The Total Synthesis of Kalihinol C and Related Natural Products

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To the past and future members of the Wood lab

Abstract

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Kalihinol A (**1**) was isolated in 1984 from the marine sponge *Acanthella cavernosa*. The structure and isolation of nearly forty additional natural products related to kalihinol A were later described and shown to possess a variety of biological activities. In particular, kalihinol A was shown to exhibit potent antimalarial activity against *P. falciparum*. Reported herein is a multi-faceted strategy for the total synthesis of kalihinol A and related natural products.

Based in part on extensive model system studies which culminated in the total syntheses of (±)-10-isocyano-4-cadinene (**15**) and (±)-10-isothiocyanato-4-cadinene (**16**), efforts directed toward kalihinol A led to the first total syntheses of (±)-kalihinol C (**42**) and (±)-*epi*-C(14)-kalihinol C (**185**). The successful synthetic strategy utilized a series of substrate-controlled, diastereoselective reactions in which a conformationally rigid decalin core was used to dictate introduction of the requisite functionality. The synthetic sequence was highlighted by a diastereoselective (i) IMDA cycloaddition of **109**, (ii) epoxidation of cis-decalin **110**, (iii) aziridination of olefin **45**, and (iv) anti-Felkin propiolate addition to methyl ketone **141**. Future efforts will focus upon the advancement of **155** to kalihinol A and related kalihinols.

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Ryan D. White

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List of Abbreviations

AFA	acetic formic anhydride
aq	aqueous
$BF_3 \cdot Et_2O$	boron trifluoride diethyl etherate
Bn	benzyl
BORSM	based on recovered starting material
Bu	butyl
C	carbon
°C	degrees Celsius
calc'd	calculated
CCl_4	carbon tetrachloride
$CDCl_3$	chloroform-*d*
CH_3CN	acetonitrile
$CHCl_3$	chloroform
CH_2Cl_2	methylene chloride
CI	chemical ionization
comp	complex
$Cu(OTf)_2$	copper trifluoromethanesulfonate
Cy	cyclohexyl
δ	chemical shift in ppm downfield from Me_4Si
d	doublet
dba	dibenylideneacetone
dd	doublet of doublets
ddd	doublet of doublets of doublets
DIBAL-H	diisobutylaluminum hydride
DMDO	dimethyl dioxirane
DMF	dimethyl formamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dt	doublet of triplets
EI	electron impact
equiv	equivalent
Et	ethyl
Et_2O	ethyl ether
EtOAc	ethyl acetate
Et_2NH	diethylamine
Et_3N	triethylamine
FAB	fast atom bombardment
FTIR	Fourier transform infrared
g	gram(s)
h	hour(s)
[H]	reduction
H_2	hydrogen
H_2O	water

HCl	hydrochloric acid
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrum
Hz	hertz
hν	irradiation
J	coupling constant
L	liter(s), ligand
μ	micro
m	medium (FTIR), multiplet (NMR)
mm	millimeters
mmol	millimole
M	moles per liter, metal
Me	methyl
MeOH	methanol
mg	milligrams
$MgSO_4$	magnesium sulfate
mp	melting point
MHz	megahertz
min	minute(s)
mol	mole(s)
mmol	millimole(s)
mp	melting point
Ms	methanesulfonyl
m/z	mass to charge ratio
Na	sodium
NaN_3	sodium azide
NH_4Cl	ammonium chloride
NaCl	sodium chloride
NaH	sodium hydride
$NaHCO_4$	sodium bicarbonate
NaOMe	sodium methoxide
Na_2SO_4	sodium sulphate
NCS	N-chlorosuccinimide
NH_3	ammonia
NMR	nuclear magnetic resonance
[O]	oxidation
O_3	ozone
OAc	acetate
p	para
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium
pH	hydrogen ion concentration
PhI=NTs	(N-(*p*-tolylsulfonyl)imino)phenyliodinane
PPh_3	triphenylphosphine
ppm	parts per million
q	quartet
s	singlet (NMR), strong (FTIR)

SiO_2	silicon dioxide, silica gel
soln	solution
t	triplet
td	triplet of doublets
TBCO	2,4,4,6-Tetrabromocyclohexa-2,5-dienone
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tri(methyl)silyl
Ts	toluenesulfonyl
w	weak

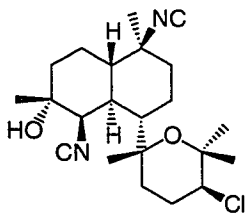
Chapter 1

The Kalihinols: A Diverse Class of Structurally and Biologically Interesting Natural Products

1.1 Isolation and Structure

In 1984, Scheuer and coworkers reported the isolation of a new, highly functionalized diterpenoid from a marine sponge.[1] The conspicuously orange colored sponge was harvested off the coast of Guam in 1981 and was identified as belonging to the genus *Acanthella*. Extraction of a freeze-dried sample (30 g) followed by chromatography yielded two bioactive fractions, 28.1 mg of a mixture of compounds requiring further purification, and 11.5 mg of the unique compound kalihinol A, named after the first author's home town of Kalihi, Hawaii. Following extensive NMR and HRFABMS studies, the relative configuration of **1** was confirmed by X-ray crystallography.

Figure 1.1

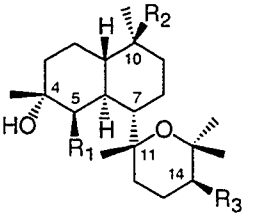


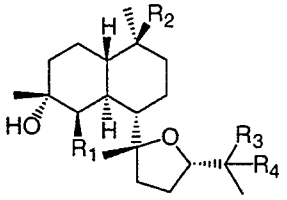
kalihinol A (**1**)

Ensuing reports over the next sixteen years by several research groups disclosed the isolation and structure of a multitude of related kalihinol natural products from the marine sponges *Acanthella klethra*, *Acanthella cavernosa*, and *Phakellia pulcherrima*. The sponge specimens were collected from various regions including off the coasts of Guam, Fiji, and Japan. *Acanthella cavernosa* was most prolific in production of kalihinane diterpenoids, and consequently these natural products were used as chemotaxonomic markers for identification of this species. In total, the kalihinane diterpenoids were categorized into three distinct subgroups based upon the stereochemistry and array of functionality on the decalin core.

The first kalihinols to be disclosed were closely related in structure to kalihinol A (Figure 1.2).[2-4] This group of compounds contained the following features: a highly functionalized *trans*-decalin core with an equatorial isonitrile, isothiocyanate, or formamide at C(10), an axial isonitrile or isothiocyanate at C(5) *anti* to a tertiary hydroxyl at C(4), and an equatorially disposed pendent chloro-tetrahydropyran or functionalized tetrahydrofuran at C(7).

Figure 1.2





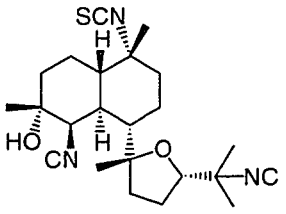
		R1	R2	R3
Kalihinol	A	NC	NC	Cl
	E	NC	NC	epi-Cl
	I	NCS	NCS	Cl
	X	NC	epi-NCS	Cl
	Z	NC	epi-NC	Cl

		R1	R2	R3	R4
Kalihinol	B	NC	NC	Cl	Me
	C	NC	NC	$=CH_2$	
	D	Cl	NC	NC	Me
	F	NC	NC	NC	Me
	G	NC	NC	NCS	Me
	H	NC	NCS	NCS	Me
isothiocyanatokalihinol	C	NC	NCS	$=CH_2$	
isothiocyanatokalihinol	G	NC	NCS	NCS	Me
bisisothiocyanatokalihinol	G	NCS	NCS	NCS	Me

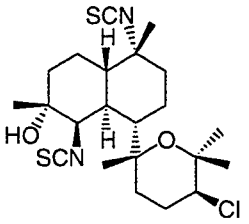
Structural assignment in this series of natural products was facilitated by diagnostic spectroscopic features. The presence of isonitrile moieties was revealed by sharp IR absorption at *ca.* 2135 cm^{-1} as well as distinctive ^{14}N coupling to both adjacent protons and carbons in the ^{1}H and ^{13}C NMR spectra respectively.[5] The pendant tetrahydrofuran or tetrahydropyran was distinguished based upon the ^{13}C NMR shifts of the ether carbons (δ 82-87 and 75-77 respectively).

More recent reports have described a second group of kalihinols which display an isomeric arrangement of functionality about the decalin skeleton when compared to the original kalihinols (Figure 1.3).[6-8] 10-*epi*-Kalihinol H (**2**) and 10-*epi*-Kalihinol I (**3**) are examples of C(10) epimers in which the isothiocyanates are axial. The isokalihinols possess a *trans*-diequatorial relationship between the isonitrile and hydroxyl at C(4)-C(5) which is reversed from the original kalihinols.

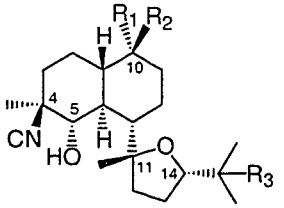
Figure 1.3



10-*epi*-kalihinol H (**2**)



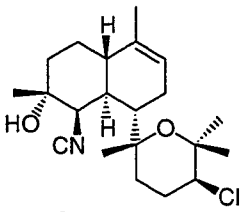
10-*epi*-kalihinol I (**3**)



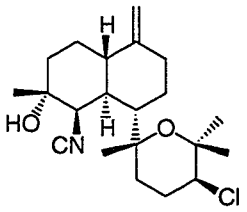
	R_1	R_2	R_3
isokalihinol F	Me	NC	NC
isokalihinol B	Me	NC	Cl
10-*epi*-isokalihinol F	NC	Me	NC
10-*epi*-isokalihinol H	NCS	Me	NC

The third and least populated group of kalihinols is best characterized as having at least one site of unsaturation associated with the decalin core (Figure 1.4).[9,10] A small number of C(6) hydroxylated kalihinols (e.g. **4**), as well as the only *cis*-decalin compounds in the kalihinol family, four in total (e.g. **5**), are represented in this category.

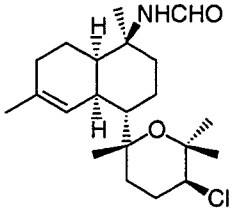
Figure 1.4



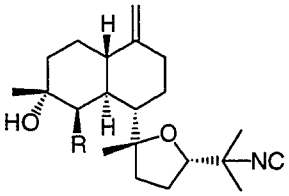
Δ^9-kalihinol Y



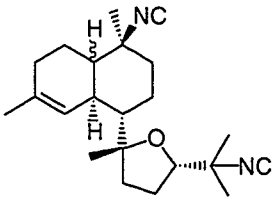
kalihinol Y



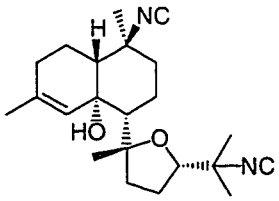
kalihinene X (**5**)



kalihinol K (R = NC)
kalihinol L (R = NCS)



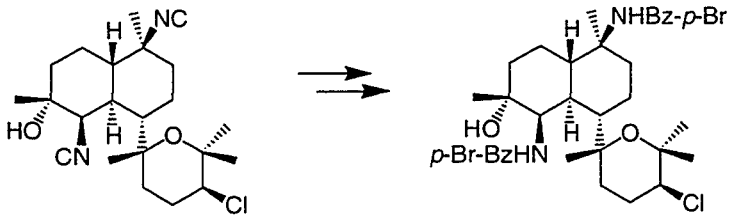
kalihinene (1-Hα)
1-*epi*-kalihinene (1-Hβ)



6-hydroxykalihinene (**4**)

Despite extensive structural studies of the kalihinols since the original isolation report, the absolute configuration was not determined until 1999 by Yamada and co-workers.[11] The circular dichroism spectra of a *p*-bromobenzamide derivative (**6**) of kalihinol A indicated the absolute configuration as shown in Figure 1.5.

Figure 1.5



1.2 Biological Activity

1.2.1 A Broad Spectrum of Activity

It has been shown that the kalihinane diterpenoids possess a wide array of important biological activities. Although not all of the kalihinols have been assayed, many of those tested exhibited similar antifungal, antimicrobial, anthelmintic, antifouling, and antimalarial properties. For example, kalihinols A, D, G, H, F, X, Y, and Z exhibited *in vitro* activity against *Bacillus subtilis*, *Staphylococcus aureus*, and *Candida albicans*.[4] Kalihinols A, Y, and Z demonstrated very high *in vitro* anthelmintic activity against parasitic stages of *Nippostrongylus brasiliensis*.[8] In search of non-toxic antifouling agents, kalihinol A, kalihinene X, and 10-formamidokalihinene were

discovered to be potent inhibitors of the attachment and metamorphosis of cyprid larvae of the barnacle *Balanus amphitrite* (EC_{50} ca. 0.09 μg/mL).[12,13] Most importantly, while several of the kalihinols were shown to have antimalarial properties, kalihinol A demonstrated particularly potent *in vitro* activity against the most virulent malaria parasite, *Plasmodium falciparum*. Compared to the efficacy of the currently-used antimalarial standard mefloquine (**7**), kalihinol A (**1**) exhibited higher activity (EC_{50} 1.2 nM) and selectivity (selectivity index = SI = 317), the latter of which is defined as a ratio of *P. falciparum* to FM3A cell cytotoxicity.[14]

Table 1.1

	P. falciparum EC_{50} (nM)	FM3A EC_{50} (nM)	SI
kalihinol A (**1**)	1.2	380	317
mefloquine (**7**)	32	2900	90

1.2.2 Malaria

1.2.2.1 A Growing Problem

Malaria remains one of the leading causes of mortality in the world today. With an estimated 300-500 million clinical cases and 1.5-2.7 million deaths per year, malaria represents a crippling health crisis in many tropical regions around the globe. Factors contributing to the persistence and reintroduction of the disease are numerous and complex, and include socioeconomic, political, and public health related issues.

Biologically, the resurgence of malaria can be traced to (i) the emergence of insecticide-resistant strains of the anopholine mosquitoes which are the vectors for transmission of the disease, and (ii) the increased prevalence of drug-resistant strains of *P. falciparum*, the parasite responsible for the pathology of the most lethal form of the disease. Despite the severity of the disease, funding for malaria research is significantly underepresentative of the number of people afflicted. Table 1.1 illustrates the disparity between the estimated annual global research expenditures and mortality for the disease compared to AIDS and asthma between 1990 and 1992.[15]

Table 1.2

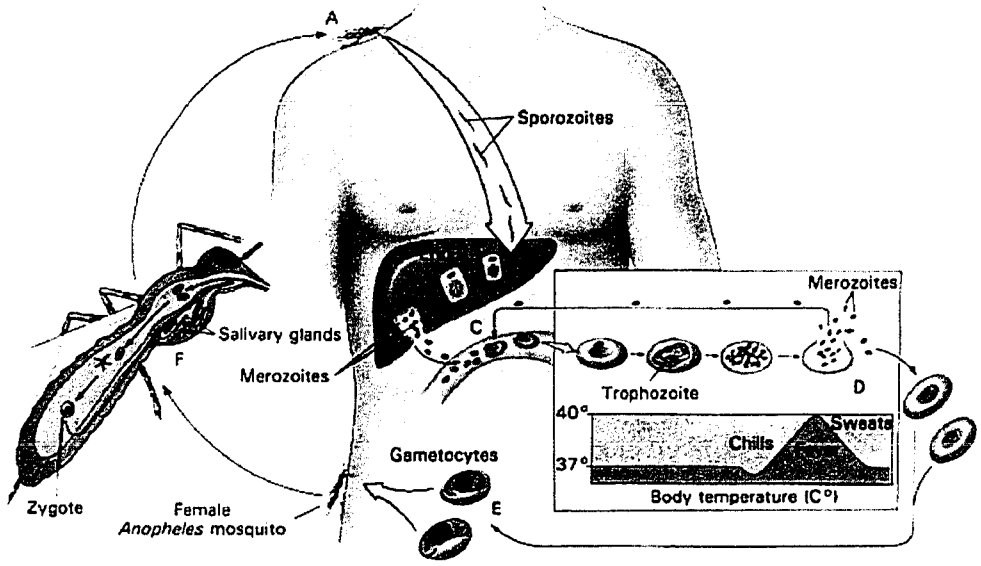
Disease	Expenditure (millions of dollars)	Mortality (thousands)	Expenditure per fatality (dollars)
HIV/AIDS	952	290.8	3274
Asthma	143	181.3	789
Malaria	60	926.4	65

1.2.2.2 Life Cycle of *P. falciparum*

The infective cycle starts by transmission of the parasite from a carrier mosquito (Figure 6, A). The transmitted sporozoites invade hepatocytes within the liver (B) and after several days the progeny merozoites enter the blood stream and infect erythrocyctes (C). Following several stages of asexual reproduction, the parasites cause rupture of the erythrocyte leading to the infection of neighboring erythrocytes (D). The formation of gametocytes is the final stage of the life cycle within the human host (E). These can be ingested by mosquitoes to initiate the sexual reproductive cycle, again producing sporozoites (F). Once extensive parasite proliferation has occurred, the cell division and

red blood cell destruction within the human host causes the well known symptoms of fever, shivering, and anemia.[16,17]

Figure 1.6

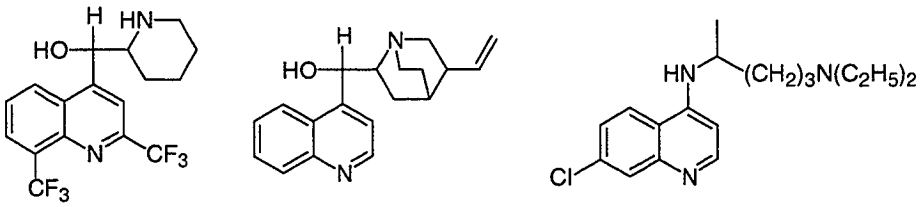


1.2.2.3 Therapeutic Inroads

One possible approach to developing therapeutic agents specific to one of the many interruptible stages in the parasite's complex life cycle is to interfere with heme detoxification. Intraerythrocytic plasmodia feed by degrading enormous amounts of human hemoglobin, a process which involves delivery to acidic food vacuoles and globin degradation by a set of specific enzymes to provide amino acids for parasite maturation. One of the by-products of this hemoglobin degradation is the liberation of free heme. Lacking the ability to catabolize heme, the parasite sequesters heme into an inert crystalline lattice called malaria pigment or hemozoin. By inhibiting this crystallization

process, the surfactant-like heme can reach concentrations as high as 400 mM within the parasite which results in the destruction of the parasitic membranes and ultimately leads to parasite death. Approaches to address this vulnerability have been taken from both the peptidyl and small molecule perspectives.[17] To date, the most effective and practical antimalarials are the amino-quinolines (Figure 1.7). Studies have concluded that these amino-quinolines are effective because of pH trapping of the drug as a protonated amine upon entry to the acidic food vacuole of the parasite as well as complexation of the quinoline ring system via π-π interactions with free heme, thus interfering with hemozoin formation and/or destabilizing hemozoin.[18-20]

Figure 1.7



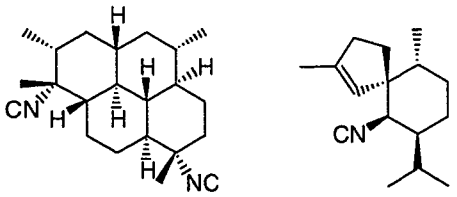
mefloquine (**7**) quinine (**8**) chloroquine (**9**)

Despite the initial effectiveness of amino-quinolines, their utility as viable drugs for long-term use is limited due to the numerous resistant organisms now proliferating in regions of Africa, South America, and Southeast Asia.[21,22] As a result, there is a pressing need to discover new therapies and drug targets for *P. falciparum*. The plight of amino-quinolines is representative of other long-used drugs and illustrates a clear need for new antimalarials with novel modes of action.[23]

1.2.2.4 Previous Antimalarial Work

In addition to the kalihinols, other isonitrile-containing natural products have been shown to exhibit antimalarial activity. For example, Wright and co-workers have shown that natural products related to diisocyanoadociane (**10**) and axisonitrile (**11**) possess remarkable antimalarial activity (IC_{50} = 14 nM and 612 nM respectively) against the chloroquine-sensitive D6 strain of *P. falciparum* (Figure 1.7). It was proposed that activity arises from the inhibition of heme detoxification.[24,25] Molecular modeling studies were used to generate a pharmacophore hypothesis consistent with experimentally derived biological activities in which the axial isonitrile is believed to bind to the heme iron. The binding event was suggested to occur in an end-on manner which "caps" heme crystallization, thereby causing free heme concentrations to build. Most importantly, both **10** and **11** demonstrate higher selectivity and inhibitory potency than chloroquine against the chloroquine-resistant W2 strain of *P. falciparum*. Axisonitrile (**11**) shows no cytotoxicity towards KB-3 cells at the maximum concentration tested, while **10** shows a higher selectivity and lower cytotoxicity than the antimalarial standard mefloquine.[26]

Figure 1.8



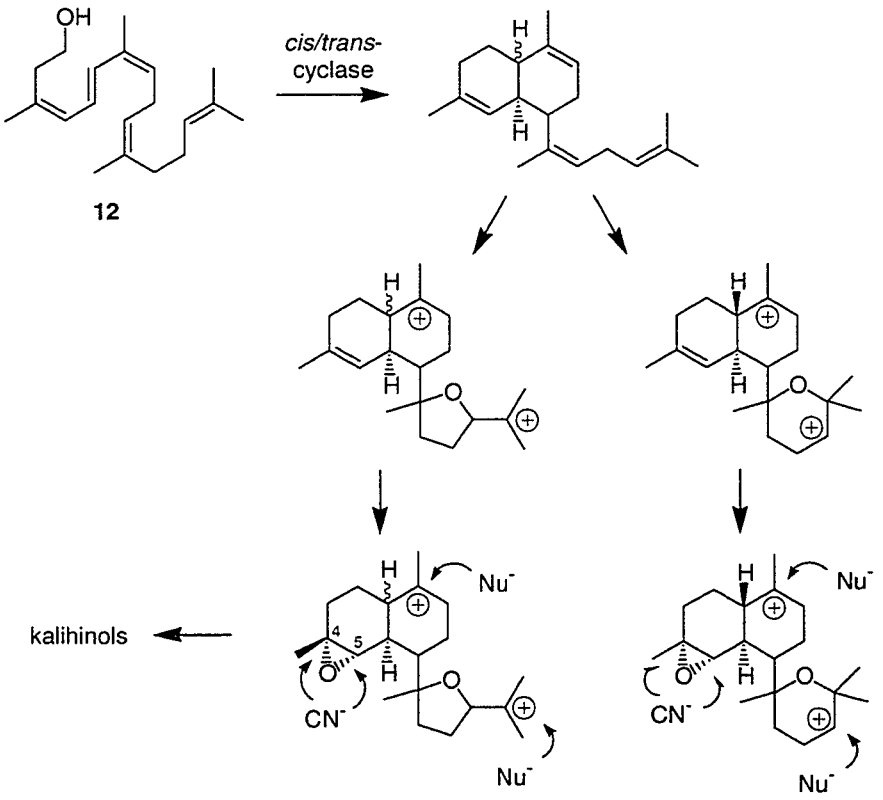
10 **11**

Furthermore, it has been recognized that isonitrile-containing compounds represent a unique approach toward antimalarial chemotherapy, and promising *in vivo* results recently disclosed by Singh and co-workers support this approach.[27] These results suggest that isonitriles may be tolerated *in vivo* despite concerns over cytotoxicity and specificity toward infected cells.

1.3 Biosynthesis

The structural features within the kalihinane family offered clues about its potential biosynthetic origins. The most recent of three proposed biosyntheses of the kalihinols took into account several factors in an attempt to elucidate a plausible biogenetic pathway.[9,28,29] The variation among the kalihinols in functionality pointed toward the intermediacy of stable secondary and tertiary carbocations along the metabolic pathway. In light of the regioisomeric relationship of the kalihinols (C(4) hydroxyl, C(5) isonitrile) with the isokalihinols (C(4) isonitrile, C(5) hydroxyl), a common epoxide intermediate was considered.

Scheme 1.1



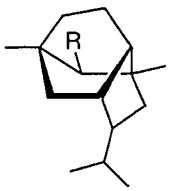
Therefore, it was envisioned that an initial cyclization beginning with a geranyl geraniol-equivalent precursor (**12**) would follow one of two paths forming a *cis* or *trans*-decalin (Scheme 1.1). An ensuing oxidative cyclization could form the requisite tetrahydropyran or tetrahydrofuran moiety. Epoxidation of the C(4)-C(5) olefin followed by addition of cyanide could give rise to most of the observed kalihinols. Origins of the chloride, found at C(5) (e.g. kalihinol D) and C(14) (e.g. kalihinol A) but not at C(10), in tetrahydropyran-containing kalihinols has not been investigated. The suggestion that the isonitriles in the kalihinols were derived from inorganic sources of cyanide was supported by feeding experiments using ^{14}C labeled cyanide.[30,31] This is in contrast to the

possibility that the isonitriles may come from dehydration of the corresponding formamide.[32]

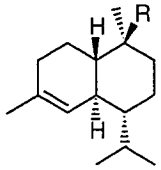
1.4 Related Natural Products

Although the kalihinols comprise a unique family of compounds, they are members of a growing class of isonitrile-containing natural products. These natural products have origins in both terrestrial and marine organisms. Terrestrial sources generally produce isonitrile-containing compounds derived from amino acids. In contrast, marine isonitrile metabolites generally have isoprenoid carbon skeletons and are often structurally complex.[29] Like the kalihinols, other marine natural products containing isonitriles have been found with the corresponding isothiocyanate and/or formamide functional groups; for example: (i) the pupukeananes (**13**), (ii) metabolites from the marine sponge *Cymbastela hooperi* (**14**), (iii) cadinenes **15** and **16**, (iv) and sesquiterpenes **11** and **17**, were all found to be related by varying nitrogen functionality.[25,28,32-34] In particular, 10-isothiocyanato-4-cadinene (**16**), axisisonitrile-3 (**11**), and axisisothiocyanate-3 (**17**) were isolated from the same species of sponge as many of the kalihinols. [26,28]

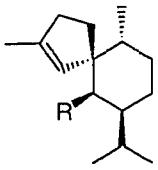
Figure 1.9



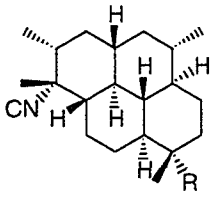
R = NC, NCS, NHCHO, **13**



10-isocyano-4-cadinene, R = NC, **15**
10-isothiocyanato-4-cadinene, R = NCS, **16**



axisonitrile-3, R = NC, **11**
axisothiocyanate-3, R = NCS, **17**



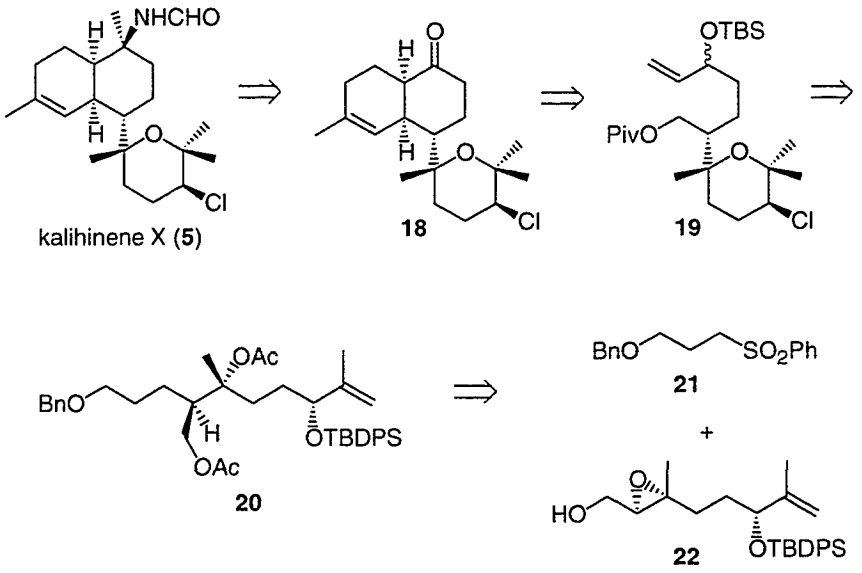
R = NC, NCS, NCO, **14**

1.5 Relevant Synthetic Efforts

1.5.1 Total Synthesis of Kalihinene X

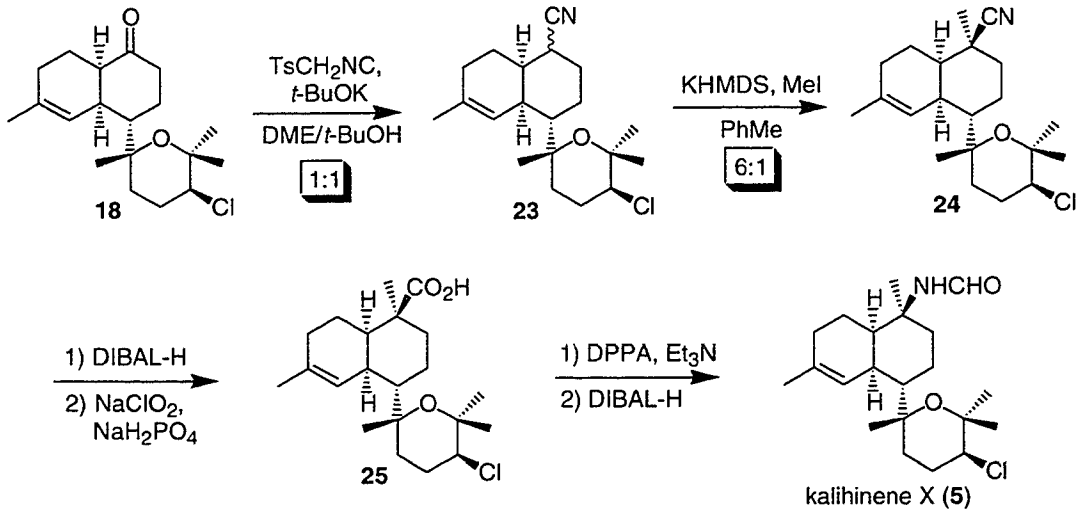
At the outset of our investigations, no synthetic efforts toward the kalihinols had been reported. After our reports pertaining to the construction of the decalin core of kalihinol A,[35] however, Yamada reported the total synthesis of kalihinene X, one of only a few kalihinols containing a *cis*-decalin.[36] The approach utilized a regioselective coupling of an alkyl sulfone with an epoxy-alcohol and an intramolecular Diels-Alder (IMDA) cycloaddition to construct the *cis*-decalin core (Scheme 1.2). In total, the synthesis required thirty-five steps overall, twenty-eight steps from known alcohol **22** with a yield of 2.9%.

Scheme 1.2



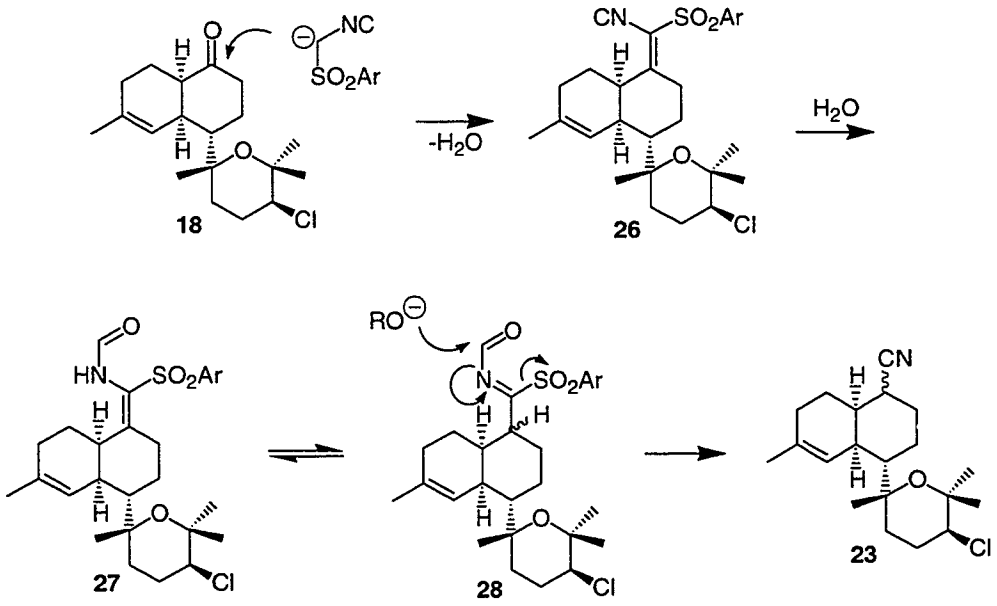
Most notable, perhaps, was the six step sequence used for installation of the tertiary formamide at C(10). Condensation of **18** with the anion of tosylmethyl isonitrile gave a 1:1 mixture of nitrile diastereomers, which were alkylated to give **24** and the undesired diastereomer in a 6:1 ratio (Scheme 1.3). The resulting tertiary nitrile was converted to the corresponding acid and treated with diphenylphosphoryl azide (DPPA) to effect a Curtius rearrangement.[37] Reduction of the intermediate isocyanate gave the desired formamide **5**.

Scheme 1.3



In particular, the conversion of **18** to **23** represents a well known but seldom utilized homologation of ketones to the next higher nitrile.[38] Prior mechanistic studies suggest that the process involves a hydrolytic deformylation as illustrated in Scheme 1.4.

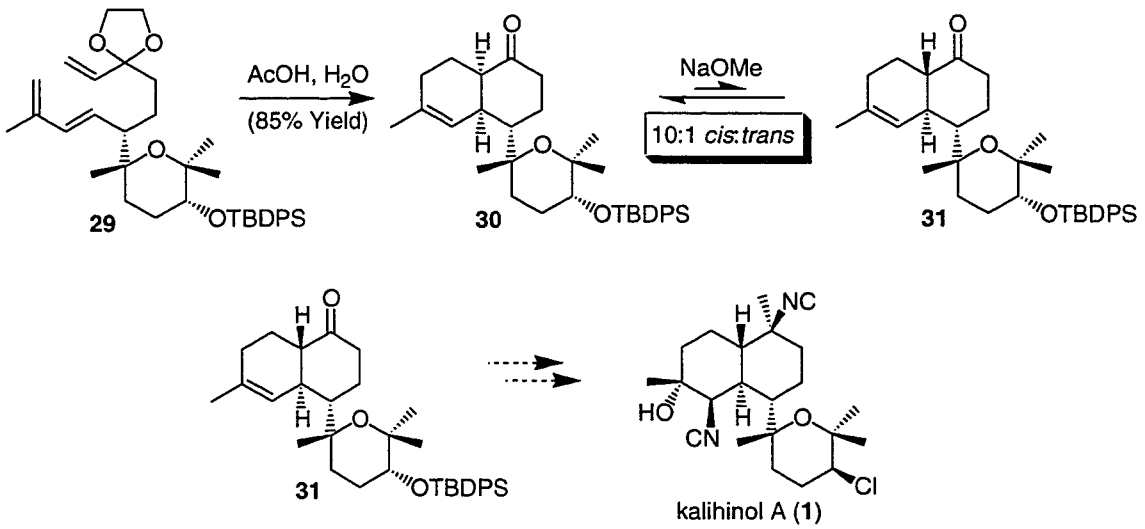
Scheme 1.4



1.5.2 Synthetic Studies Toward Kalihinol A

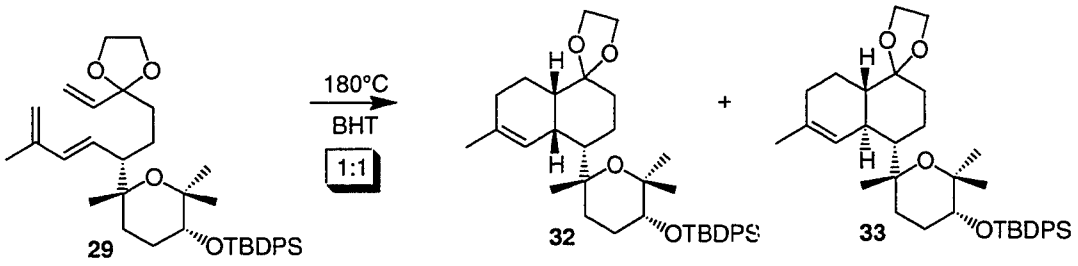
Interestingly, prior to the synthesis of kalihinene X, Yamada and coworkers attempted to synthesize kalihinol A. Although never published, some of those efforts were described at a symposium in Okinawa, Japan approximately one year after our studies on the kalihinols had been initiated.[39] Dioxolane **29**, accessed from geranyl acetate, was deprotected with acetic acid (Scheme 1.5). The resulting IMDA cycloaddition was spontaneous at room temperature to provide *cis*-decalin **30** as a single isomer. Upon treatment of **30** with base, however, the *cis*-decalin was favored 10:1 to the corresponding *trans*-decalin. This unpredicted equilibrium prevented access to significant quantities of desired *trans*-decalin **31** and precluded future synthetic endeavors toward the majority of the kalihinols.

Scheme 1.5



In an attempt to circumvent the epimerization step by obtaining the desired *trans*-decalin directly from the Diels-Alder cycloaddition, **29** was heated to 180°C in 2,6-di-*tert*-butyl-4-methyl phenol (BHT) (Scheme 1.6). The thermal cycloaddition provided a 1:1 mixture of diastereomers, **32** and **33**. The desired *trans*-decalin **33** was the most advanced intermediate described. Undoubtedly, however, conditions necessary to remove the dioxolane in **33** would have facilitated a deleterious epimerization and eventual reversion to a 10:1 *cis*:*trans*-decalin mixture. No further reports on the route were made.

Scheme 1.6



1.6 Conclusions

Considering the potent antiplasmodial activity of kalihinol A and interesting functionalization of the kalihinane family, a project directed toward their total synthesis was initiated. Ultimately, our goals included: (i) devising and executing an efficient synthesis of kalihinol A and/or other kalihinols as well as a number of carefully chosen derivatives for a structure-activity relationship study, and (ii) through collaborative work, contributing to current theories on how both isonitriles and the kalihinane-type

carbocycle are involved in anti-plasmodial activity. To accomplish these goals, a multi-faceted strategy was developed and will be described herein.

1.7 Notes and References

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Chapter 2

A Model System for the Kalihinols: The First Total Synthesis of (±)-10-Isocyanato-4-Cadinene and (±)-10-Isothiocyanato-4-Cadinene

2.1 Initial Considerations

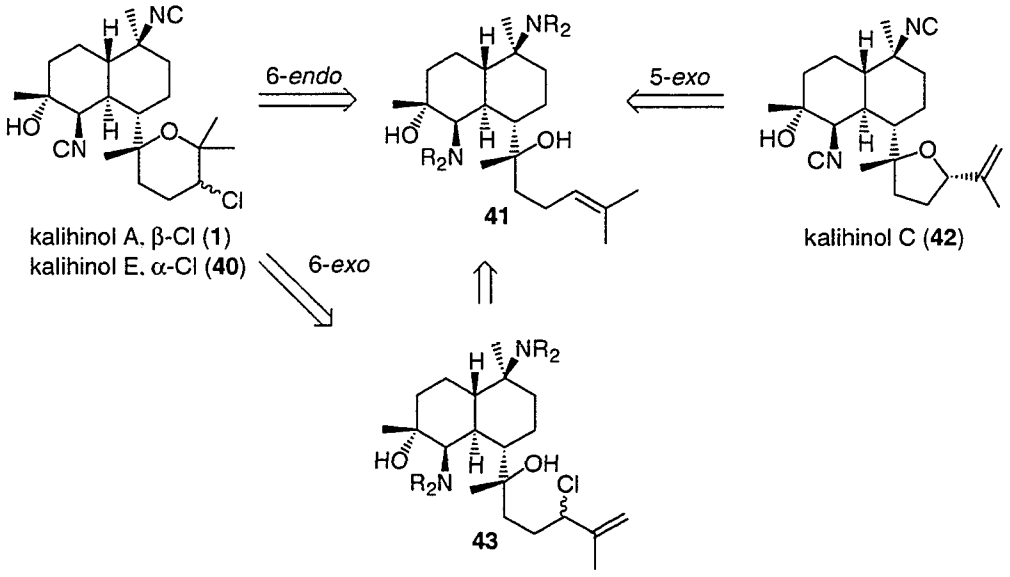
Given the structural and functional group diversity within the kalihinol family, it was recognized that the use of a common intermediate to access several kalihinols, as proposed for their biosynthesis, would be an ideal synthetic strategy. In addition, the potent antimalarial activity of kalihinol A combined with increasing interest in finding new malaria chemotherapies warranted the formulation of a flexible approach that would provide kalihinol A as well as other kalihinols. Also, the synthesis of a variety of biologically relevant analogs and kalihinols could lead to the elucidation of the structure-activity relationships within the family.

2.2 Retrosynthetic Analysis

The initial retrosynthetic analysis of kalihinol A was centered upon three major structural features: the *trans*-decalin core, the pendent chloro-tetrahydropyran, and the isonitriles. *Given the conformationally rigid nature of trans-decalins, the topology enforced by the decalin carbocycle was expected to dictate introduction of the remaining functionality through a series of substrate-controlled diastereoselective reactions.* Thus, the decalin would be constructed early in the synthesis, and the potentially delicate chloro-tetrahydropyran and isonitriles would be installed at a late stage.

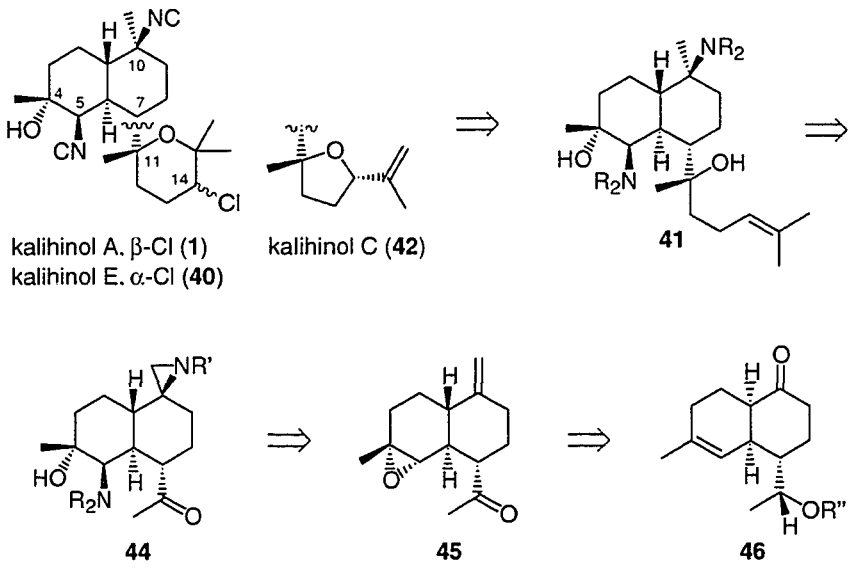
Bishomoallylic alcohol **41** was considered the key intermediate in accessing several natural products (Scheme 2.1). 5-*Exo* or 6-*endo* cyclo-etherification of **41** could give rise to the tetrahydrofuran or tetrahydropyran-containing natural products, respectively.[1,2] However, serious consideration was given to the fact that a CH_3-CH_3 1,3-diaxial interaction in the requisite tetrahydropyran might be difficult to overcome in a 6-*endo* cyclization of **41**. Therefore, formation of a tetrahydropyran via a 6-*exo* cyclization of **43**, arising via halogenation and rearrangement of **41**, was anticipated.[3]

Scheme 2.1



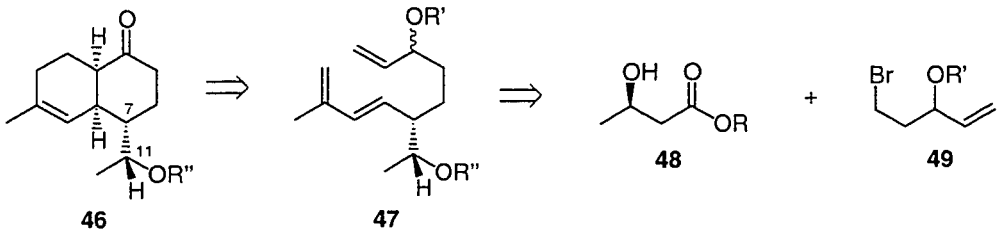
Disconnection of the prenyl side chain at C(11) in **41** and masking of the amines gives methyl ketone **44** (Scheme 2.2). Introduction of the axial C(5) nitrogen was envisioned arising from an epoxide opening with a nucleophilic nitrogen source, while the equatorial C(10) nitrogen could arise via a metal-catalyzed aziridination of an *exo*-methylene in **45**.[4] To be effective, the *trans*-decalin skeleton would have to direct the aziridination to the less hindered, β-face of the olefin. Conversely, to establish the correct stereochemistry at C(4), the corresponding *cis*-decalin, **46**, could direct an epoxidation to the less-hindered, convex face.[5] Based upon examples in the literature, it was anticipated that converting *cis*-decalin **46** to *trans*-decalin **45** would be possible under Wittig conditions needed to incorporate the exo-methylene.[6,7]

Scheme 2.2



cis-Decalin **46** was foreseen coming from an intramolecular Diels-Alder (IMDA), namely, cycloaddition of triene **47** (Scheme 2.3). The remaining disconnections would have to address the stereochemical relationship between C(7) and C(11). Although the relative stereochemical relationship between C(7) and C(11) would become irrelevant as a result of subsequent oxidation of the C(11) hydroxyl, the remaining disconnections would need to provide a *syn* or *anti* relationship with high fidelity. It was concluded that Frater alkylation of an enantiopure β-hydroxy ester **48** with bromide **49** could give the needed stereocontrol.[8,9]

Scheme 2.3



46 47 48 49

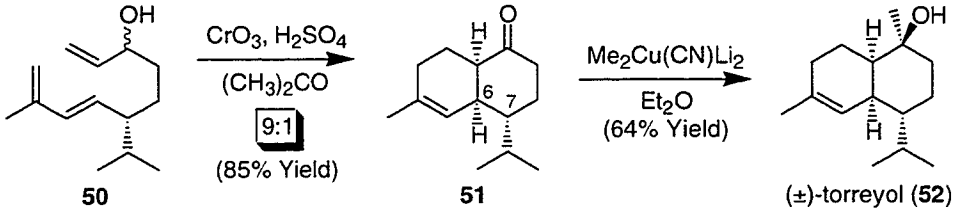
2.3 A Decalin Model System

There were initial concerns about the use of a diastereoselective aziridination to install the equatorial nitrogen at C(10), i.e. **45**→**44**. Although a metal-catalyzed aziridination seemed like a logical disconnection which could offer some flexibility, few reports existed concerning either diastereoselective aziridinations or metal-catalyzed aziridinations on even moderately functionalized compounds.[10-13] Furthermore, there was a lack of confidence that a Ritter-type aminolysis reaction could be used as an alternative method to install an equatorial nitrogen with useful selectivity.[14] Therefore, a model system was desired in order to quickly assess the aziridine disconnection.

2.3.1 Taber's Intermediate

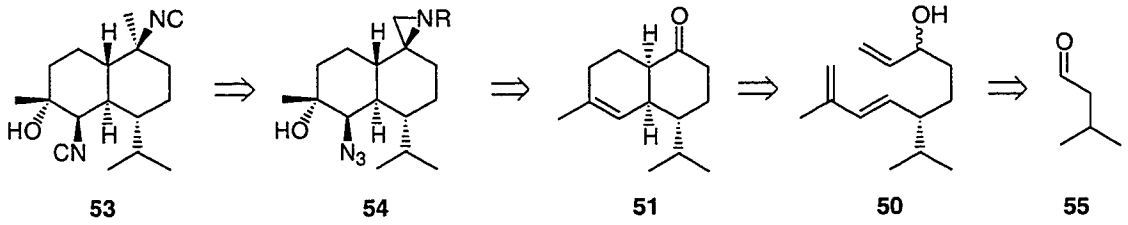
While investigating the precedence of IMDA cycloadditions in substrates similar to **47**, Taber's synthesis of (±)-torreyol (**52**) utilized triene **50** to establish the requisite *cis*-decalin (Scheme 2.4).[15] Importantly, *cis*-decalin **51** possessed the same relative stereochemistry between C(6) and C(7) as found in the kalihinols.

Scheme 2.4



Decalone **51** could serve as an adequate model scaffold to explore an effective means to introduce the β-hydroxy isonitrile and tertiary isonitrile moieties possessed by kalihinol A and related congeners. Extension of the same disconnections proposed for the fully functionalized system to *cis*-decalin **51** gives bis-isonitrile **53**, the retrosynthesis of which is shown in Scheme 2.5.

Scheme 2.5

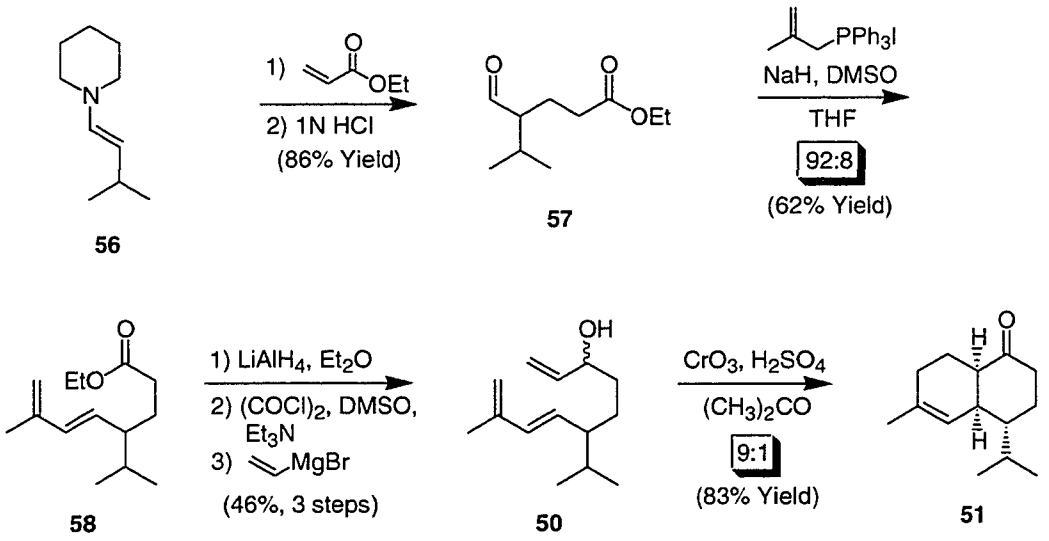


2.3.2 Accessing the *cis*-Decalin

Having identified an approach, work commenced with the preparation of triene **50** in accordance with Taber's procedure (Scheme 2.6).[15] The piperidine enamine of isovaleraldehyde was reacted with ethyl acrylate followed by acidic workup to give aldehyde **57**. Wittig olefination afforded a mixture of *E*:*Z* isomers in the ratio of 92:8 from which **58** was easily isolated. Subsequent reduction, oxidation, and addition of

vinyl magnesium bromide proceeded uneventfully to provide allylic alcohol **50**. Lastly, oxidation of **50** using Jones reagent directly afforded *cis*-decalin **51** as the major isomer in a 9:1 mixture of decalin diastereomers in 83% yield.

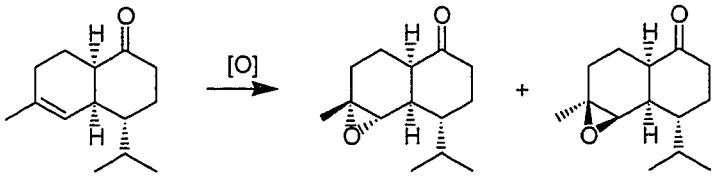
Scheme 2.6



2.3.3 Accessing the *trans*-Decalin

With *cis*-decalin **51** in hand, it was possible to examine diastereoselective installation of the requisite isonitriles for the decalin core of kalihinol A. Epoxidation of **51** was initially performed with *m*-CPBA (Scheme 2.7). Disappointingly, very little selectivity for epoxide **59** was observed (*ca.* 55:45). However, a much improved ratio was obtained by using either DMDO or Davis' oxaziridine (ca. 98:2).[16,17] The reason for this difference in diastereoselectivity is likely one of the steric environment surrounding the oxygen to be transferred. In the case of dimethyl dioxirane or Davis' oxaziridine, the oxygen is neopentyl and thereby less able to engage the concave face of the olefin.

Scheme 2.7

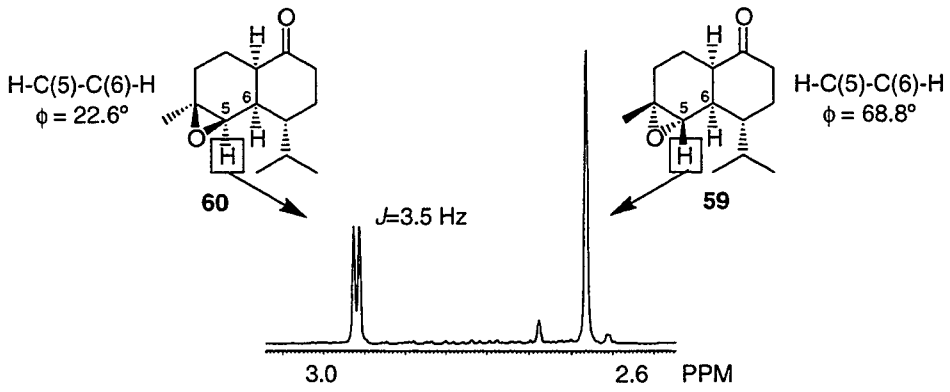


51 **59** **60**

[O]	Yield (%)	59:60
m-CPBA	91	55:45
DMDO	95	98:2
Davis' Oxaziridine	33	>98:2

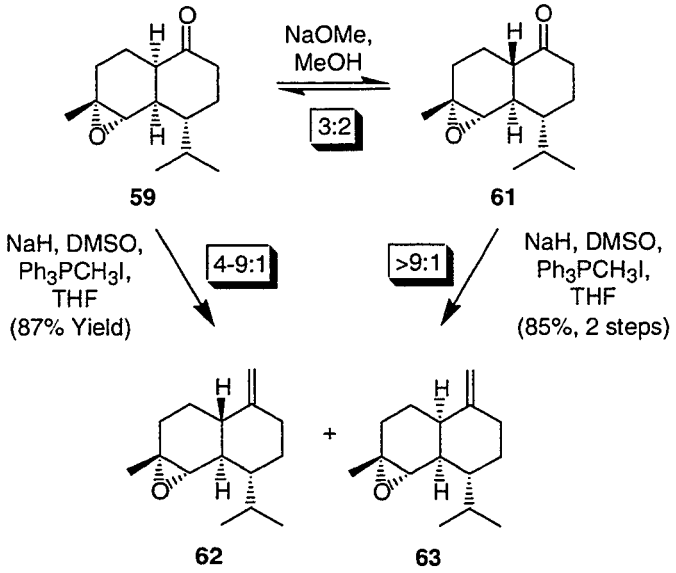
The initial stereochemical assignments of **59** and **60** were based upon NMR coupling constants. The C(5)-H of the less polar diastereomer appeared as a singlet in the ^{1}H NMR spectrum, as illustrated from the crude NMR of the *m*-CPBA reaction (Figure 2.1), whereas the C(5)-H of the more polar diastereomer appeared as a doublet (J=3.5 Hz). Using the Karplus correlation, the less polar diastereomer was assigned as having the desired epoxide stereochemistry given the H-C(5)-C(6)-H dihedral angle was calculated to be 68.8°.[18]

Figure 2.1



The ability to access usable quantities of the *trans*-decalin corresponding to epoxide **59** was imperative for the proposed synthesis to be successful. Gratifyingly, exposure of **59** to the ylide generated from triphenylphosphoniummethyl iodide and dimsyl anion afforded *trans*-decalin **62** with lesser amounts of *cis*-decalin **63** (Scheme 2.8). However, the actual ratio of **62** to **63** was variable between 4:1 and 9:1, depending upon how the experiment was conducted. Slow addition of sub-stoichiometric amounts of ylide tended to give higher *trans* selectivity, whereas adding excess ylide in one portion generally gave a lower ratio. Conducting the olefination on a 3:2 *trans* to *cis*-decalin mixture of **61** and **59** respectively, generated from epimerization of epoxide **59** (NaOMe, MeOH) at 25°C, resulted in a reproducible ratio of at least 9:1 favoring the *trans*-diastereomer **62**. Like other dynamic resolutions of this type, the conversion of **59** to **62** most likely resulted from a faster rate of olefination for the *trans*-decalin than the *cis*-decalin, and concurrent epimerization of unreacted *cis*-decalin **59**.[6,7]

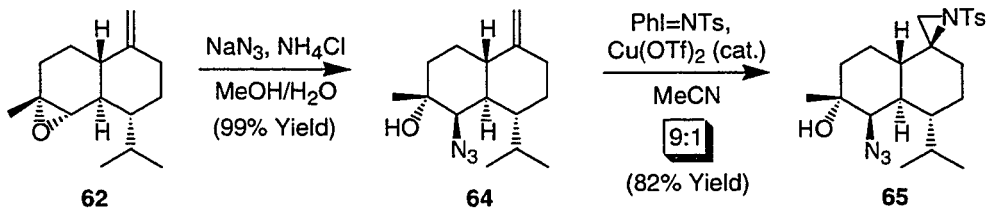
Scheme 2.8



2.3.4 Installation of the Nitrogens

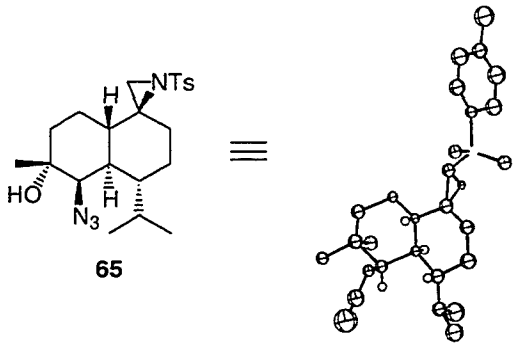
From **62**, azido-alcohol **64** was obtained in near quantitative yield by facile trans-diaxial epoxide opening with ammonium azide (Scheme 2.9).[19] Rewardingly, installation of the equatorial nitrogen at C(10) was efficiently accomplished by copper-catalyzed aziridination with (N-(*p*-tolylsulfonyl)imino)phenyliodinane (PhI=NTs) to give a 9:1 mixture of diastereomers favoring aziridine **65**.[20,21]

Scheme 2.9



Single crystal X-ray analysis of **65** revealed the correct relative configuration at all six stereocenters (Figure 2.2). The efficiency of the aziridination attested to the utility and functional group tolerance of the reaction despite very few examples of diastereoselective aziridination reactions using PhI=NTs in the context of syntheses.

Figure 2.2



65

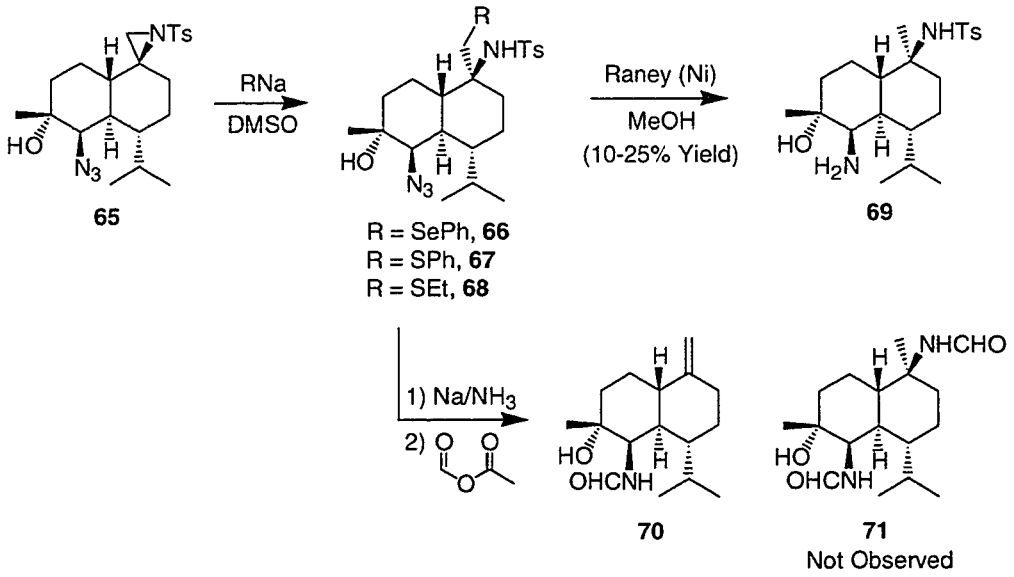
2.3.5 Unmasking the Amines

2.3.5.1 Nuclophilic Aziridine Opening

An effective method for opening the aziridine in azido-alcohol **65** to unmask the tertiary amine at C(10) was expected to involve a sulfide or selenide nucleophile which could be simultaneously removed along with the tosyl group. In the event, the aziridine could be opened quite easily with the sodium salt of thiols or selenols (Scheme 2.10).[22] However, subsequent reduction with Raney nickel or other metal catalysts provided low yields of amine **69**.[23] Alternatively, reduction of **66** or **67** with sodium metal led to elimination of the sulfonamide to give **70** after treatment with acetic formic anhydride

(AFA). Apparently, the aryl sulfide/selenide was reduced prior to reduction of the sulfonamide.

Scheme 2.10

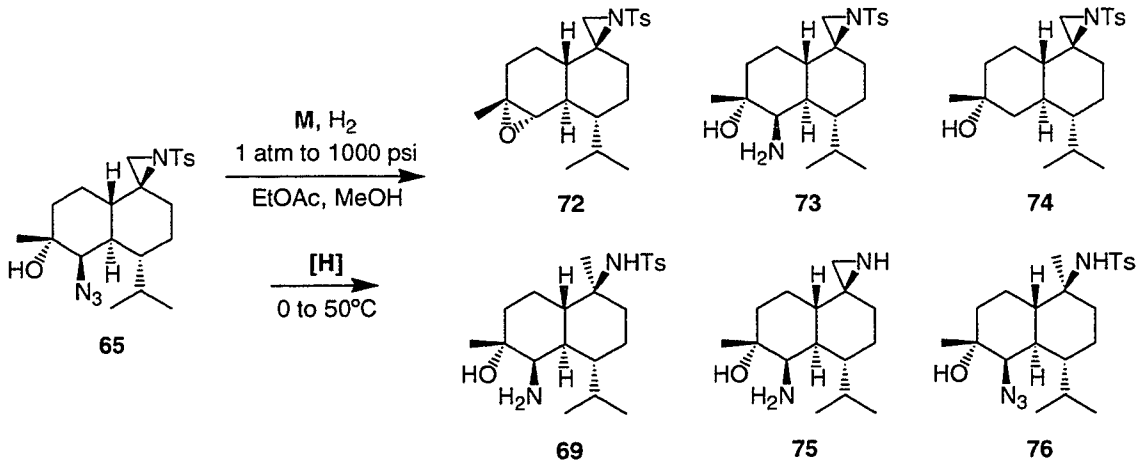


2.3.5.2 Aziridine and Azide Reduction

In order to examine reduction of the azide, opening of the aziridine, and removal of the tosyl group, a variety of hydride sources and metal catalyzed hydrogenolysis conditions were screened. Using aziridine **65**, these efforts are summarized in Table 2.1. In general, exclusive reduction of the azide was facile using PtO_2/H_2, $NiCl_2/NaBH_4$, or NaSeH to proved amine **73**. [24] However, Staudinger conditions (PPh_3, H_2O) failed to provide **73** due to the stability of the intermediate iminophosphorane towards hydrolysis and competitive opening of the aziridine by PPh_3.[25,26] In addition, most heterogeneous

metal-catalyzed hydrogenolysis conditions led to formation of the corresponding epoxide (**72**).

Table 2.1



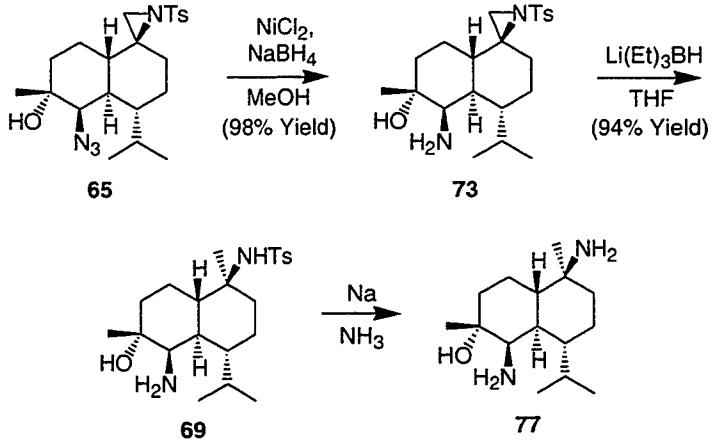
M/[H]	Product(s)	M/[H]	Product(s)
$LiAlH_4$	**73, 74, 69**	Pd/C	**72**
DIBAL	—	$Pd(OH)_2$	**72**
Red-Al	**73, 75**	$Pd/CaCO_3/Pb$	**72, 73**
$NaBH_4$	—	PtO_2	**73**
$Li(Et)_3BH$	**74, 69**	Pt	**72**
NaSeH	**73**	Rh/Al_2O_3	**72, 73**
NaTeH	**76**	R(Ni)	**72, 73**
$NaBH_4/Rh(OTf)_4$	**72, 73**	Na/NH_3	**75**
$NaBH_4/NiCl_2$	**73**	Ph_3P/H_2O	—

Aziridine opening was found to be more difficult than anticipated. Metal catalyzed hydrogenolysis altogether failed to open the aziridine even at high temperatures and pressures. Hydride sources such as $LiAlH_4$ and $LiEt_3BH$ effectively led to aziridine opened products; however, these conditions were complicated by competitive displacement of the azide. The use of NaTeH provided exclusive aziridine opening (**76**), but the reduction was difficult to reproduce.[27] As aziridine opening was complicated by

the presence of the azide, sequential azide reduction, aziridine opening, and tosyl deprotection was envisioned as the most promising order of events.

Thus, reduction of the azide with nickel boride, generated *in situ* from nickel chloride and sodium borohydride, gave amine **73** in excellent yield (Scheme 2.11).[24] Treatment of **73** with lithium triethylborohydride cleanly effected aziridine opening to provide **69**. Lastly, removal of the tosyl group with sodium furnished diamine **77**. Despite requiring three steps to deprotect the orthogonally masked amines, the selective reduction protocol was very efficient (*ca.* 88% three step yield) and allowed for sequential derivatization of each free amine to provide the functional groups required in each of the kalihinols (e.g. -NCS, -NCO, -NC).

Scheme 2.11

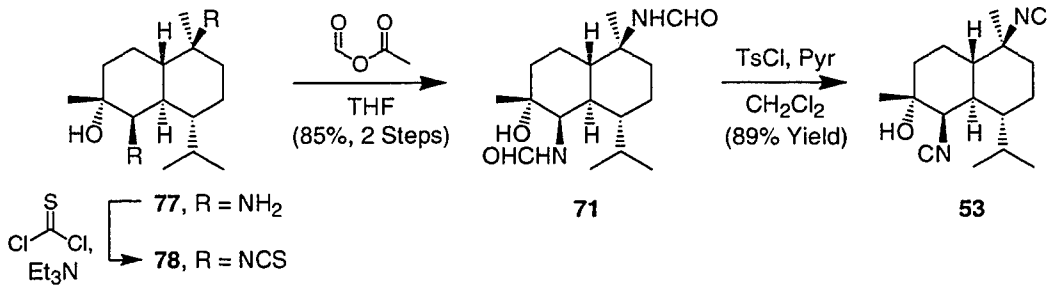


2.3.6 Incorporating the Isonitriles

Finally, bis-formylation of **77** using *N*-formyl imidazole or acetic formic anhydride followed by dehydration gave bis-isonitrile **53** (Scheme 2.12). Alternatively,

treatment of **77** with thiophosgene and triethylamine provided the corresponding isothiocyanate (**78**). The completion of the model decalin and establishment of conditions to access the kalihinol core culminated in a publication.[28]

Scheme 2.12



The synthesis of **53** from the piperidine enamine of isovaleraldehyde required fifteen steps with an overall yield of 7%. The decalin carbocycle displayed high levels of substrate control in the diastereoselective installation of the *trans*-diaxial β-hydroxy isonitrile and tertiary isonitrile functional groups. Utilization of a metal-catalyzed aziridination followed by a reductive opening protocol proved quite effective for the incorporation of a tertiary isonitrile and was later shown to be useful for the preparation of 4-amino substituted cyclopentenes by O'Brien and co-workers.[29]

2.4 Antimalarial Assays

Due to the structural similarities between the model system intermediates and the decalin core of kalihinol A, it was recognized that bisisonitrile **53** and related derivatives could be used to learn about relationships between functionality and antimalarial activity

within the kalihinol family. To this end, a collaboration with Prof. Daniel E. Goldberg, at the University of Washington in St. Louis, was initiated.

2.4.1 Synthesis of Analogs

An appropriate starting point would be to synthesize a preliminary set of compounds containing the same array of functional groups as observed within the kalihinol family (e.g. NC, NCS, NHCHO). Given that **53** and **78**, functionalized at both C(4,5) and C(10), were already in hand, additional compounds functionalized only at C(4,5) were made. This was accomplished using **64** as the common intermediate where the exo-methylene could be either retained using Na/NH_3 to reduce the azide, or reduced stereoselectively from the β-face with $NiCl_2/NaBH_4$ (Scheme 2.13).[24] The resulting stereochemistry of **82** was confirmed by single crystal X-ray analysis (Figure 2.3).

Scheme 2.13

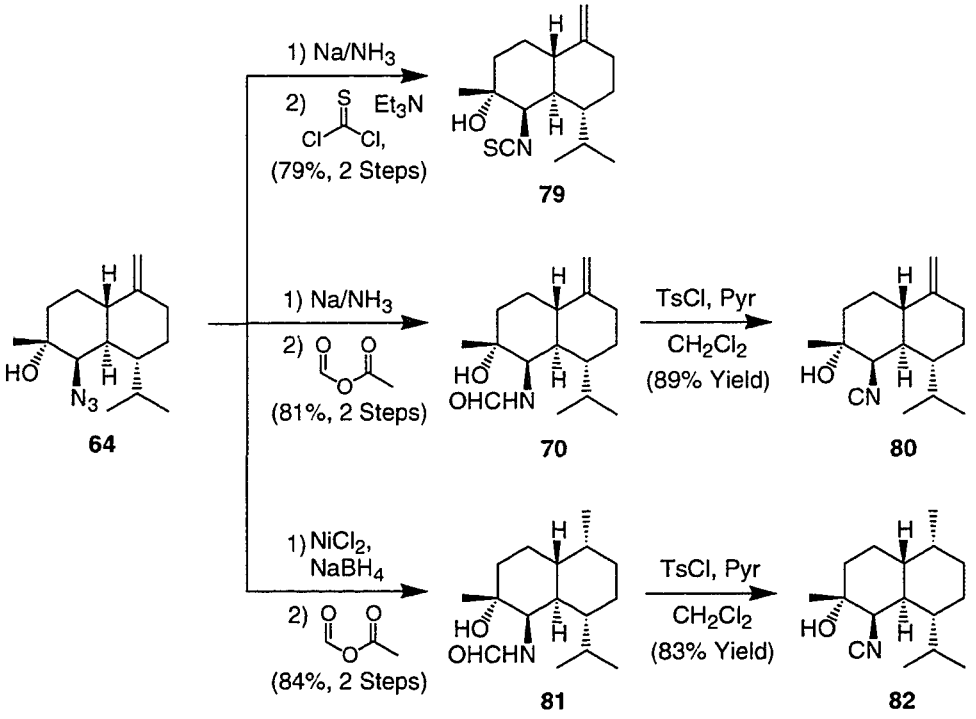
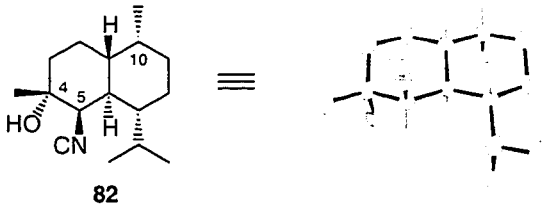


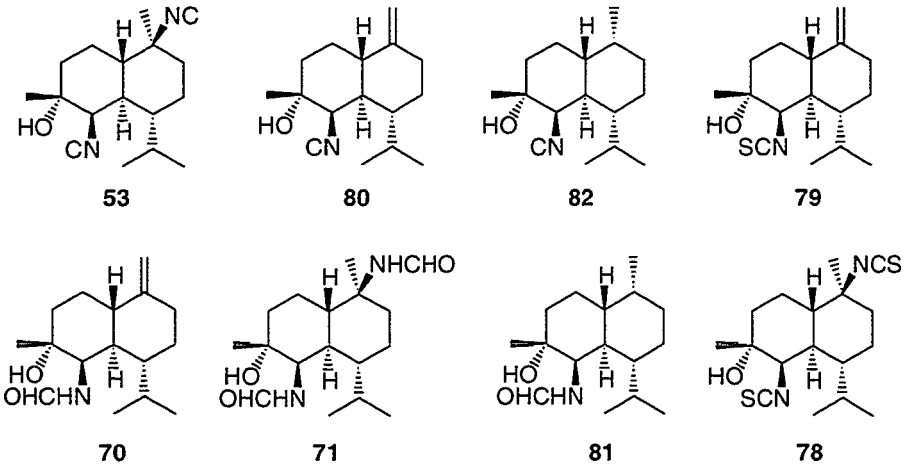
Figure 2.3



2.4.2 Antimalarial Activity

Compounds **53**, **70**, **71**, and **78-82** were evaluated by Prof. Goldberg at Washington University in St. Louis for antimalarial activity. The protocol used was a 48-hour ^{3}H-hypoxanthine incorporation assay employing both chloroquine-sensitive (HB3) and chloroquine-resistant (Dd2) strains of *P. falciparum* (Table 3).[30]

Table 2.2



		Compound								
		53	**80**	**82**	**79**	**70**	**71**	**81**	**78**	**CQ**
P. falciparum Cell Line	**HB3**	0.08	0.80	0.50	>20	>20	>20	>20	>20	0.02
	Dd2	0.08	2.00	2.00	>20	>20	>20	>20	>20	0.15

IC_{50} (μM)

The results outlined in Table 2.2 show that the isonitrile containing compounds exhibited an IC_{50} of 2 μM or less. In particular, bis-isonitrile **53** showed an 80 nM IC_{50} against both HB3 and Dd2 strains. This suggested a potentially different mode of action than the chloroquine (CQ) standard, the activity of which was strain dependent. Compared to the reported activity of kalihinol A (EC_{50} = 1.2 nM), the activity of bis-isonitrile **53** revealed that the chloro-tetrahydropyran had only a minimal influence on activity. Also, the lack of activity of the corresponding bis-formamide (**71**) suggested that bis-isonitrile **53** was not hydrolyzed to **71** under the assay conditions. Although structure-activity relationships could not yet be drawn from this preliminary group of derivatives, it was clear that future studies with a larger and more diverse group of

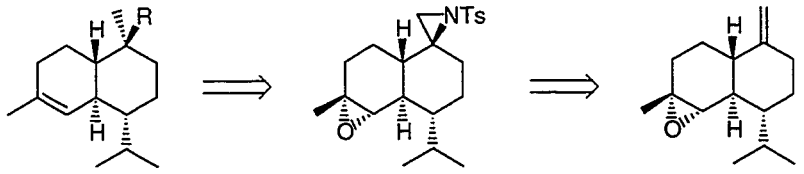
compounds could yield valuable information about the role of isonitriles in antiplasmodial activity.

2.5 Total Synthesis of (±)-10-Isocyanato-4-Cadinene and (±)-10-Isothiocyanato-4-Cadinene

2.5.1 Retrosynthesis

Pleased by the initial assay results with derivatives functionalized at C(4),C(5) or C(4),C(5) and C(10), we sought to synthesize and test compounds functionalized exclusively at C(10). Coincidentally, such compounds were natural products themselves, 10-isocyanato-4-cadinene (**15**) and 10-isothiocyanato-4-cadinene (**16**), neither of which have been previously synthesized or evaluated for antimalarial activity (Scheme 2.14).[31,32] These two natural products could arise from epoxide **62**, gram quantities of which were already in hand. It was anticipated that the epoxide in **72** would serve as protecting group for the requisite olefin in **15** and **16**.

Scheme 2.14



15, R = NC
10-isocyano-4-cadinene
16, R = NCS
10-isothiocyanato-4-cadinene

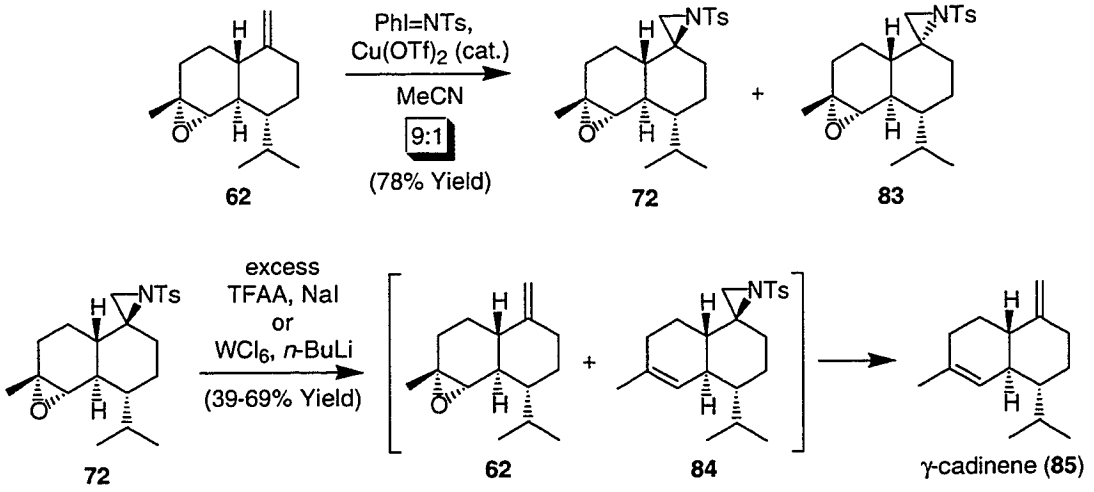
72

62

2.5.2 Epoxide Deoxygenation, an Interesting Result

Treatment of olefin **62** with PhI=NTs and catalytic $Cu(OTf)_2$ provided a mixture of diastereomers (ca. 9:1) favoring aziridine **72** (Scheme 2.15). Exposure of **72** to standard epoxide deoxygenation conditions, either TFAA/NaI or WCl_6/*n*-BuLi, gave a variable yield and ratio of **62** and **84**.[33,34] Also, the use of excess reagent, c.a. 8 eq., under either conditions led to the formation of γ-cadinene (**85**).[35]

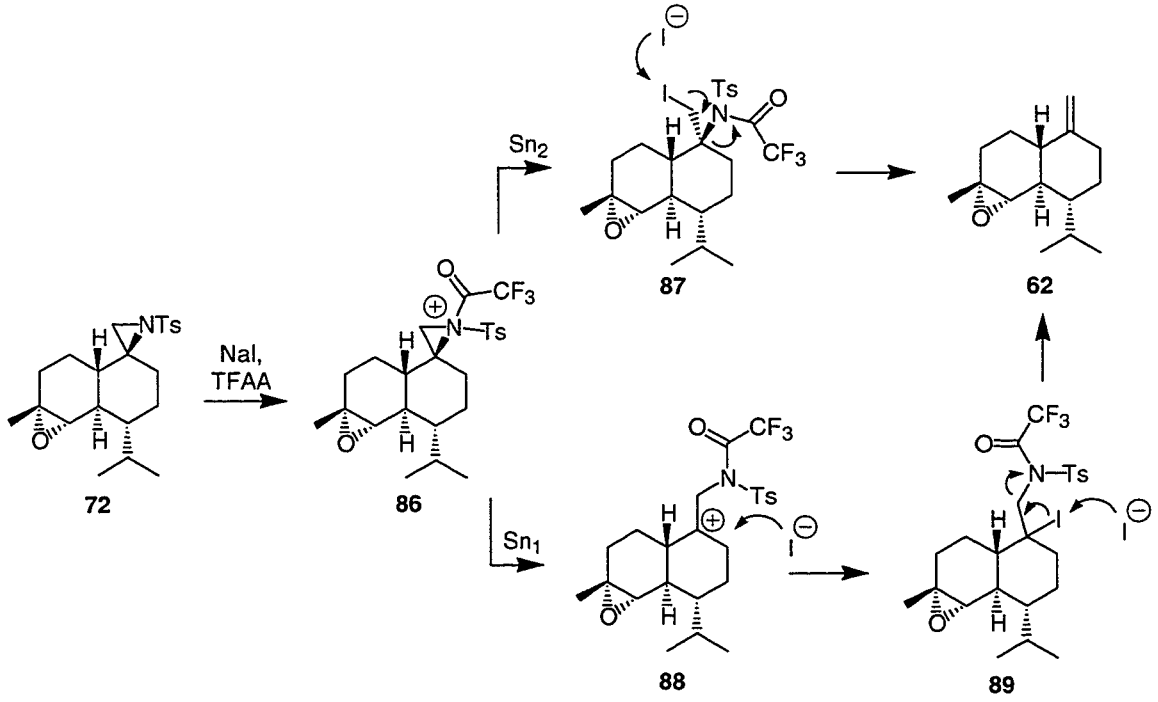
Scheme 2.15



Although deoxygenation of the epoxide was expected, deamination of the aziridine was not. This type of aziridine removal (i.e. **72**→**62** or **84**→**85**) has not been documented in the literature except with unprotected aziridines under nitrosating conditions.[36,37] However, given the lack of synthetic utility for such a transformation, additional experimentation to confirm these aziridine deamination results were not

performed. Furthermore, no reasonable speculation on the mechanism for the deamination with WCl_6/*n*-BuLi could be made without further studies. In the case of TFAA/NaI, the mechanism was most likely analogous to epoxide deoxygenation as described by Sonnet.[33] The aziridine could be acylated by the trifluoroacetyl iodide generated *in situ*, followed by opening with iodide in either an SN_1 or SN_2 mode (Scheme 2.16). Expulsion of the sulfonamide could then occur upon oxidation of the alkyl iodide to molecular iodine.

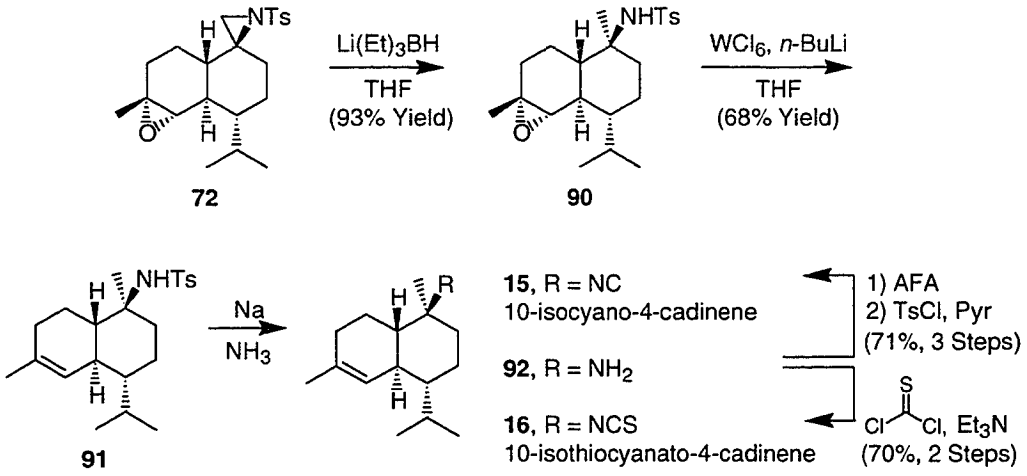
Scheme 2.16



In order to effectively remove the epoxide, the aziridine needed first to be opened. Aziridine **72** was treated with $LiEt_3BH$ to provide epoxide **90** in excellent yield (Scheme 2.17). The epoxide was then removed using WCl_6/*n*-BuLi to give olefin **91**.

Straightforward advancement of **91** led to both 10-isothiocyanato-4-cadinene (**15**) and 10-isocyanato-4-cadinene (**16**) in good yield. Thus, the first total synthesis and structural confirmation of both of these natural products was achieved.

Scheme 2.17



2.6 Conclusions

Model system studies related to the synthesis of the kalihinols, specifically kalihinols A, E and C, were presented. Using known decalin **51** as a model substrate, an efficient strategy for access to the fully functionalized decalin core of the aforementioned kalihinols was established. A series of substrate-controlled, diastereoselective reactions were employed to obtain bis-isonitrile **53**. In particular, aziridination of olefin **64** and subsequent reductive opening was shown to be an effective method for installation of a tertiary amine. Through collaboration with Prof. Daniel E. Goldberg, bis-isonitrile **53** was shown to possess an 80 nM IC_{50} against two strains of *P. falciparum*. The synthesis

of several related analogs to be assayed for antimalarial activity led to the first total syntheses of (±)-10-isocyano-4-cadinene (**15**) and (±)-10-isothiocyanato-4-cadinene (**16**).

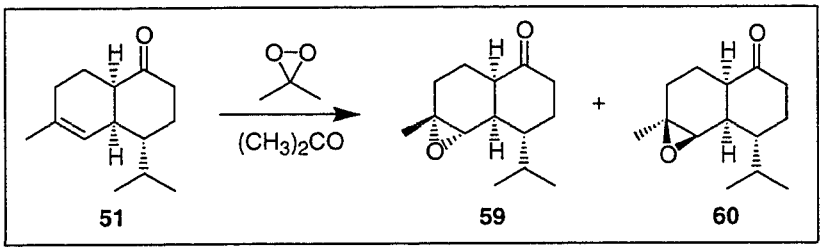
2.7 Experimental

2.7.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly distilled solvents. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone. Methylene chloride (CH_2Cl_2), and benzene were distilled from calcium hydride. Methanol (MeOH) was distilled from magnesium. All other commercially obtained reagents were used as received. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Column or flash chromatography was performed with the indicated solvents using silica gel (particle size 0.032-0.063 nm) purchased from Bodman. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance DPX-500 or Bruker Advance DPX-400 spectrometers. Chemical shifts are reported relative to internal solvent as described by Gottlieb (i.e. chloroform ^1H δ 7.26 ppm, ^{13}C δ 77.16 ppm; acetone ^1H δ 2.05 ppm, ^{13}C δ 29.84 ppm; methanol ^1H δ 3.31 ppm, ^{13}C δ 49.00 ppm).[38] Melting points were obtained on a Gallenkamp variable temperature melting point apparatus and are uncorrected. Infrared spectra were recorded on a Midac M-1200 FTIR. High resolution mass spectra were acquired at The University of Illinois Mass Spectrometry Center.

2.7.2 Preparative Procedures

Preparation of epoxides 59 and 60



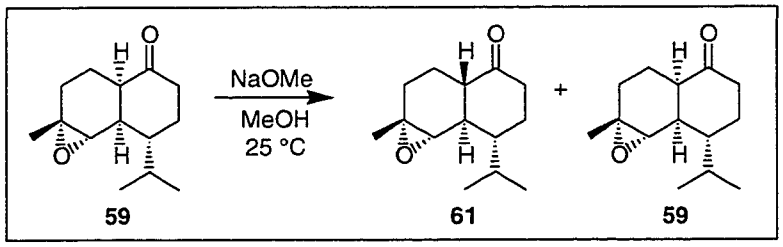
Epoxides 59 and 60. To a solution of dimethyl dioxirane (0.09 M in acetone, 145 mL, 13.1 mmol, 1.8 equiv) at –78°C, was added olefin **3** (1.52 g, 7.37 mmol, 1.0 equiv) as a solution in acetone (10 mL). After 2 h, the solution was slowly warmed to rt before removing the solvent *in vacuo*. The resulting oil was purified by silica gel column chromatography (15:1 then 8:1 hexanes:EtOAc) to afford **59** (1.55 g, 95% yield) and **60** (32 mg, 2% yield) as colorless oils.

Epoxide 59. ^{1}H NMR (400 MHz, $CDCl_3$) 2.67 (s, 1H), 2.47-2.40 (m, 1H), 2.38-2.28 (comp m, 2H), 2.21-2.12 (m, 1H), 1.97-1.70 (comp m, 6H), 1.47-1.39 (m, 1H), 1.34-1.22 (comp m, 4H), 1.02 (d, J=6.7 Hz, 3H), 0.95 (d, J=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.0, 64.0, 58.2, 44.5, 42.0, 38.4, 38.1, 28.1, 26.0, 23.6, 23.0, 21.4, 19.2, 18.9; IR (thin film/NaCl) 2958 (s), 2872 (s), 1708 (s), 1463 (m), 1420 (m), 1379 (m), 1331 (m), 1209 (m), 1139 (m), 1060 (m) cm^{-1}; HRMS (FAB) *m/z* found: 223.1698 [calc'd for $C_{14}H_{23}O_2$ (M+H): 223.1698].

Epoxide 60. ^{1}H NMR (400 MHz, $CDCl_3$) 2.97 (d, J=3.5 Hz, 1H), 2.38-2.26 (comp m, 3H), 2.19 (ddd, J=3.0, 6.8, 9.2 Hz, 1H), 2.13-2.02 (comp m, 2H), 1.99-1.77 (comp m, 3H), 1.72-1.64 (m, 1H), 1.58-1.45 (m, 1H), 1.31 (s, 3H), 1.30-1.21 (m, 1H),

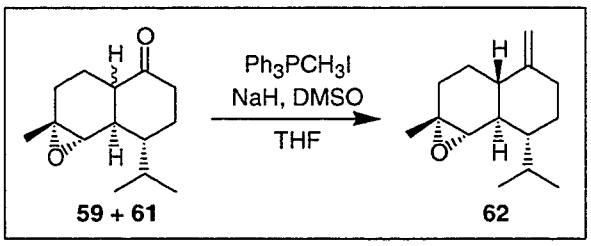
1.03 (d, J=6.8 Hz, 3H), 0.92 (d, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.5, 62.5, 59.0, 46.0, 41.6, 38.4, 38.1, 28.3, 28.2, 23.7, 23.0, 21.4, 21.3, 17.6; IR (thin film/NaCl) 2957 (s), 2872 (m), 1710 (s), 1447 (m), 1423 (m), 1368 (m), 1250 (m), 852 (m), 785 (w) cm^{-1}; HRMS (FAB) *m/z* found: 223.1698 [calc'd for $C_{14}H_{23}O_2$ (M+H): 223.1698].

Preparation of *trans*-decalin 61



***trans*-Decalin 61**. To a solution of epoxide **59** (4.69 g, 21.1 mmol, 1.0 equiv) in MeOH (50 mL) at 25°C was added NaOMe (60 mg, 1.11 mmol, 0.05 equiv). After 36 h, the solution was concentrated under reduced pressure, diluted with CH_2Cl_2 (100 mL), and washed with water (50 mL) and brine (50 mL). The solution as dried with Na_2SO_4 and cencentrated *in vacuo* to gave a 3:2 equilibrium mixture of **61** to **59**, which could be used without further purification or purified by silica gel chromatography (15:1 then 8:1 hexanes:EtOAc) to afford pure **61** (2.72 g, 58% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) 2.98 (s, 1H), 2.38-2.24 (comp m, 3H), 2.10-1.98 (comp m, 2H), 1.95-1.89 (m, 1H), 1.83-1.45 (comp m, 5H), 1.30 (s, 3H), 1.25-1.15 (m, 1H), 1.02 (d, J=7.0 Hz, 3H), 0.85 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.4, 60.9, 58.5, 50.2, 44.4, 43.6, 40.3, 29.5, 26.8, 24.8, 23.6, 21.6, 19.0, 15.6; IR (thin film/NaCl) 2958 (s), 2874 (m), 1715 (s), 1452 (m), 1424 (m), 1370 (m), 1206 (m), 1160 (m), 1089 (m), 1033 (m) cm^{-1}; HRMS (FAB) *m/z* found: 223.1698 [calc'd for $C_{14}H_{23}O_2$ (M+H): 223.1698].

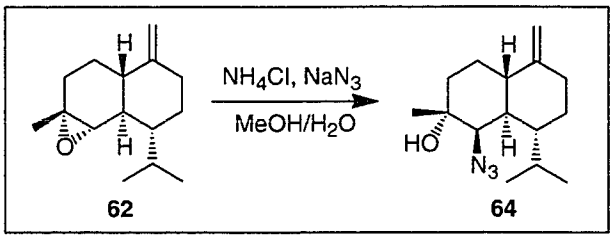
Preparation of olefin 62



Olefin 62. To a solution of DMSO (16 mL) and THF (10 mL) was added 60% NaH (1.8 g, 45 mmol, 2.0 equiv). The resulting mixture was heated at 60°C for 2 h then cooled to rt before adding a mixture of methyltriphenylphosphonium iodide (18.19 g, 45.0 mmol, 2.0 equiv) in THF (40 mL) over 2 minutes. To the resulting yellow mixture was then added a crude solution of decalins **59** and **61** (4.64 g, 20.7 mmol, 1.0 equiv) in THF (100 mL). After heating at 35°C for 5 h, the reaction was quenched with water (50 mL) and diluted with hexanes (100 mL). The aqueous layer was separated and extracted with hexanes (2 x 25 mL) and the combined organic fractions were washed with water (2 x 50 mL), dried with Na_2SO_4, and concentrated. The resulting residue was purified by silica gel column chromatography (9:1 Pentane:Et_2O) to give **62** (3.87 g, 85% yield from **59**) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64 (d, 1.5 Hz, 1H), 4.48 (d, 1.5 Hz, 1H), 2.95 (s, 1H), 2.34 (dt, *J*=6.7, 12.5 Hz, 1H), 2.29-2.23 (m, 1H), 2.12-2.07 (m, 1H), 1.97 (dt, *J*=4.3, 13.0 Hz), 1.82 (ddd, *J*=3.5, 6.8, 12.7 Hz, 1H), 1.65 (ddd, *J*=5.7, 12.6, 13.5 Hz, 1H), 1.60 (ddt, *J*=2.0, 6.0, 12.8 Hz, 1H), 1.51 (br t, *J*=11.5 Hz, 1H), 1.44 (tt, *J*=3.5, 12.0 Hz, 1H), 1.34-1.24 (comp m, 5H), 1.14 (dq, *J*=4.1, 13.0 Hz, 1H), 0.96 (d, *J*=7.0, 3H), 0.81 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3, 104.3, 61.3, 58.3, 46.0, 44.9, 43.8, 36.1, 30.4, 27.0, 26.5, 23.8, 22.6, 21.7, 15.6; IR (thin film/NaCl) 2957 (s), 2933 (s), 2875 (m), 2842 (m), 1649 (m), 1449 (m), 1378 (m), 887 (m), 807 (m),

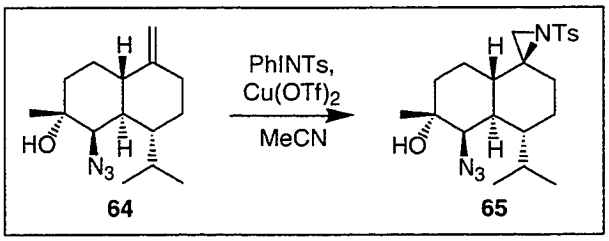
790 (w) cm^{-1}; HRMS (FAB) *m/z* found: 221.1905 [calc'd for $C_{15}H_{25}O$ (M+H): 221.1905].

Preparation of azide 64



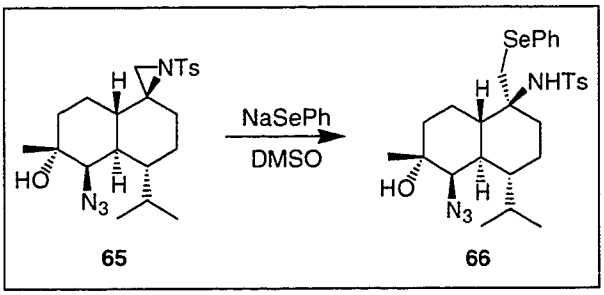
Azide 64. To a solution of olefin **62** (3.45 g, 15.7 mmol, 1.0 equiv) in 8:1 MeOH:H_2O (150 mL), was added NaN_3 (6.11 g, 94.0 mmol, 6.0 equiv) and NH_4Cl (2.51 g, 47.0 mmol, 3.0 equiv). The mixture was heated to 80°C. After 36 h, the solution was concentrated under reduced pressure, diluted with EtOAc (100 mL). After washing with water (50 mL) and brine (2 x 25 mL), the organic fraction was dried with Na_2SO_4 and concentrated to give spectroscopically pure azide **64** (4.12 g, 99% yield) as an amorphous, white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 4.68 (d, 1.5 Hz, 1H), 4.56 (d, 1.5 Hz, 1H), 3.49 (s, 1H), 2.36 (dt, *J*=3.4, 12.8 Hz, 1H), 2.02-1.93 (comp m, 2H), 1.91-1.79 (comp m, 2H), 1.73-1.47 (comp m, 6H), 1.42 (br s, 1H), 1.36 (s, 3H), 1.08 (dq, *J*=3.6, 12.4, Hz, 1H), 0.98 (d, *J*=6.8, 3H), 0.76 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 105.1, 72.5, 68.2, 44.2, 43.4, 38.5, 36.3, 33.0, 28.9, 26.2, 26.0, 24.0, 21.5, 15.4; IR (thin film/NaCl) 3439 (br m), 2959 (s), 2935 (s), 2868 (m), 2104 (s), 1644 (m), 1465 (w), 1370 (m), 1280 (m), 1029 (m) cm^{-1}; HRMS (FAB) *m/z* found: 264.2075 [calc'd for $C_{15}H_{26}N_3O$ (M+H): 264.2076].

Preparation of aziridine 65



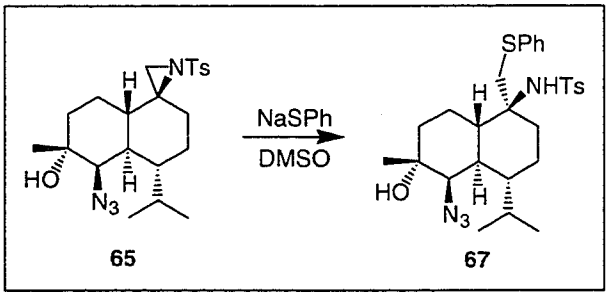
Aziridine 65. To a solution of azide **64** (1.26 g, 4.80 mmol, 1.0 equiv) in dry MeCN (250 mL) with 4 Å sieves (ca. 3 g) at 25°C, was added *N*-tosyliminophenyliodinane (3.59 g, 9.62 mmol, 2.0 equiv). After 2 minutes, $Cu(OTf)_2$ (87 mg, 0.24 mmol, 0.05 equiv) was added and the mixture was vigorously stirred for 8 h. The mixture was then diluted with EtOAc (50 mL) and filtered through a short plug of silica gel. After removing the solvent *in vacuo*, the resulting residue, ca. 9:1 mixture of aziridine diastereomers, was purified by silica gel column chromatography (hexanes:EtOAc, 11:1) to afford aziridine **65** (1.70 g, 82% yield) as a white solid. m.p. >143°C (dec) (recrystallized from 11:1 hexanes:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, 8.4 Hz, 2H), 7.31 (d, 8.0 Hz, 2H), 3.49 (s, 1H), 2.50 (s, 1H), 2.43 (s, 3H), 2.38 (d, *J*=1.8 Hz, 1H), 2.28 (dt, *J*=3.5, 12.9 Hz, 1H), 2.16-2.08 (m, 1H), 2.03-1.89 (comp m, 3H), 1.78 (dt, *J*=2.6, 11.2 Hz, 1H), 1.61-1.46 (comp m, 4H), 1.40-1.33 (comp m, 4H), 1.00 (d, *J*=7.2 Hz, 3H), 0.98-0.87 (comp m, 1H), 0.80 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.7, 138.4, 129.6, 127.3, 72.2, 67.9, 55.4, 42.7, 42.0, 37.9, 36.6, 32.6, 31.3, 29.1, 26.1, 23.8, 21.7, 21.4, 20.2, 15.4; IR (thin film/NaCl) 3507 (br m), 2958 (m), 2870 (w), 2099 (s), 1450 (m), 1313 (m), 1288 (m), 1156 (s), 1136 (m), 1094 (m) cm^{-1}; HRMS (FAB) *m/z* found: 433.2274 [calc'd for $C_{22}H_{33}N_4O_3S$ (M+H): 433.2273].

Preparation of selenide 66



Selenide 66. To a solution of **65** (20 mg, 0.046 mmol, 1.0 equiv) in DMSO (2 mL) was added the sodium salt of benzeneselenol (16 mg, 0.092 mmol, 2.0 equiv). After 24 h at room temperature, the reaction was diluted with EtOAc (30 mL) and water (10 mL). After washing the organic phase with water (2 x 10 mL), brine (10 mL), and drying with Na_2SO_4, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (9:1 hexanes:EtOAc) to afford selenide **66** (23 mg, 83%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J*=8.3 Hz, 2H), 7.52-7.49 (comp m, 2H), 7.30-7.26 (comp m, 5H), 5.04 (s, 1H), 3.43 (s, 1H), 3.28 (d, *J*=12.5 Hz, 1H), 2.89 (d, *J*=12.4 Hz, 1H), 2.43 (s, 3H), 2.25-2.16 (m, 1H), 1.95-1.78 (comp m, 3H), 1.66-1.22 (m, 1H), 0.98-0.87 (comp m, 4H), 0.71 (d, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 140.6, 133.7, 129.6, 129.5, 127.9, 127.3, 127.1, 72.3, 68.3, 62.9, 42.1, 40.6, 39.1, 35.4, 34.3, 33.1, 29.1, 25.9, 21.7, 21.3, 20.8, 19.9, 15.4; IR (thin film/NaCl) 3492 (m), 3272 (m), 2958 (s), 2871 (m), 2101 (s), 1598 (w), 1579 (w), 1451 (m), 1150 (s), 1093 (m) cm^{-1}; HRMS (FAB) *m/z* found: 590.1831 [calc'd for $C_{28}H_{39}N_4O_3SSe$ (M+H): 590.1830].

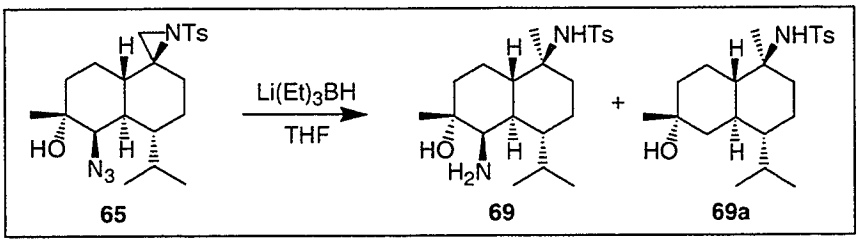
Preparation of sulfide 67



65 67

Sulfide 67. To a solution of **65** (20 mg, 0.046 mmol, 1.0 equiv) in DMSO (2 mL) was added the sodium salt of benzenethiol (12 mg, 0.092 mmol, 2.0 equiv). After 24 h at 40°C, the reaction was diluted with EtOAc (30 mL) and water (10 mL). After washing the organic phase with water (2 x 10 mL), brine (10 mL), and drying with Na_2SO_4, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (9:1 hexanes:EtOAc) to afford sulfide **67** (22 mg, 87%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J*=8.1 Hz, 2H), 7.31-7.15 (comp m, 7H), 5.02 (s, 1H), 3.37 (s, 1H), 3.18 (d, *J*=12.8 Hz, 1H), 2.84 (d, *J*=12.5 Hz, 1H), 2.36 (s, 3H), 2.12 (dt, *J*=3.0, 12.2 Hz, 1H), 1.88-1.74 (comp m, 3H), 1.70-1.64 (m, 1H), 1.58-1.52 (m, 1H), 1.44-1.15 (comp m, 10H), 0.91-0.81 (comp m, 4H), 0.65 (d, *J*=7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 140.6, 135.8, 130.7, 129.6, 129.4, 127.2, 127.1, 72.3, 68.3, 63.0, 42.1, 40.7, 39.9, 39.0, 33.2, 33.2, 29.1, 25.9, 21.7, 21.3, 20.7, 19.8, 15.4; IR (thin film/NaCl) 3492 (m), 3274 (m), 2958 (s), 2871 (m), 2101 (s), 1598 (w), 1583 (w), 1336 (s), 1151 (s), 1092 (s) cm^{-1}; HRMS (FAB) *m/z* found: 543.2462 [calc'd for $C_{28}H_{39}N_4O_3S_2$ (M+H): 543.2464].

Preparation of amines 69 and 69a



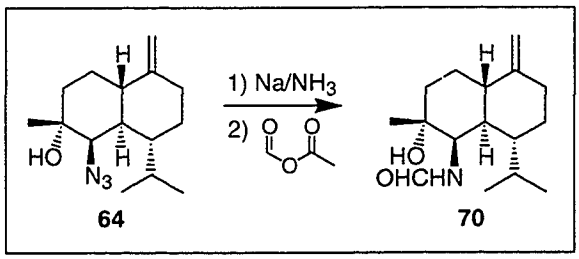
Amines 69 and 69a. To a solution of aziridine **65** (703 mg, 1.63 mmol, 1.0 equiv) in THF (30 mL) at 0°C was added $Li(Et)_3BH$ (1M in THF, 8.2 mL, 8.2 mmol, 5.0 equiv). The reaction was stirred at 0°C for 1 h before warming to 40°C for an additional 10 h. The mixture was then cooled to 0°C and diluted with EtOAc (50 mL) and water (15 mL). The organic layer was separated, washed with brine (2 x 20 mL), and dried with Na_2SO_4. After removing the solvent *in vacuo*, the resulting residue was purified by silica gel column chromatography (100% EtOAc then 10:1 EtOAc:MeOH,) to afford amines **69** (606 mg, 91% yield) and **69a** (32 mg, 5% yield) as white foams.

Amine 69. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J*=8.7 Hz, 2H), 7.16 (d, *J*=8.0 Hz, 2H), 4.39 (s, 1H), 2.60 (s, 1H), 2.33 (s, 3H), 1.80-1.70 (comp m, 2H), 1.62 (dt, *J*=3.1, 11.7 Hz, 1H), 1.50-0.88 (comp m, 20H), 0.77 (d, *J*=6.6 Hz, 3H), 0.61 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 141.0, 129.6, 127.1, 72.4, 60.9, 55.5, 42.2, 42.0, 39.6, 38.1, 32.4, 29.0, 25.4, 21.7, 21.6, 21.3, 20.2, 19.7, 15.5; IR (thin film/NaCl) 3503 (br m), 3276 (m), 2955 (s), 2933 (s), 2870 (m), 1598 (m), 1456 (m), 1384 (m), 1322 (m), 1150 (s) cm^{-1}; HRMS (FAB) *m/z* found: 409.2526 [calc'd for $C_{22}H_{37}N_2O_3S$ (M+H): 409.2525].

Amine 69a. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J*=8.5 Hz, 2H), 7.27 (d, *J*=8.0 Hz, 2H), 4.47 (s, 1H), 2.42 (s, 3H), 1.94-1.88 (m, 1H), 1.82 (ddt, *J*=3.3, 9.4, 13.6 Hz, 2H), 1.72-1.58 (comp m, 3H), 1.47- 0.82 (comp m, 18H), 0.68 (d, *J*=7.0 Hz, 3H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 142.9, 141.1, 129.6, 127.1, 77.4, 69.5, 60.7, 50.4, 47.3, 43.3, 39.5, 38.5, 35.3, 31.9, 25.9, 21.6, 21.6, 20.5, 19.5, 15.1; IR (thin film/NaCl) 3515 (br m), 3274 (m), 2957 (s), 2935 (s), 2871 (m), 2099 (m), 1599 (w), 1496 (w), 1455 (m), 1151 (s) cm^{-1}; HRMS (FAB) *m/z* found: 394.2415 [calc'd for $C_{22}H_{36}NO_3S$ (M+H): 394.2416].

Preparation of formamide 70

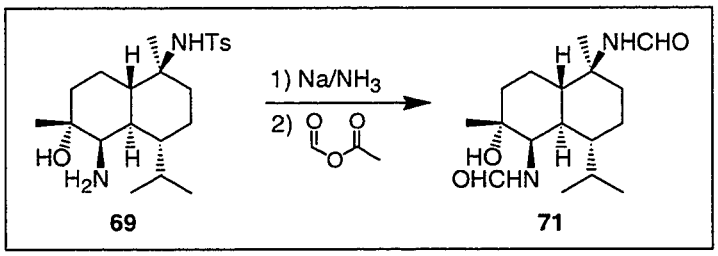


64 70

Formamide 70. To condensed ammonia (20 mL) at –78°C was added sodium (87 mg, 3.80 mmol, 10 equiv) followed by **64** (100 mg, 0.38 mmol, 1.0 equiv) in THF (4 mL). After 2 h, the blue mixture was quenched with solid ammonium chloride and the ammonia allowed to evaporate. The residue was taken up in EtOAc (30 mL), washed with 0.1 M NaOH (2 x 10 mL), brine (10 mL) and dried with Na_2SO_4. After concentration under reduced pressure, the resulting oil was dissolved in THF (10 mL) and treated with acetic formic anhydride (ca. 0.4 ml) at rt. After 4 h the solution was concentrated under reduced pressure and the residue purified by silica gel column chromatography (9:1 hexanes:EtOAc) to afford **70** (81 mg, 81% yield from **64**) as a white, amorphous solid. ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 8.02 (s, 0.9H), 7.93 (d, *J*=11.5 Hz, 0.1H), 6.98 (d, *J*=8.1 Hz, 0.9H), 6.70-6.60 (m, 0.1H), 4.49 (s, 1H), 4.41 (s, 1H), 4.04 (d, *J*=10.4 Hz, 1H), 3.38 (s, 1H), 2.69 (s, 1H), 2.17 (dt, *J*=3.3, 13.0 Hz, 1H), 2.01-1.56 (comp m, 7H), 1.46-1.35 (comp m, 3H), 1.25-1.17 (m, 1H), 1.02-0.99 (comp

m, 3H), 0.88 (dq, *J*=3.8, 12.6 Hz, 1H), 0.72 (d, *J*=7.1 Hz, 0.3H), 0.66 (d, *J*=6.9 Hz, 2.7H), 0.58 (d, *J*=6.7 Hz, 0.3H), 0.53 (d, *J*=6.9 Hz, 2.7H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 161.5, 153.9, 105.1, 71.7, 52.6, 43.9, 43.2, 40.0, 37.3, 34.3, 28.7, 26.8, 25.9, 25.1, 22.1, 15.4; IR (thin film/NaCl) 3304 (br m), 2959 (m), 2933 (m), 2866 (m), 1724 (m), 1671 (s), 1534 (m), 1466 (w), 1385 (m), 1254 (m) cm^{-1}; HRMS (FAB) *m/z* found: 266.2120 [calc'd for $C_{16}H_{28}NO_2$ (M+H): 266.2120].

Preparation of formamide 71

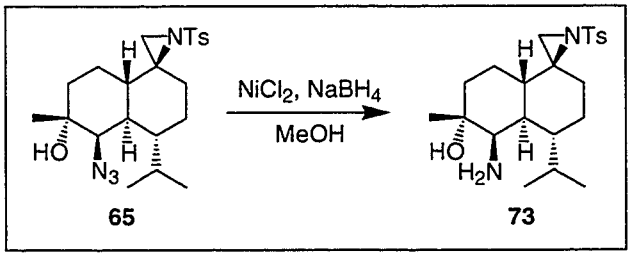


69 71

Formamide 71. To condensed ammonia (30 mL) at –78°C was added sodium (300 mg, 13.0 mmol, 10 equiv) followed by **69** (530 mg, 1.30 mmol, 1.0 equiv) in THF (5 mL). After 2 h, the blue mixture was warmed to reflux for an additional 1 h. The reaction was quenched with solid ammonium chloride and the ammonia allowed to evaporate. The resulting residue was taken up in EtOAc (30 mL), washed with 0.1 M NaOH (2 x 10 mL), brine (10 mL) and dried with Na_2SO_4. The solvent was removed *in vacuo* and the resulting oil was dissolved in THF (10 mL) and acetic formic anhydride (ca. 0.4 ml) was added at rt. After 4 h the solution was concentrated under reduced pressure and the residue purified by silica gel column chromatography (9:1 hexanes:EtOAc) to afford **71** (343 mg, 85% yield from **69**) as a white, amorphous solid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.26 (s, 0.3H) 8.12 (s, 1H), 7.89 (s, 0.7H), 4.18-4.14 (m,

1H), 2.21-1.95 (comp m, 4H), 1.87-1.80 (m, 1H), 1.66-1.42 (comp m, 6H), 1.27-1.13 (comp m, 8H), 0.88-0.76 (comp m, 6H); ^{13}C NMR (125 MHz, CD_3OD) δ 165.4, 163.7, 163.6, 163.0, 72.1, 72.0, 61.5, 58.5, 57.0, 53.3, 53.2, 45.1, 43.8, 43.7, 42.2, 40.8, 38.0 37.8, 37.8, 34.4, 34.2, 28.1, 28.0, 26.3, 22.1, 21.9, 21.9, 21.8, 20.7, 20.7, 19.8, 19.3, 15.3, 14.5; IR (thin film/NaCl) 3305 (br w), 2936 (m), 2870 (m), 2462 (w), 2361 (m), 2340 (m), 1662 (s), 1540 (m), 1386 (m), 1331 (w) cm^{-1}; HRMS (FAB) *m/z* found: 311.2335 [calc'd for $C_{17}H_{31}N_2O_3$ (M+H): 311.2335].

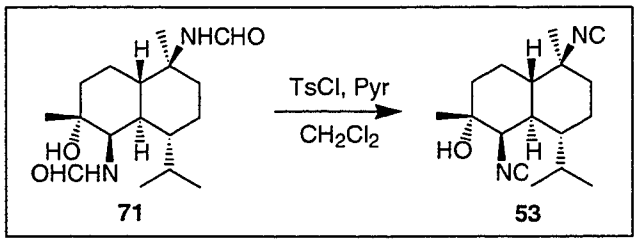
Preparation of amine 73



Amine 73. To a solution of aziridine **65** (617 mg, 1.43 mmol, 1.0 equiv) in 3:1 MeOH/THF (30 mL) at 0°C was added $NiCl_2 \cdot 6H_2O$ (542 mg, 2.28 mmol, 1.6 equiv) followed by portionwise addition of $NaBH_4$ (248 mg, 6.56 mmol, 5.0 equiv) over 10 minutes. After 30 minutes the black mixture was allowed to warm to rt, diluted with EtOAc (40 mL), and filtered through a celite plug. The solution was further diluted with EtOAc (20 mL) and washed with a 0.01M EDTA solution (25 mL, pH 7.5, K-phosphate buffer) and brine (2 x 10 mL). After removing the solvent *in vacuo*, the resulting oil was purified by silica gel column chromatography (100% EtOAc, then 12:1 EtOAc: MeOH) to give **73** (569 mg, 98% yield) as an amorphous, white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, 8.4 Hz, 2H), 7.29 (d, 8.3 Hz, 2H), 2.76 (br s, 1H), 2.50 (s, 1H), 2.42 (s,

1H), 2.42(s, 3H), 2.27 (dt, J=3.5, 13.2, Hz, 1H), 2.14-2.05 (comp m, 1H), 1.98-1.85 (comp m, 3H), 1.76-1.56 (comp m, 2H), 1.52-0.92 (comp m, 14H), 0.76 (d, J=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.7, 138.6, 129.6, 127.3, 56.0, 55.5, 42.3, 41.6, 37.1, 37.0, 31.8, 31.7, 29.0, 25.6, 24.0, 21.8, 21.7, 20.6, 15.5; IR (thin film/NaCl) 3522 (br m), 2955 (m), 2870 (m), 1598 (m), 1465 (m), 1384 (m), 1369 (m),1156 (s), 1094 (m) cm^{-1}; HRMS (FAB) *m/z* found: 407.2368 [calc'd for $C_{22}H_{35}N_2O_3S$ (M+H): 407.2368].

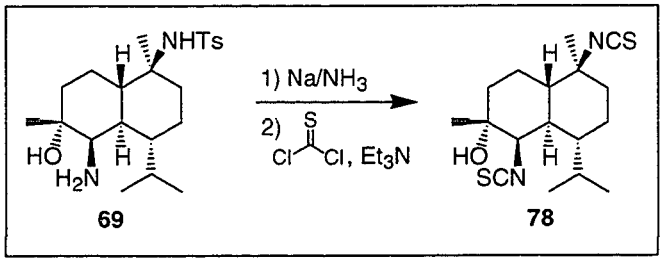
Preparation of isonitrile 53



Isonitrile 53. To a solution of **71** (122 mg, 0.39 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) at rt was added *p*-toluenesulfonyl chloride (300 mg, 1.57 mmol, 4.0 equiv) and pyridine (126 μL, 1.57 mmol, 4.0 equiv). After the reaction was complete (ca. 16 h), the solvent was removed *in vacuo* and the resulting residue was purified by silica gel column chromatography (9:1 hexanes:EtOAc) to afford **53** (95 mg, 89% yield) as a white, amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (br s, 1H), 2.06 (dt, J=3.5, 12.8 Hz, 1H), 1.94-1.42 (comp m, 13H), 1.36 (s, 3H), 1.32 (t, J=1.3 Hz, 3H), 1.12 (dq, J=3.3, 13.7 Hz, 1H), 0.95 (d, J=6.8 Hz, 3H), 0.73 (d, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6 (t, J=5.0 Hz), 152.9 (t, J=5.0 Hz), 70.5, 60.9, (t, J=5.0 Hz), 60.3, (t, J=5.0 Hz), 42.8, 42.3, 40.4, 36.2, 32.7, 28.8, 25.5, 21.4, 21.1, 20.9, 19.2, 15.1; IR (thin film/NaCl) 3419 (br m), 2955 (s), 2873 (m), 2273 (w), 2133 (s), 1467 (m), 1385 (m),

1268 (m), 1125 (m) cm^{-1}; HRMS (FAB) *m/z* found: 275.2124 [calc'd for $C_{17}H_{27}N_2O$ (M+H): 275.2123].

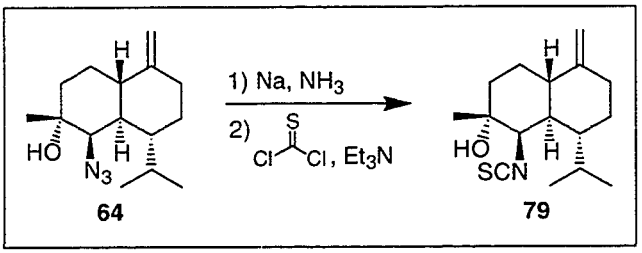
Preparation of isothiocyanate 78



Isothiocyanate 78. To condensed ammonia (20 mL) at –78°C was added sodium (17 mg, 0.73 mmol, 10 equiv) followed by **69** (30 mg, 0.073 mmol, 1.0 equiv) in THF (2 mL). After 2 h, the blue mixture was warmed to reflux for an additional 1 h. The reaction was quenched with solid ammonium chloride and the ammonia allowed to evaporate. The residue was taken up in EtOAc (30 mL), washed with 0.1 M NaOH (2 x 10 mL), brine (10 mL) and dried with Na_2SO_4. After concentration under reduced pressure, the resulting oil was dissolved in THF (10 mL) and treated with TEA (41 μL, 0.29 mmol, 4.0 equiv) and thiophosgene (12 μL, 0.15 mmol, 2.0 equiv). After 4 h the solution was concentrated under reduced pressure and the residue purified by silica gel column chromatography (9:1 then 3:1 hexanes:EtOAc) to afford **78** (16 mg, 65% yield from **69**) as a yellow oil. ^1H NMR (500 MHz, CD_3OD) δ 3.75 (s, 1H) 2.03 (dt, *J*=3.3, 13.2 Hz, 1H), 1.96-1.08 (comp m, 18H), 0.96 (d, *J*=6.9 Hz, 3H), 0.75 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 71.3, 64.3, 63.4, 44.0, 43.0, 40.7, 38.4, 33.3, 29.2, 25.7, 21.6, 21.3, 21.0, 19.8, 15.3; IR (thin film/NaCl) 3503 (br m), 2957 (m), 2871 (m), 2088

(br s), 1715 (w), 1653 (w), 1465 (m), 1382 (m), 1173 (m), 1129 (m) cm^{-1}; HRMS (FAB) *m/z* found: 280.1736 [calc'd for $C_{16}H_{26}NOS$ (M-NCS): 280.1735].

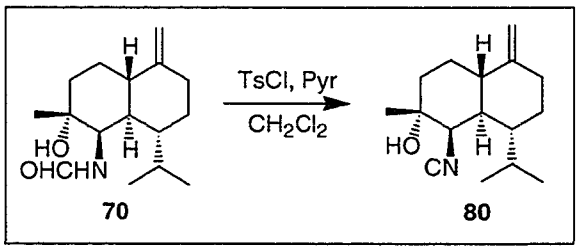
Preparation of isothiocyanate 79



Isothiocyanate 79. To condensed ammonia (20 mL) at –78°C was added sodium (25 mg, 1.10 mmol, 10 equiv) followed by **64** (26 mg, 0.11 mmol, 1.0 equiv) in THF (2 mL). After 2 h, the blue mixture was quenched with solid ammonium chloride and the ammonia allowed to evaporate. The residue was taken up in EtOAc (30 mL), washed with 0.1 M NaOH (2 x 10 mL), brine (10 mL) and dried with Na_2SO_4. After concentration under reduced pressure, the resulting oil was dissolved in THF (10 mL). To this solution was added TEA (61 μL, 0.44 mmol, 4.0 equiv) and thiophosgene (17 μL, 0.22 mmol, 2.0 equiv). After 4 h the solution was concentrated under reduced pressure and the residue purified by silica gel column chromatography (9:1 hexanes:EtOAc) to afford **79** (24 mg, 79% yield from **64**) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.73 (s, 1H), 4.61 (s, 1H), 3.73 (s, 1H), 2.39 (dt, *J*=3.3, 13.1 Hz, 1H), 2.07-1.50 (comp m, 12H), 1.38 (s, 3H), 1.09 (dq, *J*=3.7, 12.6 Hz, 1H), 0.98 (d, *J*=6.9 Hz, 3H), 0.73 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 105.8, 71.5, 63.7, 44.2, 43.8, 39.1, 36.2, 33.3, 29.1, 26.0, 25.9, 23.8, 21.5, 15.4; IR (thin film/NaCl) 3446 (br m), 2959 (m), 2934

(m), 2868 (m), 2272 (s), 2099 (m), 1645 (m), 1457 (m), 1370 (m), 891 (m) cm^{-1}; HRMS (FAB) *m/z* found: 280.1736 [calc'd for $C_{16}H_{26}NOS$ (M+H): 280.1735].

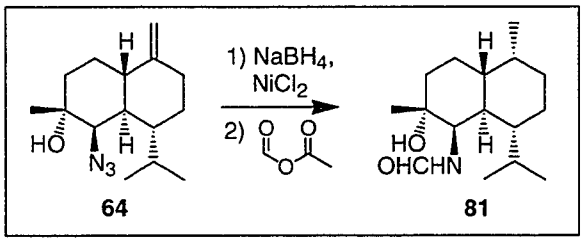
Preparation of isonitrile 80



70 **80**

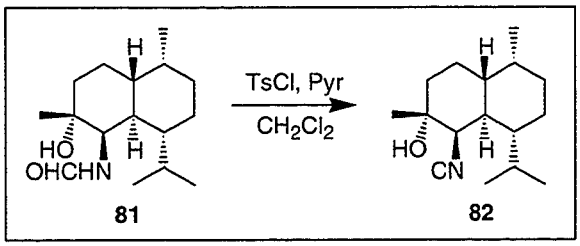
Isonitrile 80. To a solution of **70** (85 mg, 0.32 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at rt was added *p*-toluenesulfonyl chloride (122 mg, 0.64 mmol, 2.0 equiv) and pyridine (51 μL, 0.64 mmol, 2.0 equiv). After the reaction was complete (ca. 12 h), the solvent was removed *in vacuo* and the residue purified by silica gel column chromatography (9:1 hexanes:EtOAc) to afford **80** (71 mg, 89% yield) as a white, amorphous solid. ^1H NMR (400 MHz, $CDCl_3$) δ 4.74 (br s, 1H), 4.62, (br s, 1H), 3.64 (s, 1H), 2.40 (dt, *J*=3.3, 12.8 Hz, 1H), 2.08-1.55 (comp m, 10H), 1.45 (s, 3H), 1.38-1.25 (m, 1H), 1.17-1.06 (m, 1H), 0.98 (d, *J*=6.8 Hz, 3H), 0.73 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9 (t, *J*=5 Hz), 151.5, 105.8, 70.7, 61.2 (t, *J*=5 Hz), 43.2, 42.3, 38.5, 36.1, 32.8, 28.7, 25.8, 25.7, 23.7, 21.6, 15.3; IR (thin film/NaCl) 3434 (br m), 3084 (w), 2959 (s), 2869 (m), 2134 (m), 1646 (m), 1466 (m), 1371 (m), 1267 (w), 1191 (m) cm^{-1}; HRMS (FAB) *m/z* found: 248.2014 [calc'd for $C_{16}H_{26}NO$ (M+H): 248.2014].

Preparation of formamide 81



Formamide 81. To a solution of azide **64** (100 mg, 0.38 mmol, 1.0 equiv) in 3:1 MeOH/THF (10 mL) at 0°C was added $NiCl_2 \cdot 6H_2O$ (145 mg, 0.61 mmol, 1.6 equiv) followed by portionwise addition of $NaBH_4$ (72 mg, 1.90 mmol, 5.0 equiv) over 10 minutes. After 30 minutes the black mixture was allowed to warm to rt, diluted with EtOAc (20 mL), and filtered through a celite plug. The solution was further diluted with EtOAc (20 mL) and washed with a 0.01M EDTA solution (25 mL, pH 7.5, K-phosphate buffer) and brine (2 x 10 mL). After concentration under reduced pressure, the resulting oil was dissolved in THF (10 mL) and treated with acetic formic anhydride (ca. 0.4 ml) at rt. After 4 h the solution was concentrated under reduced pressure and the residue purified by silica gel column chromatography (3:1 then 1:1 hexanes:EtOAc) to afford **81** (85 mg, 84% from **64**) as a white solid. m.p. 215-217°C (recrystallized from 1:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, ~ 4:1 $(CD_3)_2CO$:$CDCl_3$) δ 8.16 (s, 0.9H), 8.01 (d, J=11.4 Hz, 0.1H), 6.88 (d, J=9.5 Hz, 0.9H), 4.18 (dd, J=3.6, 10.8 Hz, 1H), 3.46-3.37 (m, 0.3H), 3.29 (s, 0.8H), 2.09-1.95 (comp m, 4H), 1.81-1.04 (comp m, 17H), 0.88-0.75 (comp m, 8H), 0.73 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, ~ 4:1 $(CD_3)_2CO$:$CDCl_3$) δ 161.3, 71.6, 51.9, 43.3, 38.2, 34.6, 34.2, 33.8, 33.0, 30.1, 28.4, 26.4, 25.5, 21.7, 17.8, 15.2; IR (thin film/NaCl) 3379 (m), 2957 (m), 2911 (m), 2870 (m), 1674 (s), 1525 (m), 1454 (w), 1408 (w), 1383 (m), 1180 (w) cm^{-1}; HRMS (FAB) *m/z* found: 268.2275 [calc'd for $C_{16}H_{30}NO_2$ (M+H): 268.2277].

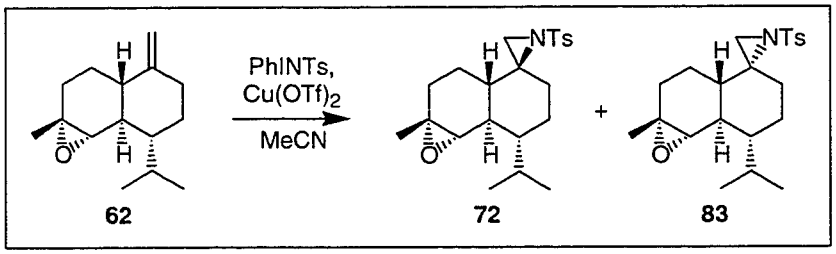
Preparation of isonitrile 82



81 82

Isonitrile 82. To a solution of **81** (85 mg, 0.32 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at rt was added *p*-toluenesulfonyl chloride (122 mg, 0.64 mmol, 2.0 equiv) and pyridine (51 μL, 0.64 mmol, 2.0 equiv). After the reaction was complete (ca. 12 h), the solvent was removed *in vacuo* and the residue purified by silica gel column chromatography (9:1 hexanes:EtOAc) to afford **82** (66 mg, 83% yield) as a white solid. m.p. 120-122°C (recrystallized from 9:1 hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 1H), 1.91-1.73 (comp m, 4H), 1.62-1.32 (comp m, 11H), 1.31-1.18 (comp m, 2H), 0.93 (d, *J*=6.9 Hz, 3H), 0.85 (d, *J*=7.0 Hz, 3H) 0.75 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0 (t, *J*=5 Hz), 70.9, 61.4 (t, *J*=5 Hz), 43.4, 37.1, 34.6, 33.2, 33.1, 32.1, 28.9, 25.8, 25.5, 21.5, 17.6, 15.4, 13.5; IR (thin film/NaCl) 3427 (br m), 2959 (s), 2931 (s), 2872 (s), 2153 (m), 2134 (m), 1466 (m), 1381 (m), 1298 (w), 1190 (m) cm^{-1}; HRMS (FAB) *m/z* found: 250.2171 [calc'd for $C_{16}H_{28}NO$ (M+H): 250.2171].

Preparation of aziridines 72 and 83

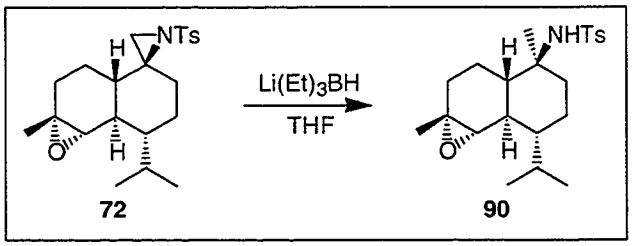


Aziridines 72 and 83. To a solution of olefin **62** (200 mg, 0.91 mmol, 1.0 equiv) in dry MeCN (15 mL) with 4 Å sieves (ca. 0.5 g) at 25°C, was added *N*-tosyliminophenyliodinane (0.68 g, 1.82 mmol, 2.0 equiv). After 2 minutes, $Cu(OTf)_2$ (16 mg, 0.046 mmol, 0.05 equiv) was added and the mixture was vigorously stirred for 8 h. EtOAc (50 mL) was added and the mixture was filtered through a short silica gel plug. After removing the solvent *in vacuo*, the residue was purified by silica gel column chromatography (9:1 then 3:1 Hexanes:EtOAc,) to afford aziridine **72** (251 mg, 71% yield) as a white solid and aziridine **83** (24 mg, 6% yield) was obtained as a white foam.

Aziridine 72. m.p. 168.0-169.0°C (recrystallized from 9:1 hexanes:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, 8.0 Hz, 2H), 7.30 (d, 8.0 Hz, 2H), 2.94 (s, 1H), 2.51 (s, 1H), 2.43 (s, 3H), 2.33-2.13 (comp m, 4H), 1.99-1.90 (comp m, 2H), 1.64-1.53 (comp m, 2H), 1.48-1.39 (comp m, 3H), 1.31-1.19 (comp m, 4H), 0.99 (d, *J*=7.0 Hz, 3H), 0.85 (d, *J*=6.7 Hz, 3H), 0.68 (dq, *J*=4.5, 12.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 138.3, 129.6, 127.3, 60.6, 58.8, 55.2, 44.1, 43.3, 43.1, 36.4, 31.0, 29.9, 26.3, 24.7, 23.6, 21.7, 21.6, 18.7, 15.5; IR (thin film/NaCl) 2958 (m), 2932 (m), 2874 (m), 2252 (w), 1598 (w), 1450 (m), 1386 (m), 1320 (m), 1206 (w), 1159 (s) cm^{-1}; HRMS (FAB) *m/z* found: 390.2104 [calc'd for $C_{22}H_{32}NO_3S$ (M+H): 390.2103].

Aziridine 83. An analytical sample was prepared using HPLC with 8:1 hexanes:EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, 8.4 Hz, 2H), 7.30 (d, 8.2 Hz, 2H), 2.97 (s, 1H), 2.48 (s, 1H), 2.47-2.40 (comp m, 5H), 2.31-2.22 (m, 1H), 2.01-1.86 (comp m, 2H), 1.79-1.49 (comp m, 4H), 1.45-1.36 (m, 1H), 1.31-1.22 (comp m, 4H), 1.16-1.04 (m, 1H), 1.01-0.92 (comp m, 4H), 0.79 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 137.8, 129.5, 127.7, 60.7, 58.2, 56.1, 44.3, 42.8, 41.7, 36.5, 30.3, 30.0, 26.5, 23.6, 23.1, 21.7, 21.4, 19.3, 15.3; IR (thin film/NaCl) 2958 (s), 2876 (m), 2250 (w), 1598 (w), 1495 (w), 1451 (m), 1381 (m), 1318 (s), 1304 (s), 1159 (s) cm^{-1}; HRMS (FAB) *m/z* found: 390.2104 [calc'd for $C_{22}H_{32}NO_3S$ (M+H): 390.2103].

Preparation of amine 90

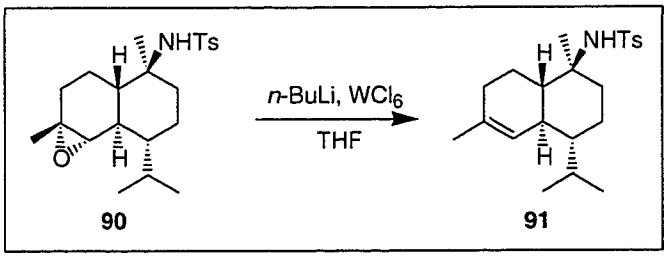


72 **90**

Amine 90. To a solution of aziridine **72** (40 mg, 1.03 mmol, 1.0 equiv) in THF (5 mL) at 0°C was added $Li(Et)_3BH$ (1M in THF, 2.1 mL, 2.06 mmol, 2.0 equiv). The reaction mixture was stirred at 0°C for 1 h before warming to rt for an additional 1 h. The mixture was then cooled to 0°C and diluted with EtOAc (20 mL) and H_2O (10 mL). The organic layer was separated, washed with brine (2 x 10 mL), and dried with Na_2SO_4. After removing the solvent *in vacuo*, the resulting residue was purified by silica gel column chromatography (3:1 hexanes:EtOAc) to afford epoxide **90** (37 mg, 93% yield) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J*=8.1 Hz, 2H), 7.28 (d, *J*=8.4 Hz, 2H), 4.56 (s, 1H), 2.84 (s, 1H), 2.43 (s, 3H), 2.23-2.13 (m, 1H), 2.04-1.96 (m, 1H),

1.76-1.37 (comp m, 6H), 1.29-0.88 (comp m, 13H), 0.80 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 140.9, 129.7, 127.0, 61.5, 60.5, 58.4, 47.3, 44.0, 40.0, 38.7, 30.5, 26.1, 23.7, 21.7, 21.6, 21.0, 20.2, 18.6, 15.6; IR (thin film/NaCl) 3270 (m), 2957 (m), 2872 (m), 1599 (w), 1496 (w), 1451 (m), 1384 (m), 1325 (m), 1304 (m), 1156 (m) cm^{-1}; HRMS (FAB) *m/z* found: 392.2259 [calc'd for $C_{22}H_{35}NO_3S$ (M+H): 392.2259].

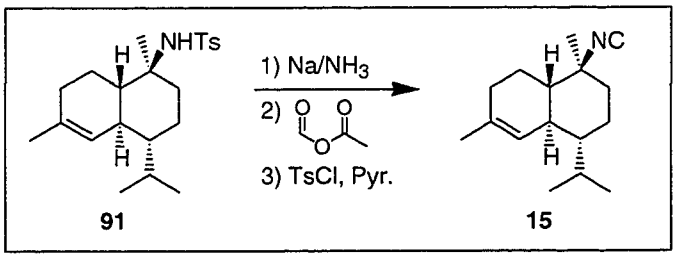
Preparation of olefin 91



Olefin 91. A mixture of WCl_6 (123 mg, 0.31 mmol, 4.0 equiv) in THF (5 mL) at –78°C was reacted with *n*-BuLi (2.2 M in hexanes, 277 μL, 0.61 mmol, 8.0 equiv). The resulting solution was allowed to warm to room temperature and **90** (30 mg, 0.077 mmol, 1.0 equiv) in THF (2 mL) was added. After 1 h, the reaction was quenched with 0.1 N NaOH (2 mL) and diluted with EtOAc (20mL). The organic layer was washed with water (10 mL), brine (10mL) and dried with Na_2SO_4. The solvent was removed *in vacuo* and the residue purified by silica gel column chromatography (9:1 hexanes:EtOAc,) to afford olefin **91** (20 mg, 68% yield) as a white, amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J=8.5, 2H), 7.27 (d, J=9.0, 2H), 5.43 (s, 1H), 4.63 (s, 1H), 2.42 (s, 3H), 2.14-2.07 (m, 1H), 1.93-1.85 (comp m, 4H), 1.80-1.72 (m, 1H), 1.63 (s, 3H), 1.59-1.53 (m, 1H), 1.47-1.42 (m, 1H), 1.32-1.27 (m, 1H), 1.21-0.88 (comp m, 6H), 0.86 (d, J=7.0 Hz, 3H), 0.71 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 141.1,

135.0, 129.6, 127.1, 122.2, 60.5, 48.6, 46.2, 39.7, 39.0, 31.0, 26.0, 23.8, 23.4, 21.6, 20.9, 18.4, 15.2; IR (thin film/NaCl) 3272 (m), 2957 (m), 2870 (m), 1599 (w), 1496 (w), 1451 (m), 1383 (m), 1323 (m), 1154 (s), 1094 (m) cm^{-1}; HRMS (FAB) *m/z* found: 376.2309 [calc'd for $C_{22}H_{34}NO_2S$ (M+H): 376.2310].

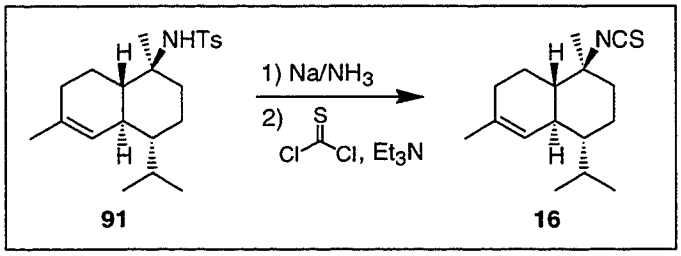
Preparation of (±)-10-Isocyanato-4-Cadinene (15)



(±)-10-Isocyanato-4-Cadinene (15). To condensed ammonia (15 mL) at –78°C was added sodium (18 mg, 0.80 mmol, 10 equiv) followed by **91** (30 mg, 0.080 mmol, 1.0 equiv) in THF (2 mL). After 2 h, the blue mixture was warmed to reflux for an additional 1 h. The reaction was quenched with solid ammonium chloride and the ammonia allowed to evaporate. The residue was taken up in EtOAc (30 mL), washed with 0.1 M NaOH (2 x 10 mL), brine (10 mL) and dried with Na_2SO_4. After concentration under reduced pressure, the resulting oil was dissolved in THF (5 mL) and treated with acetic formic anhydride (ca. 30 μL) at rt. After 4 h, the solution was concentrated under reduced pressure and the residue dissolved in CH_2Cl_2 (5 mL). To this solution was added *p*-toluenesulfonyl chloride (61 mg, 0.32 mmol, 4.0 equiv) and pyridine (26 μL, 0.32 mmol, 4.0 equiv). After the reaction was complete (ca. 12 h), the solvent was removed *in vacuo* and the residue purified by silica gel column chromatography (9:1 hexanes:EtOAc) to afford **15** (13 mg, 71% yield from **91**) as a

colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.46 (s, 1H), 2.20-1.97 (comp m, 5H), 1.87-1.69 (comp m, 2H), 1.68 (s, 3H), 1.62-1.56 (m, 1H), 1.53-1.47 (m, 1H), 1.39-1.30 (m, 1H), 1.30 (br s, 3H), 1.17-1.02 (comp m, 2H), 0.91 (d, *J*=6.9 Hz, 3H), 0.76 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$ referenced to 77.00) δ 152.1 (t, *J*=5.0 Hz), 135.3, 121.2, 60.7, (t, *J*=5.0 Hz), 48.0, 46.2, 40.6, 37.8, 30.7, 25.9, 23.8, 23.7, 21.3, 20.2, 20.0, 15.0; IR (thin film/NaCl) 2939 (s), 2871 (s), 2127 (s), 1465 (m), 1451 (m), 1383 (m), 1369 (w), 1264 (w), 1152 (w), 1129 (m) cm^{-1}; HRMS (FAB) *m/z* found: 205.1977 [calc'd for $C_{15}H_{25}$ (M-NC): 205.1957].

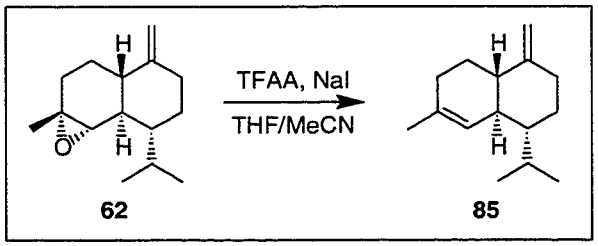
Preparation of (±)-10-Isothiocyanato-4-Cadinene (16)



(±)-10-Isothiocyanato-4-Cadinene (16). To condensed ammonia (15 mL) at –78°C was added sodium (18 mg, 0.80 mmol, 10 equiv) followed by **91** (30 mg, 0.080 mmol, 1.0 equiv) in THF (2 mL). After 2 h, the blue mixture was warmed to reflux for an additional 1 h. The reaction was quenched with solid ammonium chloride and the ammonia allowed to evaporate. The residue was taken up in EtOAc (30 mL), washed with 0.1 M NaOH (2 x 10 mL), brine (10 mL) and dried with Na_2SO_4. After concentration under reduced pressure, the resulting oil was dissolved in THF (10 mL) and treated with TEA (44 μL, 0.32 mmol, 4.0 equiv) and thiophosgene (12 μL, 0.16 mmol, 2.0 equiv). After 4 h the solution was concentrated under reduced pressure and the

residue purified by silica gel column chromatography (100% hexanes then 9:1 hexanes:EtOAc) to afford **16** (15 mg, 70% yield from **91**) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45 (s, 1H), 2.18-2.11 (m, 1H), 2.08-1.92 (comp m, 4H), 1.81-1.70 (comp m, 2H), 1.66 (s, 3H), 1.62-1.56 (m, 1H), 1.52-1.46 (m, 1H), 1.38-1.29 (m, 1H), 1.28 (s, 3H), 1.17-1.00 (comp m, 2H), 0.90 (d, *J*=6.9 Hz, 3H), 0.74 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$ referenced to 77.00) δ 158.6 (t, *J*=5.0 Hz), 152.9 (t, *J*=5.0 Hz), 70.5, 60.9, (t, *J*=5.0 Hz), 60.3, (t, *J*=5.0 Hz), 42.8, 42.3, 40.4, 36.2, 32.7, 28.8, 25.5, 21.4, 21.1, 20.9, 19.2, 15.1; IR (thin film/NaCl) 3419 (br m), 2955 (s), 2873 (m), 2273 (w), 2133 (s), 1467 (m), 1385 (m), 1268 (m), 1125 (m) cm^{-1}; HRMS (FAB) *m/z* found: 205.1977 [calc'd for $C_{15}H_{25}$ (M-NCS): 205.1957].

Preparation of (±)-γ-cadinene (85)



(±)-γ-Cadinene (85). To a mixture of sodium iodide (34 mg, 0.23 mmol, 5.0 equiv) in THF (2 mL) and MeCN (2 mL) at rt was added TFAA (8 μL, 0.055 mmol, 1.2 equiv). After cooling the yellow mixture to 0°C, a solution of **62** (10 mg, 0.045 mmol, 1.0 equiv) in THF (1 mL) was added. The mixture was warmed to 40°C after 30 min. When no sm remained by TLC (ca. 12 h), the mixture was diluted with hexanes (10 mL), washed with saturated aqueous $NaHSO_3$ (10 mL) and brine (10 mL), and dried with Na_2SO_4. After removing the solvent *in vacuo*, the residue was purified by silica gel

column chromatography (100% hexanes) to afford γ-cadinene (**85**) (270 mg, 62% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (s, 1H), 4.65 (s, 1H), 4.54 (s, 1H), 2.41-2.35 (m, 1H), 2.23-2.14 (m, 1H), 2.08-1.90 (comp m, 4H), 1.80-1.58 (comp m, 6H), 1.55-1.42 (m, 1H), 1.26-1.17 (m, 1H), 1.11 (dq, *J*=4.2, 12.2 Hz, 1H), 0.92 (d, *J*=7.0 Hz, 3H), 0.73 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 134.9, 122.6, 103.3, 47.0, 45.2, 44.3, 36.4, 30.6, 26.6, 26.3, 25.9, 24.1, 21.7, 15.3; IR (thin film/NaCl) 3079 (w), 3011 (w), 2959 (s), 2931 (s), 2861 (s), 1648 (m), 1465 (m), 1450 (m), 1441 (m), 1385 (m) cm^{-1}; HRMS (EI) *m/z* found: 204.1882 [calc'd for $C_{15}H_{24}$ (M+): 204.1878].

2.8 Notes and References

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Appendix One: Spectra Relevant

To Chapter Two

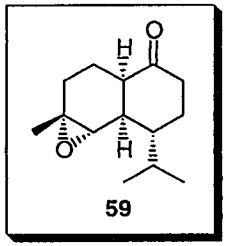


Figure A.1.1 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **59**.

Figure A.1.2 FTIR Spectrum (thin film/NaCl) of Compound **59**.

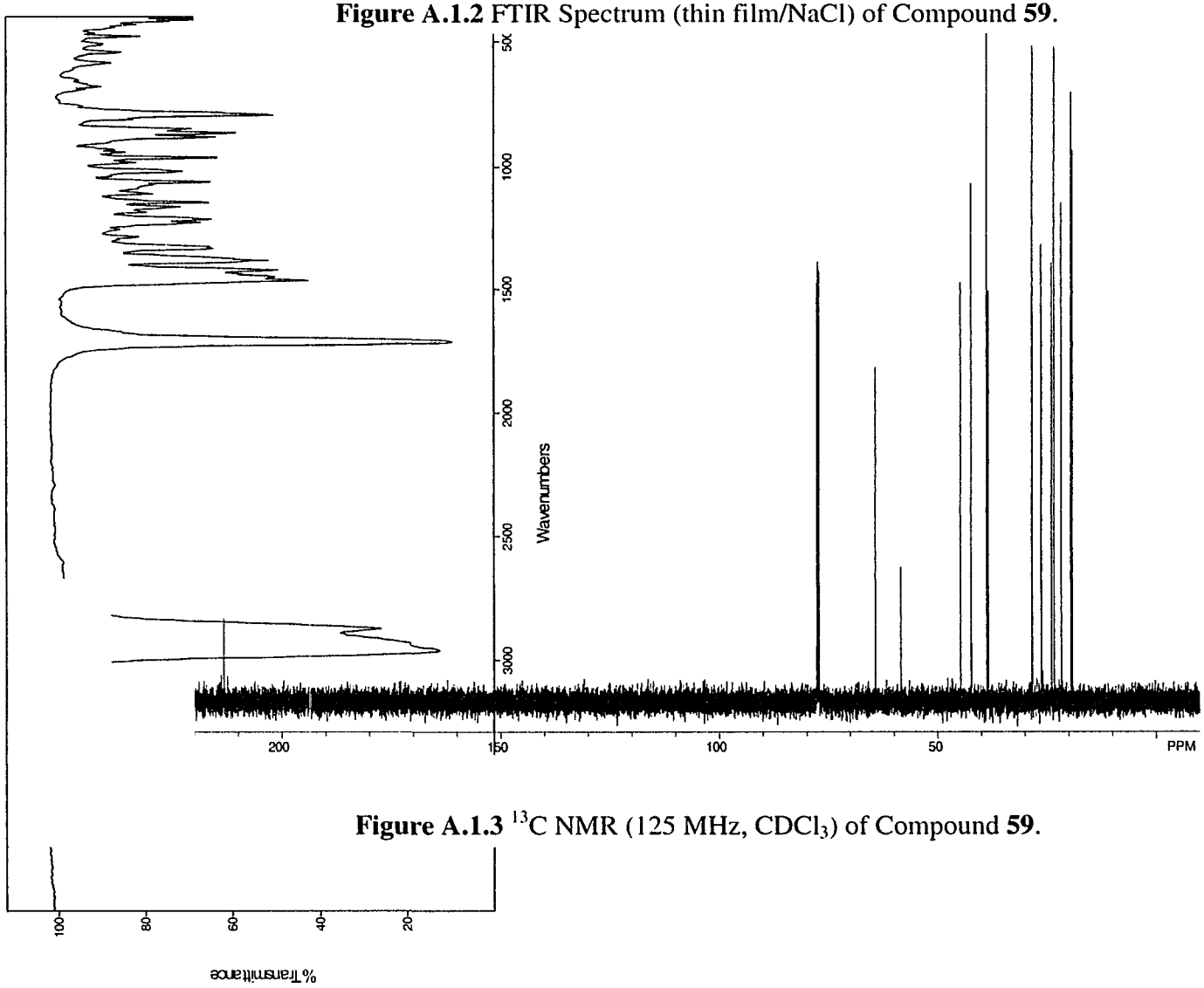
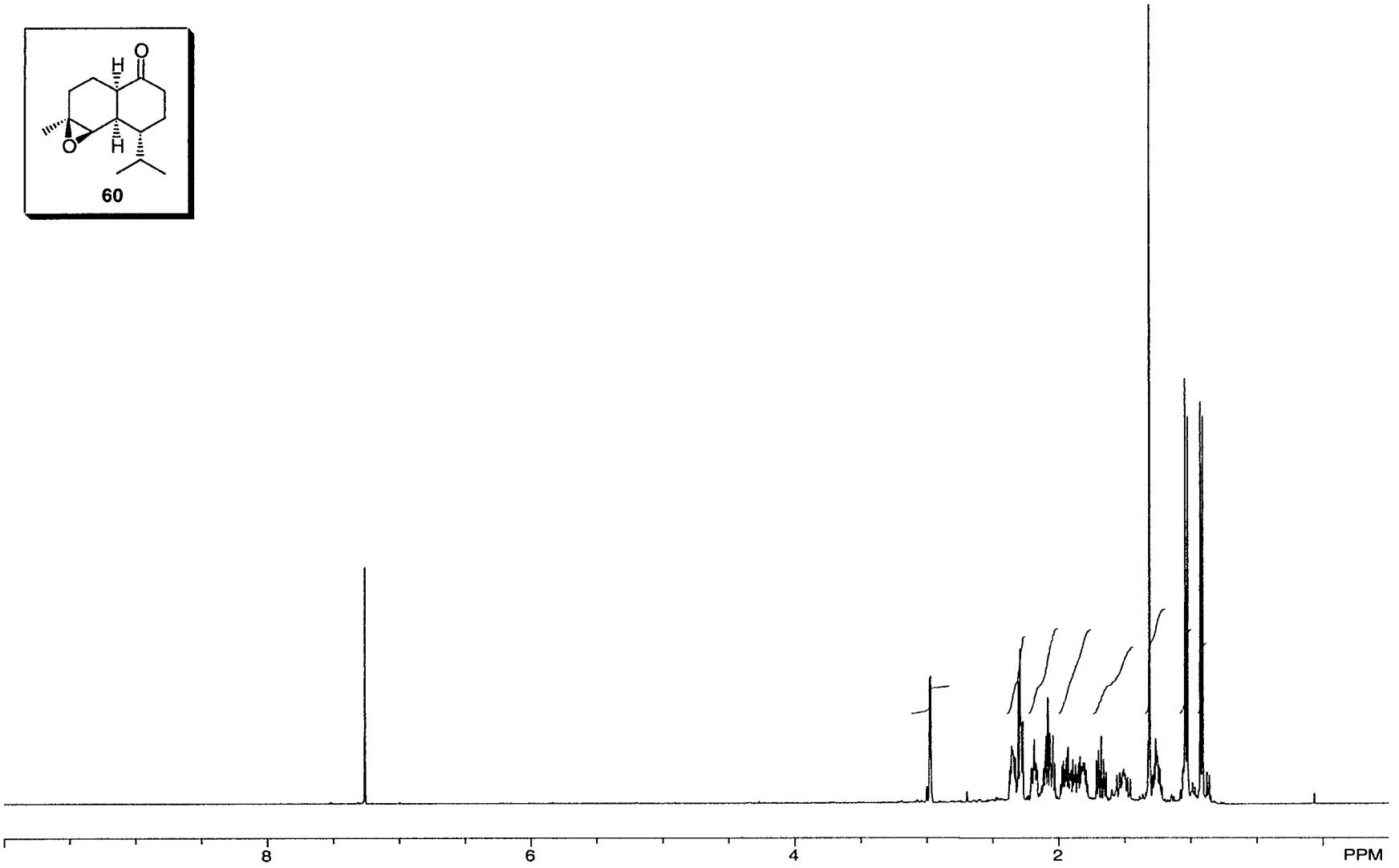


Figure A.1.3 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **59**.



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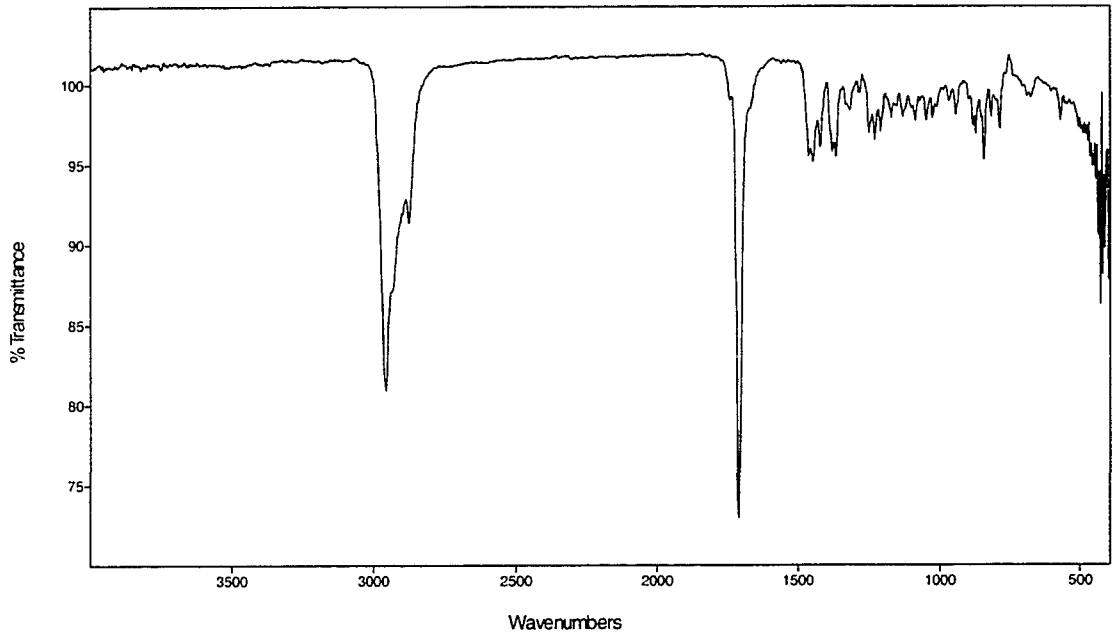
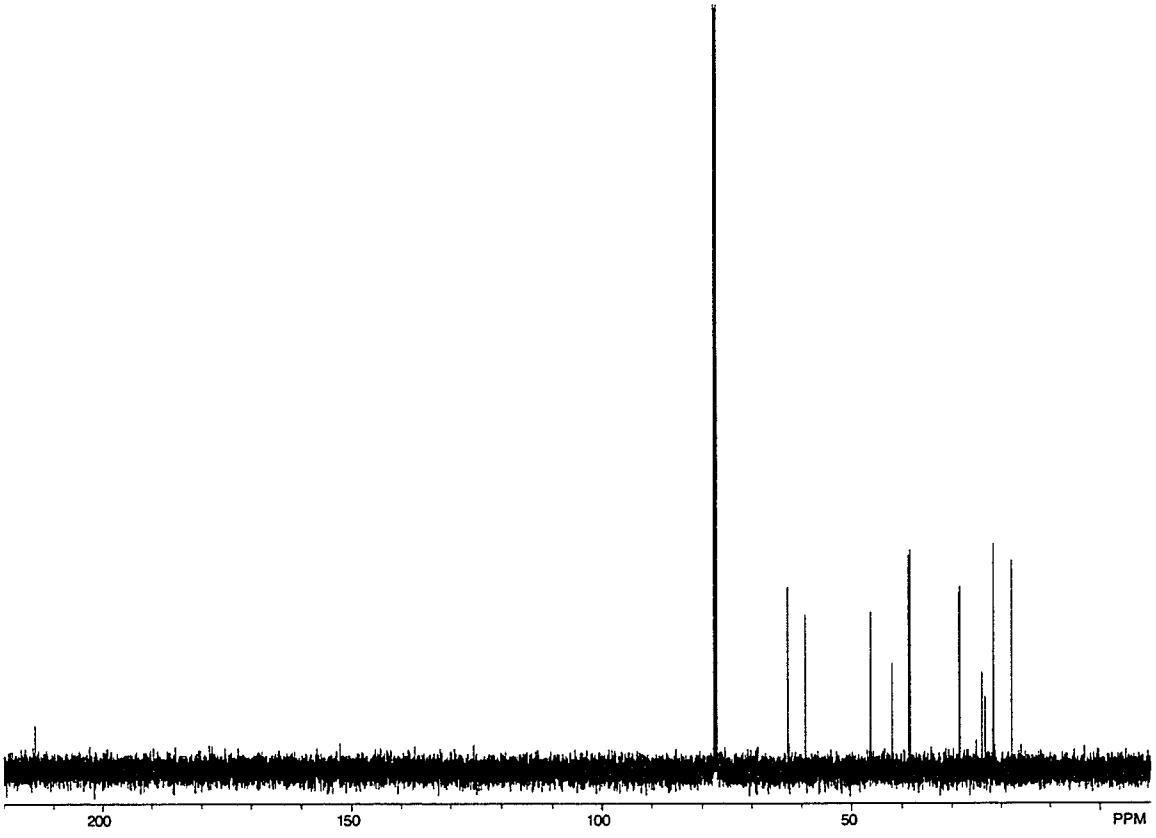


Figure A.1.5 FTIR Spectrum (thin film/NaCl) of Compound **60**.



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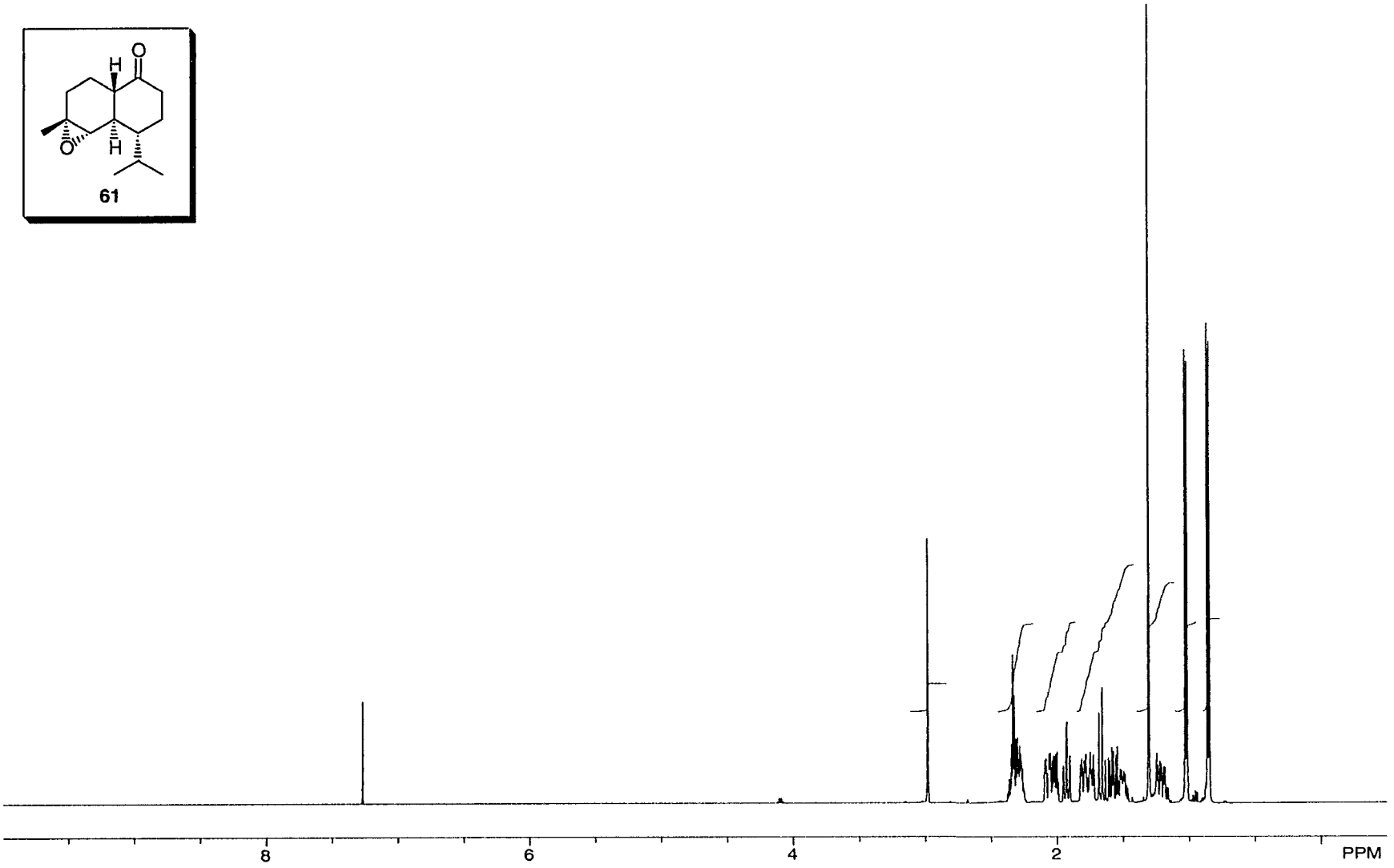


Figure A.1.7 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **61**.

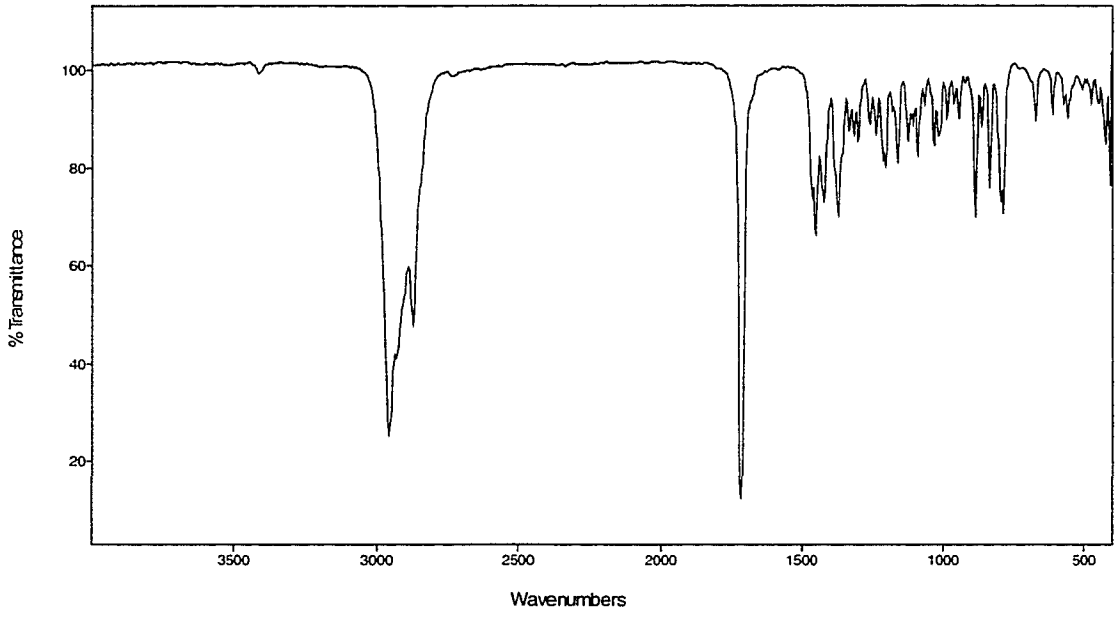
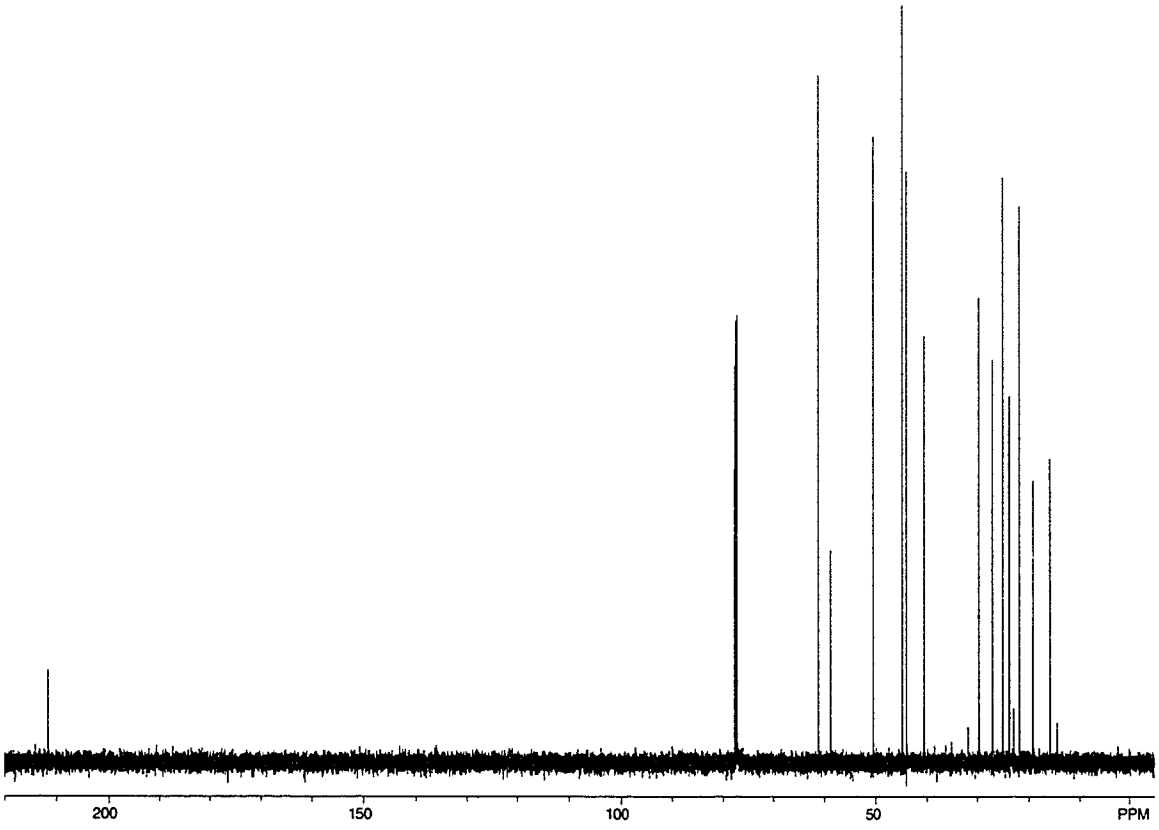


Figure A.1.8 FTIR Spectrum (thin film/NaCl) of Compound **61**.



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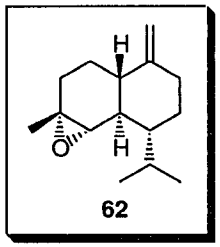

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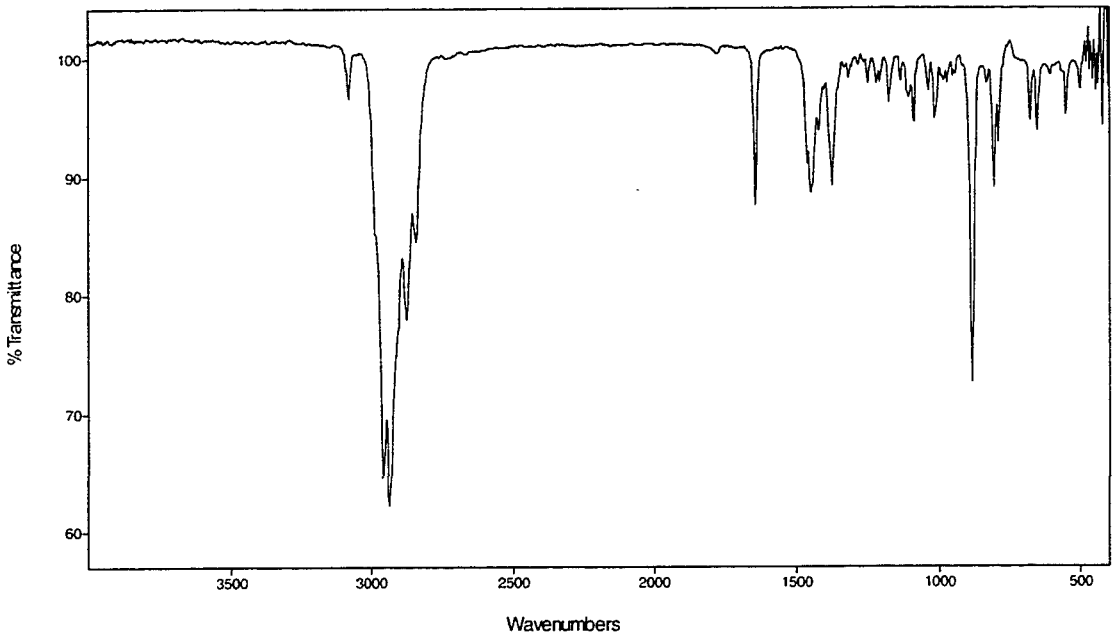

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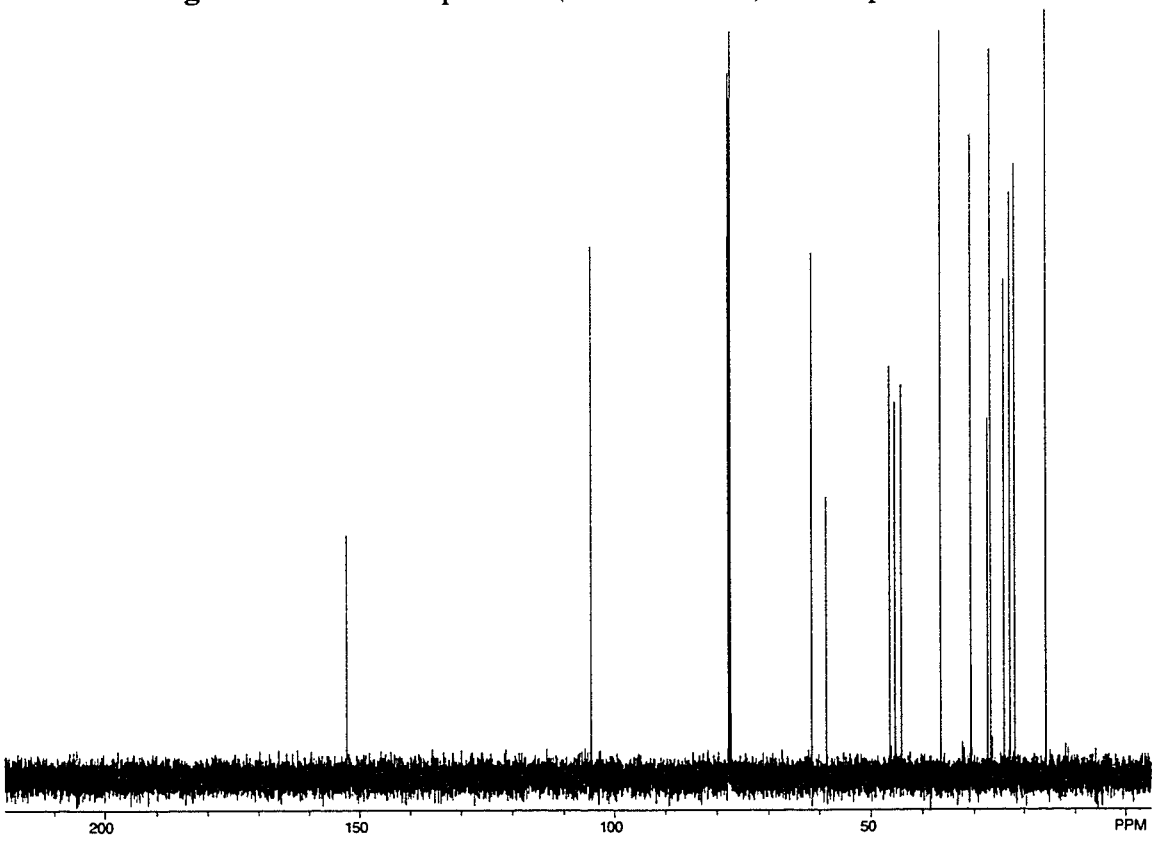

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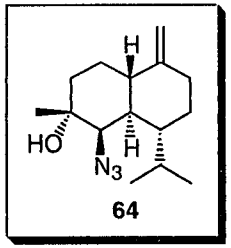


64

Figure A.1.13 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **64**.

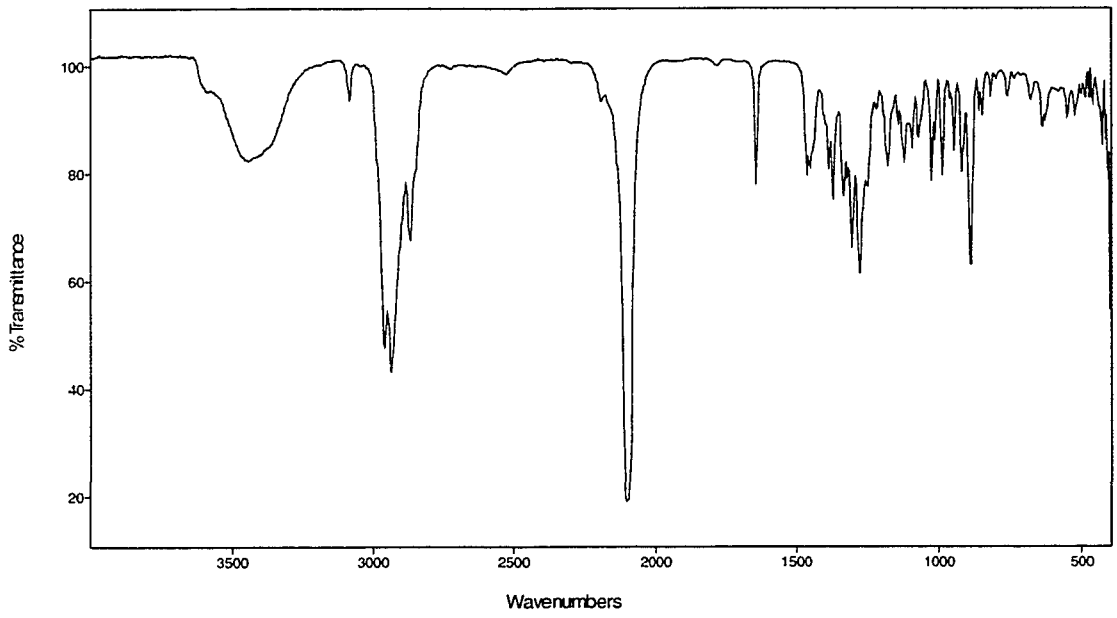
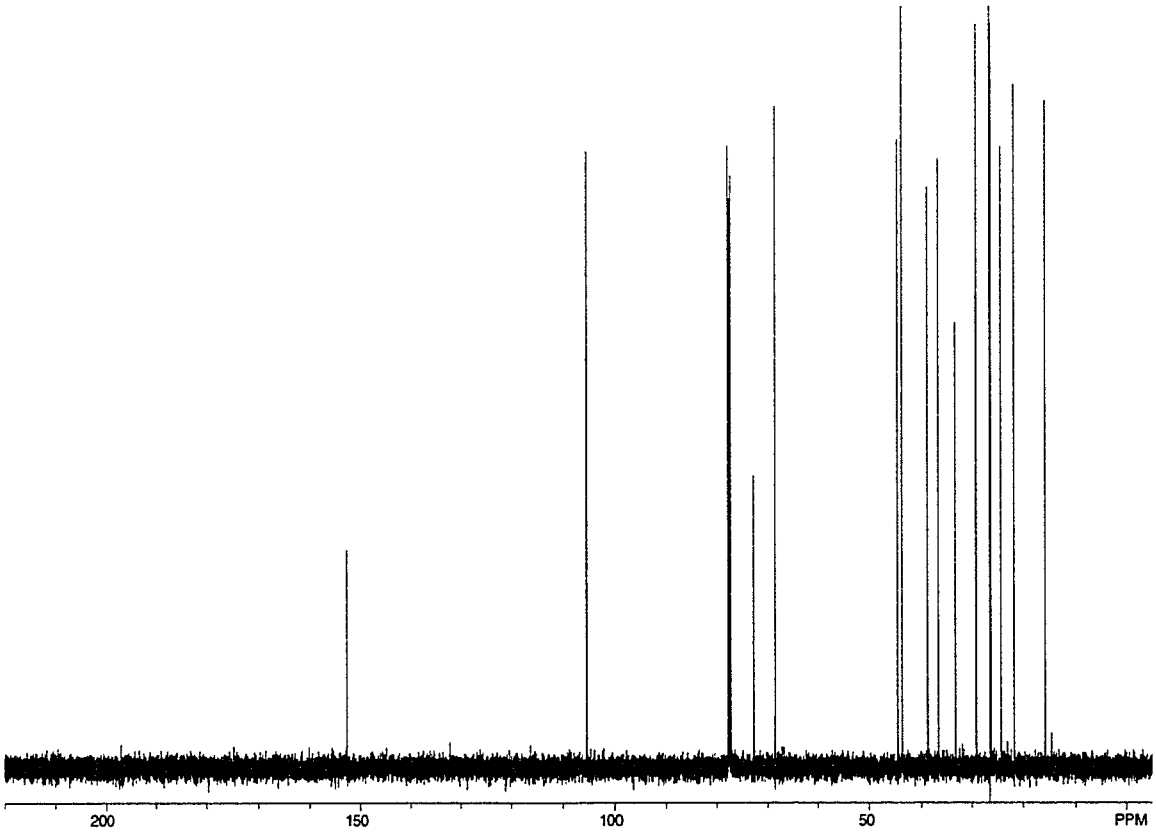


Figure A.1.14 FTIR Spectrum (thin film/NaCl) of Compound **64**.



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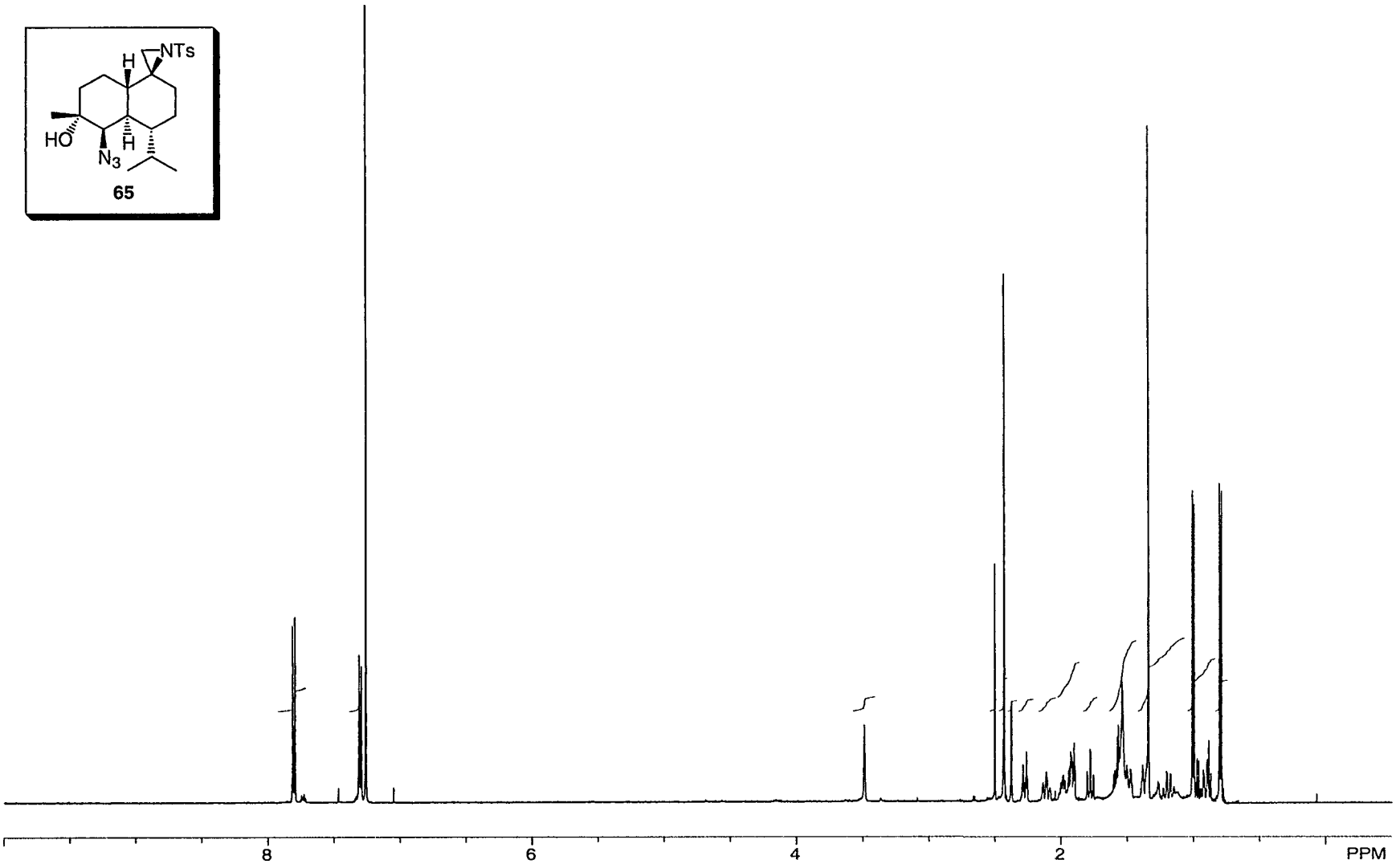


Figure A.1.16 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **65**.

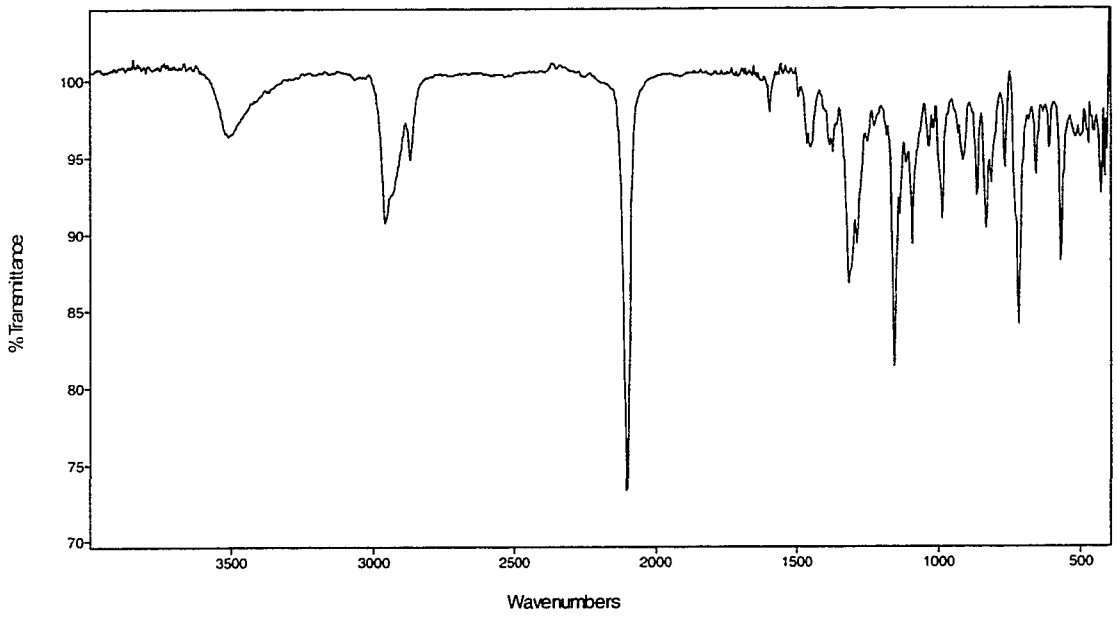


Figure A.1.17 FTIR Spectrum (thin film/NaCl) of Compound **65**.

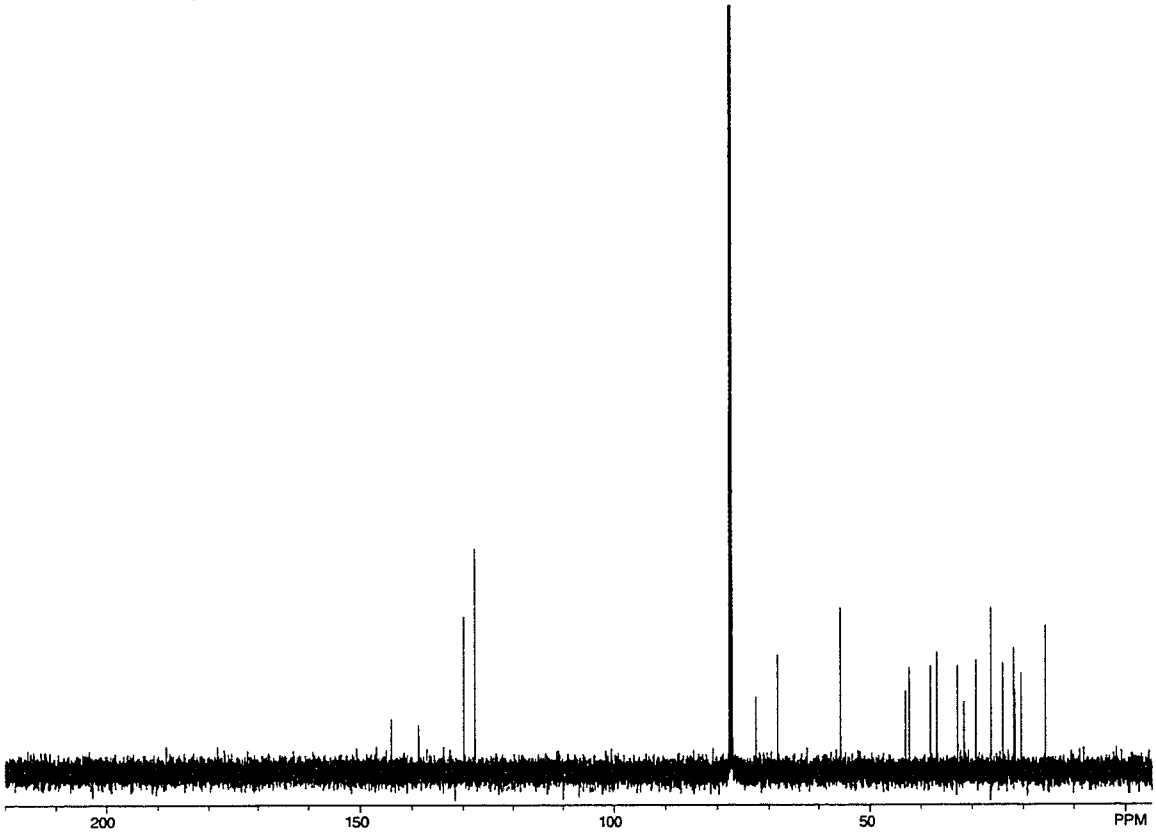


Figure A.1.18 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **65**.

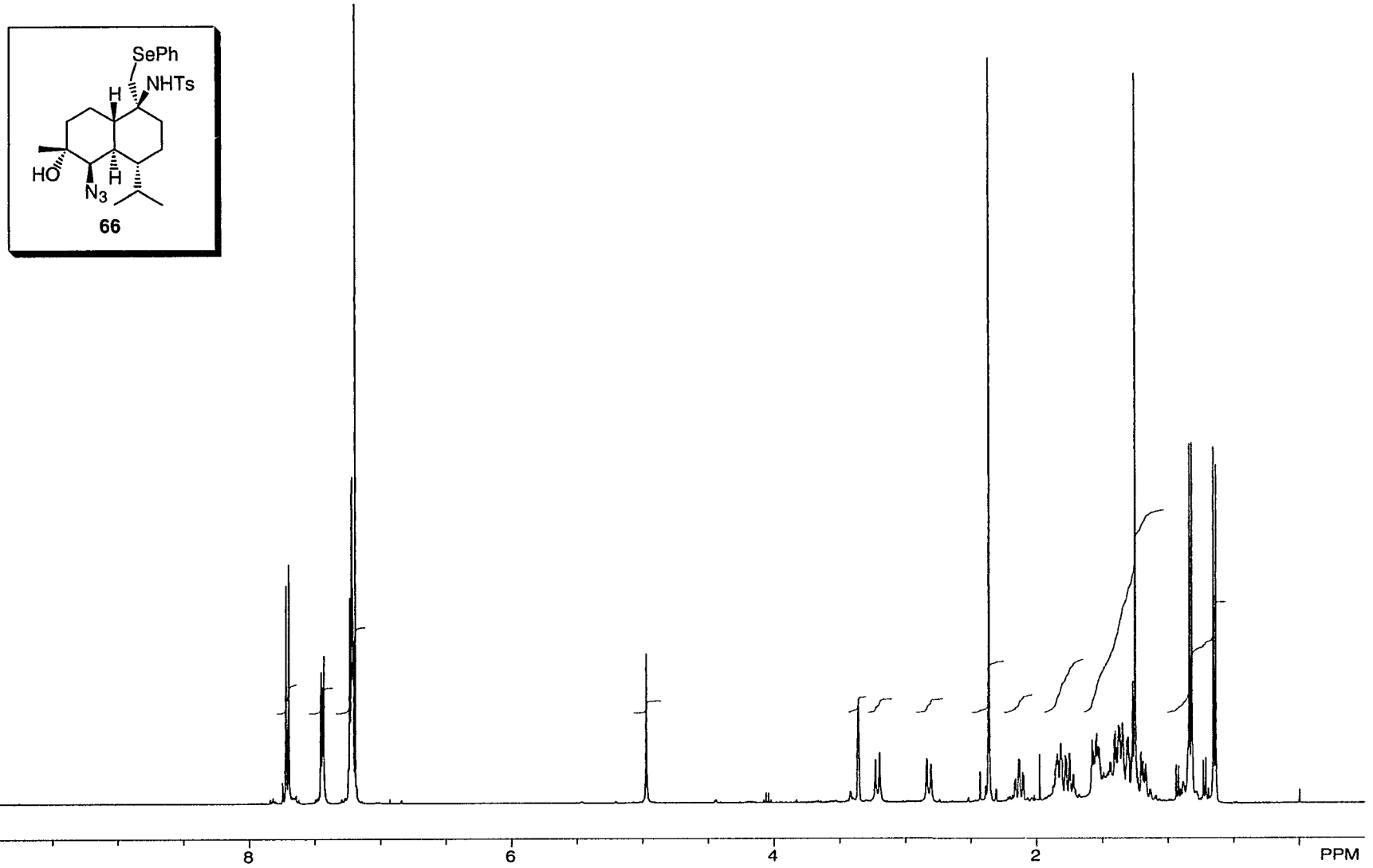


Figure A.1.19 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **66**.

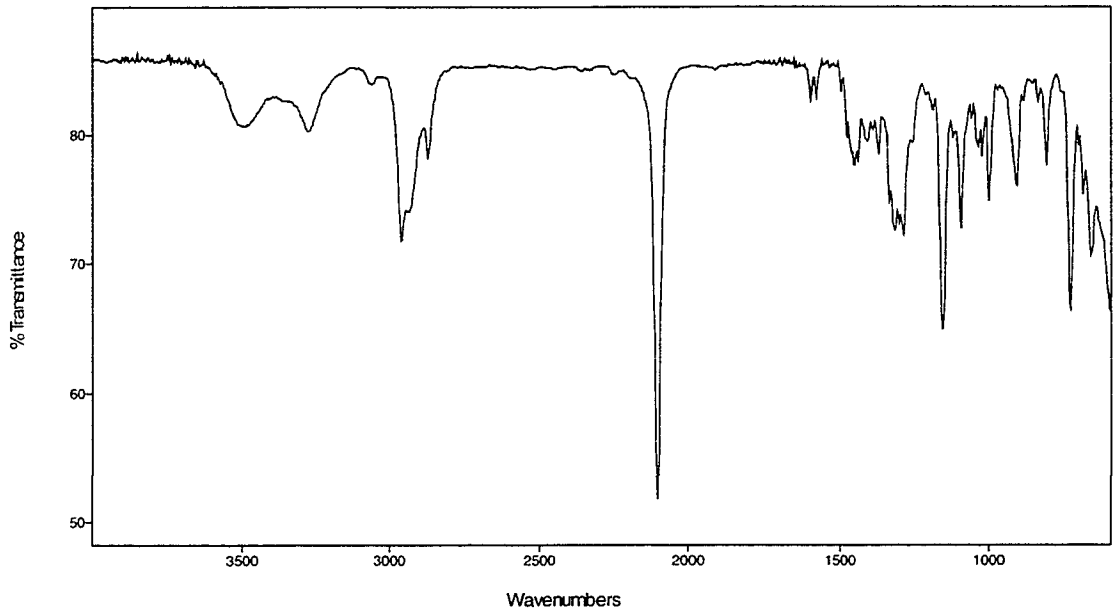


Figure A.1.20 FTIR Spectrum (thin film/NaCl) of Compound **66**.

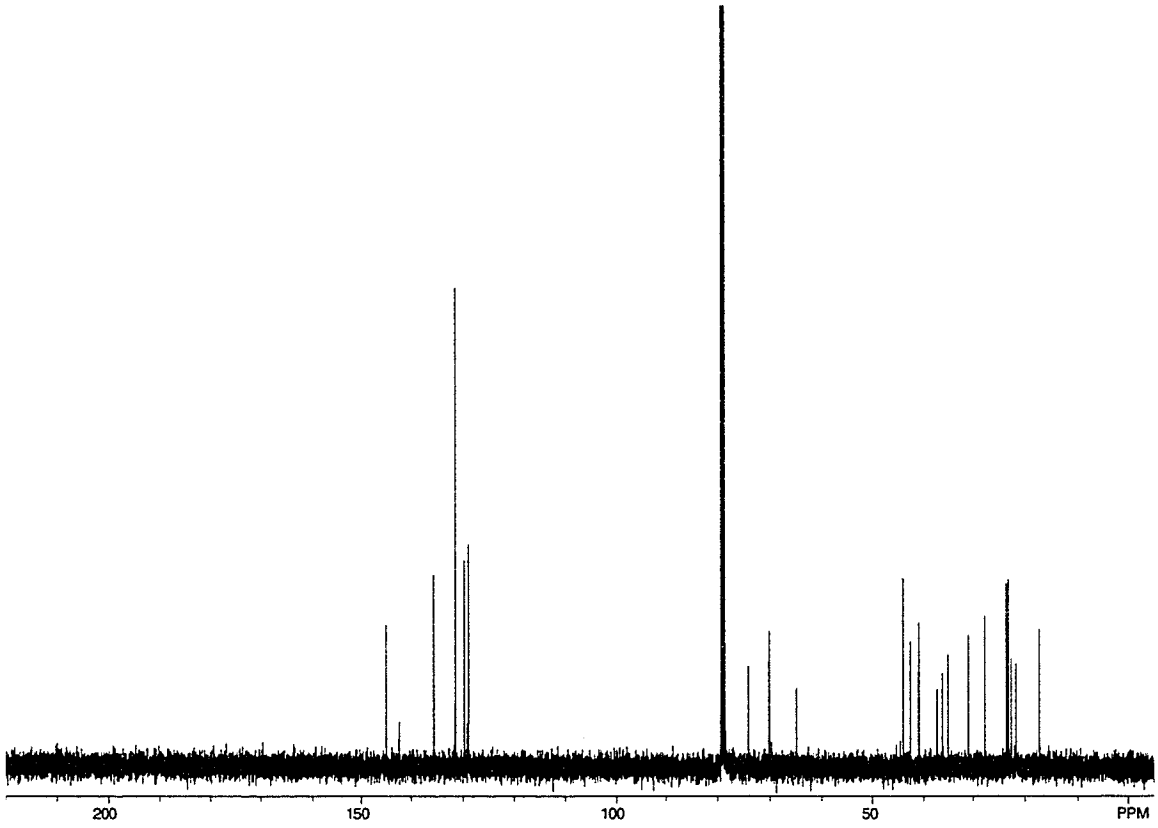


Figure A.1.21 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **66**.

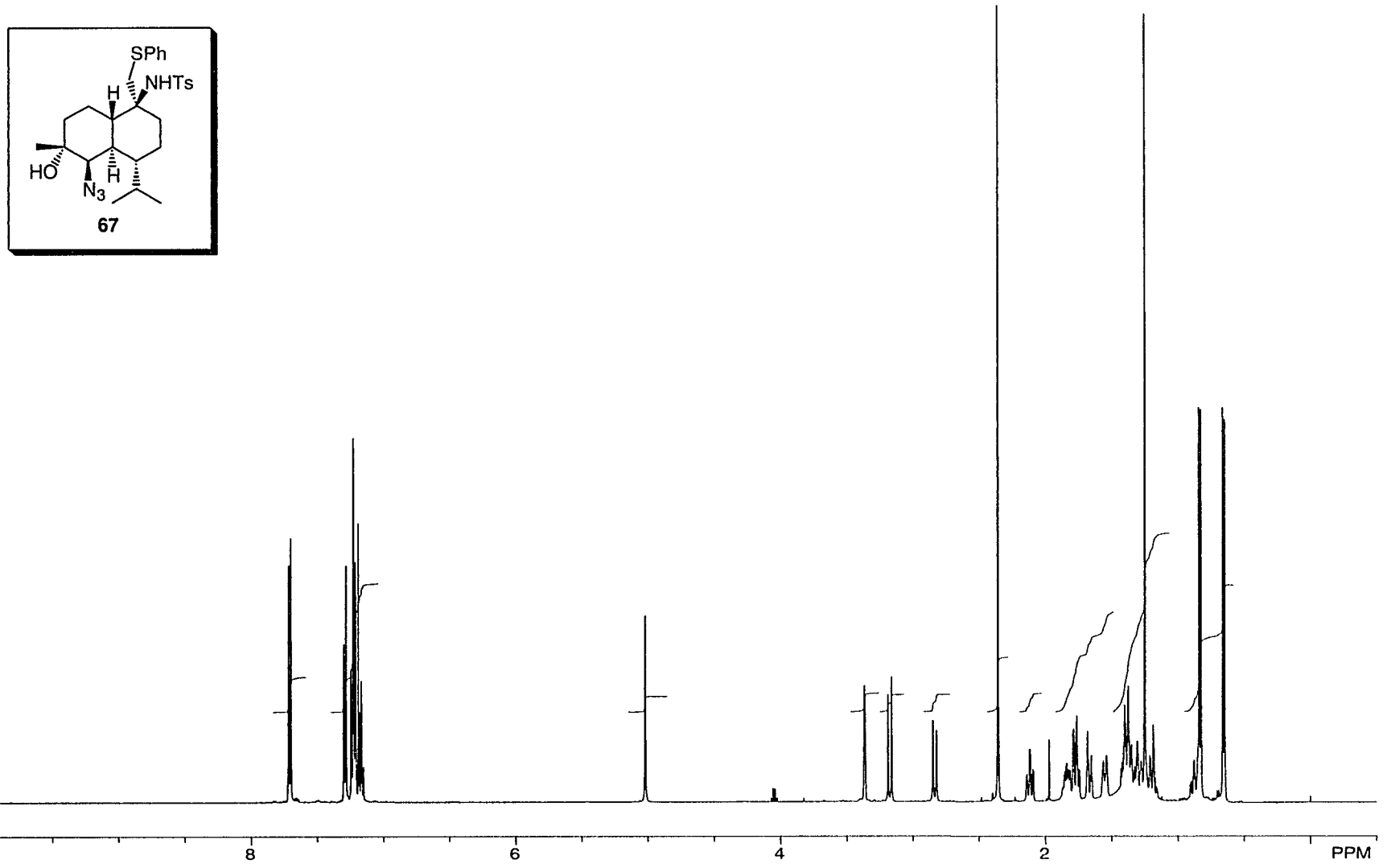


Figure A.1.22 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **67**.

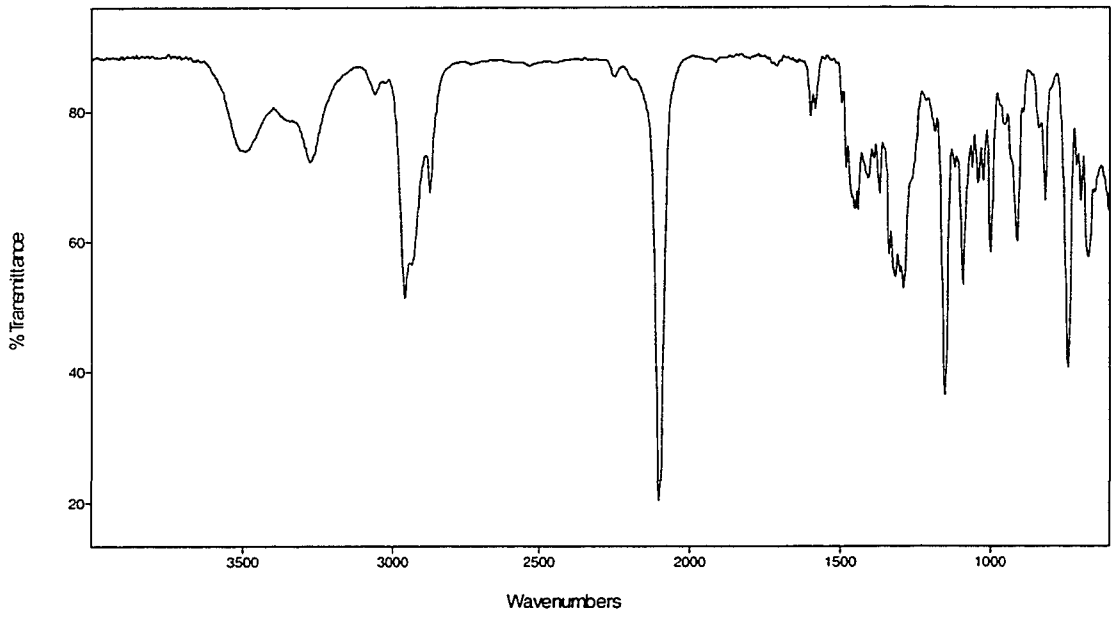


Figure A.1.23 FTIR Spectrum (thin film/NaCl) of Compound **67**.

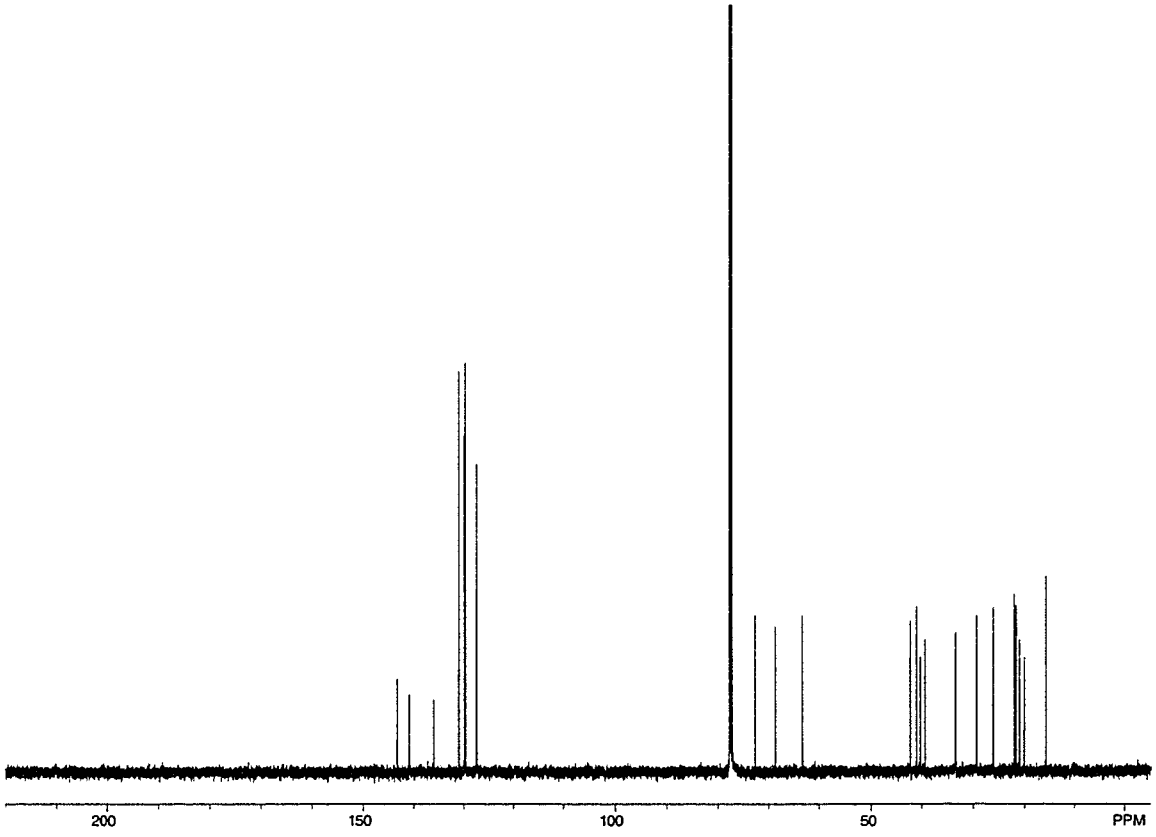


Figure A.1.24 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **67**.

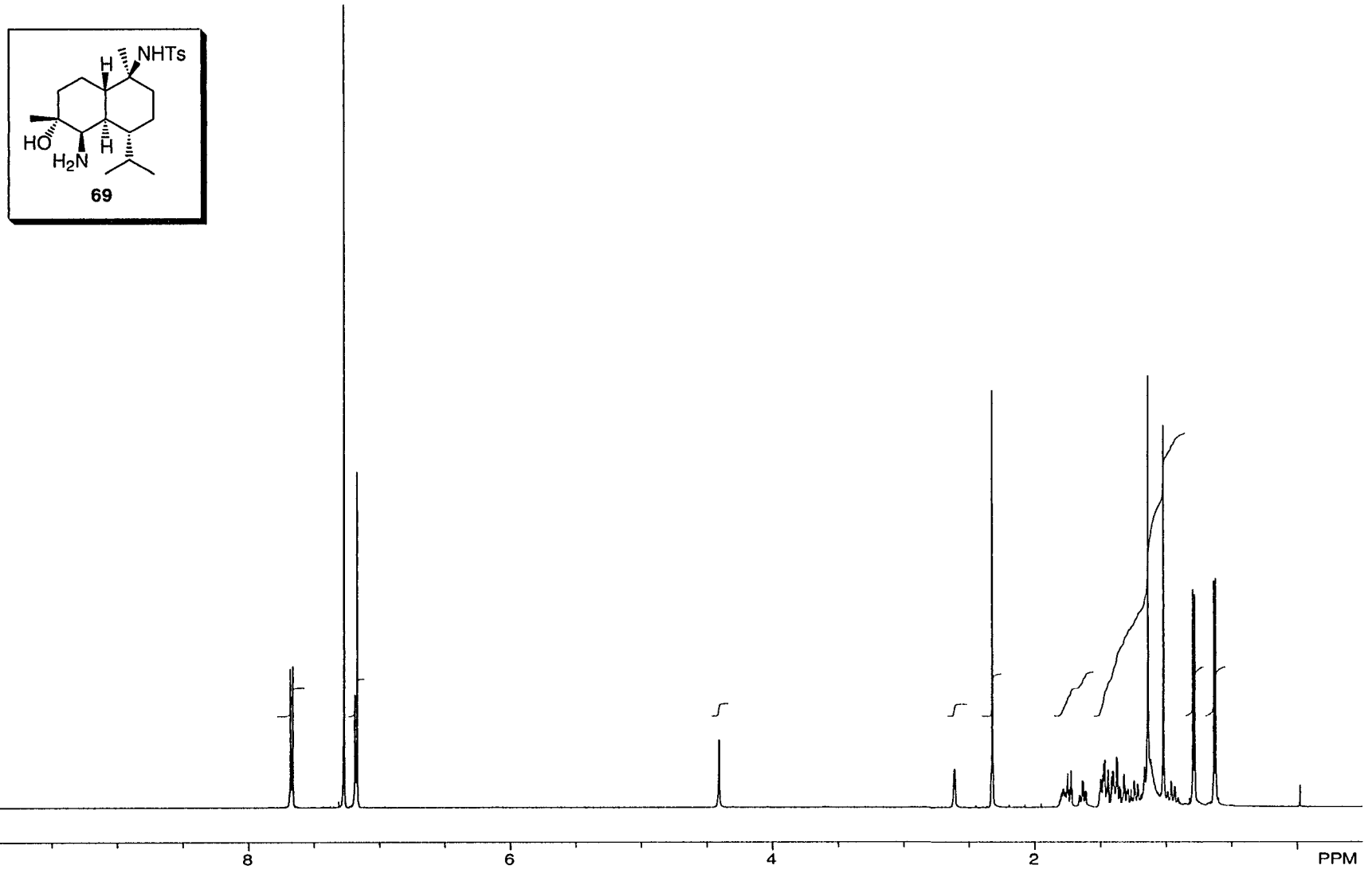


Figure A.1.25 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **69**.

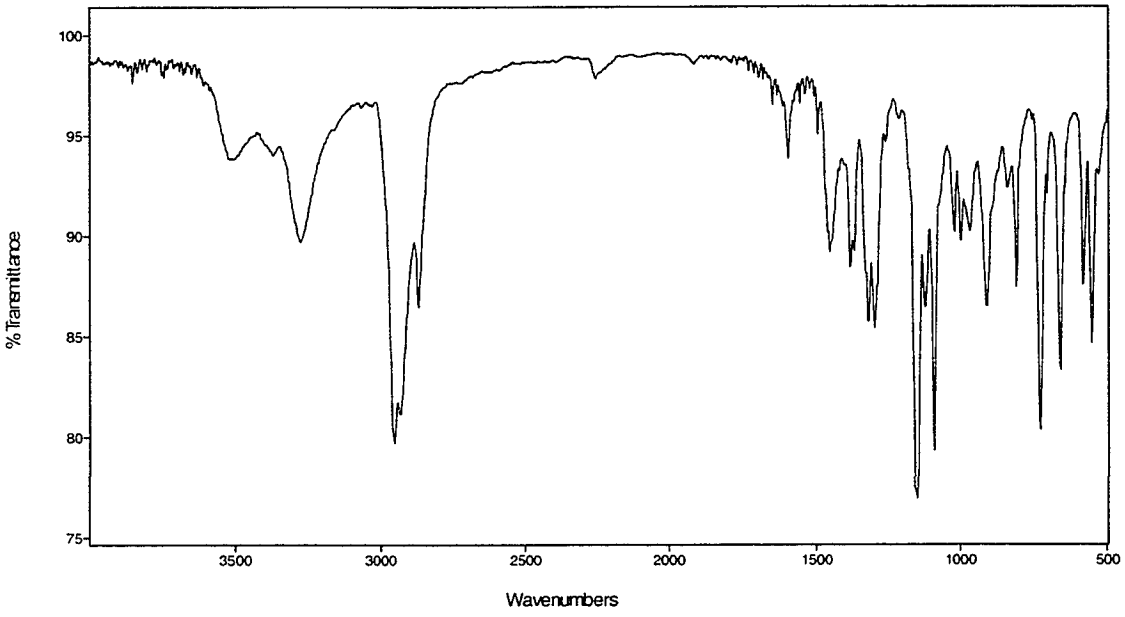


Figure A.1.26 FTIR Spectrum (thin film/NaCl) of Compound **69**.

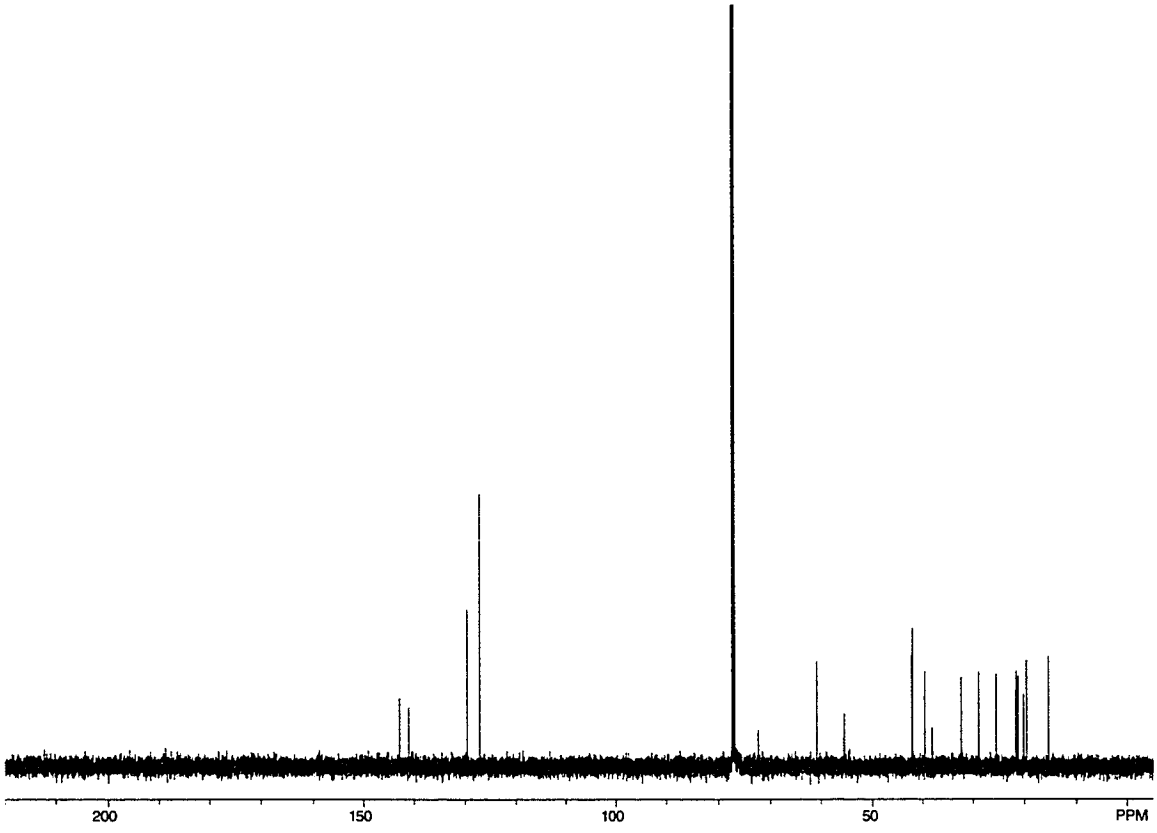
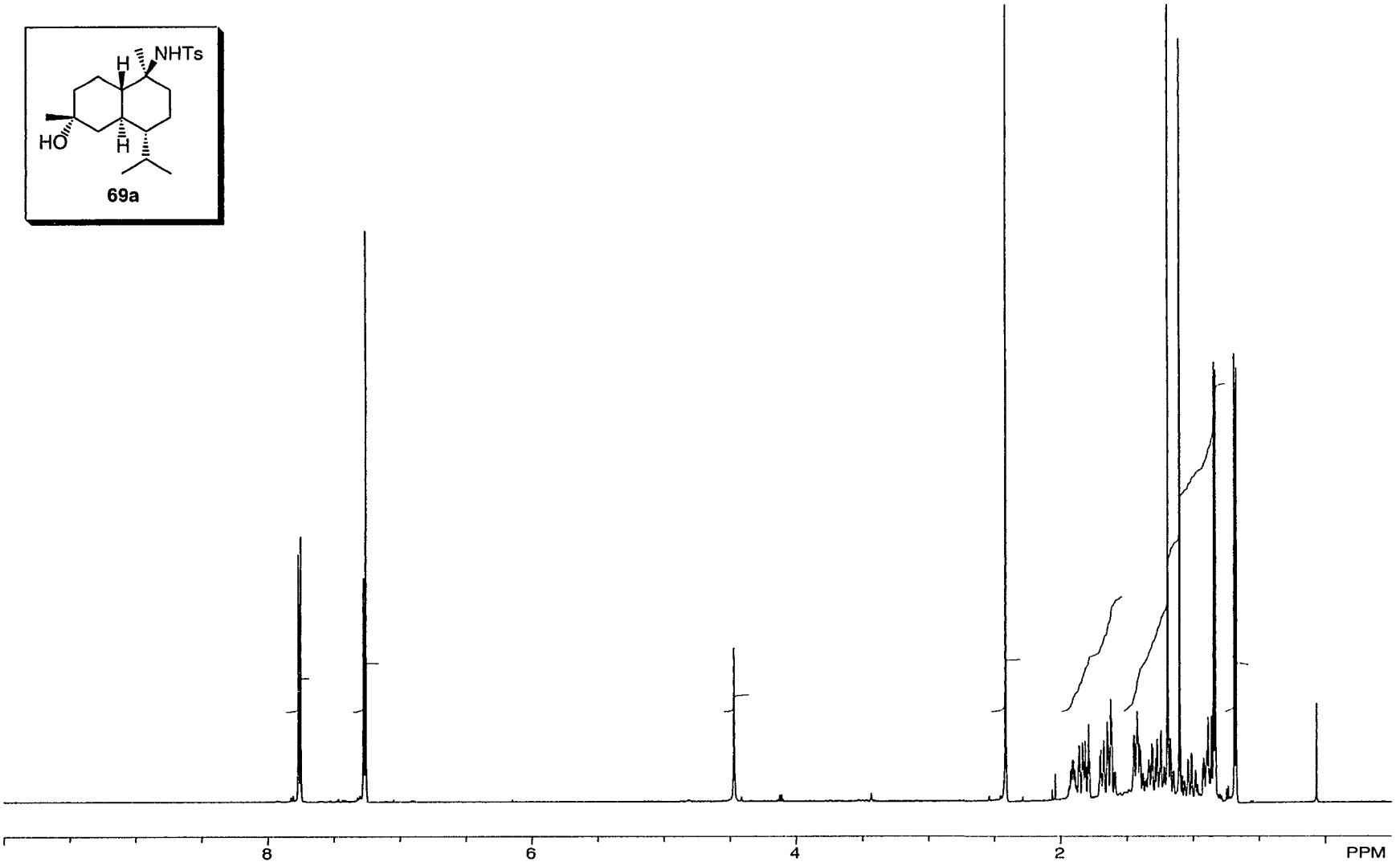


Figure A.1.27 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **69**.



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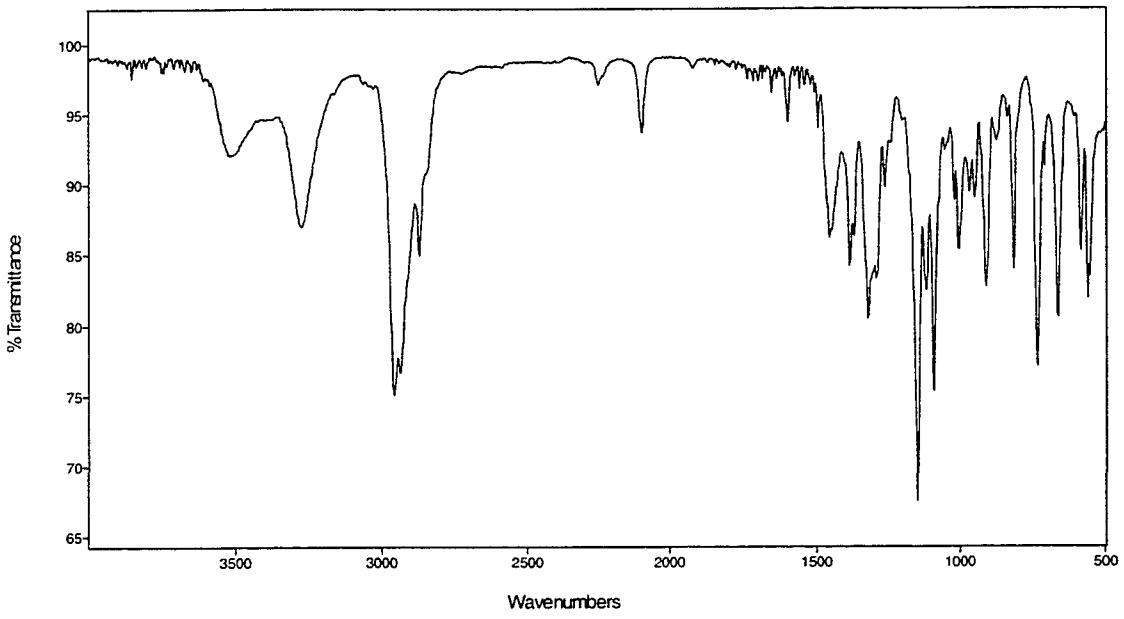


Figure A.1.29 FTIR Spectrum (thin film/NaCl) of Compound **69a**.

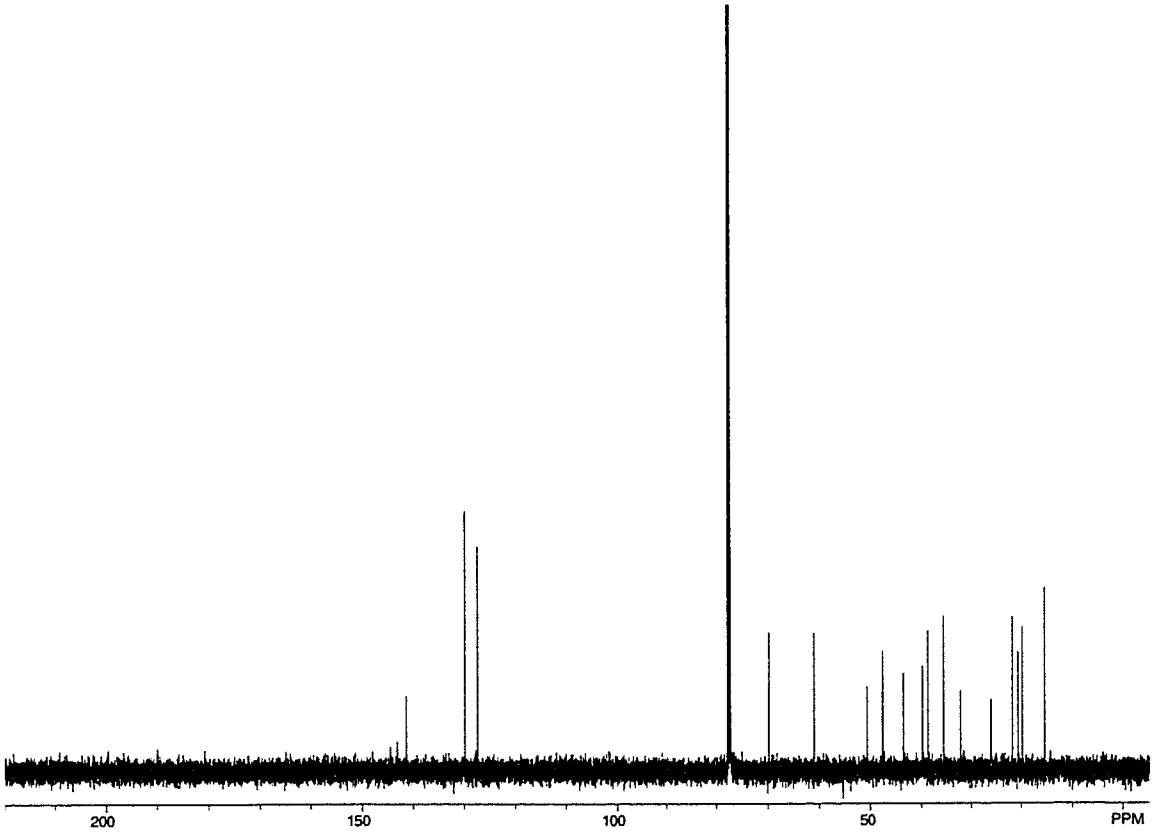


Figure A.1.30 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **69a**.

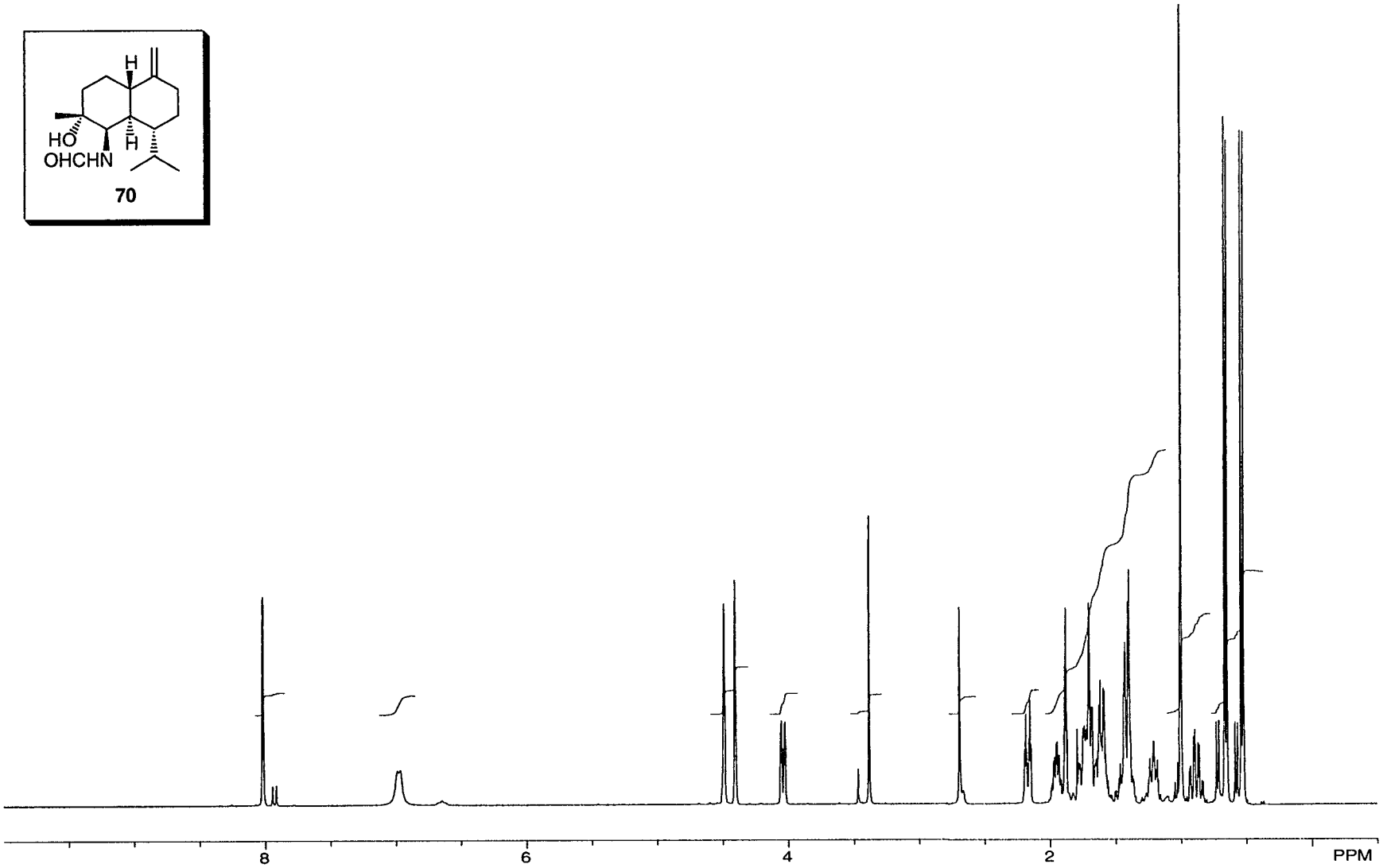


Figure A.1.31 ^{1}H NMR (400 MHz, $(CD_3)_2CO$) of Compound **70**.

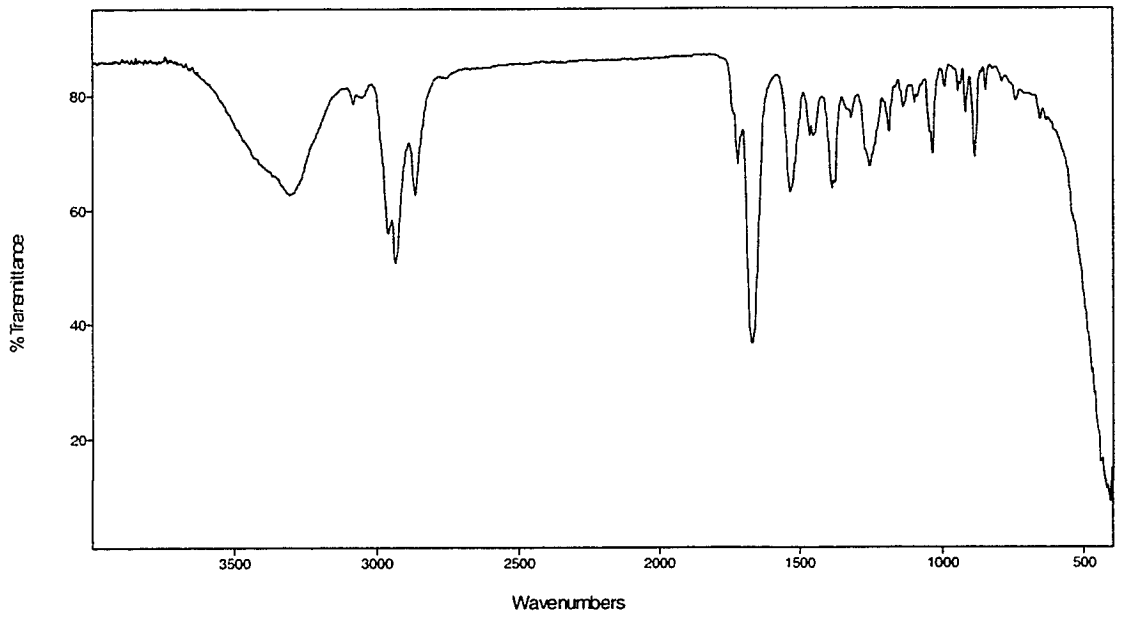


Figure A.1.32 FTIR Spectrum (thin film/NaCl) of Compound **70**.

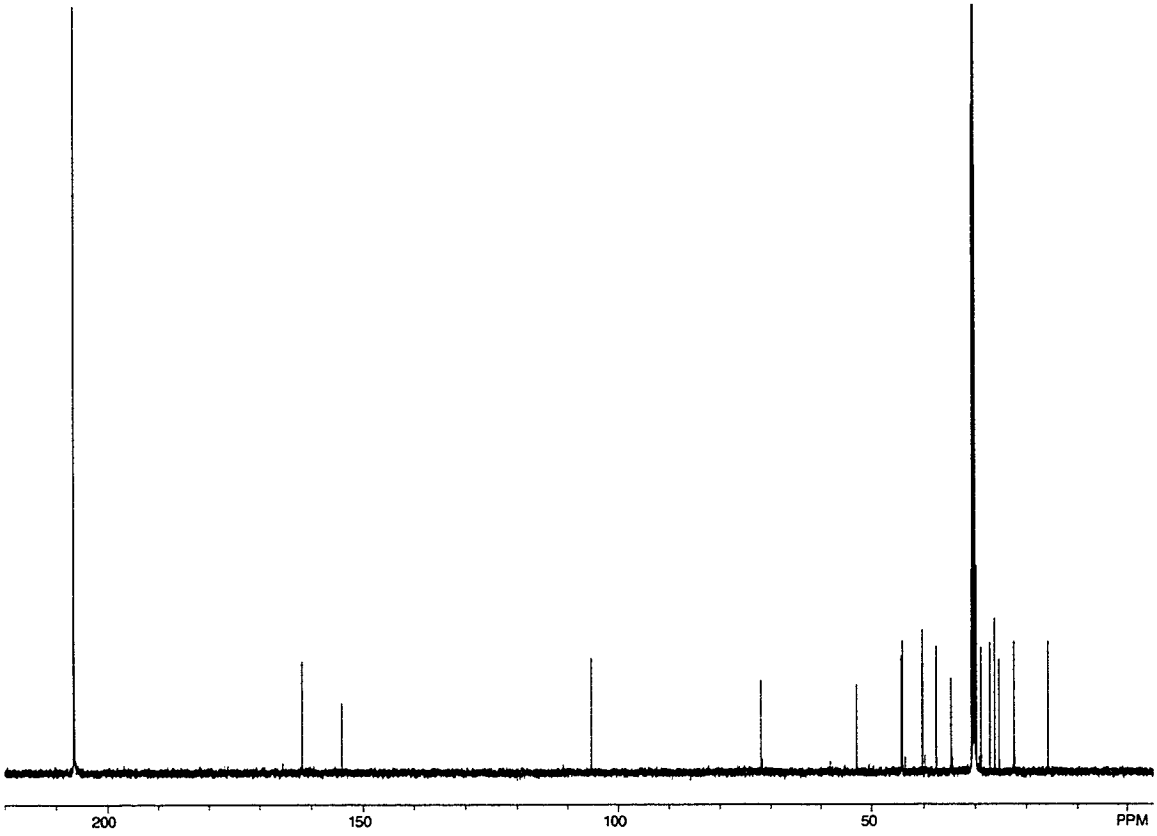


Figure A.1.33 ^{13}C NMR (125 MHz, $(CD_3)_2CO$) of Compound **70**.

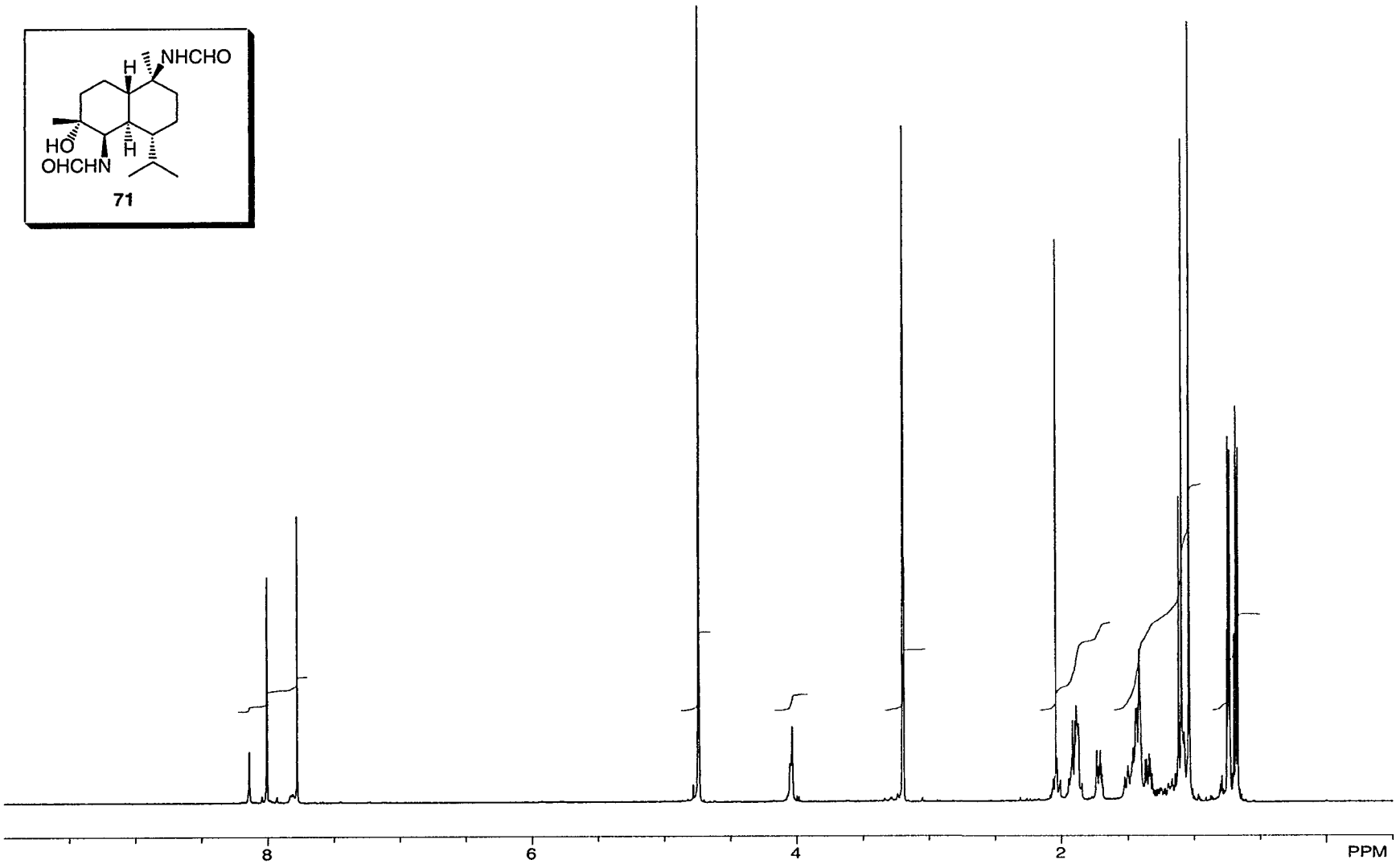


Figure A.1.34 ^{1}H NMR (500 MHz, CD_3OD) of Compound **71**.

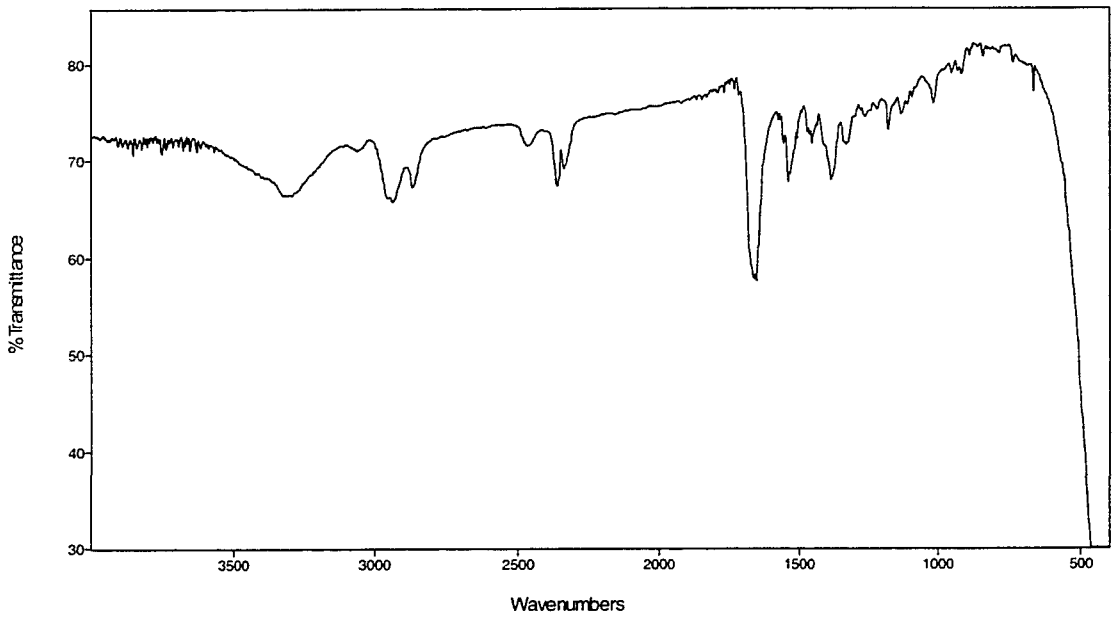


Figure A.1.35 FTIR Spectrum (thin film/NaCl) of Compound **71**.

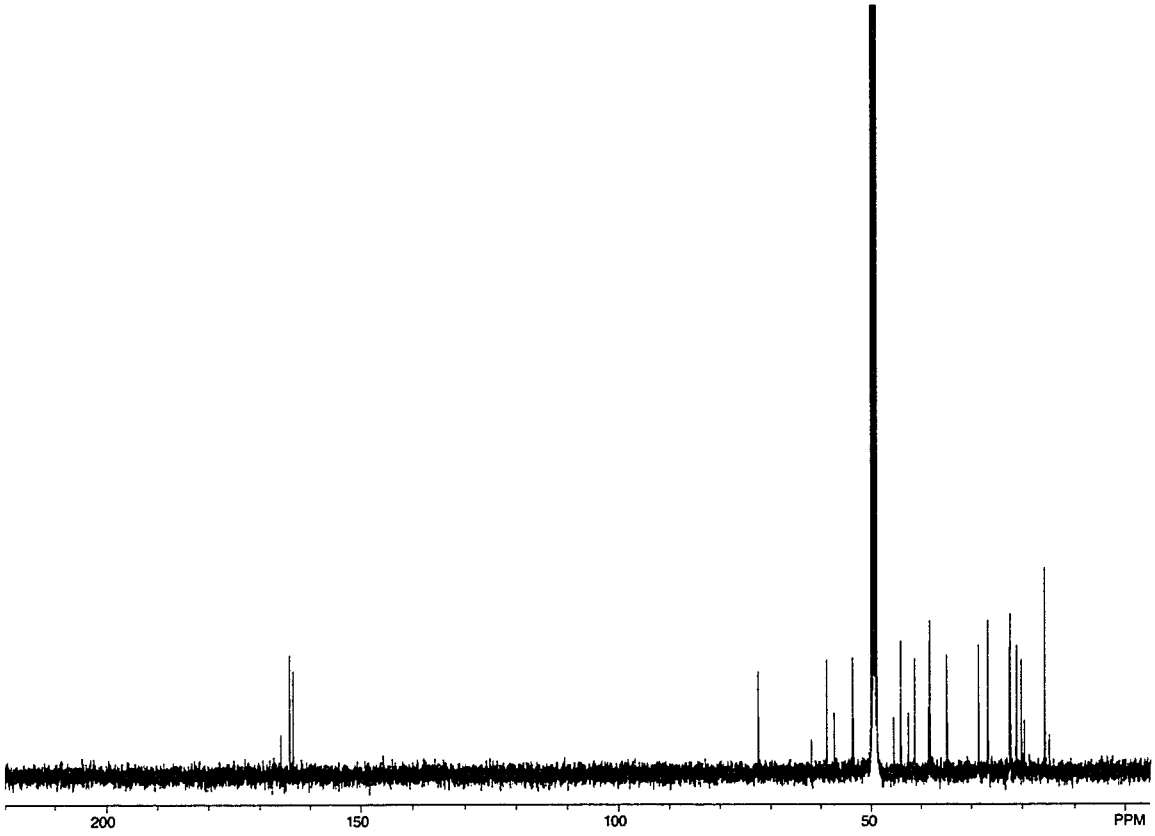


Figure A.1.36 ^{13}C NMR (125 MHz, CD_3OD) of Compound **71**.

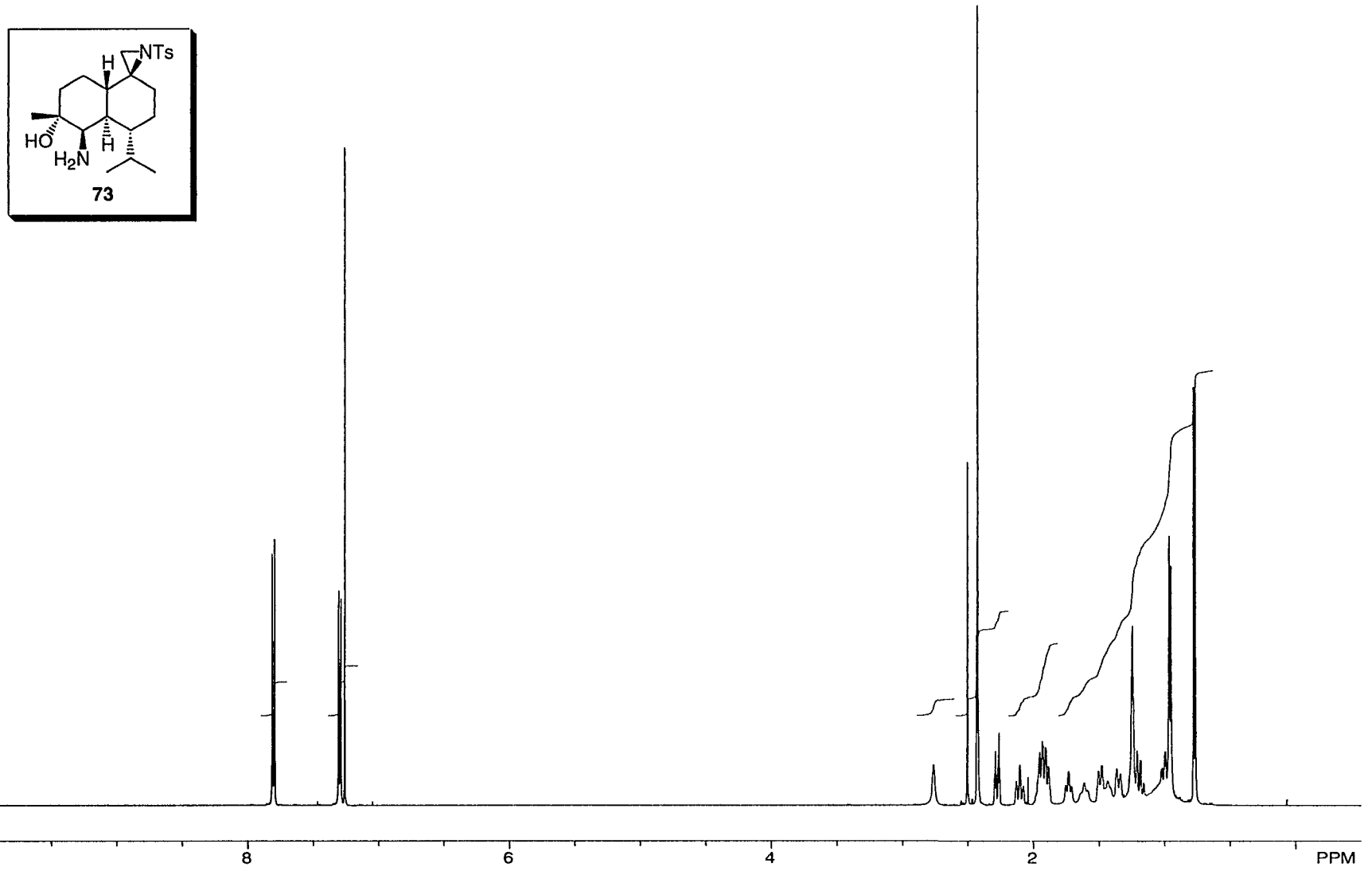


Figure A.1.37 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **73**.

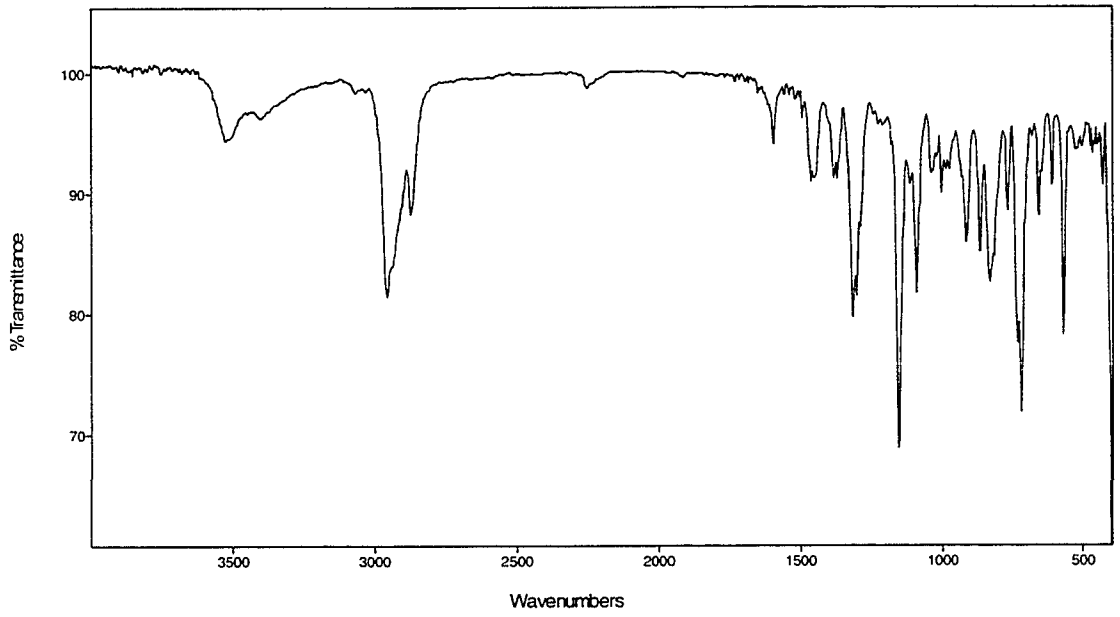


Figure A.1.38 FTIR Spectrum (thin film/NaCl) of Compound **73**.

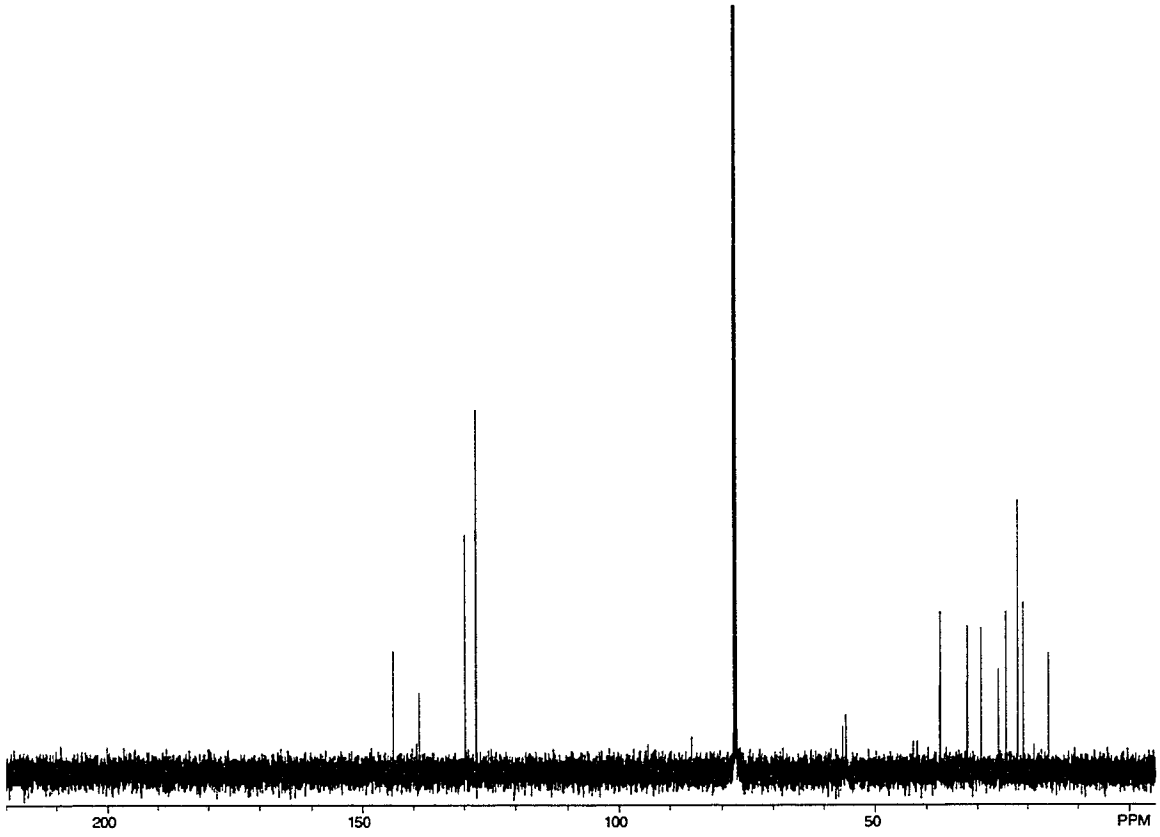


Figure A.1.39 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **73**.

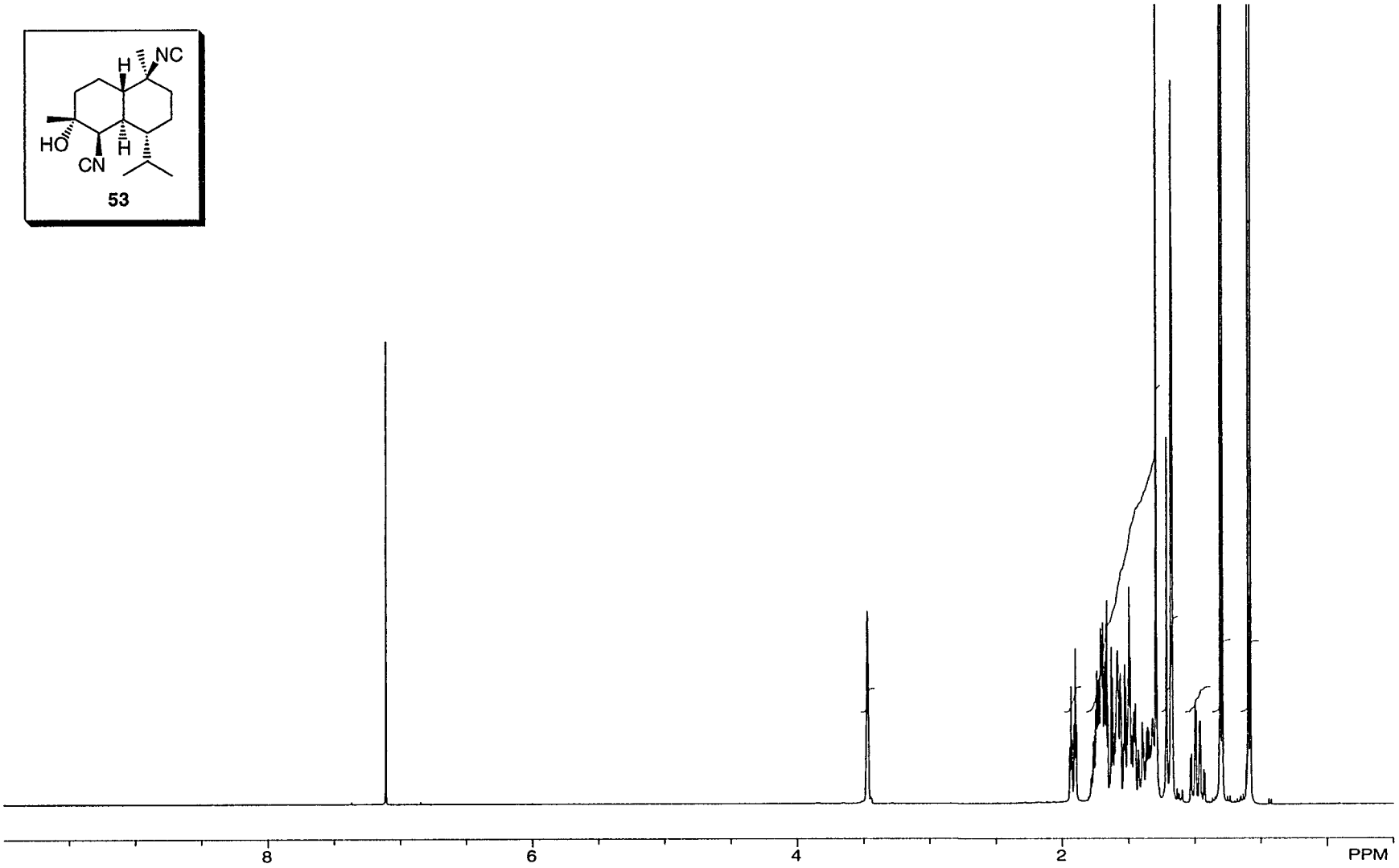


Figure A.1.40 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **53**.

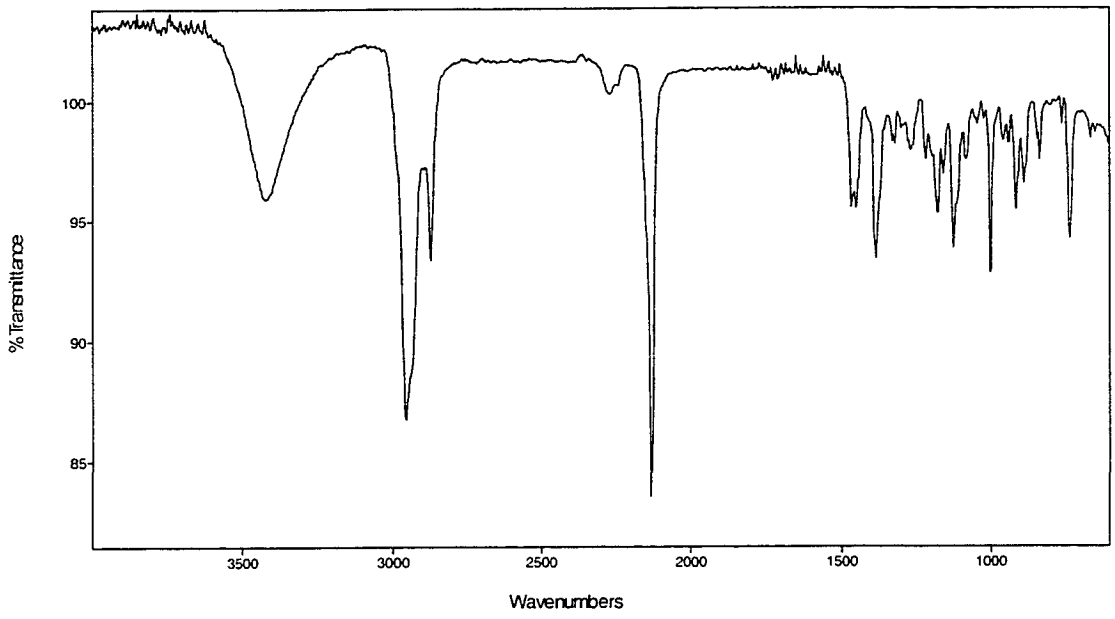


Figure A.1.41 FTIR Spectrum (thin film/NaCl) of Compound **53**.

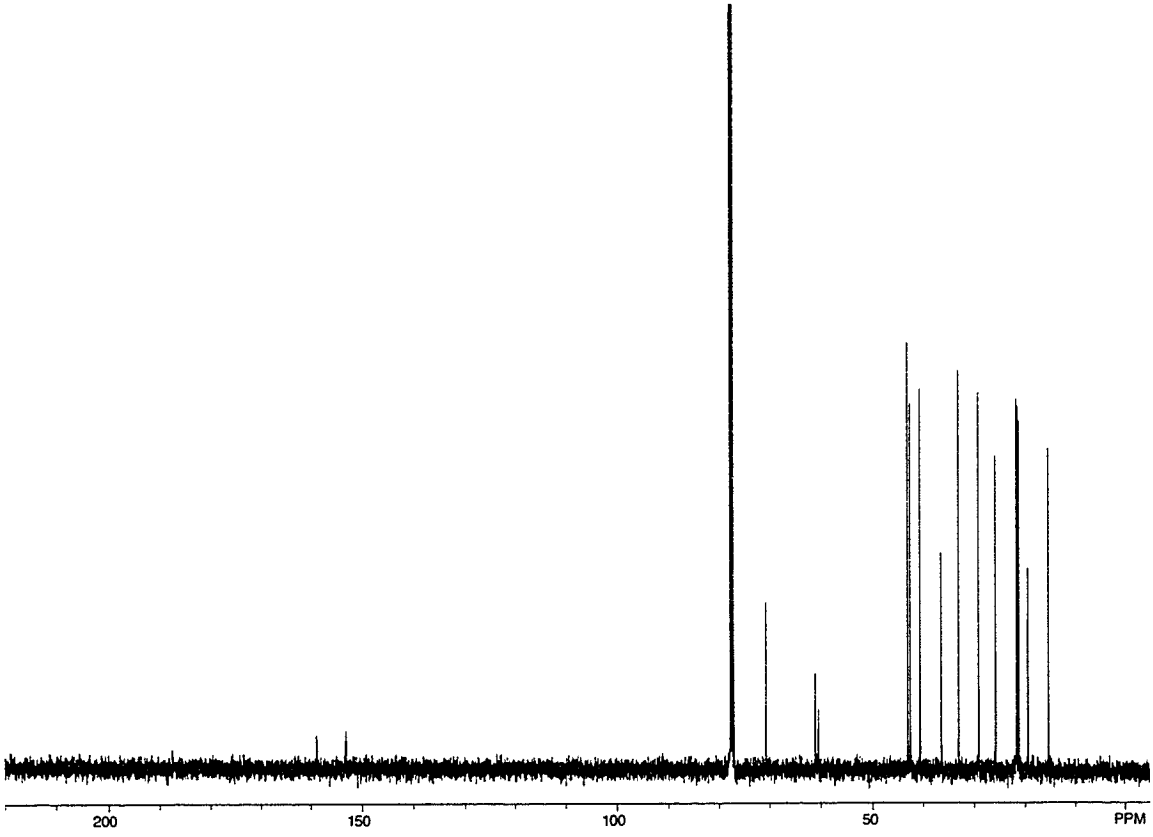


Figure A.1.42 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **53**.

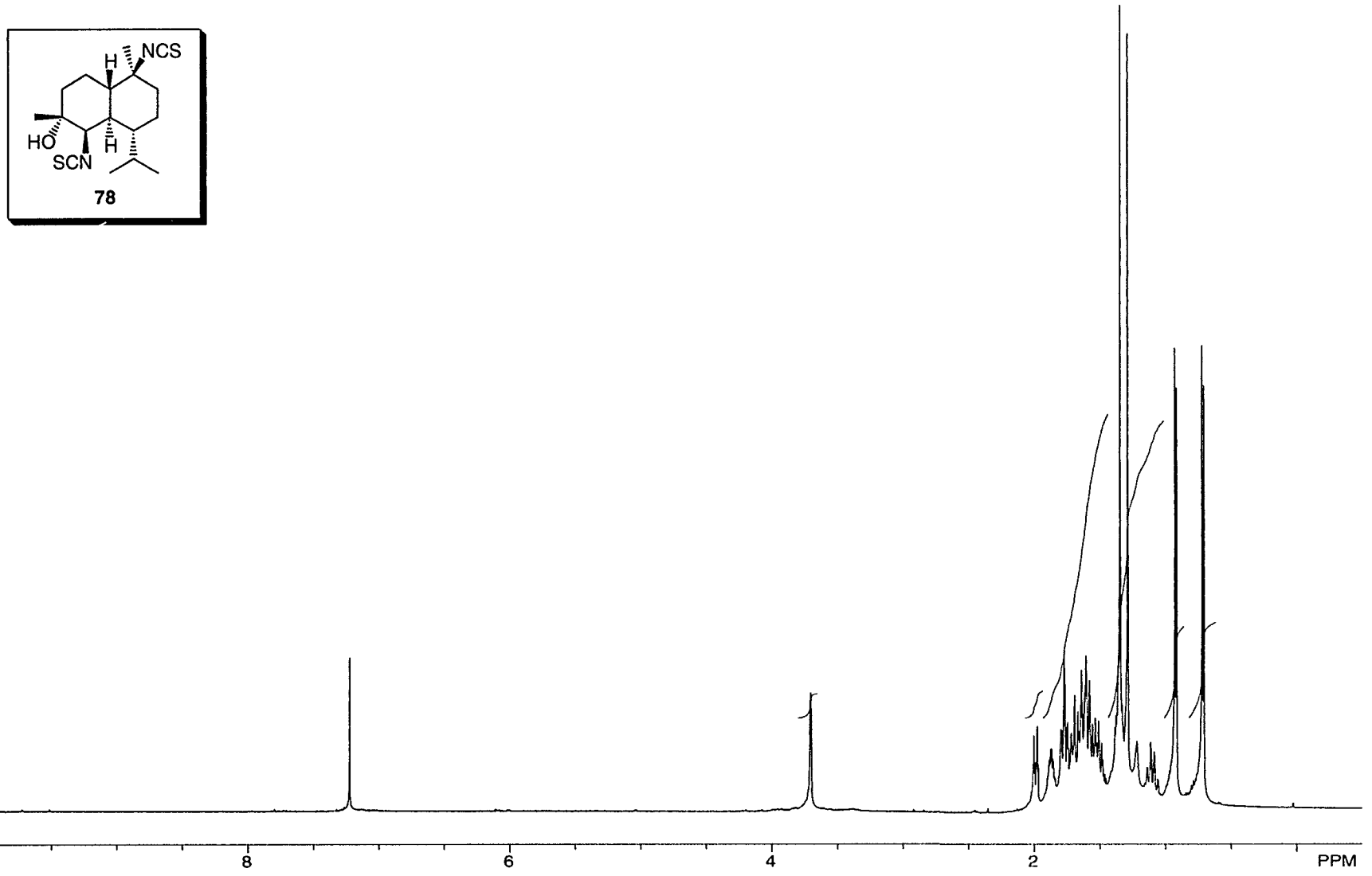


Figure A.1.43 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **78**.

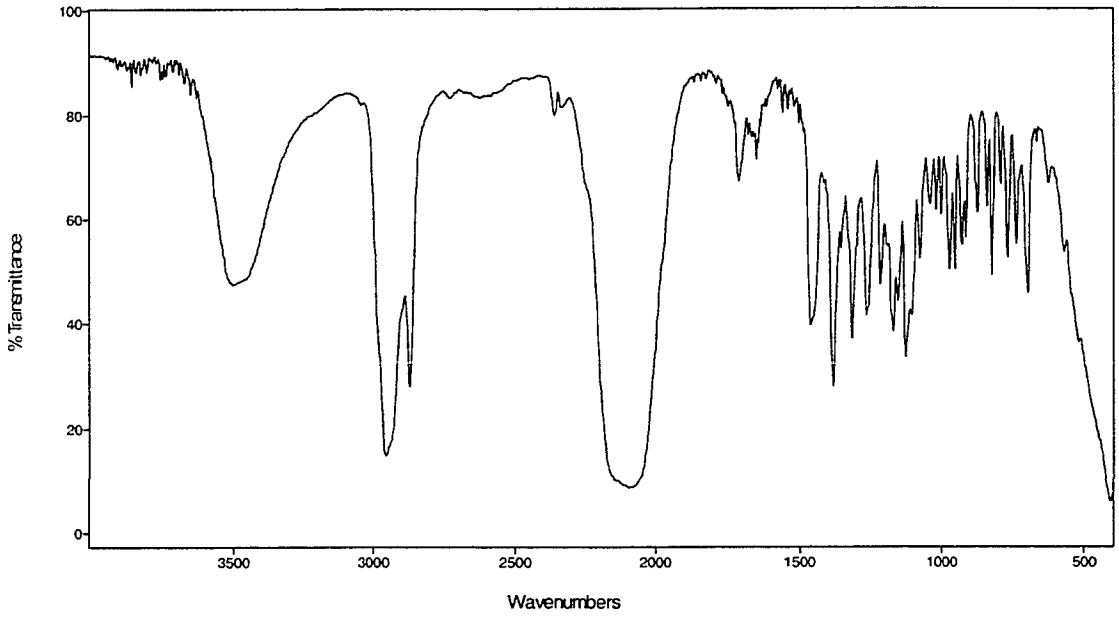


Figure A.1.44 FTIR Spectrum (thin film/NaCl) of Compound **78**.

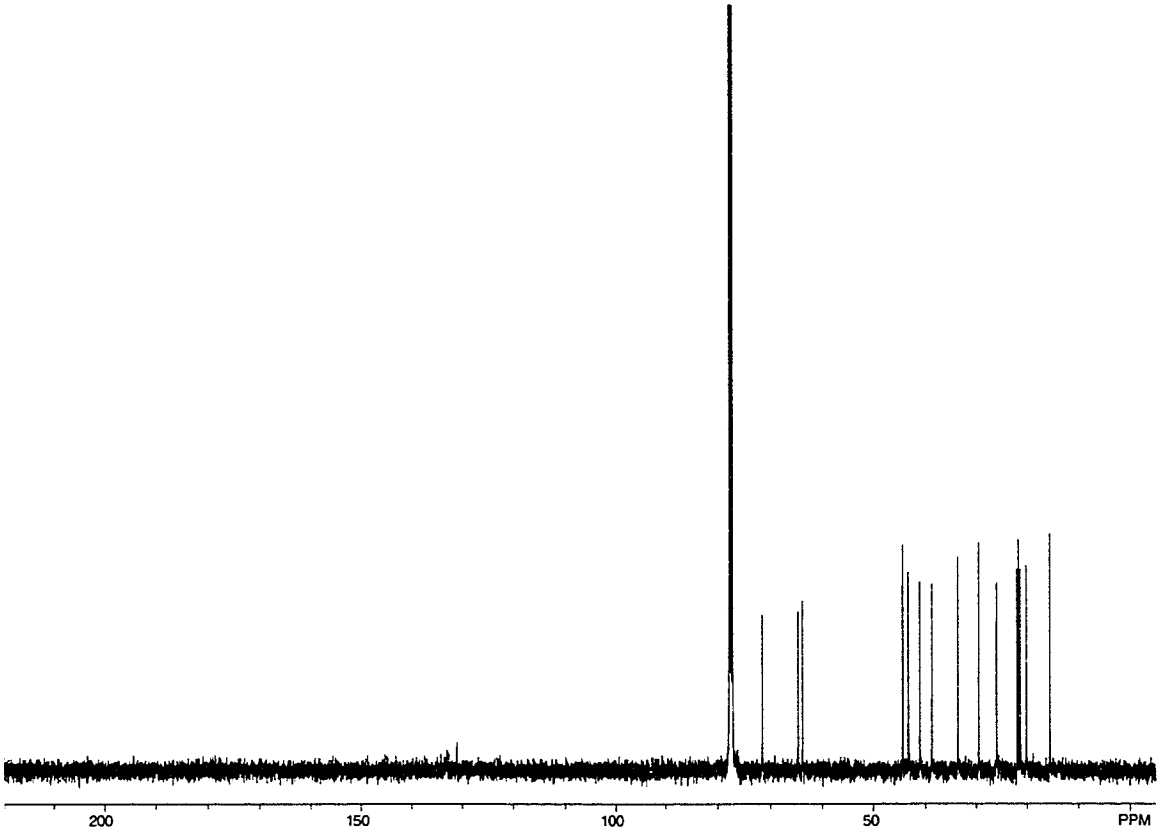


Figure A.1.45 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **78**.

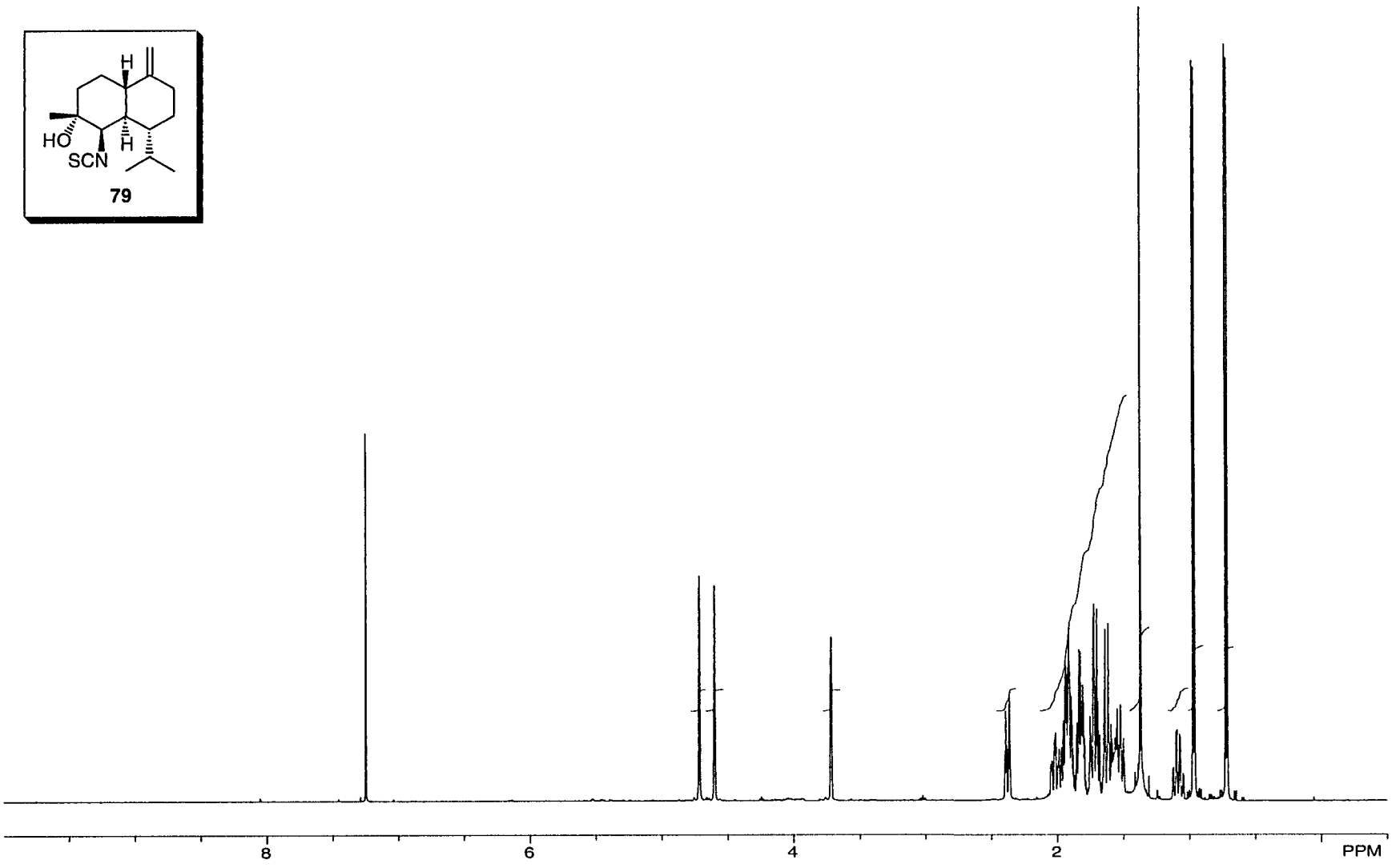


Figure A.1.46 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **79**.

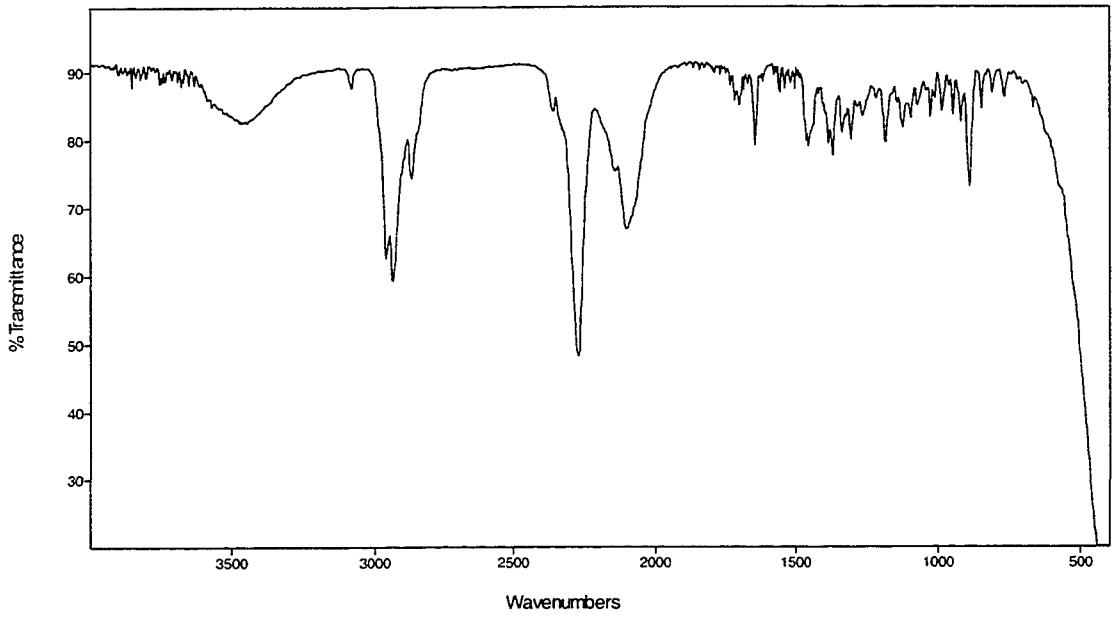


Figure A.1.47 FTIR Spectrum (thin film/NaCl) of Compound **79**.

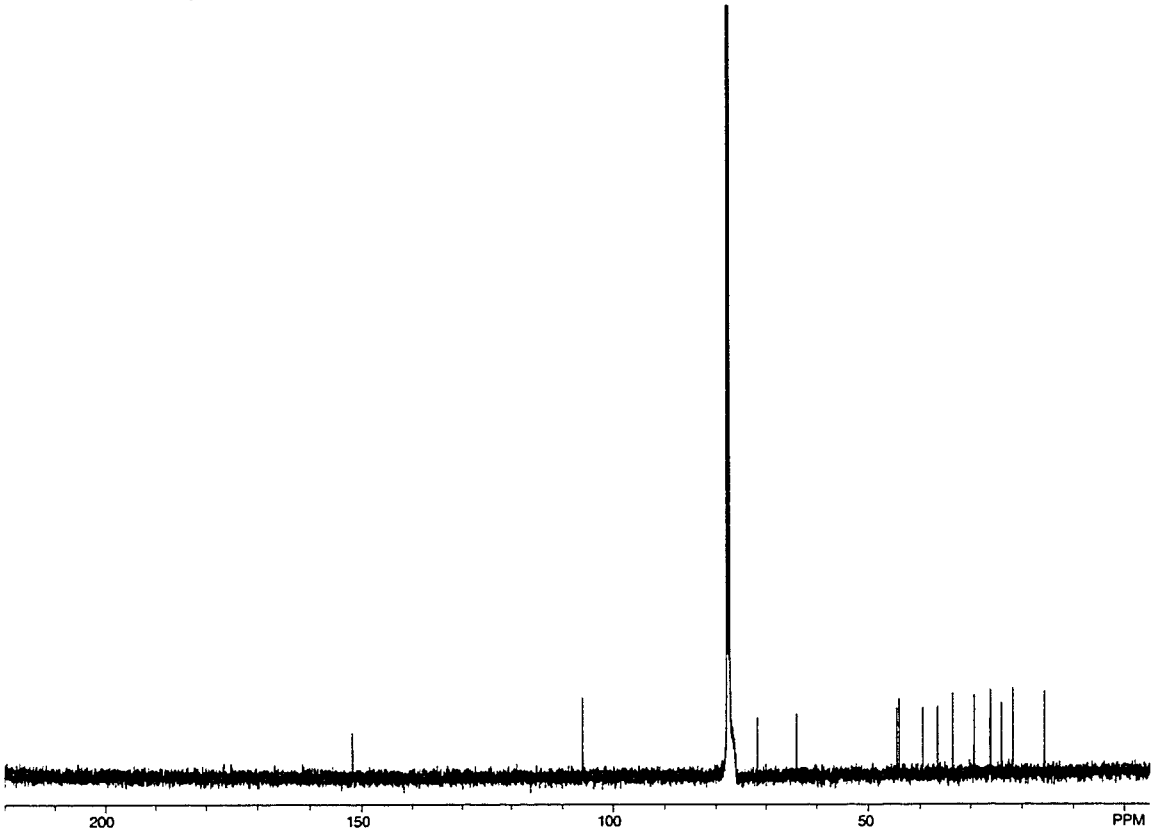


Figure A.1.48 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **79.**

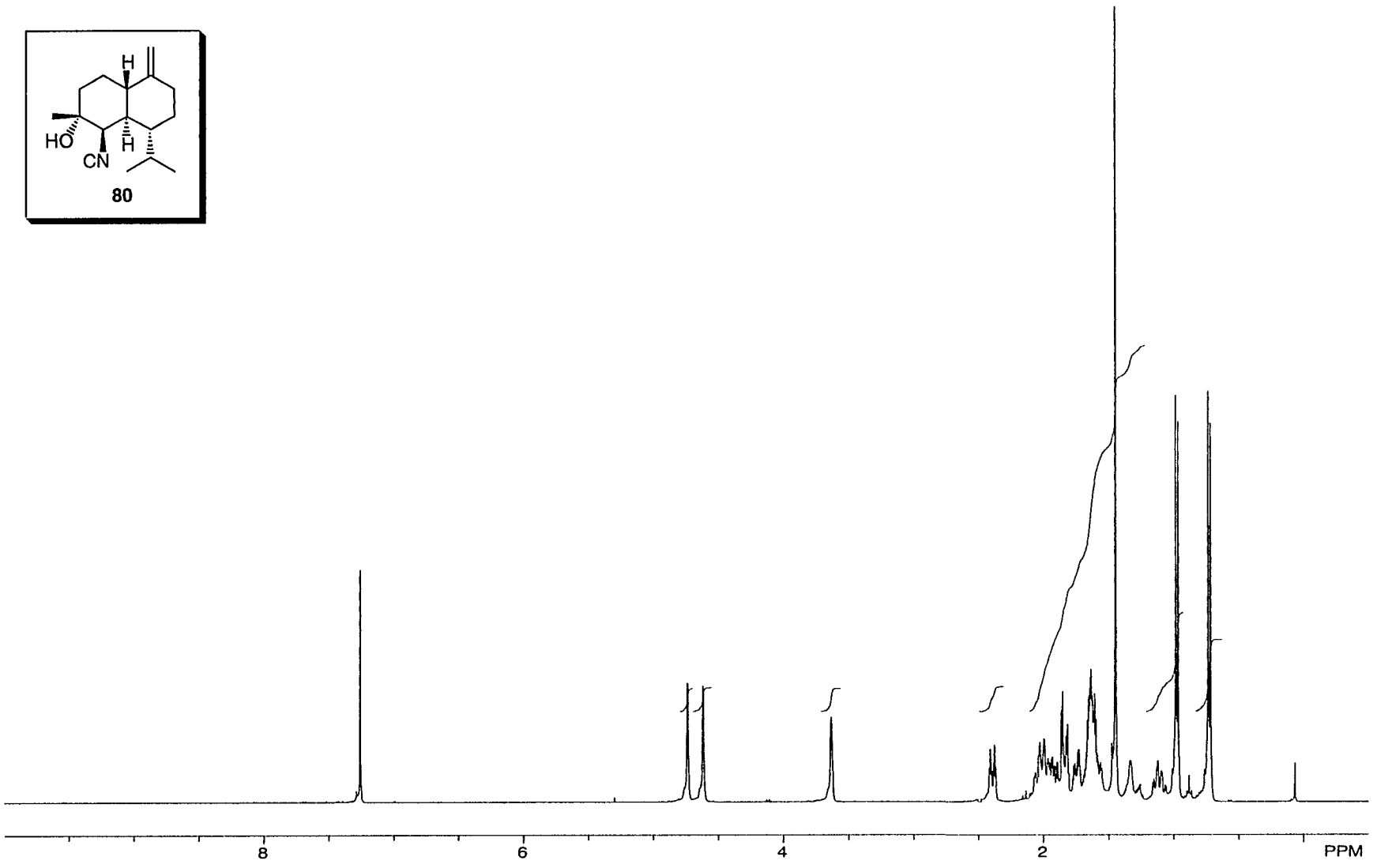


Figure A.1.49 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **80**.

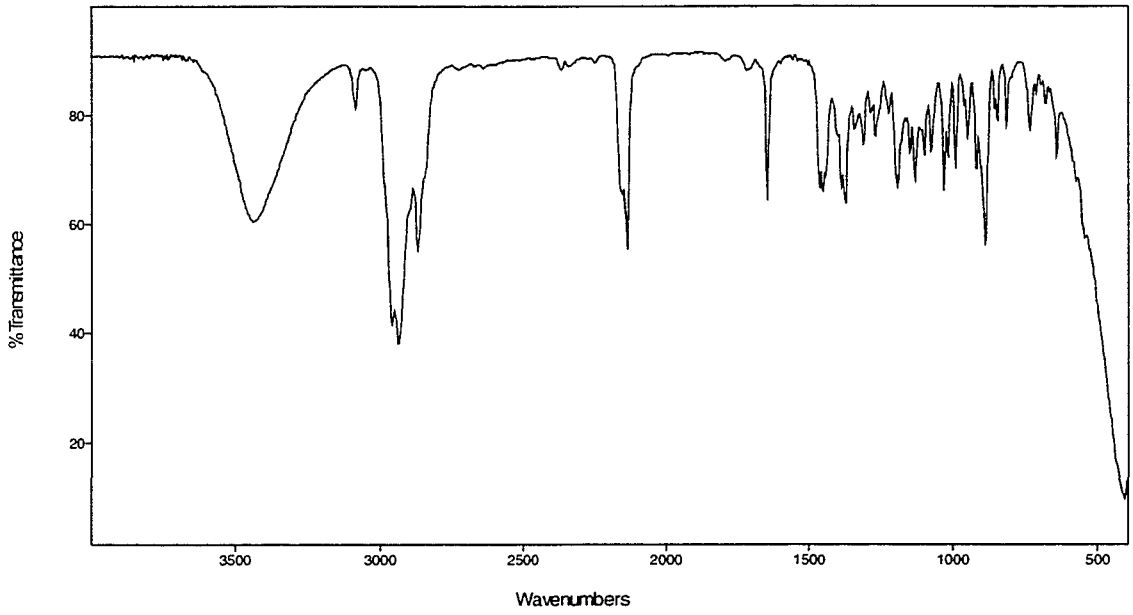


Figure A.1.50 FTIR Spectrum (thin film/NaCl) of Compound **80.**

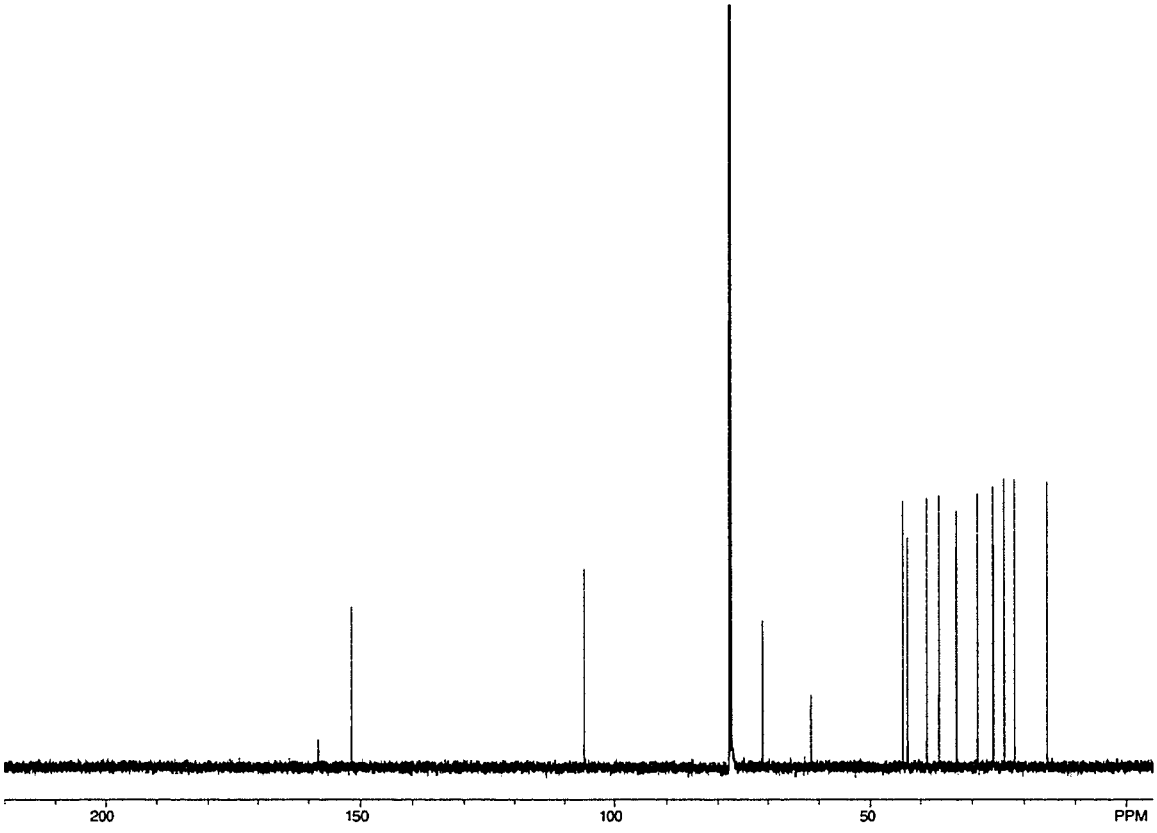


Figure A.1.51 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **80.**

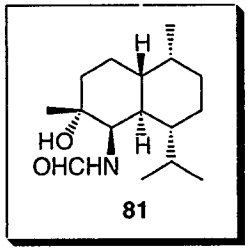


Figure A.1.52 ^{1}H NMR (400 MHz, ~4:1 $(CD_3)_2CO$:$CDCl_3$) of Compound **81**.

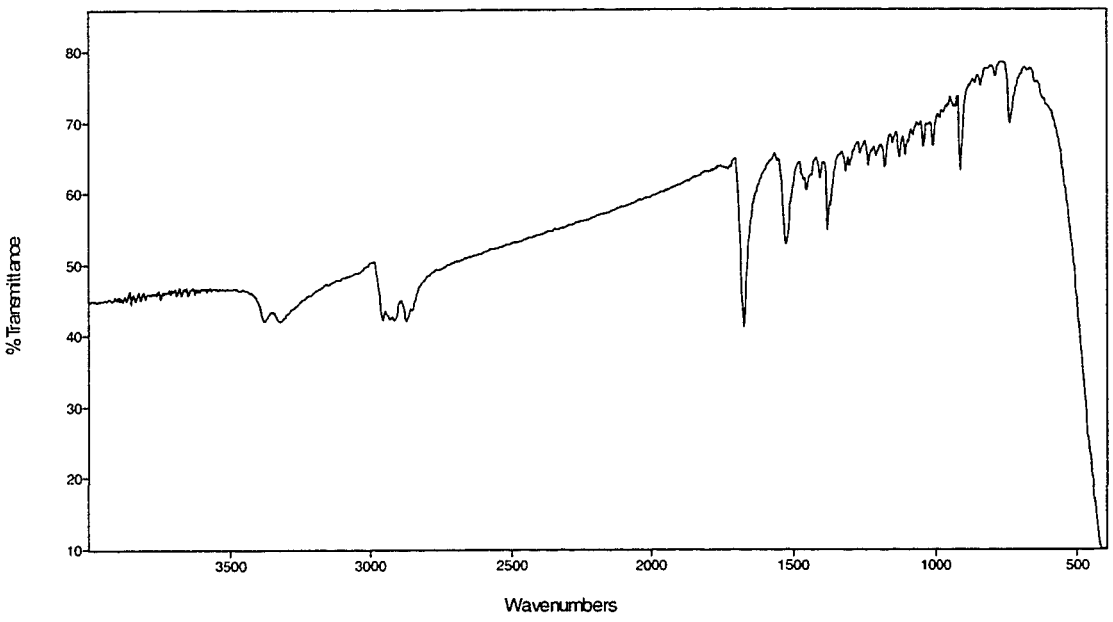


Figure A.1.53 FTIR Spectrum (thin film/NaCl) of Compound **81**.

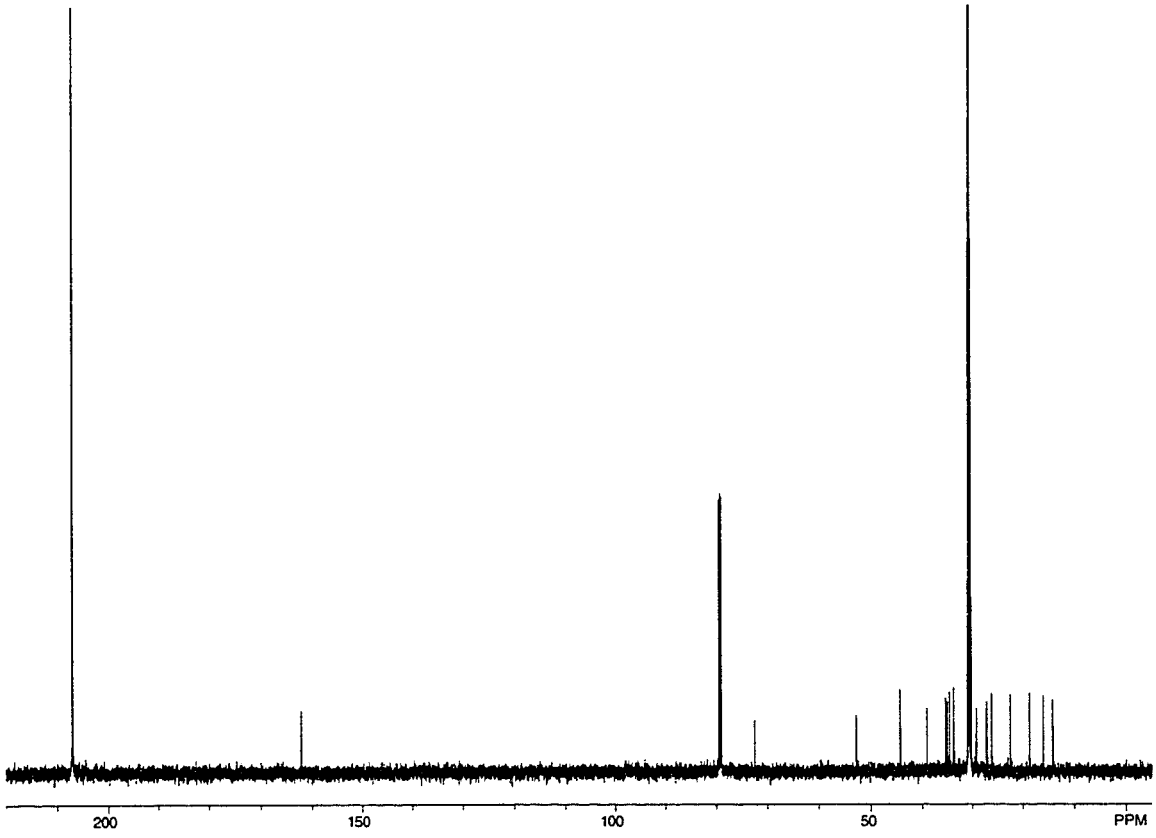
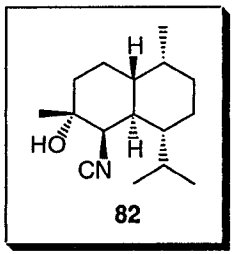


Figure A.1.54 ^{13}C NMR (125 MHz, ~4:1 $(CD_3)_2CO:CDCl_3$) of Compound **81**.



82

Figure A.1.55 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **82**.

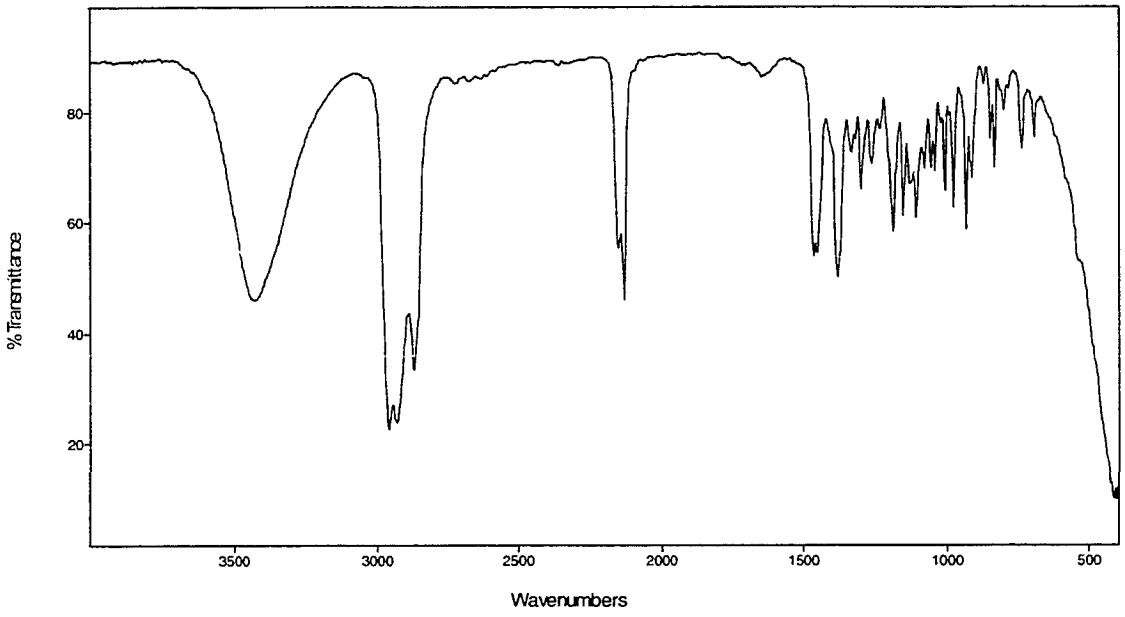


Figure A.1.56 FTIR Spectrum (thin film/NaCl) of Compound **82**.

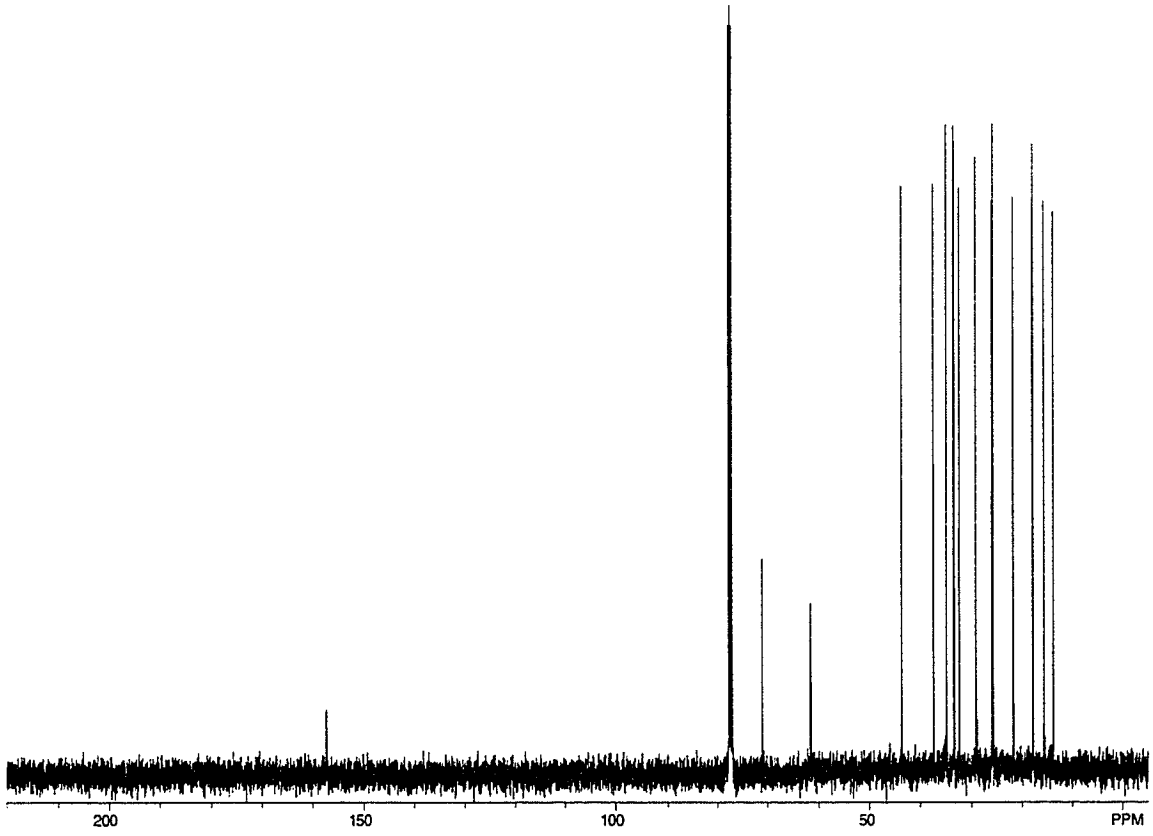


Figure A.1.57 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **82**.

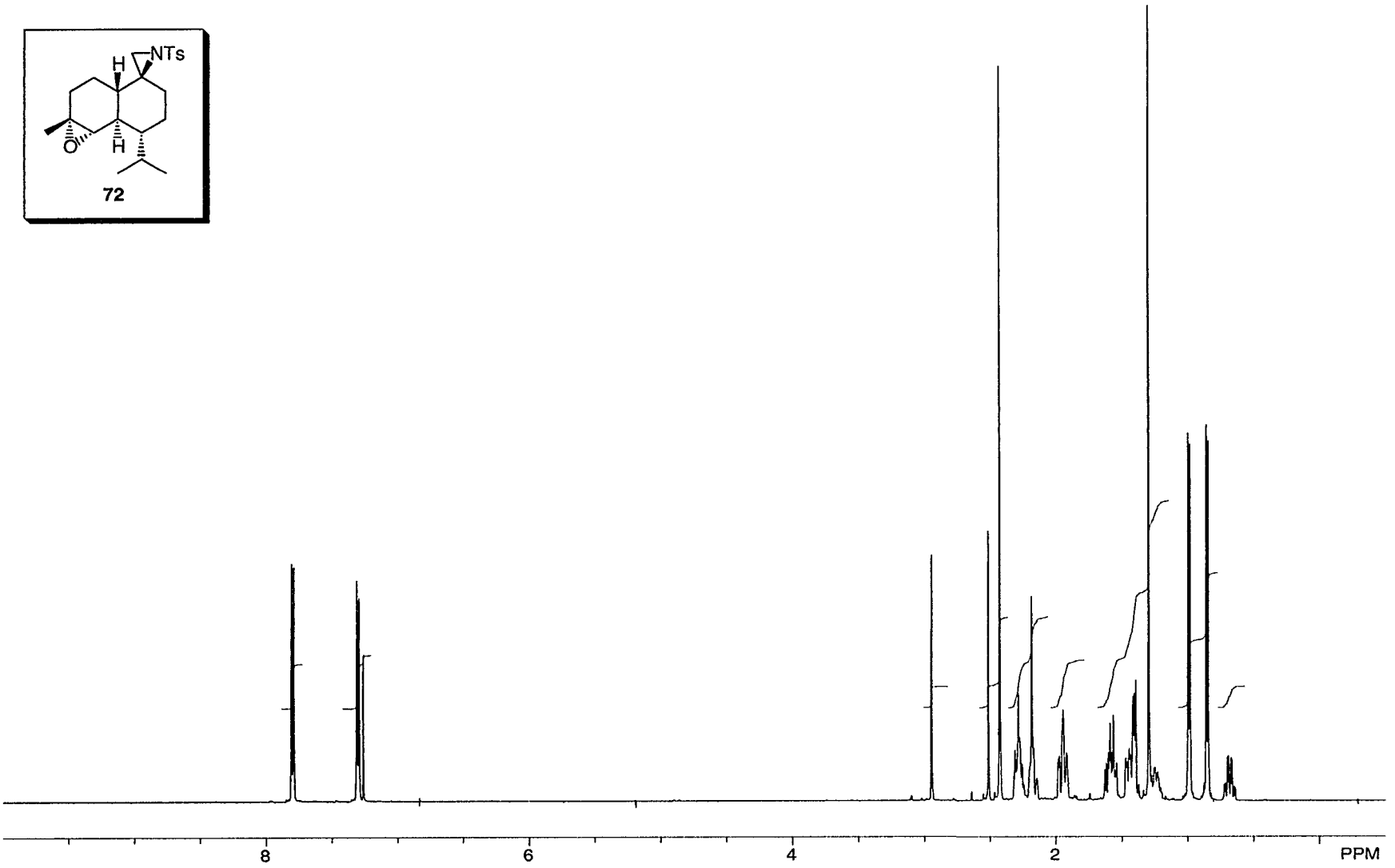


Figure A.1.58 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **72**.

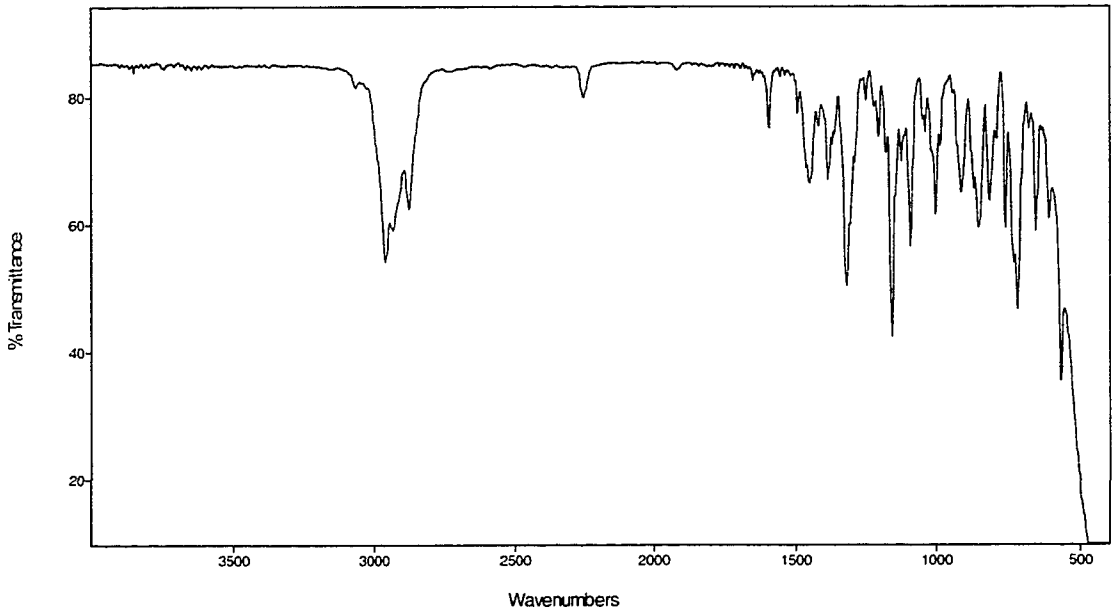


Figure A.1.59 FTIR Spectrum (thin film/NaCl) of Compound **72**.

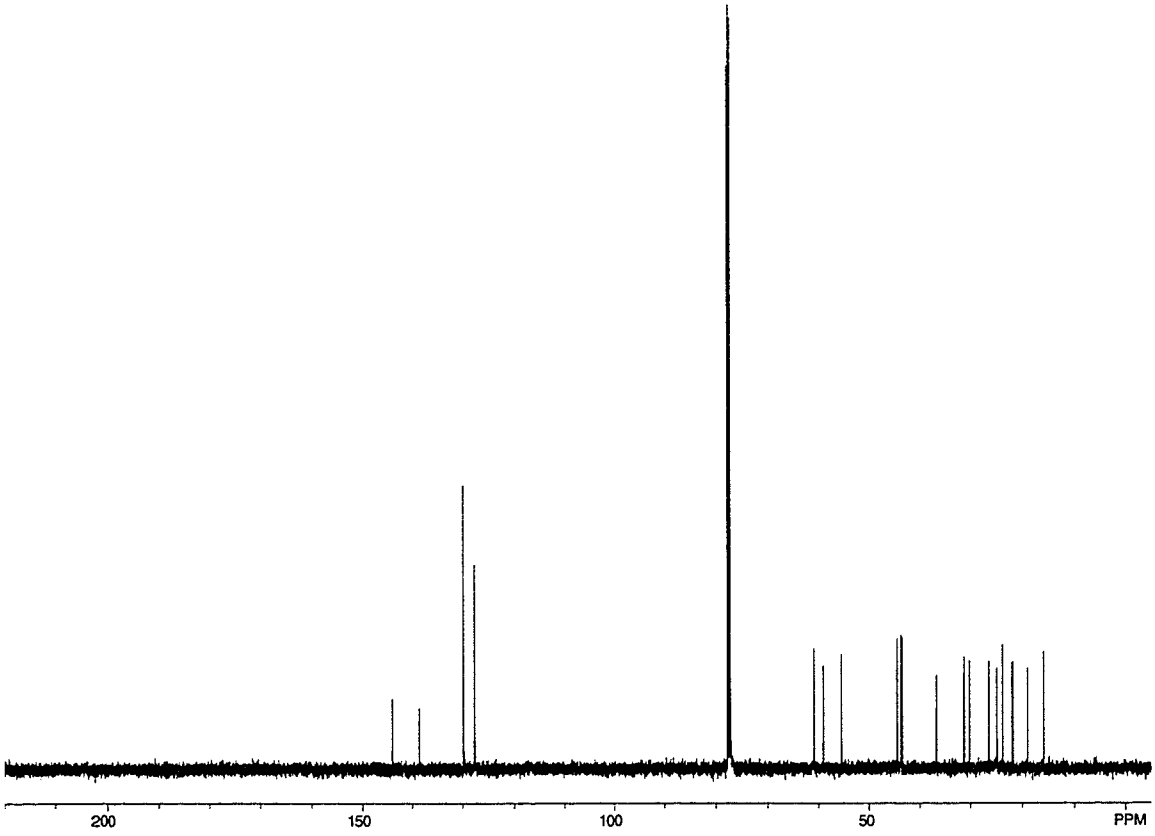


Figure A.1.60 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **72**.

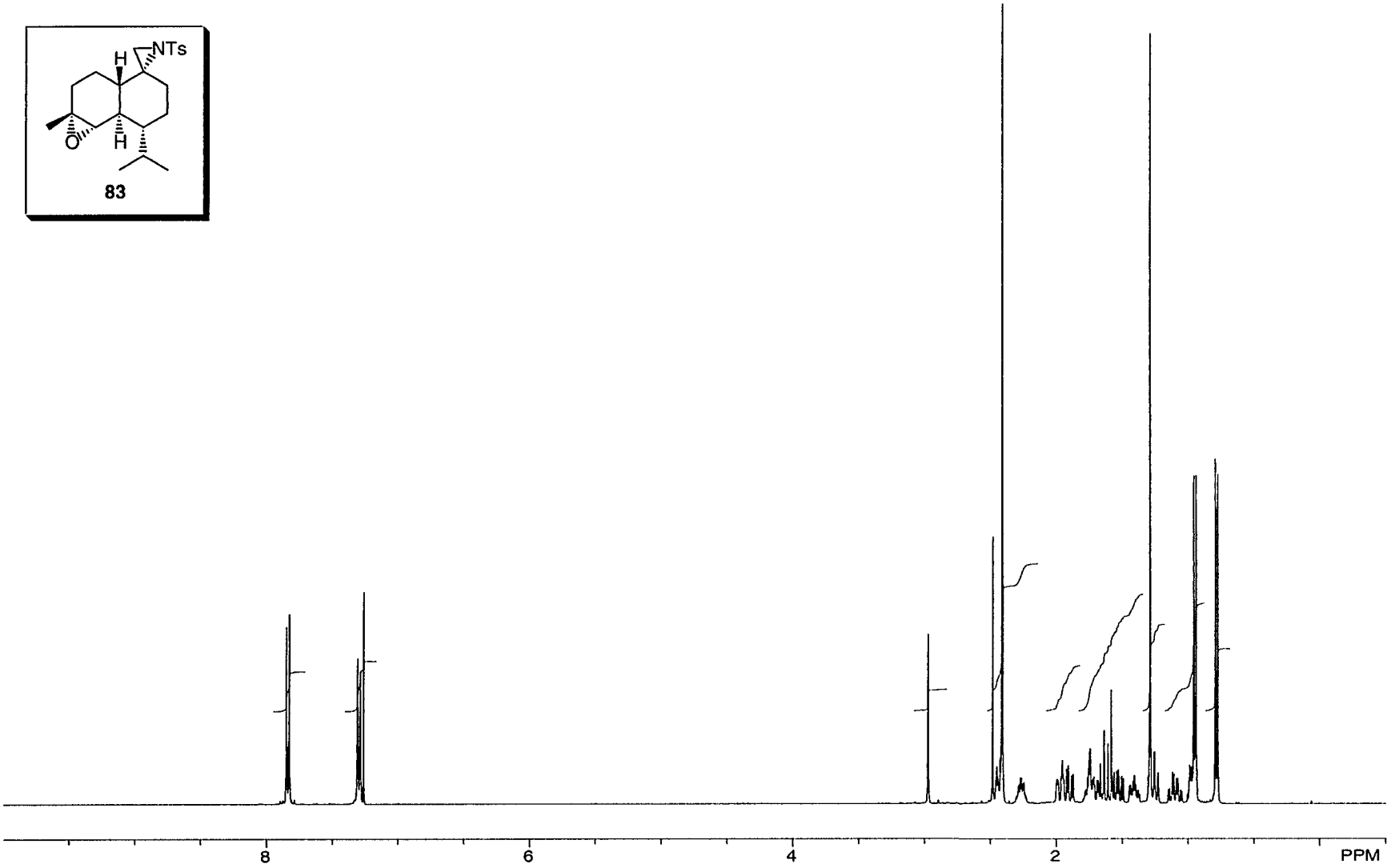


Figure A.1.61 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **83**.

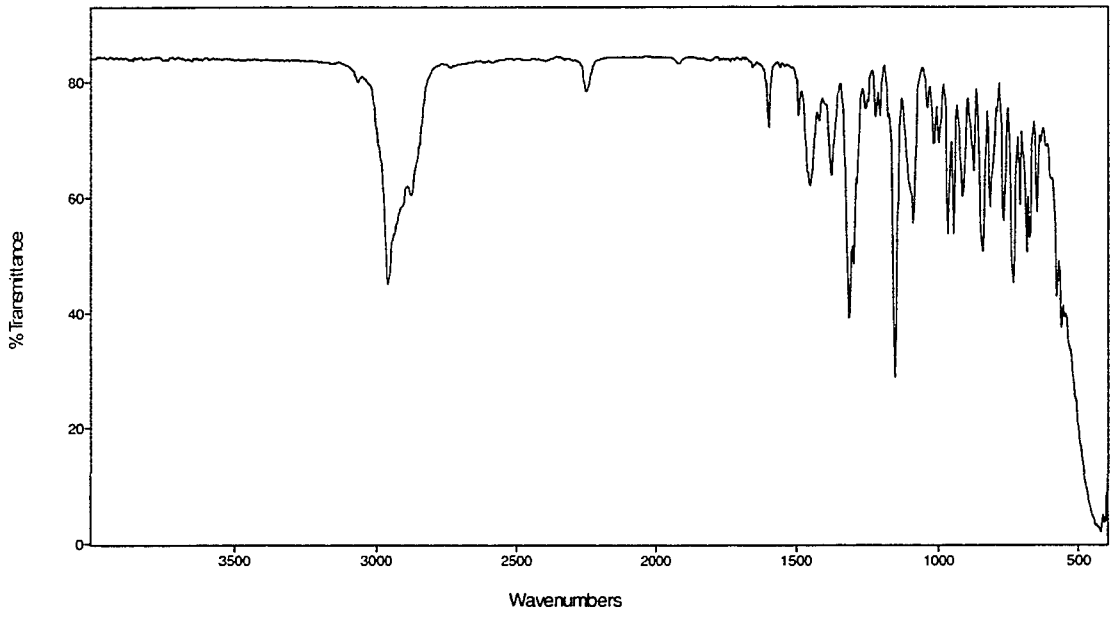


Figure A.1.62 FTIR Spectrum (thin film/NaCl) of Compound **83**.

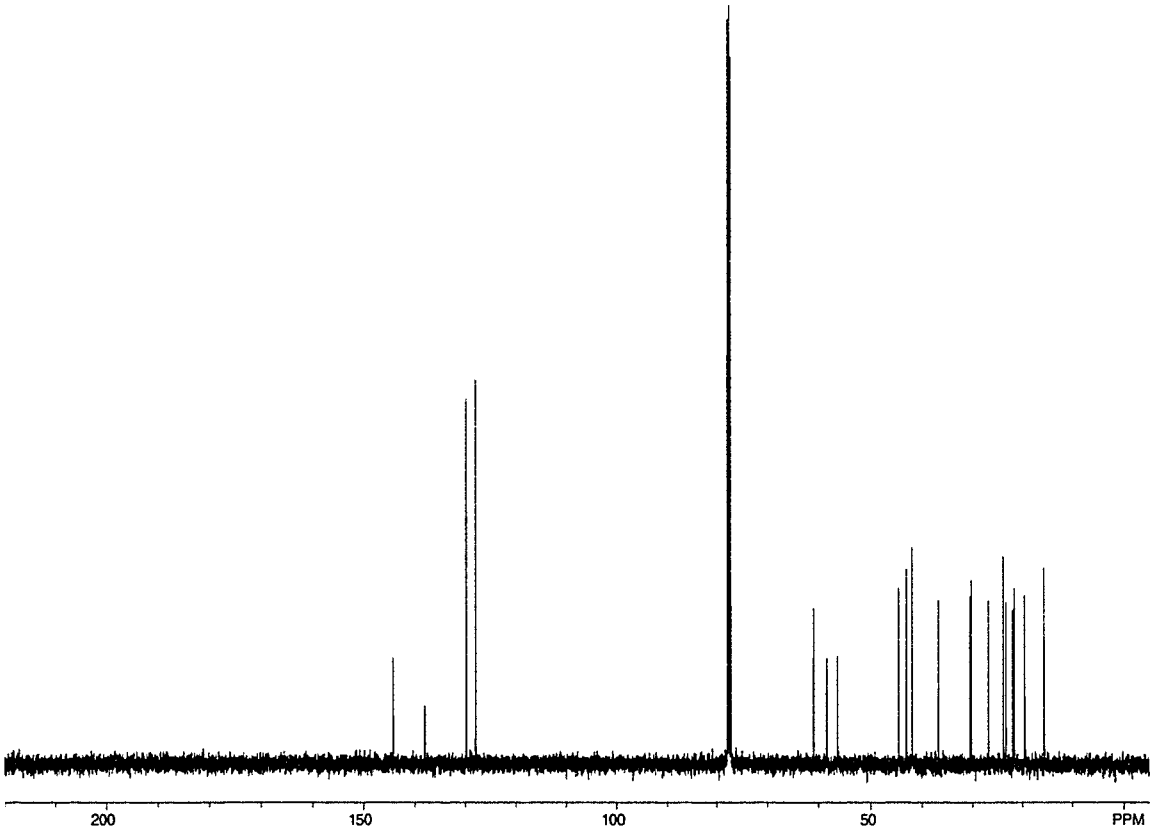


Figure A.1.63 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **83**.

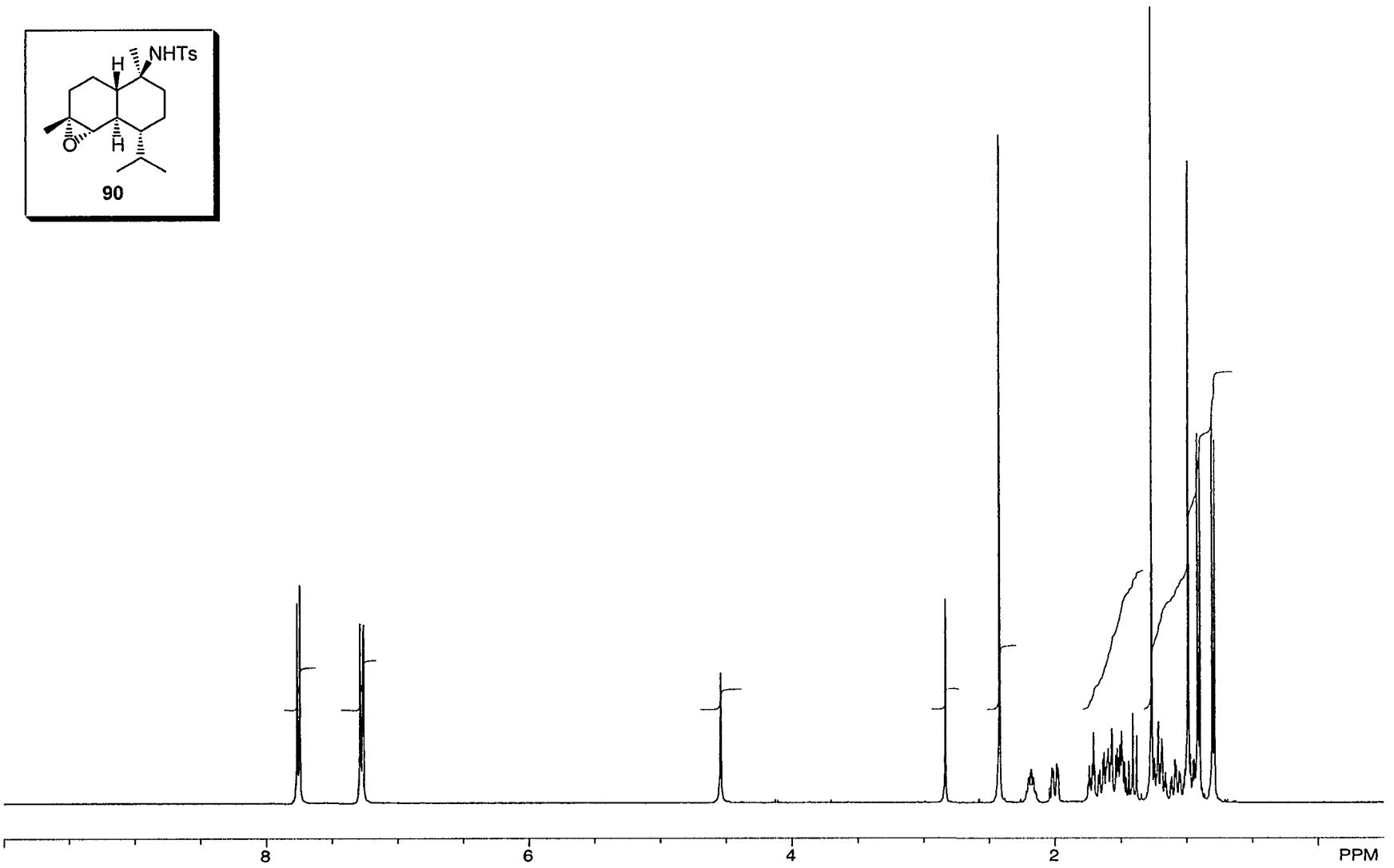


Figure A.1.64 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **90**.

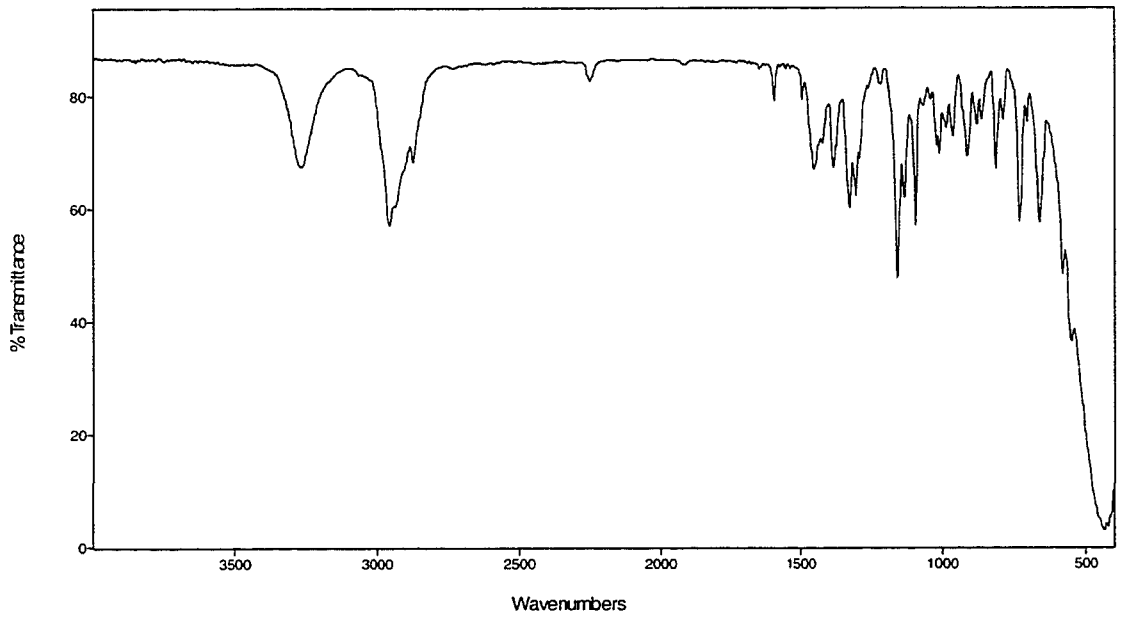


Figure A.1.65 FTIR Spectrum (thin film/NaCl) of Compound **90**.

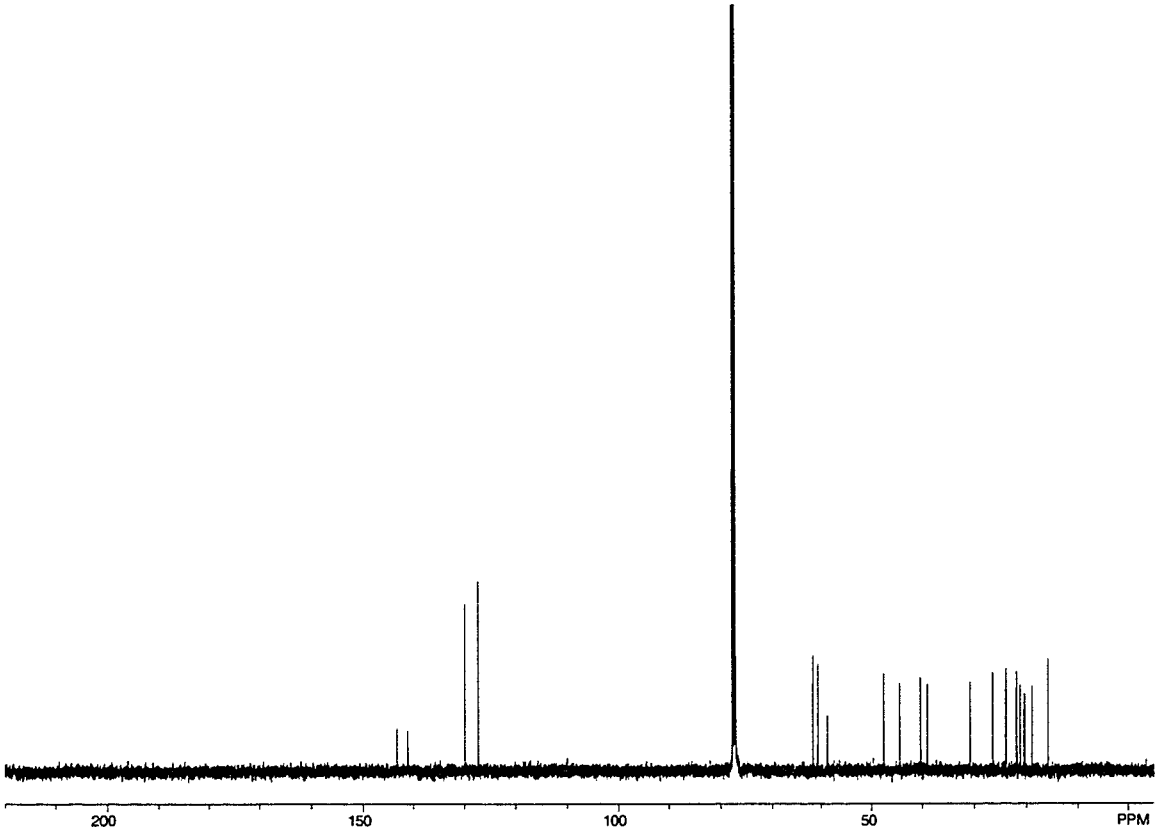


Figure A.1.66 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **90**.

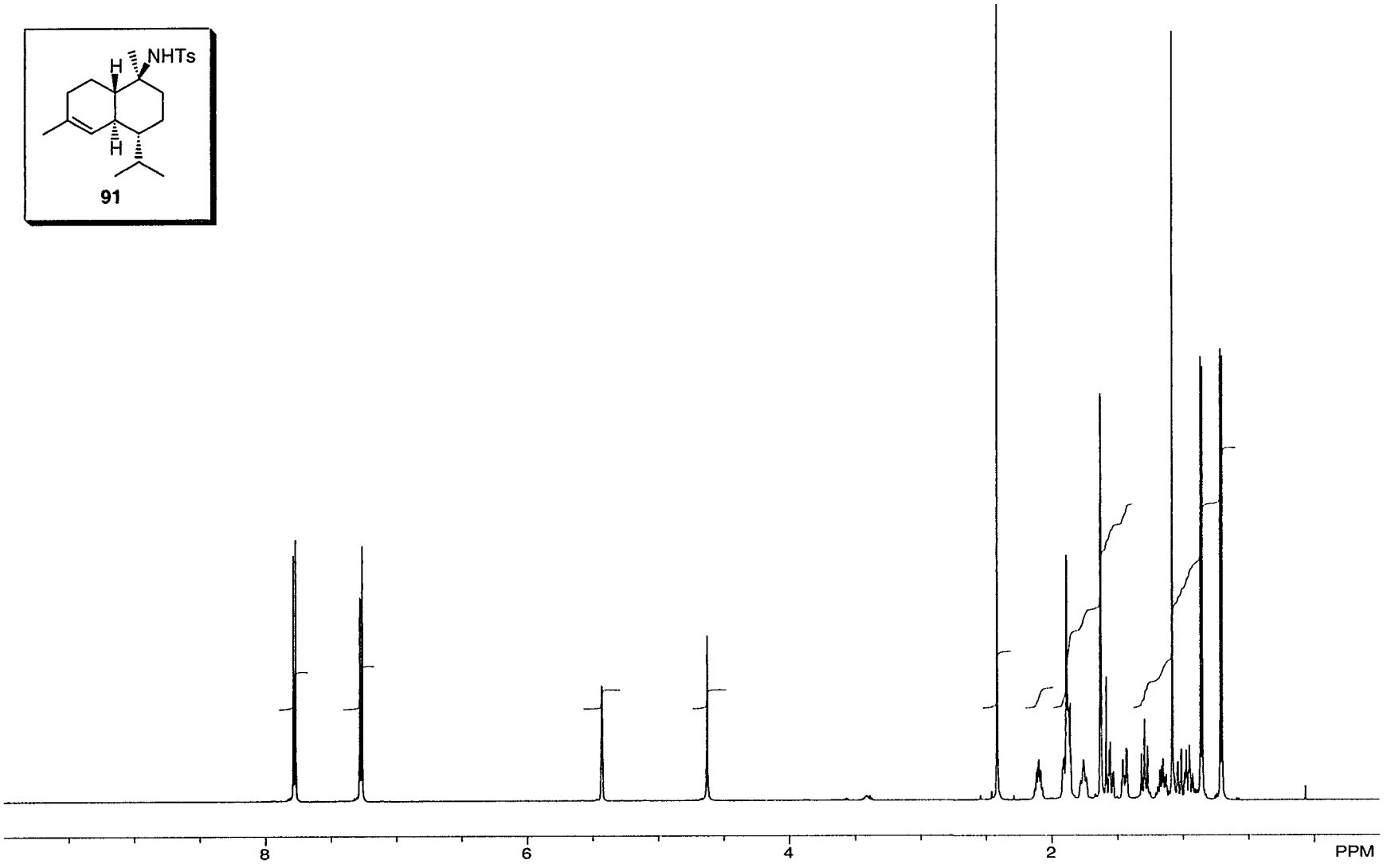


Figure A.1.67 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **91**.

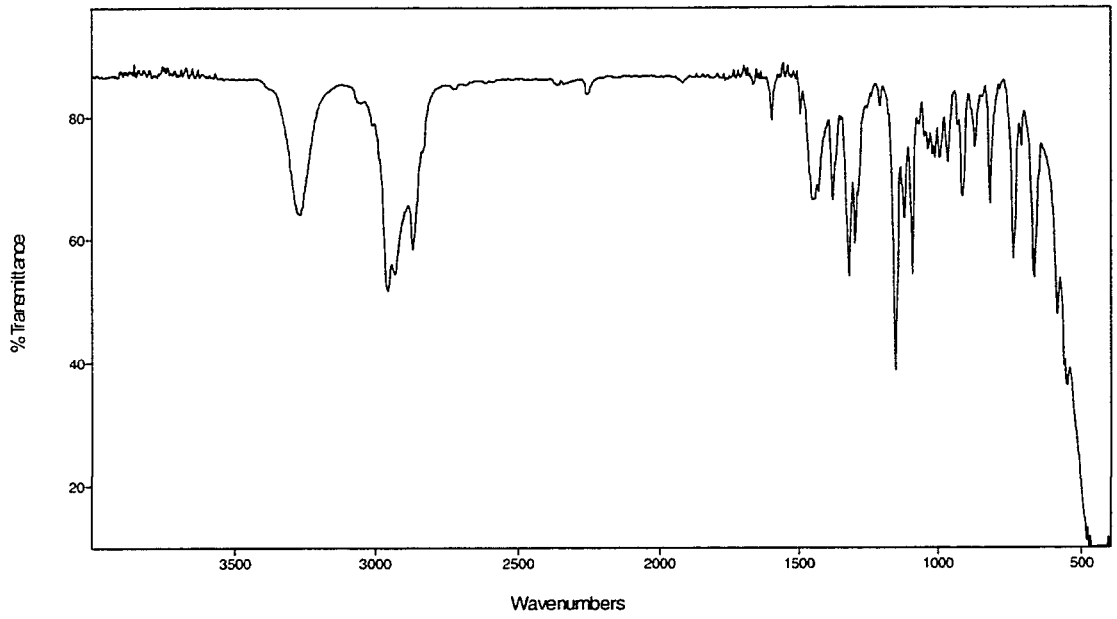


Figure A.1.68 FTIR Spectrum (thin film/NaCl) of Compound **91**.

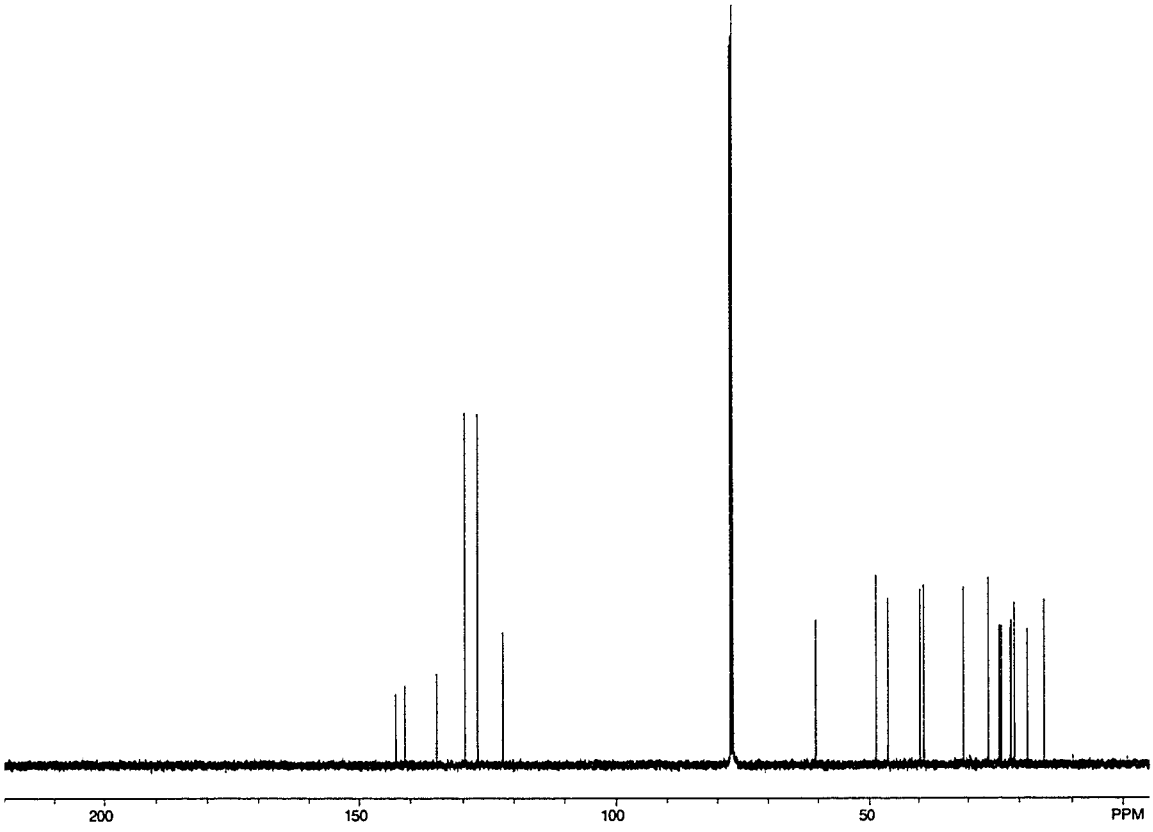


Figure A.1.69 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **91**.

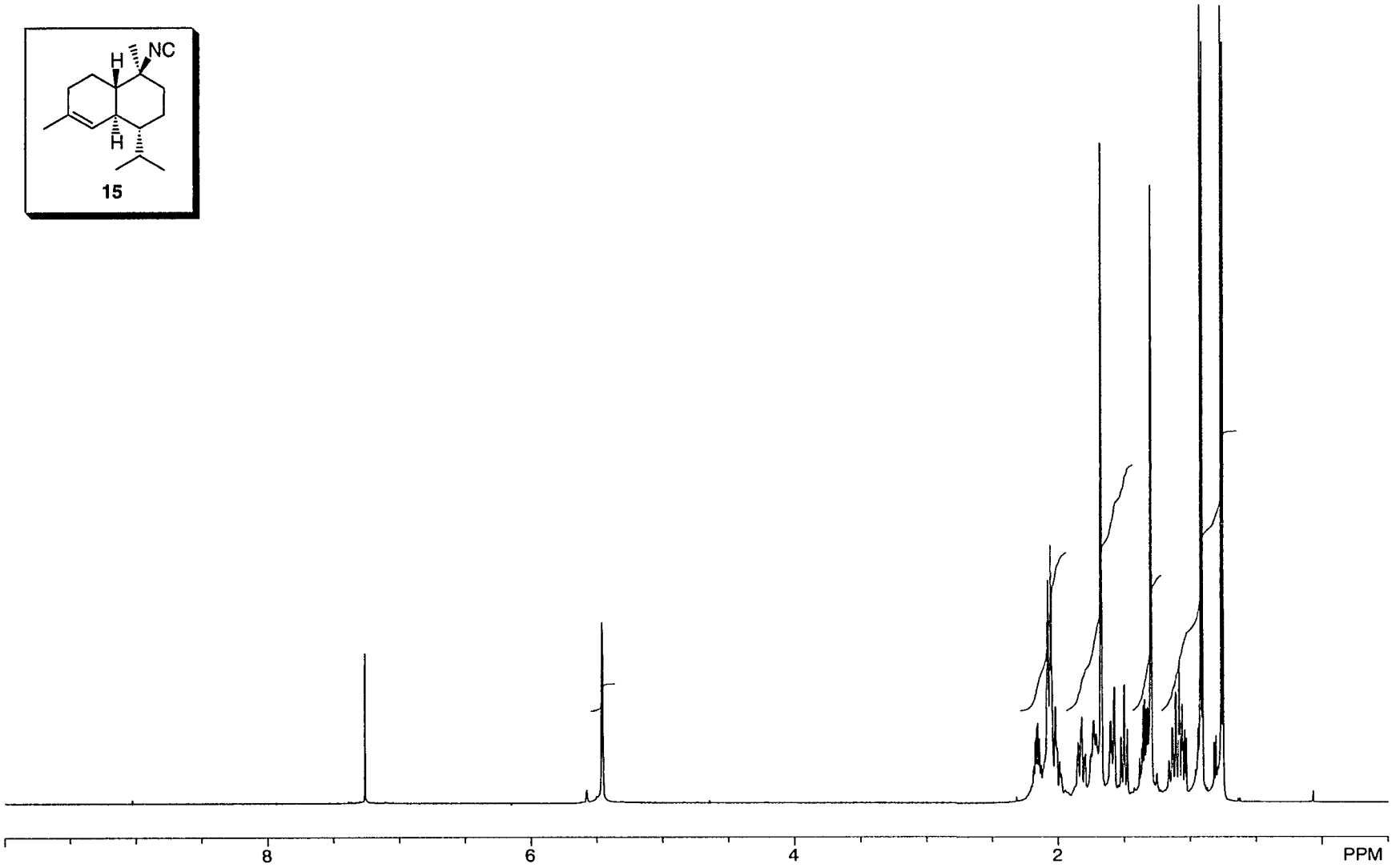


Figure A.1.70 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **15**.

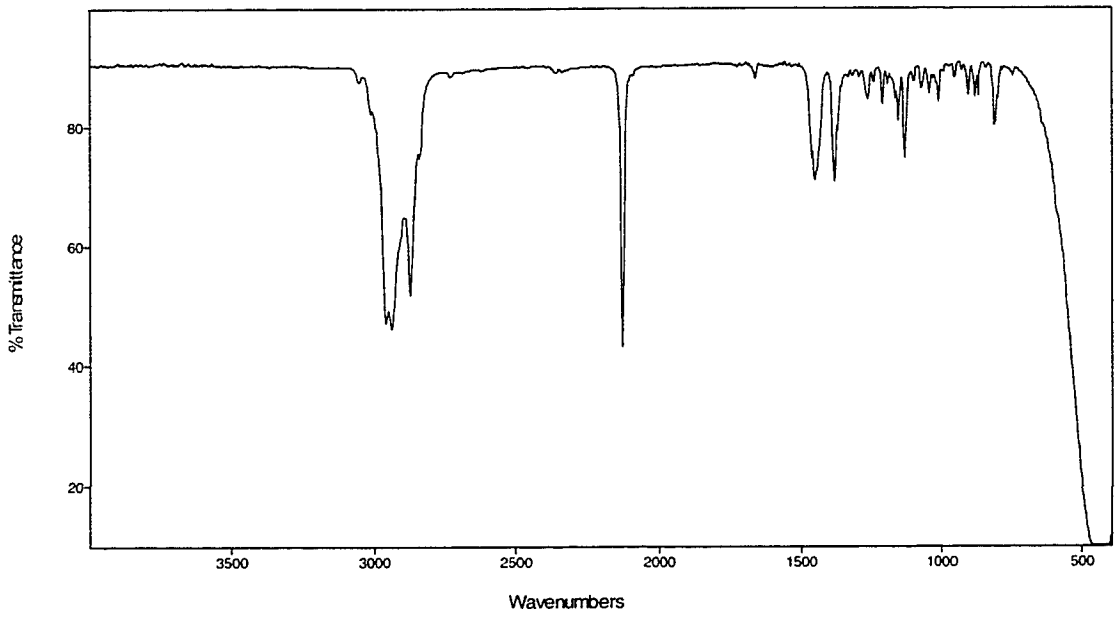


Figure A.1.71 FTIR Spectrum (thin film/NaCl) of Compound **15**.

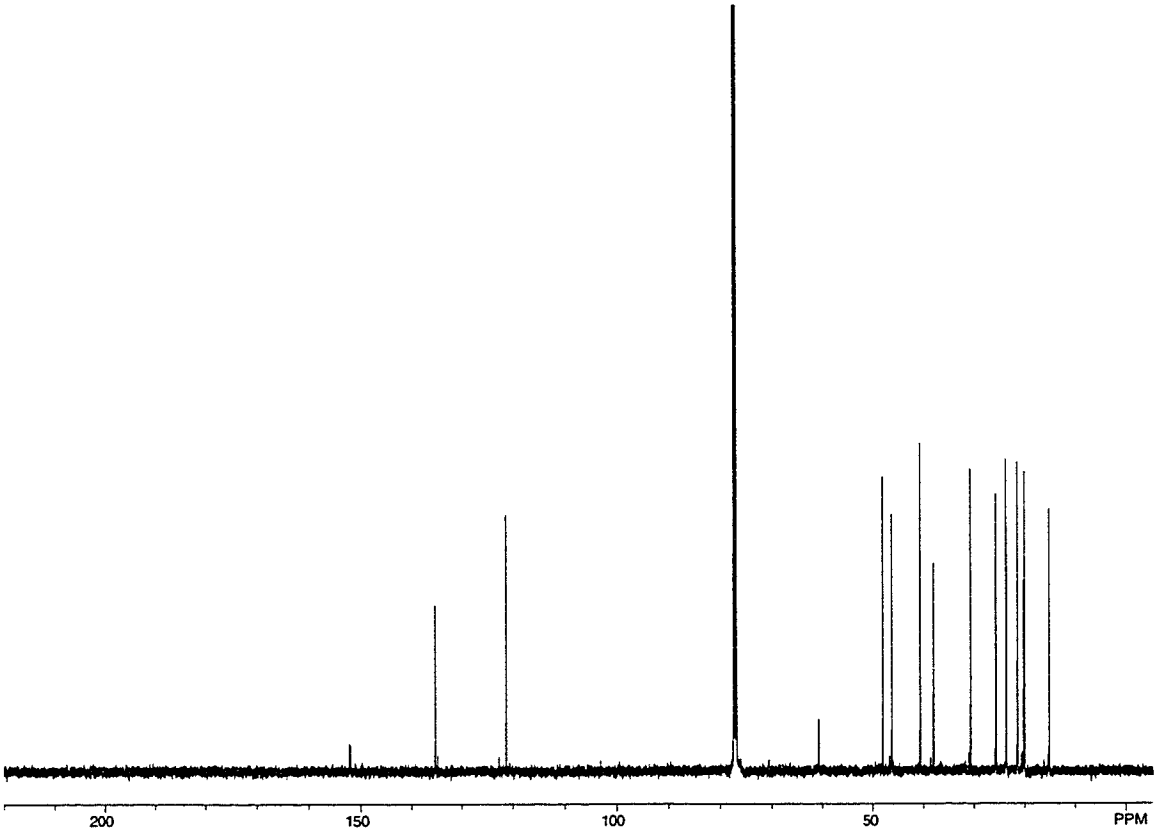


Figure A.1.72 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **15**.

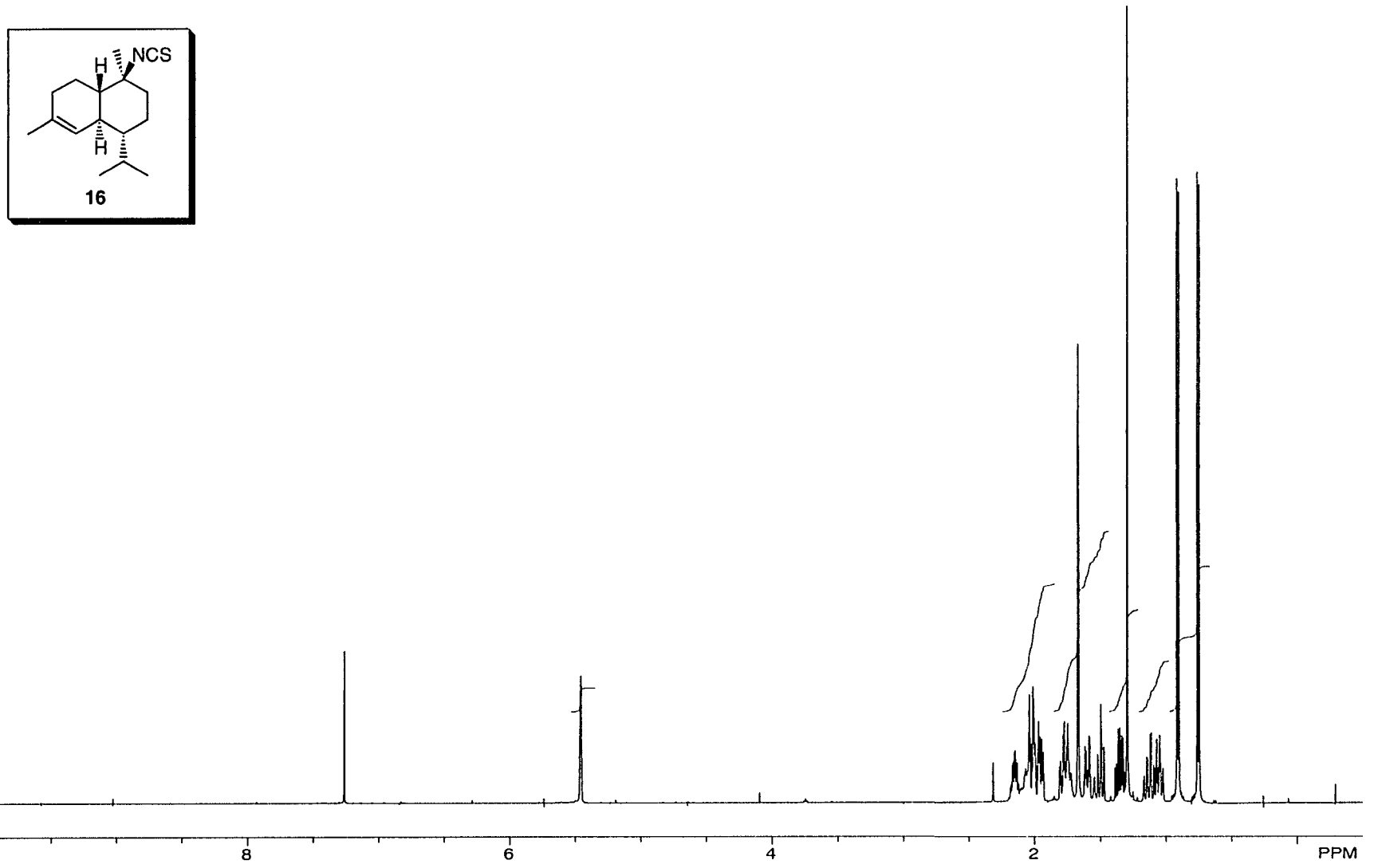


Figure A.1.73 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **16**.

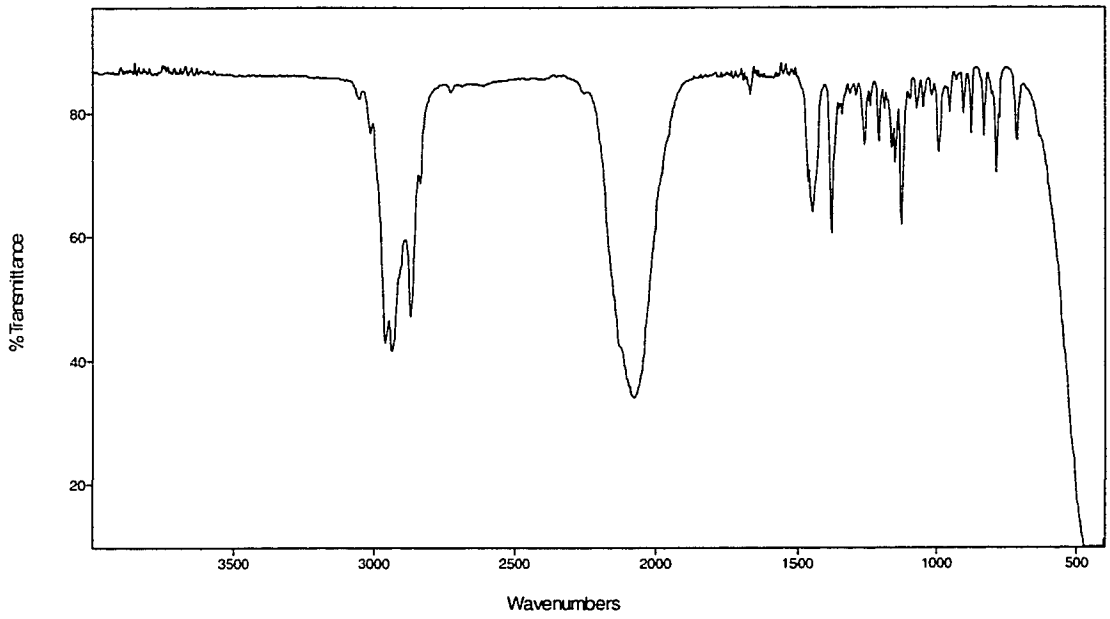


Figure A.1.74 FTIR Spectrum (thin film/NaCl) of Compound **16**.

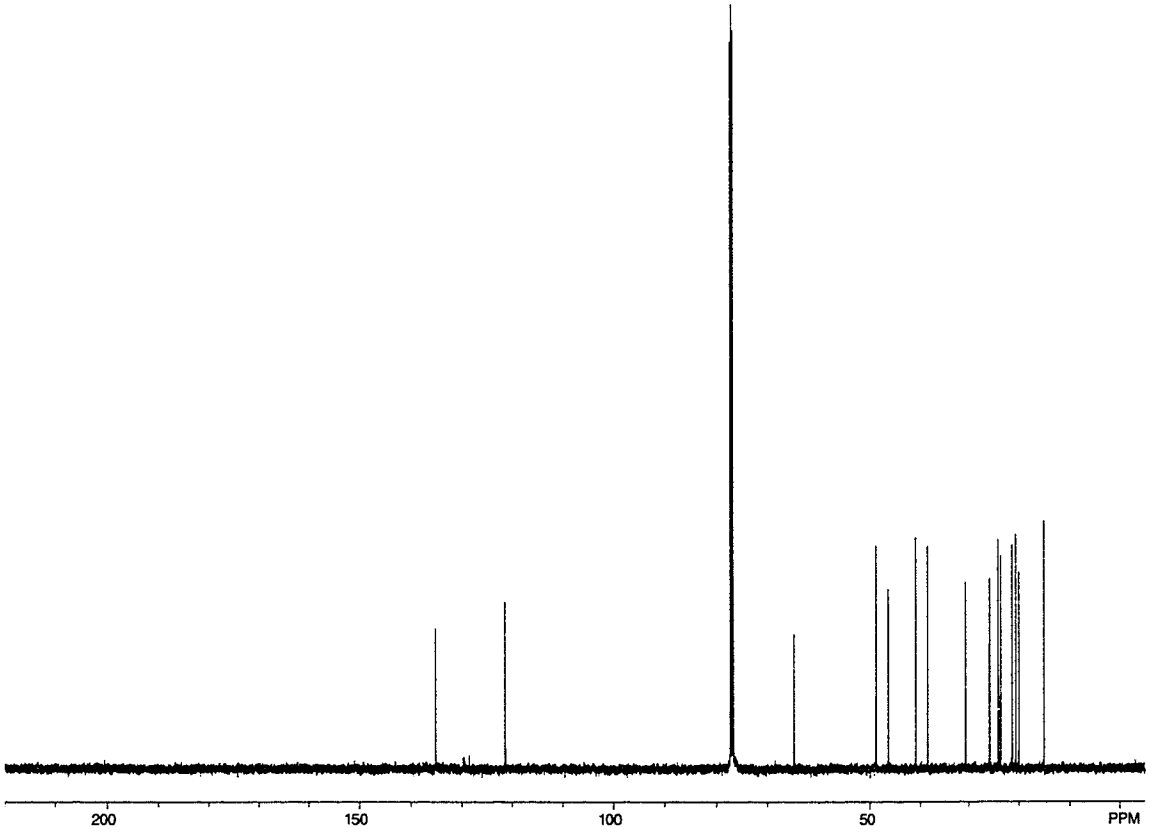


Figure A.1.75 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **16**.

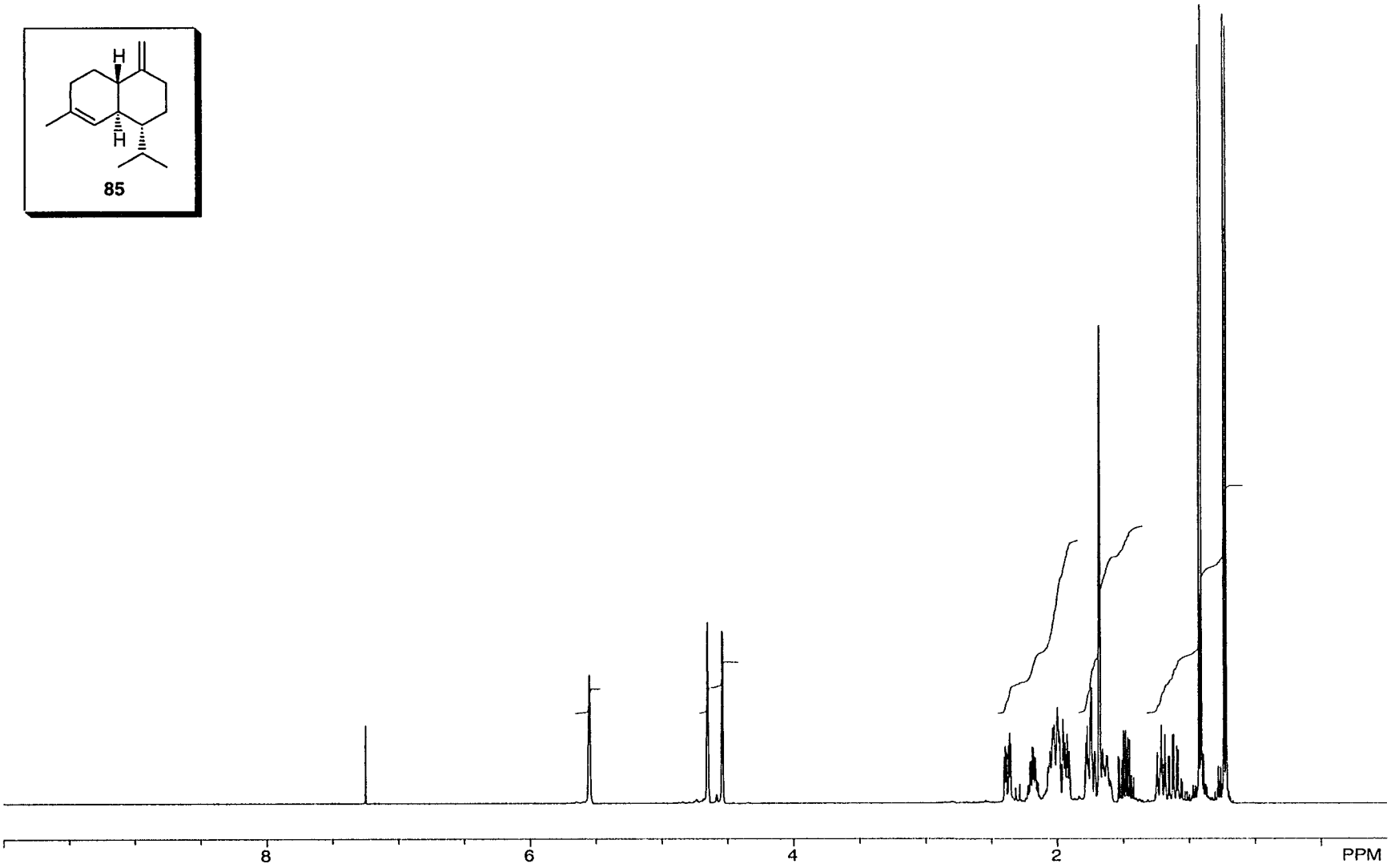


Figure A.1.76 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **85**.

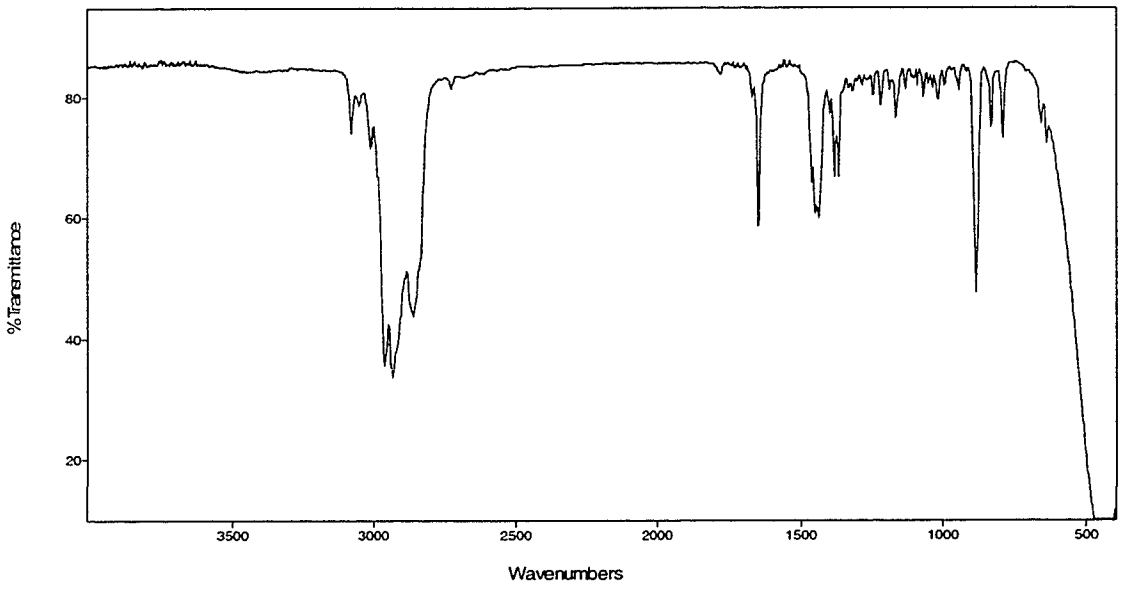


Figure A.1.77 FTIR Spectrum (thin film/NaCl) of Compound **85**.

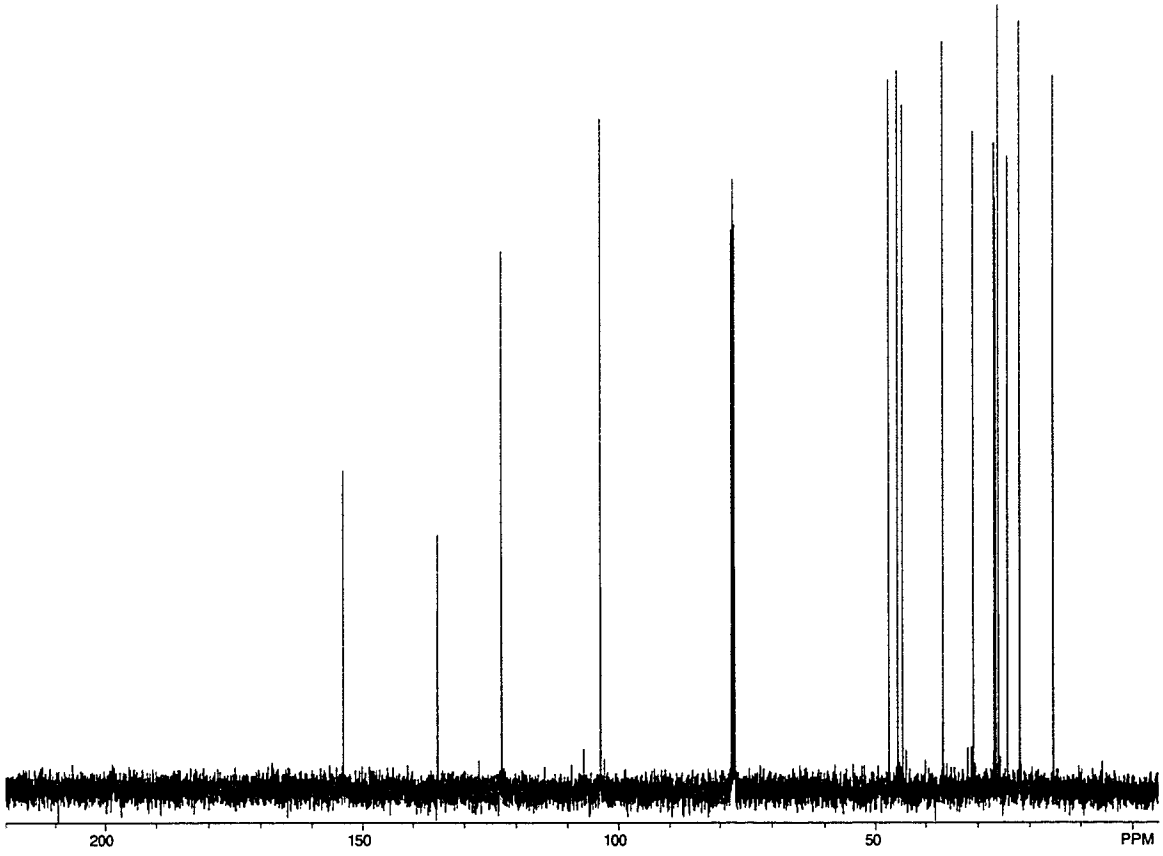


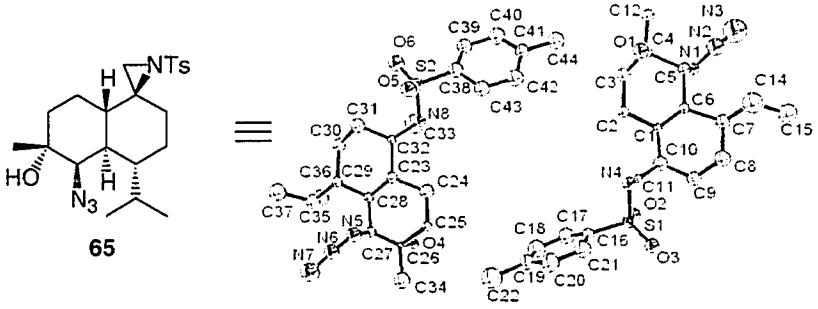
Figure A.1.78 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **85.**

Appendix Two: X-Ray Crystallography Reports

Relevant to Chapter 2

X-RAY CRYSTALLOGRAPHY REPORT FOR 65

Figure A.2.1



A.2.1.1 Crystal Data

Empirical Formula	$C_{44}H_{64}N_8O_6S_2$
Formula Weight	865.16
Crystal Color, Habit	colorless, plate
Crystal Dimensions	0.05 X 0.07 X 0.15 mm
Crystal System	orthorhombic
Lattice Type	Primitive
Lattice Parameters	a = 11.0004(5)Å b = 9.4118(4) Å c = 44.657(2) Å V = 4623.5(3) Å^3
Space Group	$Pca2_1$ (#29)
Z value	4
D_{calc}	1.243 g/cm^3
F_{000}	1856.00
μ(MoKα)	1.70 cm^{-1}

A.2.1.2 Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Take-off Angle	2.8°
Crystal to Detector Distance	60 mm
Temperature	-90.0°C

Scan Rate	54s/frame
Scan Width	0.6°/frame
$2\theta_{max}$	50.0°
No. of Reflections Measured	Total: 6348 Unique: 4147 (R_{int} = 0.040)
Corrections	Lorentz-polarization

A.2.1.3 Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights	$1/\sigma^2$(Fo)
p-factor	0.0200
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	2058
No. Variables	250
Reflection/Parameter Ratio	8.23
Residuals: R; Rw	0.068 ; 0.068
Goodness of Fit Indicator	2.47
Max Shift/Error in Final Cycle	0.04
Maximum peak in Final Diff. Map	0.60 e$^-$/Å^3
Minimum peak in Final Diff. Map	-0.50 e$^-$/Å^3

Table A.2.1 Atomic Coordinates and B_{iso}/B_{eq} for Aziridine **65**

atom	x	y	z	B_{eq}
S(1)	0.5543(3)	-0.1563(4)	0.1483	2.3(1)
S(2)	0.4506(3)	0.6548(4)	0.30373(7)	2.7(1)
O(1)	0.5556(8)	0.540(1)	0.0847(3)	2.7(2)
O(2)	0.4282(7)	-0.1862(9)	0.1523(2)	2.6(2)
O(3)	0.6220(8)	-0.2584(10)	0.1310(2)	2.7(2)
O(4)	0.4557(7)	-0.0352(9)	0.3672(2)	1.5(2)
O(5)	0.5788(8)	0.6789(10)	0.2987(3)	3.2(2)
O(6)	0.3814(9)	0.755(1)	0.3216(3)	3.6(3)
N(1)	0.2881(10)	0.325(1)	0.0626(3)	1.8(2)
N(2)	0.225(1)	0.369(1)	0.0409(4)	3.8(3)
N(3)	0.161(1)	0.395(2)	0.0230(5)	7.2(5)
N(4)	0.5630(9)	0.007(1)	0.1353(3)	2.4(3)
N(5)	0.721(1)	0.176(1)	0.3887(3)	2.8(3)
N(6)	0.771(1)	0.147(1)	0.4107(3)	3.1(3)

N(7)	0.838(1)	0.109(1)	0.4305(4)	4.7(4)
N(8)	0.4384(8)	0.491(1)	0.3154(3)	1.7(3)
C(1)	0.482(1)	0.181(1)	0.0991(3)	1.1(3)
C(2)	0.496(1)	0.294(1)	0.1226(4)	1.6(3)
C(3)	0.406(1)	0.419(1)	0.1170(4)	2.5(4)
C(4)	0.425(1)	0.495(2)	0.0904(3)	2.6(3)
C(5)	0.414(1)	0.372(2)	0.0628(4)	2.1(3)
C(6)	0.5015(10)	0.239(1)	0.0690(3)	1.4(3)
C(7)	0.478(1)	0.130(2)	0.0424(4)	2.5(3)
C(8)	0.547(1)	0.003(2)	0.0495(4)	3.2(4)
C(9)	0.523(1)	-0.059(1)	0.0806(4)	2.5(4)
C(10)	0.543(1)	0.050(2)	0.1035(4)	2.7(4)
C(11)	0.6679(10)	0.059(1)	0.1183(3)	0.9(3)
C(12)	0.339(1)	0.616(1)	0.0823(3)	1.9(3)
C(13)	0.499(1)	0.182(2)	0.0120(3)	2.5(3)
C(14)	0.630(1)	0.227(2)	0.0047(4)	4.8(4)
C(15)	0.452(1)	0.081(2)	-0.0116(4)	4.2(4)
C(16)	0.627(1)	-0.133(1)	0.1833(3)	1.8(3)
C(17)	0.570(1)	-0.140(1)	0.2090(3)	3.3(3)
C(18)	0.631(1)	-0.136(1)	0.2356(3)	4.0(3)
C(19)	0.759(1)	-0.129(1)	0.2361(3)	2.9(3)
C(20)	0.818(1)	-0.132(1)	0.2102(3)	4.4(3)
C(21)	0.757(1)	-0.138(1)	0.1822(3)	3.8(3)
C(22)	0.832(1)	-0.127(2)	0.2656(4)	5.5(4)
C(23)	0.532(1)	0.312(1)	0.3529(4)	1.8(3)
C(24)	0.512(1)	0.201(2)	0.3279(4)	2.7(4)
C(25)	0.591(1)	0.076(1)	0.3321(3)	1.2(3)
C(26)	0.5758(9)	0.018(1)	0.3660(3)	0.6(2)
C(27)	0.588(1)	0.119(1)	0.3882(3)	1.4(3)
C(28)	0.5124(10)	0.248(1)	0.3857(3)	1.3(3)
C(29)	0.524(1)	0.361(2)	0.4091(4)	1.6(3)
C(30)	0.436(1)	0.494(2)	0.4030(3)	2.6(3)
C(31)	0.467(1)	0.562(1)	0.3732(4)	2.8(4)
C(32)	0.446(1)	0.451(1)	0.3483(4)	1.2(3)
C(33)	0.328(2)	0.455(2)	0.3333(4)	5.2(5)
C(34)	0.661(1)	-0.107(2)	0.3680(4)	3.5(4)
C(35)	0.513(1)	0.302(2)	0.4424(3)	3.0(4)
C(36)	0.382(1)	0.266(1)	0.4502(4)	4.0(4)
C(37)	0.566(1)	0.406(2)	0.4661(4)	4.3(4)
C(38)	0.375(1)	0.647(1)	0.2701(4)	3.1(4)
C(39)	0.2748(10)	0.712(1)	0.2630(3)	2.9(3)
C(40)	0.220(1)	0.699(1)	0.2343(3)	3.8(3)
C(41)	0.269(1)	0.613(1)	0.2128(3)	2.8(3)
C(42)	0.367(1)	0.535(1)	0.2197(3)	3.7(3)
C(43)	0.4276(10)	0.549(1)	0.2476(3)	3.2(3)

C(44)	0.207(1)	0.597(1)	0.1826(3)	4.1(3)
H(1)	0.3978	0.1574	0.0996	1.3798
H(2)	0.5770	0.3290	0.1221	1.8952
H(3)	0.4804	0.2535	0.1418	1.8952
H(4)	0.4120	0.4836	0.1332	3.0476
H(5)	0.3255	0.3810	0.1164	3.0476
H(6)	0.4338	0.4134	0.0441	2.4898
H(7)	0.5831	0.2712	0.0677	1.7210
H(8)	0.3950	0.1038	0.0434	3.0227
H(9)	0.5271	-0.0676	0.0351	3.7681
H(10)	0.6308	0.0254	0.0481	3.7681
H(11)	0.5770	-0.1364	0.0840	2.9356
H(12)	0.4416	-0.0917	0.0817	2.9356
H(13)	0.7305	-0.0053	0.1126	0.9858
H(14)	0.7024	0.1486	0.1229	0.9858
H(15)	0.5546	0.6023	0.1034	4.1326
H(16)	0.3426	0.6872	0.0973	2.3550
H(17)	0.2583	0.5804	0.0809	2.3550
H(18)	0.3620	0.6555	0.0635	2.3550
H(19)	0.4512	0.2660	0.0102	2.9143
H(20)	0.6531	0.3026	0.0176	5.8172
H(21)	0.6341	0.2575	-0.0155	5.8172
H(22)	0.6826	0.1485	0.0076	5.8172
H(23)	0.3671	0.0656	-0.0085	5.0629
H(24)	0.4638	0.1213	-0.0309	5.0629
H(25)	0.4938	-0.0065	-0.0102	5.0629
H(26)	0.4842	-0.1488	0.2091	3.9740
H(27)	0.5872	-0.1374	0.2539	4.8060
H(28)	0.9047	-0.1301	0.2103	5.3266
H(29)	0.7998	-0.1447	0.1638	4.5400
H(30)	0.9131	-0.1578	0.2619	6.5965
H(31)	0.7951	-0.1890	0.2797	6.5965
H(32)	0.8338	-0.0332	0.2735	6.5965
H(33)	0.6140	0.3429	0.3517	2.1777
H(34)	0.4295	0.1712	0.3283	3.2118
H(35)	0.5297	0.2435	0.3092	3.2118
H(36)	0.6731	0.1023	0.3286	1.4322
H(37)	0.5679	0.0039	0.3183	1.4322
H(38)	0.5722	0.0754	0.4069	1.7467
H(39)	0.4303	0.2164	0.3865	1.6161
H(40)	0.6049	0.3962	0.4073	1.9766
H(41)	0.4461	0.5621	0.4185	3.1039
H(42)	0.3541	0.4624	0.4027	3.1039
H(43)	0.5499	0.5905	0.3731	3.3394
H(44)	0.4165	0.6421	0.3699	3.3394

H(45)	0.2717	0.5271	0.3383	6.2854
H(46)	0.2862	0.3685	0.3295	6.2854
H(47)	0.4467	-0.1088	0.3487	4.1326
H(48)	0.6396	-0.1752	0.3531	4.2207
H(49)	0.7419	-0.0768	0.3650	4.2207
H(50)	0.6536	-0.1498	0.3873	4.2207
H(51)	0.5591	0.2165	0.4435	3.6334
H(52)	0.3466	0.2120	0.4344	4.7167
H(53)	0.3366	0.3513	0.4529	4.7167
H(54)	0.3795	0.2122	0.4682	4.7167
H(55)	0.6462	0.4321	0.4606	5.1011
H(56)	0.5674	0.3602	0.4851	5.1011
H(57)	0.5162	0.4881	0.4672	5.1011
H(58)	0.2370	0.7711	0.2776	3.4821
H(59)	0.1475	0.7513	0.2300	4.5517
H(60)	0.3972	0.4691	0.2055	4.3984
H(61)	0.4999	0.4977	0.2517	3.8381
H(62)	0.2653	0.5737	0.1678	4.8943
H(63)	0.1480	0.5228	0.1838	4.8943
H(64)	0.1676	0.6833	0.1775	4.8943

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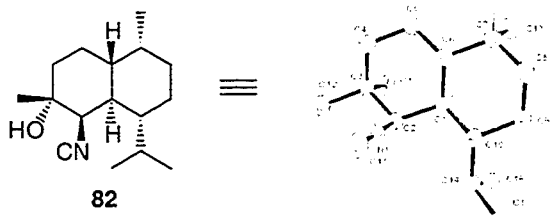
Figure A.2.2



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A.2.2.1 Crystal Data

Empirical Formula	$C_{16}H_{27}NO$
Formula Weight	249.40
Crystal Color, Habit	colorless, plate
Crystal Dimensions	0.09 X 0.16 X 0.19 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 13.762(1)Å b = 8.5793(4) Å c = 13.857(1) Å $\beta = 110.860(3)^o$ $V = 1528.8(2)$ Å^3
Space Group	$P2_1/a$ (#14)
Z value	4
Dcalc	1.083 g/cm^3
F000	552.00
μ(MoKα)	0.66 cm^{-1}

A.2.2.2 Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Take-off Angle	2.8^o
Crystal to Detector Distance	33m

Temperature	-90.0°C
Scan Rate	240s/frame
Scan Width	2.0°/frame
2θmax	55.1°
No. of Reflections Measured	Total: 3742
Corrections	Lorentz-polarization

A.2.2.3 Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w (\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$1/\sigma^2(Fo)$
p-factor	0.0100
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>5.00σ(I))	1950
No. Variables	271
Reflection/Parameter Ratio	7.20
Residuals: R; Rw	0.036 ; 0.039
Goodness of Fit Indicator	2.30
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.16 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.19 $e^-/Å^3$

Table A.2.2 Atomic Coordinates and B_{iso}/B_{eq} for Isonitrile **82**

atom	x	y	z	Beq
O(1)	1.63836(8)	0.5627(1)	0.70439(8)	2.91(3)
N(1)	1.39877(9)	0.6840(1)	0.73262(9)	2.59(3)
C(1)	1.4715(1)	0.4206(1)	0.7549(1)	2.07(3)
C(2)	1.4718(1)	0.5836(1)	0.7086(1)	2.14(3)
C(3)	1.57917(10)	0.6633(1)	0.7451(1)	2.27(3)
C(4)	1.6250(1)	0.6661(2)	0.8627(1)	2.80(4)
C(5)	1.6303(1)	0.5029(2)	0.9080(1)	2.87(4)
C(6)	1.5240(1)	0.4234(2)	0.8734(1)	2.42(3)
C(7)	1.5293(1)	0.2598(2)	0.9209(1)	3.11(4)
C(8)	1.4201(1)	0.1892(2)	0.8861(1)	3.61(4)
C(9)	1.3682(1)	0.1853(2)	0.7688(1)	3.11(4)
C(10)	1.3621(1)	0.3475(2)	0.7209(1)	2.39(3)
C(11)	1.3415(1)	0.7649(2)	0.7515(1)	3.77(4)
C(12)	1.5728(1)	0.8253(2)	0.6988(1)	2.95(4)
C(13)	1.6067(2)	0.1520(2)	0.8989(2)	3.97(5)

C(14)	1.3035(1)	0.3477(2)	0.6033(1)	3.19(4)
C(15)	1.1903(1)	0.2954(3)	0.5750(2)	4.64(5)
C(16)	1.3570(2)	0.2536(3)	0.5440(2)	5.04(6)
H(1)	1.5146(9)	0.360(1)	0.7275(8)	1.4(3)
H(2)	1.4482(9)	0.577(1)	0.634(1)	1.9(3)
H(3)	1.695(1)	0.717(2)	0.884(1)	3.3(3)
H(4)	1.581(1)	0.733(2)	0.8885(10)	2.6(3)
H(5)	1.659(1)	0.505(2)	0.984(1)	3.6(3)
H(6)	1.679(1)	0.441(2)	0.885(1)	2.9(3)
H(7)	1.4780(9)	0.487(1)	0.8991(9)	2.1(3)
H(8)	1.554(1)	0.271(2)	0.999(1)	3.7(3)
H(9)	1.374(1)	0.251(2)	0.913(1)	4.0(4)
H(10)	1.424(1)	0.081(2)	0.915(1)	4.0(3)
H(11)	1.298(1)	0.139(2)	0.751(1)	3.8(3)
H(12)	1.408(1)	0.113(2)	0.738(1)	3.2(3)
H(13)	1.3226(10)	0.413(1)	0.7502(10)	2.2(3)
H(14)	1.699(1)	0.604(2)	0.719(1)	5.5(5)
H(15)	1.546(1)	0.819(2)	0.622(1)	4.4(4)
H(16)	1.643(1)	0.868(2)	0.7195(10)	2.7(3)
H(17)	1.528(1)	0.897(2)	0.722(1)	3.5(3)
H(18)	1.681(1)	0.192(2)	0.932(1)	6.1(5)
H(19)	1.595(1)	0.141(2)	0.822(1)	4.7(4)
H(20)	1.601(1)	0.044(2)	0.925(1)	5.5(4)
H(21)	1.3002(10)	0.456(2)	0.580(1)	3.2(3)
H(22)	1.156(1)	0.356(2)	0.616(1)	6.3(5)
H(23)	1.186(1)	0.181(2)	0.588(1)	6.1(5)
H(24)	1.153(1)	0.312(2)	0.503(1)	5.2(4)
H(25)	1.360(1)	0.139(2)	0.563(1)	6.7(5)
H(26)	1.319(1)	0.268(2)	0.468(2)	6.5(5)
H(27)	1.430(2)	0.293(2)	0.557(1)	6.0(5)

Anisotropic Displacement Parameters

atom	U11	U22	U33	U12	U13	U23
O(1)	0.0305(6)	0.0317(6)	0.0546(7)	-0.0013(5)	0.0229(5)	-0.0059(5)
N(1)	0.0265(7)	0.0269(7)	0.0446(8)	0.0000(5)	0.0119(6)	0.0026(6)
C(1)	0.0271(8)	0.0239(7)	0.0286(9)	0.0014(6)	0.0110(7)	-0.0022(6)
C(2)	0.0261(8)	0.0264(8)	0.0291(9)	0.0029(6)	0.0100(7)	-0.0006(6)
C(3)	0.0242(7)	0.0239(7)	0.0391(9)	-0.0002(6)	0.0127(7)	-0.0033(6)
C(4)	0.0300(9)	0.0316(8)	0.041(1)	-0.0039(7)	0.0085(8)	-0.0060(7)
C(5)	0.0338(9)	0.0358(8)	0.033(1)	-0.0017(7)	0.0033(8)	-0.0015(7)
C(6)	0.0325(8)	0.0288(8)	0.0299(9)	0.0002(6)	0.0100(7)	-0.0020(6)
C(7)	0.0502(10)	0.0327(8)	0.030(1)	-0.0029(7)	0.0080(8)	0.0028(7)

C(8)	0.060(1)	0.0373(9)	0.040(1)	-0.0085(8)	0.0175(9)	0.0075(8)
C(9)	0.0416(10)	0.0312(9)	0.044(1)	-0.0094(8)	0.0140(8)	0.0002(7)
C(10)	0.0292(8)	0.0273(8)	0.0348(9)	-0.0037(6)	0.0123(7)	-0.0031(7)
C(11)	0.0360(9)	0.0351(9)	0.075(1)	0.0016(8)	0.0228(9)	0.0021(8)
C(12)	0.0337(10)	0.0291(8)	0.052(1)	-0.0036(7)	0.0180(9)	-0.0012(8)
C(13)	0.057(1)	0.0319(9)	0.052(1)	0.0070(9)	0.008(1)	0.0040(9)
C(14)	0.0373(9)	0.0381(9)	0.0383(10)	-0.0096(7)	0.0042(8)	0.0012(8)
C(15)	0.042(1)	0.058(1)	0.059(1)	-0.0148(9)	-0.002(1)	-0.001(1)
C(16)	0.064(1)	0.086(2)	0.037(1)	-0.013(1)	0.014(1)	-0.017(1)

Chapter 3

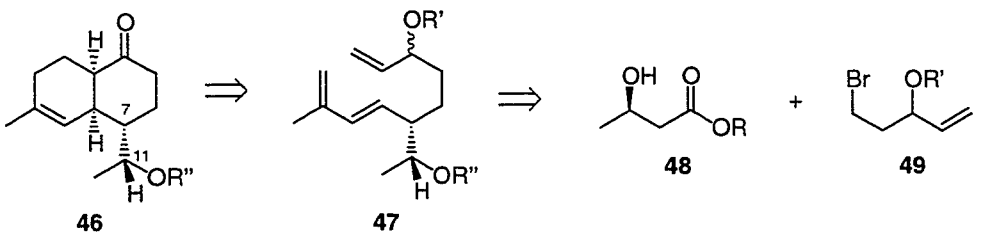
Total Synthesis of (±)-Kalihinol C and (±)-*epi*-C(14)-Kalihinol C

3.1 Establishing the Decalin Core

3.1.1 Retrosynthesis

Having established an efficient approach to the functionalized decalin core of kalihinol A and related congeners, it was then necessary to apply this strategy to a system containing a handle for installing a tetrahydropyran/furan ring. The retrosynthesis previously discussed called for a Frater alkylation of enantiopure β-hydroxy ester **48** and bromide **49** to establish the relative configuration between C(7) and C(11) in the desired *cis*-decalin intermediate **46** (Scheme 3.1).[1,2]

Scheme 3.1

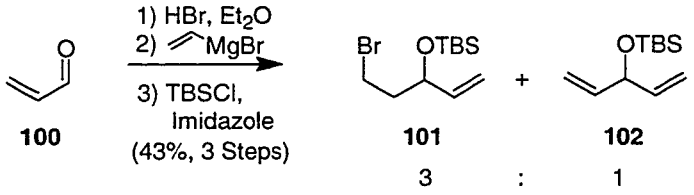


46 **47** **48** **49**

3.1.2 Preparation of Bromide 101

Work commenced with the preparation of bromide **101** (Scheme 3.2). Initially, useful quantities were obtained by ozonolysis of 4-bromo-1-butene followed by the addition of vinyl Grignard and TBS protection. However, it was obvious that the use of 4-bromo-1-butene ($400/mol) would be cost prohibitive for large scale. Alternatively, preparative quantities of **88** could be made in three steps from acrolein ($8/mol) in 32% yield (Scheme 3.1). The major by-product (**102**), resulting from elimination of the bromide, could not be entirely suppressed despite attempts to modulate the basicity of the vinyl Grignard reagent by using various additives.

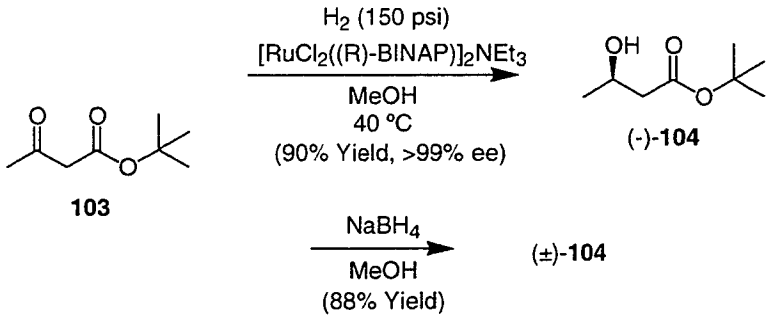
Scheme 3.2



3.1.3 Noyori Hydrogenation

The ability to access enantioenriched **104** via a Noyori hydrogenation provided entry into an asymmetric synthesis of the kalihinols.[3,4] Indeed, large quantities (ca. 500 mL) of essentially enantiopure **104** (>99% ee by chiral GC) were obtained from the reduction of *tert*-butyl acetoacetate (Scheme 3.3). However, initial studies were performed using racemic **104** from $NaBH_4$ reduction of **103**.

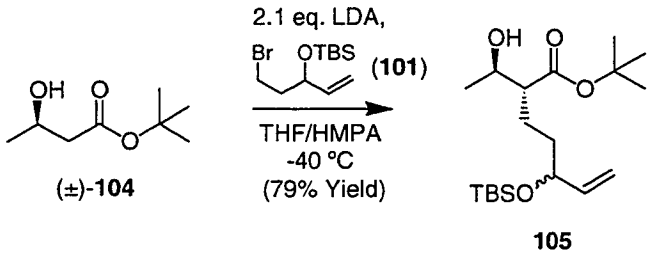
Scheme 3.3



3.1.4 Frater Alkylation

Treatment of (±)-**104** with 2.1 equiv LDA followed by **101** provided alcohol **97** as a mixture of two compounds diastereomeric only at the TBS-ether (Scheme 3.4). Only trace quantities of the corresponding *syn*-isomer were observed. Significant optimization revealed that the addition of three equivalents of HMPA and maintaining a reaction temperature of -40°C were crucial in obtaining high yields.

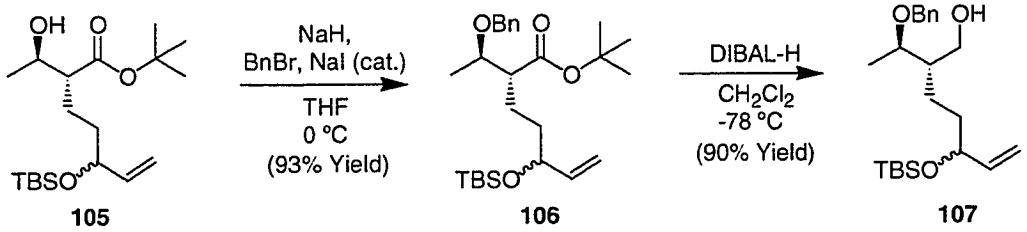
Scheme 3.4



3.1.5 Synthesis of the Intramolecular Diels-Alder Substrate

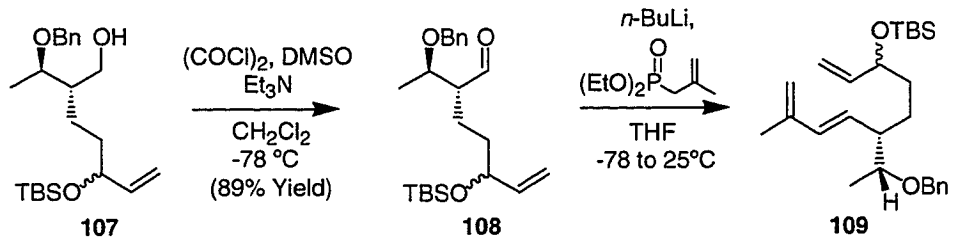
With **105** in hand, it was necessary to parlay the ester to the requisite diene for the anticipated IMDA cycloaddition. Protection of the free alcohol as the corresponding benzyl ether followed by reduction of the ester provided alcohol **107** in good yield (Scheme 3.5). Notably, maintaining anhydrous conditions during both the protection and reduction steps were necessary to avoid epimerization.

Scheme 3.5



Swern oxidation of **107** and subsequent Horner-Wadsworth-Emmons olefination gave *E* isomer **109** exclusively (Scheme 3.6).[5] However, attempts to purify **109** by silica gel chromatography resulted in significant decomposition. Therefore, **109** was advanced without further purification.

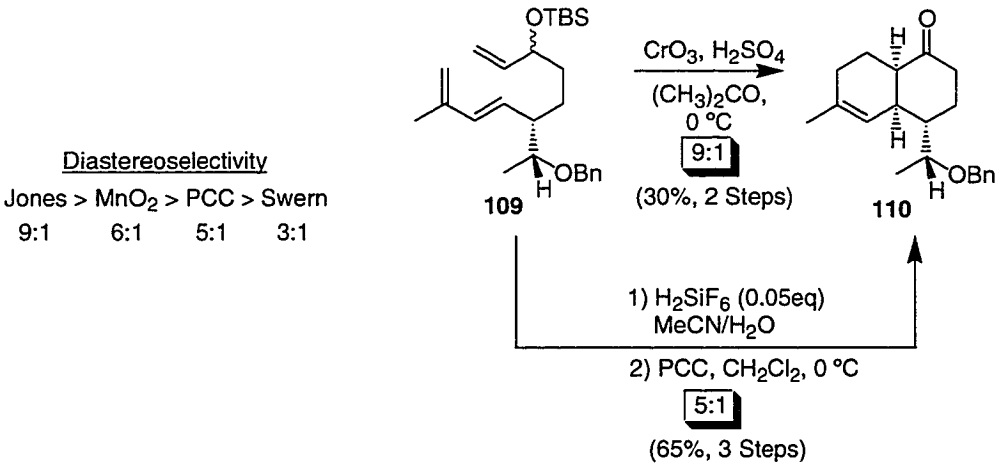
Scheme 3.6



3.1.6 Optimization of the Intramolecular Diels-Alder Cycloaddition

Crucial to the success of this approach was that the IMDA cycloaddition after deprotection and oxidation of **109**, prefer the *endo*-boat transition state as observed in the model system.[6,7] Indeed, treatment of **109** with Jones reagent gave the desired *cis*-decalin **110** as the major stereoisomer of a 9:1 mixture by GC/MS (Scheme 3.7).[8] However, **110** was isolated in only 30% yield from **109**. Given the delicate nature of **109**, it was not surprising that treatment with the strongly acidic Jones reagent gave low yields of **110**. Less acidic conditions were explored to effect either one or two-pot deprotection and oxidation. It was found that deprotection of **109** with catalytic fluorosilicic acid followed by oxidation of the resulting alcohol with PCC, afforded *cis*-decalin **110** in a much-improved 65% yield and with 5:1 diastereoselectivity. In the course of screening oxidants, a clear trend was observed in which the more Lewis acidic conditions gave a higher diastereoselectivity.

Scheme 3.7

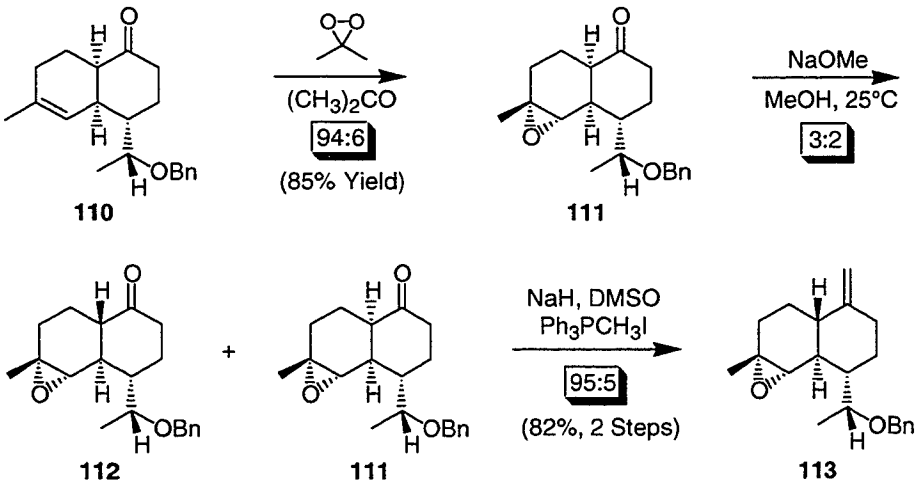


3.2 Functionalization of the Decalin Core

3.2.1 Accessing the *trans*-Decalin

Having optimized the route to **110**, the stage was set to employ the procedures worked out on the model system for further functionalization of the decalin core. Thus, epoxidation with dimethyl dioxirane proceeded with high selectivity to provide epoxide **111** (Scheme 3.8). Subsequent epimerization afforded a 3:2 mixture of decalins favoring *trans*-decalin **112**, which when methylenated under Wittig conditions, gave almost exclusively *trans*-decalin **113**.

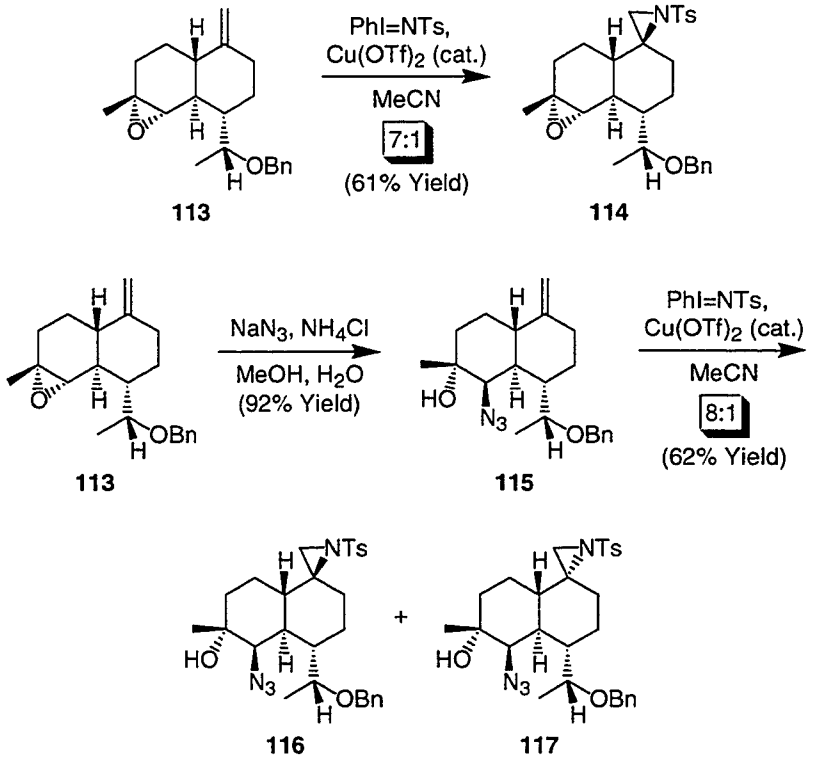
Scheme 3.8



3.2.2 Employing the Model System

By following the same order of events as used in the model system, *trans*-decalin **113** was advanced to azide **116** uneventfully (Scheme 3.9). We were pleased to observe the functional group tolerance of the aziridination conditions in the presence of either the azide or the epoxide moieties (i.e. **113**→**114** or **115**), both of which gave good yields and selectivity.

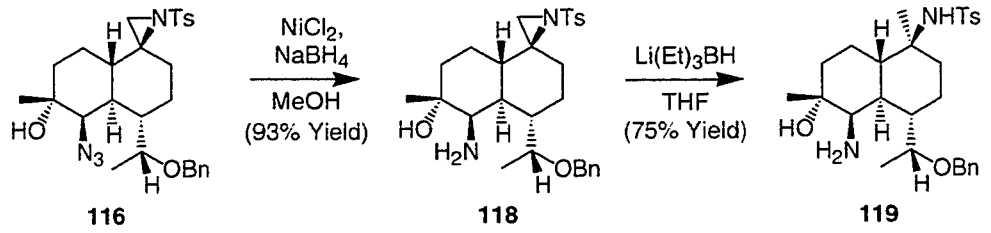
Scheme 3.9



At this stage, it was clear that the chemistry anticipated for the introduction of a functional handle at C(11), specifically a nucleophilic addition to a C(11) ketone, would not tolerate acidic protons. Therefore, deprotection of the benzyl group, oxidation, and

nucleophilic addition would best be accomplished prior to unmasking the amines (i.e. **116**→**119**, Scheme 3.10).

Scheme 3.10

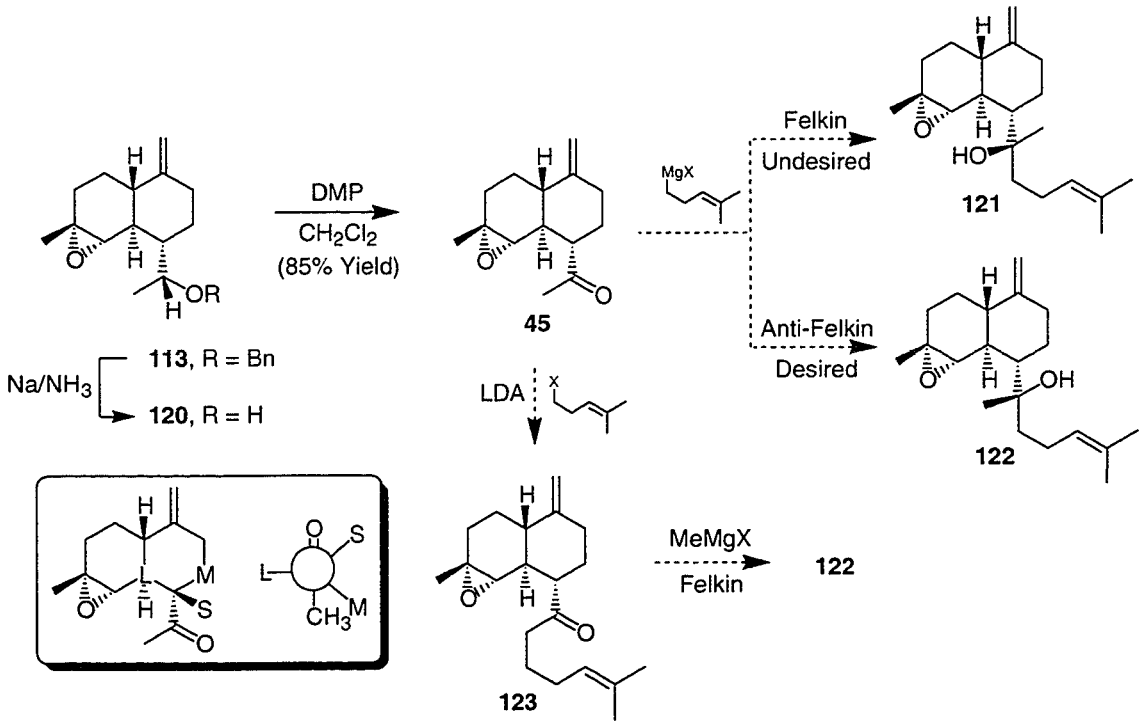


3.3 Introduction of a Tetrahydropyran/furan Handle

3.3.1 Stereochemical Analysis of a Nucleophilic Addition

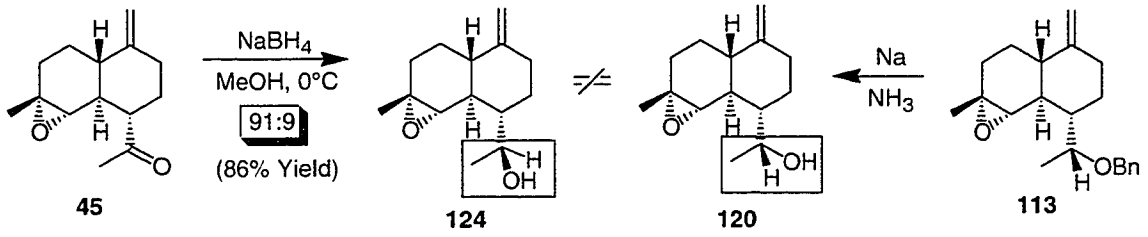
Benzyl deprotection of **113** with sodium metal followed by oxidation with Dess-Martin periodinane cleanly provided the corresponding methyl ketone, **45** (Scheme 3.11).[9] At this point, the much anticipated nucleophilic addition to introduce the desired stereochemistry at C(11) and ultimately the tetrahydropyran/furan could be studied. Using the Felkin-Ahn model, the stereochemical outcome of an addition to **45** was predicted to give the wrong configuration at C(11) (e.g. **121**).[10-13] In this event, it would be necessary to first alkylate the corresponding kinetic enolate then add a methyl nucleophile (i.e. **45**→**123**→**122**).

Scheme 3.11



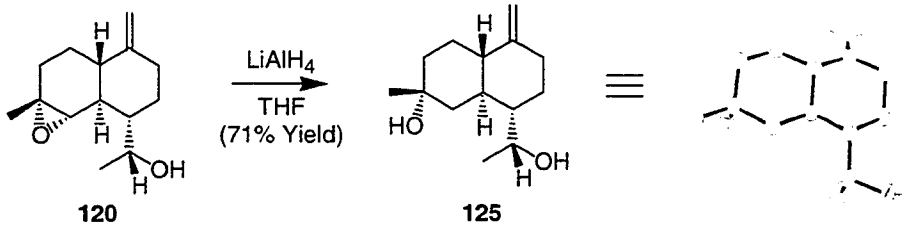
It was then necessary to examine adding a functionalized carbon nucleophile to methyl ketone **45** in order to install the tetrahydropyran. First, the diastereoselectivity and stereochemistry of the tertiary alcohol resulting from nucleophilic addition to methyl ketone **45** was examined using hydride as the nucleophile. The use of a carbon nucleophile was temporarily precluded since the resulting tertiary alcohol stereochemistry would be difficult to determine without the use of X-ray crystallography. Gratifyingly, reduction of **45** with sodium borohydride gave the desired anti-Felkin product, **124**, with excellent selectivity (Scheme 3.12). The resulting stereochemistry was determined by comparison to alcohol **120**, the product afforded by benzyl deprotection of **113**.

Scheme 3.12



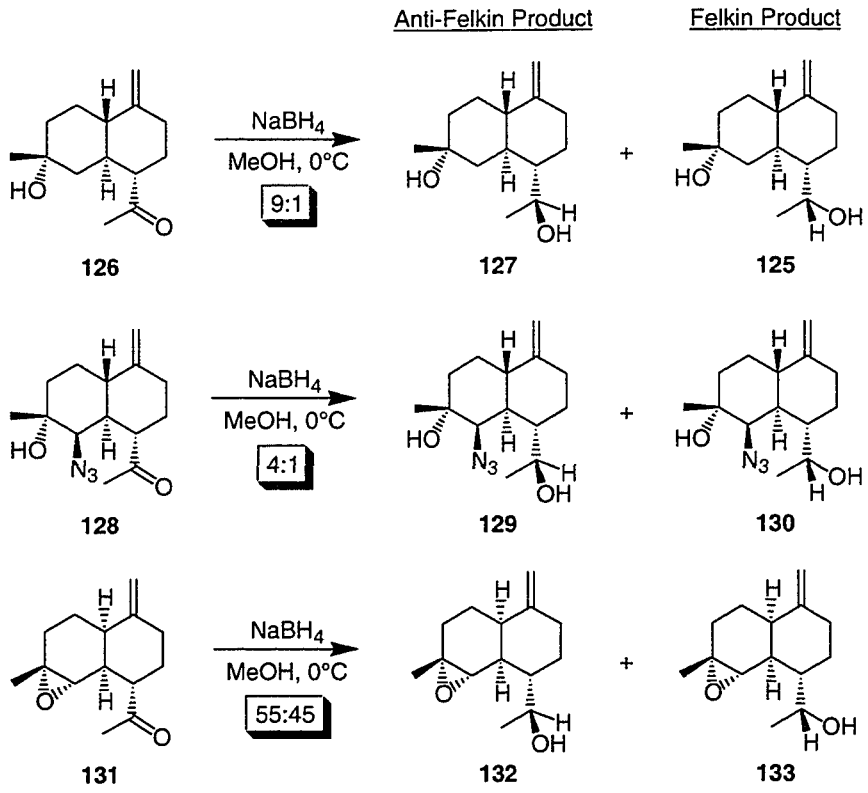
To further validate these results, alcohol **120** was reduced with $LiAlH_4$, or prolonged exposure to sodium metal, to give alcohol **125** as a solid. Single crystal X-ray analysis confirmed the initial relative stereochemical assignment at C(11) in **120** (Scheme 3.14).

Scheme 3.13



The anti-Felkin product was also heavily favored from hydride addition to similar methyl ketones derived from **113** (i.e. **126**, **127**, and **131**, Scheme 3.13). Once again, the stereochemistry at C(11) was determined by correlation to the alcohol resulting from debenzylation of the parent benzyl ether.

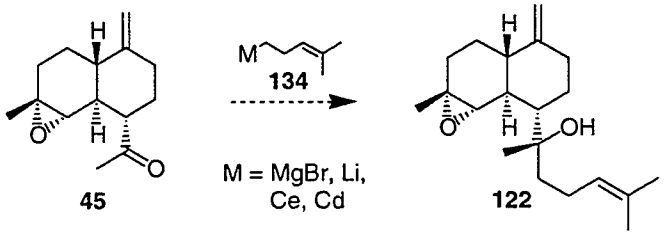
Scheme 3.14



3.3.2 Attempts to Add Carbon Nucleophiles

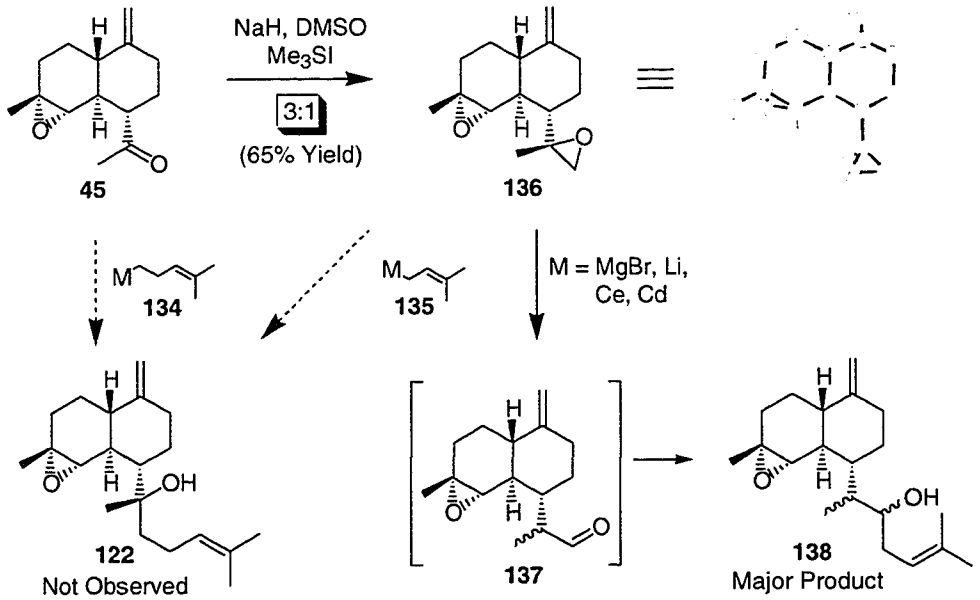
Under the assumption that carbon nucleophiles would add from the same face of the carbonyl as hydride, several homoallylic carbon nucleophiles were tested (Scheme 3.15). However, addition could not be effected under a variety of conditions using an array of methods to generate competent nucleophiles like **134**. Furthermore, a range of appropriately functionalized sp^3 or sp^2-hybridized nucleophiles including Grignard reagents, dithianes, sulfones, alkyl lithium reagents, and enolates failed to undergo addition to **45**.

Scheme 3.15



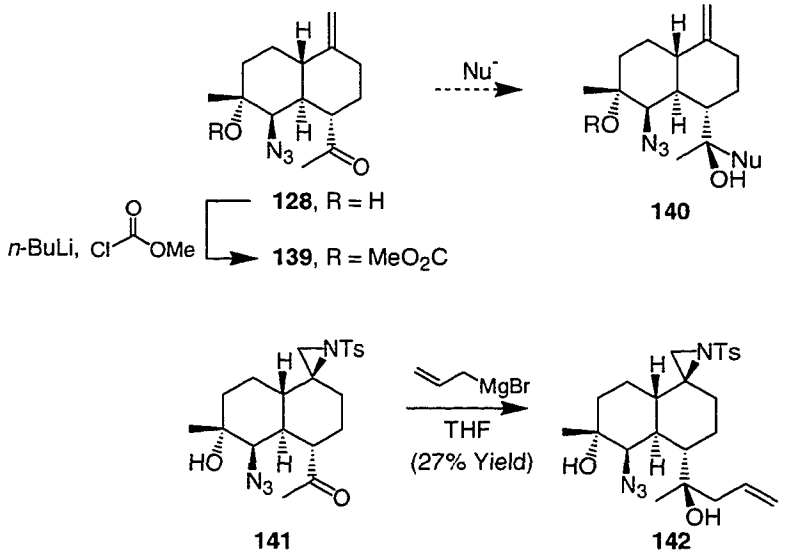
The search for synthetic handles which could add to **45** expanded to include nucleophiles which were less immediately useful than **134**. In the course of these studies, the only practical adduct observed was **136**, resulting from addition of trimethylsulfonium ylide (Scheme 3.16).[14] It was concluded from deuterium quenching experiments that competitive enolization of the methyl ketone was problematic. Attempts to modulate the nucleophile basicity by varying the counterion led to no improvement, and addition of various Lewis acids (e.g. $BF_3{\cdot}OEt_2$, $CeCl_3$, $AlCl_3$, TMSCl, etc.) to reactions with **45** or **136** resulted in undesired reactivity with the epoxide.[15] Alcohol mixture **138** presumably arose from a Lewis acid catalyzed epoxide opening followed by a 1,2-hydride shift via aldehyde **137**.[16]

Scheme 3.16



The inability to add useful nucleophiles to methyl ketone **45** prompted the preparation of related methyl ketone substrates. However, nucleophilic addition to **128**, **139**, or **141** with a variety of nucleophiles was again fruitless (Scheme 3.17). The only adduct isolated from these experiments was **142** arising from addition of allyl Grignard in 27% yield.

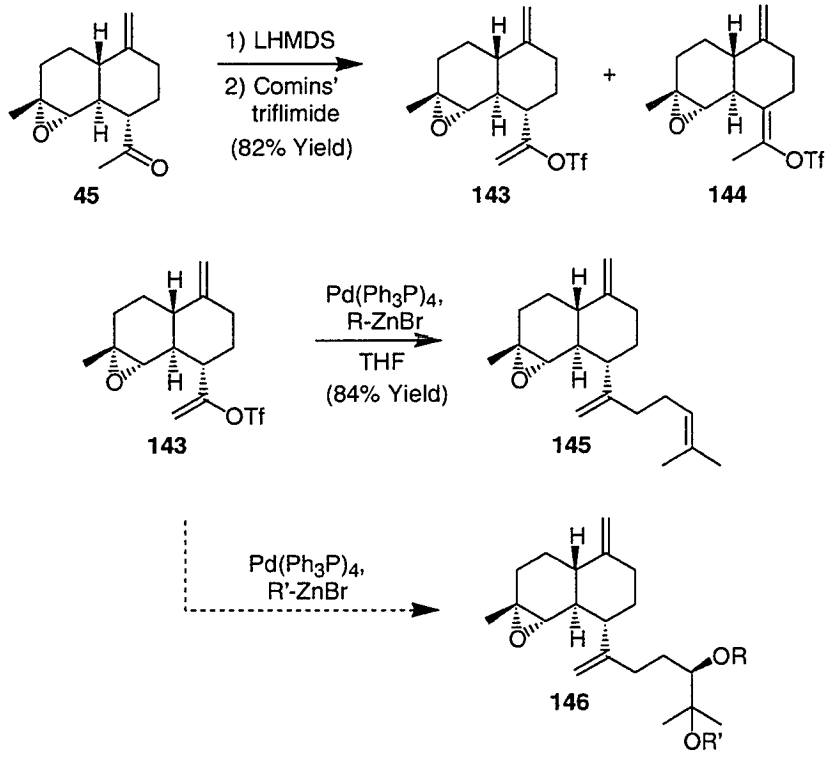
Scheme 3.17



3.3.3 Cross-Coupling

Considering enolization of the methyl ketone in **45** was observed in the presence of some basic nucleophiles, it was thought that a Negishi-type cross-coupling of the corresponding kinetic enol-triflate with an alkyl-zinc partner could be effective for incorporation of the needed sidechain.[17-19] However, after brief examination using methyl ketone **45**, cross-coupling did not offer the desired solution (Scheme 3.18). Although formation of **143** was possible using LHMDS and Comins' triflimide, even the use of optimized conditions resulted in variable ratios of **143** to **144** (ca. 1:1 to 95:5).[20] In addition, cross-coupling provided **145** by crude NMR, but an appropriately functionalized alkyl-zinc nucleophile could not be prepared such that an intermediate like **146** could be accessed.

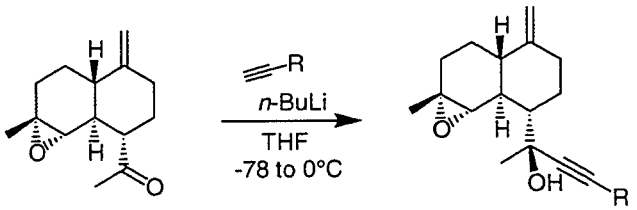
Scheme 3.18



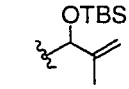
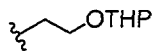
3.3.4 Acetylide Nucleophiles

From these initially discouraging results, it was concluded that methyl ketones like **45** were not only very selective towards nucleophiles, in light of the high diastereoselectivity (10:1) afforded by reduction with a reagent as small as borohydride, but also prone to enolization. Therefore, unable to exploit enolization through cross-coupling, we examined using less basic and sterically less demanding sp-hybridized nucleophiles. We were delighted to find that the lithium anion of ethyl propiolate added efficiently to **45** to provide **148** with greater than 98:2 diastereoselectivity (Scheme 3.19).

Scheme 3.19



45 **148**, R = CO_2Et

R	d.r.	Yield
	N/R	N/R
	N/R	N/R
TMS	>98:2	20%*
CO_2Et	>98:2	89%

* 60% recovered sm

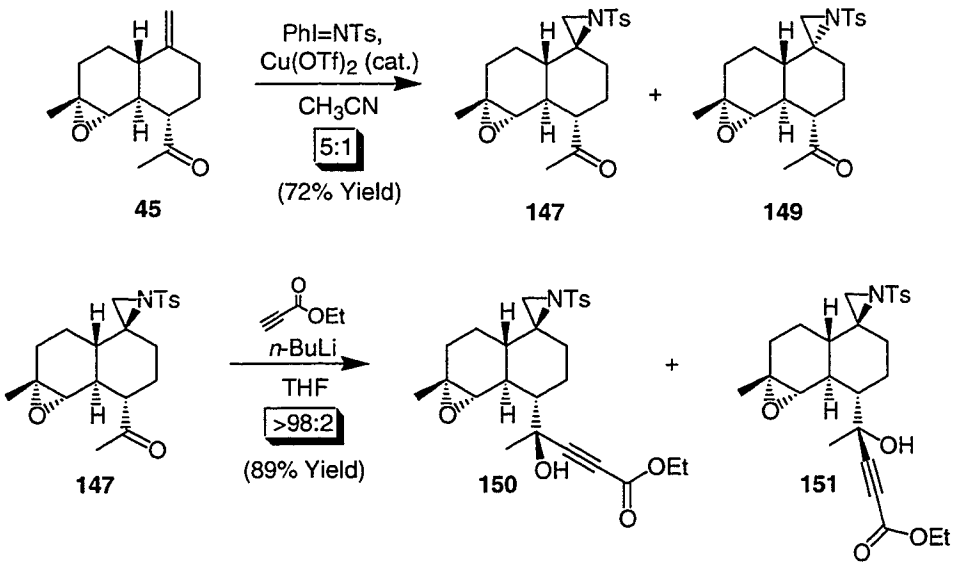
3.4 Formation of the Tetrahydrofuran

The discovery that the acetylenic anions could add efficiently to the methyl ketone refocused efforts on the original synthetic strategy. Although manipulation of a propiolate handle to the desired tetrahydropyran/furan was anticipated to be somewhat circuitous, a major problem had been solved. However, renewed confidence was tempered by the fact that the configurational assignment at C(11) in **148** was based solely on the assumption that the propiolate had added to the same face of the carbonyl as hydride and Corey's ylide. Further evidence was sought to confirm the putative stereochemistry.

3.4.1 Nucleophilic Addition to a Multi-Functional Electrophile

Aziridination of **148** might be hampered by the presence of an ynoate. Therefore, methyl ketone **45** was aziridinated prior to the ethyl propiolate addition (Scheme 3.20). Treatment of aziridine **147** with the anion of ethyl propiolate again proceeded smoothly with excellent diastereoselectivity to give **150**; importantly, the addition occurred without reactivity at the aziridine or epoxide.

Scheme 3.20

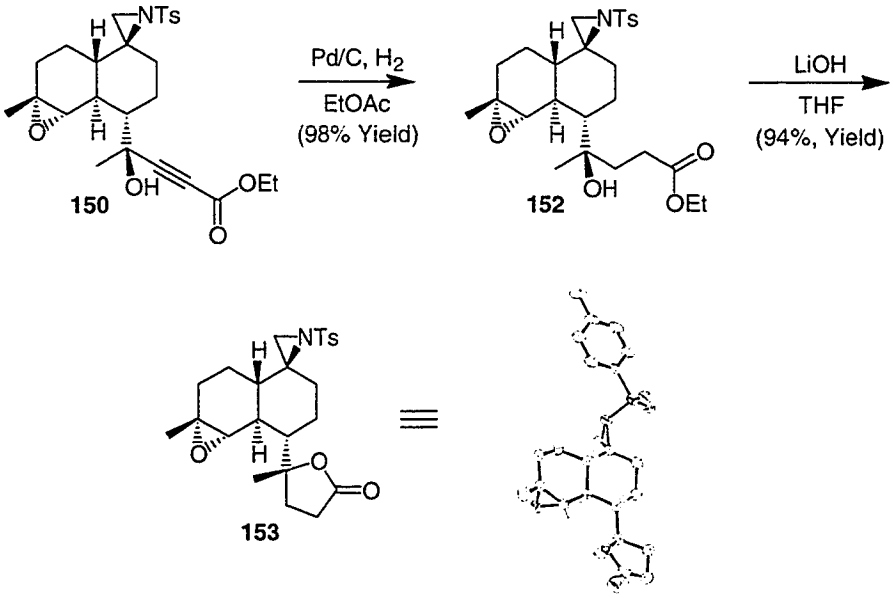


3.4.2 Advancement to a Useful Intermediate

Exposure of **150** to catalytic hydrogenation conditions cleanly provided **152** (Scheme 3.21). Gratifyingly, saponification of ester **152** afforded lactone **153**, a crystalline solid for which an X-ray structure was obtained. The ORTEP revealed that

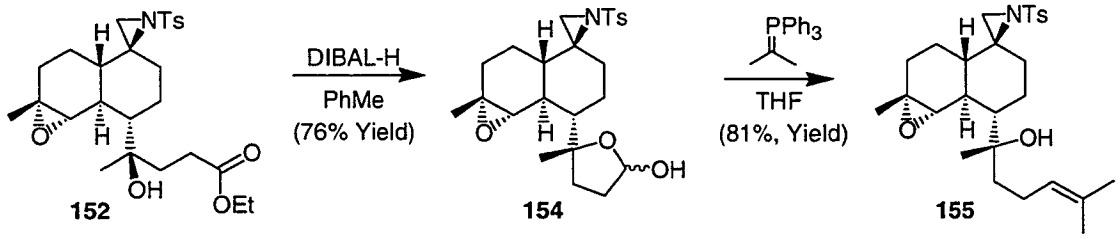
153 possessed the correct C(11) stereochemistry and confirmed addition and the anion of ethyl propiolate to methyl ketone **141** had indeed occurred in the anti-Felkin mode.

Scheme 3.21



Reduction of **153** with DIBAL-H provided lactol **154** as a mixture of epimers and was accompanied by only trace amounts of the corresponding diol (Scheme 3.22). The much anticipated bishomoallylic alcohol **155** was realized upon treatment of **154** with excess isopropyltriphenylphosphonium ylide.

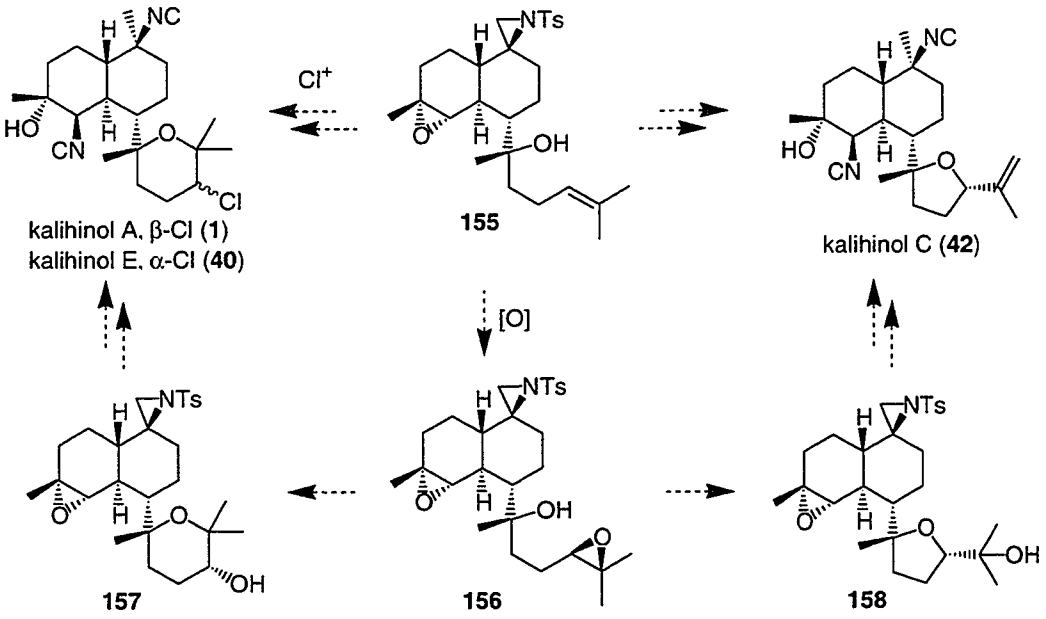
Scheme 3.22



3.4.3 A Tetrahydropyran/furan Model System

Having installed the desired tetrahydropyran/furan precursor, and with adequate quantities of **155** in hand, attention was focused upon finding appropriate cyclization conditions. Haloetherification of bishomoallylic alcohol **155** was considered the most direct route for accessing the chloro-tetrahydropyran of kalihinols A and E as well as the tetrahydrofuran of kalihinol C (Scheme 3.23). Alternatively, a diastereoselective epoxidation of **155** followed by cyclization of **156** was also considered an option.

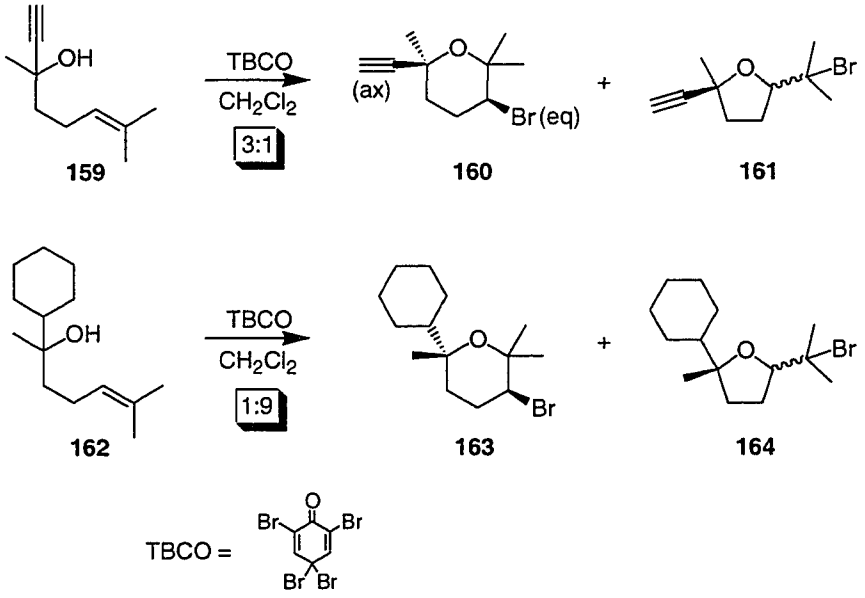
Scheme 3.23



Prior studies of haloetherification using bishomoallylic alcohols have shown that the 5-*exo* (tetrahydrofuran) to 6-*endo* (tetrahydropyran) product ratios depend upon the substitution patterns about the olefin and alcohol.[21-24] For substrates with tri-substituted olefins and tertiary alcohols, the relative size of the groups neighboring the hydroxyl

usually dictate the regiochemical preference. As shown in Scheme 3.24, propargylic alcohol **159** provided tetrahydropyran **160** as the major isomer upon treatment with an electrophilic bromine source.[25] However, substitution of the small acetylene with a larger cyclohexyl group led predominantly to tetrahydrofuran **164**.[26]

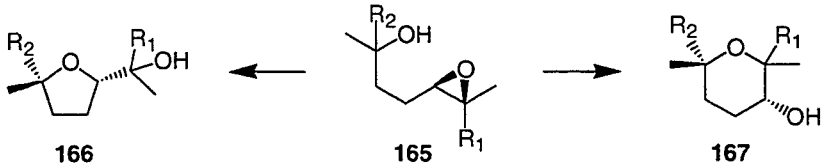
Scheme 3.24



These results suggested that a large substituent adjacent to the hydroxyl preferred an equatorial orientation in the transition state of the ring forming event, forcing the methyl group axial and resulting in a 1,3-diaxial interaction with the opposing methyl. For bishomoallylic alcohol **155**, it was clear that a 6-*endo* cyclization via haloetherification would be difficult to obtain given that the decalin would have similar steric bulk to a cyclohexyl group. However, this method was considered a viable option for obtaining the tetrahydrofuran, via 5-*exo* cyclization, found in many of the kalihinols.

Like haloetherification, opening of an epoxide by an internal oxygen nucleophile has also been shown to be governed by the substituents surrounding both the hydroxyl and epoxide. Epoxide substrates (e.g. **165**), which can arise from diastereoselective epoxidation of bishomoallylic alcohols, generally prefer 5-*exo* cyclization leading to the tetrahydrofuran (**166**).[27] However, the tetrahydropyran (**167**) can be formed when the epoxide is adjacent to a double bond or other substituent capable of stabilizing a developing electropositive charge.[28,29]

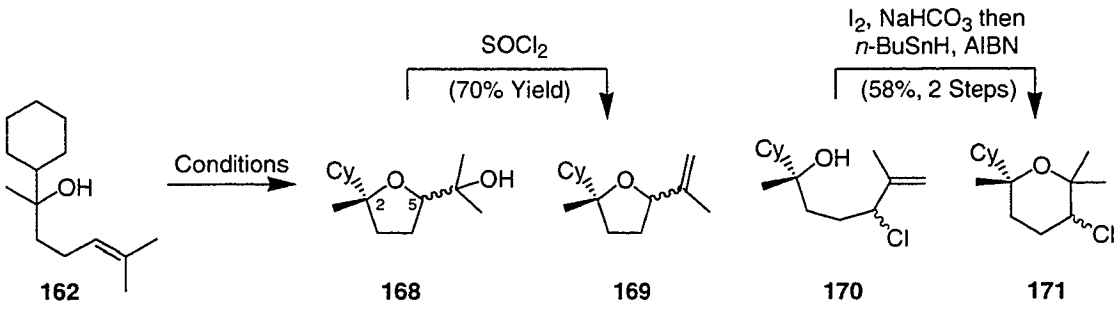
Scheme 3.25



Both haloetherification and epoxidation routes were examined with alcohol **162** as a model substrate. Preference for the 5-*exo* cyclization of alcohol **162** was confirmed using a variety of conditions (Scheme 3.25). Epoxidation using *m*-CPBA and concomitant cyclization led exclusively to tetrahydrofuran **168** as a 1:1 mixture of diastereomers. However, modest diastereoselectivity (ca. 4:1) for the desired *cis*-2,5 diastereomer was observed with vanadyl acetylacetonate and TBHP. Alcohol **168** was easily converted to **169** under dehydrating conditions. Electrophilic chlorine sources gave allylic chloride **170** as the major product, which was transformed to the tetrahydropyran mixture **171** by iodoetherification and selective dehalogenation. Seleno-

etherification of alcohol **162** followed by elimination led exclusively to tetrahydrofuran **169** as a 1:1 mixture of diastereomers (Scheme 3.25).

Scheme 3.26



Conditions	Products*	Yield
TBHP, $VO(acac)_2$	**168** (4:1/syn:anti)	78%
m-CPBA	**168**	83%
PhSeCl, then *m*-CPBA	**169**	88%
NCS	**171**:**169**:**170**, 1:2:7	86%
$Ca(OCl)_2$, AcOH	**170**	71%

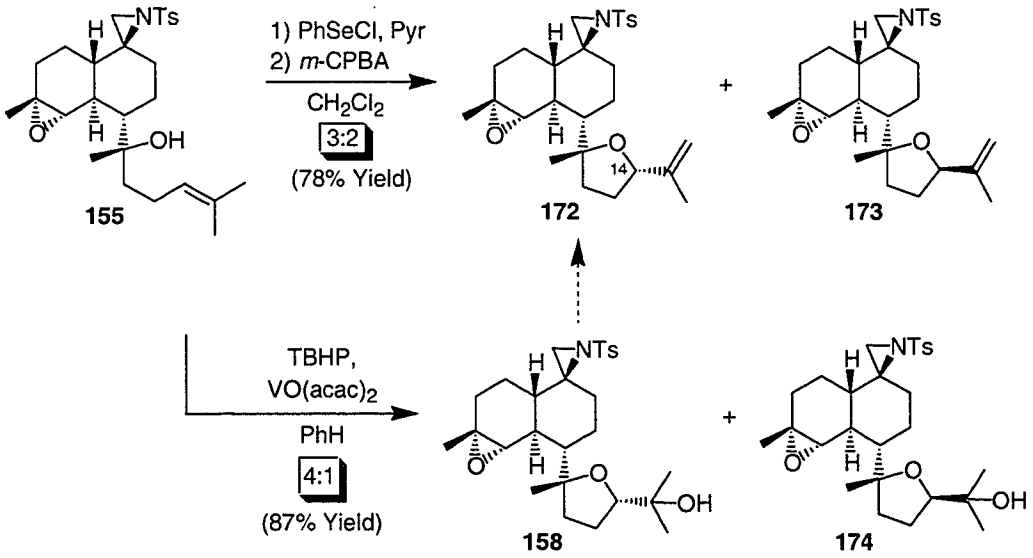
*Unless otherwise noted, all products were isolated as a 1:1 mixture of diasteromers.

3.4.4 Synthesis of Tetrahydrofuran 172

With knowledge that the desired tetrahydropyrans of kalihinols A and E, and tetrahydrofuran of kalihinol C could be accessed in a model system, a choice was made concerning which natural product would be sought out first. Considering formation of the chloro-tetrahydropyran required an additional step, i.e. dehalogenation, it was decided that synthetic efforts would initially address installation of the tetrahydrofuran for the synthesis of kalihinol C. To this end, alcohol **155** was subjected to epoxidation

conditions (Scheme 3.26). To our delight, the favorable diastereoselectivity of the vanadium-catalyzed epoxidation and subsequent Lewis acid promoted cyclization was maintained in the fully-functionalized system. However, subsequent elimination of the tertiary alcohol proved to be problematic (**158**→**172**). The variety of dehydration conditions which were examined resulted in undesired reactivity with the epoxide. In order to take advantage of the diastereoselectivity of the epoxidation, elimination at this stage (**158**) was imperative since future epoxide opening would lead to two indistinguishable tertiary alcohols.

Scheme 3.27



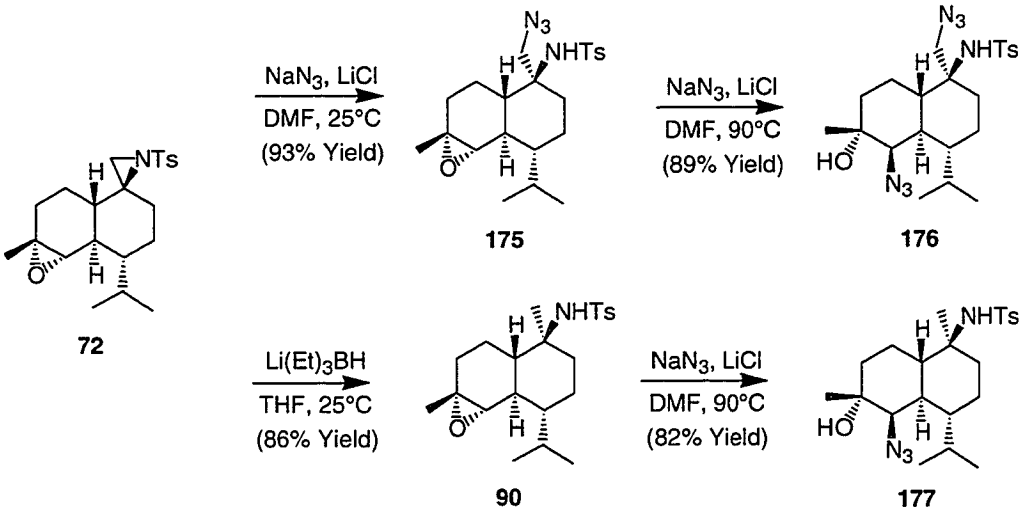
Gratifyingly, application of seleno-etherification and elimination conditions to alcohol **155** resulted in a cyclization with modest preference (3:2) for the desired C(14) epimer (**172**). The initial stereochemical assignments were based on the ^{13}C NMR shifts of the ether carbons in comparison to the reported values for the natural product.

3.5 Completion of Kalihinol C

3.5.1 Azide Addition

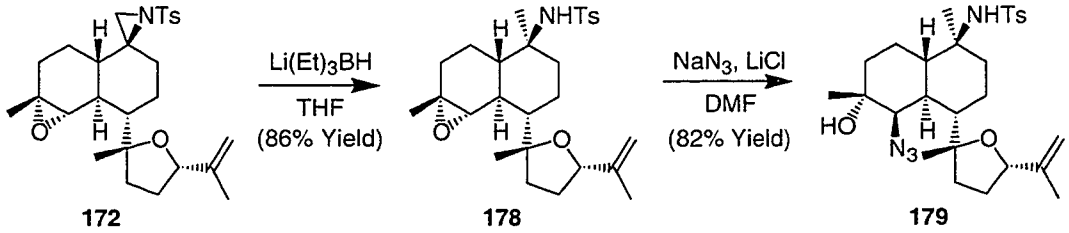
Having installed the long anticipated tetrahydrofuran, it was necessary to determine the final order of events for incorporation of the isonitriles. In order to conserve advanced material from the fully functionalized system, epoxide **72** from the previously described model system was treated independently with azide and $Li(Et)_3BH$ (Scheme 3.27). It was found that the aziridine opened in preference to the epoxide in both cases. The epoxide was subsequently opened under more forcing conditions.

Scheme 3.28



With the knowledge that the terminal aziridine would most likely react with a nucleophile before the epoxide, **172** was first treated with $Li(Et)_3BH$ followed by sodium azide to afford the desired adduct, **179** (Scheme 3.28).

Scheme 3.29

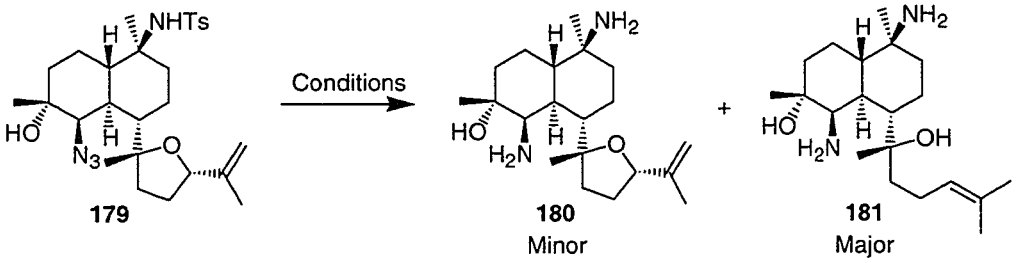


172 178 179

3.5.2 Problematic Tosyl Deprotection

The completion of the synthesis of kalihinol C seemed imminent given the extensive model system studies concerning the requisite tosyl deprotection and isonitrile formation. However, upon exposure of **179** to sodium in ammonia, both the tosyl group and the tetrahydrofuran were reduced to give amine **181** as the major product (Scheme 3.29). Although not unprecedented, two electron reduction of the tetrahydrofuran had not been anticipated.[30] Attempting the reduction under a variety of conditions (e.g. $Li/C_{10}H_8$, $Na/C_{10}H_8$, Ca, Na/Hg) revealed that selective reduction of the tosyl group would be difficult given **179** was the major product in nearly every reduction attempt.

Scheme 3.30

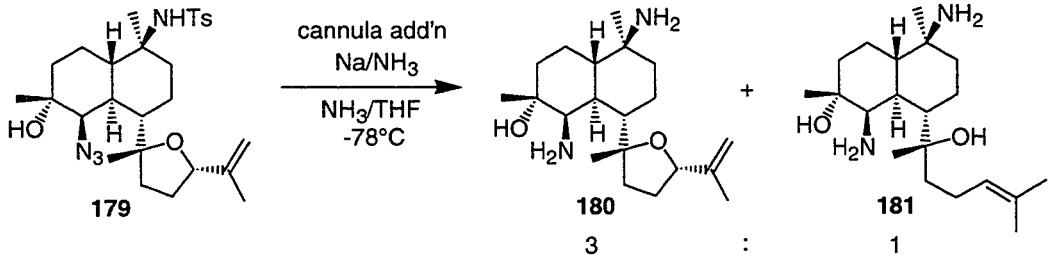


Reductant	Solvent	Temp. (°C)
Na	NH_3/THF	-78 to -33
Na	NH_3/EtOH	-78 to -33
$Na/C_{10}H_8$	DME	45

*Na/Hg, Ca, Mg did not remove tosyl

After much experimentation, the best results were obtained using sodium at low temperatures for extended reaction times to give a 3:1 mixture of **180** to **181** (Scheme 3.30). Optimized procedures required the addition of a dilute solution of sodium in ammonia via cannula to a solution of **179** in ammonia. Direct exposure of **179** to sodium metal led to highly variable ratios of **180** to **181**.

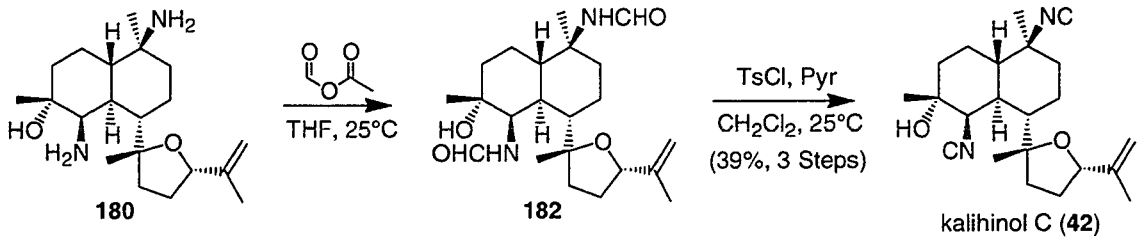
Scheme 3.31



With the penultimate intermediate in hand, the crude mixture of **180** and **181** was advanced. Gratifyingly, treatment of the mixture with acetic formic anhydride followed

by exposure to tosyl chloride and pyridine afforded **42** (Scheme 3.31). The spectroscopic and chromatographic properties of **42** were identical to those reported for kalihinol C.[31]

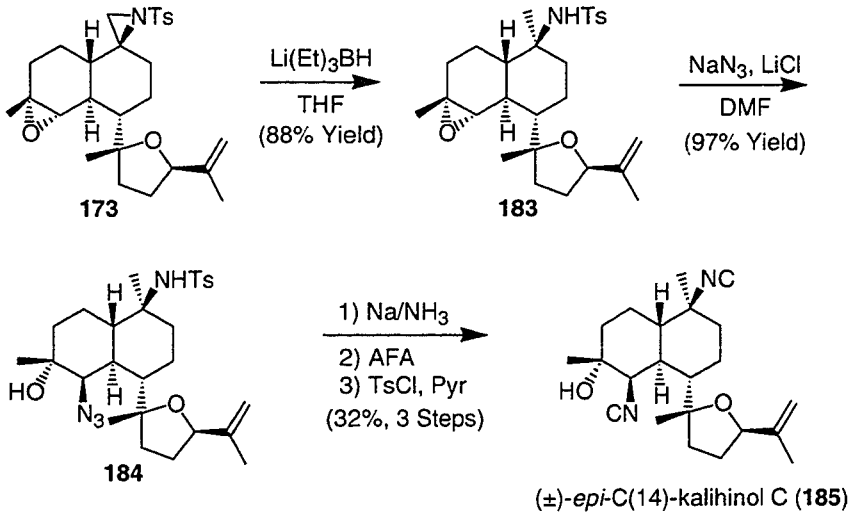
Scheme 3.32



3.5.3 Synthesis of *epi*-C(14)-Kalihinol C

In analogy to **172**, aziridine **173** was advanced (Scheme 3.32). Aziridine opening with $Li(Et)_3BH$ gave amine **183**. Addition of azide afforded **184**. Subsequent tosyl deprotection with sodium followed by formylation and dehydration provided the C(14) epimer of kalihinol C (**185**).

Scheme 3.33



3.6 Conclusions

The first total synthesis of (±)-kalihinol C (**42**) and (±)-*epi*-C(14)-kalihinol C (**185**) were presented. The successful synthetic strategy was based on a series of substrate-controlled, diastereoselective reactions in which a conformationally rigid decalin core was used to dictate introduction of the requisite functionality. Based in part on extensive model system studies, the synthetic sequence was highlighted by a diastereoselective (i) IMDA cycloaddition of **109**, (ii) epoxidation of *cis*-decalin **110**, (iii) aziridination of olefin **45**, and (iv) anti-Felkin propiolate addition to methyl ketone **141**. Future efforts will focus upon the advancement of **155** to kalihinol A and potentially other kalihinols. With continued relations between Prof. Daniel E. Goldberg and our group, it is anticipated that fruitful SAR studies involving compounds from the decalin model system as well as the fully functionalized system will contribute to the understanding of how the kalihinols exhibit antimalarial activity.

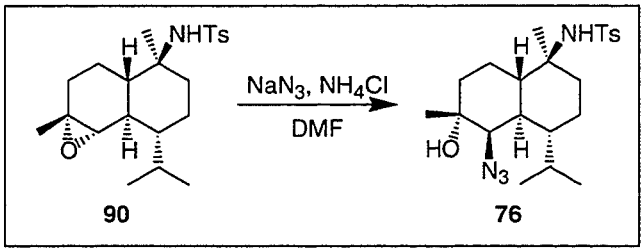
3.7 Experimental

3.7.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly distilled solvents. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone. Methylene chloride (CH_2Cl_2), and benzene were distilled from calcium hydride. Methanol (MeOH) was distilled from magnesium. All other commercially obtained reagents were used as received. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Column or flash chromatography was performed with the indicated solvents using silica gel (particle size 0.032-0.063 nm) purchased from Bodman. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance DPX-500 or Bruker Advance DPX-400 spectrometers. Chemical shifts are reported relative to internal solvent as described by Gottlieb (i.e. chloroform ^1H δ 7.26 ppm, ^{13}C δ 77.16 ppm; acetone ^1H δ 2.05 ppm, ^{13}C δ 29.84 ppm; methanol ^1H δ 3.31 ppm, ^{13}C δ 49.00 ppm).[32] Melting points were obtained on a Gallenkamp variable temperature melting point apparatus and are uncorrected. Infrared spectra were recorded on a Midac M-1200 FTIR. High resolution mass spectra were acquired at The University of Illinois Mass Spectrometry Center.

3.7.1 Preparative Procedures

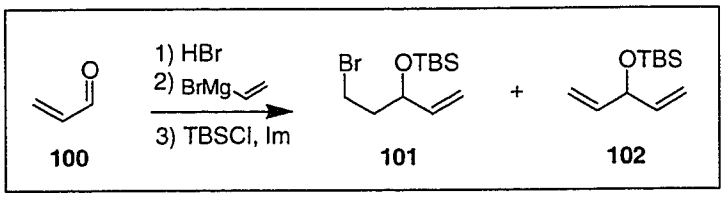
Preparation of azide 76



90 76

Azide 76. To a solution of epoxide **90** (12 mg, 0.031 mmol, 1.0 equiv) in DMF (2 mL), was added NaN_3 (12 mg, 0.18 mmol, 6.0 equiv) and NH_4Cl (5 mg, 0.093 mmol, 3.0 equiv). After heating the mixture at 75°C for 48 h, the reaction was cooled to rt and diluted with EtOAc (30 mL) and water (5 mL). The organic layer was washed with brine (2 x 10 mL) and dried with Na_2SO_4. After concentration under reduced pressure, the resulting residue was purified by silica gel column chromatography (3:1 hexanes:EtOAc) to afford **76** (11 mg, 82% yield) as an amorphous, white solid. ^{1}H NMR (500 MHz, ~ 1:1 CD_3OD:$CDCl_3$) δ 7.41 (d, *J*=8.1 Hz, 2H), 6.96 (d, *J*=8.7 Hz, 2H), 3.11 (d, *J*=2.3 Hz, 1H), 2.08 (s, 3H), 1.62-1.55 (m, 1H), 1.49 (dt, *J*=2.9, 11.4 Hz, 1H), 1.38-0.88 (comp m, 13H), 0.77-0.66 (comp m, 4H), 0.58 (d, *J*=6.7 Hz, 3H), 0.42 (d, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, ~ 1:1 CD_3OD:$CDCl_3$) δ 142.4, 140.8, 129.0, 126.3, 71.0, 68.1, 59.6, 42.1, 41.7, 38.8, 38.1, 32.3, 27.5, 25.3, 20.6, 20.5, 20.3, 19.4, 18.2, 14.3; IR (Nujol mull/NaCl) 3510 (w), 2594 (w), 2448 (s), 2094 (m), 1301 (m), 1157 (m), 888 (w), 722 (m) cm^{-1}; HRMS (ES) *m/z* found: 458.2311 [calc'd for $C_{22}H_{33}DNaN_4O_3S$ (M+Na): 458.2311].

Preparation of TBS-ethers 101 and 102



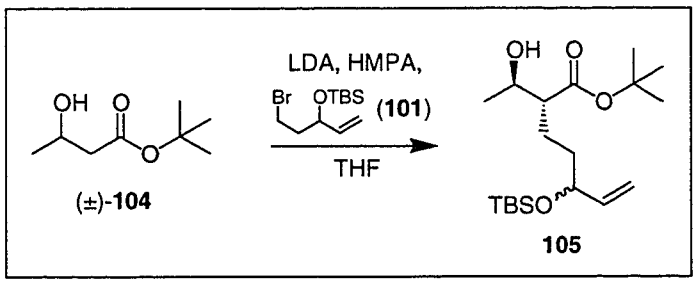
TBS-ethers 101 and 102. A solution of acrolein (20.0 mL, 300 mmol, 1.0 equiv) in Et_2O (120 mL) at 0°C was treated with anhydrous HBr. After NMR had indicated the reaction was complete (ca. 10 min), the solution was neutralized with solid $NaHCO_3$ (ca. 3 g) and filtered. The yellow solution was diluted with pentane (150 mL) and cooled to -78°C before adding vinyl magnesium bromide (1.0 M in THF, 300 mL, 1.0 equiv). After 1 h the reaction was quenched with saturated aqueous NH_4Cl (ca. 50 mL). The mixture was washed with water (2 x 100 mL), brine (100 mL), and dried with Na_2SO_4. The solvent was removed *in vacuo* and the resulting oil taken up in CH_2Cl_2 (500 mL). Imidazole (20.4 g, 300 mmol, 1.0 equiv) was added followed by TBSCl (45.0 g, 300 mmol, 1.0 equiv) and the mixture was allowed to stir for 16 h. After filtering, the solvent was removed *in vacuo* and the resulting residue purified by silica gel column chromatography (10:1 pentane:Et_2O) to afford a mixture of bromide **101** (26.8 g, 32% yield) and olefin **102** (6.5g, 11% yield) as a colorless oils which could be further purified by low pressure distillation.

TBS-ether 101. b.p. 69-70°C @1.5 mm Hg; ^1H NMR (500 MHz, $CDCl_3$) δ 5.82-5.74 (m, 1H), 5.23-5.18 (m, 1H), 5.10-5.06 (m, 1H), 4.31-4.26 (m, 1H), 3.50-3.38 (comp m, 2H), 2.08-1.92 (comp m, 2H), 0.89 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 114.9, 71.9, 41.1, 30.1, 26.0, 18.3, -4.1, -4.7; IR (thin film/NaCl) 2955 (s), 2857 (s), 1644 (w), 1472 (m), 1361 (m), 1257 (s), 1162 (w), 1092 (s), 1027 (s),

837 (s) cm^{-1}

TBS-ether 102. b.p. 30-31°C @1.5 mm Hg; ^1H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddd, *J*=5.3, 10.5, 17.0 Hz, 1H), 5.22 (dt, *J*=1.6, 17.2 Hz, 2H), 5.06 (dt, *J*=1.6, 16.9 Hz, 2H), 4.63-4.59 (m, 1H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 113.8, 74.8, 26.0, 18.5, -2.8, -4.6; IR (thin film/NaCl) 2956 (s), 2830 (s), 2858 (s), 1638 (w), 1472 (m), 1361 (m), 1254 (s), 1126 (s), 1073 (s), 922 (s) cm^{-1}

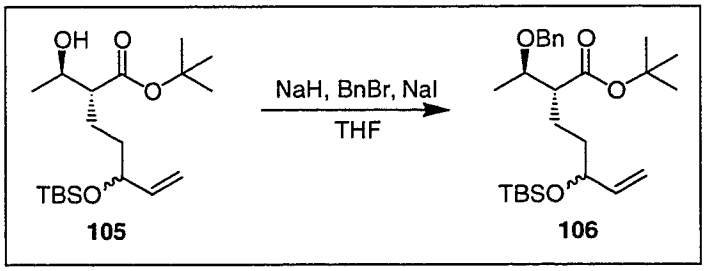
Preparation of ester 105



Ester 105. To a solution of **104** (1.00 g, 6.24 mmol, 1.0 equiv) in THF (35 mL) and HMPA (3.2 mL, 18.7 mmol, 3.0 equiv) at -40°C, was added LDA (0.5 M in THF, 26.0 mL, 13.1 mmol, 2.1 equiv). After 20 min, a solution of **101** (2.61 g, 9.36 mmol, 1.5 equiv) in THF (5 mL) was added via syringe pump over 1 h. After an additional 2 h, the reaction was warmed to 0°C for 1h then quenched with saturated aqueous $NaHCO_3$ (10 mL). EtOAc (50 mL) was added and the mixture was washed with water (25 mL), brine (25 mL), and dried with Na_2SO_4. After the solvent was removed *in vacuo*, the resulting residue was purified by silica gel column chromatography (9:1 hexanes:EtOAc) to afford ester **105** (1.77 g, 79% yield) as a colorless oil. (1:1 mixture of diastereomers) ^1H NMR (400 MHz, $CDCl_3$) δ 5.83-5.71 (m, 1H), 5.14 (d, *J*=17.0 Hz, 1H), 5.03 (d, *J*=17.0 Hz, 1H) 4.13-4.05 (m, 1H), 3.89-3.80 (m, 1H), 2.62 (br s, 1H), 2.29-2.19 (m, 1H), 1.78-1.40

(comp m, 13H), 1.27-1.15 (comp m, 3H), 0.89 (s, 9H) 0.03 (d, *J*=8.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 141.5, 141.4, 114.2, 114.1, 81.3, 73.6, 73.5, 68.6, 68.5, 53.2, 53.0, 35.5, 35.4, 28.3, 26.0, 25.2, 21.7, 21.6, 18.4, -4.2, -4.2, -4.7, -4.7; IR (thin film/NaCl) 3442 (br m), 2957 (m), 2930 (m), 2858 (m), 1728 (m), 1473 (m), 1368 (m), 1254 (m), 1156 (m), 1087 (m) cm^{-1}; HRMS (FAB) *m/z* found: 359.2618 [calc'd for $C_{19}H_{39}O_4Si$ (M+H): 359.2618].

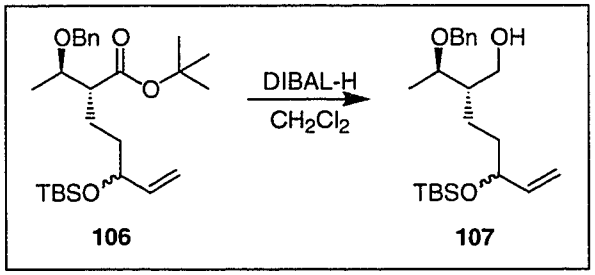
Preparation of benzyl ether 106



Benzyl ether 106. To a solution of **105** (10.4 g, 28.9 mmol, 1.0 equiv) in THF (200 mL) at 0°C was added NaH (60% in mineral oil, 1.27 g, 31.8 mmol, 1.1 equiv) followed by benzyl bromide (10.3 mL, 86.7 mmol, 3.0 equiv) and sodium iodide (1.30 g, 8.64 mmol, 0.3 equiv). The reaction was allowed to warm to rt and stirred for 12 h before quenching with water (100 mL). After diluting with hexanes (100 mL), the organic layer was separated, washed with brine (2 x 100 mL), and dried with Na_2SO_4. Removal of the solvent *in vacuo* provided a residue which was purified by silica gel column chromatography (100% hexanes then 9:1 hexanes:EtOAc) to afford **106** (12.1 g, 93% yield) as a colorless oil. (1:1 mixture of diastereomers) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.19 (comp m, 5H), 5.74 (ddd, *J*=5.9, 10.5, 16.7 Hz, 1H), 5.14-4.98 (m, 2H), 4.53 (d, *J*=11.4 Hz, 1H), 4.42 (d, *J*=11.2 Hz, 1H), 4.11-4.03 (m, 1H), 3.69 (dq,

J=6.2, 8.3 Hz, 1H), 2.42-2.33 (m, 1H), 1.59-1.37 (comp m, 13H), 1.16-1.14 (m, 3H), 0.87-0.86 (m, 9H), 0.03- -0.03 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 173.9, 141.6, 141.5, 128.3, 127.9, 127.8, 127.5, 114.1, 114.0, 80.4, 80.3, 73.8, 73.4, 71.3, 53.1, 53.0, 35.7, 35.6, 28.3, 26.0, 24.2, 23.8, 18.4, 18.4, 17.1, -4.2, -4.2, -4.7; IR (thin film/NaCl) 2957 (s), 2857 (s), 1728 (s), 1497 (w), 1472 (m), 1455 (m), 1390 (m), 1366 (s), 1254 (s), 1156 (s) cm^{-1}; HRMS (FAB) m/z found: 449.7186 [calc'd for $C_{26}H_{45}O_4Si$ (M+H): 449.7186].

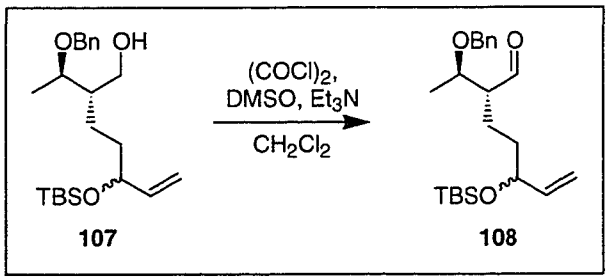
Preparation of alcohol 107



Alcohol 107. A solution of **106** (19.6 g, 43.7 mmol, 1.0 equiv) in CH_2Cl_2 (350 mL) at -78°C was treated with DIBAL-H (17.1 mL, 96.2 mmol, 2.2 equiv). After 1 h, the reaction was quenched with 20% aqueous Rochelle's salt (100 mL). The organic layer was washed with water (100 mL), brine (100 mL) and dried with Na_2SO_4. After concentration, the resulting residue was purified by silica gel column chromatography (3:1 hexanes:EtOAc) to afford **107** (14.9 g, 90%) as a colorless oil. (1:1 mixture of diastereomers) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.25 (comp m, 5H), 5.82-5.72 (m, 1H), 5.16-5.11 (m, 1H), 4.65 (d, J=11.4 Hz, 1H), 4.41-4.37 (m, 1H), 4.09-4.05 (m, 1H), 3.86-3.81 (m, 1H), 3.65-3.56 (comp m, 2H), 1.58-1.35 (comp m, 6H), 1.28 (d, J=6.0 Hz, 3H), 0.91-0.88 (comp m, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

141.7, 141.6, 138.4, 128.6, 127.9, 127.9, 127.9, 114.0, 114.0, 79.3, 79.2, 74.1, 73.9, 71.2, 71.2, 63.9, 63.7, 46.3, 46.3, 35.8, 35.7, 26.0, 24.3, 24.1, 18.4, 18.4, 17.8, 17.7, -4.2, -4.7; IR (thin film/NaCl) 3446 (br m), 2954 (m), 2928 (m), 2884 (m), 2856 (m), 1471 (m), 1455 (m), 1252 (m), 1088 (m), 1028 (m) cm^{-1}; HRMS (FAB) *m/z* found: 379.2669 [calc'd for $C_{22}H_{39}O_2Si$ (M+H): 379.2668].

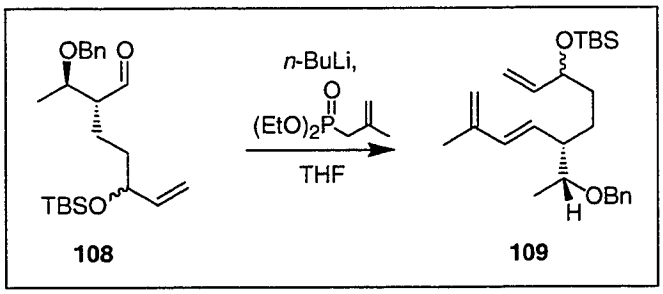
Preparation of aldehyde 108



Aldehyde 108. A solution of oxalyl chloride (3.57 mL, 40.9 mmol, 1.1 equiv) in CH_2Cl_2 (250 mL) at -78°C was treated with DMSO (5.80 mL, 81.8 mmol, 2.2 equiv) and stirred for 10 min. A solution of **107** (14.1 g, 37.2 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was then added and stirring continued for an additional 10 min. Et_3N (25.9 mL, 186 mmol, 5.0 equiv) was added and the mixture was allowed to warm to rt. Water (100 mL) was introduced and the organic layer washed with brine (100 mL) and dried with Na_2SO_4. After concentration, the resulting residue was purified by silica gel column chromatography (18:1 then 9:1 hexanes:EtOAc) to afford **108** (14.9 g, 89%) as a colorless oil. (1:1 mixture of diastereomers) ^1H NMR (500 MHz, $CDCl_3$) δ 9.68-9.66 (m, 1H), 7.36-7.26 (comp m, 5H), 5.80-5.71 (m, 1H), 5.17-5.16 (m, 1H), 5.14-5.12, (m, 1H), 5.06-5.04 (m, 1H), 5.03-5.02 (m, 1H), 4.62 (d, *J*=11.5 Hz, 1H), 4.42 (d, *J*=11.5 Hz, 1H), 4.12-4.07 (m, 1H), 3.81 (m, 1H), 2.39-2.33 (m, 1H), 1.81-1.41 (comp m, 4H), 1.27-

1.24 (comp m, 3H), 0.90-0.88 (comp m, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 204.7, 141.3, 138.4, 128.5, 127.8, 127.8, 114.2, 114.2, 74.9, 74.8, 73.6, 73.4, 70.8, 57.8, 57.7, 35.4, 35.3, 26.0, 21.6, 21.5, 18.3, 17.4, -4.2, -4.7; IR (thin film/NaCl) 2955 (s), 2930 (s), 2857 (s), 1725 (s), 1497 (w), 1472 (m), 1379 (m), 1252 (s), 1091 (s), 836 (s) cm^{-1}; HRMS (FAB) *m/z* found: 375.2355 [calc'd for $C_{22}H_{35}O_3Si$ (M-H): 375.2355].

Preparation of triene 109

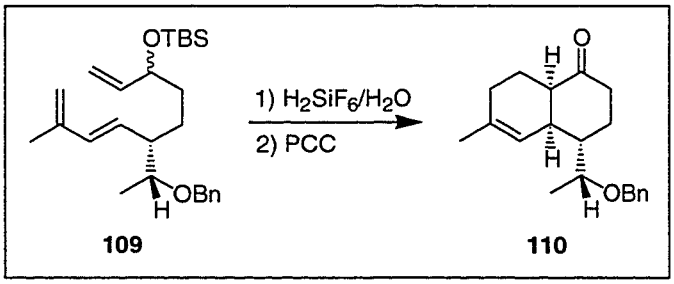


108 **109**

Triene 109. A solution of methallyl phosphonic acid diethyl ester (6.92 g, 36.0 mmol, 1.3 equiv) in THF (300 mL) at -78°C was treated with *n*-BuLi (2.3 M in hexanes, 15.7 mL, 36.0 mmol, 1.3 equiv) and the solution was stirred for 5 min. A solution of **108** (10.4 g, 27.7 mmol, 1.0 equiv) in THF (10 mL) was added and stirring continued for an additional 15 min. The reaction was warmed to rt and stirred for an additional 1 h before quenching with water (100 mL). The mixture was diluted with hexanes (200 mL) and the organic layer was washed with water (3 x 100 mL), brine (100mL), and dried with Na_2SO_4. Concentration *in vacuo* afforded **109** (24.9 g, 90%) as a colorless oil which could be advanced without further purification. An analytical sample, however, could be obtained by silica gel column chromatography (9:1 hexanes:EtOAc, 1% Et_3N). (1:1 mixture of diastereomers) ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.25 (comp m, 5H), 6.13

(d, J=15.4 Hz, 1H), 5.82-5.74 (m, 1H), 5.54-5.41 (5.16-5.10 (m, 1H), 5.04-4.99 (m, 1H), 4.89 (s, 2H), 4.58 (d, J=11.2 Hz, 1H), 4.45 (d, J=11.9 Hz, 1H), 4.10-4.05 (m, 1H), 3.53-3.48 (m, 1H), 2.21-2.12 (m, 1H), 1.85-1.83 (m, 3H), 1.70-1.25 (comp m, 4H), 1.16-1.12 (comp m, 3H), 0.90 (s, 9H), 0.05-0.03 (comp m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.3, 142.0, 141.8, 139.3, 138.5, 134.9, 134.9, 131.5, 128.6, 128.4, 128.4, 127.9, 127.8, 127.8, 127.7, 127.5, 114.7, 114.7, 113.7, 113.6, 78.0, 77.9, 74.1, 72.3, 70.9, 70.8, 49.1, 49.0, 48.9, 36.3, 36.2, 26.4, 26.3, 26.1, 18.9, 18.4, 17.2, 17.1, -4.2, -4.2, -4.6; IR (thin film/NaCl) 2955 (m), 2929 (m), 2857 (m), 1472 (w), 1454 (w), 1361 (m), 1252 (m), 1090 (m), 1028 (m), 836 (m) cm^{-1}; HRMS (FAB) *m/z* found: 415.7039 [calc'd for $C_{26}H_{43}O_2Si$ (M+H): 415.7039].

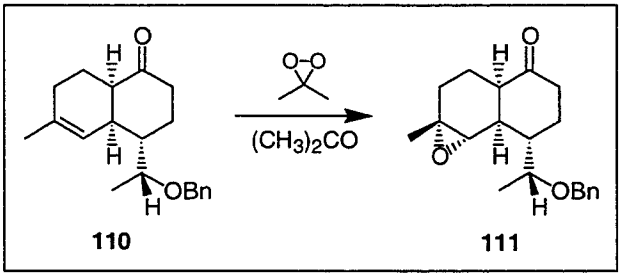
Preparation of *cis*-decalin 110



***cis*-Decalin 110**. A solution of **109** (6.92 g, 22.0 mmol, 1.0 equiv) in MeCN (225 mL) at 0°C was treated with 20% aqueous fluorosilicic acid (1.6 mL, 2.2 mmol, 0.1 equiv). After ca. 4 h, the reaction was quenched with K_2CO_3 (ca. 5g) and diluted with hexanes (100 mL) and water (100 mL). The organic layer was washed with water (100 mL), brine (100 mL) and dried with Na_2SO_4. Concentration *in vacuo* provided a residue which was taken up in CH_2Cl_2 (225 mL). The solution was cooled to 0°C and PCC (19.0 g, 88.0 mmol, 4.0 equiv) was added. After 1h, the reaction was warmed to rt and stirred

for an additional 12 h. Celite (ca 10 g) was added and the mixture was filtered. Concentration *in vacuo* followed by silica gel column chromatography (9:1 hexanes:EtOAc) afforded **110** (4.73 g, 72% yield from **109**) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.18 (comp m, 5H), 5.16-5.13 (m, 1H), 4.59 (d, *J*=12.1 Hz, 1H), 4.38 (d, *J*=12.1 Hz, 1H), 3.79-3.71 (m, 1H), 2.64 (br s, 1H), 2.24-2.15 (comp m, 3H), 2.05-1.75 (comp m, 5H), 1.61-1.52 (comp m, 4H), 1.43-1.35 (m, 1H), 1.18 (d, *J*=6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.0, 138.8, 135.6, 128.5, 127.9, 127.7, 124.0, 74.1, 70.8, 46.2, 44.3, 38.1, 37.9, 28.1, 23.8, 23.8, 22.9, 15.8; IR (thin film/NaCl) 2926 (m), 2876 (m), 1707 (s), 1496 (w), 1452 (m), 1376 (m), 1323 (w), 1121 (m), 1090 (m), 1073 (m) cm^{-1}; HRMS (FAB) *m/z* found: 299.2011 [calc'd for $C_{20}H_{27}O_2$ (M+H): 299.2011].

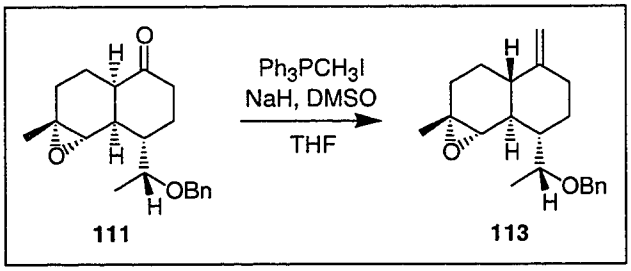
Preparation of epoxide 111



Epoxide 111. To a 0.09 M solution of dimethyl dioxirane in acetone (94.3 mL, 8.49 mmol, 1.5 equiv) at –78°C, was added olefin **110** (1.69 g, 5.65 mmol, 1.0 equiv) in acetone (10 mL). After 2 h, the solution was slowly warmed to 25°C before removing the solvent *in vacuo*. NMR of the resulting oil showed a mixture of diastereomers in the ratio of 95:5 which could be purified by silica gel column chromatography (9:1 then 3:1 hexanes:EtOAc) to afford **111** (1.51 g, 85% yield) as a colorless oil. ^{1}H NMR (500 MHz,

$CDCl_3$) δ 7.26-7.17 (comp m, 5H), 4.61 (d, J=11.7 Hz, 1H), 4.35 (d, J=11.9 Hz, 1H), 3.65-3.59 (m, 1H), 2.59 (s, 1H), 2.57-2.53 (m, 1H), 2.24-2.16 (m, 1H), 2.13-2.01 (comp m, 2H), 1.84-1.66 (comp m, 6H), 1.23-1.13 (comp m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.8, 138.5, 128.6, 128.1, 127.9, 74.6, 70.9, 63.9, 58.1, 43.8, 42.0, 38.1, 37.0, 25.9, 23.6, 23.5, 19.2, 16.3; IR (thin film/NaCl) 2957 (m), 2928 (m), 2872 (m), 1707 (s), 1495 (w), 1453 (m), 1421 (w), 1378 (m), 1330 (w), 1090 (m) cm^{-1}; HRMS (FAB) *m/z* found: 315.1959 [calc'd for $C_{20}H_{27}O_3$ (M+H): 315.1959].

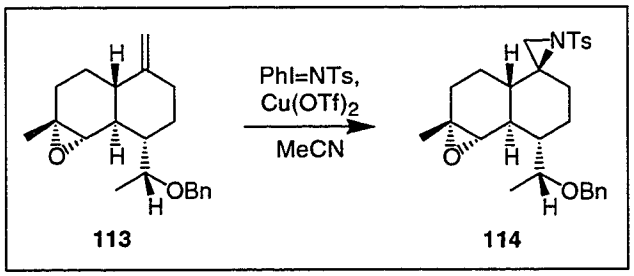
Preparation of olefin 113



Olefin 113. To a solution of epoxide **111** (1.51 g, 4.80 mmol, 1.0 equiv) in MeOH (50 mL) at rt was added NaOMe (15 mg, 0.24 mmol, 0.05 equiv). After 36 h, the solution was concentrated under reduced pressure, diluted with CH_2Cl_2 (100 mL), and washed with water (2 x 25 mL) and brine (25 mL). After drying with Na_2SO_4, concentration *in vacuo* gave a 3:2 equilibrium mixture of decalins, which could be used without further purification. A solution of DMSO (6.8 mL, 96.0 mmol, 20 equiv) in THF (20 mL) was treated with NaH (60% in mineral oil, 394 mg, 9.60 mmol, 2.0 equiv). The resulting slurry was heated at 60°C for 2 h then cooled to 25 °C before adding methyltriphenylphosphonium iodide (3.43 g, 9.60 mmol, 2.0 equiv) and THF (10 mL). The resulting yellow mixture was added in 0.1 equiv portions every 2 h to a crude

solution of decalins from **111** in THF (50 mL). After reaction was complete by TLC, it was quenched with water (50 mL) and diluted with hexanes (100 mL). The aqueous layer was separated and extracted with hexanes (2 x 25 mL) and the combined organic fractions were washed with water (3 x 50 mL), dried (Na_2SO_4), and concentrated. The resulting residue was purified by silica gel column chromatography (100% hexanes then 9:1 hexanes:EtOAc) to give **113** (1.23 g, 82% from **111**) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.16 (comp m, 5H), 4.59 (s, 1H), 4.47 (q, *J*=11.1 Hz, 1H), 4.42 (s, 1H), 3.96-3.90 (m, 1H), 2.77 (s, 1H), 2.31-2.26 (m, 1H), 2.04-1.85 (comp m, 4H), 1.63-1.43 (comp m, 3H), 1.26-1.13 (comp m, 7H), 1.08 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 139.1, 128.5, 127.6, 127.6, 104.8, 74.4, 70.5, 60.9, 58.4, 45.9, 43.6, 43.2, 35.8, 30.3, 27.3, 23.7, 22.5, 14.3; IR (thin film/NaCl) 2978 (m), 2930 (m), 2880 (m), 1648 (m), 1453 (m), 1379 (m), 1135 (m), 1101 (m), 1071 (m), 887 (m) cm^{-1}; HRMS (FAB) *m/z* found: 313.2169 [calc'd for $C_{21}H_{29}O_2$ (M+H): 313.2168].

Preparation of aziridine 114

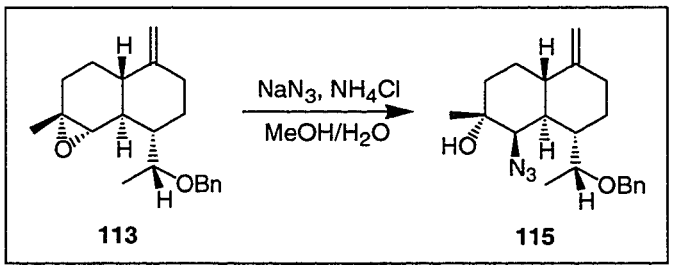


113 114

Aziridine 114. A solution of olefin **113** (60 mg, 0.192 mmol, 1.0 equiv) in dry MeCN (25 mL) with 4 Å sieves (ca. 1 g) at 25°C, was treated with *N*-tosyliminophenyliodinane (143 mg, 0.384 mmol, 2.0 equiv). After 2 minutes, $Cu(OTf)_2$ (3 mg, 0.010 mmol, 0.05 equiv) was added and the mixture was vigorously stirred for 8

h. The mixture was then diluted with EtOAc (50 mL) and filtered through a short plug of silica gel. After solvent removal *in vacuo*, the resulting residue, ca. 8:1 mixture of aziridine diastereomers, was purified by silica gel column chromatography (3:1 hexanes:EtOAc) to afford aziridine **114** (56 mg, 61% yield) as an amorphous, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J*=8.4 Hz, 2H), 7.37-7.26 (comp m, 7H), 4.56 (q, *J*=11.6 Hz, 2H), 4.05-3.98 (m, 1H), 2.85 (s, 1H), 2.53 (s, 1H), 2.44 (s, 3H), 2.36-2.30 (m, 1H), 2.25-2.16 (comp m, 3H), 2.01-1.89 (comp m, 2H), 1.67-1.18 (comp m, 12H), 0.67 (dq, *J*=4.3, 12.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 138.8, 138.2, 129.6, 128.6, 127.7, 127.7, 127.4, 74.0, 70.6, 60.2, 58.8, 54.9, 43.4, 43.0, 42.5, 36.3, 30.7, 29.9, 25.2, 23.5, 21.8, 18.6, 14.4; IR (thin film/NaCl) 2957 (m), 2927 (m), 2872 (m), 1598 (w), 1495 (w), 1452 (m), 1380 (m), 1319 (m), 1158 (m), 1093 (m) cm^{-1}; HRMS (FAB) *m/z* found: 482.2365 [calc'd for $C_{28}H_{36}NO_4S$ (M+H): 482.2365].

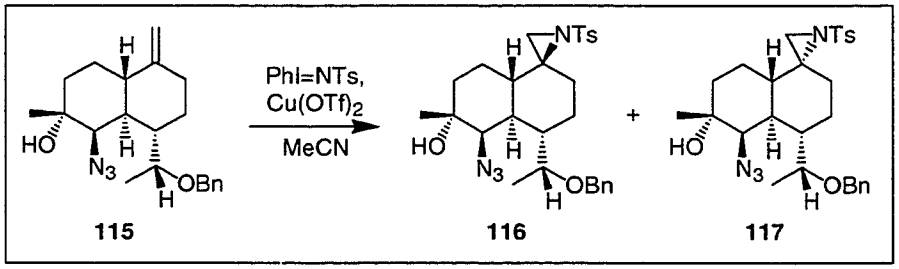
Preparation of azide 115



Azide 115. To a solution of epoxide **113** (50 mg, 0.16 mmol, 1.0 equiv) in 8:1 MeOH:H_2O (10 mL) was added NaN_3 (0 mg, 0.96 mmol, 6.0 equiv) and NH_4Cl (0 mg, 0.48 mmol, 3.0 equiv). The mixture was heated to 80°C. After 36 h, the solution was cooled to rt and diluted with EtOAc (25 mL). After washing with water (25 mL) and brine (2 x 25 mL), the organic fraction was dried with Na_2SO_4 and concentrated under

reduced pressure. Purification by silica gel column chromatography (9:1 then 3:1 hexanes:EtOAc) afforded **115** (52 mg, 92% yield) as an amorphous, white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.23 (comp m, 5H), 4.72-4.70 (m, 1H), 4.59 (d, *J*=11.8 Hz, 1H), 4.58 (s, 1H), 4.54 (d, *J*=11.8 Hz, 1H), 3.81-3.76 (m, 1H), 3.34 (s, 3H), 2.38 (dt, *J*=3.3, 12.9 Hz, 1H), 2.19-1.86 (comp m, 4H), 1.76-1.48 (comp m, 5H), 1.37-1.06 (comp m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 139.1, 128.5, 127.7, 127.6, 105.5, 74.4, 72.7, 70.7, 68.3, 44.1, 41.2, 38.4, 36.0, 33.1, 28.8, 26.4, 24.0, 14.6; IR (thin film/NaCl) 3457 (br s), 3085 (m), 2934 (s), 2527 (w), 2098 (s), 1721 (m), 1644 (s), 1496 (m), 1453 (s), 1327 (s) cm^{-1}; HRMS (FAB) *m/z* found: 328.2278 [calc'd for $C_{21}H_{30}NO_3$ (M+H-N_2): 328.2277].

Preparation of aziridines 116 and 117



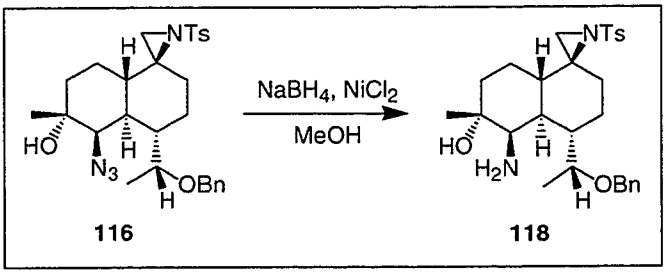
Aziridines 116 and 117. To a solution of azide **115** (80 mg, 0.225 mmol, 1.0 equiv) in dry MeCN (250 mL) with 4 Å sieves (ca. 1 g) at 25°C was added *N*-tosyliminophenyliodinane (168 mg, 0.450 mmol, 2.0 equiv). After 2 minutes, $Cu(OTf)_2$ (4 mg, 0.011 mmol, 0.05 equiv) was added and the mixture was vigorously stirred for 8 h. The mixture was then diluted with EtOAc (50 mL) and filtered through a short plug of silica gel. After solvent removal *in vacuo*, the resulting residue, ca. 8:1 mixture of aziridine diastereomers, was purified by silica gel column chromatography (3:1

hexanes:EtOAc) to afford aziridine **116** (68 mg, 58% yield) as an amorphous, white solid. Mixed fractions were analyzed by HPLC to give an analytical sample of **117** (5 mg, 4% yield) as an amorphous, white solid.

Aziridine 116. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J*=8.3 Hz, 2H), 7.39-7.26 (comp m, 7H), 4.56 (d, *J*=3.6 Hz, 2H), 3.80-3.73 (m, 1H), 3.36 (br s, 1H), 2.52 (s, 1H), 2.44 (s, 3H), 2.38 (br s, 1H), 2.34-2.06 (comp m, 4H), 1.94 (dt, *J*=3.4, 12.0 Hz, 1H), 1.74 (dt, *J*=2.5, 11.1 Hz, 1H), 1.65-1.45 (comp m, 3H), 1.41-1.12 (comp m, 9H), 0.92 (dq, *J*=3.9, 13.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 138.8, 138.4, 129.6, 128.6, 127.8, 127.7, 127.4, 74.2, 72.4, 70.8, 68.1, 55.1, 42.0, 40.6, 37.8, 36.5, 32.6, 31.1, 28.9, 24.3, 21.7, 20.2, 14.7; IR (thin film/NaCl) 3507 (br m), 2934 (m), 2871 (m), 2100 (s), 1707 (w), 1598 (w), 1496 (w), 1453 (m), 1314 (m), 1156 (m) cm^{-1}; HRMS (FAB) *m/z* found: 525.2538 [calc'd for $C_{28}H_{37}N_4O_4S$ (M+H): 525.2536].

Aziridine 117. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J*=8.3 Hz, 2H), 7.31-7.18 (comp m, 7H), 4.48 (s, 2H), 3.71-3.66 (m, 1H), 3.28 (s, 1H), 2.41 (s, 1H), 2.40-2.33 (comp m, 4H), 2.32 (s, 1H), 2.05-1.89 (comp m, 2H), 1.85-1.72 (comp m, 2H), 1.70-1.49 (comp m, 3H), 1.40-1.18 (comp m, 6H), 1.02-0.94 (comp m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 139.0, 137.9, 129.6, 128.5, 127.7, 127.7, 127.6, 74.3, 72.1, 70.6, 68.1, 56.4, 41.0, 40.6, 37.7, 36.0, 32.1, 30.1, 28.7, 22.7, 21.7, 19.7, 14.3; IR (thin film/NaCl) 3501 (br w), 2929 (m), 2872 (m), 2098 (m), 1597 (w), 1496 (w), 1453 (m), 1376 (m), 1304 (m), 1155 (m) cm^{-1}; HRMS (FAB) *m/z* found: 525.2538 [calc'd for $C_{28}H_{37}N_4O_4S$ (M+H): 525.2536].

Preparation of amine 118

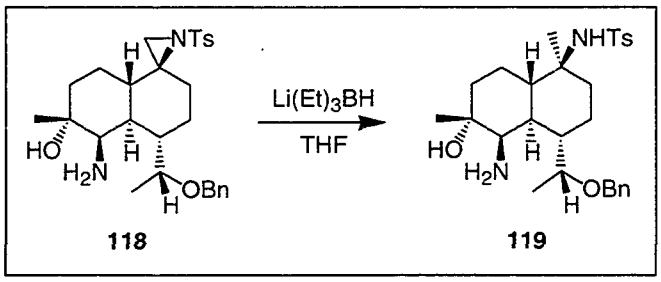


116 **118**

Amine 118. A solution of aziridine **116** (25 mg, 0.048 mmol, 1.0 equiv) in 3:1 MeOH/THF (3 mL) at 0°C was treated with $NiCl_2 \cdot 6H_2O$ (34 mg, 0.143 mmol, 3.0 equiv) followed by portionwise addition of $NaBH_4$ (11 mg, 0.286 mmol, 6.0 equiv) over 10 minutes. After 30 minutes the black mixture was allowed to warm to 25°C, diluted with EtOAc (10 mL), and filtered through a celite plug. The solution was further diluted with EtOAc (10 mL) and washed with a 0.01M EDTA solution (25 mL, pH 7.5, K-phosphate buffer) and brine (2 x 10 mL). After removing the solvent *in vacuo*, the resulting oil was purified by silica gel column chromatography (100% EtOAc, then 12:1 EtOAc: MeOH) to give **118** (22 mg, 93% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J*=8.2 Hz, 2H), 7.38-7.26 (comp m, 7H), 4.57 (d, *J*=12.0 Hz, 1H), 4.52 (d, *J*=12.0 Hz, 1H), 3.74-3.68 (m, 1H), 2.61 (br s, 1H), 2.52 (s, 1H), 2.45-2.41 (comp m, 4H), 2.33-2.27 (m, 1H), 2.19-2.10 (comp m, 2H), 2.02-1.91 (comp m, 2H), 1.73-1.58 (comp m, 2H), 1.52-1.46 (m, 1H), 1.38-1.20 (comp m, 6H), 1.11 (d, *J*=6.1 Hz, 3H), 1.03-0.93 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.7, 139.1, 138.4, 129.6, 128.5, 127.7, 127.7, 127.3, 73.5, 72.2, 70.5, 55.7, 55.6, 41.7, 40.4, 37.1, 36.9, 31.8, 31.4, 28.9, 24.4, 21.7, 20.4, 14.4; IR (thin film/NaCl) 3515 (br w), 2926 (m), 2869 (m), 1598 (w), 1495 (w), 1453 (w),

1381 (m), 1315 (m), 1156 (m) 1098 (m) cm^{-1}; HRMS (FAB) *m/z* found: 499.2631 [calc'd for $C_{28}H_{39}N_2O_4S$ (M+H): 499.2631].

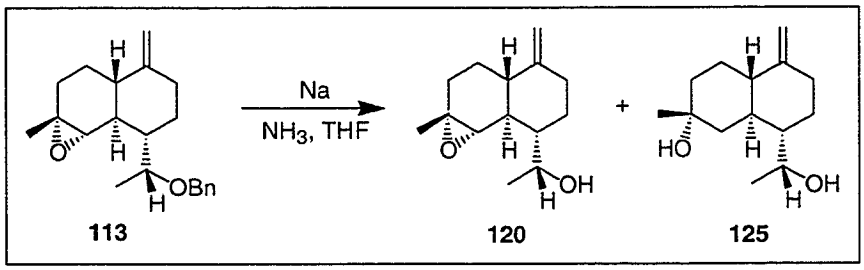
Preparation of amine 119



Amine 119. To a solution of amine **118** (40 mg, 0.080 mmol, 1.0 equiv) in THF (5 mL) at 0°C was added a 1M solution of $Li(Et)_3BH$ in THF (240 μL, 0.240 mmol, 3.0 equiv). The reaction mixture was stirred at 0°C for 1 h before warming to rt for an additional 2 h. The mixture was then cooled to 0°C and diluted with EtOAc (20 mL) and H_2O (15 mL). The organic layer was separated, washed with brine (2 x 20 mL), and dried with Na_2SO_4. After removing the solvent *in vacuo*, the resulting residue was purified by silica gel column chromatography (100% EtOAc then 5:1 EtOAc:MeCN) to afford **119** (30 mg, 75% yield) as a white foam. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J*=8.1 Hz, 2H), 7.35-7.26 (comp m, 7H), 4.68 (br s, 1H), 4.52 (d, *J*=12.1 Hz, 1H), 4.45 (d, *J*=12.3 Hz, 1H), 3.68-3.60 (m, 1H), 2.51 (br s, 1H), 2.42 (s, 3H), 1.83-1.28 (comp m, 10H), 1.18 (s, 3H), 1.16-1.09 (comp m, 4H), 1.06 (d, *J*=6.5 Hz, 3H), 1.00-0.75 (comp m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 140.9, 139.0, 129.6, 128.5, 127.7, 127.1, 77.4, 73.7, 72.2, 70.4, 60.7, 55.7, 41.9, 40.4, 39.2, 38.4, 32.4, 28.9, 21.6, 21.1, 20.6, 19.6, 14.3; IR (thin film/NaCl) 3368 (br w), 3277 (m), 2938 (m), 2874 (m), 1598 (m), 1496 (m), 1453 (m), 1384 (m), 1154 (m), 1092 (m) cm^{-1}; HRMS (FAB) *m/z* found: 501.2785

[calc'd for $C_{28}H_{41}N_2O_4S$ (M+H): 501.2787].

Preparation of alcohols 120 and 125

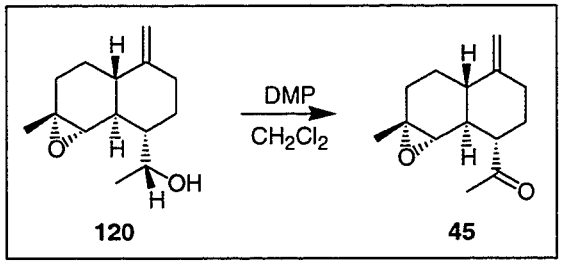


Alcohols 120 and 125. To condensed ammonia (40 mL) at –78°C was added sodium (368 mg, 16 mmol, 10.0 equiv) followed by **113** (500 mg, 1.60 mmol, 1.0 equiv), which was contaminated with ca. 1% of the corresponding *cis*-decalin, in THF (4 mL). After 1 h, the reaction was quenched with solid ammonium chloride and the ammonia allowed to evaporate. The resulting residue was taken up in EtOAc (50 mL), washed with water (2 x 25 mL), brine (25 mL) and dried with Na_2SO_4. After concentration, the resulting oil was purified by silica gel column chromatography (3:1 then 1:1 hexanes:EtOAc) to afford **120** (324 mg, 91%) and **125** (7 mg, 2%) as a white solid.

Alcohol 120. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (s, 1H), 4.50 (s, 1H), 4.38-4.32 (m, 1H), 2.98 (s, 1H), 2.40-2.34 (m, 1H), 2.12-1.95 (comp m, 3H), 1.83-1.76 (m, 1H), 1.71-1.51 (comp m, 4H), 1.32-1.12 (comp m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 104.9, 67.3, 60.9, 58.4, 46.1, 45.8, 43.5, 35.6, 30.2, 26.8, 23.7, 22.4, 17.7; IR (thin film/NaCl) 3437 (br m), 2975 (m), 2931 (m), 2878 (m), 1649 (m), 1447 (m), 1422 (w), 1379 (m), 1100 (m), 888 (m) cm^{-1}; HRMS (FAB) *m/z* found: 223.1699 [calc'd for $C_{14}H_{23}O_2$ (M+H): 223.1698].

Alcohol 125. m.p. 154-156°C (recrystallized from 3:1 hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (s, 1H), 4.60 (s, 1H), 4.16-4.09 (m, 1H), 2.43 (dt, *J*=3.3, 12.8 Hz, 1H), 2.08-1.93 (comp m, 2H), 1.82-1.38 (comp m, 8H), 1.33-1.02 (comp m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3, 104.8, 69.6, 67.2, 49.0, 45.8, 43.1, 41.2, 38.2, 36.2, 31.8, 25.9, 24.4, 16.8; IR (thin film/NaCl) 3372 (m), 3081 (w), 2964 (m), 2929 (m), 2845 (m), 1644 (m), 1443 (m), 1374 (m), 1309 (w), 1264 (w) cm^{-1}; HRMS (FAB) *m/z* found: 206.1668 [calc'd for $C_{14}H_{22}O$ (M+-H_2O): 206.1671].

Preparation of ketone 45

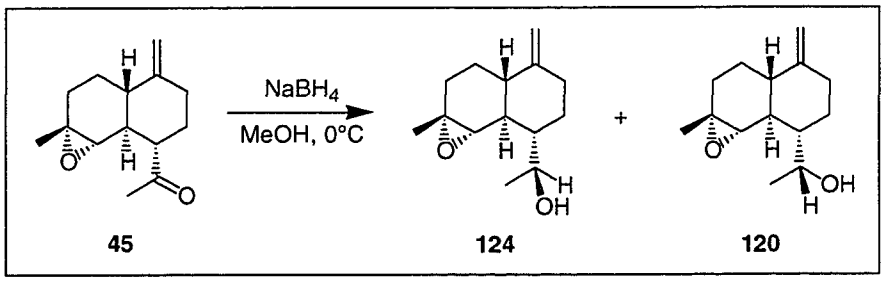


120 **45**

Ketone 45. A solution of alcohol **120** (300 mg, 1.35 mmol, 1.0 equiv) in undistilled CH_2Cl_2 (20 mL) was treated with Dess-Martin periodinane (744 mg, 1.76 mmol, 1.3 equiv) and the mixture was stirred at 0°C for 2 h. Saturated aqueous $NaHCO_3$ (5 mL) and $Na_2S_2O_3$ (5 mL) were then added. After 30 min, the organic layer was separated and dried with Na_2SO_4. Concentration *in vacuo* gave a residue which was purified by silica gel column chromatography (9:1 then 3:1 hexanes:EtOAc) to afford ketone **45** (253 mg, 85% yield) as a white, amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (d, *J*=1.1 Hz, 1H), 4.57 (d, *J*=1.1 Hz, 1H), 2.57 (dt, *J*=12.0, 3.4 Hz, 1H), 2.50 (s, 1H), 2.44-2.39 (m, 1H), 2.21 (s, 3H), 2.15-2.00 (comp m, 3H), 1.78 (t, *J*=12.0 Hz, 1H), 1.72-1.57 (comp m, 2H), 1.53-1.42 (comp m, 2H), 1.36 (dt, *J*=4.6, 11.7 Hz,

1H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.4, 149.9, 106.2, 61.9, 58.3, 56.2, 44.8, 42.8, 35.4, 31.7, 30.3, 27.9, 23.4, 22.0; IR (thin film/NaCl) 2973 (w), 2932 (m), 2887 (w), 2853 (w), 1706 (m), 1650 (w), 1440 (w), 1424 (w), 1374 (w), 1183 (w) cm^{-1}; HRMS (FAB) *m/z* found: 221.1543 [calc'd for $C_{14}H_{21}O_2$ (M+H): 221.1542].

Preparation of alcohols 124 and 120

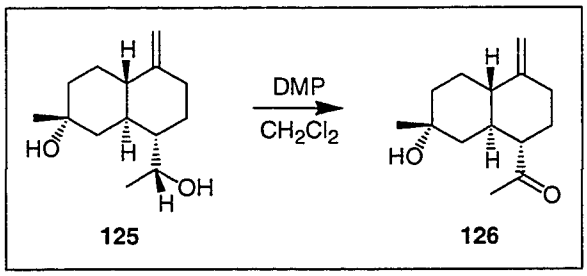


Alcohols 124 and 120. To a solution of **45** (15 mg, 0.068 mmol, 1.0 equiv) in MeOH (5 mL) at 0°C was added $NaBH_4$ (8 mg, 0.204 mmol, 3.0 equiv) in one portion. After 30 min, EtOAc (25 mL) was added and the mixture was washed with water (25 mL), brine (25 mL), and dried with Na_2SO_4. Following concentration under reduced pressure, NMR analysis of the crude residue revealed a mixture of alcohols in the ratio of ca. 91:9. Following purification of the mixture by silica gel column chromatography (3:1 hexanes:EtOAc), the major compound was revealed to be **alcohol 124** (19 mg, 77%), a colorless oil, and the minor compound was identical with material obtained from benzyl deprotection of **113** and was determined to be **120**.

Alcohol 124. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (s, 1H), 4.50 (s, 1H), 4.30-4.22 (m, 1H), 3.17 (s, 1H), 2.39-2.33 (m, 1H), 2.14-1.97 (comp m, 2H), 1.90-1.82 (m, 1H), 1.71-1.43 (comp m, 6H), 1.40-1.21 (comp m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 104.9, 67.3, 61.2, 58.6, 45.7, 44.6, 43.3, 35.7, 30.3, 27.7, 23.8, 22.6, 20.5; IR (thin

film/NaCl) 3440 (s), 2974 (s), 2932 (s), 1649 (m), 1448 (m), 1422 (w), 1378 (m), 1134 (w), 1011 (w), 887 (s) cm^{-1}; HRMS (FAB) *m/z* found: 223.1698 [calc'd for $C_{14}H_{23}O_2$ (M+H): 223.1698].

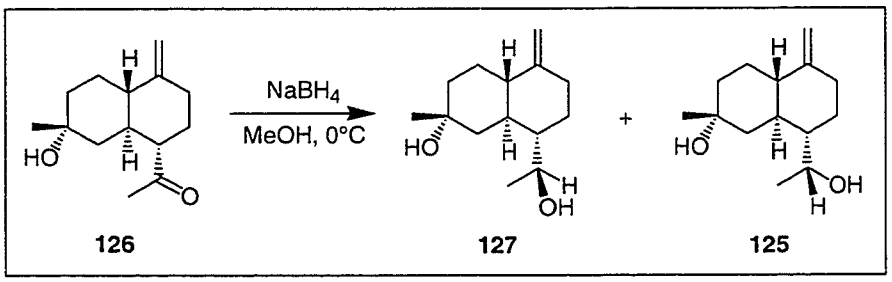
Preparation of ketone 126



125 **126**

Ketone 126. A solution of **125** (20 mg, 0.089 mmol, 1.0 equiv) in undistilled CH_2Cl_2 (10 mL) at 0°C was treated with Dess-Martin periodinane (45 mg, 0.107 mmol, 1.2 equiv). After ca. 2 h, saturated aqueous $NaHCO_3$ (5 mL) and $Na_2S_2O_3$ (5 mL) were added and the mixture was stirred for 10 min before the organic layer was separated and dried with Na_2SO_4. Concentration *in vacuo* gave a residue which was purified by silica gel column chromatography (9:1 then 3:1 hexanes:EtOAc) to afford ketone **126** (18 mg, 89% yield) as a white solid. m.p. 99.0-100.0°C (recrystallized from hexanes/EtOAc) ^1H NMR (400 MHz, $CDCl_3$) δ 4.73 (s, 1H), 4.65 (s, 1H), 2.42 (ddd, *J*=2.7, 3.7, 13.1 Hz, 1H), 2.31 (ddd, *J*=3.5, 11.2, 12.3 Hz, 1H), 2.11 (s, 3H), 2.11-2.03 (m, 1H), 1.96-1.89 (m, 1H), 1.83-1.63 (comp m, 4H), 1.60-1.23 (comp m, 5H), 1.19 (s, 3H), 1.12 (dd, *J*=12.1, 13.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3, 150.3, 106.0, 69.4, 58.5, 44.9, 44.4, 40.3, 38.2, 35.8, 31.6, 31.2, 28.5, 24.2; IR (thin film/NaCl) 3450 (br m), 3083 (w), 2929 (s), 2861 (m), 1701 (s), 1646 (m), 1443 (m), 1363 (m), 1243 (m), 1135 (m) cm^{-1}; HRMS (FAB) *m/z* found: 205.1593 [calc'd for $C_{14}H_{21}O$ (M-OH): 205.1591].

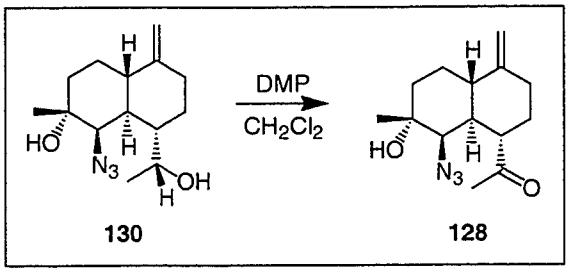
Preparation of alcohols 127 and 125



Alcohols 127 and 125. To a solution of **126** (15 mg, 0.067 mmol, 1.0 equiv) in MeOH (5 mL) at 0°C was added $NaBH_4$ (8 mg, 0.202 mmol, 3.0 equiv) in one portion. After 30 min, EtOAc (25 mL) was added and the mixture was washed with water (25 mL), brine (25 mL), and dried with Na_2SO_4. Following concentration under reduced pressure, NMR analysis of the crude residue revealed a mixture of alcohols in the ratio of ca. 90:10. Following purification of the mixture by silica gel column chromatography (3:1 hexanes:EtOAc), the major compound was revealed to be alcohol **127** (11 mg, 75%), a colorless oil, and the minor compound was identical with material obtained from treatment of **120** with $LiAlH_4$ or over-reduction of **113** and was determined to be **125**.

Alcohol 127. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (br s, 1H), 4.60 (br s, 1H), 4.16-4.09 (m, 1H), 3.49 (d, *J*=5.4 Hz, 0.6H), 2.42 (dt, *J*=3.2, 13.0 Hz, 1H), 2.08-1.93 (comp m, 2H), 1.82-1.39 (comp m, 8H), 1.27-1.08 (comp m, 6H), 1.05 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 104.8, 69.6, 67.2, 48.9, 45.7, 43.0, 41.2, 38.2, 36.2, 31.8, 25.9, 24.4, 16.8; IR (thin film/NaCl) 3360 (br m), 2963 (w), 2929 (m), 2847 (w), 1644 (w), 1455 (w), 1373 (m), 1140 (w) cm^{-1}; HRMS (FAB) *m/z* found: 206.1671 [calc'd for $C_{14}H_{22}O$ (M+-H_2O): 206.1671].

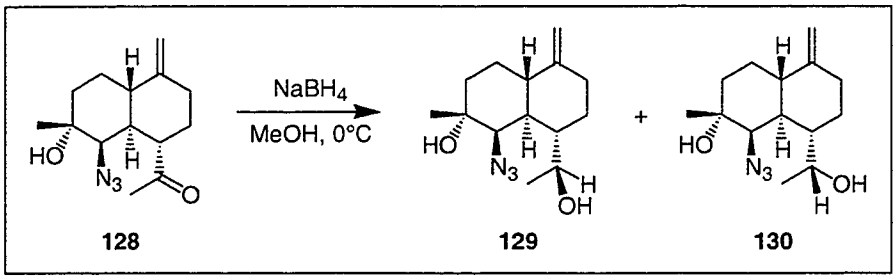
Preparation of ketone 128



130 128

Ketone 128. To a solution of **130** (46 mg, 0.175 mmol, 1.0 equiv) in undistilled CH_2Cl_2 (10 mL) at 0°C was added Dess-Martin periodinane (96 mg, 0.228 mmol, 1.3 equiv). After ca. 2 h, saturated aqueous $NaHCO_3$ (5 mL) and $Na_2S_2O_3$ (5 mL) were added and the mixture was stirred for 10 min before the organic layer was separated and dried with Na_2SO_4. Concentration *in vacuo* gave a residue which was purified by silica gel column chromatography (9:1 then 3:1 hexanes:EtOAc) to afford ketone **128** (41 mg, 88% yield) as a white, amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (s, 1H), 4.63 (s, 1H), 3.20 (br s, 1H), 2.90-2.81 (m, 1H), 2.44-2.37 (m, 1H), 2.23-2.15 (comp m, 4H), 2.12-2.02 (comp m, 2H), 1.91-1.82 (m, 1H), 1.79-1.74 (m, 1H), 1.66-1.53 (comp m, 4H), 1.39-1.28 (comp m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.8, 150.0, 106.8, 72.4, 69.9, 53.3, 42.8, 37.4, 35.8, 32.8, 31.3, 29.3, 28.8, 23.6; IR (thin film/NaCl) 3445 (br m), 2934 (m), 2861 (m), 2100 (s), 1706 (s), 1646 (m), 1450 (m), 1370 (m), 1281 (m), 1055 (m) cm^{-1}; HRMS (FAB) *m/z* found: 264.1712 [calc'd for $C_{14}H_{22}N_3O_2$ (M+H): 264.1712].

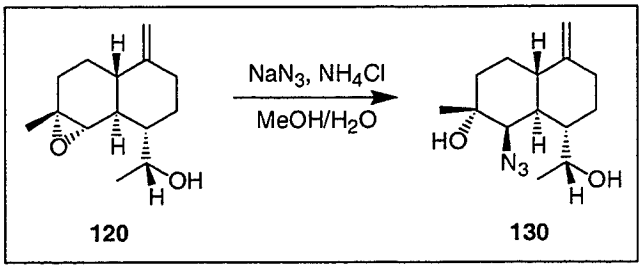
Preparation of alcohols 129 and 130



Alcohols 129 and 130. To a solution of **128** (15 mg, 0.057 mmol, 1.0 equiv) in MeOH (5 mL) at 0°C was added $NaBH_4$ (6 mg, 0.171 mmol, 3.0 equiv) in one portion. After 30 min, EtOAc (25 mL) was added and the mixture was washed with water (25 mL), brine (25 mL), and dried with Na_2SO_4. Following concentration under reduced pressure, NMR analysis of the crude residue revealed a mixture of alcohols in the ratio of ca. 4:1. Following purification of the mixture by silica gel column chromatography (3:1 hexanes:EtOAc), the major compound was an amorphous white solid which was revealed to be alcohol **129** (11 mg, 76%). The minor compound, **130**, was identical with material obtained from treatment of **120** with NaN_3.

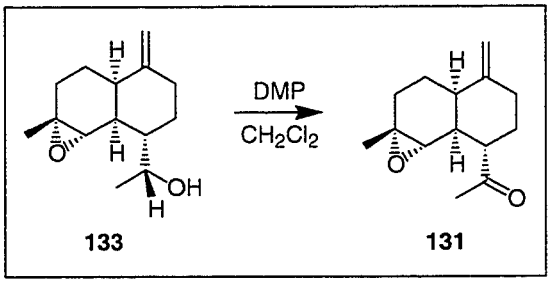
Alcohol 129. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.70 (s, 1H), 4.58 (s, 1H), 4.14-4.07 (m, 1H), 3.72 (s, 1H), 2.40-2.35 (m, 1H), 2.08-1.83 (comp m, 6H), 1.74-1.51 (comp m, 5H), 1.36 (s, 3H), 1.27-1.22 (comp m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 105.6, 72.9, 68.3, 66.9, 44.0, 42.8, 38.1, 35.9, 32.9, 29.0, 26.8, 24.1, 20.5; IR (thin film/NaCl) 3272 (br m), 2972 (m), 2924 (m), 2113 (s), 1646 (w), 1445 (w), 1351 (m), 1284 (m), 1188 (w), 1136 (m) cm^{-1}; HRMS (EI) *m/z* found: 229.1579 [calc'd for $C_{14}H_{19}N_3$ (M+-$2H_2O$): 229.1579].

Preparation of azide 130



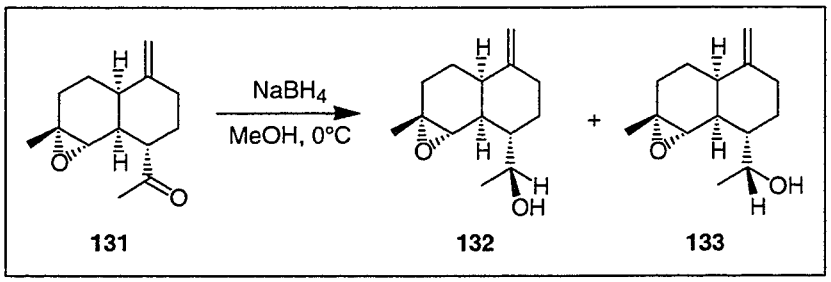
Azide 130. To a solution of olefin **120** (40 mg, 0.180 mmol, 1.0 equiv) in 8:1 MeOH:H_2O (10 mL) was added NaN_3 (70 mg, 1.08 mmol, 6.0 equiv) and NH_4Cl (29 mg, 0.540 mmol, 3.0 equiv). The mixture was heated to 80°C. After 36 h, the solution was diluted with EtOAc (50 mL), washed with water (25 mL), brine (25 mL), and dried with Na_2SO_4. Removal of the solvent in vacuo a residue which was purified by silica gel column chromatography (3:1 hexanes:EtOAc) to afford azide **130** (46 mg, 97% yield) as an amorphous, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (br s, 1H), 4.61 (br s, 1H), 4.15-4.07 (m, 1H), 3.52 (s, 1H), 2.44-2.38 (m, 1H), 2.08-1.89 (comp m, 4H), 1.80-1.50 (comp m, 5H), 1.39 (s, 3H), 1.35-1.31 (comp m, 2H), 1.19-1.14 (comp m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 105.6, 72.7, 68.5, 67.8, 44.9, 44.6, 38.3, 35.9, 33.0, 29.0, 26.5, 24.0, 18.2; IR (thin film/NaCl) 3270 (br m), 2887 (m), 2111 (s), 1642 (m), 1377 (w), 1328 (m), 1312 (m), 1282 (m), 1137 (w), 1076 (w) cm^{-1}; HRMS (EI) *m/z* found: 229.1579 [calc'd for $C_{14}H_{19}N_3$ (M+-2H_2O): 229.1579].

Preparation of ketone 131



Ketone 131. A solution of **133** (10 mg, 0.045 mmol, 1.0 equiv) in undistilled CH_2Cl_2 (10 mL) at 0°C was treated with Dess-Martin periodinane (23 mg, 0.054 mmol, 1.2 equiv). After ca. 2 h, saturated aqueous $NaHCO_3$ (5 mL) and $Na_2S_2O_3$ (5 mL) were added and the mixture was stirred for 10 min before the organic layer was separated and dried with Na_2SO_4. Concentration *in vacuo* gave a residue which was purified by silica gel column chromatography (9:1 then 3:1 hexanes:EtOAc) to afford ketone **131** (8 mg, 81% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (s, 1H), 4.53 (s, 1H), 2.88-2.76 (comp m, 2H), 2.43-2.36 (m, 1H), 2.23 (s, 3H), 2.14-2.03 (comp m, 2H), 1.90-1.82 (comp m, 4H), 1.68-1.61 (m, 1H), 1.43-1.19 (comp m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.9, 150.5, 105.4, 62.3, 58.8, 53.1, 44.1, 36.8, 35.7, 31.6, 30.5, 28.7, 24.7, 24.4; IR (thin film/NaCl) 3081 (w), 2933 (s), 2861 (m), 1711 (s), 1648 (m), 1443 (m), 1426 (m), 1378 (m), 1364 (m), 1183 (m) cm^{-1}; HRMS (FAB) *m/z* found: 221.1542 [calc'd for $C_{14}H_{21}O_2$ (M+H): 221.1542].

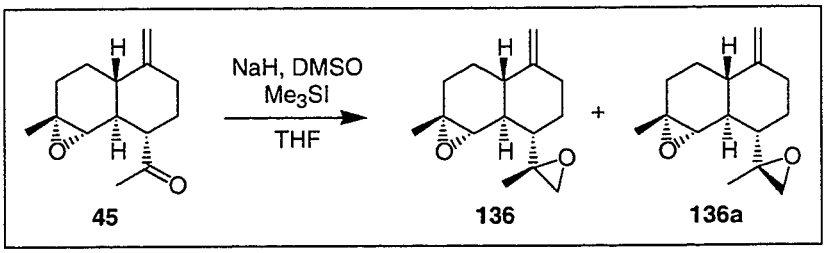
Preparation of alcohols 132 and 133



Alcohols 132 and 133. To a solution of **131** (15 mg, 0.068 mmol, 1.0 equiv) in MeOH (5 mL) at 0°C was added $NaBH_4$ (8 mg, 0.204 mmol, 3.0 equiv) in one portion. After 30 min, EtOAc (25 mL) was added and the mixture was washed with water (25 mL), brine (25 mL), and dried with Na_2SO_4. Following concentration under reduced pressure, NMR analysis of the crude residue revealed a mixture of alcohols in the ratio of ca. 55:45. Following purification of the mixture by silica gel column chromatography (3:1 hexanes:EtOAc), the major compound was a colorless oil which was revealed to be alcohol **132** (7 mg, 49%). The minor compound, **133**, was identical with material obtained from benzyl deprotection of the corresponding benzyl ether.

Alcohol 132. ^1H NMR (400 MHz, $CDCl_3$) δ 4.67 (br s, 1H), 4.50 (br s, 1H), 4.36-4.28 (m, 1H), 3.00 (br s, 1H), 2.39 (ddd, *J*=2.1, 4.3, 12.3 Hz, 1H), 2.08-1.98 (comp m, 2H), 1.91-1.80 (comp m, 4H), 1.68-1.62 (m, 1H), 1.42 (br s, 1H), 1.34-1.16 (comp m, 6H), 1.15 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5, 104.3, 67.7, 61.3, 59.2, 46.0, 45.8, 38.6, 35.9, 28.8, 27.1, 25.0, 24.7, 17.7; IR (thin film/NaCl) 3431 (br m), 2973 (m), 2932 (m), 2867 (m), 1647 (m), 1443 (m), 1378 (m), 1302 (w), 1136 (w), 1062 (m) cm^{-1}; HRMS (FAB) *m/z* found: 223.1698 [calc'd for $C_{14}H_{23}O_2$ (M+H): 223.1698].

Preparation of epoxides 136 and 136a



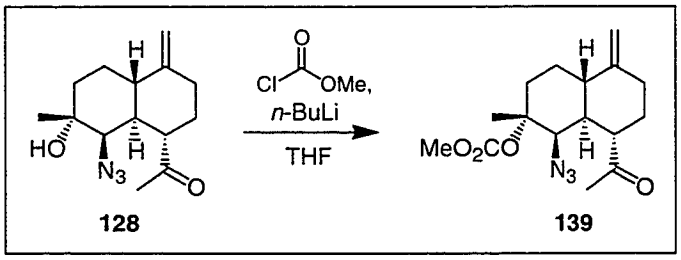
Epoxides 136 and 136a. A solution of DMSO (129 μL, 1.81 mmol, 20 equiv) in THF (3 mL) was treated with NaH (60% in mineral oil, 18 mg, 0.454 mmol, 5.0 equiv). The resulting slurry was heated at 60°C for 2 h then cooled to rt before adding trimethylsulfonium iodide (94 mg, 0.462 mmol, 5.1 equiv). After 30 min, a solution of ketone **45** (20 mg, 0.091 mmol, 1.0 equiv) in THF (1 mL) was added. After the reaction was complete by TLC, it was quenched with water (10 mL) and diluted with EtOAc (20 mL). The aqueous layer was separated and extracted with EtOAc (10 mL) and the combined organic fractions were washed with brine (25 mL), dried with Na_2SO_4, and concentrated. The resulting residue was purified by silica gel column chromatography (9:1 then 3:1 hexanes:EtOAc) to give **136** (14 mg, 65%) as a white solid and **136a** (4 mg, 21%) as a colorless oil.

Epoxide 136. m. p. 141-142°C (recrystallized from 3:1 hexanes:EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 4.68 (s, 1H), 4.53 (s, 1H), 3.35 (s, 1H), 2.58 (d, *J*=5.1 Hz, 1H), 2.52 (d, *J*=5.3 Hz, 1H), 2.36 (ddd, *J*=1.8, 2.4, 12.8 Hz, 1H), 2.13-1.99 (comp m, 2H), 1.86-1.81 (m, 1H), 1.67 (ddd, *J*=2.4, 5.4, 12.4 Hz, 1H), 1.61-1.56 (m, 1H), 1.52-1.30 (comp m, 10H), 1.26-1.89 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 105.4, 60.5, 59.1, 58.6, 52.4, 48.4, 45.7, 43.2, 35.8, 32.2, 30.4, 23.6, 22.2, 17.1; IR (thin film/NaCl) 2979 (m), 2930 (m), 2882 (m), 1649 (m), 1449 (m), 1426 (w), 1394 (m), 1378

(m), 1095 (w), 886 (m) cm^{-1}; HRMS (FAB) *m/z* found: 235.1697 [calc'd for $C_{15}H_{23}O_2$ (M+H): 235.1698].

Epoxide 136a. ^1H NMR (400 MHz, $CDCl_3$) δ 4.70 (s, 1H), 4.53 (s, 1H), 2.97 (s, 1H), 2.79 (d, *J*=5.1 Hz, 1H), 2.71 (d, *J*=5.1 Hz, 1H), 2.43-2.35 (m, 1H), 2.15-1.96 (comp m, 3H), 1.74-1.21 (comp m, 13H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 105.4, 60.5, 58.5, 57.9, 57.0, 47.7, 46.1, 43.4, 35.6, 30.4, 30.2, 23.5, 22.2, 16.8; IR (thin film/NaCl) 2980 (w), 2932 (m), 2881 (w), 1650 (w), 1449 (w), 1378 (w), 1075 (w), 886 (w) cm^{-1}; HRMS (FAB) *m/z* found: 235.1697 [calc'd for $C_{15}H_{23}O_2$ (M+H): 235.1698].

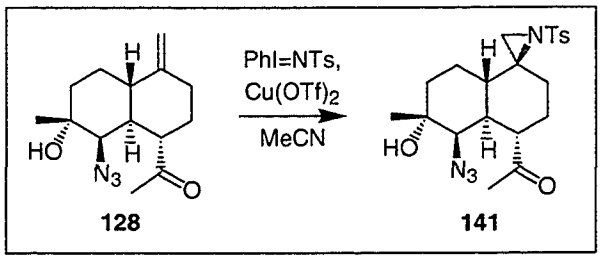
Preparation of carbonate 139



Carbonate 139. A solution of **128** (9 mg, 0.034 mmol, 1.0 equiv) in THF (4 mL) at –78°C was added *n*-BuLi (2.5 M in hexanes, 15 μL, 0.038 mmol. 1.1 equiv). After 10 min, methyl chloroformate (8 μL, 0.103 mmol, 3 equiv) was added and the solution was warmed to rt. Concentration *in vacuo* gave a residue which was purified by silica gel column chromatography (9:1 then 3:1 hexanes:EtOAc) to afford **139** (6 mg, 55%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 4.75 (s, 1H), 4.62(s, 1H), 3.90 (br s, 1H), 3.76 (s, 3H), 2.86-2.79 (m, 1H), 2.43-2.38 (m, 1H), 2.19 (s, 3H), 2.18-1.91 (comp m, 5H), 1.69-1.48 (comp m, 5H), 1.42-1.25 (comp m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 153.7, 149.7, 106.9, 83.7, 66.1, 54.6, 53.3, 42.9, 37.2, 35.6, 31.1, 30.8, 28.8, 23.5,

23.1; IR (thin film/NaCl) 2934 (m), 2859 (m), 2106 (s), 1747 (s), 1710 (m), 1646 (m), 1441 (m), 1367 (m), 1260 (s), 1098 (m) cm^{-1}; HRMS (ESI) *m/z* found: 344.1577 [calc'd for $C_{16}H_{23}NaN_3O_4$ (M+Na): 344.1586].

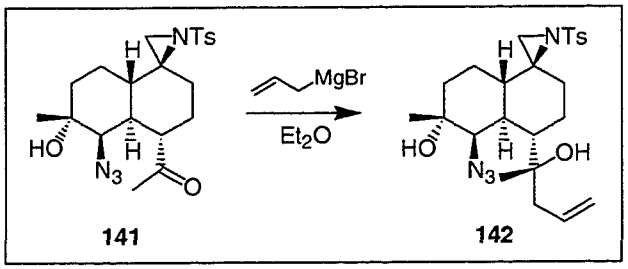
Preparation of aziridine 141



Aziridine 141. To a solution of azide **128** (200 mg, 0.759 mmol, 1.0 equiv) in dry MeCN (25 mL) with 4 Å sieves (ca. 1 g) at 25°C, was added *N*-tosyliminophenyliodinane (0.567 g, 1.52 mmol, 2.0 equiv). After 2 minutes, $Cu(tfa)_2$ (14 mg, 0.038 mmol, 0.05 equiv) was added and the mixture was vigorously stirred for 8 h. The mixture was then diluted with EtOAc (50 mL) and filtered through a short plug of silica gel. After removing the solvent *in vacuo*, the resulting residue, ca. 5:1 mixture of aziridine diastereomers, was purified by silica gel column chromatography (3:1 then 1:1 hexanes:EtOAc) to afford aziridine **141** (213 mg, 65% yield) as a white solid. m.p. 193.0-194.5°C (recrystallized from 1:1 hexanes:EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J*=8.4 Hz, 2H), 7.31 (d, *J*=8.1 Hz, 2H), 3.19 (s, 1H), 2.86 (m, 1H), 2.52-2.17 (comp m, 12H), 1.98-1.89 (m, 1H), 1.59-1.37 (comp m, 5H), 1.30 (s, 3H), 1.04-0.94 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.3, 144.0, 138.1, 129.6, 127.4, 72.1, 69.8, 54.0, 52.1, 40.8, 36.8, 36.5, 32.2, 31.0, 29.8, 29.3, 28.7, 21.7, 19.8; IR (thin film/NaCl) 3503 (m), 3064 (w), 2938 (m), 2872 (m), 2101 (s), 1708 (s), 1598 (m), 1495 (m), 1451 (m),

1372 (m) cm^{-1}; HRMS (FAB) *m/z* found: 433.1905 [calc'd for $C_{21}H_{29}N_4O_4S$ (M+H): 433.1903].

Preparation of alcohol 142

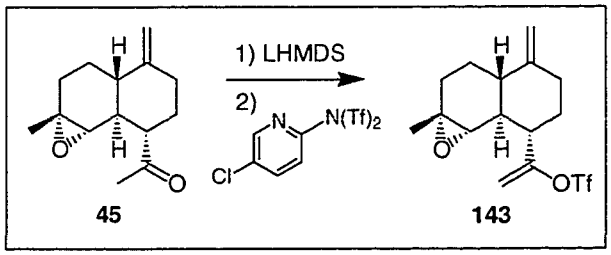


141 142

Alcohol 142. A solution of **141** (20 mg, 0.046 mmol, 1.0 equiv) in Et_2O (2 mL) at 0°C was treated with allyl magnesium bromide (1.0 M in THF, 138 μL, 0.138 mmol, 3.0 equiv). After 1 h, the solution was warmed to rt for an additional 2 h. The reaction was quenched with aqueous ammonium chloride (5 mL) and diluted with Et_2O (10 mL). The organic layer was washed with brine (25 mL) and dried with Na_2SO_4. After the solvent was removed *in vacuo*, the residue was purified by silica gel column chromatography (9:1 then 3:1 hexanes:EtOAc) to afford **142** (6 mg, 27%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J*=8.2 Hz, 2H), 7.29 (d, *J*=7.7 Hz, 2H), 5.94-5.85 (m, 1H), 5.32-5.19 (comp m, 2H), 4.30 (br s, 1H), 2.50-2.36 (comp m, 6H), 2.27-2.20 (m, 1H), 2.19-2.08 (comp m, 2H), 2.05-1.86 (comp m, 4H), 1.77-1.70 (m, 1H), 1.65-1.45 (comp m, 3H), 1.37-1.28 (comp m, 4H), 1.20-1.09 (comp m, 4H), 0.98-0.87 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 138.4, 132.7, 129.6, 127.3, 121.2, 74.6, 72.8, 69.5, 55.1, 47.6, 45.3, 41.9, 37.4, 36.6, 32.5, 31.1, 29.1, 28.2, 22.4, 21.7, 20.7; IR (thin film/NaCl) 3510 (m), 3071 (w), 2971 (m), 2935 (m), 2873 (m), 2107 (s), 1638 (w), 1598

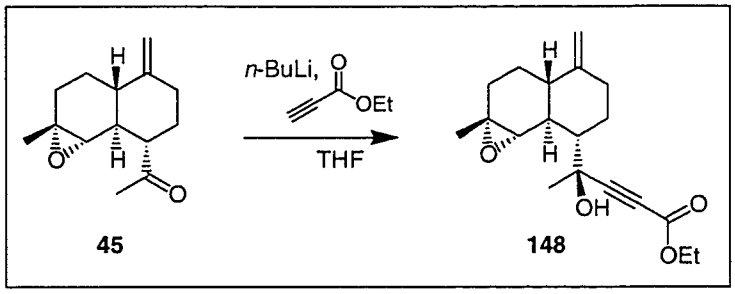
(w), 1451 (m), 1382 (m) cm^{-1}; HRMS (FAB) *m/z* found: 475.2378 [calc'd for $C_{24}H_{35}N_4O_4S$ (M+H): 475.2379].

Preparation of enol-triflate 143



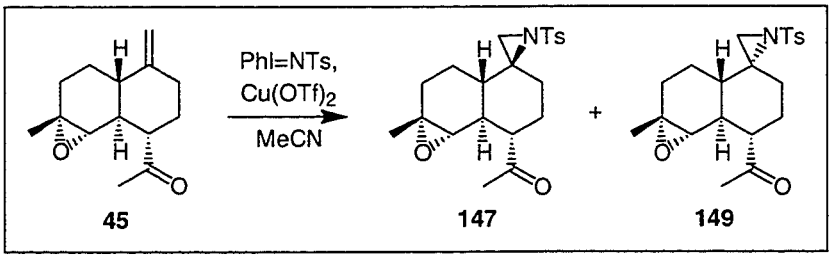
Enol-triflate 143. A solution of LHMDS (0.68 mL, 0.68 mmol, 3 equiv) in THF (8 mL) at –78°C was treated with a solution of **45** (50 mg, 0.227 mmol, 1.0 equiv) in THF (2 mL). After 8 h, a solution of 2-[N,N-bis(trifluromethylsulfonyl)amino]-5-chloropyridine in THF (1 mL) was added and stirring was continued for an additional 1 h before slowly warming to rt. The solvent was removed *in vacuo* and the residue purified by silica gel column chromatography (100% CH_2Cl_2) to afford **143** (58 mg, 72%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 5.27 (d, *J*=4.3 Hz, 1H), 5.09 (d, *J*=4.3 Hz, 1H), 4.73 (d, *J*=1.2 Hz, 1H), 4.58 (d, *J*=1.2 Hz, 1H), 2.87 (s, 1H), 2.41-2.34 (comp m, 2H), 2.25-2.20 (m, 1H), 2.16-2.03 (comp m, 2H), 1.73-1.61 (comp m, 2H), 1.59-1.53 (m, 1H), 1.51-1.28 (comp m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 149.6, 106.3, 104.6, 61.3, 58.7, 46.5, 45.4, 43.1, 35.3, 33.8, 30.2, 23.4, 22.2; IR (thin film/NaCl) 2936 (m), 2868 (m), 1662 (m), 1418 (s), 1381 (m), 1249 (m), 1212 (s), 1144 (s), 958 (m), 920 (s) cm^{-1}; HRMS (ES) *m/z* found: 203.1437 [calc'd for $C_{14}H_{19}O$ $(M\text{-}OTf)^+$: 203.1436].

Preparation of ester 148



Ester 148. A solution of ethyl propiolate (28 μL, 0.272 mmol, 4.0 equiv) in THF (3 mL) at –78°C was treated with n-BuLi (2.3 M in hexanes, 117 μL, 0.27 mmol, 4.0 equiv). After 5 min, **45** (15 mg, 0.068 mmol, 1.0 equiv) in THF (1 mL) was added. The temperature was maintained at –78°C for 30 min before slowly warming to 0°C for an additional 1 hr. Water (5 mL) was added followed by EtOAc (15 mL). The layers were separated and the aqueous portion was extracted with EtOAc (10 mL). The combined organic fractions were washed with brine (15 mL) and dried with Na_2SO_4 before concentrating *in vacuo*. Crude NMR showed ca. 98:2 mixture of diastereomers which could be purified by silica gel column chromatography (3:1 hexanes:EtOAc) to afford **148** (19 mg, 89%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.68 (s, 1H), 4.54 (s, 1H), 4.24 (q, *J*=7.2 Hz, 2H), 3.93 (s, 1H), 2.42 (s, 1H), 2.39 (dt, *J*=4.5, 13.1 Hz, 1H), 2.35-2.29 (m, 1H), 2.14-1.98 (comp m, 3H), 1.73-1.51 (comp m, 7H), 1.41-1.17 (comp m 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 151.0, 105.2, 90.9, 77.0, 72.6, 62.3, 61.1, 59.0, 48.8, 45.7, 43.0, 35.7, 32.3, 30.2, 25.0, 23.6, 22.4, 14.2; IR (thin film/NaCl) 3400 (br m), 2984 (m), 2936 (m), 2237 (m), 1712 (s), 1650 (m), 1447 (m), 1368 (m), 1246 (s), 1092 (m) cm^{-1}; HRMS (EI) *m/z* found: 318.1835 [calc'd for $C_{19}H_{26}O_4$ (M+): 318.1835].

Preparation of aziridines 147 and 149



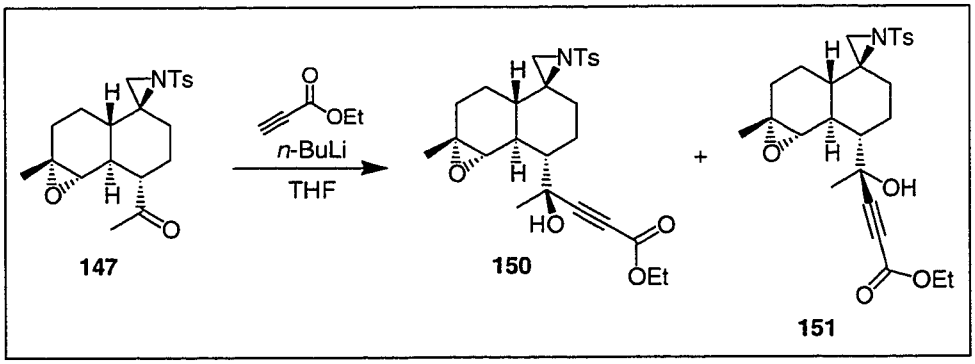
Aziridines 147 and 149. A solution of ketone **45** (1.06 g, 4.80 mmol, 1.0 equiv) in dry MeCN (250 mL) with 4 Å sieves (ca. 3 g) at 25°C, was treated with *N*-tosyliminophenyliodinane (3.59 g, 9.62 mmol, 2.0 equiv). After 2 minutes, $Cu(tfa)_2$ (87 mg, 0.24 mmol, 0.05 equiv) was added and the mixture was vigorously stirred for 8 h. The mixture was then diluted with EtOAc (50 mL) and filtered through a short plug of silica gel. After removing the solvent *in vacuo*, the resulting residue, ca. 5:1 mixture of aziridine diastereomers, was purified by silica gel column chromatography (3:1 hexanes:EtOAc) to afford aziridine **147** (1.12 g, 60% yield) as a white solid. Mixed fractions were analyzed by HPLC to give an analytical sample of **149** (37 mg, 2% yield) as a white, amorphous solid.

Aziridine 147. m.p. 195-197°C (recrystallized from 3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J*=8.5 Hz, 2H), 7.32 (d, *J*=8.6 Hz, 2H), 2.61 (dt, *J*=3.7, 12.1 Hz, 1H), 2.54 (s, 1H), 2.48 (s, 1H), 2.44 (s, 3H), 2.42-2.28 (comp m, 2H), 2.26 (s, 3H), 2.23-2.17 (comp m, 2H), 2.01-1.96 (m, 1H), 1.93 (t, *J*=11.8 Hz, 1H), 1.65-1.43 (comp m, 4H), 1.28 (s, 3H), 0.74 (dq, *J*=4.4, 12.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.5, 144.1, 137.9, 129.7, 127.4, 61.5, 58.6, 54.5, 54.0, 42.2, 42.2, 36.2, 30.6, 29.9, 29.7, 29.0, 23.2, 21.7, 18.1; IR (thin film/NaCl) 3269 (br m), 2928 (m), 2253 (w),

1708 (s), 1598 (m), 1451 (m), 1319 (s), 1159 (s), 1088 (m), 1002 (m) cm^{-1}; HRMS (EI) *m/z* found: 389.1661 [calc'd for $C_{21}H_{27}NO_4S$ (M+): 389.1661].

Aziridine 149. ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J*=7.1 Hz, 2H), 7.32 (d, *J*=7.9 Hz, 2H), 2.55-2.41 (comp m, 8H), 2.38-2.27 (m, 1H), 2.27-2.17 (comp m, 4H), 2.10-1.93 (comp m, 3H), 1.60-1.51 (m, 1H), 1.33-1.23 (comp m, 4H), 1.12 (dq, *J*=4.4, 12.1 Hz, 1H), 0.98 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.6, 144.2, 137.6, 129.7, 127.7, 61.3, 58.2, 56.4, 54.9, 42.1, 40.8, 36.9, 30.0, 30.0, 27.7, 26.5, 23.2, 21.7, 18.8; IR (thin film/NaCl) 2935 (m), 2870 (m), 2251 (w), 1707 (s), 1597 (m), 1494 (w), 1451 (m), 1379 (m), 1317 (s), 1158 (s) cm^{-1}; HRMS (FAB) *m/z* found: 390.1744 [calc'd for $C_{21}H_{28}NO_4S$ (M+H): 390.1739].

Preparation of alcohols 150 and 151



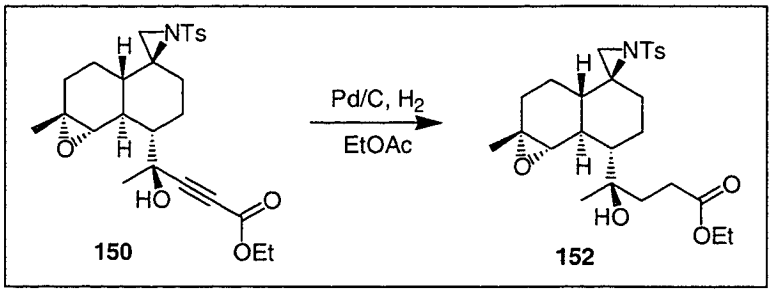
Alcohols 150 and 151. A solution of ethyl propiolate (118 μL, 1.16 mmol, 4.0 equiv) in THF (10 mL) at –78°C was treated with *n*-BuLi (2.3 M in hexanes, 0.50 mL, 1.16 mmol, 4.0 equiv). After 5 min, **147** (113 mg, 0.29 mmol, 1.0 equiv) in THF (1 mL) was added. The temperature was maintained at –78°C for 30 min before slowly warming to 0°C for an additional 1 hr. Water (10 mL) was added followed by EtOAc (30 mL). The layers were separated and the aqueous portion was extracted with EtOAc (10 mL).

The combined organic fractions were washed with brine (25 mL) and dried with Na_2SO_4 before concentrating *in vacuo*. Crude NMR showed a ~98:2 mixture of diastereomers which could be purified by silica gel column chromatography (3:1 hexanes:EtOAc) to afford **150** (125 mg, 88%) as a foam and **151** (2 mg, 1%) as a colorless oil.

Alcohol 150. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J*=8.0 Hz, 2H), 7.31 (d, *J*=8.0 Hz, 2H), 4.24 (q, *J*=7.2 Hz, 2H), 3.93 (s, 1H), 2.59 (s, 1H), 2.50 (s, 1H), 2.44-2.19 (comp m, 7H), 2.00-1.91 (comp m, 2H), 1.70-1.56 (comp m, 7H), 1.49-1.42 (m, 1H), 1.34-1.25 (comp m, 6H), 0.79-0.67 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 144.0, 138.1, 129.6, 127.4, 90.3, 77.2, 72.0, 62.4, 60.4, 59.4, 54.4, 48.1, 43.3, 42.6, 36.2, 30.8, 30.0, 29.8, 25.2, 23.4, 21.7, 18.5, 14.2; IR (thin film/NaCl) 3463 (br m), 2932 (m), 2237 (m), 1710 (s), 1598 (m), 1449 (m), 1317 (m), 1247 (s), 1158 (s), 1090 (m) cm^{-1}; HRMS (FAB) *m/z* found: 488.2109 [calc'd for $C_{26}H_{34}NO_6S$ (M+H): 488.2107].

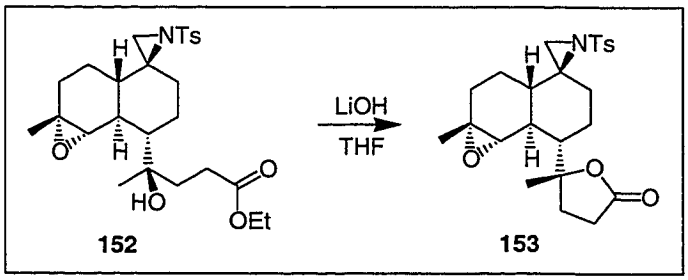
Alcohol 151. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d. *J*=8.3 Hz, 2H), 7.30 (d, *J*=8.3 Hz, 2H), 4.24 (q, *J*=7.1 Hz, 2H), 3.98 (s, 1H), 2.51-2.26 (comp m, 8H), 2.09-1.84 (comp m, 5H), 1.65-1.51 (comp m, 4H), 1.37-1.25 (comp m,7H), 1.16 (dq, *J*=4.2, 12.7 Hz, 2H), 0.98-0.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 144.0, 137.7, 129.6, 127.7, 90.4, 77.0, 73.0, 62.3, 60.4, 58.7, 55.5, 48.2, 42.3, 41.7, 36.9, 30.3, 29.8, 29.7, 24.6, 23.4, 21.7, 19.1, 14.2; IR (thin film/NaCl) 3455 (br m), 2983 (m), 2939 (m), 2240 (m), 1710 (s), 1598 (w), 1445 (w), 1451 (m), 1370 (m), 1248 (s), 1156 (s) cm^{-1}; HRMS (FAB) *m/z* found: 488.2107 [calc'd for $C_{26}H_{34}NO_6S$ (M+H): 488.2107].

Preparation of ester 152



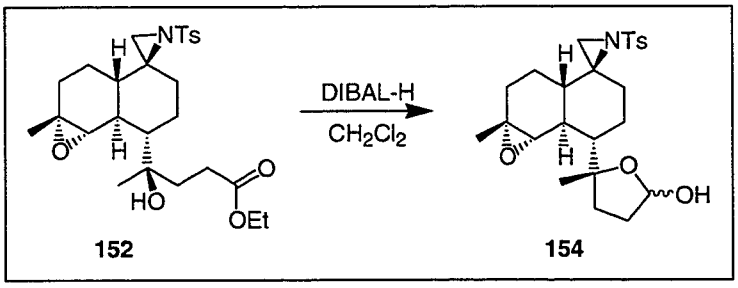
Ester 152. A solution of **150** (50 mg, 0.103 mmol, 1.0 equiv) in EtOAc (5 mL) at 0°C was treated with 10% Pd/C (5 mg) and an atmosphere of H_2 was maintained using a balloon. After 1h, the mixture was filtered through celite and concentrated. The resulting colorless oil was spectroscopically pure **152** (49 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J*=8.3 Hz, 2H), 7.30 (d, *J*=8.6 Hz, 2H), 4.19-4.12 (comp m, 3H), 2.55-2.18 (comp m, 9H), 1.99-1.89 (comp m, 3H), 1.81-1.54 (comp m, 6H), 1.48-1.41 (m, 1H), 1.30-1.09 (comp m, 10H), 0.79-0.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 143.9, 138.2, 129.6, 127.3, 75.3, 60.9, 60.9, 59.3, 54.8, 47.5, 44.2, 42.9, 37.6, 36.4, 31.1, 29.8, 29.1, 28.4, 23.6, 23.3, 21.7, 18.6, 14.3; IR (thin film/NaCl) 3499 (m), 2976 (m), 2930 (m), 2875 (m), 2251 (w), 1730 (s), 1598 (w), 1451 (m), 1380 (m), 1317 (s) cm^{-1}; HRMS (FAB) *m/z* found: 492.2420 [calc'd for $C_{26}H_{38}NO_6S$ (M+H): 492.2420].

Preparation of lactone 153



Lactone 153. A solution of **152** (0 mg, 0 mmol, 1.0 equiv) in THF (10 mL) at rt was treated with LiOH (0 mg, 0 mmol, 0.1 equiv). After 12 hr, the solvent was removed *in vacuo* and the residue purified by silica gel column chromatography (1:1 hexanes:EtOAc) to give **153** (270 mg, 94%) as a white solid. m.p. 200-201°C (recrystallized from 1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J*=8.1 Hz, 2H), 7.30 (d, *J*=8.2 Hz, 2H), 3.70 (s, 1H), 2.66-2.56 (m, 1H), 2.52-2.40 (comp m, 5H), 2.37-2.21 (comp m, 3H), 2.15-2.00 (comp m, 3H), 1.97-1.82 (comp m, 2H), 1.69-1.56 (comp m, 3H), 1.48-1.37 (comp m, 4H), 1.32-1.14 (comp m, 4H), 0.79-0.69 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 144.0, 138.0, 129.6, 127.3, 89.2, 59.7, 59.3, 54.4, 49.3, 43.7, 42.4, 26.3, 35.2, 30.9, 29.8, 28.2, 27.9, 23.4, 21.7, 19.6, 18.4; IR (thin film/NaCl) 2959 (m), 2876 (m), 2252 (w), 1770 (s), 1598 (w), 1451 (m), 1387 (m), 1317 (m), 1209 (m), 1158 (s) cm^{-1}; HRMS (FAB) *m/z* found: 446.2000 [calc'd for $C_{24}H_{32}NO_5S$ (M+H): 446.2001].

Preparation of lactol 154

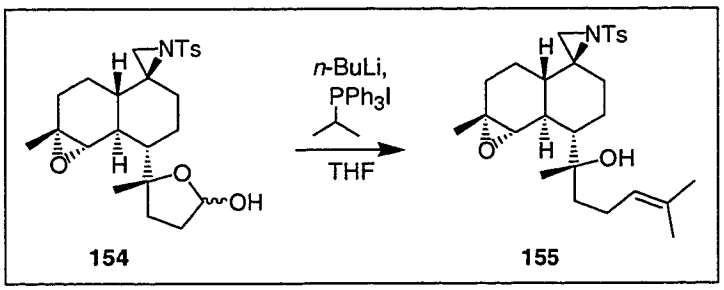


152 154

Lactol 154. To a solution of **152** (50 mg, 0.102 mmol, 1.0 equiv) in toluene (5 mL) at 0°C was added DIBAL-H (0.5 M in CH_2Cl_2, 155 μL, 0.122 mmol, 1.2 equiv). After 10 min, the solution was warmed to rt and stirred for an additional 2 h. The reaction was quenched with 20% aqueous Rochelle's salt (10 mL) and diluted with (25

mL). The organic layer was washed with water (25 mL), brine (25 mL) and dried with Na_2SO_4. After concentration, the resulting residue was purified by silica gel column chromatography (3:1 then 1:1 hexanes:EtOAc) to afford **154** (35 mg, 76%) as an amorphous, white solid. (2:1 mixture of lactol epimers) ^{1}H NMR (500 MHz, $CDCl_3$) δ δ 7.80 (d, *J*=7.9 Hz, 2H), 7.30 (d, *J*=7.9 Hz, 2H), 5.58-5.54 (comp m, 0.3H), 5.52-5.48 (comp m, 0.7H), 4.05 (s, 0.7H), 4.03 (s, 0.3H), 2.72-2.70 (m, 0.3H), 2.50-2.42 (comp m, 4.7H), 2.31-2.18 (comp m, 3H), 2.10-1.86 (comp m, 4H), 1.80-1.69 (comp m, 2H), 1.64-1.56 (comp m, 4H), 1.47-1.41 (m, 1H), 1.36 (s, 1H), 1.31-1.13 (comp m, 6H), 0.80-0.69 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 138.3, 129.6, 127.4, 99.5, 98.4, 88.3, 87.4, 60.7, 60.6, 59.3, 59.2, 55.0, 55.0, 51.6, 50.2, 44.1, 43.9, 42.7, 42.6, 38.5, 36.5, 36.3, 36.0, 32.8, 32.3, 31.2, 31.2, 30.1, 30.0, 30.0, 29.6, 23.6, 23.6, 21.7, 21.5, 20.8, 18.6, 18.5; IR (thin film/NaCl) 3435 (m), 2929 (m), 2871 (m), 2250 (w), 1738 (m), 1599 (w), 1453 (m), 1380 (m), 1318 (m), 1159 (m) cm^{-1}; HRMS (FAB) *m/z* found: 448.2157 [calc'd for $C_{24}H_{34}NO_5S$ (M+H): 448.2158].

Preparation of olefin 155

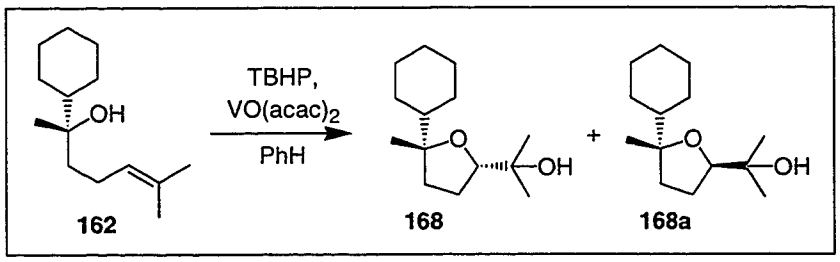


154 155

Olefin 155. A mixture of isopropyltriphenylphosponium iodide (116 mg, 0.268 mmol, 4.0 equiv) in THF (5 mL) at 0°C was treated with n-BuLi (2.3 M in hexanes, 117 μL, 0.268 mmol, 4.0 equiv). After 5 min, **154** (30 mg, 0.067 mmol, 1.0 equiv) was added

as a solution in THF (1 mL). The red solution was warmed to rt and stirred for an additional 3 h before quenching with water (5 mL) and diluting with EtOAc (25 mL). The aqueous layer was extracted with EtOAc (10 mL) and the combined organic fractions were washed with brine (25 mL) and dried with Na_2SO_4. After the solvent was removed *in vacuo*, the resulting residue was purified by silica gel column chromatography (3:1 hexanes:EtOAc) to afford **155** (26 mg, 81%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J*=8.5 Hz, 2H), 7.30 (d, *J*=8.1 Hz, 2H), 5.12 (br t, *J*=7.0 Hz, 1H), 4.21 (s, 1H), 2.49 (s, 1H), 2.43 (s, 3H), 2.30-1.89 (comp m, 7H), 1.72-1.53 (comp m, 10H), 1.47-1.36 (comp m, 3H), 1.27 (s, 3H), 1.26 (s, 3H), 1.21-1.08 (m, 1H), 0.80-0.68 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 138.4, 132.5, 129.6, 127.4, 124.1, 76.2, 61.0, 59.3, 55.1, 47.4, 44.3, 43.4, 43.0, 36.5, 31.3, 29.9, 29.4, 25.9, 23.7, 23.6, 21.7, 21.6, 18.6, 17.9; IR (thin film/NaCl) 3511 (br m), 2965 (s), 2925 (s), 2246 (w), 1598 (m), 1449 (m), 1379 (m), 1318 (s), 1208 (m), 1158 (s) cm^{-1}; HRMS (FAB) *m/z* found: 474.2679 [calc'd for $C_{27}H_{40}NO_4S$ (M+H): 474.2678].

Preparation of tetrahydrofurans 168 and 168a



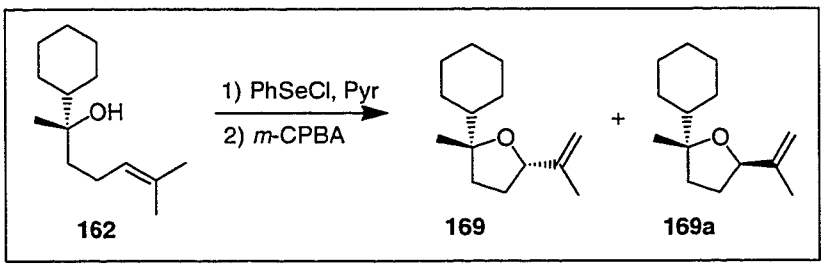
A solution of **162** (50 mg, 0.238 mmol, 1.0 equiv) in benzene (5 mL) at 25°C was treated with a solution of *tert*-butyl hydroperoxide (2.6 M in toluene, 275 μL, 0.714 mmol, 3.0 equiv) and $VO(acac)_2$ (6 mg, 0.024 mmol, 0.1 equiv). After the reaction was

complete by TLC, EtOAc (20 mL) and dimethyl sulfide (ca. 0.1 mL) were added. The organic layer was washed with brine (10 mL), dried with Na_2SO_4, and concentrated *in vacuo*. NMR analysis of the residue showed a 4:1 mixture of tetrahydrofurans which could be separated by silica gel column chromatography (9:1 then 3:1 hexanes:EtOAc) to afford a **168** (major diastereomer, 62%, 33 mg) and **168a** (14%, 7 mg) as colorless oils.

Tetrahydrofuran 168. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 (br t, *J*=7.0 Hz, 1H), 2.11 (br s, 1H), 1.90-1.53 (comp m, 9H), 1.37 (dddd, *J*=2.4, 2.8, 12.0, 12.1 Hz, 1H), 1.28-0.95 (comp m, 14H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 85.6, 84.1, 71.6, 48.4, 35.6, 28.6, 28.1, 27.6, 26.8, 26.8, 26.3, 24.4, 22.1; IR (thin film/NaCl) 3572 (m), 3453 (br m), 2971 (s), 2927 (s), 2854 (s), 1450 (m), 1374 (m), 1318 (w), 1073 (m), 948 (m) cm^{-1}.

Tetrahydrofuran 168a. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67-3.63 (m, 1H), 2.24 (br s, 1H), 1.86-1.58 (comp m, 9H), 1.38 (dddd, *J*=2.4, 2.4, 11.9, 11.9 Hz, 1H), 1.27-1.08 (comp m, 12H), 1.04-0.92 (comp m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 86.0, 85.5, 70.5, 48.4, 35.8, 28.1, 28.0, 27.9, 26.9, 26.8, 26.6, 24.2, 23.8; IR (thin film/NaCl) 3461 (br m), 2972 (s), 2927 (s), 2853 (s), 1451 (m), 1374 (m), 1305 (w), 1185 (w), 1058 (m), 890 (m) cm^{-1}; HRMS (EI) *m/z* found: 227.2008 [calc'd for $C_{14}H_{27}O_2$ (M+H): 227.2011].

Preparation of tetrahydrofurans 169 and 169a



Tetrahydrofurans 169 and 169a. A solution of **162** (50 mg, 0.238 mmol, 1.0

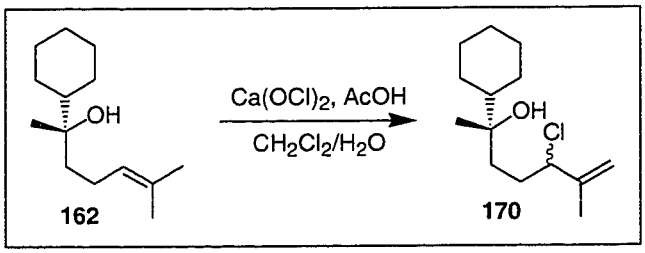
equiv) in CH_2Cl_2 (5 mL) at –78°C was treated with pyridine (30 μL, 0.286 mmol, 1.2 equiv) and PhSeCl (65 mg, 0.333 mmol, 1.4 equiv). After ca. 10 minutes, saturated aqueous $NaHCO_3$ (1 mL) was added and the mixture was allowed to warm to rt. The organic layer was washed with brine (10 mL) and dried with Na_2SO_4. After concentration *in vacuo*, the resulting residue was dissolved in CH_2Cl_2 (5 mL), cooled to –78°C, and reacted with *m*-CPBA (57 mg, 0.333 mmol, 1.4 equiv). Saturated aqueous $NaHCO_3$ (1 mL) was added after ca. 20 minutes and the mixture was allowed to warm to rt. The organic layer was washed with brine (10 mL), dried with Na_2SO_4, and concentrated *in vacuo*. NMR analysis of the residue showed a 1:1 mixture of tetrahydrofurans which could be separated by silica gel column chromatography (9:1 then 3:1 hexanes:EtOAc) to afford a **169** (46%, 23 mg) and **169a** (42%, 21 mg) as colorless oils.

Tetrahydrofuran 169. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.02 (br s, 1H), 4.78 (br s, 1H), 4.35 (br t, *J*=6.4 Hz, 1H), 2.08-2.00 (m, 1H), 1.93-1.52 (comp m, 9H), 1.45-1.38 (m, 1H), 1.29-0.94 (comp m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.2, 110.2, 85.7, 80.9, 48.5, 35.4, 31.5, 28.6, 28.0, 26.9, 26.9, 23.0, 18.3; IR (thin film/NaCl) 2967 (m), 2926 (s), 2853 (m), 1450 (m), 1372 (m), 1082 (m), 1028 (m), 893 (m) cm^{-1}; HRMS (CI) *m/z* found: 209.1901 [calc'd for $C_{14}H_{25}O$ (M+H): 209.1905].

Tetrahydrofuran 169a. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.00 (br s, 1H), 4.78 (br s, 1H), 4.25 (dd, *J*=6.1, 9.4 Hz, 1H), 2.01-1.94 (m, 1H), 1.89-1.52 (comp m, 10H), 1.45-1.38 (m, 1H), 1.27-0.94 (comp m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.4, 110.3, 85.9, 82.8, 48.4, 35.5, 31.6, 28.3, 28.2, 26.9, 26.8, 24.1, 18.0; IR (thin film/NaCl) 2968 (m), 2926 (s), 2853 (m), 1652 (w), 1451 (m), 1373 (m), 1307 (w), 1144 (w), 1082 (m),

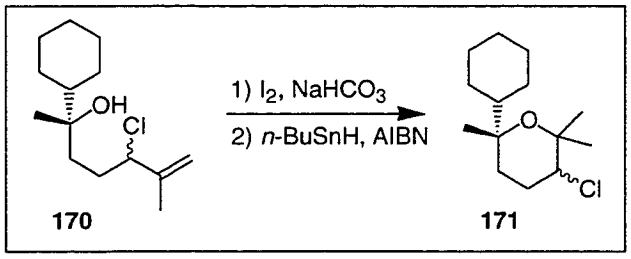
894 (m) cm^{-1}; HRMS (CI) *m/z* found: 209.1903 [calc'd for $C_{14}H_{25}O$ (M+H): 209.1905].

Preparation of chloride 170



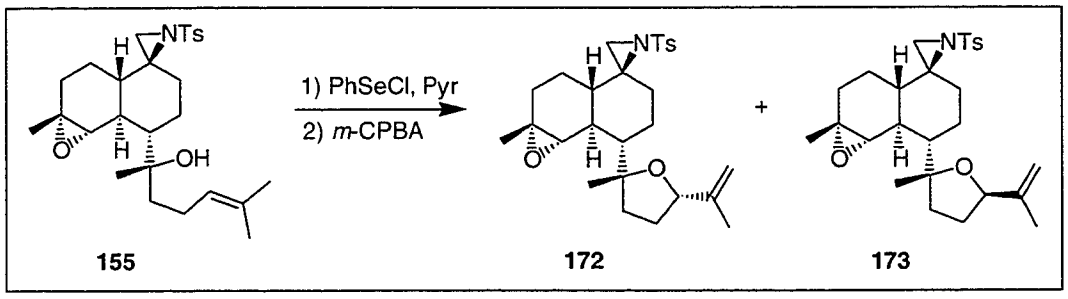
Chloride 170. A solution of **162** (100 mg, 0.475 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at 0°C was treated with $Ca(OCl)_2$ (54 mg, 0.380 mmol, 0.8 equiv) followed by water (5 mL) and AcOH (44 μL, 0.760 mmol, 1.6 equiv). After ca. 2 h, saturated aqueous $NaHCO_3$ (2 mL) was added and the mixture was diluted with CH_2Cl_2 (10 mL). The organic layer was washed with brine (5 mL) and dried with Na_2SO_4. Concentration *in vacuo* gave a residue which could be advanced without further purification. An analytical sample could be obtained after purification by silica gel column chromatography (9:1 then 3:1 hexanes:EtOAc) to give chloride **170** (1:1 mixture of diastereomers, 82 mg, 71% yield) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 5.01 (br s, 1H), 4.89 (br s, 1H), 4.35 (dt, *J*=2.5, 7.1 Hz, 1H), 2.00-1.55 (comp m, 11H), 1.44-0.93 (comp m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 144.5, 114.3, 114.3, 74.2, 74.2, 67.7, 67.7, 47.8, 47.5, 37.1, 37.0, 30.8, 30.7, 27.7, 27.0, 26.9, 26.8, 26.6, 24.0, 23.9, 17.2, 17.1; IR (thin film/NaCl) 3453 (br m), 3079 (w), 2928 (s), 2853 (s), 1646 (m), 1449 (m), 1376 (m), 1117 (m), 905 (m), 780 (m) cm^{-1}.

Preparation of tetrahydropyran 171



Tetrahydropyrans 171. To a solution of **170** (50 mg, 0.205 mmol, 1.0 equiv) in Et_2O (3 mL) was added water (3 mL) and the mixture was cooled to 0°C. Solid $NaHCO_3$ (86 mg, 1.03 mmol, 5.0 equiv) and I_2 (0.518 g, 2.05 mmol, 10 equiv) were added. After warming to rt and stirring overnight, the reaction was diluted with Et_2O (10 mL), washed with brine (10 mL), and concentrated under reduced pressure. The resulting residue was dissolved in toluene (10 mL) and treated with *n*-Bu_3SnH (105 μL, 0.308 mmol, 1.5 equiv) and AIBN (3 mg, 0.021 mmol, 0.1 equiv). After refluxing overnight, the reaction was diluted with EtOAc (20 mL), washed with brine (20 mL), and dried with Na_2SO_4. Concentration *in vacuo* gave a residue which was purified by silica gel column chromatography (18:1 then 9:1 hexanes:EtOAc) to afford tetrahydropyran mixture **171** (1:1 mixture of diastereomers, 29 mg, 58% from **170**) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 3.92 (dd, *J*=3.4, 6.9 Hz, 1H), 3.69 (dd, *J*=4.3, 12.2 Hz, 0.75H), 2.23-1.45 (comp m, 20H), 1.36-0.85 (comp m, 30H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.9, 75.3, 75.1, 74.2, 65.8, 65.3, 50.9, 48.1, 34.5, 30.7, 29.8, 29.1, 28.0, 27.5, 27.4, 27.2, 27.0, 27.0, 26.9, 26.1, 24.4, 22.9, 22.2; IR (thin film/NaCl) 2976 (m), 2929 (s), 2853 (m), 1450 (m), 1376 (m), 1228 (m), 1126 (m), 1050 (m), 1010 (m), 979 (m) cm^{-1}.

Preparation of tetrahydrofurans 172 and 173



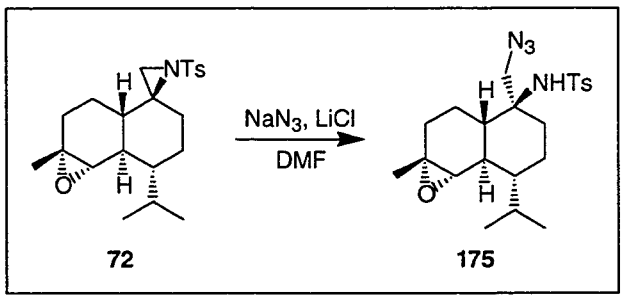
Tetrahydrofurans 172 and 173. A solution of **155** (30 mg, 0.063 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at –78°C was treated with pyridine (8 μL, 0.076 mmol, 1.2 equiv) and PhSeCl (17 mg, 0.088 mmol, 1.4 equiv). After ca. 10 minutes, saturated aqueous $NaHCO_3$ (1 mL) was added and the mixture was allowed to warm to rt. The organic layer was washed with brine (10 mL) and dried with Na_2SO_4. After concentration, the resulting residue was dissolved in CH_2Cl_2 (5 mL), cooled to –78°C, and reacted with *m*-CPBA (15 mg, 0.088 mmol, 1.4 equiv). After ca. 20 minutes, saturated aqueous $NaHCO_3$ (1 mL) was added and the mixture was allowed to warm to rt. The organic layer was washed with brine (10 mL), dried with Na_2SO_4, and concentrated *in vacuo*. NMR analysis of the residue showed a 3:2 mixture of tetrahydrofurans which could be separated by silica gel column chromatography (9:1 then 3:1 hexanes:EtOAc) to afford **172** (major diastereomer, 48%, 14 mg) and **173** (30%, 9 mg) as colorless oils.

Tetrahydrofuran 172. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J*=8.2 Hz, 2H), 7.30 (d, *J*=8.2 Hz, 2H), 4.91 (s, 1H), 4.73 (s, 1H), 4.46-4.42 (m, 1H), 4.20 (s, 1H), 2.50 (s, 1H), 2.43 (s, 3H), 2.29-2.23 (comp m, 2H), 2.21 (s, 1H), 2.14-2.03 (m, 1H), 2.00-1.90 (comp m, 2H), 1.75-1.53 (comp m, 9H), 1.47-1.40 (m, 1H), 1.32-1.16 (comp m, 8H), 0.81-0.68 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.7, 143.8, 138.3, 129.6, 127.4, 109.3, 86.6, 80.7, 60.8, 59.1, 55.1, 50.4, 43.9, 43.0, 38.1, 36.5, 31.3, 30.3, 30.1, 28.7,

23.4, 21.7, 19.4, 18.9, 18.5; IR (thin film/NaCl) 2965 (m), 2878 (m), 2249 (w), 1651 (w), 1599 (m), 1495 (w), 1451 (m), 1379 (m), 1321 (s), 1159 (s) cm^{-1}; HRMS (FAB) *m/z* found: 472.2522 [calc'd for $C_{27}H_{38}NO_4S$ (M+H): 472.2522].

Tetrahydrofuran 173. ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J*=8.3 Hz, 2H), 7.31 (d, *J*=8.3 Hz, 2H), 4.98 (s, 1H), 4.74 (s, 1H), 4.34 (dd, *J*=5.6, 9.6 Hz, 1H), 4.14 (s, 1H), 2.50 (s, 1H), 2.43 (s, 3H), 2.31-2.25 (comp m, 2H), 2.23 (s, 1H), 2.04-1.89 (comp m, 3H), 1.86-1.80 (comp m, 2H), 1.76-1.54 (comp m, 8H), 1.46-1.39 (m, 1H), 1.29-1.18 (comp m, 7H), 0.82-0.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 143.9, 138.3, 129.6, 127.4, 109.2, 86.1, 82.5, 60.7, 59.3, 55.3, 50.8, 44.0, 42.9, 39.9, 36.6, 31.4, 30.5, 29.9, 29.9, 23.6, 21.8, 21.8, 18.8, 18.4; IR (thin film/NaCl) 2967 (m), 2931 (m), 2872 (m), 2248 (w), 1652 (w), 1598 (w), 1495 (w), 1450 (m), 1320 (m), 1159 (m) cm^{-1}; HRMS (FAB) *m/z* found: 472.2522 [calc'd for $C_{27}H_{38}NO_4S$ (M+H): 472.2522].

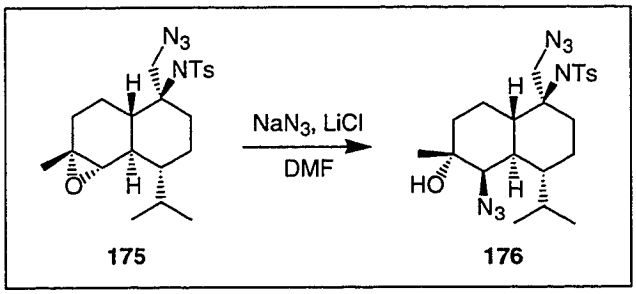
Preparation of azide 175



Azide 175. To a solution of aziridine **72** (15 mg, 0.035 mmol, 1.0 equiv) in DMF (2 mL), was added NaN_3 (13 mg, 0.208 mmol, 6.0 equiv) and LiCl (4 mg, 0.104 mmol, 3.0 equiv). After stirring the mixture at rt for 24 h, the reaction was diluted with EtOAc (30 mL) and water (5 mL). The organic layer was washed with brine (2 x 10 mL), and dried with Na_2SO_4. The solvent was removed under reduced pressure and the resulting

residue was purified by silica gel column chromatography (3:1 hexanes:EtOAc) to afford **175** (14 mg, 93% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J*=8.4 Hz, 2H), 7.30 (d, *J*=8.3 Hz, 2H), 4.97 (s, 1H), 3.48 (d, *J*=13.1 Hz, 1H), 3.25 (d, *J*=12.8 Hz, 1H), 2.84 (s, 1H), 2.43 (s, 3H), 2.24-2.15 (m, 1H), 2.02-1.95 (m, 1H), 1.80-1.64 (comp m, 4H), 1.57-1.46 (comp m, 2H), 1.41 (t, *J*=12.0 Hz, 1H), 1.29-1.23 (comp m, 4H), 1.05-0.89 (comp m, 5H), 0.81 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 140.5, 129.7, 126.9, 62.5, 61.4, 58.5, 52.6, 44.7, 43.8, 40.3, 32.2, 30.6, 26.1, 23.5, 21.7, 21.5, 20.7, 20.0, 15.6; IR (thin film/NaCl) 3266 (m), 2958 (m), 2873 (m), 2249 (w), 2105 (s), 1598 (w), 1495 (w), 1450 (m), 1378 (m), 1156 (s) cm^{-1}; HRMS (FAB) *m/z* found: 455.2082 [calc'd for $C_{22}H_{32}NaN_4O_3S$ (M+Na): 455.2093].

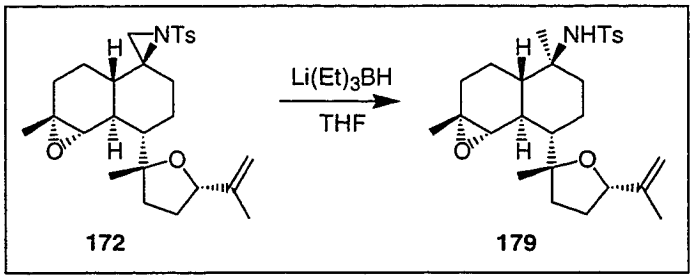
Preparation of azide 176



Azide 176. To a solution of azide **175** (20 mg, 0.046 mmol, 1.0 equiv) in DMF (3 mL), was added NaN_3 (19 mg, 0.278 mmol, 6.0 equiv) and LiCl (6 mg, 0.139 mmol, 3.0 equiv). After 48 h at 90°C, the reaction was diluted with EtOAc (30 mL) and water (10 mL). The organic layer was washed with brine (2 x 10 mL), and dried with Na_2SO_4. After concentration under reduced pressure, the resulting residue was purified by silica gel column chromatography (3:1 hexanes:EtOAc) to afford **176** (19 mg, 89% yield) as an amorphous, white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J*=8.7 Hz, 2H), 7.30 (d,

J=8.3 Hz, 2H), 4.79 (s, 1H), 3.53 (d, *J*=12.7 Hz, 1H), 3.43 (s, 1H), 3.39 (d, *J*=13.0 Hz, 1H), 2.43 (s, 3H), 2.00-1.88 (comp m, 2H), 1.85-1.77 (comp m, 2H), 1.71 (dt, *J*=3.6, 13.7 Hz, 1H), 1.59-1.50 (comp m, 2H), 1.47-1.11 (comp m, 8H), 0.99-0.89 (comp m, 4H), 0.75 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 140.4, 129.7, 127.1, 72.2, 68.2, 62.5, 53.6, 42.2, 40.3, 39.1, 33.3, 33.6, 29.1, 25.9, 21.7, 21.3, 20.8, 19.7, 15.4; IR (thin film/NaCl) 3502 (m), 3272 (m), 2959 (s), 2873 (m), 2102 (s), 1598 (w), 1495 (w), 1453 (m), 1372 (m), 1154 (s) cm^{-1}; HRMS (FAB) *m/z* found: 476.2445 [calc'd for $C_{22}H_{34}N_7O_3S$ (M+H): 476.2444].

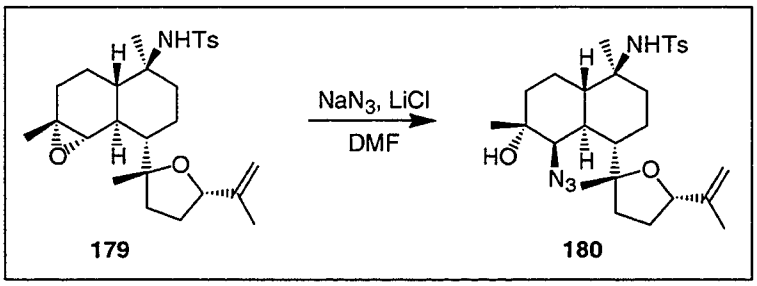
Preparation of amine 179



Amine 179. To a solution of aziridine **172** (30 mg, 0.064 mmol, 1.0 equiv) in THF (5 mL) at 0°C was added a 1M solution of $Li(Et)_3BH$ in THF (191 μL, 0.191 mmol, 3.0 equiv). The reaction mixture was stirred at 0°C for 1 h before warming to rt for an additional 2 h. The reaction was quenched with H_2O (5 mL) and diluted with EtOAc (25 mL). The organic layer was separated, washed with brine (2 x 10 mL), and dried with Na_2SO_4. After removing the solvent *in vacuo*, the resulting residue was purified by silica gel column chromatography (3:1 hexanes:EtOAc) to afford **179** (26 mg, 86% yield) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J*=8.1 Hz, 2H), 7.27 (d, *J*=7.9 Hz, 2H), 4.88 (s, 1H), 4.82 (s, 1H), 4.71 (s, 1H), 4.43-4.38 (m, 1H), 4.11 (s, 1H), 2.42 (s, 3H),

2.10-1.90 (comp m, 2H), 1.76-1.42 (comp m, 12H), 1.30-1.19 (comp m, 5H), 1.13 (s, 3H), 1.12-0.96 (comp m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 143.0, 140.9, 129.7, 127.0, 109.2, 86.7, 80.5, 61.5, 60.3, 58.8, 50.1, 47.2, 40.4, 39.2, 37.9, 30.7, 28.7, 26.7, 23.4, 21.7, 19.9, 19.3, 18.8, 18.7; IR (thin film/NaCl) 3267 (m), 2965 (m), 2871 (m), 1652 (w), 1599 (w), 1496 (w), 1453 (m), 1379 (m), 1326 (m), 1158 (s) cm^{-1}; HRMS (FAB) *m/z* found: 474.2678 [calc'd for $C_{27}H_{40}NO_4S$ (M+H): 474.2678].

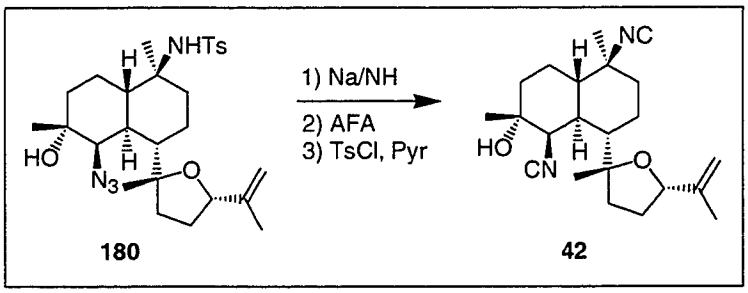
Preparation of azide 180



Azide 180. To a solution of **179** (30 mg, 0.063 mmol, 1.0 equiv) in 8:1 MeOH:H_2O (7 mL) was added NaN_3 (25 mg, 0.378 mmol, 6.0 equiv) and NH_4Cl (10 mg, 0.189 mmol, 3.0 equiv). The mixture was heated to 80°C. After ca. 72 h, the solution was cooled to rt and diluted with EtOAc (25 mL). After washing with water (25 mL) and brine (2 x 25 mL), the organic fraction was dried with Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel column chromatography (3:1 hexanes:EtOAc) afforded azide **180** (27 mg, 82% yield) as an amorphous, white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J*=8.4 Hz, 2H), 7.27 (d, *J*=8.4 Hz, 2H), 4.93-4.91 (m, 1H), 4.74-4.71 (m, 1H), 4.46 (dd, *J*=3.4, 9.5 Hz, 1H), 4.40 (s, 1H), 4.07 (s, 1H), 2.42 (s, 3H), 2.11-2.05 (m, 1H), 1.95 (dd, *J*=2.7, 11.0 Hz, 1H), 1.85 (ddd, *J*=3.3, 3.3, 12.9 Hz, 1H), 1.72-1.50 (comp m, 11H), 1.44-1.36 (comp m, 2H), 1.32-1.22 (comp m, 4H), 1.19-

1.01 (comp m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.8, 143.0, 140.8, 129.6, 127.2, 111.0, 86.7, 81.6, 73.4, 69.1, 60.0, 46.8, 42.2, 39.5, 38.5, 38.0, 33.2, 29.0, 28.8, 25.5, 21.6, 21.5, 19.1, 18.3, 17.4; IR (thin film/NaCl) 3530 (m), 3271 (m), 2966 (w), 2871 (w), 2103 (s), 1455 (w), 1383 (m), 1318 (m), 1286 (m), 1265 (m) cm^{-1}; HRMS (FAB) *m/z* found: 517.2849 [calc'd for $C_{27}H_{41}N_4O_4S$ (M+H): 517.2849].

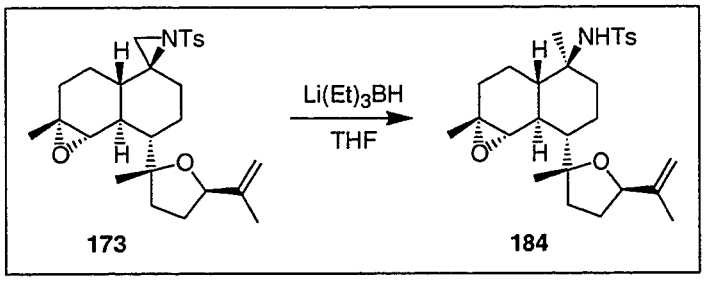
Preparation of (±)-kalihinol C (42)



(±)-Kalihinol C (42). To condensed ammonia (20 mL) at –78°C was added sodium (3 mg, 0.116 mmol, 4 equiv). After 5 min, the sodium/ammonia solution was added via cannula to a solution of **180** (15 mg, 0.029 mmol, 1.0 equiv) in THF (2 mL) and ammonia (5 mL) at –78°C. After ca. 1 h, the reaction was quenched with solid ammonium chloride and the ammonia allowed to evaporate. The resulting residue was taken up in EtOAc (30 mL), washed with 0.1 M NaOH (2 x 10 mL), brine (10 mL) and dried with Na_2SO_4. After concentration under reduced pressure, the resulting oil was dissolved in THF (10 mL) and acetic formic anhydride (ca. 0.1 ml) was added at rt. After 6 h the solution was concentrated under reduced pressure and the resulting residue was taken up in CH_2Cl_2 (5 mL). The solution was treated with pyridine (9 μL, 0.116 mmol, 4.0 equiv) and *p*-toluenesulfonyl chloride (22 mg, 0.116 mmol, 4.0 equiv) at rt. After the reaction was complete (ca. 16 hr), the solvent was removed *in vacuo* and the resulting

residue was purified by silica gel column chromatography (9:1 then 3:1 hexanes:EtOAc) to afford **42** (4 mg, 39% yield from **180**) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, referenced to 77.0) δ 5.04 (s, 1H), 4.77 (s, 1H), 4.50 (br s, 1H), 4.41 (dd, *J*=3.6, 9.4 Hz, 1H), 1.73 (s, 3H), 1.43 (s, 3H), 1.34 (br s, 3H), 1.05 (s, 3H), 2.13-1.04 (complex); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.27, 109.98, 86.23, 80.85, 70.59, 63.18 (t, *J*=5 Hz), 59.91 (t, *J*=5 Hz), 46.31, 42.18, 39.93, 38.18, 36.08, 32.65, 28.82, 28.74, 24.30, 21.65, 20.73, 18.25, 18.16; IR (thin film/NaCl) 3416 (br m), 2968 (m), 2875 (m), 2137 (m), 1653 (w), 1455 (m), 1384 (m), 1273 (w), 1189 (w), 1101 (w) cm^{-1}; HRMS (FAB) *m/z* found: 330.2433 [calc'd for $C_{21}H_{32}NO_2$ (M-NC)$^+$: 330.2433].

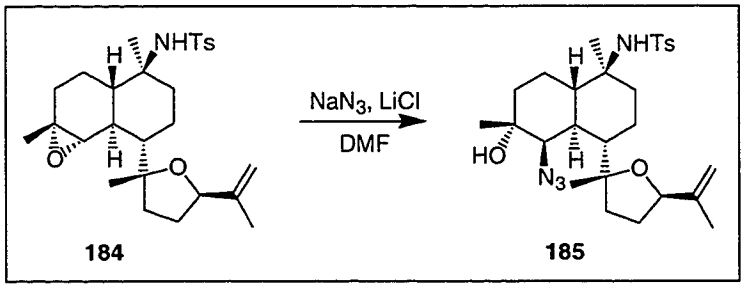
Preparation of amine 184



Amine 184. To a solution of aziridine **173** (30 mg, 0.064 mmol, 1.0 equiv) in THF (5 mL) at 0°C was added a 1M solution of $Li(Et)_3BH$ in THF (191 μL, 0.191 mmol, 3.0 equiv). The reaction mixture was stirred at 0°C for 1 h before warming to rt for an additional 2 h. The reaction was quenched with H_2O (5 mL) and diluted with EtOAc (25 mL). The organic layer was separated, washed with brine (2 x 10 mL), and dried with Na_2SO_4. After removing the solvent *in vacuo*, the resulting residue was purified by silica gel column chromatography (3:1 hexanes:EtOAc) to afford **184** (27 mg, 88% yield) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J*=8.3 Hz, 2H), 7.27 (d, *J*=8.7 Hz,

2H), 4.95 (s, 1H), 4.71 (s, 1H), 4.68 (s, 1H), 4.27 (dd, *J*=5.3, 9.8 Hz, 1H), 4.07 (s, 1H), 2.42 (s, 3H), 1.97-1.91 (comp m, 2H), 1.81-1.41 (comp m, 12H), 1.27-1.20 (comp m, 5H), 1.14 (s, 3H), 1.07-0.98 (comp m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 143.0, 140.8, 129.7, 127.0, 109.2, 86.1, 82.4, 61.2, 60.4, 58.9, 50.6, 47.2, 40.6, 39.7, 39.5, 30.6, 30.4, 26.5, 23.6, 21.9, 21.7, 19.8, 18.7; IR (thin film/NaCl) 3269 (br m), 2967 (s), 2869 (m), 2247 (w), 1652 (w), 1599 (w), 1496 (w), 1451 (m), 1379 (m), 1326 (s), 1158 (s) cm^{-1}; HRMS (FAB) *m/z* found: 474.2676 [calc'd for $C_{27}H_{40}NO_4S$ (M+H): 474.2678].

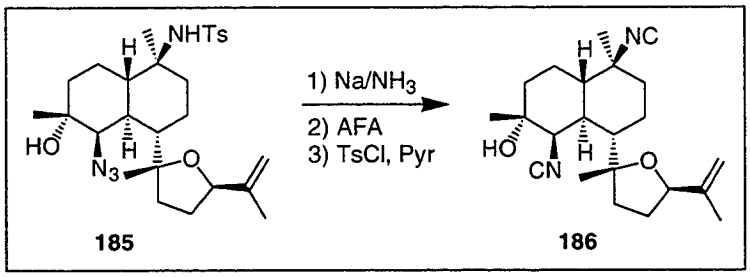
Preparation of azide 185



Azide 185. To a solution of **184** (30 mg, 0.063 mmol, 1.0 equiv) in 8:1 MeOH:H_2O (7 mL), was added NaN_3 (25 mg, 0.378 mmol, 6.0 equiv) and NH_4Cl (10 mg, 0.189 mmol, 3.0 equiv). The mixture was heated to 80°C. After ca. 72 h, the solution was cooled to rt and diluted with EtOAc (25 mL). After washing with water (25 mL) and brine (2 x 25 mL), the organic fraction was dried with Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel column chromatography (3:1 hexanes:EtOAc) afforded azide **185** (32 mg, 97% yield) as an amorphous, white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J*=8.5 Hz, 2H), 7.28 (d, *J*=8.6 Hz, 2H), 4.95 (s, 1H), 4.74 (s, 1H), 4.40 (dd, *J*=5.2, 10.3 Hz, 1H), 4.32 (s, 1H), 4.22 (br s, 1H), 2.43 (s, 3H), 2.02-1.85 (comp m, 3H), 1.78-1.23 (comp m, 18H), 1.14-1.01 (comp m, 7H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 146.5, 143.0, 140.8, 129.6, 127.2, 109.3, 86.0, 82.5, 72.6, 69.2, 60.1, 47.8, 42.4, 40.3, 39.6, 38.4, 33.0, 30.6, 29.2, 25.1, 21.7, 21.5, 21.4, 19.2, 18.7; IR (thin film/NaCl) 3511 (m), 3271 (m), 2944 (w), 2870 (w), 2099 (s), 1739 (w), 1598 (w), 1453 (w), 1370 (m), 1286 (m) cm^{-1}; HRMS (FAB) *m/z* found: 517.2849 [calc'd for $C_{27}H_{41}N_4O_4S$ (M+H): 517.2849].

Preparation of (±)-*epi*-C(14)-kalihinol C (186)



(±)-*epi*-C(14)-Kalihinol C (186). To condensed ammonia (20 mL) at –78°C was added sodium (3 mg, 0.116 mmol, 4 equiv) followed by **185** (15 mg, 0.029 mmol, 1.0 equiv) in THF (2 mL). After ca. 1 h, the reaction was quenched with solid ammonium chloride and the ammonia allowed to evaporate. The resulting residue was taken up in EtOAc (30 mL), washed with 0.1 M NaOH (2 x 10 mL), brine (10 mL) and dried with Na_2SO_4. After concentration under reduced pressure, the resulting oil was dissolved in THF (10 mL) and acetic formic anhydride (ca. 0.1 ml) was added at rt. After 6 h the solution was concentrated under reduced pressure and the resulting residue was taken up in CH_2Cl_2 (5 mL). The solution was treated with pyridine (9 μL, 0.116 mmol, 4.0 equiv) and *p*-toluenesulfonyl chloride (22 mg, 0.116 mmol, 4.0 equiv) at rt. After the reaction was complete (ca. 16 hr), the solvent was removed *in vacuo* and the resulting residue was purified by silica gel column chromatography (9:1 then 3:1 hexanes:EtOAc) to afford **186**

(3 mg, 32% yield from **185**) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (s, 1H), 4.77 (s, 1H), 4.56 (br s, 1H), 4.32 (dd, *J*=5.1, 10.2 Hz, 1H), 2.07-1.52 (comp m, 18H), 1.41 (s, 3H), 1.34 (br s, 3H), 1.27-1.09 (m, 1H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1 (t, *J*=5 Hz), 153.4 (t, *J*=5 Hz), 145.9, 109.7, 85.4, 83.0, 70.5, 63.4 (t, *J*=5 Hz), 60.2 (t, *J*=5 Hz), 46.6, 42.6, 40.4, 39.9, 36.4, 32.7, 30.5, 29.0, 24.0, 21.8, 21.6, 21.0, 18.9; IR (thin film/NaCl) 3414 (m), 2968 (s), 2940 (s), 2873 (m), 2136 (s), 1653 (w), 1452 (m), 1384 (m), 1273 (w), 1098 (w) cm^{-1}; HRMS (FAB) *m/z* found: 357.2543 [calc'd for $C_{22}H_{33}N_2O_2$ (M+H): 357.2542].

3.8 Notes and References

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Appendix Three: Spectra Relevant

To Chapter Three

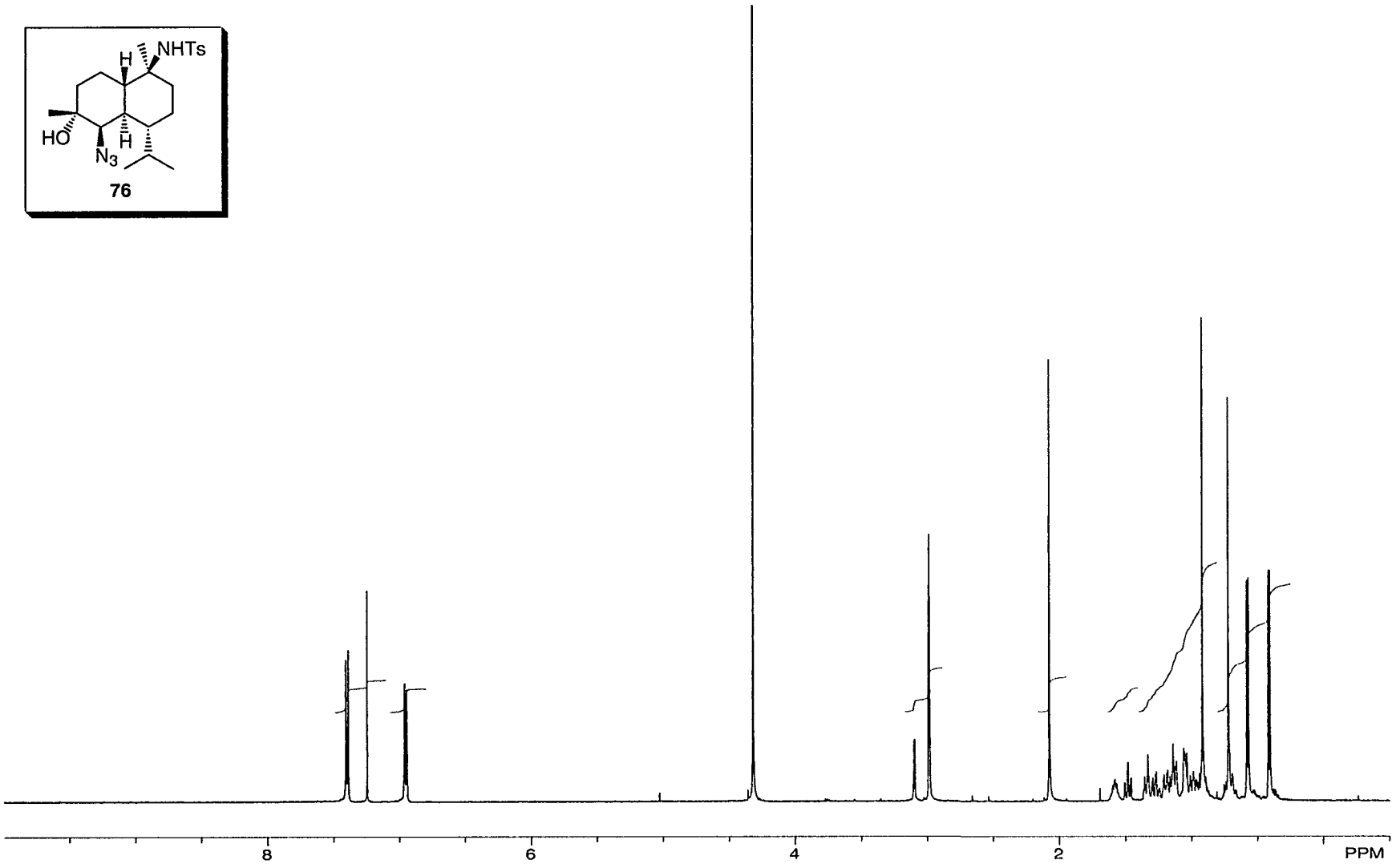


Figure A.3.1 ^{1}H NMR (500 MHz, 1:1 CD_3OD:$CDCl_3$) of Compound **76**.

Figure A.3.2 FTIR Spectrum (Nujol mull/NaCl) of Compound **76**.

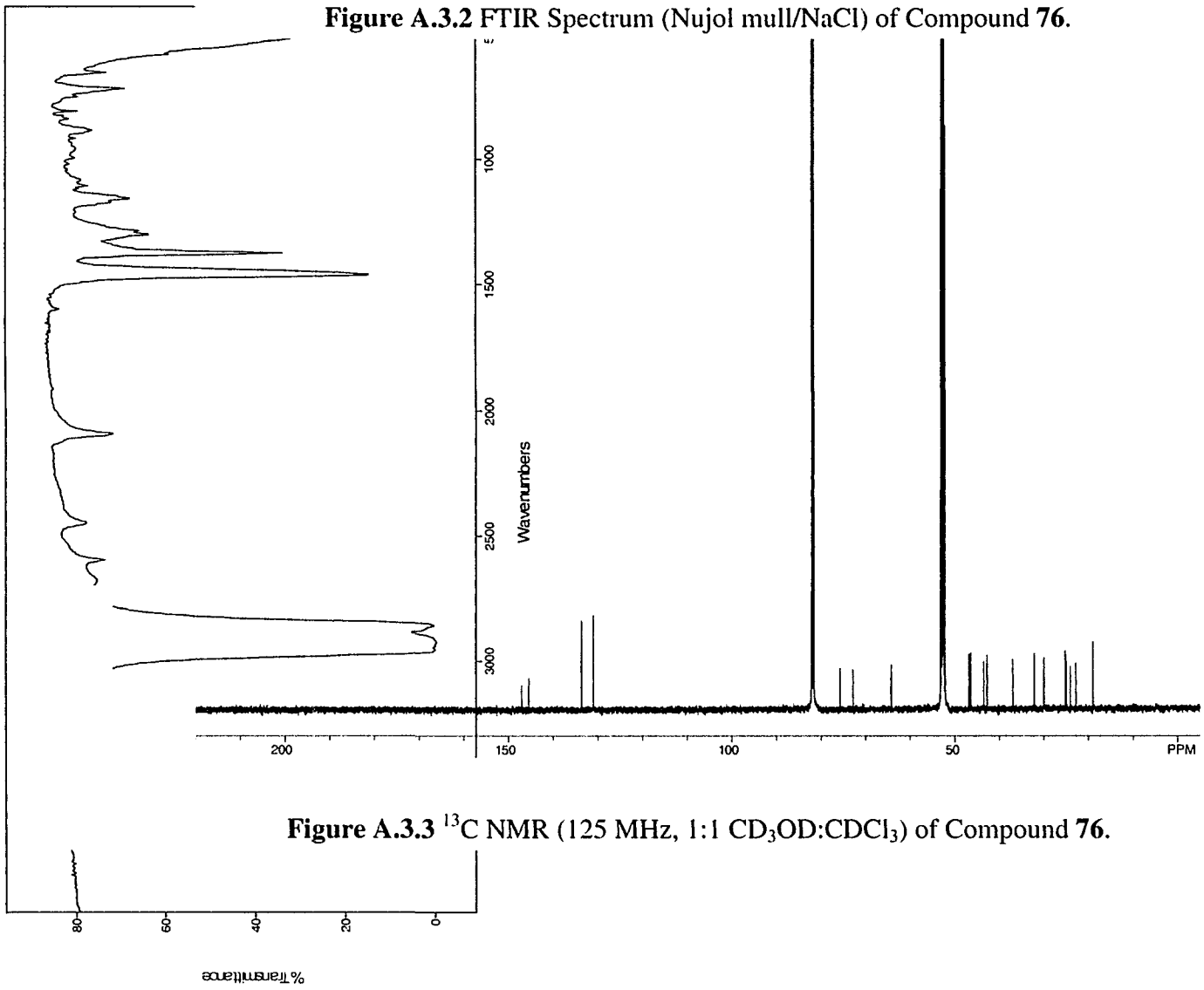


Figure A.3.3 ^{13}C NMR (125 MHz, 1:1 CD_3OD:$CDCl_3$) of Compound **76**.

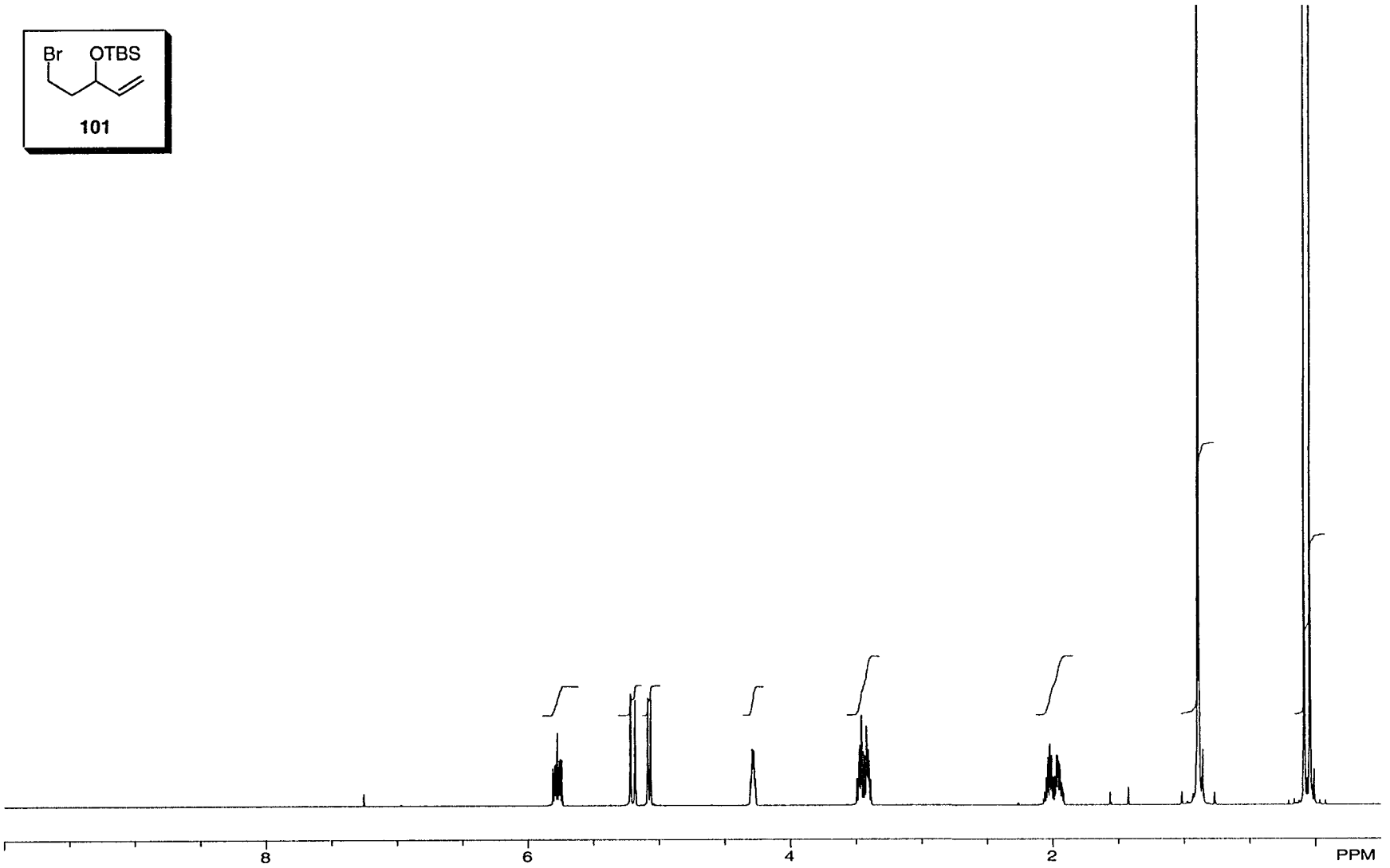


Figure A.3.4 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **101**.

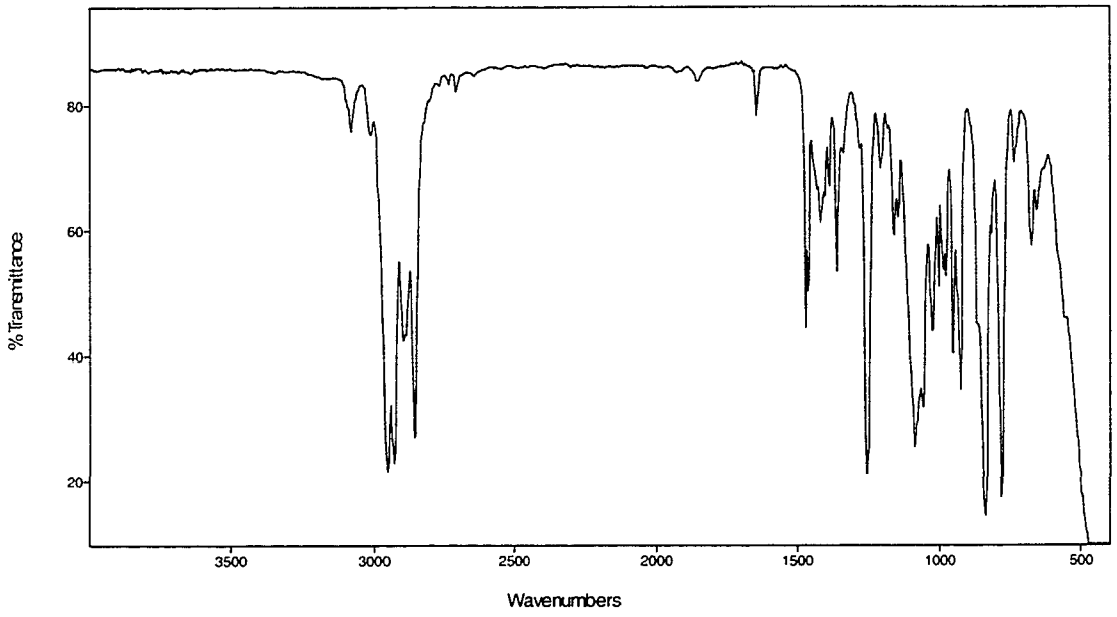


Figure A.3.5 FTIR Spectrum (thin film/NaCl) of Compound **101**.

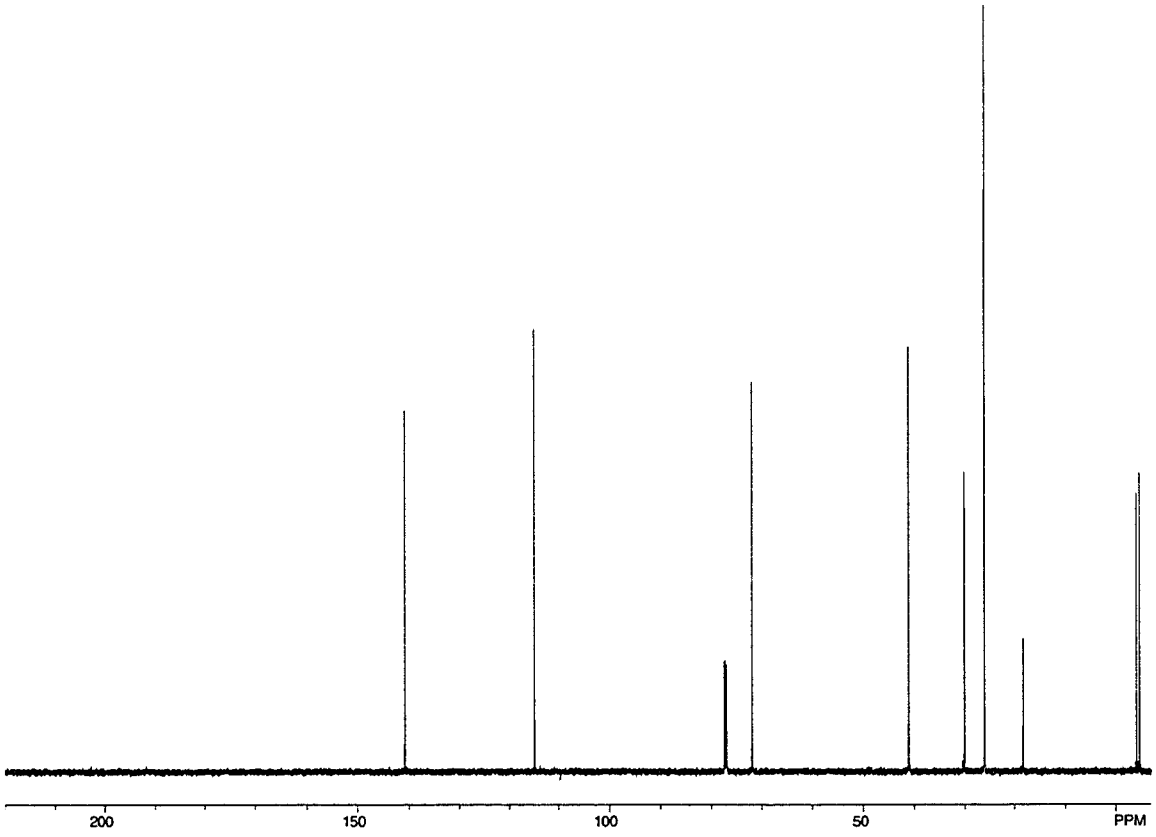


Figure A.3.6 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **101**.

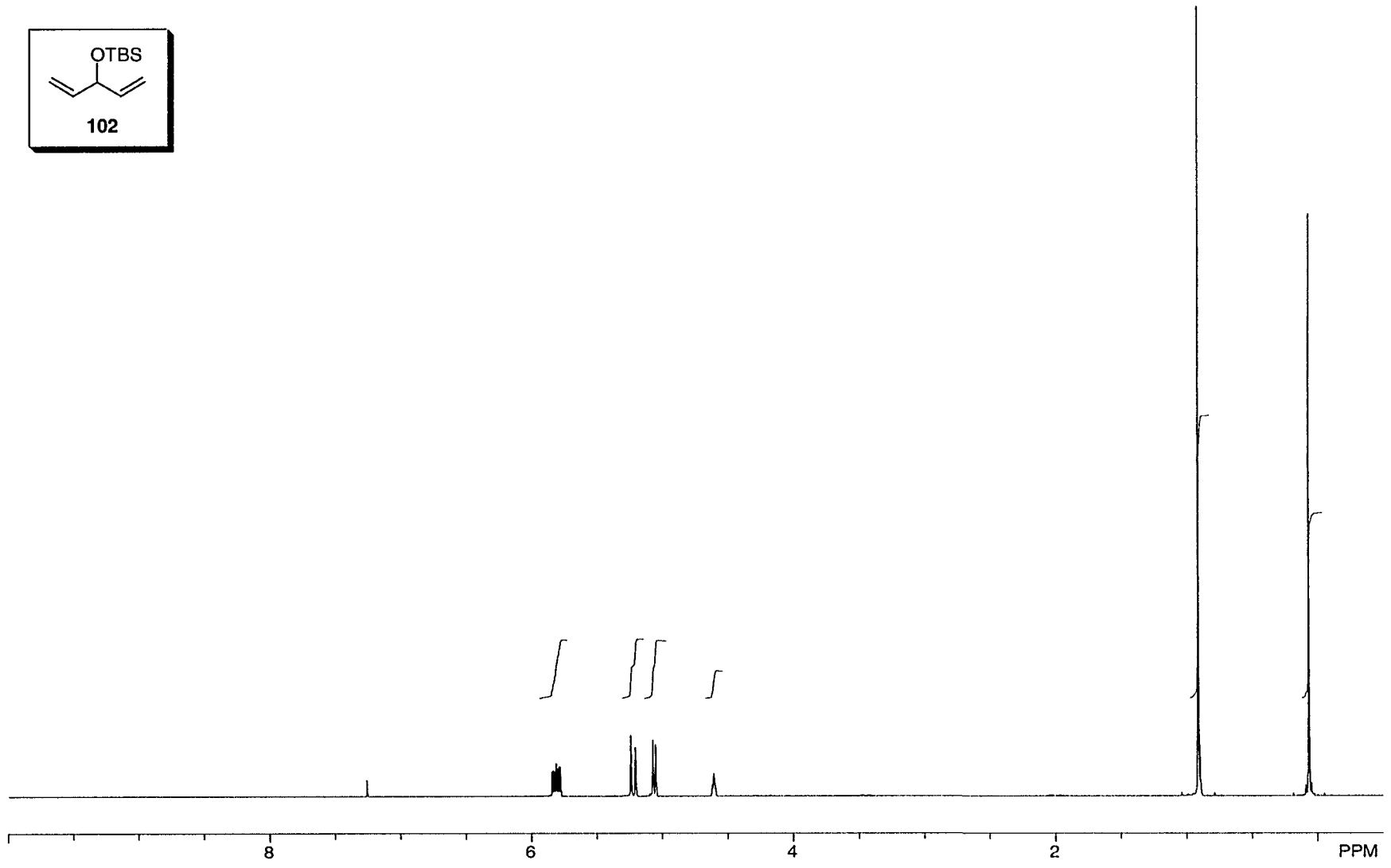


Figure A.3.7 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **102**.

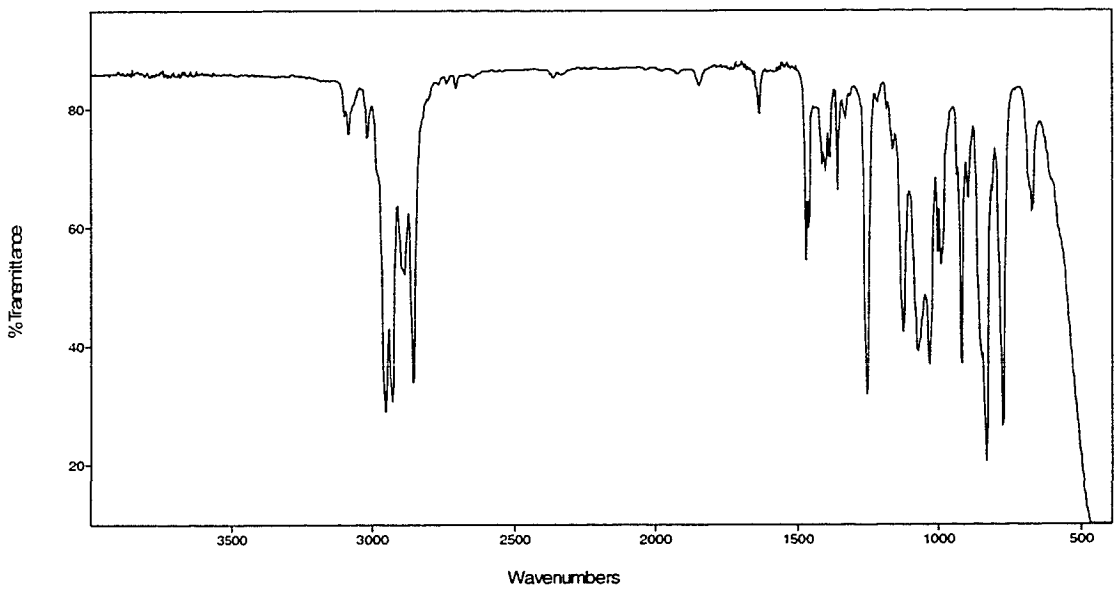


Figure A.3.8 FTIR Spectrum (thin film/NaCl) of Compound **102.**

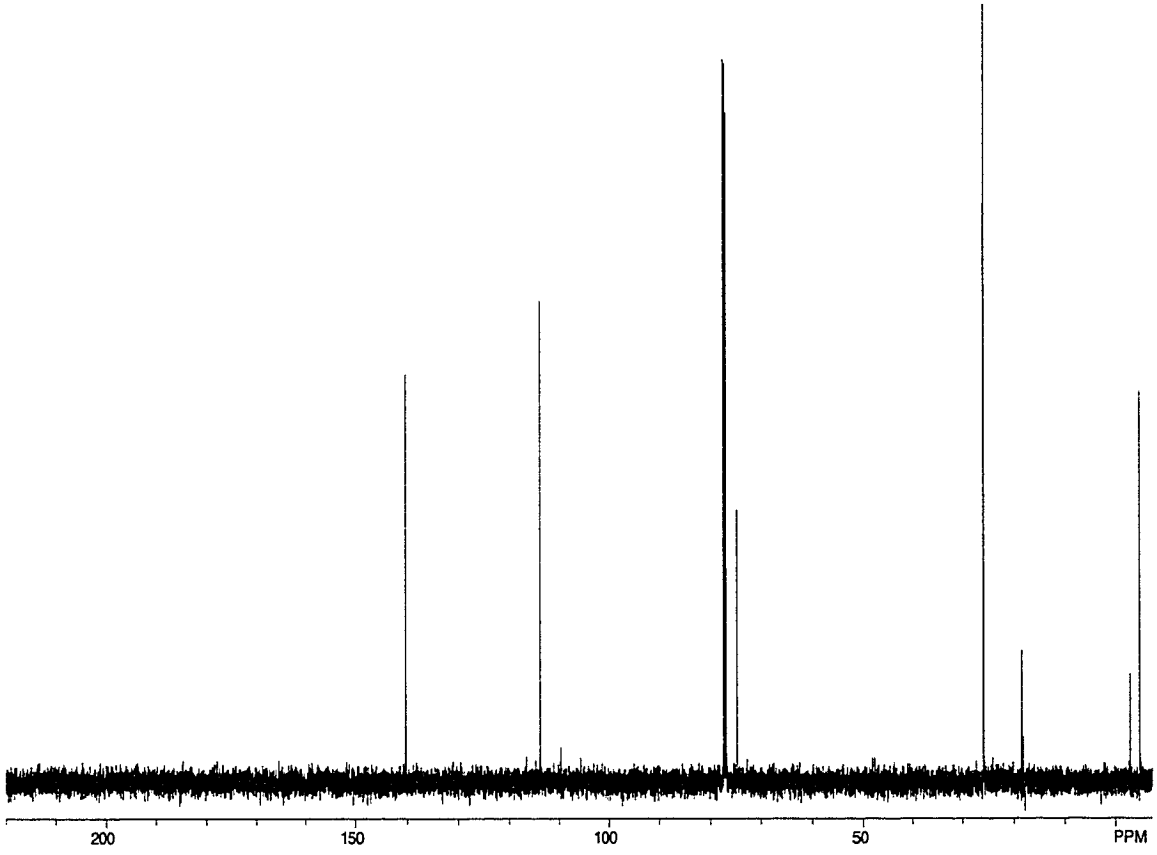


Figure A.3.9 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **102.**

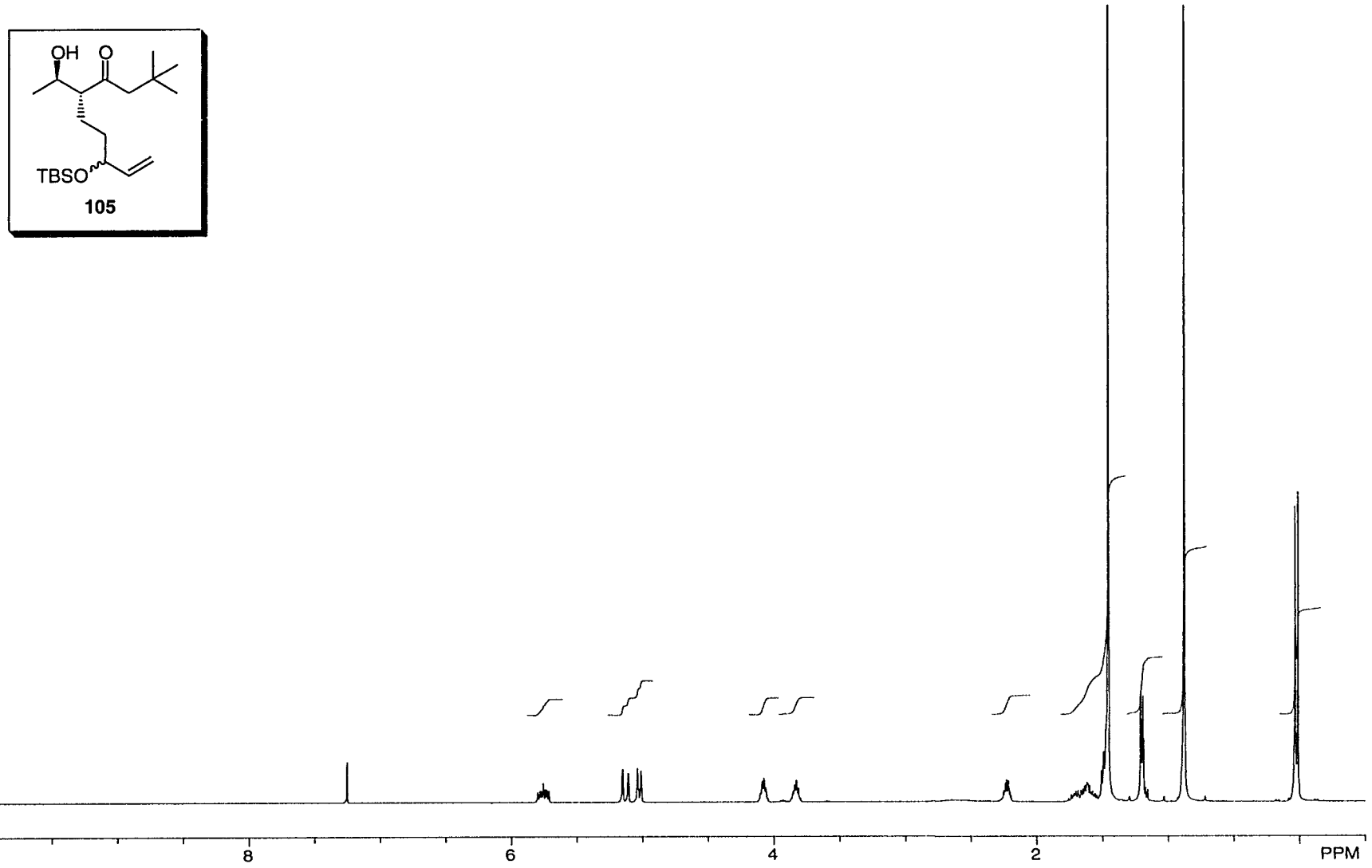


Figure A.3.10 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **105**.

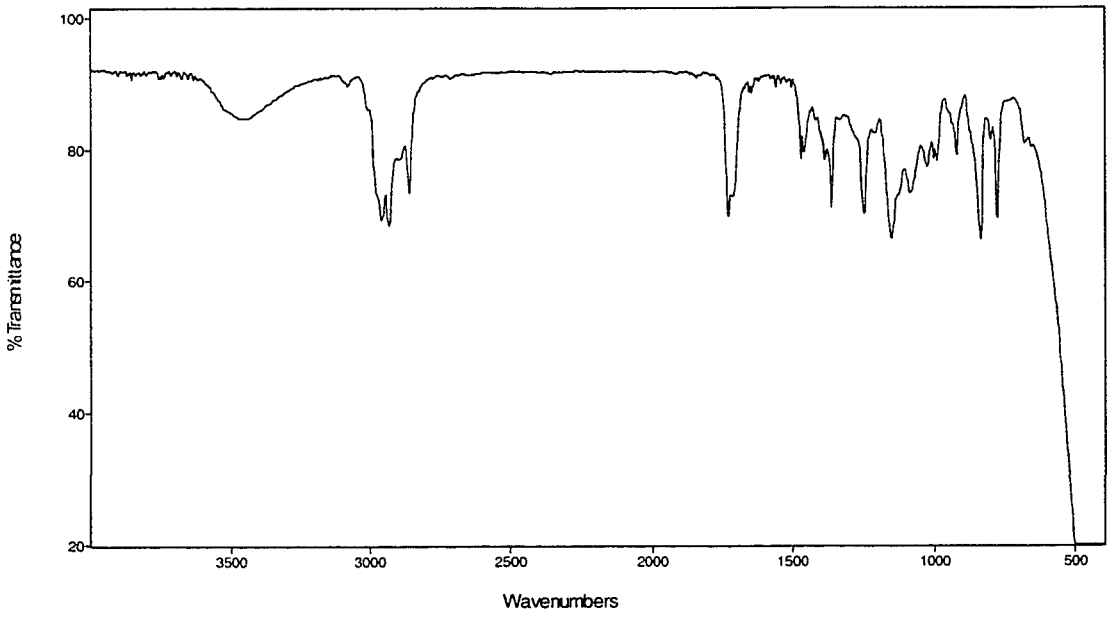


Figure A.3.11 FTIR Spectrum (thin film/NaCl) of Compound **105**.

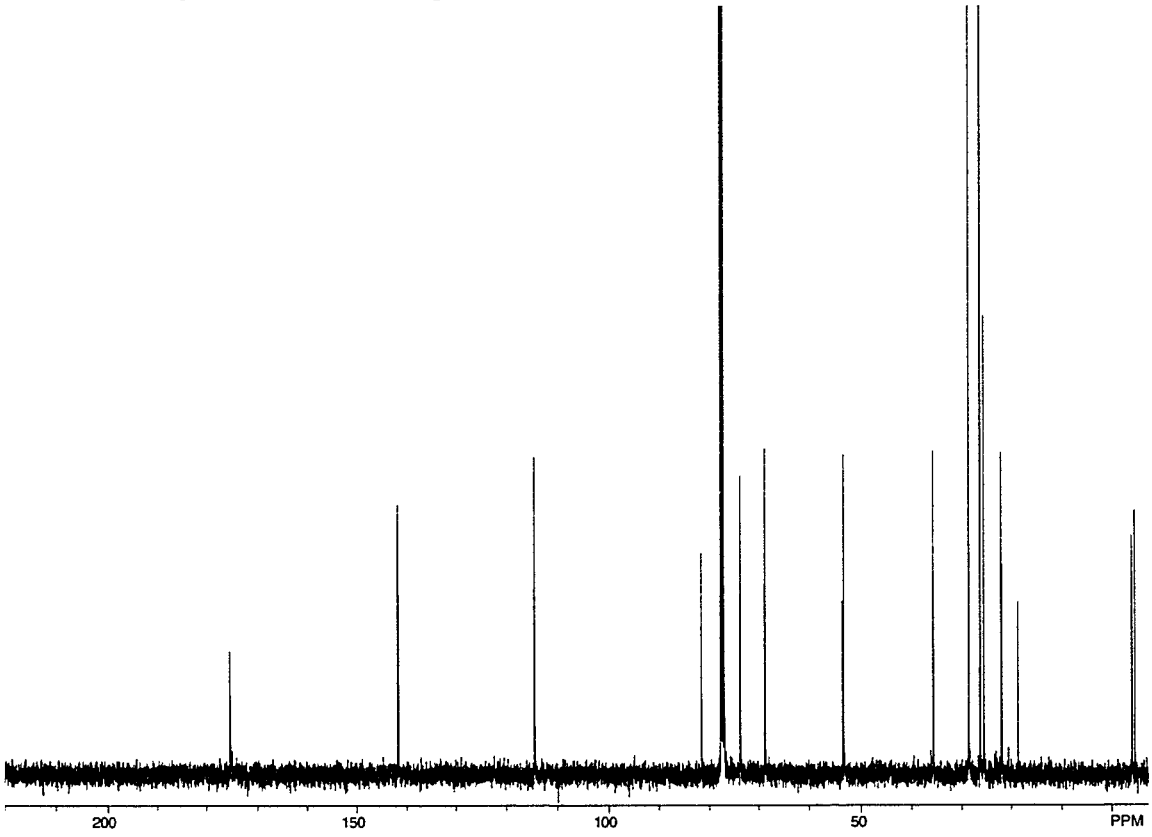


Figure A.3.12 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **105**.

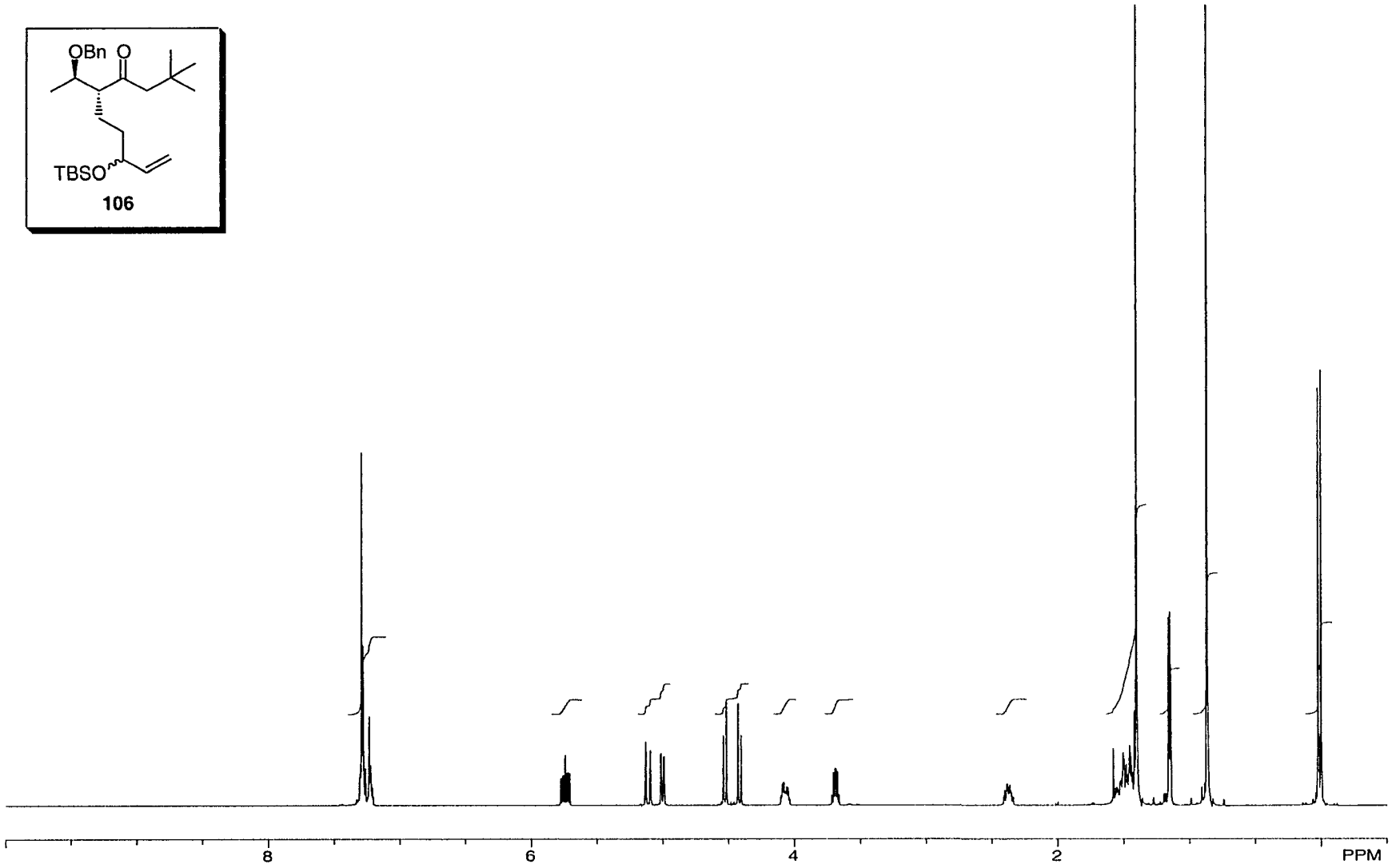


Figure A.3.13 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **106**.

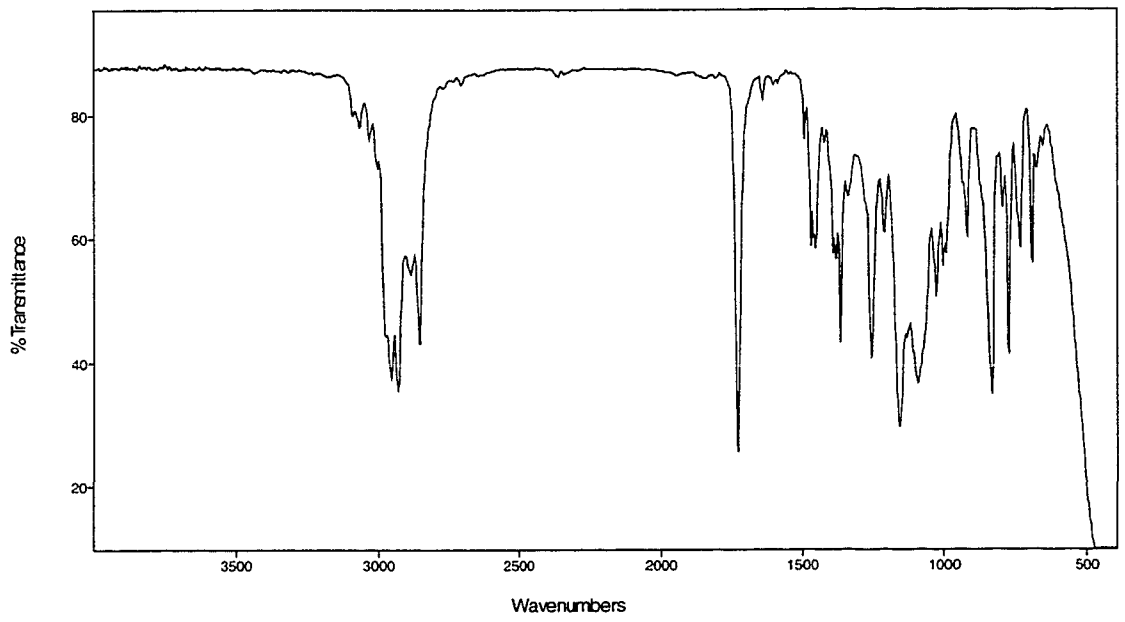


Figure A.3.14 FTIR Spectrum (thin film/NaCl) of Compound **106**.

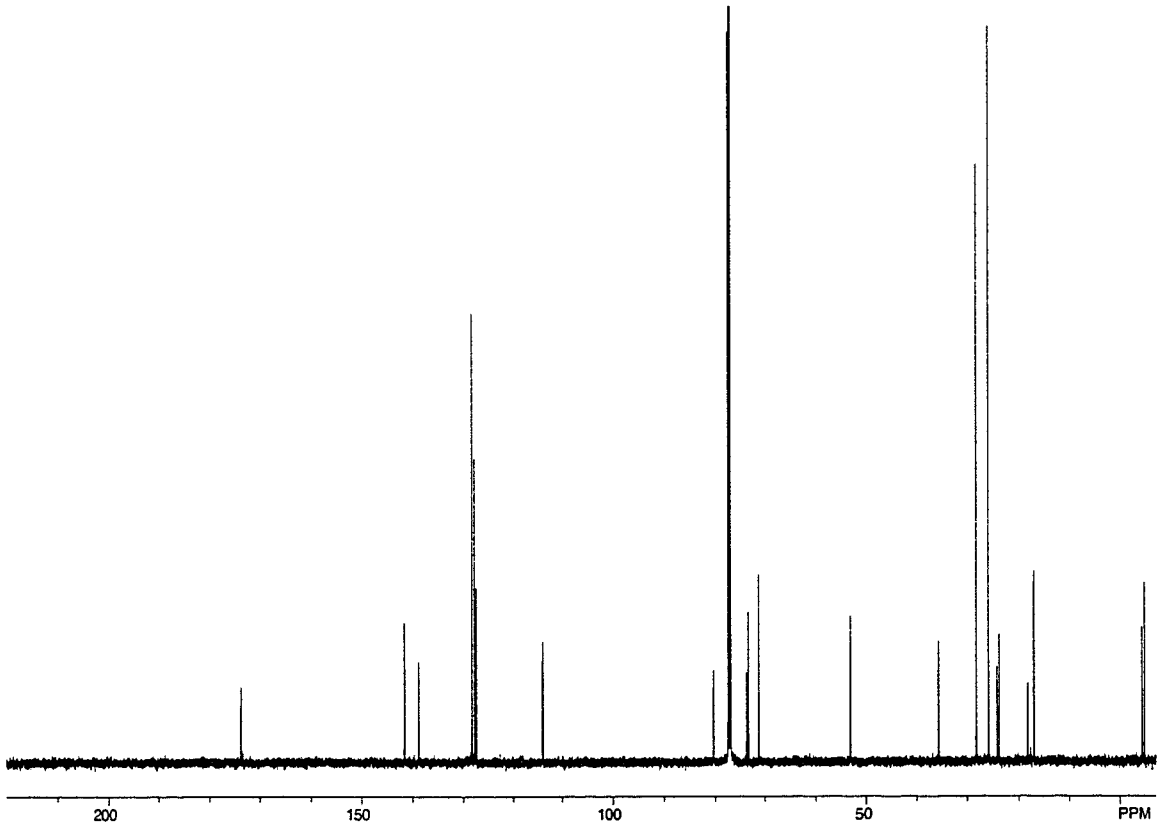


Figure A.3.15 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **106**.

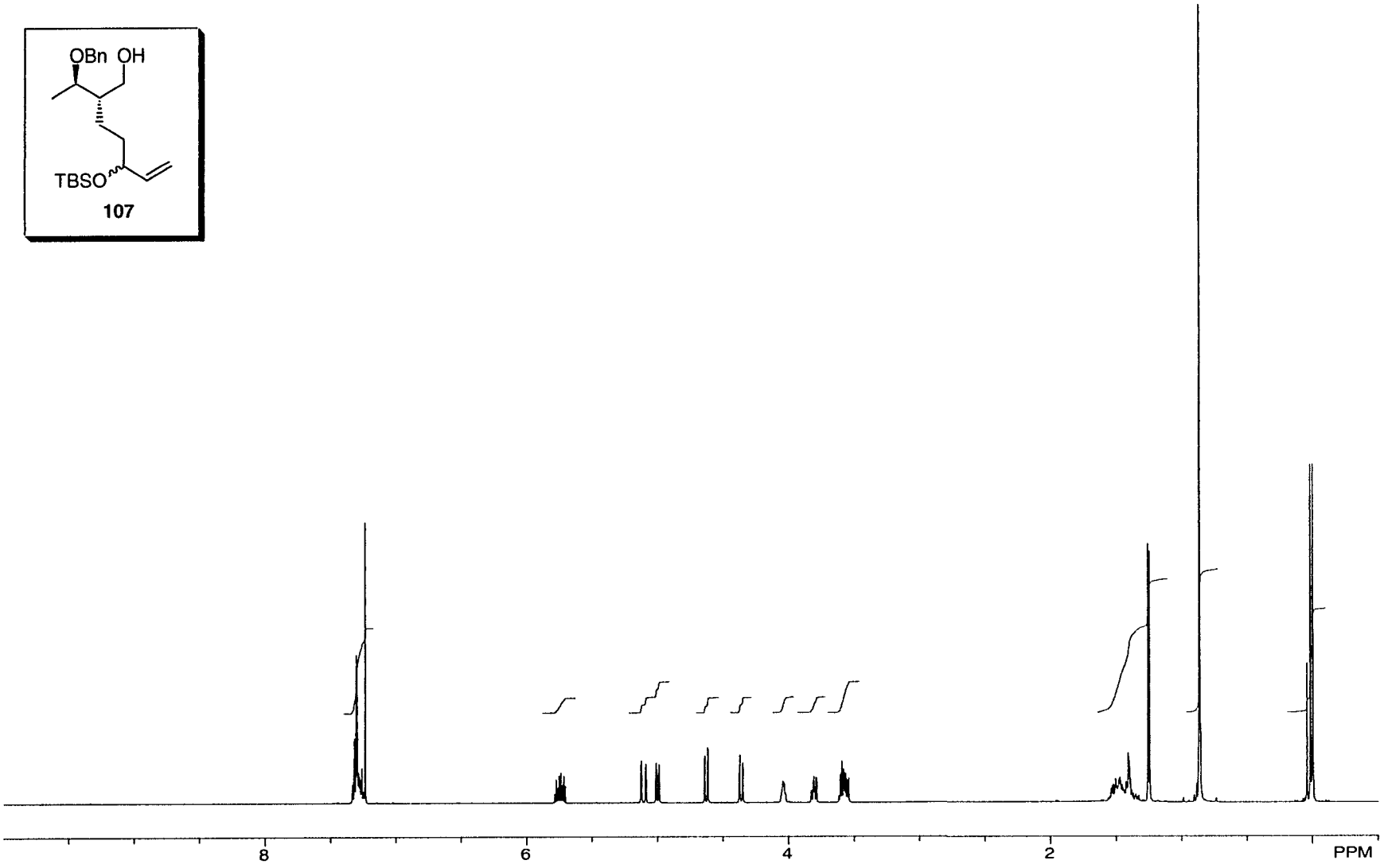


Figure A.3.16 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **107**.

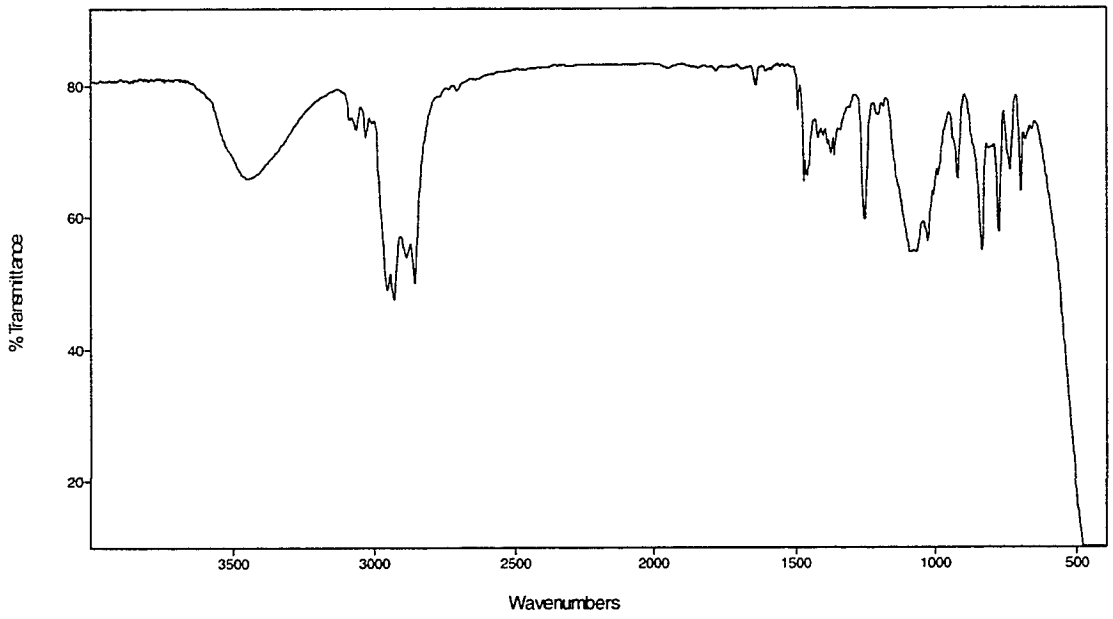


Figure A.3.17 FTIR Spectrum (thin film/NaCl) of Compound **107**.

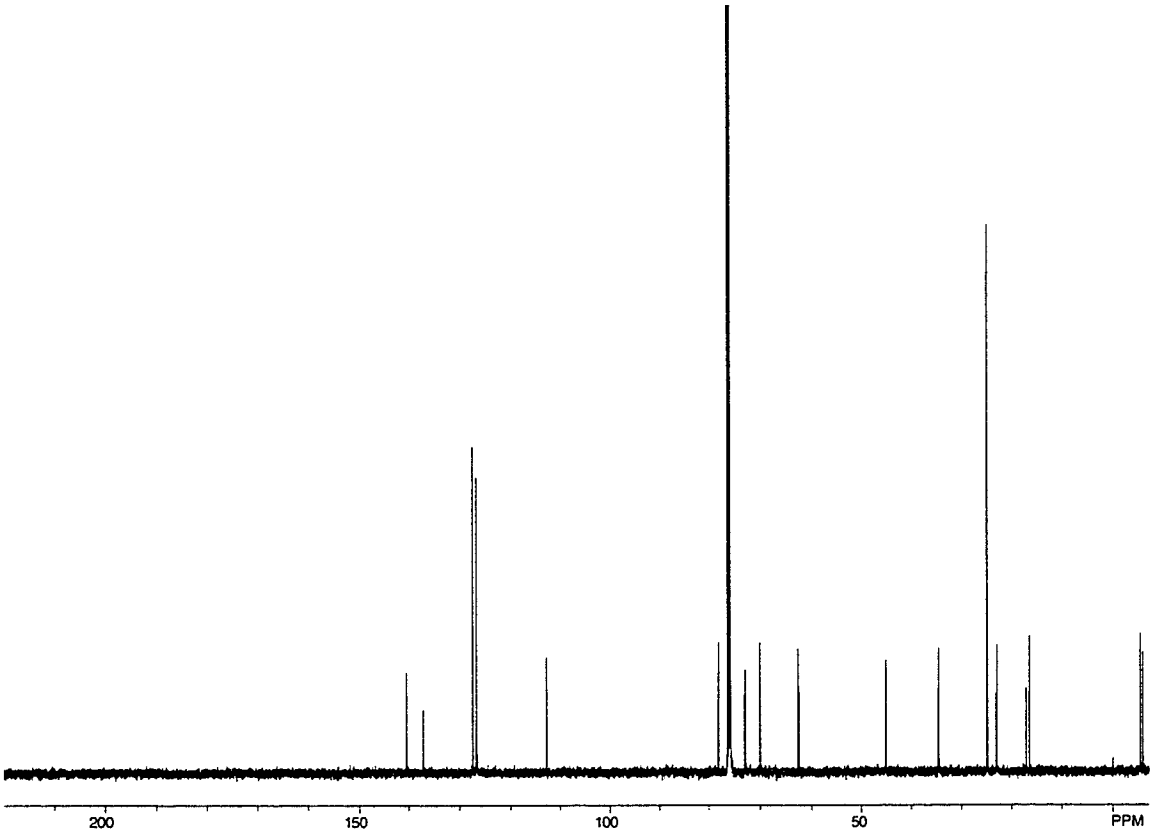


Figure A.3.18 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **107**.

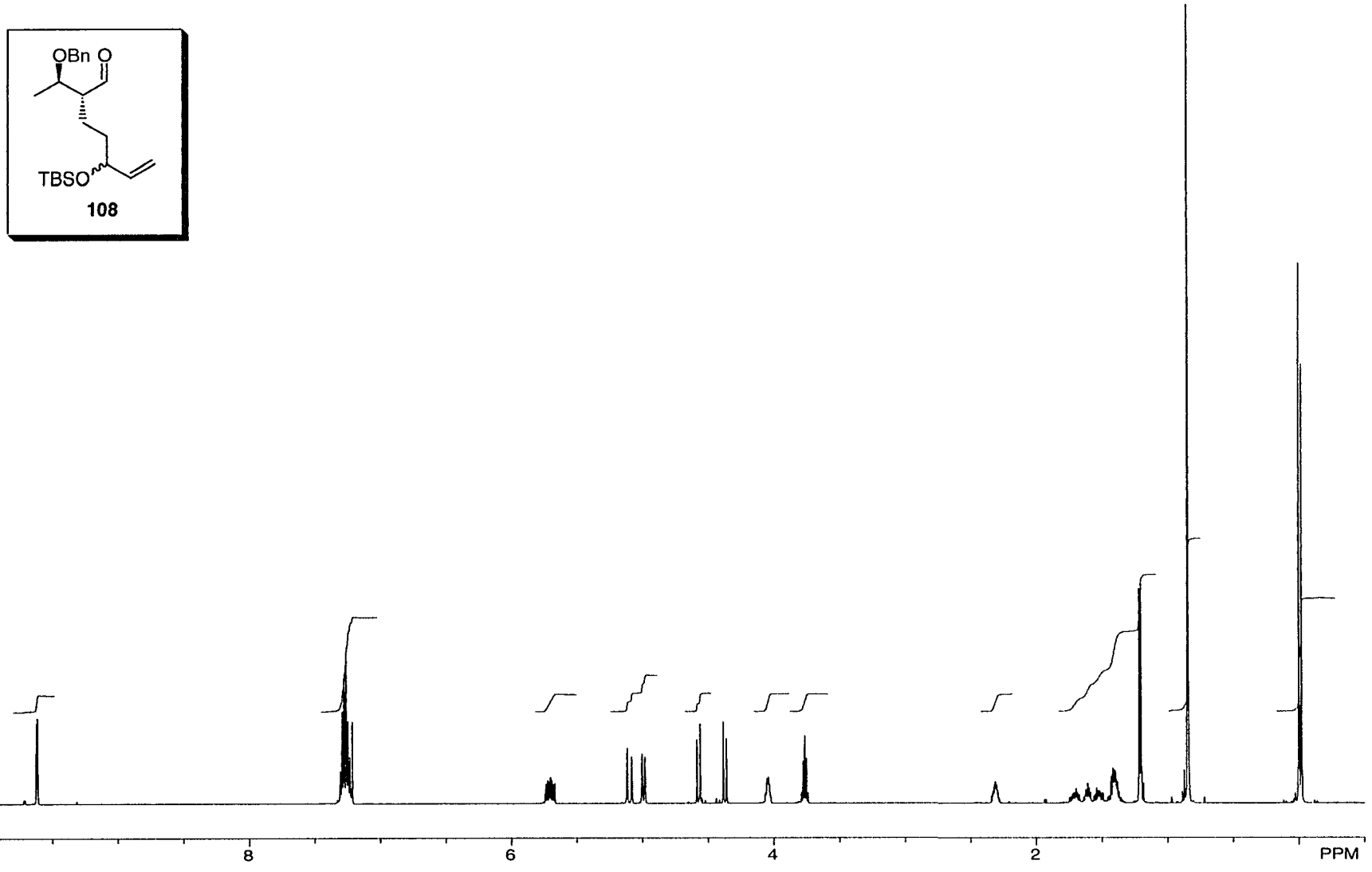


Figure A.3.19 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **108**.

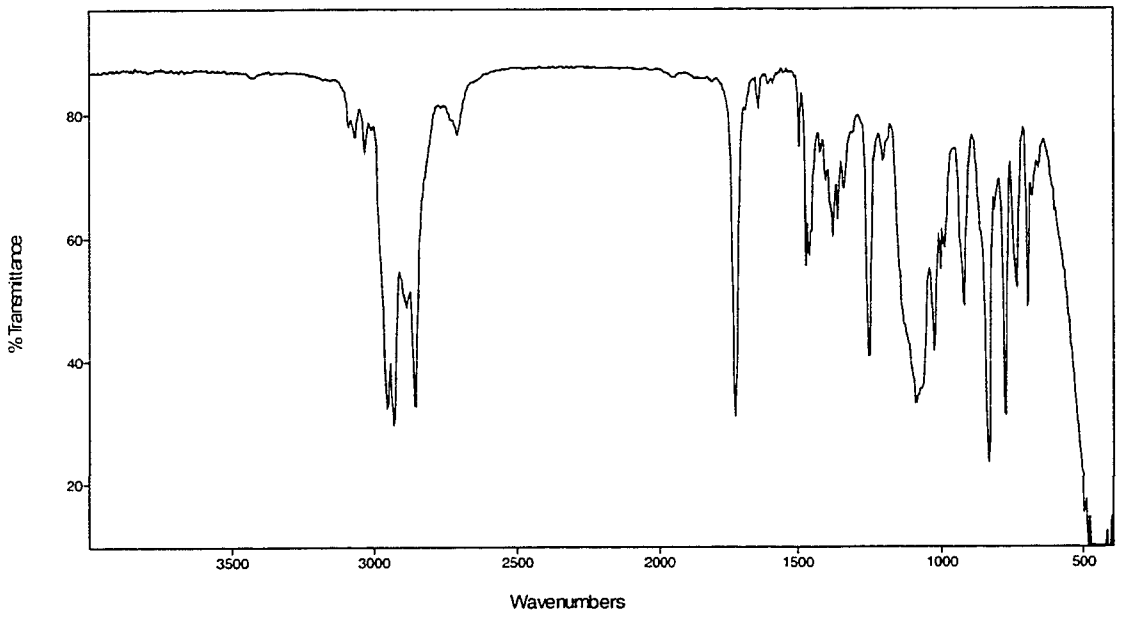


Figure A.3.20 FTIR Spectrum (thin film/NaCl) of Compound **108**.

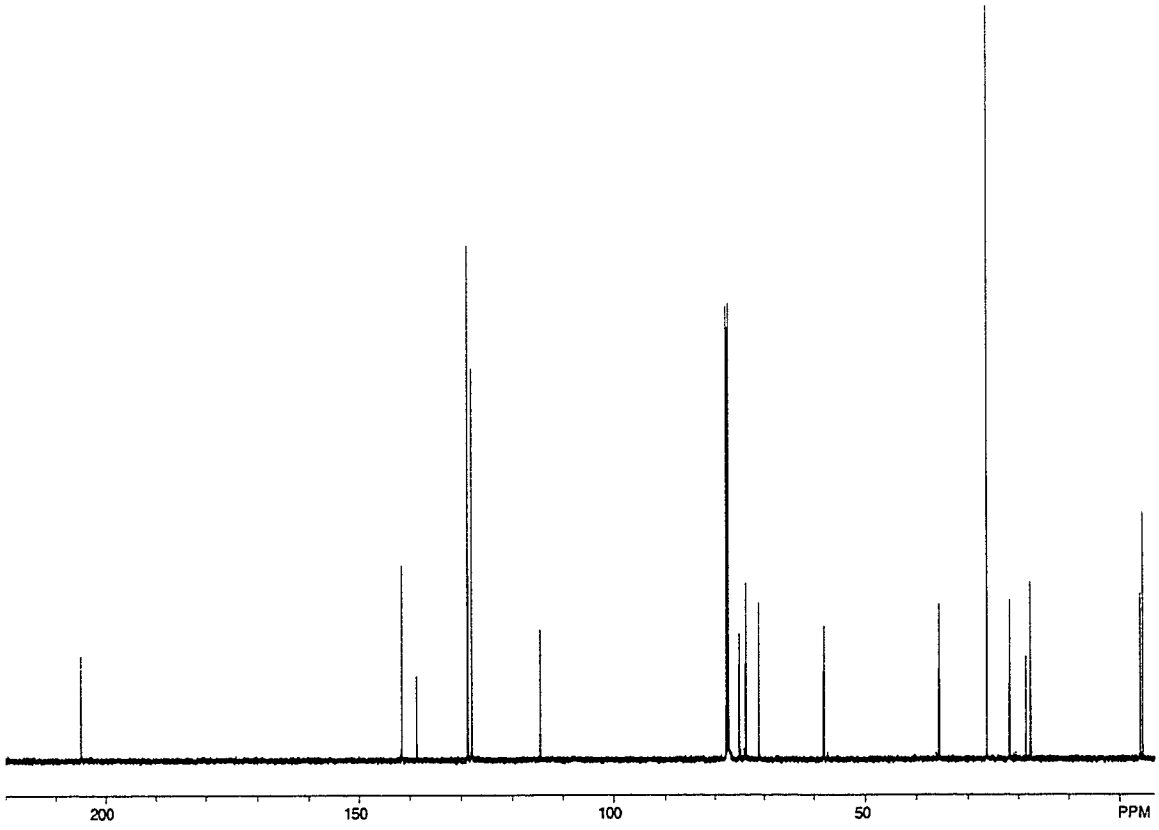


Figure A.3.21 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **108**.

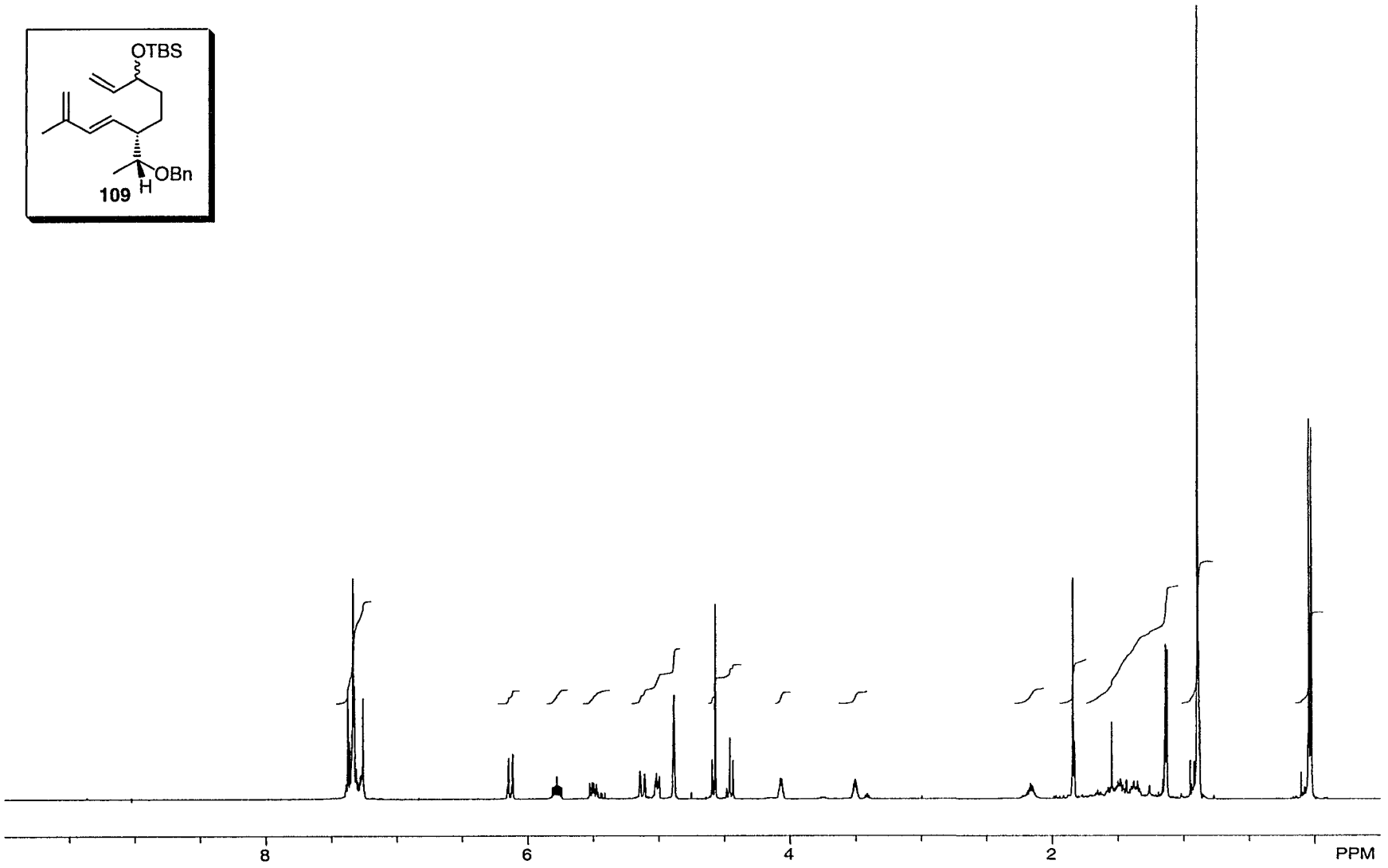


Figure A.3.22 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **109**.

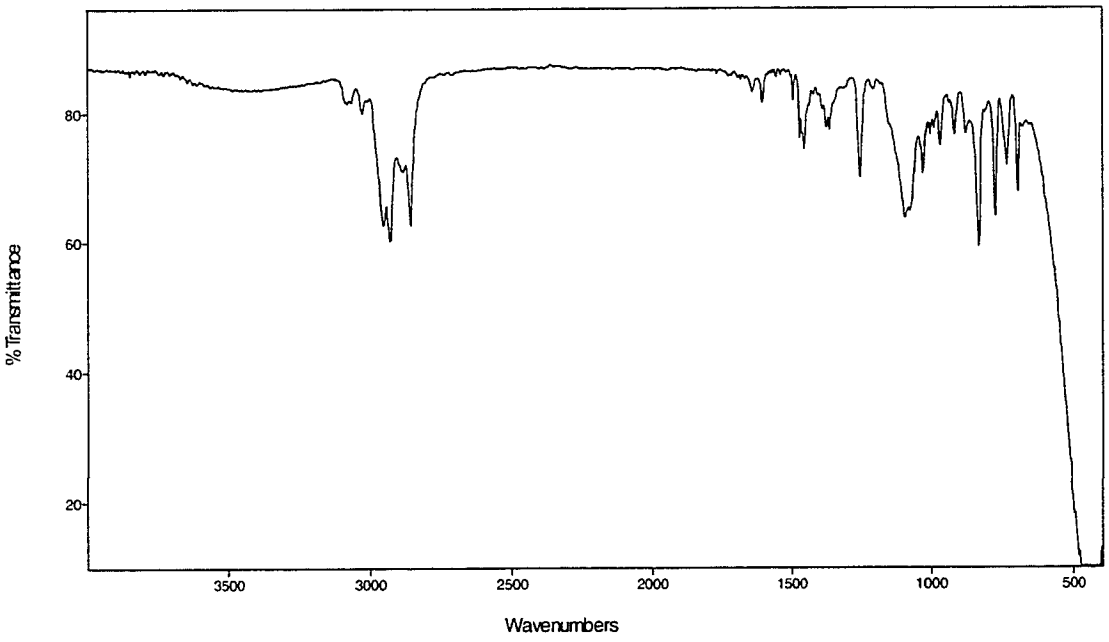


Figure A.3.23 FTIR Spectrum (thin film/NaCl) of Compound **109**.

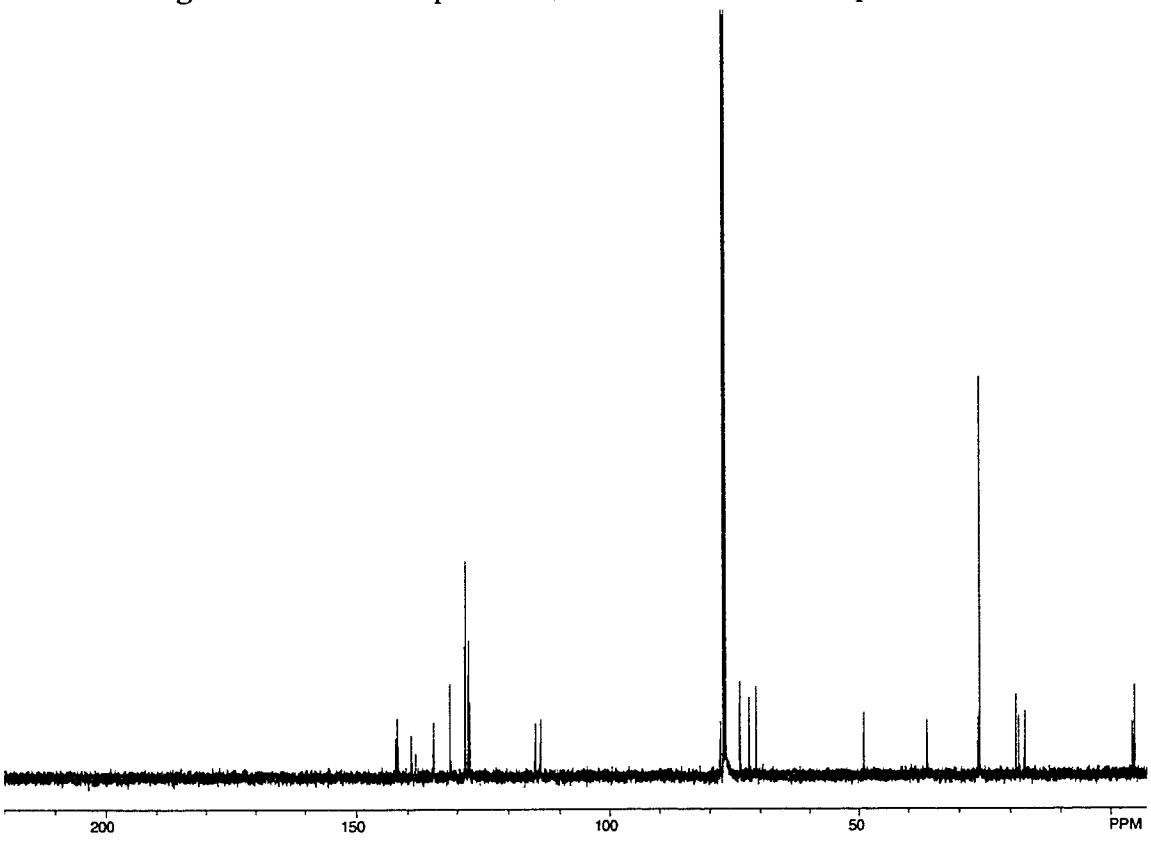


Figure A.3.24 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **109**.

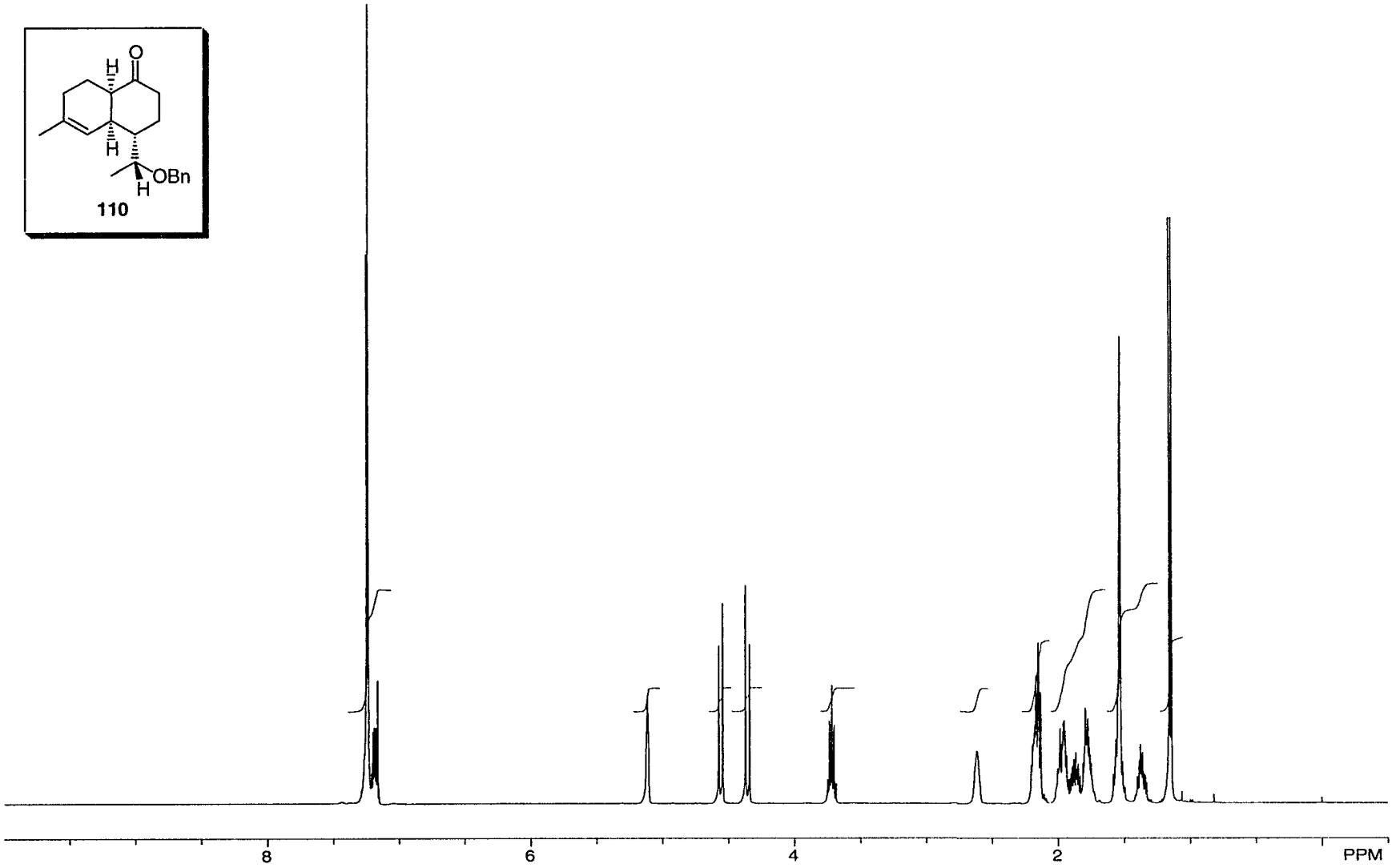


Figure A.3.25 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **110**.

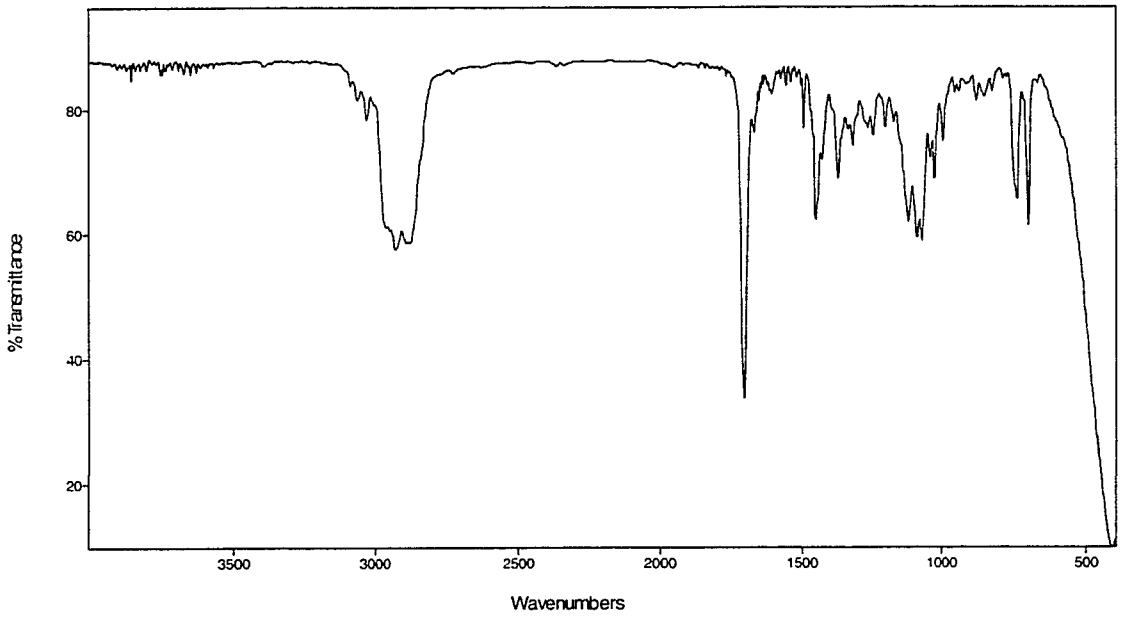


Figure A.3.26 FTIR Spectrum (thin film/NaCl) of Compound **110**.

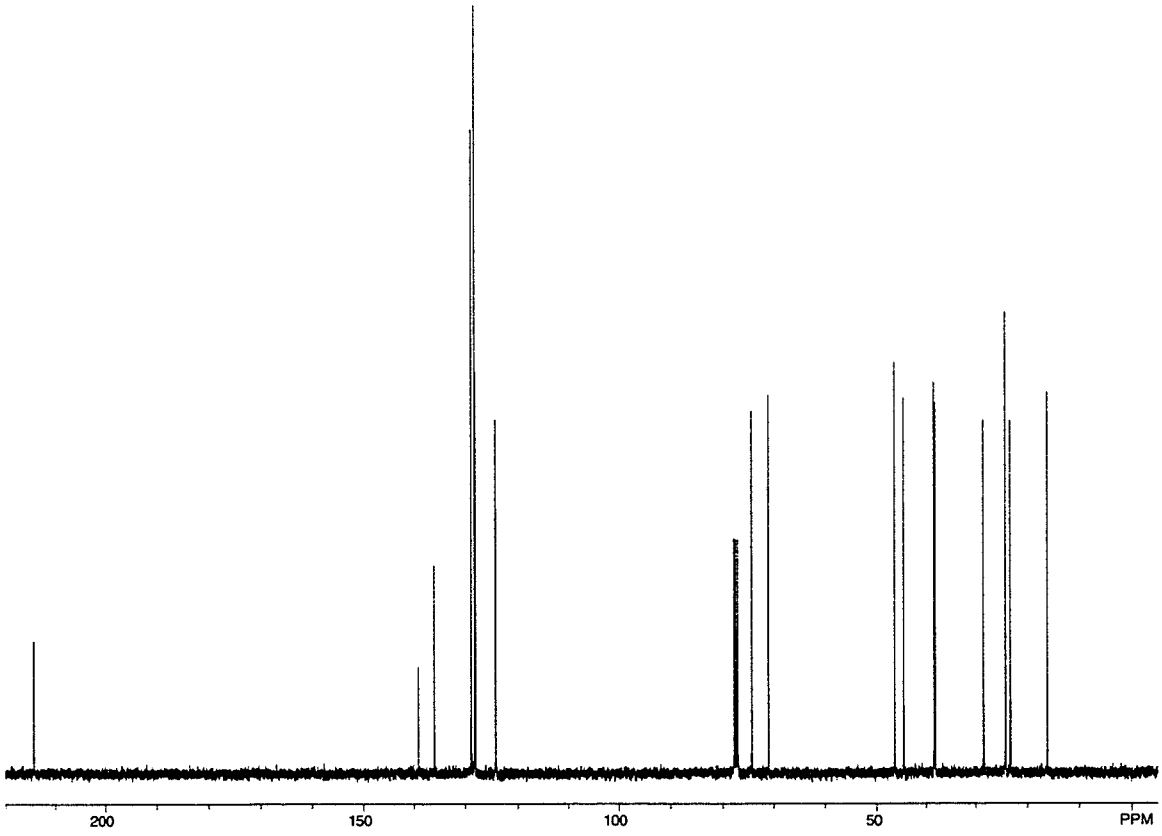


Figure A.3.27 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **110**.

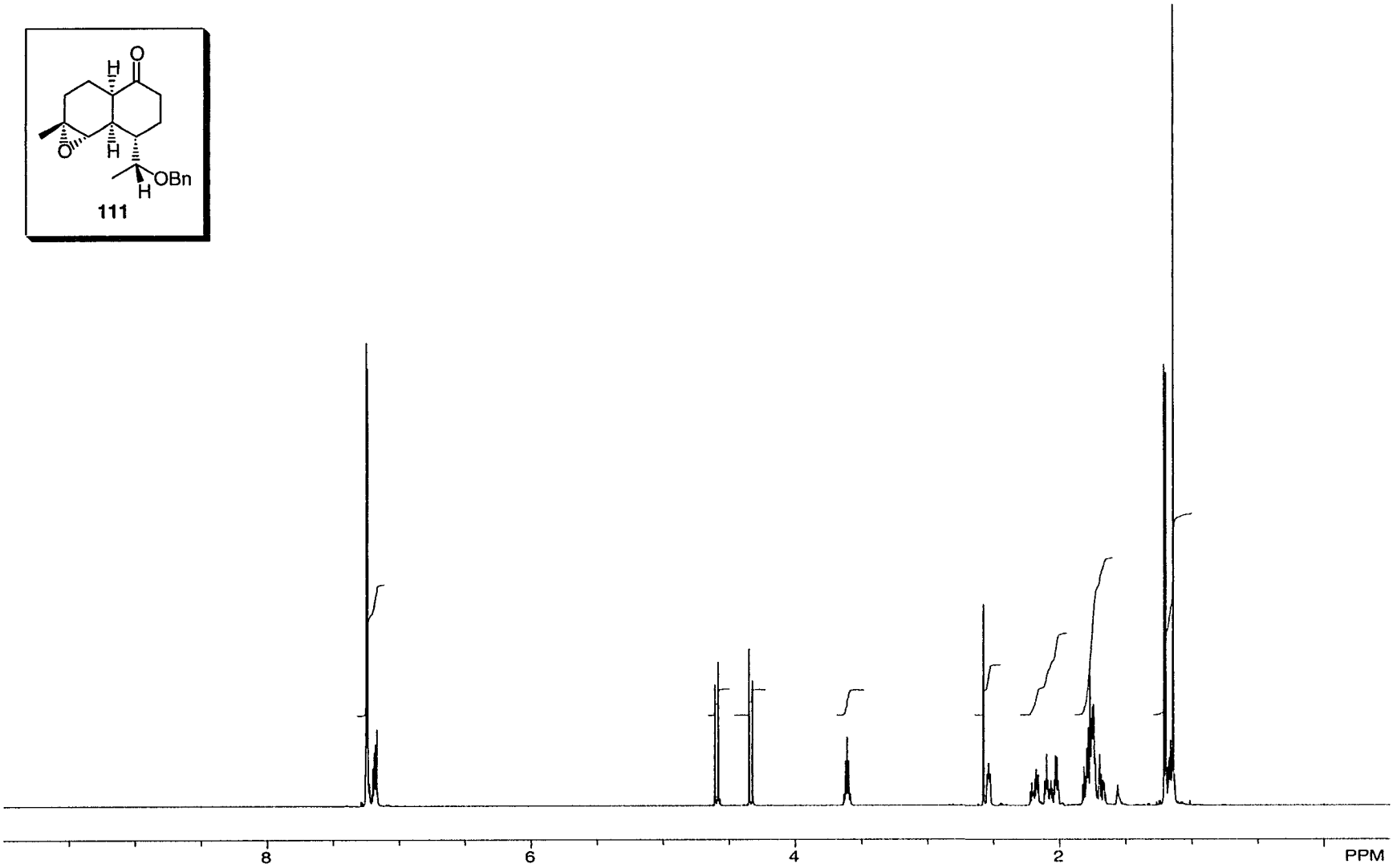


Figure A.3.28 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **111**.

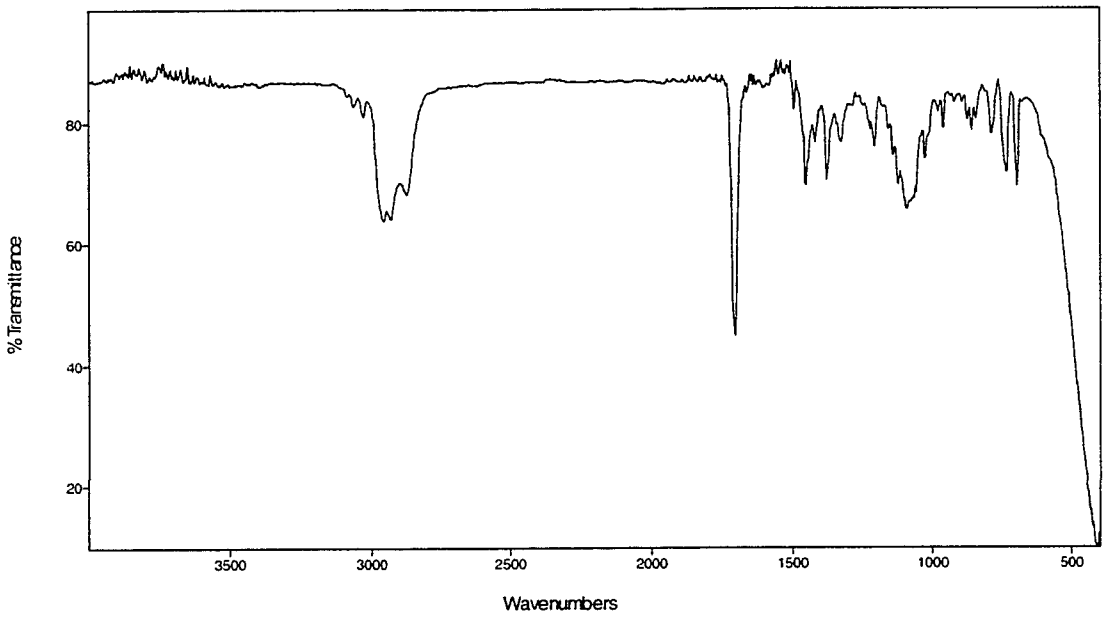


Figure A.3.29 FTIR Spectrum (thin film/NaCl) of Compound **111**.

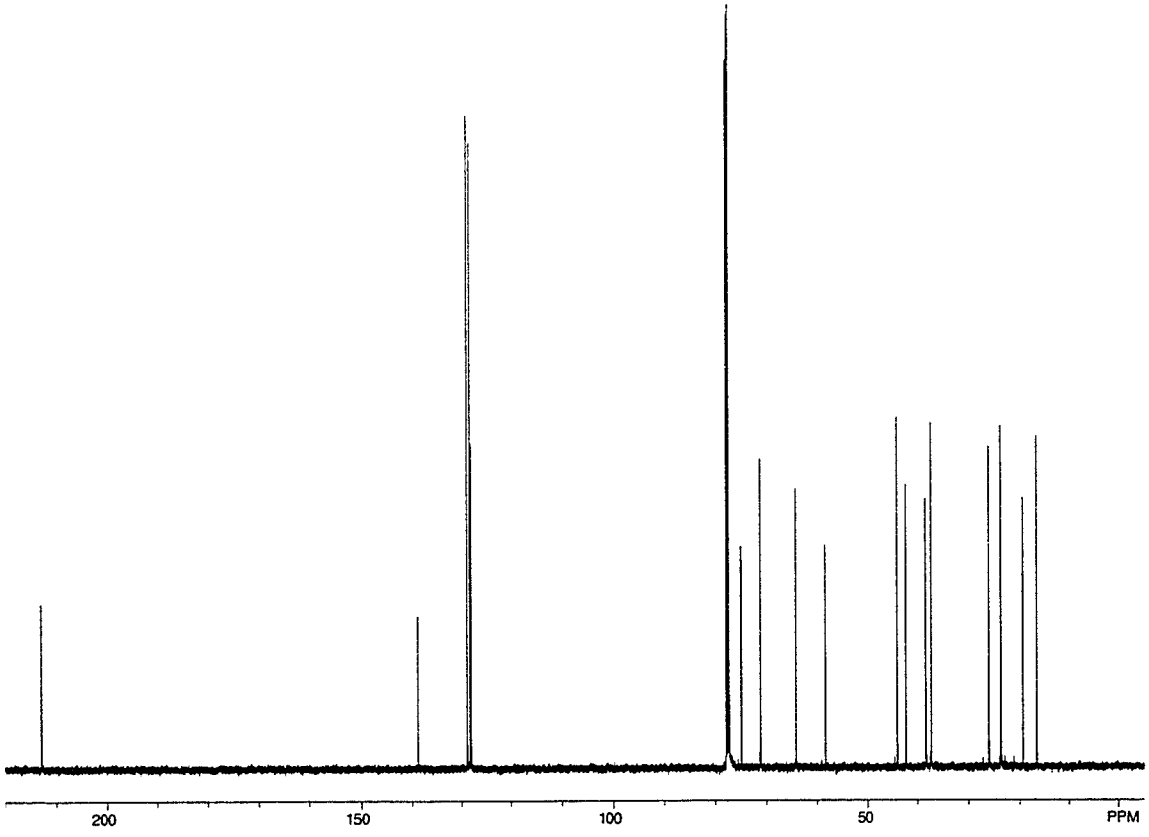


Figure A.3.30 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **111**.

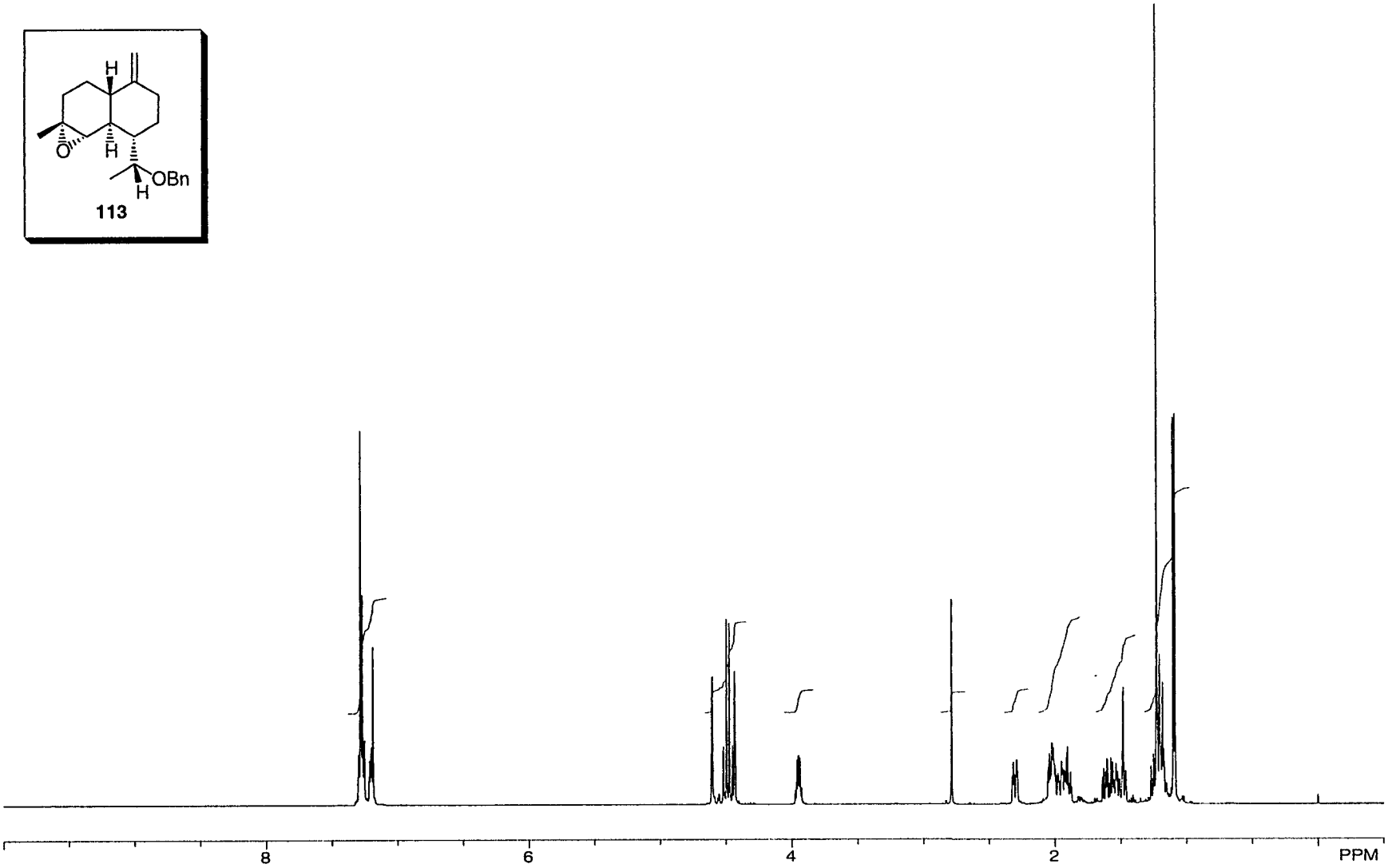


Figure A.3.31 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **113**.

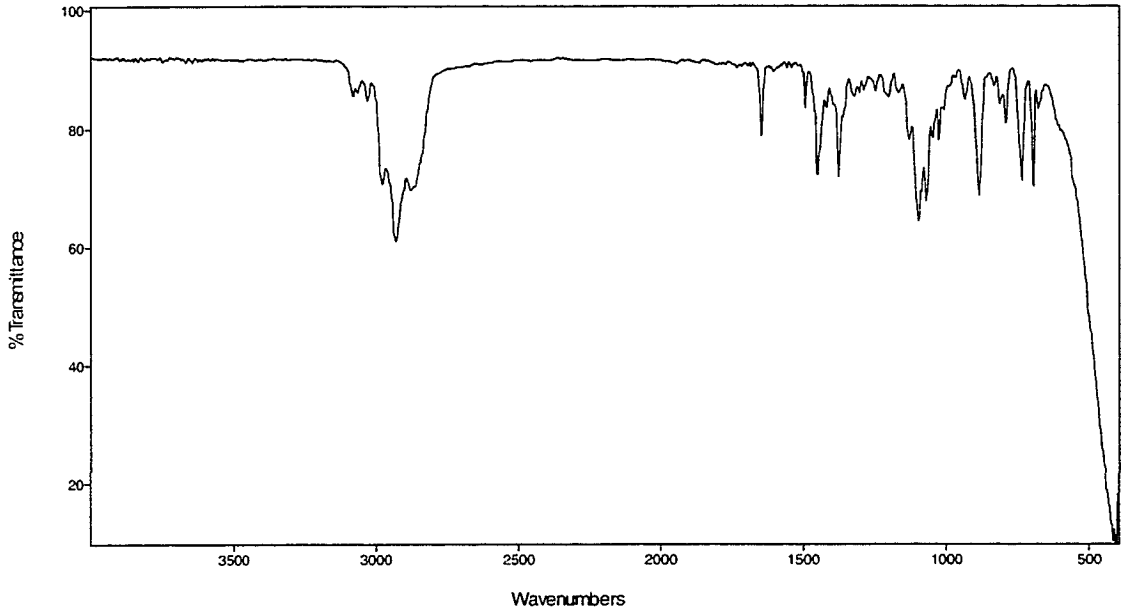


Figure A.3.32 FTIR Spectrum (thin film/NaCl) of Compound **113**.

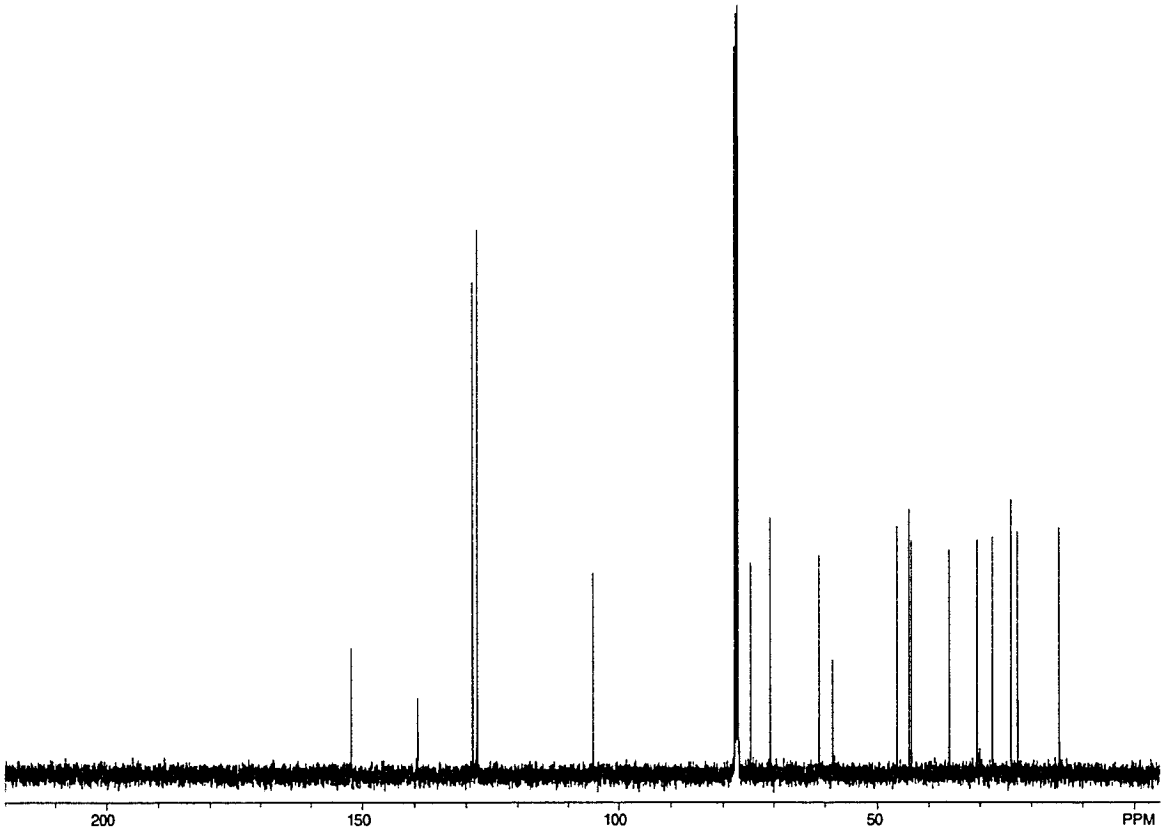


Figure A.3.33 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **113**.

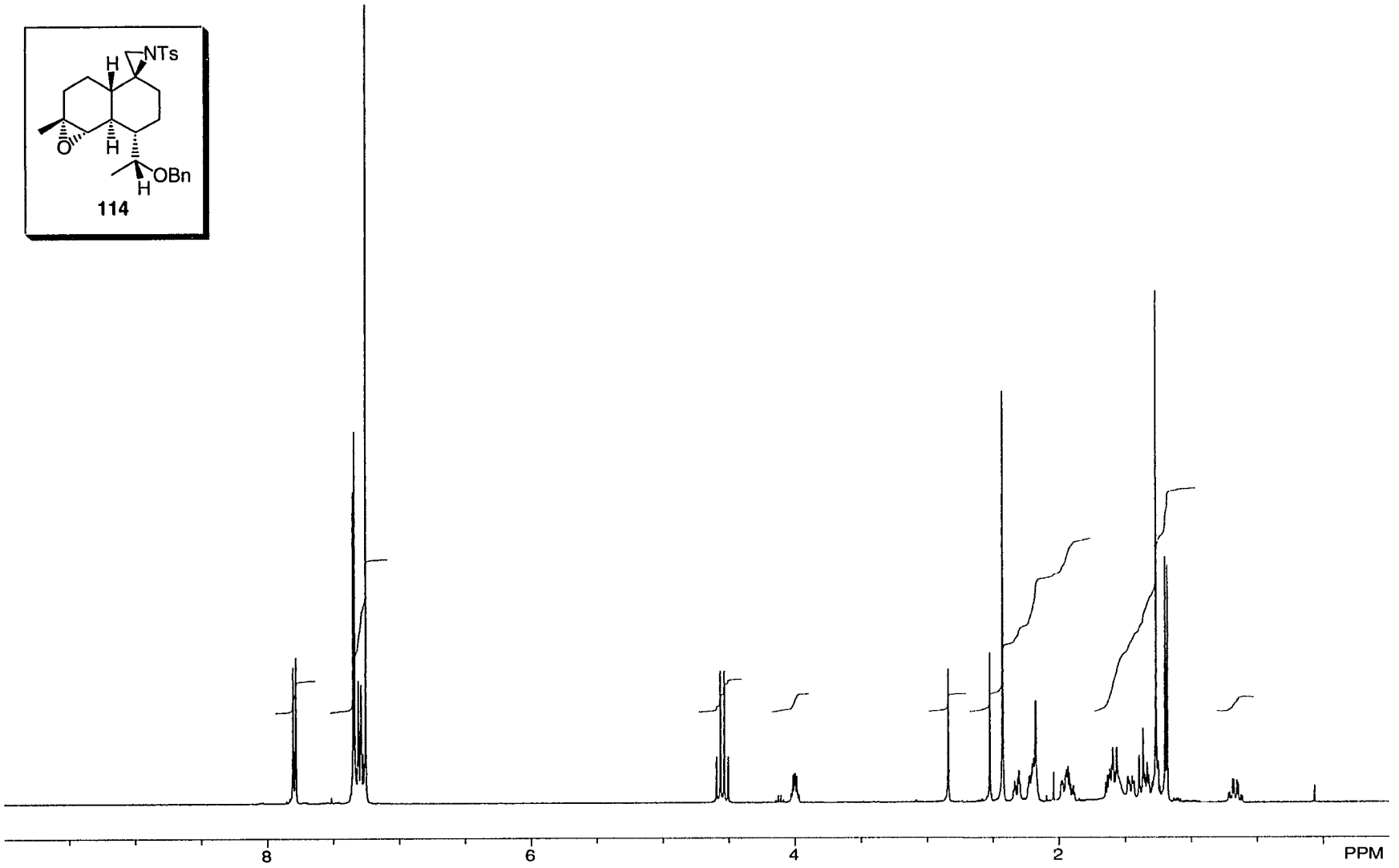


Figure A.3.34 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **114**.

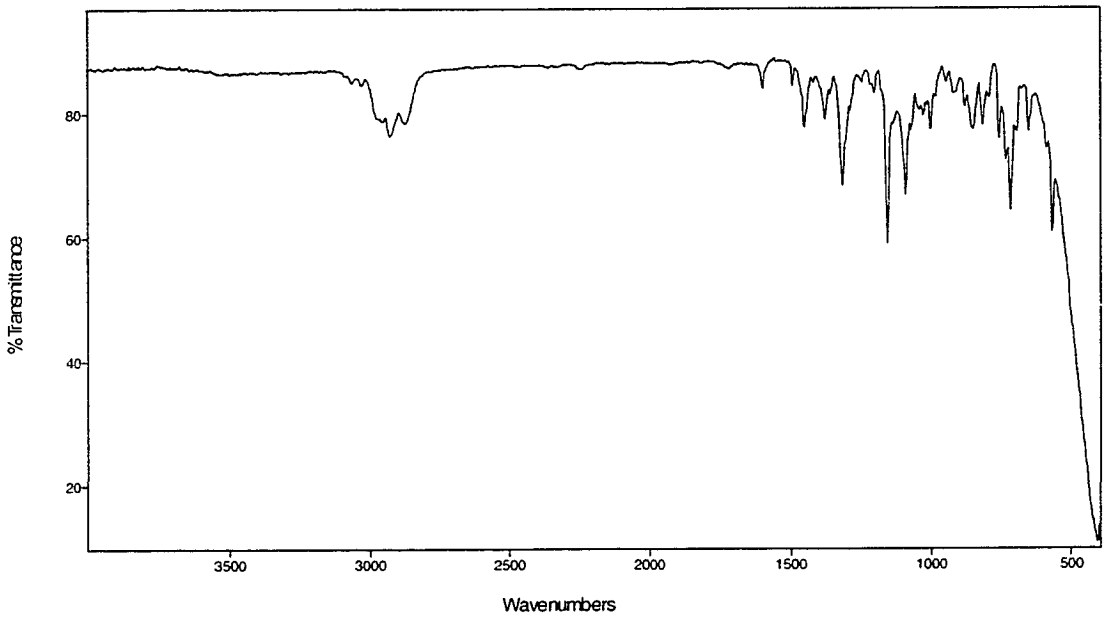


Figure A.3.35 FTIR Spectrum (thin film/NaCl) of Compound **114**.

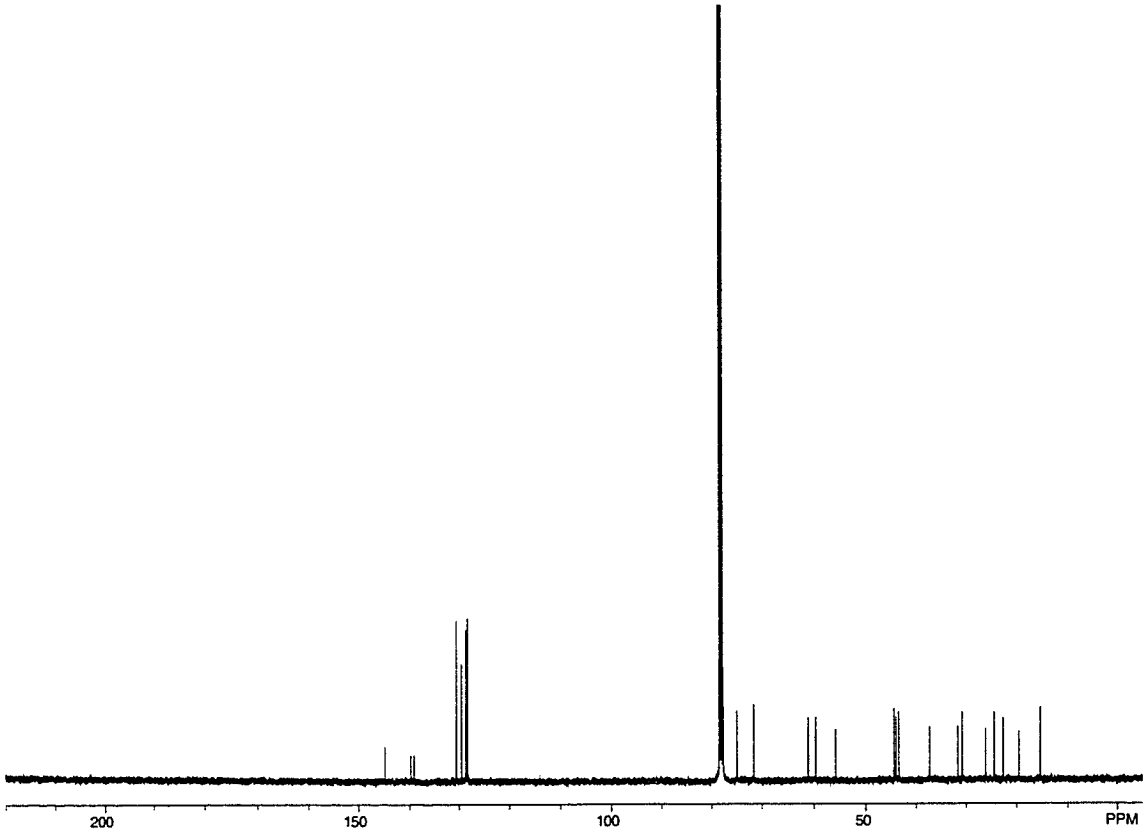


Figure A.3.36 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **114**.

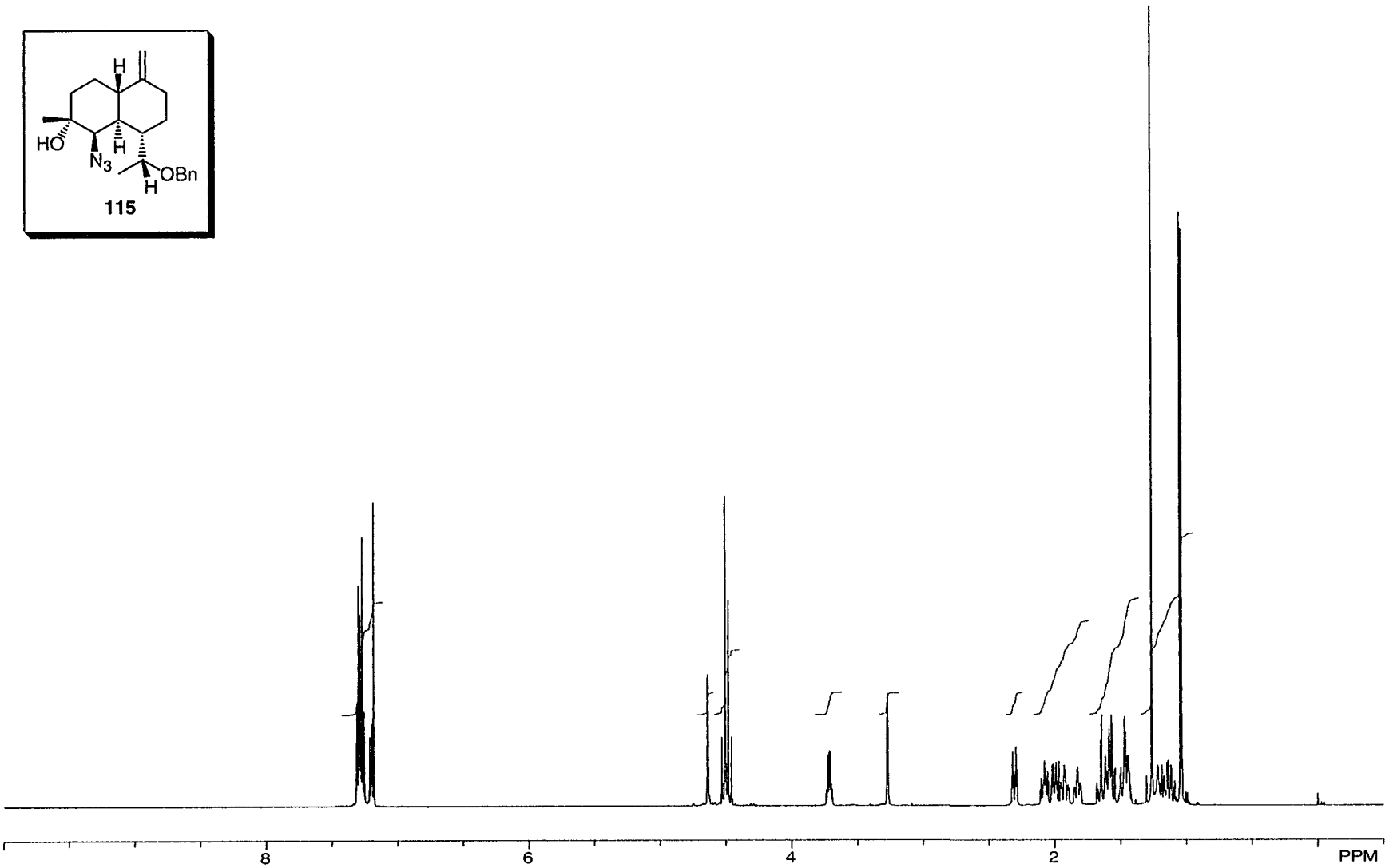


Figure A.3.37 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **115**.

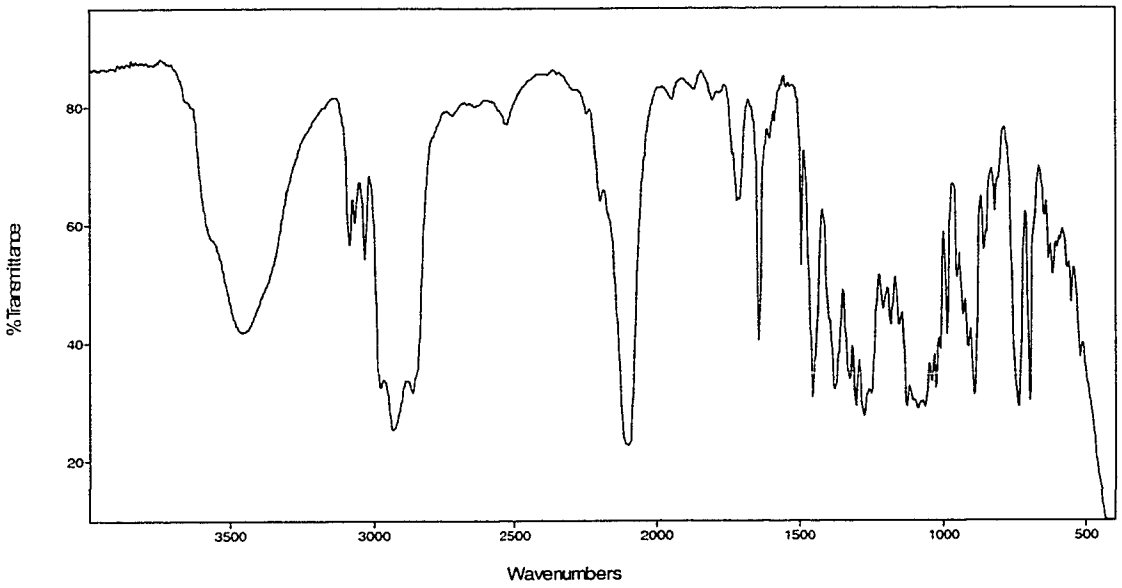


Figure A.3.38 FTIR Spectrum (thin film/NaCl) of Compound **115**.

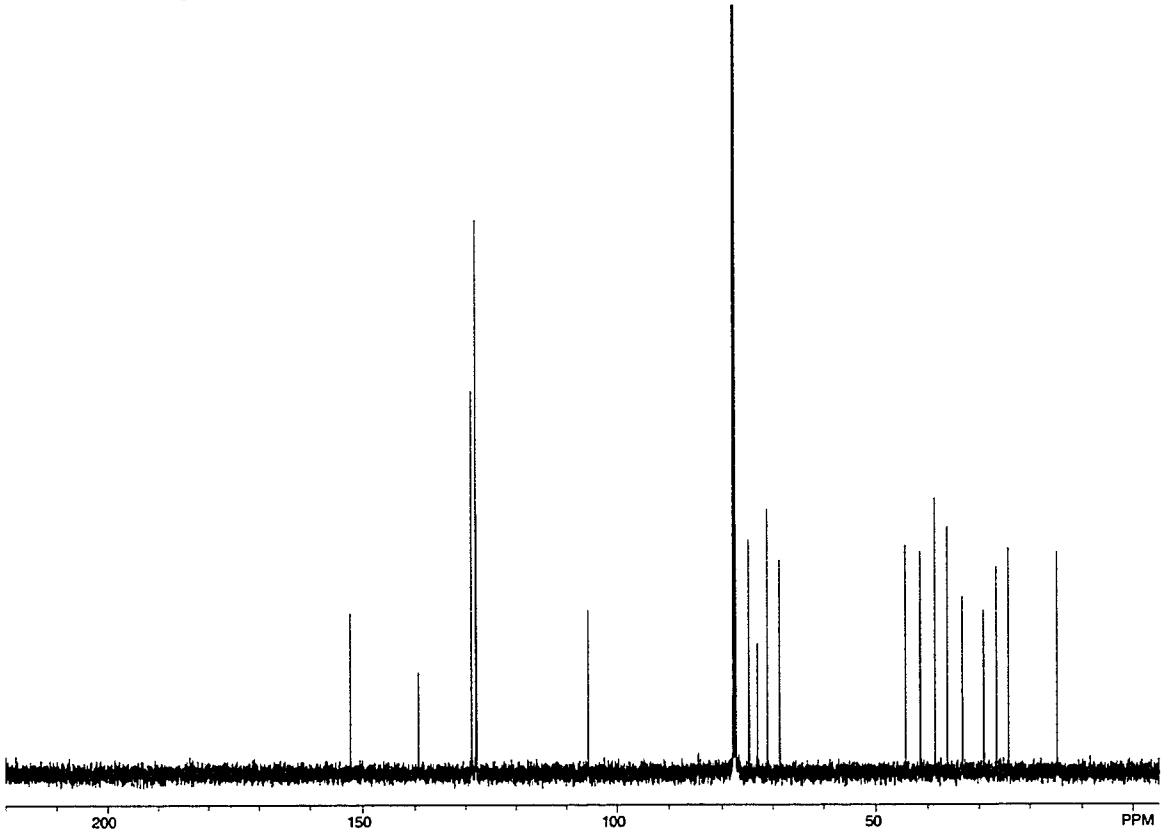


Figure A.3.39 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **115**.

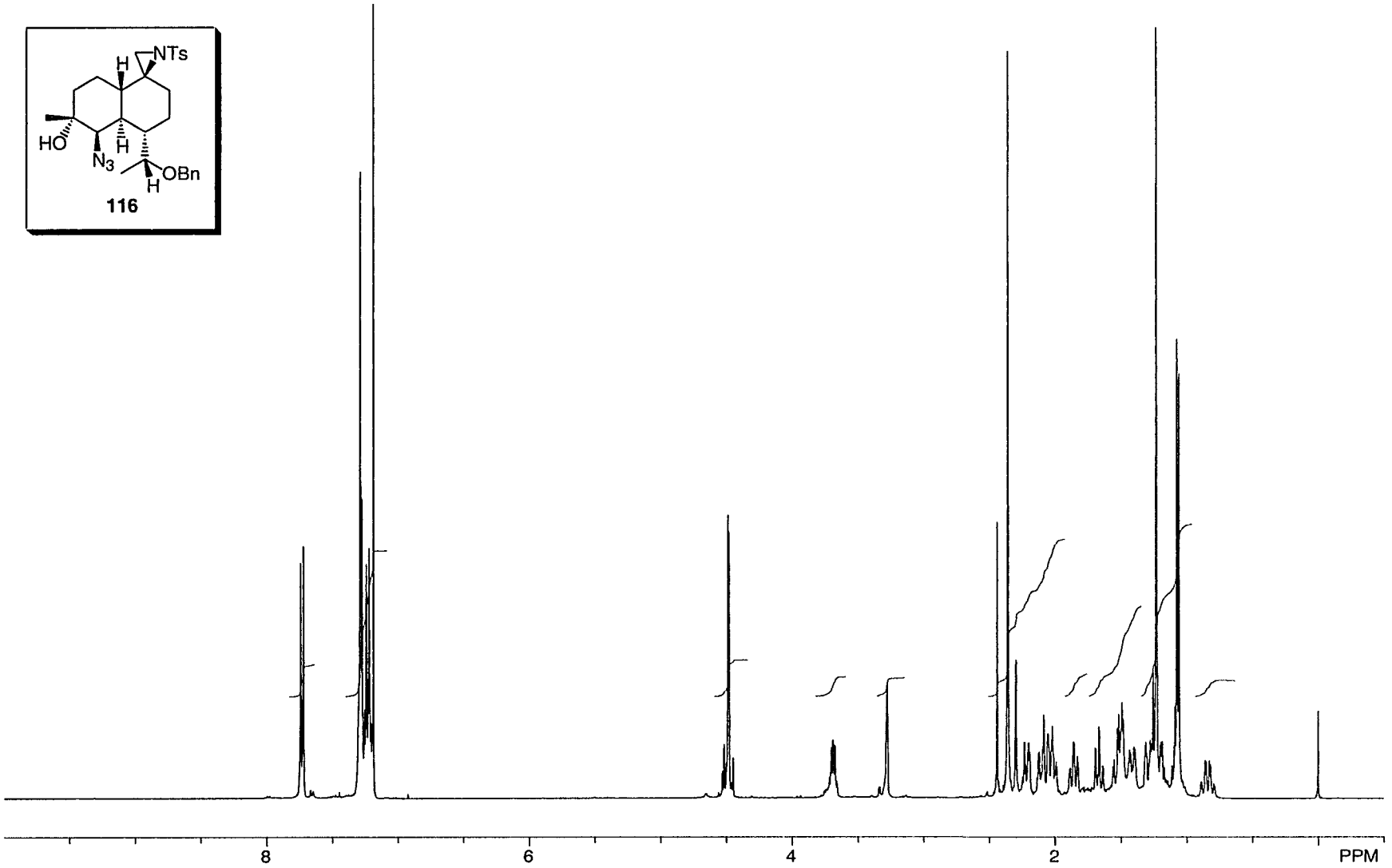


Figure A.3.40 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **116**.

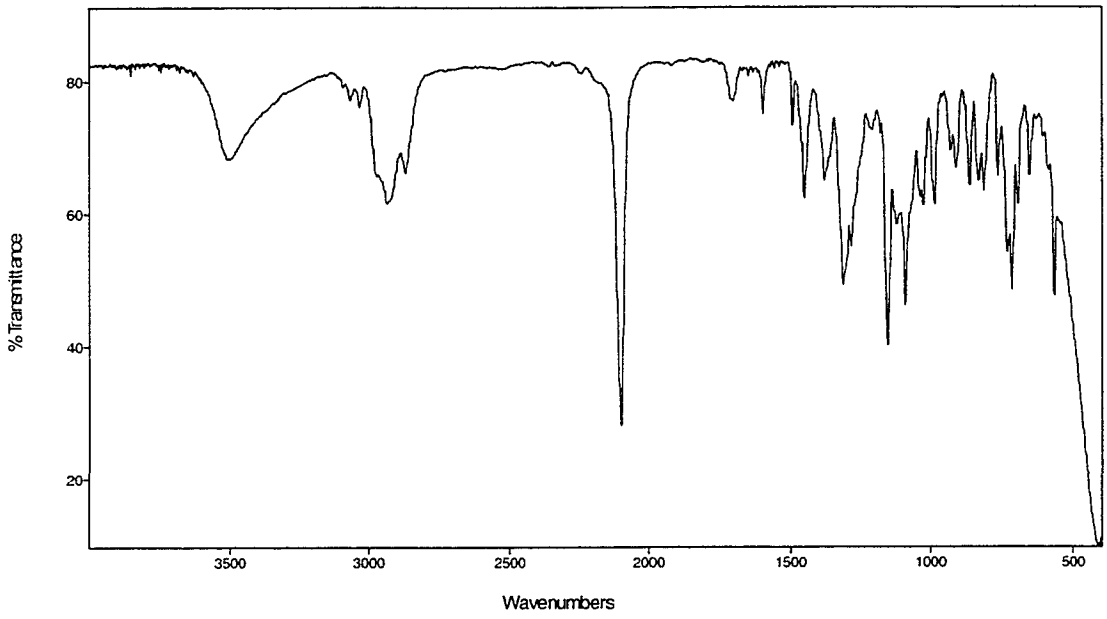


Figure A.3.41 FTIR Spectrum (thin film/NaCl) of Compound **116**.

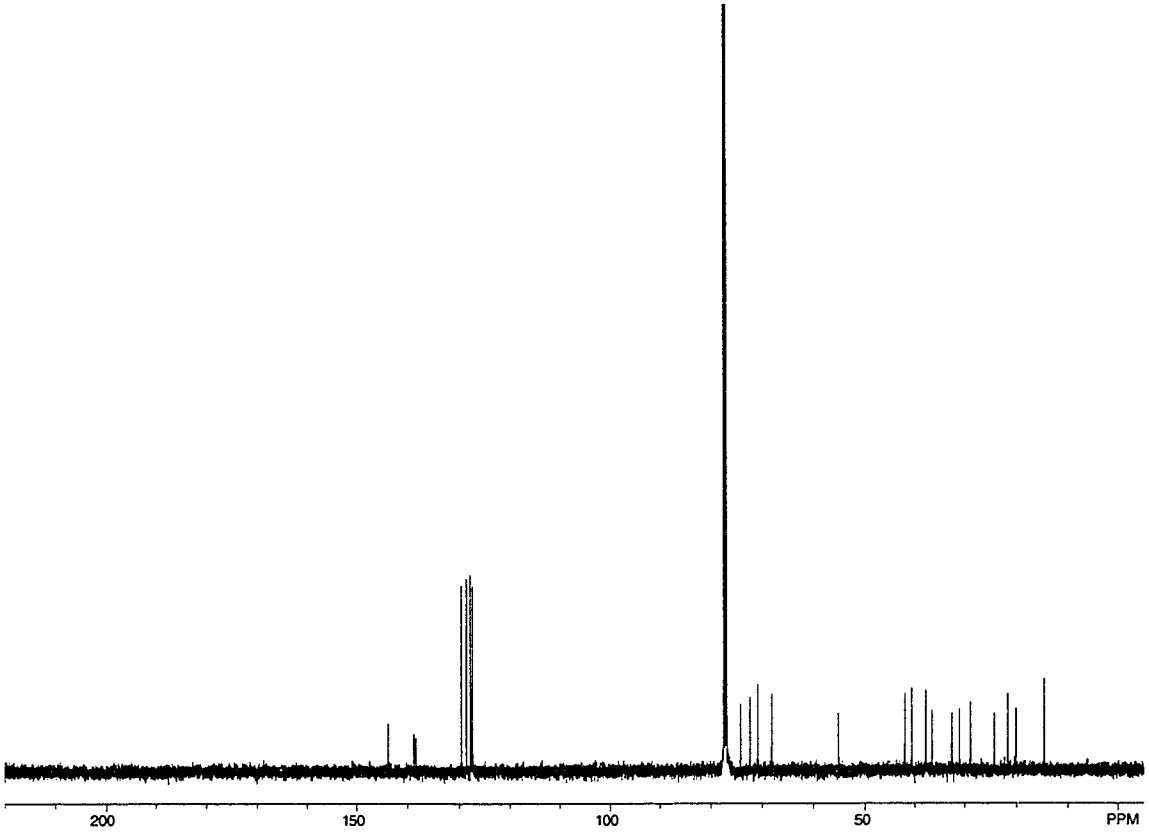


Figure A.3.42 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **116**.

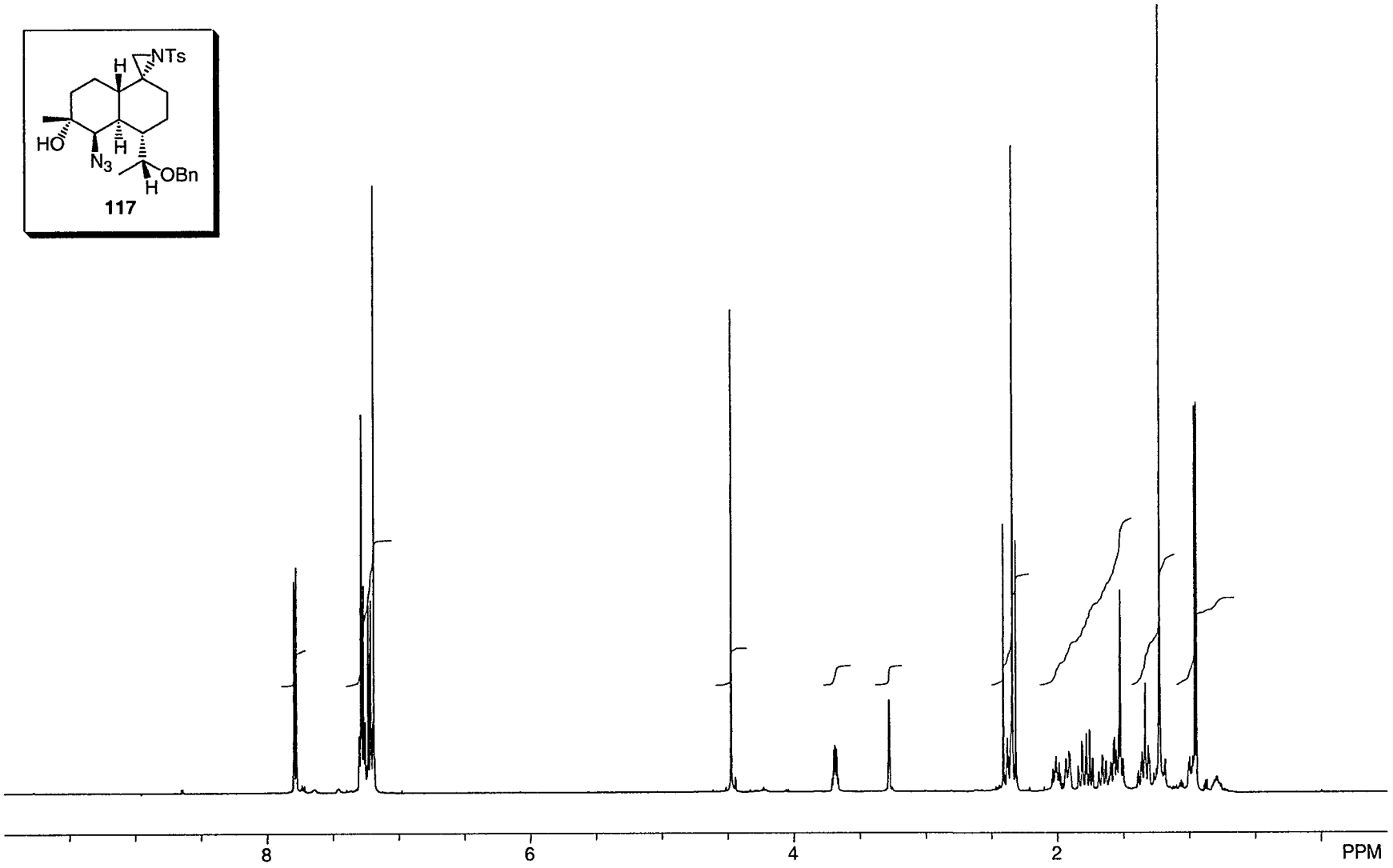


Figure A.3.43 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **117**.

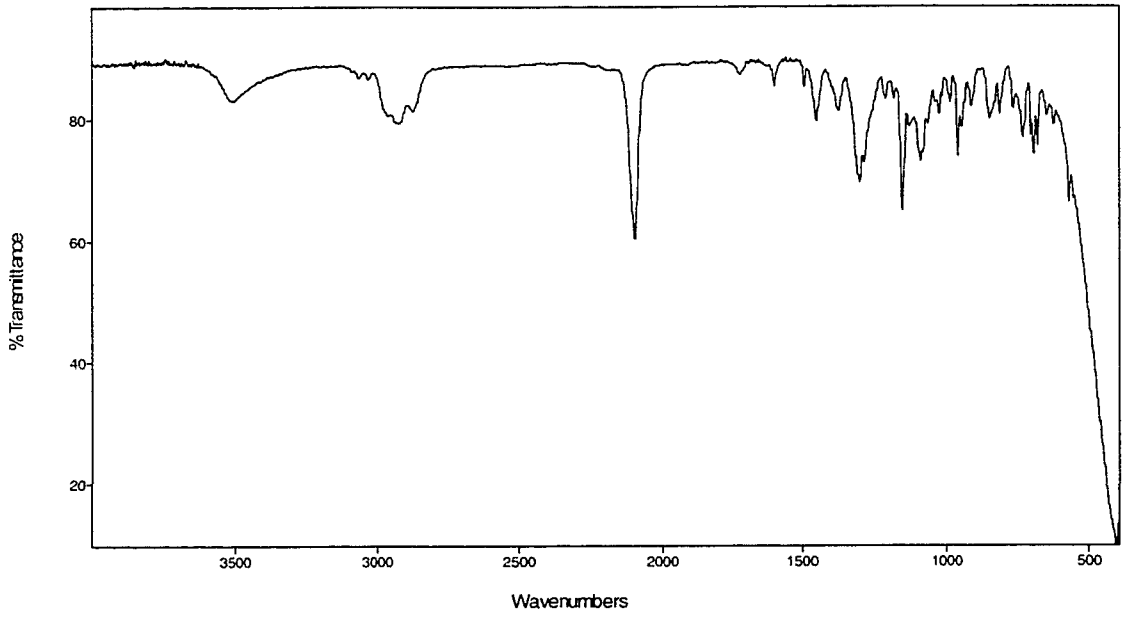


Figure A.3.44 FTIR Spectrum (thin film/NaCl) of Compound **117**.

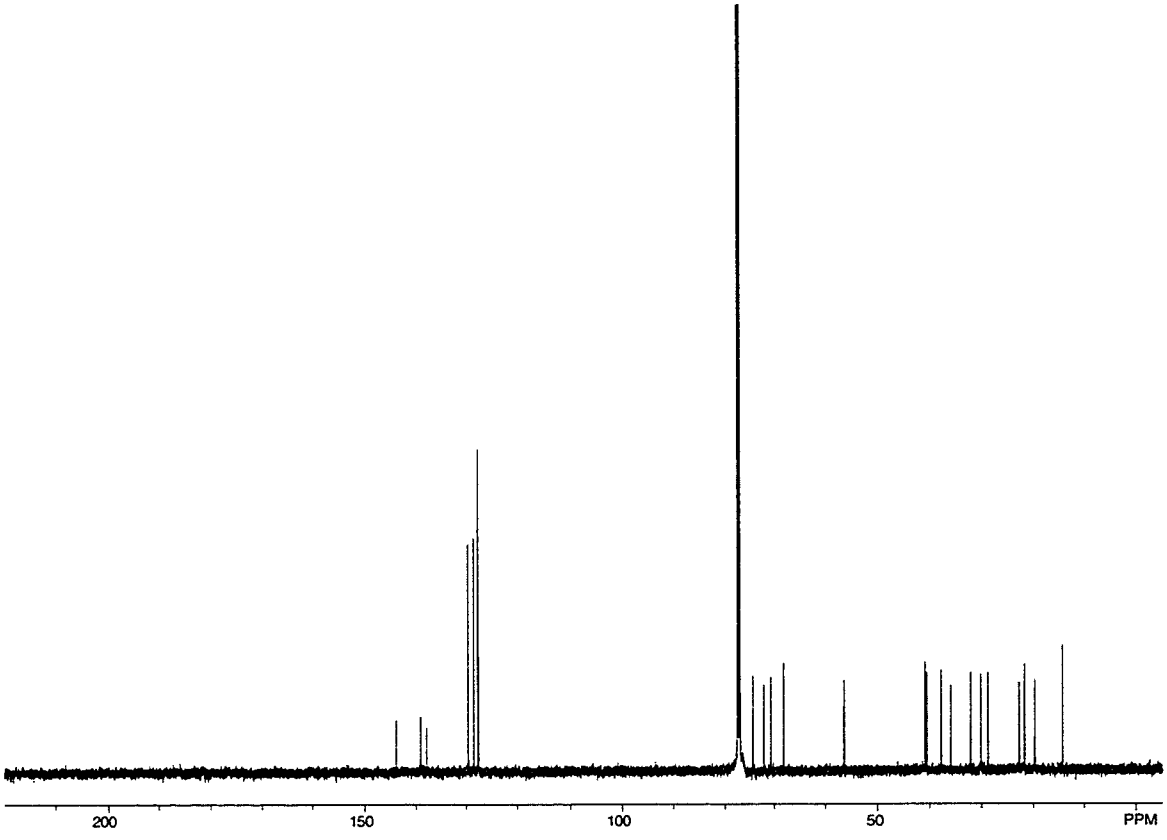


Figure A.3.45 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **117**.

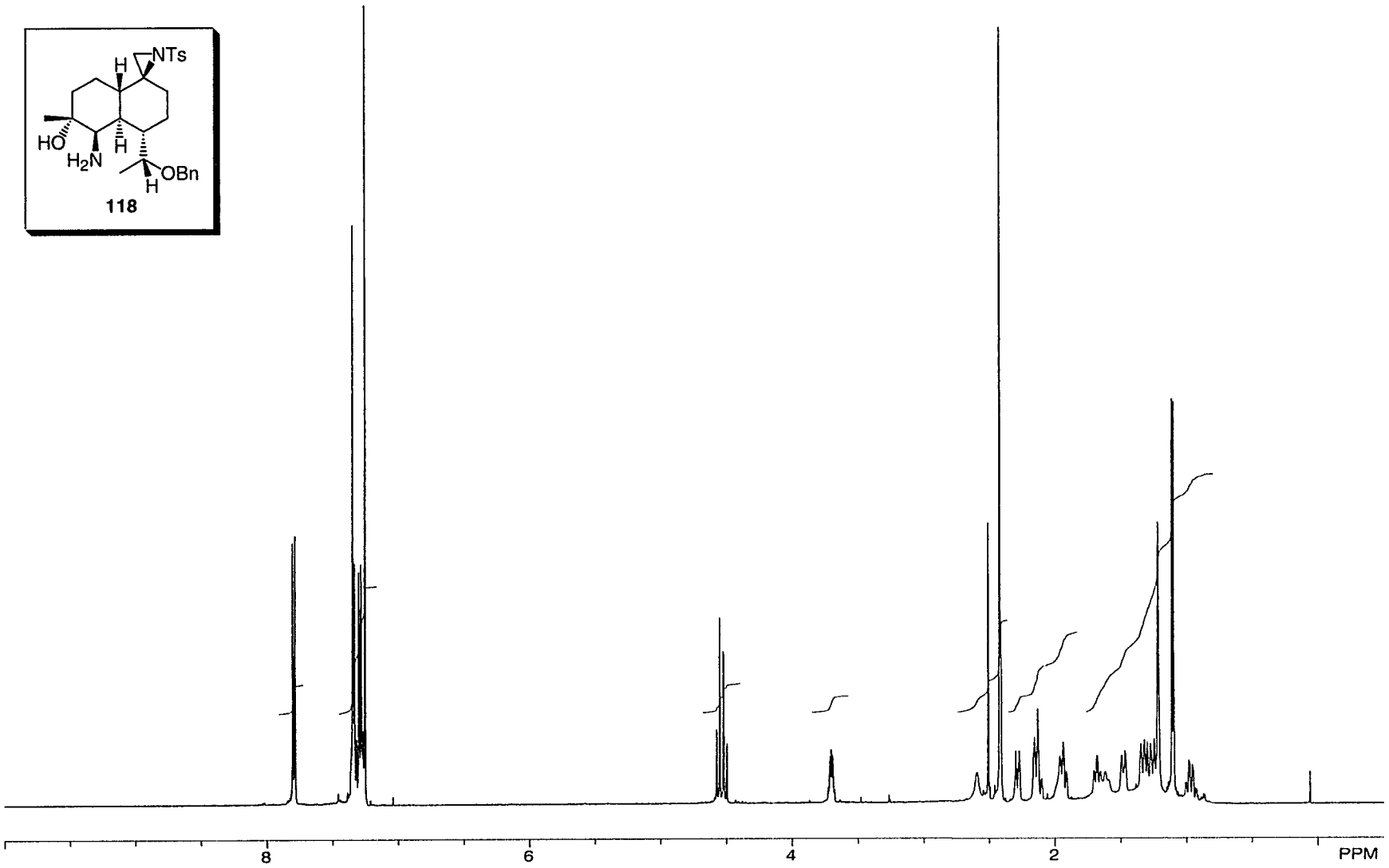


Figure A.3.46 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **118**.

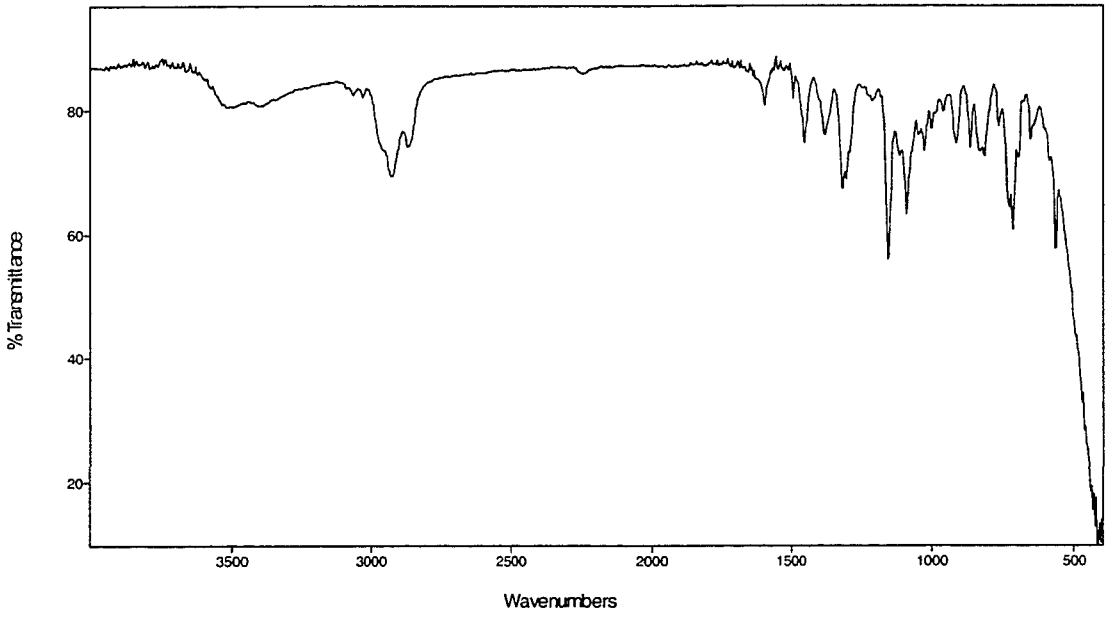


Figure A.3.47 FTIR Spectrum (thin film/NaCl) of Compound **118**.

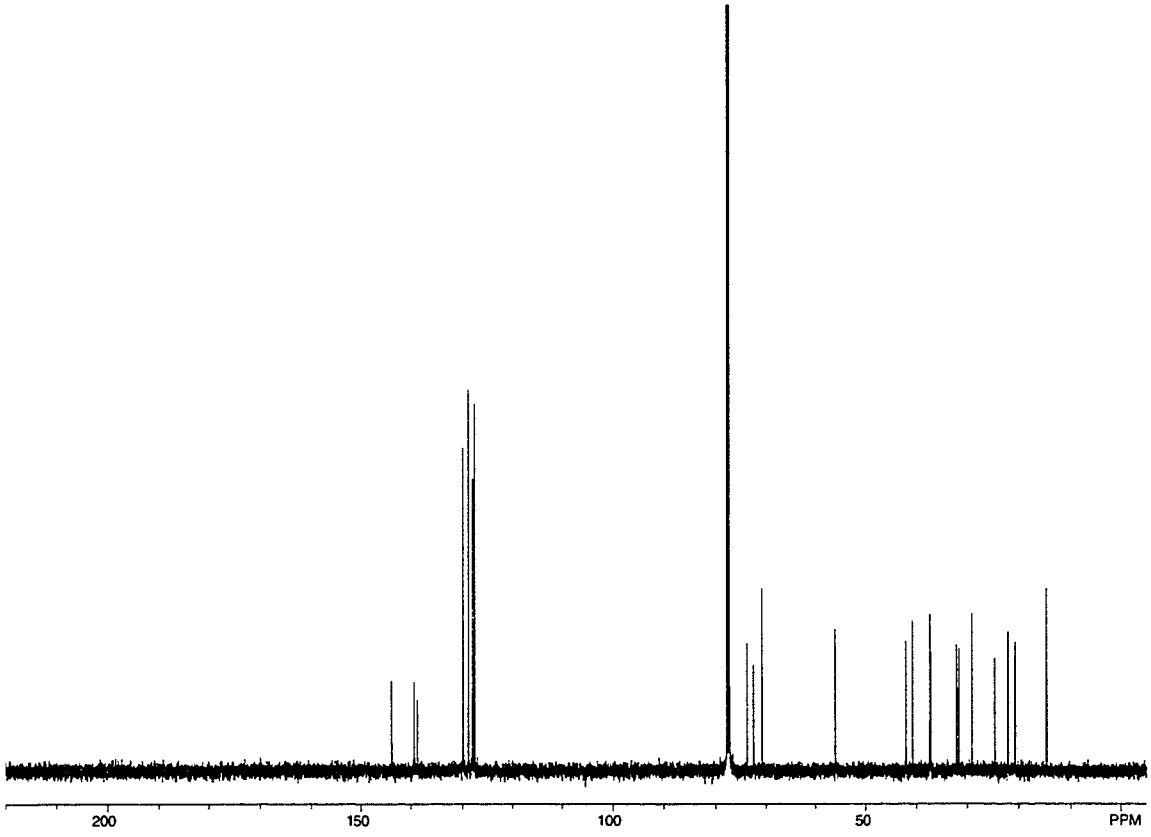


Figure A.3.48 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **118.**

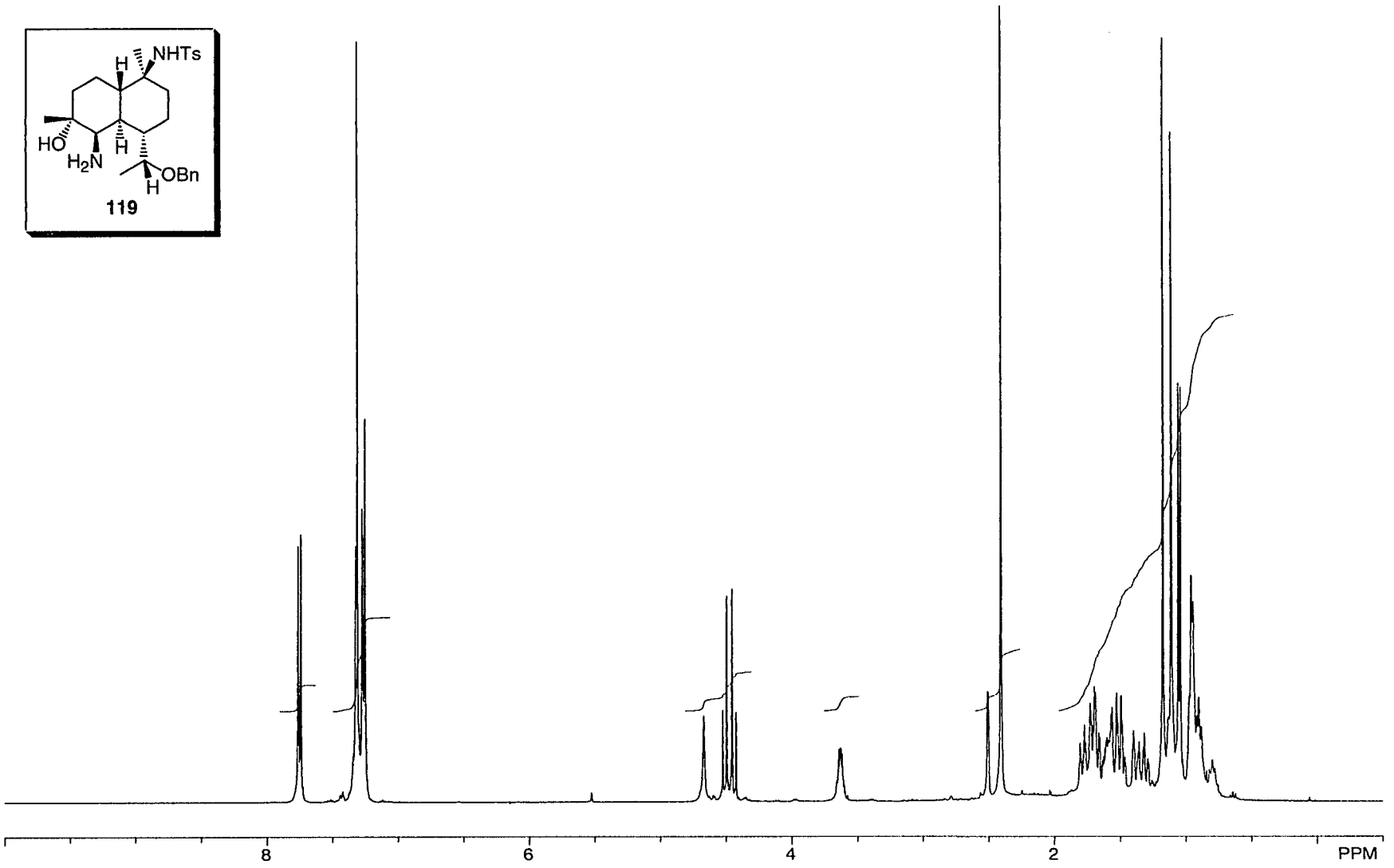


Figure A.3.49 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **119**.

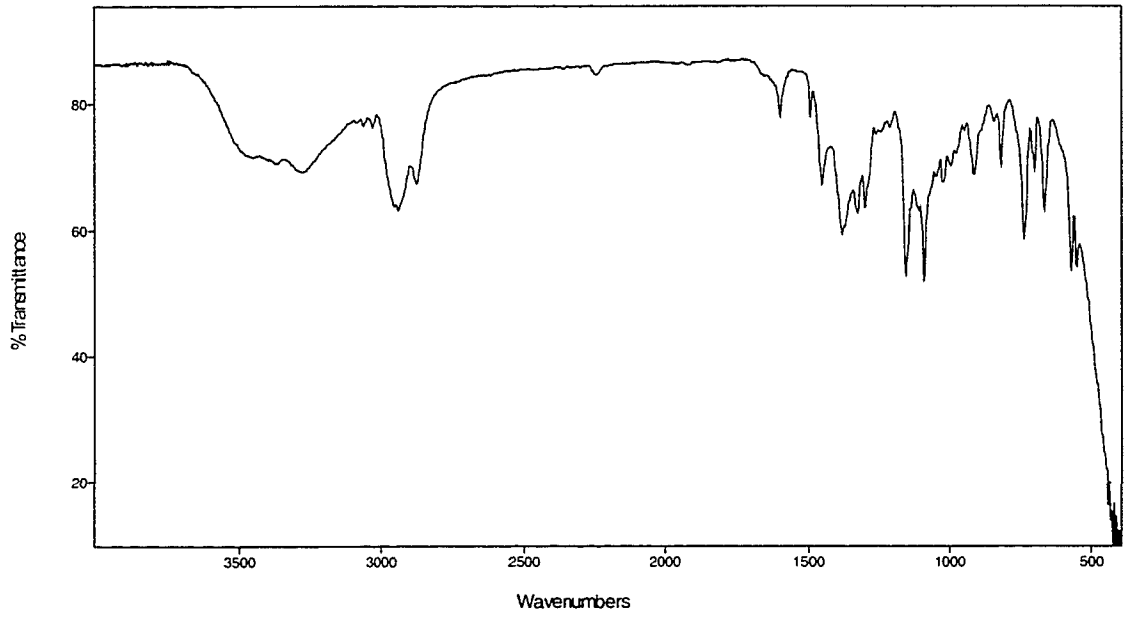


Figure A.3.50 FTIR Spectrum (thin film/NaCl) of Compound **119**.

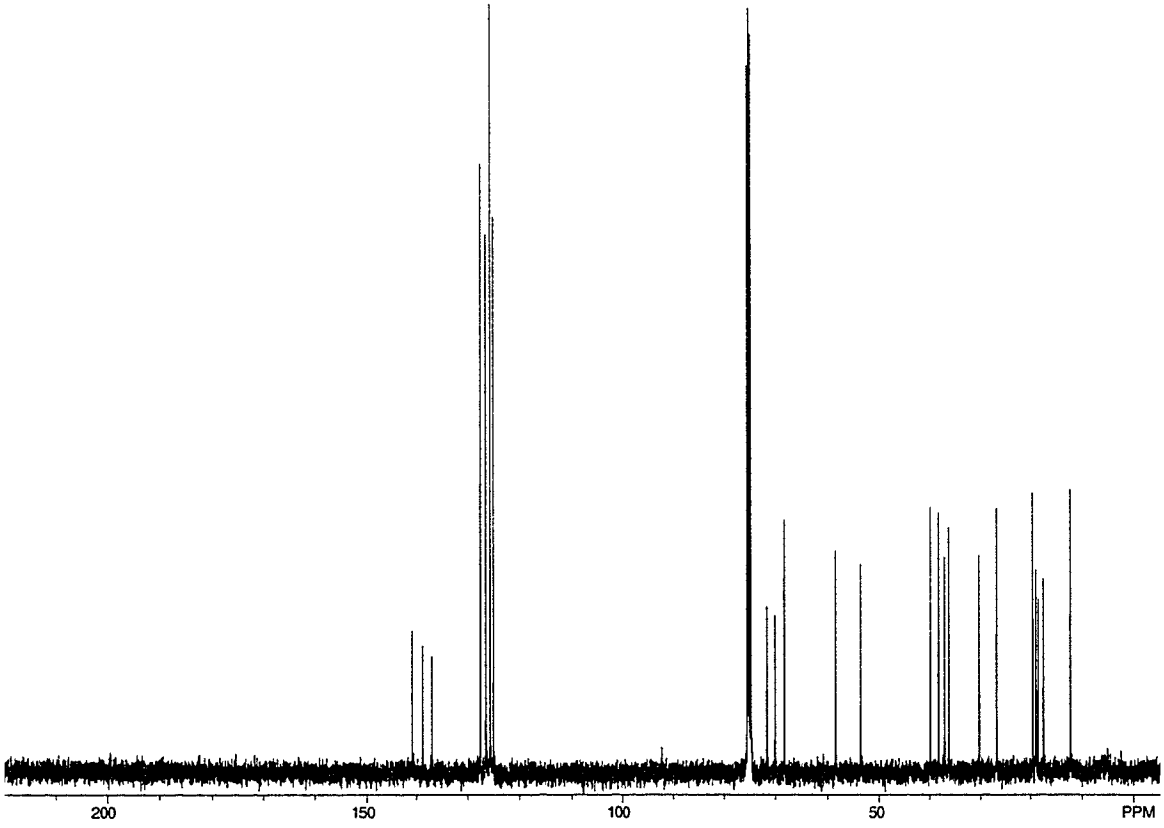


Figure A.3.51 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **119.**

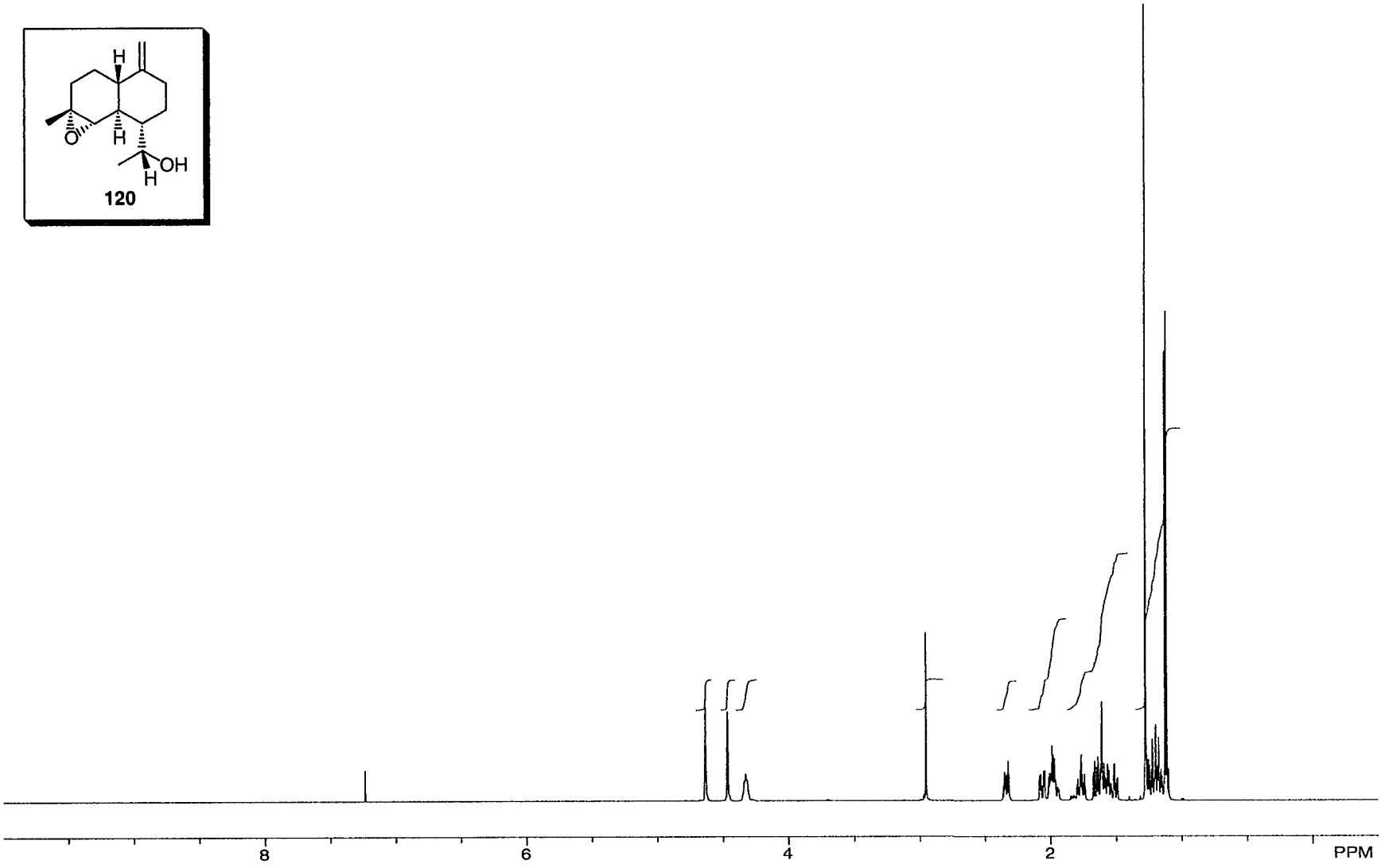


Figure A.3.52 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **120**.

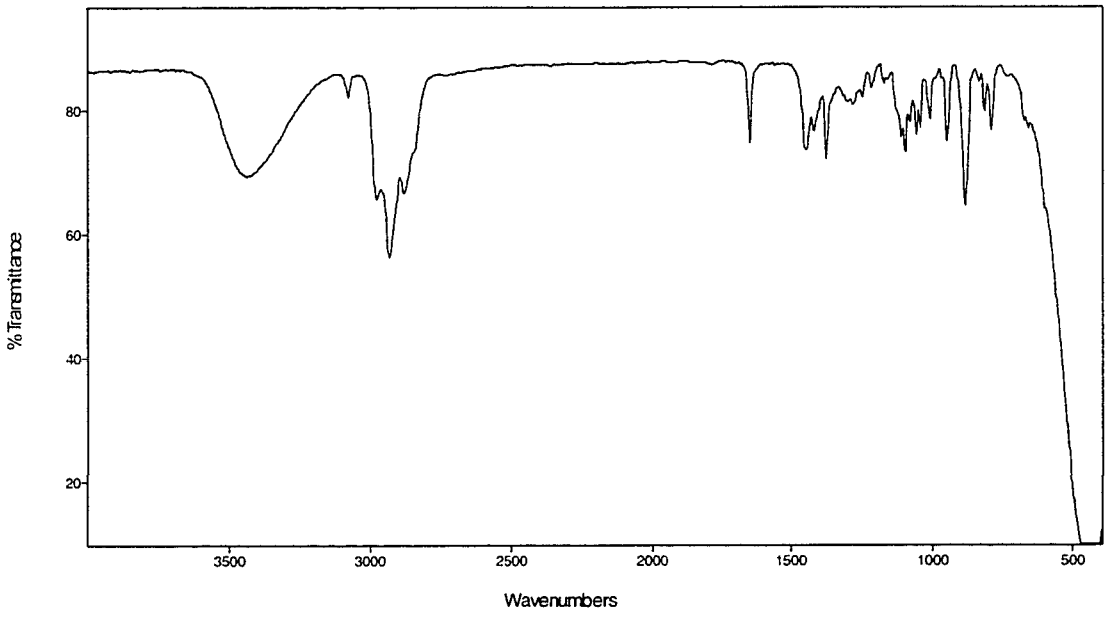


Figure A.3.53 FTIR Spectrum (thin film/NaCl) of Compound **120**.

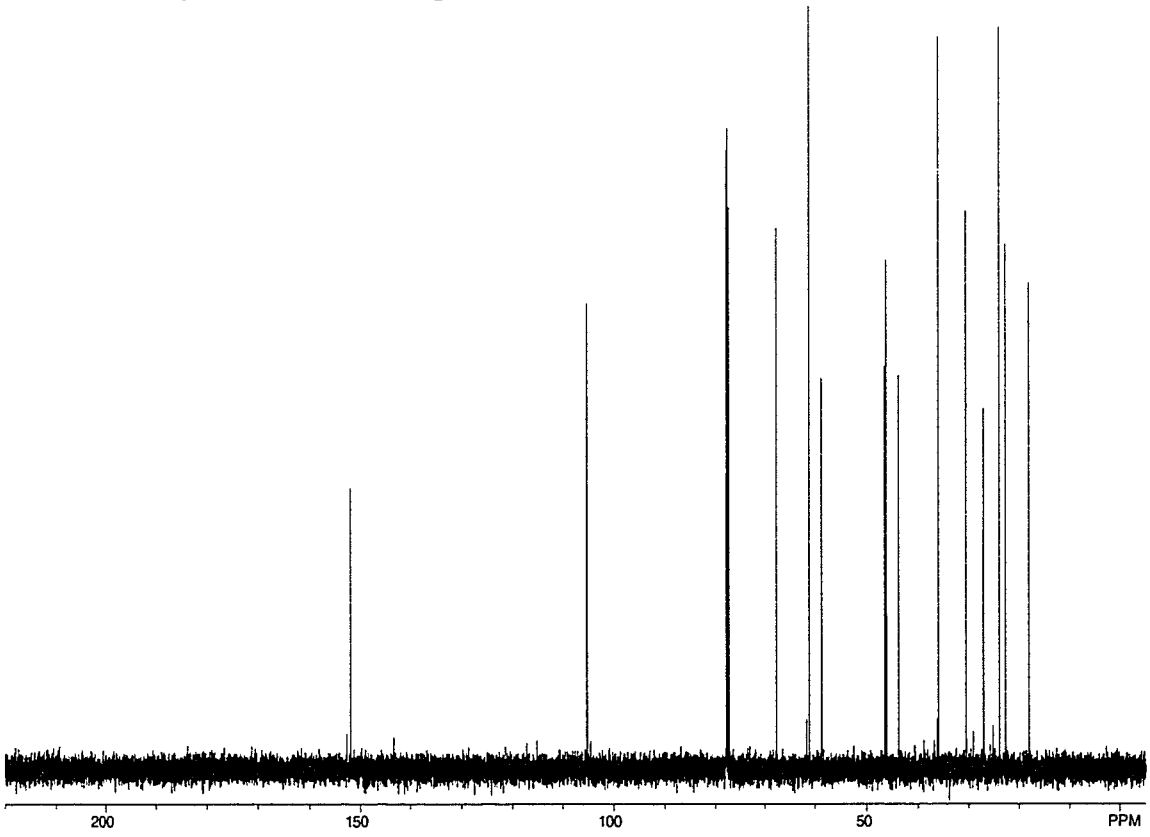


Figure A.3.54 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **120**.

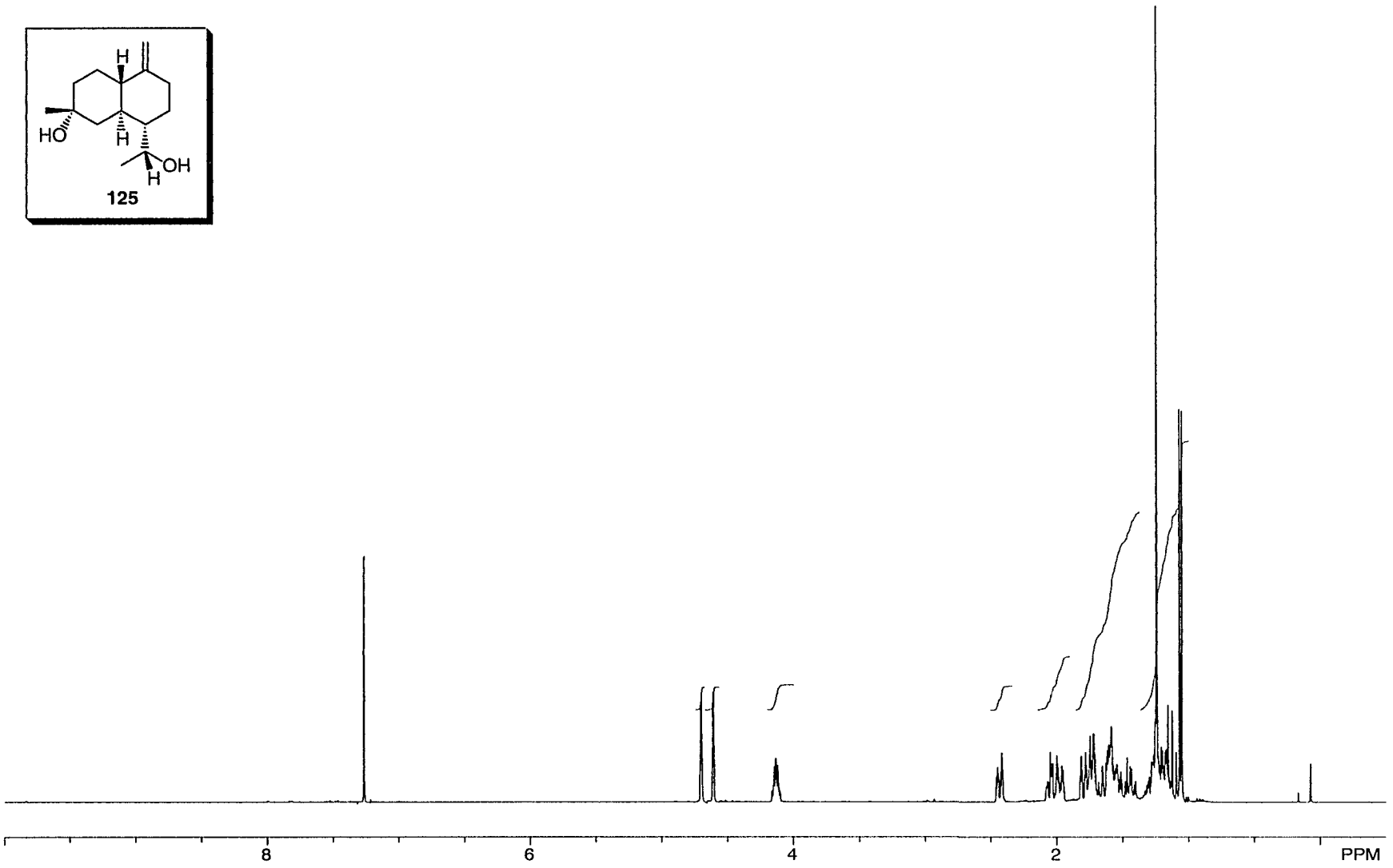


Figure A.3.55 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **125**.

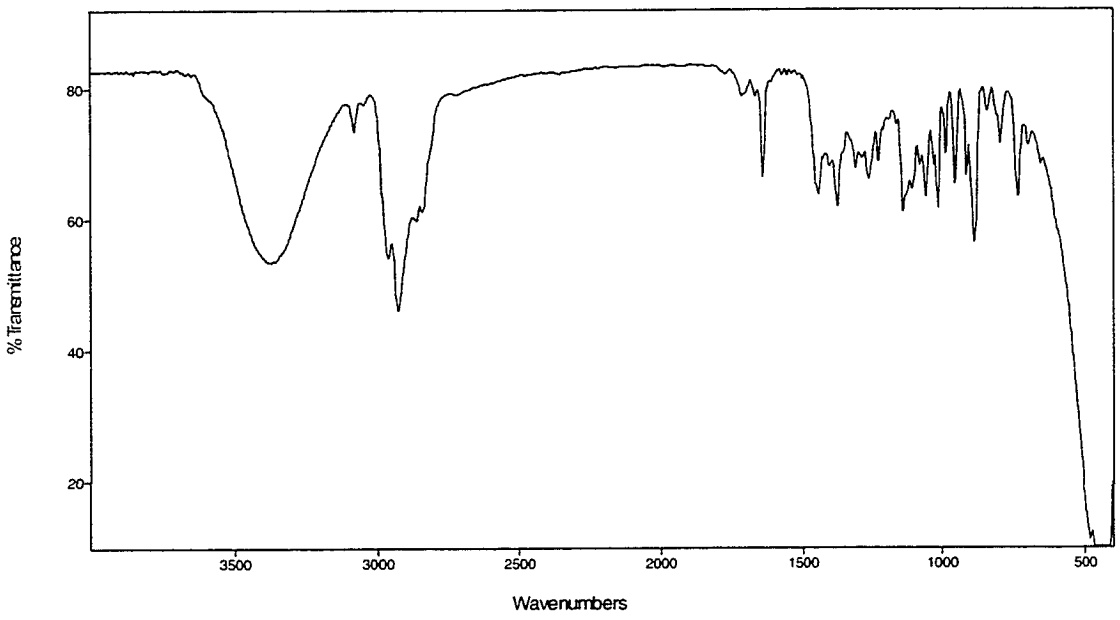


Figure A.3.56 FTIR Spectrum (thin film/NaCl) of Compound **125**.

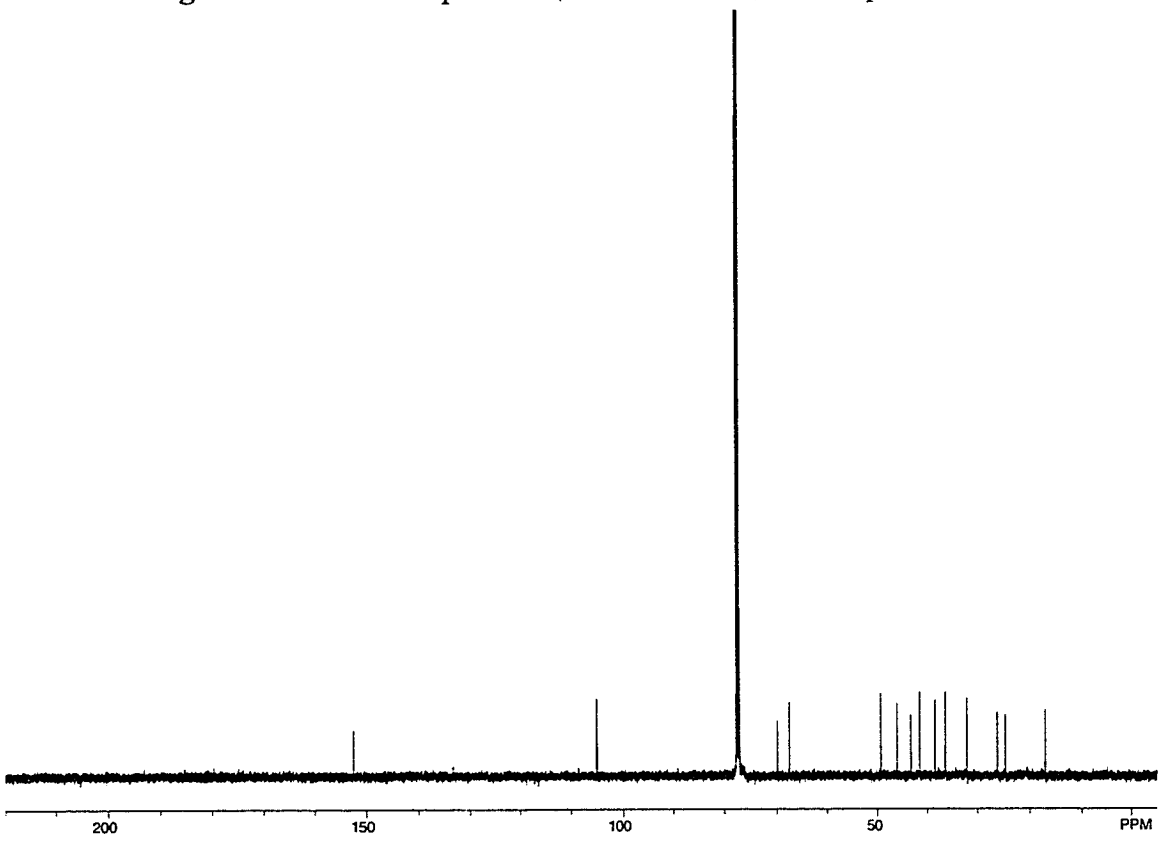


Figure A.3.57 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **125**.

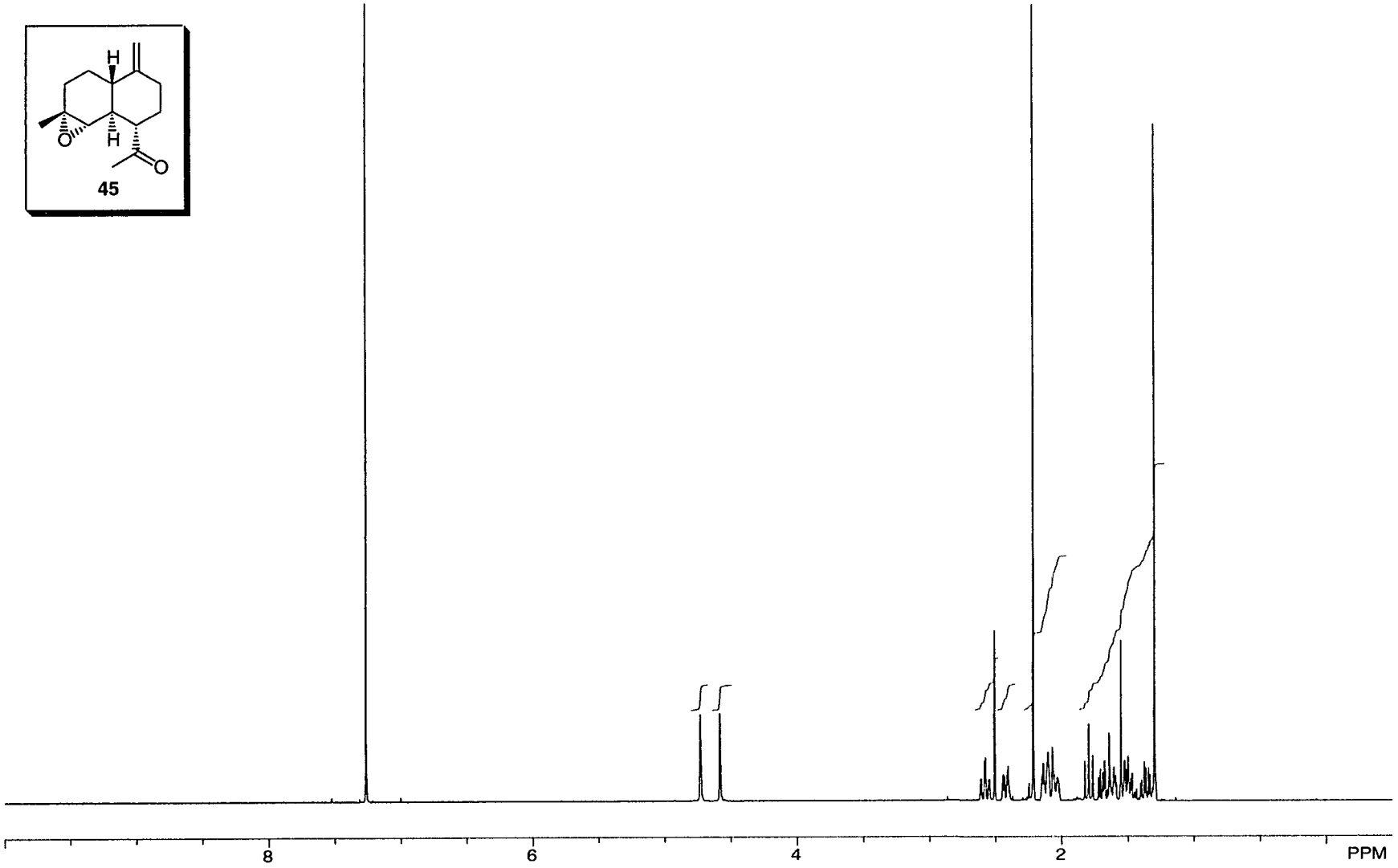


Figure A.3.58 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **45**.

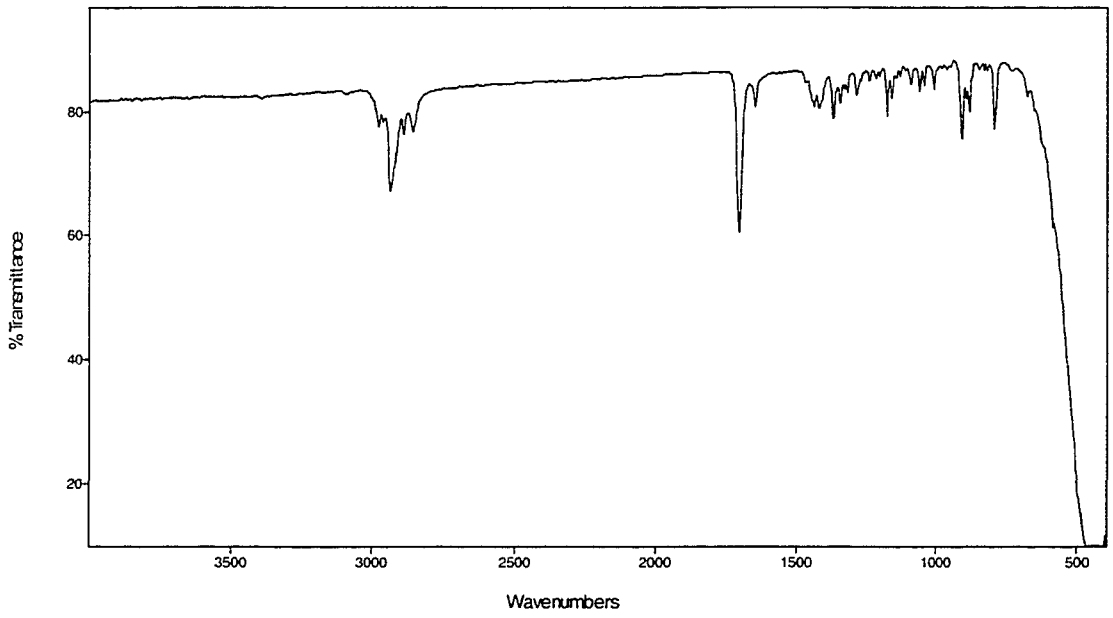


Figure A.3.59 FTIR Spectrum (thin film/NaCl) of Compound **45**.

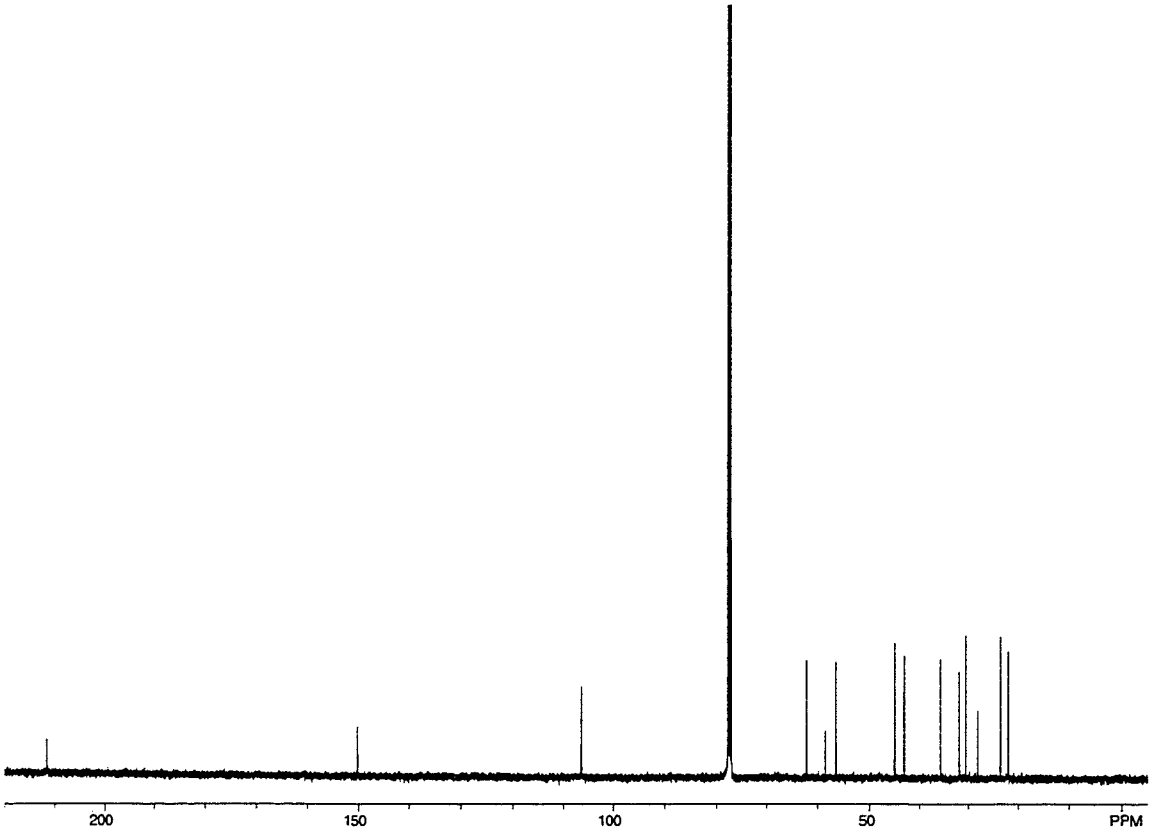


Figure A.3.60 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **45**.

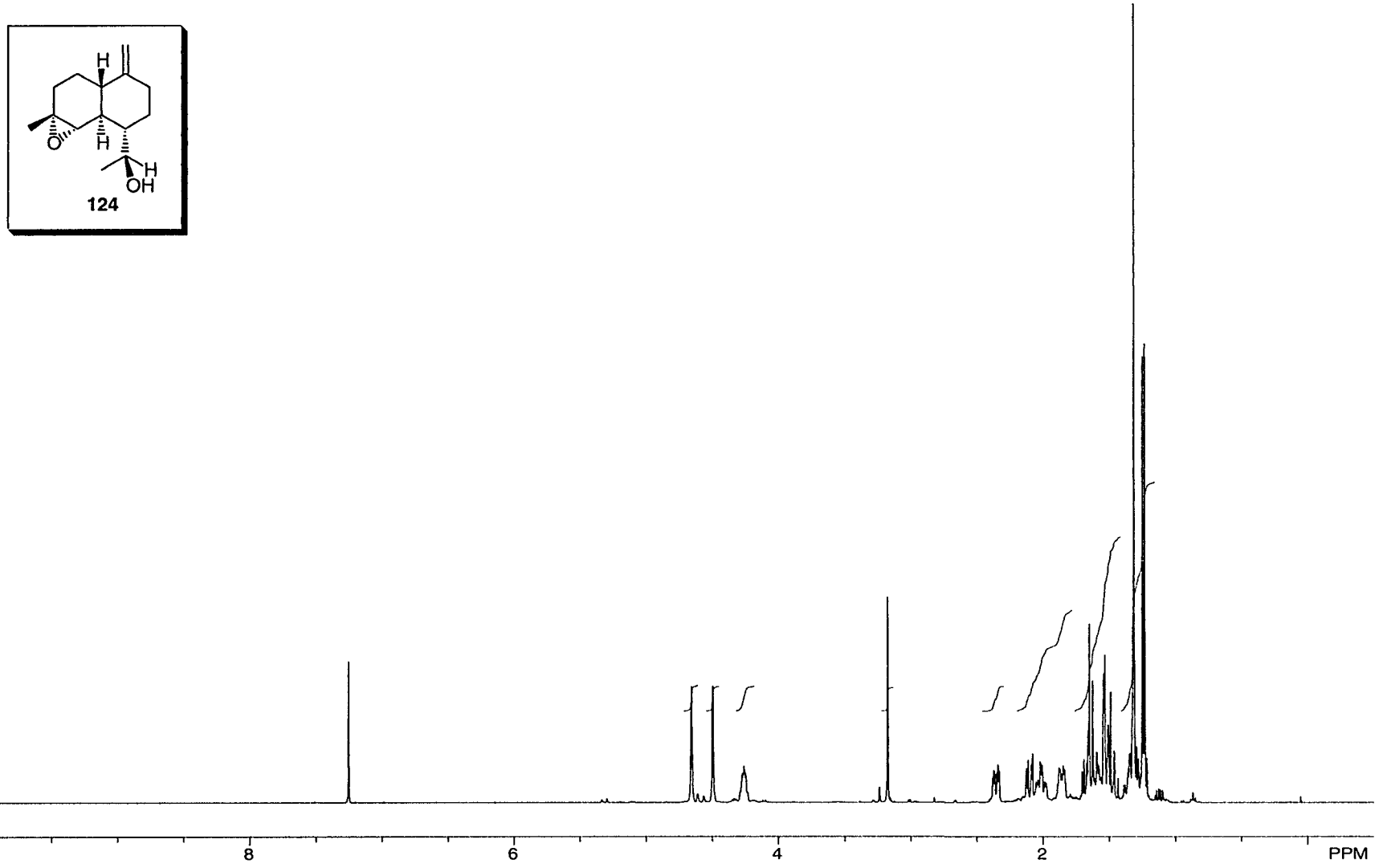


Figure A.3.61 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **124**.

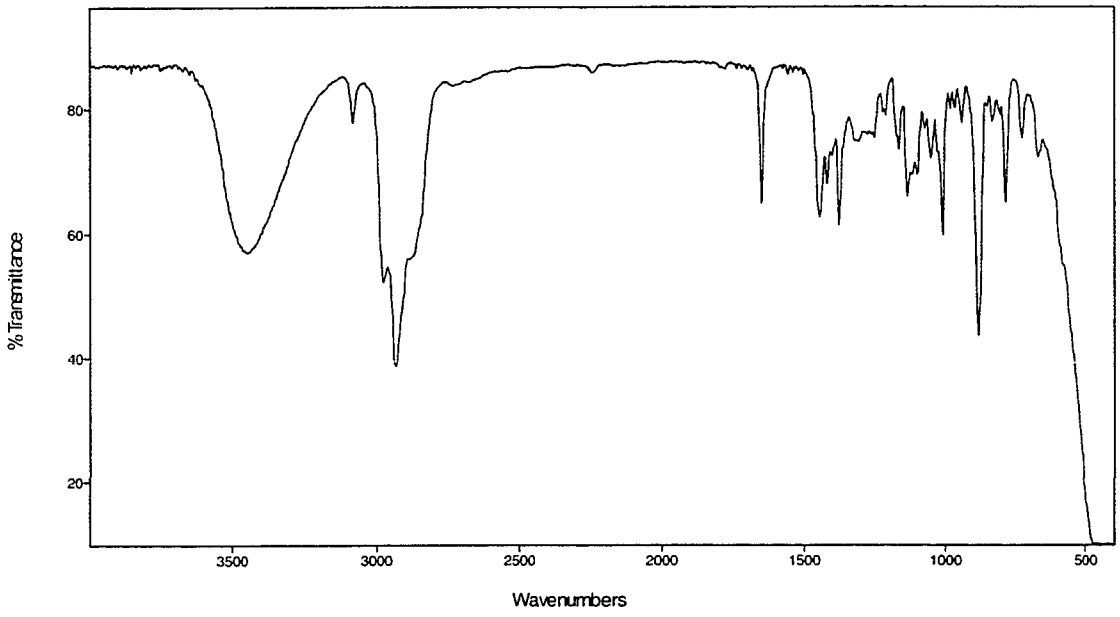


Figure A.3.62 FTIR Spectrum (thin film/NaCl) of Compound **124**.

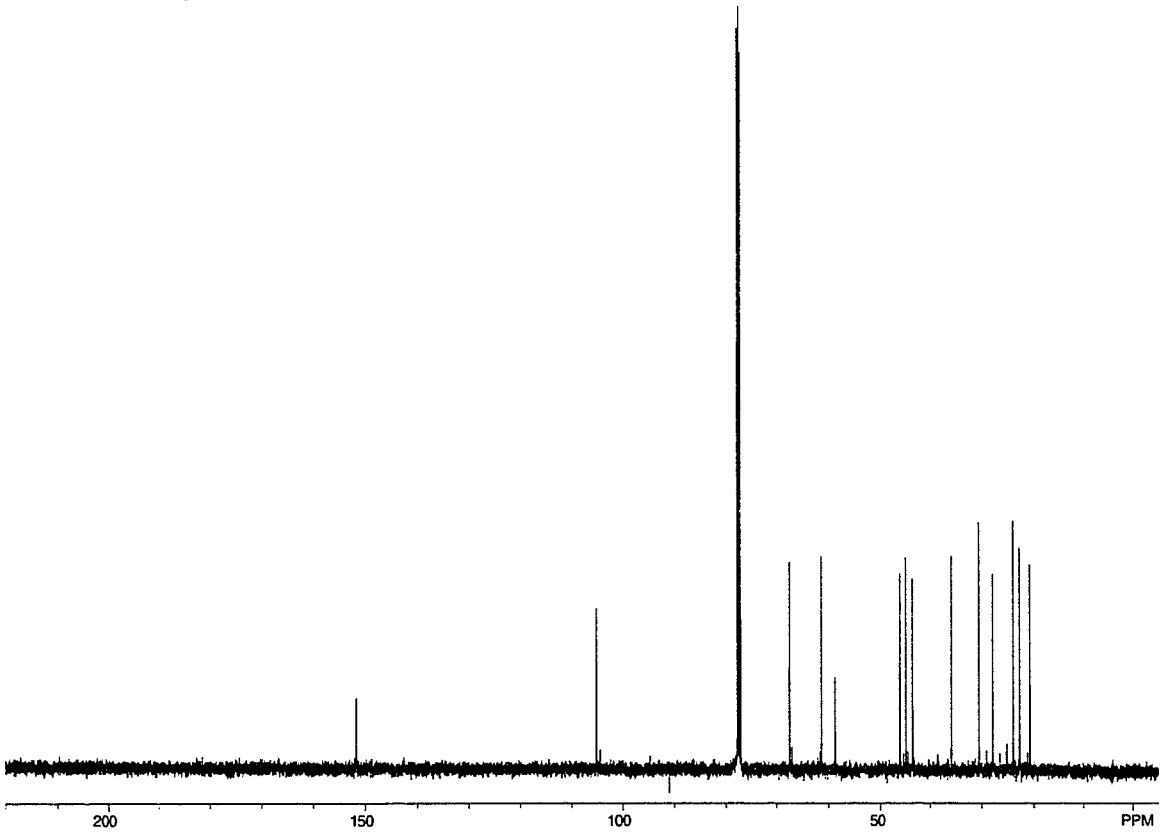


Figure A.3.63 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **124**.

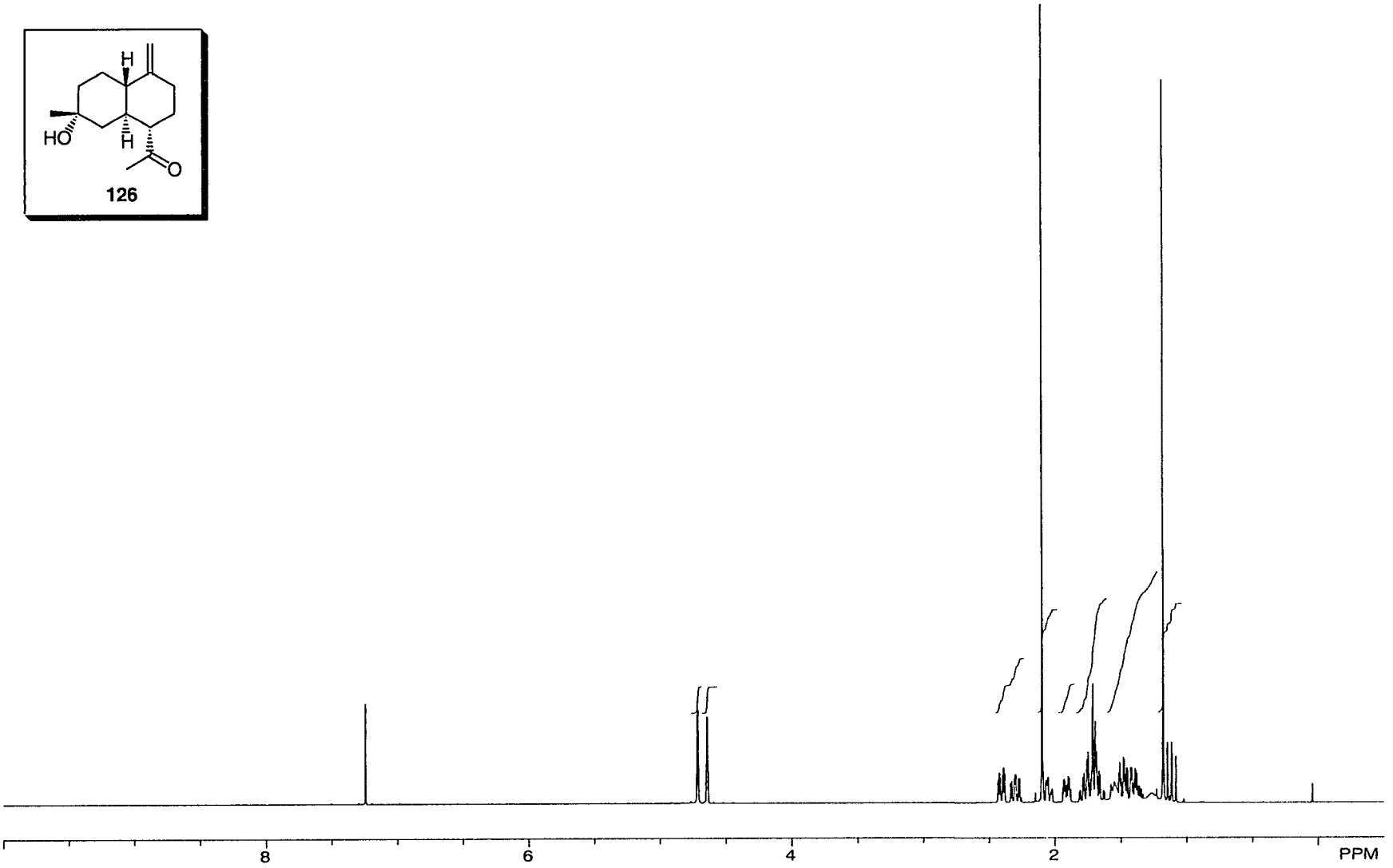


Figure A.3.64 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **126**.

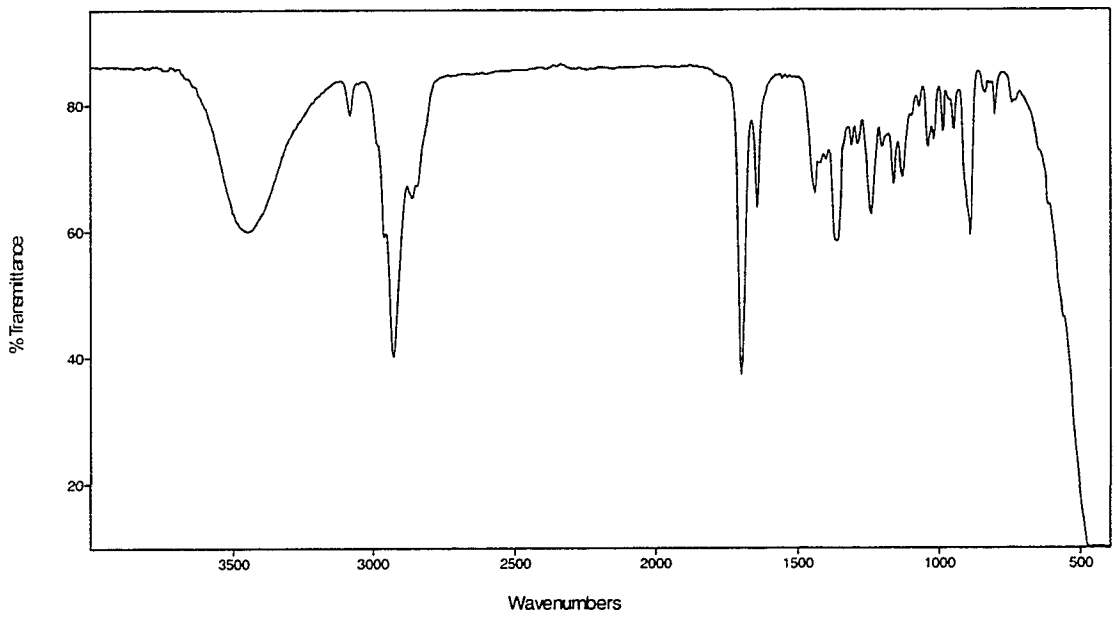


Figure A.3.65 FTIR Spectrum (thin film/NaCl) of Compound **126.**

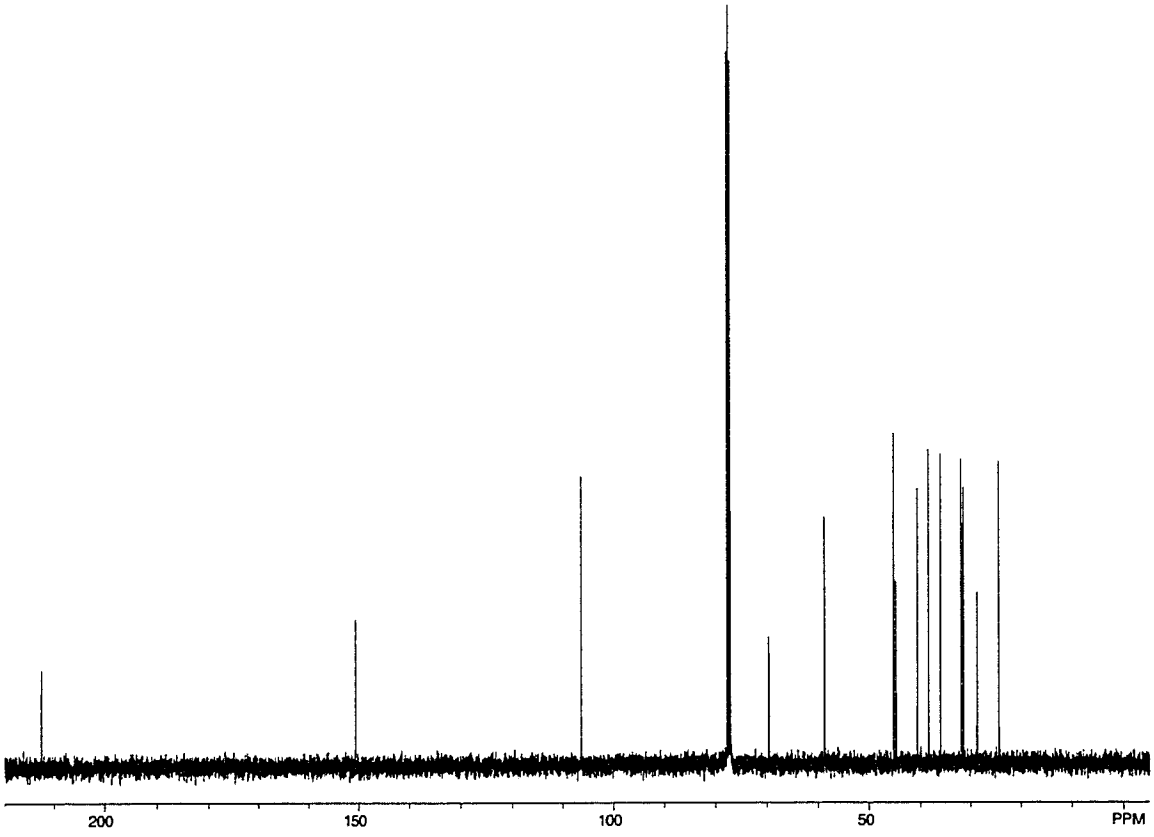


Figure A.3.66 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **126.**

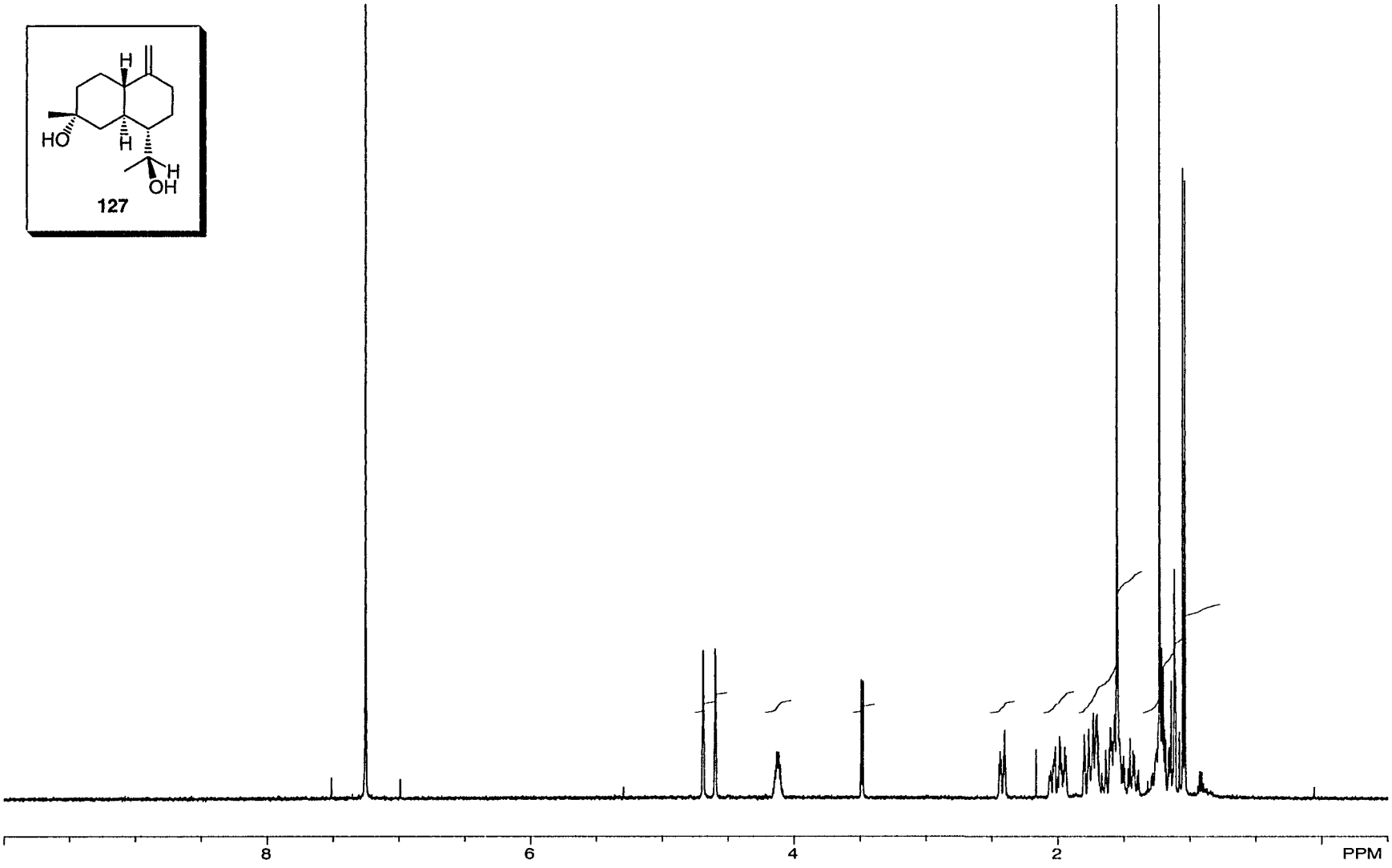


Figure A.3.67 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **127**.

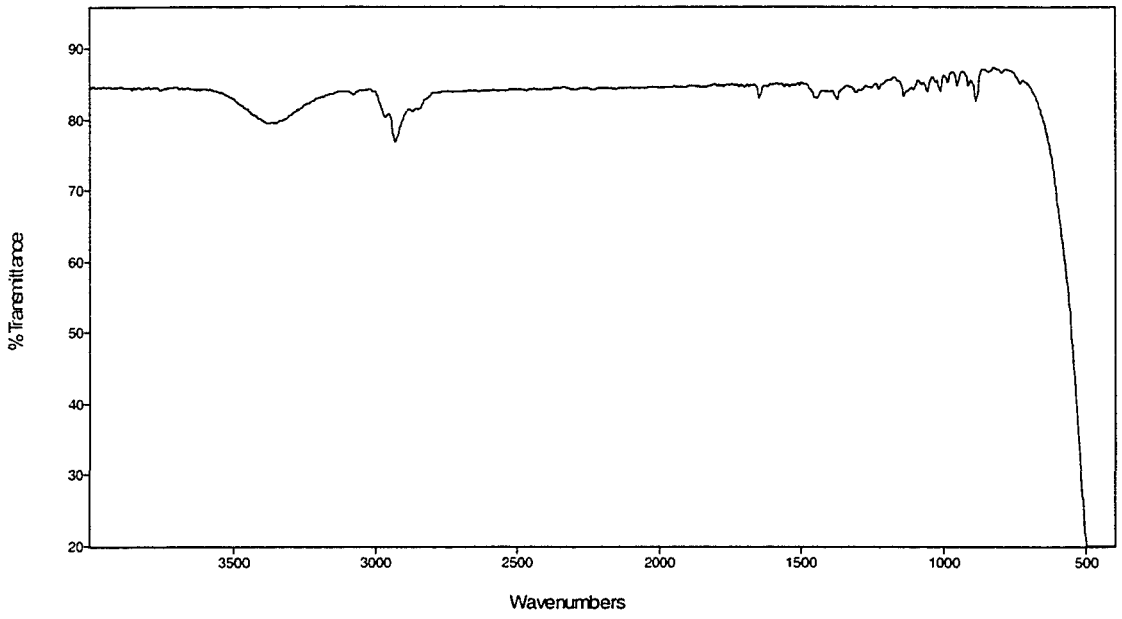


Figure A.3.68 FTIR Spectrum (thin film/NaCl) of Compound **127**.

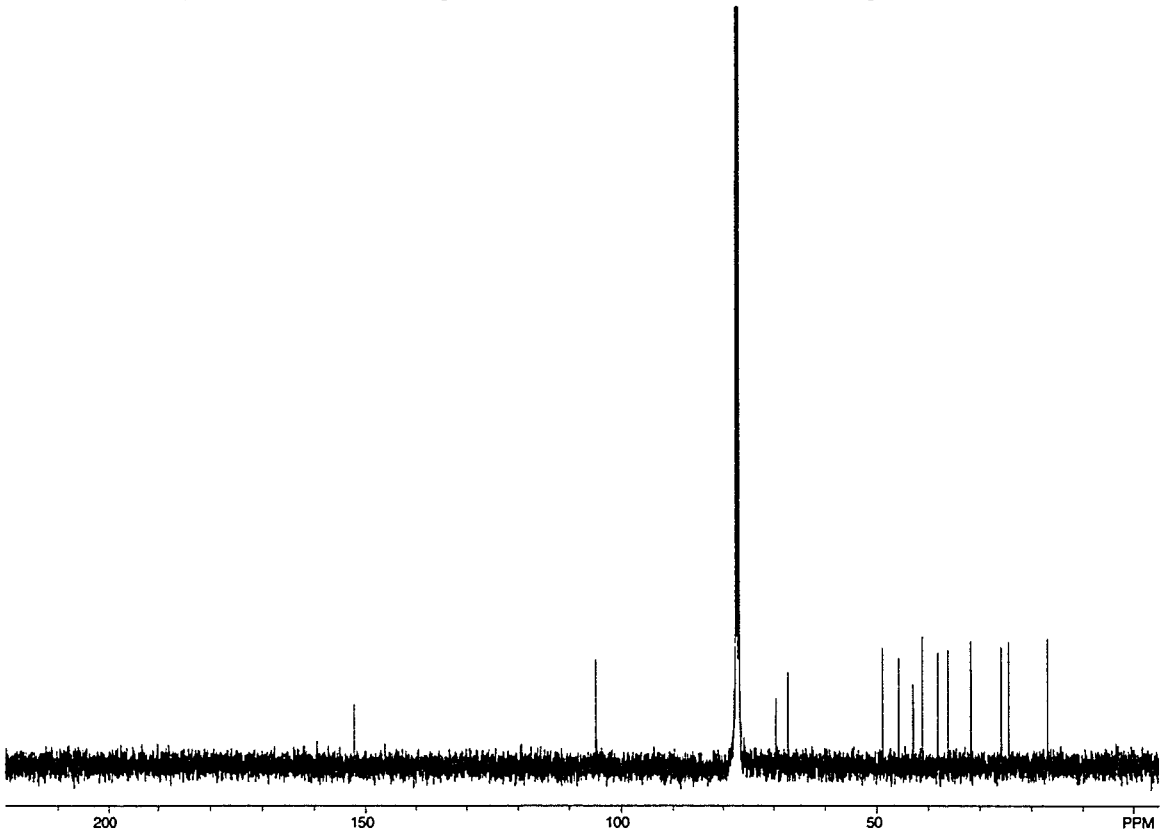


Figure A.3.69 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **127**.

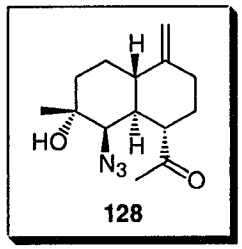


Figure A.3.70 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **128**.

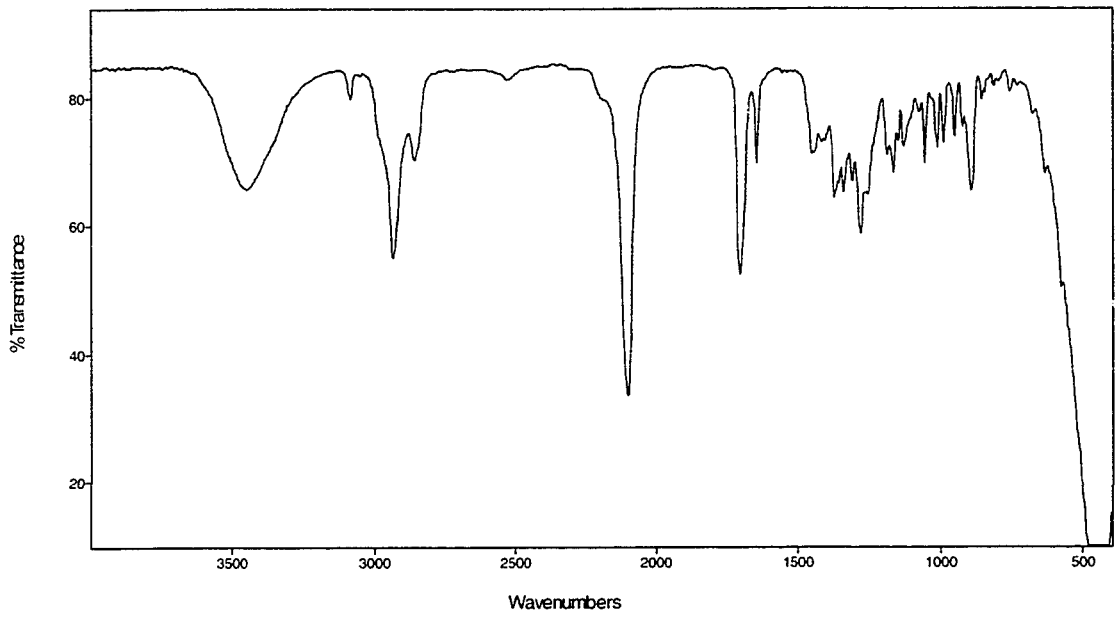


Figure A.3.71 FTIR Spectrum (thin film/NaCl) of Compound **128**.

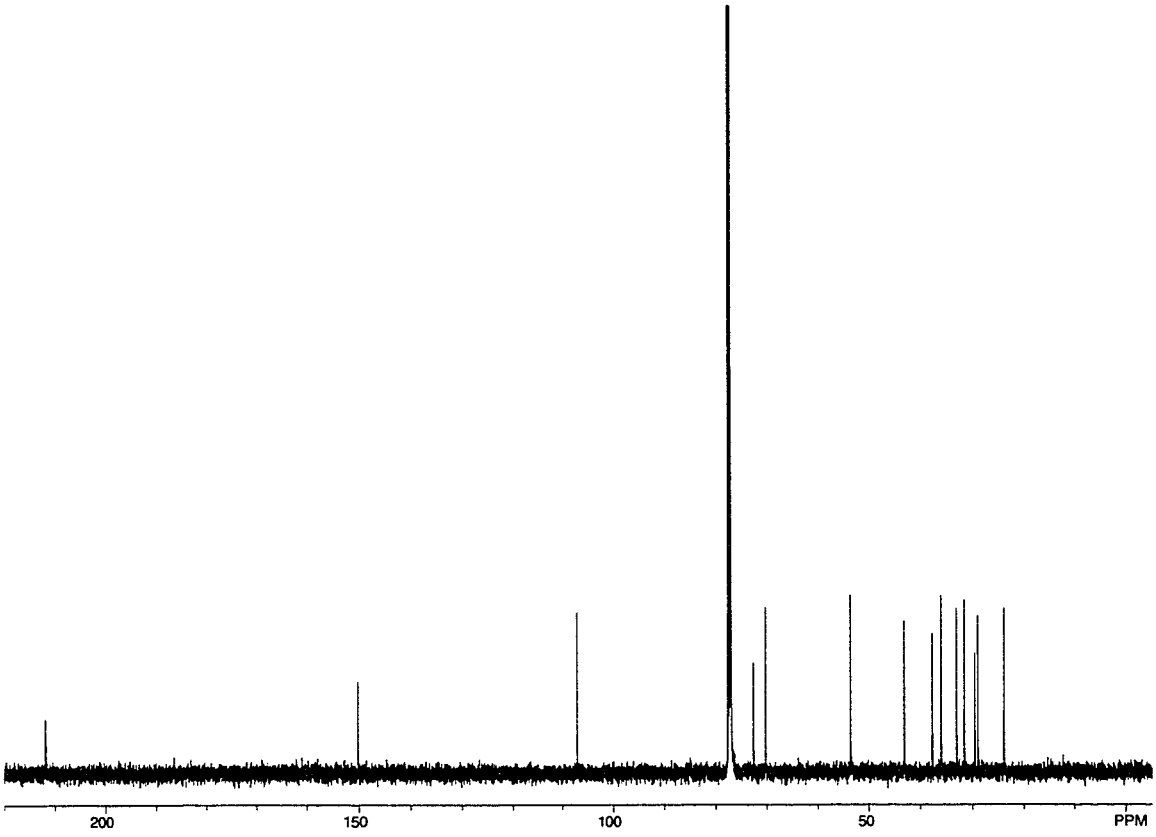


Figure A.3.72 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **128**.

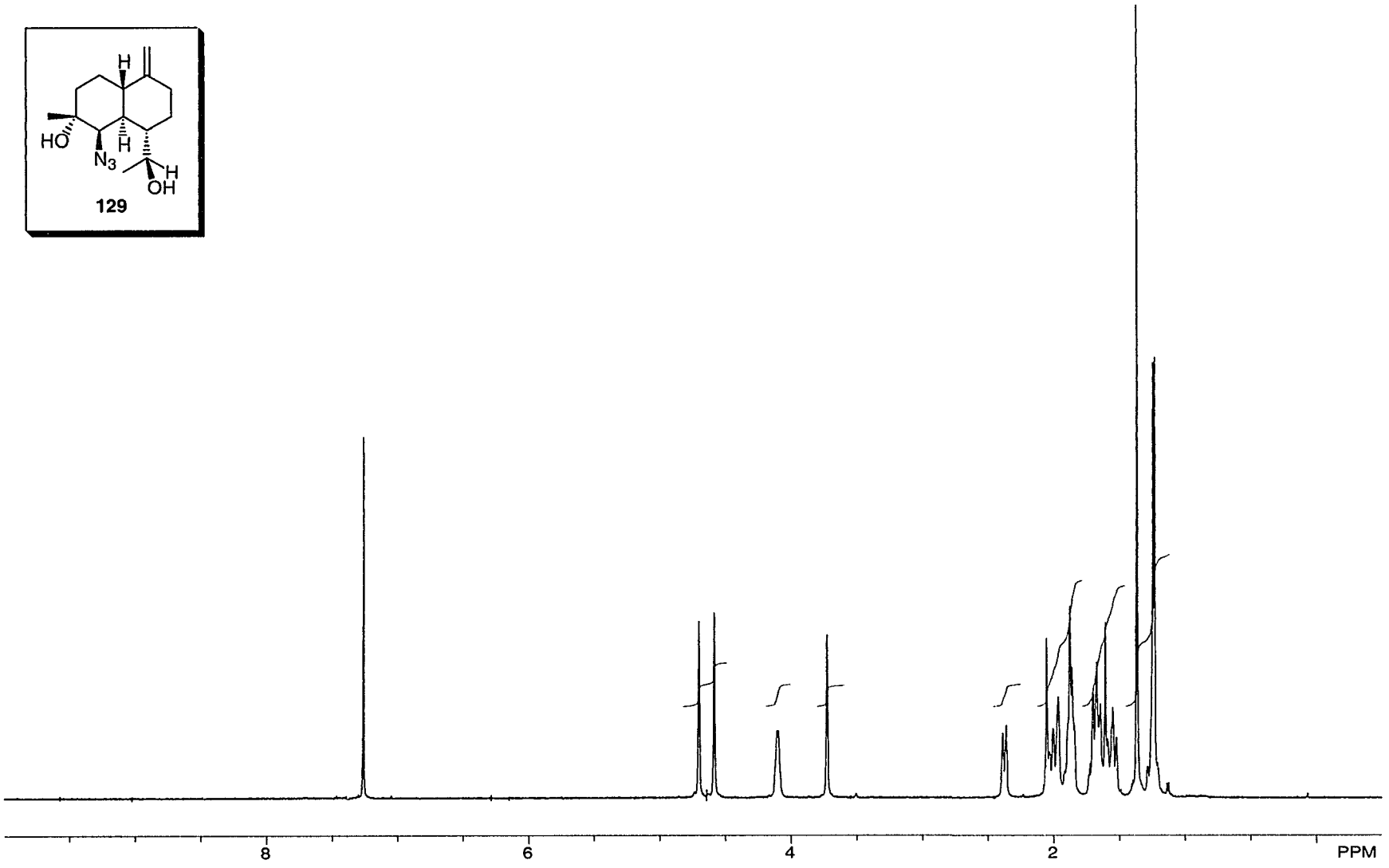


Figure A.3.73 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **129**.

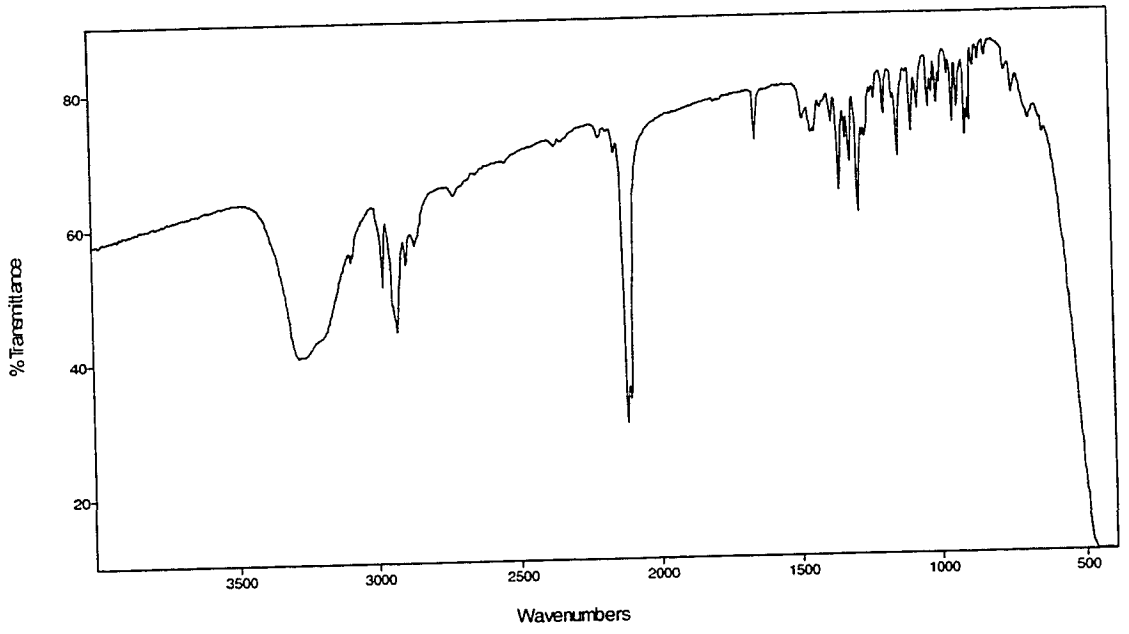


Figure A.3.74 FTIR Spectrum (thin film/NaCl) of Compound **129**.

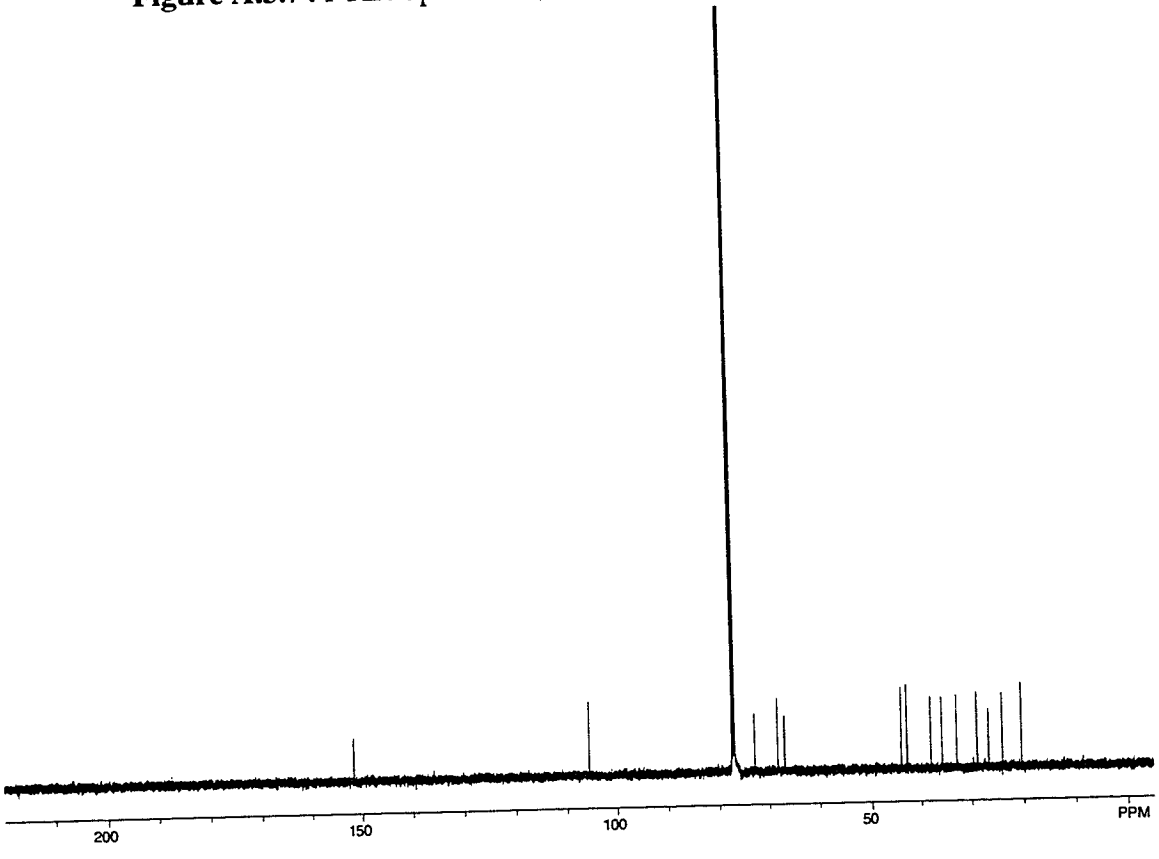


Figure A.3.75 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **129**.

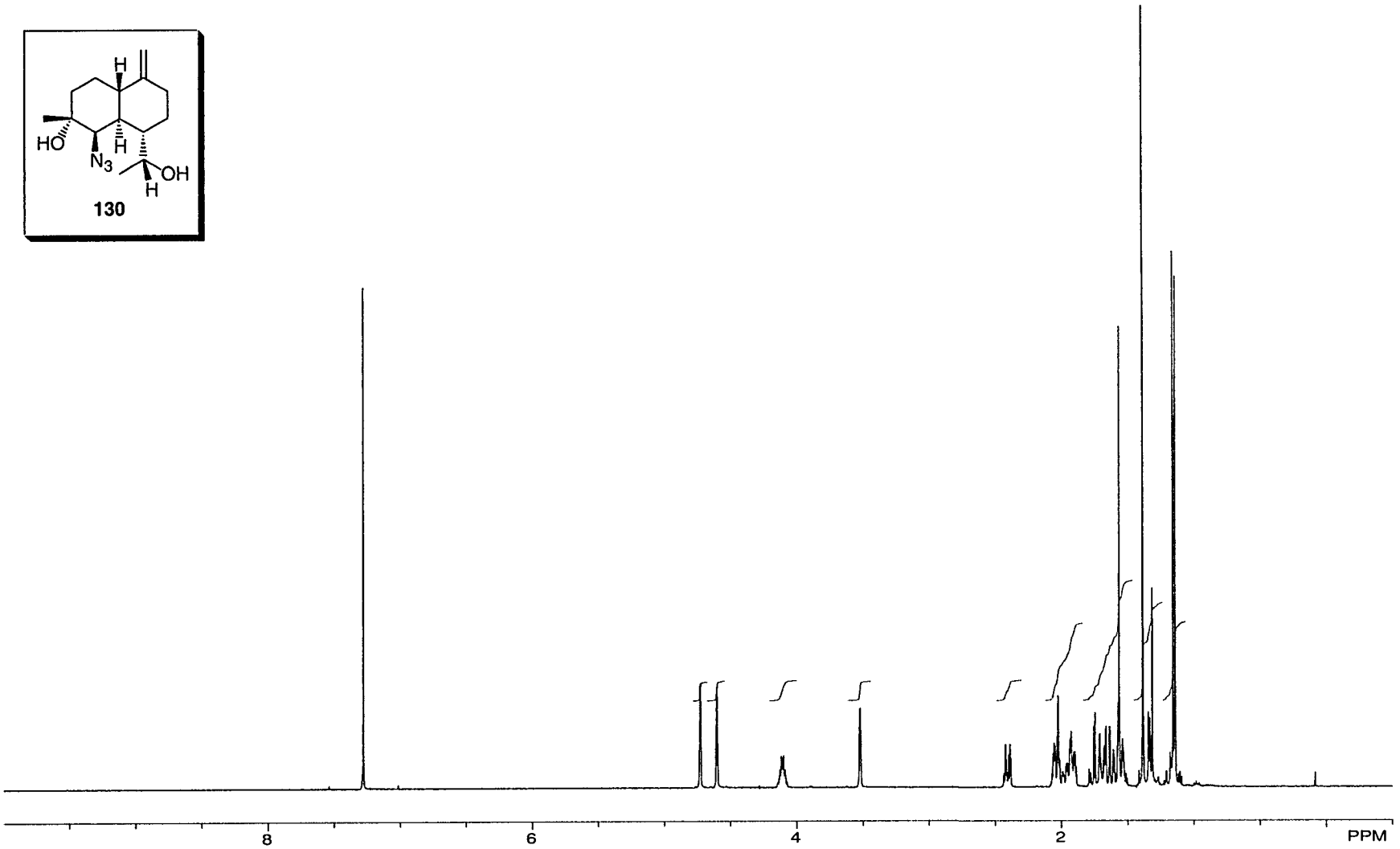


Figure A.3.76 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **130**.

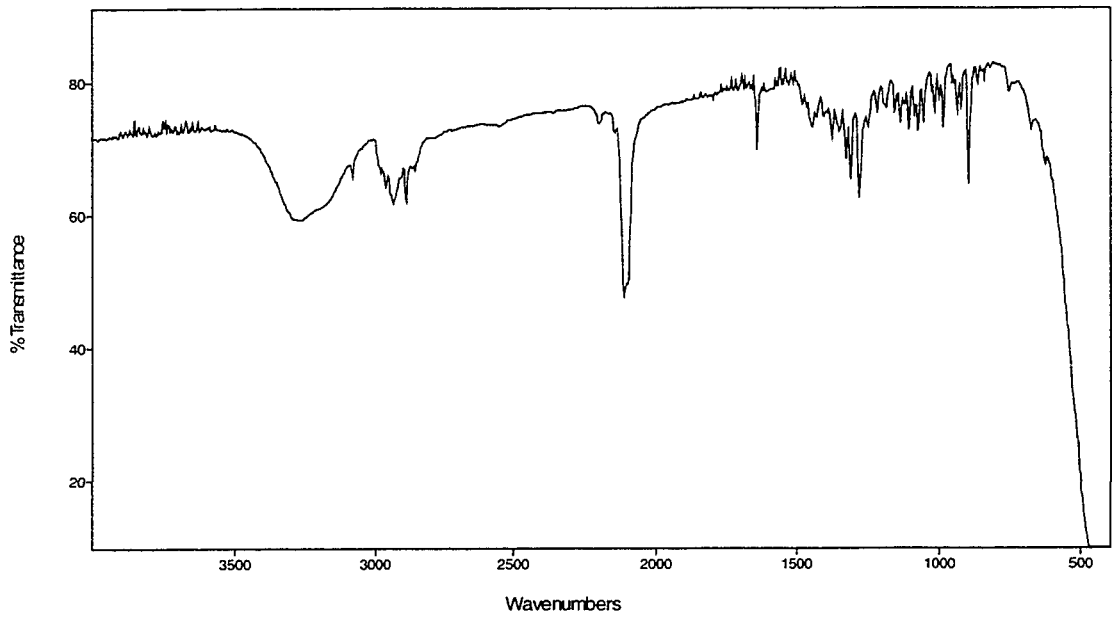


Figure A.3.77 FTIR Spectrum (thin film/NaCl) of Compound **130**.

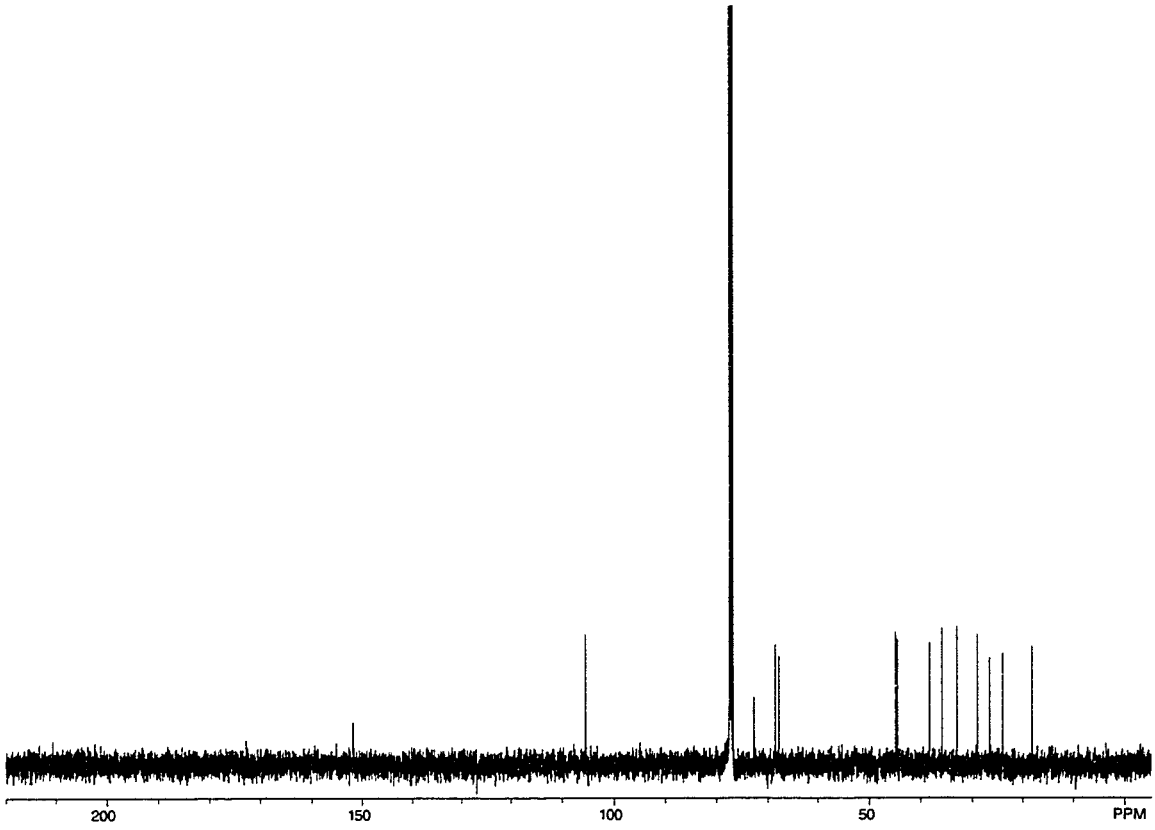


Figure A.3.78 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **130.**

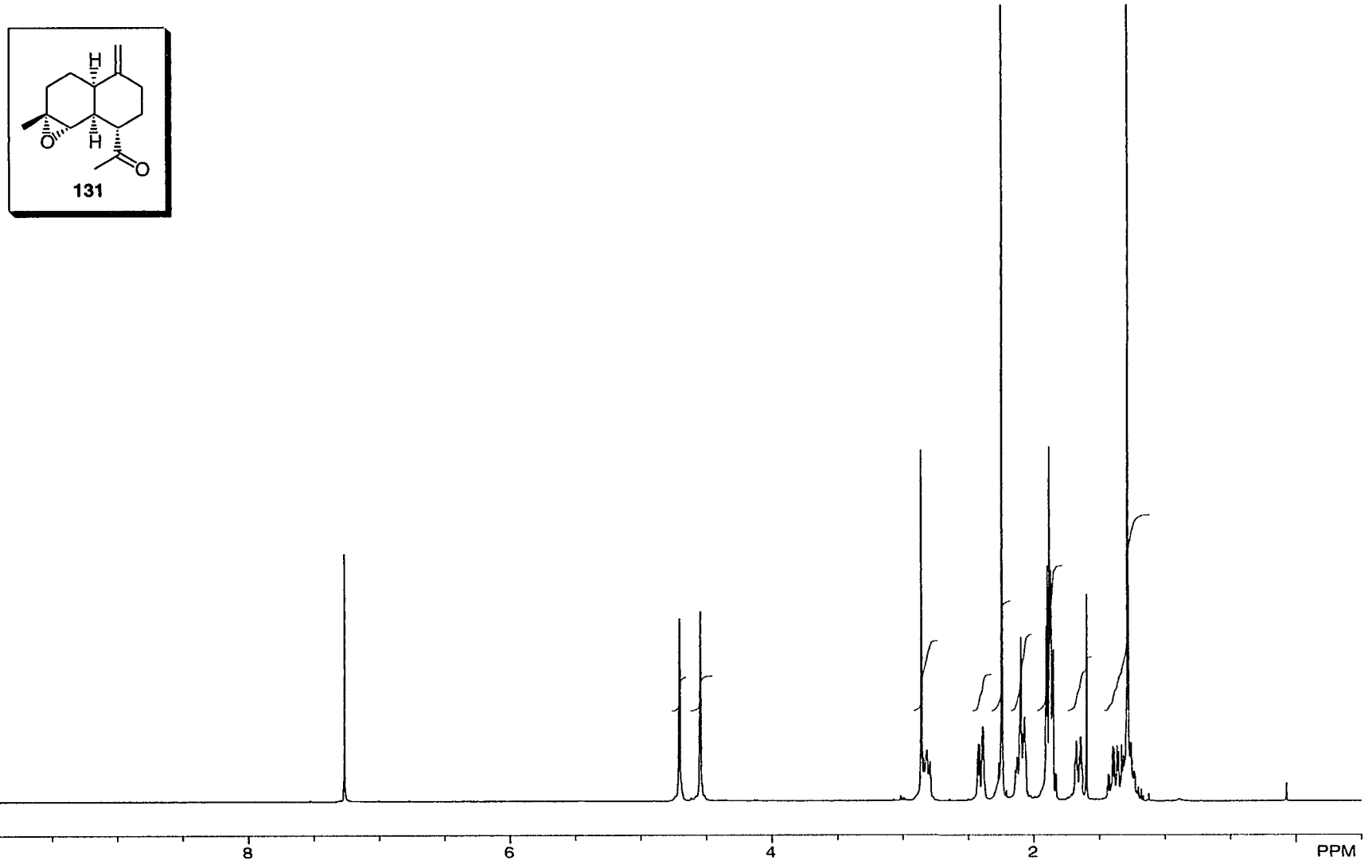


Figure A.3.79 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **131**.

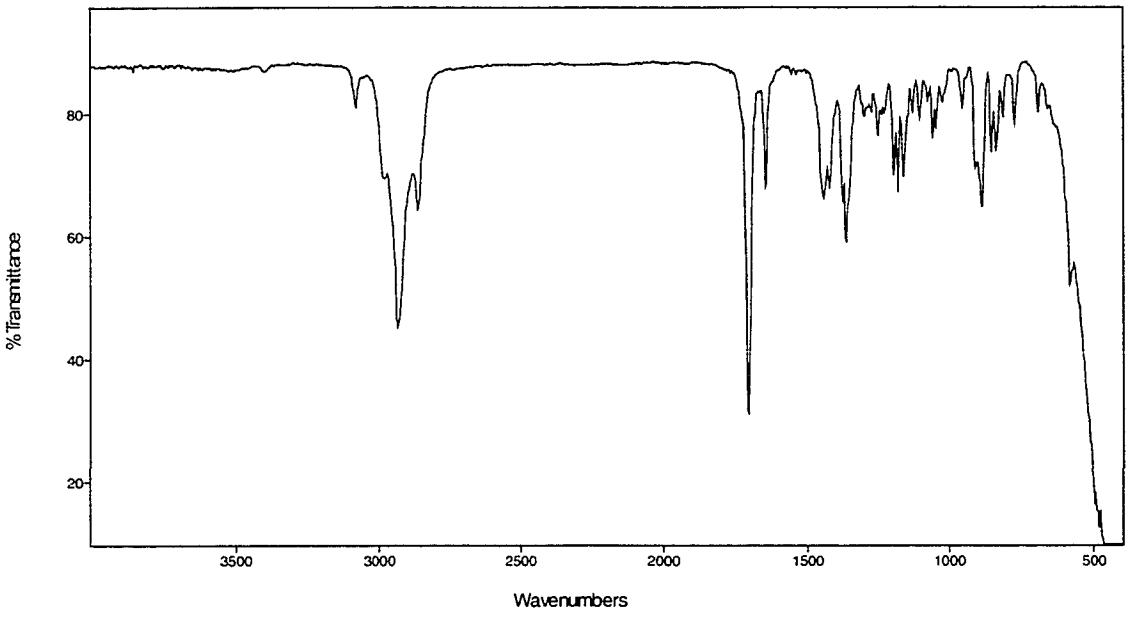


Figure A.3.80 FTIR Spectrum (thin film/NaCl) of Compound **131**.

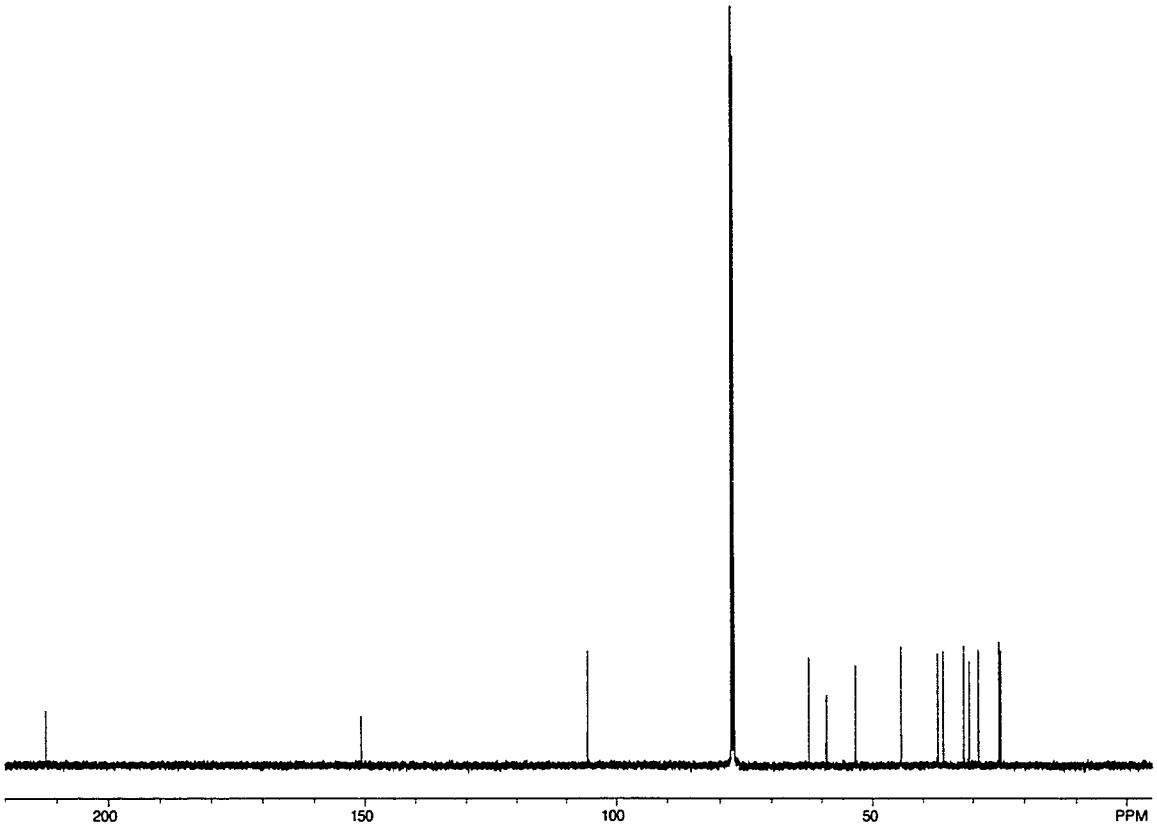


Figure A.3.81 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **131.**

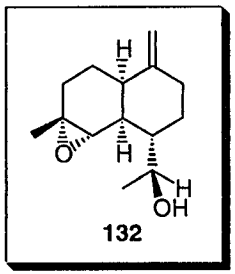


Figure A.3.82 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **132**.

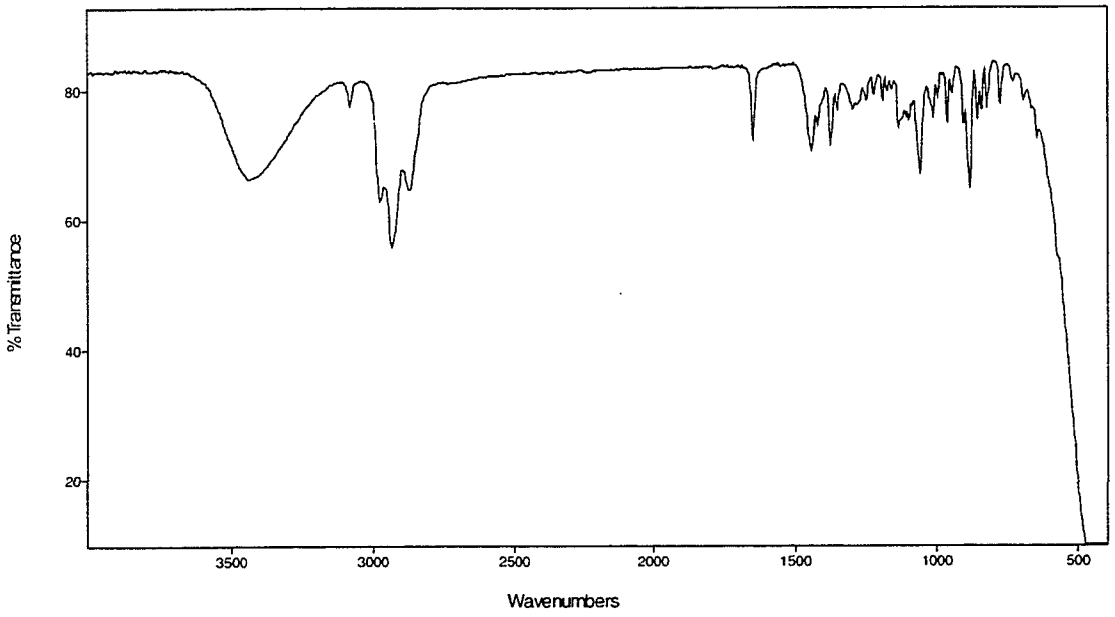


Figure A.3.83 FTIR Spectrum (thin film/NaCl) of Compound **132.**

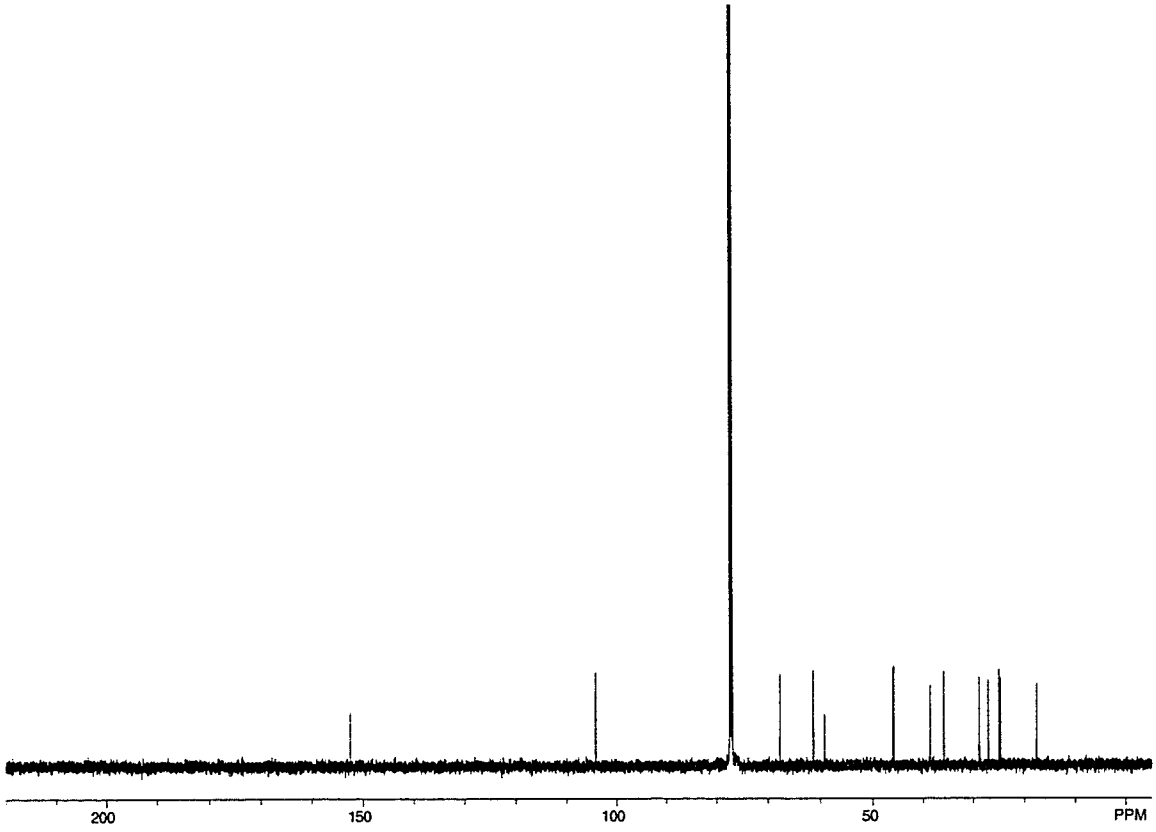


Figure A.3.84 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **132.**

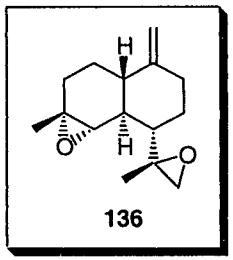


Figure A.3.85 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **136**.

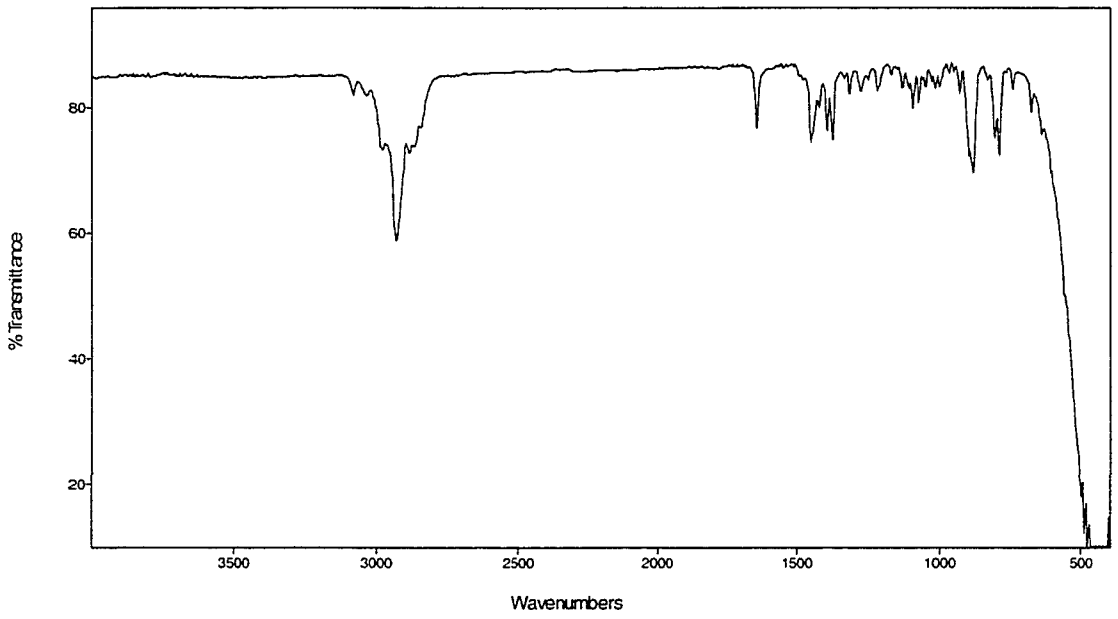


Figure A.3.86 FTIR Spectrum (thin film/NaCl) of Compound **136**.

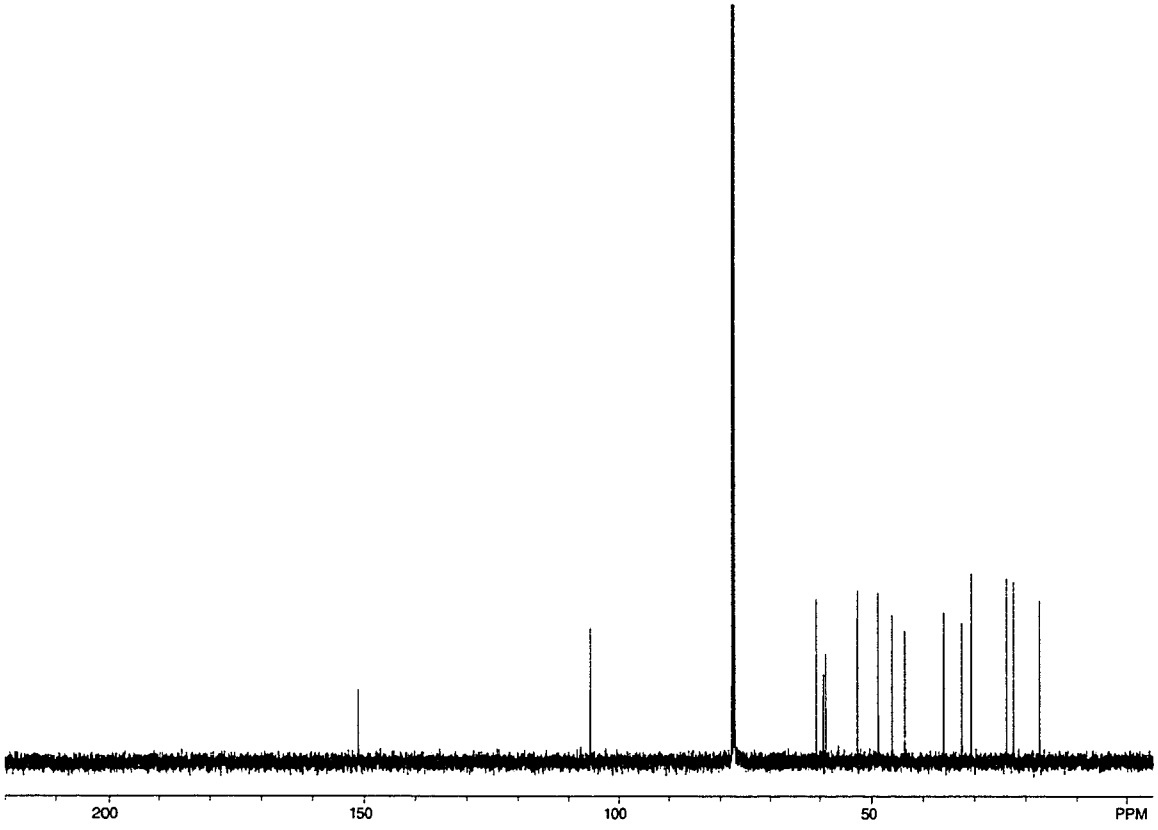


Figure A.3.87 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **136.**

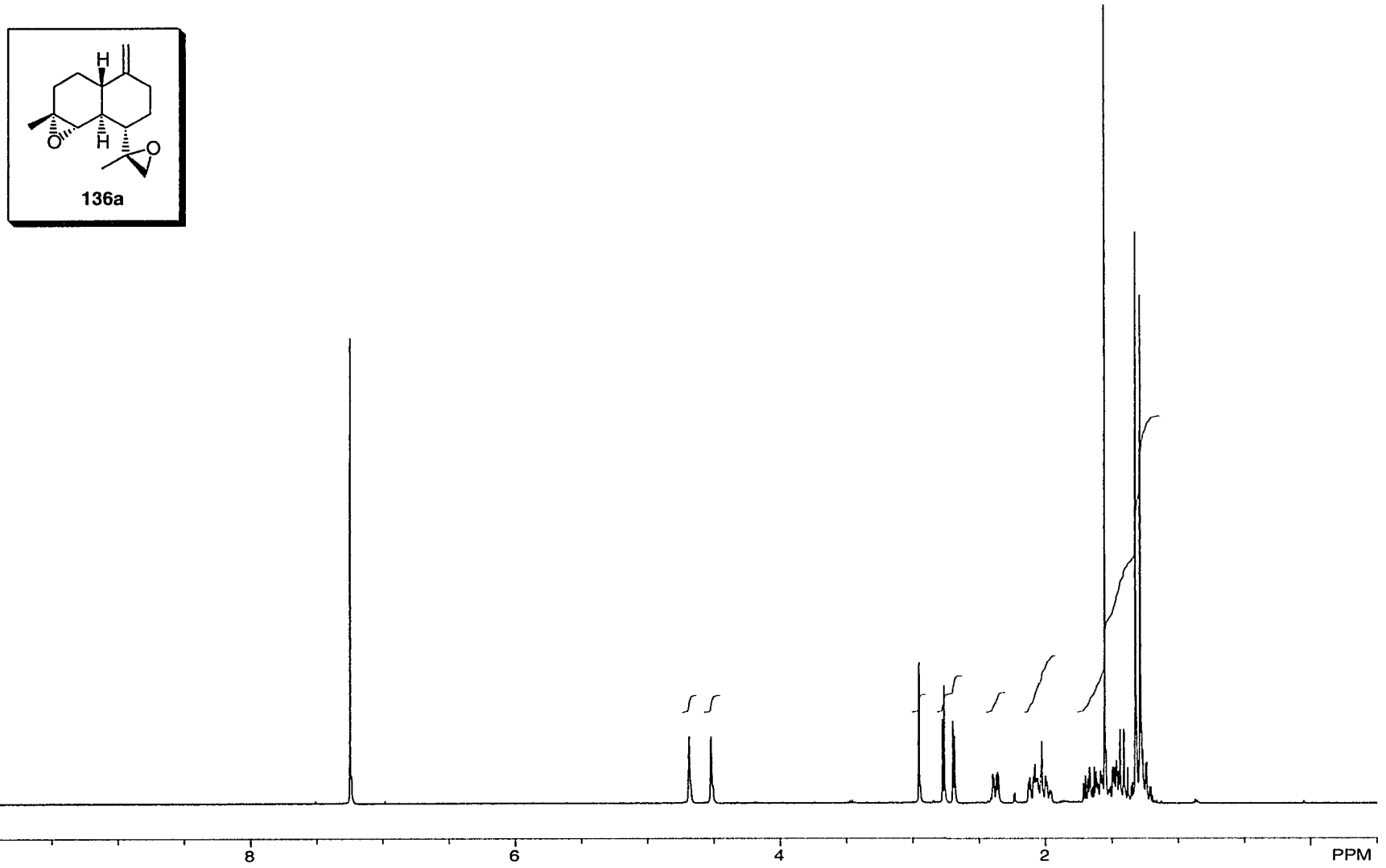


Figure A.3.88 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **136a**.

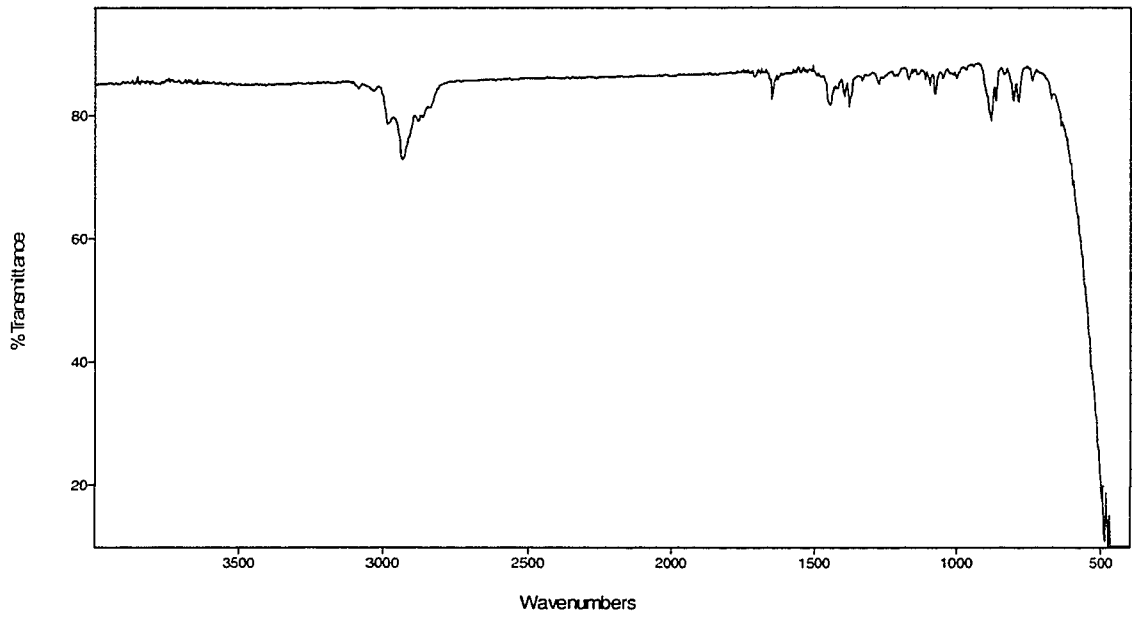


Figure A.3.89 FTIR Spectrum (thin film/NaCl) of Compound **136a**.

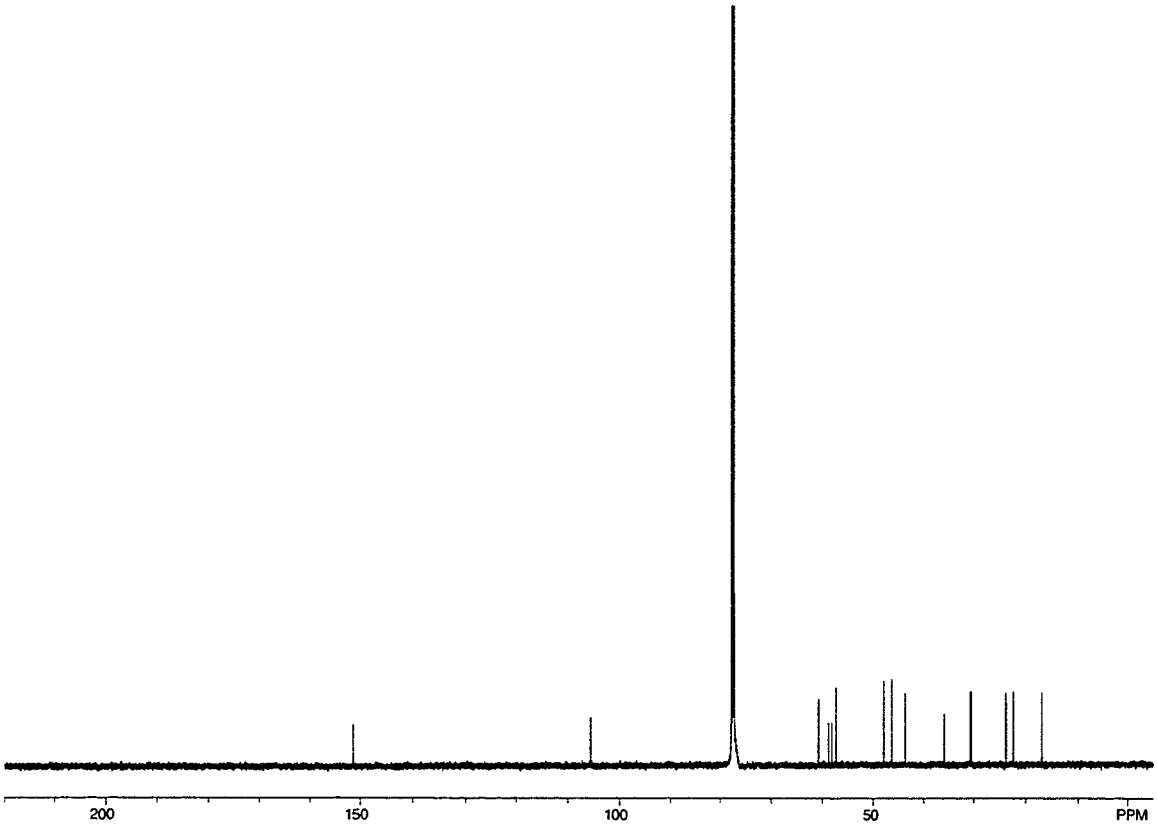


Figure A.3.90 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **136a.**

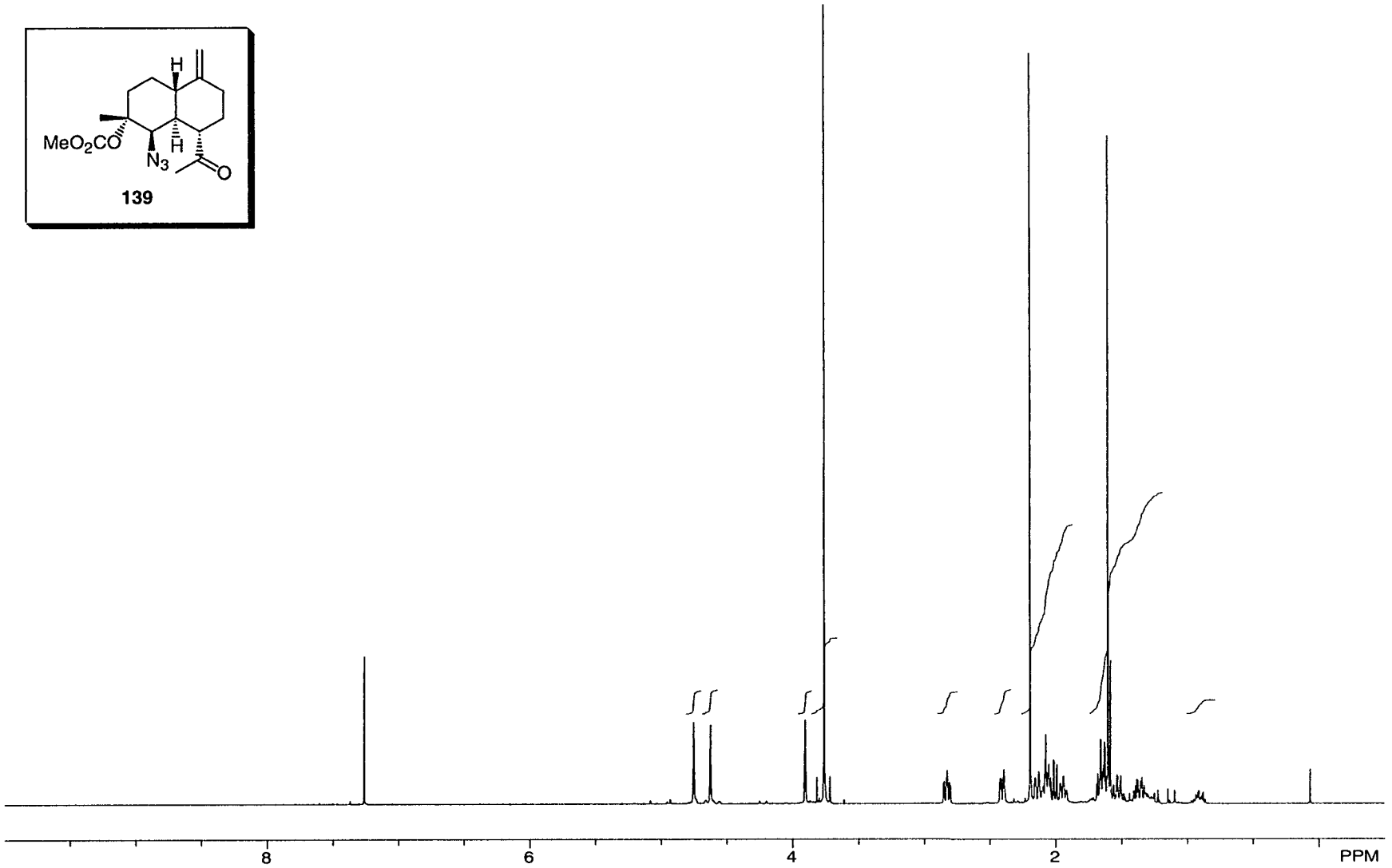


Figure A.3.91 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **139**.

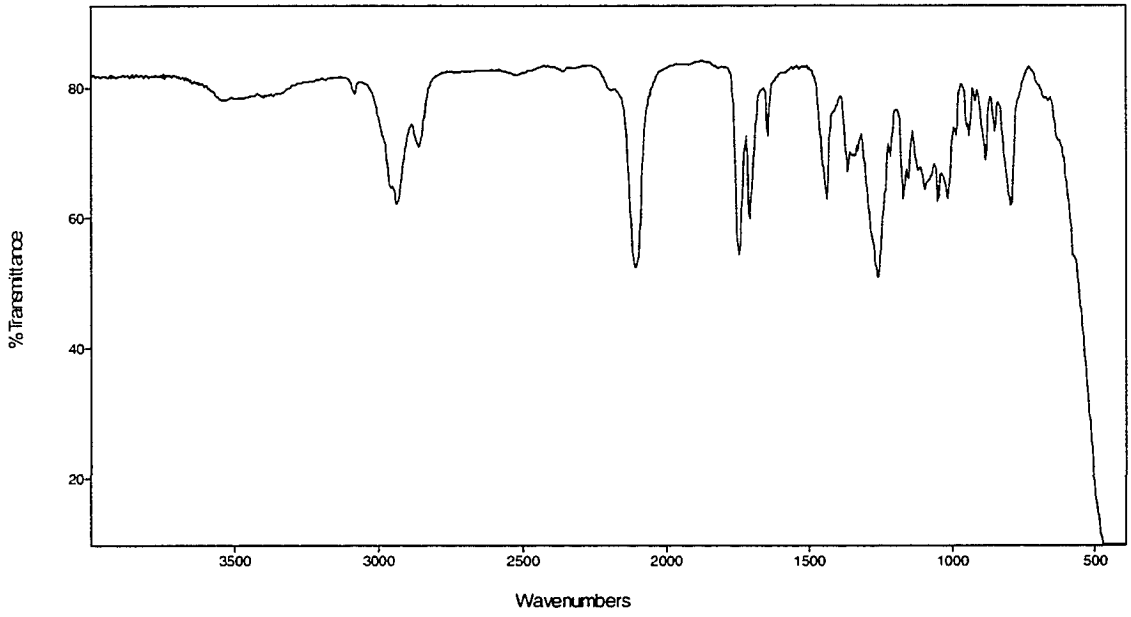


Figure A.3.92 FTIR Spectrum (thin film/NaCl) of Compound **139**.

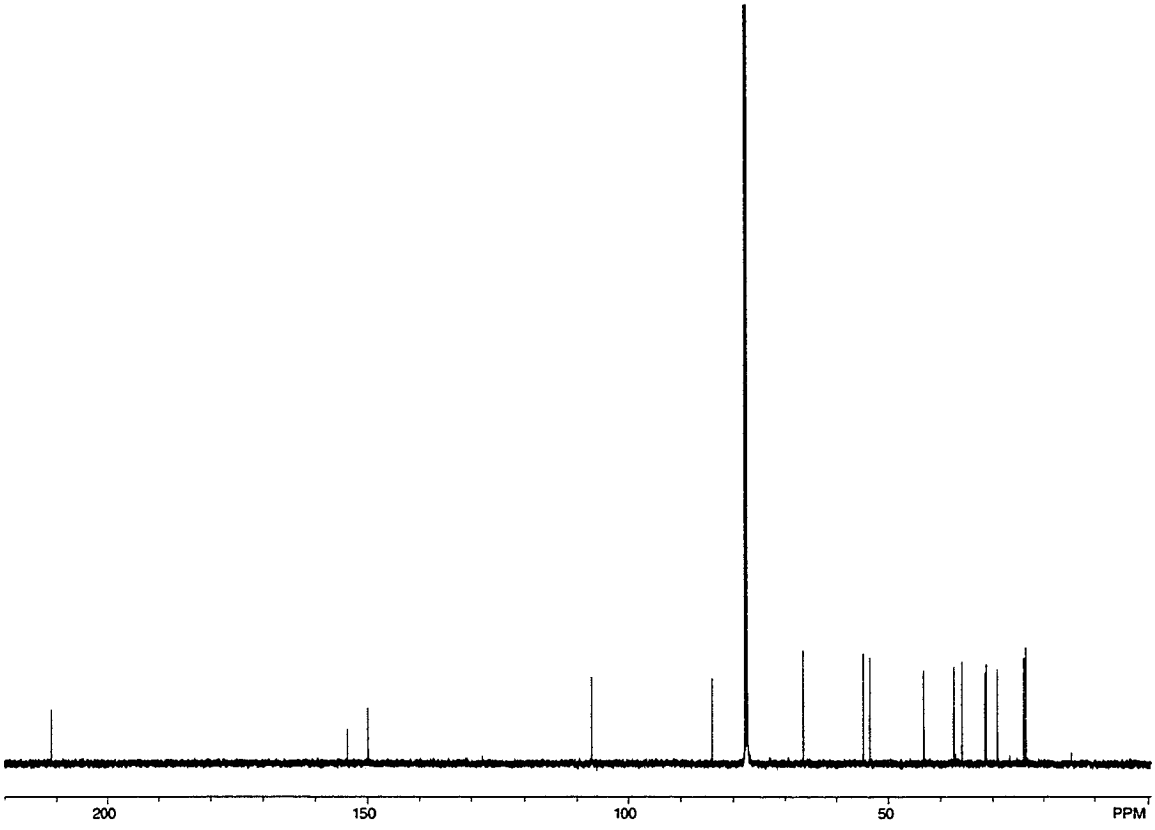


Figure A.3.93 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **139.**

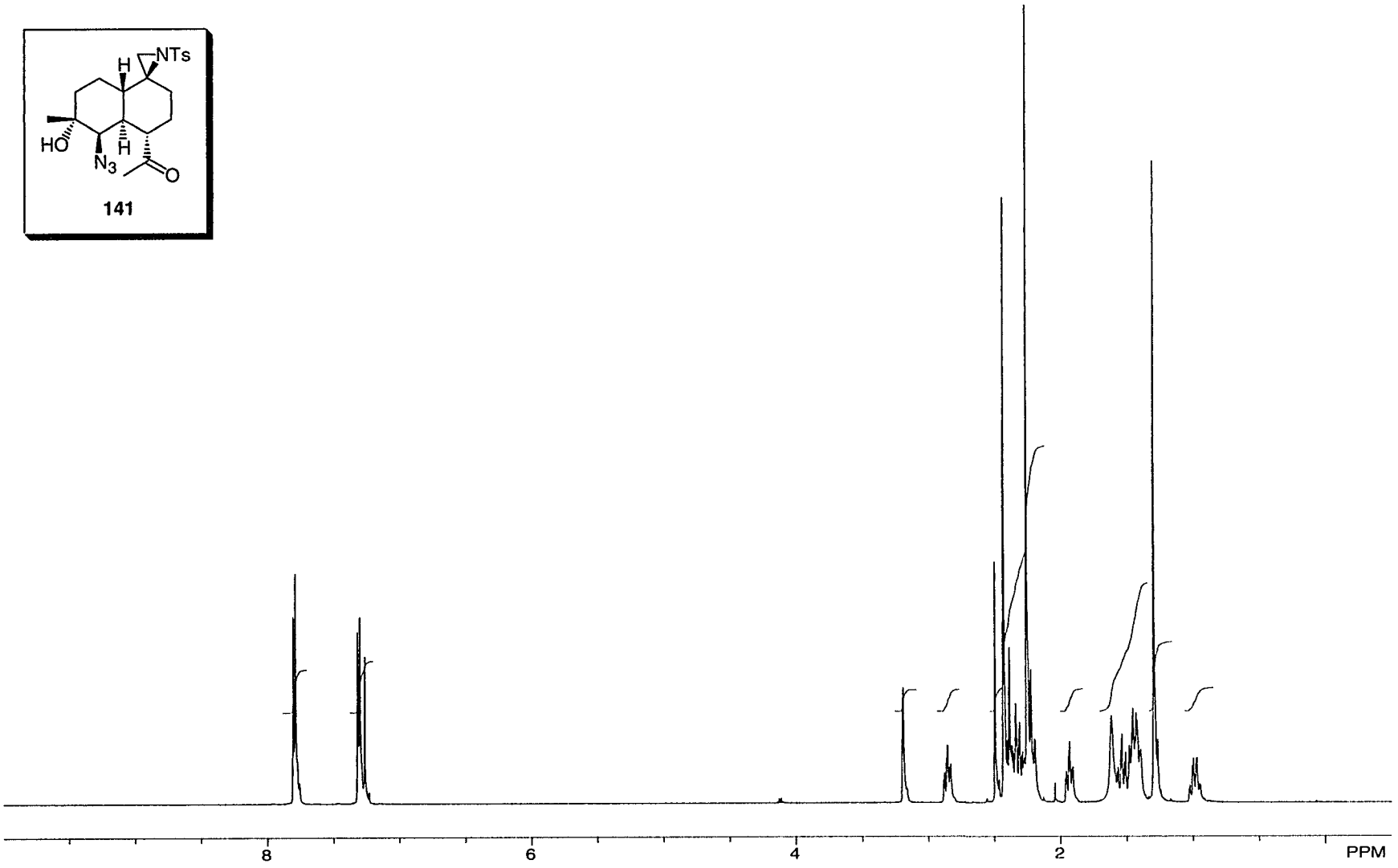


Figure A.3.94 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **141**.

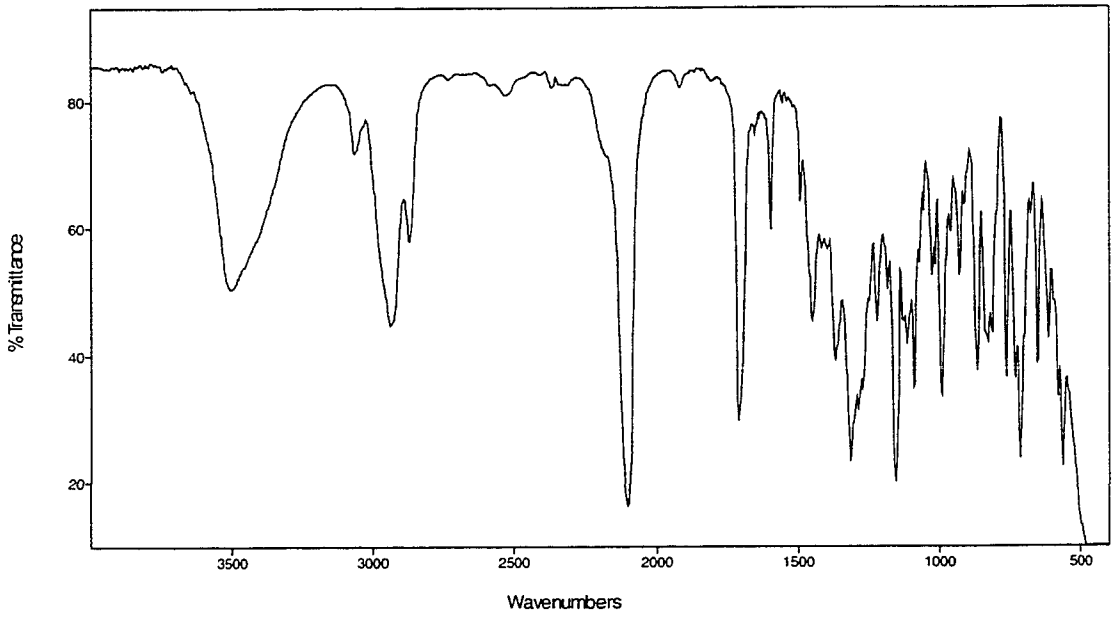


Figure A.3.95 FTIR Spectrum (thin film/NaCl) of Compound **141.**

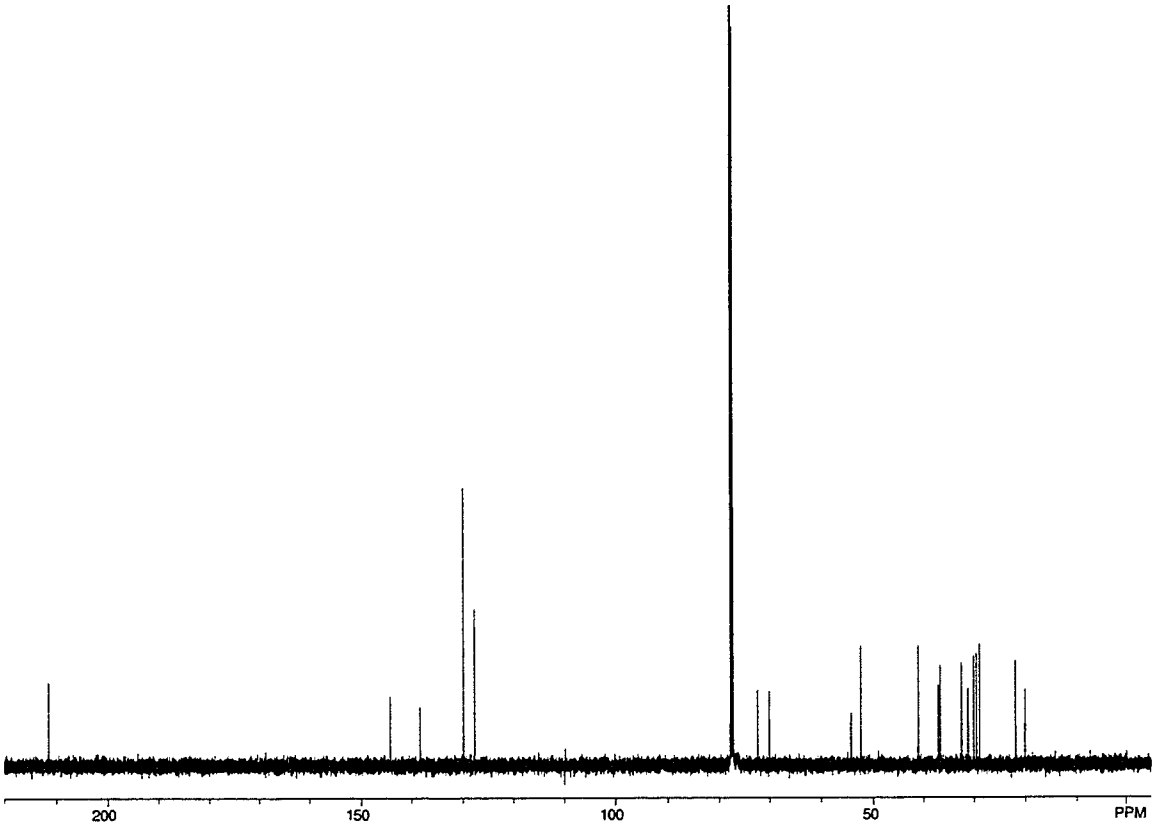


Figure A.3.96 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **141.**

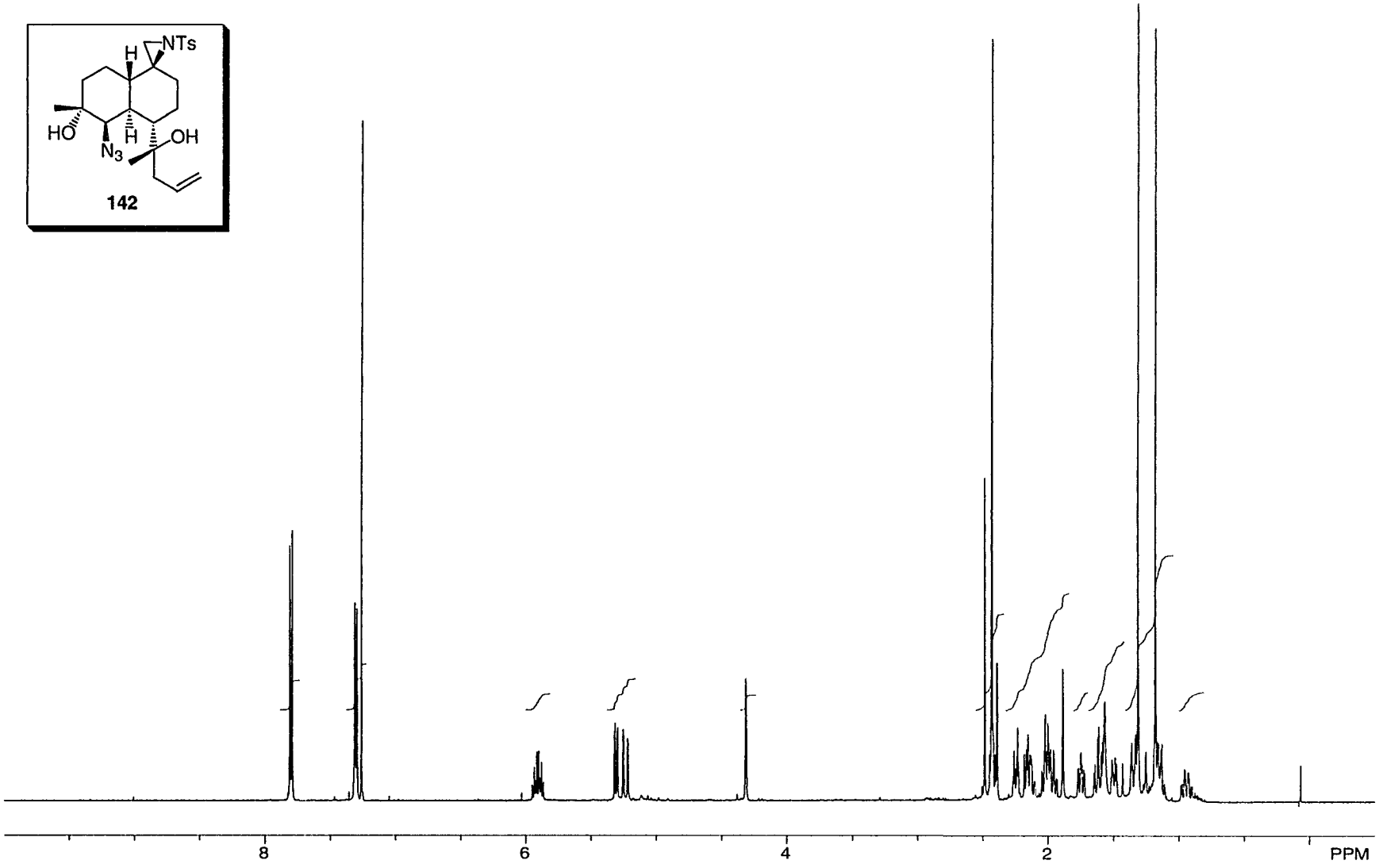


Figure A.3.97 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **142**.

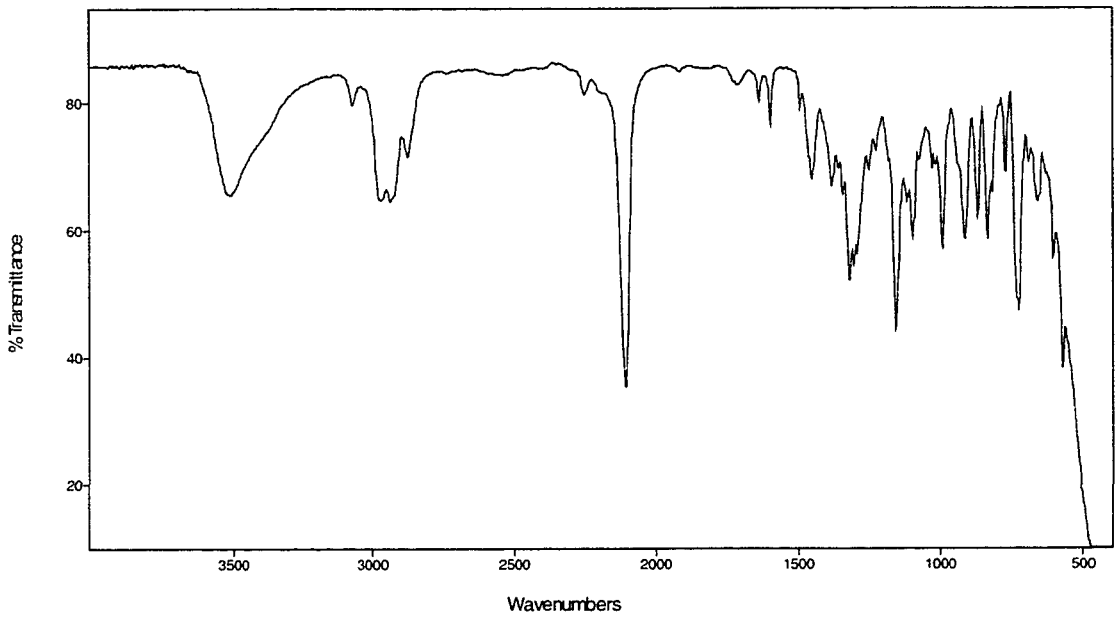


Figure A.3.98 FTIR Spectrum (thin film/NaCl) of Compound **142**.

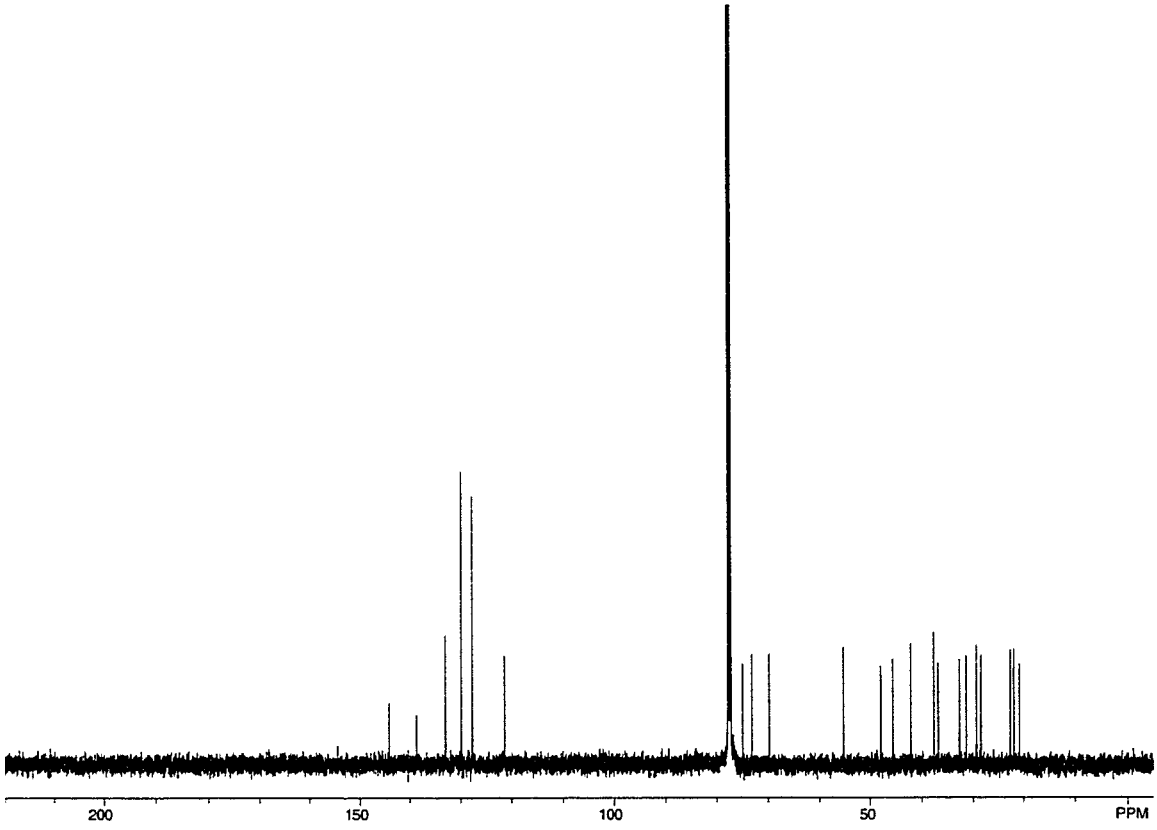
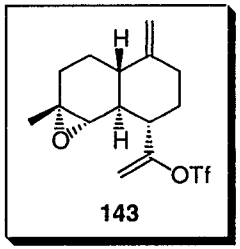


Figure A.3.99 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **142.**



143

Figure A.3.100 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **143**.

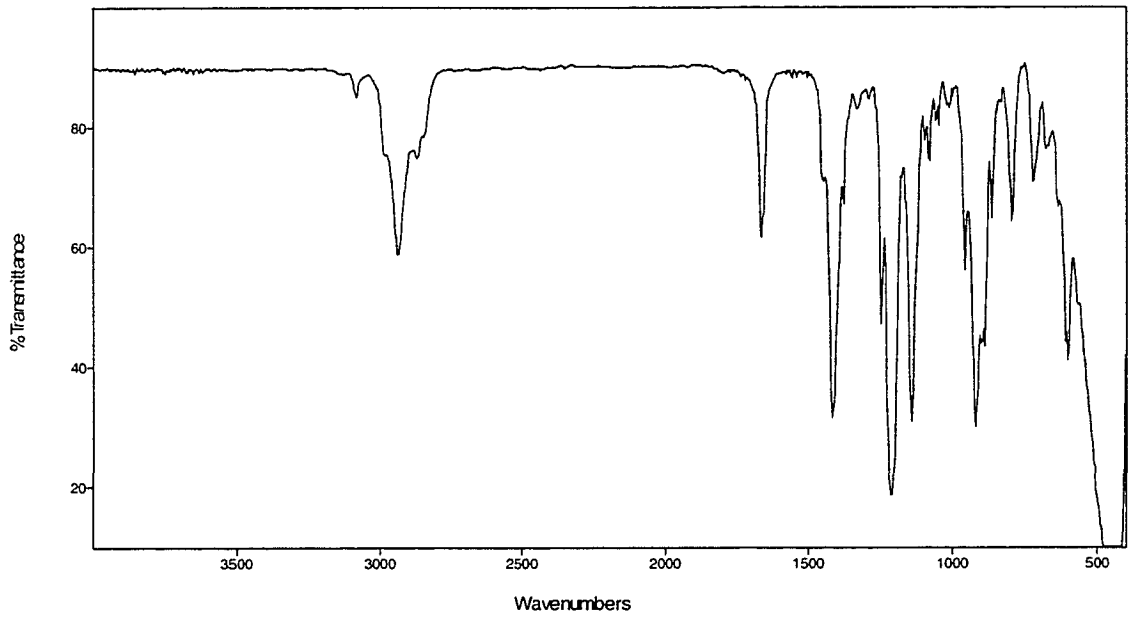


Figure A.3.101 FTIR Spectrum (thin film/NaCl) of Compound **143**.

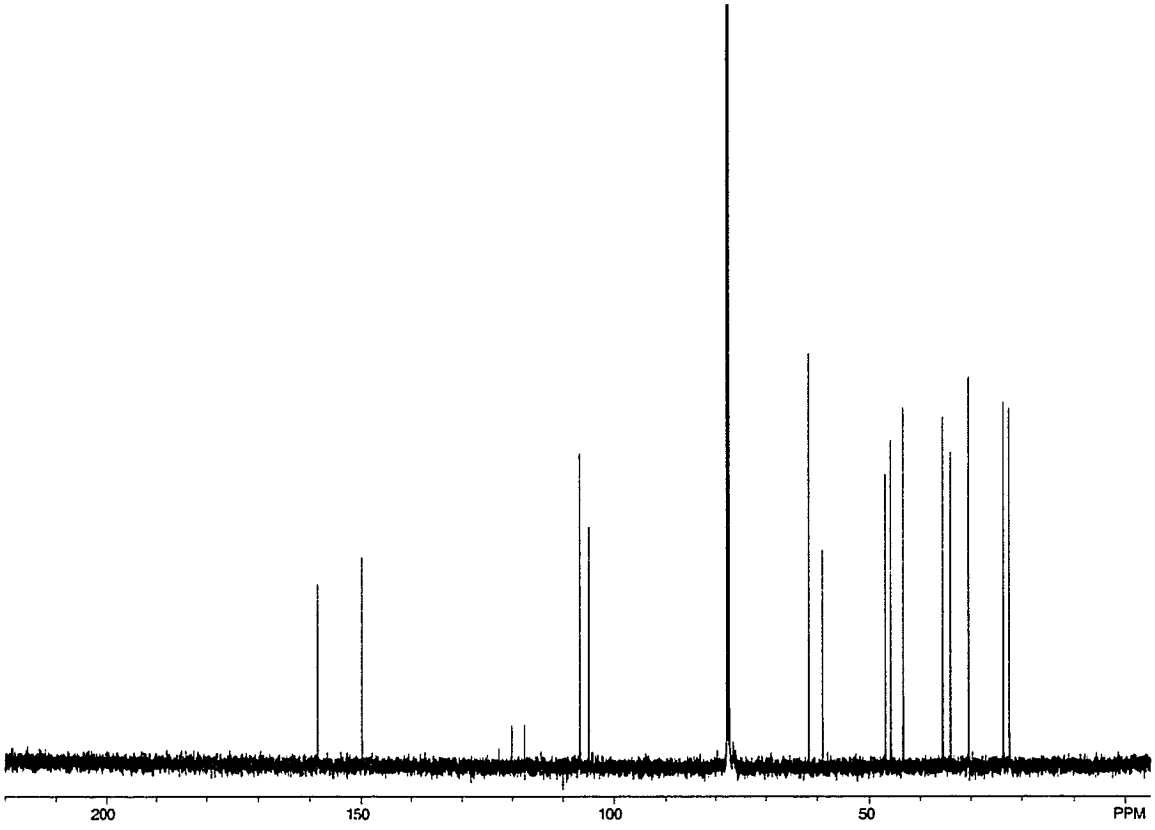


Figure A.3.102 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **143.**

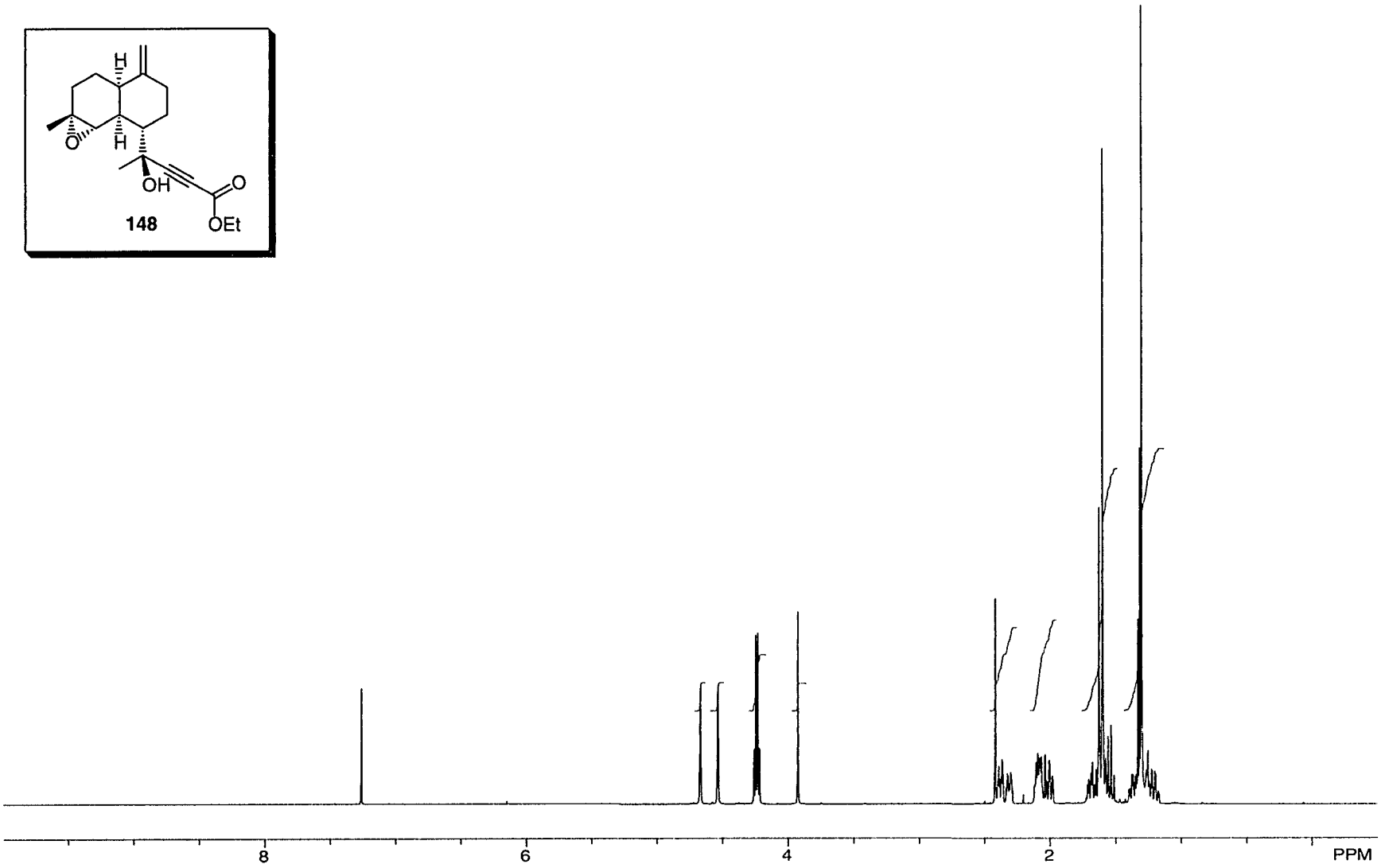


Figure A.3.103 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **148**.

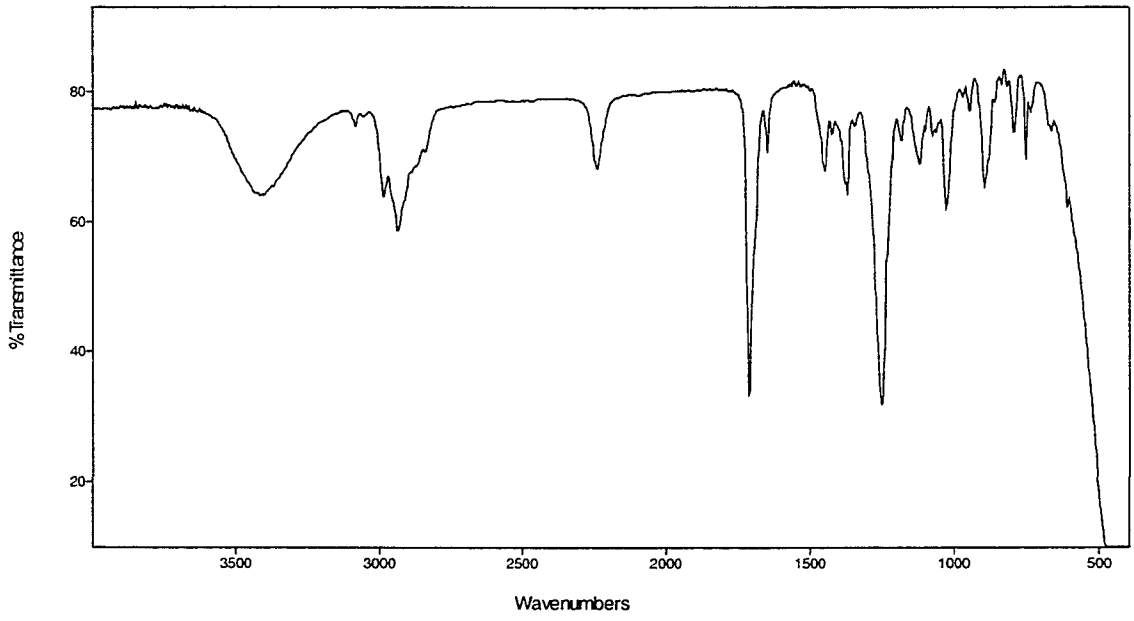


Figure A.3.104 FTIR Spectrum (thin film/NaCl) of Compound **148**.

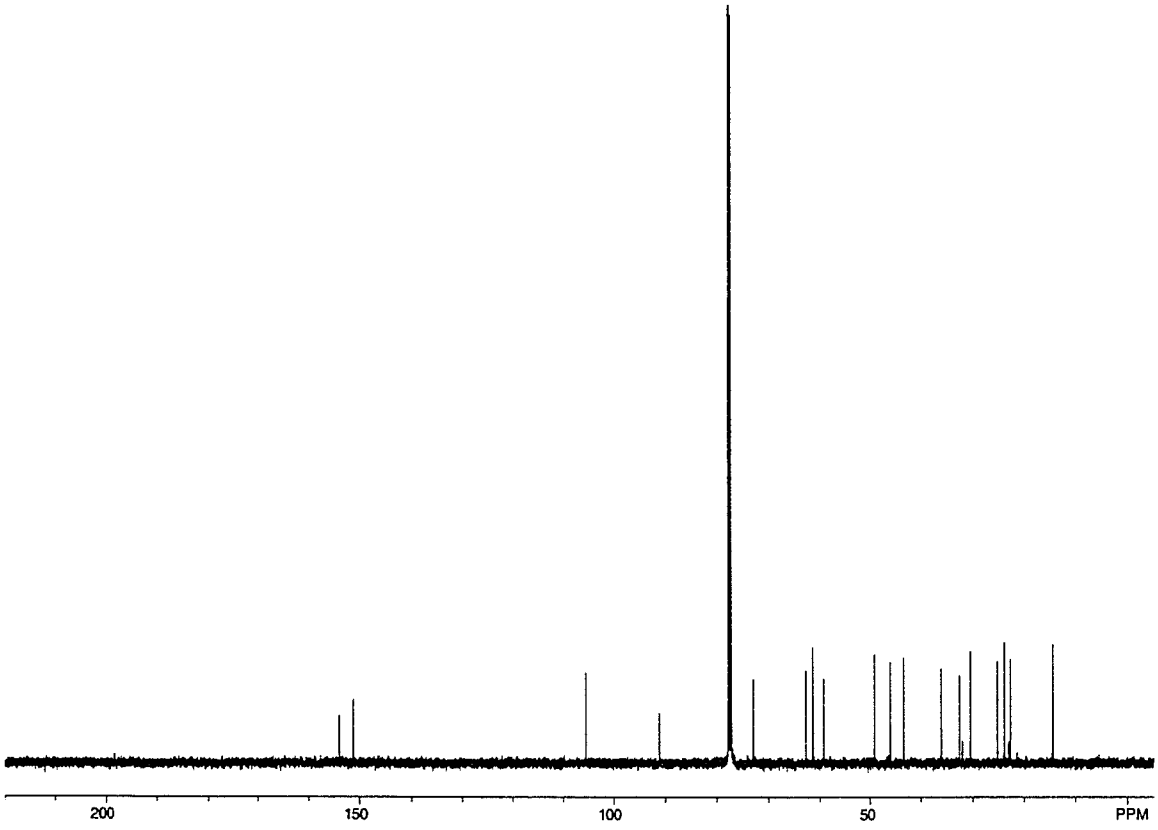


Figure A.3.105 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **148.**

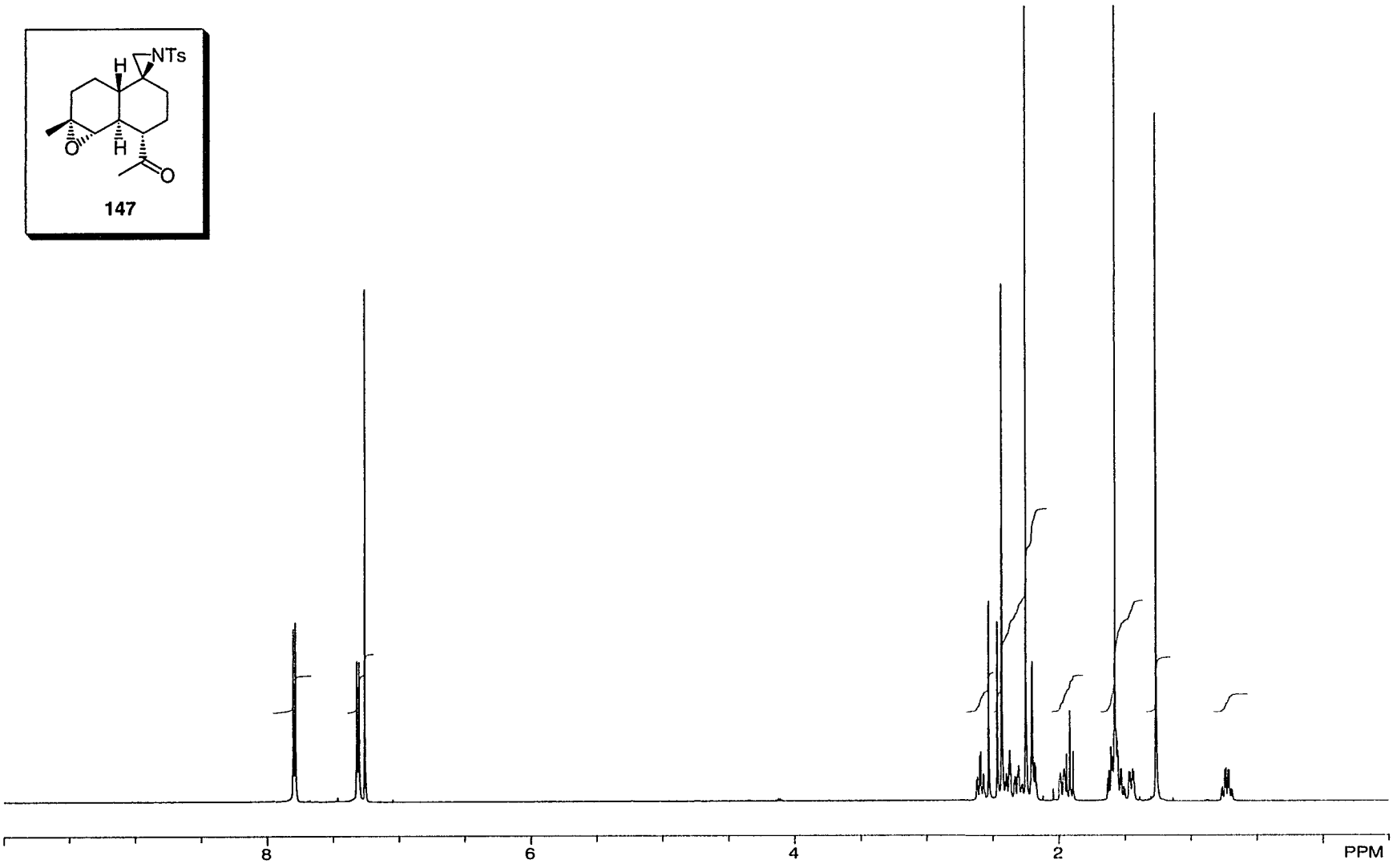


Figure A.3.106 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **147**.

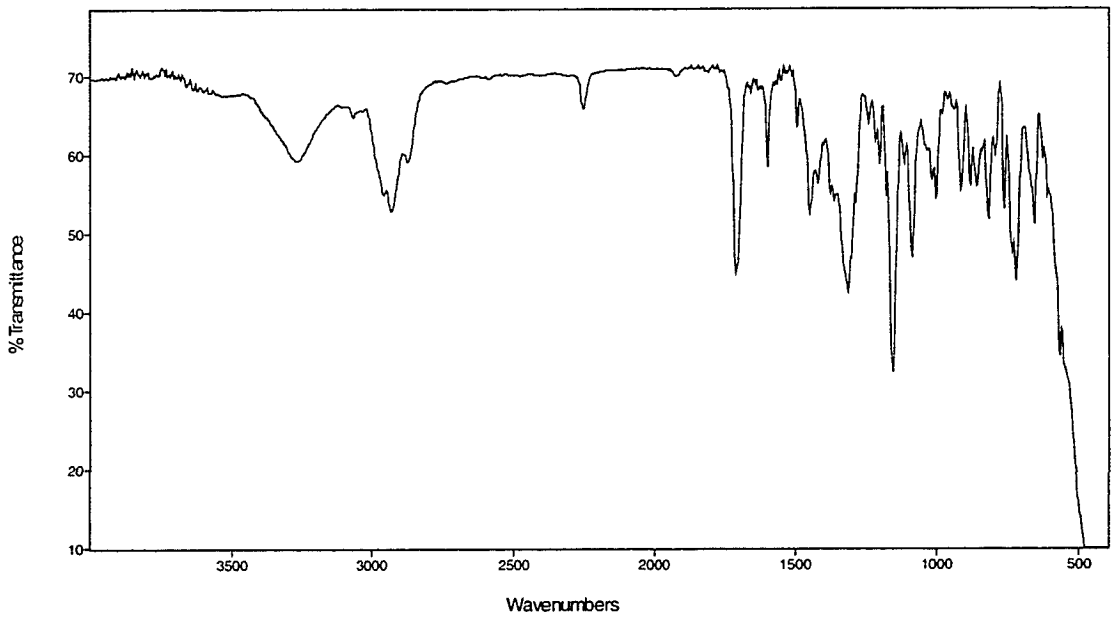


Figure A.3.107 FTIR Spectrum (thin film/NaCl) of Compound **147.**

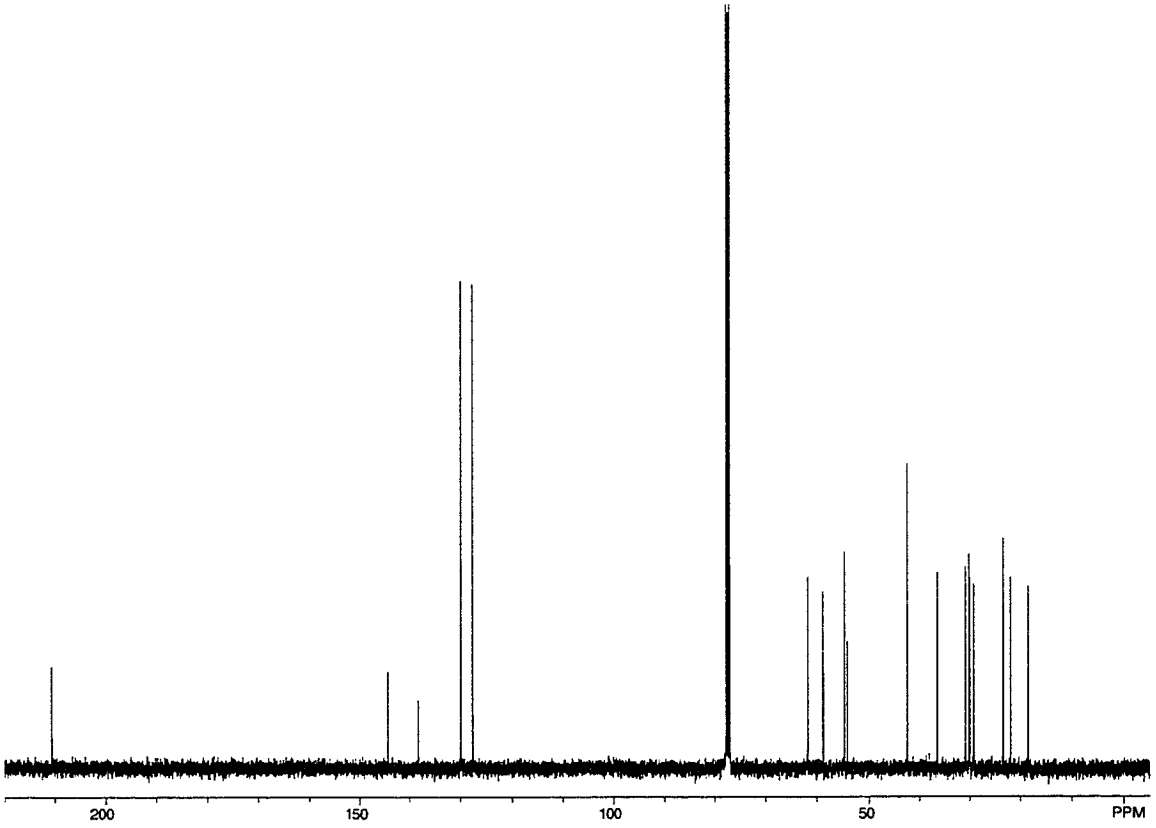


Figure A.3.108 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **147.**

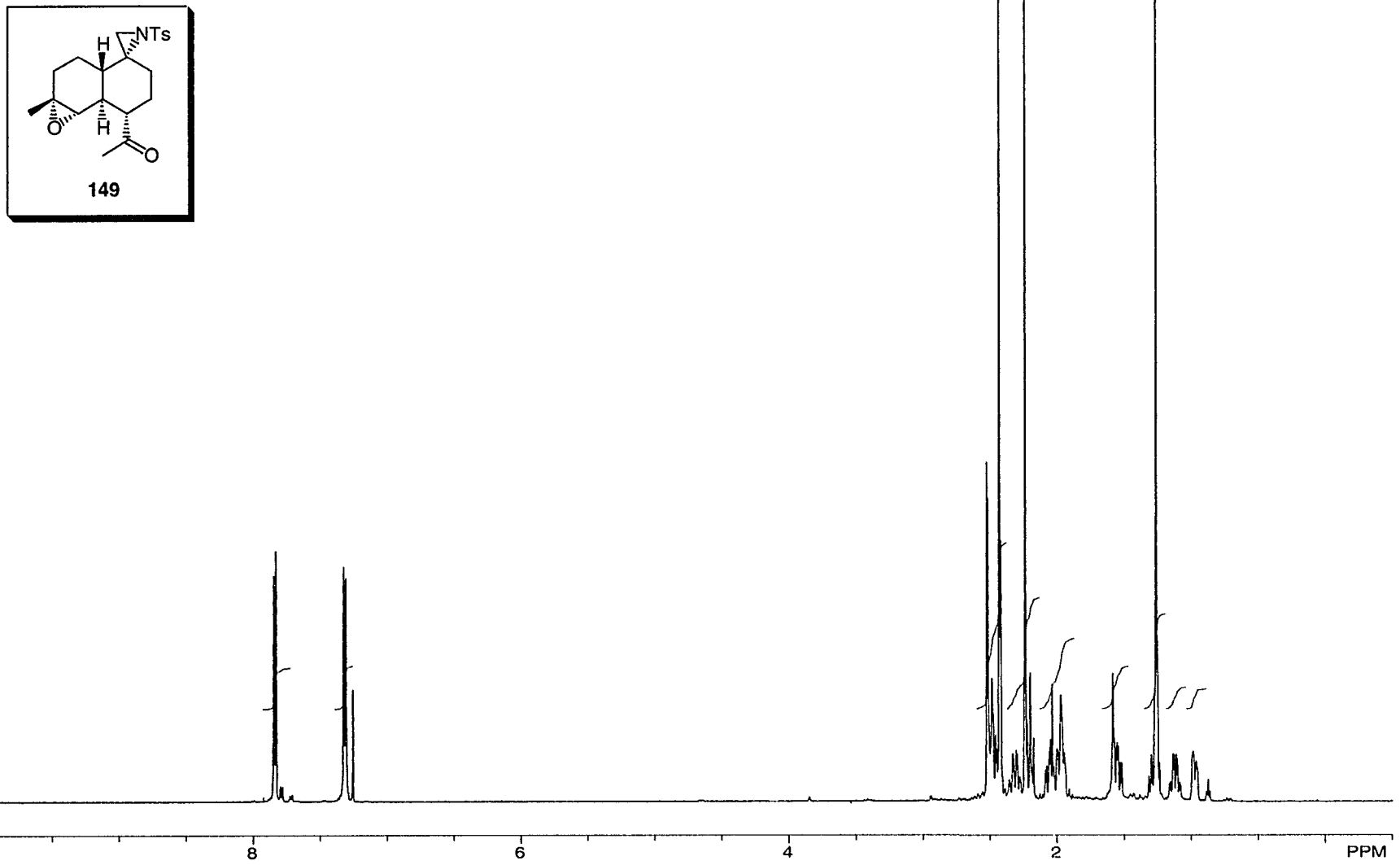


Figure A.3.109 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **149**.

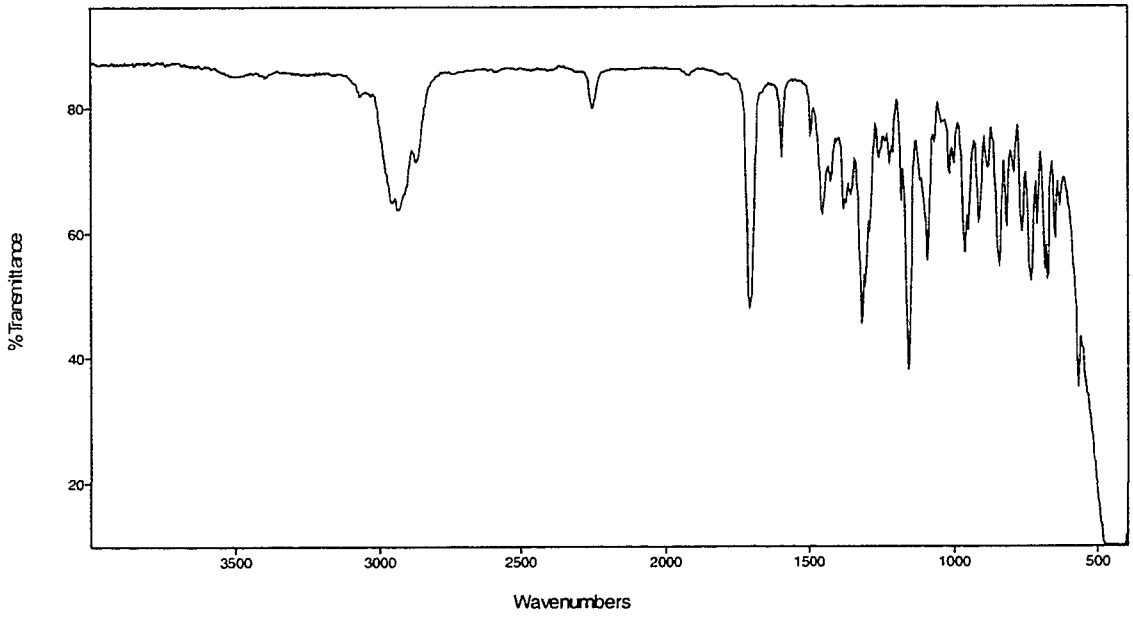


Figure A.3.110 FTIR Spectrum (thin film/NaCl) of Compound **149**.

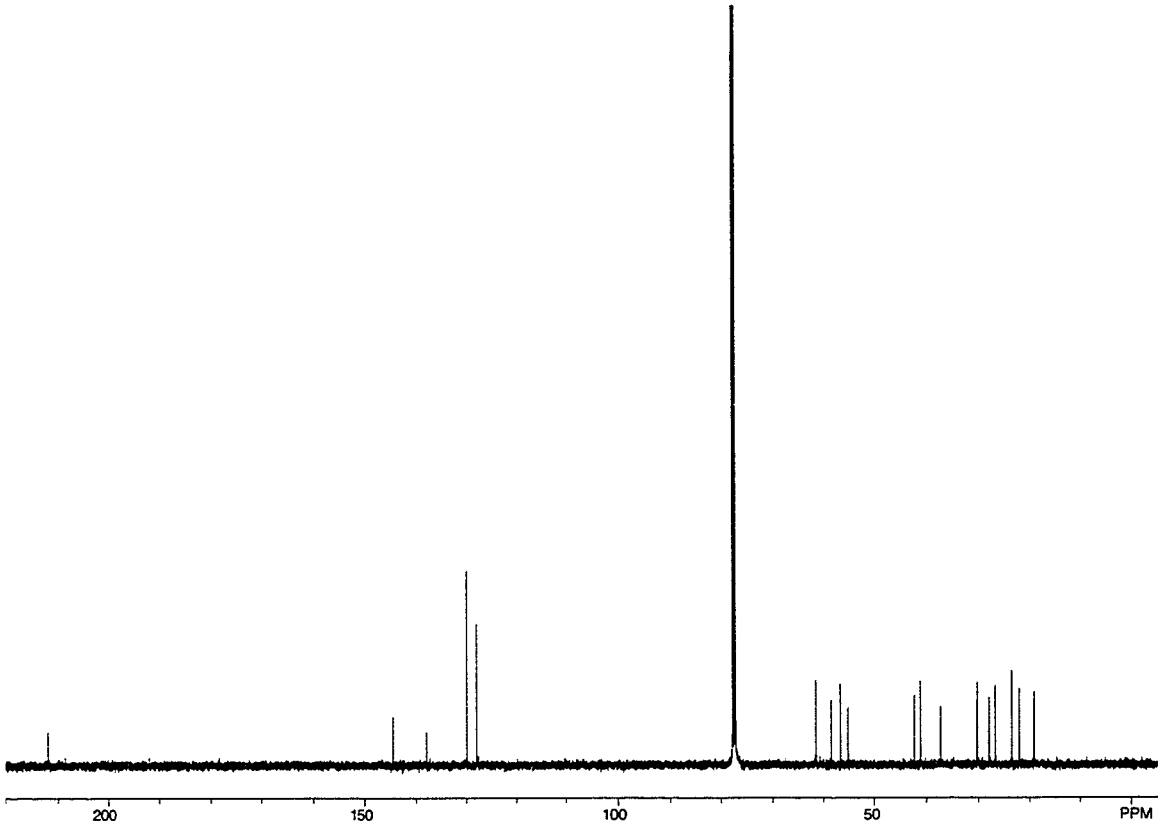


Figure A.3.111 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **149.**

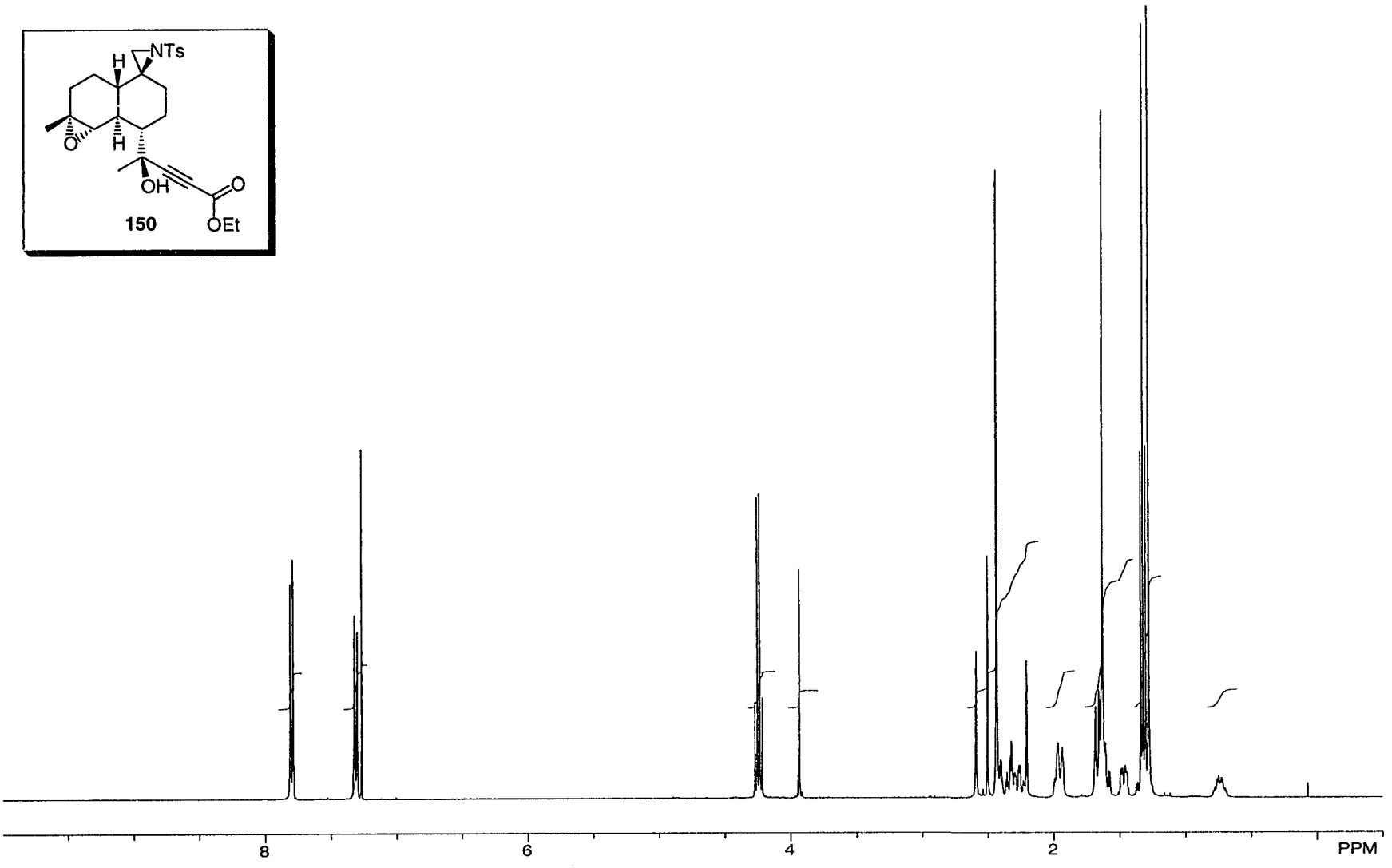


Figure A.3.112 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **150**.

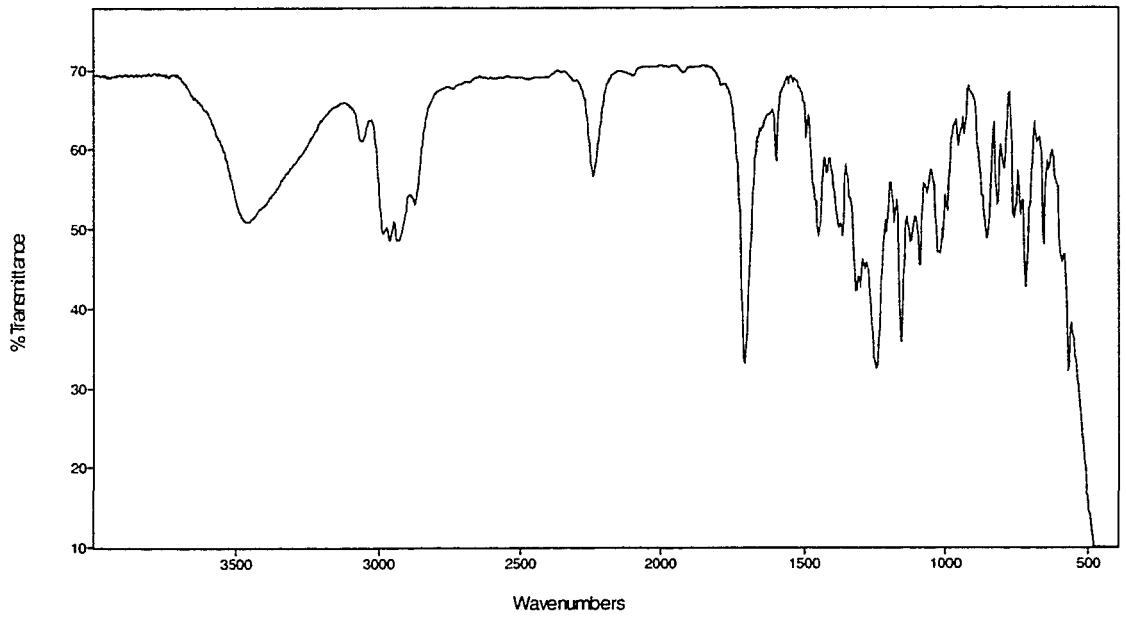


Figure A.3.113 FTIR Spectrum (thin film/NaCl) of Compound **150**.

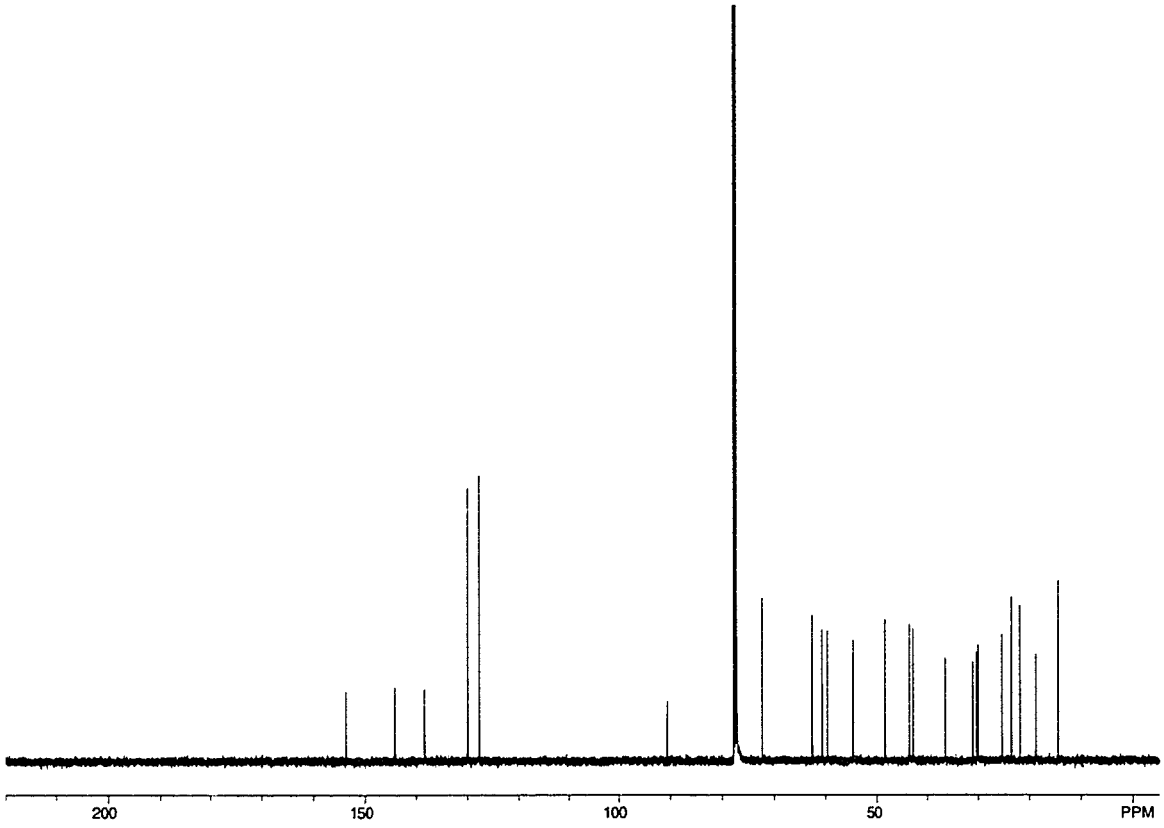


Figure A.3.114 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **150.**

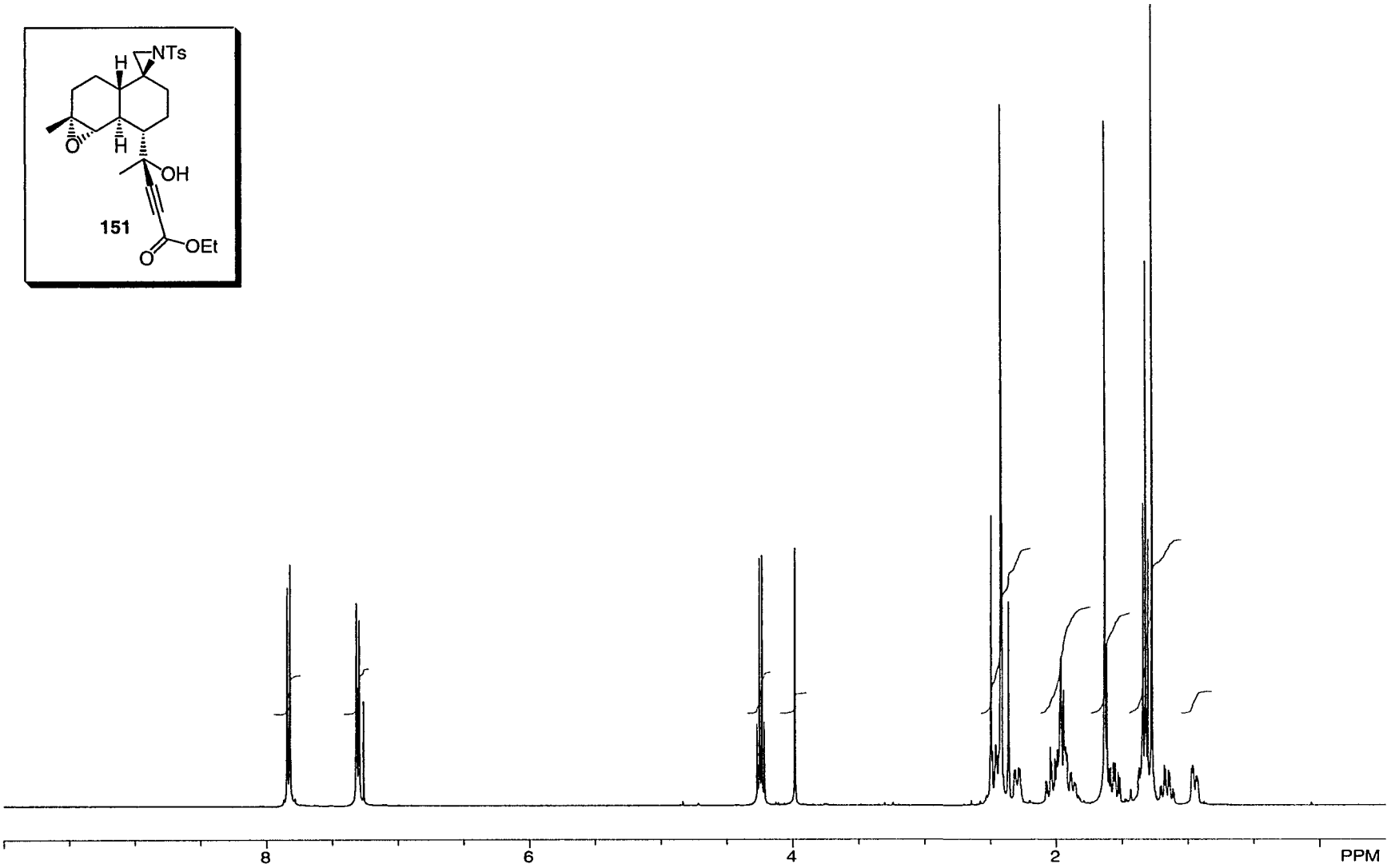


Figure A.3.115 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **151'**.

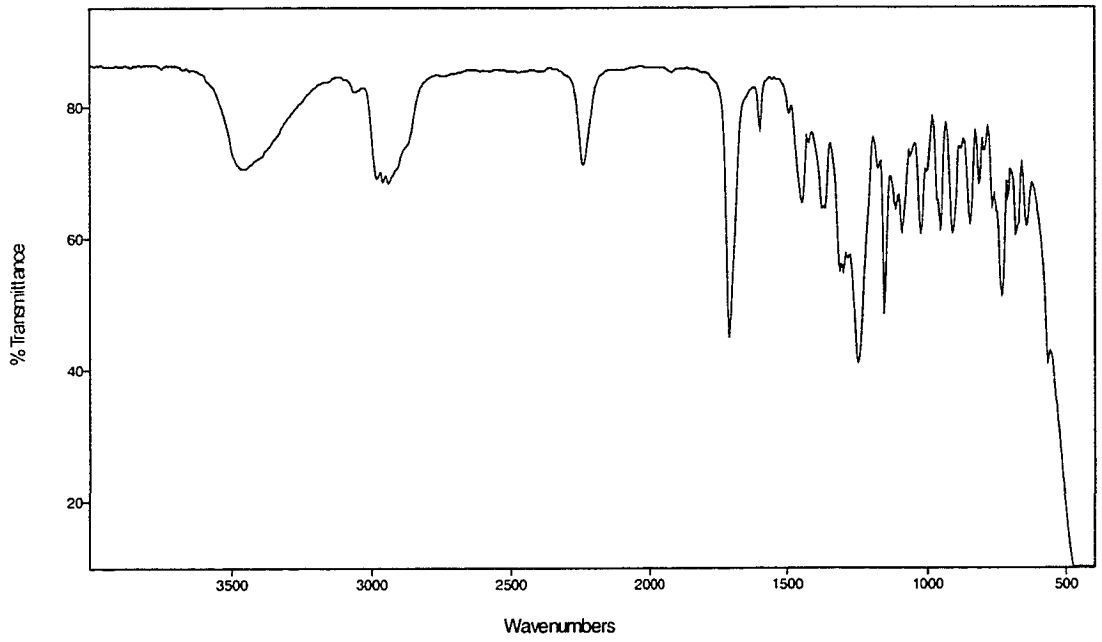


Figure A.3.116 FTIR Spectrum (thin film/NaCl) of Compound **151**.

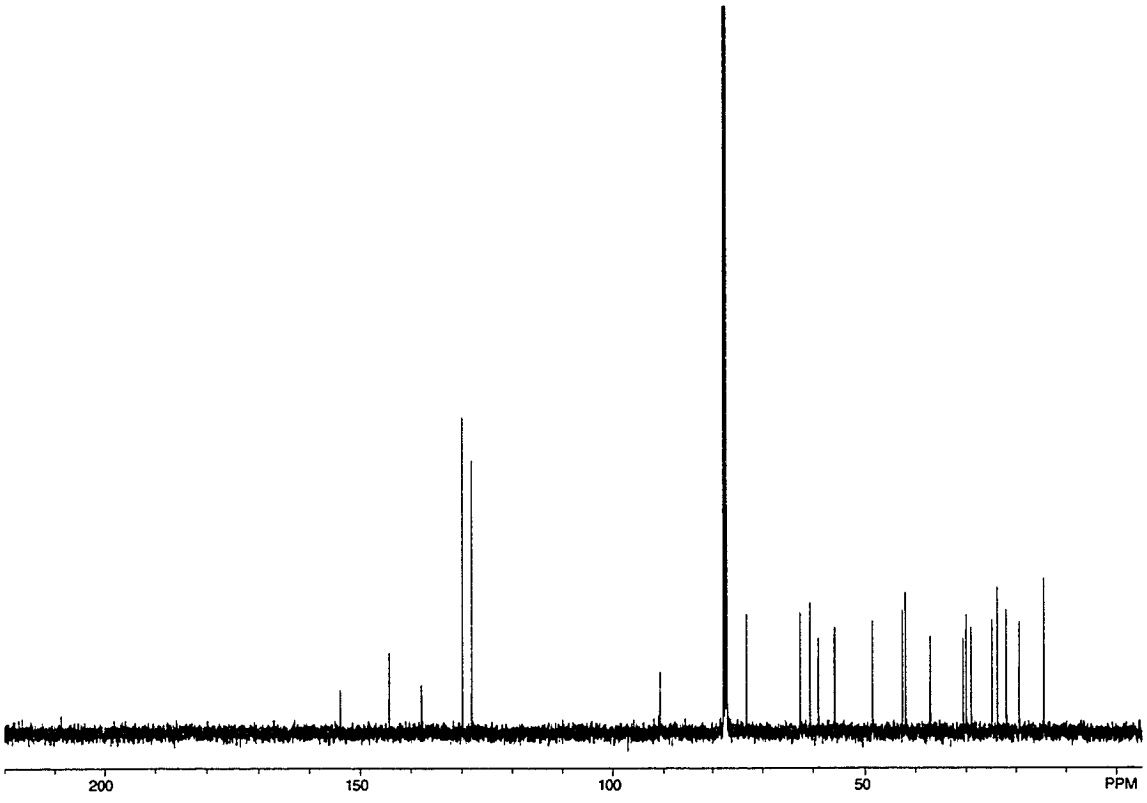


Figure A.3.117 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **151.**

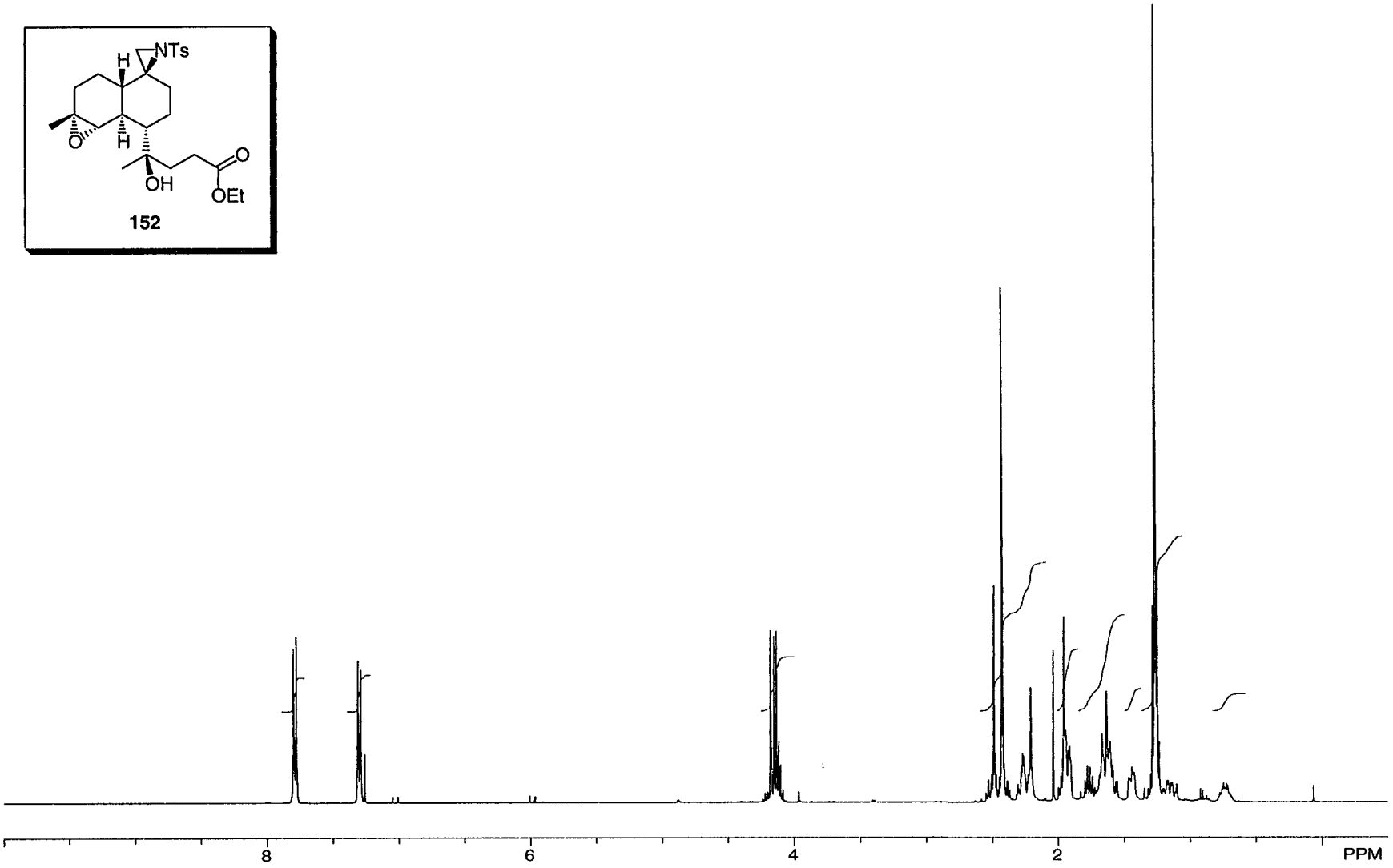


Figure A.3.118 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **152**.

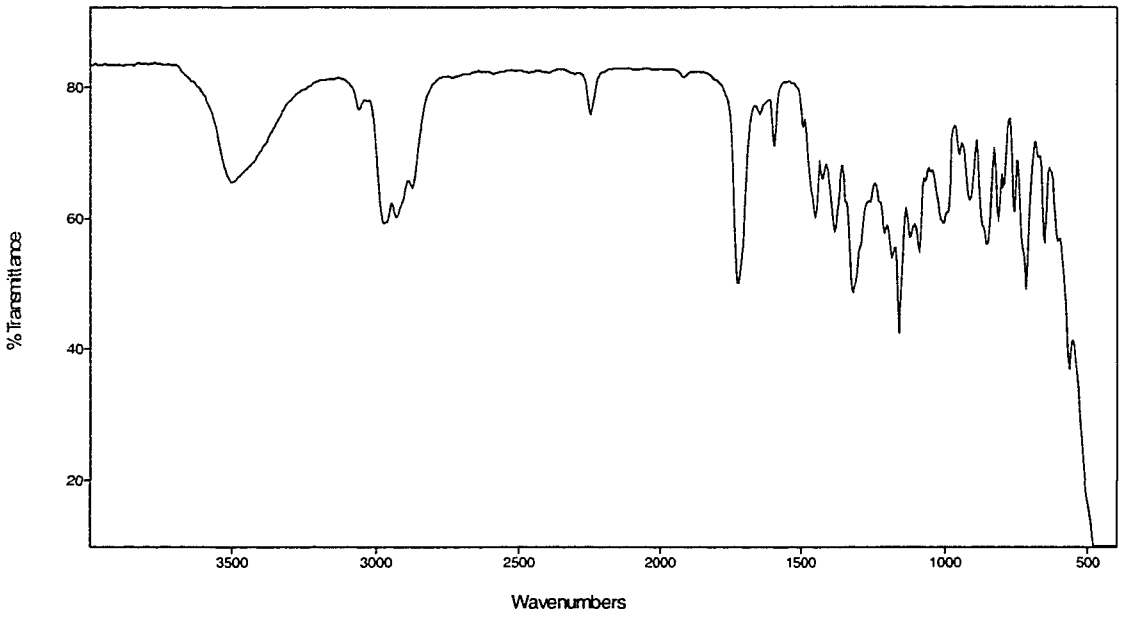


Figure A.3.119 FTIR Spectrum (thin film/NaCl) of Compound **152.**

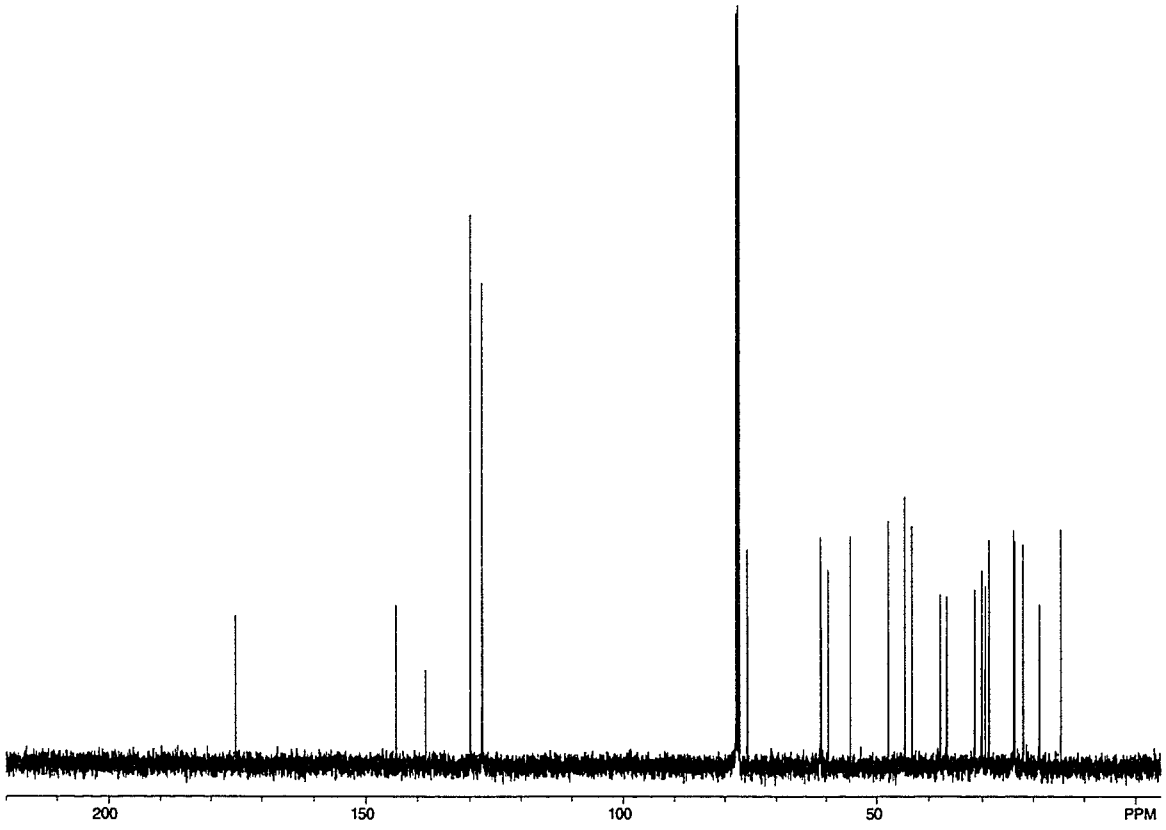


Figure A.3.120 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **152.**

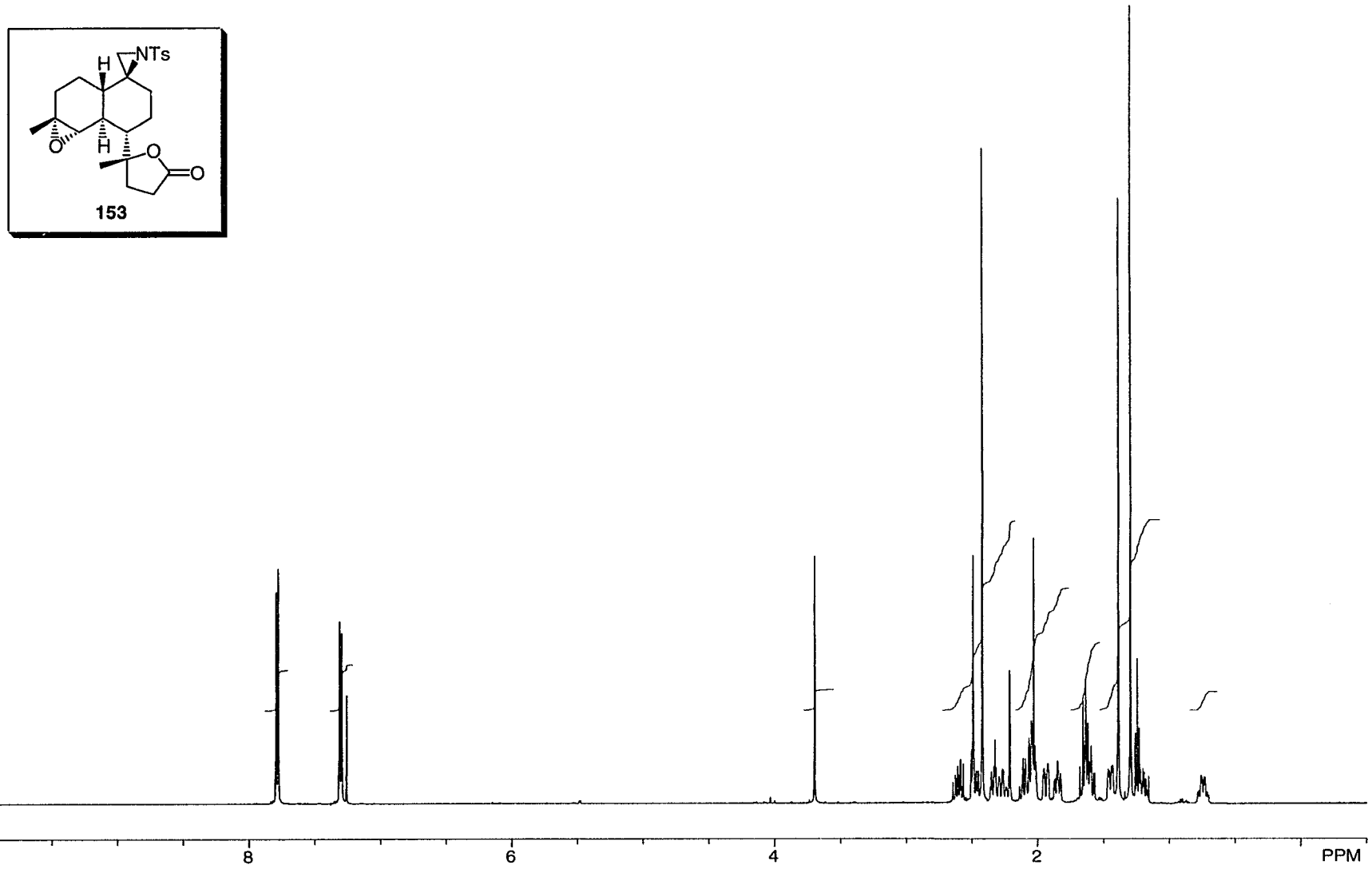


Figure A.3.121 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **153**.

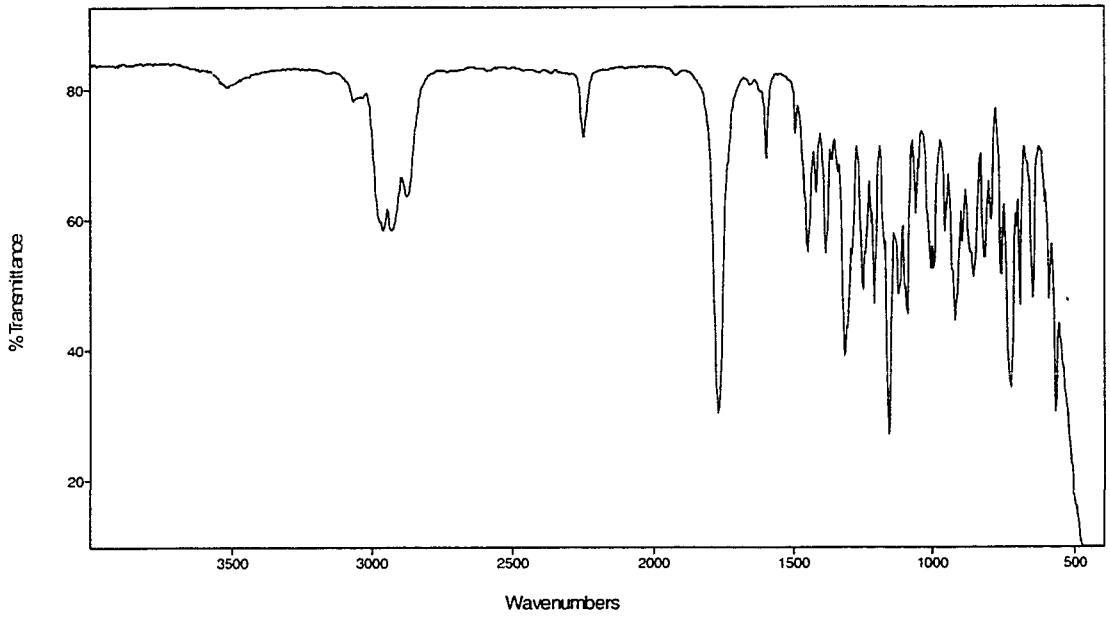


Figure A.3.122 FTIR Spectrum (thin film/NaCl) of Compound **153.**

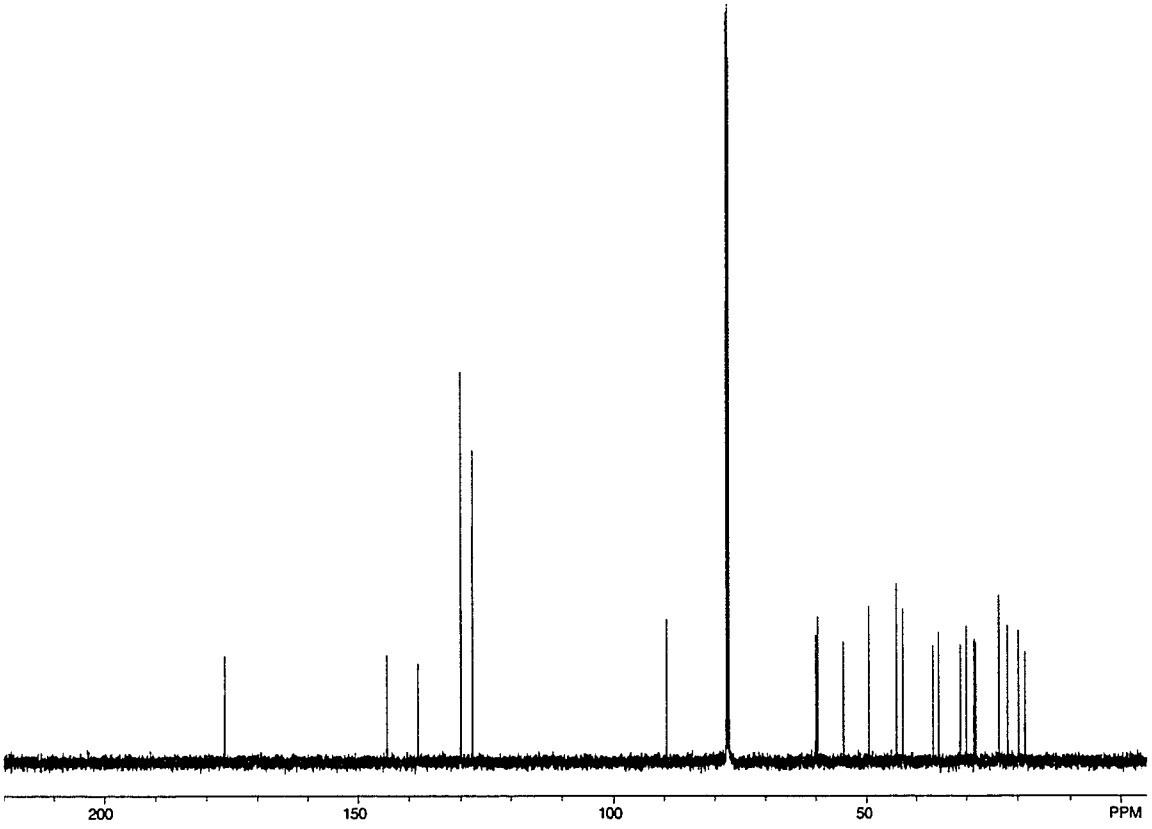


Figure A.3.123 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **153.**

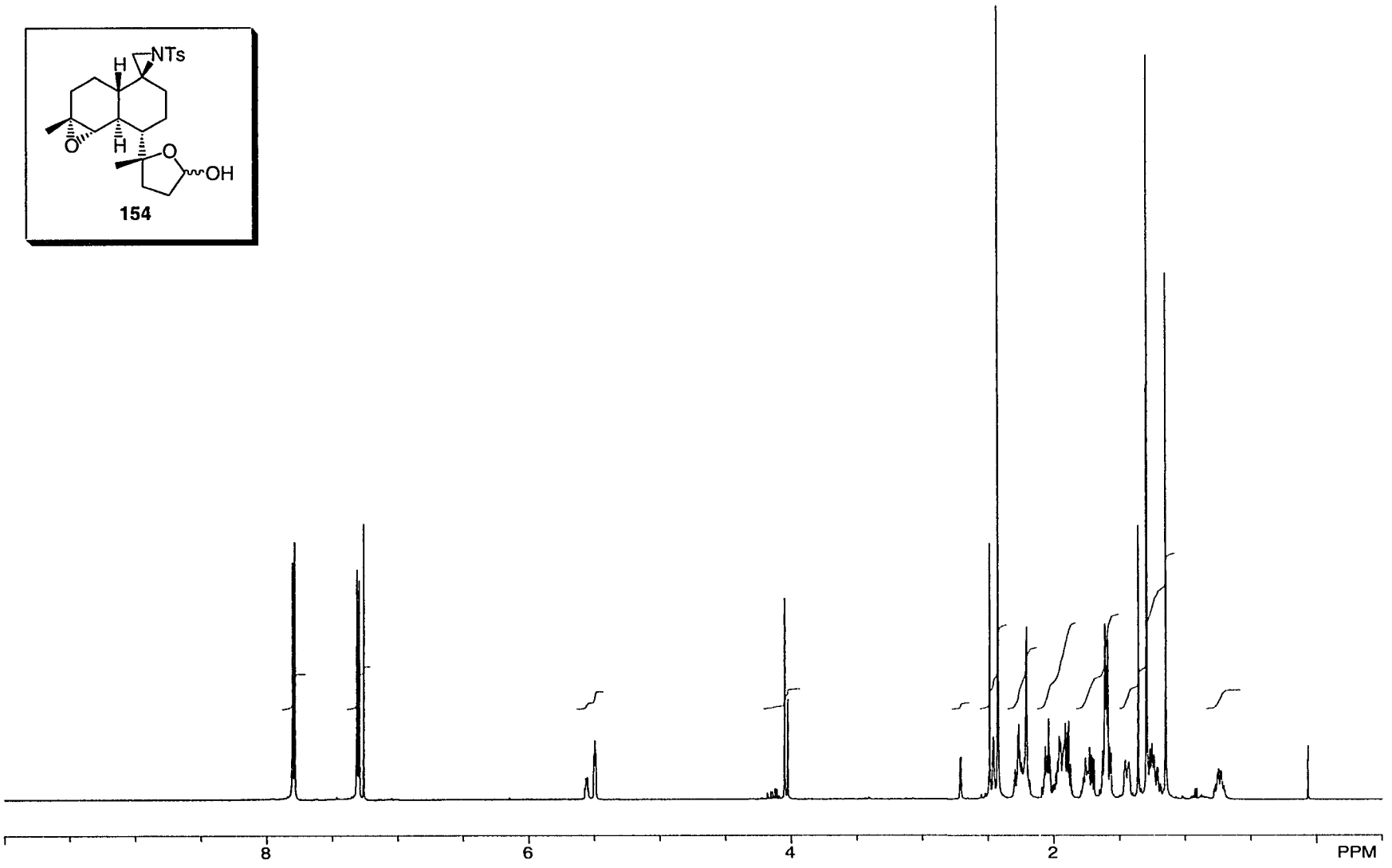


Figure A.3.124 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **154**.

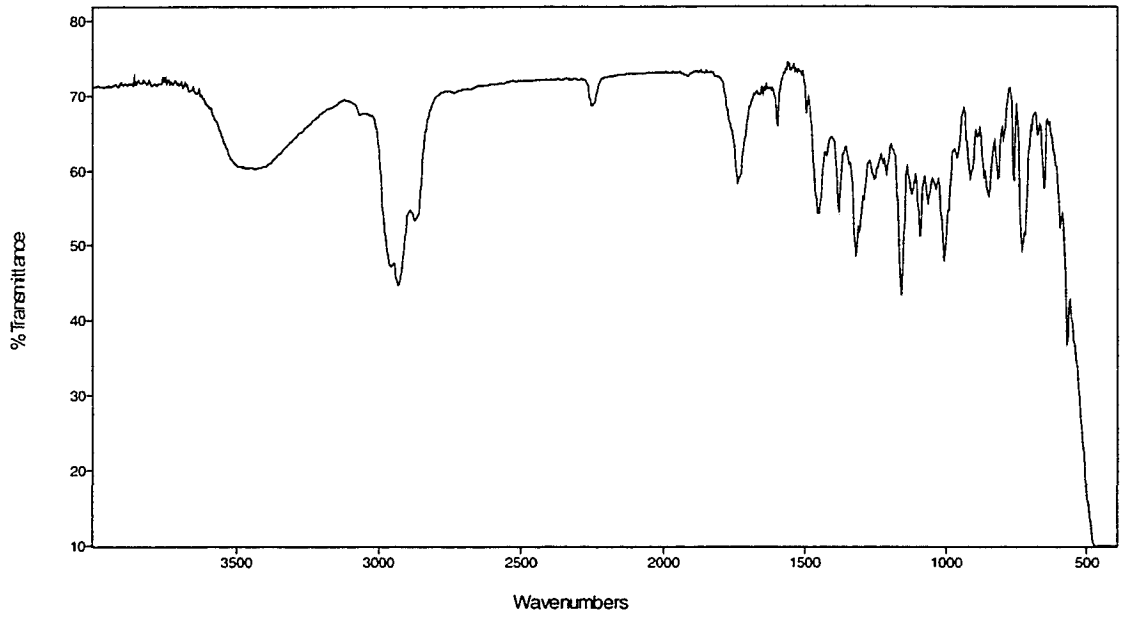


Figure A.3.125 FTIR Spectrum (thin film/NaCl) of Compound **154**.

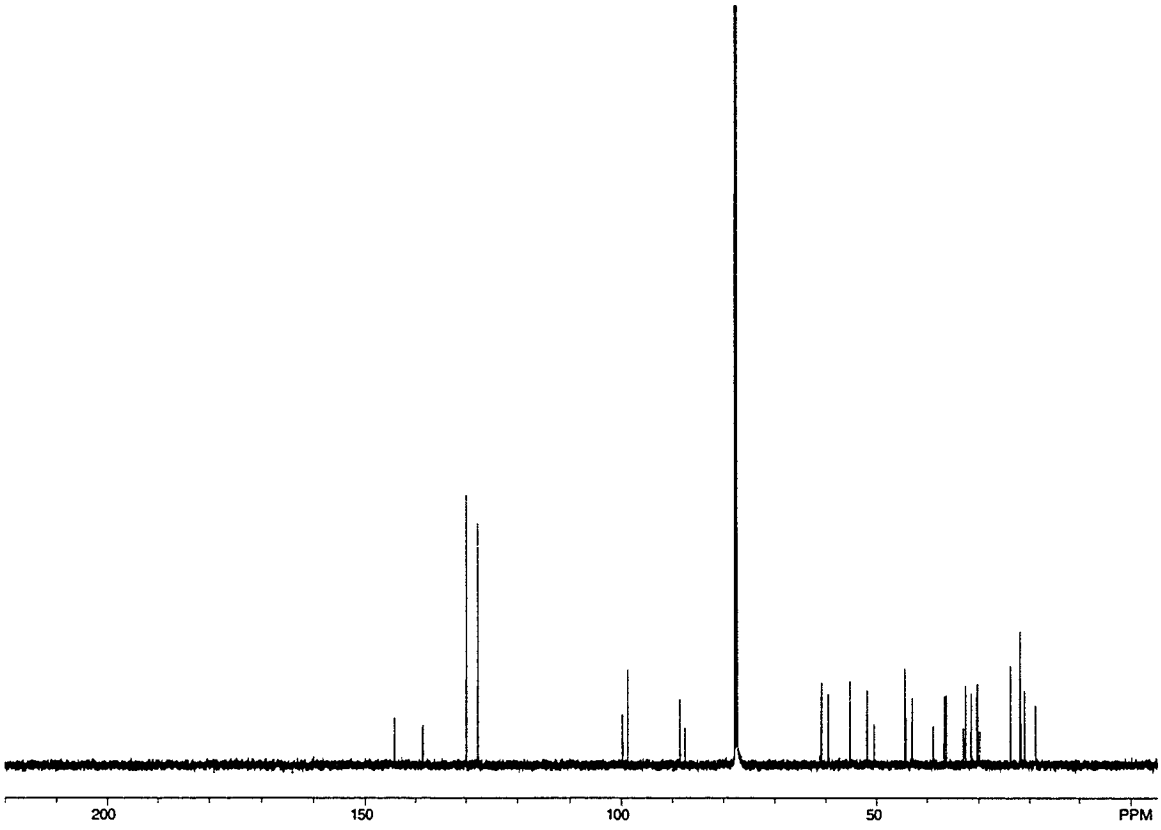


Figure A.3.126 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **154.**

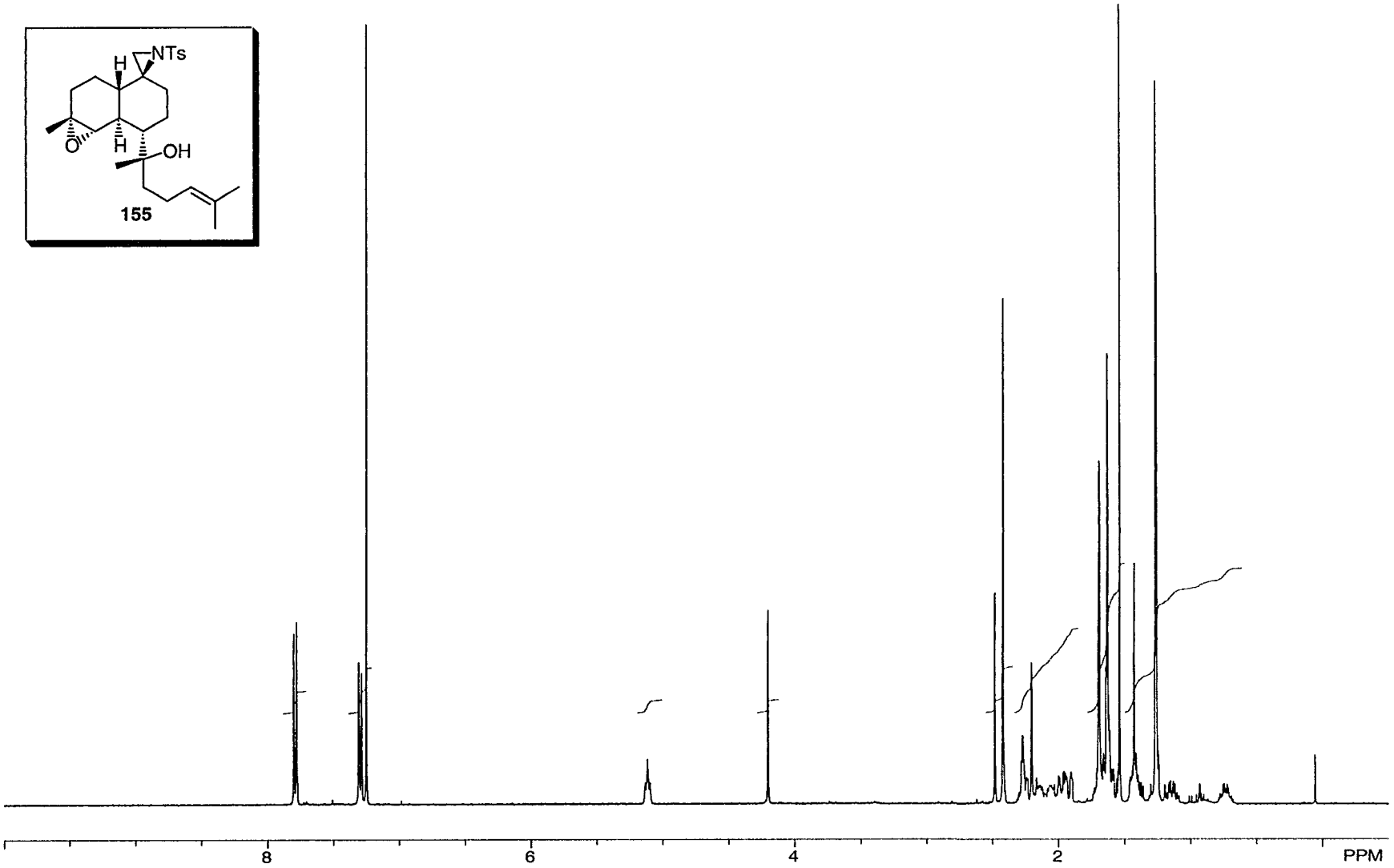


Figure A.3.127 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **155**.

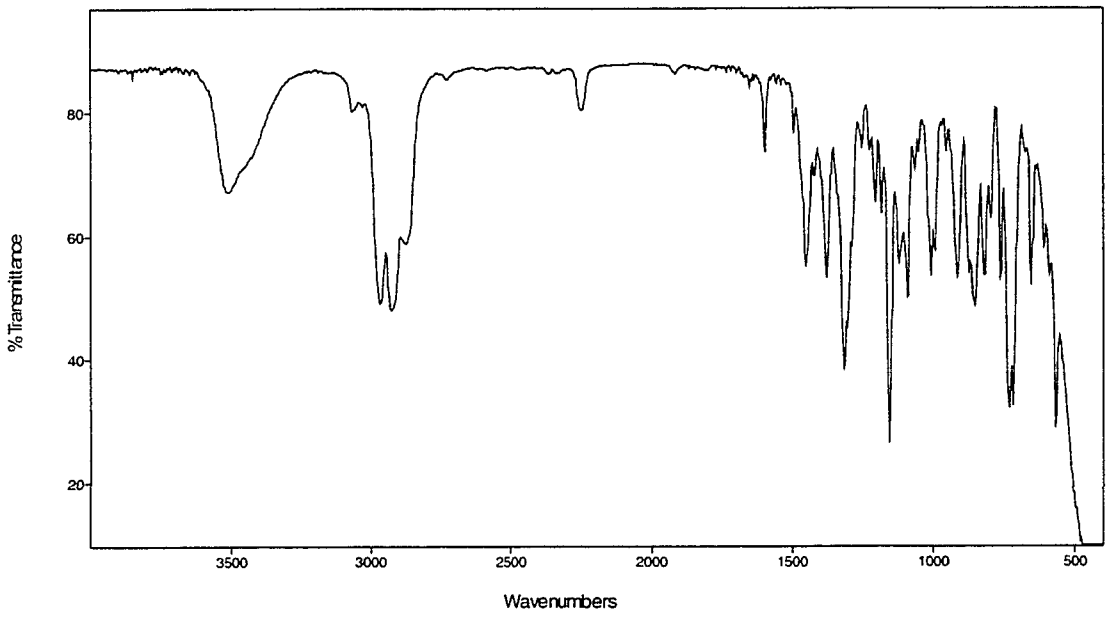


Figure A.3.128 FTIR Spectrum (thin film/NaCl) of Compound **155**.

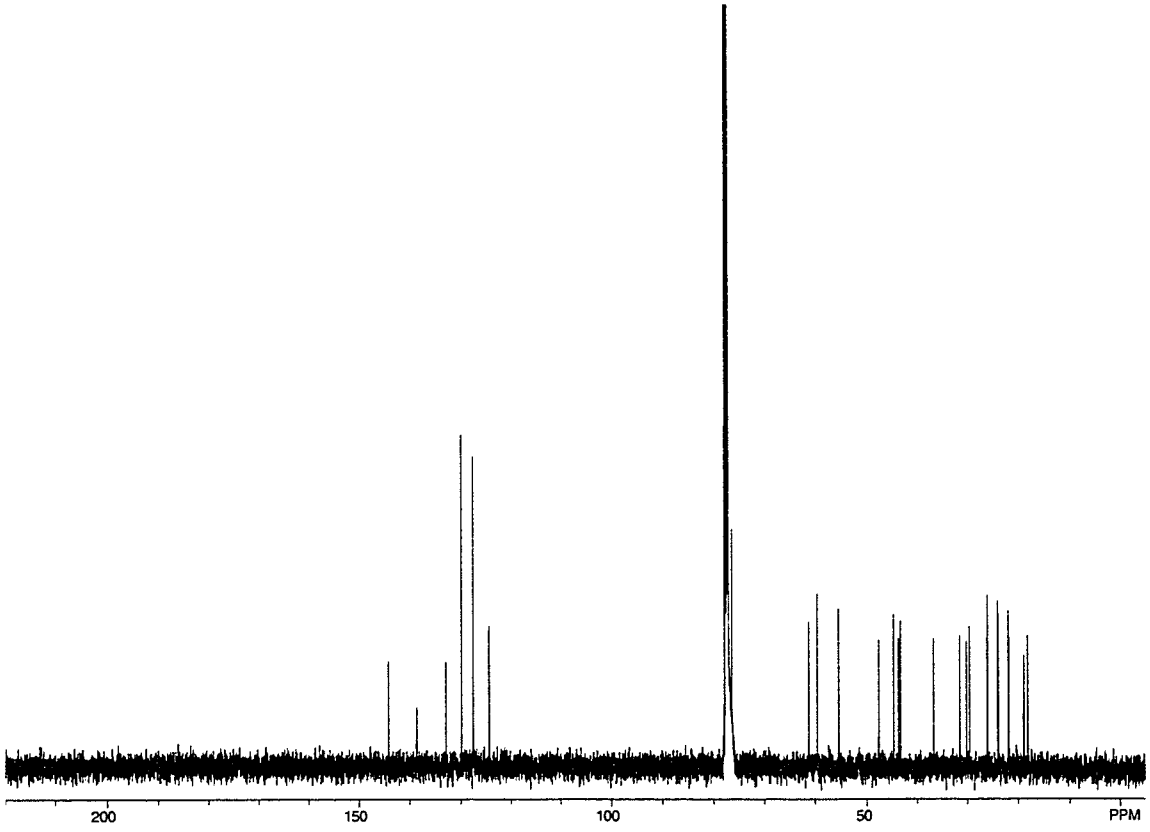


Figure A.3.129 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **155.**

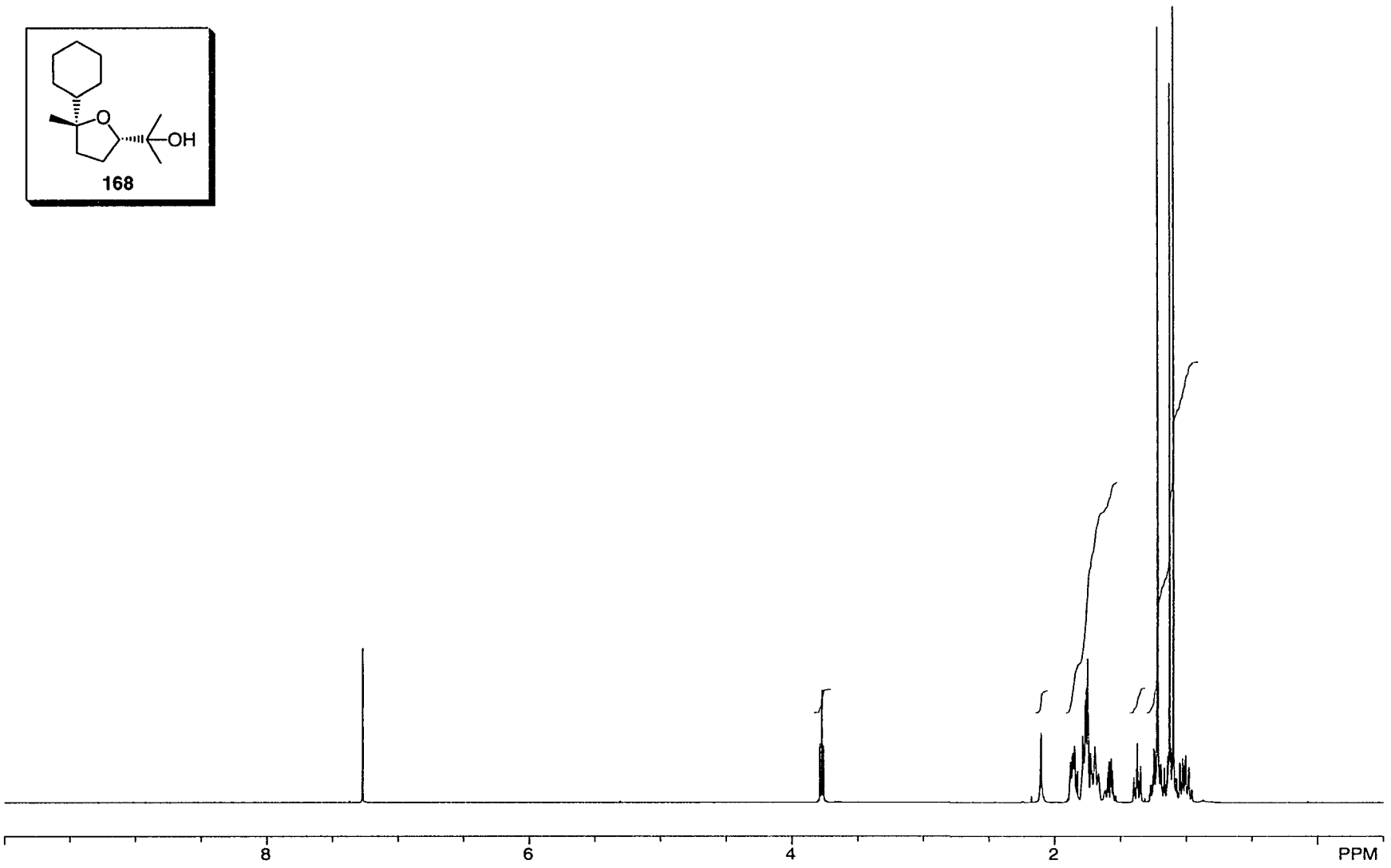


Figure A.3.130 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **168**.

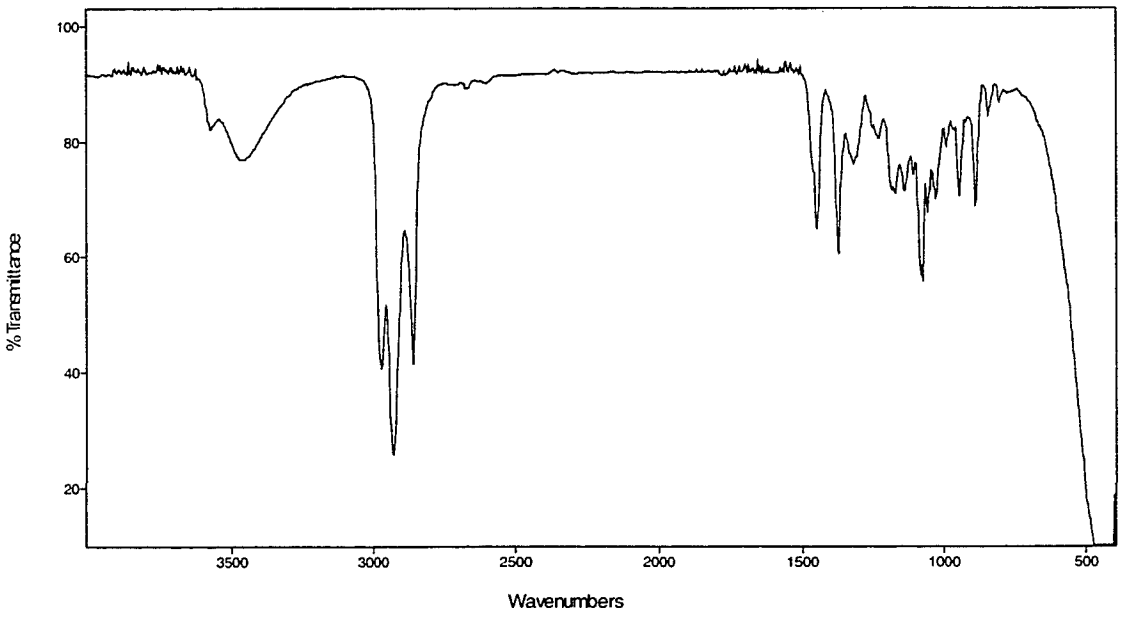


Figure A.3.131 FTIR Spectrum (thin film/NaCl) of Compound **168.**

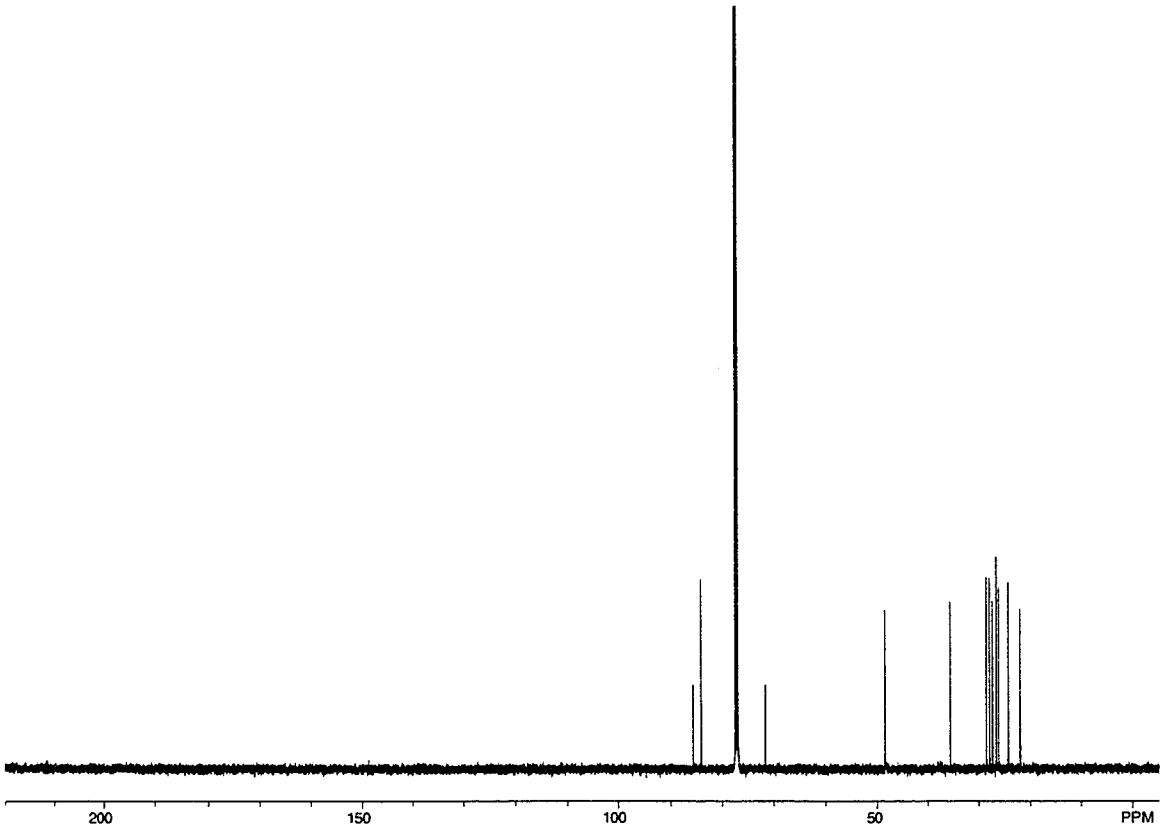


Figure A.3.132 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **168.**

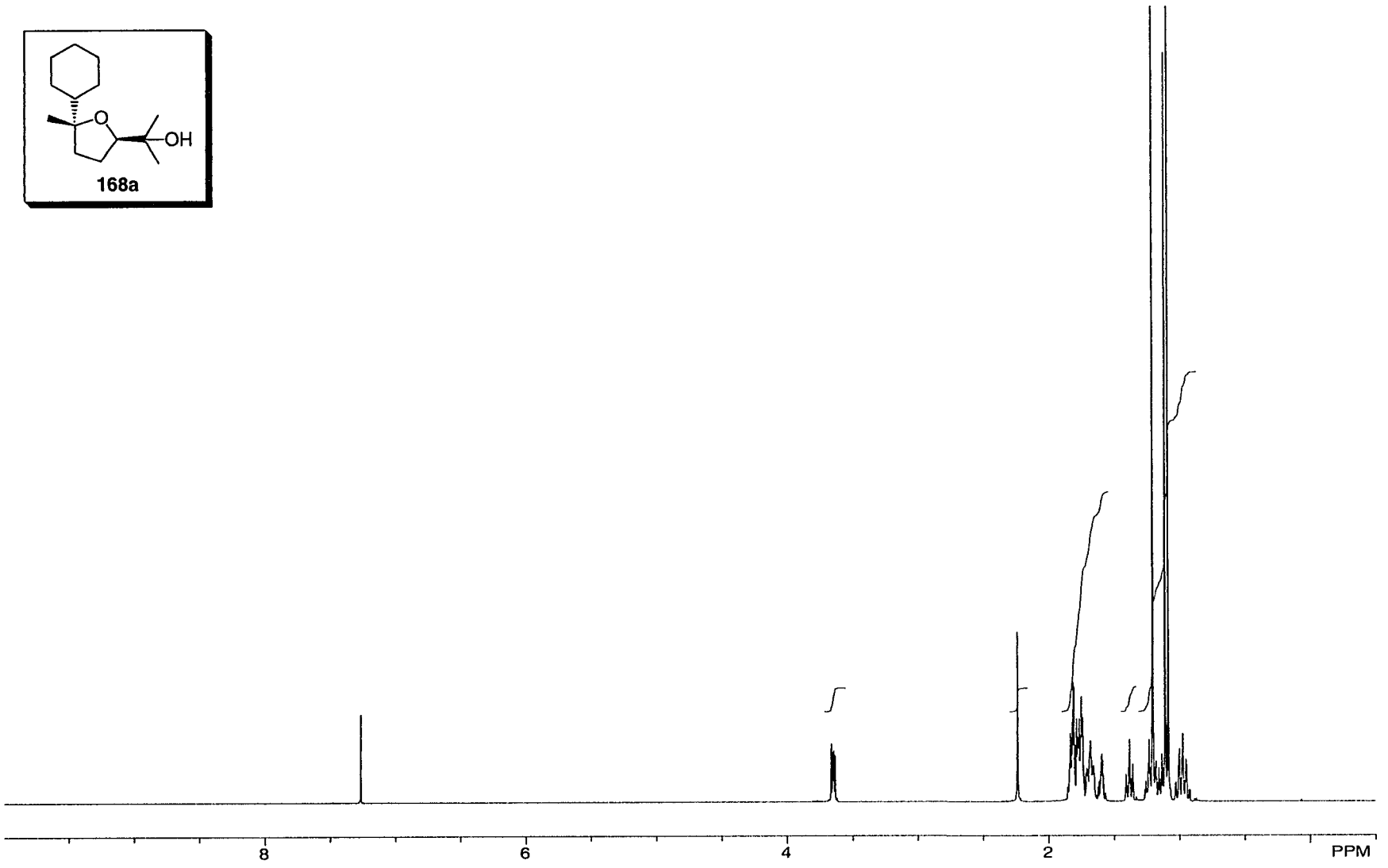


Figure A.3.133 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **168a**.

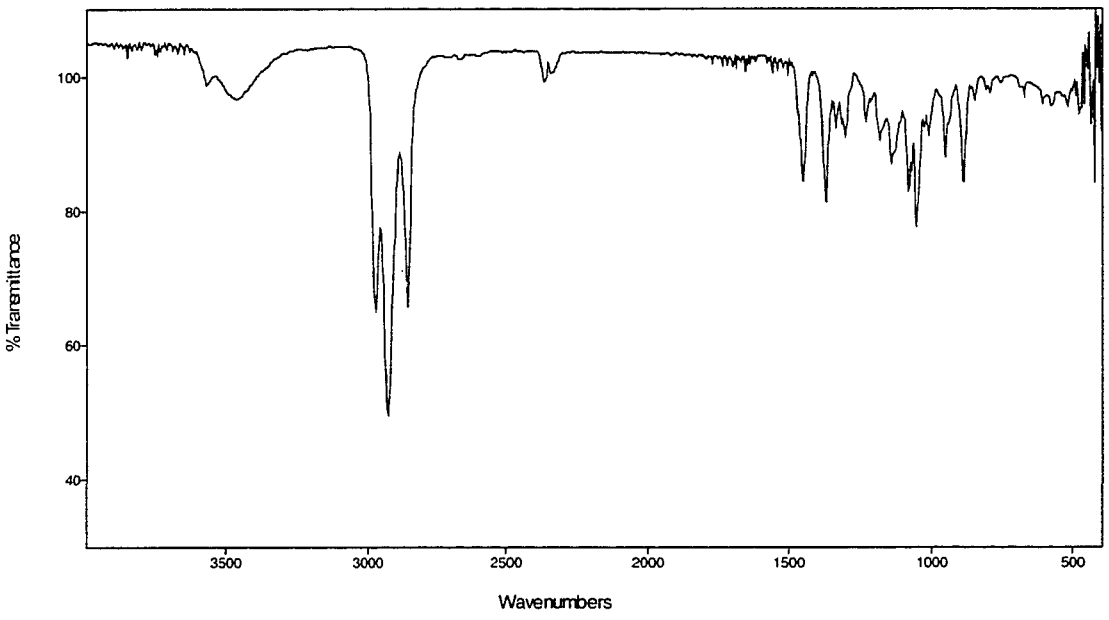


Figure A.3.134 FTIR Spectrum (thin film/NaCl) of Compound **168a**.

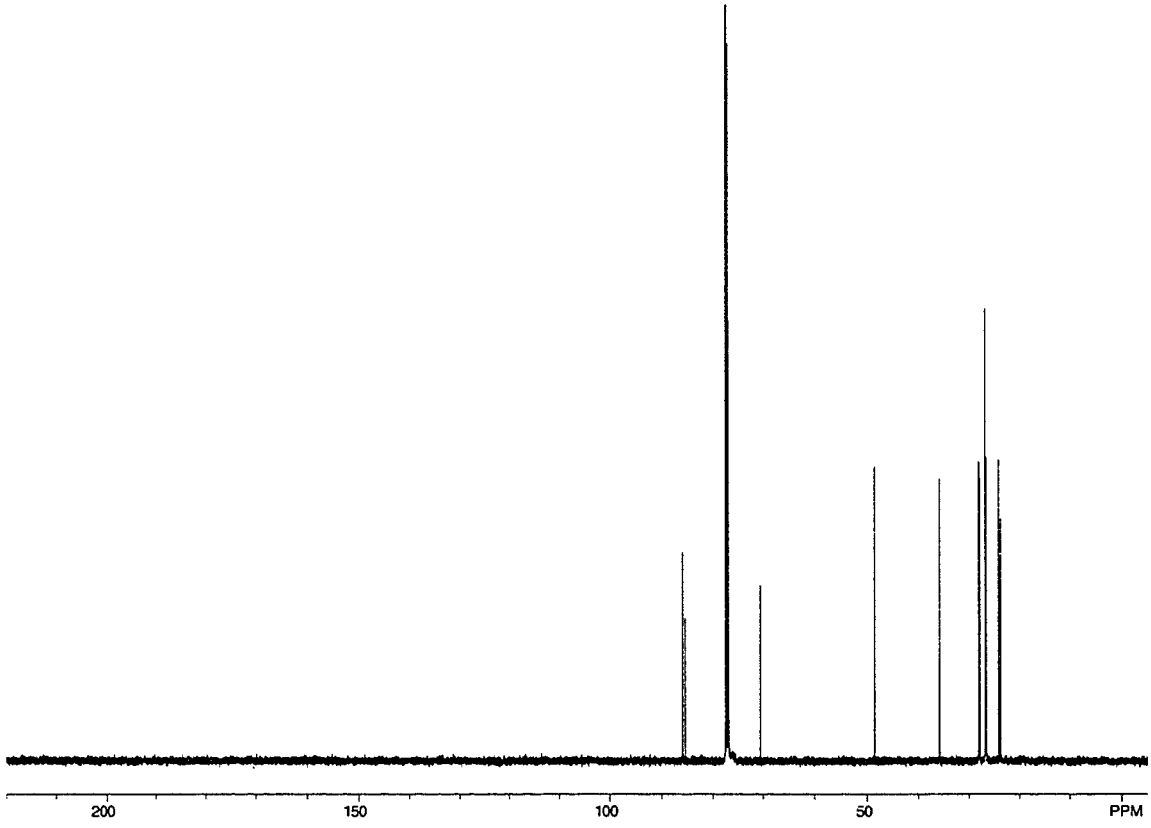


Figure A.3.135 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **168a.**

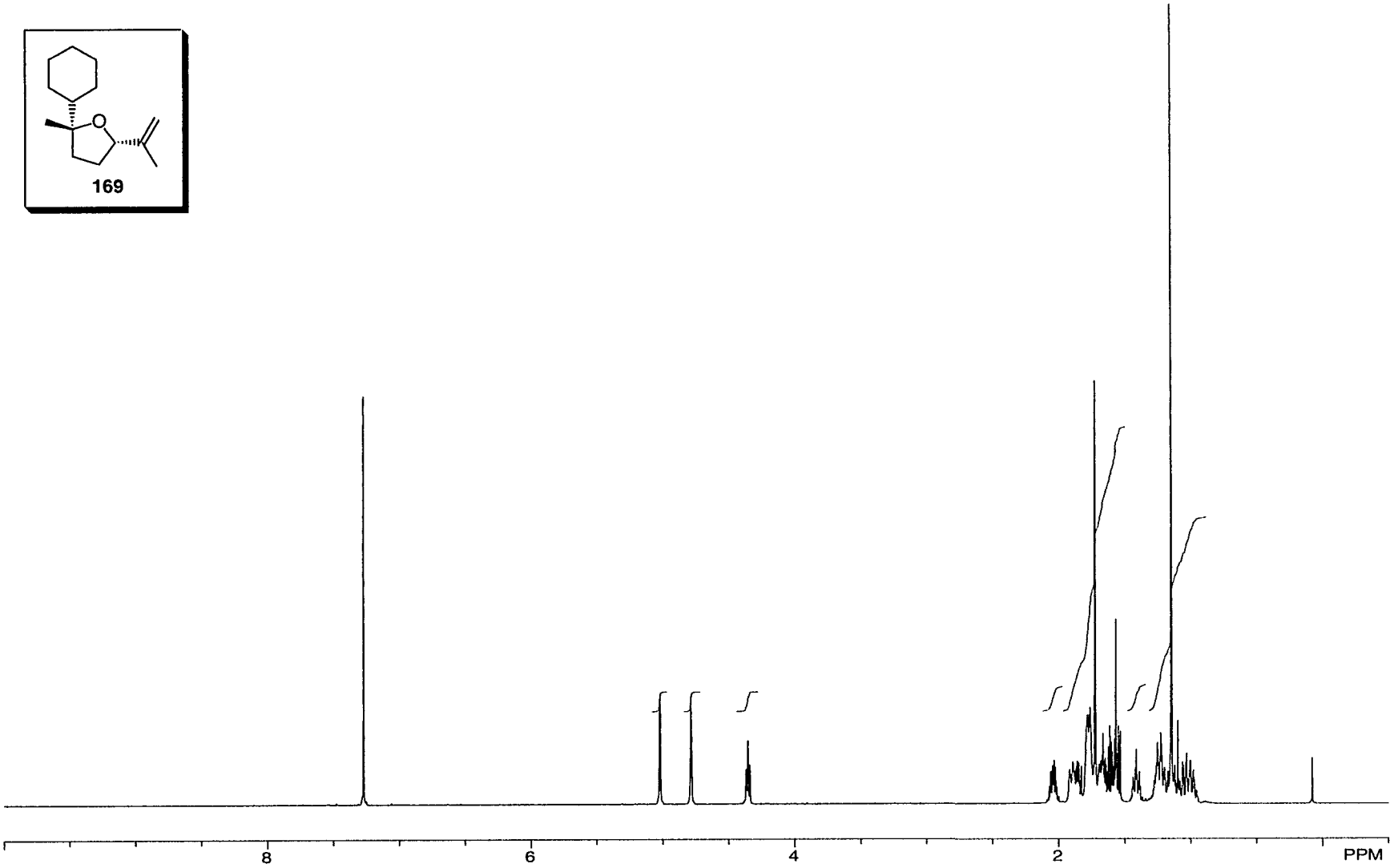


Figure A.3.136 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **169**.

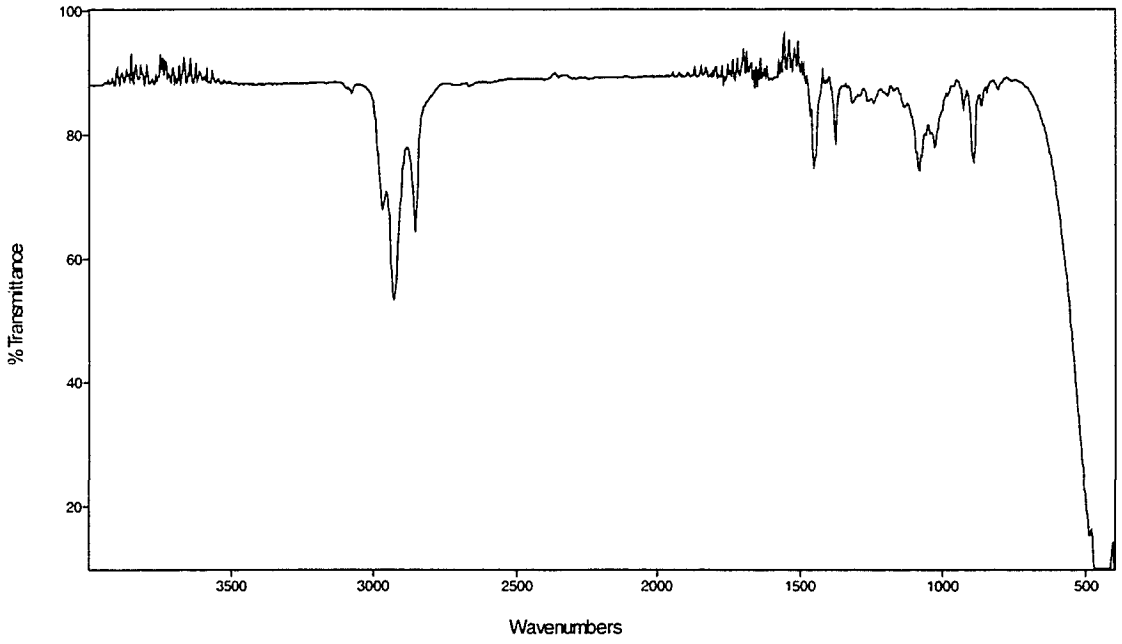


Figure A.3.137 FTIR Spectrum (thin film/NaCl) of Compound **169**.

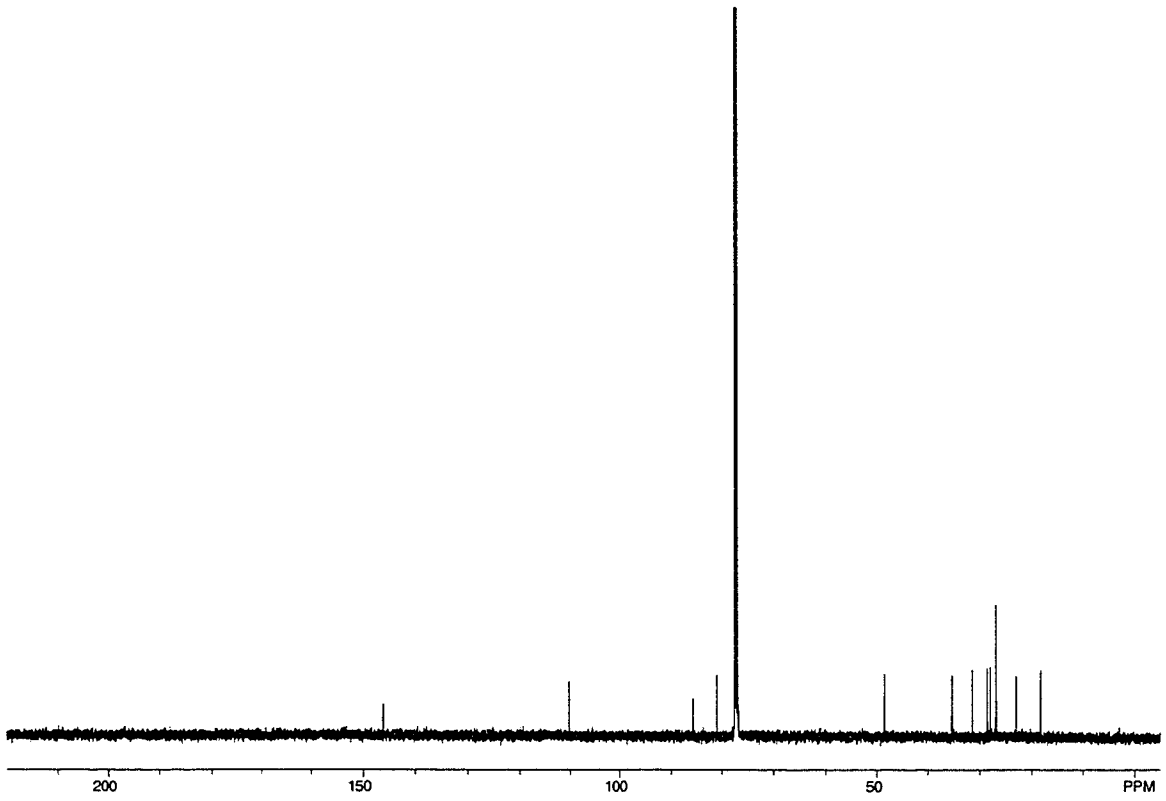


Figure A.3.138 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **169.**

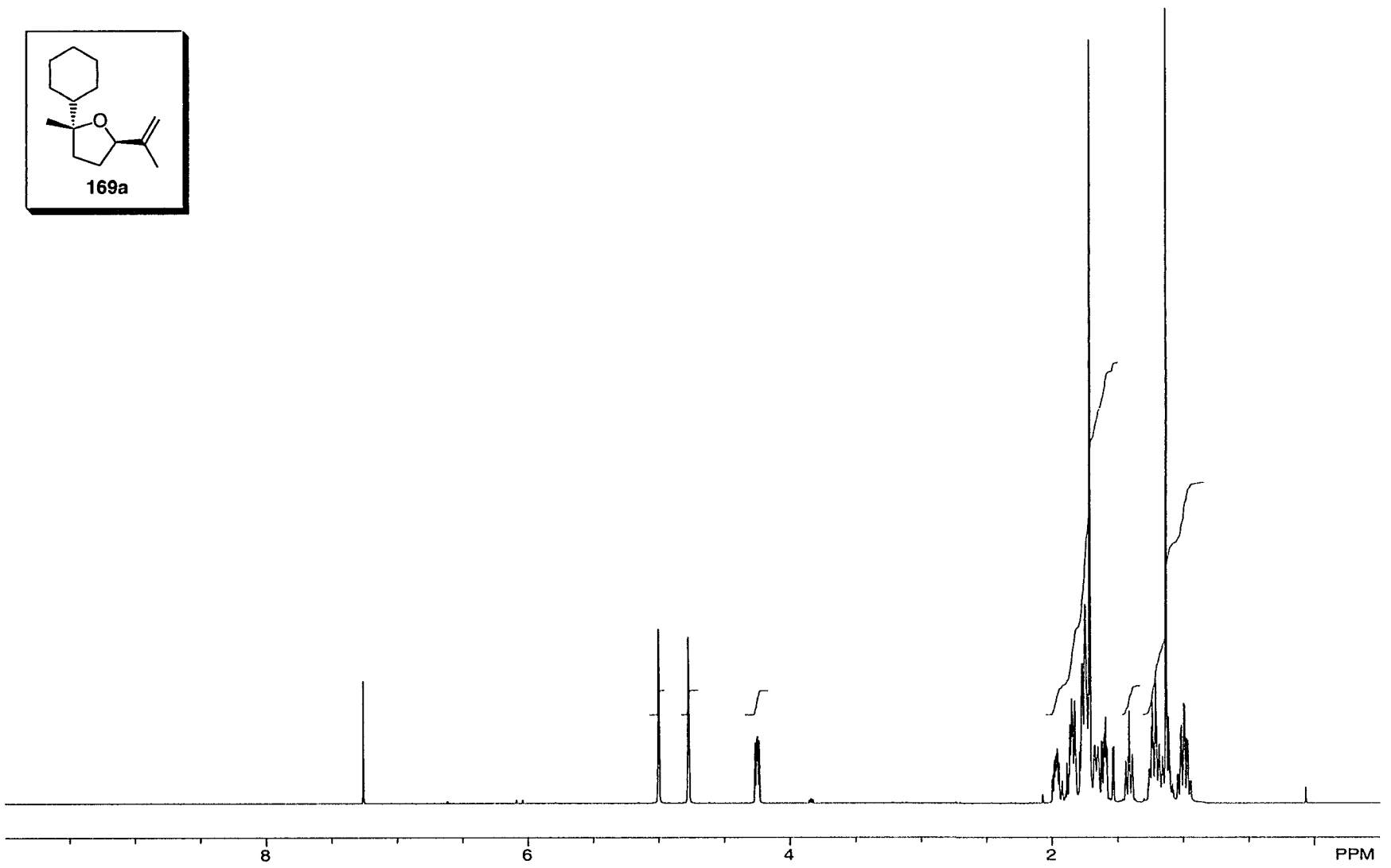


Figure A.3.139 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **169a**.

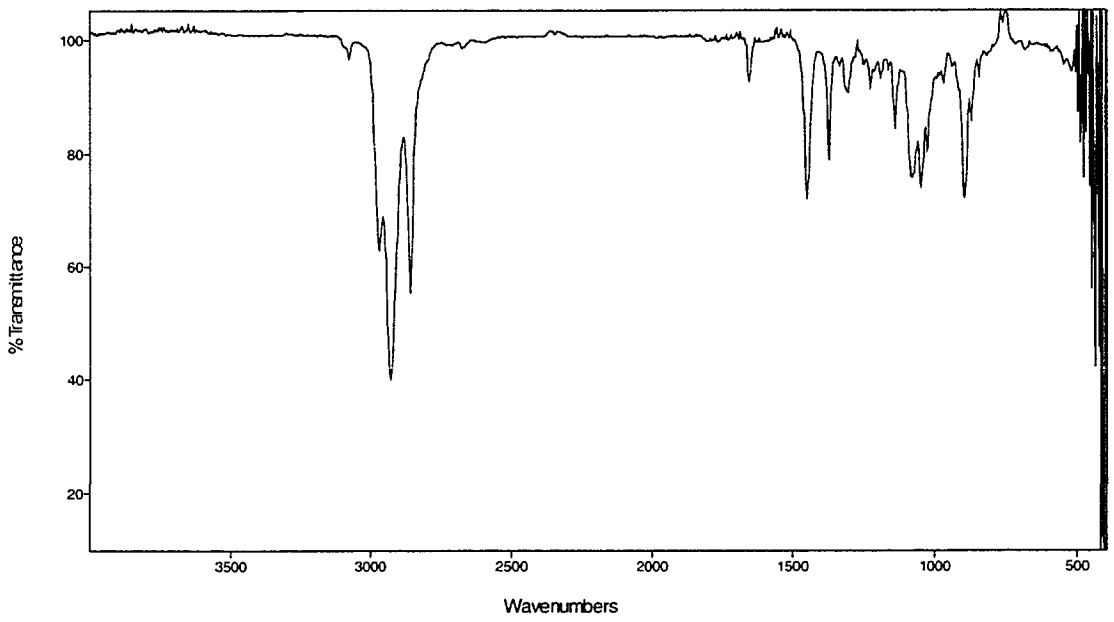


Figure A.3.140 FTIR Spectrum (thin film/NaCl) of Compound **169a**.

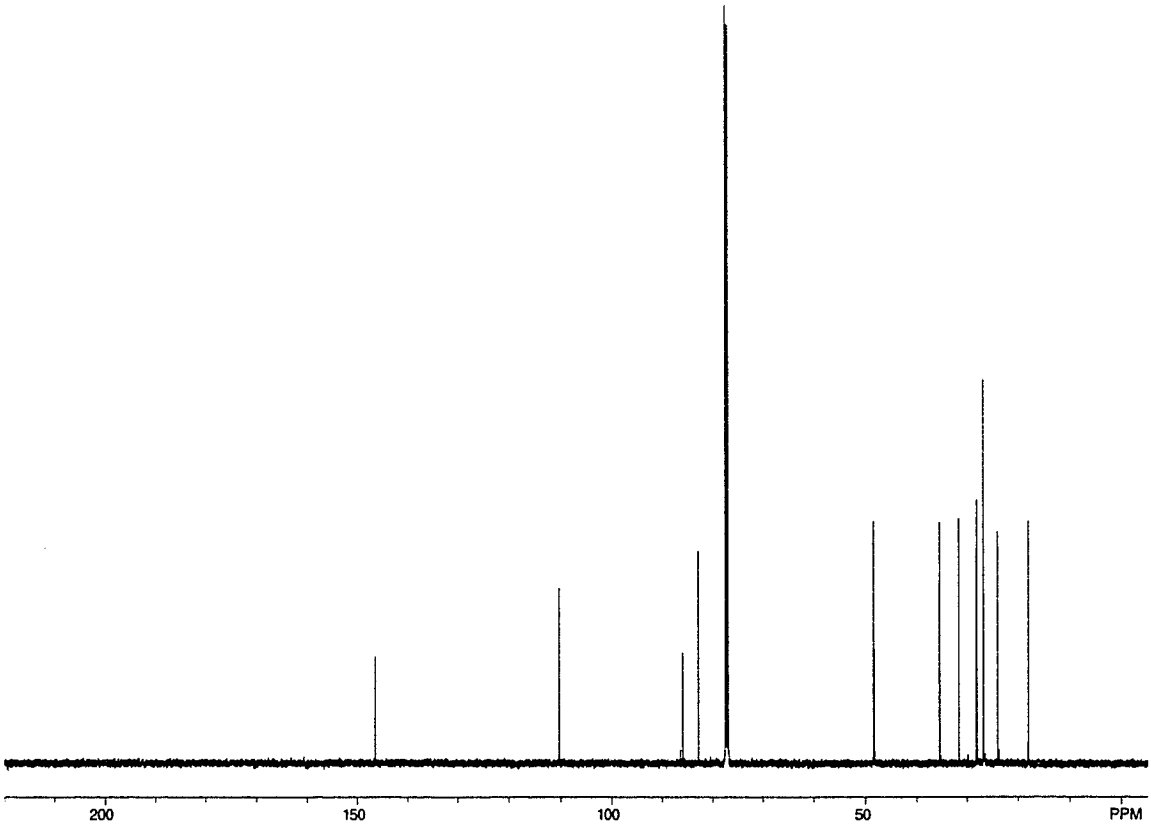


Figure A.3.141 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **169a.**

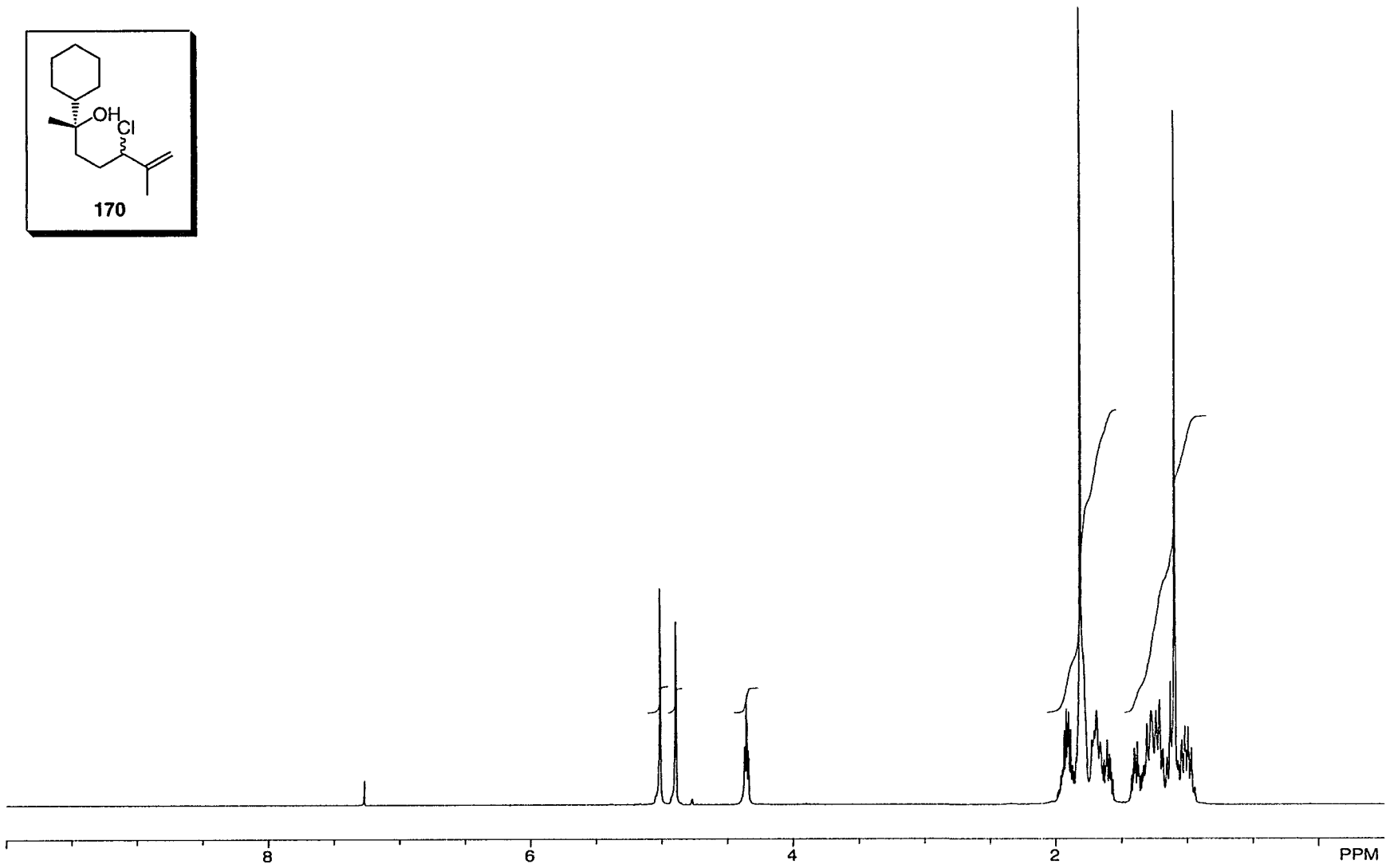


Figure A.3.142 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **170**.

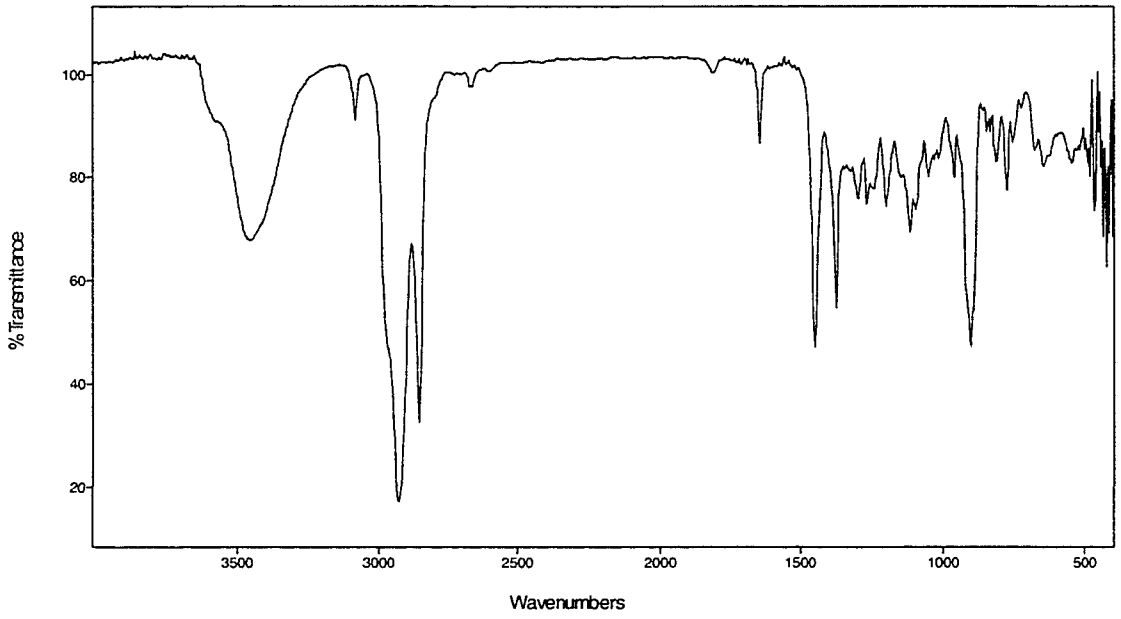


Figure A.3.143 FTIR Spectrum (thin film/NaCl) of Compound **170**.

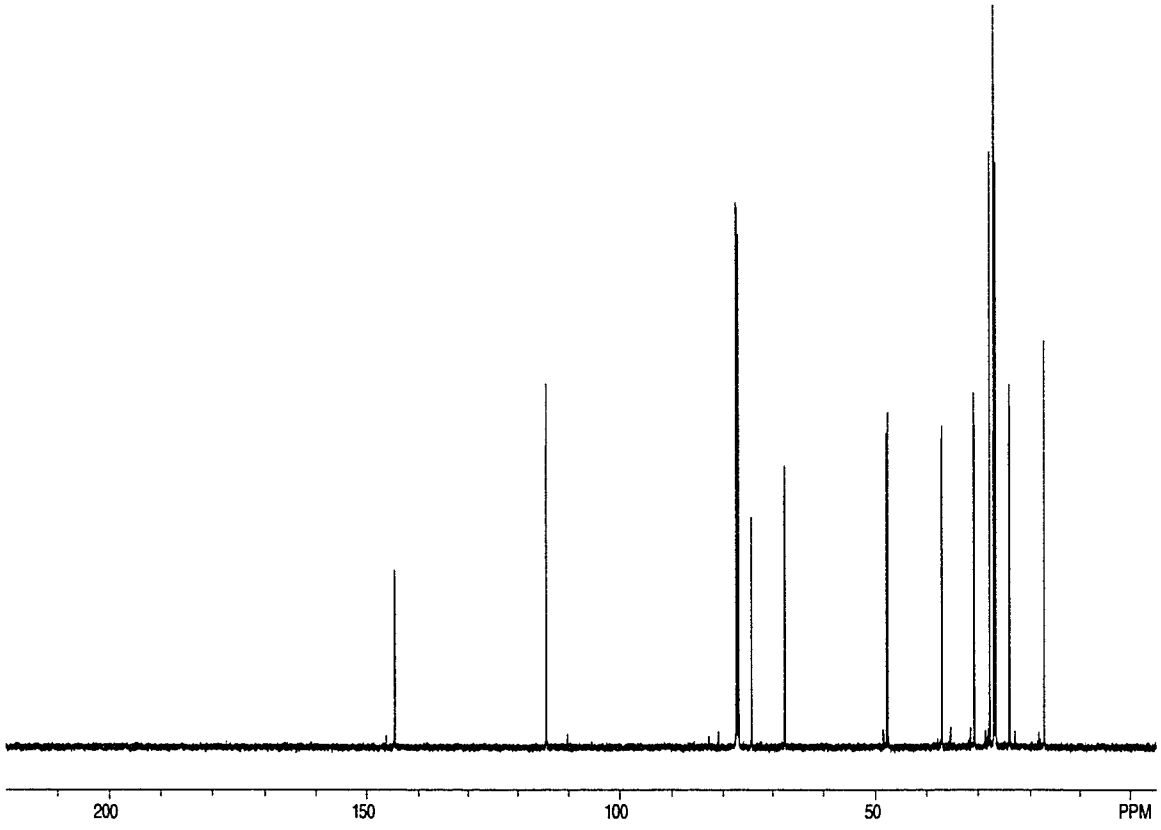


Figure A.3.144 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **170.**

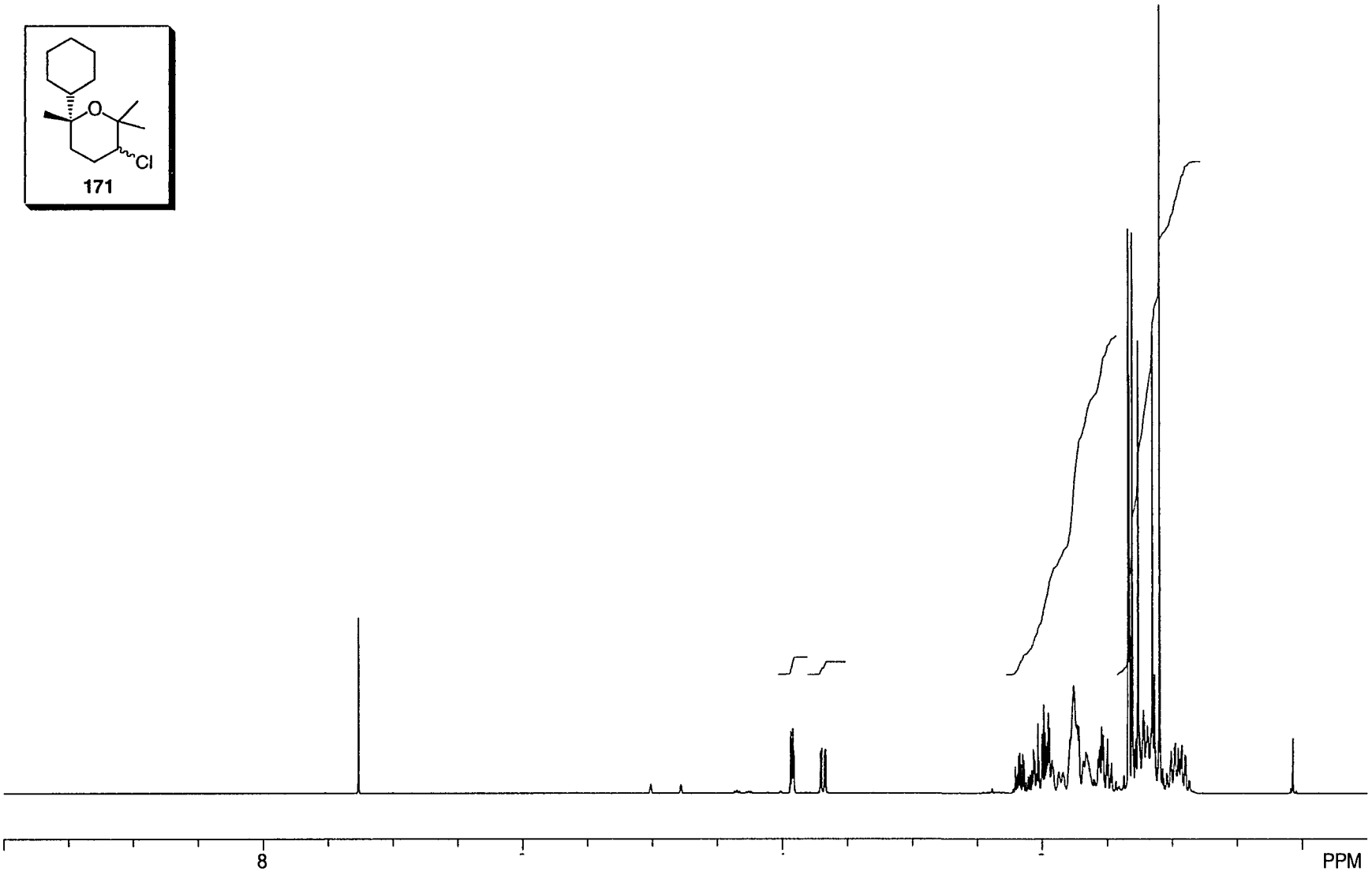


Figure A.3.145 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **171**.

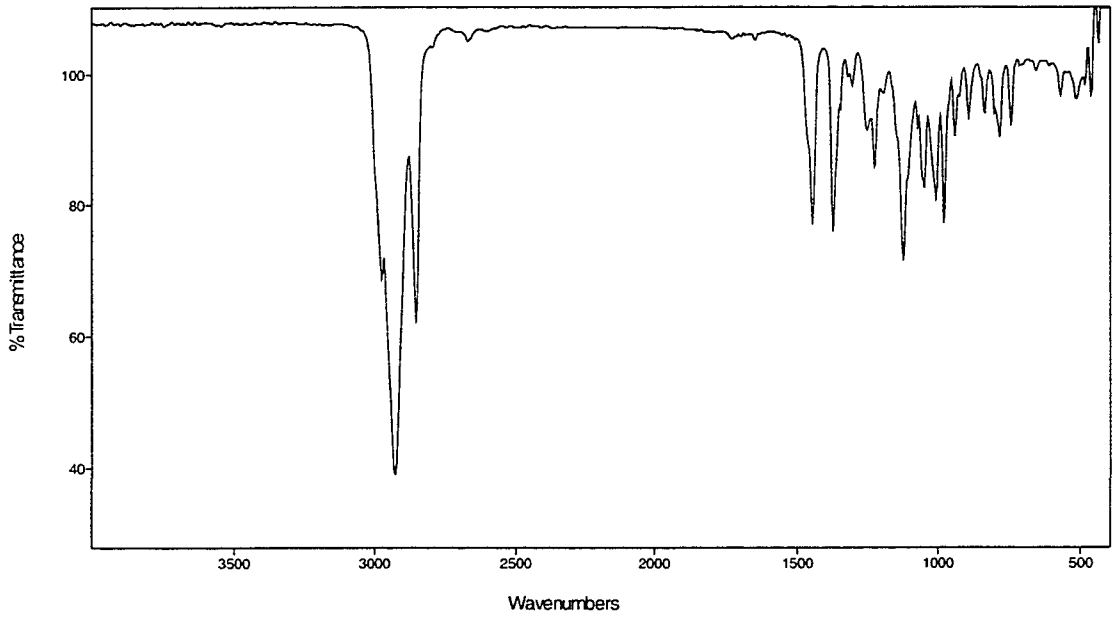


Figure A.3.146 FTIR Spectrum (thin film/NaCl) of Compound **171**.

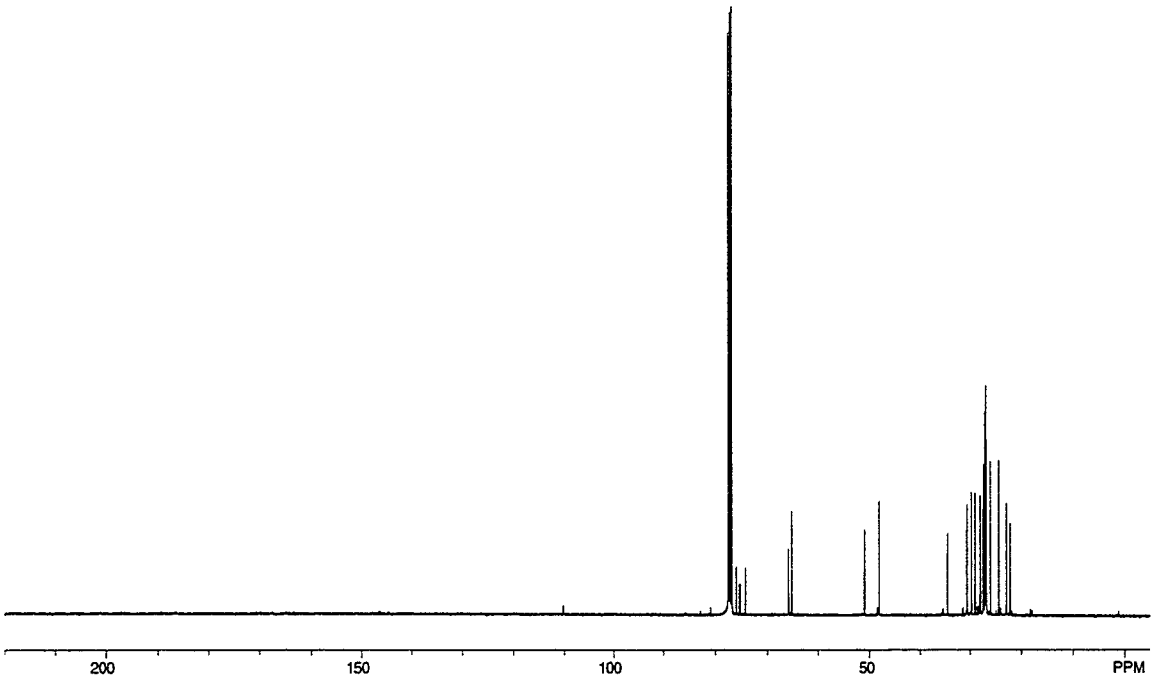


Figure A.3.147 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **171.**

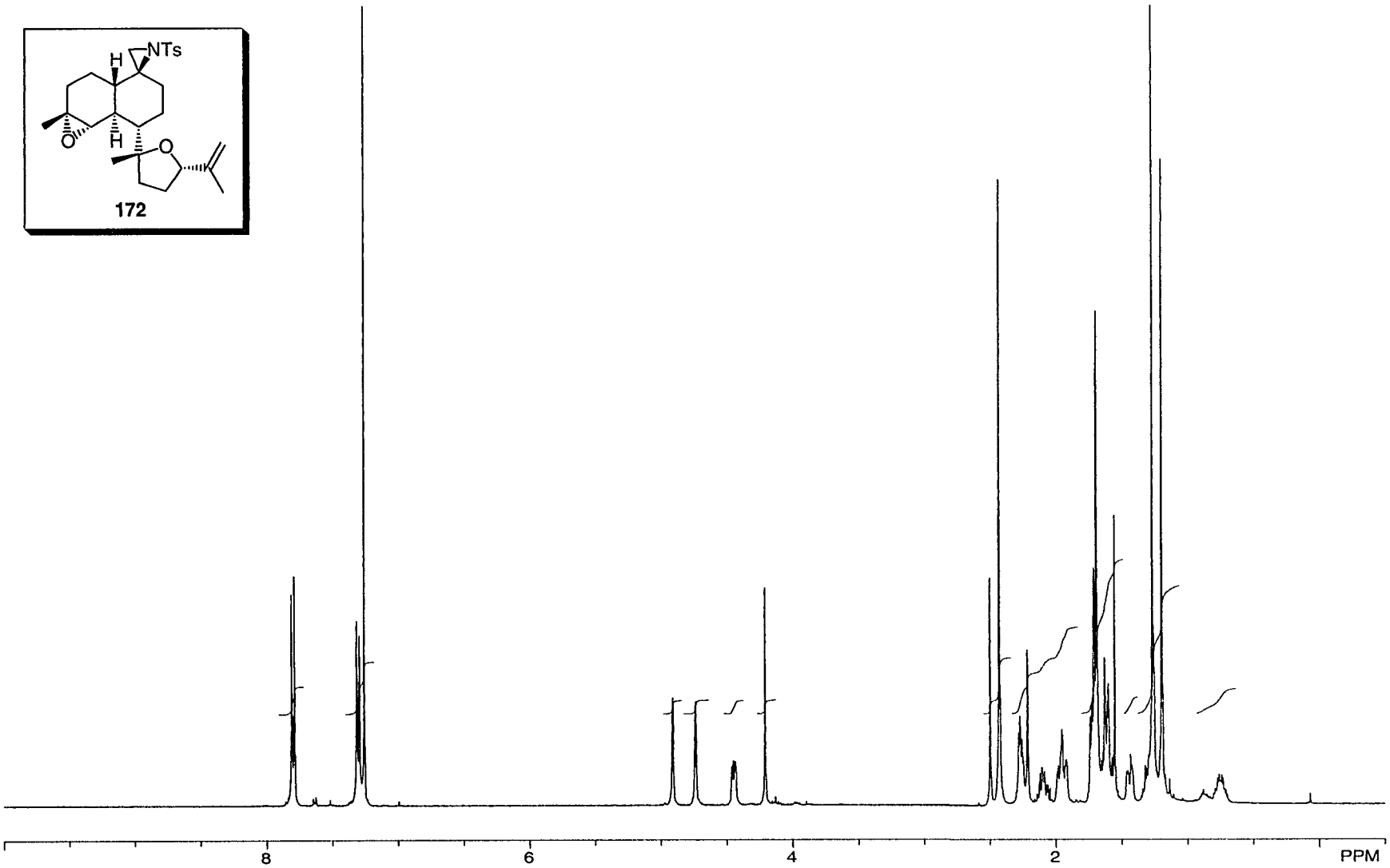


Figure A.3.148 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **172**.

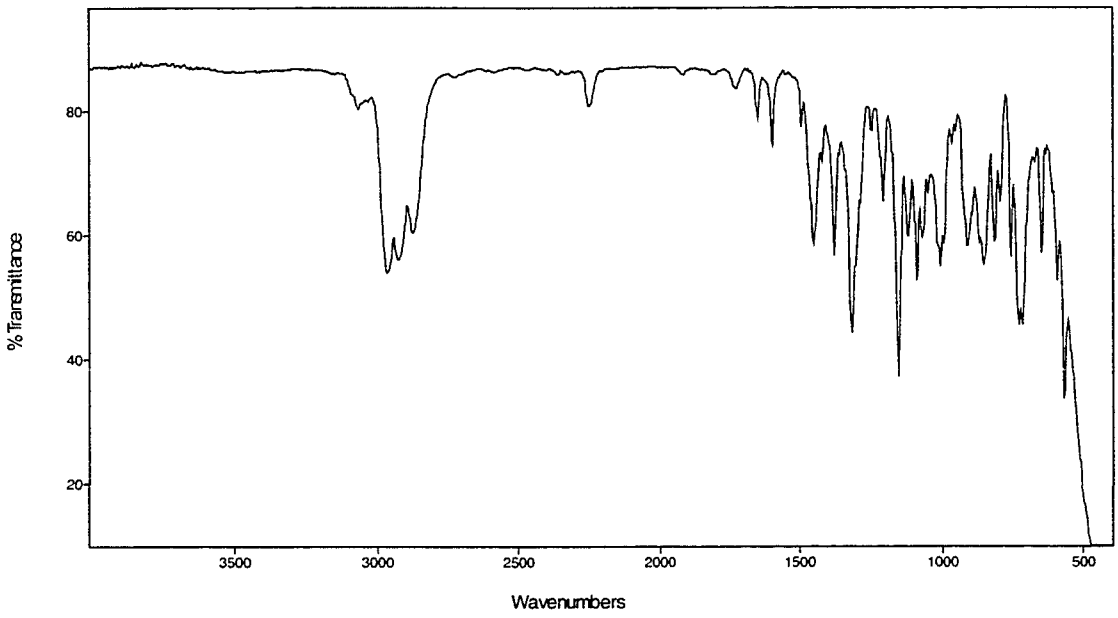


Figure A.3.149 FTIR Spectrum (thin film/NaCl) of Compound **172.**

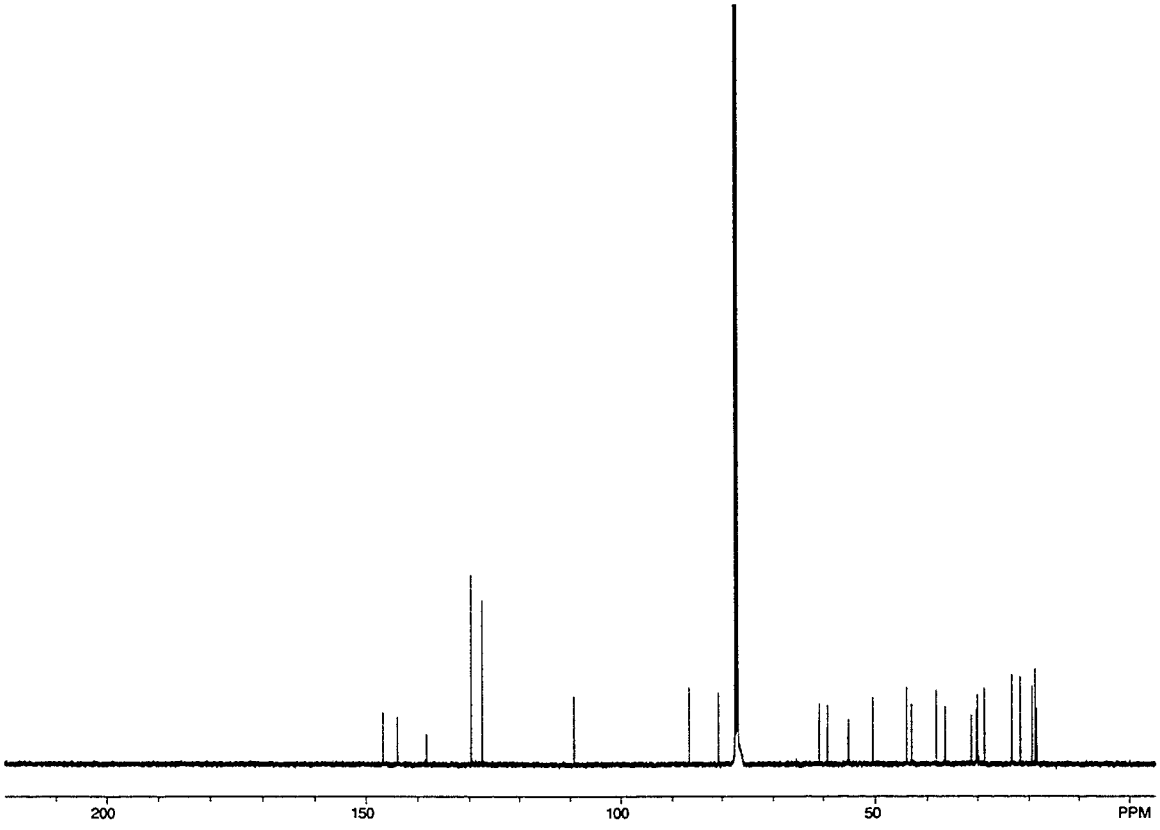


Figure A.3.150 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **172.**

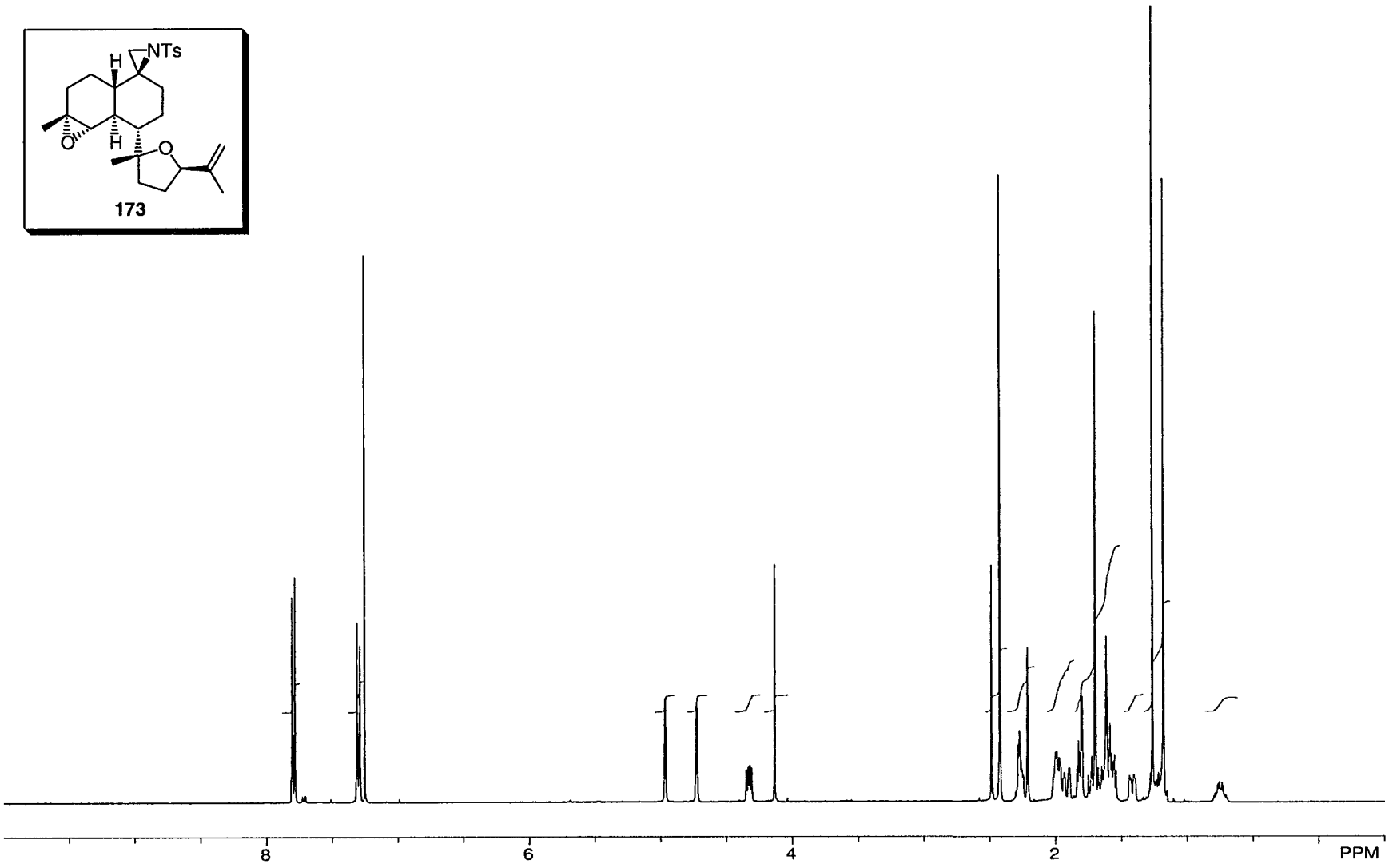


Figure A.3.151 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **173**.

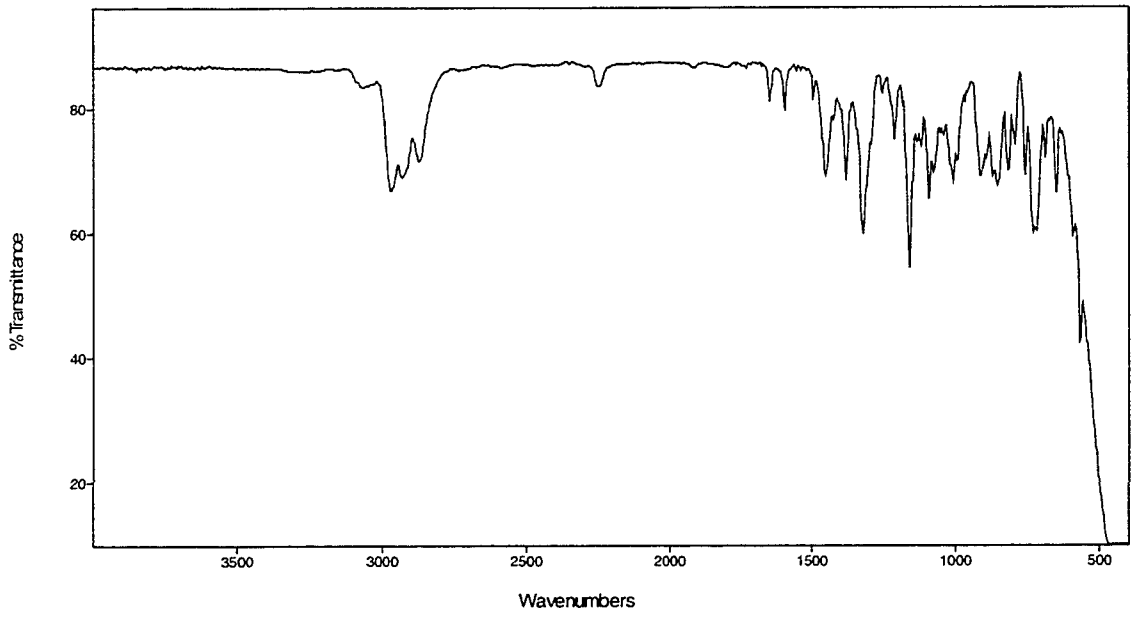


Figure A.3.152 FTIR Spectrum (thin film/NaCl) of Compound **173.**

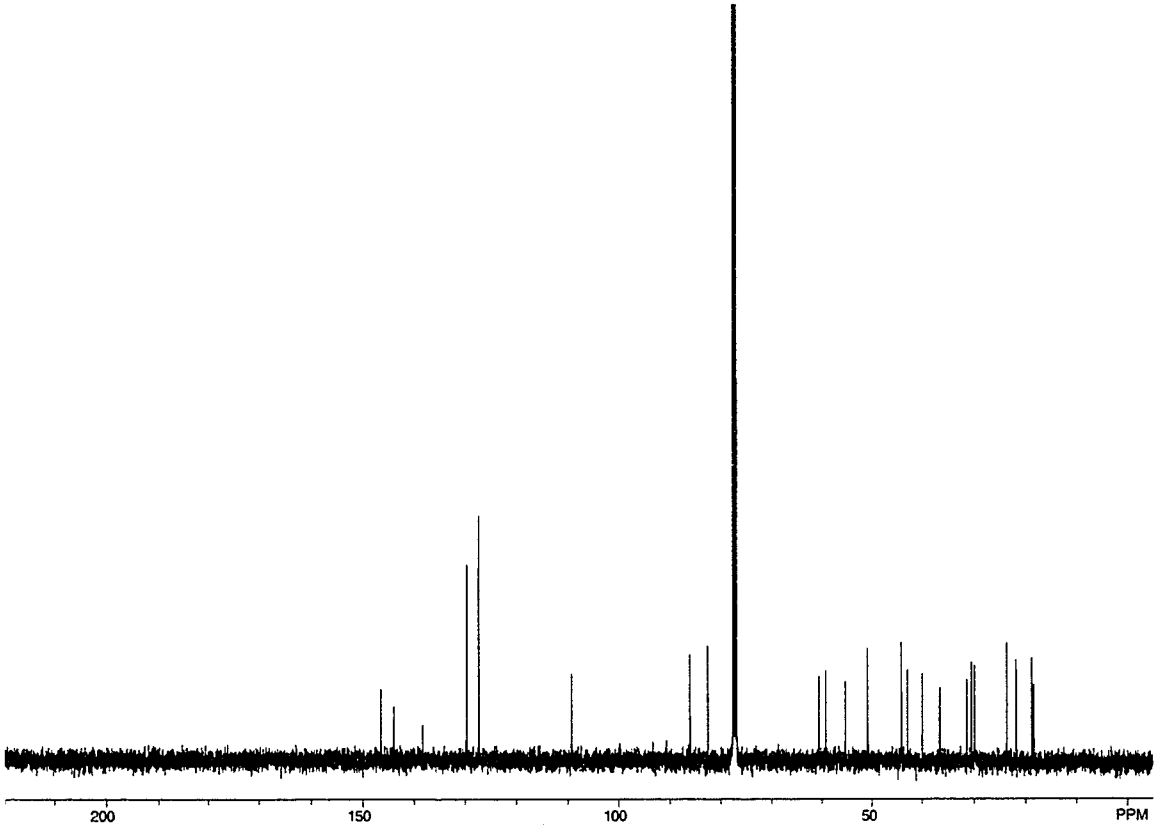


Figure A.3.153 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **173.**

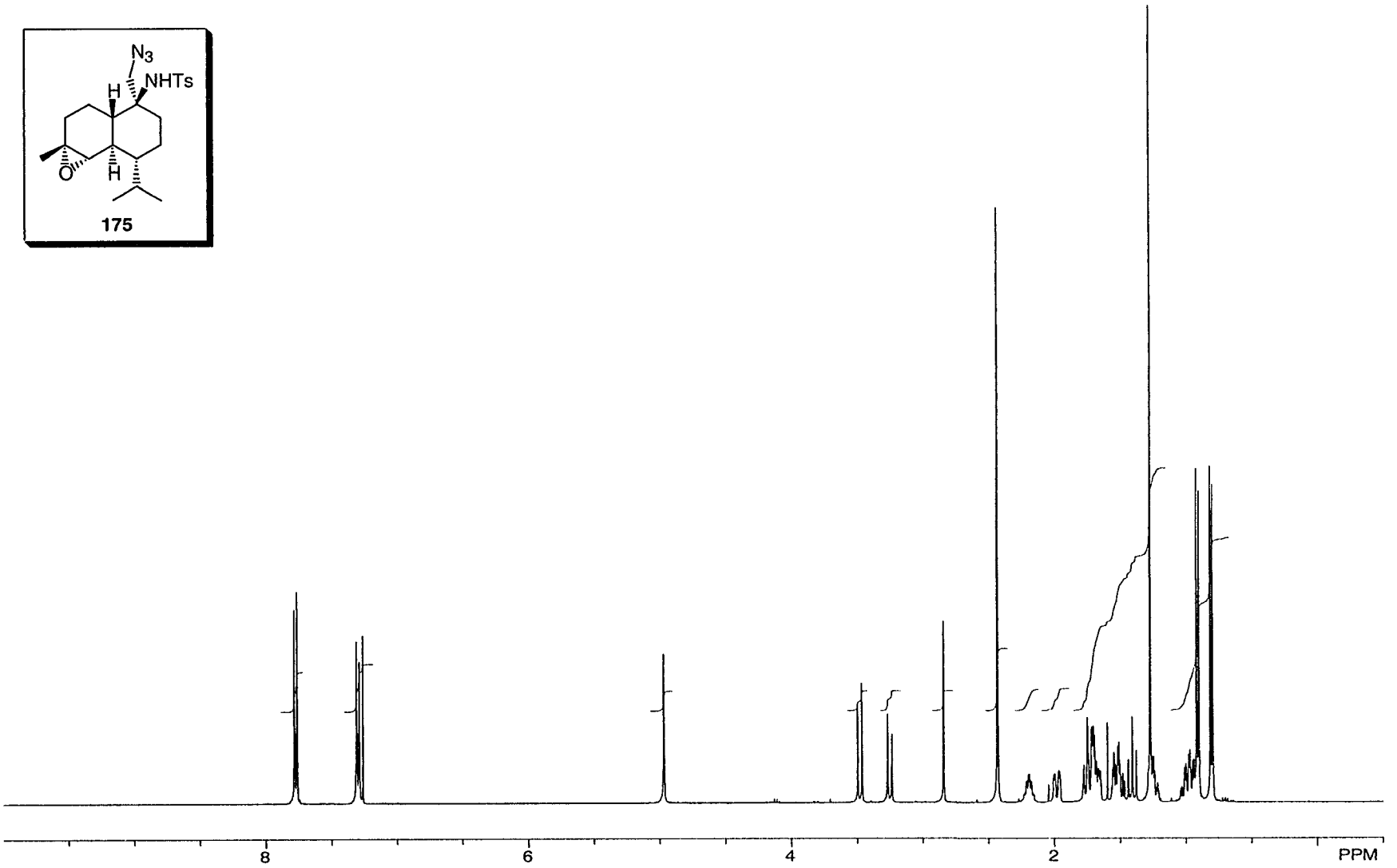


Figure A.3.154 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **175**.

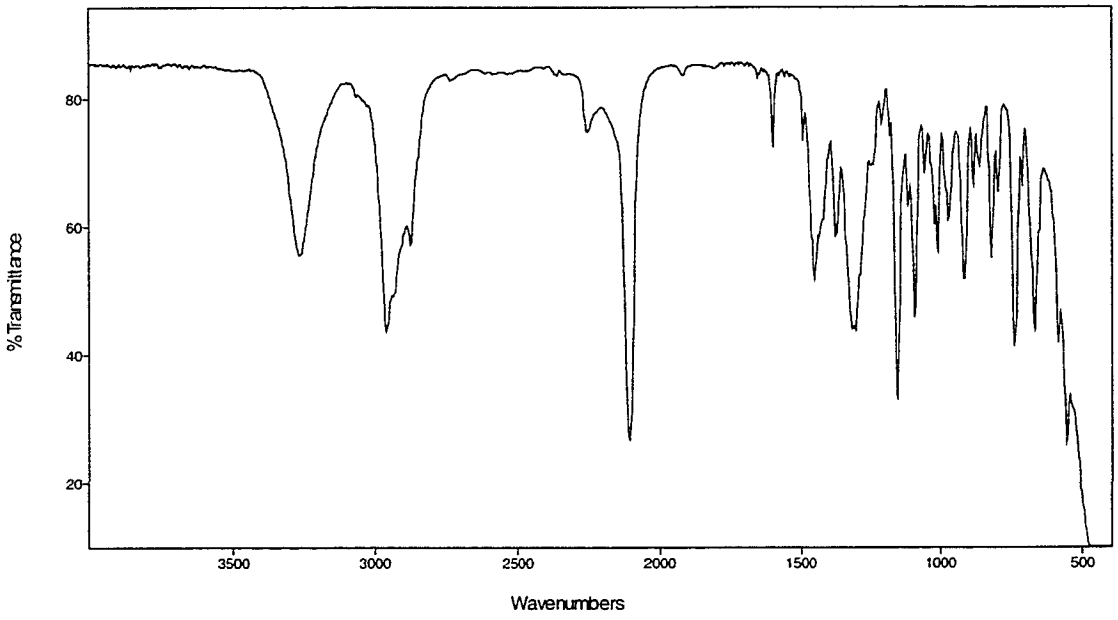


Figure A.3.155 FTIR Spectrum (thin film/NaCl) of Compound **175**.

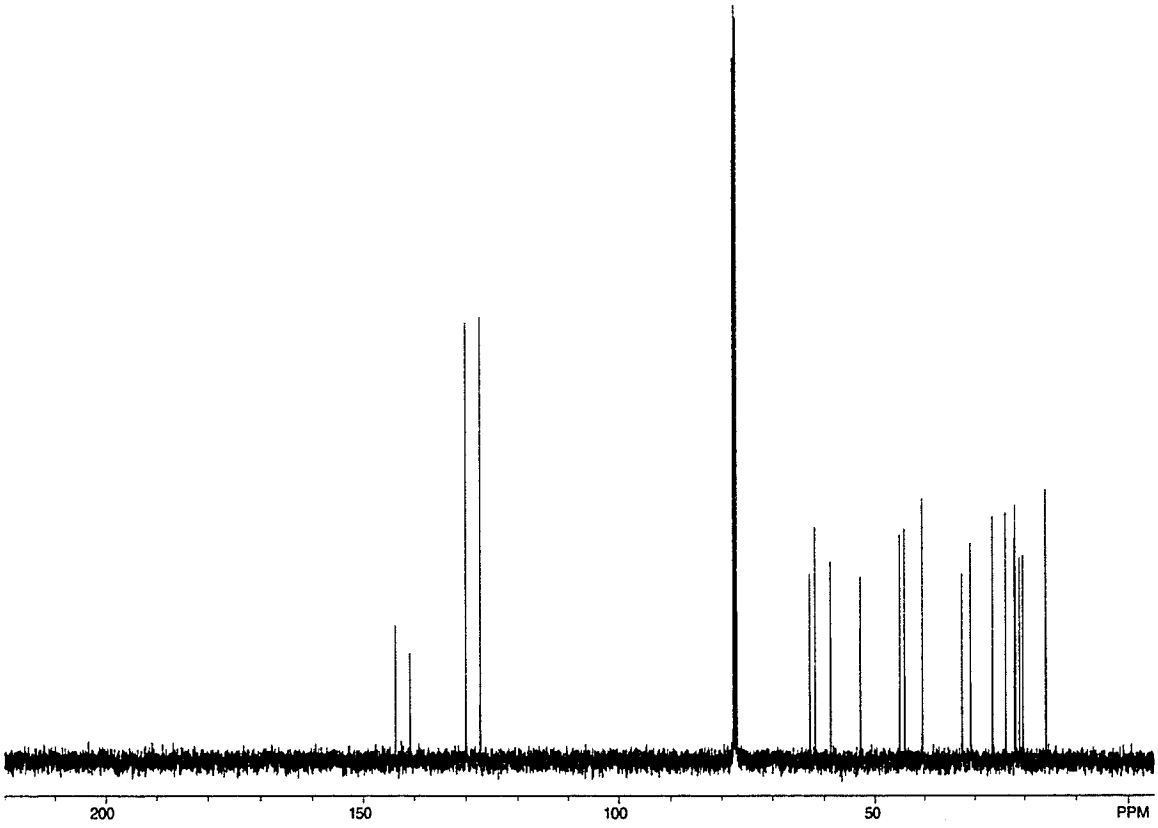


Figure A.3.156 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **175.**

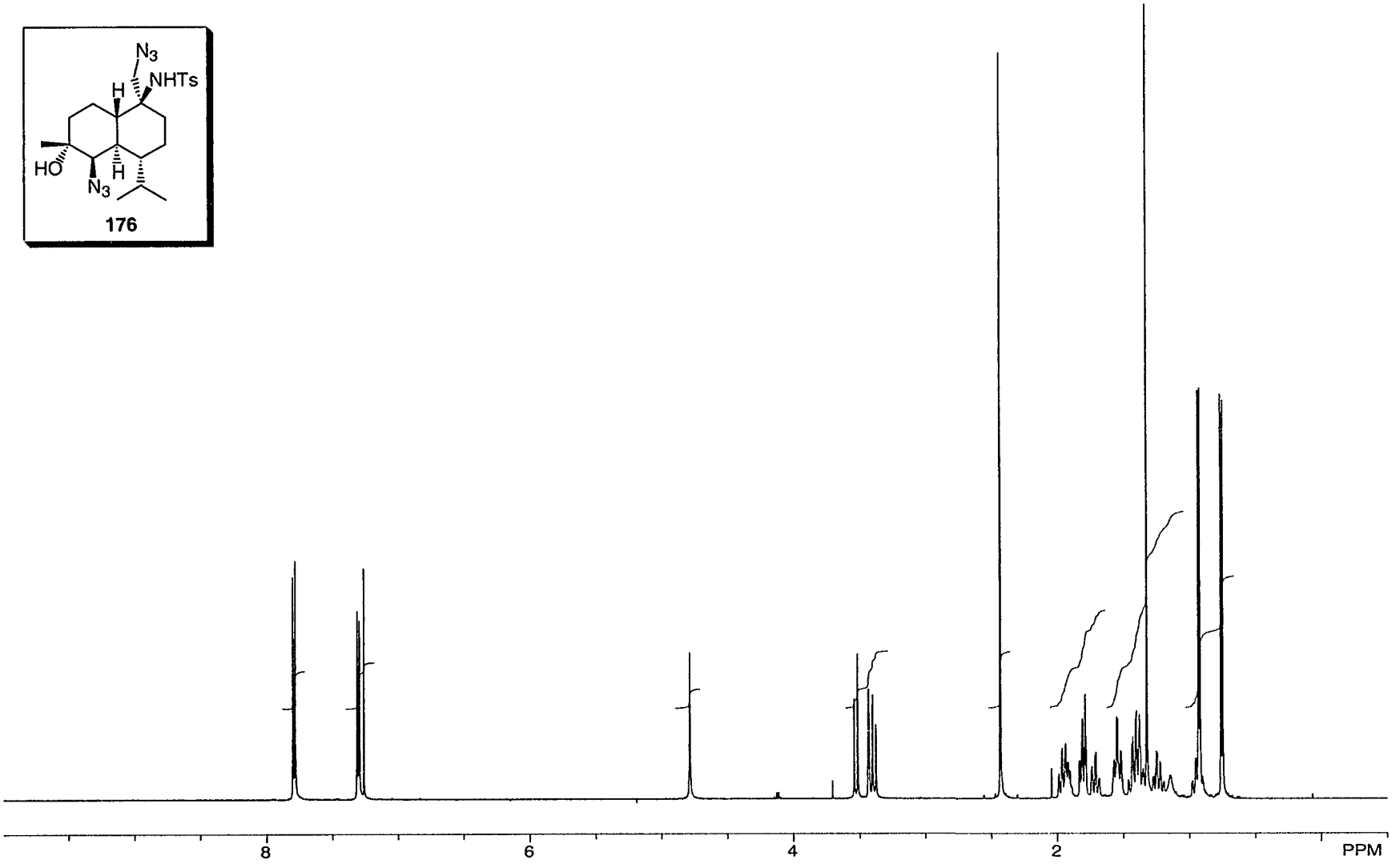


Figure A.3.157 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **176**.

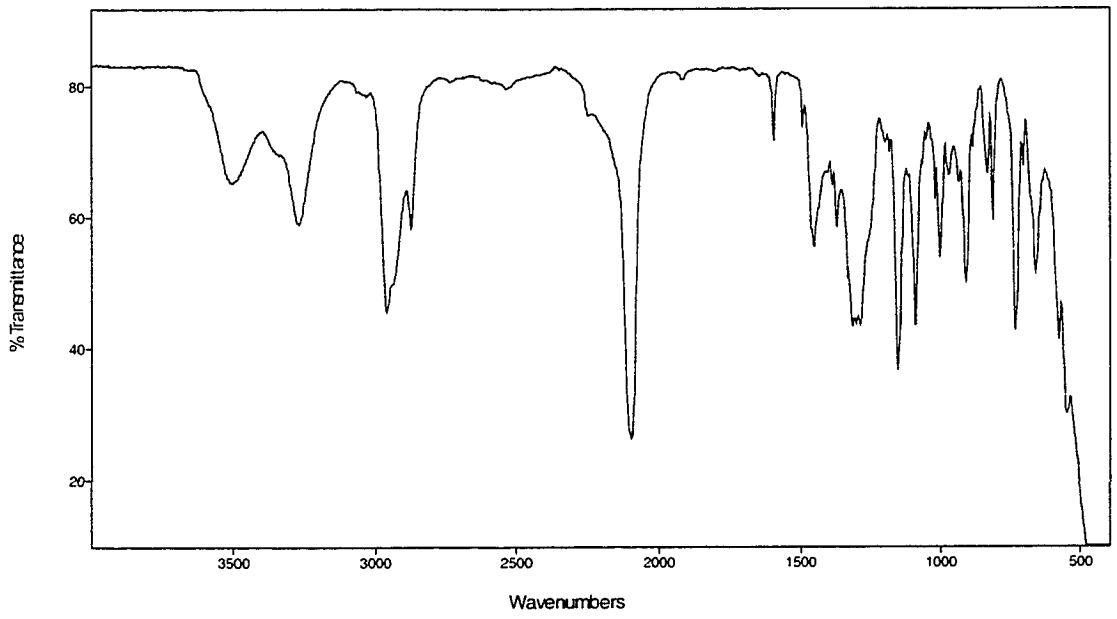


Figure A.3.158 FTIR Spectrum (thin film/NaCl) of Compound **176**.

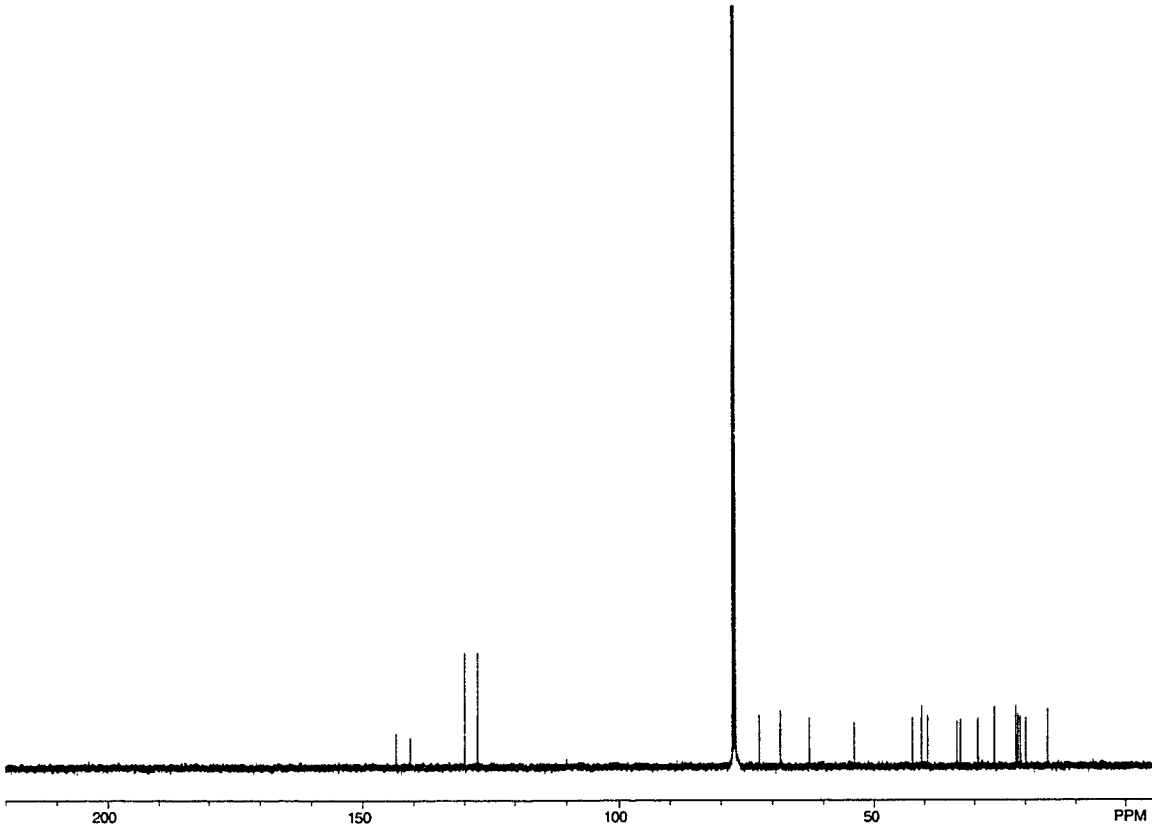


Figure A.3.159 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **176.**

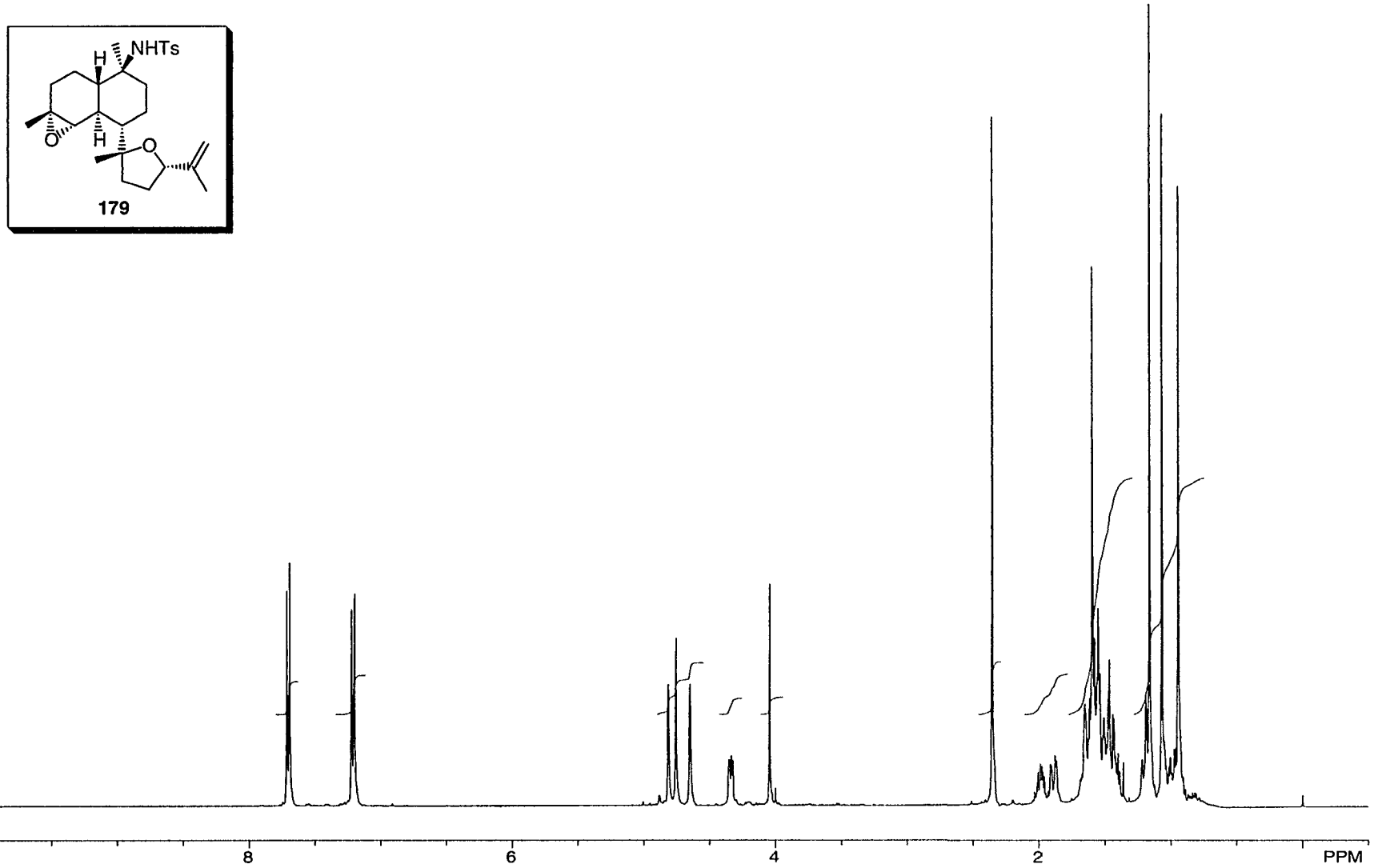


Figure A.3.160 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **179**.

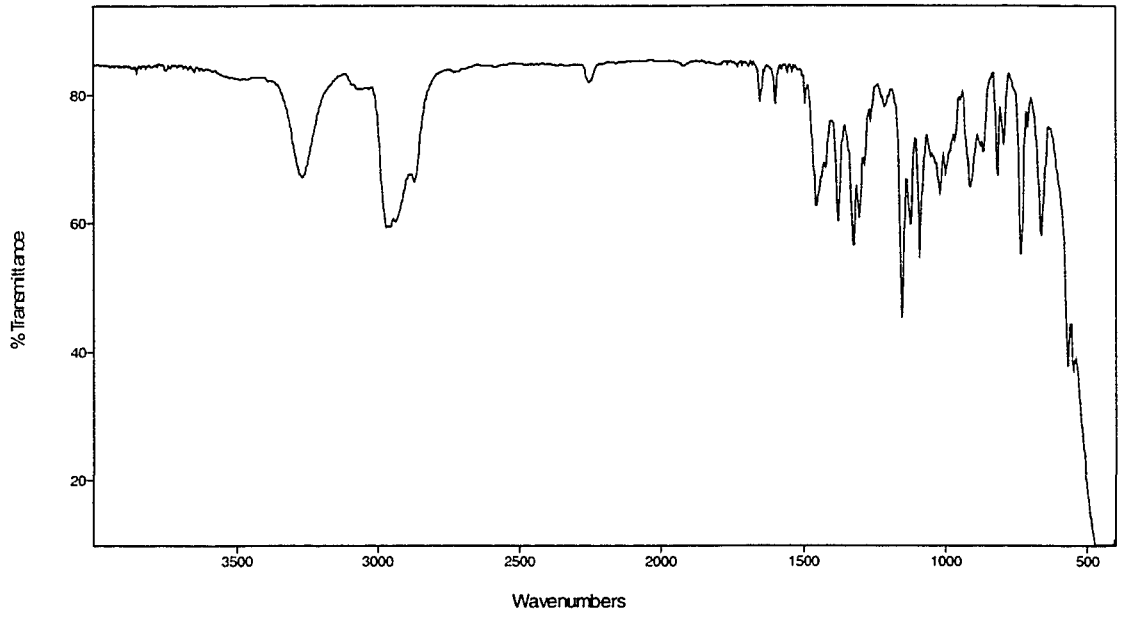


Figure A.3.161 FTIR Spectrum (thin film/NaCl) of Compound **179**.

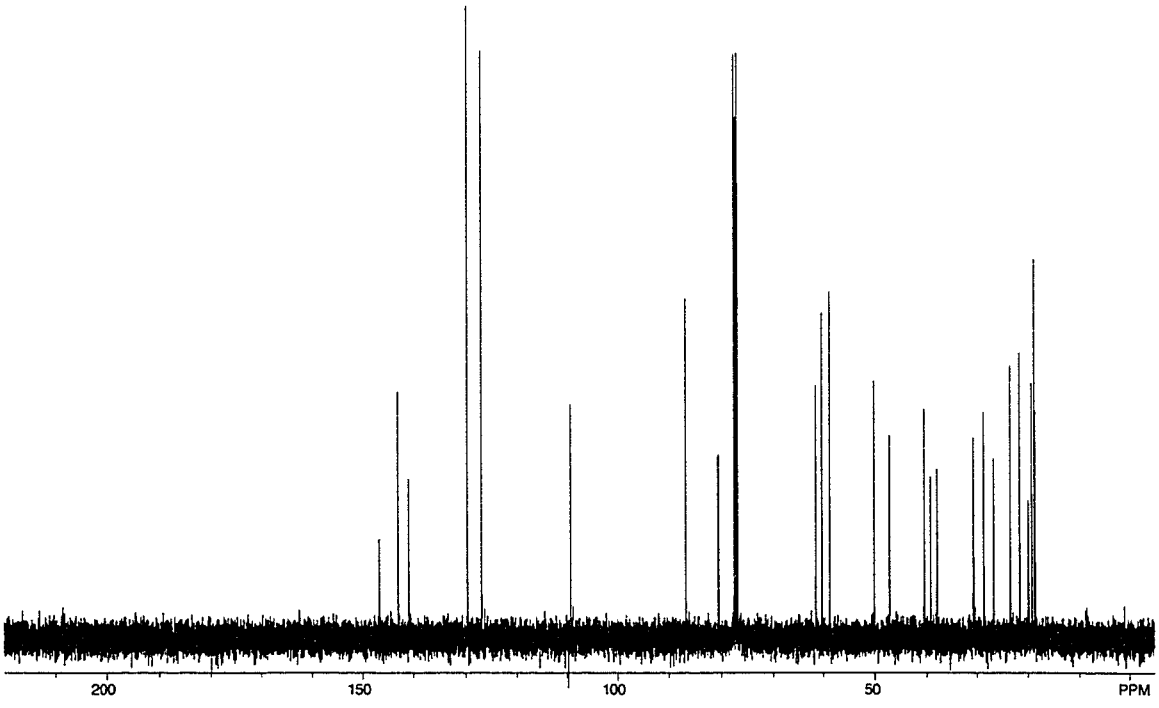


Figure A.3.162 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **179.**

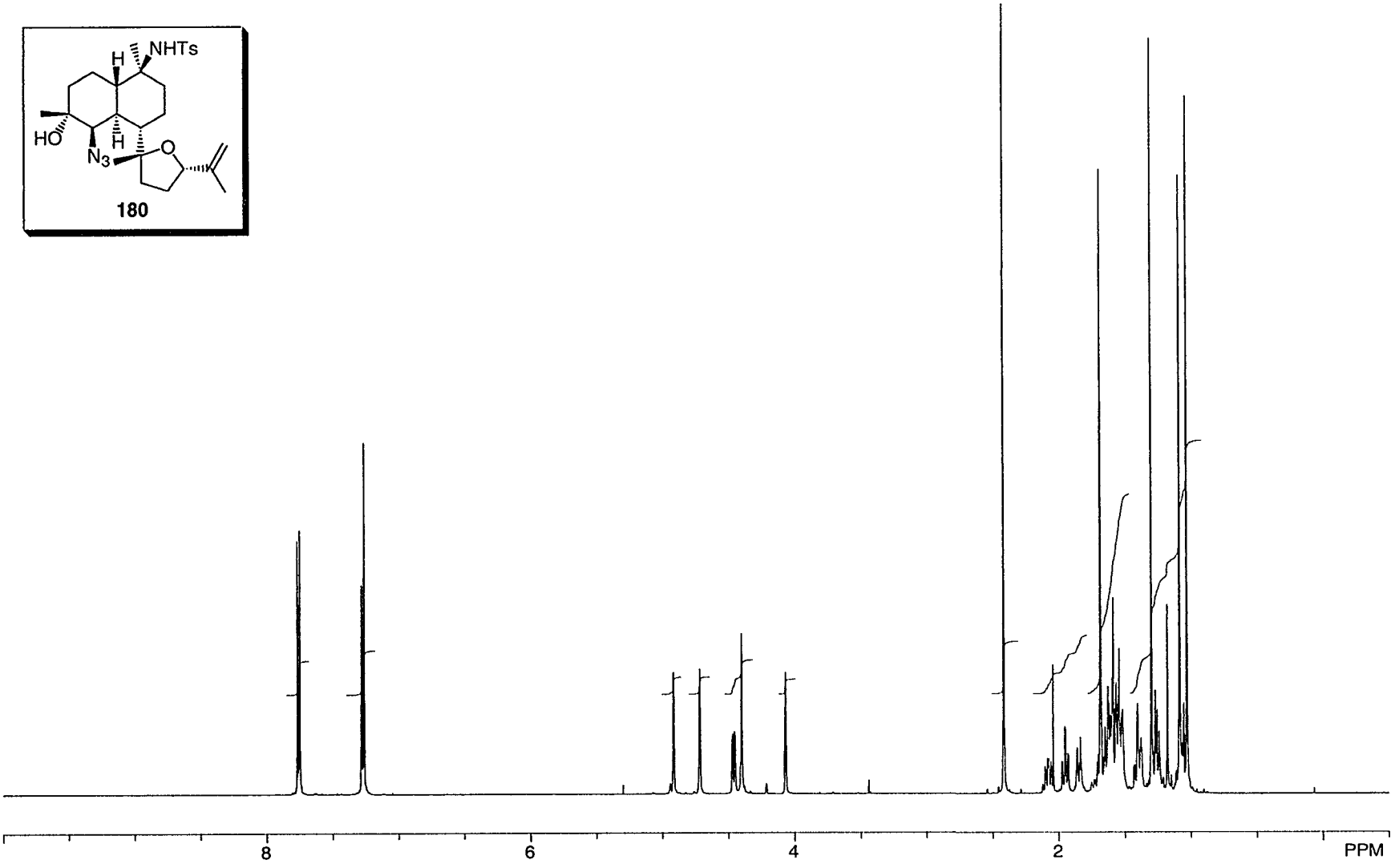


Figure A.3.163 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **180**.

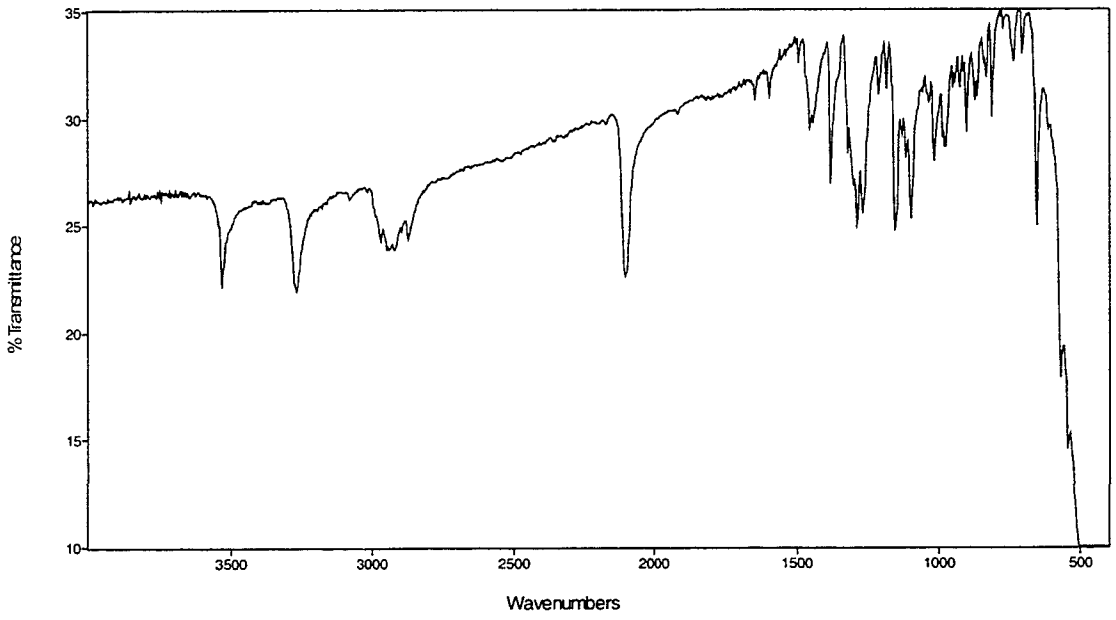


Figure A.3.164 FTIR Spectrum (thin film/NaCl) of Compound **180**.

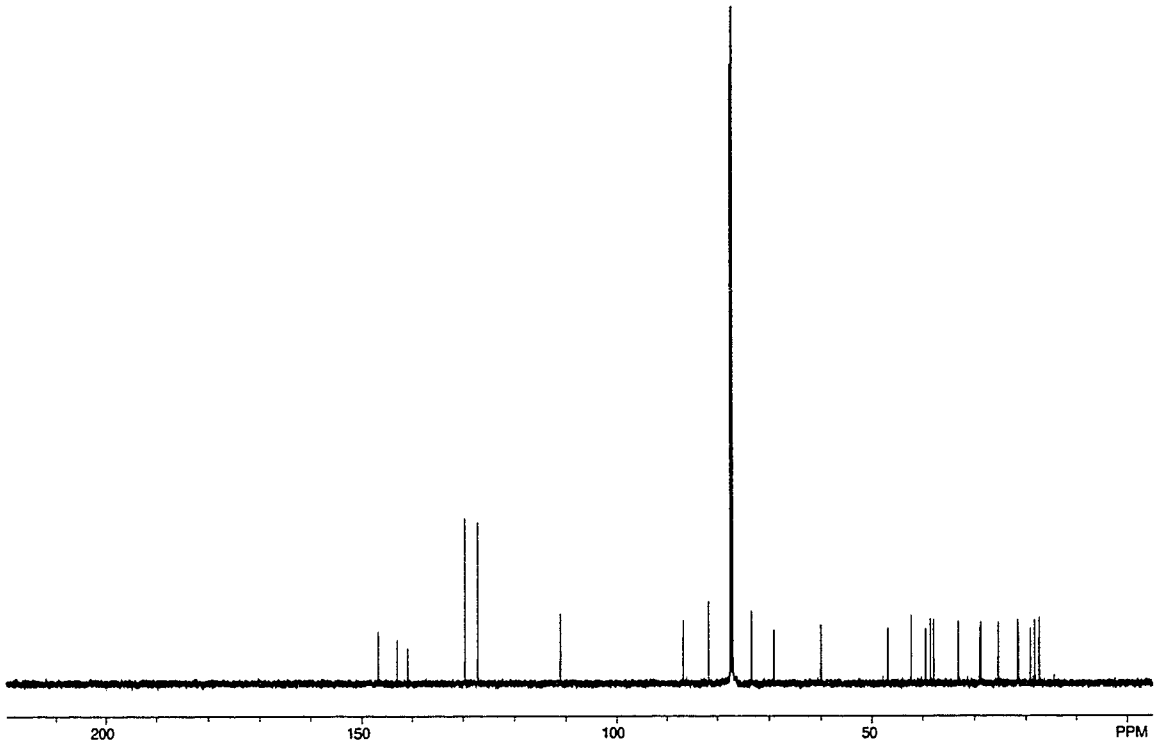


Figure A.3.165 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **180.**

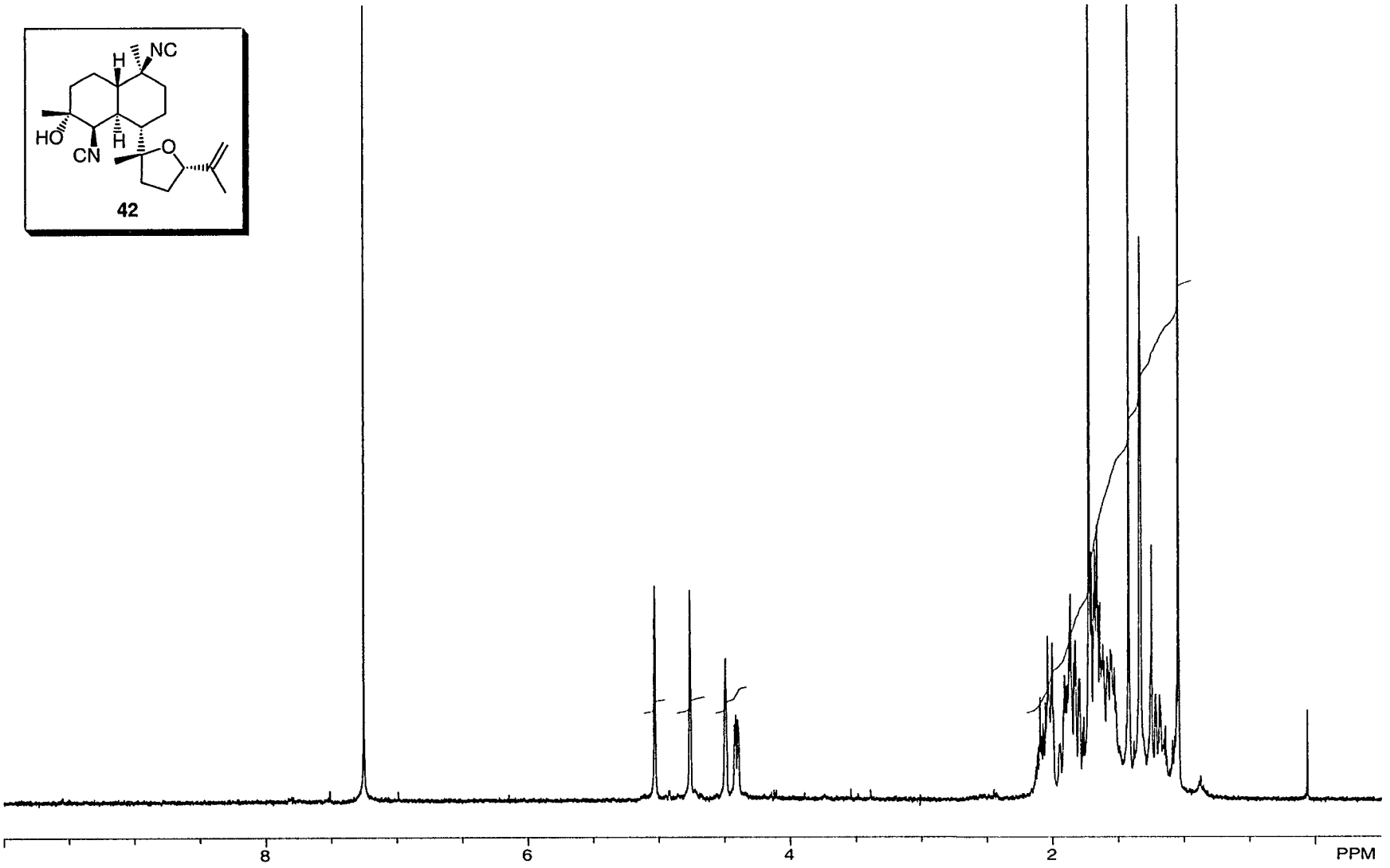


Figure A.3.166 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **42**.

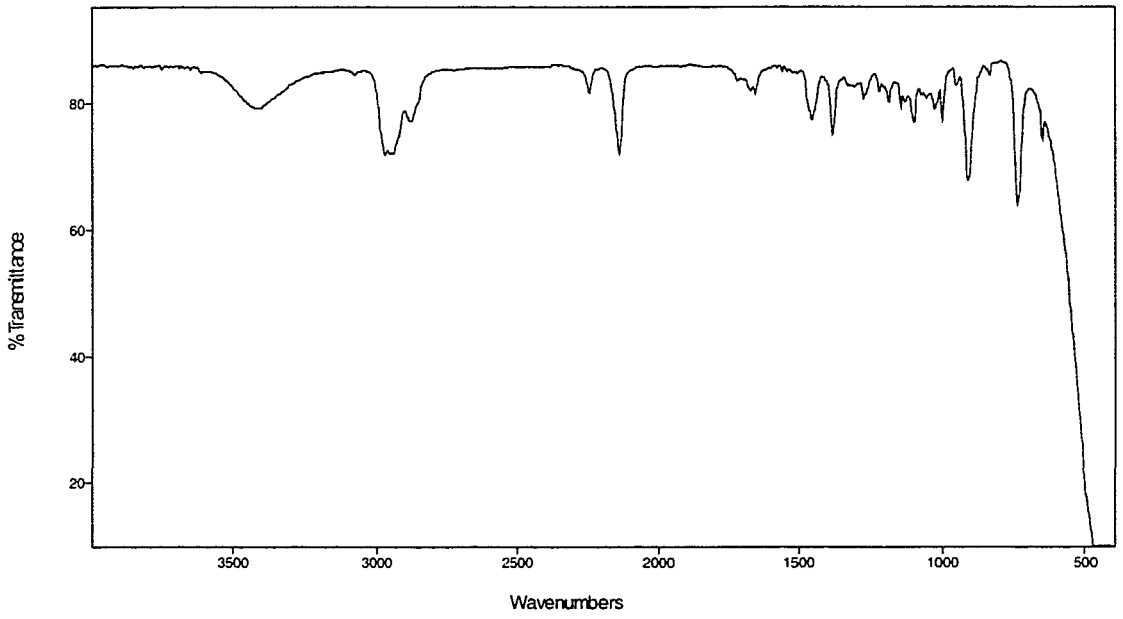


Figure A.3.167 FTIR Spectrum (thin film/NaCl) of Compound **42**.

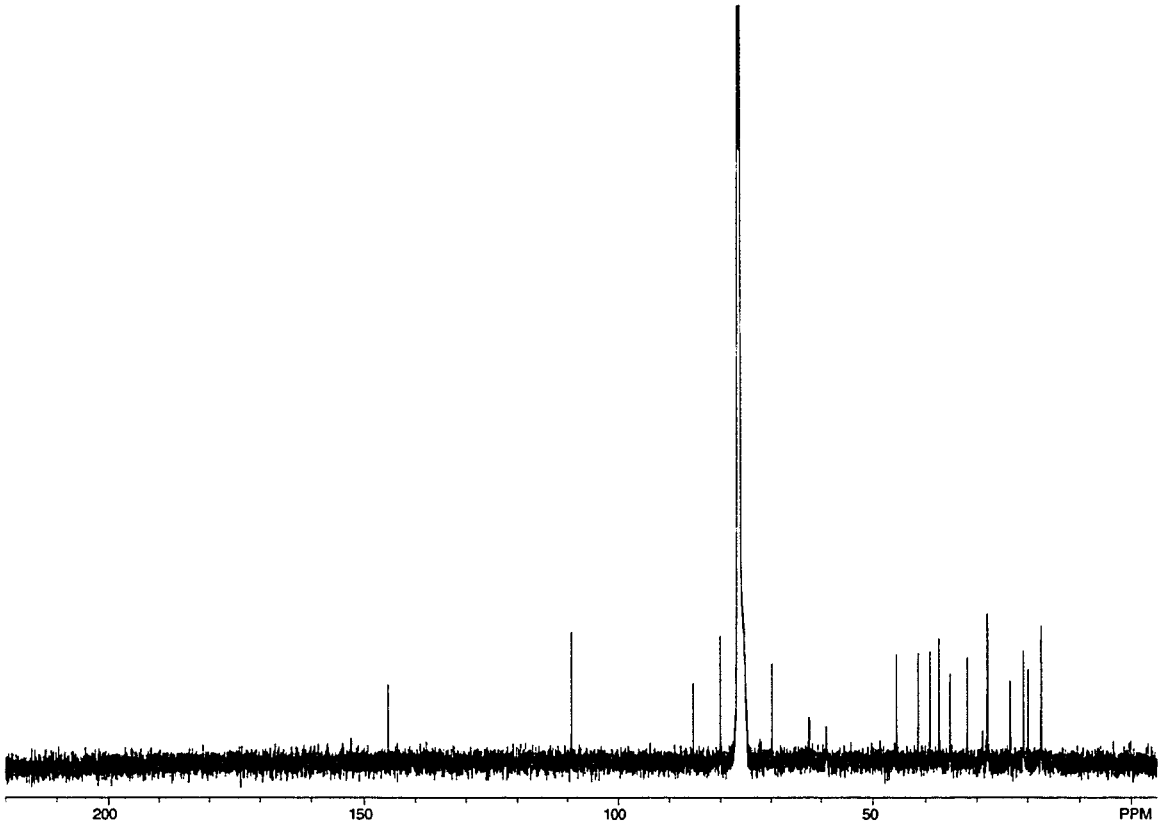


Figure A.3.168 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **42.**

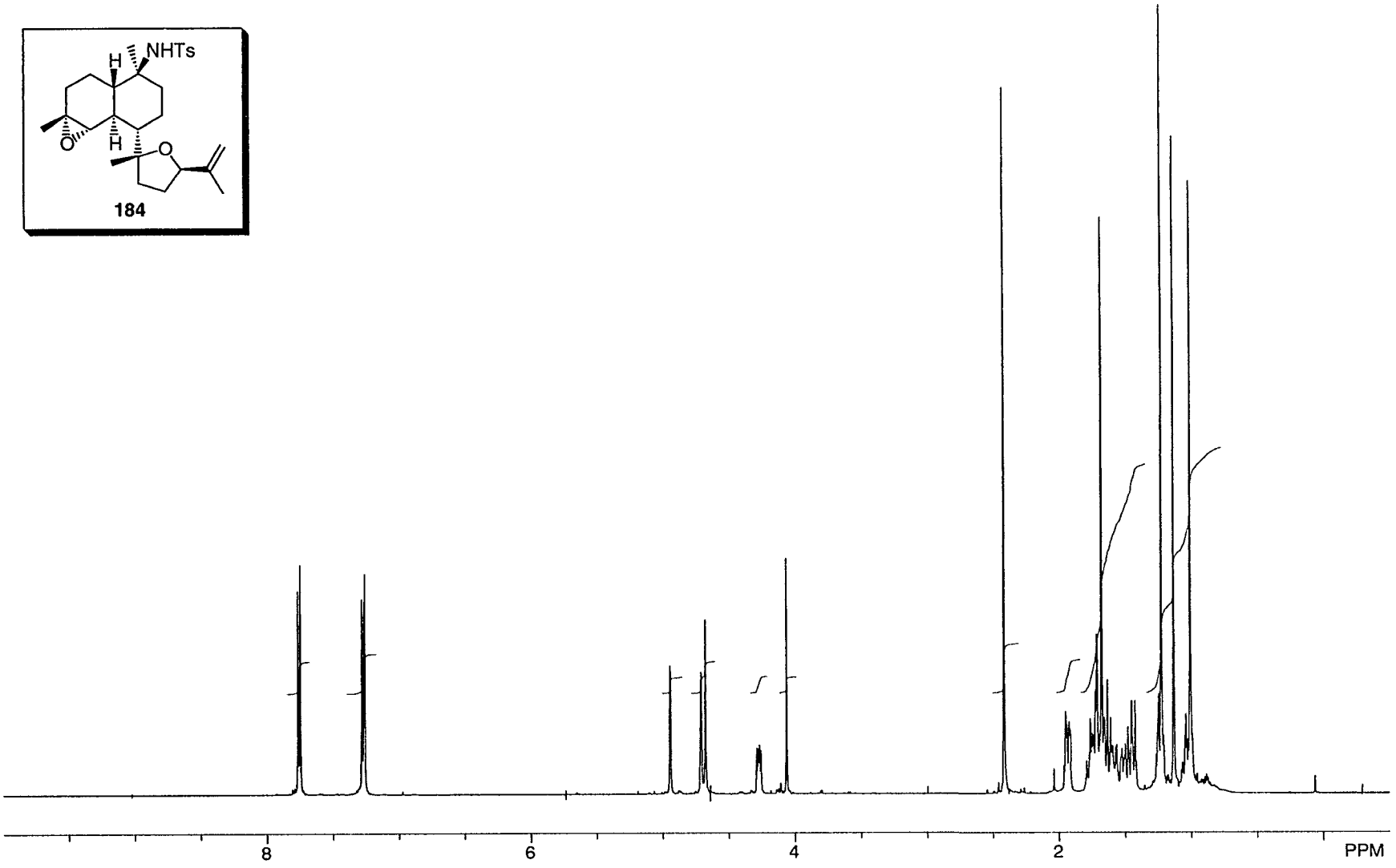


Figure A.3.169 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **184**.

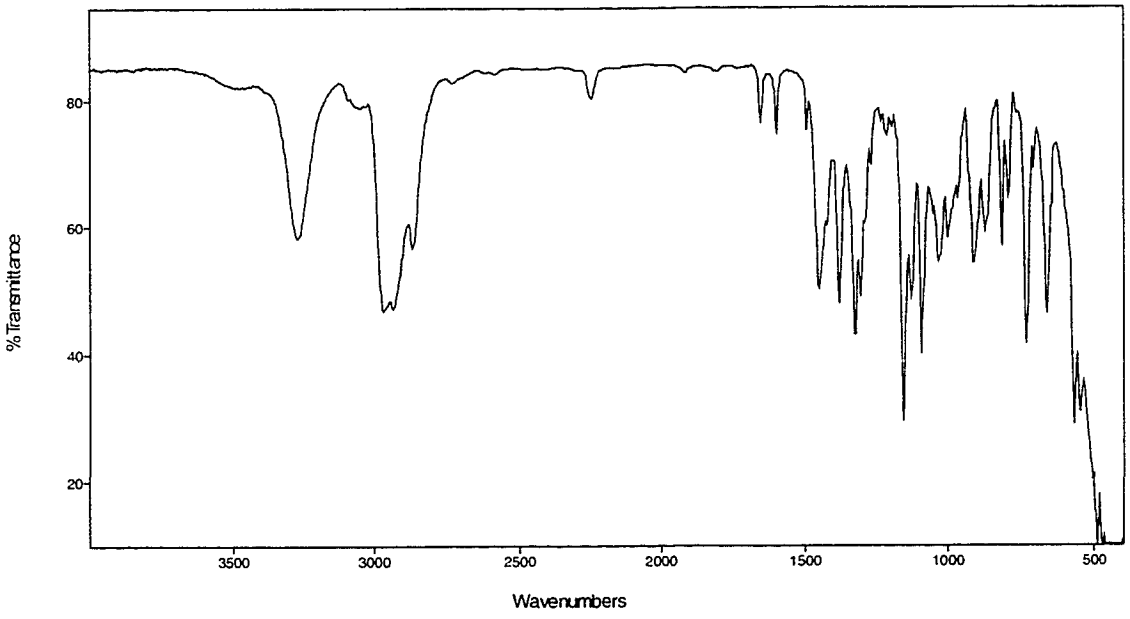


Figure A.3.170 FTIR Spectrum (thin film/NaCl) of Compound **184**.

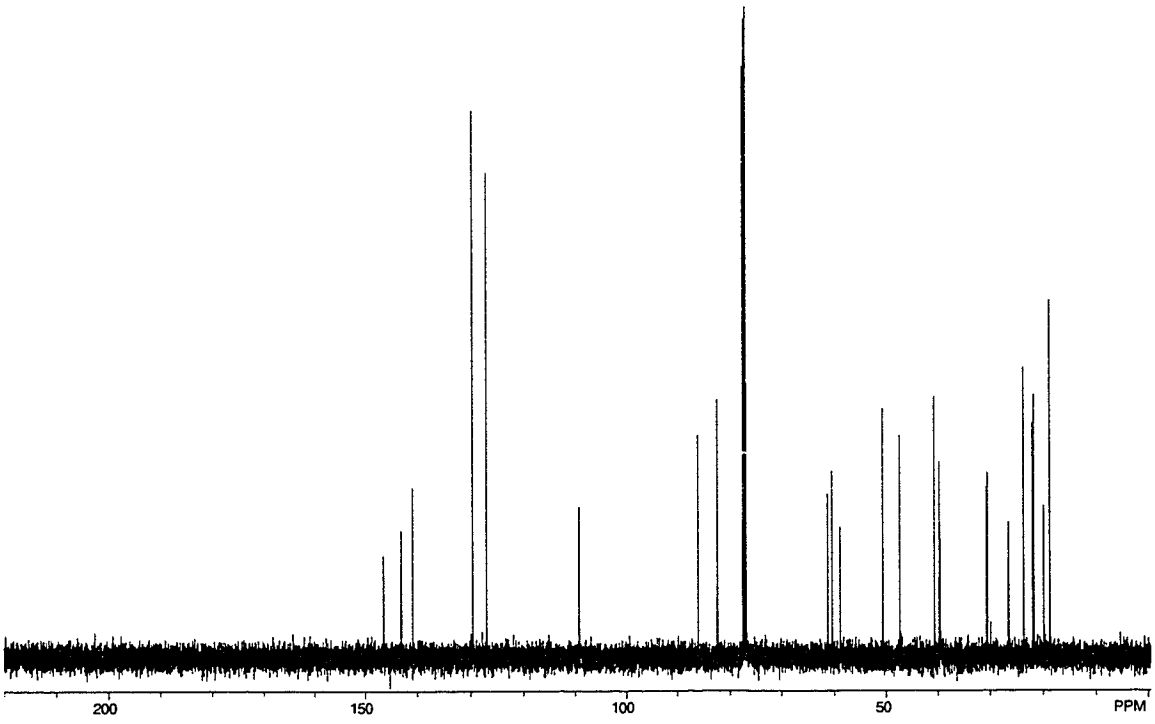


Figure A.3.171 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **184.**

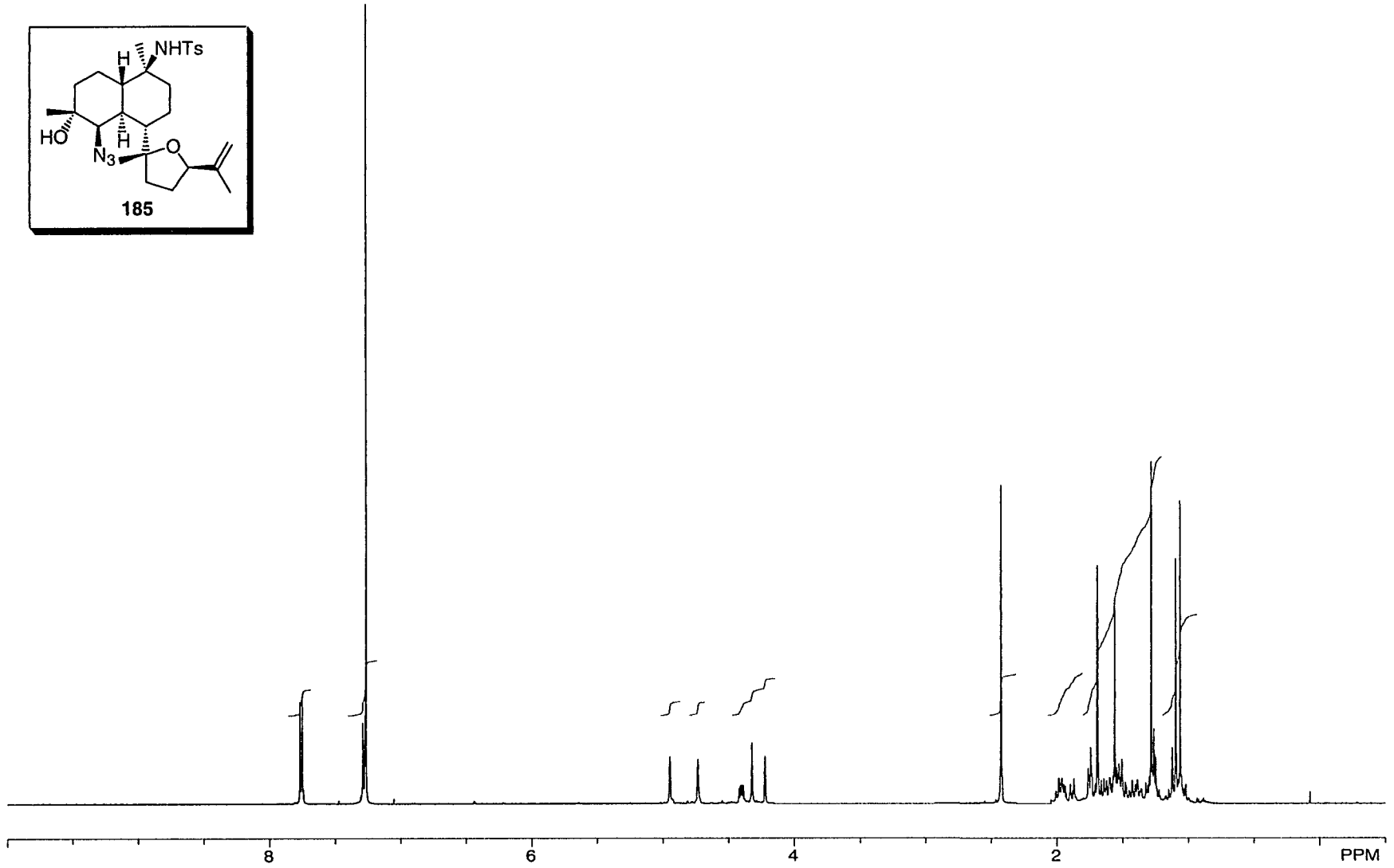


Figure A.3.172 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **185**.

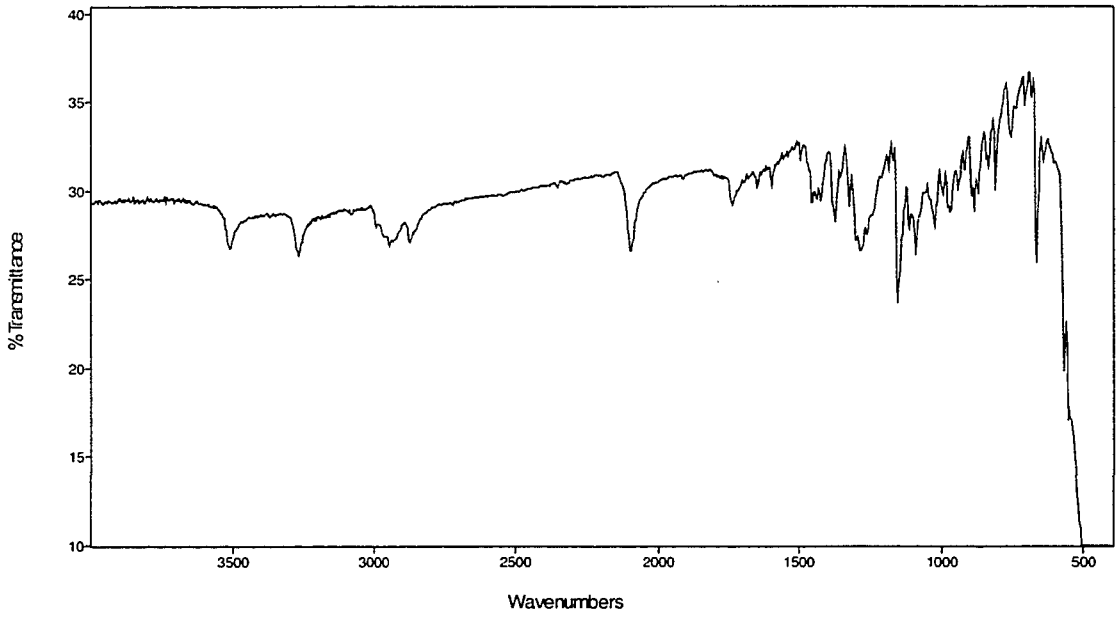


Figure A.3.173 FTIR Spectrum (thin film/NaCl) of Compound **185.**

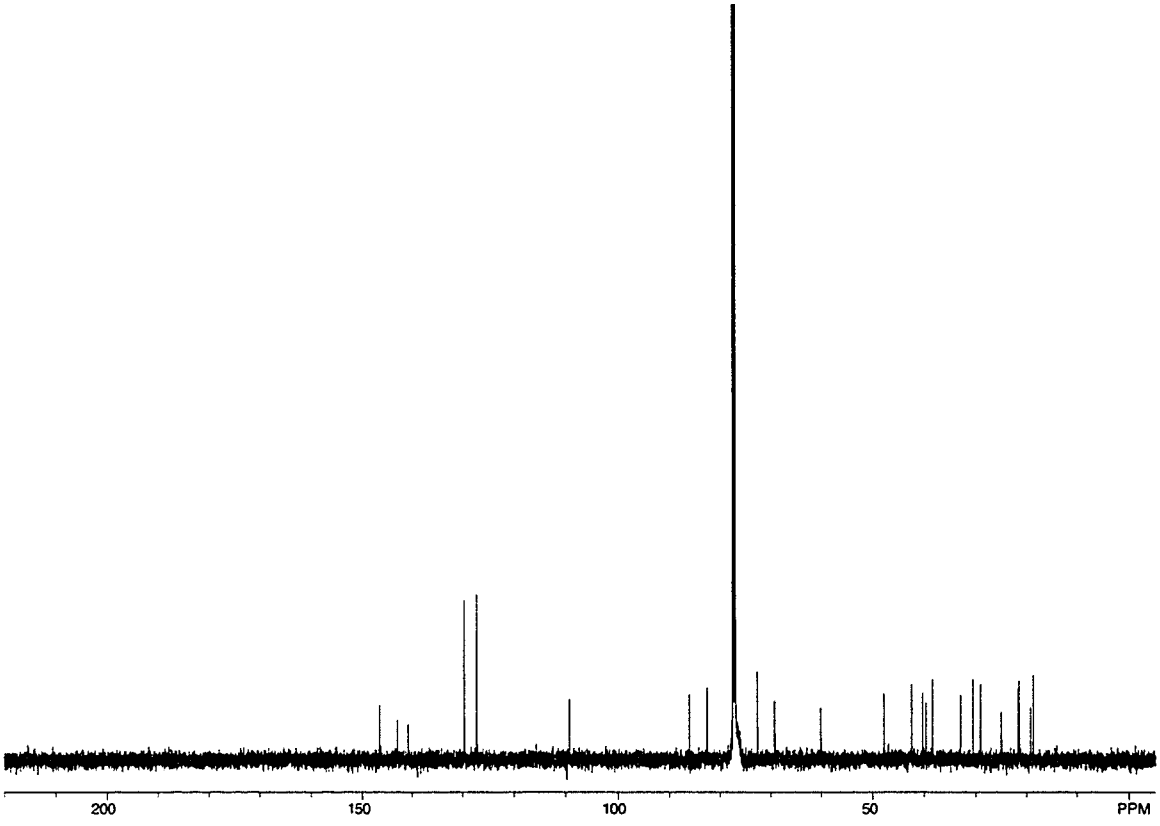


Figure A.3.174 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **185.**

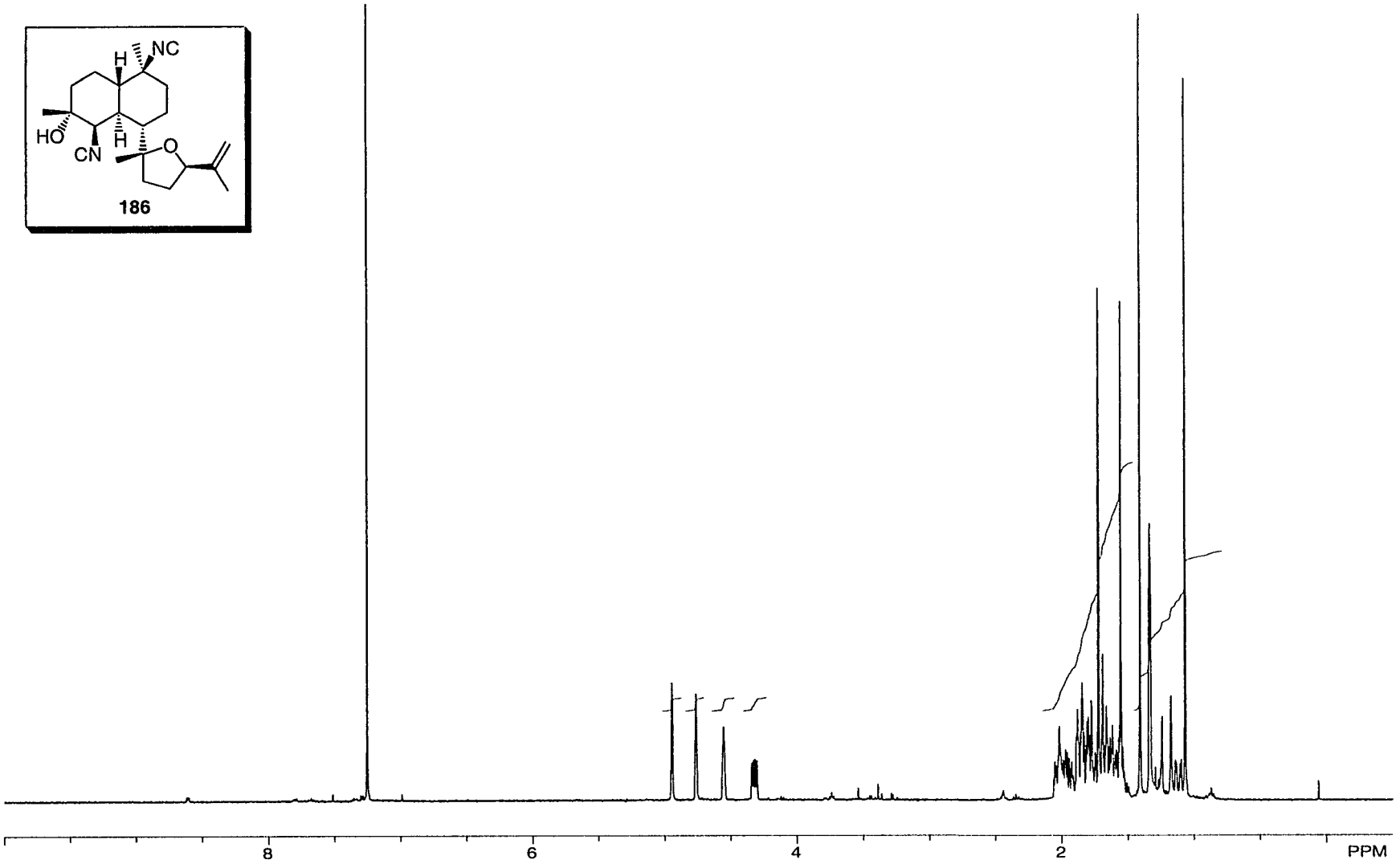


Figure A.3.175 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **186**.

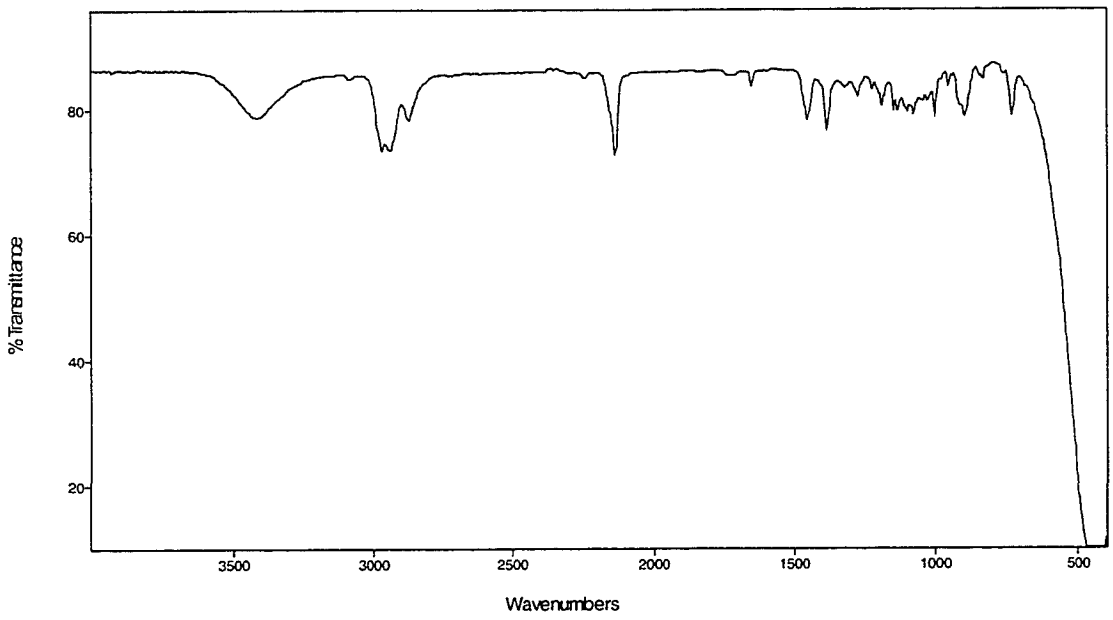


Figure A.3.176 FTIR Spectrum (thin film/NaCl) of Compound **186.**

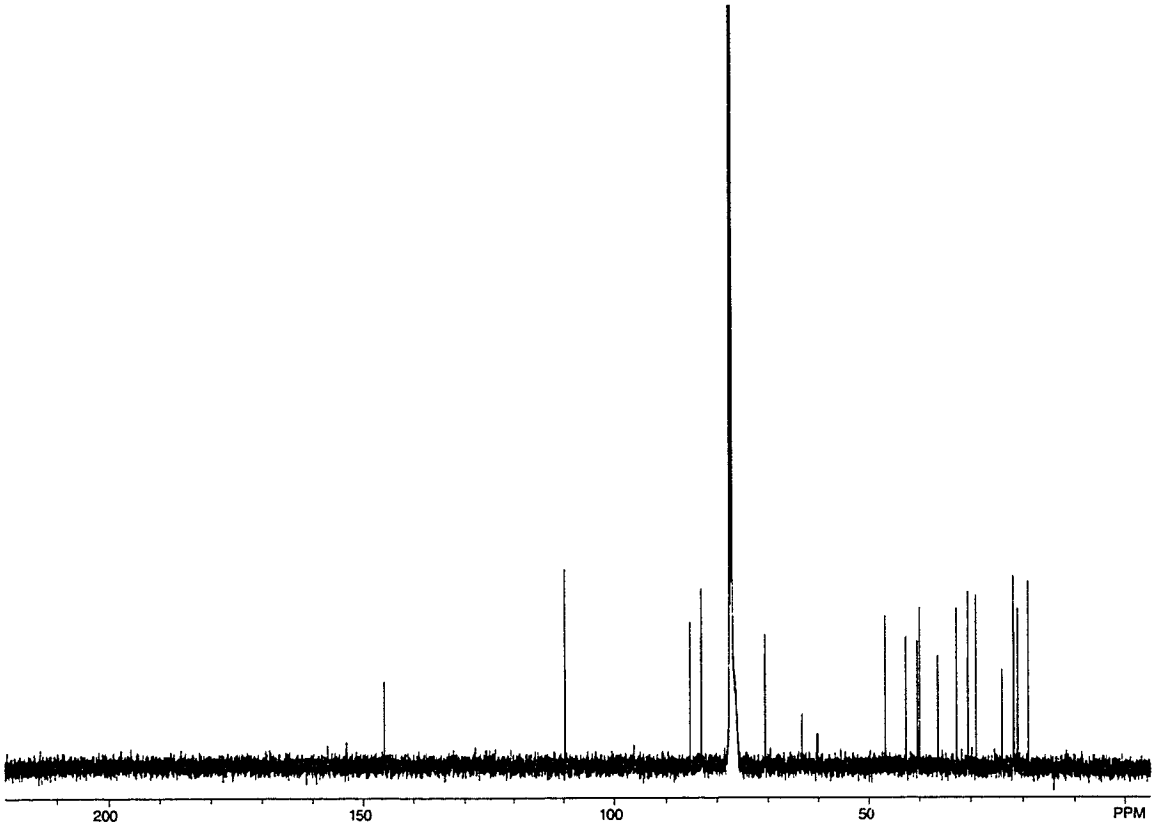


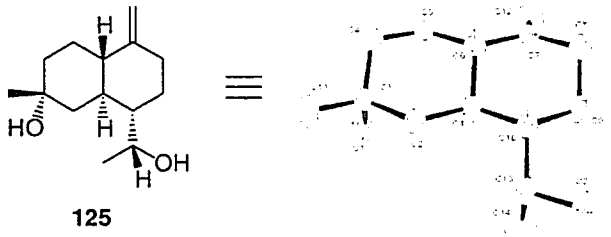
Figure A.3.177 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **186.**

Appendix Four: X-Ray Crystallography Reports

Relevant to Chapter 3

X-RAY CRYSTALLOGRAPHY REPORT FOR 125

Figure A.4.1



125

A.4.1.1 Crystal Data

Empirical Formula	$C_{14}H_{24}O_2$
Formula Weight	224.34
Crystal Color, Habit	colorless, column
Crystal Dimensions	0.09 X 0.09 X 0.22 mm
Crystal System	orthorhombic
Lattice Type	C-centered
Lattice Parameters	a = 12.942(1)Å b = 24.047(1) Å c = 17.485(1) Å V = 5441.6(5) Å^3
Space Group	Ccca (#68)
Z value	16
D_{calc}	1.095 g/cm^3
F_{000}	1984.00
μ(MoKα)	0.71 cm^{-1}

A.4.1.2 Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Take-off Angle	2.8°
Crystal to Detector Distance	35 mm
Temperature	-90.0°C
Scan Rate	234s/frame
Scan Width	1.8°/frame
$2\theta_{max}$	54.9°
No. of Reflections Measured	Total: 3428
Corrections	Lorentz-polarization

A.4.1.3 Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights	$1/\sigma^2$(Fo)
p-factor	0.0200
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1797
No. Variables	249
Reflection/Parameter Ratio	7.22
Residuals: R; Rw	0.042; 0.040
Goodness of Fit Indicator	1.87
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.14 e$^-$/Å^3
Minimum peak in Final Diff. Map	-0.15 e$^-$/Å^3

Table A.4.1 Atomic Coordinates and B_{iso}/B_{eq} for Alcohol **125**

atom	x	y	z	B_{eq}
O(1)	0.2789(1)	0.05450(6)	-0.09984(8)	3.37(3)
O(2)	-0.0348(1)	0.06436(5)	0.17258(7)	3.22(3)
C(1)	0.1762(1)	0.11195(6)	0.03389(8)	2.38(4)
C(2)	0.1273(1)	0.09328(8)	-0.04167(8)	2.53(4)
C(3)	0.1987(1)	0.09544(6)	-0.11131(8)	2.74(4)
C(4)	0.2511(2)	0.15196(7)	-0.11676(9)	3.25(4)
C(5)	0.3049(1)	0.16787(7)	-0.04301(10)	3.11(4)
C(6)	0.2299(1)	0.16899(6)	0.02409(8)	2.59(4)
C(7)	0.2765(1)	0.18789(6)	0.09882(9)	3.14(4)
C(8)	0.1997(2)	0.19044(8)	0.1630(1)	3.83(5)
C(9)	0.1466(2)	0.13405(8)	0.17342(10)	3.48(5)
C(10)	0.0965(1)	0.11355(7)	0.09938(9)	2.53(4)
C(11)	0.1385(2)	0.08161(10)	-0.18342(10)	3.87(5)
C(12)	0.3754(2)	0.19950(8)	0.1091(1)	4.38(6)
C(13)	0.0391(1)	0.05833(6)	0.11131(9)	2.63(4)
C(14)	0.1077(1)	0.00875(8)	0.1271(1)	3.57(5)
H(1)	0.232(1)	0.0843(5)	0.0487(7)	2.30(3)
H(2)	0.103(1)	0.0543(7)	-0.0379(8)	2.90(3)
H(3)	0.066(1)	0.1171(6)	-0.0549(8)	3.20(3)
H(4)	0.302(1)	0.1514(6)	-0.1586(9)	3.00(3)
H(5)	0.197(1)	0.1804(7)	-0.1308(8)	3.80(4)
H(6)	0.364(1)	0.1412(6)	-0.0305(8)	3.30(4)

H(7)	0.341(1)	0.2036(7)	-0.0492(8)	3.50(4)
H(8)	0.174(1)	0.1962(6)	0.0102(7)	2.30(3)
H(9)	0.234(1)	0.2021(7)	0.2096(10)	4.30(4)
H(10)	0.141(1)	0.2181(7)	0.1485(9)	4.80(4)
H(11)	0.199(1)	0.1070(7)	0.1901(9)	4.30(4)
H(12)	0.094(1)	0.1380(6)	0.2126(10)	4.20(4)
H(13)	0.044(1)	0.1412(5)	0.0859(8)	2.30(3)
H(14a)	0.326(3)	0.059(1)	-0.125(2)	2.40(9)
H(14b)	0.258(6)	0.017(3)	-0.100(2)	10.0(1)
H(15)	0.079(2)	0.1093(8)	-0.192(1)	5.90(5)
H(16)	0.182(1)	0.0822(6)	-0.2248(10)	4.40(4)
H(17)	0.108(1)	0.0427(8)	-0.1809(9)	4.80(4)
H(18)	0.399(1)	0.2098(7)	0.158(1)	5.40(5)
H(19)	0.427(1)	0.1971(7)	0.069(1)	5.20(5)
H(20)	-0.002(1)	0.0508(5)	0.0644(8)	2.30(3)
H(21a)	-0.011(4)	0.063(2)	0.217(2)	7.00(1)
H(21b)	-0.092(4)	0.061(2)	0.160(2)	4.00(1)
H(22)	0.157(1)	0.0025(7)	0.0831(9)	4.80(4)
H(23)	0.151(1)	0.0156(7)	0.1716(9)	4.20(4)
H(24)	0.065(1)	-0.0256(7)	0.1353(9)	4.50(4)

Anisotropic Displacement Parameters

atom	U11	U22	U33	U12	U13	U23
O(1)	0.0345(8)	0.0371(8)	0.0565(8)	0.0014(6)	0.0130(7)	-0.0086(6)
O(2)	0.0282(8)	0.0666(9)	0.0277(7)	-0.0008(6)	0.0043(7)	0.0012(6)
C(1)	0.0294(9)	0.0299(9)	0.0311(9)	0.0032(7)	0.0000(8)	0.0026(7)
C(2)	0.0307(10)	0.035(1)	0.0299(9)	0.0017(8)	0.0026(7)	-0.0004(8)
C(3)	0.0355(10)	0.0337(10)	0.0347(9)	0.0020(8)	0.0083(7)	-0.0030(7)
C(4)	0.052(1)	0.0353(10)	0.036(1)	-0.0016(9)	0.0154(10)	0.0008(8)
C(5)	0.045(1)	0.0279(10)	0.046(1)	-0.0076(9)	0.0097(9)	0.0000(8)
C(6)	0.038(1)	0.0266(9)	0.0336(9)	0.0041(8)	0.0013(8)	0.0007(7)
C(7)	0.050(1)	0.0282(9)	0.0411(10)	-0.0045(8)	-0.0031(9)	0.0029(8)
C(8)	0.064(1)	0.052(1)	0.029(1)	-0.014(1)	-0.003(1)	-0.0037(9)
C(9)	0.051(1)	0.053(1)	0.029(1)	-0.011(1)	-0.0028(9)	0.0006(9)
C(10)	0.0322(9)	0.0380(10)	0.0259(8)	0.0038(8)	-0.0006(8)	0.0016(7)
C(11)	0.053(1)	0.064(1)	0.030(1)	-0.007(1)	0.012(1)	-0.0058(10)
C(12)	0.057(2)	0.050(1)	0.059(1)	-0.010(1)	-0.008(1)	-0.004(1)
C(13)	0.0272(9)	0.047(1)	0.0259(9)	-0.0012(8)	0.0024(8)	-0.0006(8)
C(14)	0.035(1)	0.043(1)	0.057(1)	-0.0027(9)	0.007(1)	0.0089(10)

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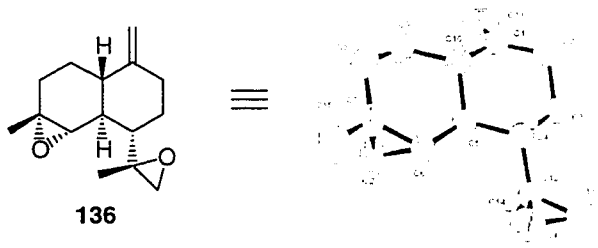
Figure A.4.2



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A.4.2.1 Crystal Data

Empirical formula	$C_{15}H_{22}O_2$	
Formula weight	234.33	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.6380(15) Å	α = 111.47(3)°
	b = 8.6448(17) Å	β = 92.36(3)°
	c = 11.767(2) Å	γ = 106.44(3)°
Volume	684.3(2) $Å^3$	
Z	2	
Density (calculated)	1.137 g/cm^3	
Absorption coefficient	0.73 cm^{-1}	
F(000)	256	
Crystal size	0.30 x 0.30 x 0.25 mm^3	

A.4.2.2 Intensity Measurements

Temperature	296(2) K
Wavelength	0.71073 Å
Theta range for data collection	2.82 to 28.11°.
Index ranges	-9<=h<=10, -7<=k<=11, -15<=l<=13
Reflections collected	3159
Independent reflections	2583 [R(int) = 0.0268]
Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å)

A.4.2.3 Structure Solution and Refinement

Completeness to theta = 28.11°	77.2 %
Absorption correction	None
Max. and min. transmission	0.9819 and 0.9783

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2583 / 0 / 154
Goodness-of-fit on F^2	1.199
Final R indices [I>2sigma(I)]	R1 = 0.0502, wR2 = 0.1325
R indices (all data)	R1 = 0.0808, wR2 = 0.1482
Largest diff. peak and hole	0.142 and -0.128 e.$Å^{-3}$

Table A.4.2 Atomic coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for Epoxide **136**

atom	x	y	z	U(eq)
O(1)	3694(2)	7752(1)	3147(1)	72(1)
O(2)	-2196(1)	4738(2)	2459(1)	73(1)
C(1)	838(2)	938(2)	2335(2)	66(1)
C(2)	2892(2)	1642(2)	2606(2)	67(1)
C(3)	3526(2)	3594(2)	3435(1)	55(1)
C(4)	2684(2)	4626(2)	2901(1)	45(1)
C(5)	584(2)	3827(2)	2620(1)	45(1)
C(6)	-367(2)	4840(2)	2152(1)	53(1)
C(7)	-1970(2)	3994(2)	1168(2)	64(1)
C(8)	-2696(2)	2041(3)	583(2)	79(1)
C(9)	-2084(2)	1162(2)	1350(2)	74(1)
C(10)	-10(2)	1873(2)	1742(1)	54(1)
C(11)	-123(3)	-310(2)	2674(2)	101(1)
C(12)	3370(2)	6548(2)	3760(1)	50(1)
C(13)	5238(2)	7553(2)	3750(2)	72(1)
C(14)	2512(2)	7123(2)	4907(1)	65(1)
C(15)	-2418(3)	4926(3)	405(2)	94(1)

Anisotropic displacement parameters ($Å^2$x 10^3)

atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	77(1)	58(1)	89(1)	41(1)	12(1)	18(1)
O(2)	55(1)	97(1)	67(1)	19(1)	15(1)	41(1)
C(1)	75(1)	39(1)	73(1)	12(1)	11(1)	16(1)

C(2)	74(1)	53(1)	73(1)	17(1)	3(1)	29(1)
C(3)	55(1)	49(1)	59(1)	19(1)	1(1)	18(1)
C(4)	43(1)	45(1)	45(1)	16(1)	7(1)	15(1)
C(5)	44(1)	45(1)	44(1)	14(1)	9(1)	14(1)
C(6)	46(1)	60(1)	54(1)	18(1)	9(1)	23(1)
C(7)	49(1)	82(1)	56(1)	17(1)	4(1)	28(1)
C(8)	48(1)	91(1)	71(1)	12(1)	-7(1)	12(1)
C(9)	52(1)	61(1)	78(1)	6(1)	3(1)	3(1)
C(10)	50(1)	46(1)	54(1)	9(1)	8(1)	12(1)
C(11)	110(2)	61(1)	133(2)	44(1)	17(1)	20(1)
C(12)	50(1)	44(1)	54(1)	19(1)	4(1)	14(1)
C(13)	56(1)	55(1)	96(1)	27(1)	6(1)	9(1)
C(14)	75(1)	54(1)	58(1)	10(1)	9(1)	23(1)
C(15)	80(1)	130(2)	85(1)	44(1)	-3(1)	54(1)

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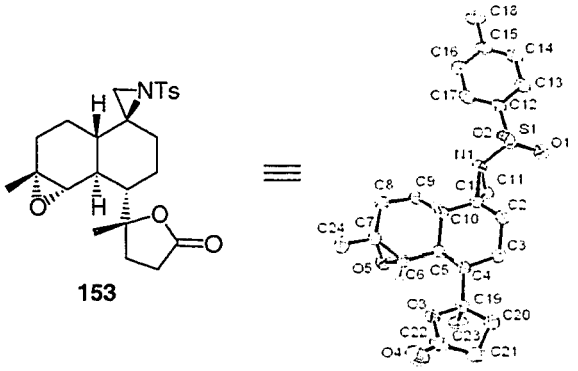
Figure A.4.3



A.4.3.1 Crystal Data

Empirical formula	$C_{24}H_{31}NO_5S$
Formula weight	445.56
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 13.313(3) Å α= 90°
	b = 13.970(3) Å β= 94.52(3)°
	c = 11.953(2) Å γ = 90°
Volume	2216.1(8) $Å^3$
Z	4
Density (calculated)	1.335 g/cm^3
Absorption coefficient	1.82 cm^{-1}
F(000)	952
Crystal size	0.30 x 0.25 x 0.25 mm^3

A.4.3.2 Intensity Measurements

Temperature	183(2) K
Wavelength	0.71073 Å
Theta range for data collection	2.12 to 27.90°.
Index ranges	-17<=h<=17, -14<=k<=18, -15<=l<=15
Reflections collected	8290
Independent reflections	5283 [R(int) = 0.0353]
Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å)

A.4.3.3 Structure Solution and Refinement

Completeness to theta = 27.90°	99.3 %
Absorption correction	None
Max. and min. transmission	0.9559 and 0.9474
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5283 / 0 / 280
Goodness-of-fit on F^2	1.079
Final R indices [I>2sigma(I)]	R1 = 0.0524, wR2 = 0.1347
R indices (all data)	R1 = 0.0990, wR2 = 0.1518
Largest diff. peak and hole	0.449 and -0.376 e.Å^{-3}

Table A.4.3 Atomic Coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for Alcohol **125**

atom	x	y	z	U(eq)
S(1)	1162(1)	9217(1)	8667(1)	35(1)
N(1)	1435(1)	8868(1)	9970(1)	31(1)
O(1)	1905(1)	8945(1)	7919(1)	47(1)
O(2)	886(1)	10209(1)	8708(1)	43(1)
O(3)	4449(1)	11275(1)	13801(1)	37(1)
O(4)	5005(2)	12574(2)	14729(2)	78(1)
O(5)	2717(1)	8993(1)	14522(1)	43(1)
C(1)	2321(2)	9252(1)	10682(2)	31(1)
C(2)	2999(2)	9983(2)	10194(2)	38(1)
C(3)	3961(2)	10117(2)	10955(2)	37(1)
C(4)	3733(2)	10429(2)	12147(2)	29(1)
C(5)	3066(1)	9655(1)	12636(2)	28(1)
C(6)	2819(2)	9840(2)	13835(2)	31(1)
C(7)	1838(2)	9597(2)	14256(2)	35(1)
C(8)	1037(2)	9147(2)	13474(2)	37(1)
C(9)	1430(2)	8754(2)	12410(2)	34(1)
C(10)	2084(2)	9490(1)	11880(2)	28(1)
C(11)	2320(2)	8248(2)	10266(2)	38(1)
C(12)	74(2)	8521(2)	8325(2)	32(1)
C(13)	-110(2)	8189(2)	7241(2)	40(1)
C(14)	-990(2)	7678(2)	6955(2)	46(1)

C(15)	-1672(2)	7490(2)	7717(2)	39(1)
C(16)	-1480(2)	7832(2)	8798(2)	41(1)
C(17)	-614(2)	8359(2)	9109(2)	39(1)
C(18)	-2614(2)	6910(2)	7391(2)	54(1)
C(19)	4719(2)	10678(2)	12851(2)	32(1)
C(20)	5406(2)	11341(2)	12249(2)	46(1)
C(21)	5901(2)	11952(2)	13188(2)	51(1)
C(22)	5112(2)	12004(2)	13995(2)	49(1)
C(23)	5279(2)	9807(2)	13342(2)	46(1)
C(24)	1495(2)	10127(2)	15248(2)	49(1)

Anisotropic displacement parameters ($Å^2 x\ 10^3$)

atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	38(1)	38(1)	29(1)	-1(1)	-6(1)	0(1)
N(1)	36(1)	29(1)	28(1)	0(1)	-8(1)	3(1)
O(1)	42(1)	67(1)	33(1)	-6(1)	3(1)	0(1)
O(2)	51(1)	34(1)	40(1)	4(1)	-11(1)	1(1)
O(3)	38(1)	40(1)	32(1)	-7(1)	-1(1)	-8(1)
O(4)	92(2)	67(1)	73(1)	-36(1)	-3(1)	-21(1)
O(5)	38(1)	50(1)	39(1)	17(1)	-4(1)	2(1)
C(1)	29(1)	34(1)	28(1)	-4(1)	-5(1)	1(1)
C(2)	41(1)	46(1)	26(1)	-4(1)	3(1)	-4(1)
C(3)	32(1)	48(1)	33(1)	-5(1)	4(1)	-6(1)
C(4)	29(1)	30(1)	28(1)	-1(1)	0(1)	0(1)
C(5)	25(1)	29(1)	29(1)	-1(1)	-2(1)	2(1)
C(6)	33(1)	33(1)	29(1)	5(1)	-2(1)	-3(1)
C(7)	33(1)	40(1)	31(1)	5(1)	0(1)	-1(1)
C(8)	32(1)	43(1)	36(1)	7(1)	3(1)	-5(1)
C(9)	33(1)	34(1)	34(1)	1(1)	-6(1)	-6(1)
C(10)	28(1)	26(1)	30(1)	-1(1)	-3(1)	1(1)
C(11)	41(1)	37(1)	34(1)	-5(1)	-11(1)	10(1)
C(12)	35(1)	30(1)	29(1)	0(1)	-9(1)	8(1)
C(13)	42(1)	42(1)	33(1)	-7(1)	-6(1)	6(1)

C(14)	51(2)	47(2)	37(1)	-16(1)	-13(1)	6(1)
C(15)	40(1)	31(1)	43(1)	-4(1)	-12(1)	7(1)
C(16)	40(1)	42(1)	38(1)	0(1)	-5(1)	-1(1)
C(17)	44(1)	42(1)	30(1)	-6(1)	-7(1)	0(1)
C(18)	47(2)	48(2)	63(2)	-11(1)	-17(1)	-3(1)
C(19)	30(1)	37(1)	30(1)	0(1)	0(1)	-3(1)
C(20)	39(1)	61(2)	38(1)	3(1)	0(1)	-15(1)
C(21)	48(2)	49(2)	53(2)	7(1)	-9(1)	-19(1)
C(22)	54(2)	44(2)	47(2)	-2(1)	-14(1)	-11(1)
C(23)	32(1)	47(2)	57(2)	1(1)	-13(1)	4(1)
C(24)	47(2)	64(2)	37(1)	-2(1)	11(1)	-9(1)

Appendix Five: Note Book Cross-Reference

Notebook Cross Reference

The following notebook cross reference has been included to facilitate access to the original spectroscopic data obtained for the compounds presented in this work. For each compound, a folder name is given which corresponds to an archived characterization folder hard copy and folders stored on CD. The folder name also corresponds to a notebook volume and page number where further details for each compound can be found (e.g. rwIII31 denotes notebook volume 3, page 31). The spectrum code for ^{1}H NMR, ^{13}C NMR, and FTIR refers to the file name given for individual spectra. The characterization notebook, spectral data, and discs are stored in the Wood Group archives.

Table A.5.1 Notebook Cross Reference for Compounds in Chapter 2.

Compound	Folder	^{1}H NMR	^{13}C NMR	FTIR
59	rwIII18a	rwIII18aH	rwIII18aC	rwIII18a.spc
60	rwIII18b	rwIII18bH	rwIII18bC	rwIII18b.spc
61	rwIII26a	rwIII26aH	rwIII26aC	rwIII26a.spc
62	rwIII27a	rwIII27aH	rwIII27aC	rwIII27a.spc
64	rwIII31	rwIII31H	rwIII31C	rwIII31.spc
65	rwIII37a	rwIII37aH	rwIII37aC	rwIII37a.spc
66	rwIV133	rwIV133H	rwIV133C	rwIV133.spc
67	rwIV135	rwIV135H	rwIV135C	rwIV135.spc

69	rwIII45b	rwIII45bH	rwIII45bC	rwIII45b.spc
69a	rwIII45a	rwIII45aH	rwIII45aC	rwIII45a.spc
70	rwIII284	rwIII284H	rwIII284C	rwIII284.spc
71	rwIV14	rwIV14H	rwIV14C	rwIV14.spc
73	rwIII63b	rwIII63bH	rwIII63bC	rwIII63b.spc
53	rwIII107	rwIII107H	rwIII107C	rwIII107.spc
78	rwIV13	rwIV13H	rwIV13C	rwIV13.spc
79	rwIV17	rwIV17H	rwIV17C	rwIV17.spc
80	rwIII288a	rwIII288aH	rwIII288aC	rwIII288a.spc
81	rwIII282	rwIII282H	rwIII282C	rwIII282.spc
82	rwIII286a	rwIII286aH	rwIII286aC	rwIII286a.spc
72	rwVIII194a	rwVIII194aH	rwVIII194aC	rwVIII194a.spc
83	rwVIII198	rwVIII198H	rwVIII198C	rwVIII198.spc
90	rwVIII226	rwVIII226H	rwVIII226C	rwVIII226.spc
91	rwIX214	rwIX214H	rwIX214C	rwIX214.spc
15	rwIX226	rwIX226H	rwIX226C	rwIX226.spc
16	rwIX230	rwIX230H	rwIX230C	rwIX230.spc
85	rwV82b	rwV82bH	rwV82bC	rwV82b.spc

Table A.5.2 Notebook Cross Reference for Compounds in Chapter 3.

Compound	Folder	^{1}H NMR	^{13}C NMR	FTIR
76	rwVIII234	rwVIII234H	rwVIII234C	rwVIII234.spc
101	rwIX249	rwIX249H	rwIX249C	rwIX249.spc
102	rwIX248	rwIX248H	rwIX248C	rwIX248.spc
105	rwIII168	rwIII168H	rwIII168C	rwIII168.spc
106	rwVII208b	rwVII208bH	rwVII208bC	rwVII208b.spc
107	rwV42	rwV42H	rwV42C	rwV42.spc
108	rwV26	rwV26H	rwV26C	rwV26.spc

109	rwIII144a	rwIII144aH	rwIII144aC	rwIII144a.spc
110	rwIV24	rwIV24H	rwIV24C	rwIV24.spc
111	rwIV38	rwIV38H	rwIV38C	rwIV38.spc
113	rwIV57b	rwIV57bH	rwIV57bC	rwIV57b.spc
114	rwIV99a	rwIV99aH	rwIV99aC	rwIV99a.spc
115	rwIV63	rwIV63H	rwIV63C	rwIV63.spc
116	rwIV86b	rwIV86bH	rwIV86bC	rwIV86b.spc
117	rwIV90d	rwIV90dH	rwIV90dC	rwIV90d.spc
118	rwIV105a	rwIV105aH	rwIV105aC	rwIV105a.spc
119	rwIV110	rwIV110H	rwIV110C	rwIV110.spc
120	rwV144	rwV144H	rwV144C	rwV144.spc
125	rwV62b	rwV62bH	rwV62bC	rwV62b.spc
45	rwV148a	rwV148aH	rwV148aC	rwV148a.spc
124	rwVIII148a	rwVIII148aH	rwVIII148aC	rwVIII148a.spc
126	rwVII66a	rwVII66aH	rwVII66aC	rwVII66a.spc
127	rwIX237	rwIX237H	rwIX237C	rwIX237.spc
128	rwV58	rwV58H	rwV58C	rwV58.spc
129	rwIX239	rwIX239H	rwIX239C	rwIX239.spc
130	rwIX238	rwIX238H	rwIX238C	rwIX238.spc
131	rwVIII152a	rwVIII152aH	rwVIII152aC	rwVIII152a.spc
132	rwIX235	rwIX235H	rwIX235C	rwIX235.spc
136	rwVI40a	rwVI40aH	rwVI40aC	rwVI40a.spc
136a	rwVI82b	rwVI82bH	rwVI82bC	rwVI82b.spc
139	rwVII144	rwVII144H	rwVII144C	rwVII144.spc
141	rwV104d	rwV104dH	rwV104dC	rwV104d.spc
142	rwV130a	rwV130aH	rwV130aC	rwV130a.spc
143	rwV252	rwV252H	rwV252C	rwV252.spc
148	rwVII170a	rwVII170aH	rwVII170aC	rwVII170a.spc
141	rwVIII30	rwVIII30H	rwVIII30C	rwVIII30.spc

149	rwVIII169	rwVIII169H	rwVIII169C	rwVIII169.spc
150	rwVIII58a	rwVIII58aH	rwVIII58aC	rwVIII58a.spc
151	rwVIII177c	rwVIII177cH	rwVIII177cC	rwVIII177c.spc
152	rwVIII71	rwVIII71H	rwVIII71C	rwVIII71.spc
153	rwVIII184	rwVIII184H	rwVIII184C	rwVIII184.spc
154	rwVIII48a	rwVIII48aH	rwVIII48aC	rwVIII48a.spc
155	rwVIII78	rwVIII78H	rwVIII78C	rwVIII78.spc
168	gkIV121b	gkIV121bH	gkIV121bC	gkIV121b.spc
168a	gkIV163	gkIV163H	gkIV163C	gkIV163.spc
169	gkIV165	gkIV165H	gkIV165C	gkIV165.spc
169a	gkIV163	gkIV163H	gkIV163C	gkIV163.spc
170	gkVII291	gkVII291H	gkVII291C	gkVII291.spc
171	gkVIII59	gkVIII59H	gkVIII59C	gkVIII59.spc
172	rwIX98	rwIX98H	rwIX98C	rwIX98.spc
173	rwIX58	rwIX58H	rwIX58C	rwIX58.spc
175	rwVIII214	rwVIII214H	rwVIII214C	rwVIII214.spc
176	rwVIII216	rwVIII216H	rwVIII216C	rwVIII216.spc
179	rwIX101	rwIX101H	rwIX101C	rwIX101.spc
180	rwIX104	rwIX104H	rwIX104C	rwIX104.spc
42	rwIX168	rwIX168H	rwIX168C	rwIX168.spc
184	rwIX103	rwIX103H	rwIX103C	rwIX103.spc
185	rwIX106	rwIX106H	rwIX106C	rwIX106.spc
186	rwIX142	rwIX142H	rwIX142C	rwIX142.spc

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About the Author

Ryan D. White was born January 28, 1977, in Akron, Ohio to Sherry A. and Roger D. White. Following his older siblings Erik and Jennifer, Ryan attended elementary, middle, and high school in the Springfield Township School District. During this time, Ryan enjoyed spending much of his time enjoying the outdoors and playing golf. In his sophomore year he qualified for Regional golf competition; this was the first time Springfield High had been represented in over twenty years.

After graduating from high school in 1995, Ryan moved to Alliance, Ohio were he attended Mount Union College to pursue a long standing interest in chemistry. The small campus facilitated Ryan's involvement in a number of activities including serving as a resident assistant, preview guide, chess club president, and chemistry tutor. His appeal to chemistry was nurtured by the one-on-one attention from his chemistry Profs. Truman Turnquist, Arthur Murdoch, and Faye Hollaway; in two classes he was only student. Ryan spent his summers working on a variety of research projects including the synthesis of water-soluble polymers at the University of Akron under the guidance of Prof. William Brittain.

In May of 1999 Ryan graduated *summa cum laude* from Mount Union College with a Bachelor's Degree in chemistry. In June of 1999, Ryan left the beloved confines of Ohio to begin graduate studies at Yale University. He received his Master's Degree in 2000 and Doctorate in 2003 under the direction of Professor John L. Wood. Ryan will be moving to Cambridge, Massachusetts where he has accepted a medicinal chemistry position with Amgen.