NOTE TO USERS

Synthetic Studies on the Kalihinane Diterpenoids

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Abstract

Synthetic Studies on the Kalihinane Diterpenoids

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Kalihinol A (**1**) was isolated from the Guamanian marine sponge *Acanthella cavernosa* in 1984. To date, more than forty compounds (**2-46**) related to **1** have been isolated, and many of these highly-functionalized diterpenoids possess very unique biological activities. In particular, **1** has been shown to exhibit extremely potent antimalarial activity against *Plasmodium falciparum*.

In light of the fascinating chemical structures and intriguing biological profile of members of the kalihinane family, a project directed towards the total synthesis of **1** and related kalihinanes has been conducted. In 2003, the first total synthesis of (±)-kalihinol C ((±)-**3**) was accomplished, the synthetic strategy of which relied upon a series of substrate-controlled, diastereoselective reactions in order to functionalize the decalin core (**66→67**, **68→69**, **77→82**) and install the pendant tetrahydrofuran ring (**82→83**, **82→84**, **88→89**). Current efforts in our laboratory have been focused upon the total synthesis of **1** with an emphasis upon improving the efficiency of the aziridination reaction (**77→150a**, **77→174**) and the development of novel synthetic methodology. Such efforts have led to the application of rhodium (II) perfluorobutyramide (**199**) in conducting a variety of olefin aziridinations (**200→202-4**). Furthermore, a series of kalihinane analogs have been synthesized and assayed in an effort to understand the role of the kalihinane carbocycle and the isonitriles in antimalarial activity.

To W6

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I would first like to express my sincere appreciation for my advisor, Professor John L. Wood. I admire John on several levels – as a chemist, as a teacher, and as a mentor. I've seen John give several presentations at conferences, and he always attributes the successes of his laboratory to his students' efforts instead of his own. It is this selfless attitude which drives each member of this research group to respect one another and support each other's projects wholeheartedly, and it is this support system which leads to the group's successes. I'm sure such camaraderie is not the norm in most synthetic chemistry laboratories around the world, but it certainly has been the case during my time at the hallowed center of the Sterling Chemistry Laboratory. And despite John's modest assertions, he's the one responsible for creating this environment and bringing the group to the level at which it is today.

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List of Abbreviations

$[\alpha]^{20}_D$	specific rotation at 20°C and wavelength of sodium D line
AcOH	acetic acid
AFA	acetic formic anhydride
$AgClO_4$	silver perchlorate
aq	aqueous
Boc	*tert*-butoxycarbonyl
Boc_2O	di-*tert*-butyl dicarbonate
Bn	benzyl
BORSM	based on recovered starting material
Bu	butyl
BuLi	butyl lithium
c	concentration in g/mL
C	carbon
°C	degrees Celsius
calc'd	calculated
CCl_4	carbon tetrachloride
$CDCl_3$	chloroform-*d*
C_6H_6	benzene
CH_3CN	acetonitrile
$CHCl_3$	chloroform
CH_2Cl_2	methylene chloride
CI	chemical ionization
comp	complex
*m*CPBA	*meta*-chloroperoxybenzoic acid
$Cu(OTf)_2$	copper trifluoromethanesulfonate
Cy	cyclohexyl
δ	chemical shift in ppm downfield from Me_4Si
d	doublet
dd	doublet of doublets
ddd	doublet of doublets of doublets
DIBAL	diisobutylaluminum hydride
DMDO	dimethyl dioxirane
DMEM	Dulbecco's Eagle Medium
DMF	dimethyl formamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dt	doublet of triplets
ee	enantiomeric excess
EI	electron impact
equiv	equivalent
Et	ethyl
Et_2O	ethyl ether
EtOAc	ethyl acetate

Et_2NH	diethylamine
Et_3N	triethylamine
FAB	fast atom bombardment
FC-72	perfluoro-*n*-hexane
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
IC_{50}	inhibitory concentration (50% observed inhibition)
J	coupling constant
L	liter(s), ligand
LDA	lithium diisopropylamide
μ	micro
m	medium (FTIR), multiplet (NMR)
mm	millimeters
mmol	millimole
M	moles per liter, metal
Me	methyl
MeOH	methanol
mg	milligrams
MgO	magnesium oxide
$MgSO_4$	magnesium sulfate
mp	melting point
MHz	megahertz
min	minute(s)
mol	mole(s)
mmol	millimole(s)
mp	melting point
Ms	methanesulfonyl
MTS	(3-(4,5-dimethylthiazol-2-yl)-5-(3-carbomethoxyphenyl)-2-(4-sulfophenyl-2H-tetrazolium salt
m/z	mass to charge ratio
Na	sodium
$NaBH_4$	sodium borohydride
NaN_3	sodium azide
NH_4Cl	ammonium chloride
NaCl	sodium chloride
NaH	sodium hydride
Na_2CO_3	sodium carbonate

$NaHCO_3$	sodium bicarbonate
NaOAc	sodium acetate
NaOMe	sodium methoxide
Na_2SO_4	sodium sulfate
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
PhINNs	(N-(*p*-nitrobenzenesulfonyl)imino)phenyliodinane
PhINTs	(N-(*p*-tolylsulfonyl)imino)phenyliodinane
$PhI(OAc)_2$	Diacetoxyiodobenzene
PPh_3	triphenylphosphine
ppm	parts per million
q	quartet
$Rh_2(OAc)_4$	rhodium (II) acetate
$Rh_2(pfb)_4$	rhodium (II) perfluorobutyrate
$Rh_2(pfm)_4$	rhodium (II) perfluorobutyramide
$Rh_2(tfacam)_4$	rhodium (II) trifluoroacetamide
s	singlet (NMR), strong (FTIR)
SiO_2	silicon dioxide, silica gel
soln	solution
t	triplet
td	triplet of doublets
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tri(methyl)silyl
Ns	*para*-nitrobenzenesulfonyl
Ts	toluenesulfonyl
w	weak

Chapter 1

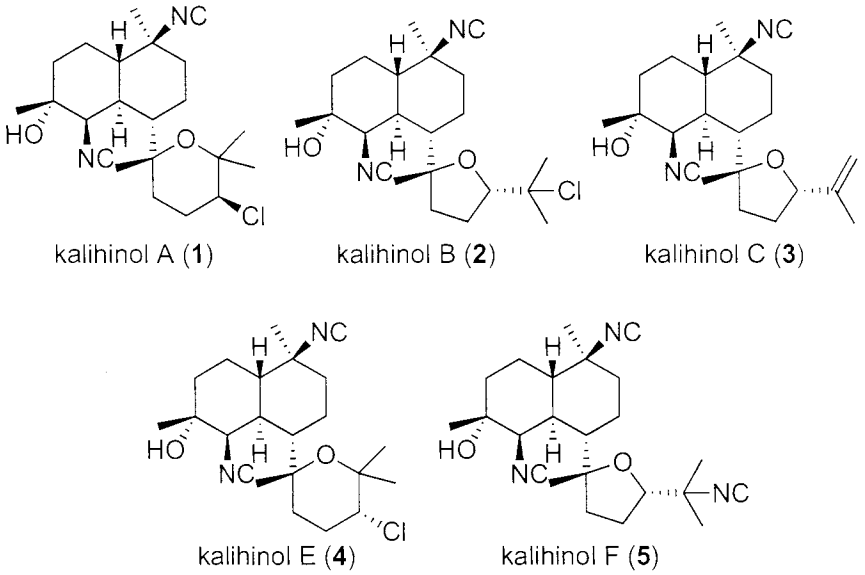
The Kalihinane Family: A Unique Class of Structurally Intriguing and Biologically Active Natural Products

1.1 The Kalihinane Family: Isolation

1.1.1 Scheuer's Initial Isolations from *Acanthella* sp.

In the spring of 1981, Prof. Paul J. Scheuer and co-workers collected an orange-red tuberculate sponge from Apra Harbor off the coast of Guam.[1-3] The lyophilized sponge, identified as belonging to *Acanthella* sp., was extracted using the Kupchan partition scheme[4] and was purified by gel chromatography (Sephadex LH-20) into three major fractions. Each of these fractions was assayed against *Bacillus subtilis, Staphylococcus aureus, Candida albicans, Pseudomonas aeruginosa*, and *Escherichia coli*, and the third fraction collected proved to be the most active. As a result, this fraction was further separated (BioSil A column) into two groups of compounds. Each compound was resolved using reverse-phase (KC 18F) thin-layer chromatography. After spectroscopic analysis, these isolates were determined to be highly functionalized tricyclic diterpenes, and they were named the kalihinanes in honor of Kalihi, Hawaii, the childhood residence of Prof. Scheuer (Figure 1.1).

Figure 1.1

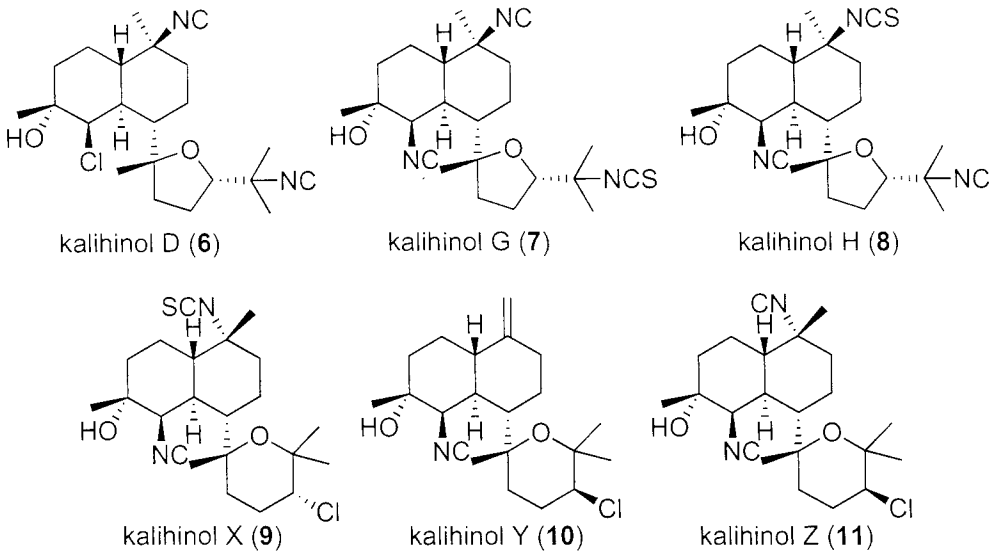


Kalihinol A ((**1**), 11.5 mg, α_D +16° (*c* 1, $CHCl_3$, mp 233°C)), recrystallized from hexanes) was the major constituent of the less polar compounds isolated from the BioSil A column. The other two less polar compounds, kalihinol B ((**2**), 1 mg, α_D +10° (*c* 1, $CHCl_3$)) and kalihinol C ((**3**), 2 mg, α_D +6° (*c* 1, $CHCl_3$)) could not be recrystallized. The two more polar compounds, kalihinol E ((**4**), 5 mg, α_D +4° (*c* 1.0, $CHCl_3$, mp 197-199 °C)) and kalihinol F ((**5**), 20 mg, α_D +8° (*c* 1.0, $CHCl_3$, mp 176-178°C)), were both recrystallized from hexanes/acetone, and kalihinol F (**5**) was elucidated structurally by X-ray diffraction analysis. The assignment of kalihinol A (**1**) and its C(14) epimer, kalihinol E (**4**), are reversed in the initial communications;[2,3] these compounds are correctly re-assigned in a later publication.[1]

Scheuer and co-workers reported the isolation of six additional members of the kalihinane family three years after their seminal disclosure.[1] Trace quantities of

kalihinols D (**6**), G (**7**), and H (**8**) were extracted from the Guamian *Acanthella* sp., and kalihinols X (**9**), Y (**10**), and Z (**11**) were found in a Fijian *Acanthella* sp. (Figure 1.2).

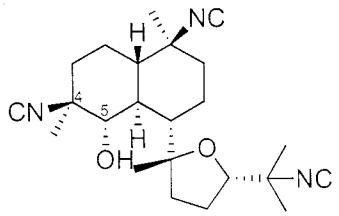
Figure 1.2



1.1.2 Crews' Isolation from *Acanthella cavernosa*

Concurrent with Scheuer's isolation efforts off the coasts of Guam and Fiji, Crews and co-workers of the University of California Santa Cruz were also harvesting sponges in the Fijian coral reefs. In 1988, Crews revealed the discovery of a new member of the kalihinane family, isokalihinol F (**12**) (Figure 1.3).[5] Isokalihinol F (**12**) was extracted from the Fijian *Acanthella cavernosa* sponge along with kalihinols A (**1**) and F (**5**). The isolation of **12**, with its transposed functional groups at the C(4)-C(5) positions, provided significant insight into the mechanism of isonitrile diterpenoid biosynthesis (*vide infra*).

Figure 1.3

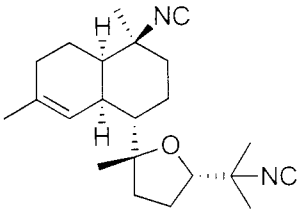


isokalihinol F (**12**)

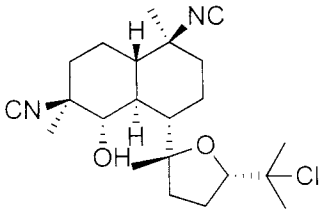
1.1.3 Fusetani's and Clardy's Isolation from *Acanthella klethra*

In 1990, researchers at the University of Tokyo and at Cornell University jointly reported the isolation of two new kalihinane diterpenes, kalihinene (**13**) and isokalihinol B (**14**), from *Acanthella klethra* which was collected near Kuchinoerabu Island of the Satsunan Archipelago (Figure 1.4).[6] Both **13** and **14** demonstrated antifungal activity against *Mortierella ramannianus* and *Penicillium chrysogenum* as well as cytotoxic activity against P388 murine leukemia cells. Notably, kalihinene (**13**) was structurally dissimilar from all the other kalihinanes known at that time due to its *cis*-decalin ring framework and unsaturation at the C(4)-C(5) positions.

Figure 1.4



kalihinene (**13**)

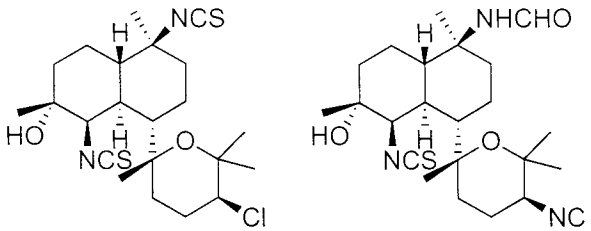


isokalihinol B (**14**)

1.1.4 Crews' Second Isolation from *Acanthella cavernosa*

In 1991, Crews disclosed the isolation of two new kalihinanes, kalihinol I (**15**) and kalihinol J (**16**), from the *Acanthella cavernosa* sponge harvested off the coast of Thailand (Figure 1.5).[7] The presence of an isonitrile on the tetrahydropyran ring of **16** was unprecedented for the kalihinane family at the time of this disclosure and remains so to this day.

Figure 1.5

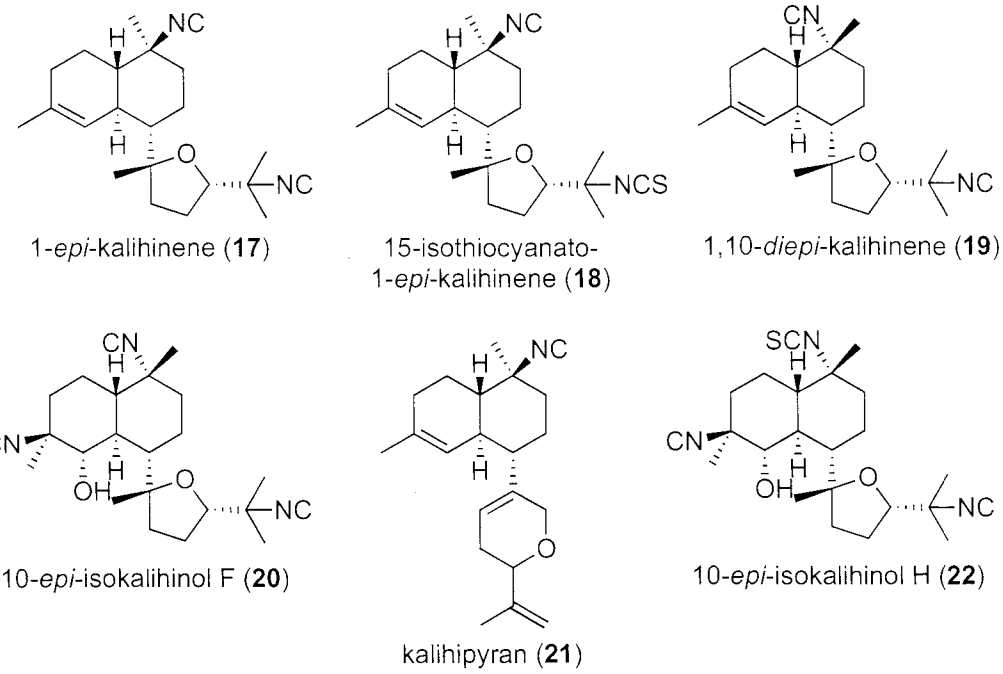


kalihinol I (**15**) kalihinol J (**16**)

1.1.5 Faulkner's Isolation from *Acanthella cavernosa*

Three years later, Faulkner and co-workers discovered six more kalihinanes from a specimen of *Acanthella cavernosa* in the Seychelles. These compounds were named 1-*epi*-kalihinene (**17**), 15-isothiocyanato-1-*epi*-kalihinene (**18**), 1,10-*diepi*-kalihinene (**19**), 10-*epi*-isokalihinol F (**20**), kalihipyran (**21**), and 10-*epi*-isokalihinol H (**22**) (Figure 1.6).[8]

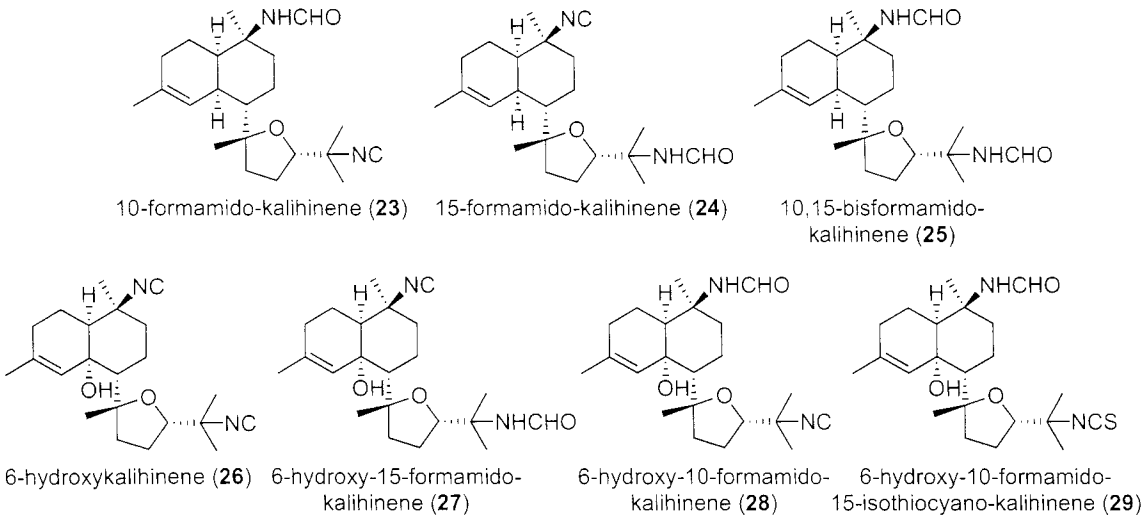
Figure 1.6



1.1.6 Crews' and Clardy's Isolation from *Acanthella cavernosa*

In 1994, Crews and Clardy reported the discovery of additional kalihinanes isolated from a Fijian *Acanthella cavernosa* sponge which had been transplanted into an aquarium in the Crews' laboratory in the early 1990s. In addition to previously isolated kalihinol A (**1**), isokalihinol F (**12**), and kalihinene (**13**), the transplanted sponge produced seven new compounds: 10-formamido-kalihinene (**23**), 15-formamido-kalihinene (**24**), 10,15-bisformamido-kalihinene (**25**), 6-hydroxy-kalihinene (**26**), 6-hydroxy-15-formamido-kalihinene (**27**), 6-hydroxy-10-formamido-kalihinene (**28**), and 6-hydroxy-10-formamido-15-isothiocyano-kalihinene (**29**) (Figure 1.7).[9] In addition to substantially increasing the number of known kalihinanes in the literature, this report also served to augment the known diversity of the kalihinane family by revealing the existence of kalihinanes bearing an axial hydroxyl group at the C(6) position.

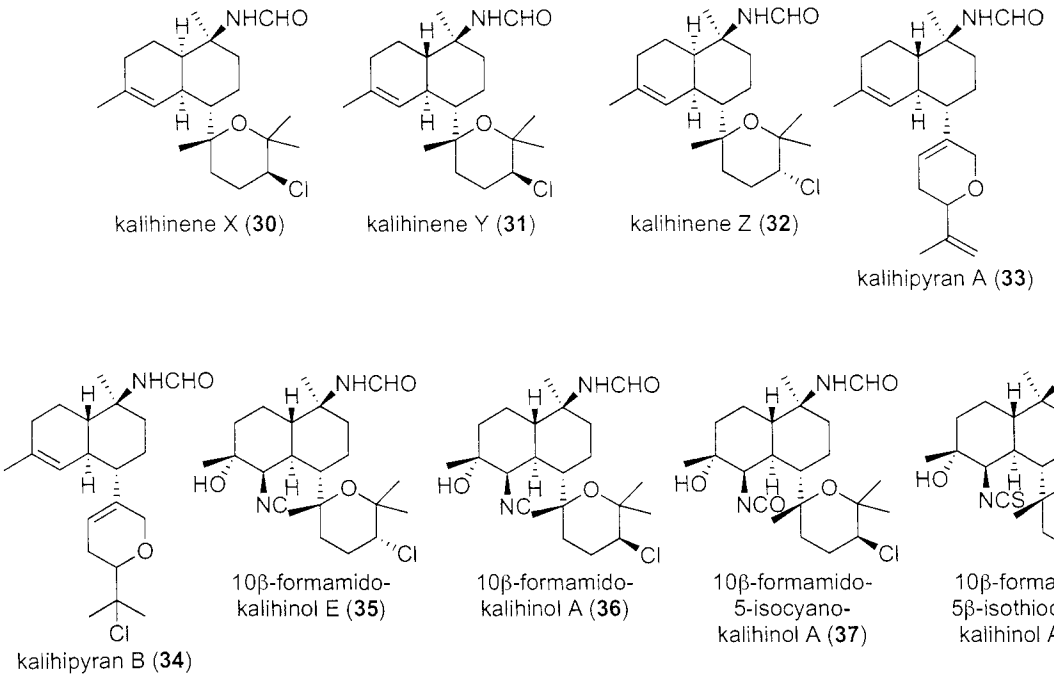
Figure 1.7



1.1.7 Fusetani's Isolations from *Acanthella cavernosa*

In three publications in 1995 and 1996, Fusetani and co-workers disclosed the isolation of nine novel kalihinanes from *Acanthella cavernosa* which exhibited antifouling activity against larvae of the barnicle *Balanus amphitrite*.[10-12] These compounds became known as kalihinene X (**30**), kalihinene Y (**31**), kalihinene Z (**32**), kalihipyran A (**33**), kalihipyran B (**34**), 10β-formamido-kalihinol E (**35**), 10β-formamido-kalihinol A (**36**), 10β-formamido-5-isocyanokalihinol A (**37**), and 10β-formamido-5β-isocyanokalihinol A (**38**) (Figure 1.8).

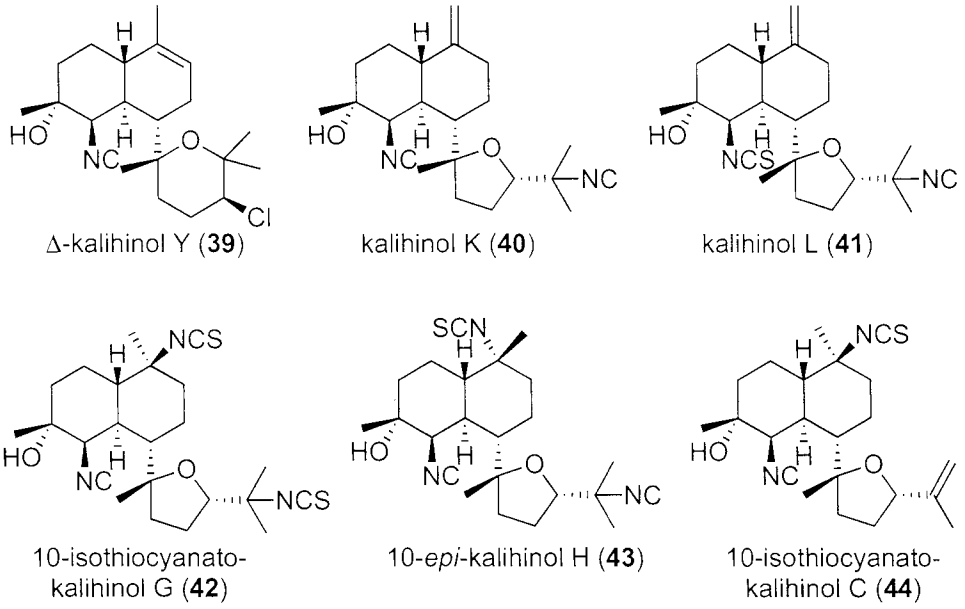
Figure 1.8



1.1.8 Schmitz's Isolation from *Phakellia pulcherrima*

In 1996, Schmitz and co-workers discovered six new kalihinanes (Δ-kalihinol Y (**39**), kalihinol K (**40**), kalihinol L (**41**), 10-isothiocyanatokalihinol G (**42**), 10-*epi*-kalihinol H (**43**), and 10-isothiocyanatokalihinol C (**44**)) from the sponge *Phakellia pulcherrima* originating in the Phillippines (Figure 1.9).[13] Interestingly, these kalihinanes were the first to be isolated from a sponge other than *Acanthella* sp.

Figure 1.9



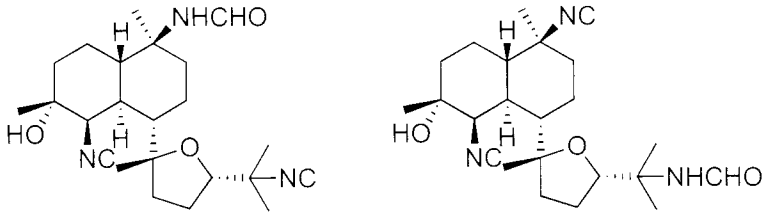
Δ-kalihinol Y (**39**) kalihinol K (**40**) kalihinol L (**41**)

10-isothiocyanato-kalihinol G (**42**) 10-*epi*-kalihinol H (**43**) 10-isothiocyanato-kalihinol C (**44**)

1.1.9 Ireland's Isolation from *Acanthella cavernosa*

Most recently, Ireland and co-workers at the University of Utah, in collaboration with the University of the Philippines and Wyeth Research, have isolated two new analogs of kalihinol F entitled 10-formamido-kalihinol F (**45**) and 15-formamido-kalihinol F (**46**) (Figure 1.10).[14] These research groups analyzed two species of *Acanthella cavernosa* extracts in an effort to detect novel bacterial folate biosynthesis inhibitors through a structure-activity relationship study.

Figure 1.10



10-formamido-kalihinol F (**45**) 15-formamido-kalihinol F (**46**)

1.2 The Kalihinane Family: Classification

1.2.1 The Kalihinane Subclasses

To date, forty-six members of the kalihinane family have been isolated from three marine sponges: *Acanthella cavernosa*, *Acanthella klethra*, and *Phakellia pulcherrima*. All members of this family possess several similar structural features such as a decalin core, a pendant ring, and a variety of functionalization including isonitrile, isothiocyanate, chlorine, formamide, isocyanate, and/or hydroxyl groups. This diverse class of natural products can be divided into two general subclasses based upon the nature of the pendant ring: 1) the tetrahydrofuran subclass, and 2) the di- and tetrahydropyran subclass.

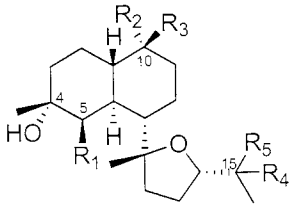
1.2.2 Tetrahydrofuran Subclass

The tetrahydrofuran subclass can be further classified into three groups: the kalihinols, the isokalihinols, and the kalihinenes. As illustrated in Figure 1.11, the kalihinols, the most populated group of tetrahydrofuran-containing kalihinanes, have a common *trans*-decalin framework, an α-hydroxyl group at C(4), and a variety of functionality at the C(5), C(10), and C(15) positions. The second group is the isokalihinols: *trans*-decalin diterpenoids in which the hydroxyl group and isonitrile at the C(4) and C(5) positions have been inverted. The third group is known as the kalihinenes, and these compounds have unsaturation between the C(4) and C(5) positions with varying functionality at C(10) and C(15). Interestingly, the kalihinenes are the only

group in which some of the members possess a *cis*-decalin backbone and/or a hydroxyl group at C(6).

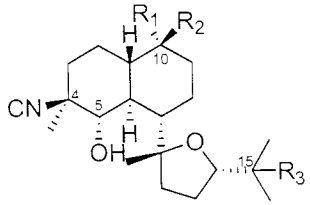
Figure 1.11

Tetrahydrofuran-containing *trans*-decalin kalihinols



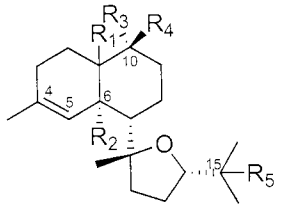
R_1 = NC, Cl, NCS
R_2 = CH_3, olefin, NCS
R_3 = NC, NCS, olefin, CH_3, NHCHO
R_4 = Cl, olefin, NC, NCS, NHCHO
R_5 = CH_3, olefin

Tetrahydrofuran-containing *trans*-decalin isokalihinols



R_1 = CH_3, NC, NCS
R_2 = NC, CH_3
R_3 = NC, Cl

Tetrahydrofuran-containing *trans*-and *cis*-decalin kalihinenes



R_1 = α-H, β-H
R_2 = H, OH
R_3 = CH_3, NC
R_4 = NC, CH_3, NHCHO
R_5 = NC, NCS, NHCHO, NCS

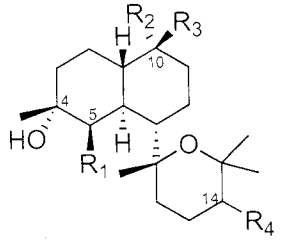
1.2.3 Di- and tetrahydropyran Subclass

While the tetrahydrofuran kalihinanes are decorated with a diverse array of functional groups appended to the sidechain of the tetrahydrofuran ring, the di- and tetrahydropyran kalihinanes lack such diversity. In fact, with the exception of kalihinol J (**16**), all of the tetrahydropyran kalihinanes bear a chlorine at the C(14) position. As illustrated in Figure 1.12, the di- and tetrahydropyran subclass can be divided into three groups: the tetrahydropyran *trans*-decalin kalihinols, the chlorotetrahydropyran *trans*- and *cis*-decalin kalihinenes, and the *trans*-decalin kalihipyrans. The decalin core of these compounds is functionalized in a manner similar to that of the tetrahydrofuran series, bearing common functional groups at the C(4), C(5), C(10), and C(14) positions. This repetitive structural pattern is suggestive of the biosynthesis mechanism performed by the

marine sponges, and a discussion of this process, as it relates to kalihinol A (**1**), is addressed in the following section.

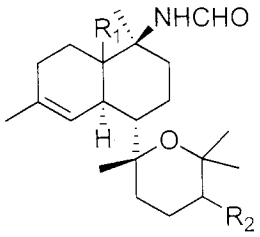
Figure 1.12

Tetrahydropyran-containing *trans*-decalin kalihinols



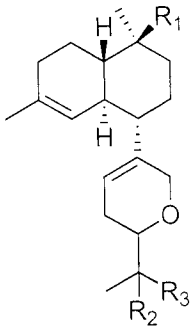
R_1 = NC, NCS, NCO
R_2 = CH_3, NCS, olefin, NC
R_3 = NC, CH_3, olefin, NCS, NHCHO
R_4 = α-Cl, β-Cl, NC

Chlorotetrahydropyran-containing *trans*-and *cis*-decalin kalihinenes



R_1 = α-H, β-H
R_2 = α-Cl, β-Cl

Dihydropyran-containing *trans*-decalin kalihinenes



R_1 = NC, NHCHO
R_2 = Cl, olefin
R_3 = CH_3, olefin

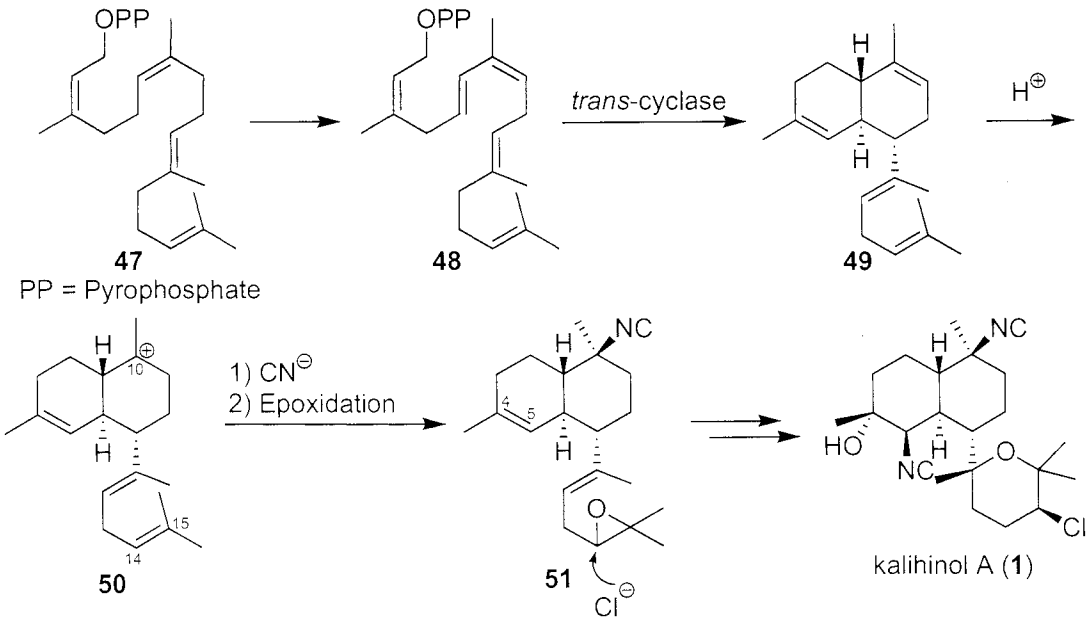
1.3 Biosynthesis of Kalihinol A and Related Kalihinanes

The unique structural motifs of the kalihinane family provide tremendous insight into the biosynthesis of this class of natural products. The frequent incorporation of the rare isonitrile functional group is of particular interest, and Scheuer and co-workers have conducted extensive studies in order to determine the specific precursor of this functionality. Initally, it was believed that formamides were the biosynthetic precursors to isonitriles in the marine sponge *Halichondria* sp.[15] More than one decade later, however, Scheuer disproved his own hypothesis by conducting an incorporation experiment with the marine sponge *Acanthella* sp. utilizing [^{14}C]-labeled cyanide.[16,17]

This label was traced to the isonitriles of kalihinol F (**5**), which conclusively determined that inorganic cyanide from the ocean was in fact the biosynthetic precursor to the isonitrile functional group in these marine diterpenoids.[18]

The biosynthesis of the kalihinanes has been explained by Crews and Clardy[9] in 1994, and their work was recently reviewed by Prof. Mary J. Garson, an expert in the field of marine natural product biosynthesis.[19,20] The structural variation among the kalihinane diterpenoids suggests the intermediacy of stable secondary and tertiary carbocations throughout the biosynthesis. A summary of the proposed biosynthesis of kalihinol A is shown in Scheme 1.1.

Scheme 1.1



It is proposed that the biosynthesis of kalihinol A (**1**) originates from geranyl geraniol pyrophosphate (**47**), which undergoes oxidation to tetraene **48** and cyclization in the presence of *trans*-cyclase to afford *trans*-decalin **49**. Formation of a stable, tertiary

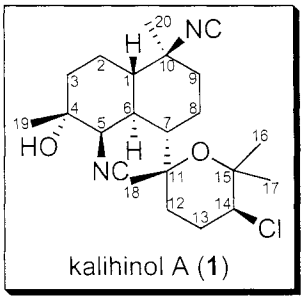
carbocation **50** is followed by cyanide incorporation at the C(10) position, and epoxidation of the C(14)-C(15) olefin provides epoxide **51**. At this intermediate, the biosynthetic pathways for the tetrahydrofuran and tetrahydropyran subclasses diverge based upon the regioselectivity of the nucleophilic addition at the epoxide. In the case of kalihinol A (**1**), a nucleophilic source of chloride, which is plentiful in ocean waters, is thought to open the epoxide at the less hindered C(14) position. Tetrahydropyran formation, followed by epoxidation of the C(4)-C(5) olefin and cyanide delivery, leads to formation of the natural product.

1.4 Structural Proof of Kalihinol A

1.4.1 ^{1}H NMR and ^{13}C NMR Spectroscopy

The structural characteristics of the kalihinanes have been elucidated by a variety of techniques including ^{1}H NMR, ^{13}C NMR, IR, HREIMS, circular dichroism, and X-ray crystallographic analysis. For kalihinol A, initial ^{1}H NMR and ^{13}C NMR studies provided tremendous insight into the structure of this highly-functionalized diterpenoid (Figure 1.13). The ^{1}H NMR and ^{13}C NMR data for the discernable peaks in the kalihinol A spectra is listed in Table 1.1.[1]

Figure 1.13



kalihinol A (**1**)

Table 1.1

Carbon	^{1}H NMR (ppm)	^{13}C NMR (ppm)
1		42.3
2		21.6
3		32.0
4		70.3
5	4.51 (1H, br s)	63.7 (br t)
6		35.9
7		48.4
8		21.9
9		39.7
10		59.7 (br t)
11		77.0
12		37.9
13		27.3
14	3.72 (1H, dd, J = 12, 5 Hz)	64.1
15		75.9
16	1.33 (3H, s)	22.7
17	1.33 (3H, s)	30.5
18	1.15 (3H, s)	19.1
19	1.40 (3H, s)	28.8
20	1.29 (3H, br t)	20.7

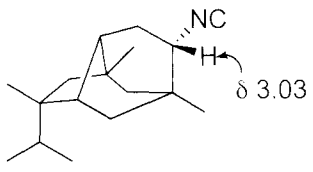
The five methyl peaks, C(16) through C(20), in kalihinol A (**1**) were assigned unambiguously due to their characteristic chemical shifts and peak types. The C(20)

methyl protons, which are adjacent to the C(10) isonitrile, appeared as a triplet because protons and carbons in close proximity to isonitriles are known to frequently undergo coupling with the ^{14}N atom.[21] The phenomenon was also observed in the C(5) and C(10) carbon signals which appeared as broad triplets.

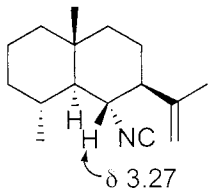
Additionally, the ^{13}C NMR provided tremendous insight when discerning between kalihinanes bearing a tetrahydrofuran or tetrahydropyran ring. For example, the ether carbons (C(11) and C(15)) in kalihinol A (**1**) appeared at δ 77.0 and δ 75.9, respectively, whereas tetrahydrofuran kalihinanes displayed ether carbons at lower field (i.e., δ 87.3 and δ 82.8 for kalihinol F (**5**)).

While the spectral data logically pointed to a diterpenoid with two isonitrile groups, two signals were particularly difficult to assign. First, the assignment of the signal at δ 4.51 to the C(5) proton (adjacent to the isonitrile) was questioned because it was remarkably far downfield for a hydrogen adjacent to an isonitrile. The chemical shifts for methines attached to isonitriles had been reported at δ 3.03 and δ 3.27 in the natural products 2-isocyanopupukeanane (**52**)[22] and acanthellin-1 (**53**),[23] respectively (Figure 1.14).

Figure 1.14



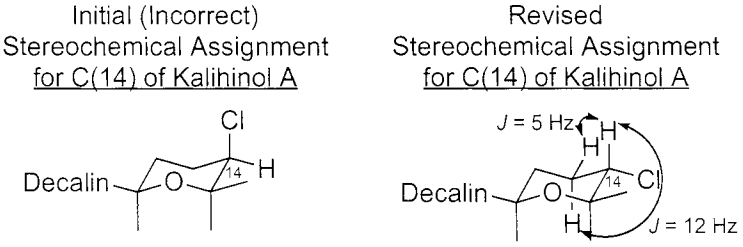
2-isocyanopupukeanane (**52**)



acanthellin-1 (**53**)

In addition, the signal at δ 3.72 in the ^{1}H NMR of kalihinol A (**1**) was also problematic to assign, and in Scheuer's preliminary communications,[2,3] this peak was incorrectly assigned as the β, equatorially-oriented hydrogen adjacent to the chlorine at C(14) (Figure 1.15). Reassessment of the coupling constant of this doublet of doublets (*J* = 12, 5 Hz) was indicative of an axially-oriented hydrogen.[24] As a result, the stereochemical assignment of the C(14) chlorine was re-assigned in a subsequent disclosure.[1] Ultimately, X-ray crystallographic analysis proved that the signals at δ 4.51 and δ 3.72 were correctly assigned to the C(5) and C(14) α-hydrogens, respectively.[1]

Figure 1.15



1.4.2 IR and MS Spectroscopy

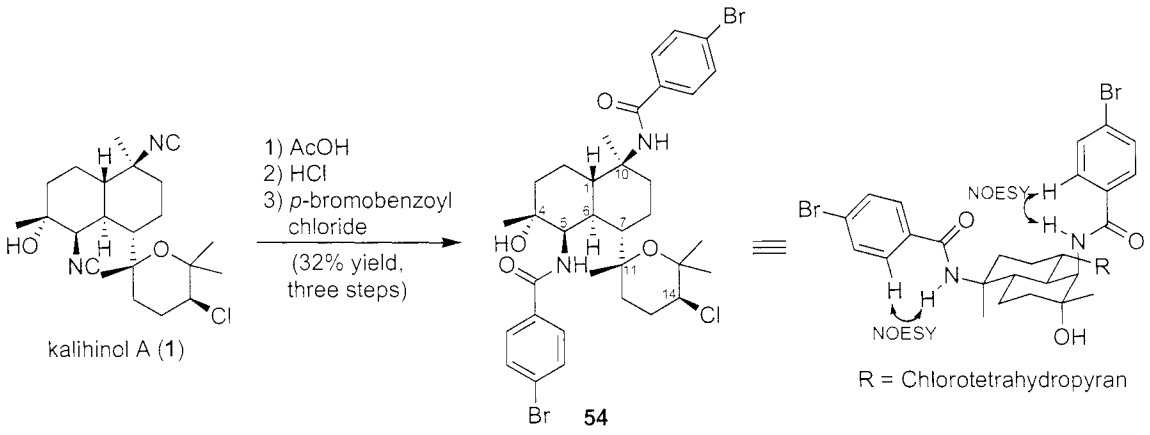
The application of IR spectroscopy was also an important component in the structural elucidation of kalihinol A (**1**). For example, the assumed presence of an isonitrile was corroborated by a band in the IR spectrum at the distinctive absorbance for the isonitrile functionality (2135 cm^{-1}). In addition, the broad bands at 3595 and 3390 cm^{-1} in the IR spectrum indicated the presence of a free hydroxyl group, and this functionality was deemed to be tertiary based upon its lack of reactivity when exposed to acetic anhydride in pyridine.[1]

Lastly, the use of high-resolution electron ionization mass spectroscopy (HREIMS) confirmed the structure of kalihinol A (**1**). Two major peaks in the HREIMS were observed at *m/z* 357.2561 and *m/z* 330.2424 which corresponded to the [$M^{+\cdot}$ - Cl] (calc. for $C_{22}H_{33}N_2O_2$ 357.2542) and [$M^{+\cdot}$ - Cl - HCN] (calc. for $C_{21}H_{32}NO_2$ 330.2433) molecular ions, respectively.

1.4.3 Determination of Absolute Configuration

In 1999, Yamada and co-workers determined the absolute configuration of kalihinol A (**1**) using the CD exciton chirality method.[25,26,27] Kalihinol A (**1**) was converted into bis-*para*-bromobenzamide **54** over three steps in 32% yield (Scheme 1.2). The conformation of the two bromobenzamido functionalities was determined to be *s-trans* by a NOESY correlation. The CD spectrum of **54** indicated negative chirality between the two chromophores, and thus the absolute stereochemistry for the eight chiral centers in kalihinol A (**1**) was determined to be 1*S*, 4*R*, 5*R*, 6*S*, 7*S*, 10*S*, 11*R*, and 14*S*.

Scheme 1.2



1.5 Prior Work by Others

1.5.1 Assessment of the Biological Activity of the Kalihinanes

Several members of the kalihinane family have demonstrated potent *in vitro* activity in biological assays. The first kalihinane isolates from *Acanthella cavernosa* were determined to be active against *Bacillus subtilis, Staphylococcus aureus,* and *Candida albicans*, and during the course of the past twenty years, additional biological screens of these and other kalihinanes have revealed antimicrobial, antifungal, cytotoxic, antifouling, and anthelmintic properties as well.[2,1,6,11,3,7,29,5,12] Most notably, several kalihinane diterpenoids have exhibited remarkable antimalarial activity, and kalihinol A (**1**) in particular has demonstrated extremely potent inhibitory activity against the most lethal form of the malaria parasite, *Plasmodium falciparum*.[30] A detailed discussion of the antimalarial activity of kalihinol A (**1**) and related compounds is provided in Chapter 4.

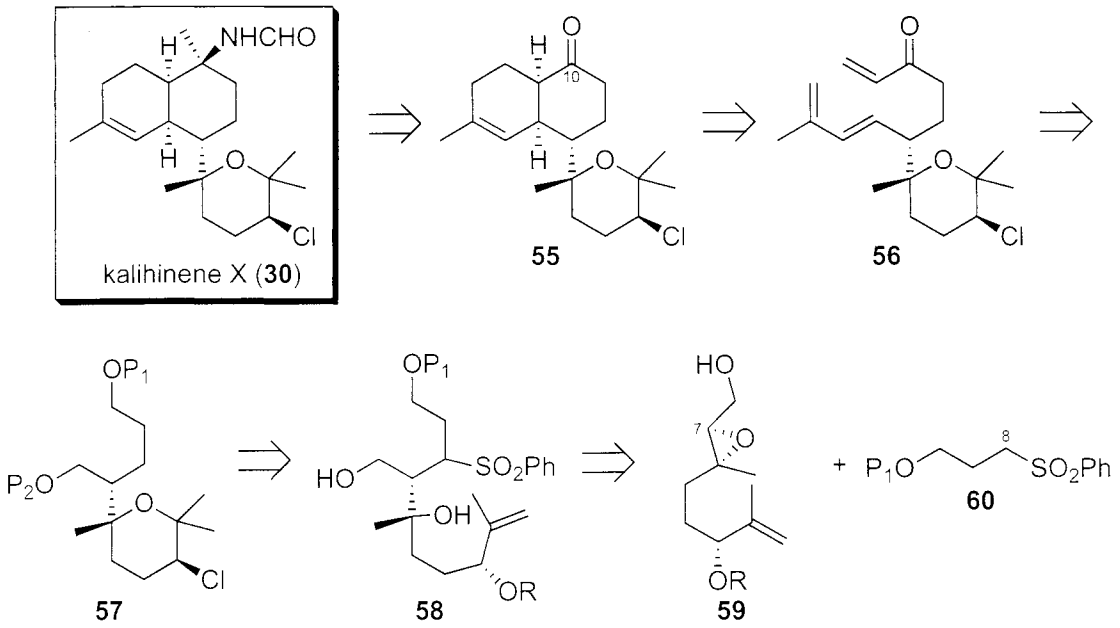
1.5.2 Yamada's Total Synthesis of (+)-Kalihinene X

While kalihinol A (**1**) has been the focus of a variety of biological studies, there are no published reports of total synthesis projects directed toward **1** by other research groups. However, during the course of our studies on (±)-kalihinol C (**3**), Yamada and co-workers reported the total synthesis of (+)-kalihinene X (**30**), the first total synthesis of a member of the kalihinane family.[28] Kalihinene X (**30**) is a chlorotetrahydropyran *cis*-decalin kalihinene bearing an equatorial formamide at the C(10) position. The completion of this enantioselective total synthesis required twenty-eight steps in 2.9%

overall yield. The optical rotation of their synthetic material ($[\alpha]^{27}_D$ +24.4 (*c* 0.34, $CHCl_3$)) matched the sign and magnitude of the natural kalihinene X (**30**) ($[\alpha]^{23}_D$ +26.7 (*c* 0.31, $CHCl_3$)), a result which was consistent with Yamada's determination of absolute stereochemistry for kalihinol A (**1**).

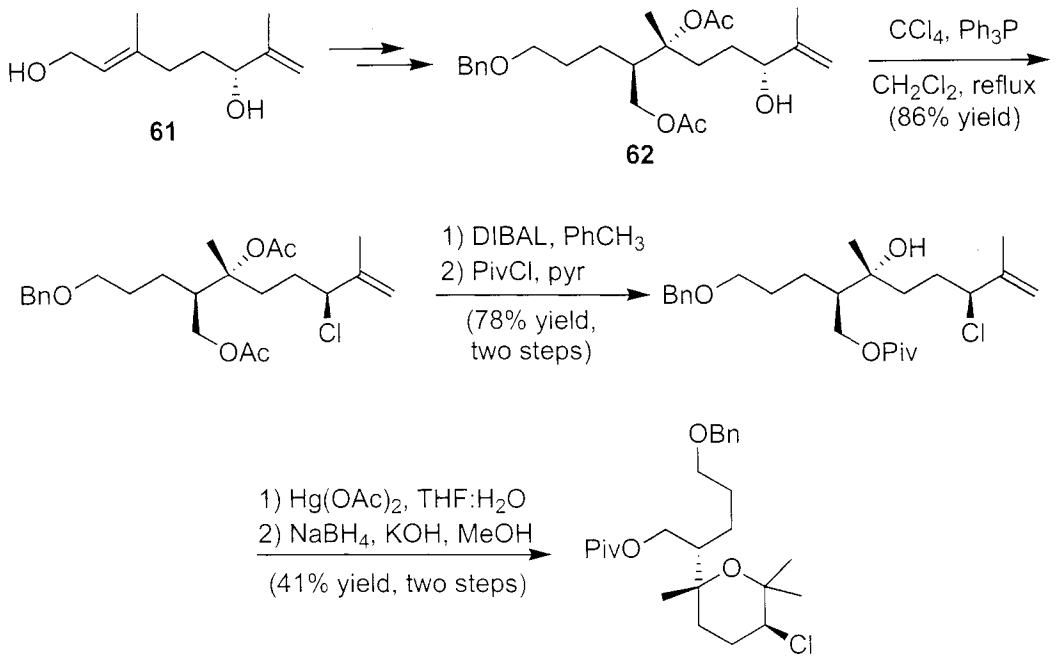
Yamada's initial retrosynthetic disconnections focused upon the establishment of the *cis*-decalin framework and installation of the quaternary C(10) stereocenter (Scheme 1.3). The formamide of kalihinene X (**30**) was thought to arise from ketone **55**, and the decalin core from an intramolecular Diels-Alder reaction of triene **56**. The protected diol **57** with pendant chlorotetrahydropyran was thought to come from a 6-*exo* cyclization of allylic alcohol **58**. A regioselective coupling reaction between epoxide **59** and sulfone **60** was anticipated to provide the C(7)-C(8) bond.

Scheme 1.3



Kalihinene X (**30**) and kalihinol A (**1**) bear several common structural features and, in particular, both of these compounds contain an identical chlorotetrahydropyran ring. As shown in the forward direction in Scheme 1.4, Yamada and co-workers installed the chlorine stereoselectively from allylic alcohol **62**, the stereochemistry of which was derived from known (E,R)-3,7-dimethylocta-2,7-diene-1,6-diol (**61**). After deprotecting the tertiary alcohol, the chlorotetrahydropyran ring was formed via an oxymercuration/demercuration protocol in 41% yield over two steps.

Scheme 1.4

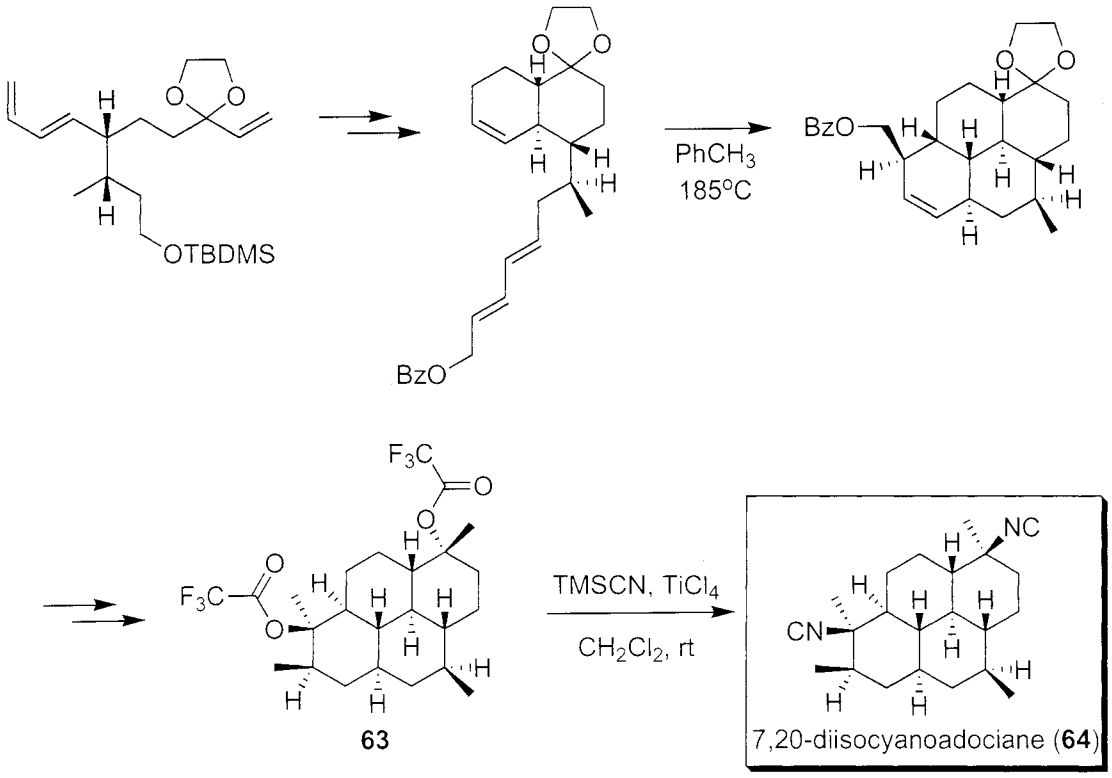


1.5.3 Corey's Total Synthesis of 7,20-Diisocyanoadociane

While Yamada's total synthesis of (+)-kalihinene X (**30**) and our total synthesis of (±)-kalihinol C (*vide infra*) represent the only published synthetic efforts towards the kalihinane diterpenoids, other related isonitrile-containing natural products from marine

sponges have been targeted by synthetic chemists. For example, Corey and co-workers at Harvard University have completed the total syntheses of the isonitrile-containing marine diterpenoid 7,20-diisocyanoadociane (**64**).[31] 7,20-Diisocyanoadociane (**64**) was isolated from the marine sponge *Adocia* sp. in the Great Barrier Reef in Australia in 1976.[32] Corey's approach relied upon two intramolecular Diels-Alder cyclizations to form the tetracyclic core (Scheme 1.5). In a final elegant step, Corey installed the two isonitrile groups in a single biomimetic operation from bistrifluoroacetate **63**.

Scheme 1.5



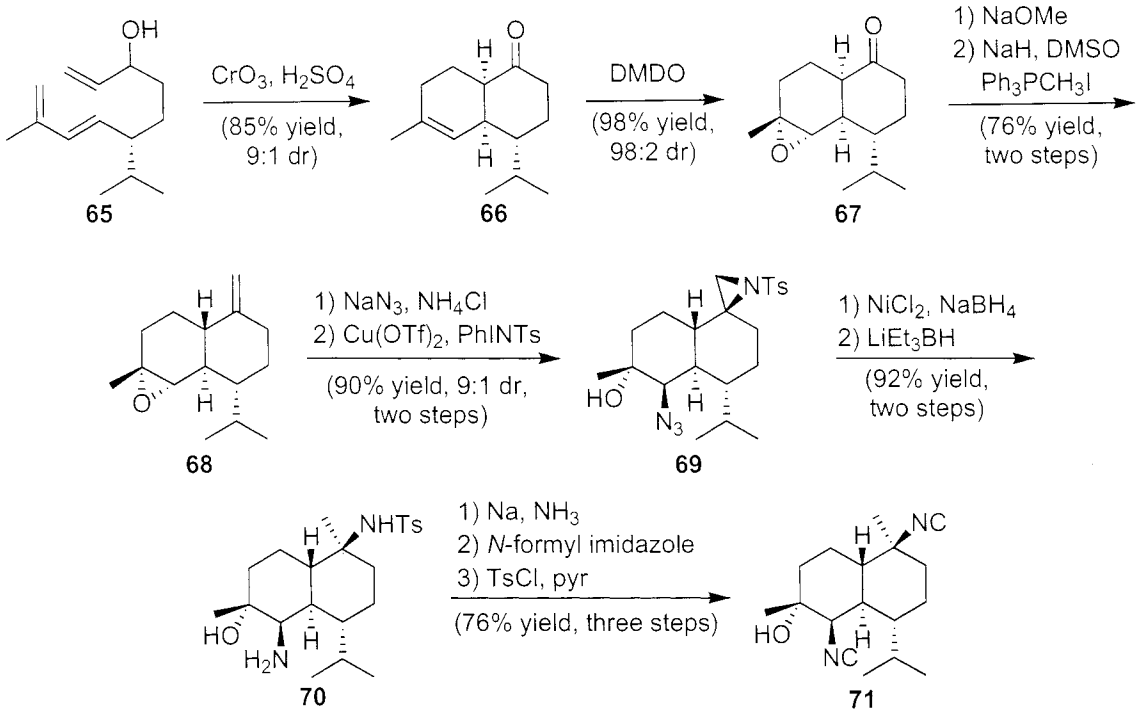
1.6 Prior work by the Wood Group

1.6.1 Progress through Spring 2001

1.6.1.1 Kalihinane Model System

In the spring of 2000, graduate student Ryan D. White in Prof. John L. Wood's laboratory at Yale University initiated studies directed towards the total synthesis of members of the kalihinane family. In an effort to examine the formation and functionalization of the decalin core, a model system was explored. *cis*-Decalin **66** was prepared from triene **65** based upon Taber's synthesis of the natural product (±)-torreyol (Scheme 1.6).[33] Taking advantage of the conformational bias afforded by the *cis*-decalin core, **66** was epoxidized using dimethyldioxirane (DMDO). Next, the *cis*-decalin **67** was converted into a mixture of *cis*- and *trans*-decalins upon exposure to base, and the decalin mixture was olefinated under Wittig conditions to afford *exo*-methylene **68**. Azide-induced opening of the C(4)-C(5) epoxide **68**, followed by copper-catalyzed aziridination, provided aziridine **69** in 90% yield over two steps. Nickel boride reduction of the azide **69** and reductive opening of the tosyl aziridine provided sulfonamide **70** in 92% yield over two steps. After exposure to dissolving metal conditions to affect tosyl deprotection, the resulting bisamine was formylated and subsequently dehydrated to afford bis-isonitrile **71**.[34]

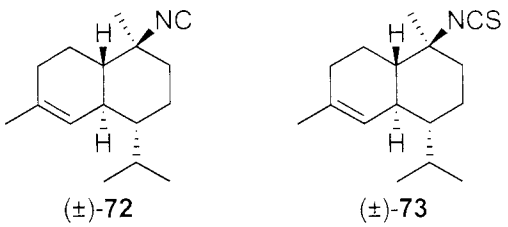
Scheme 1.6



1.6.1.2 Synthesis of (±)-10-Isocyano-4-cadinene and (±)-10-Isothiocyano-4-cadinene

In addition to exploring the functionalization of the decalin core with these model system substrates, White synthesized two natural products, (±)-10-isocyano-4-cadinene ((±)-**72**) and (±)-10-isothiocyano-4-cadinene ((±)-**73**), both of which were isolated from *Acanthella cavernosa* (Figure 1.16).[35,36]

Figure 1.16

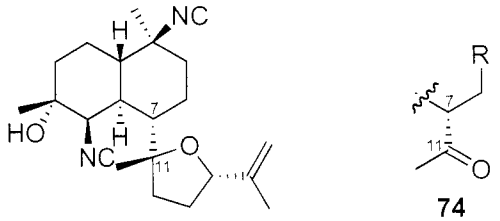


1.6.2 Progress from Spring 2001 through Spring 2003: Total Synthesis of (±)-Kalihinol C

1.6.2.1 Transition from Model System to Real System

With a viable model system approach established, synthetic efforts directed at the total synthesis of (±)-kalihinol C (**3**) were begun in the spring of 2001. While the model system work framed the approach to form and functionalize the decalin core, it was necessary at this time to incorporate a handle with which to install the pendant ring. It was envisioned that a methyl ketone such as **74** could serve this purpose (Figure 1.17).

Figure 1.17



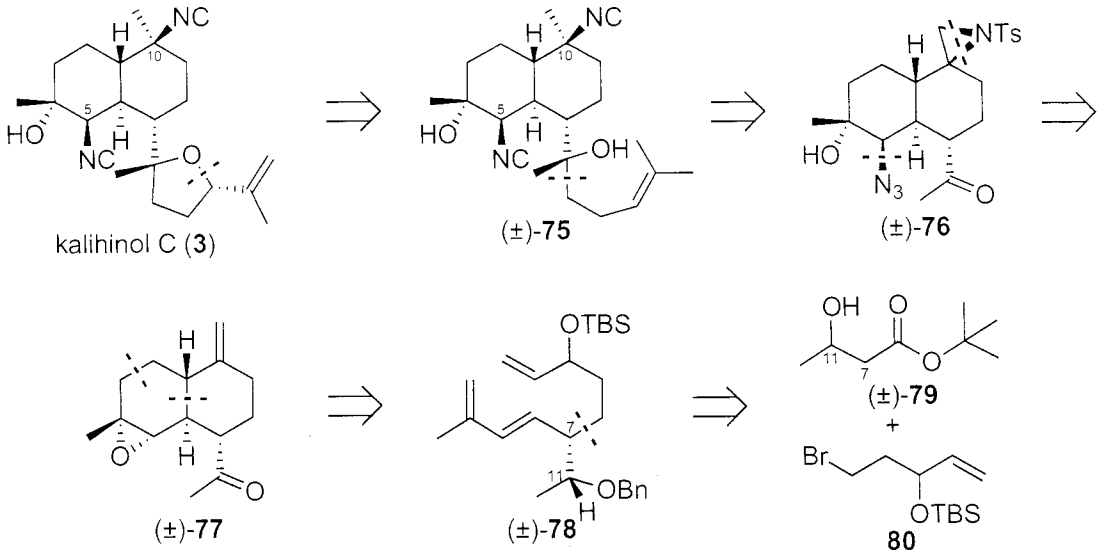
kalihinol C (**3**) **74**

1.6.2.2 Retrosynthesis

The retrosynthetic analysis for (±)-kalihinol C, shown in Scheme 1.7, was focused on three major structural features: the tetrahydrofuran ring, the two isonitrile groups, and the *trans*-decalin core. It was envisioned that late-stage formation of the tetrahydrofuran ring could be achieved by a 5-*exo* cyclization of bishomoallylic alcohol (±)-**75**. The C(10) tertiary, equatorially-oriented isonitrile could arise from tosyl aziridine (±)-**76**, which in turn could come from a metal-catalyzed aziridination of *exo*-methylene (±)-**77**. The isonitrile at the C(5) position, which is secondary and axial, could be derived from its

corresponding azide. The decalin core was thought to arise from an intramolecular Diels-Alder cyclization of triene (±)-**78**, which could be derived from (±)-*tert*-butyl-3-hydroxybutyrate ((±)-**79**) and alkyl bromide **80**.

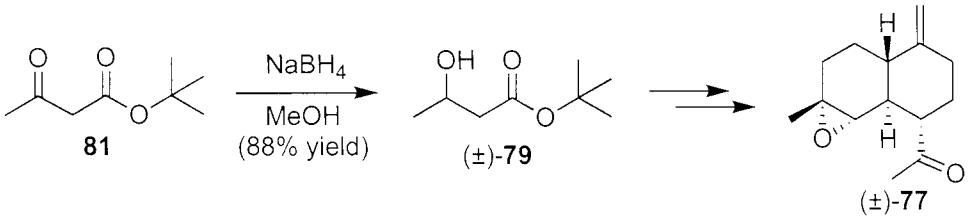
Scheme 1.7



1.6.2.3 Toward the Synthesis of (±)-Kalihinol C: Formation of Methyl Ketone

For (±)-kalihinol C, *tert*-butyl-3-hydroxybutyrate (**79**) was accessed in racemic form by reduction of commercially-available *tert*-butyl acetoacetate (**81**) with sodium borohydride (Scheme 1.8). In the synthetic approach toward (+)-kalihinol A (see Chapter 2), a Noyori hydrogenation of **81** was utilized to access **79** in enantiopure form. Since the route toward (+)-kalihinol A is identical to that of (±)-kalihinol C through the methyl ketone intermediate ((±)-**77**), a detailed discussion of these reactions will be addressed in Chapter 2. Thus, the overview of the total synthesis of (±)-kalihinol C will begin at methyl ketone (±)-77.

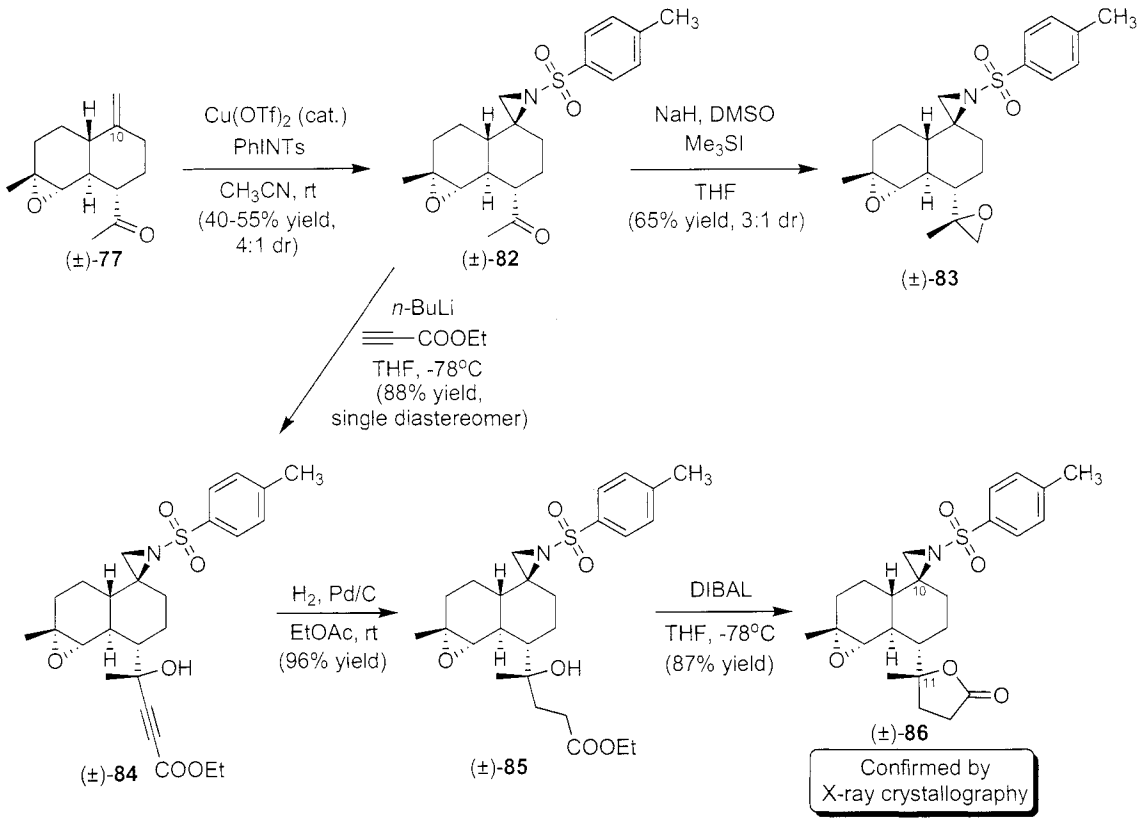
Scheme 1.8



1.6.2.4 Toward the Synthesis of (±)-Kalihinol C: Formation of the Lactone

In order to install the equatorial nitrogen at C(10), *exo*-methylene (±)-**77** was treated with tosyliminophenyliodinane (PhINTs) in the presence of copper triflate to afford the desired aziridine in 40-55% yield and modest 4:1 diastereoselectivity (Scheme 1.9).[37] Functionalization of the C(11) ketone proved to be far more challenging than initially anticipated. After a multitude of nucleophiles failed to affect nucleophilic addition, it was found that ketone (±)-**82** could be converted either into epoxide (±)-**83** using Corey's ylide[38] or propiolate ester (±)-**84**. Due to an inability to further functionalize (±)-**83**, advancement of the propiolate adduct (±)-**84** was pursued. The alkyne was hydrogenated to provide ester (±)-**85**, and lactonization occurred upon treatment with diisobutylaluminum hydride to afford a crystalline solid amenable for X-ray crystallographic analysis. The X-ray structure of lactone (±)-**86** confirmed that the desired stereochemistry was obtained at the C(10) and C(11) positions.

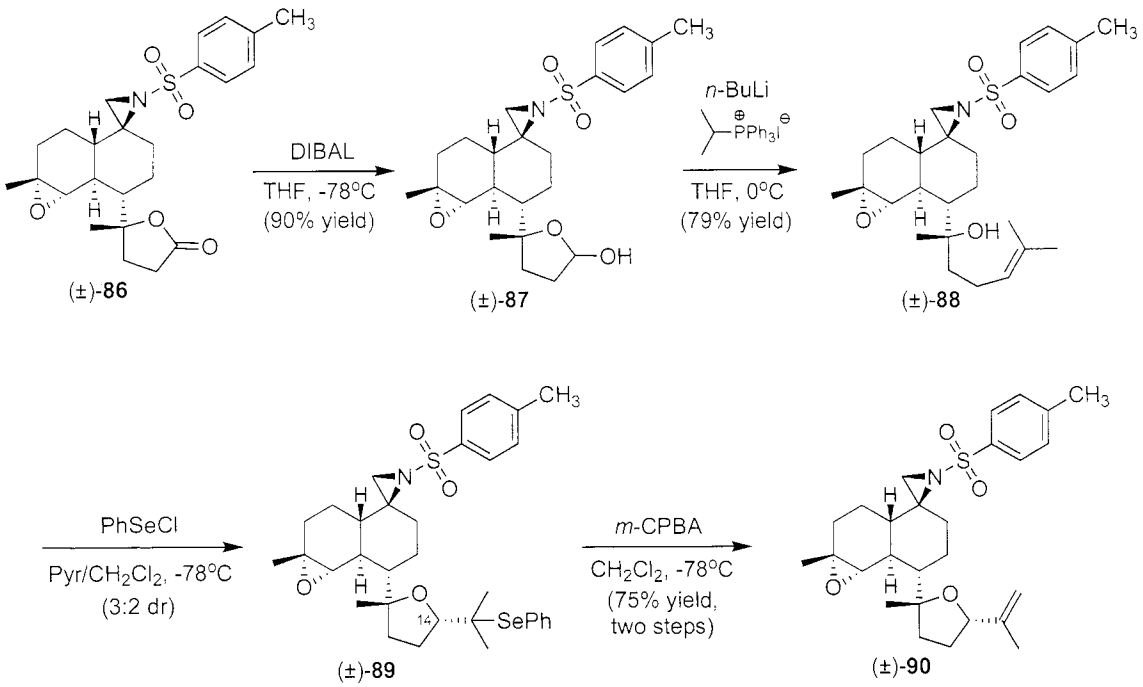
Scheme 1.9



1.6.2.5 Toward the Synthesis of (±)-Kalihinol C: Formation of the Tetrahydrofuran

With the desired stereochemistry confirmed by X-ray crystallography, lactone (±)-**86** was reduced with diisobutylaluminum hydride to provide lactol (±)-**87**, which was homologated under Horner-Wadsworth-Emmons olefination conditions to provide bishomoallylic alcohol (±)-**88** (Scheme 1.10). It was found that exposure of (±)-**88** to phenyl selenyl chloride induced selenoetherification to provide a 3:2 ratio of diastereomers favoring the desired, α-oriented epimer ((±)-**89**).[39] Next, (±)-**89** was treated with *m*-CPBA to affect oxidation and *in situ* elimination of the selenide to afford tetrahydrofuran (±)-**90**.

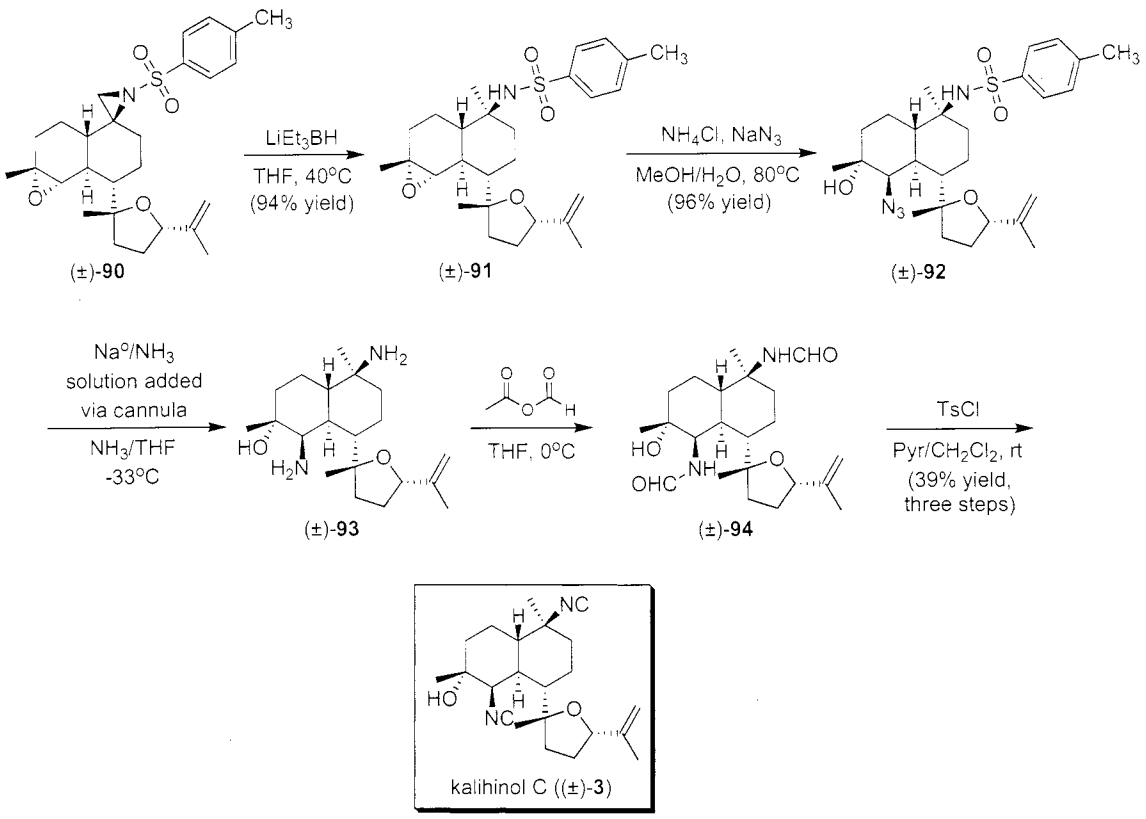
Scheme 1.10



1.6.2.6 Completion of the Total Synthesis of (±)-Kalihinol C

With the tetrahydrofuran and *trans*-decalin core of (±)-kalihinol C ((±)-**3**) in place, completion of the natural product required installation of the isonitriles. To this end, aziridine (±)-**90** was opened regioselectively with lithium triethylborohydride to give sulfonamide (±)-**91**, and the C(5) nitrogen was introduced by a *trans*-diaxial epoxide opening with azide (Scheme 1.11). After considerable experimentation, it was found that azide reduction and tosyl deprotection of azido alcohol (±)-**92** could be accomplished simultaneously upon careful exposure to a dilute solution of sodium metal in ammonia.[40] The resulting bisamine (±)-**93** was converted into bisformamide (±)-**94** with formic acetic anhydride, and lastly, dehydration of (±)-**94** with toluenesulfonyl chloride in pyridine provided (±)-kalihinol C ((±)-**3**).[41]

Scheme 1.11



1.7 Conclusions

Since the initial isolation and characterization of the kalihinanes by Scheuer and co-workers in the early 1980s, this highly functionalized family of natural products has generated tremendous interest among scientists in the fields of synthetic organic chemistry, marine biology, and infectious disease medicine. Compelled by the fascinating structures and diverse biological activities of the kalihinanes, a project directed towards the total syntheses of members of this family was initiated. During the

first four years of this project, a model system study was conducted and the first total synthesis of (±)-kalihinol C was achieved. Our current efforts towards the enantioselective total synthesis of (+)-kalihinol A, the most biologically intriguing member of the kalihinane family, are described in the following chapter.

1.8 Notes and References

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Chapter 2

Progress Towards the Total Synthesis of (+)-Kalihinol A

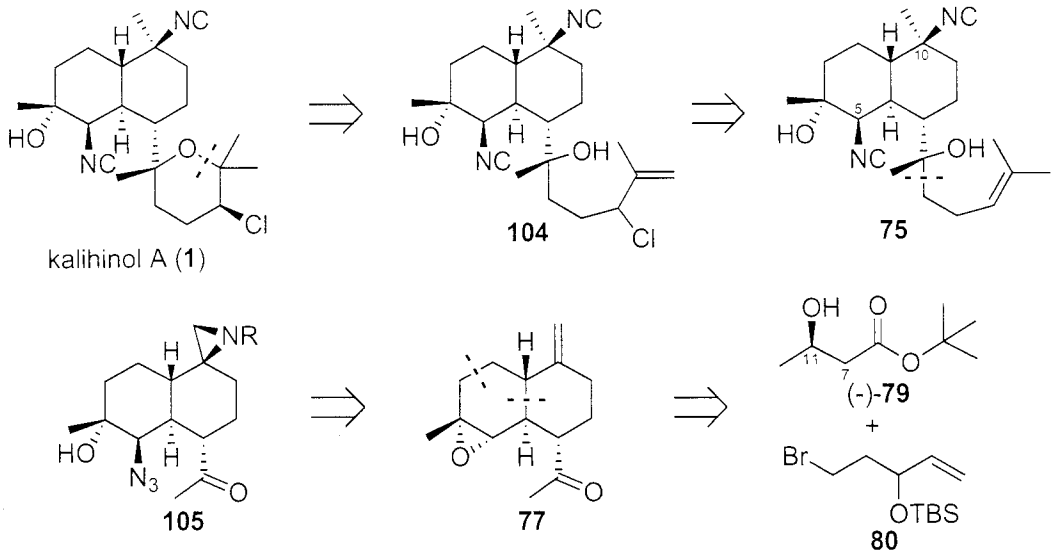
2.1 Introduction and Retrosynthesis

Kalihinol A is the most biologically active and well-studied member of the kalihinane family. This natural product possesses a pendent chlorotetrahydropyran ring at C(7), and despite the fact that chlorotetrahydropyrans occur frequently in natural products, the current synthetic methodology used to form these rings often requires several steps and has been plagued with low-yielding reactions.[1-3]

While the only structural difference between kalihinol A and kalihinol C is the nature of the pendant ring, it was recognized that our synthetic strategy would need to address the installation and potential reactivity of the 2,2,6,6-tetrasubstituted chlorotetrahydropyran. The retrosynthetic analysis for (+)-kalihinol A (**1**), as shown in Scheme 2.1, was anticipated to involve late-stage formation of the chlorotetrahydropyran and the isonitriles. In light of the strong regiochemical preference for 5-*exo* cyclization of bishomoallylic alcohols such as **75**, it was anticipated that 6-*exo* cyclization of allylic chloride **104** would be the most efficient manner to form the chlorotetrahydropyran. Allylic chloride **104** could arise from an allylic transposition of bishomoallylic alcohol **75**, and the two isonitriles at the C(5) and C(10) positions could be derived from the

corresponding azido aziridine **105**. *trans*-Decalin methyl ketone **77** could be prepared in enantiopure form from (-)-(R)-*tert*-butyl 3-hydroxybutyrate (**79**).

Scheme 2.1

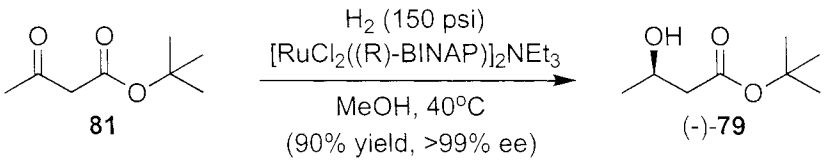


2.2. Approaches Toward (+)-Kalihinol A

2.2.1 Synthesis of the Intramolecular Diels-Alder Precursor

It was envisioned that the coupling of β-hydroxy ester **79** and alkyl bromide **80** would provide an ideal entry into the synthesis of (+)-kalihinol A. (-)-*tert*-Butyl 3-hydroxybutyrate (-)-(**79**) was prepared as a single enantiomer using a Noyori hydrogenation of *tert*-butyl acetoacetate (**81**) (Scheme 2.2).[4]

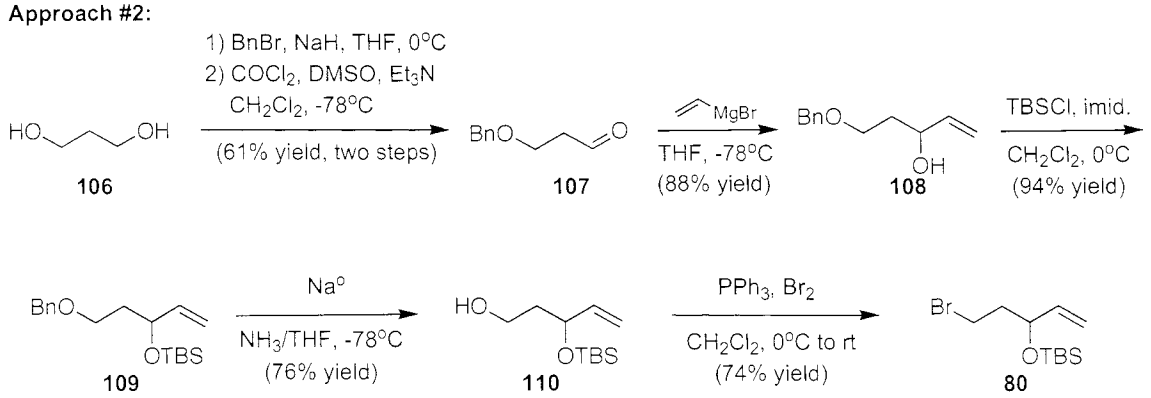
Scheme 2.2



While alkyl bromide **80** was structurally simple, its large-scale synthesis was problematic and required a significant amount of optimization. Over the course of the synthesis, three distinct routes were utilized to obtain adequate quantities of **80**. Initially, acrolein was converted in three steps to **80** (Approach #1, scheme not shown).[5] While this procedure benefited from low-cost starting materials and reagents, the formation of significant quantities of undesired side products could not be circumvented.

Approach #2 began with commercially-available 1,3-propanediol (**106**), which is monobenzylated and oxidized using Swern conditions to aldehyde **107** according to literature procedure (Scheme 2.3).[6] Aldehyde **107** was treated with vinyl magnesium bromide to cleanly afford allylic alcohol **108**.[7,8] Protection of **108** provided silyl ether **109**, which was debenzylated under dissolving metal conditions to give alcohol **110**.[9] Bromination of the primary alcohol delivered the desired alkyl bromide **80**.

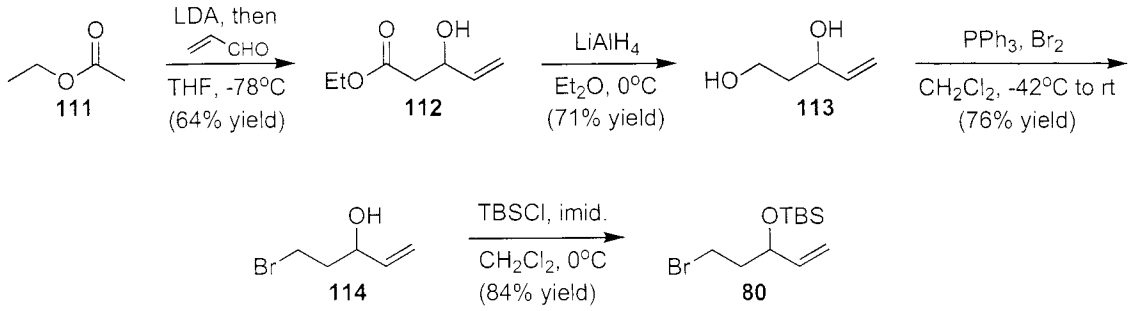
Scheme 2.3



While Approach #2 was successful in producing large quantities of **80**, this six-step procedure proved to be rather time-consuming. As a result, a shorter, more efficient approach was sought. In Approach #3, ethyl acetate (**111**) was enolized and reacted with acrolein to afford β-hydroxy ester **112** (Scheme 2.4).[10] Reduction of **112** with lithium aluminum hydride yielded diol **113**,[11] and then the primary alcohol was selectively brominated to provide bromide **114**. Finally, silylation of the alcohol gave the desired alkyl bromide **80** in 29% yield over four steps. This procedure was found to be the most efficient method of scaling up the synthesis to make large quantities of **80**.

Scheme 2.4

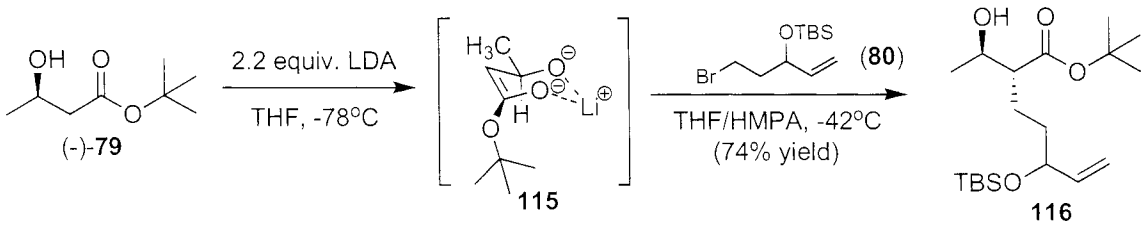
Approach #3:



The major complication encountered in all of these approaches was the large-scale purification of **80**. Distillation was not an option because the primary bromide readily eliminated upon heating to liberate hydrobromic acid, which in turn reacted with **80** to remove the TBS protecting group. Column chromatography was thus required, and it was found that purification with a pentane/ether solvent system followed by careful solvent evaporation led to the greatest material recovery. This approach was utilized to produce more than 500 grams of **80**.[12]

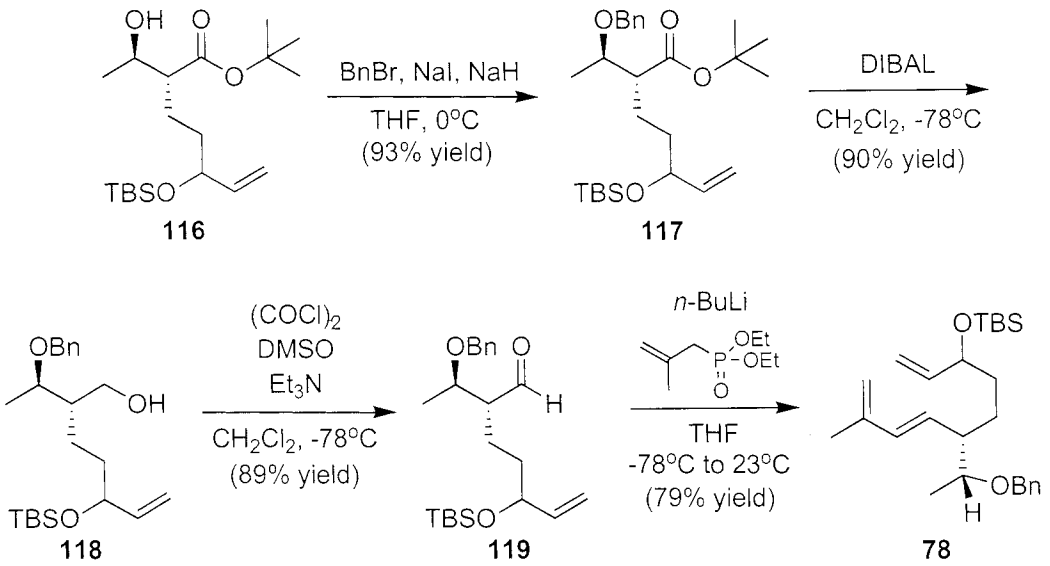
Next, the coupling reaction of β-hydroxy ester (-)-**79** and alkyl bromide **80** was examined. It was found that treatment of (-)-*tert*-butyl 3-hydroxybutyrate ((-)-**79**) with two equivalents of LDA in a solution of THF at -78°C provided the dianion **115** (Scheme 2.5). After addition of HMPA and warming the reaction to -42°C, **80** was added dropwise via syringe pump over an extended period of time. The temperature, rate of alkyl bromide addition, and number of equivalents of HMPA significantly affected the yield of this reaction. The stereocontrol of the Frater alkylation[13] can be attributed to coordination of the dianion with a lithium cation in chair-like transition state **115** such that the electrophile (alkyl bromide, in this case) approaches on the less-hindered face. The alkylation product **116** is diastereomeric only at the silyl ether stereocenter, and since this position is later oxidized in the synthesis, the ratio is inconsequential.

Scheme 2.5



Alcohol **116** was then protected as its benzyl ether **117**; it was necessary to conduct this reaction under strictly anhydrous conditions to prevent epimerization of the adjacent stereocenter (Scheme 2.6). Next, DIBAL reduction of the ester gave alcohol **118**, which was oxidized using Swern conditions to provide aldehyde **119**. Exposure of **119** to Horner-Wadsworth-Emmons olefination conditions led to formation of the desired *E*-triene **78**.

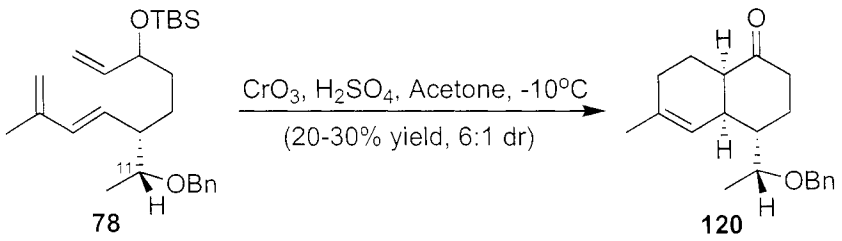
Scheme 2.6



2.2.2 The Intramolecular Diels-Alder Reaction

With the desired triene **78** in hand, the crucial intramolecular Diels-Alder cycloaddition was explored. The model system Diels-Alder cyclization, conducted with Jones' reagent, gave the decalin product in 85% yield as a 9:1 mixture of diastereomers (see Chapter 1, Scheme 1.6). On the real system, triene **78**, when exposed to these conditions, did indeed provide the desired *cis*-decalin **120** as the major stereoisomer (Scheme 2.7).[14] However, the isolated yield of **120** was consistently low (20-30% yield), presumably due to the harsh conditions employed in the reaction. Unfortunately, modifications such as lowering the temperature and varying the sulfuric acid concentration did not lead to a substantial increase in yield.

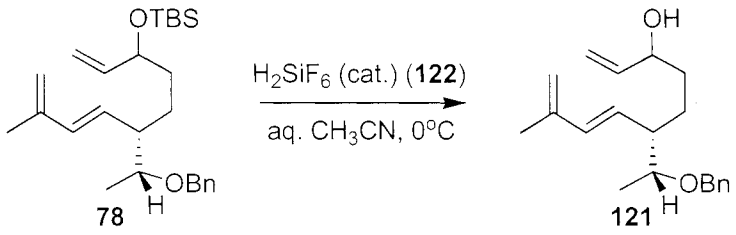
Scheme 2.7



Even prior to attempting the intramolecular Diels-Alder reaction, the stability of the triene **78** had been a major concern. It was observed that **78** slowly decomposed on silica gel chromatography and at room temperature to several unidentified products.[15] Furthermore, not only was it apparent that the triene functionality was susceptible to decomposition, but it was also anticipated that the benzyl protecting group at C(11) might not be stable to the Jones' oxidation conditions. As a result, a two-step deprotection/oxidation protocol was investigated.

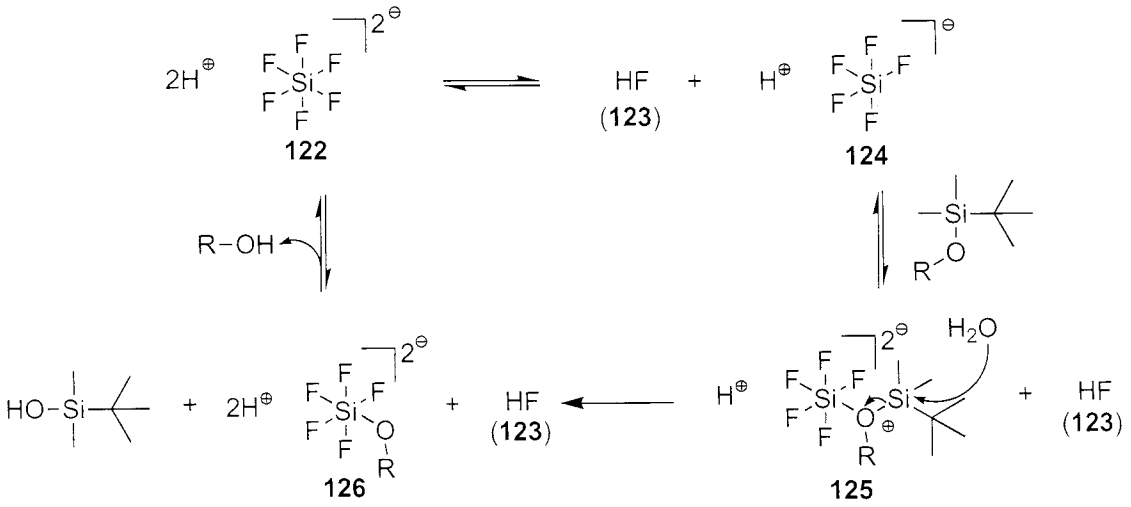
To this end, a series of standard silyl deprotection conditions (TBAF, HF•pyridine, 1N HCl, SiF_4, etc.) were screened; however, all led to significant decomposition of **78**. Ultimately, it was found that treatment of **78** with catalytic fluorosilicic acid (**122**) in acetonitrile cleanly affected deprotection to provide the desired alcohol **121** (Scheme 2.8).

Scheme 2.8



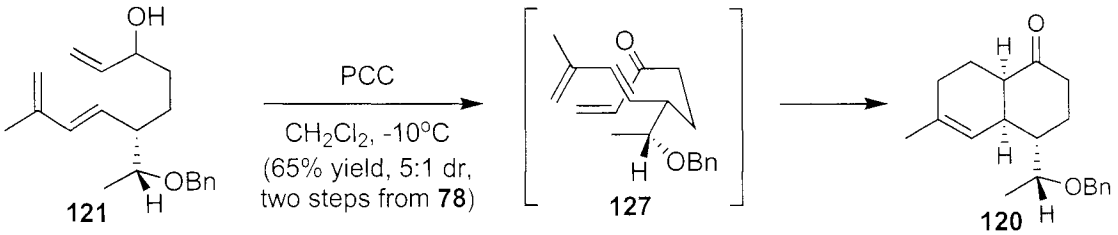
The ability of catalytic fluorosilicic acid to remove TBS groups was known,[16,17] and its mild acidity and short reaction times likely account for its ability to deprotect delicate substrates such as **78**. Unlike most fluoride-based deprotection reagents, fluorosilicic acid can be used catalytically, and the catalytic cycle for this reaction is shown in Scheme 2.9.[16] In solution, fluorosilicic acid (**122**) is in equilibrium with its dissociated forms, hydrofluoric acid (**123**) and pentafluorosilicate anion **124**. If hydrofluoric acid (**123**) deprotects the TBS group, then the reagent is clearly not catalytic. However, because the pentafluorosilicate anion **124** is highly Lewis acidic, it is possible to invoke an alternative mechanism which involves the coordination of **124** with the basic non-bonding lone pair electrons on the silyl ether oxygen to give intermediate **125**. The activated silicon-oxygen bond can then be fragmented by attack of water on the silicon, and hydrolysis of hexavalent silicate **126** ultimately regenerates of the fluorosilicic acid reagent.

Scheme 2.9



With a successful deprotection protocol established, several oxidizing conditions to trigger the Diels-Alder reaction were next screened. It was found that chromium-based oxidants produced the highest degree of diastereoselectivity in the cyclization. Oxidation of crude allylic alcohol **121** with PCC generated the activated trienone intermediate **127** which underwent immediate, *in situ* Diels-Alder cyclization via the anticipated *endo*-boat transition state[18] to form the desired *cis*-decalin **120** with 5:1 diastereoselectivity in 65% yield over two steps (Scheme 2.10)[19,20] It was necessary to conduct the Diels-Alder reaction using crude **121** since purification by silica gel chromatography led to significant decomposition.

Scheme 2.10

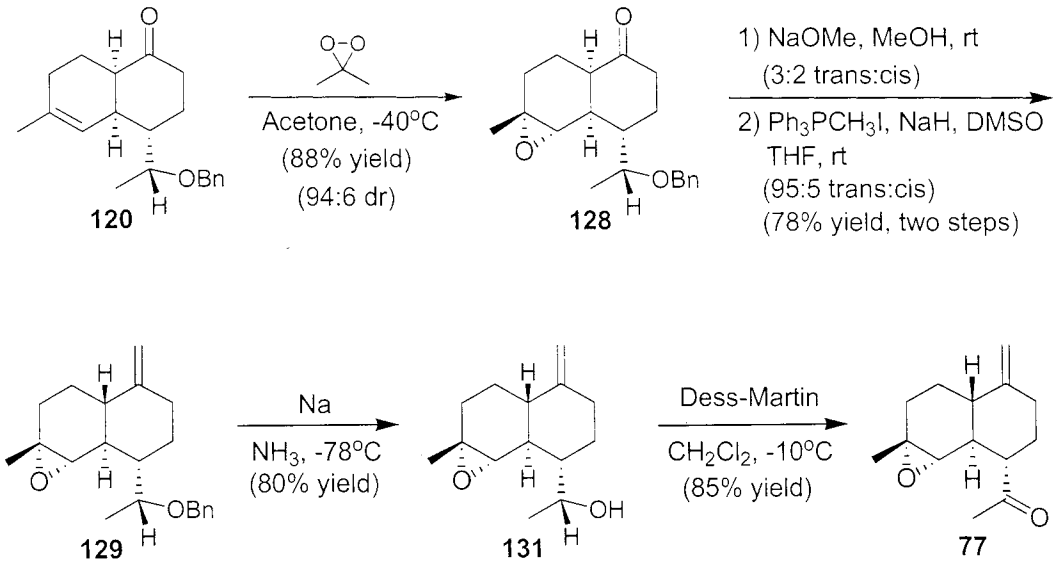


2.2.3 Advancement to the Methyl Ketone

The next stage of the synthesis required functionalization of this newly formed decalin core. It was envisioned that the conformational bias afforded by the decalin core could serve to direct functionalization through a series of substrate-controlled, diastereoselective reactions. To this end, epoxidation of *cis*-decalin **120** proceeded in 88% yield in 94:6 diastereoselectivity favoring epoxidation on the less hindered, convex face (Scheme 2.11). Next, the *cis*-decalin **128** was converted into the more stable *trans*-decalin upon exposure to basic methanol for several days providing an equilibration ratio of 3:2 *trans*- to *cis*-decalin isomers. This *trans*- and *cis*-decalin mixture could be transformed into a 95:5 ratio of *trans*- to *cis*-decalin olefinated products upon exposure to aliquots of methyl triphenylphosphonium ylide added over an extended period of time. This dynamic equilibrium can be understood based upon the Curtin-Hammett principle.[21] The *cis*- and *trans*-decalin ketones are rapidly equilibrating under the basic reaction conditions. Olefination of the less hindered *trans*-decalin ketone occurs at a faster rate (i.e., via a lower activation energy barrier) than olefination of the more hindered *cis*-decalin ketone **128**. Provided that the rate of decalin equilibration is faster than the rate of *cis*-decalin olefination, the reaction is funneled through the pathway of lower activation energy to form almost exclusively *trans*-decalin **129**. Formation of methyl

ketone **77** was then accomplished in two steps from **129**. Dissolving sodium metal was employed to remove the benzyl protecting group to provide alcohol **131**, and oxidation with Dess-Martin periodinane delivered methyl ketone **77**.[22]

Scheme 2.11

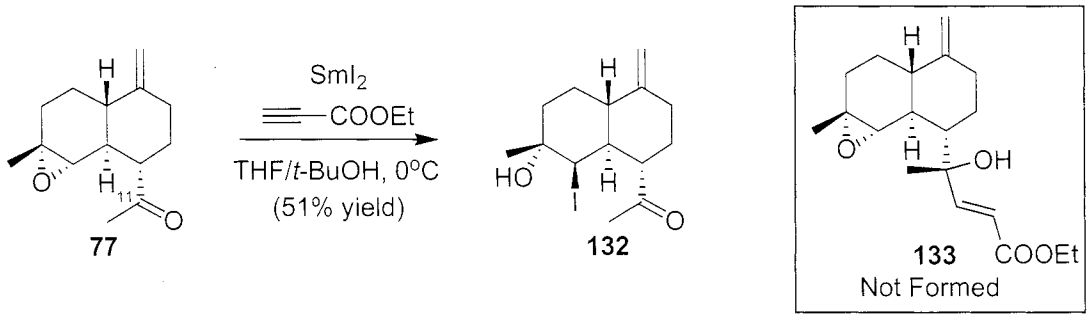


2.2.4 Attempted Nucleophilic Addition to the Methyl Ketone

At this juncture in the synthesis, functionalization of the C(11) ketone was examined. A wide array of nucleophiles (Grignards, alkyl lithiums, dithianes, sulfones, enolates, etc.) were screened, but unfortunately, none of these nucleophiles successfully added to the methyl ketone. Furthermore, attempted nucleophilic addition in the presence of a variety of Lewis acids ($BF_3 \bullet Et_2O$, $CeCl_3$, $AlCl_3$, etc.) was also unsuccessful and frequently led to undesired reactivity at the C(4)-C(5) epoxide. A deuterium-quenching experiment revealed that this hindered ketone was undergoing enolization under the reaction conditions.

In light of this observation and after numerous failed attempts with standard nucleophiles and Lewis acids, a ketone/alkyne reductive coupling was explored. It was known in the literature that samarium could mediate the coupling of propiolate esters with hindered ketones under mild conditions.[23,24] It was found, however, that subjection of **77** to samarium (II) iodide and ethyl propiolate led exclusively to formation of the undesired iodohydrin (Scheme 2.12). No addition to the C(11) carbonyl to give adduct **133** was observed, attesting once again to the highly hindered nature of this functionality.

Scheme 2.12

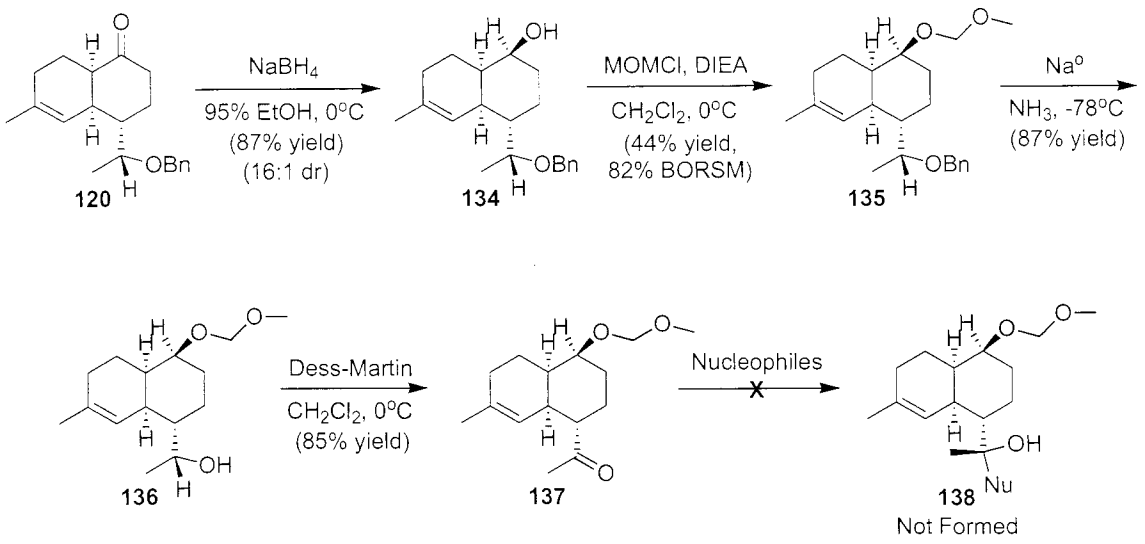


Due to the tremendous difficulties encountered while attempting to add nucleophiles to *trans*-declin ketone **77**, the thought of installing the sidechain on an earlier intermediate was entertained. It was hypothesized that the C(11) ketone might be situated in a drastically different steric environment when appended to the *cis*-decalin framework. As a result, *cis*-decalin Diels-Alder adduct **120** was investigated with hopes that advancement of this substrate to a *cis*-decalin methyl ketone might be fruitful.

cis-Decalin **120** was treated with sodium borohydride to produce alcohol **134** as the major diastereomer (Scheme 2.13). After protection of the alcohol as its acetal **135**, the benzyl protecting group was cleaved using dissolving metal conditions to make

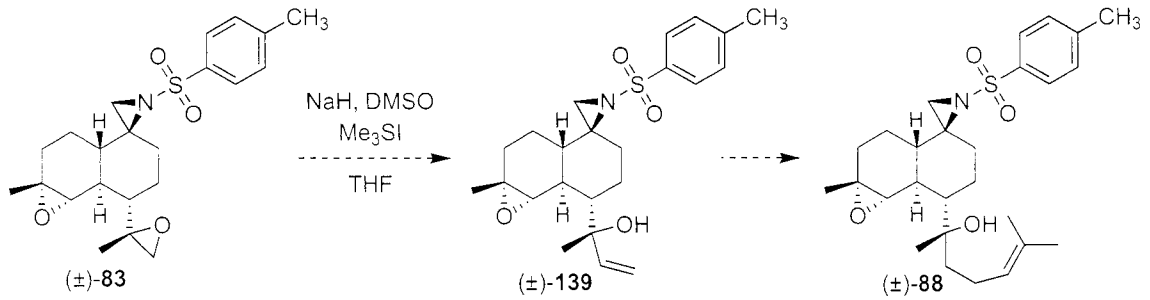
alcohol **136**. Dess-Martin periodinane oxidation of **136** gave the much anticipated *cis*-decalin methyl ketone **137**. A battery of alkyl lithium and Grignard reagents were screened for their reactivity towards **137**; disappointingly, however, **137** proved to be completely recalcitrant to nucleophilic addition as well (alcohol **138** was not observed).

Scheme 2.13



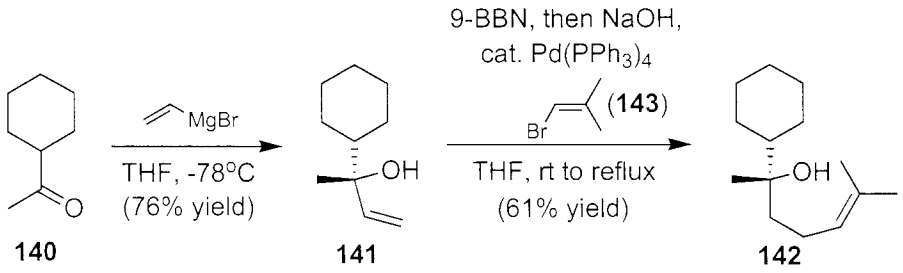
Faced with the inability to functionalize *cis*-decalin ketone **137**, we returned to screening nucleophiles on *trans*-decalin substrates. It had been previously found that exposure of methyl ketone (±)-**82** to trimethylsulfonium ylide provided epoxide (±)-**83** (see Chapter 1, Scheme 1.9).[25,5] It is known that epoxides can be homologated to their corresponding allylic alcohols upon exposure to excess trimethylsulfonium ylide,[26] and it was anticipated that such a handle could be advanced to the desired bishomoallylic alcohol (±)-**88** via alcohol (±)-**139** (Scheme 2.14).

Scheme 2.14



In order to explore the transformation of allylic alcohol (±)-**139** to (±)-**88**, a model system study was initiated. Model allylic alcohol **141** was prepared via vinyl magnesium bromide addition to cyclohexyl methyl ketone (**140**) (Scheme 2.15). Application of *B*-alkyl Suzuki cross coupling conditions with 1-bromo-2-methylpropene (**143**) smoothly provided model bishomoallylic alcohol **142** in 61% yield.[27,28]

Scheme 2.15

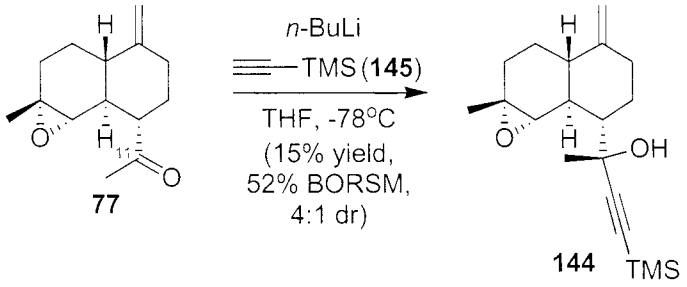


With a model system method to install the sidechain in hand, advancement of the fully functionalized epoxide (±)-**83** was probed (see Scheme 2.14). However, all attempts to convert (±)-**83** into allylic alcohol (±)-**139** were unsuccessful.

After continued screening of more nucleophiles in an effort to add to *trans*-decalin ketone **77**, it was ultimately found that treatment with the lithium anion of

trimethylsilyl acetylene (**145**) provided alcohol **144** with 4:1 diastereoselectivity (Scheme 2.16).

Scheme 2.16

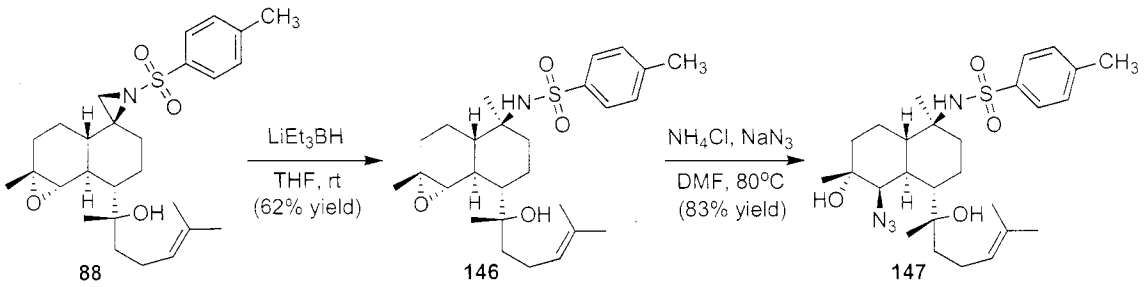


While this result was encouraging, the conversion for this reaction (15% yield, 52% BORSM) was not acceptable for synthetic advancement. The success of **145** was likely due to the small size and lower basicity of this sp-hybridized nucleophile. Thus, nucleophilic addition with the lithium anion of ethyl propiolate was next attempted. While ethyl propiolate had previously failed to add to the C(11) ketone under reductive coupling conditions, it was anticipated that this small, electron-poor, sp-hybridized nucleophile might be able to favor nucleophilic addition over enolization. Gratifyingly, the lithium anion of ethyl propiolate added to the C(11) carbonyl in high conversion and diastereoselectivity(see Chapter 1, Scheme 1.9).[5]

2.2.5 Advancement of the Tosyl Aziridination Approach

In the initial approach towards (+)-kalihinol A (**1**), bishomoallylic alcohol **88** was converted in two steps to azido alcohol **147** via epoxide **146** (Scheme 2.17).

Scheme 2.17



While it was conceivable that **147** could have been advanced to kalihinol A (**1**), there were significant drawbacks associated with this approach. As encountered in the synthesis of (±)-kalihinol C, the tosyl protecting group was found to be remarkably difficult to remove, even when subjected to dissolving metal conditions in refluxing ammonia for extended periods of time.[5] Thus, these forcing conditions greatly limited the potential substrates on which tosyl deprotection would be feasible. Moreover, in evaluating the kalihinol C synthesis in hindsight, it was recognized that the aziridination reaction to install the tosyl-protecting group consistently proved to be a tremendous bottleneck. The tosyl aziridination (see Chapter 1, Scheme 1.9, (±)-**77** → (±)-**82**) was by far the lowest yielding, most capricious, and difficult to purify reaction in the synthesis of (±)-kalihinol C.

2.2.6 Advancement of the Nosyl Aziridination Approach

2.2.6.1 Rationale

In deciding upon an efficient route towards (+)-kalihinol A, it was clear that the method of installing the C(10) nitrogen would require optimization. While a variety of synthetic methods existed for the stereoselective installation of nitrogen-containing

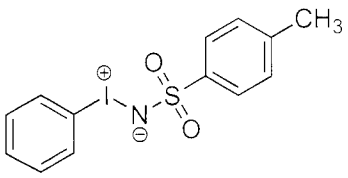
functionality, the fact that the C(10) nitrogen in kalihinol A is tertiary and equatorial substantially limited the number of potential procedures. Since it had previously been shown that the aziridination reaction was a viable means to install the C(10) nitrogen, it was believed that this chemistry could be applied to kalihinol A as long as the experimental procedure was improved. It was envisioned that modification of the nitrene source could conceivably improve the yield and simplify the purification for this reaction. Furthermore, since the protecting group would be installed concomitantly with the nitrogen itself in the aziridination reaction, we hoped that the judicious selection of nitrene source could also serve to mitigate late-stage deprotection difficulties.

While the work of many research groups during the past decade has greatly improved upon the efficiency and substrate scope of olefin aziridinations, the selection of the nitrene source to this day remains fairly limited.[29-32] This limitation arises from the fact that nitrenes (and their precursors) are notoriously unstable. Alkyl nitrene precursors, for instance, have been found to be highly explosive.[33,34] The most stable nitrene precursors are typically conjugated with an electron-withdrawing group in order to stabilize the negative charge located on the nitrogen atom, and thus it is not surprising that the vast majority of nitrene precursors are derived from sulfonamides.[34,35]

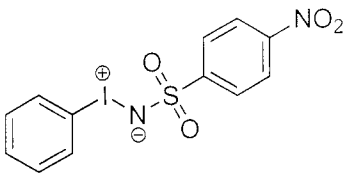
The most common nitrene precursor for olefin aziridination is *para*-toluenesulfonyliminophenyliodinane ((**148**), PhINTs) (Figure 2.1).[36] Early methodology in the field of metal-catalyzed aziridinations relied upon this nitrene precursor exclusively due to its unique effectiveness and stability.[30,31] Recently, the related reagent *para*-nitrobenzenesulfonyliminoiodinane ((**149**), PhINNs) has gained significant

popularity, fueled to a large extent by the variety of methods developed for regioselective aziridine ring opening and mild deprotection methods of nosyl aziridines.[37-44]

Figure 2.1



PhINTs (**148**)

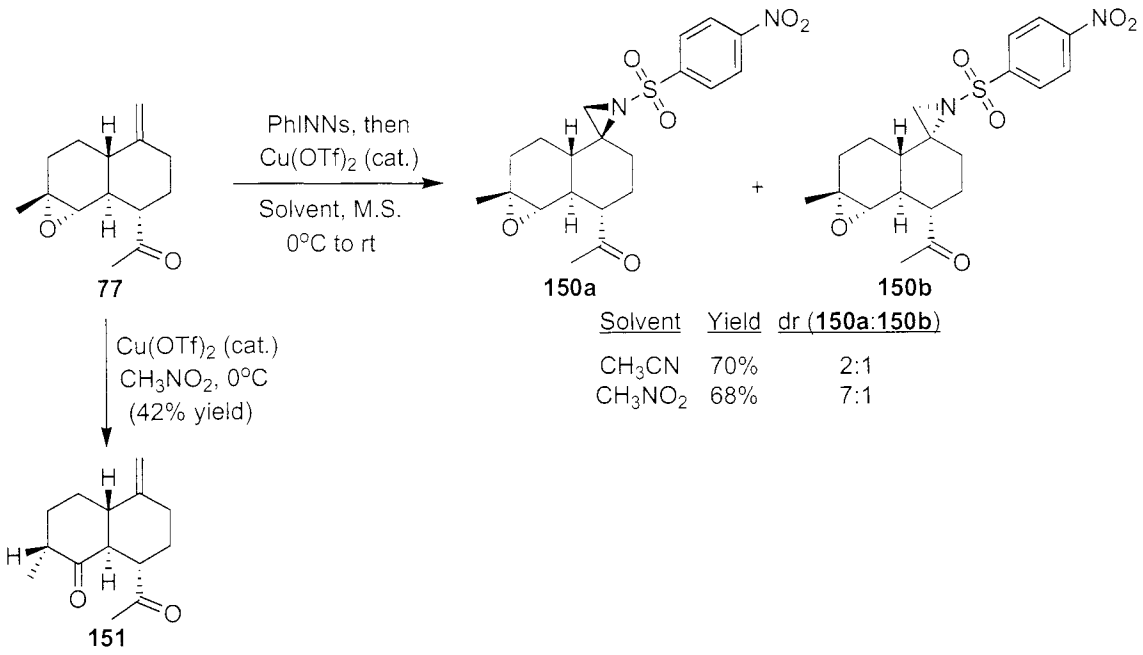


PhINNs (**149**)

2.2.6.2 Optimization of the Nosyl Aziridination

para-Nitrobenzenesulfonyliminoiodinane ((**149**), PhINNs) was prepared[40] and exposed to *exo*-methylene **77** in the presence of catalytic copper (II) triflate (Scheme 2.18). When acetonitrile was used as the solvent, the aziridinated product was obtained in 70% yield as a 2:1 mixture of diastereomers favoring the desired β-aziridine (**150a**).[45] Interestingly, when the highly-coordinating solvent nitromethane was used in place of acetonitrile, the yield remained essentially the same while the diastereomeric ratio increased dramatically to 7:1 (**150a**:**150b**). Both of these conditions demonstrated a remarkable improvement in yield over the tosyl aziridination, and furthermore, the desired nosyl aziridine **150a** could be readily separated from the minor diastereomer **150b** and other reaction side products. Additionally, it is worth noting that the order of reagent addition in this reaction was absolutely critical. It was found that exposure of **77** to catalytic copper (II) triflate prior to addition of the iminoiodinane ylide led to undesired rearrangement of the epoxide to diketone **151** via a 1,2-hydride shift.

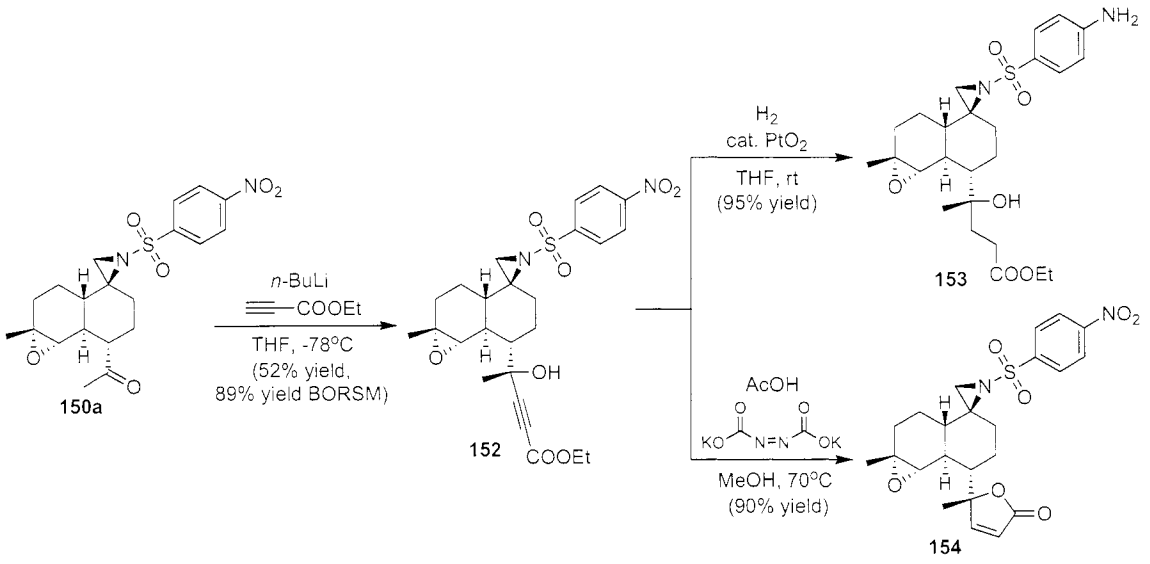
Scheme 2.18



2.2.6.3 First Generation Nosyl Approach

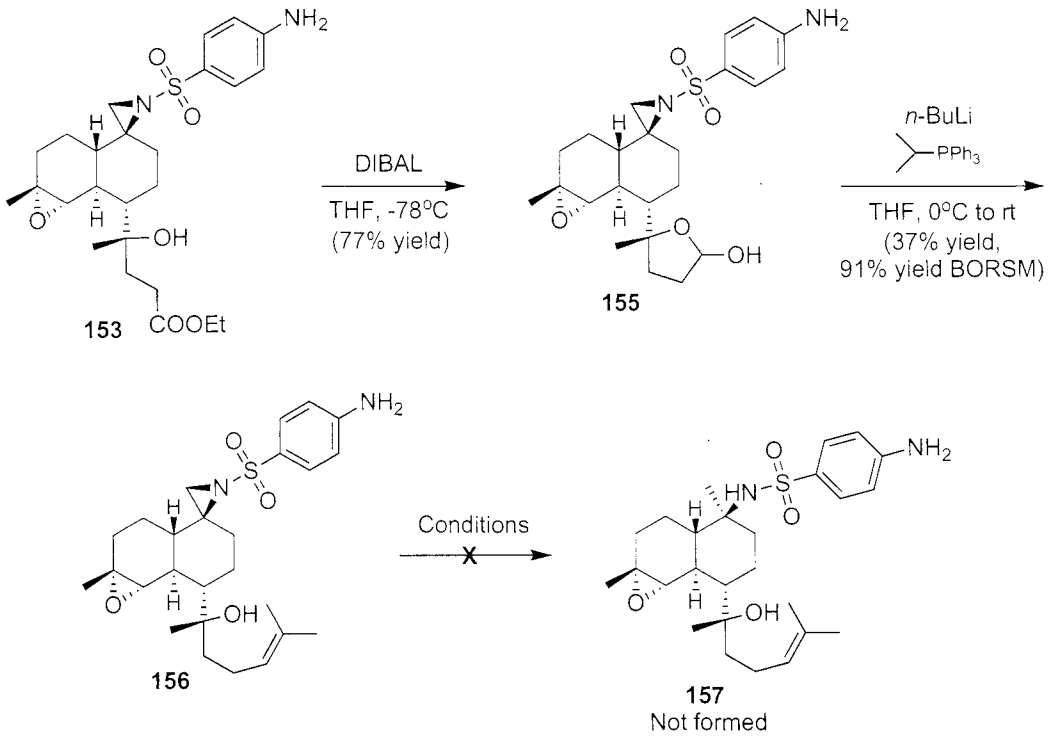
Emboldened by the improved yield and diastereoselectivity of the nosyl aziridination, we next focused our attention on the advancement of **150a**. Treatment of **150a** with the lithium anion of ethyl propiolate provided the desired ester **152** with complete diastereoselectivity (Scheme 2.19). It is particularly noteworthy that this nucleophilic addition occurred chemoselectivity in the presence of the sensitive epoxide and nosyl aziridine functionalities. In the following step, hydrogenation of the alkyne with platinum (II) oxide catalyst proceeded in high yield to give ester **153**; however, under these reaction conditions, the nitro group on the aryl ring was also reduced.[46] Alternatively, selective alkyne reduction could be achieved upon exposure of **152** to diimide, generated *in situ*, to form butenolide **153** in 90% yield.[47]

Scheme 2.19



In spite of the observation that the nitro group reduction might complicate subsequent aziridine opening, the aniline-sulfonamide **153** was advanced with anticipation that this potential incompatibility could be resolved on a later intermediate. To this end, reduction of **153** was accomplished using standard DIBAL conditions, and the resulting lactol **155** was olefinated uneventfully to arrive at bishomoallylic alcohol **156** (Scheme 2.20). With the bishomoallylic alcohol installed, the aziridine opening needed to be addressed. Despite attempts to open the aziridine under a variety of nucleophilic hydride conditions ($LiAlH_4$, $LiEt_3BH$, etc.) to form sulfonamide **157**, none of the conditions was effective and led to either recovery of starting material or substrate decomposition. Furthermore, efforts to deprotect the aniline-sulfonyl protecting group prior to aziridine opening (either by direct removal or by functionalization of the aryl ring before removal) were unsuccessful as well.

Scheme 2.20



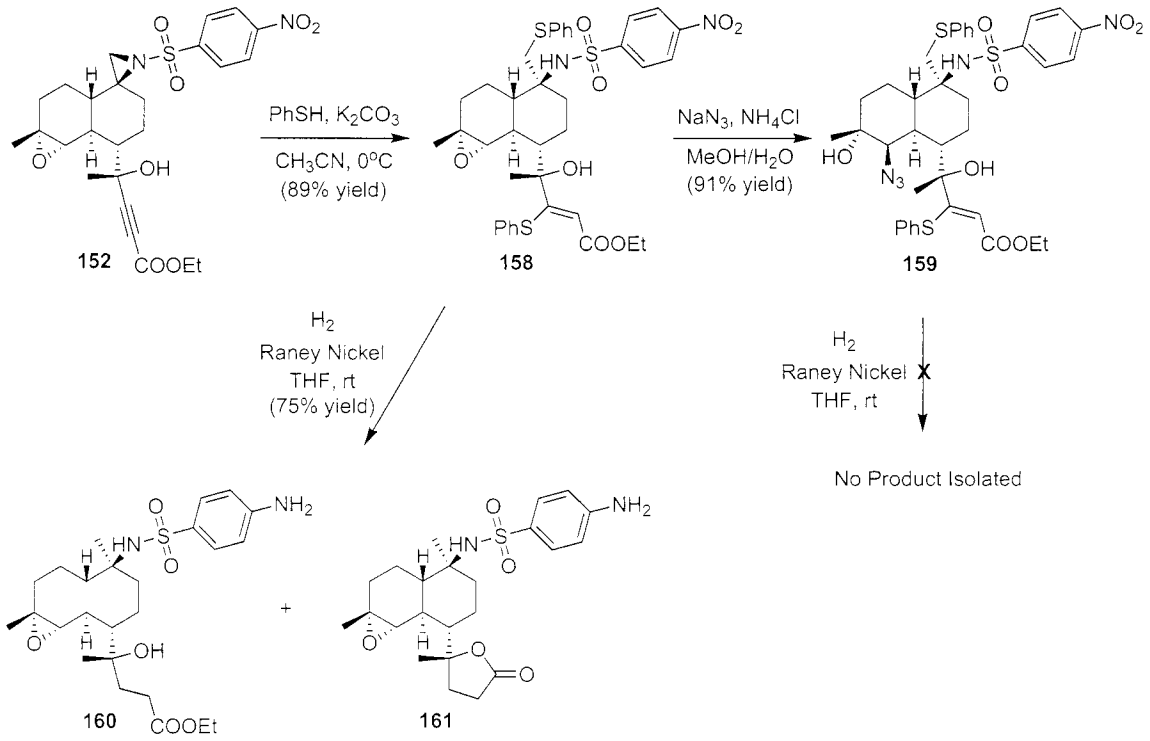
2.2.6.4 Second Generation Nosyl Approach

Based upon the inability to open the aniline-sulfonyl protected aziridine, an approach which involved ring opening prior to alkyne reduction was investigated. Surprisingly, upon exposure of nosyl aziridine **152** to hydride sources, the aziridine remained intact even under forcing conditions (see Scheme 2.19). Upon surveying the literature, no examples of hydride-induced nosyl aziridine ring opening were found, a fact which was not only troubling but also rather astounding given the growing popularity of this functional group. It was found that the only reported nucleophiles capable of opening nosyl aziridines were thiols,[39,41,43] amines,[38] alkoxides,[38] azides,[48] and nitriles.[38]

Of these potential nucleophiles, the thiolate nucleophile was most appealing because the resulting carbon-sulfur bond could potentially be cleaved by a variety of

known conditions.[49-52] As a result, aziridine **152** was treated with the potassium anion of thiophenol at low temperature. Under these reaction conditions, aziridine opening occurred with concomitant conjugate addition to the ynoate moiety (Scheme 2.21). Next, azido alcohol **159** was formed by treatment of **158** with ammonum azide in refluxing aqueous methanol. Exhaustive reduction of **159** was then attempted in anticipation that reduction of the thioethers and azide could be performed simultaneously. However, it was found that the material recovery for this reaction was very low, and none of the desired product was obtained. Next, the global reduction was attempted on epoxide **158**. Exhaustive reduction with Raney nickel cleaved the two thioethers, reduced the conjugated double bond, and reduced aryl nitro group in 75% yield.[53,54]

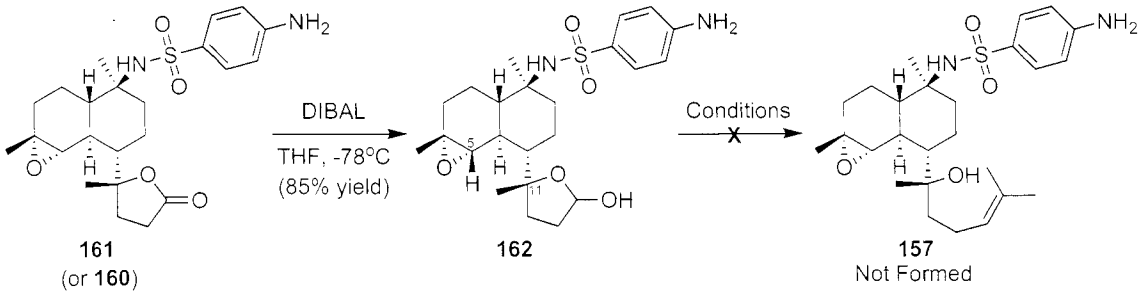
Scheme 2.21



Interestingly, the relative ratio of ester **160** to lactone **161** was dependent upon whether or not the Raney nickel was thoroughly washed with water and THF prior to introduction to the reaction. When the Raney nickel was washed thoroughly, ester **160** was the major product; when not washed, lactone **161** was the major product. Although speculative, this result may arise from the fact that sodium hydroxide is used in the process of synthesizing Raney nickel on an industrial scale.[55] The residual sodium hydroxide in the reaction mixture (from not washing the Raney nickel with copious amounts of water) might explain the observed lactonization event.

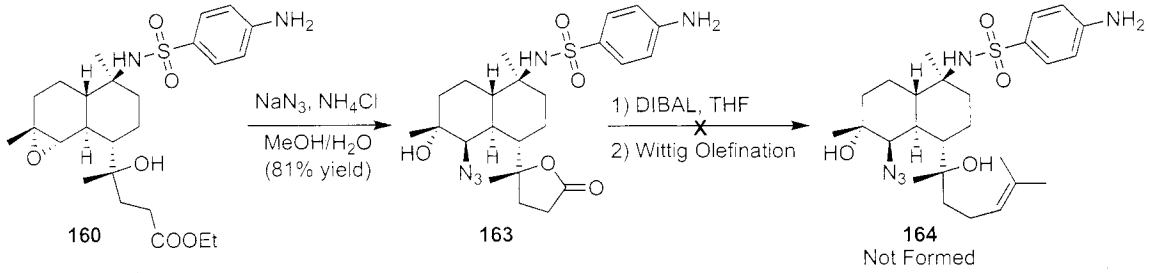
Reduction of either **160** or **161** to the corresponding lactol **162** proceeded uneventfully, and at this stage in the synthesis, we were poised to conduct the Wittig homologation to form bishomoallylic alcohol **157** (Scheme 2.22). Surprisingly, lactol **162** proved to be completely inert to several olefination conditions. A variety of bases (*n*-BuLi, *t*-BuLi, LiHMDS, NaH, KHMDS, $NaNH_2$, and NaH) to generate the ylide were screened; however, in all circumstances, the starting material was isolated unchanged. Furthermore, modifying the order of addition, reaction concentration, and solvent proved to be ineffective. Additionally, nucleophiles such as isopropenyl magnesium bromide failed to react with **162** as well.

Scheme 2.22



While not immediately obvious from a two-dimensional representation of **162**, there was reason to believe that there might be a steric interaction between the lactol functionality and the C(5) proton.[56] It was hypothesized that this interaction might be responsible for the lack of lactol reactivity, and that changing the conformation of the ring by opening the epoxide might alleviate this interaction. To this end, epoxide **160** was treated with ammonium azide to form azido alcohol **163** with concurrent lactonization (Scheme 2.23). However, upon two-electron reduction of **163** and attempted olefination, the latter reaction was once again unsuccessful and none of the desired bishomoallylic alcohol **164** was formed.

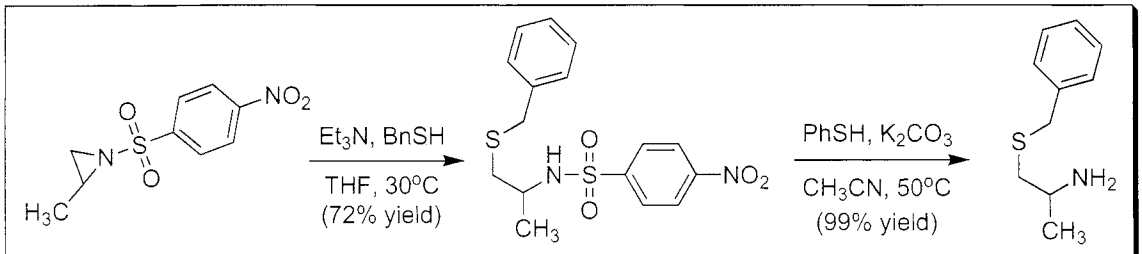
Scheme 2.23



2.2.6.5 Third Generation Nosyl Approach

While the origin of the lactol unreactivity in the second generation approach remained an enigma, it was clear from the first generation approach that opening the aziridine *and* deprotecting the nosyl group prior to alkyne reduction would be necessary. As explained in the previous section, the options available for nosyl aziridine opening (thiols, amines, alkoxides, azides, and nitriles) were rather limited and unattractive since they would most certainly add steps to the synthesis. However, it was recognized that a thiol nucleophile could potentially serve two purposes, since thiophenol was known to open nosyl aziridines and deprotect the nosyl protecting group (Scheme 2.24).[38,57]

Scheme 2.24



Maligres, P.E. et al. *Tetrahedron Lett.*, **1997**, *38(30)*, 5253-5256.

While this tandem aziridine opening/nosyl deprotection concept was very intriguing, the selectivity at elevated temperature on the highly functionalized intermediate **152**, *bearing five distinct electrophiles*, could prove uniquely challenging (Scheme 2.25). Indeed, treatment of aziridine **152** with thiophenol anion led to a mixture of products: sulfonamide **158**, amine **165** (desired), and tris-thioether **166**. Furthermore, it was found that the product distribution in this reaction was heavily dependent upon the nature of thiophenol counterion (Table 2.1).[58] When **152** was treated with the lithium

anion of thiophenol, sulfonamide **158**, which had undergone aziridine opening and Michael addition to the ynoate, was the sole product. Switching bases to sodium carbonate led predominantly to the formation of **158** and a small amount of desired amine **165**. Next, a 3:1 ratio of **158** to **165** was obtained when potassium carbonate was used. Upon exposure of **152** to the cesium anion of thiophenol, a significant amount of undesired tris-thioether **166** was formed arising from *trans*-diaxial opening of the C(4)-C(5) epoxide.

Scheme 2.25

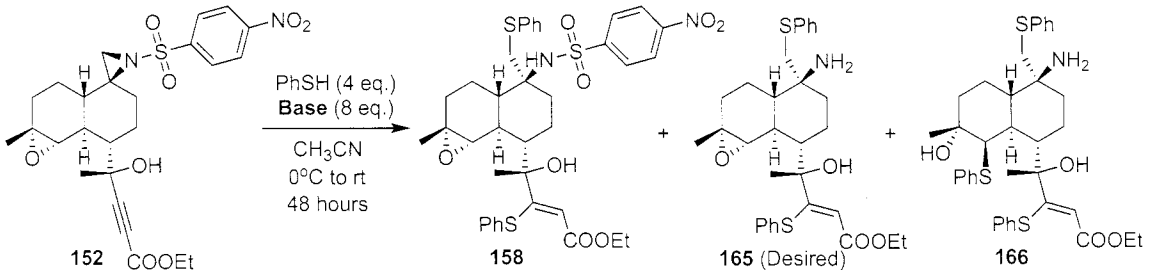


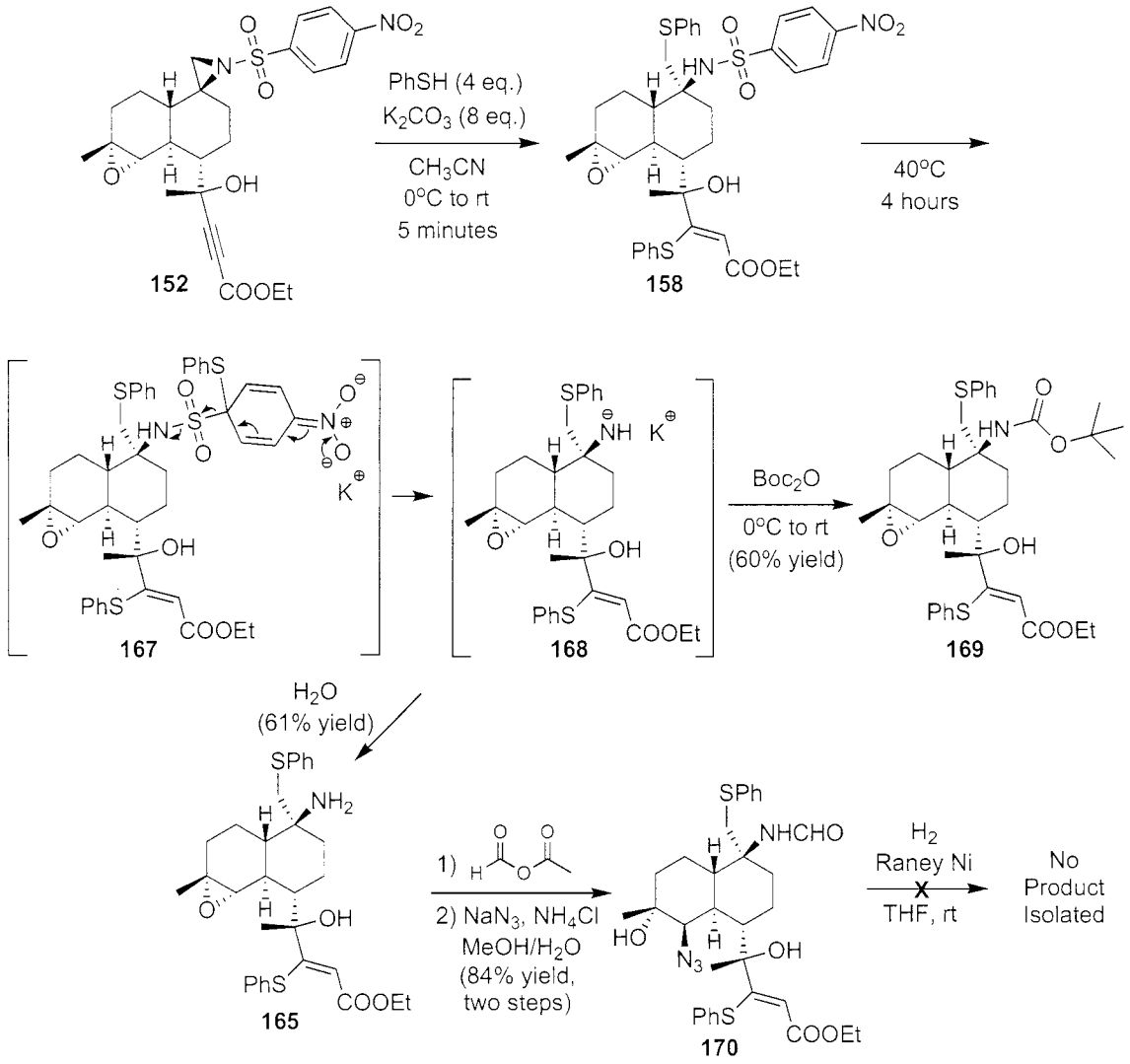
Table 2.1

Base	158	165 (Desired)	166
Li_2CO_3	100%	0%	0%
Na_2CO_3	95%	5%	0%
K_2CO_3	78%	22%	0%
Cs_2CO_3	43%	14%	43%

In light of these results, it was believed that advancement of **152** using potassium carbonate as the base at slightly elevated temperature may favor formation of desired amine **165**. In the event, **152** was converted into bis-thioether **158** immediately upon exposure to the potassium anion of thiophenol (Scheme 2.26). Upon gentle heating of the reaction at 40°C for a four-hour period, nucleophilic addition to the aromatic ring

occurred to give the transient Meisenheimer complex **167**[38] which fragmented to extrude the aryl ring and sulfur dioxide. The resulting amine **165** could be isolated at this time, or the anion **168** could be treated directly with di-*tert*-butyl dicarbonate in the same pot to provide carbamate **169** in 60% overall yield from **152**. Alternatively, addition of acetic formic anhydride to **165**, followed by purification and subjection to the previously described azidization conditions, afforded azido alcohol **170**. Raney nickel reduction of **170** failed to provide the desired product, a result which was reminiscent of an earlier attempt to reduce another azide-containing substrate under these conditions (see Scheme 2.21).

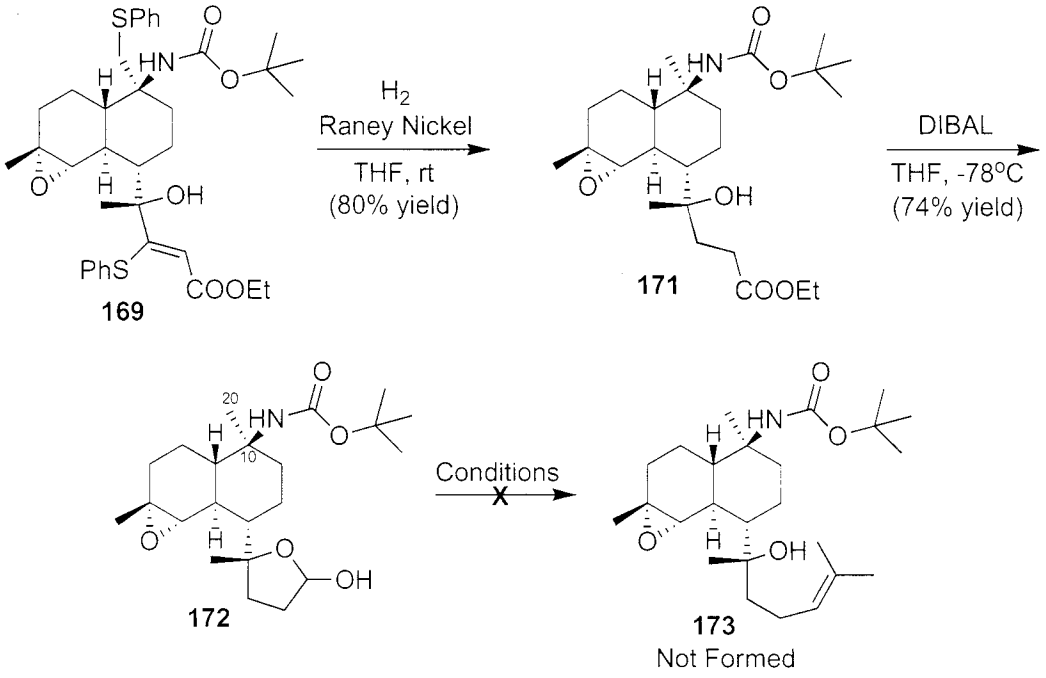
Scheme 2.26



While global reduction of **170** failed, it was found that the same conditions when applied to carbamate **169** proceeded to give the desired ester **171** in 80% yield (Scheme 2.27). Diisobutylaluminum hydride reduction of **171** provided lactol **172**, a key intermediate which we felt was ideally poised for advancement for the following two reasons. First, the C(10) nitrogen of **172**, protected with a *tert*-butoxycarbonyl (BOC) group, could be cleaved more easily than either of the previously-utilized nosyl or

aniline-sulfonyl groups. Second, while aziridine opening had been problematic on earlier substrates, **172** already possessed the necessary C(20) methyl group and required no additional manipulation. Hopeful that the major challenges to the bishomoallylic alcohol had been circumvented, we treated lactol **172** with isopropyl triphenylphosphonium ylide; to our tremendous disappointment, however, **172** was found to be completely unreactive. Other conditions (Grignards, organolithiums, Tebbe reagent,[59] etc.) were also unsuccessful and did not lead to the formation of bishomoallylic alcohol **173**.

Scheme 2.27



It was recognized that this lack of lactol reactivity had been observed previously on aniline-sulfonamide **162** (**162** → **157**, see Scheme 2.22) in which the C(10) nitrogen was also secondary. In all successful olefinations to date (**87** → **88**, see Scheme 1.10, **155** → **156**, Scheme 2.20), the reaction had been conducted with the aziridine ring in tact

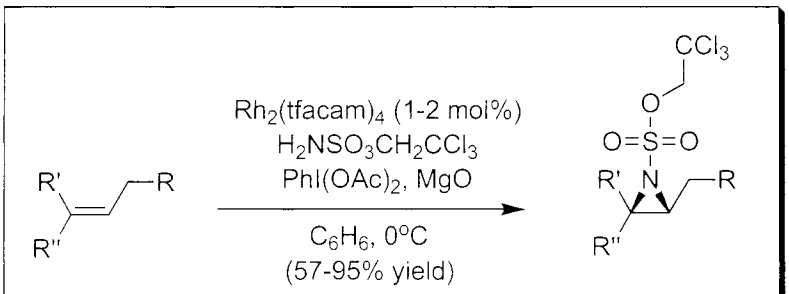
(i.e., tertiary nitrogen with no free hydrogen). Carbamate **171** was subjected to a variety of formylation and silyation conditions in an attempt to convert the secondary nitrogen into a tertiary nitrogen. However, no reaction was observed, presumably due to the hindered nature and low nucleophilicity of the C(10) nitrogen. The origin for this apparent interference of the free N-H with lactol opening is still unclear at this time.

2.2.7 Advancement of the Trichloroethoxysulfonyl Aziridination Approach

2.2.7.1 Optimization of the Aziridination Reaction

While efforts to advance the nosyl aziridination route were ongoing, we became interested in a recent report by Du Bois and co-workers in which olefins were converted into trichloroethoxysulfonyl aziridines in good yields (Scheme 2.28).[60] Although this novel aziridination procedure has been cited several times in recent review articles,[61,62,33,63] there are no reports in the literature to date reporting the application of this aziridination chemistry in a total synthesis effort.

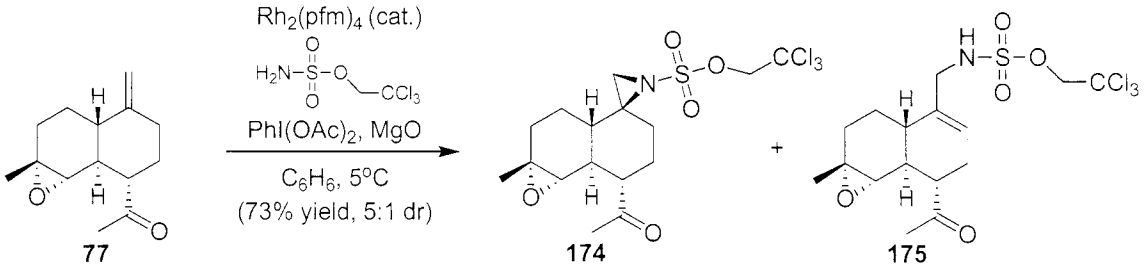
Scheme 2.28



Du Bois, J. et al. *J. Am. Chem. Soc.*, **2002**, *124*, 13672-13673.

Given the impressive yields and facile aziridine manipulations reported by Du Bois in his initial publication, these conditions were used in an attempt to install the C(10) nitrogen of kalihinol A. After much experimentation, it was found that rhodium (II) perfluorobutyramide ($Rh_2(pfm)_4$), a catalyst which was electronically similar to Du Bois' rhodium (II) trifluoroacetamide ($Rh_2(tfacam)_4$), successfully catalyzed the conversion of *exo*-methylene **77** to aziridine **174** in 73% yield and 5:1 diastereoselectivity (Scheme 2.29).[64] Upon silica gel chromatography, it was observed that **174** (and its diastereomer, not shown) partially decomposed to form allylic sulfamate ester **175**. This deleterious aziridine opening, which was presumably promoted by the acidic silica gel, demonstrated the instability of these aziridinated substrates.

Scheme 2.29

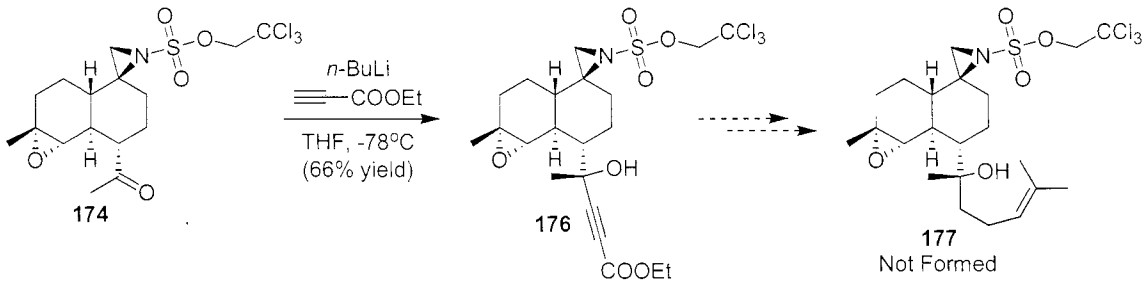


2.2.7.2 First Generation Trichloroethoxysulfonyl Approach

With the desired aziridine in place, **174** was advanced in a route analogous to the first generation nosyl aziridination approach (see Scheme 2.19). While the first generation nosyl aziridination approach had been unsuccessful due to difficulties resulting from nitro group reduction, such problems were not expected to affect these trichloroethoxysulfonyl-containing substrates. Treatment of **174** with the lithium anion

of ethyl propiolate provided ester **176** as a single diastereomer, albeit in lower yield than expected (Scheme 2.30). Next, a series of transformations (hydrogenation, ester reduction, and olefination) were attempted in an effort to make bishomoallylic alcohol **177**. However, throughout this sequence, the trichloroethoxysulfonyl aziridine was found to be highly unstable and decomposed rapidly at room temperature. Thus, this direct approach to **177** was abandoned, and a different approach involving opening of the unstable aziridine ring at an earlier stage was sought.

Scheme 2.30



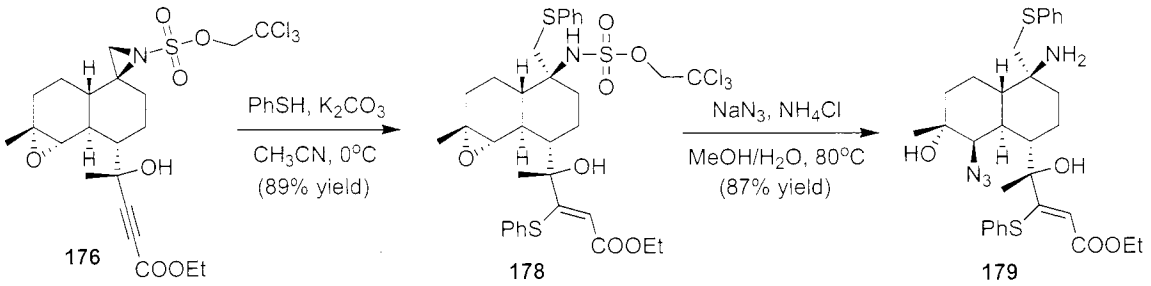
2.2.7.3 Second Generation Trichloroethoxysulfonyl Approach

In the second-generation approach, the goal was to open the trichloroethoxysulfonyl aziridine earlier in the sequence with nucleophilic sources of hydride. As stated previously, Du Bois' seminal publication on trichloroethoxysulfonyl aziridines remained the only account in the literature for their installation and manipulation.[60] It was reported that trichloroethoxysulfonyl aziridines could be regioselectively opened with azides, alcohols, amines, and thiols.[60] Similar to the reports on nosyl aziridines, there was no mention of hydride being used as a nucleophile. In an attempt to open the aziridine, aziridine **176** (see Scheme 2.30) was subjected to a variety

of hydride sources (Super-Hydride, $LiAlH_4$, DIBAL, L-Selectride, $NiCl_2/NaBH_4$, $((PPh_3)CuH)_6$,[65] etc.), and while several products resulted corresponding to 1,2- and 1,4-reduction of the ynoate, the aziridine remained intact under these conditions.[66]

As a result, we reluctantly turned to thiol nucleophiles to affect this transformation (Scheme 2.31). Aziridine opening and conjugate addition readily occurred upon exposure of aziridine **176** to thiophenol to afford bis-thioether **178**. Bis-thioether **178** was next reacted with ammonium azide at elevated temperature. We were pleased to find that the cleavage of the trichloroethoxysulfonyl protecting group unexpectedly accompanied the anticipated *trans*-diaxial epoxide opening to give azido alcohol **179**. The only known procedure for trichloroethoxysulfonyl deprotection requires the use of zinc/copper couple in acetic acid.[60] Thus, these azidization conditions represent a novel, unprecedented method of trichloroethoxysulfonyl protecting group cleavage.

Scheme 2.31

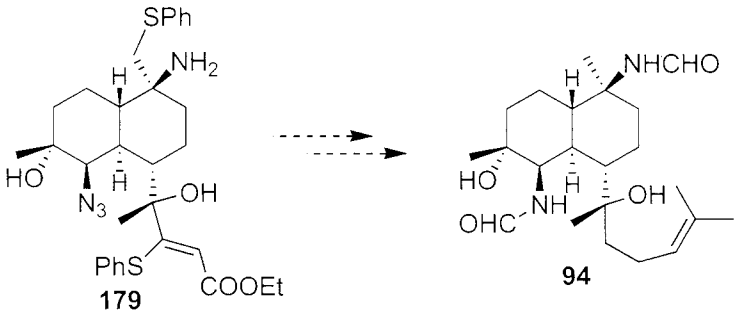


2.2.8 Future Directions: Implementation of the Model System

Amine **179** is currently the most advanced synthetic intermediate towards the total synthesis of (+)-kalihinol A. To date, efforts to reductively cleave the thioethers (and/or

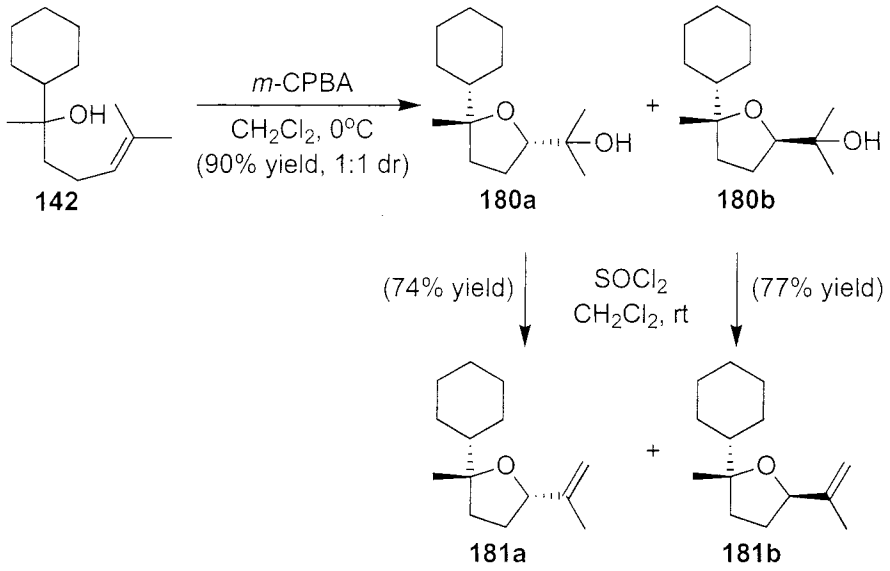
their corresponding sulfones) of **179** and related intermediates have met with little success. In the event that appropriate reaction conditions are realized, the goal is to gain access to the versatile intermediate bishomoallylic alcohol **94** (Scheme 2.32).

Scheme 2.32



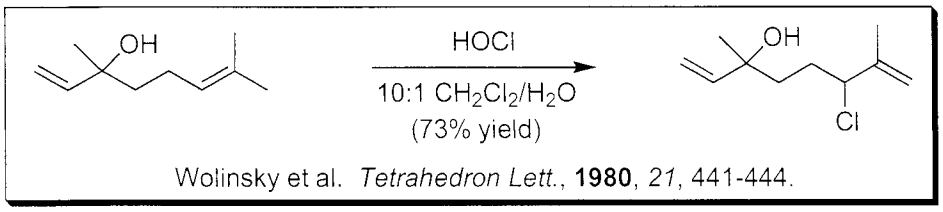
In preparation for installation of the chlorotetrahydropyran on fully functionalized **94**, model bishomoallylic alcohol **142**, which had been synthesized previously for studies on nucleophilic addition to the C(11) ketone (see Scheme 2.15), was used to assess the regiochemical preference for cyclization (Scheme 2.33). It was found that exposure of **142** to a wide range of electrophiles consistently demonstrated a preference for the 5-*exo* over 6-*endo* mode of cyclization. For example, **142** was readily converted into diastereomeric tetrahydrofurans **180a** and **180b** and separated by silica gel chromatography (Scheme 2.33). The tertiary alcohols were then eliminated to afford the tetrahydrofurans with isopropenyl sidechains **181a** and **181b**. This regioselectivity in the cyclization was not unexpected based upon literature precedent, and similar chemistry was utilized efficiently in the total synthesis of (±)-kalihinol C.[5,67,68,28]

Scheme 2.33



For kalihinol A, however, it was clear that a different cyclization protocol would be necessary to form the six-membered ring. Formation of a 2,2,6,6-tetrasubstituted tetrahydropyran presents a unique challenge. It was recognized that 6-*endo* cyclization of a bishomoallylic alcohol would not be feasible, due in large part to the anticipated steric interaction experienced by the two axial methyl groups in the transition state. In 2001, Urones and co-workers reported the formation of a 2,2,6,6-tetrasubstituted tetrahydropyran by employing a 6-*exo* cyclization.[69] Prior to this disclosure, Wolinsky and co-workers reported that a bishomoallylic alcohol was directly converted into an allylic chloride (Scheme 2.34).[70]

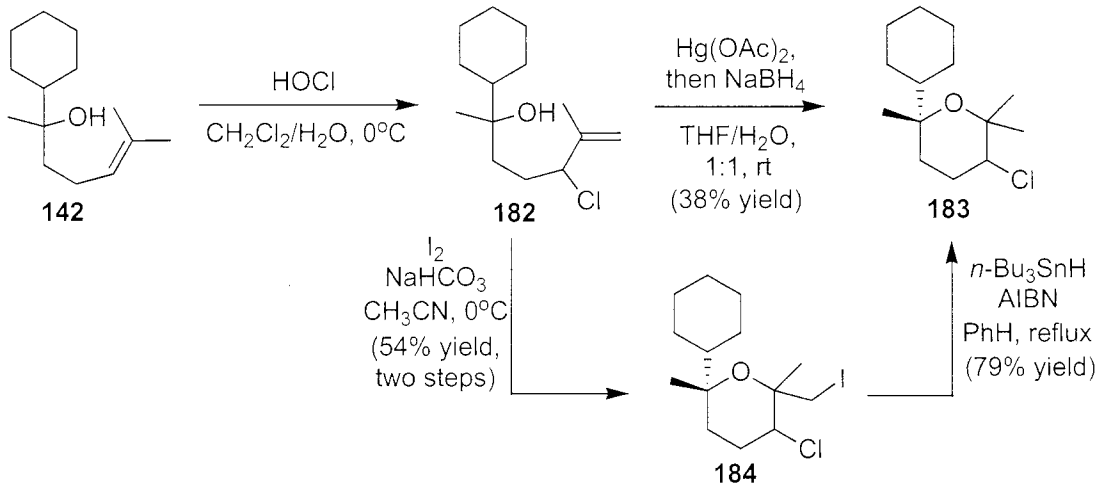
Scheme 2.34



Wolinsky et al. *Tetrahedron Lett.*, **1980**, *21*, 441-444.

It was found that exposure of model bishomoallylic alcohol **142** to hypochlorous acid provided allylic chloride **182** (Scheme 2.35). The chlorotetrahydropyran **183** could be formed directly from **182** using an oxymercuration/demercuration protocol. Unfortunately, the optimized conditions for this reaction provided the product in only 38% yield. As a result, an alternative method was devised in which iodoetherification of **182** provided a mixture of iodide diastereomers **184**. Selective removal of the primary iodide in the presence of the secondary chloride was achieved under radical conditions to afford **183**.

Scheme 2.35



It is anticipated that the completion of (+)-kalihinol A can be achieved by implementation of these model system conditions on bishomoallylic alcohol **94** (see Scheme 2.32) followed by dehydration of the two formamides to arrive at the natural product.

2.3 Conclusions

While efforts towards (+)-kalihinol A have not resulted in the completion of its total synthesis, several noteworthy accomplishments have been realized. Early challenges in the synthesis, namely the intramolecular Diels-Alder cyclization and nucleophilic addition to the C(11) ketone, were solved due to detailed analysis of reaction results. The previously employed tosyl aziridination, which had serious limitations when applied to the synthesis of (+)-kalihinol A, was initially replaced with a much improved nosyl aziridination reaction. Most recently, the trichloroethoxysulfonyl aziridination approach has led not only to the development of a novel aziridination catalyst (rhodium (II) perfluorobutyramide) but also has uncovered an unprecedented method for trichloroethoxysulfonyl deprotection. Lastly, a protocol representing a novel, effective method of forming 2,2,6,6-tetrasubstituted tetrahydropyrans has been devised. The ability of rhodium (II) perfluorobutyramide to catalyze the aziridination of olefins with different nitrene sources is discussed in detail in the following chapter.

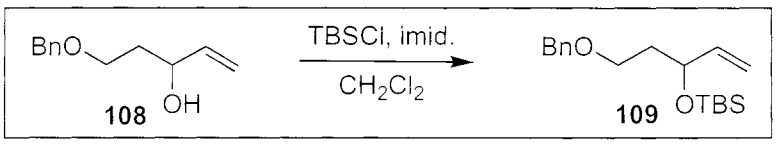
2.4 Experimentals

2.4.1 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). 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.

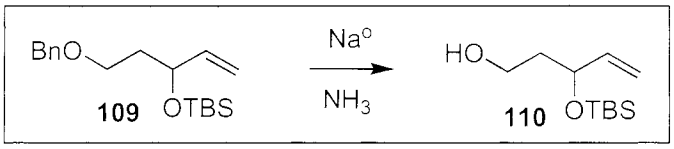
2.4.2 Preparative Procedures

Preparation of silyl ether 109



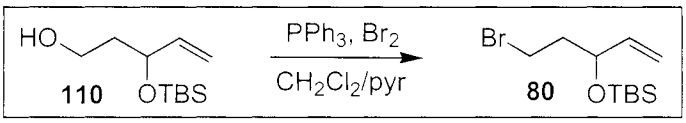
Silyl ether 109. To a solution of alcohol **108** (16.7 g, 87.0 mmol, 1.0 equiv.) in CH_2Cl_2 (500 mL) was added imidazole (7.1 g, 104.3 mmol, 1.2 equiv.) at 0°C followed by *tert*-butyldimethylsilyl chloride (15.7 g, 104.3 mmol, 1.2 equiv.). The reaction was allowed to warm to rt over 3 hours. Additional imidazole (2.4 g, 35.3 mmol, 0.41 equiv.) and *tert*-butyldimethylsilyl chloride (5.2 g, 34.5 mmol, 0.40 equiv.) were added at room temperature. The reaction was filtered to remove hydrochloride salts and the fitrate was concentrated *in vacuo*. The filtrate was purified by silica gel column chromatography (18:1 hexanes:ethyl acetate) to afford **109** (25.0 g, 94% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.28 (comp m, 5H), 5.92-5.80 (m, 1H), 5.20 (td, *J*=1.5, 17.2 Hz, 1H), 5.07 (td, *J*=1.3, 10.4 Hz, 1H), 4.53 (q, *J*=11.8 Hz, 2H), 4.36 (q, *J*=6.3 Hz, 1H), 3.68-3.50 (m, 2H), 1.88-1.80 (m, 2H), 0.95 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 138.6, 128.4, 127.8, 127.6, 113.8, 73.1, 70.9, 66.8, 38.2, 26.0, 26.0, 25.8, -2.8, -4.2, -4.8 ppm; IR (thin film/NaCl) 3088 (w), 3066 (w), 3031 (w), 2955 (s), 2929 (s), 2886 (s), 2857 (s), 1496 (w), 1472 (s), 1405 (m), 1361 (m), 1253 (s), 1093 (s), 1028 (s), 837 (s), 776 (s) cm^{-1}; HRMS (FAB) *m/z* found: 329.1909 [calc'd for $C_{18}H_{30}O_2NaSi$ (M+Na): 329.1913].

Preparation of alcohol 110



Alcohol 110. Ammonia gas (150 mL) was condensed at -78°C into a round-bottom flask. Pieces of sodium metal (5.0 grams, 218 mmol, 5.0 equiv.) was added slowly, and the resulting blue solution was stirred for 10 minutes. Next, benzyl ether **109** (13.47 g, 44.02 mmol, 1.0 equiv.) was added slowly as a solution in THF (20 mL). The reaction was stirred at -78°C for 2 hours before quenching carefully with NH_4Cl (10 grams). The reaction was allowed to warm to rt to evaporate ammonia, and the resulting oil was dissolved in ethyl acetate (300 mL) and hexanes (300 mL). After washing the organic layers were brine (3 x 100 mL), the organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The resulting oil was purified by silica gel column chromatography (12:1 to 1:1 hexanes:ethyl acetate) to afford **110** (7.22 g, 76% yield) as a clear oil. The spectroscopic characteristics were identical to those reported in the literature: Hatakeyama, S.; Okano, T.; Maeyama, J.; Esumi, T.; Hiyamizu, H.; Iwabuchi, Y.; Nakagawa, K.; Ozono, K.; Kawase, A.; Kubodera, N. *Bioorganic & Medicinal Chemistry* **2001,** *9*, 403-415.

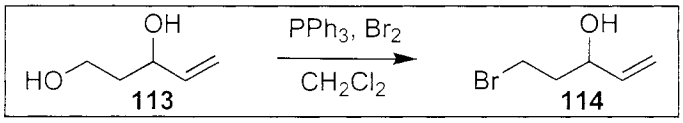
Preparation of bromide 80



Bromide 80. To a solution of triphenylphosphine (22.6 g, 86.2 mmol, 1.3 equiv.) in dichloromethane (380 mL) at 0°C was added bromine (4.4 mL, 86.2 mmol, 1.3 equiv.) dropwise. The reaction was stirred at 0°C for 15 minutes and then warmed to rt. The reaction was then cooled back to 0°C and pyridine (14.0 mL, 172.4 mmol, 2.6 equiv.)

was added, followed by addition of alcohol **110** (14.3 g, 66.3 mmol, 1.0 equiv.) as a solution in dichloromethane (20 mL). The reaction was allowed to warm to rt and run overnight. The organic layer was washed with saturated sodium sulfite solution (1 x 100 mL) and brine (2 x 100 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The resulting oil was suspended in ether (100 mL) and hexanes (100 mL) and stirred overnight. The suspension was cooled to 0°C and filtered to remove salts. After concentration *in vacuo*, the resulting oil was purified by silica gel column chromatography (9:1 pentane:ether) to afford **80** (13.7 g, 74% yield) as a clear oil. The spectroscopic characteristics were identical to those reported in the thesis dissertation of Dr. Ryan D. White, Yale University (2003).

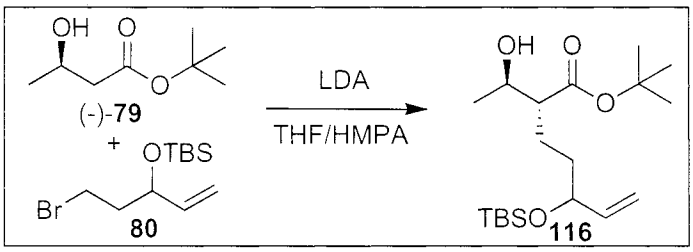
Preparation of bromide 114



Bromide 114. To a solution of triphenylphosphine (11.8 g, 45.1 mmol, 1.0 equiv.) and imidazole (3.1 g, 45.1 mmol, 1.0 equiv.) in CH_2Cl_2 (300 mL) at 0°C was added bromine (3.1 g, 45.1 mmol, 1.0 equiv.) dropwise. The ice bath was removed and the reaction was stirred at rt for 15 minutes. The reaction was then cooled to -42°C and alcohol **113** (4.60 g, 45.1 mmol, 1.0 equiv.) was added as a solution in CH_2Cl_2 (25 mL). The reaction was warmed to rt and stirred at rt for at least 5 hours. (It is imperative for the reaction to stir at rt for an extended period of time to fully convert triphenylphosphonium salt intermediate into desired bromide). The reaction was then

filtered and the filtrate was concentrated *in vacuo*. The crude ^{1}H NMR showed approximately a 6:1 ratio of primary:secondary alcohol displacement products. The filtrate was purified by silica gel column chromatography (7:1 hexanes:ethyl acetate to 2:1 ethyl acetate:hexane) to give bromide **114** (5.68 g, 76% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93-5.80 (m, 1H), 5.30 (dt, *J*=1.3, 17.3 Hz, 1H), 5.17 (dt, *J*=1.2, 10.4 Hz, 1H), 4.35 (br s, 1H), 3.62-3.40 (m, 2H), 2.14-1.99 (m, 2H), 1.73 (d, *J*=4.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 115.8, 71.1, 39.5, 30.0 ppm; IR (thin film/NaCl) 3355 (br s), 2967 (m), 2901 (w), 1422 (m), 1257 (sh s), 1034 (s), 992 (s), 927 (s), 800 (w) cm^{-1}; HRMS (EI) *m/z* found: 163.9837 [calc'd for C_5H_9BrO (M+): 163.9837].

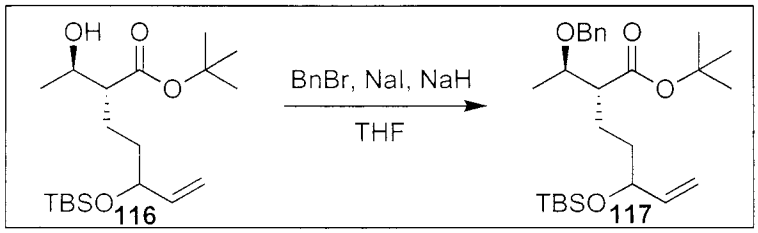
Preparation of alcohol 116



Alcohol 116. To a solution of β-hydroxy ester (-)-**79** (1.00 g, 6.24 mmol, 1.0 equiv) in THF (35 mL) at -78°C was added LDA (0.5 M in THF, 26.0 mL, 13.1 mmol, 2.1 equiv). After 20 minutes, the reaction was warmed to -42°C, HMPA (3.2 mL, 18.7 mmol, 3.0 equiv) was added, followed by a solution of alkyl bromide **80** (2.61 g, 9.36 mmol, 1.5 equiv) in THF (5 mL) added via syringe pump over 1 hour. After an additional 2 hours, the reaction was warmed to 0°C for 1 hour 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 **80** (1.65 g, 74% yield, 55:45 mixture of diastereomers) as a clear oil. ^{1}H 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]; $[\alpha]_D^{20}$ +2.9° (*c* 1.00, $CHCl_3$).

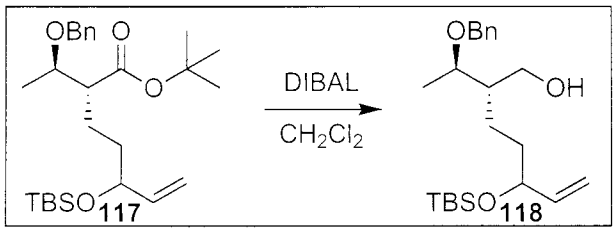
Preparation of benzyl ether 117



Benzyl ether 117. To a solution of alcohol **116** (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 hours 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 **117** (12.1 g, 93% yield, 1:1 mixture of diastereomers) as a clear oil. ^{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]; $[\alpha]_D^{20}$ -2.3° (*c* 1.00, $CHCl_3$).

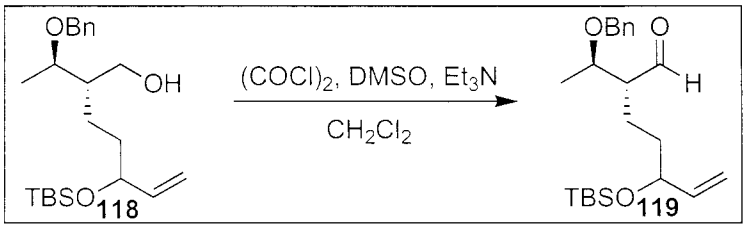
Preparation of alcohol 118



Alcohol 118. To a solution of **117** (19.6 g, 43.7 mmol, 1.0 equiv) in CH_2Cl_2 (350 mL) at -78°C was added diisobutylaluminum hydride (17.1 mL, 96.2 mmol, 2.2 equiv). After 1 hour, the reaction was quenched with aqueous Rochelle's salt (100 mL, 20% *w/v*). 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 **118** (14.9 g, 90%, 1:1 mixture of diastereomers) as a clear oil. ^{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]; $[\alpha]_D^{20}$ -24.3° (*c* 1.00, $CHCl_3$).

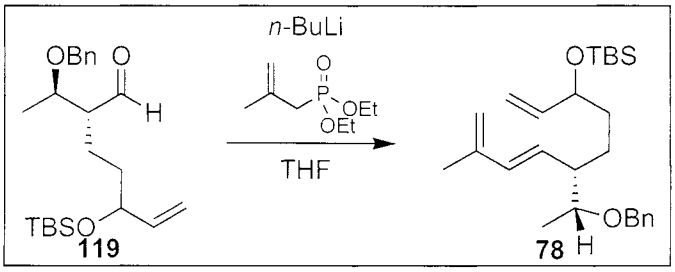
Preparation of aldehyde 119



Aldehyde 119. To a solution of oxalyl chloride (3.57 mL, 40.9 mmol, 1.1 equiv) in CH_2Cl_2 (250 mL) at -78°C was added DMSO (5.80 mL, 81.8 mmol, 2.2 equiv) and stirred for 10 min. A solution of **118** (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 reaction was allowed to warm to rt. Water (100 mL) was added and the organic layer washed with brine (100 mL) and dried with Na_2SO_4.

After concentration *in vacuo*, the resulting residue was purified by silica gel column chromatography (18:1 then 9:1 hexanes:EtOAc) to afford **119** (14.9 g, 89%, 1:1 mixture of diastereomers) as a clear oil. ^{1}H 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]; $[\alpha]_D^{20}$ -22.6° (*c* 1.00, $CHCl_3$).

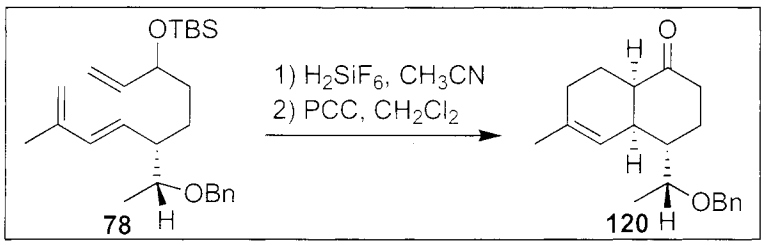
Preparation of triene 78



Triene 78. To 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 added *n*-BuLi (15.7 mL, 36.0 mmol, 2.3 M in hexanes, 1.3 equiv) and the solution was stirred for 5 min. A solution of **119** (10.4 g, 27.7 mmol, 1.0 equiv) in THF (10 mL) was added and stirring continued for an

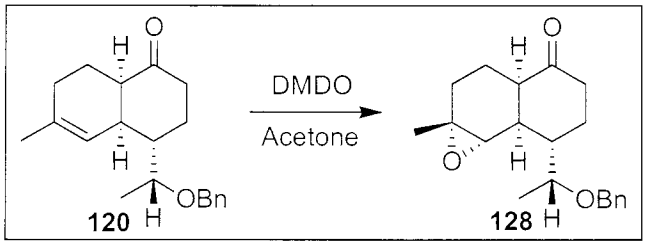
additional 15 minutes. The reaction was warmed to rt and stirred for an additional 1 hour before quenching with water (100 mL). The mixture was diluted with hexanes (200 mL) and the organic layer was washed with water (3 x 100 mL), brine (1 x 100 mL), and dried with Na_2SO_4. Concentration *in vacuo* afforded **78** (21.9 g, 79%, 1:1 mixture of diastereomers) as a clear 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}H 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]; $[\alpha]_D^{20}$ +10.3° (*c* 1.00, $CHCl_3$).

Preparation of *cis*-decalin 120



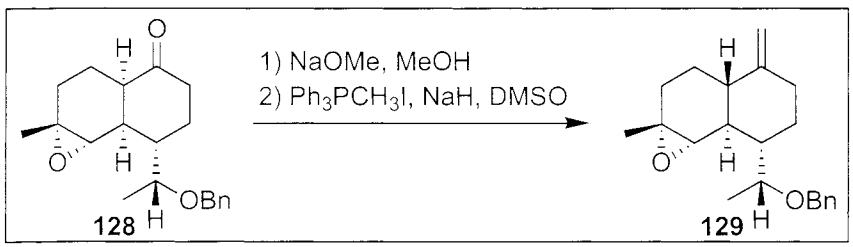
***cis*-Decalin 120.** To a solution of **78** (6.92 g, 22.0 mmol, 1.0 equiv) in acetonitrile (225 mL) at 0°C was added 20% aqueous fluorosilicic acid (1.6 mL, 2.2 mmol, 0.1 equiv). After 4 hours, the reaction was quenched with K_2CO_3 (approximately 5 grams) and diluted with hexanes (100 mL) and water (100 mL). The organic layer was washed with water (1 x 100 mL), brine (1 x 100 mL) and dried with Na_2SO_4. Concentration *in vacuo* provided a residue which was dissolved 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 1 hour, the reaction was warmed to rt and stirred for an additional 12 hours. Celite was added and the mixture was filtered. Concentration *in vacuo* followed by silica gel column chromatography (9:1 hexanes:EtOAc) afforded **120** (4.27 g, 65% yield from **78**) as a clear 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]; $[\alpha]_D^{20}$ -52.8° (*c* 0.97, $CHCl_3$).

Preparation of epoxide 128



Epoxide 128. 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 **120** (1.69 g, 5.65 mmol, 1.0 equiv) in acetone (10 mL). After 2 hours, the solution was slowly warmed to 25°C and dimethyl sulfide (5 mL) was added in order to quench any excess dimethyl dioxirane. The reaction was then concentrated *in vacuo*. ^{1}H NMR of the resulting oil showed a mixture of diastereomers in the ratio of 94:6 which could be purified by silica gel column chromatography (9:1 then 3:1 hexanes:EtOAc) to afford **128** (1.56 g, 88% yield) as a clear 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]; $[\alpha]_D^{20}$ -87.0° (*c* 0.96, $CHCl_3$).

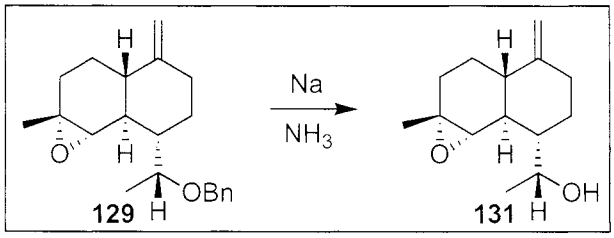
Preparation of olefin 129



128 129

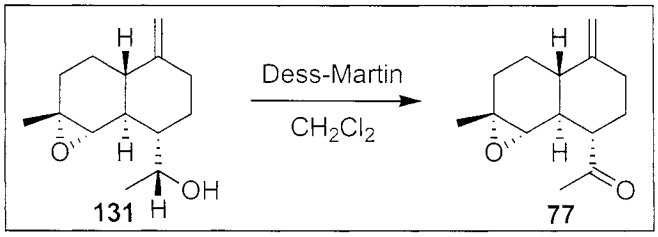
Olefin 129. To a solution of epoxide **128** (1.51 g, 4.80 mmol, 1.0 equiv) in MeOH (50 mL) at rt was added NaOMe (15 mg, 0.24 mmol, 0.05 equiv.). After 36 hours, the solution was concentrated *in vacuo*. ^{1}H NMR showed a 3:2 equilibrium mixture of *trans*- to *cis*-decalins which could be used without 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 hours, and then cooled to 25°C before adding methyltriphenylphosphonium iodide (3.43 g, 9.60 mmol, 2.0 equiv.) and THF (10 mL). After stirring for 30 minutes, the resulting yellow mixture was added in 0.1 equiv. portions every 2 hours to a crude mixture of decalins in THF (50 mL). After the 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 with Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (100% hexanes then 9:1 hexanes:EtOAc) to give **129** (1.17 g, 78% yield) as a clear 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]; $[\alpha]_D^{20}$ -33.2° (*c* 1.15, $CHCl_3$).

Preparation of alcohol 131



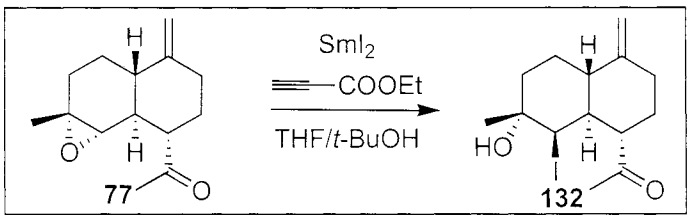
Alcohol 131. Ammonia gas (40 mL) was condensed at –78°C and sodium metal (368 mg, 16 mmol, 10.0 equiv.) was added followed by benzyl ether **129** (500 mg, 1.60 mmol, 1.0 equiv.) in THF (4 mL). After 1 hour, the reaction was quenched with solid ammonium chloride (1 g) and the ammonia allowed to evaporate by warming to rt. The resulting residue was taken up in EtOAc (50 mL), washed with water (2 x 25 mL), brine (1 x 25 mL) and dried with Na_2SO_4. The organic extracts were concentrated *in vacuo* and the resulting oil was purified by silica gel column chromatography (3:1 then 1:1 hexanes:EtOAc) to afford **131** (285 mg, 80%) as a clear oil. ^{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]; $[\alpha]_D^{20}$ -51.7° (*c* 1.04, $CHCl_3$).

Preparation of ketone 77



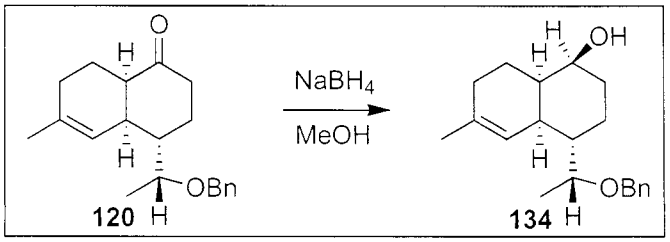
Ketone 77. To a solution of alcohol **131** (300 mg, 1.35 mmol, 1.0 equiv) in undistilled CH_2Cl_2 (20 mL) was added Dess-Martin periodinane (744 mg, 1.76 mmol, 1.3 equiv). The mixture was stirred at -10°C for 2 hours and then allowed to warm to rt overnight. Saturated aqueous $NaHCO_3$ (5 mL) and $Na_2S_2O_3$ (5 mL) were then added. After 30 minutes, the organic layer was separated and dried with Na_2SO_4. The solvent was concentrated *in vacuo* to give a residue which was purified by silica gel column chromatography (9:1 then 3:1 hexanes:EtOAc) to afford ketone **77** (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]; $[\alpha]_D^{20}$ -97.8° (*c* 0.90, $CHCl_3$).

Preparation of iodide 132



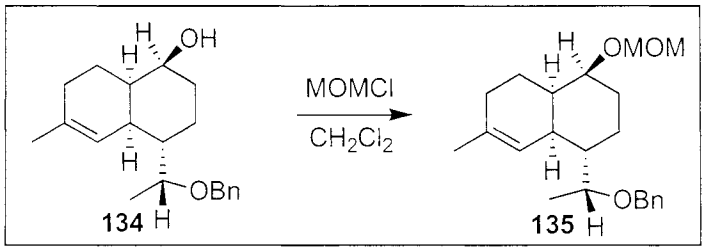
Iodide 132. To a solution of freshly-made samarium (II) iodide (1.15 mL, 0.115 mmol, 0.1 M, 5 equiv., prepared from Sm metal (300 mg, 2.0 mmol, 2.0 equiv.) and diiodoethane (282 mg, 1.0 mmol, 1.0 equiv.) in THF (10 mL)) was added *t*-butanol (5 μL, 0.046 mmol, 2.0 equiv.), ethyl propiolate (23 μL, 0.23 mmol, 10 equiv.) and ketone **77** (5.0 mg, 0.023 mmol, 1.0 equiv.) in THF (1 mL) at 0°C. The reaction was stirred for 5 minutes and quenched with 1N HCl (approximately 500 μL) dropwise. The reaction was diluted with Et_2O (10 mL) and washed with brine (3 x 10 mL). The organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (12:1 hexanes:ethyl acetate) to provide **132** (4 mg, 51% yield) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.77 (s, 1H), 4.69 (s, 1H), 4.27-4.22 (m, 1H), 2.97-2.87 (m, 1H), 2.42 (td, *J*=3.1, 10.7 Hz, 1H), 2.24 (s, 3H), 2.19-1.98 (comp m, 3H), 1.87-1.57 (comp m, 4H), 1.51 (s, 3H), 1.46-1.19 (comp m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.5, 149.8, 107.6, 72.4, 58.1, 52.0, 43.1, 39.2, 36.3, 33.4, 32.7, 31.2, 30.7, 24.4 ppm; IR (thin film/NaCl) 3456 (br m), 2930 (s), 2858 (m), 2093 (w), 1737 (m), 1721 (s), 1710 (s), 1693 (s), 1643 (m), 1485 (m) cm^{-1}; HRMS (EI) *m/z* found: 330.0480 [calc'd for $C_{14}H_{19}IO$ (M-H_2O): 330.0480].

Preparation of alcohol 134



Alcohol 134. To a solution of ketone **120** (150 mg, 0.503 mmol, 1.0 equiv.) in aqueous EtOH (95% *v/v*, 5 mL) was added $NaBH_4$ (23 mg, 0.603 mmol, 1.2 equiv.) at 0°C. After 20 minutes, additional $NaBH_4$ (23 mg, 0.603 mmol, 1.2 equiv.) was added at 0°C. After 20 additional minutes, the reaction was quenched by the slow addition of aqueous acetic acid (1 mL, 10% *v/v*) at 0°C and diluted with ethyl acetate (10 mL). The organic layer was washed with brine (3 x 10 mL), the organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. ^{1}H NMR of the crude reaction mixture indicated a 16:1 ratio of diastereomers. The resulting oil was purified by silica gel column chromatography (12:1 to 9:1 hexanes:ethyl acetate) to afford major diastereomer **134** (131 mg, 87% yield) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.22 (comp m, 5H), 5.40 (br s, 1H), 4.49 (d, *J*=2.0 Hz, 2H), 3.83-3.74 (comp m, 2H), 2.09-1.92 (comp m, 4H), 1.88-1.71 (comp m, 5H), 1.66 (s, 3H), 1.61-1.50 (comp m, 2H), 1.44 (dq, *J*=3.2, 12.9 Hz, 1H), 1.12 (d, *J*=6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4, 135.4, 128.4, 127.6, 127.4, 123.3, 75.0, 73.0, 70.5, 42.4, 40.6, 38.1, 30.8, 29.8, 23.9, 22.8, 16.8, 14.2 ppm; IR (thin film/NaCl) 3295 (br m), 3063 (w), 3028 (w), 2931 (s), 2890 (s), 2867 (s), 2830 (m), 1496 (w), 1452 (sh s), 1379 (m), 1353 (m), 1297 (w), 1100 (s), 1067 (sh s), 1052 (s), 873 (m) cm^{-1}; HRMS (EI) *m/z* found: 300.2096 [calc'd for $C_{20}H_{28}O_2$ (M): 300.2089].

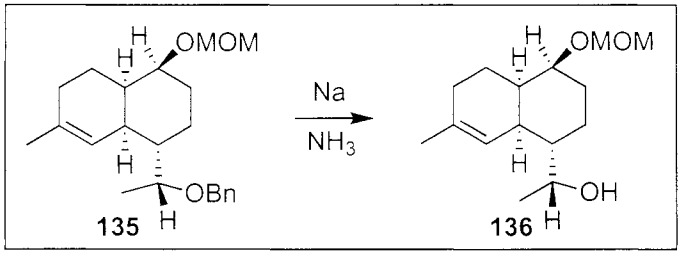
Preparation of acetal 135



Acetal 135. To a solution of alcohol **134** (125 mg, 0.416 mmol, 1.0 equiv.) in CH_2Cl_2 (3 mL) at 0°C was added diisopropylethylamine (724 μL, 4.16 mmol, 10.0 equiv.) and MOMCl (158 μL, 2.08 mmol, 5.0 equiv). The reaction was allowed to warm to rt gradually. After 5 hours, additional diisopropylethylamine (724 μL, 4.16 mmol, 10.0 equiv.) and MOMCl (158 μL, 2.08 mmol, 5.0 equiv) were added at rt, and the reaction proceeded overnight. The reaction was then diluted with CH_2Cl_2 (10 mL) and washed with brine (3 x 10 mL). The organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (100% hexanes to 18:1 to 12:1 hexanes:ethyl acetate) to afford **135** (63 mg, 44% yield) as a clear oil and recovered starting material **134** (58 mg, 45% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.21 (comp m, 5H), 5.40 (br s, 1H), 4.69 (s, 2H), 4.49 (s, 2H), 3.84-3.74 (m, 1H), 3.73-3.63 (m, 1H), 3.38 (s, 3H), 2.13-1.93 (comp m, 3H), 1.92-1.71 (comp m, 4H), 1.70-1.24 (comp m, 6H), 1.22-0.98 (comp m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 135.3, 128.3, 127.5, 127.3, 123.3, 94.7, 77.8, 75.0, 70.4, 55.3, 42.4, 38.5, 38.0, 30.8, 27.0, 23.8, 22.7, 17.3, 14.0 ppm; IR (thin film/NaCl) 3030 (w), 2935 (s), 2881 (s), 1724 (w), 1496 (w), 1452 (m), 1378 (m), 1353 (w), 1181 (w),

1138 (s), 1105 (s), 1070 (s), 1040 (s), 916 (m) cm^{-1}; HRMS (CI) *m/z* found: 344.2352 [calc'd for $C_{22}H_{32}O_3$ (M+): 344.2351].

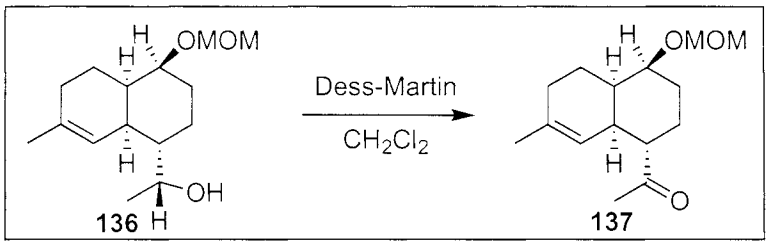
Preparation of alcohol 136



Alcohol 136. Ammonia gas (10 mL) was condensed into a three-neck round bottom flask with dry ice/acetone condenser at -78°C. Sodium metal (150 mg, 6.52 mmol, 35.6 equiv.) was added and stirred for 10 minutes. To this solution was added benzyl ether **135** (63 mg, 0.183 mmol, 1.0 equiv.) in THF (2 mL). The reaction was stirred at -78°C for 20 minutes, and then solid NH_4Cl (approximately 1 g) and hexanes (10 mL) were added. The reaction was allowed to warm to rt, and the organic layer was extracted with brine (3 x 10 mL). The organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting oil was purified by silica gel column chromatography (9:1 to 4:1 hexanes:ethyl acetate) to afford **136** (40 mg, 87% yield) as a clear oil. ^1H NMR (500 MHz, $CDCl_3$) δ 5.44 (br s, 1H), 4.66 (s, 2H), 4.11-4.02 (m, 1H), 3.68-3.61 (m, 1H), 3.35 (s, 3H), 2.11-1.93 (comp m, 3H), 1.86-1.70 (comp m, 4H), 1.68-1.39 (comp m, 8H), 1.09 (d, *J*=6.4 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.0, 123.6, 95.1, 78.1, 68.2, 55.6, 46.1, 38.9, 38.8, 31.1, 27.3, 24.1, 22.8, 17.6, 17.3 ppm; IR (thin film/NaCl) 3423 (br m), 2934 (s), 2884 (s), 2830 (m), 1449 (m), 1400 (w), 1375

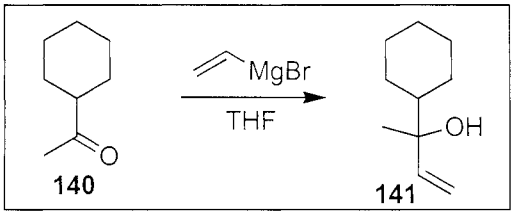
(m), 1298 (w), 1212 (w), 1178 (w), 1143 (s), 1105 (s), 1038 (s), 1021 (s), 952 (m) cm^{-1}; HRMS (EI) *m/z* found: 272.2499 [calc'd for $C_{15}H_{28}O_4$ ($M+H_2O$): 272.1988].

Preparation of ketone 137



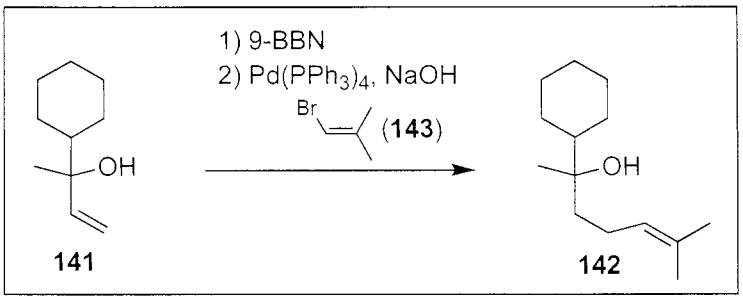
Ketone 137. To a solution of alcohol **136** (40 mg, 0.157 mmol, 1.0 equiv.) in undistilled CH_2Cl_2 (5 mL) was added Dess-Martin periodinane (80 mg, 0.189 mmol, 1.2 equiv.) at 0°C. The reaction was allowed to warm to rt gradually overnight. The reaction was quenched with $Na_2S_2O_3$ and diluted with CH_2Cl_2 (10 mL). The organic layer was washed with brine (3 x 10 mL) and the organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting oil was purified by silica gel column chromatography (12:1 to 9:1 hexanes:ethyl acetate) to afford **137** (33 mg, 85% yield) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.30-5.25 (m, 1H), 4.66 (s, 2H), 3.72-3.64 (m, 1H), 3.35 (s, 3H), 2.44 (dt, *J*=3.4, 12.2 Hz, 1H), 2.31-2.25 (m, 1H), 2.12 (s, 3H), 2.09-2.02 (m, 1H), 2.00-1.92 (m, 2H), 1.85-1.73 (comp m, 3H), 1.59 (s, 3H), 1.53-1.39 (comp m, 2H), 1.29 (dq, *J*=3.3, 12.9 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.3, 135.7, 123.1, 95.0, 55.4, 53.2, 37.8, 37.7, 30.7, 30.2, 27.7, 26.6, 26.6, 23.7, 17.3 ppm; IR (thin film/NaCl) 2936 (s), 2882 (s), 2831 (m), 1711 (sh s), 1447 (m), 1361 (m), 1297 (w), 1229 (m), 1146 (s), 1106 (s), 1080 (m), 1044 (s), 917 (m) cm^{-1}; HRMS (EI) *m/z* found: 252.1726 [calc'd for $C_{15}H_{24}O_3$ (M+): 272.1725].

Preparation of alcohol 141



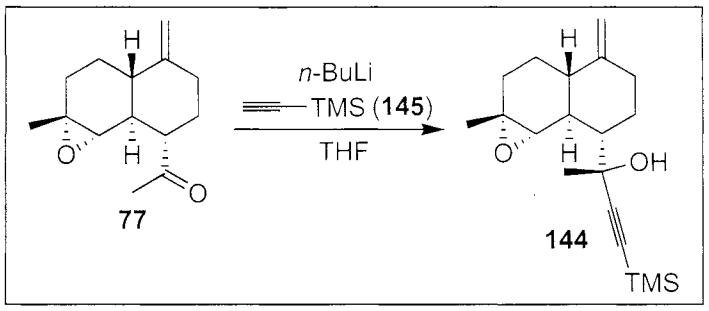
Alcohol 141. To a solution of cyclohexyl methyl ketone (**140**) (3.5 mL, 25.43 mmol, 1.0 equiv.) was added vinyl magnesium bromide (28.0 mL, 27.97 mmol, 1M in THF, 1.1 equiv.) in THF (150 mL) at -78°C. After 30 min, an additional aliquot of vinyl magnesium bromide (10.0 mL, 10.0 mmol, 1M in THF, 0.39 equiv.) was added at -78°C. After quenching with saturated NH_4Cl solution (30 mL), the reaction was warmed to rt and diluted with hexanes. The organic layer was washed with 1N HCl (1 x 30 mL) and brine (2 x 30 mL). The organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting oil was purified by silica gel column chromatography (12:1 to 9:1 hexanes:ethyl acetate) to provide **141** (3.02 g, 76% yield) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (dd, *J*=10.7, 17.2 Hz, 1H), 5.16 (dd, *J*=1.5, 17.4 Hz, 1H), 5.03 (dd, *J*=1.5, 10.8 Hz, 1H), 1.85-1.67 (m, 4H), 1.67-1.57 (m, 1H), 1.54 (s, 1H), 1.38-0.80 (comp m, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 112.0, 75.3, 48.1, 27.5, 27.1, 26.7, 26.6, 26.6, 25.2 ppm; IR (thin film/NaCl) 3438 (br m), 3084 (w), 2979 (m), 2930 (s), 2853 (s), 1641 (w), 1451 (m), 1412 (m), 1370 (m), 1292 (m), 1131 (m), 1091 (m), 996 (m), 919 (m), 893 (m) cm^{-1}; HRMS (CI) *m/z* found: 155.1436 [calc'd for $C_{10}H_{19}O$ (M+H): 155.1436].

Preparation of bishomoallylic alcohol 142



Bishomoallylic alcohol 142. To a solution of allylic alcohol **141** (1.25 g, 8.12 mmol, 1.0 equiv.) in THF (15 mL) was added 9-BBN (24.3 mL, 12.17 mmol, 0.5 M in THF, 1.5 equiv.) and stirred overnight at rt. An aqueous NaOH solution (8.0 mL, 24.36 mmol, 3.0 M, 3.0 equiv.) was added at rt, and the reaction was cannulated into a solution of $Pd(PPh_3)_4$ (469 mg, 0.406 mmol, 0.05 equiv.) and vinyl bromide (1.79 mL, 17.46 mmol, 2.15 equiv.) in THF (5 mL) at rt. The reaction was heated to reflux and the reaction was run for 5 hrs. The reaction was then cooled to rt, diluted with hexanes and washed with brine (3 x 15 mL). The organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure. The resulting oil was purified by silica gel column chromatography (12:1 to 9:1 hexanes:ethyl acetate) to afford **142** (1.05 g, 61% yield) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.15-5.10 (m, 1H), 2.08-2.00 (comp m, 2H), 1.86-1.70 (comp m, 4H), 1.68 (s, 3H), 1.62 (s, 3H), 1.49 (d, *J*=6.8 Hz, 1H), 1.47 (d, *J*=7.0 Hz, 1H), 1.36-1.29 (m, 2H), 1.28-0.93 (comp m, 7H), 1.10 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.8, 124.8, 74.7, 47.6, 39.8, 27.8, 27.0, 27.0, 27.0, 26.7, 25.9, 24.0, 22.3, 17.8 ppm; IR (thin film/NaCl) 3441 (br m), 2967 (m), 2926 (s), 2854 (s), 1449 (m), 1376 (m), 1112 (w) cm^{-1}; HRMS (EI) *m/z* found: 192.1878 [calc'd for $C_{14}H_{24}$ (M-H_2O): 192.1878].

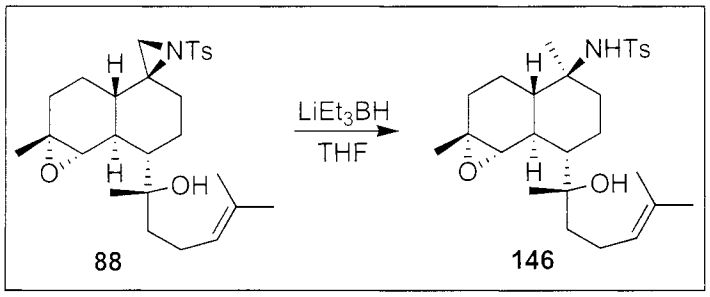
Preparation of propargylic alcohol 144



Propargylic alcohol 144. To a solution of trimethylsilyl acetylene (**145**, 32 μL, 0.227 mmol, 5.0 equiv.) in hexane (2 mL) at -78°C was added *n*-BuLi (99 μL, 0.227 mmol, 2.3M in hexanes, 5.0 equiv.) and stirred for 10 minutes. Ketone **77** (7.0 mg, 0.045 mmol, 1.0 equiv.) in hexanes (500 μL) was then added at -78°C. The reaction was run at -78°C for 10 minutes and quenched with H_2O (500 μL). The reaction was warmed to rt, diluted with hexanes (10 mL), washed with brine (3 x 5 mL), and dried with Na_2SO_4. The organic extracts were concentrated *in vacuo* and purified by silica gel column chromatography (12:1 hexanes:ethyl acetate) to afford **144** (1.5 mg, 15% yield) as a clear oil and recovered starting material **77** (5 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (d, *J*=1.2 Hz, 1H), 4.52 (d, *J*=1.2 Hz, 1H), 4.00 (s, 1H), 2.42-2.30 (comp m, 2H), 2.14-2.02 (comp m, 3H), 1.91 (dt, *J*=3.5, 11.2 Hz, 1H), 1.74-1.51 (comp m, 6H + H_2O peak), 1.30 (s, 3H), 1.28-1.12 (comp m, 3H), 0.16 (s, 6H), 0.07 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 104.8, 90.9, 89.1, 72.6, 61.4, 49.2, 45.8, 43.0, 35.9, 32.3, 30.3, 29.8, 26.0, 23.7, 22.5, 1.2, 0.1, -0.7 ppm; IR (thin film/NaCl) 3451 (br s), 2957 (s),

2917 (s), 2849 (m), 1250 (s), 1113 (m), 1023 (m), 934 (s), 887 (s), 843 (s) cm^{-1}; HRMS (EI) *m/z* found: 318.2021 [calc'd for $C_{19}H_{30}O_2Si$ (M+): 318.2015].

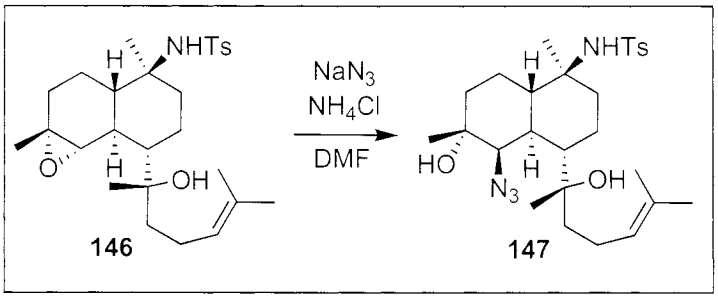
Preparation of sulfonamide 146



Sulfonamide 146. To a solution of aziridine **88** (26.0 mg, 0.055 mmol, 1.0 equiv) in THF (3 mL) at 0°C was added lithium triethylborohydride (Super-Hydride®) (275 μL, 0.275 mmol, 1M in THF, 5.0 equiv.). The reaction was allowed to warm to rt over 1 hour. The reaction was then cooled to 0°C, quenched with H_2O (500 μL), and diluted with ethyl acetate (10 mL). The organic layer was washed with brine (3 x 5 mL) and the organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (3:1 hexanes:ethyl acetate) to provide **146** (16 mg, 62% yield) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J*=8.0 Hz, 2H), 7.31-7.25 (m, 2H), 5.08 (t, *J*=7.1 Hz, 1H), 4.68 (br s, 1H), 4.07 (s, 1H), 2.42 (s, 3H), 2.20-1.88 (comp m, 3H), 1.82-1.11 (comp m, 22 H), 1.08-0.86 (comp m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 140.8, 132.3, 129.6, 127.0, 124.1, 76.1, 62.0, 60.1, 58.9, 47.2, 47.0, 43.1, 40.8, 39.1, 30.5, 25.9, 25.7, 23.7, 23.6, 21.6, 21.5, 20.2, 18.6, 17.9 ppm; IR (thin film/NaCl) 3491 (br m), 4267 (br m), 2963 (s), 2926 (s), 1450

(w), 1380 (m), 1325 (s), 1304 (s), 1262 (w), 1156 (sh s), 1124 (m), 1094 (s) cm^{-1}; HRMS (FAB) *m/z* found: 476.2834 [calc'd for $C_{27}H_{42}NO_4S$ (M+H): 476.2834].

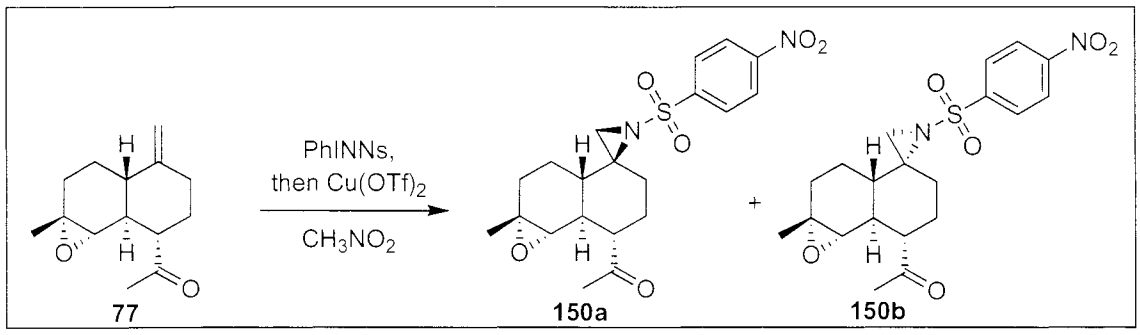
Preparation of azide 147



Azide 147. To a solution of epoxide **146** (16 mg, 0.034 mmol, 1.0 equiv.) in DMF (2 mL) was added sodium azide (44 mg, 0.672 mmol, 20.0 equiv.) and ammonium chloride (7.0 mg, 0.134 mmol, 4.0 equiv.) and heated to 80°C for 36 hours. The reaction was then cooled to rt, diluted with ethyl acetate (10 mL), and washed with water (1 x 5 mL) and brine (2 x 5 mL). The organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (4:1 to 1:1 hexanes:ethyl acetate) to give **147** (15 mg, 83% yield) as an amorphous, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J*=8.0 Hz, 2H), 7.26 (m, 2H), 5.15 (t, *J*=6.6 Hz, 1H), 4.40-4.21 (comp m, 2H), 2.42 (s, 3H), 2.23-1.79 (comp m, 4H), 1.76-1.18 (comp m, 20H), 1.17-0.79 (comp m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 139.5, 132.1, 128.5, 126.0, 123.0, 75.0, 71.7, 68.7, 58.8, 43.1, 41.6, 41.5, 38.4, 37.4, 31.8, 27.9, 24.8, 23.5, 22.0, 20.5, 20.5, 20.3, 17.9, 16.8 ppm; IR (thin film/NaCl) 3550 (m), 3239 (br m), 2961 (s), 2924 (s), 2871 (m), 2360 (w), 2107 (sh s),

1311 (s), 1117 (s) cm^{-1}; HRMS (FAB) *m/z* found: 519.3000 [calc'd for $C_{27}H_{43}NO_4S$ (M+H): 519.3005].

Preparation of aziridines 150a and 150b

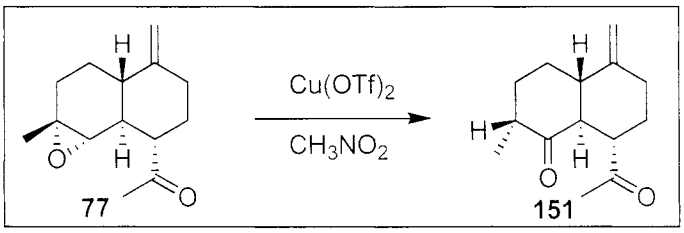


Aziridines 150a and 150b. To a solution of nosyliminophenyliodinane (PhINNs, 2.30 g, 5.80 mmol, 1.5 equiv.) in nitromethane (50 mL) with molecular sieves (approximately 2 g) was added *exo*-olefin **77** (850 mg, 3.86 mmol, 1.0 equiv.). The reaction was cooled to 0°C and copper (II) triflate (70.0 mg, 0.0193 mmol, 0.05 equiv.) was added. After 2 hours at 0°C, additional nosyliminophenyliodinane (1.50 g, 3.71 mmol, 0.96 equiv.) and copper (II) triflate (70.0 mg, 0.0193 mmol, 0.05 equiv.) were added and the reaction was allowed to warm to rt. After 4 hours, the reaction was filtered through celite and washed thoroughly with ethyl acetate (100 mL). The filtrate was concentrated *in vacuo* and the crude ^{1}H NMR of the residue showed a 7:1 ratio of aziridine diastereomers. The resulting residue was immediately subjected to silica gel column chromatography (6:1 to 1:1 hexanes:ethyl acetate to 2:1 ethyl acetate:hexanes) to afford major diastereomer **150a** (966 mg, 59% yield) and minor diastereomer **150b** (138 mg, 9% yield).

Major aziridine diastereomer **150a**. White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J*=9.1 Hz, 2H), 8.10 (d, *J*=9.1 Hz, 2H), 2.69-2.58 (comp m, 2H), 2.48 (s, 1H), 2.45-2.29 (comp m, 3H), 2.26 (s, 3H), 2.03-1.89 (comp m, 2H), 1.69-1.49 (comp m, 4H), 1.42-1.34 (m, 1H), 1.27 (s, 3H), 0.76 (dq, *J*=4.4, 12.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1, 150.4, 146.2, 128.7, 124.4, 61.4, 58.5, 55.5, 54.2, 42.2, 42.1, 37.3, 31.2, 29.9, 29.7, 29.1, 23.1, 18.2 ppm; IR (thin film/NaCl) 3106 (m), 2958 (m), 2932 (m), 2871 (m), 2254 (w), 1709 (sh s), 1607 (m), 1531 (sh s), 1451 (m), 1350 (sh s), 1331 (s), 1310 (s), 1206 (m), 1164 (sh s), 767 (s), 743 (s) cm^{-1}; HRMS (FAB) *m/z* found: 421.1434 [calc'd for $C_{20}H_{25}N_2O_6S$ (M+H): 421.1433]; $[\alpha]_D^{20}$ +1.36° (*c* 1.03, $CHCl_3$).

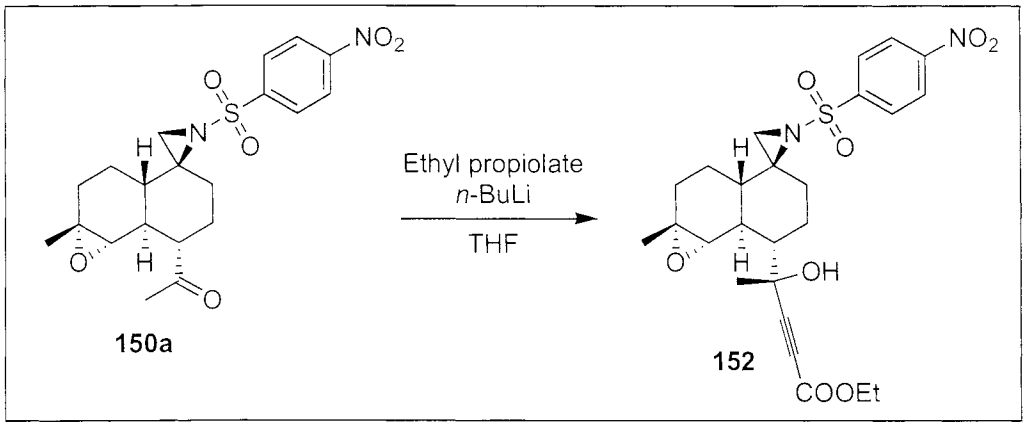
Minor aziridine diastereomer **150b**. White foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J*=8.5 Hz, 2H), 8.14 (d, *J*=8.9 Hz, 2H), 2.61 (s, 1H), 2.59-2.52 (comp m, 2H), 2.51 (s, 1H), 2.46-2.40 (m, 1H), 2.37-2.10 (comp m, 5H), 2.09-1.95 (comp m, 2H), 1.79-1.69 (br s, 1H), 1.61-1.52 (m, 1H), 1.38-1.21 (comp m, 4H), 1.08 (dq, *J*=4.8, 12.8 Hz, 1H), 1.01-0.94 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.5, 150.8, 146.2, 129.2, 124.7, 61.9, 58.6, 56.6, 56.0, 42.0, 41.1, 38.3, 30.8, 30.0, 28.0, 27.4, 23.4, 19.0 ppm; IR (thin film/NaCl) 3310 (br w), 3106 (m), 2937 (m), 1721 (m), 1710 (sh s), 1692 (m), 1606 (m), 1530 (s), 1351 (s), 1309 (s), 1162 (s), 1092 (m), 855 (m), 747 (s) cm^{-1}; HRMS (FAB) *m/z* found: 421.1457 [calc'd for $C_{20}H_{25}N_2O_6S$ (M+H): 421.1433]; $[\alpha]_D^{20}$ -6.80° (*c* 1.09, $CHCl_3$).

Preparation of ketone 151



Ketone 151. To a solution of epoxide **77** (404 mg, 1.85 mmol, 1.0 equiv.) was added copper (II) triflate (100 mg, 0.278 mmol, 0.15 equiv.) in nitromethane (30 mL) with molecular sieves (1 g). The reaction unexpectedly turned a pale red color. The reaction was then cooled to 0°C and nosyl iminophenyliodinane (1.12 g, 2.78 mmol, 1.5 equiv.) was added. The reaction was run for 5 minutes, filtered through a celite plug, and washed with dichloromethane (30 mL). The resulting solution was concentrated *in vacuo* and purified by silica gel column chromatography (6:1 hexanes:ethyl acetate) to give **151** (171 mg, 42% yield) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (d, *J*=1.4 Hz, 1H), 4.69 (d, *J*=1.2 Hz, 1H), 2.79-2.72 (m, 2H), 2.53-2.42 (m, 1H), 2.39-2.29 (m, 1H), 2.22 (s, 3H), 2.03-1.72 (comp m, 7H), 1.22-1.09 (comp m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.4, 210.9, 148.9, 106.9, 52.9, 49.3, 46.6, 43.8, 35.0, 31.4, 29.8, 29.3, 22.6, 16.6 ppm; IR (thin film/NaCl) 3397 (w), 3084 (m), 2969 (s), 2932 (s), 2861 (s), 1707 (s), 1647 (sh s), 1455 (s), 1443 (s), 1424 (m), 1374 (s), 1351 (s), 1324 (m), 1297 (s), 1280 (s), 1233 (s), 1174 (s), 1162 (s) cm^{-1}; HRMS (FAB) *m/z* found: 221.1542 [calc'd for $C_{14}H_{21}O_2$ (M+H): 221.1541]; $[\alpha]_D^{20}$ -134.8° (*c* 1.00, $CHCl_3$).

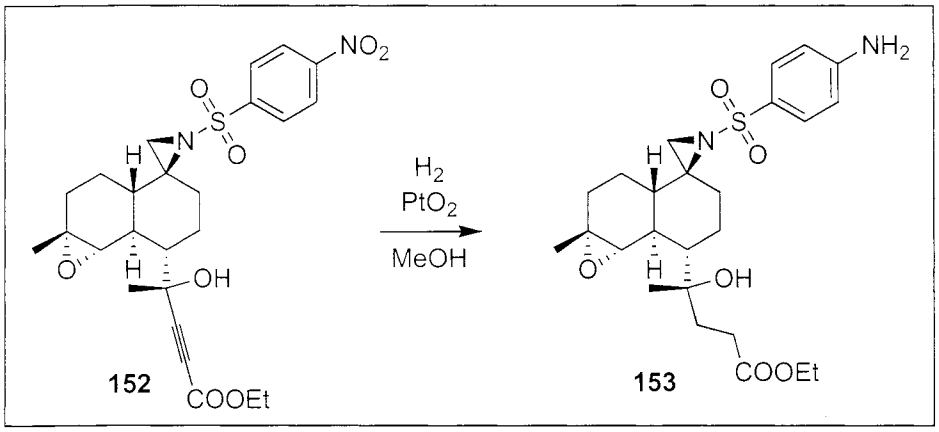
Preparation of ester 152



Ester 152. To a solution of ethyl propiolate (94 μL, 0.932 mmol, 8.0 equiv.) in THF (3 mL) at -78°C was added *n*-BuLi (424 μL, 0.932 mmol, 2.1 M in hexanes, 8.0 equiv.) and stirred for 10 minutes. Next, ketone **150a** (49.0 mg, 0.117 mmol, 1.0 equiv.) was added as a solution in THF (2 mL) dropwise. The reaction was carefully maintained at -78°C for 20 minutes and then quenched with H_2O (1 mL). The reaction was warmed to rt, diluted with ethyl acetate (20 mL), and washed with brine (3 x 5 mL). The organic extracts were concentrated *in vacuo* and purified by silica gel column chromatography (6:1 to 2:1 hexanes:ethyl acetate) to afford **152** (32 mg, 52% yield) as a cream-colored foam and recovered starting material **150a** (20 mg, 41% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J*=8.9 Hz, 2H), 8.10 (d, *J*=8.8 Hz, 2H), 4.25 (q, *J*=7.2 Hz, 2H), 3.94 (s, 1H), 2.60 (s, 1H), 2.51-2.24 (comp m, 5H), 2.04-1.92 (comp m, 2H), 1.74-1.57 (comp m, 6H), 1.43-1.27 (comp m, 8H), 0.77 (dq, *J*=4.7, 12.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 150.4, 146.3, 128.6, 124.3, 90.0, 77.4, 71.9, 62.4, 60.2, 59.3, 55.9, 48.0, 43.3, 42.4, 37.3, 31.4, 30.0, 29.7, 25.3, 23.3, 18.6, 14.1 ppm; IR (thin film/NaCl) 3478 (br m), 3106 (w), 2961 (m), 2935 (m), 2873 (m), 2239 (m), 1709 (s), 1607 (w), 1532 (s),

1450 (w), 1349 (s), 1309 (m), 1248 (s), 1164 (m), 1093 (w) cm^{-1}; HRMS (FAB) *m/z* found: 518.1723 [calc'd for $C_{25}H_{30}N_2O_8S$ (M): 518.1723]; $[\alpha]_D^{20}$ +15.2° (*c* 0.58, $CHCl_3$).

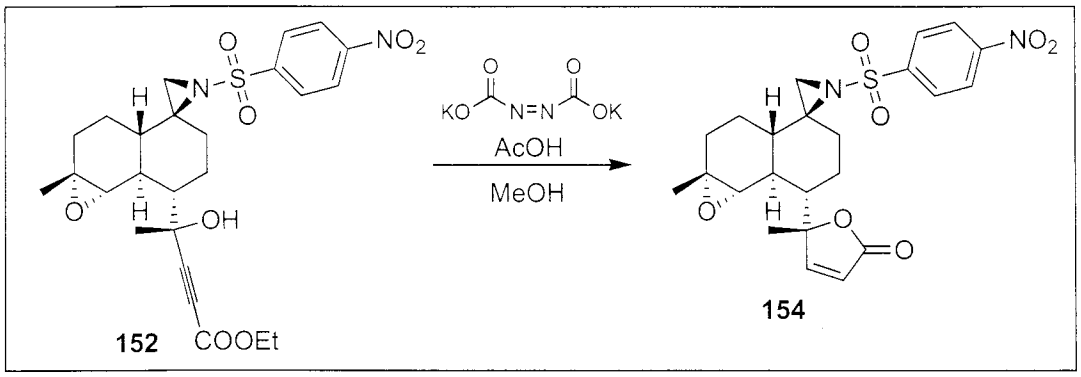
Preparation of aniline 153



Aniline 153. To a solution of aziridine **152** (4.0 mg, 0.0077 mmol, 1.0 equiv.) in ethyl acetate (2 mL) at rt was added platinum (II) oxide catalyst (approx. 10 mg) and hydrogen gas (1 balloon, 1 atm). The reaction was stirred at rt overnight and was then filtered through a celite plug and washed with ethyl acetate (10 mL). The fitrate was concentrated *in vacuo* and the resulting residue was purified by silica gel column chromatography (3:1 ethyl acetate:hexane) to afford **153** (4 mg, 95% yield) as a cream-colored foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J*=8.6 Hz, 2H), 6.67 (d, *J*=8.5 Hz, 2H), 4.19-4.09 (comp m, 5H), 2.57-2.35 (comp m, 4H), 2.33-2.26 (m, 1H), 2.24-2.13 (comp m, 2H), 2.01-1.88 (comp m, 3H), 1.84 (s, 1H), 1.81-1.58 (comp m, 5H), 1.51-1.44 (m, 1H), 1.32-1.24 (comp m, 9H), 0.80-0.69 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 150.8, 129.6, 129.5, 128.9, 113.9, 77.4, 75.4, 61.0, 60.9, 59.3, 54.3, 47.5, 44.3, 42.9, 37.6, 35.9, 30.9, 29.9, 29.1, 28.4, 23.6, 23.3, 18.6, 14.3 ppm; IR (thin film/NaCl)

3465 (m), 3370 (s), 2962 (m), 2927 (m), 1725 (m), 1631 (m), 1597 (sh s), 1503 (w), 1302 (m), 1152 (s), 1091 (m), 885 (m), 724 (m) cm^{-1}; HRMS (FAB) *m/z* found: 493.2373 [calc'd for $C_{25}H_{37}N_2O_6S$ (M+H): 493.2372].

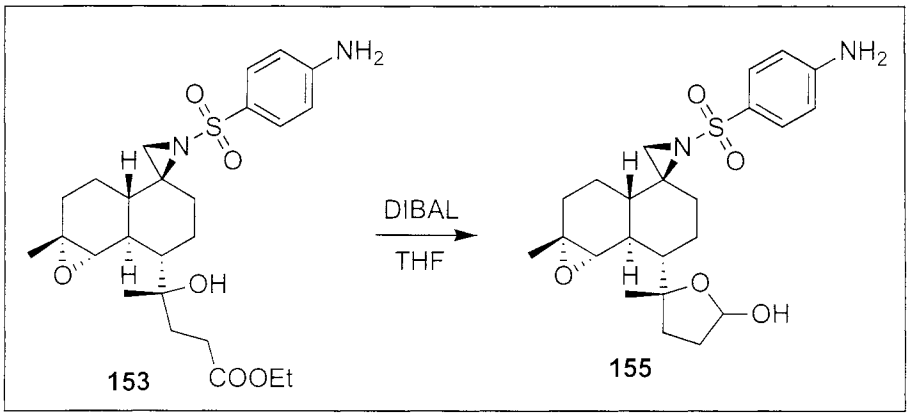
Preparation of butenolide 154



Butenolide 154. To a solution of ester **152** (160 mg, 0.309 mmol, 1.0 equiv.) in methanol (5 mL) at rt was added dipotassium azodicarboxylate (900 mg, 4.63 mmol, 15.0 equiv.). The reaction was heated to 70°C and glacial acetic acid (177 μL, 3.09 mmol, 10.0 equiv.) was added dropwise (**CAUTION**: vigorous bubbling). (It is imperative to add acetic acid while the reaction is at high temperature because addition at rt followed by heating led to no reaction.) Additional dipotassium azodicarboxylate (450 mg, 2.32 mmol, 7.5 equiv.) and glacial acetic acid (89 μL, 1.55 mmol, 5.0 equiv.) were added at 70°C. The reaction was run for 30 minutes, cooled to rt, diluted with ethyl acetate (10 mL), and washed with sodium bicarbonate solution (5 mL) and brine (2 x 5 mL). The organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (1:1 hexanes:ethyl acetate to 3:1 ethyl acetate:hexanes) to afford **154** (131 mg, 90% yield) as a white solid, m.p. 213-

215 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J*=7.7 Hz, 2H), 8.10 (d, *J*=7.7 Hz, 2H), 7.58 (d, *J*=5.8 Hz, 1H), 6.11 (d, *J*=5.8 Hz, 1H), 3.62 (s, 1H), 2.61 (s, 1H), 2.43-2.23 (comp m, 3H), 2.12-2.01 (m, 1H), 2.01-1.93 (m, 1H), 1.86 (dt, *J*=2.7, 11.9 Hz, 1H), 1.73-1.47 (comp m, 7H), 1.44-1.21 (comp m, 4H), 0.76 (dq, *J*=4.6, 12.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 160.7, 150.4, 146.2, 128.6, 124.4, 120.7, 91.0, 60.0, 59.5, 55.5, 48.1, 43.6, 42.2, 37.2, 31.1, 30.1, 29.5, 23.4, 19.9, 18.6 ppm; IR (thin film/NaCl) 3105 (w), 3017 (m), 2934 (m), 2872 (m), 1756 (s), 1607 (w), 1532 (s), 1349 (s), 1310 (m), 1162 (s), 1090 (m), 950 (m), 768 (s), 747 (s) cm^{-1}; HRMS (FAB) *m/z* found: 475.1539 [calc'd for $C_{23}H_{27}N_2O_7S$ (M+H): 475.1539]; $[\alpha]_D^{20}$ -13.4° (*c* 1.72, $CHCl_3$).

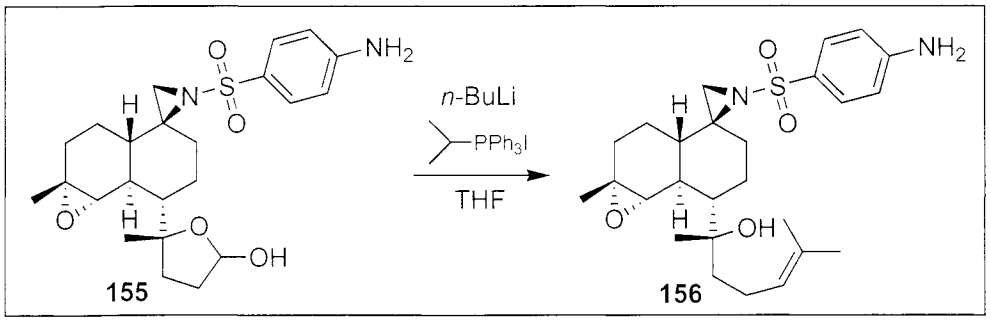
Preparation of lactol 155



Lactol 155. To a solution of ester **153** (31.0 mg, 0.070 mmol, 1.0 equiv.) in THF (3 mL) at -78°C was added diisobutylaluminum hydride (140 μL, 0.140 mmol, 1 M in CH_2Cl_2, 2.0 equiv.). After 10 minutes, additional diisobutylaluminum hydride (140 μL, 0.140 mmol, 1 M in CH_2Cl_2, 2.0 equiv.) was added and stirred for 20 minutes. The

reaction was then quenched with Rochelle's salt aqueous solution (20% *w/v*, 1 mL) and warmed to rt. After diluting with ethyl acetate (10 mL), the organic layer was washed with brine (3 x 5 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (1:1 to 3:1 ethyl acetate:hexanes) followed by HPLC (2:1 hexanes:ethyl acetate to 3:1 ethyl acetate:hexanes) to afford **155** (24 mg, 77% yield, 11:9 mixture of lactol diastereomers) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J*=8.5 Hz, 2H), 6.67 (d, *J*=8.6 Hz, 2H), 5.56 (br s, 0.45H), 5.50 (br s, 0.55H), 4.13 (br s, 2H), 4.08-4.00 (m, 1H), 2.74-1.85 (comp m, 11H), 1.84-1.11 (comp m, 12H + H_2O peak), 0.82-0.67 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 128.5, 128.4, 112.8, 98.3, 97.3, 87.2, 86.2, 59.6, 59.5, 58.2, 58.1, 53.3, 50.5, 49.0, 43.0, 42.7, 41.6, 41.5, 37.4, 34.9, 34.8, 34.8, 31.6, 31.2, 29.8, 29.8, 29.0, 28.9, 28.9, 22.5, 20.4, 19.6, 17.4, 17.3 ppm; IR (thin film/NaCl) 3469 (m), 3370 (s), 2964 (m), 2931 (m), 1635 (m), 1597 (sh s), 1503 (m), 1302 (s), 1152 (s), 1008 (m), 760 (s) cm^{-1}; HRMS (FAB) *m/z* found: 449.2110 [calc'd for $C_{23}H_{33}N_2O_5S$ (M+H): 449.2110]; $[\alpha]_D^{20}$ +5.5° (*c* 0.60, $CHCl_3$).

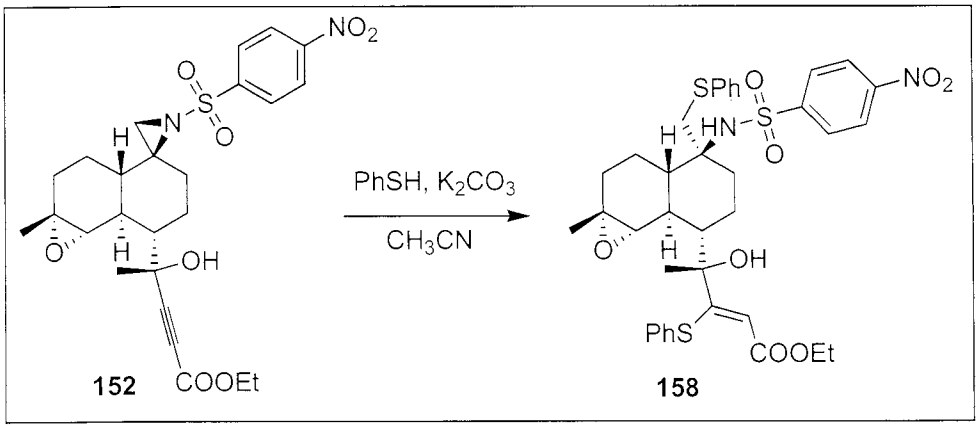
Preparation of bishomoallylic alcohol 156



155 156

Bishomoallylic alcohol 156. To a solution of isopropyltriphenylphosphonium iodide (521 mg, 1.21 mmol, 10.0 equiv, ground with mortar and pestle) in THF (3 mL) at 0°C was added *n*-BuLi (550 μL, 1.21 mmol, 2.2 M in hexanes, 10.0 equiv) and stirred for 10 minutes. Next, lactol **155** (54 mg, 0.121 mmol, 1.0 equiv.) in THF (1 mL) was added via syringe and the reaction was warmed to rt. After stirring at rt for 1 hour, the reaction was cooled to 0°C and H_2O (500 μL) was added to quench. The reaction was diluted with ethyl acetate (10 mL), washed with brine (3 x 5 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The resulting oil was purified by silica gel column chromatography (1:1 hexanes:ethyl acetate to 3:1 ethyl acetate:hexanes) to afford **156** (21 mg, 37% yield) as a clear oil and recovered starting material **155** (32 mg, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J*=9.1 Hz, 2H), 6.67 (d, *J*=9.1 Hz, 2H), 5.12 (dt, *J*=1.3, 7.0 Hz, 1H), 4.21 (s, 1H), 4.14 (br s, 2H), 2.43 (s, 1H), 2.29 (td, *J*=3.5, 13.3 Hz, 1H), 2.25-1.88 (comp m, 6H), 1.75-1.54 (comp m, 11H), 1.51-1.34 (comp m, 3H), 1.30-1.24 (comp m, 6H), 1.20-1.05 (comp m, 1H), 0.74 (dq, *J*=4.4, 12.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 132.5, 129.5, 124.0, 113.9, 90.8, 76.2, 61.0, 59.4, 54.5, 47.2, 44.2, 43.2, 42.9, 36.1, 31.0, 29.9, 29.3, 25.9, 23.7, 23.6, 21.5, 18.6, 17.9 ppm; IR (thin film/NaCl) 3501 (br m), 3370 (m), 2965 (m), 2926 (m), 1635 (m), 1597 (sh s), 1505 (m), 1379 (w), 1301 (sh s), 1151 (sh s), 1090 (m), 1008 (m), 852 (m), 762 (m), 725 (s) cm^{-1}; HRMS (FAB) *m/z* found: 475.2631 [calc'd for $C_{26}H_{39}N_2O_4S$ (M+H): 475.2630].

Preparation of bis-thioether 158

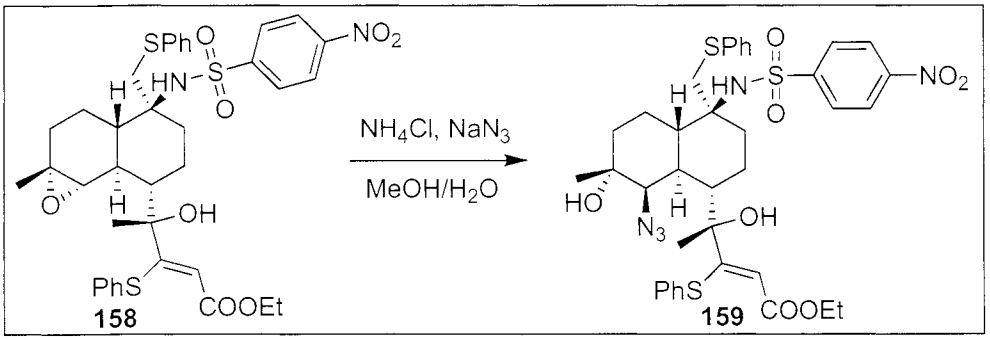


152 158

Bis-thioether 158. To a solution of aziridine **152** (60.0 mg, 0.116 mmol, 1.0 equiv.) in CH_3CN (4.9 mL) and DMSO (0.1 mL) at 0°C was added K_2CO_3 (128 mg, 0.928 mmol, 8.0 equiv.) and thiophenol (71 μL, 0.695 mmol, 6.0 equiv.). The reaction was stirred for 20 minutes at 0°C and then diluted with ethyl acetate (10 mL). The reaction was washed with brine (3 x 5 mL), and the organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting oil was purified by silica gel column chromatography (4:1 to 1:1 hexanes:ethyl acetate) to afford **158** (76 mg, 89% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J*=8.7 Hz, 2H), 8.06 (d, *J*=9.0 Hz, 2H), 7.50-7.41 (m, 1H), 7.38-7.11 (comp m, 10H), 6.24 (s, 1H), 5,34 (s, 1H), 3.97 (s, 1H), 3.86-3.68 (comp m, 2H), 3.21 (d, *J*=13.3 Hz, 1H), 2.90-2.80 (comp m, 2H), 2.15-1.55 (comp m, 6H), 1.52 (s, 3H), 1.46-1.36 (m, 2H), 1.34-1.22 (comp m, 3H), 1.14 (dq, *J*=4.6, 12.6 Hz, 1H), 1.00 (t, *J*=6.9 Hz, 3H), 0.90-0.77 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 157.1, 149.9, 149.0, 135.0, 134.5, 130.2, 130.1, 129.5, 129.3, 128.1, 127.4, 127.2, 124.4, 121.6, 79.4, 63.5, 61.0, 60.7, 59.3, 46.2, 46.0, 40.9, 38.4, 32.8, 30.5, 26.1, 23.4, 22.3, 19.6, 14.0 ppm; IR (thin film/NaCl) 3452 (w), 3290 (w), 2936 (m), 1721 (s), 1607 (m), 1530 (sh s), 1479 (m), 1440 (m), 1349 (sh s), 1307 (s), 1160 (sh s), 1092

(m), 1025 (m), 737 (s) cm^{-1}; HRMS (FAB) *m/z* found: 739.2189 [calc'd for $C_{37}H_{43}N_2O_8S_3$ (M+H): 739.2181]; $[\alpha]_D^{20}$ +46.2° (*c* 1.29, $CHCl_3$).

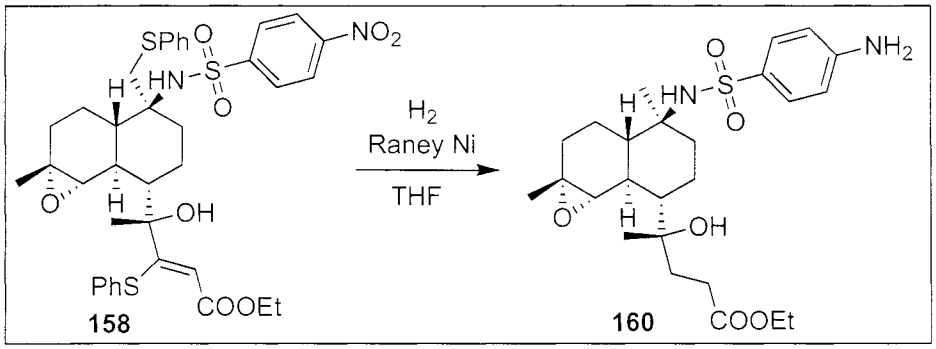
Preparation of azido alcohol 159



Azido alcohol 159. To a solution of epoxide **158** (44.0 mg, 0.060 mmol, 1.0 equiv.) in MeOH/THF/H_2O (16:2:1, 19 mL total volume) was added sodium azide (200 mg, 2.98 mmol, 50.0 equiv.) and ammonium chloride (5.0 mg, 0.090 mmol, 1.5 equiv.) and the reaction was heated to 80°C for 12 hours. The reaction was then cooled to rt, diluted with ethyl acetate (20 mL), and washed with brine (3 x 5 mL). The organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting oil was purified by silica gel column chromatography (6:1 to 2:1 to 1:1 hexanes:ethyl acetate) to afford **159** (42 mg, 91% yield) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J*=9.0 Hz, 2H), 8.07 (d, *J*=8.7 Hz, 2H), 7.44-7.18 (comp m, 10H), 6.22 (s, 1H), 5.32 (s, 1H), 4.23 (s, 1H), 3.91-3.78 (m, 2H), 3.18 (d, *J*=13.6 Hz, 1H), 3.03 (s, 1H), 2.94 (d, *J*=13.2 Hz, 1H), 2.26-2.10 (comp m, 2H), 1.97-1.89 (m, 1H), 1.79-1.50 (comp m, 4H), 1.48-1.23 (comp m, 10H), 1.06 (t, *J*=7.2 Hz, 3H), 0.87-0.74 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 156.1, 149.9, 148.9, 135.2, 133.9, 130.9, 130.5, 129.5, 129.3,

128.3, 127.6, 127.3, 124.3, 122.6, 79.5, 72.9, 69.5, 63.4, 60.8, 43.1, 41.3, 39.4, 38.8, 32.9, 32.6, 28.9, 25.0, 21.4, 21.1, 14.1 ppm; IR (thin film/NaCl) 3481 (br s), 4277 (s), 2940 (s), 2872 (w), 2107 (sh s), 1716 (s), 1607 (m), 1582 (m), 1530 (sh s), 1349 (sh s), 1478 (s), 1440 (s), 1349 (sh s), 1306 (s), 1159 (s), 1093 (s), 1025 (s), 999 (s), 749 (s) cm^{-1}; HRMS (FAB) *m/z* found: 820.1939 [calc'd for $C_{37}H_{43}N_5O_8S_3K$ (M+K): 820.1911]; $[\alpha]_D^{20}$ +13.3° (*c* 0.81, $CHCl_3$).

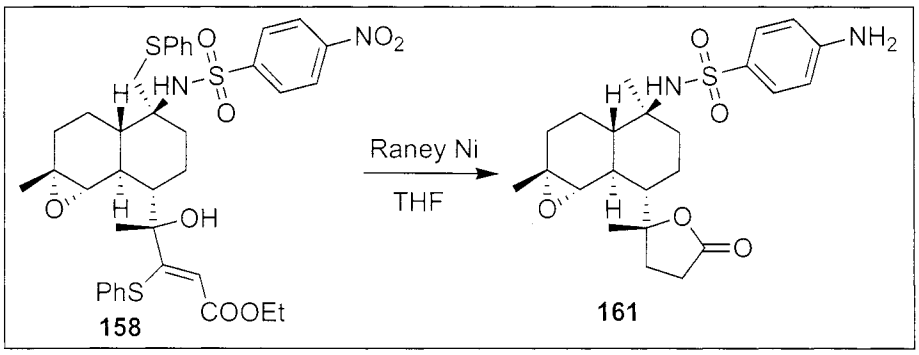
Preparation of ester 160



Ester 160. To a solution of ester **158** (26.0 mg, 0.035 mmol, 1.0 equiv.) in THF (2 mL) at rt was added Raney nickel (approximately 3 g, washed repeatedly with THF (10 mL) to remove H_2O) in THF (3 mL). Hydrogen gas (1 balloon, 1 atm) was added, and the reaction was run at rt for 1 hour. The reaction was then filtered through celite and washed repeatedly with ethyl acetate (15 mL). (**CAUTION**: It is imperative to flush the celite pad with nitrogen gas and to avoid complete drying of the Raney nickel.) The filtrate was concentrated *in vacuo* and the resulting residue was purified by silica gel column chromatography (1:1 hexanes:ethyl acetate) to afford **160** (12 mg, 75% yield) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J*=8.8 Hz, 2H), 6.66 (d, *J*=8.8 Hz,

2H), 4.40 (s, 1H), 4.18-4.07 (comp m, 4H), 4.04 (s, 1H), 2.52-2.30 (comp m, 2H), 1.97 (dd, *J*=2.7, 14.1 Hz, 1H), 1.93-1.84 (m, 1H), 1.81-1.42 (comp m, 10H), 1.30-1.17 (comp m, 8H), 1.08-0.79 (comp m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 150.2, 132.1, 129.1, 114.1, 77.4, 75.4, 61.9, 60.9, 59.7, 58.9, 47.0, 40.8, 38.9, 37.4, 30.5, 28.4, 25.6, 23.7, 23.5, 20.2, 18.7, 14.4 ppm; IR (thin film/NaCl) 3467 (br m), 3370 (s), 3258 (s), 2960 (s), 2927 (s), 1718 (s), 1630 (m), 1518 (sh s), 1503 (w), 1449 (m), 1380 (m), 1301 (s), 1261 (m), 1148 (s), 1093 (s), 1020 (m) cm^{-1}; HRMS (FAB) *m/z* found: 495.2529 [calc'd for $C_{25}H_{39}N_2O_6S$ (M+H): 495.2529]; $[\alpha]_D^{20}$ +33.6° (*c* 0.90, $CHCl_3$).

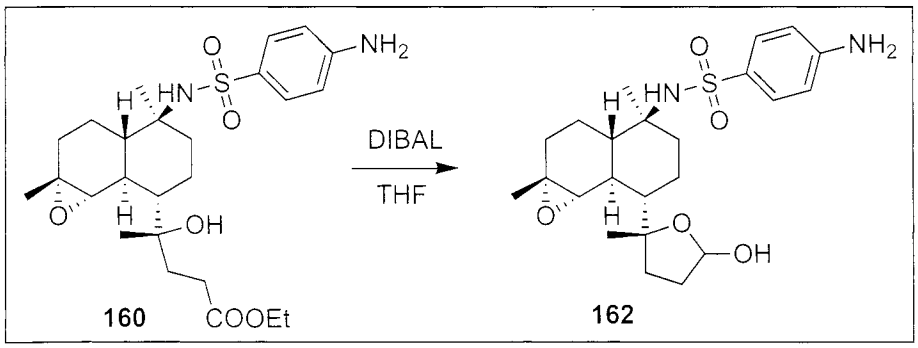
Preparation of lactone 161



Lactone 161. To a solution of ester **158** (25.0 mg, 0.034 mmol, 1.0 equiv.) in THF (2 mL) at rt was added Raney nickel (approximately 3g, water was decanted but nickel was not washed). Hydrogen gas (1 balloon, 1 atm) was added, and the reaction was run at rt for 1 hour. The reaction was then filtered through celite and washed repeatedly with ethyl acetate (15 mL). (**CAUTION**: It is imperative to flush the celite pad with nitrogen gas and to avoid complete drying of the Raney nickel.) The filtrate was concentrated *in vacuo* and the resulting residue was purified by silica gel column

chromatography (1:1 hexanes:ethyl acetate) to afford **161** (17 mg, 75% yield) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J*=8.7 Hz, 2H), 6.67 (d, *J*=8.9 Hz, 2H), 4.43 (br s, 1H), 4.15-4.08 (m, 1H), 3.62 (s, 1H), 2.64-2.52 (m, 1H), 2.49-2.40 (m, 1H), 2.09-1.39 (comp m, 8H + H_2O peak), 1.35 (s, 3H), 1.30-1.14 (comp m, 6H), 1.13-0.78 (comp m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 150.3, 131.9, 129.1, 114.1, 89.4, 77.4, 60.4, 59.6, 59.0, 49.2, 46.5, 40.4, 38.8, 35.0, 30.4, 28.0, 24.8, 23.5, 19.9, 19.7, 18.8 ppm; IR (thin film/NaCl) 3371 (m), 3284 (m), 2931 (m), 2872 (w), 1761 (sh s), 1700 (m), 1653 (m), 1635 (m), 1597 (sh s), 1457 (m), 1301 (m), 1149 (s), 1093 (m), 756 (s) cm^{-1}; HRMS (FAB) *m/z* found: 449.2116 [calc'd for $C_{23}H_{33}N_2O_5S$ (M+H): 449.2110]; $[\alpha]_D^{20}$ +22.6° (*c* 0.72, $CHCl_3$).

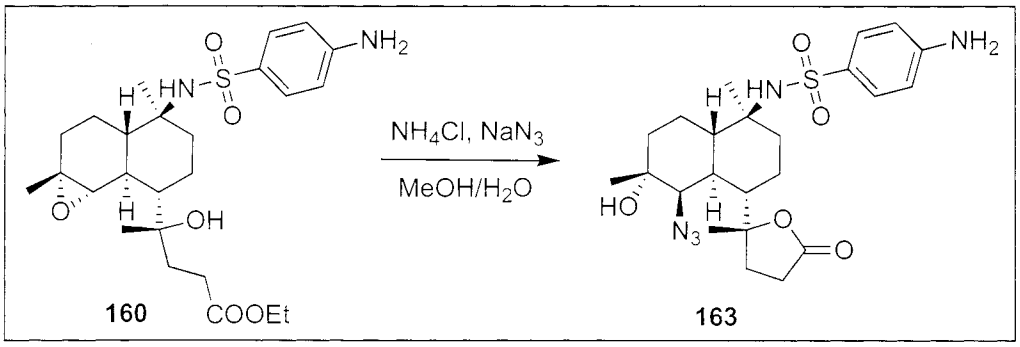
Preparation of lactol 162



Lactol 162. To a solution of ester **160** (40.0 mg, 0.090 mmol, 1.0 equiv.) in THF (5 mL) at -78°C was added diisobutylaluminum hydride (270 μL, 0.270 mmol, 1 M in CH_2Cl_2, 3.0 equiv). The reaction was run at -78°C for 20 minutes and quenched with Rochelle's salt aqueous solution (1 mL, 20% *w/v*). After warming to rt, the reaction was diluted with ethyl acetate (10 mL) and washed with brine (3 x 5 mL). The organic

extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (49:1 dichloromethane:methanol) to afford **162** (35 mg, 85% yield) as a white foam, 3:2 mixture of lactol diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J*=8.6 Hz, 2H), 6.66 (d, *J*=8.8 Hz, 2H), 5.52 (br s, 0.4H), 5.48 (br d, *J*=3.2 Hz, 0.6H), 4.34-4.26 (m, 1H), 4.09 (br s, 2H), 3.98 (s, 0.6H), 3.93 (s, 0.4H), 2.56 (br d, *J*=2.5 Hz, 0.4H), 2.32 (br s, 0.6H), 2.17 (s, 1H), 2.05-1.42 (comp m, 8H + H_2O peak), 1.35-1.16 (comp m, 7H), 1.14-0.92 (comp m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 132.1, 129.1, 114.1, 99.4, 98.4, 88.4, 87.5, 77.4, 61.4, 61.3, 60.0, 58.9, 51.5, 50.0, 47.0, 46.9, 40.7, 40.5, 39.1, 38.3, 35.8, 32.7, 32.2, 30.7, 26.7, 26.1, 23.7, 21.6, 20.8, 20.0, 18.8 ppm; IR (thin film/NaCl) 3496 (m), 3367 (s), 3291 (m), 2935 (s), 2871 (m), 2250 (w), 1635 (m), 1598 (sh s), 1505 (m), 1381 (m), 1317 (m), 1149 (s), 1093 (m), 1007 (m) cm^{-1}; HRMS (FAB) *m/z* found: 451.2267 [calc'd for $C_{23}H_{35}N_2O_5S$ (M+H): 451.2266]; $[\alpha]_D^{20}$ +42.5° (*c* 0.96, $CHCl_3$).

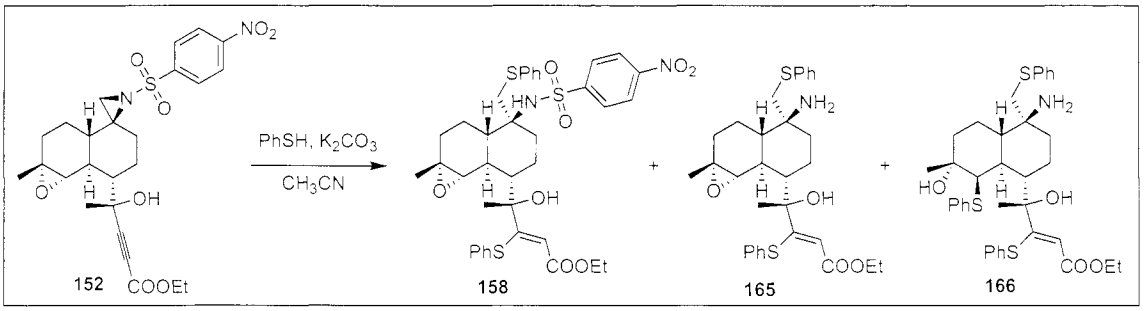
Preparation of azide 163



Azide 163. To a solution of epoxide **160** (33.0 mg, 0.074 mmol, 1.0 equiv.) in methanol (8 mL) and H_2O (1 mL) was added sodium azide (120 mg, 1.840 mmol, 25.0

equiv.) followed by ammonium chloride (6.0 mg, 0.111 mmol, 1.5 equiv.). The reaction was heated to 80°C and maintained at this temperature overnight. After cooling to rt, the reaction was diluted with ethyl acetate (10 mL) and washed with brine (3 x 5 mL). The organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (29:1 dichloromethane:methanol) to afford **163** (29 mg, 81% yield) as a white solid, m.p. 168-169°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J*=8.5 Hz, 2H), 6.66 (d, *J*=8.4 Hz, 2H), 4.36 (s, 1H), 4.11 (br s, 2H), 3.90 (s, 1H), 2.64-2.41 (m, 2H), 2.11-1.87 (comp m, 4H), 1.82-1.71 (m, 1H), 1.70-1.18 (comp m, 14H), 1.16-0.95 (comp m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 150.3, 131.9, 129.2, 114.1, 89.1, 77.4, 72.8, 68.2, 59.4, 46.8, 41.8, 39.0, 38.2, 35.3, 33.0, 28.9, 27.9, 23.4, 21.3, 19.2 ppm; IR (thin film/NaCl) 3485 (m), 3365 (m), 3233 (w), 2981 (m), 2107 (sh s), 1763 (s), 1597 (sh s), 1503 (m), 1291 (m), 1144 (s), 1092 (s), 998 (m), 932 (w), 750 (s) cm^{-1}; HRMS (FAB) *m/z* found: 492.2281 [calc'd for $C_{23}H_{34}N_5O_5S$ (M+H): 492.2280]; $[\alpha]_D^{20}$ +14.9° (*c* 1.10, $CHCl_3$).

Preparation of sulfonamide 158, amine 165, and tristhioether 166



Sulfonamide 158, amine 165, and tristhioether 166. To a solution of thiophenol (81μL, 0.788 mmol, 4.0 equiv.) in acetonitrile (2 mL) was added K_2CO_3 (218

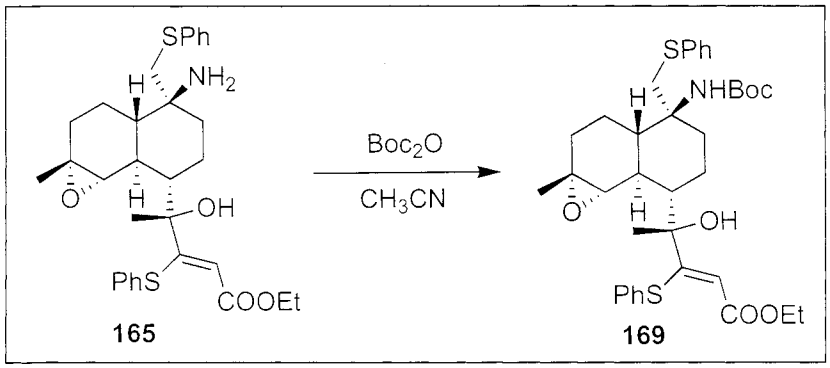
mg, 1.58 mmol, 8.0 equiv.) at 0°C. After stirring for 5 minutes, aziridine **152** (102 mg, 0.197 mmol, 1.0 equiv.) in CH_3CN (2 mL) was added via syringe. The ice bath was removed immediately and the reaction was warmed to 40°C using a pre-heated oil bath for 4 hours. The reaction was cooled to rt, quenched with H_2O (1 mL), diluted with ethyl acetate (10 mL), and washed with brine (3 x 5 mL). The organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (9:1 to 3:1 hexanes:ethyl acetate, then 9:1 dichloromethane:methanol) to afford **165** (66 mg, 61% yield) and trace quantities of **158** and **166** as side-products.

Sulfonamide 158. The spectral data for **158** is listed above in this Experimental Section.

Amine 165. Clear foam. ^{1}H NMR (500 MHz, CD_3OD) δ 7.48-7.43 (comp m, 2H), 7.34-7.23 (comp m, 6H), 7.22-7.17 (comp m, 2H), 6.38 (s, 1H), 3.85 (s, 1H), 3.75-3.62 (m, 2H), 3.27 (d, *J*=13.1 Hz, 1H), 2.87 (d, *J*=13.1 Hz, 1H), 2.11-1.98 (comp m, 3H), 1.90 (t, *J*=11.5 Hz, 1H), 1.74-1.52 (comp m, 3H), 1.50 (s, 3H), 1.28-1.15 (comp m, 7H), 1.14-1.04 (comp m, 2H), 1.01 (t, *J*=7.2 Hz, 4H) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ 167.3, 161.0, 138.7, 136.5, 131.5, 131.2, 130.0, 130.0, 127.9, 127.5, 120.1, 79.8, 64.0, 61.3, 60.7, 55.0, 50.3, 49.6, 47.1, 40.8, 37.9, 31.8, 26.0, 25.3, 23.7, 20.4, 14.3 ppm; IR (thin film/NaCl) 3440 (br s), 2929 (s), 1717 (m), 1715 (m), 1500 (m), 1182 (s), 1026 (m), 748 (m) cm^{-1}; HRMS (FAB) *m/z* found: 576.2222 [calc'd for $C_{31}H_{39}NO_4S_2Na$ (M+Na): 576.2219]; $[\alpha]_D^{20}$ +38.6° (*c* 0.80, $CHCl_3$).

Tristhioether 166. Clear foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.33 (comp m, 5H), 7.32-7.03 (comp m, 9H), 6.95 (t, *J*=7.5 Hz, 1H), 6.13 (s, 1H), 4.34 (br s, 1H), 3.18 (d, *J*=12.5 Hz, 1H), 2.95 (d, *J*=12.4 Hz, 1H), 2.51-2.36 (comp m, 2H), 2.08-1.72 (comp m, 5H), 1.70-1.21 (comp m, 14H), 1.14 (br t, *J*=13.2 Hz, 1H), 1.05 (t, *J*=7.3 Hz, 3H), 0.85-0.72 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 156.2, 137.5, 135.0, 130.3, 130.2, 130.0, 129.7, 129.1, 129.1, 128.9, 128.9, 126.7, 126.4, 126.0, 80.3, 74.1, 60.6, 59.4, 53.7, 46.8, 42.9, 41.1, 38.7, 37.6, 34.3, 30.6, 25.6, 21.5, 19.8, 14.0 ppm; IR (thin film/NaCl) 3348 (br m), 3057 (w), 2979 (m), 2930 (s), 2861 (w), 2362 (w), 2339 (w), 1718 (sh s), 1582 (sh s), 1480 (sh s), 1438 (sh s), 1388 (m), 1367 (m), 1205 (m), 1184 (s), 1025 (sh s), 737 (s) cm^{-1}; HRMS (FAB) *m/z* found: 664.2589 [calc'd for $C_{37}H_{46}NO_4S_3$ (M+H): 664.2589].

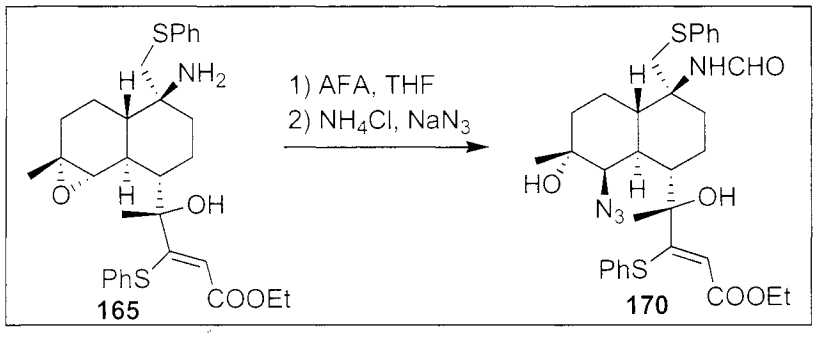
Preparation of carbamate 169



Carbamate 169. To a solution of amine **165** (5.0 mg, 0.009 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) was added triethylamine (8 μL, 0.054 mmol, 6.0 equiv.) and di-*tert*-butyl dicarbonate (11 μL, 0.045 mmol, 5.0 equiv.) at rt. The reaction proceeded at rt for 2 days. The reaction was diluted with CH_2Cl_2 (5 mL), washed with brine (3 x 5 mL), dried

with Na_2SO_4, and concentrated *in vacuo*. The resulting oil was purified by silica gel column chromatography (3:1 hexanes:ethyl acetate) to afford **169** (5 mg, 86% yield) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.14 (comp m, 10H), 6.29 (s, 1H), 4.90 (br s, 1H), 4.01 (s, 1H), 3.85-3.75 (m, 2H), 3.30 (d, *J*=12.7 Hz, 1H), 2.79 (d, *J*=12.7 Hz, 1H), 2.74 (s, 1H), 2.48 (br t, *J*=13.3 Hz, 1H), 2.27 (br t, *J*=12.1 Hz, 1H), 2.08-1.99 (comp m, 2H), 1.96-1.82 (comp m, 2H), 1.74-1.62 (comp m, 2H), 1.62-1.49 (comp m, 7H + H_2O peak), 1.42 (s, 9H), 1.31-1.23 (comp m, 4H), 1.13 (dq, *J*=4.4, 12.5 Hz, 1H), 1.04 (t, *J*=7.1 Hz, 3H), 1.02-0.94 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 157.4, 154.3, 136.1, 134.9, 130.2, 129.3, 129.2, 127.1, 126.8, 121.5, 79.8, 61.3, 60.6, 59.3, 58.0, 46.7, 40.5, 37.9, 32.0, 30.8, 28.6, 26.6, 23.5, 22.3, 19.7, 14.1 ppm; IR (thin film/NaCl) 3491 (br m), 3056 (w), 2978 (m), 2934 (m), 2869 (m), 2249 (m), 1717 (s), 1696 (s), 1582 (m), 1480 (s), 1366 (s), 1169 (s), 1025 (m), 739 (s) cm^{-1}; HRMS (FAB) *m/z* found: 676.2722 [calc'd for $C_{36}H_{47}NO_6S_2Na$ (M+Na): 676.2743]; $[\alpha]_D^{20}$ +14.8° (*c* 0.48, $CHCl_3$).

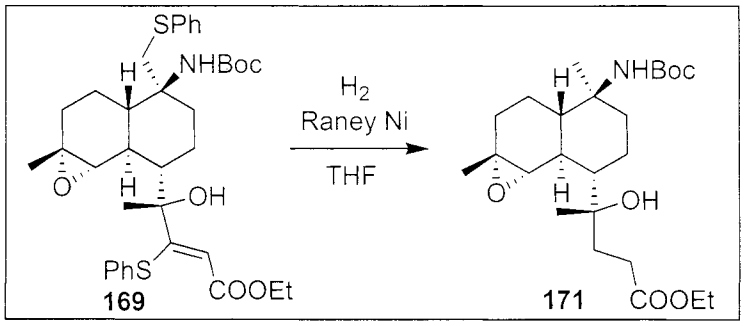
Preparation of formamide 170



Formamide 170. To a solution of amine **165** (16.0 mg, 0.0268 mmol, 1.0 equiv.) in THF (2 mL) was added acetic formic anhydride (50 μL, 0.536 mmol, 20.0 equiv.) at

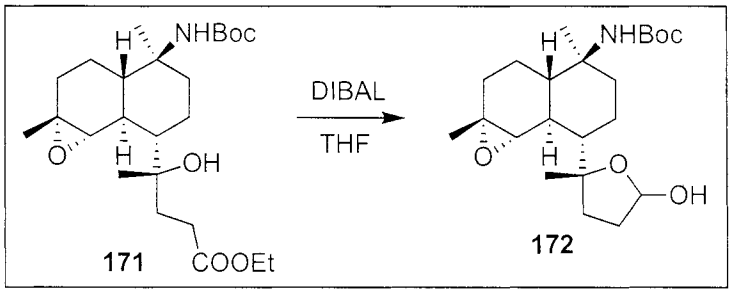
0°C. The reaction was allowed to warm to rt and run overnight. After diluting with ethyl acetate (10 mL), the organic layer was washed with saturated sodium bicarbonate solution (5 mL) and brine (2 x 5 mL). The organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting crude oil treated with sodium azide (43 mg, 0.67 mmol, 25.0 equiv.) and ammonium chloride (3.0 mg, 0.067 mmol, 2.5 equiv.) in methanol (2 mL) and water (200 μL) and heated at 80°C for 12 hours. After diluting with ethyl acetate (10 mL), the organic layer was washed with saturated sodium bicarbonate solution (5 mL) and brine (2 x 5 mL). The organic extracts were dried with Na_2SO_4, concentrated *in vacuo*, and purified by silica gel column chromatography (12:1 dichloromethane:methanol) to provide **170** (14 mg, 84% yield, 11:9 mixture of rotomers) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J*=12.6 Hz, 0.45 H), 8.06 (d, *J*=1.9 Hz, 0.55H), 7.59-7.18 (comp m, 10H), 6.27 (d, *J*=1.9 Hz, 1H), 5.82 (d, *J*=12.3 Hz, 0.45H), 5.46 (s, 0.55H), 4.27 (d, *J*=11.5 Hz, 1H), 3.93-3.84 (m, 2H), 3.28 (dd, *J*=12.9, 16.9 Hz, 1H), 3.04 (d, *J*=12.4 Hz, 1H), 2.29-1.91 (comp m, 4H), 1.82-1.21 (comp m, 14H), 1.10 (td, *J*=7.1, 14.3 Hz, 3H), 0.96 (br t, *J*=13.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 162.7, 160.6, 156.4, 155.6, 136.0, 135.7, 134.5, 133.8, 131.2, 131.1, 130.8, 130.6, 129.4, 129.4, 129.3, 129.3, 127.7, 127.5, 127.3, 127.1, 123.0, 122.4, 79.8, 79.7, 77.4, 73.1, 72.8, 69.7, 69.4, 61.0, 60.8, 59.7, 57.7, 44.1, 43.4, 39.2, 38.8, 38.5, 38.4, 38.2, 35.7, 33.2, 33.1, 32.5, 29.1, 28.9, 25.1, 24.8, 21.7, 21.5, 21.4, 20.7, 14.1, 14.1 ppm; IR (thin film/NaCl) 3403 (br s), 2935 (m), 2107 (s), 1667 (s), 1479 (m), 1440 (m), 1369 (w), 1295 (m), 1191 (m), 1025 (m), 752 (s) cm^{-1}; HRMS (FAB) *m/z* found: 625.2518 [calc'd for $C_{32}H_{41}N_4O_5S_2$ (M+H): 625.2518]; $[\alpha]_D^{20}$ -4.4° (*c* 0.7, $CHCl_3$).

Preparation of ester 171



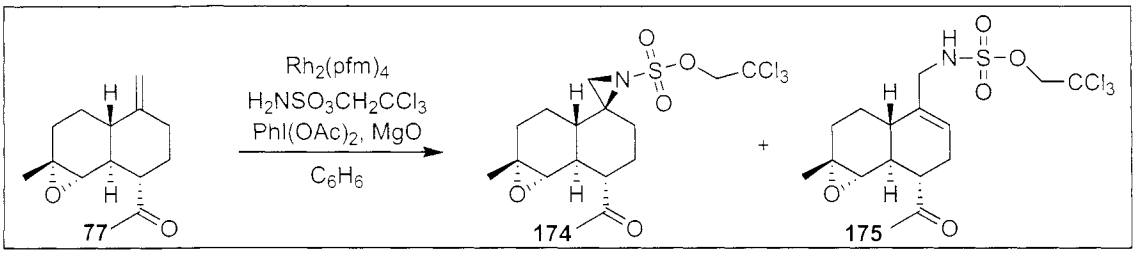
Ester 171. To a solution of ester **169** (50.0 mg, 0.076 mmol, 1.0 equiv.) in THF (6 mL) at rt was added Raney nickel (approximately 3 g, washed repeatedly with THF (10 mL) to remove H_2O). Hydrogen gas (1 balloon, 1 atm) was added and the reaction was run overnight. The reaction was then filtered through celite and washed with methanol (10 mL) to remove Raney nickel (**CAUTION**: Nitrogen should be used to flush and the Raney nickel should not be allowed to dry) and the organic filtrate was concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography to afford **171** (27 mg, 80% yield) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.36 (br s, 1H), 4.24-4.04 (comp m, 3H), 2.61-0.96 (comp m, 37H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 154.2, 75.5, 62.1, 60.8, 59.1, 55.4, 47.2, 43.2, 40.6, 37.6, 36.5, 30.8, 28.6, 28.4, 25.9, 23.7, 23.6, 20.2, 19.6, 14.3 ppm; IR (thin film/NaCl) 3451 (br m), 3331 (m), 2978 (s), 2937 (s), 2871 (m), 1717 (s), 1699 (s), 1520 (m), 1456 (m), 1367 (m), 1242 (m), 1171 (s), 1076 (m) cm^{-1}; HRMS (FAB) *m/z* found: 462.2820 [calc'd for $C_{24}H_{41}NO_6Na$ (M+Na): 462.2832]; $[\alpha]_D^{20}$ +24.9° (*c* 0.75, $CHCl_3$).

Preparation of lactol 172



Lactol 172. To a solution of ester **171** (9.0 mg, 0.0205 mmol, 1.0 equiv.) in THF (1 mL) was added diisobutylaluminum hydride (62 μL, 0.0615 mmol, 1.0 M in hexanes, 3.0 equiv.) at -78°C. After 45 minutes, the reaction was quenched with Rochelle's salt solution (500 μL, *w/v*) and warmed to rt. After diluting with ethyl acetate (10 mL), the organic layer was washed with brine (2 x 5 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The resulting oil was purified by silica gel column chromatography (4:1 to 1:1 hexanes:ethyl acetate) to afford **172** (6 mg, 74% yield, 3:2 ratio of lactol epimers) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (br s, 0.4H), 5.47 (br s, 0.6H), 4.41-4.33 (m, 1H), 4.16-4.10 (m, 1H), 4.03 (s, 0.6H), 3.99 (s, 0.4H), 2.56-2.09 (comp m, 3H), 2.08-1.51 (comp m, 9H), 1.50-0.76 (comp m, 29H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 99.4, 98.4, 88.7, 87.7, 77.4, 75.6, 62.1, 61.5, 60.8, 59.0, 55.6, 55.5, 55.4, 51.8, 51.8, 40.6, 40.5, 40.3, 35.9, 32.8, 32.3, 30.9, 29.9, 28.6, 28.4, 26.9, 26.4, 25.9, 23.7, 23.7, 23.6, 20.9, 20.0, 19.7, 19.7, 14.4 ppm; IR (thin film/NaCl) 3451 (m), 3363 (m), 2975 (s), 2931 (s), 2870 (m), 1712 (s), 1694 (s), 1514 (m), 1501 (m), 1460 (m), 1379 (m), 1366 (m), 1279 (m), 1248 (s), 1170 (s), 1074 (m), 1004 (m), 756 (m) cm^{-1}; HRMS (FAB) *m/z* found: 396.2750 [calc'd for $C_{22}H_{38}NO_5$ (M+H): 396.2750]; $[\alpha]_D^{20}$ +29.0° (*c* 0.30, $CHCl_3$).

Preparation of aziridine 174 and sulfamate ester 175



Aziridine 174 and sulfamate ester 175. To a solution of $H_2NSO_3CH_2CCl_3$ (57.0 mg, 0.250 mmol, 1.1 equiv.) in benzene (1 mL) at 5°C was added olefin **77** (50.0 mg, 0.227 mmol, 1.0 equiv.), magnesium oxide (21.0 mg, 0.522 mmol, 2.3 equiv.), phenyliodiacetate ($PhI(OAc)_2$, 95.0 mg, 0.295 mmol, 1.3 equiv.), and rhodium (II) perfluorobutyramide ($Rh_2(pfm)_4$, 4.0 mg, 0.006 mmol, 0.03 equiv.). The reaction was allowed to gradually warmed to rt over a 10-hour period. The reaction was filtered through a celite plug, washed thoroughly with dichloromethane (10 mL), and the filtrate was concentrated *in vacuo*. A ^1H NMR of the crude reaction mixture showed a 5:1 ratio of aziridine diastereomers. The resulting residue was purified by silica gel column chromatography (6:1 to 1:1 hexanes:ethyl acetate) to afford major aziridine diastereomer **174** (62 mg, 61% yield) and the minor aziridine diastereomer. It was noted that a new spot appeared by TLC upon silica gel chromatography. This compound was further purified by HPLC (3:1 to 1:1 hexanes:ethyl acetate) and was determined to be sulfamate ester **175**.

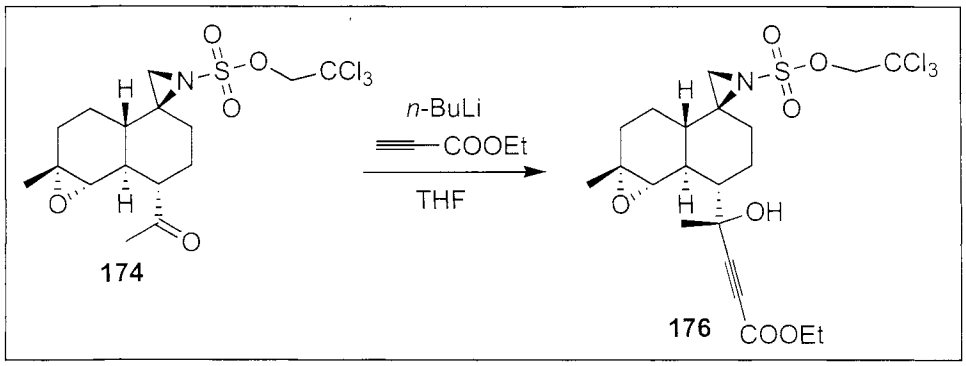
Major aziridine diastereomer 174. White foam. ^1H NMR (500 MHz, $CDCl_3$) δ 4.77 (s, 2H), 2.64-2.56 (comp m, 2H), 2.48 (s, 1H), 2.46 (s, 1H), 2.26 (s, 3H), 2.24-2.01 (comp

m, 4H), 1.95 (t, *J*=12.0 Hz, 1H), 1.68-1.43 (comp m, 4H), 1.28 (s, 3H), 0.84 (dq, *J*=4.4, 12.7 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.1, 93.3, 79.6, 61.3, 58.5, 54.2, 53.2, 42.2, 41.8, 37.8, 30.2, 30.0, 29.4, 29.1, 23.2, 18.1 ppm; IR (thin film/NaCl) 2956 (m), 2930 (m), 2872 (m), 1709 (s), 1450 (m), 1424 (w), 1366 (s), 1222 (w), 1180 (s), 1094 (m), 1046 (w), 1003 (s), 855 (s), 784 (s) cm^{-1}; HRMS (FAB) *m/z* found: 468.0168 [calc'd for $C_{16}H_{22}Cl_3NO_5SNa$ (M+Na): 468.0182]; $[\alpha]_D^{20}$ +14.4° (*c* 1.18, $CHCl_3$).

Minor aziridine diastereomer. White foam. Despite repeated efforts to purify and characterize this compound, this minor diastereomer proved to be unstable at rt and decomposed rapidly.

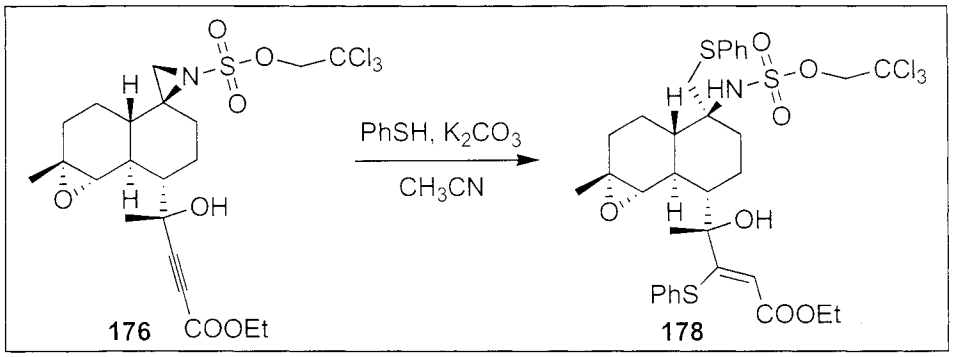
Sulfamate ester 175. Clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (br s, 1H), 4.81 (t, *J*=5.9 Hz, 1H), 4.64 (s, 2H), 3.91-3.83 (m, 1H), 3.76-3.69 (m, 1H), 2.71 (dt, *J*=6.0, 11.5 Hz, 1H), 2.59 (s, 1H), 2.54-2.11 (comp m, 6H), 2.00-1.61 (comp m, 4H), 1.40-1.23 (comp m, 3H), 1.13 (dq, *J*=5.0, 12.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3, 134.7, 125.5, 93.7, 78.3, 61.9, 58.2, 51.6, 47.7, 41.7, 38.0, 30.8, 29.6, 28.2, 23.4, 22.5 ppm; IR (thin film/NaCl) 3229 (br m), 2959 (s), 2924 (s), 1708 (s), 1440 (s), 1369 (s), 1260 (m), 1182 (s), 1090 (m), 1047 (m), 1016 (s), 854 (s), 755 (s) cm^{-1}; HRMS (FAB) *m/z* found: 446.0363 [calc'd for $C_{16}H_{23}Cl_3NO_5S$ (M+H): 446.0362]; $[\alpha]_D^{20}$ +14.5° (*c* 0.58, $CHCl_3$).

Preparation of ester 176



Ester 176. To a solution of ethyl propiolate (1.00 mL, 9.81 mmol, 10.0 equiv.) in THF (30 mL) at -78°C was added *n*-BuLi (3.90 mL, 9.81 mmol, 2.5 M in hexanes, 10.0 equiv.) and stirred for 10 minutes. A solution of ketone **174** (438 mg, 0.98 mmol, 1.0 equiv.) in THF (5 mL) was added dropwise. The reaction was run at -78°C for 10 minutes and quenched with solid NH_4Cl (300 mg). The reaction was allowed to warm to room temperature and was diluted with ethyl acetate (100 mL). The organic layer was washed with brine (3 x 20 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The resulting oil was purified by silica gel column chromatography (9:1 to 2:1 hexanes:ethyl acetate) to afford **176** (349 mg, 66% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (s, 2H), 4.24 (q, *J*=7.0 Hz, 2H), 3.95 (s, 1H), 2.61-2.56 (m, 2H), 2.50-2.39 (comp m, 2H), 2.21-1.92 (comp m, 4H), 1.73-1.58 (comp m, 6H), 1.52-1.42 (m, 1H), 1.41-1.27 (comp m, 7H), 0.85 (dq, *J*=4.2, 12.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 93.3, 90.0, 79.5, 77.3, 71.9, 62.4, 60.2, 59.4, 53.6, 47.9, 43.2, 42.1, 37.9, 30.3, 29.7, 29.6, 25.3, 23.4, 18.4, 14.2 ppm; IR (thin film/NaCl) 3422 (br m), 2983 (m), 2959 (m), 2936 (m), 2874 (m), 2237 (m), 1710 (s), 1449 (m), 1366 (s), 1250 (s), 1180 (s), 1092 (m), 1021 (s), 1006 (s), 856 (s), 786 (s), 755 (s) cm^{-1}; HRMS (FAB) *m/z* found: 566.0546 [calc'd for $C_{21}H_{28}Cl_3NO_7SNa$ (M+Na): 566.0550]; $[\alpha]_D^{20}$ +14.3° (*c* 1.19, $CHCl_3$).

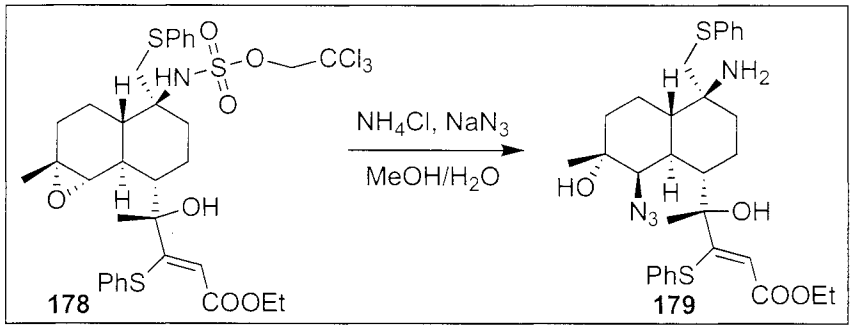
Preparation of bis-thioether 178



Bis-thioether 178. To a solution of aziridine **176** (50.0 mg, 0.092 mmol, 1.0 equiv.) in acetonitrile (3 mL) at 0°C was added thiophenol (29 μL, 0.276 mmol, 3.0 equiv.) and potassium carbonate (77 mg, 0.552 mmol, 6.0 equiv.). The reaction was run for 30 minutes at 0°C and quenched with H_2O (1 mL). The reaction was then diluted with ethyl acetate (10 mL) and the organic layers were washed with brine (3 x 5 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The resulting oil was purified by silica gel column chromatography (9:1 hexanes:ethyl acetate to 2:1 ethyl acetate:hexanes) to afford **178** (62 mg, 89% yield) as a clear viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.16 (comp m, 10H), 6.30 (s, 1H), 5.23 (s, 1H), 4.65 (q, *J*=10.7 Hz, 2H), 3.99 (s, 1H), 3.88-3.76 (m, 2H), 3.32 (d, *J*=13.3 Hz, 1H), 2.84 (d, *J*=13.3 Hz, 1H), 2.78 (s, 1H), 2.21-2.14 (m, 2H), 2.11-2.02 (comp m, 2H), 1.98 (dt, *J*=3.6, 12.0 Hz, 1H), 1.86 (t, *J*=11.6 Hz, 1H), 1.80-1.53 (comp m, 6H), 1.35-1.22 (comp m, 3H), 1.22-1.10 (m, 1H), 1.05 (t, *J*=7.1 Hz, 3H), 1.01-0.89 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 157.0, 135.0, 134.5, 130.7, 130.2, 129.6, 129.2, 127.6, 127.3, 121.8, 93.5, 79.6, 78.5, 63.7, 61.1, 60.7, 59.3, 46.3, 44.4, 41.0, 38.7, 32.6, 30.5, 26.3, 23.4, 22.6, 19.9, 14.1 ppm; IR (thin

film/NaCl) 3228 (br m), 2938 (s), 1717 (s), 1700 (s), 1684 (m), 1653 (w), 1582 (w), 1559 (w), 1474 (s), 1456 (s), 1439 (s), 1387 (s), 1362 (s), 1302 (s), 1273 (s), 1177 (sh s), 1025 (s), 752 (s) cm^{-1}; HRMS (FAB) *m/z* found: 786.0967 [calc'd for $C_{33}H_{40}Cl_3NO_7S_3Na$ (M+Na): 786.0930]; $[\alpha]_D^{20}$ +30.3° (*c* 2.02, $CHCl_3$).

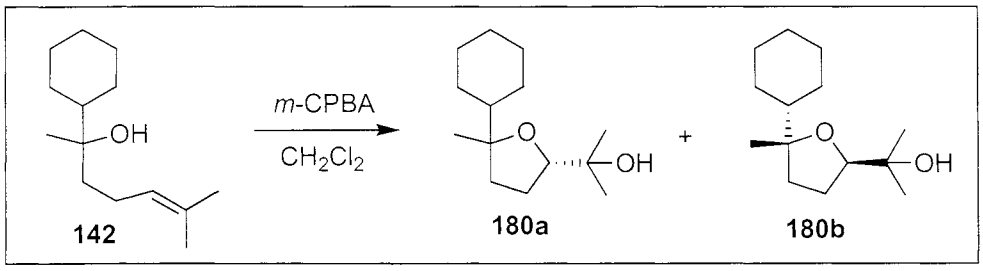
Preparation of amine 179



Amine 179. To a solution of epoxide **178** (19.0 mg, 0.025 mmol, 1.0 equiv.) in methanol (3.2 mL) and water (400 μL) was added sodium azide (81 mg, 1.24 mmol, 50.0 equiv.) and ammonium chloride (4.0 mg, 0.075 mmol, 3.0 equiv.) and heated to 80°C overnight. The reaction was then cooled to rt, diluted with ethyl acetate (10 mL), and washed with sodium bicarbonate solution (1 x 5 mL) and brine (2 x 5 mL). The organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (20:1 to 9:1 dichloromethane:methanol) to afford **179** (13 mg, 87% yield) as a white foam. ^{1}H NMR (500 MHz, CD_3OD) δ 7.75-7.16 (comp m, 10H), 6.19 (s, 1H), 4.34 (br s, 2H), 3.77-3.63 (m, 2H), 3.02 (d, *J*=13.0 Hz, 1H), 2.24 (dt, *J*=2.4, 10.8 Hz, 1H), 2.19-2.12 (m, 1H), 2.10-2.04 (m, 1H), 1.69-1.11 (comp m, 15H), 1.05 (t, *J*=7.3 Hz, 3H), 0.96-0.82 (m, 3H) ppm; ^{13}C NMR (125 MHz,

CD_3OD) δ 167.4, 161.2, 132.3, 131.8, 131.8, 130.1, 129.9, 129.9, 127.9, 127.7, 120.0, 80.4, 73.4, 70.9, 62.8, 61.4, 44.8, 39.2, 34.0, 32.8, 28.7, 25.4, 23.3, 21.5, 14.5, 14.4, 14.3 ppm; IR (thin film/NaCl) 3412 (br m), 2927 (s), 2850 (m), 2104 (sh s), 1733 (s), 1717 (s), 1700 (s), 1288 (s), 1260 (s), 1033 (s), 1024 (s), 747 (s) cm^{-1}; HRMS (FAB) *m/z* found: 597.2571 [calc'd for $C_{31}H_{41}N_4O_4S_2$ (M+H): 597.2569]; $[\alpha]_D^{20}$ +10.0° (*c* 0.10, $CHCl_3$).

Preparation of alcohols 180a and 180b



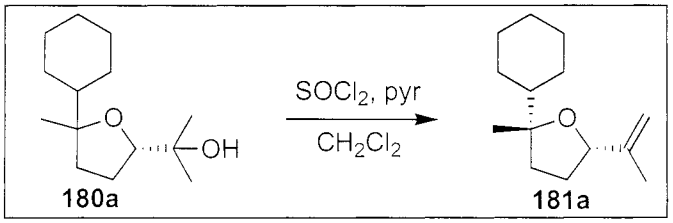
Alcohols 180a and 180b. To a solution of bishomoallylic alcohol **142** (500 mg, 2.31 mmol, 1.0 equiv.) was added *m*-CPBA (recrystallized, 558 mg, 3.24 mmol, 1.4 equiv.) in CH_2Cl_2 (25 mL) at 0°C. After 1 hour, the reaction was quenched with saturated $NaHCO_3$ solution (5 mL) and washed with brine (2 x 10 mL). The organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting oil was purified by silica gel column chromatography (15:1 to 12:1 hexanes:ethyl acetate) to afford **180a** and **180b** (3.76 g total, 90% yield, 1:1 mixture of diastereomers) as a clear oil.

Alcohol 180a. Clear oil. ^1H NMR (500 MHz, $CDCl_3$) δ 3.76 (t, *J*=7.5 Hz, 1H), 2.10 (br s, 1H), 1.90-1.52 (comp m, 9H), 1.40-1.32 (m, 1H), 1.28-0.94 (comp m, 5H), 1.21 (s,

3H), 1.12 (s, 3H), 1.09 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 85.6, 84.1, 71.6, 48.4, 35.6, 28.6, 28.0, 27.5, 26.8, 26.8, 26.3, 24.4, 22.1 ppm; IR (thin film/NaCl) 3572 (br w), 3453 (br m), 2971 (s), 2927 (s), 2854 (s), 1450 (m), 1374 (sh m), 1080 (m), 1073 (m) cm^{-1}; HRMS (CI) *m/z* found: 225.1854 [calc'd for $C_{14}H_{25}O_2$ (M-H): 225.1855].

Alcohol 180b. Clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67-3.62 (m, 1H), 2.23 (s, 1H), 1.86-1.55 (comp m, 9H), 1.42-1.33 (m, 1H), 1.27-1.12 (comp m, 6H), 1.11 (s, 3H), 1.08 (s, 3H), 1.04-0.91 (m, 2H) ppm; ^{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 ppm; IR (thin film/NaCl) 3461 (br w), 2972 (s), 2927 (s), 2853 (s), 1451 (m), 1374 (m), 1338 (w), 1305 (w), 1234 (w), 1185 (w), 1145 (m), 1083 (m), 1058 (m), 890 (m) cm^{-1}; HRMS (FAB) *m/z* found: 227.2008 [calc'd for $C_{14}H_{27}O_2$ (M+H): 227.2011].

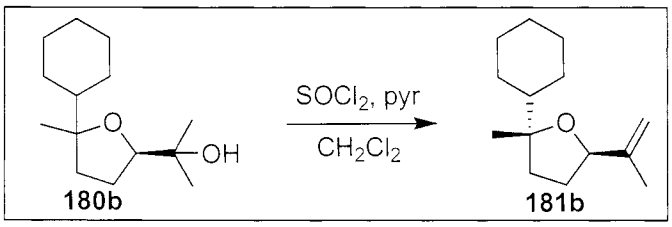
Preparation of olefin 181a



Olefin 181a. To a solution of alcohol **180a** (30.0 mg, 0.132 mmol, 1.0 equiv.) in CH_2Cl_2 (3 mL) and pyridine (0.5 mL) was added thionyl chloride (100 μL, 1.37 mmol, 10.4 equiv.). The reaction was run at rt overnight. The reaction was washed with 1N HCl (5 mL) and brine (2 x 5 mL). The organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting oil was purified by silica gel column

chromatography (12:1:0.5 hexane:ethyl acetate:triethylamine) to afford **181a** (20 mg, 74% yield) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (s, 1H), 4.78 (s, 1H), 4.34 (t, *J*=6.7 Hz, 1H), 2.08-1.98 (comp m, 1H), 1.93-1.73 (comp m, 5H), 1.71 (s, 3H), 1.70-1.50 (comp m, 4H), 1.40 (dt, *J*=2.9, 12.1 Hz, 1H, 1.29-0.91 (comp m, 7H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.2, 110.2, 85.7, 80.9, 48.4, 35.4, 31.5, 28.6, 28.0, 26.9, 26.9, 23.0, 18.3 ppm; IR (thin film/NaCl) 2967 (m), 2926 (s), 2853 (m), 1450 (m), 1372 (w), 1082 (m), 1028 (w), 893 (m) cm^{-1}; HRMS (CI) *m/z* found: 209.1901 [calc'd for $C_{14}H_{25}O$ (M+H): 209.1905].

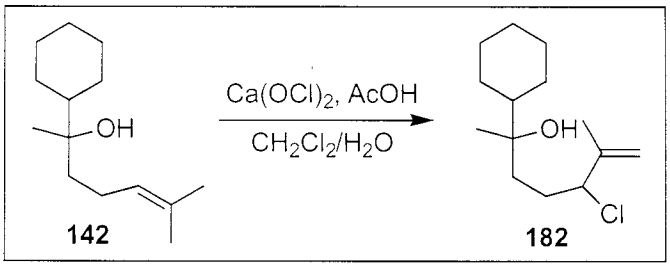
Preparation of olefin 181b



Olefin 181b. To a solution of alcohol **180b** (100.0 mg, 0.442 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) and pyridine (1.5 mL) was added thionyl chloride (330 μL, 4.52 mmol, 10.2 equiv.). The reaction was run at rt overnight. The reaction was washed with 1N HCl (5 mL) and brine (2 x 5 mL). The organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting oil was purified by silica gel column chromatography (12:1:0.5 hexane:ethyl acetate:triethylamine) to afford **181b** (71 mg, 77% yield) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.00 (br s, 1H), 4.78 (br s, 1H), 4.25 (dd, *J*=5.9, 9.5 Hz, 1H), 2.01-1.94 (m, 1H), 1.93-1.51 (comp m, 11H), 1.45-1.37 (m,

1H), 1.28-0.91 (comp m, 8H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.4, 110.2, 85.9, 82.8, 48.4, 35.5, 31.6, 28.2, 28.1, 26.9, 26.8, 24.1, 18.0 ppm; IR (thin film/NaCl) 2968 (m), 2926 (s), 2853 (s), 1652 (w), 1451 (m), 1373 (m), 1307 (w), 1144 (w), 1082 (m), 1048 (m), 1027 (m) cm^{-1}; HRMS (CI) *m/z* found: 209.1903 [calc'd for $C_{14}H_{25}O$ (M+H): 209.1905].

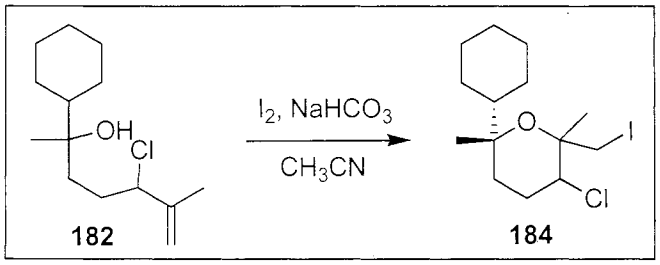
Preparation of chloride 182



Chloride 182. To a solution of bishomoallylic alcohol **142** (500 mg, 2.38 mmol, 1.0 equiv.) was added calcium hypochlorite (272 mg, 1.90 mmol, 0.8 equiv.) in CH_2Cl_2 (2 mL) and water (5 mL). The reaction mixture was cooled to 0°C and glacial acetic acid (218 μL, 3.81 mmol, 1.6 equiv.) was added dropwise. After 1 hour, an additional amount of calcium hypochlorite (136 mg, 1.19 mmol, 0.4 equiv.) and glacial acetic acid (109 μL, 1.90 mmol, 0.8 equiv.) were added. After 1 hour, the reaction was quenched with saturated $NaHCO_3$ solution (2 mL), diluted with CH_2Cl_2 (10 mL), and the organic layer was washed with brine (3 x 10 mL). The organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting oil could be advanced with further purification, or purified by silica gel column chromatography (12:1 to 9:1 hexanes:ethyl acetate) to afford **182** (308 mg, 53% yield, 1:1 mixture of diastereomers) as a clear oil. ^1H NMR

(500 MHz, $CDCl_3$) δ 5.00 (s, 1H), 4.88 (s, 1H), 4.35 (dt, *J*=2.6, 7.4 Hz, 1H), 1.99-1.85 (comp m, 2H), 1.84-1.54 (comp m, 9H), 1.44-0.91 (comp m, 11H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 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, 17.1, 17.1 ppm; IR (thin film/NaCl) 3453 (br m), 2928 (s), 2853 (s), 1646 (w), 1449 (m), 1376 (m), 1299 (w), 1268 (w), 1202 (w), 1117 (m), 905 (m) cm^{-1}; HRMS (EI) *m/z* found: 208.1827 [calc'd for $C_{14}H_{24}O$ (M-[HCl]): 208.1827].

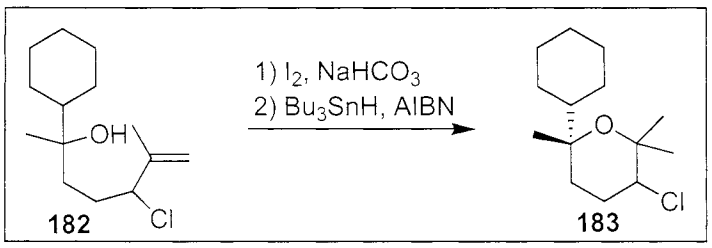
Preparation of iodo-chlorotetrahydropyran 184



Iodo-chlorotetrahydropyran 184. To a solution of crude allylic chloride **182** (580 mg, 2.38 mmol, 1.0 equiv.) in CH_3CN (25 mL) was added $NaHCO_3$ (1.20 g, 14.26 mmol, 6.0 equiv.). The reaction was cooled to 0°C and and I_2 (3.60 g, 14.26 mmol, 6.0 equiv.) was added. The reaction was allowed to warm to rt and stirred for 5 hours. After diluting with hexanes (50 mL), the organic layer was washed with saturated $Na_2S_2O_3$ solution (1 x 20 mL) and brine (2 x 20 mL). The organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (hexane to 19:1 hexane:ethyl acetate) to provide **184** (477 mg, 54% yield over two steps from bishomoallylic alcohol, mixture of three inseparable

diastereomers) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21-4.17 (m, 0.25H), 3.98 (ddd, *J*=4.0, 8.1, 12.3 Hz, 0.75H), 3.68 (d, *J*=11.0 Hz, 0.6H), 3.61 (d, *J*=11.0 Hz, 0.6H), 3.43 (s, 0.6H), 3.30 (d, *J*=4.2 Hz, 0.25H), 2.41-0.81 (comp m, 21H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 76.8, 76.6, 76.3, 74.6, 74.1, 73.2, 63.0, 62.4, 61.9, 51.1, 51.1, 50.6, 35.2, 34.8, 29.9, 27.6, 27.4, 27.3, 27.2, 27.0, 26.9, 26.9, 26.9, 26.8, 26.8, 26.2, 26.1, 25.3, 23.1, 21.4, 21.3, 21.1, 20.4, 19.3, 16.7 ppm; IR (thin film/NaCl) 2978 (m), 2927 (s), 2852 (s), 1465 (m), 1450 (m), 1419 (w), 1376 (m), 1248 (w), 1196 (m), 1158 (m), 1100 (m), 1029 (m), 793 (m) cm^{-1}; HRMS (FAB) *m/z* found: 371.0637 [calc'd for $C_{14}H_{25}ClIO$ (M+H): 371.0638].

Preparation of chlorotetrahydropyran 183



Chlorotetrahydropyran 183. To a solution of iodo-chlorotetrahydropyran **182** (100 mg, 0.270 mmol, 1.0 equiv.) in benzene (3 mL) was added *n*-Bu_3SnH (73 μL, 0.270 mmol, 1.0 equiv.) and AIBN (4.4 mg, 0.027 mmol, 0.1 equiv.) and heated to reflux. After 1.5 hours, the reaction was cooled to rt and concentrated *in vacuo* with concomitant absorption onto silica gel. The reaction was purified by silica gel column chromatography (100% benzene) to provide **183** (52 mg, 79% yield, 1:1 mixture of diastereomers) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (dd, *J*=3.5, 6.8 Hz, 0.5

H), 3.68 (dd, *J*=4.3, 12.1 Hz, 0.5 H), 2.22-1.45 (comp m, 10 H), 1.36-0.83 (comp m, 14 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.7, 74.2, 74.0, 73.1, 64.7, 64.1, 49.8, 46.9, 33.4, 29.5, 28.6, 27.9, 26.8, 26.3, 26.2, 26.0, 26.0, 25.9, 25.8, 25.8, 25.8, 25.8, 25.8, 25.7, 24.9, 23.3, 21.8, 21.1 ppm; IR (thin film/NaCl) 2976 (m), 2929 (s), 2853 (m), 1450 (m), 1376 (m), 1228 (w), 1126 (m), 1050 (w), 979 (m) cm^{-1}; HRMS (FAB) *m/z* found: 245.1509 [calc'd for $C_{14}H_{26}ClO$ (M+H): 245.1672].

2.5 Notes and References

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46. The screening of other heterogenous catalysts (palladium on carbon, palladium hydroxide, etc.) and solvents (Et_2O, EtOAc, EtOH, etc.) did not afford any selectivity for alkyne reduction over nitro reduction.

47. Advancement of butenolide **154** was ultimately not successful due to decomposition of the nosyl aziridine in the olefination step to form the bishomoallylic alcohol (route not characterized).

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57. As a testament to the mild conditions necessary for nosyl deprotection, Fukuyama and co-workers have recently reported such a transformation on a highly advanced intermediate en route to the total synthesis of (-)-strychnine. Kaburagi, Y.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2004,** *126*, 10246-10247.

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Appendix One:

Spectra Relevant to Chapter 2

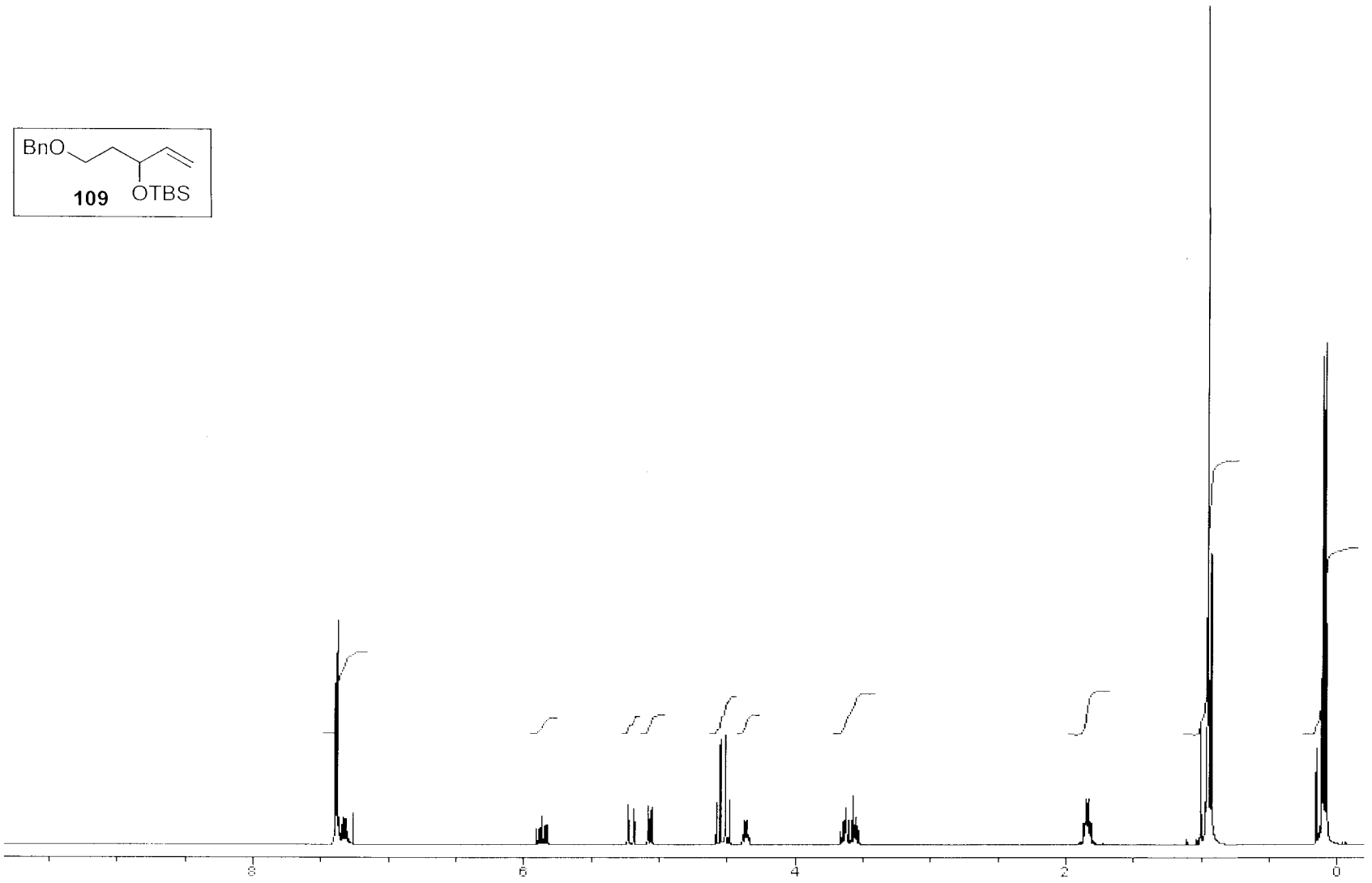


Figure A.1.1 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **109**

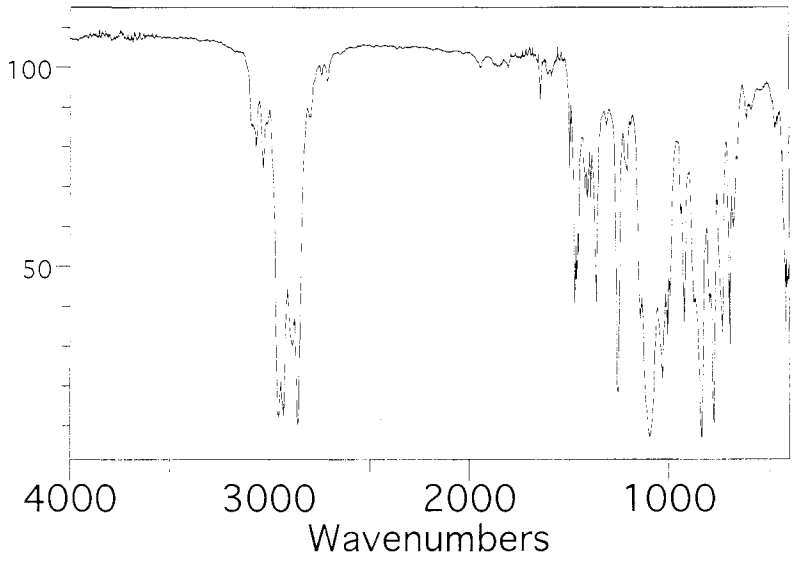


Figure A.1.2 FTIR Spectrum (thin film/NaCl) of Compound **109**

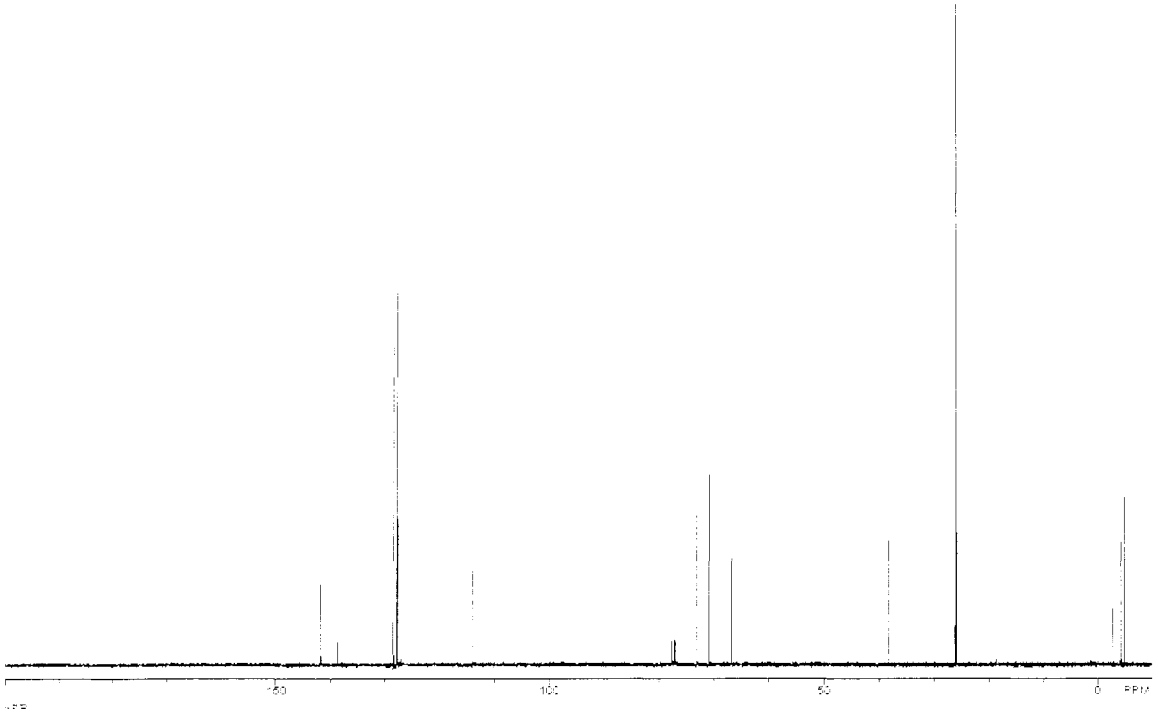


Figure A.1.3 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **109**

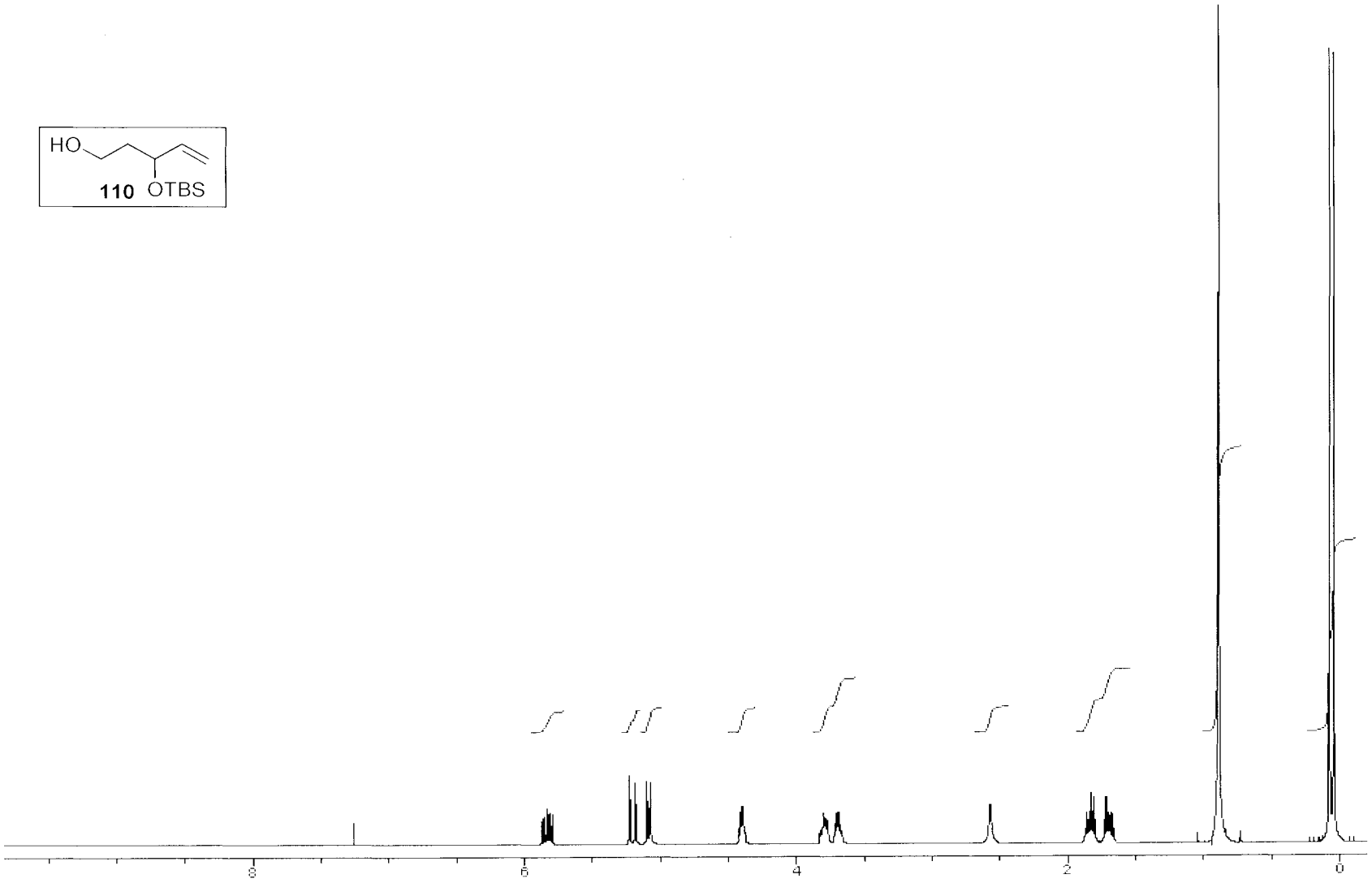


Figure A.1.4 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **110**

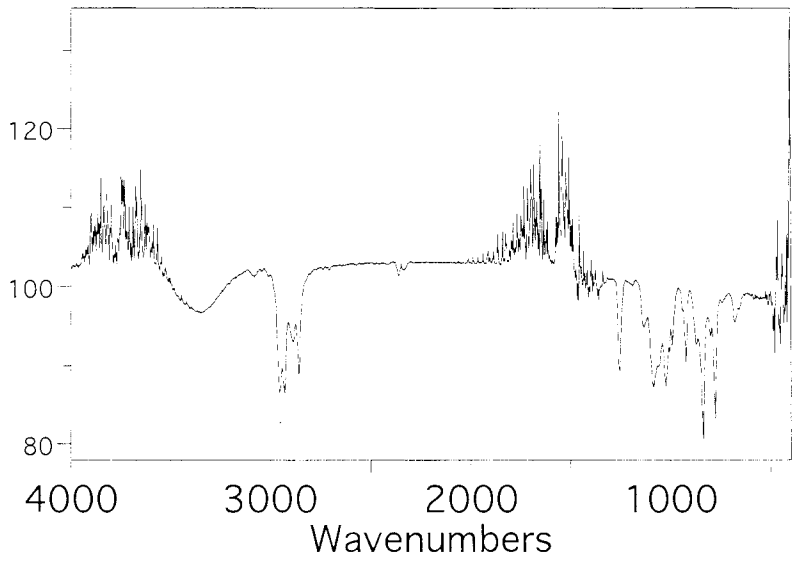


Figure A.1.5 FTIR Spectrum (thin film/NaCl) of Compound **110**

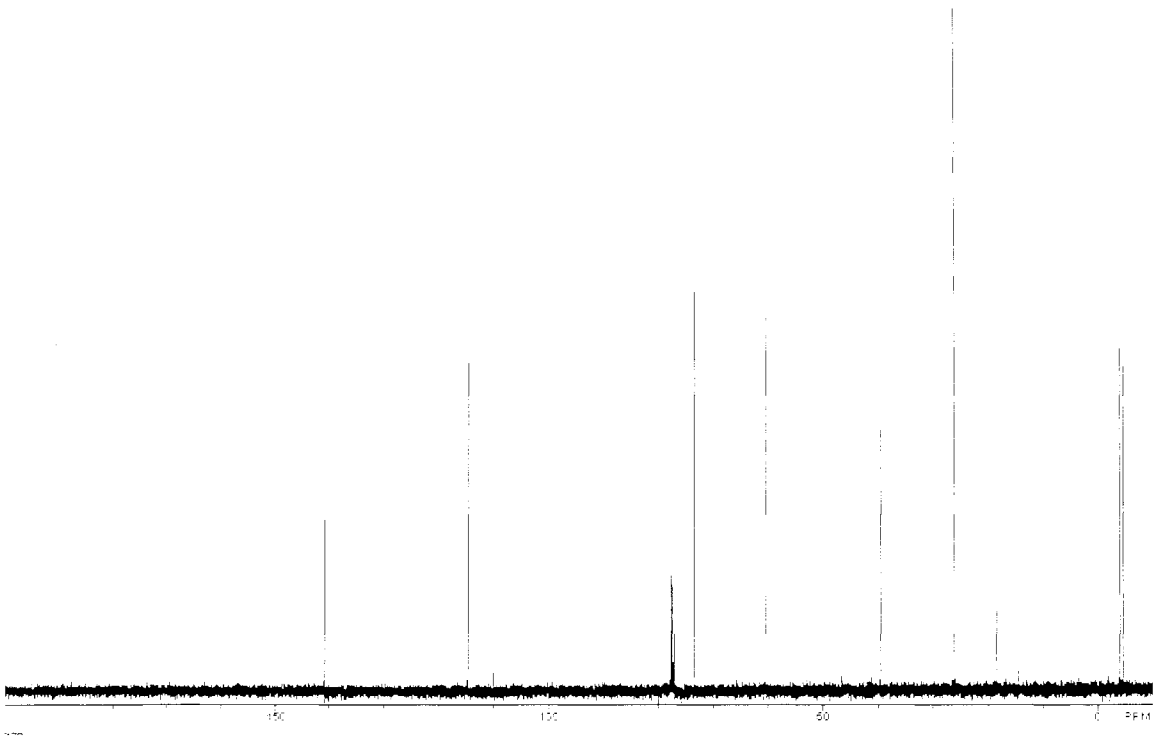
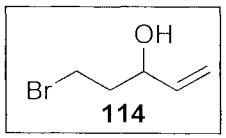


Figure A.1.6 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **110**



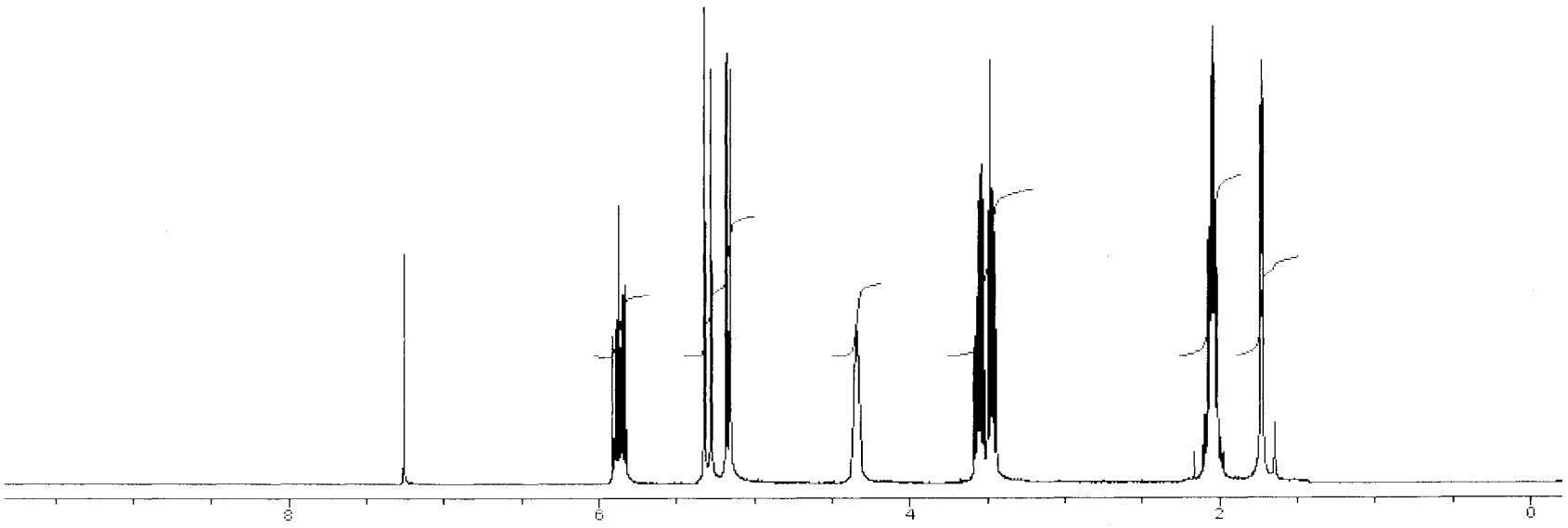


Figure A.1.7 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **114**

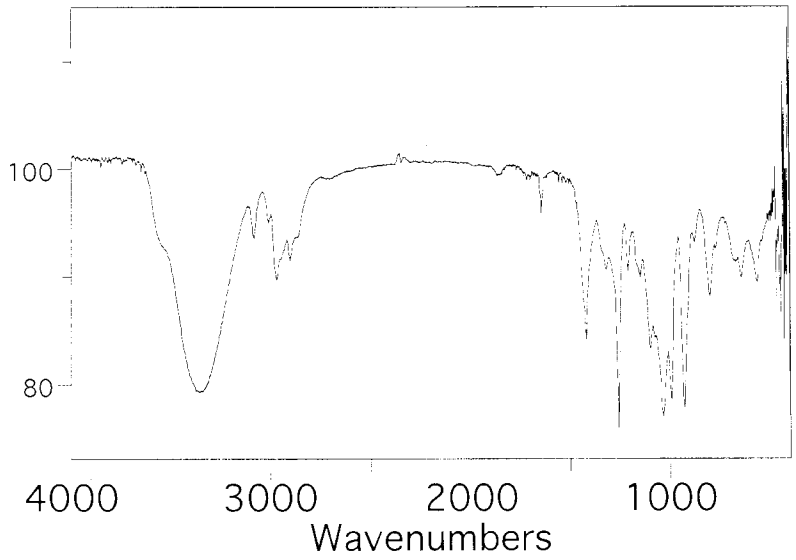


Figure A.1.8 FTIR Spectrum (thin film/NaCl) of Compound **114**

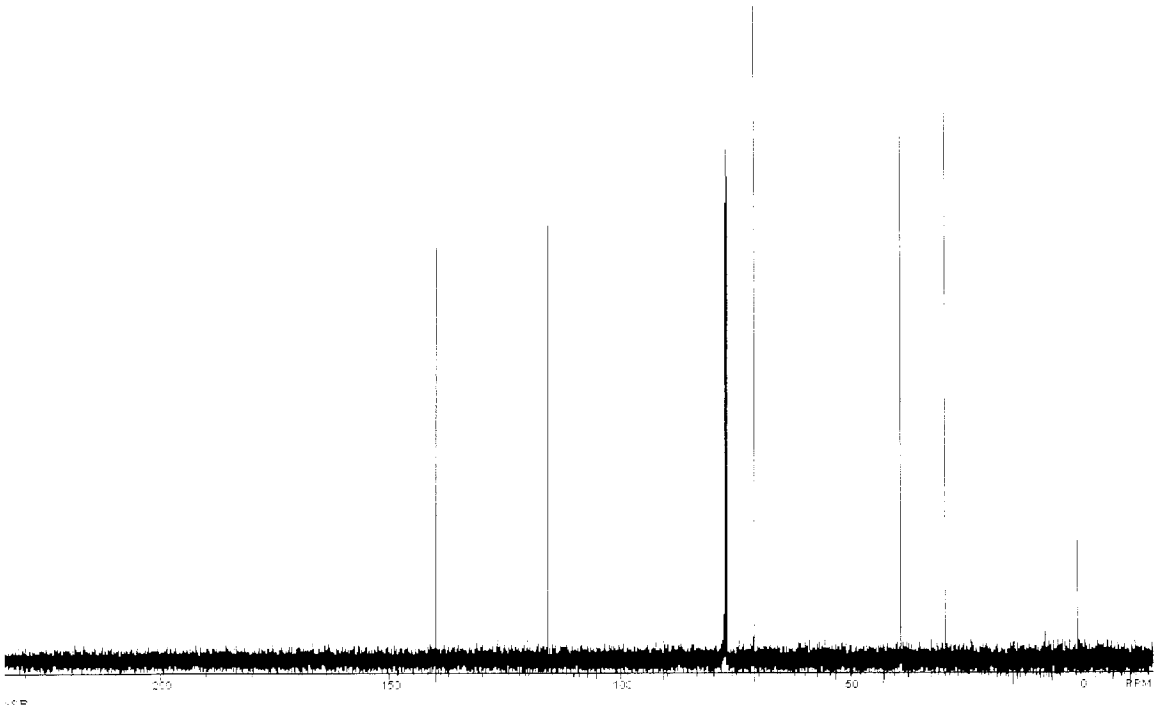


Figure A.1.9 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **114**

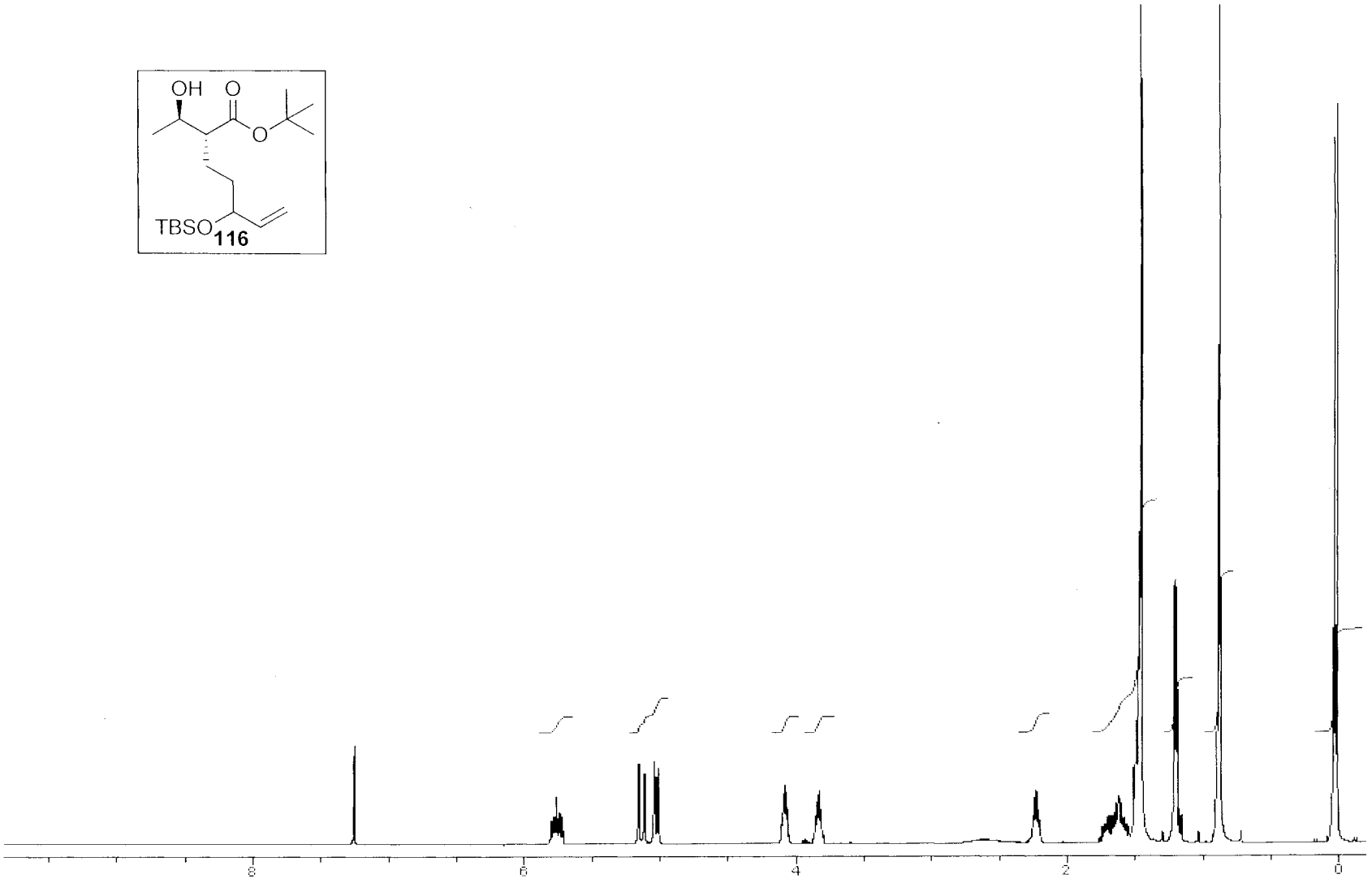


Figure A.1.10 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **116**

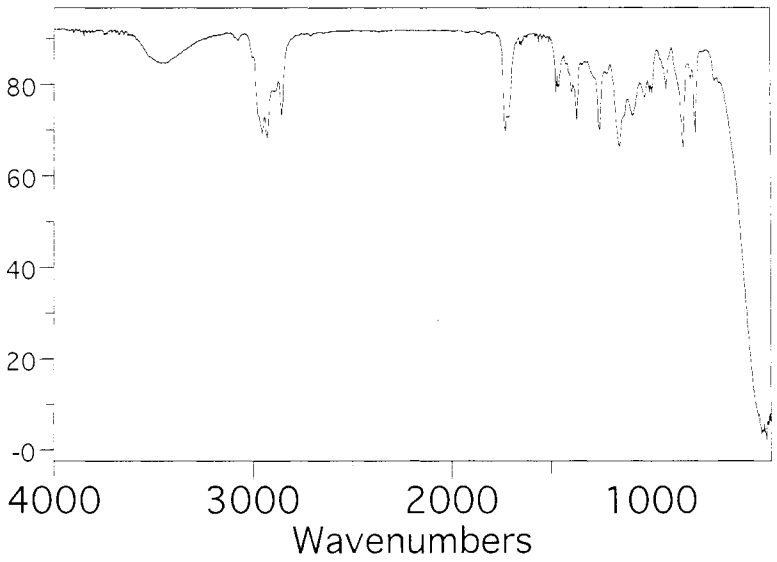


Figure A.1.11 FTIR Spectrum (thin film/NaCl) of Compound **116**

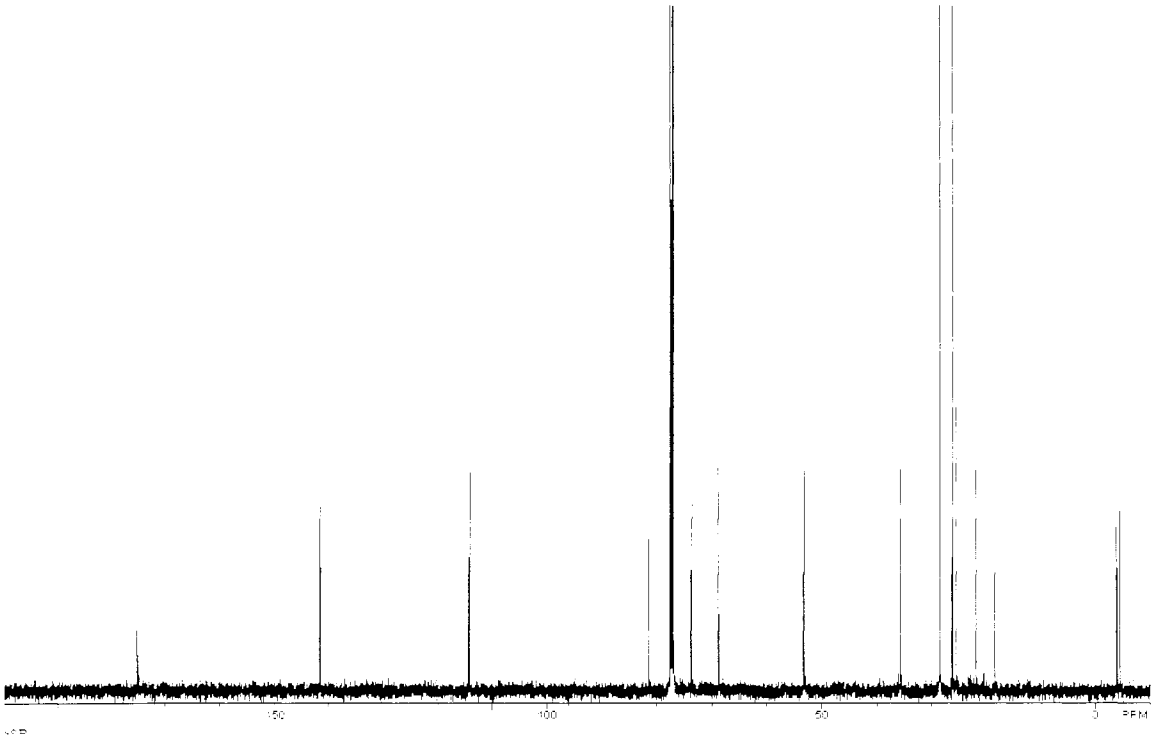


Figure A.1.12 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **116**

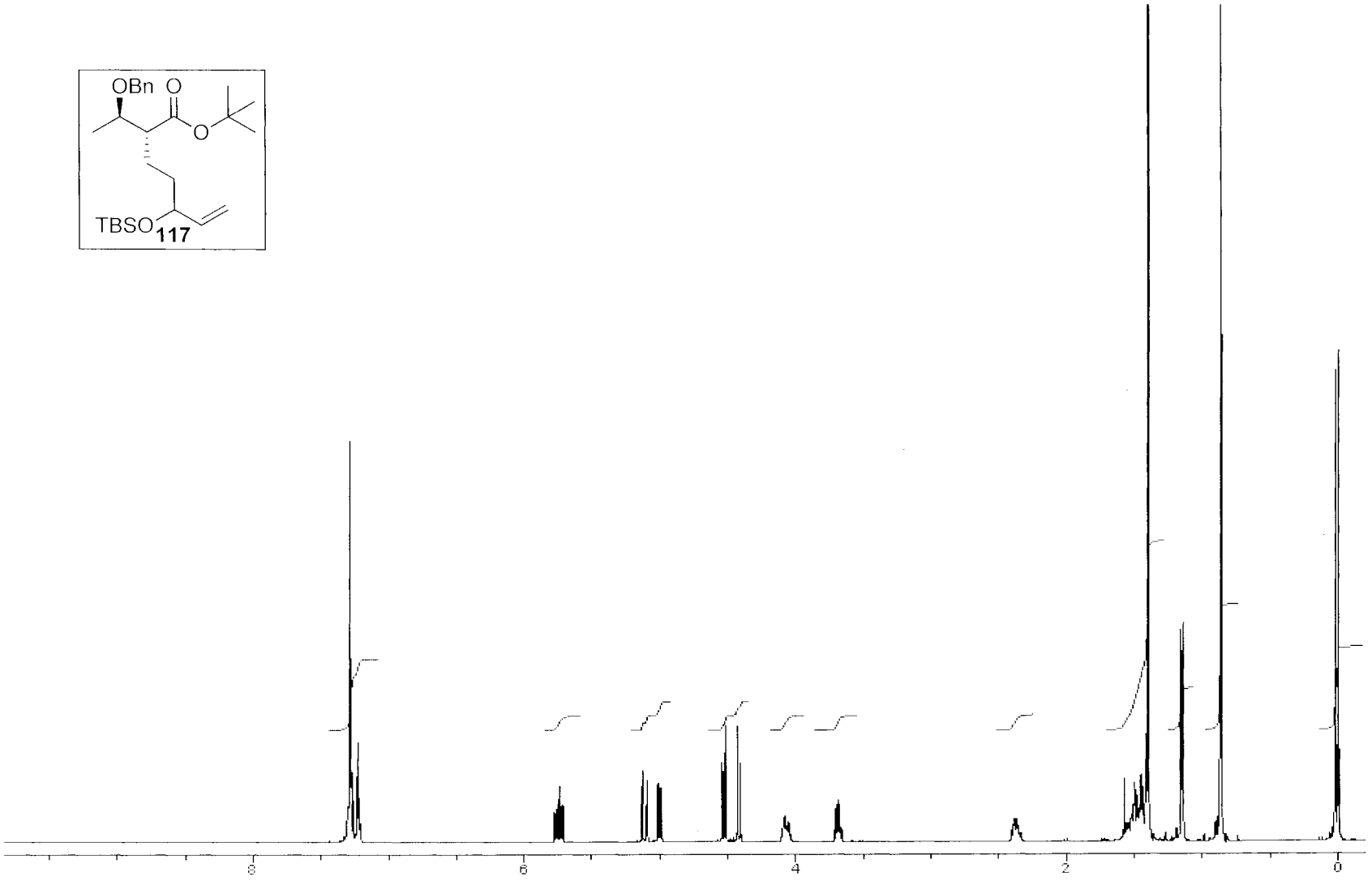


Figure A.1.13 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **117**

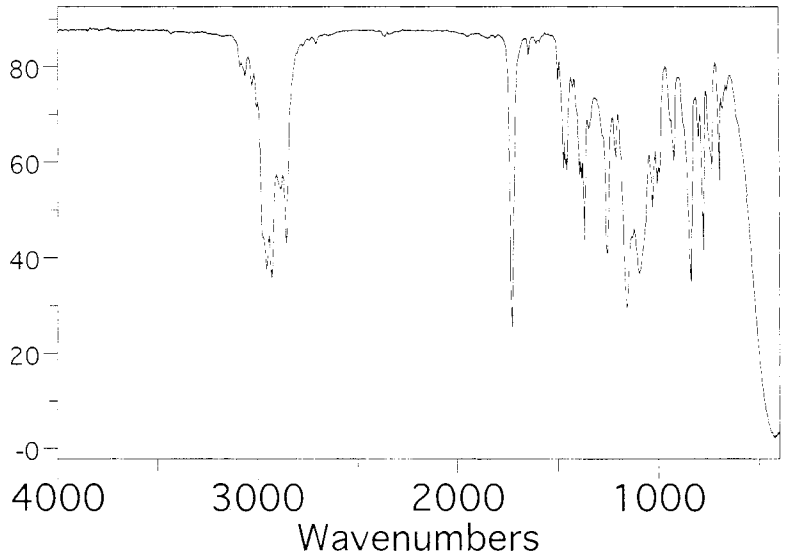


Figure A.1.14 FTIR Spectrum (thin film/NaCl) of Compound **117**

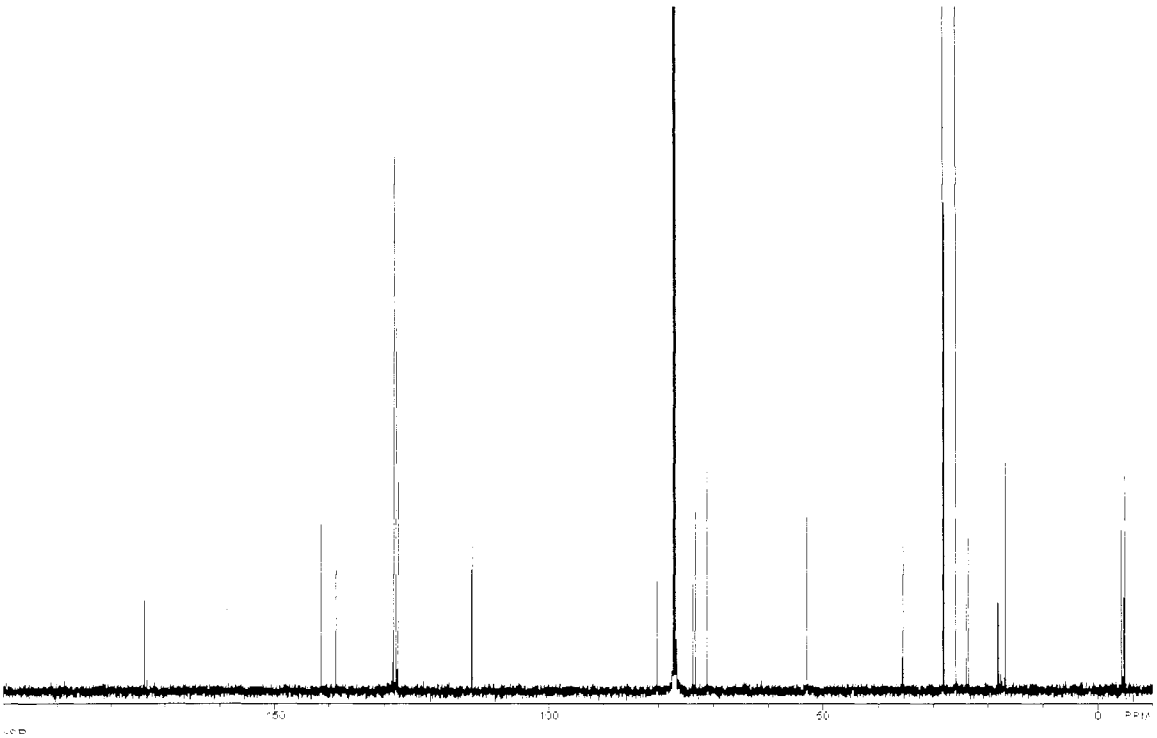


Figure A.1.15 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **117**

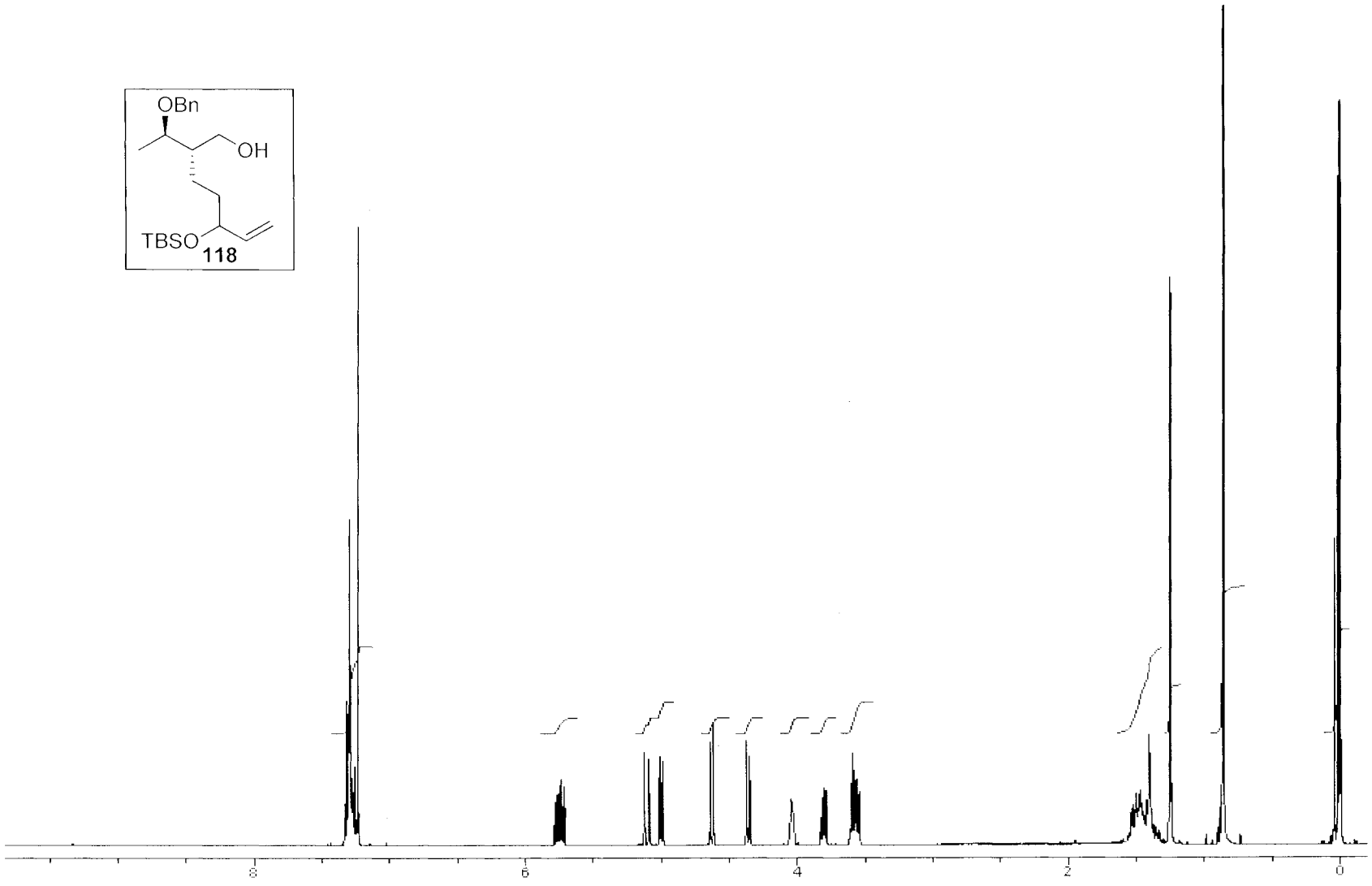


Figure A.1.16 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **118**

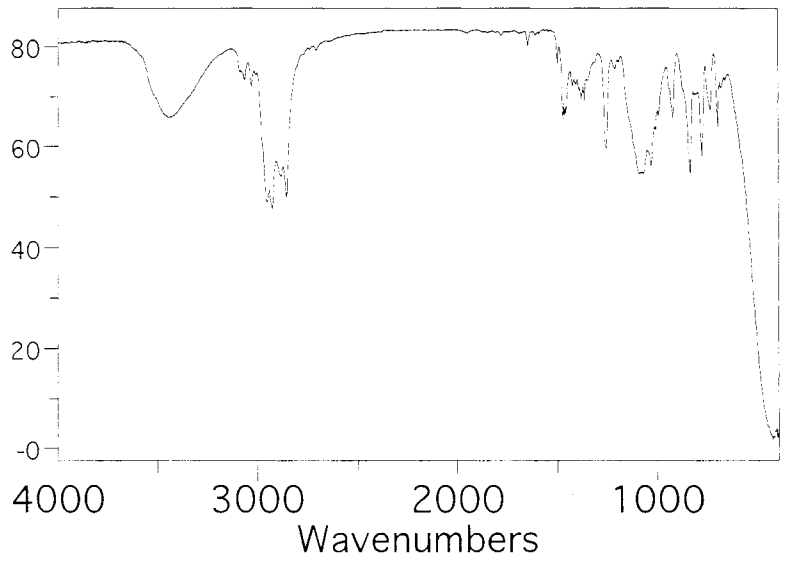


Figure A.1.17 FTIR Spectrum (thin film/NaCl) of Compound **118**

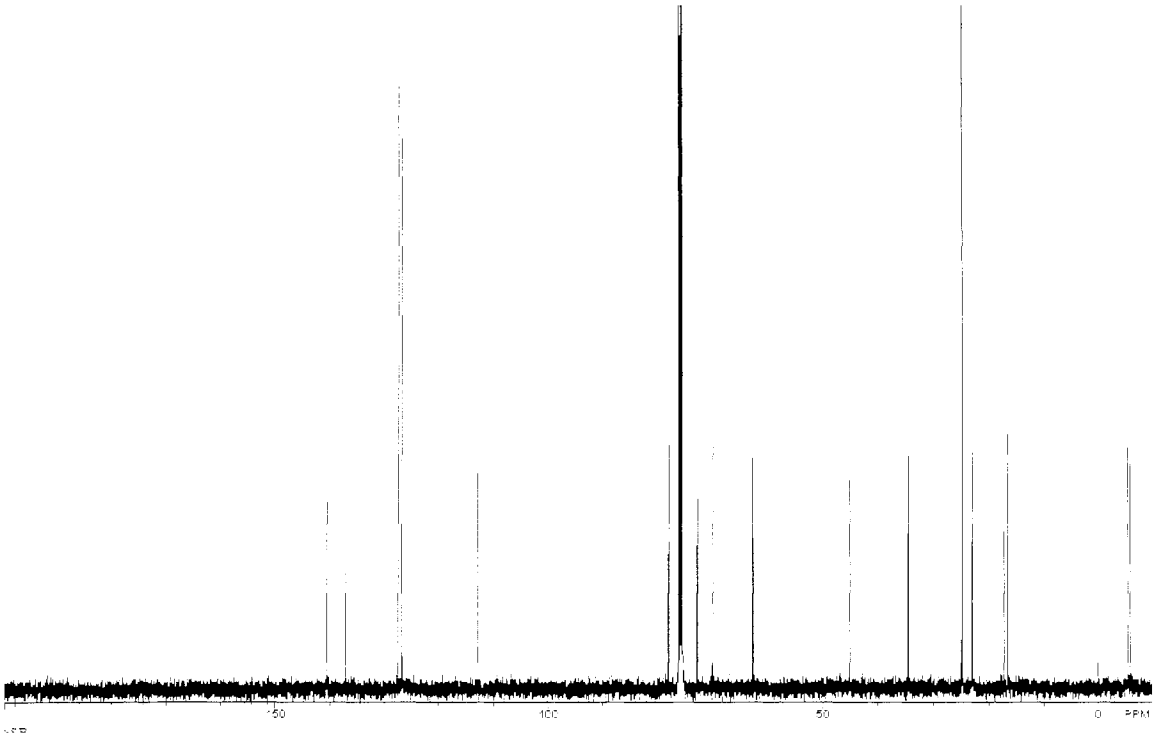


Figure A.1.18 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **118**

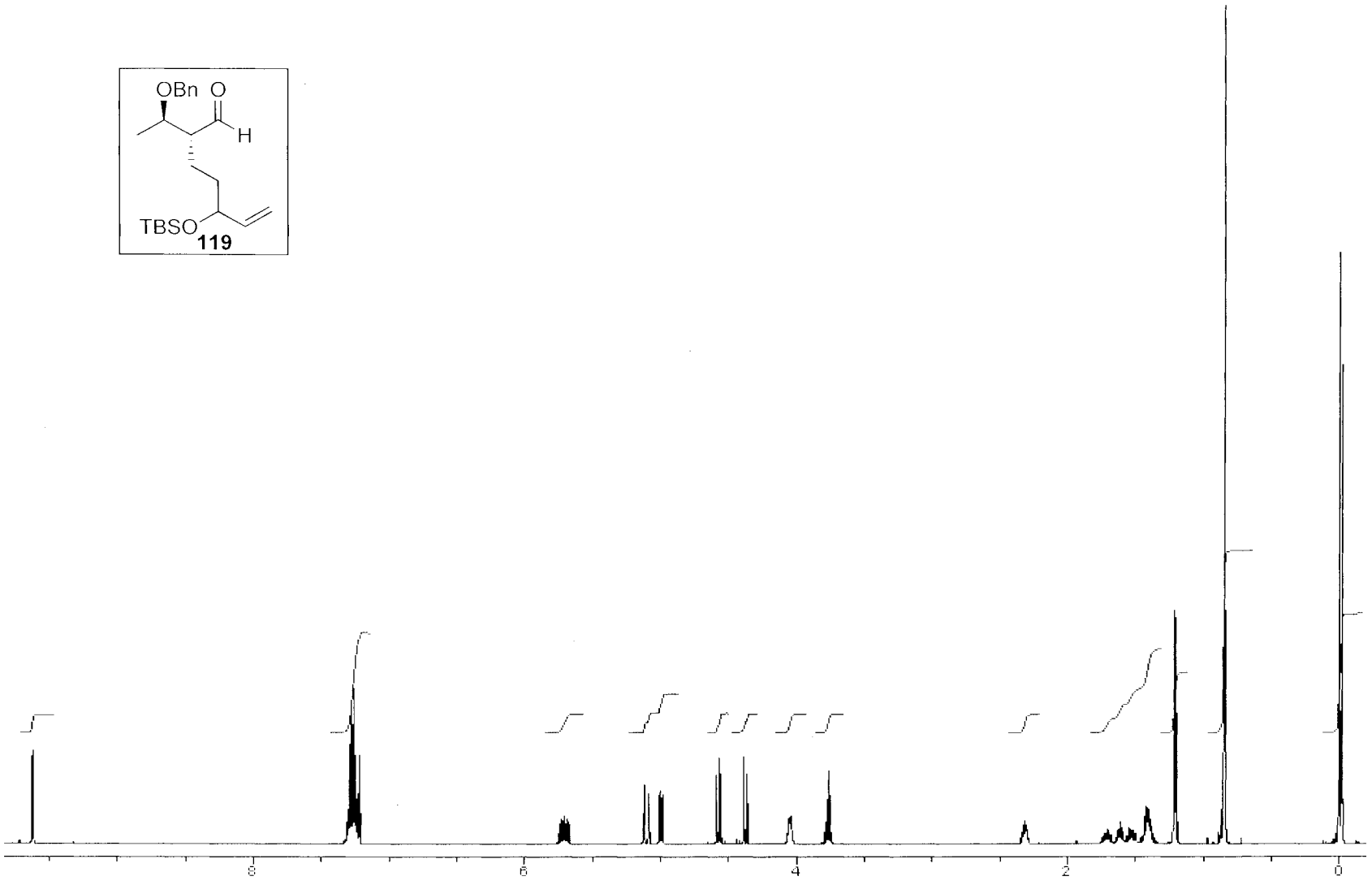


Figure A.1.19 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **119**

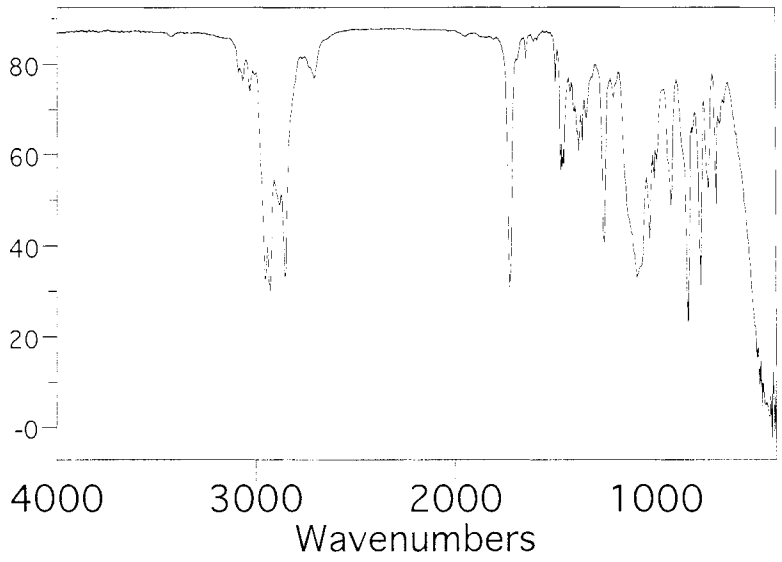


Figure A.1.20 FTIR Spectrum (thin film/NaCl) of Compound **119**

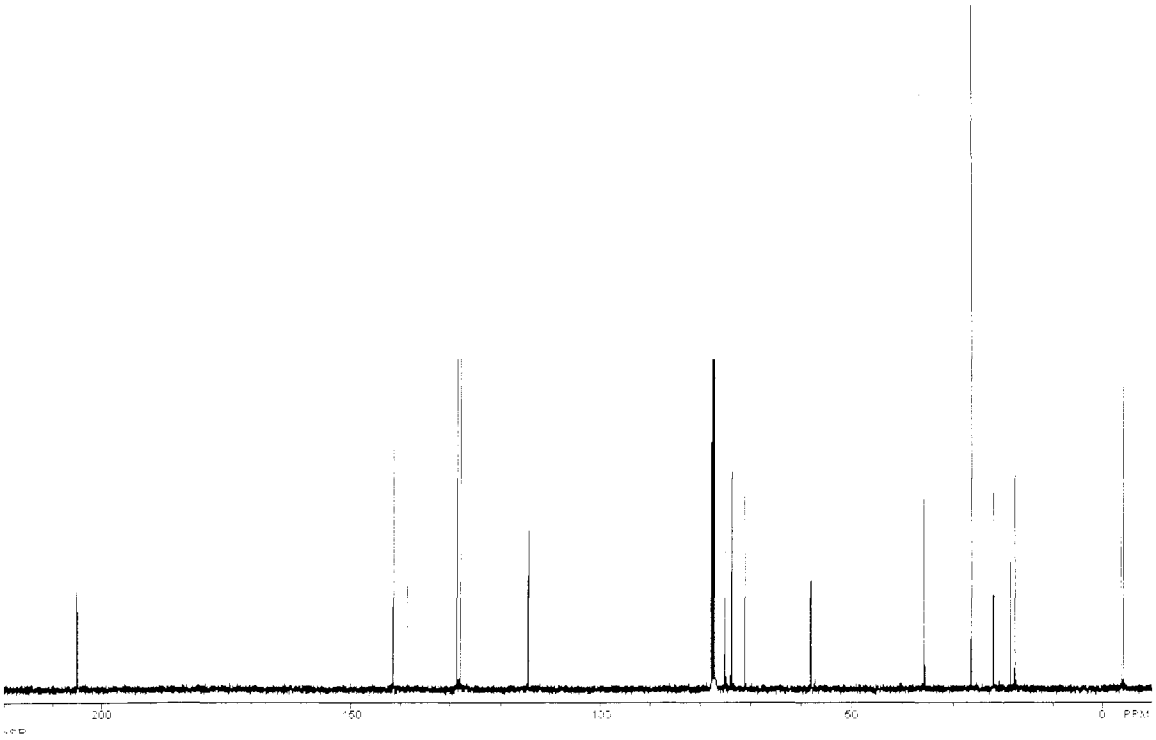


Figure A.1.21 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **119**

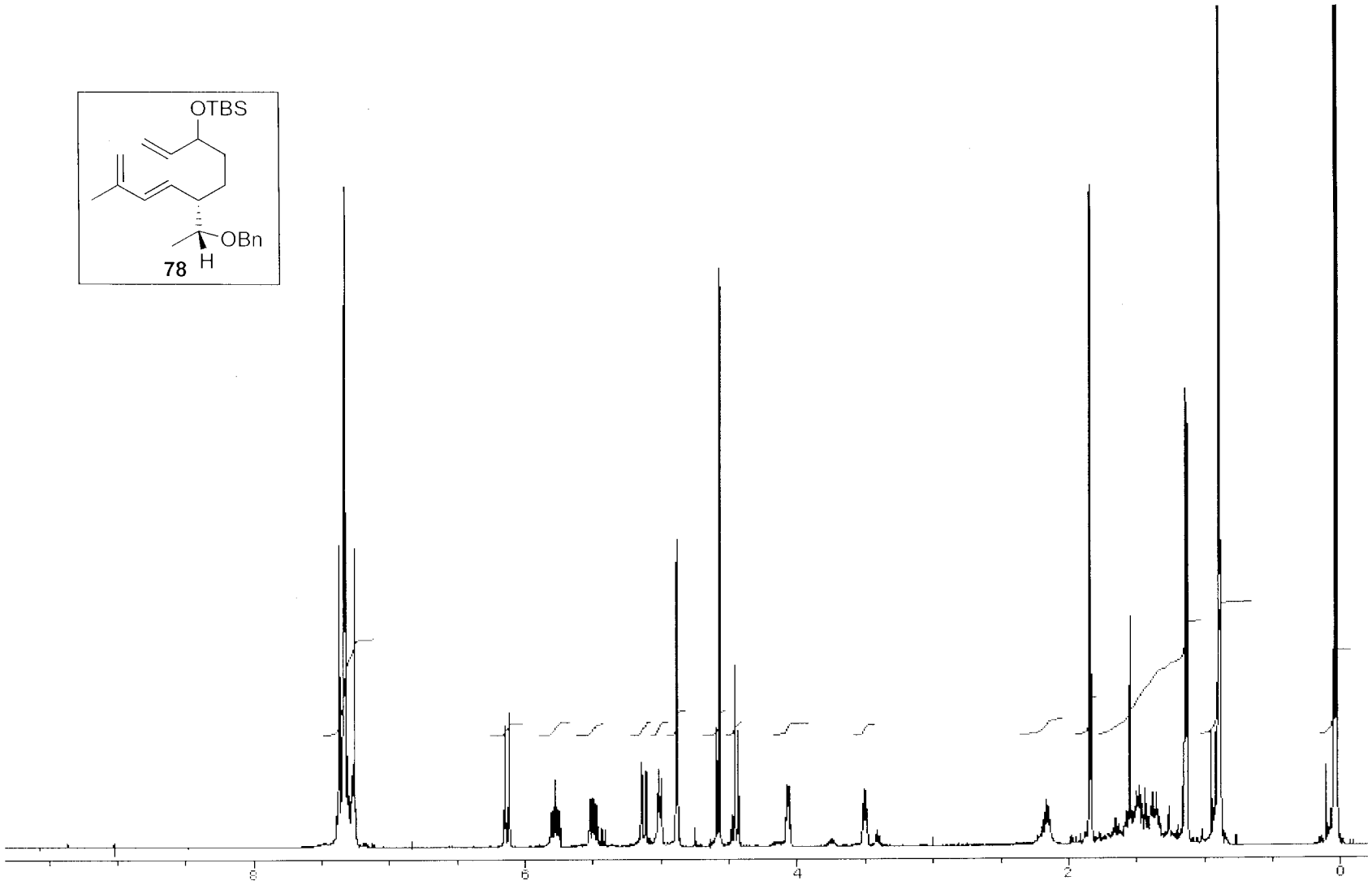


Figure A.1.22 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **78**

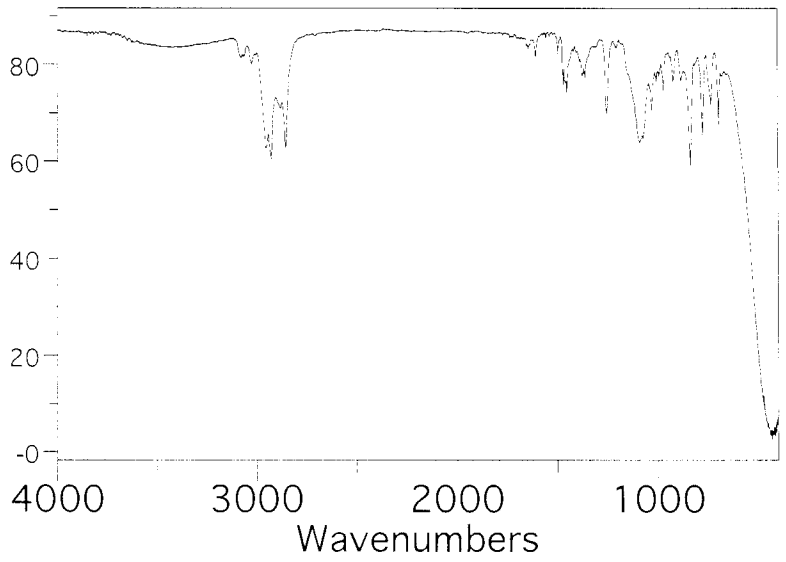


Figure A.1.23 FTIR Spectrum (thin film/NaCl) of Compound **78**

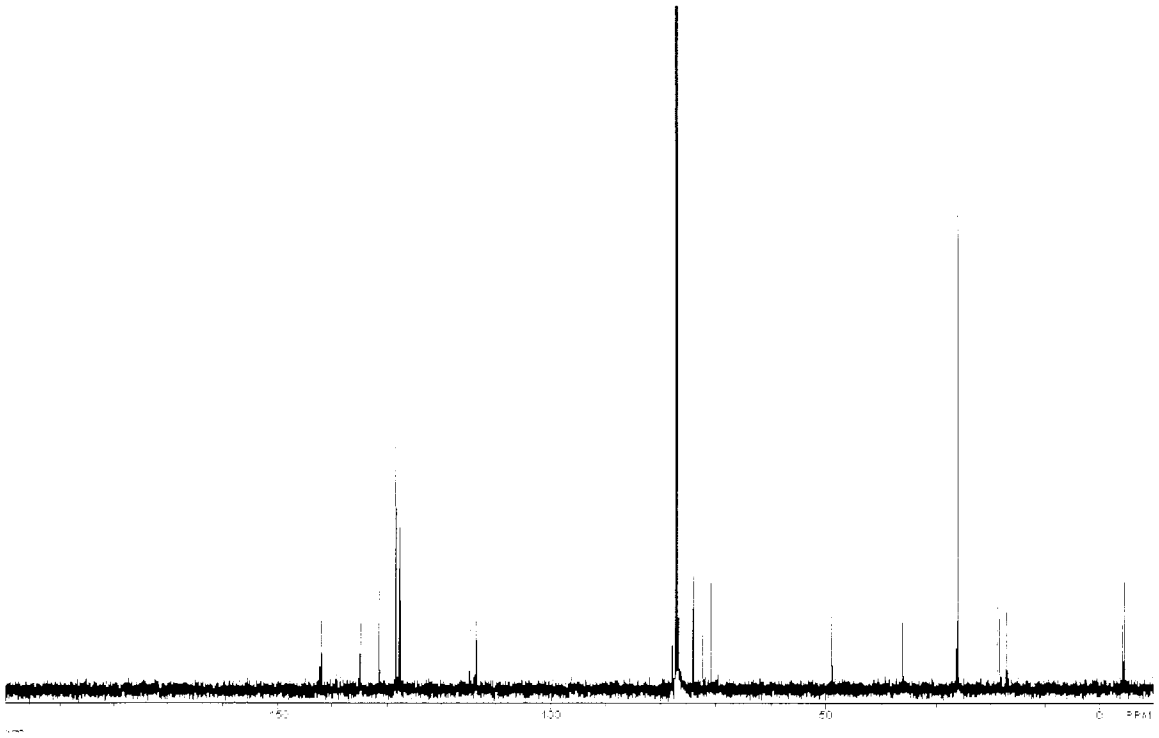


Figure A.1.24 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **78**

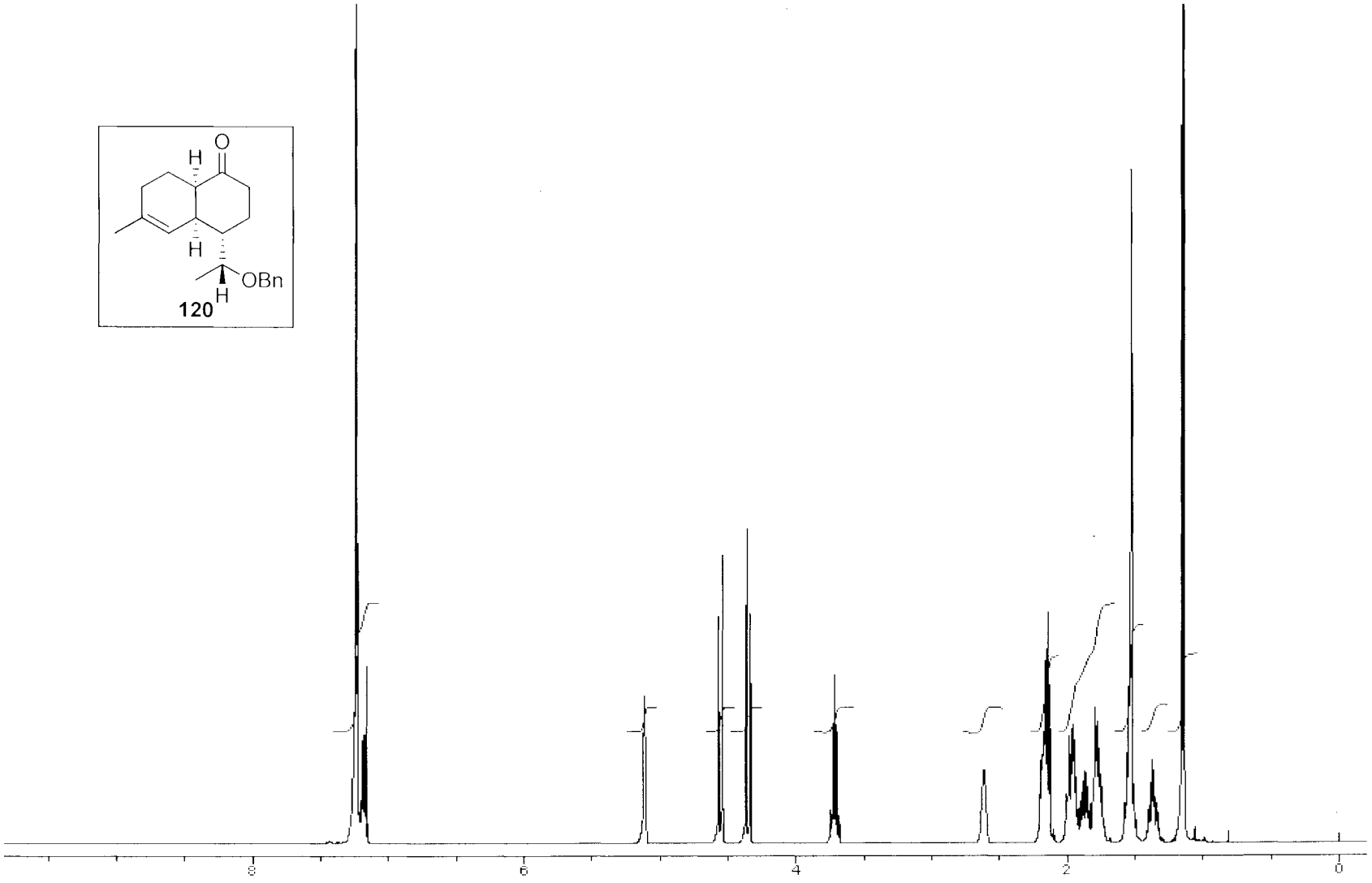


Figure A.1.25 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **120**

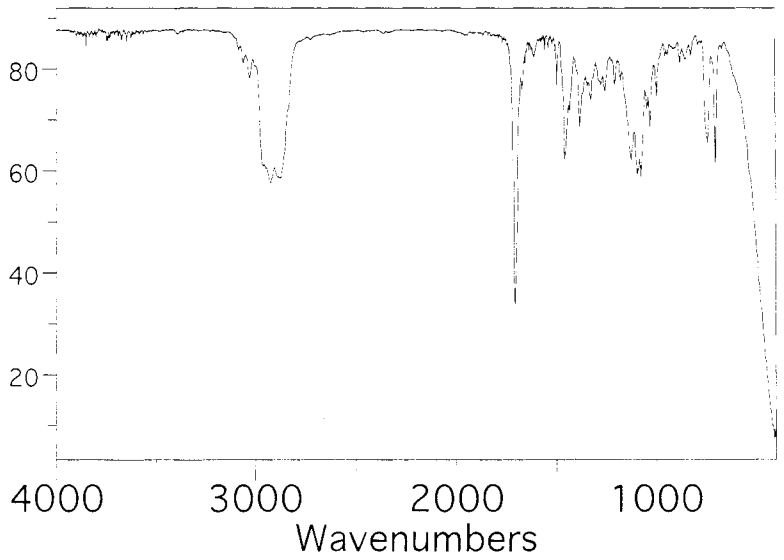


Figure A.1.26 FTIR Spectrum (thin film/NaCl) of Compound **120**

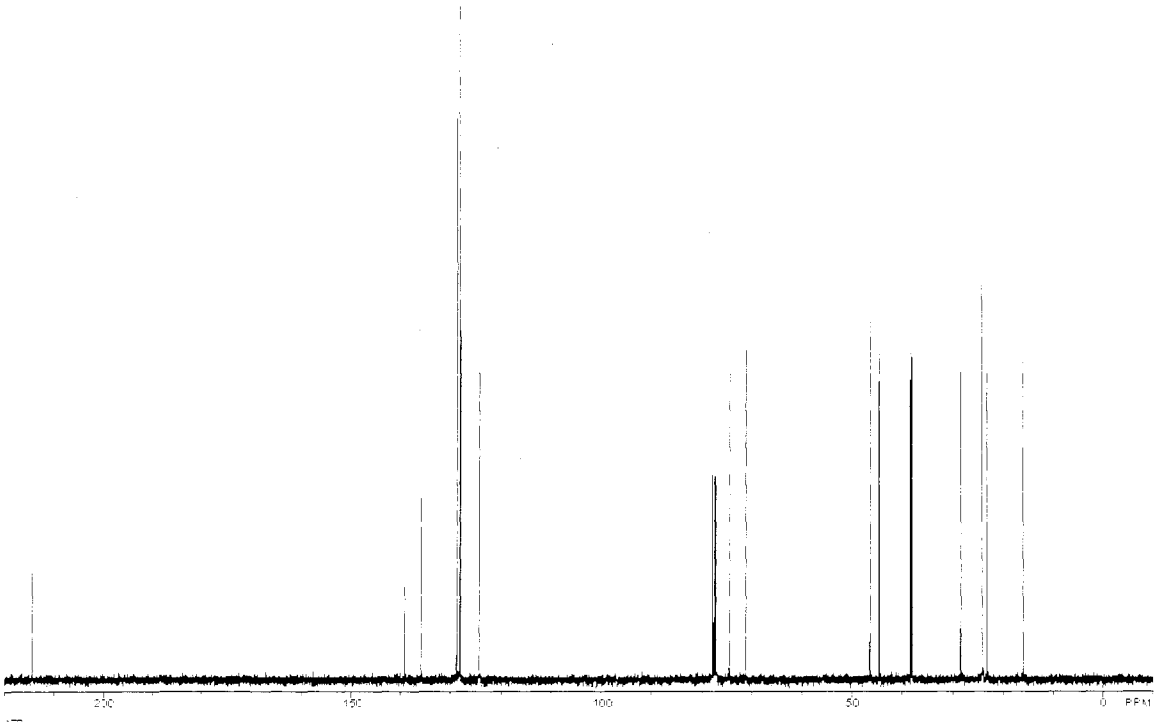


Figure A.1.27 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **120**

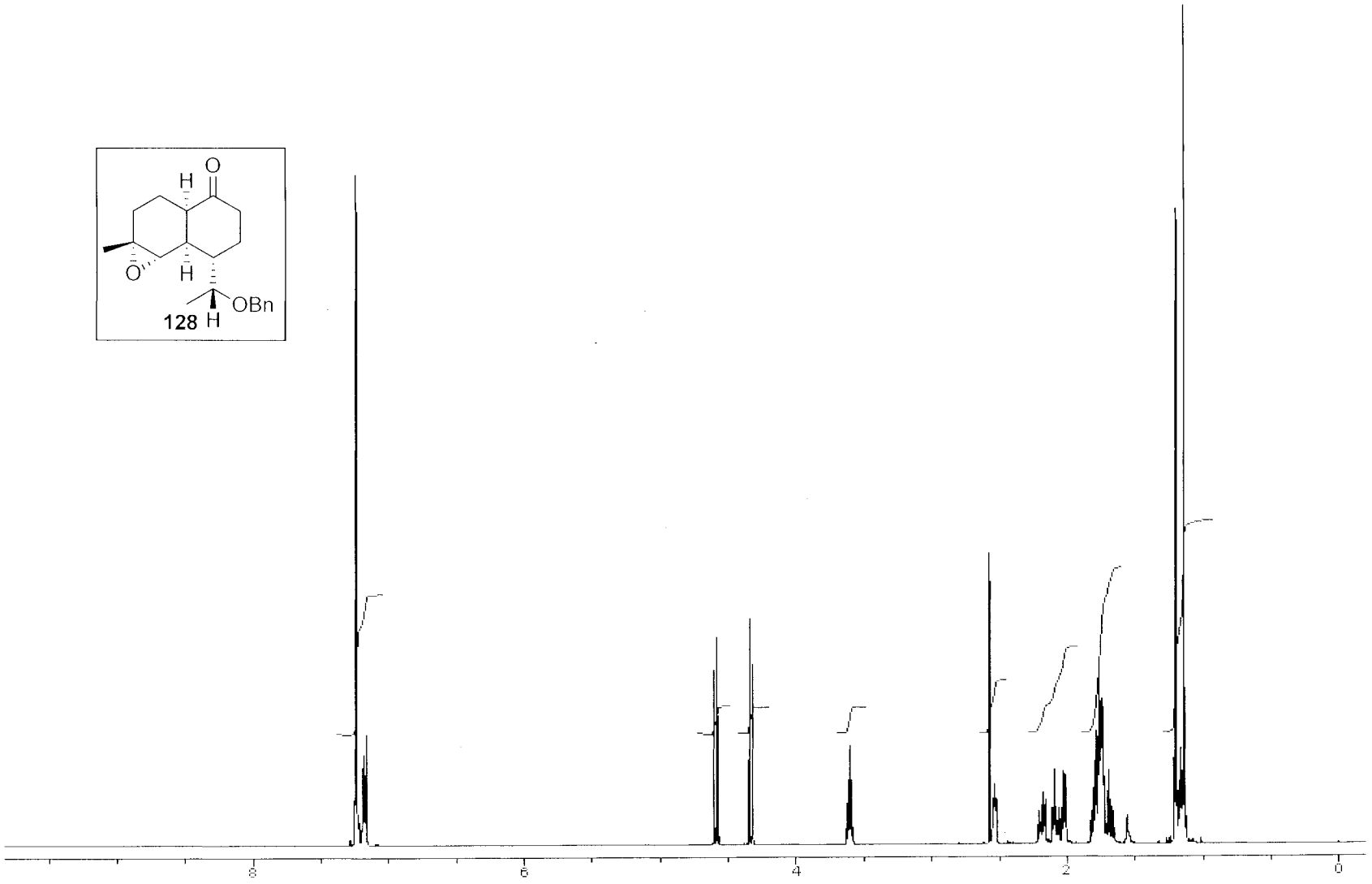


Figure A.1.28 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **128**

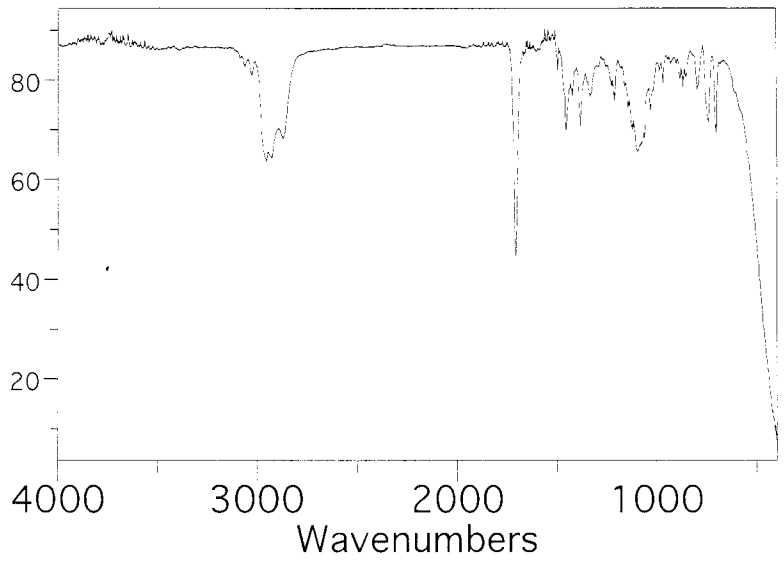


Figure A.1.29 FTIR Spectrum (thin film/NaCl) of Compound **128**

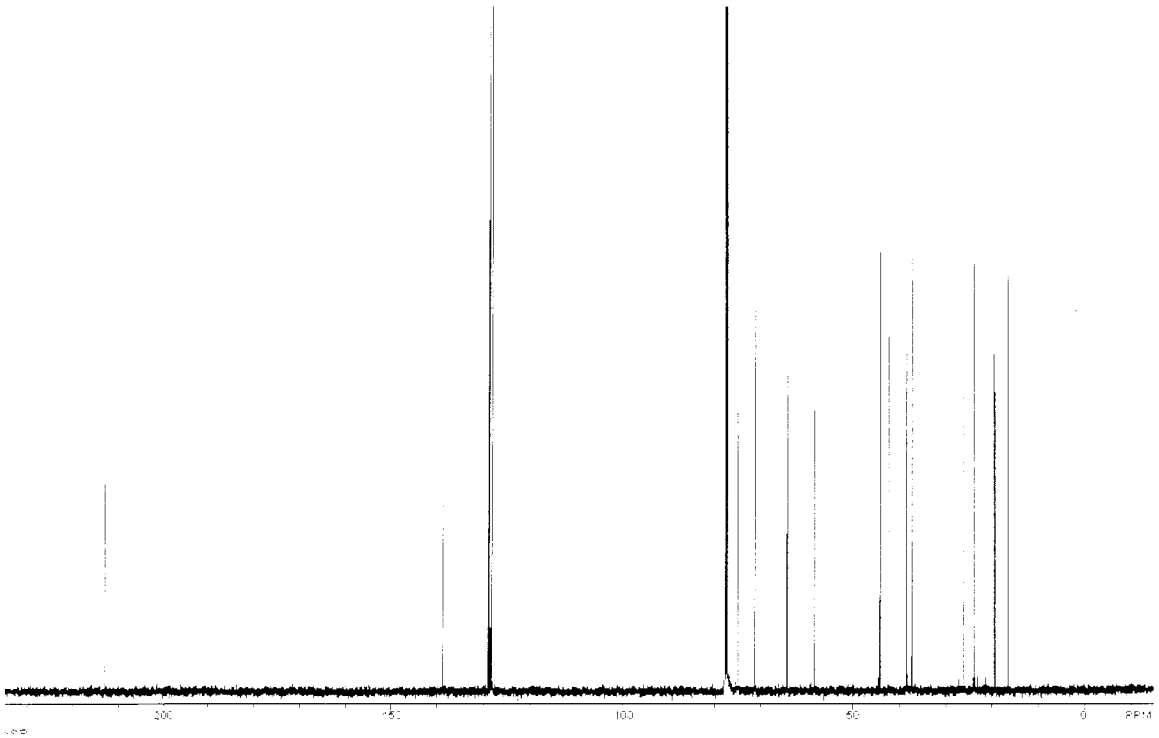


Figure A.1.30 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **128**

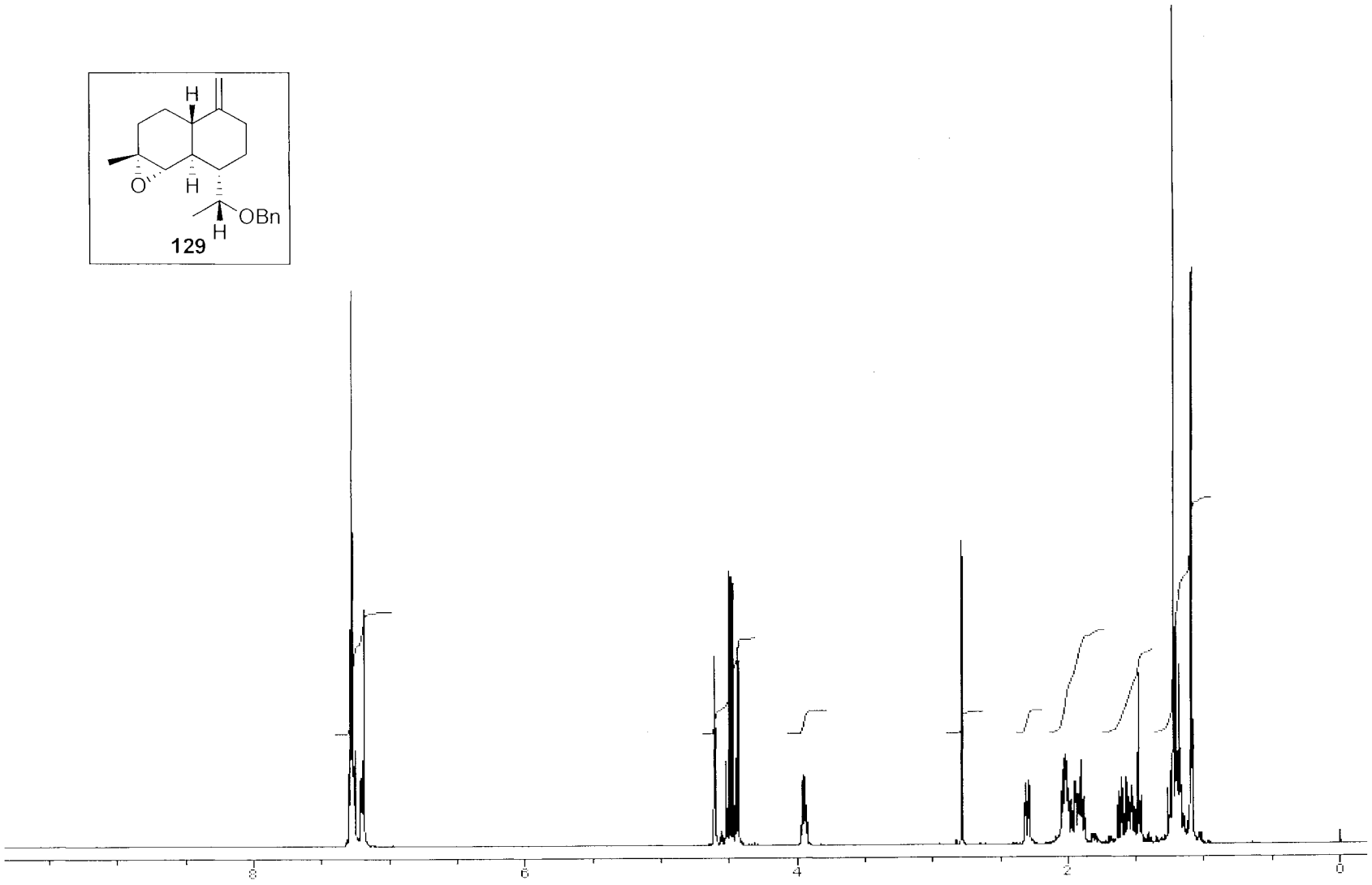


Figure A.1.31 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **129**

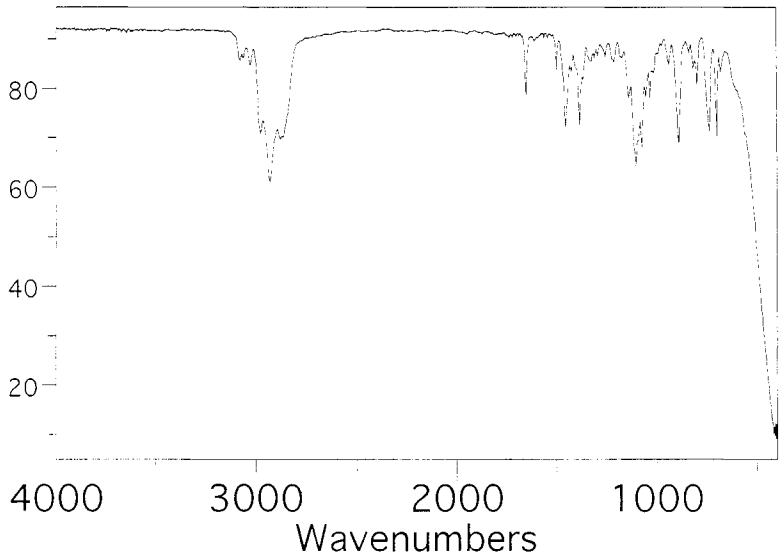


Figure A.1.32 FTIR Spectrum (thin film/NaCl) of Compound **129**

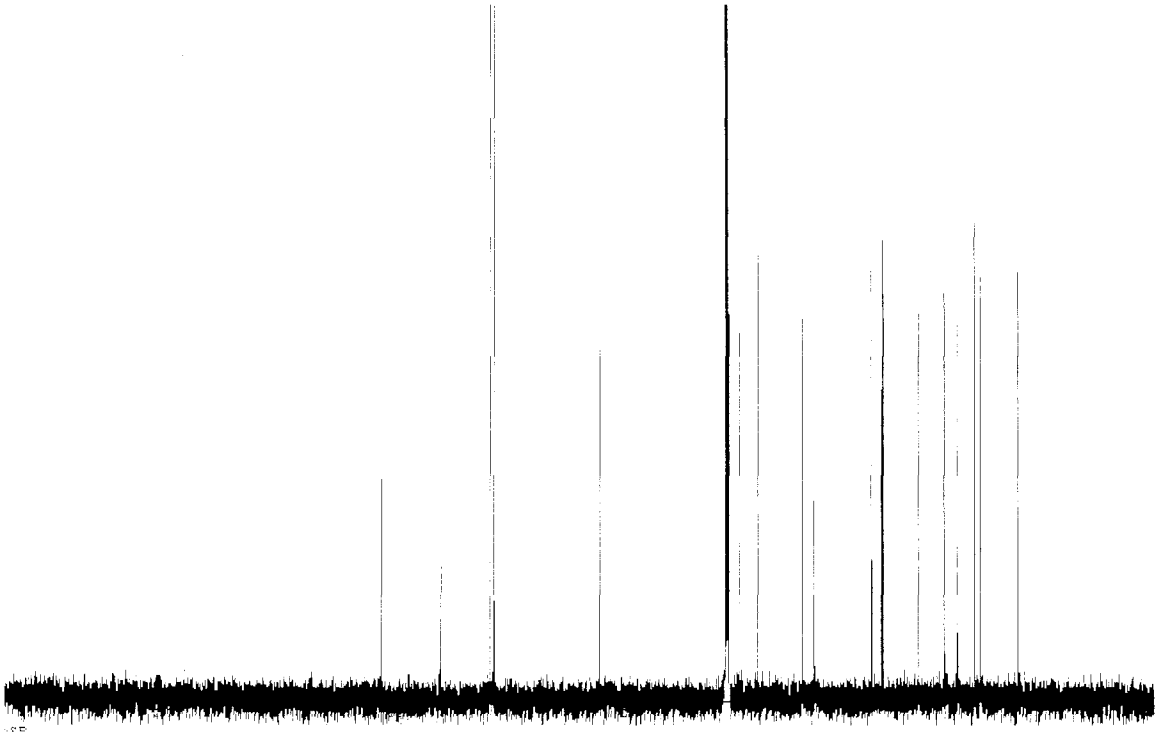


Figure A.1.33 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **129**

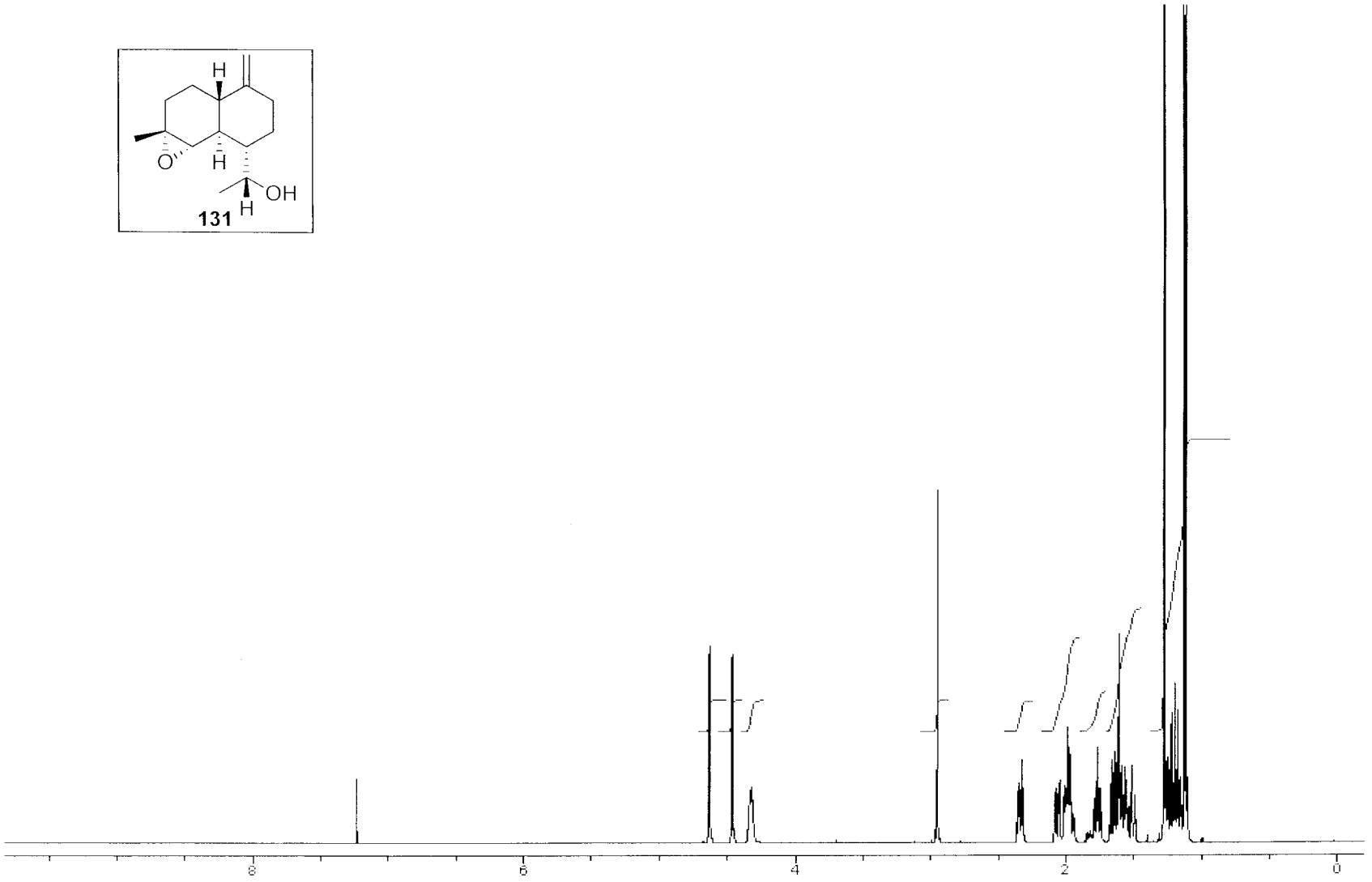


Figure A.1.34 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **131**

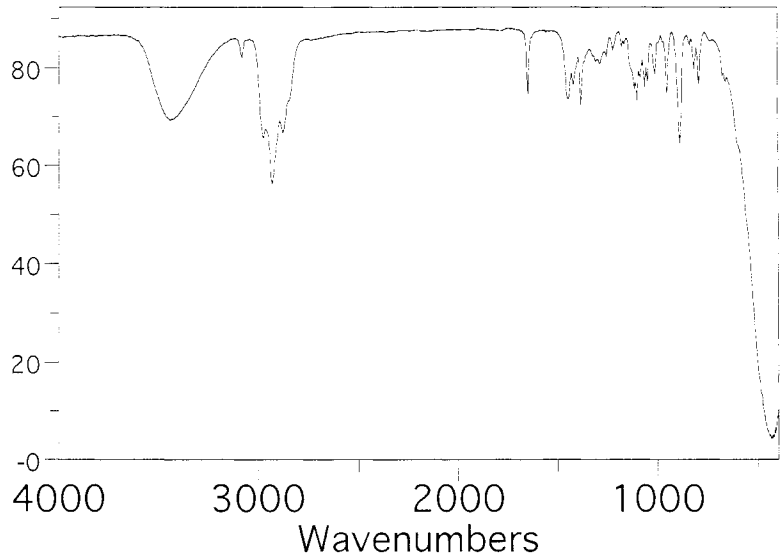


Figure A.1.35 FTIR Spectrum (thin film/NaCl) of Compound **131**

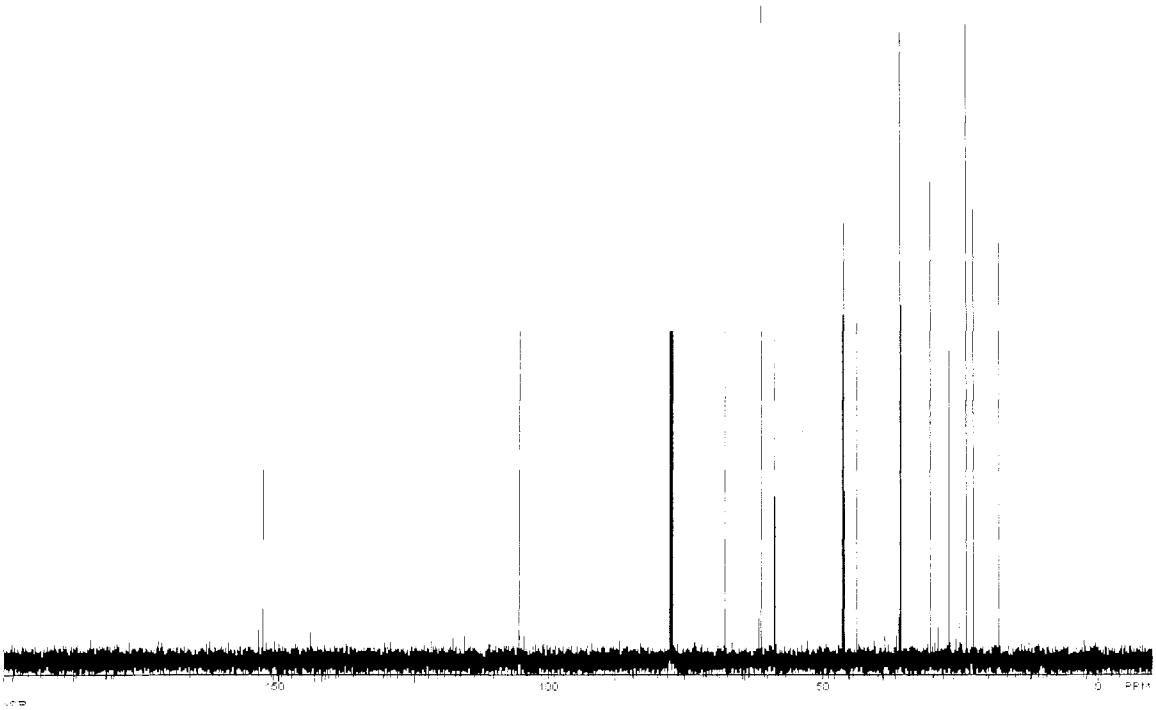


Figure A.1.36 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **131**

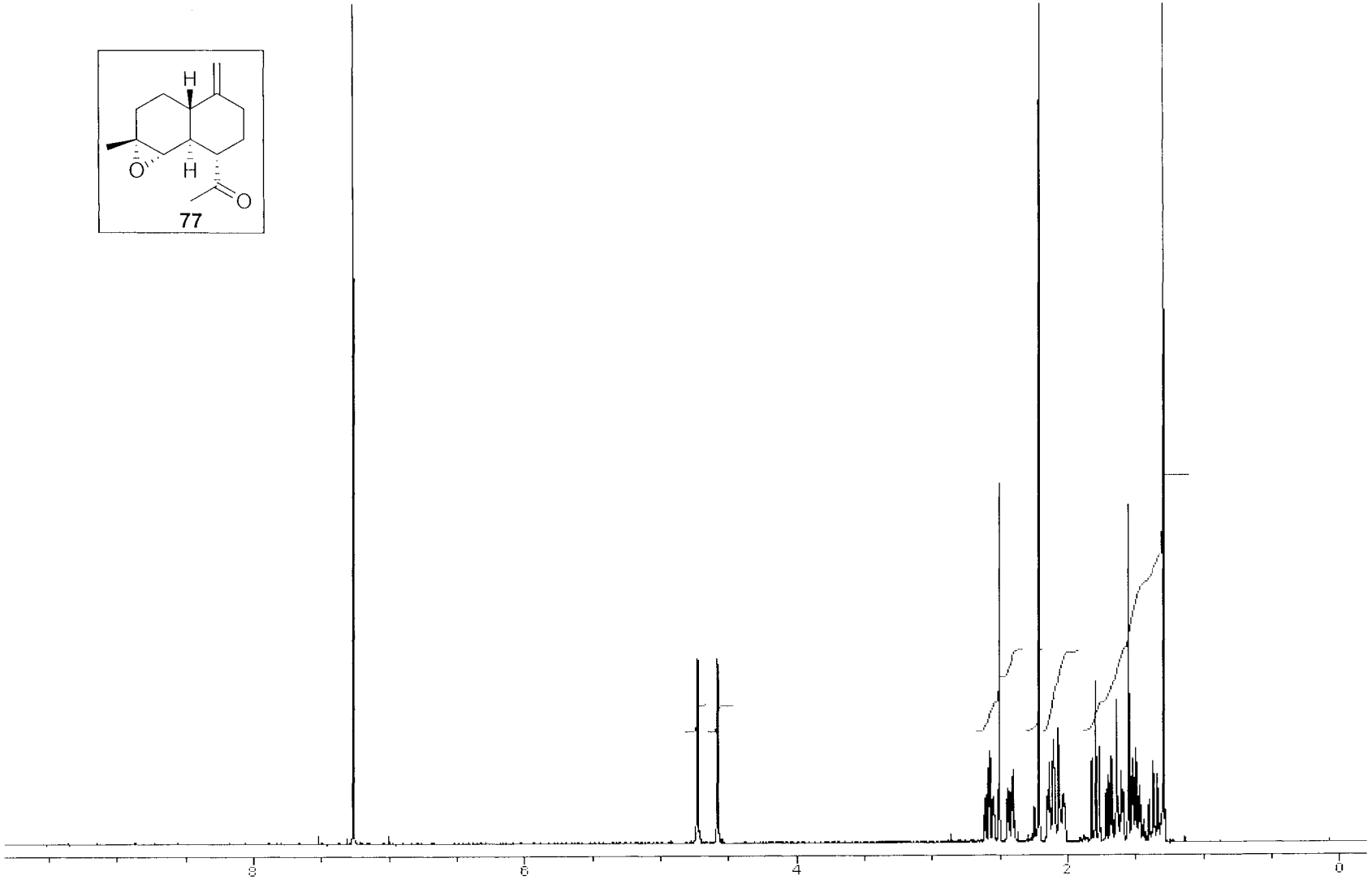


Figure A.1.37 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **77**

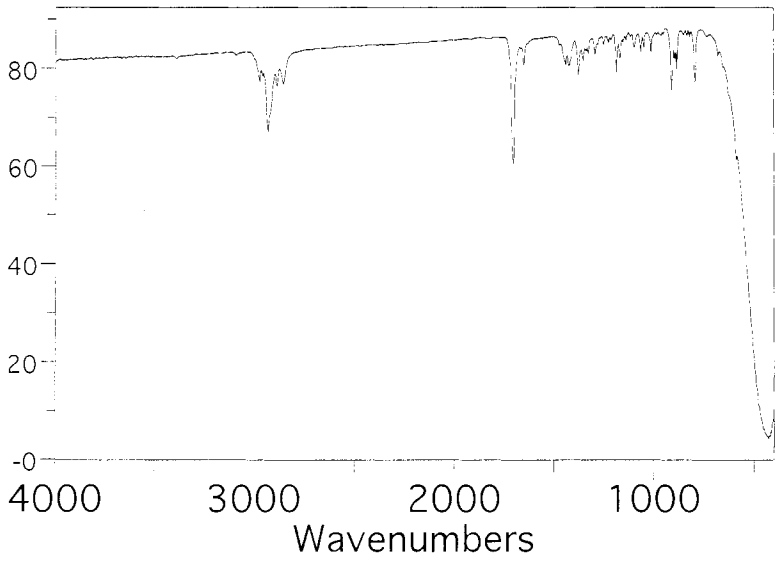


Figure A.1.38 FTIR Spectrum (thin film/NaCl) of Compound **77**

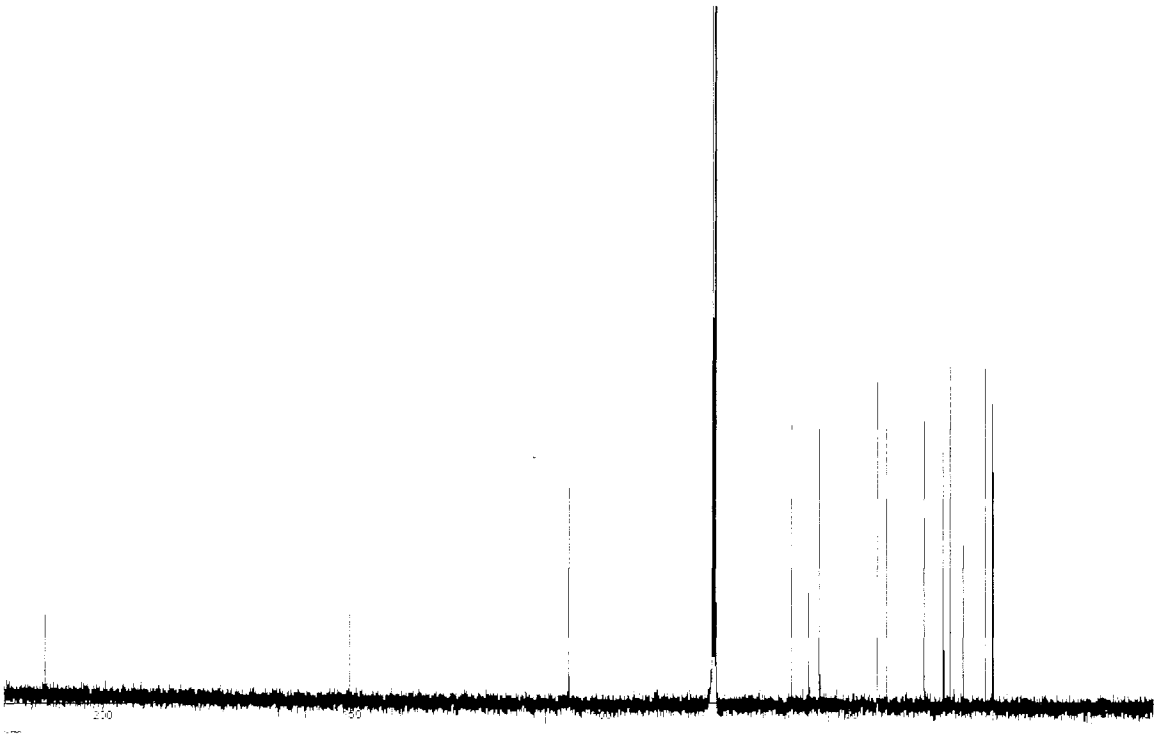


Figure A.1.39 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **77**

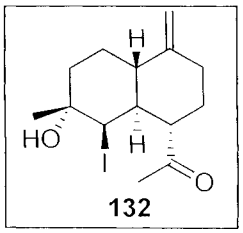


Figure A.1.40 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **132**

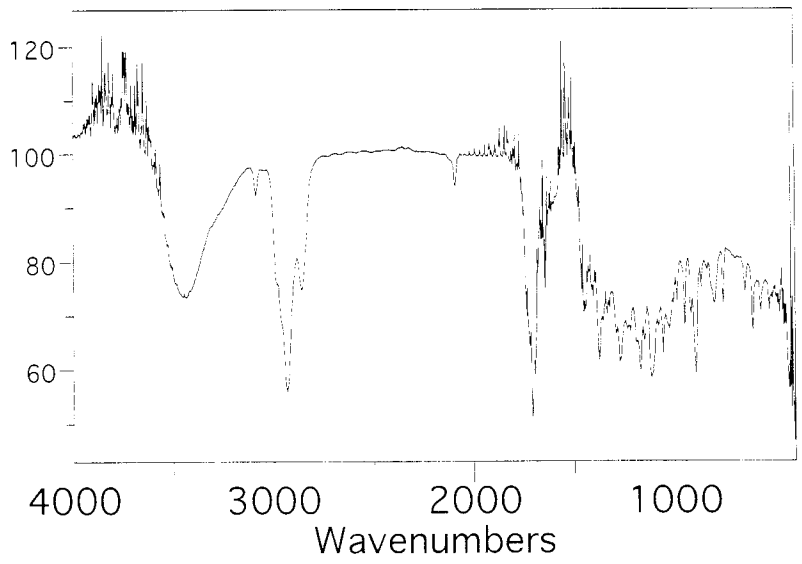


Figure A.1.41 FTIR Spectrum (thin film/NaCl) of Compound **132**

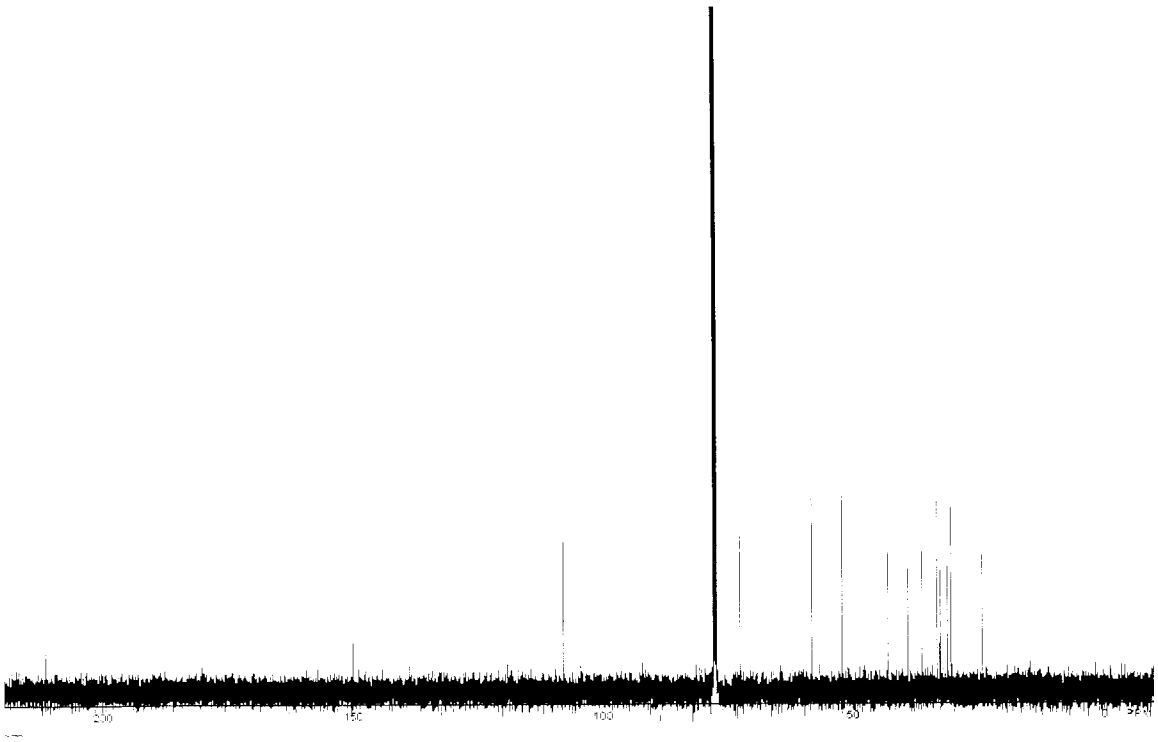


Figure A.1.42 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **132**

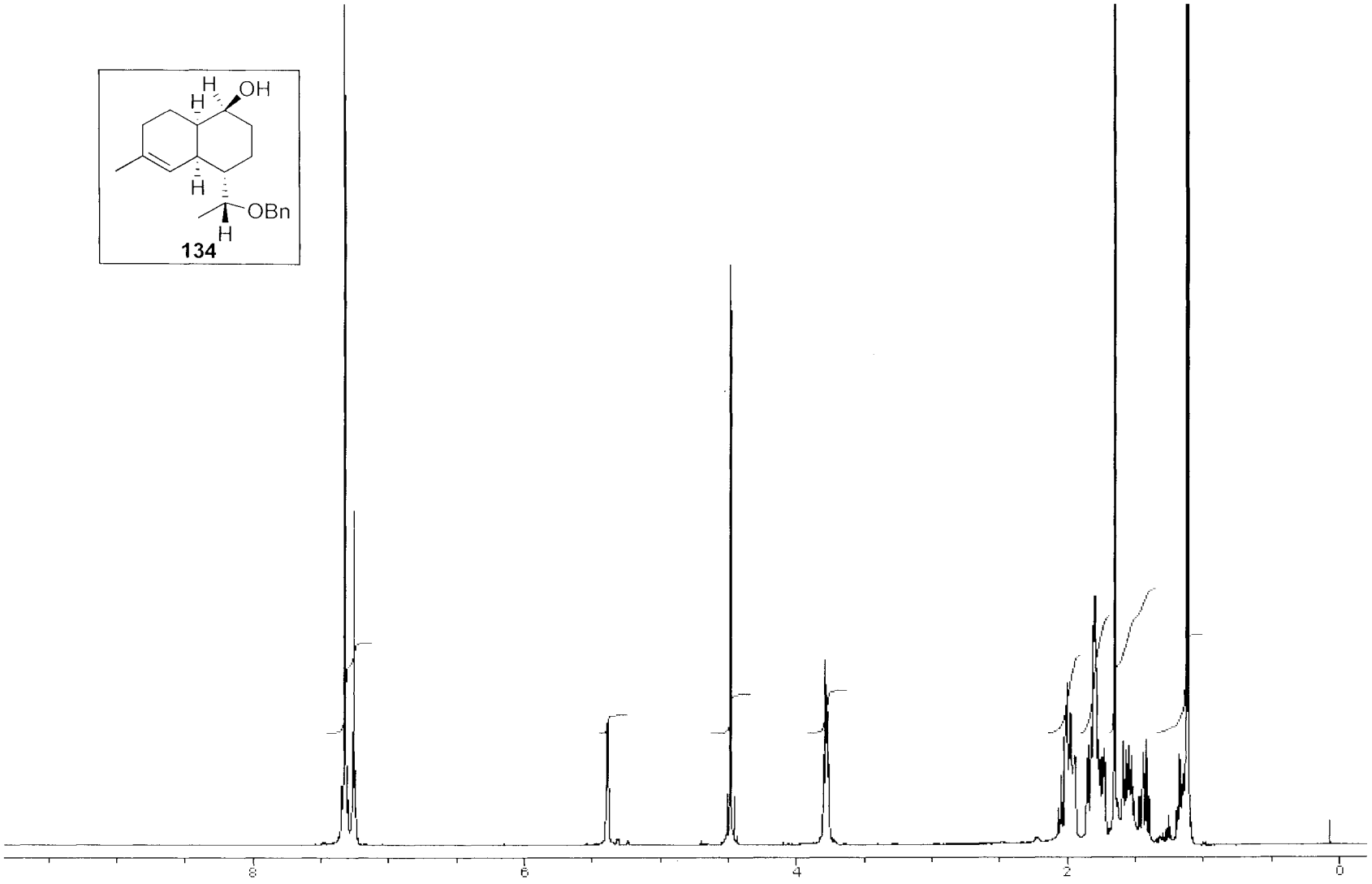


Figure A.1.43 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **134**

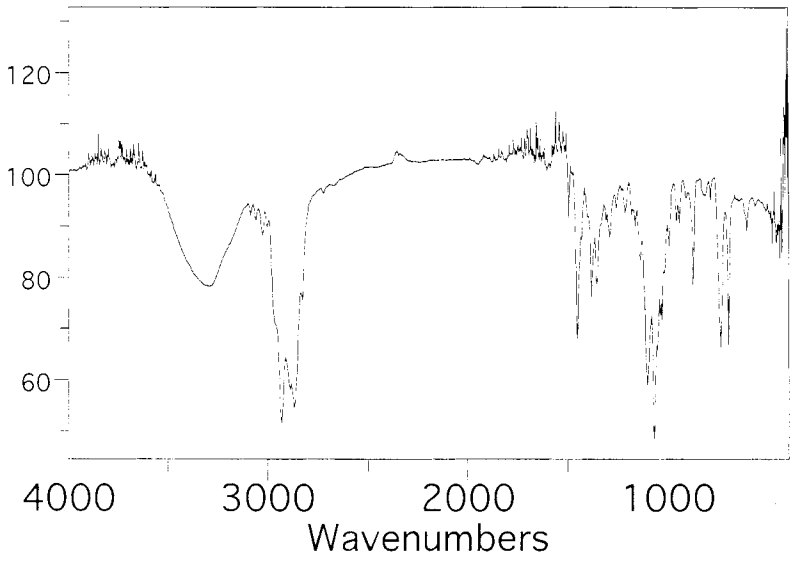


Figure A.1.44 FTIR Spectrum (thin film/NaCl) of Compound **134**

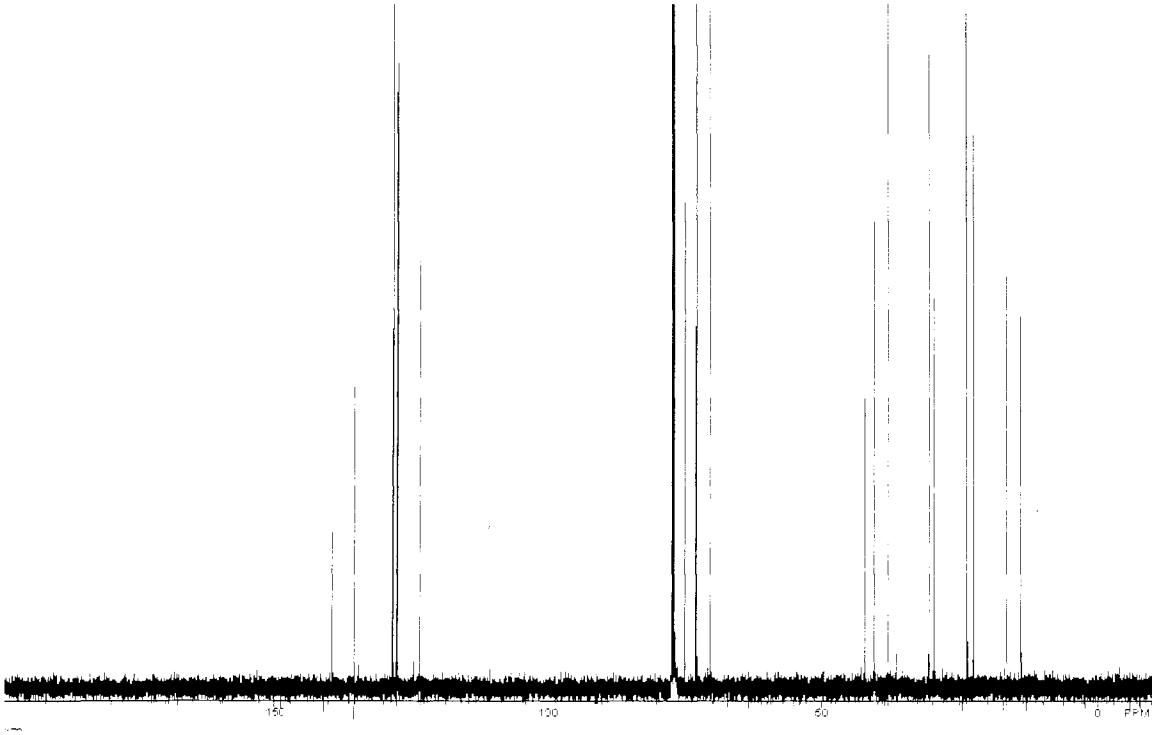


Figure A.1.45 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **134**

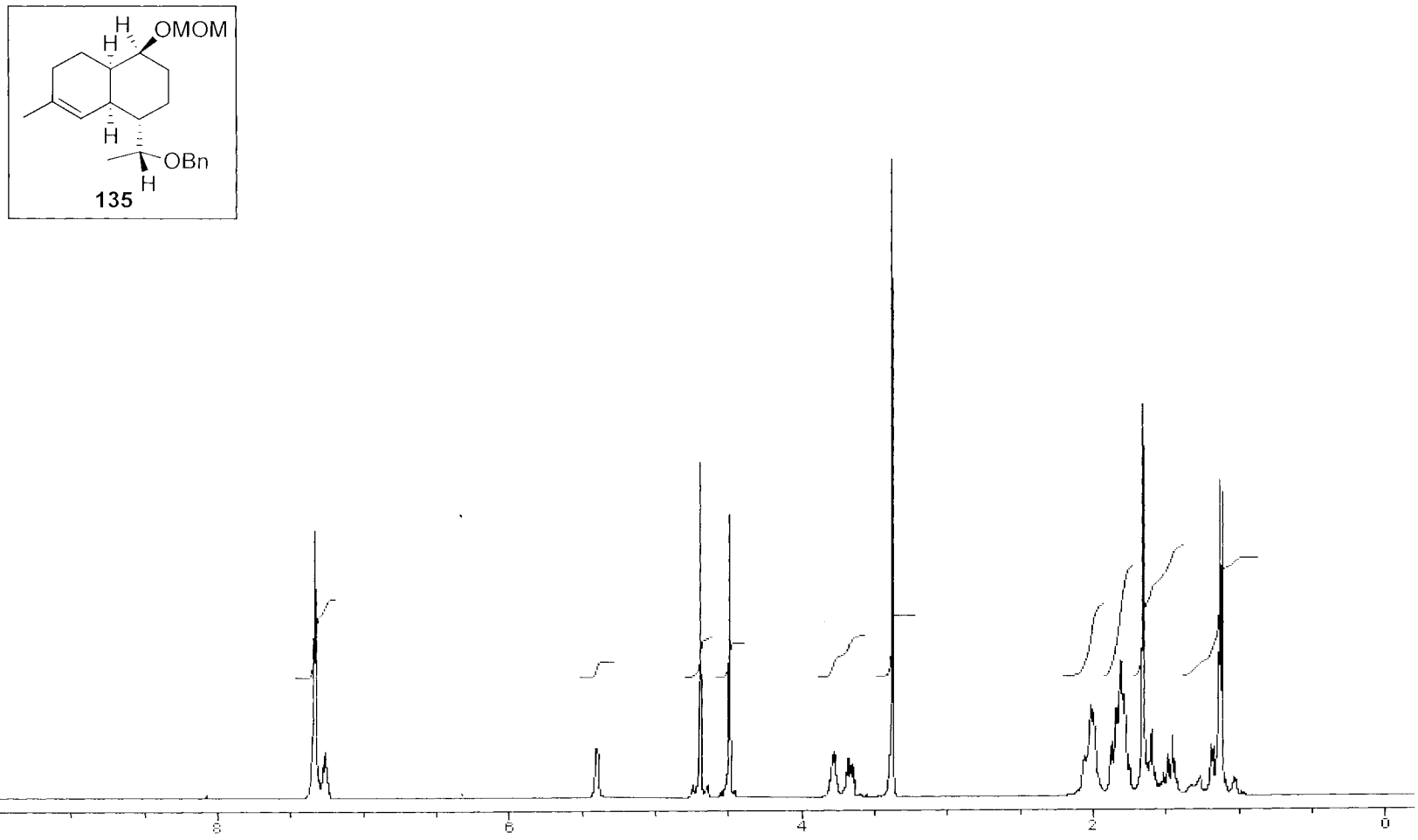


Figure A.1.46 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **135**

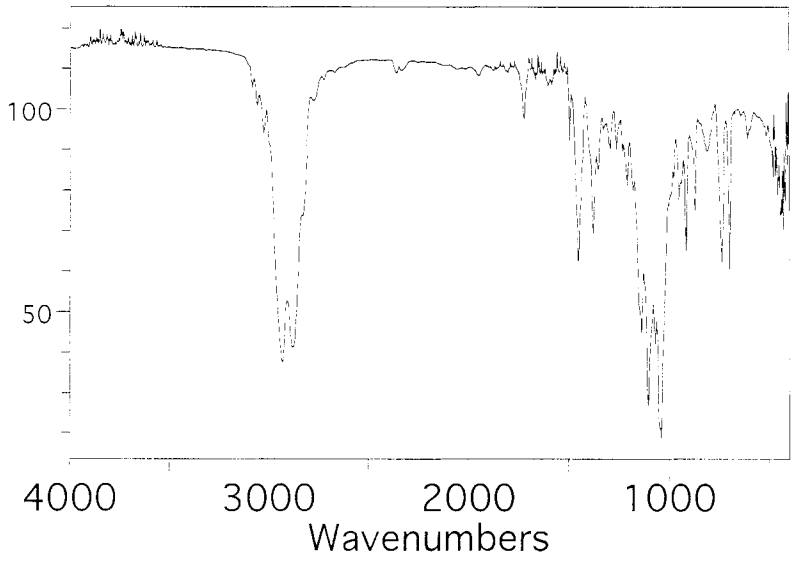


Figure A.1.47 FTIR Spectrum (thin film/NaCl) of Compound **135**

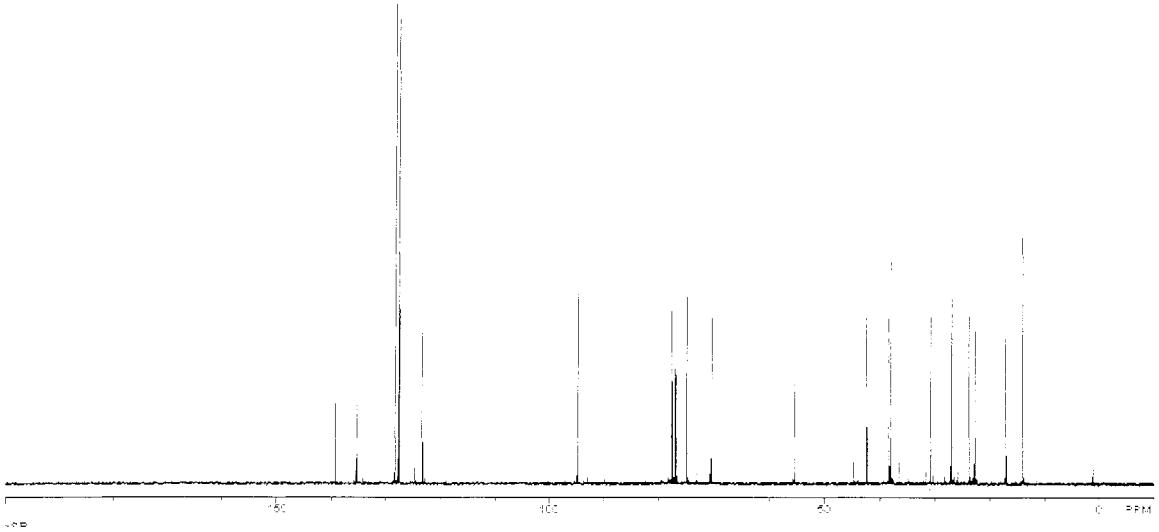


Figure A.1.48 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **135**

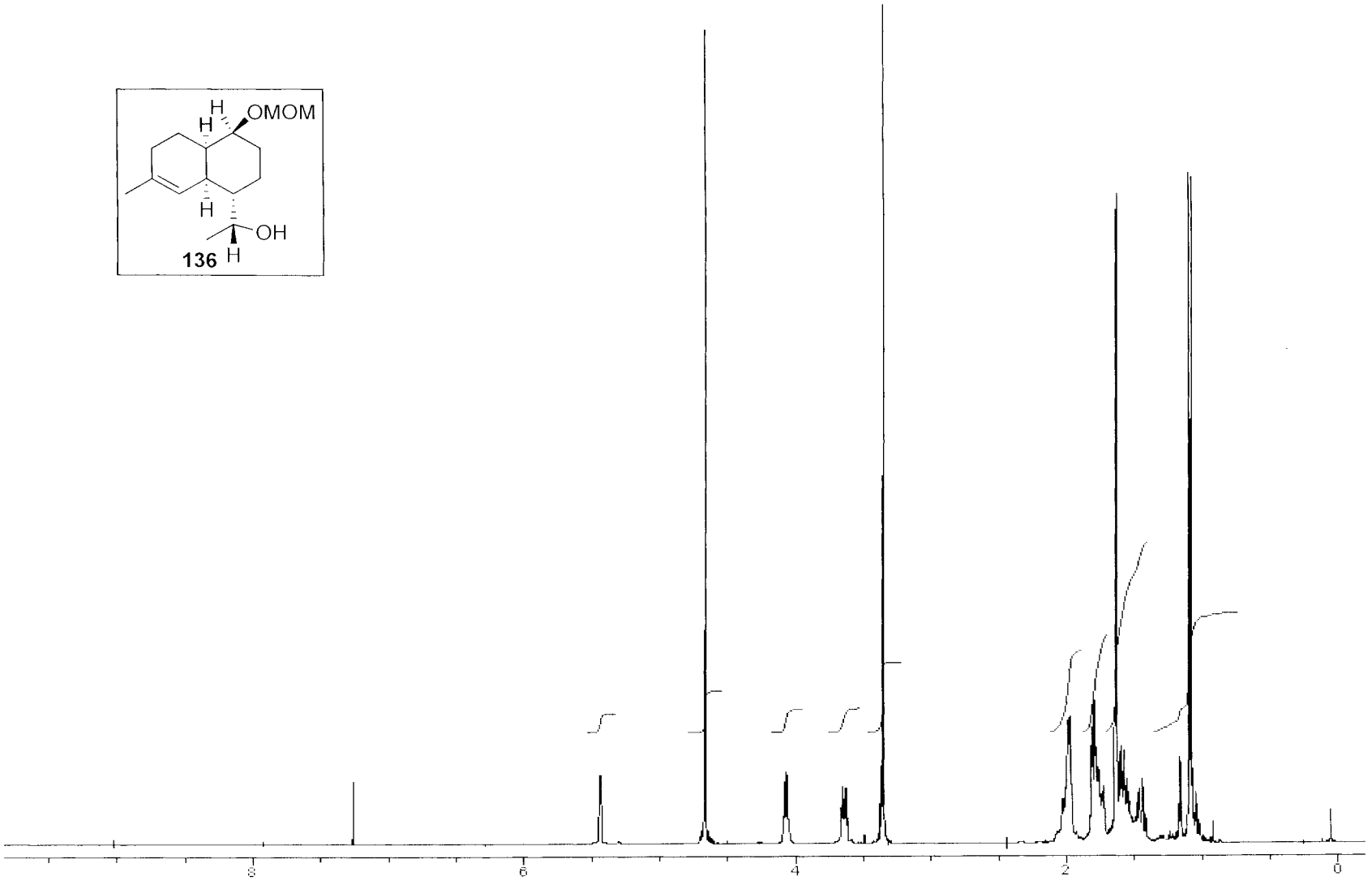


Figure A.1.49 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **136**

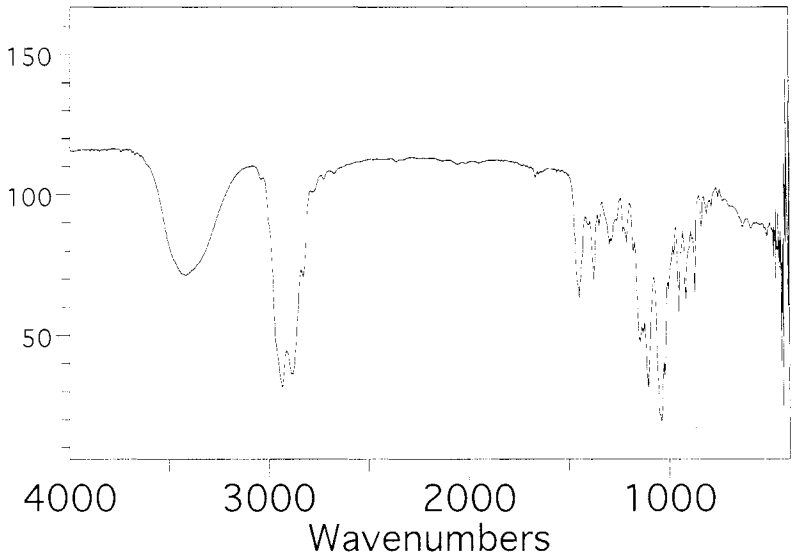


Figure A.1.50 FTIR Spectrum (thin film/NaCl) of Compound **136**

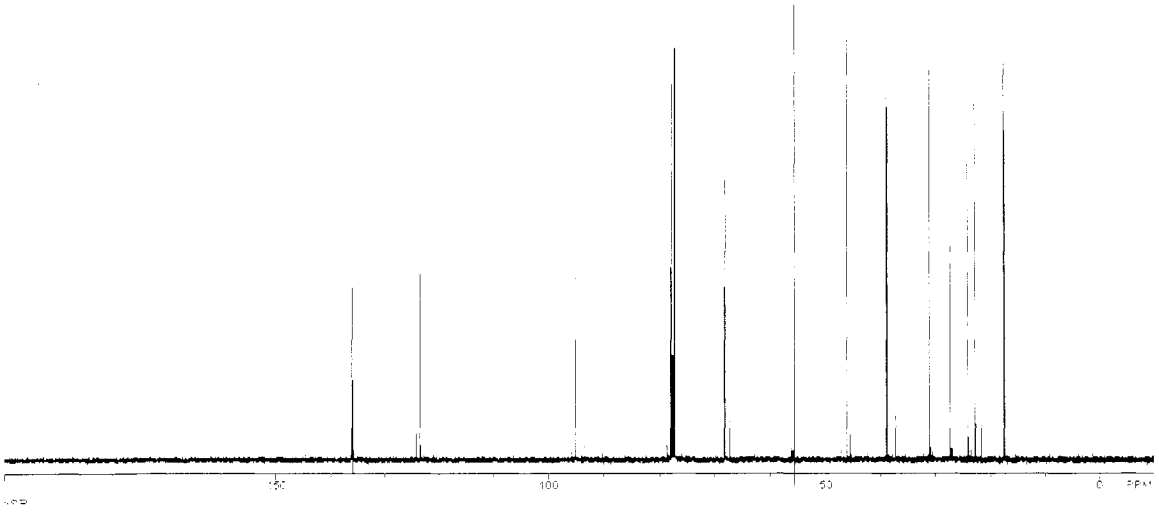


Figure A.1.51 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **136**

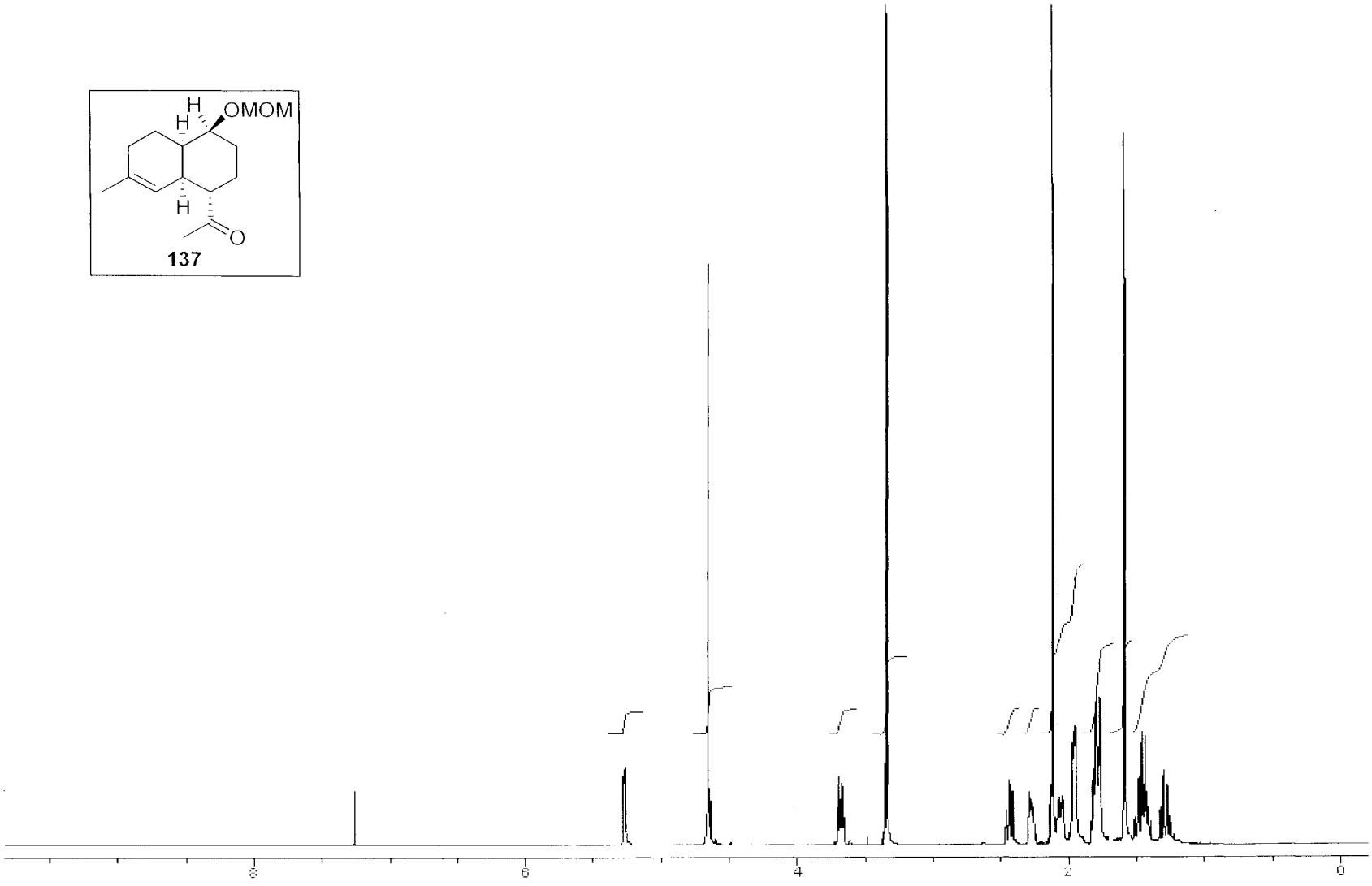


Figure A.1.52 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **137**

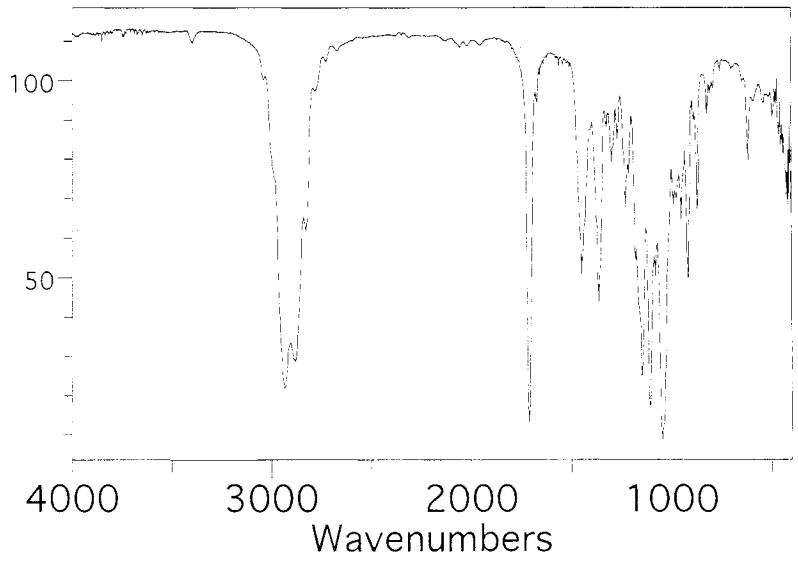


Figure A.1.53 FTIR Spectrum (thin film/NaCl) of Compound **137**

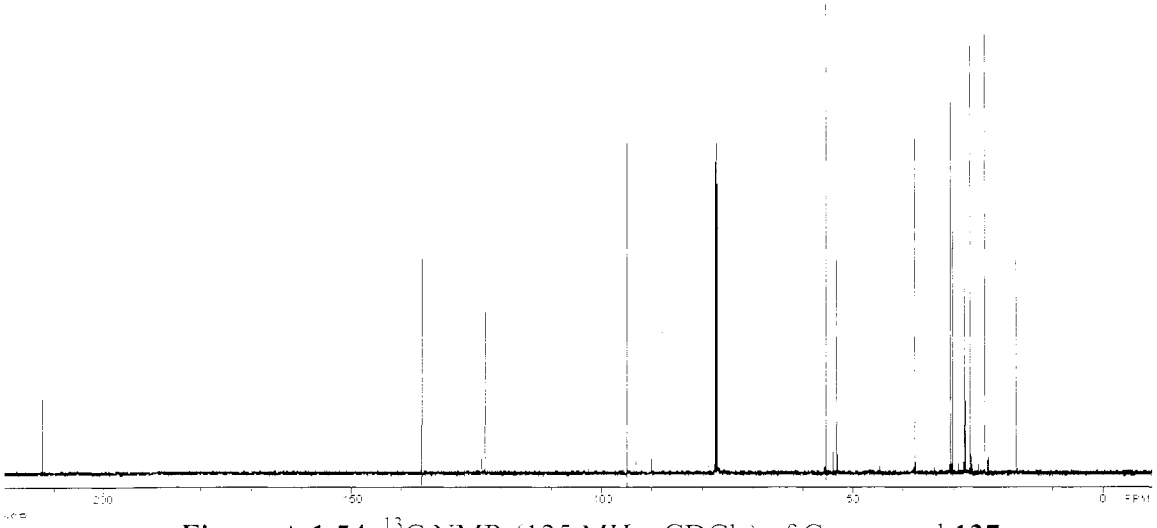


Figure A.1.54 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **137**

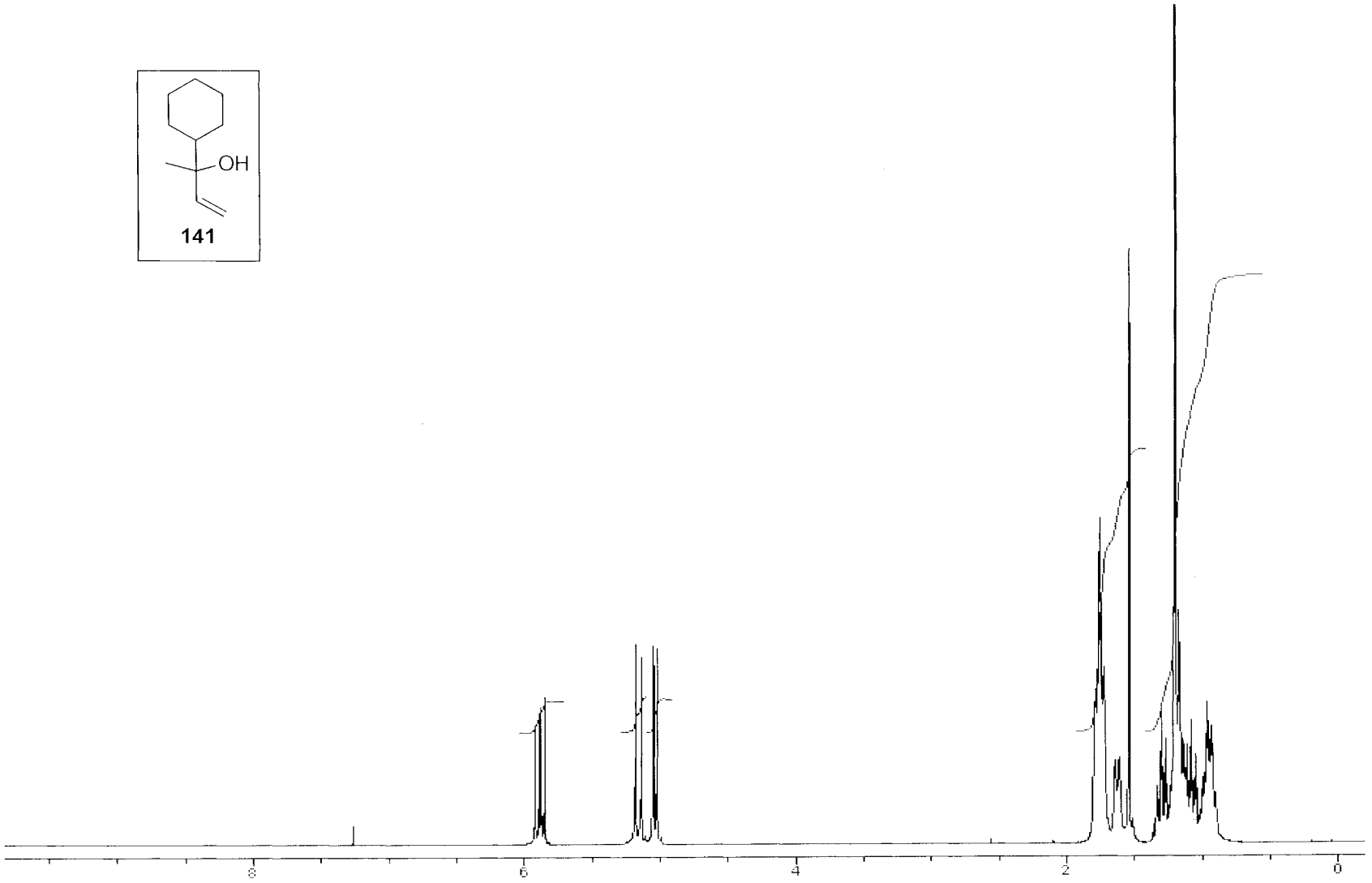


Figure A.1.55 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **141**

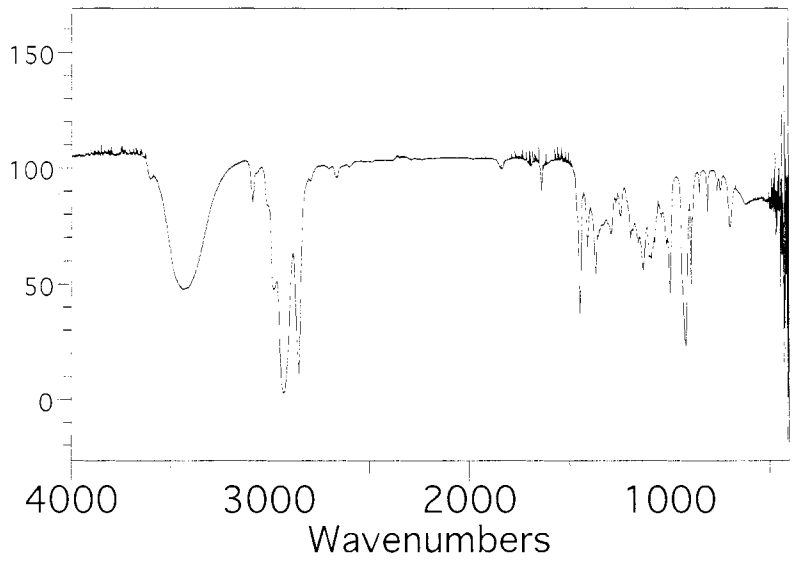


Figure A.1.56 FTIR Spectrum (thin film/NaCl) of Compound **141**

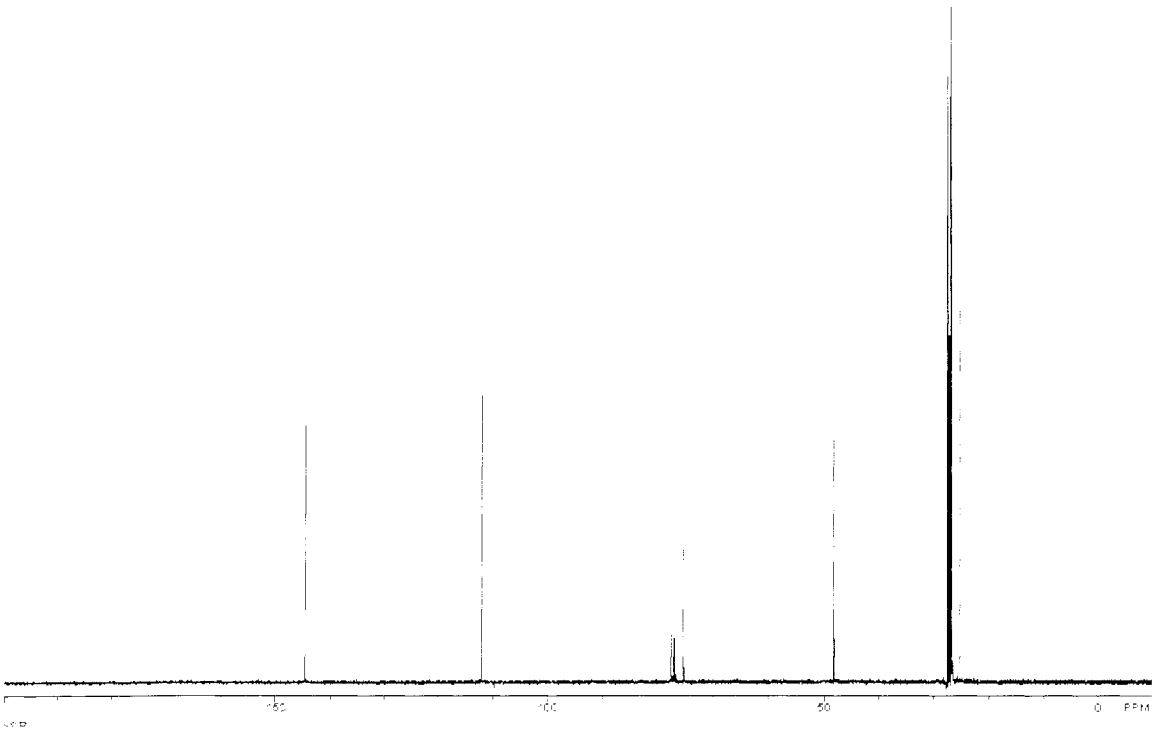


Figure A.1.57 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **141**

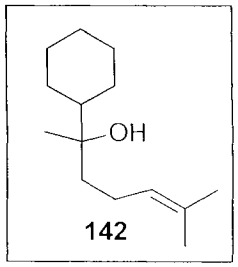


Figure A.1.58 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **142**

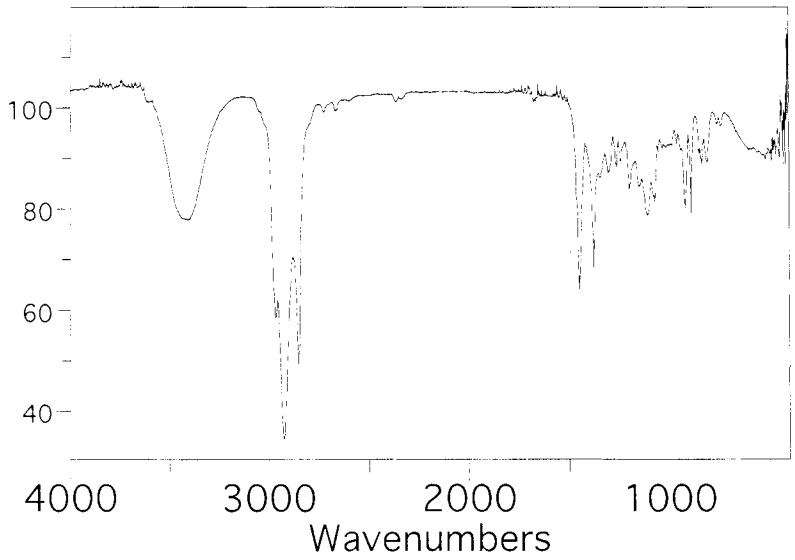


Figure A.1.59 FTIR Spectrum (thin film/NaCl) of Compound **142**

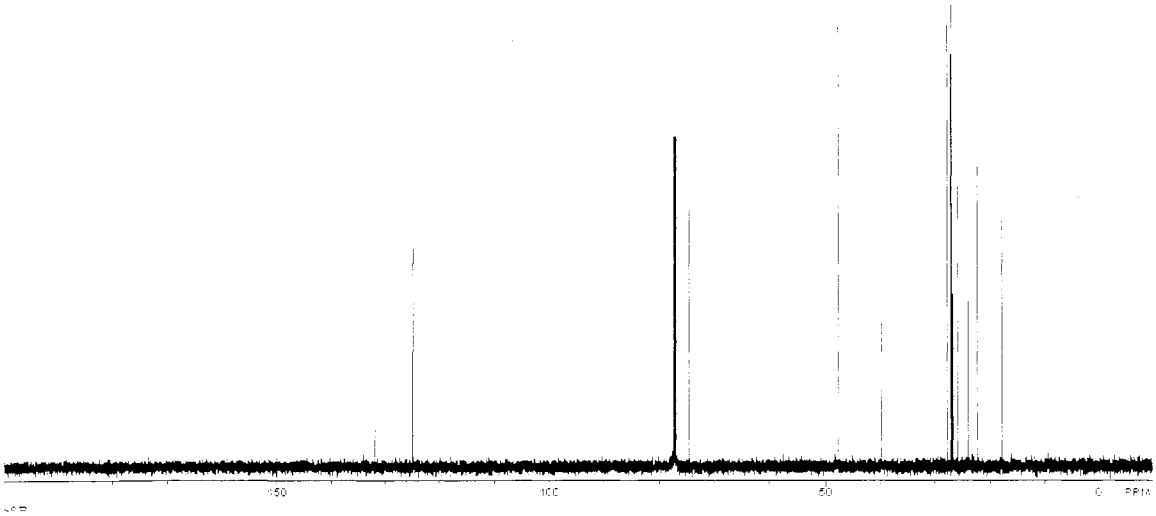


Figure A.1.60 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **142**

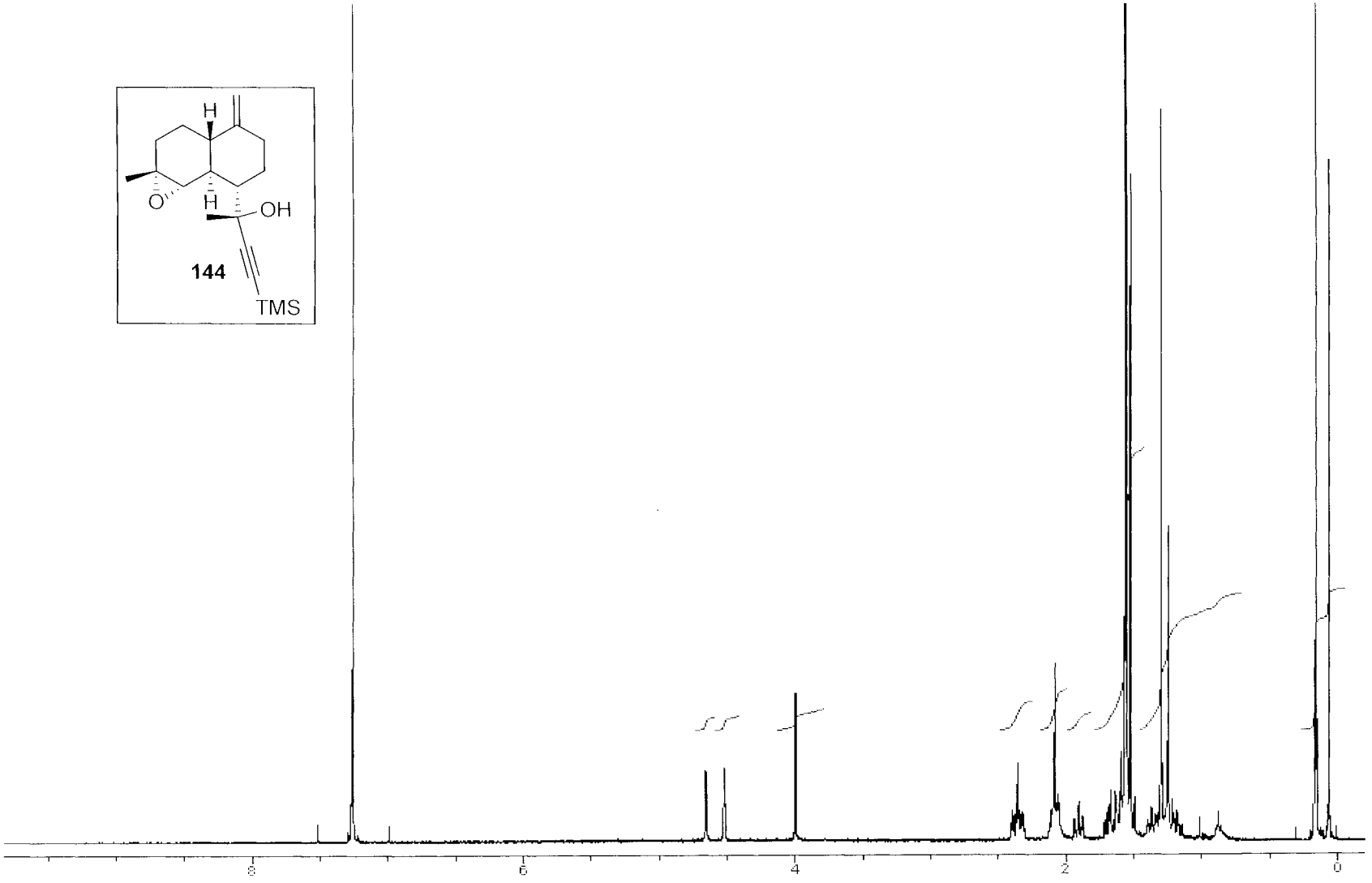


Figure A.1.61 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **144**

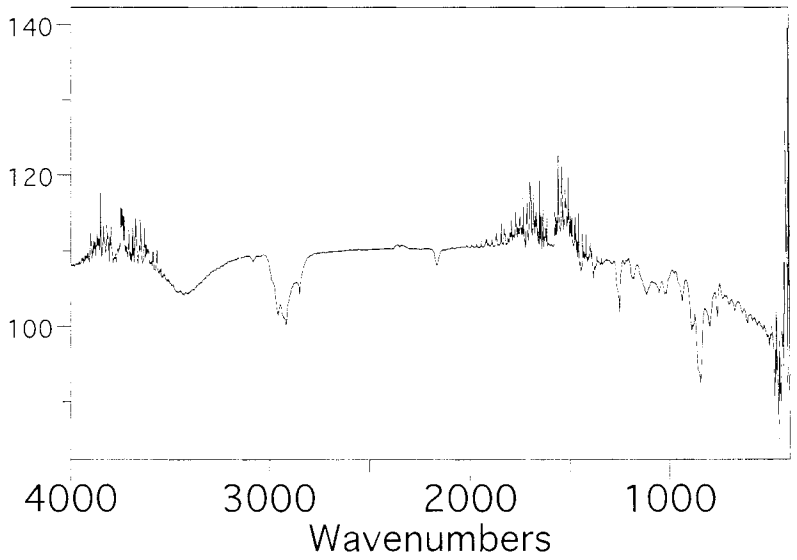


Figure A.1.62 FTIR Spectrum (thin film/NaCl) of Compound **144**

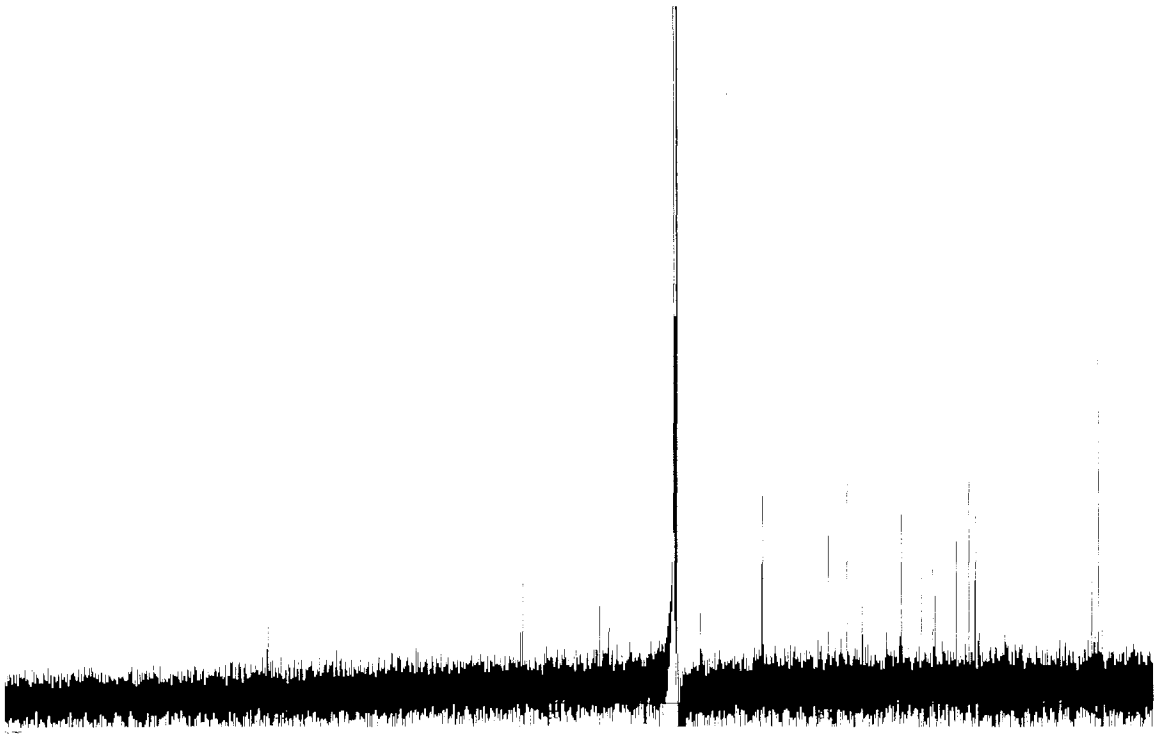
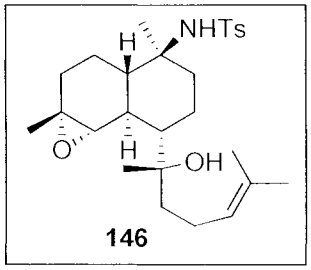


Figure A.1.63 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **144**



146

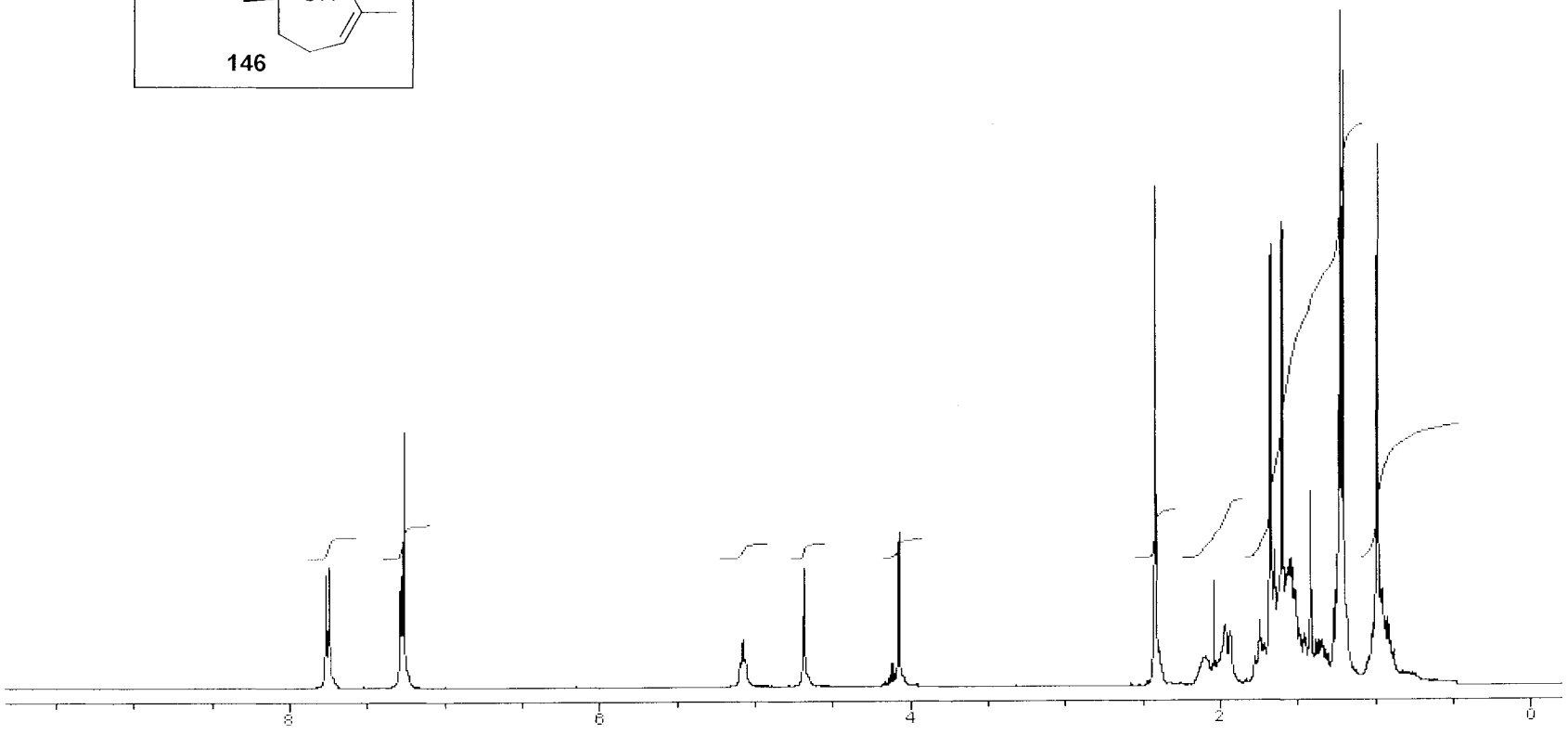


Figure A.1.64 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **146**

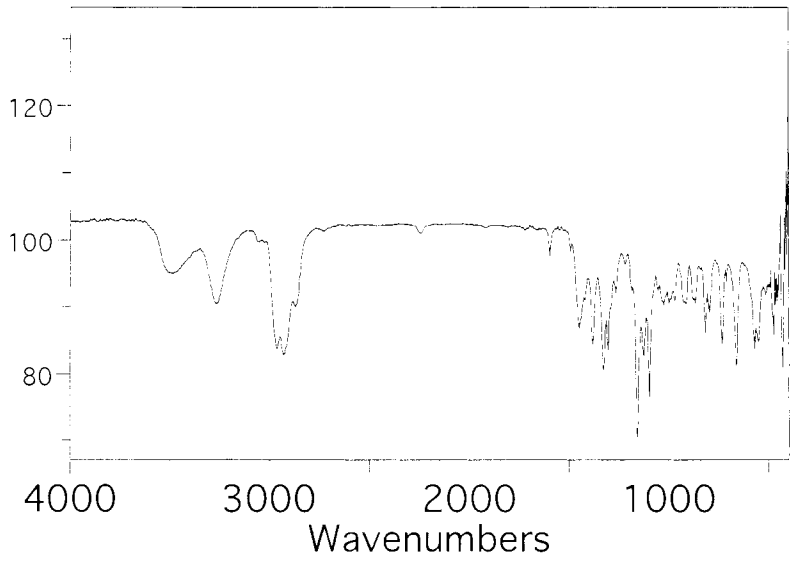


Figure A.1.65 FTIR Spectrum (thin film/NaCl) of Compound **146**

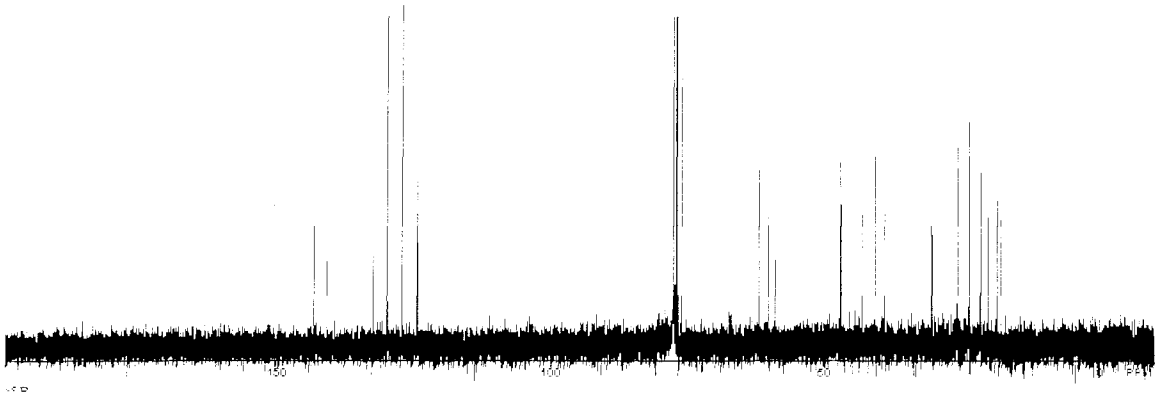
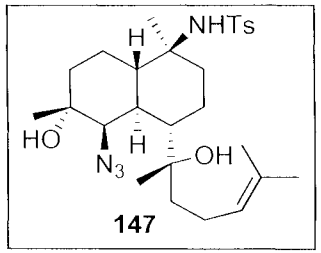


Figure A.1.66 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **146**



147

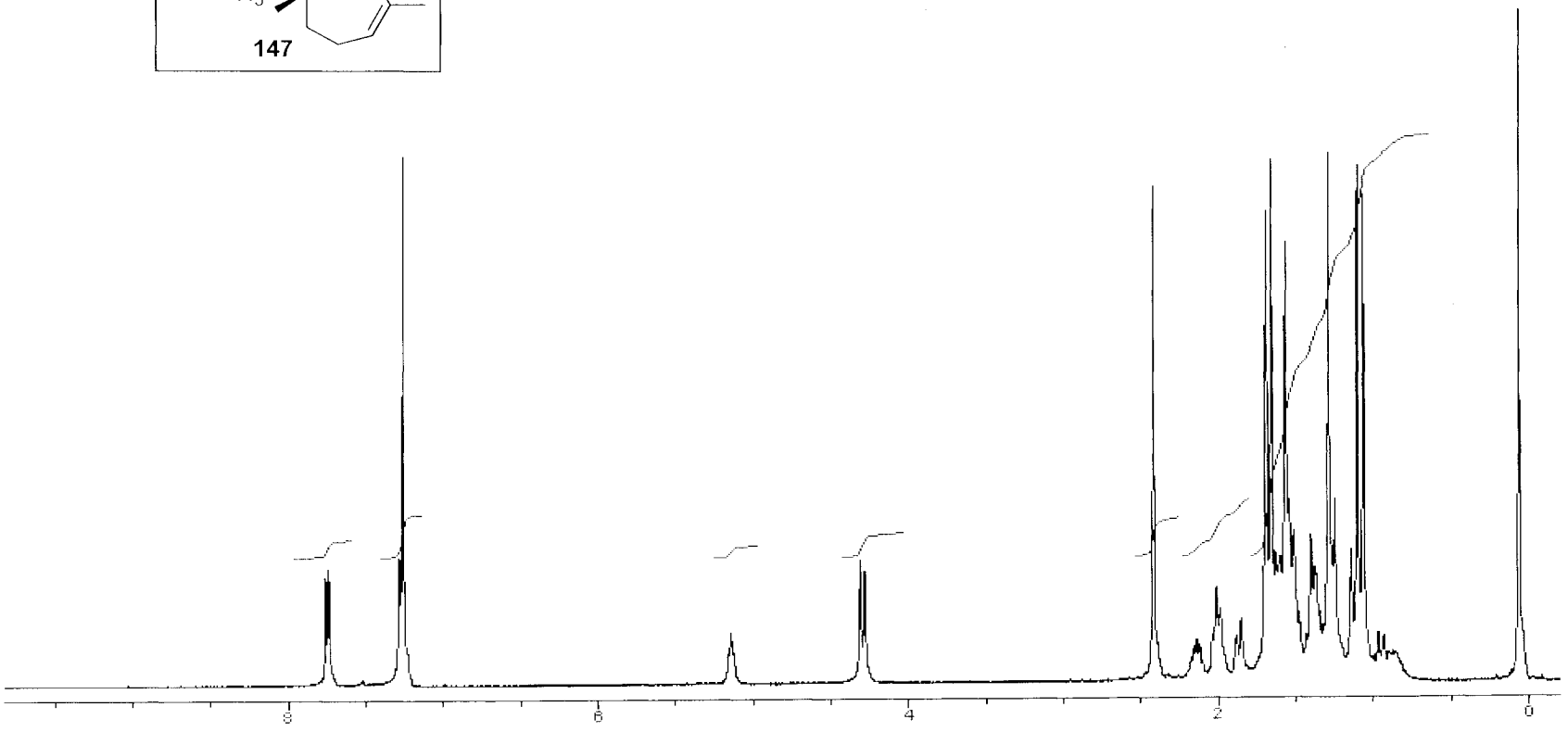


Figure A.1.67 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **147**

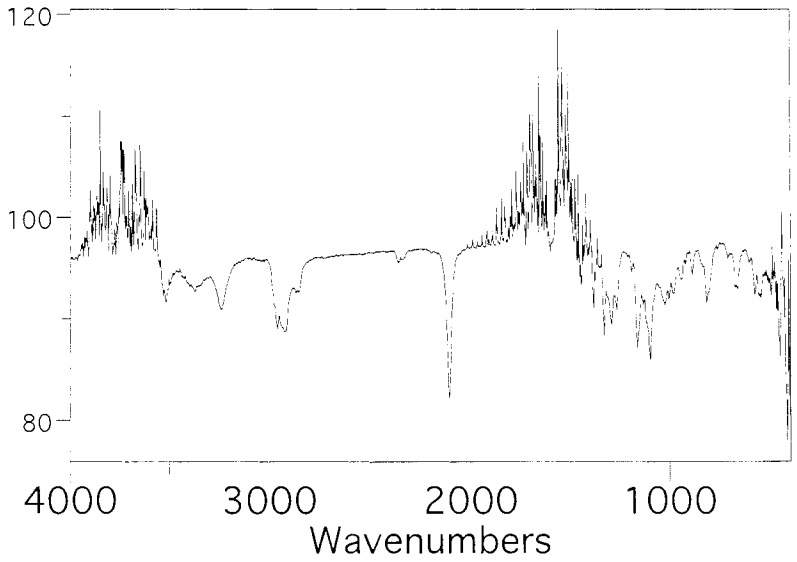


Figure A.1.68 FTIR Spectrum (thin film/NaCl) of Compound **147**

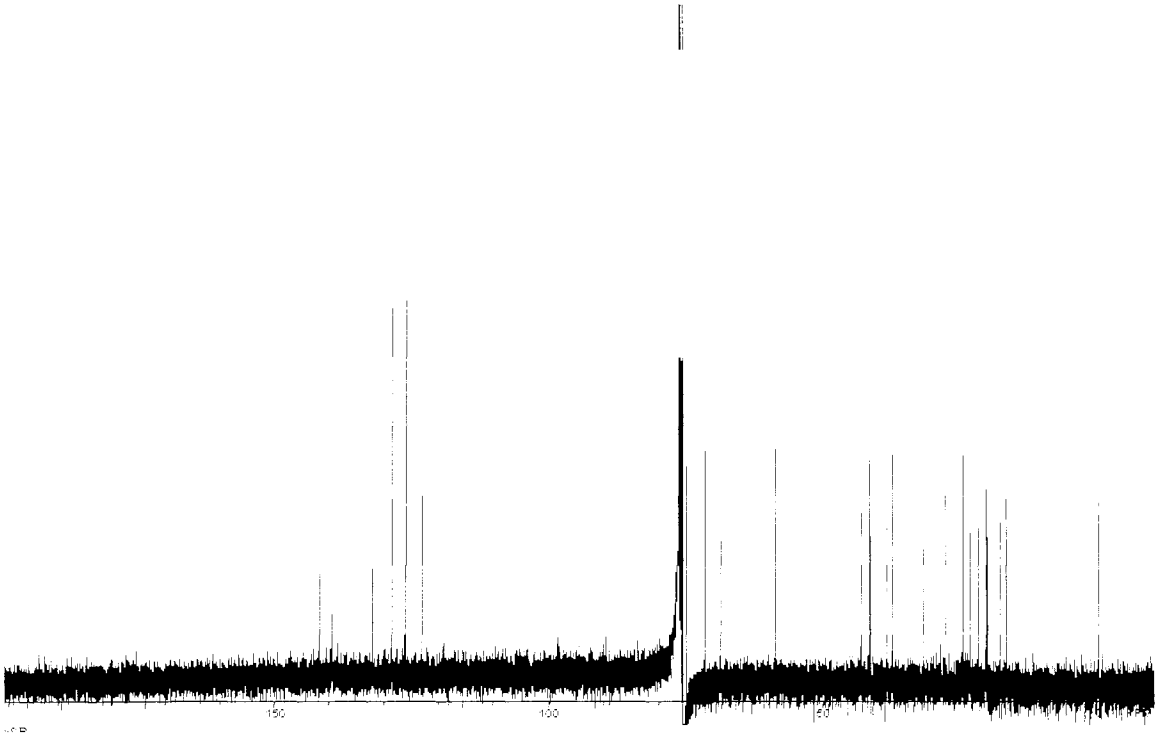


Figure A.1.69 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **147**

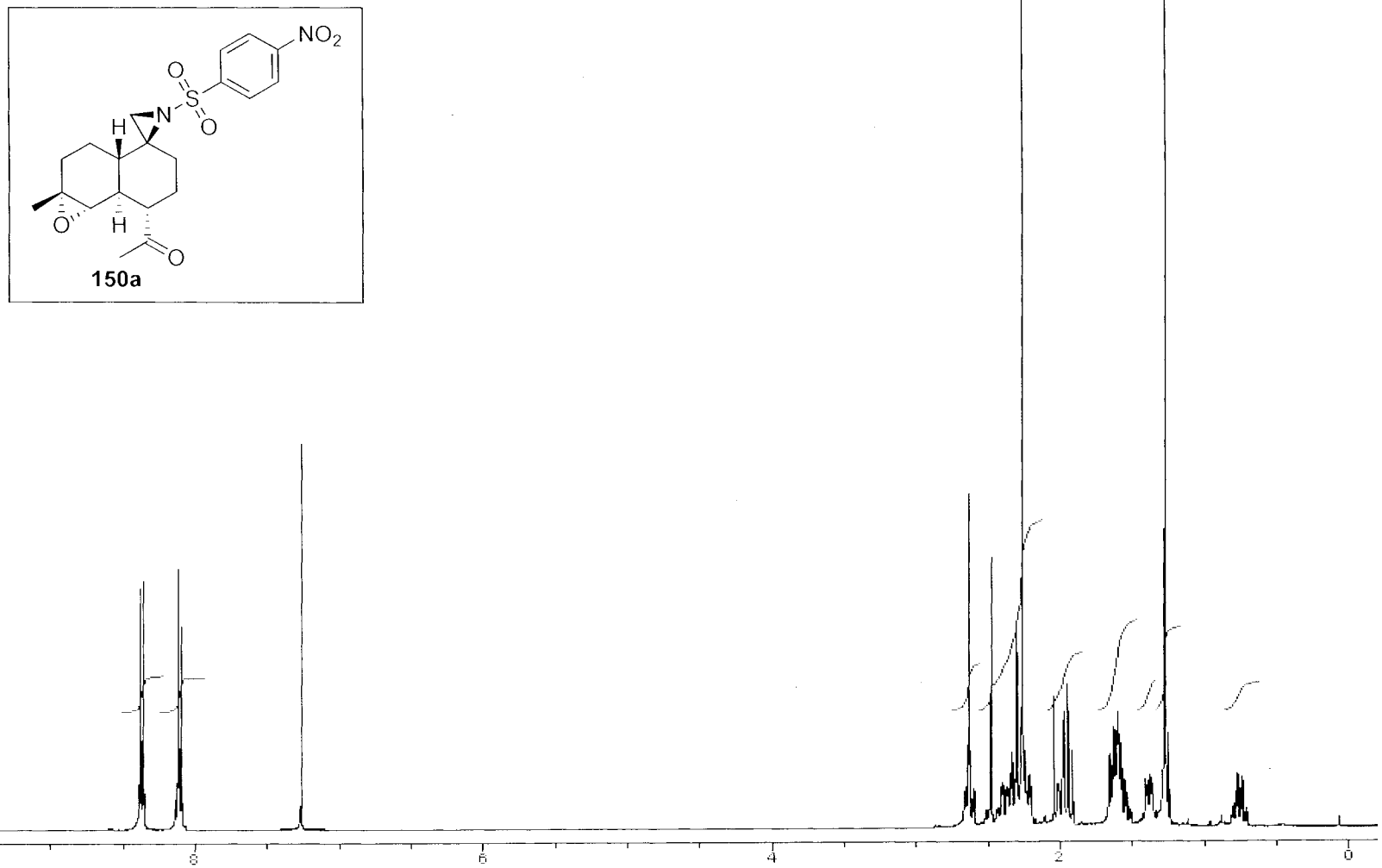


Figure A.1.70 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **150a**

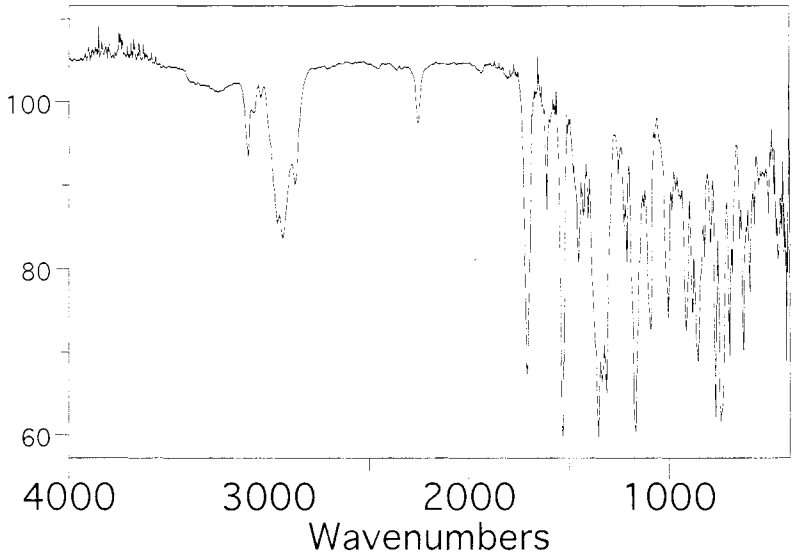


Figure A.1.71 FTIR Spectrum (thin film/NaCl) of Compound **150a**

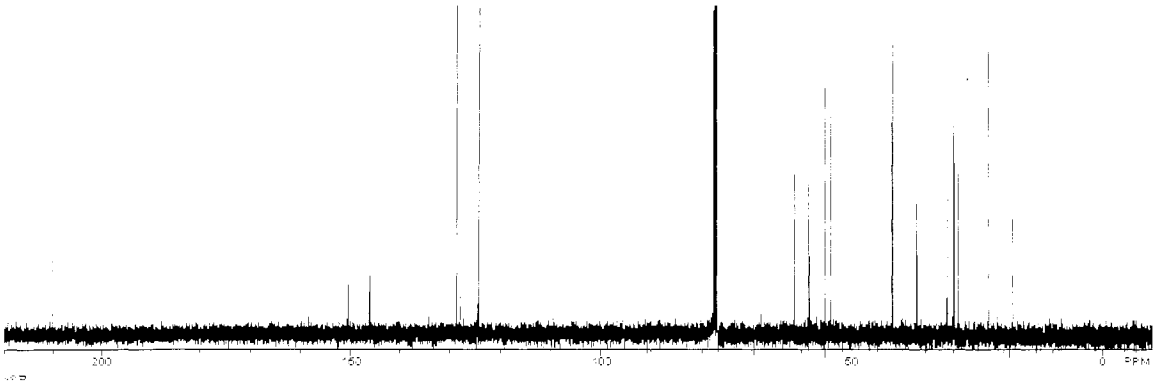
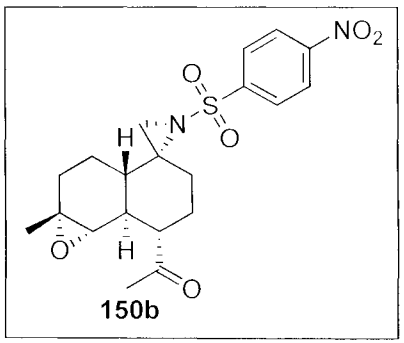


Figure A.1.72 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **150a**



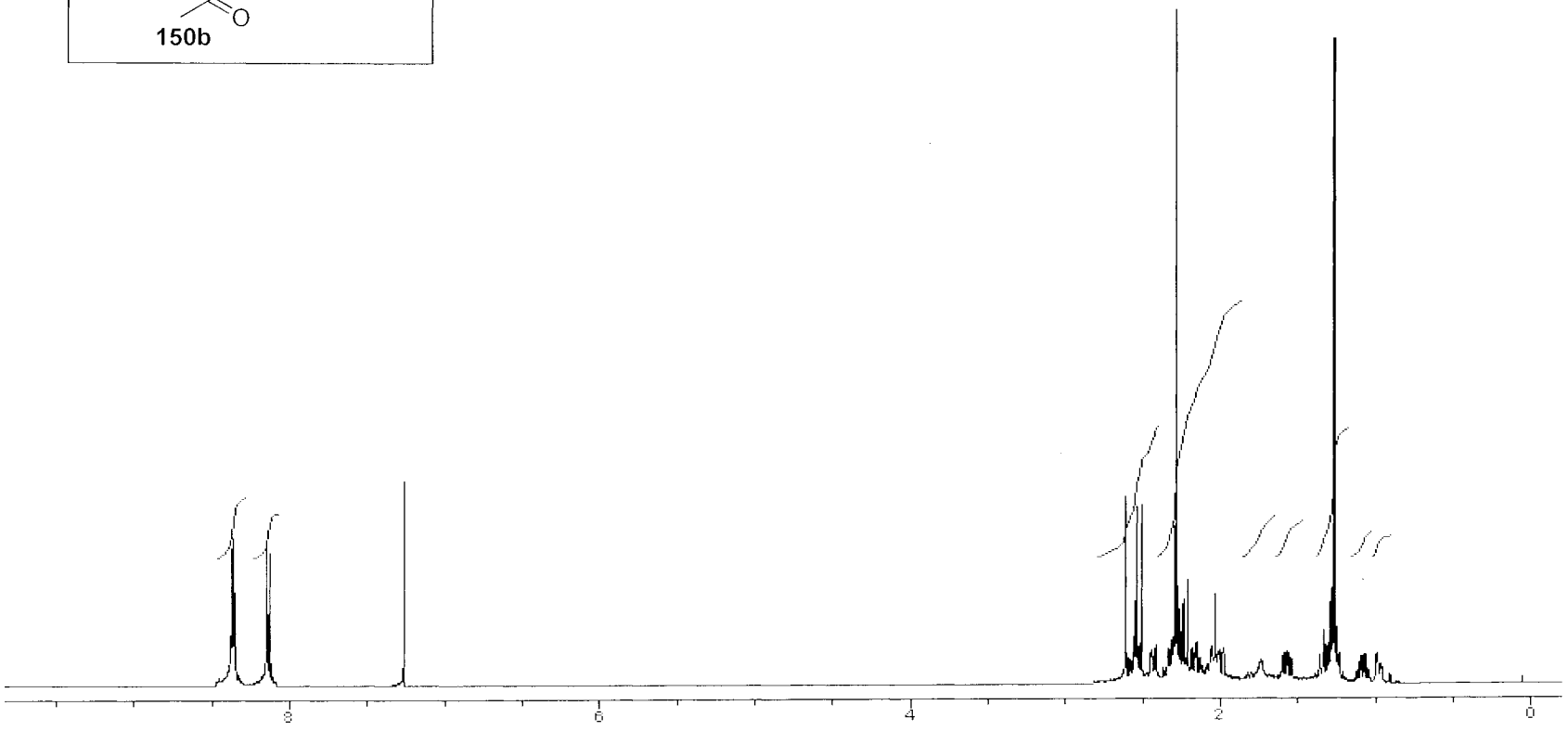


Figure A.1.73 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **150b**

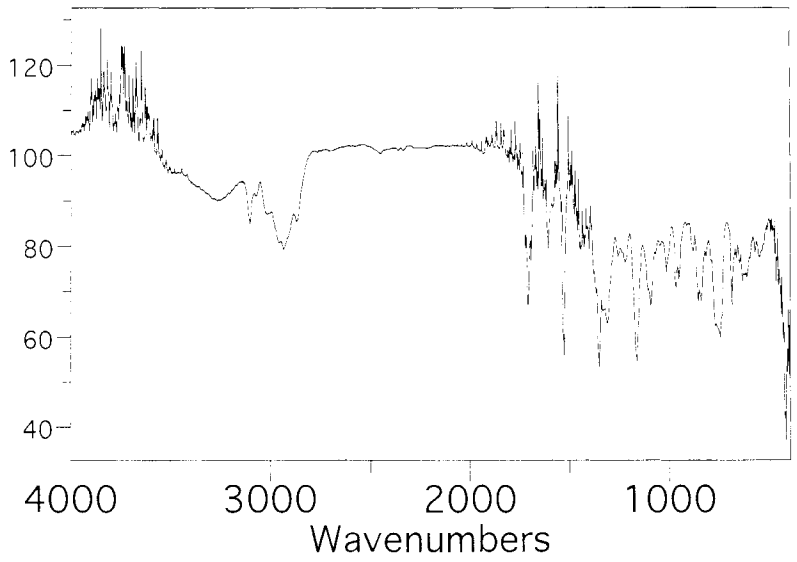


Figure A.1.74 FTIR Spectrum (thin film/NaCl) of Compound **150b**

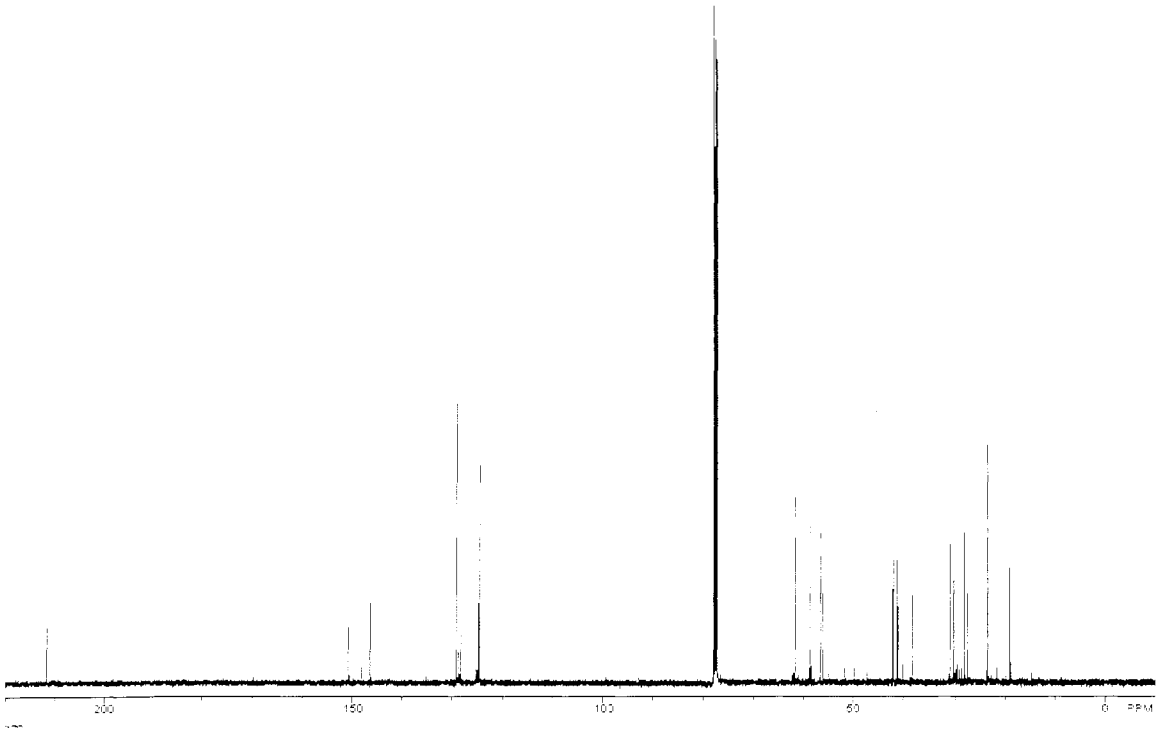


Figure A.1.75 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **150b**

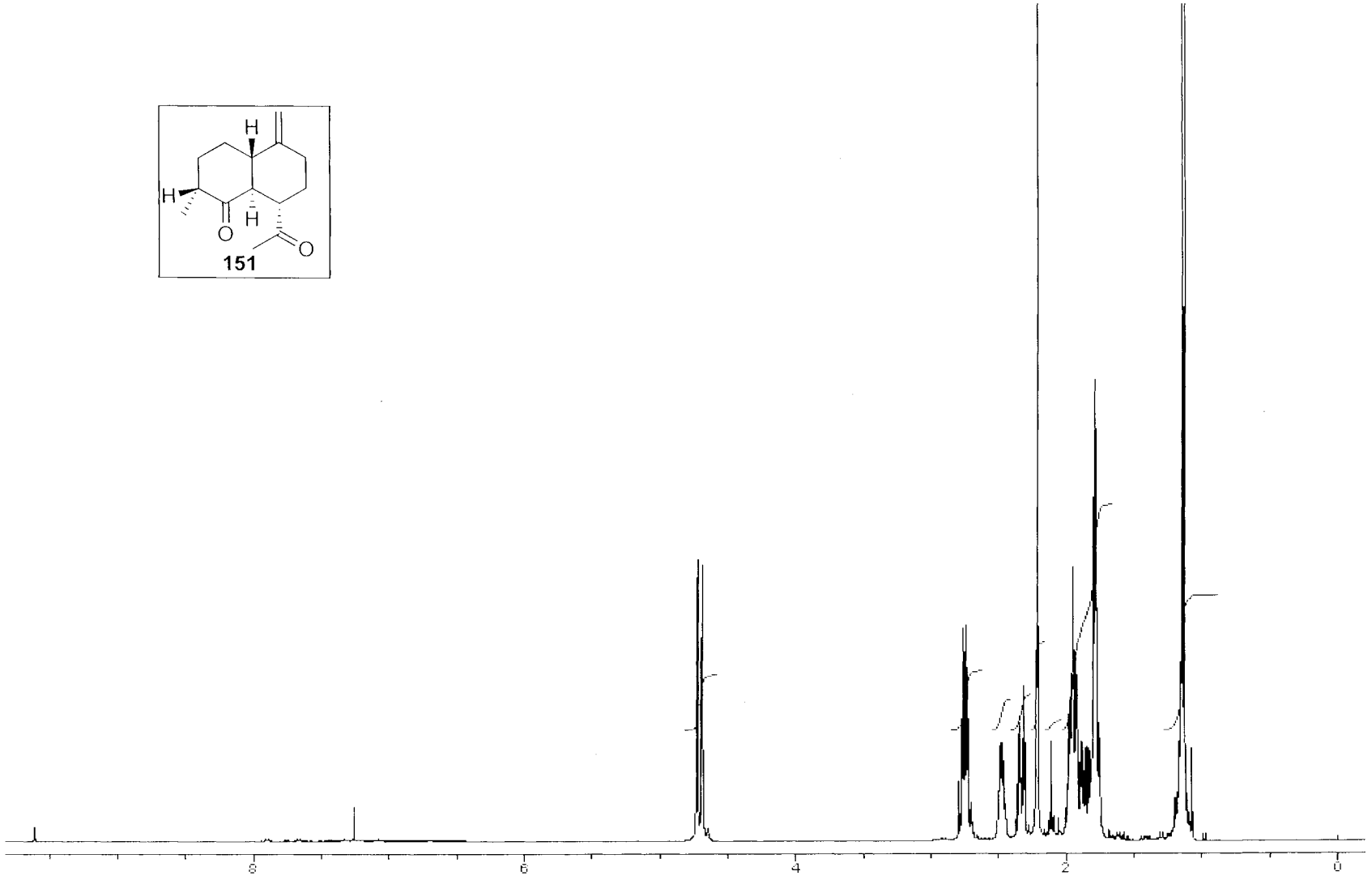


Figure A.1.76 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **151**

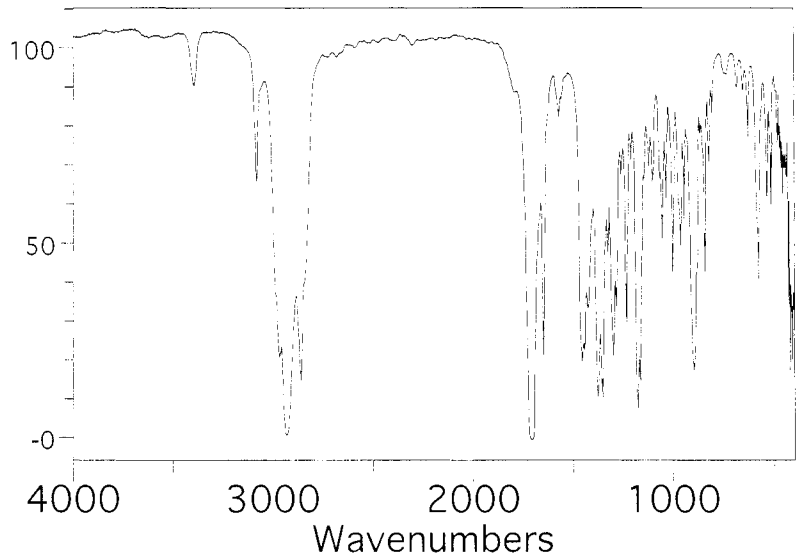


Figure A.1.77 FTIR Spectrum (thin film/NaCl) of Compound **151**

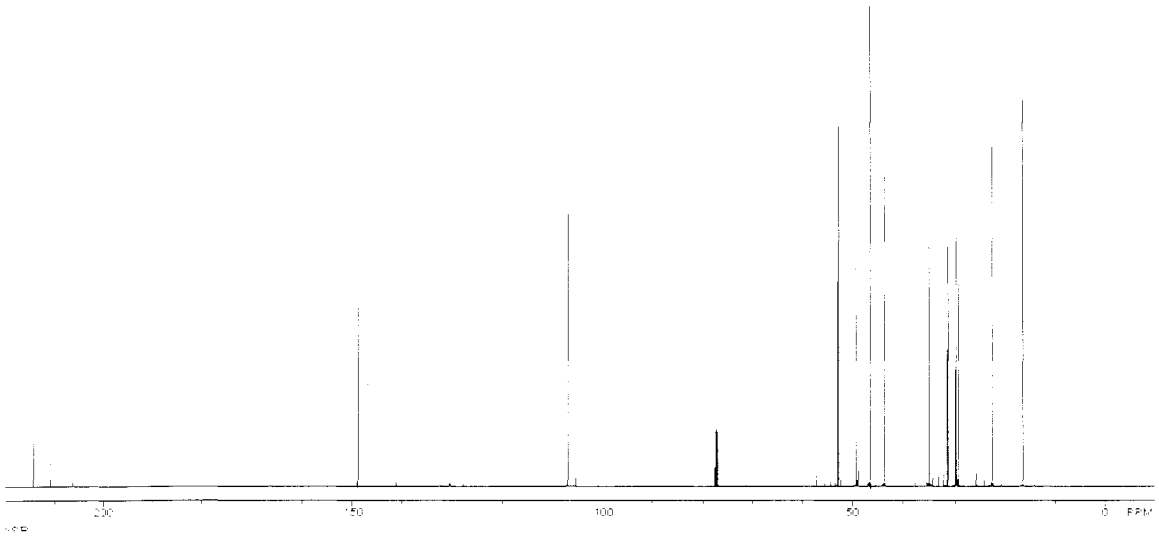


Figure A.1.78 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **151**

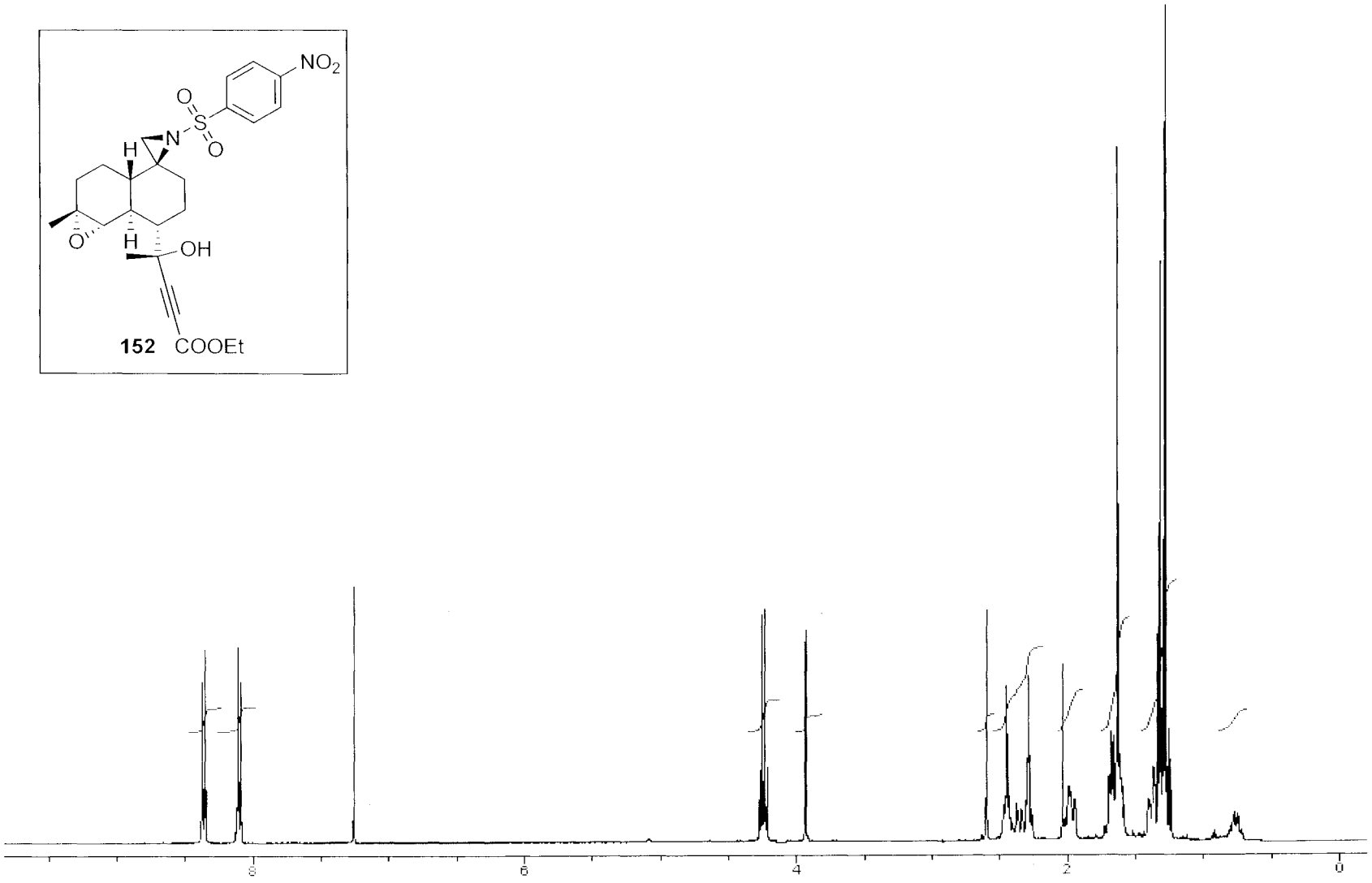


Figure A.1.79 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **152**

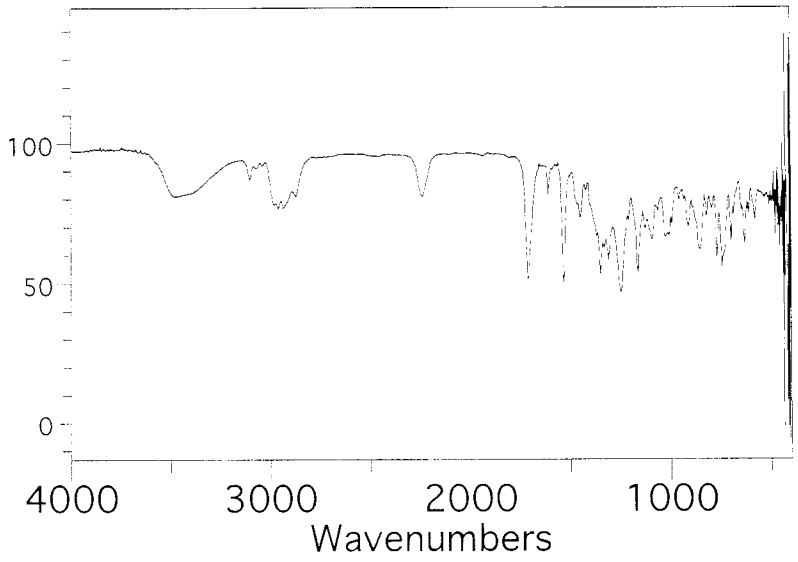


Figure A.1.80 FTIR Spectrum (thin film/NaCl) of Compound **152**

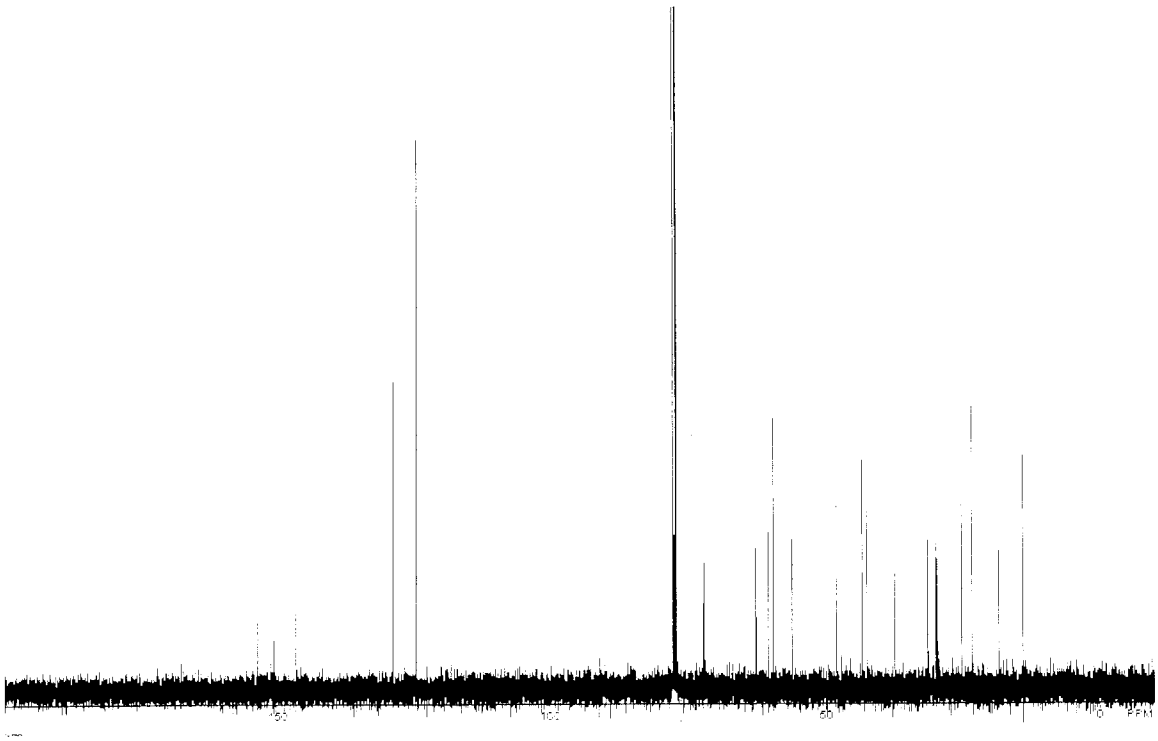


Figure A.1.81 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **152**

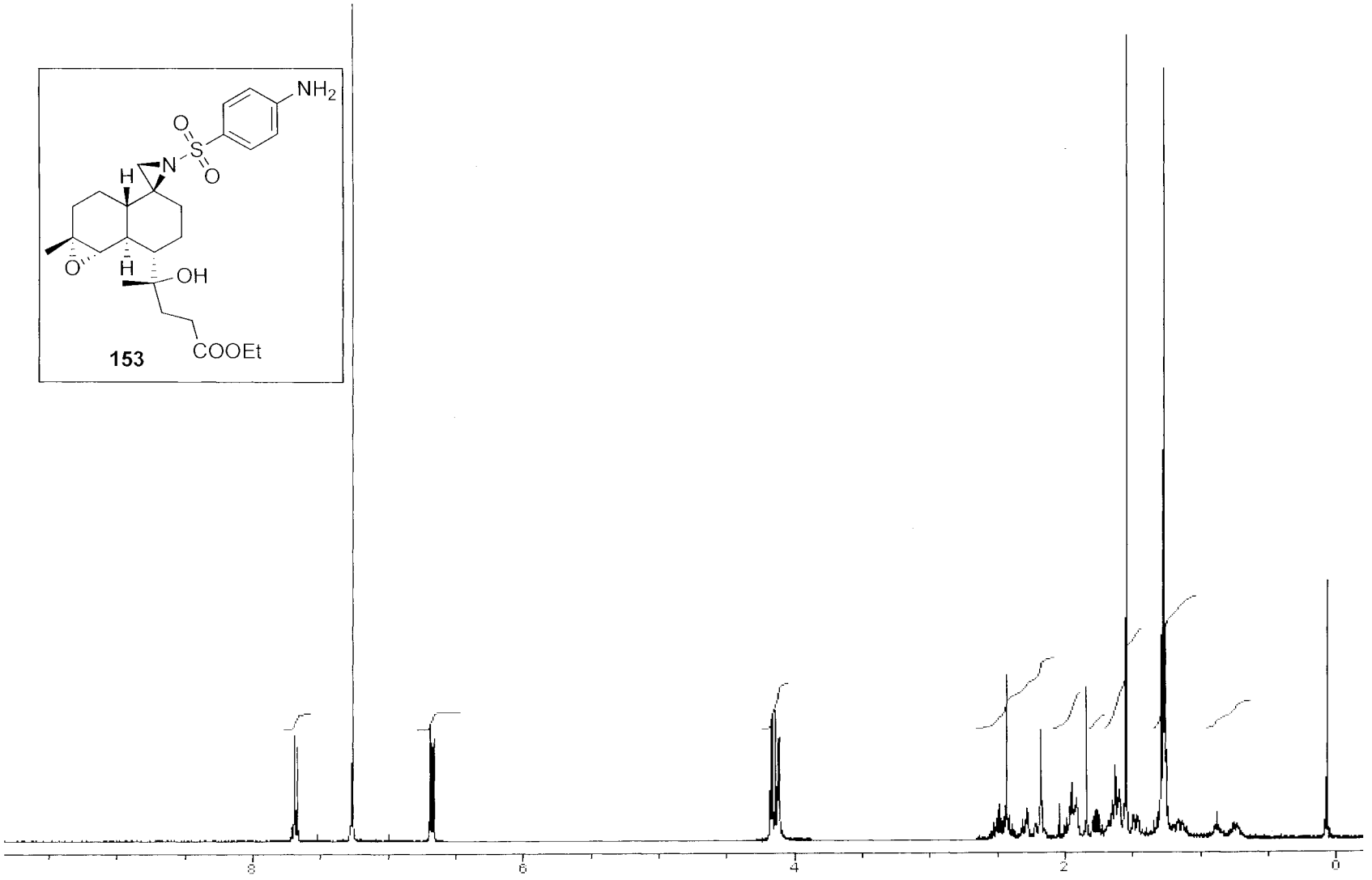


Figure A.1.82 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **153**

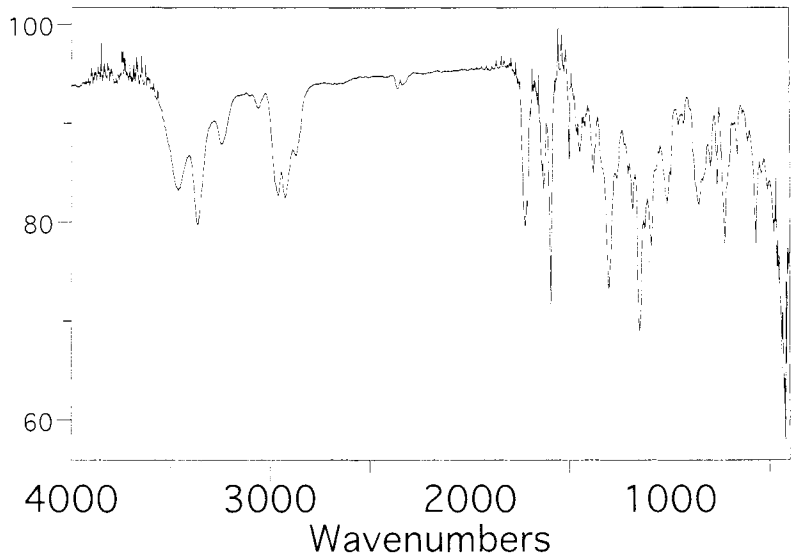


Figure A.1.83 FTIR Spectrum (thin film/NaCl) of Compound **153**

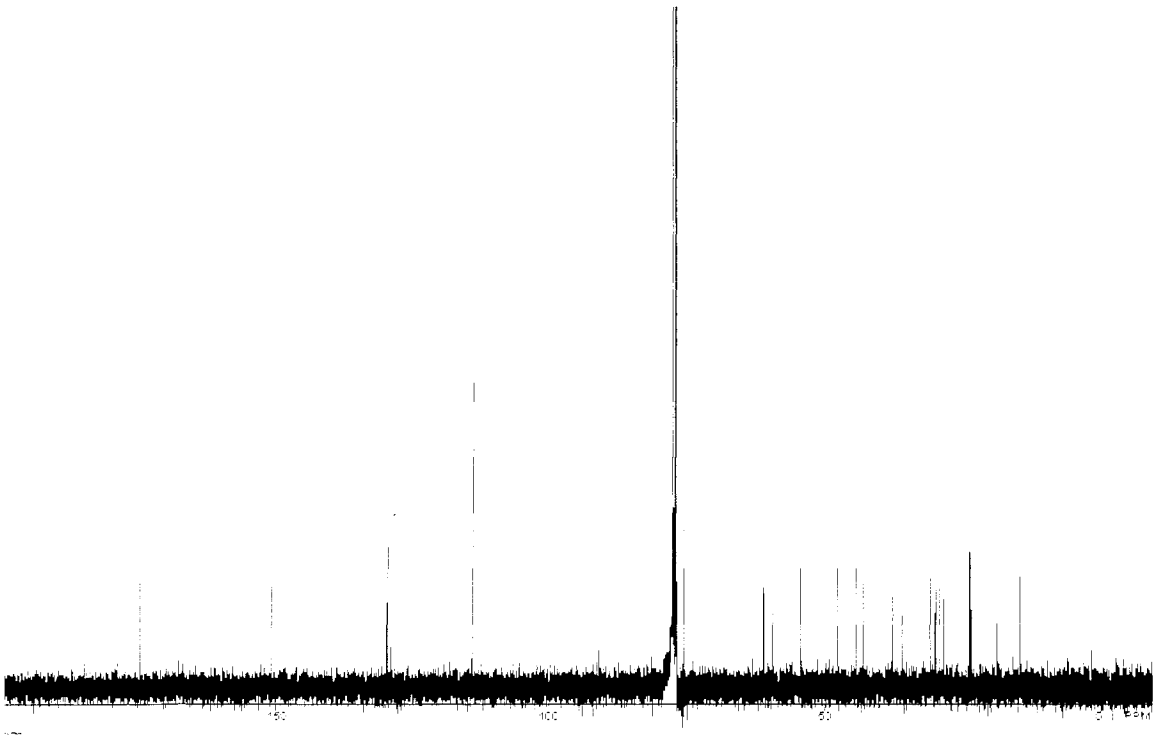
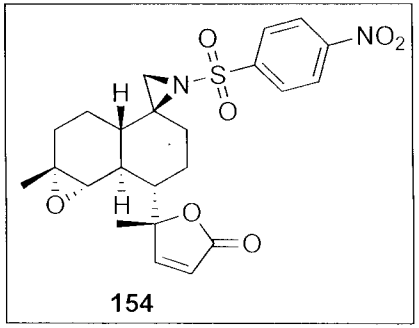


Figure A.1.84 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **153**



154

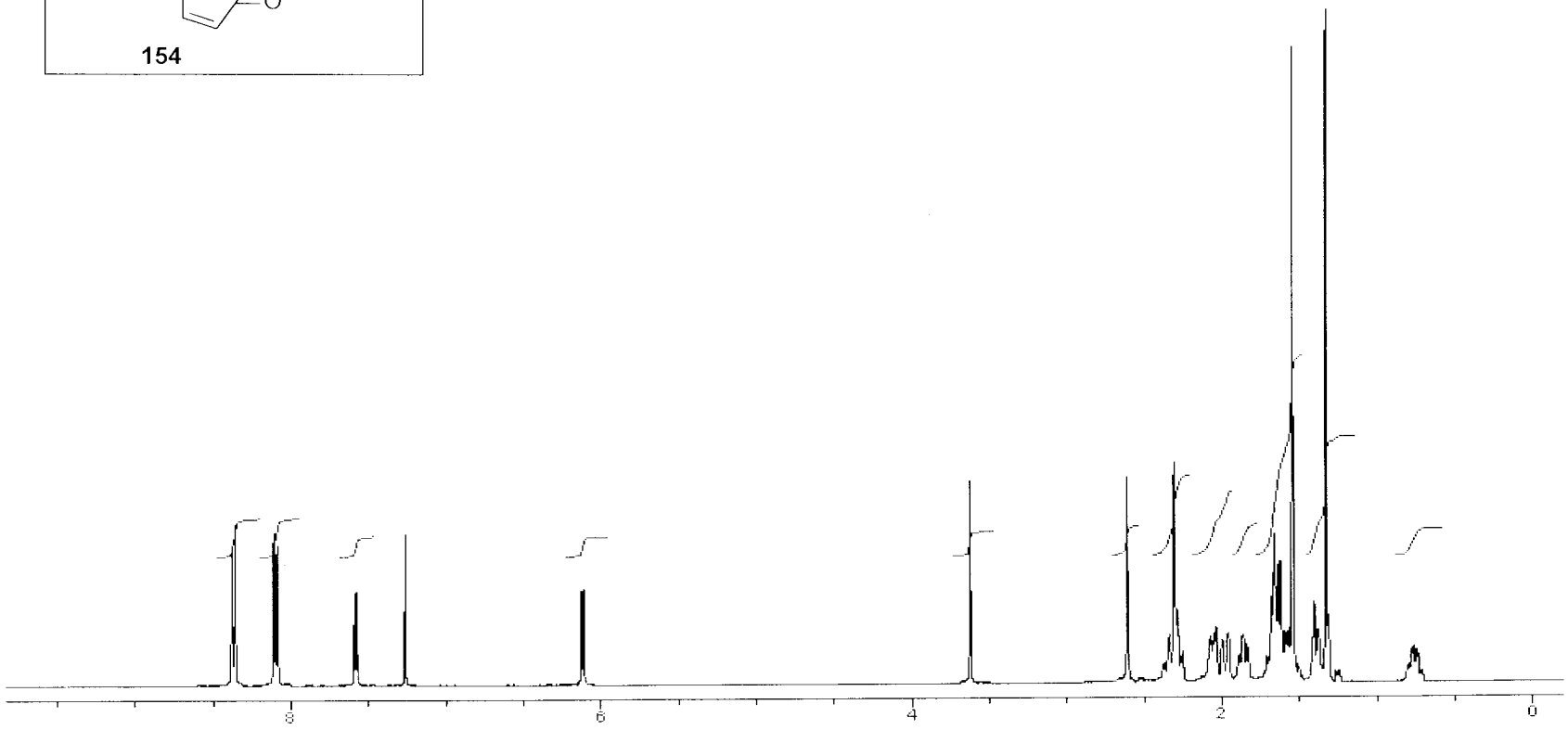


Figure A.1.85 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **154**

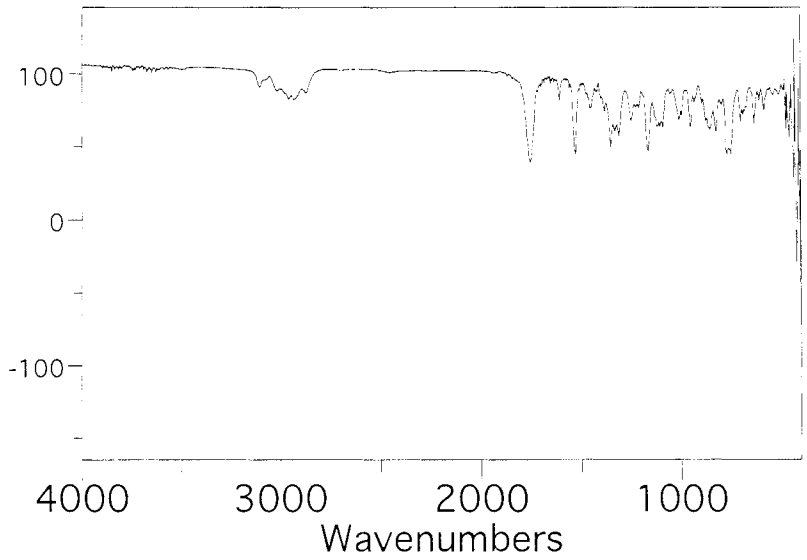


Figure A.1.86 FTIR Spectrum (thin film/NaCl) of Compound **154**

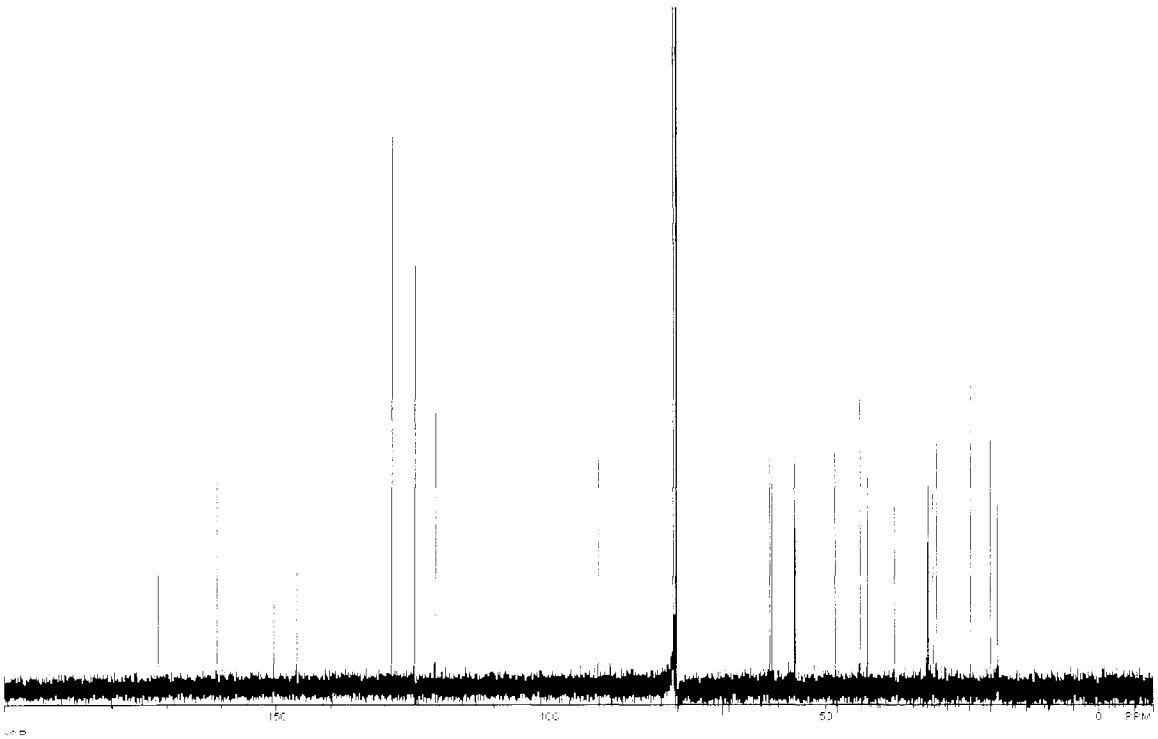
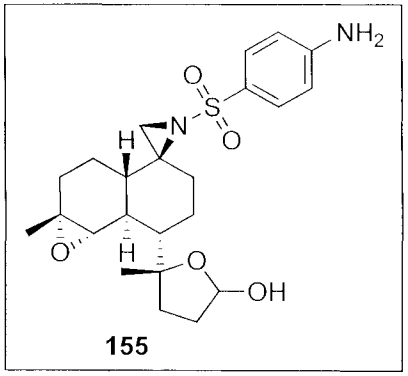


Figure A.1.87 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **154**



155

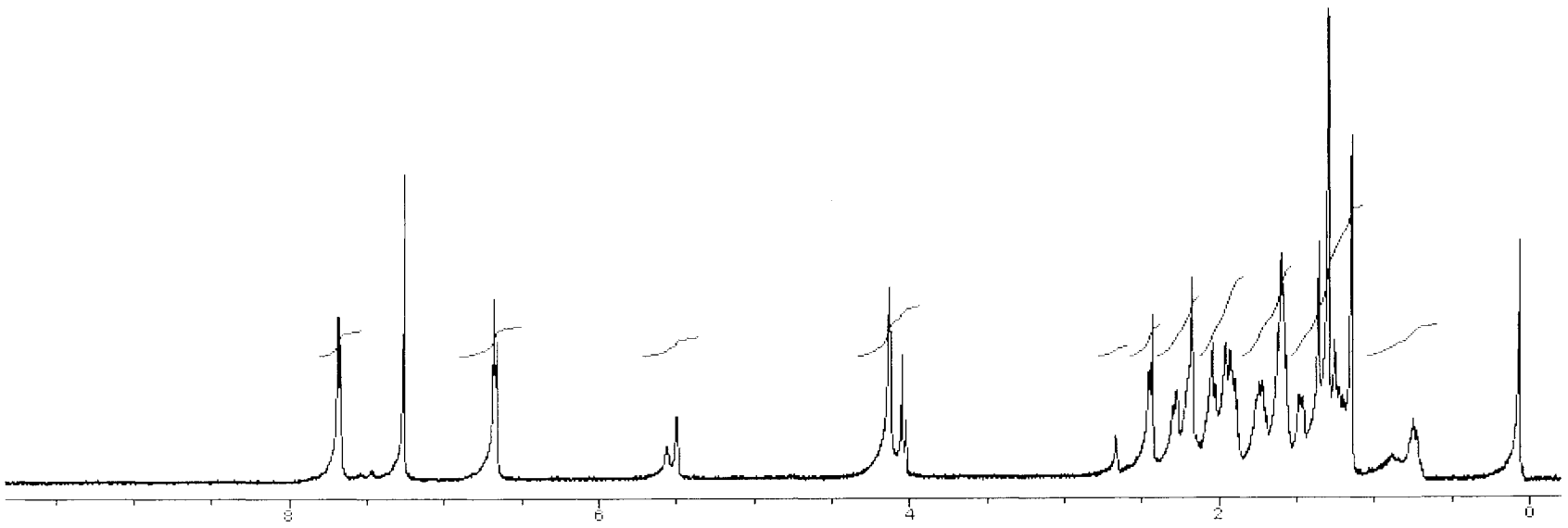


Figure A.1.88 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **155**

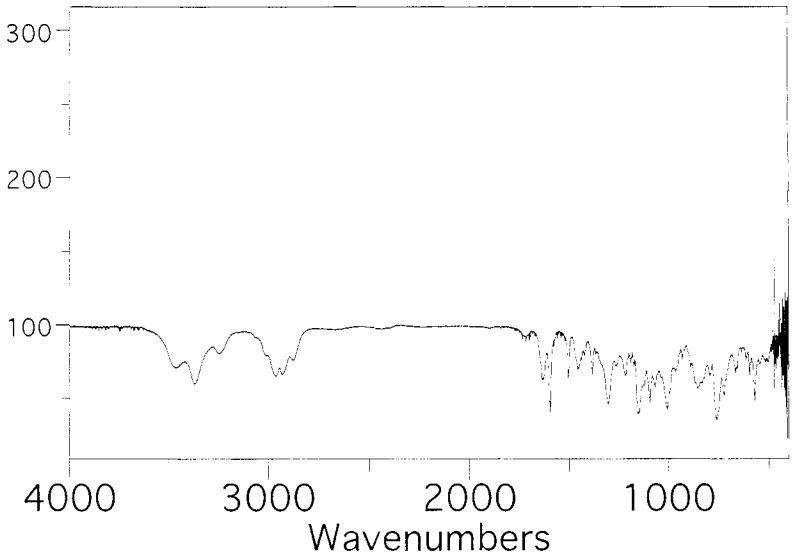


Figure A.1.89 FTIR Spectrum (thin film/NaCl) of Compound **155**

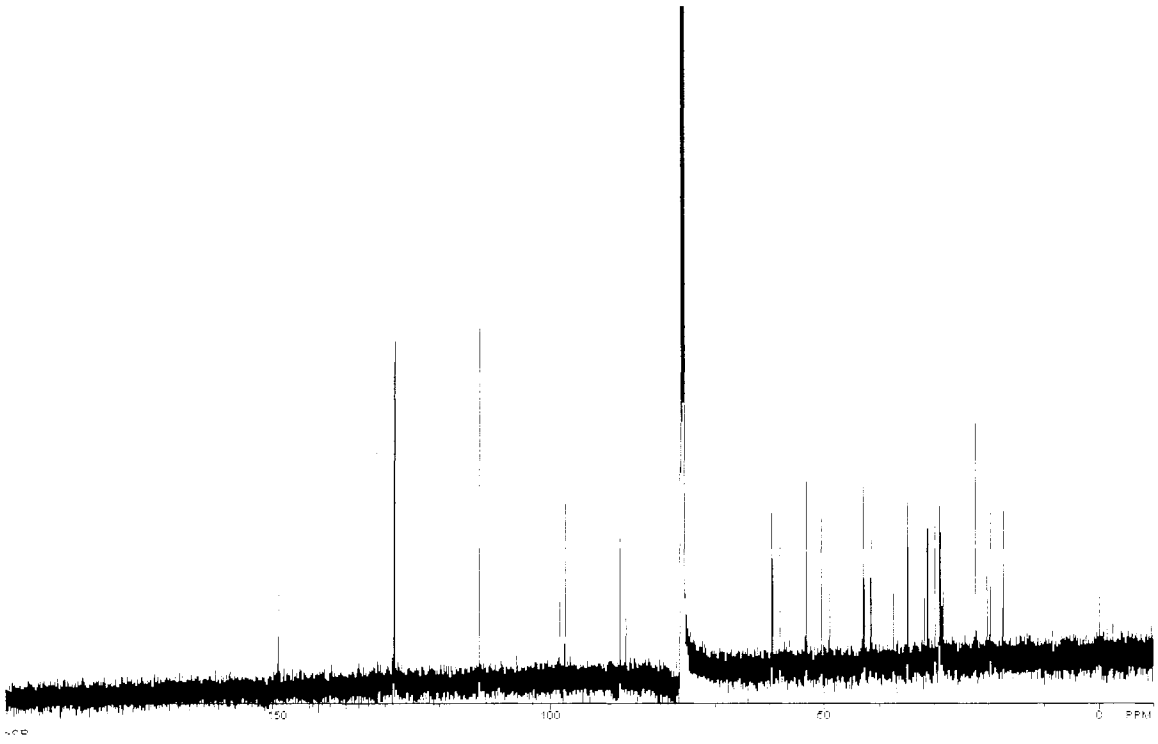


Figure A.1.90 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **155**

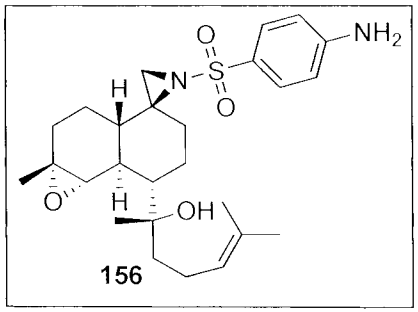


Figure A.1.91 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **156**

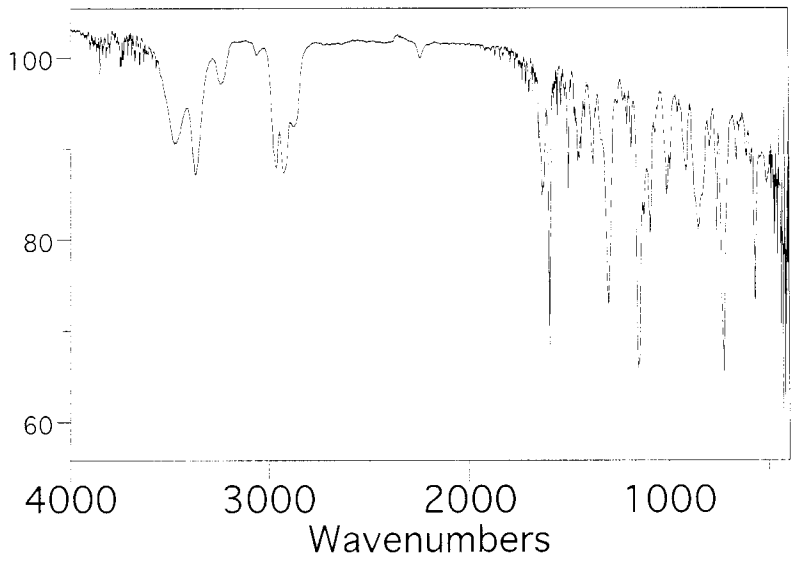


Figure A.1.92 FTIR Spectrum (thin film/NaCl) of Compound **156**

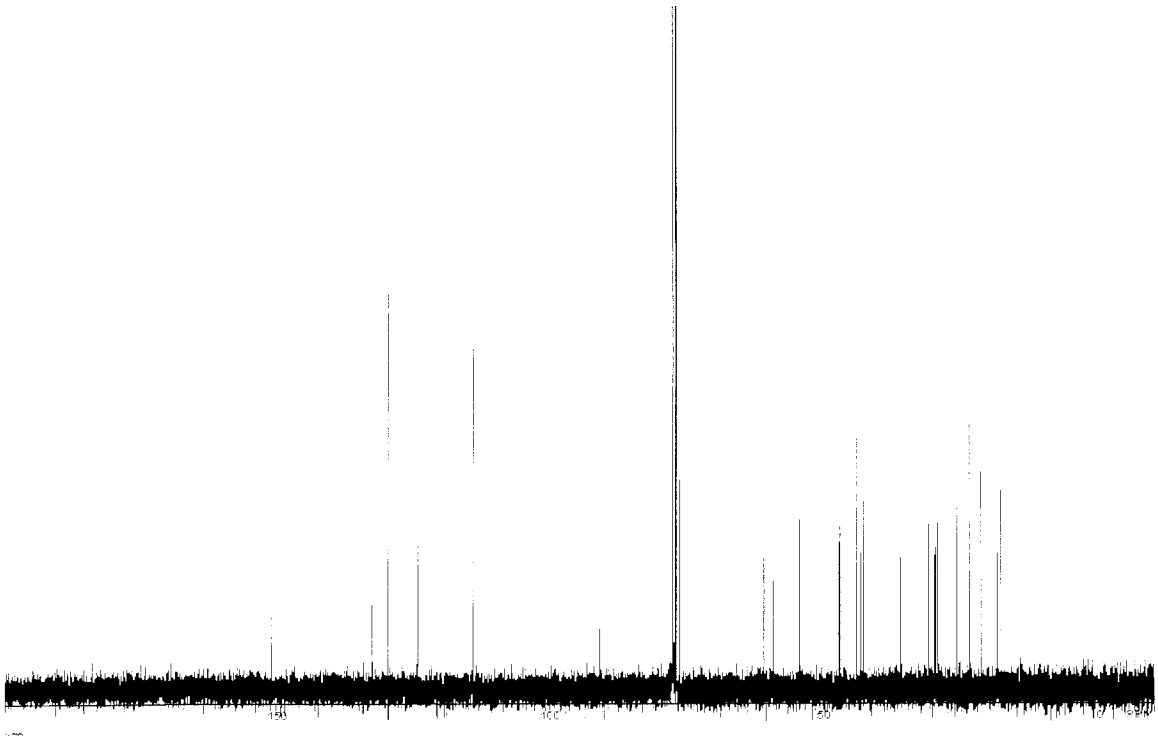


Figure A.1.93 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **156**

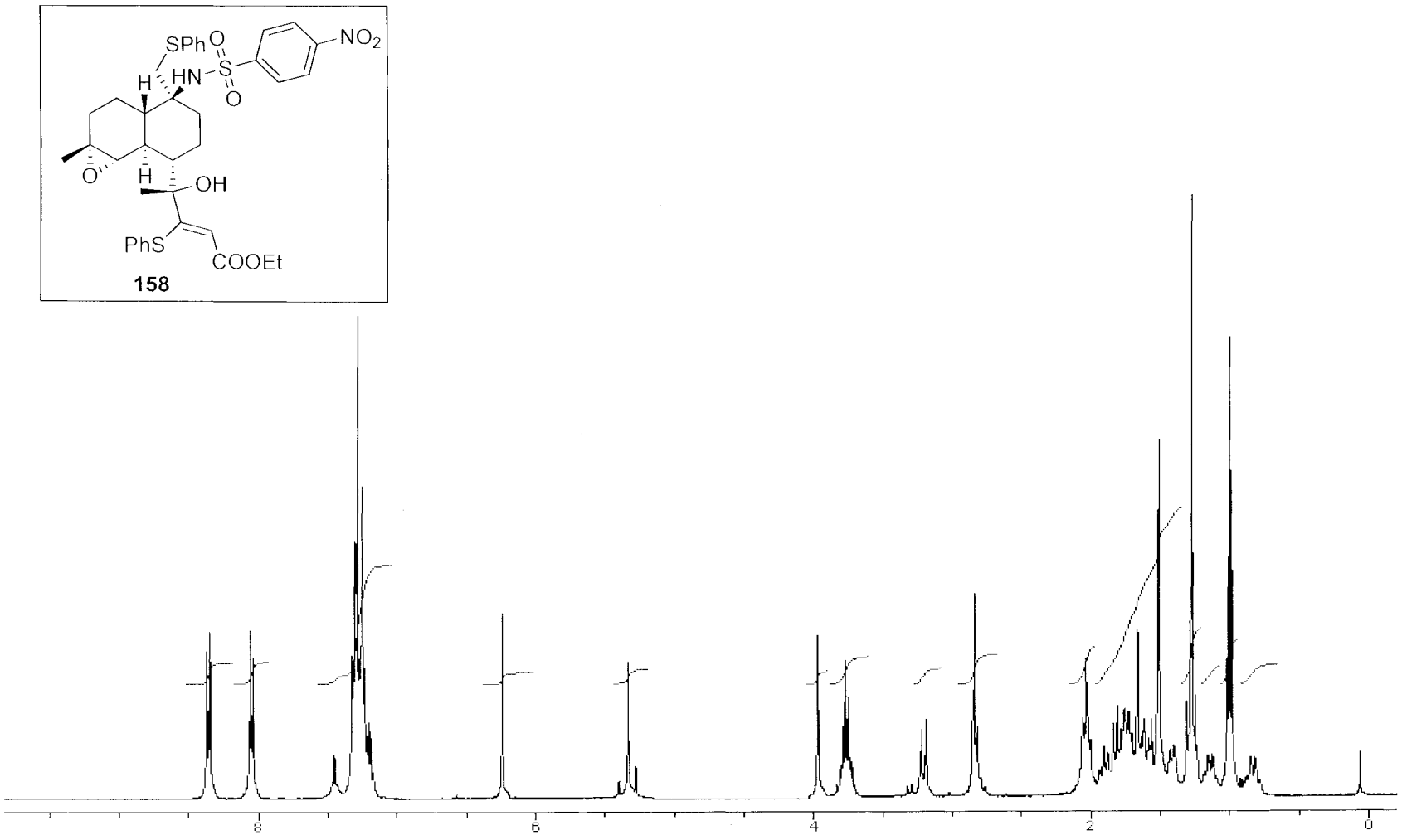


Figure A.1.94 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **158**

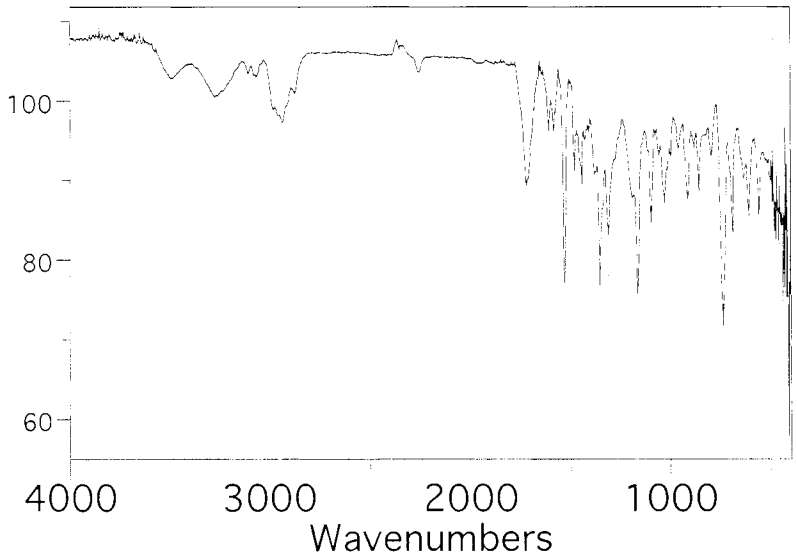


Figure A.1.95 FTIR Spectrum (thin film/NaCl) of Compound **158**

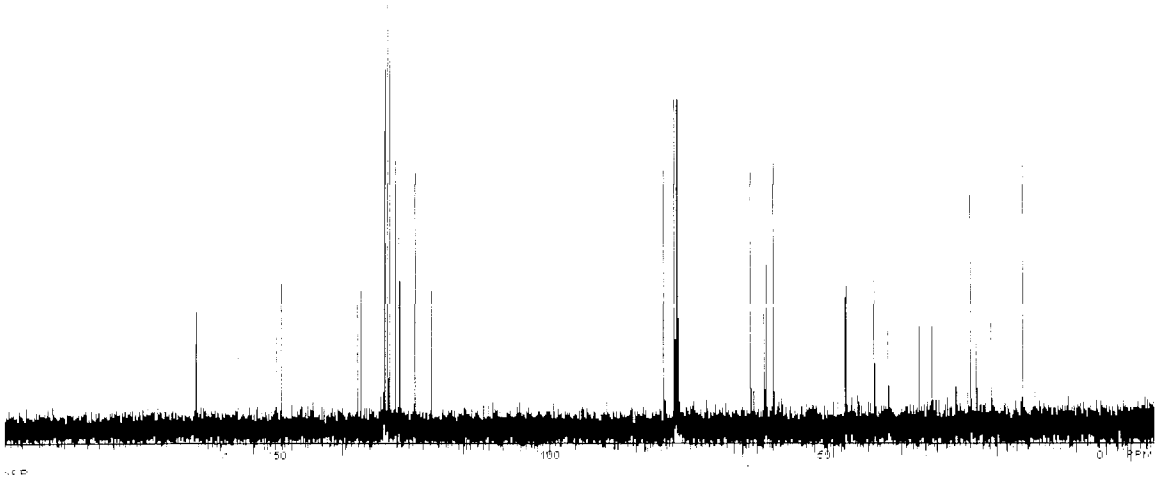
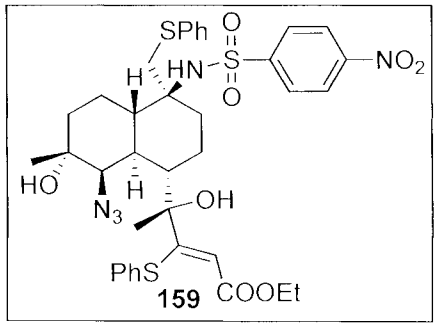


Figure A.1.96 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **158**



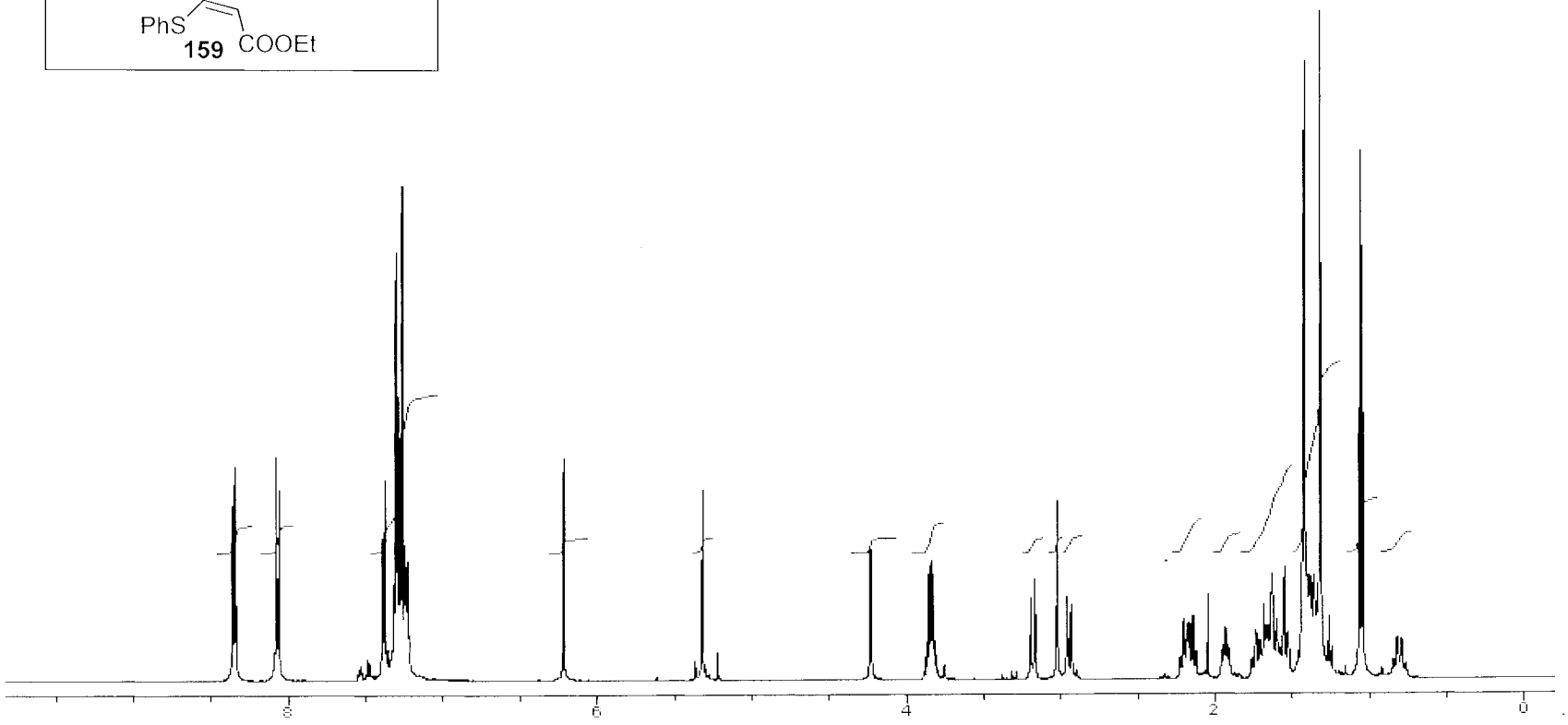


Figure A.1.97 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **159**

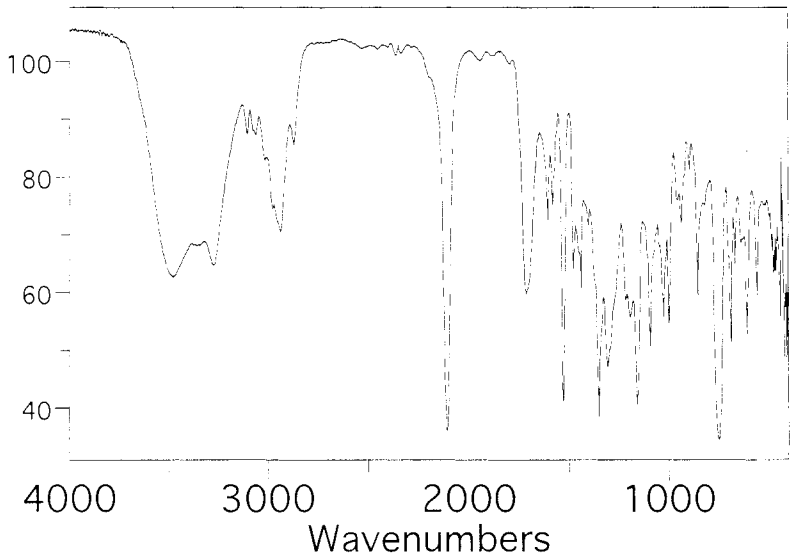


Figure A.1.98 FTIR Spectrum (thin film/NaCl) of Compound **159**

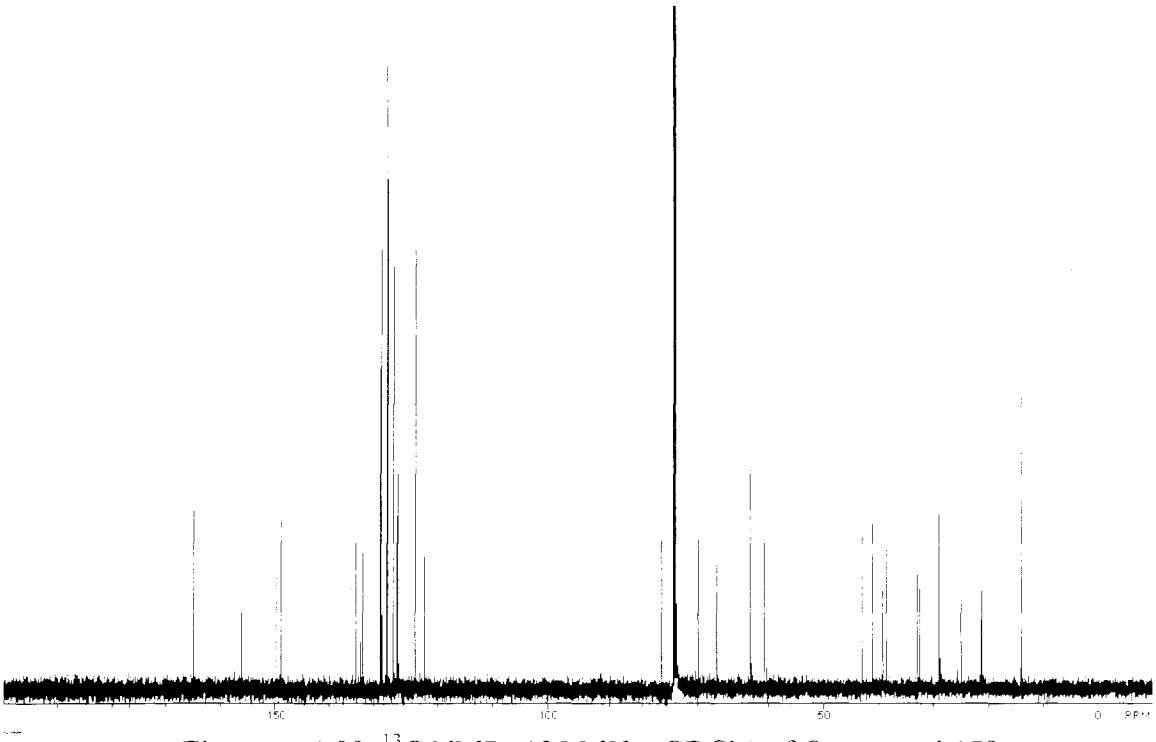


Figure A.1.99 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **159**

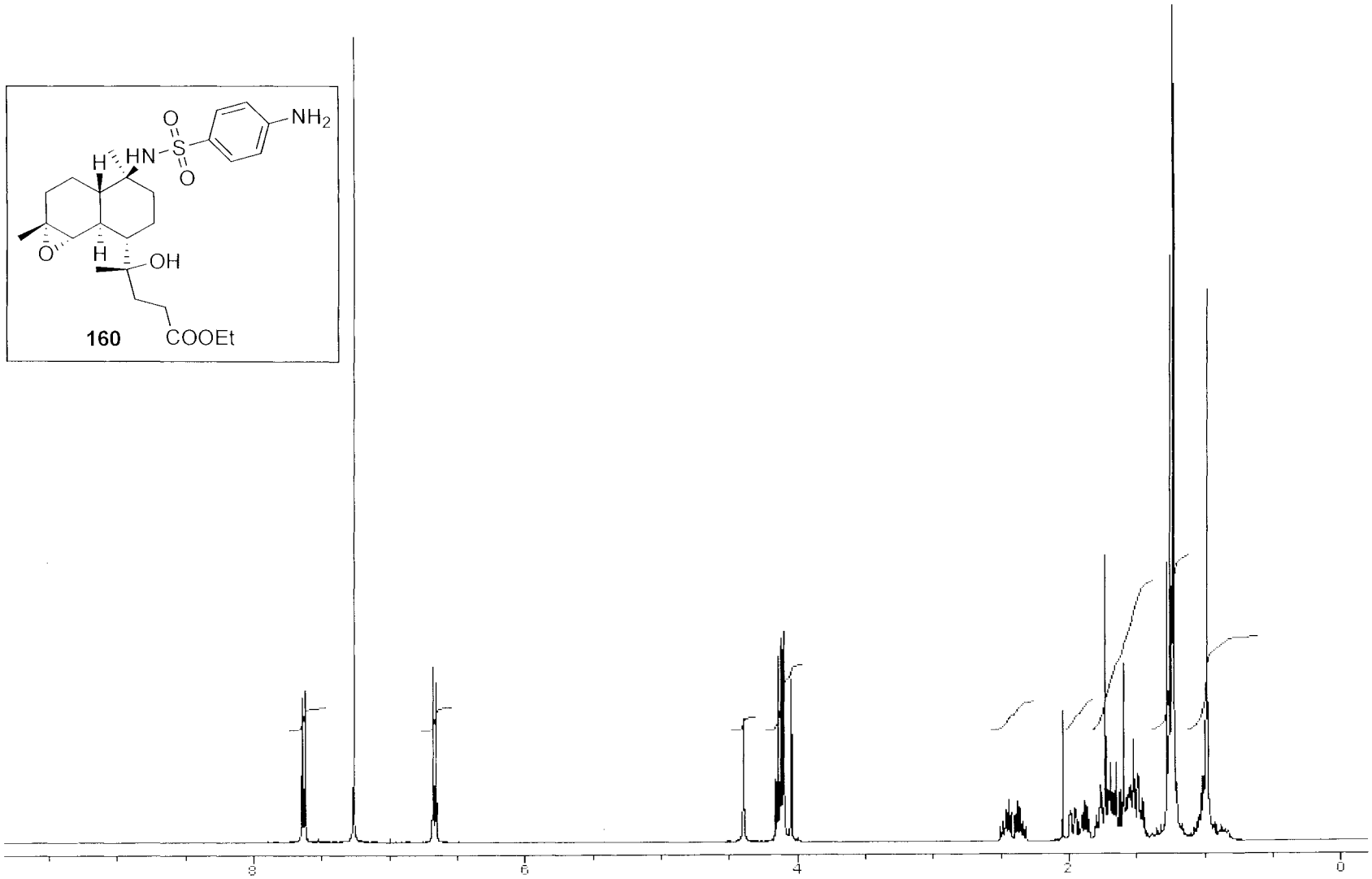


Figure A.1.100 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **160**

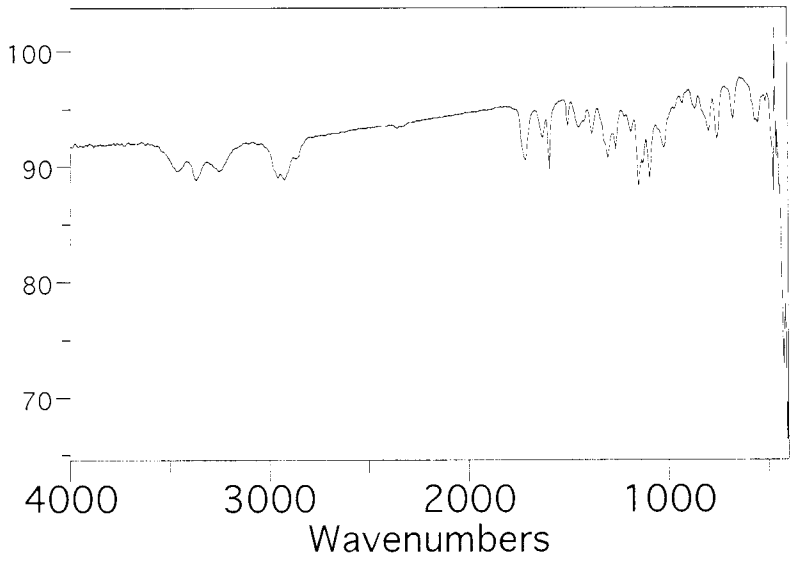


Figure A.1.101 FTIR Spectrum (thin film/NaCl) of Compound **160**

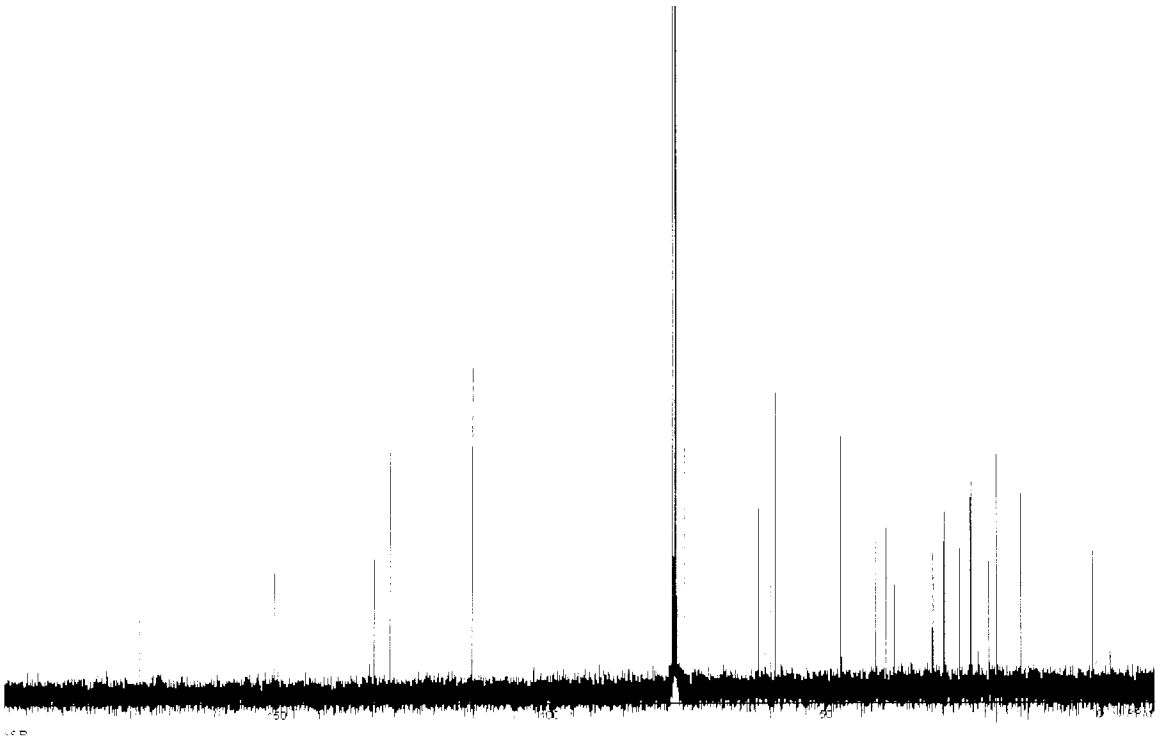


Figure A.1.102 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **160**

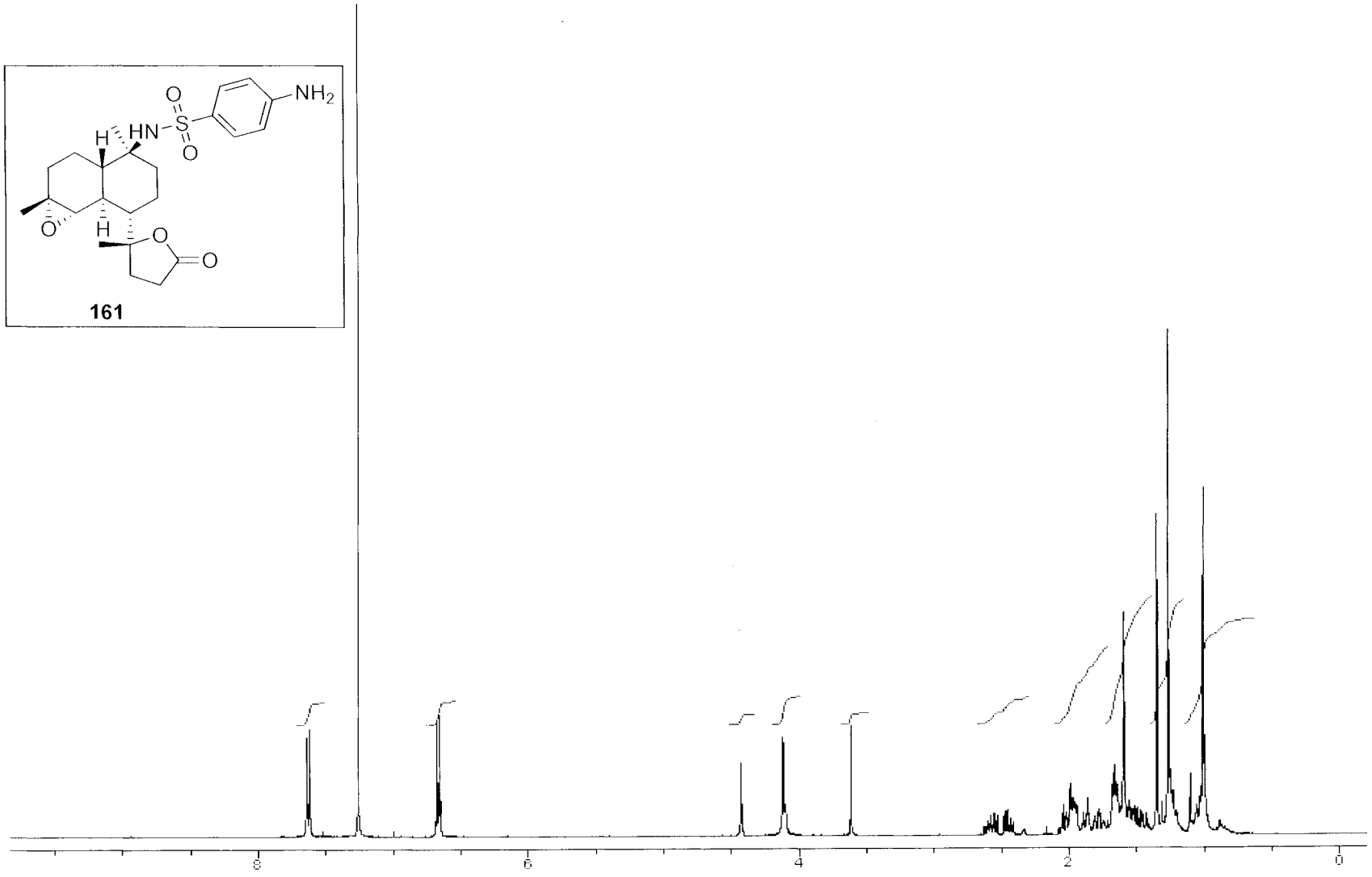


Figure A.1.103 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **161**

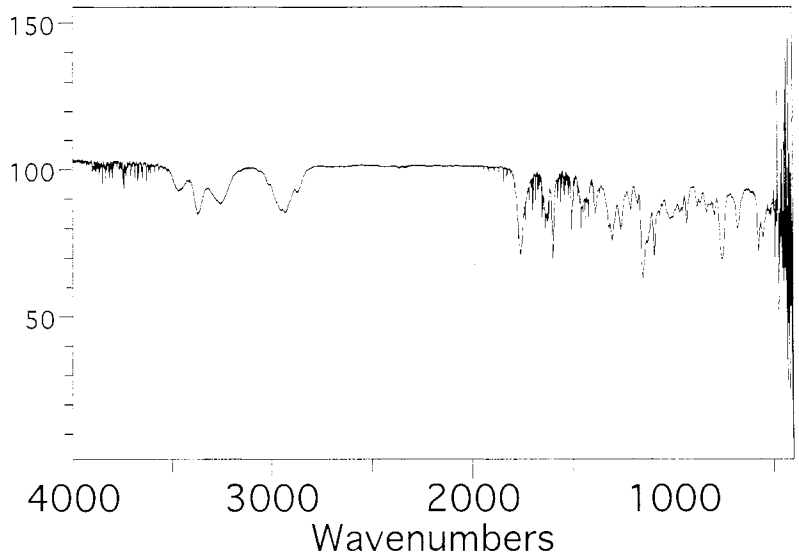


Figure A.1.104 FTIR Spectrum (thin film/NaCl) of Compound **161**

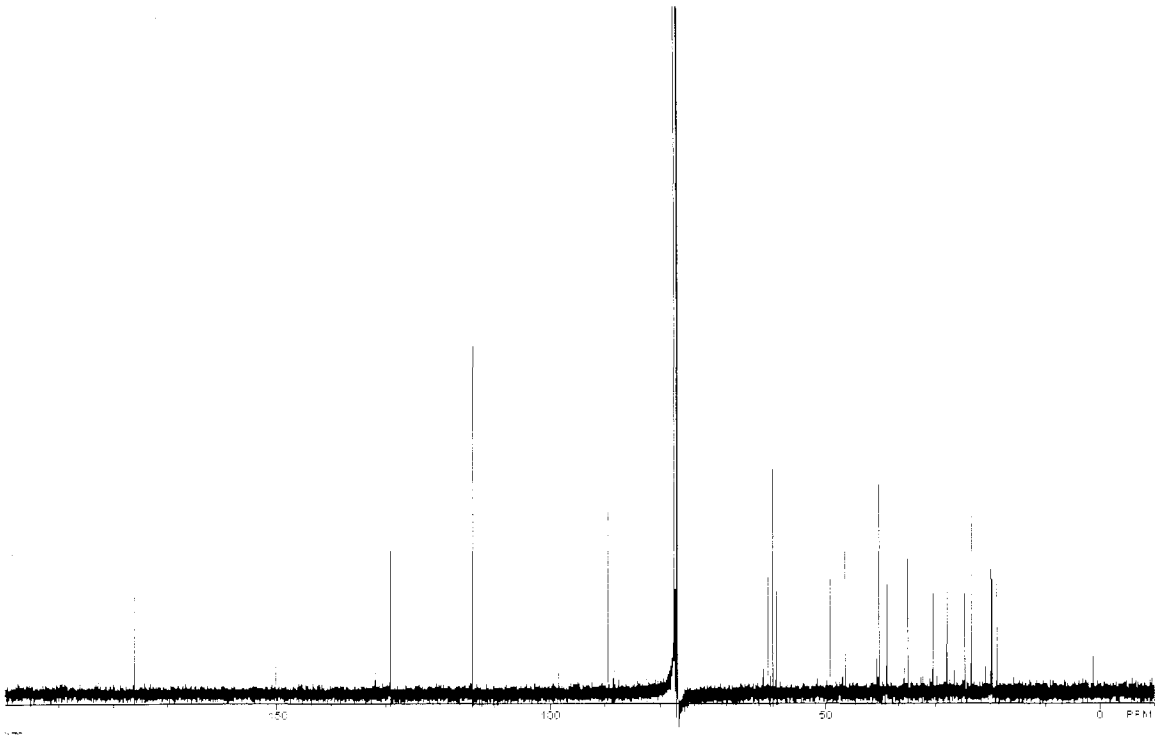


Figure A.1.105 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **161**

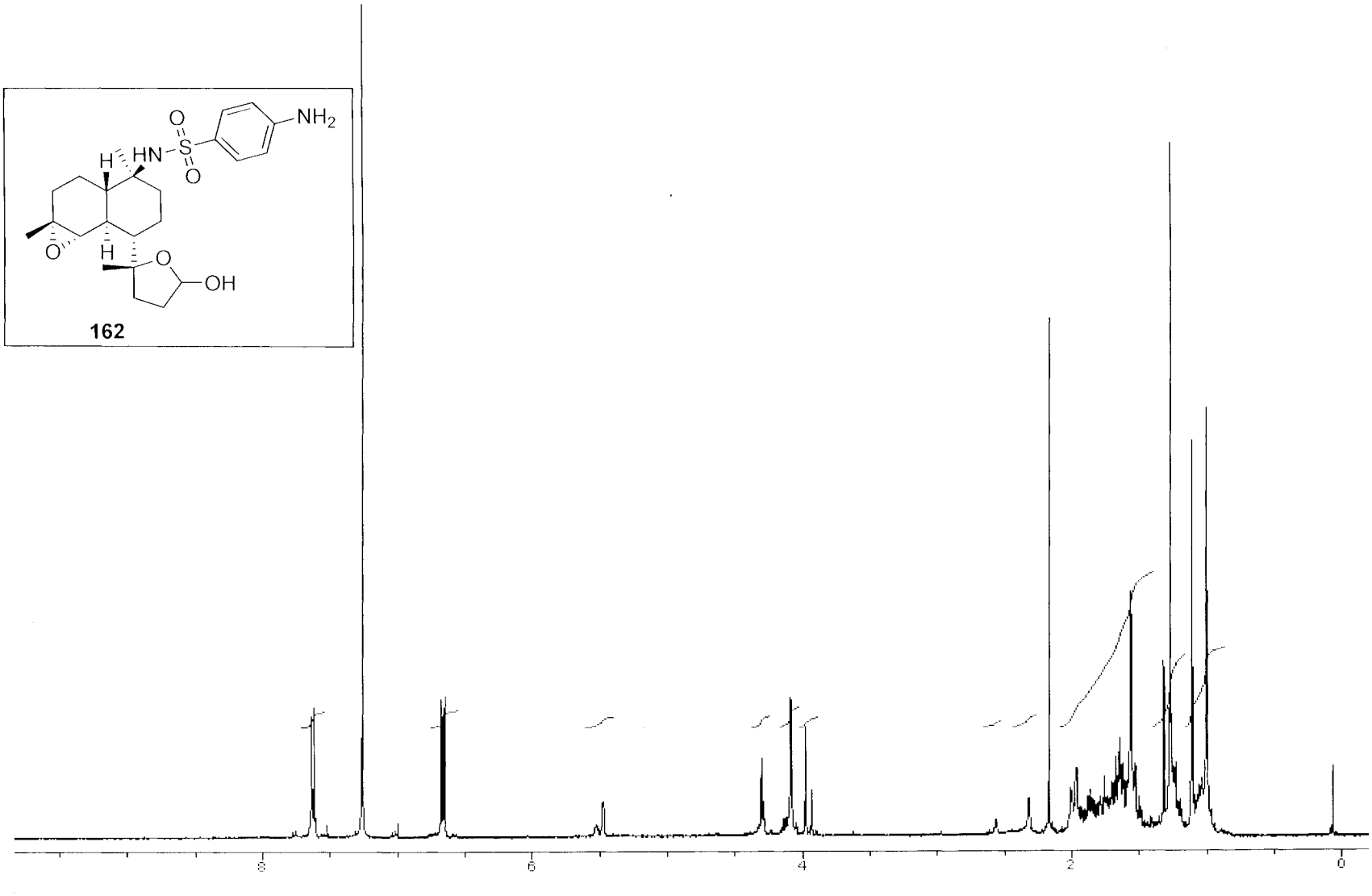


Figure A.1.106 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **162**

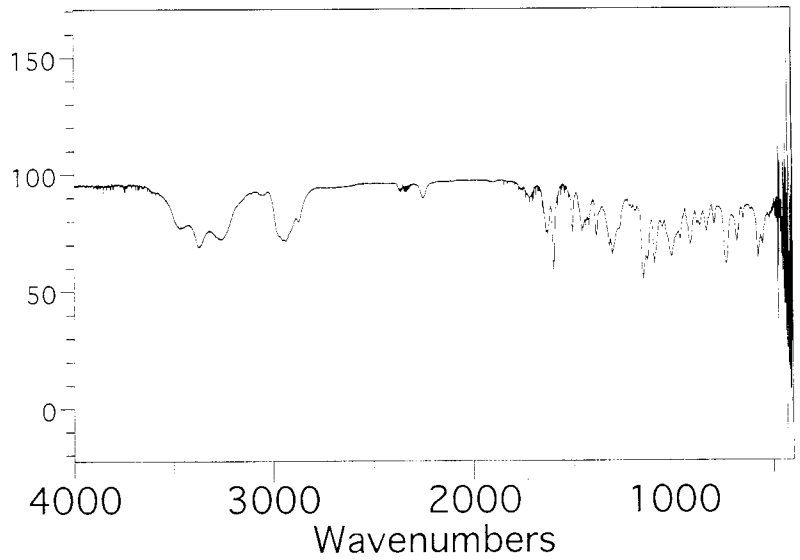


Figure A.1.107 FTIR Spectrum (thin film/NaCl) of Compound **162**

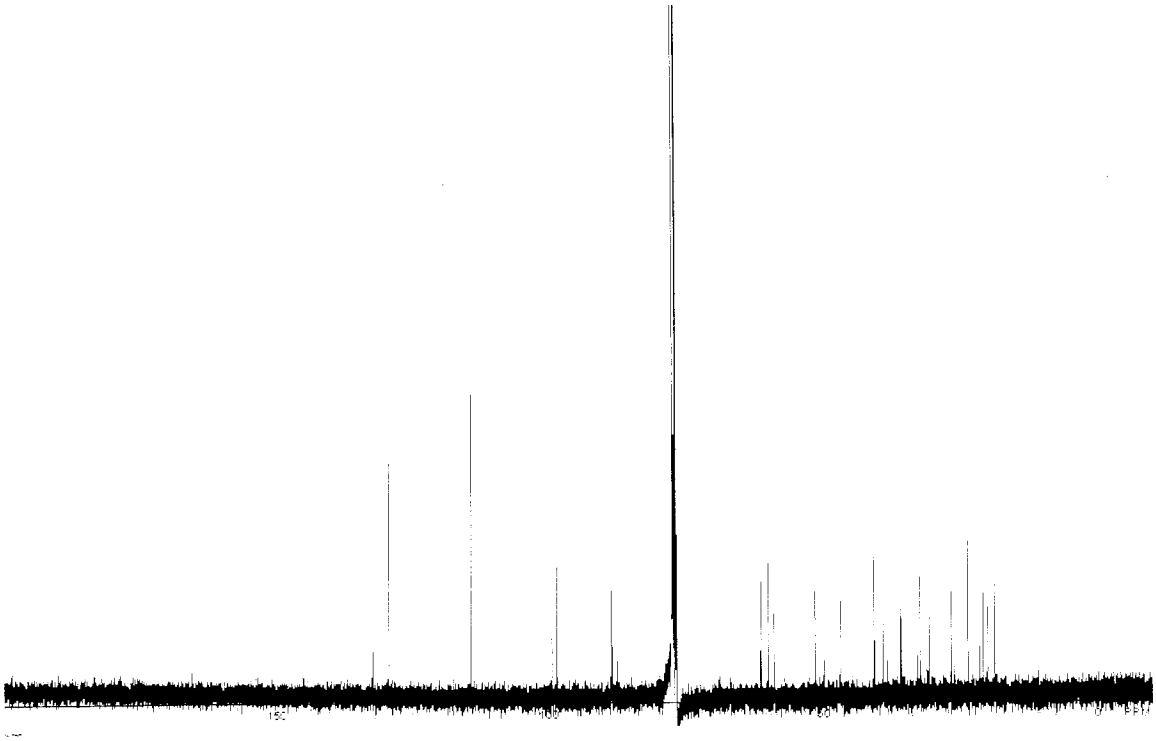
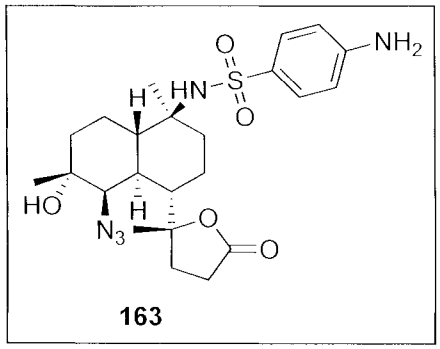


Figure A.1.108 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **162**



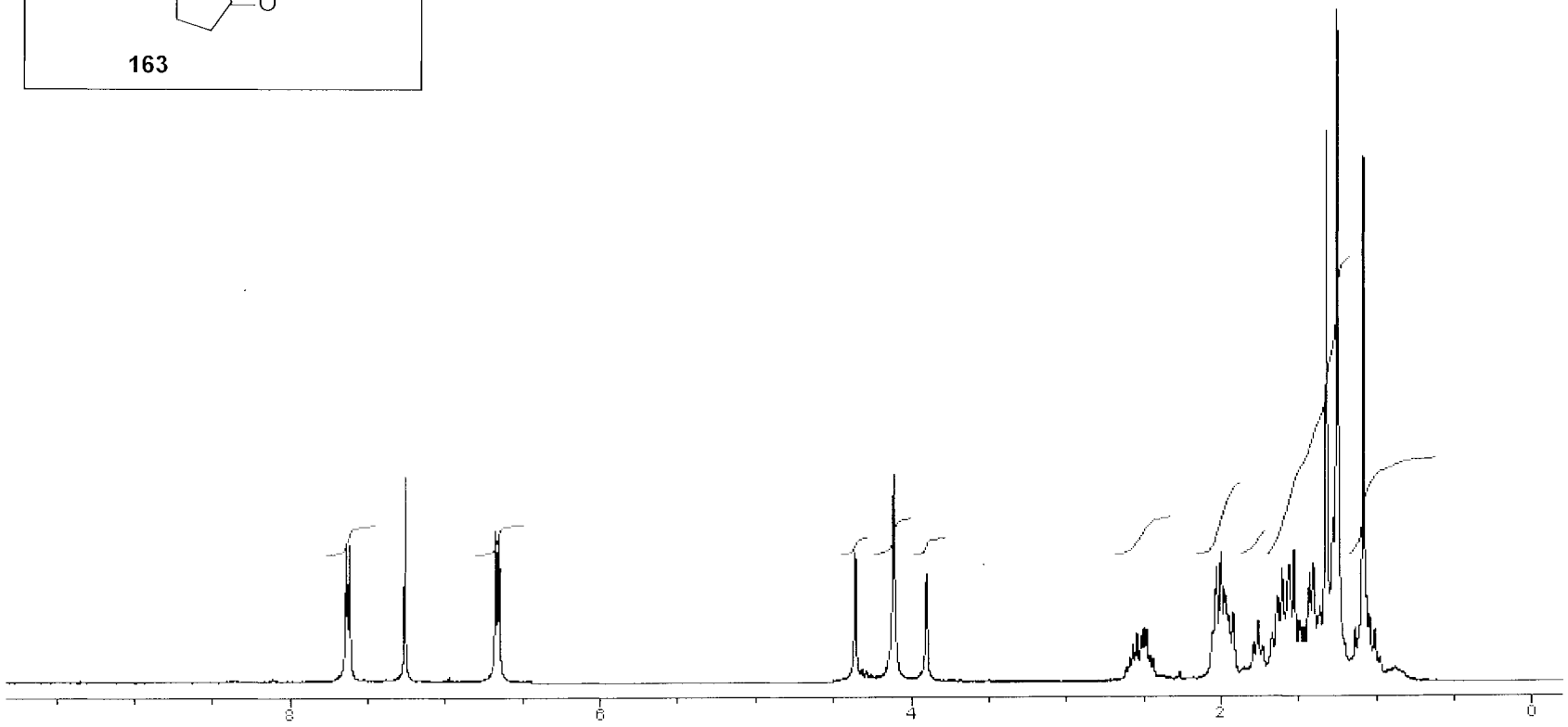


Figure A.1.109 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **163**

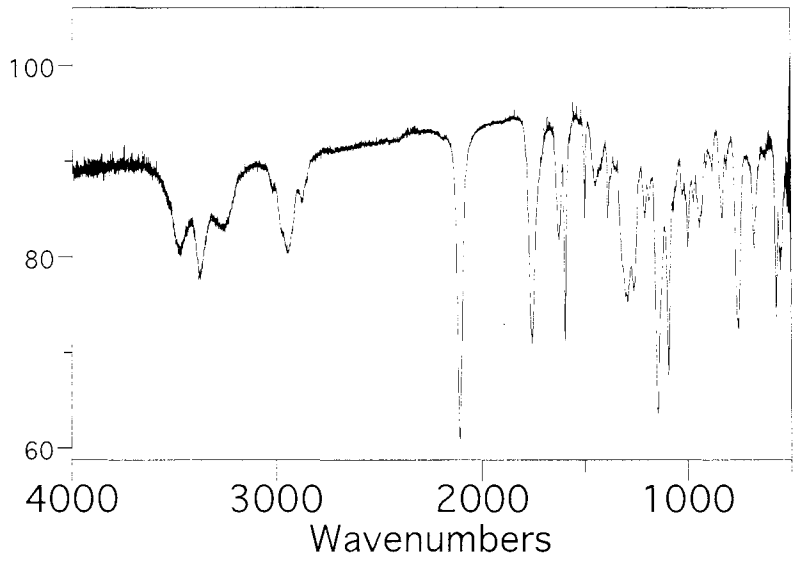


Figure A.1.110 FTIR Spectrum (thin film/NaCl) of Compound **163**

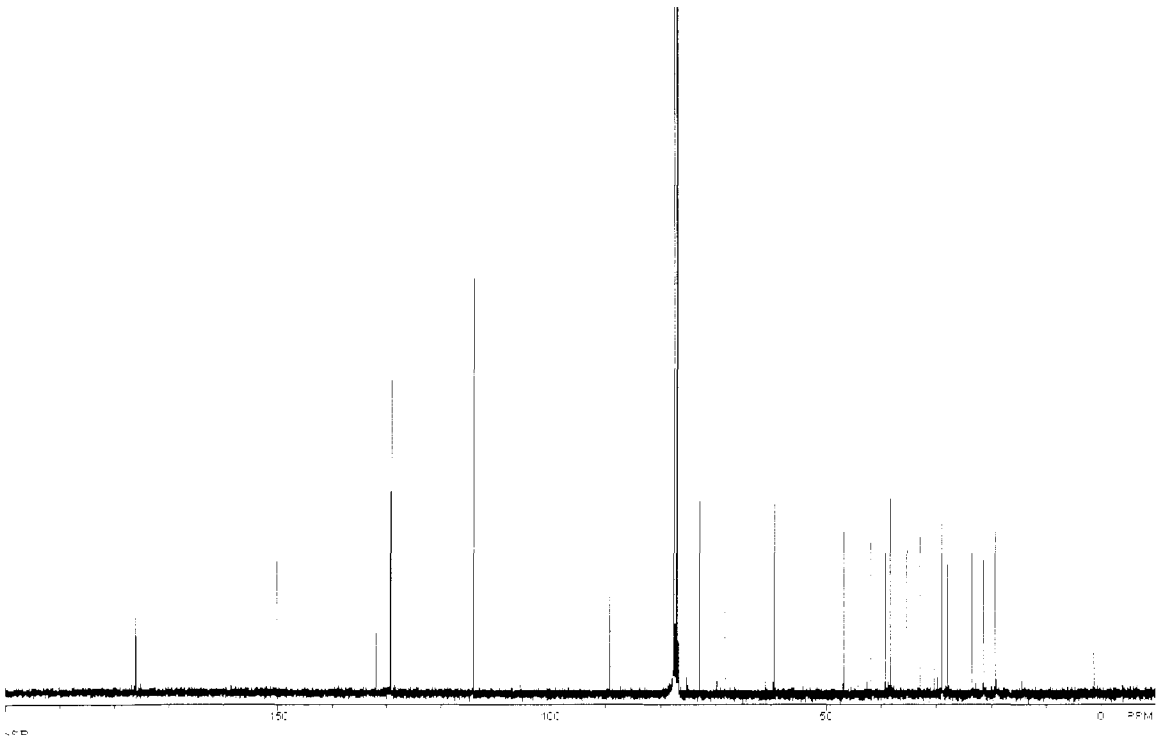


Figure A.1.111 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **163**

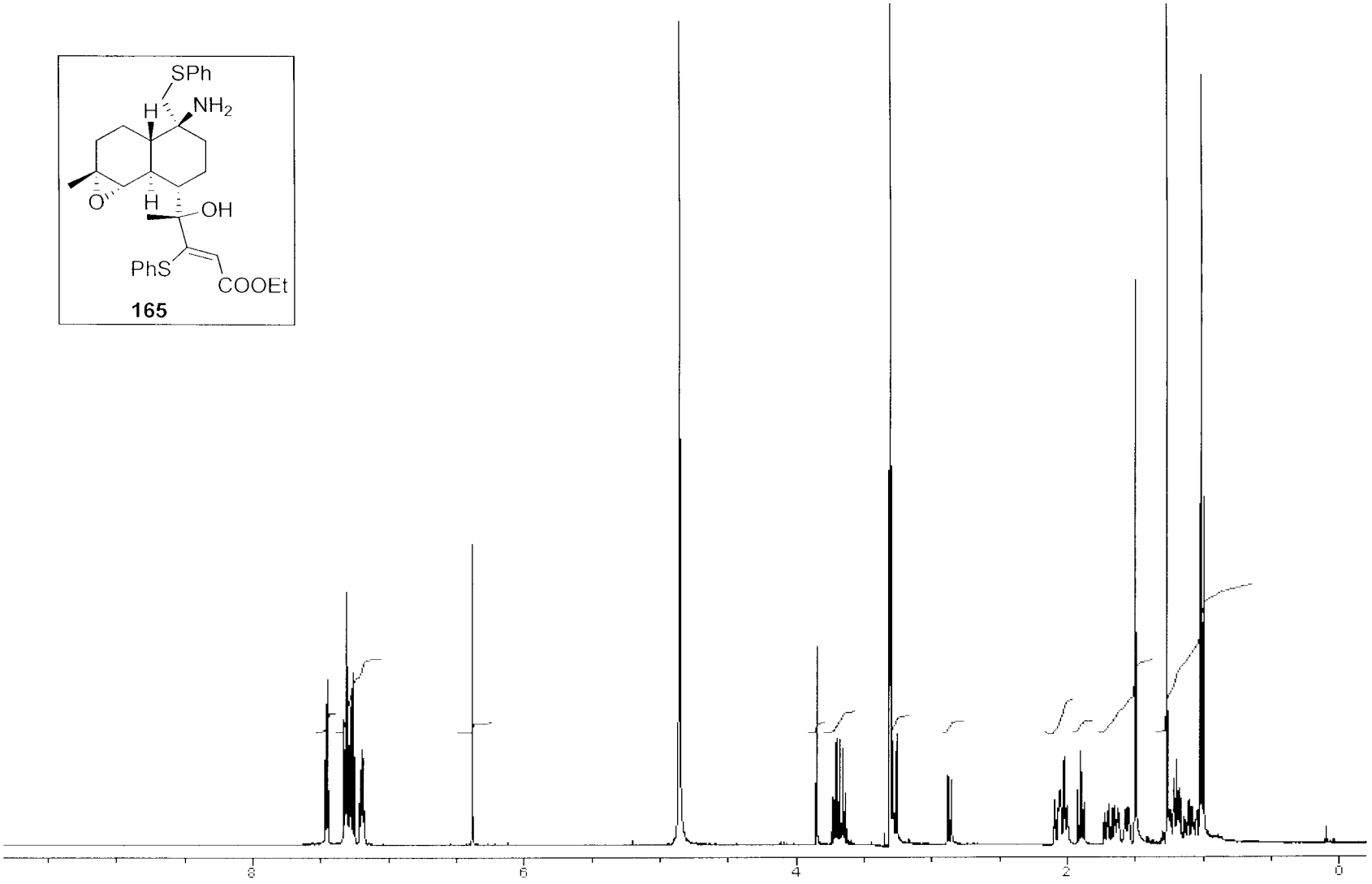


Figure A.1.112 ^{1}H NMR (400 MHz, CD_3OD) of Compound **165**

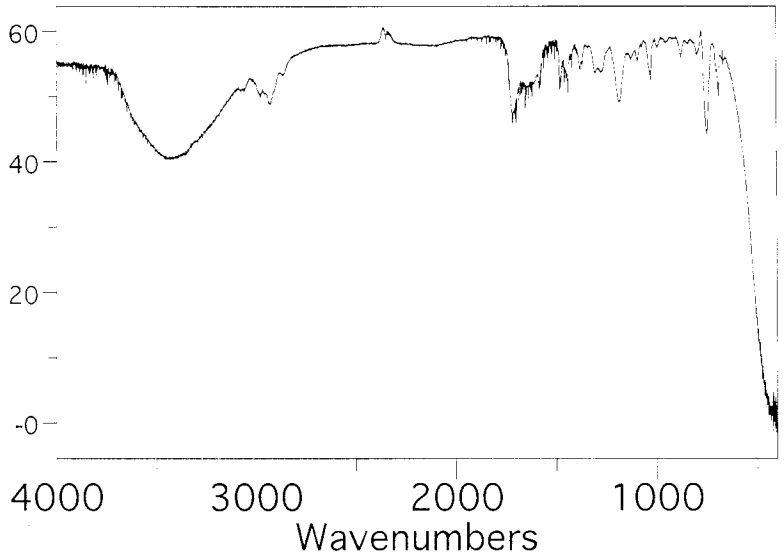


Figure A.1.113 FTIR Spectrum (thin film/NaCl) of Compound **165**

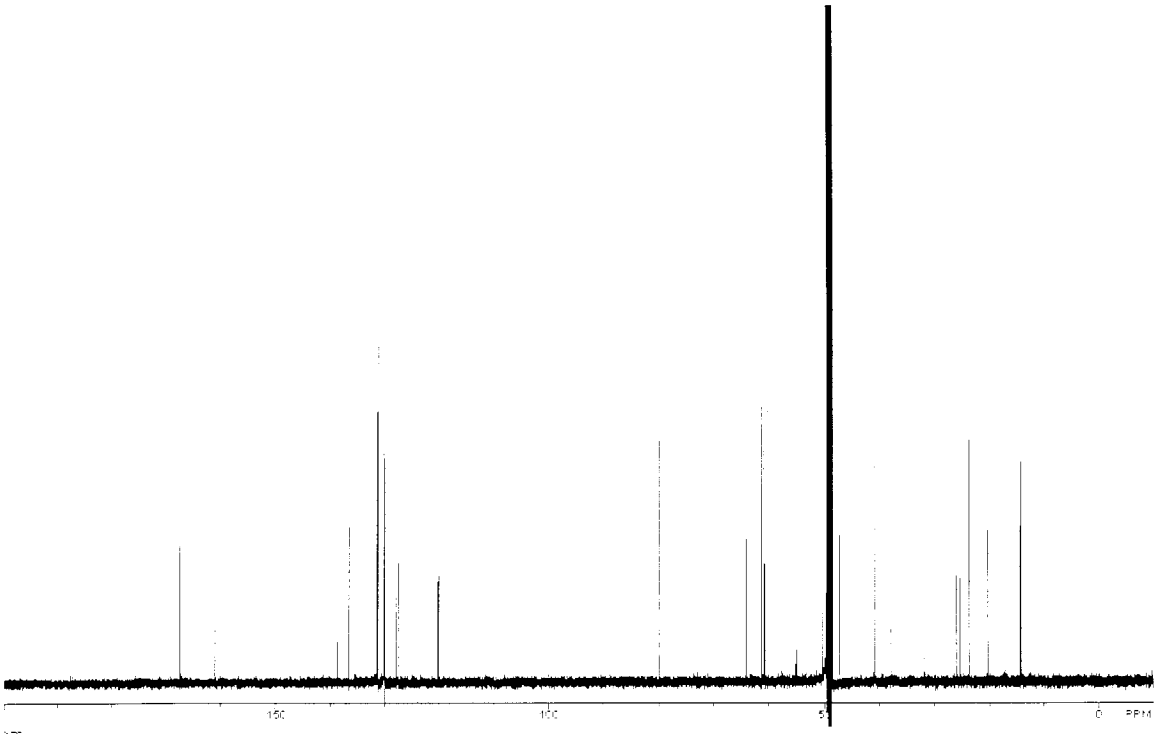
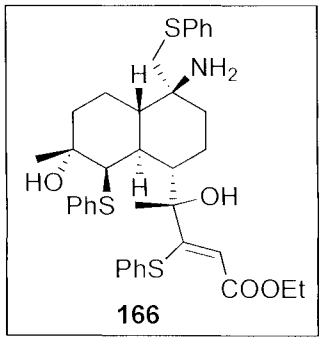


Figure A.1.114 ^{13}C NMR (100 MHz, CD_3OD) of Compound **165**



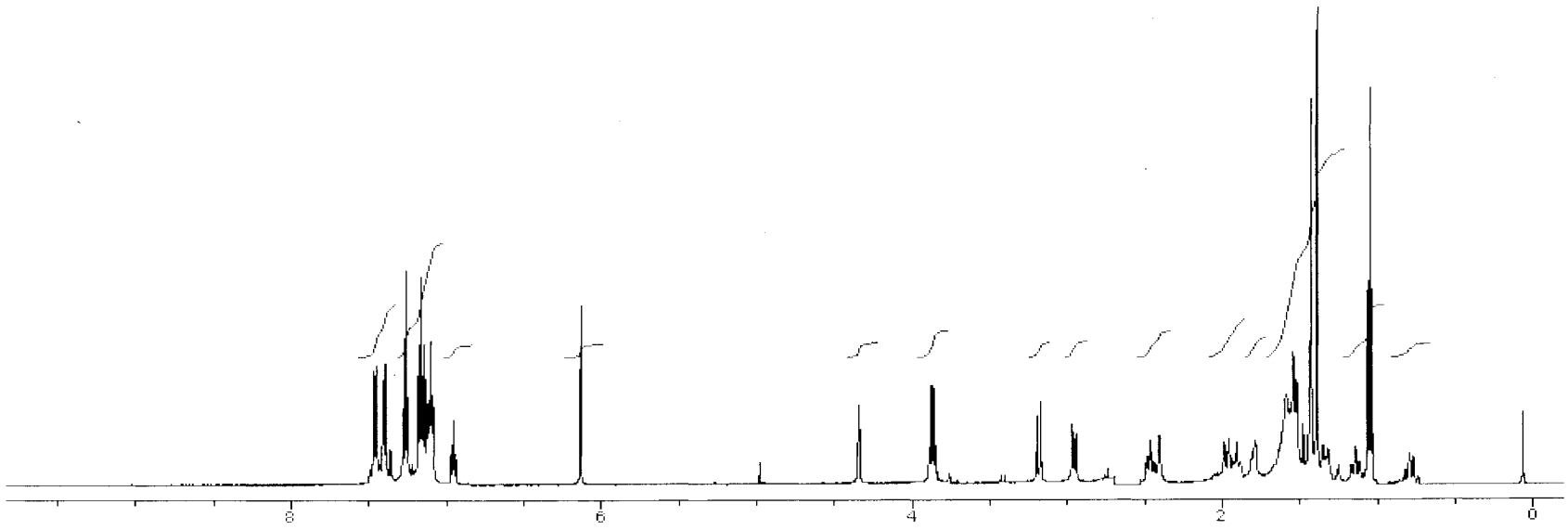


Figure A.1.115 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **166**

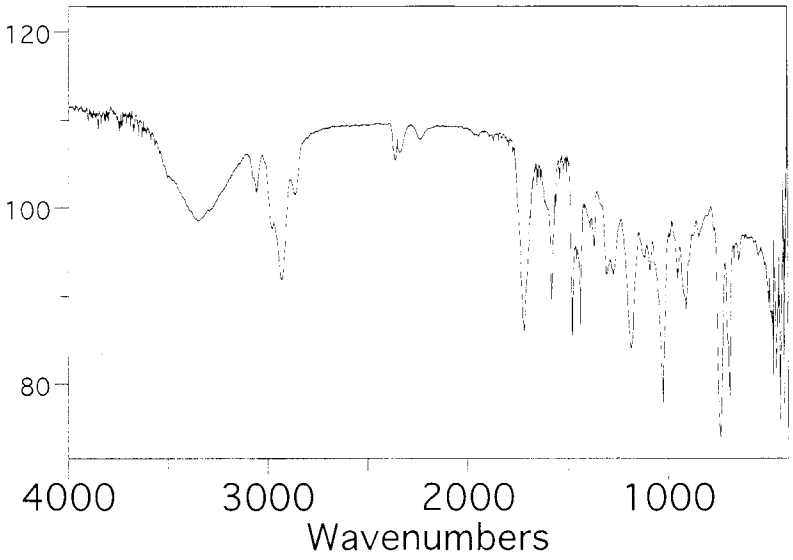


Figure A.1.116 FTIR Spectrum (thin film/NaCl) of Compound **166**

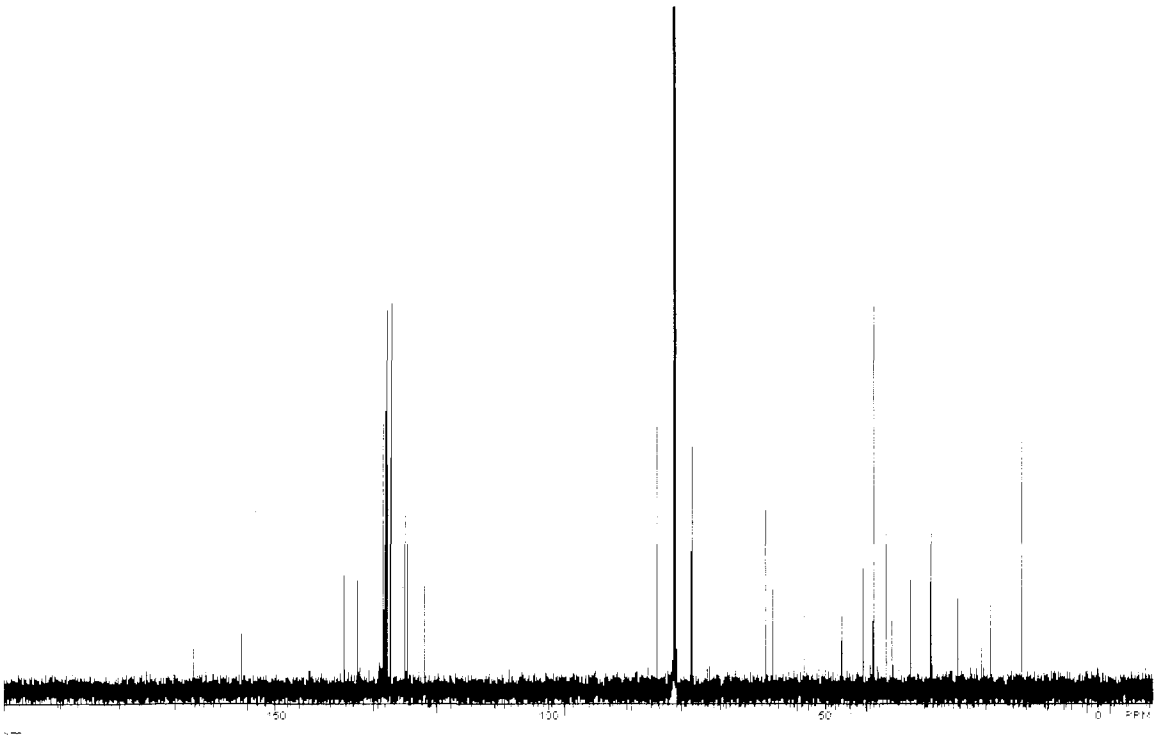


Figure A.1.117 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **166**

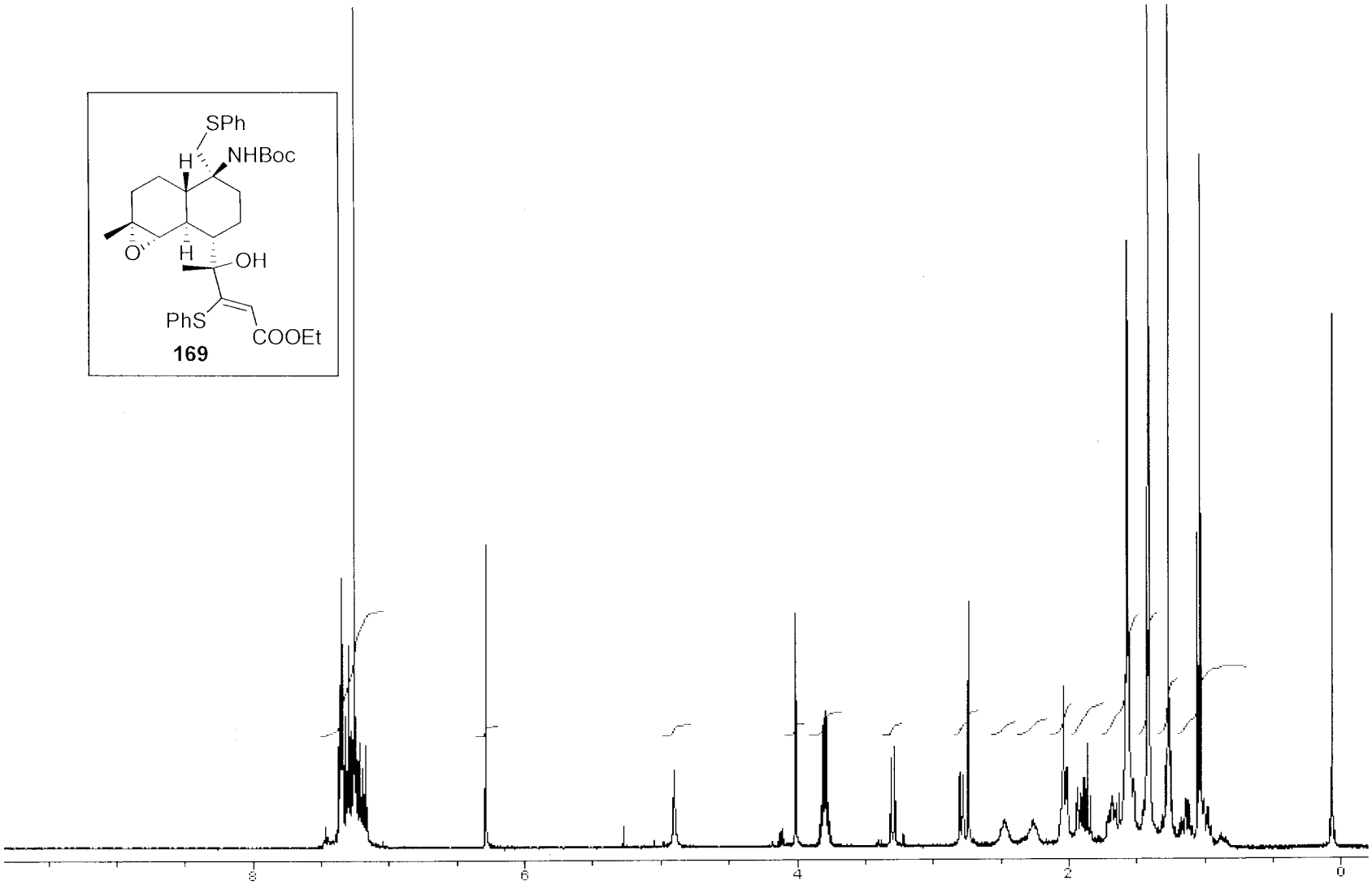


Figure A.1.118 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **169**

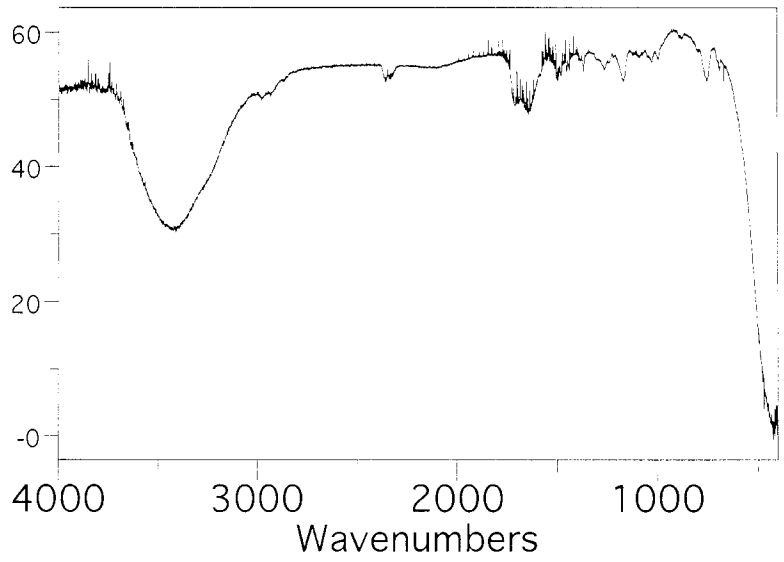


Figure A.1.119 FTIR Spectrum (thin film/NaCl) of Compound **169**

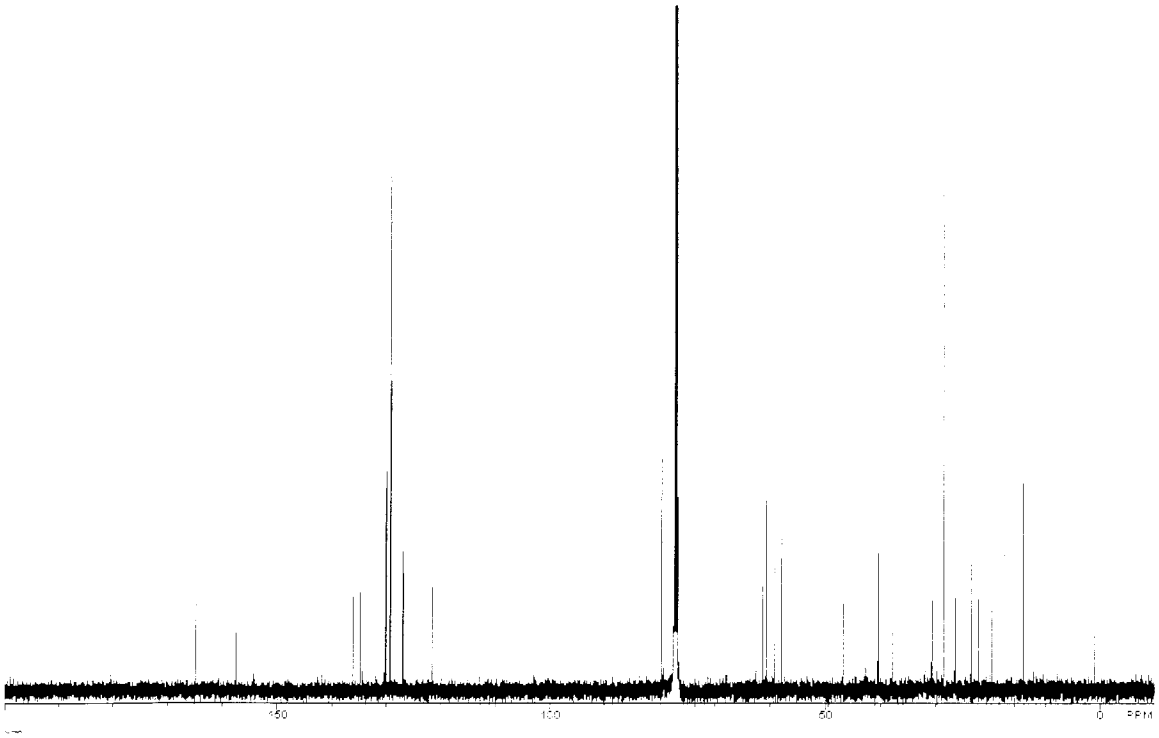


Figure A.1.120 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **169**

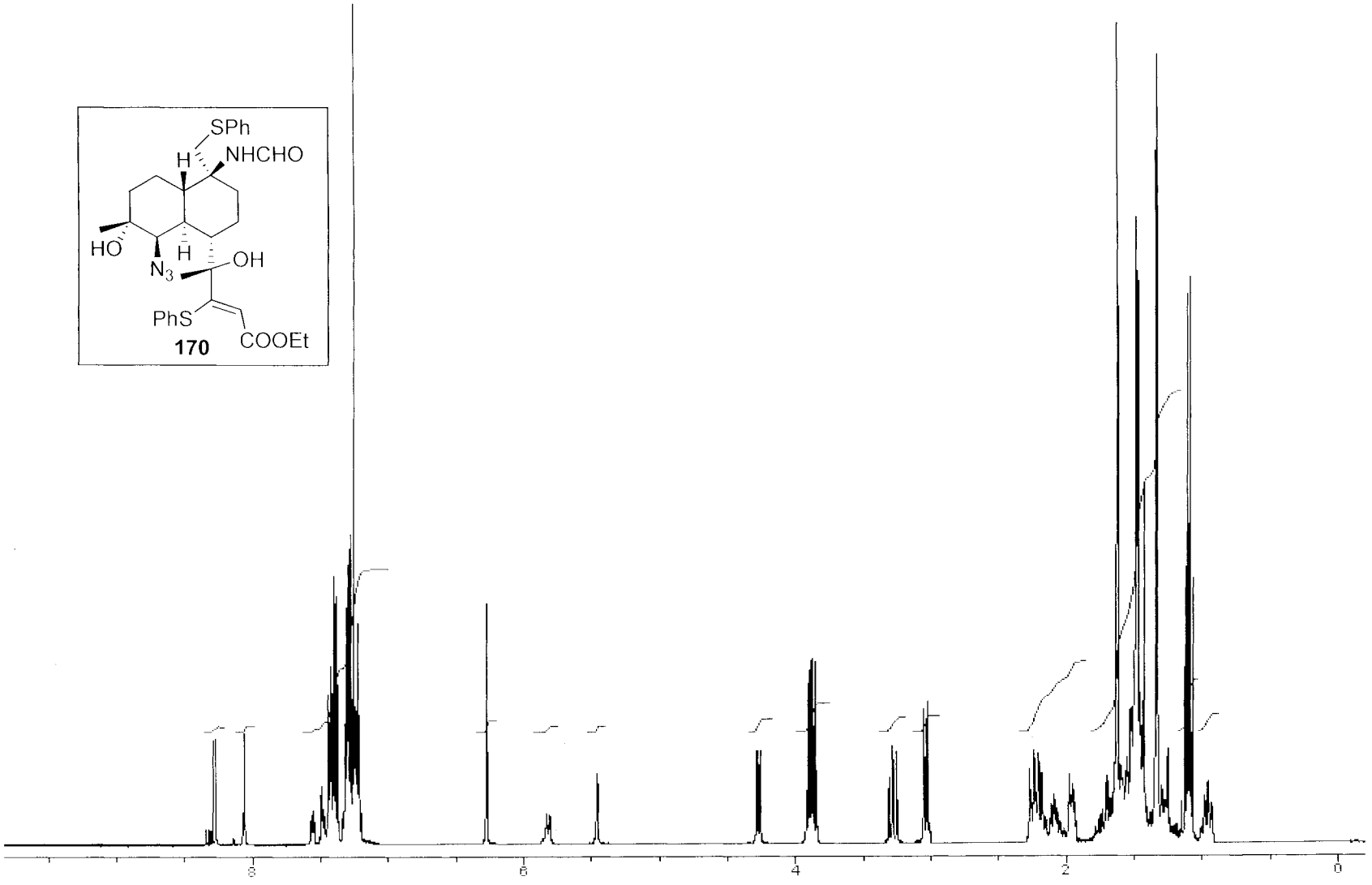


Figure A.1.121 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **170**

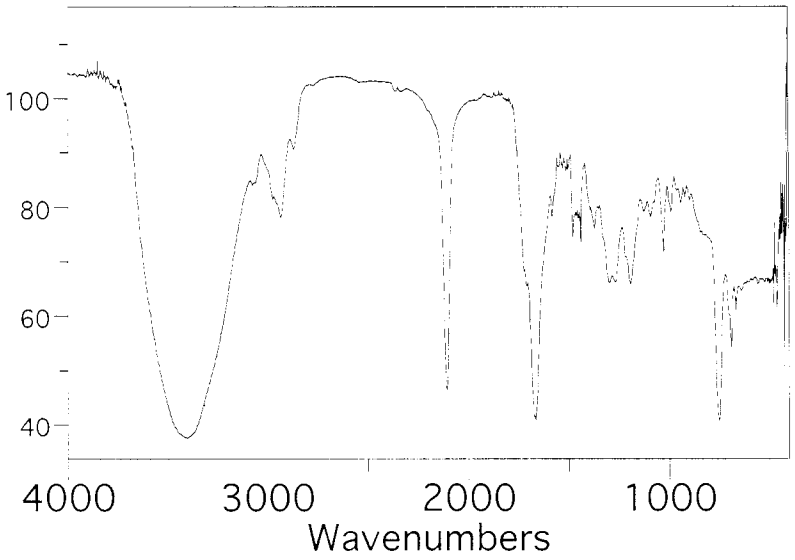


Figure A.1.122 FTIR Spectrum (thin film/NaCl) of Compound **170**

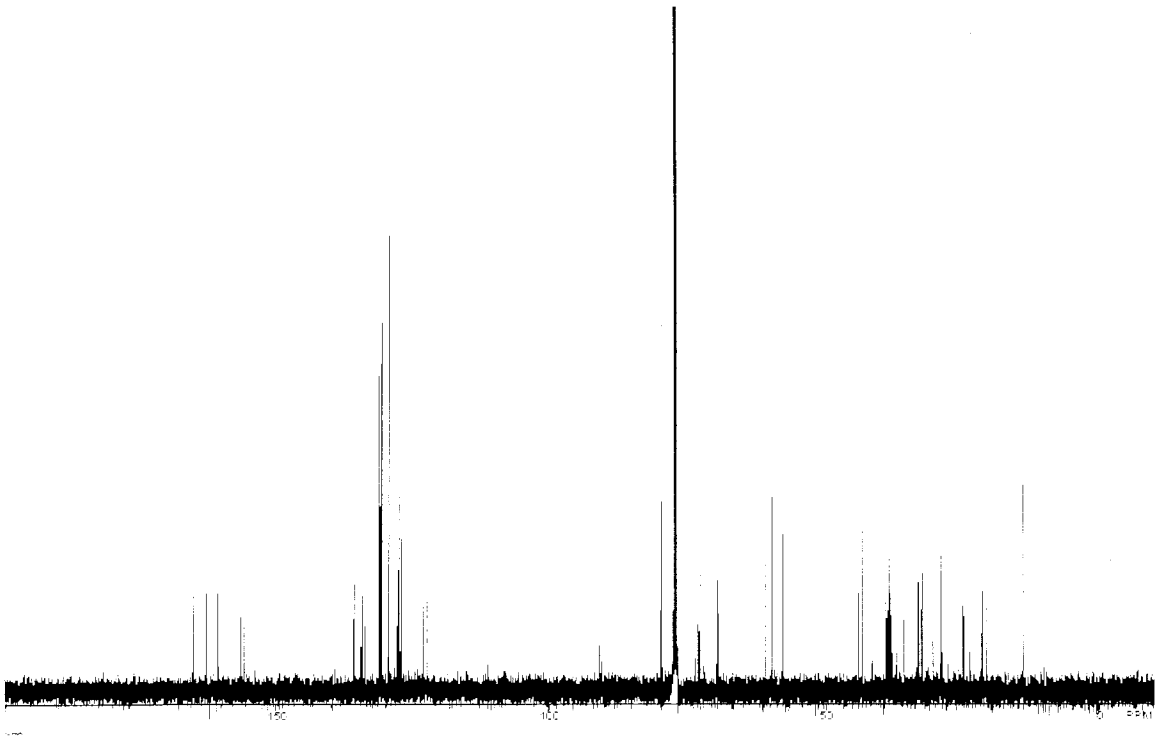


Figure A.1.123 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **170**

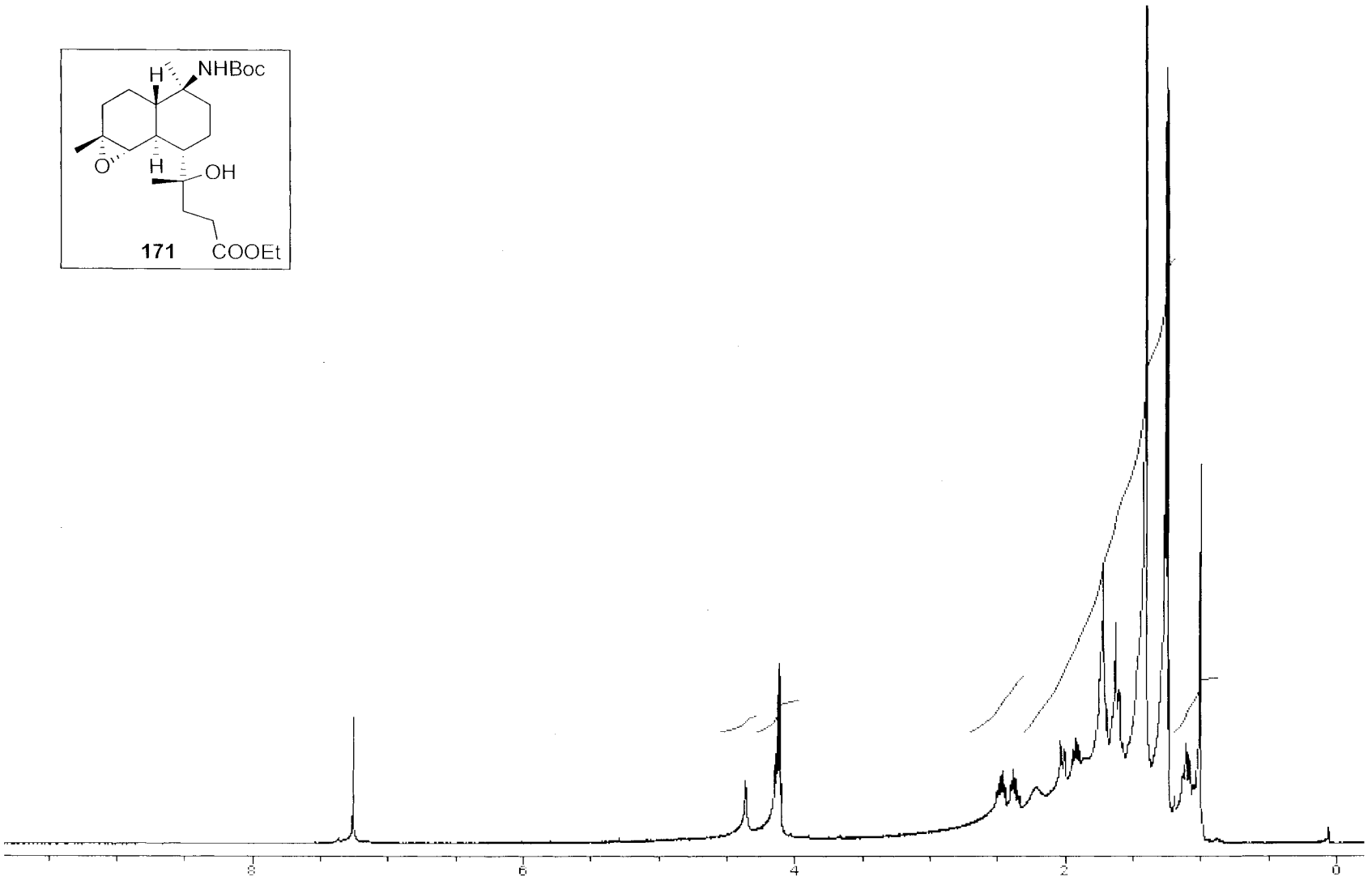


Figure A.1.124 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **171**

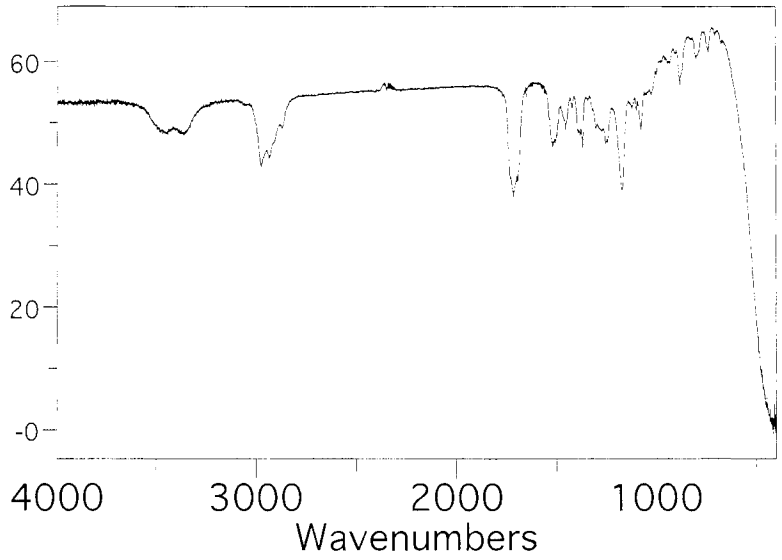


Figure A.1.125 FTIR Spectrum (thin film/NaCl) of Compound **171**

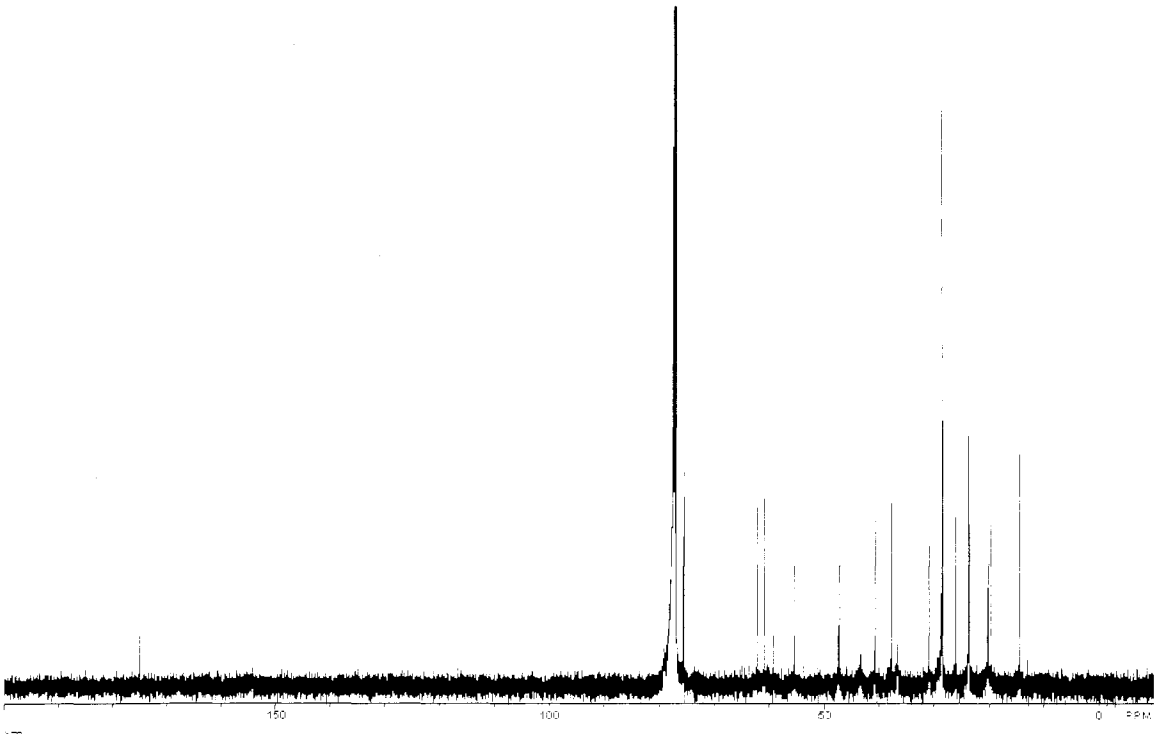


Figure A.1.126 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **171**

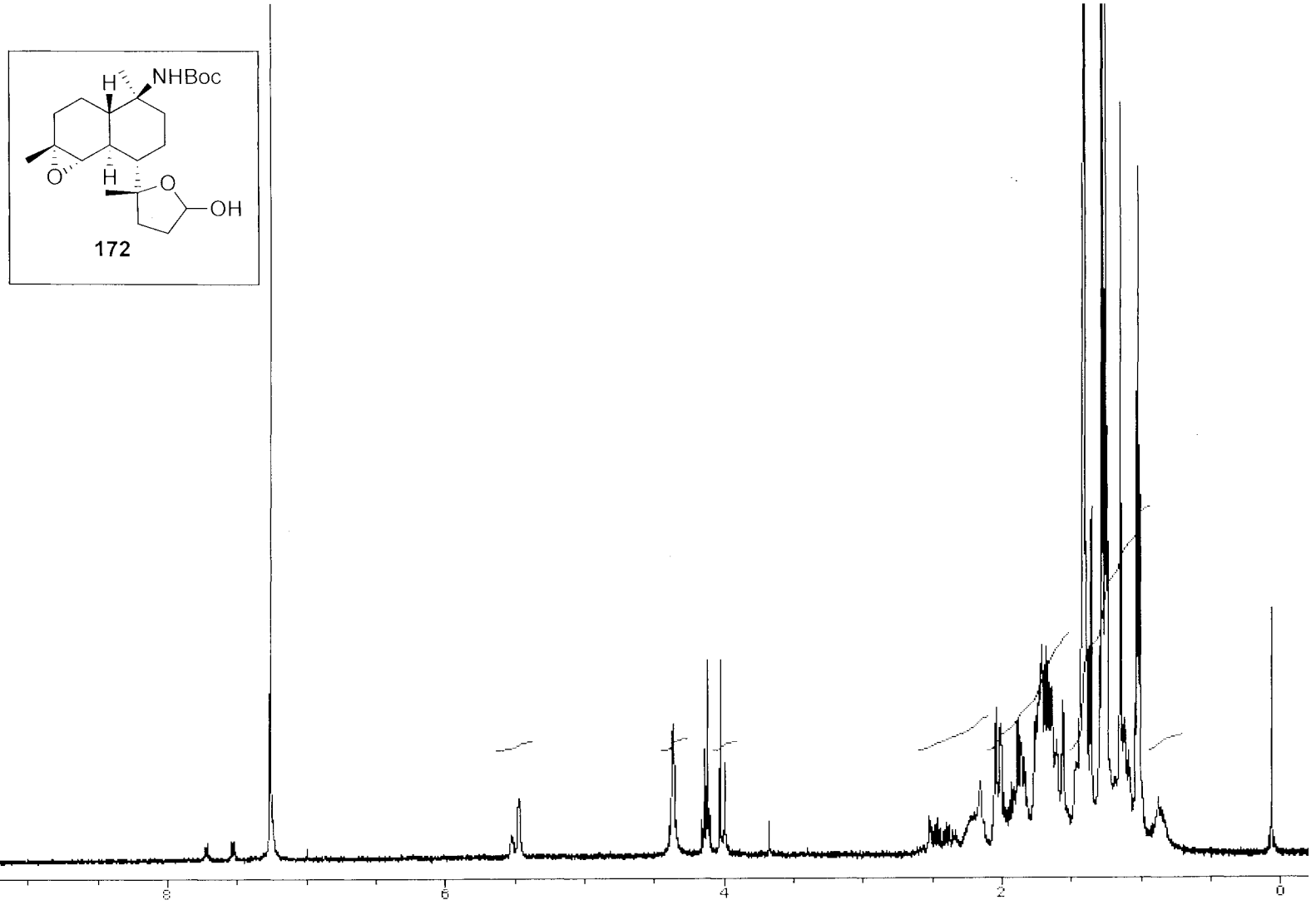


Figure A.1.127 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **172**

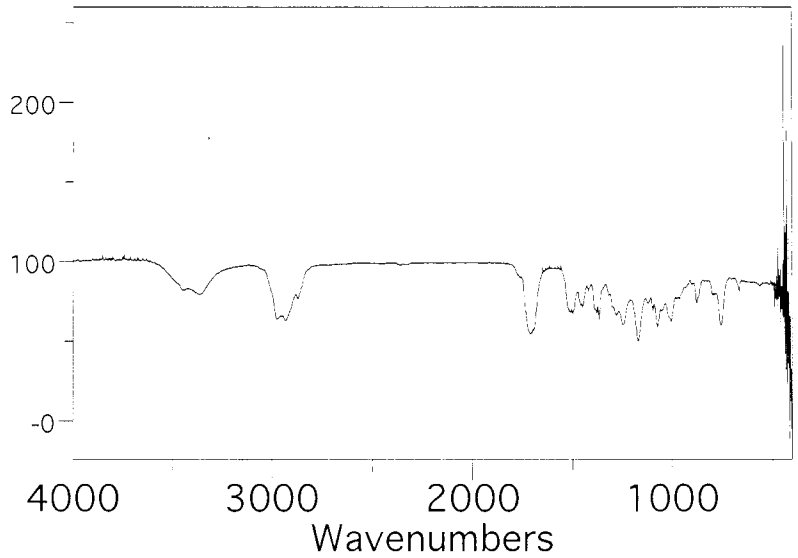


Figure A.1.128 FTIR Spectrum (thin film/NaCl) of Compound **172**

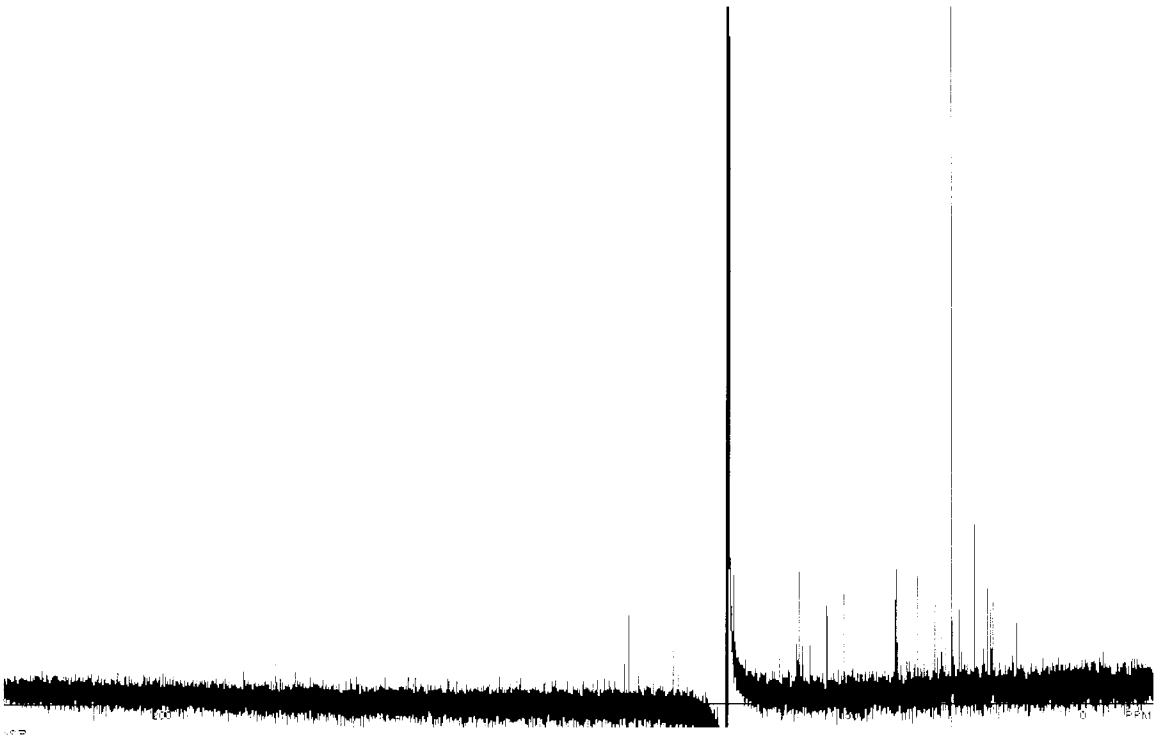


Figure A.1.129 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **172**

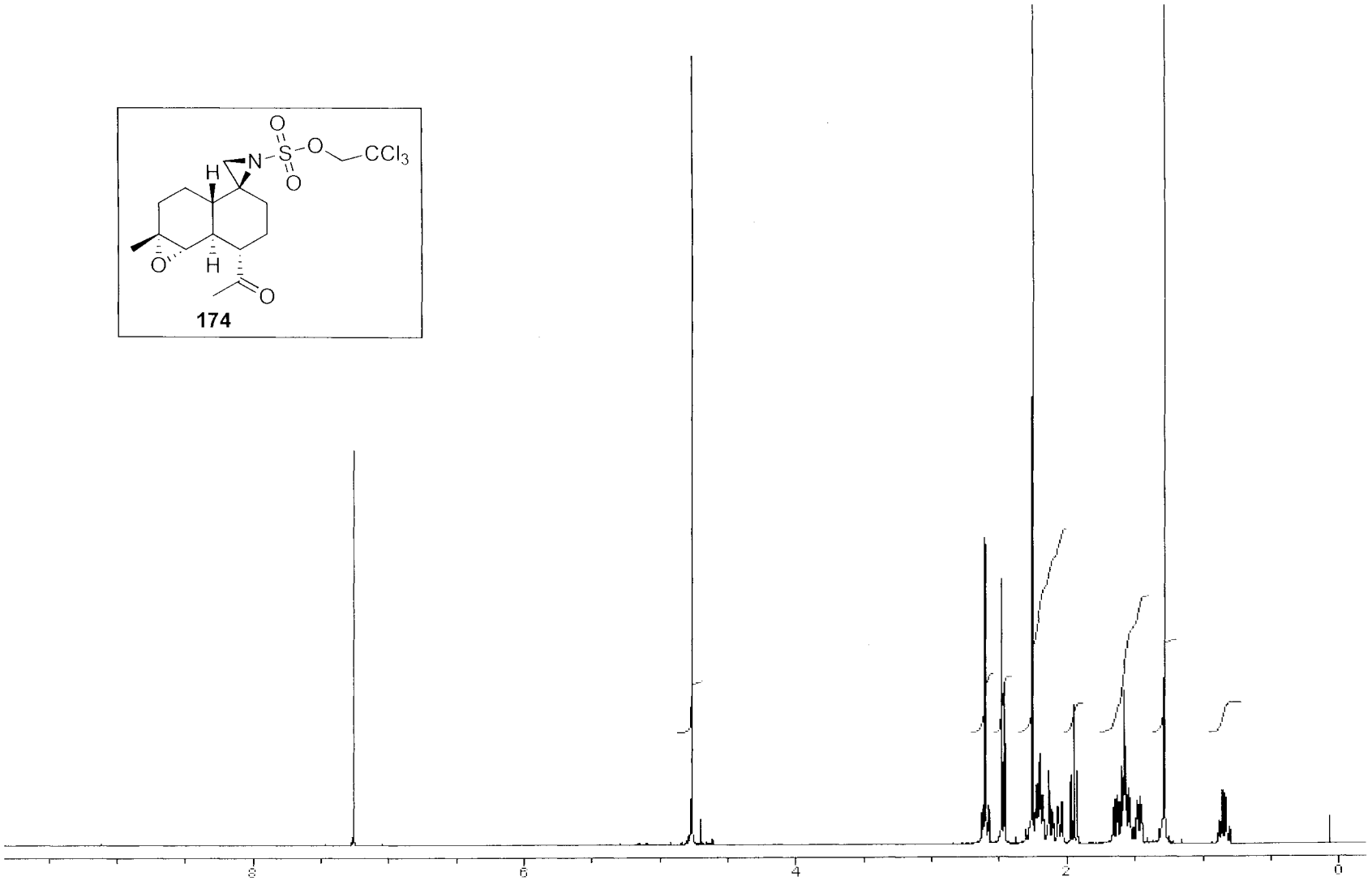


Figure A.1.130 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **174**

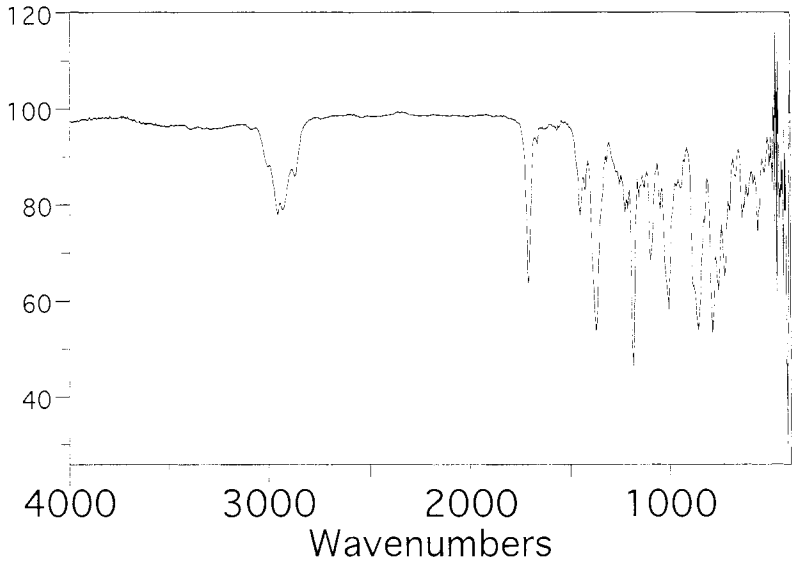


Figure A.1.131 FTIR Spectrum (thin film/NaCl) of Compound **174**

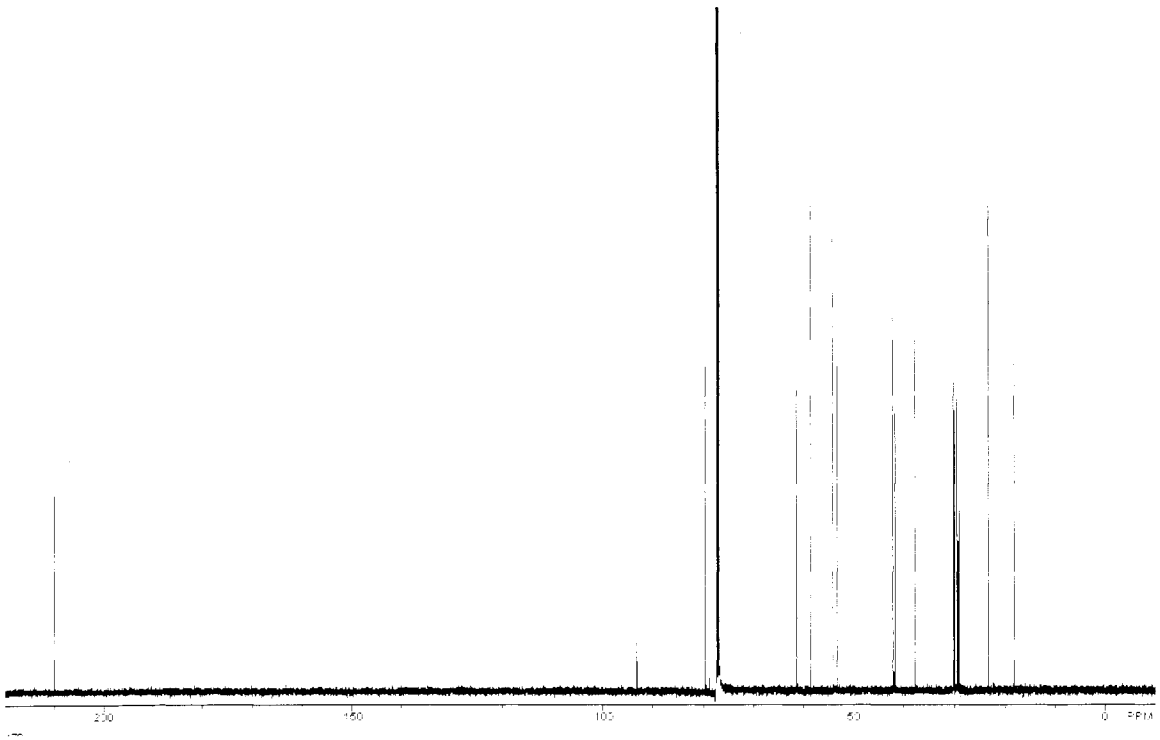


Figure A.1.132 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **174**

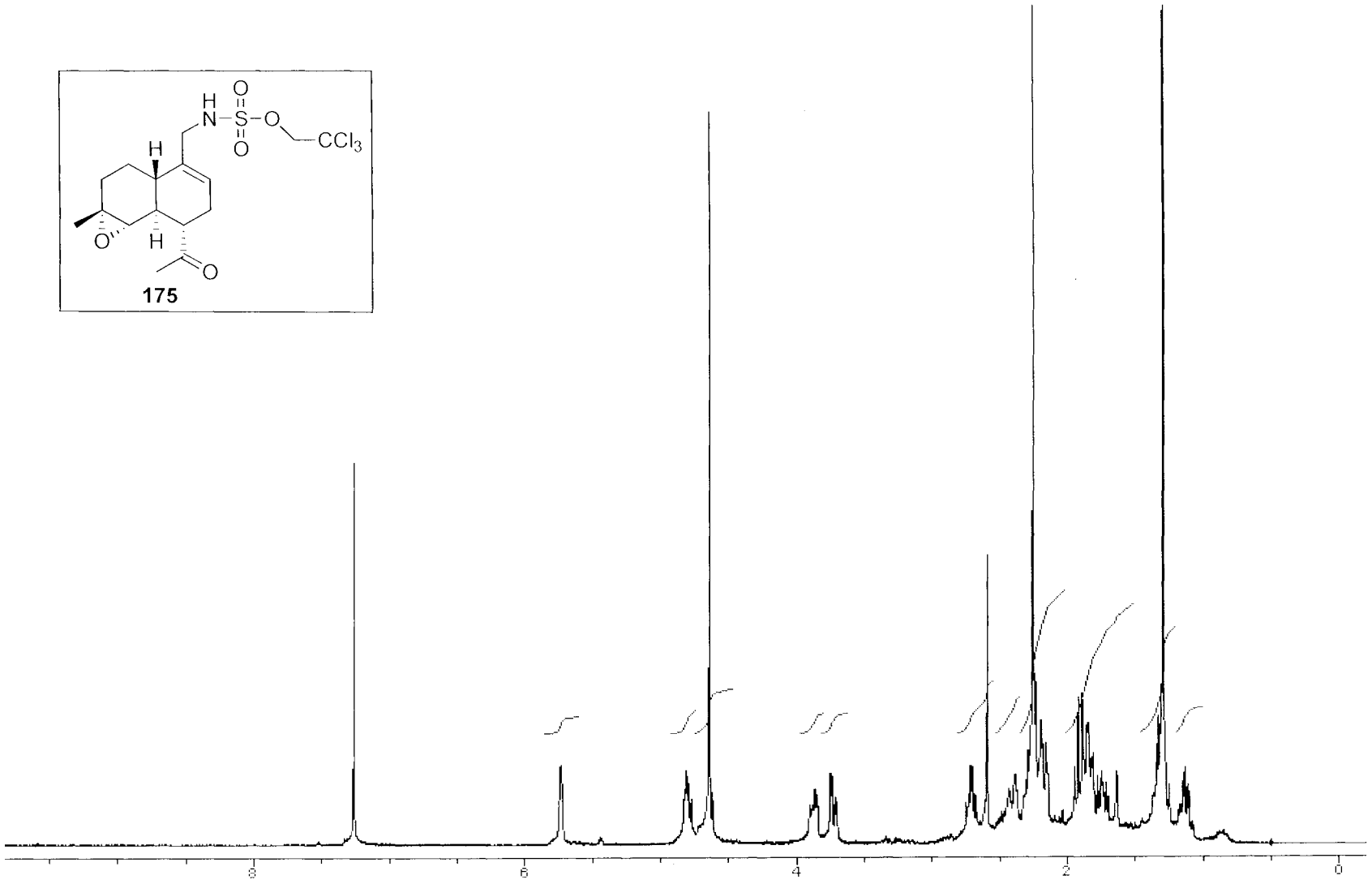


Figure A.1.133 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **175**

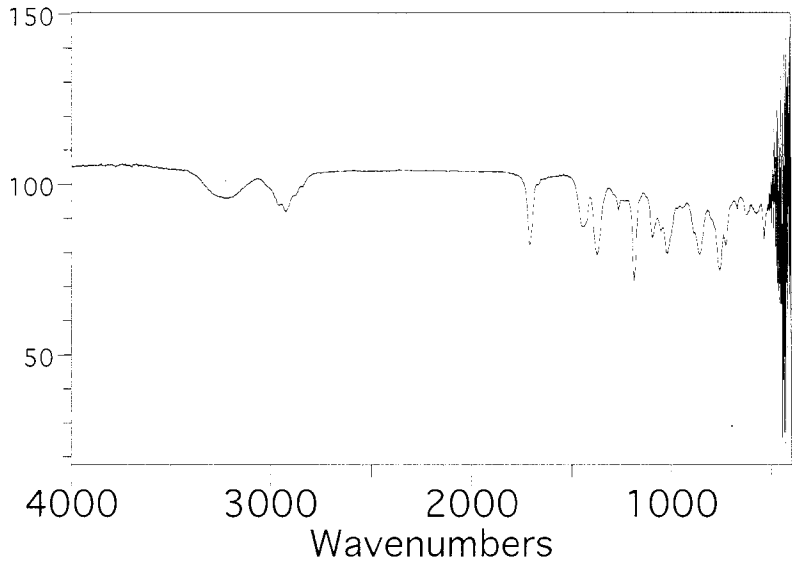


Figure A.1.134 FTIR Spectrum (thin film/NaCl) of Compound **175**

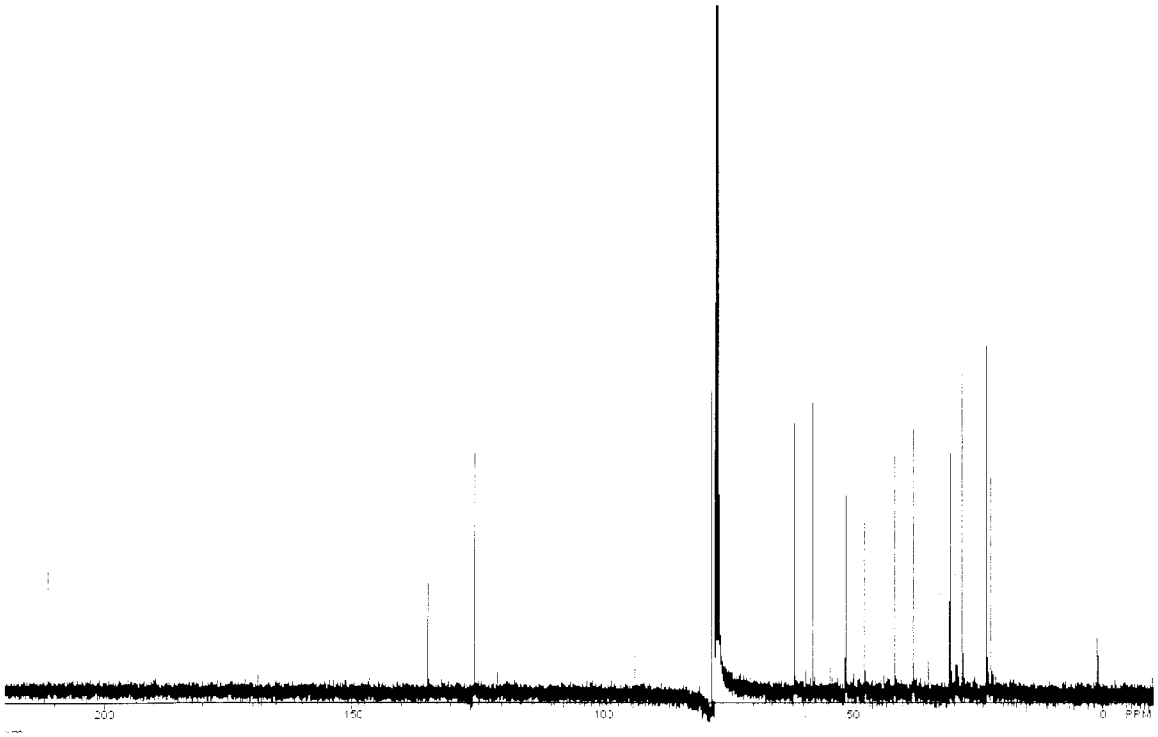


Figure A.1.135 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **175**

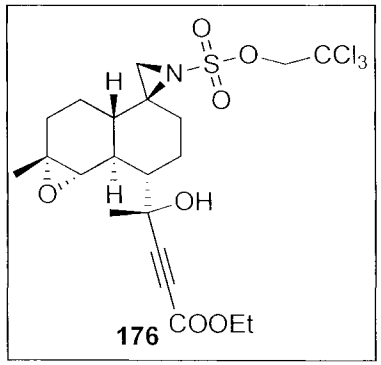


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Figure A.1.136 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **176**

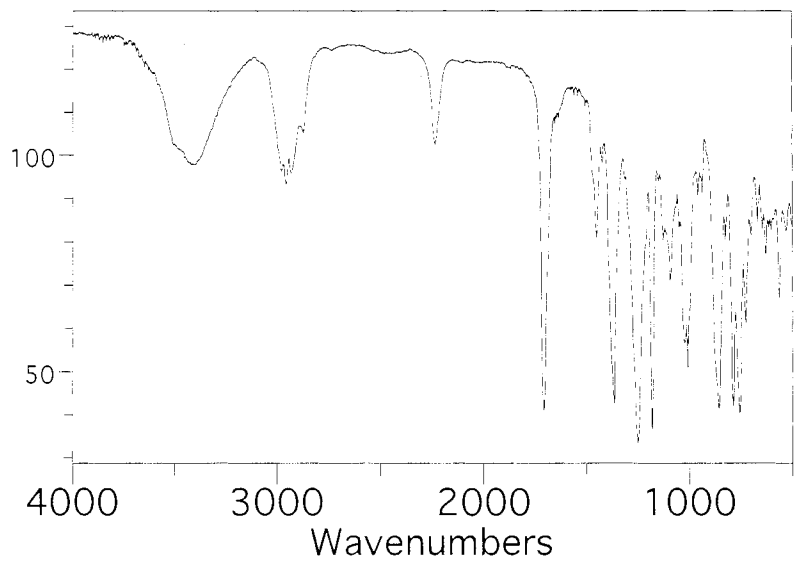


Figure A.1.137 FTIR Spectrum (thin film/NaCl) of Compound **176**

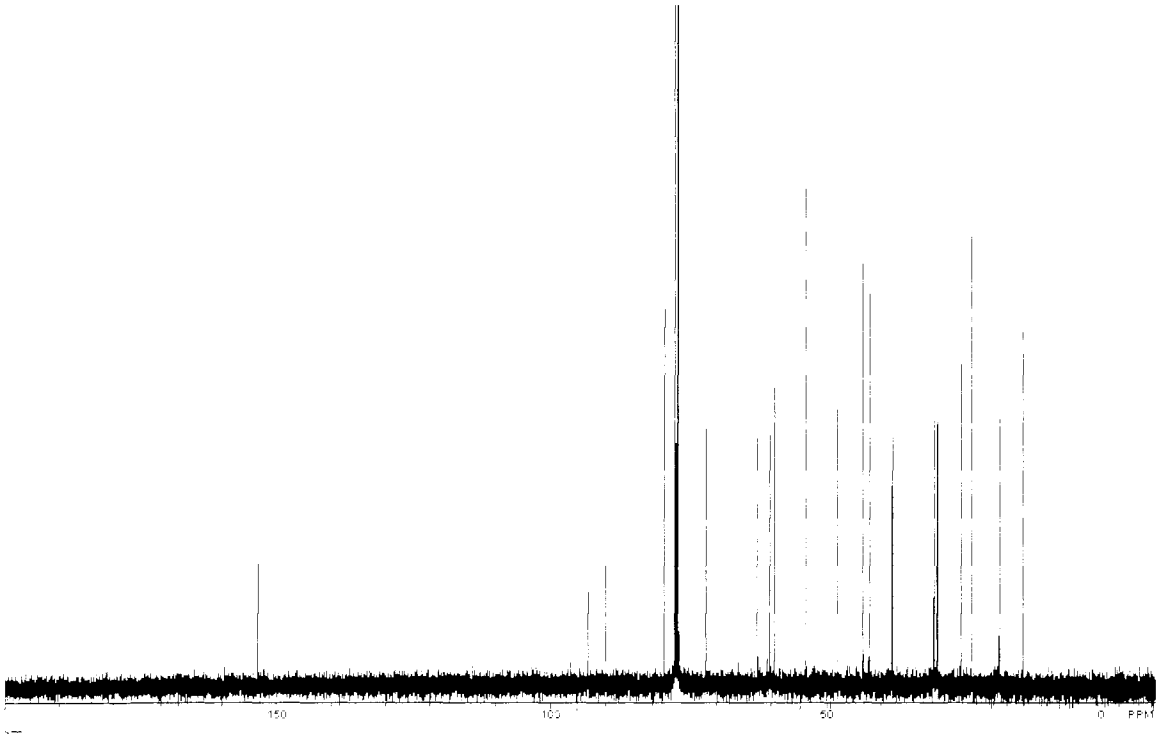


Figure A.1.138 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **176**

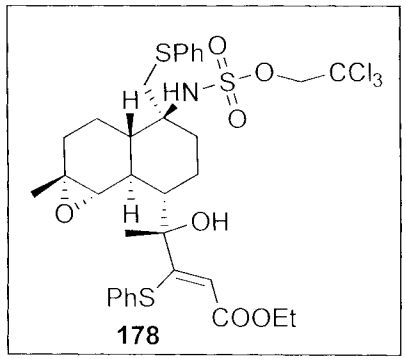


Figure A.1.139 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **178**

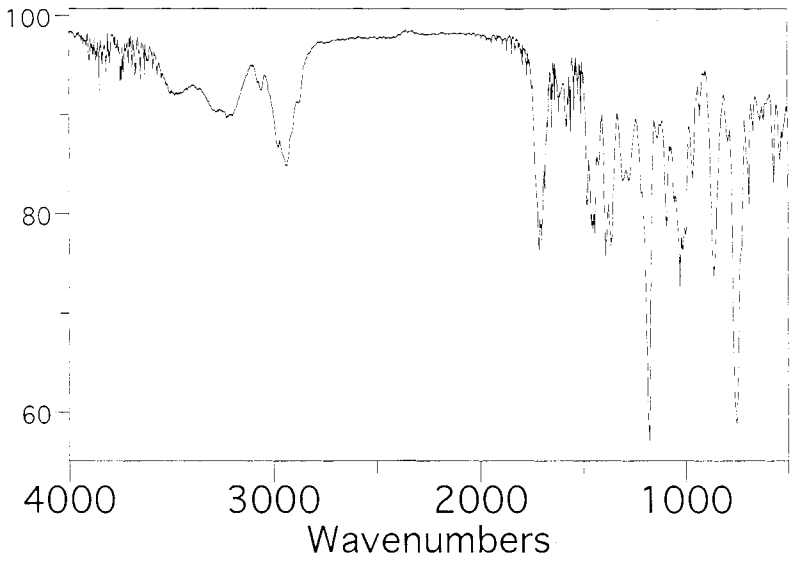


Figure A.1.140 FTIR Spectrum (thin film/NaCl) of Compound **178**

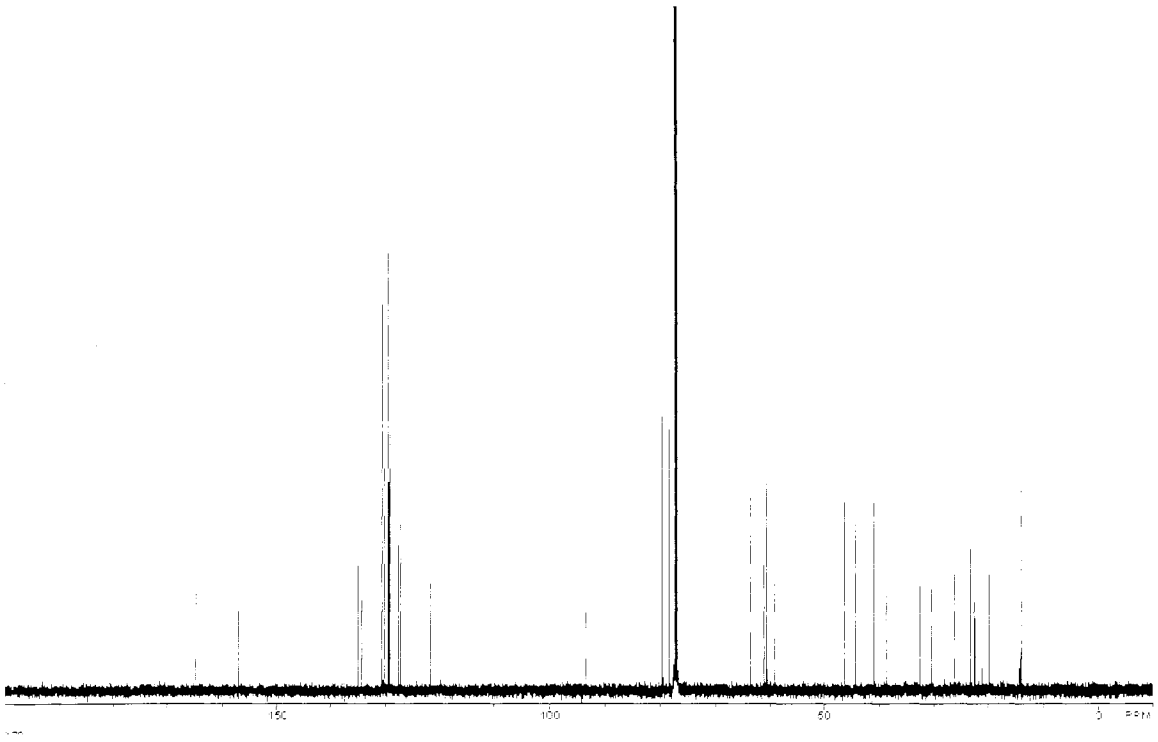


Figure A.1.141 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **178**

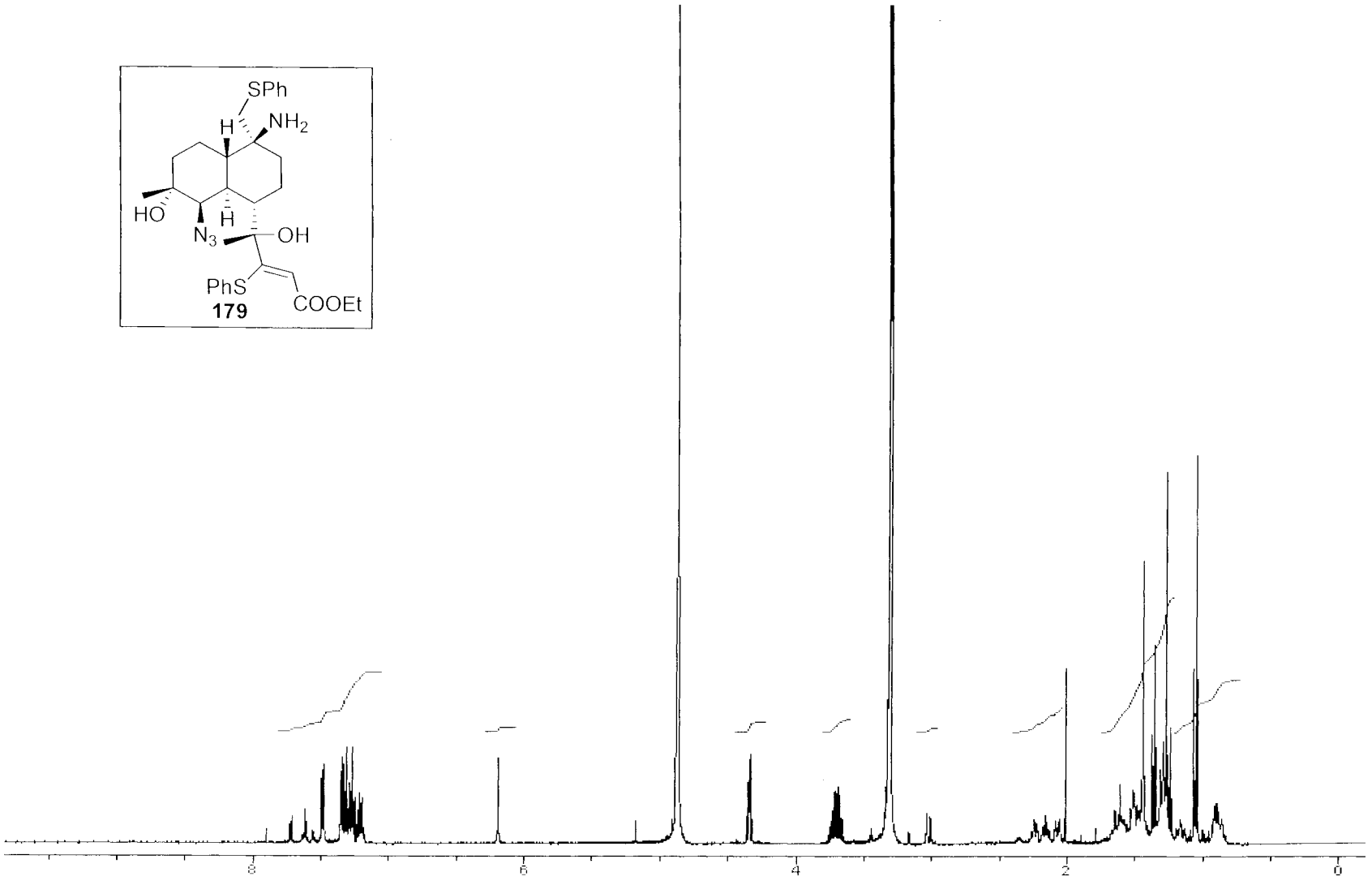


Figure A.1.142 ^{1}H NMR (400 MHz, CD_3OD) of Compound **179**

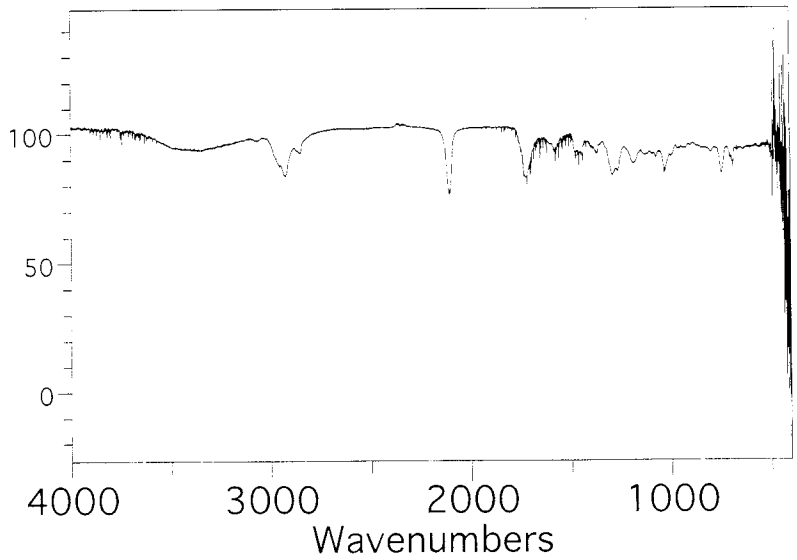


Figure A.1.143 FTIR Spectrum (thin film/NaCl) of Compound **179**

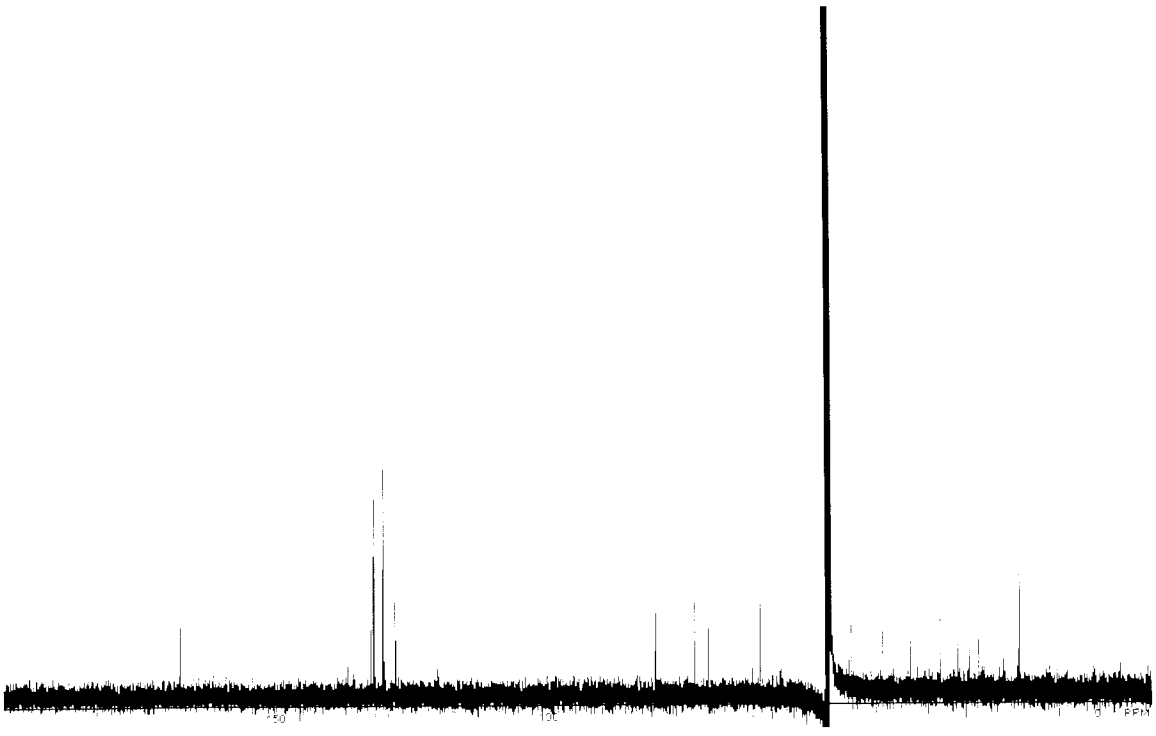


Figure A.1.144 ^{13}C NMR (100 MHz, CD_3OD) of Compound **179**

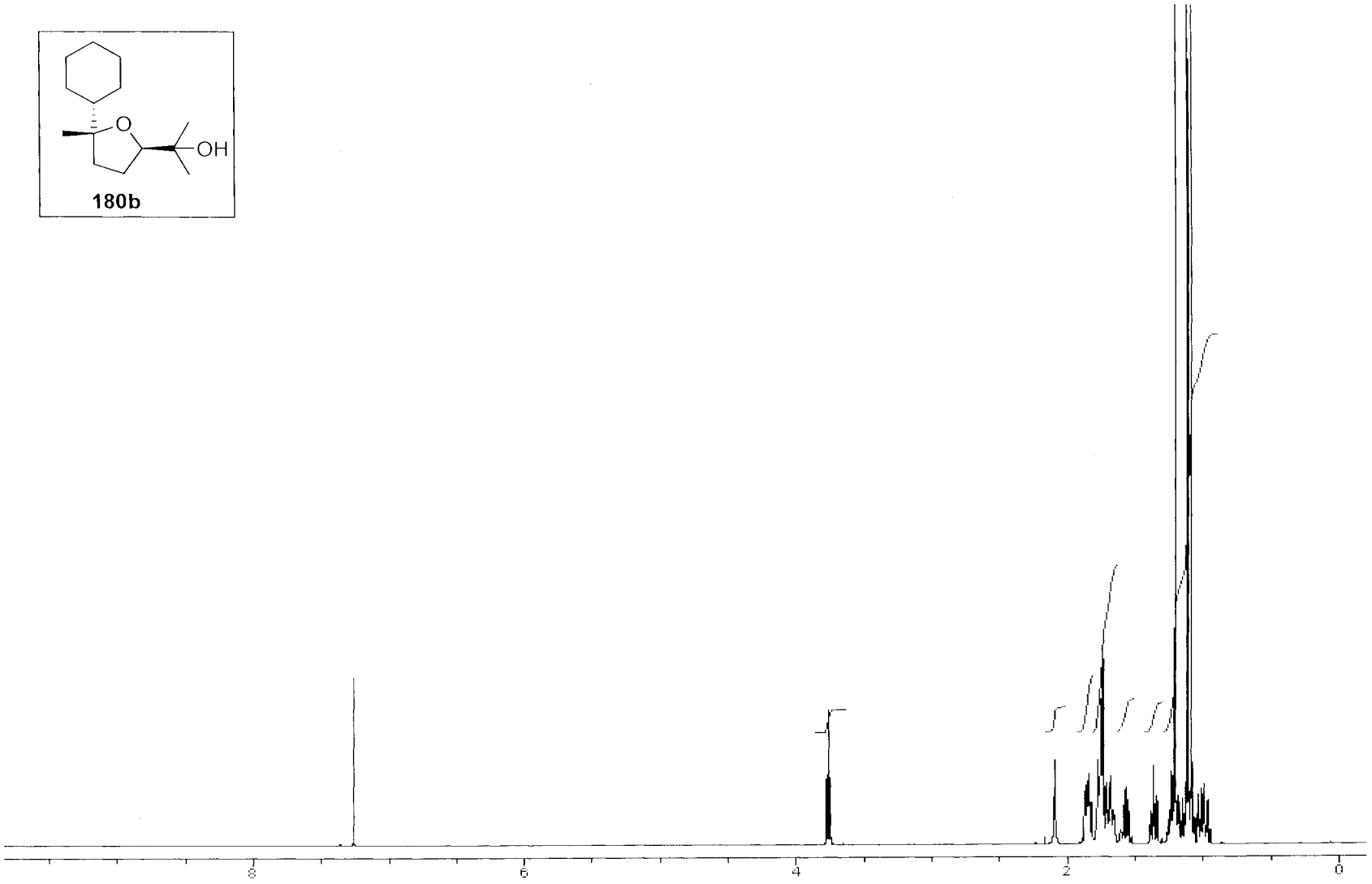


Figure A.1.145 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **180a**

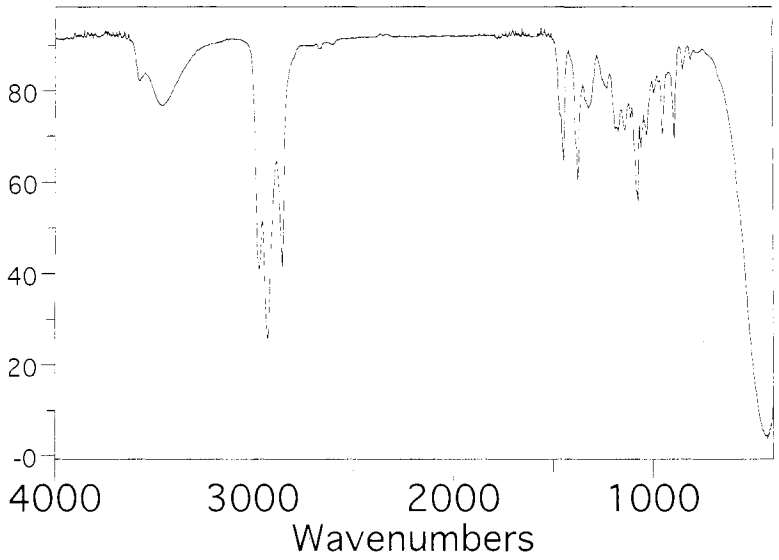


Figure A.1.146 FTIR Spectrum (thin film/NaCl) of Compound **180a**

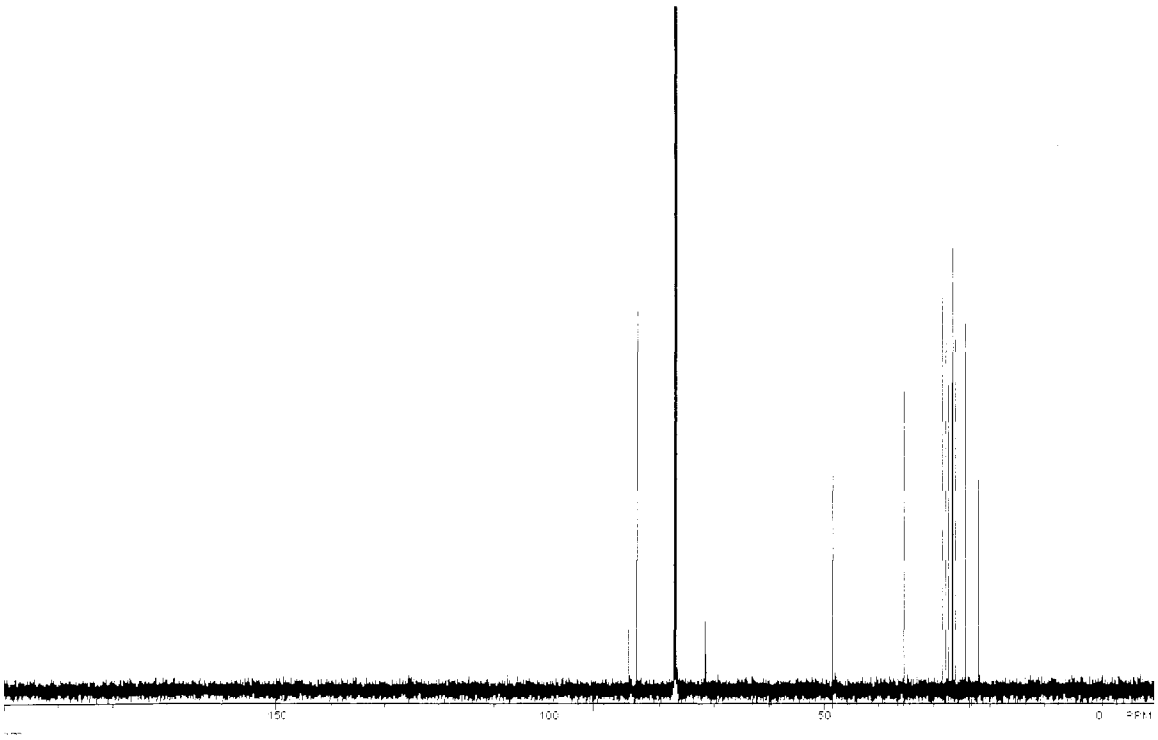


Figure A.1.147 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **180a**

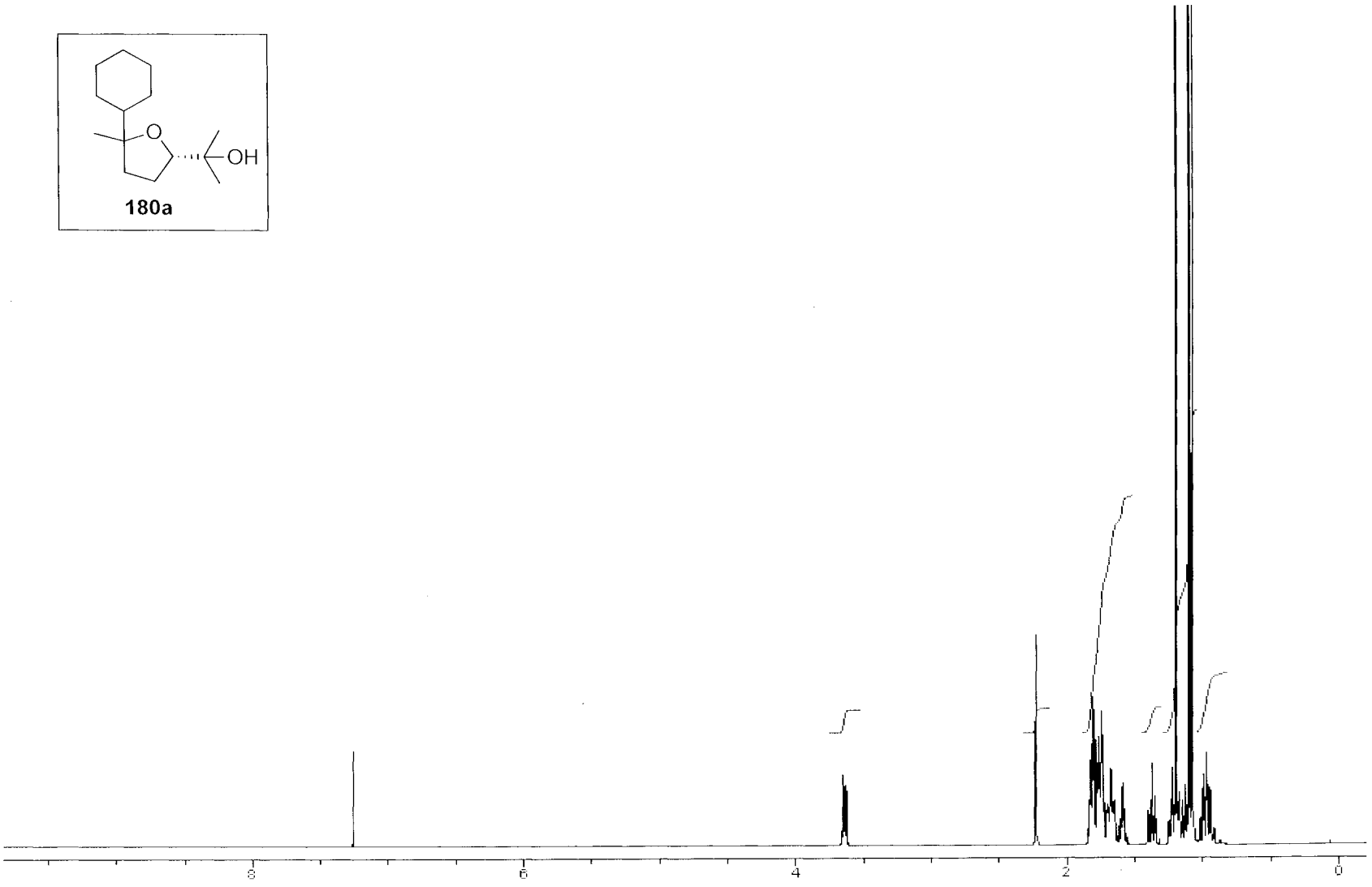


Figure A.1.148 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **180b**

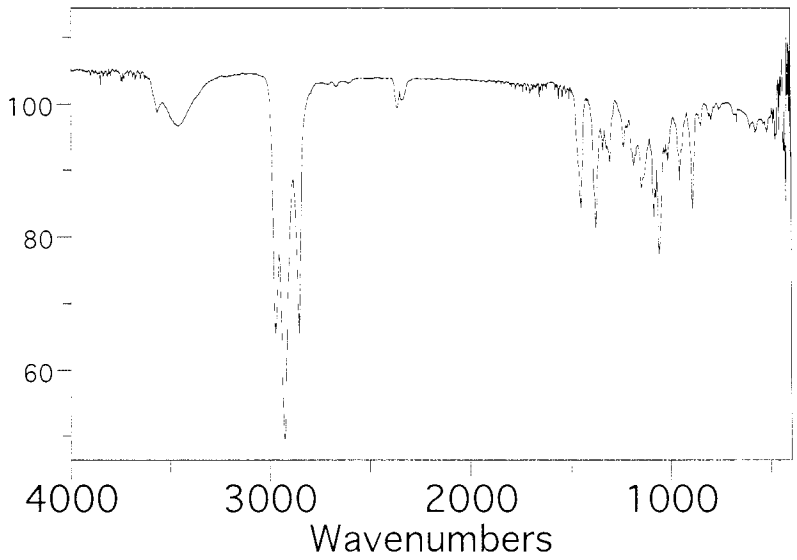


Figure A.1.149 FTIR Spectrum (thin film/NaCl) of Compound **180b**

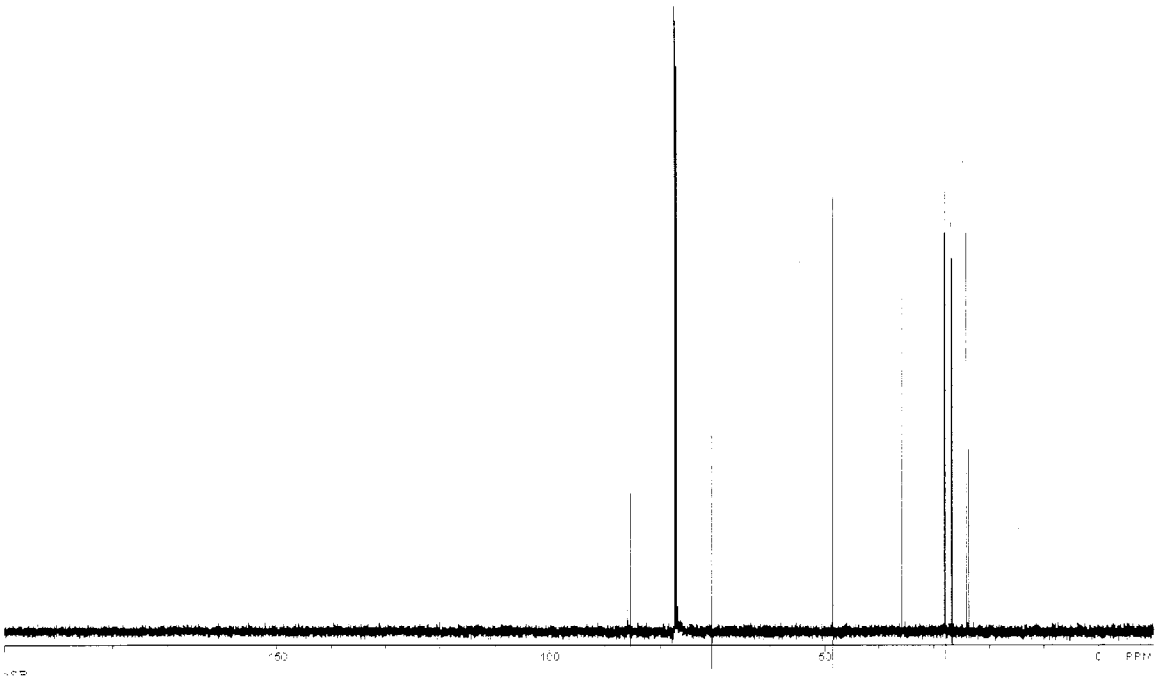


Figure A.1.150 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **180b**

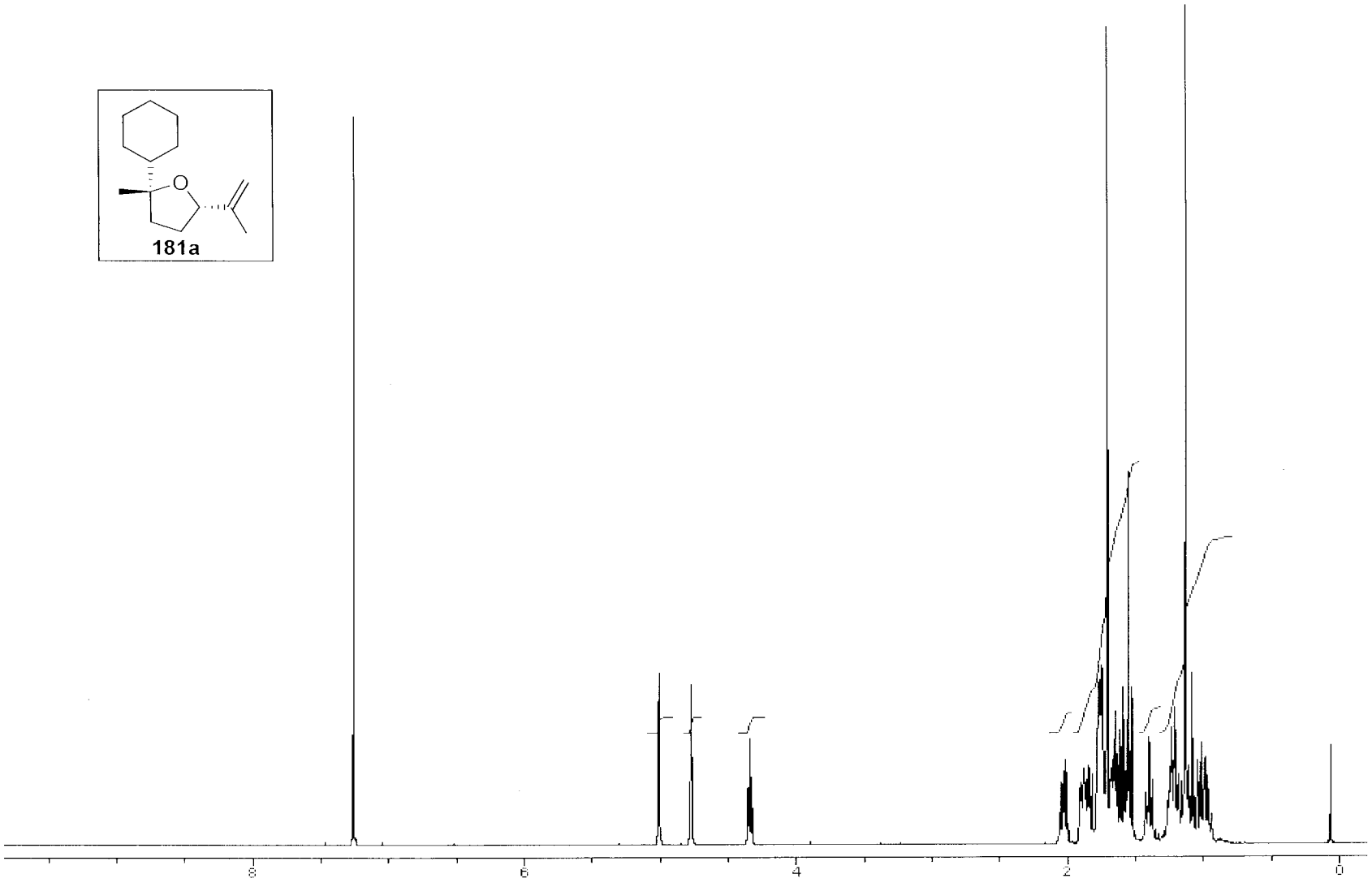


Figure A.1.151 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **181a**

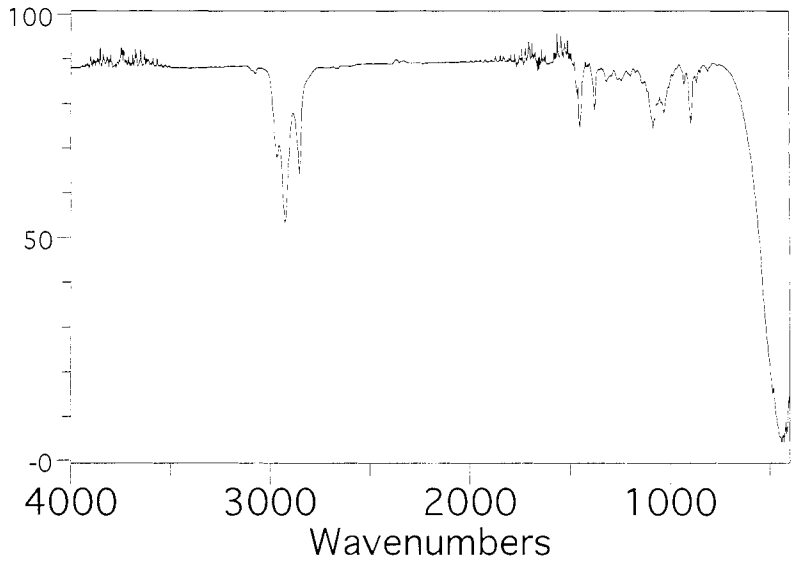


Figure A.1.152 FTIR Spectrum (thin film/NaCl) of Compound **181a**

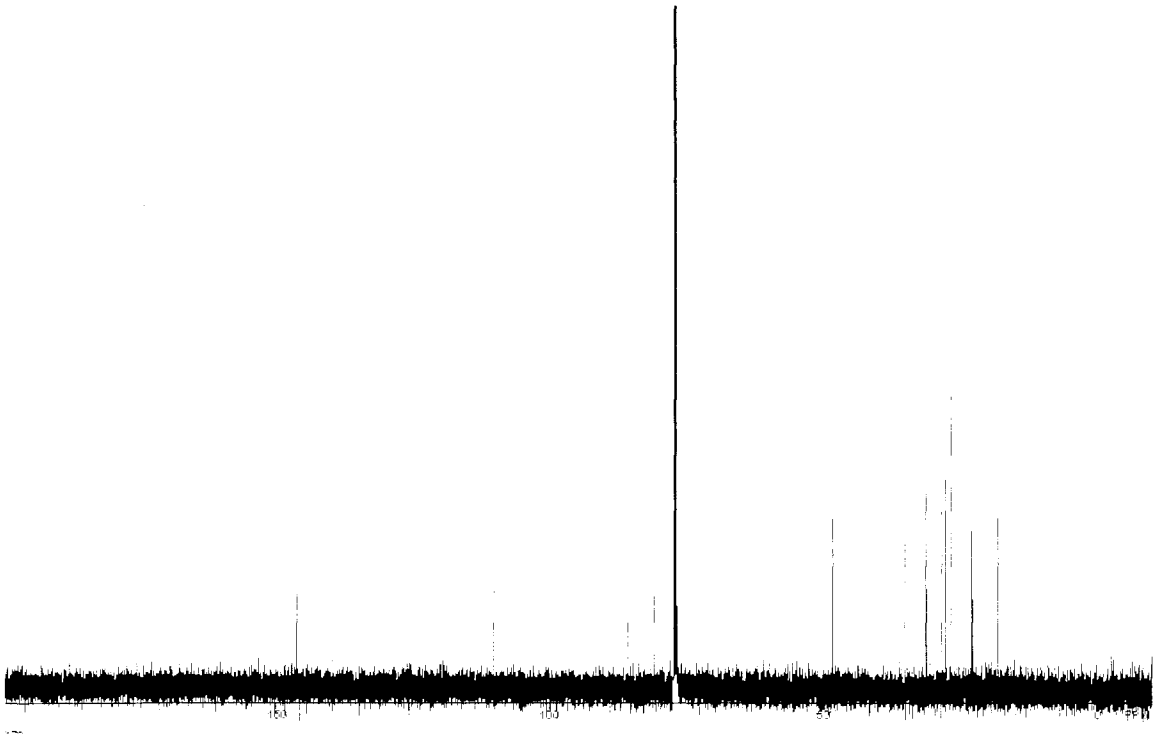


Figure A.1.153 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **181a**

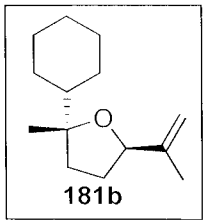


Figure A.1.154 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **181b**

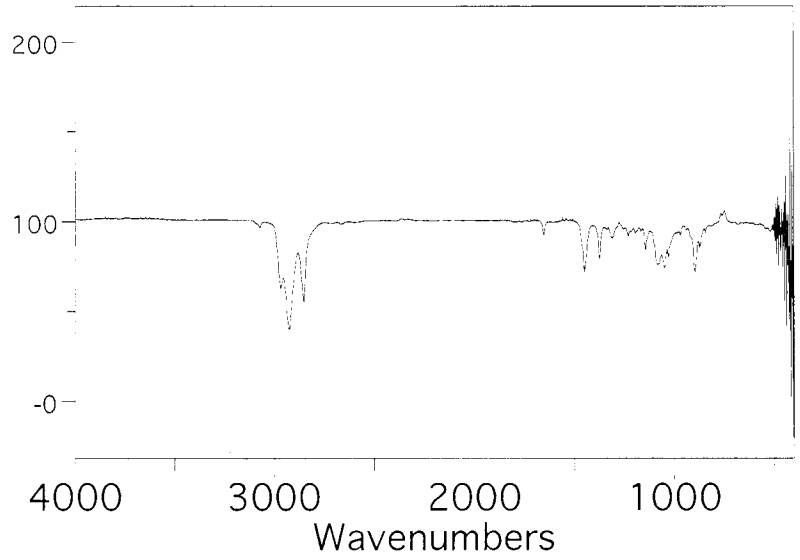


Figure A.1.155 FTIR Spectrum (thin film/NaCl) of Compound **181b**

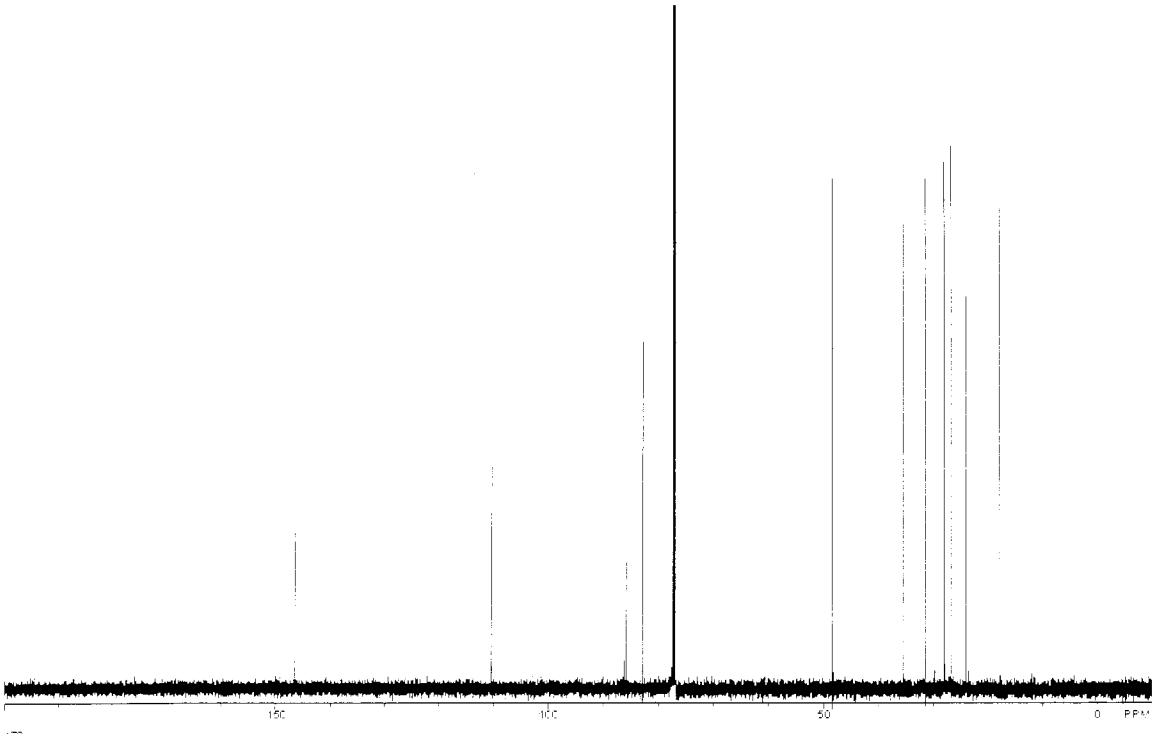


Figure A.1.156 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **181b**

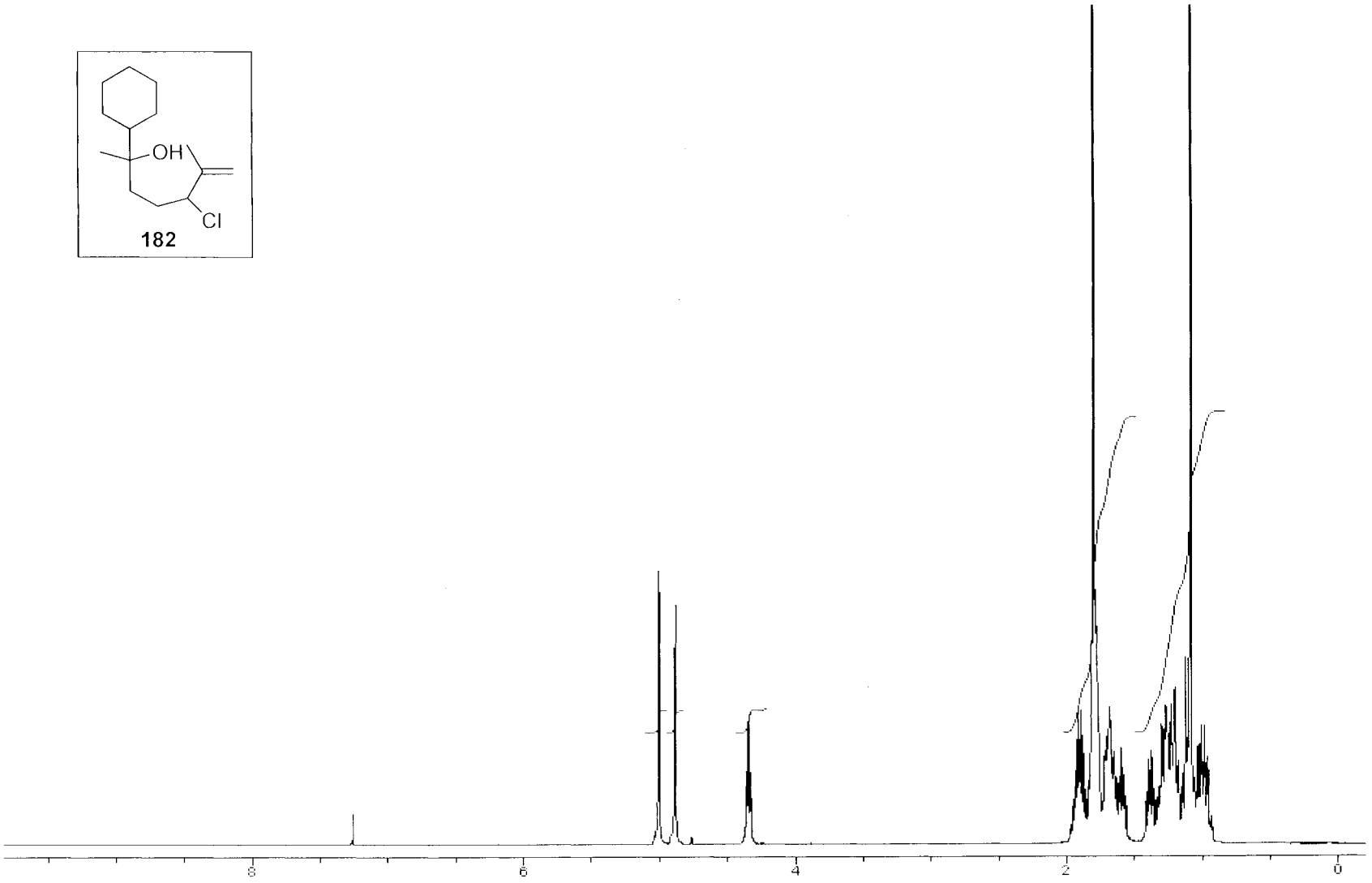


Figure A.1.157 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **182**

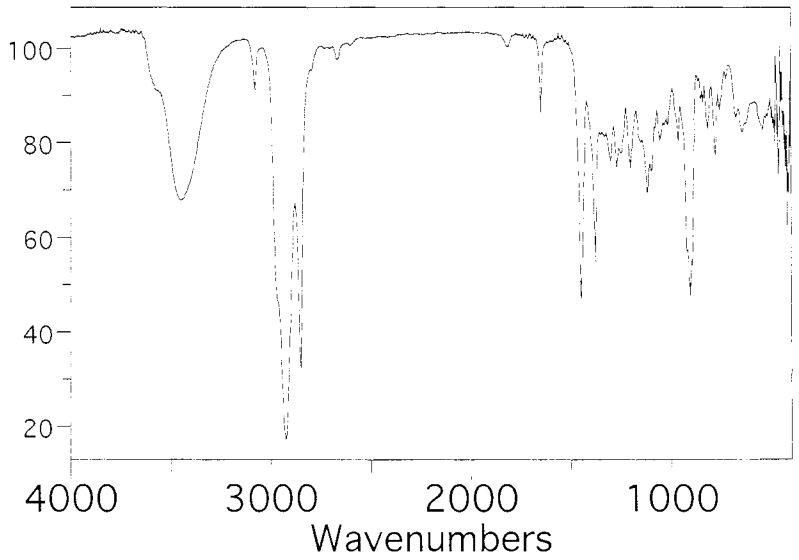


Figure A.1.158 FTIR Spectrum (thin film/NaCl) of Compound **182**

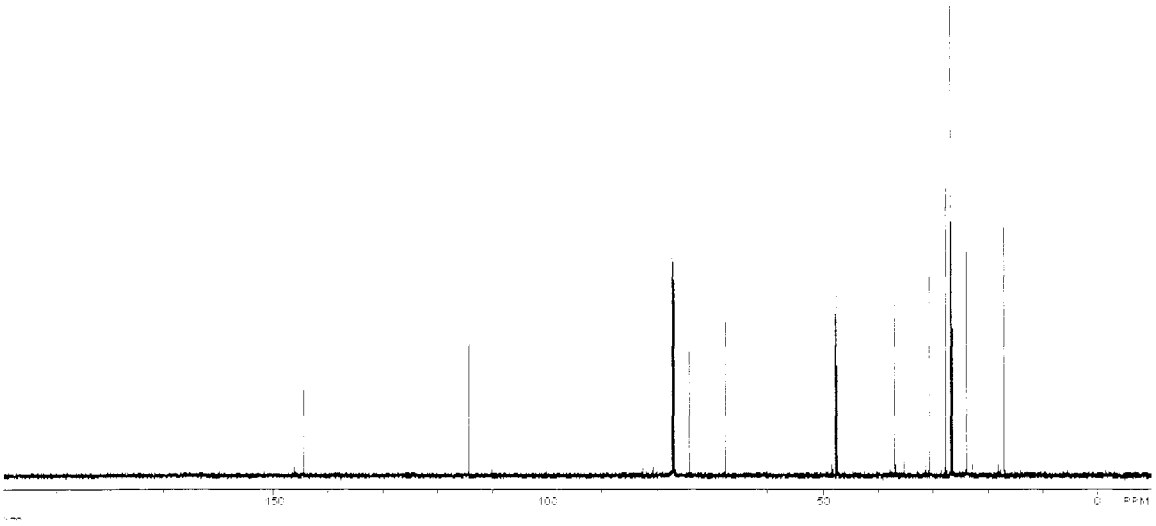


Figure A.1.159 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **182**

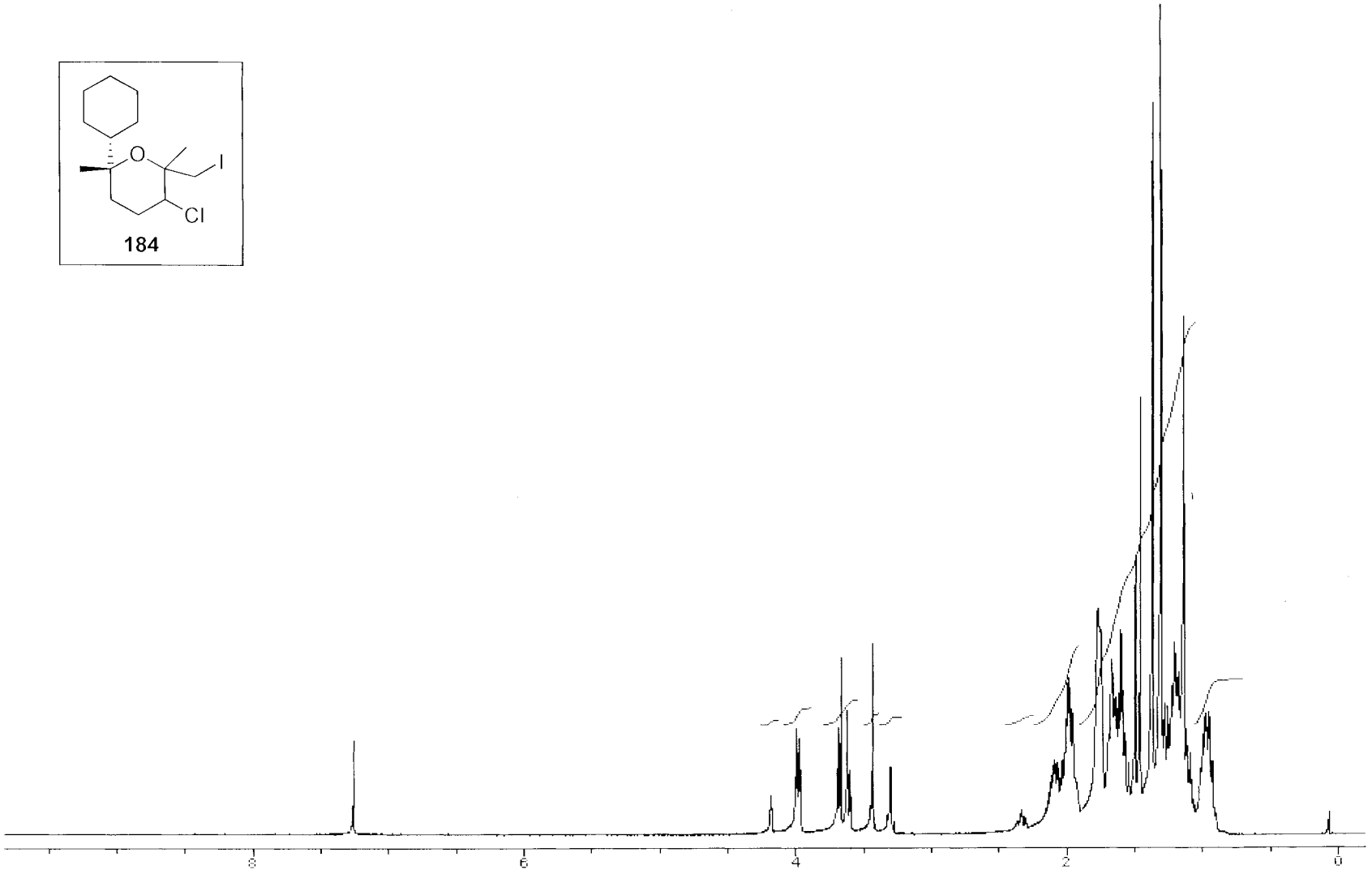


Figure A.1.160 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **184**

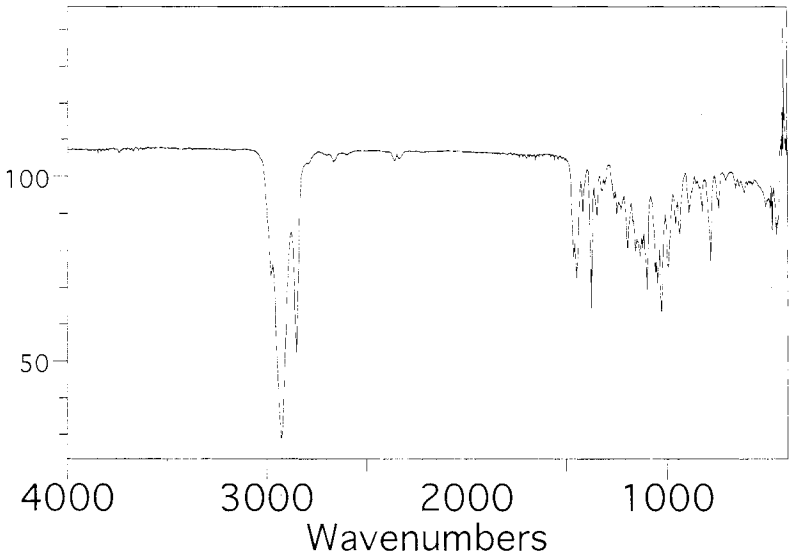


Figure A.1.161 FTIR Spectrum (thin film/NaCl) of Compound **184**

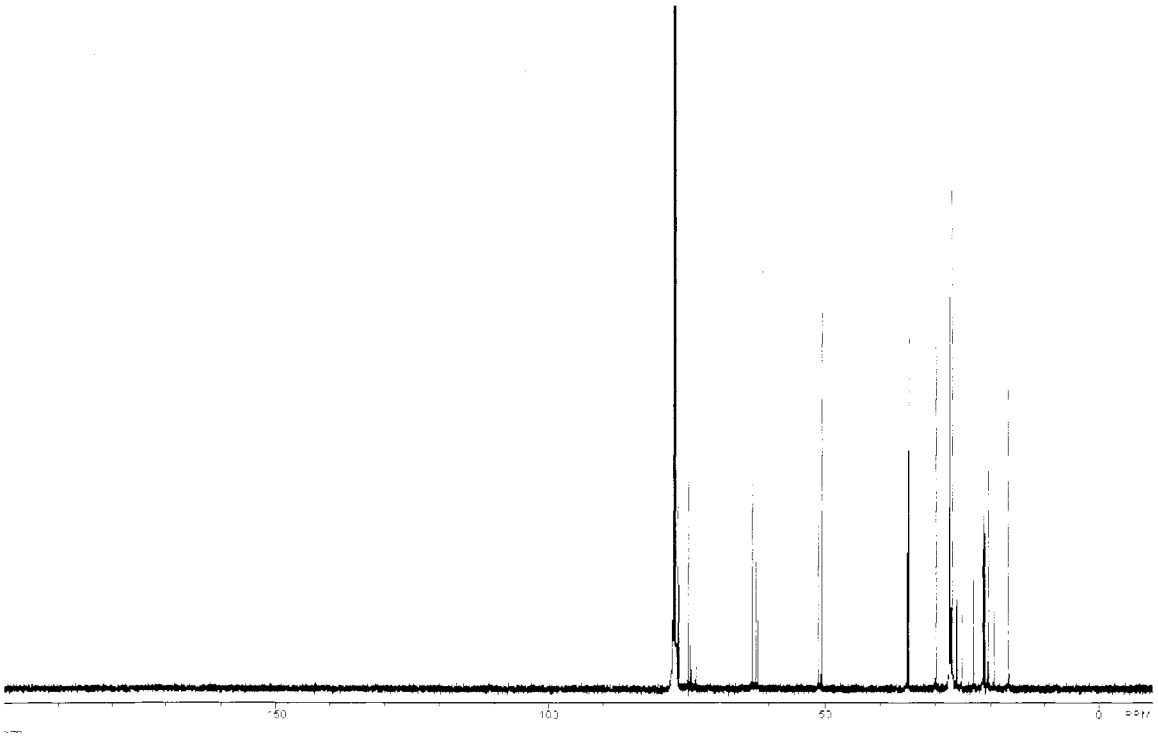


Figure A.1.162 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **184**

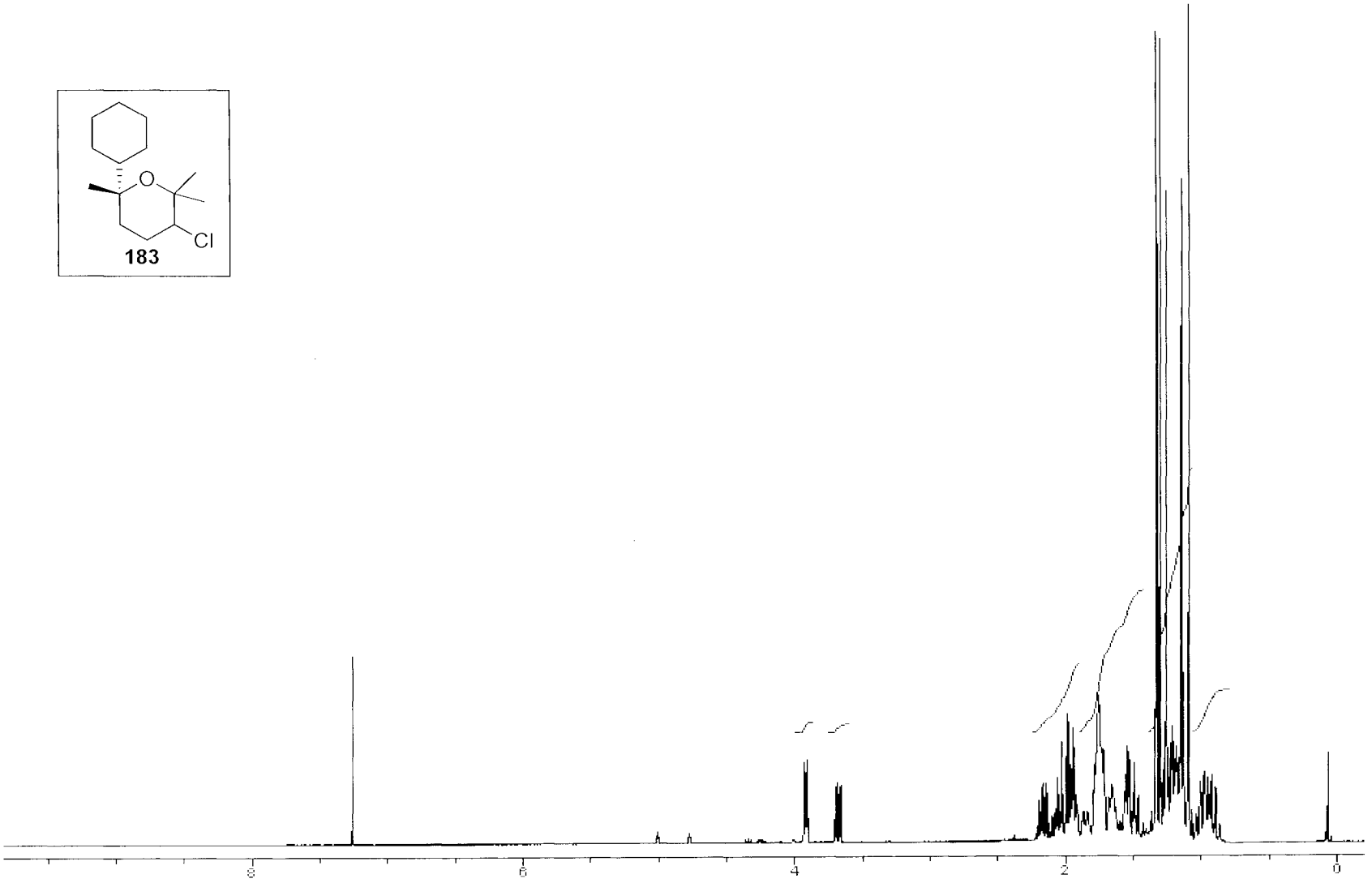


Figure A.1.163 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **183**

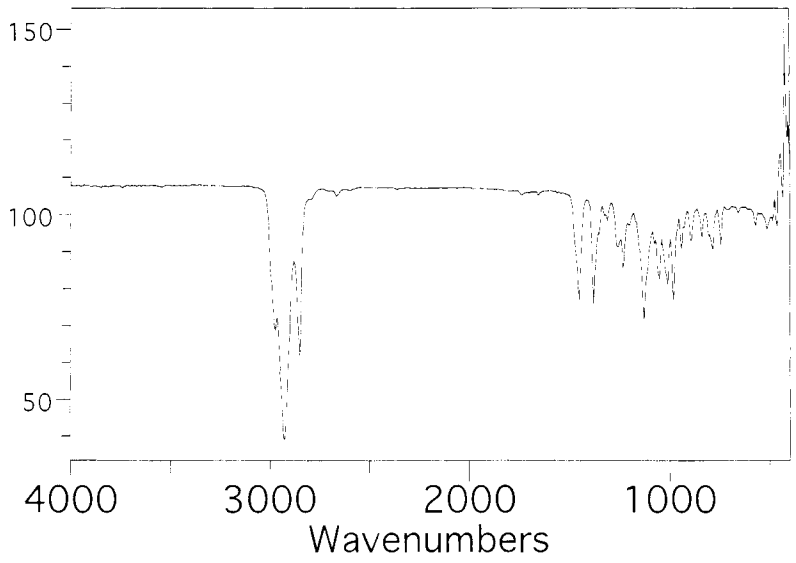


Figure A.1.164 FTIR Spectrum (thin film/NaCl) of Compound **183**

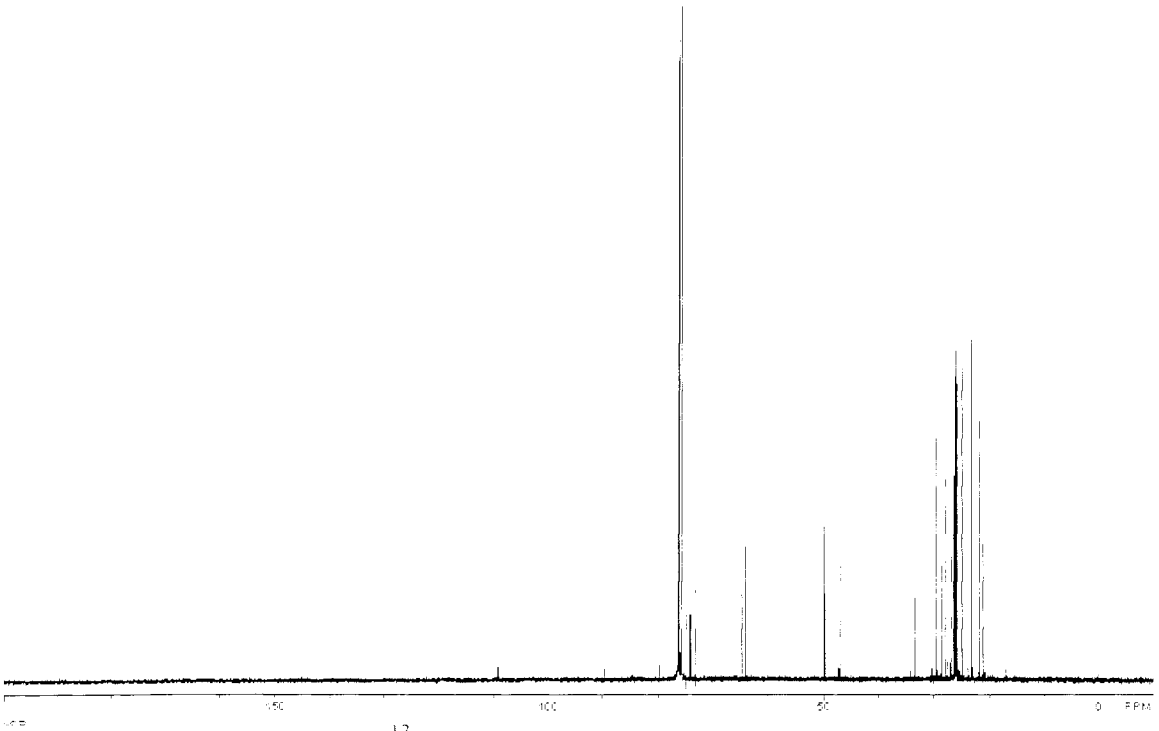


Figure A.1.165 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **183**

Chapter 3

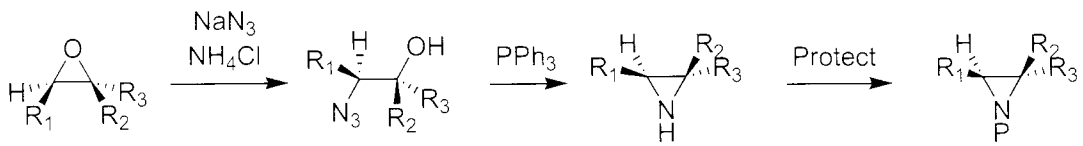
Rhodium perfluorobutyramide ($Rh_2(pfm)_4$): A Synthetically Useful Catalyst for a Variety of Olefin Aziridinations

3.1 Background

3.1.1 Multi-step Installation of Protected Aziridines

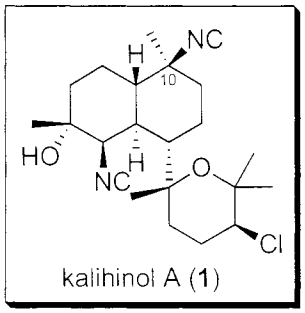
Aziridines have become prolific functional groups in organic synthesis. The most common method for aziridine installation is shown in Scheme 3.1. An epoxide, which can be installed stereoselectively through a variety of known protocols, is opened regioselectively with azide. Reduction of the azide and intramolecular displacement of the adjacent alcohol provides the aziridine. Triphenylphosphine is commonly employed for this latter reaction since this reagent can affect simultaneous azide reduction and alcohol activation.[1] Aziridines are frequently protected at this stage since ring opening often requires that an electron-withdrawing group be attached to the nitrogen.

Scheme 3.1

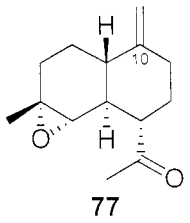


While this method for aziridine installation is effective, it has three major limitations. First, installation of the protected aziridine requires three steps from an epoxide (four steps from an alkene, the most common epoxide precursor). Second, azide addition to hindered epoxides (for example, tri- and tetra-substituted epoxides) can often lead to a variety of side products. Third, there is also the issue of stereoselectivity. For example, in the case of (+)-kalihinol A, the C(10) nitrogen is tertiary and equatorial (Figure 3.1). It is unlikely that this nitrogen could be installed with the correct stereochemistry by using the previously described method. Since epoxidation of *exo*-methylene **77** would be expected to occur on the less-hindered, β-face, it is very improbable that the azide anion would add *syn* to the epoxide *and* at the more substituted carbon to give the correct stereochemistry.

Figure 3.1



kalihinol A (**1**)



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3.1.2 One-step, Metal-Catalyzed Installation of Protected Aziridines

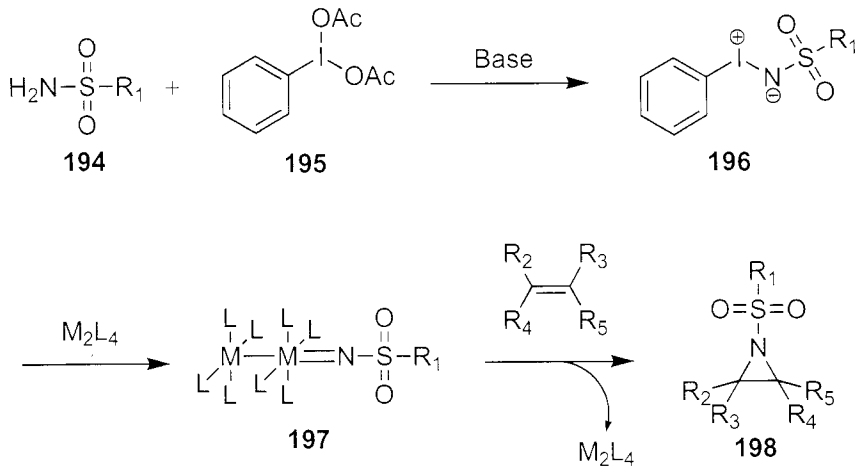
Breslow[2] and Mansuy[3] and co-workers in the early 1980s discovered that iminoiodinanes could serve as nitrene precursors, and their pioneering work has spurred several research groups to investigate metal-catalyzed aziridinations over the past two decades.[4-8] Several transition metal complexes (copper,[5,9,10] rhodium,[11-13] manganese,[14-17]

ruthenium,[18] etc.) have been shown to catalyze nitrene transfer from an iminoiodinane reagent to an olefin to afford the aziridine product with varying success.

Copper is the most commonly-utilized catalyst in olefin aziridination reactions, in large part due to its ability to favor aziridination over competing allylic C-H insertion.[19] Several rhodium catalysts (rhodium (II) acetate, in particular) have been shown to mediate aziridinations with high fidelity; however, the products of these reactions have frequently been contaminated with significant amounts of C-H insertion by-products.[12,20] Due to the improved efficiency of metal-catalyzed aziridinations in recent years, these reactions have been applied to highly functionalized intermediates in total syntheses.[21,22-24]

The process of nitrene formation and metal-catalyzed nitrene transfer is illustrated in Scheme 3.2. The nitrogen source (**194**), which is typically a sulfonamide or sulfamate ester, is treated with phenyliododiacetate (**195**, $PhI(OAc)_2$) in the presence of a base to generate to iminoiodinane ylide **196**. The stability of **196** varies dramatically depending upon the nature of the stabilizing group attached to the nitrogen.[4] Next, the ylide reacts with the metal catalyst to produce a transient metal nitrene species (**197**), which in turn reacts with olefins in a stereospecific manner to afford aziridine **198**.[25]

Scheme 3.2

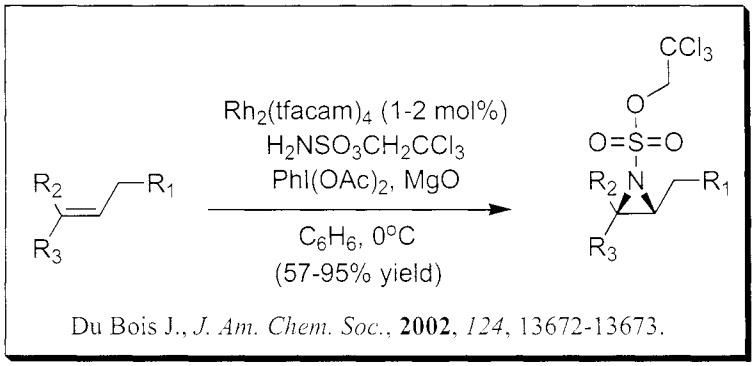


3.2 Use of Rhodium (II) Perfluorobutyramide Towards the Synthesis of (+)-Kalihinol A

3.2.1 Du Bois' catalyst: Rhodium (II) Trifluoroacetamide ($Rh_2(tfacam)_4$)

In the course of recent studies towards the total synthesis of (+)-kalihinol A, a novel protocol was developed by Du Bois and co-workers in which trichloroethoxysulfonyl aziridines were formed from olefins using rhodium trifluoroacetamide ($Rh_2(tfacam)_4$) as the catalyst (Scheme 3.3).[26] The use of rhodium trifluoroacetamide for olefin aziridination and the use of trichloroethylsulfamate ester as a nitrene source were both unprecedented at the time of Du Bois' publication.

Scheme 3.3



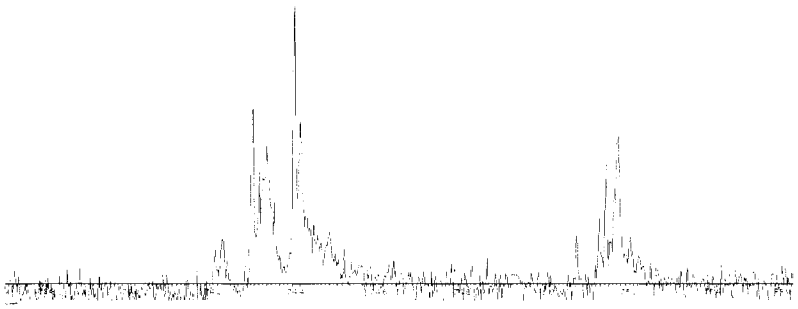
Du Bois J., *J. Am. Chem. Soc.*, **2002**, *124*, 13672-13673.

While attempting this protocol to install the C(10) nitrogen in our synthesis of (+)-kalihinol A, we encountered difficulty in preparing the $Rh_2(tfacam)_4$ catalyst required for this reaction. The preparative procedure reported by Du Bois, which required a forty-eight hour distillation accompanied by constant monitoring,[26] was somewhat tedious, and complications regarding the formation of this complex have been documented.[27,28]

The spectroscopic data for rhodium trifluoroacetamide is reported as a single peak (singlet) at δ -74.4 in the ^{19}F NMR (CD_3CN).[26] The complex obtained after following Du Bois' procedure was not pure as evidenced by ^{19}F NMR (Figure 3.2). The spectroscopic data suggested that a mixture of partially-fluorinated rhodium complexes, resulting from incomplete acetate/trifluoroacetamide ligand exchange, was present. Resubjection to the reaction conditions did not substantially increase the amount of rhodium trifluoroacetamide in the reaction mixture (as observed by ^{19}F NMR).

Figure 3.2

^{19}F NMR (CD_3CN) of rhodium trifluoroacetamide (after chromatography)

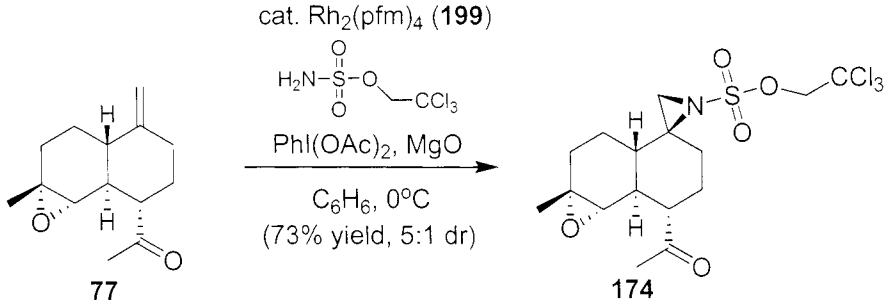


3.2.2 The Discovery of a Novel Aziridination Catalyst

Since the preparation of rhodium trifluoroacetamide remained problematic, other copper and rhodium catalysts were screened in an effort to conduct this trichloroethoxysulfonyl aziridination. Six of the seven catalysts (copper (I) triflate, copper (II) triflate, rhodium (II) octanoate, rhodium (II) acetate, rhodium (II) trifluoroacetate, and rhodium (II) perfluorobutyrate) which were screened produced no appreciable reaction, despite the fact that most of these catalysts were well precedented to perform similar aziridinations.[9,5,12] In stark contrast to the other catalysts, it was found that rhodium (II) perfluorobutyramide (**199**, $Rh_2(pfm)_4$) delivered the desired trichloroethoxysulfonyl aziridine **174** as the sole product in 73% yield as a 5:1 mixture of diastereomers (Scheme 3.4, also see Chapter 2). Upon checking the literature, it was revealed that there were no examples describing the use of rhodium perfluorobutyramide

(**199**) for olefin aziridination. As a result, a methodology project directed at determining the substrate and nitrene source scope of the catalyst was initiated.

Scheme 3.4



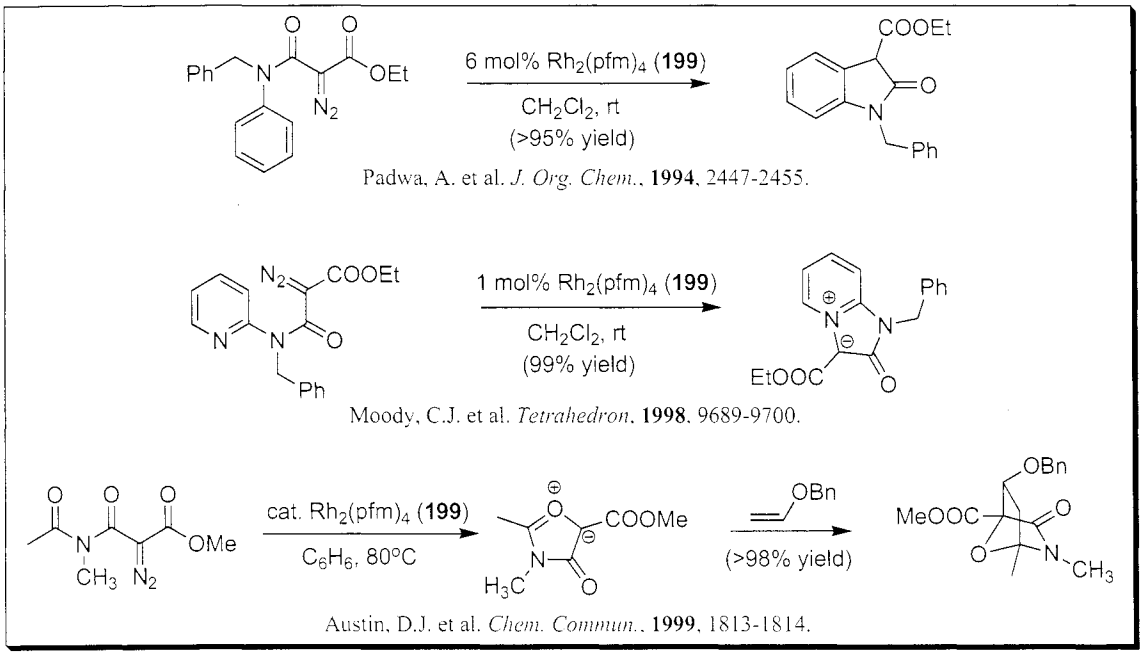
3.3 Prior Applications of Rhodium Perfluorobutyramide

Rhodium perfluorobutyramide (**199**) was first used in 1994 by Padwa and co-workers to conduct aryl C-H insertions.[27] To date, there have been eight additional reports in the literature describing the use of **199**, all of which have emanated from three research groups: Padwa et al. at Emory University,[27,29,30] Austin et al. at Yale University,[31-34] and Moody et al. at Loughborough University (U.K.).[35,36]

A representative example from each research group is highlighted in Scheme 3.5. In the first example, **199** catalyzed an intramolecular aryl C-H insertion of an α-diazoamide. Interestingly, this aryl C-H insertion occurred chemoselectively over benzylic C-H insertion, the latter of which was the commonly-observed product when non-fluorinated rhodium catalysts were used.[27] In the second example, Moody and co-

workers have found that an *N*-pyridyl diazoamide could be converted into a pyridinium ylide in quantitative yield in the presence of **199**.[35] Most recently, Austin and co-workers have shown that **199** catalyzed the intramolecular O-H insertion/1,3-dipolarcycloaddition of α-diazoimides with alkyl vinyl ethers.[31]

Scheme 3.5



3.4 Preparation of Rhodium Perfluorobutyramide Catalyst

3.4.1 Literature Precedence for the Preparation of Rhodium Perfluorobutyramide

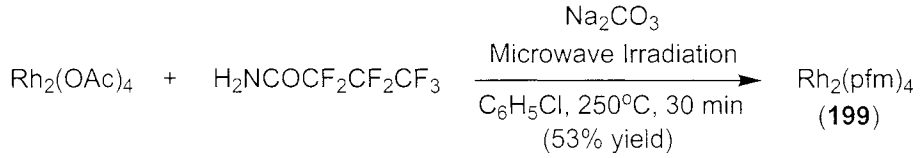
Rhodium perfluorobutyramide (**199**) has been prepared by refluxing rhodium acetate and perfluorobutyramide in chlorobenzene for sixty hours under a Soxhlet extraction apparatus.[27] Purification of **199** required sublimation (to remove excess

perfluorobutyramide), silica gel column chromatography, and HPLC. While this procedure was conducted in our laboratory[37] and found to be effective, its lengthy reaction time and time-consuming purification represented two major drawbacks.

3.4.2 Microwave-Accelerated Preparation of Rhodium Perfluorobutyramide

In order to make the aziridination methodology as operationally simple as possible, the initial goal was to improve the preparation of rhodium perfluorobutyramide catalyst.[27] Microwave acceleration of organic reactions has become a commonly-used technique to reduce reaction times, and its popularity has soared in recent years.[38] It was recognized that microwave irradiation might facilitate the rapid assembly of **199**. Using the identical starting materials and solvent as Padwa, **199** could be prepared under microwave irradiation *in only 30 minutes* in 53% yield after silica gel column chromatography (Scheme 3.6).[27] This microwave-accelerated reaction required less maintenance and proceeded at a much faster rate than Padwa's previously-described procedure.

Scheme 3.6



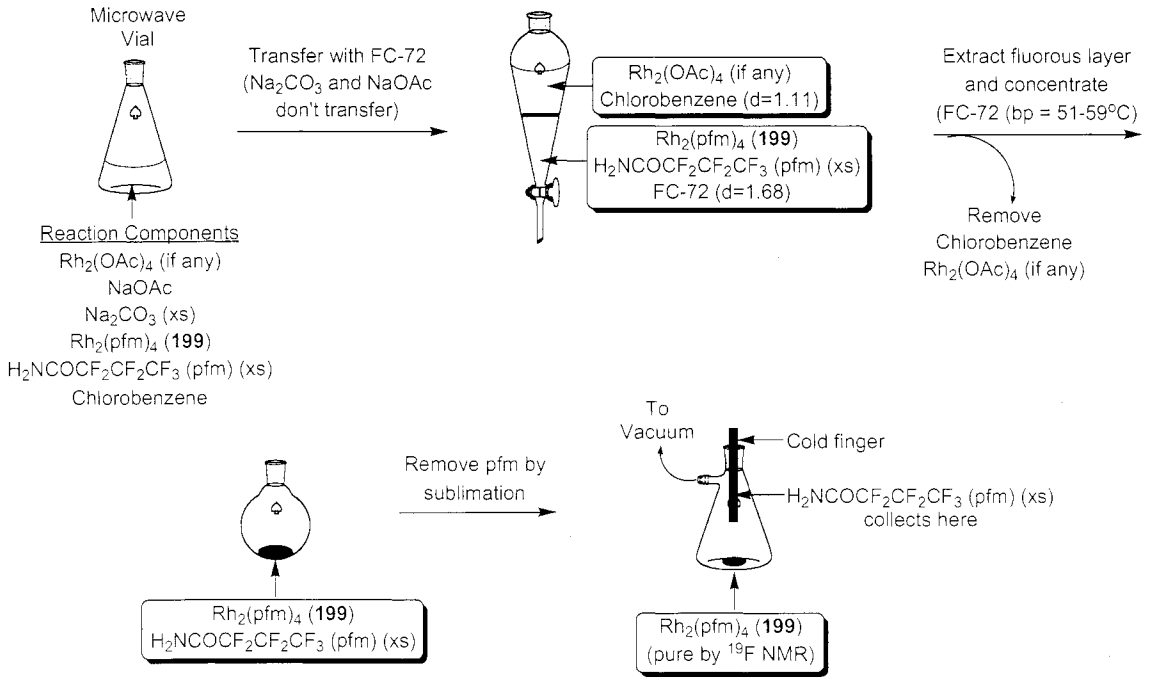
3.4.3 Improved Purification of Rhodium Perfluorobutyramide

As stated previously, Padwa has reported that rhodium perfluorobutyramide (**199**) was purified by sublimation, silica gel column chromatography, and then finally by

HPLC.[27] In an effort to make the aziridination procedure as practical as possible, the time-consuming chromatography steps in Padwa's procedure would need to be adapted.

To this end, an extraction procedure was designed to separate **199** from any remaining rhodium acetate present in the reaction mixture (Figure 3.3).[39] The reaction components in chlorobenzene were transferred with FC-72 (perfluoro-*n*-hexane) to a separatory funnel. Phase separation of the organic (chlorobenzene) and fluorous (FC-72) layers partitioned the two rhodium complexes. After extraction, the fluorous layer was concentrated, and the excess perfluorobutyramide reagent was removed by standard sublimation to provide **199**.

Figure 3.3

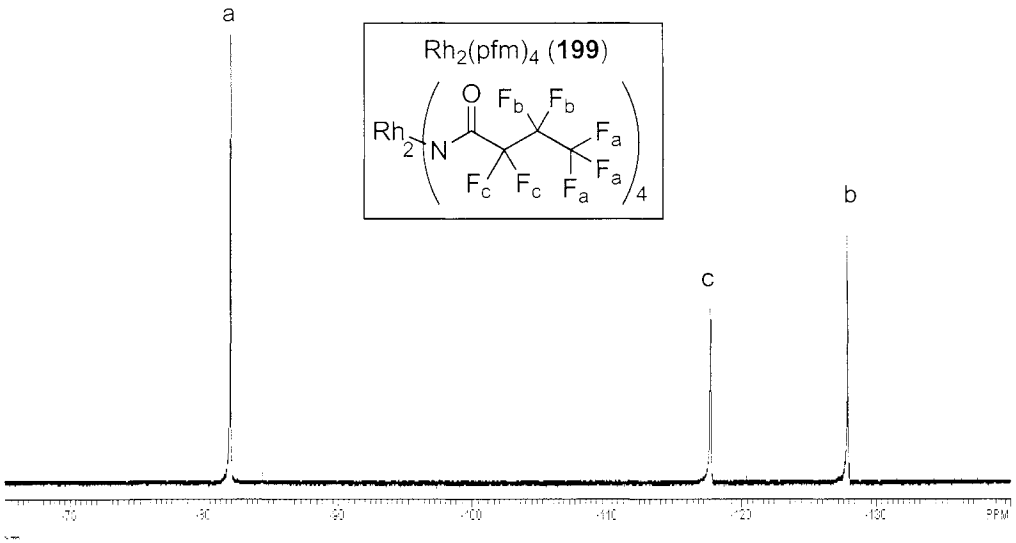


The catalyst obtained from this extraction procedure was found to be pure by ^{19}F NMR and identical to the previously-synthesized **199** prepared in our laboratory by the

Padwa method (Figure 3.4).[27] It is important to note the significant difference in purity between rhodium perfluorobutyramide (**199**, Figure 3.4, prepared by microwave irradiation) and rhodium trifluoroacetamide (see Figure 3.2, prepared by standard distillation) as judged by their respective ^{19}F NMRs.

Figure 3.4

^{19}F NMR (CD_3CN, crude after fluorous extraction and sublimation)



3.5 Aziridination with Rhodium Perfluorobutyramide: Substrate and Nitrene Source Scope

3.5.1 Rationale

Next, the substrate and nitrene source scope of rhodium perfluorobutyramide for olefin aziridination was explored. To determine substrate scope, eight olefinic substrates,

which included conjugated (entries 1-4), endocyclic (entry 5), and acyclic isolated olefins (entries 6-8), were selected (Table 3.1).

3.5.2 Trichloroethoxysulfonyl Aziridinations

First, the ability of rhodium perfluorobutyramide (**199**) to conduct trichloroethoxysulfonyl aziridinations on selected substrates was investigated. The spectroscopic data for trichloroethoxysulfonyl azirdines **202a-e** were known from Du Bois' original publication.[26] As shown in Table 3.1, **199** successfully catalyzed the conversion of olefins **200a-e** to aziridines **202a-e** in 58-87% yields, values which were comparable to those reported by Du Bois.[26,40] In addition, three acyclic olefins (**200f-h**) were converted to trichloroethoxysulfonyl aziridines (**202f-h**) in 55-76% yields.

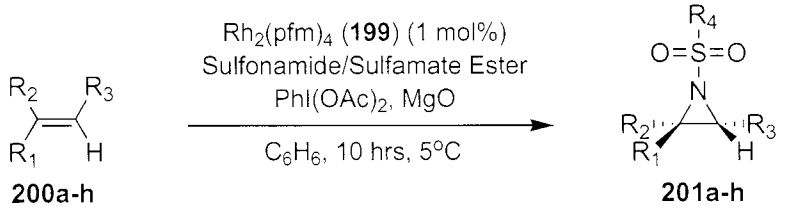
While these aziridinations were conducted using **199** which had been purified by silica gel column chromatography, it had not yet been determined whether or not this chromatography was necessary. To this end, olefin **200a** was treated under the reaction conditions with crude **199** (after fluorous work-up) and aziridine **202a** was isolated in 73% yield. While this yield was somewhat lower than the reaction with purified **199**, this result demonstrated that the catalyst continued to be effective even without chromatographic purification.[41] This data demonstrates that rhodium perfluorobutyramide (**199**) can perform trichloroethoxysulfonyl aziridinations on a variety of substrates in good yields.

3.5.3 Nosyl and Tosyl Aziridinations

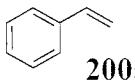
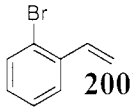
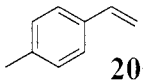
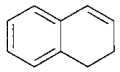
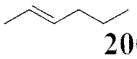
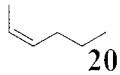
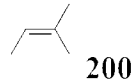
As stated previously, Du Bois and co-workers were the first to report that rhodium trifluoroacetamide was capable of conducting aziridinations with sulfamate esters as nitrene precursors. In this same publication, this catalyst was also reported to conduct aziridinations using phosphoramidates as the nitrene precursor.[26] Interestingly, Du Bois and co-workers make no mention of any attempt to use rhodium trifluoroacetamide to conduct nosyl and tosyl aziridinations, despite the fact that these are the most synthetically-versatile and common aziridines found in the literature today.

In an effort to determine whether rhodium perfluorobutyramide (**199**) could facilitate nosyl and tosyl aziridinations, olefins **200a-h** were subjected to the same reaction conditions except that *para*-nitrobenzenesulfonamide and *para*-toluenesulfonamide replaced the sulfamate ester as the nitrene source (Table 3.1). It was found that **199** converted olefins **200a-h** to nosyl aziridines **203a-h** in 31-79% yields.[42] Furthermore, tosyl aziridines **204a-h** were formed in 37-73% yields under these reaction conditions as well.[5,43-45] While the yields of the nosyl and tosyl aziridinations were typically lower than the corresponding trichloroethoxysulfonyl aziridination, these results demonstrate that **199** is also a viable catalyst for these more familiar aziridination procedures. Thus, the application of our method to sulfonamide-based nitrene precursors is an expansion of the current scope of fluorinated rhodium catalysts in olefin aziridination.

Table 3.1



Aziridinations Using Rhodium Perfluorobutyramide Catalyst[a]

Entry	Substrate	Yield (%)		
		Trichloro-ethoxysulfonyl[b]	Nosyl[c]	Tosyl[d]
1	 **200a**	87(73)[e] **202a**	79 **203a**	73 **204a**
2	 **200b**	71 **202b**	71 **203b**	64 **204b**
3	 **200c**	58 **202c**	58 **203c**	47 **204c**
4	 **200d**	60 **202d**	42 **203d**	54 **204d**
5	 **200e**	80 **202e**	46 **203e**	48 **204e**
6	 **200f**	72 **202f**	44 **203f**	44 **204f**
7	 **200g**	55 **202g**	32 **203g**	37(75)[f] **204g**
8	 **200h**	76 **202h**	31 **203h**	54 **204h**

[a] Reactions were run using 1.0 equiv. olefin, 1.1 equiv. sulfonamide/sulfamate ester, 1.3 equiv. $PhI(OAc)_2$, 2.3 equiv. MgO, and 0.01 equiv. $Rh_2(pfm)_4$ at 0.5 M [olefin] in C_6H_6 unless otherwise specified. [b] $R_4 = OCH_2CCl_3$. [c] $R_4 = Ph\text{-}p\text{-}NO_2$. [d] $R_4 = Ph\text{-}p\text{-}CH_3$. [e] Yield when crude $Rh_2(pfm)_4$ was used. [f] Yield when 5.0 equiv. olefin were used.

3.5.4 Olefinic Substrate as a Limiting Reagent in Aziridination Methodology

One of the most noteworthy attributes of Du Bois' aziridination protocol is that the yields in this publication were based upon the use of the olefinic substrate as the limiting reagent.[26] As noted by Du Bois in his communication, while such conditions are clearly considered to be optimal, the vast majority of metal-catalyzed aziridination methodologies require that the olefinic substrate be used in large excess, and thus the yields are based upon the limiting iminoiodinane ylide (i.e, "standard" conditions).[12,42,8,20,5,43,14,46]

It is very important to note that the isolated yields reported in Table 3.1 with **199** were obtained using a limiting amount of olefinic substrate (analogous to Du Bois' methodology). In fact, the yields of **203a-h** and **204a-h** in this study are comparable to those of other rhodium-catalyzed aziridinations in which the olefinic substrate was present in 5- to 20-fold excess (i.e., "standard" conditions). For example, a limiting amount of styrene (**200a**) was transformed into its tosyl aziridine **204a** in 73% yield (Table 3.1). In comparison, Muller and Evans have independently shown that rhodium (II) acetate catalyzed the conversion of **200a** into **204a** in 59% and 48% yields, respectively, when twenty and five equivalents, respectively, of **200a** were used.[12,5]

In an effort to quantify the disparity between these protocols, the tosyl aziridination reaction was conducted once again on olefin **200g**, except in this case, five equivalents of **200g** were used to mimic "standard" conditions. Under these conditions, the tosyl aziridine **204g** was obtained in 75% yield (Table 3.1). Thus, this modification led to a marked improvement in the yield of this reaction which reflects the dramatic

differences between this aziridination protocol in comparison with the "standard" conditions in the literature.[12,42,8,20,5,43,14,46]

3.6 Conclusions

In the course of efforts towards the total synthesis of (+)-kalihinol A, the catalyst rhodium perfluorobutyramide was found to conduct trichloroethoxysulfonyl aziridinations. As a result, a methodology project ensued resulting in the development of an improved, microwave-assisted method for the preparation of the catalyst. Futhermore, it has been demonstrated that the aziridination procedure can be utilized to perform sulfonamide-based aziridinations as well. The optimized aziridination protocol has several advantages over current methods in the literature such as the *in situ* generation of the iminoiodinane ylide, the low catalyst requirement, and, most notably, the practical use of the olefinic substrate as the limiting reagent.

3.7 Experimentals

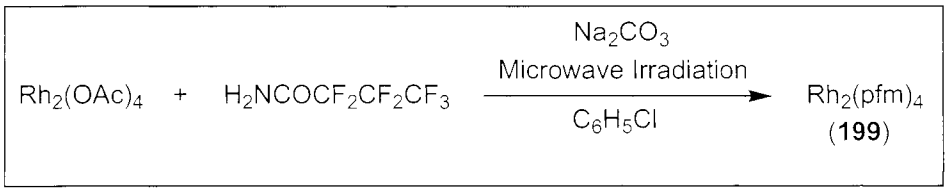
3.7.1 Materials and Methods

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. ^{1}H 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 ^{1}H δ 7.26 ppm, ^{13}C δ 77.16 ppm; acetone ^{1}H δ 2.05 ppm, ^{13}C δ 29.84 ppm; methanol ^{1}H δ 3.31 ppm, ^{13}C δ 49.00 ppm). 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

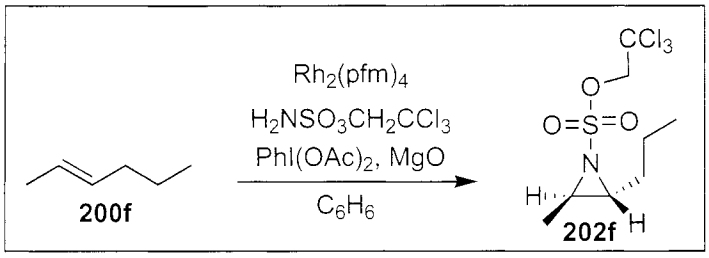
Preparation of Rhodium perfluorobutyramide (199)



Rhodium perfluorobutyramide (199). Rhodium acetate (25 mg, 0.056 mmol, 1.0 equiv.), perfluorobutyramide (120 mg, 0.56 mmol, 10.0 equiv.), and Na_2CO_3 (60 mg, 0.56 mmol, 10.0 equiv.) were dissolved in chlorobenzene (3 mL) in a microwave vial.

The reaction was conducted under microwave irradiation (Biotage Initiator, 205 W) for 30 minutes at 250°C. The purple reaction mixture was cooled to room temperature and extracted with FC-72 (perfluoro-*n*-hexane, Acros) three times. The fluorous extracts were concentrated under reduced pressure. Excess perfluorobutyramide was removed by sublimation. The complex could be used without further purification, or purified by silica gel chromatography (9:1 to 3:1 hexanes/ethyl acetate) to give $Rh_2(pfm)_4$ (31 mg, 53% yield) as a blue solid. ^{19}F NMR (376 MHz, CD_3CN, $C_6H_5CF_3$ standard at -63.7 ppm) -82.0, -117.8, -127.9 ppm.

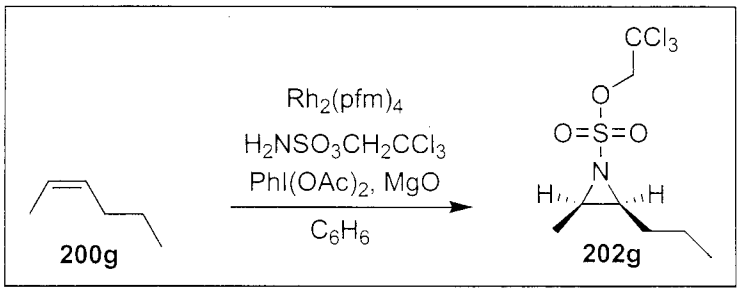
Preparation of trichloroethoxylsulfonyl aziridine 202f



Trichloroethoxysulfonylaziridine 202f. To a solution of $H_2NSO_3CH_2CCl_3$ (126 mg, 0.55 mmol, 1.1 equiv.) in benzene (1 mL) was added *trans*-2-hexene (**200f**) (63 μL, 0.50 mmol, 1.0 equiv.), magnesium oxide (46 mg, 1.15 mmol, 2.3 equiv.), and rhodium (II) perfluorobutyramide (5.3 mg, 0.005 mmol, 0.01 equiv.). The suspension was cooled to 5°C and phenyliododiacetate ($PhI(OAc)_2$, 209 mg, 0.65 mmol, 1.3 equiv.) was added. The reaction was allowed to gradually warm to rt over 2 hours and was run at rt for 8 additional hours. The reaction was then filtered through Celite, washed repeatedly with

CH_2Cl_2 (15 mL), and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (6:1 to 3:1 hexanes:ethyl acetate) to afford **202f** (112 mg, 72% yield) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.78 (s, 2H), 2.79-2.69 (comp m, 2H), 1.77-1.41 (comp m, 4H), 1.53 (d, *J*=5.8 Hz, 3H), 0.96 (t, *J*=7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 93.3, 79.5, 50.8, 46.0, 32.0, 20.2, 14.7, 13.7 ppm; IR (thin film/NaCl) 2962 (m), 2935 (m), 2876 (w), 1450 (w), 1366 (s), 1250 (w), 1181 (s), 1166 (m) cm^{-1}; HRMS (FAB) *m/z* found: 309.9839 [calc'd for $C_8H_{15}Cl_3NO_3S$ (M+H): 309.9838].

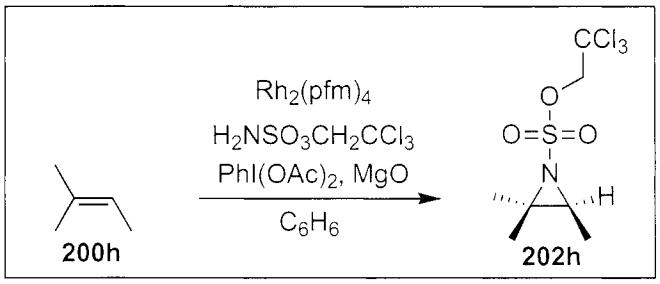
Preparation of trichloroethoxylsulfonyl aziridine 202g



Trichloroethoxysulfonylaziridine 202g. To a solution of $H_2NSO_3CH_2CCl_3$ (126 mg, 0.55 mmol, 1.1 equiv.) in benzene (1 mL) was added *cis*-2-hexene (**200g**) (61 μL, 0.50 mmol, 1.0 equiv.), magnesium oxide (46 mg, 1.15 mmol, 2.3 equiv.), and rhodium (II) perfluorobutyramide (5.3 mg, 0.005 mmol, 0.01 equiv.). The suspension was cooled to 5°C and phenyliodiodiacetate ($PhI(OAc)_2$, 209 mg, 0.65 mmol, 1.3 equiv.) was added. The reaction was allowed to gradually warm to rt over 2 hours and was run at rt for 8 additional hours. The reaction was then filtered through Celite, washed repeatedly with

CH_2Cl_2 (15 mL), and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (4:1 hexanes:ethyl acetate) to afford **202g** (85 mg, 55% yield) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.79 (d, *J*=10.5 Hz, 1H), 4.76 (d, *J*=10.8 Hz, 1H), 3.03-2.96 (m, 1H), 2.91-2.85 (m, 1H), 1.60-1.45 (comp m, 4H), 1.31 (d, *J*=6.1 Hz, 3H), 0.99 (t, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 93.2, 79.4, 47.0, 42.5, 28.3, 20.4, 13.8, 12.0 ppm; IR (thin film/NaCl) 2962 (m), 2876 (w), 1466 (w), 1450 (w), 1379 (s), 1367 (s), 1254 (w), 1181 (s) cm^{-1}; HRMS (FAB) *m/z* found: 309.9839 [calc'd for $C_8H_{15}Cl_3NO_3S$ (M+H): 309.9838].

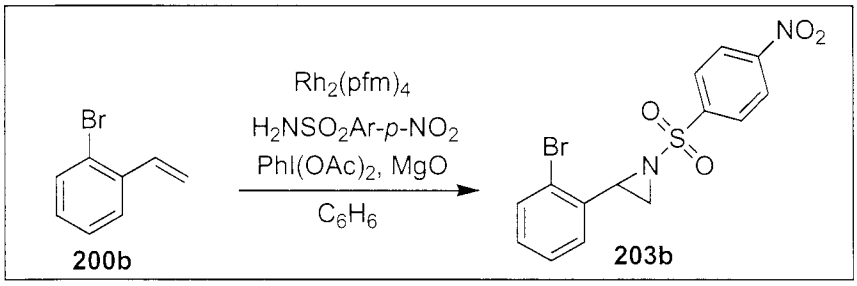
Preparation of trichloroethoxylsulfonyl aziridine 202h



Trichloroethoxysulfonylaziridine 202h. To a solution of $H_2NSO_3CH_2CCl_3$ (126 mg, 0.55 mmol, 1.1 equiv.) in benzene (1 mL) was added 2-methyl-2-butene (**200h**) (53 μL, 0.50 mmol, 1.0 equiv.), magnesium oxide (46 mg, 1.15 mmol, 2.3 equiv.), and rhodium (II) perfluorobutyramide (5.3 mg, 0.005 mmol, 0.01 equiv.). The suspension was cooled to 5°C and phenyliododiacetate ($PhI(OAc)_2$, 209 mg, 0.65 mmol, 1.3 equiv.) was added. The reaction was allowed to gradually warm to rt over 2 hours and was run at rt for 8 additional hours. The reaction was then filtered through Celite, washed

repeatedly with CH_2Cl_2 (15 mL), and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (9:1 to 6:1 hexanes:ethyl acetate) to afford **202h** (113 mg, 76% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (d, *J*=10.8 Hz, 1H), 4.71 (d, *J*=10.8 Hz, 1H), 2.97 (q, *J*=5.9 Hz, 1H), 1.62 (s, 3H), 1.32 (s, 3H), 1.29 (d, *J*=5.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 93.3, 79.3, 51.7, 50.1, 20.9, 20.4, 13.0 ppm; IR (thin film/NaCl) 3000 (m), 2972 (s), 2936 (m), 1626 (w), 1462 (s), 1415 (m), 1366 (s), 1253 (m), 1181 (s), 1090 (s) cm^{-1}; HRMS (FAB) *m/z* found: 295.9681 [calc'd for $C_7H_{13}Cl_3NO_3S$ (M+H): 295.9681].

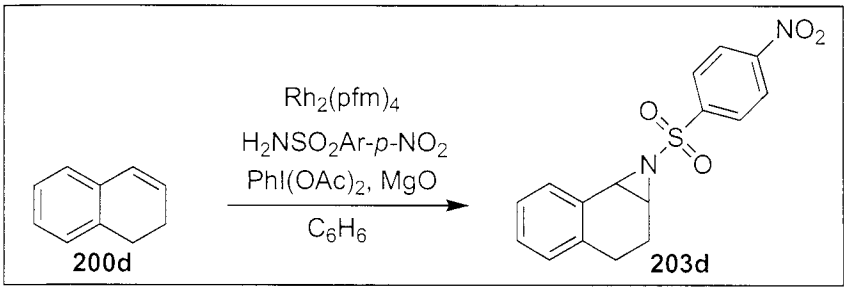
Preparation of nosyl aziridine 203b



Nosyl aziridine 203b. To a solution of *para*-nitrobenzenesulfonamide (111 mg, 0.55 mmol, 1.1 equiv.) in benzene (1 mL) was added *ortho*-bromostyrene (**200b**) (63 μL, 0.50 mmol, 1.0 equiv.), magnesium oxide (46 mg, 1.15 mmol, 2.3 equiv.), and rhodium (II) perfluorobutyramide (5.3 mg, 0.005 mmol, 0.01 equiv.). The suspension was cooled to 5°C and phenyliodosodiacetate ($PhI(OAc)_2$, 209 mg, 0.65 mmol, 1.3 equiv.) was added. The reaction was allowed to gradually warm to rt over 2 hours and was run at rt for 8 additional hours. The reaction was then filtered through Celite, washed repeatedly with

CH_2Cl_2 (15 mL), and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (6:1 to 1:1 hexanes:ethyl acetate) to afford **203b** (137 mg, 71% yield) as a cream-colored solid, m.p. 131-132°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J*=8.6 Hz, 2H), 8.11 (d, *J*=8.6 Hz, 2H), 7.41 (d, *J*=7.8 Hz, 1H), 7.15-6.98 (comp m, 3H), 4.03 (dd, *J*=4.7, 7.4 Hz, 1H), 3.04 (d, *J*=7.2 Hz, 1H), 2.29 (d, *J*=4.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 143.7, 134.0, 132.7, 130.1, 129.5, 129.5, 127.9, 127.5, 124.5, 124.5, 123.5, 42.1, 36.5 ppm; IR (thin film/NaCl) 3106 (m), 2871 (w), 1728 (w), 1607 (m), 1531 (s), 1349 (s), 1311 (m), 1167 (s), 1092 (m) cm^{-1}; HRMS (FAB) *m/z* found: 382.9701 [calc'd for $C_{14}H_{12}BrN_2O_4S$ (M+H): 382.9701].

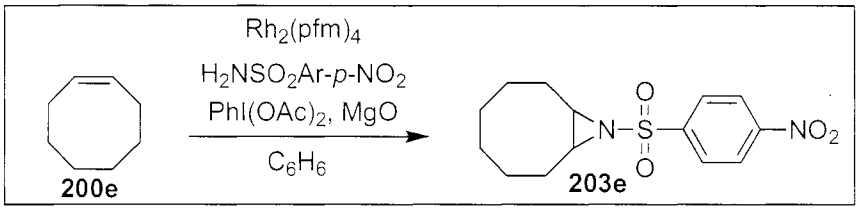
Preparation of nosyl aziridine 203d



Nosyl aziridine 203d. To a solution of *para*-nitrobenzenesulfonamide (111 mg, 0.55 mmol, 1.1 equiv.) in benzene (1 mL) was added 1,2-dihydronaphthalene (**200d**) (65 μL, 0.50 mmol, 1.0 equiv.), magnesium oxide (46 mg, 1.15 mmol, 2.3 equiv.), and rhodium (II) perfluorobutyramide (5.3 mg, 0.005 mmol, 0.01 equiv.). The suspension was cooled to 5°C and phenyliododiacetate ($PhI(OAc)_2$, 209 mg, 0.65 mmol, 1.3 equiv.) was added. The reaction was allowed to gradually warm to rt over 2 hours and was run at

rt for 8 additional hours. The reaction was then filtered through Celite, washed repeatedly with CH_2Cl_2 (15 mL), and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (8:1 to 3:1 hexanes:ethyl acetate) to afford **203d** (70 mg, 42% yield) as a cream-colored foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J*=8.8 Hz, 2H), 8.13 (d, *J*=9.2 Hz, 2H), 7.31 (d, *J*=7.6 Hz, 1H), 7.27-7.23 (m, 1H), 7.18 (t, *J*=7.6 Hz, 1H), 7.07 (d, *J*=7.4 Hz, 1H), 3.93 (d, *J*=7.0 Hz, 1H), 3.72 (br d, *J*=7.0 Hz, 1H), 2.79-2.68 (m, 1H), 2.59 (dd, *J*=5.4, 15.8 Hz, 1H), 2.34-2.28 (m, 1H), 1.75 (tdd, *J*=1.7, 5.5, 14.7 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 144.7, 136.6, 129.6, 129.2, 129.0, 128.9, 128.9, 128.6, 126.7, 124.4, 124.4, 43.4, 42.9, 24.7, 20.1 ppm; IR (thin film/NaCl) 3106 (m), 3039 (w), 2940 (m), 2855 (w), 1731 (w), 1607 (m), 1531 (s), 1400 (m), 1349 (s), 1333 (s), 1162 (s), 1090 (m) cm^{-1}; HRMS (FAB) *m/z* found: 331.0752 [calc'd for $C_{16}H_{15}N_2O_4S$ (M+H): 331.0752].

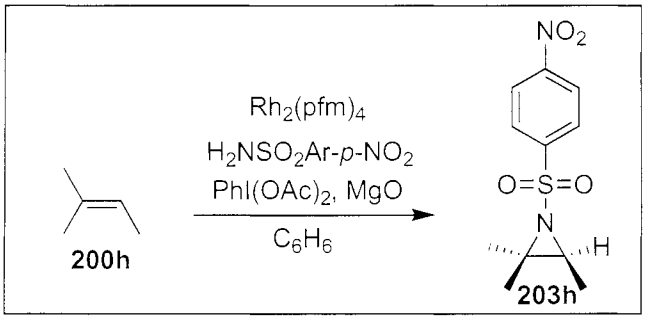
Preparation of nosyl aziridine 203e



Nosyl aziridine 203e. To a solution of *para*-nitrobenzenesulfonamide (111 mg, 0.55 mmol, 1.1 equiv.) in benzene (1 mL) was added cyclooctene (**200e**) (65 μL, 0.50 mmol, 1.0 equiv.), magnesium oxide (46 mg, 1.15 mmol, 2.3 equiv.), and rhodium (II) perfluorobutyramide (5.3 mg, 0.005 mmol, 0.01 equiv.). The suspension was cooled to

5°C and phenyliodosodiacetate ($PhI(OAc)_2$, 209 mg, 0.65 mmol, 1.3 equiv.) was added. The reaction was allowed to gradually warm to rt over 2 hours and was run at rt for 8 additional hours. The reaction was then filtered through Celite, washed repeatedly with CH_2Cl_2 (15 mL), and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (6:1 to 3:1 hexanes:ethyl acetate) to afford **203e** (71 mg, 46% yield) as a cream-colored solid, m.p. 143-144°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J*=8.7 Hz, 2H), 8.14 (d, *J*=8.9 Hz, 2H), 2.94-2.87 (m, 2H), 2.07-1.98 (m, 2H), 1.67-1.22 (comp m, 10H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 145.0, 129.0, 124.4, 45.1, 26.4, 26.3, 25.3 ppm; IR (thin film/NaCl) 3105 (m), 3070 (w), 2924 (s), 2858 (m), 1530 (s), 1351 (s), 1304 (s), 1295 (s), 1159 (s) cm^{-1}; HRMS (FAB) *m/z* found: 311.1065 [calc'd for $C_{14}H_{19}N_2O_4S$ (M+H): 311.1065].

Preparation of nosyl aziridine 203h



Nosyl aziridine 203h. To a solution of *para*-nitrobenzenesulfonamide (111 mg, 0.55 mmol, 1.1 equiv.) in benzene (1 mL) was added 2-methyl-2-butene (**200h**) (53 μL, 0.50 mmol, 1.0 equiv.), magnesium oxide (46 mg, 1.15 mmol, 2.3 equiv.), and rhodium

(II) perfluorobutyramide (5.3 mg, 0.005 mmol, 0.01 equiv.). The suspension was cooled to 5°C and phenyliododiacetate ($PhI(OAc)_2$, 209 mg, 0.65 mmol, 1.3 equiv.) was added. The reaction was allowed to gradually warm to rt over 2 hours and was run at rt for 8 additional hours. The reaction was then filtered through Celite, washed repeatedly with CH_2Cl_2 (15 mL), and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (9:1 to 3:1 hexanes:ethyl acetate) to afford **203h** (50 mg, 31% yield) as a white solid, m.p. 114-116°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J*=8.8 Hz, 2H), 8.11 (d, *J*=8.8 Hz, 2H), 3.06 (q, *J*=6.1 Hz, 1H), 1.76 (s, 3H), 1.33 (s, 3H), 1.17 (d, *J*=6.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3, 147.3, 128.4, 128.4, 124.3, 124.3, 53.6, 49.3, 21.9, 20.9, 13.0 ppm; IR (thin film/NaCl) 3116 (m), 3000 (w), 2968 (w), 2931 (w), 2867 (w), 1607 (m), 1531 (s), 1460 (w), 1380 (m), 1351 (s), 1319 (s), 1300 (s), 1162 (s) cm^{-1}; HRMS (FAB) *m/z* found: 271.0753 [calc'd for $C_{11}H_{15}N_2O_4S$ (M+H): 271.0752].

3.8 Notes and References

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37. This procedure was conducted by George A. Moniz, Ph.D., Yale University.

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40. With the exception of *para*-methyl styrene, all of these yields were within 8% of Du Bois' reported yields obtained with rhodium trifluoroacetamide.

41. In the reaction using crude catalyst, there may have been some residual perfluorobutyramide present in the mixture. As a result, a possible reason for the diminished yield might be that the actual amount of rhodium perfluorobutyramide used in this reaction was slightly less than 1 mol% due to contamination.

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Appendix Two:

Spectra Relevant to Chapter 3

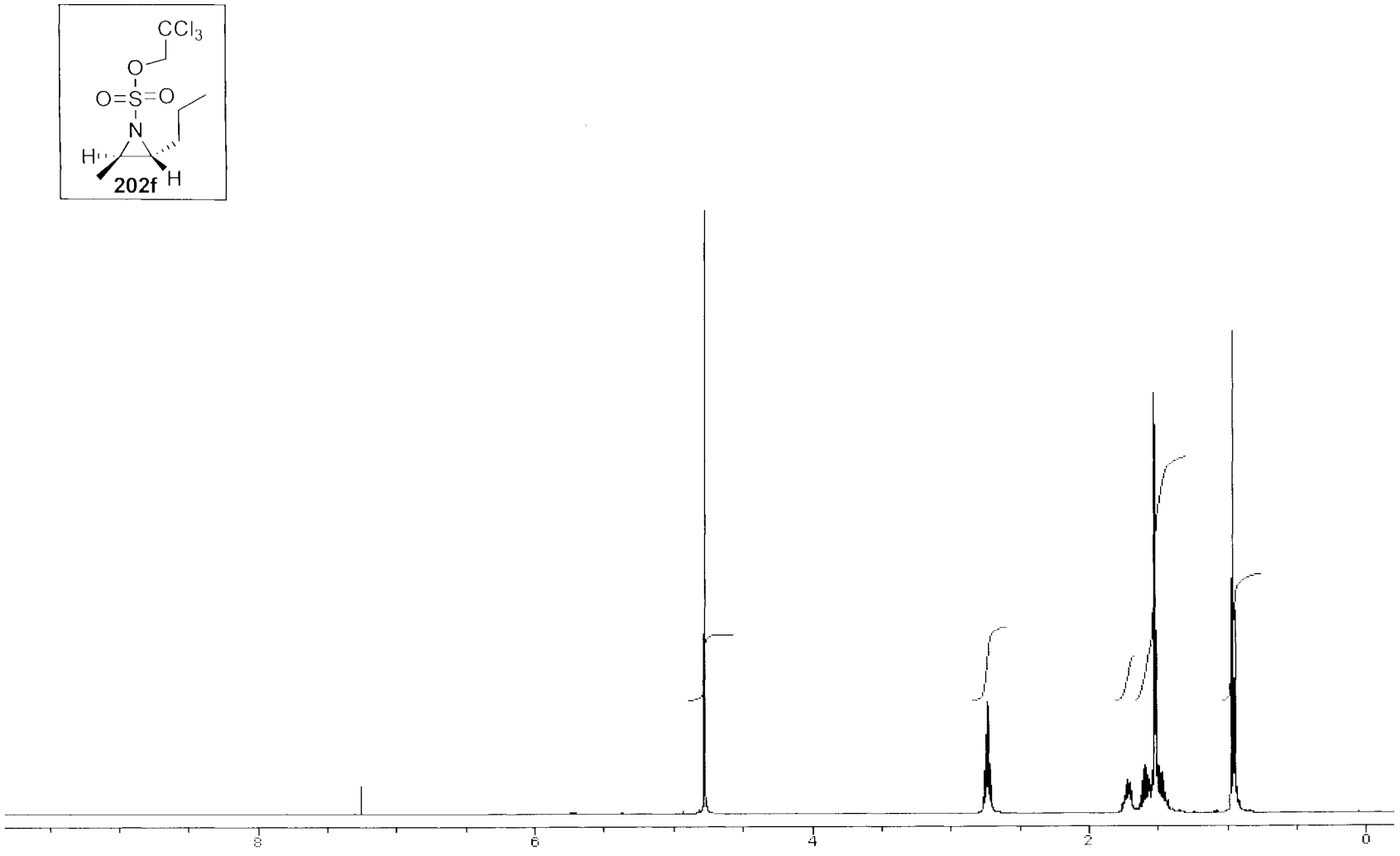


Figure A.2.1 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **202f**

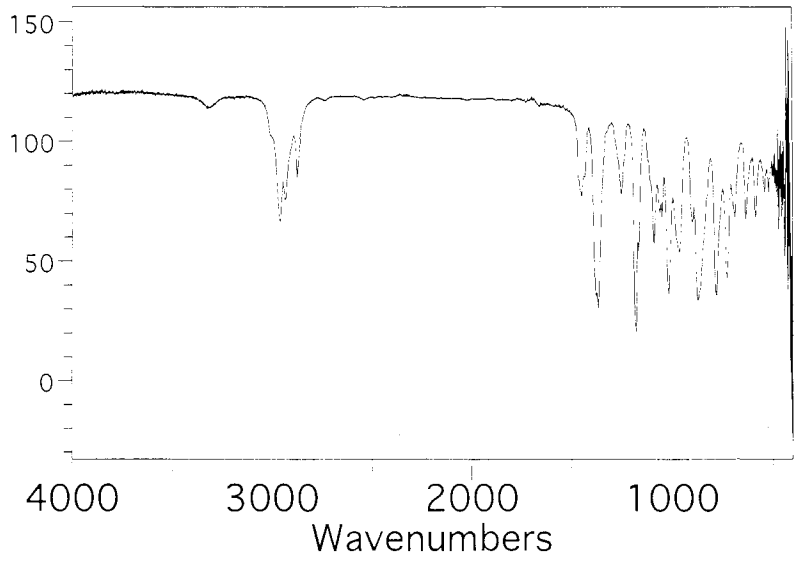


Figure A.2.2 FTIR Spectrum (thin film/NaCl) of Compound **202f**

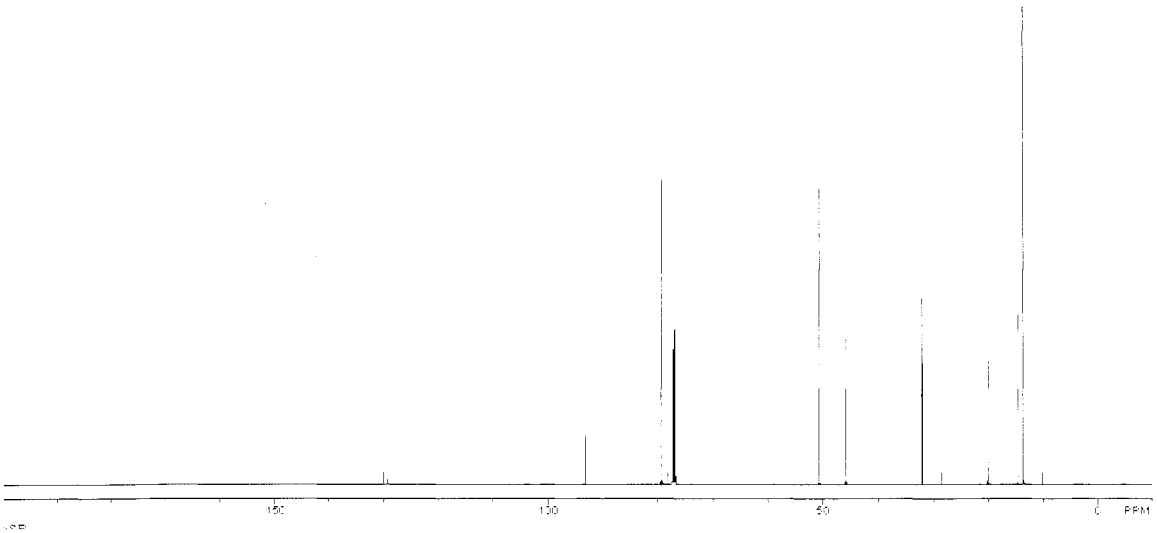


Figure A.2.3 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **202f**

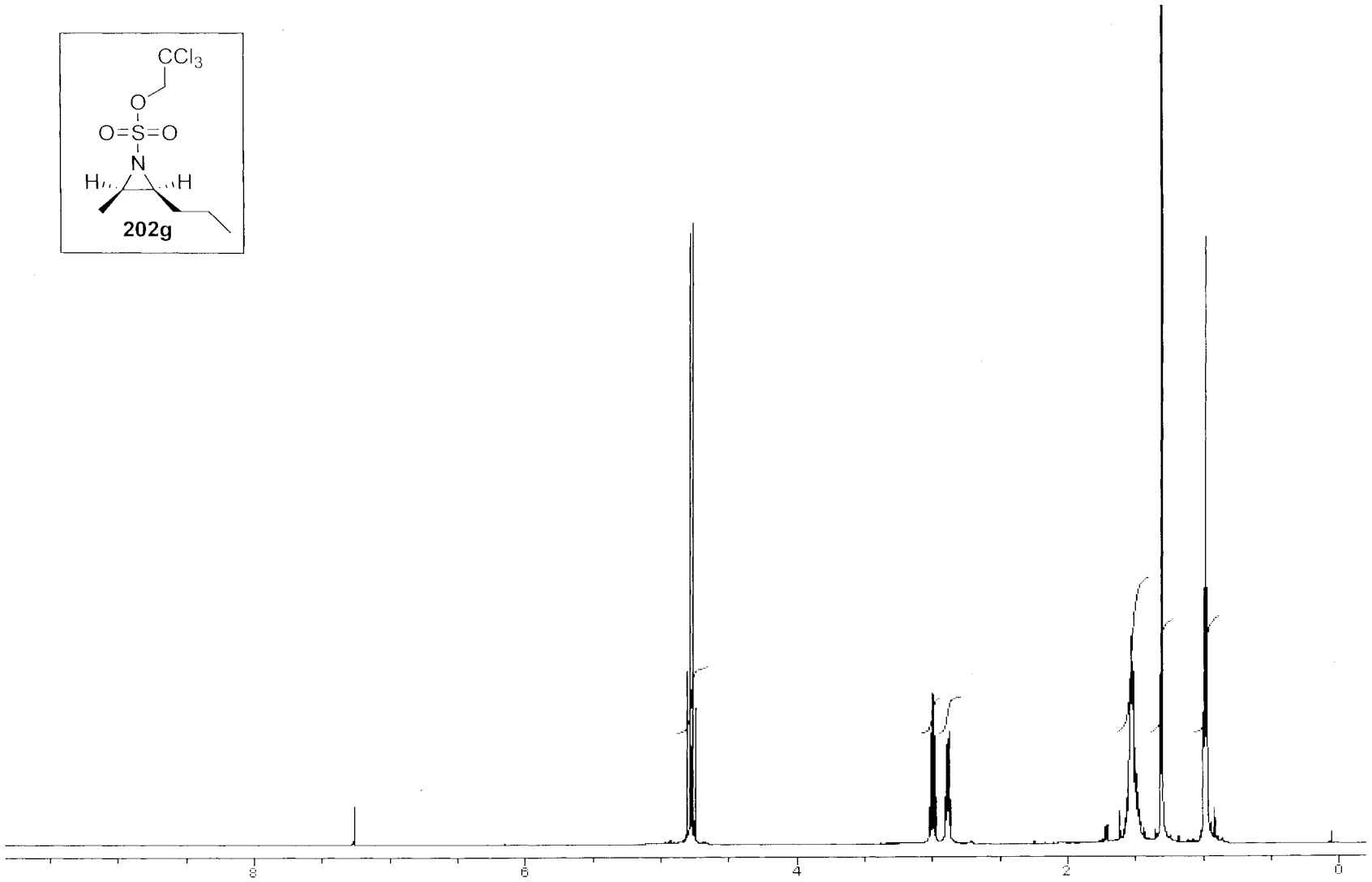


Figure A.2.4 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **202g**

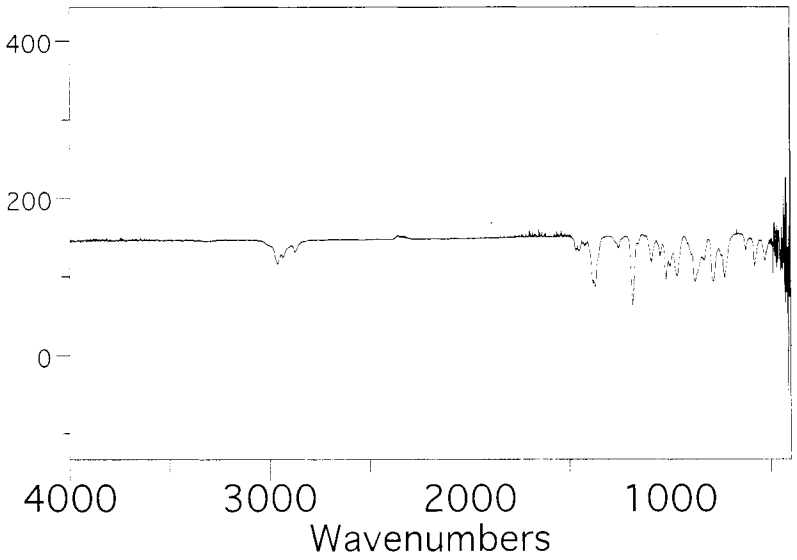


Figure A.2.5 FTIR Spectrum (thin film/NaCl) of Compound **202g**

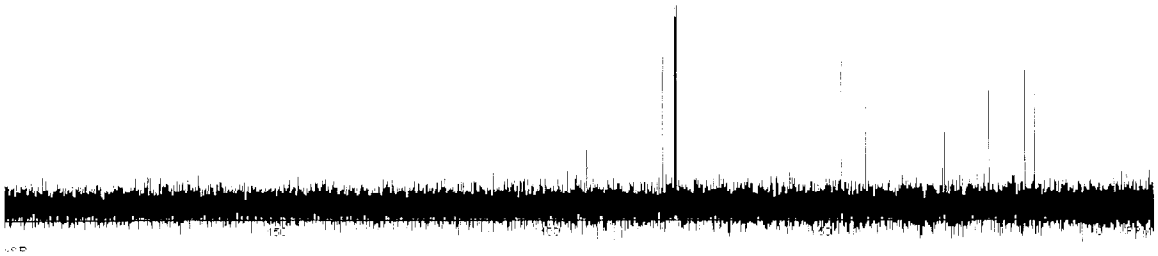


Figure A.2.6 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **202g**

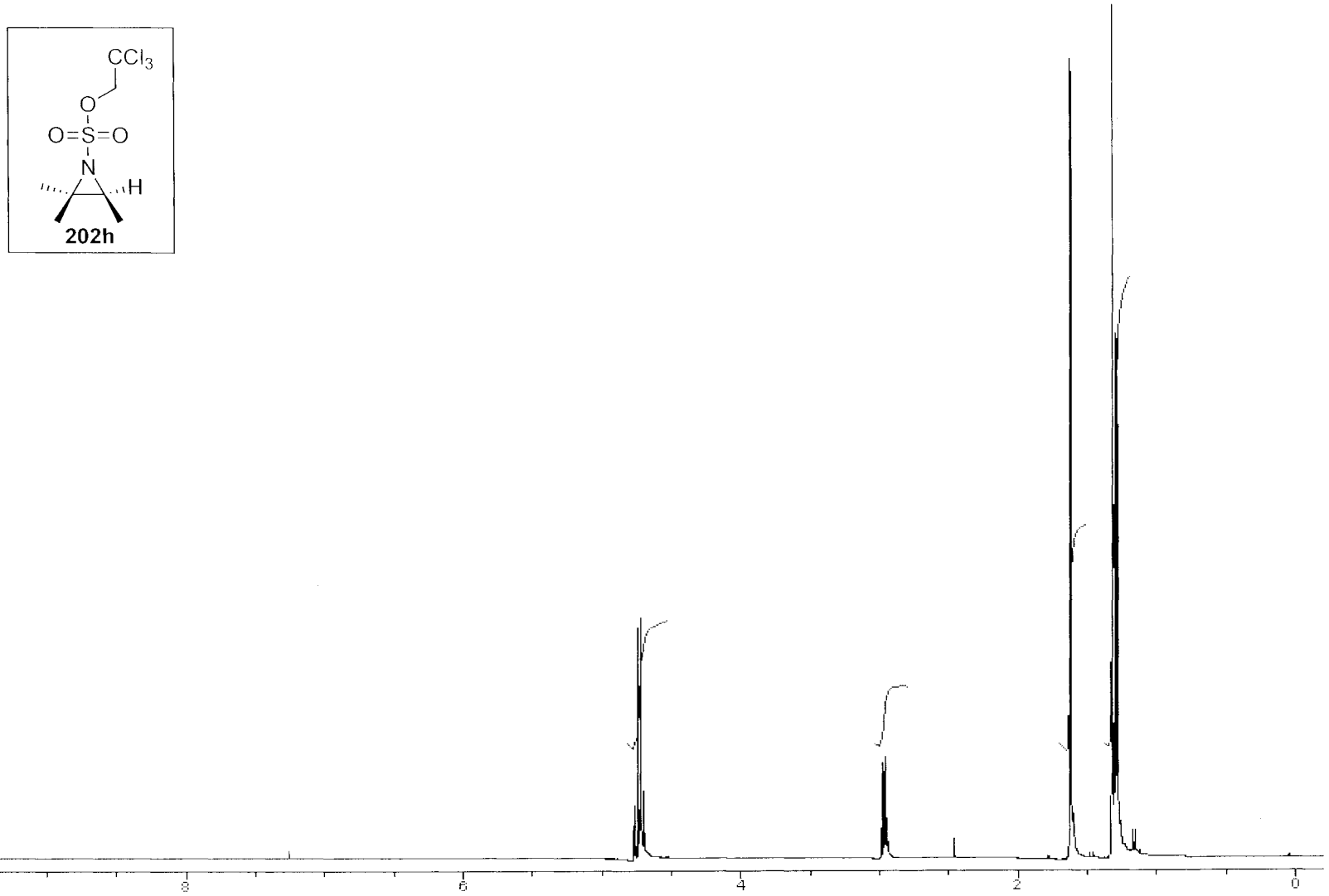


Figure A.2.7 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **202h**

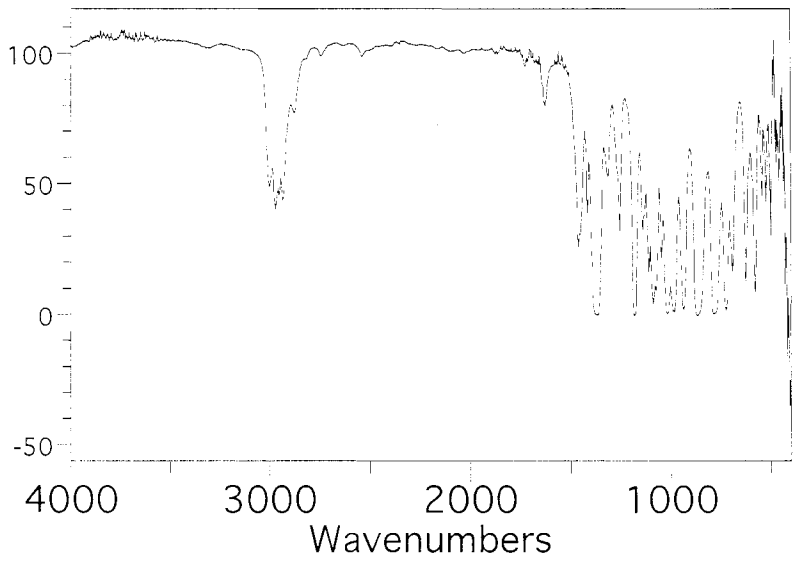


Figure A.2.8 FTIR Spectrum (thin film/NaCl) of Compound **202h**

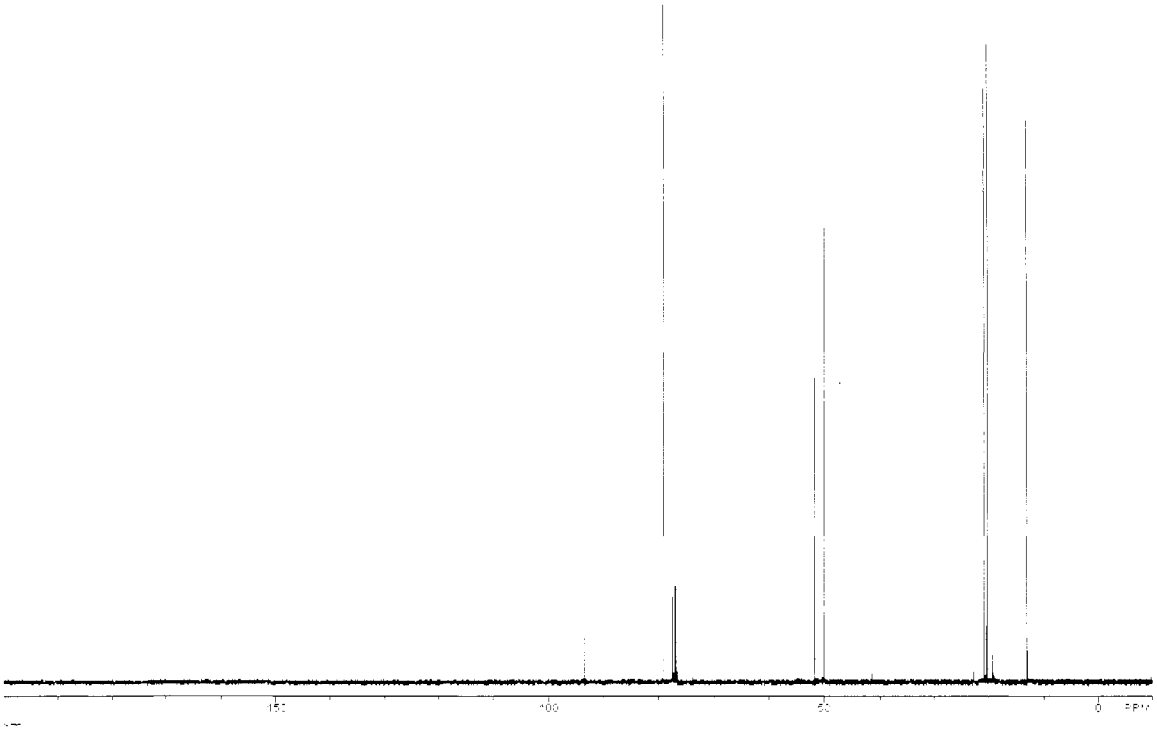
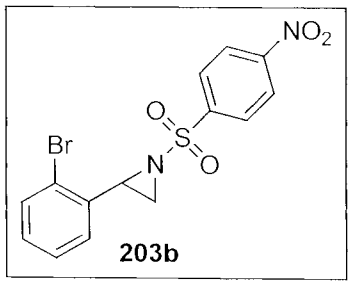


Figure A.2.9 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **202h**



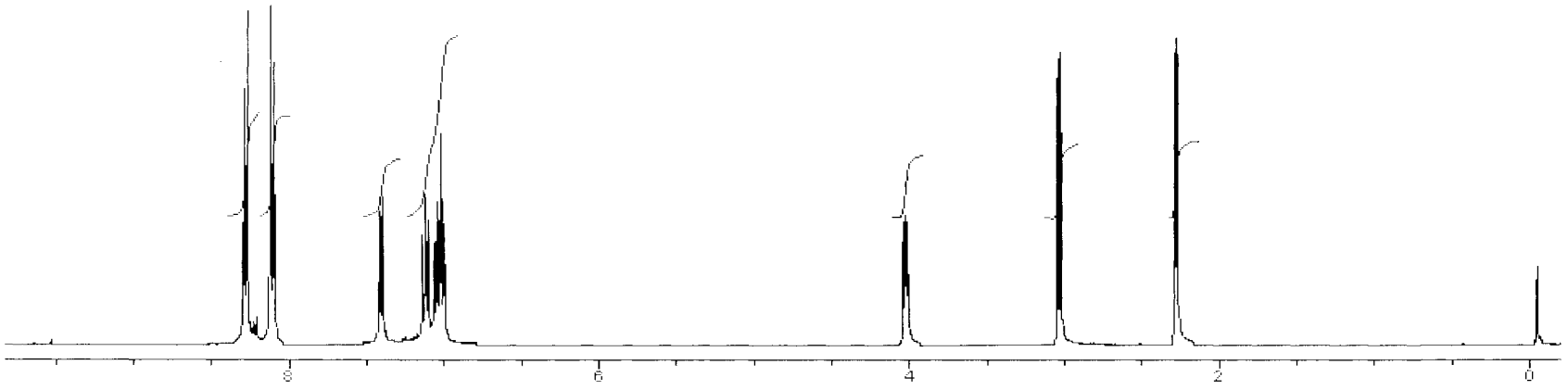


Figure A.2.10 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **203b**

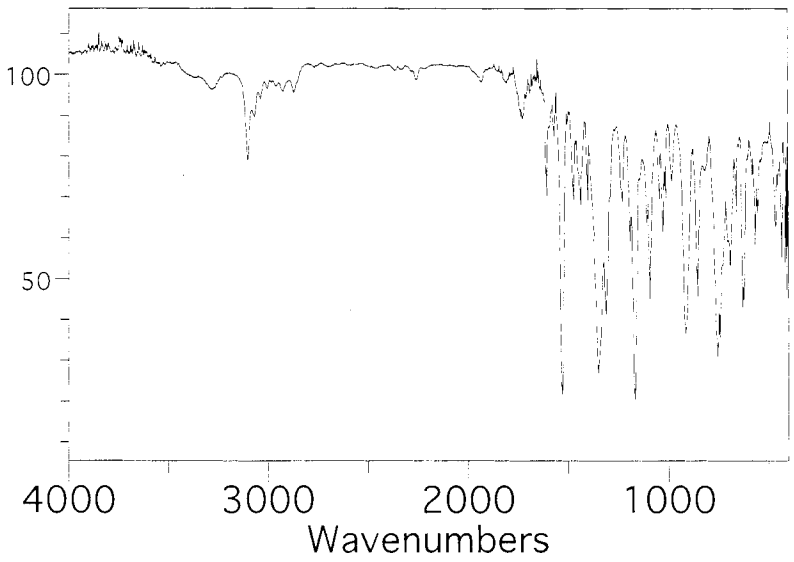


Figure A.2.11 FTIR Spectrum (thin film/NaCl) of Compound **203b**

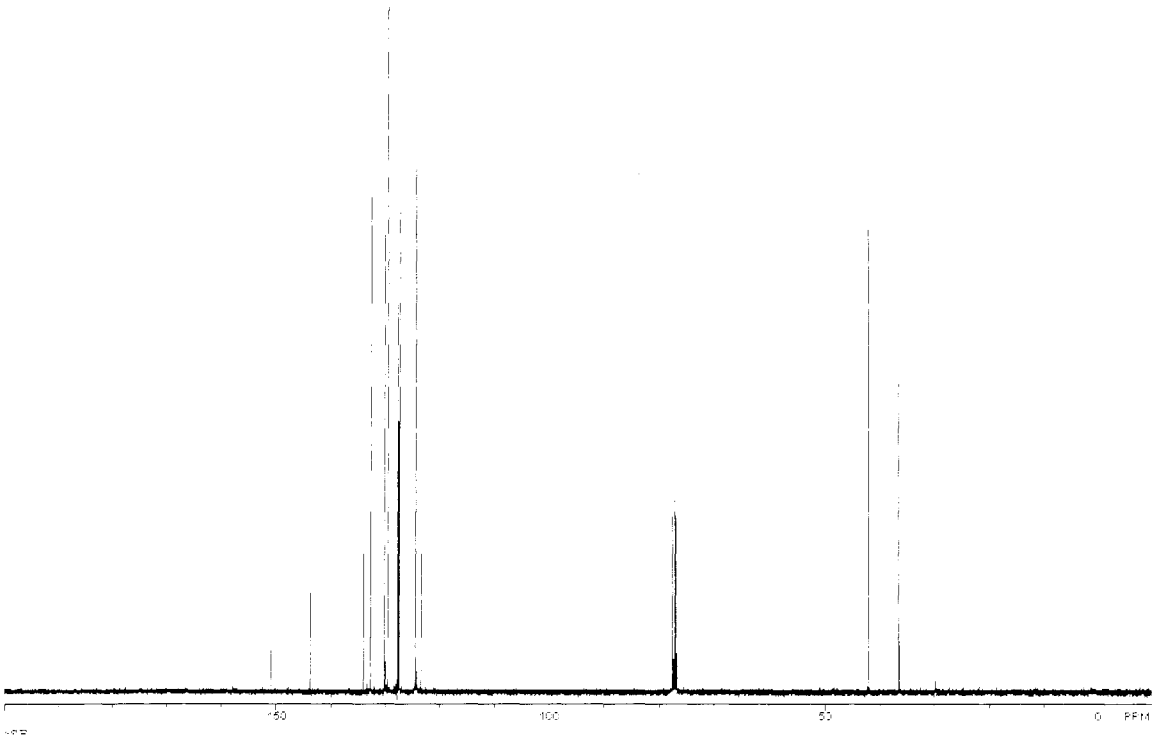
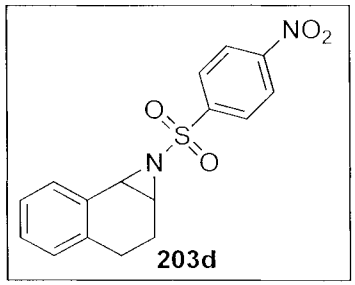


Figure A.2.12 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **203b**



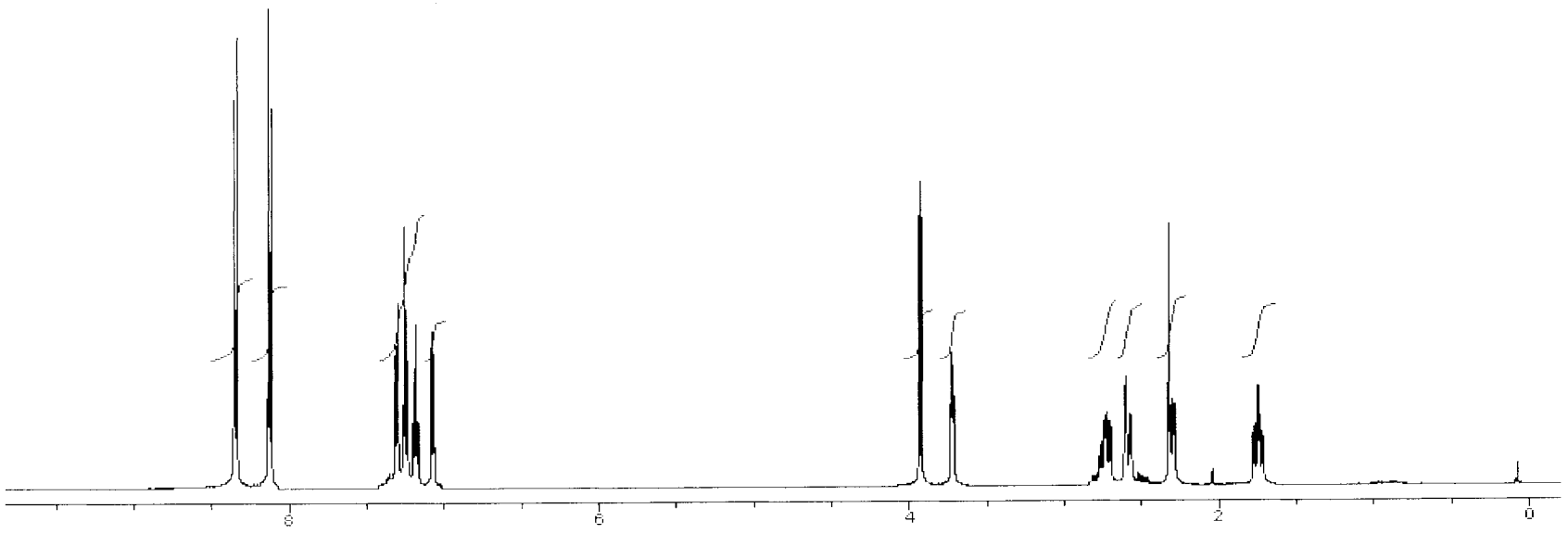


Figure A.2.13 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **203d**

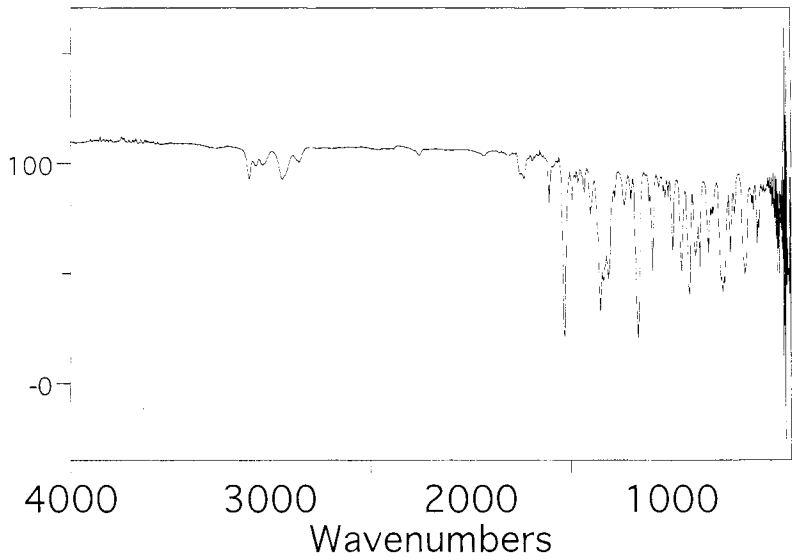


Figure A.2.14 FTIR Spectrum (thin film/NaCl) of Compound **203d**

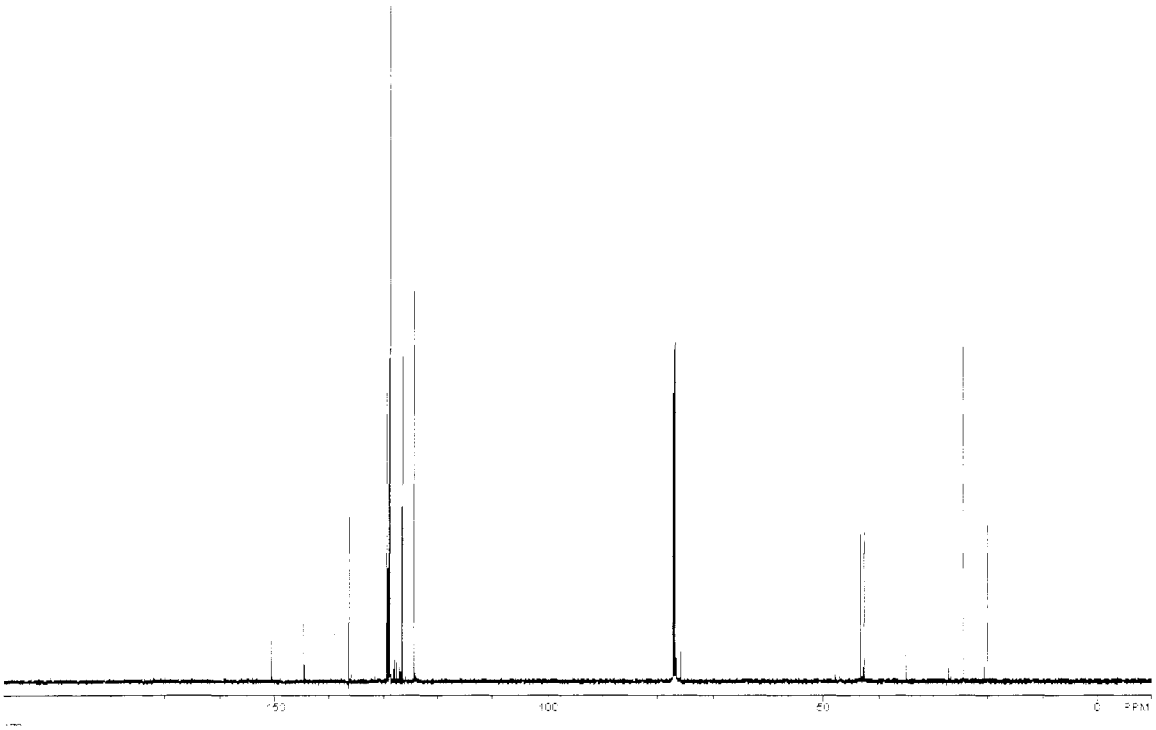
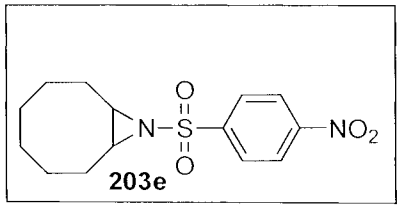


Figure A.2.15 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **203d**



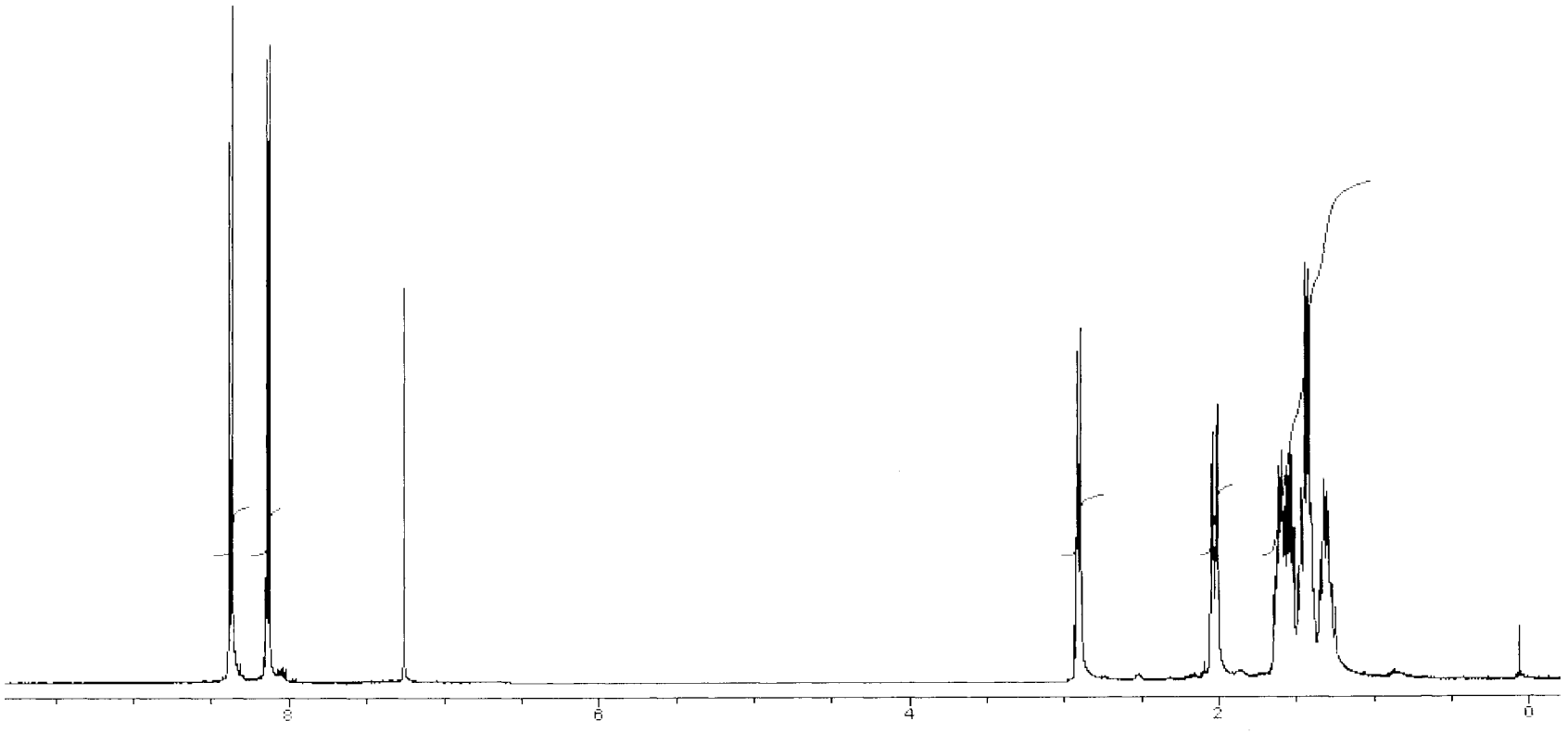


Figure A.2.16 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **203e**

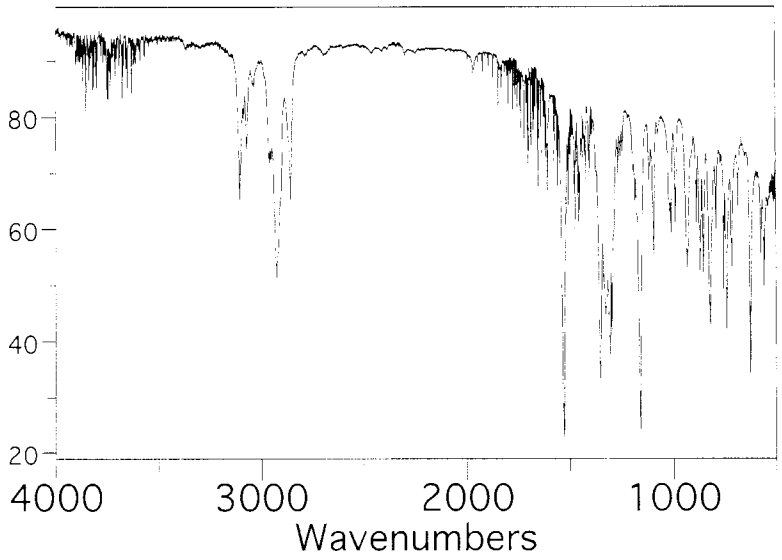


Figure A.2.17 FTIR Spectrum (thin film/NaCl) of Compound **203e**

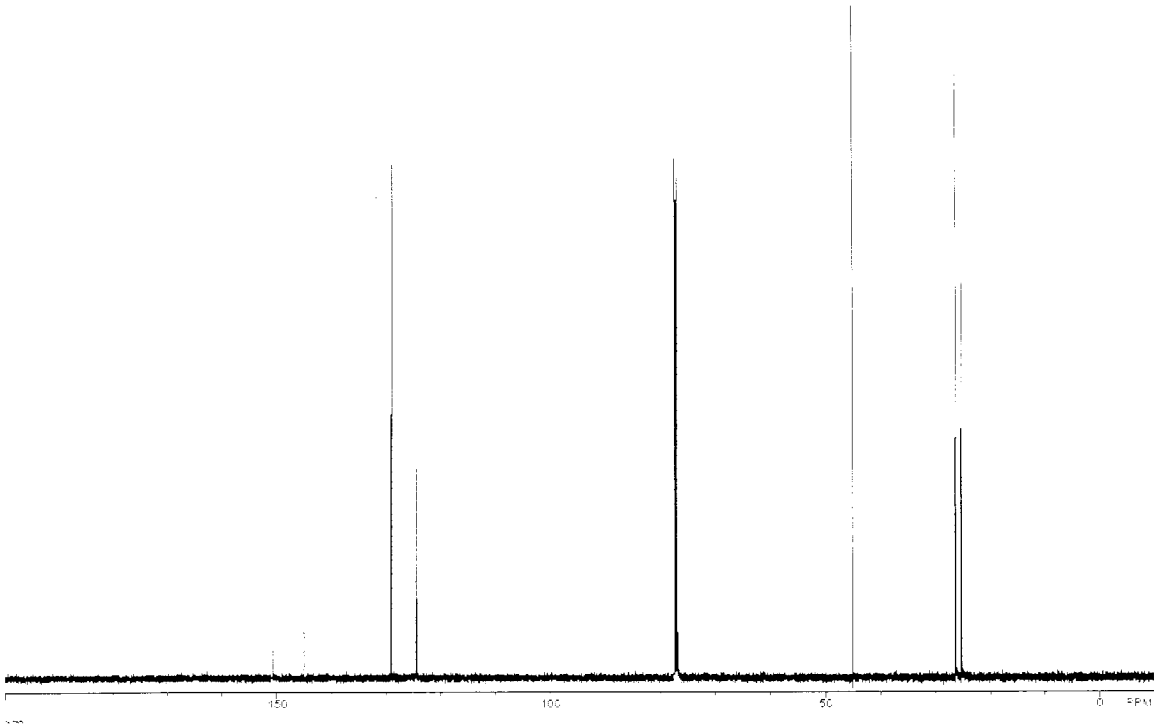


Figure A.2.18 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **203e**

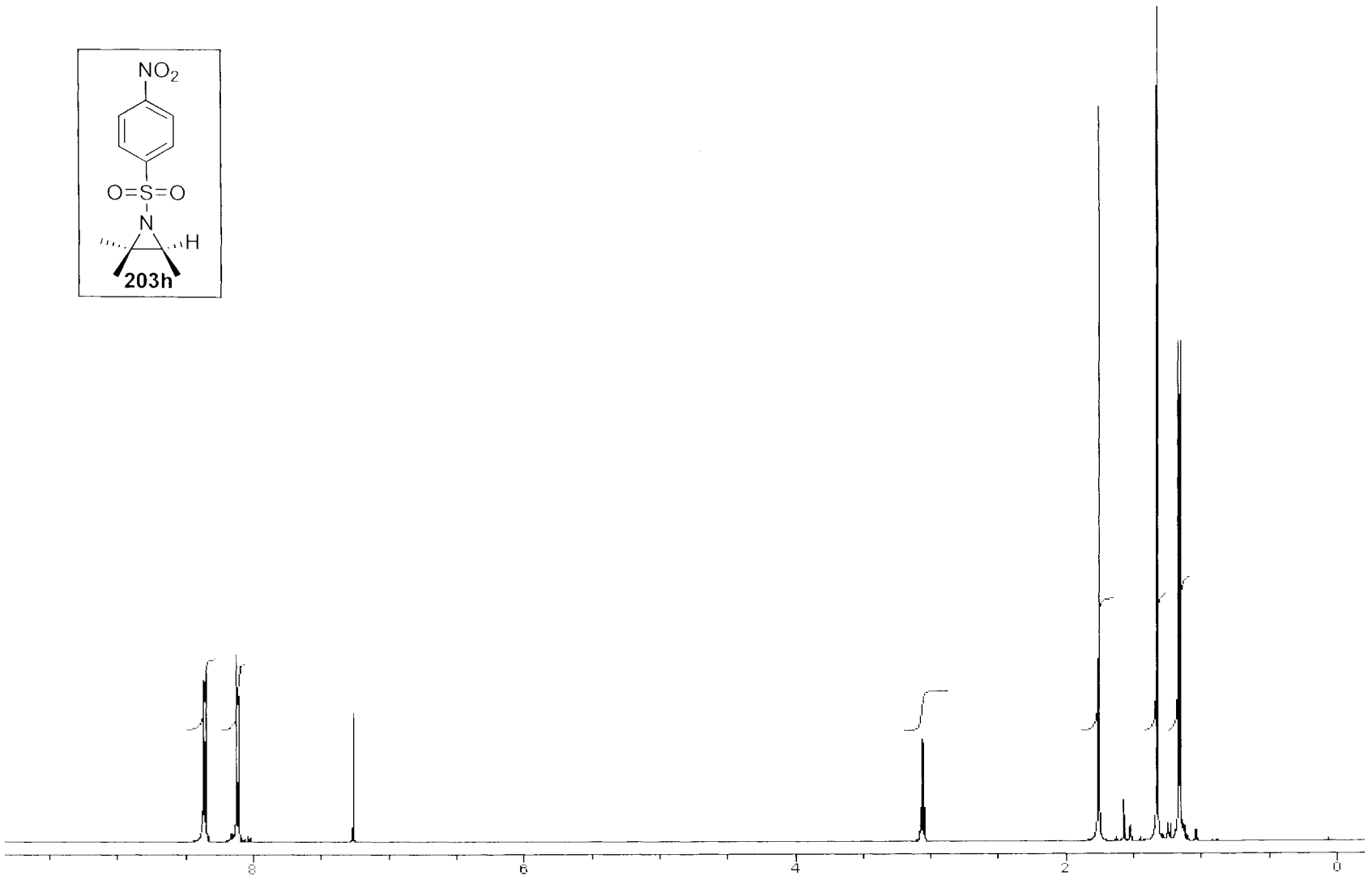


Figure A.2.19 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **203h**

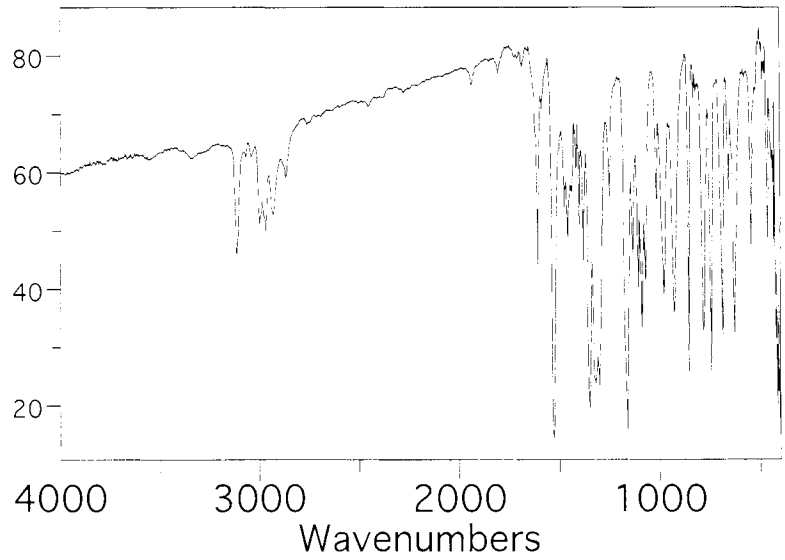


Figure A.2.20 FTIR Spectrum (thin film/NaCl) of Compound **203h**

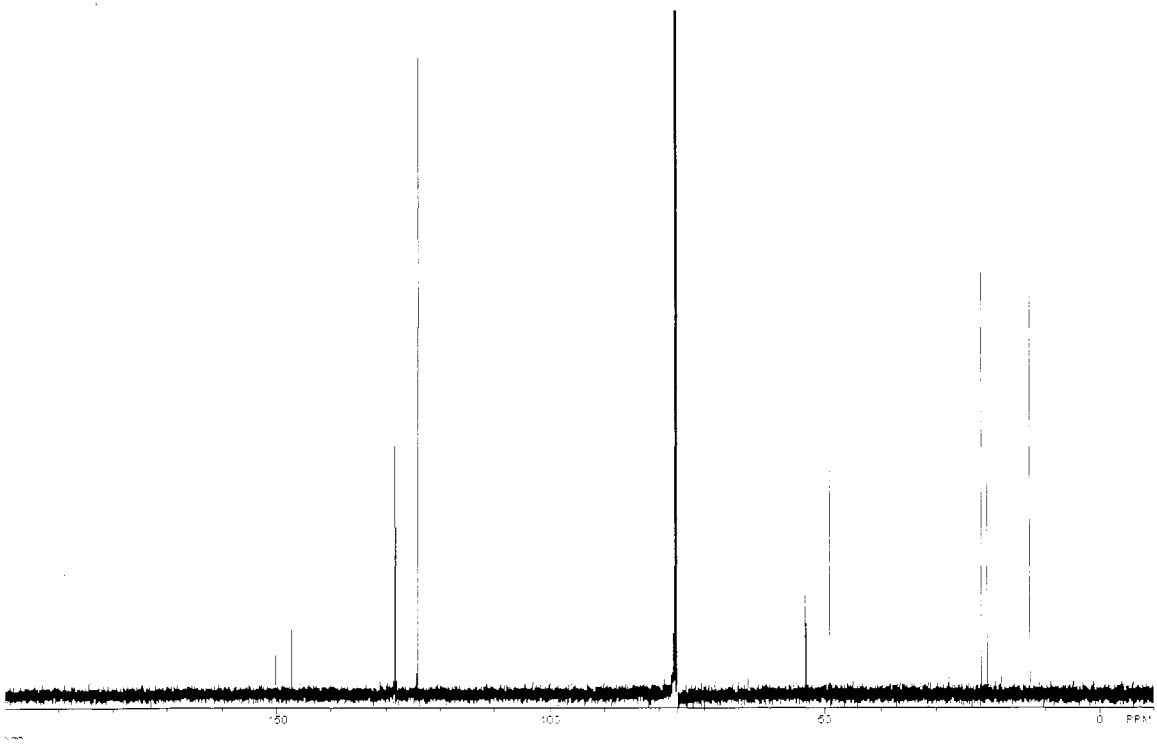


Figure A.2.21 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **203h**

Chapter 4

Synthesis of Kalihinane Analogs and Evaluation of their Antimalarial Activity

4.1 Malaria

4.1.1 Background

Approximately two billion people in the world today are currently at risk for contracting malaria.[1] Every year, 300-500 million people suffer from this disease, and more than two million die annually as a result of infection.[2] The global distribution of malaria has been evaluated very recently, and the disease remains endemic in areas of Africa, Southeast Asia, and South America (Figure 4.1, light shading, hypoendemic (areas in which childhood infection prevalence is less than 10%); medium shading, mesoendemic (areas with infection prevalence between 11% and 50%); dark shading, hyperendemic and holoendemic (areas with an infection prevalence of 50% or more)).[3] The incidence of the most lethal form of the malaria parasite, *Plasmodium falciparum*, is increasing at an alarming rate, predominantly due to the fact that the parasite has developed resistance against chloroquine, the most commonly-used treatment for the disease.[4] Furthermore, the development of novel antimalarial agents has been neglected

over the past fifty years in large part due to a lack of interest by the pharmaceutical industry worldwide.

Figure 4.1

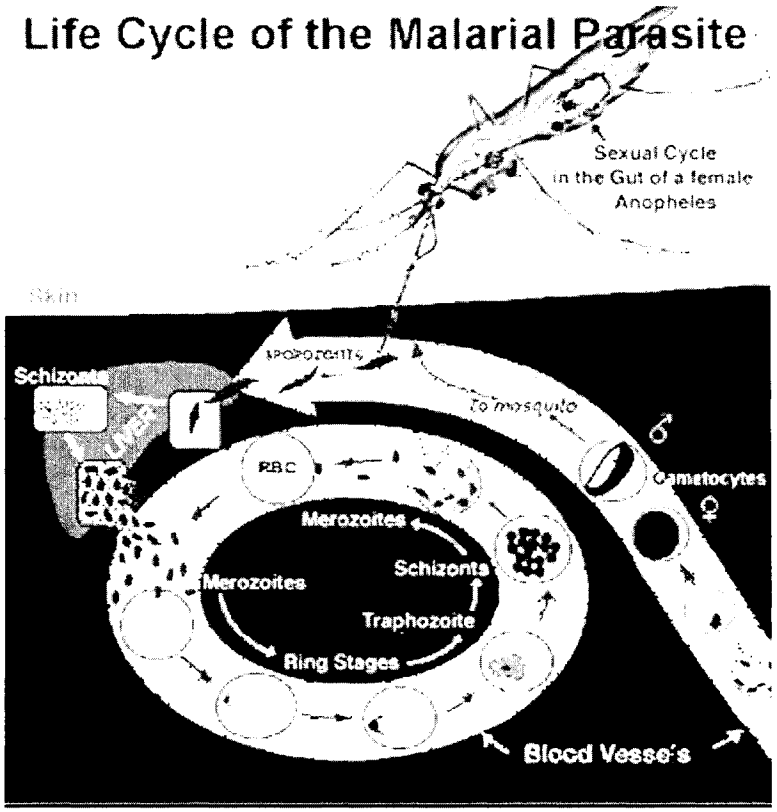
4.1.2 Biology of Infection

4.1.2.1 Parasite Life Cycle

There are four different species of *Plasmodium* capable of infecting humans: *P. falciparum* (malaria tropica), *P. vivax* (malaria tertiana), *P. malariae* (malaria tertiana), and *P. ovale* (malaria quartana).[2] The life cycle of *P. falciparum* is shown in Figure 4.2.[5] The parasite is introduced to the human body through the blood meal of a female *Anopheles* mosquito. The parasite in sporozoite form then travels through the blood stream and establishes itself within the hepatocytes to begin an asymptomatic incubation period. The sporozoites mature over a period of one to two weeks into merozoites, at which point these merozoites are released into the blood stream. Once the parasite has invaded a erythrocyte, it multiplies asexually which triggers the physical manifestations (chills, fever, nausea, fatigue, etc.) of the disease. Next, the merozoites develop into ring-

like trophozoites which undergo asexual replication to form schizonts. Ultimately, the erythrocyte bursts, releasing merozoites into the bloodstream, leading to the invasion of other erythrocytes and repetition of the cycle. Throughout this entire process, some of the parasites have developed into gametocytes, a sexual form which is readily transmitted to another *Anopheles* mosquito to infect another human and continue the cycle of infection.

Figure 4.2



4.1.2.2 Hemoglobin Degradation by Parasite Proteases

While inside the erythrocyte, the parasite is unable to synthesize large amounts of amino acids required for its own sustenance. As a result, it degrades human hemoglobin

to gain access to amino acids needed for protein synthesis. Human hemoglobin is then transported to the parasitic food vacuole, a highly sophisticated organelle designed to catabolize hemoglobin. This hemoglobin degradation is carried out meticulously by four distinct parasitic proteases: two plasmepsins, falcipain, and falcilysin.[5]

The plasmepsins are aspartic proteases which cleave hemoglobin between the phenylalanine (residue 33) and leucine (residue 34) on the α-subunit. These site-specific proteases denature hemoglobin and expose susceptible regions of the polypeptide to falcipain degradation. After extensive fragmentation of the polypeptide as a result of falcipain cleavage, the zinc metalloprotease falcilysin cleaves the remaining peptides at polar residues to produce single amino acids. The design of small molecules which can act as inhibitors of these proteases is currently an active area of malaria research.[6-8]

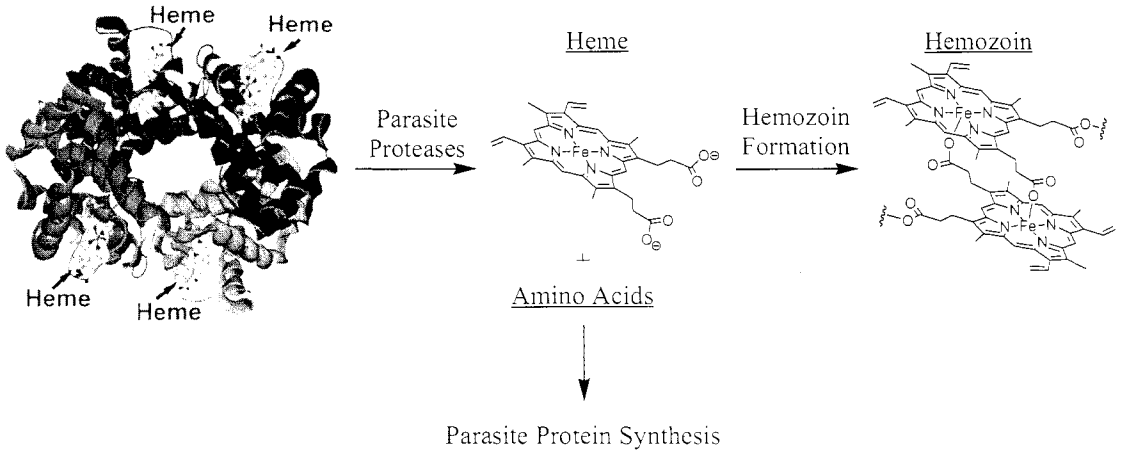
4.1.2.3 Liberation of Free Heme: The Achilles Heel of the Parasite

As the globin polypeptide is consumed by the parasite within the food vacuole, the iron-containing porphyrin (free heme) is liberated (Figure 4.3). Once released, this free heme is oxidized from iron (II) to iron (III) with concomitant product of hydrogen peroxide. Both free heme and hydrogen peroxide are toxic to *P. falciparum*, and if allowed to accumulate, the surfactant-like free heme leads to rupture of parasitic membranes.[9]

In order to avoid the accumulation of free heme within the food vacuole, the parasite has developed a detoxification process in which the free heme is crystallized into an inert, hydrogen-bonded array of coordinated dimers known as hemozoin (Figure 4.3). This detoxification process is carried out at an exceptionally fast rate in order to prevent a

buildup of free heme. It has been said that this delicate balance between hemoglobin degradation and free heme detoxification has caused the parasite to "live on a knife's edge".[9] In other words, if the parasite degrades too little hemoglobin, the lack of amino acids available for protein synthesis will lead to parasite death. On the other hand, if the parasite degrades too much hemoglobin, the elevated level of free heme which results from overwhelming its own detoxification mechanisms will lead to vacuolar rupture. As a result of this predicament, the parasite is highly susceptible to chemotherapeutic intervention at this stage.[10]

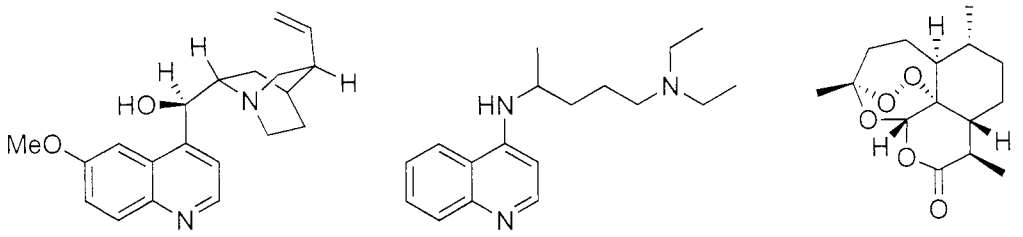
Figure 4.3



4.1.3 Current Treatments

Several approaches, such as vaccinations and distribution of mosquito nets, have been undertaken to curb the spread of malaria. However, neither of these options has achieved widespread success. To date, orally-available small molecule drugs have been the most effective treatments, and some of the most common antimalarials are shown in Figure 4.4.

Figure 4.4



Quinine (**214**) Chloroquine (**215**) Artemisinin (**216**)

Quinine (**214**), first isolated from the bark of cinchona trees in 1820, is a quinoline-containing natural product which inspired the development of numerous synthetic aminoquinoline antimalarials.[5] The synthetic antimalarial chloroquine (**215**) was once an extremely effective treatment for malaria. The efficacy of chloroquine can be attributed to its ability to π-stack with free heme and prevent hemozoin formation (thereby leading to a buildup of toxic free heme within the parasite food vacuole).[11] Furthermore, the activity of **215** is enhanced by an increase in its effective concentration within the acidic food vacuole due to pH trapping.[12] However, despite its initial effectiveness, resistance to **215** has become so ubiquitous in recent years that the drug has become virtually useless in most regions of the world today.[11,2]

Artemisinin (**216**), also known as qinghaosu, is a natural product derived from the plant *Artemisia annua* which was first used by Chinese herbal medicine practitioners nearly 2000 years ago. Artemisinin (**216**) has received tremendous attention in recent years because this endoperoxide-containing compound is not susceptible to the resistance mechanisms developed by *P. falciparum* against the aminoquinolines such as chloroquine (**215**). The key pharmacophore in artemisinin is the bridging endoperoxide; this

functionality reacts with the iron in free heme to trigger a cascade of radical-initiated damage to parasite membranes and enzymes.[13] Several research groups have developed effective artemisinin derivatives and synthetic endoperoxides which are orally-active, highly potent, and inexpensive. The remarkable contributions of these groups have produced a variety of drug candidates which will become the first line of malaria treatment worldwide within the next decade.[7,14,12,15-18,4,19-24]

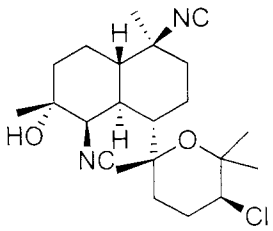
4.1.4 Isonitrile-Containing Compounds with Antimalarial Activity

Several isonitrile-containing natural products have demonstrated antimalarial activity against *P. falciparum* and related parasites. Kalihinol A (**1**) and other members of the kalihinane family have exhibited potent *in vitro* inhibitory activity against the FCR-3 strain of *P. falciparum* (Figure 4.5, Table 4.1).[25] Notably, **1** demonstrated higher potency and selectivity than the antimalarial standard mefloquine (SI = Selectivity Index, ratio of FM3A/FCR-3 cytoxicity).

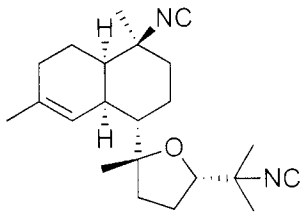
Table 4.1

Compound	*P. falciparum* FCR-3 IC_{50} (M)	FM3A IC_{50} (M)	Selectivity Index (SI)
kalihinol A (**1**)	1.2×10^{-9}	3.8×10^{-7}	317
kalihinene (**13**)	1.0×10^{-8}	3.7×10^{-8}	4
6-hydroxykalihinene (**26**)	8.0×10^{-8}	1.2×10^{-6}	15
Mefloquine	3.2×10^{-8}	2.9×10^{-6}	90

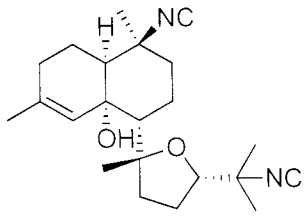
Figure 4.5



kalihinol A (**1**)



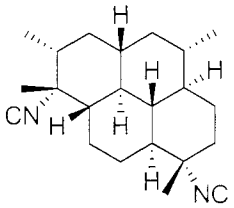
kalihinene (**13**)



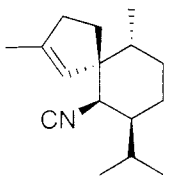
6-hydroxykalihinene (**26**)

In another study, Wright and co-workers have shown that 7,20-diisocyanoadociane (**64**) and axisonitrile (**217**) exhibit strong *in vitro* antimalarial activity (IC_{50} = 14 nM and 612 nM, respectively, chloroquine-sensitive D6 strain) (Figure 4.6).[26,9] Analog **218**, a compound related to **64**, has been synthesized and evaluated for its biological activity (IC_{50} = 109 ng/mL, chloroquine-resistant K1 strain).[27] Recently, adamantyl isonitrile (**219**) was tested *in vivo* against a multi-resistant strain of *P. yoelli* in Swiss mice and demonstrated complete suppression of the parasite after four days of treatment (50 mg/kg/day).[28]

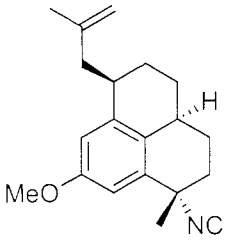
Figure 4.6



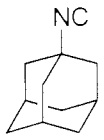
7,20-Diisocyanoadociane (**64**)



Axisonitrile (**217**)



218



Adamantyl isonitrile (**219**)

4.2 Key Considerations for Analog Design

4.2.1 Prior SAR Efforts by Others

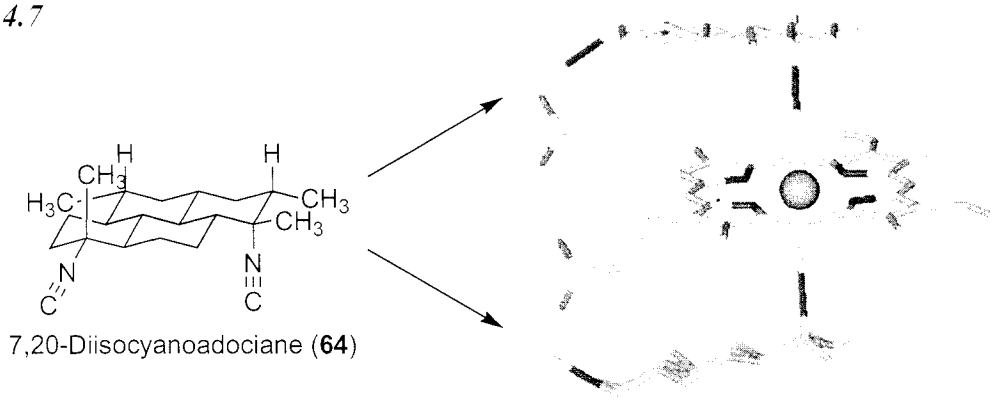
In light of the potent antimalarial activity of kalihinol A and related kalihinanes, a series of kalihinane analogs were synthesized in order to understand the relevant structure-activity relationships (SAR). At the outset of this project, the SAR data of known active compounds **1**, **13**, **26**, **64**, **217-219** (see Figures 4.5 and 4.6) as well as several inactive compounds (structures not shown) led us to make the following general observations:

1) The isonitrile functionality appeared to be necessary for antimalarial activity.
2) All of the active compounds contained a lipophilic backbone.
3) The compounds with two isonitriles demonstrated significantly higher potency than those with only one isonitrile.

In 2001, Wright and co-workers conducted a molecular modeling study on a series of terpene isonitriles with antimalarial activity and found that the drug target for these compounds was free heme.[9] From this result, they determined that there were three interactions which contributed to the binding of free heme. First and most importantly, the isonitrile was found to directly coordinate to the iron in free heme (Figure 4.7). It was speculated that this coordination prevented the parasite from conducting its detoxification process of converting free heme into hemozoin. Second, the lipophilic backbone of terpene isonitriles was thought to enhance the antimalarial activity by engaging in van der Waals interactions with the flat heme porphyrin. Third, the equatorial isonitrile (which is not involved iron coordination) was thought to participate

in an electrostatic interaction with the propionate moieties of the free heme. A computer-generated model of 7,20-diisocyanoadociane (**64**) binding to free heme, shown in Figure 4.7, serves to illustrate these three interactions.

Figure 4.7



7,20-Diisocyanoadociane (**64**)

4.2.2 Goals of the SAR Study

In light of previous SAR data for isonitrile-containing compounds, we had three primary objectives in mind for this kalihinane analog project:

1) To understand how the positioning of the isonitrile affects antimalarial activity.
2) To determine whether other functional groups could serve as isonitrile surrogates and impart antimalarial activity.
3) To ascertain the role of the lipophilic kalihinane carbocycle in antimalarial activity.

4.2.2.1 Goal #1: Understanding Isonitrile Positioning

Based upon the SAR data available at the outset of this project, the isonitrile functionality appeared to be primarily responsible for binding heme.[9] However, the

relevance of the orientation of the isonitrile (axial versus equatorial, for example) on the decalin core was significantly less clear. To explore this point, we intended to synthesize analogs containing one C(5) axial isonitrile and one C(10) equitorial isonitrile for comparison.

4.2.2.2 Goal #2: Determining Antimalarial Activity of Related Functional Groups

Isonitriles are rather unique functional groups in that they can behave as nucleophiles as well as electrophiles. While this promiscuity makes isonitriles very versatile intermediates in organic synthesis,[29] this reactivity also renders such groups "un-druggable" due to their anticipated instability *in vivo*. As a result, we sought to determine whether related functional groups could potentially serve as surrogates to isonitriles. Attention was focused on four related nitrogen-containing functional groups: formamides, isothiocyanates, nitriles, and azides. Formamides and isothiocyanates were selected because these functionalities are frequently isolated along with isonitriles in marine natural product isolations. Furthermore, formamides could conceivably act as prodrugs to isonitriles via a dehydration mechanism. Nitriles were chosen due to their isosteric relationship with isonitriles. The azide functionality was selected because azide anion is known to bind to the iron of metmyoglobin.[30,31]

4.2.2.3 Goal #3: Understanding the Role of the Kalihinane Carbocycle

Lastly, we aimed to determine the level of structural and stereochemical complexity necessary to maintain antimalarial activity. To do so, we planned to screen

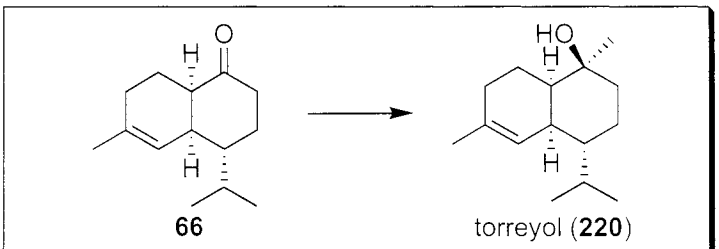
simple, commercially-available, isonitrile-containing compounds and compare their activities with those of the highly-functionalized, isonitrile-containing kalihinane analogs.

4.3 Synthesis of Kalihinane Analogs

4.3.1 Prior Work by the Wood Group

In order to explore the functionalization of the decalin core prior to commencing work on the synthesis of (±)-kalihinol C, Ryan D. White of the Wood group conducted exploratory studies on a decalin model system (see Section 1.6.1.1).[32,33] The *cis*-decalin **66**, a known intermediate from the synthesis of (±)-torreyol (**220**) by Taber and co-workers,[34] was used as a starting point for decalin fucntionalization (Scheme 4.1).

Scheme 4.1



66 torreyol (**220**)

Taber, D.F. et al. *J. Am. Chem. Soc.*, **1979**, *101(14)*, 3992-3993.

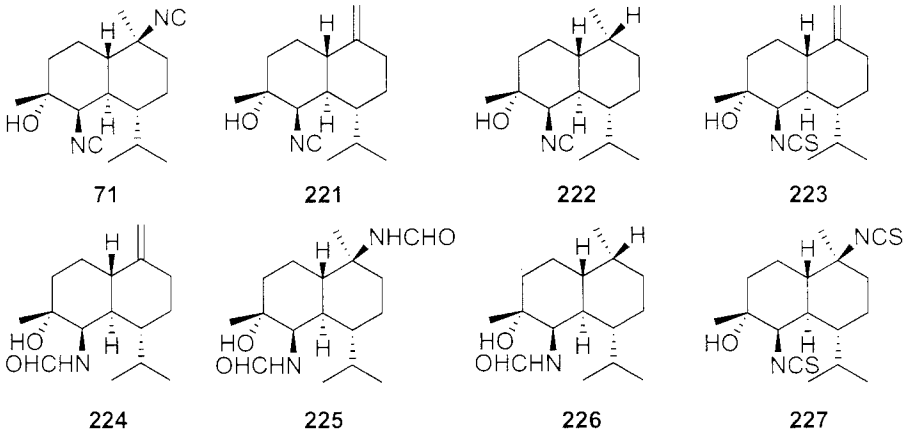
In assessing the requisite structural components for kalihinane analogs, it was recognized that (±)-**66** could serve as an ideal scaffold for analog development. The only difference between analogs of **66** and the fully functionalized kalihinanes was that the

pendant ring would be replaced with an isopropyl group. Earlier SAR studies have suggested that the presence of the pendant ring contributes little (if any) to the antimalarial activity of the kalihinanes.[25]

Analog development based upon **66** possessed three major advantages over the fully-functionalized system. First, **66** could be readily synthesized from inexpensive starting materials using a highly scalable reaction sequence. Second, replacement of the pendant ring with an isopropyl group reduced the number of steps to the decalin core. Third, exclusion of the pendant ring also augmented the selection of compatible reagents at our disposal (the isopropyl group, unlike the chlorotetrahydropyran or tetrahydrofuran, would be completely inert to all reagents).

Eight compounds, shown in Figure 4.8, were screened for antimalarial activity by Professor Daniel E. Goldberg at the Washington University School of Medicine in 2001.[33] These compounds will be referred to herein as the "first generation analogs". The antimalarial activity and SAR information for these compounds will be discussed in Section 4.4.2.

Figure 4.8

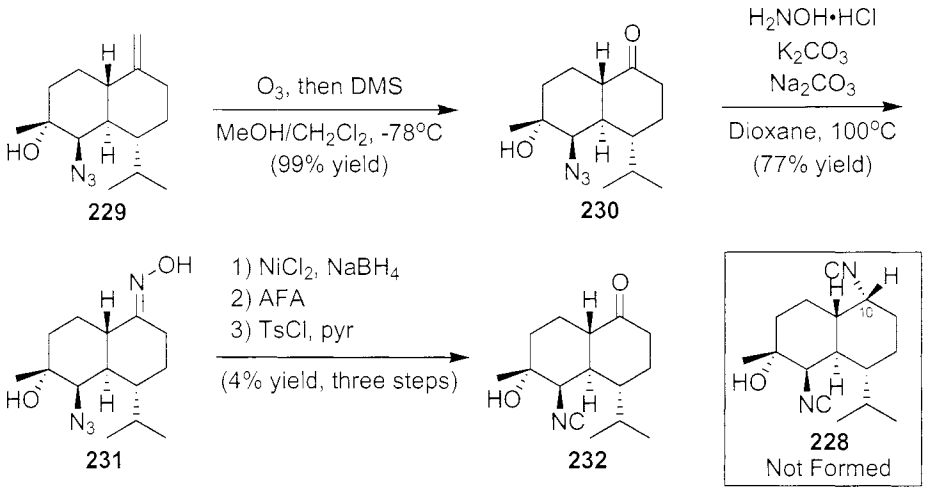


4.3.2 Synthesis of Second Generation Kalihinane Analogs

4.3.2.1 Isonitrile-Containing Kalihinane Analogs

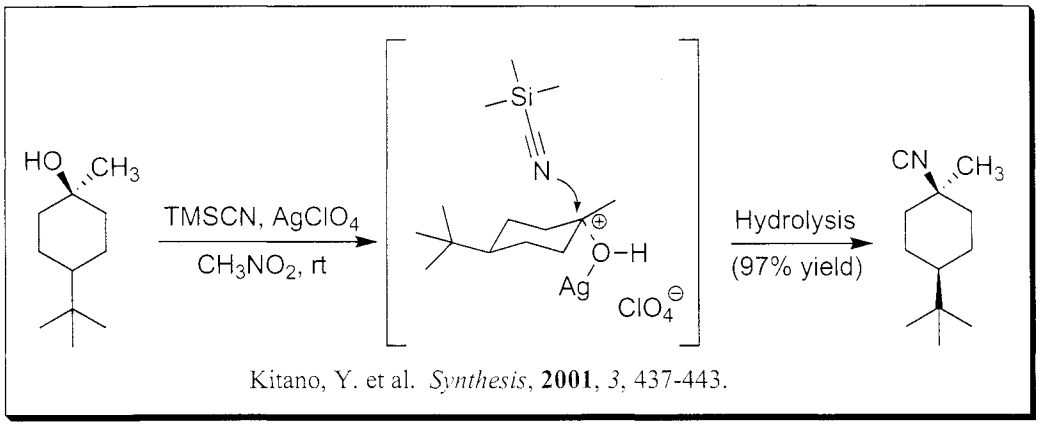
In an effort to examine how the orientation of the isonitrile may influence antimalarial activity, the synthesis of bis-isonitrile **228**, a compound in which both isonitriles reside in an axial orientation, was sought. Toward this goal, olefin **229**[33] was ozonolyzed to provide ketone **230** in quantitative yield, and the corresponding oxime **231** was formed upon exposure of **230** to hydroxyamine hydrochloride and base (Scheme 4.2). Unfortunately, reduction of the azide using standard hydrogenation conditions was met with little success. It was ultimately found that nickel boride reduced the azide, albeit in very low yield. In addition, under these experimental conditions, the oxime was replaced with a ketone, presumably upon hydrolysis of an intermediate imine during workup. Ultimately, a three-step protocol involving nickel boride reduction, formylation, and dehydration was implemented to provide an adequate quantity of mono-isonitrile **232** for assay.

Scheme 4.2



After failing to install an axial C(10) isonitrile from the oxime, it was recognized from a search of the literature that isonitriles could be accessed from tertiary alcohols upon exposure to trimethylsilyl cyanide and silver perchlorate (Scheme 4.3).[35]

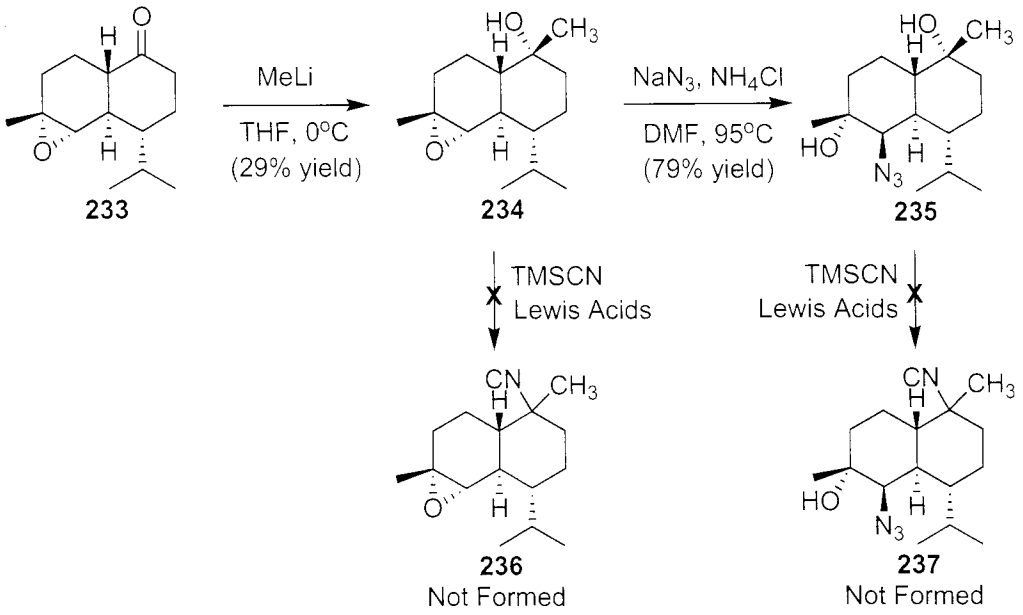
Scheme 4.3



Kitano, Y. et al. *Synthesis*, **2001**, *3*, 437-443.

In an effort to install the C(10) isonitrile on the kalihinane scaffold using this approach, tertiary alcohols **234** and **235** were prepared from ketone **233**[33] (Scheme 4.4). Disappointingly, however, exposure of **234** and **235** to trimethylsilyl cyanide and a variety of Lewis acids resulted in starting material decomposition and failed to produce isonitriles **236** and **237**.

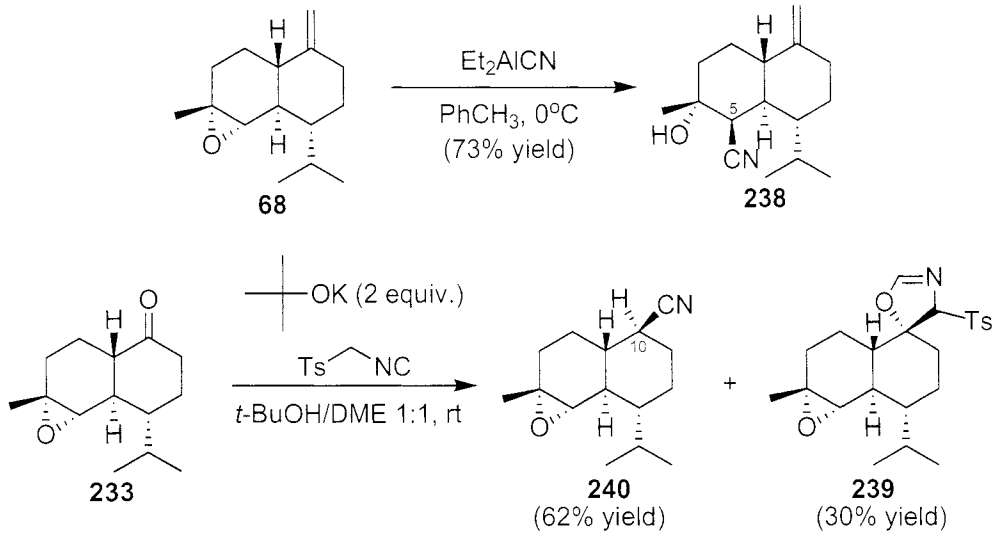
Scheme 4.4



4.3.2.2 Kalihinane Analogs with Related Functional Groups

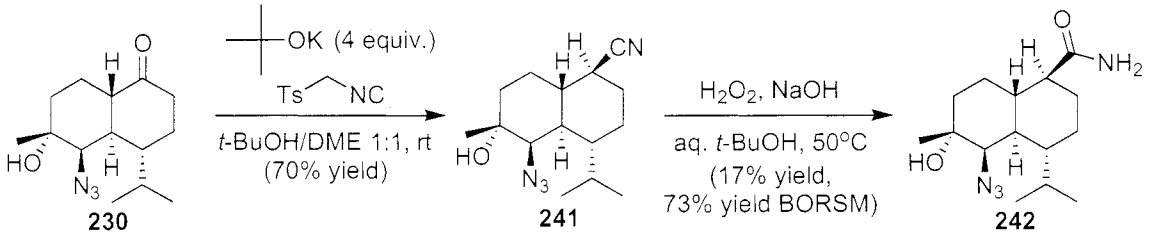
A series of kalihinane analogs containing azides and nitriles was synthesized. The axial C(5) nitrile **238** was installed with excellent regioselectivity by treatment of **68** with diethyl aluminum cyanide (Scheme 4.5). The C(10) nitrile was formed upon treating **233**[33] with tosyl methyl isocyanide and base to give approximately a 2:1 ratio of nitrile **240** to oxazoline **239**.[36,37,38]

Scheme 4.5



In an analogous manner, ketone **230** was parlayed into nitrile **241**, the exclusive product when four equivalents of base were used in this reaction (Scheme 4.6). Nitrile **241** was hydrolyzed to amide **242** in low conversion in order to install a polar functional group at the C(10) position.

Scheme 4.6



Seven of the above compounds, along with four additional analogs which had been characterized previously (**69**, **72**, **73**, and **243**, see Figure 4.9),[33] were submitted for

antimalarial activity screening. The assay results of first and second generation analogs are described in the following section.

4.4 Testing of Antimalarial Activity

4.4.1 Antimalarial and Cytotoxicity Assays

The antimalarial and cytotoxicity assays were conducted by Dr. Daniel E. Goldberg, Professor of Medicine and Co-Chief of the Department of Infectious Diseases at Washington University School of Medicine in St. Louis, Missouri. All of the compounds were assayed *in vitro* against cultured intraerythrocytic asexual forms of *P. falciparum* in triplicate. The assay was performed using a semi-automated microdilution method developed by Desjardins and co-workers, and the cells were cultured according to the conditions established by Trager and co-workers.[39-40] All of the compounds and the antimalarial standard chloroquine were individually dissolved in dimethyl sulfoxide. Each stock solution was diluted at varying concentrations and treated with asynchronous, ~0.5% parasitemia Hb-3 (chloroquine-sensitive) and Dd-2 (chloroquine-resistant) cultures. After a 48-hour incubation period, an aliquot of each stock solution was then treated with 0.5 μC [^{3}H]-hypoxanthine, a nucleic acid precursor used by the parasite. The amount of hypoxanthine incorporated by the parasite was measured using a scintillation counter after 24 hours and correlated to its growth rate. Thus, inhibition of [^{3}H]-hypoxanthine uptake by the parasite was indicative of the antimalarial activity of the

compound in solution. The antimalarial activity was expressed as an IC_{50} value (the concentration of the compound at which 50% inhibition of *P. falciparum* was induced).[41]

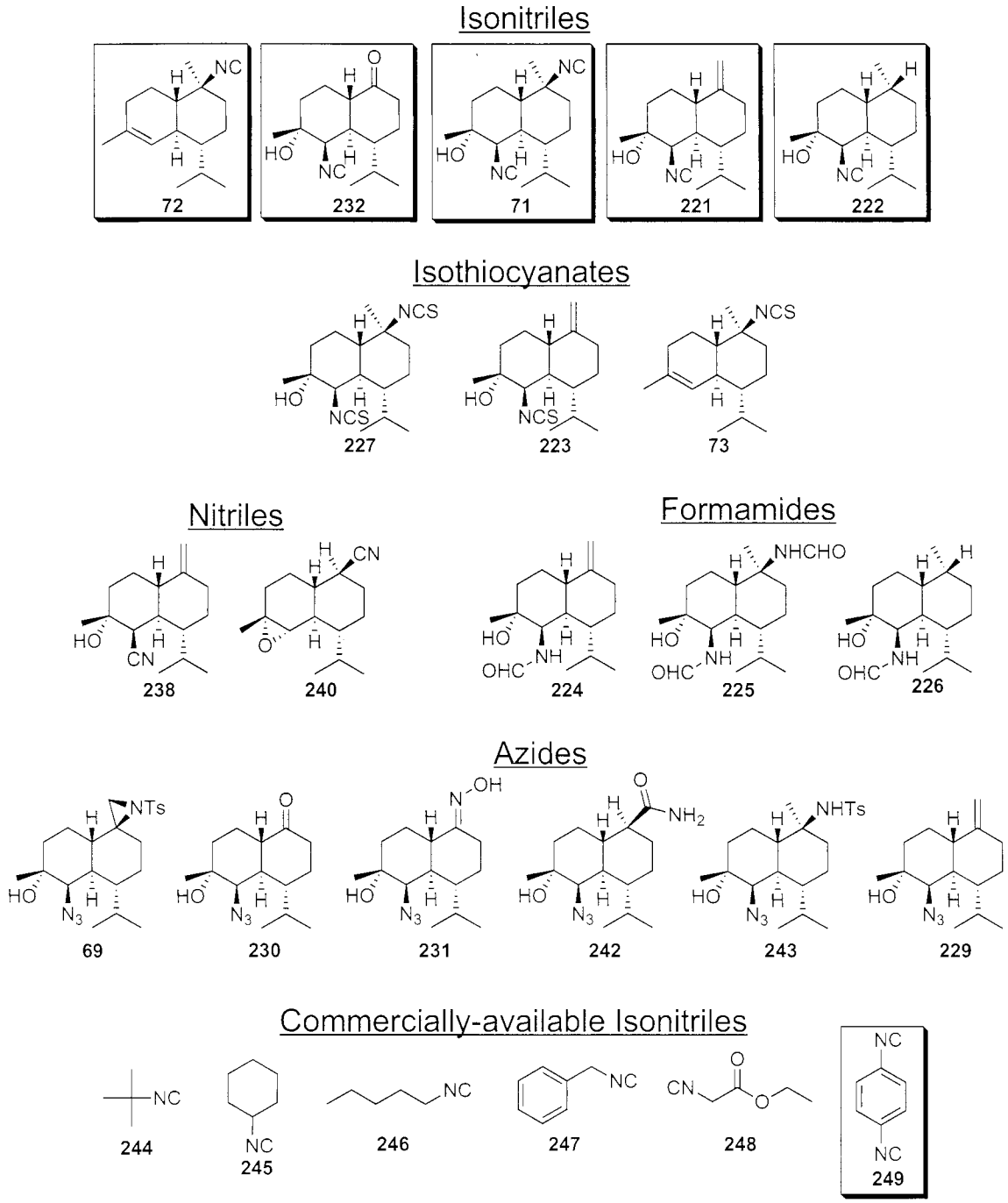
In order to determine whether or not the observed antimalarial activity merely resulted from a cytotoxic effect, the six active compounds (*vide infra*) were assayed for general cytotoxicity against the African green monkey kidney (Vero) cell line.[41] These cells, grown in Dulbecco's Eagle Medium (DMEM) and supplemented with 10% fetal calf serum and 1% L-glutamine, were cultured in the growth media at 37°C and distributed in 96-well plates. A stock solution of the active compounds in dimethyl sulfoxide was then added to the wells. After twenty hours, tetrazolium salt dye (3-(4,5-dimethylthiazol-2-yl)-5-(3-carbomethoxyphenyl)-2-(4-sulfophenyl-2H-tetrazolium (MTS) was added. Since this dye is metabolized by the cells, the difference in optical density between the experimental and control wells (measured by an ELISA microtiter plate reader) could be correlated to cell survival. For example, a highly cytotoxic compound would destroy all living cells in that well; since no living cells would be present to metabolize the dye, its concentration (measured as optical density) would remain unchanged and therefore indicate a high level of compound cytotoxicity. These qualitative measurements were carried out in triplicate at 25 μM and 100 μM compound concentrations.

4.4.2 Results from Antimalarial Activity Screen

Nineteen kalihinane analogs, along with six commercially-available isonitriles purchased from Aldrich, were subjected to antimalarial and cytotoxicity assays. Of these twenty-five compounds, it was found that *all of the isonitrile-containing kalihinane*

analogs (**71**, **72**, **221**, **222**, and **232**) *and one of the commercially-available isonitriles (1,4-diisocyanobenzene* (**249**)*) were found to be active* in vitro *(IC_{50} < 20 μM)* (Figure 4.9). All of the kalihinane analogs which did not contain an isonitrile, as well as five of the six commericially-available isonitriles (**244**-**248**), were found to be devoid of antimalarial activity.

Figure 4.9

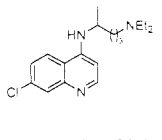
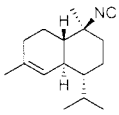
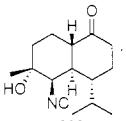
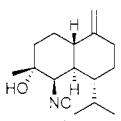
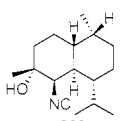
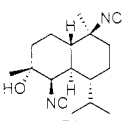
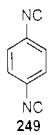


A detailed assessment of the antimalarial activity of the six active compounds and the antimalarial standard chloroquine is depicted in Table 4.2. Each compound was

tested against a chloroquine-sensitive (HB-3) and chloroquine-resistant (Dd-2) strain of *P. falciparum*. In addition, the cytotoxicity data for each of these compounds is shown.

Table 4.2

Antimalarial Activity (*in vitro*)
IC_{50} (μM)

	 Chloroquine (215)	 72	 232	 221	 222	 71	 249
HB-3 Strain	0.02	2.20	2.20	0.80	0.50	0.08	0.50
Dd-2 Strain	0.20	2.20	2.20	2.00	2.00	0.08	0.50

Cytotoxicity (*in vitro*)
(Assessed at two compound concentrations)

[100 μM]	Not Tested	Yes	No	No	No	No	Yes
[25 μM]	Not Tested	Yes	No	No	No	No	Yes

4.4.3 Structure-Activity Relationship Analysis

From the assay data of these twenty-five compounds, several relationships between the structure of the compound and its antimalarial activity can be drawn. First, since all of the compounds without an isonitrile were inactive, it is clear that the isonitrile functional group plays a critical role in parasite inhibition. However, the mere presence of an isonitrile is not sufficient to exert antimalarial activity, as evidenced by the five

inactive commercially-available isonitriles (**244**-**248**, see Figure 4.9). Thus, this data suggests that while the isonitrile is the primary pharmacophore, the skeletal framework to which the isonitrile is attached is also an important contributor to the antimalarial activity.

As illustrated in Table 4.2, the four mono-isonitriles (**72**, **221**, **222**, and **232**) exhibited a range of 0.50-2.20 μM IC_{50} values against the chloroquine-sensitive HB-3 strain and a range of 2.00-2.20 μM IC_{50} values against the chloroquine-resistant Dd-2 strain. For **72** and **232**, the IC_{50} values against both strains of the parasite were identical, whereas **221** and **222** showed greater activity against the HB-3 strain. While the latter result suggests that the chloroquine-resistant strain may be demonstrating some resistance to these kalihinane analogs, it is difficult to reach a conclusion with certainty from this small disparity and data set. Interestingly, **72**, which bears an equitorial C(10) isonitrile, demonstrated identical activity to the axial C(5) mono-isonitrile **232**. This result infers that the positioning of the isonitrile on the decalin core may be less important than initially anticipated based upon previous assertions.[9] Once again, however, a larger group of compounds would need to be assayed in order to allege this claim with confidence. Lastly, while **221**, **222**, and **232** showed no general toxicity, **72** was found to be cytotoxic at both 25 μM and 100 μM. The origin of this toxicity is unclear at this time.

The most potent compound tested in the assay was bis-isonitrile **71** which demonstrated an 80 nM IC_{50} against both the HB-3 and Dd-2 strains of the parasite. This potent activity was comparable to that of the antimalarial standard chloroquine (**215**) and furthermore, **71** exhibited no cytotoxicity at 100 μM. The decalin core of **71** is identical

in structure to that of kalihinol A (**1**), and this similarity highlights the importance of utilizing the "privileged structures" of natural products to guide analog development.[42] While **71** exhibited remarkable antimalarial activity, the activity of kalihinol A (**1**, IC_{50} = 1.2 nM) remained superior.[43] This result suggests that the pendant chlorotetrahydropyran may contribute modestly to the activity of **1**, possibly as a result of increased van der Waals interactions between the heme porphyrin and the tricyclic framework.

Of particular interest was the antimalarial potency of 1,4-diisocyanobenzene (**249**), the only commercially-available isonitrile to demonstrate activity. Unlike the other commercially-available compounds, **249** has two isonitrile groups. In a recent report in the literature, Posner and co-workers have shown that dimers of artemisinin analogs exhibit substantially enhanced potency over their monomers.[21] Although speculative, it is possible to consider the two isonitriles in **71** and **249** as "dimeric mono-isonitriles" which behave synergistically to exert their antimalarial activity. One possible explanation for their antimalarial efficacy is that the presence of one isonitrile in close proximity to another may produce a large increase in the effective concentration of free heme within the food vacuole. Future analog development will undoubtedly lead to new small molecules which utilize this unique structural characteristic.

4.5 Conclusions

Malaria is a growing epidemic, and the opportunities to treat the disease with conventional medicines are narrowing due to rampant parasite resistance. Motivated by

the remarkable antimalarial activity of kalihinol A, a series of analogs have been synthesized in order to gain an understanding of the structural components which are required for antimalarial activity. The assay data has confirmed that the isonitrile is the primary pharmacophore responsible for antimalarial activity. Furthermore, the presence of the kalihinane carbocycle contributes significantly to potency as well. While the presumed instability of isonitriles *in vivo* would prevent these analogs from becoming viable drug candidates, the knowledge gained from such SAR studies is worthwhile since it contributes to the understanding of malaria chemotherapy as a whole.

4.6 Experimentals

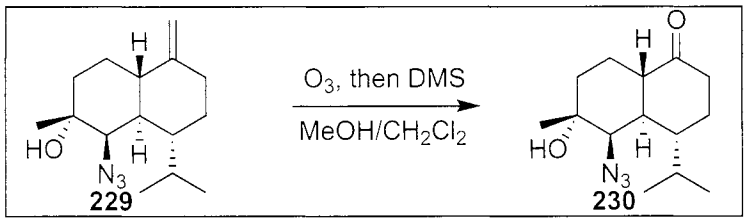
4.6.1 Materials and Methods

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. ^{1}H 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 ^{1}H δ 7.26 ppm, ^{13}C δ 77.16 ppm; acetone ^{1}H δ 2.05 ppm, ^{13}C δ 29.84 ppm; methanol ^{1}H δ 3.31 ppm, ^{13}C δ 49.00 ppm). 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.

4.6.2 Preparative Procedures

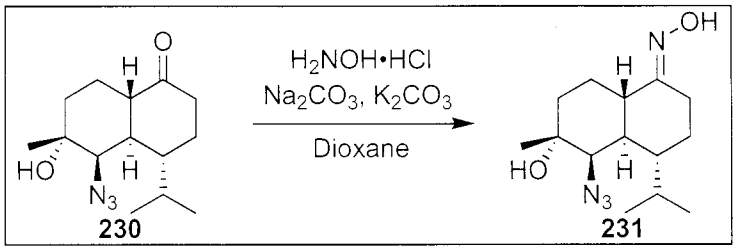
Preparation of ketone 230



Ketone 230. To a solution of olefin **229** (1.75 g, 6.65 mmol, 1.0 equiv.) in MeOH (100 mL) and CH_2Cl_2 (10 mL) was bubbled through O_3 gas (excess) at -78°C. After 20 minutes, dimethyl sulfide (20 mL) was added and the reaction was warmed to rt and diluted with CH_2Cl_2 (200 mL). The organic layer was washed with brine (3 x 20 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (4:1 hexanes:ethyl acetate) to afford **230** (1.75 g, 99% yield) as a white solid, m.p. 132-134°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 (s, 1H), 2.43-1.93 (comp m, 7H), 1.87-1.75 (m, 1H), 1.73-1.61 (m, 1H), 1.57-1.34 (comp m, 4H), 1.31 (s, 3H), 1.00 (d, *J*=6.8 Hz, 3H), 0.75 (d, *J*=6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.2, 72.2, 68.2, 46.7, 44.2, 42.7, 41.4, 32.6, 29.0, 26.5, 24.9, 21.8, 20.7, 15.6

ppm; IR (thin film/NaCl) 3459 (br s), 2962 (s), 2872 (s), 2527 (w), 2247 (w), 2197 (m), 2107 (s), 1700 (s), 1455 (m), 1432 (m), 1372 (s), 1337 (s), 1281 (s), 734 (s) cm^{-1}; HRMS (FAB) *m/z* found: 288.1700 [calc'd for $C_{14}H_{23}N_3O_2Na$ (M+Na): 288.1688].

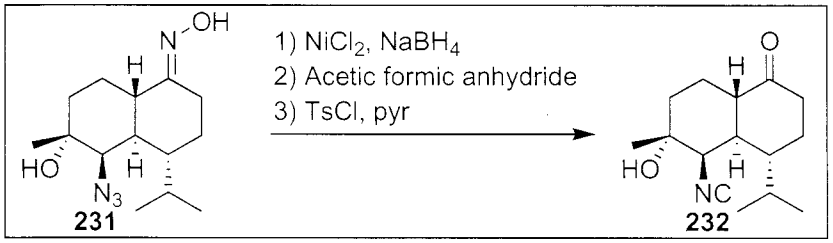
Preparation of oxime 231



Oxime 231. To a solution of ketone **230** (500 mg, 1.89 mmol, 1.0 equiv.) in dioxane (25 mL) was added potassium carbonate (1.57 g, 11.3 mmol, 6.0 equiv.), sodium carbonate (1.57 g, 14.7 mmol, 7.8 equiv.), and hydroxylamine hydrochloride (1.04 g, 15.1 mmol, 8.0 equiv.). The reaction was heated to reflux and run for a total of 6 hours. The reaction mixture was cooled to rt, filtered, and washed with hot dioxane (20 mL). The filtrate was concentrated *in vacuo* and purified by silica gel column chromatography (6:1 hexanes:ethyl acetate) to afford **231** (406 mg, 77% yield) of a white solid, m.p. 191-192°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (br s, 1H), 3.52 (s, 1H), 3.40 (td, *J*=3.6, 14.1 Hz, 1H), 2.22-1.83 (comp m, 4H), 1.81-1.44 (comp m, 7H), 1.35 (s, 3H), 1.29-1.13 (m, 1H), 1.00 (d, *J*=6.8 Hz, 3H), 0.77 (d, *J*=6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 72.3, 67.9, 43.7, 42.8, 39.0, 32.7, 28.8, 26.3, 24.1, 23.5, 21.8, 21.5, 15.5 ppm; IR (thin film/NaCl) 3419 (br s), 2960 (m), 2870 (w), 2361 (w), 2339 (w), 2104 (s), 1699 (w),

1651 (m), 1457 (w), 1263 (m), 750 (s) cm^{-1}; HRMS (FAB) *m/z* found: 281.1977 [calc'd for $C_{14}H_{25}N_4O_2$ (M+H): 281.1977].

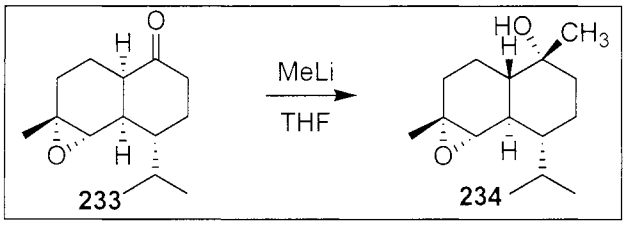
Preparation of isonitrile 232



Isonitrile 232. To a solution of azide **231** (200 mg, 0.714 mmol, 1.0 equiv.) in methanol (8 mL) and THF (8 mL) at 0°C was added nickel (II) chloride hexahydrate (850 mg, 3.57 mmol, 5.0 equiv.) followed by the slow addition of sodium borohydride (271 mg, 7.14 mmol, 10.0 equiv.). Vigorous bubbling was observed and the reaction turned black in color. The reaction was allowed to warm to rt and stirred over a 6-hour period. After filtering through celite and washing with ethyl acetate (20 mL), the filtrate was concentrated *in vacuo* and the resulting crude oil (20 mg, 0.083 mmol, 1.0 equiv.) was treated with acetic formic anhydride (44 μL, 0.500 mmol, 6.0 equiv.) in THF (3 mL) at 0°C for 4 hours. After concentration *in vacuo*, the resulting oil was advanced without further purification by treating a solution of the resulting oil (12.0 mg, 0.045 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) with pyridine (66 μL, 0.82 mmol, 18.2 equiv.) and *para*-toluenesulfonyl chloride (77 mg, 0.41 mmol, 9.1 equiv.) at 0°C. The reaction was allowed to warm to rt overnight and concentrated *in vacuo* with concomitant adsorption onto silica gel. The material was purified by silica gel column chromatography (6:1

hexanes:ethyl acetate) to afford **232** (8 mg, 4% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (br s, 1H), 2.52-2.27 (comp m, 3H), 2.13-1.95 (comp m, 3H), 1.91-1.55 (comp m, 5H + H_2O peak), 1.51-1.46 (m, 1H), 1.44 (s, 3H), 1.36 (s, 1H), 1.04 (d, *J*=7.0 Hz, 3H), 0.77 (d, *J*=6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3, 158.8 (t, *J*=5.2 Hz), 70.4, 61.1 (t, *J*=5.5 Hz), 46.4, 42.4, 42.1, 41.1, 32.2, 28.7, 25.8, 24.2, 21.6, 20.2, 15.2 ppm; IR (thin film/NaCl) 3455 (br m), 2959 (s), 2932 (s), 2872 (m), 2359 (w), 2135 (sh s), 1708 (s), 1453 (w), 1377 (m), 1127 (w), 1033 (w) cm^{-1}; HRMS (FAB) *m/z* found: 250.1804 [calc'd for $C_{15}H_{24}NO_2$ (M+H): 250.1807].

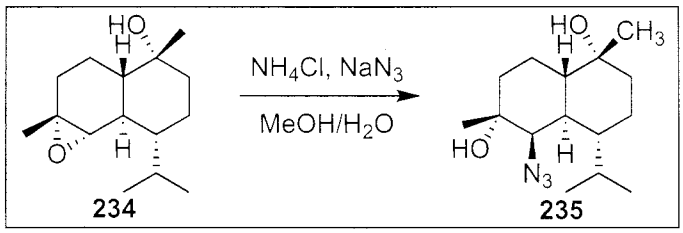
Preparation of alcohol 234



Alcohol 234. To a solution of ketone **233** (200 mg, 0.901 mmol, 1.0 equiv.) in THF (10 mL) was added MeLi (1.3 mL, 1.802 mmol, 1.4M in Et_2O, 2.0 equiv.) at 0°C. The reaction was allowed to warm to rt overnight and then quenched with NH_4Cl. The reaction was diluted with hexane (20 mL) and the organic layer was washed with brine (3 x 10 mL). The organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (9:1 to 6:1 to 3:1 to 1:1 hexanes:ethyl acetate) to provide **234** (61 mg, 29% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.92 (br s, 1H), 2.30-2.17 (m, 1H), 2.12-2.02 (m, 1H), 1.73-1.31

(comp m, 8H), 1.28 (s, 3H), 1.24-1.07 (comp m, 6H), 0.94 (d, *J*=7.0 Hz, 3H), 0.86 (d, *J*=6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.4, 61.5, 58.2, 47.4, 44.7, 39.9, 38.7, 30.8, 28.7, 26.4, 23.7, 21.5, 20.0, 19.7, 15.6 ppm; IR (thin film/NaCl) 3477 (br m), 2957 (s), 2872 (s), 2848 (s), 1462 (m), 1367 (m), 1243 (m), 1170 (m), 1135 (m), 1003 (m), 913 (m), 876 (s), 792 (m) cm^{-1}; HRMS (FAB) *m/z* found: 261.1822 [calc'd for $C_{15}H_{26}O_2Na$ (M+Na): 261.1831].

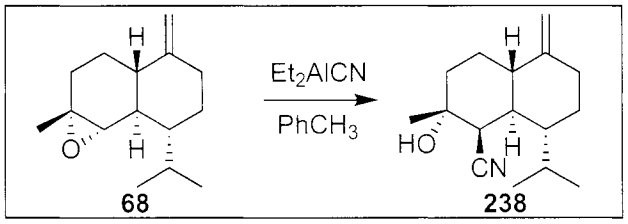
Preparation of azide 235



Azide 235. To a solution of epoxide **234** (12.0 mg, 0.0504 mmol, 1.0 equiv.) in *N,N*-dimethyl formamide (2 mL) was added sodium azide (49.0 mg, 0.756 mmol, 15.0 equiv.) and ammonium chloride (27.0 mg, 0.504 mmol, 10.0 equiv.) and heated to 95°C overnight. The reaction was cooled to rt, diluted with hexanes (10 mL), and washed with brine (3 x 5 mL). The organic layers were dried with Na_2SO_4, concentrated *in vacuo*, and purified by silica gel column chromatography (6:1 hexanes:ethyl acetate) to afford **235** (11 mg, 79% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53 (br s, 1H), 2.07-1.79 (comp m, 3H), 1.73-1.36 (comp m, 9H), 1.33 (s, 3H), 1.30-1.10 (comp m, 5H), 0.97 (d, *J*=6.8 Hz, 3H), 0.87 (d, *J*=6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.3, 71.0, 68.3, 43.1, 42.3, 40.3, 37.6, 32.9, 28.9, 28.5, 26.1, 21.4, 20.3, 18.9, 15.4 ppm; IR

(thin film/NaCl) 3390 (br s), 2959 (s), 2099 (sh s), 1653 (m), 1559 (m), 1457 (m), 1285 (m), 993 (m) cm^{-1}; HRMS (EI) *m/z* found: 264.2075 [calc'd for $C_{15}H_{26}N_3O$ (M-[H_2O]+H): 264.2075].

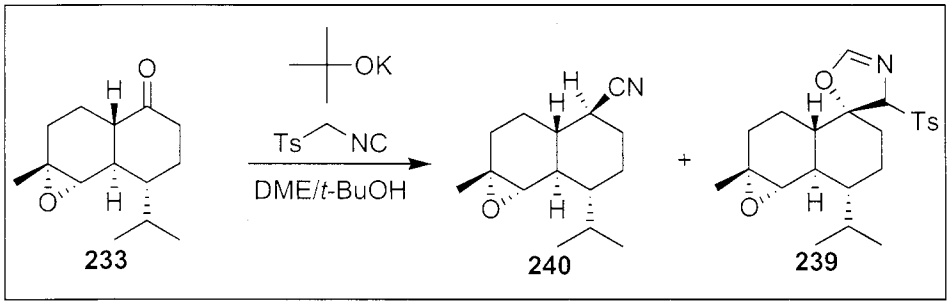
Preparation of nitrile 238



Nitrile 238. To a solution of epoxide **68** (10 mg, 0.045 mmol, 1.0 equiv.) in toluene (3 mL) was added diethylaluminum cyanide (272 μL, 0.272 mmol, 1M in toluene, 6.0 equiv.) at 0°C. The reaction was allowed to warm gradually to rt over 2 hours. After quenching with Rochelle's salt solution (1 mL, 20% *w/v)*, the reaction was diluted with ethyl acetate (10 mL) and washed with brine (2 x 5 mL). The resulting residue was dried with Na_2SO_4, concentrated *in vacuo*, and purified by silica gel column chromatography (6:1 hexanes:ethyl acetate) to afford **238** (8 mg, 73% yield) as a white, amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (d, *J*=1.5 Hz, 1H), 4.63 (d, *J*=1.3 Hz, 1H), 2.88-2.83 (m, 1H), 2.40 (td, *J*=3.3, 13.1 Hz, 1H), 2.12-1.21 (comp m, 11H +H_2O peak), 1.17-1.01 (m, 2H), 0.97 (d, *J*=6.8 Hz, 3H), 0.95-0.85 (comp m, 2H), 0.72 (d, *J*=6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 119.4, 105.9, 70.5, 44.9, 42.3, 41.5, 40.7, 36.1, 34.8, 30.1, 26.1, 25.8, 23.9, 21.6, 15.0 ppm; IR (thin film/NaCl) 3472 (br m), 2959 (s), 2935 (s), 2869 (m), 2238 (m), 1644 (m), 1467 (m), 1452 (s), 1402 (w), 1378

(m), 1370 (m), 1266 (m), 1183 (m), 1127 (m), 891 (s) cm^{-1}; HRMS (FAB) *m/z* found: 248.2010 [calc'd for $C_{16}H_{26}NO$ (M+H): 248.2014].

Preparation of oxazoline 239 and nitrile 240



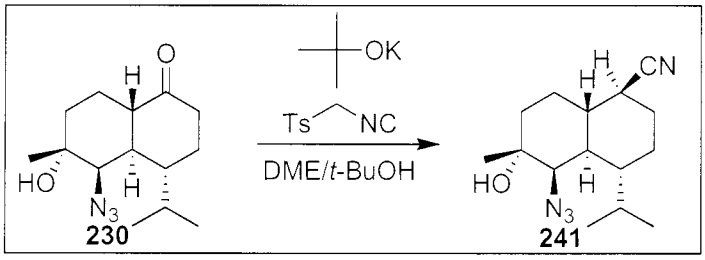
Oxazoline 239 and nitrile 240. To a solution of ketone **233** (50 mg, 0.225 mmol, 1.0 equiv.) in dimethoxyethane (5 mL) and *tert*-butanol (1 mL) at 0°C was added tosyl methyl isocyanide (66 mg, 0.338 mmol, 1.5 equiv.) followed by potassium *tert*-butoxide (55 mg, 0.450 mmol, 2.0 equiv.) as a solution in dimethoxyethane:*tert*-butanol (1:1 *v/v*). The reaction was allowed to warm to rt and run for 4 hours. The reaction was diluted with hexanes (20 mL), washed with brine (3 x 10 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (15:1 to 9:1 hexanes:ethyl acetate) to afford oxazoline **239** (28 mg, 30% yield) and nitrile **240** (31 mg, 62% yield).

Oxazoline 239. Clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J*=8.2 Hz, 2H), 7.36 (d, *J*=8.0 Hz, 2H), 7.02 (br s, 1H), 4.67 (d, *J*=1.9 Hz, 1H), 2.96 (br s, 1H), 2.73 (td, *J*=3.2, 14.5 Hz, 1H), 2.44 (s, 3H), 2.42-2.20 (comp m, 2H), 2.06-1.98 (m, 1H), 1.86-1.55 (comp

m, 4H), 1.47-1.21 (comp m, 6H), 1.16-1.06 (m, 1H), 1.00 (d, *J*=7.0 Hz, 3H), 0.88 (d, *J*=7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 152.3, 145.4, 142.0, 135.8, 130.1, 129.8, 129.6, 89.8, 89.4, 60.9, 57.8, 47.8, 43.5, 40.0, 30.4, 26.3, 23.5, 21.9, 21.5, 20.9, 19.8, 15.4 ppm; IR (thin film/NaCl) 2958 (s), 2872 (w), 1618 (sh s), 1447 (w), 1379 (w), 1322 (s), 1291 (m), 1151 (sh s), 1120 (m), 1085 (m), 814 (m) cm^{-1}; HRMS (FAB) *m/z* found: 418.2052 [calc'd for $C_{23}H_{32}NO_4S$ (M+H): 418.2052].

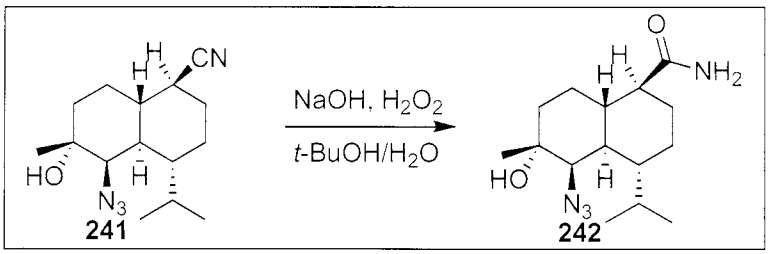
Nitrile 240. White foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.92 (s, 1H), 2.80-2.74 (m, 1H), 2.33-2.22 (m, 1H), 2.14-2.00 (m, 2H), 1.77-1.62 (comp m, 3H), 1.61-1.38 (comp m, 3H), 1.37-1.21 (comp m, 5H), 1.19-1.10 (m, 1H), 0.97 (d, *J*=7.1 Hz, 3H), 0.91 (d, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.4, 60.6, 58.4, 44.5, 40.8, 40.4, 34.1, 30.4, 29.1, 26.6, 25.9, 24.0, 21.8, 21.4, 15.9 ppm; IR (thin film/NaCl) 2958 (s), 2925 (s), 2871 (s), 2235 (m), 1733 (w), 1448 (m), 1419 (w), 1374 (m), 1290 (w), 1195 (w), 1100 (w), 869 (m), 801 (m) cm^{-1}; HRMS (FAB) *m/z* found: 256.1676 [calc'd for $C_{15}H_{23}NONa$ (M+Na): 256.1678].

Preparation of nitrile 241



Nitrile 241. To a solution of ketone **230** (500 mg, 1.89 mmol, 1.0 equiv.) was added tosylmethylisocyanide (736 mg, 3.77 mmol, 2.0 equiv.) and potassium *tert*-butoxide (921 mg, 7.54 mmol, 4.0 equiv.) in dimethoxyethane (25 mL) and *tert*-butanol (5 mL) at 0°C. The reaction was allowed to warm to rt gradually over 5 hours. The reaction was then cooled to 0°C, quenched with H_2O (1 mL), and diluted with hexanes (20 mL) and ethyl acetate (20 mL). The organic layer was extracted with brine (3 x 10 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (6:1 to 1:1 hexanes:ethyl acetate) to afford **241** (367 mg, 70% yield) as a white solid, m.p. 161-162°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (s, 1H), 2.19-2.05 (comp m, 2H), 2.02-1.87 (comp m, 2H), 1.80 (dq, *J*=3.3, 13.5 Hz, 1H), 1.73-1.29 (comp m, 11H), 1.09-0.99 (m, 1H), 0.97 (d, *J*=6.9 Hz, 3H), 0.77 (d, *J*=6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.0, 72.4, 67.2, 42.2, 41.9, 37.2, 35.5, 32.8, 29.6, 29.0, 26.9, 26.0, 23.1, 21.2, 15.2 ppm; IR (thin film/NaCl) 3451 (br m), 2959 (s), 2934 (s), 2869 (m), 2241 (w), 2101 (sh s), 1450 (w), 1370 (w), 1315 (m), 1296 (m), 1259 (m), 1143 (w), 965 (m) cm^{-1}; HRMS (FAB) *m/z* found: 299.1857 [calc'd for $C_{15}H_{24}N_4ONa$ (M+Na): 299.1848].

Preparation of amide 242



Amide 242. To a solution of nitrile **241** (176 mg, 0.629 mmol, 1.0 equiv.) in *tert*-butanol (6 mL) at rt was added an aqueous NaOH solution (4.0 mL, 1.88 mmol, 0.47 M, 3.0 equiv.) followed by hydrogen peroxide (280 μL, 2.52 mmol, 30% solution in H_2O, 4.0 equiv.). The reaction was run at 50°C overnight. An additional aliquot of aqueous NaOH solution (560 μL, 5.00 mmol, 8.9 M, 8.0 equiv.) was added and heated to 50°C for 12 hours. The reaction was cooled to rt and the solvent volume was reduced *in vacuo*. The concentrate was diluted with CH_2Cl_2 (20 mL) and 1N HCl (5 mL) was added. The organic layer was extracted with brine (2 x 5 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (100% ethyl acetate to 9:1:1 ethyl acetate:methanol:dichloromethane) to afford **242** (31 mg, 17% yield) as a white foam and recovered starting material **241** (113 mg, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (br s, 1H), 5.60 (br s, 1H), 3.50 (s, 1H), 2.07-1.37 (comp m, 11 H), 1.33 (s, 3H), 1.32-1.16 (comp m, 2H), 1.13-0.99 (m, 1H), 0.96 (d, *J*=7.0 Hz, 3H), 0.77 (d, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 72.4, 67.6, 51.9, 42.5, 41.8, 36.4, 32.9, 29.9, 29.0, 26.4, 26.1, 23.4, 21.3, 15.3 ppm; IR (thin film/NaCl) 3343 (m), 3196 (m), 2960 (s), 2932 (s), 2868 (m), 2101 (sh s), 1663 (s), 1654 (s), 1615 (m), 1457 (w), 1291 (m), 1146 (w), 911 (m), 734 (s) cm^{-1}; HRMS (FAB) *m/z* found: 295.2131 [calc'd for $C_{15}H_{27}N_4O_2$ (M+H): 295.2134].

4.7 Notes and References

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29. This rare reactivity of isonitriles has been exploited in organic synthesis most commonly in multi-component reactions (MCRs) such as the Ugi reaction.

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38. The oxazoline is an isolable intermediate en route to the nitrile. The isolated oxazoline can be directly converted to the nitrile upon prolonged exposure to base.

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43. While this statement is likely accurate, it is difficult to directly compare the activities of **71** and **1** since each was tested against different strains of the parasite (HB-3/Dd-2 for **71**, FCR-3 for **1**).

Appendix Three:
Spectra Relevant to Chapter 4

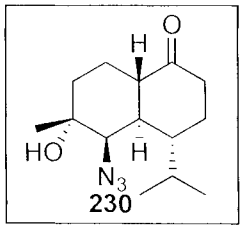

Figure A.3.1 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **230**

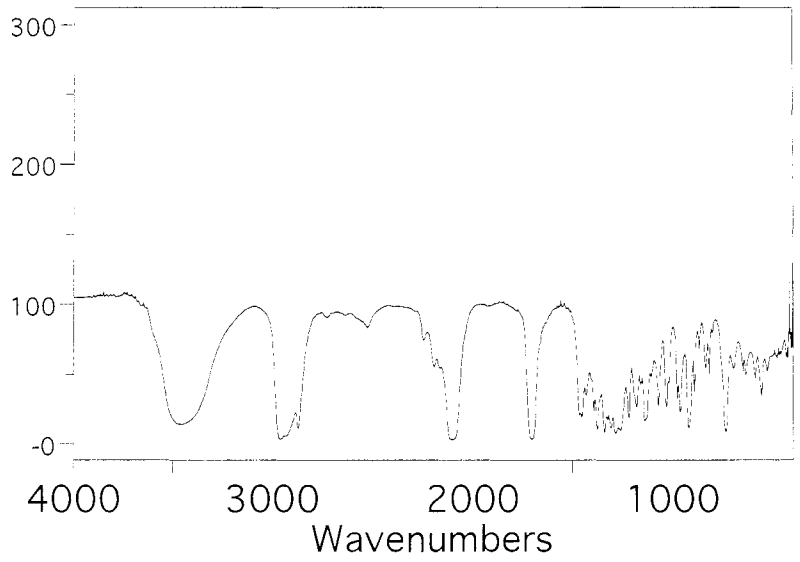

Figure A.3.2 FTIR Spectrum (thin film/NaCl) of Compound **203h**

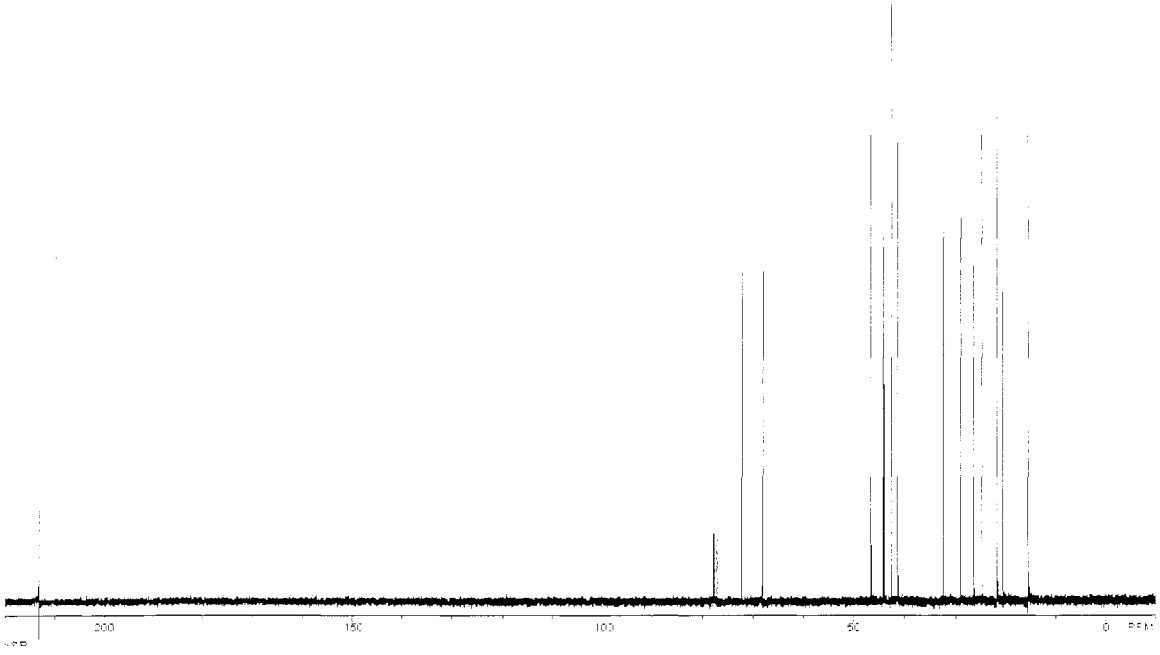

Figure A.3.3 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **203h**

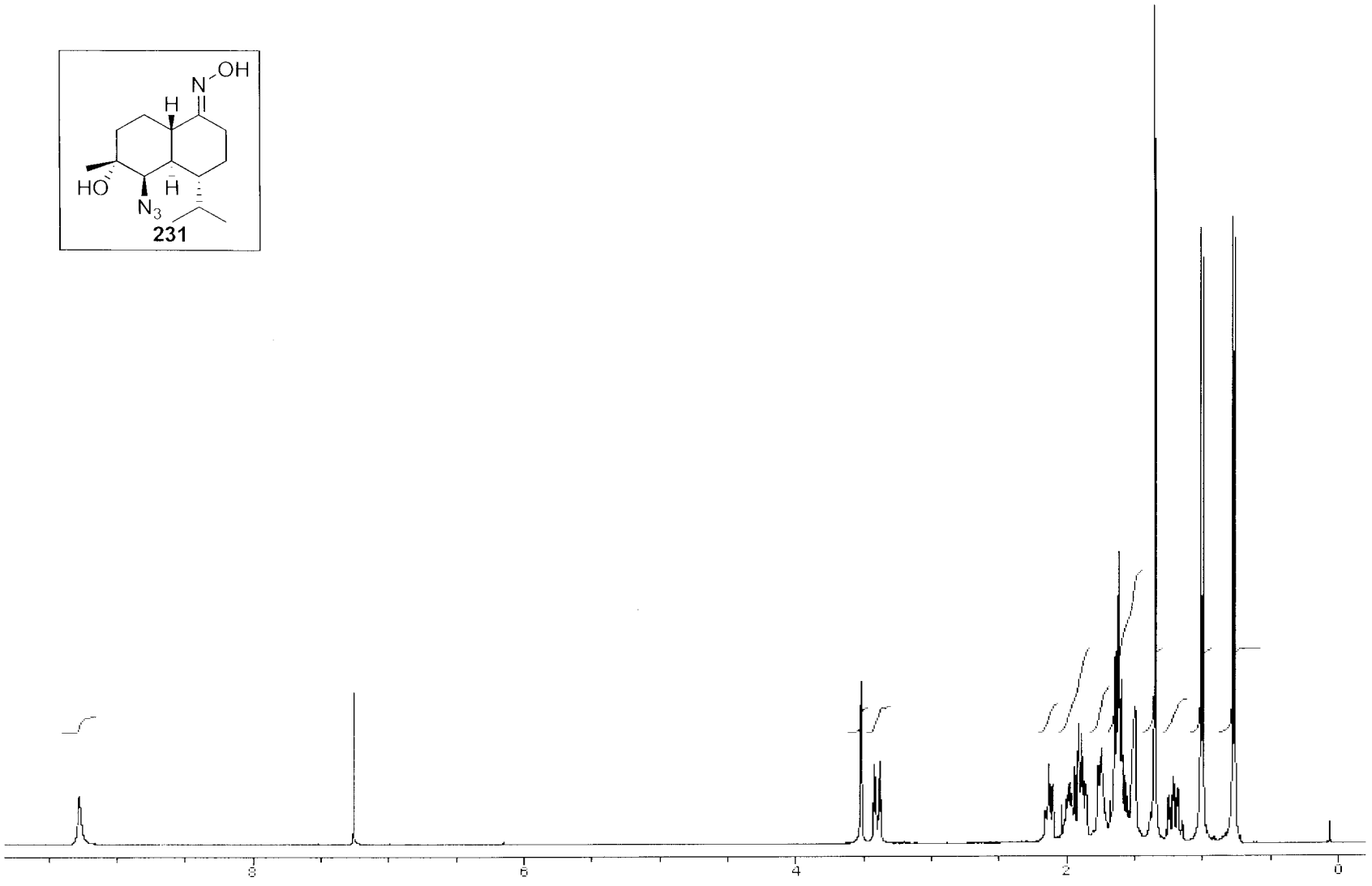

Figure A.3.4 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **231**

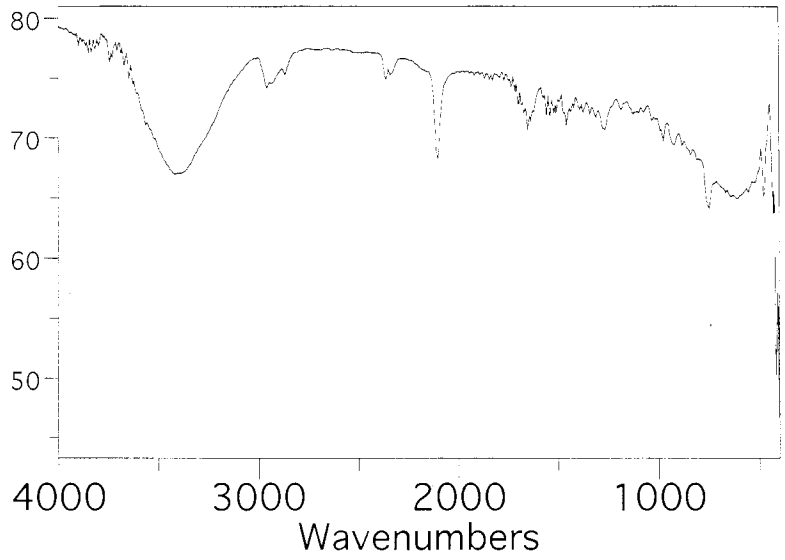

Figure A.3.5 FTIR Spectrum (thin film/NaCl) of Compound **231**

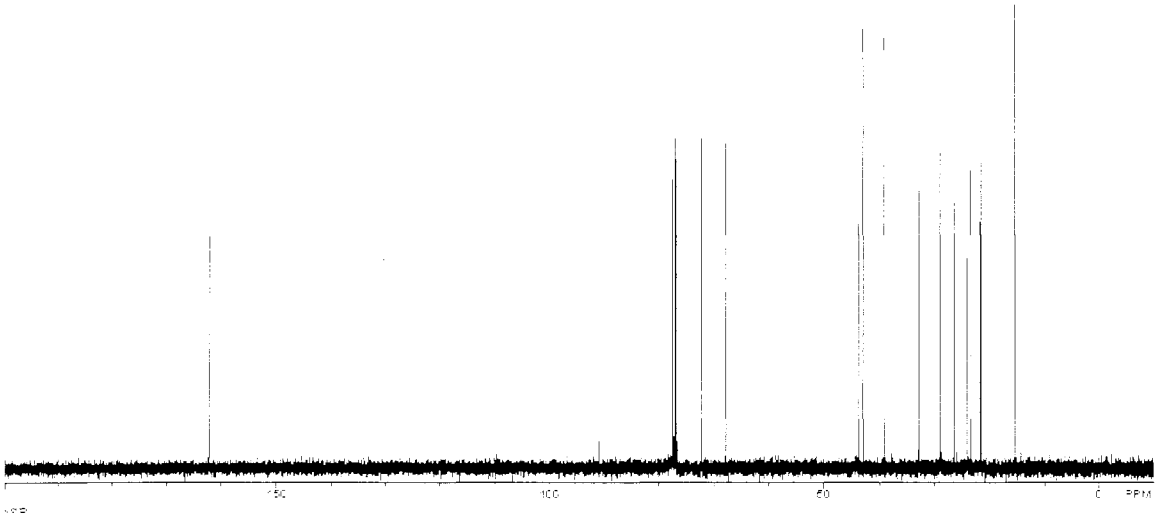

Figure A.3.6 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **231**

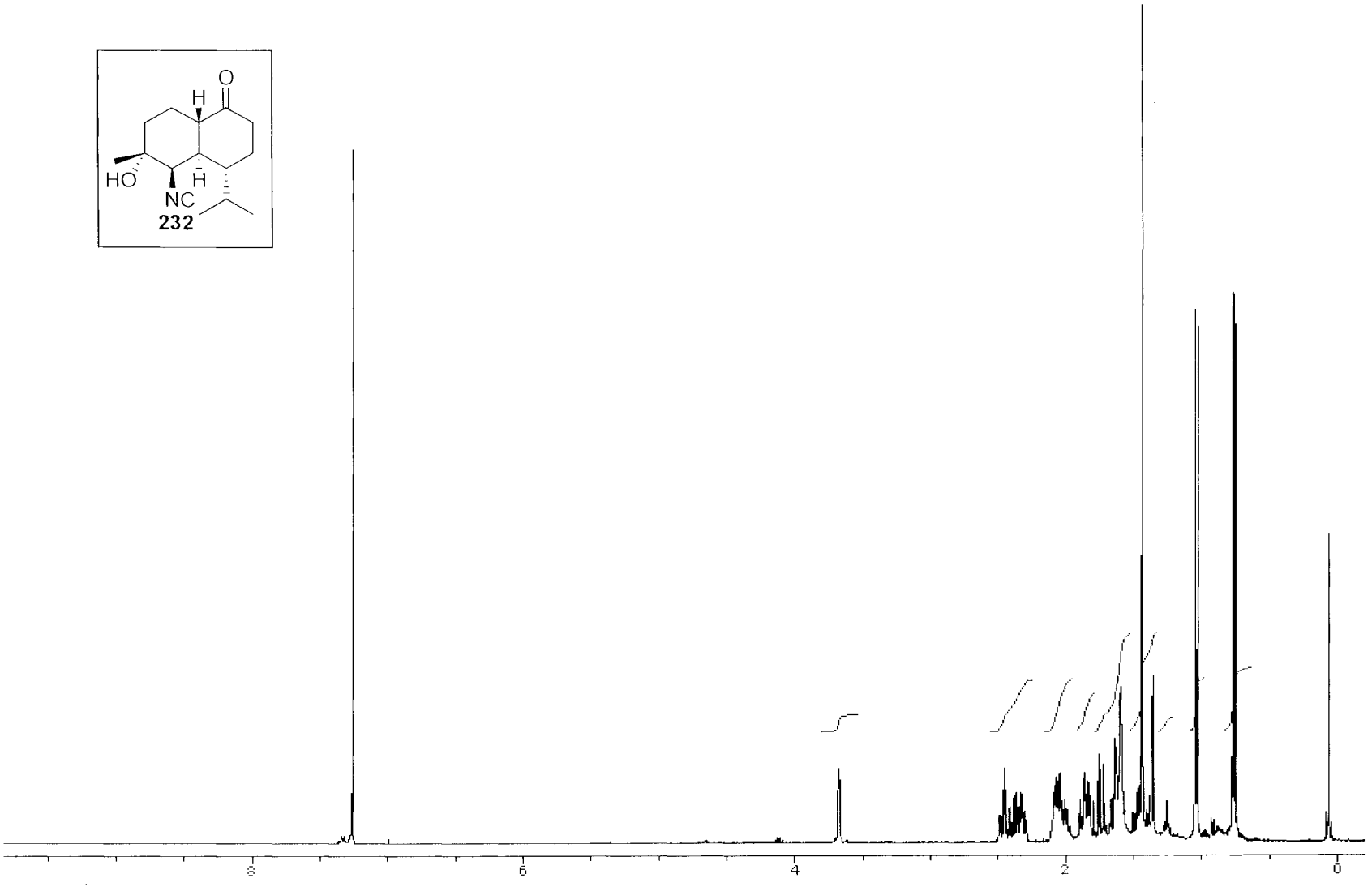

Figure A.3.7 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **232**

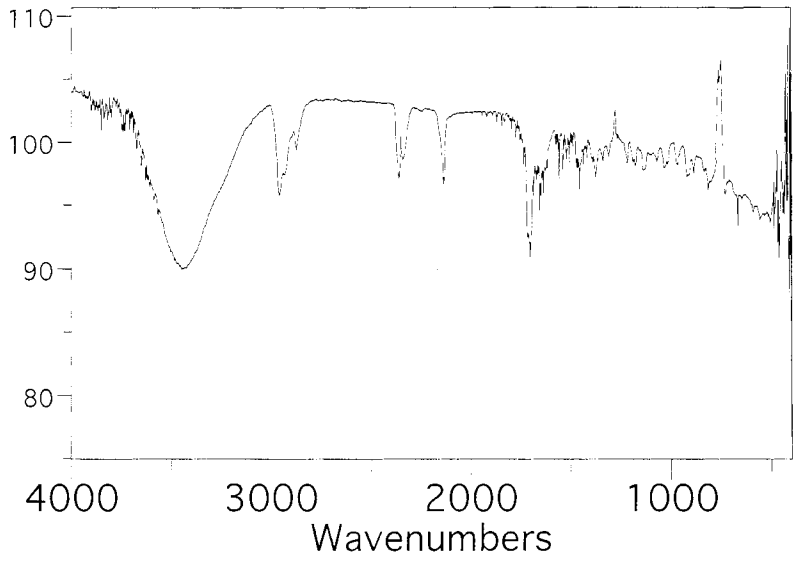

Figure A.3.8 FTIR Spectrum (thin film/NaCl) of Compound **232**

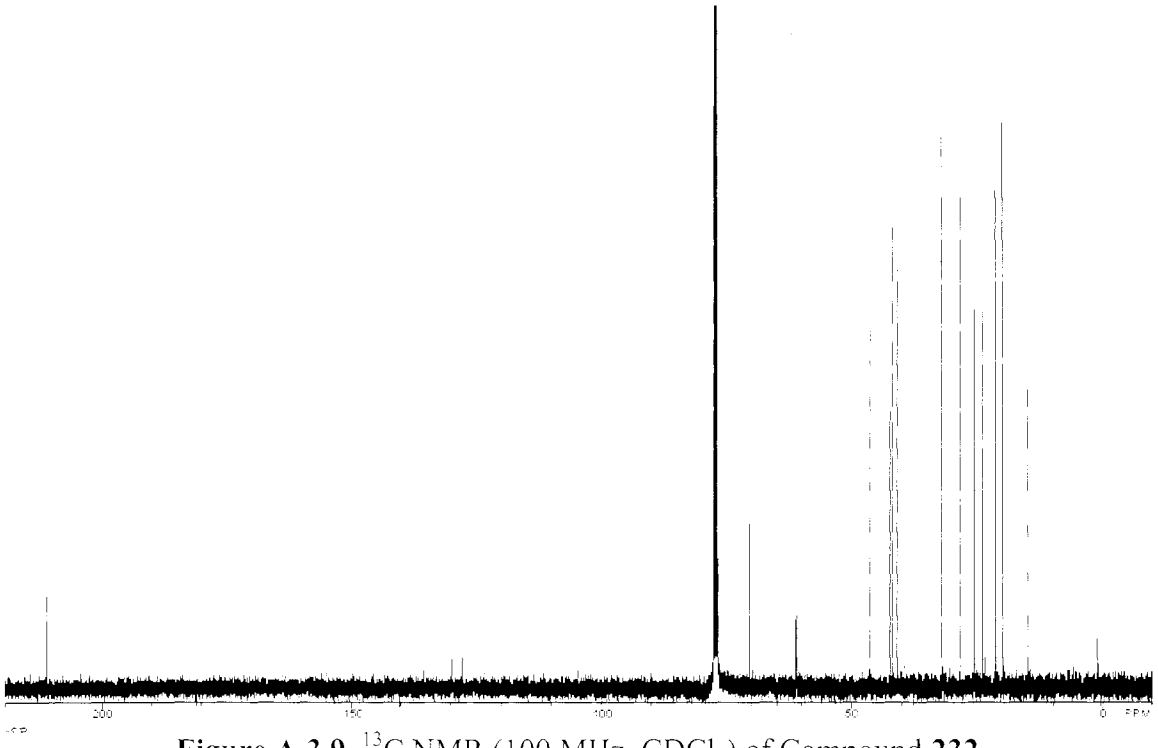

Figure A.3.9 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **232**

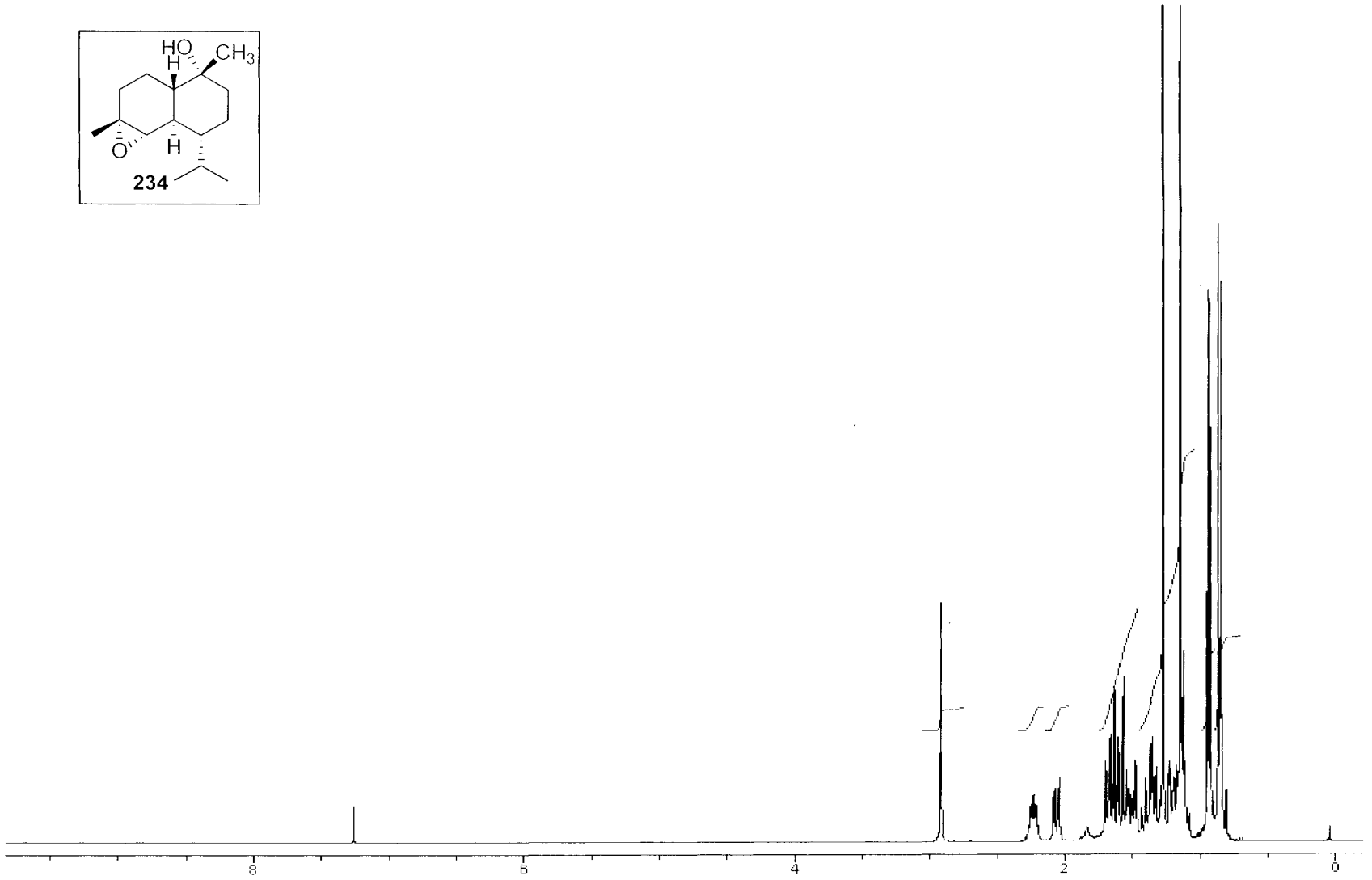

Figure A.3.10 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **234**

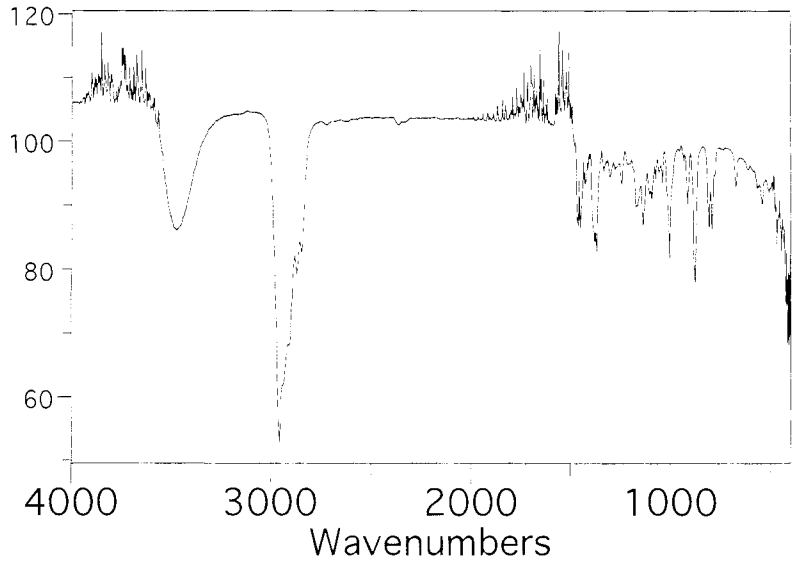

Figure A.3.11 FTIR Spectrum (thin film/NaCl) of Compound **234**

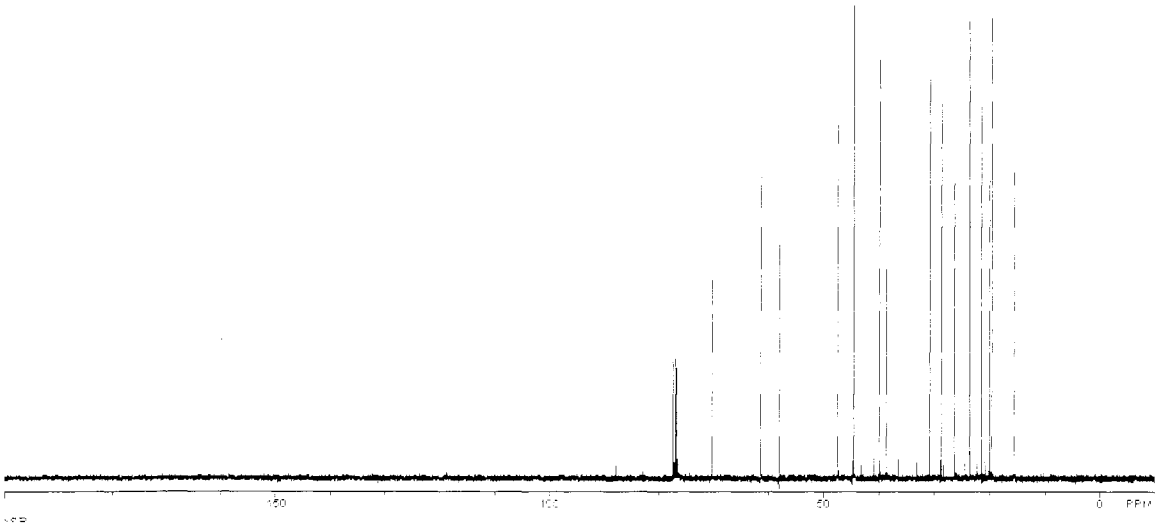

Figure A.3.12 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **234**

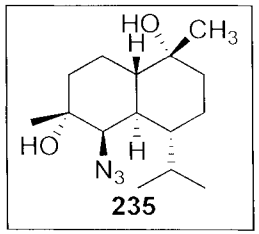

Figure A.3.13 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **235**

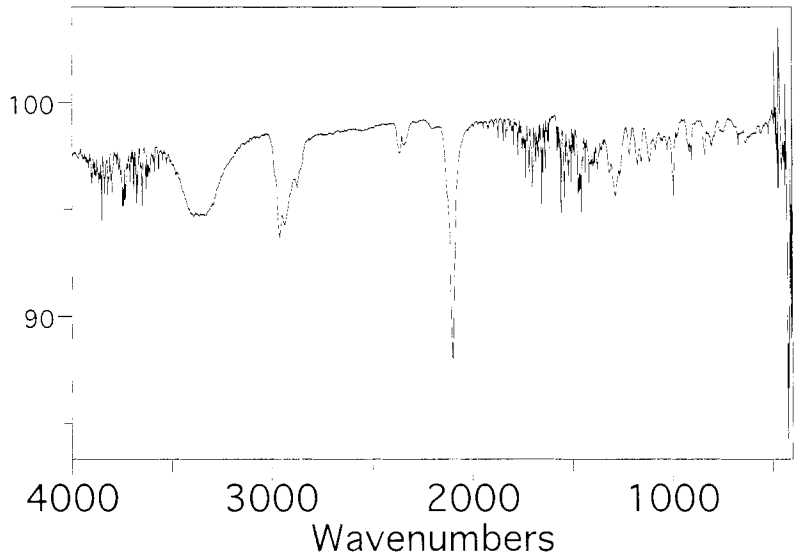

Figure A.3.14 FTIR Spectrum (thin film/NaCl) of Compound **235**

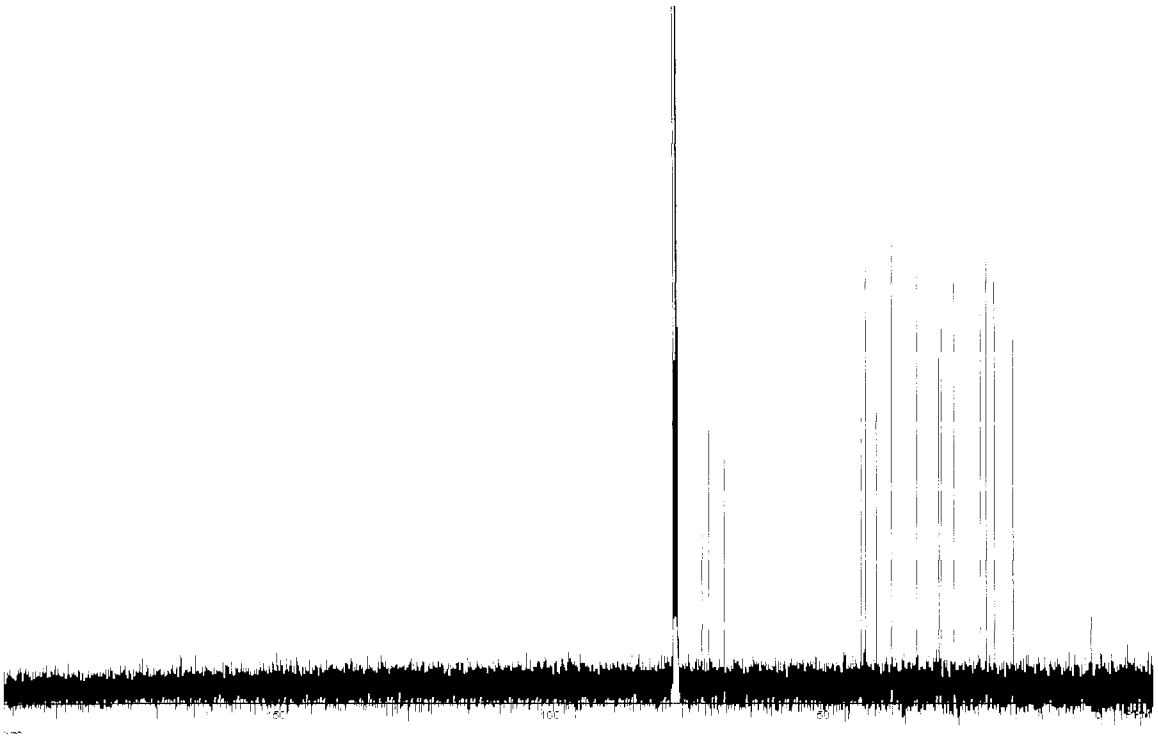

Figure A.3.15 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **235**

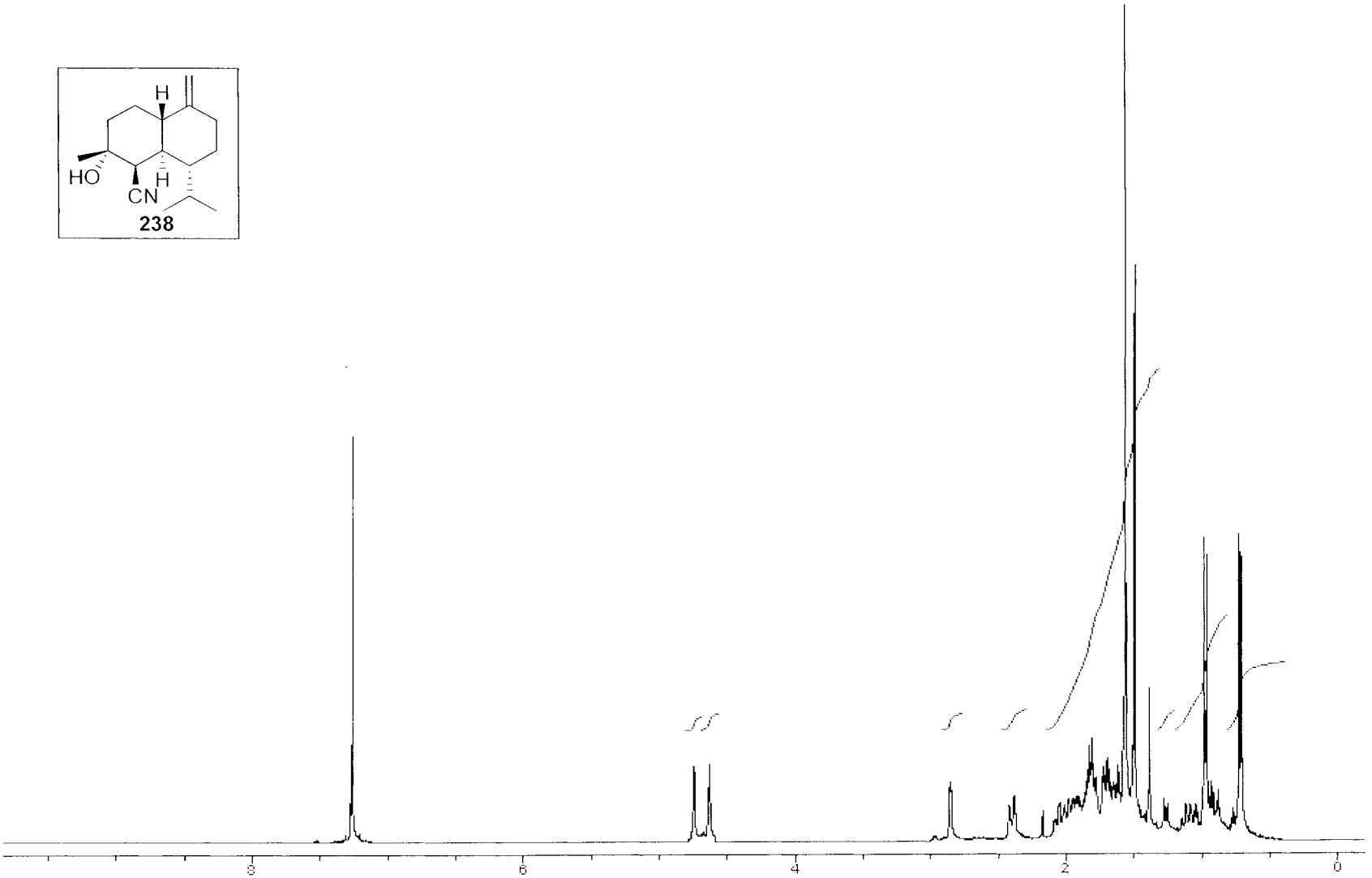

Figure A.3.16 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **238**

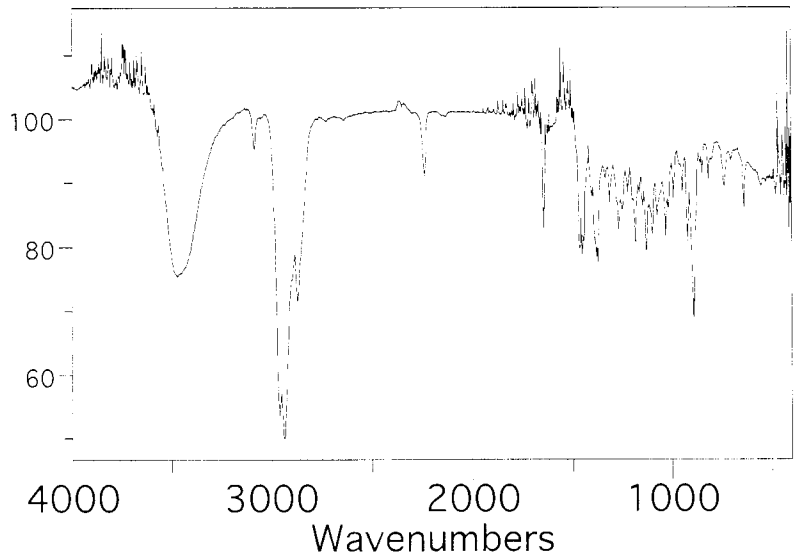

Figure A.3.17 FTIR Spectrum (thin film/NaCl) of Compound **238**

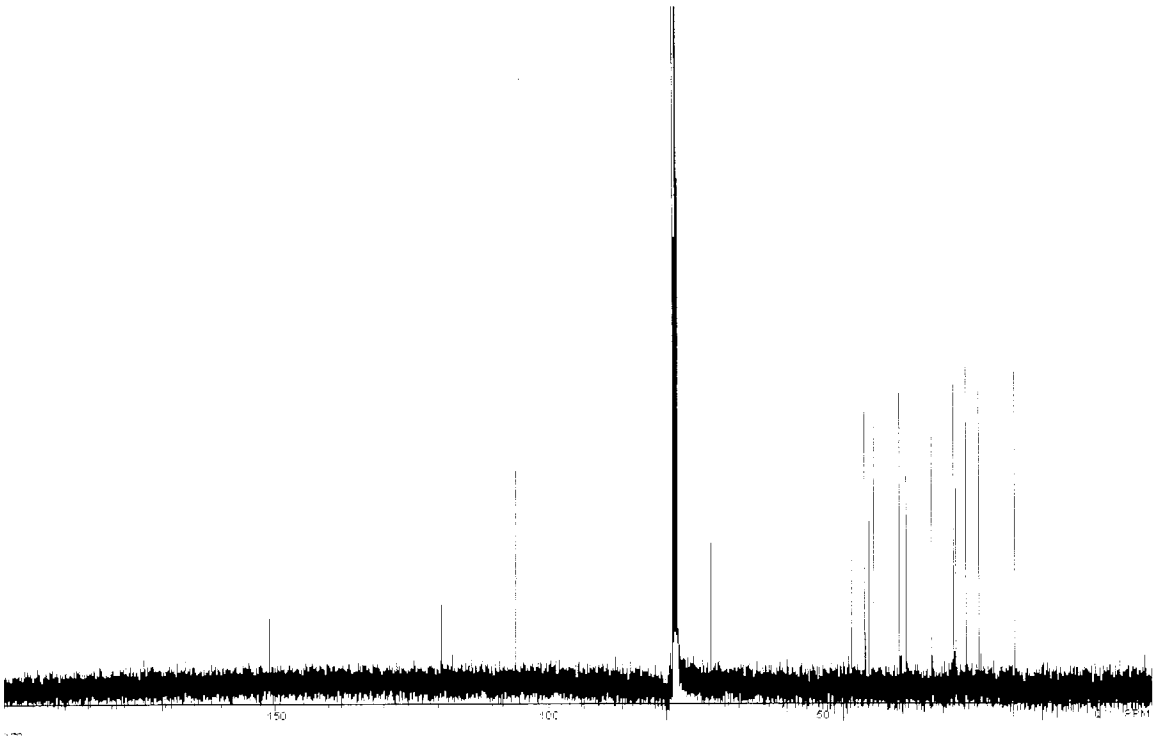

Figure A.3.18 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **238**

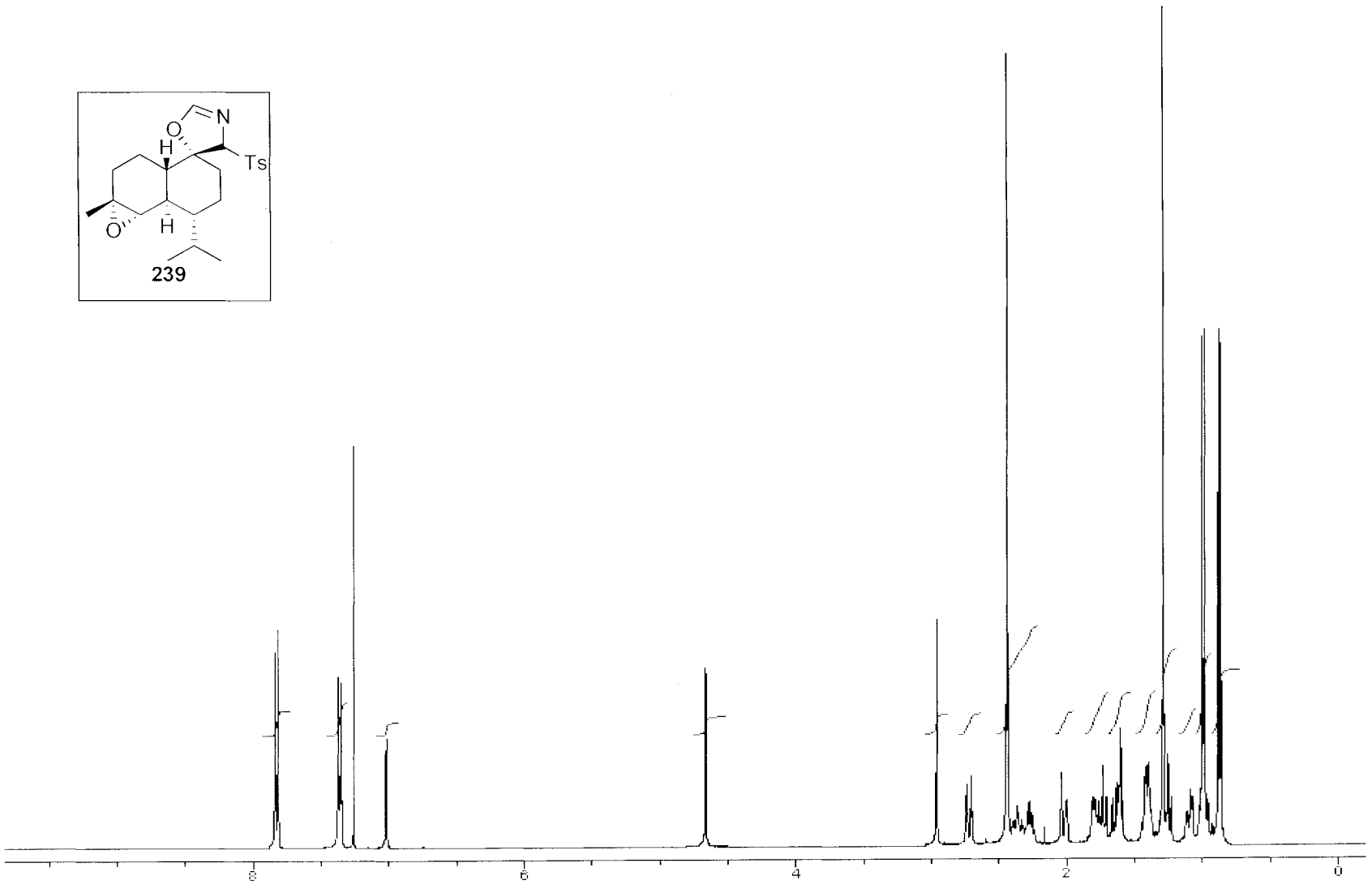

Figure A.3.19 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **239**

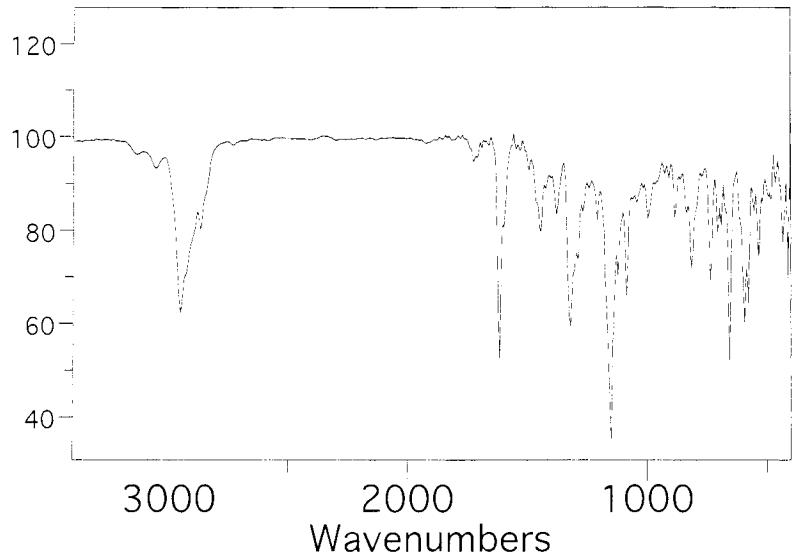

Figure A.3.20 FTIR Spectrum (thin film/NaCl) of Compound **239**

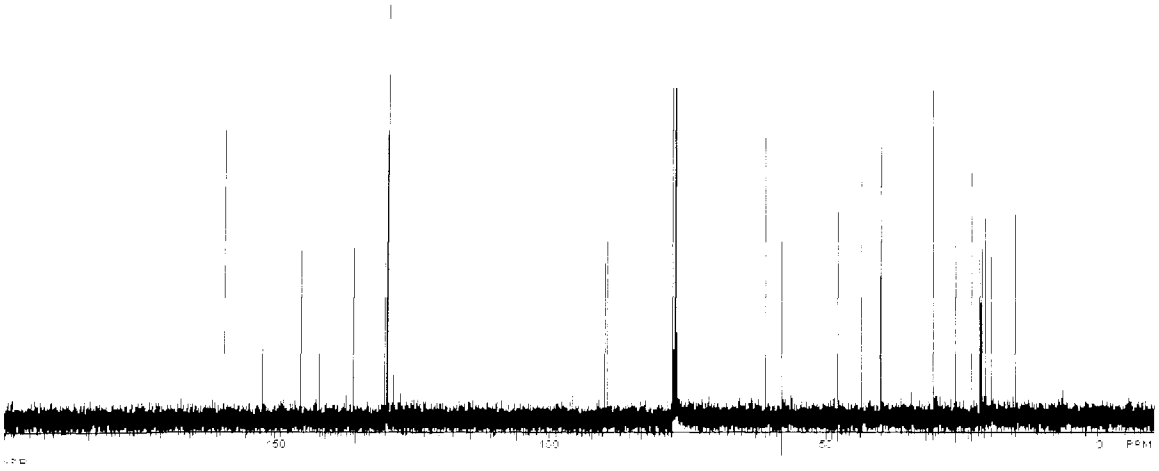

Figure A.3.21 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **239**

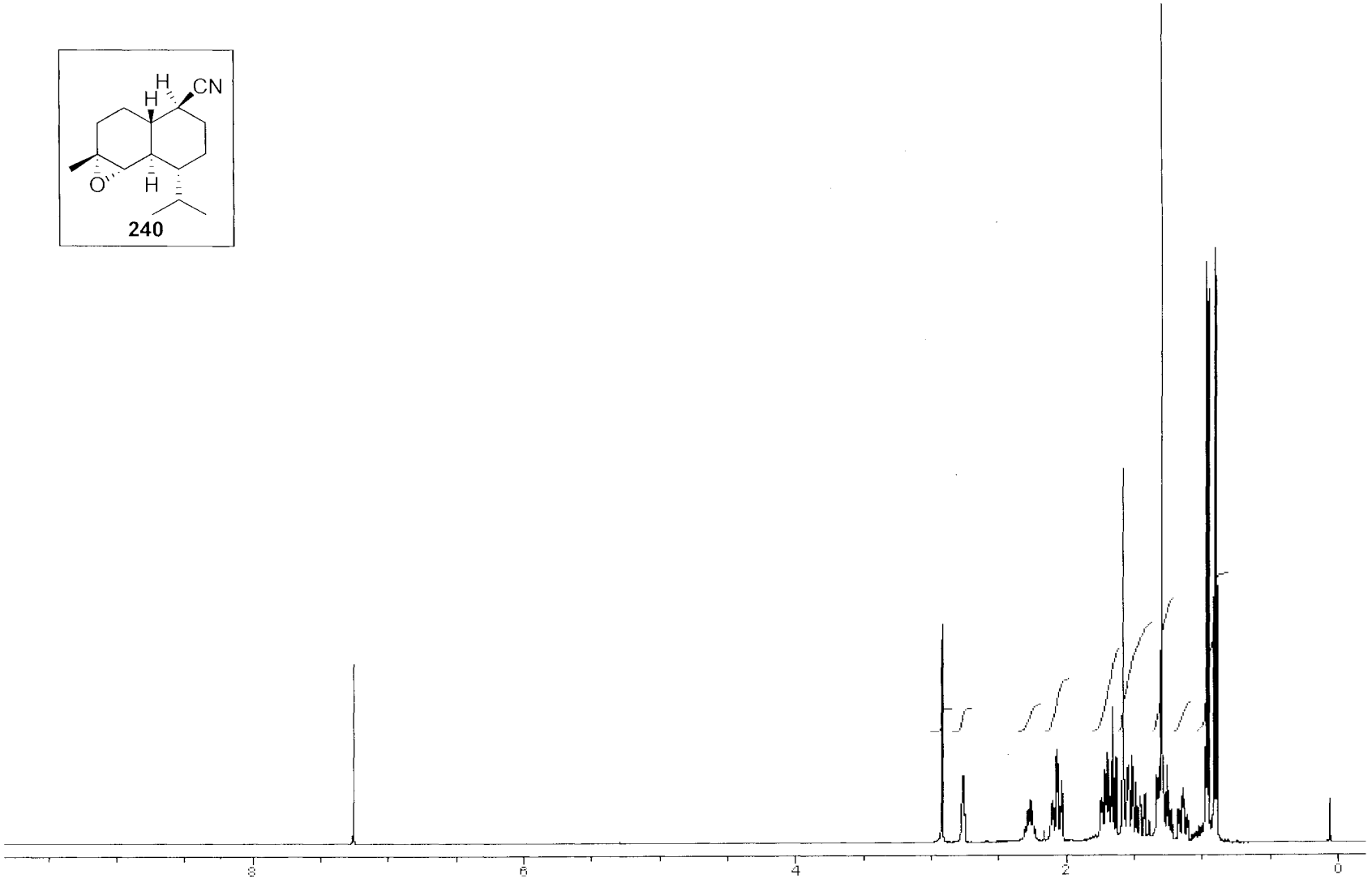

Figure A.3.22 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **240**

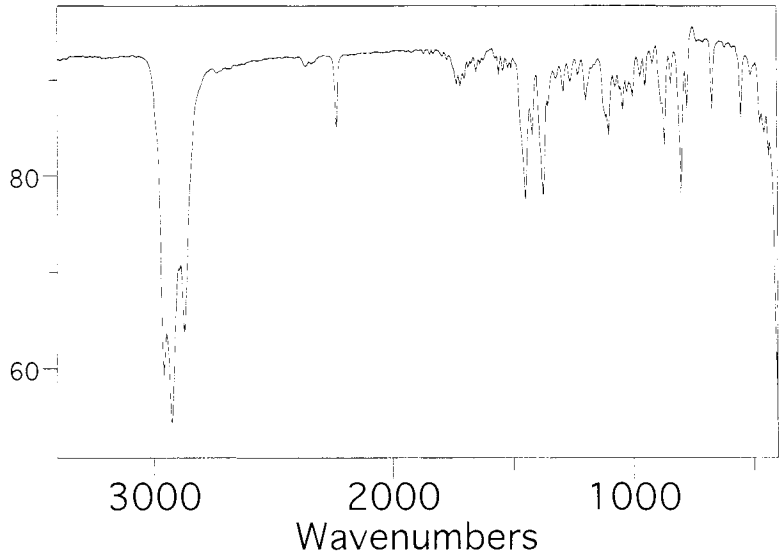

Figure A.3.23 FTIR Spectrum (thin film/NaCl) of Compound **240**

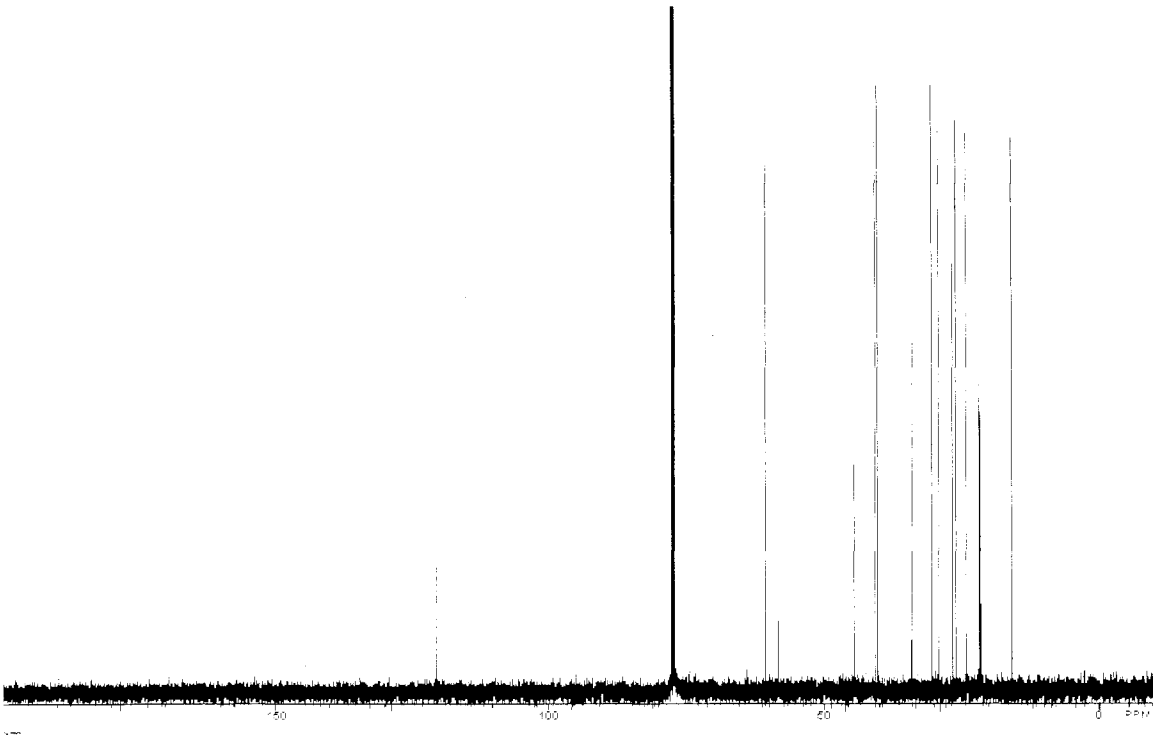

Figure A.3.24 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **240**

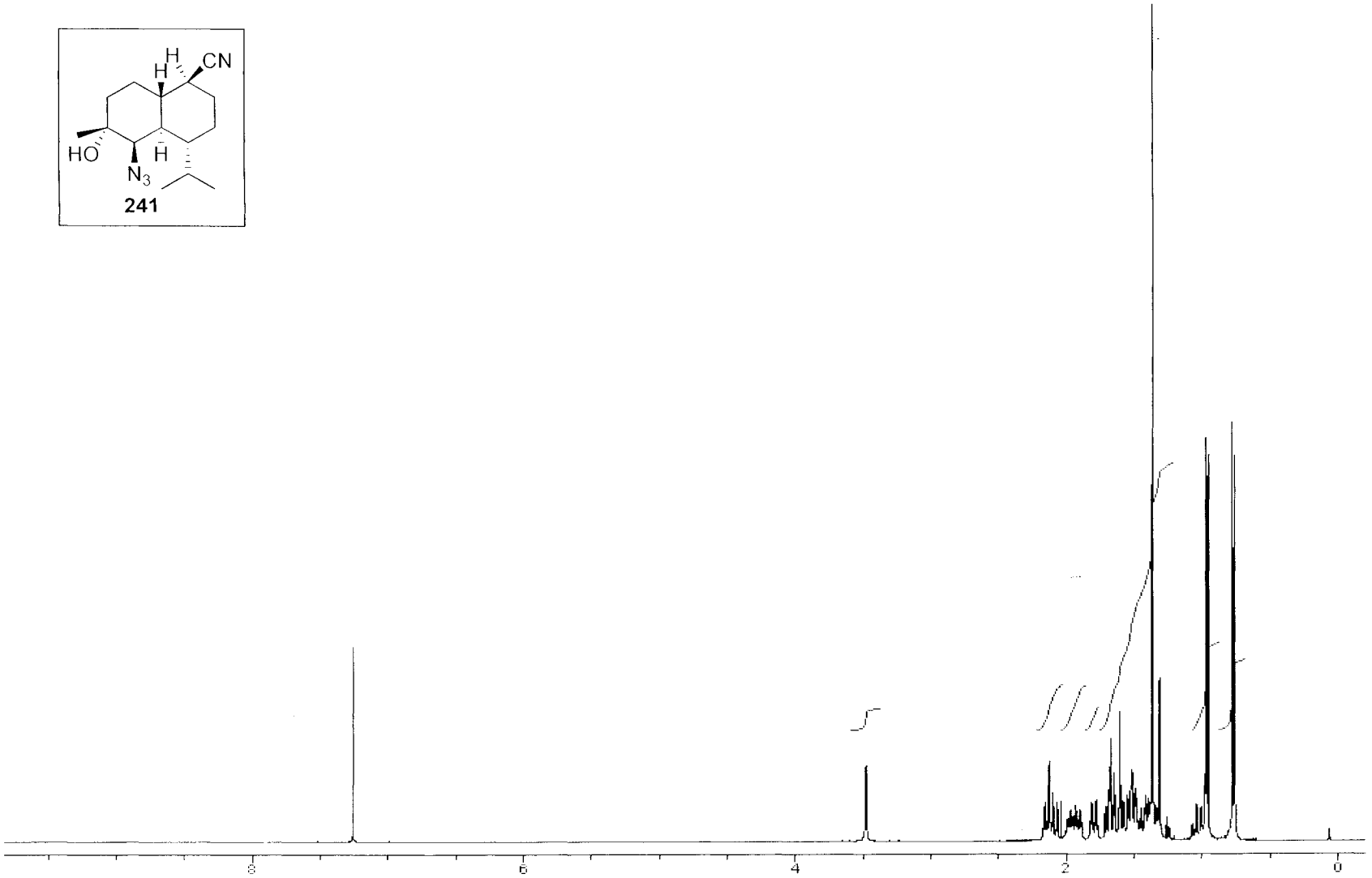

Figure A.3.25 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **241**

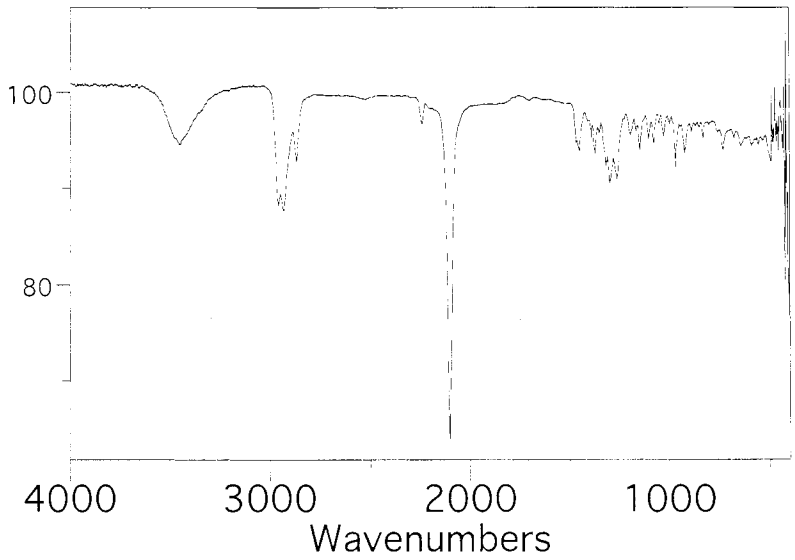

Figure A.3.26 FTIR Spectrum (thin film/NaCl) of Compound **241**

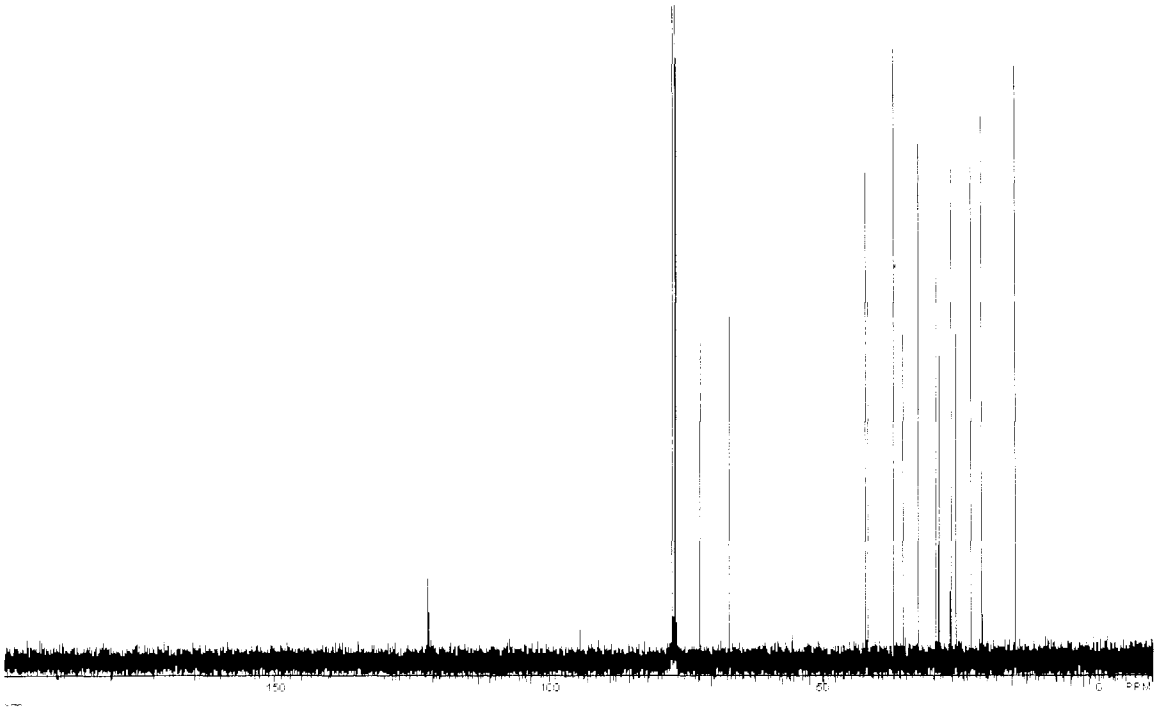

Figure A.3.27 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **241**

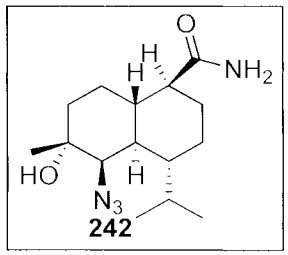

Figure A.3.28 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **242**

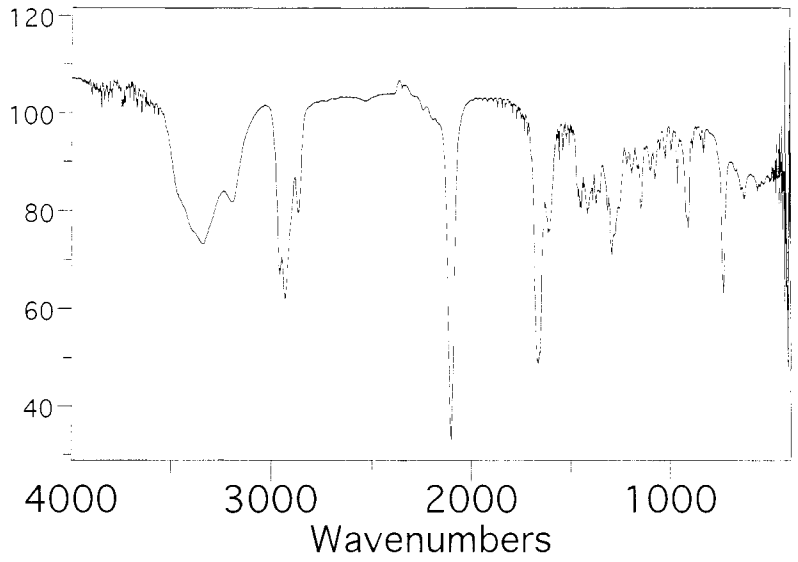

Figure A.3.29 FTIR Spectrum (thin film/NaCl) of Compound **242**

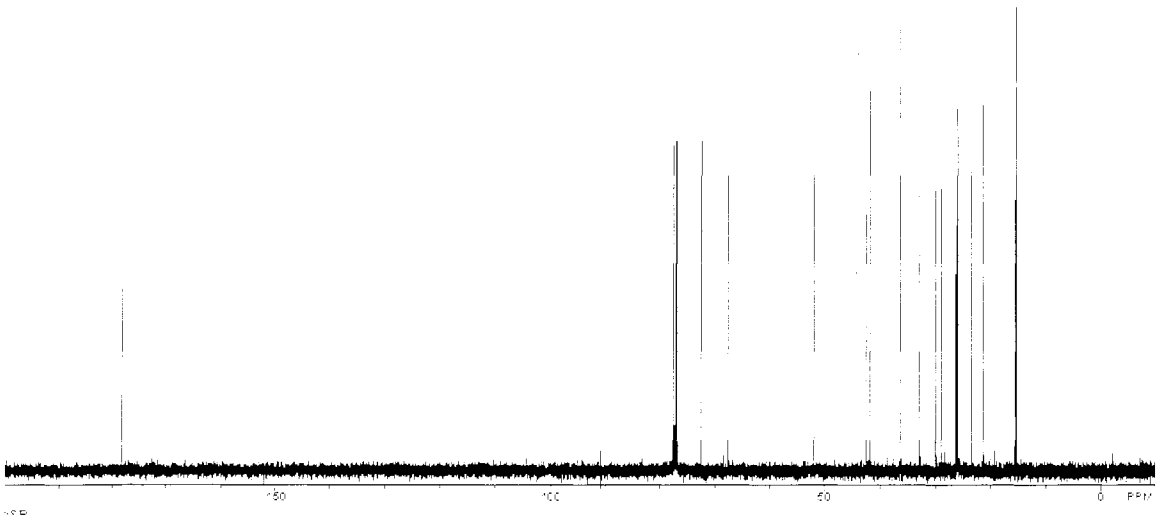

Figure A.3.30 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **242**

Appendix Four:
Notebook Cross-Reference

Notebook Cross Reference

The following notebook cross reference has been included to facilitate access to the original spectroscopic data obtained for the compounds presented in this 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. GK-IV-165 denotes notebook volume 4, page 165). 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.4.1 Notebook Cross Reference for Compounds in Chapter 2.

Cmpd	Folder	^{1}H NMR	^{13}C NMR	FTIR
77	GK-XV-197	GK-XV-197prot	GK-XV-197carb	GK-XV-197ir
78	GK-XV-187	GK-XV-187prot	GK-XV-187carb	GK-XV-187ir
109	GK-XI-137	GK-XI-137prot	GK-XI-137carb	GK-XI-137ir
110	GK-XI-115	GK-XI-115prot	GK-XI-115carb	GK-XI-115ir
114	GK-XI-251	GK-XI-251prot	GK-XI-251carb	GK-XI-251ir
116	GK-XV-179	GK-XV-179prot	GK-XV-179carb	GK-XV-179ir
117	GK-XV-181	GK-XV-181prot	GK-XV-181carb	GK-XV-181ir
118	GK-XV-183	GK-XV-183prot	GK-XV-183carb	GK-XV-183ir
119	GK-XV-185	GK-XV-185prot	GK-XV-185carb	GK-XV-185ir

120	GK-XV-189	GK-XV-189prot	GK-XV-189carb	GK-XV-189ir
128	GK-XV-191	GK-XV-191prot	GK-XV-191carb	GK-XV-191ir
129	GK-XV-193	GK-XV-193prot	GK-XV-193carb	GK-XV-193ir
131	GK-XV-195	GK-XV-195prot	GK-XV-195carb	GK-XV-195ir
132	GK-VII-31	GK-VII-31prot	GK-VII-31carb	GK-VII-31ir
134	GK-VI-247	GK-VI-247prot	GK-VI-247carb	GK-VI-247ir
135	GK-VI-251A	GK-VI-251Aprot	GK-VI-251Acarb	GK-VI-251Air
136	GK-VI-259	GK-VI-259prot	GK-VI-259carb	GK-VI-259ir
137	GK-VI-261	GK-VI-261prot	GK-VI-261carb	GK-VI-261ir
141	GK-VI-23	GK-VI-23prot	GK-VI-23carb	GK-VI-23ir
142	GK-V-279	GK-V-279prot	GK-V-279carb	GK-V-279ir
144	GK-VII-51	GK-VII-51prot	GK-VII-51carb	GK-VII-51ir
146	GK-IX-279	GK-IX-279prot	GK-IX-279carb	GK-IX-279ir
147	GK-IX-281	GK-IX-281prot	GK-IX-281carb	GK-IX-281ir
150a	GK-IX-103	GK-IX-103prot	GK-IX-103carb	GK-IX-103ir
150b	GK-XIII-141B	GK-XIII-141Bprot	GK-XIII-141Bcarb	GK-XIII-141Bir
151	GK-XII-11B	GK-XII-11Bprot	GK-XII-11Bcarb	GK-XII-11Bir
152	GK-IX-109	GK-IX-109prot	GK-IX-109carb	GK-IX-109ir
153	GK-IX-217	GK-IX-217prot	GK-IX-217carb	GK-IX-217ir
154	GK-XIV-19	GK-XIV-19prot	GK-XIV-19carb	GK-XIV-19ir
155	GK-XIII-255	GK-XIII-255prot	GK-XIII-255carb	GK-XIII-255ir
156	GK-IX-235	GK-IX-235prot	GK-IX-235carb	GK-IX-235ir
158	GK-X-27	GK-X-27prot	GK-X-27carb	GK-X-27ir
159	GK-XIII-69	GK-XIII-69prot	GK-XIII-69carb	GK-XIII-69ir
160	GK-XII-135	GK-XII-135prot	GK-XII-135carb	GK-XII-135ir
161	GK-XII-159A	GK-XII-159Aprot	GK-XII-159Acarb	GK-XII-159Air
162	GK-XII-203	GK-XII-203prot	GK-XII-203carb	GK-XII-203ir
163	GK-XII-259B	GK-XII-259Bprot	GK-XII-259Bcarb	GK-XII-259Bir
165	GK-XIII-231B	GK-XIII-231Bprot	GK-XIII-231Bcarb	GK-XIII-231Bir

166	GK-X-85A	GK-X-85Aprot	GK-X-85Acarb	GK-X-85Air
169	GK-XV-65	GK-XV-65prot	GK-XV-65carb	GK-XV-65ir
170	GK-XIII-127	GK-XIII-127prot	GK-XIII-127carb	GK-XIII-127ir
171	GK-XIII-203	GK-XIII-203prot	GK-XIII-203carb	GK-XIII-203ir
172	GK-XV-155	GK-XV-155prot	GK-XV-155carb	GK-XV-155ir
174	GK-XIV-165	GK-XIV-165prot	GK-XIV-165carb	GK-XIV-165ir
175	GK-XV-165B	GK-XV-165Bprot	GK-XV-165Bcarb	GK-XV-165Bir
176	GK-XIV-255	GK-XIV-255prot	GK-XIV-255carb	GK-XIV-255ir
178	GK-XIV-231	GK-XIV-231prot	GK-XIV-231carb	GK-XIV-231ir
179	GK-XIII-107	GK-XIII-107prot	GK-XIII-107carb	GK-XIII-107ir
180a	GK-IV-121B	GK-IV-121Bprot	GK-IV-121Bcarb	GK-IV-121Bir
180b	GK-IV-121A	GK-IV-121Aprot	GK-IV-121Acarb	GK-IV-121Air
181a	GK-IV-165	GK-IV-165prot	GK-IV-165carb	GK-IV-165ir
181b	GK-IV-163	GK-IV-163prot	GK-IV-163carb	GK-IV-163ir
182	GK-VII-291	GK-VII-291prot	GK-VII-291carb	GK-VII-291ir
183	GK-VIII-59	GK-VIII-59prot	GK-VIII-59carb	GK-VIII-59ir
184	GK-VIII-93	GK-VIII-93prot	GK-VIII-93carb	GK-VIII-93ir

Table A.4.2 Notebook Cross Reference for Compounds in Chapter 3.

Cmpd	Folder	^{1}H NMR	^{13}C NMR	FTIR
202f	GK-XV-85	GK-XV-85prot	GK-XV-85carb	GK-XV-85ir
202g	GK-XV-75	GK-XV-75prot	GK-XV-75carb	GK-XV-75ir
202h	GK-XV-121	GK-XV-121prot	GK-XV-121carb	GK-XV-121ir
203b	GK-XV-99	GK-XV-99prot	GK-XV-99carb	GK-XV-99ir
203d	GK-XV-107	GK-XV-107prot	GK-XV-107carb	GK-XV-107ir
203e	GK-XV-69	GK-XV-69prot	GK-XV-69carb	GK-XV-69ir
203h	GK-XV-125	GK-XV-125prot	GK-XV-125carb	GK-XV-125ir

Table A.4.3 Notebook Cross Reference for Compounds in Chapter 4.

Cmpd	Folder	^{1}H NMR	^{13}C NMR	FTIR
230	GK-XI-49	GK-XI-49prot	GK-XI-49carb	GK-XI-49ir
231	GK-XI-55	GK-XI-55prot	GK-XI-55carb	GK-XI-55ir
232	GK-XI-77	GK-XI-77prot	GK-XI-77carb	GK-XI-77ir
234	GK-X-273A	GK-XI-273Aprot	GK-XI-273Acarb	GK-XI-273Air
235	GK-X-193	GK-X-193prot	GK-X-193carb	GK-X-193ir
238	GK-X-213	GK-X-213prot	GK-X-213carb	GK-X-213ir
239	GK-X-261B	GK-X-261Bprot	GK-X-261Bcarb	GK-X-261Bir
240	GK-X-261D	GK-X-261Dprot	GK-X-261Dcarb	GK-X-261Dir
241	GK-XI-57A	GK-XI-57Aprot	GK-XI-57Acarb	GK-XI-57Air
242	GK-XI-119C	GK-XI-119Cprot	GK-XI-119Ccarb	GK-XI-119Cir

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About the Author

Gregg F. Keaney was born on August 19th, 1978, in Melrose, Massachusetts to Anna and Richard C. Keaney. He was raised in Lynnfield, Massachusetts, a small community approximately 10 miles north of Boston, where he attended elementary, middle, and high school. During his spare time in high school, Gregg participated in several sports including indoor track and tennis.

After graduating from Lynnfield High School in 1996, Gregg became an intern at Procyon Pharmaceuticals Inc., a local biotechnology company in Woburn, Massachusetts. At Procyon, Gregg first learned the basics of purifying organic compounds and performed computer programming of scientific software applications. In the fall of 1996, Gregg enrolled in Tufts University in Medford, Massachusetts and decided to major in chemistry after his freshman year. After taking organic chemistry during his sophomore year, Gregg was drawn to the power of this science and its capacity to make compounds to better human life. With the goal of working in the field of drug discovery, Gregg became an intern at Eisai Research Institute in Wilmington, Massachusetts. Under the direction of Dr. Edward M. Suh, Gregg established a company-wide compound library database and assisted in the total synthesis of an anti-cancer natural product. Gregg credits his wonderful experiences at Eisai as his primary motivation for going to graduate school. In Prof. Krishna Kumar's laboratory at Tufts during his senior year, Gregg worked to synthesize fluorinated amino acids for incorporation into a mimic of the leucine zipper region of the GCN4 polypeptide.

In the spring of 2000, Gregg graduated from Tufts University *cum laude* with a Bachelor of Science degree in chemistry. The following summer, Gregg began his graduate studies with Prof. John L. Wood at Yale University. There he received his Master's degree in 2001 and Doctorate in 2005 after working in Prof. Wood's laboratory on a project directed toward the total synthesis of the kalihinane diterpenoids. Gregg has accepted a Research Scientist position at Infinity Pharmaceuticals in Cambridge, Massachusetts.