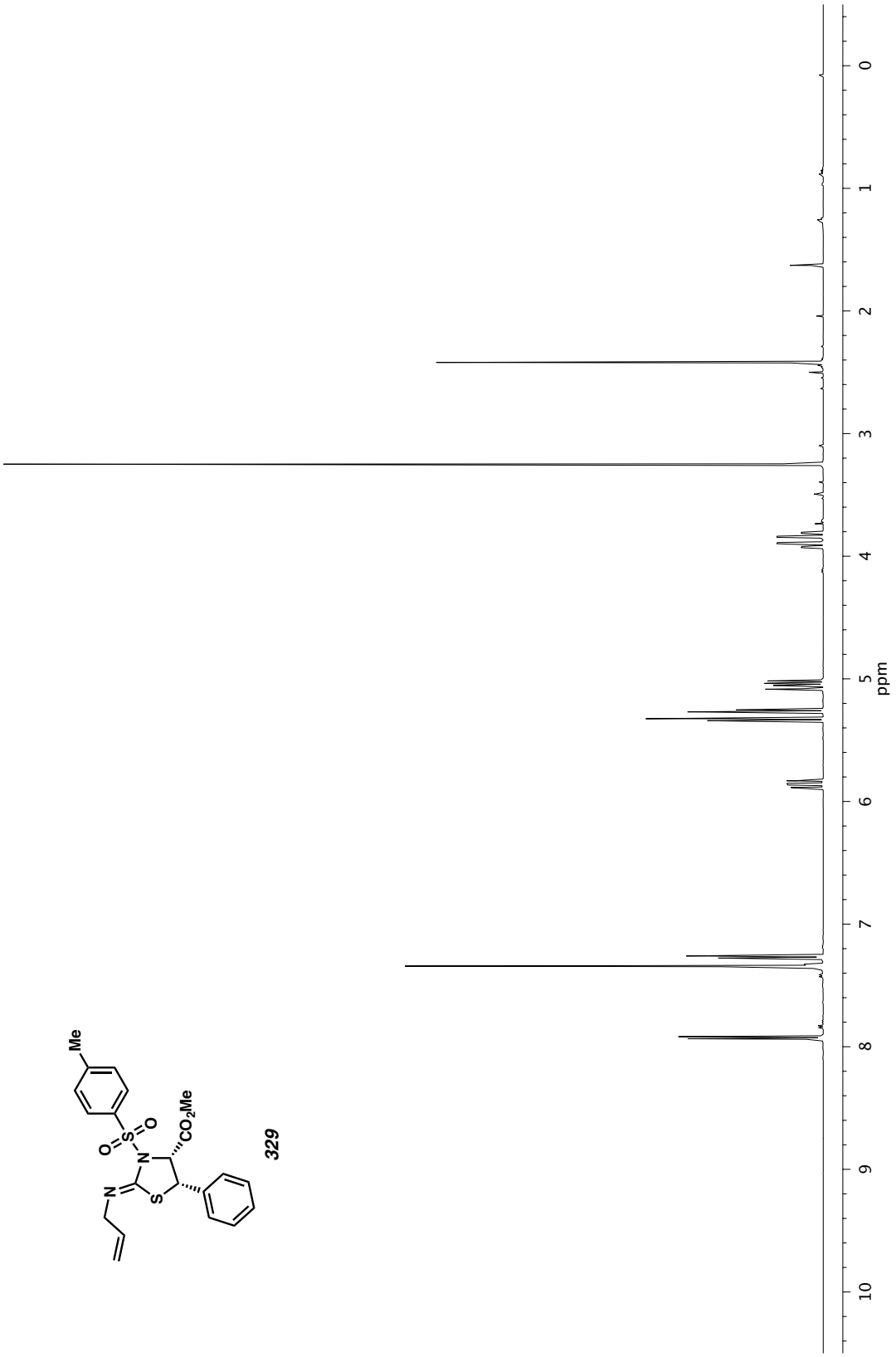


Figure A5.105 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **329**.

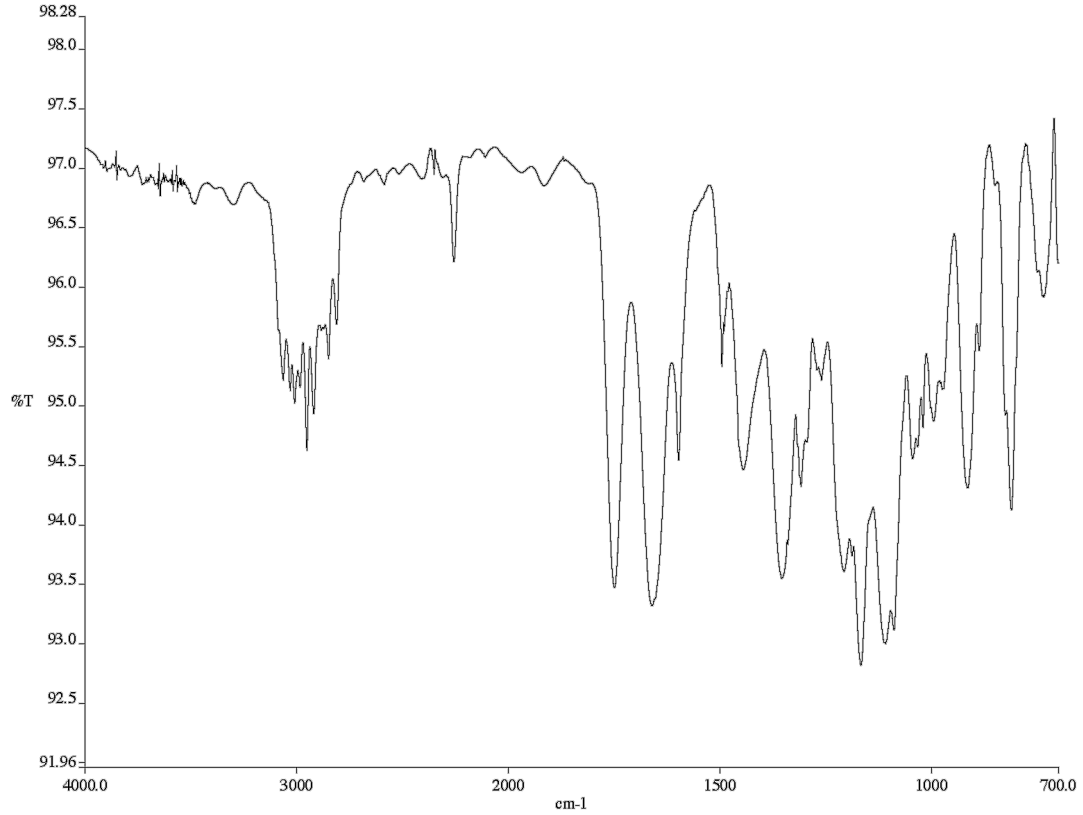


Figure A5.106 Infrared spectrum (thin film/NaCl) of compound **329**.

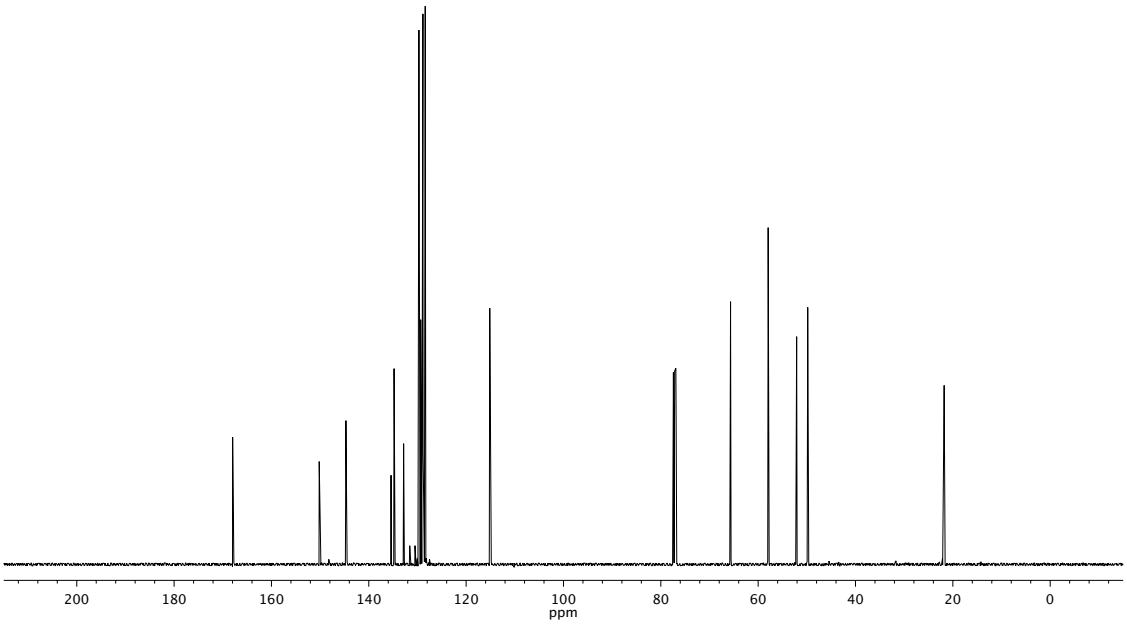


Figure A5.107 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **329**.

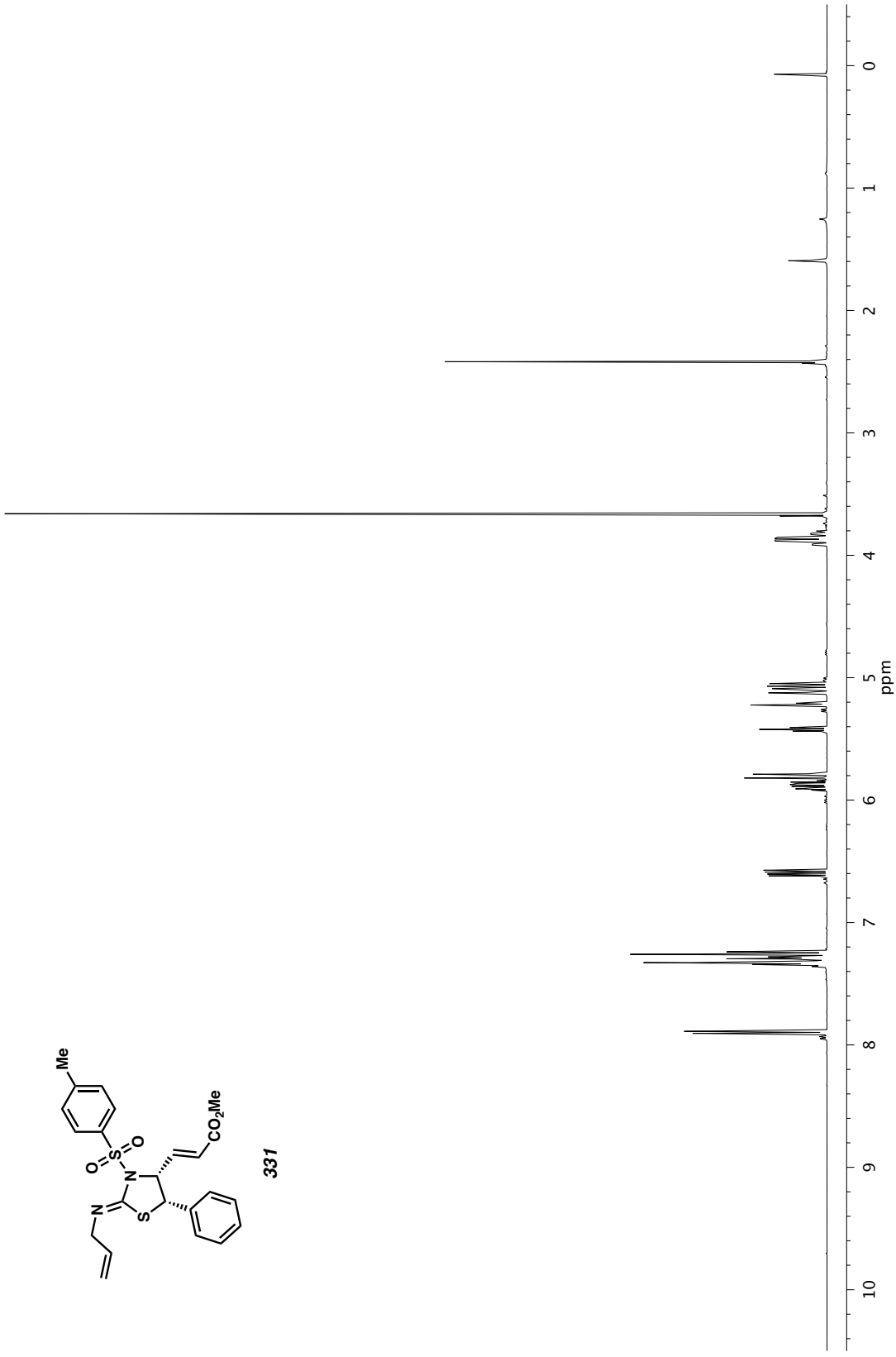


Figure A5.108 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **331**.

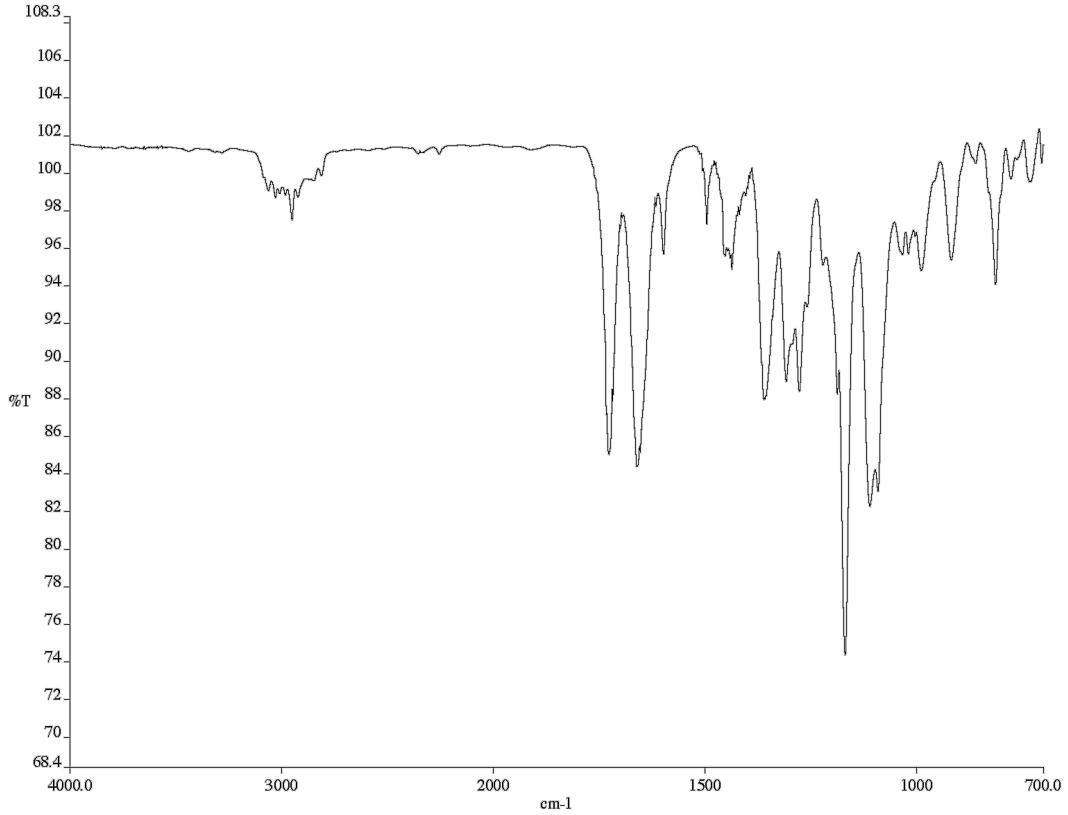


Figure A5.109 Infrared spectrum (thin film/NaCl) of compound **331**.

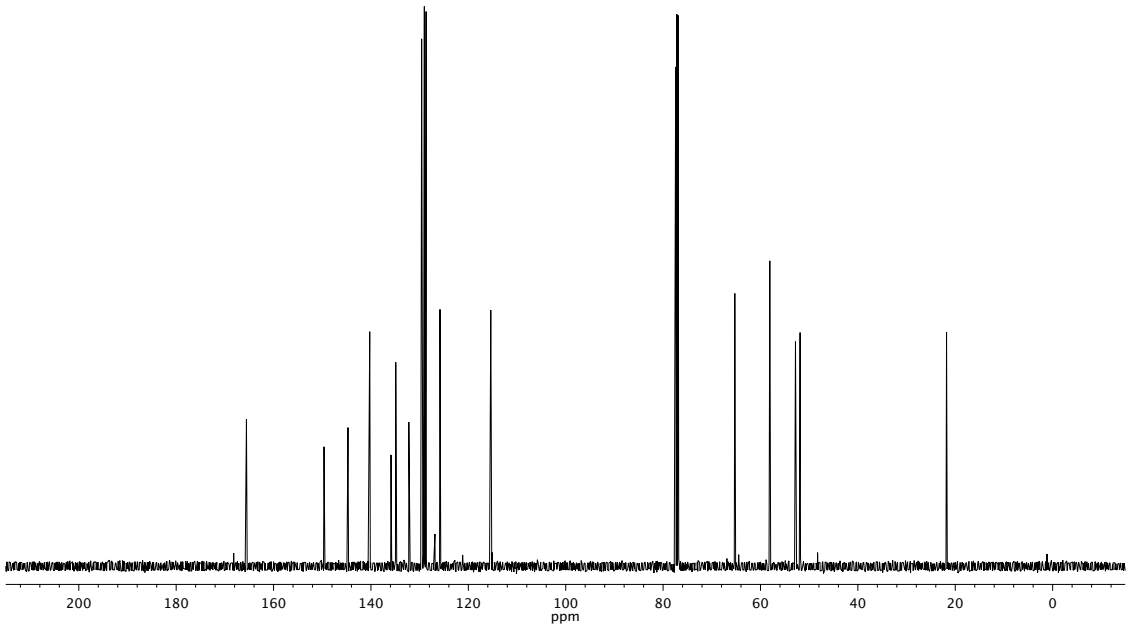


Figure A5.110 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **331**.

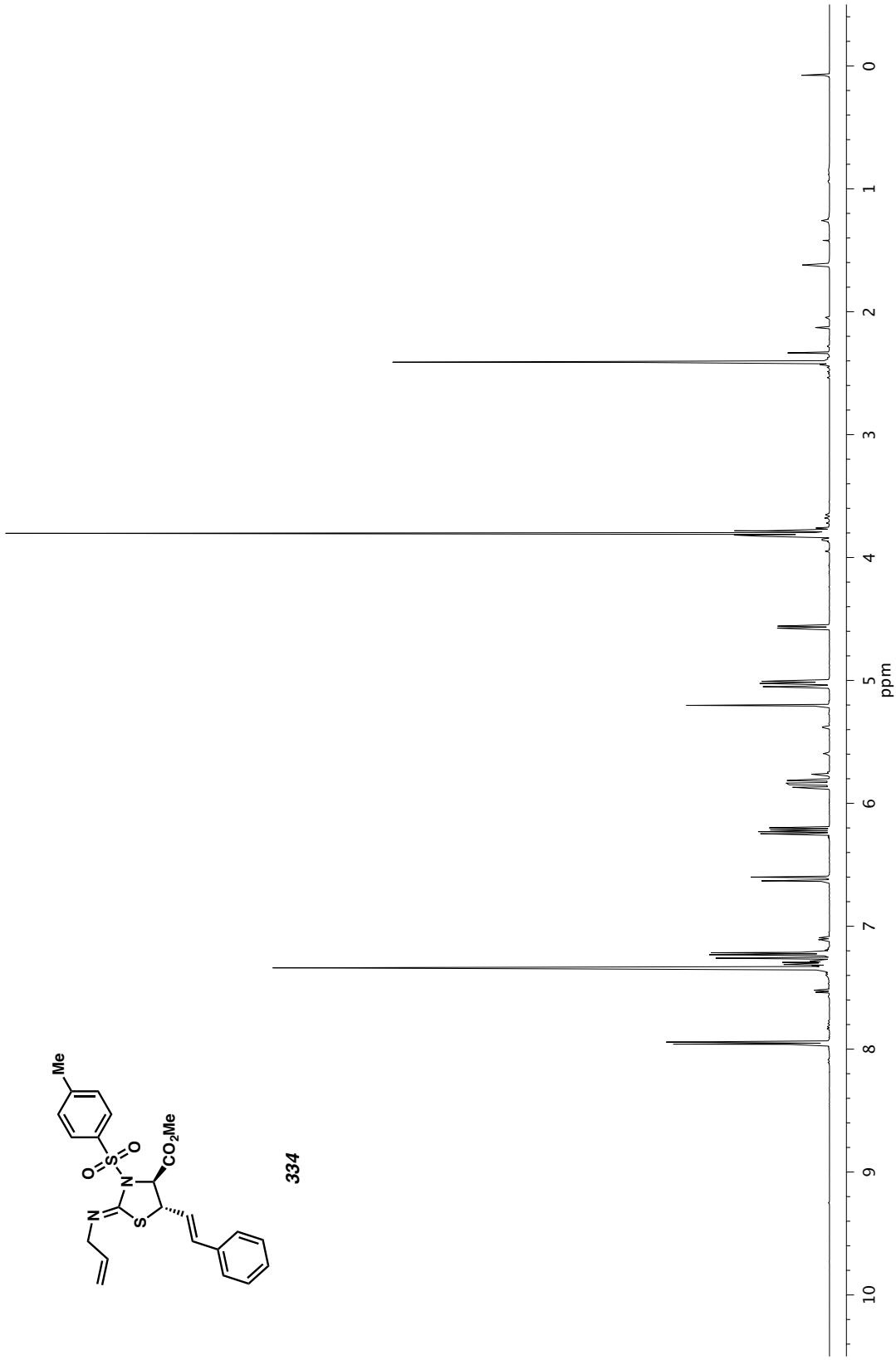


Figure A5.111 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **324**.

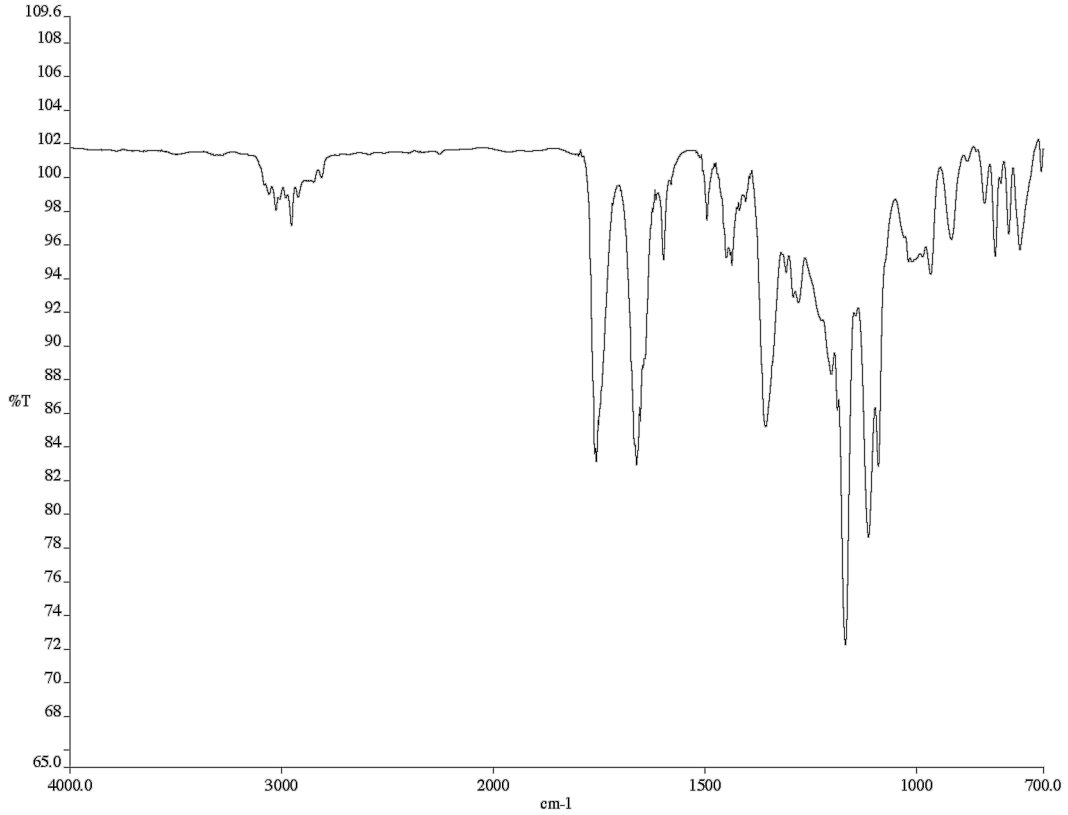


Figure A5.112 Infrared spectrum (thin film/NaCl) of compound **334**.

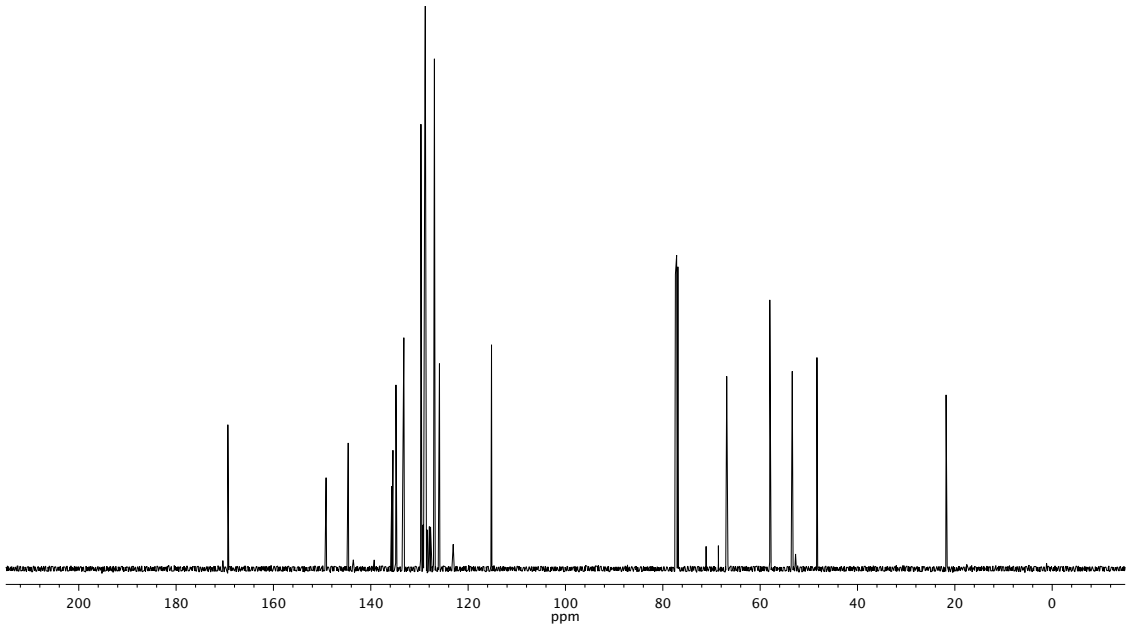


Figure A5.113 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **334**.

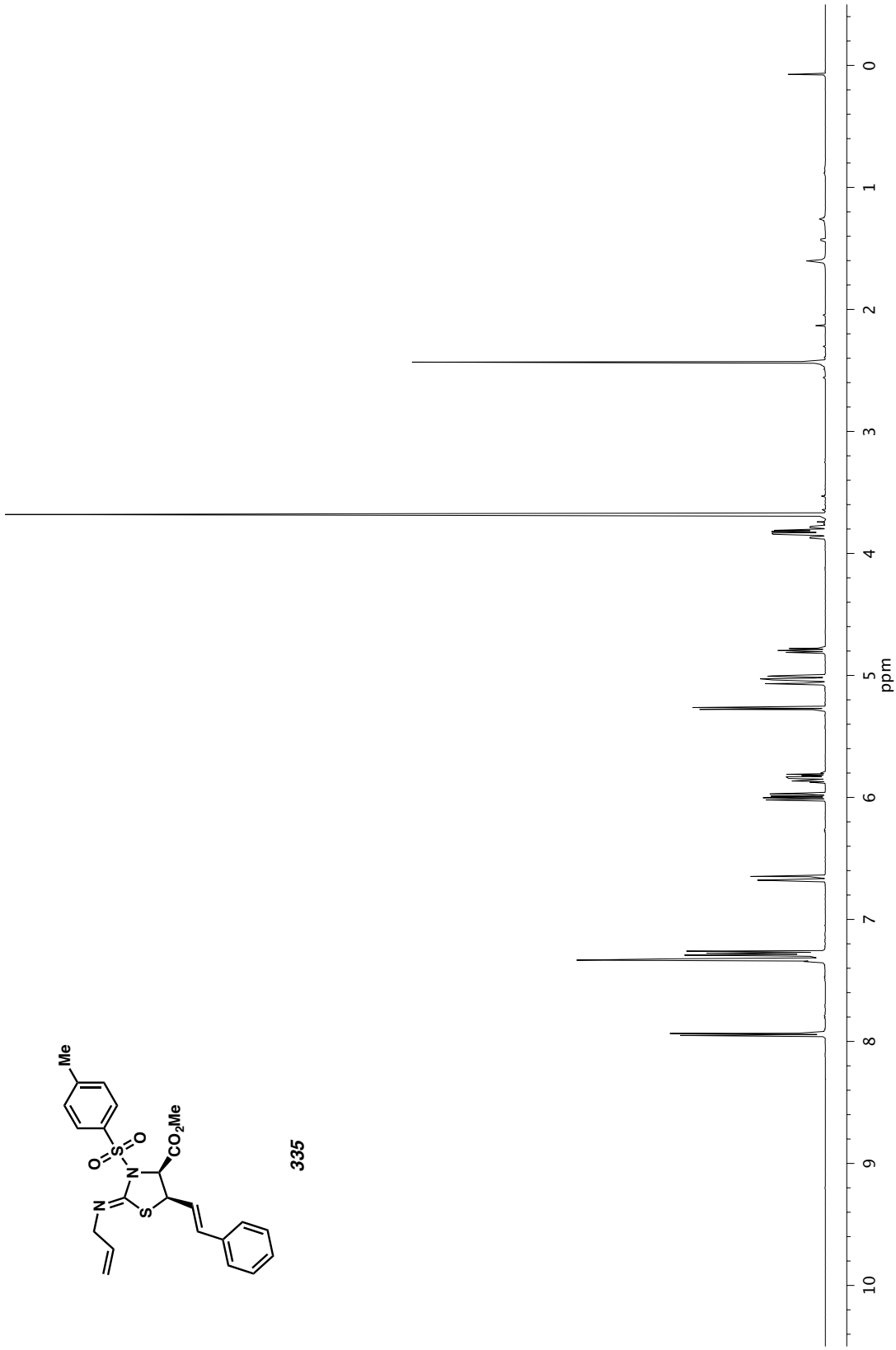


Figure A5.114 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **335**.

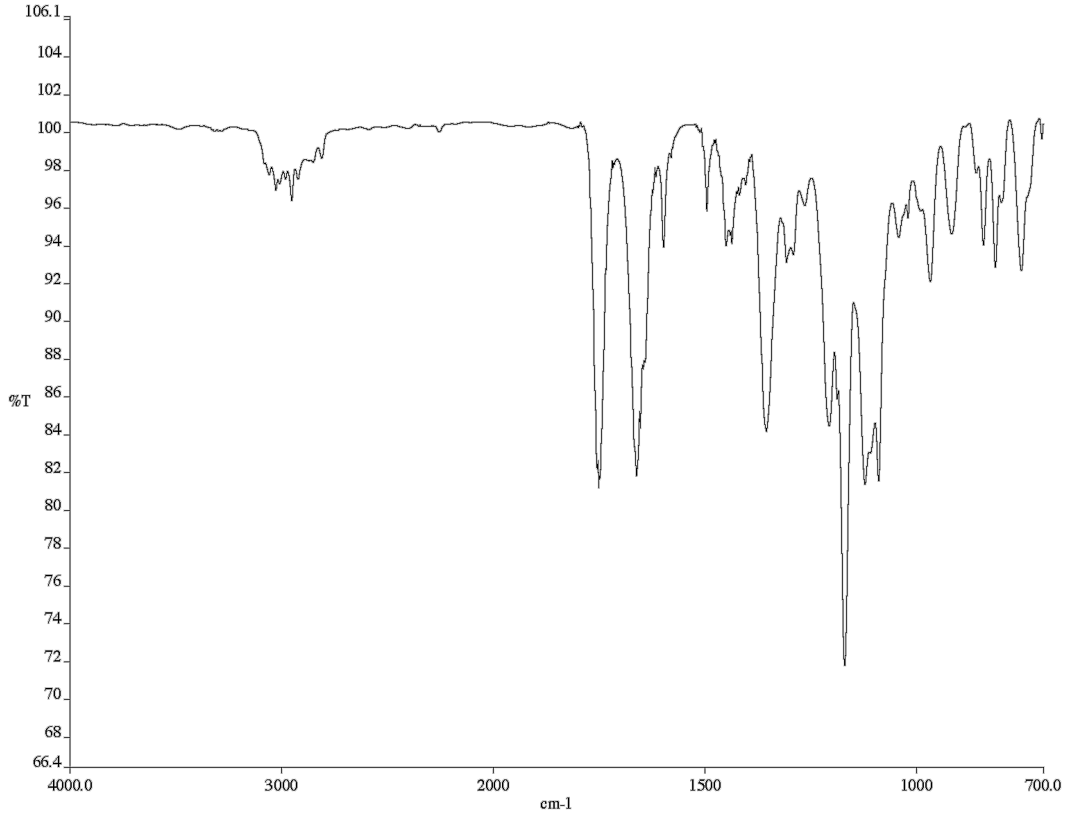


Figure A5.115 Infrared spectrum (thin film/NaCl) of compound **335**.

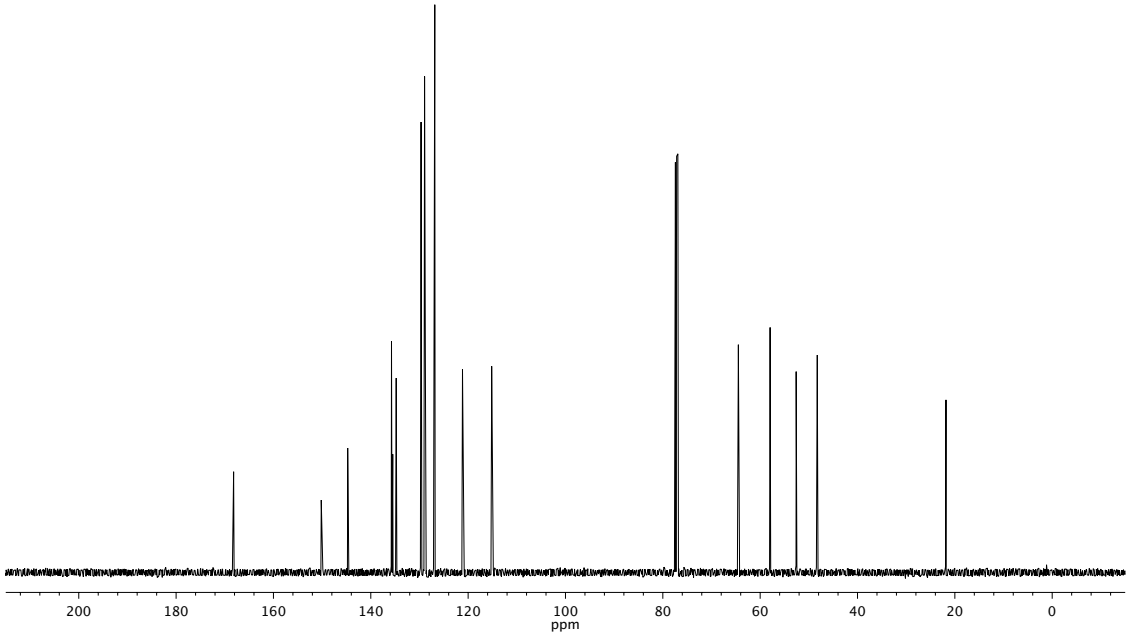
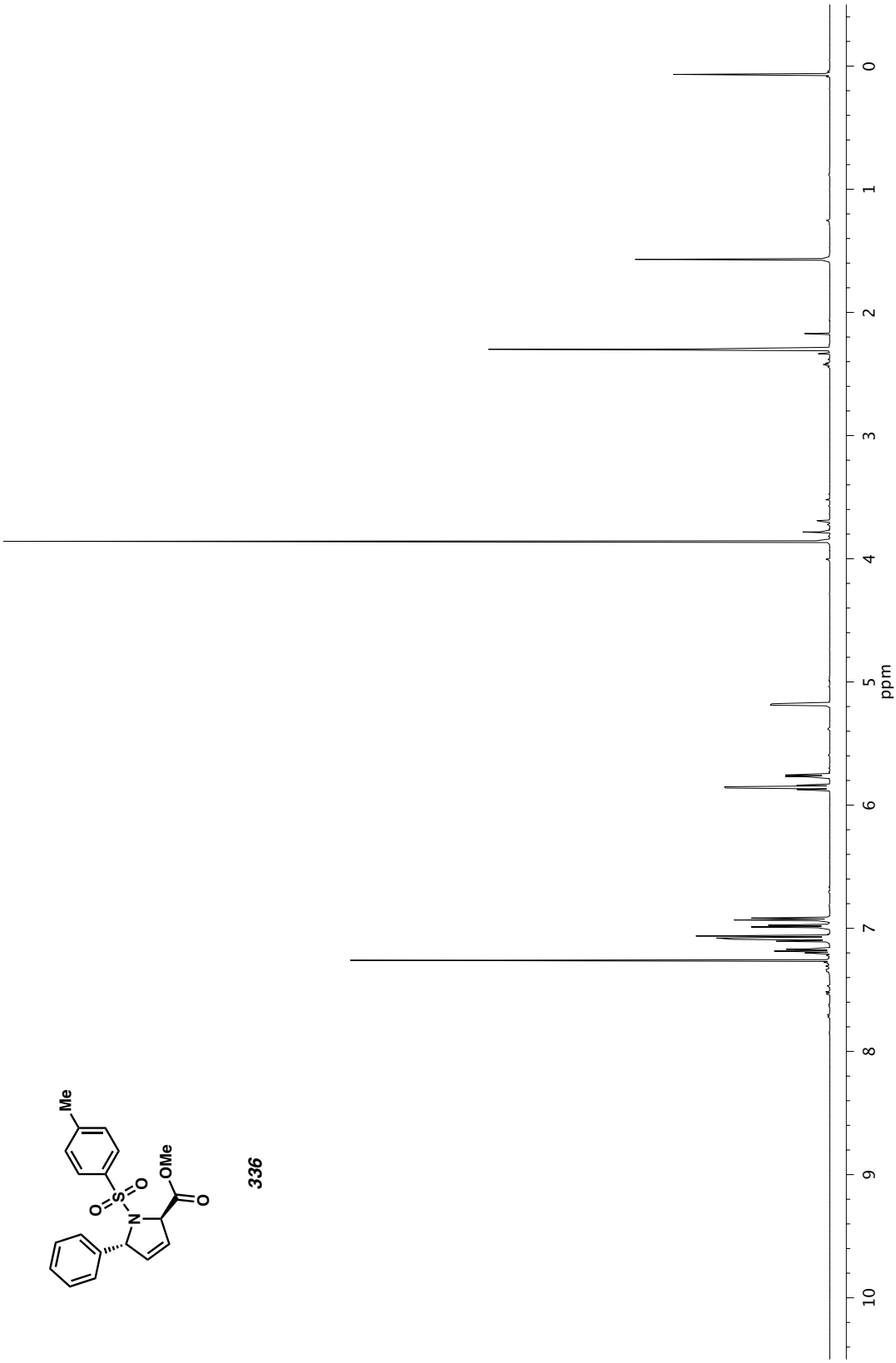


Figure A5.116 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **335**.



336

Figure A5.117 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **336**.

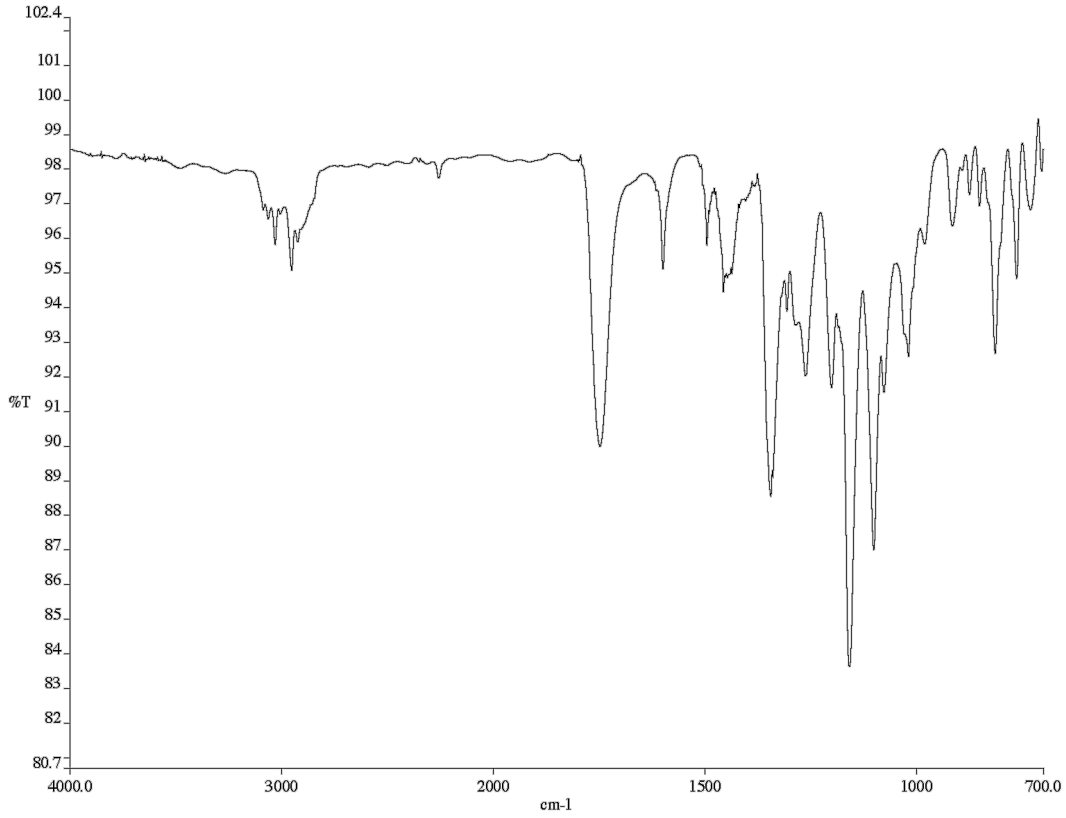


Figure A5.118 Infrared spectrum (thin film/NaCl) of compound **336**.

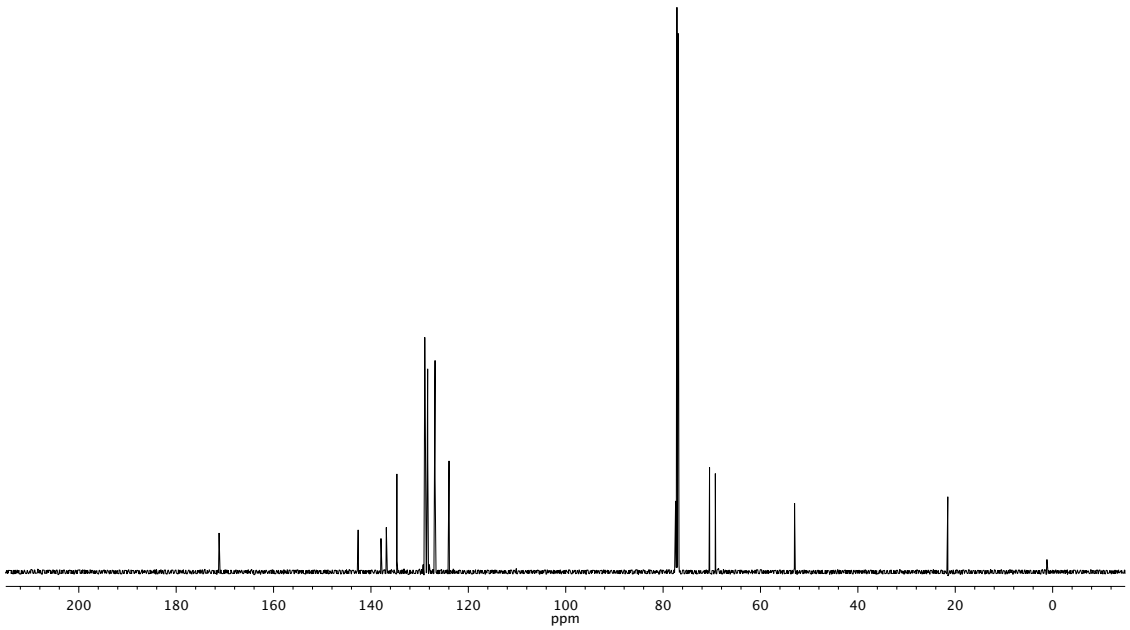


Figure A5.119 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **336**.

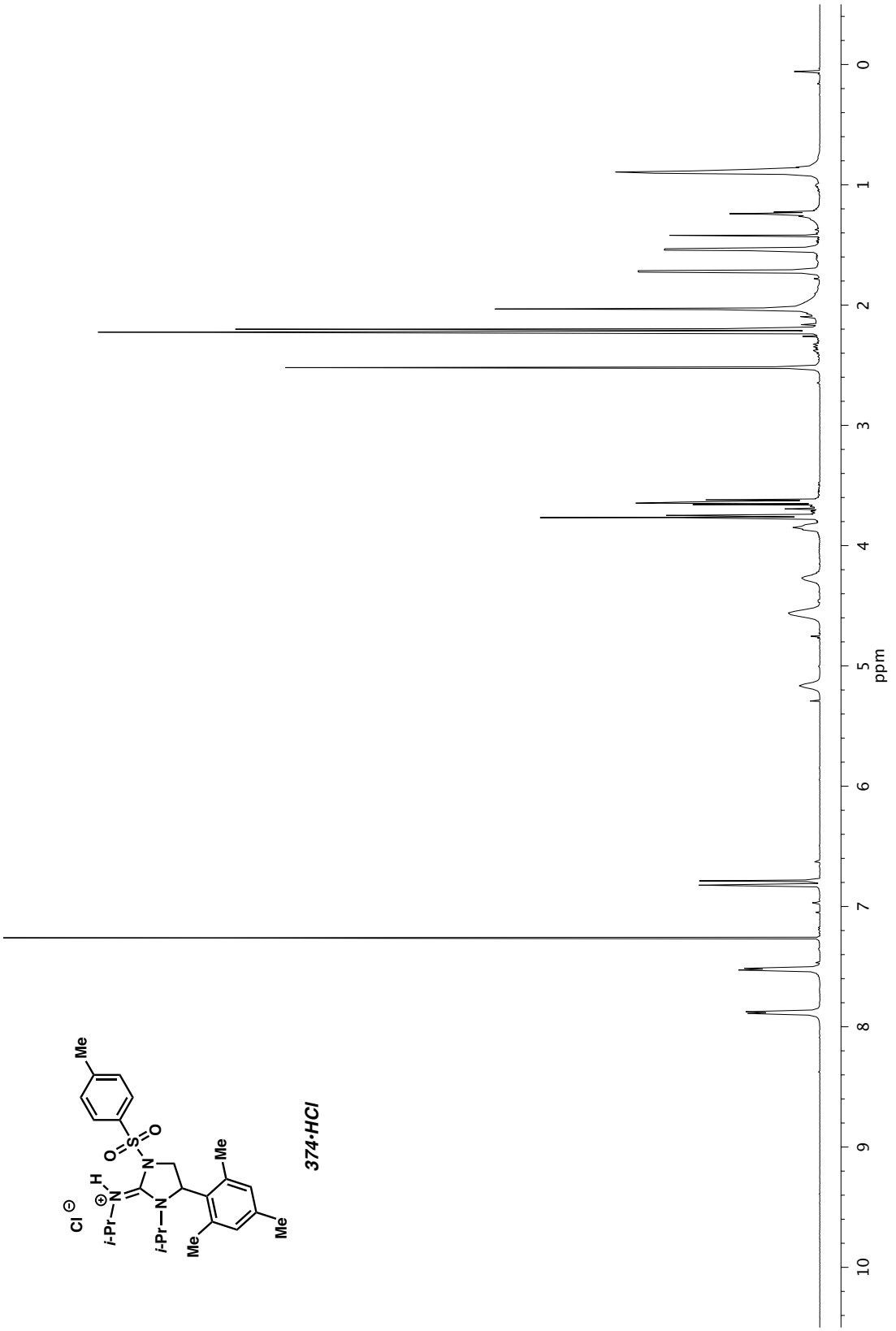


Figure A5.120 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **374•HCl**.

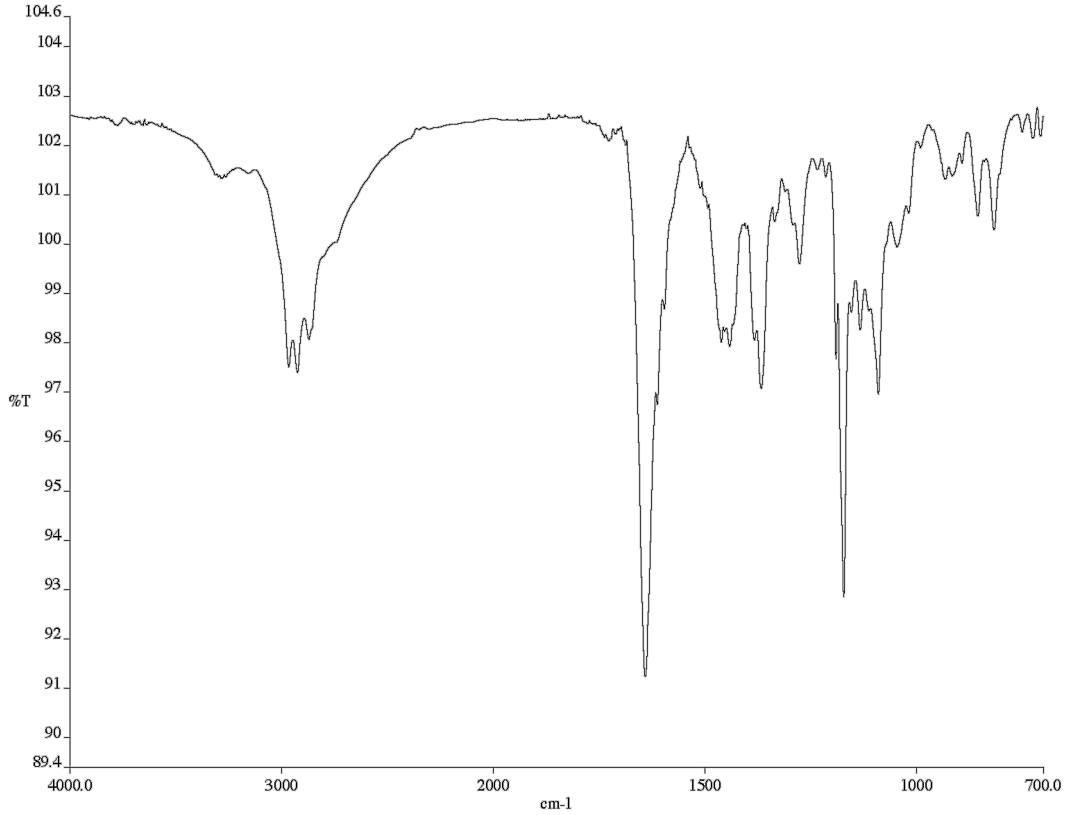


Figure A5.121 Infrared spectrum (Thin Film, NaCl) of compound **374•HCl**.

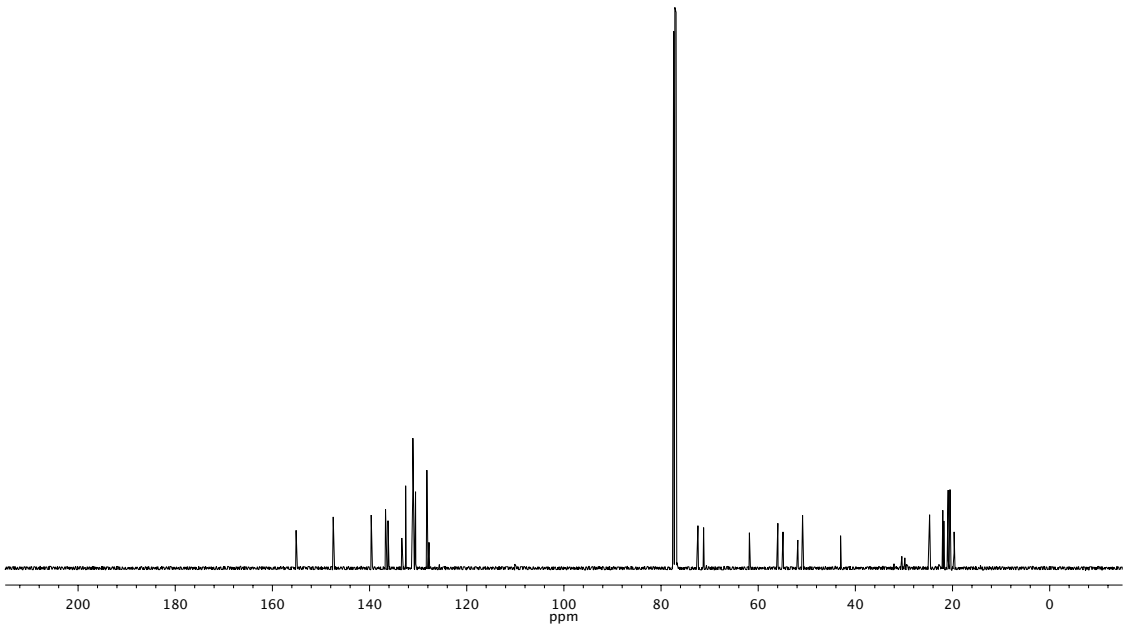


Figure A5.122 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **374•HCl**.

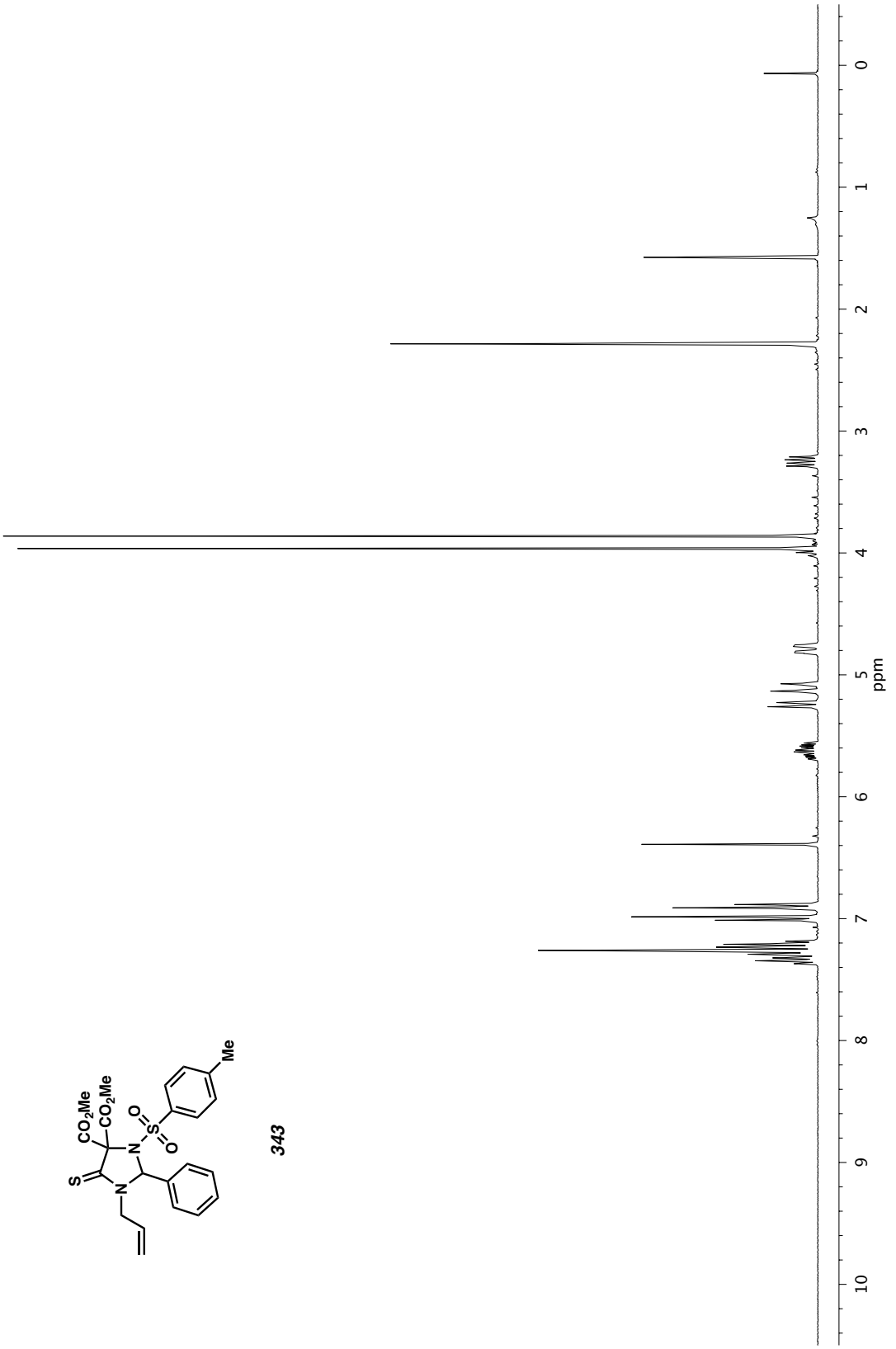


Figure A5.123 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **343**.

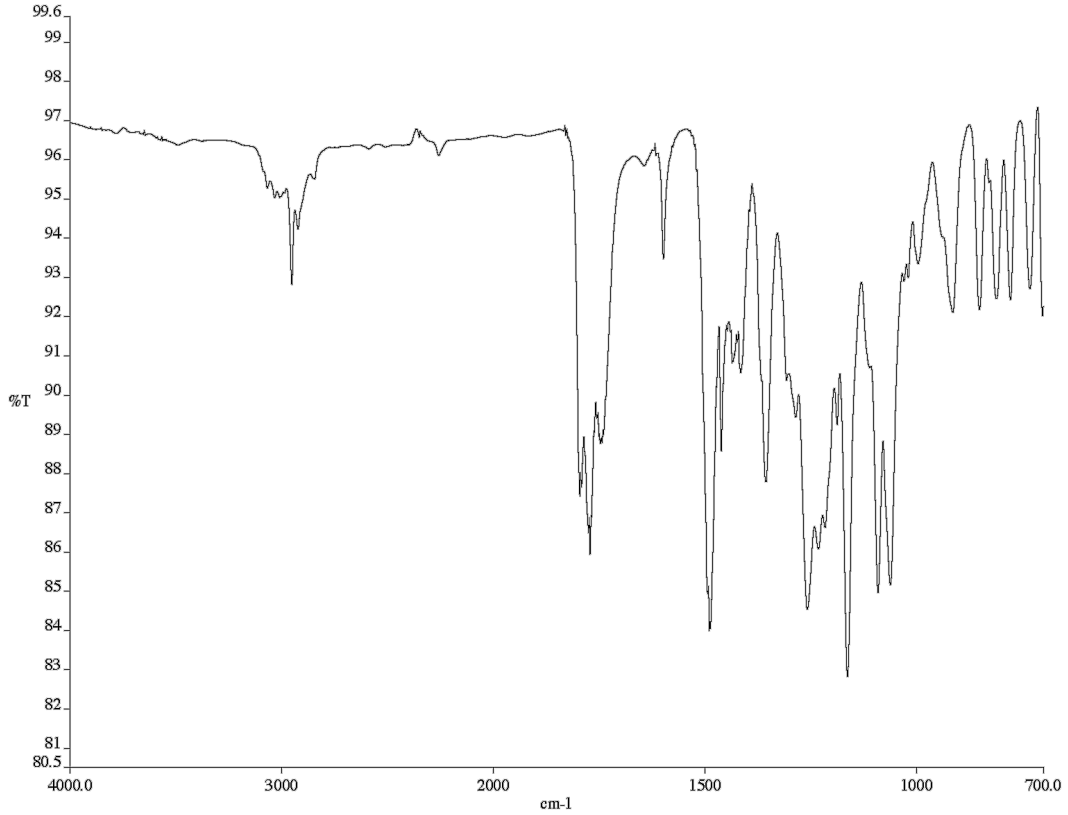


Figure A5.124 Infrared spectrum (thin film/NaCl) of compound **343**.

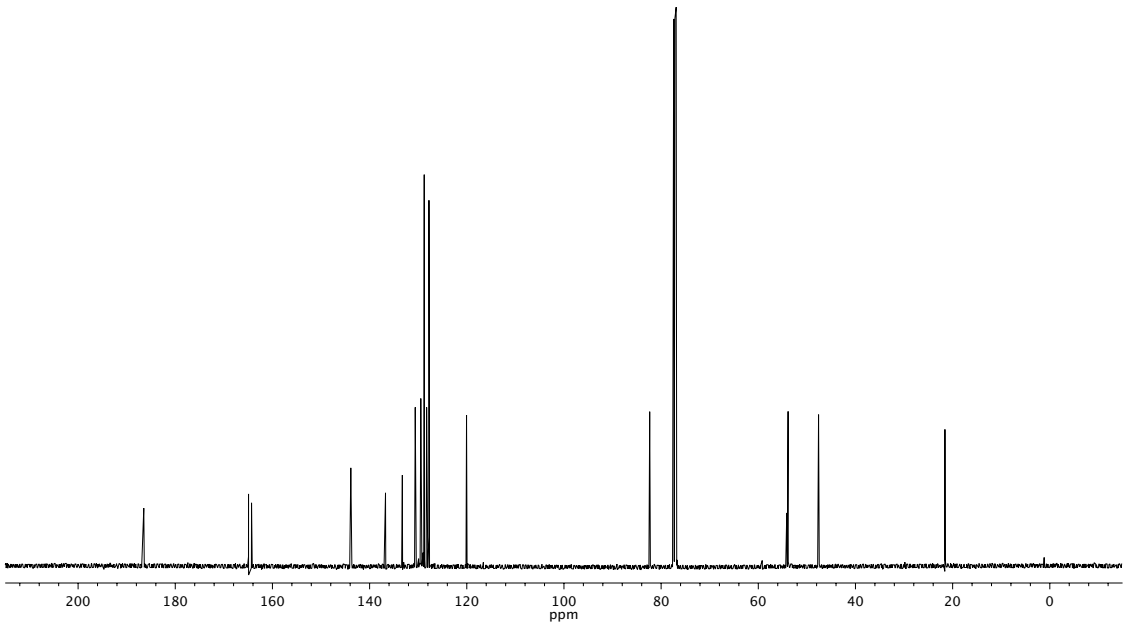


Figure A5.125 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **343**.

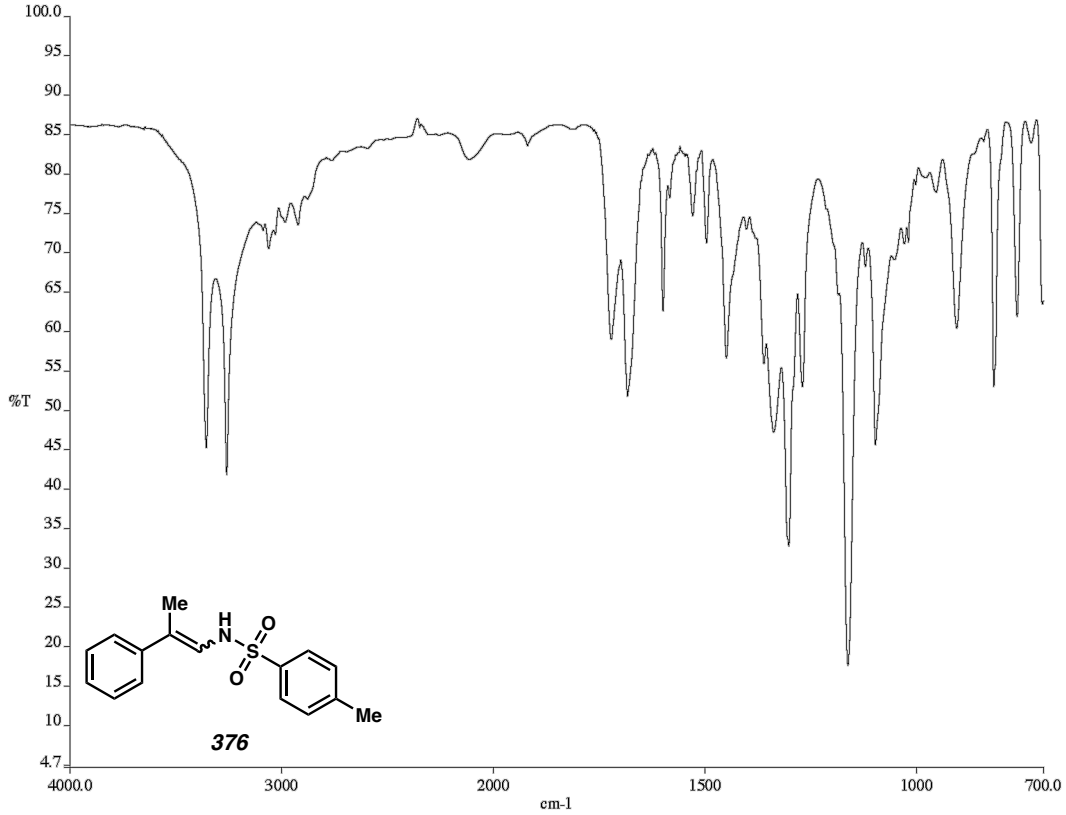


Figure A5.126 Infrared spectrum (thin film/NaCl) of compound **376**.

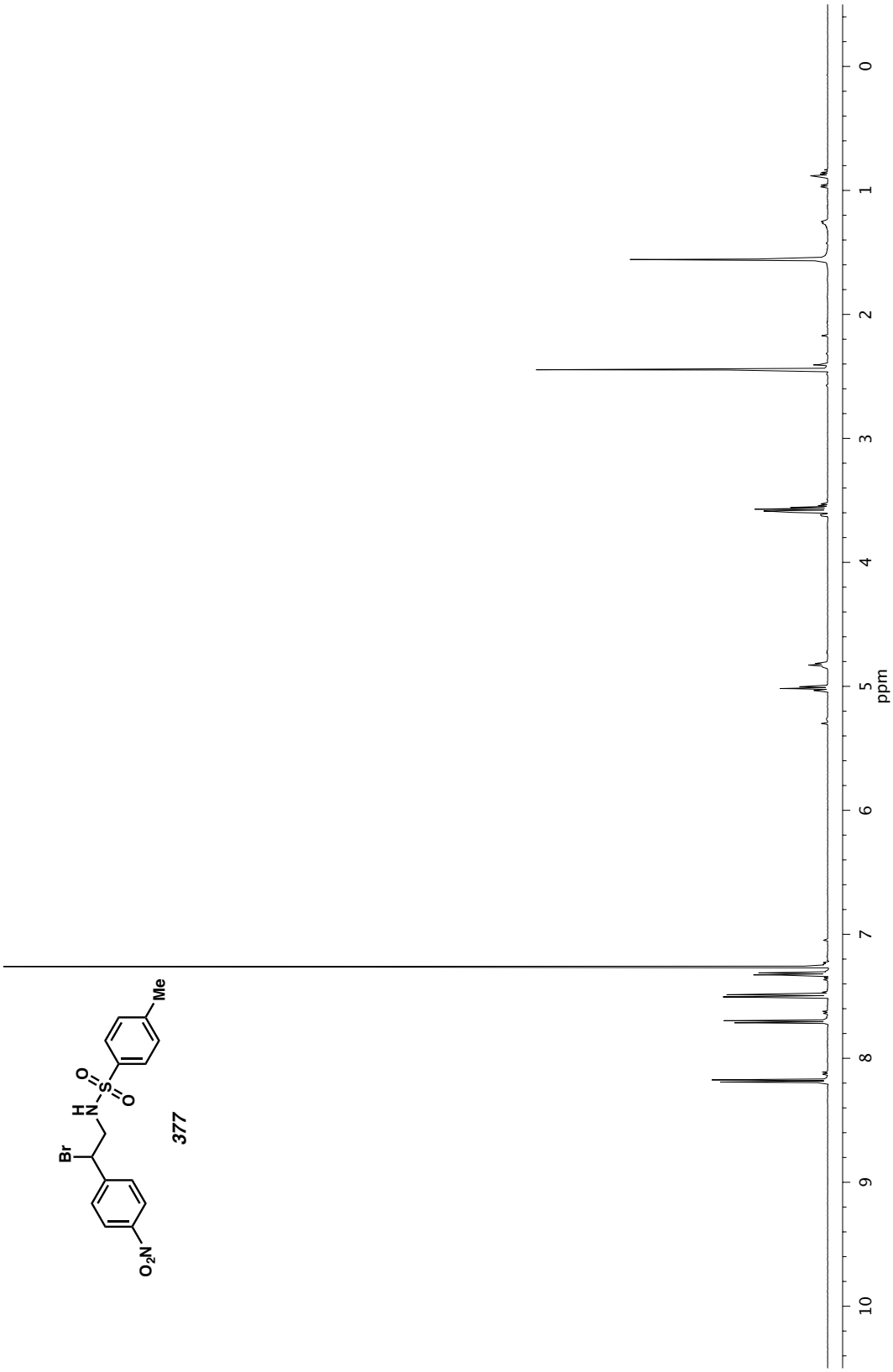


Figure A5.127 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **377**.

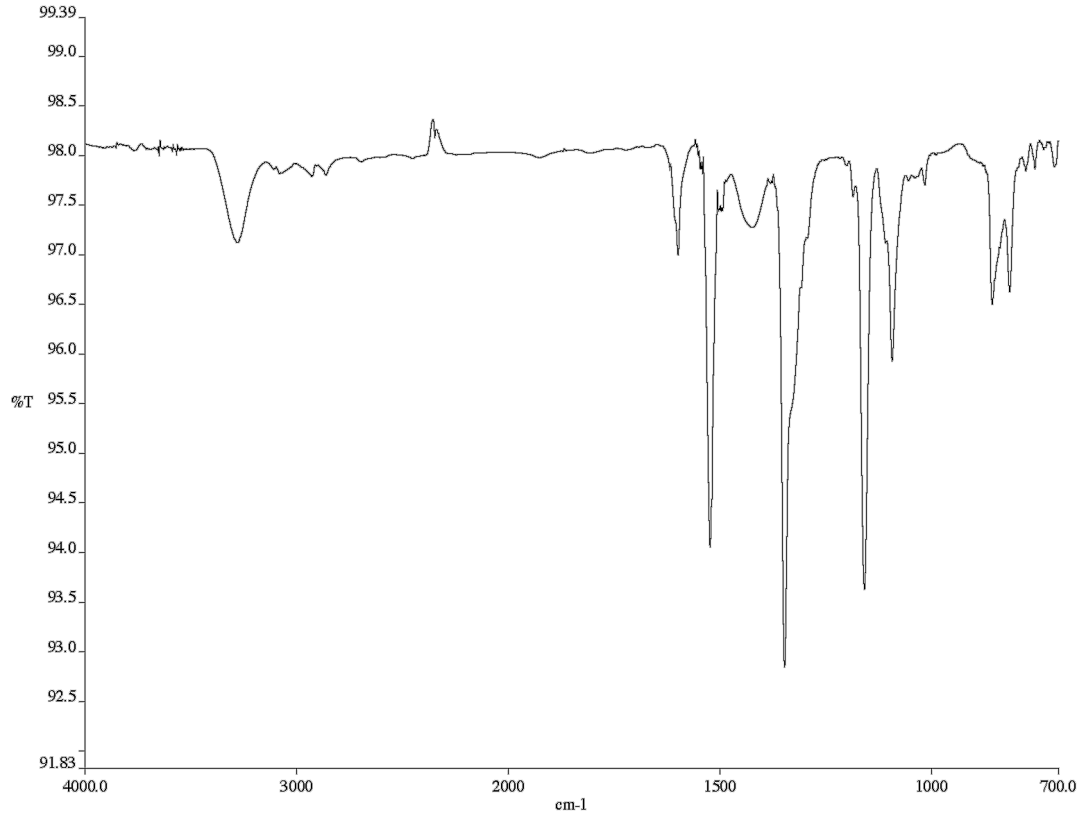


Figure A5.128 Infrared spectrum (thin film/NaCl) of compound **377**.

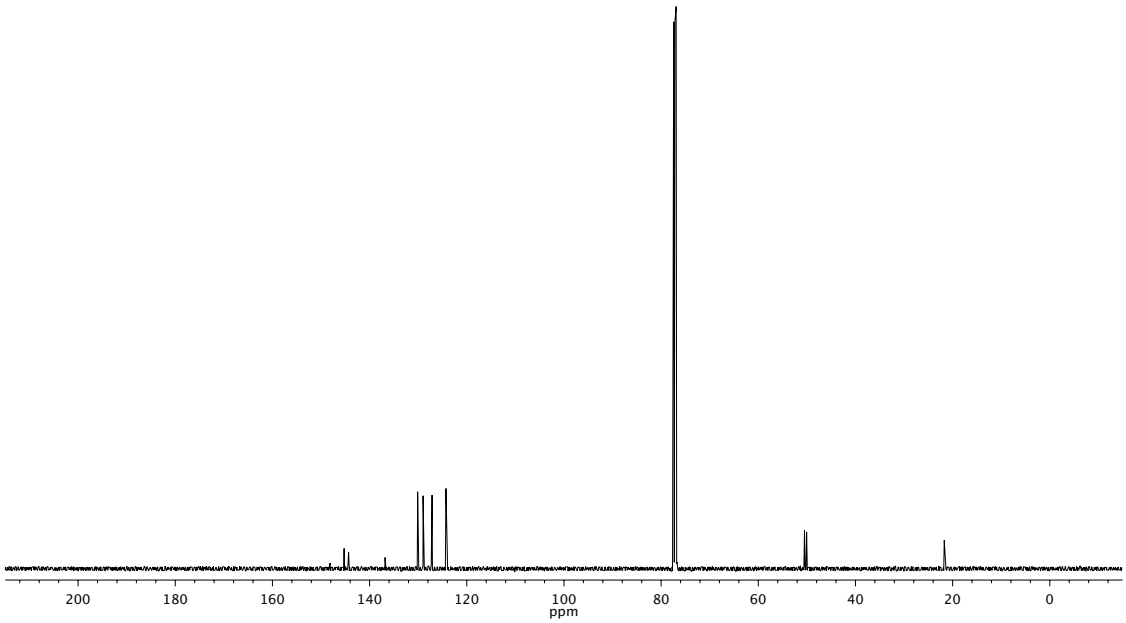


Figure A5.129 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **377**.

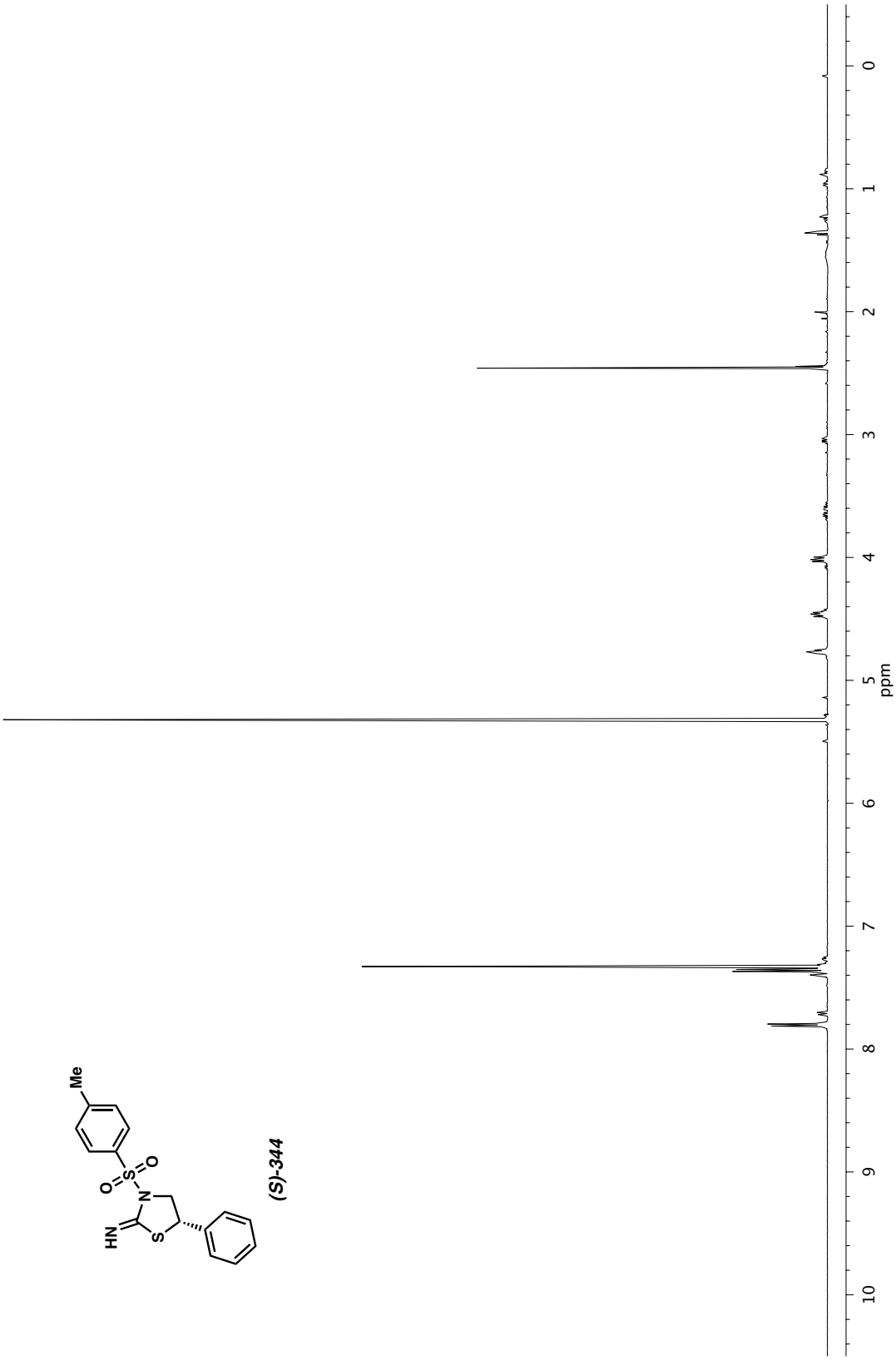


Figure A5.130 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **(*S*)-344**.

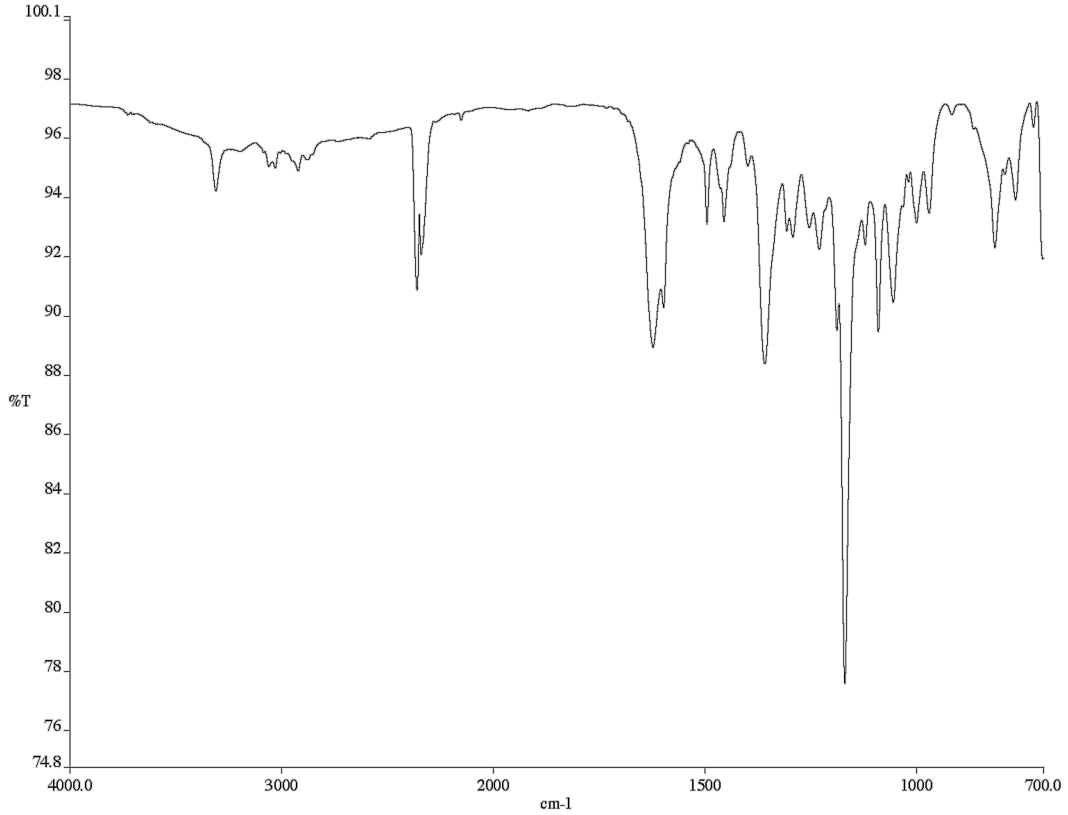


Figure A5.131 Infrared spectrum (Thin Film, NaCl) of compound **(*S*)-344**.

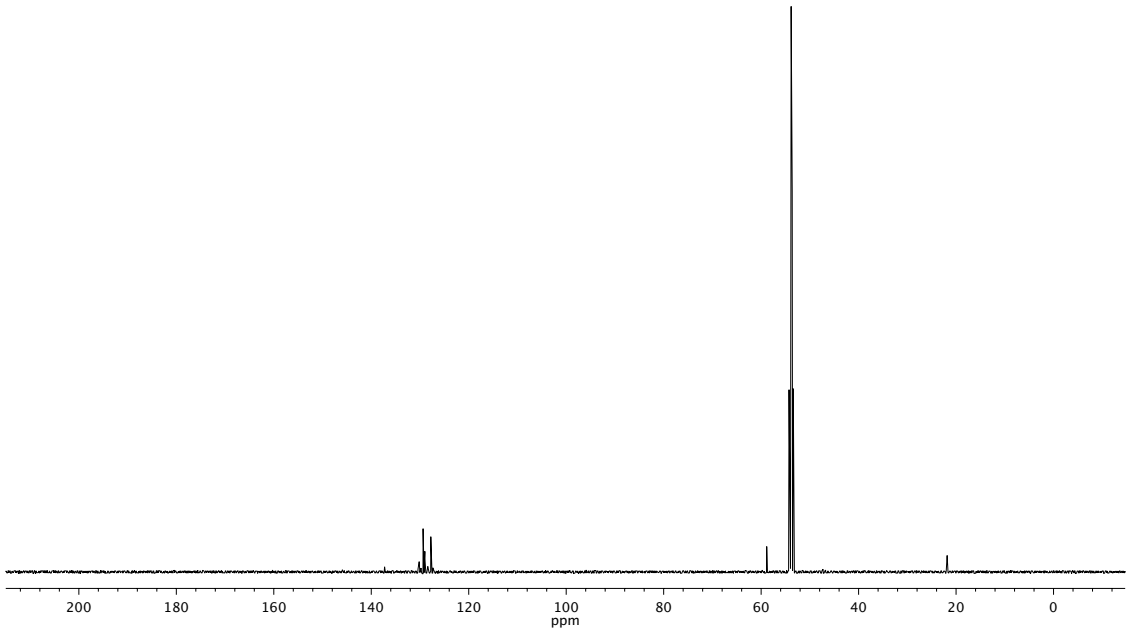


Figure A.5.132 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **(*S*)-344**.

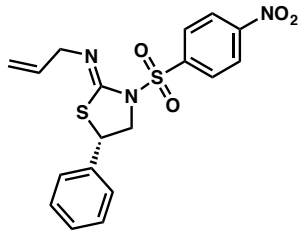
APPENDIX 6

X-Ray Crystallography Reports Relevant to Chapter 3:

Stereoselective Lewis Acid Mediated (3 + 2) Cycloadditions of

N-*H- and* N-*Sulfonylaziridines with Heterocumulenes*

A6.1 X-RAY CRYSTAL STRUCTURE ANALYSIS OF THIAZOLIDINE (*S*)-315



(S)-315

Contents

Figure A6.1.1 X-ray crystal structure of thiazolidine ***(S)-315***

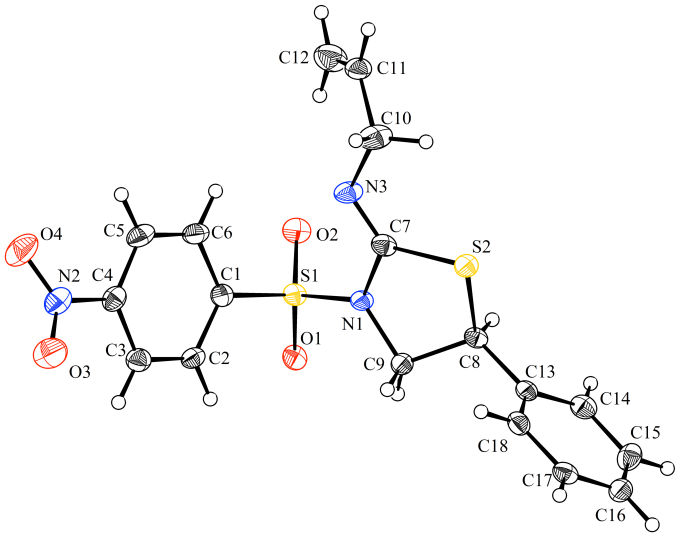


Table A6.1.1. Experimental details for X-ray structure determination of thiazolidine ***(S)-315***

Low-temperature diffraction data (and scans) were collected on a Bruker Kappa diffractometer coupled to a Apex II CCD detector with graphite monochromated Mo *K* radiation (= 0.71073 Å) for the structure of thiazolidine **(*S*)-315**. The structure was solved by direct methods using SHELXS and refined against F^2 on all data by full-matrix least squares with SHELXL-2013 refinement using established techniques. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the *U* value of the atoms they are linked to (1.5 times for methyl groups). All disordered atoms were refined with the help of similarity restraints on the 1,2- and 1,3- distances and displacement parameters as well as rigid bond restraints for anisotropic displacement parameters.

Table A6.1.2 Crystal data and structure refinement for thiazolidine ***(S)-315***

Caltech Identification code	a13024
CCDC Deposition Number	973929
Empirical formula	C18 H17 N3 O4 S2
Formula weight	433.95
Crystallization solvent	Ethyl Acetate/Heptane/Benzene
Crystal shape	blade
Crystal color	colourless
Crystal size	0.04 x 0.11 x 0.40 mm
Preliminary photograph(s)	rotation
Type of diffractometer	Bruker APEX-II CCD
Wavelength	0.71073 Å MoK

Table A6.1.2 (cont'd)

Data collection temperature	100 K	
Theta range for 9894 reflections used in lattice determination	2.34 to 26.36°	
Unit cell dimensions	a = 29.071(2) Å b = 6.0386(5) Å c = 23.0477(19) Å	α= 90° β= 94.233(3)° γ = 90°
Volume	4034.9(6) $Å^3$	
Z	8	
Crystal system	monoclinic	
Space group	C 1 2 1 (# 5)	
Density (calculated)	1.429 g/cm^3	
F(000)	1802	
Theta range for data collection	1.6 to 33.0°	
Completeness to theta = 25.000°	99.9%	
Index ranges	$-42 \le h \le 44, -8 \le k \le 9, -35 \le l \le 35$	
Reflections collected	71248	
Independent reflections	12862 [R_{int}= 0.0785]	
Reflections > 2s(I)	8839	
Average s(I)/(net I)	0.0814	
Absorption coefficient	0.30 mm^{-1}	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.8747	
Primary solution method	dual	
Hydrogen placement	geom	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	12862 / 57 / 594	
Treatment of hydrogen atoms	constr	
Goodness-of-fit on F^2	1.01	
Final R indices [I>2s(I), 8839 reflections]	R1 = 0.0523, wR2 = 0.1051	
R indices (all data)	R1 = 0.0985, wR2 = 0.1215	
Type of weighting scheme used	calc	
Weighting scheme used	w=1/[^2^(Fo^2^)+(0.0559P)^2^+1.2322P] where P=(Fo^2^+2Fc^2^)/3	
Max shift/error	0.001	

Table A6.1.2 (cont'd)

Average shift/error	0.000
Absolute structure parameter	0.08(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.63 and -0.45 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)

Table A6.1.3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for thiazolidine ***(S)-315****. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U_{eq}
S(1)	8262(1)	-810(2)	7758(1)	19(1)
S(2)	7657(1)	76(2)	9340(1)	21(1)
O(1)	8012(1)	158(4)	7260(1)	22(1)
O(2)	8329(1)	-3134(4)	7794(1)	25(1)
O(3)	10067(1)	5822(5)	8110(1)	40(1)
O(4)	10425(1)	2713(5)	8234(1)	44(1)
N(1)	7986(1)	23(5)	8320(1)	20(1)
N(2)	10073(1)	3806(6)	8126(1)	28(1)
N(3)	8456(1)	-1870(5)	9026(1)	26(1)
C(1)	8809(1)	482(6)	7843(1)	20(1)
C(2)	8859(1)	2557(6)	7599(1)	20(1)
C(3)	9278(1)	3659(6)	7690(1)	24(1)
C(4)	9634(1)	2609(6)	8012(1)	23(1)
C(5)	9595(1)	498(6)	8237(1)	26(1)
C(6)	9177(1)	-574(6)	8158(1)	24(1)

Table A6.1.3 (cont'd)

C(7)	8098(1)	-772(6)	8892(1)	21(1)
C(8)	7276(1)	855(5)	8701(1)	18(1)
C(9)	7616(1)	1693(6)	8273(1)	20(1)
C(10)	8540(1)	-2675(7)	9616(1)	35(1)
C(11)	8739(1)	-4949(7)	9632(1)	26(1)
C(12)	8780(1)	-6214(7)	9179(2)	38(1)
C(13)	6914(1)	2514(6)	8844(1)	19(1)
C(14)	6448(1)	1979(6)	8723(1)	24(1)
C(15)	6108(1)	3500(6)	8831(1)	27(1)
C(16)	6225(1)	5531(6)	9070(1)	26(1)
C(17)	6686(1)	6055(6)	9207(1)	22(1)
C(18)	7027(1)	4541(5)	9093(1)	22(1)
S(1A)	1850(1)	2774(2)	7236(1)	24(1)
S(2A)	2370(2)	1779(14)	5621(2)	32(1)
S(2AA)	2253(3)	897(17)	5560(2)	29(1)
O(1A)	2091(1)	1685(4)	7716(1)	27(1)
O(2A)	1813(1)	5115(5)	7229(1)	31(1)
O(3A)	-335(1)	-199(6)	6712(2)	52(1)
O(4A)	-13(1)	-3389(5)	6842(1)	46(1)
N(1A)	2107(1)	1906(5)	6660(1)	25(1)
N(2A)	0(1)	-1372(6)	6830(1)	33(1)
N(3A)	1711(1)	4307(6)	5995(1)	32(1)
C(1A)	1291(1)	1635(6)	7142(1)	22(1)
C(2A)	1220(1)	-452(6)	7371(1)	26(1)
C(3A)	792(1)	-1444(6)	7274(2)	28(1)
C(4A)	450(1)	-287(7)	6954(2)	28(1)
C(5A)	509(1)	1817(7)	6744(2)	31(1)
C(6A)	940(1)	2785(7)	6830(1)	28(1)
C(7A)	1997(1)	2800(7)	6099(1)	25(1)
C(8A)	2550(1)	-700(8)	6107(2)	39(1)
C(9A)	2328(4)	-430(20)	6676(4)	32(2)
C(9AA)	2448(5)	360(20)	6736(6)	18(3)
C(10A)	1625(1)	5058(8)	5392(1)	38(1)
C(11A)	1359(2)	7136(9)	5353(2)	55(1)

Table A6.1.3 (cont'd)

C(12A)	1227(2)	8304(9)	5780(2)	66(2)
C(13A)	3068(1)	-809(7)	6117(1)	23(1)
C(14A)	3272(1)	-2798(6)	5960(1)	28(1)
C(15A)	3756(1)	-2909(9)	5974(2)	43(1)
C(16A)	4014(1)	-1147(10)	6144(2)	51(1)
C(17A)	3809(2)	801(9)	6298(2)	55(1)
C(18A)	3343(2)	954(7)	6286(2)	39(1)
C(19)	50(20)	8890(100)	4820(20)	234(16)
C(20)	-10(17)	6960(100)	5284(17)	235(14)
C(21)	-90(18)	5080(100)	4796(17)	219(12)
C(22)	168(14)	3320(90)	5179(15)	209(12)
C(23)	33(10)	1280(80)	4797(11)	170(10)
C(24)	9986(11)	1970(170)	10141(12)	340(30)
C(25)	10106(12)	3650(130)	9638(15)	360(30)
C(26)	10000	5830(130)	10000	360(30)
C(27)	9890(13)	7930(120)	9647(18)	370(30)
C(28)	9970(16)	9370(170)	10187(16)	340(30)

Table A6.1.4 Bond lengths [Å] and angles [°] for thiazolidine ***(S)-315***

S(1)-O(1)	1.437(2)
S(1)-O(2)	1.418(3)
S(1)-N(1)	1.653(3)
S(1)-C(1)	1.767(3)
S(2)-C(7)	1.780(3)
S(2)-C(8)	1.839(3)
O(3)-N(2)	1.218(4)
O(4)-N(2)	1.228(4)
N(1)-C(7)	1.416(4)
N(1)-C(9)	1.473(4)
N(2)-C(4)	1.472(4)
N(3)-C(7)	1.253(4)
N(3)-C(10)	1.447(4)
C(1)-C(2)	1.386(5)
C(1)-C(6)	1.401(4)
C(2)-H(2)	0.9500
C(2)-C(3)	1.389(5)
C(3)-H(3)	0.9500
C(3)-C(4)	1.382(4)
C(4)-C(5)	1.384(5)
C(5)-H(5)	0.9500
C(5)-C(6)	1.378(5)
C(6)-H(6)	0.9500
C(8)-H(8)	1.0000
C(8)-C(9)	1.533(4)
C(8)-C(13)	1.508(4)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-H(10C)	0.9900
C(10)-H(10D)	0.9900
C(10)-C(11)	1.490(5)
C(11)-H(11)	0.9500
C(11)-C(12)	1.306(5)
C(12)-H(12C)	0.9500

Table A6.1.4 (cont'd)

C(12)-H(12D)	0.9500
C(13)-C(14)	1.399(4)
C(13)-C(18)	1.383(5)
C(14)-H(14)	0.9500
C(14)-C(15)	1.384(5)
C(15)-H(15)	0.9500
C(15)-C(16)	1.376(5)
C(16)-H(16)	0.9500
C(16)-C(17)	1.390(5)
C(17)-H(17)	0.9500
C(17)-C(18)	1.389(5)
C(18)-H(18)	0.9500
S(1A)-O(1A)	1.426(2)
S(1A)-O(2A)	1.418(3)
S(1A)-N(1A)	1.656(3)
S(1A)-C(1A)	1.763(3)
S(2A)-C(7A)	1.718(4)
S(2A)-C(8A)	1.919(6)
S(2AA)-C(7A)	1.886(7)
S(2AA)-C(8A)	1.763(6)
O(3A)-N(2A)	1.218(4)
O(4A)-N(2A)	1.219(4)
N(1A)-C(7A)	1.415(4)
N(1A)-C(9A)	1.548(12)
N(1A)-C(9AA)	1.364(14)
N(2A)-C(4A)	1.472(5)
N(3A)-C(7A)	1.243(5)
N(3A)-C(10A)	1.465(4)
C(1A)-C(2A)	1.388(5)
C(1A)-C(6A)	1.389(5)
C(2A)-H(2A)	0.9500
C(2A)-C(3A)	1.384(5)
C(3A)-H(3A)	0.9500
C(3A)-C(4A)	1.384(5)

Table A6.1.4 (cont'd)

C(4A)-C(5A)	1.375(6)
C(5A)-H(5A)	0.9500
C(5A)-C(6A)	1.383(5)
C(6A)-H(6A)	0.9500
C(8A)-H(8A)	1.0000
C(8A)-H(8AA)	1.0000
C(8A)-C(9A)	1.512(10)
C(8A)-C(9AA)	1.630(13)
C(8A)-C(13A)	1.506(5)
C(9A)-H(9AA)	0.9900
C(9A)-H(9AB)	0.9900
C(9AA)-H(9AC)	0.9900
C(9AA)-H(9AD)	0.9900
C(10A)-H(10A)	0.9900
C(10A)-H(10B)	0.9900
C(10A)-C(11A)	1.473(6)
C(11A)-H(11A)	0.9500
C(11A)-C(12A)	1.293(6)
C(12A)-H(12A)	0.9500
C(12A)-H(12B)	0.9500
C(13A)-C(14A)	1.399(5)
C(13A)-C(18A)	1.370(5)
C(14A)-H(14A)	0.9500
C(14A)-C(15A)	1.409(5)
C(15A)-H(15A)	0.9500
C(15A)-C(16A)	1.343(7)
C(16A)-H(16A)	0.9500
C(16A)-C(17A)	1.378(7)
C(17A)-H(17A)	0.9500
C(17A)-C(18A)	1.358(7)
C(18A)-H(18A)	0.9500
C(19)-C(19)#1	0.90(10)
C(19)-C(20)	1.60(2)
C(19)-C(20)#1	1.20(4)

Table A6.1.4 (cont'd)

C(19)-C(23)#2	1.45(4)
C(19)-C(23)#3	1.72(4)
C(20)-C(19)#1	1.20(4)
C(20)-C(20)#1	1.31(8)
C(20)-C(21)#1	1.19(4)
C(20)-C(21)	1.60(2)
C(21)-C(20)#1	1.19(4)
C(21)-C(21)#1	1.04(7)
C(21)-C(22)#1	1.09(4)
C(21)-C(22)	1.54(2)
C(22)-C(21)#1	1.09(4)
C(22)-C(22)#1	1.23(7)
C(22)-C(23)#1	1.37(4)
C(22)-C(23)	1.55(2)
C(23)-C(19)#4	1.72(4)
C(23)-C(19)#5	1.45(4)
C(23)-C(22)#1	1.37(4)
C(23)-C(23)#1	0.97(4)
C(24)-C(24)#6	0.66(5)
C(24)-C(25)	1.60(2)
C(24)-C(25)#6	1.18(5)
C(24)-C(28)#5	1.57(7)
C(24)-C(28)#7	1.75(6)
C(25)-C(24)#6	1.18(5)
C(25)-C(25)#6	1.82(7)
C(25)-C(26)	1.60(2)
C(26)-C(25)#6	1.60(2)
C(26)-C(27)#6	1.53(2)
C(26)-C(27)	1.53(2)
C(27)-C(27)#6	1.70(8)
C(27)-C(28)	1.52(2)
C(27)-C(28)#6	1.02(6)
C(28)-C(24)#8	1.75(6)
C(28)-C(24)#2	1.57(7)

Table A6.1.4 (cont'd)

C(28)-C(27)#6	1.02(6)
C(28)-C(28)#6	0.89(9)
O(1)-S(1)-N(1)	104.85(13)
O(1)-S(1)-C(1)	107.87(15)
O(2)-S(1)-O(1)	120.48(15)
O(2)-S(1)-N(1)	109.13(15)
O(2)-S(1)-C(1)	108.25(15)
N(1)-S(1)-C(1)	105.26(14)
C(7)-S(2)-C(8)	91.39(14)
C(7)-N(1)-S(1)	122.3(2)
C(7)-N(1)-C(9)	114.6(2)
C(9)-N(1)-S(1)	123.0(2)
O(3)-N(2)-O(4)	123.6(3)
O(3)-N(2)-C(4)	118.4(3)
O(4)-N(2)-C(4)	118.0(3)
C(7)-N(3)-C(10)	119.3(3)
C(2)-C(1)-S(1)	118.3(2)
C(2)-C(1)-C(6)	121.5(3)
C(6)-C(1)-S(1)	120.2(3)
C(1)-C(2)-H(2)	120.4
C(1)-C(2)-C(3)	119.3(3)
C(3)-C(2)-H(2)	120.4
C(2)-C(3)-H(3)	120.8
C(4)-C(3)-C(2)	118.3(3)
C(4)-C(3)-H(3)	120.8
C(3)-C(4)-N(2)	118.4(3)
C(3)-C(4)-C(5)	123.0(3)
C(5)-C(4)-N(2)	118.6(3)
C(4)-C(5)-H(5)	120.7
C(6)-C(5)-C(4)	118.6(3)
C(6)-C(5)-H(5)	120.7
C(1)-C(6)-H(6)	120.4
C(5)-C(6)-C(1)	119.2(3)
C(5)-C(6)-H(6)	120.4

Table A6.1.4 (cont'd)

N(1)-C(7)-S(2)	108.5(2)
N(3)-C(7)-S(2)	129.0(2)
N(3)-C(7)-N(1)	122.5(3)
S(2)-C(8)-H(8)	108.9
C(9)-C(8)-S(2)	102.8(2)
C(9)-C(8)-H(8)	108.9
C(13)-C(8)-S(2)	112.5(2)
C(13)-C(8)-H(8)	108.9
C(13)-C(8)-C(9)	114.6(3)
N(1)-C(9)-C(8)	103.2(2)
N(1)-C(9)-H(9A)	111.1
N(1)-C(9)-H(9B)	111.1
C(8)-C(9)-H(9A)	111.1
C(8)-C(9)-H(9B)	111.1
H(9A)-C(9)-H(9B)	109.1
N(3)-C(10)-H(10C)	109.3
N(3)-C(10)-H(10D)	109.3
N(3)-C(10)-C(11)	111.8(3)
H(10C)-C(10)-H(10D)	107.9
C(11)-C(10)-H(10C)	109.3
C(11)-C(10)-H(10D)	109.3
C(10)-C(11)-H(11)	117.4
C(12)-C(11)-C(10)	125.3(3)
C(12)-C(11)-H(11)	117.4
C(11)-C(12)-H(12C)	120.0
C(11)-C(12)-H(12D)	120.0
H(12C)-C(12)-H(12D)	120.0
C(14)-C(13)-C(8)	119.0(3)
C(18)-C(13)-C(8)	122.0(3)
C(18)-C(13)-C(14)	119.0(3)
C(13)-C(14)-H(14)	119.9
C(15)-C(14)-C(13)	120.2(3)
C(15)-C(14)-H(14)	119.9
C(14)-C(15)-H(15)	119.8

Table A6.1.4 (cont'd)

C(16)-C(15)-C(14)	120.4(3)
C(16)-C(15)-H(15)	119.8
C(15)-C(16)-H(16)	120.1
C(15)-C(16)-C(17)	119.8(3)
C(17)-C(16)-H(16)	120.1
C(16)-C(17)-H(17)	120.1
C(18)-C(17)-C(16)	119.9(3)
C(18)-C(17)-H(17)	120.1
C(13)-C(18)-C(17)	120.6(3)
C(13)-C(18)-H(18)	119.7
C(17)-C(18)-H(18)	119.7
O(1A)-S(1A)-N(1A)	104.59(15)
O(1A)-S(1A)-C(1A)	108.09(16)
O(2A)-S(1A)-O(1A)	120.09(16)
O(2A)-S(1A)-N(1A)	110.18(16)
O(2A)-S(1A)-C(1A)	108.57(17)
N(1A)-S(1A)-C(1A)	104.15(15)
C(7A)-S(2A)-C(8A)	93.6(2)
C(8A)-S(2AA)-C(7A)	93.3(2)
C(7A)-N(1A)-S(1A)	121.7(3)
C(7A)-N(1A)-C(9A)	115.8(5)
C(9A)-N(1A)-S(1A)	118.7(4)
C(9AA)-N(1A)-S(1A)	118.7(6)
C(9AA)-N(1A)-C(7A)	119.5(6)
O(3A)-N(2A)-O(4A)	124.1(4)
O(3A)-N(2A)-C(4A)	118.0(3)
O(4A)-N(2A)-C(4A)	117.9(3)
C(7A)-N(3A)-C(10A)	118.3(3)
C(2A)-C(1A)-S(1A)	118.0(3)
C(2A)-C(1A)-C(6A)	121.7(3)
C(6A)-C(1A)-S(1A)	120.3(3)
C(1A)-C(2A)-H(2A)	120.4
C(3A)-C(2A)-C(1A)	119.2(3)
C(3A)-C(2A)-H(2A)	120.4

Table A6.1.4 (cont'd)

C(2A)-C(3A)-H(3A)	121.0
C(2A)-C(3A)-C(4A)	118.0(3)
C(4A)-C(3A)-H(3A)	121.0
C(3A)-C(4A)-N(2A)	118.2(3)
C(5A)-C(4A)-N(2A)	118.4(3)
C(5A)-C(4A)-C(3A)	123.4(3)
C(4A)-C(5A)-H(5A)	120.8
C(4A)-C(5A)-C(6A)	118.4(4)
C(6A)-C(5A)-H(5A)	120.8
C(1A)-C(6A)-H(6A)	120.4
C(5A)-C(6A)-C(1A)	119.1(4)
C(5A)-C(6A)-H(6A)	120.4
N(1A)-C(7A)-S(2A)	109.7(3)
N(1A)-C(7A)-S(2AA)	107.2(3)
N(3A)-C(7A)-S(2A)	125.7(3)
N(3A)-C(7A)-S(2AA)	127.5(3)
N(3A)-C(7A)-N(1A)	124.0(3)
S(2A)-C(8A)-H(8A)	108.0
S(2AA)-C(8A)-H(8AA)	108.6
C(9A)-C(8A)-S(2A)	107.8(5)
C(9A)-C(8A)-H(8A)	108.0
C(9AA)-C(8A)-S(2AA)	108.1(6)
C(9AA)-C(8A)-H(8AA)	108.6
C(13A)-C(8A)-S(2A)	105.7(3)
C(13A)-C(8A)-S(2AA)	118.1(4)
C(13A)-C(8A)-H(8A)	108.0
C(13A)-C(8A)-H(8AA)	108.6
C(13A)-C(8A)-C(9A)	118.8(5)
C(13A)-C(8A)-C(9AA)	104.6(6)
N(1A)-C(9A)-H(9AA)	110.5
N(1A)-C(9A)-H(9AB)	110.5
C(8A)-C(9A)-N(1A)	106.3(7)
C(8A)-C(9A)-H(9AA)	110.5
C(8A)-C(9A)-H(9AB)	110.5

Table A6.1.4 (cont'd)

H(9AA)-C(9A)-H(9AB)	108.7
N(1A)-C(9AA)-C(8A)	109.4(9)
N(1A)-C(9AA)-H(9AC)	109.8
N(1A)-C(9AA)-H(9AD)	109.8
C(8A)-C(9AA)-H(9AC)	109.8
C(8A)-C(9AA)-H(9AD)	109.8
H(9AC)-C(9AA)-H(9AD)	108.2
N(3A)-C(10A)-H(10A)	109.2
N(3A)-C(10A)-H(10B)	109.2
N(3A)-C(10A)-C(11A)	112.0(3)
H(10A)-C(10A)-H(10B)	107.9
C(11A)-C(10A)-H(10A)	109.2
C(11A)-C(10A)-H(10B)	109.2
C(10A)-C(11A)-H(11A)	116.5
C(12A)-C(11A)-C(10A)	127.0(4)
C(12A)-C(11A)-H(11A)	116.5
C(11A)-C(12A)-H(12A)	120.0
C(11A)-C(12A)-H(12B)	120.0
H(12A)-C(12A)-H(12B)	120.0
C(14A)-C(13A)-C(8A)	118.4(4)
C(18A)-C(13A)-C(8A)	122.1(4)
C(18A)-C(13A)-C(14A)	119.5(3)
C(13A)-C(14A)-H(14A)	120.8
C(13A)-C(14A)-C(15A)	118.4(4)
C(15A)-C(14A)-H(14A)	120.8
C(14A)-C(15A)-H(15A)	119.8
C(16A)-C(15A)-C(14A)	120.4(4)
C(16A)-C(15A)-H(15A)	119.8
C(15A)-C(16A)-H(16A)	119.7
C(15A)-C(16A)-C(17A)	120.5(4)
C(17A)-C(16A)-H(16A)	119.7
C(16A)-C(17A)-H(17A)	119.9
C(18A)-C(17A)-C(16A)	120.2(4)
C(18A)-C(17A)-H(17A)	119.9

Table A6.1.4 (cont'd)

C(13A)-C(18A)-H(18A)	119.6
C(17A)-C(18A)-C(13A)	120.9(4)
C(17A)-C(18A)-H(18A)	119.6
C(19)#1-C(19)-C(20)#1	98(4)
C(19)#1-C(19)-C(20)	48(2)
C(19)#1-C(19)-C(23)#2	91(2)
C(19)#1-C(19)-C(23)#3	57.4(16)
C(20)#1-C(19)-C(20)	54(4)
C(20)#1-C(19)-C(23)#2	164(6)
C(20)-C(19)-C(23)#3	104(3)
C(20)#1-C(19)-C(23)#3	155(5)
C(23)#2-C(19)-C(20)	139(4)
C(23)#2-C(19)-C(23)#3	34.3(18)
C(19)#1-C(20)-C(19)	34(4)
C(19)#1-C(20)-C(20)#1	79(4)
C(19)-C(20)-C(21)	94(3)
C(19)#1-C(20)-C(21)	123(4)
C(20)#1-C(20)-C(19)	47.3(19)
C(20)#1-C(20)-C(21)	46.9(19)
C(21)#1-C(20)-C(19)	124(4)
C(21)#1-C(20)-C(19)#1	157(7)
C(21)#1-C(20)-C(20)#1	79(3)
C(21)#1-C(20)-C(21)	41(3)
C(20)#1-C(21)-C(20)	54(4)
C(20)#1-C(21)-C(22)	129(4)
C(21)#1-C(21)-C(20)#1	92(4)
C(21)#1-C(21)-C(20)	48(2)
C(21)#1-C(21)-C(22)	44.9(19)
C(21)#1-C(21)-C(22)#1	93(3)
C(22)#1-C(21)-C(20)#1	174(6)
C(22)#1-C(21)-C(20)	132(4)
C(22)-C(21)-C(20)	93(2)
C(22)#1-C(21)-C(22)	53(4)
C(21)#1-C(22)-C(21)	42(4)

Table A6.1.4 (cont'd)

C(21)#1-C(22)-C(22)#1	83(3)
C(21)#1-C(22)-C(23)#1	142(5)
C(21)#1-C(22)-C(23)	139(4)
C(21)-C(22)-C(23)	97(2)
C(22)#1-C(22)-C(21)	44.5(17)
C(22)#1-C(22)-C(23)#1	73(2)
C(22)#1-C(22)-C(23)	57.5(18)
C(23)#1-C(22)-C(21)	117(3)
C(23)#1-C(22)-C(23)	38.1(19)
C(19)#5-C(23)-C(19)#4	31(3)
C(19)#5-C(23)-C(22)	140(4)
C(22)-C(23)-C(19)#4	115(2)
C(22)#1-C(23)-C(19)#5	156(4)
C(22)#1-C(23)-C(19)#4	131(3)
C(22)#1-C(23)-C(22)	50(3)
C(23)#1-C(23)-C(19)#5	88(2)
C(23)#1-C(23)-C(19)#4	57.4(15)
C(23)#1-C(23)-C(22)	61(2)
C(23)#1-C(23)-C(22)#1	81.2(19)
C(24)#6-C(24)-C(25)#6	118(3)
C(24)#6-C(24)-C(25)	40(2)
C(24)#6-C(24)-C(28)#5	94(2)
C(24)#6-C(24)-C(28)#7	63.7(17)
C(25)#6-C(24)-C(25)	80(5)
C(25)#6-C(24)-C(28)#5	146(3)
C(25)-C(24)-C(28)#7	103(3)
C(25)#6-C(24)-C(28)#7	171(4)
C(28)#5-C(24)-C(25)	134(4)
C(28)#5-C(24)-C(28)#7	31(4)
C(24)#6-C(25)-C(24)	21.4(19)
C(24)-C(25)-C(25)#6	40(2)
C(24)#6-C(25)-C(25)#6	60(2)
C(24)#6-C(25)-C(26)	115(4)
C(26)-C(25)-C(24)	95(4)

Table A6.1.4 (cont'd)

C(26)-C(25)-C(25)#6	55.3(15)
C(25)-C(26)-C(25)#6	69(3)
C(27)-C(26)-C(25)	116.5(19)
C(27)#6-C(26)-C(25)	157(2)
C(27)-C(26)-C(25)#6	157(2)
C(27)#6-C(26)-C(25)#6	116.5(19)
C(27)#6-C(26)-C(27)	68(3)
C(26)-C(27)-C(27)#6	56.2(17)
C(28)#6-C(27)-C(26)	116(5)
C(28)-C(27)-C(26)	91(4)
C(28)#6-C(27)-C(27)#6	62(3)
C(28)-C(27)-C(27)#6	36(3)
C(28)#6-C(27)-C(28)	35(5)
C(24)#2-C(28)-C(24)#8	22.2(18)
C(27)#6-C(28)-C(24)#2	149(4)
C(27)-C(28)-C(24)#8	100(3)
C(27)-C(28)-C(24)#2	121(4)
C(27)#6-C(28)-C(24)#8	152(6)
C(27)#6-C(28)-C(27)	82(6)
C(28)#6-C(28)-C(24)#8	63.7(17)
C(28)#6-C(28)-C(24)#2	86(2)
C(28)#6-C(28)-C(27)	40(3)
C(28)#6-C(28)-C(27)#6	105(7)

Symmetry transformations used to generate equivalent atoms:
#1 -x,y,-z+1 #2 x,y+1,z #3 -x,y+1,-z+1 #4 -x,y-1,-z+1
#5 x,y-1,z #6 -x+2,y,-z+2 #7 -x+2,y-1,-z+2
#8 -x+2,y+1,-z+2

Table A6.1.5 Anisotropic displacement parameters ($Å^2x10^3$) for thiazolidine ***(S)-315****. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$.*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	238(4)	213(4)	119(3)	-6(3)	17(3)	23(3)
S(2)	242(4)	282(4)	118(3)	15(3)	13(3)	50(3)
O(1)	256(11)	298(13)	112(9)	4(10)	11(8)	11(10)
O(2)	328(13)	232(13)	197(11)	-32(10)	9(10)	17(11)
O(3)	336(15)	298(16)	559(18)	-20(14)	-52(13)	-32(12)
O(4)	236(13)	475(18)	579(18)	-18(16)	-69(12)	67(14)
N(1)	236(13)	233(14)	117(11)	37(11)	22(9)	60(12)
N(2)	242(15)	320(20)	285(15)	-33(13)	-11(11)	40(13)
N(3)	339(16)	298(17)	139(12)	30(12)	2(11)	116(13)
C(1)	232(15)	216(19)	140(13)	-14(12)	31(11)	28(12)
C(2)	219(15)	213(18)	167(14)	-4(13)	9(11)	63(13)
C(3)	260(17)	233(19)	213(15)	9(13)	21(12)	27(13)
C(4)	212(15)	260(18)	214(15)	-36(14)	13(12)	33(14)
C(5)	243(17)	290(20)	239(17)	4(14)	-41(13)	88(14)
C(6)	283(17)	234(19)	210(15)	33(14)	14(12)	84(14)
C(7)	289(16)	198(16)	150(14)	2(14)	25(11)	21(14)
C(8)	230(15)	171(15)	133(13)	3(11)	4(11)	-2(12)
C(9)	206(15)	249(17)	130(13)	22(13)	14(11)	39(13)
C(10)	480(20)	430(30)	142(15)	30(15)	1(14)	196(19)
C(11)	307(17)	262(18)	198(15)	49(15)	29(13)	72(16)
C(12)	500(20)	260(20)	390(20)	26(18)	74(18)	21(18)
C(13)	229(15)	231(18)	113(13)	50(12)	28(11)	30(13)
C(14)	271(17)	259(18)	170(14)	19(13)	-21(12)	-16(14)
C(15)	195(16)	380(20)	218(16)	4(15)	-18(12)	29(14)
C(16)	247(17)	330(20)	194(15)	60(14)	44(12)	81(14)
C(17)	317(18)	165(16)	177(14)	3(13)	50(12)	8(13)
C(18)	233(16)	236(19)	186(14)	32(12)	36(12)	-16(13)
S(1A)	327(4)	267(5)	126(3)	-18(3)	-5(3)	-33(4)
S(2A)	324(16)	500(30)	143(9)	71(12)	55(9)	189(17)
S(2AA)	313(19)	400(30)	162(12)	-68(14)	22(11)	50(20)
O(1A)	313(13)	344(15)	152(11)	14(10)	-14(9)	-53(11)

Table A6.1.5 (cont'd)

O(2A)	425(14)	302(14)	193(11)	-37(11)	-40(10)	-56(12)
O(3A)	272(15)	510(20)	770(20)	-73(18)	-53(14)	63(14)
O(4A)	383(17)	385(19)	600(20)	13(16)	-35(14)	-55(14)
N(1A)	313(15)	304(16)	129(12)	11(12)	29(11)	-16(13)
N(2A)	288(17)	370(20)	343(17)	-34(14)	13(13)	-2(14)
N(3A)	427(18)	369(18)	152(13)	16(13)	-6(12)	57(15)
C(1A)	277(17)	226(18)	150(14)	-37(13)	39(12)	-15(14)
C(2A)	272(17)	330(20)	198(15)	25(14)	51(12)	18(14)
C(3A)	309(19)	280(20)	244(17)	29(14)	56(14)	0(14)
C(4A)	242(17)	340(20)	281(18)	-55(16)	41(13)	6(14)
C(5A)	303(19)	320(20)	300(19)	-35(17)	-45(15)	49(16)
C(6A)	366(19)	245(19)	239(16)	-45(16)	-8(14)	13(16)
C(7A)	248(16)	370(20)	113(13)	-1(15)	-10(11)	-51(16)
C(8A)	350(20)	620(30)	197(16)	42(18)	76(14)	120(20)
C(9A)	360(50)	390(70)	200(30)	20(40)	80(30)	150(40)
C(9AA)	260(60)	170(70)	110(40)	-40(40)	40(40)	60(40)
C(10A)	510(20)	520(30)	105(14)	-12(17)	-3(14)	130(20)
C(11A)	770(30)	660(30)	204(19)	90(20)	-10(20)	330(30)
C(12A)	1110(40)	550(30)	330(20)	60(20)	70(30)	370(30)
C(13A)	273(16)	291(18)	128(13)	27(14)	11(11)	69(15)
C(14A)	420(20)	270(20)	139(14)	41(13)	6(13)	-3(15)
C(15A)	370(20)	680(30)	245(18)	180(20)	48(16)	220(20)
C(16A)	290(20)	890(40)	360(20)	340(30)	-41(16)	-50(20)
C(17A)	610(30)	580(30)	420(20)	310(20)	-230(20)	-280(30)
C(18A)	650(30)	260(20)	240(18)	41(16)	-118(18)	-90(20)
C(19)	1400(200)	2800(400)	2700(300)	0(200)	-600(200)	-300(200)
C(20)	1970(190)	2600(400)	2500(200)	-50(180)	200(200)	-100(200)
C(21)	2200(200)	2200(300)	2200(200)	-100(160)	430(180)	70(190)
C(22)	2300(200)	2200(300)	1810(190)	320(160)	500(160)	300(180)
C(23)	1900(200)	2000(300)	1310(170)	170(140)	850(160)	450(190)
C(24)	950(140)	8800(900)	600(160)	500(200)	610(130)	400(300)
C(25)	1010(160)	8800(900)	1100(200)	300(200)	-70(140)	200(200)
C(26)	320(70)	8700(900)	1600(200)	0	-210(100)	0
C(27)	1240(180)	8500(900)	1300(200)	100(200)	60(160)	-400(200)

Table A6.1.5 (cont'd)

C(28)	1070(170)	8300(900)	860(190)	-100(300)	-550(170)	-700(300)

Table A6.1.6 Hydrogen coordinates (x10^3) and isotropic displacement parameters (Å^{2}x10^3) for thiazolidine ***(S)-315***

	x	y	z	U_{iso}
H(2)	861	322	737	24
H(3)	932	510	754	28
H(5)	985	-20	844	31
H(6)	914	-201	831	29
H(8)	712	-51	854	21
H(9A)	747	176	787	23
H(9B)	774	318	839	23
H(10C)	825	-268	981	42
H(10D)	876	-166	984	42
H(11)	885	-552	1000	31
H(12C)	868	-570	880	46
H(12D)	891	-765	923	46
H(14)	636	57	857	28
H(15)	579	314	874	32
H(16)	599	657	914	31
H(17)	677	744	938	26
H(18)	734	490	919	26
H(2A)	146	-119	759	32
H(3A)	74	-288	742	33
H(5A)	26	259	654	37
H(6A)	100	422	668	34
H(8A)	242	-207	591	46
H(8AA)	243	-224	609	46
H(9AA)	256	-55	701	38
H(9AB)	209	-158	672	38
H(9AC)	235	-83	700	21
H(9AD)	273	105	692	21
H(10A)	145	390	516	46
H(10B)	192	528	522	46
H(11A)	128	768	497	66
H(12A)	130	784	617	79

Table A6.1.6 (cont'd)

H(12B)	106	963	570	79
H(14A)	309	-405	585	33
H(15A)	390	-424	586	52
H(16A)	434	-124	616	62
H(17A)	400	204	641	66
H(18A)	320	230	640	47

A6.2 X-RAY CRYSTAL STRUCTURE ANALYSIS OF THIAZOLIDINE 329

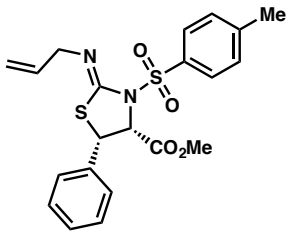


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*Figure A6.2.1 X-ray crystal structure of thiazolidine **329***

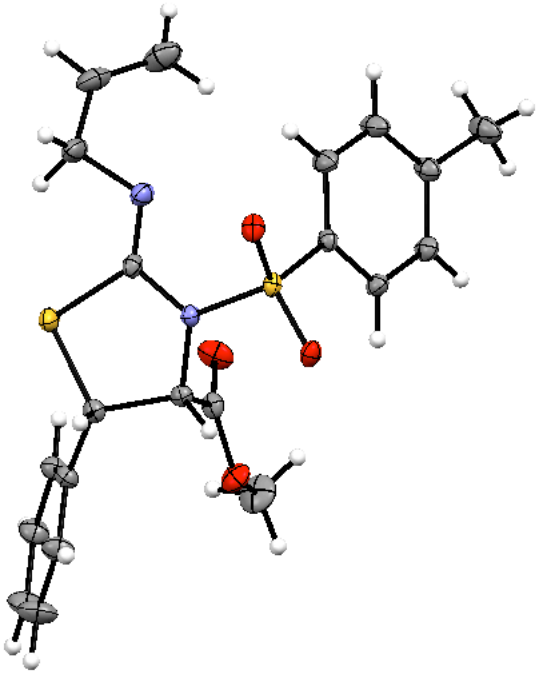


*Table A6.2.1 Experimental details for X-ray structure determination of thiazolidine **329***

Low-temperature diffraction data (and scans) were collected on a Bruker Kappa diffractometer coupled to a Apex II CCD detector with graphite monochromated Mo *K* radiation (=0.71073 Å) for the structure of thiazolidine **329**. The structure was solved by direct methods using SHELXS and refined against F^2 on all data by full-matrix least squares with SHELXL-2013 refinement using established techniques. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the *U* value of the atoms they are linked to (1.5 times for methyl groups). All disordered atoms were refined with the help of similarity restraints on the 1,2- and 1,3- distances and displacement parameters as well as rigid bond restraints for anisotropic displacement parameters.

Thiazolidine **329** crystallizes in the triclinic space group *P*-1 with one molecule in the asymmetric unit along with 0.389(2) molecules of benzene and 0.111(2) molecules of ethyl acetate. The partially occupied benzene and ethyl acetate molecules are located at mutually exclusive positions near a crystallographic inversion center and are disordered accordingly. This leads to non-integer values for the atoms in the empirical formula. The carbon atoms in the benzene were restrained to be flat. The 1,2- and 1,3- distances for the ethyl acetate were restrained to be similar to the distances in the ester moiety of the main molecule.

*Table A6.2.2 Crystal data and structure refinement for thiazolidine **329***

Caltech Identification code	rac15	
CCDC Deposition Number	956878	
Empirical formula	C23.78 H25.22 N2 O4.22 S2	
Formula weight	470.68	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 8.0719(4) Å	α= 108.416(4)°.
	b = 10.9911(6) Å	β= 102.525(3)°.
	c = 14.6381(8) Å	γ = 100.436(2)°.
Volume	1158.33(11) $Å^3$	
Z	2	
Density (calculated)	1.349 Mg/m^3	
Absorption coefficient	0.264 mm^{-1}	
F(000)	495	
Crystal size	0.450 x 0.400 x 0.050 mm^3	
Theta range for data collection	2.028 to 30.611°.	
Index ranges	$-11 \le h \le 11, -15 \le k \le 15, -20 \le l \le 20$	
Reflections collected	73111	
Independent reflections	7117 [R(int) = 0.0401]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7461 and 0.6920	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7117 / 241 / 375	
Goodness-of-fit on F^2	1.045	
Final R indices [I>2sigma(I)]	R1 = 0.0335, wR2 = 0.0852	
R indices (all data)	R1 = 0.0411, wR2 = 0.0910	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.519 and -0.298 $e \cdot Å^{-3}$	

Table A6.2.3 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for thiazolidine ***329****. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U(eq)
O(1)	6720(1)	912(1)	6958(1)	19(1)
O(2)	7685(1)	-166(1)	5483(1)	18(1)
S(1)	7769(1)	1012(1)	6298(1)	14(1)
C(1)	9977(1)	1738(1)	7028(1)	15(1)
C(2)	10368(2)	2473(1)	8051(1)	22(1)
C(3)	12116(2)	2931(1)	8639(1)	25(1)
C(4)	13466(2)	2658(1)	8223(1)	21(1)
C(5)	13041(1)	1962(1)	7189(1)	20(1)
C(6)	11303(1)	1495(1)	6586(1)	18(1)
C(7)	15338(2)	3066(2)	8883(1)	30(1)
N(1)	7101(1)	1999(1)	5728(1)	14(1)
C(8)	6907(1)	3260(1)	6257(1)	16(1)
N(2)	7432(1)	3818(1)	7202(1)	20(1)
C(11)	6995(2)	5071(1)	7627(1)	27(1)
C(12)	8307(2)	6001(1)	8604(1)	30(1)
C(13)	9751(2)	5797(2)	9062(1)	37(1)
S(2)	5817(1)	3868(1)	5380(1)	19(1)
C(9)	5708(1)	2434(1)	4293(1)	15(1)
C(14)	5921(1)	2800(1)	3405(1)	17(1)
C(15)	4955(2)	1907(1)	2438(1)	25(1)
C(16)	5200(2)	2182(2)	1604(1)	33(1)
C(17)	6411(2)	3338(2)	1730(1)	31(1)
C(18)	7365(2)	4231(1)	2688(1)	24(1)
C(19)	7112(2)	3970(1)	3524(1)	18(1)
C(10)	7117(1)	1788(1)	4692(1)	14(1)
C(20)	8939(1)	2443(1)	4674(1)	17(1)
O(3)	9954(1)	3388(1)	5361(1)	27(1)
O(4)	9225(1)	1840(1)	3801(1)	25(1)
C(21)	10843(2)	2499(2)	3681(1)	39(1)
C(1S)	11128(19)	-483(17)	9748(10)	51(2)

Table A6.2.3 (cont'd)

C(2S)	10130(17)	77(11)	9173(10)	49(2)
C(3S)	8871(17)	592(13)	9507(10)	53(3)
C(4S)	8570(20)	585(17)	10386(11)	58(2)
C(5S)	9491(17)	-5(13)	10916(10)	53(2)
C(6S)	10810(18)	-484(13)	10638(9)	48(2)
C(1T)	11250(60)	-420(70)	9690(20)	54(4)
C(2T)	10990(40)	-780(20)	8564(14)	69(5)
O(1T)	12404(19)	-714(14)	10186(10)	63(3)
O(2T)	9820(20)	-163(16)	9947(14)	51(3)
C(3T)	10080(30)	210(30)	11027(16)	56(4)
C(4T)	8270(30)	370(20)	11135(15)	62(5)

*Table A6.2.4 Bond lengths [Å] and angles [°] for thiazolidine **329***

O(1)-S(1)	1.4310(8)
O(2)-S(1)	1.4361(8)
S(1)-N(1)	1.6597(9)
S(1)-C(1)	1.7533(11)
C(1)-C(6)	1.3894(14)
C(1)-C(2)	1.3904(15)
C(2)-C(3)	1.3888(17)
C(2)-H(2)	0.9500
C(3)-C(4)	1.3931(16)
C(3)-H(3)	0.9500
C(4)-C(5)	1.3938(16)
C(4)-C(7)	1.5053(16)
C(5)-C(6)	1.3880(15)
C(5)-H(5)	0.9500
C(6)-H(6)	0.9500
C(7)-H(7A)	0.9800
C(7)-H(7B)	0.9800
C(7)-H(7C)	0.9800
N(1)-C(8)	1.4129(13)
N(1)-C(10)	1.4640(13)
C(8)-N(2)	1.2593(14)
C(8)-S(2)	1.7704(11)
N(2)-C(11)	1.4617(15)
C(11)-C(12)	1.4965(19)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(13)	1.307(2)
C(12)-H(12)	0.9500
C(13)-H(13A)	0.9500
C(13)-H(13B)	0.9500
S(2)-C(9)	1.8239(11)
C(9)-C(14)	1.5114(14)
C(9)-C(10)	1.5510(14)

Table A6.2.4 (cont'd)

C(9)-H(9)	1.0000
C(14)-C(15)	1.3929(15)
C(14)-C(19)	1.3949(15)
C(15)-C(16)	1.3908(18)
C(15)-H(15)	0.9500
C(16)-C(17)	1.389(2)
C(16)-H(16)	0.9500
C(17)-C(18)	1.3827(18)
C(17)-H(17)	0.9500
C(18)-C(19)	1.3898(15)
C(18)-H(18)	0.9500
C(19)-H(19)	0.9500
C(10)-C(20)	1.5249(14)
C(10)-H(10)	1.0000
C(20)-O(3)	1.1980(14)
C(20)-O(4)	1.3313(14)
O(4)-C(21)	1.4494(16)
C(21)-H(21A)	0.9800
C(21)-H(21B)	0.9800
C(21)-H(21C)	0.9800
C(1S)-C(6S)	1.381(9)
C(1S)-C(2S)	1.396(10)
C(1S)-H(1S)	0.9500
C(2S)-C(3S)	1.358(9)
C(2S)-H(2S)	0.9500
C(3S)-C(4S)	1.363(10)
C(3S)-H(3S)	0.9500
C(4S)-C(5S)	1.348(11)
C(4S)-H(4S)	0.9500
C(5S)-C(6S)	1.354(9)
C(5S)-H(5S)	0.9500
C(6S)-H(6S)	0.9500
C(1T)-O(1T)	1.202(18)
C(1T)-O(2T)	1.340(18)

Table A6.2.4 (cont'd)

C(1T)-C(2T)	1.529(17)
C(2T)-H(2T1)	0.9800
C(2T)-H(2T2)	0.9800
C(2T)-H(2T3)	0.9800
O(2T)-C(3T)	1.458(18)
C(3T)-C(4T)	1.539(18)
C(3T)-H(3T1)	0.9900
C(3T)-H(3T2)	0.9900
C(4T)-H(4T1)	0.9800
C(4T)-H(4T2)	0.9800
C(4T)-H(4T3)	0.9800

O(1)-S(1)-O(2)	119.28(5)
O(1)-S(1)-N(1)	107.46(5)
O(2)-S(1)-N(1)	103.82(5)
O(1)-S(1)-C(1)	108.38(5)
O(2)-S(1)-C(1)	108.19(5)
N(1)-S(1)-C(1)	109.37(5)
C(6)-C(1)-C(2)	121.16(10)
C(6)-C(1)-S(1)	119.28(8)
C(2)-C(1)-S(1)	119.42(8)
C(3)-C(2)-C(1)	118.85(10)
C(3)-C(2)-H(2)	120.6
C(1)-C(2)-H(2)	120.6
C(2)-C(3)-C(4)	121.14(11)
C(2)-C(3)-H(3)	119.4
C(4)-C(3)-H(3)	119.4
C(3)-C(4)-C(5)	118.72(10)
C(3)-C(4)-C(7)	120.57(11)
C(5)-C(4)-C(7)	120.68(11)
C(6)-C(5)-C(4)	121.06(10)
C(6)-C(5)-H(5)	119.5
C(4)-C(5)-H(5)	119.5
C(5)-C(6)-C(1)	118.98(10)

Table A6.2.4 (cont'd)

C(5)-C(6)-H(6)	120.5
C(1)-C(6)-H(6)	120.5
C(4)-C(7)-H(7A)	109.5
C(4)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
C(4)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5
H(7B)-C(7)-H(7C)	109.5
C(8)-N(1)-C(10)	114.00(8)
C(8)-N(1)-S(1)	122.79(7)
C(10)-N(1)-S(1)	121.40(7)
N(2)-C(8)-N(1)	123.68(10)
N(2)-C(8)-S(2)	127.37(8)
N(1)-C(8)-S(2)	108.95(7)
C(8)-N(2)-C(11)	116.34(10)
N(2)-C(11)-C(12)	113.38(11)
N(2)-C(11)-H(11A)	108.9
C(12)-C(11)-H(11A)	108.9
N(2)-C(11)-H(11B)	108.9
C(12)-C(11)-H(11B)	108.9
H(11A)-C(11)-H(11B)	107.7
C(13)-C(12)-C(11)	126.39(12)
C(13)-C(12)-H(12)	116.8
C(11)-C(12)-H(12)	116.8
C(12)-C(13)-H(13A)	120.0
C(12)-C(13)-H(13B)	120.0
H(13A)-C(13)-H(13B)	120.0
C(8)-S(2)-C(9)	93.46(5)
C(14)-C(9)-C(10)	114.60(9)
C(14)-C(9)-S(2)	112.74(7)
C(10)-C(9)-S(2)	105.20(7)
C(14)-C(9)-H(9)	108.0
C(10)-C(9)-H(9)	108.0
S(2)-C(9)-H(9)	108.0

Table A6.2.4 (cont'd)

C(15)-C(14)-C(19)	119.35(10)
C(15)-C(14)-C(9)	118.64(10)
C(19)-C(14)-C(9)	121.95(9)
C(16)-C(15)-C(14)	119.89(11)
C(16)-C(15)-H(15)	120.1
C(14)-C(15)-H(15)	120.1
C(17)-C(16)-C(15)	120.38(12)
C(17)-C(16)-H(16)	119.8
C(15)-C(16)-H(16)	119.8
C(18)-C(17)-C(16)	119.95(12)
C(18)-C(17)-H(17)	120.0
C(16)-C(17)-H(17)	120.0
C(17)-C(18)-C(19)	119.94(11)
C(17)-C(18)-H(18)	120.0
C(19)-C(18)-H(18)	120.0
C(18)-C(19)-C(14)	120.48(10)
C(18)-C(19)-H(19)	119.8
C(14)-C(19)-H(19)	119.8
N(1)-C(10)-C(20)	110.41(8)
N(1)-C(10)-C(9)	104.82(8)
C(20)-C(10)-C(9)	111.54(8)
N(1)-C(10)-H(10)	110.0
C(20)-C(10)-H(10)	110.0
C(9)-C(10)-H(10)	110.0
O(3)-C(20)-O(4)	125.32(10)
O(3)-C(20)-C(10)	123.43(10)
O(4)-C(20)-C(10)	111.24(9)
C(20)-O(4)-C(21)	114.48(11)
O(4)-C(21)-H(21A)	109.5
O(4)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
O(4)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5

Table A6.2.4 (cont'd)

C(6S)-C(1S)-C(2S)	119.1(7)
C(6S)-C(1S)-H(1S)	120.5
C(2S)-C(1S)-H(1S)	120.5
C(3S)-C(2S)-C(1S)	118.6(7)
C(3S)-C(2S)-H(2S)	120.7
C(1S)-C(2S)-H(2S)	120.7
C(2S)-C(3S)-C(4S)	121.8(8)
C(2S)-C(3S)-H(3S)	119.1
C(4S)-C(3S)-H(3S)	119.1
C(5S)-C(4S)-C(3S)	119.2(8)
C(5S)-C(4S)-H(4S)	120.4
C(3S)-C(4S)-H(4S)	120.4
C(4S)-C(5S)-C(6S)	121.2(8)
C(4S)-C(5S)-H(5S)	119.4
C(6S)-C(5S)-H(5S)	119.4
C(5S)-C(6S)-C(1S)	120.0(8)
C(5S)-C(6S)-H(6S)	120.0
C(1S)-C(6S)-H(6S)	120.0
O(1T)-C(1T)-O(2T)	125(2)
O(1T)-C(1T)-C(2T)	120(2)
O(2T)-C(1T)-C(2T)	111.4(18)
C(1T)-C(2T)-H(2T1)	109.5
C(1T)-C(2T)-H(2T2)	109.5
H(2T1)-C(2T)-H(2T2)	109.5
C(1T)-C(2T)-H(2T3)	109.5
H(2T1)-C(2T)-H(2T3)	109.5
H(2T2)-C(2T)-H(2T3)	109.5
C(1T)-O(2T)-C(3T)	111.6(19)
O(2T)-C(3T)-C(4T)	102.8(17)
O(2T)-C(3T)-H(3T1)	111.2
C(4T)-C(3T)-H(3T1)	111.2
O(2T)-C(3T)-H(3T2)	111.2
C(4T)-C(3T)-H(3T2)	111.2
H(3T1)-C(3T)-H(3T2)	109.1

Table A6.2.4 (cont'd)

C(3T)-C(4T)-H(4T1)	109.5
C(3T)-C(4T)-H(4T2)	109.5
H(4T1)-C(4T)-H(4T2)	109.5
C(3T)-C(4T)-H(4T3)	109.5
H(4T1)-C(4T)-H(4T3)	109.5
H(4T2)-C(4T)-H(4T3)	109.5

Symmetry transformations used to generate equivalent atoms:

*Table A6.2.5 Anisotropic displacement parameters ($Å^2x10^3$) for thiazolidine **329**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$.*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	17(1)	20(1)	26(1)	14(1)	11(1)	6(1)
O(2)	19(1)	13(1)	23(1)	5(1)	6(1)	5(1)
S(1)	13(1)	13(1)	18(1)	8(1)	6(1)	4(1)
C(1)	13(1)	17(1)	16(1)	7(1)	5(1)	5(1)
C(2)	19(1)	32(1)	18(1)	8(1)	9(1)	9(1)
C(3)	21(1)	38(1)	15(1)	6(1)	6(1)	7(1)
C(4)	16(1)	27(1)	18(1)	9(1)	4(1)	4(1)
C(5)	15(1)	25(1)	20(1)	6(1)	7(1)	6(1)
C(6)	16(1)	19(1)	16(1)	4(1)	6(1)	6(1)
C(7)	17(1)	46(1)	22(1)	10(1)	2(1)	4(1)
N(1)	16(1)	12(1)	15(1)	6(1)	5(1)	5(1)
C(8)	18(1)	14(1)	19(1)	9(1)	8(1)	6(1)
N(2)	27(1)	17(1)	18(1)	7(1)	9(1)	9(1)
C(11)	44(1)	21(1)	21(1)	6(1)	12(1)	17(1)
C(12)	44(1)	21(1)	24(1)	3(1)	17(1)	8(1)
C(13)	32(1)	32(1)	33(1)	-3(1)	11(1)	2(1)
S(2)	27(1)	18(1)	19(1)	10(1)	9(1)	12(1)
C(9)	14(1)	15(1)	17(1)	7(1)	4(1)	2(1)
C(14)	16(1)	18(1)	16(1)	7(1)	4(1)	4(1)
C(15)	25(1)	23(1)	19(1)	5(1)	3(1)	-2(1)
C(16)	38(1)	35(1)	16(1)	4(1)	4(1)	-2(1)
C(17)	36(1)	37(1)	19(1)	12(1)	10(1)	5(1)
C(18)	26(1)	25(1)	22(1)	12(1)	8(1)	3(1)
C(19)	20(1)	17(1)	17(1)	7(1)	5(1)	2(1)
C(10)	13(1)	13(1)	15(1)	4(1)	4(1)	2(1)
C(20)	14(1)	19(1)	21(1)	10(1)	6(1)	4(1)
O(3)	20(1)	28(1)	24(1)	9(1)	2(1)	-7(1)
O(4)	22(1)	28(1)	29(1)	9(1)	16(1)	8(1)
C(21)	27(1)	51(1)	51(1)	23(1)	27(1)	11(1)
C(1S)	55(4)	24(4)	77(4)	14(3)	33(3)	12(3)
C(2S)	84(6)	18(3)	38(3)	9(3)	18(3)	0(3)

Table A6.2.5 (cont'd)

C(3S)	54(5)	22(3)	53(4)	0(3)	-16(3)	5(3)
C(4S)	52(5)	21(3)	87(5)	-2(3)	30(3)	6(3)
C(5S)	64(5)	35(4)	38(3)	-4(2)	16(3)	-13(3)
C(6S)	45(4)	38(5)	50(4)	25(4)	-5(3)	-5(3)
C(1T)	64(7)	30(9)	58(6)	10(8)	14(6)	3(7)
C(2T)	104(15)	48(10)	60(7)	23(9)	25(8)	30(10)
O(1T)	62(7)	50(7)	56(7)	6(6)	3(6)	9(6)
O(2T)	66(6)	25(6)	52(4)	13(4)	7(4)	8(5)
C(3T)	63(8)	33(9)	53(5)	5(7)	12(6)	-6(8)
C(4T)	58(9)	49(10)	41(8)	-12(8)	-6(6)	0(8)

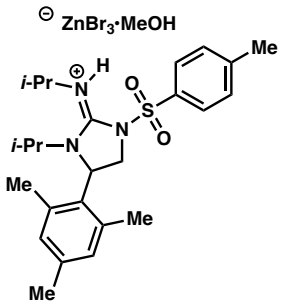
Table A6.2.6 Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x10^3$) for thiazolidine ***329***

	x	y	z	U(eq)
H(2)	9455	2659	8342	27
H(3)	12396	3439	9338	30
H(5)	13956	1805	6891	24
H(6)	11024	1016	5883	21
H(7A)	15481	2462	9246	46
H(7B)	15613	3979	9367	46
H(7C)	16140	3022	8464	46
H(11A)	5821	4873	7734	33
H(11B)	6918	5519	7136	33
H(12)	8068	6820	8923	36
H(13A)	10049	4993	8773	44
H(13B)	10502	6453	9683	44
H(9)	4525	1788	4083	18
H(15)	4130	1113	2348	30
H(16)	4535	1575	946	40
H(17)	6585	3514	1157	37
H(18)	8191	5023	2775	29
H(19)	7755	4592	4182	22
H(10)	6777	813	4282	17
H(21A)	11839	2619	4251	59
H(21B)	10772	3370	3658	59
H(21C)	11013	1953	3053	59
H(1S)	12012	-858	9531	61
H(2S)	10329	97	8561	59
H(3S)	8179	967	9116	63
H(4S)	7723	992	10623	69
H(5S)	9209	-86	11495	64
H(6S)	11517	-821	11054	57
H(2T1)	12065	-360	8455	103
H(2T2)	10010	-464	8284	103

Table A6.2.6 (cont'd)

H(2T3)	10709	-1751	8229	103
H(3T1)	11018	1056	11413	67
H(3T2)	10402	-495	11258	67
H(4T1)	7342	-330	10569	93
H(4T2)	8170	1244	11135	93
H(4T3)	8157	295	11769	93

A6.3 X-RAY CRYSTAL STRUCTURE ANALYSIS OF IMIDAZOLIDINIUM 374•($ZnBr_3$•MeOH)



374·($ZnBr_3$·MeOH)

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Figure A6.3.1 X-ray crystal structure of imidazolidinium ***374•($ZnBr_3$•MeOH)***

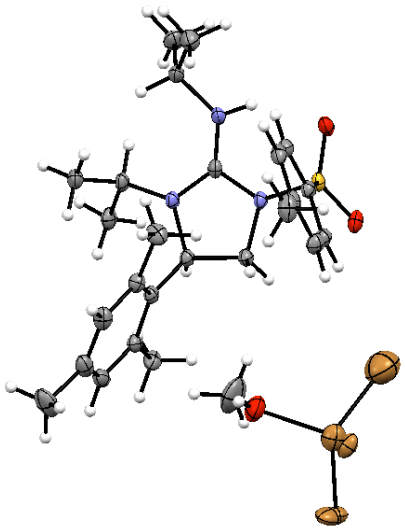

Table A6.3.1 Experimental details for X-ray structure determination of imidazolidinium ***374•(ZnBr$_3$•MeOH)***

Low-temperature diffraction data (and scans) were collected on a Bruker Kappa diffractometer coupled to a Apex II CCD detector with graphite monochromated Mo *K* radiation (= 0.71073 Å) for the structure of imidazolidinium **374•(ZnBr$_3$•MeOH)**. The structure was solved by direct methods using SHELXS and refined against F^2 on all data by full-matrix least squares with SHELXL-2013 using established refinement techniques. All non-hydrogen atoms were refined anisotropically. Unless otherwise noted, all hydrogen atoms were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the *U* value of the atoms they are linked to (1.5 times for methyl and hydroxide groups). All disordered atoms were refined with the help of similarity restraints on the 1,2- and 1,3- distances and displacement parameters as well as rigid bond restraints for anisotropic displacement parameters.

Imidazolidinium **374•(ZnBr$_3$•MeOH)** crystallizes in the triclinic space group *P*-1 with one molecule in the asymmetric unit along with one molecule of methanol. The coordinates for the hydrogen atoms on N3 and O3were taken from the difference Fourier synthesis and refined semi-freely with the help of a distance restraint, 0.91(2) and 0.83(2) Å respectively. An additional restraint was required for the hydrogen atom bound to O3 and the atoms Zn1, O3, C31 and H3O were restrained to be flat. All three bromine atoms were disordered over two positions. The solvent methanol had vey elongated ellipsoids and was disordered over two positions. The methanol is not very stable and the C-O distance was restrained to 1.43(2) Å. Additionally, the anisotropic displacement parameters for the two atoms in the second component of the disorder were constrained

to be equivalent. Even with the disorder the methanol has elongated ellipsoids, however, refinement of additional components was not successful.

Table A6.3.2 Crystal data and structure refinement for imidazolidinium ***374•($ZnBr_3$•MeOH)***

Caltech Identification code	rac14	
CCDC Deposition Number	956877	
Empirical formula	C27 H44 Br3 N3 O4 S Zn	
Formula weight	811.81	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 10.5054(14) Å	α= 103.177(3)°.
	b = 12.5274(17) Å	β= 109.093(2)°.
	c = 14.785(2) Å	γ = 102.841(3)°.
Volume	1694.7(4) $Å^3$	
Z	2	
Density (calculated)	1.591 Mg/m^3	
Absorption coefficient	4.357 mm^{-1}	
F(000)	820	
Crystal size	0.580 x 0.380 x 0.270 mm^3	
Theta range for data collection	1.764 to 30.560°.	
Index ranges	$-15 \le h \le 15, -17 \le k \le 17, -21 \le l \le 21$	
Reflections collected	100294	
Independent reflections	10353 [R(int) = 0.0346]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.1292 and 0.0684	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10353 / 82 / 412	
Goodness-of-fit on F^2	1.096	
Final R indices [I>2sigma(I)]	R1 = 0.0332, wR2 = 0.0793	
R indices (all data)	R1 = 0.0418, wR2 = 0.0842	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.878 and -0.917 $e \cdot Å^{-3}$	

Table A6.3.3 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for imidazolidinium ***374•(ZnBr$_3$•MeOH)***. *U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U(eq)
O(1)	4177(2)	6547(2)	5223(1)	24(1)
O(2)	4429(2)	8386(1)	4821(1)	24(1)
S(1)	4213(1)	7168(1)	4530(1)	18(1)
C(1)	2695(2)	6459(2)	3406(2)	18(1)
C(2)	2284(2)	7039(2)	2722(2)	21(1)
C(3)	1068(2)	6464(2)	1841(2)	24(1)
C(4)	270(2)	5323(2)	1631(2)	24(1)
C(7)	-1077(2)	4724(3)	691(2)	33(1)
C(5)	717(2)	4751(2)	2324(2)	24(1)
C(6)	1922(2)	5310(2)	3212(2)	22(1)
N(1)	5573(2)	6976(2)	4235(1)	18(1)
C(8)	6315(2)	7626(2)	3813(2)	18(1)
N(3)	6281(2)	8679(2)	3862(2)	22(1)
C(11)	6662(2)	9434(2)	3284(2)	22(1)
C(12)	5359(3)	9741(2)	2755(2)	31(1)
C(13)	7911(3)	10511(2)	4005(2)	31(1)
N(2)	7008(2)	7029(2)	3402(1)	18(1)
C(14)	8269(2)	7560(2)	3202(2)	20(1)
C(15)	7914(2)	7273(2)	2070(2)	25(1)
C(16)	9538(2)	7195(2)	3714(2)	24(1)
C(9)	6792(2)	5874(2)	3547(2)	17(1)
C(21)	6427(2)	4851(2)	2623(2)	18(1)
C(22)	7171(2)	4051(2)	2748(2)	20(1)
C(27)	8267(2)	4165(2)	3761(2)	25(1)
C(23)	6873(2)	3098(2)	1914(2)	25(1)
C(24)	5860(2)	2920(2)	967(2)	28(1)
C(28)	5587(3)	1911(3)	62(2)	44(1)
C(25)	5097(2)	3697(2)	865(2)	26(1)

Table A6.3.3 (cont'd)

C(26)	5343(2)	4650(2)	1680(2)	21(1)
C(29)	4402(2)	5400(2)	1501(2)	28(1)
C(10)	5663(2)	5793(2)	4001(2)	19(1)
Zn(1)	727(1)	1039(1)	2621(1)	25(1)
O(3)	1824(2)	1549(2)	1805(2)	42(1)
C(31)	3303(4)	2206(4)	2288(4)	69(1)
Br(1)	-1687(2)	97(1)	1446(2)	31(1)
Br(2)	1081(1)	2756(1)	3849(1)	16(1)
Br(3)	1841(2)	-171(2)	3374(2)	30(1)
Br(1A)	-1582(4)	220(5)	1241(6)	39(1)
Br(2A)	1081(4)	2743(3)	3828(3)	83(3)
Br(3A)	1793(7)	-231(6)	3212(7)	47(1)
O(1S)	10478(14)	1719(7)	9938(6)	64(2)
C(1S)	8692(15)	1307(5)	9413(8)	65(3)
O(1T)	11160(20)	2063(15)	10107(8)	46(3)
C(1T)	9360(20)	1417(16)	9601(11)	46(3)

Table A6.3.4 Bond lengths [Å] and angles [°] for imidazolidinium ***374•($ZnBr_3$•MeOH)***

O(1)-S(1)	1.4260(16)
O(2)-S(1)	1.4310(17)
S(1)-N(1)	1.6740(17)
S(1)-C(1)	1.748(2)
C(1)-C(2)	1.387(3)
C(1)-C(6)	1.398(3)
C(2)-C(3)	1.387(3)
C(2)-H(2)	0.9500
C(3)-C(4)	1.392(3)
C(3)-H(3)	0.9500
C(4)-C(5)	1.397(3)
C(4)-C(7)	1.504(3)
C(7)-H(7A)	0.9800
C(7)-H(7B)	0.9800
C(7)-H(7C)	0.9800
C(5)-C(6)	1.384(3)
C(5)-H(5)	0.9500
C(6)-H(6)	0.9500
N(1)-C(8)	1.389(2)
N(1)-C(10)	1.475(3)
C(8)-N(3)	1.314(3)
C(8)-N(2)	1.334(2)
N(3)-C(11)	1.485(3)
N(3)-H(3N)	0.868(17)
C(11)-C(12)	1.518(3)
C(11)-C(13)	1.524(3)
C(11)-H(11)	1.0000
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800

Table A6.3.4 (cont'd)

N(2)-C(9)	1.490(3)
N(2)-C(14)	1.497(2)
C(14)-C(15)	1.525(3)
C(14)-C(16)	1.526(3)
C(14)-H(14)	1.0000
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
C(9)-C(21)	1.515(3)
C(9)-C(10)	1.538(3)
C(9)-H(9)	1.0000
C(21)-C(26)	1.407(3)
C(21)-C(22)	1.409(3)
C(22)-C(23)	1.397(3)
C(22)-C(27)	1.514(3)
C(27)-H(27A)	0.9800
C(27)-H(27B)	0.9800
C(27)-H(27C)	0.9800
C(23)-C(24)	1.386(4)
C(23)-H(23)	0.9500
C(24)-C(25)	1.396(3)
C(24)-C(28)	1.512(3)
C(28)-H(28A)	0.9800
C(28)-H(28B)	0.9800
C(28)-H(28C)	0.9800
C(25)-C(26)	1.395(3)
C(25)-H(25)	0.9500
C(26)-C(29)	1.512(3)
C(29)-H(29A)	0.9800
C(29)-H(29B)	0.9800
C(29)-H(29C)	0.9800

Table A6.3.4 (cont'd)

C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
Zn(1)-O(3)	2.030(2)
Zn(1)-Br(3A)	2.310(6)
Zn(1)-Br(2A)	2.314(4)
Zn(1)-Br(2)	2.3423(6)
Zn(1)-Br(3)	2.369(2)
Zn(1)-Br(1)	2.3860(13)
Zn(1)-Br(1A)	2.408(4)
O(3)-C(31)	1.428(4)
O(3)-H(3O)	0.816(18)
C(31)-H(31A)	0.9800
C(31)-H(31B)	0.9800
C(31)-H(31C)	0.9800
O(1S)-C(1S)	1.680(8)
O(1S)-H(1S)	0.8400
C(1S)-H(1S1)	0.9800
C(1S)-H(1S2)	0.9800
C(1S)-H(1S3)	0.9800
O(1T)-C(1T)	1.704(14)
O(1T)-H(1T)	0.8400
C(1T)-H(1T1)	0.9800
C(1T)-H(1T2)	0.9800
C(1T)-H(1T3)	0.9800

O(1)-S(1)-O(2)	121.07(10)
O(1)-S(1)-N(1)	103.94(9)
O(2)-S(1)-N(1)	106.90(9)
O(1)-S(1)-C(1)	108.90(10)
O(2)-S(1)-C(1)	109.46(10)
N(1)-S(1)-C(1)	105.36(9)
C(2)-C(1)-C(6)	121.2(2)
C(2)-C(1)-S(1)	119.77(16)
C(6)-C(1)-S(1)	119.03(16)

Table A6.3.4 (cont'd)

C(3)-C(2)-C(1)	118.8(2)
C(3)-C(2)-H(2)	120.6
C(1)-C(2)-H(2)	120.6
C(2)-C(3)-C(4)	121.3(2)
C(2)-C(3)-H(3)	119.3
C(4)-C(3)-H(3)	119.3
C(3)-C(4)-C(5)	118.9(2)
C(3)-C(4)-C(7)	120.8(2)
C(5)-C(4)-C(7)	120.3(2)
C(4)-C(7)-H(7A)	109.5
C(4)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
C(4)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5
H(7B)-C(7)-H(7C)	109.5
C(6)-C(5)-C(4)	120.9(2)
C(6)-C(5)-H(5)	119.6
C(4)-C(5)-H(5)	119.6
C(5)-C(6)-C(1)	119.0(2)
C(5)-C(6)-H(6)	120.5
C(1)-C(6)-H(6)	120.5
C(8)-N(1)-C(10)	110.49(16)
C(8)-N(1)-S(1)	127.75(15)
C(10)-N(1)-S(1)	117.14(13)
N(3)-C(8)-N(2)	129.07(18)
N(3)-C(8)-N(1)	120.52(18)
N(2)-C(8)-N(1)	110.40(18)
C(8)-N(3)-C(11)	131.07(17)
C(8)-N(3)-H(3N)	112.5(19)
C(11)-N(3)-H(3N)	116.4(19)
N(3)-C(11)-C(12)	108.11(18)
N(3)-C(11)-C(13)	109.48(19)
C(12)-C(11)-C(13)	111.6(2)
N(3)-C(11)-H(11)	109.2

Table A6.3.4 (cont'd)

C(12)-C(11)-H(11)	109.2
C(13)-C(11)-H(11)	109.2
C(11)-C(12)-H(12A)	109.5
C(11)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(11)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(11)-C(13)-H(13A)	109.5
C(11)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
C(11)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
C(8)-N(2)-C(9)	111.32(16)
C(8)-N(2)-C(14)	124.62(17)
C(9)-N(2)-C(14)	119.92(15)
N(2)-C(14)-C(15)	111.62(17)
N(2)-C(14)-C(16)	111.36(17)
C(15)-C(14)-C(16)	110.66(17)
N(2)-C(14)-H(14)	107.7
C(15)-C(14)-H(14)	107.7
C(16)-C(14)-H(14)	107.7
C(14)-C(15)-H(15A)	109.5
C(14)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
C(14)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
C(14)-C(16)-H(16A)	109.5
C(14)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
C(14)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5

Table A6.3.4 (cont'd)

H(16B)-C(16)-H(16C)	109.5
N(2)-C(9)-C(21)	116.28(16)
N(2)-C(9)-C(10)	103.46(15)
C(21)-C(9)-C(10)	114.31(16)
N(2)-C(9)-H(9)	107.4
C(21)-C(9)-H(9)	107.4
C(10)-C(9)-H(9)	107.4
C(26)-C(21)-C(22)	119.84(19)
C(26)-C(21)-C(9)	122.58(18)
C(22)-C(21)-C(9)	117.50(18)
C(23)-C(22)-C(21)	119.3(2)
C(23)-C(22)-C(27)	118.13(19)
C(21)-C(22)-C(27)	122.50(19)
C(22)-C(27)-H(27A)	109.5
C(22)-C(27)-H(27B)	109.5
H(27A)-C(27)-H(27B)	109.5
C(22)-C(27)-H(27C)	109.5
H(27A)-C(27)-H(27C)	109.5
H(27B)-C(27)-H(27C)	109.5
C(24)-C(23)-C(22)	121.5(2)
C(24)-C(23)-H(23)	119.3
C(22)-C(23)-H(23)	119.3
C(23)-C(24)-C(25)	118.4(2)
C(23)-C(24)-C(28)	121.0(2)
C(25)-C(24)-C(28)	120.6(2)
C(24)-C(28)-H(28A)	109.5
C(24)-C(28)-H(28B)	109.5
H(28A)-C(28)-H(28B)	109.5
C(24)-C(28)-H(28C)	109.5
H(28A)-C(28)-H(28C)	109.5
H(28B)-C(28)-H(28C)	109.5
C(26)-C(25)-C(24)	122.0(2)
C(26)-C(25)-H(25)	119.0
C(24)-C(25)-H(25)	119.0

Table A6.3.4 (cont'd)

C(25)-C(26)-C(21)	118.7(2)
C(25)-C(26)-C(29)	117.7(2)
C(21)-C(26)-C(29)	123.54(19)
C(26)-C(29)-H(29A)	109.5
C(26)-C(29)-H(29B)	109.5
H(29A)-C(29)-H(29B)	109.5
C(26)-C(29)-H(29C)	109.5
H(29A)-C(29)-H(29C)	109.5
H(29B)-C(29)-H(29C)	109.5
N(1)-C(10)-C(9)	103.18(15)
N(1)-C(10)-H(10A)	111.1
C(9)-C(10)-H(10A)	111.1
N(1)-C(10)-H(10B)	111.1
C(9)-C(10)-H(10B)	111.1
H(10A)-C(10)-H(10B)	109.1
O(3)-Zn(1)-Br(3A)	102.1(2)
O(3)-Zn(1)-Br(2A)	104.27(11)
Br(3A)-Zn(1)-Br(2A)	116.2(3)
O(3)-Zn(1)-Br(2)	104.66(6)
O(3)-Zn(1)-Br(3)	105.41(9)
Br(2)-Zn(1)-Br(3)	110.95(5)
O(3)-Zn(1)-Br(1)	106.04(9)
Br(2)-Zn(1)-Br(1)	113.94(4)
Br(3)-Zn(1)-Br(1)	114.79(6)
O(3)-Zn(1)-Br(1A)	96.5(3)
Br(3A)-Zn(1)-Br(1A)	117.44(17)
Br(2A)-Zn(1)-Br(1A)	115.77(13)
C(31)-O(3)-Zn(1)	120.9(2)
C(31)-O(3)-H(3O)	120(3)
Zn(1)-O(3)-H(3O)	118(3)
O(3)-C(31)-H(31A)	109.5
O(3)-C(31)-H(31B)	109.5
H(31A)-C(31)-H(31B)	109.5
O(3)-C(31)-H(31C)	109.5

Table A6.3.4 (cont'd)

H(31A)-C(31)-H(31C)	109.5
H(31B)-C(31)-H(31C)	109.5
C(1S)-O(1S)-H(1S)	109.5
O(1S)-C(1S)-H(1S1)	109.5
O(1S)-C(1S)-H(1S2)	109.5
H(1S1)-C(1S)-H(1S2)	109.5
O(1S)-C(1S)-H(1S3)	109.5
H(1S1)-C(1S)-H(1S3)	109.5
H(1S2)-C(1S)-H(1S3)	109.5
C(1T)-O(1T)-H(1T)	109.5
O(1T)-C(1T)-H(1T1)	109.5
O(1T)-C(1T)-H(1T2)	109.5
H(1T1)-C(1T)-H(1T2)	109.5
O(1T)-C(1T)-H(1T3)	109.5
H(1T1)-C(1T)-H(1T3)	109.5
H(1T2)-C(1T)-H(1T3)	109.5

Symmetry transformations used to generate equivalent atoms:

Table A6.3.5 Anisotropic displacement parameters ($Å^2x10^3$) for imidazolidinium ***374•($ZnBr_3$•MeOH)***. *The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$.*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	21(1)	34(1)	21(1)	12(1)	12(1)	9(1)
O(2)	23(1)	23(1)	27(1)	3(1)	15(1)	6(1)
S(1)	16(1)	22(1)	19(1)	6(1)	11(1)	6(1)
C(1)	15(1)	22(1)	21(1)	8(1)	10(1)	7(1)
C(2)	21(1)	23(1)	26(1)	9(1)	13(1)	10(1)
C(3)	24(1)	33(1)	23(1)	12(1)	13(1)	15(1)
C(4)	17(1)	35(1)	21(1)	7(1)	10(1)	10(1)
C(7)	20(1)	49(2)	23(1)	8(1)	7(1)	7(1)
C(5)	18(1)	26(1)	28(1)	8(1)	10(1)	3(1)
C(6)	18(1)	24(1)	25(1)	10(1)	10(1)	6(1)
N(1)	15(1)	20(1)	20(1)	7(1)	11(1)	6(1)
C(8)	15(1)	21(1)	15(1)	3(1)	7(1)	3(1)
N(3)	26(1)	18(1)	26(1)	5(1)	19(1)	6(1)
C(11)	26(1)	19(1)	26(1)	6(1)	17(1)	6(1)
C(12)	35(1)	34(1)	34(1)	14(1)	19(1)	16(1)
C(13)	32(1)	21(1)	36(1)	6(1)	18(1)	1(1)
N(2)	15(1)	18(1)	20(1)	5(1)	10(1)	4(1)
C(14)	17(1)	22(1)	23(1)	6(1)	12(1)	4(1)
C(15)	28(1)	26(1)	25(1)	8(1)	17(1)	9(1)
C(16)	17(1)	30(1)	28(1)	9(1)	13(1)	5(1)
C(9)	14(1)	19(1)	20(1)	7(1)	8(1)	5(1)
C(21)	14(1)	19(1)	20(1)	6(1)	8(1)	4(1)
C(22)	16(1)	22(1)	25(1)	9(1)	12(1)	7(1)
C(27)	22(1)	34(1)	29(1)	16(1)	12(1)	15(1)
C(23)	24(1)	20(1)	36(1)	8(1)	18(1)	7(1)
C(24)	23(1)	24(1)	31(1)	0(1)	14(1)	1(1)
C(28)	38(1)	36(1)	42(2)	-11(1)	16(1)	4(1)
C(25)	19(1)	29(1)	22(1)	3(1)	7(1)	1(1)

Table A6.3.5 (cont'd)

C(26)	16(1)	23(1)	22(1)	7(1)	6(1)	4(1)
C(29)	21(1)	34(1)	26(1)	10(1)	4(1)	12(1)
C(10)	18(1)	22(1)	23(1)	9(1)	11(1)	8(1)
Zn(1)	24(1)	22(1)	29(1)	9(1)	12(1)	7(1)
O(3)	50(1)	47(1)	36(1)	19(1)	25(1)	11(1)
C(31)	53(2)	75(3)	85(3)	35(2)	44(2)	0(2)
Br(1)	27(1)	37(1)	25(1)	12(1)	7(1)	2(1)
Br(2)	18(1)	14(1)	17(1)	3(1)	8(1)	4(1)
Br(3)	31(1)	24(1)	36(1)	14(1)	12(1)	11(1)
Br(1A)	28(1)	42(1)	36(2)	9(1)	8(1)	4(1)
Br(2A)	85(3)	84(3)	96(4)	48(3)	40(2)	32(2)
Br(3A)	42(2)	36(1)	85(3)	32(2)	35(2)	27(1)
O(1S)	112(6)	44(3)	47(3)	14(3)	51(4)	17(4)
C(1S)	118(6)	31(2)	69(5)	15(3)	71(5)	16(4)
O(1T)	74(8)	40(5)	25(3)	15(3)	18(4)	14(5)
C(1T)	74(8)	40(5)	25(3)	15(3)	18(4)	14(5)

Table A6.3.6 Hydrogen coordinates (x10^4) and isotropic displacement parameters (Å^{2}x10^3) for imidazolidinium ***374•(ZnBr$_3$•MeOH)***

	x	y	z	U(eq)
H(2)	2826	7815	2855	25
H(3)	773	6857	1372	29
H(7A)	-1896	4599	880	49
H(7B)	-1048	3976	329	49
H(7C)	-1164	5207	252	49
H(5)	187	3969	2183	29
H(6)	2219	4918	3681	26
H(3N)	5930(30)	8950(20)	4288(19)	26
H(11)	6941	9000	2765	27
H(12A)	4592	9033	2276	47
H(12B)	5597	10263	2389	47
H(12C)	5047	10125	3259	47
H(13A)	7661	10915	4539	46
H(13B)	8132	11027	3630	46
H(13C)	8744	10285	4311	46
H(14)	8547	8420	3501	24
H(15A)	7648	6434	1758	37
H(15B)	8747	7664	1967	37
H(15C)	7118	7537	1759	37
H(16A)	9696	7321	4426	36
H(16B)	10389	7658	3672	36
H(16C)	9345	6373	3372	36
H(9)	7696	5909	4079	20
H(27A)	8580	3481	3698	38
H(27B)	7844	4227	4264	38
H(27C)	9085	4860	3978	38
H(23)	7376	2560	1999	30
H(28A)	6006	2192	-376	66
H(28B)	4559	1533	-317	66
H(28C)	6019	1353	294	66

Table A6.3.6 (cont'd)

H(25)	4387	3573	222	31
H(29A)	3713	5092	795	41
H(29B)	4989	6193	1641	41
H(29C)	3893	5402	1951	41
H(10A)	4736	5221	3507	23
H(10B)	5966	5574	4621	23
H(3O)	1370(40)	1460(30)	1211(15)	62
H(31A)	3421	3011	2631	103
H(31B)	3714	2180	1779	103
H(31C)	3791	1876	2786	103
H(1S)	10767	1332	9552	96
H(1S1)	8373	1939	9684	98
H(1S2)	8297	623	9573	98
H(1S3)	8364	1119	8677	98
H(1T)	11346	2769	10163	70
H(1T1)	8935	1883	9964	70
H(1T2)	9141	641	9663	70
H(1T3)	8973	1354	8884	70

Table A6.3.7 Hydrogen bonds for imidazolidinium ***374•(ZnBr$_3$•MeOH)*** *[Å and °]*

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(2)-H(2)...Br(3)#1	0.95	2.97	3.584(3)	123.6
C(2)-H(2)...Br(3A)#1	0.95	2.90	3.519(6)	123.9
C(6)-H(6)...Br(2)	0.95	2.81	3.545(2)	135.1
N(3)-H(3N)...O(2)	0.868(17)	2.05(2)	2.767(2)	140(3)
C(16)-H(16A)...Br(2)#2	0.98	2.93	3.855(2)	156.7
C(16)-H(16B)...Br(3)#3	0.98	3.01	3.872(3)	147.4
C(16)-H(16B)...Br(3A)#3	0.98	3.06	3.925(7)	147.6
C(9)-H(9)...Br(2)#2	1.00	2.82	3.523(2)	127.7
C(10)-H(10B)...Br(2)#2	0.99	3.08	3.550(2)	110.5
O(3)-H(3O)...O(1S)#4	0.816(18)	1.95(2)	2.741(7)	164(3)
O(3)-H(3O)...O(1T)#4	0.816(18)	1.92(3)	2.645(11)	148(4)
O(1S)-H(1S)...Br(1)#5	0.84	2.61	3.440(6)	170.0
C(1S)-H(1S2)...Br(1)#6	0.98	2.99	3.753(8)	136.0
C(1S)-H(1S3)...Br(3)#5	0.98	2.91	3.845(8)	159.8
C(1T)-H(1T3)...Br(3A)#5	0.98	2.85	3.749(18)	153.3

Symmetry transformations used to generate equivalent atoms:

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

#4 x-1,y,z-1 #5 -x+1,-y,-z+1 #6 x+1,y,z+1

A6.4 X-RAY CRYSTAL STRUCTURE ANALYSIS OF IMIDAZOLIDINE 343

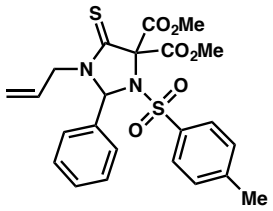

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Figure A6.4.1 X-ray crystal structure of imidazolidine ***343***

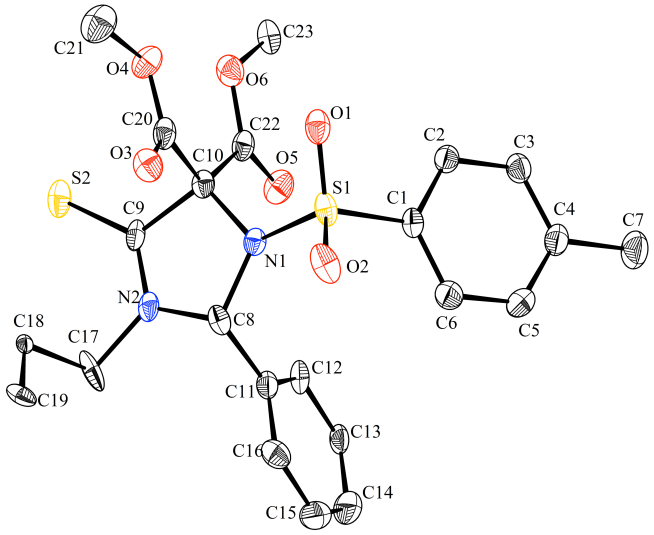


*Table A6.4.1 Experimental details for X-ray structure determination of imidazolidine **343***

Low-temperature diffraction data (and scans) were collected on a Bruker Kappa diffractometer coupled to a Apex II CCD detector with graphite monochromated Mo *K* radiation (= 0.71073 Å) for the structure of imidazolidine **343**. The structure was solved by direct methods using SHELXS and refined against F^2 on all data by full-matrix least squares with SHELXL-2013 using established refinement techniques. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the *U* value of the atoms they are linked to (1.5 times for methyl groups).

Imidazolidine **343** crystallizes in the orthorhombic space group *Pbca* with one molecule in the asymmetric unit. A majority of the molecule was disordered over two positions. All disordered atoms were refined with the help of similarity restraints on the 1,2- and 1,3- distances. All atoms were refined with the help of similarity as well as rigid bond restraints for anisotropic displacement parameters.

Table A6.4.2 Crystal data and structure refinement for imidazolidine ***343***

Caltech Identification code	rac16	
CCDC Deposition Number	973927	
Empirical formula	C23 H24 N2 O6 S2	
Formula weight	488.56	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P b c a	
Unit cell dimensions	a = 7.5481(4) Å	α= 90°.
	b = 21.3568(13) Å	β= 90°.
	c = 28.1256(18) Å	γ = 90°.
Volume	4533.9(5) $Å^3$	
Z	8	
Density (calculated)	1.431 Mg/m^3	
Absorption coefficient	0.278 mm^{-1}	
F(000)	2048	
Crystal size	0.400 x 0.250 x 0.150 mm^3	
Theta range for data collection	1.907 to 30.677°.	
Index ranges	$-10 \le h \le 10, -30 \le k \le 30, -39 \le l \le 40$	
Reflections collected	98231	
Independent reflections	7007 [R(int) = 0.0490]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7461 and 0.6817	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7007 / 1023 / 507	
Goodness-of-fit on F^2	1.116	
Final R indices [I>2sigma(I)]	R1 = 0.0505, wR2 = 0.1269	
R indices (all data)	R1 = 0.0597, wR2 = 0.1324	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.662 and -0.538 $e \cdot Å^{-3}$	

*Table A6.4.3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for imidazolidine **343**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U(eq)
O(1)	5335(2)	1620(1)	1380(1)	26(1)
O(2)	4409(2)	2342(1)	726(1)	31(1)
S(1)	4127(1)	2069(1)	1184(1)	21(1)
C(1)	3945(2)	2681(1)	1599(1)	20(1)
C(2)	4527(2)	2582(1)	2061(1)	22(1)
C(3)	4518(2)	3079(1)	2378(1)	24(1)
C(4)	3935(2)	3668(1)	2242(1)	26(1)
C(5)	3339(3)	3752(1)	1780(1)	32(1)
C(6)	3336(3)	3263(1)	1455(1)	28(1)
C(7)	3924(3)	4209(1)	2587(1)	37(1)
N(1)	2138(13)	1760(4)	1128(4)	18(1)
C(8)	877(12)	1912(3)	744(3)	21(1)
C(11)	-60(19)	2527(4)	804(4)	21(1)
C(12)	-830(30)	2682(7)	1243(5)	21(2)
C(13)	-1790(30)	3228(7)	1286(4)	21(2)
C(14)	-1950(20)	3623(6)	896(4)	33(2)
C(15)	-1186(18)	3468(5)	464(4)	32(2)
C(16)	-231(16)	2926(4)	418(4)	26(1)
N(2)	-368(12)	1385(3)	805(3)	20(1)
C(17)	-1909(11)	1330(3)	484(2)	29(2)
C(18)	-1271(4)	782(1)	140(1)	11(1)
C(19)	-1060(4)	1020(2)	-290(1)	20(1)
C(9)	88(11)	951(4)	1108(4)	21(1)
S(2)	-891(4)	277(1)	1228(1)	28(1)
C(10)	1879(10)	1142(3)	1327(2)	18(1)
C(20)	3219(6)	664(2)	1106(2)	23(1)
O(3)	3612(9)	724(3)	689(2)	27(1)
O(4)	3688(6)	201(2)	1380(2)	26(1)
C(21)	4655(6)	-280(2)	1124(2)	39(1)
C(22)	1640(20)	1198(6)	1871(3)	21(1)

Table A6.4.3 (cont'd)

O(5)	720(20)	1617(8)	2024(6)	28(2)
O(6)	2335(18)	750(5)	2130(2)	27(1)
C(23)	2074(14)	822(5)	2643(3)	26(1)
N(1A)	2257(12)	1661(4)	1182(4)	17(1)
C(8A)	967(11)	1778(3)	803(3)	16(1)
C(11A)	53(16)	2403(4)	818(4)	17(1)
C(12A)	-880(30)	2594(7)	1223(5)	22(2)
C(13A)	-1780(30)	3161(7)	1216(4)	28(2)
C(14A)	-1815(18)	3529(5)	811(4)	31(2)
C(15A)	-907(16)	3334(4)	410(4)	31(1)
C(16A)	12(14)	2775(4)	415(4)	23(1)
N(2A)	-258(11)	1253(3)	881(3)	17(1)
C(17A)	-1788(11)	1187(3)	566(2)	23(1)
C(18A)	-1586(8)	1051(4)	20(2)	64(2)
C(19A)	-321(12)	812(4)	-170(3)	92(3)
C(9A)	244(10)	839(3)	1203(3)	17(1)
S(2A)	-720(4)	172(1)	1345(1)	22(1)
C(10A)	1983(9)	1075(3)	1432(2)	18(1)
C(20A)	3358(5)	561(2)	1297(2)	19(1)
O(3A)	4024(5)	193(2)	1558(2)	29(1)
O(4A)	3553(8)	579(2)	823(2)	25(1)
C(21A)	4614(4)	87(2)	615(2)	33(1)
C(22A)	1630(20)	1207(6)	1960(2)	20(1)
O(5A)	920(20)	1681(7)	2086(5)	33(2)
O(6A)	2257(17)	779(5)	2248(2)	28(1)
C(23A)	1896(15)	893(5)	2748(3)	36(2)

Table A6.4.4 Bond lengths [Å] and angles [°] for imidazolidine ***343***

O(1)-S(1)	1.4335(14)
O(2)-S(1)	1.4295(14)
S(1)-N(1)	1.648(9)
S(1)-N(1A)	1.659(8)
S(1)-C(1)	1.7562(16)
C(1)-C(6)	1.387(2)
C(1)-C(2)	1.387(2)
C(2)-C(3)	1.387(2)
C(2)-H(2)	0.9500
C(3)-C(4)	1.388(2)
C(3)-H(3)	0.9500
C(4)-C(5)	1.387(3)
C(4)-C(7)	1.508(2)
C(5)-C(6)	1.386(3)
C(5)-H(5)	0.9500
C(6)-H(6)	0.9500
C(7)-H(7A)	0.9800
C(7)-H(7B)	0.9800
C(7)-H(7C)	0.9800
N(1)-C(10)	1.446(8)
N(1)-C(8)	1.476(8)
C(8)-N(2)	1.476(8)
C(8)-C(11)	1.500(8)
C(8)-H(8)	1.0000
C(11)-C(16)	1.385(8)
C(11)-C(12)	1.407(9)
C(12)-C(13)	1.378(9)
C(12)-H(12)	0.9500
C(13)-C(14)	1.387(9)
C(13)-H(13)	0.9500
C(14)-C(15)	1.383(8)
C(14)-H(14)	0.9500
C(15)-C(16)	1.371(7)

Table A6.4.4 (cont'd)

C(15)-H(15)	0.9500
C(16)-H(16)	0.9500
N(2)-C(9)	1.307(6)
N(2)-C(17)	1.477(7)
C(17)-C(18)	1.593(5)
C(17)-H(17A)	0.9900
C(17)-H(17B)	0.9900
C(18)-C(19)	1.323(4)
C(18)-H(18)	0.9500
C(19)-H(19A)	0.9500
C(19)-H(19B)	0.9500
C(9)-C(10)	1.542(8)
C(9)-S(2)	1.653(6)
C(10)-C(22)	1.544(8)
C(10)-C(20)	1.567(7)
C(20)-O(3)	1.215(6)
C(20)-O(4)	1.301(6)
O(4)-C(21)	1.451(6)
C(21)-H(21A)	0.9800
C(21)-H(21B)	0.9800
C(21)-H(21C)	0.9800
C(22)-O(5)	1.209(9)
C(22)-O(6)	1.312(9)
O(6)-C(23)	1.464(7)
C(23)-H(23A)	0.9800
C(23)-H(23B)	0.9800
C(23)-H(23C)	0.9800
N(1A)-C(10A)	1.450(7)
N(1A)-C(8A)	1.466(7)
C(8A)-N(2A)	1.469(7)
C(8A)-C(11A)	1.503(7)
C(8A)-H(8A)	1.0000
C(11A)-C(16A)	1.383(7)
C(11A)-C(12A)	1.400(9)

Table A6.4.4 (cont'd)

C(12A)-C(13A)	1.387(9)
C(12A)-H(12A)	0.9500
C(13A)-C(14A)	1.384(9)
C(13A)-H(13A)	0.9500
C(14A)-C(15A)	1.384(8)
C(14A)-H(14A)	0.9500
C(15A)-C(16A)	1.381(6)
C(15A)-H(15A)	0.9500
C(16A)-H(16A)	0.9500
N(2A)-C(9A)	1.320(5)
N(2A)-C(17A)	1.463(7)
C(17A)-C(18A)	1.569(6)
C(17A)-H(17C)	0.9900
C(17A)-H(17D)	0.9900
C(18A)-C(19A)	1.207(7)
C(18A)-H(18A)	0.9500
C(19A)-H(19C)	0.9500
C(19A)-H(19D)	0.9500
C(9A)-C(10A)	1.546(7)
C(9A)-S(2A)	1.649(6)
C(10A)-C(22A)	1.535(7)
C(10A)-C(20A)	1.557(7)
C(20A)-O(3A)	1.187(5)
C(20A)-O(4A)	1.342(5)
O(4A)-C(21A)	1.444(6)
C(21A)-H(21D)	0.9800
C(21A)-H(21E)	0.9800
C(21A)-H(21F)	0.9800
C(22A)-O(5A)	1.199(9)
C(22A)-O(6A)	1.310(8)
O(6A)-C(23A)	1.452(7)
C(23A)-H(23D)	0.9800
C(23A)-H(23E)	0.9800
C(23A)-H(23F)	0.9800

Table A6.4.4 (cont'd)

O(2)-S(1)-O(1)	121.63(8)
O(2)-S(1)-N(1)	102.3(4)
O(1)-S(1)-N(1)	110.4(3)
O(2)-S(1)-N(1A)	109.8(3)
O(1)-S(1)-N(1A)	101.0(2)
O(2)-S(1)-C(1)	107.88(8)
O(1)-S(1)-C(1)	106.97(8)
N(1)-S(1)-C(1)	106.8(4)
N(1A)-S(1)-C(1)	109.0(4)
C(6)-C(1)-C(2)	120.95(15)
C(6)-C(1)-S(1)	119.99(13)
C(2)-C(1)-S(1)	118.93(12)
C(3)-C(2)-C(1)	119.01(15)
C(3)-C(2)-H(2)	120.5
C(1)-C(2)-H(2)	120.5
C(2)-C(3)-C(4)	121.20(16)
C(2)-C(3)-H(3)	119.4
C(4)-C(3)-H(3)	119.4
C(5)-C(4)-C(3)	118.54(16)
C(5)-C(4)-C(7)	120.23(17)
C(3)-C(4)-C(7)	121.22(17)
C(6)-C(5)-C(4)	121.41(16)
C(6)-C(5)-H(5)	119.3
C(4)-C(5)-H(5)	119.3
C(5)-C(6)-C(1)	118.88(16)
C(5)-C(6)-H(6)	120.6
C(1)-C(6)-H(6)	120.6
C(4)-C(7)-H(7A)	109.5
C(4)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
C(4)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5
H(7B)-C(7)-H(7C)	109.5
C(10)-N(1)-C(8)	113.4(6)

Table A6.4.4 (cont'd)

C(10)-N(1)-S(1)	116.9(6)
C(8)-N(1)-S(1)	124.7(6)
N(2)-C(8)-N(1)	99.1(5)
N(2)-C(8)-C(11)	110.7(7)
N(1)-C(8)-C(11)	114.5(8)
N(2)-C(8)-H(8)	110.7
N(1)-C(8)-H(8)	110.7
C(11)-C(8)-H(8)	110.7
C(16)-C(11)-C(12)	120.3(7)
C(16)-C(11)-C(8)	119.6(8)
C(12)-C(11)-C(8)	120.0(8)
C(13)-C(12)-C(11)	119.6(9)
C(13)-C(12)-H(12)	120.2
C(11)-C(12)-H(12)	120.2
C(12)-C(13)-C(14)	119.3(9)
C(12)-C(13)-H(13)	120.3
C(14)-C(13)-H(13)	120.3
C(15)-C(14)-C(13)	120.9(8)
C(15)-C(14)-H(14)	119.5
C(13)-C(14)-H(14)	119.5
C(16)-C(15)-C(14)	120.2(7)
C(16)-C(15)-H(15)	119.9
C(14)-C(15)-H(15)	119.9
C(15)-C(16)-C(11)	119.6(7)
C(15)-C(16)-H(16)	120.2
C(11)-C(16)-H(16)	120.2
C(9)-N(2)-C(8)	116.7(5)
C(9)-N(2)-C(17)	123.3(6)
C(8)-N(2)-C(17)	119.5(6)
N(2)-C(17)-C(18)	101.0(6)
N(2)-C(17)-H(17A)	111.6
C(18)-C(17)-H(17A)	111.6
N(2)-C(17)-H(17B)	111.6
C(18)-C(17)-H(17B)	111.6

Table A6.4.4 (cont'd)

H(17A)-C(17)-H(17B)	109.4
C(19)-C(18)-C(17)	108.0(4)
C(19)-C(18)-H(18)	126.0
C(17)-C(18)-H(18)	126.0
C(18)-C(19)-H(19A)	120.0
C(18)-C(19)-H(19B)	120.0
H(19A)-C(19)-H(19B)	120.0
N(2)-C(9)-C(10)	107.7(5)
N(2)-C(9)-S(2)	129.3(5)
C(10)-C(9)-S(2)	122.8(5)
N(1)-C(10)-C(9)	101.9(5)
N(1)-C(10)-C(22)	109.1(7)
C(9)-C(10)-C(22)	108.3(8)
N(1)-C(10)-C(20)	110.8(6)
C(9)-C(10)-C(20)	103.6(6)
C(22)-C(10)-C(20)	121.3(6)
O(3)-C(20)-O(4)	125.8(4)
O(3)-C(20)-C(10)	118.1(5)
O(4)-C(20)-C(10)	115.8(5)
C(20)-O(4)-C(21)	112.4(4)
O(4)-C(21)-H(21A)	109.5
O(4)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
O(4)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5
O(5)-C(22)-O(6)	124.8(10)
O(5)-C(22)-C(10)	118.5(10)
O(6)-C(22)-C(10)	116.5(7)
C(22)-O(6)-C(23)	114.6(7)
O(6)-C(23)-H(23A)	109.5
O(6)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
O(6)-C(23)-H(23C)	109.5

Table A6.4.4 (cont'd)

H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
C(10A)-N(1A)-C(8A)	113.8(5)
C(10A)-N(1A)-S(1)	125.0(5)
C(8A)-N(1A)-S(1)	118.5(6)
N(1A)-C(8A)-N(2A)	100.3(5)
N(1A)-C(8A)-C(11A)	115.8(6)
N(2A)-C(8A)-C(11A)	112.6(6)
N(1A)-C(8A)-H(8A)	109.2
N(2A)-C(8A)-H(8A)	109.2
C(11A)-C(8A)-H(8A)	109.2
C(16A)-C(11A)-C(12A)	119.2(7)
C(16A)-C(11A)-C(8A)	119.8(6)
C(12A)-C(11A)-C(8A)	120.8(7)
C(13A)-C(12A)-C(11A)	119.4(9)
C(13A)-C(12A)-H(12A)	120.3
C(11A)-C(12A)-H(12A)	120.3
C(14A)-C(13A)-C(12A)	121.0(8)
C(14A)-C(13A)-H(13A)	119.5
C(12A)-C(13A)-H(13A)	119.5
C(15A)-C(14A)-C(13A)	119.3(7)
C(15A)-C(14A)-H(14A)	120.4
C(13A)-C(14A)-H(14A)	120.4
C(16A)-C(15A)-C(14A)	120.1(7)
C(16A)-C(15A)-H(15A)	119.9
C(14A)-C(15A)-H(15A)	119.9
C(15A)-C(16A)-C(11A)	121.0(6)
C(15A)-C(16A)-H(16A)	119.5
C(11A)-C(16A)-H(16A)	119.5
C(9A)-N(2A)-C(17A)	125.3(5)
C(9A)-N(2A)-C(8A)	115.6(5)
C(17A)-N(2A)-C(8A)	118.6(5)
N(2A)-C(17A)-C(18A)	122.3(7)
N(2A)-C(17A)-H(17C)	106.8

Table A6.4.4 (cont'd)

C(18A)-C(17A)-H(17C)	106.8
N(2A)-C(17A)-H(17D)	106.8
C(18A)-C(17A)-H(17D)	106.8
H(17C)-C(17A)-H(17D)	106.6
C(19A)-C(18A)-C(17A)	126.1(8)
C(19A)-C(18A)-H(18A)	117.0
C(17A)-C(18A)-H(18A)	117.0
C(18A)-C(19A)-H(19C)	120.0
C(18A)-C(19A)-H(19D)	120.0
H(19C)-C(19A)-H(19D)	120.0
N(2A)-C(9A)-C(10A)	108.1(4)
N(2A)-C(9A)-S(2A)	128.1(5)
C(10A)-C(9A)-S(2A)	123.7(4)
N(1A)-C(10A)-C(22A)	109.4(7)
N(1A)-C(10A)-C(9A)	101.6(4)
C(22A)-C(10A)-C(9A)	108.5(7)
N(1A)-C(10A)-C(20A)	113.3(6)
C(22A)-C(10A)-C(20A)	118.7(5)
C(9A)-C(10A)-C(20A)	103.7(5)
O(3A)-C(20A)-O(4A)	125.9(4)
O(3A)-C(20A)-C(10A)	126.7(4)
O(4A)-C(20A)-C(10A)	107.2(4)
C(20A)-O(4A)-C(21A)	116.2(4)
O(4A)-C(21A)-H(21D)	109.5
O(4A)-C(21A)-H(21E)	109.5
H(21D)-C(21A)-H(21E)	109.5
O(4A)-C(21A)-H(21F)	109.5
H(21D)-C(21A)-H(21F)	109.5
H(21E)-C(21A)-H(21F)	109.5
O(5A)-C(22A)-O(6A)	124.5(10)
O(5A)-C(22A)-C(10A)	121.2(9)
O(6A)-C(22A)-C(10A)	114.1(6)
C(22A)-O(6A)-C(23A)	114.6(7)
O(6A)-C(23A)-H(23D)	109.5

Table A6.4.4 (cont'd)

O(6A)-C(23A)-H(23E)	109.5
H(23D)-C(23A)-H(23E)	109.5
O(6A)-C(23A)-H(23F)	109.5
H(23D)-C(23A)-H(23F)	109.5
H(23E)-C(23A)-H(23F)	109.5

Symmetry transformations used to generate equivalent atoms:

*Table A6.4.5 Anisotropic displacement parameters ($Å^2x10^3$) for imidazolidine **343**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$.*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	19(1)	26(1)	34(1)	-10(1)	3(1)	-3(1)
O(2)	26(1)	47(1)	19(1)	-7(1)	6(1)	-12(1)
S(1)	16(1)	27(1)	21(1)	-8(1)	5(1)	-7(1)
C(1)	20(1)	20(1)	19(1)	-4(1)	2(1)	-5(1)
C(2)	25(1)	19(1)	22(1)	0(1)	-1(1)	-3(1)
C(3)	28(1)	24(1)	21(1)	-4(1)	-2(1)	-2(1)
C(4)	26(1)	20(1)	31(1)	-6(1)	0(1)	-2(1)
C(5)	41(1)	19(1)	34(1)	1(1)	-7(1)	2(1)
C(6)	36(1)	26(1)	22(1)	1(1)	-6(1)	-2(1)
C(7)	41(1)	28(1)	41(1)	-14(1)	-2(1)	0(1)
N(1)	15(2)	17(2)	22(3)	-3(2)	3(2)	-2(2)
C(8)	18(2)	25(3)	19(2)	-4(2)	-1(2)	-6(2)
C(11)	17(2)	19(3)	26(2)	-7(2)	-2(2)	0(2)
C(12)	24(3)	20(4)	19(2)	-7(2)	3(2)	-10(3)
C(13)	23(2)	18(3)	23(3)	-10(2)	-3(3)	-1(2)
C(14)	43(3)	24(4)	32(4)	-8(3)	-3(3)	4(3)
C(15)	38(4)	28(4)	31(3)	-1(3)	-7(2)	6(2)
C(16)	27(3)	32(4)	18(2)	-2(3)	-2(2)	1(3)
N(2)	17(2)	17(3)	26(3)	-11(2)	2(2)	2(2)
C(17)	16(2)	51(4)	21(2)	-22(3)	0(2)	-7(2)
C(18)	8(1)	11(1)	15(1)	-4(1)	-2(1)	2(1)
C(19)	14(1)	32(2)	14(2)	-5(1)	-3(1)	10(1)
C(9)	14(2)	15(3)	33(4)	-10(2)	2(2)	-2(2)
S(2)	24(1)	24(1)	35(1)	-9(1)	6(1)	-9(1)
C(10)	16(2)	19(2)	20(2)	-7(2)	4(2)	1(1)
C(20)	14(2)	21(2)	35(3)	-8(2)	2(2)	-3(1)
O(3)	26(2)	32(3)	24(2)	-9(2)	4(2)	3(2)
O(4)	27(2)	21(2)	31(2)	-2(2)	10(2)	3(1)
C(21)	34(2)	33(2)	51(3)	-5(2)	9(2)	5(2)
C(22)	18(2)	18(2)	26(3)	-3(2)	4(3)	-6(2)

Table A6.4.5 (cont'd)

O(5)	36(3)	25(3)	24(4)	-7(2)	8(3)	3(3)
O(6)	31(2)	29(2)	21(3)	-7(2)	0(3)	1(1)
C(23)	25(2)	27(2)	27(3)	-7(2)	-1(2)	-7(2)
N(1A)	14(2)	16(2)	21(2)	-2(2)	-3(1)	-3(2)
C(8A)	17(2)	15(2)	16(2)	-3(2)	3(1)	0(2)
C(11A)	17(2)	15(2)	18(2)	-2(2)	-2(1)	-5(2)
C(12A)	19(3)	17(3)	29(3)	-6(2)	1(2)	-2(3)
C(13A)	25(2)	26(3)	32(4)	-14(3)	2(3)	-4(2)
C(14A)	31(3)	21(3)	42(4)	-10(2)	-9(3)	2(2)
C(15A)	33(4)	28(4)	31(3)	2(3)	-4(2)	6(2)
C(16A)	22(3)	20(3)	26(2)	-1(2)	-6(2)	1(2)
N(2A)	15(2)	11(2)	26(2)	-4(2)	-2(1)	-1(2)
C(17A)	18(2)	27(2)	24(2)	-6(2)	-3(2)	0(1)
C(18A)	55(3)	89(5)	50(3)	-38(3)	-13(3)	3(3)
C(19A)	107(6)	83(5)	87(6)	-44(4)	53(5)	-25(4)
C(9A)	16(2)	15(2)	21(3)	-4(1)	3(1)	1(2)
S(2A)	22(1)	18(1)	26(1)	0(1)	-1(1)	-7(1)
C(10A)	14(2)	14(2)	24(2)	1(2)	-1(2)	-4(1)
C(20A)	16(1)	16(2)	26(2)	0(2)	-1(2)	-3(1)
O(3A)	27(2)	22(1)	40(2)	1(2)	-8(2)	3(1)
O(4A)	24(1)	25(2)	27(2)	-11(2)	2(2)	2(1)
C(21A)	16(1)	24(2)	59(2)	-27(2)	6(1)	0(1)
C(22A)	18(2)	21(2)	21(2)	-2(2)	2(2)	-7(2)
O(5A)	50(5)	23(3)	26(4)	-4(2)	6(3)	5(3)
O(6A)	33(2)	32(2)	20(3)	-3(2)	-8(3)	6(1)
C(23A)	37(3)	53(4)	19(3)	-3(3)	-6(2)	7(2)

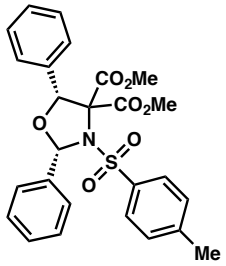
*Table A6.4.6 Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x10^3$) for imidazolidine **343***

	x	y	z	U(eq)
H(2)	4925	2180	2158	26
H(3)	4920	3014	2694	29
H(5)	2924	4152	1683	38
H(6)	2923	3327	1140	34
H(7A)	2760	4236	2740	55
H(7B)	4166	4599	2416	55
H(7C)	4838	4142	2829	55
H(8)	1472	1890	427	25
H(12)	-697	2412	1509	26
H(13)	-2345	3334	1579	26
H(14)	-2581	4005	926	39
H(15)	-1326	3739	199	39
H(16)	310	2823	123	31
H(17A)	-2122	1724	307	35
H(17B)	-2996	1213	660	35
H(18)	-1076	358	229	14
H(19A)	-1288	1452	-345	24
H(19B)	-680	760	-544	24
H(21A)	5017	-609	1346	59
H(21B)	5708	-95	976	59
H(21C)	3893	-459	877	59
H(23A)	2690	483	2810	40
H(23B)	805	803	2715	40
H(23C)	2550	1226	2746	40
H(8A)	1560	1725	487	19
H(12A)	-896	2339	1499	26
H(13A)	-2382	3298	1494	33
H(14A)	-2456	3912	809	38
H(15A)	-915	3585	132	37
H(16A)	624	2643	137	27

Table A6.4.6 (cont'd)

H(17C)	-2485	1578	595	27
H(17D)	-2531	848	699	27
H(18A)	-2549	1167	-179	77
H(19C)	673	689	15	111
H(19D)	-320	748	-504	111
H(21D)	4647	139	269	50
H(21E)	4094	-321	693	50
H(21F)	5821	109	742	50
H(23D)	2360	545	2938	54
H(23E)	614	927	2797	54
H(23F)	2470	1283	2847	54

A6.5 X-RAY CRYSTAL STRUCTURE ANALYSOS OF OXAZOLIDINE 375



375

Contents

Figure A6.5.1 X-ray crystal structure of oxazolidine ***375***

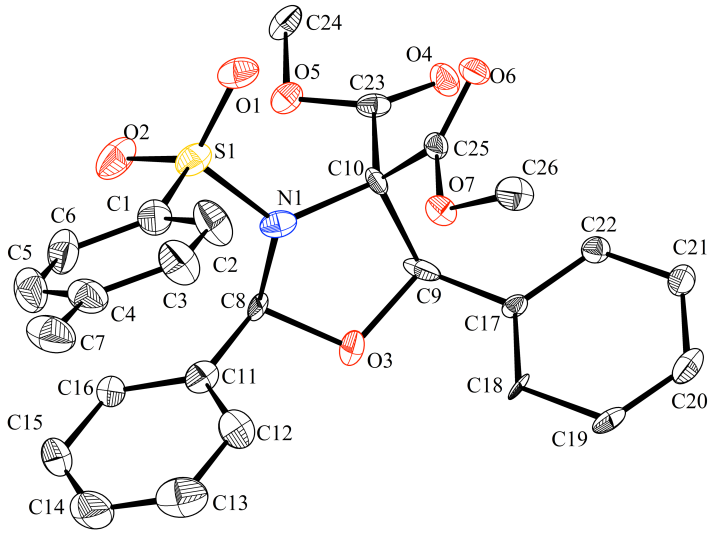


*Table A6.5.1 Experimental details for X-ray structure determination of oxazolidine **375***

Low-temperature diffraction data (and scans) were collected on a Bruker Kappa diffractometer coupled to a Apex II CCD detector with graphite monochromated Mo *K* radiation (= 0.71073 Å) for the structure of oxazolidine **375**. The structure was solved by direct methods using SHELXS and refined against F^2 on all data by full-matrix least squares with SHELXL-2013 refinement using established techniques. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the *U* value of the atoms they are linked to (1.5 times for methyl groups). All disordered atoms were refined with the help of similarity restraints on the 1,2- and 1,3- distances and displacement parameters as well as rigid bond restraints for anisotropic displacement parameters.

*Table A6.5.2 Crystal data and structure refinement for oxazolidine **375***

Empirical formula	C26 H25 N O7 S
CCDC Deposition Number	973928
Formula weight	495.53
Crystallization solvent	Ethyl Acetate
Crystal shape	block
Crystal color	colourless
Crystal size	0.34 x 0.39 x 0.41 mm
Preliminary photograph(s)	rotation
Type of diffractometer	Bruker APEX-II CCD
Wavelength	0.71073 Å MoK
Data collection temperature	100 K
Theta range for 9033 reflections used in lattice determination	2.40 to 34.83°
Unit cell dimensions	a = 26.2830(13) Å α= 90° b = 10.5471(5) Å β= 90° c = 8.4772(4) Å γ = 90°
Volume	2350.0(2) $Å^3$
Z	4
Crystal system	orthorhombic
Space group	P c a 21 (# 29)
Density (calculated)	1.401 g/cm^3
F(000)	1040
Theta range for data collection	1.9 to 35.2°
Completeness to theta = 25.000°	99.8%
Index ranges	$-42 \le h \le 41, -16 \le k \le 16, -13 \le l \le 13$
Reflections collected	85187
Independent reflections	10087 [R_{int}= 0.0399]
Reflections > 2s(I)	9439
Average s(I)/(net I)	0.0240
Absorption coefficient	0.19 mm^{-1}
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.0000 and 0.9213
Primary solution method	dual
Hydrogen placement	geom
Refinement method	Full-matrix least-squares on F^2

Table A6.5.2 (cont'd)

Data / restraints / parameters	10087 / 13 / 538
Treatment of hydrogen atoms	constr
Goodness-of-fit on F^2	1.19
Final R indices [I>2σ(I), 9439 reflections]	R1 = 0.0430, wR2 = 0.1033
R indices (all data)	R1 = 0.0470, wR2 = 0.1048
Type of weighting scheme used	calc
Max shift/error	0.001
Average shift/error	0.000
Absolute structure parameter	0.044(12)
Extinction coefficient	n/a
Largest diff. peak and hole	0.33 and -0.36 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)

*Table A6.5.3 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for oxazolidine **375**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U_{eq}
S(1)	8926(1)	6201(1)	5357(1)	24(1)
O(1)	8757(1)	5962(1)	6946(2)	28(1)
O(2)	8828(1)	5297(2)	4131(2)	35(1)
N(1)	8669(1)	7567(1)	4885(2)	21(1)
C(1)	9589(1)	6443(2)	5403(3)	26(1)
C(2)	9800(1)	7205(3)	6560(3)	36(1)
C(3)	10325(1)	7313(3)	6651(3)	38(1)
C(4)	10644(1)	6666(2)	5619(2)	32(1)
C(5)	10424(1)	5912(2)	4466(3)	37(1)
C(6)	9899(1)	5798(2)	4339(3)	32(1)
C(7)	11214(1)	6743(3)	5801(3)	41(1)
O(3)	8454(4)	9290(10)	3416(13)	31(2)
O(4)	7331(1)	7845(3)	6401(4)	23(1)
O(5)	7789(6)	6381(13)	5033(14)	20(1)
O(6)	8103(1)	8362(3)	8651(3)	20(1)
O(7)	8770(1)	9307(3)	7484(3)	18(1)
C(8)	8655(4)	7986(7)	3269(11)	13(2)
C(9)	8056(7)	9322(18)	4700(20)	22(3)
C(10)	8209(5)	8173(18)	5850(20)	16(2)
C(11)	9116(4)	8065(15)	2442(16)	21(2)
C(12)	9471(3)	8980(7)	2868(7)	26(1)
C(13)	9938(2)	9060(6)	2102(10)	40(1)
C(14)	10053(3)	8198(8)	966(11)	44(2)
C(15)	9701(3)	7272(7)	552(10)	44(2)
C(16)	9233(3)	7206(6)	1270(9)	29(1)
C(17)	8091(3)	10654(7)	5427(12)	13(1)
C(18)	8430(3)	11443(5)	4959(11)	16(1)
C(19)	8464(3)	12722(6)	5697(9)	24(1)
C(20)	8107(2)	13055(4)	6806(6)	25(1)

Table A6.5.3 (cont'd)

C(21)	7731(2)	12188(4)	7246(5)	19(1)
C(22)	7720(2)	10989(4)	6570(5)	16(1)
C(23)	7715(2)	7381(7)	5901(9)	17(1)
C(24)	7324(6)	5619(14)	5180(20)	23(2)
C(25)	8350(2)	8604(3)	7505(4)	14(1)
C(26)	8860(2)	10020(4)	8925(4)	26(1)
O(3A)	8459(2)	9216(8)	3393(7)	13(1)
O(4A)	7556(1)	7446(3)	7202(4)	30(1)
O(5A)	7767(6)	6217(12)	5341(14)	22(1)
O(6A)	8992(1)	9186(3)	7025(4)	23(1)
O(7A)	8266(1)	8980(3)	8372(3)	22(1)
C(8A)	8668(6)	8051(11)	3175(15)	37(3)
C(9A)	8106(5)	9189(15)	4546(18)	13(2)
C(10A)	8303(5)	8102(13)	5730(17)	11(1)
C(11A)	9229(3)	8166(12)	2597(11)	17(1)
C(12A)	9556(2)	8999(5)	3331(6)	19(1)
C(13A)	10052(2)	9131(4)	2790(6)	26(1)
C(14A)	10225(2)	8406(6)	1527(6)	31(1)
C(15A)	9903(3)	7558(7)	790(6)	30(1)
C(16A)	9402(2)	7438(6)	1290(7)	25(1)
C(17A)	8008(3)	10427(7)	5241(10)	15(1)
C(18A)	8397(5)	11464(10)	5114(14)	45(3)
C(19A)	8298(3)	12553(7)	5784(10)	38(2)
C(20A)	7868(3)	12772(5)	6675(6)	39(1)
C(21A)	7503(2)	11837(5)	6819(5)	36(1)
C(22A)	7578(2)	10668(4)	6104(5)	26(1)
C(23A)	7845(2)	7284(7)	6149(8)	16(1)
C(24A)	7299(7)	5528(16)	5250(30)	41(4)
C(25A)	8564(2)	8793(3)	7139(4)	14(1)
C(26A)	8481(2)	9837(5)	9541(4)	31(1)

*Table A6.5.4 Bond lengths [Å] and angles [°] for oxazolidine **375***

S(1)-O(1)	1.4406(16)
S(1)-O(2)	1.4334(17)
S(1)-N(1)	1.6401(16)
S(1)-C(1)	1.762(2)
N(1)-C(8)	1.440(10)
N(1)-C(10)	1.592(12)
N(1)-C(8A)	1.537(13)
N(1)-C(10A)	1.326(11)
C(1)-C(2)	1.384(3)
C(1)-C(6)	1.393(3)
C(2)-H(2)	0.9500
C(2)-C(3)	1.386(3)
C(3)-H(3)	0.9500
C(3)-C(4)	1.390(3)
C(4)-C(5)	1.386(4)
C(4)-C(7)	1.510(3)
C(5)-H(5)	0.9500
C(5)-C(6)	1.389(4)
C(6)-H(6)	0.9500
C(7)-H(7A)	0.9800
C(7)-H(7B)	0.9800
C(7)-H(7C)	0.9800
O(3)-C(8)	1.478(14)
O(3)-C(9)	1.51(2)
O(4)-C(23)	1.198(8)
O(5)-C(23)	1.301(19)
O(5)-C(24)	1.47(2)
O(6)-C(25)	1.196(5)
O(7)-C(25)	1.330(5)
O(7)-C(26)	1.454(5)
C(8)-H(8)	1.0000
C(8)-C(11)	1.403(16)
C(9)-H(9)	1.0000

Table A6.5.4 (cont'd)

C(9)-C(10)	1.60(3)
C(9)-C(17)	1.54(2)
C(10)-C(23)	1.546(18)
C(10)-C(25)	1.52(2)
C(11)-C(12)	1.389(12)
C(11)-C(16)	1.379(16)
C(12)-H(12)	0.9500
C(12)-C(13)	1.393(10)
C(13)-H(13)	0.9500
C(13)-C(14)	1.359(12)
C(14)-H(14)	0.9500
C(14)-C(15)	1.389(11)
C(15)-H(15)	0.9500
C(15)-C(16)	1.374(9)
C(16)-H(16)	0.9500
C(17)-C(18)	1.283(10)
C(17)-C(22)	1.418(11)
C(18)-H(18)	0.9500
C(18)-C(19)	1.490(9)
C(19)-H(19)	0.9500
C(19)-C(20)	1.374(9)
C(20)-H(20)	0.9500
C(20)-C(21)	1.396(6)
C(21)-H(21)	0.9500
C(21)-C(22)	1.389(6)
C(22)-H(22)	0.9500
C(24)-H(24A)	0.9800
C(24)-H(24B)	0.9800
C(24)-H(24C)	0.9800
C(26)-H(26A)	0.9800
C(26)-H(26B)	0.9800
C(26)-H(26C)	0.9800
O(3A)-C(8A)	1.358(15)
O(3A)-C(9A)	1.348(18)

Table A6.5.4 (cont'd)

O(4A)-C(23A)	1.185(8)
O(5A)-C(23A)	1.334(17)
O(5A)-C(24A)	1.43(2)
O(6A)-C(25A)	1.203(5)
O(7A)-C(25A)	1.320(4)
O(7A)-C(26A)	1.455(5)
C(8A)-H(8A)	1.0000
C(8A)-C(11A)	1.558(17)
C(9A)-H(9A)	1.0000
C(9A)-C(10A)	1.61(2)
C(9A)-C(17A)	1.456(19)
C(10A)-C(23A)	1.523(15)
C(10A)-C(25A)	1.558(16)
C(11A)-C(12A)	1.378(11)
C(11A)-C(16A)	1.423(12)
C(12A)-H(12A)	0.9500
C(12A)-C(13A)	1.391(7)
C(13A)-H(13A)	0.9500
C(13A)-C(14A)	1.393(7)
C(14A)-H(14A)	0.9500
C(14A)-C(15A)	1.380(8)
C(15A)-H(15A)	0.9500
C(15A)-C(16A)	1.390(8)
C(16A)-H(16A)	0.9500
C(17A)-C(18A)	1.500(13)
C(17A)-C(22A)	1.371(11)
C(18A)-H(18A)	0.9500
C(18A)-C(19A)	1.307(14)
C(19A)-H(19A)	0.9500
C(19A)-C(20A)	1.379(11)
C(20A)-H(20A)	0.9500
C(20A)-C(21A)	1.381(9)
C(21A)-H(21A)	0.9500
C(21A)-C(22A)	1.388(6)

Table A6.5.4 (cont'd)

C(22A)-H(22A)	0.9500
C(24A)-H(24D)	0.9800
C(24A)-H(24E)	0.9800
C(24A)-H(24F)	0.9800
C(26A)-H(26D)	0.9800
C(26A)-H(26E)	0.9800
C(26A)-H(26F)	0.9800

O(1)-S(1)-N(1)	104.74(9)
O(1)-S(1)-C(1)	108.06(10)
O(2)-S(1)-O(1)	120.43(10)
O(2)-S(1)-N(1)	109.52(9)
O(2)-S(1)-C(1)	106.81(11)
N(1)-S(1)-C(1)	106.53(8)
C(8)-N(1)-S(1)	120.8(3)
C(8)-N(1)-C(10)	110.1(8)
C(10)-N(1)-S(1)	122.7(7)
C(10A)-N(1)-C(8A)	111.5(8)
C(2)-C(1)-S(1)	119.77(16)
C(2)-C(1)-C(6)	120.5(2)
C(6)-C(1)-S(1)	119.58(17)
C(1)-C(2)-H(2)	120.4
C(1)-C(2)-C(3)	119.1(2)
C(3)-C(2)-H(2)	120.4
C(2)-C(3)-H(3)	119.2
C(2)-C(3)-C(4)	121.6(2)
C(4)-C(3)-H(3)	119.2
C(3)-C(4)-C(7)	120.5(2)
C(5)-C(4)-C(3)	118.4(2)
C(5)-C(4)-C(7)	121.1(2)
C(4)-C(5)-H(5)	119.4
C(4)-C(5)-C(6)	121.2(2)
C(6)-C(5)-H(5)	119.4
C(1)-C(6)-H(6)	120.4

Table A6.5.4 (cont'd)

C(5)-C(6)-C(1)	119.2(2)
C(5)-C(6)-H(6)	120.4
C(4)-C(7)-H(7A)	109.5
C(4)-C(7)-H(7B)	109.5
C(4)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7C)	109.5
H(7B)-C(7)-H(7C)	109.5
C(8)-O(3)-C(9)	109.2(11)
C(23)-O(5)-C(24)	105.8(12)
C(25)-O(7)-C(26)	114.3(3)
N(1)-C(8)-O(3)	102.4(6)
N(1)-C(8)-H(8)	109.6
O(3)-C(8)-H(8)	109.6
C(11)-C(8)-N(1)	118.1(8)
C(11)-C(8)-O(3)	107.2(10)
C(11)-C(8)-H(8)	109.6
O(3)-C(9)-H(9)	110.4
O(3)-C(9)-C(10)	104.1(13)
O(3)-C(9)-C(17)	105.5(12)
C(10)-C(9)-H(9)	110.4
C(17)-C(9)-H(9)	110.4
C(17)-C(9)-C(10)	115.7(13)
N(1)-C(10)-C(9)	100.7(11)
C(23)-C(10)-N(1)	115.9(12)
C(23)-C(10)-C(9)	102.4(12)
C(25)-C(10)-N(1)	114.0(11)
C(25)-C(10)-C(9)	113.2(13)
C(25)-C(10)-C(23)	109.7(10)
C(12)-C(11)-C(8)	119.4(11)
C(16)-C(11)-C(8)	120.9(9)
C(16)-C(11)-C(12)	119.6(10)
C(11)-C(12)-H(12)	119.5
C(11)-C(12)-C(13)	120.9(8)

Table A6.5.4 (cont'd)

C(13)-C(12)-H(12)	119.5
C(12)-C(13)-H(13)	120.5
C(14)-C(13)-C(12)	119.0(6)
C(14)-C(13)-H(13)	120.5
C(13)-C(14)-H(14)	119.9
C(13)-C(14)-C(15)	120.1(6)
C(15)-C(14)-H(14)	119.9
C(14)-C(15)-H(15)	119.4
C(16)-C(15)-C(14)	121.3(7)
C(16)-C(15)-H(15)	119.4
C(11)-C(16)-H(16)	120.5
C(15)-C(16)-C(11)	119.0(7)
C(15)-C(16)-H(16)	120.5
C(18)-C(17)-C(9)	120.7(11)
C(18)-C(17)-C(22)	121.8(7)
C(22)-C(17)-C(9)	117.4(9)
C(17)-C(18)-H(18)	120.0
C(17)-C(18)-C(19)	119.9(9)
C(19)-C(18)-H(18)	120.0
C(18)-C(19)-H(19)	120.7
C(20)-C(19)-C(18)	118.6(5)
C(20)-C(19)-H(19)	120.7
C(19)-C(20)-H(20)	120.1
C(19)-C(20)-C(21)	119.9(4)
C(21)-C(20)-H(20)	120.1
C(20)-C(21)-H(21)	120.0
C(22)-C(21)-C(20)	120.1(4)
C(22)-C(21)-H(21)	120.0
C(17)-C(22)-H(22)	120.2
C(21)-C(22)-C(17)	119.7(4)
C(21)-C(22)-H(22)	120.2
O(4)-C(23)-O(5)	131.1(9)
O(4)-C(23)-C(10)	119.8(8)
O(5)-C(23)-C(10)	107.1(10)

Table A6.5.4 (cont'd)

O(5)-C(24)-H(24A)	109.5
O(5)-C(24)-H(24B)	109.5
O(5)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
O(6)-C(25)-O(7)	125.5(3)
O(6)-C(25)-C(10)	123.6(7)
O(7)-C(25)-C(10)	110.8(7)
O(7)-C(26)-H(26A)	109.5
O(7)-C(26)-H(26B)	109.5
O(7)-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
C(9A)-O(3A)-C(8A)	111.0(10)
C(23A)-O(5A)-C(24A)	125.9(13)
C(25A)-O(7A)-C(26A)	113.7(3)
N(1)-C(8A)-H(8A)	112.3
N(1)-C(8A)-C(11A)	108.6(9)
O(3A)-C(8A)-N(1)	100.0(8)
O(3A)-C(8A)-H(8A)	112.3
O(3A)-C(8A)-C(11A)	110.8(10)
C(11A)-C(8A)-H(8A)	112.3
O(3A)-C(9A)-H(9A)	107.5
O(3A)-C(9A)-C(10A)	104.2(11)
O(3A)-C(9A)-C(17A)	113.3(11)
C(10A)-C(9A)-H(9A)	107.5
C(17A)-C(9A)-H(9A)	107.5
C(17A)-C(9A)-C(10A)	116.3(11)
N(1)-C(10A)-C(9A)	101.5(10)
N(1)-C(10A)-C(23A)	117.3(10)
N(1)-C(10A)-C(25A)	107.1(9)
C(23A)-C(10A)-C(9A)	107.1(9)

Table A6.5.4 (cont'd)

C(23A)-C(10A)-C(25A)	115.7(9)
C(25A)-C(10A)-C(9A)	106.7(9)
C(12A)-C(11A)-C(8A)	119.8(9)
C(12A)-C(11A)-C(16A)	119.7(7)
C(16A)-C(11A)-C(8A)	120.4(8)
C(11A)-C(12A)-H(12A)	120.0
C(11A)-C(12A)-C(13A)	120.0(6)
C(13A)-C(12A)-H(12A)	120.0
C(12A)-C(13A)-H(13A)	119.8
C(12A)-C(13A)-C(14A)	120.3(5)
C(14A)-C(13A)-H(13A)	119.8
C(13A)-C(14A)-H(14A)	119.9
C(15A)-C(14A)-C(13A)	120.2(5)
C(15A)-C(14A)-H(14A)	119.9
C(14A)-C(15A)-H(15A)	119.9
C(14A)-C(15A)-C(16A)	120.2(5)
C(16A)-C(15A)-H(15A)	119.9
C(11A)-C(16A)-H(16A)	120.3
C(15A)-C(16A)-C(11A)	119.5(6)
C(15A)-C(16A)-H(16A)	120.3
C(9A)-C(17A)-C(18A)	120.4(10)
C(22A)-C(17A)-C(9A)	121.8(8)
C(22A)-C(17A)-C(18A)	117.7(8)
C(17A)-C(18A)-H(18A)	120.8
C(19A)-C(18A)-C(17A)	118.3(11)
C(19A)-C(18A)-H(18A)	120.8
C(18A)-C(19A)-H(19A)	118.4
C(18A)-C(19A)-C(20A)	123.2(8)
C(20A)-C(19A)-H(19A)	118.4
C(19A)-C(20A)-H(20A)	120.0
C(19A)-C(20A)-C(21A)	119.9(5)
C(21A)-C(20A)-H(20A)	120.0
C(20A)-C(21A)-H(21A)	120.1
C(20A)-C(21A)-C(22A)	119.8(5)

Table A6.5.4 (cont'd)

C(22A)-C(21A)-H(21A)	120.1
C(17A)-C(22A)-C(21A)	121.0(5)
C(17A)-C(22A)-H(22A)	119.5
C(21A)-C(22A)-H(22A)	119.5
O(4A)-C(23A)-O(5A)	114.2(8)
O(4A)-C(23A)-C(10A)	126.9(8)
O(5A)-C(23A)-C(10A)	118.7(9)
O(5A)-C(24A)-H(24D)	109.5
O(5A)-C(24A)-H(24E)	109.5
O(5A)-C(24A)-H(24F)	109.5
H(24D)-C(24A)-H(24E)	109.5
H(24D)-C(24A)-H(24F)	109.5
H(24E)-C(24A)-H(24F)	109.5
O(6A)-C(25A)-O(7A)	124.5(3)
O(6A)-C(25A)-C(10A)	120.7(5)
O(7A)-C(25A)-C(10A)	114.6(5)
O(7A)-C(26A)-H(26D)	109.5
O(7A)-C(26A)-H(26E)	109.5
O(7A)-C(26A)-H(26F)	109.5
H(26D)-C(26A)-H(26E)	109.5
H(26D)-C(26A)-H(26F)	109.5
H(26E)-C(26A)-H(26F)	109.5

Symmetry transformations used to generate equivalent atoms:

*Table A6.5.5 Anisotropic displacement parameters ($Å^2x10^3$) for oxazolidine **375**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$.*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	307(2)	186(2)	231(2)	33(2)	-63(2)	-10(2)
O(1)	299(7)	260(6)	277(7)	110(5)	-33(6)	3(5)
O(2)	504(10)	189(6)	359(8)	-28(6)	-108(7)	-39(6)
N(1)	222(7)	202(6)	190(6)	63(5)	-40(5)	-31(5)
C(1)	303(8)	267(8)	212(7)	15(7)	-14(8)	46(6)
C(2)	286(10)	507(13)	276(10)	-125(9)	36(8)	-28(9)
C(3)	307(11)	485(13)	337(11)	-73(10)	37(9)	-18(10)
C(4)	296(9)	390(10)	257(10)	110(8)	35(7)	86(8)
C(5)	410(12)	399(12)	294(10)	26(9)	30(9)	217(10)
C(6)	417(11)	278(9)	275(9)	-42(7)	-51(8)	135(9)
C(7)	304(10)	553(15)	381(12)	187(11)	61(9)	93(10)
O(3)	460(40)	160(30)	310(40)	0(20)	120(30)	110(30)
O(4)	174(12)	241(13)	269(14)	-59(11)	87(10)	-40(10)
O(5)	190(17)	160(30)	240(40)	-20(20)	-30(20)	-50(20)
O(6)	217(12)	216(13)	152(11)	5(9)	47(9)	-27(10)
O(7)	153(13)	231(13)	161(11)	-15(10)	-1(10)	-22(11)
C(8)	230(30)	62(19)	100(30)	-50(18)	-40(20)	-7(18)
C(9)	150(30)	330(60)	170(40)	120(40)	70(20)	30(30)
C(10)	160(50)	180(30)	140(20)	-39(17)	70(30)	0(30)
C(11)	240(40)	190(20)	200(30)	0(20)	-60(20)	-20(30)
C(12)	250(30)	340(20)	200(30)	-40(20)	-40(20)	-1(19)
C(13)	240(20)	470(30)	510(40)	130(30)	-50(20)	-60(20)
C(14)	290(30)	460(40)	590(50)	160(40)	210(30)	110(30)
C(15)	500(40)	320(30)	490(40)	40(30)	300(40)	140(30)
C(16)	410(40)	180(20)	280(20)	-15(17)	140(30)	0(20)
C(17)	90(30)	90(20)	200(30)	15(18)	7(19)	-23(16)
C(18)	220(20)	15(15)	230(30)	-4(13)	16(19)	2(14)
C(19)	320(30)	90(20)	330(20)	38(15)	50(20)	-60(18)
C(20)	340(20)	119(15)	290(20)	-3(14)	-48(18)	14(15)
C(21)	245(17)	156(15)	180(16)	-8(13)	-10(14)	27(13)

Table A6.5.5 (cont'd)

C(22)	171(16)	153(15)	149(15)	-6(11)	-8(12)	-31(12)
C(23)	190(30)	180(20)	140(20)	25(15)	-25(17)	-80(20)
C(24)	220(30)	130(20)	350(50)	10(30)	-40(30)	-10(30)
C(25)	133(15)	148(13)	145(15)	4(11)	12(12)	34(12)
C(26)	303(19)	281(18)	184(16)	-36(13)	-26(13)	-96(15)
O(3A)	140(20)	190(30)	70(20)	66(16)	-31(17)	-61(18)
O(4A)	256(14)	344(14)	299(15)	-66(12)	118(12)	-107(12)
O(5A)	260(20)	140(30)	270(40)	0(20)	-50(30)	-14(18)
O(6A)	177(13)	288(13)	215(12)	-71(10)	12(10)	-61(10)
O(7A)	191(11)	331(15)	125(10)	-33(10)	4(9)	-16(10)
C(8A)	500(60)	380(50)	210(30)	200(30)	-110(30)	-90(30)
C(9A)	70(30)	190(20)	120(30)	32(17)	-20(30)	-40(30)
C(10A)	150(40)	90(20)	90(30)	0(17)	30(20)	-30(20)
C(11A)	220(40)	210(30)	90(20)	-4(17)	10(20)	20(30)
C(12A)	210(20)	216(16)	150(20)	-35(17)	29(16)	-32(15)
C(13A)	225(18)	255(18)	290(20)	37(15)	101(16)	-5(14)
C(14A)	260(20)	390(20)	290(20)	84(19)	134(17)	40(20)
C(15A)	320(30)	390(30)	182(17)	24(19)	100(20)	120(20)
C(16A)	310(30)	270(30)	175(16)	2(16)	17(19)	21(19)
C(17A)	140(30)	140(30)	170(20)	58(19)	-45(16)	-15(17)
C(18A)	500(50)	630(60)	210(30)	0(30)	10(30)	250(40)
C(19A)	540(50)	150(20)	440(30)	31(19)	-160(30)	-80(30)
C(20A)	660(40)	220(20)	290(20)	-85(19)	-130(30)	210(20)
C(21A)	550(30)	320(20)	207(17)	30(16)	42(19)	250(20)
C(22A)	310(20)	248(18)	212(18)	64(14)	66(15)	117(16)
C(23A)	160(30)	163(16)	140(20)	-14(14)	-3(16)	-17(18)
C(24A)	420(50)	300(50)	510(80)	-30(50)	-110(50)	-210(30)
C(25A)	146(15)	150(13)	116(12)	12(10)	-2(12)	17(12)
C(26A)	312(18)	480(20)	150(14)	-139(15)	-44(13)	16(17)

Table A6.5.6 Hydrogen coordinates (x10^4) and isotropic displacement parameters (Å^{2}x10^3) for oxazolidine ***375***

	x	y	z	U_{iso}
H(2)	959	765	728	43
H(3)	1047	784	744	45
H(5)	1064	546	375	44
H(6)	975	529	354	39
H(7A)	1131	760	612	62
H(7B)	1138	654	479	62
H(7C)	1133	614	661	62
H(8)	841	745	266	16
H(9)	771	918	425	26
H(12)	939	956	369	31
H(13)	1017	971	237	48
H(14)	1037	823	45	53
H(15)	979	667	-24	52
H(16)	899	658	96	35
H(18)	866	1121	414	19
H(19)	873	1330	541	29
H(20)	811	1387	727	30
H(21)	748	1242	801	23
H(22)	747	1040	687	19
H(24A)	737	481	462	35
H(24B)	704	608	471	35
H(24C)	725	545	629	35
H(26A)	909	1074	870	38
H(26B)	902	947	971	38
H(26C)	854	1034	933	38
H(8A)	846	751	246	44
H(9A)	778	889	407	15
H(12A)	944	948	421	23
H(13A)	1028	972	329	31
H(14A)	1057	850	117	38

Table A6.5.6 (cont'd)

H(15A)	1003	706	-6	36
H(16A)	918	687	76	30
H(18A)	871	1133	456	54
H(19A)	853	1323	565	45
H(20A)	782	1356	719	47
H(21A)	720	1199	740	43
H(22A)	733	1003	622	31
H(24D)	706	597	455	62
H(24E)	715	547	631	62
H(24F)	736	467	485	62
H(26D)	851	1069	909	47
H(26E)	882	954	985	47
H(26F)	826	986	1047	47

CHAPTER 4

Progress toward the Total Synthesis of Calophyline A

4.1 INTRODUCTION

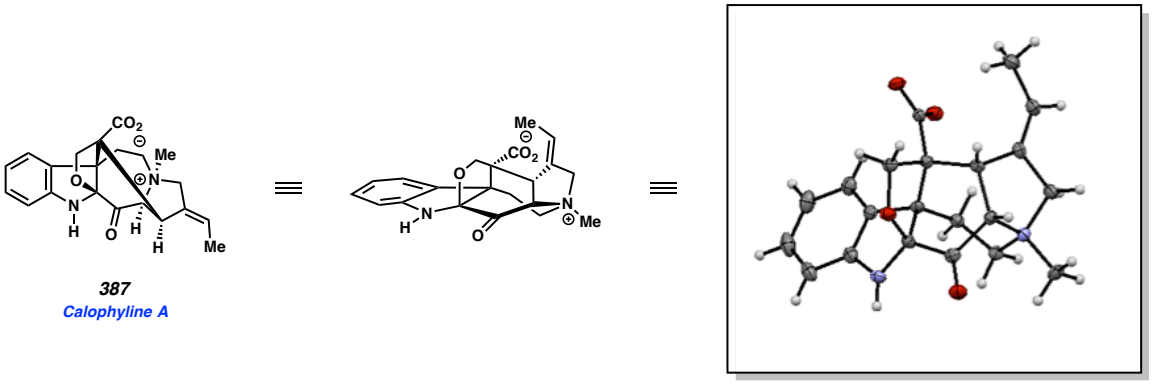
Calophyline A is a monoterpenoid indole alkaloid isolated in 2012. Although it has no known biological activity, we were interested in its unusual caged structure, likely the result of a rearrangement of an akuammaline alkaloid precursor. This chapter briefly describes the isolation and proposed biosynthesis of calophyline A, summarizes a total synthesis recently disclosed by Zu and co-workers, and then proceeds to discuss the various synthetic strategies pursued by our research laboratory.

4.1.1 ISOLATION AND PROPERTIES OF CALOPHYLINE A

Calophyline A (**387**, Figure 4.1) is a monoterpenoid alkaloid isolated by Zou, Li, and co-workers in 2012 from the trunk bark of the *Winchia calophylla* A. DC. (Apocynaceae) tree of Yunnan Province and Hainan island in southern China.[1] The leaves and trunk bark of *W. calophylla* have been used in traditional Chinese medicine for the treatment of

various respiratory conditions. The structure of **387** was determined by spectroscopic methods and confirmed by X-ray crystallographic analysis. Although other compounds found in the bark of *W. calophylla* are known to posess modest activity against prostate and breast cancer, calophyline A displayed no such activity.

Figure 4.1 Structure of calophyline A

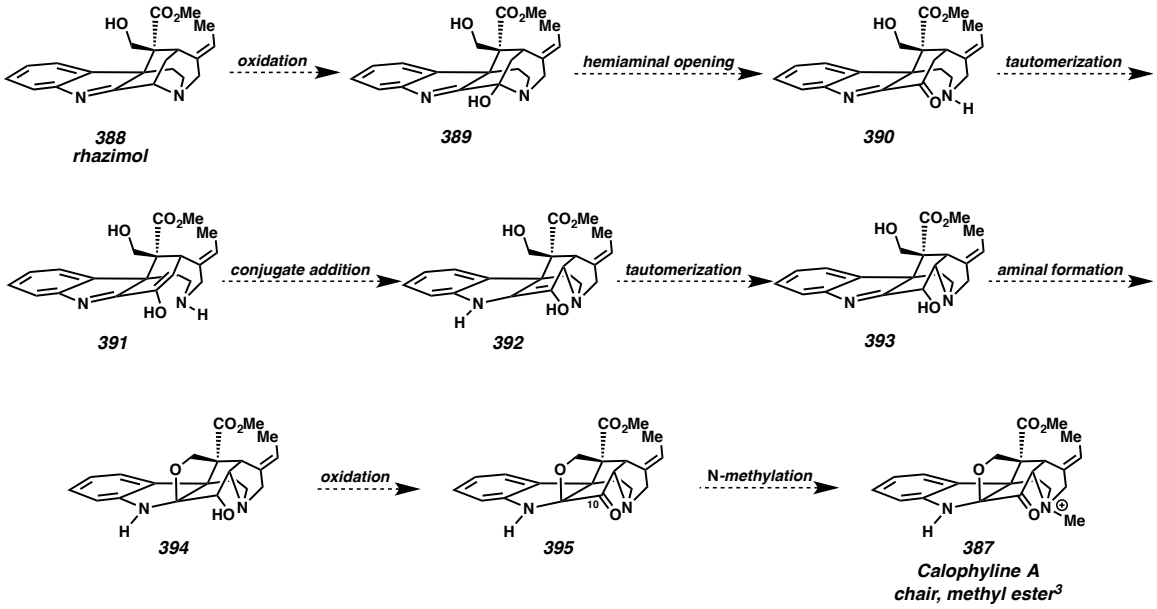


4.1.2 TANTILLO'S BIOSYNTHETIC PROPOSAL

In their isolation report, Zou, Li, and co-workers recognized calophylin A as a rearranged monoterpenoid indole alkaloid with an unpreccedented 7/5 ring system and proposed the known alkaloid rhazimol (**388**, Scheme 4.1) as a biosynthetic precursor. Their isolation report includes a proposed biosynthesis from rhazimol,[1] but subsequent computational studies by Tantillo and co-workers found a key rearrangement step to be energetically unviable.[2] Tantillo proposed the alternative biosynthesis shown in Scheme 4.1, which avoids this unlikely rearrangement and relies instead upon biologically precedented oxidations and simple carbonyl chemistry. In this route, rhazimol is

oxidized to hemiaminal **389**, which opens to ketone **390**. Tautomerization to the enol (**391**) and conjugate addition of the secondary amino group into the α,β-unsaturated imine affords enamine **392**, which tautomerizes to imine **393**. Formation of the tetrahydrofuran ring provides **394** and oxdiation to reform the C10 ketone and *N*-methylation complete the biosynthesis of calophyline A.

Scheme 4.1 Tantillo's proposal for the biosynthesis of calophyline A[3]

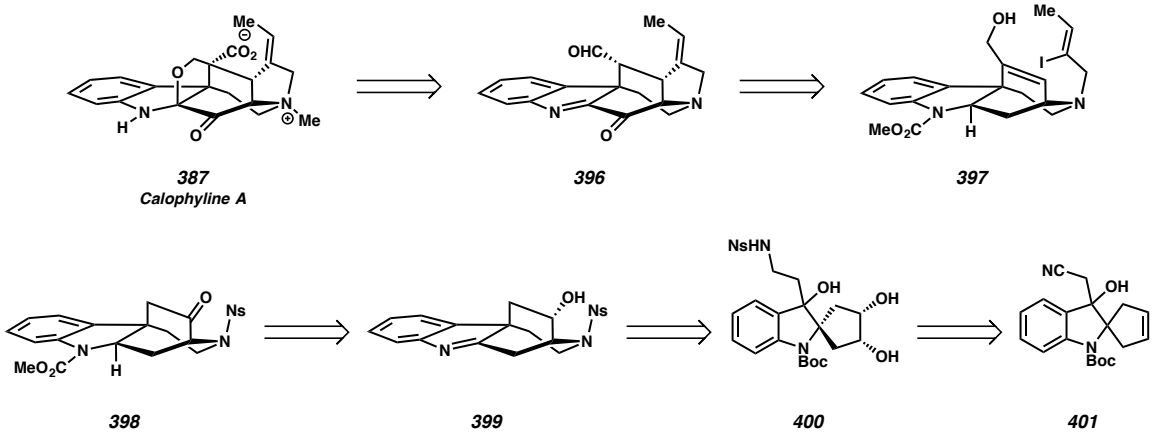


4.1.3 ZU'S TOTAL SYNTHESIS

In 2016, Zu and co-workers reported the first total synthesis of calophyline A. Retrosynthetically, they simplified calophyline A to **396** by a late-stage aldol addition into formaldehyde (Scheme 4.2). This was further diconnected using a Heck cyclization to afford iodide **397**, which would be accessed from cyclohexanol **399** via ketone **398**. In

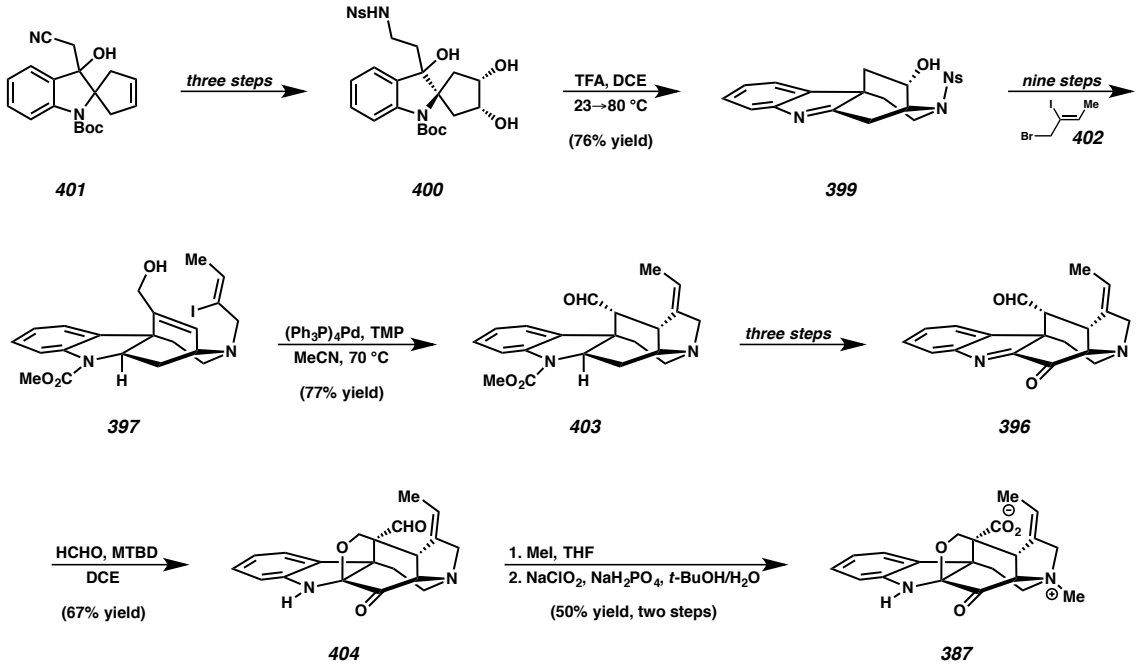
the key step, **399** would be formed by an aza-pinacol rearrangement[4,5] of spirocycle **400**, itself readily available from known indoline **401**.[4]

Scheme 4.2 Zu's retrosynthesis of calophyline A



In the forward direction, **401** was advanced to aza-pinacol substrate **400** over a three step sequence (Scheme 4.3). Heating triol **400** with trifluoroacetic acid promoted the key cascade reaction, which consists of indoline deprotection, aza-pinacol rearrangement, selective dehydration to form an α,β-unsaturated imine, and conjugate addition of the sulfonamide group, affording **399** in 76% yield. A series of functional group interconversions and alkylation with bromide **402** furnished vinyl iodide **397**, which was advanced to aldehyde **403** by an intramolecular Heck reaction. A three step sequence effected indoline deprotection, indolenine formation, and ketone installation to afford **404**. Finally, aldol reaction with formaldehyde installed the hydroxymethyl bridge and a one-pot *N*-methylation and Pinnick sequence delivered the natural product.

Scheme 4.3 Zu's total synthesis of calophyline A



4.2 INVESTIGATION OF A CYCLOPROPANE CYCLOADDITION ROUTE TOWARD THE SYNTHESIS OF CALOPHYLINE A

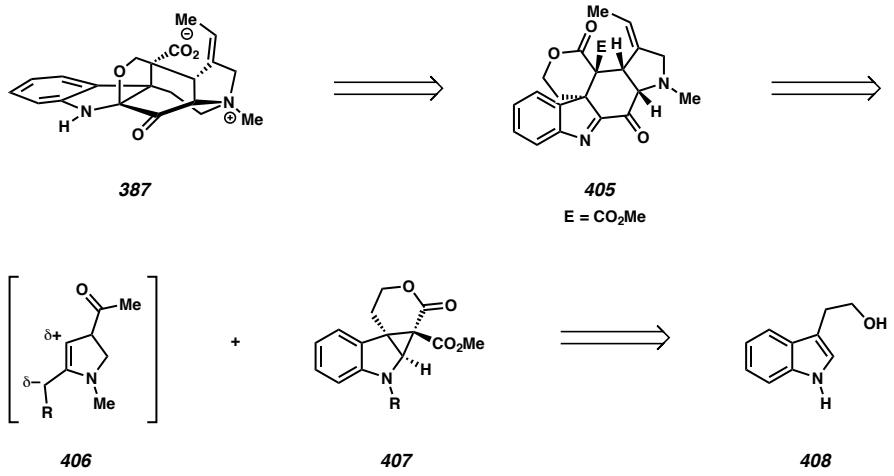
Our initial synthetic plan was inspired by our previous studies of formal cycloadditions of cyclopropanes. We predicted that a C2–C3 cyclopropanated indole would be reactive enough to undergo formal (3 + 3) cycloaddition with an appropriate 1,3-dipole to construct the central cyclohexanone ring.

4.2.1 RETROSYNTEHTIC ANALYSIS

Retrosynthetically we envisioned calophyline A would arise from pentacycle **405** by hemiaminal construction, lactone hydrolysis, and formation of the quaternary ammonium

salt (Scheme 4.4). The cyclohexanone ring of **405** would be assembled by a (3 + 3) reaction between a cyclopropanated indole such as **407** and a suitable dipole (**406**). Cyclopropane **407** would be accessed from commercially available tryptophol (**408**).

Scheme 4.4 Initial retrosynthetic analysis



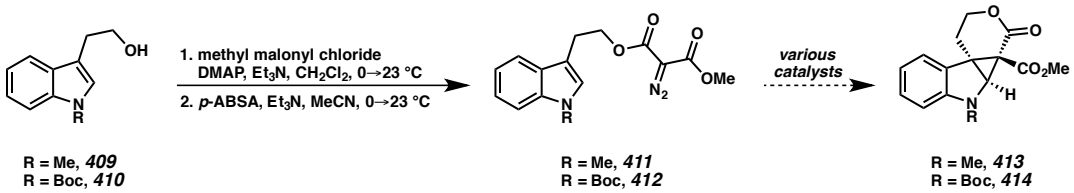
4.2.2 ATTEMPTS TO SYNTHESIZE CYCLOPROPANATED INDOLES

Although (3 + 3) cycloadditions between cyclopropanes and 1,3-dipoles are not commonly known,[6] we initially approached the route with a focus on exploring the reactivity of cyclopropanated indoles such as **407** (Scheme 4.4). While the synthesis and reactivity of several cyclopropanated indoles have been disclosed,[7,8] we were interested in compounds posessing two geminal acceptor groups, which should increase the cyclopropane reactivity and would be synthetically useful in a route to calophyline A.

We began our studies with efforts to synthesize a variety of C2–C3 cyclopropanated indoles beginning with those posessing geminal acceptor groups. To investigate the effect of the indole nitrogen electronics, protected trytophols (**409** and **410**) were

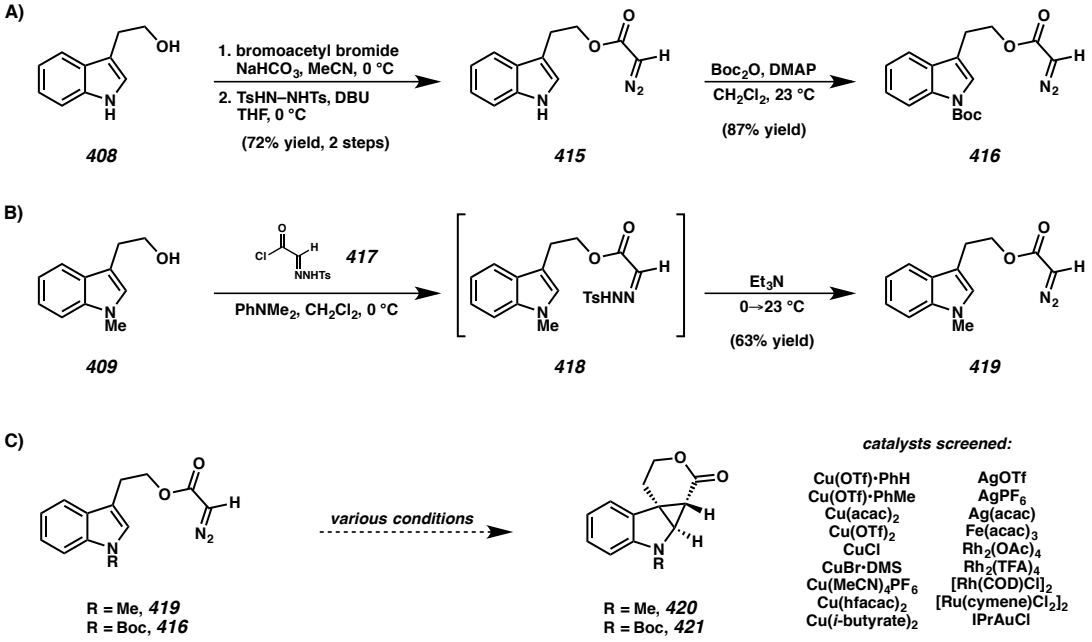
subjected to the two-step sequence shown in Scheme 4.5 to access diazomaloantes **411** and **412**. Upon treatment with various cyclopropanation conditions,[9] however, only decomposition, carbenoid dimerization, or Boc cleavage results were obtained.

Scheme 4.5 Attempted syntheses of cyclopropanated indoles with two acceptor groups



Suspecting that the combination of two acceptor groups and a strong nitrogen donor group was too polarizing for cyclopropane stability, we chose to synthesize various cyclopropanes with only one acceptor group in the hope they would be isolable. Trytophol (**408**) was advanced to **415** in good yield using Fukuyama's procedure for diazoacetate synthesis (Scheme 4.6A).[10] Protection of the indole nitrogen with a Boc group furnished diazoacetate **416**. A more electron-rich indole was incorporated by reacting *N*-methyl tryptophol (**409**) with acid chloride **417** and *in situ* sulfinate elimination (Scheme 4.6B).[11] Unfortunately, despite an examination of various catalysts, we were unable to form the desired cyclopropanes (**420** and **421**), with most conditions resulting in decomposition (Scheme 4.6C).

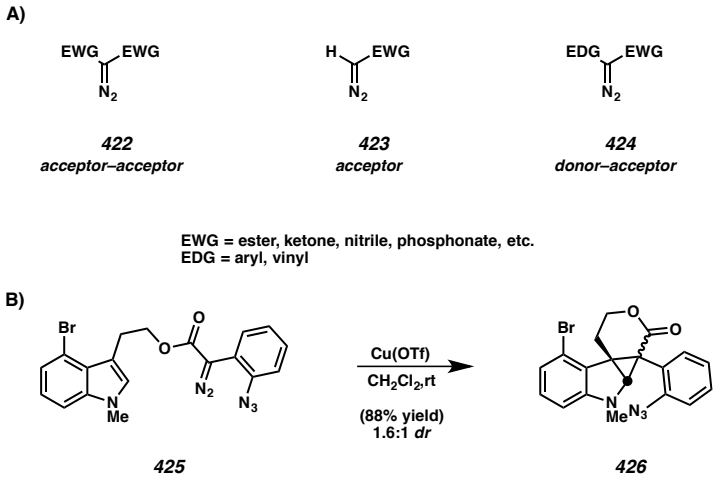
Scheme 4.6 Attempted syntheses of cyclopropanated indoles with one acceptor group



4.2.3 DISCOVERY OF A (3 + 2) CYCLOADDITION RESULT AND THE DESIGN OF A NEW SYNTHETIC STRATEGY

In light of our inability to achieve an indole cyclopropanation using either acceptor–acceptor diazo substrates such as **411** or **412** or acceptor diazo substrates like **416** or **419**, we chose to investigate a donor–acceptor diazo substrate. Reactions of donor–acceptor carbenoids (derived from donor–acceptor diazo compounds) are often more selective than those of other carbenoids due to the stabilizing effect of the electron-donating group (Scheme 4.7A).[12] Furthermore, Qin and co-workers made use of a donor–acceptor diazo substrate in their indole cyclopropanation en route to communesin F (Scheme 4.7B).[7c]

Scheme 4.7 A) General classes of diazo compounds. B) Qin's use of a donor–acceptor diazo compound cyclopropanation in a total synthesis



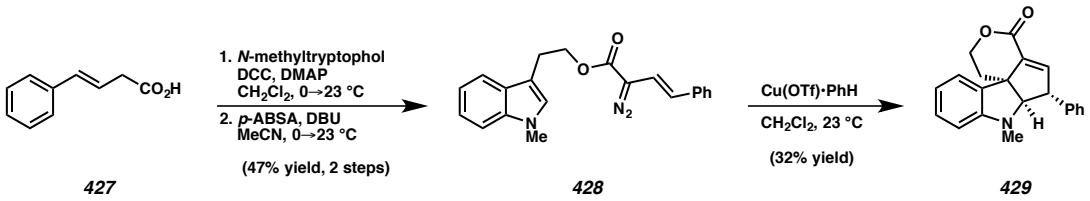
In our case, cyclopropanation with an aryldiazo compound similar to **425** would produce a cyclopropane likely insufficiently reactive to undergo a desired cycloaddition reaction. Additionally, the aryl group would ultimately need to be removed, which we anticipated to be challenging. However, Davies and co-workers have shown that styrenyl diazoacetates also form donor–acceptor carbenoids when treated with rhodium catalysts.[13] If we were to use a styrenyl diazoacetate substrate in our cyclopropanation,[13] a simple oxidative cleavage of the styrene olefin could install an acceptor group where needed on the cyclopropane framework.

4.2.4 ATTEMPTS TO FORM THE CALOPHYLINE CORE BY A (3 + 2)/CYCLOPROPANATION/FRAGMENTATION STRATEGY

To explore this idea, we synthesized diazoester **428** from known carboxylic acid **427** and subjected it to cyclopropanation conditions. Although we did not observe formation of the desired cyclopropanated indole, exposure to copper(I) triflate benzene complex in

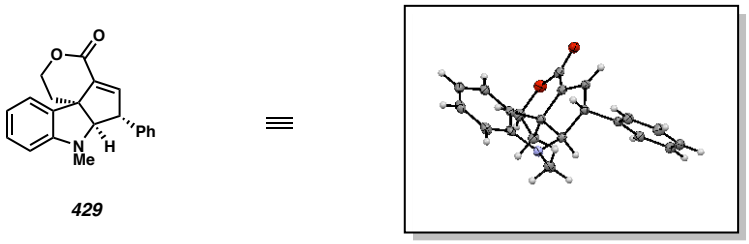
dichloromethane furnished tetracycle **429** in 32% yield (Scheme 4.8 and Figure 4.2). This result is perhaps unsurprising, as Davies has reported the analgous rhodium-catalyzed intermolecular (3 + 2) cyloaddition between indoles and vinyl diazoacetates.[14]

Scheme 4.8 Synthesis and reaction of styrenyl diazoacetate ***428***



427 ***428*** ***429***

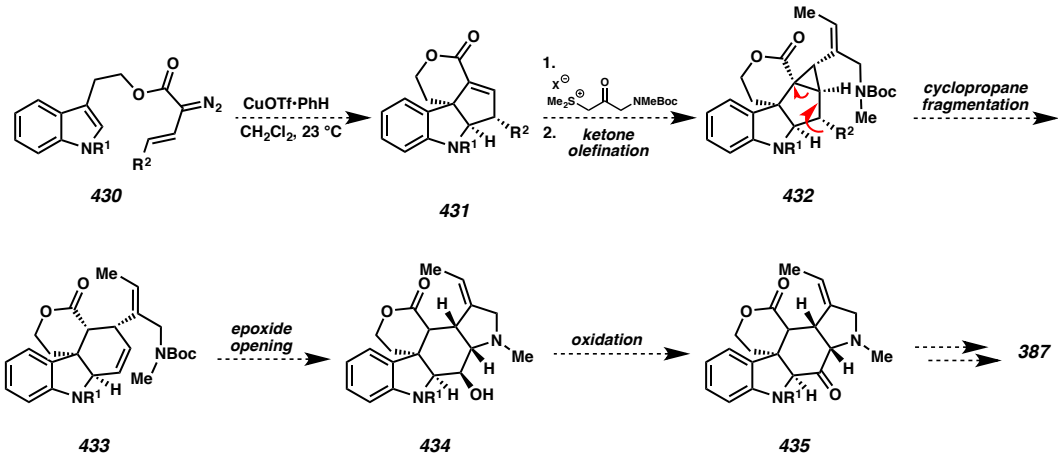
Figure 4.2 Crystal structure of tetracycle ***429***



429

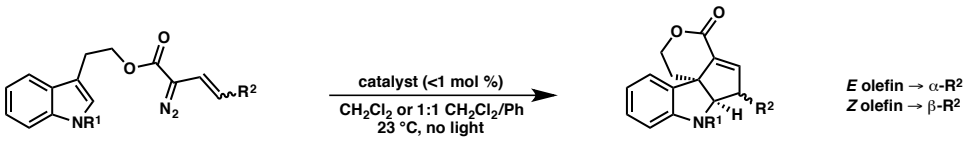
We imagined a (3 + 2) cycloaddition reaction could be productive if the phenyl substitutent was replaced with a group that could act as an electrofuge in a later fragmentation step (**432**→**433**, Scheme 4.9). More specifically, we envisioned (3 + 2) cycloadduct could be cyclopropanated to afford **432**, which could then be converted to tetracycle **433** by a cyclopropane fragmentation step. Closure of the pyrrolidine ring by epoxide opening would furnish **434**, which after oxidation would be advanced to calophyline A as in our initial synthetic plan.

Scheme 4.9 Revised synthetic plan for calophyline A



To explore the feasibility of this revised plan, we synthesized a variety of vinyl diazoacetates and subjected them to metal-catalyzed dediazotization conditions. The results are shown in Scheme 4.10. Unfortunately, despite investigating compounds with either olefin geometry containing various R^2 groups which could serve as the deisred electrofuge (or readily be converted to an electrofugre) such as carboxylates and a furan rings (entries 2–8), we were unable to observe the desired cycloaddition reaction. The use of a diazo enol silane substrate, which would form a cyclopentanone product following desilylation, was also unsuccessful. Our attempts to investigate substrates containing other R^2 groups, including TMS, $SnBu_3$, and styrenyl, were frustrated by difficulties in their synthesis.

Scheme 4.10 Unsuccessful (3 + 2) cycloadditions of various vinyl diazoacetates



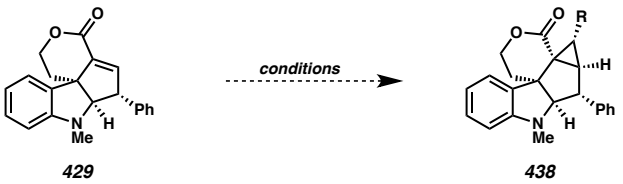
436 ***437***

Entry	*R1*	*R2*	*Olefin Geometry*	*Catalyst*	*Result*
1	Me	Ph	*E*	Cu(OTf)·PhH	32% yield
2	Me	CO_2Me	*Z*	Cu(OTf)·PhH	pyrazole formation
3	Me	CO_2Me	*Z*	$Rh_2(OAc)_4$	pyrazole formation
4	Boc	CO_2Me	*Z*	Cu(OTf)·PhH	no reaction
5	Boc	CO_2Me	*Z*	$Rh_2(OAc)_4$	pyrazole formation
6	Boc	$CO_2CH_2CH_2TMS$	*E*	Cu(OTf)·PhH	pyrazole formation
7	Boc	$CO_2CH_2CH_2TMS$	*E*	$Rh_2(OAc)_4$	pyrazole formation
8	Boc	2-furyl	*E*	Cu(OTf)·PhH	decomposition
9	Me	H: 1,1-disub. TBS enol silane	N/A	Cu(OTf)·PhH; TBAF	ester hydrolysis
10	Me	H: 1,1-disub. TBS enol silane	N/A	$Rh_2(OAc)_4$	dimerization

Reactions conducted on approx. 0.05 mmol scale by adding a solution of the substrate to a solution of the catalyst over one hour.

Concurrently with our efforts to indentify a (3 + 2) cycloaddition substrate, we briefly examined a few cyclopropanation conditions, using tetracycle **429** as a model system (Scheme 4.11). To our disappointment, treatment with either standard Corey–Chaykovsky conditions (entry 1) or a substituted sulfur ylide (entry 2) resulted in little reaction. Exposure to the rhodium carbenoid derived from ethyl diazoacetate led to decomposition (entry 3). At this point we concluded our studies of an indole-vinyl diazoacetate (3 + 2) cycloaddition/cyclopropanation/fragmentation approach in favor of other synthetic routes.

Scheme 4.11 Attempts to cyclopropanate tetracycle ***429***



429 ***438***

Entry	*Conditions*	*R*	*Result*
1	$Me_3S(O)I$, NaH, DMF, 23 °C	H	low conversion
2	$[PhC(O)CH_2SMe_2]Br$, K_2CO_3, MeCN, 23→80 °C	C(O)Ph	no reaction
3	EDA, $Rh_2(OAc)_4$, CH_2Cl_2, 23→50 °C	CO_2Et	decomposition

4.3 INVESTIGATION OF A [4 + 2] CYCLOADDITION ROUTE TOWARD THE SYNTHESIS OF CALOPHYLINE A

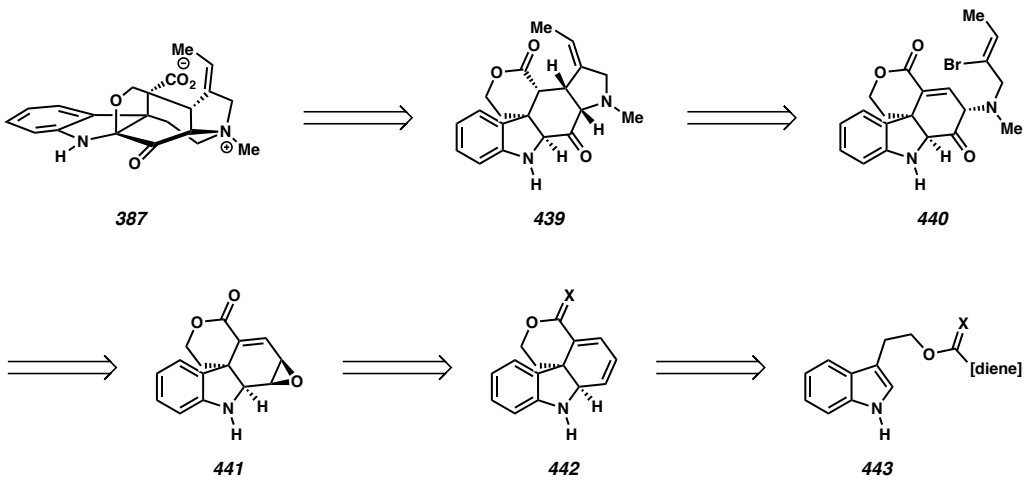
After our lack of success with the initial (3 + 3) disconnection or the (3 + 2)/cyclopropanation/fragmentation sequence, we began to consider disconnections not involving cyclopropane intermediates. Our efforts toward a synthesis with a key [4 + 2] cycloaddition step are presented in this section.

4.3.1 RETROSYNTHETIC ANALYSIS

Preserving our endgame strategy, we envisioned that calophyline could be accessed by a series of transformations from a pentacycle such as **439**, which itself could arise from enone **440** by a radical conjugate addition (Scheme 4.12). Installation of the allylamino group would be accomplished by amine opening of epoxide **441**, which would in turn be accessed from cyclohexadiene **442**.[15] We planned to construct the cyclohexadiene ring by a cascade reaction initiated by an intramolecular [4 + 2] cycloaddition between the indole C2–C3 bond and a diene appended by an ester (X = O)

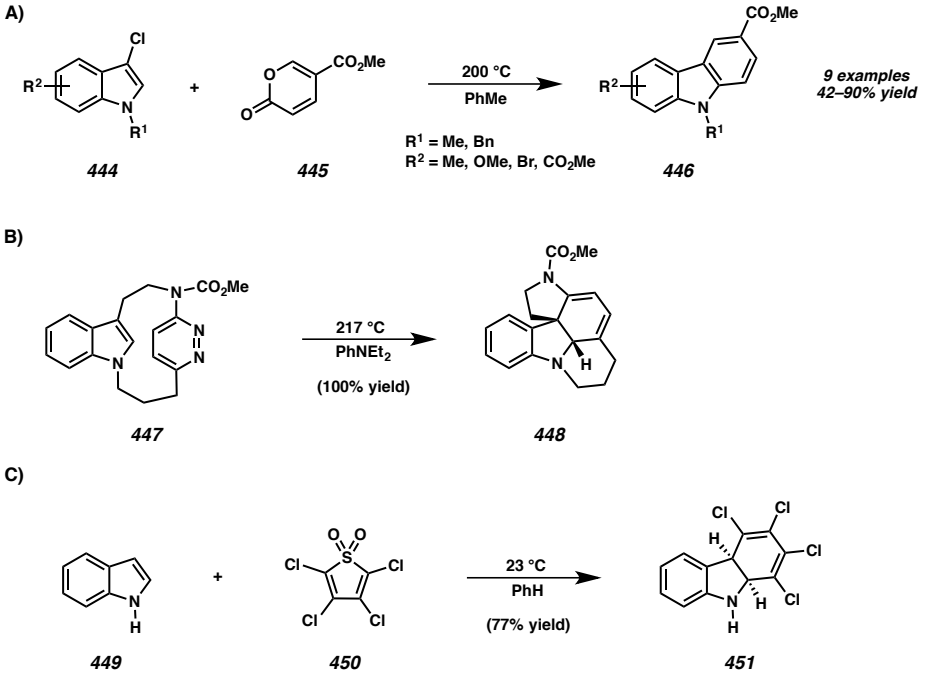
or ether (X = H_2) linkage. Cycloaddition precursors would be readily aviailable from tryptophol.

Scheme 4.12 General retrosynthetic analysis for a [4 + 2] route to calophyline A



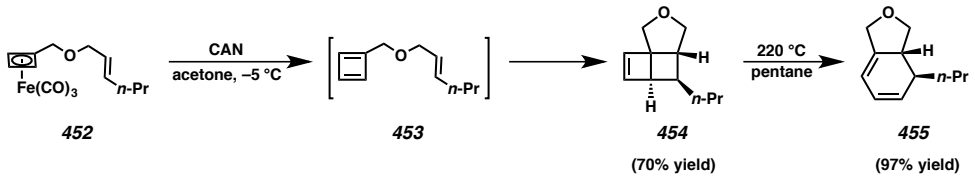
Perhaps the most common cycloddition approach for the formation of cyclohexadienes is a [4 + 2]/retro-[4 + 2] stragey. This is often carried out with pyrone dienes, extruding carbon dioxide to afford cyclohexadiene products, a strategy commonly seen in complex molecule synthesis.[16] While only a single report of pyrone-indole cycloaddition reactions is known (Scheme 4.13A),[17] similar reactions of pyridazines (extruding nitrogen gas)[18] and thiophene-1,1-dioxides (extruding sulfur dioxide)[19] have been successfully carried out with indole dipolarophiles, leading to the fused cyclohexadiene products in good yields (Scheme 4.13B and C).

Scheme 4.13 Reaction of pyrones (A), pyridazines (B), and thiophene-1,1-dioxides (C) in [4 + 2]/retro [4 + 2] sequences



An alternative cycloaddition-based approach could involve application of a cyclobutadiene cycloaddition. Snapper and co-workers have reported that tethered cyclobutadienes (unmasked *in situ* from the cyclobutadienyliron tricarbonyl complex by treatment with an oxidant) readily undergo cycloadditions with proximal olefins to afford fused cyclobutene products (Scheme 4.14).[20] Upon heating, these strained products are smoothly converted to the cyclohexadienes by a 4π electrocyclic ring opening step. A unique advantage of the method is the ability to engage non-activated olefins as dienophiles in the [4 + 2] step, presumably due to the extreme reactivity of the cyclobutadiene moiety.

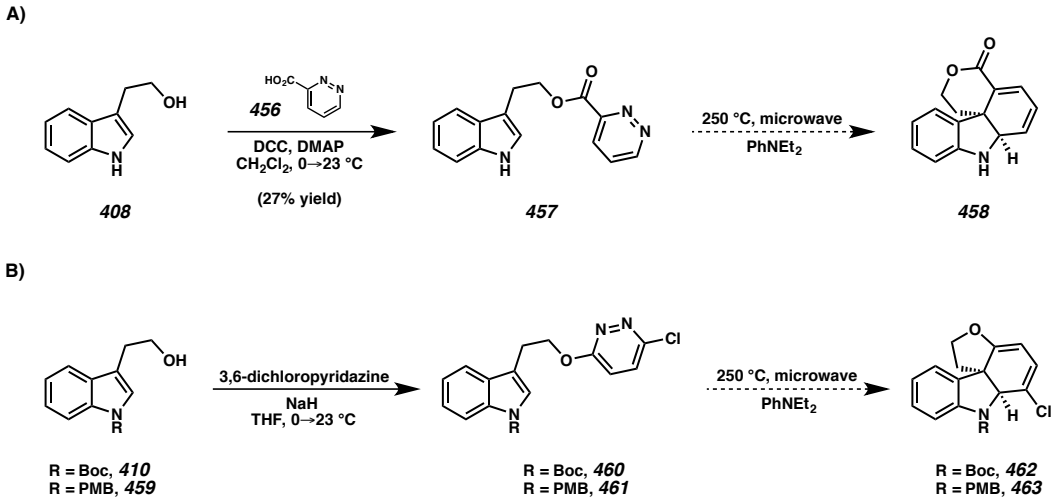
Scheme 4.14 Reaction of a cyclobutadienyliron complex in a [4 + 2]/electrocyclic ring opening sequence



4.3.2 ATTEMPTS TO ACHIEVE THE DESIRED [4 + 2] CYCLOADDITION

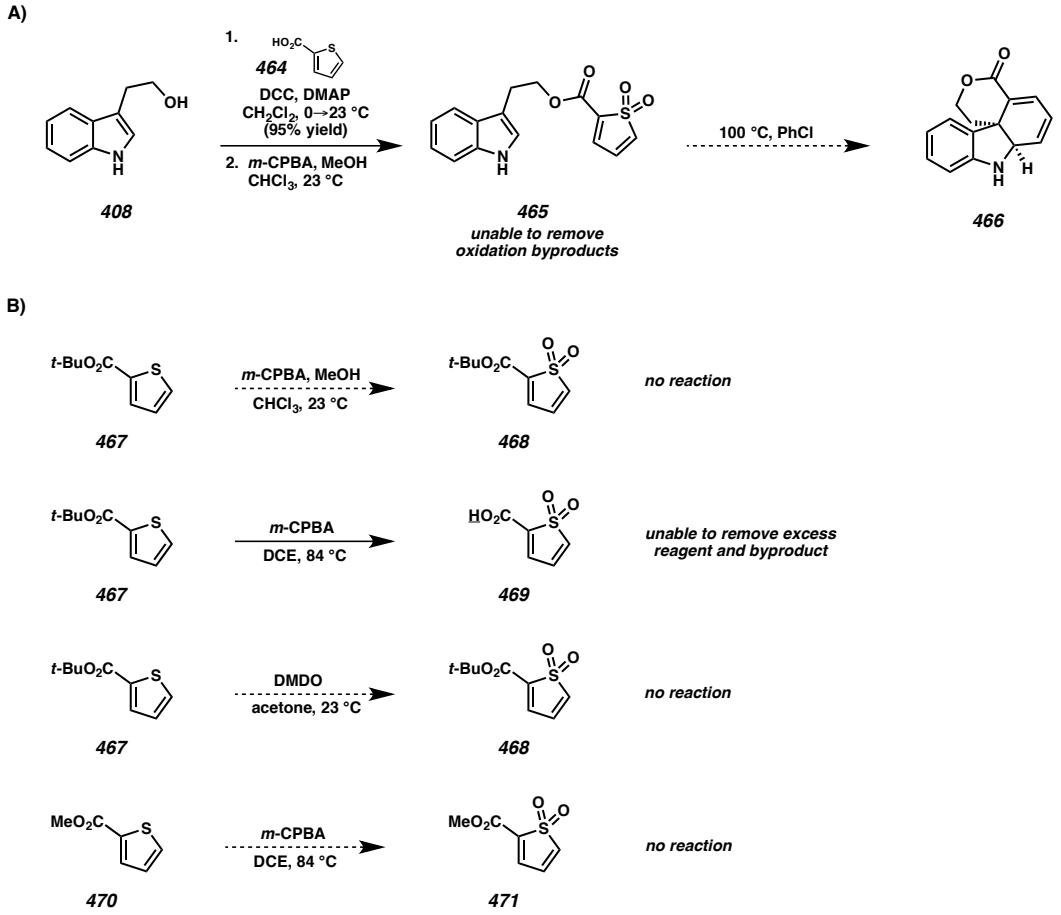
In the forward direction, we began our studies with a pyridazine diene. Coupling of 3-pyridazine carboxylic acid (**456**) with tryptophol afforded ester **457**, which was heated in diethylaniline in a microwave (Scheme 4.15A). Unfortunately, no reaction was observed, which may be due to the preferred *s-cis* conformation of the ester linkage[21] preventing the substrate from adopting a reactive orientation. Although we were unable to access a 3-hydroxymethylpyridazine building block to create the necessary ether linkage (which would require a subsequent allylic oxidation to install the ester functional group), we thought it would remain feasible to access the product from a substrate with a three-carbon ether tether, such as **462** (Scheme 4.15B). To this end, we synthesized aryl ethers **460** and **461** by nucleophilic aromatic substitution reactions with readily avialable 3,6-dichloropyridazine and heated them in diethylaniline. Unsurprisingly, the Boc group of **460** was lost, but no further reactivity was observed. In the case of the very electron-rich indole **461**, no reactivity was detected whatesoever.

Scheme 4.15 Attempts to apply an indole-pyridazine [4 +2]/retro-[4 + 2] cycloaddition toward the synthesis of calophyline A



Concurrently with our investigations into indole-pyridazine cycloadditions, we carried out studies of similar cycloadditions of thiophene-1,1-dioxides. We initially synthesized an ester-linked substrate by coupling tryptophol with thiophene-2-carboxylic acid and subsequent oxidation of the thiophene sulfur using *m*-CPBA (Scheme 4.16A). While the oxidation was successful, the thiophene-1,1-dioxide was impossible to separate from excess reagent and benzoic acid byproduct. The mixture was heated in chlorobenzene to promote the desired cycloaddition cascade, but no reaction was observed.

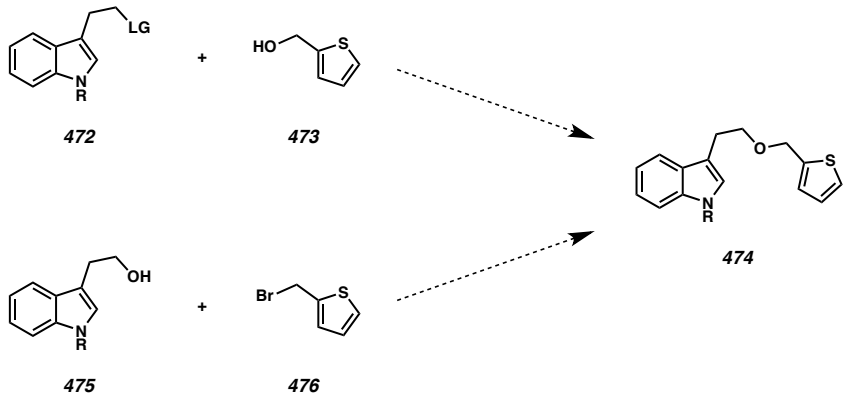
Scheme 4.16 A) An attempt to apply an ester-linked indole-thiophene-1,1-dioxide [4 +2]/retro-[4 + 2] cycloaddition toward the synthesis of calophyline A. B) Attempts to oxidize thiopene-2-carboxylic esters.



To circumvent the issues with purification of the coupled thiophene-1,1-dioxide, we attempted to couple a tryptophol partner to the fully oxidized thiophene dioxide directly. A straightforwad approach would involve oxidation of a simpler thiophene-2-carboxylic ester, cleavage to the carboxylic acid, and coupling to tryptophol. Unfortunately, attempts to access the necessary thiophene dioxides using several different conditions were not successful (Scheme 4.16B). Oxidations of protected 2-hydroxymetylthiophenes were also unsuccessful.

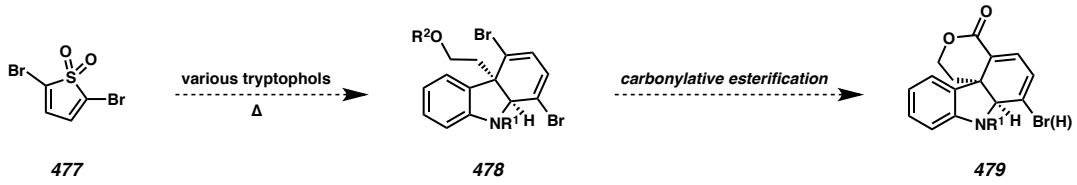
Realizing that the ester linkage between the indole and diene fragments was likely problematic, we directed efforts toward the synthesis of an ether-linked substrate. Despite exploring a variety of bases, solvents, and leaving groups, efforts to couple 2-hydroxymethylthiophene (**473**) with indole-containing electrophiles and efforts to couple 2-bromomethylthiophene (**476**) with tryptophols were not successful (Scheme 4.17).

Scheme 4.17 Attempted synthesis of an ether-linked indole-thiophene-1,1-dioxide cycloaddition substrate



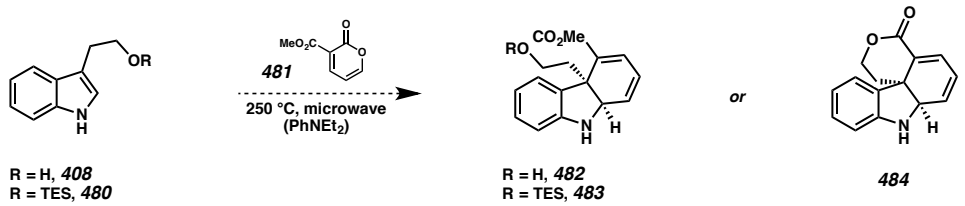
As an alternative to the intramolecular cycloadditions discussed above, we also briefly examined the possibility of an intermolecular reaction. If known 2,5-dibromothiophene-1,1-dioxide (**477**, Scheme 4.18) were used as the diene, a palladium-catalyzed carbonylative esterification reaction would transform the cycloadduct (**478**) into a cyclohexadiene very similar to the desired intramolecular cycloaddition products (**479**). Disappointingly, **477** failed to show any reactivity when heated with tryptophol or protected variants. Diene **477** also failed to react with indole, suggesting it may not be sufficiently reactive for our application.

Scheme 4.18 Unsuccessful intermolecular cycloadditions with 2,5-dibromothiophene-1,1-dioxide



Despite only a single method for pyrone-indole [4 + 2] reactions, we briefly explored such an approach in our synthesis. Perhaps unsurprisingly, the intermolecular reactions were unsuccessful, with no reactivity observed (Scheme 4.19).

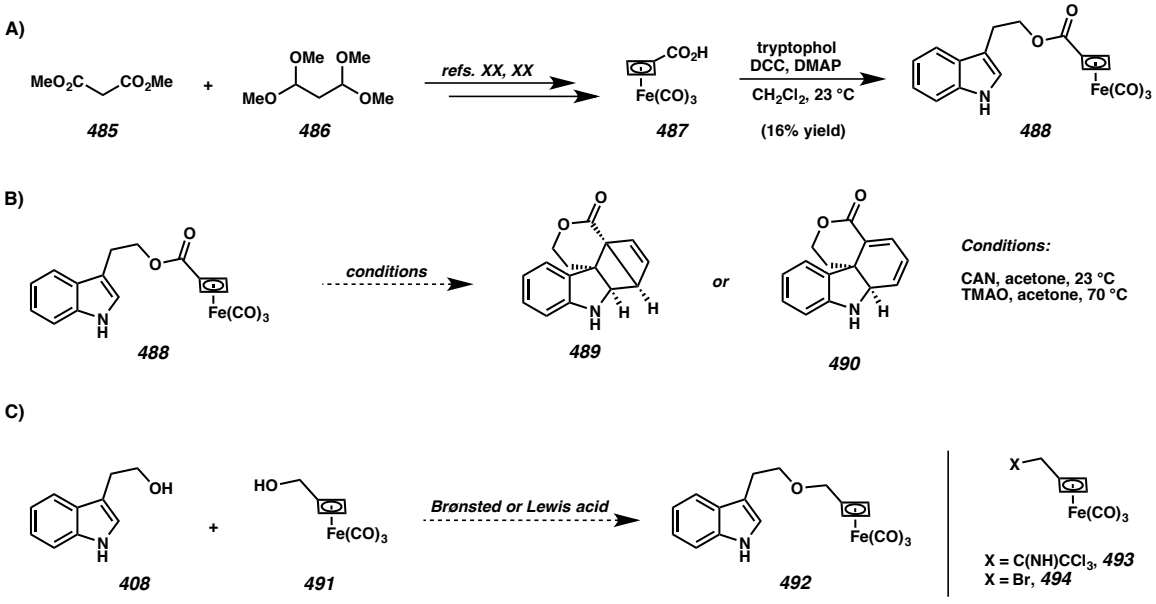
Scheme 4.19 Unsuccessful intermolecular cycloadditions with a pyrone diene



Finding the [4 + 2]/retro-[4 + 2] step to be challenging, we turned our attention to a final [4 + 2] strategy: the use of a cyclobutadiene Diels–Alder/electrocyclic ring opening sequence. Iron complex **487** was prepared from dimethyl malonate (**485**) and 1,1,3,3-tetramethoxypropane (**486**) according to literature proceedures (Scheme 4.20A).[22,23] The ester-linked cycloaddition substrate was available in a single step by DCC coupling, albeit in low yield. Exposure to ceric ammonium nitrate (CAN) to promote oxidative unmasking of the cyclobutadiene moeity and cycloaddition resulted in only unidentifiable decomposition products, likely due to competitive oxidation or nitration of the indole ring (Scheme 4.20B).[24] The use of trimethylamine *N*-oxide (TMAO) in place of CAN was also unsuccessful.

The preparation of an ether-linked substrate was briefly attempted, using known hydroxymethyl-substituted cyclobutadienyliron complex **491**[25] (Scheme 4.20C). We were disappointed to note that Brønsted or Lewis acid catalyzed methods were not able to successfully couple **491** to tryptophol. Future studies could include reaction of a tryptophol derivative with the trichloroacetimidate **493**[25] or known bromomethyl-substituted cyclobutadienyliron complex **494**.[26]

Scheme 4.20 Exploration of an indole-cyclobutadiene [4 + 2]/electrocyclic ring opening sequence



4.4 INVESTIGATION OF A [2 + 2 + 2] CYCLOADDITION ROUTE TOWARD THE SYNTHESIS OF CALOPHYLINE A

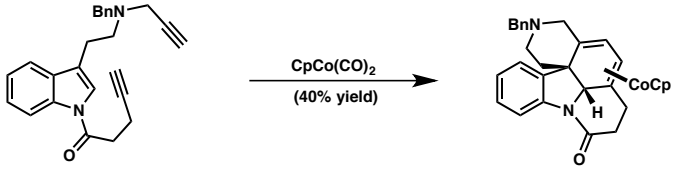
Despite our lack of success with a [4 + 2] cycloaddition strategy, we remained interested in the potential of a cyclohexadiene intermediate and considered accessing

such a compound by a different method. We focused on an intramolecular [2 + 2 + 2] cycloaddition between two alkynes and an alkene, a method frequently used for the construction of complex cyclohexadienes from relatively simple precursors.[27]

4.4.1 SYNTHETIC PRECEDENT AND RETROSYNTHETIC ANALYSIS

We reasoned that engaging the indole C2–C3 bond as the alkene partner in an intramolecular alkene-alkyne-alkyne [2 + 2 + 2] cycloaddition could form a cyclohexadiene similar to the desired intermediate of the [4 + 2] route previsouly discussed. Examples of [2 + 2 + 2] cycloadditions utilizing the indole C2–C3 bond as a 2π component are known, with Vollhardt reporting several examples.[28] Substrates with the alkyne units tethered at either the indole nitrogen or at both the nitrogen and the C3 position are known to be successful, and some intermolecular examples are shown as well. One example from Vollhardt's laboratory is shown in Scheme 4.21.

Scheme 4.21 An example of a [2 + 2 + 2] cycloaddition engaging the indole C2–C3 bond[28c]

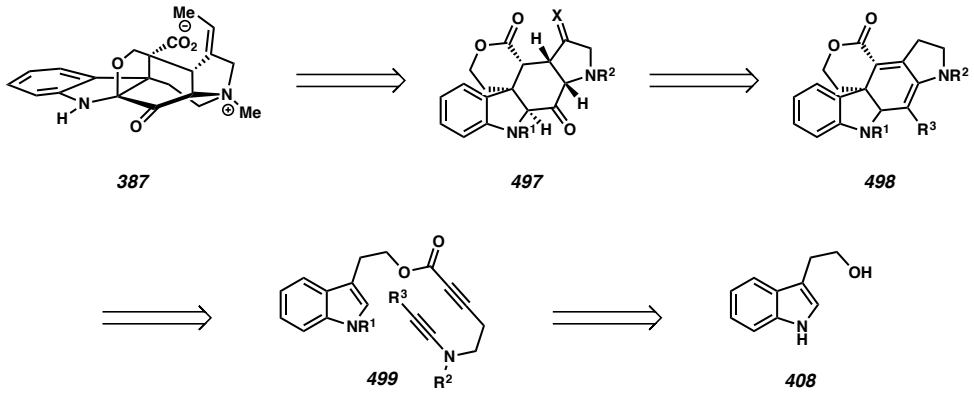


495 ***496***

Retrosynthetically, we envisioned that calophyline could be accessed from pentacycle **497**, itself formed from cyclohexadiene **498** by various olefin functionalizations (Scheme 4.22). The cyclohexadiene would be formed by an intramolecular [2 + 2 + 2]

cycloadditions of a substrate such as **499**, which would be available from tryptophol (**408**).

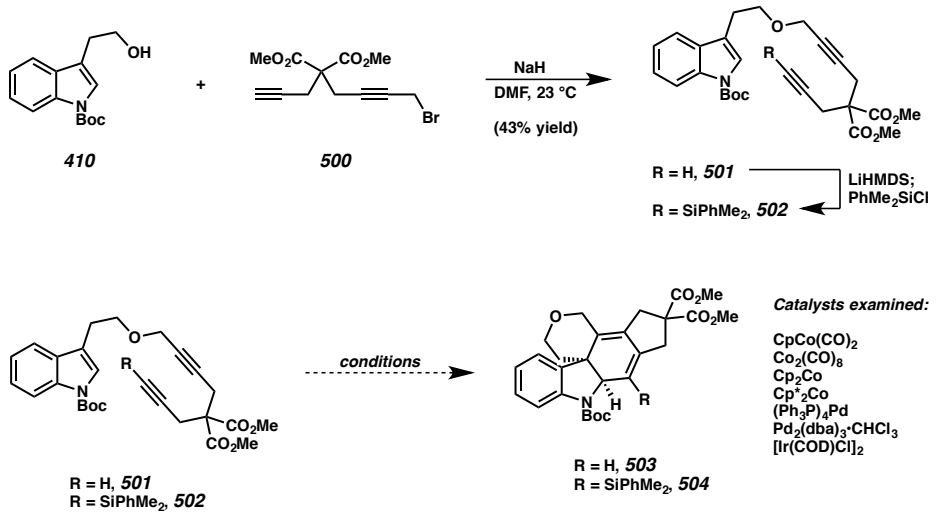
Scheme 4.22 Retrosynthetic analysis employing a [2 + 2 + 2] cycloaddition



4.4.2 EXPLORATION OF A [2 + 2 + 2] STRATEGY

Given that no examples existed of intramolecular [2 + 2 + 2] cycloadditions between an indole C2–C3 bond and a diyne fragment tethered at the indole 3-position, we chose to perform preliminary studies on a more readily available model system rather than the ynamide shown in Scheme 4.22. To construct such a system, *N*-Boc tryptophol was *O*-propargylated with bromide **500** to afford diyne **501** (Scheme 4.23). A portion of this material was subjected to silylation of the terminal alkyne to install a group suitable for subsequent Tamao–Fleming oxidation. With these two substrates in hand, a variety of catalysts were screened for activity in the desired cycloaddition reaction. Unfortunately, only decomposition or a lack of reactivity were observed. Given the difficulties in achieving the necessary reactivity in a simple model system, we elected to conclude explorations of the [2 + 2 + 2] cycloadditions route at this point.

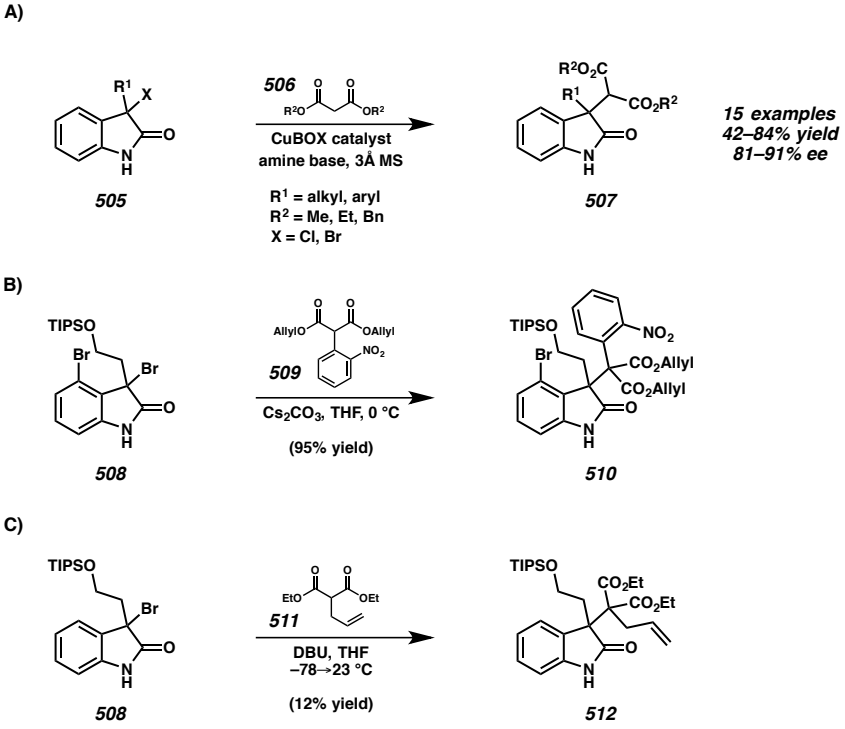
Scheme 4.23 Investigation of an intramolecular [2 + 2 + 2] cycloaddition toward the total synthesis of calophyline A



4.5 FUTURE DIRECTION: CONSIDERATION OF A BROMOOXINDOLE ALKYLATION ROUTE TOWARD THE SYNTHESIS OF CALOPHYLINE A

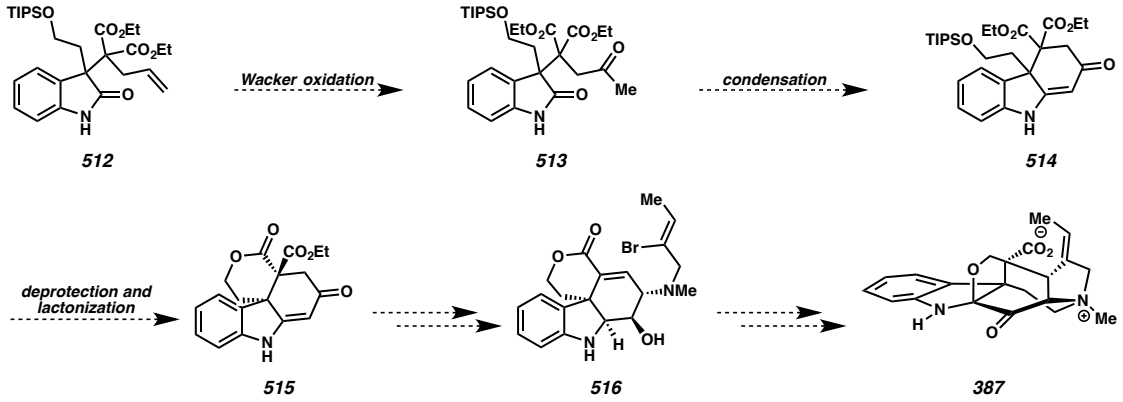
A potential future route to explore involves the creation of the quaternary stereocenter at the indole C3 position by using the bromooxindole alkylation methodology previously developed in our laboratory. In 2007, our research group reported the facile reaction of unsubstituted malonates with 3-bromooxindoles to form all-carbon quaternary stereocenters,[29] and the asymmetric variant was reported in 2009 (Scheme 4.24A).[30] Our laboratory later applied the analogous reaction with a 2-aryl malonate in the formal syntheses of communesin F and perophoramidine (Scheme 4.24B).[31] Although the conditions as presently optimized are not ideal for reactions of 2-alkylmalonate nucleophiles, an unpublished example with 2-allyl diethyl malonate is known, forming 3-allyloxindole **512** in low yield (Scheme 4.24C).[32]

Scheme 4.24 Reactions of 3-bromooxindoles with malonate nucleophiles



The proposed route to calophyline A would commence with an alkylation product such as **512** (Scheme 4.24C). Wacker oxidation would afford methyl ketone **513**, which would then undergo an intramolecular condensation[33] to furnish tricycle **514**. This intermediate could be converted to tetracycle **515** by hydroxyl deprotection and diastereoselective lactonization. This compound could conceivably be advanced to calophyline A by way of an intermediate such as enoate **516**.

Scheme 4.25 A potential oxindole alkylation route to calophyline A



4.6 CONCLUSIONS

In summary, our efforts toward the total synthesis of calophyline A are described, including routes featuring a cyclopropanated indole (3 + 3) cycloaddition, an indole-vinyl diazoacetate (3 + 2) cycloaddition, an indole-diene [4 + 2]/retro-[4 + 2] or [4 + 2]/electrocyclic ring opening cascade, and an indole-diyne [2 + 2 + 2] cycloaddition. Future studies may include consideration of a bromooxindole alkylation approach.

4.7 EXPERIMENTAL SECTION

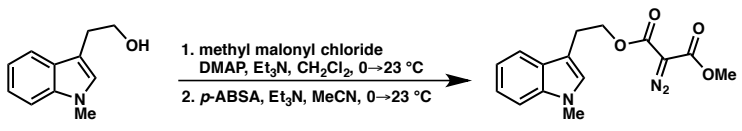
4.7.1 MATERIALS AND METHODS

Unless noted in the specific procedure, reactions were performed flame- or oven-dried glassware under an argon or nitrogen atmosphere. Dried and deoxygated solvents (Fisher Scientific) were prepared by passage through columns of activated aluminum before use.[34] Triethylamine was distilled from calcium hydride immediated prior to use. *p*-Acetamidobenzenesulfonyl azide (*p*-ABSA),[35] *N*-methyl tryptophol (**409**),[36] *N*-Boc

tryptophol (**410**),[37] acid chloride **417**,[11] carboxylic acid **427**,[38] *N*-(4-methoxybenzyl)tryptophol (**459**),[37] thiophene **467**,[39] thiophene **470**,[40] thiophene dioxide **477**,[41] pyrone **481**,[22] iron complex **487**,[23] iron complex **491**,[25] malonate **517**,[42] and dibromide **518**[43] were prepared according to literature procedures. *N*,*N*'-ditosylhydrazine was prepared as described by Fukuyama.[10] Tryptophol (**408**) is commercially available, but may also be synthesized according to a literature proceedure.[44] Thiophene-2-carboyxlic acid (**454**), pyridazine-3-carboxylic acid (**456**), dimethylmalonate (**485**), 1,1,3,3,-tetramethoxypropane (**486**), and 3,6-dichloropyridazine were purchased from commercial suppliers and used as received, as were all other reagents. Copper(I) trifluoromethanesulfonate benzene comples, copper(I) trifluoromethanesulfonate toluene complex, copper(II) acetylacetonate, copper(II) trifluoromethanesulfonate, copper(I) chloride, copper(I) bromide dimethylsulfide complex, tetrakis(acetonitrile)copper(I) hexafluorophosphate, copper(II) hexafluoroacetylacetonate, copper(II) isobutyrate, silver(I) trifluoromethanesulfonate, silver(I) hexafluorophosphate, silver(I) acetylacetonate, iron(III) acetylacetonate, rhodium(II) acetate, rhodium(II) trifluoroacetate, cyclooctadiene rhodium chloride dimer, cymeme ruthenium dichloride dimer, IPrAuCl, cyclopentadienylcobalt chloride dicarbonyl, dicobalt octacarbonyl, cobaltocene, decamethylcobaltocene, tetrakis(triphenylphosphine)palladium(0), cyclooctadiene iridium chloride dimer, and lithium hexamethyldisilazide were stored in a nitrogen-filled glovebox. Brine is defined as a saturated aqueous solution of sodium chloride. Reactions requiring external heat were modulated to the specified temperatures using an IKAmag temperature controller. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-LCMS. TLC was performed using E.

Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040–0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 spectrometer (500 MHz and 126 MHz, respectively), a Bruker AV III HD spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe (400 MHz and 101 MHz, respectively), or a Varian 300 spectrometer (300 MHz and 75 MHz, respectively) and are reported in terms of chemical shift relative to residual $CDCl_3$ (δ 7.26 and δ 77.16 ppm, respectively). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Abbreviations are used as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = complex multiplet. Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer using thin film samples on NaCl plates, or a Thermo Scientific Nicolet iS5 attenuated total reflectance spectrometer using neat solid, neat oil, or $CDCl_3$ or C_6H_6 solution samples, 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 with fast atom bombardment (FAB+) ionization mode.

4.7.2 PROCEDURES AND CHARACTERIZATION DATA



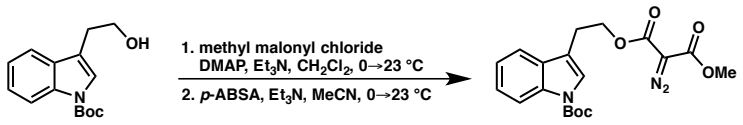
409 *411*

1-methyl 3-(2-(1-methyl-1*H*-indol-3-yl)ethyl) 2-diazomalonate (411):

To a flame-dried round bottom flask equipped with a magnetic stir bar was added **409** (602 mg, 3.44 mmol). The flask was capped with a rubber septum and evacuated and backfilled with nitrogen three times. Dichloromethane (38 mL) was added by syringe. The septum was quickly removed to allow for the addition of DMAP (42 mg, 0.34 mmol). Triethylamine (1.44 mL, 10.31 mmol) was added by syringe and the mixture was cooled to 0 °C in an ice water bath. Methyl malonyl chloride (1.11 mL, 10.31 mmol) was added slowly dropwise. The mixture was allowed to warm to 23 °C and stir overnight. Upon completion (as determined by TLC analysis), the reaction mixture was quenched with saturated aqueous ammonium chloride solution. The aqueous layer was extracted with dichloromethane (1 x 30 mL) and the combined organic layers were washed with saturated sodium bicarbonate solution (1 x 30 mL). The organic layers were dried over magensium sulfate, filtered, and concentrated to afford the crude product, which was purified by silica gel chromatography (20% ethyl acetate in hexanes) to afford 699 mg of the product malonate (74% yield).

A solution of the malonate (699 mg, 2.54 mmol) in acetonitrile (2 mL) was added dropwise to a 0 °C stirring solution of *p*-ABSA (610 mg, 2.54 mmol) and triethlamine (375 μL) in acetonitrile (7 mL) in a flame-dried flask under nitrogen. The mixture was allowed to warm to 23 °C and stir overnight. Upon completion (as determined by TLC analysis), the reaction mixture was filtered through celite, washing with ether. The filtrate was concentrated to afford the crude product, which was purified by silica gel chromatography (25% ethyl acetate in hexanes) to afford 781 mg of diazomaloante **411** (quantitative yield, 74% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61 (dt, *J* = 7.9, 1.0, 1H), 7.30 (dt, *J* = 8.2, 0.9, 1H), 7.23 (ddd, *J* = 8.2, 6.9, 1.2, 1H), 7.12 (ddd, *J* =

8.0, 6.9, 1.1, 1H), 6.92 (d, J = 0.9, 1H), 4.48 (t, J = 7.2, 2H), 3.85 (s, 3H), 3.76 (s, 3H), 3.14 (td, J = 7.2, 0.8, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8, 161.0, 137.0, 127.9, 127.2, 121.8, 119.1, 118.9, 110.0, 109.4, 66.0, 52.7, 32.8, 24.8; ATR-IR ($CDCl_3$ solution) 2954, 2134, 1754, 1731, 1475, 1438, 1328, 1270, 1086, 760, 740 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{15}H_{16}N_3O_4$ $[M+H]^+$: 302.1141, found 302.1136.



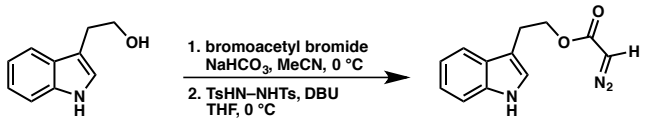
410 ***412***

1-(2-(1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)ethyl) 3-methyl 2-diazomalonate (412):

To a flame-dried round bottom flask equipped with a magnetic stir bar was added **410** (1.369 g, 5.24 mmol). The flask was capped with a rubber septum and evacuated and backfilled with nitrogen three times. Dichloromethane (58 mL) was added by syringe. The septum was quickly removed to allow for the addition of DMAP (64 mg, 0.52 mmol). Triethylamine (2.19 mL, 15.72 mmol) was added by syringe and the mixture was cooled to 0 °C in an ice water bath. Methyl malonyl chloride (1.69 mL, 15.72 mmol) was added slowly dropwise. The mixture was allowed to warm to 23 °C and stir overnight. Upon completion (as determined by TLC analysis), the reaction mixture was quenched with saturated aqueous ammonium chloride solution. The aqueous layer was extracted with dichloromethane (1 x 50 mL) and the combined organic layers were washed with saturated sodium bicarbonate solution (1 x 50 mL). The organic layers were dried over magensium sulfate, filtered, and concentrated to afford the crude product, which was

purified by silica gel chromatography (15% ethyl acetate in hexanes) to afford 1.5908 g of the product malonate (84% yield).

A solution of the malonate (1.59 g, 4.40 mmol) in acetonitrile (3.5 mL) was added dropwise to a 0 °C stirring solution of *p*-ABSA (1.06 g, 4.40 mmol) and triethlamine (650 μL) in acetonitrile (12 mL) in a flame-dried flask under nitrogen. The mixture was allowed to warm to 23 °C and stir overnight. Upon completion (as determined by TLC analysis), the reaction mixture was filtered through celite, washing with acetonitrile. The filtrate was concentrated to afford the crude product, which was purified by silica gel chromatography (20% ethyl acetate in hexanes) to afford 1.56 g of diazomaloante **412** (91% yield, 76% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.13 (s, 1H), 7.58–7.52 (m, 1H), 7.45 (s, 1H), 7.32 (ddd, *J* = 8.4, 7.2, 1.3, 1H), 7.27–7.23 (m, 1H), 4.51 (t, *J* = 7.0, 2H), 3.85 (s, 3H), 3.09 (td, *J* = 7.0, 1.0, 2H), 1.68 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 161.8, 161.0, 149.9, 130.5, 124.7, 123.7, 122.8, 119.0, 116.3, 115.5, 83.8, 65.0, 52.8, 41.6, 28.4, 24.8; ATR-IR ($CDCl_3$ solution) 2979, 2135, 1759, 1458, 1369, 1324, 1270, 1255, 1158, 1089, 760 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{21}N_3O_6$ [M•]$^{+}$: 387.1430, found 387.1441.



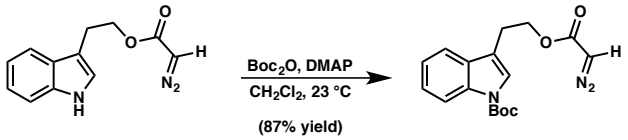
408 *415*

2-(1*H*-indol-3-yl)ethyl 2-diazoacetate (415):

To a flame-dried round bottom flask equipped with a magnetic stir bar were added **408** (950 mg, 5.89 mmol), sodium bicarbonate (1.49 g, 17.67 mmol), and acetonitrile (30

mL). After cooling to 0 °C, bromoacetyl bromide (770 μL) was added dropwise and the reaction was stirred for 20 minutes. After TLC analysis indicated consumption of the starting material, the mixture was quenched with water at 0 °C and the aqueous layer was extracted with dichloromethane (3 x 40 mL). The organic layers were washed with brine (1 x 30 mL), dried over magnesium sulfate, and concentrated to give the crude product, which was used without further purification.

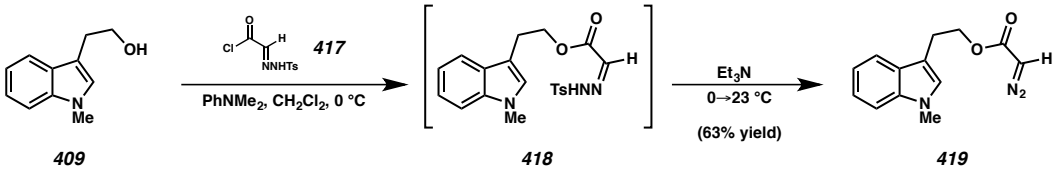
To a flame-dried round bottom flask equipped with a magnetic stir bar were added the crude product from the previous step and N,N'-ditosylhydrazine (4.01 g, 11.78 mmol). THF (30 mL) was added and the mixture was cooled to 0 °C. DBU was added dropwise and the mixture was stirred under nitrogen for 45 minutes. After TLC analysis indicated consumption of the starting material, the mixture was quenched with saturated aqueous sodium bicarbonate solution and extracted with ether (3 x 50 mL). The organic layers were washed with brine (1 x 50 mL), dried over magnesium sulfate, and concentrated to afford the crude product, which was purified by silica gel chromatography (25% ethyl acetate in hexanes) to afford 974 mg of diazoacetate **415** (72% yield over two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.01 (s, 1H), 7.63 (d, *J* = 7.8, 1H), 7.42–7.33 (m, 1H), 7.17 (dddd, *J* = 21.6, 8.0, 7.1, 1.2, 2H), 7.05 (d, *J* = 2.4, 1H), 4.74 (s, 1H), 4.44 (t, *J* = 7.1, 2H), 3.12 (td, *J* = 7.1, 0.8, 2H).



415 *416*

***tert*-butyl 3-(2-(2-diazoacetoxy)ethyl)-1*H*-indole-1-carboxylate (416):**

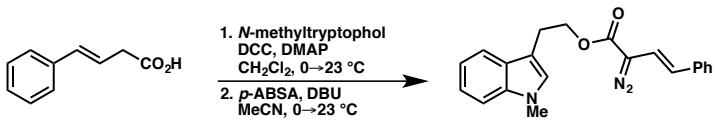
Diazoacetate **415** (974 mg, 4.28 mmol) was dissolved in dichloromethane (10 mL). Di-*tert*-butyl dicarbonate (1.02 g, 4.67 mmol) was added, followed by DMAP (53 mg, 0.43 mmol). The mixture was stirred for 7 hours at 23 °C. TLC analysis showed incomplete conversion, so additional DMAP (50 mg) and di-*tert*-butyl dicarbonate (400 mg) were added and the mixture was allowed to stir at 23 °C overnight. Upon completion, the reaction solution was washed with brine (1 x 20 mL), dried over sodium sulfate, filtered, and evaporated to give the crude product, which was purified by silica gel chromatography (15% ethyl acetate in hexanes) to afford 1.23 g of diazoacetate **416** (87% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.12 (s, 1H), 7.88–7.75 (m, 1H), 7.56–7.49 (m, 1H), 7.48–7.40 (m, 1H), 7.32 (tdd, *J* = 7.0, 3.6, 1.9, 1H), 4.82–4.70 (m, 1H), 4.44 (t, *J* = 7.0, 2H), 3.05 (td, *J* = 7.0, 1.1, 2H), 1.74–1.60 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.3, 149.8, 128.6, 124.6, 123.9, 123.5, 122.6, 119.0, 116.6, 115.4, 115.2, 64.2, 43.1, 28.4, 24.8; ATR-IR ($CDCl_3$ solution) 2979, 2112, 1729, 1698, 1458, 1368, 1253, 1151, 1091, 737 cm^{-1}.



2-(1-methyl-1*H*-indol-3-yl)ethyl 2-diazoacetate (419):

To a flame-dried round bottom flask equipped with a magnetic stir bar were added **409** (500 mg, 2.85 mmol) and dichloromethane (22 mL) under argon. Acid chloride **417** (892 mg, 3.42 mmol) was added, and the mixture was cooled to 0 °C before dimethylaniline (398 μL, 3.14 mmol) was added dropwise. The solution was allowed to

stir at 0 °C for 30 minutes, at which point triethylamine (1.99 mL, 14.3 mmol) was added. The reaction was stirred at 0 °C for 30 minutes followed by 23 °C for 15 minutes. TLC analysis indicated the presence of starting material, so the mixture was allowed to stir overnight. After a second TLC analysis showed no change in conversion, the mixture was concentrated and partitioned between water (30 mL) and ether (30 mL). The aqueous layer was extracted with ether (1 x 30 mL), washed with saturated sodium bicarbonate solution (1 x 30 mL), dried over magnesium sulfate, filtered, and concentrated to give the crude product, which was purified by silica gel chromatography (10% ethyl acetate in hexanes) to afford 436 mg of diazoacetate **419** (63% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.61 (dt, *J* = 7.9, 1.0, 1H), 7.30 (dt, *J* = 8.2, 1.0, 1H), 7.26–7.19 (m, 1H), 7.13 (ddd, *J* = 8.0, 6.9, 1.1, 1H), 6.90 (d, *J* = 0.8, 1H), 4.75 (s, 1H), 4.42 (t, *J* = 7.1, 2H), 3.77 (s, 3H), 3.11 (td, *J* = 7.1, 0.8, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.7, 137.0, 129.7, 128.0, 127.0, 125.4, 121.8, 119.0, 110.4, 109.4, 65.3, 32.8, 25.0; ATR-IR (neat oil) 3100, 2951, 2105, 1684, 1394, 1333, 1237, 1126, 1011, 730 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{13}H_{13}N_3O_2$ $[M\bullet]^+$: 243.1008, found 243.1004.



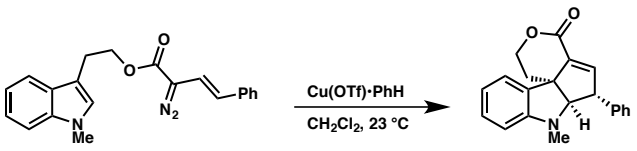
427 ***428***

2-(1-methyl-1*H*-indol-3-yl)ethyl (*E*)-2-diazo-4-phenylbut-3-enoate (428):

To an oven-dried vial equipped with a magnetic stir bar were added, in order, carboxylic acid **427** (624 mg, 3.85 mmol), dichloromethane (4 mL), DMAP (30 mg), and *N*-methyltryptophol (676 mg, 3.85 mmol). The mixture was cooled to 0 °C and DCC

(874 mg, 4.24 mmol) was added. The reaction was stirred for 5 minutes at 0 °C and then allowed to warm to 23 °C and stir overnight. Upon completion (as determined by TLC analysis), the reaction mixture was filtered through Celite and concentrated. The residue was suspended in dichloromethane and filtered through Celite again. The filtrate was washed with 0.5 N aqueous hydrochloric acid (2 x 10 mL) and saturated aquous sodium bicarbonate (1 x 10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrate to give the crude product, which was purified by silica gel chromatography (10% ethyl acetate in hexanes) to afford 870 mg of the ester product (71% yield).

To a flame-dried round bottom flask equipped with a magnetic stir bar were added the ester (879 mg, 2.72 mmol), *p*-ABSA (784 mg, 3.26 mmol), and acetonitrile (72 mL) under argon. The mixture was cooled to 0 °C and DBU (447 μL) was added rapidly by syringe. The reaction was allowed to warm to 23 °C and stir overnight. Upon completion (as determined by TLC analysis), the mixture was quenced with saturated aqueous ammonium chloride solution and extracted with ether (3 x 50 mL). The combined organic layers were washed with brine (1 x 50 mL), dried over sodium sulfate, filtered, and concentrated to give the crude product, which was purified by silica gel chromatography (15% hexanes in ethyl acetate) to afford 617 mg of diazoester **428** (66% yield, 47% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.63 (dt, J = 7.9, 1.0, 1H), 7.36–7.29 (m, 5H), 7.24–7.17 (m, 1H), 6.92 (d, J = 0.8, 1H), 6.47 (d, J = 16.3, 1H), 6.19 (d, J = 16.3, 1H), 4.50 (t, J = 7.1, 2H), 3.77 (s, 3H), 3.16 (td, J = 7.1, 0.8, 2H).

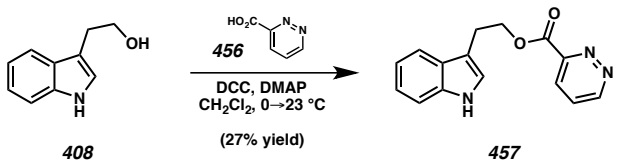


428 ***429***

7-methyl-6-phenyl-1,2,6a,7-tetrahydropyrano[4',3':2,3]cyclopenta[1,2-*b*]indol-4(6*H*)-one (429):

In a nitrogen-filled govebox, a dry vial equipped with a magnetic stir bar was charged with copper(I) trifluoromethanesulfonate (<1 mg) and sealed with a cap containing a septum, wrapping electrical tape around the cap to prevent the entry of oxygen. The vial was then removed from the glovebox and put under a nitrogen atmosphere. Dichloromethane (1 mL) was added, and then a solution of diazoester **428** (24 mg, 0.07 mmol) in dichloromethane (1 mL) was added by syringe pump over 1 hour. After stirring for an additional 45 minutes, TLC analysis indicated the presence of starting material, but the reaction mixture was nevertheless adsorbed onto Celite and purified by silica gel chromatography (10% to 25% ethyl acetate in hexanes) to afford 7 mg of tetracycle **429** (32% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.41–7.34 (m, 2H), 7.33–7.27 (m, 1H), 7.23 (td, *J* = 7.7, 1.2, 1H), 7.20–7.16 (m, 2H), 7.10 (dd, *J* = 7.4, 1.2, 1H), 6.80 (d, *J* = 2.0, 1H), 6.76 (td, *J* = 7.4, 1.0, 1H), 6.53 (d, *J* = 7.8, 1H), 4.86 (td, *J* = 12.1, 3.7, 1H), 4.59 (ddd, *J* = 12.1, 5.5, 2.3, 1H), 4.13 (d, *J* = 6.0, 1H), 3.96 (dd, *J* = 6.0, 2.0, 1H), 2.80 (s, 3H), 2.25 (ddd, *J* = 13.6, 12.1, 5.5, 1H), 2.17–2.08 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.6, 144.4, 142.4, 135.1, 129.8, 129.4, 129.3, 128.3, 127.5, 124.3, 118.2, 110.4, 110.2, 107.3, 88.4, 67.2, 55.6, 34.6, 33.4; ATR-IR (neat solid) 3050, 2945, 1593, 1521, 1448, 1339, 1003, 818, 744 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{21}H_{20}NO_2$ $[M+H]^+$: 318.1494, found 318.1490.

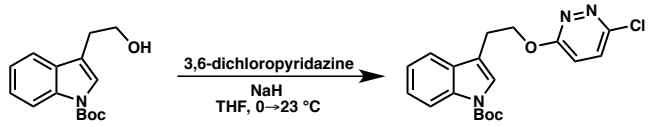
X-ray quality single crystals of tetracycle **429** were produced by vapor diffusion of heptane (containing 2% benzene) into a solution of **429** in ethyl acetate.



2-(1*H*-indol-3-yl)ethyl pyridazine-3-carboxylate (457):

To an oven-dried vial equipped with a magnetic stir bar were added, in order, carboxylic acid **456** (100 mg, 0.81 mmol), dichloromethane (0.81 mL), DMAP (13 mg), and tryptophol (**408**, 131 mg, 0.81 mmol). The mixture was cooled to 0 °C and DCC (183 mg, 0.87 mmol) was added. The reaction was stirred for 5 minutes at 0 °C and then allowed to warm to 23 °C and stir overnight. Upon completion (as determined by TLC analysis), the reaction mixture was filtered through Celite and concentrated. The residue was suspended in dichloromethane and filtered through Celite again. The filtrate was washed with 0.5 N aqueous hydrochloric acid (2 x 10 mL) and saturated aquous sodium bicarbonate (1 x 10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrate to give the crude product, which was subjected to silica gel chromatography (10% methanol in dichloromethane) to afford 58 mg of ester **457** (27% yield), which was contaminated with dicyclohexylurea. An attempt to purify further by colum chromatography (75% ethyl acetate in hexanes) was unsuccessful, so the material was carried on impure. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.36 (ddt, J = 5.0, 1.7, 0.8, 1H), 8.16 (ddt, J = 8.5, 1.8, 0.8, 2H), 7.71–7.66 (m, 1H), 7.63 (ddt, J = 8.4, 5.1, 0.9, 1H), 7.37

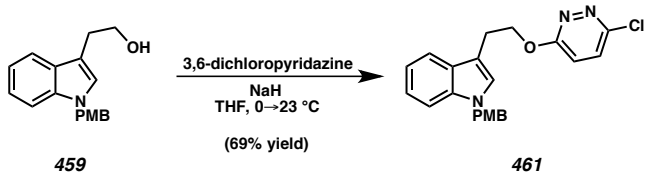
(d, *J* = 8.1, 1H), 7.24–7.16 (m, 2H), 7.13 (tq, *J* = 7.0, 0.9, 1H), 4.76 (t, *J* = 7.3, 2H), 3.33 (td, *J* = 7.4, 1.0, 2H).



410 ***460***

***tert*-butyl 3-(2-((6-chloropyridazin-3-yl)oxy)ethyl)-1*H*-indole-1-carboxylate (460):**

To an oven-dried vial equipped with a magnetic stir bar were added alcohol **410** (274 mg, 1.05 mmol) and THF (750 μL). The solution was cooled to 0 °C in an ice water bath and sodium hydride (60% dispersion in mineral oil, 50 mg, 1.25 mmol) was added. The mixture was stirred at 0 °C for 10 minutes and 3,6-dichloropyridazine (150 mg, 1.00 mmol) was added. The reaction was allowed to warm to 23 °C and stir for 9 hours. Although TLC analysis revealed the presence of starting material, the mixture was quenched by pouring into saturated aqueous ammonium chloride solution. The aqueous layer was extracted with ether (1 x 5 mL) and the organic layer was washed with water (1 x 5 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to give the crude product, which was subjected to silica gel chromatography (25% ethyl acetate in hexanes). Chromatography was not successful in proving pure **460**, but the impure product was carried on as it was. The yield was not determined. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.13 (d, *J* = 8.1, 1H), 7.65–7.58 (m, 1H), 7.52–7.46 (m, 2H), 7.39–7.27 (m, 2H), 6.94 (dd, *J* = 9.2, 0.8, 1H), 4.79 (t, *J* = 6.9, 2H), 3.23 (td, *J* = 6.9, 1.0, 2H), 1.67 (s, 9H). HRMS (FAB+) *m/z* calc'd for $C_{19}H_{21}ClN_3O_3$ $[M+H]^+$: 374.1271, found 374.1275.

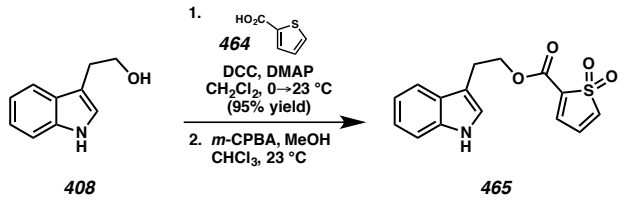


459 *461*

3-(2-((6-chloropyridazin-3-yl)oxy)ethyl)-1-(4-methoxybenzyl)-1*H*-indole (461):

To an oven-dried vial equipped with a magnetic stir bar were added alcohol **459** (841 mg, 2.99 mmol) and THF (3.1 mL). The solution was cooled to 0 °C in an ice water bath and sodium hydride (60% dispersion in mineral oil, 143 mg, 3.56 mmol) was added. The mixture was stirred at 0 °C for 10 minutes and 3,6-dichloropyridazine (425 mg, 2.85 mmol) was added. The reaction was allowed to warm to 23 °C and stir for 5 hours. Although LCMS analysis revealed the presence of a small amount of starting material, the mixture was quenched by pouring into saturated aqueous ammonium chloride solution. The aqueous layer was extracted with ether (1 x 10 mL) and the organic layer was washed with water (1 x 10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to give the crude product, which was purified by silica gel chromatography (25% ethyl acetate in hexanes) to afford 771 mg of arene **461** (69% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.68 (ddd, *J* = 7.8, 1.2, 0.7, 1H), 7.34 (d, *J* = 9.1, 1H), 7.29 (dt, *J* = 8.2, 0.9, 1H), 7.18 (ddd, *J* = 8.2, 7.0, 1.2, 1H), 7.12 (ddd, *J* = 8.0, 7.0, 1.1, 1H), 7.08–7.04 (m, 2H), 6.99 (d, *J* = 0.9, 1H), 6.92 (d, *J* = 9.1, 1H), 6.86–6.81 (m, 2H), 4.77 (t, *J* = 7.1, 2H), 3.78 (s, 3H), 3.29 (td, *J* = 7.1, 0.9, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.5, 159.3, 151.1, 136.7, 131.0, 129.7, 128.5, 128.4, 126.3, 122.0, 120.5, 119.3, 119.3, 114.3, 111.2, 109.9, 68.3, 55.5, 49.6, 25.1; ATR-IR (neat solid) 3055, 2949,

1585, 1442, 1377, 1278, 1246, 1148, 1029, 811, 733, 678 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{22}H_{21}ClN_3O_2$ $[M+H]^+$: 394.1322, found 394.1322.

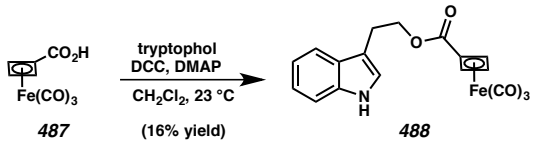


2-(1*H*-indol-3-yl)ethyl thiophene-2-carboxylate 1,1-dioxide (465):

To an oven-dried vial equipped with a magnetic stir bar were added, in order, carboxylic acid **464** (397 mg, 3.10 mmol), dichloromethane (3.1 mL), DMAP (50 mg), and tryptophol (**408**, 500 mg, 3.10 mmol). The mixture was cooled to 0 °C and DCC (704 mg, 3.41 mmol) was added. The reaction was stirred for 5 minutes at 0 °C and then allowed to warm to 23 °C and stir for 5 hours. Upon completion (as determined by TLC analysis), the reaction mixture was filtered through Celite and concentrated. The residue was suspended in dichloromethane and filtered through Celite again. The filtrate was washed with 0.5 N aqueous hydrochloric acid (2 x 20 mL) and saturated aquous sodium bicarbonate (1 x 20 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to give the crude product, which was purified by silica gel chromatography (25% ethyl acetate in hexanes) to afford 798 mg of thiophene **465** (95% yield).

A solution of thiophene **465** (798 mg, 2.94 mmol) and *m*-CPBA (70–75% purity, 1.27 g, 7.35 mmol) in methanol (12 mL) and chloroform (12 mL) was stirred at 23 °C for 2 hours. TLC analysis showed low conversion, so additional *m*-CPBA (635 mg) was added and the reaction mixture allowed to stir for an additional 15 hours. TLC analysis still

revealed incomplete conversion, but the reaction mixture was poured into a seperatory funned and diluted with dichloromethane (10 mL). The organic layer was washed with saturated aqueous sodium thiosulfate (1 x 20 mL) and saturated aqueous sodium bicarbonate (3 x 20 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated to give the crude product. Attempts to purify by silica gel chromatography were only partially successful in removing the oxidation byproducts, so the material was carried on to the next step as it was. A yield was not determined for this step. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.77 (d, *J* = 8.4, 1H), 8.49 (d, *J* = 1.8, 1H), 7.96 (dd, *J* = 8.1, 1.5, 1H), 7.78 (dd, *J* = 3.8, 1.3, 1H), 7.64–7.50 (m, 3H), 7.24–7.15 (m, 1H), 7.08 (td, *J* = 4.7, 3.8, 1H), 4.73 (t, *J* = 6.3, 2H), 3.51 (t, *J* = 6.4, 2H).

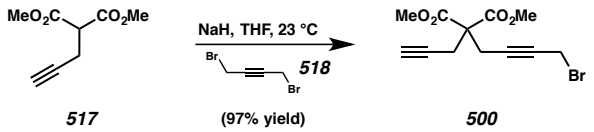


487 **(16% yield)** ***488***

2-(1*H*-indol-3-yl)ethyl cyclobutadienylirontricarbonyl carboxylate (488):

To an oven-dried vial equipped with a magnetic stir bar were added, in order, carboxylic acid **487** (100 mg, 0.42 mmol), dichloromethane (0.42 mL), DMAP (13 mg), and tryptophol (**408**, 68 mg, 0.42 mmol). The mixture was cooled to 0 °C and DCC (93 mg, 0.45 mmol) was added. The reaction was stirred for 5 minutes at 0 °C and then allowed to warm to 23 °C and stir for 2 hours. Upon completion (as determined by TLC analysis), the reaction mixture was filtered through Celite and concentrated. The residue was suspended in dichloromethane and filtered through Celite again. The filtrate was washed with 0.5 N aqueous hydrochloric acid (2 x 10 mL) and saturated aquous sodium bicarbonate (1 x 10 mL). The organic layer was dried over magnesium sulfate, filtered,

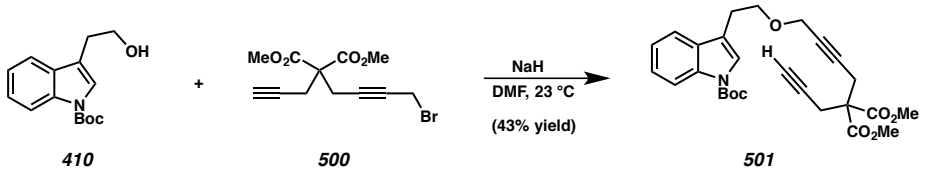
and concentrate to give the crude product, which was subjected to silica gel chromatography (20% ethyl acetate in hexanes) to afford 27 mg of ester **488** (16% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.05 (s, 1H), 7.63 (dd, *J* = 7.4, 1.2, 1H), 7.37 (dt, *J* = 8.0, 0.9, 1H), 7.21 (ddd, *J* = 8.1, 7.0, 1.4, 1H), 7.14 (ddd, *J* = 8.0, 7.1, 1.1, 1H), 7.03 (d, *J* = 2.2, 1H), 4.50 (s, 2H), 4.36 (t, *J* = 7.2, 2H), 4.27 (s, 1H), 3.08 (td, *J* = 7.2, 0.8, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.1, 167.2, 136.2, 127.5, 122.1, 119.4, 118.8, 111.7, 111.2, 67.7, 65.3, 65.0, 64.9, 62.5, 24.6; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{13}FeNO_5$ $[M\bullet]^+$: 379.0143, found 379.0154.



dimethyl 2-(4-bromobut-2-yn-1-yl)-2-(prop-2-yn-1-yl)malonate (500):

A flame-dried round bottom flask equipped with a magnetic stir bar was charged with sodium hydride (60% dispersion in mineral oil, 303 mg, 7.56 mmol) and THF (7.4 mL). Malonate **517** (1.00 mL, 6.58 mmol) was added neat dropwise by syringe and the mixture was stirred at 23 °C for 1 hour before being transferred by syringe to a solution of dibromide **518** (4.18 g, 19.74 mmol) in THF (30 mL). This mixture was stirred at 23 °C for 3 hours. Upon completion, the reaction was quenched with water (50 mL) and extracted with ether (3 x 40 mL). The organic layers were washed with water (1 x 40 mL) and brine (1 x 40 mL), dried over sodium sulfate, filtered, and concentrated to give the crude product, which was purified by silica gel chromatography (10% ethyl acetate in hexanes) to provide 1.92 g of malonate **500** (97% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.86 (td, *J* = 2.4, 0.7, 2H), 3.78 (d, *J* = 0.8, 6H), 3.06 (td, *J* = 2.4, 0.7, 2H), 2.97 (dd, *J* =

2.7, 0.7, 2H), 2.05 (t, J = 2.7, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 81.8, 78.8, 78.4, 72.0, 56.7, 53.4, 23.3, 22.9, 14.7; ATR-IR ($CDCl_3$ solution) 3291, 2955, 1737, 1436, 1326, 1293, 1206, 1056, 977, 657 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{12}H_{14}BrO_4$ $[M+H]^+$: 301.0075, found 301.0075.

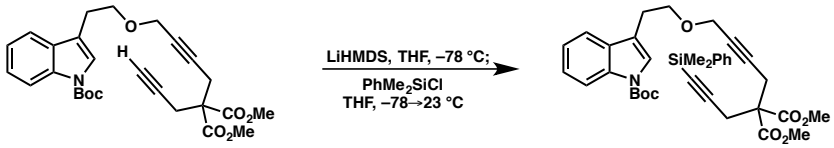


410 *500* *501*

dimethyl 2-(4-(2-(1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)ethoxy)but-2-yn-1-yl)-2-(prop-2-yn-1-yl)malonate (501):

To a flame-dried round bottom flask equipped with a magnetic stir bar were added sodium hydride (60% dispersion in mineral oil, 187 mg, 3.89 mmol) and DMF (4 mL). A solution of alcohol **410** (1.02 g) in DMF (9.2 mL) was added dropwise by syringe and the mixture was stirred at 23 °C for 1 hour. A solution of bromide **500** (1.17 g, 3.89 mmol) in DMF (2.8 mL) was added dropwise by syringe and the mixture was stirred at 23 °C for 1 hour, until TLC analysis showed complete consumption of the starting material. The reaction mixture was quenched with water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over sodium sulfate, filtered, and concentrated to give the crude product, which was purified by silica gel chromatography (20% ethyl acetate in hexanes) to provide 811 mg of diyne **501** (43% yield). Note that some material was lost during the workup, so the yield may be artificially low. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.63–7.57 (m, 1H), 7.34–7.30 (m, 1H), 7.23 (ddd, J = 8.2, 7.0, 1.2, 1H), 7.19–7.10 (m, 1H), 7.04 (d, J = 1.0, 1H), 4.79 (t, J

= 2.2, 2H), 4.38–4.27 (m, 2H), 3.68 (s, 6H), 3.12 (td, *J* = 7.6, 0.9, 2H), 3.01 (t, *J* = 2.3, 2H), 2.96 (d, *J* = 2.6, 2H), 2.05 (t, *J* = 2.7, 1H), 1.49 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 153.7, 128.4, 125.5, 122.1, 119.6, 119.2, 110.9, 109.6, 109.4, 82.1, 79.9, 78.4, 72.0, 67.0, 56.6, 53.3, 36.1, 29.9, 27.9, 25.0, 23.1, 23.0; IR (Neat Film, NaCl) 3286, 2979, 1740, 1467, 1436, 1369, 1278, 1255, 1213, 1162, 1101, 1056, 963, 859, 794, 742, 650 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{27}H_{31}NO_7$ [M•]$^+$: 481.2100, found 481.2103.



501 ***502***

dimethyl 2-(4-(2-(1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)ethoxy)but-2-yn-1-yl)-2-(3-(triethylsilyl)prop-2-yn-1-yl)malonate (502):

A flame-dried round bottom flask equipped with a magnetic stir bar was charged with diyne **501** (500 mg, 1.04 mmol) and placed under a nitrogen atmostphere. THF (11.2 mL) was added the the mixture cooled to –78 °C in a dry ice/acetone bath. A solution of LiHMDS (263 mg, 1.57 mmol) in THF (1.5 mL) was added dropwise by syringe, and the mixture was stirred at –78 °C for 45 minutes. A solution of phenyldimethylsilyl chloride (262 μL, 1.56 mmol) in THF (5.6 mL) was added dropwise by syringe, and the reaction nmixture was allowed to warm to 23 °C and stir overnight. Upon completion (as determined by TLC analysis), the mixture was diluted with ether (50 mL) and poured into saturated aqueous ammonium chloride solution (50 mL). The ether layer was separated and washed with brine (1 x 50 mL), dried over magnesium sulfate, filtered, and concentrated to give the crude product. Silica gel colum chromatography was not able to

deliver pure silane **502**, and the material was carried forward impure. A yield for the reaction was was not determined. Integrals are approximate. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.64–7.55 (m, 3H), 7.44–7.31 (m, 4H), 7.24 (ddd, *J* = 8.2, 7.1, 1.2, 1H), 7.14 (ddd, *J* = 7.9, 7.0, 1.0, 1H), 7.04 (d, *J* = 0.8, 1H), 4.79 (t, *J* = 2.2, 2H), 4.33 (dd, *J* = 7.9, 7.2, 2H), 3.65 (s, 6H), 3.12 (ddd, *J* = 8.1, 7.2, 0.9, 2H), 3.04 (s, 2H), 3.02 (t, *J* = 2.3, 2H), 1.50 (s, 9H), 0.42 (s, 3H), 0.38 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 153.6, 139.2, 137.0, 136.1, 133.7, 133.7, 129.8, 129.5, 128.4, 128.0, 128.0, 125.5, 122.1, 119.5, 119.1, 110.9, 109.6, 102.6, 86.8, 82.0, 80.0, 77.6, 67.0, 56.9, 53.1, 36.1, 27.9, 25.0, 24.5, 23.2, 0.1, -0.7; ATR-IR (C_6H_6 solution) 2955, 2180, 1736, 1456, 1428, 1368, 1275, 1250, 1208, 1158, 1026, 817, 782, 735, 702 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{35}H_{41}NO_7Si$ $[M\bullet]^+$: 615.2652, found 615.2642.

4.8 NOTES AND REFERENCES

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(2) Hudson, B. M.; Harrison, J. G.; Tantillo, D. J. *Tetrahedron Lett.* **2013**, *54*, 2952–2955.

(3) Tantillo and co-workers draw the six-membered ring fused to the indole C2–C3 bond of calophyline A as a chair in their report, and their drawings have been reproduced (in a different orientation) in this scheme. However the crystal structure of calophyline A obtained by Zou, Li, and co-workers shows this ring to have more of a boat-like conformation as shown in Figure 4.1. The still images of calculated structures provided by Tantillo are unclear, as other bonds are obscuring the view of the ring of interest. Tantillo and co-workers also label the methyl ester of calophyline A as the natural product when the carboxylic acid is the actual structure.

(4) Zu previously utilized this strategy in a formal synthesis of minfiensine: Yu, Y.; Li, G.; Jiang, L.; Zu, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 12627–12631.

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(9) See Scheme 4.5.C for a list of catalysts examined.

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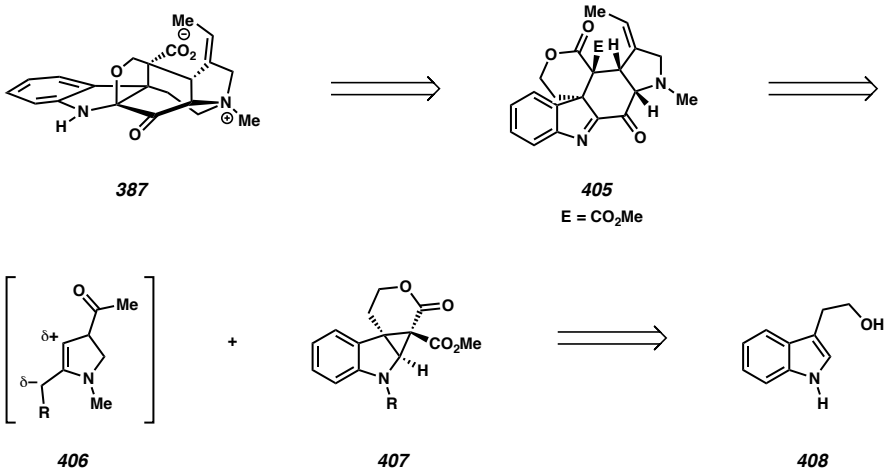
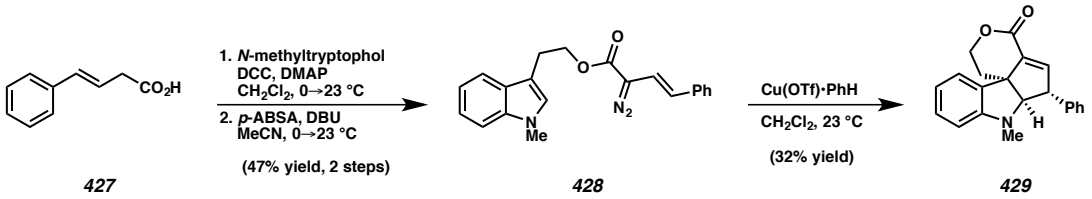
APPENDIX 7

Synthetic Summary toward the Total Synthesis of Calophyline A

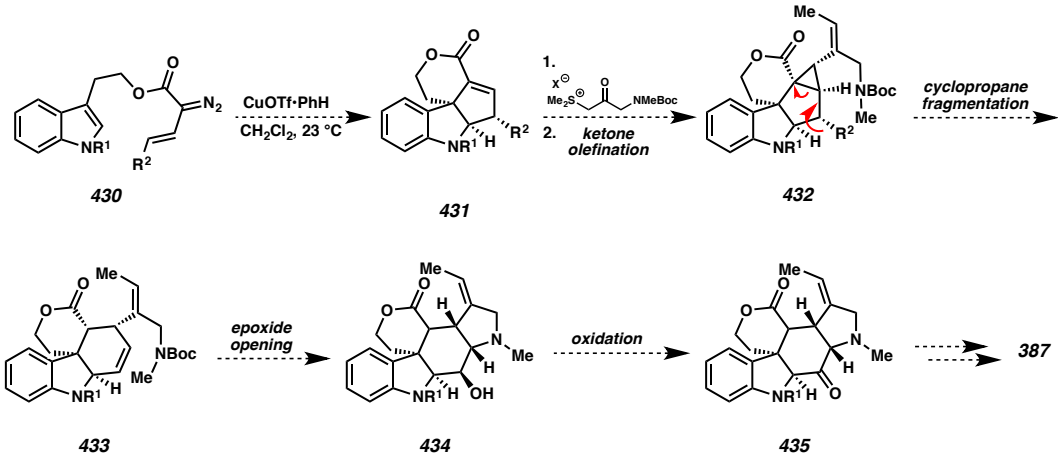
Scheme A7.1 Initial retrosynthetic analysis



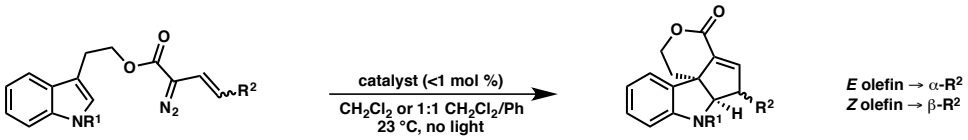
*Scheme A7.2 Formation of tetracycle **429***



Scheme A7.3 Revised synthetic plan



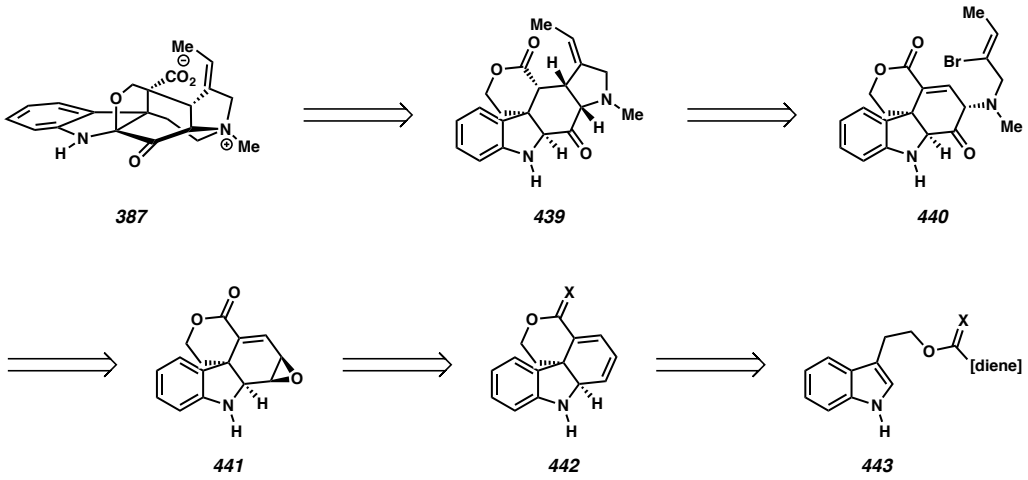
Scheme A7.4 Attempted (3 + 2) cycloadditions



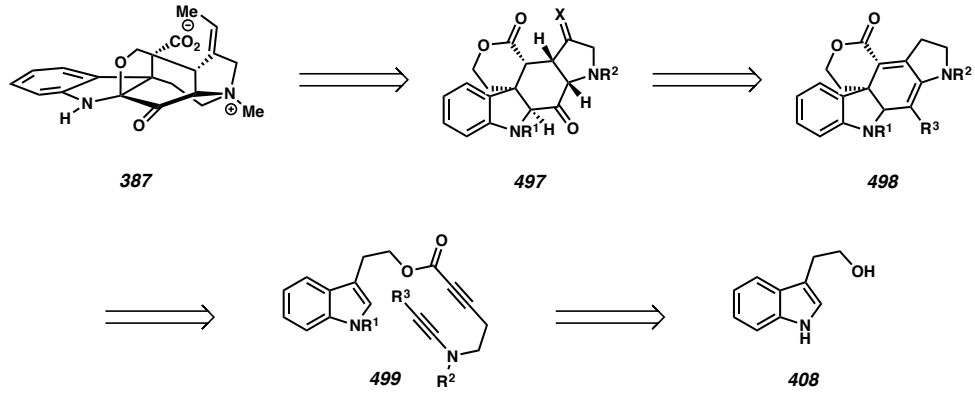
Entry	*R¹*	*R²*	*Olefin Geometry*	*Catalyst*	*Result*
1	Me	Ph	*E*	Cu(OTf)·PhH	32% yield
2	Me	CO_2Me	*Z*	Cu(OTf)·PhH	pyrazole formation
3	Me	CO_2Me	*Z*	$Rh_2(OAc)_4$	pyrazole formation
4	Boc	CO_2Me	*Z*	Cu(OTf)·PhH	no reaction
5	Boc	CO_2Me	*Z*	$Rh_2(OAc)_4$	pyrazole formation
6	Boc	$CO_2CH_2CH_2TMS$	*E*	Cu(OTf)·PhH	pyrazole formation
7	Boc	$CO_2CH_2CH_2TMS$	*E*	$Rh_2(OAc)_4$	pyrazole formation
8	Boc	2-furyl	*E*	Cu(OTf)·PhH	decomposition
9	Me	H: 1,1-disub. TBS enol silane	N/A	Cu(OTf)·PhH; TBAF	ester hydrolysis
10	Me	H: 1,1-disub. TBS enol silane	N/A	$Rh_2(OAc)_4$	dimerization

Reactions conducted on approx. 0.05 mmol scale by adding a solution of the substrate to a solution of the catalyst over one hour.

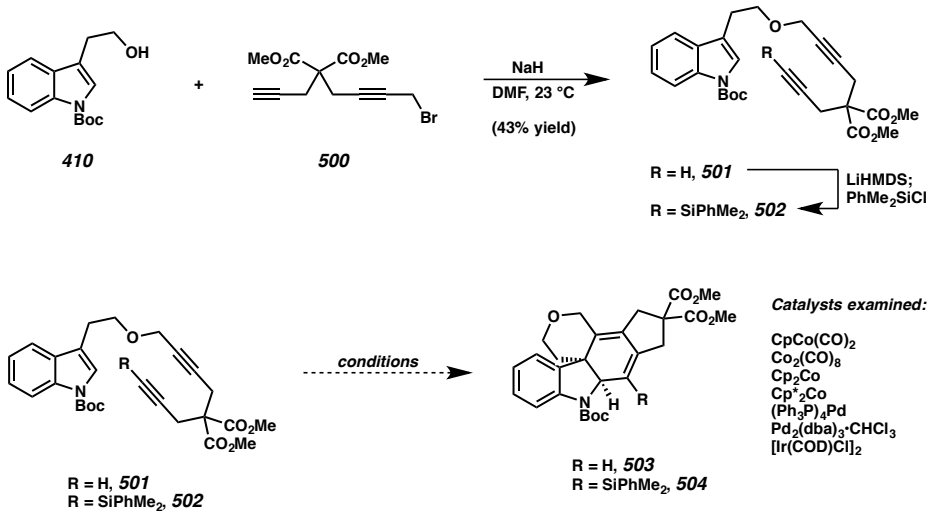
Scheme A7.5 Retrosynthesis incorporating a [4 + 2] cycloaddition



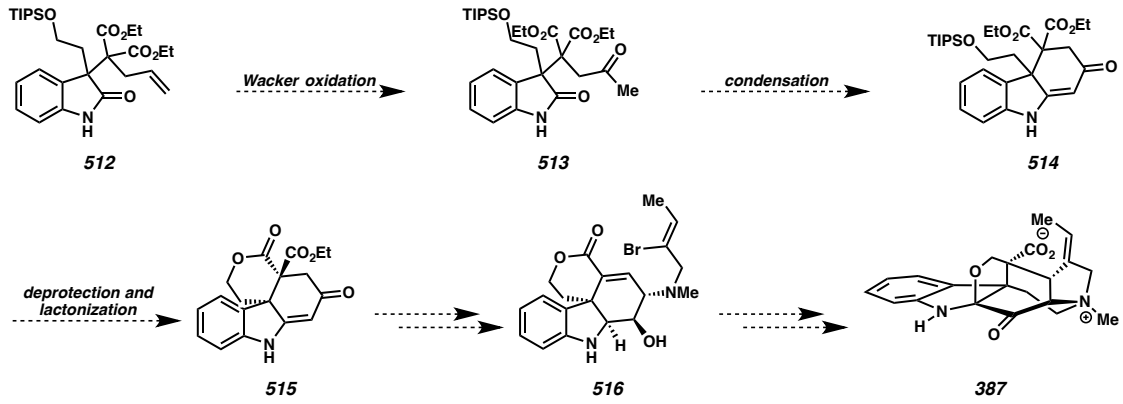
Scheme A7.6 Retrosynthetic analysis employing a [2 + 2 + 2] cycloaddition



Scheme A7.7 Investigation of an intramolecular [2 + 2 + 2] cycloaddition



*Scheme A7.8 Proposed synthetic route procceing via bromoxindole alkylation product **512***



APPENDIX 8

Spectra Relevant to Chapter 4:

Progress Toward the Total Synthesis of Calophyline A

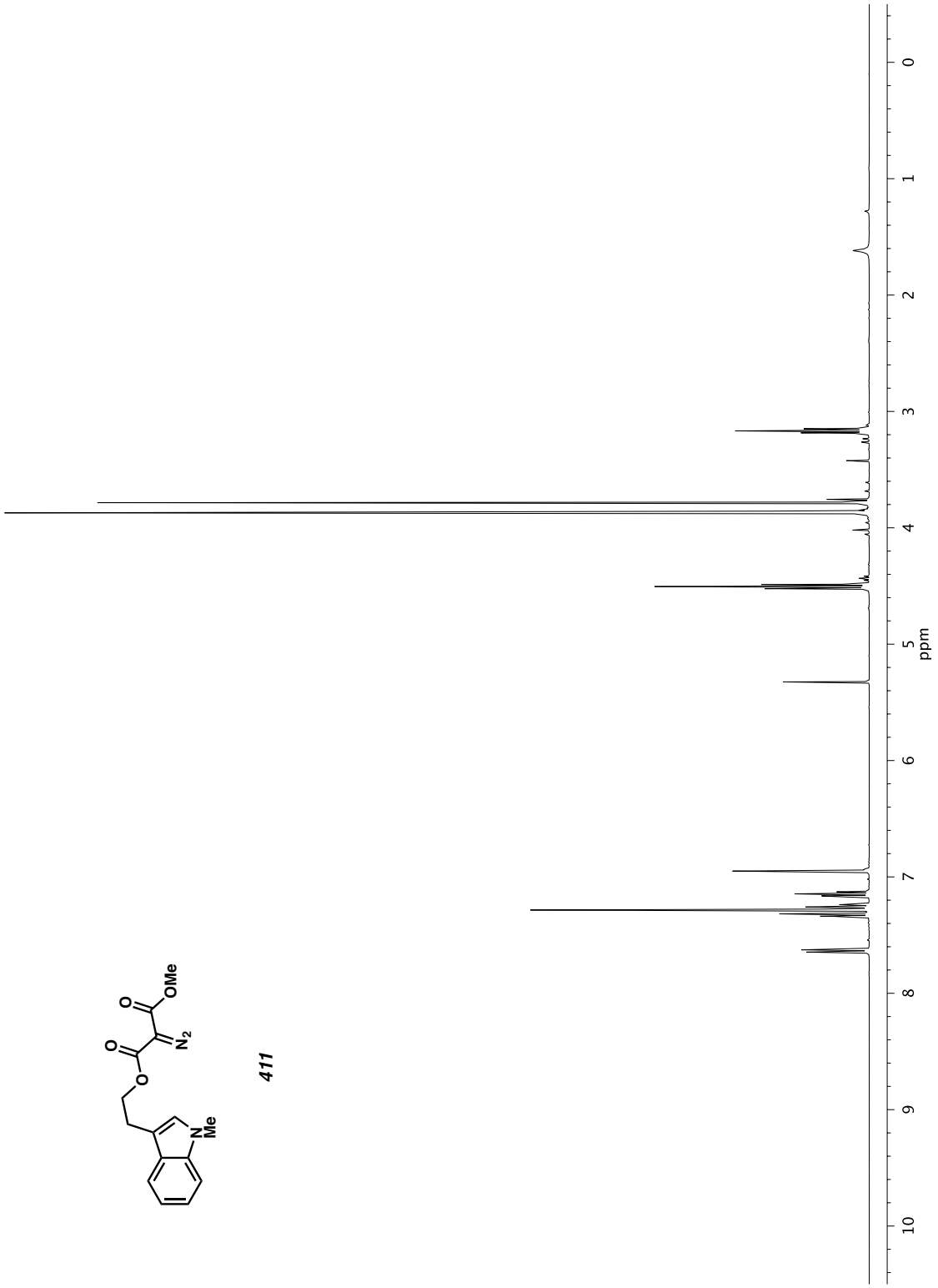


Figure A8.1 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **411**.

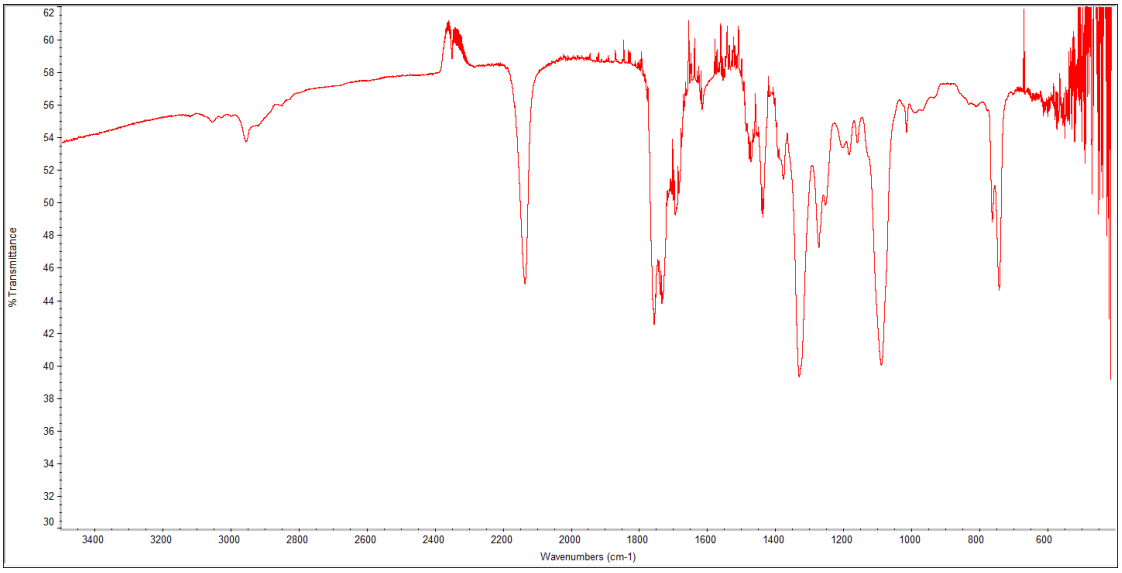


Figure A8.2 ATR-IR ($CDCl_3$ solution) of compound **411**.

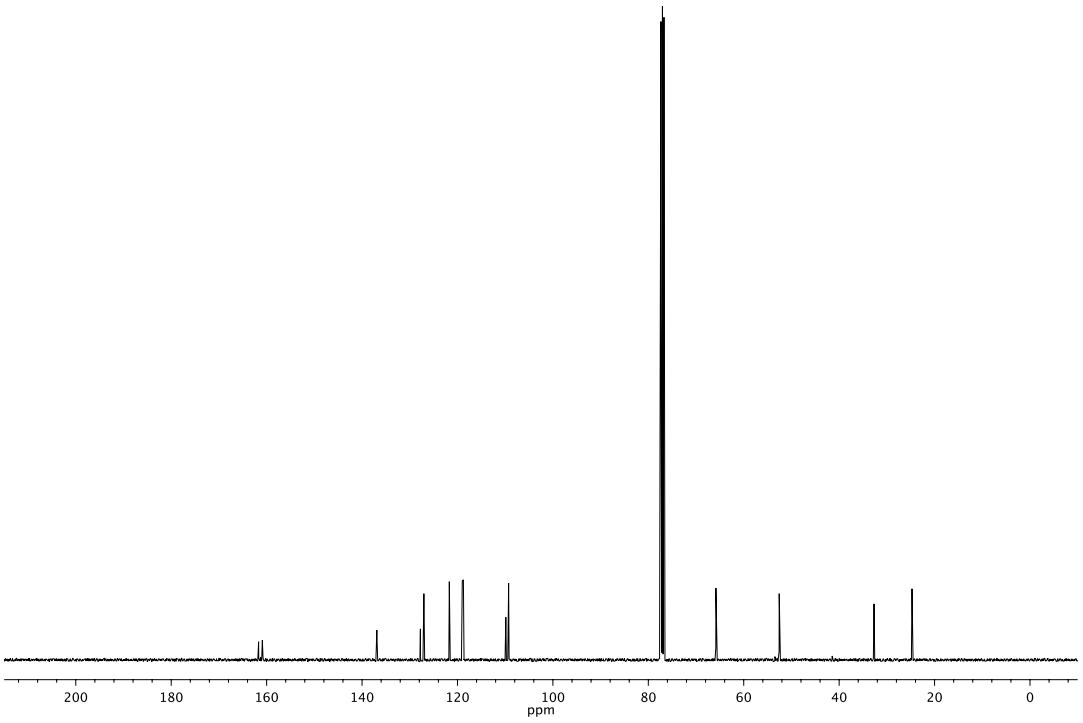


Figure A8.3 ^{13}C NMR (101 MHz, $CDCl_3$) of compound **411**.

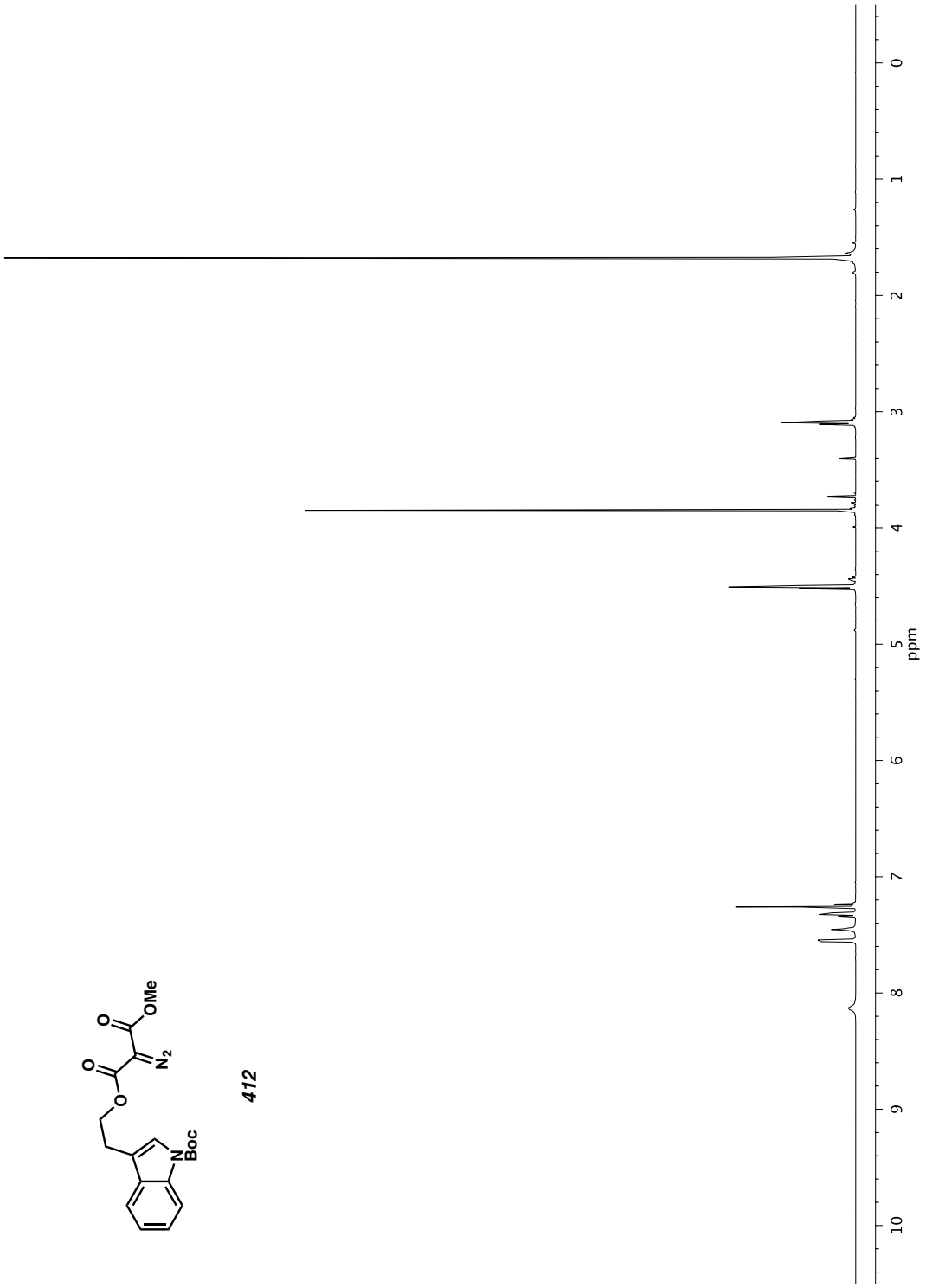


Figure A8.4 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **412**.

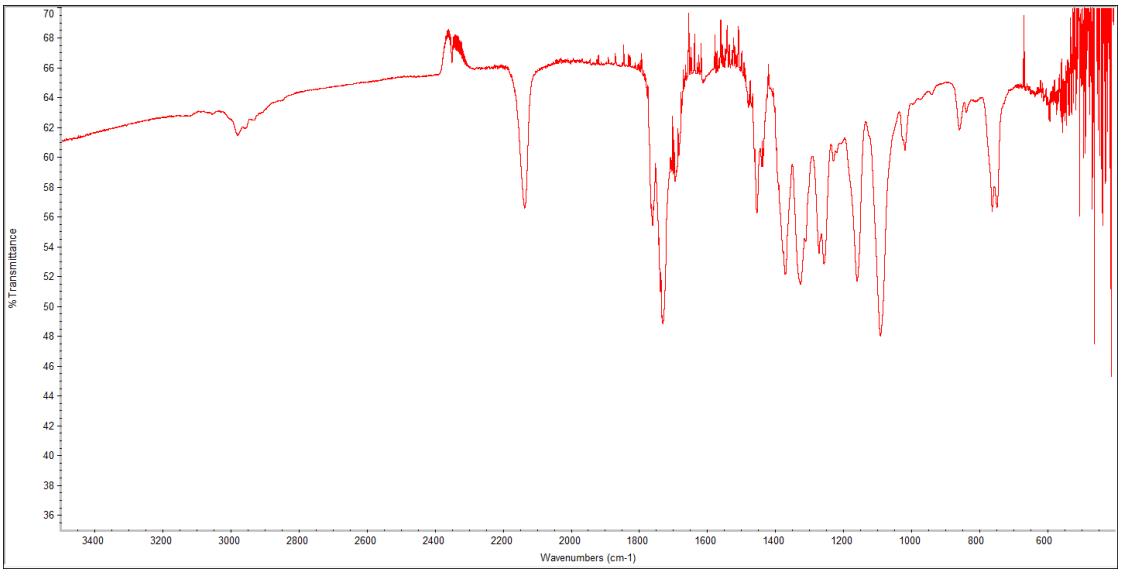


Figure A8.5 ATR-IR ($CDCl_3$ solution) of compound **412**.

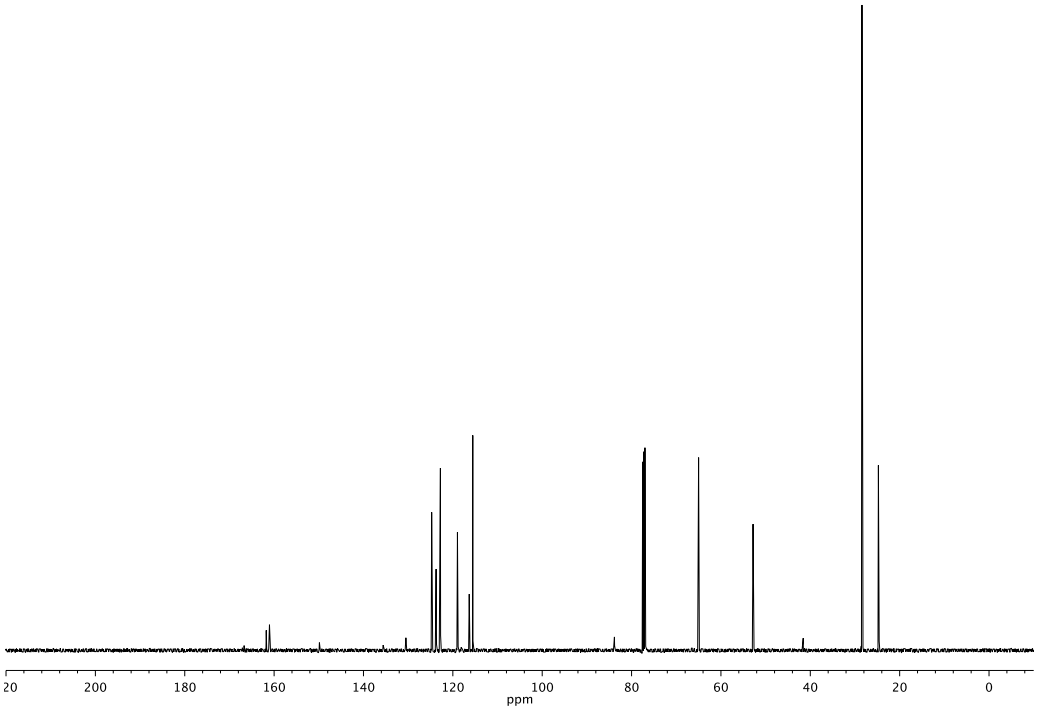


Figure A8.6 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **412**.

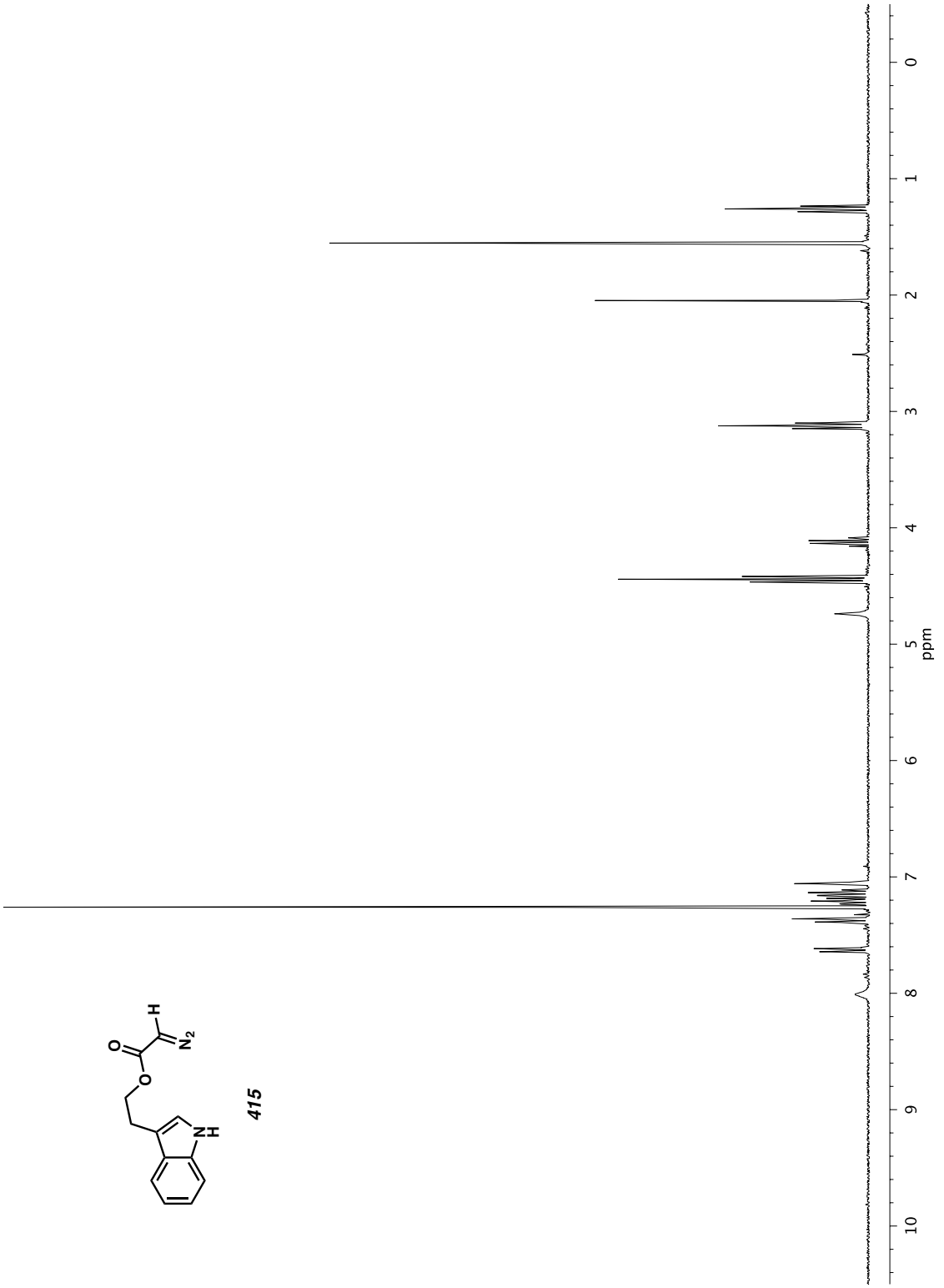


Figure A8.7 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **415**.

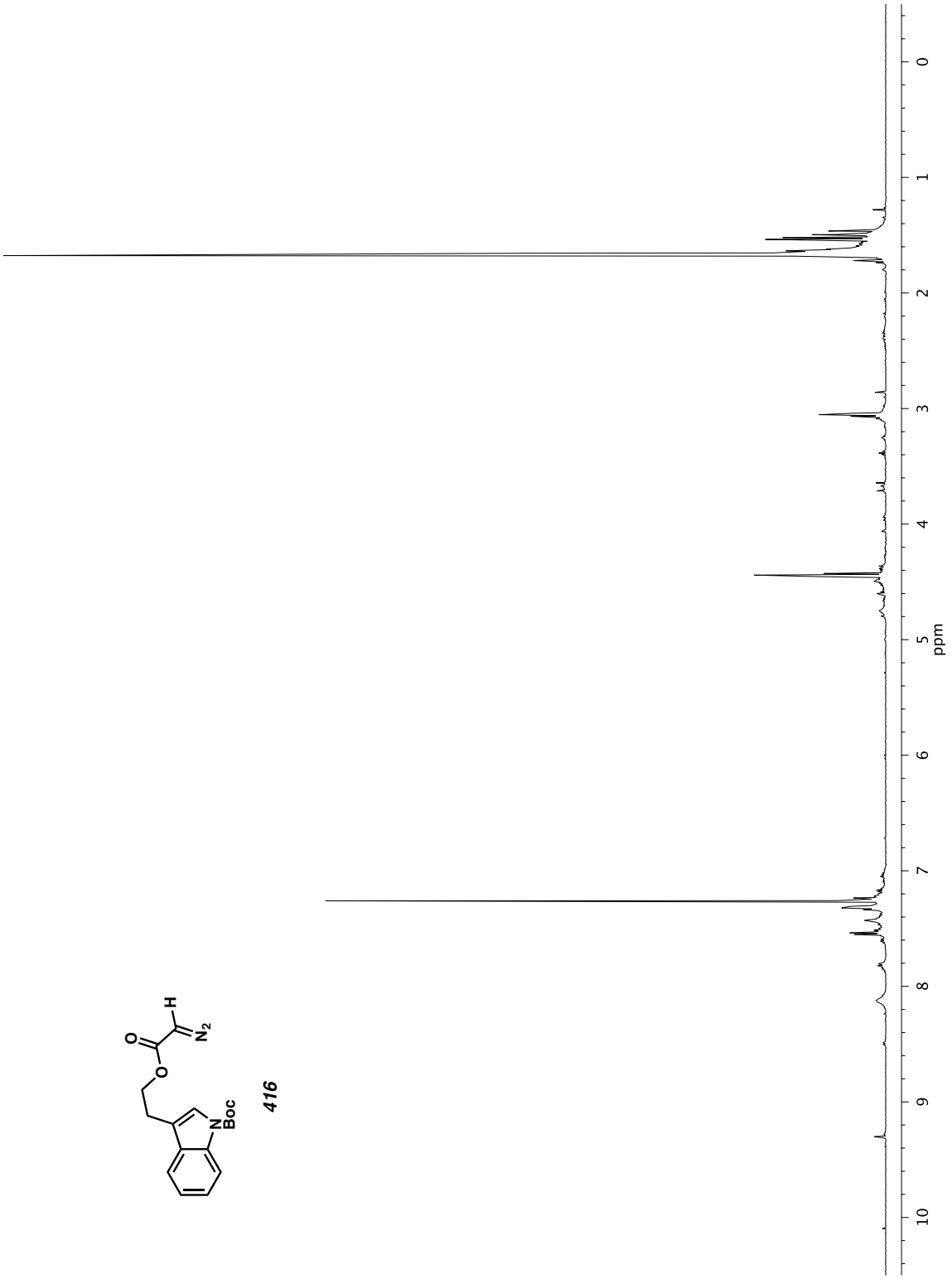


Figure A8.8 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **416**.

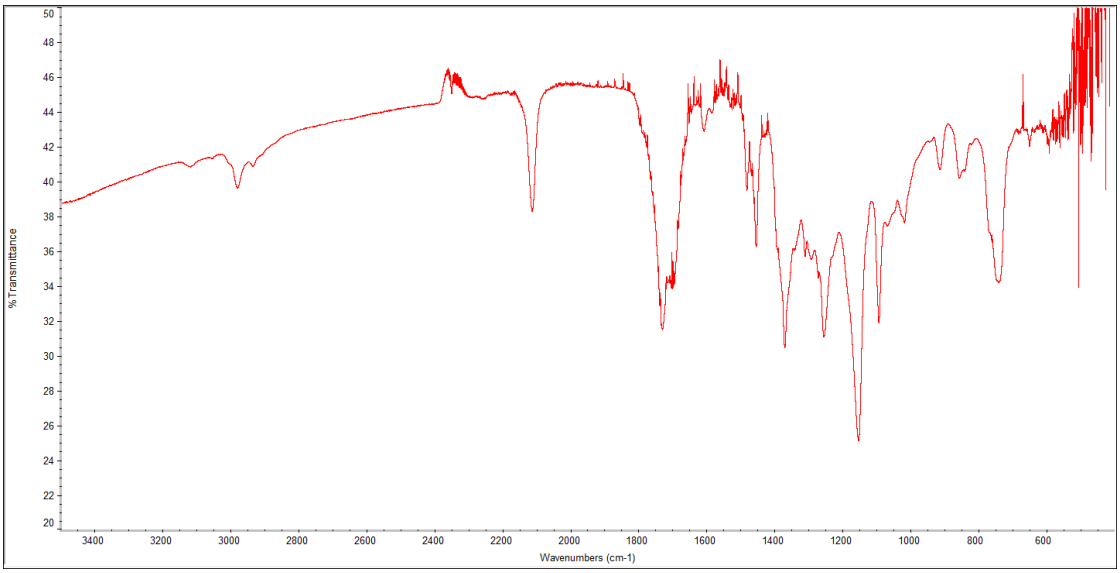


Figure A8.9 ATR-IR ($CDCl_3$ solution) of compound **416**.

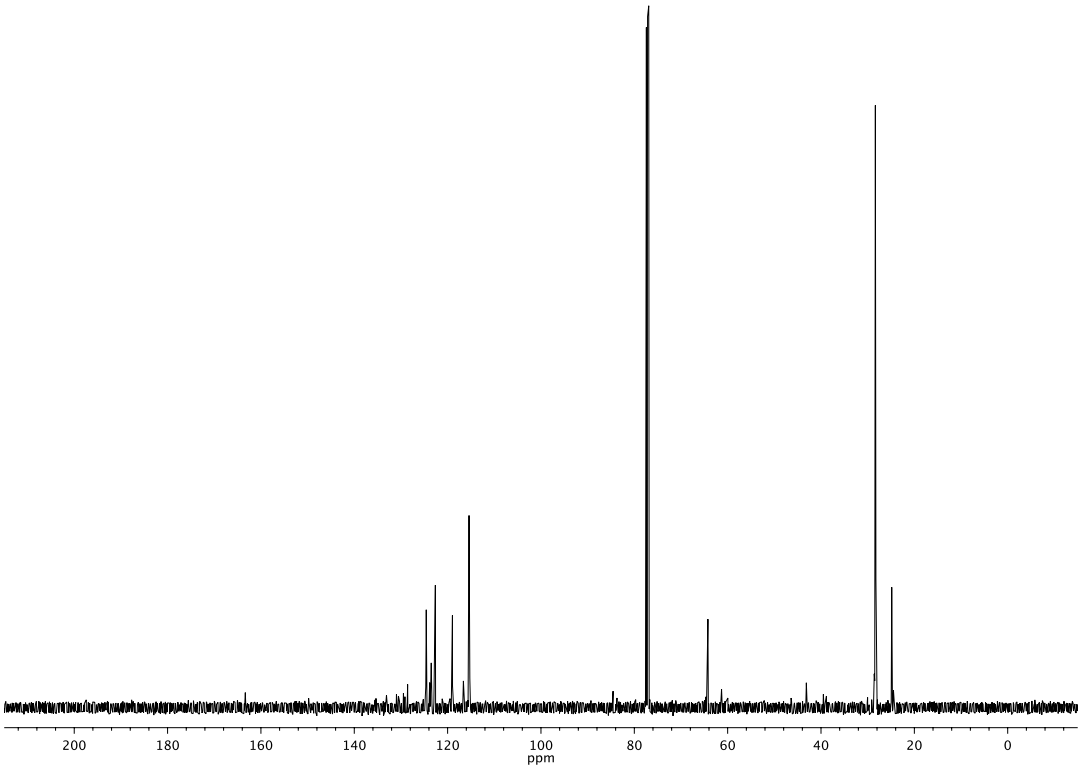
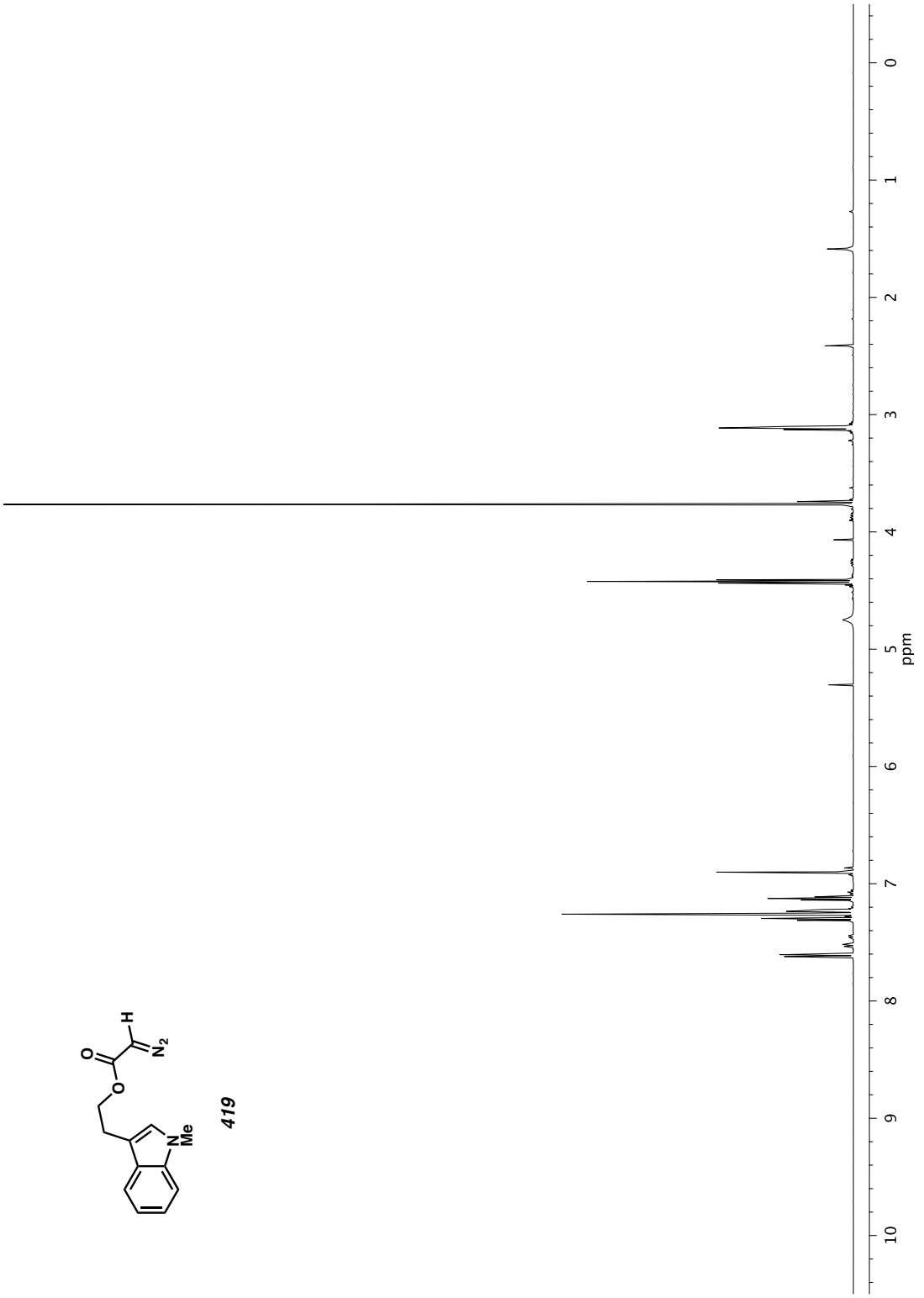


Figure A8.10 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **416**.



419

Figure A8.11 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **419**.

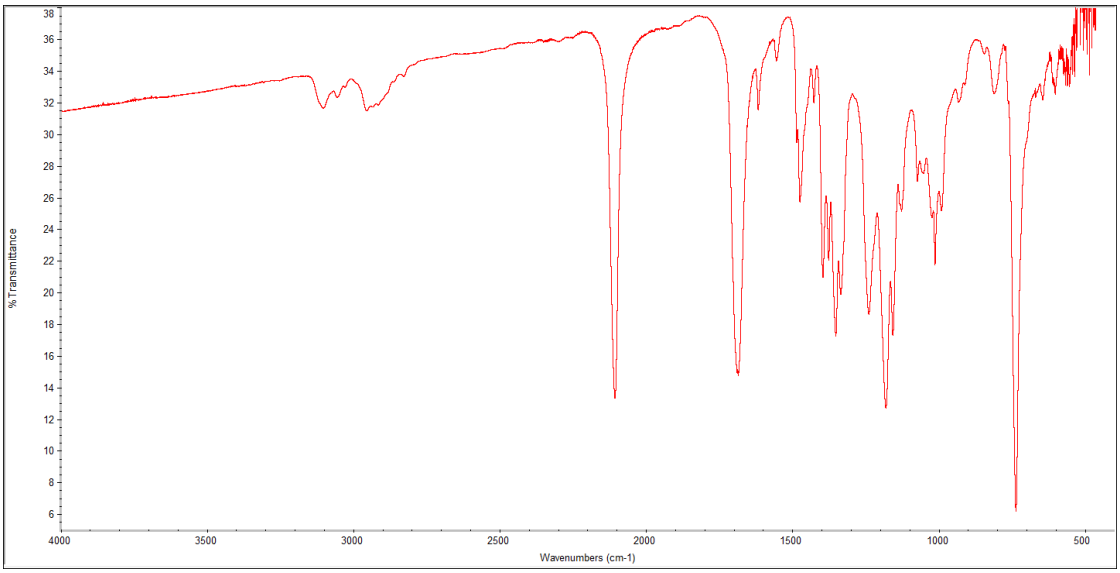


Figure A8.12 ATR-IR (neat oil) of compound **419**.

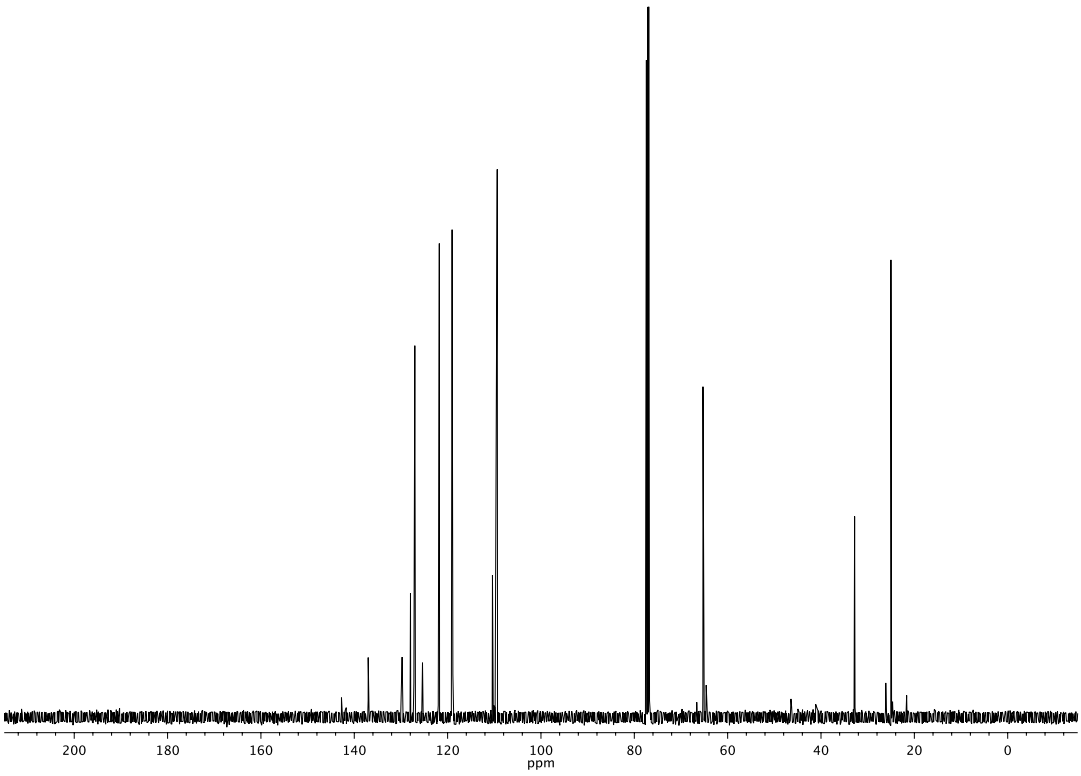


Figure A8.13 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **419**.

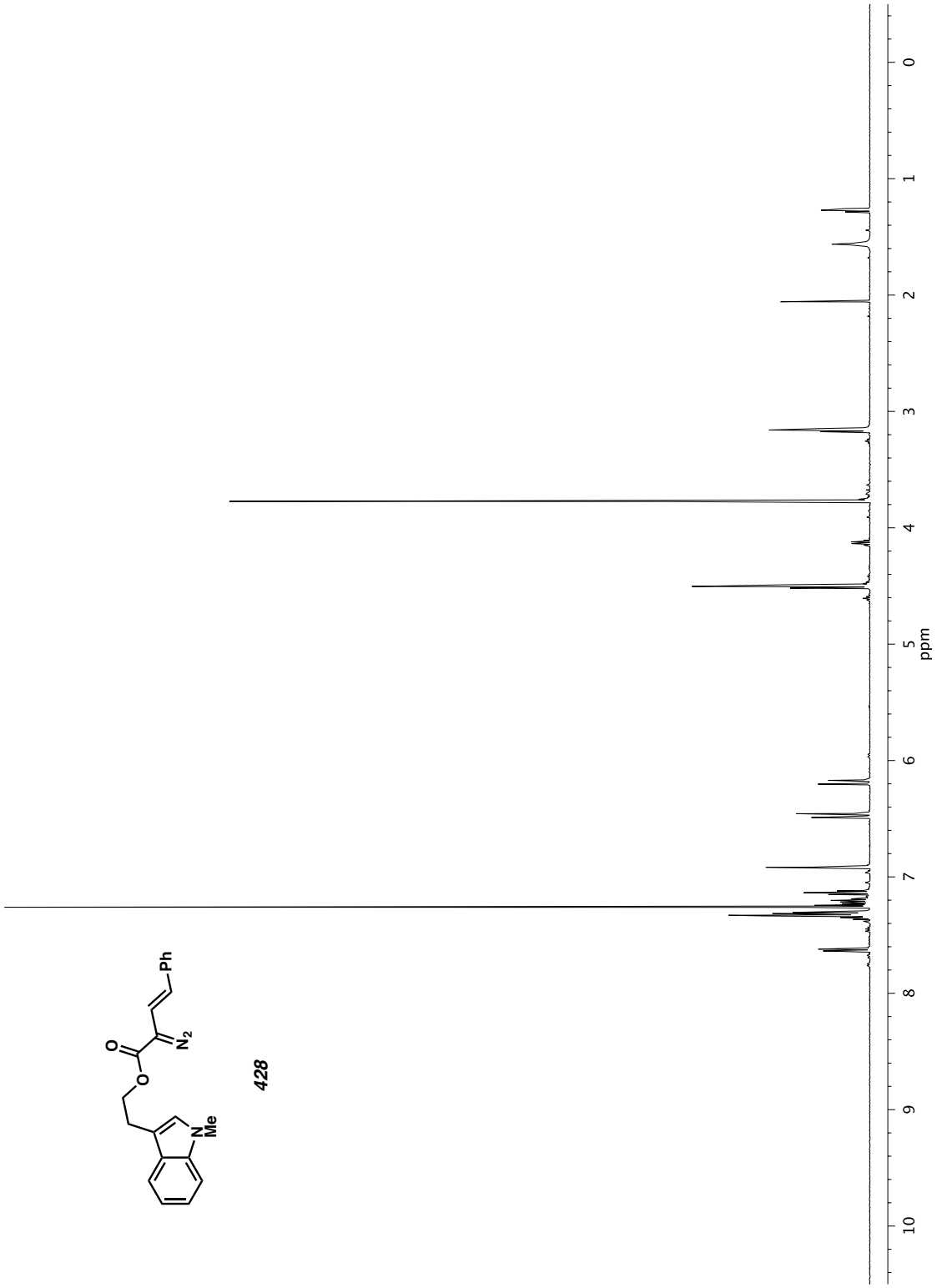


Figure A8.14 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **428**.

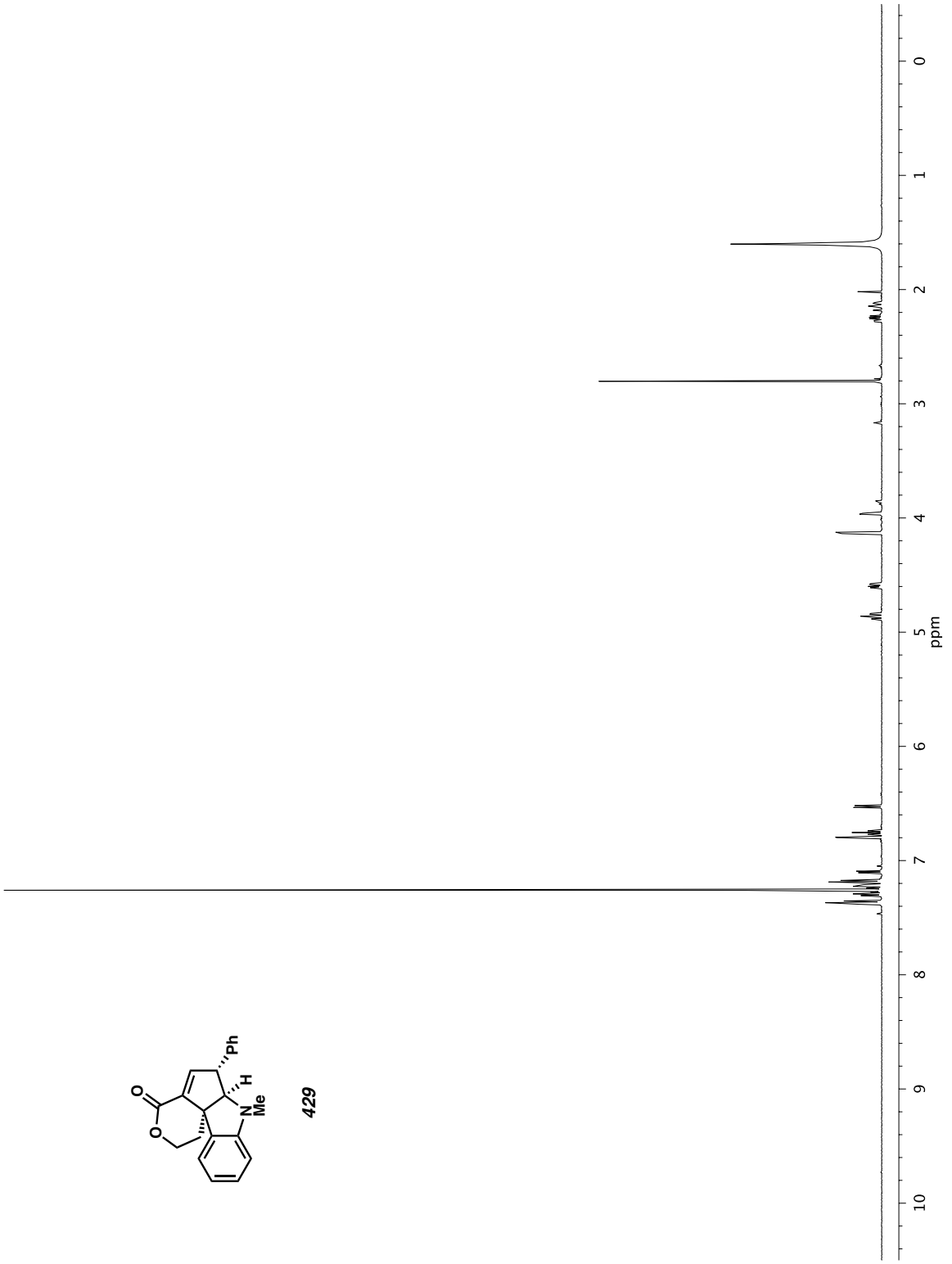


Figure A8.15 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **429**.

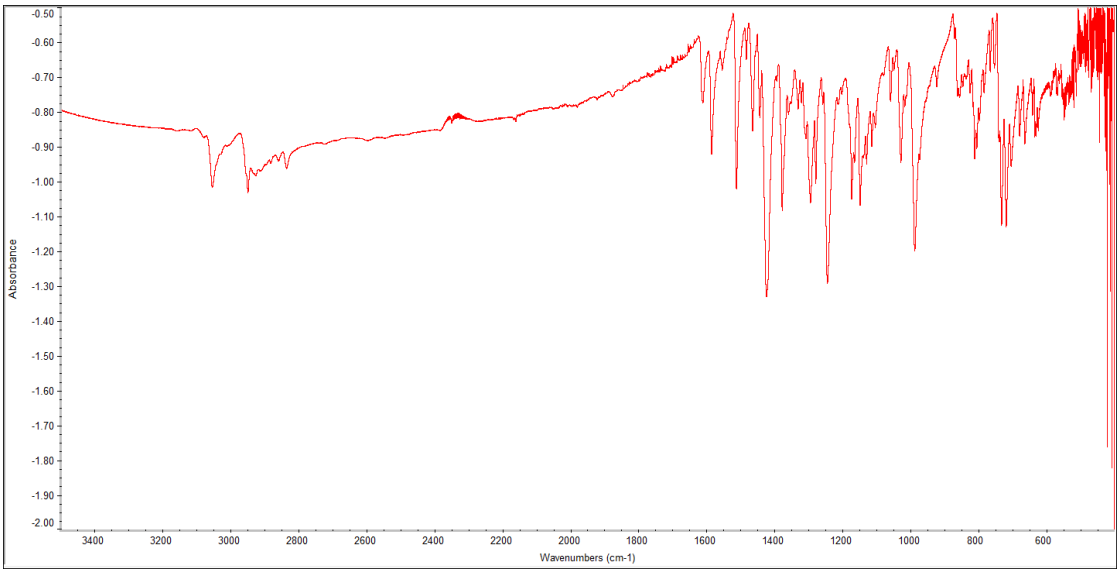


Figure A8.16 ATR-IR (neat solid) of compound **429**.

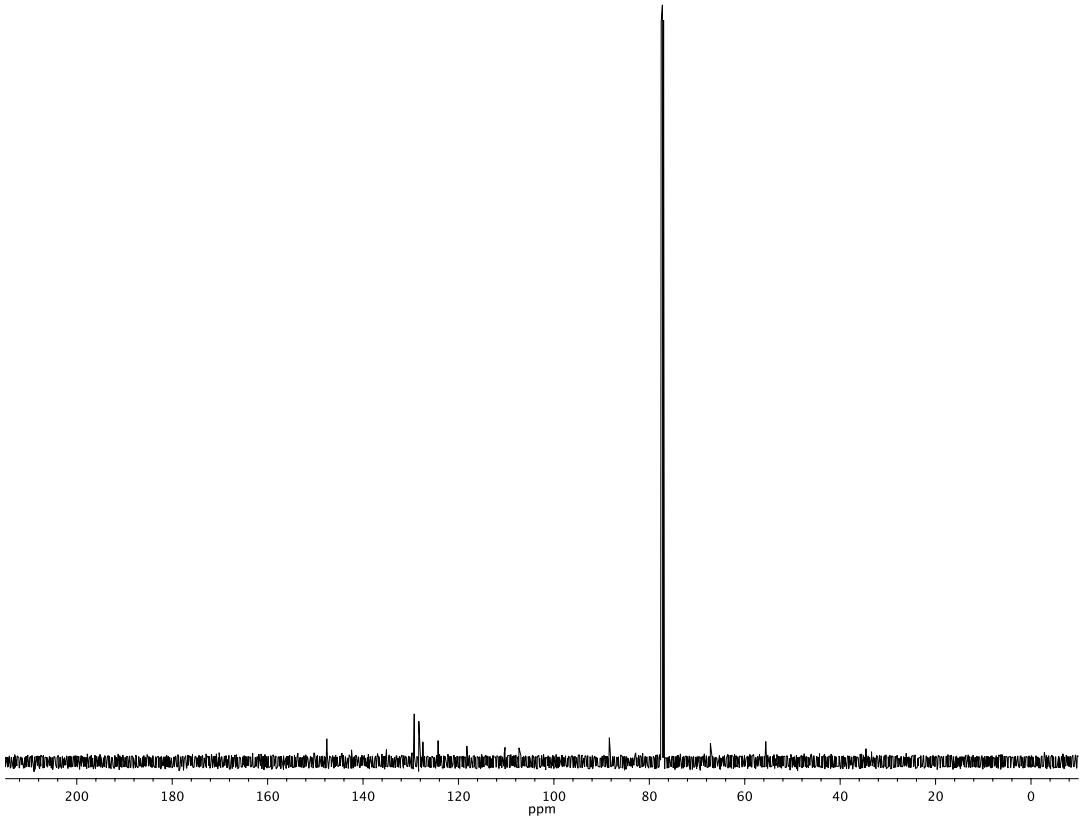


Figure A8.17 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **429**.

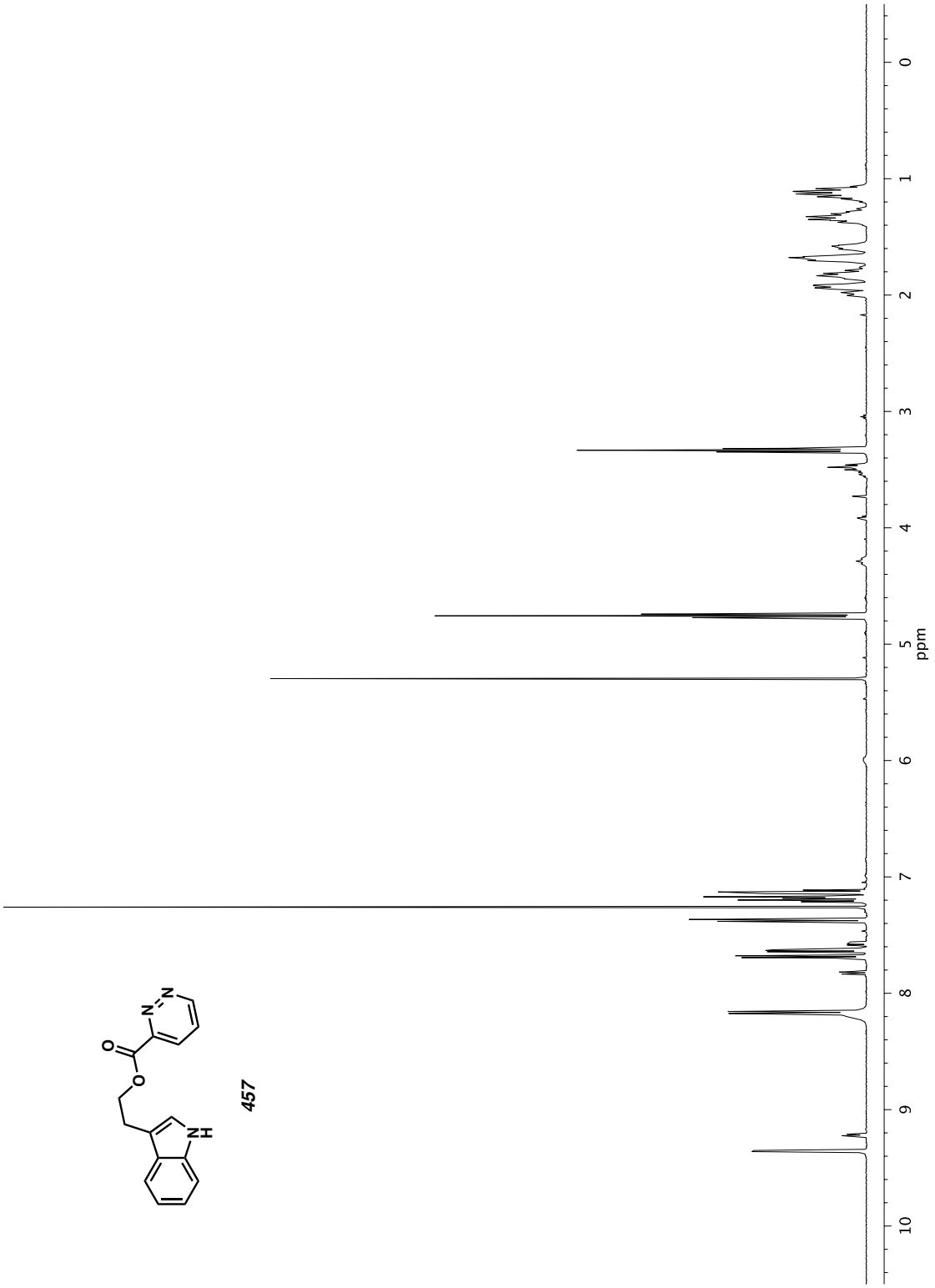


Figure A8.18 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **457**.

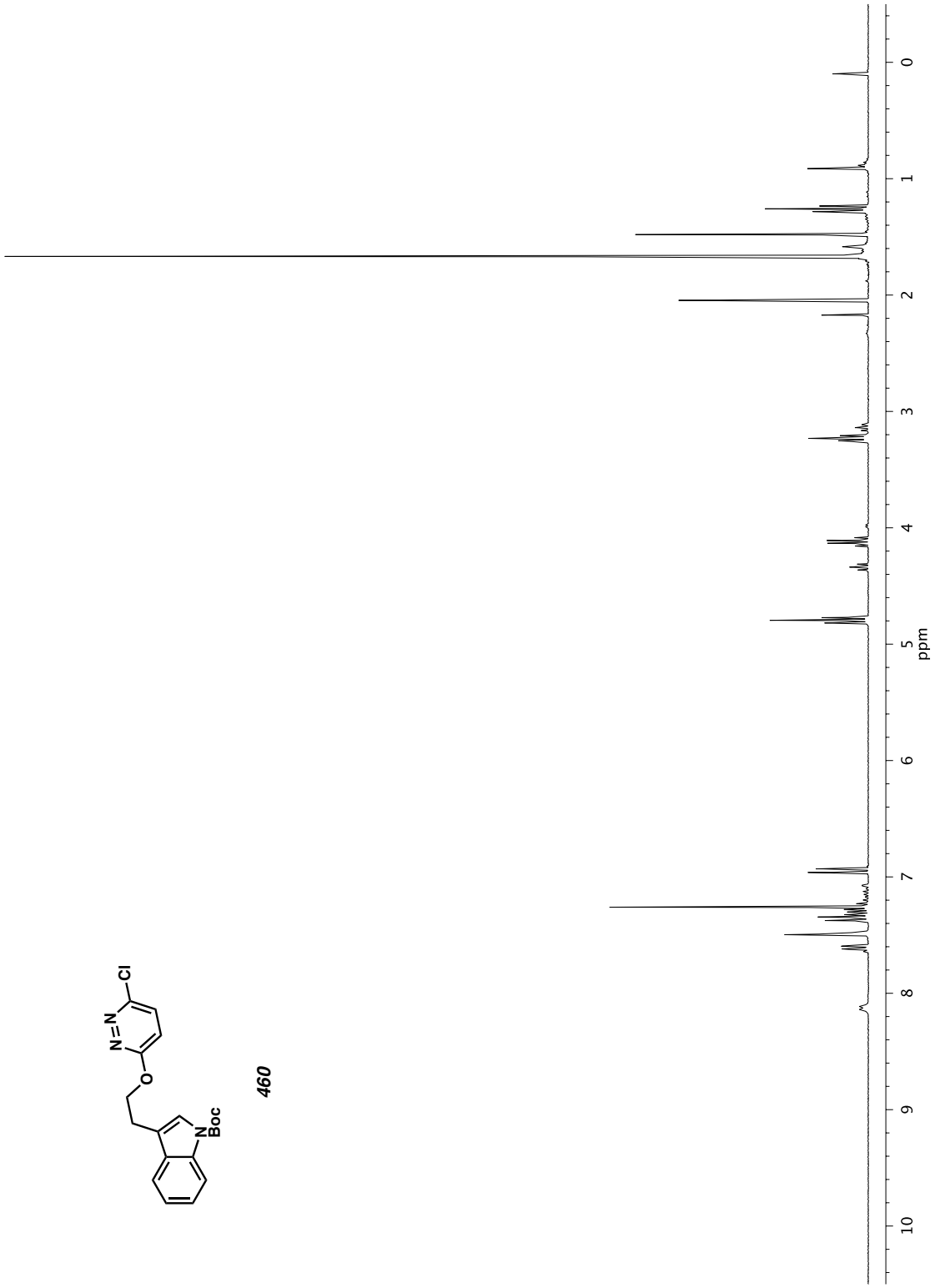


Figure A8.19 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **460**.

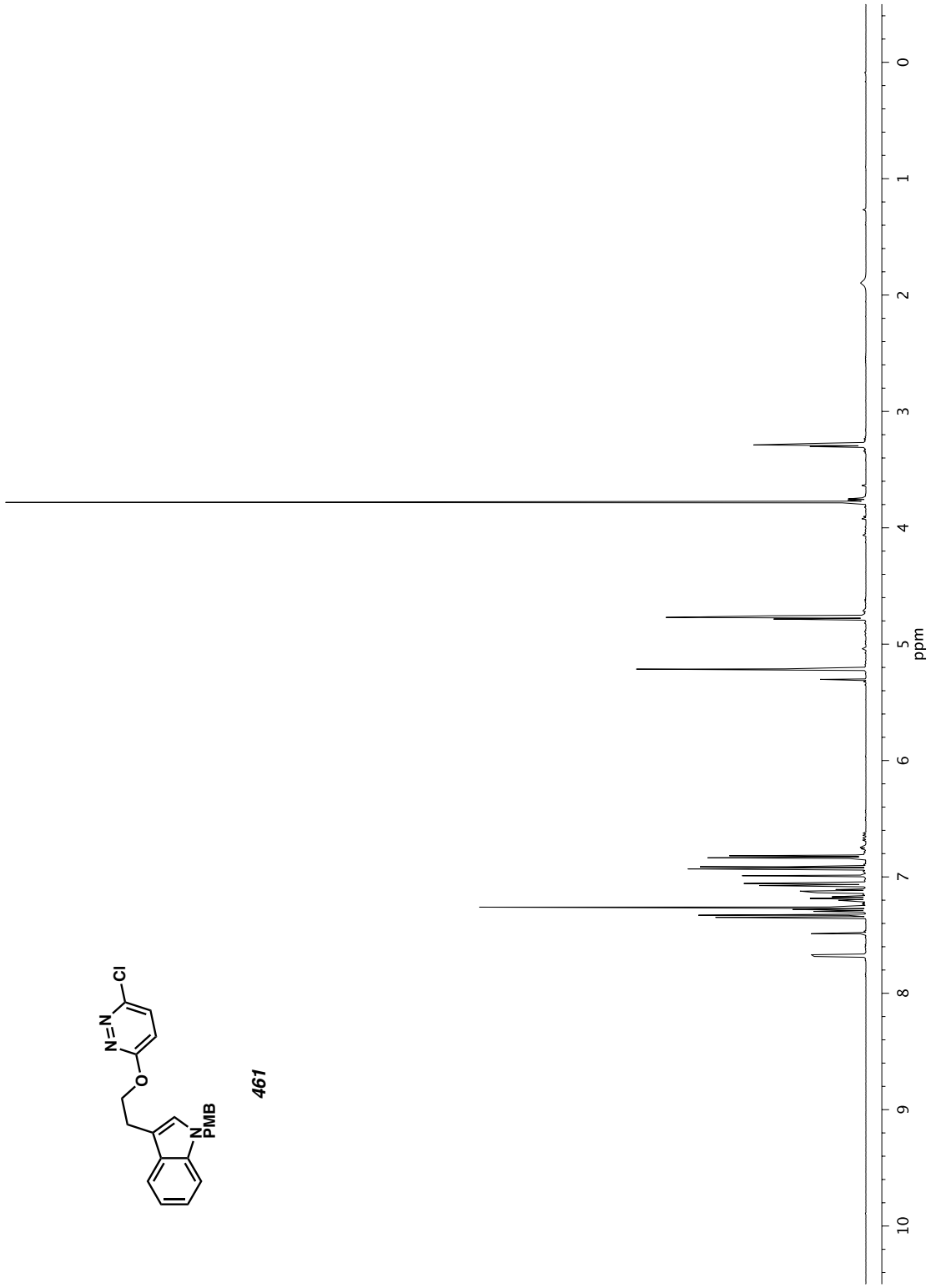


Figure A8.20 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **461**.

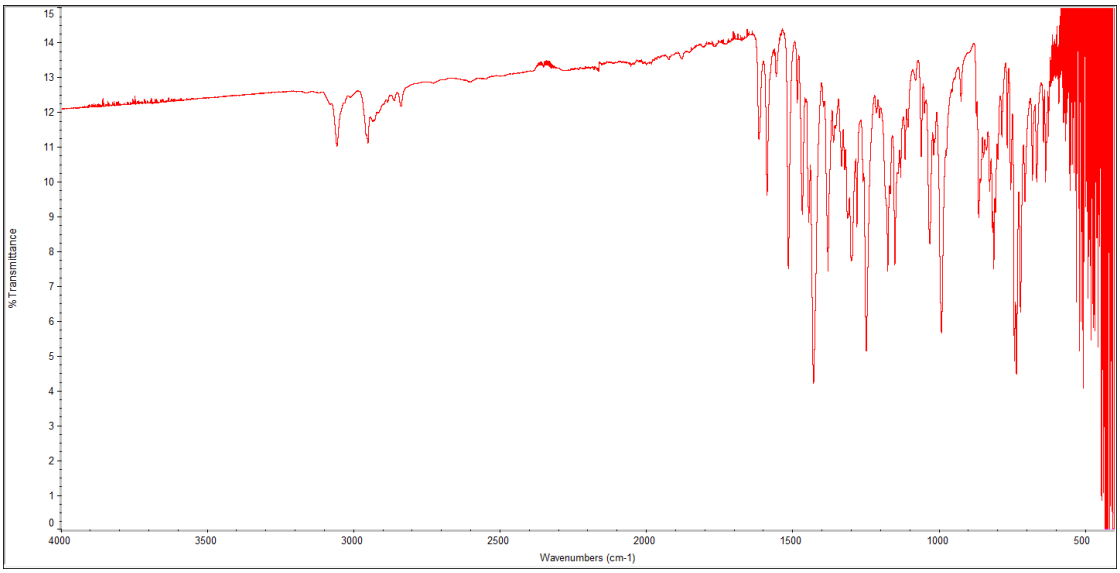


Figure A8.21 ATR-IR (neat solid) of compound **461**.

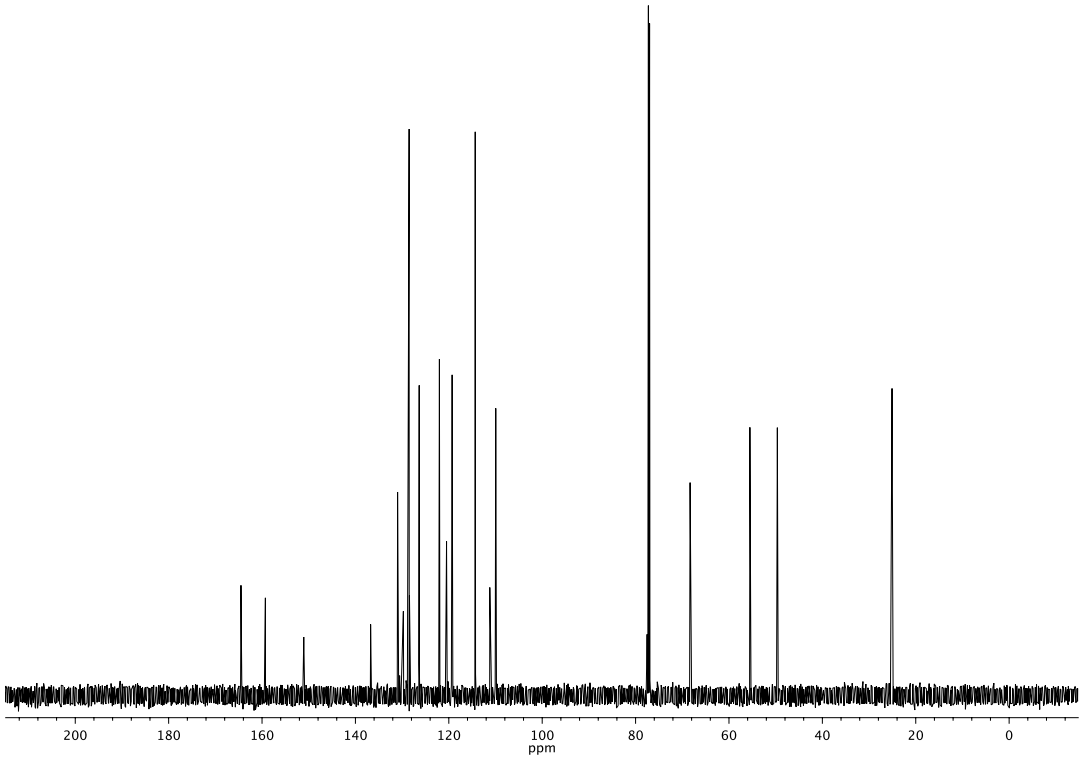
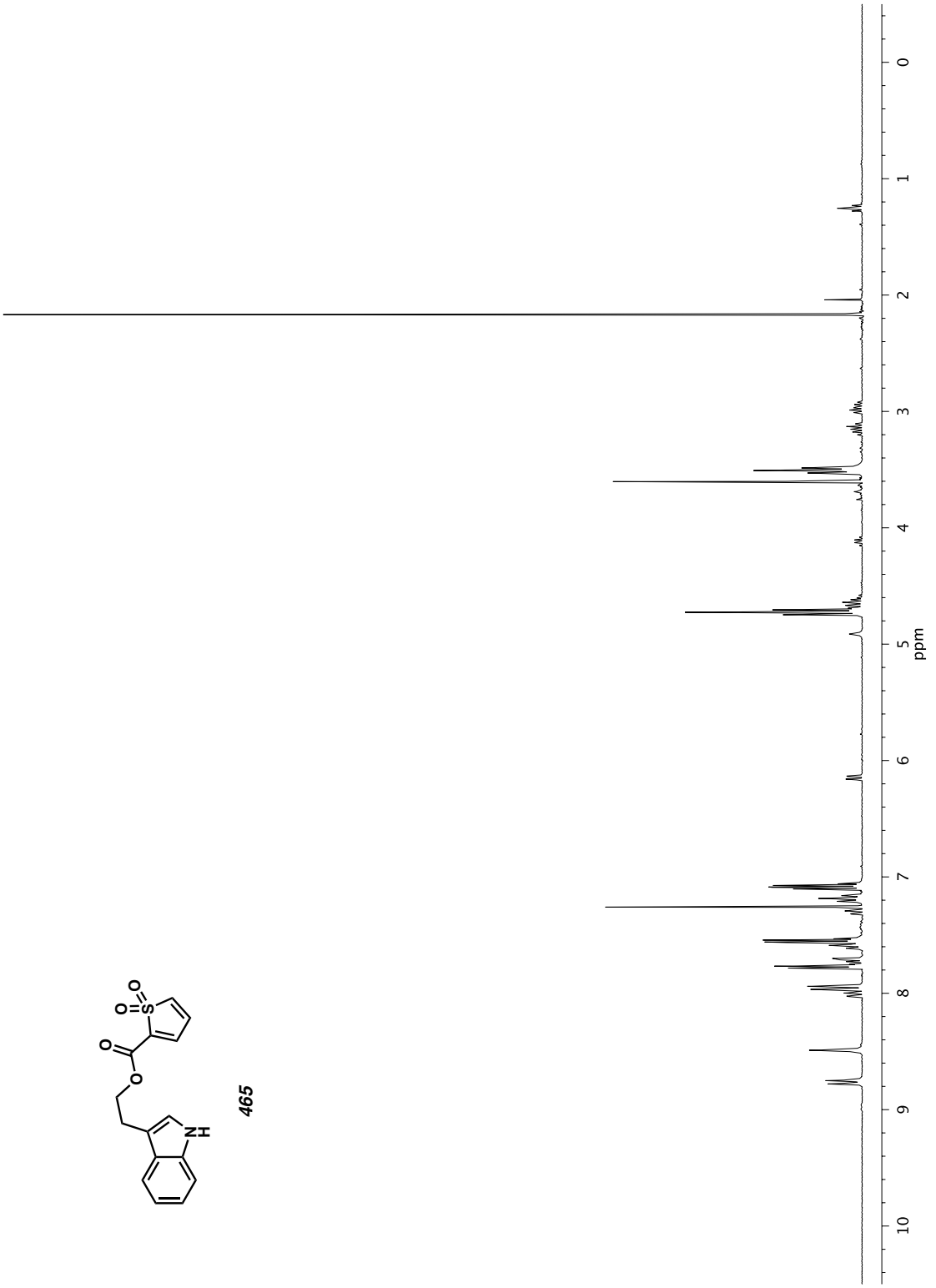


Figure A8.22 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **461**.



465

Figure A8.23 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **465**.

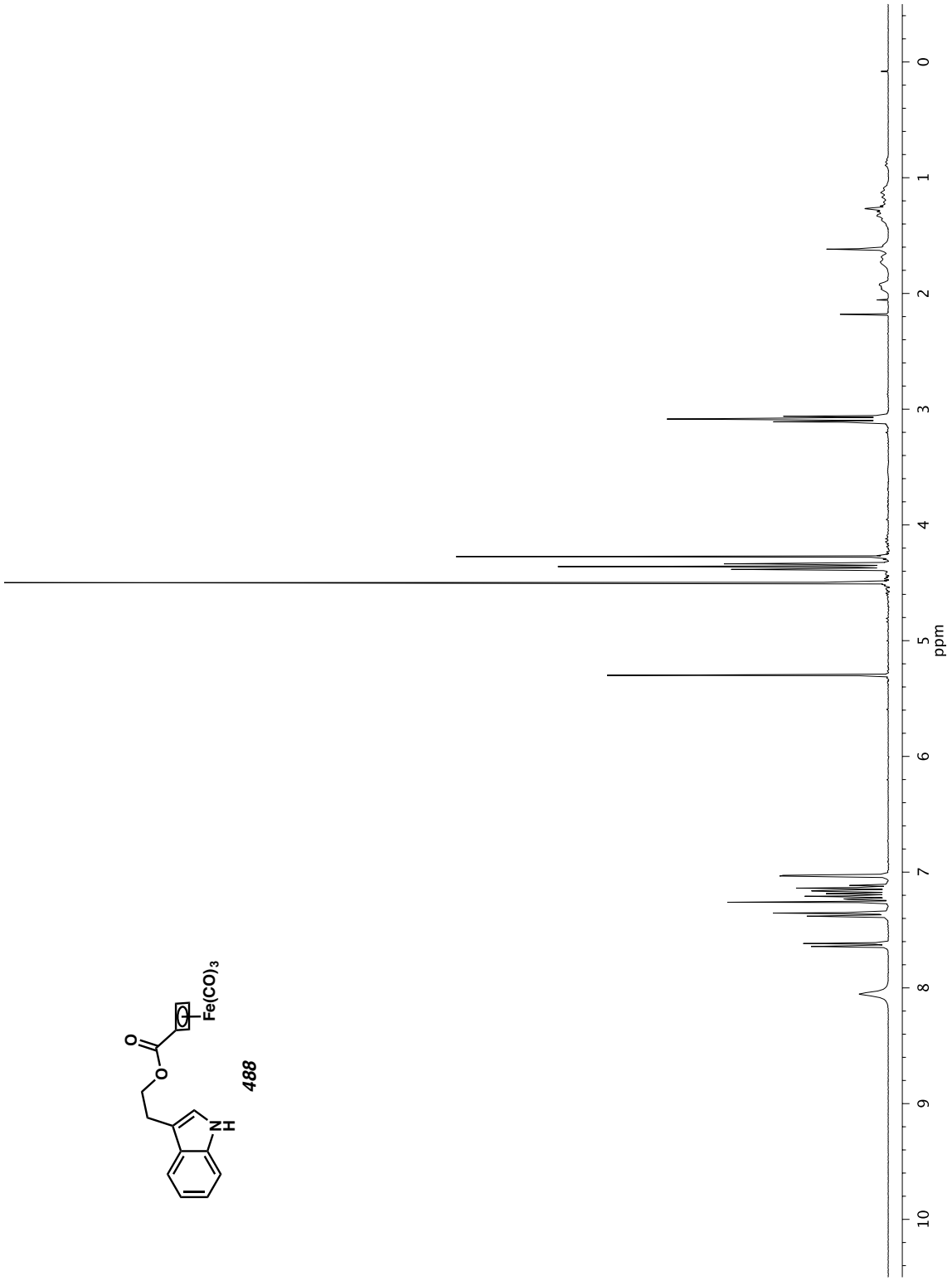


Figure A8.24 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **488**.

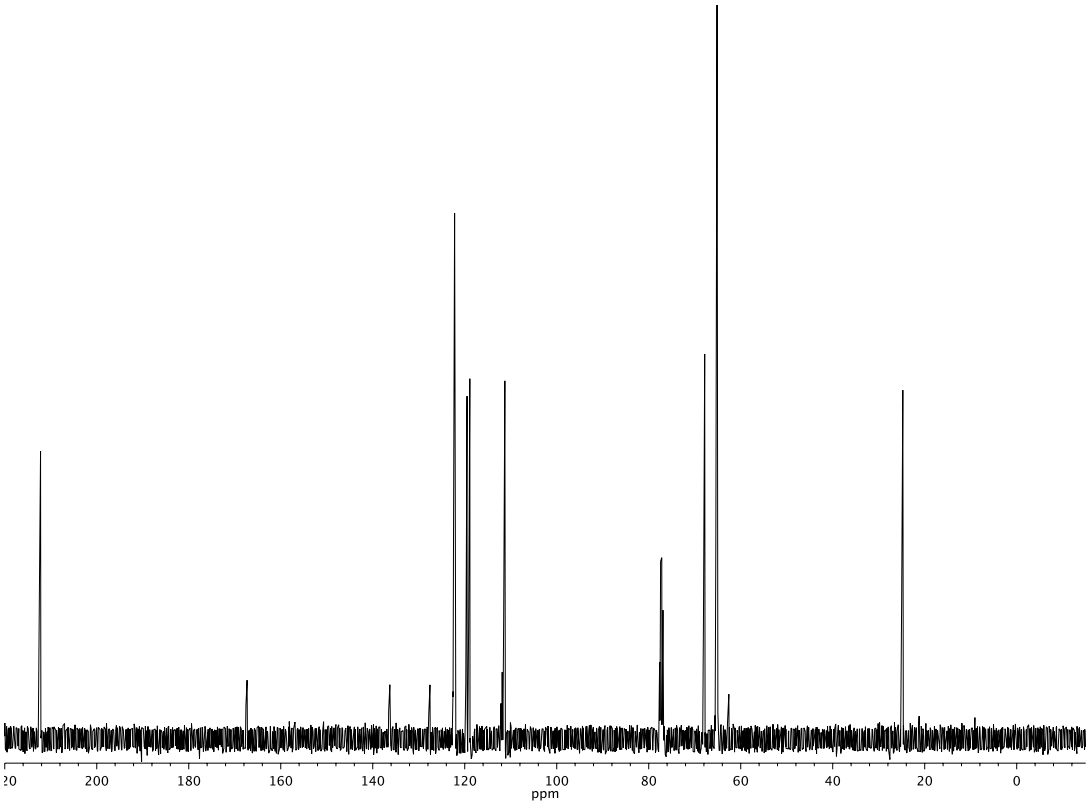


Figure A8.25 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **488**.

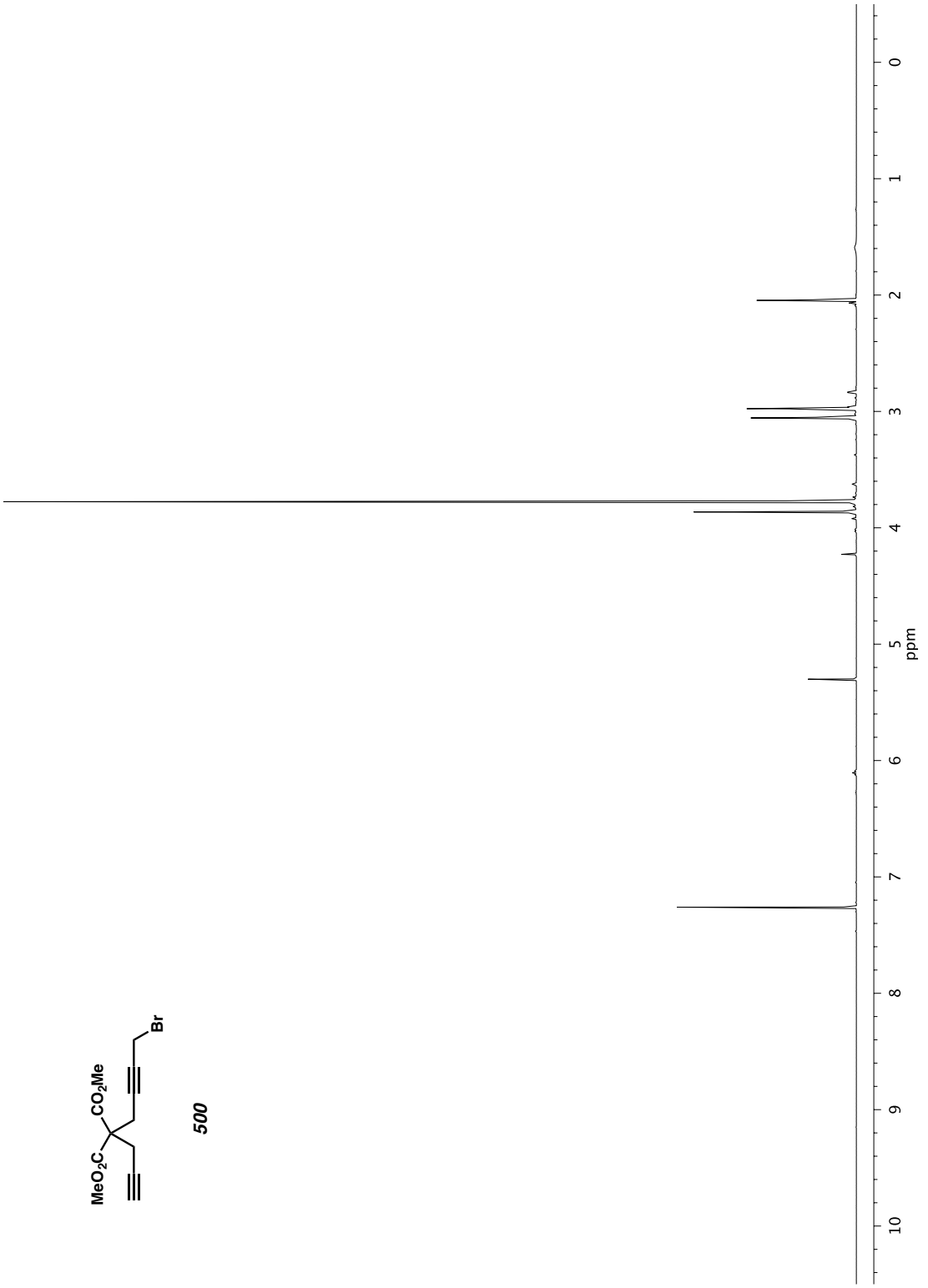


Figure A8.26 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **500**.

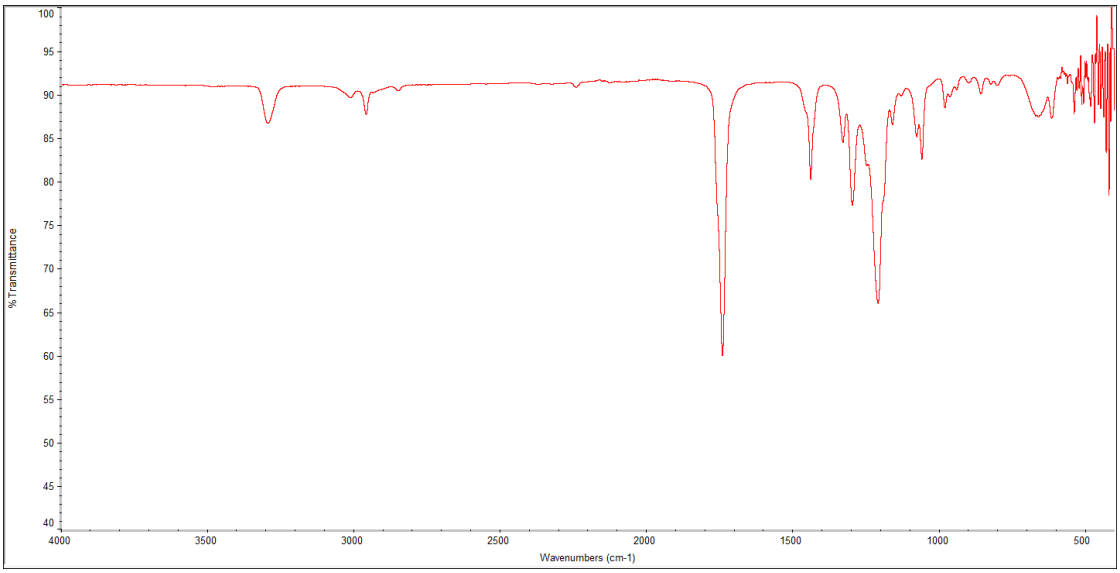


Figure A8.27 ATR-IR ($CDCl_3$ solution) of compound **500**.

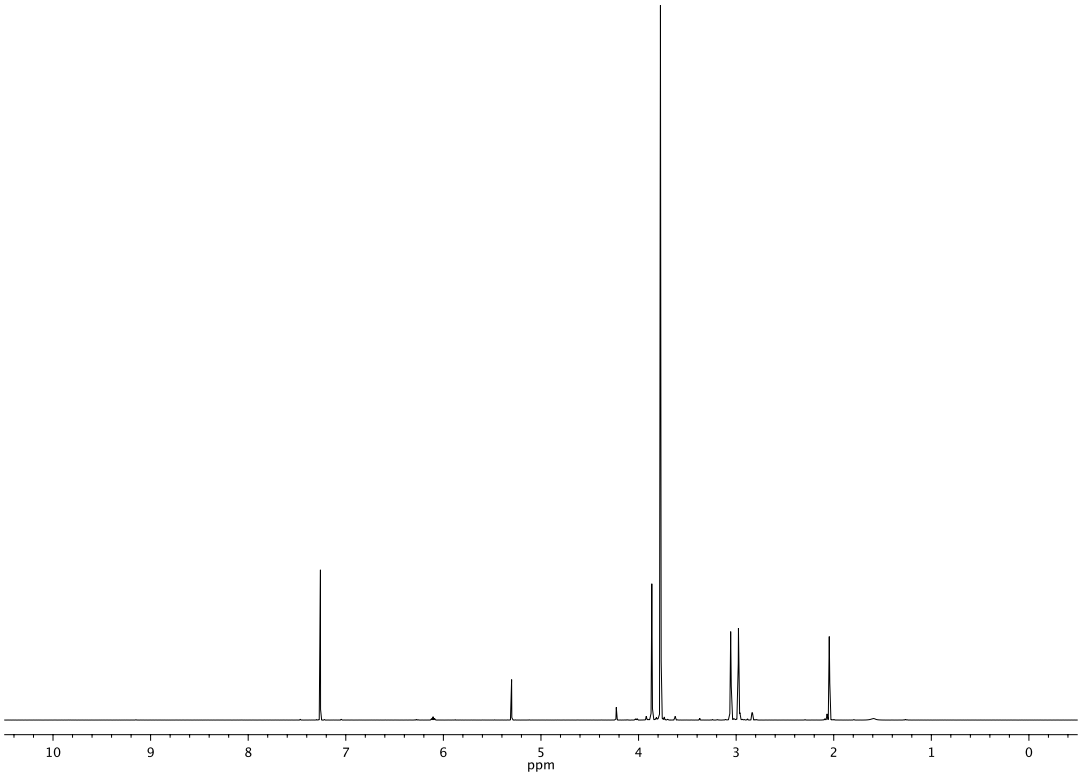


Figure A8.28 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **500**.

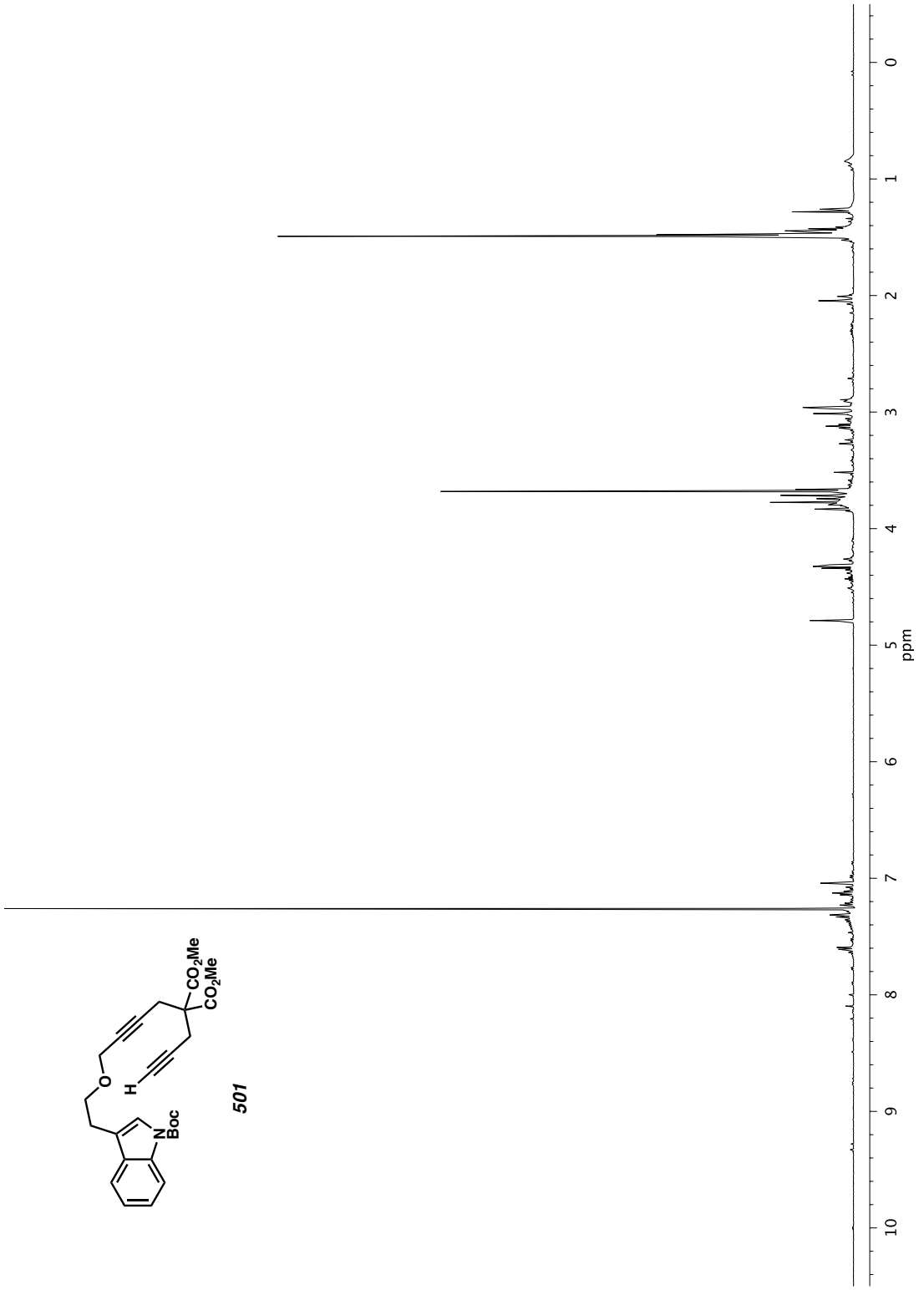


Figure A8.29 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **501**.

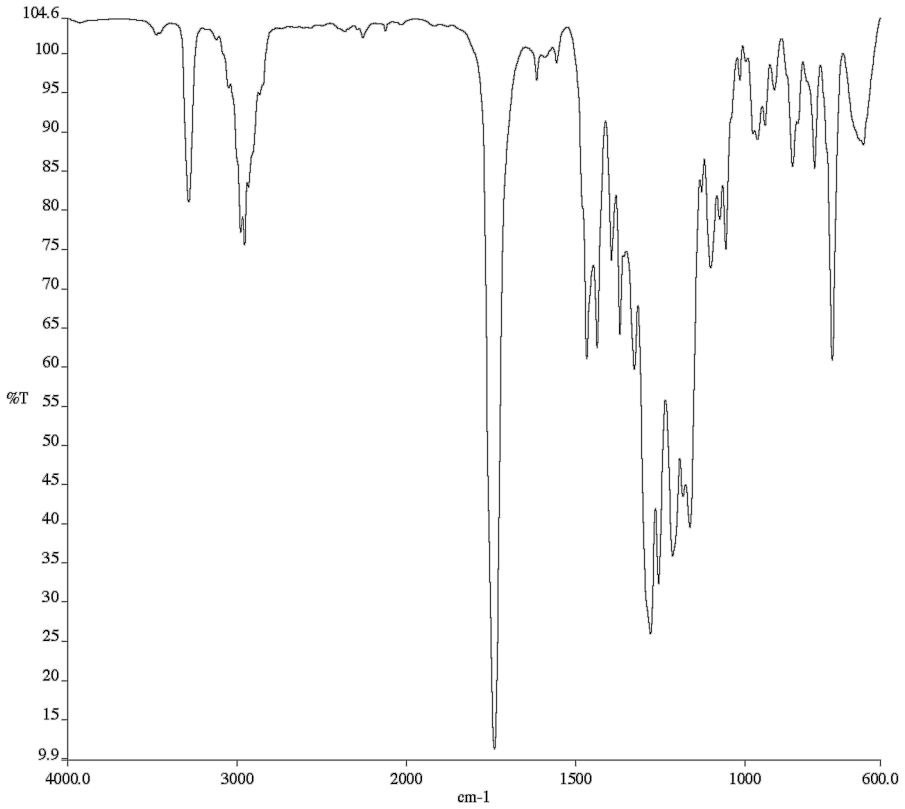


Figure A8.30 Infrared spectrum (thin film/NaCl) of compound **501**.

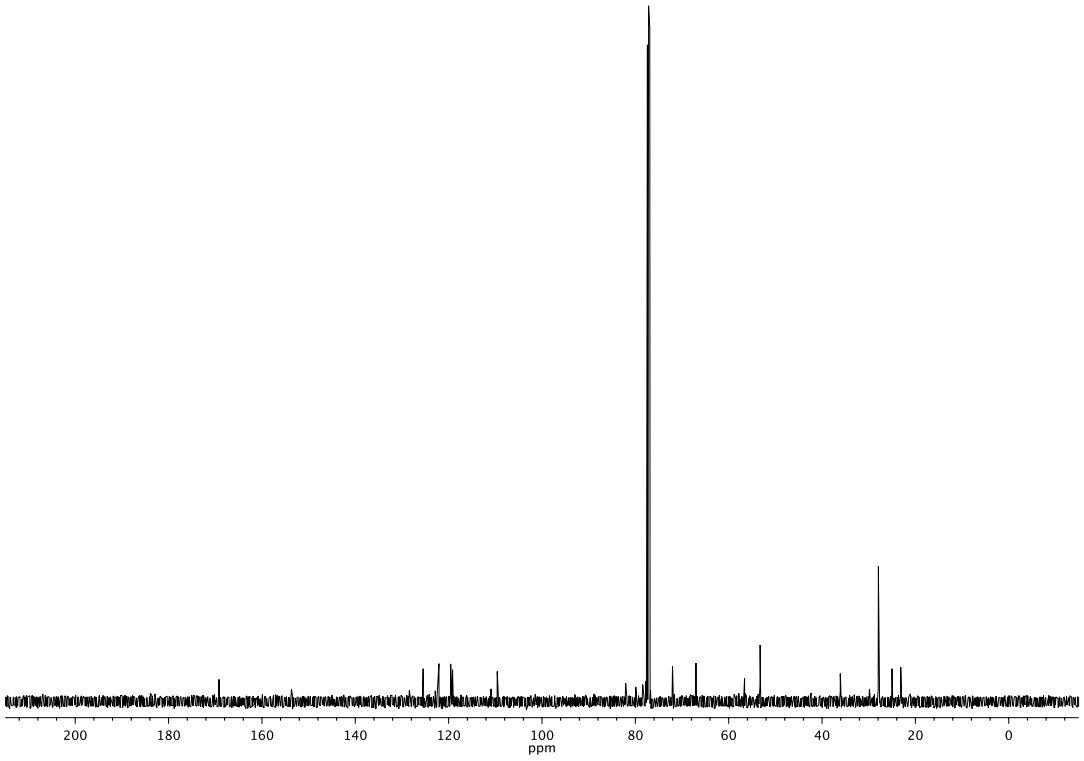


Figure A8.31 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **501**.

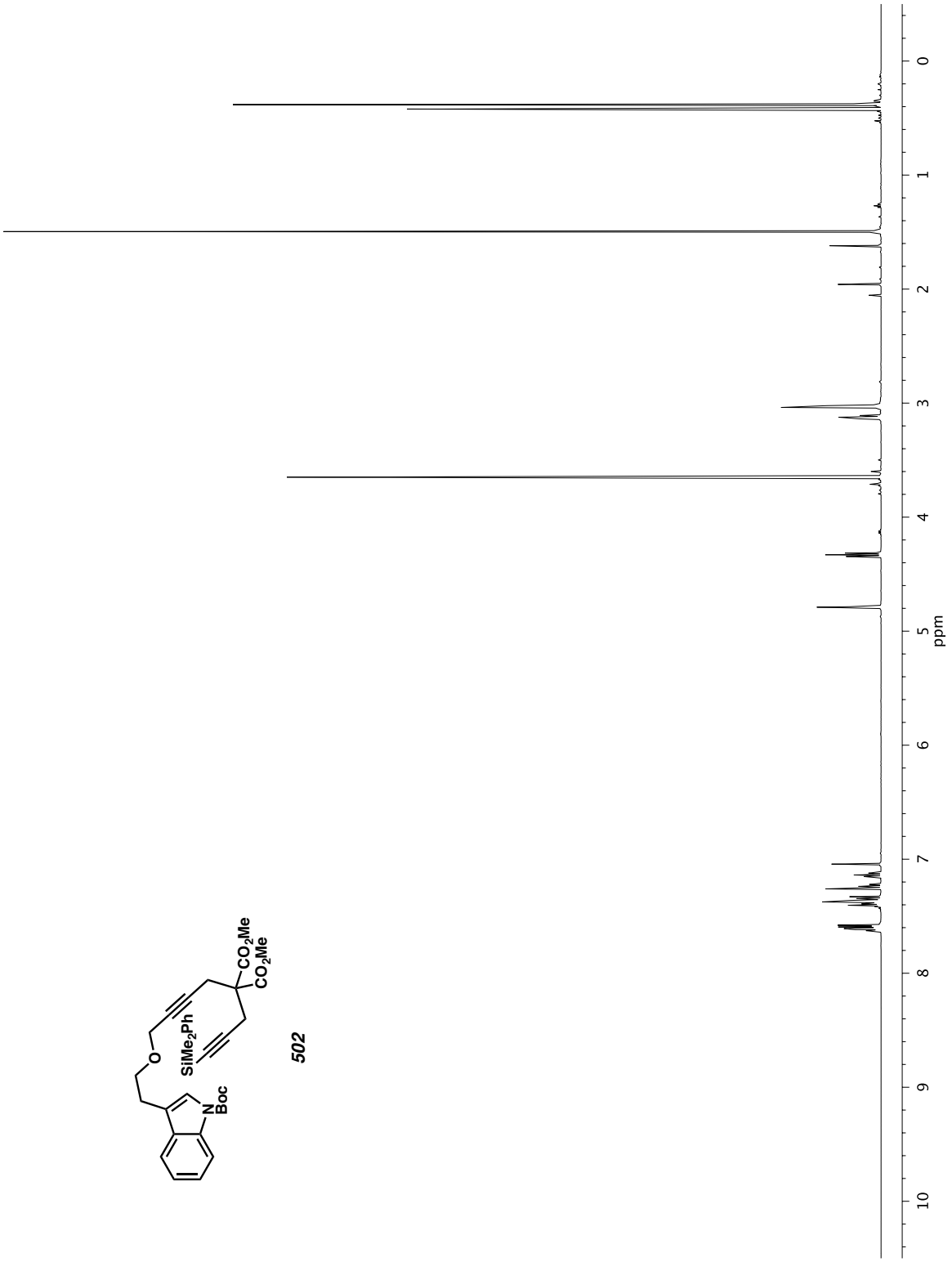


Figure A8.32 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **502**.

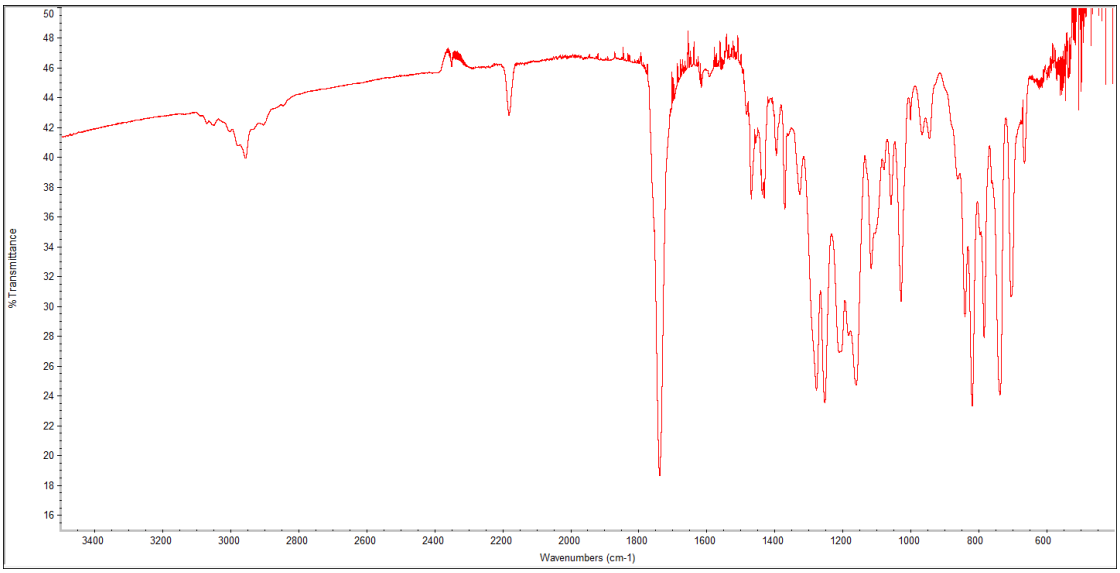


Figure A8.33 ATR-IR (C_6H_6 solution) of compound **502**.

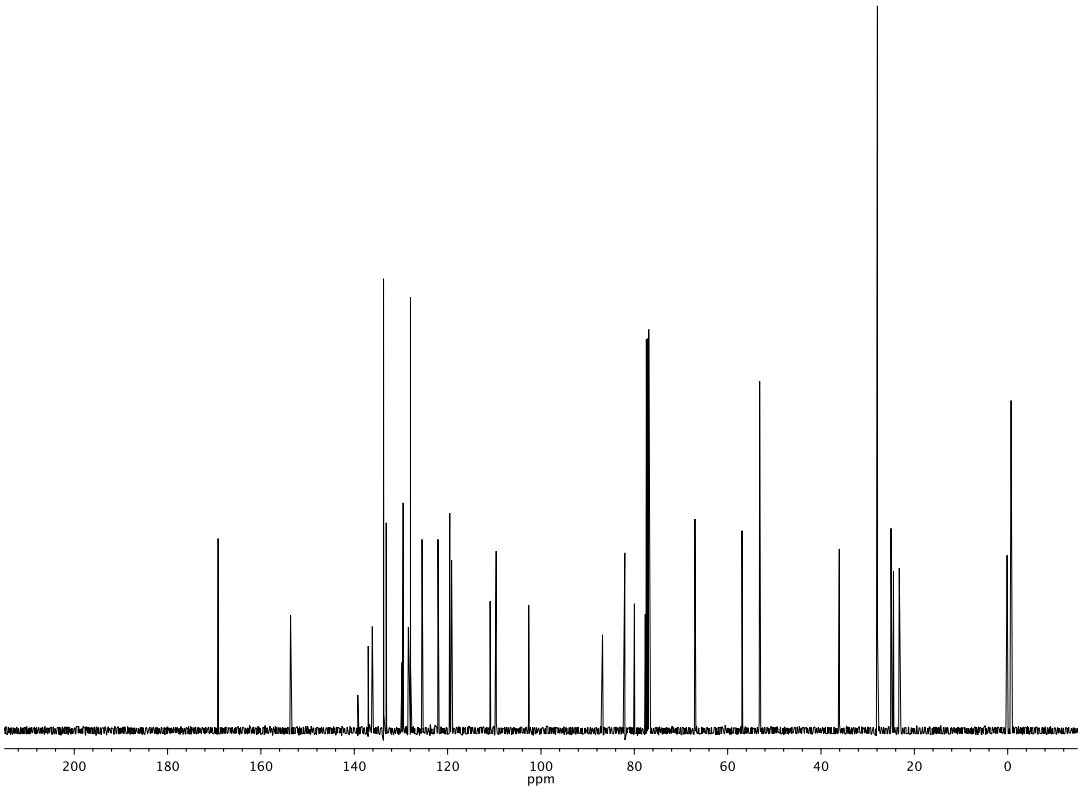


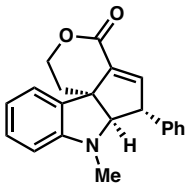
Figure A8.34 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **502**.

APPENDIX 9

X-Ray Crystallography Report Relevant to Chapter 4:

Progress Toward the Total Synthesis of Calophyline A

A9.1 X-RAY CRYSTAL STRUCTURE ANALYSIS OF TETRACYCLE 429



429

Contents

Figure A9.1.1 X-ray crystal structure of tetracycle ***429***

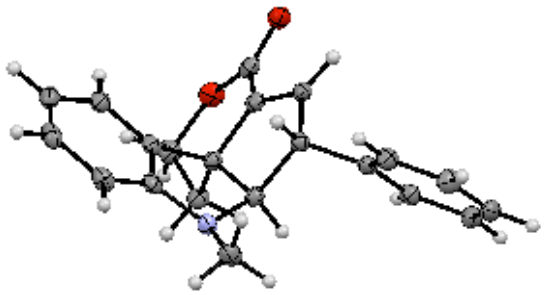


Table A9.1.1 Experimental details for X-ray structure determination of tetracycle ***429***

Low-temperature diffraction data (ϕ-and ω-scans) were collected on a Bruker AXS D8 VENTURE KAPPA diffractometer coupled to a PHOTON 100 CMOS detector with Cu K_α radiation (λ = 1.54178 Å) from an IμS micro-source for the structure of tetracycle **429**. The structure was solved by direct methods using SHELXS and refined against F^2 on all data by full-matrix least squares with SHELXL-2014 using established refinement techniques. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms they are linked to (1.5 times for methyl groups).

Tetracycle **429** crystallizes in the orthorhombic space group $P2_12_12_1$ with one molecule in the asymmetric unit.

Table A9.1.2 Crystal data and structure refinement for tetracycle ***429***

Identification code	P16006	
Empirical formula	C21 H19 N O2	
Formula weight	317.37	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 5.8176(2) Å	a= 90°.
	b = 9.2250(2) Å	b= 90°.
	c = 29.7053(8) Å	g = 90°.
Volume	1594.21(8) Å^3	
Z	4	

Density (calculated)	1.322 Mg/m^3
Absorption coefficient	0.673 mm^{-1}
F(000)	672
Crystal size	0.250 x 0.100 x 0.050 mm^3
Theta range for data collection	2.975 to 74.451°.
Index ranges	-6<=h<=7, -10<=k<=11, -37<=l<=36
Reflections collected	12810
Independent reflections	3243 [R(int) = 0.0250]
Completeness to theta = 67.679°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7538 and 0.6734
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3243 / 0 / 218
Goodness-of-fit on F^2	1.055
Final R indices [I>2sigma(I)]	R1 = 0.0258, wR2 = 0.0660
R indices (all data)	R1 = 0.0264, wR2 = 0.0665
Absolute structure parameter	-0.03(5)
Extinction coefficient	n/a
Largest diff. peak and hole	0.143 and -0.190 $e.Å^{-3}$

*Table A9.1.3 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for tetracycle **429**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U(eq)
O(1)	1980(2)	638(1)	7386(1)	25(1)
C(1)	1514(3)	358(2)	6952(1)	19(1)
O(2)	7(2)	-500(1)	6862(1)	24(1)
C(2)	2985(2)	1067(2)	6609(1)	18(1)
C(3)	3162(2)	650(2)	6180(1)	18(1)
C(4)	5049(2)	1452(2)	5935(1)	17(1)
C(5)	6455(3)	2135(2)	6334(1)	17(1)
C(15)	6456(2)	509(2)	5621(1)	18(1)
C(16)	7614(3)	-704(2)	5785(1)	20(1)
C(17)	8944(3)	-1561(2)	5500(1)	22(1)
C(18)	9105(3)	-1218(2)	5046(1)	24(1)
C(19)	7952(3)	-23(2)	4879(1)	25(1)
C(20)	6632(3)	840(2)	5164(1)	22(1)
C(6)	5386(3)	4518(2)	6388(1)	19(1)
N(1)	7201(2)	3621(1)	6264(1)	19(1)
C(21)	8635(3)	3957(2)	5880(1)	24(1)
C(7)	5021(3)	5957(2)	6267(1)	22(1)
C(8)	3088(3)	6656(2)	6444(1)	24(1)
C(9)	1569(3)	5948(2)	6727(1)	23(1)
C(10)	1937(3)	4492(2)	6842(1)	20(1)
C(11)	3845(3)	3786(2)	6671(1)	17(1)
C(12)	4709(2)	2228(2)	6729(1)	16(1)
C(13)	5642(3)	1910(2)	7202(1)	20(1)
C(14)	3647(3)	1736(2)	7525(1)	23(1)

*Table A9.1.4 Bond lengths [Å] and angles [°] for tetracycle **429***

O(1)-C(1)	1.3431(17)
O(1)-C(14)	1.463(2)
C(1)-O(2)	1.2107(19)
C(1)-C(2)	1.4819(19)
C(2)-C(3)	1.334(2)
C(2)-C(12)	1.510(2)
C(3)-C(4)	1.511(2)
C(3)-H(3)	0.9500
C(4)-C(15)	1.5160(19)
C(4)-C(5)	1.5721(19)
C(4)-H(4)	1.0000
C(5)-N(1)	1.4527(18)
C(5)-C(12)	1.5547(19)
C(5)-H(5)	1.0000
C(15)-C(16)	1.393(2)
C(15)-C(20)	1.396(2)
C(16)-C(17)	1.393(2)
C(16)-H(16)	0.9500
C(17)-C(18)	1.389(2)
C(17)-H(17)	0.9500
C(18)-C(19)	1.382(2)
C(18)-H(18)	0.9500
C(19)-C(20)	1.393(2)
C(19)-H(19)	0.9500
C(20)-H(20)	0.9500
C(6)-N(1)	1.391(2)
C(6)-C(7)	1.393(2)
C(6)-C(11)	1.402(2)
N(1)-C(21)	1.4477(18)
C(21)-H(21A)	0.9800
C(21)-H(21B)	0.9800
C(21)-H(21C)	0.9800
C(7)-C(8)	1.399(2)
C(7)-H(7)	0.9500

Table A9.1.4 (cont'd)

C(8)-C(9)	1.384(2)
C(8)-H(8)	0.9500
C(9)-C(10)	1.402(2)
C(9)-H(9)	0.9500
C(10)-C(11)	1.383(2)
C(10)-H(10)	0.9500
C(11)-C(12)	1.5325(19)
C(12)-C(13)	1.5336(18)
C(13)-C(14)	1.514(2)
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900
C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900

C(1)-O(1)-C(14)	122.64(11)
O(2)-C(1)-O(1)	118.93(13)
O(2)-C(1)-C(2)	123.73(13)
O(1)-C(1)-C(2)	117.25(13)
C(3)-C(2)-C(1)	124.96(14)
C(3)-C(2)-C(12)	112.28(12)
C(1)-C(2)-C(12)	122.26(12)
C(2)-C(3)-C(4)	112.02(12)
C(2)-C(3)-H(3)	124.0
C(4)-C(3)-H(3)	124.0
C(3)-C(4)-C(15)	114.05(12)
C(3)-C(4)-C(5)	102.18(11)
C(15)-C(4)-C(5)	114.37(12)
C(3)-C(4)-H(4)	108.6
C(15)-C(4)-H(4)	108.6
C(5)-C(4)-H(4)	108.6
N(1)-C(5)-C(12)	104.56(11)
N(1)-C(5)-C(4)	115.16(11)
C(12)-C(5)-C(4)	104.56(11)
N(1)-C(5)-H(5)	110.7

Table A9.1.4 (cont'd)

C(12)-C(5)-H(5)	110.7
C(4)-C(5)-H(5)	110.7
C(16)-C(15)-C(20)	118.68(13)
C(16)-C(15)-C(4)	120.51(12)
C(20)-C(15)-C(4)	120.81(13)
C(15)-C(16)-C(17)	120.80(13)
C(15)-C(16)-H(16)	119.6
C(17)-C(16)-H(16)	119.6
C(18)-C(17)-C(16)	119.93(14)
C(18)-C(17)-H(17)	120.0
C(16)-C(17)-H(17)	120.0
C(19)-C(18)-C(17)	119.74(14)
C(19)-C(18)-H(18)	120.1
C(17)-C(18)-H(18)	120.1
C(18)-C(19)-C(20)	120.41(14)
C(18)-C(19)-H(19)	119.8
C(20)-C(19)-H(19)	119.8
C(19)-C(20)-C(15)	120.43(14)
C(19)-C(20)-H(20)	119.8
C(15)-C(20)-H(20)	119.8
N(1)-C(6)-C(7)	127.91(14)
N(1)-C(6)-C(11)	110.96(13)
C(7)-C(6)-C(11)	121.13(14)
C(6)-N(1)-C(21)	121.26(13)
C(6)-N(1)-C(5)	107.25(12)
C(21)-N(1)-C(5)	119.16(12)
N(1)-C(21)-H(21A)	109.5
N(1)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
N(1)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5
C(6)-C(7)-C(8)	117.69(14)
C(6)-C(7)-H(7)	121.2

Table A9.1.4 (cont'd)

C(8)-C(7)-H(7)	121.2
C(9)-C(8)-C(7)	121.61(14)
C(9)-C(8)-H(8)	119.2
C(7)-C(8)-H(8)	119.2
C(8)-C(9)-C(10)	120.18(15)
C(8)-C(9)-H(9)	119.9
C(10)-C(9)-H(9)	119.9
C(11)-C(10)-C(9)	118.98(14)
C(11)-C(10)-H(10)	120.5
C(9)-C(10)-H(10)	120.5
C(10)-C(11)-C(6)	120.40(13)
C(10)-C(11)-C(12)	131.56(13)
C(6)-C(11)-C(12)	108.04(12)
C(2)-C(12)-C(11)	114.88(12)
C(2)-C(12)-C(13)	108.44(12)
C(11)-C(12)-C(13)	113.50(11)
C(2)-C(12)-C(5)	102.47(11)
C(11)-C(12)-C(5)	100.41(11)
C(13)-C(12)-C(5)	116.71(12)
C(14)-C(13)-C(12)	109.23(12)
C(14)-C(13)-H(13A)	109.8
C(12)-C(13)-H(13A)	109.8
C(14)-C(13)-H(13B)	109.8
C(12)-C(13)-H(13B)	109.8
H(13A)-C(13)-H(13B)	108.3
O(1)-C(14)-C(13)	113.70(12)
O(1)-C(14)-H(14A)	108.8
C(13)-C(14)-H(14A)	108.8
O(1)-C(14)-H(14B)	108.8
C(13)-C(14)-H(14B)	108.8
H(14A)-C(14)-H(14B)	107.7

Symmetry transformations used to generate equivalent atoms:

Table A9.1.5 Anisotropic displacement parameters ($Å^2x10^3$) for tetracycle ***429****. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$.*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	26(1)	29(1)	19(1)	3(1)	4(1)	-3(1)
C(1)	19(1)	17(1)	21(1)	2(1)	3(1)	4(1)
O(2)	22(1)	21(1)	29(1)	2(1)	5(1)	-1(1)
C(2)	16(1)	16(1)	21(1)	2(1)	1(1)	2(1)
C(3)	16(1)	17(1)	22(1)	0(1)	0(1)	1(1)
C(4)	17(1)	18(1)	16(1)	0(1)	0(1)	0(1)
C(5)	17(1)	19(1)	16(1)	-1(1)	1(1)	1(1)
C(15)	17(1)	19(1)	18(1)	-3(1)	1(1)	-3(1)
C(16)	22(1)	20(1)	18(1)	0(1)	0(1)	-2(1)
C(17)	21(1)	20(1)	26(1)	-2(1)	-1(1)	1(1)
C(18)	21(1)	29(1)	23(1)	-8(1)	3(1)	1(1)
C(19)	27(1)	32(1)	17(1)	-2(1)	2(1)	1(1)
C(20)	22(1)	25(1)	18(1)	0(1)	-1(1)	2(1)
C(6)	22(1)	21(1)	14(1)	-3(1)	-2(1)	-3(1)
N(1)	20(1)	19(1)	18(1)	-2(1)	3(1)	-3(1)
C(21)	24(1)	26(1)	21(1)	-1(1)	6(1)	-6(1)
C(7)	30(1)	19(1)	17(1)	1(1)	-1(1)	-5(1)
C(8)	36(1)	16(1)	21(1)	-1(1)	-6(1)	2(1)
C(9)	24(1)	22(1)	23(1)	-4(1)	-3(1)	4(1)
C(10)	21(1)	22(1)	17(1)	-1(1)	-2(1)	0(1)
C(11)	21(1)	18(1)	13(1)	-1(1)	-2(1)	-2(1)
C(12)	16(1)	18(1)	15(1)	-1(1)	1(1)	1(1)
C(13)	21(1)	24(1)	17(1)	1(1)	-1(1)	2(1)
C(14)	26(1)	26(1)	16(1)	1(1)	0(1)	1(1)

Table A9.1.6 Hydrogen coordinates ($x10^3$) and isotropic displacement parameters ($Å^2x10^3$) for tetracycle ***429***

	x	y	z	U(eq)
H(3)	2213	-66	6045	21
H(4)	4341	2254	5756	20
H(5)	7787	1503	6416	21
H(16)	7494	-949	6095	24
H(17)	9740	-2378	5616	27
H(18)	10005	-1803	4850	29
H(19)	8060	211	4568	30
H(20)	5846	1659	5046	26
H(21A)	7684	3999	5608	35
H(21B)	9807	3203	5845	35
H(21C)	9384	4896	5927	35
H(7)	6049	6448	6071	26
H(8)	2810	7641	6367	29
H(9)	274	6449	6844	28
H(10)	891	3998	7033	24
H(13A)	6570	1010	7197	25
H(13B)	6642	2716	7302	25
H(14A)	4257	1473	7825	28
H(14B)	2849	2679	7555	28

Table A9.1.7 Torsion angles [°] for tetracycle ***429***

C(14)-O(1)-C(1)-O(2)	-175.30(13)
C(14)-O(1)-C(1)-C(2)	8.0(2)
O(2)-C(1)-C(2)-C(3)	-14.2(2)
O(1)-C(1)-C(2)-C(3)	162.33(14)
O(2)-C(1)-C(2)-C(12)	174.58(14)
O(1)-C(1)-C(2)-C(12)	-8.9(2)
C(1)-C(2)-C(3)-C(4)	-171.71(13)
C(12)-C(2)-C(3)-C(4)	0.29(17)
C(2)-C(3)-C(4)-C(15)	139.24(13)
C(2)-C(3)-C(4)-C(5)	15.29(15)
C(3)-C(4)-C(5)-N(1)	-138.10(12)
C(15)-C(4)-C(5)-N(1)	98.16(14)
C(3)-C(4)-C(5)-C(12)	-23.96(13)
C(15)-C(4)-C(5)-C(12)	-147.70(11)
C(3)-C(4)-C(15)-C(16)	-57.99(18)
C(5)-C(4)-C(15)-C(16)	59.13(18)
C(3)-C(4)-C(15)-C(20)	122.41(15)
C(5)-C(4)-C(15)-C(20)	-120.48(14)
C(20)-C(15)-C(16)-C(17)	0.8(2)
C(4)-C(15)-C(16)-C(17)	-178.83(13)
C(15)-C(16)-C(17)-C(18)	-0.7(2)
C(16)-C(17)-C(18)-C(19)	0.3(2)
C(17)-C(18)-C(19)-C(20)	0.0(2)
C(18)-C(19)-C(20)-C(15)	0.0(2)
C(16)-C(15)-C(20)-C(19)	-0.4(2)
C(4)-C(15)-C(20)-C(19)	179.20(14)
C(7)-C(6)-N(1)-C(21)	-18.5(2)
C(11)-C(6)-N(1)-C(21)	161.92(12)
C(7)-C(6)-N(1)-C(5)	-160.28(14)
C(11)-C(6)-N(1)-C(5)	20.17(15)
C(12)-C(5)-N(1)-C(6)	-29.67(14)
C(4)-C(5)-N(1)-C(6)	84.47(14)
C(12)-C(5)-N(1)-C(21)	-172.36(12)
C(4)-C(5)-N(1)-C(21)	-58.22(18)

Table A9.1.7 (cont'd)

N(1)-C(6)-C(7)-C(8)	-178.36(14)
C(11)-C(6)-C(7)-C(8)	1.1(2)
C(6)-C(7)-C(8)-C(9)	-0.5(2)
C(7)-C(8)-C(9)-C(10)	-0.4(2)
C(8)-C(9)-C(10)-C(11)	0.7(2)
C(9)-C(10)-C(11)-C(6)	0.0(2)
C(9)-C(10)-C(11)-C(12)	-179.62(14)
N(1)-C(6)-C(11)-C(10)	178.68(12)
C(7)-C(6)-C(11)-C(10)	-0.9(2)
N(1)-C(6)-C(11)-C(12)	-1.64(15)
C(7)-C(6)-C(11)-C(12)	178.78(12)
C(3)-C(2)-C(12)-C(11)	91.92(15)
C(1)-C(2)-C(12)-C(11)	-95.83(15)
C(3)-C(2)-C(12)-C(13)	-139.91(13)
C(1)-C(2)-C(12)-C(13)	32.34(17)
C(3)-C(2)-C(12)-C(5)	-15.92(16)
C(1)-C(2)-C(12)-C(5)	156.32(12)
C(10)-C(11)-C(12)-C(2)	54.7(2)
C(6)-C(11)-C(12)-C(2)	-124.89(13)
C(10)-C(11)-C(12)-C(13)	-70.84(19)
C(6)-C(11)-C(12)-C(13)	109.53(13)
C(10)-C(11)-C(12)-C(5)	163.84(15)
C(6)-C(11)-C(12)-C(5)	-15.79(13)
N(1)-C(5)-C(12)-C(2)	145.53(11)
C(4)-C(5)-C(12)-C(2)	24.11(14)
N(1)-C(5)-C(12)-C(11)	26.93(13)
C(4)-C(5)-C(12)-C(11)	-94.49(12)
N(1)-C(5)-C(12)-C(13)	-96.18(14)
C(4)-C(5)-C(12)-C(13)	142.40(12)
C(2)-C(12)-C(13)-C(14)	-53.11(16)
C(11)-C(12)-C(13)-C(14)	75.84(16)
C(5)-C(12)-C(13)-C(14)	-168.10(12)
C(1)-O(1)-C(14)-C(13)	-32.47(19)
C(12)-C(13)-C(14)-O(1)	55.15(17)

Table A9.1.7 (cont'd)

Symmetry transformations used to generate equivalent atoms:

CHAPTER 5[†]

Palladium(II)-Catalyzed Allylic C–H Oxidation of Hindered Substrates Featuring Tunable Selectivity Over Extent of Oxidation

5.1 INTRODUCTION

Recent developments in C–H functionalization have made major contributions to organic chemistry and are beginning to change the way chemists approach synthetic transformations.[1] Allylic C–H acetoxylation[2,3] and other functionalizations[4] of terminal olefins have received considerable attention over the past decade as allyl groups are versatile and widespread in synthetic organic chemistry. After the seminal report by White and co-workers of palladium-catalyzed allylic acetoxylation,[3a] numerous research groups have developed alternative conditions for this transformation, mainly differing in the identity of the terminal oxidant.[3]

Complementing reports of the two-electron oxidation of allyl groups to allylic acetates, the four-electron oxidation of allyl groups to enones or enals has also been

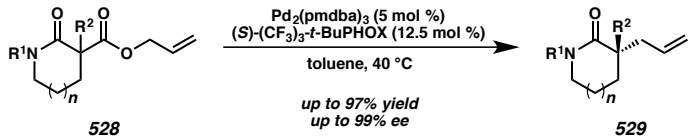
[†] This work was performed in collaboration with Dr. Xiangyou Xing, alumnus of the Stoltz group. This work has been published, with portions of this chapter adapted with permission from Xing, X.; O'Connor, N. R.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 11186–11190.

described. While the oxidation of olefins, particularly cycloalkenes, to enones is well precedented,[5] few examples exist of the transformation of allyl groups to enals.[6,7] Of these limited cases, most produce the enals in low yield and with poor selectivity over other oxidation products, and/or require activated allylic C–H bonds (*i.e.* allylbenzenes). None of these methods are reported to be effective on complex or sterically hindered substrates.

5.1.1 ENANTIOSELECTIVE SYNTHESIS OF QUATERNARY α-ALLYL LACTAMS AND ATTEMPTED ALLYLIC FUNCTIONALIZATION

Our research group has had a longstanding interest in the asymmetric synthesis of α-quaternary carbonyl compounds via catalytic decarboxylative enantioselective allylic alkylation.[8,9] In 2012 we reported the construction of quaternary α-allyl lactams (**529**) in excellent yield and *ee* using this strategy (Scheme 5.1).[8c]

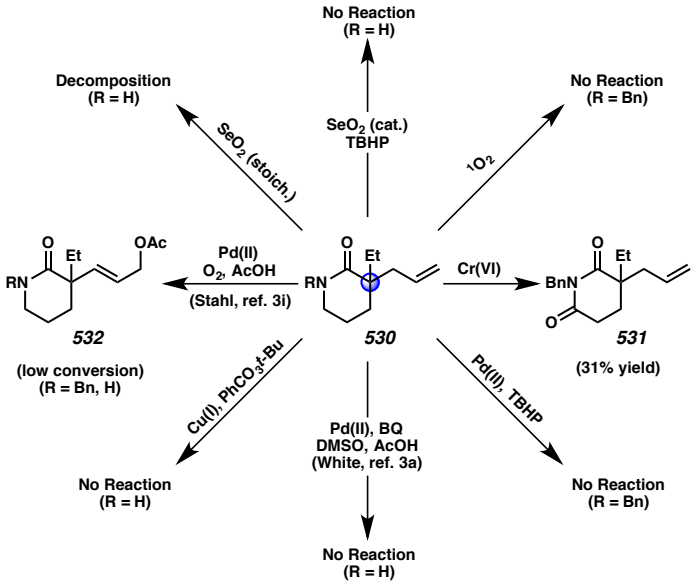
Scheme 5.1 Enantioselective synthesis of α-quaternary lactams by palladium-catalyzed decarboxylative allylic alkylation



Given our interest in C–H activation,[10] the utility of allyl groups as functional handles, and the known status of allylic C–H bonds as a privileged motif in the C–H activation literature, we investigated the use of several reported procedures for the C–H functionalization of our lactam products (Scheme 5.2).[11] Interestingly, use of classical conditions for allylic oxidation[12] such as selenium dioxide,[13] singlet oxygen, and

Kharasch–Sosnovsky conditions[14] resulted in either decomposition or no reaction. Use of a palladium(II) catalyst with *tert*-butylhydroperoxide also resulted in no reaction.[15] Oxidation with chromium trioxide unexpectedly gave imide **531** in low yield.[16] The conditions recently developed by White and co-workers (Pd(II), benzoquinone, DMSO, acetic acid)[3a] showed no reactivity, and those reported by Stahl and co-workers (Pd(II), oxygen, acetic acid)[3i] only produced the desired allylic acetates in low yields, leaving most of the starting materials unreacted.

*Scheme 5.2 Investigation into the allylic oxidation of lactam **530***



5.2 DEVELOPMENT OF A NOVEL PALLADIUM(II)-CATALYZED ALLYLIC ACETOXYLATION REACTION

We attribute the absence of the desired reactivity to the sterically demanding quaternary center at the homoallylic position. This hypothesis is corroborated by the paucity of examples of such sterically encumbered allylic oxidations in the methods

literature. Realizing the amide functional group could act as an internal ligating group, we chose to develop conditions for the substrate-directed palladium-catalyzed allylic C–H acetoxylation of these molecules. We hoped that the use of a directing group, largely unknown in allylic C–H oxygenation reactions,[17] would enable reactivity even in the most sterically hindered and challenging substrates.

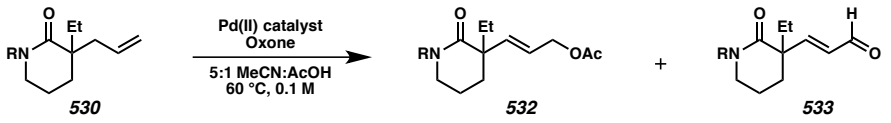
5.2.1 OPTIMIZATION OF THE ALLYLIC ACETOXYLATION

We began our studies by screening various palladium(II) catalysts, oxidants, and solvents in the allylic acetoxylation of an *N*-benzoyl lactam (Scheme 5.3, entry 1), accessable via our allylic alkylation chemistry.[8c] Gratifyingly, exposure of the substrate to palladium(II) acetate and Oxone in a mixture of acetonitrile and acetic acid produced trace amounts of allylic acetate **532** and enal **533**. We were pleased to find that Oxone was superior to other oxidants examined, as it is readily available, inexpensive, stable, relatively non-toxic, and environmentally safe.[18] To our knowledge, this is the first report of Oxone as an oxidant for an allylic C–H functionalization reaction.

Although the benzoyl-protected lactam was poorly reactive under our conditions, use of the free *N–H* lactam resulted in moderate conversion to a separable mixture of allylic acetate **532** and enal **533** products (Scheme 5.3, entry 2). Further optimization revealed *N*-benzyl lactams to be superior to the free lactams, giving full conversion within a matter of hours (entries 3–6). Subsequent experiments showed that the addition of acetic anhydride and molecular sieves was necessary to obtain the allylic acetate product in good yield. An examination of other palladium(II) precursors (entries 4–6) led us to select palladium(II) hexafluoroacetylacetonate, as it resulted in the shortest reaction time

while maintaining a good ratio of the desired allylic acetate (**532**) to the undesired enal (**533**, entry 6). With all substrates, we found that acetonitrile was necessary as a solvent, as its omission led to a significant decrease in reactivity. In all cases, we observed little or no formation of the methyl ketone or aldehyde products expected from Wacker–Tsuji reactivity.

Scheme 5.3 Optimization of the allylic acetoxylation



Entry	*R*	*Catalyst (mol %)*	*Oxone Equiv*	*Time (h)*	*Conversion (%)*[a]	*Yield (%)*[b]	*Products (532:533)*[c]
1	Bz	$Pd(OAc)_2$ (5.0)	1.5	96	31	trace	6:1
2	H	$Pd(OAc)_2$ (5.0)	1.5	3	100	41	8:1
3[d]	Bn	$Pd(OAc)_2$ (7.5)	2.5	10	100	62	8:1
4[d]	Bn	$Pd(TFA)_2$ (7.5)	2.5	10	100	62	9:1
5[d]	Bn	$Pd(acac)_2$ (7.5)	2.5	10	90	55	7:1
6[d]	Bn	$Pd(hfacac)_2$ (7.5)	2.5	4	100	65	8:1

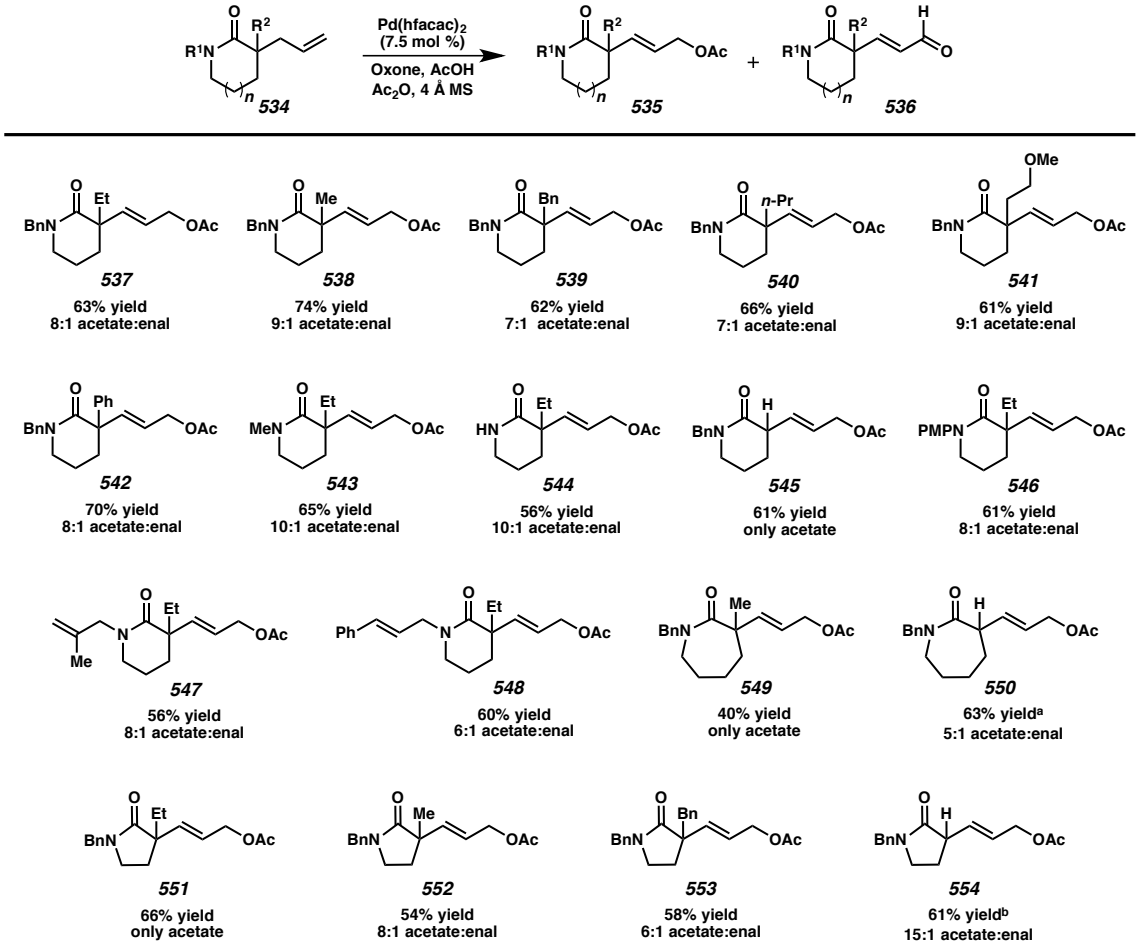
Conditions: lactam *530* (0.10 mmol), catalyst (0.05 or 0.075 equiv; see table), Oxone (1.5 or 2.5 equiv; see table), MeCN (714 μL), and AcOH (286 μL) at 60 °C for 96 h or until full conversion by TLC. [a] Conversion was determined from the yield of the isolated recovered starting material. [b] Yield is that of isolated combined producs *532* and *533*. [c] Ratio determined by ^{1}H NMR analysis of the crude reaction mixture. [d] A solvent mixture of 5:1:1 MeCN/AcOH/Ac_2O was used, and 4Å MS (80 mg) were added.

5.2.2 SUBSTRATE SCOPE OF THE ALLYLIC ACETOXYLATION

With the optimized conditions in hand, we investigated the substrate scope of the reaction. We quickly found that the lactam nature of the substrate was critical to achieving good reactivity. Interestingly, cyclic compounds lacking an amide functional group gave only low conversion under our conditions, as did a wide variety of linear amides investigated (see Appendix 10). The scope of allylic acetoxylation of lactam substrates is shown in Scheme 5.4. Substrates incorporating alkyl groups at the α-position were well tolerated, furnishing the corresponding allylic acetates (**537, 538, 540, 541**) in

good yields and selectivities. Substrates with benzyl (**539**) or aryl (**542**) groups at the α-position were also competent.[19] The identity of the amide substituent is not limited to a benzyl group, and replacement with alkyl or aryl groups (**543** and **546**), or even olefin-containing groups (**547** and **548**) did not reduce the yield or selectivity.[19] The free *N–H* lactam was also a successful substrate (**544**). A quaternary stereocenter was not found to be necessary, as an α-tertiary lactam underwent acetoxylation in good yield and exclusive selectivity over enal formation (**545**). Finally, substrates derived from caprolactam (**549, 550**) and butyrolactam (**551–554**), readily accessed via our decarboxylative allylic alkylation chemistry, also reacted smoothly.[20]

Scheme 5.4 Substrate scope of the allylic acetoxylation



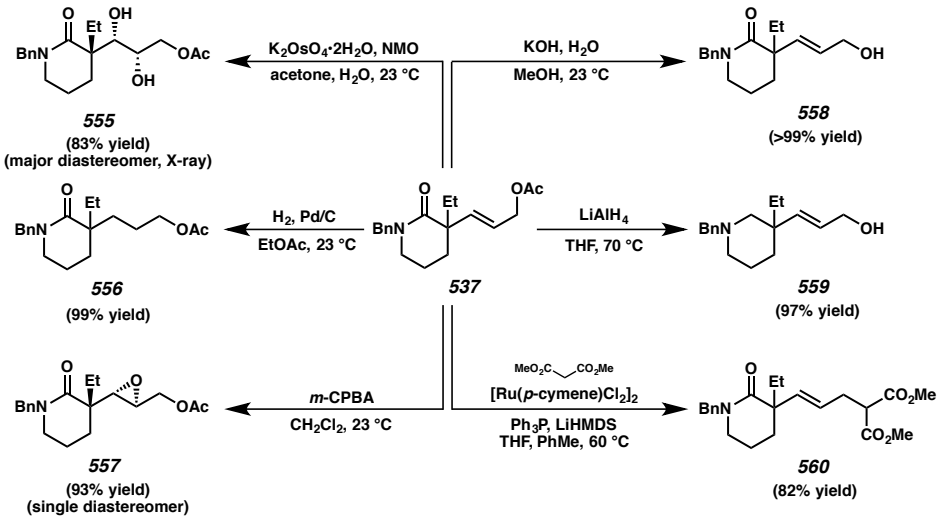
Conditions: lactam *534* (0.2 mmol), $Pd(hfacac)_2$ (0.075 equiv), Oxone (2.5 equiv), MeCN (1.43 mL), $AcOH/Ac_2O$ (1:1, 750 μL), and 4Å MS (160 mg) at 60 °C for 3–6 h. Yields are combined of the isolated separable acetate and enal products. [a] Reaction time = 24 h. [b] Reaction time = 11 h.

5.2.3 SYNTHETIC UTILITY OF ALLYLIC ACETATES

The synthetic utility of allylic acetates is well known in the literature, and using standard conditions we were able to further derivatize products as sterically hindered as **537** (Scheme 5.5). Osmium-catalyzed dihydroxylation provided diol **555** in good yield and diastereoselectivity.[21] Hydrogenation of the olefin proceeded smoothly, giving aliphatic acetate **556** in excellent yield. Epoxidation was also facile, furnishing the product (**557**) as a single diastereomer in excellent yield.[22] Hydrolysis of the acetate to

reveal allylic alcohol **558** as well as global reduction of the amide and ester functionalities to afford amine **559** were also successful. Finally, realizing the synthetic utility of allylic acetates in transition-metal-catalyzed allylic substitution reactions, we were pleased to find that ruthenium-mediated substitution with dimethyl malonate produced malonate **560** in good yield.[23]

Scheme 5.5 Synthetic utility of an allylic acetate product



5.3 DEVELOPMENT OF THE ALLYLIC OXIDATION REACTION TO FORM ENAL PRODUCTS

5.3.1 OPTIMIZATION OF THE ENAL FORMATION

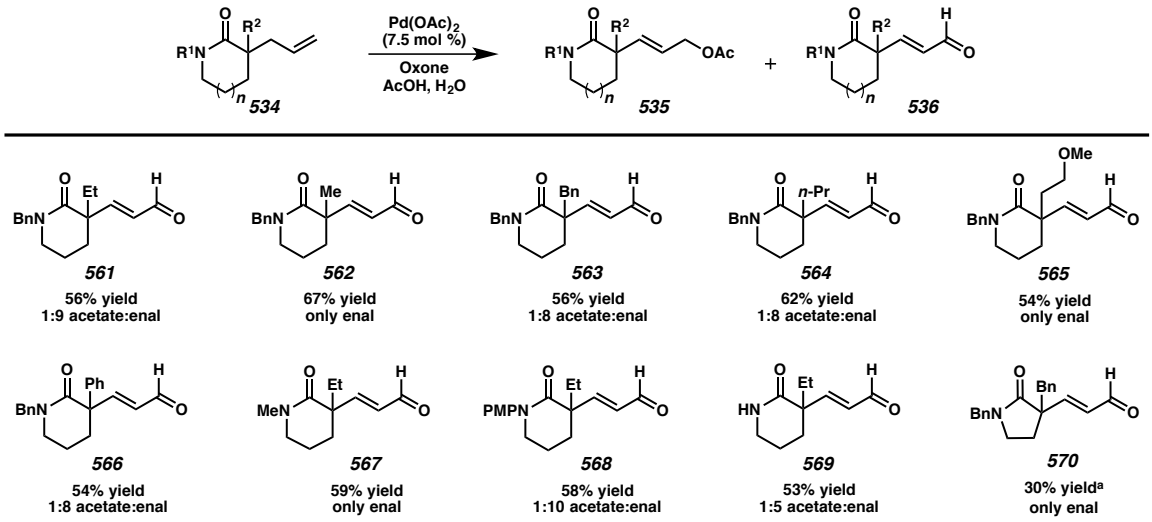
After exploring the scope of the acetoxylation reaction, we were intrigued about the possibility of optimizing for the enal product seen in small amounts in most acetoxylations. During early optimization studies of the allylic acetoxylation reaction, we observed that the omission of molecular sieves or acetic anhydride resulted in a higher

degree of enal formation. Using this as a starting point, we identified optimal conditions for enal formation (Scheme 5.6). Remarkably, only simple changes to the reaction conditions allow for a significant change in the product ratio, allowing for facile control of the degree of oxidation. Essentially, only the presence or absence of water controls switch between a two-electron oxidation of the allyl group to the allylic acetate (i.e. **534→535**) and a four-electron oxidation of the allyl group to the enal (i.e. **534→536**). While palladium(II) hexafluoroacetylacetonate is an effective catalyst for oxidation to the enal, we opted to use the cheaper and more widely available palladium(II) acetate, as the results were similar. We found the presence of small amounts of water to be necessary to achieve high conversion, and the presence of acetic acid aided in suppressing formation of the methyl ketone (*i.e.* standard Wacker–Tsuji oxidation).[24]

5.3.2 SUBSTRATE SCOPE OF THE ENAL FORMATION

The scope of the enal formation is shown in Scheme 5.6. We found that *N*-benzyl valerolactams with a variety of alkyl groups at the α-position were well tolerated, furnishing the enal products (**561, 562, 564, 565**) in good yields and selectivities over the allylic acetates. Substrates with α-benzyl and α-phenyl substituents were also successfully oxidized to enals **563** and **566**, respectively. As with the allylic acetoxylation reaction, we found that the benzyl-protected nitrogen was not critical, and that the *N*-methyl, *N*-aryl, and *N–H* substrates were also suitable (**567**, **568**, and **569**). Unfortunately, lactams of other ring sizes showed low conversion (**570**), and α-tertiary substrates gave predominately the methyl ketone product of a Wacker–Tsuji oxidation (not shown).

Scheme 5.6 Substrate scope of the enal formation

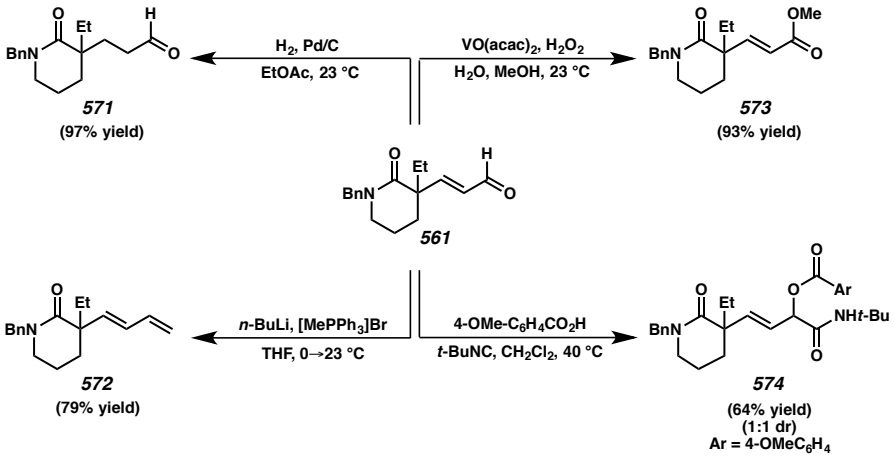


Conditions: lactam *534* (0.2 mmol), $Pd(OAc)_2$ (0.075 equiv), Oxone (2.5 equiv), AcOH (16.0 equiv), H_2O (8.0 equiv), and MeCN (1.82 mL) at 50 °C for 1–2 h. Yields are combined of the isolated separable acetate and enal products. [a] Starting material not fully consumed.

5.3.3 SYNTHETIC UTILITY OF AN ENAL PRODUCT

Similar to allylic acetates, enals are useful synthetic intermediates, and we were able to subject enal **561** to a variety of transformations (Scheme 5.7). Reduction to the aliphatic aldehyde (**571**) by hydrogenation was facile, as was a one-carbon homologation to diene **572** under Wittig conditions. We also found that the enal could be oxidized directly to the methyl ester (**573**) in excellent yield using a protocol developed by Thakur and coworkers.[25] Finally, a Passerini multicomponent coupling with *t*-butyl isocyanide and *p*-anisic acid provided adduct **574** in good yield, albeit as a mixture of diastereomers.[26]

Scheme 5.7 Synthetic utility of an enal product



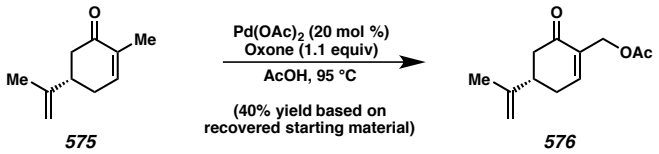
5.4 CONCLUSIONS AND FUTURE DIRECTIONS

In summary, we have reported a novel protocol for palladium-catalyzed allylic C–H oxidation using inexpensive, non-toxic, and safe Oxone as the terminal oxidant. This method is far more tolerant of steric bulk than previously known examples, possibly as a result of substrate-directed reactivity. Furthermore, we have discovered that a minor change in conditions allows for access to either the allylic acetate products of a two-electron oxidation or the enal products of a four-electron oxidation. This reactivity switch demonstrates an unusual ability to selectively achieve different increases in oxidation state by a single palladium-catalyzed system. The synthetic utility of the products resulting from these new C–H functionalization methods has been demonstrated by conversion of the prototypical products to a range of functionalized heterocycles.

Although the allylic oxidation chemistry reported herein has certain scope limitations, the complete applicability of these new conditions for C–H functionalization is not yet fully realized. For example, exposure of (S)-carvone (**575**) to similar reaction conditions

resulted in selective allylic acetoxylation in moderate yield (Scheme 5.8). Future directions may include further exploration of this reactivity.

Scheme 5.8 Selective allylic acetoxylation of carvone



575 *576*

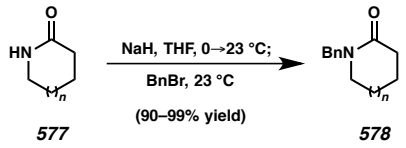
5.5 EXPERIMENTAL SECTION

5.5.1 MATERIALS AND METHODS

Unless noted in the specific procedure, reactions were performed in non-dry glassware under an air atmosphere. Dried and deoxygated solvents (Fisher Scientific) were prepared by passage through columns of activated aluminum before use.[27] Anhydrous carbon tetrachloride was purchased from Sigma Aldrich and used as received. Methanol (Fisher Scientific) was distilled from magnesium methoxide immediately prior to use. Commercial reagents (Sigma Aldrich or Alfa Aesar) were used as received with the exception of δ-valerolactam (Oakwood Chemical), dichloro(*p*-cymene)ruthenium(II) dimer (Strem Chemicals), triphenylphosphine (Sigma Aldrich) , lithium hexamethyldisilazide (Sigma Aldrich), zinc(II) chloride (Sigma Aldrich), and lithium tri-*tert*-butoxyaluminum hydride (Sigma Aldrich) which were stored in a nitrogen-filled govebox. Diisopropylamine (Oakwood Chemical) and trimethylsilyl chloride (Alfa Aesar) were distilled from calcium hydride immediately prior to use. The acetic acid (J. T. Baker) and acetic anhydride (Sigma Aldrich) used in the allylic acetoxylation reactions were stored in a 1:1 mixture over activated 4 Å MS. Brine is

defined as a saturated aqueous solution of sodium chloride. Reactions requiring external heat were modulated to the specified temperatures using an IKAmag temperature controller. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-LCMS. TLC was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 spectrometer (500 MHz and 126 MHz, respectively) or a Bruker AV III HD spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe (400 MHz and 101 MHz, respectively), and are reported in terms of chemical shift relative to residual $CHCl_3$ (δ 7.26 and δ 77.16 ppm, respectively). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Abbreviations are used as follows: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = complex multiplet. Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer using thin film samples on NaCl plates, 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 with fast atom bombardment (FAB+) ionization mode or were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+) mode. Melting points were measured with a BÜCHI Melting Point B-545 apparatus.

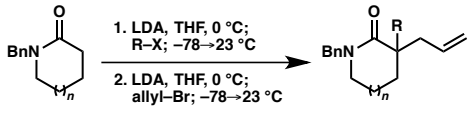
5.5.2 GENERAL EXPERIMENTAL PROCEDURES



577 ***578***

General Procedure A. *Benzyl protection of lactams.*

To a flame-dried round-bottom flask with a magnetic stir bar were added sodium hydride (60% dispersion in mineral oil, 56.5 mmol, 1.13 equiv) and THF (16 mL). The flask was capped with a rubber septum, put under a nitrogen atmosphere, and cooled to 0 °C using an ice water bath. A solution of lactam ***577*** (50.0 mmol, 1.00 equiv) in THF (75 mL) was added rapidly dropwise by syringe, and the resulting mixture was allowed to warm to 23 °C and stir for 2 hours. Benzyl bromide (53.5 mmol, 1.07 equiv) was added dropwise by syringe, and the mixture stirred for another 2 hours. Upon completion (as determined by TLC analysis), the suspension was diluted with water (300 mL) and extracted with ethyl acetate (3 x 300 mL). The combined organic layers were washed with brine (1 x 300 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography, using mixture of hexanes and ethyl acetate as eluent. The products were obtained in 90–99% yield.



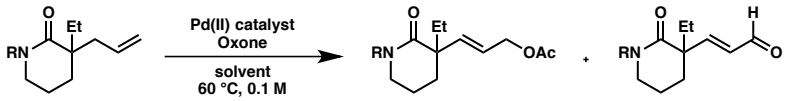
578 ***579***

General Procedure B. *Installation of the α-substituents.*

To a flame-dried round-bottom flask with a magnetic stir bar were added diisopropylamine (25.4 mmol, 1.2 equiv) and THF (13 mL) by syringe. The solution was stirred under nitrogen and cooled to 0 °C using an ice water bath. *n*-Butyllithium (2.5 M in hexane, 25.1 mmol, 1.19 equiv) was added rapidly dropwise by syringe, and the solution was allowed to stir at 0 °C for 20 minutes. Meanwhile, lactam **578** (21.1 mmol, 1.00 equiv) was dissolved in THF (200 mL) in a flame-dried round-bottom flask under nitrogen and cooled to 0 °C using an ice water bath. The freshly prepared LDA solution was transferred to the lactam solution rapidly dropwise via syringe, and the mixture was allowed to stir at 0 °C for 45 minutes. The solution was then cooled to –78 °C using a dry ice and acetone bath, and the appropriate alkyl halide (27.5 mmol, 1.30 equiv) was added dropwise by syringe. The flask was placed in an ice water bath and allowed to gradually warm to 23 °C overnight. Upon completion (as determined by TLC analysis), the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution (400 mL), and the aqueous layer extracted with chloroform (3 x 300 mL). The combined organic layers were washed with brine (1 x 300 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using mixtures of hexanes and ethyl acetate as eluent.

To a flame-dried round-bottom flask with a magnetic stir bar were added diisopropylamine (29.3 mmol, 1.50 equiv) and THF (15 mL) by syringe. The solution was stirred under nitrogen and cooled to 0 °C using an ice water bath. *n*-Butyllithium (2.5 M in hexane, 29.1 mmol, 1.49 equiv) was added rapidly dropwise by syringe, and the solution was allowed to stir at 0 °C for 20 minutes. Meanwhile, the mono-alkylated intermediate lactam (19.5 mmol, 1.00 equiv) was dissolved in THF (61 mL) in a flame-

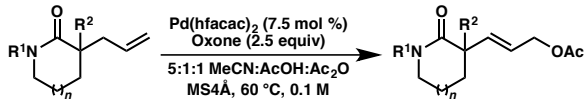
dried round-bottom flask under nitrogen and cooled to 0 °C using an ice water bath. The freshly prepared LDA solution was transferred to the lactam solution rapidly dropwise via syringe, and the mixture was allowed to stir at 0 °C for 45 minutes. The solution was then cooled to –78 °C using a dry ice and acetone bath, and allyl bromide (117.0 mmol, 6.00 equiv) was added dropwise by syringe. The flask was placed in an ice water bath and allowed to gradually warm to 23 °C overnight. Upon completion (as determined by TLC analysis), the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution (300 mL), and the aqueous layer extracted with chloroform (3 x 200 mL). The combined organic layers were washed with brine (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using mixtures of hexanes and ethyl acetate as eluent. The products were obtained in 8–40% yield over two steps.



General Procedure C. *Optimization of the allylic acetoxylation reaction.*

To a flame-dried 25 mL round-bottom flask with a magnetic stir bar were added, in order, the appropriate lactam **530** (0.10 mmol, 1.00 equiv), the appropriate palladium(II) catalyst (0.075 mmol or 0.05 mmol, 0.075 equiv or 0.05 equiv), Oxone (0.15 mmol or 0.25 mmol, 1.50 equiv or 2.50 equiv), and (if indicated) hot, activated 4 Å molecular sieves (80 mg). The flask was then capped with a rubber septum and evacuated and backfilled twice with nitrogen. The appropriate solvent mixture (total volume 1 mL, 5:2 acetonitrile:acetic acid or 5:1:1 acetonitrile:acetic acid:acetic anhydride) was added by

syringe. The resulting suspension was stirred under nitrogen for 5 minutes at 23 °C and then heated to 60 °C in an oil bath. Upon completion (as determined by TLC analysis), the flask was allowed to cool to 23 °C and the contents were filtered through a short plug of silica gel, rinsing with ethyl acetate. The filtrate was adsorbed onto silica gel (approx. 1 g), which was then flushed with ethyl acetate. The eluent was concentrated to give the crude product as an oil. After NMR analysis to determine the acetate:enal ratio, the crude residue was purified by silica gel column chromatography, using mixtures of hexanes and ethyl acetate as eluent.

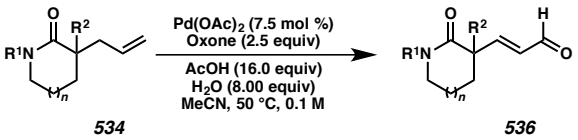


534 ***535***

General Procedure D. *Allylic acetoxylation of α-allyl lactams.*

To a flame-dried 25 mL round-bottom flask with a magnetic stir bar were added, in order, lactam **534** (0.20 mmol, 1.00 equiv), palladium(II) hexafluoroacetylacetonate (8 mg, 0.015 mmol, 0.075 equiv), Oxone (154 mg, 0.50 mmol, 2.50 equiv), and hot, activated 4 Å molecular sieves (160 mg). The flask was then capped with a rubber septum and evacuated and backfilled twice with nitrogen. Acetonitrile (1.43 mL) and 1:1 acetic acid:acetic anhydride (571 μL) were added by syringe. The resulting suspension was stirred under nitrogen for 5 minutes at 23 °C and then heated to 60 °C in an oil bath. Upon completion (as determined by TLC analysis), the flask was allowed to cool to 23 °C and the contents were filtered through a short plug of silica gel, rinsing with ethyl acetate. The filtrate was adsorbed onto silica gel (approx. 2 g), which was then flushed with ethyl acetate. The eluent was concentrated to give the crude product as an oil. After

NMR analysis to determine the acetate:enal ratio, the crude residue was purified by silica gel column chromatography, using mixtures of hexanes and ethyl acetate as eluent.

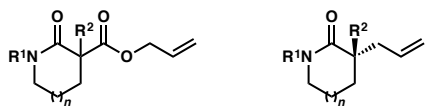


534 *536*

General Procedure E. *Enal formation from α-allyl lactams.*

To a 25 mL round-bottom flask with a magnetic stir bar were added, in order, lactam **534** (0.20 mmol, 1.00 equiv), palladium(II) acetate (3 mg, 0.015 mmol, 0.075 equiv), and Oxone (154 mg, 0.50 mmol, 2.50 equiv). Acetonitrile (1.82 mL), acetic acid (183 μL, 3.20 mmol, 16.00 equiv), and water (29 μL, 1.60 mmol, 8.00 equiv) were added by syringe. The resulting suspension was stirred for 5 minutes at 23 °C and then heated to 50 °C in an oil bath. Upon completion (as determined by TLC analysis), the flask was allowed to cool to 23 °C and anhydrous magnesium sulfate (approx. 200 mg) was added. After stirring for 5 minutes the contents were filtered through a short plug of silica gel, rinsing with ethyl acetate. The filtrate was adsorbed onto silica gel (approx. 2 g), which was then flushed with ethyl acetate. The eluent was concentrated to give the crude product as an oil. After NMR analysis to determine the acetate:enal ratio, the crude residue was purified by silica gel column chromatography, using mixtures of hexanes and ethyl acetate as eluent.

5.5.3 SUBSTRATE SYNTHESIS AND CHARACTERIZATION DATA



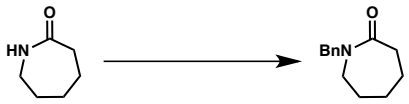
528 *529*

Compounds of the general structures **528** (not used in this work) and **529**, including one used in this work (R^1 = Bz, R^2 = Et, n = 1; starting material for entry 1 of Scheme 1) may be prepared as previously reported by our research group.[8c]

580 ***581***

1-benzylpiperidin-2-one (581):

Lactam **581** was prepared from δ-valerolactam (**580**) using General Procedure A. Characterization data match those reported in the literature.[28]



582 ***583***

1-benzylazepan-2-one (583):

Lactam **583** was prepared from ε-caprolactam (**582**) using General Procedure A. Characterization data match those reported in the literature.[29]

584 ***585***

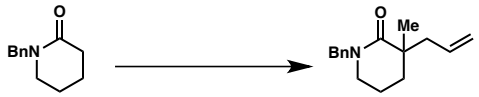
1-benzylpyrrolidin-2-one (584):

Lactam **584** was prepared from 2-pyrrolidinone (**584**) using General Procedure A. Characterization data match those reported in the literature.[30]

581 ***586***

3-allyl-1-benzyl-3-ethylpiperidin-2-one (586):

Lactam **586** was prepared from **581** using General Procedure B. R*f* = 0.40 (33% ethyl acetate in hexanes); ^{1}H NMR (CDCl3, 500 MHz) δ 7.34–7.27 (m, 2H), 7.26–7.20 (m, 3H), 5.78 (dddd, *J* = 16.7, 10.5, 8.1, 6.7 Hz, 1H), 5.10–5.05 (m, 1H), 5.06–5.03 (m, 2H), 4.60 (d, *J* = 14.6 Hz, 1H), 4.56 (d, *J* = 14.6 Hz, 1H), 3.22–3.10 (m, 2H), 2.55 (ddt, *J* = 13.5, 6.7, 1.3 Hz, 1H), 2.21 (ddt, *J* = 13.5, 8.0, 1.1 Hz, 1H), 1.83 (dq, *J* = 13.6, 7.5 Hz, 1H), 1.78–1.63 (m, 3H), 1.52 (dq, *J* = 13.6, 7.5 Hz, 1H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (CDCl3, 126 MHz) δ 174.5, 137.7, 135.0, 128.6, 128.1, 127.3, 117.8, 50.6, 47.8, 45.3, 31.6, 28.9, 19.8, 8.9; IR (Neat Film, NaCl) 2938, 1633, 1488, 1453, 1352, 1196, 913, 736 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{24}NO$ $[M+H]^+$: 258.1852, found 258.1856.

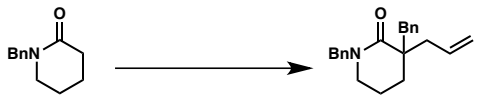


581 ***587***

3-allyl-1-benzyl-3-methylpiperidin-2-one (587):

Lactam **587** was prepared from **581** using General Procedure B. R*f* = 0.50 (33% ethyl acetate in hexanes); ^{1}H NMR (CDCl3, 500 MHz) δ 7.32–7.27 (m, 2H), 2.26–2.20 (m, 3H), 5.81–5.71 (m, 1H), 5.11–5.04 (m, 2H), 4.62 (d, *J* = 14.6 Hz, 1H), 4.50 (d, *J* = 14.6 Hz, 1H), 3.24–3.10 (m, 2H), 2.57 (ddt, *J* = 13.5, 6.7, 1.3 Hz, 1H), 2.23 (ddt, *J* = 13.4, 8.1, 1.0 Hz, 1H) 1.89–1.80 (m, 1H), 1.80–1.69 (m, 2H), 1.58–1.47 (m, 1H), 1.25 (s, 3H); ^{13}C

NMR ($CDCl_3$, 126 MHz) δ 175.1, 137.7, 143.6, 128.6, 128.0, 127.3, 118.1, 50.5, 47.9, 44.5, 41.6, 32.6, 26.0, 19.4; IR (Neat Film, NaCl) 2936, 1634, 1488, 1432, 1349, 1196, 914, 750 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{16}H_{22}NO$ $[M+H]^+$: 244.1696, found 244.1699.



581 ***588***

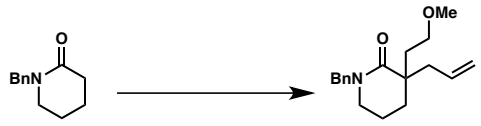
3-allyl-1,3-dibenzylpiperidin-2-one (588):

Lactam **588** was prepared from **581** using General Procedure B. R*f* = 0.40 (33% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 500 MHz) 7.32–7.13 (m, 10H), 5.82 (dddd, *J* = 16.8, 10.6, 8.2, 6.5 Hz, 1H), 5.15–5.11 (m, 1H), 5.11–5.06 (m, 1H), 4.68 (d, *J* = 14.5 Hz, 1H), 4.48 (d, *J* = 14.6 Hz, 1H), 3.38 (d, *J* = 13.0 Hz, 1H), 3.06 (ddd, *J* = 12.0, 7.4, 4.6 Hz, 1H), 2.99–2.87 (m, 1H), 2.72 (ddt, *J* = 13.4, 6.5, 1.4 Hz, 1H), 2.61 (d, *J* = 13.1 Hz, 1H), 2.21 (ddt, *J* = 13.4, 8.2, 1.0 Hz, 1H), 1.78–1.68 (m, 2H), 1.64 (qdd, *J* = 11.9, 5.9, 2.7 Hz, 1H), 1.46–1.34 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.8, 138.3, 137.4, 134.5, 130.8, 128.5, 128.1, 128.1, 127.3, 126.4, 118.5, 50.8, 47.8, 46.7, 44.8, 44.6, 28.6, 19.7; IR (Neat Film, NaCl) 3027, 2939, 1631, 1495, 1453, 1353, 1194, 916, 742 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{22}H_{26}NO$ $[M+H]^+$: 320.2009, found 320.2019.

581 ***589***

3-allyl-1-benzyl-3-propylpiperidin-2-one (589):

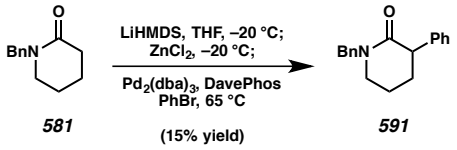
Lactam **589** was prepared from **581** using General Procedure B. R*f* = 0.50 (33% ethyl acetate in hexanes); ^{1}H NMR (CDCl3, 500 MHz) δ 7.35–7.29 (m, 2H), 7.27–7.20 (m, 3H), 5.90–5.66 (m, 1H), 5.10–5.06 (m, 1H), 5.06–5.04 (m, 1H), 4.61 (d, *J* = 14.5 Hz, 1H), 4.55 (d, *J* = 14.5 Hz, 1H), 3.16 (td, *J* = 5.4, 4.6, 2.2 Hz, 2H), 2.56 (ddt, *J* = 13.5, 6.7, 1.3 Hz, 1H), 2.22 (ddt, *J* = 13.5, 8.1, 1.0 Hz, 1H), 1.83–1.57 (m, 5H), 1.55–1.41 (m, 1H), 1.41–1.32 (m, 1H), 1.32–1.21 (m, 1H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (CDCl3, 126 MHz) δ 174.4, 137.7, 134.9, 128.5, 128.1, 127.2, 117.8, 50.5, 47.7, 45.1, 43.7, 41.4, 29.5, 19.8, 17.6, 14.8; IR (Neat Film, NaCl) 2955, 1632, 1487, 1437, 1350, 1194, 913, 734 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{18}H_{26}NO$ [M+H]$^{+}$: 272.2009, found 272.2014.



581 ***590***

3-allyl-1-benzyl-3-(2-methoxyethyl)piperidin-2-one (590):

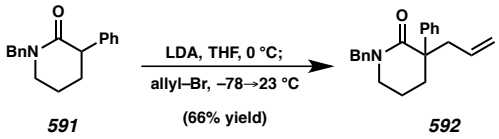
Lactam **590** was prepared from **581** using General Procedure B. R*f* = 0.3 (33% ethyl acetate in hexanes); ^{1}H NMR (CDCl3, 500 MHz) δ 7.34–7.27 (m, 2H), 7.27–7.20 (m, 3H), 5.86–5.65 (m, 1H), 5.08 (dtd, *J* = 13.3, 2.4, 1.1 Hz, 2H), 4.62 (d, *J* = 14.6 Hz, 1H), 4.52 (d, *J* = 14.5 Hz, 1H), 3.56–3.37 (m, 2H), 3.29 (s, 3H), 3.24–3.12 (m, 2H), 2.56 (ddt, *J* = 13.6, 6.7, 1.3 Hz, 1H), 2.26 (ddt, *J* = 13.5, 8.0, 1.0 Hz, 1H), 2.09 (ddd, *J* = 14.1, 7.7, 6.5 Hz, 1H), 1.83–1.63 (m, 5H); ^{13}C NMR (CDCl3, 126 MHz) δ 173.9, 137.7, 134.4, 128.6, 128.1, 127.3, 118.4, 69.7, 58.7, 50.7, 47.9, 44.0, 43.7, 38.0, 30.1, 19.7; IR (Neat Film, NaCl) 2925, 1632, 1487, 1452, 1195, 1114, 915, 736 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{18}H_{26}NO_2$ [M+H]$^{+}$: 288.1958, found 288.1966.



581 *591*

1-benzyl-3-phenylpiperidin-2-one (591):

Lactam **591** was prepared from **581** following a known procedure.[2a] To a flame-dried round-bottom flask with a magnetic stir bar were added lactam **581** (662 mg, 3.50 mmol, 2.20 equiv) and THF (6.4 mL). The solution was stirred under nitrogen and cooled to –20 °C using a dry ice and acetone bath. A solution of lithium hexamethyldisilazide (532 mg, 3.18 mmol, 2.00 equiv) in THF (1.4 mL) was added by syringe, and the reaction mixture was allowed to stir at –20 °C for 20 minutes. A solution of zinc(II) chloride (477 mg, 3.50 mmol, 2.20 equiv) in THF (7 mL) was added, and the reaction mixture was allowed to stir at –20 °C for another 20 minutes, after which it was transferred via syringe to a flame-dried round-bottom flask with a magnetic stir bar and a reflux condenser containing tris(dibenzylideneacetone)dipalladium(0) (23 mg, 0.025 mmol, 0.015 equiv), DavePhos (30 mg, 0.076 mmol, 0.048 equiv), bromobenzene (169 μL, 1.59 mmol, 1.00 equiv), and THF (3.2 mL). The mixture was heated to 65 °C for 10 hours. Upon completion (as determined by TLC analysis), the reaction mixture was allowed to cool to 23 °C, quenched by the addition of saturated aqueous ammonium chloride solution (100 mL), and the aqueous layer was extracted with ether (3 x 200 mL). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (20% ethyl aceate in hexanes to 25% ethyl acetate in hexanes) to provide lactam **591** as a colorless oil (141 mg, 15% yield). Characterization data match those reported in the literature.[5]

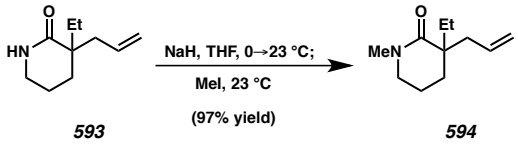


591 *592*

3-allyl-1-benzyl-3-phenylpiperidin-2-one (592):

To a flame-dried round-bottom flask with a magnetic stir bar were added diisopropylamine (348 μL, 2.48 mmol, 1.50 equiv) and THF (1.3 mL) by syringe. The solution was stirred under nitrogen and cooled to 0 °C using an ice water bath. *n*-Butyllithium (2.5 M in hexane, 983 μL, 2.46 mmol, 1.49 equiv) was added rapidly dropwise by syringe, and the solution was allowed to stir at 0 °C for 20 minutes. Meanwhile, lactam **591** (439 mg, 1.65 mmol, 1.00 equiv) was dissolved in THF (5.3 mL) in a flame-dried round-bottom flask under nitrogen and cooled to 0 °C using an ice water bath. The freshly prepared LDA solution was transferred to the lactam solution rapidly dropwise via syringe, and the mixture was allowed to stir at 0 °C for 45 minutes. The solution was then cooled to –78 °C using a dry ice and acetone bath, and allyl bromide (857 μL, 9.90 mmol, 6.00 equiv) was added dropwise by syringe. The flask was placed in an ice water bath and allowed to gradually warm to 23 °C overnight. Upon completion (as determined by TLC analysis), the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution (100 mL), and the aqueous layer extracted with chloroform (3 x 75 mL). The combined organic layers were washed with brine (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (5% ethyl aceate in hexanes) to provide lactam **592** as a colorless oil (332 mg, 66% yield). R*f* = 0.4 (10% ethyl acetate in hexanes); ^{1}H NMR (CDCl3, 500 MHz) δ 7.41–7.26 (m, 9H), 7.25–7.19

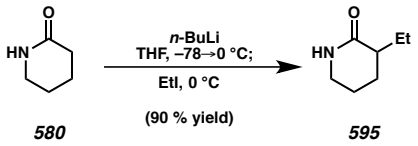
(m, 1H), 5.76 (dddd, J = 17.1, 10.2, 8.2, 6.1 Hz, 1H), 5.14–5.04 (m, 2H), 4.69 (s, 2H), 3.28–3.16 (m, 1H), 3.12 (dddd, J = 12.1, 5.2, 3.7, 1.3 Hz, 1H), 2.96 (ddt, J = 13.5, 6.1, 1.4 Hz, 1H), 2.53 (ddt, J = 13.6, 8.2, 1.0 Hz, 1H), 2.19 (dtd, J = 13.9, 4.0, 1.3 Hz, 1H), 2.12–1.97 (m, 1H), 1.72–1.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 172.4, 144.0, 137.6, 135.4, 128.7, 128.5, 128.3, 127.4, 126.8, 126.6, 118.2, 51.2, 50.8, 47.5, 45.8, 31.4, 19.0; IR (Neat Film, NaCl) 3061, 2943, 1635, 1495, 1442, 1352, 1197, 916, 761, 699 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{21}H_{24}NO$ $[M+H]^+$: 306.1852, found 306.1850.



3-allyl-3-ethyl-1-methylpiperidin-2-one (594):

To a flame-dried round-bottom flask with a magnetic stir bar were added sodium hydride (60% dispersion in mineral oil, 122 mg, 3.06 mmol, 1.10 equiv) and THF (5 mL). The flask was capped with a rubber septum, put under a nitrogen atmosphere, and cooled to 0 °C using an ice water bath. A solution of lactam **593** (preparation described below, 465 mg, 2.78 mmol, 1.00 equiv) in THF (15 mL) was added rapidly dropwise by syringe, and the resulting mixture was allowed to warm to 23 °C and stir for 2 hours. Methyl iodide (191 μL, 3.06 mmol, 1.10 equiv) was added dropwise by syringe, and the mixture stirred for another 2 hours. Upon completion (as determined by TLC analysis), the suspension was diluted with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (1 x 100 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (40% ethyl acetate in hexanes) to provide lactam

594 as a colorless oil (490 mg, 97% yield). R*f* = 0.4 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.77–5.61 (m, 1H), 5.05–5.01 (m, 1H), 5.00 (t, *J* = 1.2 Hz, 1H), 3.29–3.15 (m, 2H), 2.89 (s, 3H), 2.45 (ddt, *J* = 13.6, 6.7, 1.4 Hz, 1H), 2.15 (ddt, *J* = 13.6, 8.1, 1.1 Hz, 1H), 1.84–1.58 (m, 5H), 1.46 (dq, *J* = 13.7, 7.4 Hz, 1H), 0.82 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 174.6, 135.1, 117.6, 50.5, 45.1, 43.0, 35.2, 31.3, 28.9, 19.7, 8.0; IR (Neat Film, NaCl) 2938, 1635, 1499, 1458, 1398, 1357, 1201, 911 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{11}H_{20}NO$ $[M+H]^+$: 182.1539, found 182.1542.

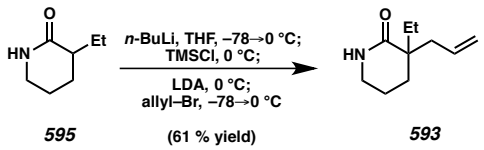


580 ***595***

3-ethylpiperidin-2-one (595):

Lactam **595** was prepared from **580** following a known procedure.[31] To a flame-dried round-bottom flask with a magnetic stir bar were added lactam **580** (2.25 g, 22.7 mmol, 1.00 equiv) and THF (50 mL). The solution was stirred under nitrogen and cooled to –78 °C using a dry ice and acetone bath. *n*-Butyllithium (2.5 M in hexane, 18.3 mL, 45.7 mmol, 2.01 equiv) was added dropwise by syringe, and the reaction mixture was allowed to warm to 0 °C and stir for 1 hour. Ethyl iodide (2.73 mL, 34.1 mmol, 1.50 equiv) was added dropwise by syringe, and the solution was stirred for 45 minutes at 0 °C. Upon completion (as determined by TLC analysis), the mixture was quenched with saturated aqueous ammonium chloride solution (100 mL) and the aqueous layer was extracted with chloroform (3 x 200 mL). The combined organic layers were washed with brine (1 x 200 mL), dried over sodium sulfate, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (ethyl acetate) to provide lactam **595** as a

white solid (2.60 g mg, 90% yield). Characterization data match those reported in the literature.[7]

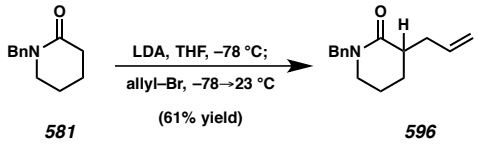


595 (61 % yield) ***593***

3-allyl-3-ethylpiperidin-2-one (593):

Lactam **593** was prepared from **595** following a known procedure.[6] To a flame-dried round-bottom flask with a magnetic stir bar were added lactam **595** (2.60 g, 20.4 mmol, 1.00 equiv) and THF (60 mL). The solution was stirred under nitrogen and cooled to –78 °C using a dry ice and acetone bath. *n*-Butyllithium (2.5 M in hexane, 8.24 mL, 20.6 mmol, 1.01 equiv) was added dropwise by syringe, and the reaction mixture was allowed to warm to 0 °C and stir for 1.25 hours. Trimethylsilyl chloride (3.77 mL, 22.5 mmol, 1.10 equiv) was added rapidly by syringe, and the reaction mixture was allowed to stir for 1.75 hours at 0 °C. Meanwhile, to a flame-dried round-bottom flask with a magnetic stir bar were added diisopropylamine (4.29 mL, 30.6 mmol, 1.50 equiv) and THF (15 mL) by syringe. The amine solution was stirred under nitrogen and cooled to 0 °C using an ice water bath. *n*-Butyllithium (2.5 M in hexane, 12.2 mL, 30.4 mmol, 1.49 equiv) was added rapidly dropwise by syringe, and the solution was allowed to stir at 0 °C for 20 minutes. The freshly prepared LDA solution was then added to the reaction mixture rapidly by syringe, and the resulting solution was stirred for 45 minutes at 0 °C. The solution was then cooled to –78 °C using a dry ice and acetone bath, and allyl bromide (21 mL, 250 mmol, 12.3 equiv) was added dropwise by syringe. The reaction mixture was allowed to warm to 0 °C and stir for 1.25 hours. Upon completion (as determined by

TLC analysis), the mixture was quenched with saturated aqueous ammonium chloride solution (100 mL) and the aqueous layer was extracted with chloroform (3 x 200 mL). The combined organic layers were washed with 1 M aqueous hydrochloric acid (2 x 100 mL), water (1 x 100 mL), brine (1 x 100 mL), dried over sodium sulfate, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (50% ethyl acetate in hexanes) to provide lactam **593** as a colorless oil (2.09 g, 61% yield). Characterization data match those reported in the literature.[8]

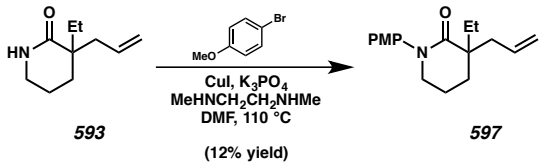


581 ***596***

3-allyl-1-benzylpiperidin-2-one (596):

To a flame-dried round-bottom flask with a magnetic stir bar were added diisopropylamine (2.91 mL, 20.8 mmol, 1.05 equiv) and THF (10 mL) by syringe. The solution was stirred under nitrogen and cooled to 0 °C using an ice water bath. *n*-Butyllithium (2.5 M in hexane, 8.71 mL, 21.8 mmol, 1.10 equiv) was added rapidly dropwise by syringe, and the solution was allowed to stir at 0 °C for 30 minutes before being cooled to –78 °C in a dry ice and acetone bath. A solution of lactam **581** (3.75 g, 19.8 mmol, 1.00 equiv) in THF (60 mL) was added dropwise by cannula. The reaction mixture was stirred at –78 °C for 4 hours. Allyl bromide (1.79 mL, 20.8 mmol, 1.05 equiv) was added dropwise by syringe, and the reaction mixture was allowed to gradually warm to 23 °C and stir for 16 h. Upon completion (as determined by TLC analysis) the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution (200 mL), and the aqueous layer extracted with chloroform (3 x 200 mL). The

combined organic layers were washed with brine (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (25% ethyl aceate in hexanes) to provide lactam **596** as a colorless oil (2.77 g, 61% yield). R*f* = 0.7 (50% ethyl acetate in hexanes); characterization data match those reported in the literature.[32]

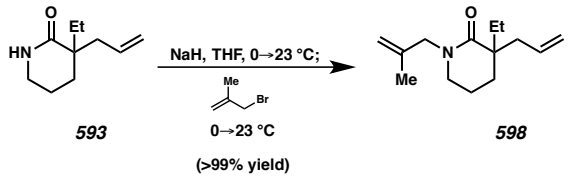


593 ***597***

3-allyl-3-ethyl-1-(4-methoxyphenyl)piperidin-2-one (597):

The conditions for this transformation were adapted from a known procedure.[33] To a flame-dried round-bottom flask with a magnetic stir bar were added lactam **593** (1.00 g, 5.98 mmol, 1.20 equiv) and DMF (6 mL). The solution was stirred under nitrogen and copper(I) iodide (190 mg, 1.00 mmol, 0.20 equiv), potassium phosphate tribasic (2.12 g, 10.0 mmol, 2.00 equiv), *N*,*N*'-dimethylethylenediamine (108 μL), and 4-bromoanisole (630 μL, 5.04 mmol, 1.00 equiv) were added. The heterogeneous mixture was then heated to 110 °C under nitrogen for 20 hours. Upon completion (as determined by LCMS analysis), the mixture was filtered through a plug of sodium sulfate, rinsing with dichloromethane. The filtrate was washed with water (3 x 100 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (20% ethyl acetate in hexanes) to provide lactam **597** as a colorless oil (203 mg, 12% yield). R*f* = 0.3 (20% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.17–7.04 (m, 2H), 6.95–6.83 (m, 2H), 6.01–5.69 (m, 1H), 5.14–

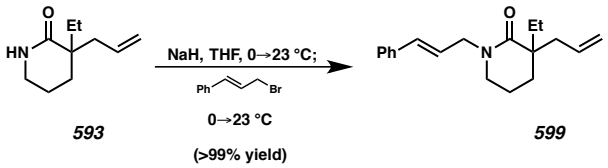
5.10 (m, 1H), 5.10 (s, 1H), 3.80 (s, 3H), 3.58 (t, J = 5.9 Hz, 2H), 2.60 (ddt, J = 13.5, 6.7, 1.3 Hz, 1H), 2.23 (ddt, J = 13.4, 8.1, 1.0 Hz, 1H), 2.00–1.77 (m, 5H), 1.57 (dq, J = 13.6, 7.4 Hz, 1H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 174.9, 158.0, 137.0, 135.1, 127.5, 118.0, 114.4, 55.6, 52.5, 45.7, 43.7, 31.9, 29.3, 20.6, 9.0; IR (Neat Film, NaCl) 3072, 2937, 1646, 1511, 1457, 1293, 1243, 1199, 1105, 1134, 913, 829 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{24}NO_2$ $[M+H]^+$: 274.1802, found 274.1813.



3-allyl-3-ethyl-1-(2-methylallyl)piperidin-2-one (598):

To a flame-dried round-bottom flask with a magnetic stir bar were added lactam **593** (400 mg, 2.40 mmol, 1.00 equiv) and THF (12 mL). The flask was capped with a rubber septum, put under an argon atmosphere, and cooled to 0 °C using an ice water bath. Sodium hydride (60% dispersion in mineral oil, 192 mg, 4.80 mmol, 2.00 equiv) was then added in one portion, and the suspension was allowed to warm to 23 °C and stir for 2 hours. The suspension was then cooled to 0 °C using an ice water bath, and 3-bromo-2-methylpropene (267 μL, 2.64 mmol, 1.10 equiv) was added by syringe. The suspension was allowed to warm to 23 °C and stir for 1 hour. Upon completion (as determined by TLC analysis), the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (10% ethyl acetate in hexanes)

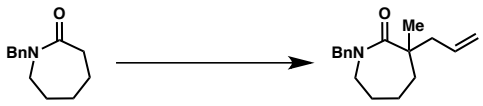
to provide lactam **598** as a colorless oil (531 mg, >99% yield). R*f* = 0.5 (20% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.86–5.62 (m, 1H), 5.07–5.04 (m, 1H), 5.04–5.02 (m, 1H), 4.85 (q, *J* = 1.5 Hz, 1H), 4.76 (dt, *J* = 2.4, 1.1 Hz, 1H), 4.02–3.80 (m, 2H), 3.24–3.08 (m, 2H), 2.58–2.38 (m, 1H), 2.18 (ddt, *J* = 13.5, 8.2, 1.1 Hz, 1H), 1.89–1.68 (m, 5H), 1.67 (s, 3H), 1.56–1.45 (m, 1H), 0.87 (td, *J* = 7.4, 1.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 174.3, 140.9, 135.1, 117.8, 112.0, 52.7, 47.6, 45.3, 43.4, 31.6, 29.0, 20.2, 19.9, 8.9; IR (Neat Film, NaCl) 3074, 2939, 1637, 1488, 1458, 1440, 1346, 1285, 1197, 1000, 911 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{14}H_{24}NO$ $[M+H]^+$: 222.1852, found 222.1860.



3-allyl-1-cinnamyl-3-ethylpiperidin-2-one (599):

To a flame-dried round-bottom flask with a magnetic stir bar were added lactam **593** (400 mg, 2.40 mmol, 1.00 equiv) and THF (12 mL). The flask was capped with a rubber septum, put under an argon atmosphere, and cooled to 0 °C using an ice water bath. Sodium hydride (60% dispersion in mineral oil, 192 mg, 4.80 mmol, 2.00 equiv) was then added in one portion, and the suspension was allowed to warm to 23 °C and stir for 2 hours. The suspension was then cooled to 0 °C using an ice water bath, and 3-bromo-1-phenyl-1-propene (520 mg, 2.64 mmol, 1.10 equiv) was added by syringe. The suspension was allowed to warm to 23 °C and stir for 2 hours. Upon completion (as determined by TLC analysis), the reaction mixture was diluted with water (100 mL) and

extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (20% ethyl acetate in hexanes) to provide lactam **599** as a colorless oil (676 mg, >99% yield). R*f* = 0.3 (20% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39–7.33 (m, 2H), 7.31 (ddd, *J* = 7.7, 6.7, 1.2 Hz, 2H), 7.26–7.20 (m, 1H), 6.48 (dt, *J* = 15.7, 1.5 Hz, 1H), 6.14 (dt, *J* = 15.8, 6.5 Hz, 1H), 5.90–5.57 (m, 1H), 5.08 (ddt, *J* = 5.0, 2.3, 1.3 Hz, 1H), 5.06 (t, *J* = 1.2 Hz, 1H), 4.14 (dd, *J* = 6.5, 1.4 Hz, 2H), 3.42–3.13 (m, 2H), 2.54 (ddt, *J* = 13.5, 6.7, 1.3 Hz, 1H), 2.20 (ddt, *J* = 13.5, 8.1, 1.0 Hz, 1H), 1.95–1.65 (m, 5H), 1.52 (dq, *J* = 13.5, 7.4 Hz, 1H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 174.3, 136.8, 135.1, 132.6, 128.7, 127.7, 126.5, 125.0, 117.8, 49.5, 47.9, 45.4, 43.4, 31.6, 28.9, 20.0, 8.9; IR (Neat Film, NaCl) 2938, 1631, 1487, 1448, 1352, 1282, 1196, 965, 912, 746 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{19}H_{26}NO$ $[M+H]^+$: 284.2009, found 284.2019.

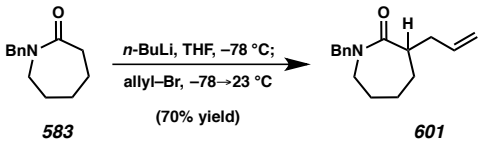


583 ***600***

3-allyl-1-benzyl-3-methylazepan-2-one (600):

Lactam **600** was prepared from **583** using General Procedure B. R*f* = 0.4 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33–7.27 (m, 2H), 7.26–7.21 (m, 3H), 5.94–5.72 (m, 1H), 5.12–5.07 (m, 1H), 5.06 (t, *J* = 1.2 Hz, 1H), 4.69 (d, *J* = 14.6 Hz, 1H), 4.52 (d, *J* = 14.6 Hz, 1H), 3.42 (ddd, *J* = 15.2, 7.9, 4.0 Hz, 1H), 3.28 (ddd, *J* = 15.2, 6.3, 3.9 Hz, 1H), 2.54–2.34 (m, 2H), 1.76–1.59 (m, 3H), 1.59–1.45 (m, 3H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.5, 138.5, 135.0, 128.5, 128.1, 127.2, 117.7, 53.2,

47.0, 46.3, 44.2, 34.9, 27.4, 26.2, 23.1; IR (Neat Film, NaCl) 2930, 1626, 1495, 1453, 1359, 1244, 913, 746 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{24}NO$ $[M+H]^+$: 258.1852, found 258.1853.



583 ***601***

3-allyl-1-benzylazepan-2-one (601):

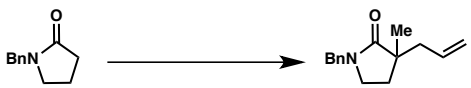
To a flame-dried round-bottom flask with a magnetic stir bar were added lactam **583** (1.00 g, 4.92 mmol, 1.00 equiv) and THF (26 mL). The solution was stirred under nitrogen and cooled to –78 °C using a dry ice and acetone bath. *n*-Butyllithium (2.5 M in hexane, 2.16 mL, 5.41 mmol, 1.10 equiv) was added dropwise by syringe, and the solution was allowed to stir at –78 °C for 1 hour. Allyl bromide (510 μL, 5.90 mmol, 1.20 equiv) was then added dropwise by syringe, and the solution was allowed to gradually warm to 23 °C and stir for 17 hours. Upon completion (as determined by LCMS analysis), the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution (100 mL), and the aqueous layer extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (20% ethyl aceate in hexanes) to provide lactam **601** as a colorless oil (838 mg, 70% yield). R*f* = 0.2 (25% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34–7.28 (m, 2H), 7.27–7.22 (m, 3H), 5.88 (dddd, *J* = 17.1, 10.2, 7.9, 5.6 Hz, 1H), 5.14–4.95 (m, 2H), 4.75 (d, *J* = 14.6 Hz, 1H), 4.45 (d, *J* = 14.6 Hz, 1H), 3.56–3.40 (m, 1H), 3.17 (dddd, *J* = 15.3, 5.7, 2.1, 1.1 Hz, 1H), 2.66 (dtt, *J* = 14.3, 5.7, 1.5 Hz, 1H),

2.59 (dtd, *J* = 10.4, 6.7, 6.0, 1.5 Hz, 1H), 2.12 (dtt, *J* = 14.0, 7.6, 1.1 Hz, 1H), 1.92–1.83 (m, 1H), 1.76 (dtd, *J* = 13.9, 4.7, 1.3 Hz, 1H), 1.64 (ddt, *J* = 13.9, 5.3, 4.0 Hz, 1H), 1.51 (dtt, *J* = 13.8, 12.4, 3.9 Hz, 1H), 1.34 (dddd, *J* = 13.8, 12.5, 10.5, 3.1 Hz, 1H), 1.28–1.12 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 176.7, 138.2, 137.5, 128.6, 128.3, 127.3, 116.3, 51.2, 48.1, 43.5, 36.8, 29.5, 29.3, 27.6; IR (Neat Film, NaCl) 2929, 1646, 1477, 1430, 1358, 1263, 1217, 912, 736 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{16}H_{22}NO$ $[M+H]^+$: 244.1696, found 244.1708.

584 ***602***

3-allyl-1-benzyl-3-methylazepan-2-one (602):

Lactam **602** was prepared from **584** using General Procedure B. R*f* = 0.4 (20% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34–7.19 (m, 5H), 5.73 (dddd, *J* = 16.8, 10.1, 8.3, 6.5 Hz, 1H), 5.16–4.97 (m, 2H), 4.47 (d, *J* = 14.6 Hz, 1H), 4.42 (d, *J* = 14.6 Hz, 1H), 3.13–3.03 (m, 2H), 2.35 (ddt, *J* = 13.6, 6.5, 1.3 Hz, 1H), 2.19 (ddt, *J* = 13.5, 8.3, 1.0 Hz, 1H), 1.97–1.86 (m, 1H), 1.86–1.77 (m, 1H), 1.64 (dq, *J* = 13.7, 7.5 Hz, 1H), 1.52 (dq, *J* = 13.7, 7.4 Hz, 1H), 0.87 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.7, 136.8, 134.3, 128.7, 128.3, 127.6, 118.3, 48.2, 46.8, 43.9, 41.6, 30.0, 26.8, 8.8; IR (Neat Film, NaCl) 3065, 2965, 1684, 1495, 1430, 1265, 1080, 1001, 916, 743 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{16}H_{22}NO$ $[M+H]^+$: 244.1696, found 244.1705.



584 ***603***

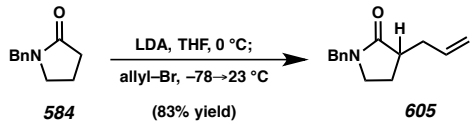
3-allyl-1-benzyl-3-methylpyrrolidin-2-one (603):

Lactam **603** was prepared from **584** using General Procedure B. R*f* = 0.4 (40% ethyl acetate in hexanes); ^{1}H NMR (CDCl3, 500 MHz) δ 7.35–7.19 (m, 5H), 5.74 (dddd, *J* = 16.9, 10.1, 8.1, 6.7 Hz, 1H), 5.15–4.98 (m, 2H), 4.46 (d, *J* = 14.7 Hz, 1H), 4.42 (d, *J* = 14.6 Hz, 1H), 3.19–3.01 (m, 2H), 2.33 (ddt, *J* = 13.6, 6.6, 1.3 Hz, 1H), 2.21 (ddt, *J* = 13.7, 8.1, 1.0 Hz, 1H), 1.99 (ddd, *J* = 12.8, 8.2, 6.4 Hz, 1H), 1.69 (ddd, *J* = 12.8, 7.9, 5.5 Hz, 1H), 1.16 (s, 3H); ^{13}C NMR (CDCl3, 126 MHz) δ 178.7, 136.9, 134.3, 128.8, 128.3, 127.7, 118.5, 47.0, 44.2, 43.6, 42.4, 30.6, 23.3; IR (Neat Film, NaCl) 2962, 1685, 1495, 1430, 1290, 917, 739 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{15}H_{20}NO$ [M+H]$^{+}$: 230.1539, found 230.1539.

584 ***604***

3-allyl-1,3-dibenzylpyrrolidin-2-one (604):

Lactam **604** was prepared from **584** using General Procedure B. R*f* = 0.6 (33% ethyl acetate in hexanes); ^{1}H NMR (CDCl3, 500 MHz) δ 7.29–7.15 (m, 8H), 7.09–7.03 (m, 2H), 5.79 (dddd, *J* = 16.7, 10.1, 8.5, 6.2 Hz, 1H), 5.18–5.07 (m, 2H), 4.47 (d, *J* = 14.7 Hz, 1H), 4.16 (d, *J* = 14.7 Hz, 1H), 3.09 (d, *J* = 13.2 Hz, 1H), 2.86 (td, *J* = 9.2, 4.9 Hz, 1H), 2.63 (d, *J* = 13.2 Hz, 1H), 2.52 (ddt, *J* = 13.6, 6.3, 1.4 Hz, 1H), 2.39–2.19 (m, 2H), 1.98–1.78 (m, 2H); ^{13}C NMR (CDCl3, 126 MHz) δ 177.0, 137.0, 136.4, 134.0, 130.3, 128.6, 128.2, 128.2, 127.4, 126.6, 118.8, 49.5, 46.8, 43.8, 43.2, 42.8, 26.1; IR (Neat Film, NaCl) 2915, 1771, 1683, 1495, 1436, 1249, 917, 744 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{21}H_{24}NO$ [M+H]$^{+}$: 306.1852, found 306.1857.



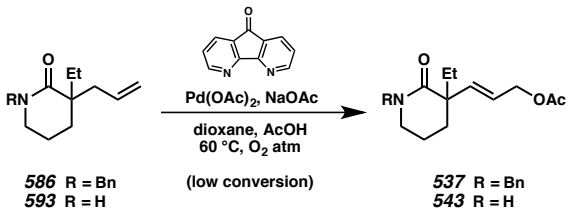
584 **(83% yield)** ***605***

3-allyl-1-benzylpyrrolidin-2-one (605):

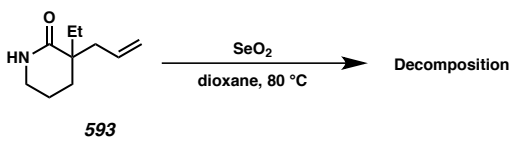
To a flame-dried round-bottom flask with a magnetic stir bar were added diisopropylamine (479 μL, 3.42 mmol, 1.20 equiv) and THF (1.72 mL) by syringe. The solution was stirred under nitrogen and cooled to 0 °C using an ice water bath. *n*-Butyllithium (2.5 M in hexane, 1.36 mL, 3.39 mmol, 1.19 equiv) was added rapidly dropwise by syringe, and the solution was allowed to stir at 0 °C for 20 minutes. Meanwhile, lactam **584** (500 mg, 2.85 mmol, 1.00 equiv) was dissolved in THF (9 mL) in a flame-dried round-bottom flask under nitrogen and cooled to 0 °C using an ice water bath. The freshly prepared LDA solution was transferred to the lactam solution rapidly dropwise via syringe, and the mixture was allowed to stir at 0 °C for 45 minutes. The solution was then cooled to –78 °C using a dry ice and acetone bath, and allyl bromide (321 μL, 3.71 mmol, 1.30 equiv) was added dropwise by syringe. The flask was placed in an ice water bath, allowed to gradually warm to 23 °C, and stirred for 20 hours. Upon completion (as determined by TLC analysis), the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution (100 mL), and the aqueous layer extracted with chloroform (3 x 100 mL). The combined organic layers were washed with 1 M aqueous hydrochloric acid (2 x 100 mL), water (1 x 100 mL), brine (1 x 100 mL), dried over sodium sulfate, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (20% ethyl aceate in hexanes) to provide

lactam **605** as a colorless oil (509 mg, 83% yield). R*f* = 0.3 (20% ethyl acetate in hexanes); characterization data match those reported in the literature.[34]

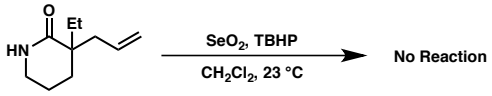
5.5.4 PROCEDURES FOR UNSUCCESSFUL ALLYLIC OXIDATIONS



Allylic acetates **537** and **543** were prepared from **586** and **593** following a known procedure.[3i] To a round-bottom flask with a magnetic stir bar were added, in order, sodium acetate (3.5 mg, 0.043 mmol, 0.20 equiv), palladium(II) acetate (2.4 mg, 0.011 mmol, 0.05 equiv), diazefluorenone ligand (1.9 mg, 0.011 mmol, 0.05 equiv), dioxane (600 μL), and acetic acid (190 μL). The appropriate lactam substrate (**586** or **593**, 0.21 mmol, 1.00 equiv) was added, and the flask was capped with a rubber septum. The solution was stirred vigorously while oxygen was bubbled through for 15 minutes. The solution was then stirred at 60 °C under an oxygen atmosphere for 41 hours. TLC analysis throughout this time showed little conversion of the starting material. After 41 hours, the reaction mixture was filtered through a plug of silica gel, rinsing with ethyl acetate, and concentrated to give the crude residue. In the case of either lactam substrate, NMR and LCMS analysis showed small amounts of the corresponding allylic acetate product (**537** or **543**). Characterization data for **537** and **543** are provided below.

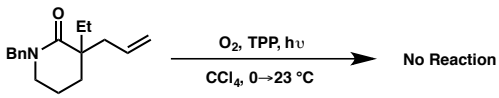


To a 1 dram screw-top vial with a magnetic stir bar were added lactam **593** (25 mg, 0.15 mmol, 1.00 equiv) and dioxane (1.5 mL). Selenium dioxide (83 mg, 5.00 equiv) was added and the reaction mixture was stirred at 80 ºC for 2h. At this time, TLC analysis showed only baseline material, and the mixture was filtered through a plug of silica gel, rinsing with ethyl acetate. The filtrate was concentrated and NMR and LCMS analysis showed complete decomposition of the starting material.



593

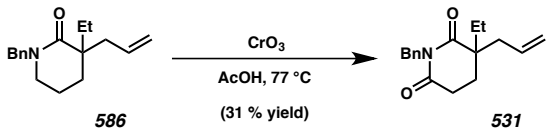
The conditions for this transformation were adapted from a known procedure.[35] To a 1 dram screw-top vial with a magnetic stir bar were added lactam **593** (27 mg, 0.16 mmol, 1.00 equiv) and dichlomethane (1.5 mL). Selenium dioxide (9 mg, 0.08 mmol, 0.50 equiv) and TBHP (5 M in decane, 160 μL, 0.80 mmol, 5.00 equiv) were added and the reaction mixture was stirred at 23 °C for 5 hours. TLC analysis throughout this time showed no conversion of the starting material. After 5 hours, the reaction mixture was filtered through a plug of silica gel, rinsing with ethyl acetate, and concentrated to give the crude residue. NMR and LCMS analysis showed only starting material **593** and trace impurities.



586

To a 1 dram screw-top vial with a magnetic stir bar were added lactam **586** (10 mg, 0.039 mmol, 1.00 equiv) and carbon tetrachloride (2 mL). Tetraphenylporphyrin (6 mg,

0.20 mmol, 5 mM in reaction solution) was added, the vial was capped with a septum, and oxygen was bubbled through the stirring solution for 2 minutes. The vial was cooled to 0 °C using an ice water bath, and a 500 W halogen floodlight was placed at a distance d = 10 cm from the vial. The solution was irradiated and allowed to gradually warm to 23 °C over a period of 2 hours, and was further irradiated at 23 °C for an additional 12 hours. TLC analysis throughout this time showed no reactivity. After 14 hours total reaction time, the mixture was filtered through a plug of silica gel, rinsing with ethyl acetate. The filtrate was concentrated, and NMR and LCMS analysis showed only starting material **586** and tetraphenylporphyrin.

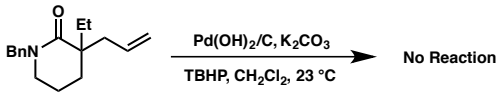


586 ***531***

3-allyl-1-benzyl-3-ethylpiperidine-2,6-dione (531):

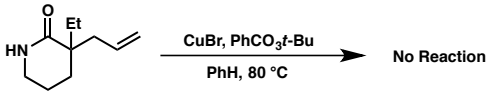
Imide **531** was prepared from **586** following a known procedure.[36] Lactam **586** (20 mg, 0.078 mmol, 1.00 equiv) was dissolved in 3.1 mL acetic acid in a 20 mL vial with a stir bar and heated to 77 °C. A solution of chromium(VI) oxide (31 mg, 0.31 mmol, 4.00 equiv) in acetic acid (1.6 mL) was added dropwise by pipette. The vial was sealed with a Teflon-lined cap and stirred at 77 °C for 1 hour. LCMS analysis at 1 hour showed full conversion of the starting material. The mixture was cooled to 23 °C, and filtered through a plug of silica gel, rinsing with ethyl acetate. The filtrate was diluted with heptanes and concentrated. The crude residue was purified by silica gel column chromatography (20% ethyl aceate in hexanes) to provide imide **531** as a colorless oil (6.6 mg, 31% yield). Rf = 0.6 (25% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500

MHz) δ 7.34–7.26 (m, 4H), 7.25–7.20 (m, 1H), 5.66 (dddd, *J* = 17.0, 10.2, 7.8, 6.9 Hz, 1H), 5.13–5.00 (m, 2H), 4.95 (s, 2H), 2.79–2.63 (m, 2H), 2.49 (ddt, *J* = 13.8, 6.9, 1.3 Hz, 1H), 2.29 (ddt, *J* = 13.9, 7.8, 1.1 Hz, 1H), 1.92–1.77 (m, 2H), 1.72 (dq, *J* = 14.0, 7.5 Hz, 1H), 1.68–1.58 (m, 1H), 0.84 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 176.5, 172.2, 137.7, 133.0, 128.7, 128.5, 127.4, 119.3, 45.2, 43.2, 40.2, 29.3, 28.7, 24.8, 8.3; IR (Neat Film, NaCl) 2967, 1722, 1676, 1455, 1345, 1164 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{22}NO_2$ $[M+H]^+$: 272.1645, found 272.1632.



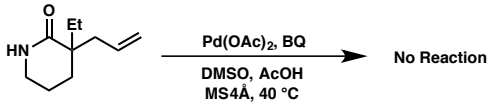
586

The conditions for this transformation were adapted from a known procedure.[15] To an oven-dried 1 dram screw-top vial with a magnetic stir bar were added, in order, lactam **586** (35 mg, 0.14 mmol, 1.00 equiv) potassium carbonate (5 mg, 0.036 mmol, 0.26 equiv), and dichloromethane (750 μL). Palladium hydroxide on carbon (20 wt. %, 11 mg) and *tert*-butyl hydroperoxide (5.0 M in decane, 137 μL, 0.69 mmol, 5.00 equiv) were added. The vial was sealed with a Teflon-lined cap and the reaction mixture was stirred at 23 °C for 48 hours. TLC analysis throughout this time showed very little conversion of the starting material. After 48 hours, the mixture was filtered through Celite, rinsing first with dichloromethane and later with ethyl acetate. The filtrate was concentrated and NMR and LCMS analysis showed starting material **586** with trace impurities.



593

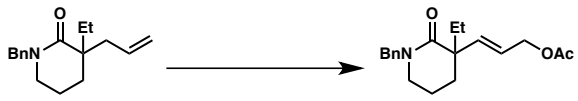
The conditions for this transformation were adapted from a known procedure.[37] To a 1 dram screw-top vial with a magnetic stir bar were added lactam **593** (17 mg, 0.10 mmol, 1.00 equiv) and benzene (1 mL). Copper(I) bromide (16 mg, 0.11 mmol, 1.10 equiv) and *tert*-butyl peroxybenzoate (110 μL, 0.60 mmol, 6.00 equiv) were added and the reaction mixture was heated to 80 °C and stirred for 5 hours. TLC and LCMS analysis throughout this time showed no conversion of the starting material. After 5 hours, the mixture was filtered through a plug of silica gel, rinsing with ethyl acetate. The filtrate was concentrated and NMR and LCMS analysis showed only starting material **593**.



593

The conditions for this reaction were adapted from a known procedure.[3a] To a round-bottom flask with a magnetic stir bar were added, in order, palladium(II) acetate (5.5 mg, 0.025 mmol, 0.10 equiv), benzoquinone (53 mg, 0.50 mmol, 2.00 equiv), and activated 4 Å molecular sieves (53 mg). DMSO (740 μL), lactam **593** (41 mg, 0.25 mmol, 1.00 equiv), and acetic acid (740 μL) were added. The vial was sealed with a Teflon-lined cap and heated to 40 °C for 15 hours. TLC analysis throughout this time showed no conversion of the starting material. After 15 hours, the reaction mixture was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with water (1 x 10 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. NMR and LCMS analysis of the crude product showed only starting material **593** and trace impurities.

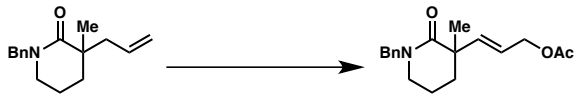
5.5.5 ALLYLIC ACETATE CHARACTERIZATION DATA



586 ***537***

(*E*)-3-(1-benzyl-3-ethyl-2-oxopiperidin-3-yl)allyl acetate (597):

Acetate **537** was prepared from **586** using General Procedure D. 56% isolated yield, 63% combined yield with enal. R*f* = 0.3 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34–7.28 (m, 2H), 7.28–7.20 (m, 3H), 5.88 (dt, *J* = 16.0, 1.3 Hz, 1H), 5.61 (dt, *J* = 15.9, 6.2 Hz, 1H), 4.65 (d, *J* = 14.5 Hz, 1H), 4.59–4.54 (m, 2H), 4.51 (d, *J* = 14.6 Hz, 1H), 3.26–3.04 (m, 2H), 2.06 (s, 3H), 1.95–1.84 (m, 1H), 1.84–1.70 (m, 4H), 1.70–1.59 (m, 1H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 172.7, 171.0, 139.5, 137.6, 128.7, 128.1, 127.4, 123.7, 65.2, 50.7, 48.5, 47.8, 31.9, 29.1, 21.2, 19.3, 8.6; IR (Neat Film, NaCl) 2939, 1738, 1634, 1495, 1453, 1361, 1231, 1028, 969, 736 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{19}H_{26}NO_3$ $[M+H]^+$: 316.1907, found 316.1913.



587 ***538***

(*E*)-3-(1-benzyl-3-methyl-2-oxopiperidin-3-yl)allyl acetate (538):

Acetate **538** was prepared from **587** using General Procedure D. 67% isolated yield, 74% combined yield with enal. R*f* = 0.2 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35–7.26 (m, 3H), 7.26–7.20 (m, 2H), 5.91 (dt, *J* = 15.8, 1.3 Hz, 1H), 5.63 (dt, *J* = 15.8, 6.2 Hz, 1H), 4.62 (d, *J* = 14.6 Hz, 1H), 4.56 (dt, *J* = 6.3, 1.5 Hz, 2H), 4.52 (d, *J* = 14.5 Hz, 1H), 3.29–3.06 (m, 2H), 2.06 (s, 3H), 1.95–1.86 (m, 1H), 1.86–

1.78 (m, 1H), 1.78–1.69 (m, 2H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.1, 170.9, 140.5, 137.6, 128.7, 128.1, 127.4, 123.2, 65.1, 50.6, 47.9, 44.7, 34.2, 26.6, 21.2, 19.5; IR (Neat Film, NaCl) 2936, 1738, 1634, 1489, 1453, 1361, 1232, 1028, 976, 736 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{18}H_{24}NO_3$ $[M+H]^+$: 302.1751, found 302.1755.

588 ***539***

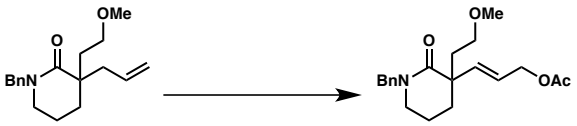
(*E*)-3-(1,3-dibenzyl-2-oxopiperidin-3-yl)allyl acetate (539):

Acetate **529** was prepared from **588** using General Procedure D. 54% isolated yield, 62% combined yield with enal. R*f* = 0.3 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30–7.26 (m, 2H), 7.26–7.12 (m, 8H), 5.88 (dt, *J* = 15.9, 1.4 Hz, 1H), 5.63 (dt, *J* = 15.9, 6.1 Hz, 1H), 4.76 (d, *J* = 14.6 Hz, 1H), 4.68–4.52 (m, 2H), 4.43 (d, *J* = 14.6 Hz, 1H), 3.38 (d, *J* = 13.2 Hz, 1H), 3.16–2.99 (m, 2H), 2.79 (d, *J* = 13.2 Hz, 1H), 2.08 (s, 3H), 1.87–1.53 (m, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.8, 171.0, 139.4, 137.4, 137.3, 131.2, 128.6, 128.1, 128.0, 127.4, 126.6, 124.4, 65.0, 50.9, 49.8, 47.9, 45.0, 29.8, 21.2, 19.2; IR (Neat Film, NaCl) 2940, 1738, 1634, 1495, 1453, 1360, 1233, 1193, 1028, 979, 743 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{24}H_{28}NO_3$ $[M+H]^+$: 378.2064, found 378.2067.

589 ***540***

(*E*)-3-(1-benzyl-2-oxo-3-propylpiperidin-3-yl)allyl acetate (540):

Acetate **540** was prepared from **589** using General Procedure D. 58% isolated yield, 66% combined yield with enal. R*f* = 0.3 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34–7.26 (m, 3H), 7.26–7.20 (m, 2H), 5.89 (dt, *J* = 16.0, 1.4 Hz, 1H), 5.61 (dt, *J* = 16.0, 6.2 Hz, 1H), 4.62 (d, *J* = 14.5 Hz, 1H), 4.57 (dt, *J* = 6.3, 1.5 Hz, 2H), 4.53 (d, *J* = 14.6 Hz, 1H), 3.30–3.01 (m, 2H), 2.06 (s, 3H), 1.89–1.76 (m, 4H), 1.76–1.69 (m, 1H), 1.61 (ddd, *J* = 13.4, 12.3, 4.4 Hz, 1H), 1.39–1.14 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 172.7, 171.0, 139.8, 137.6, 128.7, 128.2, 127.4, 123.5, 65.3, 50.7, 48.4, 47.8, 41.6, 29.9, 21.2, 19.4, 17.5, 14.7; IR (Neat Film, NaCl) 2955, 1739, 1635, 1495, 1453, 1360, 1230, 1027, 979, 736 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{20}H_{28}NO_3$ $[M+H]^+$: 330.2064, found 330.2067.

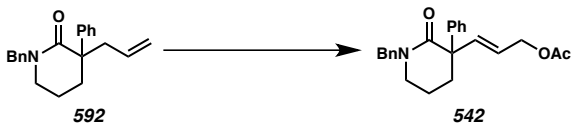


590 ***541***

(*E*)-3-(1-benzyl-3-(2-methoxyethyl)-2-oxopiperidin-3-yl)allyl acetate (541):

Acetate **541** was prepared from **590** using General Procedure D. 55% isolated yield, 61% combined yield with enal. R*f* = 0.2 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.31 (m, 3H), 7.30–7.25 (m, 2H), 5.91 (dt, *J* = 15.9, 1.3 Hz, 1H), 5.68 (dt, *J* = 15.9, 6.2 Hz, 1H), 4.69 (d, *J* = 14.5 Hz, 1H), 4.67–4.59 (m, 2H), 4.57 (d, *J* = 14.6 Hz, 1H), 3.57–3.45 (m, 2H), 3.34 (s, 3H), 3.30–3.17 (m, 2H), 2.24–2.14 (m, 1H), 2.12 (s, 3H), 2.02–1.71 (m, 5H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 172.0, 170.8, 139.0, 137.4, 128.6, 128.0, 127.3, 124.0, 69.5, 64.9, 58.5, 50.6, 47.7, 47.3, 38.4, 30.8, 21.0, 19.2; IR (Neat Film, NaCl) 2936, 2872, 1738, 1634, 1489, 1453, 1360, 1240, 1196, 1113,

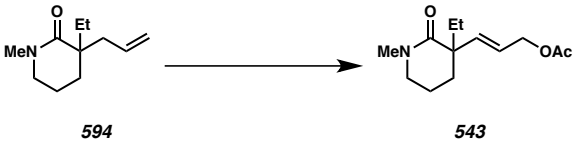
1028, 972, 736 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{20}H_{28}NO_4$ $[M+H]^+$: 346.2013, found 346.2023.



592 ***542***

(*E*)-3-(1-benzyl-2-oxo-3-phenylpiperidin-3-yl)allyl acetate (541):

Acetate **542** was prepared from **592** using General Procedure D. 62% isolated yield, 70% combined yield with enal. R*f* = 0.8 (50% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.27 (m, 8H), 7.25–7.18 (m, 2H), 6.38 (dt, *J* = 16.0, 1.4 Hz, 1H), 5.69 (dt, *J* = 16.0, 6.2 Hz, 1H), 4.82 (d, *J* = 14.4 Hz, 1H), 4.64 (dt, *J* = 6.2, 1.2 Hz, 2H), 4.54 (d, *J* = 14.4 Hz, 1H), 3.34–3.12 (m, 2H), 2.32–2.13 (m, 2H), 2.08 (s, 3H), 1.83–1.71 (m, 1H), 1.71–1.59 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.4, 171.0, 143.3, 139.3, 137.4, 128.8, 128.6, 128.5, 127.6, 127.5, 126.9, 123.7, 65.2, 53.9, 51.0, 47.6, 33.3, 21.2, 18.9; IR (Neat Film, NaCl) 2934, 1737, 1636, 1494, 1445, 1352, 1231, 1195, 1027, 761, 700 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{23}H_{26}NO_3$ $[M+H]^+$: 364.1906, found 364.1901.

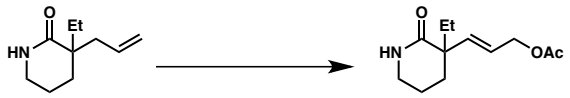


594 ***543***

(*E*)-3-(3-ethyl-1-methyl-2-oxopiperidin-3-yl)allyl acetate (543):

Acetate **543** was prepared from **594** using General Procedure D. 59% isolated yield, 65% combined yield with enal. R*f* = 0.1 (50% ethyl acetate in hexanes); ^{1}H NMR

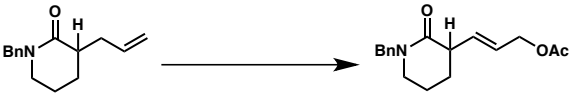
($CDCl_3$, 500 MHz) δ 5.83 (dt, *J* = 16.0, 1.4 Hz, 1H), 5.55 (dt, *J* = 16.0, 6.2 Hz, 1H), 4.70–4.32 (m, 2H), 3.35–3.26 (m, 1H), 3.25–3.15 (m, 1H), 2.92 (s, 3H), 2.05 (s, 3H), 1.91–1.76 (m, 5H), 1.64 (dq, *J* = 13.7, 7.5 Hz, 1H), 0.80 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 172.8, 171.0, 139.4, 123.5, 65.2, 50.5, 48.3, 35.3, 31.7, 29.1, 21.2, 19.3, 8.5; IR (Neat Film, NaCl) 2940, 1739, 1636, 1500, 1446, 1362, 1242, 1026, 981 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{13}H_{21}NO_3$ $[M+H]^+$: 240.1594, found 240.1598.



593 ***544***

(*E*)-3-(3-ethyl-2-oxopiperidin-3-yl)allyl acetate (544):

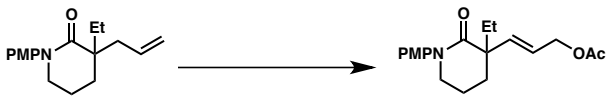
Acetate **544** was prepared from **593** using General Procedure D. 51% isolated yield, 56% combined yield with enal. R*f* = 0.1 (67% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.00 (s, 1H), 5.82 (dt, *J* = 16.0, 1.3 Hz, 1H), 5.62 (dt, *J* = 15.9, 6.2 Hz, 1H), 4.68–4.41 (m, 2H), 3.28 (qd, *J* = 4.2, 3.6, 1.7 Hz, 2H), 2.05 (s, 3H), 1.96–1.70 (m, 5H), 1.63 (dq, *J* = 13.7, 7.5 Hz, 1H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 175.0, 171.0, 138.9, 123.9, 65.1, 48.2, 42.8, 31.4, 29.0, 21.2, 19.2, 8.5; IR (Neat Film, NaCl) 3203, 2941, 1740, 1657, 1490, 1361, 1231, 1027, 980 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{12}H_{20}NO_3$ $[M+H]^+$: 226.1438, found 226.1430.



596 ***545***

(*E*)-3-(1-benzyl-2-oxopiperidin-3-yl)allyl acetate (545):

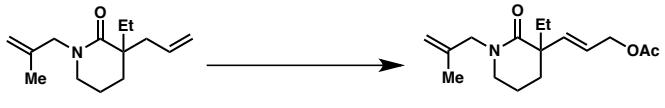
Acetate **545** was prepared from **596** using General Procedure D. 61% isolated yield. R*f* = 0.2 (33% ethyl acetate in hexanes); ^{1}H NMR (CDCl3, 500 MHz) δ 7.37–7.19 (m, 5H), 6.06 (dd, *J* = 15.7, 6.4 Hz, 1H), 5.71 (dt, *J* = 15.2, 6.3 Hz, 1H), 4.78–4.38 (m, 4H), 3.22 (t, *J* = 5.9 Hz, 2H), 3.16 (q, *J* = 7.0 Hz, 1H), 2.07 (d, *J* = 1.6 Hz, 3H), 2.06–1.70 (m, 4H); ^{13}C NMR (CDCl3, 126 MHz) δ 171.0, 170.3, 137.3, 134.2, 128.7, 128.3, 127.5, 125.6, 65.1 50.5, 47.5, 44.7, 27.2, 21.4, 21.2; IR (Neat Film, NaCl) 3225, 2936, 1738, 1618, 1494, 1453, 1361, 1234, 1028, 737 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{22}NO_3$ $[M+H]^+$: 288.1594, found 288.1607.



597 ***546***

(*E*)-3-(3-ethyl-1-(4-methoxyphenyl)-2-oxopiperidin-3-yl)allyl acetate (546):

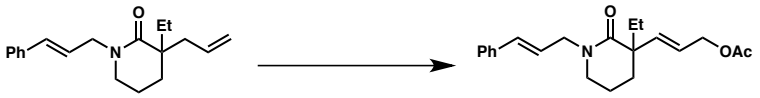
Acetate **546** was prepared from **597** using General Procedure D. 54% isolated yield, 61% combined yield with enal. R*f* = 0.2 (33% ethyl acetate in hexanes); ^{1}H NMR (CDCl3, 500 MHz) δ 7.15–7.06 (m, 2H), 6.96–6.84 (m, 2H), 5.91 (dt, *J* = 15.9, 1.3 Hz, 1H), 5.68 (dt, *J* = 15.9, 6.2 Hz, 1H), 4.71–4.52 (m, 2H), 3.80 (s, 3H), 3.70–3.48 (m, 2H), 2.08 (s, 3H), 2.04–1.82 (m, 5H), 1.69 (dq, *J* = 13.6, 7.4 Hz, 1H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (CDCl3, 126 MHz) δ 173.1, 171.0, 158.2, 139.5, 136.7, 127.6, 123.7, 114.5, 65.3, 55.6, 52.5, 48.8, 32.0, 29.4, 21.2, 20.0, 8.7; IR (Neat Film, NaCl) 2939, 1739, 1645, 1607, 1511, 1464, 1294, 1243, 1030, 825 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{19}H_{26}NO_4$ $[M+H]^+$: 332.1856, found 332.1871.



598 ***547***

(*E*)-3-(3-ethyl-1-(2-methylallyl)-2-oxopiperidin-3-yl)allyl acetate (547):

Acetate **547** was prepared from **598** using General Procedure D. 50% isolated yield, 56% combined yield with enal. R*f* = 0.2 (33% ethyl acetate in hexanes); ^{1}H NMR (CDCl3, 500 MHz) δ 5.85 (dt, *J* = 15.9, 1.3 Hz, 1H), 5.60 (dt, *J* = 15.9, 6.2 Hz, 1H), 4.86 (h, *J* = 1.3 Hz, 1H), 4.74 (qt, *J* = 1.6, 0.7 Hz, 1H), 4.63–4.49 (m, 2H), 4.02–3.95 (m, 1H), 3.94–3.87 (m, 1H), 3.32–3.05 (m, 2H), 2.06 (s, 3H), 1.95–1.74 (m, 5H), 1.73–1.49 (m, 4H), 0.84 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (CDCl3, 126 MHz) δ 172.5, 171.0, 140.7, 139.6, 123.6, 112.0, 65.2, 52.7, 48.6, 47.7, 31.9, 29.3, 21.2, 20.2, 19.4, 8.7; IR (Neat Film, NaCl) 2939, 1740, 1636, 1489, 1441, 1362, 1230, 1198, 1025, 967, 896 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{16}H_{26}NO_3$ $[M+H]^+$: 280.1907, found 280.1914.

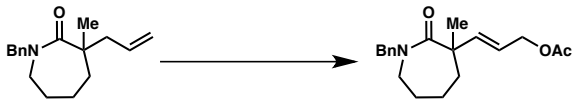


599 ***548***

(*E*)-3-(1-cinnamyl-3-ethyl-2-oxopiperidin-3-yl)allyl acetate (548):

Acetate **548** was prepared from **599** using General Procedure D. 51% isolated yield, 60% combined yield with enal. R*f* = 0.3 (33% ethyl acetate in hexanes); ^{1}H NMR (CDCl3, 500 MHz) δ 7.39–7.28 (m, 4H), 7.26–7.19 (m, 1H), 6.48 (dd, *J* = 15.9, 1.4 Hz, 1H), 6.14 (dt, *J* = 15.8, 6.5 Hz, 1H), 5.87 (dt, *J* = 15.9, 1.3 Hz, 1H), 5.60 (dt, *J* = 15.9, 6.2 Hz, 1H), 4.65–4.48 (m, 2H), 4.21–4.07 (m, 2H), 3.37–3.20 (m, 2H), 2.06 (s, 3H), 1.91–1.76 (m, 4H), 1.73–1.61 (m, 2H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (CDCl3, 126 MHz)

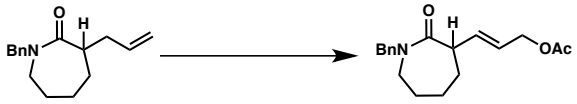
δ 172.5, 171.0, 139.5, 136.7, 132.9, 128.7, 127.8, 126.5, 124.7, 123.6, 65.3, 49.6, 48.5, 47.9, 31.8, 29.1, 21.2, 19.4, 8.6; IR (Neat Film, NaCl) 2939, 1740, 1636, 1490, 1448, 1361, 1232, 1026, 967, 750, 694 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{21}H_{28}NO_3$ $[M+H]^+$: 342.2066, found 342.2077.



600 ***549***

(*E*)-3-(1-benzyl-3-methyl-2-oxoazepan-3-yl)allyl acetate (549):

Acetate **549** was prepared from **600** using General Procedure D. 40% isolated yield. R*f* = 0.3 (33% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.34–7.28 (m, 2H), 7.26–7.22 (m, 3H), 5.94 (dt, *J* = 16.0, 1.4 Hz, 1H), 5.54 (dt, *J* = 16.0, 6.3 Hz, 1H), 4.80 (d, *J* = 14.6 Hz, 1H), 4.55 (dt, *J* = 6.1, 1.3 Hz, 2H), 4.45 (d, *J* = 14.6 Hz, 1H), 3.51 (ddt, *J* = 15.2, 11.3, 1.1 Hz, 1H), 3.08 (ddd, *J* = 15.2, 5.7, 2.1 Hz, 1H), 2.03 (s, 3H), 1.84–1.64 (m, 4H), 1.64–1.52 (m, 2H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 176.4, 170.9, 138.9, 138.4, 128.6, 128.3, 127.3, 123.3, 65.1, 53.0, 48.5, 47.6, 36.6, 27.9, 25.3, 21.1; IR (Neat Film, NaCl) 2925, 1740, 1636, 1419, 1363, 1236, 1028, 965, 745 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{19}H_{26}NO_3$ $[M+H]^+$: 316.1907, found 316.1921.



601 ***550***

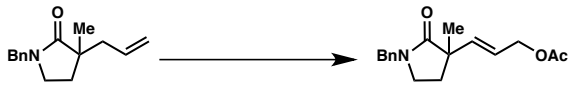
(*E*)-3-(1-benzyl-2-oxoazepan-3-yl)allyl acetate (550):

Acetate **550** was prepared from **601** using General Procedure D. 53% isolated yield, 63% combined yield with enal. R*f* = 0.2 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.22 (m, 5H), 6.18 (ddt, *J* = 15.6, 8.4, 1.3 Hz, 1H), 5.58 (dtd, *J* = 15.6, 6.3, 1.0 Hz, 1H), 4.71 (d, *J* = 14.6 Hz, 1H), 4.65–4.51 (m, 2H), 4.47 (d, *J* = 14.6 Hz, 1H), 3.44 (dd, *J* = 15.3, 11.1 Hz, 1H), 3.37–3.12 (m, 2H), 2.06 (s, 3H), 1.90 (dd, *J* = 11.1, 4.6 Hz, 1H), 1.84–1.71 (m, 1H), 1.71–1.57 (m, 2H), 1.36–1.17 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 175.5, 171.0, 137.9, 135.7, 128.7, 128.5, 127.5, 123.8, 65.2, 51.4, 48.0, 47.7, 31.1, 28.8, 27.6, 21.2; IR (Neat Film, NaCl) 2931, 1740, 1639, 1442, 1364, 1235, 1197, 1028, 972 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{18}H_{24}NO_3$ $[M+H]^+$: 302.1751, found 302.1758.

602 ***551***

(*E*)-3-(1-benzyl-3-ethyl-2-oxopyrrolidin-3-yl)allyl acetate (551):

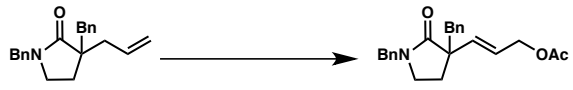
Acetate **551** was prepared from **602** using General Procedure D. 66% isolated yield. R*f* = 0.1 (25% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35–7.26 (m, 3H), 7.23–7.17 (m, 2H), 5.87 (dt, *J* = 15.9, 1.3 Hz, 1H), 5.64 (dt, *J* = 15.9, 6.2 Hz, 1H), 4.61–4.52 (m, 2H), 4.50 (d, *J* = 14.7 Hz, 1H), 4.41 (d, *J* = 14.7 Hz, 1H), 3.23–3.02 (m, 2H), 2.11–2.02 (m, 1H), 2.07 (s, 3H), 2.00–1.92 (m, 1H), 1.78–1.63 (m, 1H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 176.2, 170.9, 136.7, 136.6, 128.8, 128.2, 127.7, 123.9, 65.0, 50.9, 46.9, 43.6, 29.7, 28.2, 21.1, 8.8; IR (Neat Film, NaCl) 2925, 1740, 1636, 1419, 1363, 1236, 1028, 965, 745 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{18}H_{24}NO_3$ $[M+H]^+$: 302.1751, found 302.1759.



603 ***552***

(*E*)-3-(1-benzyl-3-methyl-2-oxopyrrolidin-3-yl)allyl acetate (552):

Acetate **552** was prepared from **603** using General Procedure D. 48% isolated yield, 54% combined yield with enal. R*f* = 0.1 (40% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35–7.26 (m, 3H), 7.24–7.18 (m, 2H), 5.89 (dt, *J* = 15.8, 1.3 Hz, 1H), 5.66 (dt, *J* = 15.8, 6.2 Hz, 1H), 4.56 (dt, *J* = 6.2, 1.5 Hz, 2H), 4.46 (d, *J* = 3.3 Hz, 2H), 3.26–3.05 (m, 2H), 2.12 (ddd, *J* = 12.8, 7.5, 5.5 Hz, 1H), 2.07 (s, 3H), 1.89 (ddd, *J* = 12.7, 7.7, 6.4 Hz, 1H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 176.7, 170.9, 137.5, 136.6, 128.8, 128.2, 127.7, 123.4, 64.9, 47.1, 46.7, 43.3, 32.5, 32.1, 21.1; IR (Neat Film, NaCl) 2927, 1738, 1689, 1495, 1428, 1361, 1233, 1028, 972, 740 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{22}NO_3$ $[M+H]^+$: 288.1594, found 288.1593.

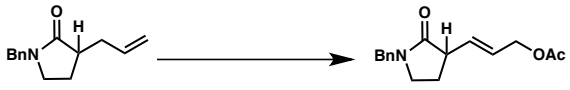


604 ***553***

(*E*)-3-(1,3-dibenzyl-2-oxopyrrolidin-3-yl)allyl acetate (553):

Acetate **553** was prepared from **604** using General Procedure D. 50% isolated yield, 58% combined yield with enal. R*f* = 0.2 (40% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29–7.26 (m, 1H), 7.26–7.20 (m, 5H), 7.20–7.14 (m, 2H), 7.11–7.06 (m, 2H), 5.97 (dt, *J* = 15.9, 1.4 Hz, 1H), 5.63 (dt, *J* = 15.8, 6.1 Hz, 1H), 4.63–4.51 (m, 2H), 4.45 (d, *J* = 14.7 Hz, 1H), 4.27 (d, *J* = 14.7 Hz, 1H), 3.15 (d, *J* = 13.3 Hz, 1H), 2.98 (ddd, *J* = 9.6, 8.0, 6.2 Hz, 1H), 2.77 (d, *J* = 13.3 Hz, 1H), 2.61 (ddd, *J* = 9.6, 8.3, 4.9

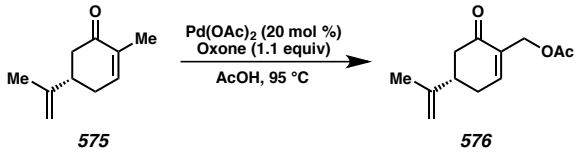
Hz, 1H), 2.07 (s, 3H), 2.06–1.99 (m, 1H), 1.94 (ddd, *J* = 13.0, 8.0, 4.9 Hz, 1H); ^{13}C NMR (CDCl3, 126 MHz) δ 175.4, 170.9, 137.0, 137.0, 136.3, 130.5, 128.7, 128.2, 128.2, 127.6, 126.8, 124.1, 64.8, 51.8, 47.0, 43.5, 43.0, 28.0, 21.1; IR (Neat Film, NaCl) 2920, 1740, 1685, 1495, 1437, 1361, 1230, 1028, 973, 743 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{23}H_{26}NO_3$ [M+H]$^+$: 364.1907, found 364.1931.



605 ***555***

(*E*)-3-(1-benzyl-2-oxopyrrolidin-3-yl)allyl acetate (555):

Acetate **555** was prepared from **605** using General Procedure D. 57% isolated yield, 61% combined yield with enal. R*f* = 0.3 (50% ethyl acetate in hexanes); ^{1}H NMR (CDCl3, 500 MHz) δ 7.36–7.27 (m, 3H), 7.25–7.19 (m, 2H), 5.92 (ddt, *J* = 15.5, 6.6, 1.3 Hz, 1H), 5.76 (dtd, *J* = 15.6, 6.1, 1.4 Hz, 1H), 4.59 (dq, *J* = 6.3, 1.2 Hz, 2H), 4.49 (d, *J* = 14.6 Hz, 1H), 4.44 (d, *J* = 14.7 Hz, 1H), 3.28–3.12 (m, 3H), 2.26 (dddd, *J* = 12.8, 8.8, 6.7, 4.1 Hz, 1H), 2.08 (s, 3H), 1.91 (dq, *J* = 12.7, 8.5 Hz, 1H); ^{13}C NMR (CDCl3, 126 MHz) δ 174.2, 170.9, 136.5, 132.2, 128.9, 128.3, 127.8, 126.7, 64.8, 47.1, 45.0, 44.9, 25.0, 21.1; IR (Neat Film, NaCl) 2923, 1735, 1685, 1430, 1363, 1238, 1027, 971 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{16}H_{20}NO_3$ [M+H]$^+$: 274.1438, found 274.1447.



575 ***576***

(*S*)-(6-oxo-4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl acetate (576):

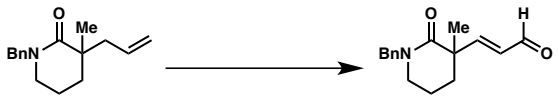
To a flame-dried 25 mL round-bottom flask with a magnetic stir bar were added, in order, (*S*)-carvone (**575**, 30 mg, 0.2 mmol, 1.00 equiv), palladium(II) acetate (9 mg, 0.04 mmol, 0.20 equiv), and Oxone (68 mg, 0.22 mmol, 1.10 equiv). The flask was then capped with a rubber septum and evacuated and backfilled twice with nitrogen. Acetic acid (1.00 mL) was added by syringe. The resulting suspension was stirred under nitrogen for 5 minutes at 23 °C and then heated to 95 °C in an oil bath. Although TLC analysis did not show full consumption of **575**, the reaction was stopped at 16 hours. The flask was allowed to cool to 23 °C and the contents were filtered through a short plug of silica gel, rinsing with ethyl acetate. The filtrate was adsorbed onto silica gel (approx. 2 g), which was then flushed with ethyl acetate. The eluent was concentrated to give the crude product as an oil. The crude residue was purified by silica gel column chromatography (15% ethyl acetate in hexanes) to provide recovered (*S*)-carvone (14 mg, 0.096 mmol, 48% yield, 52% conversion) and acetate **576** as a colorless oil (8.7 mg, 21% yield, 40% yield based on recovered starting material). R*f* = 0.3 (25% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.75 (ddq, *J* = 5.6, 2.8, 1.4 Hz, 1H), 5.18 (q, *J* = 0.9 Hz, 1H), 5.05 (dd, *J* = 1.3, 0.7 Hz, 1H), 4.61 (dd, *J* = 12.8, 1.0 Hz, 1H), 4.59–4.53 (m, 1H), 2.87–2.74 (m, 1H), 2.64 (ddd, *J* = 16.0, 3.7, 1.6 Hz, 1H), 2.53 (dddt, *J* = 18.2, 6.0, 4.5, 1.5 Hz, 1H), 2.40 (dd, *J* = 16.1, 13.2 Hz, 1H), 2.35–2.26 (m, 1H), 2.10 (s, 3H), 1.80 (dt, *J* = 2.6, 1.4 Hz, 3H).; ^{13}C NMR ($CDCl_3$, 126 MHz) δ 199.3, 170.8, 145.4, 144.3, 135.8, 113.8, 65.9, 43.2, 38.6, 31.5, 21.1, 15.9; IR (Neat Film, NaCl) 2923, 1741, 1673, 1433, 1371, 1227, 1109, 1029, 903 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{12}H_{17}O_3$ $[M+H]^+$: 209.1178, found 209.1187.

5.5.6 ENAL CHARACTERIZATION DATA

586 ***561***

(*E*)-3-(1-benzyl-3-ethyl-2-oxopiperidin-3-yl)acrylaldehyde (591):

Enal **591** was prepared from **586** using General Procedure E. 50% isolated yield, 56% combined yield with allylic acetate. R*f* = 0.2 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.57 (d, *J* = 7.6 Hz, 1H), 7.37–7.27 (m, 3H), 7.25–7.18 (m, 2H), 7.06 (d, *J* = 16.2 Hz, 1H), 6.13 (dd, *J* = 16.2, 7.7 Hz, 1H), 4.70 (d, *J* = 14.5 Hz, 1H), 4.49 (d, *J* = 14.5 Hz, 1H), 3.45–3.05 (m, 2H), 2.03–1.89 (m, 3H), 1.85–1.69 (m, 3H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 194.2, 171.4, 161.9, 137.1, 131.6, 128.8, 128.1, 127.7, 50.9, 49.8, 47.7, 31.6, 28.5, 19.5, 8.6; IR (Neat Film, NaCl) 2940, 1713, 1689, 1634, 1606, 1495, 1453, 1356, 1262, 1198, 982, 735 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{22}NO_2$ $[M+H]^+$: 272.1645, found 272.1647.



587 ***562***

(*E*)-3-(1-benzyl-3-methyl-2-oxopiperidin-3-yl)acrylaldehyde (562):

Enal **562** was prepared from **587** using General Procedure E. 67% isolated yield. R*f* = 0.1 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.57 (d, *J* = 7.6 Hz, 1H), 7.37–7.27 (m, 3H), 7.25–7.17 (m, 2H), 7.08 (d, *J* = 16.1 Hz, 1H), 6.15 (dd, *J* = 16.1, 7.6 Hz, 1H), 4.61 (d, *J* = 14.5 Hz, 1H), 4.56 (d, *J* = 14.5 Hz, 1H), 3.33–3.10 (m, 2H), 2.09–1.94 (m, 1H), 1.94–1.71 (m, 3H), 1.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 194.2, 171.7, 162.5, 137.1, 130.9, 128.9, 128.2, 127.7, 50.8, 47.8, 45.8, 33.4, 26.3, 19.5;

IR (Neat Film, NaCl) 2931, 1689, 1638, 1488, 1453, 1351, 1198, 1106, 978, 735, 702 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{16}H_{20}NO_2$ $[M+H]^+$: 258.1489, found 258.1500.

588 ***563***

(*E*)-3-(1,3-dibenzyl-2-oxopiperidin-3-yl)acrylaldehyde (563):

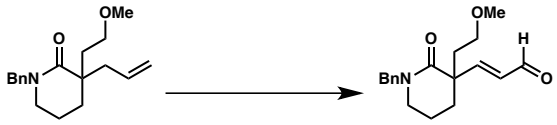
Enal **563** was prepared from **588** using General Procedure E. 50% isolated yield, 56% combined yield with allylic acetate. R*f* = 0.4 (33% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.59 (d, *J* = 7.6 Hz, 1H), 7.32–7.26 (m, 4H), 7.26–7.23 (m, 2H), 7.20–7.10 (m, 4H), 7.04 (d, *J* = 16.2 Hz, 1H), 6.10 (dd, *J* = 16.1, 7.6 Hz, 1H), 4.79 (d, *J* = 14.5 Hz, 1H), 4.41 (d, *J* = 14.5 Hz, 1H), 3.46 (d, *J* = 13.3 Hz, 1H), 3.22–3.00 (m, 2H), 2.88 (d, *J* = 13.3 Hz, 1H), 1.99–1.77 (m, 2H), 1.79–1.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 194.0, 170.4, 161.6, 136.8, 136.2, 132.0, 131.0, 128.8, 128.3, 128.1, 127.6, 127.1, 51.2, 51.1, 47.8, 44.5, 29.3, 19.5; IR (Neat Film, NaCl) 2924, 1689, 1636, 1494, 1453, 1355, 1194, 982, 743 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{22}H_{24}NO_2$ $[M+H]^+$: 334.1802, found 334.1802.

589 ***564***

(*E*)-3-(1-benzyl-2-oxo-3-propylpiperidin-3-yl)acrylaldehyde (564):

Enal **564** was prepared from **589** using General Procedure E. 55% isolated yield, 62% combined yield with allylic acetate. R*f* = 0.5 (33% ethyl acetate in hexanes); ^1H

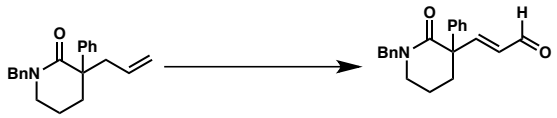
NMR ($CDCl_3$, 500 MHz) δ 9.57 (d, *J* = 7.7 Hz, 1H), 7.36–7.26 (m, 3H), 7.25–7.19 (m, 2H), 7.06 (d, *J* = 16.2 Hz, 1H), 6.12 (dd, *J* = 16.2, 7.6 Hz, 1H), 4.67 (d, *J* = 14.5 Hz, 1H), 4.51 (d, *J* = 14.6 Hz, 1H), 3.40–3.03 (m, 2H), 1.93 (dd, *J* = 7.3, 4.6 Hz, 2H), 1.91–1.84 (m, 1H), 1.84–1.68 (m, 3H), 1.38–1.15 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 194.2, 171.4, 162.1, 137.1, 131.4, 128.8, 128.2, 127.7, 51.0, 49.7, 47.7, 41.1, 29.2, 19.6, 17.5, 14.5; IR (Neat Film, NaCl) 2957, 1688, 1634, 1489, 1453, 1352, 1196, 982, 736 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{18}H_{24}NO_2$ $[M+H]^+$: 286.1802, found 286.1808.



590 ***565***

(*E*)-3-(1-benzyl-3-(2-methoxyethyl)-2-oxopiperidin-3-yl)acrylaldehyde (565):

Enal **565** was prepared from **590** using General Procedure E. 54% isolated yield. R*f* = 0.3 (50% ethyl acetate in hexanes); 9.57 (d, *J* = 7.6 Hz, 1H), 7.36–7.27 (m, 3H), 7.25–7.21 (m, 2H), 7.03 (d, *J* = 16.1 Hz, 1H), 6.16 (dd, *J* = 16.2, 7.6 Hz, 1H), 4.71 (d, *J* = 14.5 Hz, 1H), 4.48 (d, *J* = 14.5 Hz, 1H), 3.46 (td, *J* = 6.4, 1.7 Hz, 2H), 3.28 (s, 3H), 3.26–3.16 (m, 2H), 2.22 (dt, *J* = 14.1, 6.6 Hz, 1H), 2.13–2.02 (m, 2H), 1.97 (dddd, *J* = 13.8, 6.7, 3.3, 1.1 Hz, 1H), 1.83 (ddtd, *J* = 13.5, 6.7, 5.0, 3.4 Hz, 1H), 1.79–1.66 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 194.1, 170.9, 161.6, 137.1, 131.6, 128.8, 128.2, 127.7, 69.2, 58.7, 51.0, 48.7, 47.8, 38.2, 30.2, 19.6; IR (Neat Film, NaCl) 2927, 1685, 1636, 1490, 1452, 1355, 1196, 1112, 979, 736 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{18}H_{24}NO_3$ $[M+H]^+$: 302.1751, found 302.1759.



592 ***566***

(*E*)-3-(1-benzyl-2-oxo-3-phenylpiperidin-3-yl)acrylaldehyde (566):

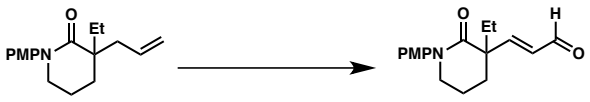
Enal **566** was prepared from **592** using General Procedure E. 48% isolated yield, 54% combined yield with allylic acetate. R*f* = 0.2 (20% ethyl acetate in hexanes); ^{1}H NMR (CDCl3, 500 MHz) δ 9.61 (d, *J* = 7.7 Hz, 1H), 7.53 (d, *J* = 16.2 Hz, 1H), 7.42–7.26 (m, 8H), 7.25–7.21 (m, 2H), 6.17 (dd, *J* = 16.2, 7.7 Hz, 1H), 4.83 (d, *J* = 14.3 Hz, 1H), 4.59 (d, *J* = 14.3 Hz, 1H), 3.38–3.17 (m, 2H), 2.37 (ddd, *J* = 13.5, 5.5, 3.3 Hz, 1H), 2.30–2.07 (m, 1H), 1.83–1.61 (m, 2H); ^{13}C NMR (CDCl3, 126 MHz) δ 194.4, 169.9, 161.3, 140.8, 137.0, 130.5, 128.9, 128.5, 127.8, 127.6, 127.3, 54.6, 51.1, 47.4, 32.0, 18.7; IR (Neat Film, NaCl) 2937, 1683, 1634, 1494, 1446, 1352, 1196, 763 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{21}H_{22}NO_2$ $[M+H]^+$: 320.1645, found 320.1658.

594 ***567***

(*E*)-3-(3-ethyl-1-methyl-2-oxopiperidin-3-yl)acrylaldehyde (567):

Enal **567** was prepared from **594** using General Procedure E. 59% isolated yield. R*f* = 0.2 (33% ethyl acetate in hexanes); ^{1}H NMR (CDCl3, 500 MHz) δ 9.55 (d, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 16.2 Hz, 1H), 6.09 (dd, *J* = 16.2, 7.7 Hz, 1H), 3.35 (ddd, *J* = 11.9, 8.7, 5.0 Hz, 1H), 3.25 (ddd, *J* = 12.1, 5.8, 4.9 Hz, 1H), 2.95 (s, 3H), 1.97–1.72 (m, 6H), 0.84 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (CDCl3, 126 MHz) δ 194.2, 171.4, 161.9, 131.6, 50.4, 49.6,

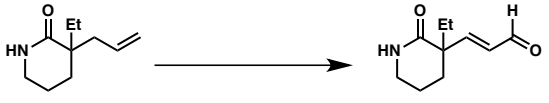
35.5, 31.4, 28.5, 19.5, 8.5; IR (Neat Film, NaCl) 2939, 1688, 1635, 1506, 1456, 1257, 1204, 1104 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{11}H_{18}NO_2$ $[M+H]^+$: 196.1332, found 196.1328.



597 ***568***

(*E*)-3-(3-ethyl-1-(4-methoxyphenyl)-2-oxopiperidin-3-yl)acrylaldehyde (568):

Enal **568** was prepared from **597** using General Procedure E. 53% isolated yield, 58% combined yield with allylic acetate. R*f* = 0.2 (33% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.58 (d, *J* = 7.6 Hz, 1H), 7.14–7.10 (m, 2H), 7.07 (d, *J* = 16.2 Hz, 1H), 6.94–6.87 (m, 2H), 6.19 (dd, *J* = 16.2, 7.6 Hz, 1H), 3.81 (s, 3H), 3.66 (ddd, *J* = 12.1, 8.7, 5.0 Hz, 1H), 3.62–3.52 (m, 1H), 2.16–1.89 (m, 5H), 1.83 (dq, *J* = 13.7, 7.5 Hz, 1H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 194.2, 171.7, 161.9, 158.4, 136.2, 131.6, 127.5, 114.6, 55.6, 52.5, 50.1, 31.7, 28.7, 20.1, 8.6; IR (Neat Film, NaCl) 2938, 1685, 1647, 1510, 1295, 1243, 1130, 1032, 982, 827 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{22}NO_3$ $[M+H]^+$: 288.1594, found 288.1604.

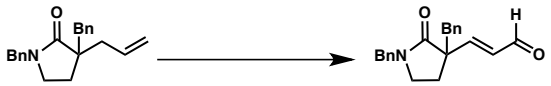


593 ***569***

(*E*)-3-(3-ethyl-2-oxopiperidin-3-yl)acrylaldehyde (569):

Enal **569** was prepared from **593** using General Procedure E. 44% isolated yield, 53% combined yield with allylic acetate. R*f* = 0.1 (20% ethyl acetate in hexanes); ^1H

NMR ($CDCl_3$, 500 MHz) δ 9.55 (d, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 16.1 Hz, 1H), 6.14 (dd, *J* = 16.2, 7.6 Hz, 1H), 5.85 (s, 1H), 3.46–3.26 (m, 2H), 2.01–1.90 (m, 3H), 1.90–1.84 (m, 1H), 1.84–1.73 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 194.1, 173.4, 161.1, 131.8, 49.4, 42.8, 31.1, 28.3, 19.3, 8.4; IR (Neat Film, NaCl) 3287, 2941, 1687, 1662, 1489, 1464, 1354, 1107, 983 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{10}H_{16}NO_2$ $[M+H]^+$: 182.1176, found 182.1177.

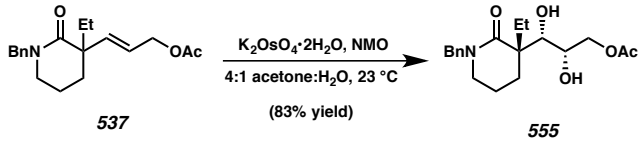


604 ***570***

(*E*)-3-(1,3-dibenzyl-2-oxopyrrolidin-3-yl)acrylaldehyde (570):

Enal **570** was prepared from **604** using General Procedure E. 30% isolated yield. R*f* = 0.4 (33% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.58 (d, *J* = 7.6 Hz, 1H), 7.30–7.26 (m, 3H), 7.26–7.22 (m, 3H), 7.20–7.14 (m, 2H), 7.12–7.04 (m, 3H), 6.12 (dd, *J* = 16.0, 7.6 Hz, 1H), 4.45 (d, *J* = 14.7 Hz, 1H), 4.26 (d, *J* = 14.6 Hz, 1H), 3.24 (d, *J* = 13.4 Hz, 1H), 3.07–2.88 (m, 1H), 2.83 (d, *J* = 13.4 Hz, 1H), 2.69–2.52 (m, 1H), 2.18 (ddd, *J* = 13.3, 8.2, 5.2 Hz, 1H), 2.11–1.98 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 193.8, 173.8, 158.9, 135.9, 131.7, 130.4, 128.9, 128.6, 128.3, 127.9, 127.4, 53.1, 47.3, 43.5, 42.8, 27.4; IR (Neat Film, NaCl) 2921, 1738, 1683, 1495, 1454, 1246, 981, 745, 702 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{21}H_{22}NO_2$ $[M+H]^+$: 320.1645, found 320.1640.

5.5.7 ALLYLIC ACETATE DERIVATIZATION PROCEDURES AND CHARACTERIZATION DATA

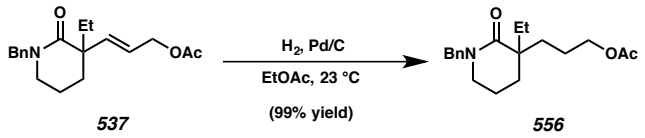


537 *555*

3-(1-benzyl-3-ethyl-2-oxopiperidin-3-yl)-2,3-dihydroxypropyl acetate (555):

To a 1 dram screw-top vial with a magnetic stir bar were added, in order, acetate **537** (18 mg, 0.057 mmol, 1.00 equiv), acetone (reagent grade, 540 μL), deionized water (180 μL), potassium osmate(VI) dehydrate (2 mg, 0.006 mmol, 0.10 equiv), and 4-methylmorpholine *N*-oxide (13 mg, 0.144 mmol, 2.00 equiv). The vial was sealed with a Teflon-lined cap and the purple solution was stirred at 23 °C for 3 hours. Upon completion (as determined by TLC analysis), the reaction mixture was adsorbed onto Celite and purified by silica gel column chromatography (50% ethyl acetate in hexanes) to provide the major diastereomer **555** as colorless crystals (16.5 mg, 83% yield). R*f* = 0.3 (50% ethyl acetate in hexanes); ^{1}H NMR (CDCl3, 500 MHz) δ 7.36–7.30 (m, 2H), 7.29–7.26 (m, 2H), 7.26–7.23 (m, 1H), 5.96 (d, *J* = 8.5 Hz, 1H), 4.60 (d, *J* = 14.7 Hz, 1H), 4.56 (d, *J* = 14.8 Hz, 1H), 4.28 (dd, *J* = 11.5, 7.5 Hz, 1H), 4.22 (dd, *J* = 11.5, 4.8 Hz, 1H), 3.96 (dddd, *J* = 9.6, 7.5, 4.8, 1.5 Hz, 1H), 3.52 (dd, *J* = 8.5, 1.4 Hz, 1H), 3.31–3.07 (m, 2H), 2.27 (d, *J* = 9.7 Hz, 1H), 2.10 (s, 3H), 2.03–1.93 (m, 1H), 1.93–1.85 (m, 1H), 1.85–1.77 (m, 2H), 1.77–1.63 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (CDCl3, 126 MHz) δ 176.9, 171.3, 136.7, 128.8, 128.1, 127.6, 75.8, 69.8, 67.5, 50.5, 47.1, 45.4, 30.2, 27.3, 21.2, 20.0, 8.1; IR (Neat Film, NaCl) 3382, 2936, 2878, 1736, 1606, 1495, 1453, 1362, 1248, 1206, 1039, 737 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{19}H_{28}NO_5$ $[M+H]^+$: 350.1962, found 350.1977.

Colorless, translucent X-ray quality crystals of diol **555** were obtained by slow diffusion of 2% benzene in pentane into a solution of **555** in ether at –20 °C, mp: 86–88 °C.

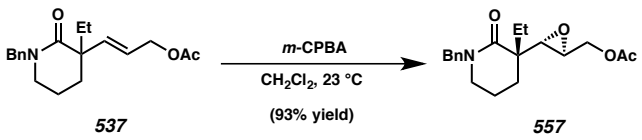


537 *556*

3-(1-benzyl-3-ethyl-2-oxopiperidin-3-yl)propyl acetate (556):

To a round-bottom flask with a magnetic stir bar were added acetate **537** (40 mg, 0.13 mmol, 1.00 equiv) and ethyl acetate (750 μL). Palladium on carbon (10 wt. %, 2 mg) was added, and the suspension was stirred vigorously while the air atmosphere was replaced with hydrogen by three evacuation/back-fill cycles. The reaction mixture was then stirred at 23 °C under an atmosphere of hydrogen (supplied by a balloon) for 5 hours. As TLC analysis showed remaining starting material, an additional 5 mg of palladium on carbon (10 wt. %) was added. After letting the reaction mixture stir for an additional 19 hours, TLC analysis showed full conversion. The mixture was filtered through Celite, rinsing with ethyl acetate. The filtrate was concentrated and the crude residue was purified by silica gel column chromatography (25% ethyl acetate in hexanes) to provide aliphatic acetate **556** as a colorless oil (34.0 mg, 99% yield). R*f* = 0.7 (50% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.27 (m, 2H), 7.25–7.19 (m, 3H), 4.66 (d, *J* = 14.5 Hz, 1H), 4.50 (d, *J* = 14.5 Hz, 1H), 4.22–3.85 (m, 2H), 3.29–3.13 (m, 2H), 2.05 (s, 3H), 1.94–1.50 (m, 10H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 174.6, 171.3, 137.8, 128.7, 128.2, 127.4, 65.1, 50.7, 47.8, 44.9, 34.9, 31.6, 29.4, 24.0, 21.2, 20.0, 8.9; IR (Neat Film, NaCl) 2936, 1737, 1631, 1453,

1362, 1241, 1038, 738, 701 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{19}H_{28}NO_3$ $[M+H]^+$: 318.2064, found 318.2051.

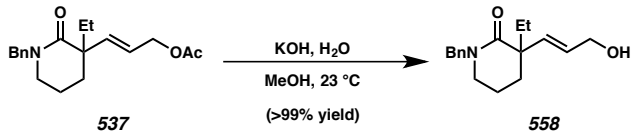


537 ***557***

(3-(1-benzyl-3-ethyl-2-oxopiperidin-3-yl)oxiran-2-yl)methyl acetate (557):

To a 1 dram screw-top vial with a magnetic stir bar were added, in order, acetate **537** (10 mg, 0.032 mmol, 1.00 equiv), 3-chloroperbezoic acid (54 mg, 0.32 mmol, 10.00 equiv), and dichloromethane (320 μL). The vial was sealed with a Teflon-lined cap and the pale yellow solution was stirred at 23 °C for 12 hours. Upon completion (as determined by TLC analysis), the reaction mixture was diluted with dichloromethane (3 mL) and quenched with saturated aqueous sodium thiosulfate (3 mL). The organic layer was separated and washed with saturated aqueous sodium bicarbonate solution (3 x 3 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. NMR analysis of the crude reaction mixture showed a single diasteromer. The crude was residue purified by silica gel column chromatography (25% ethyl acetate and 1% triethylamine in hexanes) to provide epoxide **557** as a colorless oil (9.9 mg, 93% yield, single diastereomer). R*f* = 0.5 (50% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36–7.27 (m, 3H), 7.24 (ddt, *J* = 7.6, 1.4, 0.7 Hz, 2H), 4.67 (d, *J* = 14.6 Hz, 1H), 4.56 (d, *J* = 14.6 Hz, 1H), 4.42 (dd, *J* = 12.2, 3.1 Hz, 1H), 3.97 (dd, *J* = 12.3, 6.3 Hz, 1H), 3.46 (d, *J* = 2.3 Hz, 1H), 3.20–3.15 (m, 2H), 3.13 (ddd, *J* = 6.3, 3.1, 2.4 Hz, 1H), 2.11 (s, 3H), 1.90 (dq, *J* = 13.8, 7.5 Hz, 1H), 1.85–1.72 (m, 1H), 1.68 (dt, *J* = 13.8, 7.5 Hz, 1H), 1.61–1.51 (m, 2H), 0.91 (t, *J* = 7.5 Hz, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 172.6, 170.9, 137.3, 128.8, 128.0,

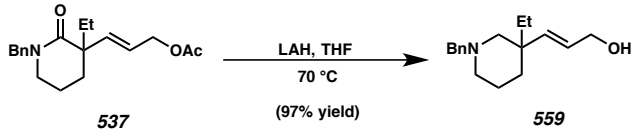
127.5, 64.8, 60.9, 52.2, 50.9, 47.6, 45.4, 28.9, 24.2, 20.9, 19.8, 8.7; IR (Neat Film, NaCl) 2940, 1744, 1632, 1494, 1453, 1364, 1232, 1037, 907, 735 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{19}H_{26}NO_4$ $[M+H]^+$: 332.1856, found 332.1853.



537 ***558***

(*E*)-1-benzyl-3-ethyl-3-(3-hydroxyprop-1-en-1-yl)piperidin-2-one (558):

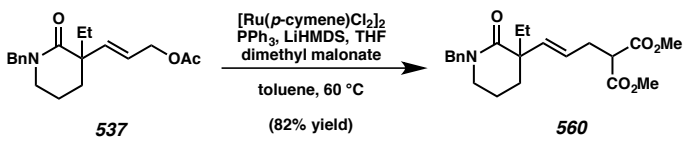
To a 1 dram screw-top vial with a magnetic stir bar were added, in order, acetate **537** (102 mg, 0.32 mmol, 1.00 equiv), freshly powdered potassium hydroxide (27 mg, 0.49 mmol, 1.50 equiv), methanol (1.3 mL), and water (300 μL). The vial was sealed with a Teflon-lined cap and the solution was stirred at 23 °C for 4 minutes. Upon completion (as determined by TLC analysis), the reaction mixture was adsorbed onto Celite and purified by silica gel column chromatography (50% ethyl acetate in hexanes) to provide allylic alcohol **558** as a colorless oil (88.0 mg, >99% yield). R*f* = 0.2 (50% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35–7.26 (m, 3H), 7.25–7.21 (m, 2H), 5.83 (dt, *J* = 15.9, 1.4 Hz, 1H), 5.75–5.65 (m, 1H), 4.68 (d, *J* = 14.5 Hz, 1H), 4.50 (d, *J* = 14.6 Hz, 1H), 4.26–4.05 (m, 2H), 3.35–3.06 (m, 2H), 1.97–1.86 (m, 1H), 1.86–1.64 (m, 6H), 0.86 (td, *J* = 7.4, 1.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.1, 137.6, 136.6, 128.8, 128.7, 128.2, 127.4, 63.9, 50.7, 48.4, 47.9, 32.0, 29.3, 19.4, 8.7; IR (Neat Film, NaCl) 3402, 2936, 2863, 1617, 1494, 1452, 1353, 1196, 981, 734, 701 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{24}NO_2$ $[M+H]^+$: 274.1802, found 274.1803.



537 ***559***

(*E*)-3-(1-benzyl-3-ethylpiperidin-3-yl)prop-2-en-1-ol (559):

To an oven-dried 1 dram screw-top vial with a magnetic stir bar were added, in order, acetate **537** (30 mg, 0.095 mmol, 1.00 equiv), lithium aluminum hydride (72 mg, 1.90 mmol, 20.00 equiv), and THF (500 μL). The vial was sealed with a Teflon-lined cap and the suspension was stirred at 70 °C for 10 hours. Upon completion (as determined by TLC analysis), the reaction mixture cooled to 0 °C using an ice water bath. 1.5 mL water was added slowly dropwise, followed by 1.5 mL NaOH (15 wt. %), followed by 4.5 mL water. The suspension was stirred until the color turned white (45 minutes), after which it was filtered through Celite, rinsing with ether. The filtrate was concentrated and the crude residue was purified by silica gel column chromatography (50% ethyl acetate and 1% triethylamine in hexanes with) to provide amine **559** as a colorless oil (23.9 mg, 97 % yield). R*f* = 0.3 (50% ethyl acetate in hexanes); ^{1}H NMR (CDCl3, 500 MHz) δ 7.33–7.27 (m, 4H), 7.26–7.21 (m, 1H), 5.58 (dt, *J* = 16.0, 5.7 Hz, 1H), 5.50 (dt, *J* = 15.9, 1.0 Hz, 1H), 4.12 (d, *J* = 5.6 Hz, 2H), 3.44 (s, 2H), 2.51–1.95 (m, 4H), 1.75 (s, 1H), 1.59 (m, 1H), 1.50 (d, *J* = 15.5 Hz, 3H), 1.37 (dt, *J* = 13.8, 7.2 Hz, 2H), 0.70 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (CDCl3, 126 MHz) δ 139.7, 139.0, 129.1, 128.2, 127.6, 127.0, 64.5, 63.7, 62.8, 54.8, 39.3, 33.4, 22.3, 7.9; IR (Neat Film, NaCl) 3326, 2934, 1453, 1349, 1091, 974, 739, 698 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{26}NO$ $[M+H]^+$: 260.2009, found 260.2018.

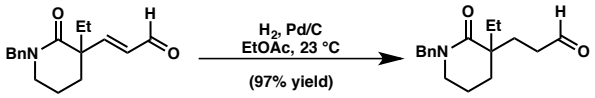


537 ***560***

dimethyl (*E*)-2-(3-(1-benzyl-3-ethyl-2-oxopiperidin-3-yl)allyl)malonate (560):

The conditions for the transformation were adapted from a known procedure.[23] In a nitrogen-filled glovebox, an oven-dried 1 dram screw-top vial with a magnetic stir bar was charged with dichloro(*p*-cymene)ruthenium(II) dimer (12 mg, 0.019 mmol, 0.50 equiv), triphenylphosphine (10 mg, 0.038 mmol, 1.00 equiv), and toluene (150 μL). To this solution was added a solution of acetate **537** (12 mg, 0.038 mmol, 1.00 equiv) in toluene (100 μL). Dimethyl malonate (7 μL, 0.057 mmol, 1.50 equiv) was then added, followed by a solution of lithium hexamethyldisilazide (9 mg, 0.052 mmol, 1.40 equiv) in THF (100 μL). The vial was sealed with a Teflon-lined cap and heated at 60 °C for 90 hours. Upon completion (as determined by LCMS analysis) the reaction was removed from the glovebox, adsorbed onto Celite, and purified by silica gel column chromatography (20% ethyl acetate in hexanes) to provide malonate **560** as a colorless oil (12.1 mg, 82% yield. R*f* = 0.2 (25% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35–7.28 (m, 3H), 7.25–7.20 (m, 2H), 5.65 (dt, *J* = 15.8, 1.3 Hz, 1H), 5.44 (dt, *J* = 15.8, 7.0 Hz, 1H), 4.62 (d, *J* = 14.6 Hz, 1H), 4.53 (d, *J* = 14.5 Hz, 1H), 3.71 (s, 3H), 3.71 (s, 3H), 3.45 (t, *J* = 7.6 Hz, 1H), 3.32–3.04 (m, 2H), 2.66 (ddd, *J* = 7.5, 7.0, 1.3 Hz, 2H), 1.84 (dq, *J* = 13.5, 7.4 Hz, 1H), 1.80–1.67 (m, 4H), 1.67–1.58 (m, 1H), 0.83 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.0, 169.5, 169.5, 138.1, 137.7, 128.7, 128.1, 127.4, 125.0, 52.6, 52.6, 52.0, 50.6, 48.6, 47.8, 32.3, 32.1, 29.3, 19.3, 8.6; IR (Neat Film, NaCl) 2952, 1734, 1635, 1437, 1350, 1261, 1195, 1153, 740 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{22}H_{30}NO_5$ $[M+H]^+$: 388.2118, found 388.2110.

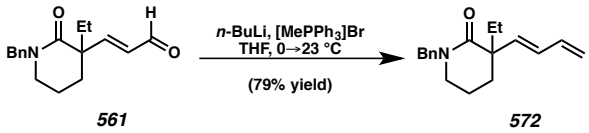
5.5.8 ENAL DERIVATIZATION PROCEDURES AND CHARACTERIZATION DATA



561 *571*

3-(1-benzyl-3-ethyl-2-oxopiperidin-3-yl)propanal (571):

To a round-bottom flask with a magnetic stir bar were added enal **561** (30 mg, 0.11 mmol, 1.00 equiv) and ethyl acetate (320 μL). Palladium on carbon (10 wt. %, 2 mg) was added, and the suspension was stirred vigorously while the air atmosphere was replaced with hydrogen by three evacuation/back-fill cycles. The reaction mixture was then stirred at 23 °C under one atmosphere of hydrogen (supplied by a balloon) for 1.25 hours. After completion (as determined by TLC analysis), the mixture was filtered through Celite, rinsing with ethyl acetate. The filtrate was concentrated and the crude residue was purified by silica gel column chromatography (25% ethyl acetate in hexanes) to provide aliphatic aldehyde **571** as a colorless oil (29.3 mg, 97% yield). R*f* = 0.5 (50% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.77 (t, *J* = 1.5 Hz, 1H), 7.37–7.27 (m, 3H), 7.25–7.18 (m, 2H), 4.65 (d, *J* = 14.5 Hz, 1H), 4.48 (d, *J* = 14.5 Hz, 1H), 3.36–3.06 (m, 2H), 2.59 (dddd, *J* = 17.4, 10.1, 5.7, 1.6 Hz, 1H), 2.49 (dddd, *J* = 17.3, 10.1, 5.6, 1.5 Hz, 1H), 1.98 (ddd, *J* = 14.0, 10.1, 5.6 Hz, 1H), 1.93–1.85 (m, 1H), 1.85–1.71 (m, 3H), 1.67–1.50 (m, 3H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 202.6, 174.1, 137.7, 128.7, 128.1, 127.5, 50.7, 47.8, 44.4, 39.8, 31.1, 30.3, 29.9, 19.7, 8.6; IR (Neat Film, NaCl) 2937, 1722, 1628, 1494, 1452, 1351, 1194, 736, 701 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{24}NO_2$ $[M+H]^+$: 274.1802, found 274.1805.

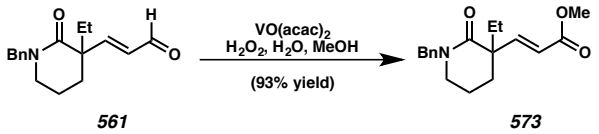


561 *572*

(*E*)-1-benzyl-3-(buta-1,3-dien-1-yl)-3-ethylpiperidin-2-one (572):

To a flame-dried round-bottom flask with a magnetic stir bar were added methyl triphenylphosphonium bromide (64 mg, 0.18 mmol, 1.25 equiv) and THF (0.9 mL). The white suspension was cooled to 0 °C using an ice water bath and *n*-butyllithium (2.5 M in hexanes, 72 μL, 1.25 equiv) was added dropwise by syringe. The mixture was stirred for 15 minutes at 0 °C and a solution of enal **561** (40 mg, 0.15 mmol, 1.00 equiv) in THF (180 μL) was added dropwise by syringe. The mixture was stirred for 1 hour at 0 °C and 20 hours at 23 °C. As the reaction was not progressing, additional ylide (1.25 equiv, generated as described above) was added by syringe at 0 °C. The reaction was allowed to stir at 23 °C for 5 hours, at which point additional ylide (2.50 equiv, generated as described above) was added at 0 °C. After stirring for 3 hours at 23 °C, TLC analysis showed complete consumption of the starting material. The reaction was quenched by addition of saturated aqueous ammonium chloride solution (5 mL). The mixture was extracted with ether (3 x 5 mL), and the combined organic layers were washed with brine (1 x 5 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (20% ethyl aceate in hexanes) to provide diene **572** as a colorless oil (32.1 mg, 79% yield). R*f* = 0.5 (25% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34–7.26 (m, 2H), 7.26–7.21 (m, 3H), 6.35 (dtd, *J* = 16.9, 10.2, 0.7 Hz, 1H), 6.10 (ddd, *J* = 15.7, 10.2, 0.7 Hz, 1H), 5.81 (dd, *J* = 15.7, 0.8 Hz, 1H), 5.14 (ddt, *J* = 17.0, 1.6, 0.7 Hz, 1H), 5.03 (ddt, *J* = 10.1, 1.6, 0.7 Hz, 1H), 4.62 (d, *J* = 14.6 Hz, 1H), 4.57 (d, *J* = 14.6 Hz, 1H), 3.35–2.98 (m, 2H), 1.90 (dq, *J*

= 13.6, 7.5 Hz, 1H), 1.86–1.78 (m, 3H), 1.78–1.64 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (CDCl3, 126 MHz) δ 172.9, 139.0, 137.7, 137.3, 130.3 128.7, 128.2, 127.4, 116.4, 50.7, 48.8, 47.9, 32.2, 29.4, 19.5, 8.8; IR (Neat Film, NaCl) 2966, 1635, 1600, 1488, 1452, 1352, 1196, 1007, 733, 701 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{18}H_{24}NO$ $[M+H]^+$: 270.1853, found 270.1851.

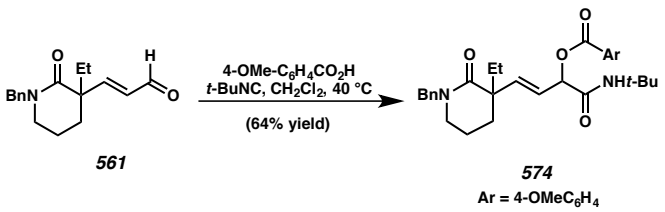


561 *573*

(*E*)-1-benzyl-3-(buta-1,3-dien-1-yl)-3-ethylpiperidin-2-one (573):

The conditions for the transformation were adapted from a known procedure.[25] To a 1 dram screw-top vial with a magnetic stir bar were added, in order, vanadyl acetylacetonate (1 mg, 0.001 mmol, 0.04 equiv) and hydrogen peroxide (35 wt. % in water, 50 μL). A solution of enal **561** (10 mg, 0.04 mmol, 1.00 equiv) in methanol (200 μL) was then added. The vial was sealed with a Teflon-lined cap and the solution was stirred at 23 °C for 17 hours. Upon completion (as determined by TLC analysis), the reaction mixture was diluted with dichloromethane (3 mL), adsorbed onto Celite and purified by silica gel column chromatography (25% ethyl acetate in hexanes) to provide enoate **573** as a colorless oil (11.2 mg, 93% yield). R*f* = 0.4 (10% ethyl acetate in hexanes); ^{1}H NMR (CDCl3, 500 MHz) δ 7.37–7.26 (m, 3H), 7.25–7.18 (m, 2H), 7.04 (d, *J* = 16.1 Hz, 1H), 5.90 (d, *J* = 16.1 Hz, 1H), 4.68 (d, *J* = 14.5 Hz, 1H), 4.51 (d, *J* = 14.5 Hz, 1H), 3.74 (s, 3H), 3.32–3.09 (m, 2H), 1.95 (dq, *J* = 13.5, 7.4 Hz, 1H), 1.91–1.82 (m, 2H), 1.82–1.67 (m, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (CDCl3, 126 MHz) δ 171.4, 167.2, 152.6, 137.4, 128.8, 128.2, 127.5, 120.8, 51.7, 50.9, 49.3, 47.8, 31.6, 29.3, 19.5,

8.7; IR (Neat Film, NaCl) 2946, 1723, 1631, 1434, 1341, 1273, 1197, 1020, 701 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{18}H_{24}NO_3$ $[M+H]^+$: 302.1751, found 302.1754.



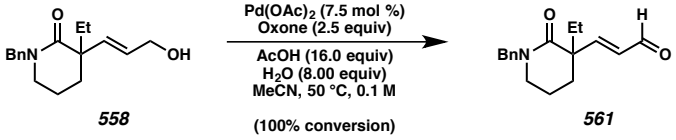
561 ***574***
Ar = 4-OMeC$_6$H$_4$

(*E*)-4-(1-benzyl-3-ethyl-2-oxopiperidin-3-yl)-1-(*tert*-butylamino)-1-oxobut-3-en-2-yl 4-methoxybenzoate (574):

The conditions for the transformation were adapted from a known procedure.[26] To a 0.5 dram screw-top vial with a magnetic stir bar were added, in order, enal **561** (10 mg, 0.037 mmol, 1.00 equiv), *tert*-butyl isocyanide (42 μL, 0.37 mmol, 10.0 equiv), 4-methoxybenzoic acid (56 mg, 0.37 mmol, 10.0 equiv), and dichloromethane (50 μL). The vial was sealed with a Teflon-lined cap and the white suspension was stirred at 23 °C for 21 hours, and then at 40 °C for 12 additional hours. Upon completion (as determined by LCMS analysis), the reaction mixture was diluted with dichloromethane (2 mL) and washed with saturated aqueous sodium bicarbonate solution (1 x 2 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (25% ethyl acetate in hexanes) to provide the product (**574**) as an inseparable 1:1 mixture of diastereomers (12.1 mg, 64% yield). R*f* = 0.3 (25% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.04 (dd, *J* = 2.1, 1.5 Hz, 1H), 8.03 (dd, *J* = 2.1, 1.5 Hz, 1H), 7.35–7.27 (m, 1H), 7.25–7.16 (m, 3H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.94 (t, *J* = 2.4 Hz, 1H), 6.07 (ddd, *J* = 15.9, 9.9, 1.2 Hz, 1H), 5.87 (d, *J* = 8.6 Hz, 1H), 5.78 (ddd, *J* = 15.9, 9.8, 6.7 Hz, 1H), 5.69 (ddd, *J* =

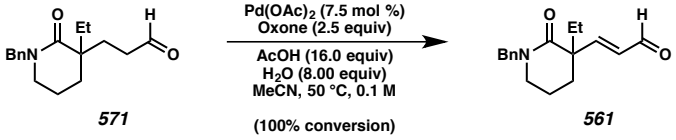
6.9, 3.3, 1.2 Hz, 1H), 4.64 (dd, *J* = 26.6, 14.6 Hz, 1H), 4.52 (dd, *J* = 14.6, 6.6 Hz, 1H), 3.88 (d, *J* = 1.1 Hz, 3H), 3.33–3.02 (m, 2H), 1.96–1.80 (m, 3H), 1.80–1.61 (m, 1H), 1.35 (d, *J* = 1.7 Hz, 9H), 0.86 (td, *J* = 7.4, 5.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 172.7, 172.7, 167.8, 167.7, 164.8, 163.9, 163.9, 140.0, 139.8, 137.5, 132.4, 132.0, 132.0, 128.7, 128.7, 128.0, 128.0, 127.4, 127.4, 124.2, 124.0, 121.9, 121.9, 114.0, 114.0, 113.8, 75.0, 74.8, 55.7, 51.5, 51.5, 50.7, 50.6, 48.7, 48.6, 47.8, 47.8, 36.8, 32.0, 31.7, 29.1, 29.1, 28.8, 24.8, 19.4, 19.3, 8.6, 8.6; IR (Neat Film, NaCl) 3320, 2965, 1691, 1606, 1453, 1256, 1168, 1102, 1028 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{30}H_{39}N_2O_5$ $[M+H]^+$: 507.2853, found 507.2857.

5.5.9 MECHANISTIC INVESTIGATION EXPERIMENTS



Oxidation of allylic alcohol 558 to enal 561:

To a 0.5 dram vial with a magnetic stir bar were added, in order, allylic alcohol **558** (11 mg, 0.04 mmol, 1.00 equiv), palladium(II) acetate (1 mg, 0.03 mmol, 0.075 equiv), and Oxone (31 mg, 0.10 mmol, 2.5 equiv). Acetonitrile (400 μL), acetic acid (37 μL, 3.2 mmol, 16.00 equiv), and water (6 μL, 1.6 mmol, 8.00 equiv) were added by syringe. The resulting suspension was stirred for 5 minutes at 23 °C and then heated to 50 °C in an oil bath. Upon completion (as determined by TLC analysis), the flask was allowed to cool to 23 °C. The reaction mixture was filtered through a plug of silica gel, rinsing with ethyl acetate, and concentrated to give the crude product, which was identical to **561** by ^{1}H NMR, TLC, and LCMS analysis.



Oxidation of aliphatic aldehyde 571 to enal 561:

To a 0.5 dram vial with a magnetic stir bar were added, in order, aliphatic aldehyde **571** (3 mg, 0.011 mmol, 1.00 equiv), palladium(II) acetate (<1 mg, 0.015 mmol, 0.075 equiv), and Oxone (8 mg, 0.028 mmol, 2.5 equiv). Acetonitrile (100 μL), acetic acid (10 μL, 3.2 mmol, 16.00 equiv), and water (2 μL, 1.6 mmol, 8.00 equiv) were added by syringe. The resulting suspension was stirred for 5 minutes at 23 °C and then heated to 50 °C in an oil bath. Upon completion (as determined by TLC analysis), the flask was allowed to cool to 23 °C. The reaction mixture was filtered through a plug of silica gel, rinsing with ethyl acetate, and concentrated to give the crude product, which was identical to **561** by ^{1}H NMR, TLC, and LCMS analysis.

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(16) For an example of Cr(VI)-mediated oxidation of an *N*-benzyl lactam, see: a) Moreaux, V.; Warren, H.; Williams, J. M. *Tetrahedron Lett.* **1997**, *38*, 4655–4658. For an example of Cr(VI)-mediated oxidation of an *N*,*N*-diacyl-1,2-diamine moiety, see: b) Mitchell, J. P.; Draffan, A. G.; Sanford, V. A.; Bond, S.; Lim, C. Y.; Mayes, P. A. Polycyclic Agents for the Treatment of Respiratory Syncytial Virus Infections. Worldwide Patent Application WO 2008/037011 A1, April 3 2008.

(17) For an example of substrate-directed allylic acetoxylation of terminal olefins with stoichiometric palladium, see ref. 3m.

(18) a) Oxone is $KHSO_5 \bullet \frac{1}{2}KHSO_4 \bullet \frac{1}{2}K_2SO_4$. For information on the safety, reactivity profile, and chemical stability of Oxone, see: DuPont Oxone Monopersulfate Compound General Technical Attributes; Technical Report K-20102, October 2008; b) Sigma Aldrich price, January 27, 2017: $22/kg.

(19) Substrates incorporating terminal olefins provided inseparable mixtures of multiple oxidation products upon subjection to either the allylic acetoxylation or enal formation conditions. The mixtures included allylic acetates, enals, methyl ketones, and other compounds.

(20) A β-lactam substrate provided a mixture of the allylic acetate, enal, and methyl ketone products upon treatment with the conditions for allylic acetoxylation. The same substrate furnished only the methyl ketone product in moderate yield upon subjection to the enal conditions.

(21) The relative stereochemistry of diol **555** was assigned by X-ray crystallography. The supplementary crystallographic data has been deposited in the Cambridge Crystallographic Data Centre, CCDC 1057691. See Appendix 12 for details.

(22) The relative stereochemistry of epoxide **557** was assigned by analogy to diol **555**.

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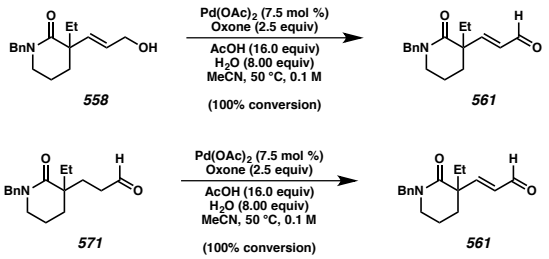
(24) It is possible that both the allylic acetate and enal products are formed through a palladium(II)-π-allyl intermediate, although other pathways, particularly Wacker-type activation of the olefin, may also be envisioned. The requirement of an electron-rich lactam moiety in the substrate suggests intramolecular direction may play a role in the mechanism. Control experiments investigating the formation of the enal product show that both the allylic alcohol **558** and the aliphatic aldehyde **571** are smoothly converted to the enal (**561**) under the reaction conditions, indicating that either could serve as a mechanistic intermediate. See Section 5.5.9 for details.



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APPENDIX 10[†]

Supplementary Synthetic Information Relevant to Chapter 5

A10.1 INTRODUCTION

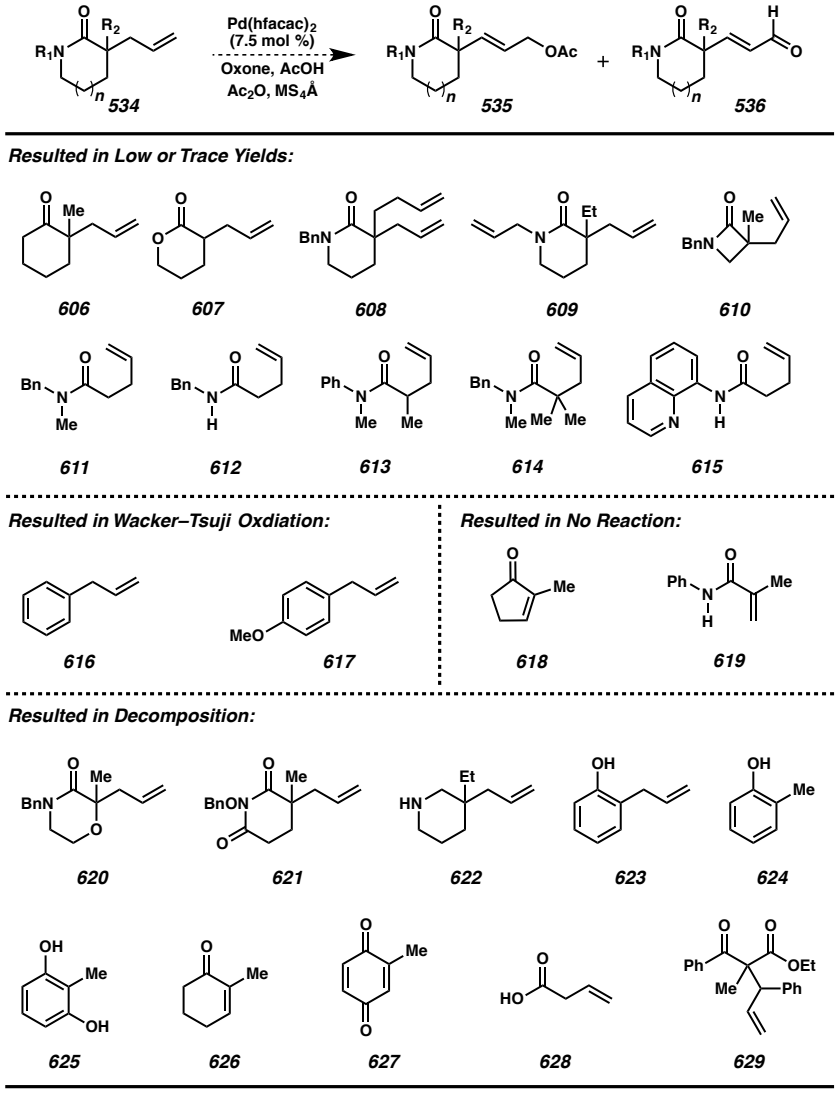
This section presents poor substrates for the C–H allylic acetoxylation and enal formation reactions. The substrates were either unreactive, gave low yields of the desired products as the only isolable material, afforded primarily Wacker–Tsuji oxidation products, or decomposed.

A10.2 UNSUCCESSFUL SUBSTRATES IN THE ALLYLIC ACETOXYLATION REACTION

Figure A10.1 presents those substrates that performed poorly under the allylic acetoxylation conditions. The decomposition observed with **622** suggests amide coordination may play a role in the allylic C–H functionalization.

[†] This work was performed in collaboration with Dr. Xiangyou Xing, alumnus of the Stoltz group. This work has been published, with selected data in this appendix reproduced with permission from Xing, X.; O'Connor, N. R.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 11186–11190.

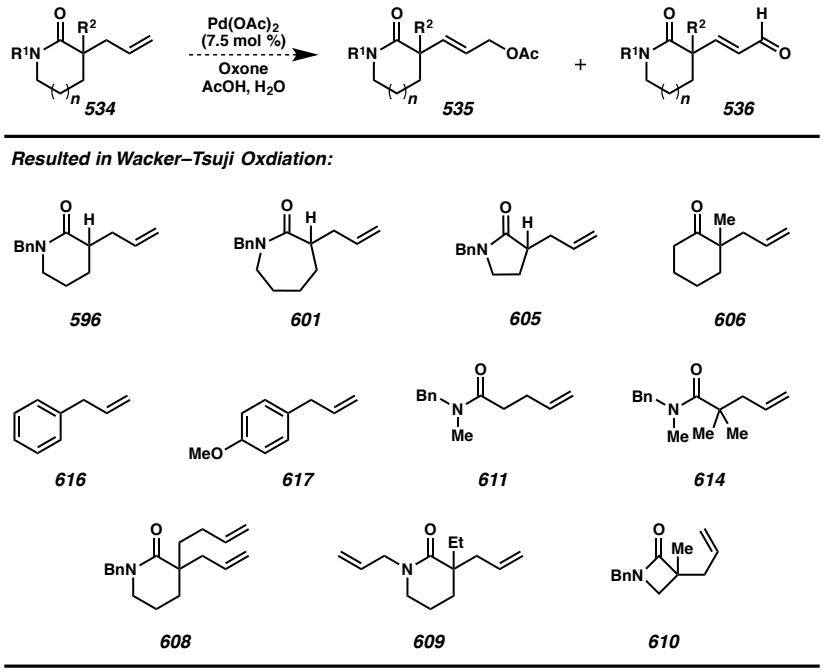
Figure A10.1 Poor substrates in the allylic acetoxylation reaction



A10.3 UNSUCCESSFUL SUBSTRATES IN THE ENAL FORMATION REACTION

Under the optimized conditions for the formation of enals, many attempted substrates instead underwent Wacker–Tsuji oxidation to afford the methyl ketones. A selection of these substrates is shown in Figure A10.2.

Figure A10.2 Poor substrates in the enal formation reaction



A10.4 CONCLUSIONS

These problematic substrates illustrate the limitations of this palladium(II)/Oxone catalyst system in the realm of allylic C–H functionalization reactions. Further exploration of this system might involve substrates with strongly coordinating directing groups (similar to **615**) or examination of the role of olefin directing groups, which may be responsible for the unexpected C–H acetoxylation of carvone discussed in Section 5.5.

APPENDIX 11

Spectra Relevant to Chapter 5:

Palladium(II)-Catalyzed Allylic C–H Oxidation of Hindered Substrates

Featuring Tunable Selectivity Over Extent of Oxidation

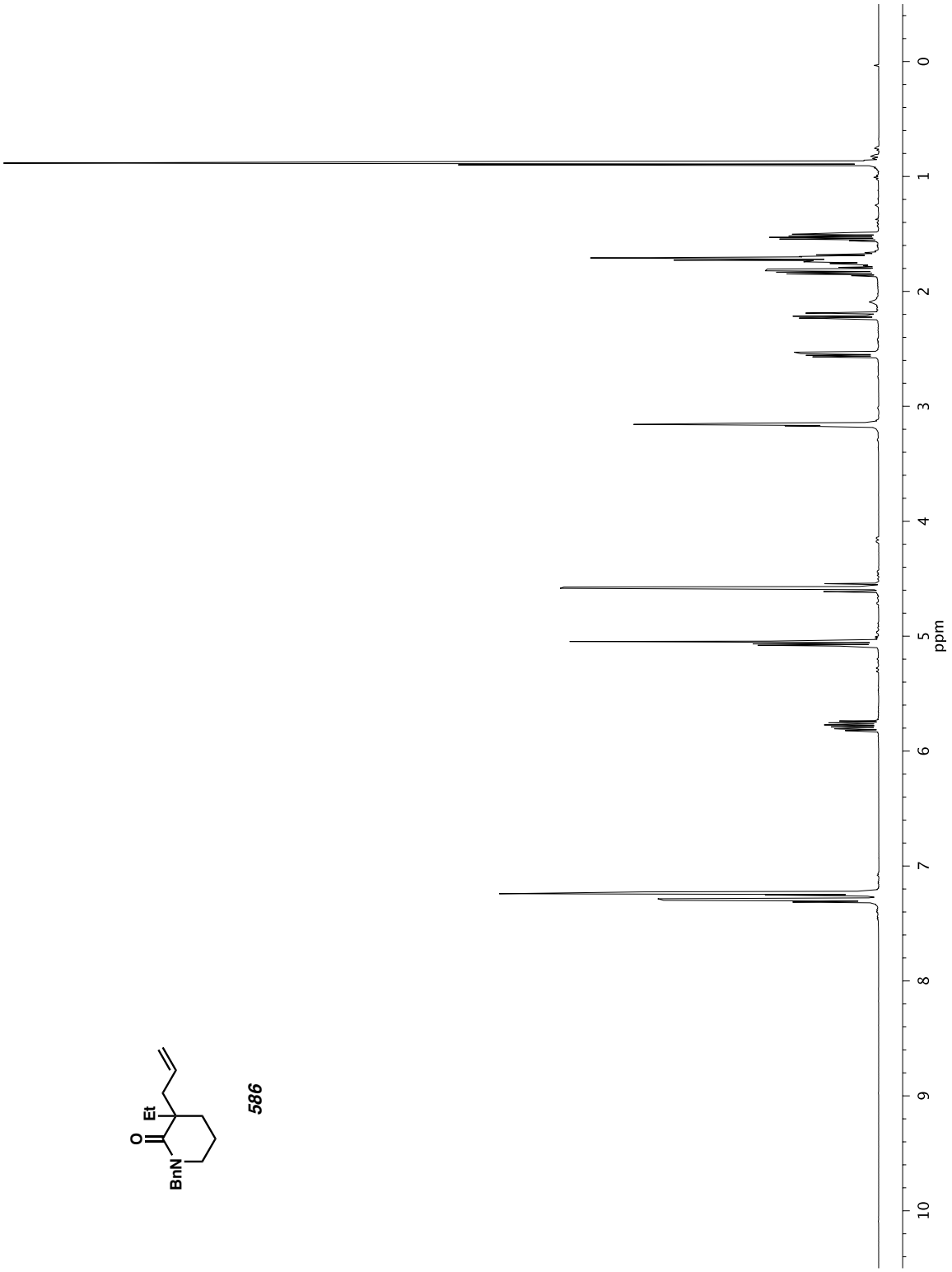


Figure 11.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **586**.

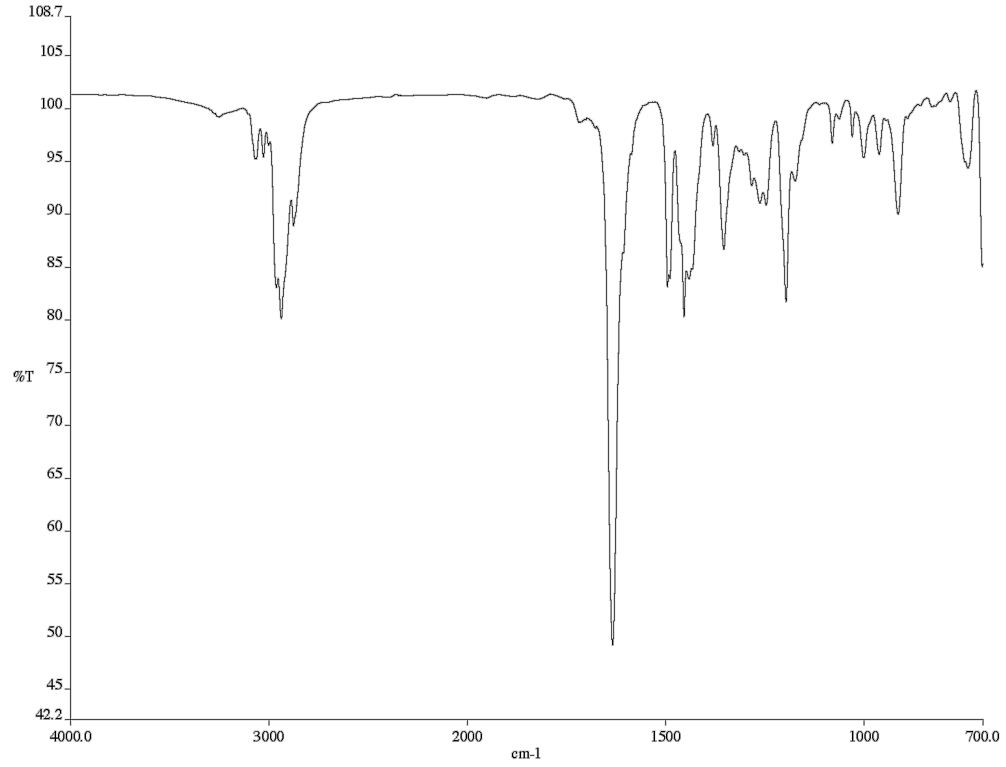


Figure A11.2 Infrared spectrum (thin film/NaCl) of compound **586**.

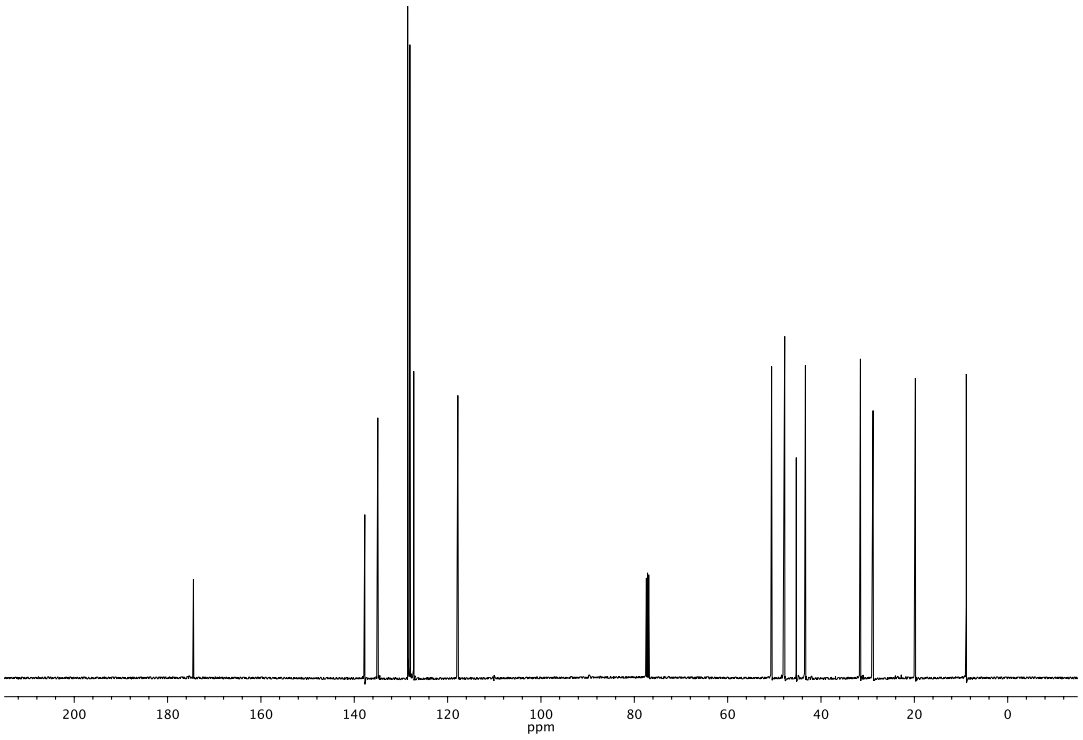


Figure 11.3 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **586**.

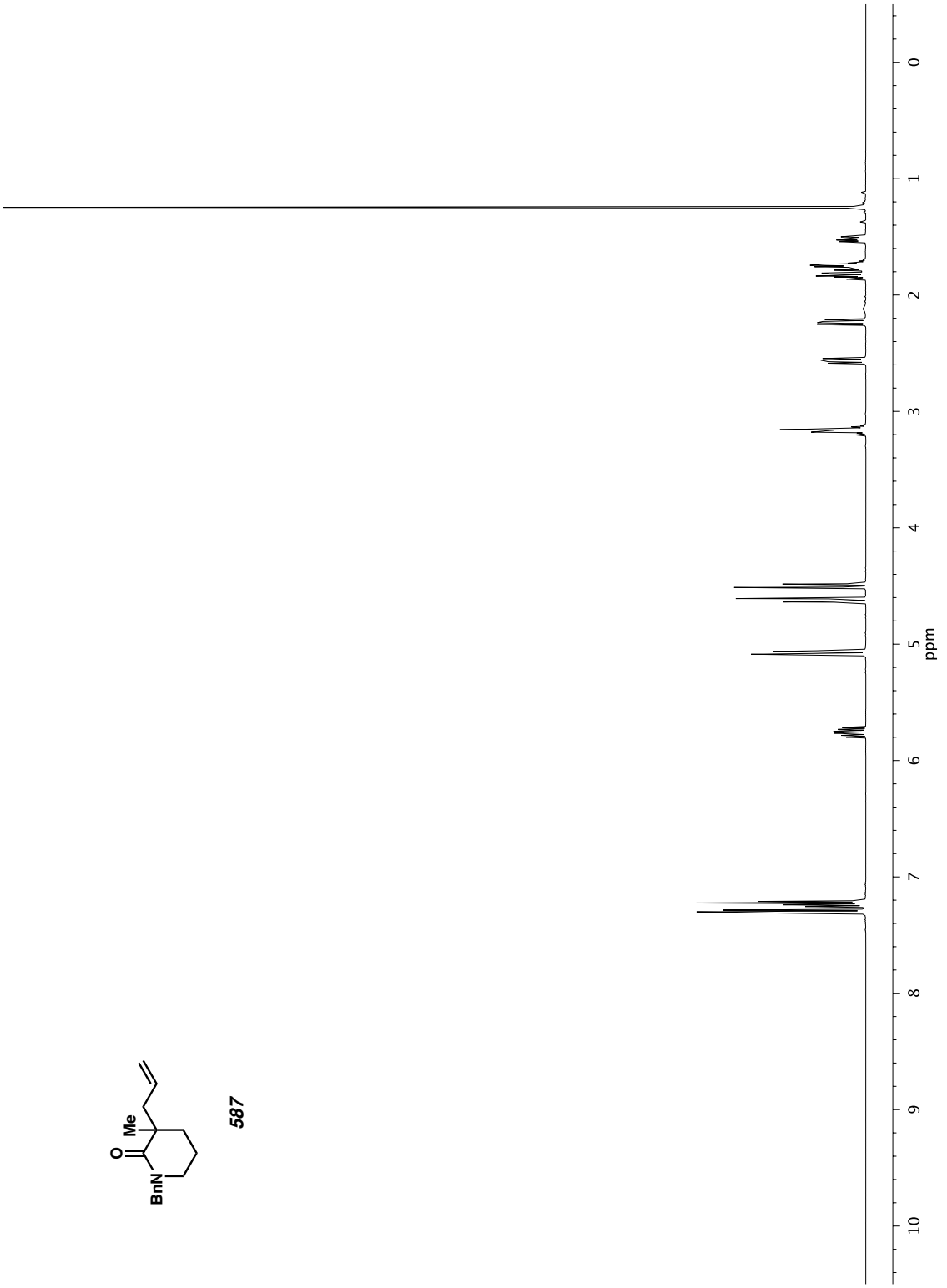


Figure A11.4 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **587**.

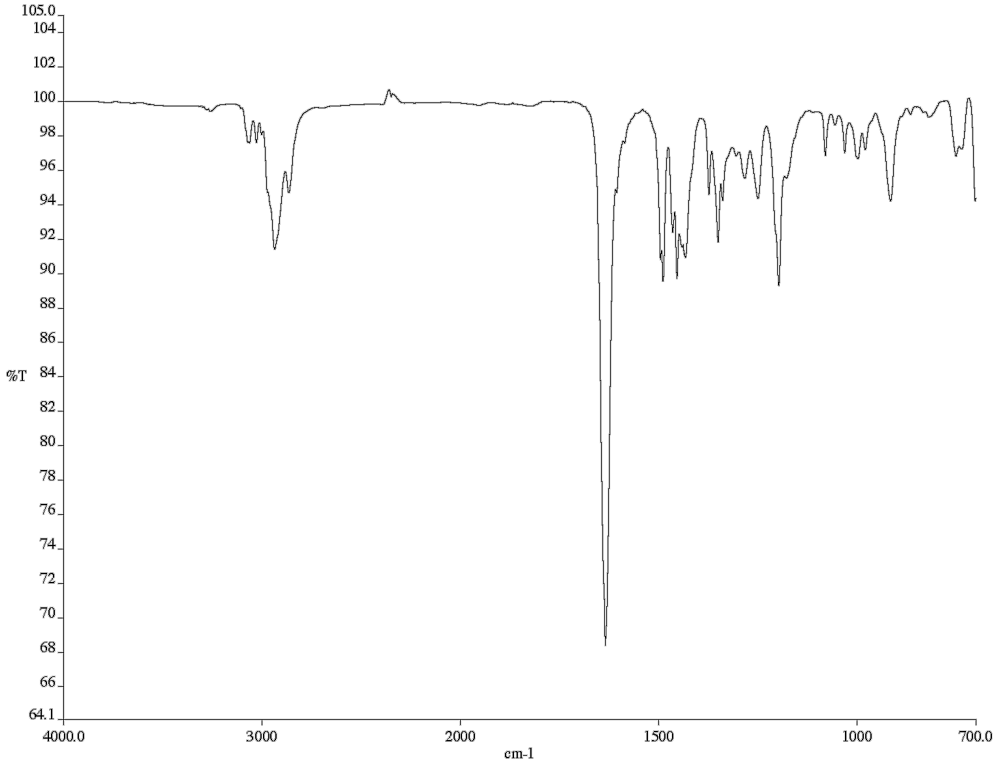


Figure A11.5 Infrared spectrum (thin film/NaCl) of compound **587**.

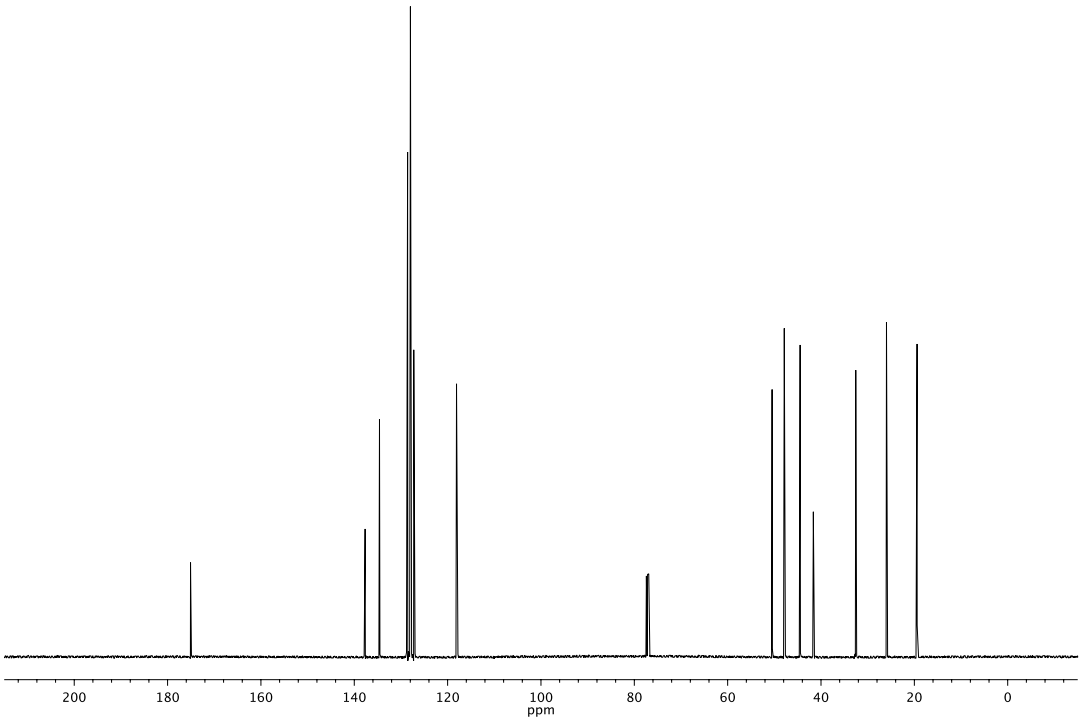


Figure A11.6 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **587**.

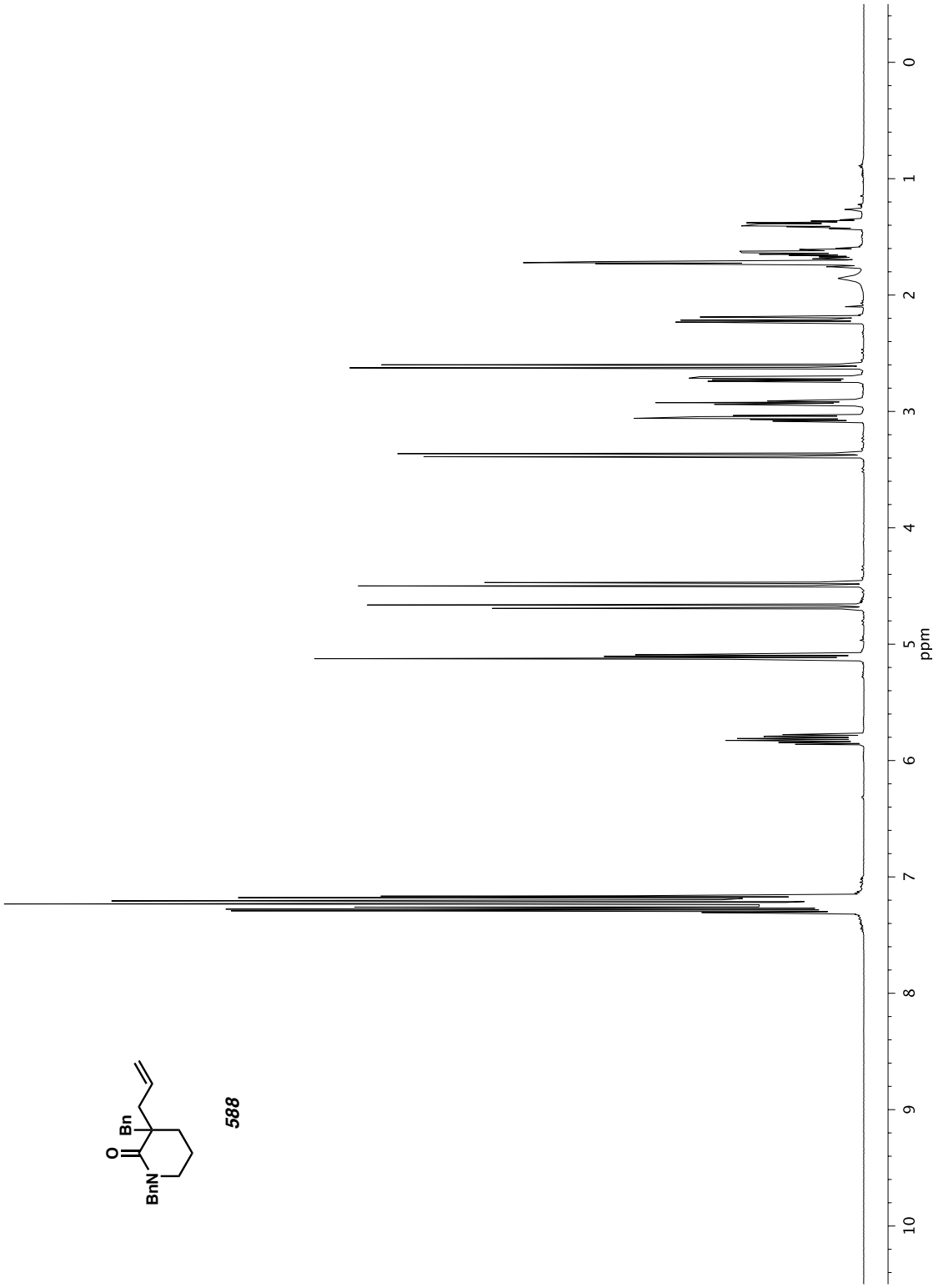


Figure A11.7 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **588**.

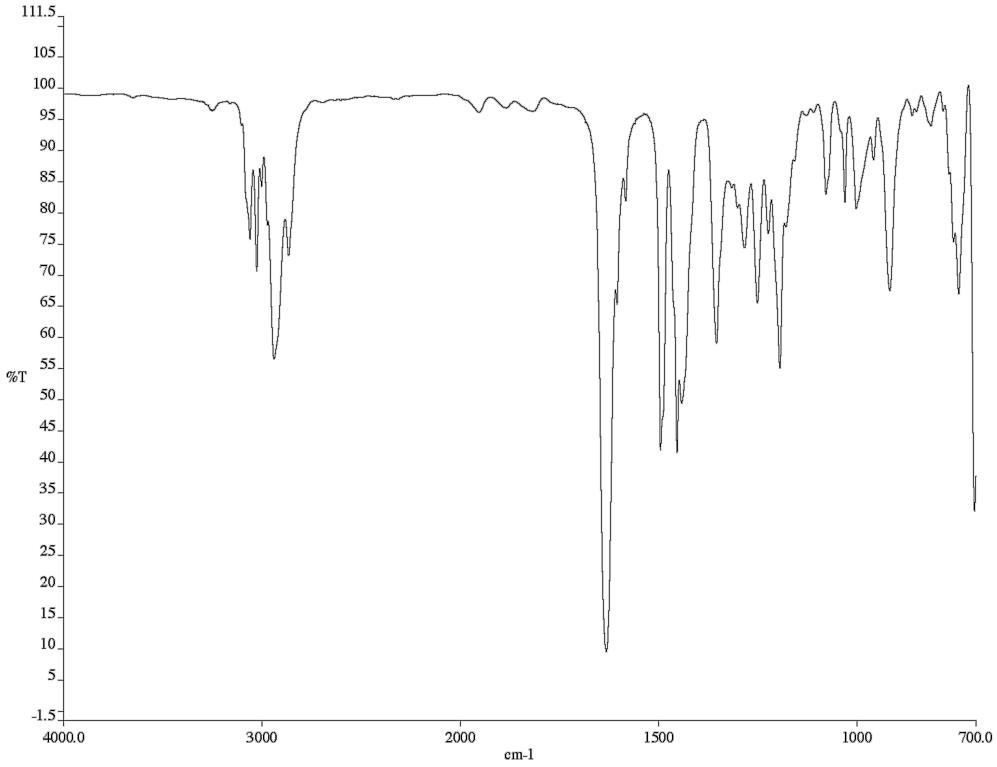


Figure A11.8 Infrared spectrum (thin film/NaCl) of compound **588**.

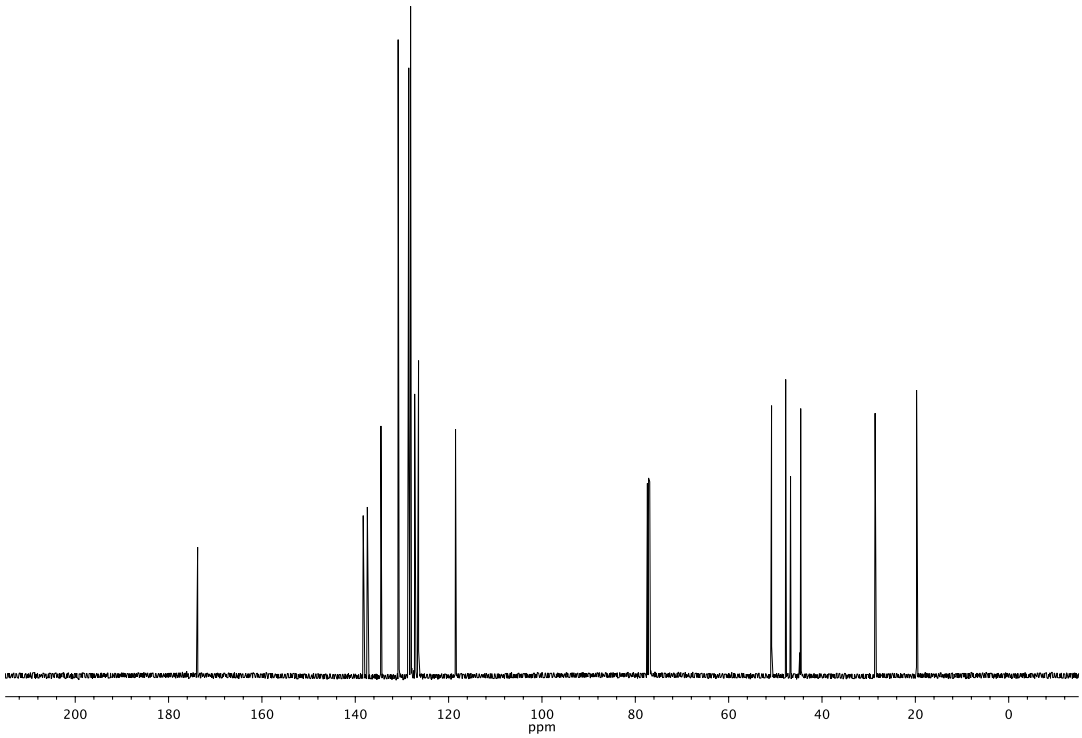


Figure A11.9 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **588**.

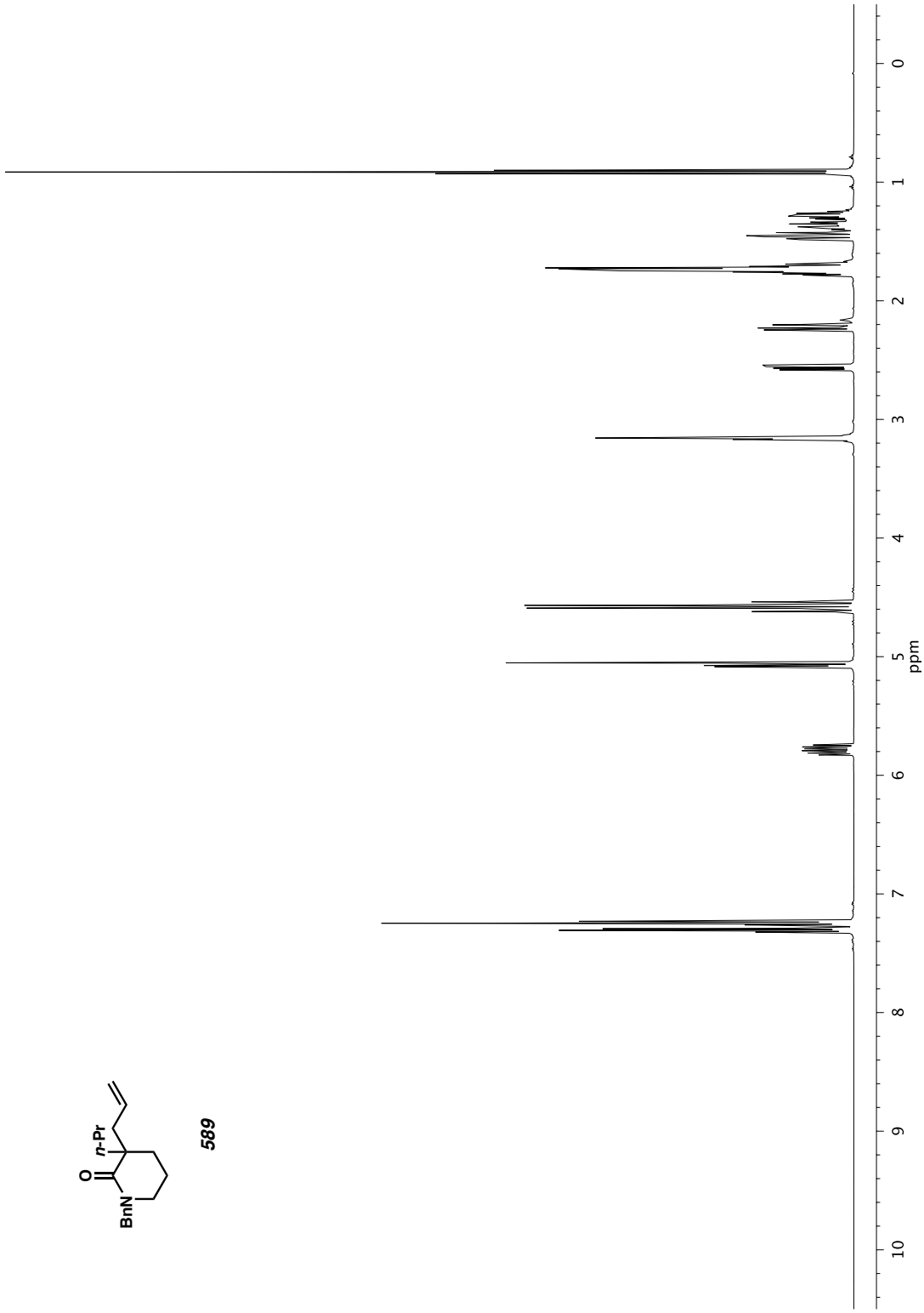


Figure A11.10 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **589**.

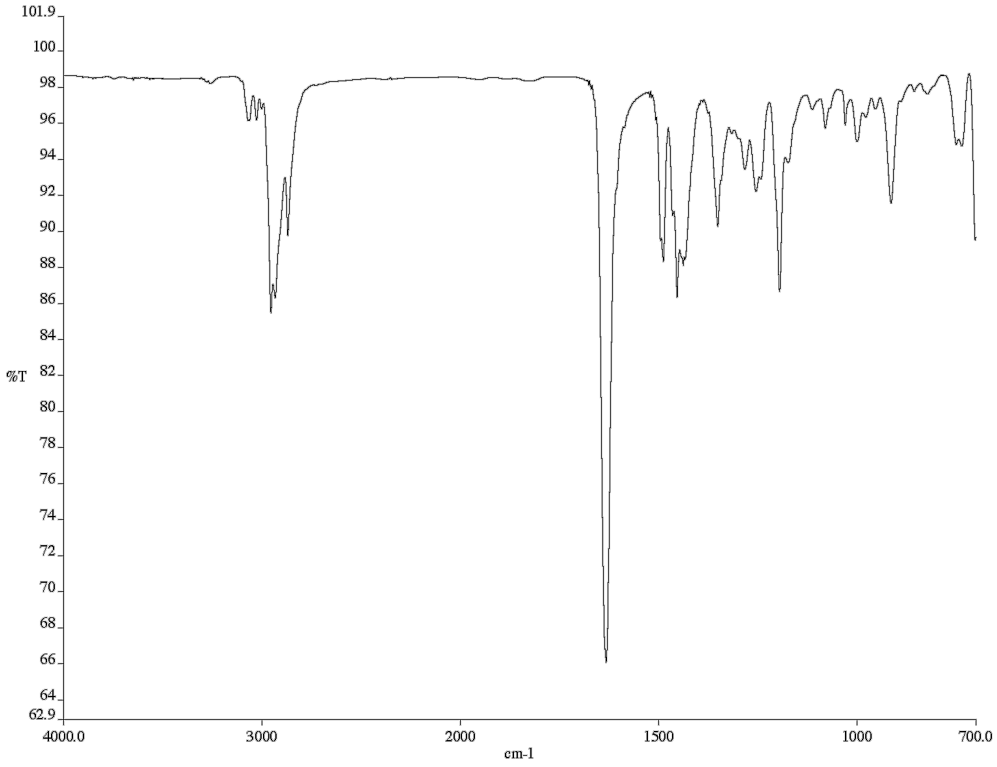


Figure A11.11 Infrared spectrum (thin film/NaCl) of compound **589**.

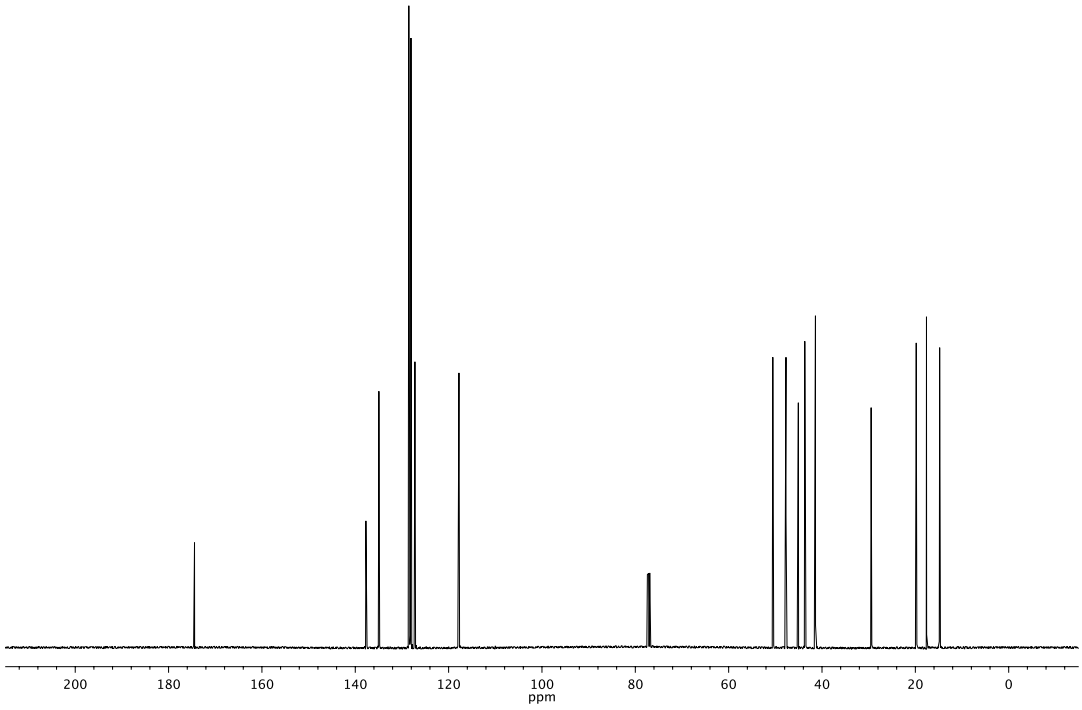


Figure A11.12 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **589**.

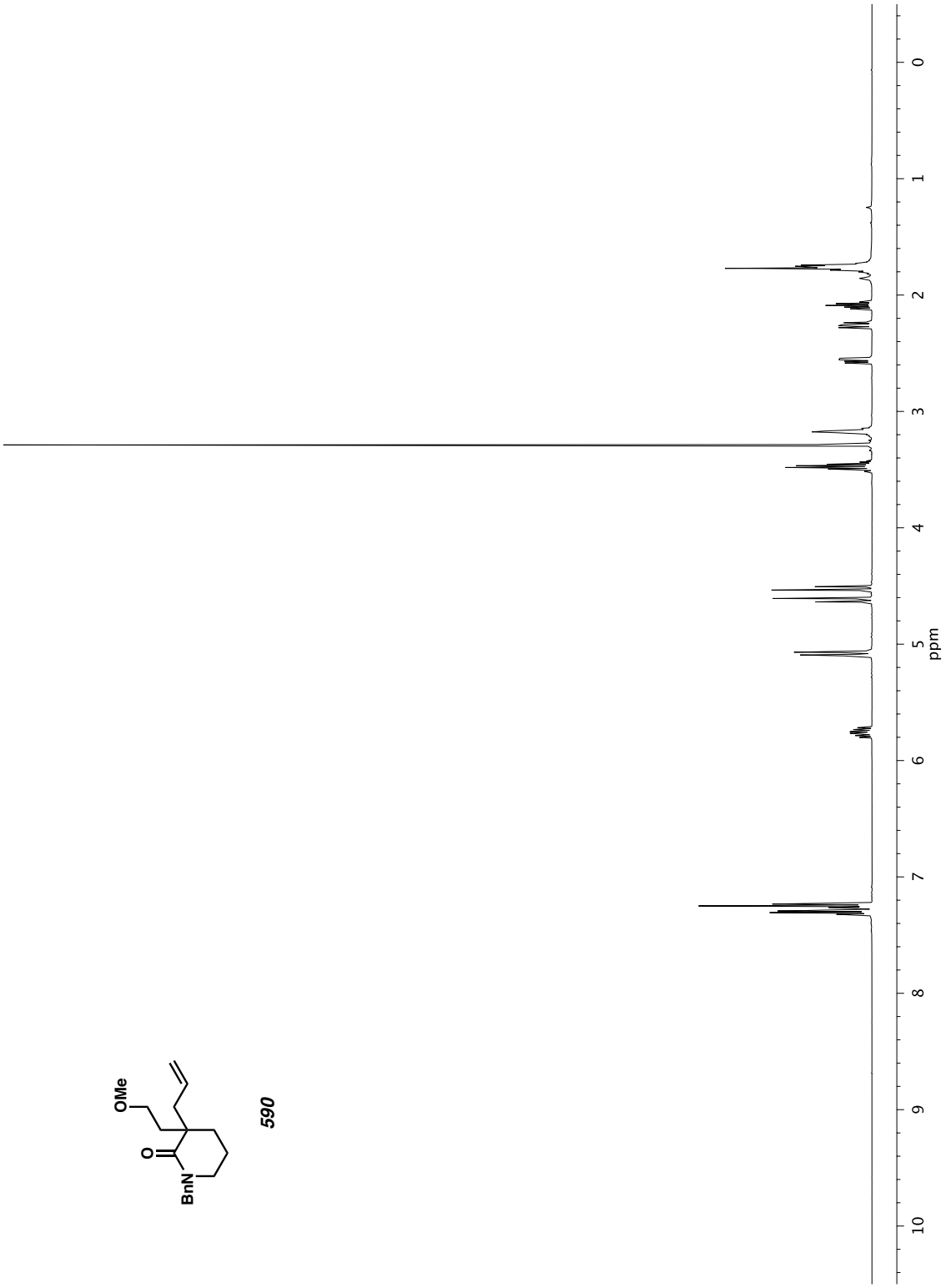


Figure A11.13 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **590**.

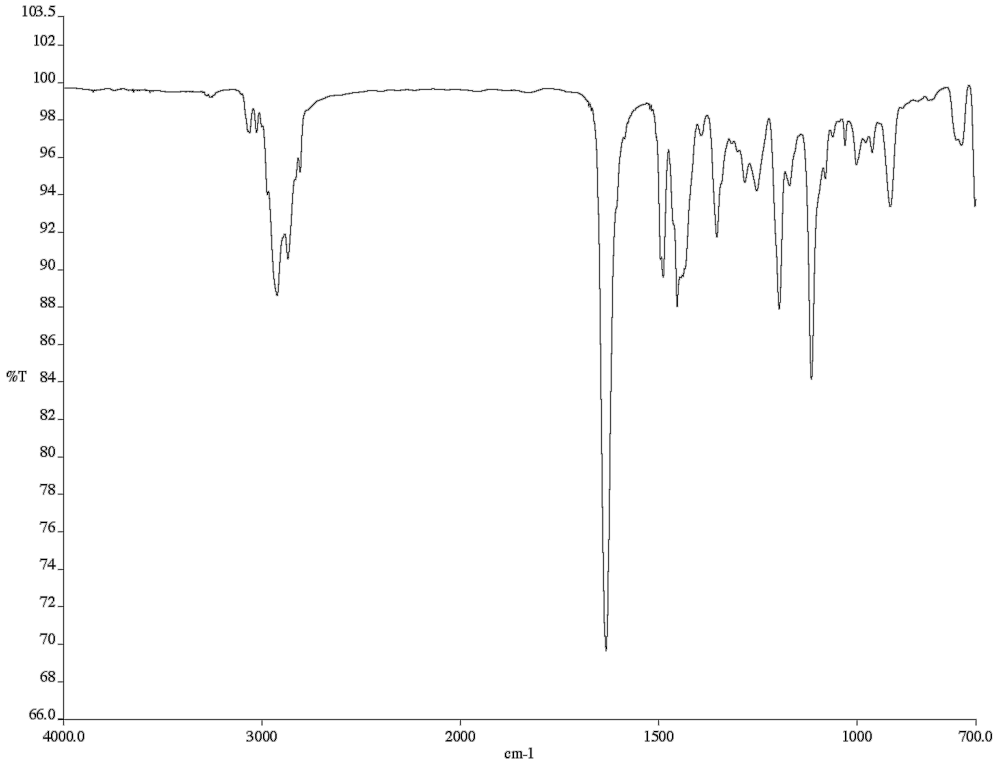


Figure A11.14 Infrared spectrum (thin film/NaCl) of compound **590**.

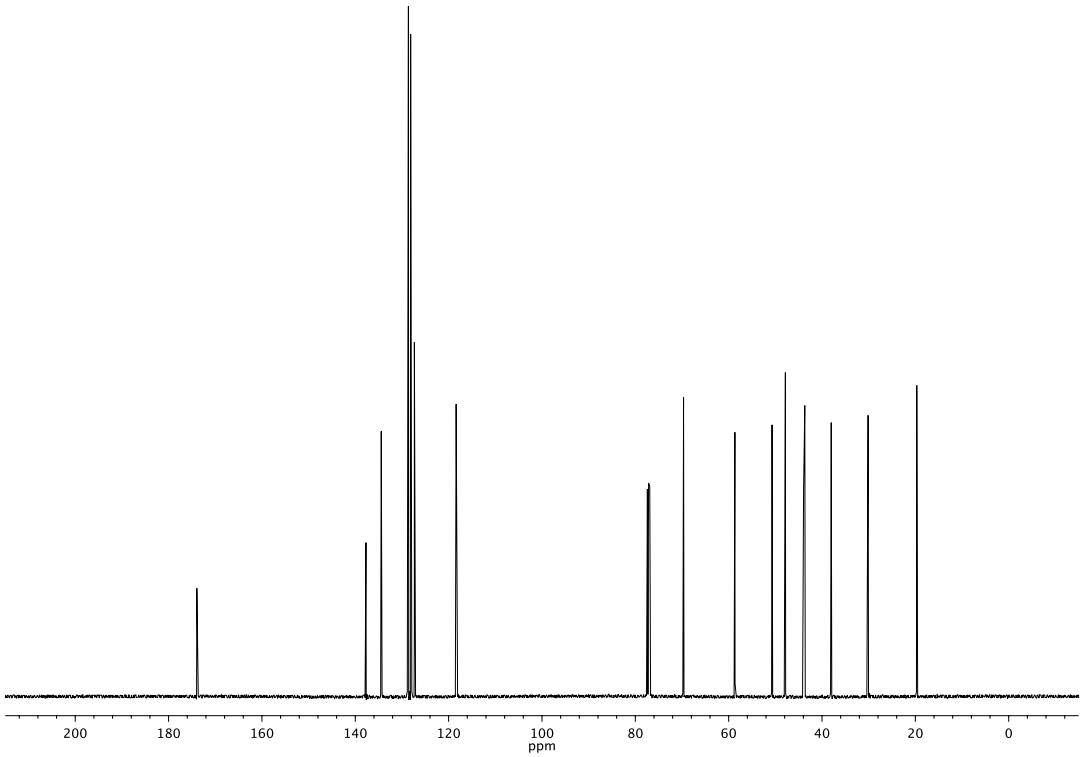


Figure A11.15 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **590**.

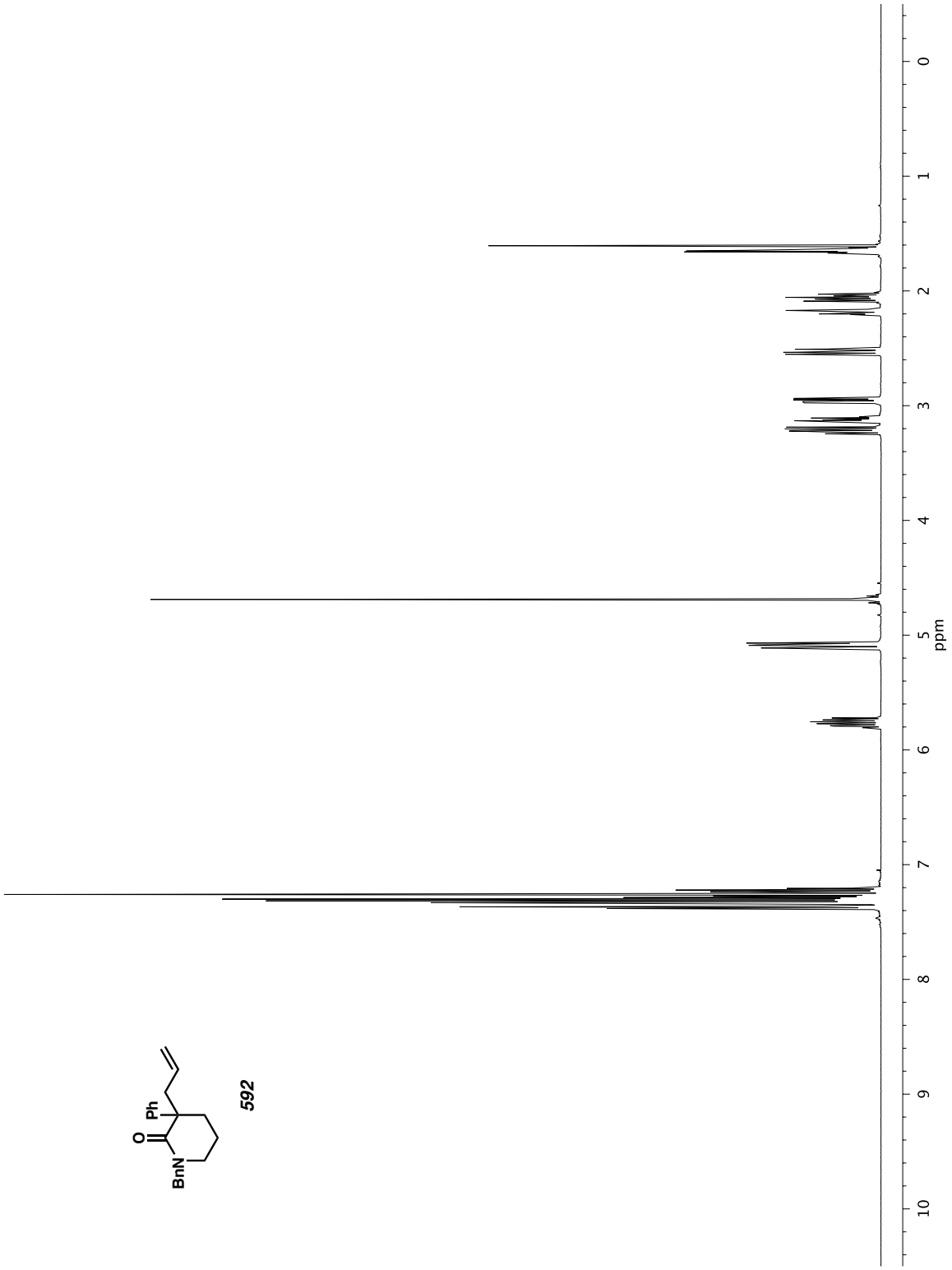


Figure A11.16 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **592**.

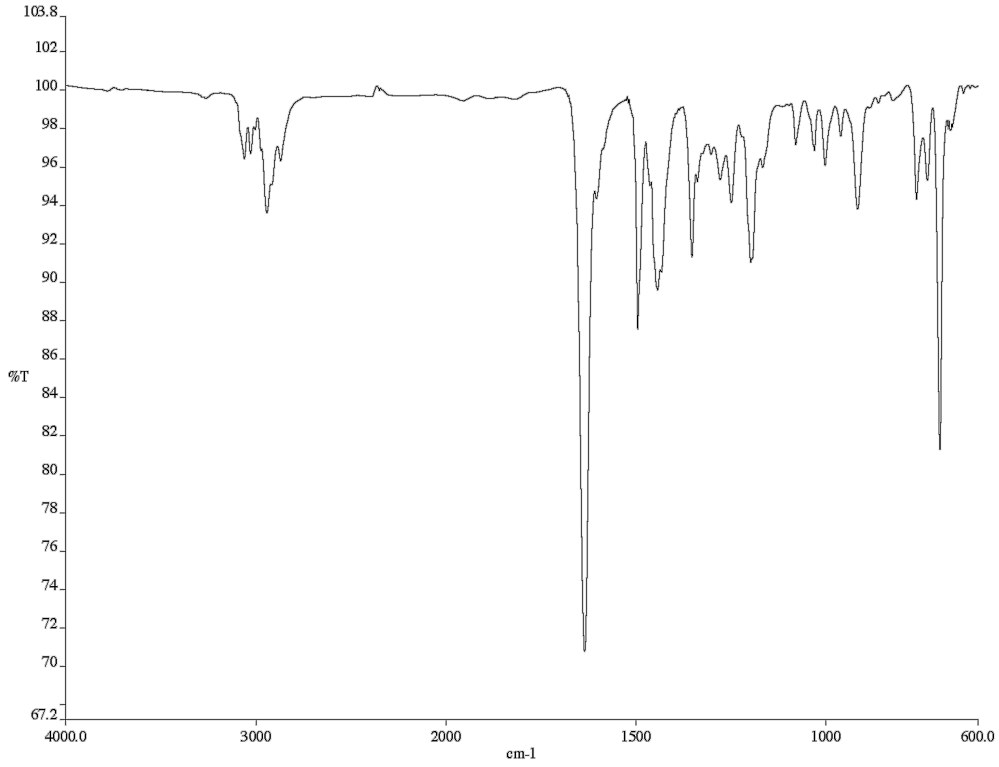


Figure A11.17 Infrared spectrum (thin film/NaCl) of compound **592**.

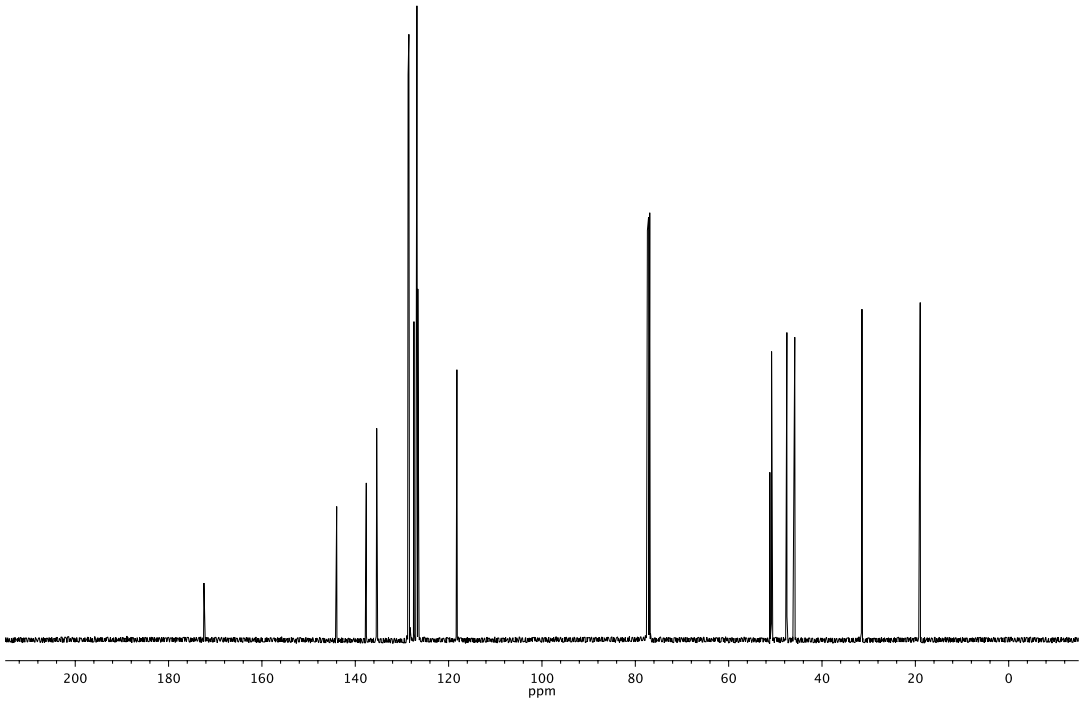
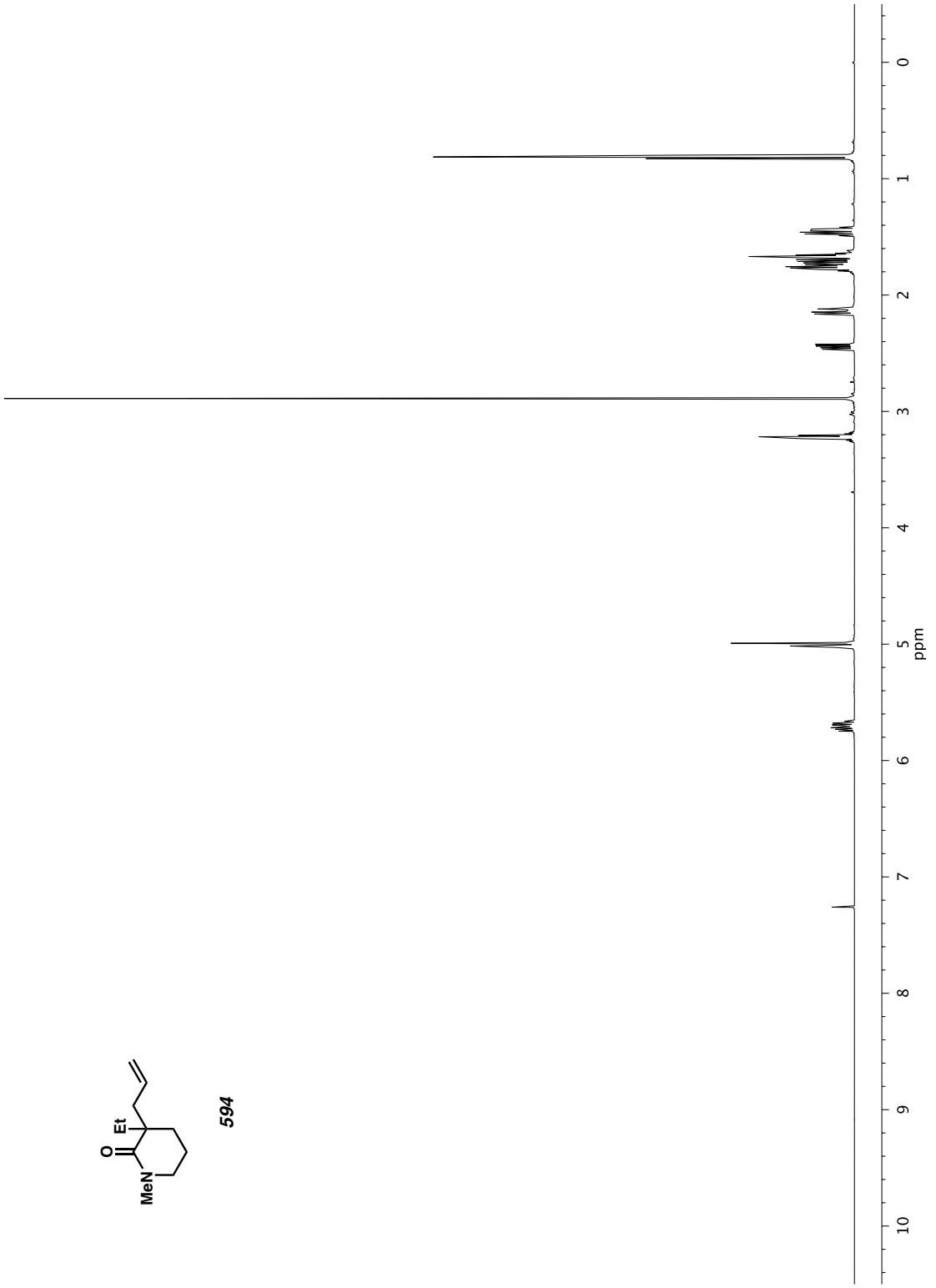


Figure A11.18. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **592**.



594

Figure A11.19 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **594**.

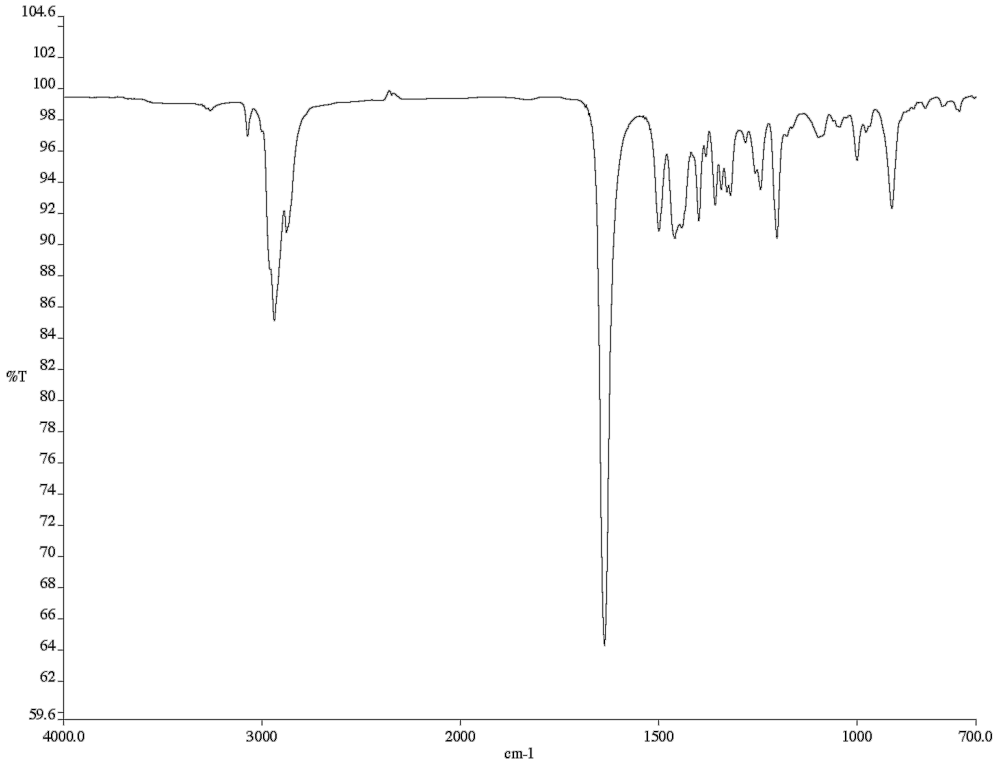


Figure A11.20 Infrared spectrum (thin film/NaCl) of compound **594**.

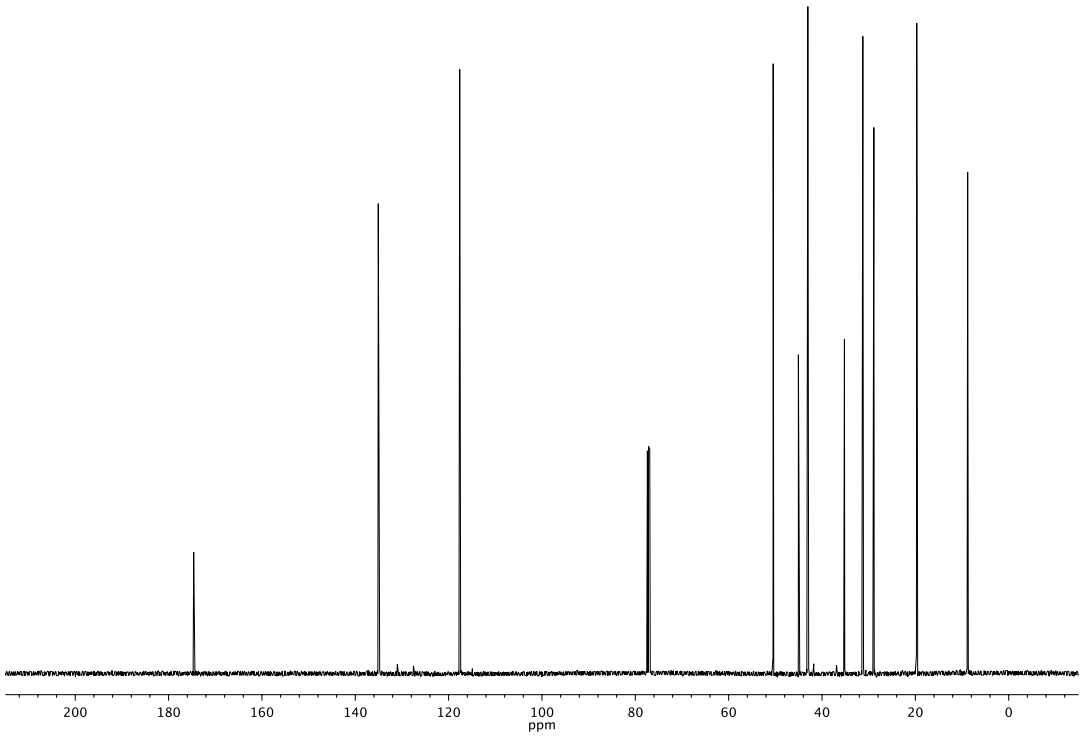


Figure A11.21 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **594**.

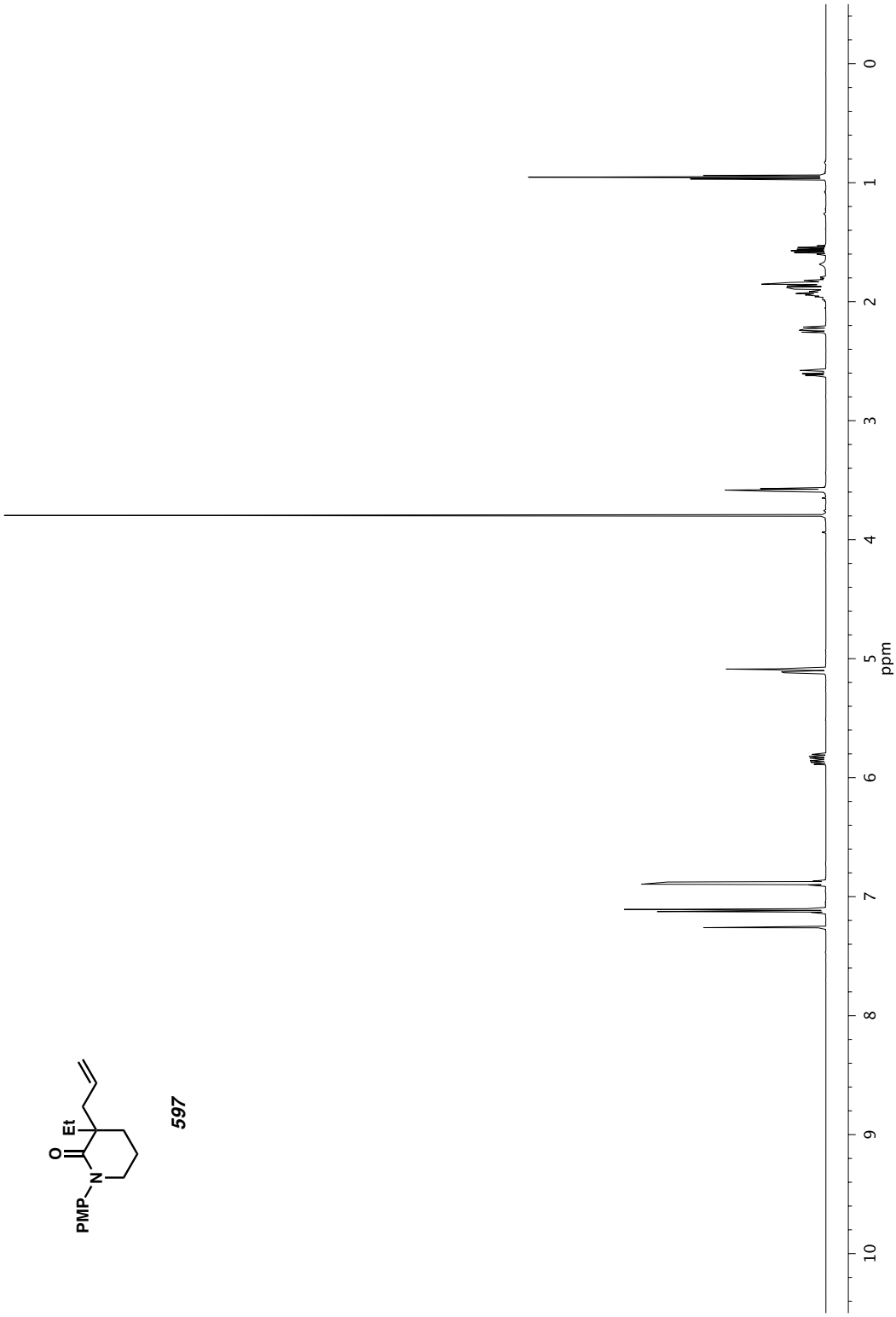


Figure A11.22 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **597**.

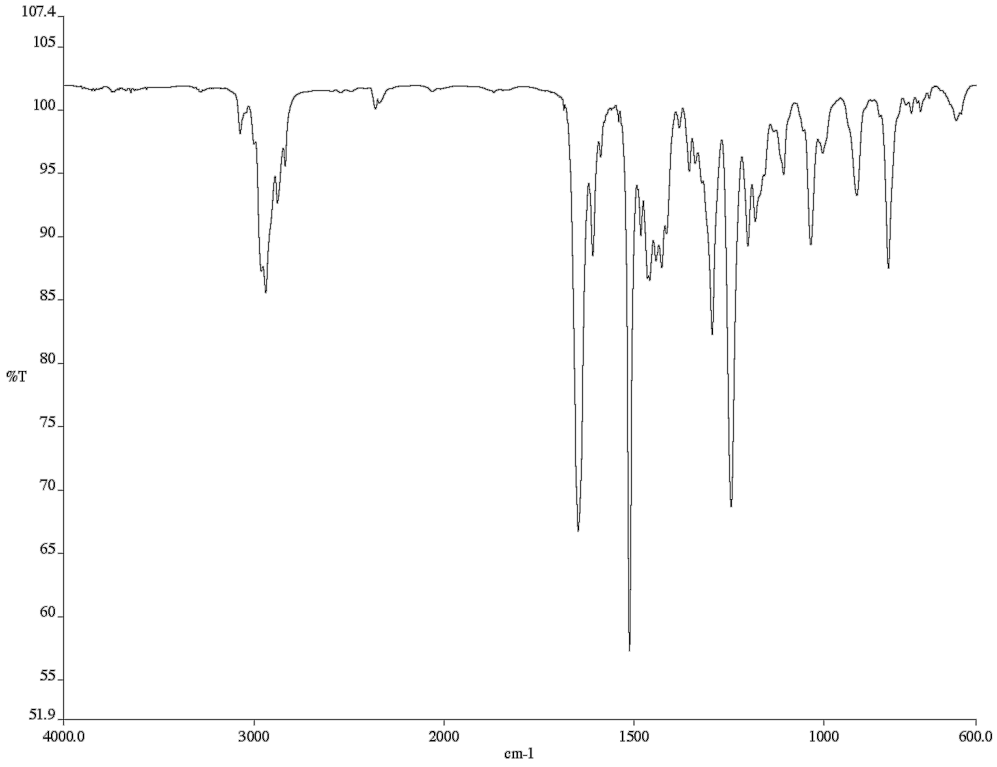


Figure A11.23 Infrared spectrum (thin film/NaCl) of compound **597**.

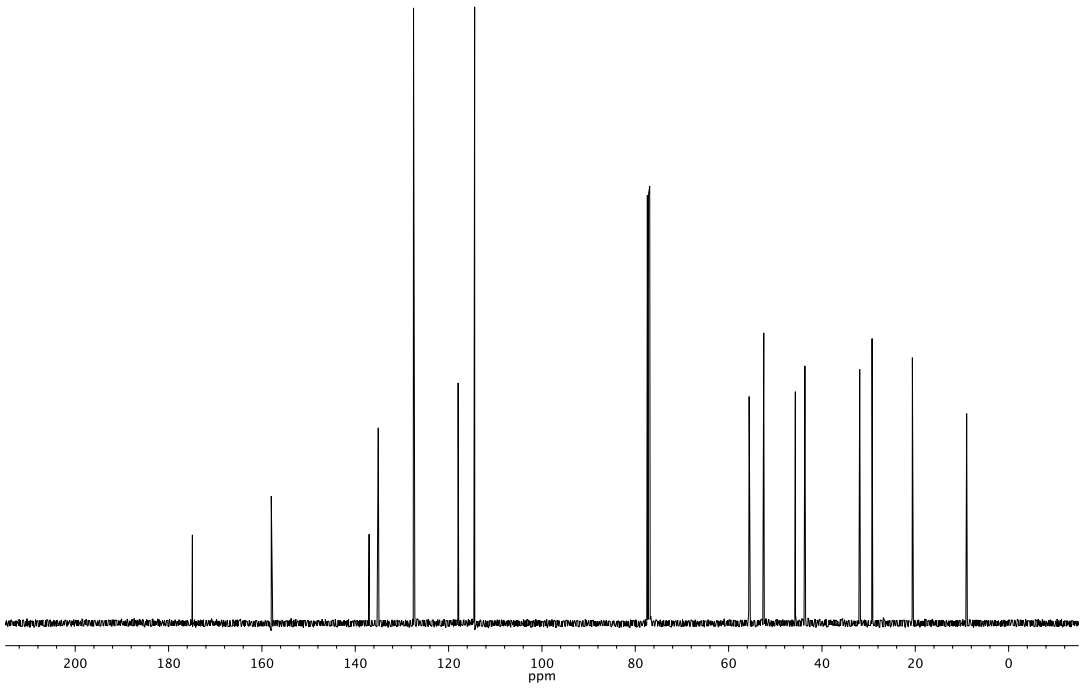


Figure A11.24 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **597**.

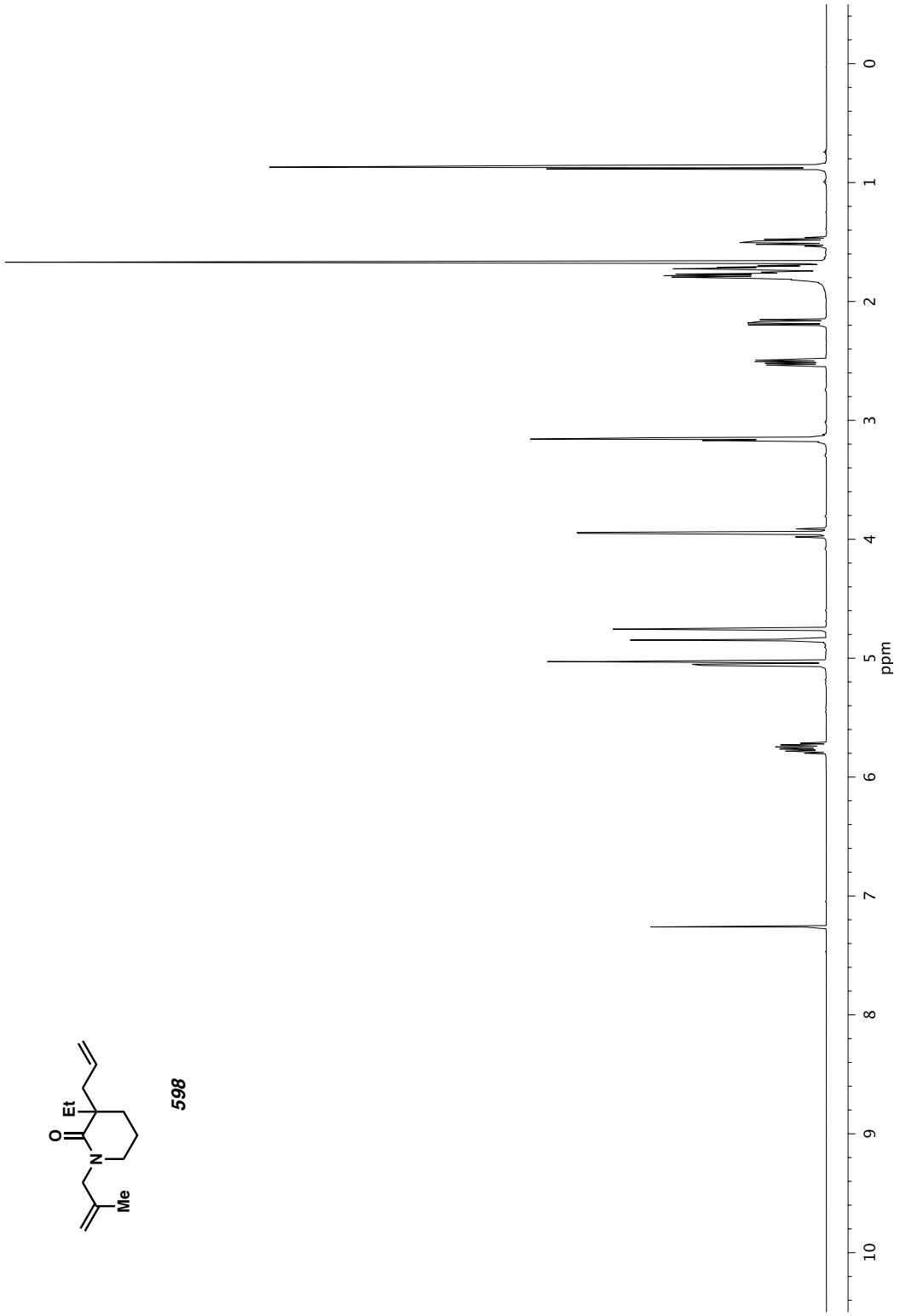


Figure A11.25 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **598**.

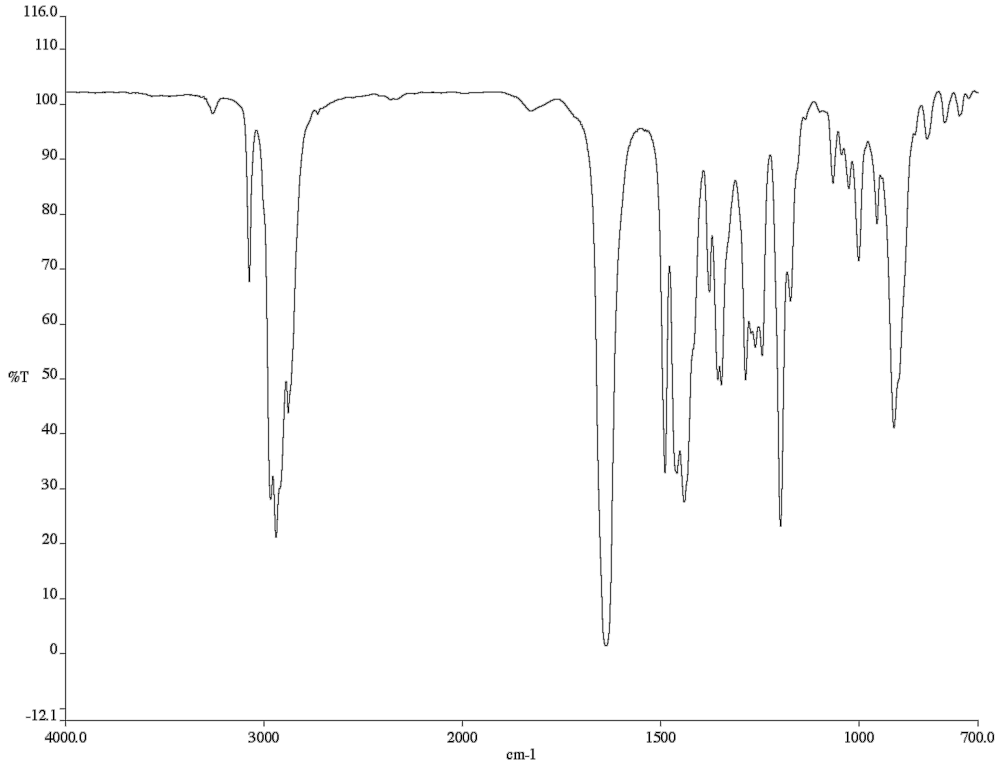


Figure A11.26 Infrared spectrum (thin film/NaCl) of compound **598**.

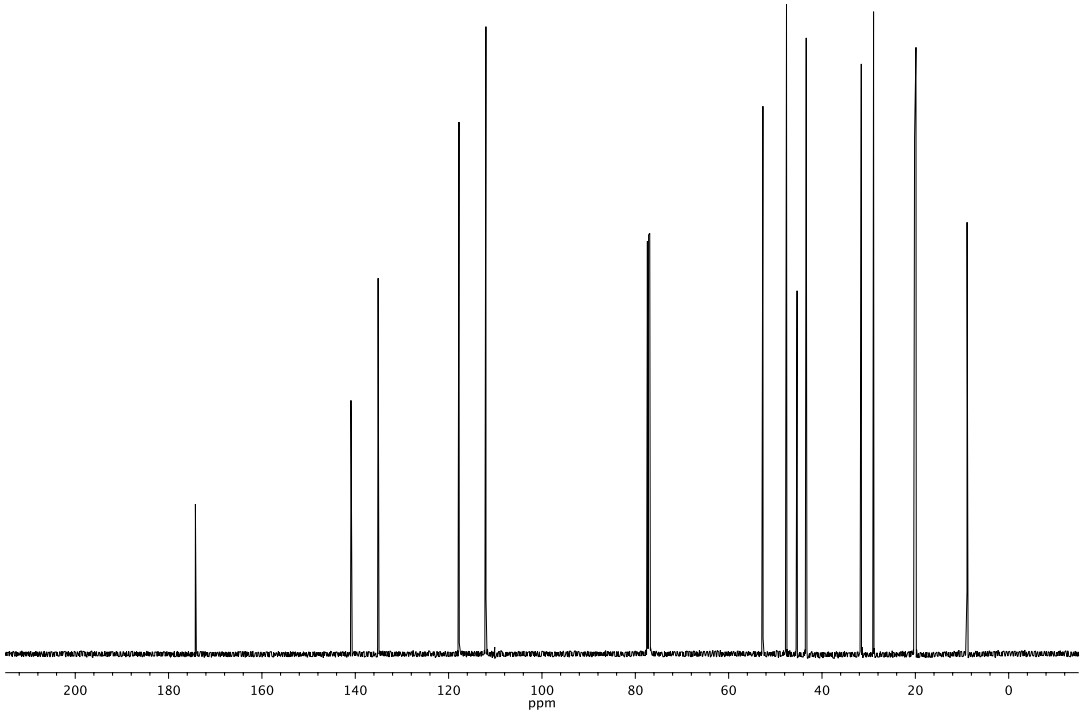


Figure A11.27 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **598**.

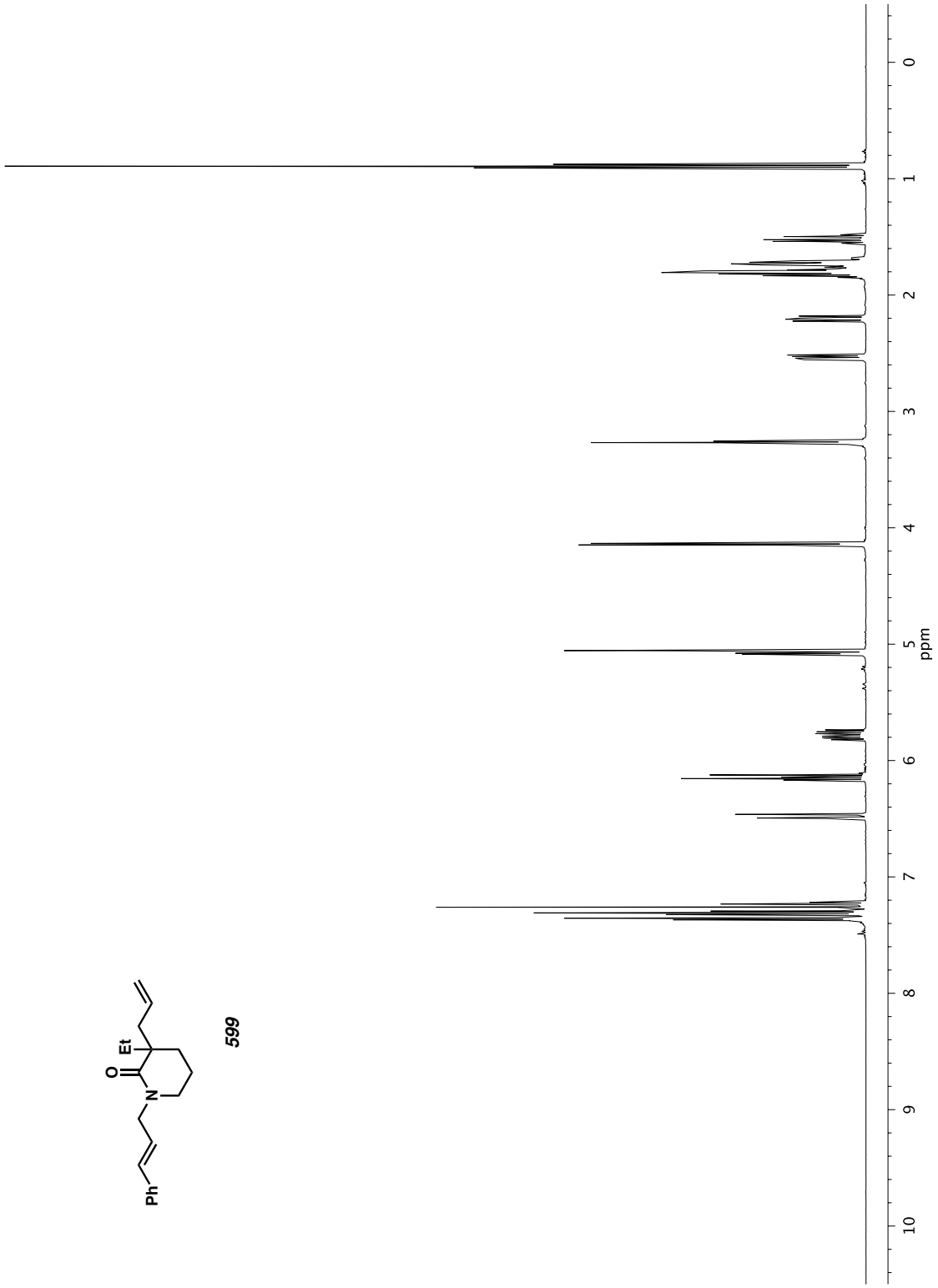


Figure A11.28 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **599**.

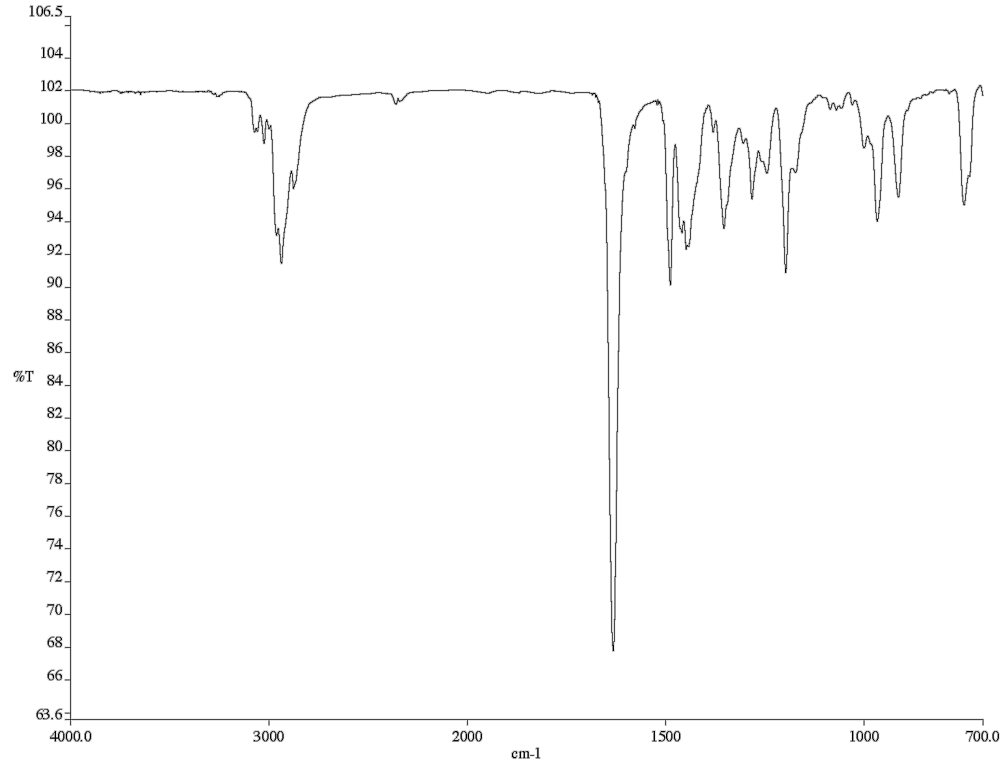


Figure A11.29 Infrared spectrum (thin film/NaCl) of compound **599**.

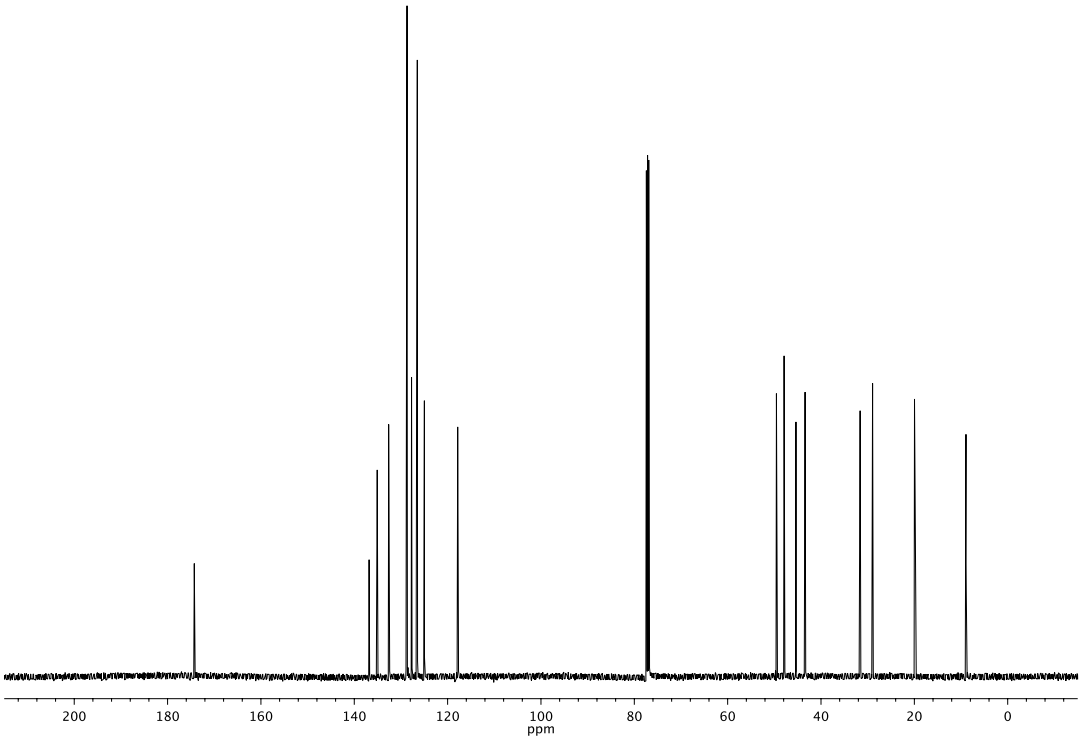


Figure A11.30 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **599**.

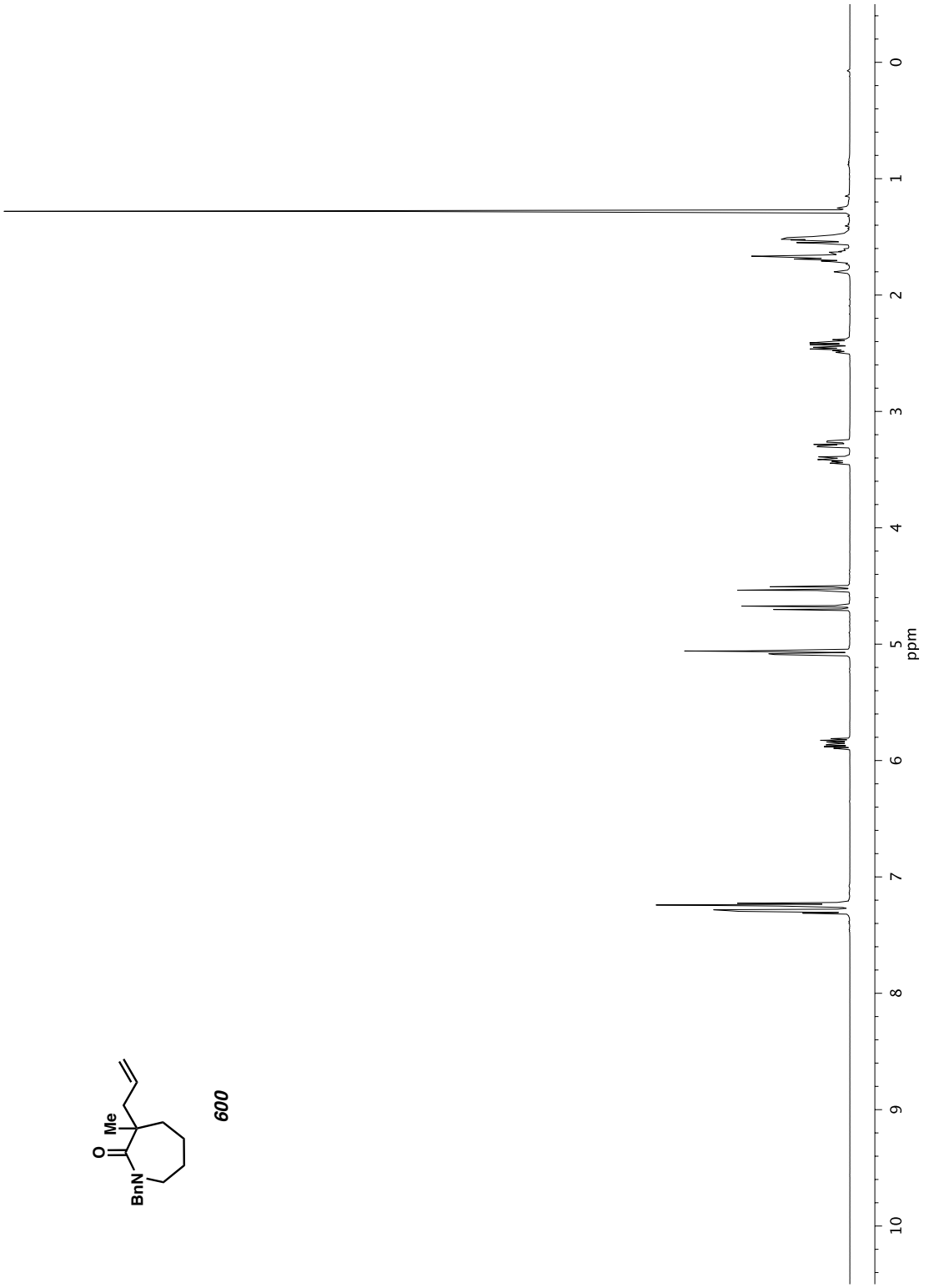


Figure A11.31 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **600**.

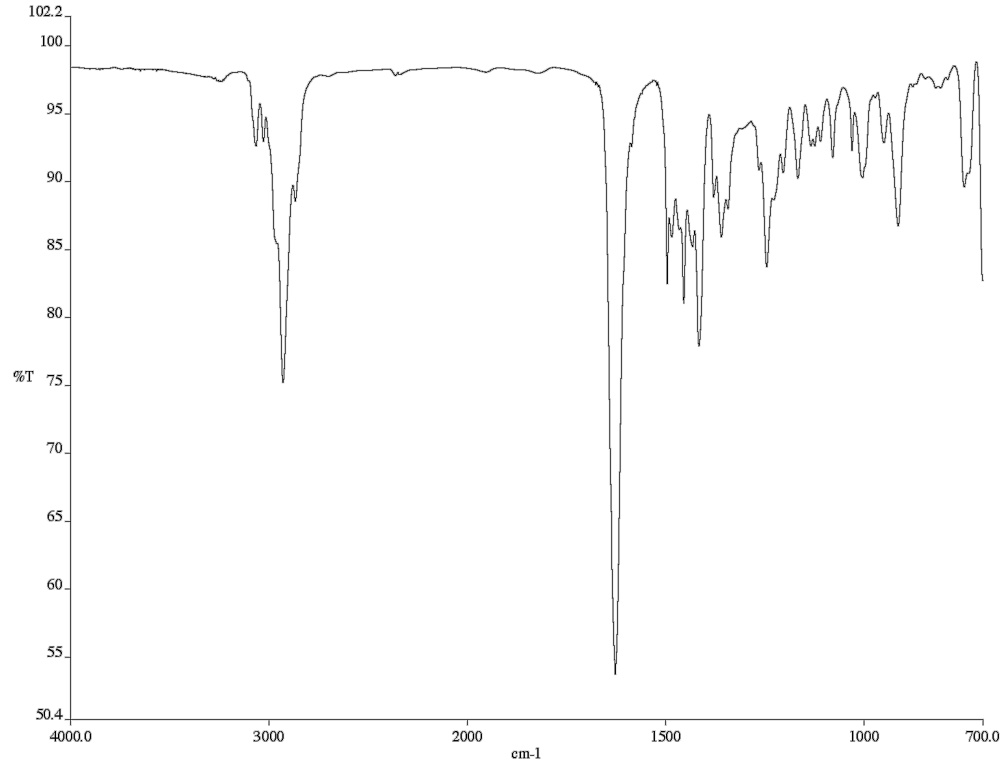


Figure A11.32 Infrared spectrum (thin film/NaCl) of compound **600**.

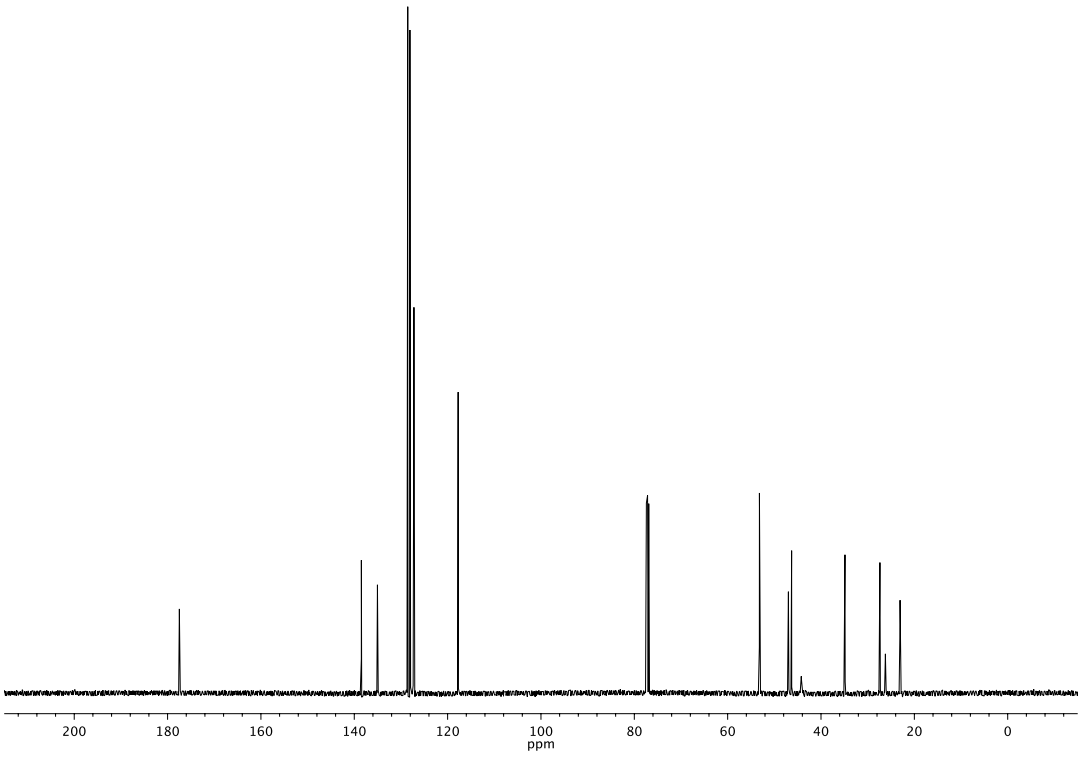


Figure A11.33 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **600**.

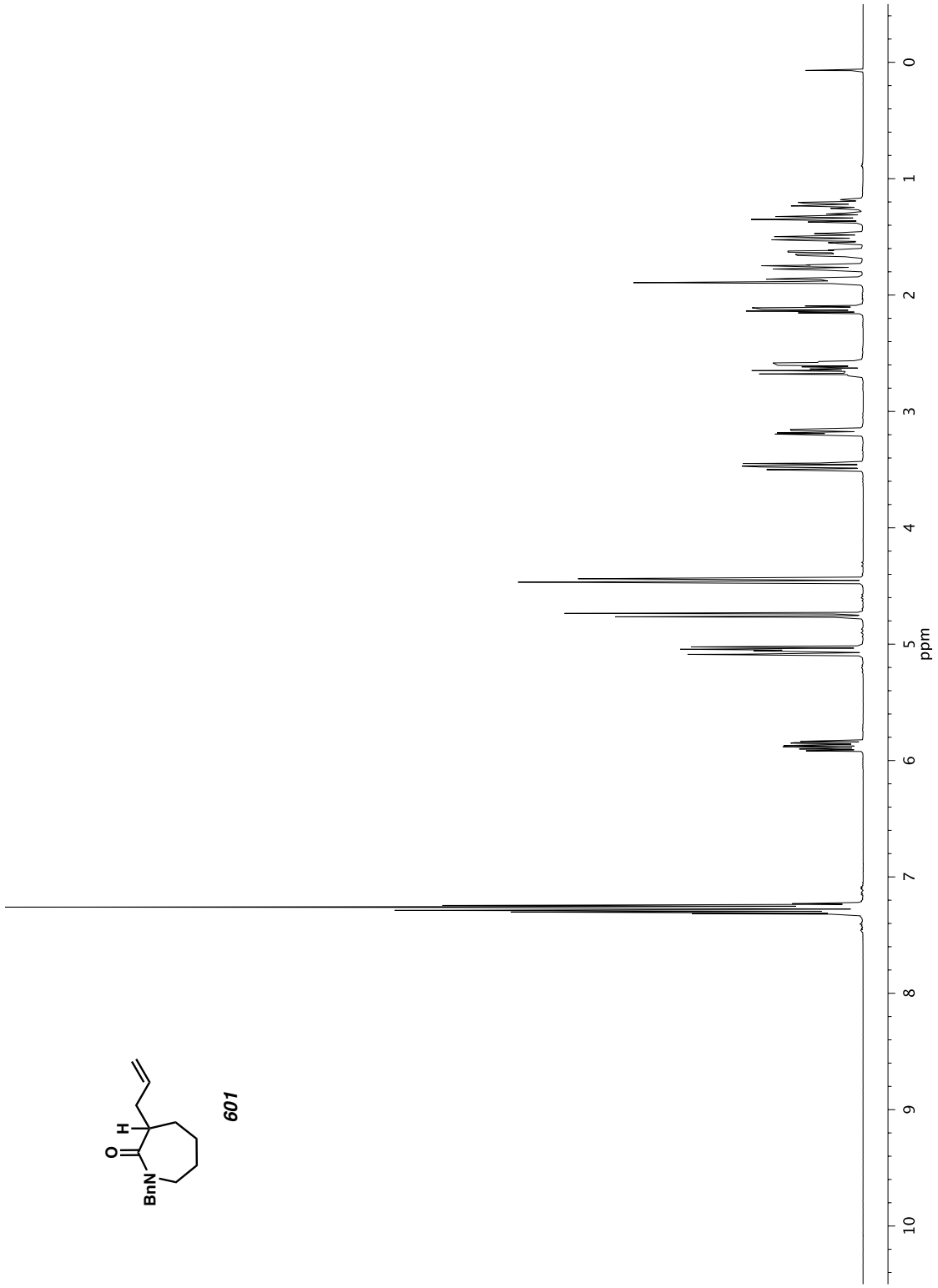


Figure A11.34 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **601**.

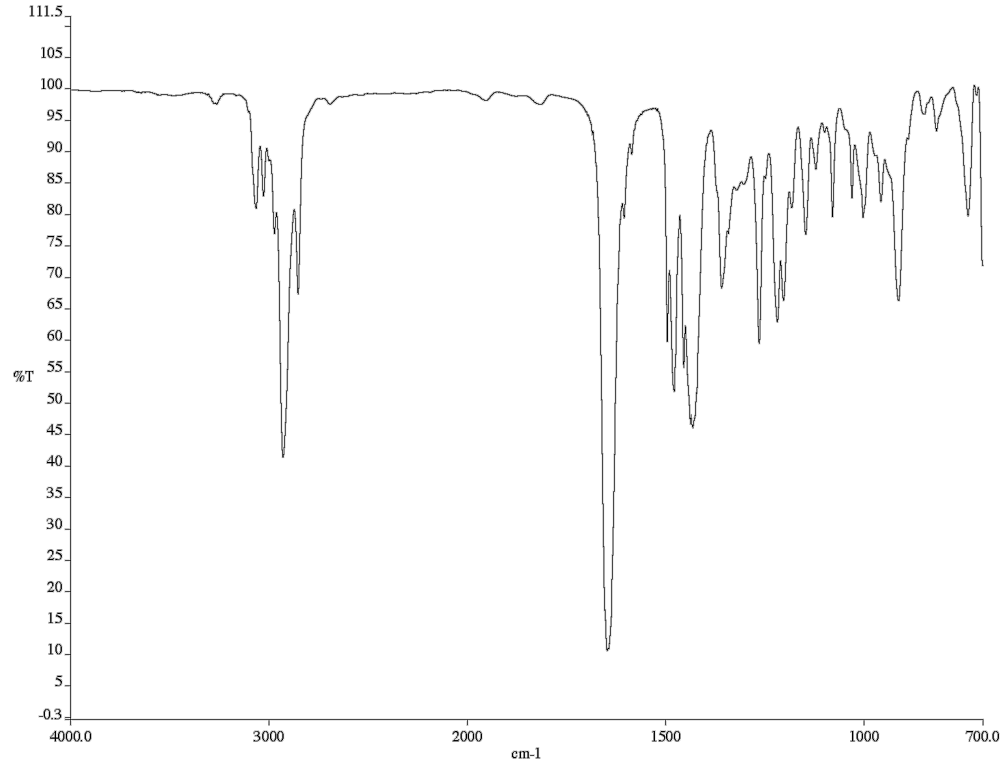


Figure A11.35 Infrared spectrum (thin film/NaCl) of compound **601**.

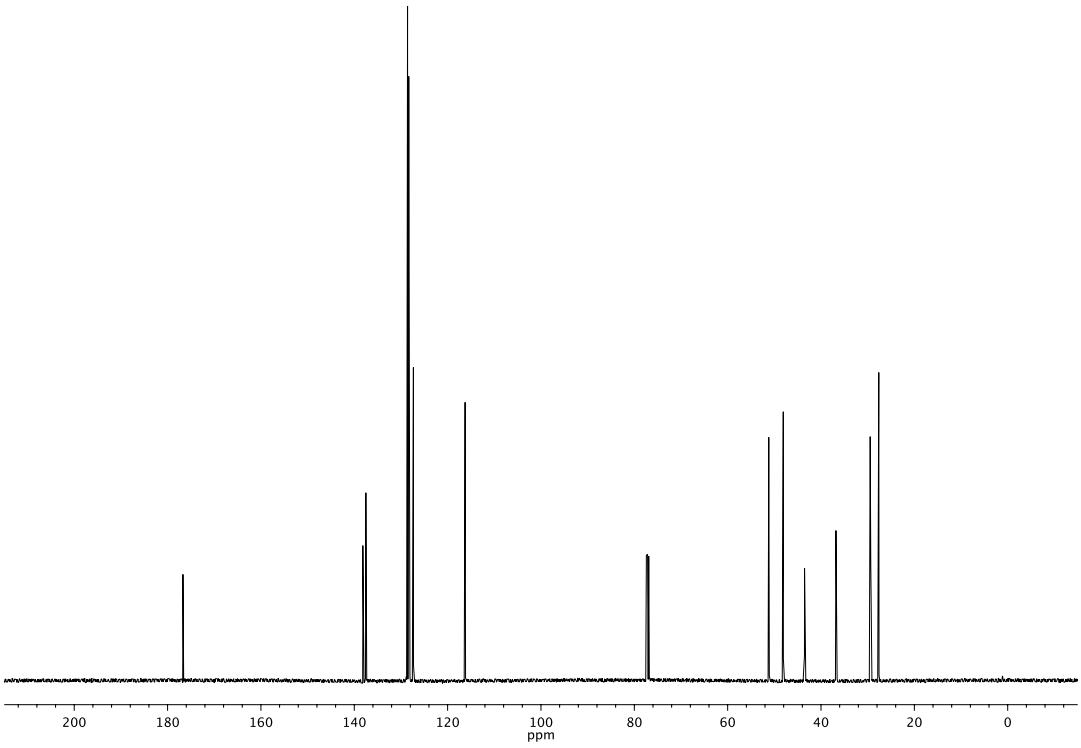


Figure A11.36 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **601**.

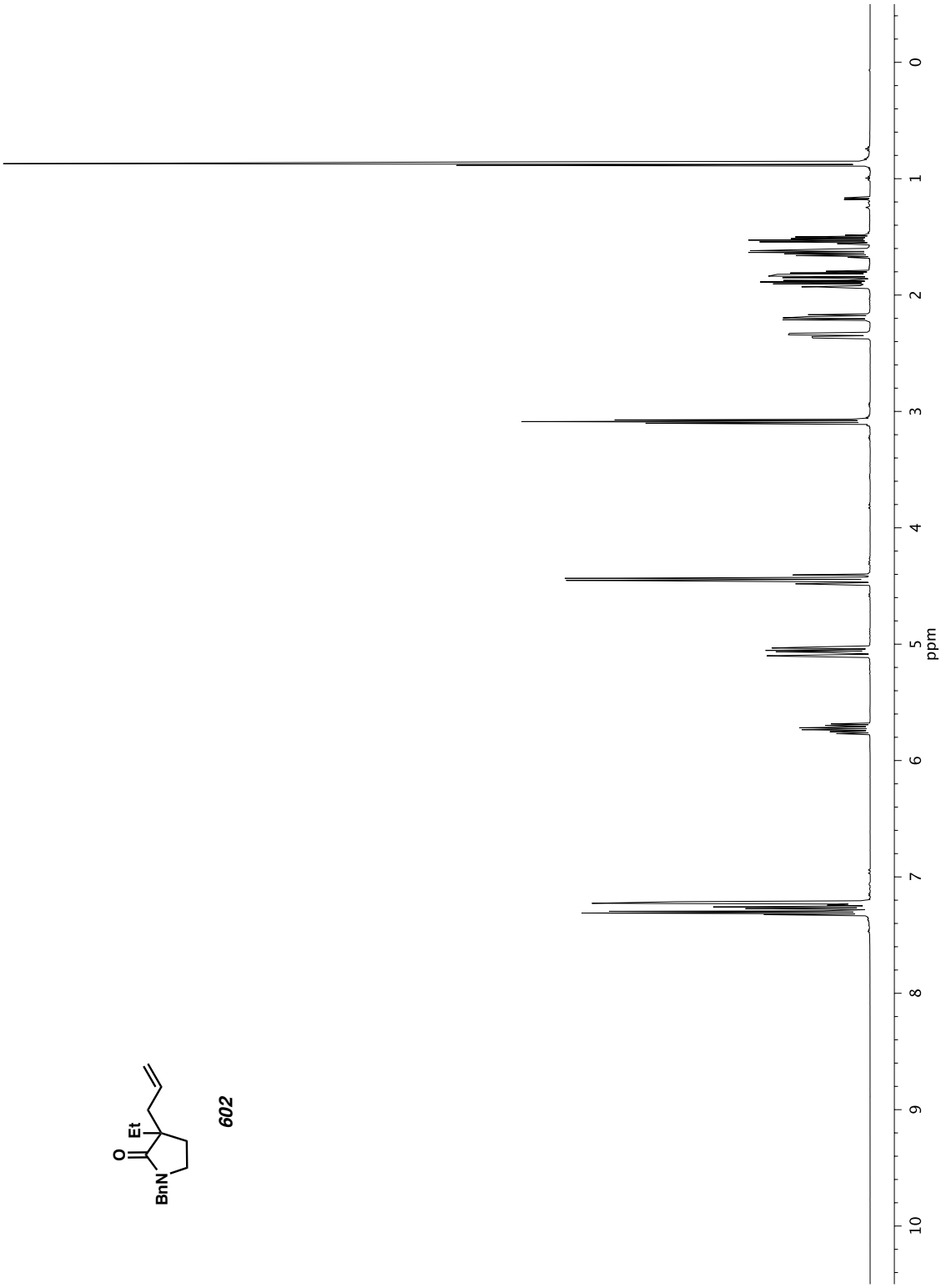


Figure A11.37 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **602**.

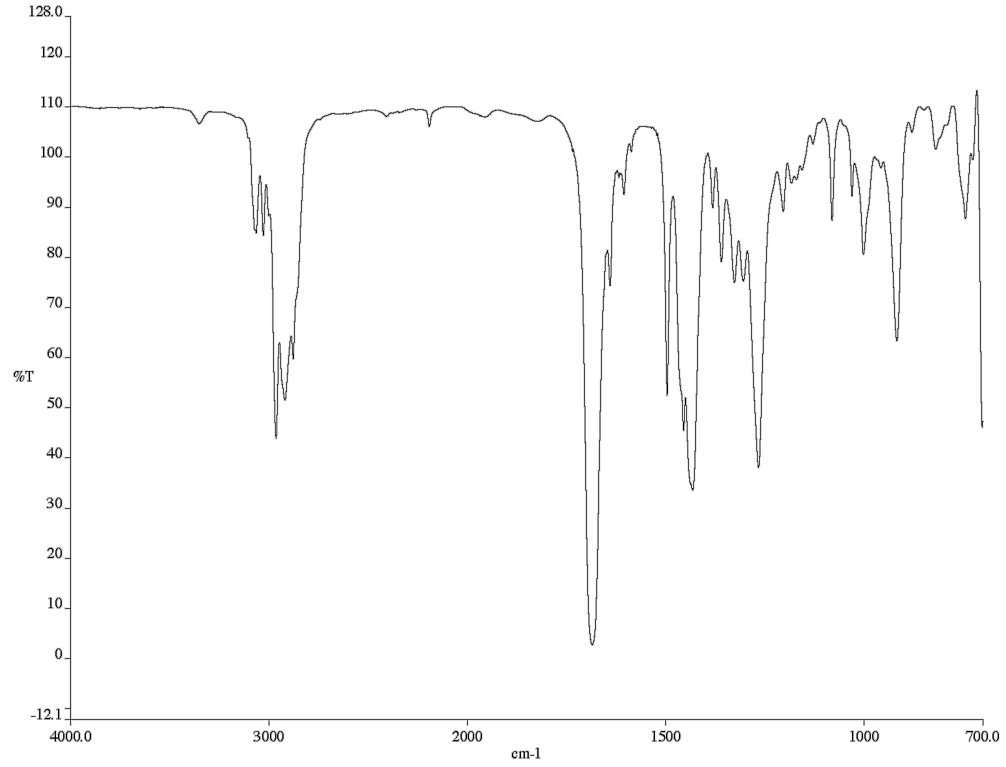


Figure A11.38 Infrared spectrum (thin film/NaCl) of compound **602**.

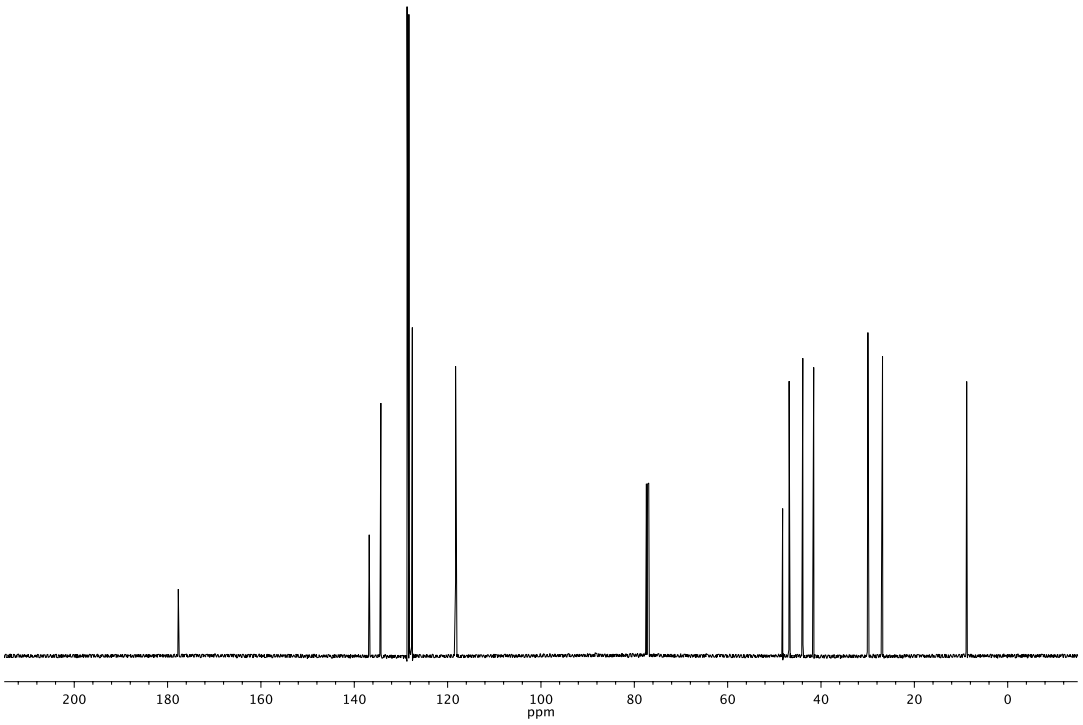


Figure A11.39 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **602**.

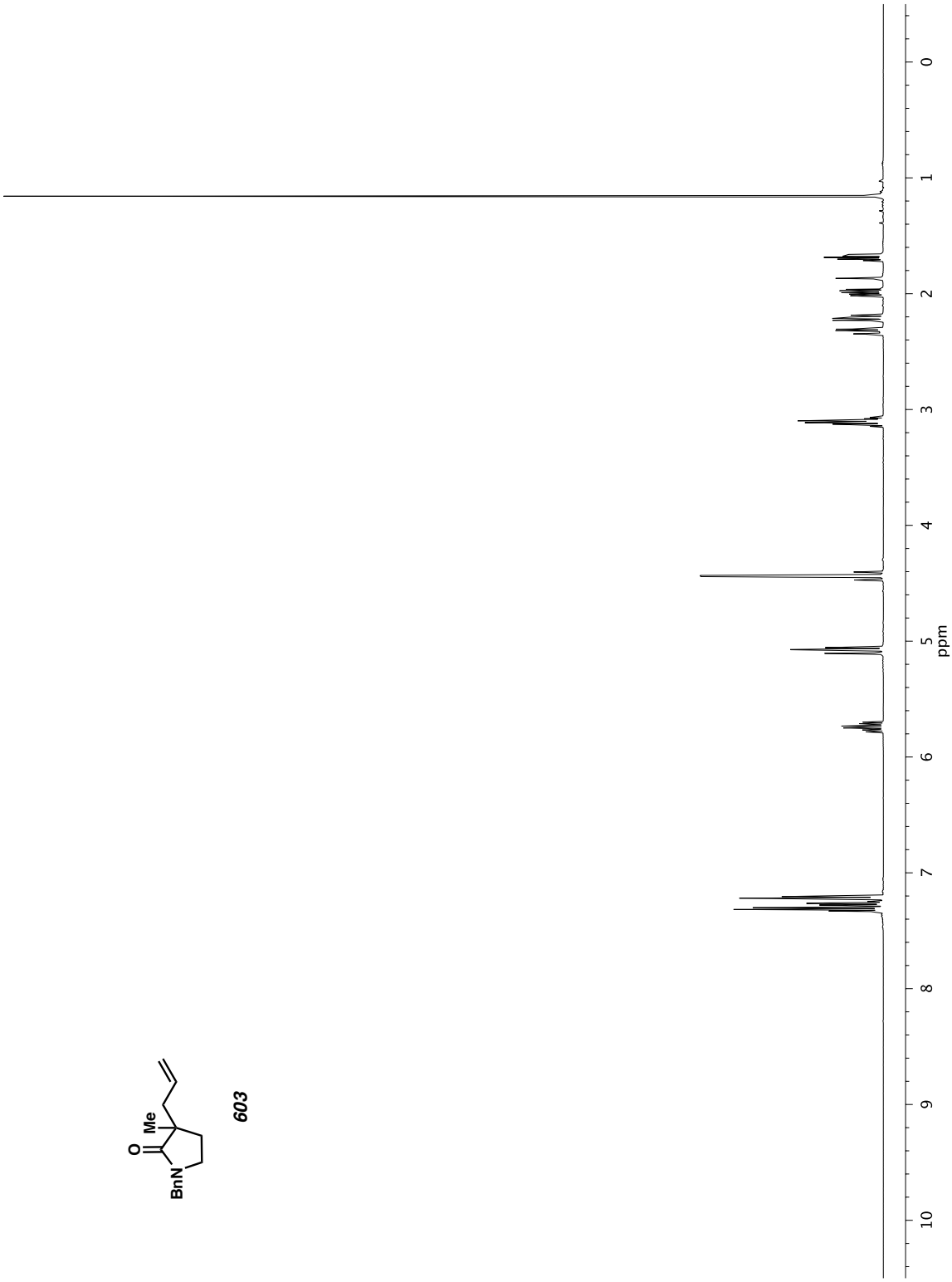


Figure A11.40 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **603**.

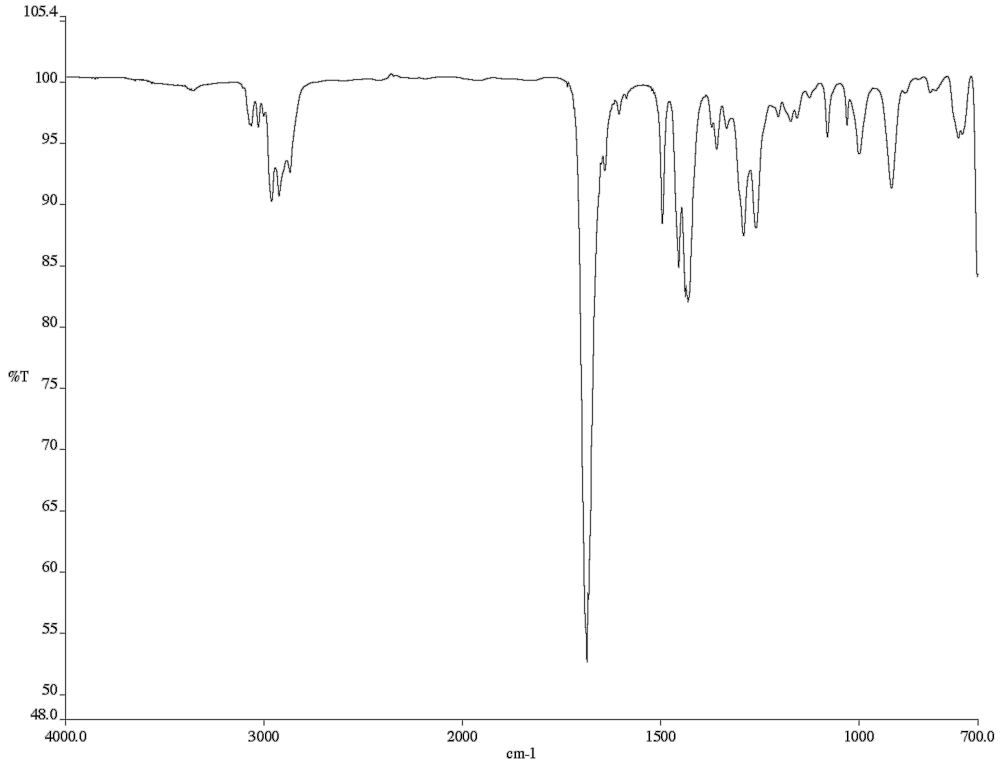


Figure A11.41 Infrared spectrum (thin film/NaCl) of compound **603**.

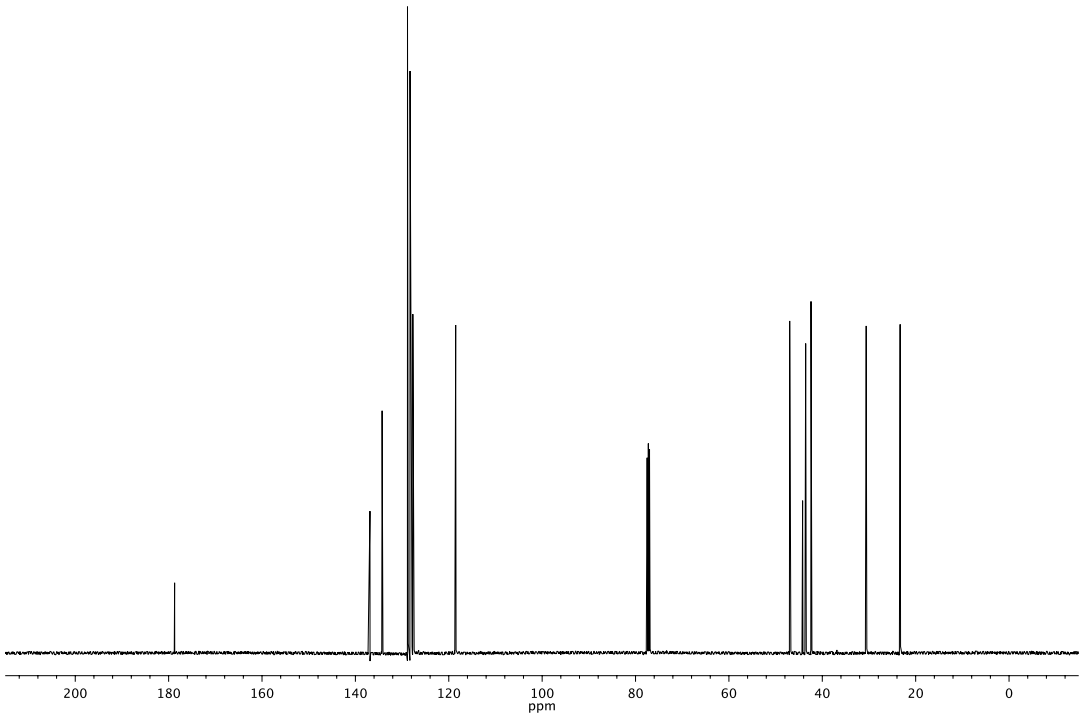


Figure A11.42 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **603**.

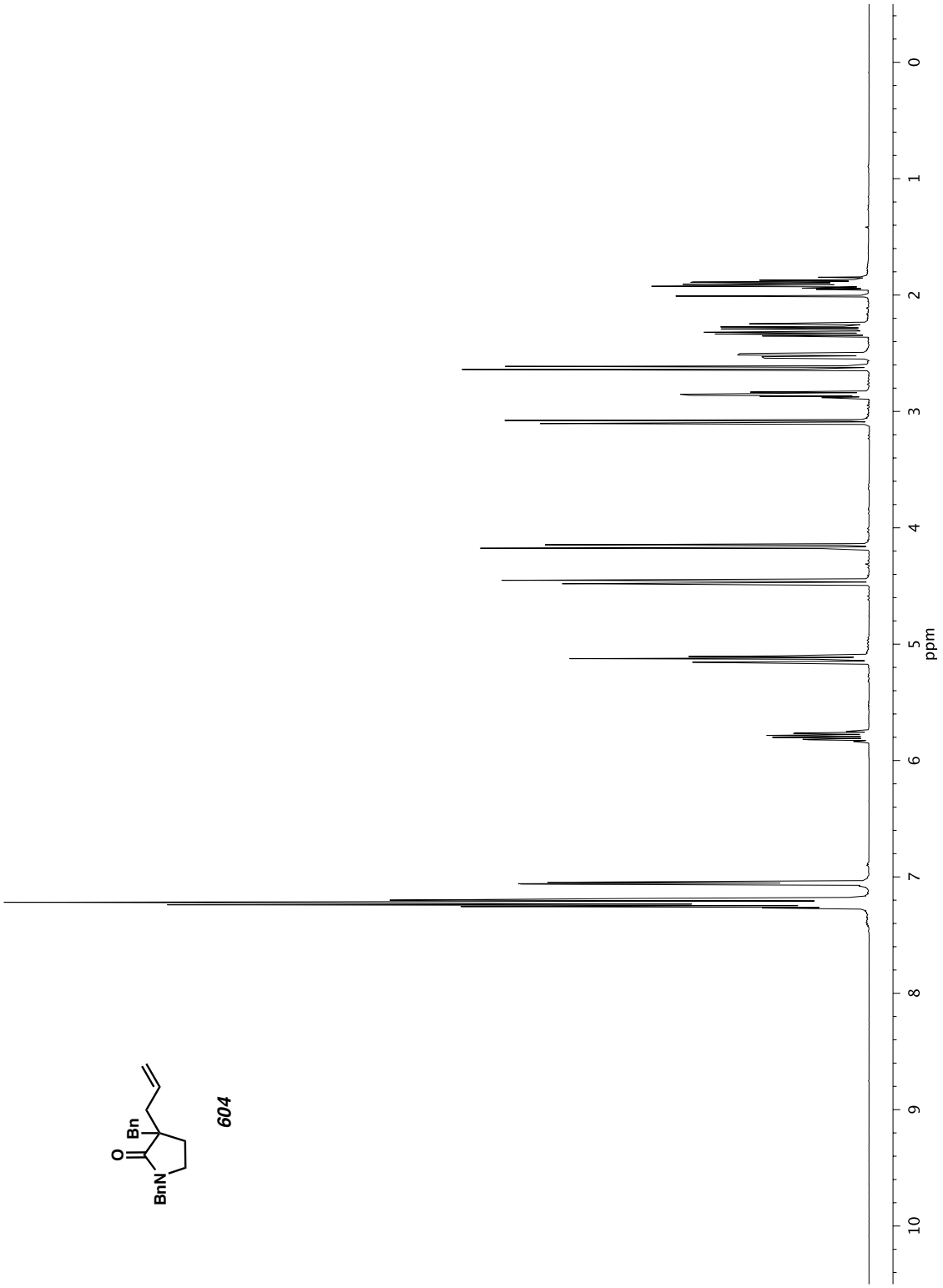


Figure A11.43 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **604**.

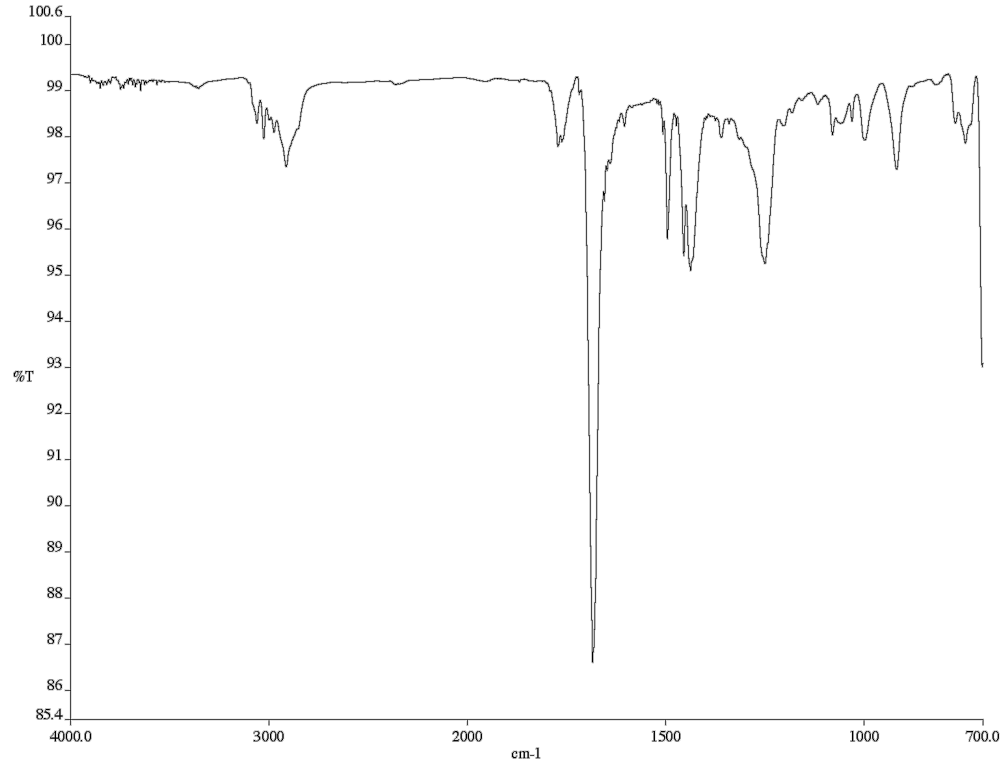


Figure A11.44 Infrared spectrum (thin film/NaCl) of compound **604**.

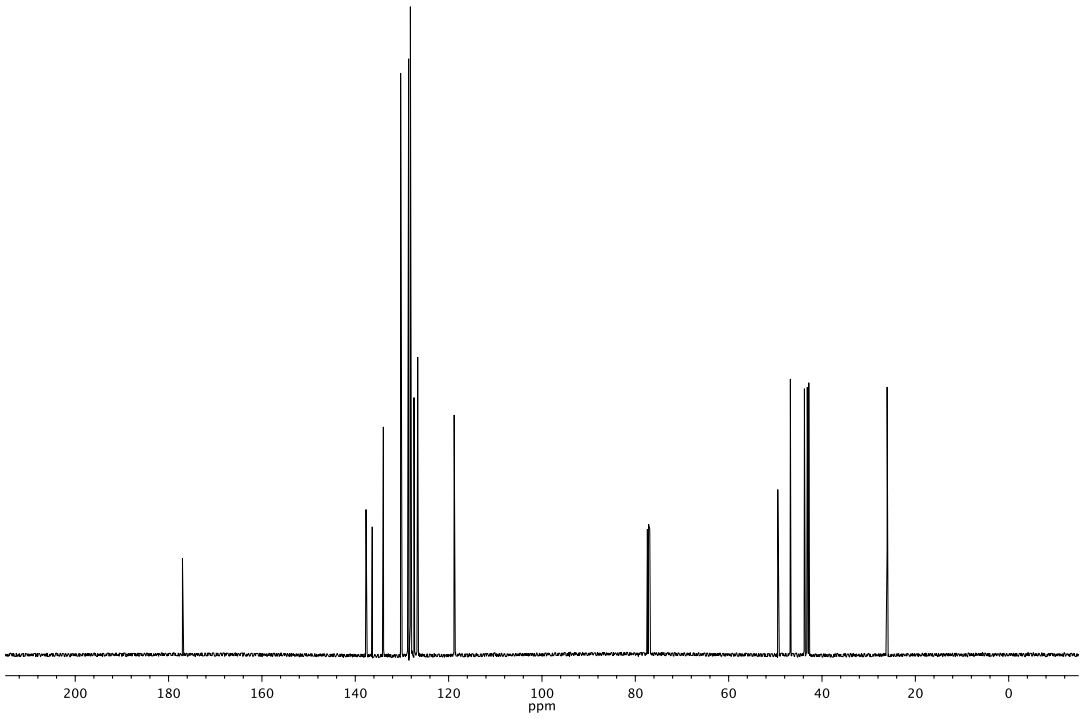


Figure A11.45 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **604**.

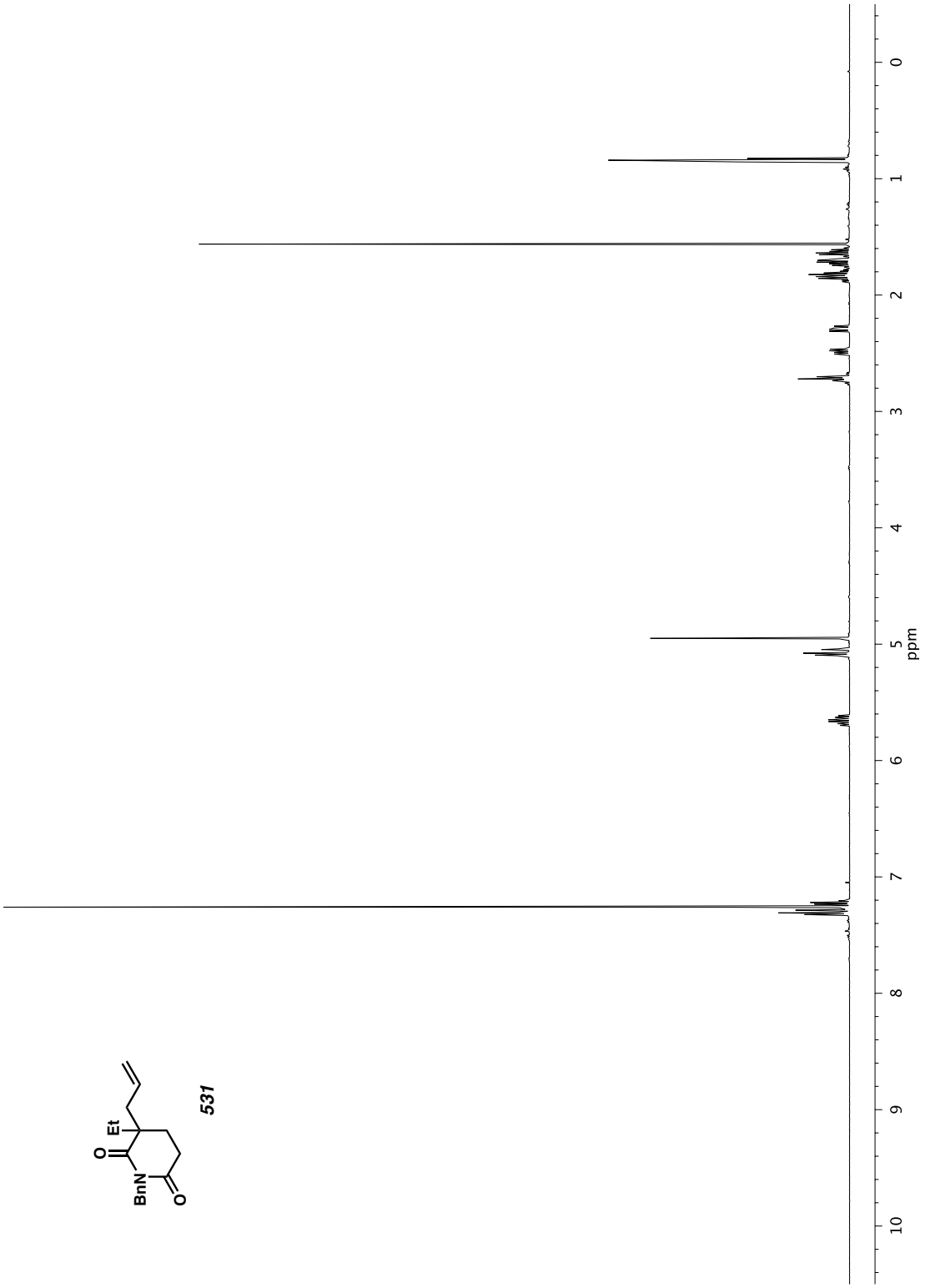


Figure A11.46 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **531**.

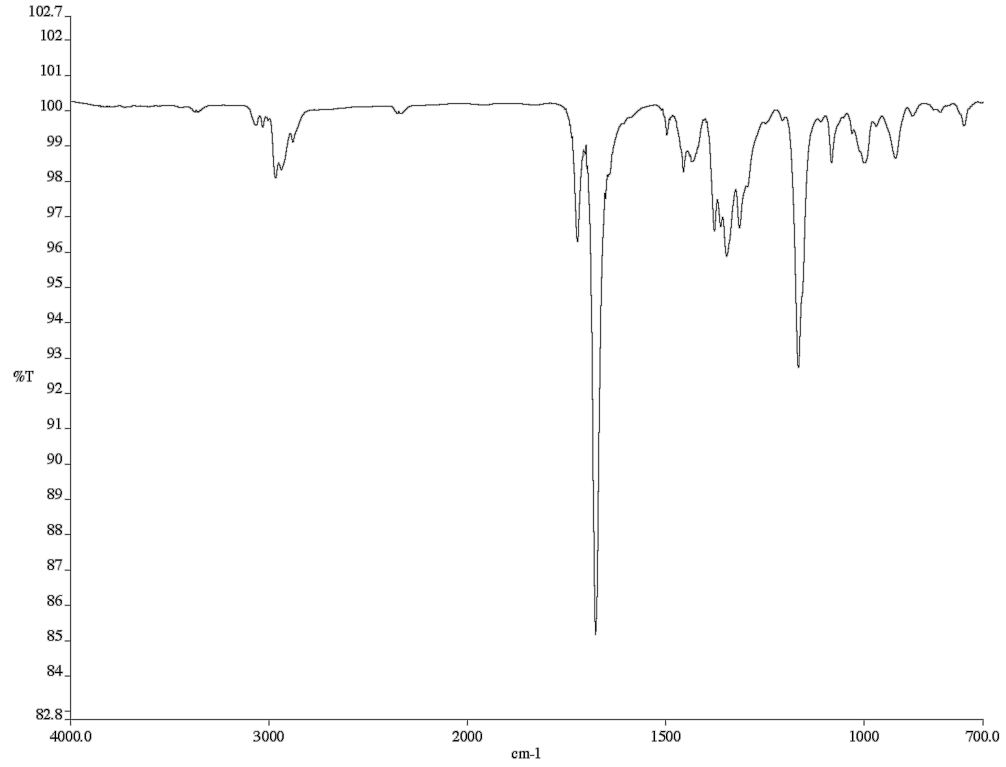


Figure A11.47 Infrared spectrum (thin film/NaCl) of compound **531**.

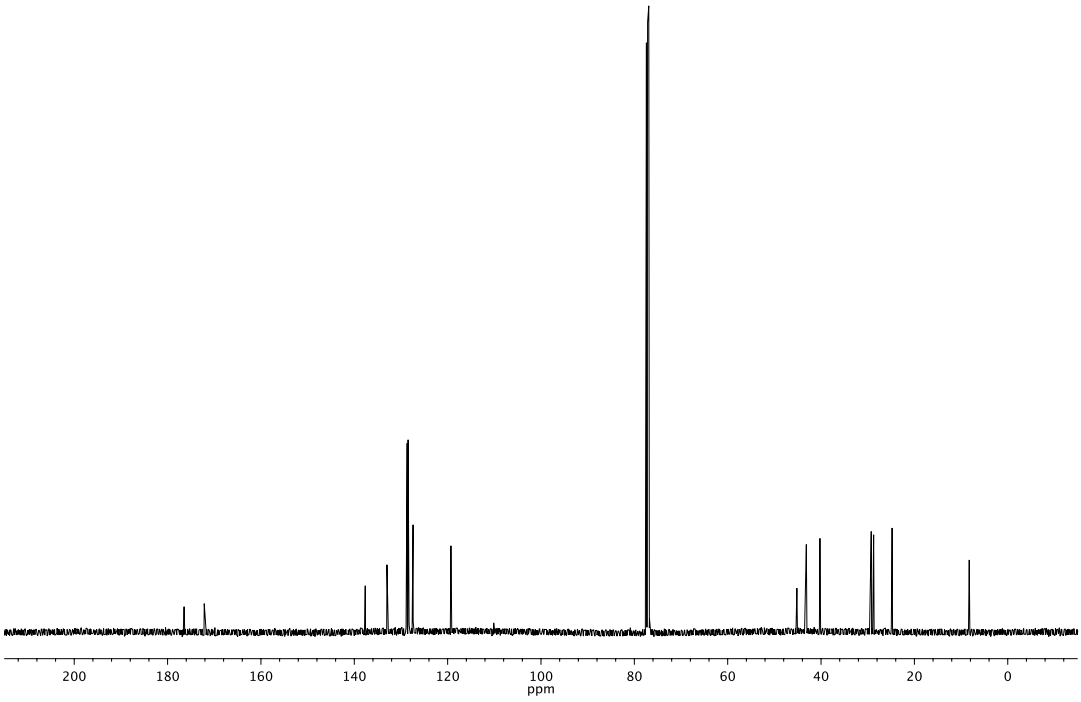


Figure A11.48 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **531**.

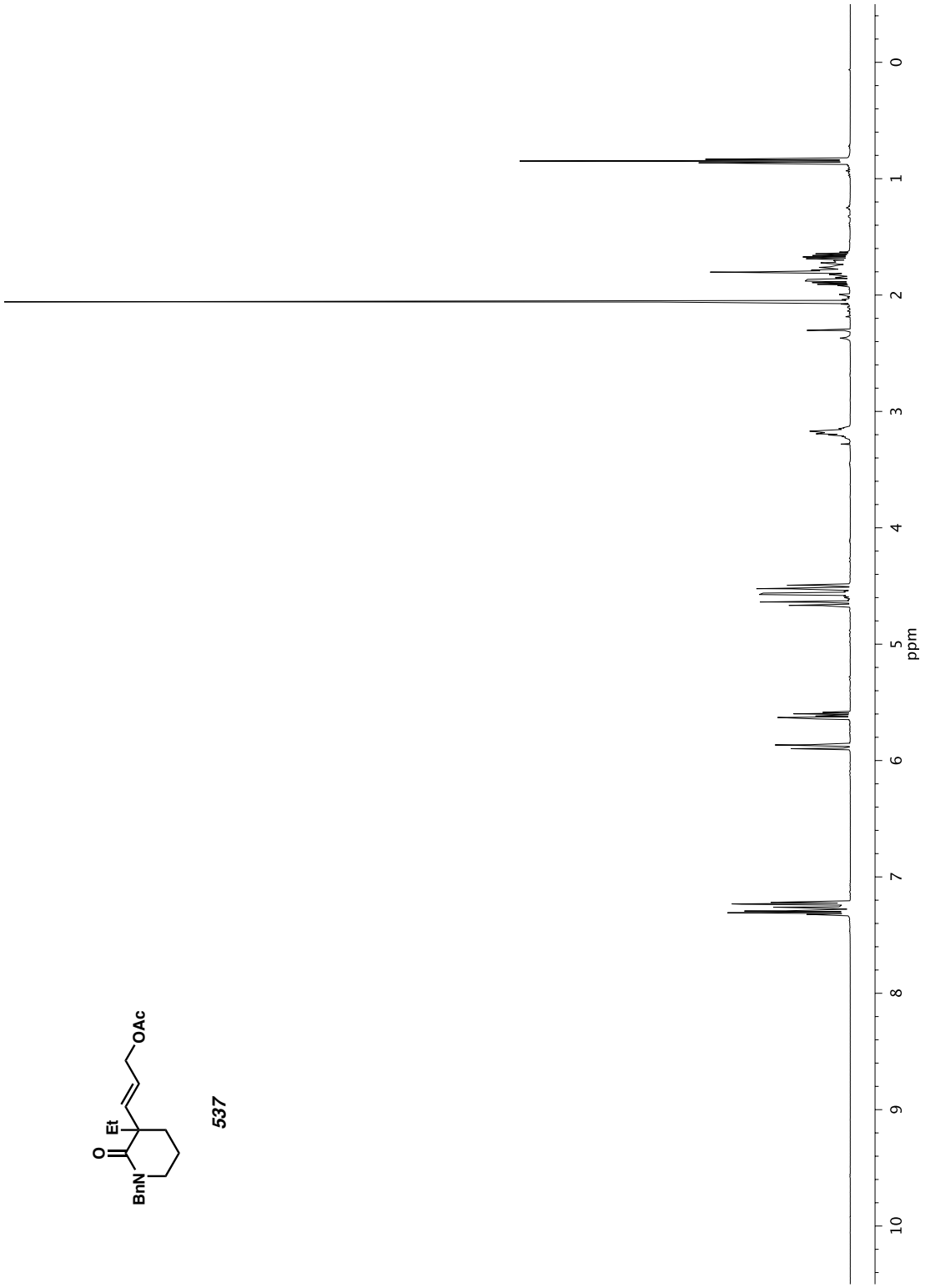


Figure A11.49 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **537**.

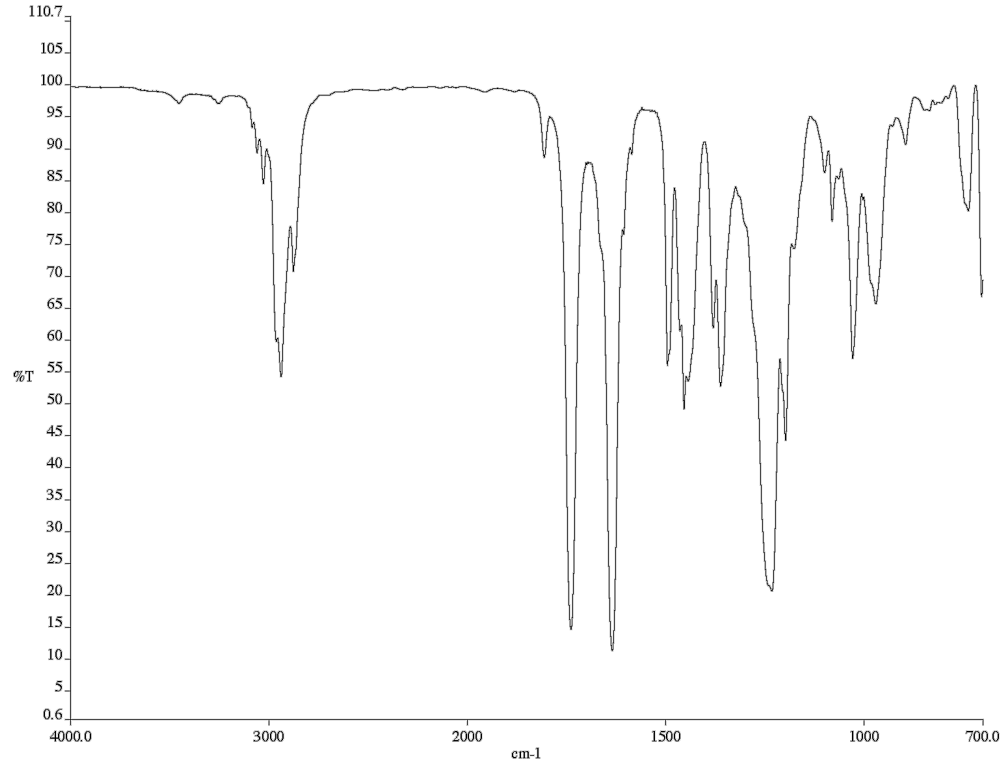


Figure A11.50 Infrared spectrum (thin film/NaCl) of compound **537**.

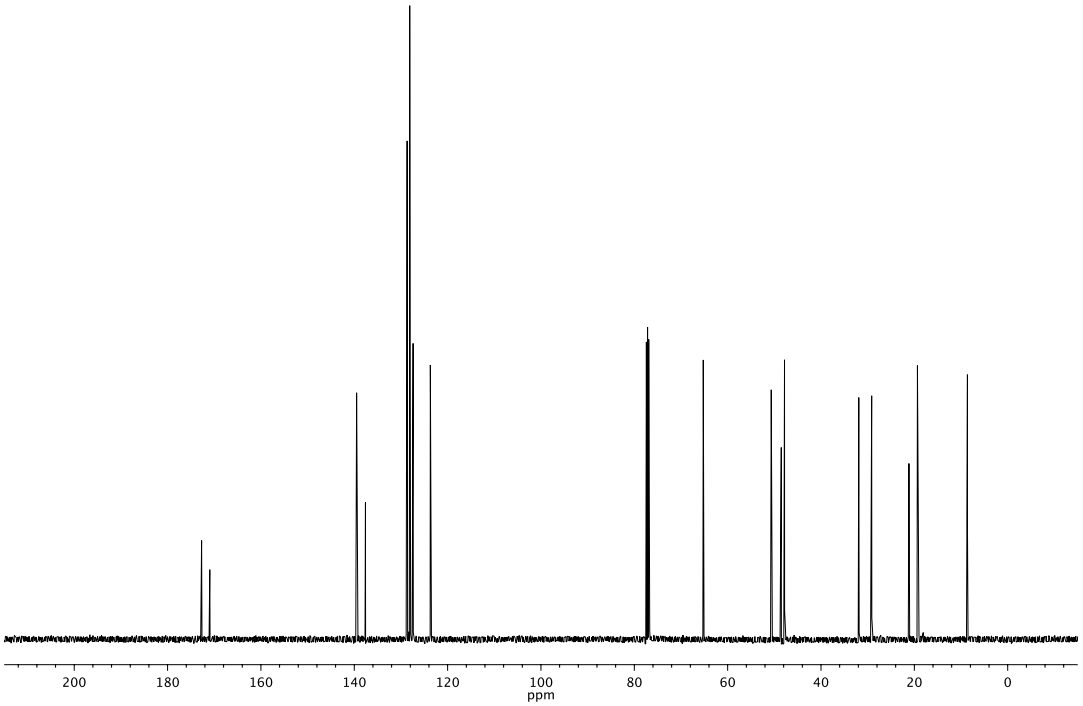


Figure A11.51 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **537**.

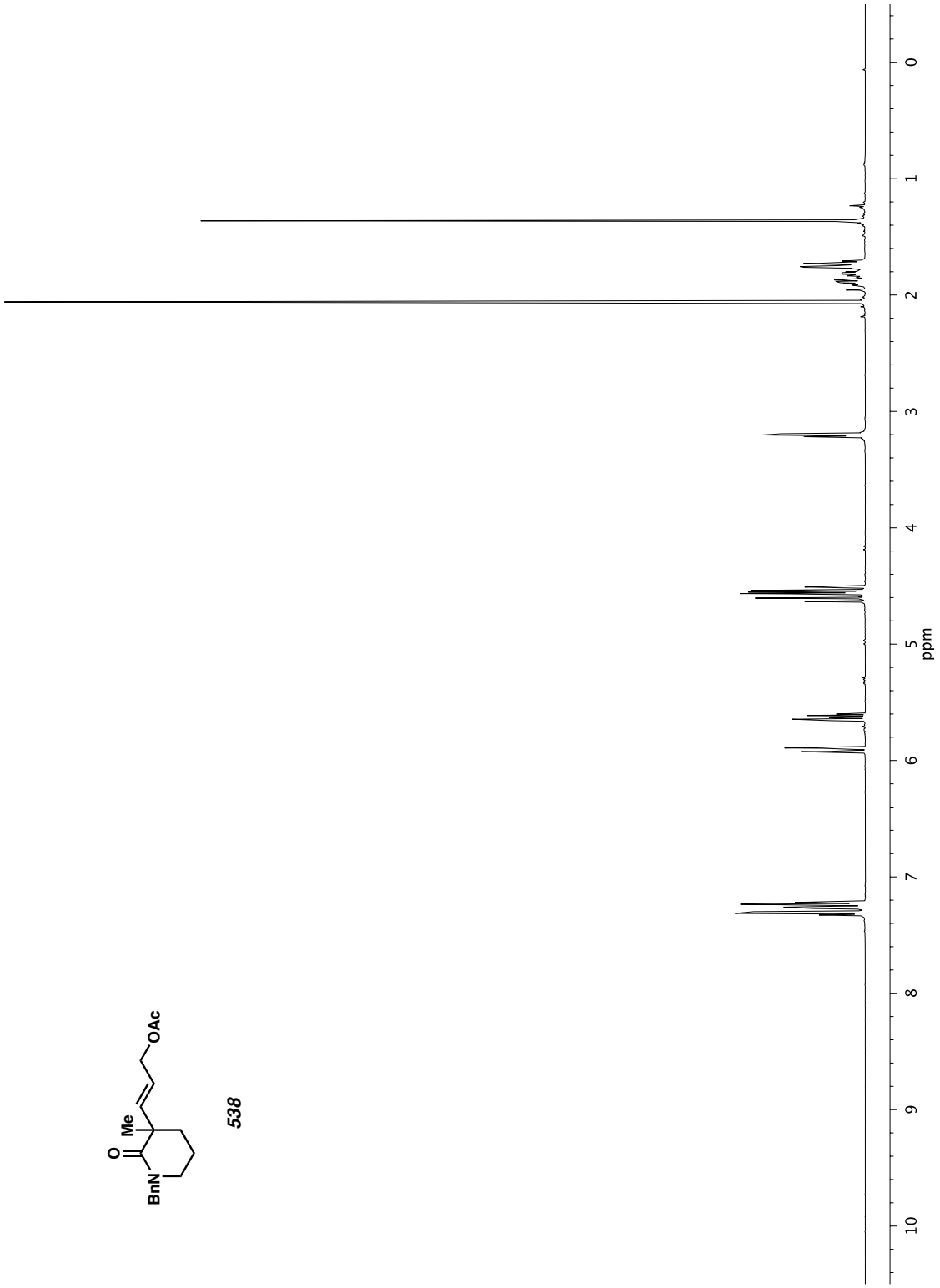


Figure A11.52 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **538**.

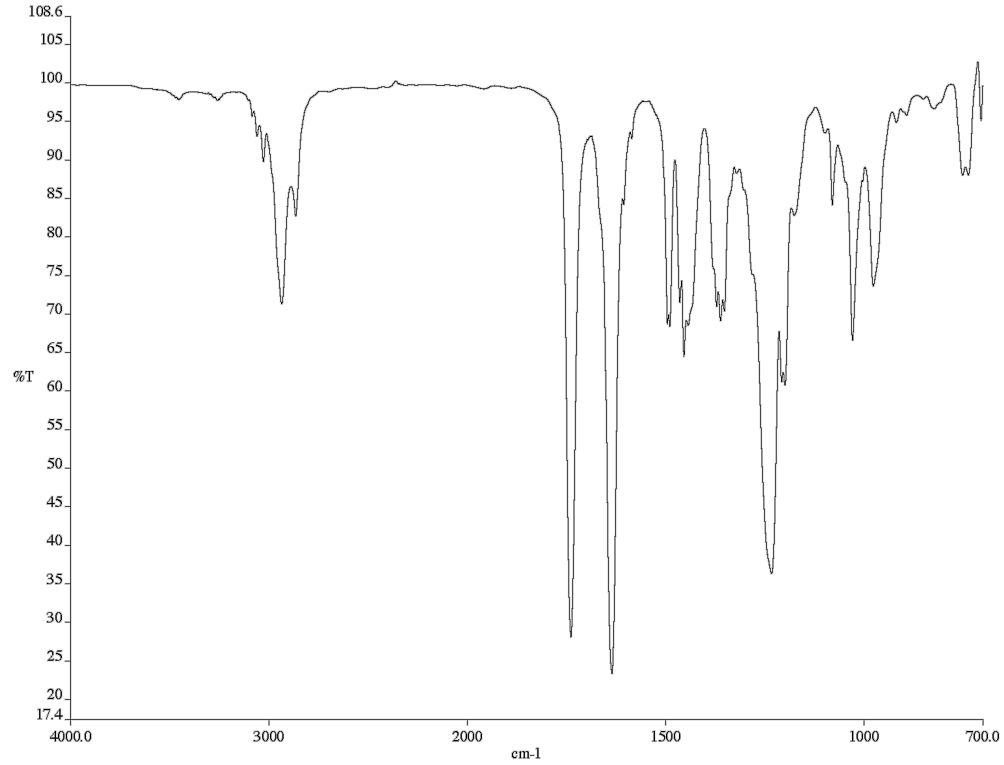


Figure A11.53 Infrared spectrum (thin film/NaCl) of compound **538**.

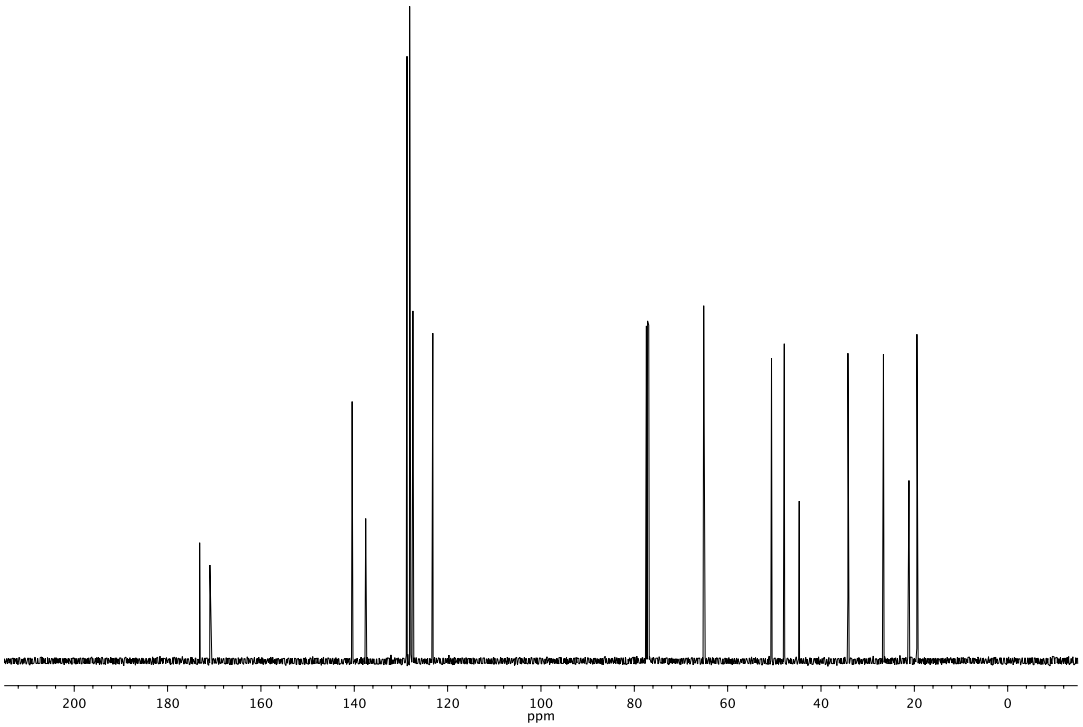


Figure A11.54 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **538**.

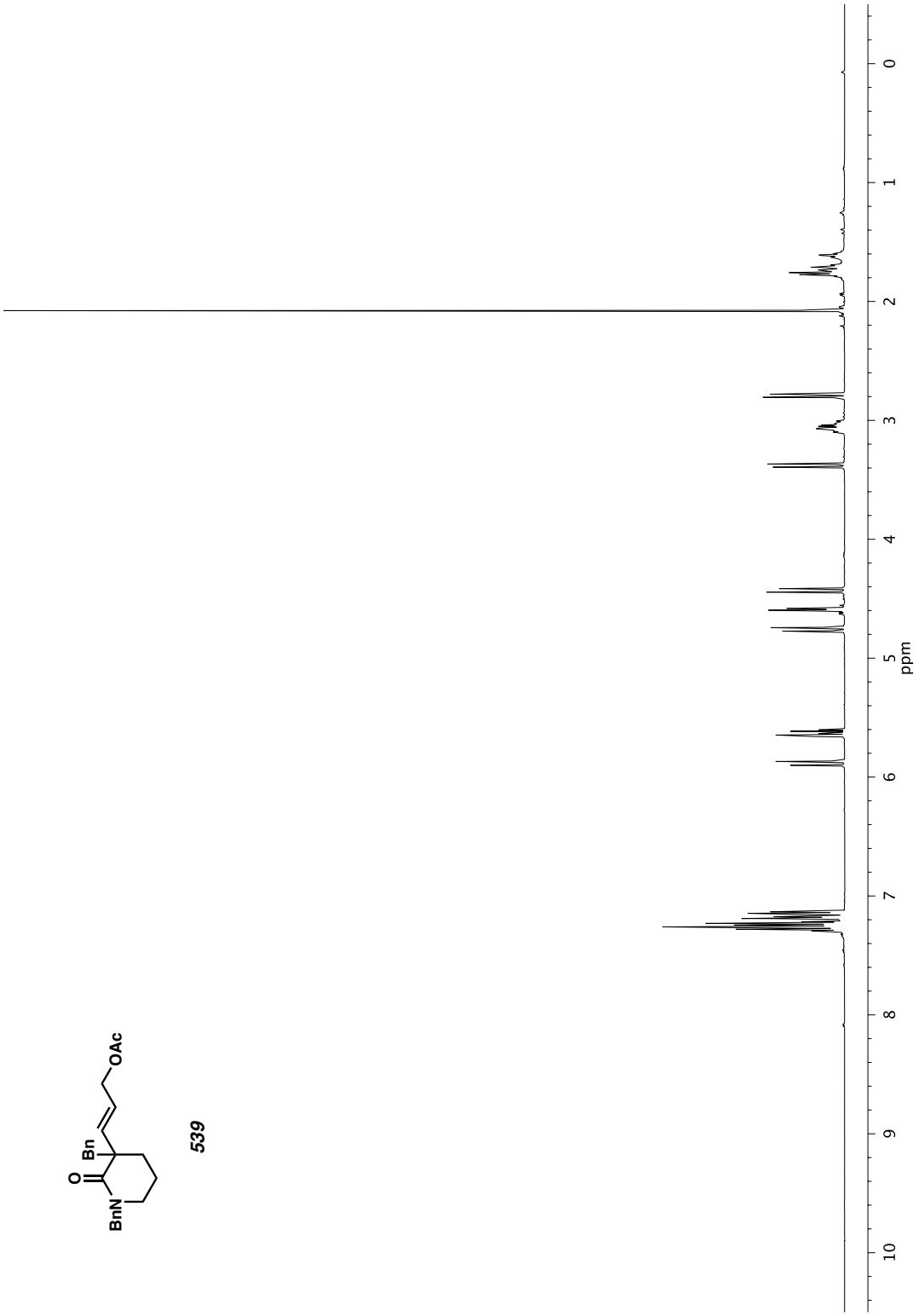


Figure A11.55 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **539**.

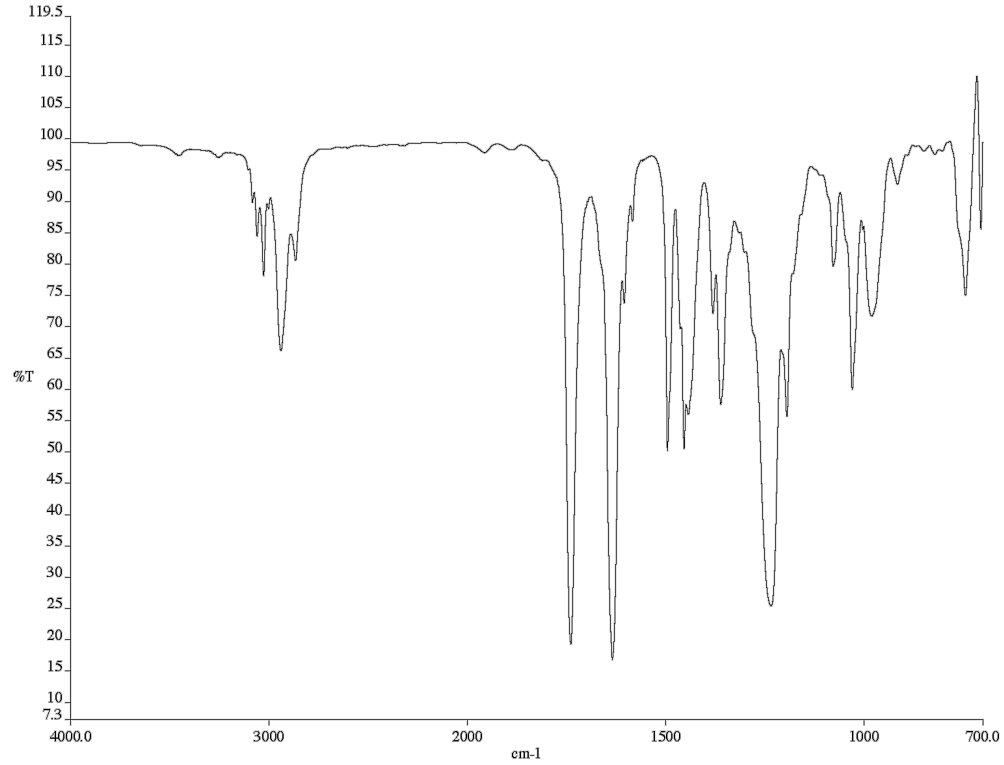


Figure A11.56 Infrared spectrum (thin film/NaCl) of compound **539**.

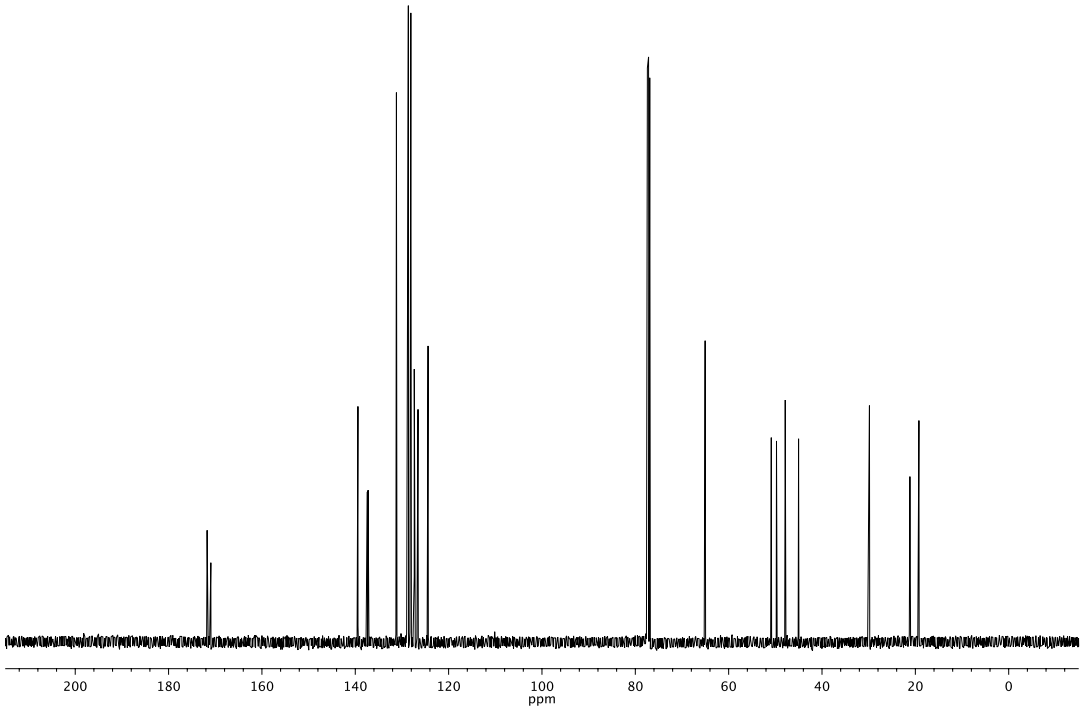
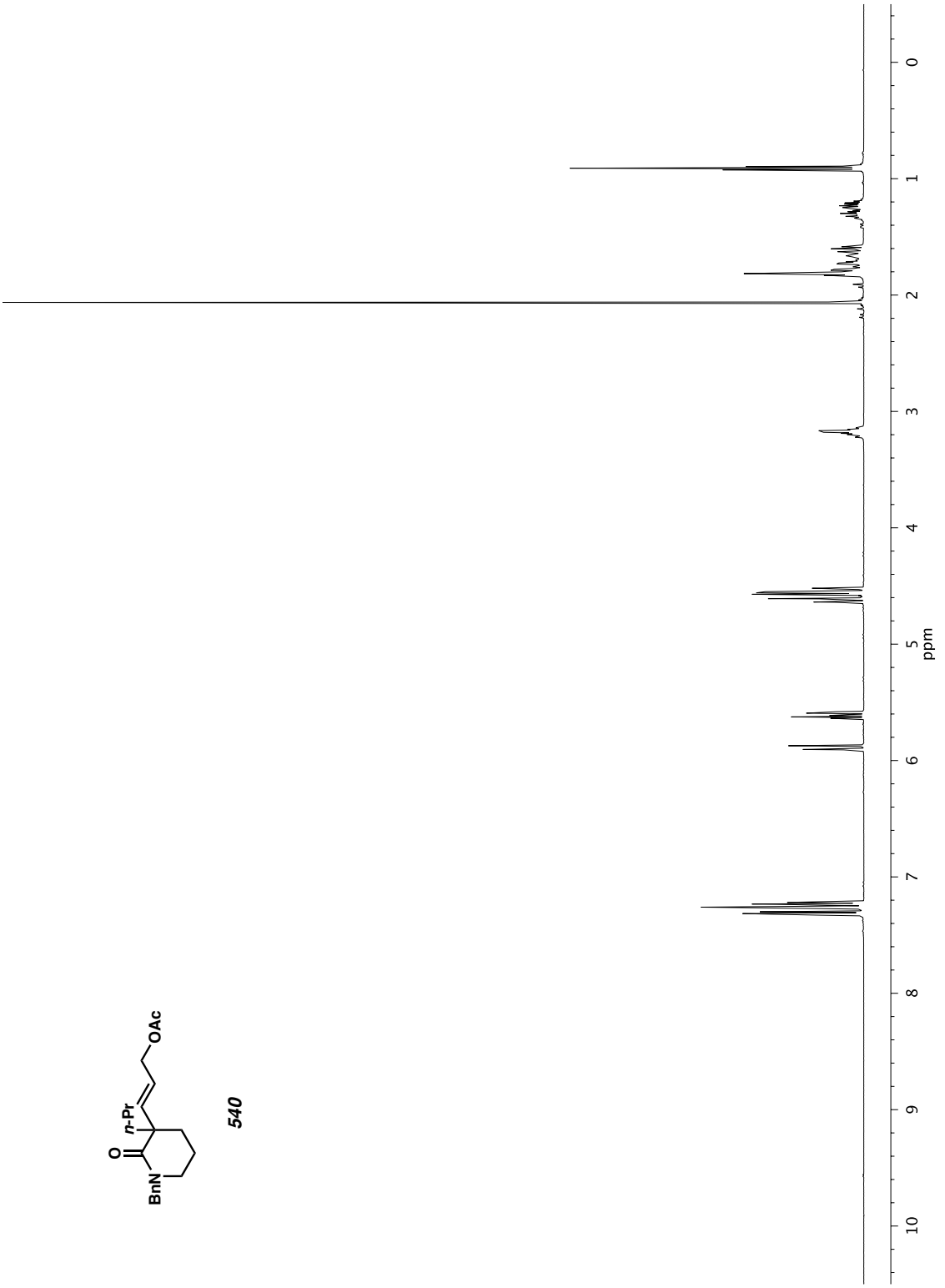


Figure A11.57 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **539**.



540

Figure A11.58 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **540**.

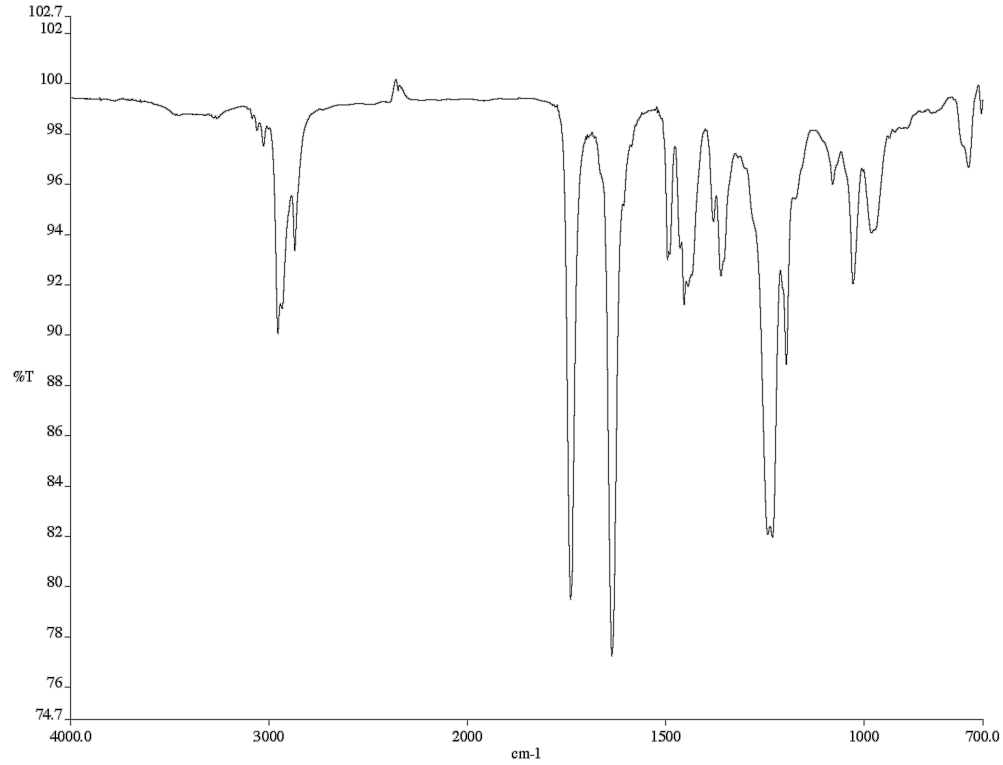


Figure A11.59 Infrared spectrum (thin film/NaCl) of compound **540**.

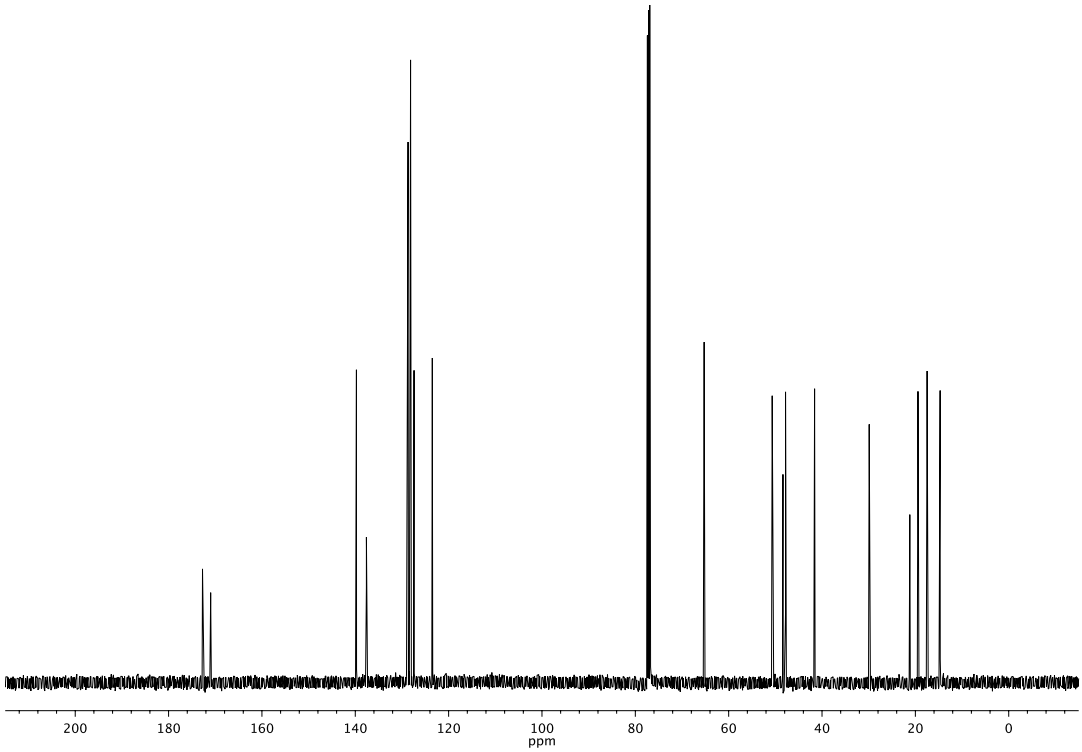


Figure A11.60 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **540**.

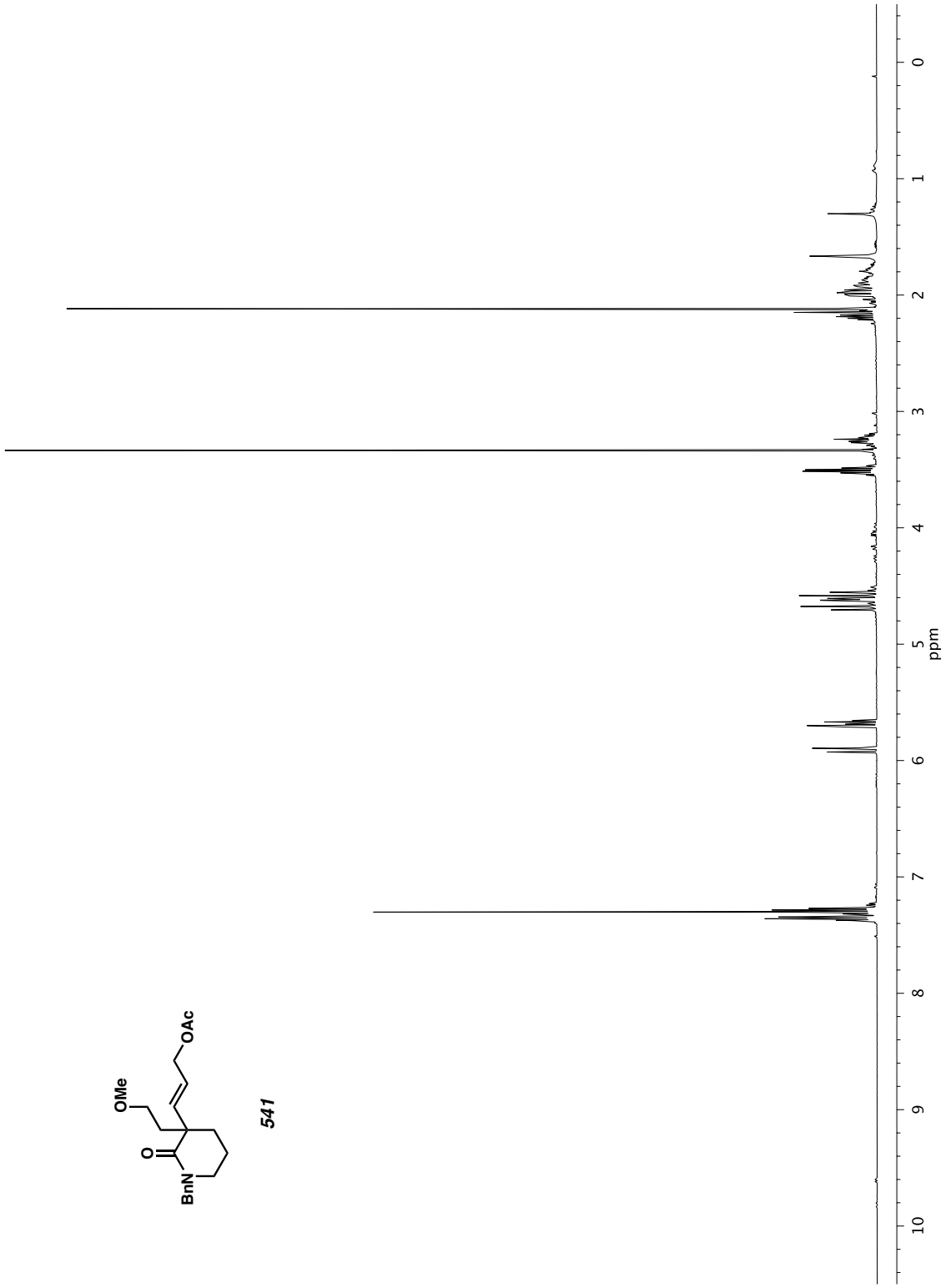


Figure A11.61 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **541**.

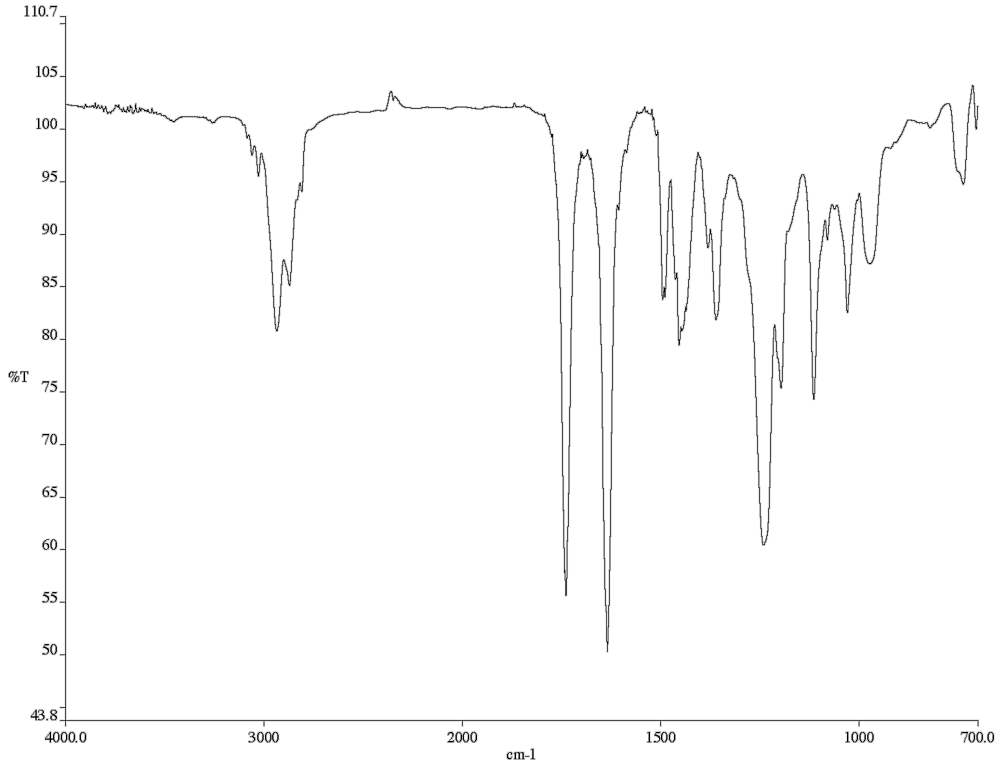


Figure A11.62 Infrared spectrum (thin film/NaCl) of compound **541**.

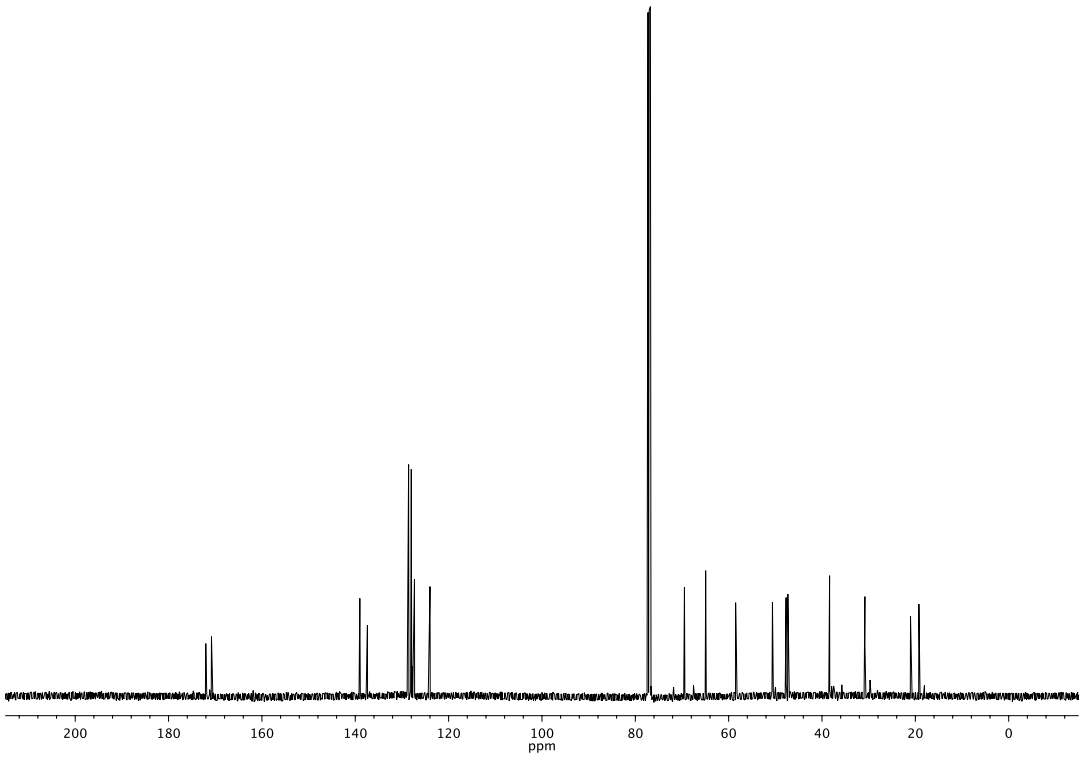


Figure A11.63 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **541**.

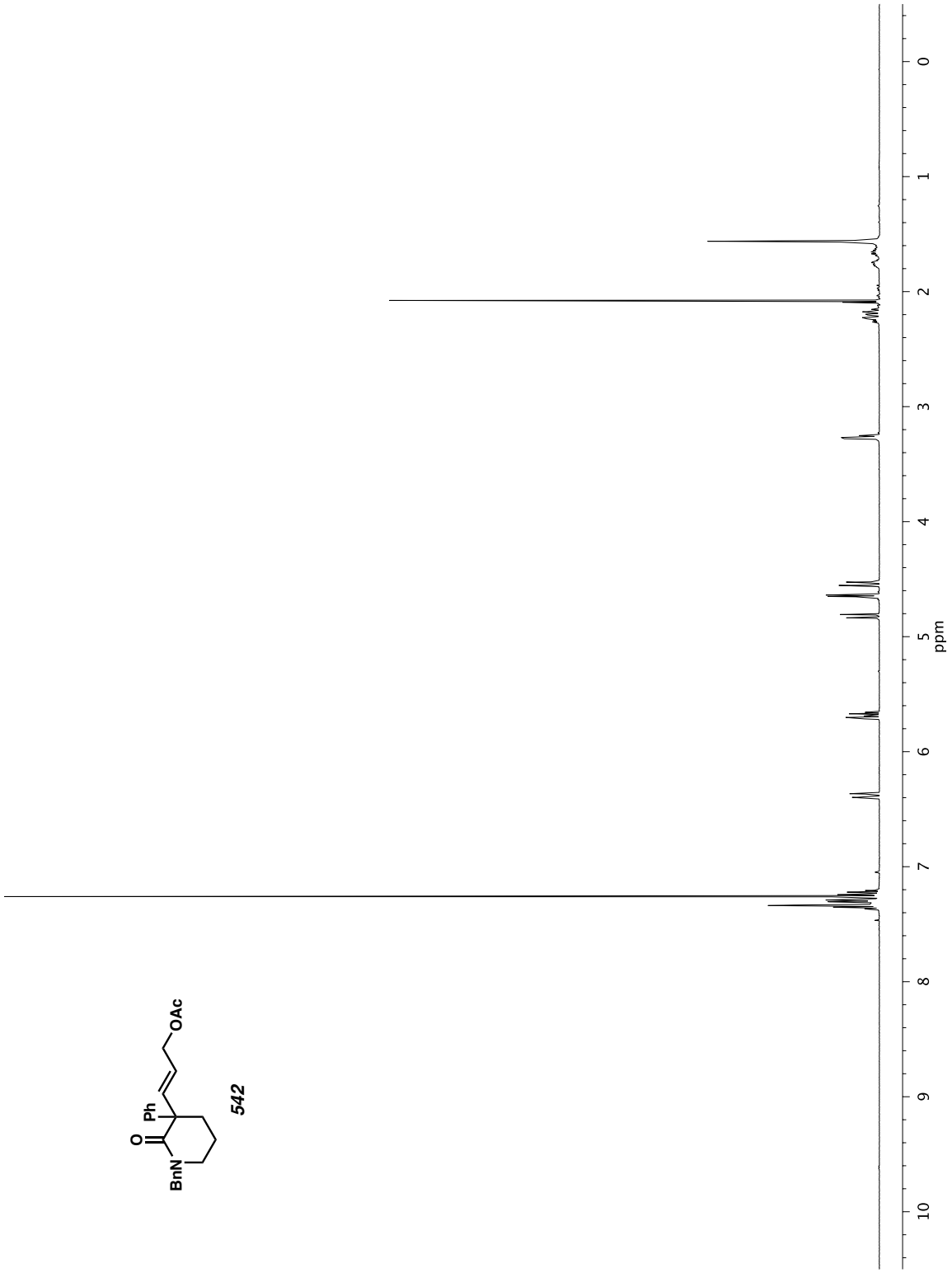


Figure A11.64 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **542**.

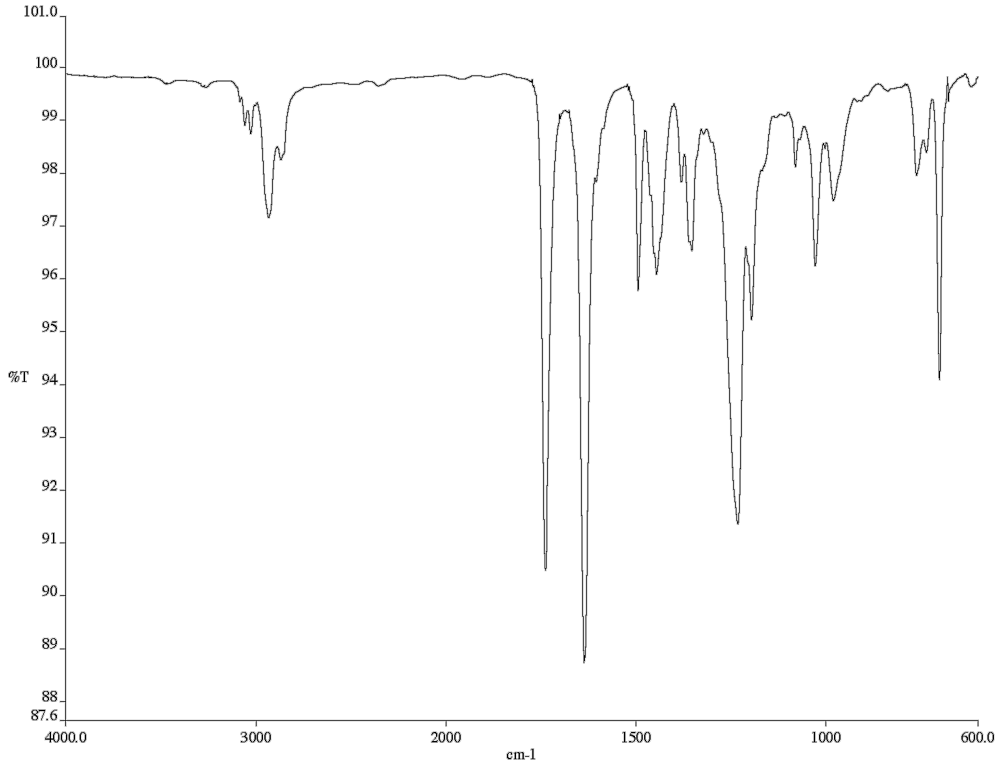


Figure A11.65 Infrared spectrum (thin film/NaCl) of compound **542**.

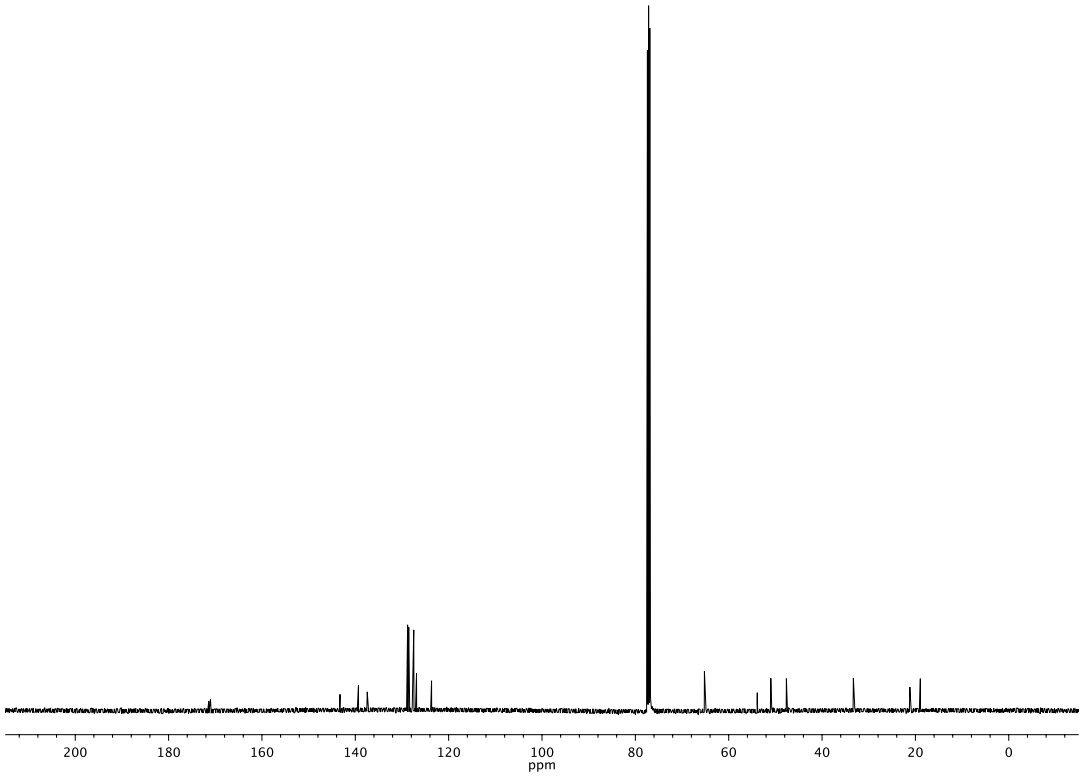


Figure A11.66 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **542**.

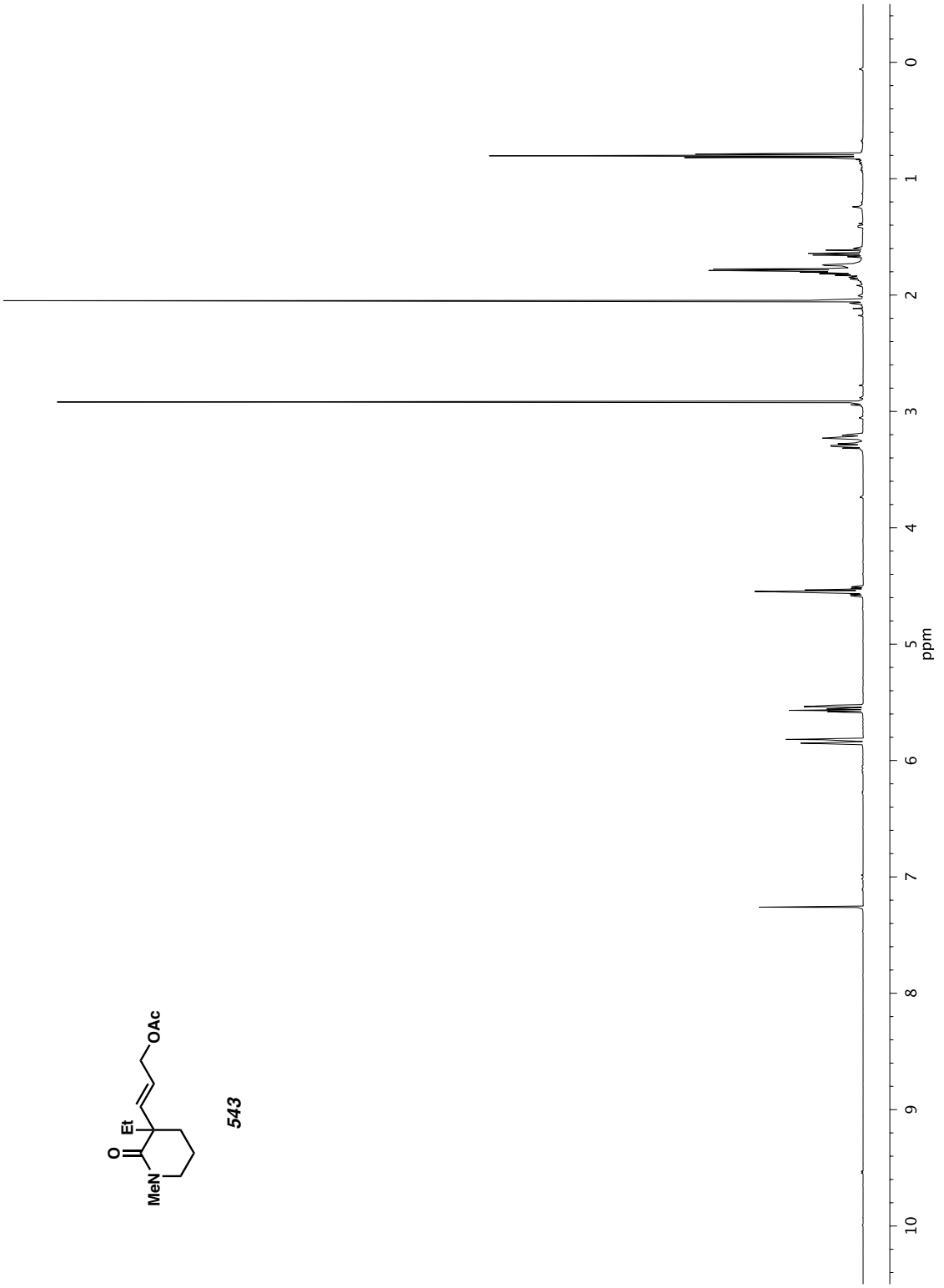


Figure A11.67 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **543**.

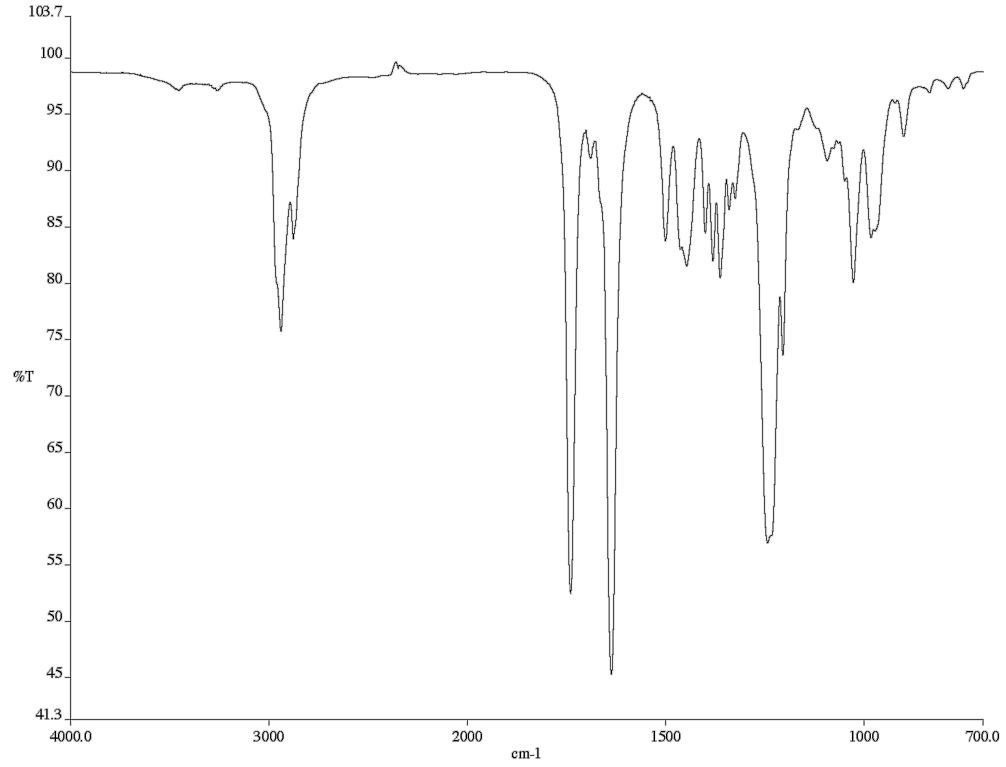


Figure A11.68 Infrared spectrum (thin film/NaCl) of compound **543**.

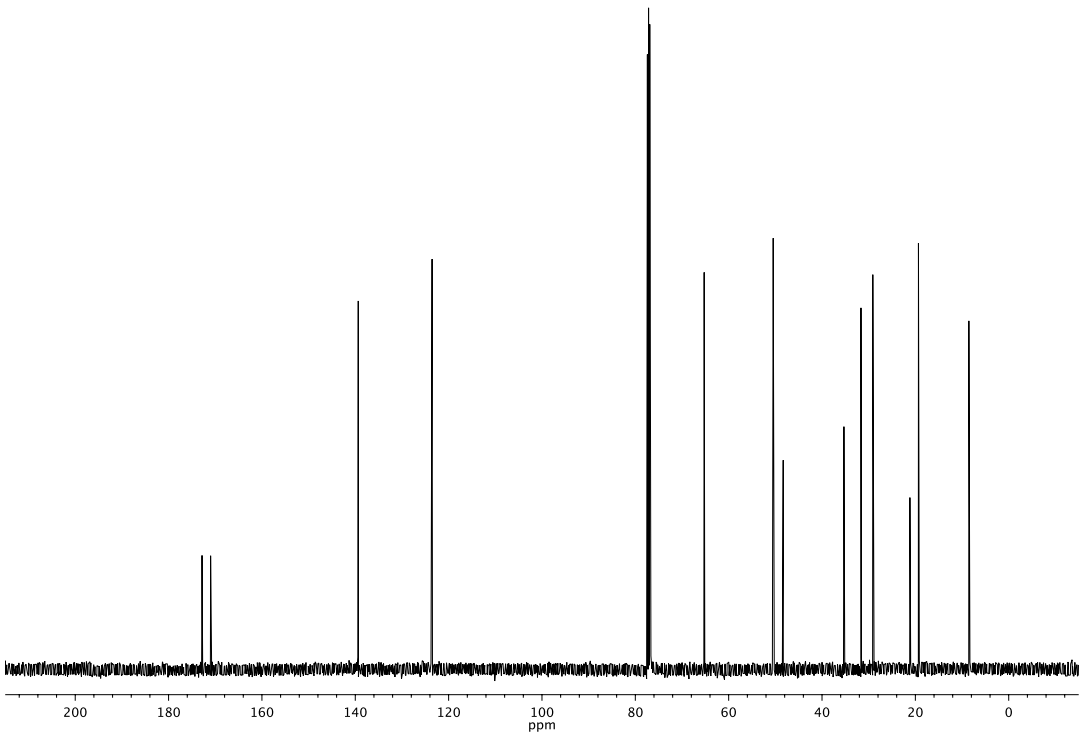


Figure A11.69 ^{13}C NMR (101 MHz, $CDCl_3$) of compound **543**.

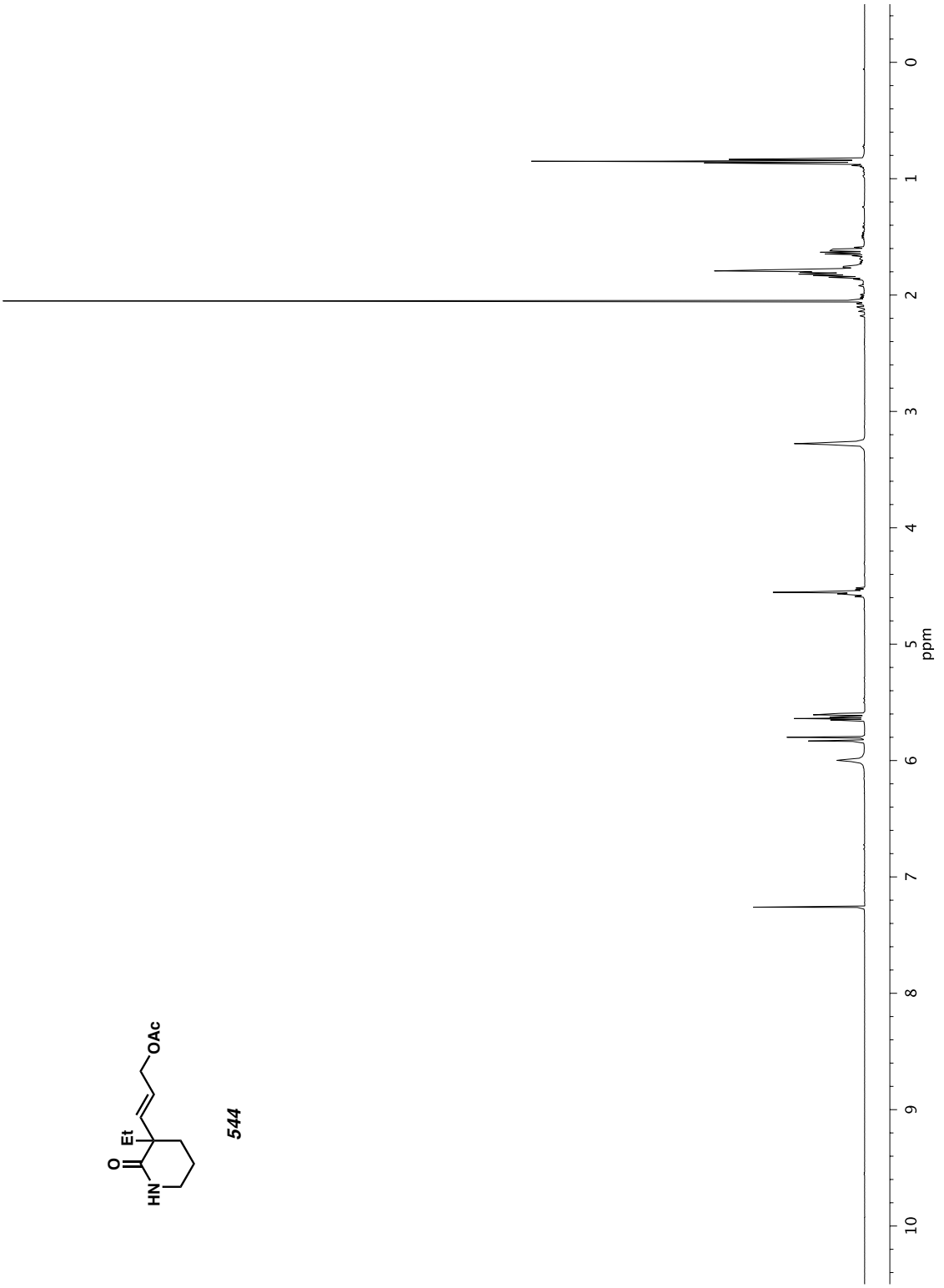


Figure A11.70 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **544**.

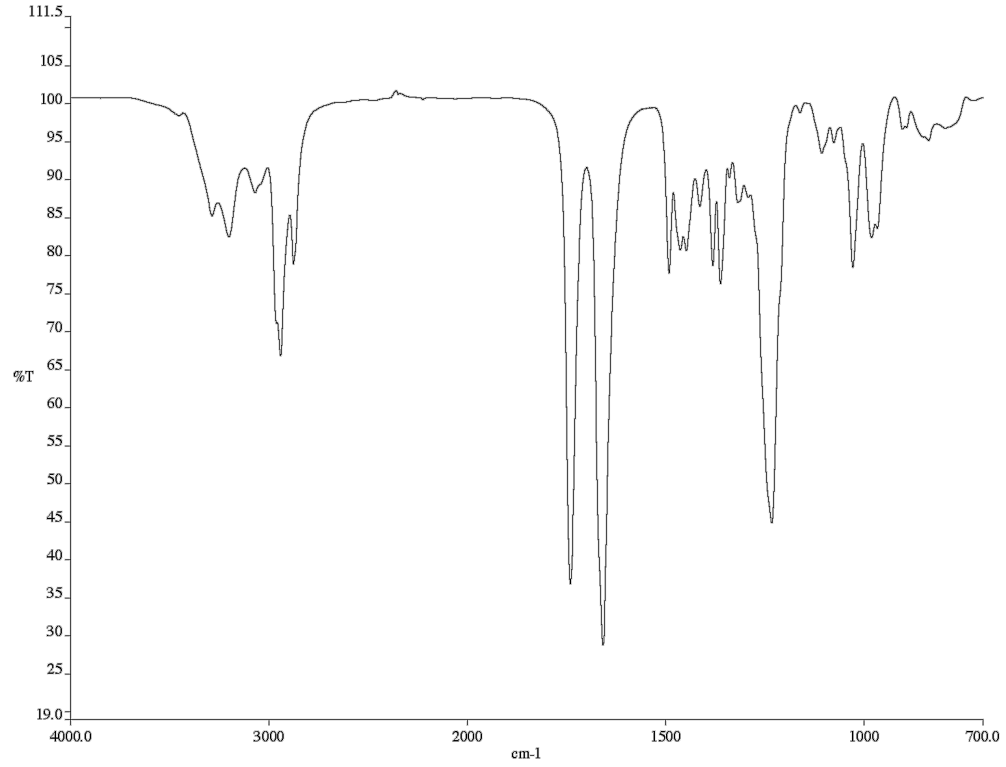


Figure A11.71 Infrared spectrum (thin film/NaCl) of compound **544**.

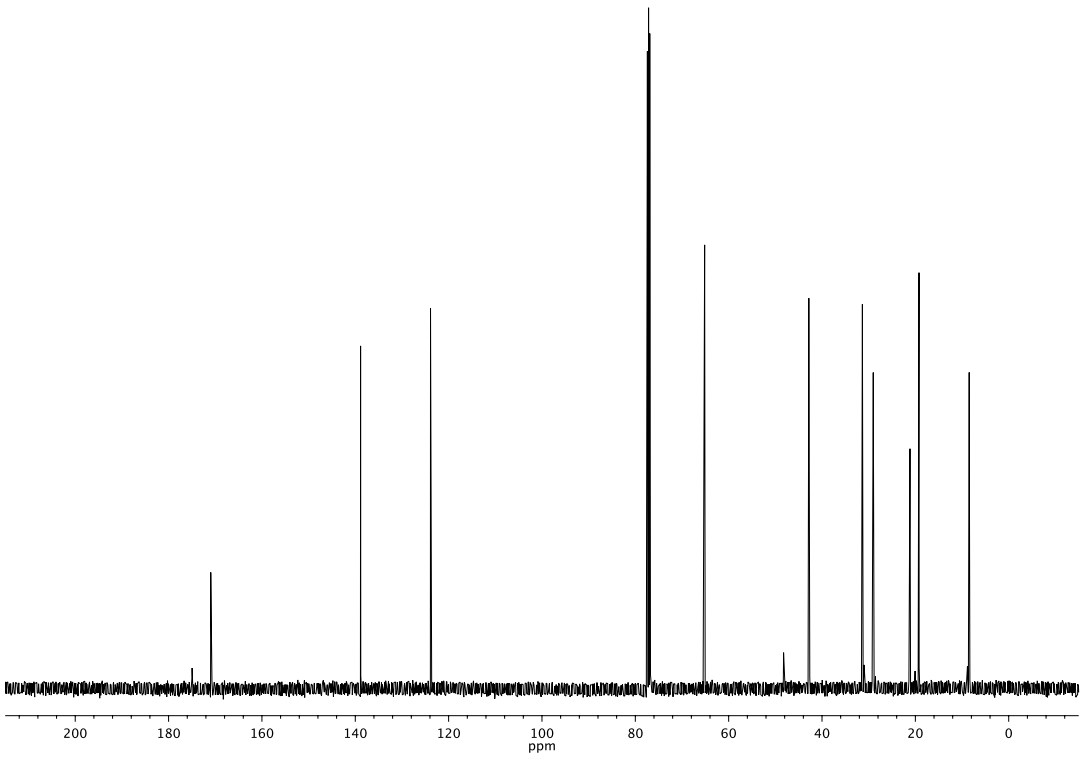


Figure A11.72 ^{13}C NMR (101 MHz, $CDCl_3$) of compound **544**.

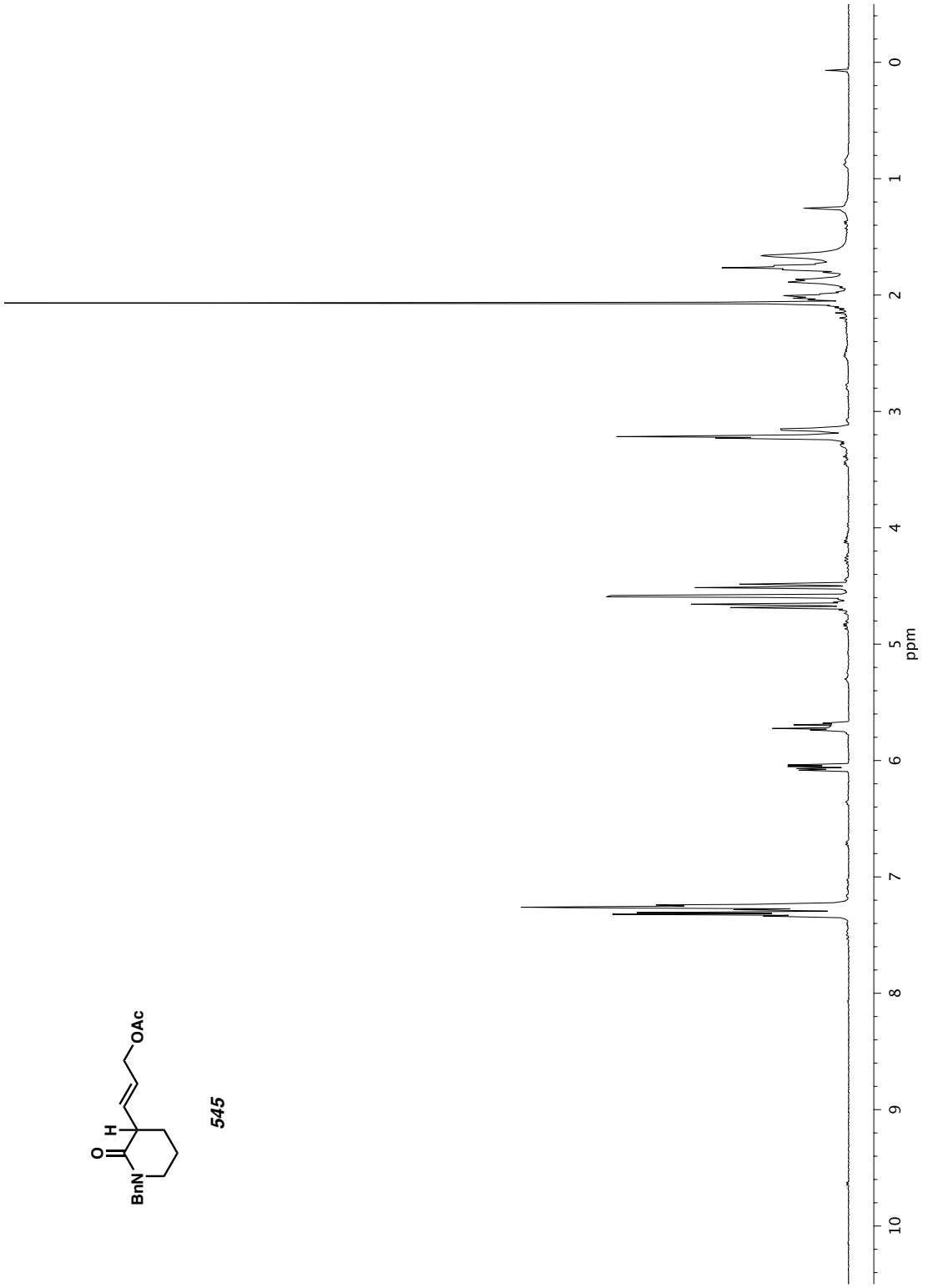


Figure A11.73 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **545**.

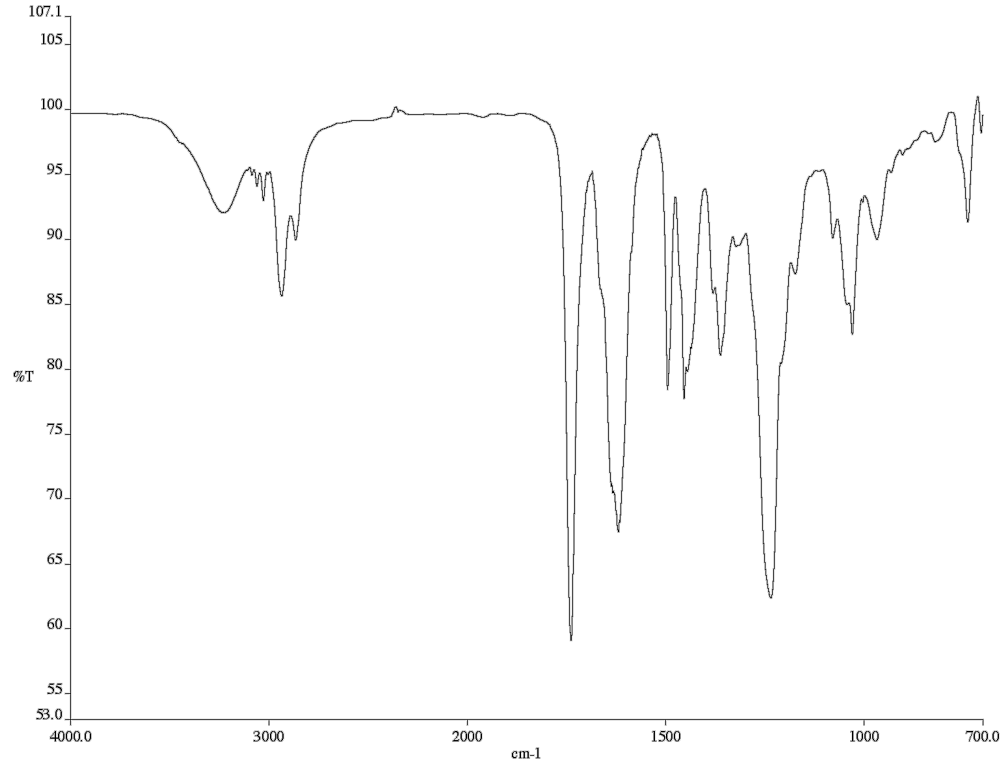


Figure A11.74 Infrared spectrum (thin film/NaCl) of compound **545**.

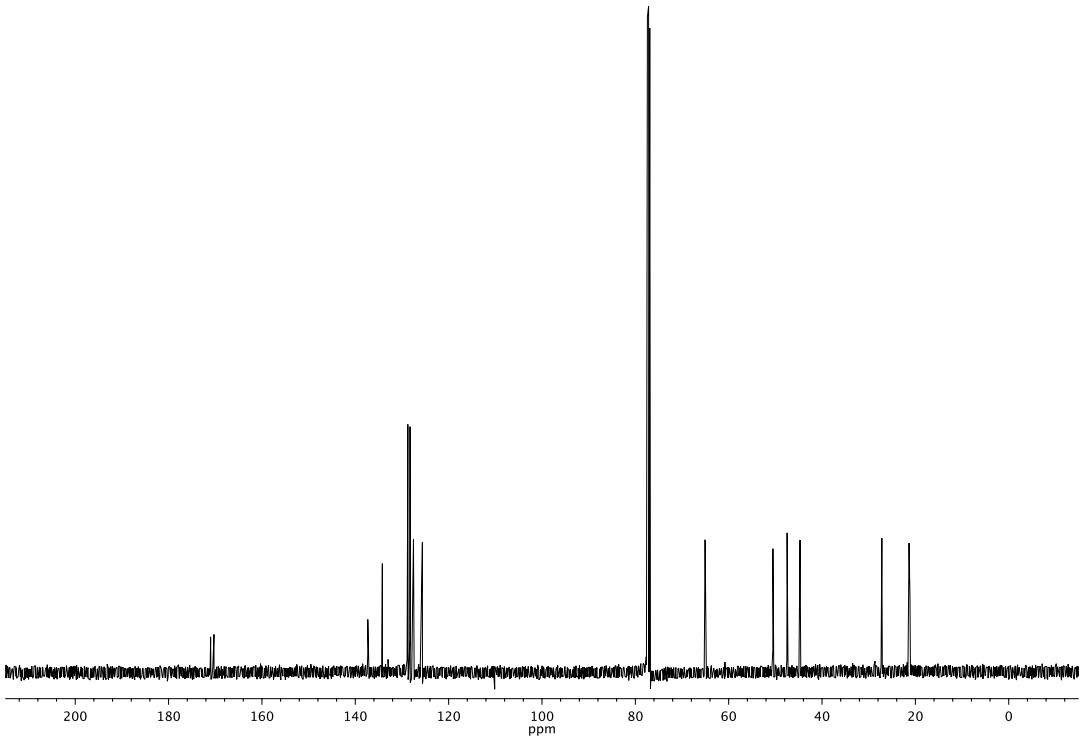


Figure A11.75 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **545**.

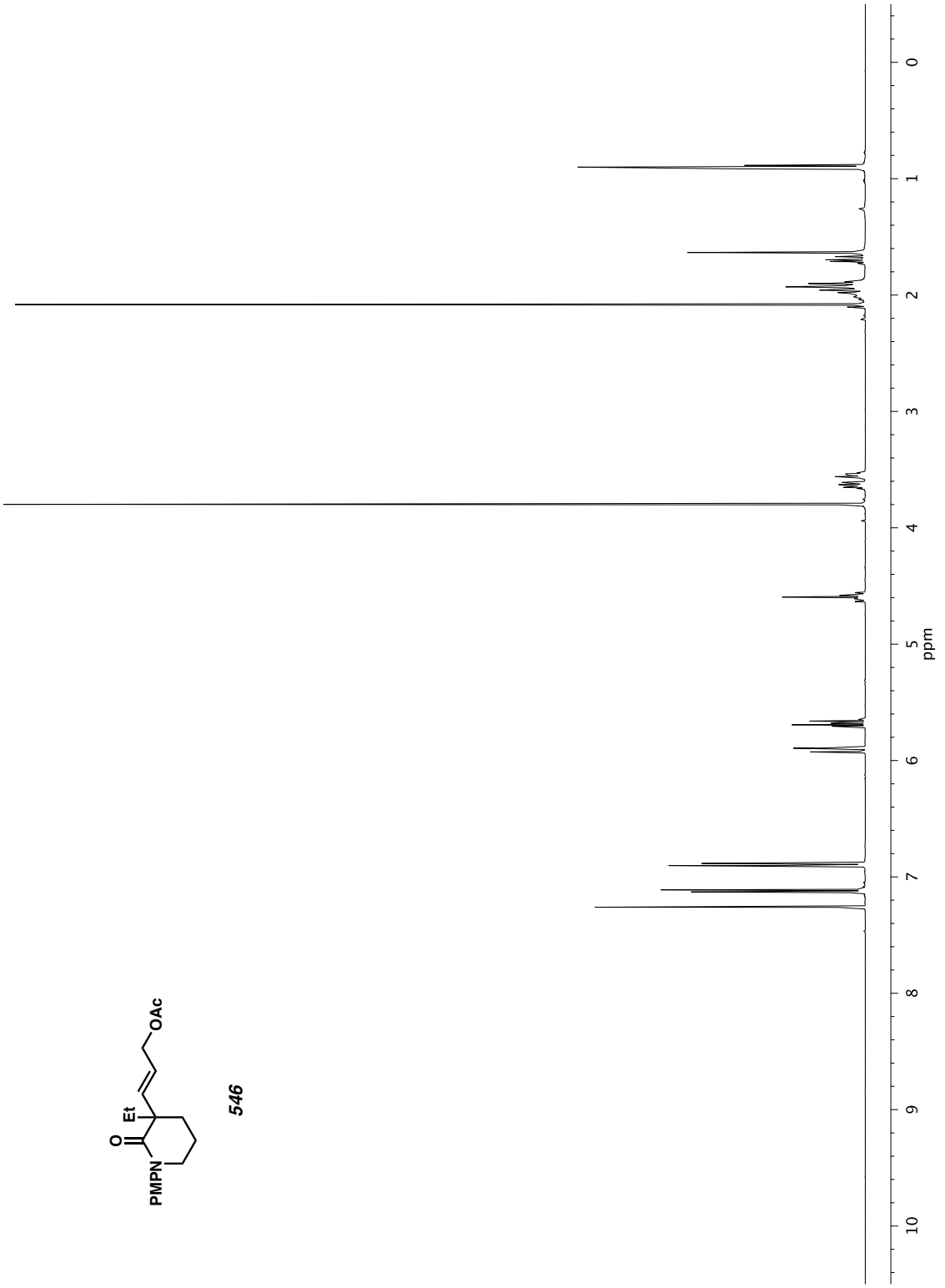


Figure A11.76 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **546**.

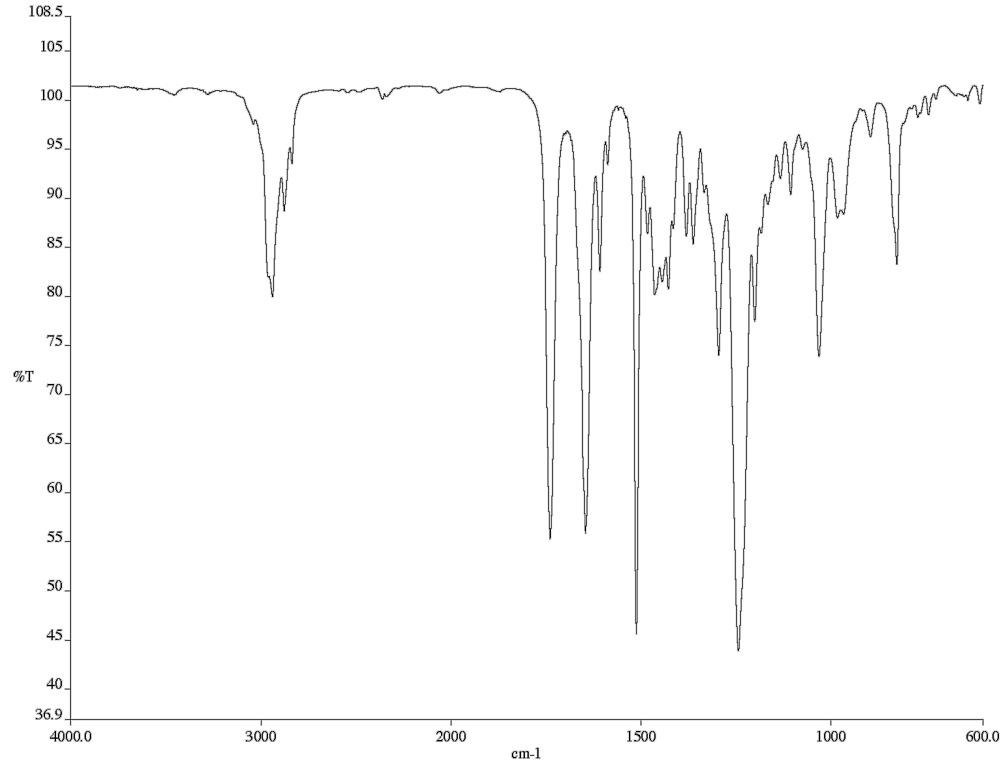


Figure A11.77 Infrared spectrum (thin film/NaCl) of compound **546**.

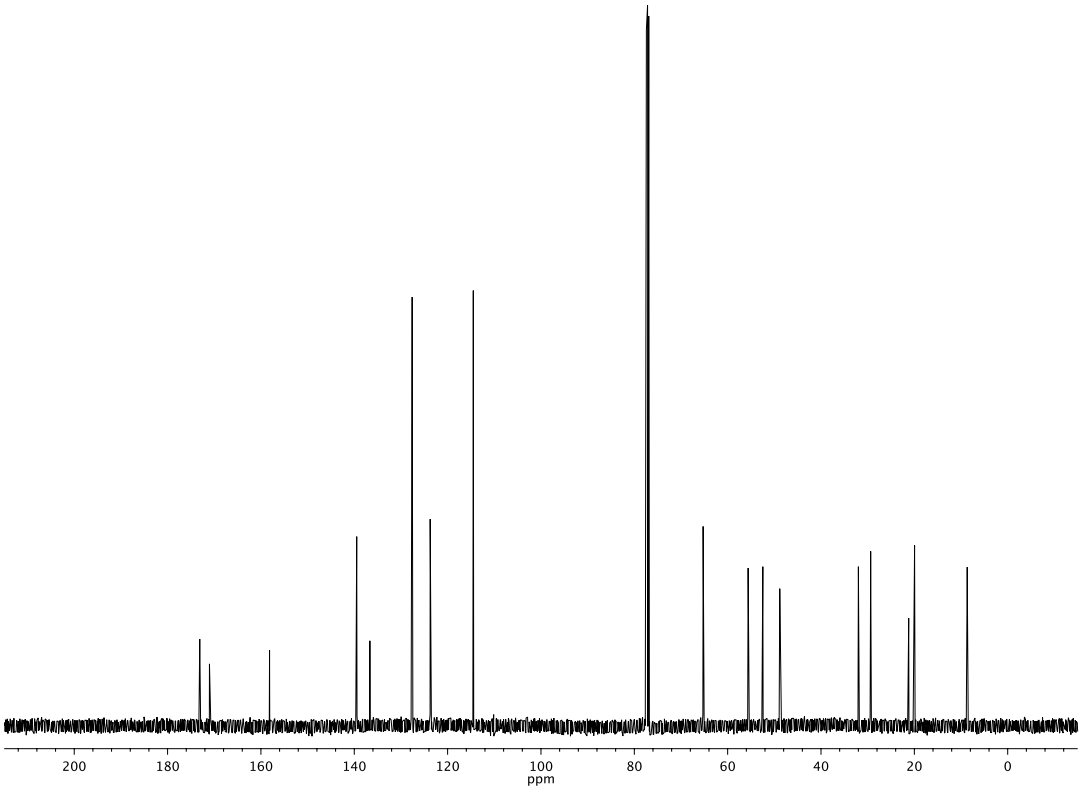


Figure A11.78 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **546**.

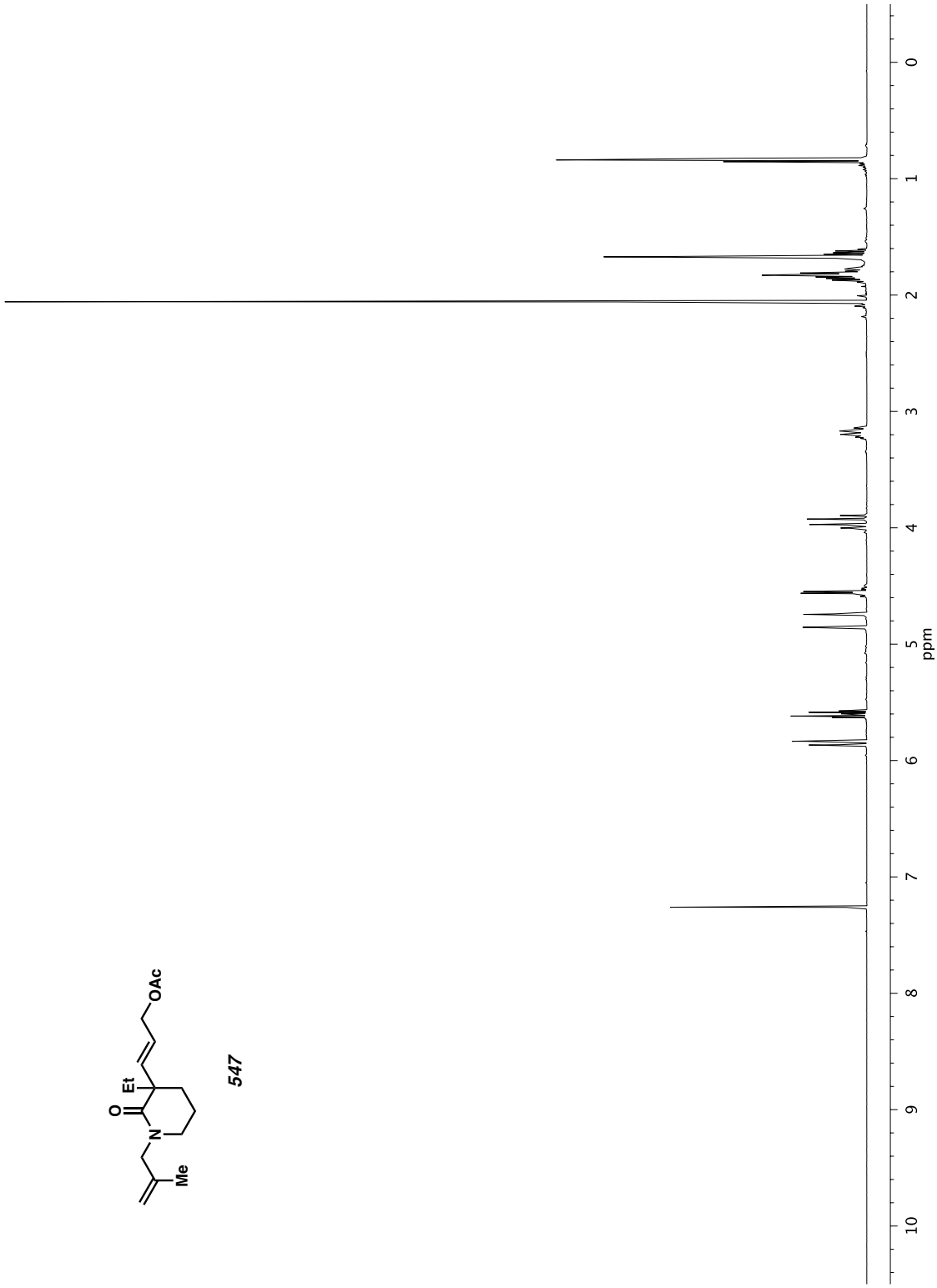


Figure A11.79 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **547**.

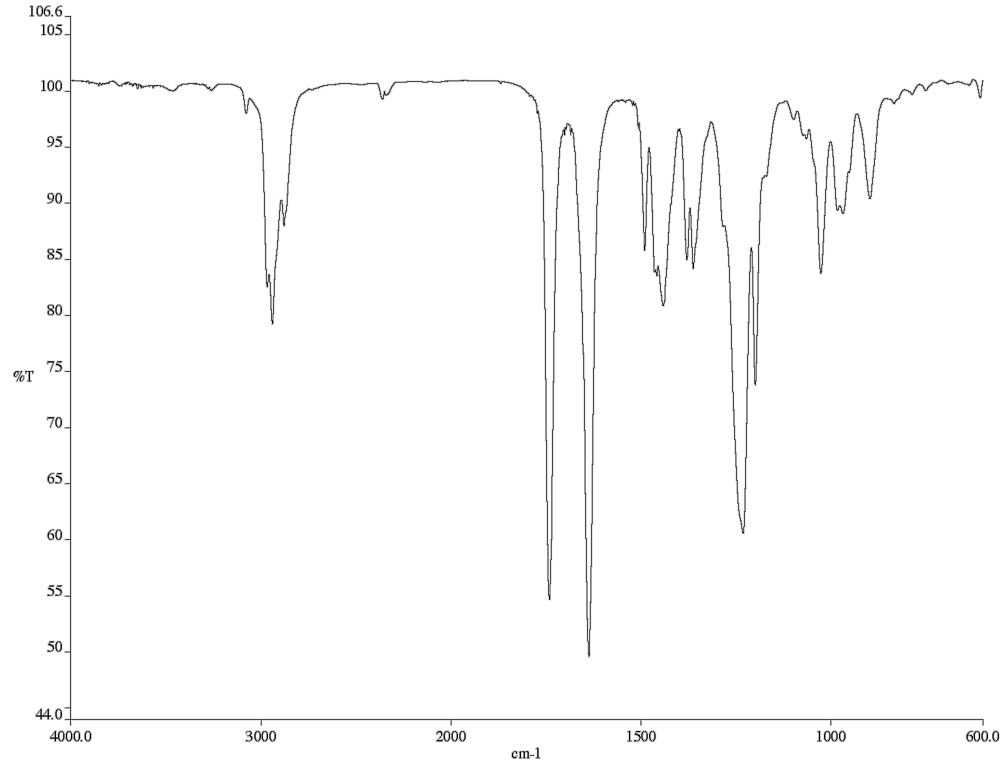


Figure A11.80 Infrared spectrum (thin film/NaCl) of compound **547**.

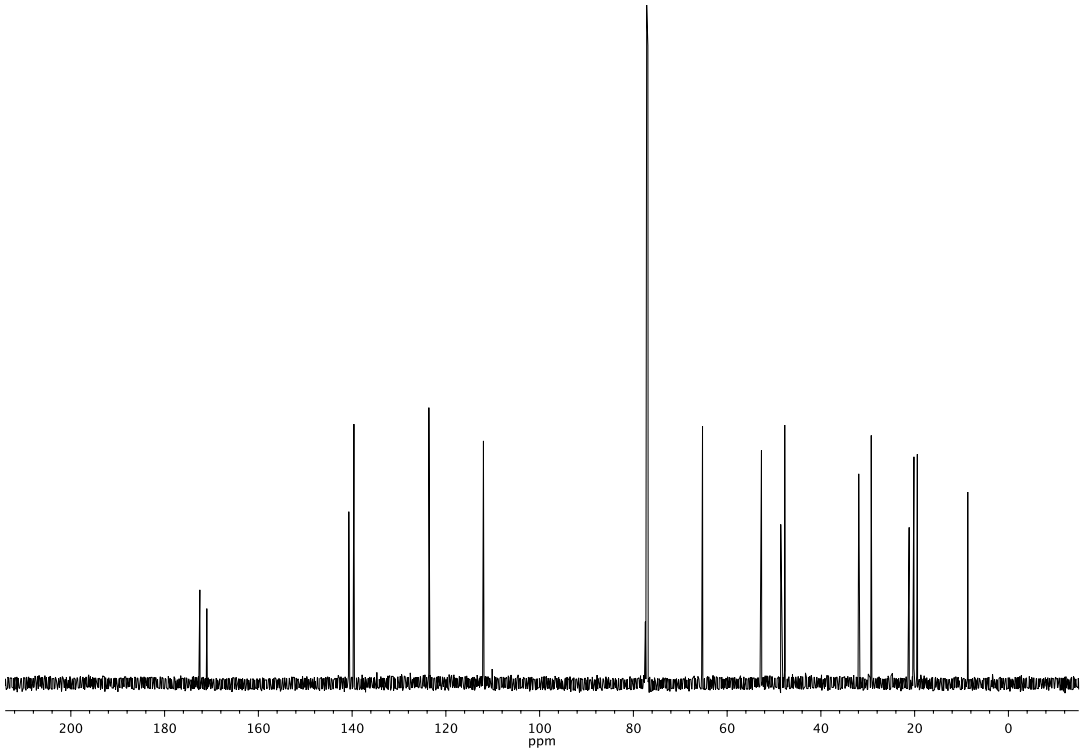


Figure A11.81 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **547**.

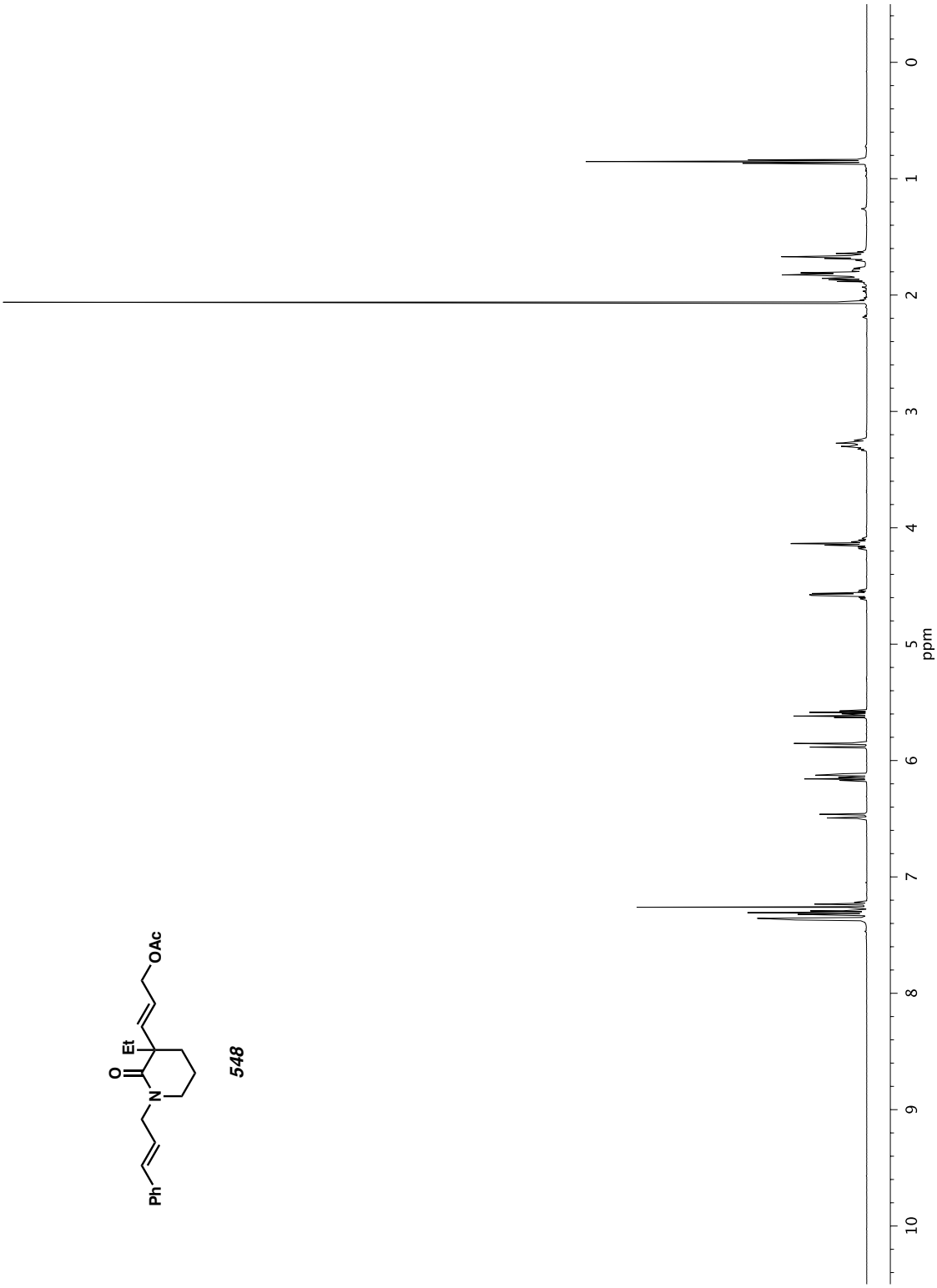


Figure A11.82 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **548**.

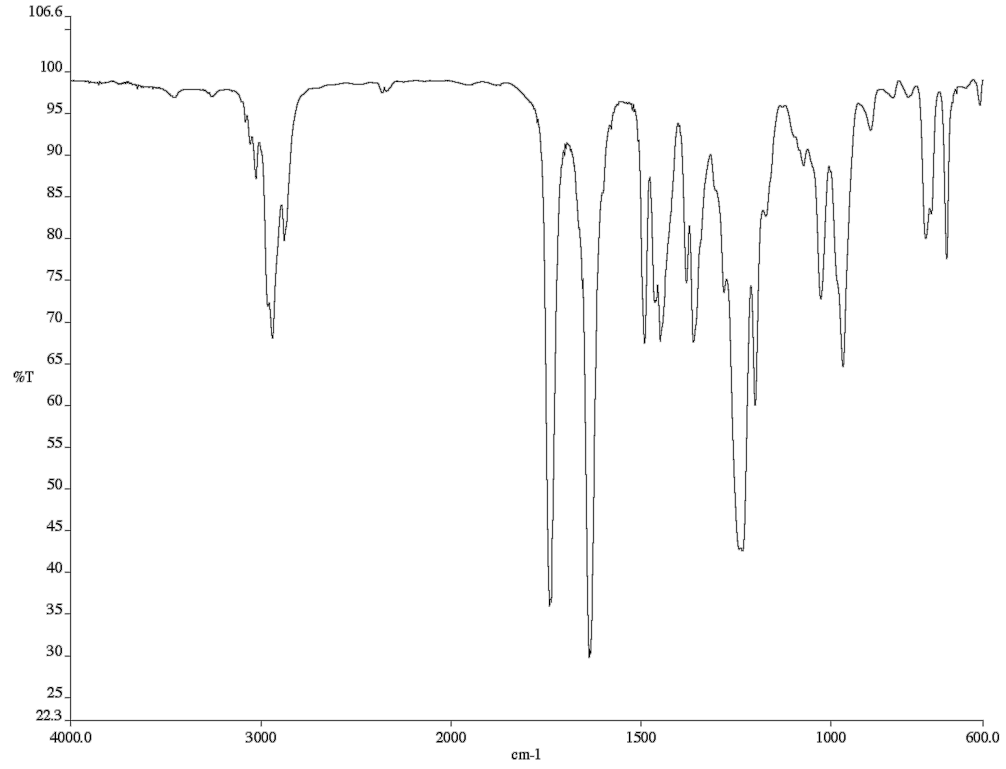


Figure A11.83 Infrared spectrum (thin film/NaCl) of compound **548**.

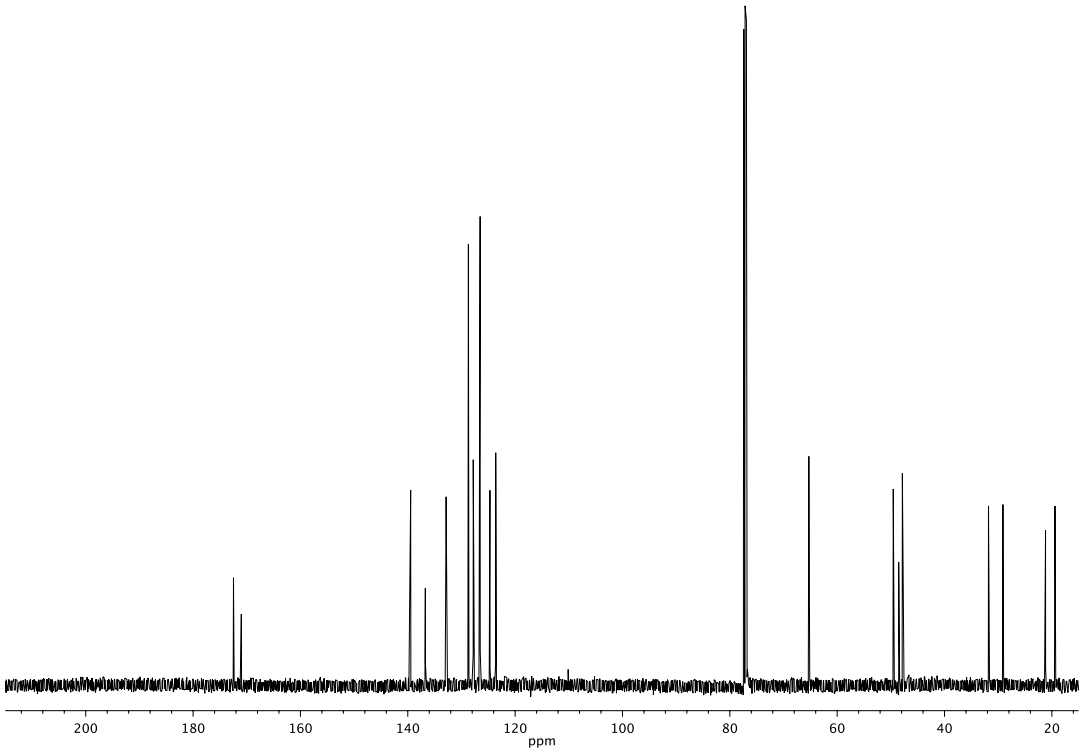


Figure A11.84 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **548**.

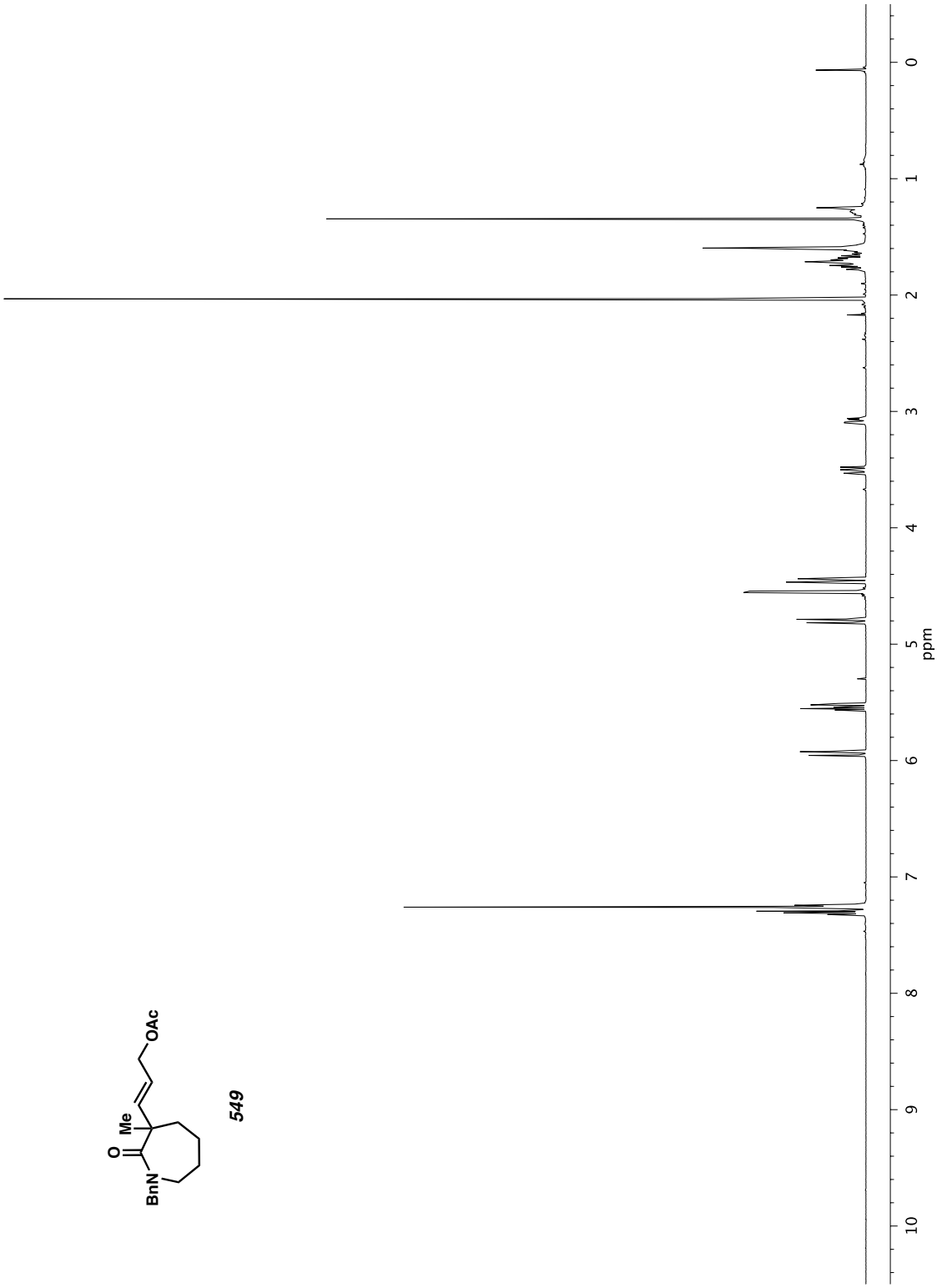


Figure A11.85 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **549**.

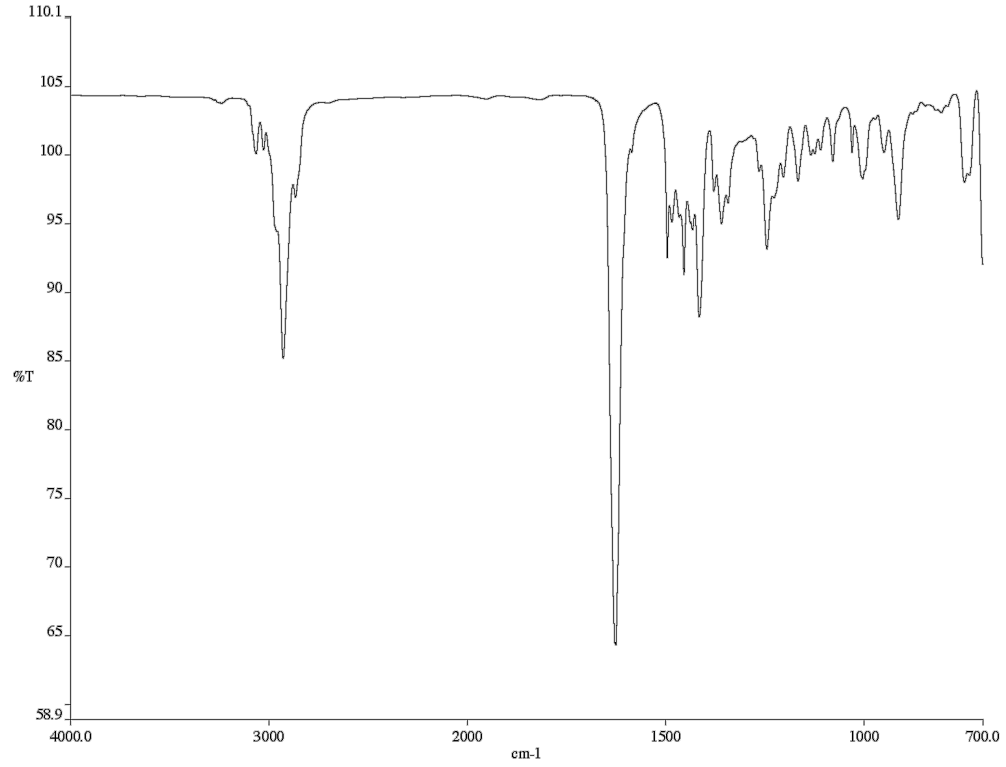


Figure A11.86 Infrared spectrum (thin film/NaCl) of compound **549**.

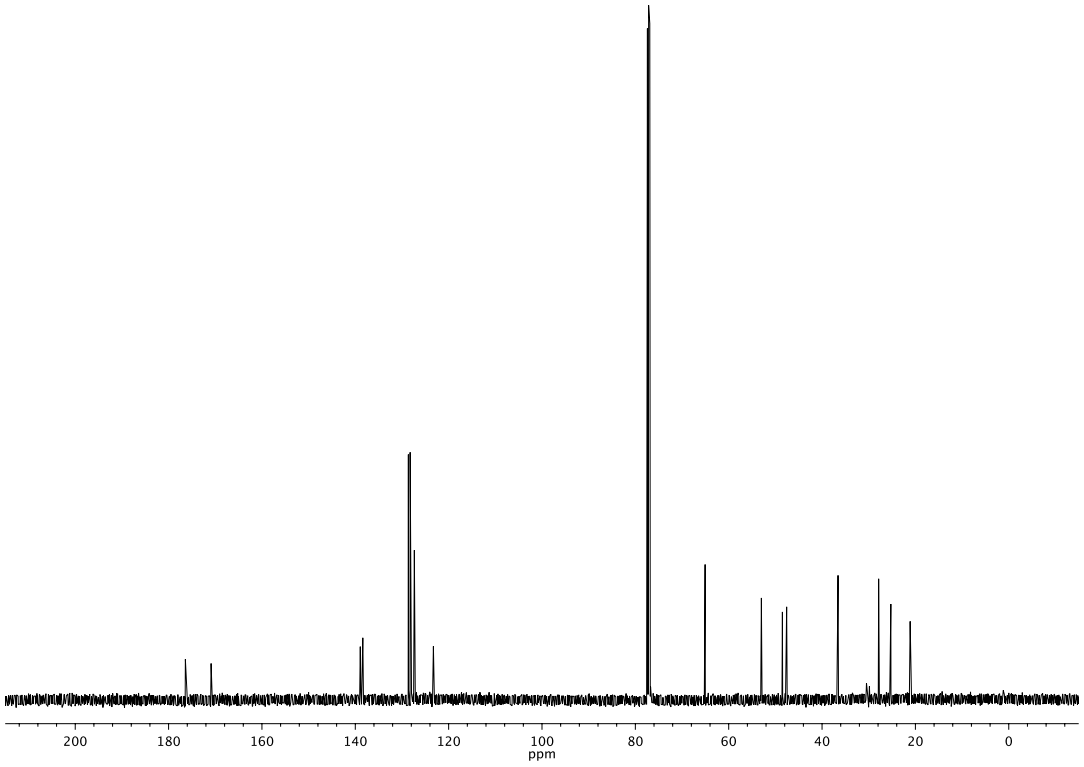


Figure A11.87 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **549**.

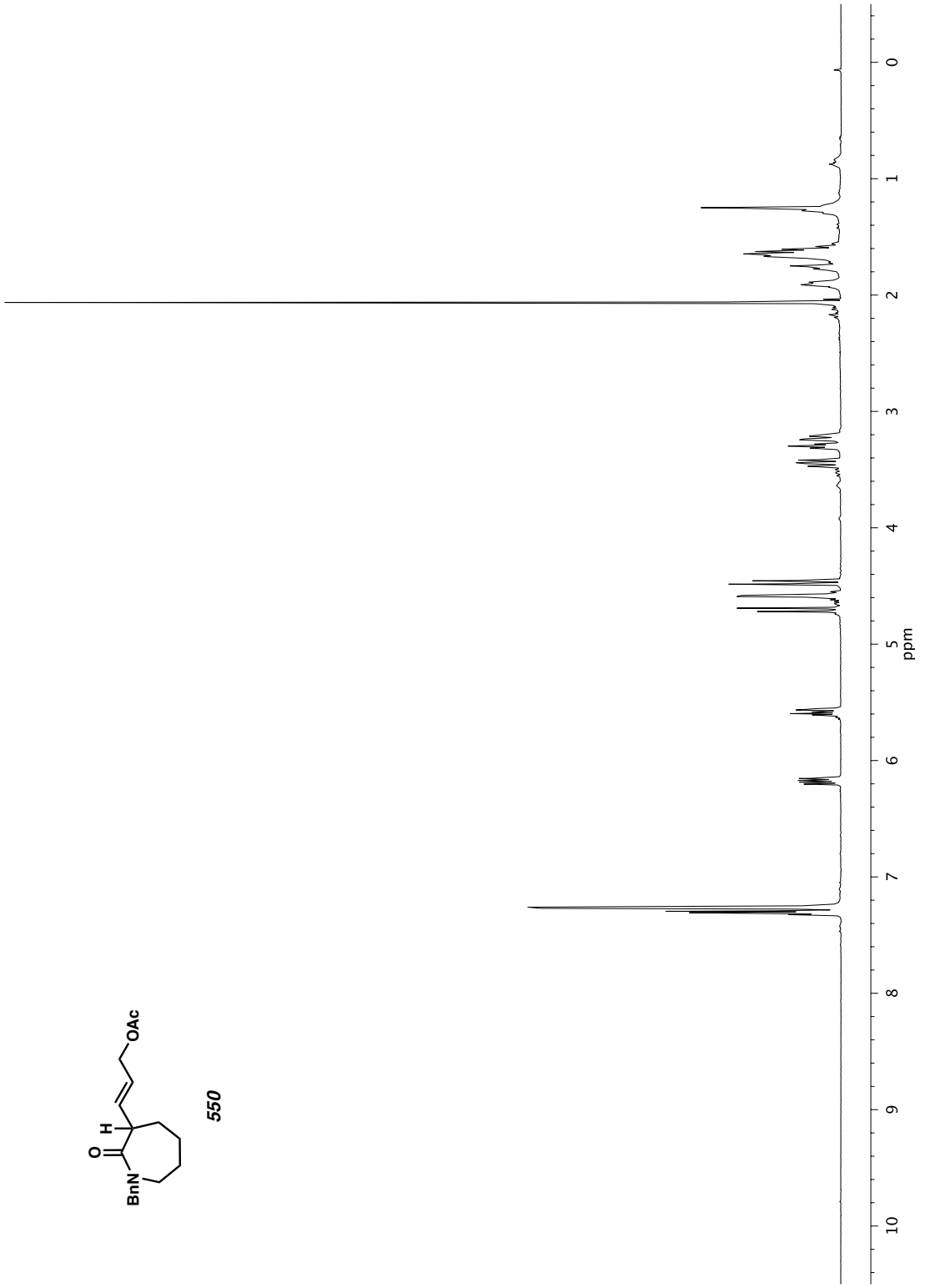


Figure A11.88 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **550**.

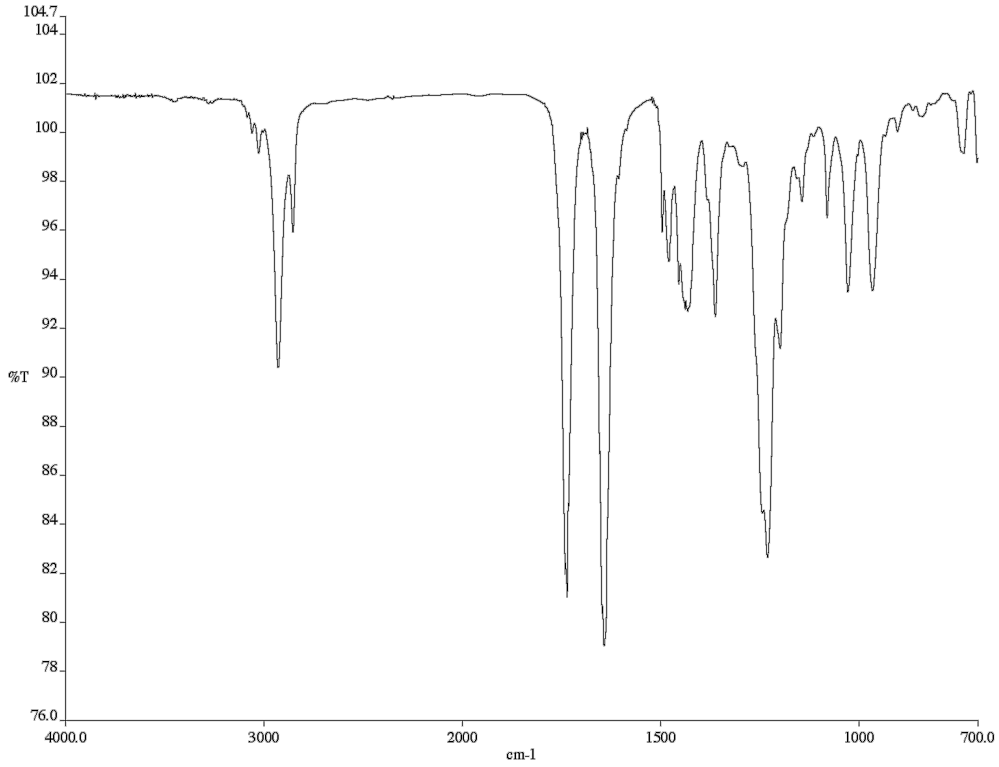


Figure A11.89 Infrared spectrum (thin film/NaCl) of compound **550**.

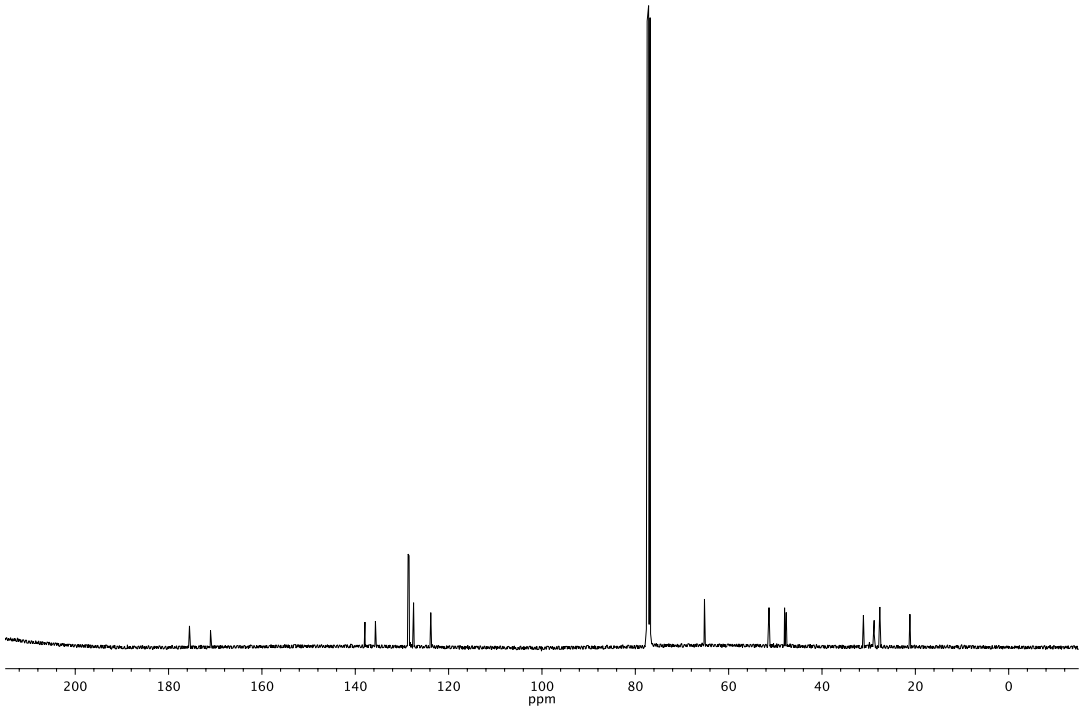


Figure A11.90 ^{13}C NMR (101 MHz, $CDCl_3$) of compound **550**.

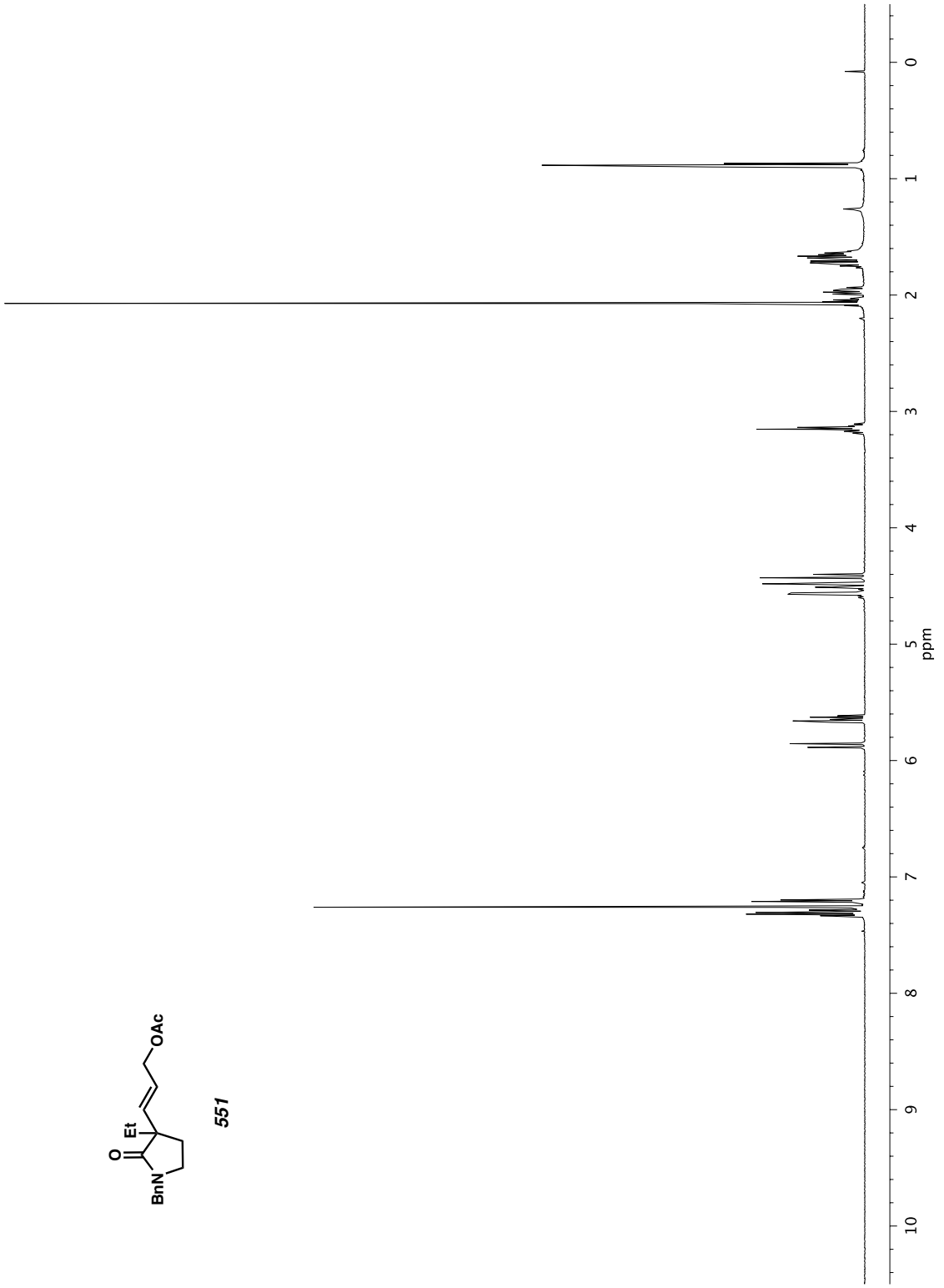


Figure A11.91 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **551**.

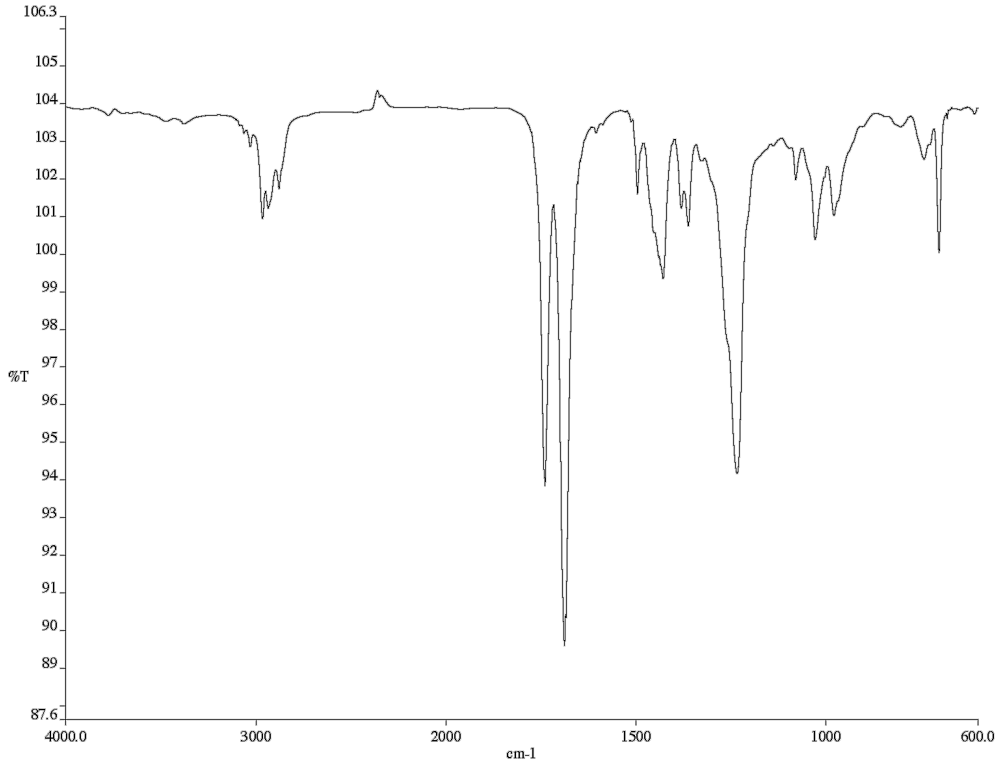


Figure A11.92 Infrared spectrum (thin film/NaCl) of compound **551**.

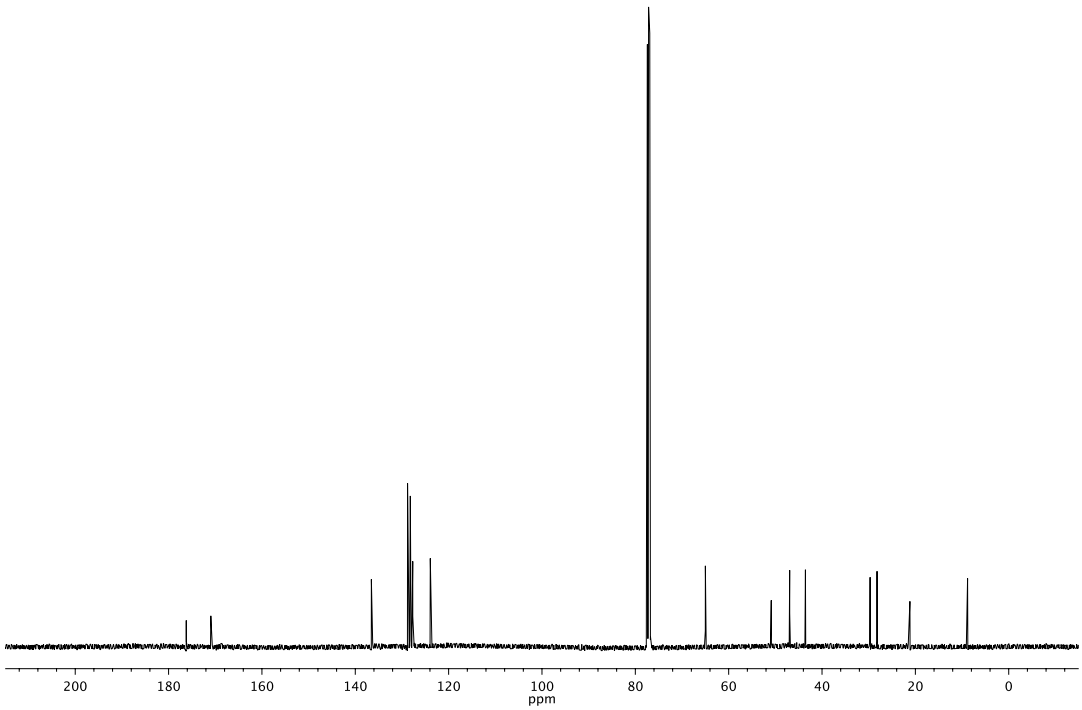


Figure A11.93 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **551**.

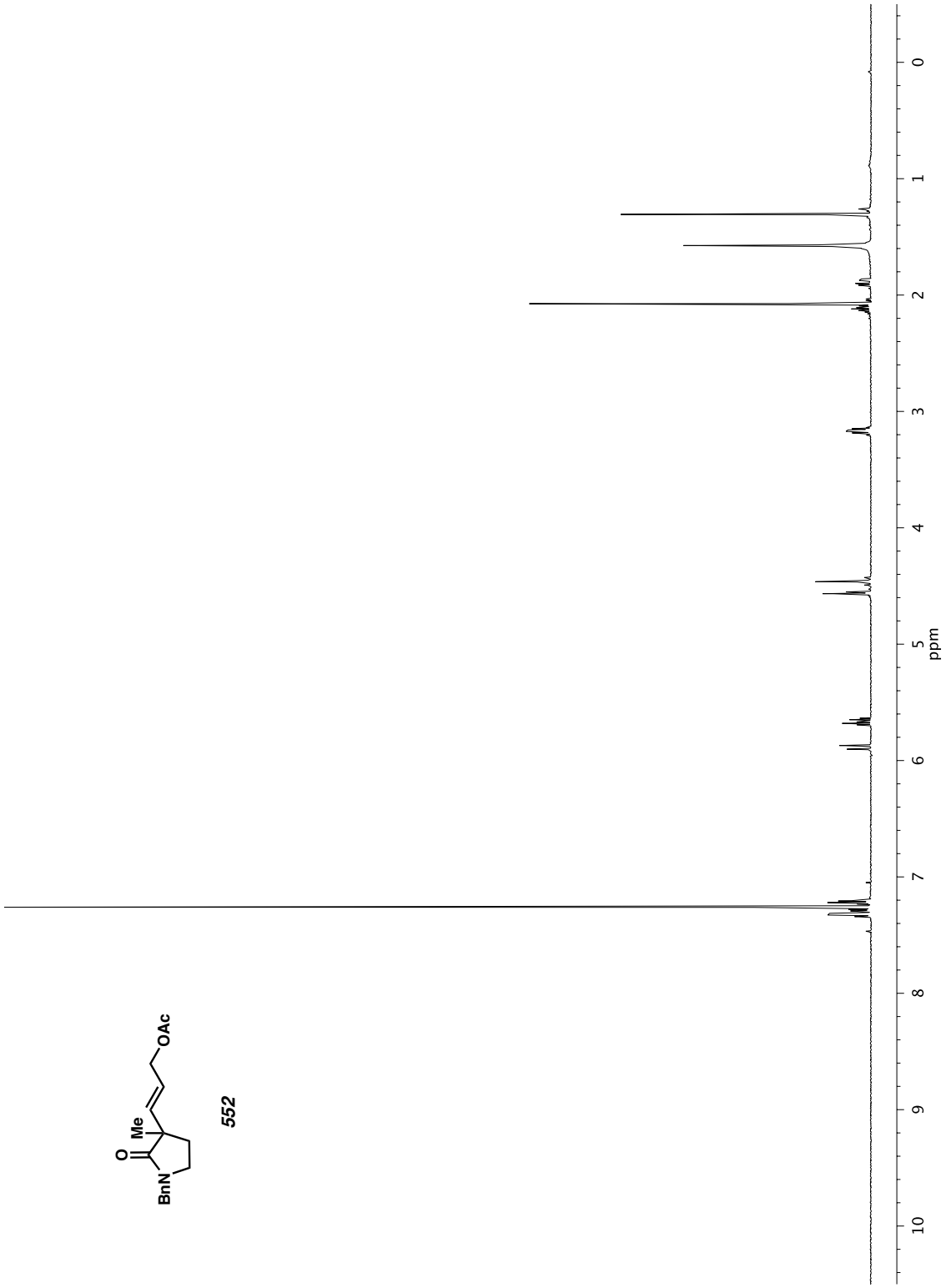


Figure A11.94 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **552**.

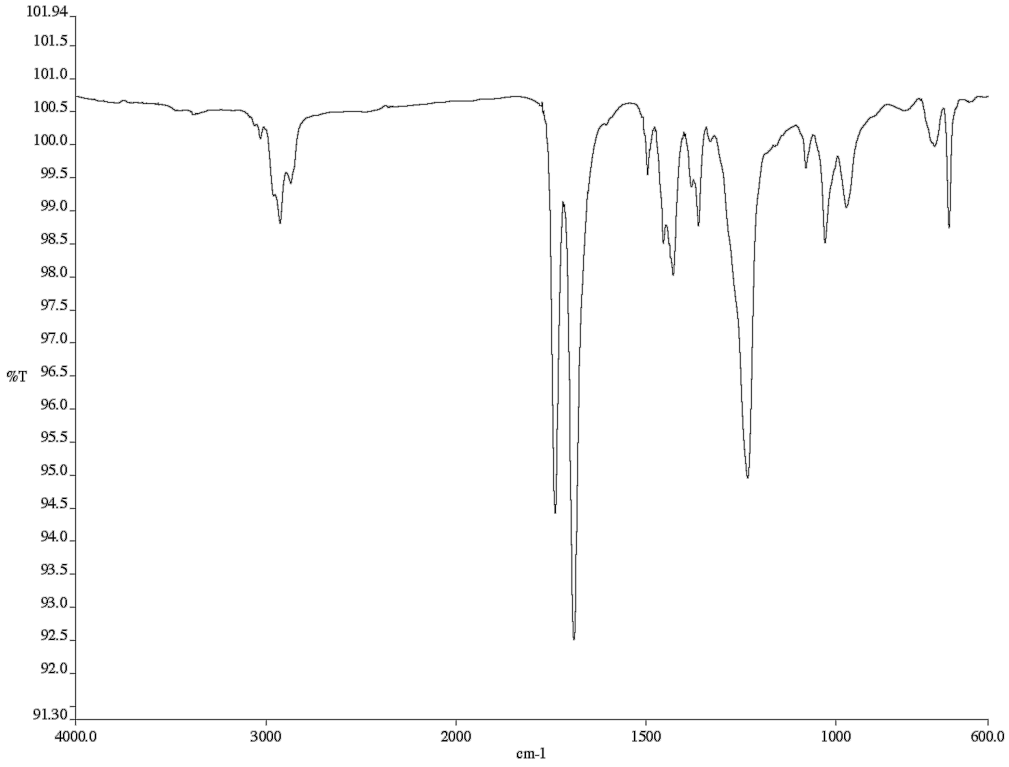


Figure A11.95 Infrared spectrum (thin film/NaCl) of compound **552**.

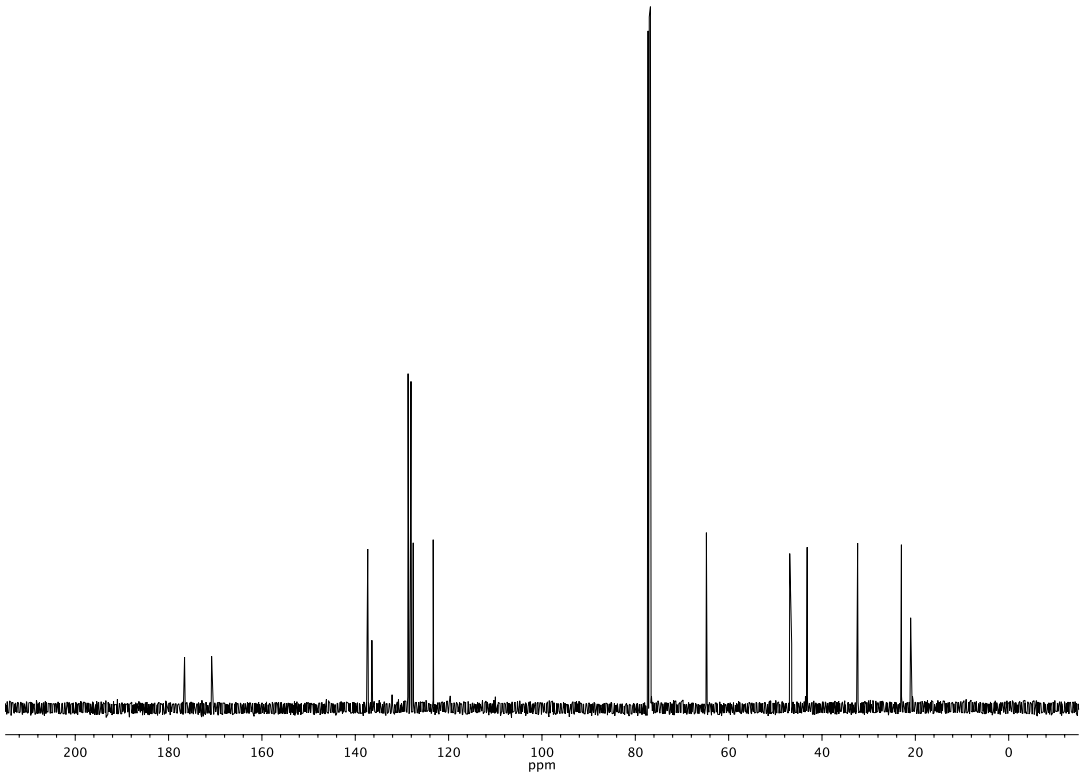


Figure A11.96 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **552**.

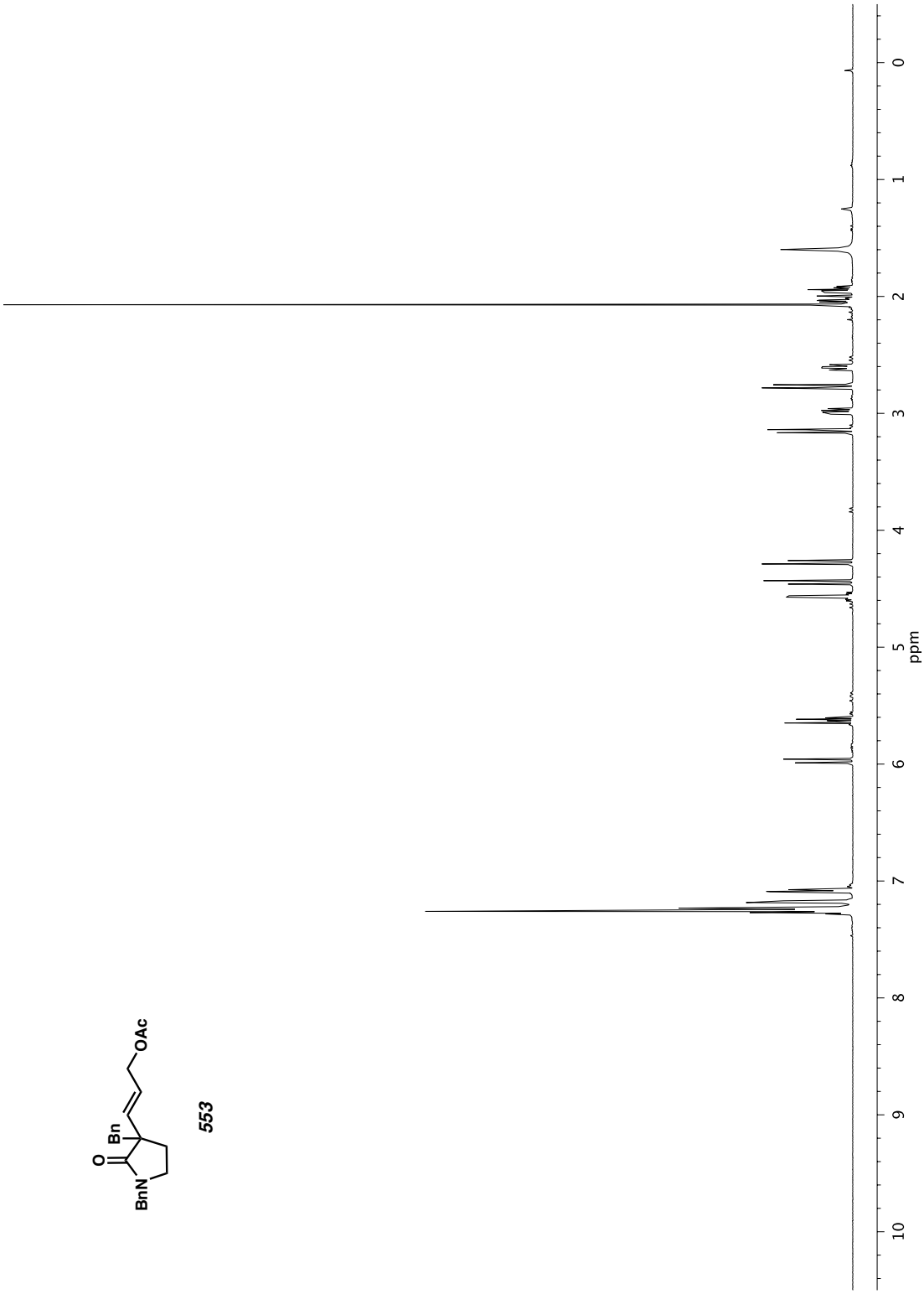


Figure A11.97 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **553**.

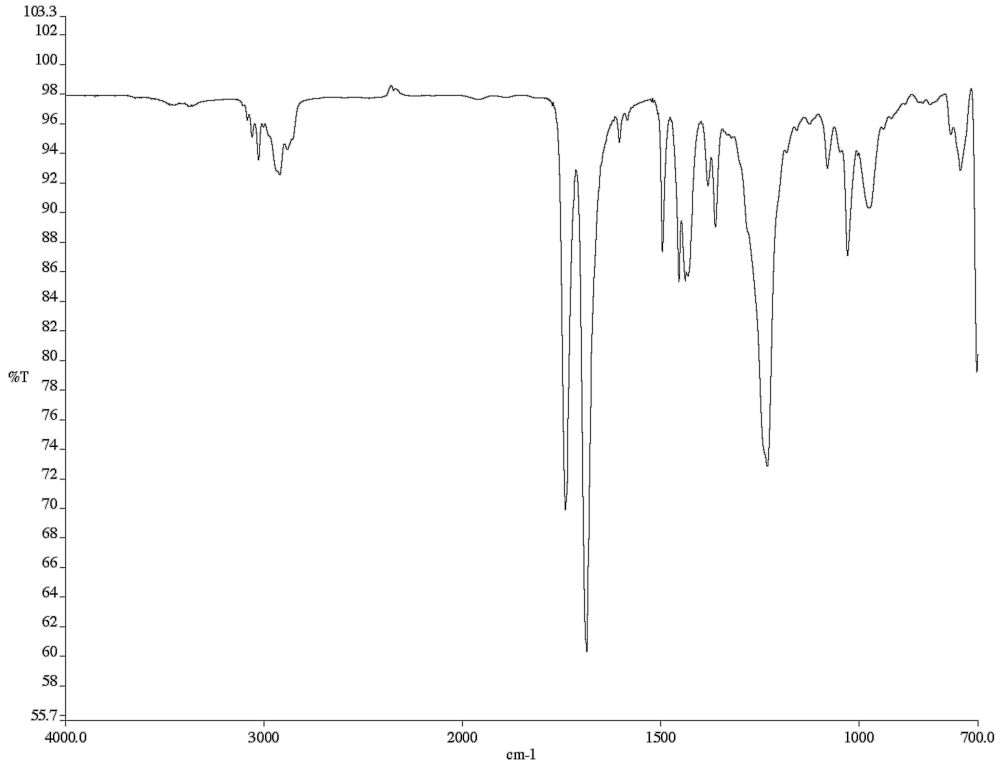


Figure A11.98 Infrared spectrum (thin film/NaCl) of compound **553**.

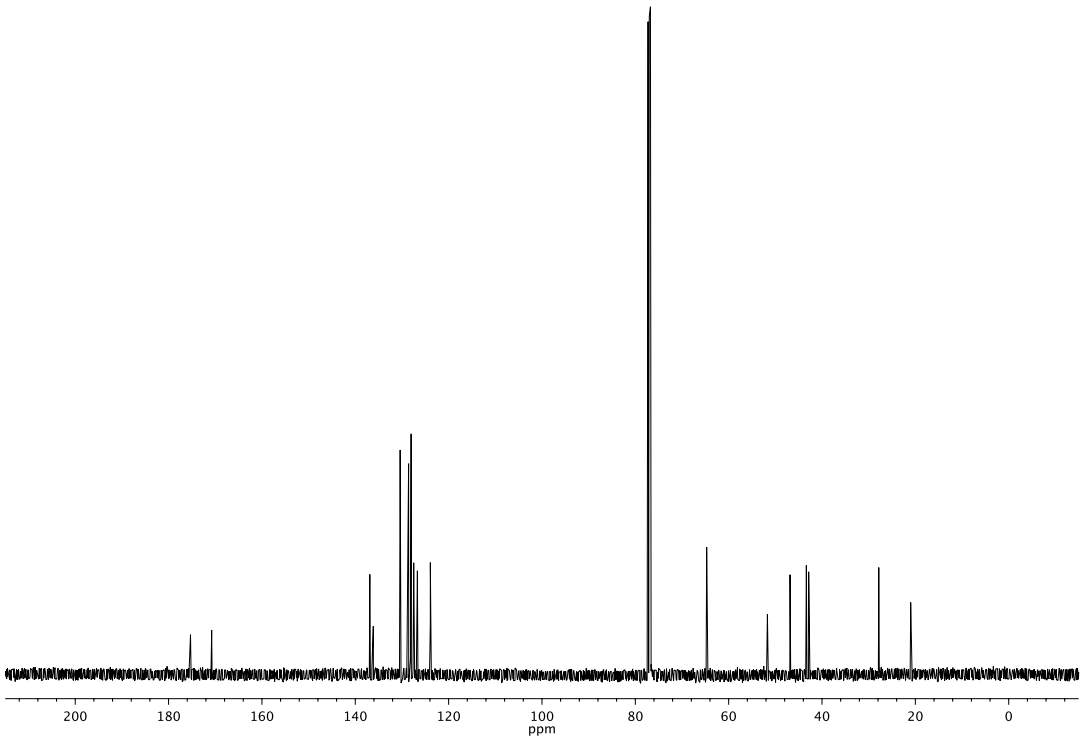


Figure A11.99 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **553**.

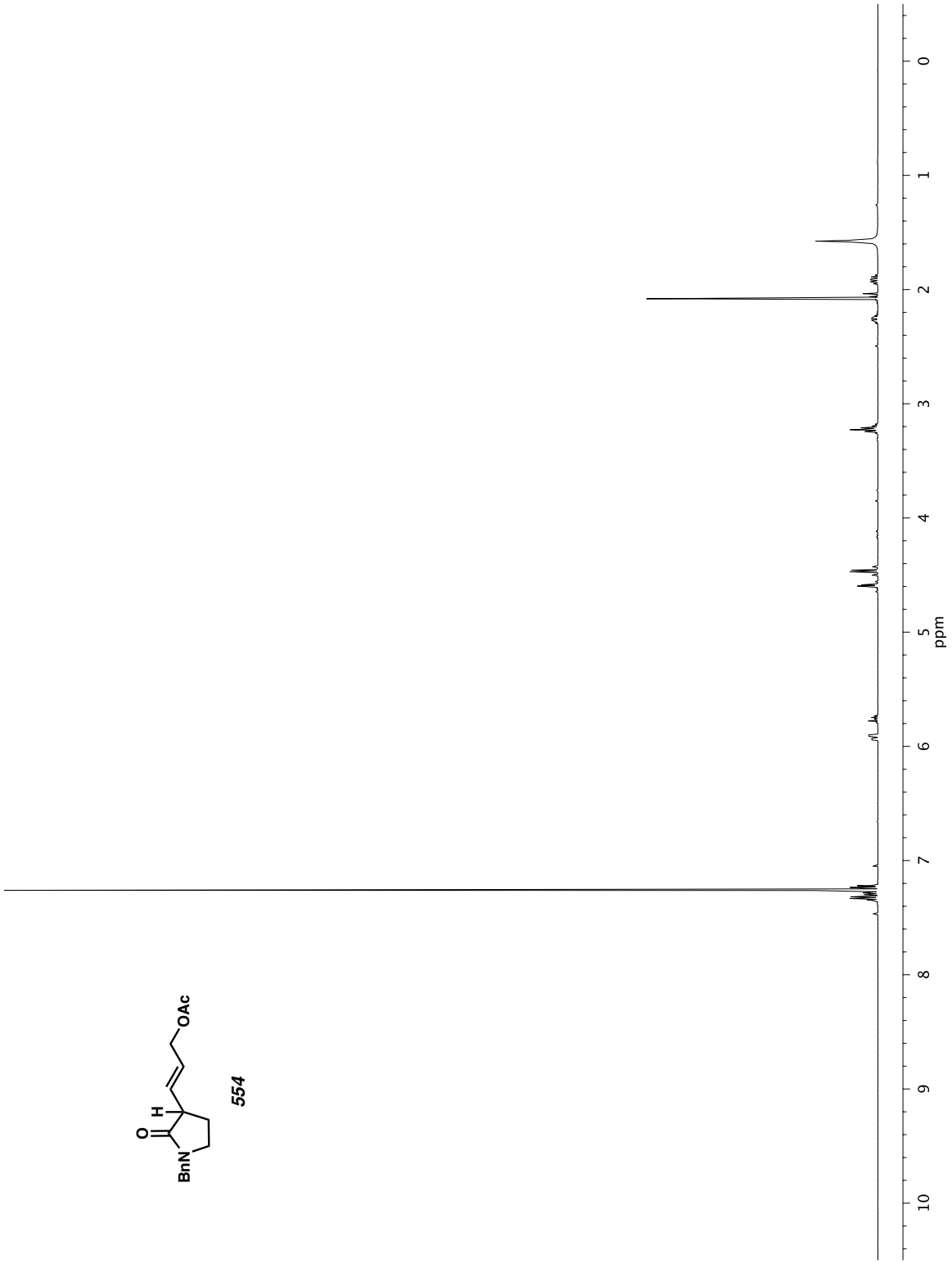


Figure A11.100 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **554**.

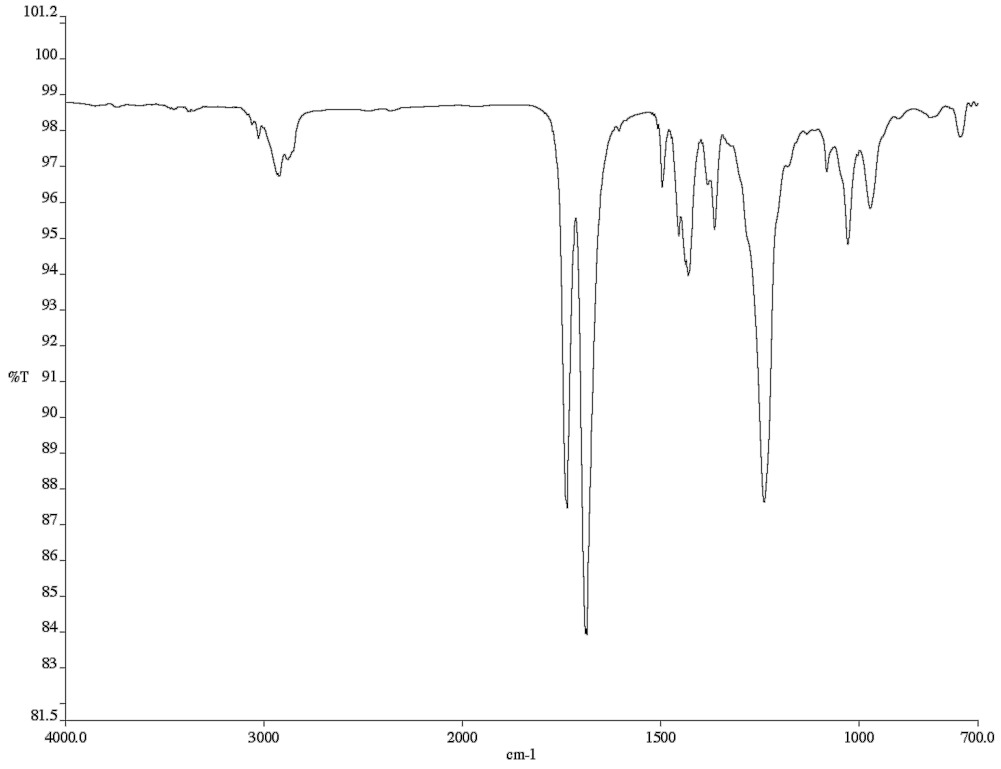


Figure A11.101 Infrared spectrum (thin film/NaCl) of compound **554**.

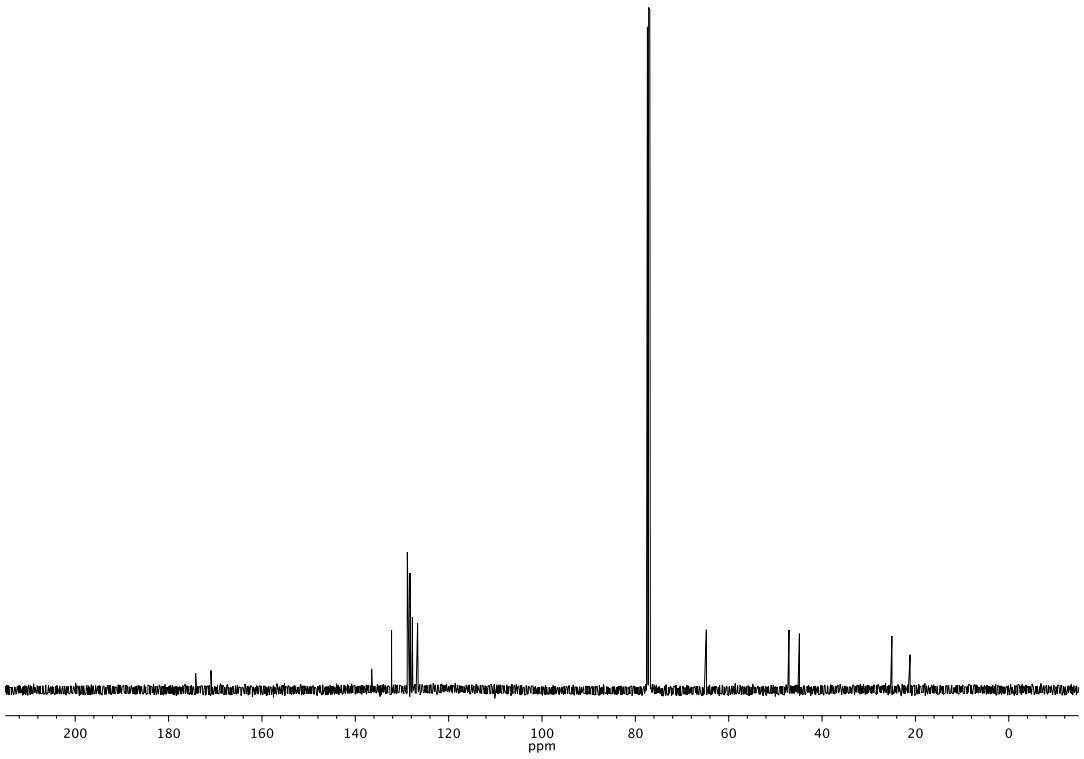


Figure A11.102 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **554**.

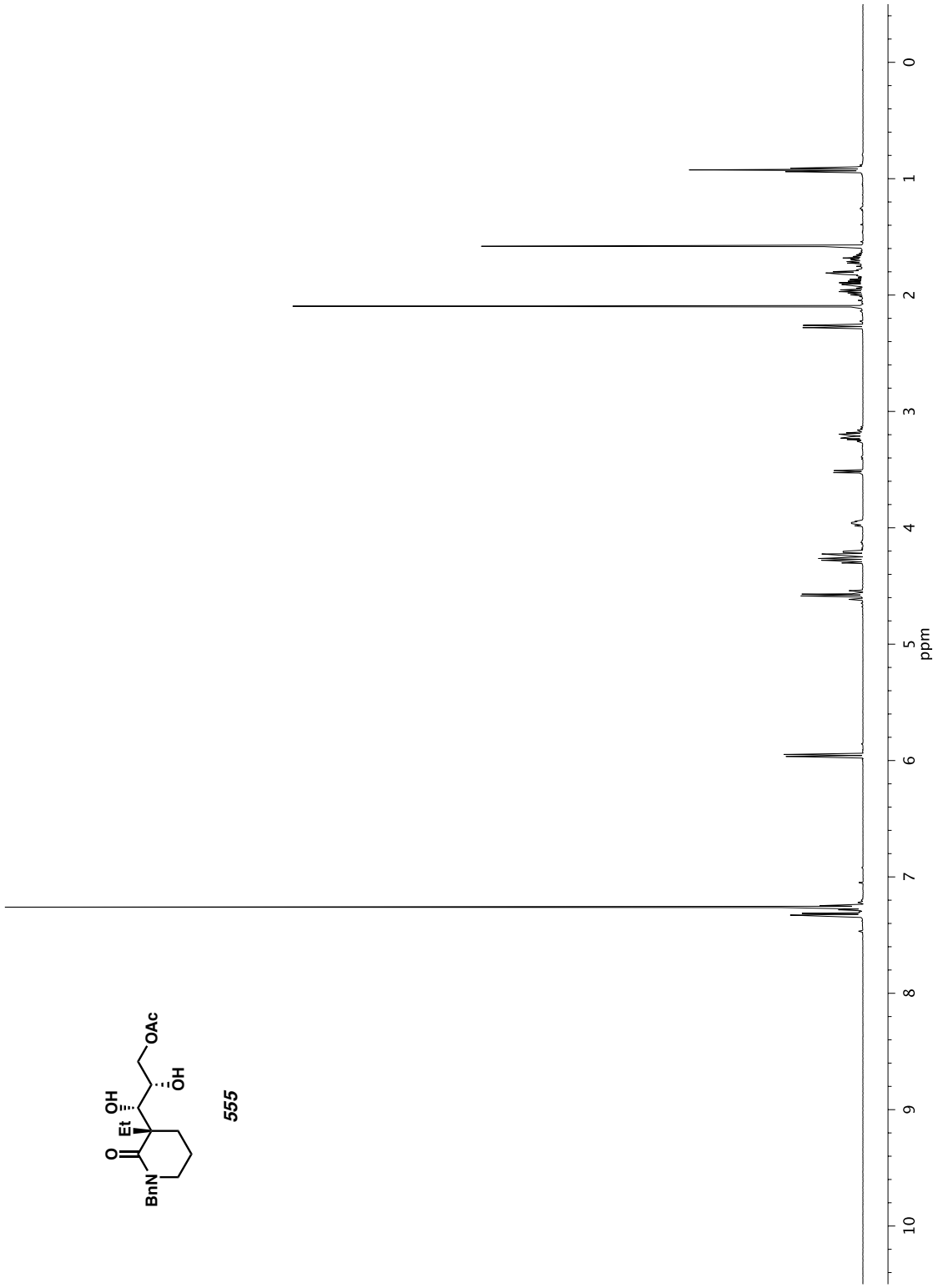


Figure A11.103 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **555**.

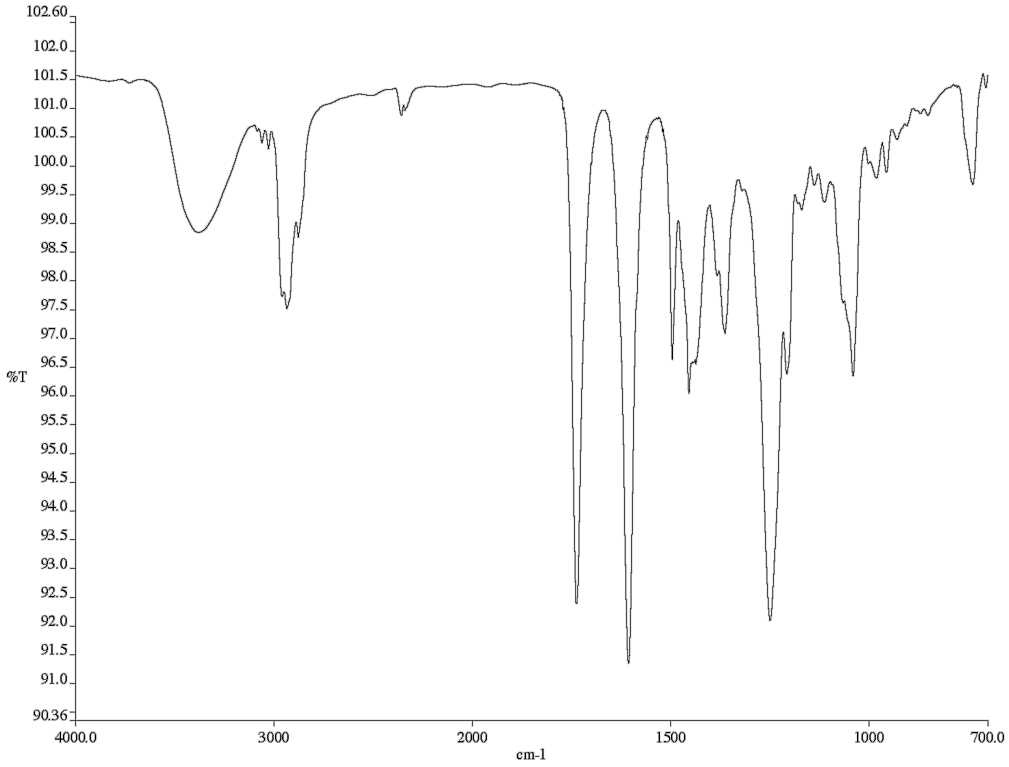


Figure A11.104 Infrared spectrum (thin film/NaCl) of compound **555**.

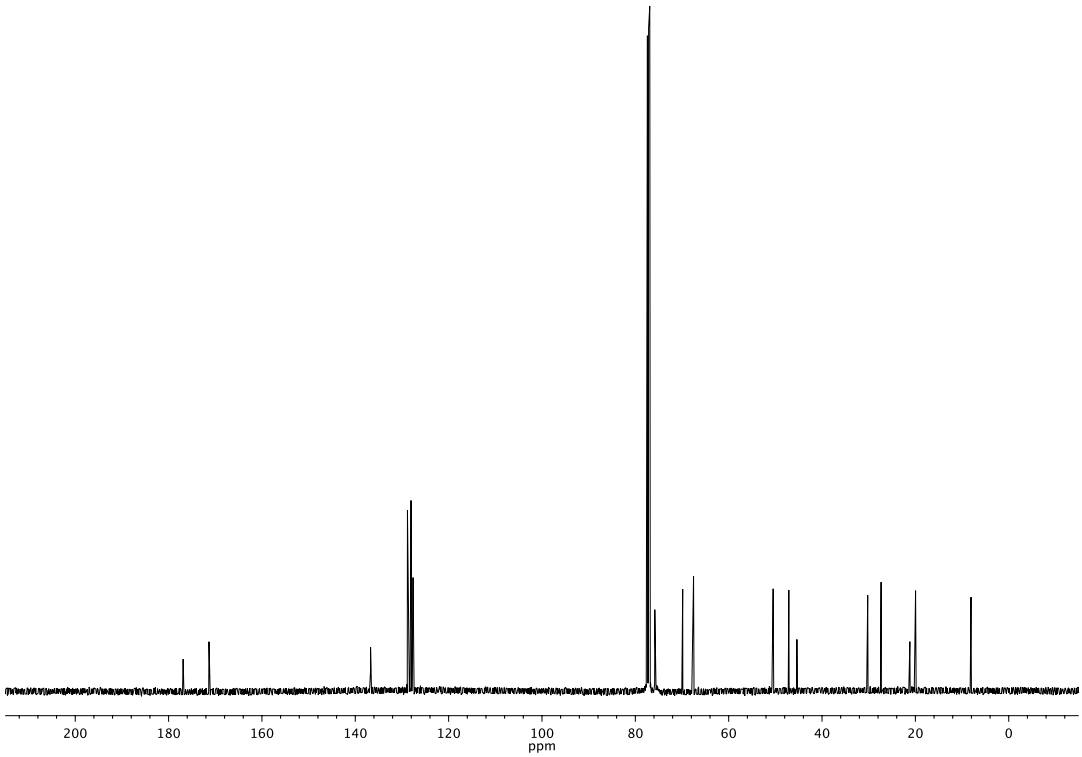


Figure A11.105 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **555**.

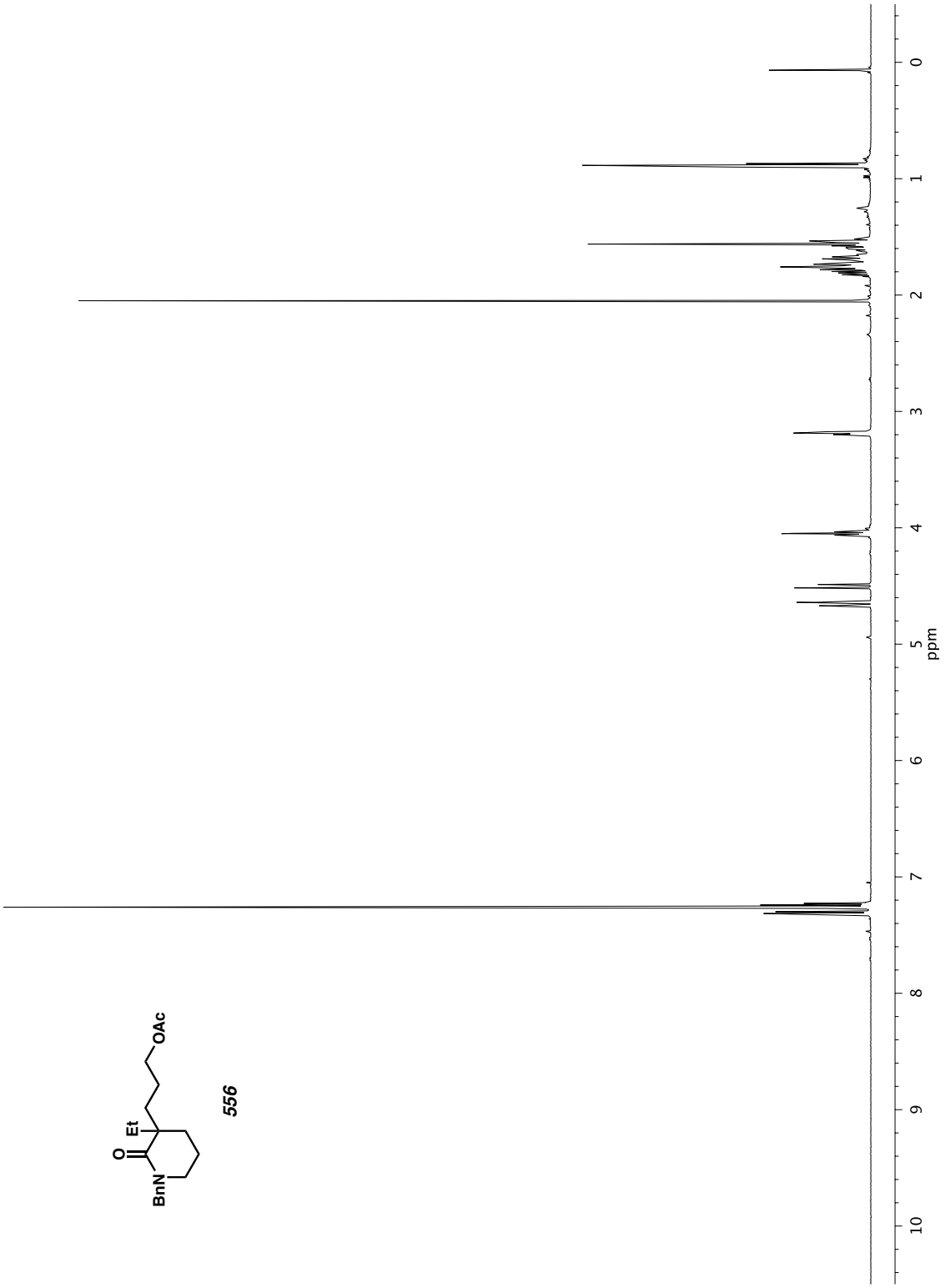


Figure A11.106 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **556**.

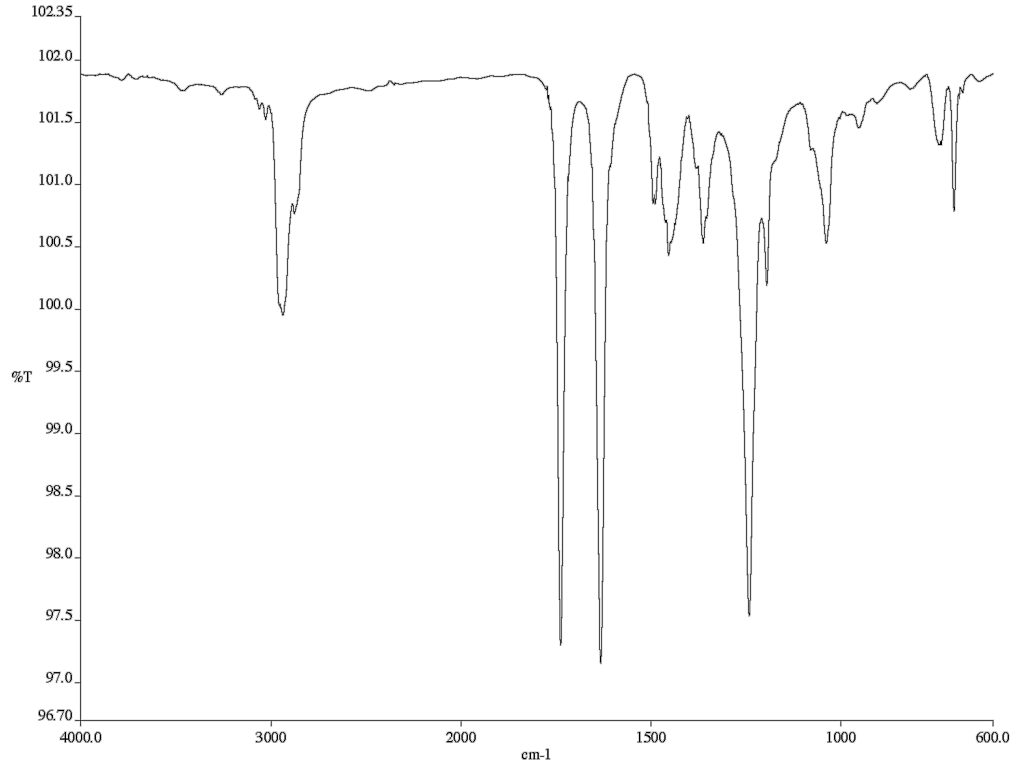


Figure A11.107 Infrared spectrum (thin film/NaCl) of compound **556**.

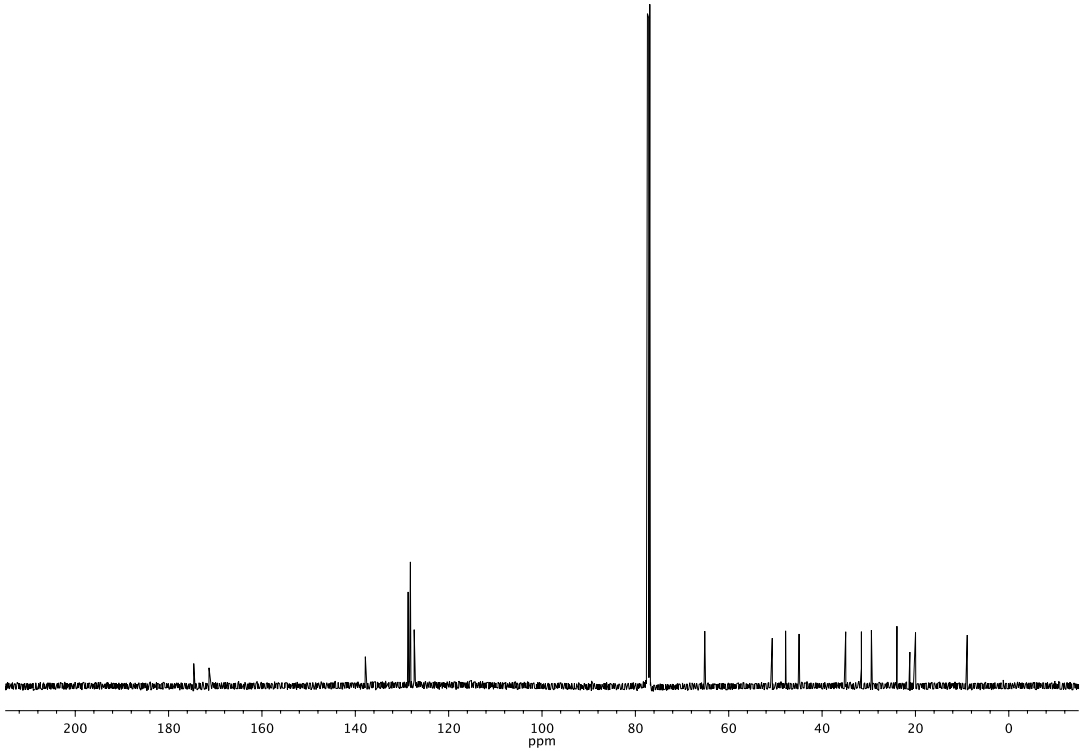


Figure A11.108 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **556**.

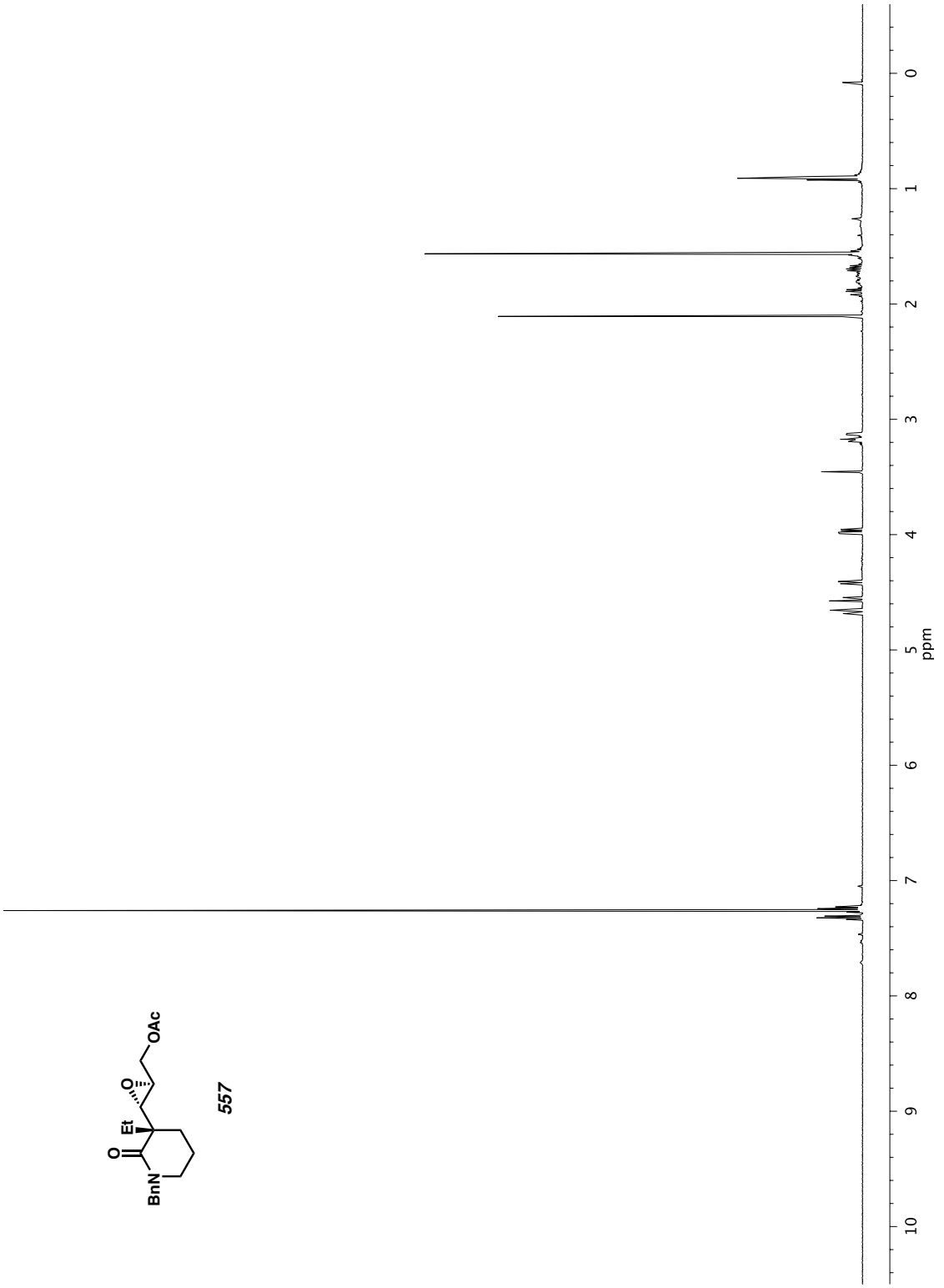


Figure A11.109 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **557**.

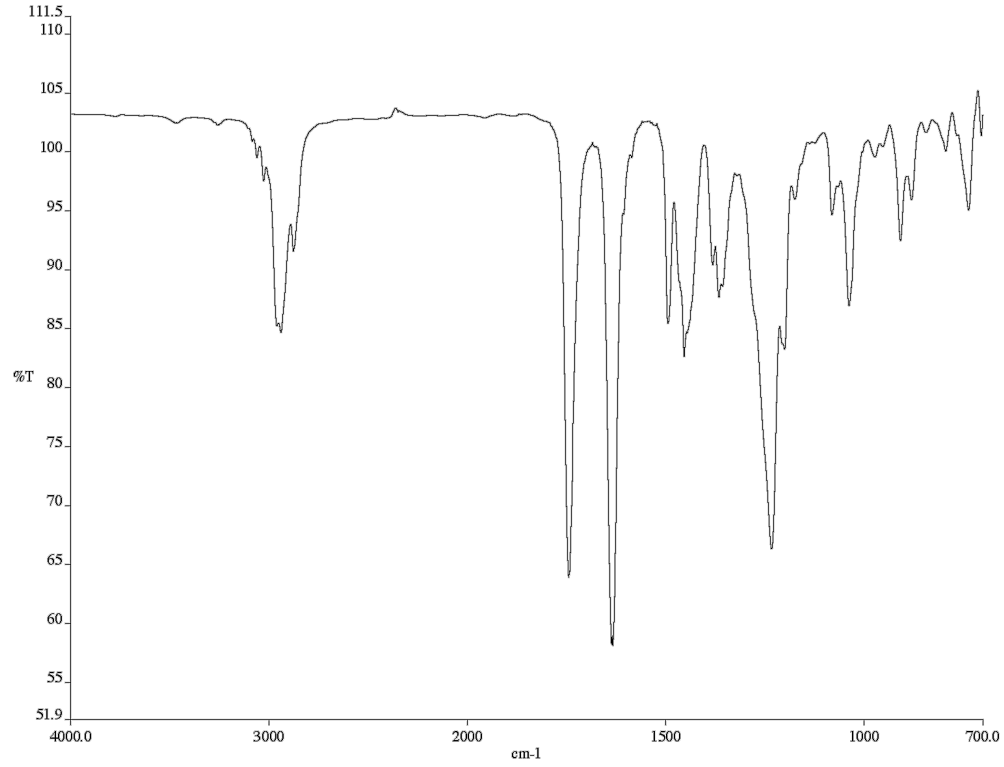


Figure A11.110 Infrared spectrum (thin film/NaCl) of compound **557**.

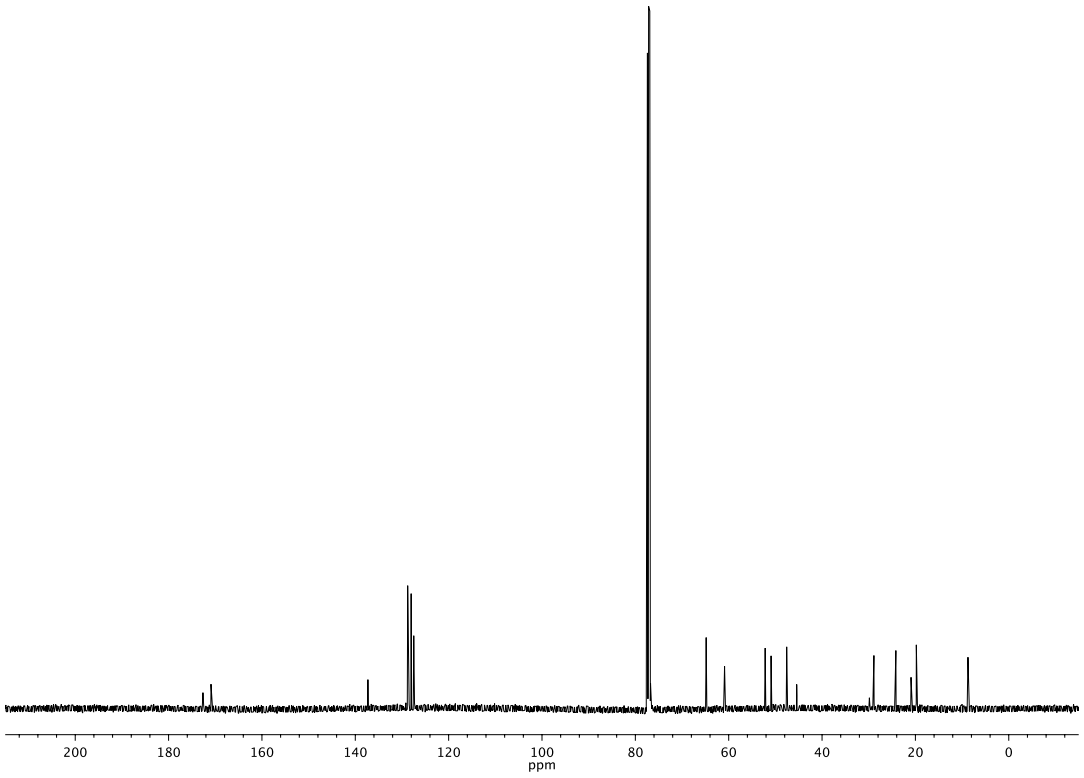


Figure A11.111 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **557**.

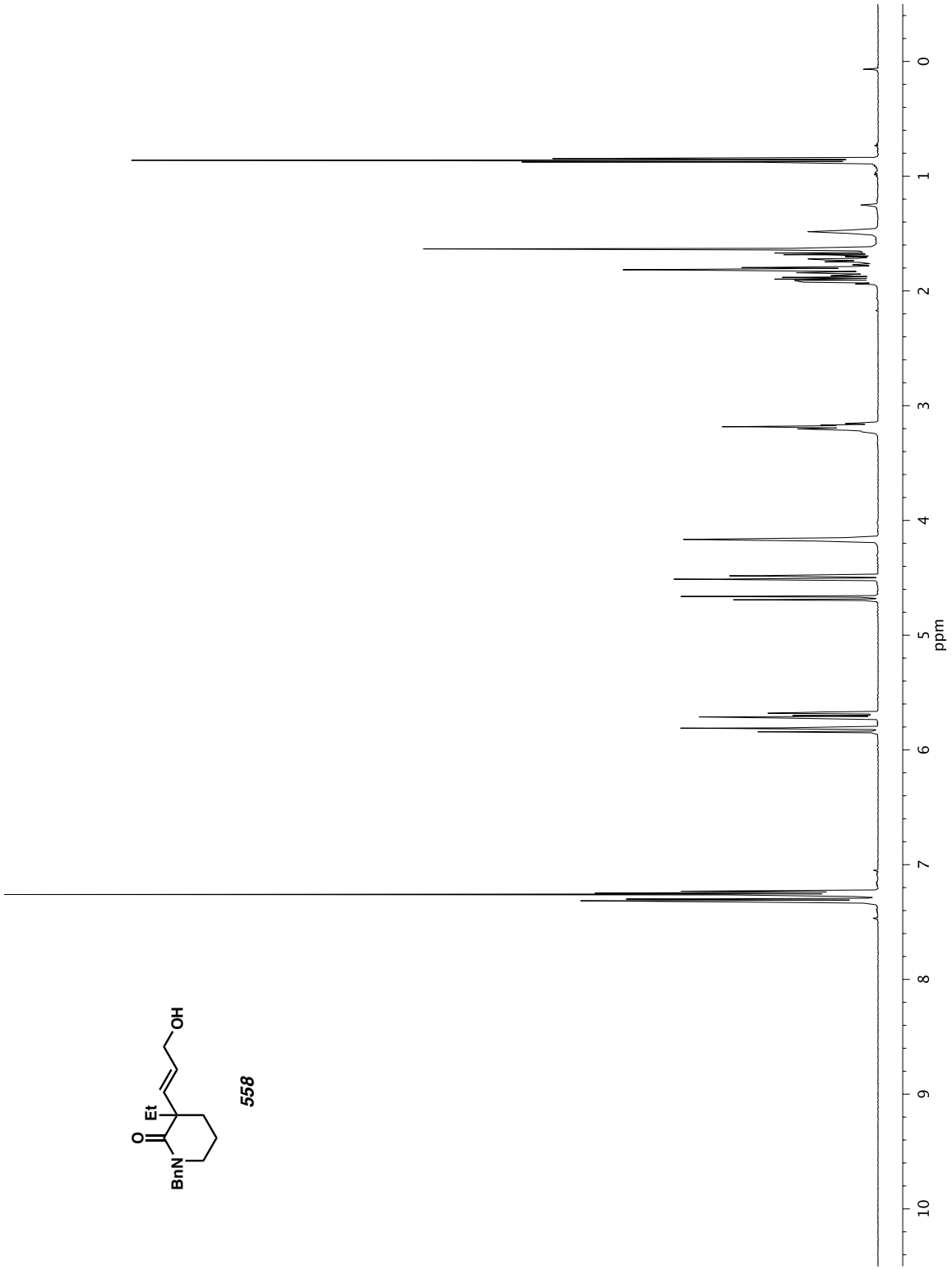


Figure A11.112 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **558**.

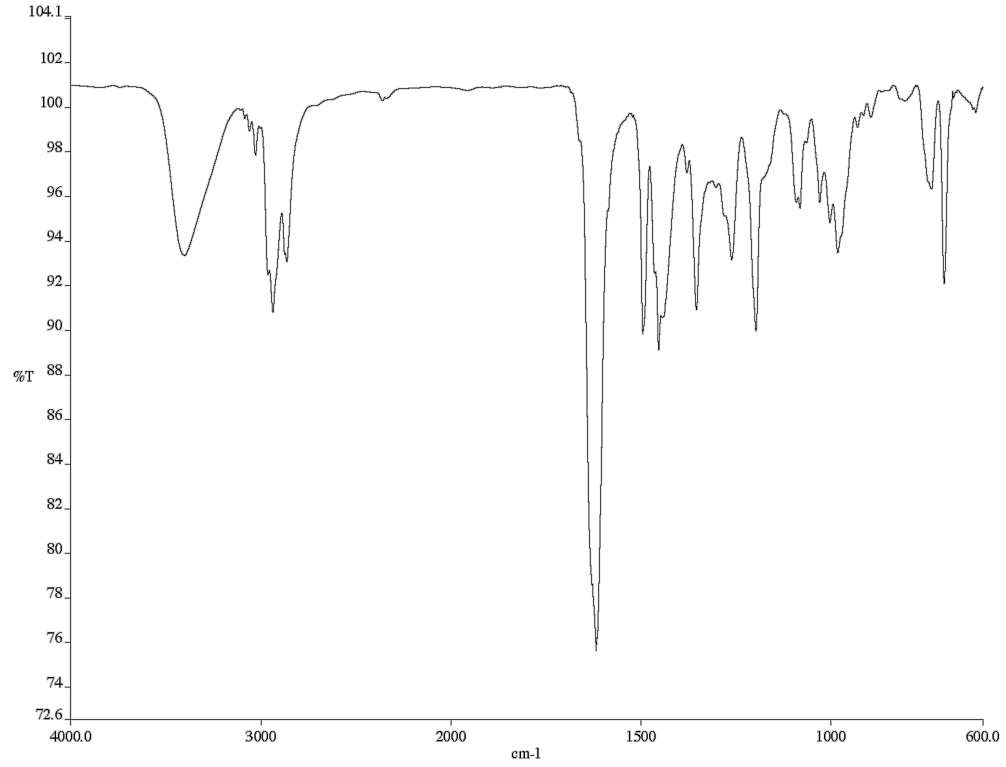


Figure A11.113 Infrared spectrum (thin film/NaCl) of compound **558**.

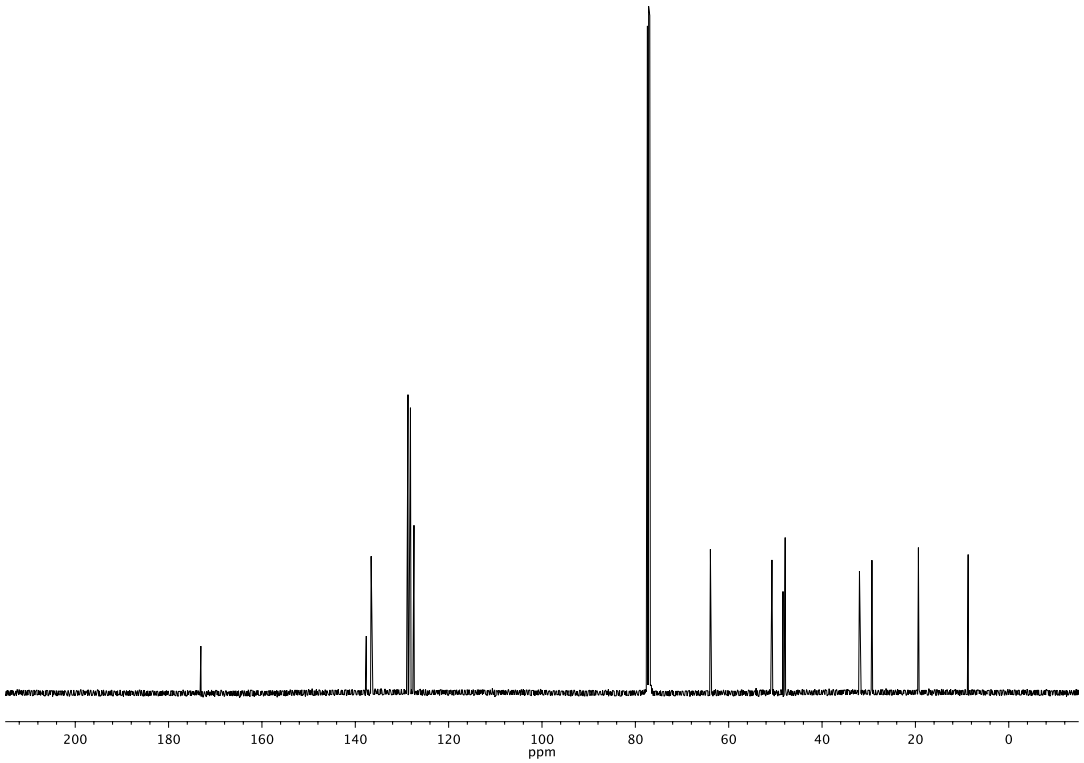


Figure A11.114 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **558**.

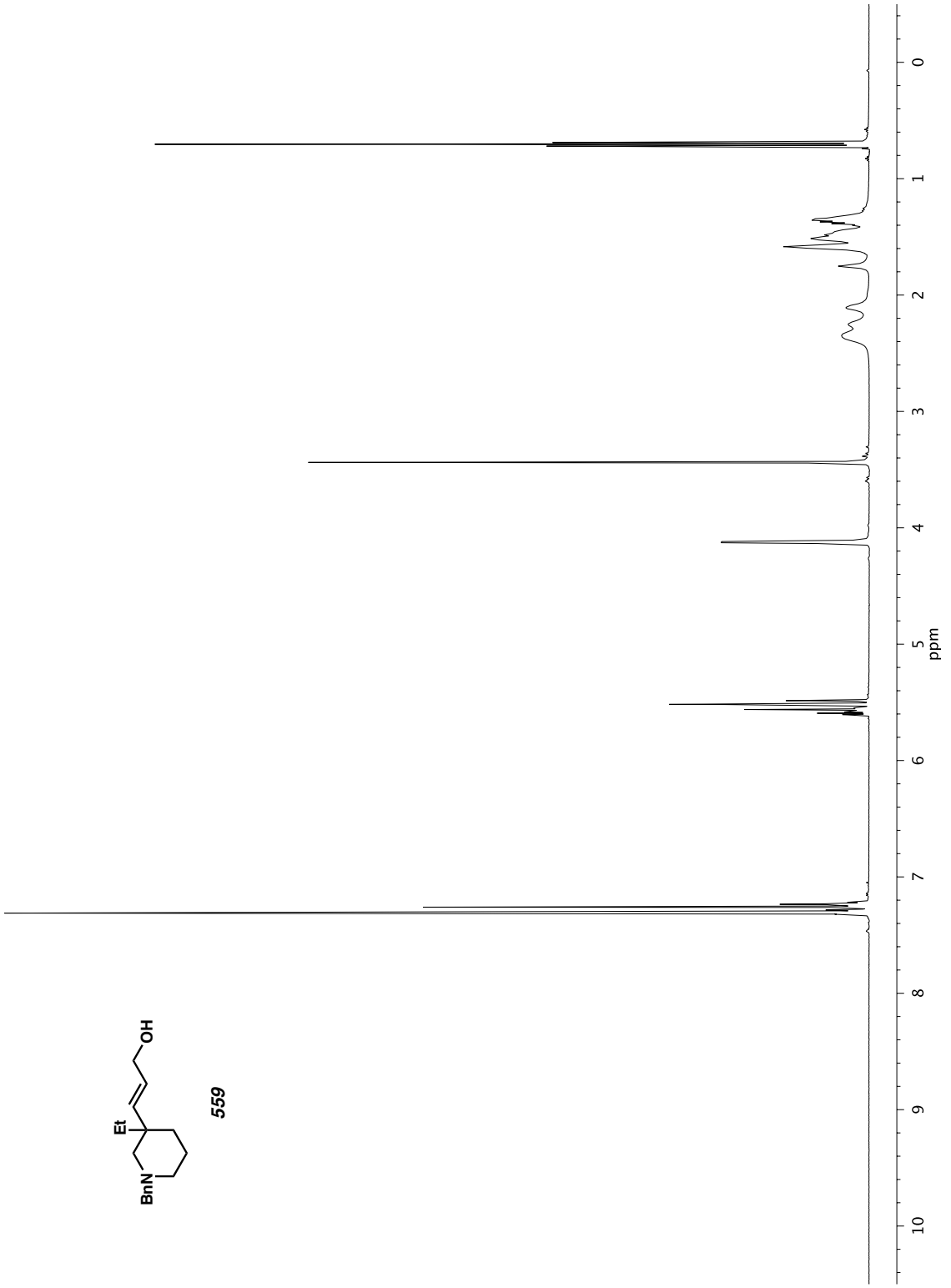


Figure A11.115 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **559**.

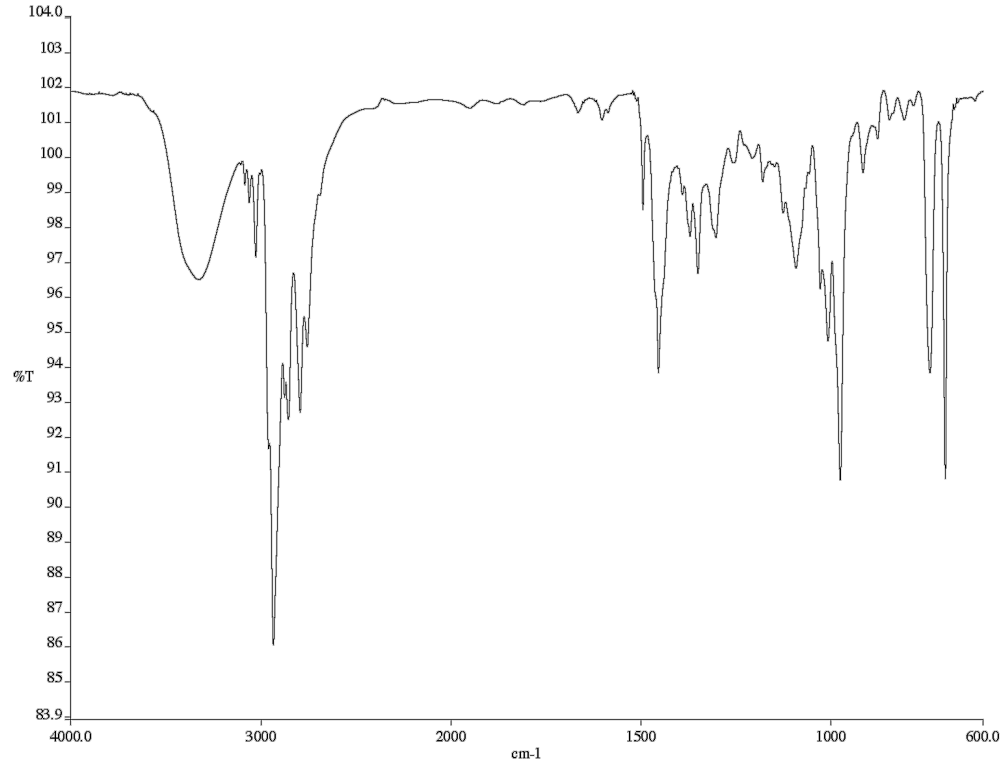


Figure A11.116 Infrared spectrum (thin film/NaCl) of compound **559**.

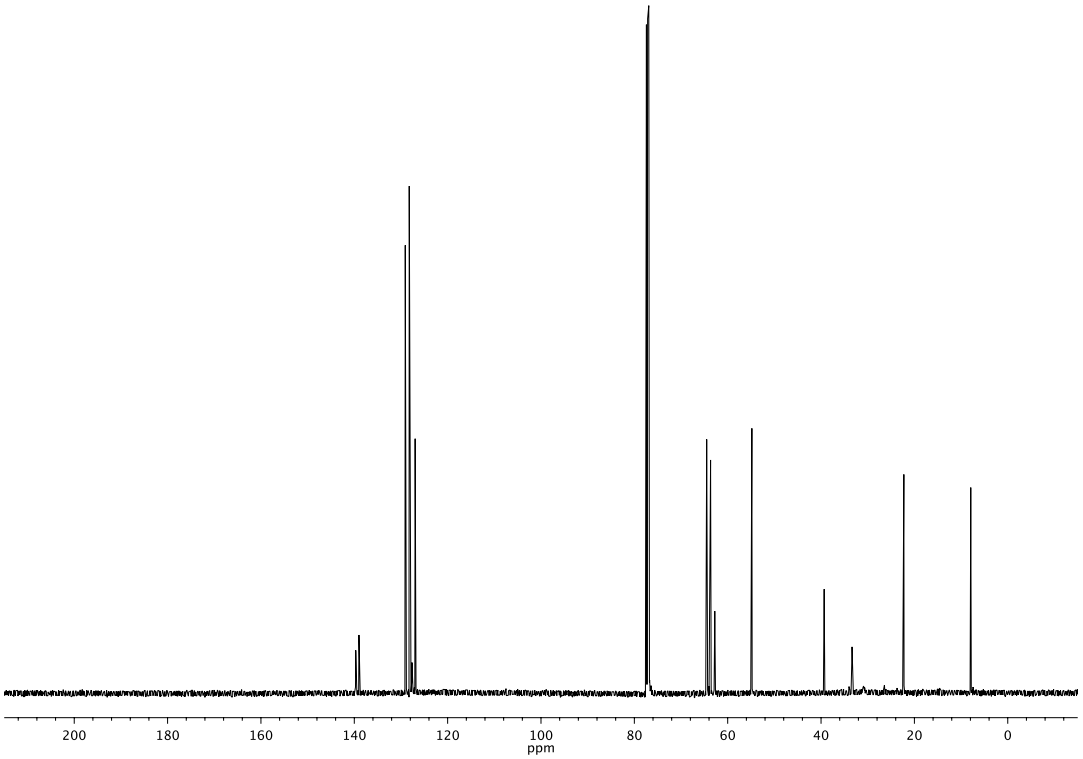


Figure A11.117 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **559**.

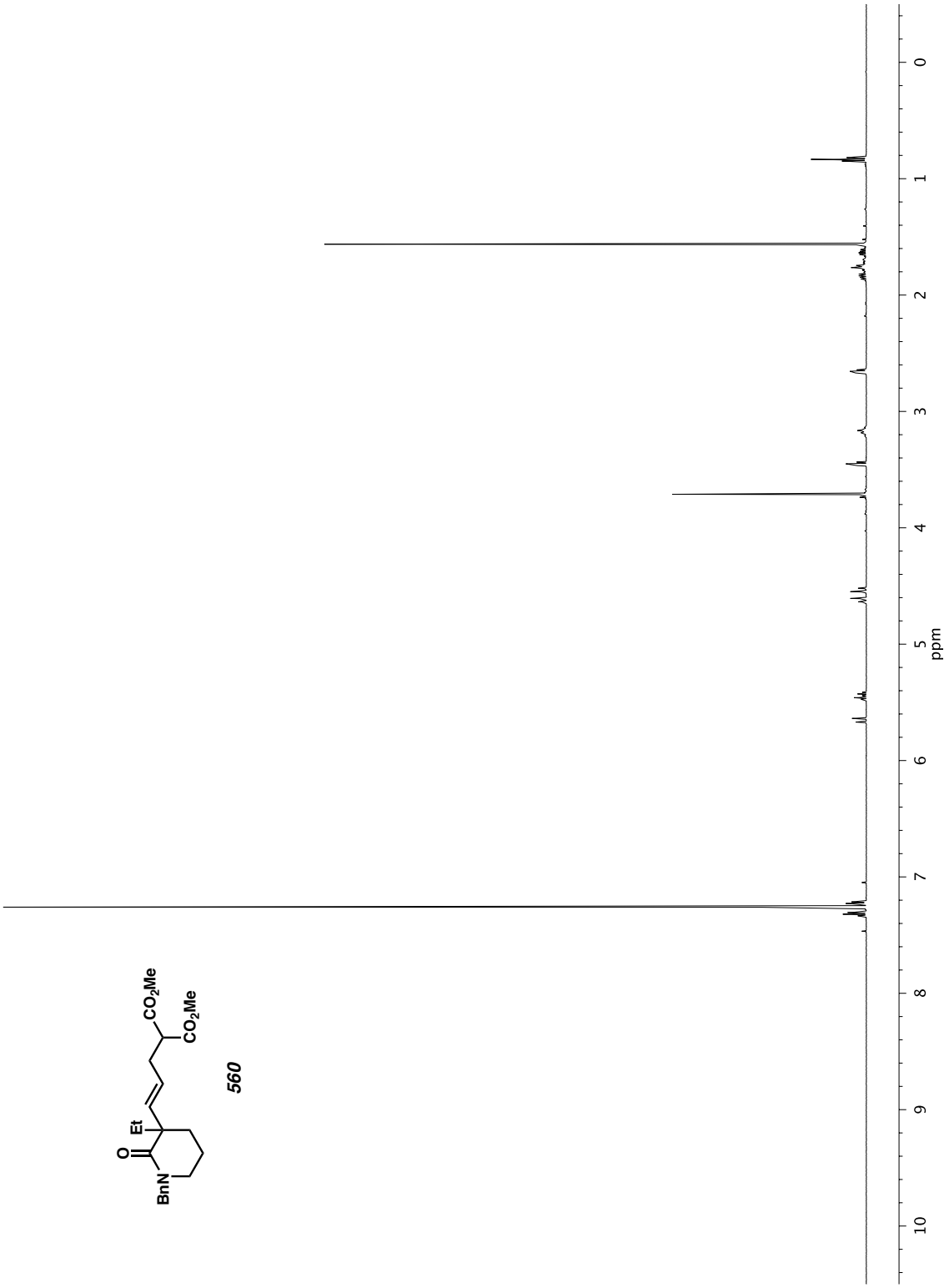


Figure A11.118 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **560**.

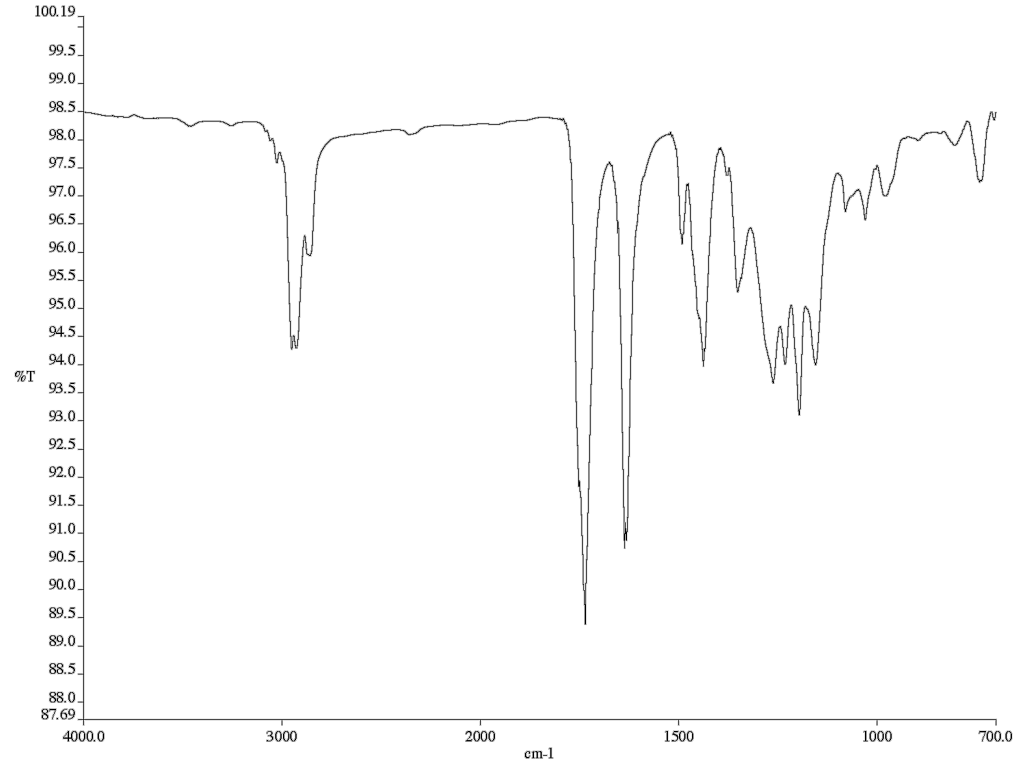


Figure A11.119 Infrared spectrum (thin film/NaCl) of compound **560**.

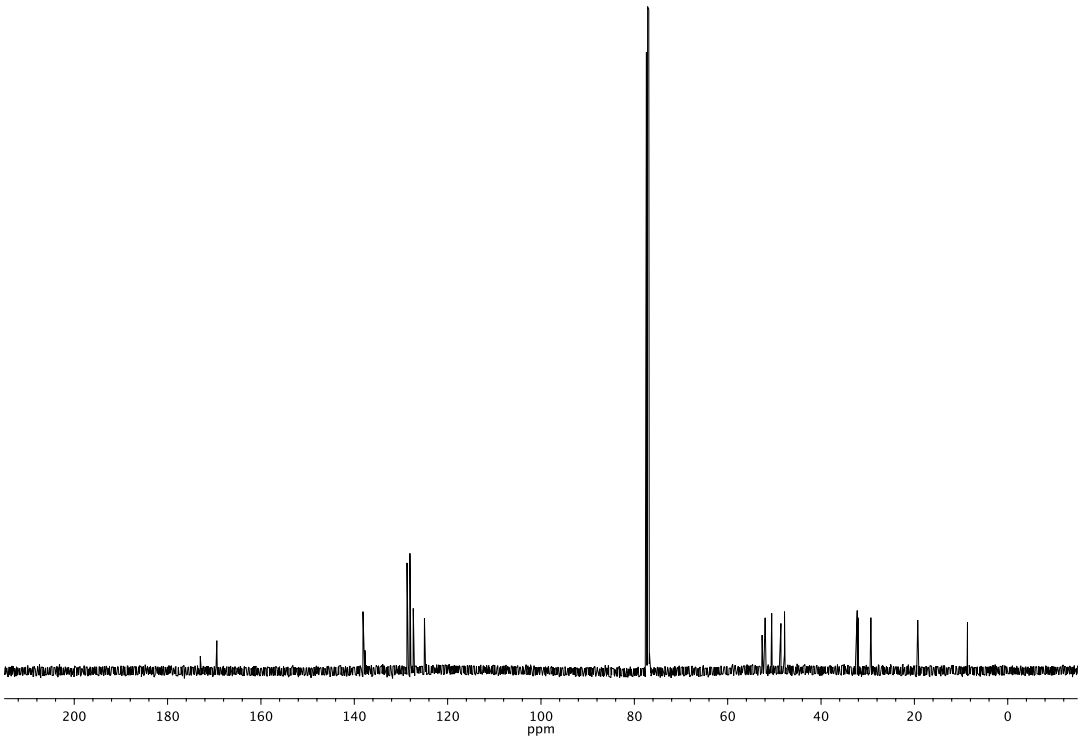


Figure A11.120 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **560**.

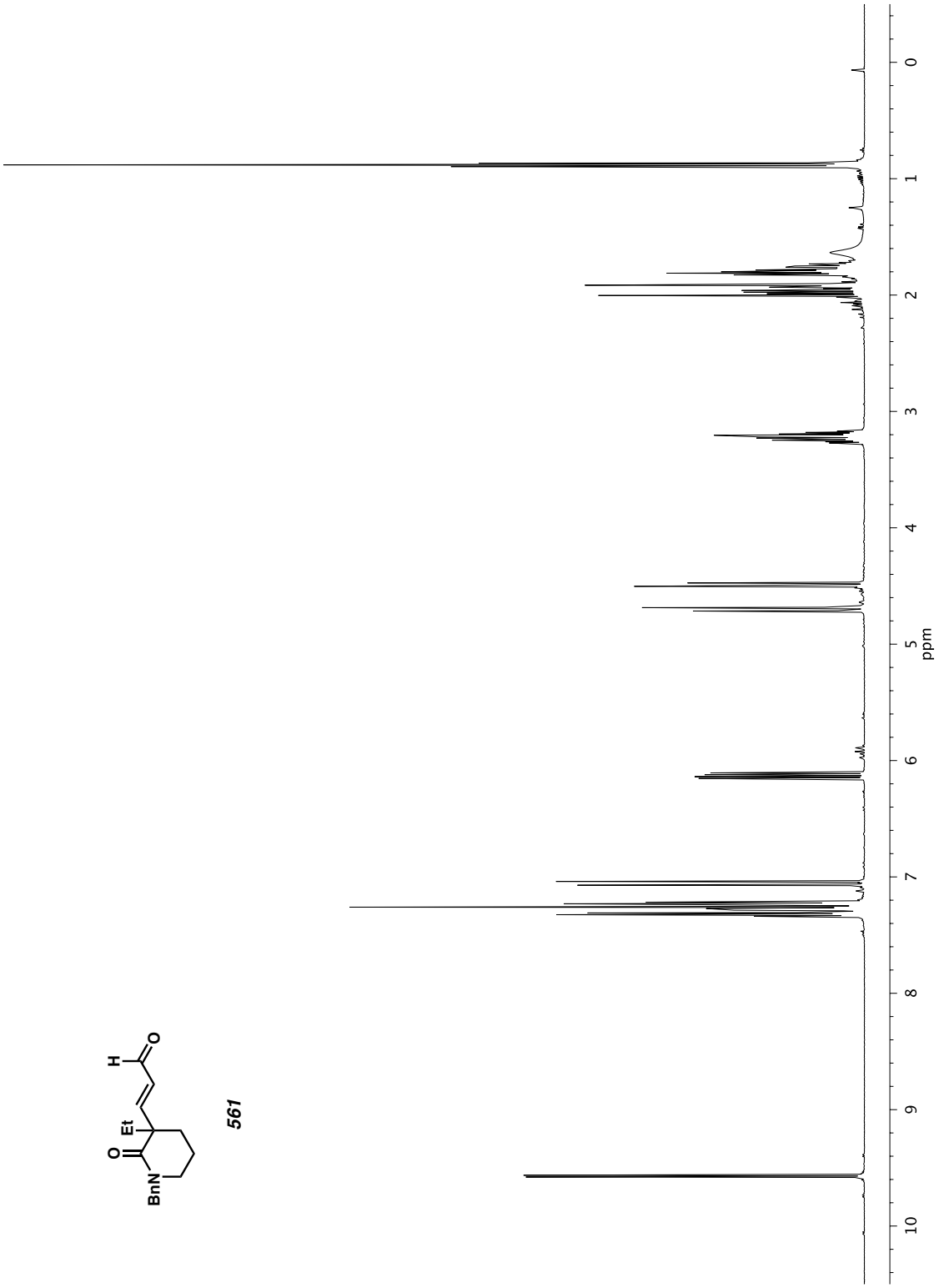


Figure A11.121 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **561**.

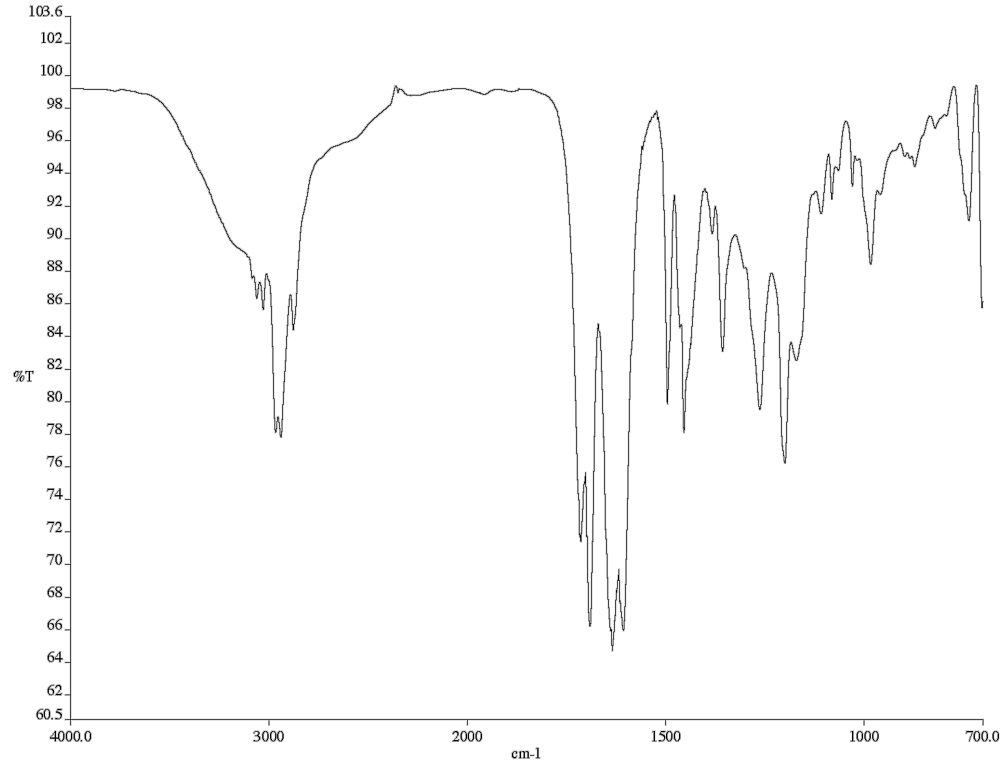


Figure A11.122 Infrared spectrum (thin film/NaCl) of compound **561**.

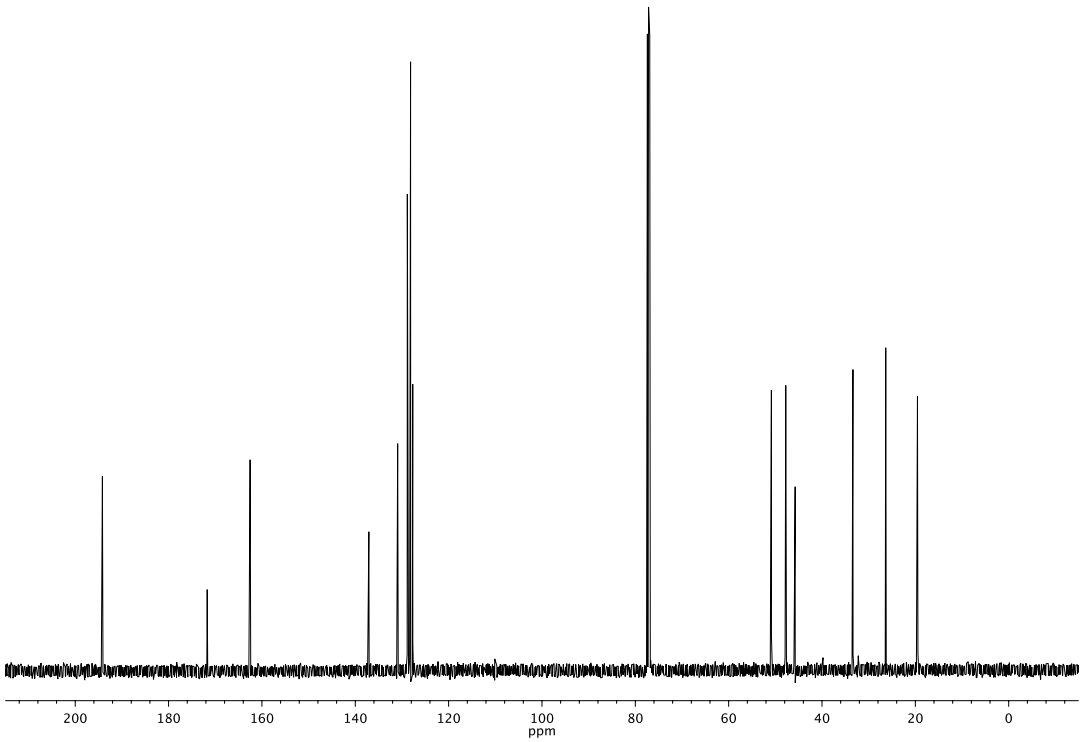


Figure A11.123 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **561**.

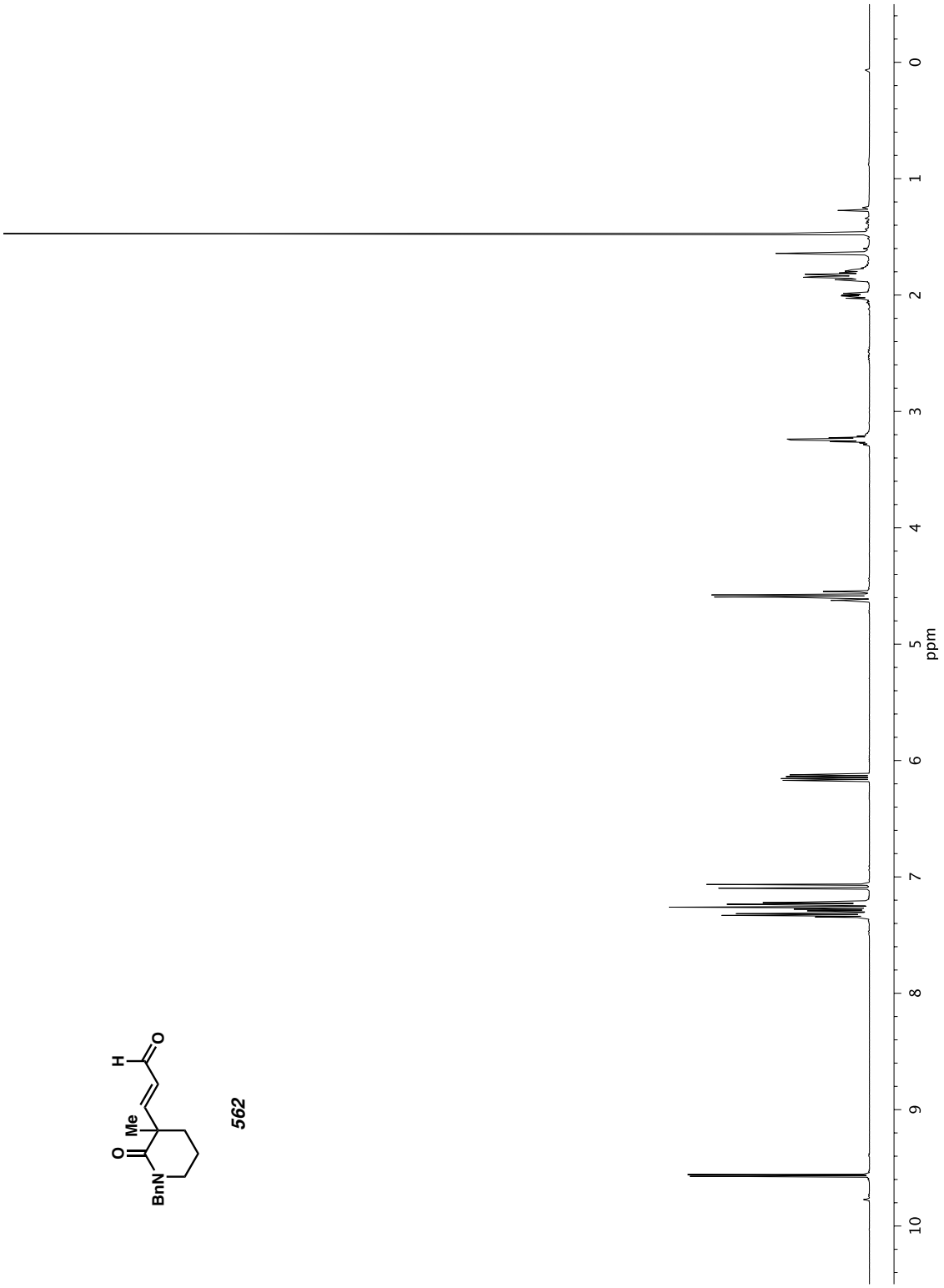


Figure A11.124 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **562**.

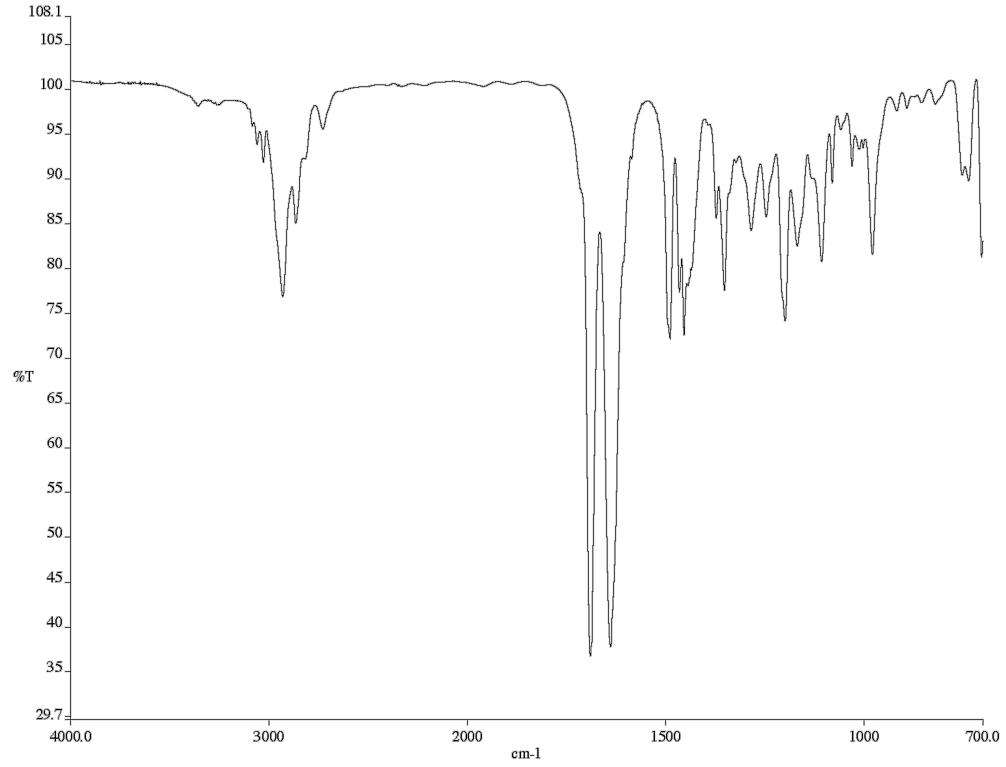


Figure A11.125 Infrared spectrum (thin film/NaCl) of compound **562**.

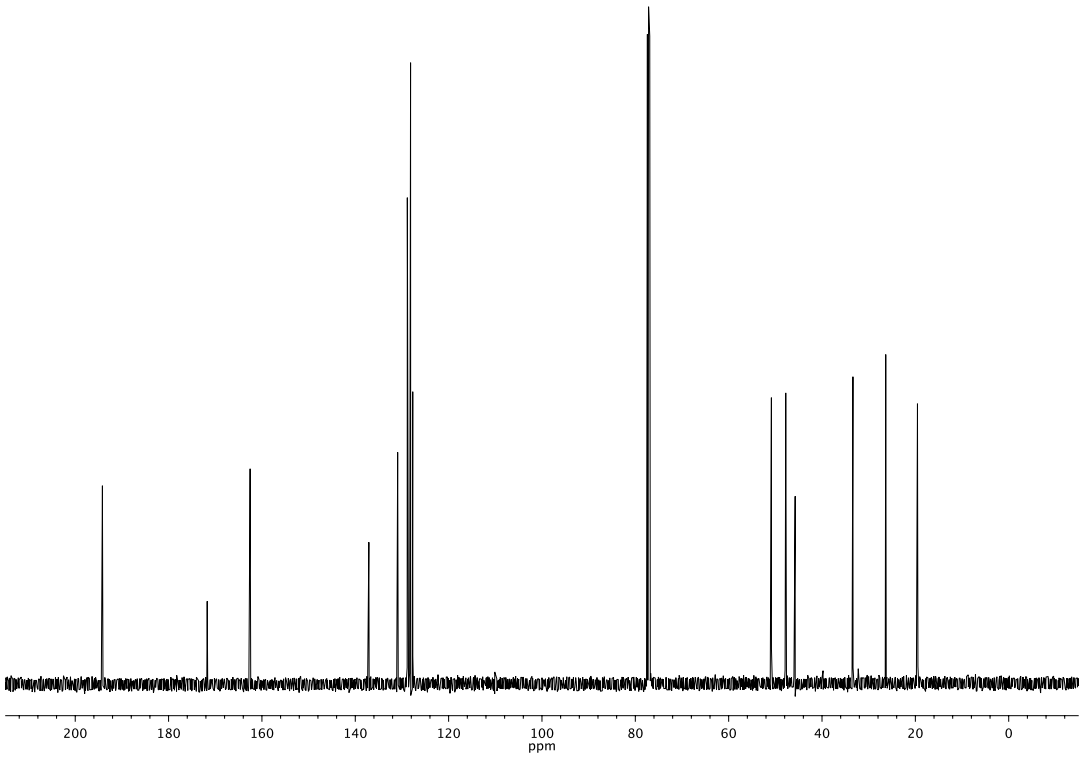


Figure A11.126 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **562**.

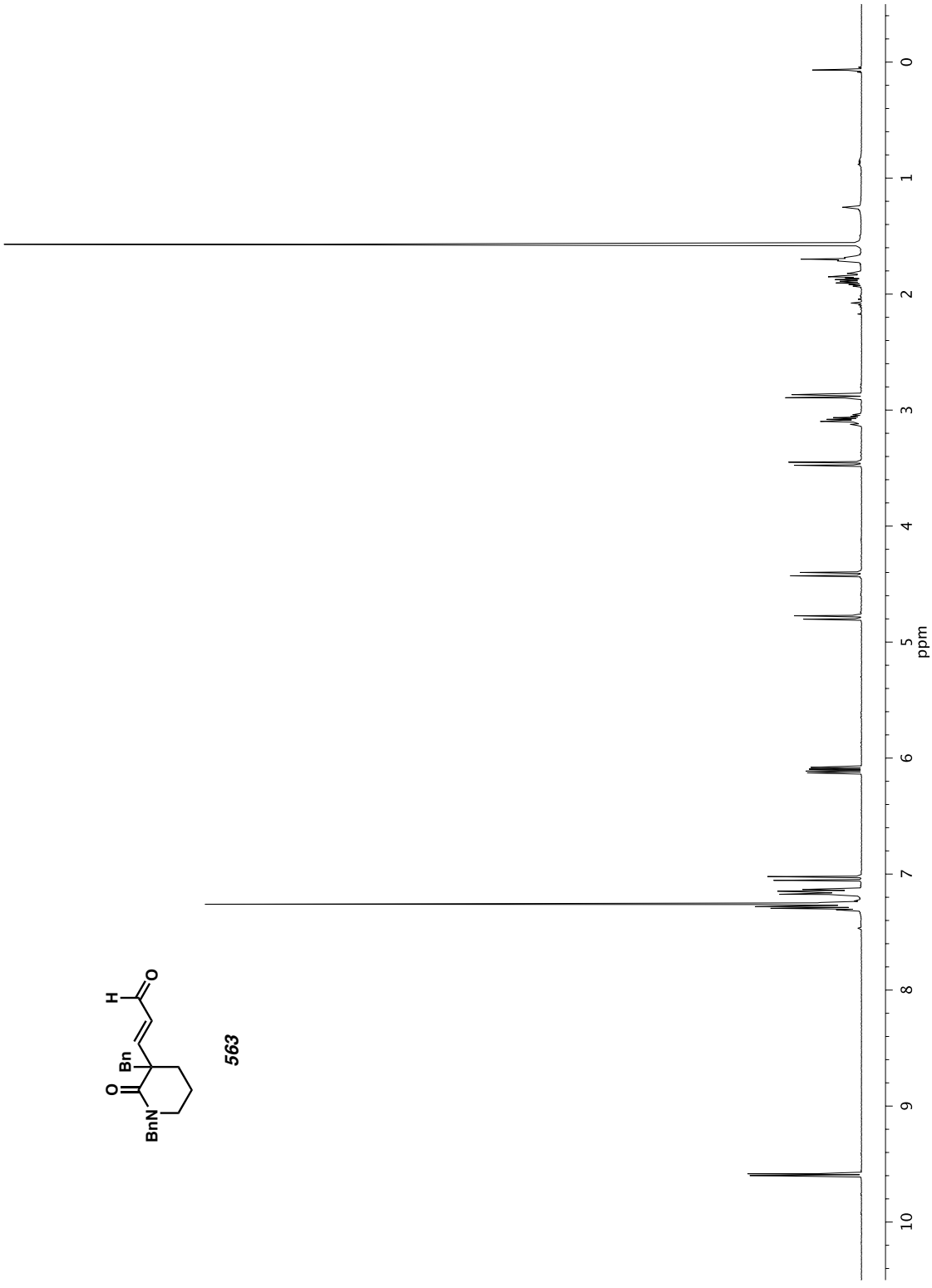


Figure A11.127 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **563**.

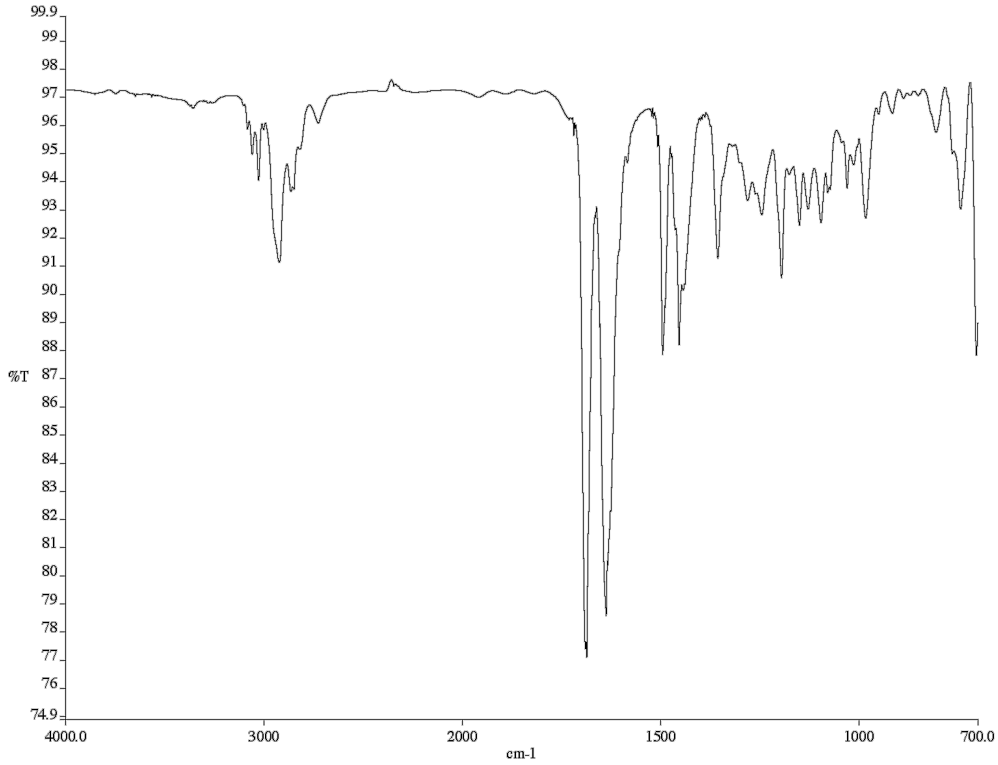


Figure A11.128 Infrared spectrum (thin film/NaCl) of compound **563**.

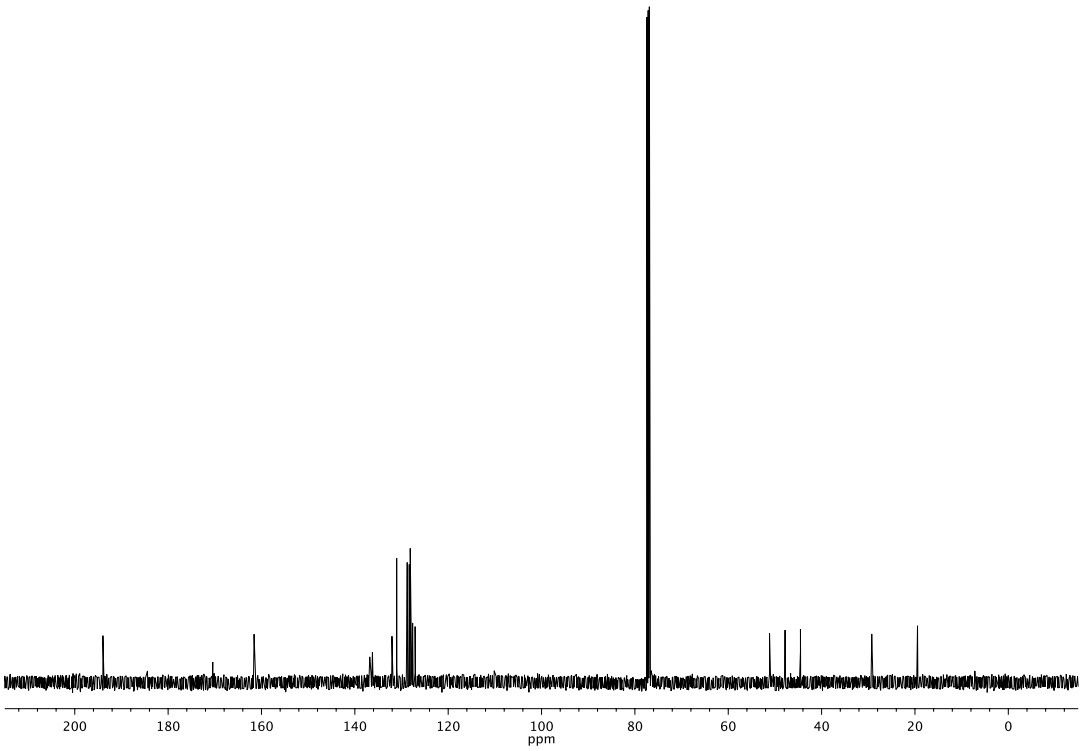


Figure A11.129 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **563**.

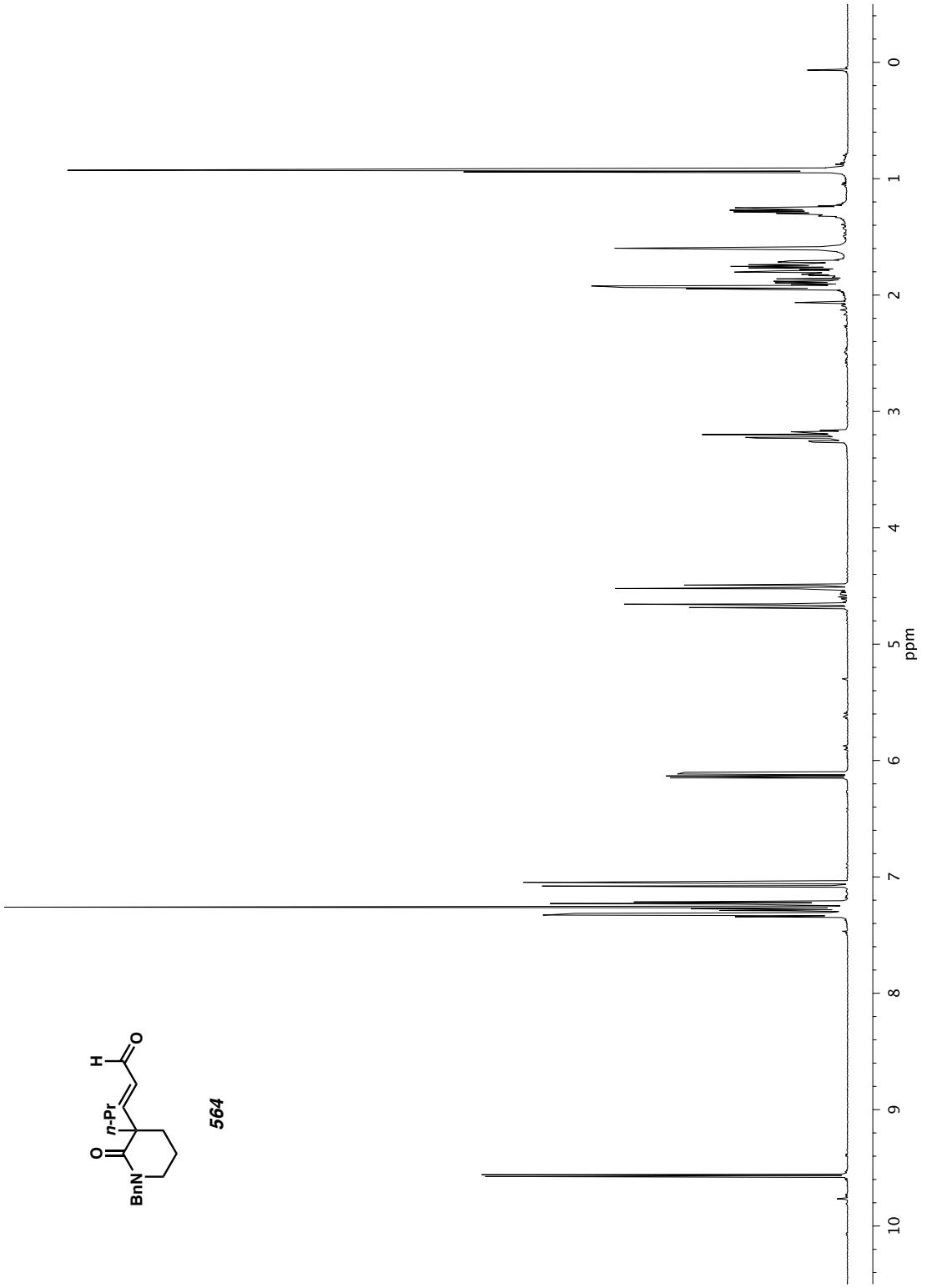


Figure A11.130 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **564**.

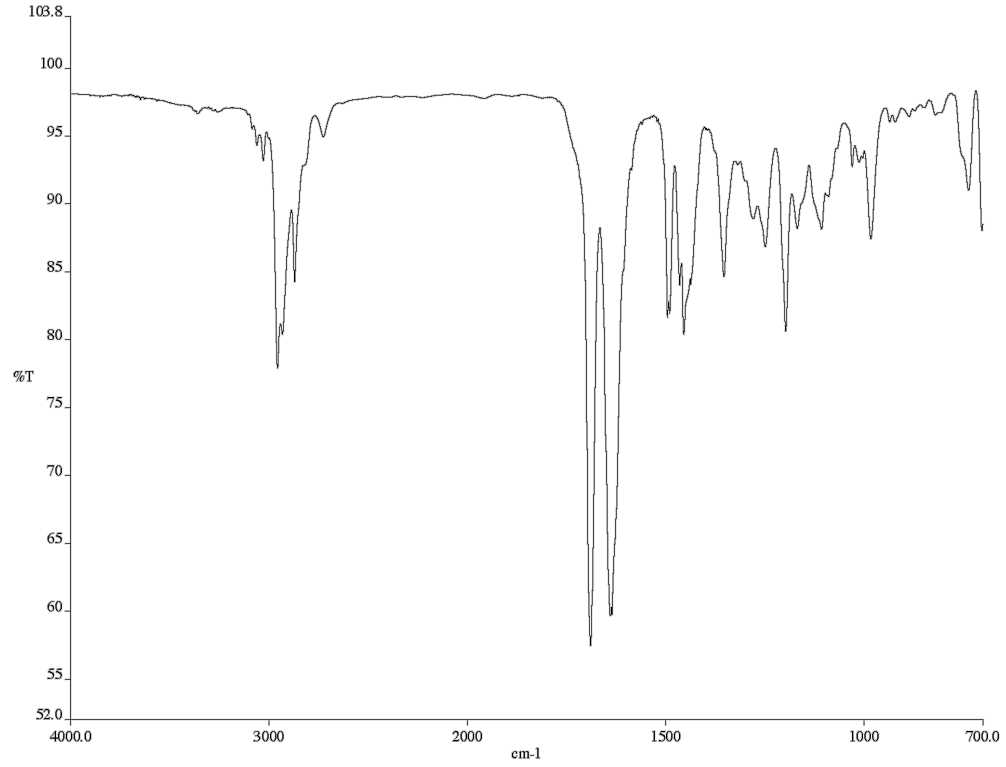


Figure A11.131 Infrared spectrum (thin film/NaCl) of compound **564**.

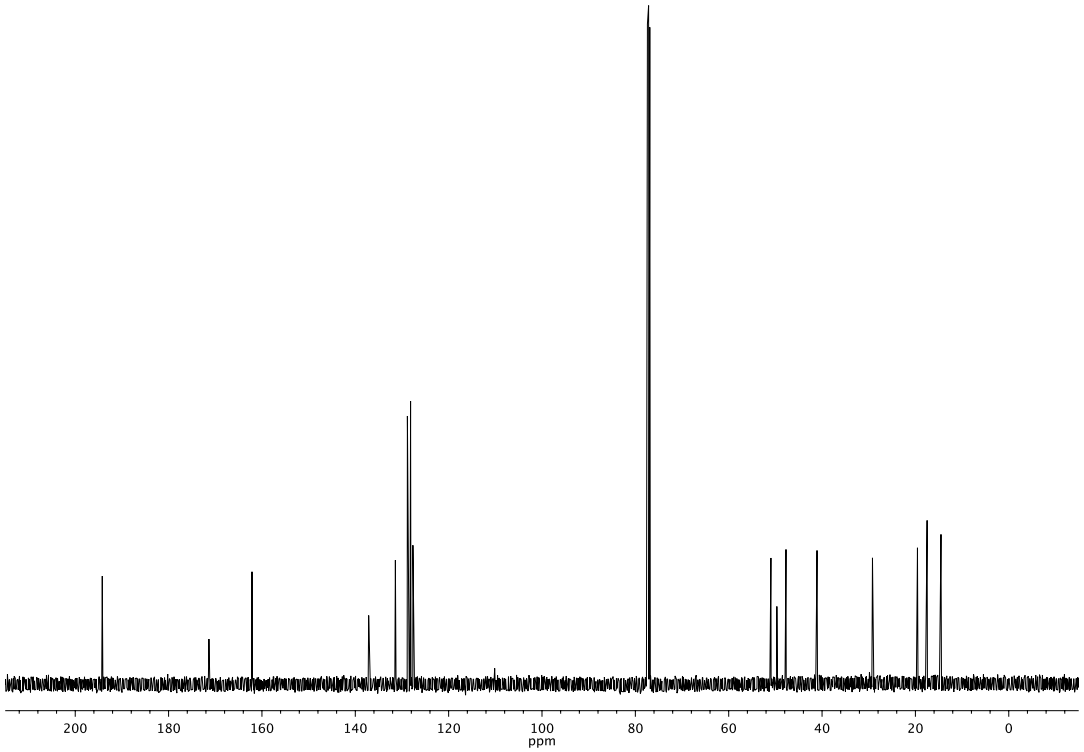


Figure A11.132 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **564**.

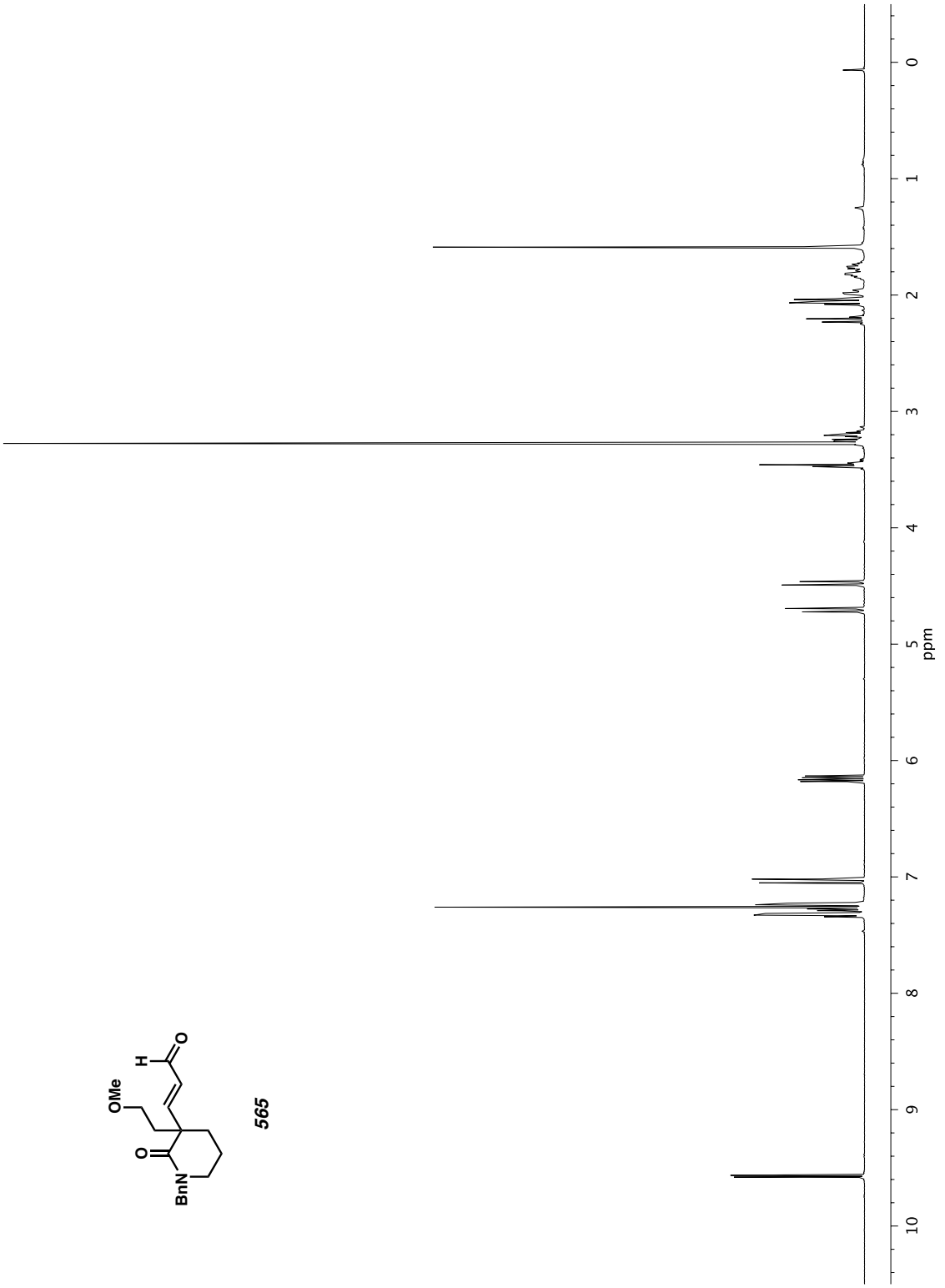


Figure A11.133 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **565**.

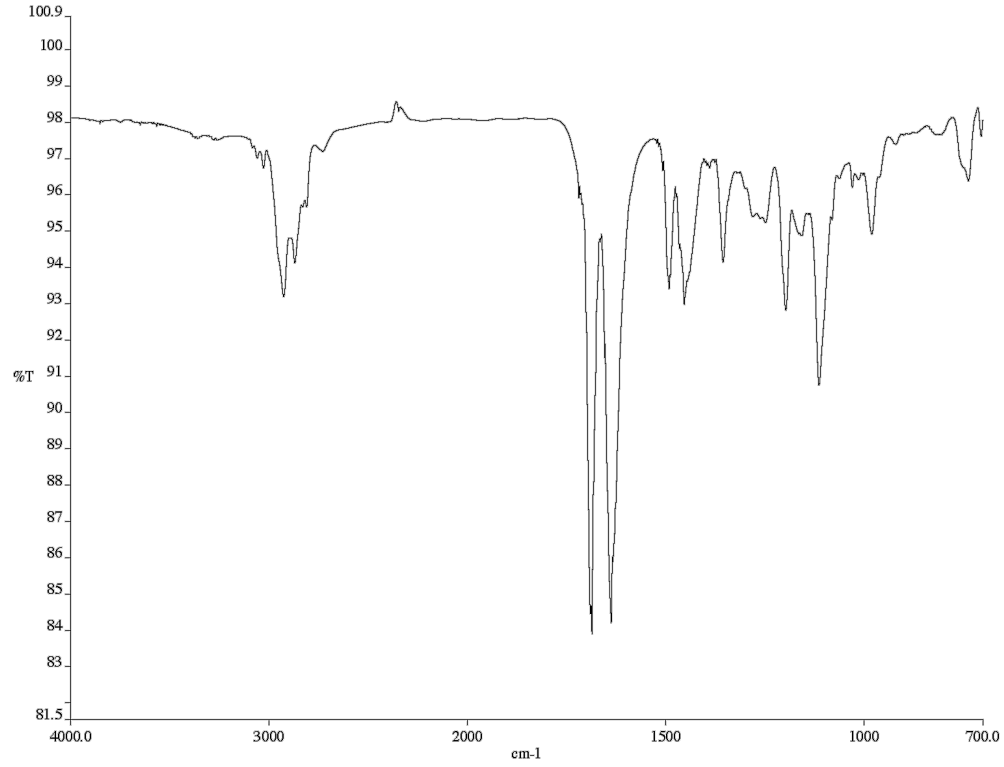


Figure A11.134 Infrared spectrum (thin film/NaCl) of compound **565**.

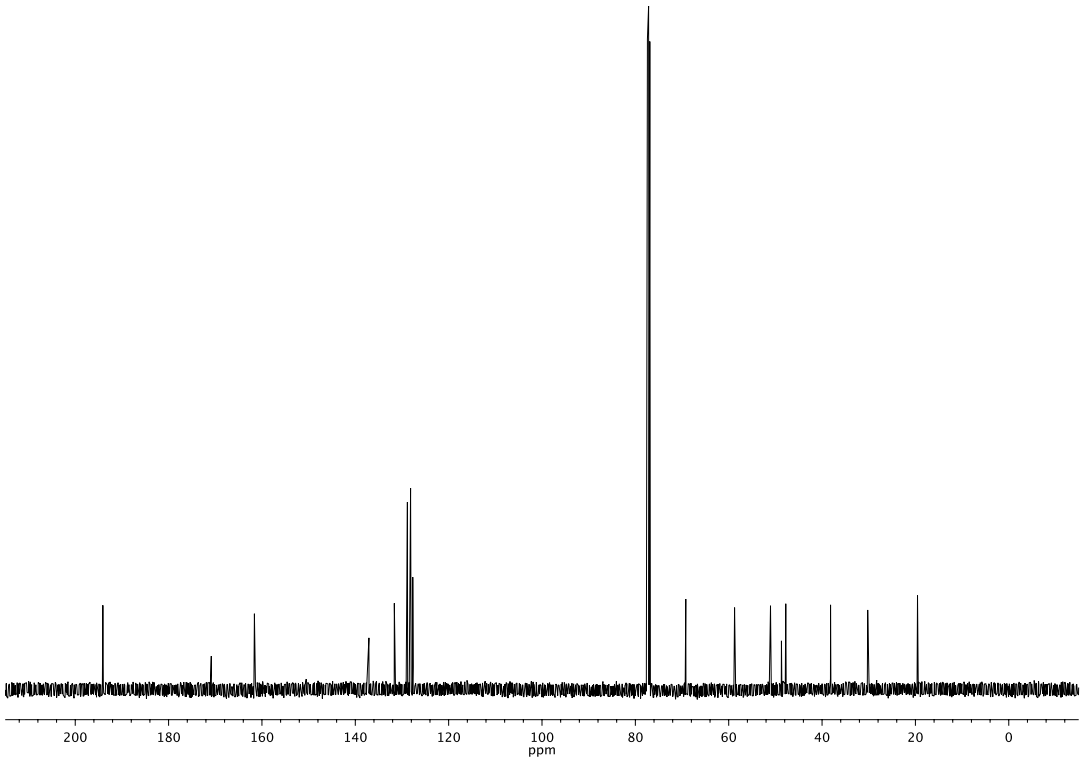


Figure A11.135 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **565**.

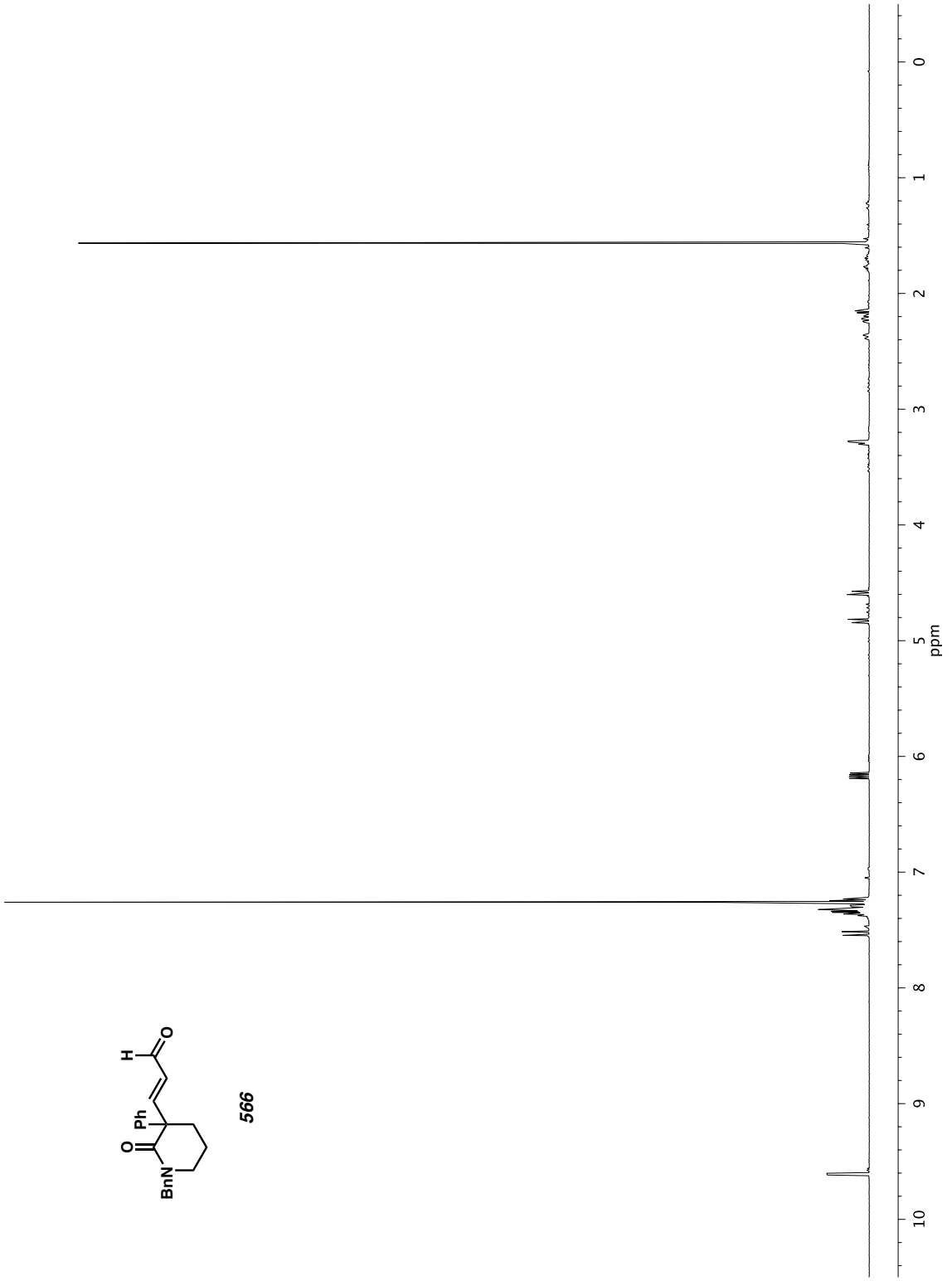


Figure A11.136 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **566**.

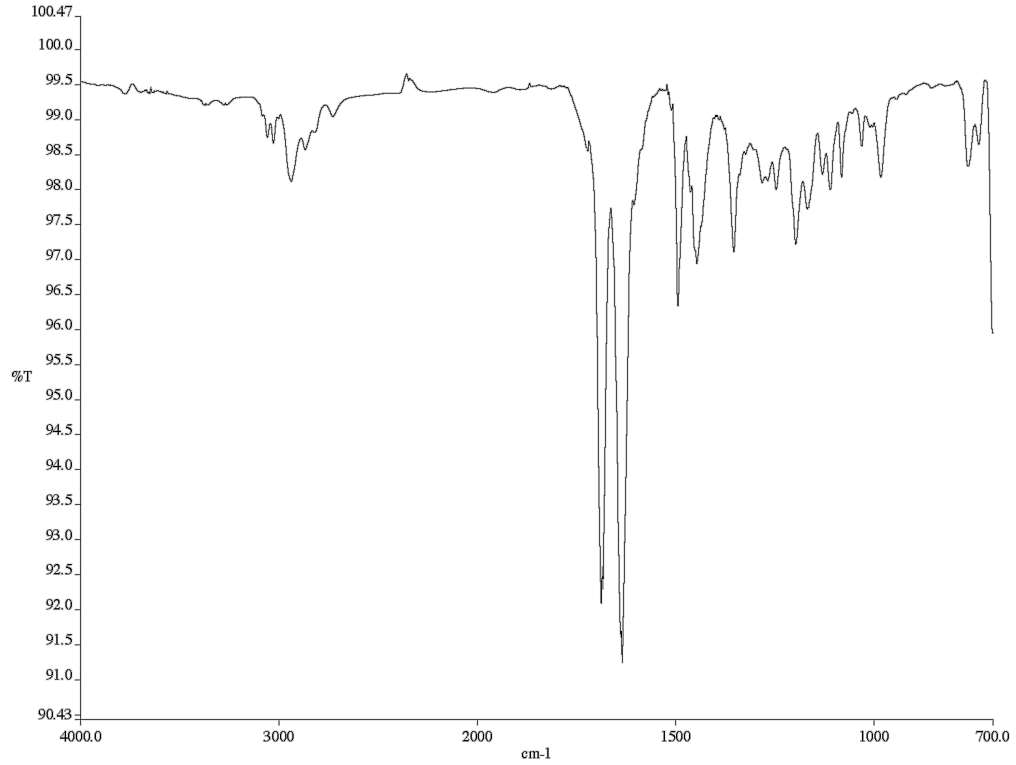


Figure A11.137 Infrared spectrum (thin film/NaCl) of compound **566**.

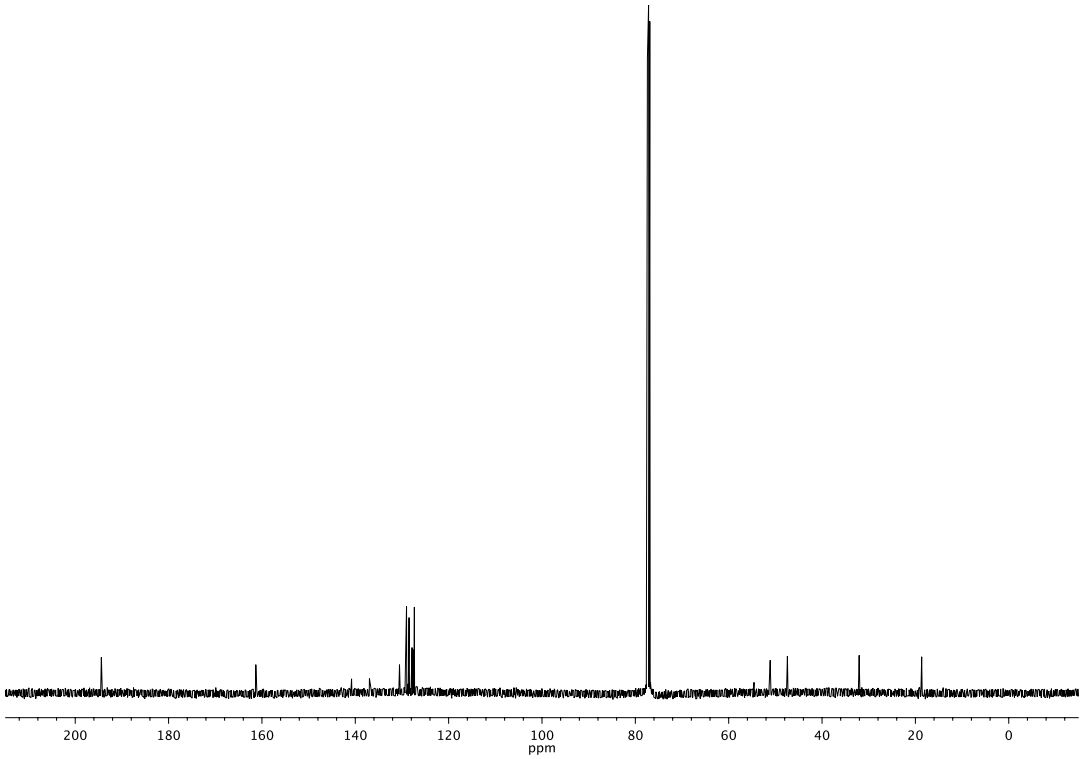


Figure A11.138 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **566**.

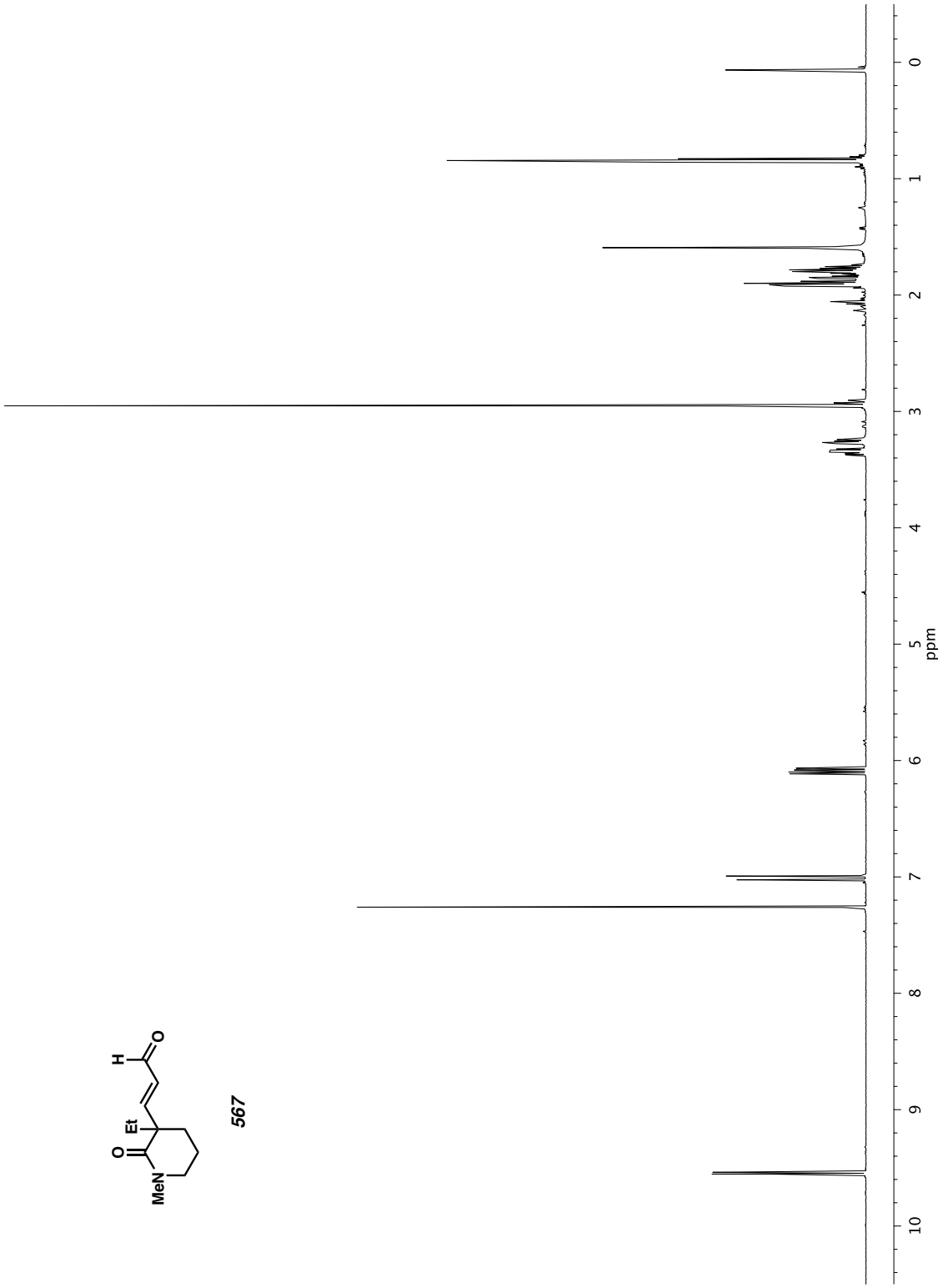


Figure A11.139 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **567**.

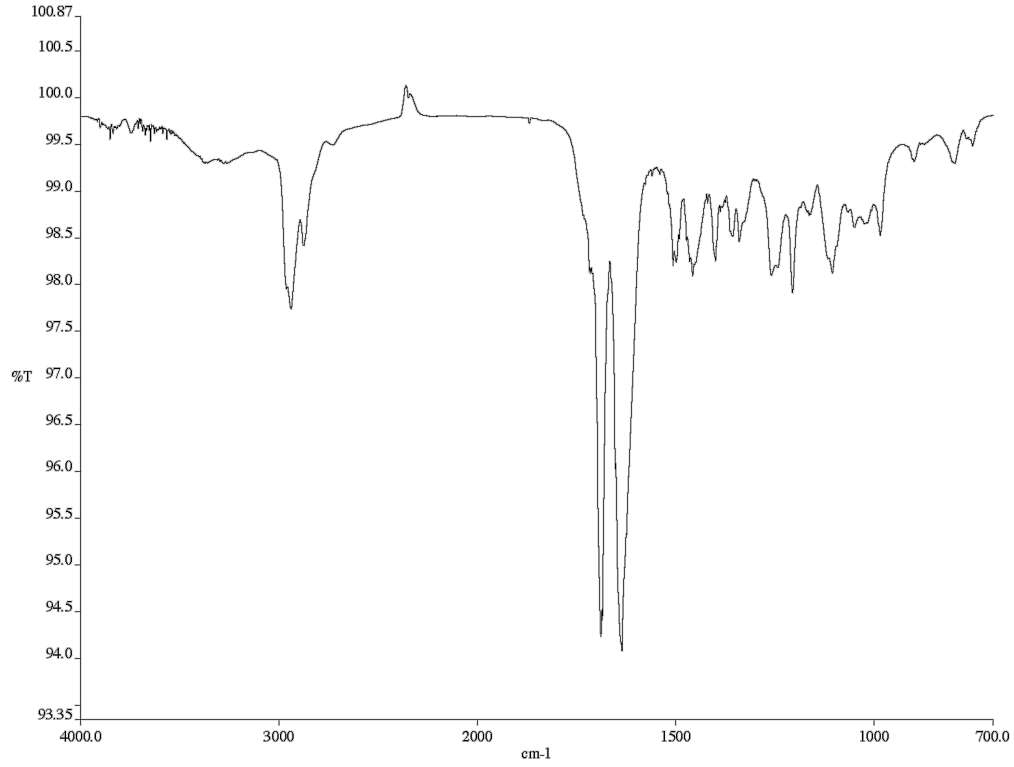


Figure A11.140 Infrared spectrum (thin film/NaCl) of compound **567**.

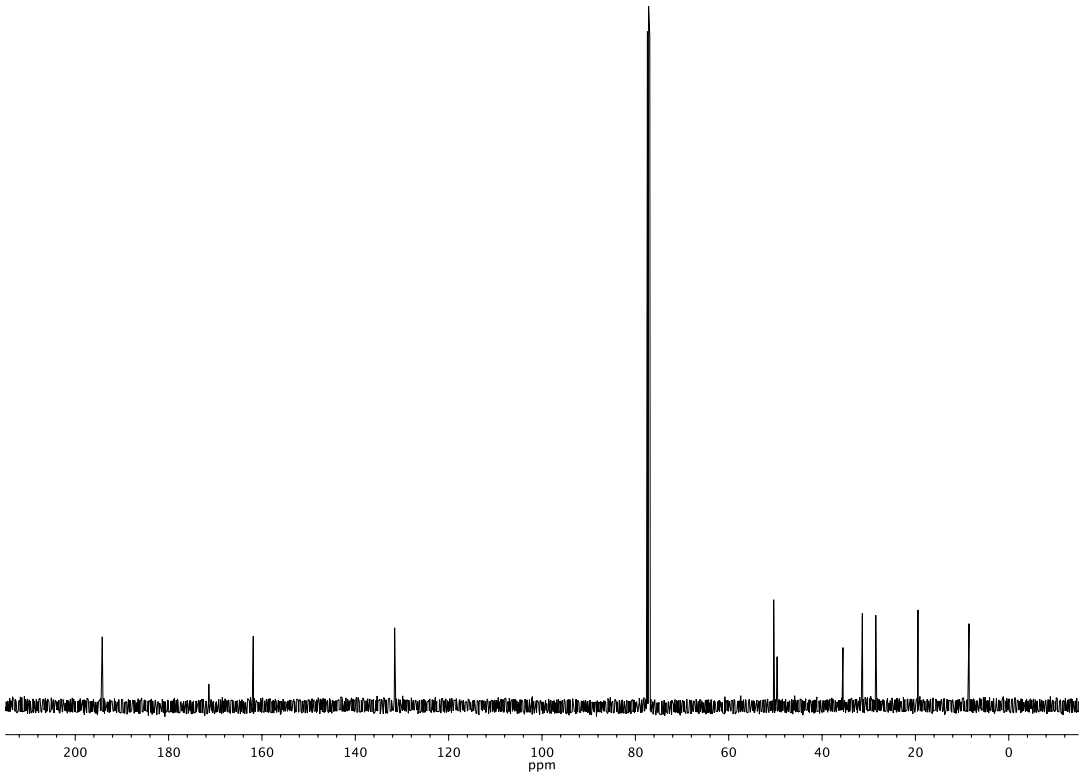


Figure A11.141 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **567**.

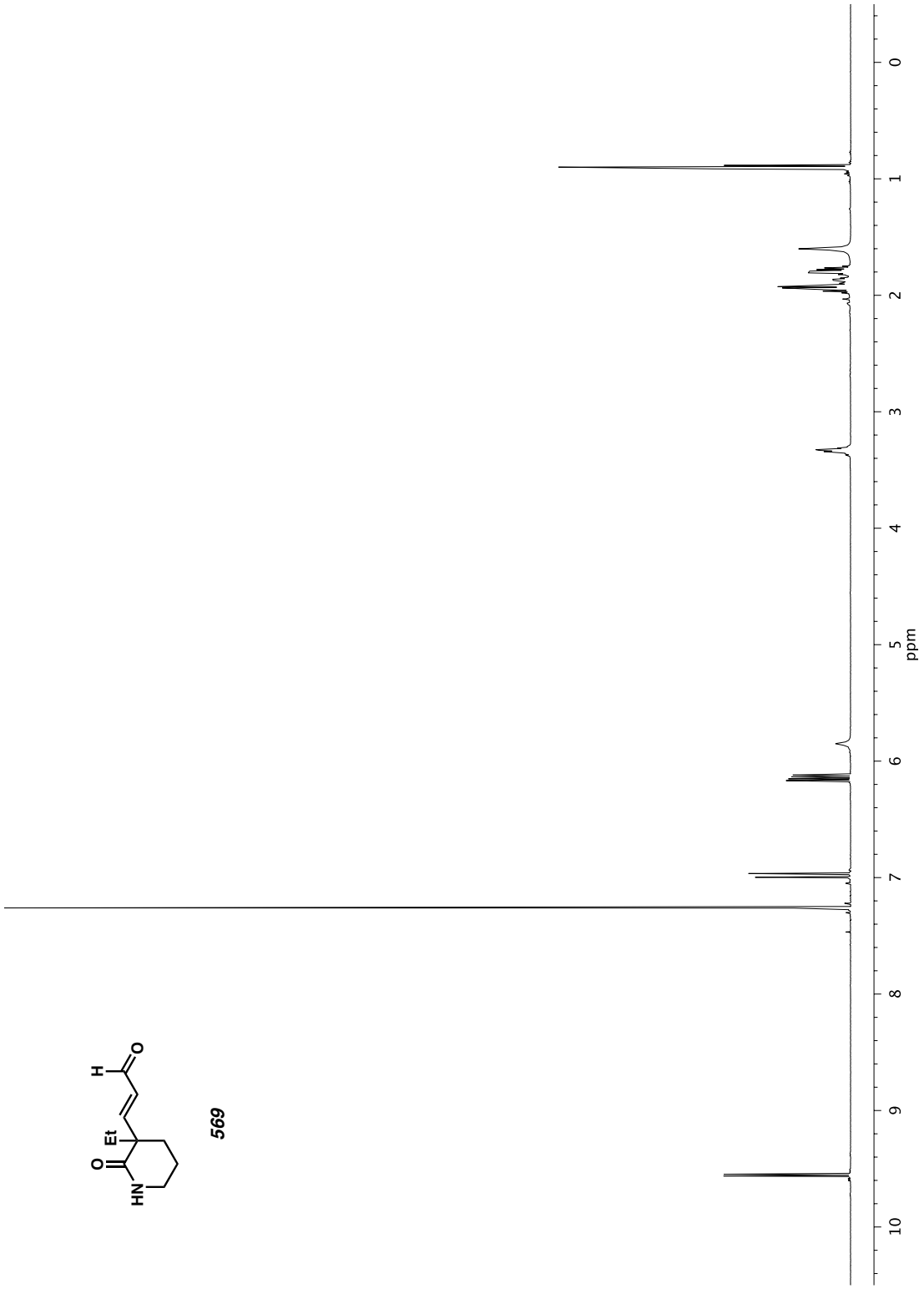


Figure A11.142 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **569**.

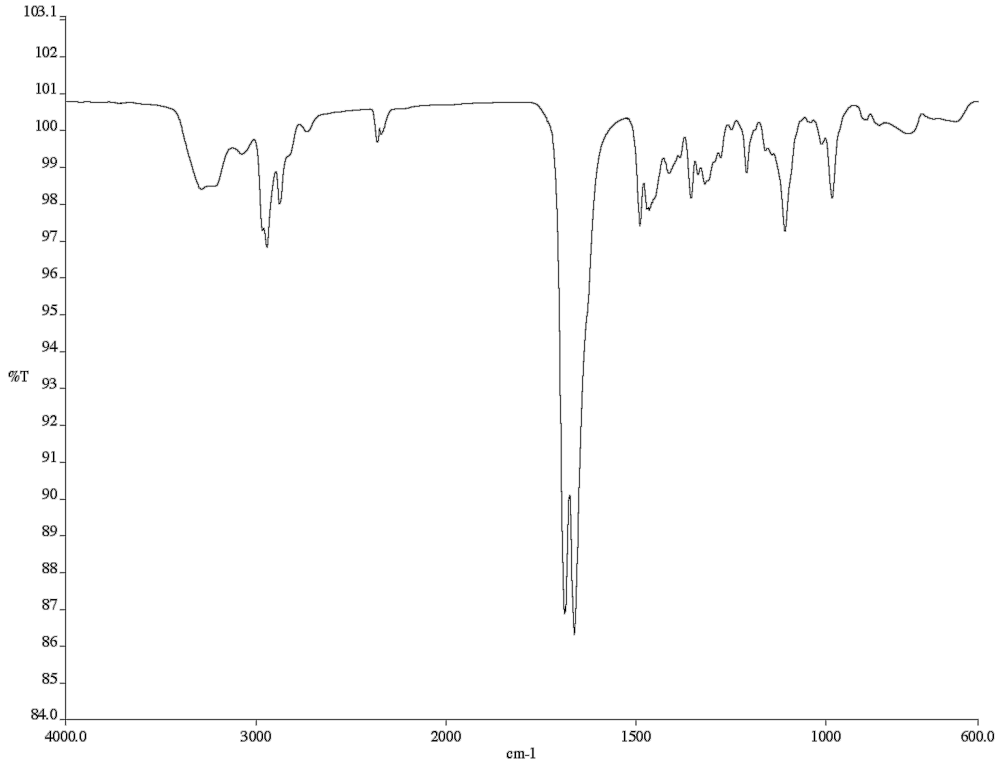


Figure A11.143 Infrared spectrum (thin film/NaCl) of compound **569**.

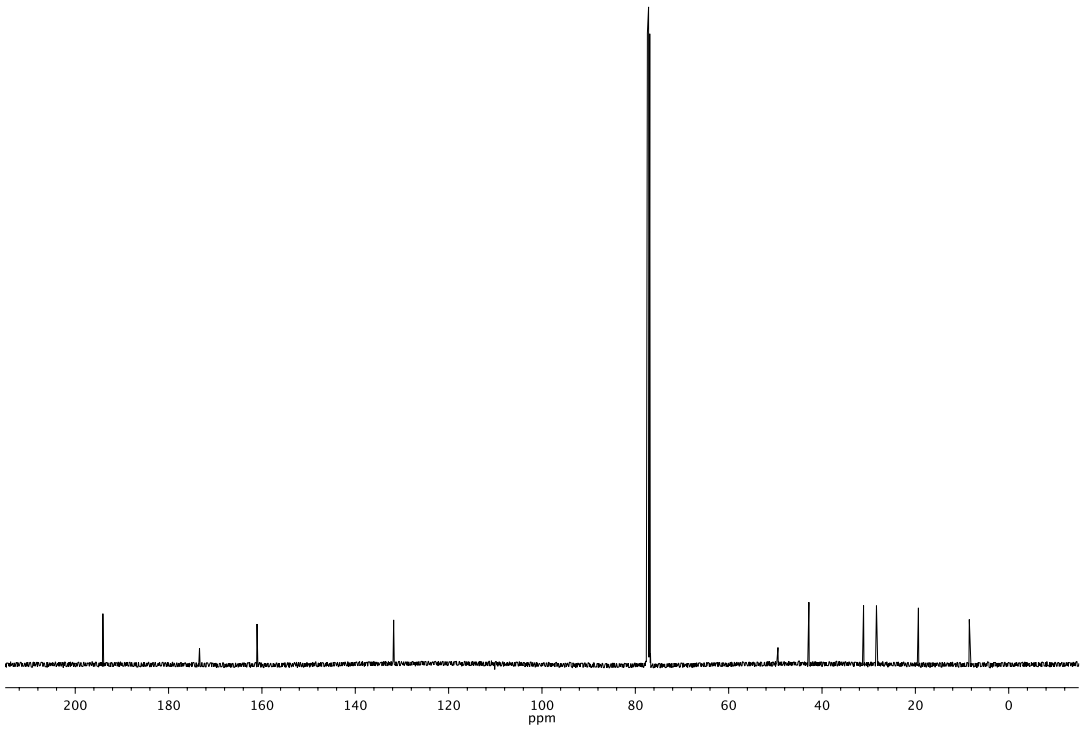


Figure A11.144 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **569**.

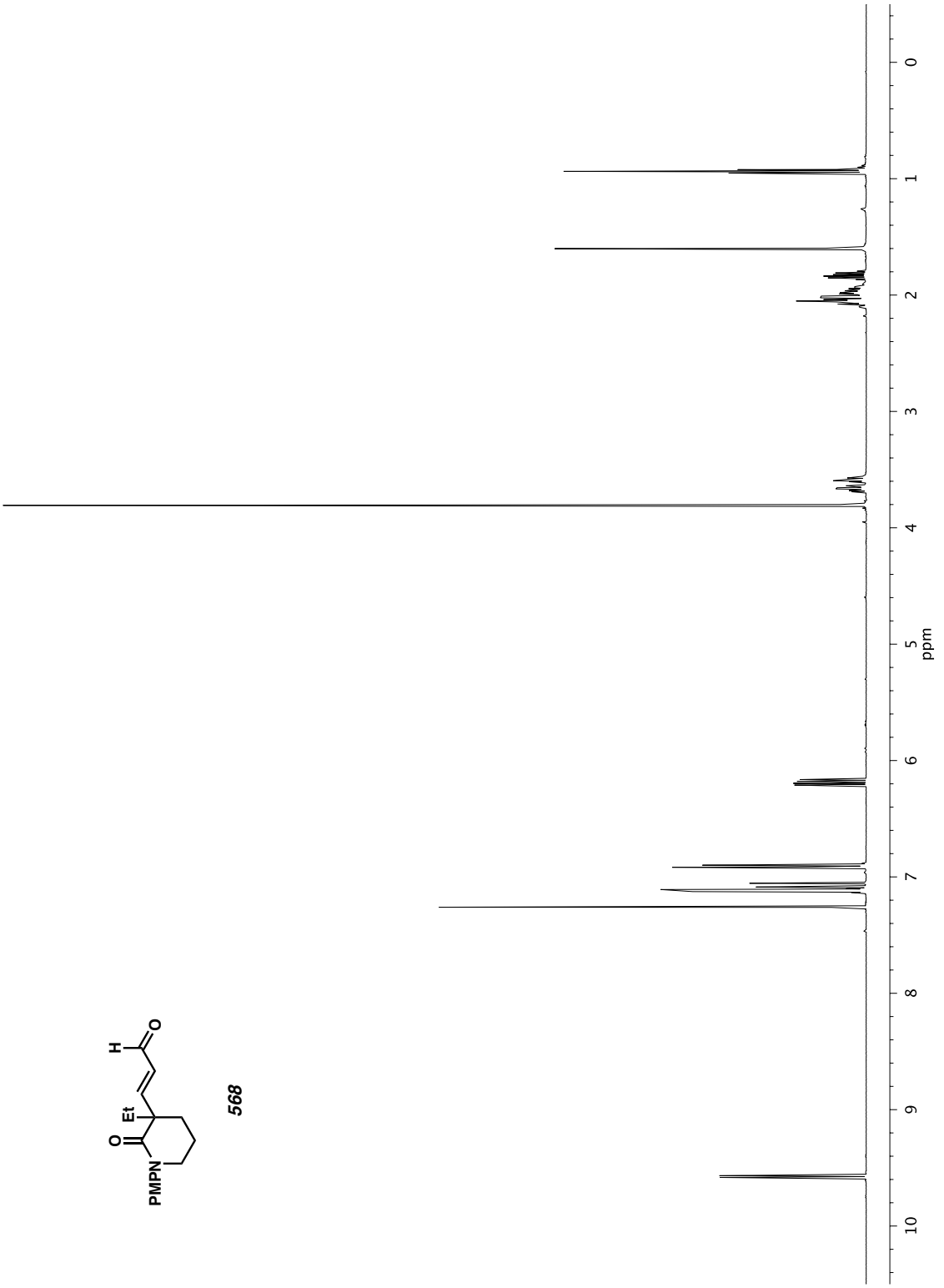


Figure A11.145 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **568**.

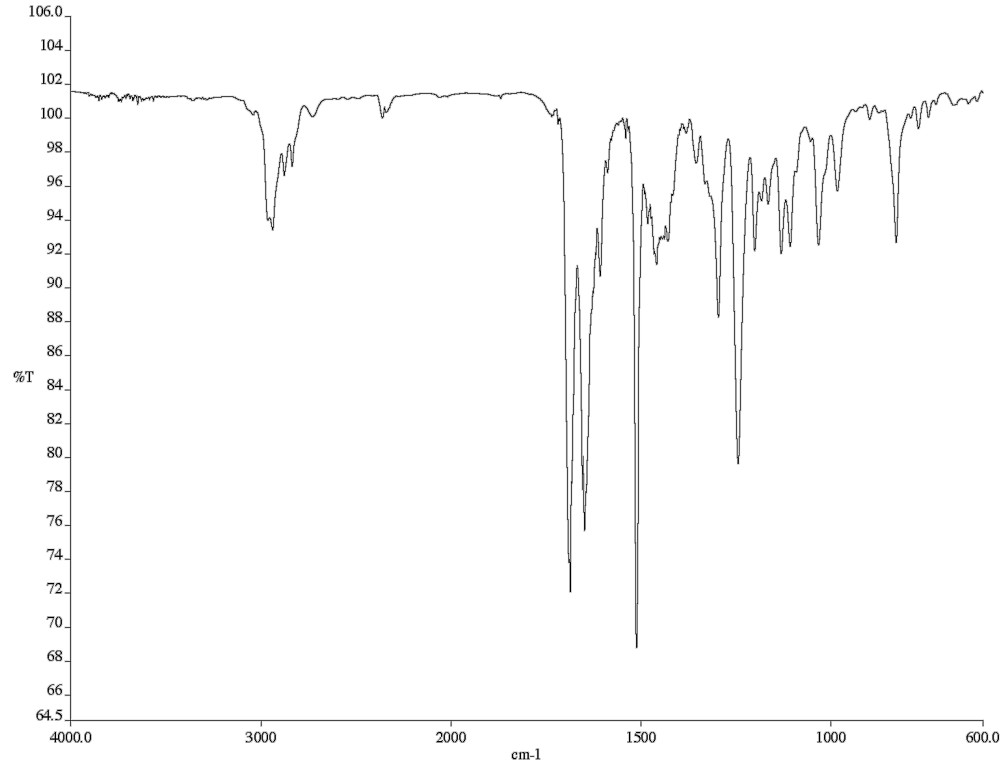


Figure A11.146 Infrared spectrum (thin film/NaCl) of compound **568**.

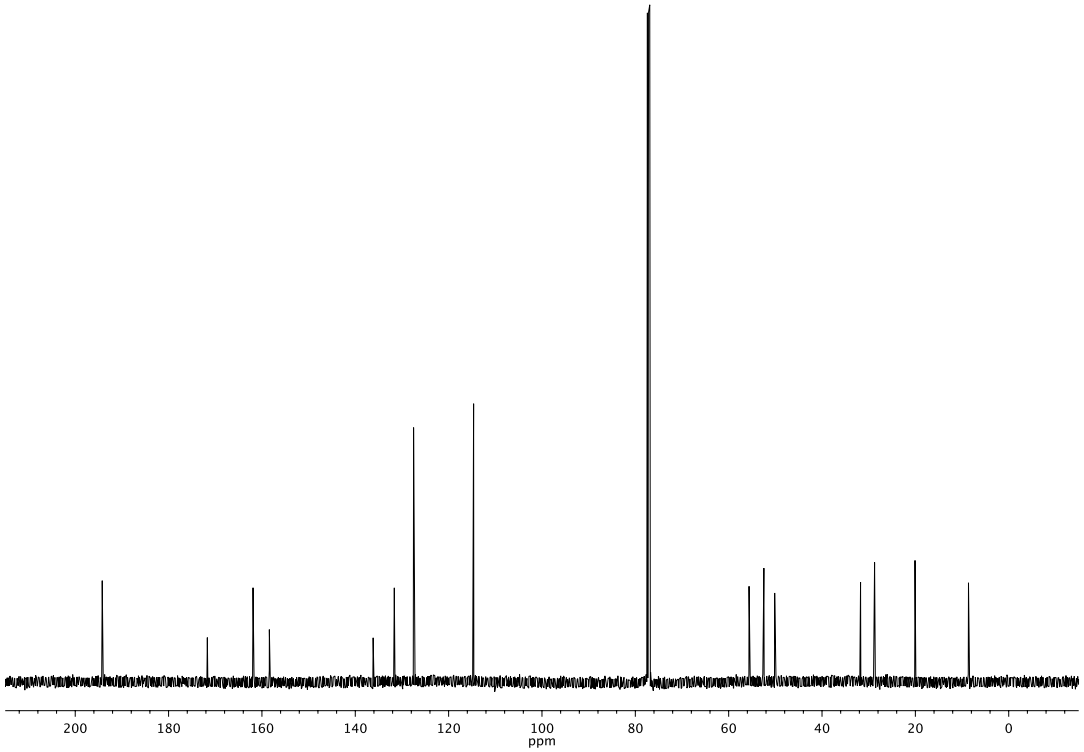


Figure A11.147 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **568**.

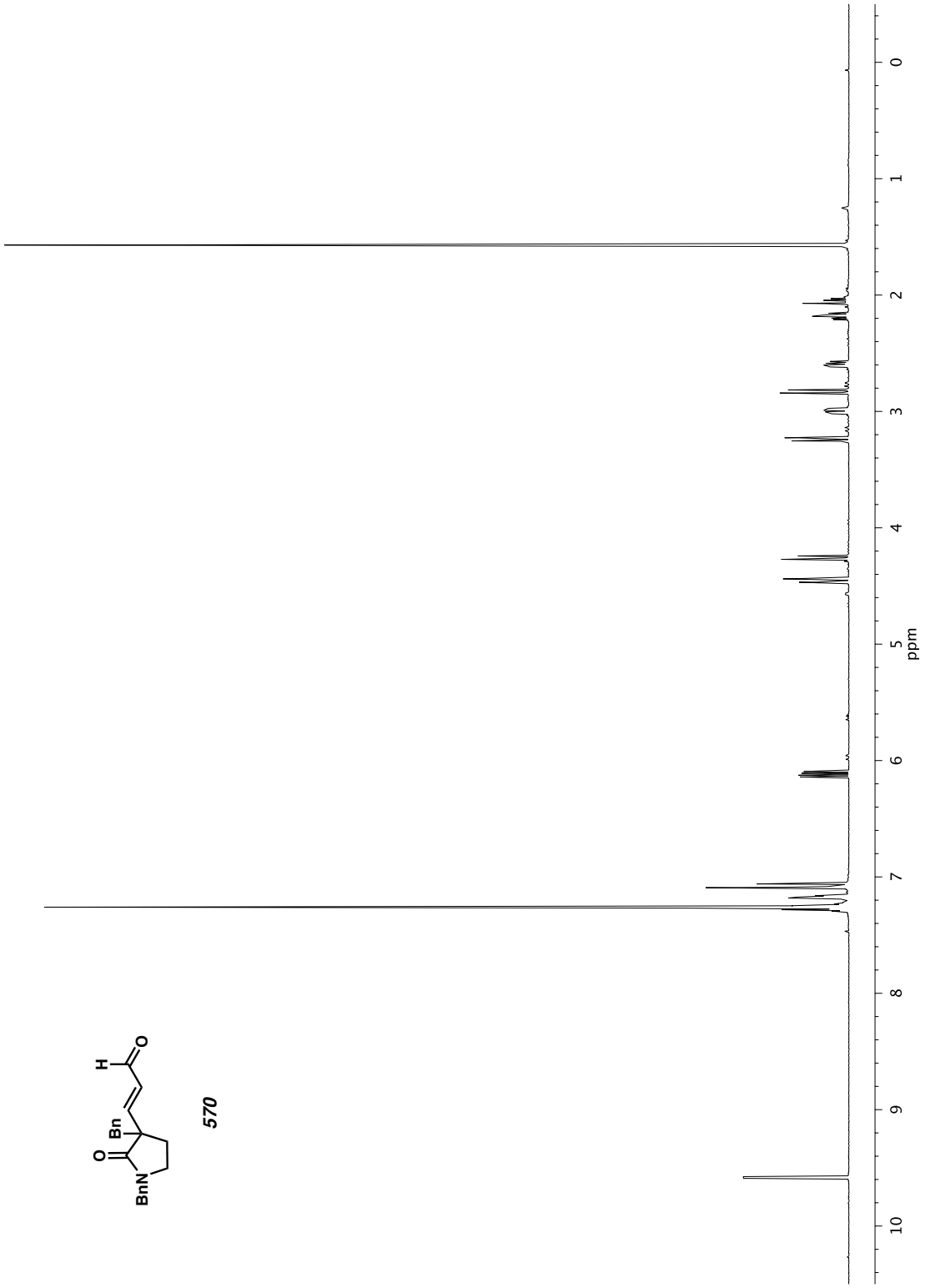


Figure A11.148 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **570**.

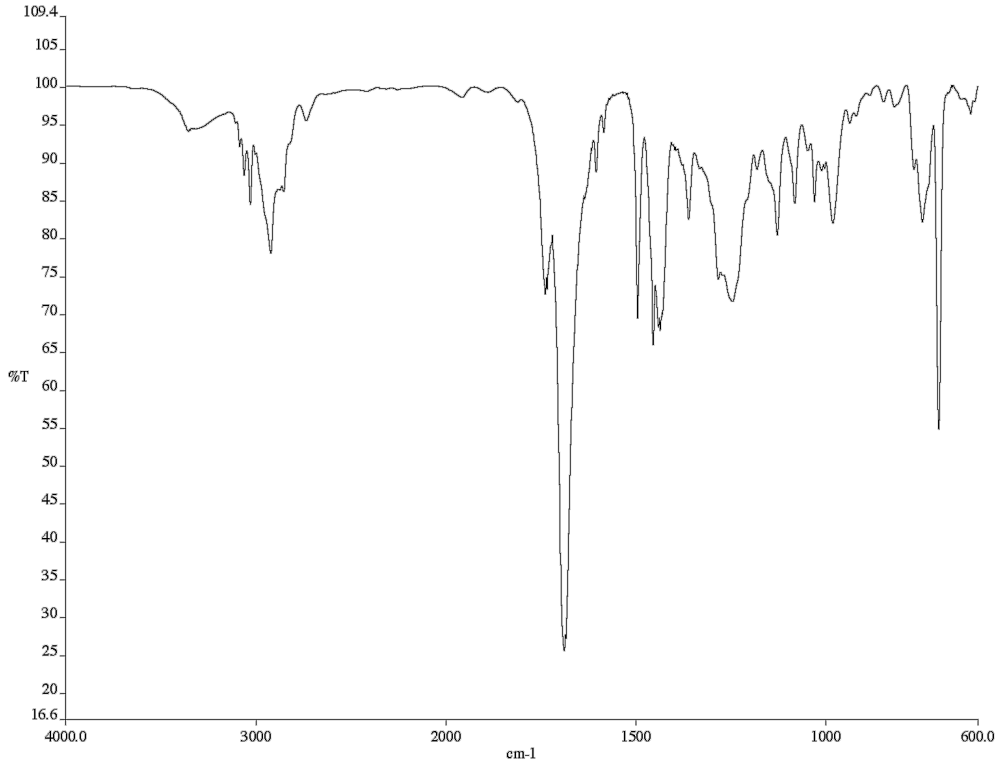


Figure A11.149 Infrared spectrum (thin film/NaCl) of compound **570**.

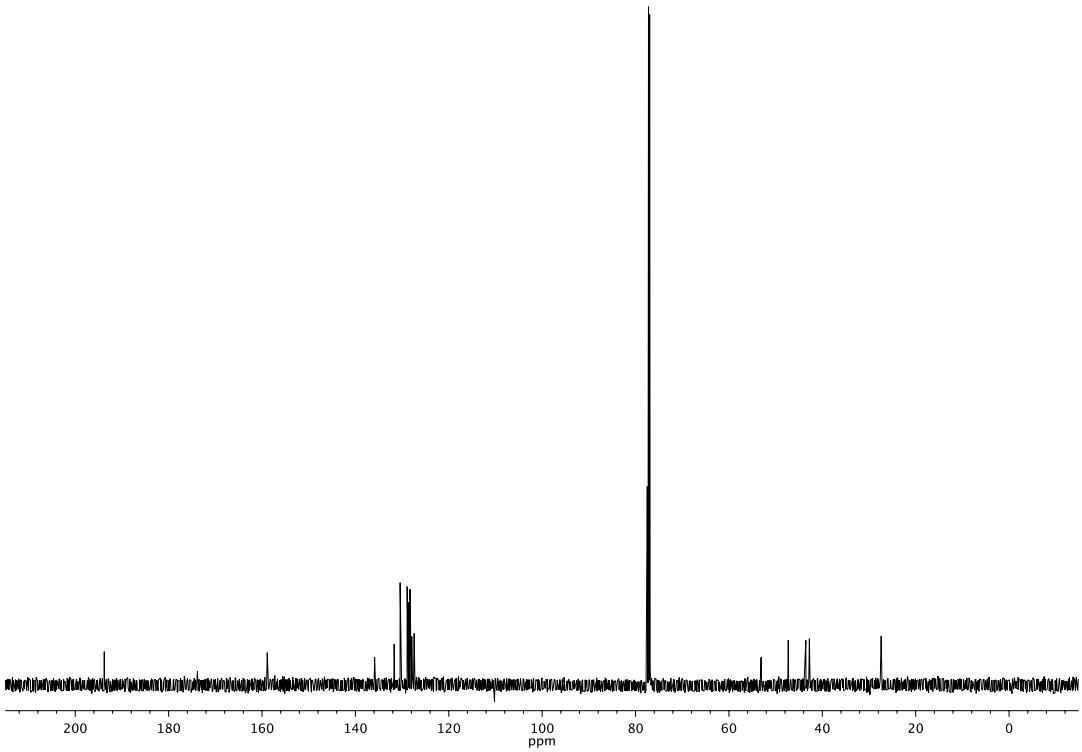


Figure A11.150 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **570**.

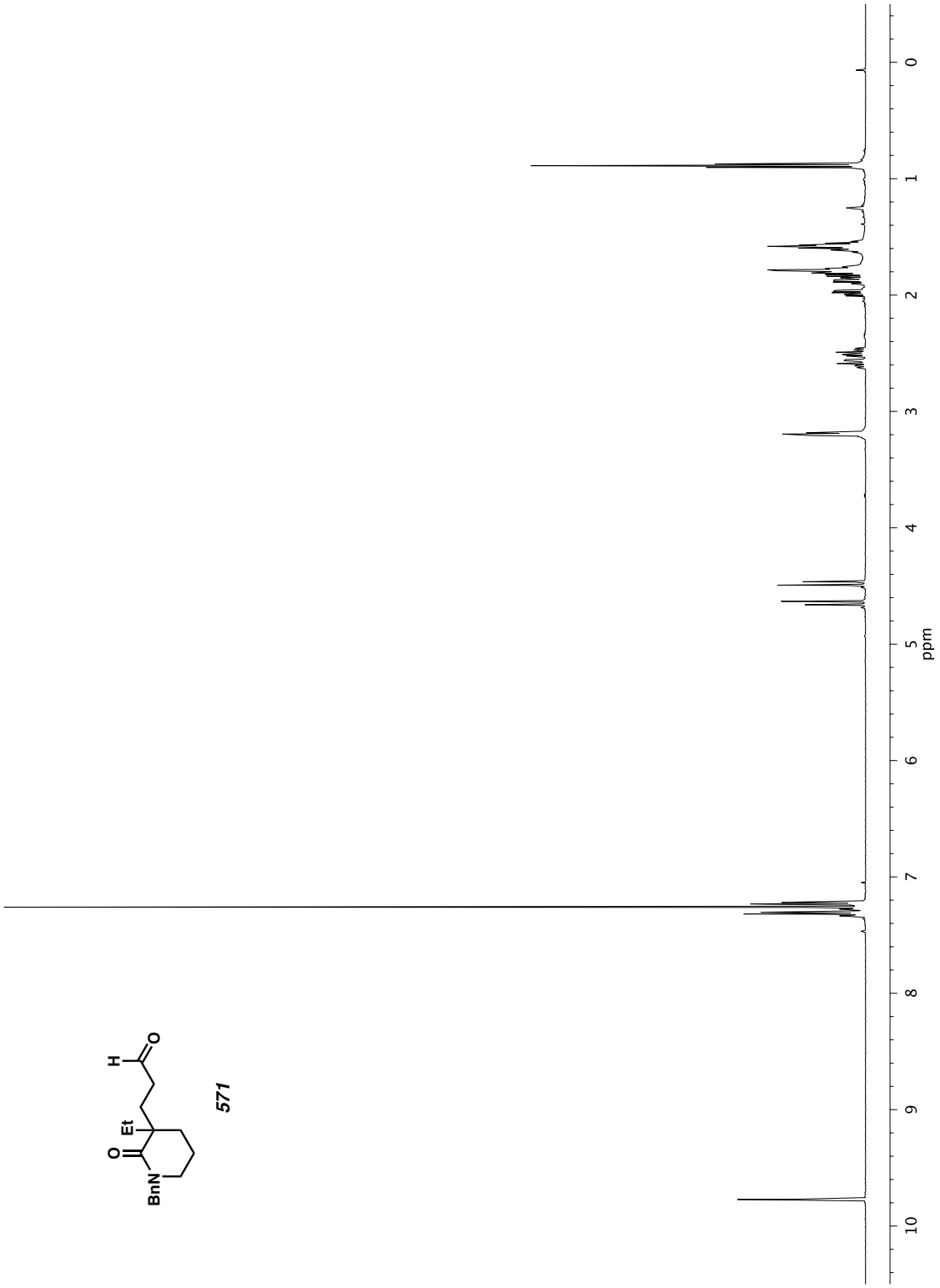


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Figure A11.151 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **571**.

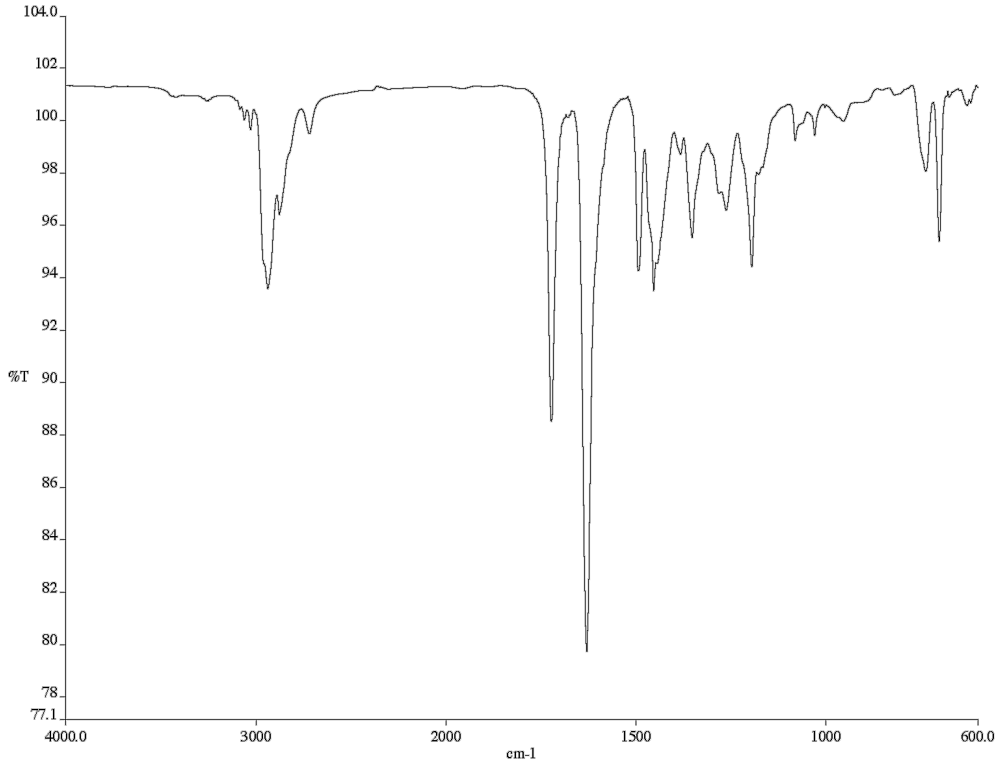


Figure A11.152 Infrared spectrum (thin film/NaCl) of compound **571**.

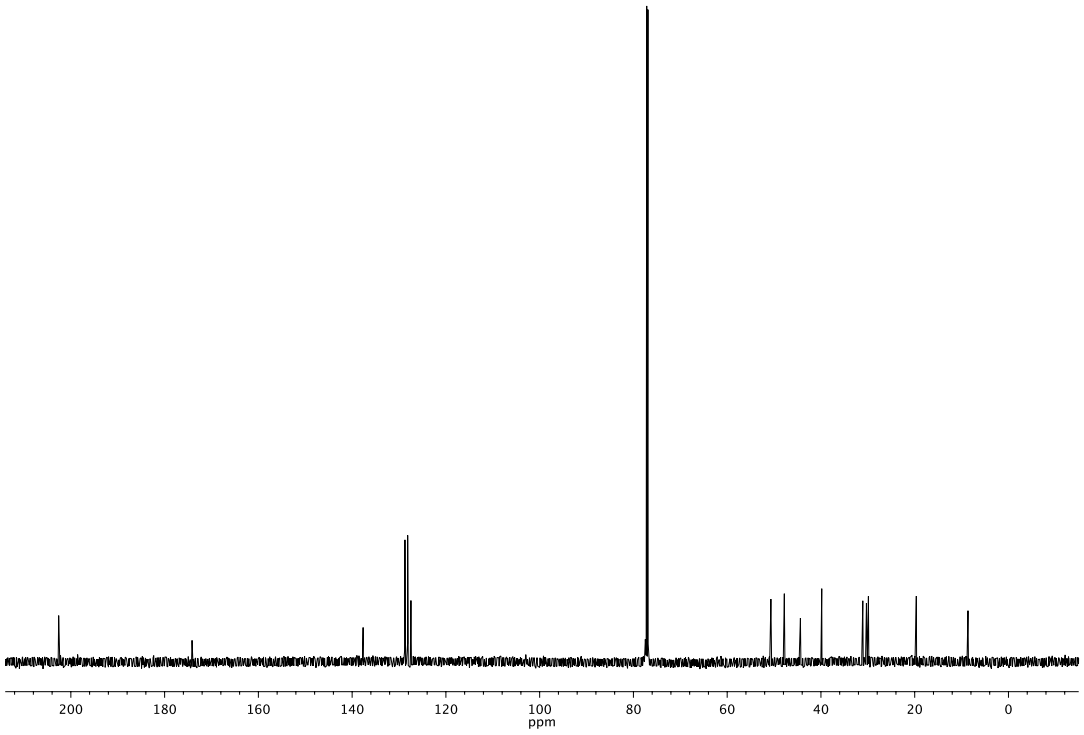


Figure A11.153 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **571**.

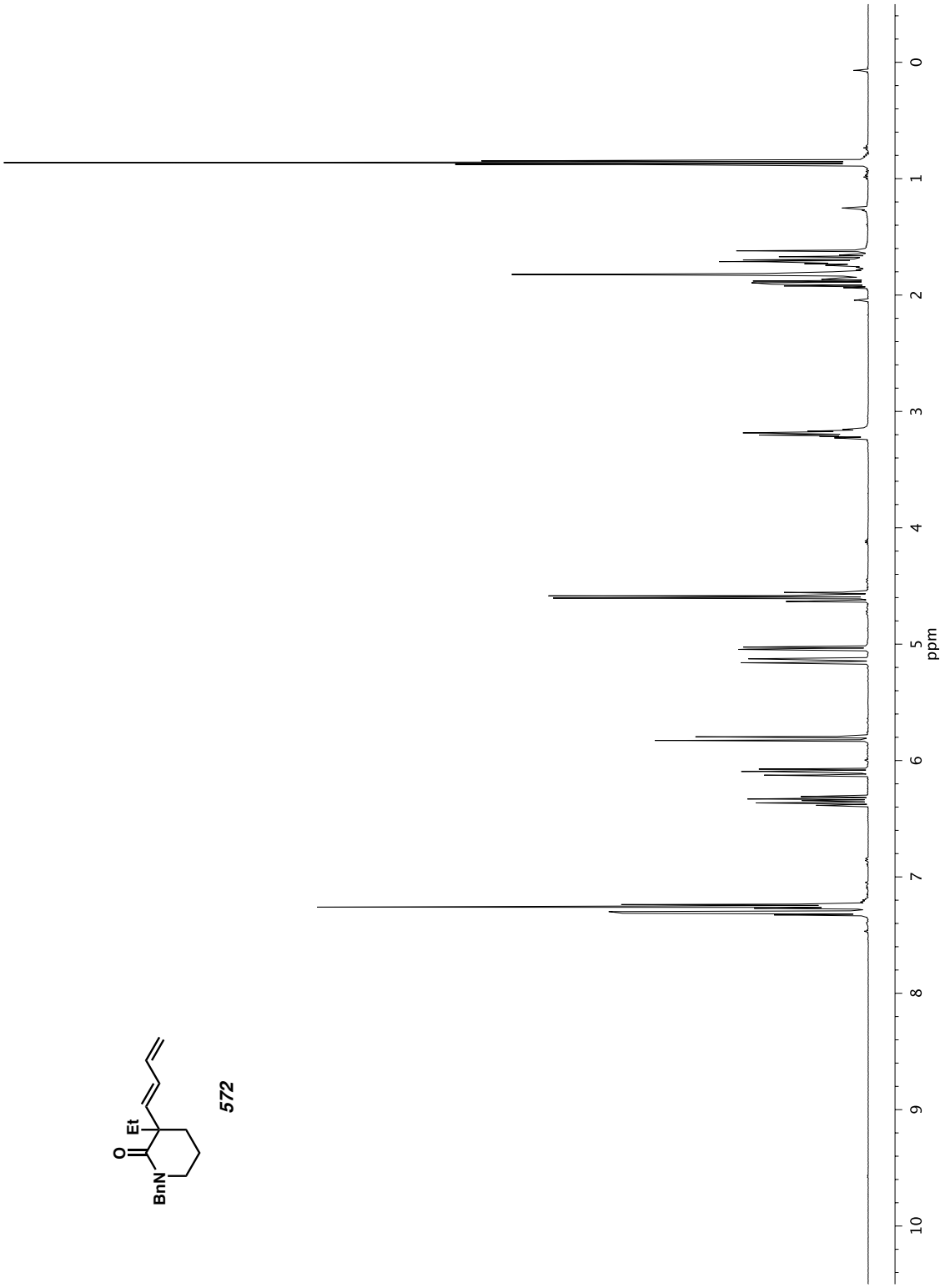


Figure A11.154 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **572**.

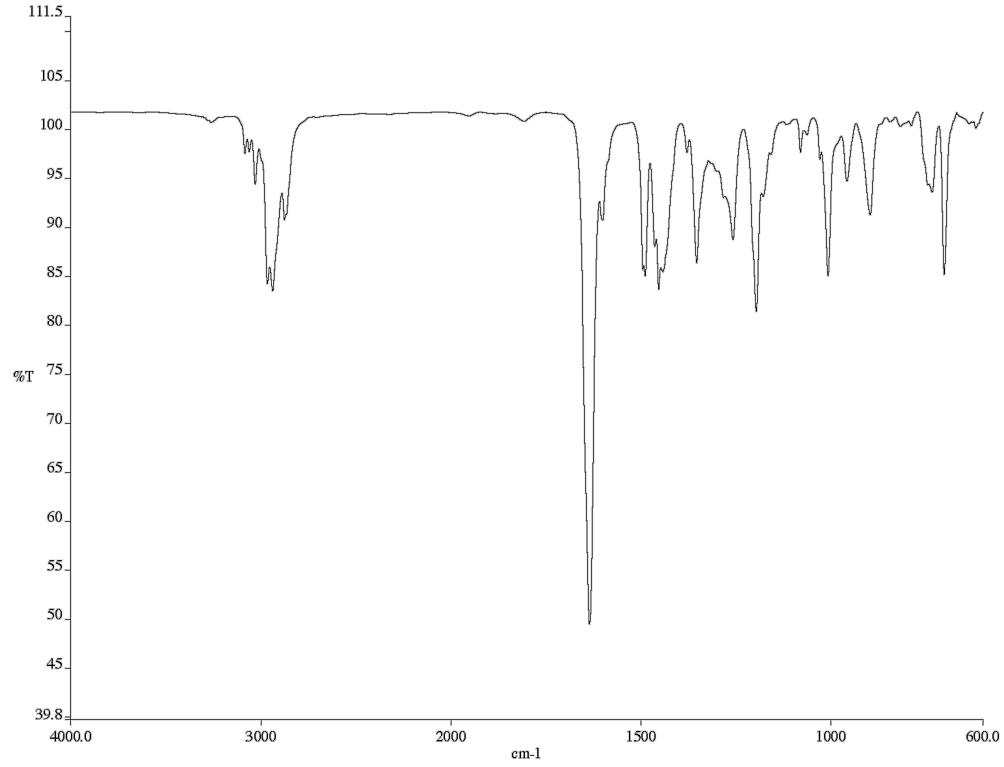


Figure A11.155 Infrared spectrum (thin film/NaCl) of compound **572**.

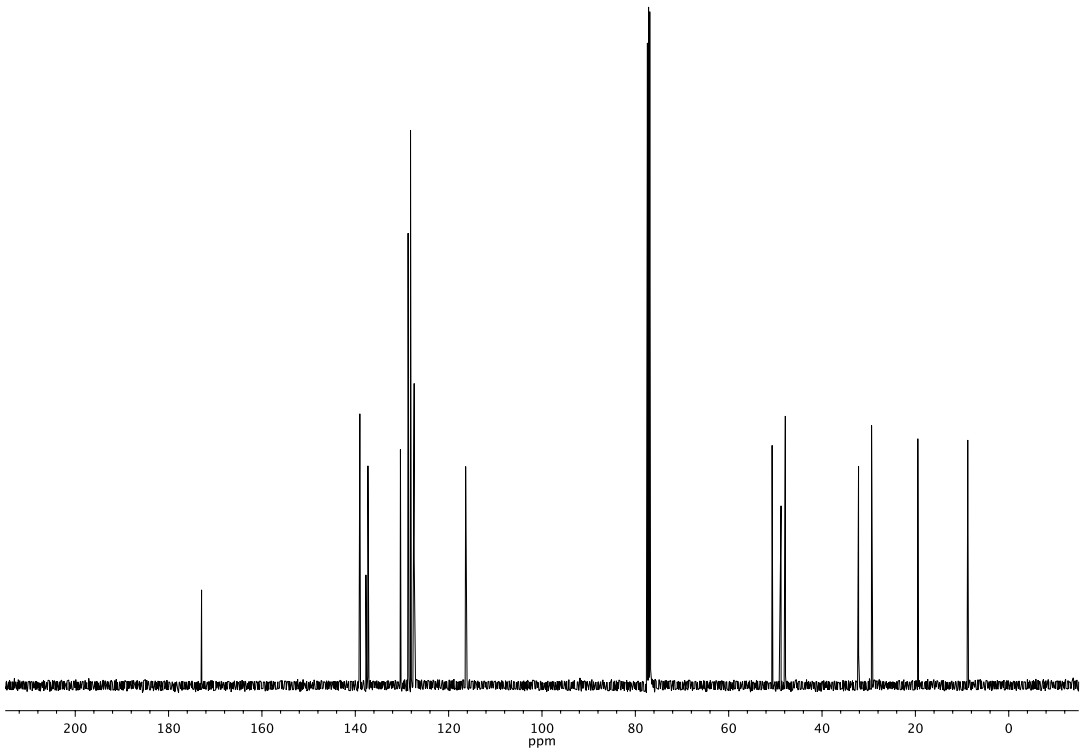


Figure A11.156 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **572**.

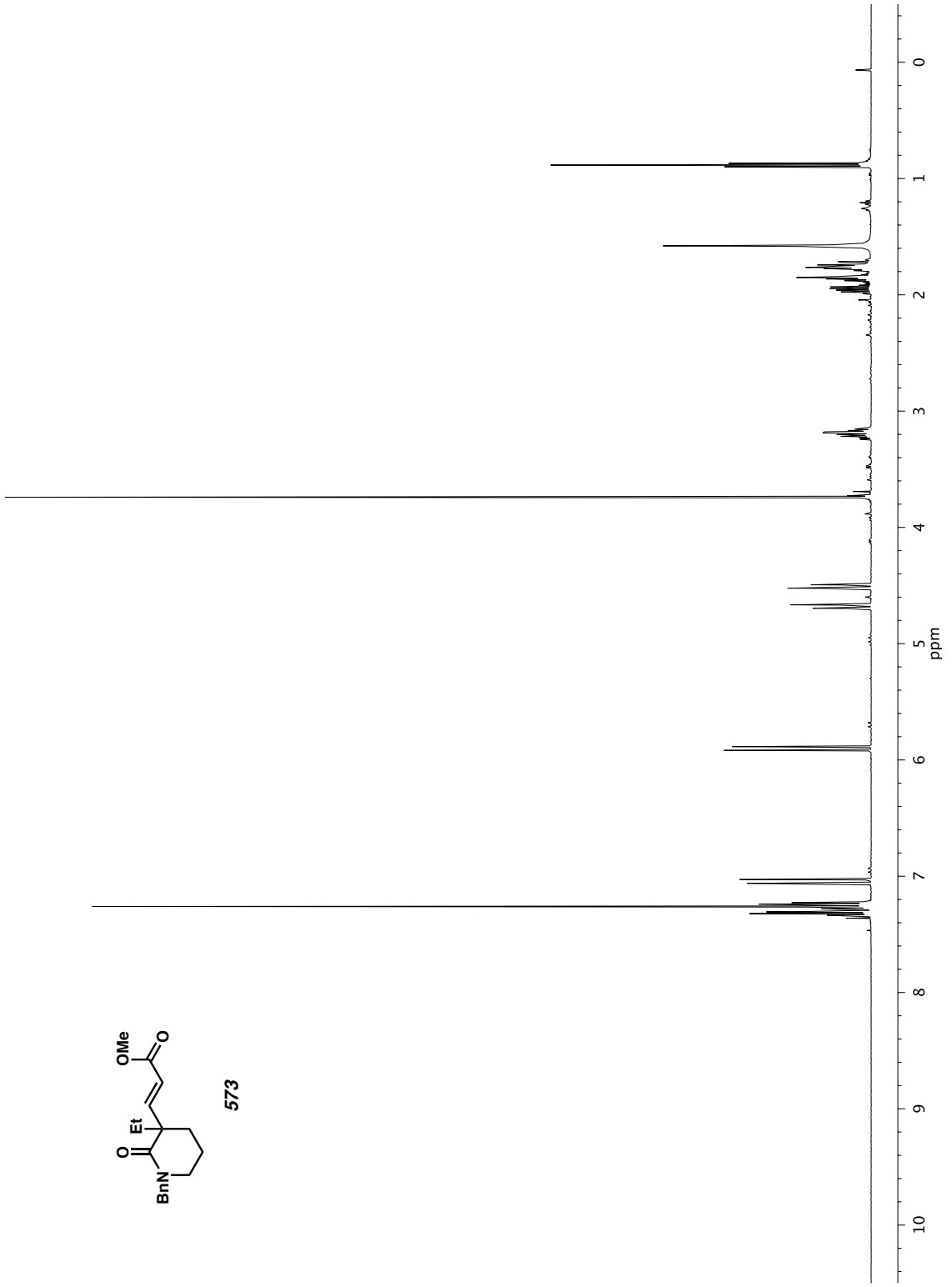


Figure A11.157 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **573**.

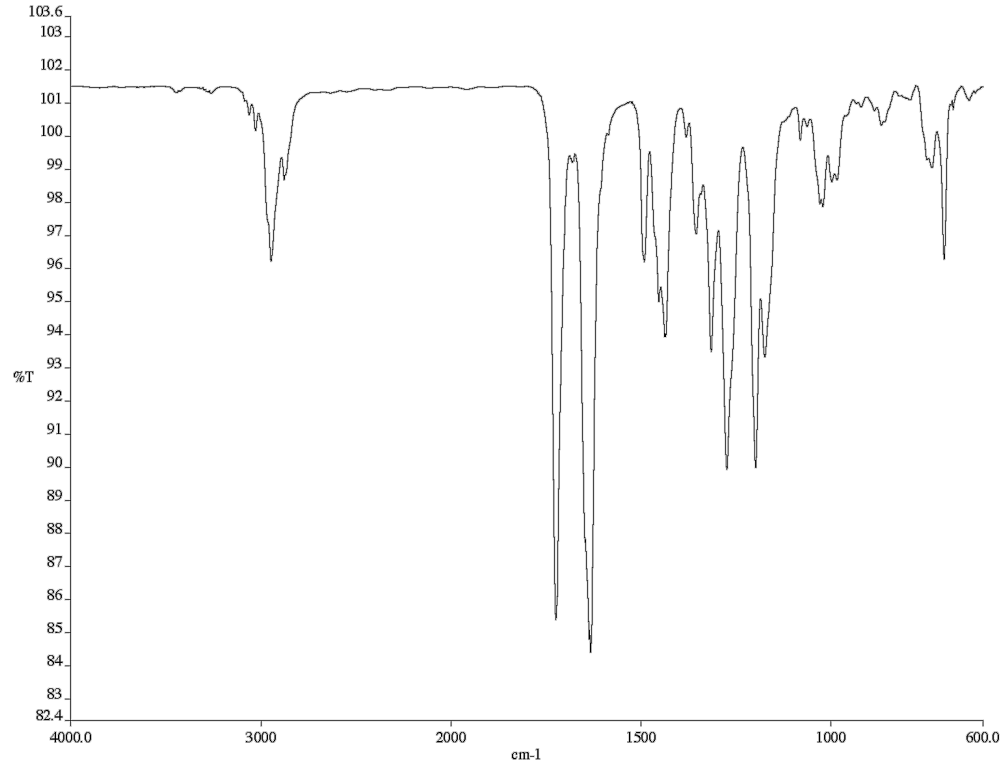


Figure A11.158 Infrared spectrum (thin film/NaCl) of compound **573**.

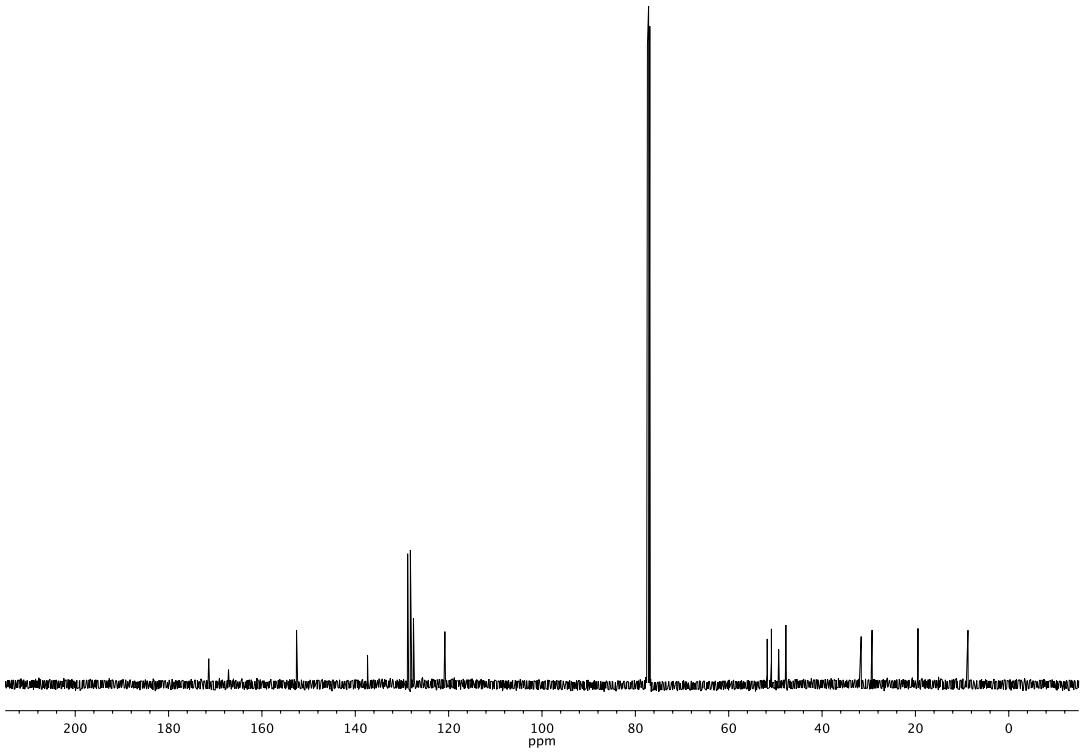


Figure A11.159 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **573**.

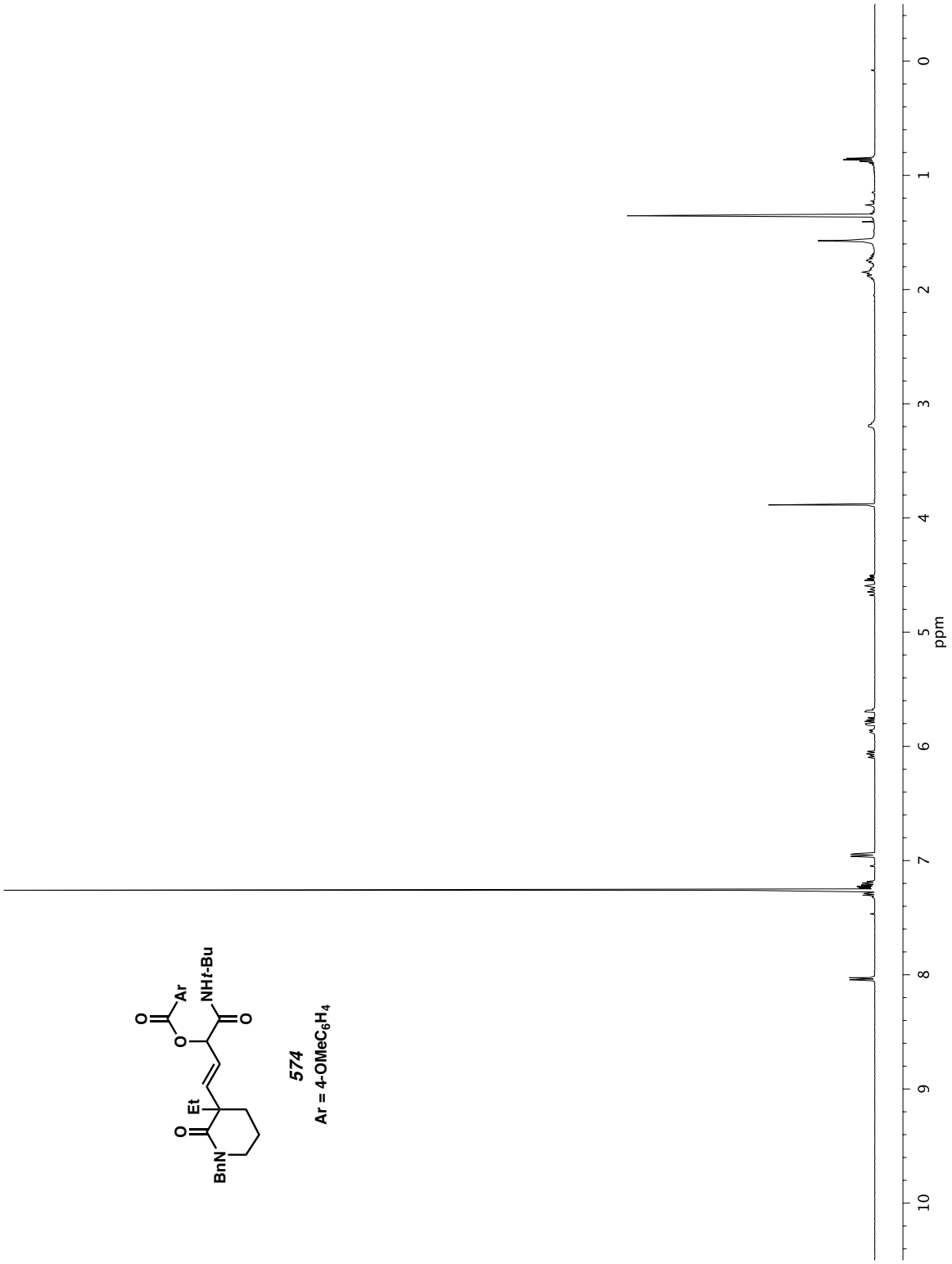


Figure A11.160 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **574**.

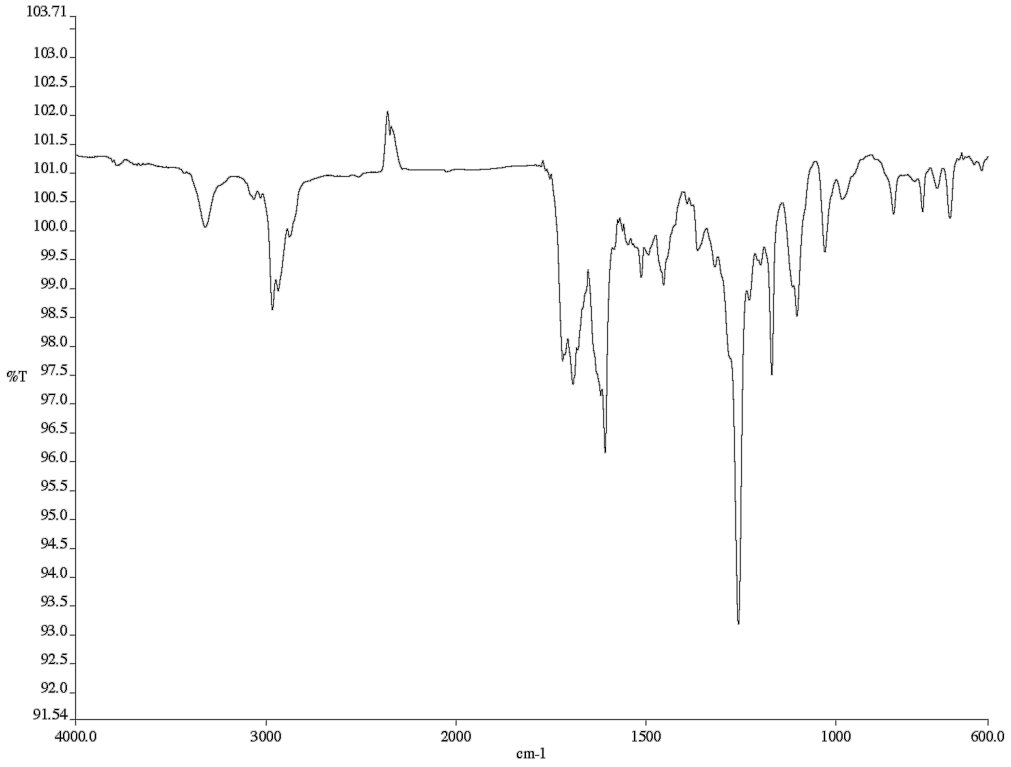


Figure A11.161 Infrared spectrum (thin film/NaCl) of compound **574**.

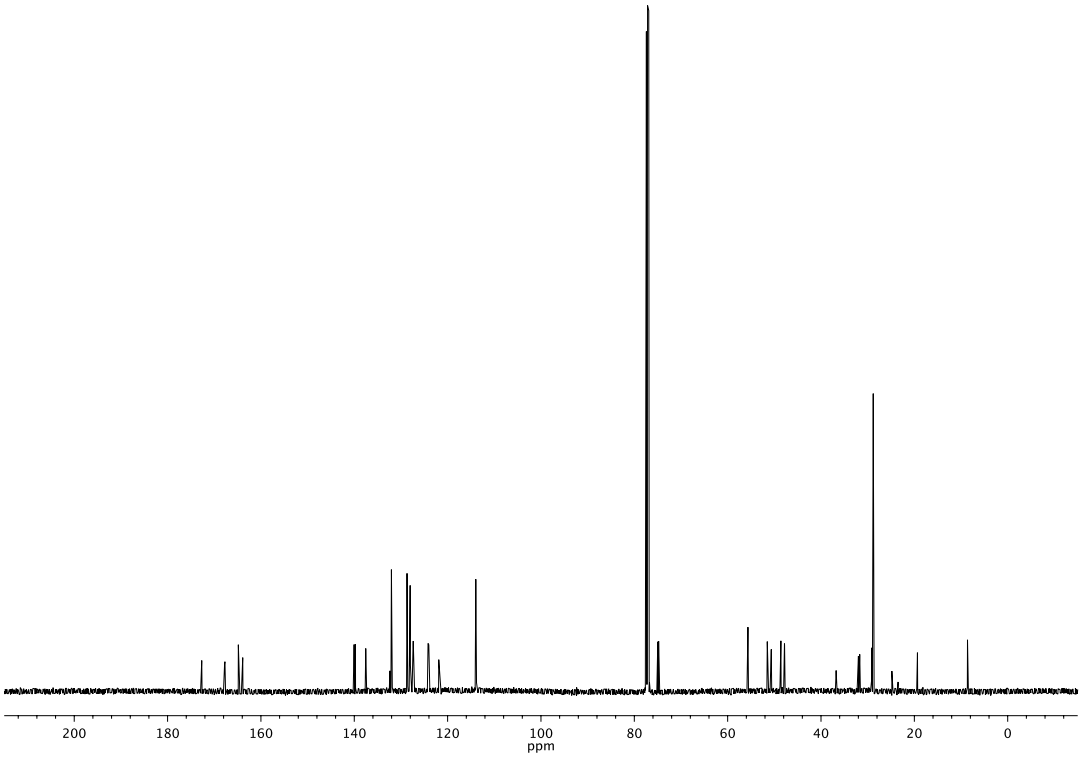


Figure A11.162 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **574**.

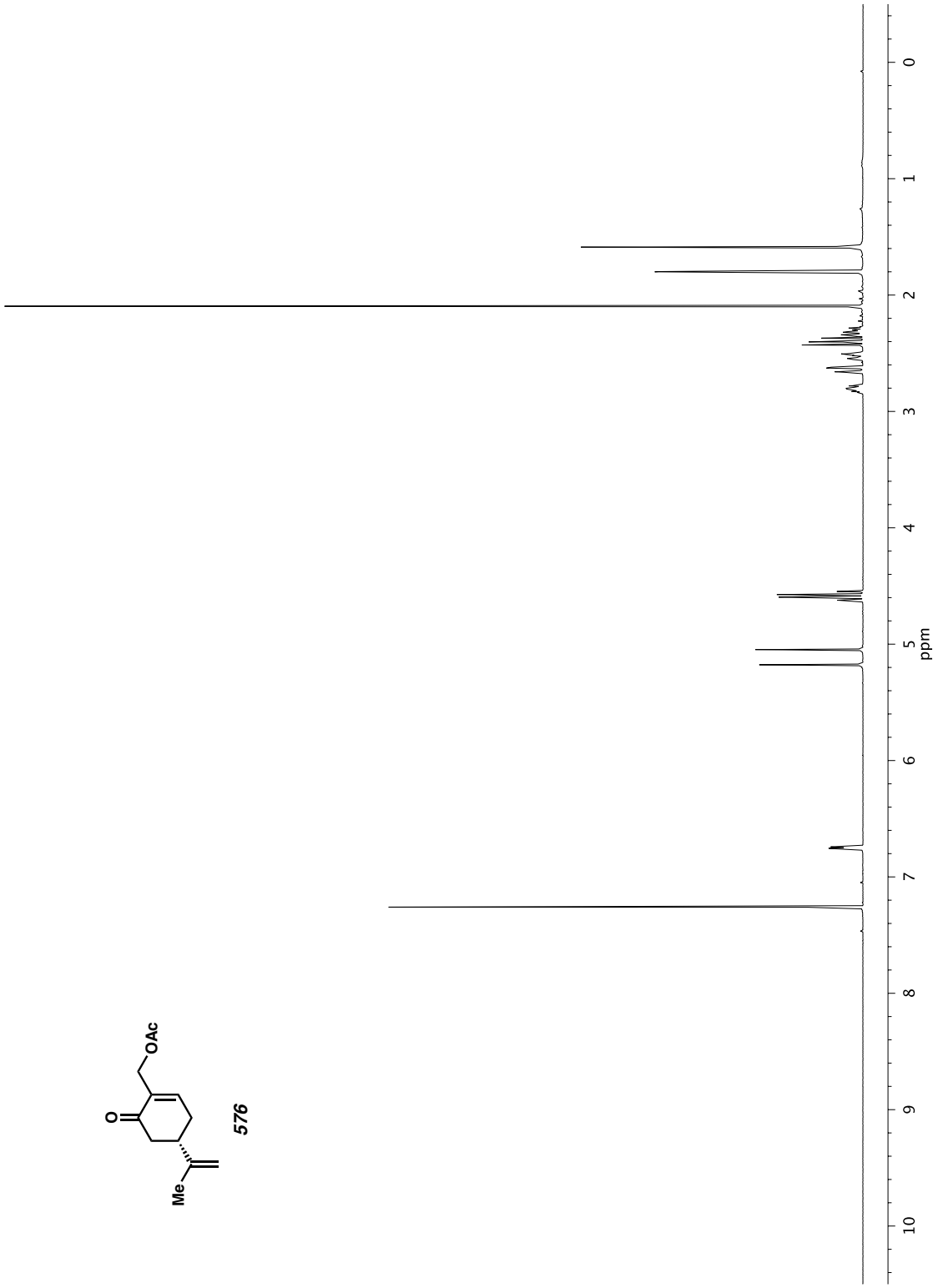


Figure A11.163 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **576**.

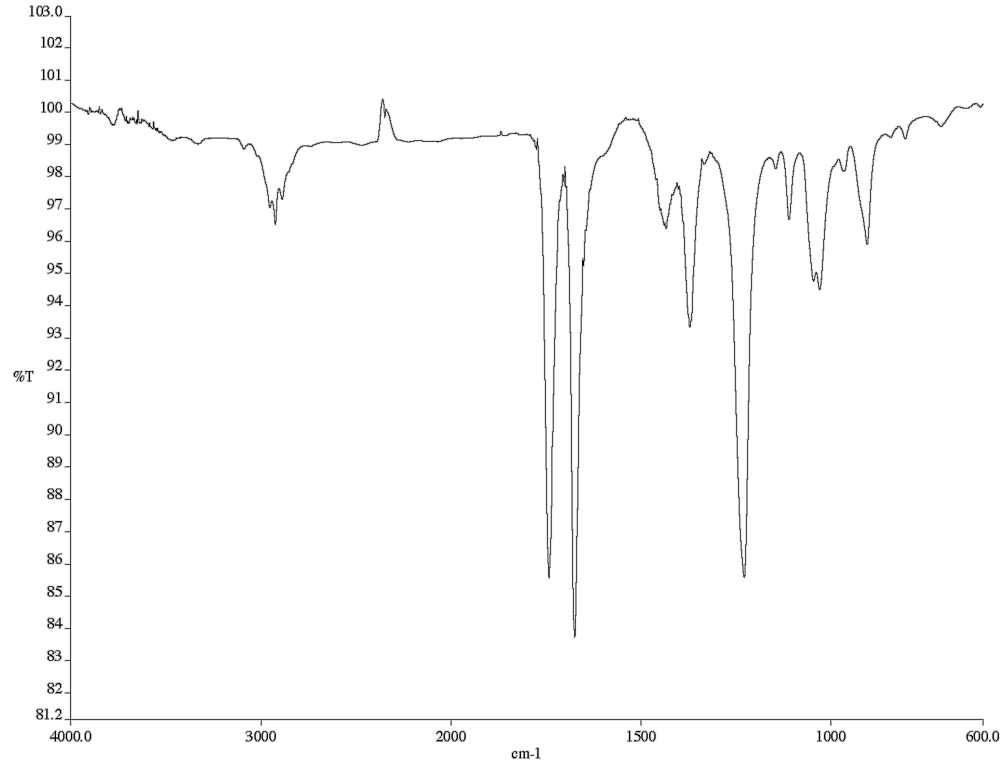


Figure A11.164 Infrared spectrum (thin film/NaCl) of compound **576**.

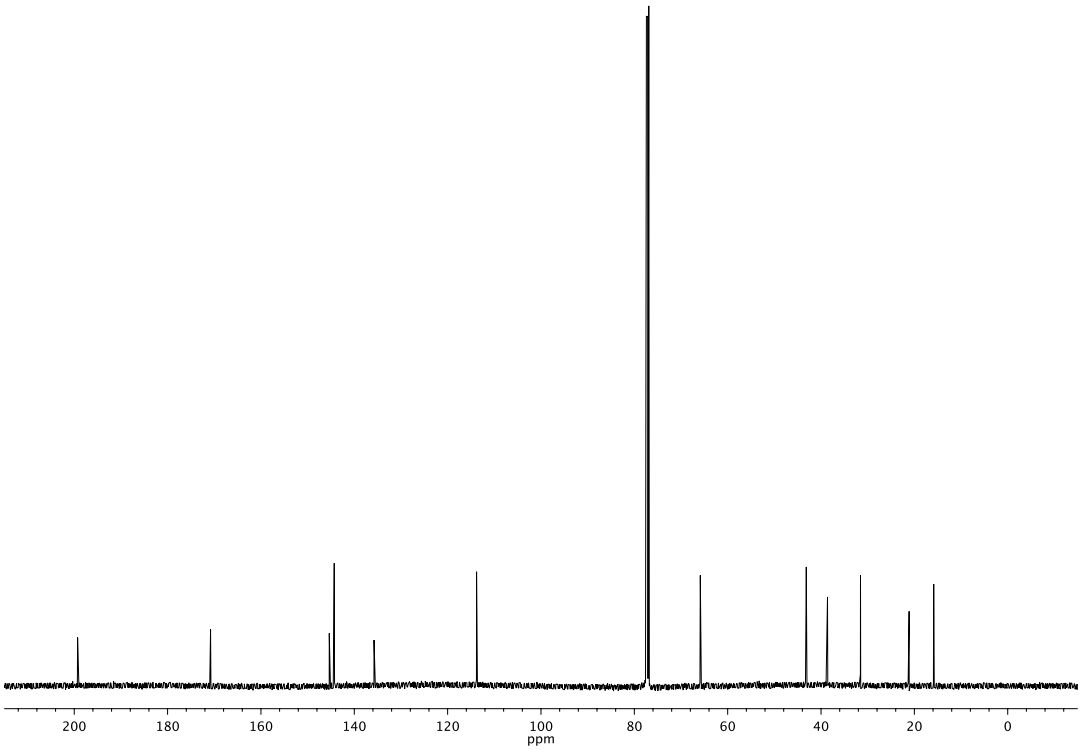


Figure A11.165 ^{13}C NMR (126 MHz, $CDCl_3$) of compound **576**.

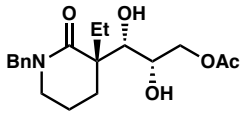
APPENDIX 12

X-Ray Crystallography Report Relevant to Chapter 5:

Palladium(II)-Catalyzed Allylic C–H Oxidation of Hindered Substrates

Featuring Tunable Selectivity Over Extent of Oxidation

A12.1 X-RAY CRYSTAL STRUCTURE ANALYSIS OF DIOL 555



555

Contents

Figure A12.1.1 X-ray crystal structure of diol ***555***

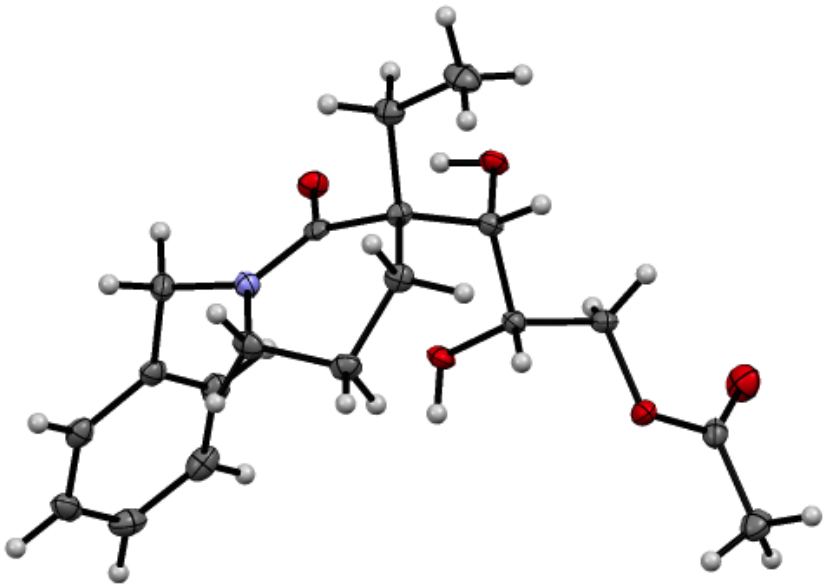


*Table A12.1.1 Experimental details for X-ray structure determination of diol **555***

Low-temperature diffraction data (ϕ-and ω-scans) were collected on a Bruker AXS D8 VENTURE KAPPA diffractometer coupled to a PHOTON 100 CMOS detector with Cu K_α radiation (λ = 1.54178 Å) from an IμS micro-source for the structure of diol **555**. The structure was solved by direct methods using SHELXS and refined against F^2 on all data by full-matrix least squares with SHELXL-2014 using established refinement techniques. All non-hydrogen atoms were refined anisotropically. Unless otherwise noted, all hydrogen atoms were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms they are linked to (1.5 times for methyl groups).

Diol **555** crystallizes in the orthorhombic space group $P2_12_12_1$ with one molecule in the asymmetric unit. The coordinates for the hydrogen atoms bound to O2 and O3 were located in the difference Fourier synthesis and refined semi-freely with the help of a restraint on the O-H distance (0.84(4) Å).

*Table A12.1.2 Crystal data and structure refinement for diol **555***

CCDC deposition number	1057691
Empirical formula	C19 H27 N O5
Formula weight	349.41
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$

Table A12.1.2 *(cont'd)*

Unit cell dimensions	a = 7.8598(4) Å	a= 90°.
	b = 11.0342(6) Å	b= 90°.
	c = 20.5656(13) Å	g = 90°.
Volume	1783.58(17) $Å^3$	
Z	4	
Density (calculated)	1.301 Mg/m^3	
Absorption coefficient	0.767 mm^{-1}	
F(000)	752	
Crystal size	0.150 x 0.100 x 0.100 mm^3	
Theta range for data collection	4.299 to 74.529°.	
Index ranges	-9<=h<=9, -8<=k<=13, -25<=l<=25	
Reflections collected	12461	
Independent reflections	3592 [R(int) = 0.0553]	
Completeness to theta = 67.679°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7538 and 0.6907	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3592 / 2 / 234	
Goodness-of-fit on F^2	1.056	
Final R indices [I>2sigma(I)]	R1 = 0.0368, wR2 = 0.0729	
R indices (all data)	R1 = 0.0470, wR2 = 0.0765	
Absolute structure parameter	0.00(14)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.182 and -0.201 $e.Å^{-3}$	

*Table A12.1.3 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for diol **555**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U(eq)
N(1)	3370(3)	3133(2)	986(1)	16(1)
C(13)	1612(3)	3420(2)	809(1)	18(1)
C(21)	831(3)	4438(2)	1206(1)	16(1)
C(22)	282(3)	5492(2)	901(1)	18(1)
C(23)	-554(3)	6393(2)	1254(1)	21(1)
C(24)	-825(3)	6248(2)	1914(1)	23(1)
C(25)	-244(3)	5205(2)	2224(1)	22(1)
C(26)	579(3)	4304(2)	1873(1)	19(1)
C(1)	3702(3)	2140(2)	1342(1)	14(1)
O(1)	2533(2)	1498(1)	1558(1)	17(1)
C(2)	5551(3)	1718(2)	1435(1)	13(1)
C(6)	5875(3)	1416(2)	2158(1)	14(1)
O(2)	4694(2)	530(1)	2395(1)	16(1)
C(7)	5905(3)	2505(2)	2618(1)	14(1)
O(3)	4348(2)	3153(2)	2569(1)	17(1)
C(8)	6201(3)	2075(2)	3309(1)	17(1)
O(4)	6995(2)	3075(1)	3653(1)	17(1)
O(5)	6468(3)	2166(2)	4609(1)	26(1)
C(9)	7090(3)	2982(2)	4303(1)	18(1)
C(10)	8103(4)	4004(2)	4588(1)	23(1)
C(11)	5664(3)	524(2)	1031(1)	18(1)
C(12)	7406(4)	-94(2)	1031(2)	25(1)
C(3)	6887(3)	2629(2)	1183(1)	16(1)
C(4)	6245(3)	3928(2)	1163(1)	19(1)
C(5)	4663(3)	3988(2)	751(1)	18(1)

*Table A12.1.4 Bond lengths [Å] and angles [°] for diol **555***

N(1)-C(1)	1.343(3)
N(1)-C(13)	1.464(3)
N(1)-C(5)	1.469(3)
C(13)-C(21)	1.519(3)
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900
C(21)-C(22)	1.390(3)
C(21)-C(26)	1.394(4)
C(22)-C(23)	1.395(4)
C(22)-H(22)	0.9500
C(23)-C(24)	1.384(4)
C(23)-H(23)	0.9500
C(24)-C(25)	1.392(4)
C(24)-H(24)	0.9500
C(25)-C(26)	1.388(4)
C(25)-H(25)	0.9500
C(26)-H(26)	0.9500
C(1)-O(1)	1.241(3)
C(1)-C(2)	1.539(3)
C(2)-C(3)	1.543(3)
C(2)-C(6)	1.544(3)
C(2)-C(11)	1.560(3)
C(6)-O(2)	1.434(3)
C(6)-C(7)	1.530(3)
C(6)-H(6)	1.0000
O(2)-H(2O)	0.83(2)
C(7)-O(3)	1.421(3)
C(7)-C(8)	1.517(3)
C(7)-H(7)	1.0000
O(3)-H(3O)	0.83(2)
C(8)-O(4)	1.452(3)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
O(4)-C(9)	1.344(3)

Table A12.1.4 (cont'd)

O(5)-C(9)	1.203(3)
C(9)-C(10)	1.499(4)
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800
C(11)-C(12)	1.529(4)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(3)-C(4)	1.521(3)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(5)	1.505(4)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900

C(1)-N(1)-C(13)	119.7(2)
C(1)-N(1)-C(5)	124.7(2)
C(13)-N(1)-C(5)	115.59(19)
N(1)-C(13)-C(21)	114.0(2)
N(1)-C(13)-H(13A)	108.8
C(21)-C(13)-H(13A)	108.8
N(1)-C(13)-H(13B)	108.8
C(21)-C(13)-H(13B)	108.8
H(13A)-C(13)-H(13B)	107.6
C(22)-C(21)-C(26)	119.3(2)
C(22)-C(21)-C(13)	120.0(2)
C(26)-C(21)-C(13)	120.6(2)
C(21)-C(22)-C(23)	120.6(3)
C(21)-C(22)-H(22)	119.7

Table A12.1.4 (cont'd)

C(23)-C(22)-H(22)	119.7
C(24)-C(23)-C(22)	120.0(2)
C(24)-C(23)-H(23)	120.0
C(22)-C(23)-H(23)	120.0
C(23)-C(24)-C(25)	119.6(2)
C(23)-C(24)-H(24)	120.2
C(25)-C(24)-H(24)	120.2
C(26)-C(25)-C(24)	120.5(3)
C(26)-C(25)-H(25)	119.7
C(24)-C(25)-H(25)	119.7
C(25)-C(26)-C(21)	120.1(2)
C(25)-C(26)-H(26)	120.0
C(21)-C(26)-H(26)	120.0
O(1)-C(1)-N(1)	121.1(2)
O(1)-C(1)-C(2)	118.8(2)
N(1)-C(1)-C(2)	119.9(2)
C(1)-C(2)-C(3)	113.80(19)
C(1)-C(2)-C(6)	109.93(19)
C(3)-C(2)-C(6)	110.59(19)
C(1)-C(2)-C(11)	104.10(18)
C(3)-C(2)-C(11)	109.40(19)
C(6)-C(2)-C(11)	108.73(19)
O(2)-C(6)-C(7)	109.6(2)
O(2)-C(6)-C(2)	111.61(19)
C(7)-C(6)-C(2)	115.36(18)
O(2)-C(6)-H(6)	106.6
C(7)-C(6)-H(6)	106.6
C(2)-C(6)-H(6)	106.6
C(6)-O(2)-H(2O)	104(2)
O(3)-C(7)-C(8)	110.8(2)
O(3)-C(7)-C(6)	109.76(19)
C(8)-C(7)-C(6)	109.65(18)
O(3)-C(7)-H(7)	108.9
C(8)-C(7)-H(7)	108.9

Table A12.1.4 (cont'd)

C(6)-C(7)-H(7)	108.9
C(7)-O(3)-H(3O)	109(2)
O(4)-C(8)-C(7)	106.53(18)
O(4)-C(8)-H(8A)	110.4
C(7)-C(8)-H(8A)	110.4
O(4)-C(8)-H(8B)	110.4
C(7)-C(8)-H(8B)	110.4
H(8A)-C(8)-H(8B)	108.6
C(9)-O(4)-C(8)	116.82(19)
O(5)-C(9)-O(4)	123.7(2)
O(5)-C(9)-C(10)	125.1(2)
O(4)-C(9)-C(10)	111.1(2)
C(9)-C(10)-H(10A)	109.5
C(9)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
C(9)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
C(12)-C(11)-C(2)	115.3(2)
C(12)-C(11)-H(11A)	108.4
C(2)-C(11)-H(11A)	108.4
C(12)-C(11)-H(11B)	108.4
C(2)-C(11)-H(11B)	108.4
H(11A)-C(11)-H(11B)	107.5
C(11)-C(12)-H(12A)	109.5
C(11)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(11)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(4)-C(3)-C(2)	113.4(2)
C(4)-C(3)-H(3A)	108.9
C(2)-C(3)-H(3A)	108.9
C(4)-C(3)-H(3B)	108.9

Table A12.1.4 (cont'd)

C(2)-C(3)-H(3B)	108.9
H(3A)-C(3)-H(3B)	107.7
C(5)-C(4)-C(3)	109.3(2)
C(5)-C(4)-H(4A)	109.8
C(3)-C(4)-H(4A)	109.8
C(5)-C(4)-H(4B)	109.8
C(3)-C(4)-H(4B)	109.8
H(4A)-C(4)-H(4B)	108.3
N(1)-C(5)-C(4)	111.0(2)
N(1)-C(5)-H(5A)	109.4
C(4)-C(5)-H(5A)	109.4
N(1)-C(5)-H(5B)	109.4
C(4)-C(5)-H(5B)	109.4
H(5A)-C(5)-H(5B)	108.0

Symmetry transformations used to generate equivalent atoms:

*Table A12.1.5 Anisotropic displacement parameters ($Å^2x10^3$) for diol **555**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$.*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	16(1)	15(1)	16(1)	2(1)	-1(1)	0(1)
C(13)	19(1)	20(1)	16(1)	-1(1)	-5(1)	3(1)
C(21)	12(1)	16(1)	21(1)	-2(1)	-2(1)	-2(1)
C(22)	15(1)	21(1)	19(1)	0(1)	-1(1)	-4(1)
C(23)	18(1)	14(1)	31(2)	1(1)	-2(1)	-1(1)
C(24)	18(1)	21(1)	31(2)	-9(1)	3(1)	-2(1)
C(25)	18(1)	31(1)	18(2)	-4(1)	1(1)	-5(1)
C(26)	17(1)	21(1)	20(1)	2(1)	-1(1)	-2(1)
C(1)	17(1)	13(1)	11(1)	-4(1)	-1(1)	-1(1)
O(1)	14(1)	17(1)	21(1)	0(1)	2(1)	-3(1)
C(2)	11(1)	14(1)	14(1)	-1(1)	1(1)	-1(1)
C(6)	12(1)	11(1)	17(1)	0(1)	1(1)	0(1)
O(2)	20(1)	11(1)	19(1)	2(1)	1(1)	-2(1)
C(7)	14(1)	12(1)	16(1)	0(1)	-1(1)	1(1)
O(3)	18(1)	10(1)	22(1)	-1(1)	-1(1)	3(1)
C(8)	22(1)	11(1)	17(1)	-2(1)	-2(1)	0(1)
O(4)	22(1)	15(1)	14(1)	-1(1)	-4(1)	-1(1)
O(5)	30(1)	31(1)	18(1)	3(1)	2(1)	-5(1)
C(9)	17(1)	21(1)	15(1)	-1(1)	-2(1)	4(1)
C(10)	22(1)	25(1)	21(1)	-6(1)	-2(1)	2(1)
C(11)	20(1)	16(1)	18(1)	-1(1)	2(1)	0(1)
C(12)	29(2)	20(1)	27(2)	-4(1)	5(1)	6(1)
C(3)	14(1)	18(1)	17(1)	1(1)	2(1)	-2(1)
C(4)	20(1)	16(1)	20(1)	1(1)	1(1)	-4(1)
C(5)	22(1)	16(1)	18(1)	3(1)	3(1)	-1(1)

Table A12.1.6 Hydrogen coordinates (x10^3) and isotropic displacement parameters (Å^{2}x10^3) for diol ***555***

	x	y	z	U(eq)
H(13A)	908	2683	862	22
H(13B)	1579	3649	343	22
H(22)	477	5599	449	22
H(23)	-936	7107	1040	25
H(24)	-1403	6857	2155	28
H(25)	-414	5109	2678	27
H(26)	972	3595	2089	23
H(6)	7029	1037	2181	16
H(2O)	3780(30)	710(30)	2213(14)	25
H(7)	6860	3054	2489	17
H(3O)	4550(40)	3884(19)	2621(15)	25
H(8A)	5108	1855	3517	20
H(8B)	6954	1356	3312	20
H(10A)	7558	4284	4989	34
H(10B)	8156	4674	4275	34
H(10C)	9258	3723	4685	34
H(11A)	4815	-56	1203	22
H(11B)	5347	708	576	22
H(12A)	8281	495	905	38
H(12B)	7400	-766	719	38
H(12C)	7654	-405	1467	38
H(3A)	7903	2591	1467	20
H(3B)	7241	2385	740	20
H(4A)	5988	4211	1609	22
H(4B)	7132	4463	977	22
H(5A)	4197	4821	763	22
H(5B)	4954	3793	295	22

Table A12.1.7 Torsion angles [°] for diol ***555***

C(1)-N(1)-C(13)-C(21)	103.5(3)
C(5)-N(1)-C(13)-C(21)	-76.4(3)
N(1)-C(13)-C(21)-C(22)	119.0(2)
N(1)-C(13)-C(21)-C(26)	-64.2(3)
C(26)-C(21)-C(22)-C(23)	-1.7(4)
C(13)-C(21)-C(22)-C(23)	175.1(2)
C(21)-C(22)-C(23)-C(24)	0.7(4)
C(22)-C(23)-C(24)-C(25)	0.6(4)
C(23)-C(24)-C(25)-C(26)	-1.0(4)
C(24)-C(25)-C(26)-C(21)	-0.1(4)
C(22)-C(21)-C(26)-C(25)	1.4(4)
C(13)-C(21)-C(26)-C(25)	-175.4(2)
C(13)-N(1)-C(1)-O(1)	-4.4(3)
C(5)-N(1)-C(1)-O(1)	175.6(2)
C(13)-N(1)-C(1)-C(2)	169.9(2)
C(5)-N(1)-C(1)-C(2)	-10.1(3)
O(1)-C(1)-C(2)-C(3)	-176.6(2)
N(1)-C(1)-C(2)-C(3)	9.0(3)
O(1)-C(1)-C(2)-C(6)	-51.9(3)
N(1)-C(1)-C(2)-C(6)	133.7(2)
O(1)-C(1)-C(2)-C(11)	64.4(3)
N(1)-C(1)-C(2)-C(11)	-110.0(2)
C(1)-C(2)-C(6)-O(2)	56.0(2)
C(3)-C(2)-C(6)-O(2)	-177.47(19)
C(11)-C(2)-C(6)-O(2)	-57.3(2)
C(1)-C(2)-C(6)-C(7)	-69.9(2)
C(3)-C(2)-C(6)-C(7)	56.6(3)
C(11)-C(2)-C(6)-C(7)	176.78(19)
O(2)-C(6)-C(7)-O(3)	-70.0(2)
C(2)-C(6)-C(7)-O(3)	57.0(3)
O(2)-C(6)-C(7)-C(8)	52.0(3)
C(2)-C(6)-C(7)-C(8)	178.9(2)
O(3)-C(7)-C(8)-O(4)	-84.9(2)
C(6)-C(7)-C(8)-O(4)	153.74(19)

Table A12.1.7 (cont'd)

C(7)-C(8)-O(4)-C(9)	168.1(2)
C(8)-O(4)-C(9)-O(5)	-4.8(4)
C(8)-O(4)-C(9)-C(10)	173.7(2)
C(1)-C(2)-C(11)-C(12)	179.2(2)
C(3)-C(2)-C(11)-C(12)	57.3(3)
C(6)-C(2)-C(11)-C(12)	-63.6(3)
C(1)-C(2)-C(3)-C(4)	24.6(3)
C(6)-C(2)-C(3)-C(4)	-99.7(2)
C(11)-C(2)-C(3)-C(4)	140.5(2)
C(2)-C(3)-C(4)-C(5)	-56.6(3)
C(1)-N(1)-C(5)-C(4)	-23.0(3)
C(13)-N(1)-C(5)-C(4)	156.9(2)
C(3)-C(4)-C(5)-N(1)	55.1(3)

Symmetry transformations used to generate equivalent atoms:

*Table A12.1.8 Hydrogen bonds for diol **555** [Å and °]*

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2O)...O(1)	0.83(2)	1.88(2)	2.645(2)	152(3)
O(3)-H(3O)...O(2)#1	0.83(2)	1.91(2)	2.730(2)	169(3)
C(10)-H(10C)...O(5)#2	0.98	2.47	3.374(3)	153.9
C(4)-H(4A)...O(2)#1	0.99	2.57	3.530(3)	163.7
C(4)-H(4A)...O(3)	0.99	2.63	3.364(3)	131.0

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

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ABOUT THE AUTHOR

Nicholas R. O'Connor was born in Boston, MA on April 23rd, 1989 to Janet and Kevin O'Connor as the first of what would eventually be five children. He grew up in Beaverton, OR, where he became interested in science at a young age, dismantling household appliances to reach the circuit boards within. In seventh grade he began volunteering at the Oregon Museum of Science and Industry, where he worked on the laboratory preparation of fossilized triceratops bones for display.

Although initially unsure whether to pursue scientific studies at Macalester College, his hesitation disappeared as he took his first course in organic chemistry. Nick was fascinated by the relationship between molecular structure and reactivity and appreciated the importance of organic synthesis to other fields of science, as well as engineering and medicine. He began laboratory research under the direction of Professor Rebecca Hoye at Macalester College in the fall of 2009, working on the synthesis of novel auxin mimics for probing plant signaling pathways. He later studied hetero-Diels–Alder reactions under Dr. Poonsakdi Ploypradith at the Chulabhorn Research Institute in Bangkok, Thailand during summer 2010 and interned in under Mr. Dan Kohlman at Eli Lilly and Company during summer 2011.

In the fall of 2011, Nick moved to the California Institute of Technology to pursue graduate studies in the laboratories of Professor Brian M. Stoltz. His graduate research focused on cycloadditions of strained rings and allylic C–H activation of sterically hindered substrates. Nick will continue his education as a postdoctoral scholar in the laboratories of Professor Richmond Sarpong at the University of California, Berkeley, beginning in March 2017.