Progress Toward the Total Synthesis of Securamine A: Construction of the Securamine Macrocyclic Core

A Dissertation
Presented to the Faculty of the Graduate School
of
Yale University
in Candidacy for the Degree of
Doctor of Philosophy

by
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August 2003

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Abstract

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2003

Securamine A (**1**) is an unprecedented halogenated indole-imidazole alkaloid isolated from *Securiflustra securifrons*, a marine bryozoan native to the North Sea. It is one of seven natural product congeners, each composed of a pyrolloindole core along with a substituted imidazole connected by a modified isoprene unit on one end and a rare enamide moiety on the other. Herein are described efforts toward the total synthesis of this structurally unique alkaloid natural product.

Applying knowledge gained from previous synthetic efforts has led to two corresponding synthetic approaches to the securamine A macrocyclic core. The first approach attempts to employ a copper mediated cross coupling between a primary amide and (*Z*)-vinyl iodide. The second strategy relies upon a well precedented lactone-to-lactam ring expansion (**217-218**).

In the latter sequence, an iodine monochloride reaction is employed to successfully functionalize the C2-C3 imidazole side chain. With the completed securamine macrocycle in hand, work stands only a few steps away from a completed natural product.

To Dad, Mom, and Soula

Acknowledgements

The first person that I would like to acknowledge is of course, Professor John L Wood. He not only cares about his graduate students as chemists but also as people. He has shown a great deal of respect for me and I hope that I have returned that respect in kind. I owe him everything for a good start to my career in chemistry. I would also like to thank Prof. David Austin and Prof. Martin Saunders for serving on my thesis committee.

I would next like to thank Dr. Stuart C. Chaffee who allowed me to work on a project which was started by him and thrived underneath him. He not only allowed me to make starting material on the project, but also allowed me to perform frontier reactions eventually leading to my own synthetic route. Along these same lines, I would like to acknowledge Dr. J. Brad Shotwell whom I would not have made it through my graduate work without. If it were not for him, I certainly would not have as much chemistry to write about in this dissertation. He joined the project at a difficult time and helped it prosper. I am forever grateful to both of these people. To the remaining members of the Wood Lab that I had the privilege to work with, I am honored to have called you all my colleagues and am even more delighted to consider you all my friends.

To the rest of the chemistry department that I have been able to work with, thank you for a wonderful experience and for four years full of wonderful memories.

To Ingrid Sprinz, I am forever grateful for you standing by me while I was finishing up my graduate school career. I not only would have had a more stressful time

writing my thesis if it were not for you, but certainly would not have been able to complete in on time. My only regret is that I didn't meet you earlier.

To my family, (Mom, Dad and Soula) who have shown me all the love and support a son or brother could ever ask for, I certainly cannot put into words how much I owe you and how much you all mean to me but can only hope to show you over time. I love you all.

Go Yale Chemistry Softball!!!

Peter Korakas

New Haven, CT

September, 2003

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List of Abbreviations

aq	aqueous
$BF_3 \bullet Et_2O$	boron trifluoride diethyl etherate
Bn	benzyl
Boc	*t*-butoxycarbonyl
BORSM	based on recovered starting material
Bu	butyl
$(Bu)_4NHSO_3$	tetrabutyl ammonium hydrogen sulfate
C	carbon
°C	degrees Celsius
calcd	calculated
CCl_4	carbon tetrachloride
CI_4	carbon tetraiodide
$CDCl_3$	chloroform-*d*
CH_3CN	acetonitrile
$CHCl_3$	chloroform
CH_2Cl_2	methylene chloride
CI	chemical ionization
CuI	copper iodide
CuTC	copper thiophenecarboxylate
Cy	cyclohexyl
δ	chemical shift in ppm downfield from Me_4Si
d	doublet
dba	dibenylideneacetone
dd	doublet of doublets
ddd	doublet of doublets of doublets
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	dimethyl formamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dt	doublet of triplets
ea	each
EI	electron impact
equiv	equivalent
Et	ethyl
Et_2O	ethyl ether
EtOAc	ethyl acetate
EtMgBr	ethyl magnesium bromide
Et_2NH	diethylamine
Et_3N	triethylamine
FAB	fast atom bombardment
FTIR	Fourier transform infrared
g	gram(s)
h	hour(s)

H_2	hydrogen
H_2O	water
H_2O_2	hydrogen peroxide
HCl	hydrochloric acid
$HgCl_2$	mercury(II) chloride
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrum
Hz	hertz
hν	irradiation
ICl	iodine monochloride
J	coupling constant
KF	potassium fluoride
L	liter(s), ligand
lit.	literature
μ	micro
m	medium (FTIR), multiplet (NMR)
mm	millimeters
mmol	millimole
M	moles per liter
Me	methyl
MeOH	methanol
mg	milligrams
$MgSO_4$	magnesium sulfate
mp	melting point
MHz	megahertz
min	minute(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl
m/z	mass to charge ratio
Na	sodium
NH_4Cl	ammonium chloride
NH_4OH	ammonium hydroxide
$NaBH_4$	sodium borohydride
NaCl	sodium chloride
NaH	sodium hydride
$NaHCO_4$	sodium bicarbonate
NaOH	sodium hydroxide
Na_2SO_4	sodium sulphate
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
NH_3	ammonia
NMO	4-methylmorpholine N-oxide
NMR	nuclear magnetic resonance
[O]	oxidation
O_3	ozone

OAc	acetate
p	para
$P(Bu)_3$	tri(*n*-butyl)phosphine
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium
$Pd(PPh_3)_2Cl_2$	dichlorobis(triphenylphosphine)palladium
pH	hydrogen ion concentration
$P(o\text{-tolyl})_3$	tri(*ortho*-tolyl)phosphine
PPh_3	triphenylphosphine
ppm	parts per million
q	quartet
quint	quintet
$RuCl_3$	ruthenium(III) chloride
s	singlet (NMR), strong (FTIR)
SiO_2	silicon dioxide, silica gel
soln	solution
t	triplet
td	triplet of doublets
TBAF	tetrabutyl ammoniumflouride
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tri(methyl)silyl
Ts	toluenesulfonyl
TsOH	toluenesulfonic acid
ttmpp	tris(trimethoxyphenyl)phosphine
w	weak

Chapter One

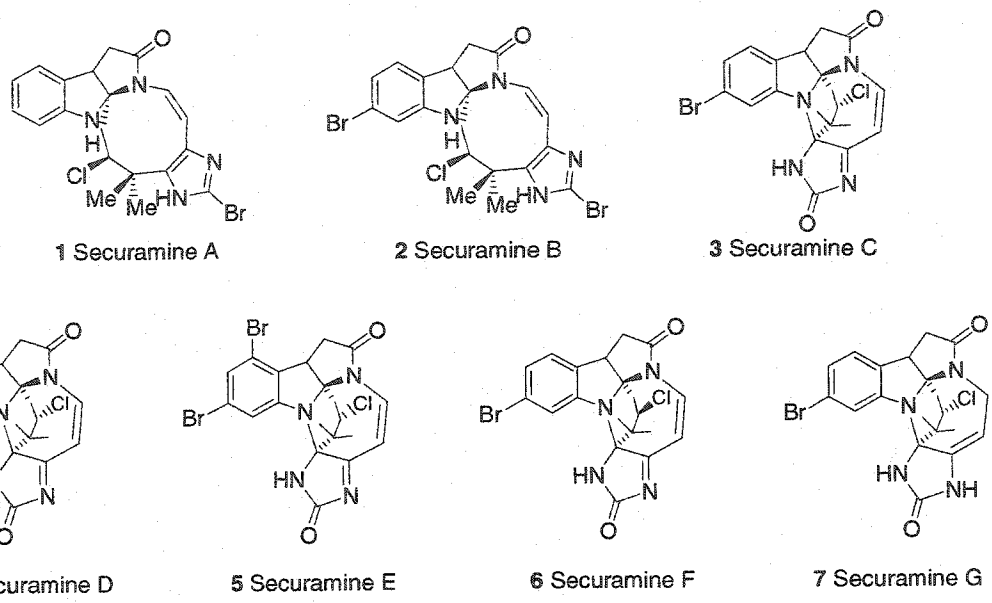
Securamine A: A Structurally Unique Indole-Imidazole Containing Natural Product

1.1 Background and Introduction to the Securamines.

1.1.1 Isolation and Structural Elucidation.

In 1996, researchers at the University of Denmark isolated four halogenated indole-imidazole alkaloid natural products, securamines A-D (**1-4**), from the marine bryozoan *Securiflustra securifrons.*[1] After extensive NMR and mass spectrometry analysis the structures of these alkaloids were determined to be as shown in Figure 1.1.1. A subsequent reinvestigation of the producing organism afforded securamines E-G (**5-7**).[2] The securamines are structurally very similar, containing a pyrollo-indole core and an imidazole, linked on one end by a modified isoprene unit and on the other by a potentially labile enamide functionality.

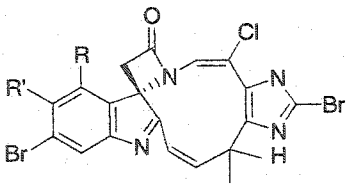
Figure 1.1.1



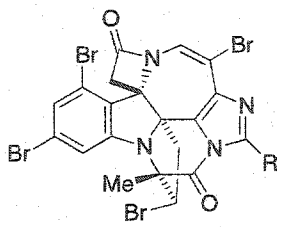
1.1.2 Related Natural Products: The Chartelline and Chartellamide Alkaloids

The chartellines (**8-10**) and chartellamides (**11-12**) shown in Figure 1.1.2, are structurally similar to the securamines in that they both contain a halogenated imidazole ring along with an enamide containing macrocycle and geminal dimethyl quaternary center.[3,4] However, there remain some subtle differences. While the securamines contain a γ-lactam pyrolloindole core, the chartellines and chartellamides contain a spirocyclic β-lactam core along with a olefin in conjugation with the indole aromatic ring in place of the neopentyl chlorine of the securamines. Both the chartellines and chartellamides are structurally unique and represent challenging synthetic targets.

Figure 1.1.2



8 R, R' = Br (chartelline A)
9 R = Br, R' = H (chartelline B)
10 R, R' = H (chartelline C)

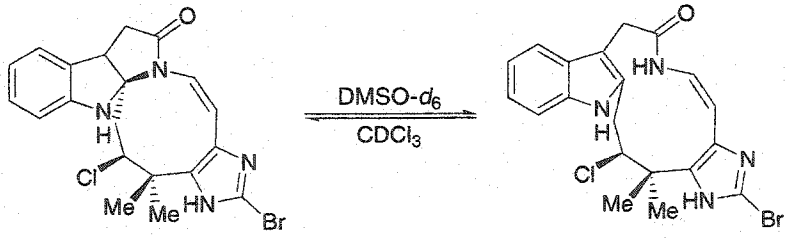


11 R = H (chartellamide A)
12 R = Br (chartellamide B)

1.1.3 An Interesting Tautomeric Equilibrium

A unprecedented equilibrium was reported in the isolation paper with respect to the pyrolloindole core of securamine A. Upon solvation in DMSO, **1** ring opens to the corresponding indole macrolactam securine A (**13**) (Scheme 1.1.2).

Scheme 1.1.2



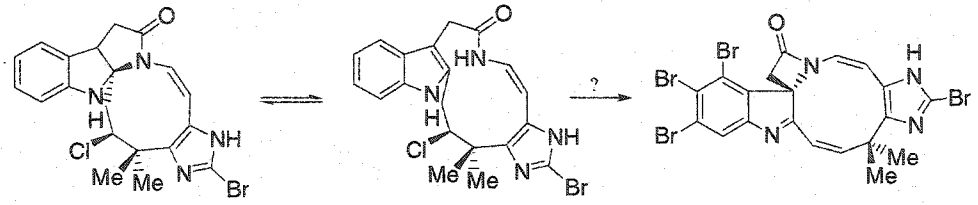
1 Securamine A

13 Securine A

With this equilibrium in mind it seems likely that **13** serves as the biogenetic precursor for this natural product class.[5] In targeting securine A synthetically, a possible plan to exploit this equilibrium presented itself. Securine A may also serve as the

precursor for chartelline A (**8**), formally derived via reaction of the amide nitrogen with the indole 3-position, the chartelline skeleton is formed (Scheme 1.1.3).

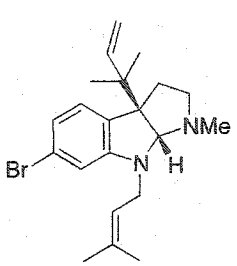
Scheme 1.1.3



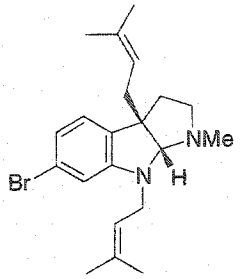
1.2 Biological Activity

Although the biological activity of the Securamine alkaloids has yet to be determined, insight into their possible significance can be arrived at by observance of other natural products isolated from the *Flustridae* family of bryozoans (which *Securiflustra Securifrons* is a member of). Flustramine A (**14**) and B (**15**) (Figure 1.2.1), isolated almost twenty years prior to the securamines, are two brominated indole alkaloids known to exhibit antibiotic and muscle relaxant activity.[6,7]

Figure 1.2.1



14 Flustramine A



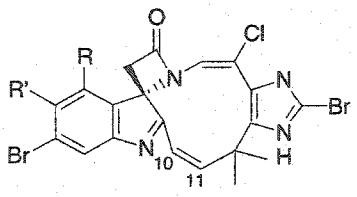
15 Flustramine B

1.3 Weinreb's Approach Toward the Chartellines and Chartellamides

1.3.1 Model Studies Directed Toward the Chartelline Skeleton

The chartellines are a structurally similar class of molecules with respect to the securamines. The major difference once again being the spirocyclic β-lactam ring rather than the γ–lactam ring seen in the Securamine skeleton.

Figure 1.3.1

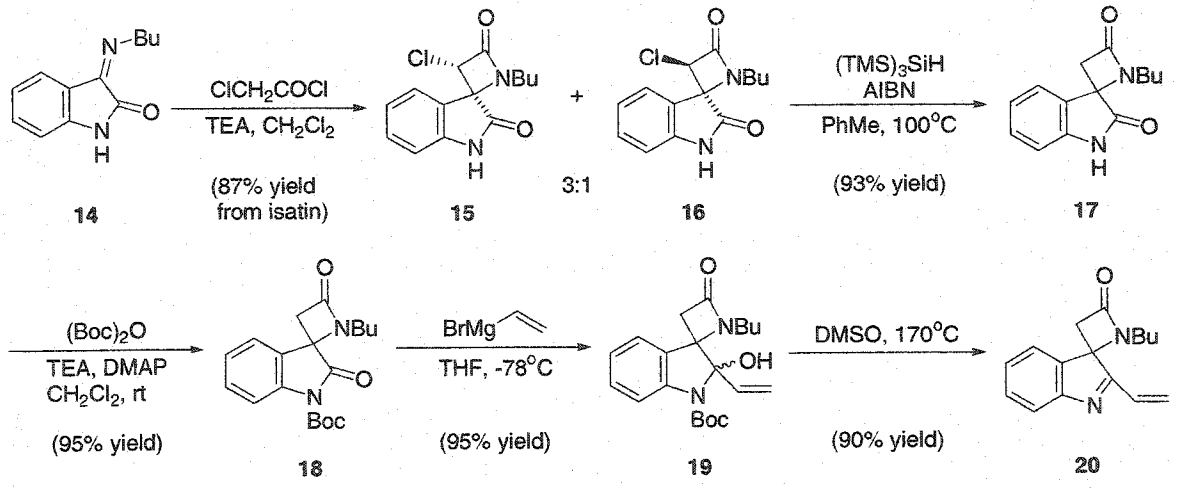


8 R, R' = Br (chartelline A)
9 R = Br, R' = H (chartelline B)
10 R, R' = H (chartelline C)

Weinreb's synthetic approach toward the chartelline skeleton focuses mainly on preparing this spirocyclic lactam core.[8] To construct this unique functionality a

Staudinger ketene-imine cycloaddition of **14** was employed (Scheme 1.3.1). Dehalogenation proceeded smoothly to provide **17** in excellent yield. Treatment of **17** with Boc_2O protected the lactam N-H as it's Boc derivative. At this point addition of vinyl magnesium bromide to the lactam carbonyl installed the chartelline C-10,11 olefin. Simply heating **19** at 170°C in DMSO removed the Boc protecting group to furnish the desired chartelline model system which contained both the spirocyclic β-lactam and the α,β-unsaturated imine functionality.

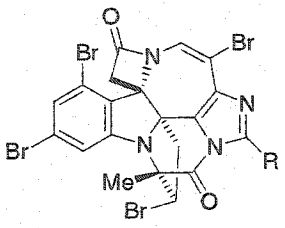
Scheme 1.3.1



1.3.2 Feasibility Studies on the Total Synthesis of the Chartellamides

In a more recent account, Weinreb describes efforts toward the Chartellamides using his previously developed Staudinger type cycloaddition strategy.[9]

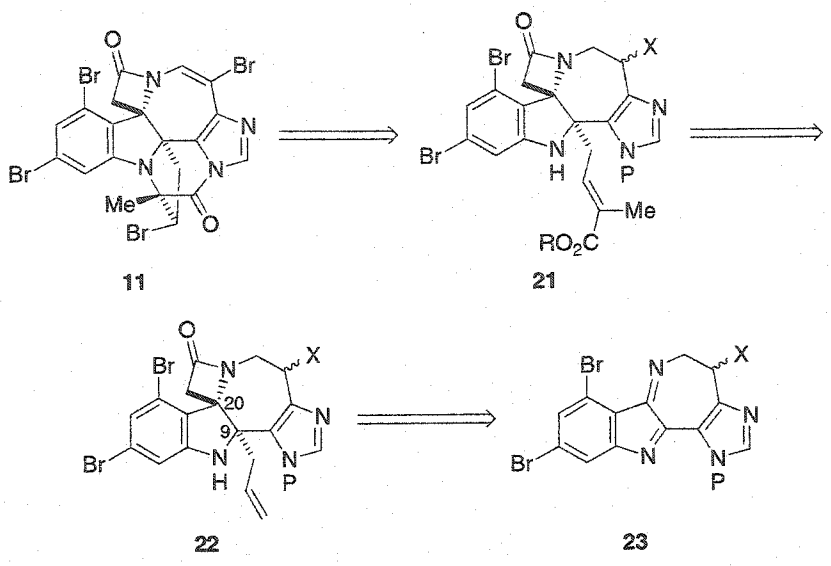
Figure 1.3.2



11 R = H (chartellamide A)
12 R = Br (chartellamide B)

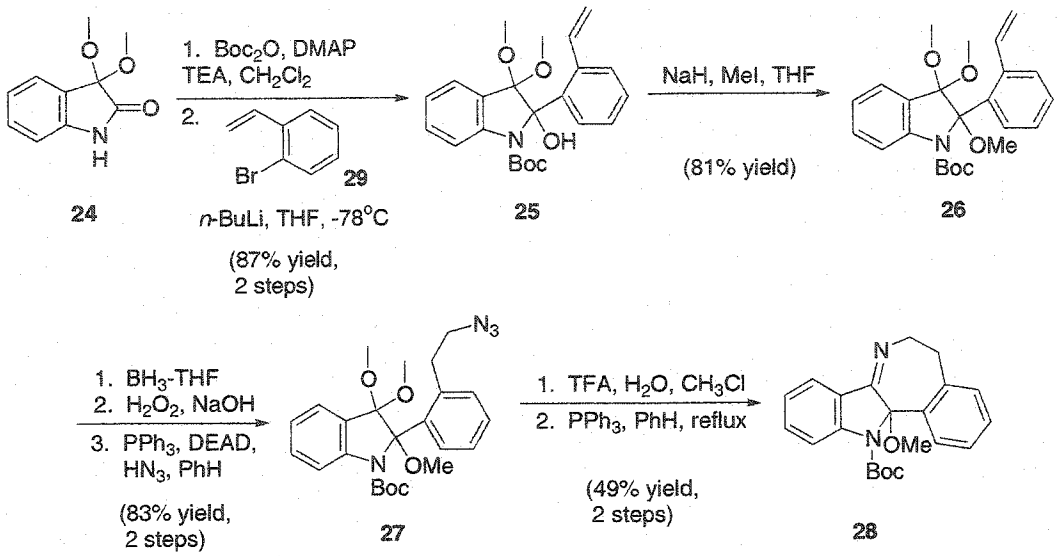
This Staudinger cycloaddition is hoped to provide the unique ring system of the chartellamides in a stereoselective fashion. Thus a retrosynthetic analysis was developed wherein the appropriate bonds were disconnected to provide intermediate **21** (Scheme 1.3.2). Adduct **21** contains an α,β-unsaturated ester side chain at the C-9 quarternary center. This ester side chain could be arrived at via olefin metathesis of the corresponding allylic side chain with methacrylate. Staudinger cycloaddition of bis-imine **23** followed by alkylation at the C-9 center should allow access to the spirocyclic β-lactam and quaternary center respectively.

Scheme 1.3.2



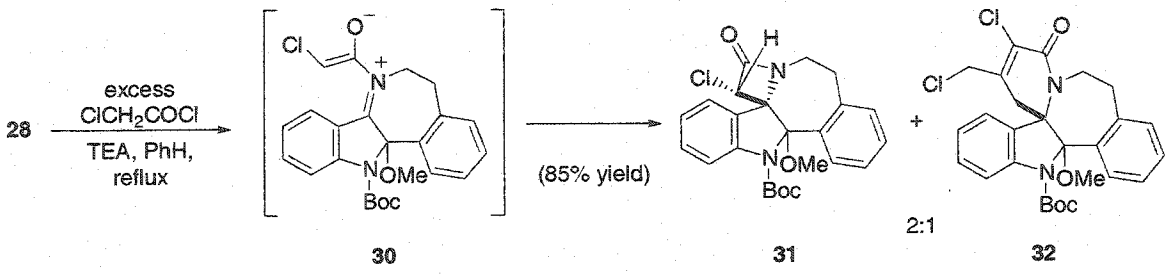
For simplicity in this model study the imidazole aromatic ring has been replaced by a benzene ring. In a forward sense, known isatin methyl ketal **24** was exposed to Boc_2O in the presence of triethylamine and DMAP to provide the corresponding Boc derivative (Scheme 1.3.3). An alkylation was then effected by addition of the lithium derivative of **29** into the amide carbonyl. Conversion of the resulting alcohol (**25**) to its methyl derivative was accomplished via alkylation of the corresponding alkoxide with methyl iodide. This phenyl side chain was elaborated via hydroboration to provide the primary alcohol, which could cleanly be converted to azide **27** under Mitsonobu conditions. Deprotection of the methyl ketal immediately followed by reduction of the primary azide furnished imine **28**.

Scheme 1.3.3



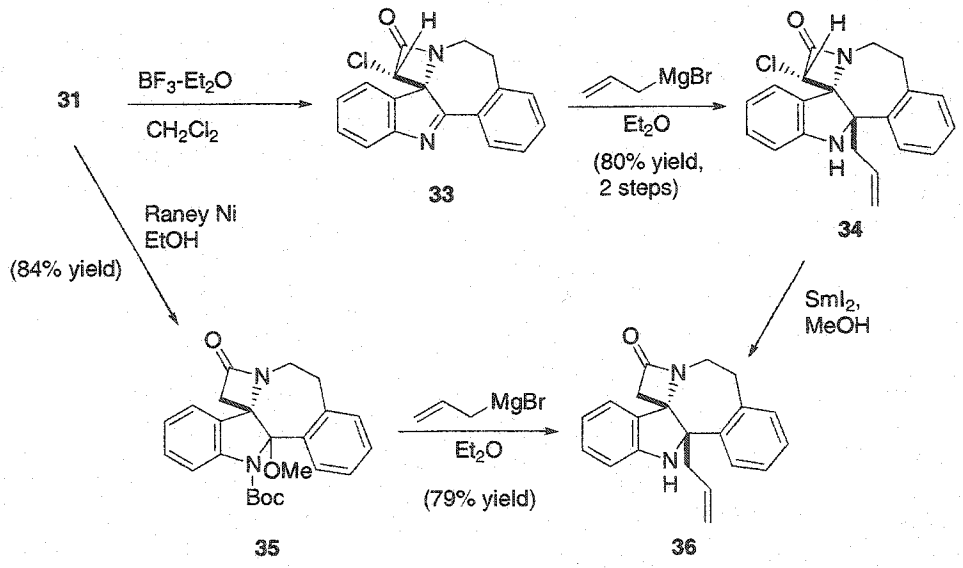
Construction of the β-lactam ring system of chartellamide A was next accomplished by exposure to Staudinger conditions to generate a 2:1 mixture of **31** and **32** (Scheme 1.3.4). There were no optimization attempts at these reaction conditions made, however, it was postulated that both chloro β-lactam **31** and oxazine **32** are arrived at through a zwitterion intermediate (**30**).

Scheme 1.3.4



At this point attention was refocused on introduction of the allyl moiety at the C-9 position. It was found that cyclic imine **33** could be formed by treatment of **31** with boron trifluoride diethyletherate (Scheme 1.3.5). Addition of allyl magnesium bromide to imine **33** *in situ* lead to a single stereoisomeric alkylation product **34**. Unfortunately, upon obtaining x-ray crystallographic data for allylic adduct **34** it was confirmed that **34** contained the incorrect C-9,20 relative stereochemistry for chartellamide A. In hopes that removal of the chlorine would provide the inverse selectivity, **31** was subjected to Raney nickel in ethanol which effectively removed the halogen and gave **35** upon isolation. However, once again, addition of allyl magnesium bromide provided alkylation product **36** which still contained the incorrect stereochemistry. This is confirmed by dechlorination of **34** using SmI_2.

Scheme 1.3.5

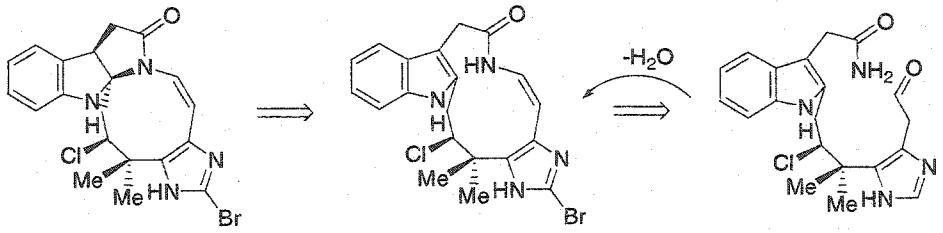


1.4 First Generation Synthetic Studies From the Wood Labs

1.4.1 Introduction and Retrosynthetic Analysis

Prior synthetic work in the Wood Labs generated a versatile approach toward the securine carbon skeleton.[10] The enamide portion of securine A was believed to be the most unstable portion of the natural product. It was therefore proposed that this enamide should be installed at a late stage synthetically (Scheme 1.4.1). Along those same lines the possibly reactive aromatic bromine would be introduced late as well via a electrophilic halogen source. It was initially envisoned that the enamide be introduced by an acid-catalyzed condensation reaction between a primary amide at the indole 3-position and a homo benzylic aldehyde. Additionally, a secondary alcohol could serve as a precursor for the neopentyl chlorine.

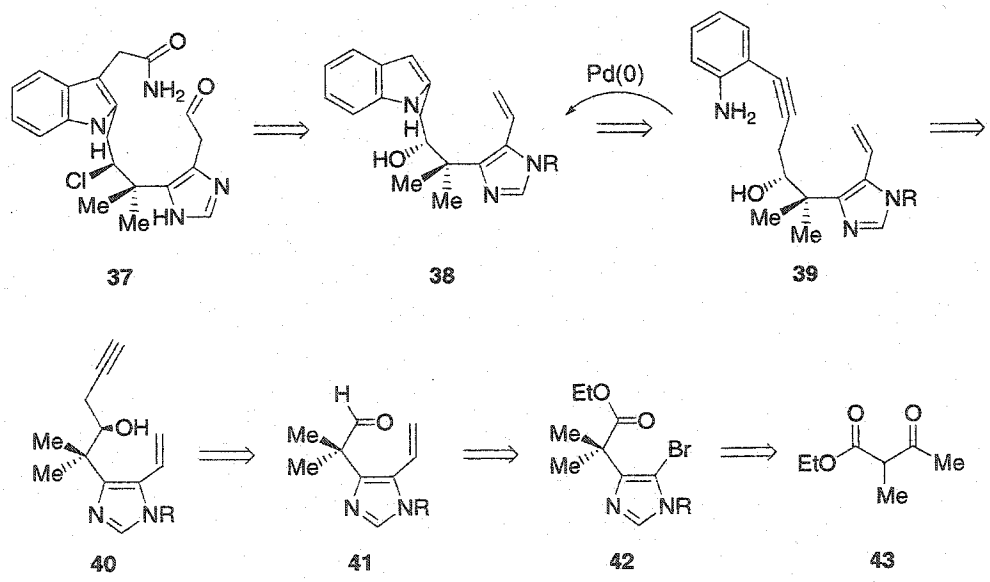
Scheme 1.4.1



The amide side chain could be installed by alkylation at the nucleophilic indole 3-position (Scheme 1.4.2). The homobenzylic aldehyde could be generated via

hydroboration of the vinyl imidazole followed by oxidation of the resulting primary alcohol. Construction of the indole core of securine A could take place by palladium cyclization of aniline **39**. This internal alkyne could be produced by a coupling reaction of an aryl halide with terminal acetylene **40**. Addition of propargyl magnesium bromide into aldehyde **41** would provide **40.** A cross coupling reaction with bromo imidazole **42** will functionalize the imidazole scaffold with the desired vinyl side chain. It was expected that imidazole **42** will arise from a commercially available ethyl-2-methyl acetoacetate (**43**).

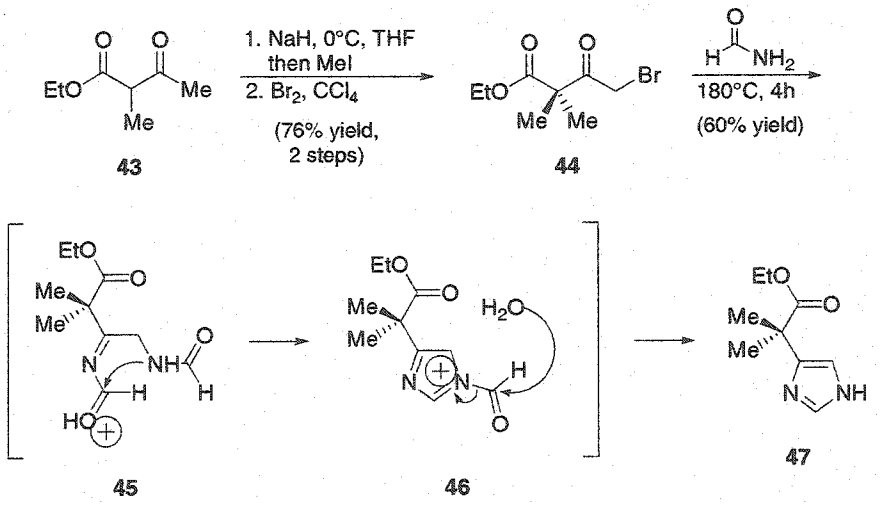
Scheme 1.4.2



1.4.2 Imidazole Construction and Elaboration

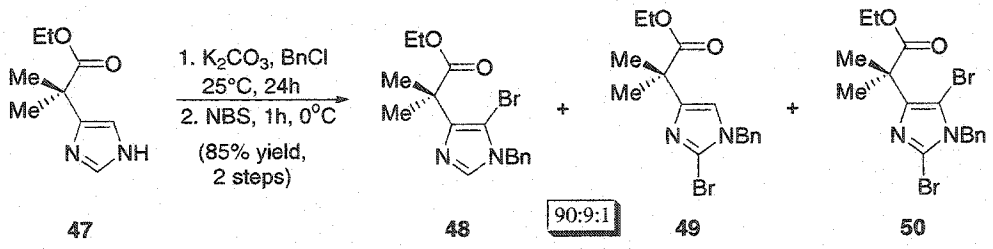
Construction of the imidazole subunit began by treatment of β-keto ester **43** with sodium hydride followed by alkylation with MeI to incorporate the geminal dimethyl quarternary center (Scheme 1.4.3). Slow addition of bromine to the corresponding ester provided monohalogenated α-bromo ketone **44**. Dissolution of **44** neat in formamide and prolonged heating (180°C, 4h) afforded imidazole **47** in good yield following recrystallization.[11] This reaction likely proceeds through a mechanism as shown in Scheme 1.4.3, wherein one equivalent of formamide displaces the bromine while another condenses onto the ketone carbonyl to provide intermediate **45**. Condensation of one equivalent of formamide onto the other cyclizes to intermediate **46**. This is followed by deformylation and aromatization to provide the observed imidazole heterocycle.

Scheme 1.4.3



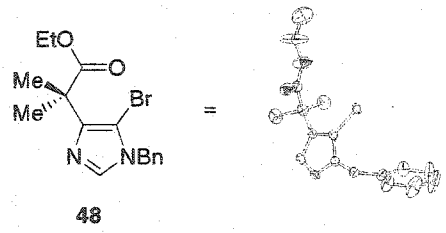
Before focusing on construction of the indole portion of the natural product some work elaborating the imidazole heterocycle remained. The first situation that demanded attention was protection of the potentially problematic imidazole NH. It was decided that this proton would be protected as a benzyl derivative. Therefore treatment of **47** with potassium carbonate and benzyl chloride effected a regioselective protection of imidazole **47** in an excellent yield (Scheme 1.4.4). Treatment of this suitably protected substrate with an electrophilic bromine source generated a mixture of three compounds. Fortunately the desired 5-brominated imidazole (**48**) was present as the major product. This important intermediate was easily separated from the various byproducts by silica gel chromatography.

Scheme 1.4.4



The regioselective nature of the bromination was confirmed in Figure 1.4.1 upon obtaining an x-ray crystal structure of the major isomer.

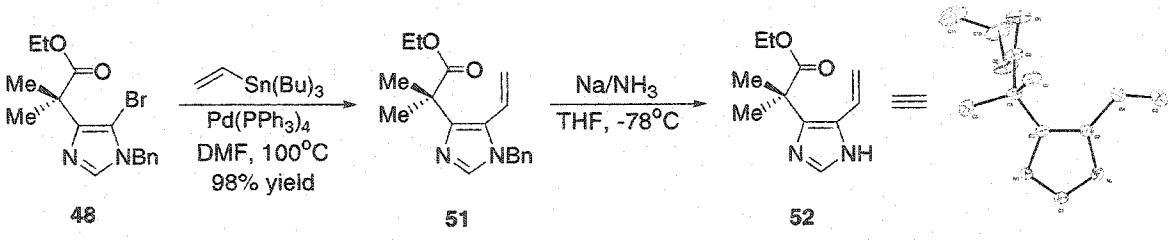
Figure 1.4.1



48

This 5-bromoimidazole (**48**) provided a nice handle to install the desired vinyl side chain. To accomplish this end, a Stille coupling protocol was employed yielding vinyl imidazole **51** (Scheme 1.4.5).[12,13] Upon removal of the benzyl protecting group this coupling product was also confirmed by x-ray crystallography.

Scheme 1.4.5



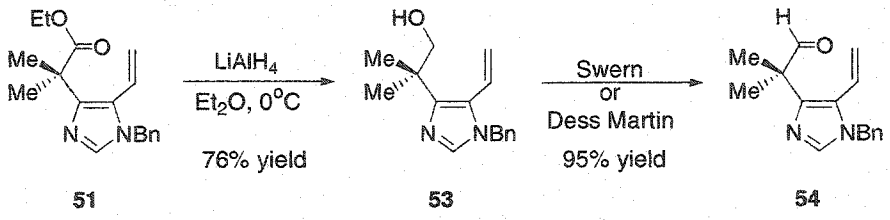
48 51 52

1.4.2 Chlorine Introduction

With a suitable imidazole scaffold elaborated, attention was shifted to construction of the indole portion of securamine A. The ethyl ester portion of imidazole

51 furnished a nice handle to build upon (Scheme 1.4.6). Adjustment of the oxidation state of ester **51** by first reducing with $LiAlH_4$ yielded alcohol **53**. Subsequent oxidation of this alcohol under either Swern or Dess-Martin conditions provided aldehyde **54** in a 72% yield over two steps.

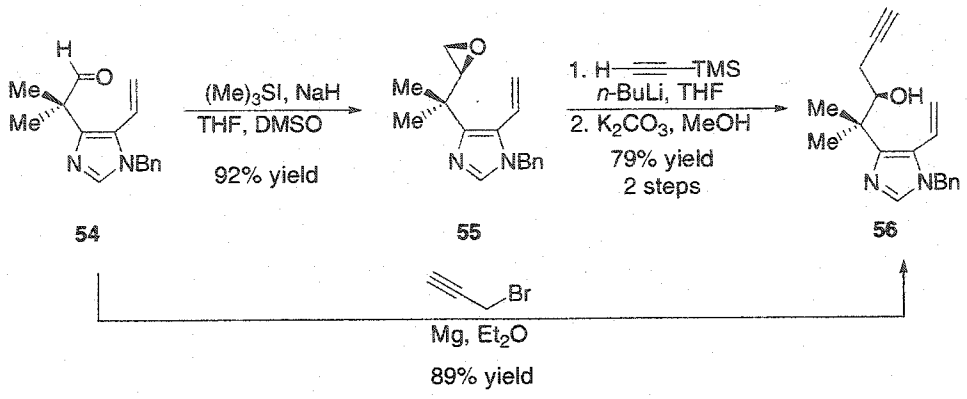
Scheme 1.4.6



51 **53** **54**

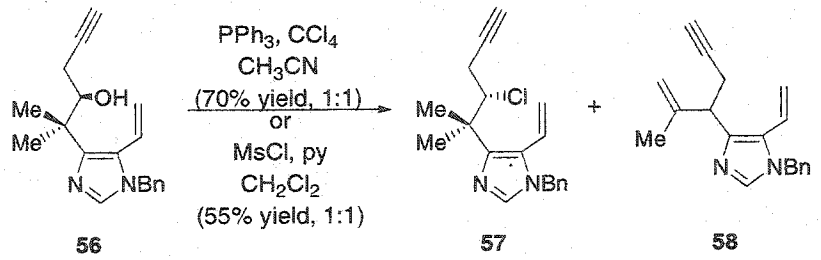
A one carbon homologation was then achieved via a Corey-Chaykovsky reaction to provide terminal epoxide **55** (Scheme 1.4.7).[14-18] Addition of a TMS-acetylene anion to the less sterically hindered position of this epoxide followed by immediate deprotection provided neopentyl alcohol **56**. This alcohol could also be arrived at in a one step fashion by treatment of aldehyde **58** with the Grignard reagent derived from propargyl bromide.

Scheme 1.4.7



At this point installation of the neopentyl chlorine was explored (Scheme 1.4.8). Upon treatment of alcohol **56** with PPh_3 in a mixture of refluxing CCl_4 and CH_3CN the desired neopentyl chlorine (**57**) was provided. Along with chloride **57** was isolated **58** which arose via rearrangement of the alcohol substrate's carbon framework.

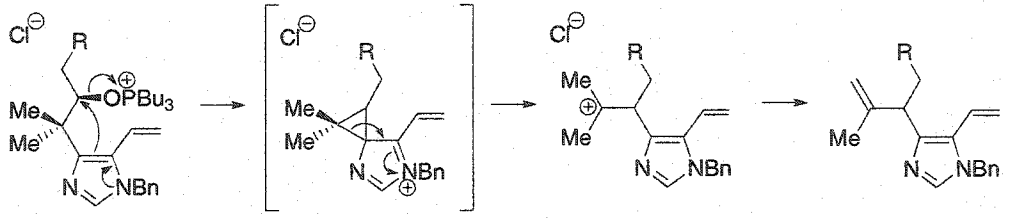
Scheme 1.4.8



Scheme 1.4.9 outlines a possible mechanistic explanation for this rearrangement. It is postulated that electrons from the imidazole ring displace the chlorine generating a spirocyclopropane intermediate (**60**). Intermediate **60** then fragments producing a tertiary

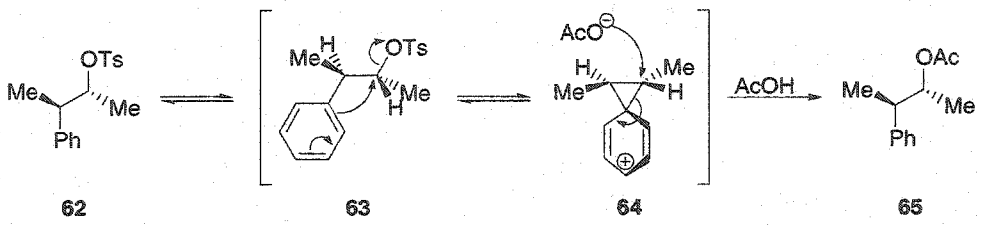
carbocation which upon elimination of a proton provides the observed rearrangement framework (**58**).

Scheme 1.4.9



Good precedent for such a mechanism was reported by Cram et. al. (Scheme 1.4.10).[19-21] Cram found that activated homo benzylic alcohols (**62**) can proceed through reactions wherein electrons from the aromatic ring assist in displacement generating spirocyclopropane intermediates (**64**) much like the one proposed above.

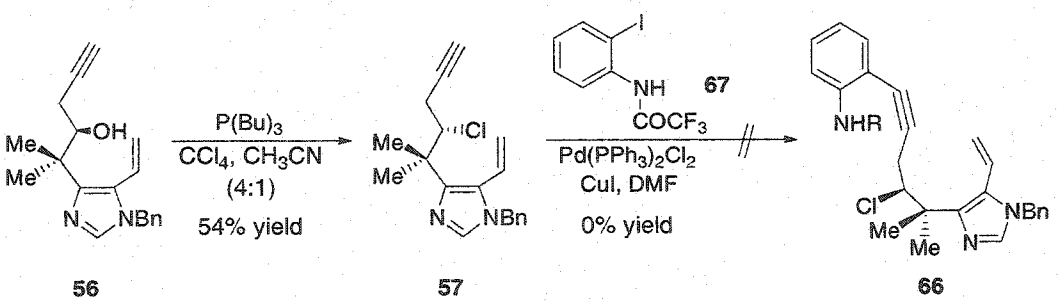
Scheme 1.4.10



1.4.2 Indole Construction

With the neopentyl chlorine promptly installed attention could be turned to construction of the indole portion of the natural product. Unfortunately all attempts at effecting a Sonogashira coupling to produce a possible indole cyclization precursor failed (Scheme 1.4.11).[22,23] When coupled with a moderately yielding chlorination step, these problems called for a reordering of the reaction sequence.

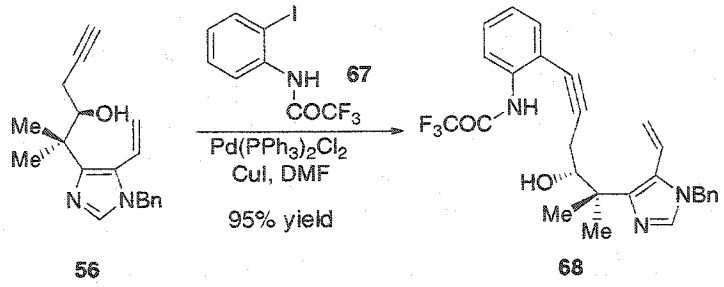
Scheme 1.4.11



56 **57** **66**

Sonogashira coupling of terminal acetylene **56** with a trifluroacetate protected o-iodo aniline (**66**) provided **67** in good yield (Scheme 1.4.12).[24] The stage was now set for an attempt at a cyclization reaction to generate the desired indole portion of securamine A.

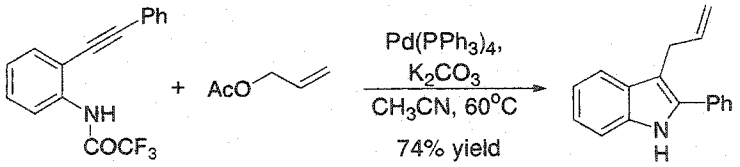
Scheme 1.4.12



56 68

To accomplish this tandem indole cyclization-alkylation, a protocol developed by Cacchi and coworkers was employed.[25] They have shown that treatment of alkynyl anilines (**69**) with the appropriate palladium catalysts and electrophiles (**70**) effects a tandem cyclization-alkylation to generate 2,3-disubstituted indoles (**71**) (Scheme 1.4.13).

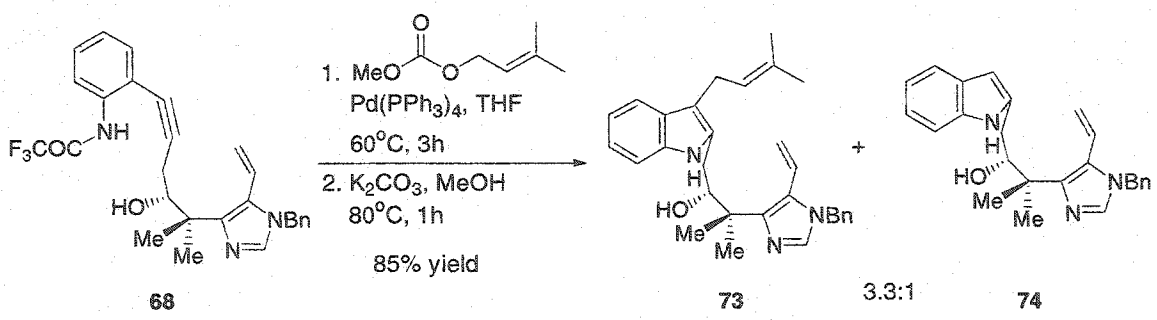
Scheme 1.4.13



69 **70** **71**

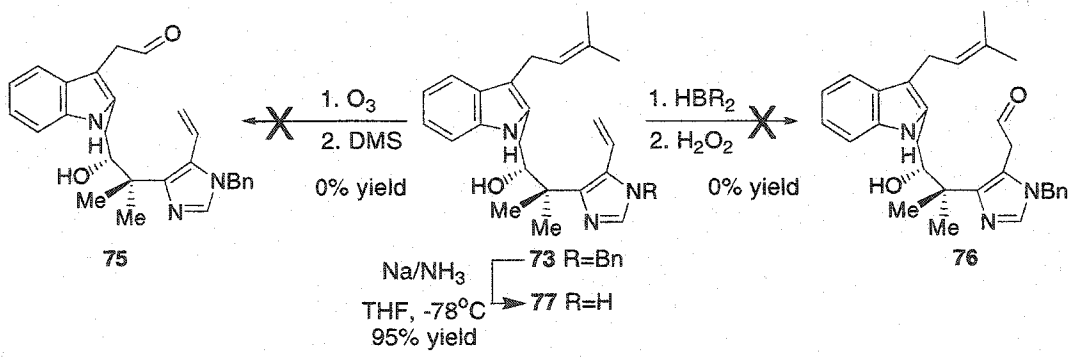
Indeed exposure of aniline **68** to $Pd(PPh_3)_4$ in the presence of allylic carbonate **72** effected a cyclization-alkylation to provide **73** containing the desired 2,3-disubstituted indole core along with a minor amount of unalkylated byproduct (**74**) (Scheme 1.4.14).[26]

Scheme 1.4.14



Unfortunately, all attempts at oxidizing either olefin led to only extensive decomposition (Scheme 1.4.15). In light of this unexpected set back it was thought that more appropriate side chains could be installed with respect to the needed oxidation states at these positions.

Scheme 1.4.15

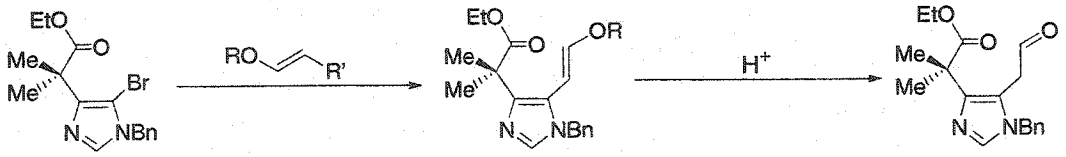


1.5 Second Generation Synthetic Studies From the Wood Labs

1.5.1 An Aldehyde Equivalent

The first problem addressed in this more advanced approach was that of the desired aldehyde side chain at the imidazole 5-position. In the previous approach the vinyl olefin was resistant to ozonolysis oxidation conditions. Unfortunately ozonolysis would only have led to an aldehyde that was one carbon short of that needed to effect a ring closure via condensation. What was decided therefore was to install an enol ether type side chain which upon cleavage of the ether protecting group would unmask the desired aldehyde containing the correct orientation of the aldehyde as well (Scheme 1.5.1).

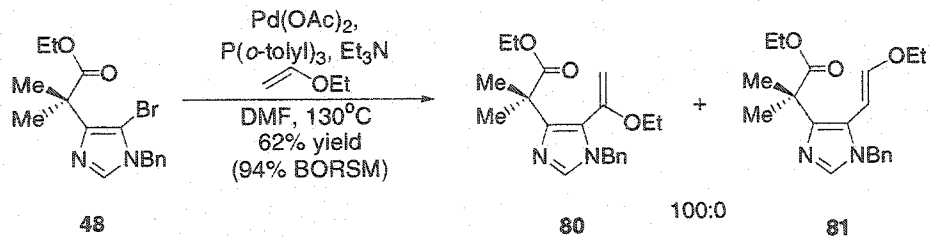
Scheme 1.5.1



48 **78** **79**

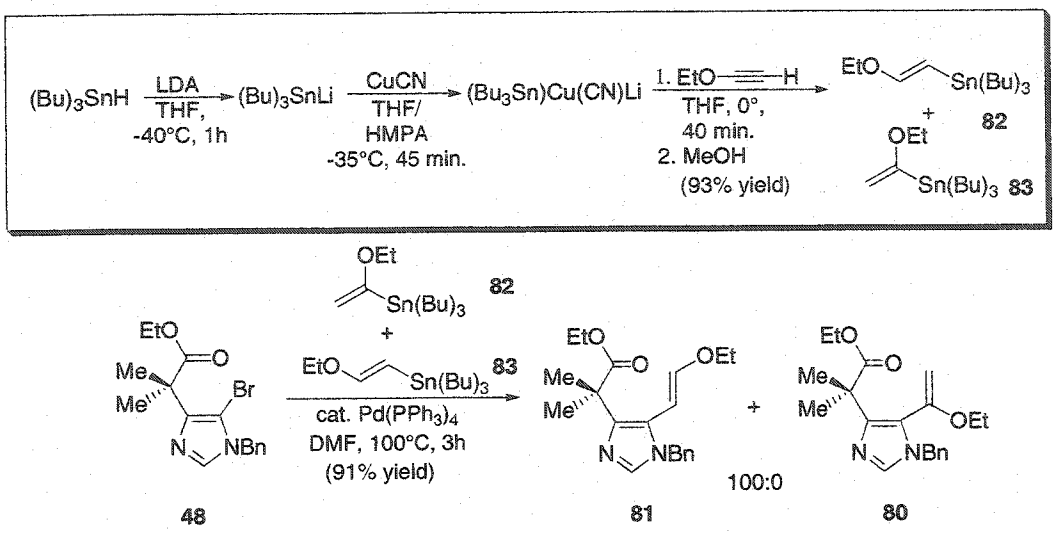
However, installation of this enol ether side chain was not as trivial as originally hoped. Heck coupling of commercially available ethyl vinyl ether with 5-bromo imidazole **48** provided exclusively the anticipated undesired coupling product (**80**).[27-29]

Scheme 1.5.2



At this point attention was turned back to the previously successful Stille coupling conditions. Rather then effect a coupling with the commercially available vinyl tributyltin, it was found that generation of a mixture of α and β-tin enol ethers (**82**&**83**) followed by coupling with **48** provided the desired imidazole scaffold (**81**) (Scheme 1.5.3).[30] This fully elaborated imidazole now contained the desired aldehyde oxidation state at the 5-position side chain. Moreover, it was also found that due to conjugation of the enol ether side chain with the imidazole, **81** was surprisingly stable, and could be handled without concern for hydrolysis.

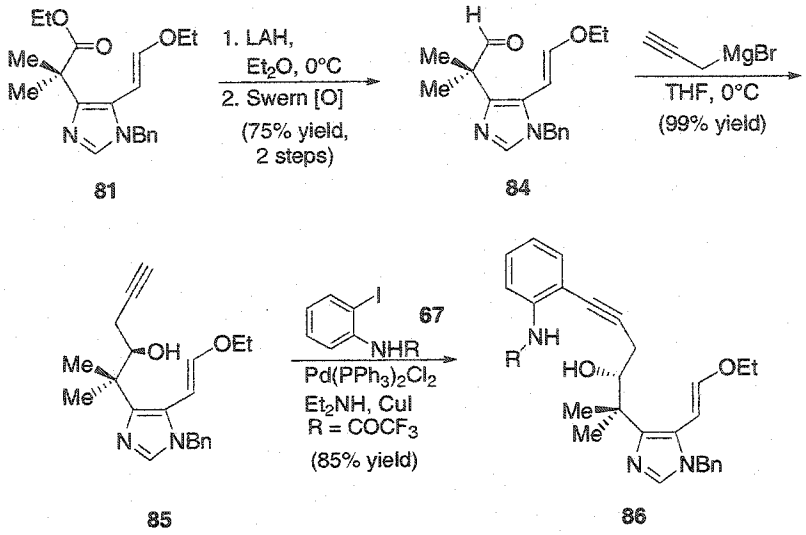
Scheme 1.5.3



1.5.2 Toward a Second Generation Indole Synthesis

Efforts were now shifted once again toward construction of the indole portion of the natural product. Employing the earlier successful results to elaborate the ethyl ester proved fruitful in that reduction of **81** provided the corresponding alcohol (Scheme 1.5.4). Subsequent oxidation using Swern conditions generated the aldehyde (**84**). Addition of propargyl magnesium bromide proceeded smoothly to afford the terminal acetylene (**85**). Sonogashira coupling of this acetylene with iodoaniline derivative **67** sets the stage once again for an attempt at indole cyclization.

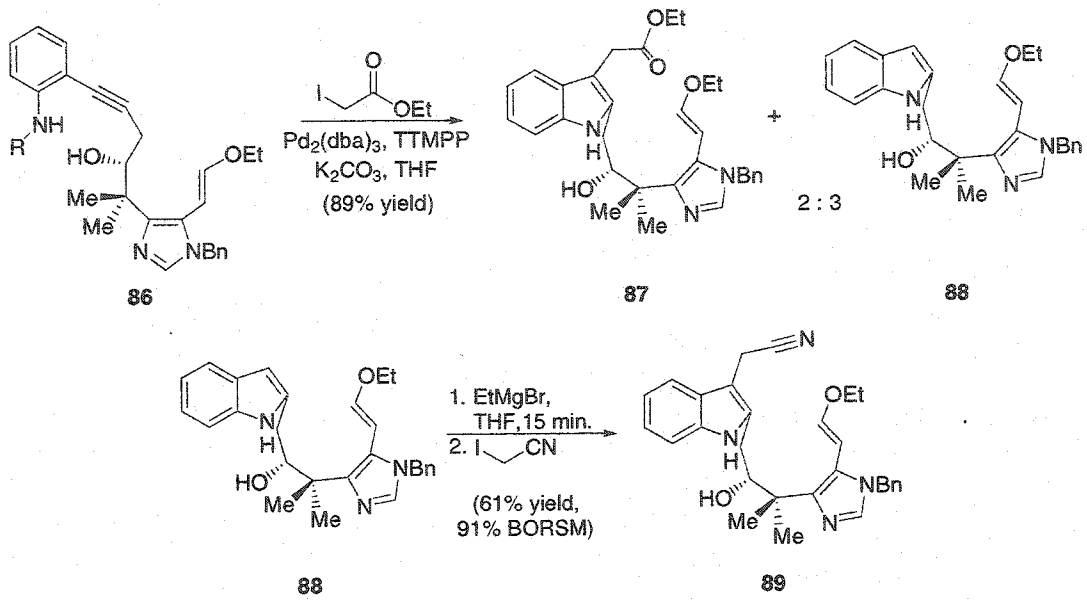
Scheme 1.5.4



1.5.3 Addressing the Indole 3-Position

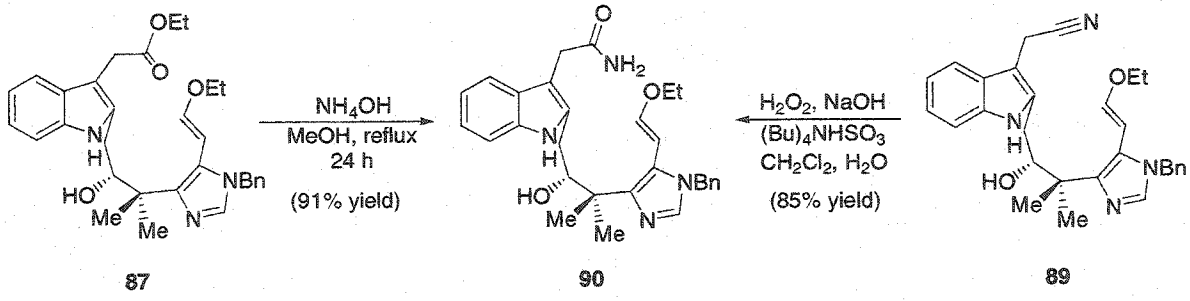
The success of the previous Cacchi indole protocol called for a return to this methodology. However, the issue of the oxidation state of the indole side chain still needed to be addressed. Interestingly, it was found that incorporation of the cacchi indole synthesis with an ethyl iodoacetate electrophile in place of the carbonate electrophile provided a mixture of alkylated and unalkylated indole products (**87**&**88**) (Scheme 1.5.5).[31] Unfortunately, unalkylated indole **88** was present as the major product. However, it was found that the unalkylated system could be salvaged by treatment with ethyl magnesium bromide followed by an iodoacetonitrile electrophile to afford alkylated indole **89**.[32]

Scheme 1.5.5



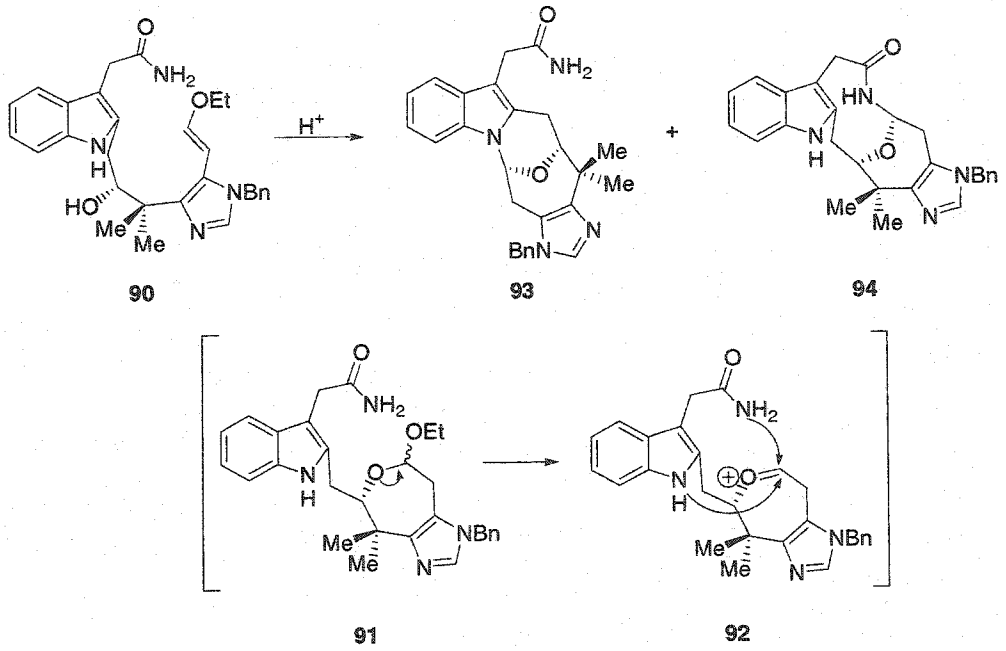
Conversion of either indole side chain to the desired primary amide was fairly straightforward (Scheme 1.5.6). First exposure of ester **87** to refluxing ammonium hydroxide provided the primary amide (**90**) in excellent yield. Along those same lines, treatment of nitrile **89** with basic peroxide under phase transfer conditions provided amide **90** in a comparable yield.

Scheme 1.5.6



With the correct indole side chain now in place, hydrolysis of the enol ether and dehydrative macrolactamization is all that remained. Unfortunately upon exposure of **90** to acidic conditions, reaction with the secondary alcohol is observed rather than with the primary amide to generate a mixture of macrocyclic hemiaminals **93** and **94** (Scheme 1.5.7).

Scheme 1.5.7

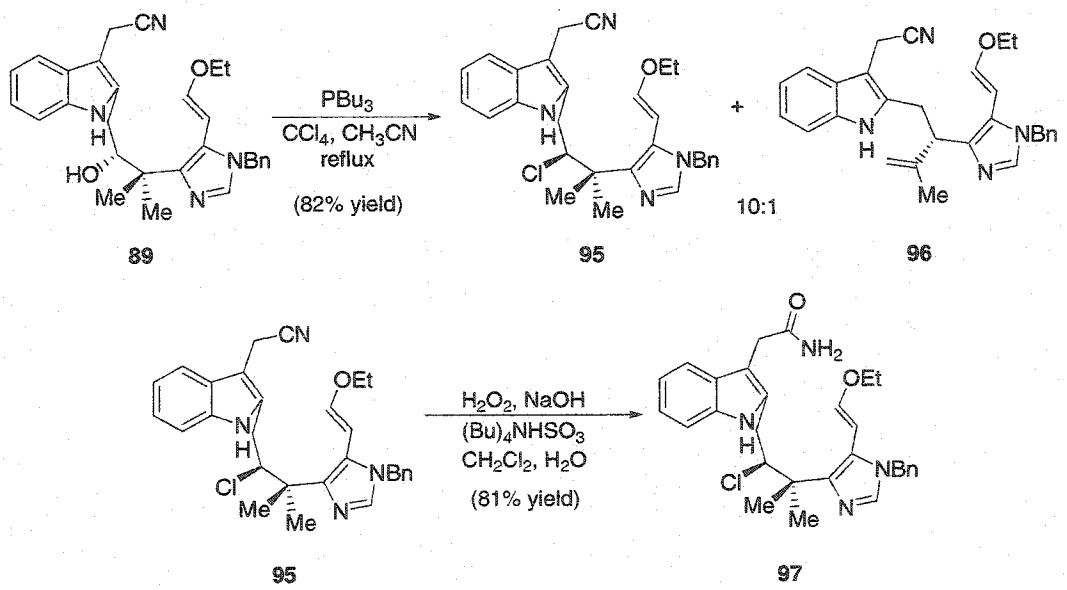


It was obvious from this disappointing result that installation of the neopentyl chlorine could no longer be delayed.

1.5.4 Chlorination

The free amide with two potentially problematic acidic protons would most likely have presented problems with respect to chlorination of the neopentyl alcohol, therefore focus was turned back to it's nitrile precursor (**89**). When the aforementioned chlorination conditions are employed halogenation does indeed take place to provide a mixture of neopentyl chlorine **95** along with a minor portion of the expected rearrangement byproduct (**96**) (Scheme 1.5.8). Exposure of **95** to the basic peroxide protocol once again furnished primary amide **97** which is now only a condensation step away from the Securamine A macrocycle.

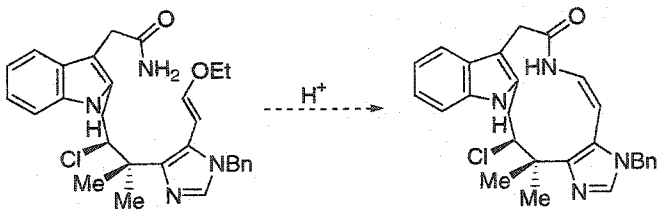
Scheme 1.5.8



1.5.5 Condensation Attempts

Unfortunately all attempts to date at condensing the primary amide onto the aldehyde have failed. While there is some precedent for forming enamides in this manner, the conditions used are generally acid catalyzed. Upon exposure of **97** to acidic conditions the compound simply precipitates out of solution likely due to protonation of the nitrogen heterocycles. Therefore, although this synthetic approach has certainly proved fruitful in providing access to the full carbon skeleton of securamine A, it has been unfortunately deemed a dead end.

Scheme 1.5.9



97 **1**

1.6 Conclusions

With a potentially versatile approach to the carbon skeleton of securamine A in hand, this lab immediately set out to salvage the previously discussed synthesis. Incorporation of a new macrocyclization protocol seemed necessary and will be discussed in the following chapters.

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Chapter Two

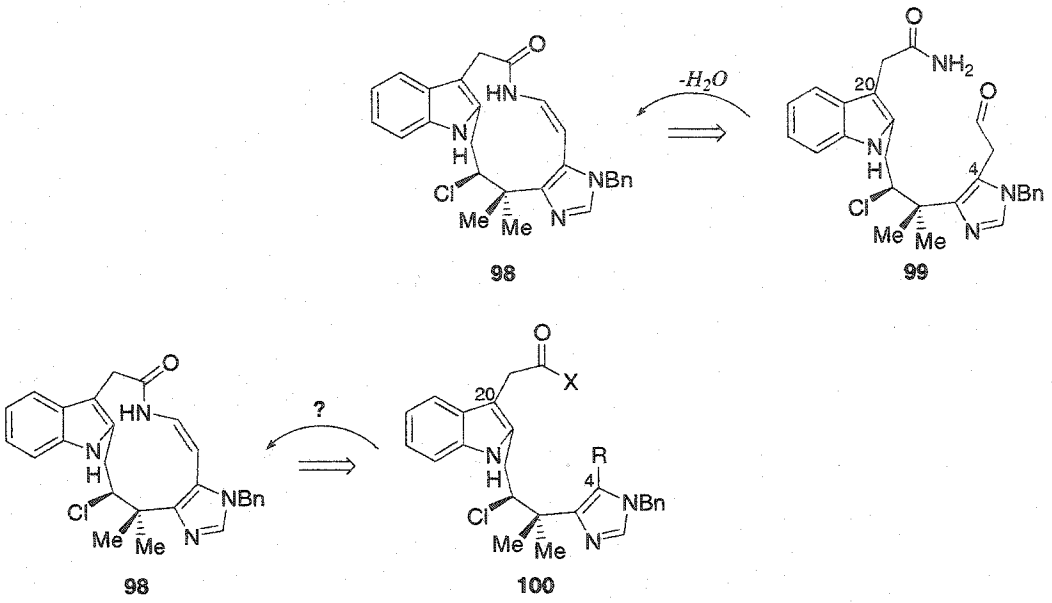
A Modified Approach Toward Securamine A:

Incorporation of a Copper Mediated Cross-Coupling Protocol

2.1 Initial Considerations

It was clear from prior experimentation that advanced intermediates in the progress toward the total synthesis of securamine A could be isolated in an efficient manner. Unfortunately, completion of the natural product failed due to an inability to complete the carbocyclic framework by installing the elusive enamide macrocycle. All attempts made to install the enamide were by simple condensation of an aldehyde side chain on the imidazole ring with a primary amide located at the 3-position of the indole. Despite its intuitive nature, to date only 6-membered ring enamides have been prepared using this strategy. However, by simply varying the C4 and C20 side chains a variety of ways to access the desired macrocycle could be envisioned (Figure 2.1.1).

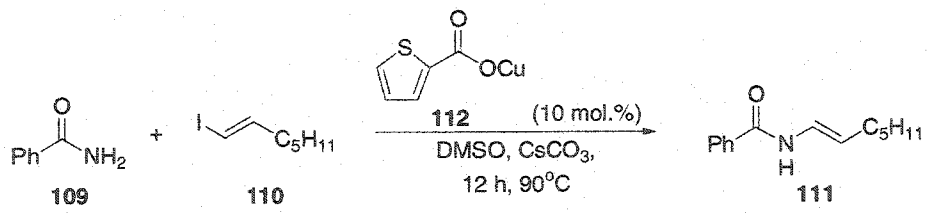
Figure 2.1.1



2.1.1 Porco Enamide Coupling

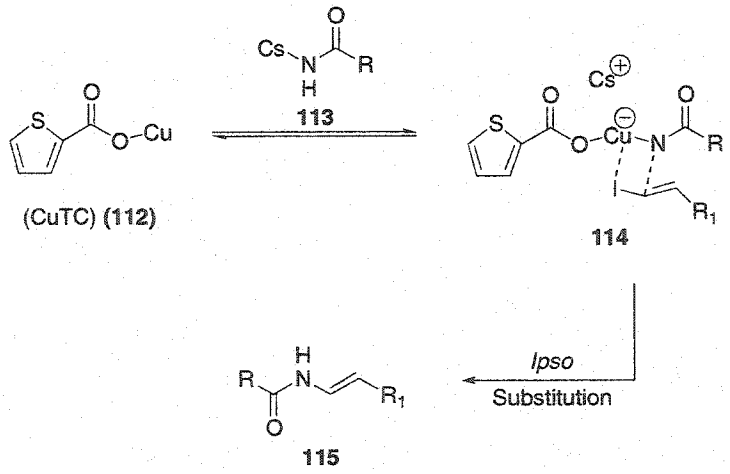
A thorough reinvestigation of suitable methods for the installation of the macrocyclic enamide revealed a novel protocol recently developed by Porco and coworkers (Scheme 2.1.2).[1] Porco demonstrated that simple treatment of vinyl iodide **110** with primary amides **109** in the presence of the appropriate copper(I) catalysts (**112**) and cesium carbonate generated the desired enamide (**111**) in moderate to good yields. This newly developed methodology provides a mild, efficient manner for producing enamides.

Scheme 2.1.1



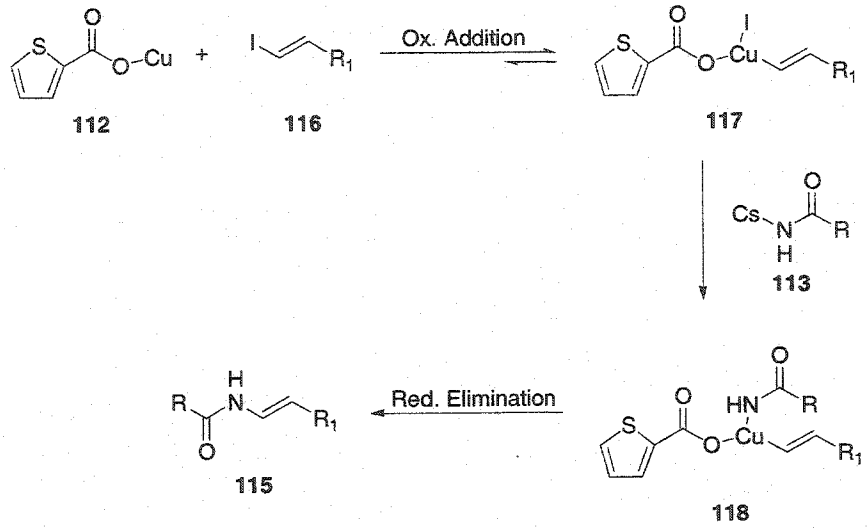
In the absence of a detailed mechanistic investigation of the copper carboxylate-mediated vinylic substitution there are two tentative proposals outlined by Porco. In the first scenario, a cesium carboxamide (**113**) can react with the CuTC to afford a cuprate-like intermediate (**114**) which subsequently forms the enamide (**115**) via a four-centered ipso substitution of the vinyl iodide moiety (Scheme 2.1.3). A related mechanism was recently proposed by Buchwald and coworkers to explain the role of cesium in copper catalyzed substitution reactions of aryl halides with phenols.[2]

Scheme 2.1.2



In the second proposal, oxidation of the vinyl iodide by CuTC occurs as proposed by Liebeskind and coworkers (Scheme 2.1.4).[3,4] Displacement of the copper iodide intermediate (**117**) by the cesium carboxamide (**113**) is followed by reductive elimination to afford the observed enamide product (**115**).

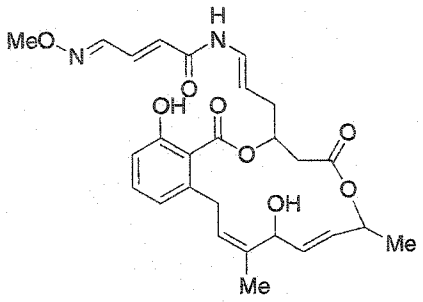
Scheme 2.1.3



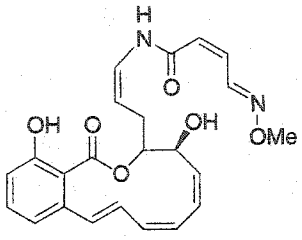
2.1.2 Total Syntheses Using the Porco Enamide Coupling

While there are no examples of utilizing the Porco cross-coupling protocol for an intramolecular ring closure, there is precedent for using the methodology to prepare both *Z* and *E* enamides in natural product total synthesis as Porco has demonstrated in his total syntheses of Lobatamide C and Oximidine II (Figure 2.1.2).[5,6]

Figure 2.1.2



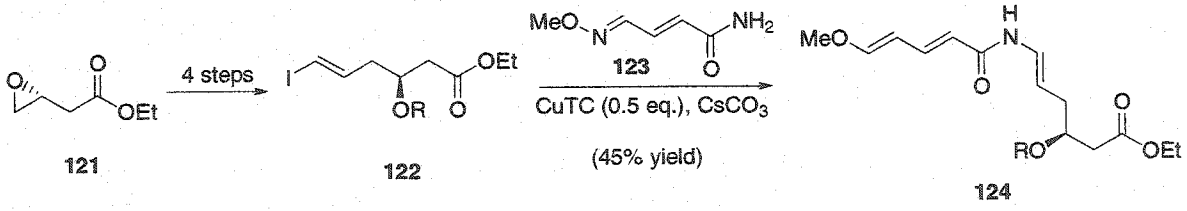
119: Lobatamide C



120: Oximidine II

In the lobatamide synthesis the enamide is installed early in the synthetic approach using the copper coupling chemistry. Commercially available **121** is advanced in four steps to (*Z*)-vinyl iodide **122** (Scheme 2.1.5). This intermediate is exposed to E-O-methyloxime amide **123** in the presence of the copper coupling conditions to provide the (Z)-enamide (**124**) in a moderate 45% yield. Enamide **124** was then used to advance to the desired natural product (**119**).

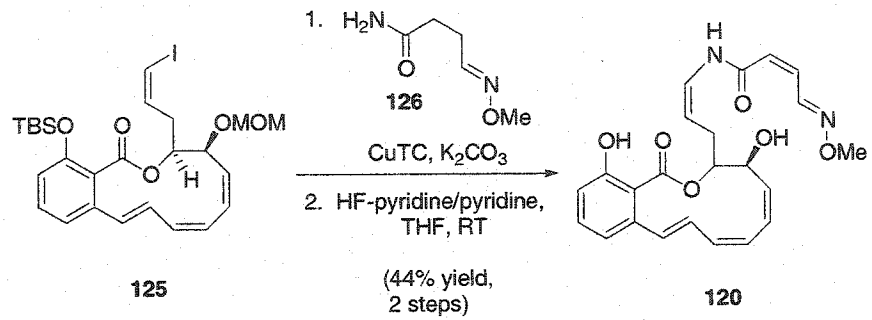
Scheme 2.1.4



In the oximidine synthesis, the copper catalyzed cross coupling is utilized at a later stage in the synthetic route owing to the usefulness of this methodology. Moreover, the side chain produced in this successful synthetic route is an (*E*)-enamide.

The oximidine core (**125**) is produced in a maximum ten step convergent synthetic sequence (Scheme 2.1.6). Vinyl iodide **125** is subsequently treated with amide **126** and the copper(I) carboxylate catalyst (**112**) in the presence of potassium carbonate to effect the cross coupling which is immediately subjected to deprotection conditions to provide Oximidine II (**120**) in 44% yield over two steps.

Scheme 2.1.5



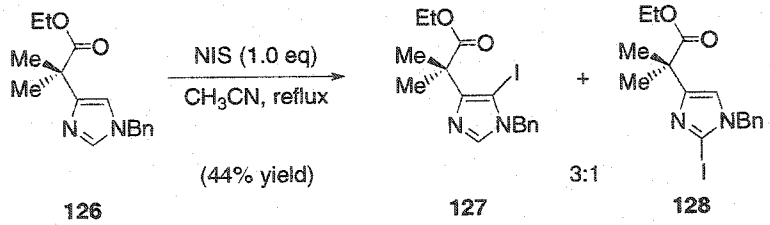
Porco and coworkers have clearly demonstrated the flexibility of this methodology with respect to natural product total synthesis. The cross-coupling protocol has not only been used early on in synthetic routes, but also as a late-stage key step. With this in mind, Porco's enamide coupling seemed perfectly suited for the previously developed securamine synthetic route. Moreover, it was hoped that the scope of this methodology could be further explored by using it as an intramolecular coupling to form the complete macrocyclic core of securamine A.

2.2 Early Model Studies

2.2.1 Early Attempts at Vinyl Iodide Installation

Before setting out to synthesize the fully elaborated cross coupling substrate, developing a model system to test this chemistry with the elaborate imidazole functionality seemed prudent. Therefore construction of the vinyl iodide side chain onto the imidazole 5-position was the first task at hand. The first attempt at installation of this vinyl iodide was via an alkynyl iodide intermediate.[7] As outlined in Scheme 2.2.1 treatment of imidazole **126** with *n*-iodosuccinimide (NIS) in refluxing acetonitrile provided the 5-iodoimidazole (**127**) along with the expected 2-iodoimidazole by-product (**128**) in moderate yield.[8,9] These two compounds were readily separable by silica gel chromatography.

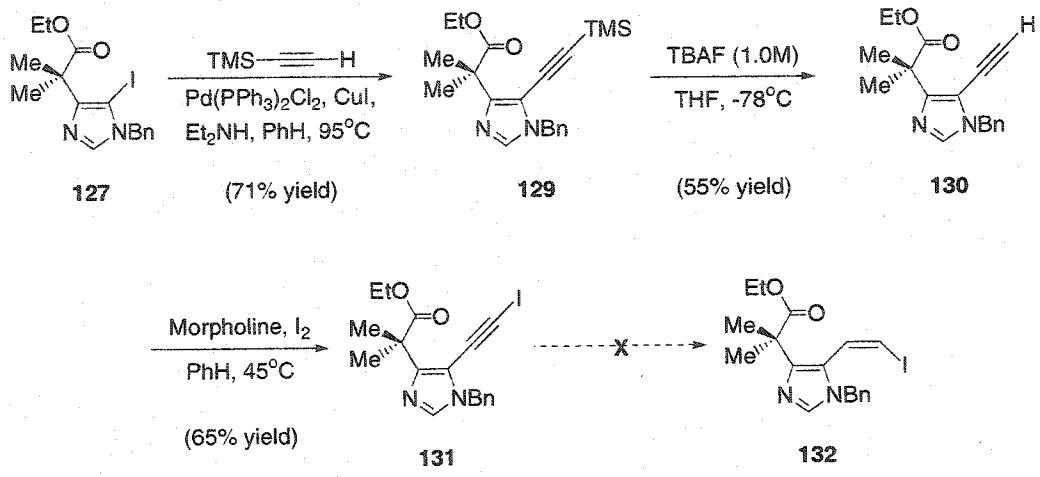
Scheme 2.2.1



Sonogashira coupling of 5-iodoimidazole **127** with TMS-acetylene is then followed by deprotection with TBAF to provide terminal alkyne **130** (Scheme 2.2.2). Iodination is then accomplished by exposure of **130** to morpholine in the presence of iodine to generate iodoalkyne **131**.[10] Unfortunately, all attempts at reduction of the

alkyne triple bond simultaneously reduced the C2 iodide and provided none of the desired iodo olefin (**132**).

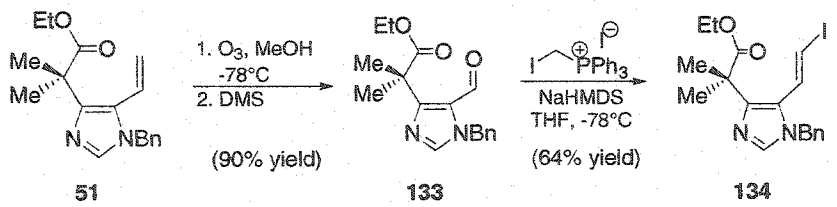
Scheme 2.2.2



2.2.2 A Working Model System

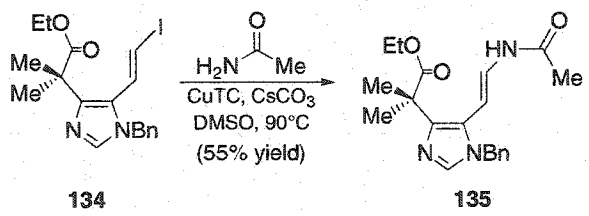
Construction of the working model system commenced by first subjecting vinyl imidazole **51** to ozonolysis conditions in methanol at -78°C to provide the expected aldehyde (**133**) (Scheme 2.2.3). Treatment of **133** with the corresponding ylide and a NaHMDS base provided exclusively the (*Z*)-vinyl iodide **134**.[11,12] While the selectivity of this olefination chemistry was certainly unfortunate, the feasibility of the cross coupling chemistry could still be tested with the (*Z*)-isomer.

Scheme 2.2.3



Treatment of **134** with acetamide in DMSO using the aforementioned Porco cross-coupling conditions provided the expected enamide (**135**) in 55% yield (Scheme 2.2.4).

Scheme 2.2.4



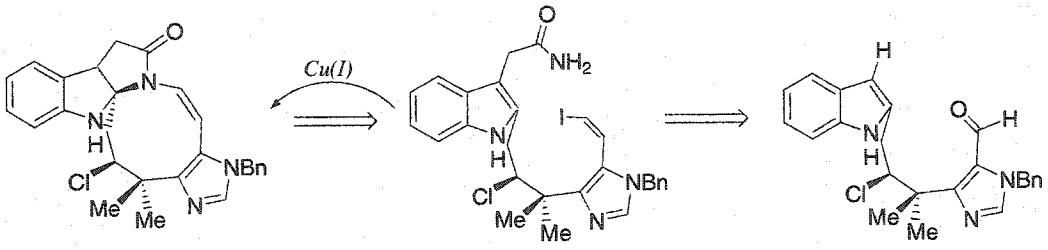
With this encouraging result in hand, focus immediately shifted to generation of the fully elaborated cross-coupling substrate.

2.3 Retrosynthetic Analysis

Porco's copper chemistry can be smoothly incorporated into the previously developed approach toward securamine A (Scheme 2.3.1). Disconnection of the enamide bond provides a primary amide at the indole 3-position along with a (*E*)-vinyl iodide attached to the imidazole 5-position. The desired primary amide should be accessible

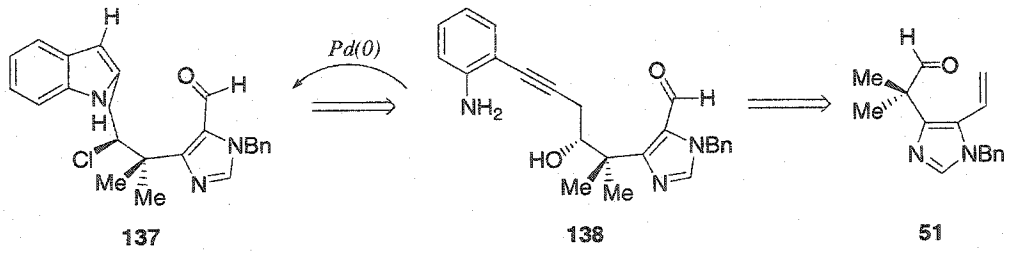
once again from the corresponding nitrile. It is at this point that our retrosynthesis may have to be reworked in order to allow for installation of the (*E*)-vinyl iodide side chain. This side chain can be arrived at via olefination of the corresponding aldehyde.

Scheme 2.3.1



At this point much of the same chemistry should hold true with a protected form of this aldehyde side chain on our imidazole ring, ultimately leading back to **51** (Scheme 2.3.2). Ozonolytic cleavage of vinyl imidazole **51** should result in the desired aldehyde. Fortunately **51** had already been used in a previous synthetic route toward Securamine A.

Scheme 2.3.2

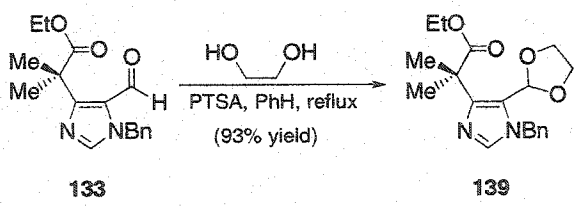


2.4 Construction of the Fully Elaborated System

2.4.1 Protection of the Aldehyde and Turning to The Previously Developed System

Before attempting to construct the indole portion of Securamine A some attention would have to be focused on protecting the aldehyde side chain. Two methods of masking this important functionality were considered. The first strategy considered was to reduce the aldehyde selectively using $NaBH_4$ and protect the resulting primary alcohol. However, due to problems experienced in the past with oxidation chemistry in the presence of the free indole N-H, this was decided against. Instead, the aldehyde side chain would be left in the correct oxidation state and masked as an acetal. This transformation was accomplished smoothly using standard conditions to generate **139**.[13]

Scheme 2.4.1

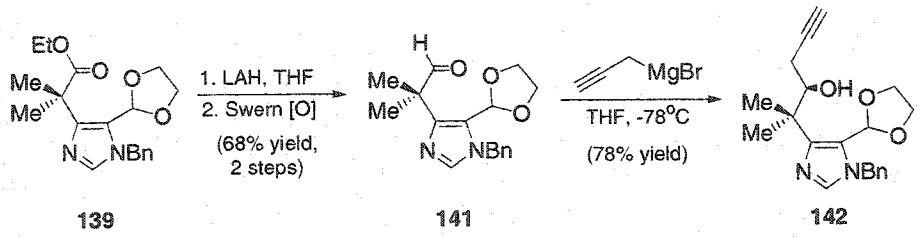


133 **139**

This suitably protected substrate (**139**) could now be subjected to the previously developed synthetic route. First adjustment of the ester oxidation state by treatment with with $LiAlH_4$ followed by Swern oxidation provides aldehyde **141** in very good yield. Addition of propargyl magnesium bromide into this aldehyde proceeded smoothly in 78% yield to provide alcohol **142**. Chlorination was not attempted at this point due to

failure of the subsequent Sonogashira coupling in the presence of the neopentyl chlorine in previous synthetic efforts. Therefore, advancement of alcohol **142** toward indole construction was explored.

Scheme 2.4.2

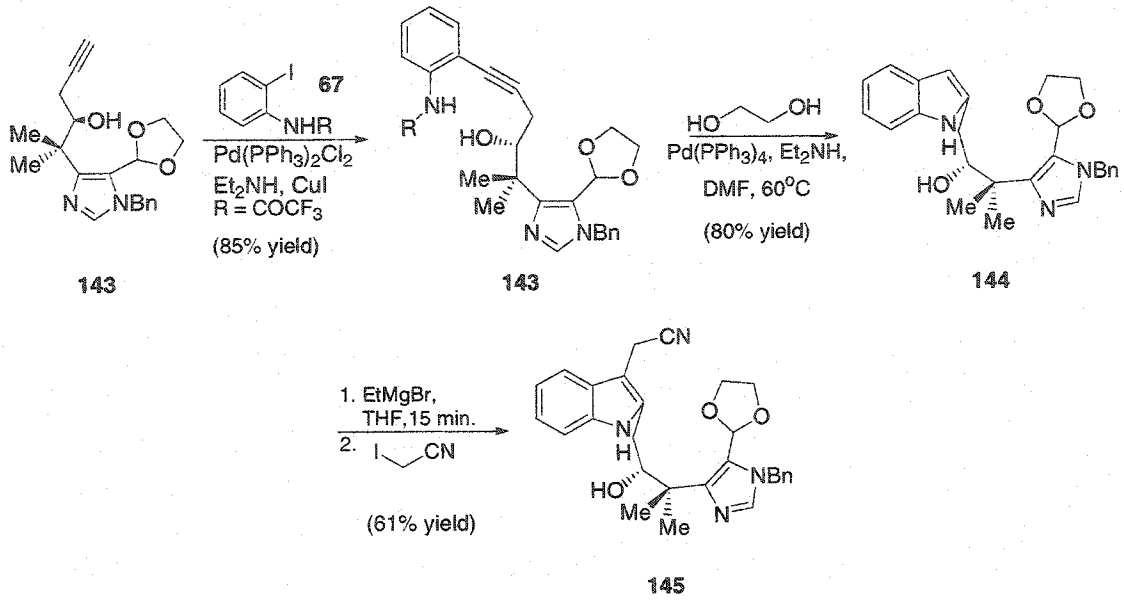


139 **141** **142**

2.4.2 Elaboration of the Indole Ring

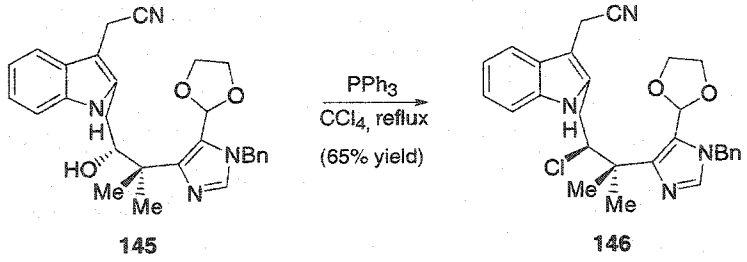
First, Sonogashira coupling with iodoaniline **67** was effected to provide aniline **143.** At this point, construction of the 2,3-disubstituted indole core using the Cacchi protocol was avoided due to the formation of inseparable mixtures of alkylated and unalkylated products. (Scheme 2.4.3). This now sets the stage once again for indole cyclization. Therefore aniline derivative **143** is exposed to Pd(0) catalyst in the presence of an ethylene glycol proton source to furnish exclusively the unalkylated indole ring (**144**) in a very good 80% yield. Alkylation with iodoacetonitrile provided the 2,3-disubstituted indole core (**145**) once again in good yield.[14]

Scheme 2.4.3



At this point, installation of the neopentyl chlorine can no longer be delayed in fear that the resulting aldehyde upon acetal deprotection would simply provide the corresponding six-membered hemi-acetal (Scheme 1.5.7). Therefore treatment of secondary alcohol **145** with triphenylphosphine in refluxing carbon tetrachloride furnished exclusively chloride **146** in 65% yield (Scheme 2.4.4).

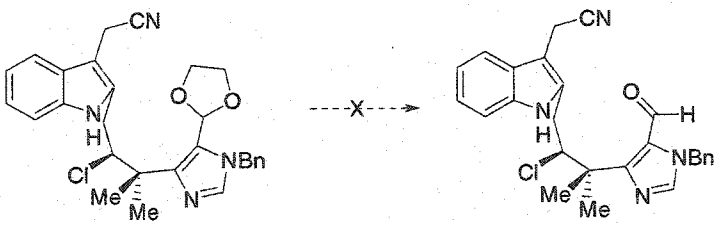
Scheme 2.4.4



2.4.3 Problems Installing the Vinyl Iodide

With the neopentyl chlorine installed attention was focused on elaboration of the imidazole side chain. Unfortunately all attempts at deprotecting the benzylic acetal led to only decomposition presumably due to protonation of the free indole ring (Scheme 2.4.5). Moreover, orthogonal protection of the free indole proton with respect to the acetal side chain also failed. Therefore it seemed prudent to install the neopentyl chlorine after introduction of the appropriate imidazole side chain.

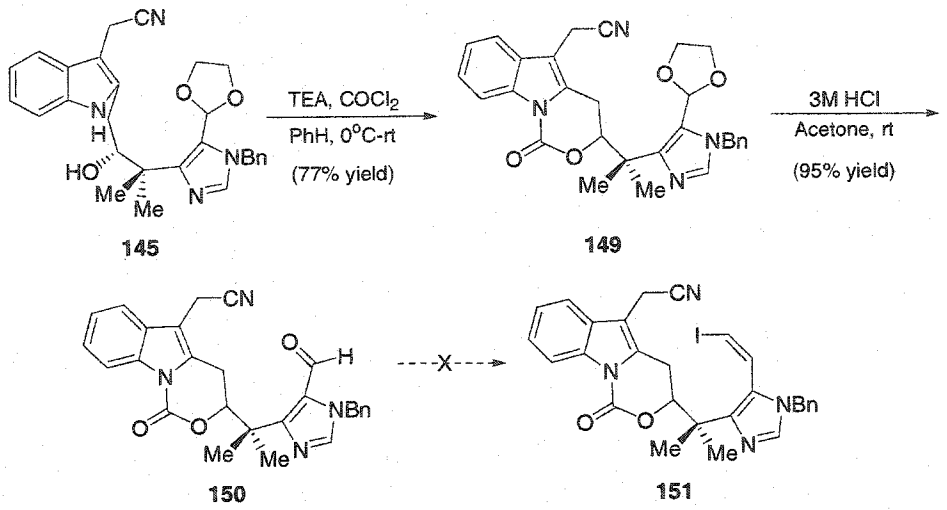
Scheme 2.4.5



Treatment of chloride precursor **145** with phosgene in the presence of triethylamine protected the indole and free alcohol as the acid stable carbamate (**149**) (Scheme 2.4.6).[15] Unmasking the aldehyde side chain proceeded smoothly at this point by simple exposure to 3M HCl in acetone at room temperature to provide aldehyde **150**.[16] Unfortunately, treatment of the aldehyde with our aforementioned olefination conditions led to only extensive decomposition perhaps due to the acidic protons α to the indole 3-position and the labile nature of the carbamate protecting group with respect to basic conditions. It therefore seemed that installation of the vinyl iodide side chain would not

only have to take place before installation of the neopentyl chlorine but would also have to precede alkylation of the indole core.

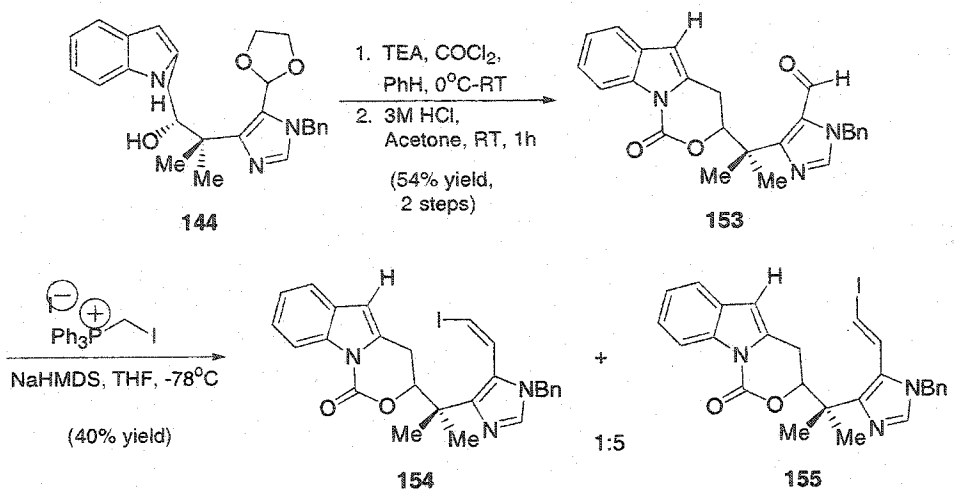
Scheme 2.4.6



2.4.4 Installation of the Vinyl Iodide

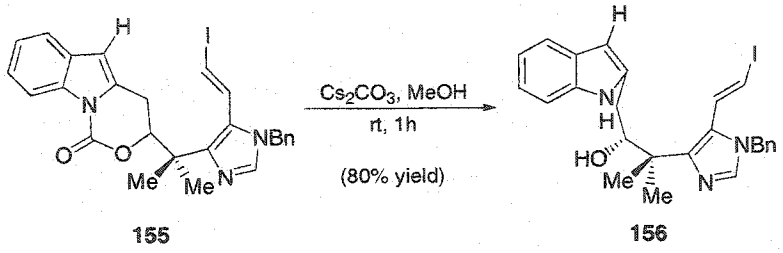
After encountering numerous problems with the installation of the vinyl iodide side chain focus was turned back to the unalkylated system in hopes that olefination of the aldehyde side chain could take place prior to installation of the primary amide portion of the desired cross-coupling substrate. Alcohol **144** was then treated with the same protection conditions as mentioned previously to provide the cyclic carbamate (**153**) (Scheme 2.4.7). Unmasking of the benzylic aldehyde once again proceeded smoothly to provide **153**. Exposure of the aldehyde side chain to the same olefination conditions as in the model system generated a 1:5 mixture of *E*:*Z* vinyl iodides **154** and **155**.

Scheme 2.4.7



Unfortunately, the major product isolated was the (*E*)-vinyl iodide (**155**). These two compounds turned out to be readily separable from each other but not from the various by-products formed in the reaction. Therefore, it was decided that the carbamate protecting group be removed on the crude compounds. Subjection of crude **155** to cesium carbonate in methanol at room temperature removed the cyclic carbamate protecting group unmasking the neopentyl alcohol and the indole N-H to provide **156** (Scheme 2.4.8).[17]

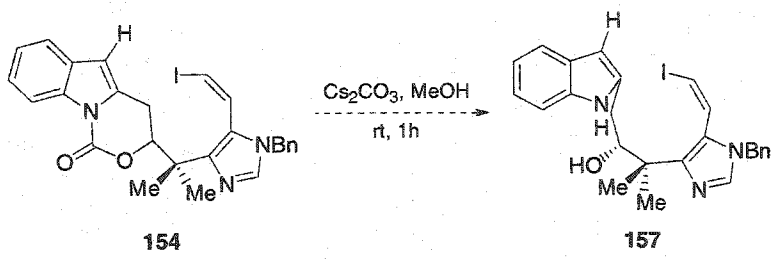
Scheme 2.4.8



2.5 Attempts at Developing a Fully Elaborated Coupling Substrate

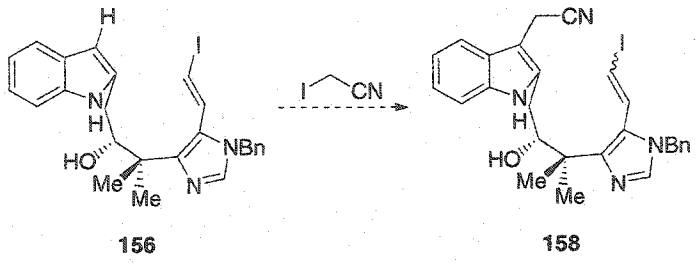
It now appeared as though all that remained for generation of a fully elaborated cross-coupling substrate was alkylation of the indole ring followed by hydration of the nitrile. However, isolation and advancement of the correct (*Z*)-isomer (**154**) still remained. Unfortunately exposure of (*Z*)-vinyl iodide **154** to cesium carbonate failed to provide the desired indole (**157**) (Scheme 2.5.1).

Scheme 2.5.1



Moreover, all attempts at alkylation of the (*E*)-vinyl iodide (**156**) have failed to date, generating mainly decomposition products (Scheme 2.5.2). It is speculated that the failure of this alkylation may be due to incompatibility of the metal bases with the vinyl iodide side chains.

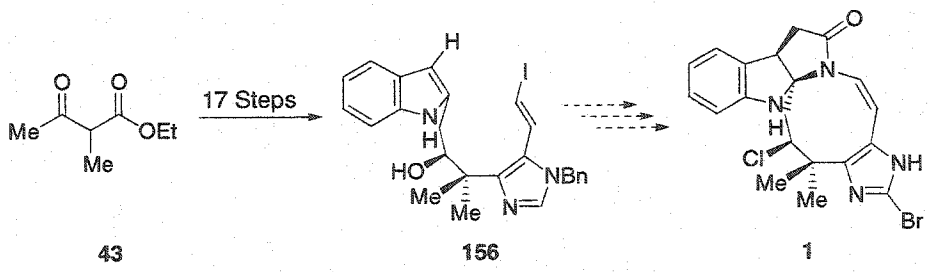
Scheme 2.5.2



2.6 Conclusions

In an efficient 17-step sequence, this lab has been able to advance the commercially available β-keto ester **43** to vinyl iodide **156**. This advanced intermediate in the progress toward the total synthesis of securamine A is only two steps away from a fully elaborated cross-coupling substrate.

Scheme 2.6.1



However, due to the numerous roadblocks faced in this route and the inability to maneuver around potential dead-ends, this synthetic route was ultimately abandoned. It was believed that production of either vinyl iodide side chain would potentially have lead to the (Z)-enamide macrocycle of securamine A due to the potential conversion of the

(*E*)-enamide to the (*Z*) configuration.[18-23] Unfortunately, production of the macrocycle would have to come about using an alternative method.

2.7 Experimental Section.

2.7.1 Materials and Methods.

Unless stated otherwise, reactions were performed in flame dried glassware under a nitrogen atmosphere using freshly distilled solvents. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methylene chloride (CH_2Cl_2), benzene (PhH), toluene (PhMe), triethylamine (Et_3N), pyridine, and piperidine were distilled from calcium hydride. Methyl sulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF) were either purchased from the Aldrich Chemical Company in Sure/Seal™ containers and used as received or stored over molecular sieves. All other commercially obtained reagents were used as received.

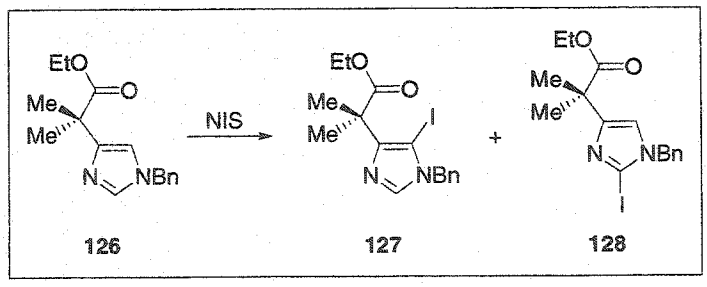
Unless stated otherwise, all reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm). Column or flash chromatography was performed with the indicated solvents using silica gel (230-400 mesh) purchased from Bodman. Concentration *in vacuo* refers to the removal of solvent with a Buchi R-3000 rotary evaporator at normal aspirator pressure followed by further evacuation with a two stage mechanical pump. When reactions were adsorbed onto silica gel, the amount of silica gel used was equal to two times the weight of the reagents.

All melting points were obtained on a Gallenkamp variable temperature capillary melting point apparatus (model: MPD350.BM2.1) and are uncorrected. Infrared spectra were recorded on a Midac M1200 FTIR. ^1H and ^{13}C NMR spectra were recorded on a

Bruker AM-500, Bruker Avance DPX-500, or Bruker Avance DPX-400 spectrometer. Chemical shifts are reported relative to internal chloroform (^{1}H, δ 7.27 ppm; ^{13}C, δ 77.0 ppm), methanol (^{1}H, δ 3.31 ppm; ^{13}C, δ 49.0 ppm), or DMSO (^{1}H, δ 2.50 ppm; ^{13}C, δ 39.50 ppm). High resolution mass spectra were performed at the University of Illinois Mass Spectrometry Center. High performance liquid chromatography (HPLC) was performed on a Waters 510 solvent delivery system using a Rainin Microsorb 80-199-C5 column, or a Rainin Dynamax SD-200 solvent delivery system using a Rainin Microsorb 80-120-C5 column. Single crystal X-ray analyses were performed by Christopher Incarvito of Yale University.

2.7.2 Preparative Procedures.

Preparation of Iodoimidazoles 127, 128:



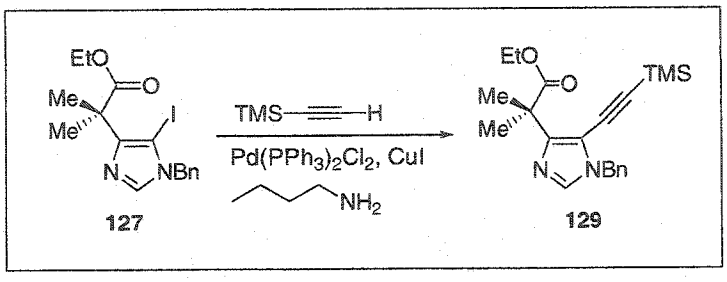
Iodoimidazoles 127, 128. To a stirred solution of **126** (500 mg, 1.84 mmol, 1.0 equiv.) in CH_3CN (20 mL) at 0°C was added NIS (412 mg, 1.84 mmol, 1.0 equiv.) in 1 portion and stirred at reflux for 24 hours. After removal of the solvent *in vacuo*, the mixture was dissolved in $CHCl_3$ (50 mL) and washed with water (3 x 20 mL). The

organic layer was dried with $MgSO_4$, filtered and chromatographed on silica gel (30% EtOAc/Hexanes) to afford **127** (233 mg, 32% yield), and **128** (77 mg, 11% yield) as white solids.

Iodoimidazole 127. FTIR (thin film/NaCl) 3139 (w), 3094 (w), 2974 (m), 1724 (s), 1496 (m), 1457 (m), 1419 (m), 1370 (m), 1258 (s), 1219 (m), 1153 (s), 1027 (m), 979 (m), 801 (w), 735 (m), 715 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.40-7.29 (m, 3H), 7.10 (d, *J*=7.2 Hz, 2H), 5.14 (s, 2H), 4.19 (q, *J*=7.2 Hz, 2H), 1.67 (s, 6H), 1.24 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.3, 148.7, 138.5, 135.9, 129.3, 128.6, 127.5, 68.8, 61.4, 52.0, 44.2, 26.1, 14.6; HRMS (EI) *m/z* 399.0570 [calculated for $C_{16}H_{20}IN_2O_2$ (M^+) 399.0570].

Iodoimidazole 128. FTIR (thin film/NaCl) 3142 (w), 2975 (w), 1724 (s), 1473 (w), 1438 (w), 1376 (w), 1259 (m), 1222 (w), 1153 (m), 1108 (w), 1027 (w), 980 (w), 938 (w), 799 (w), 715 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.32 (m, 3H), 7.16 (d, *J*=6.8 Hz, 2H), 6.89 (s, 1H), 5.07 (s, 2H), 4.14 (q, *J*=7.1 Hz, 2H), 1.55 (s, 6H), 1.22 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.3, 150.3, 136.0, 129.4, 128.6, 127.6, 119.7, 90.4, 61.2, 53.6, 43.7, 25.8, 14.5; HRMS (EI) *m/z* 399.0569 [calculated for $C_{16}H_{20}IN_2O_2$ (M^+) 399.0570].

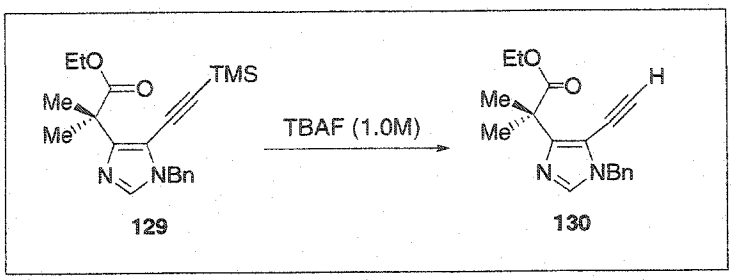
Preparation of TMS-Acetylene 129:



TMS-Acetylene 129. To a solution of **127** (220 mg, 0.55 mmol, 1.0 equiv.) in PhH (4.5 mL) and *n*-butylamine (1.5 mL) was added TMS-acetylene (160 µl, 1.11 mmol, 2.0 equiv.), *trans*-dichlorobis(triphenylphosphine)palladium(II) ($Pd(PPh_3)_2Cl_2$) (16 mg, 0.02 mmol, 0.04 equiv.), and CuI (8.4 mg, 0.04 mmol, 0.08 equiv.). The mixture was heated to 95°C and stirred for 48 hours. The reaction mixture was then cooled and the solvent removed *in vacuo*. The reaction was then chromatographed on silica gel (30% Ethyl Acetate/Hexanes) to afford **129** (1.40 g, 71% yield) as a red oil.

TMS-Acetylene 129. FTIR (thin film/NaCl) 3032 (w), 2978 (m), 2961 (m), 2153 (m), 1732 (s), 1455 (m), 1382 (w), 1362 (w), 1250 (s), 1137 (s), 1029 (m), 861 (s), 845 (s), 760 (m), 730 (m), 701 (m), cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.38-7.30 (m, 3H), 7.22 (d, *J*=7.6 Hz, 2H), 5.12 (s, 2H), 4.16 (q, *J*=7.0 Hz, 2H), 1.66 (s, 6H), 1.21 (t, *J*=7.0 Hz, 3H), 0.21 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 150.8, 136.3, 129.2, 128.5, 128.1, 112.3, 105.9, 93.5, 61.1, 49.8, 44.6, 25.8, 14.5, 00.1; HRMS (EI) *m/z* 369.1996 [calculated for $C_{21}H_{29}N_2O_2Si$ (M^+) 369.1998].

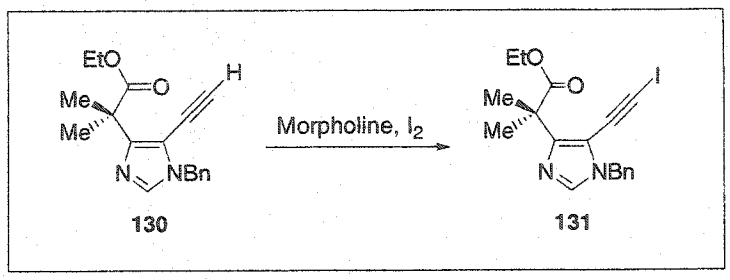
Preparation of Acetylene 130.



Acetylene 130. To a stirred solution of TBAF (1.0 M) (1.21 mL, 1.21 mmol, 3.0 equiv.) in THF (1 mL) at 0°C was added **129** (144 mg, 0.41 mmol, 1.0 equiv.) in THF (4 mL) dropwise. The mixture was stirred for 30 minutes at 0°C and then quenched by addition of H_2O (10 mL). The reaction was then extracted with Et_2O (3 x 5 mL). The organic layers were combined, washed with brine (10 mL) and dried with $MgSO_4$. Silica gel chromatography (30% EtOAc/Hexanes) afforded **130** (65 mg, 55% yield) as a dark red oil.

Acetylene 130. FTIR (thin film/NaCl) 3279 (m), 3032 (w), 2980 (m), 2935 (m), 2872 (w), 2105 (w), 1728 (s), 1489 (m), 1456 (m), 1383 (m), 1362 (m), 1257 (m), 1243 (m), 1136 (s), 1028 (m), 859 (w), 730 (m), 697 (m), 655 (m), cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.39-7.31 (m, 3H), 7.20 (d, *J*=7.2 Hz, 2H), 5.16 (s, 2H), 4.18 (q, *J*=7.1 Hz, 2H), 3.61 (s, 1H), 1.67 (s, 6H), 1.23 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 151.2, 136.3, 129.3, 128.6, 127.8, 111.2, 86.1, 72.9, 61.2, 49.6, 44.6, 25.8, 14.5; HRMS (EI) *m/z* 297.1602 [calculated for $C_{18}H_{21}N_2O_2$ (M^+) 297.1603].

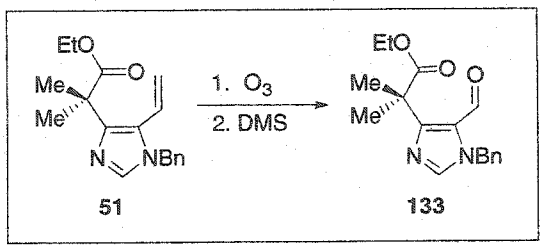
Preparation of Iodoacetylene 131:



Iodoacetylene 131. To a stirred solution of **130** (45 mg, 0.15 mmol, 1.0 equiv.) in PhH (2 mL) at room temperature was added morpholine (133 μL, 1.52 mmol, 10.0 equiv.) and I_2 (193 mg, 0.76 mmol, 5.0 equiv.). The solution was heated to 45°C and stirred for 1 hour. The reaction mixture was then cooled and the solvent removed *in vacuo*. The reaction was then chromatographed on silica gel (40% Ethyl Acetate/Hexanes) to afford **131** (1.40 g, 71% yield) as a red oil.

Iodoacetylene 131. FTIR (thin film/NaCl) 3420 (m), 3286 (m). 3112 (m), 2982 (s), 2934 (m), 2901 (m), 2869 (m), 2253 (w), 2159 (w), 2102 (w), 1723 (s), 1497 (s), 1472 (s), 1457 (s), 1440 (m), 1389 (m), 1362 (m), 1339 (m), 1241 (s), 1192 (m), 1170 (m), 1129 (s), 1009 (s), 909 (m), 847 (m), 821 (m), 725 (s), 701 (m), 667 (m), 648 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (m, 4H), 7.18 (d, *J*=6.5 Hz, 2H), 5.08 (s, 2H), 4.15 (q, *J*=7.2 Hz, 2H), 1.62 (s, 6H), 1.21 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 151.5, 136.1, 136.0, 129.3, 128.6, 128.0, 112.7, 83.0, 61.3, 49.8, 44.6, 26.0, 18.1, 14.6; HRMS (EI) *m/z* 423.0569 [calculated for $C_{18}H_{20}N_2O_2I$ (M^+) 423.0570].

Preparation of Aldehyde 133:

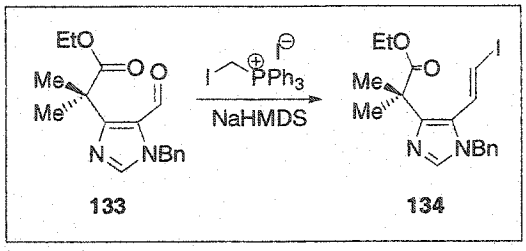


51 133

Aldehyde 133. A solution of vinyl imidazole **51** (11.4 g, 38.21 mmol) was stirred at -78°C in MeOH (390 mL). Ozone was passed over the reaction until consumption of the starting material as indicated by TLC, at which time dimethyl sulfide (14 mL) was added. The reaction was allowed to warm to room temperature and stirred for 12 hours. After removal of the solvent *in vacuo*, the mixture was chromatographed on silica gel (30% EtOAc/Hexanes) to afford **133** (10.5 g, 91% yield) as a colorless oil.

Aldehyde 133. FTIR (thin film/NaCl) 3108 (w), 3065 (w), 3032 (w), 2982 (m), 2936 (m), 2871 (w), 2769 (w), 1729 (s), 1665 (s), 1517 (m), 1499 (m), 1455 (m), 1384 (w), 1353 (m), 1323 (m), 1256 (s), 1139 (s), 1027 (m), 769 (w), 724 (m), 701 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.87 (d, *J*=0.9 Hz, 1H), 7.56 (s, 1H), 7.39-7.29 (m, 3H), 7.18 (d, *J*=6.7 Hz, 2H), 5.51 (s, 2H), 4.17 (q, *J*=7.1 Hz, 2H), 1.70 (s, 6H), 1.20 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 176.4, 158.7, 141.2, 136.0, 129.3, 128.7, 127.8, 126.1, 61.7, 51.3, 45.0, 27.5, 14.4; HRMS (EI) *m/z* 301.1553 [calculated for $C_{17}H_{21}N_2O_3$ (M^+) 301.1552].

Preparation of Vinyliodide 134:

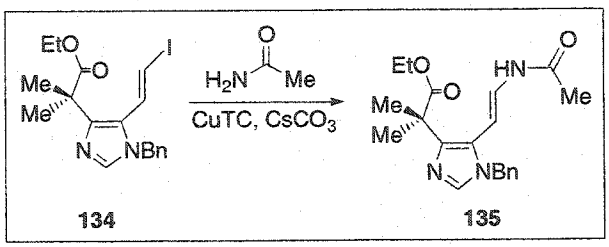


Vinyl Iodide 134. To a stirred solution of Iodomethyltriphenylphosphonium iodide (683 mg, 1.77 mmol, 5.1 equiv.) in THF (4 mL) at room temperature was added NaHMDS (2.0M) (870 µL, 1.75 mmol, 5.0 equiv.) dropwise. The solution was stirred for 15 minutes and then cooled to -78°C at which time was added aldehyde **133** (100 mg, .350 mmol, 1.0 equiv.) in THF (1 mL). The reaction was stirred for another 20 minutes at -78°C and then quenched by addition of H_2O (5 mL). The reaction was extracted with Et_2O (3 x 25 mL). The organic layers were combined, washed with brine (25 mL) and dried with $MgSO_4$. After removal of the solvent *in vacuo*, the mixture was chromatographed on silica gel (40% EtOAc/Hexanes) to afford **134** (95 mg, 64% yield) as a viscous, colorless oil.

Vinyl Iodide 134. FTIR (thin film/NaCl) 2979 (m), 2935 (m), 2870 (w), 1724 (s), 1506 (w), 1497 (m), 1455 (m), 1383 (w), 1362 (w), 1301 (w), 1256 (m), 1209 (w), 1174 (m), 1135 (m), 1078 (w), 1027 (m), 942 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.42-7.31 (m, 3H), 7.15 (d, *J*=15.3 Hz, 1H), 7.07 (d, *J*=7.8 Hz, 1H), 6.33 (d, *J*=15.3 Hz, 1H), 5.11 (s, 2H), 4.16 (q, *J*=7.2 Hz, 2H), 1.62 (s, 6H), 1.23 (t, *J*=7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 136.9, 136.0, 132.4, 129.6, 128.7, 127.0, 125.9,

81.6, 61.5, 49.8, 44.2, 26.8, 19.7, 14.6; HRMS (EI) *m/z* 425.0727 [calculated for $C_{18}H_{22}N_2O_2I$ (M^+) 425.0726].

Preparation of Enamide 135:

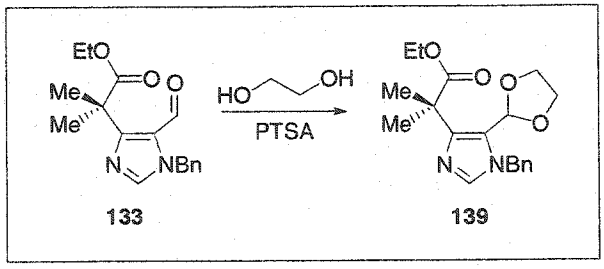


Enamide 139. To a stirred solution of **134** (50 mg, 0.12 mmol, 1.0 equiv.) in DMSO (2 mL) at room temperature was added acetamide (11 mg, 1.8 mmol, 1.5 equiv.), cesium carbonate (58 mg, 1.8 mmol, 1.5 equiv.) and copper thiophene carboxylate (**112**) (10 mg, 0.05 mmol, 0.30 equiv.). The reaction mixture was heated to 90°C and allowed to stir for 4 hours. After dilution with Et_2O the reaction was washed with H_2O, brine and dried with $MgSO_4$. The solvent was then removed *in vacuo* and chromatographed on silica gel (60% EtOAc/Hexanes) to afford **135** (23 mg, 55% yield) as a colorless oil.

Enamide 139. FTIR (thin film/NaCl) 3268 (m), 2979 (m), 2929 (m), 1725 (s), 1698 (m), 1684 (m), 1653 (s), 1559 (m), 1497 (m), 1455 (m), 1371 (m), 1281 (m), 1258 (m), 1174 (m), 1135 (m), 1028 (m), 965 (m), 859 (w), 809 (w), 772 (w), 729 (m), 697 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.38-7.29 (m, 3H), 7.04 (d, *J*=6.8 Hz, 2H), 6.90 (dd, *J*=10.7 Hz, 14.9 Hz, 1H), 5.72 (d, *J*=14.9 Hz, 1H), 5.11 (s, 2H), 4.11 (q, *J*=7.3 Hz, 2H), 2.04 (s, 3H), 1.60 (s, 3H), 1.19 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 167.6, 143.4, 136.6, 136.5, 129.3, 128.4, 127.2, 127.0, 123.2, 99.0, 61.3,

49.5, 43.9, 26.5, 23.6, 14.5; HRMS (EI) *m/z* 356.1979 [calculated for $C_{20}H_{26}N_3O_3$ (M^+) 356.1974].

Preparation of Acetal 139:

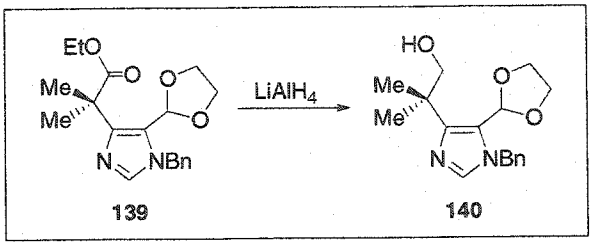


Acetal 139. To a stirred solution of **133** (10.5 g, 34.96 mmol, 1.0 equiv.) in PhH (350 mL) at room temperature was added ethylene glycol (19.5 mL, 350 mmol, 10.0 equiv.) and *p*-toluenesulfonic acid (1.6 g, 8.6 mmol, 0.25 equiv.). The solution was equipped with a Dean-Stark apparatus and stirred at reflux for 24 hours. After removal of the solvent *in vacuo,* the mixture was dissolved in Et_2O (200 mL) and washed with $NaHCO_3$ (sat., aq.) (100 mL). The organic layer was dried with $MgSO_4$ and filtered. Upon removal of the solvent *in vacuo*, the resulting oil was chromatographed on silica gel (30% EtOAc/Hexanes) to afford **139** (11.2 g, 93% yield) as a white solid.

Acetal 139. FTIR (thin film/NaCl) 3130 (w), 2977 (s), 2932 (m), 2899 (m), 2870 (m), 1722 (s), 1572 (w), 1508 (w), 1468 (m), 1441 (m), 1391 (s), 1359 (w), 1257 (s), 1179 (m), 1139 (s), 1074 (s), 1017 (s), 950 (s), 844 (w), 820 (w), 797 (w), 770 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.29 (m, 3H), 7.29 (s, 1H), 7.17 (d, *J*=6.8 Hz, 2H), 5.22 (s, 2H), 4.16 (q, *J*=7.1 Hz, 2H), 4.04-3.87 (m, 4H), 1.63 (s, 6H), 1.23 (t, *J*=7.1 Hz,

3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5, 146.5, 137.6, 136.9, 129.1, 128.2, 127.7, 121.1, 97.8, 65.1, 61.2, 50.2, 43.8, 27.3, 14.3; HRMS (EI) *m/z* 345.1815 [calculated for $C_{19}H_{25}N_2O_4$ (M^+) 345.1814].

Preparation of Alcohol 140:



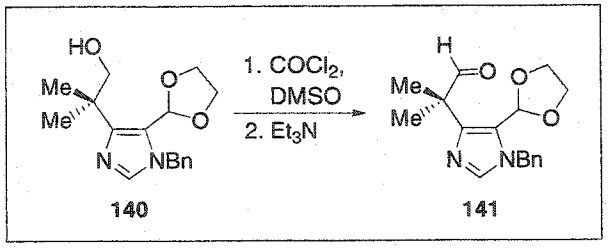
139 140

Alcohol 140. To a stirred solution of $LiAlH_4$ (2.95 g, 77.50 mmol, 3.0 equiv.) in Et_2O (100 mL) at 0°C was added dropwise **139** (8.90 g, 25.84 mmol, 1.0 equiv.) in THF (260 mL). The solution was allowed to warm to room temperature and stirred for 1 hour. H_2O (3.0 mL), NaOH (aq., 1N) (6.0 mL), and KF (sat., aq.) (9.0 mL) were added dropwise sequentially. The solution was decanted off and the solid precipitate washed with EtOAc (5 x 20 mL). The organic layers were combined, dried with $MgSO_4$ and reduced to a residue *in vacuo*. The mixture was chromatographed on silica gel (80% EtOAc/Hexanes) to afford **140** (7.5 g, 96% yield) as a colorless oil.

Alcohol 140. FTIR (thin film/NaCl) 3383 (s), 2963 (s), 2891 (s), 2241 (w), 1958 (w), 1812 (w), 1649 (w), 1606 (w), 1564 (m), 1503 (s), 1455 (s), 1391 (s), 1248 (s), 1155 (m), 1068 (s), 1017 (s), 951 (s), 815 (m), 781 (m), 733 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.30 (m, 3H), 7.21 (s, 1H), 7.20 (d, *J*=6.9 Hz, 2H), 6.19 (s, 1H), 5.22 (s,

2H), 4.65 (bs, 1H), 4.08-3.93 (m, 4H), 3.70 (s, 2H), 1.35 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5, 137.8, 136.9, 129.1, 128.3, 127.6, 120.9, 98.1, 73.3, 65.1, 50.4, 37.9, 26.8; HRMS (EI) *m/z* 303.1710 [calculated for $C_{17}H_{23}N_2O_3$ (M^+) 303.1709].

Preparation of Aldehyde 141:



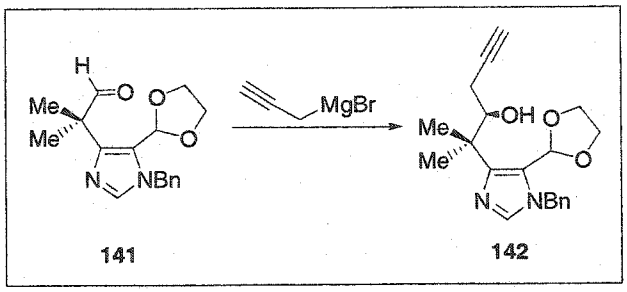
140 **141**

Aldehyde 141. To a solution of oxalyl chloride (2.4 mL, 27.30 mmol, 1.1 equiv.) in CH_2Cl_2 (150 mL) at -78°C was added DMSO (3.9 mL, 54.60 mmol, 2.2 equiv.) dropwise. The solution was stirred for 10 minutes followed by the addition of **140** (7.5 g, 24.80 mmol, 1.0 equiv.) in CH_2Cl_2 (100 mL) dropwise. Stirring of the solution for another 10 minutes, was followed by the addition of Et_3N (17.30 mL, 124 mmol, 5.0 equiv.). After being allowed to warm to room temperature, H_2O (150 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 200 mL) and the organic layers combined and dried with $MgSO_4$. Removal of the solvent *in vacuo* provided an oil that was chromatographed on silica gel (50% EtOAc/Hexanes) to afford **141** (5.30 g, 70% yield) as a colorless oil.

Aldehyde 141. FTIR (thin film/NaCl) 3423 (m), 2975 (s), 2893 (s), 2813 (m), 2714 (m), 2252 (w), 2214 (w), 1963 (w), 1811 (w), 1722 (s), 1606 (m), 1563 (s), 1500

(s), 1455 (s), 1394 (s), 1309 (m), 1256 (s), 1213 (s), 1159 (s), 1077 (s), 1023 (s), 954 (s), 842 (m), 813 (m), 778 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.37 (s, 1H), 7.39-7.29 (m, 3H), 7.17 (d, *J*=6.5 Hz, 2H), 5.73 (s, 1H), 5.21 (s, 2H), 4.03-3.86 (m, 4H), 1.49 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.3, 143.4, 138.6, 129.1, 128.3, 127.6, 122.6, 97.4, 65.0, 50.2, 48.2, 23.1; HRMS (EI) *m/z* 301.1553 [calculated for $C_{17}H_{21}N_2O_3$ (M^+) 301.1552].

Preparation of Acetylene 142:



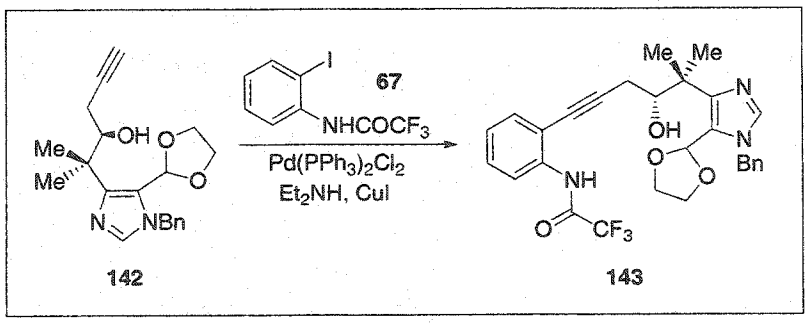
141 142

Acetylene 142. To a stirred suspension of dry Mg turnings (2.19 g, 89.90 mmol, 7.5 equiv.) in THF (100 mL) at room temperature was added propargyl bromide (80 wt. % solution in toluene) (9.35 mL, 83.90 mmol, 7.0 equiv.) and $HgCl_2$ (163 mg, 0.60 mmol, 0.05 equiv.). The suspension was fitted with a reflux condenser and heated with a heat gun to the point of a self-sustaining reflux. After consumption of most of the Mg turnings, the solution was cannulated into a stirred solution of **141** (3.6 g, 11.99 mmol, 1.0 equiv.) in THF (100 mL). The reaction was stirred at room temperature for 30 minutes and then quenched by addition of H_2O (200 mL). The mixture was extracted with EtOAc (3 x 150 mL), washed with brine (100 mL), and dried with $MgSO_4$. The

solvent was removed *in vacuo* and the resulting oil chromatographed on silica gel (35% Acetone/Hexanes) to afford **142** (3.18 g, 78% yield) as a colorless oil.

Acetylene 141. FTIR (thin film/NaCl) 3290 (m), 2971 (m), 2890 (m), 2244 (w), 2117 (w), 1560 (m), 1506 (m), 1455 (m), 1391 (m), 1250 (m), 1158 (w), 1068 (s), 1015 (m), 952 (m), 845 (w), 816 (w), 734 (s), 649 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.29 (m, 3H), 7.25 (s, 1H), 7.18 (d, *J*=6.6 Hz, 2H), 619 (s, 1H), 5.22 (s, 2H), 4.04-3.92 (m 4H), 3.82 (dd, *J*=3.3 Hz, 9.4 Hz, 1H), 2.45 (dt, *J*=3.1, 16.7 Hz, 1H), 2.22 (ddd, *J*=2.6 Hz, 9.4 Hz, 16.9 Hz, 1H), 2.00 (t, *J*=2.7 Hz, 1H), 1.44 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 137.9, 136.7, 129.2, 128.4, 127.9, 121.8, 98.1, 83.4, 79.0, 69.7, 65.2, 65.1, 50.7, 40.9, 27.8, 25.3, 23.3; HRMS (EI) *m/z* 341.1861 [calculated for $C_{20}H_{25}N_2O_3$ (M^+) 341.1865].

Preparation of Acetanilide 143:

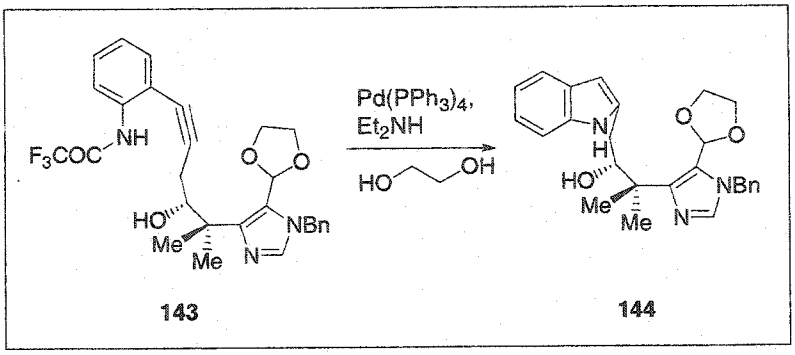


Acetanilide 143. To a solution of **142** (1.0 g, 2.94 mmol, 1.0 equiv.) in PhH (15 mL) and TEA (15 mL) was added 2-iodotrifluoroacetanilide (**67**) (1.39 g, 4.41 mmol, 1.5 equiv.), *trans*-dichlorobis(triphenylphosphine)palladium(II) ($Pd(PPh_3)_2Cl_2$) (83 mg, 0.12 mmol, 0.04 equiv.), and CuI (46 mg, 0.24 mmol, 0.08 equiv.). The mixture was stirred at

room temperature for 8 hours at which time the solvent was removed *in vacuo*. The reaction was then chromatographed on silica gel (30% Acetone/Hexanes) to afford **143** (1.31 g, 85% yield) as a viscous colorless oil.

Acetanilide 143. FTIR (thin film/NaCl) 3355 (m), 2970 (m), 2891 (m), 2227 (w), 1732 (s), 1583 (m), 1543 (m), 1507 (m), 1454 (m), 1391 (m), 1287 (m), 1195 (s), 1155 (s), 1070 (s), 1014 (m), 951 (m), 903 (w), 762 (m), 734 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.11 (bs, 1H), 8.35 (d, *J*=8.5 Hz, 1H), 7.43 (dd, *J*=1.5 Hz, 7.6 Hz, 1H), 7.40-7.30 (m, 4H), 7.23 (s, 1H), 7.19-7.11 (m, 3H), 6.20 (s, 1H), 5.66 (bs, 1H), 5.21 (d, *J*=15.3 Hz, 1H), 5.19 (d, *J*=15.3 Hz, 1H), 4.08-3.94 (m, 4H), 3.88 (dd, *J*=3.2 Hz, 9.2 Hz, 1H), 2.77 (dd, *J*=9.2 Hz, 16.9 Hz, 1H), 1.49 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3 (q, *J*=37.7 Hz), 148.8, 137.9, 137.2, 136.6, 131.7, 129.2, 128.5, 128.0, 125.5, 121.8, 120.0, 117.5, 114.8, 98.5, 98.0, 79.3, 76.2, 65.2, 65.1, 50.7, 40.8, 28.5, 25.2, 24.3; HRMS (EI) *m/z* 528.2110 [calculated for $C_{28}H_{29}F_3N_3O_4$ (M^+) 528.2110].

Preparation of Indole 144:

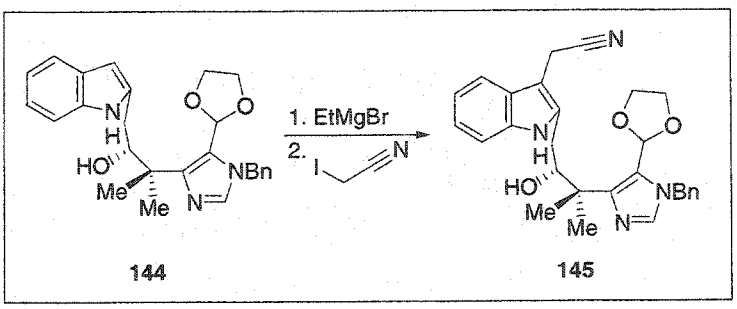


Indole 144. To a stirred solution of **143** (2.8 g, 5.31 mmol, 1 equiv.) in DMF (43 mL) and ethylene glycol (10 mL) was added Et_2NH (1.6 mL, 26.6 mmol, 5.0 equiv.) and $Pd(PPh_3)_4$ (307 mg, 0.27 mmol, 0.05 equiv.). The mixture was heated to 60°C for 12 hours and then poured into Et_2O (200 mL). The reaction was washed with H_2O (3 x 50 mL), brine (50 mL), and dried with $MgSO_4$. The solvent was removed *in vacuo* and the crude mixture chromatographed on silica gel (40% EtOAc/Hexanes) to afford **144** (1.84 g, 80% yield) as a yellow foam.

Indole 144. FTIR (thin film/NaCl) 3343 (m), 2971 (m), 2891 (m), 2245 (w), 1553 (m), 1506 (m), 1456 (m), 1391 (m), 1289 (m), 1251 (m), 1212 (m), 1069 (s), 1015 (m), 951 (m), 901 (m), 783 (m), 733 (s), 654 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.33 (bs, 1H), 7.53 (d, J=7.9 Hz, 1H), 7.42-7.29 (m, 4H), 7.27 (s, 1H), 7.22-7.17 (m, 2H), 7.14-7.02 (m, 2H), 6.24 (s, 2H), 5.25 (s, 2H), 4.08-3.94 (m, 4H), 3.00 (dd, J=1.6 Hz, 15.3 Hz, 1H), 2.73 (ddd, J=0.8 Hz, 10.3 Hz, 14.1 Hz, 1H), 1.50 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 139.3, 137.9, 136.5, 129.2, 128.7, 128.4, 127.9, 121.5,

121.1, 119.9, 119.5, 111.0, 100.1, 98.1, 80.9, 65.2, 65.1, 50.8, 40.9, 31.0, 27.9, 25.1; HRMS (EI) *m/z* 432.2281 [calculated for $C_{26}H_{30}N_3O_3$ (M^+) 432.2287].

Preparation of Nitrile 145:

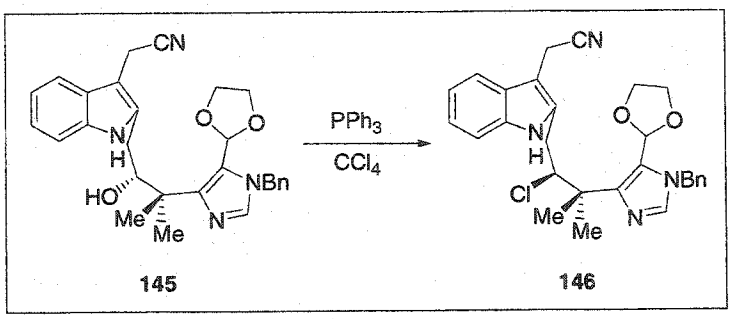


Nitrile 145. To a stirred solution of EtMgBr (1.0 M) (2.32 mL, 2.32 mmol, 4.0 equiv.) in THF (2 mL) at room temperature was added **144** (250 mg, 0.58 mmol, 1.0 equiv.) in THF (4 mL) dropwise. The mixture was stirred for 30 minutes at room temperature. After 30 minutes iodoacetonitrile (126 µL, 1.74 mmol, 3.0 equiv.) was added. The reaction was stirred for another 30 minutes and then quenched by addition of NH_4Cl (sat. aq.) (1.0 mL). H_2O (20 mL) was added and the reaction was extracted with EtOAc (3 x 25 mL). The organic layers were combined, washed with brine (50 mL) and dried with $MgSO_4$. After removal of the solvent *in vacuo,* the mixture was chromatographed on silica gel (30% EtOAc/Hexanes) to afford **145** (167 mg, 61% yield) and **144** (60 mg, 24% yield) as yellow foams.

Nitrile 145. FTIR (thin film/NaCl) 2966 (m), 2930 (m), 2247 (w), 1558 (w), 1498 (m), 1392 (m), 1362 (m), 1247 (w), 1210 (w), 1069 (m), 1015 (m), 954 (w), 911 (w), 733 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.61 (bs, 1H), 7.55 (d, *J*=7.4 Hz, 1H),

7.44-7.30 (m, 5H), 7.23-7.10 (m, 4H), 6.23 (s, 1H), 5.22 (s, 2H), 4.10-3.97 (m, 4H), 3.77 (s, 2H), 3.03 (dd, *J*=1.6 Hz, 15.2 Hz, 1H), 2.73 (dd, *J*=10.2 Hz, 15.2 Hz, 1H), 1.52 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 137.8, 136.6, 135.6, 129.3, 128.6, 128.0, 127.3, 122.0, 118.9, 117.6, 111.4, 99.9, 97.9, 80.3, 65.3, 65.2, 50.9, 40.9, 28.5, 27.6, 25.3, 13.4; HRMS (EI) *m/z* 471.2396 [calculated for $C_{28}H_{31}N_4O_3$ (M^+) 471.2396].

Preparation of Chloride 146:

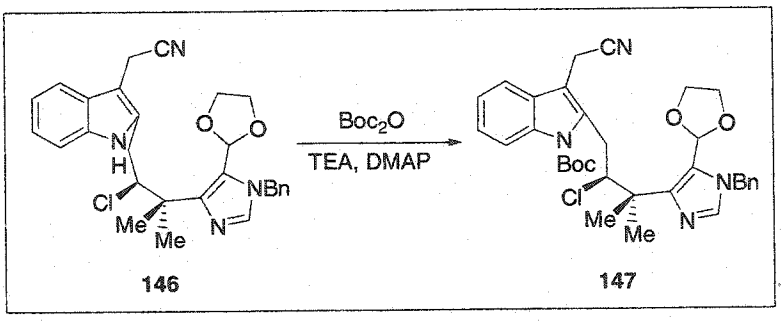


Chloride 146. To a stirred solution of **145** (1.0 g, 3.40 mmol, 1.0 equiv.) in CCl_4 (40 mL) was added triphenylphosphine (PPh_3) (1.69 mL, 6.60 mmol, 2.0 equiv.). The reaction was heated to 75°C and monitored by TLC. Upon consumption of starting material (as indicated by TLC) the reaction was cooled to room temperature and the solvent removed *in vacuo*. The mixture was chromatographed on silica gel (4% MeOH/CH_2Cl_2) to afford **146** (567 mg, 53% yield) as a colorless oil.

Chloride 146. FTIR (thin film/NaCl) 3154 (m), 3109 (m), 3062 (m), 3034 (m), 2965 (s), 2929 (s), 2870 (m), 2247 (w), 1588 (w), 1497 (m), 1460 (s), 1363 (m), 1319 (w), 1298 (m), 1245 (w), 1206 (m), 1155 (w), 1127 (s), 1059 (s), 1029 (s), 972 (w), 910

(m), 870 (w), 734 (s), 663 (m), 648 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.84 (bs, 1H), 7.68 (s, 1H), 7.59 (d, *J*=7.6 Hz, 1H), 7.38-7.27 (m, 4H), 7.24-7.11 (m, 4H), 5.44, (s, 1H), 5.24 (d, *J*=15.5 Hz, 1H), 5.19 (d, *J*=15.5 Hz, 1H), 3.88-3.76 (m, 2H), 3.81 (s, 2H), 3.74-3.66 (m, 3H), 2.95 (dd, *J*=10.4 Hz, 15.1 Hz, 1H), 3.09 (dd, *J*=1.4 Hz, 15.1 Hz, 1H), 1.45 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.6, 138.0, 135.6, 135.5, 134.7, 129.5, 128.9, 127.8, 127.3, 122.6, 121.8, 120.5, 118.5, 118.0, 111.3, 101.0, 95.9, 83.1, 67.4, 50.4, 43.6, 36.9, 26.2, 23.6, 22.6, 13.4; HRMS (EI) *m/z* 489.2056 [calculated for $C_{28}H_{30}ClN_4O_2$ (M^+) 489.2057].

Preparation of Boc-Indole 147:

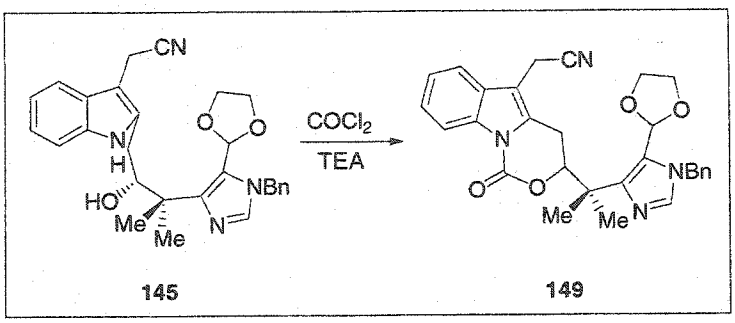


Boc-Indole 147. To a stirred solution of **146** (500 mg, 2.74 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) at room temperature was added Et_3N (423 μL, 3.02 mmol, 1.1 equiv.) and DMAP (17 mg, 0.14 mmol, 0.05 equiv.) followed by di-*t*-butyl dicarbonate (628 mg, 2.88 mmol, 1.05 equiv.). The solution was stirred for 2 hours, at which time the reaction was poured into H_2O (50 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, washed with brine (20 mL) and dried with $MgSO_4$. The resulting

oil was chromatographed on silica gel (20% EtOAc/Hexanes) to afford **147** (648 mg, 84% yield) as a colorless oil.

Boc-Indole 147. FTIR (thin film/NaCl) 3404 (m), 2973 (m), 2930 (m), 2872 (m), 2249 (w), 2209 (w), 1734 (s), 1553 (w), 1498 (w), 1456 (s), 1393 (m), 1369 (s), 1353 (s), 1326 (s), 1297 (s), 1236 (m), 1202 (m) 1158 (m), 1133 (s), 1120 (s), 1045 (m), 1030 (m), 909 (m), 843 (m), 769 (m), 723 (s), 648 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J*=7.6 Hz, 1H), 7.88 (bs, 1H), 7.64 (d, *J*=7.6 Hz, 1H), 7.38-7.30 (m, 5H), 7.19 (d, *J*=6.7 Hz, 1H), 5.31 (s, 1H), 5.26 (s, 2H), 3.96-3.90 (m, 1H), 3.90 (d, *J*=18.1 Hz, 1H), 3.83 (d, *J*=18.1 Hz, 1H), 3.79 (d, *J*=10.5 Hz, 1H), 3.71 (d, *J*=14.3 Hz, 1H), 3.68-3.60 (m, 3H), 3.02 (dd, *J*=10.5 Hz, 14.3 Hz, 1H), 1.69 (s, 9H), 1.56 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 137.3, 136.3, 135.7, 135.2, 129.5 ,129.0, 128.3, 128.1, 124.9, 123.4, 122.6, 118.3, 117.9, 116.0, 110.3, 95.8, 85.1, 82.3, 67.7, 50.7, 43.7, 37.0, 28.6, 27.0, 23.4, 22.7, 13.9; HRMS (EI) *m/z* 589.2582 [calculated for $C_{33}H_{38}N_4O_4Cl$ (M^+) 589.2582]

Preparation of Carbamate 149:



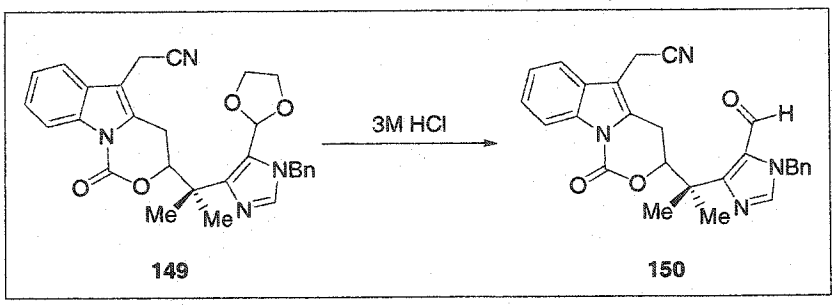
145 149

Carbamate 149. To a stirred solution of **145** (40 mg, 0.09 mmol, 1.0 equiv.) in PhH (1.0 mL) at 0°C was added Et_3N (120 μL, 0.85 mmol, 10.0 equiv.) followed by phosgene (20% in toluene) (158 μL, .29 mmol, 3.5 equiv.) dropwise. The reaction mixture was allowed to warm to room temperature, stirred for 1h and then quenched by addition of $NaHCO_3$ (sat. aq.) (2.0 mL). H_2O (2.0 mL) was added and the reaction was extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were combined, washed with brine (10 mL) and dried with $MgSO_4$. Silica gel chromatography (30% EtOAc/Hexanes) afforded **149** (31 mg, 70% yield) as a yellow foam.

Carbamate 149. FTIR (thin film/NaCl) 3061 (w), 3031 (w), 2975 (m), 2928 (m), 2895 (m), 2251 (w), 1742 (s), 1630 (m), 1558 (w), 1503 (m), 1460 (s), 1394 (s), 1326 (m), 1255 (m), 1227 (m), 1157 (m), 1134 (m), 1112 (m), 1070 (s), 1025 (m), 954 (m), 912 (m), 820 (w), 757 (m), 734 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J*=7.7 Hz, 1H), 7.58 (d, *J*=7.7 Hz, 1H), 7.43-7.32 (m, 6H), 7.23 (d, *J*=7.1 Hz, 2H), 6.33 (s, 1H), 5.29 (d, *J*=15.0 Hz, 1H), 5.25 (d, *J*=15.0 Hz, 1H), 4.75 (dd, *J*=2.8 Hz, 12.3 Hz, 1H), 4.1-3.97 (m, 4H), 3.69 (d, *J*=18.1 Hz, 1H), 3.65 (d, *J*=18.1 Hz, 1H), 3.16 (dd, *J*=2.8 Hz, 16.3

Hz, 1H), 2.81 (dd, *J*=12.3 Hz, 16.3 Hz, 1H), 1.65 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 145.0, 138.1, 136.3, 135.2, 131.9, 129.3, 128.7, 128.2, 125.6, 124.6, 123.3, 118.3, 116.9, 115.9, 105.4, 98.1, 84.8, 65.3, 65.2, 51.0, 40.5, 26.8, 24.2, 22.8, 13.2; HRMS (EI) *m/z* 497.2189 [calculated for $C_{29}H_{29}N_4O_4$ (M^+) 497.2189].

Preparation of Aldehyde 150:



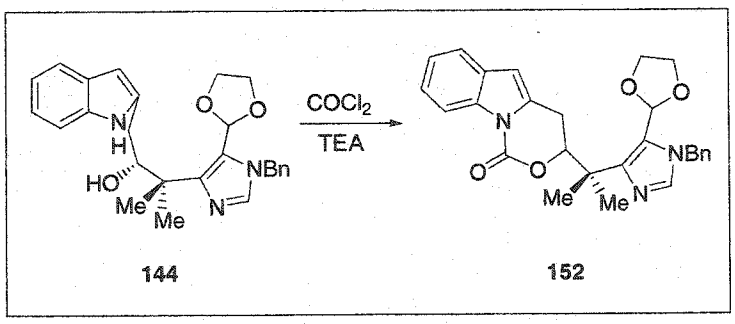
149 **150**

Aldehyde 150. To a stirred solution of **149** (18.0 mg, 0.04 mmol, 1.0 equiv.) in acetone (1.0 mL) at room temperature was added HCl (3.0 M) (1.0 mL, 3.00 mmol, 75 equiv.). The reaction was stirred at room temperature for 24 hours and then quenched by addition of $NaHCO_3$ (sat. aq.) (2.0 mL). H_2O (2.0 mL) was added and the reaction was extracted with EtoAc (3 x 5 mL). The organic layers were combined, washed with brine (5 mL) and dried with $MgSO_4$. Silica gel chromatography (50% EtOAc/Hexanes) afforded **150** (15 mg, 91% yield) as a white foam.

Aldehyde 150. FTIR (thin film/NaCl) 3109 (w), 3063 (w), 3033 (w), 2979 (m), 2926 (m), 2855 (w), 2251 (m), 1744 (s), 1659 (s), 1631 (m), 1511 (m), 1502 (m), 1460 (s), 1392 (s), 1365 (m), 1326 (s), 1257 (m), 1227 (m), 1156 (m), 1134 (m), 1111 (m), 1079 (w), 1026 (m), 972 (w), 911 (m), 757 (m), 720 (s) cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$) δ 10.3 (s, 1H), 8.3 (d, *J*=7.9 Hz, 1H), 7.6 (s, 1H), 7.55 (d, *J*=8.2 Hz, 1H), 7.44-7.31 (m, 5H), 7.22 (d, *J*=6.9 Hz, 2H), 5.56 (d, *J*=15.1 Hz, 1H), 5.48 (d, *J*=15.1 Hz, 1H), 4.92 (dd, *J*=2.7 Hz, 12.1 Hz, 1H), 3.70 (s, 2H), 3.24 (dd, *J*=2.6 Hz, 16.5 Hz, 1H), 2.92 (dd, *J*=12.6 Hz, 16.5 Hz, 1H), 1.71 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.4, 157.2, 147.8, 141.4, 135.9, 135.1, 131.4, 129.4, 128.8, 128.6, 128.4, 128.1, 125.8, 124.7, 118.2, 116.9, 105.5, 84.1, 51.7, 41.7, 26.6, 25.1, 22.8, 13.3; HRMS (EI) *m/z* 453.1929 [calculated for $C_{27}H_{25}N_4O_3$ (M^+) 453.1927].

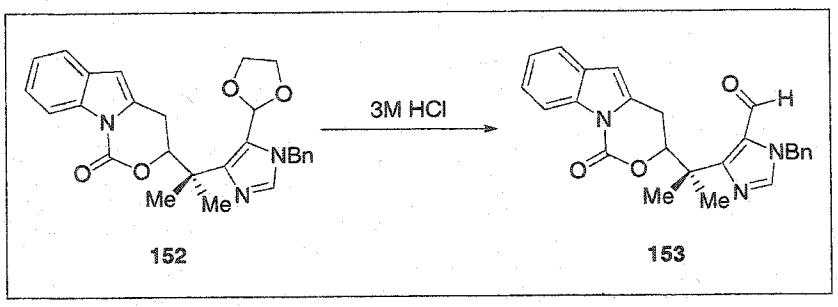
Preparation of Carbamate 152:



Carbamate 152. To a stirred solution of **144** (500 mg, 1.16 mmol, 1.0 equiv.) in PhH (12 mL) at 0°C was added Et_3N (1.62 mL, 11.6 mmol, 10.0 equiv.) followed by phosgene (20% in toluene) (2.15 mL, 4.06 mmol, 3.5 equiv.) dropwise. The reaction mixture was allowed to warm to room temperature, stirred for 1h and then quenched by addition of $NaHCO_3$ (sat. aq.) (15 mL). H_2O (15 mL) was added and the reaction was extracted with CH_2Cl_2 (3 x 25 mL). The organic layers were combined, washed with brine (50 mL) and dried with $MgSO_4$. Silica gel chromatography (30% EtOAc/Hexanes) afforded **152** (302 mg, 57% yield) as a white foam.

Carbamate 152. FTIR (thin film/NaCl) 2977 (w), 2892 (w), 1740 (s), 1605 (w), 1559 (w), 1505 (w), 1455 (s), 1380 (s), 1324 (m), 1245 (w), 1204 (m), 1110 (w), 1091 (s), 1068 (s), 1003 (s), 951 (s), 803 (w), 733 (m), 711 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J*=8.2 Hz, 1H), 7.50 (d, *J*=7.0 Hz, 1H), 7.41-7.17 (m, 8H), 6.35 (s, 1H), 6.30 (bs, 1H), 5.26 (s, 2H), 4.72 (dd, *J*=2.7 Hz, 12.6 Hz, 1H), 4.07-3.95 (m, 4H), 3.05 (dd, *J*=2.5 Hz, 16.5 Hz, 1H), 2.85 (ddd, *J*=2.0 Hz, 12.6 Hz, 16.3 Hz, 1H), 1.63 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 145.9, 138.3, 136.8, 135.5, 134.2, 130.1, 129.2, 128.4, 128.0, 124.4, 124.1, 122.9, 120.5, 115.6, 104.6, 98.4, 85.4, 65.2, 65.1, 50.7, 40.4, 26.9, 24.6, 24.1; HRMS (EI) *m/z* 414.1818 [calculated for $C_{25}H_{24}N_3O_3$ (M^+) 414.1818].

Preparation of Aldehyde 153:

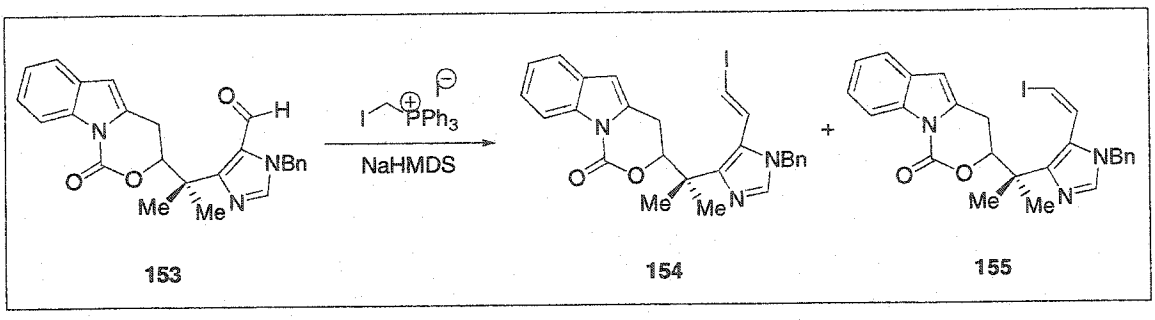


Aldehyde 153. To a stirred solution of **152** (220 mg, 0.48 mmol, 1.0 equiv.) in acetone (5.0 mL) at room temperature was added HCl (3.0 M) (5.0 mL, 15.00 mmol, 32 equiv.). The reaction was stirred at room temperature for 24 hours and then quenched by addition of $NaHCO_3$ (sat. aq.) (10.0 mL). H_2O (10 mL) was added and the reaction was extracted with EtoAc (3 x 25 mL). The organic layers were combined, washed with brine

(50 mL) and dried with $MgSO_4$. Silica gel chromatography (50% EtOAc/Hexanes) afforded **153** (190 mg, 95% yield) as a white foam.

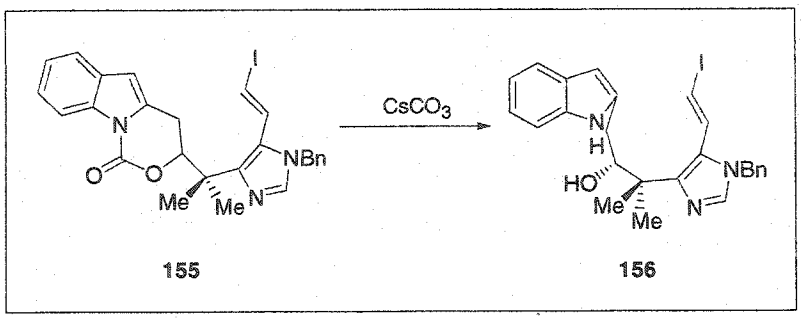
Aldehyde 153. FTIR (thin film/NaCl) 3107 (w), 3065 (w), 2978 (w), 2917 (w), 1741 (s), 1661 (s), 1606 (m), 1507 (m), 1456 (m), 1330 (m), 1325 (m), 1246 (w), 1205 (m), 1110 (m), 1091 (m), 1025 (w), 1006 (w), 967 (w), 909 (m), 802 (m), 759 (m), 728 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.3 (bs, 1H), 8.24 (d, *J*=8.4 Hz, 1H), 7.56 (s, 1H), 7.50 (d, *J*=7.6 Hz, 1H), 7.41-7.24 (m, 5H), 7.22 (d, *J*=6.6 Hz, 2H), 6.34 (bs, 1H), 5.56 (d, *J*=15.1 Hz, 1H), 5.50 (d, *J*=15.1 Hz, 1H), 4.87 (dd, *J*=2.9 Hz, 12.3 Hz, 1H), 3.13 (dd, *J*=2.6 Hz, 16.4 Hz, 1H), 2.93 (ddd, *J*=1.8 Hz, 12.5 Hz, 16.2 Hz, 1H), 1.69 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.6, 157.5, 148.2, 141.4, 136.0, 135.5, 133.5, 130.0, 129.4, 128.7, 128.5, 128.0, 124.6, 124.2, 120.6, 115.6, 104.9, 84.6, 51.7, 41.7, 26.4, 25.2, 24.5; HRMS (EI) *m/z* 414.1818 [calculated for $C_{25}H_{24}N_3O_3$ (M^+) 414.1818.

Preparation of Vinyliodides 154 and 155:



Vinyl Iodides 154 and 155. To a stirred solution of Iodomethyl-triphenylphosphonium iodide (477 mg, 1.23 mmol, 5.1 equiv.) in THF (4 mL) at room temperature was added NaHMDS (2.0M) (605 μL, 1.21 mmol, 5.0 equiv.) dropwise. The solution was stirred for 15 minutes and then cooled to -78°C at which time was added aldehyde **153** (100 mg, .242 mmol, 1.0 equiv.) in THF (1 mL). The reaction was stirred for another 20 minutes at -78°C and then quenched by addition of H_2O (5 mL). The reaction was extracted with Et_2O (3 x 25 mL). The organic layers were combined, washed with brine (25 mL) and dried with $MgSO_4$. After removal of the solvent *in vacuo*, the mixture was run through a silica plug (40% EtOAc/Hexanes) to afford **154** (35 mg, 27% yield) and **155** (17 mg, 13% yield) as white foams.

Preparation of Indole 156:



Indole 156. To a stirred solution of **155** (35 mg, 0.065 mmol, 1.0 equiv.) in MeOH (2 mL) at room temperature was added $CsCO_3$ (105 mg, 0.33 mmol, 5.0 equiv.). The reaction was stirred for 1 hour at room temperature at which time the solvent was removed *in vacuo* and the resulting residue chromatographed on silica gel (50% EtOAc/Hexanes) to afford **156** (27 mg, 80% yield) as a white foam.

Indole 156. FTIR (thin film/NaCl) 3252 (m), 3057 (m), 2971 (m), 2918 (m), 2849 (m), 1497 (m), 1456 (s), 1361 (w), 1340 (w), 1289 (m), 1237 (w), 1181 (w), 1063 (m), 1029 (w), 1000 (w), 944 (w), 909 (w), 782 (m), 731 (s), 647 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (bs, 1H), 7.52 (d, J=7.5 Hz, 1H), 7.47-7.30 (m, 5H), 7.24 (d, J=15.0 Hz, 1H), 7.14-6.96 (m, 4H), 6.45 (d, J=15.0 Hz, 1H), 6.22 (s, 1H), 4.96 (d, J=15.8 Hz, 1H), 4.90 (d, J=15.8 Hz, 1H), 3.97 (dd, J=1.5 Hz, 10.1 Hz, 1H), 3.01 (dd, J=1.5 Hz, 15.1 Hz, 1H), 2.70 (dd, J=10.1 Hz, 15.0 Hz, 1H), 1.45 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 136.5, 136.2, 135.6, 133.3, 129.6, 129.5, 128.8, 128.6, 127.3, 126.5, 121.2, 119.9, 119.6, 111.1, 100.2, 80.4, 49.8, 40.7, 30.9, 27.6, 24.2; HRMS (EI) *m/z* 512.1206 [calculated for $C_{25}H_{27}N_3OI$ (M^+) 512.1199].

2.8 Notes and References

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Appendix One: Spectra Relevant to Chapter Two

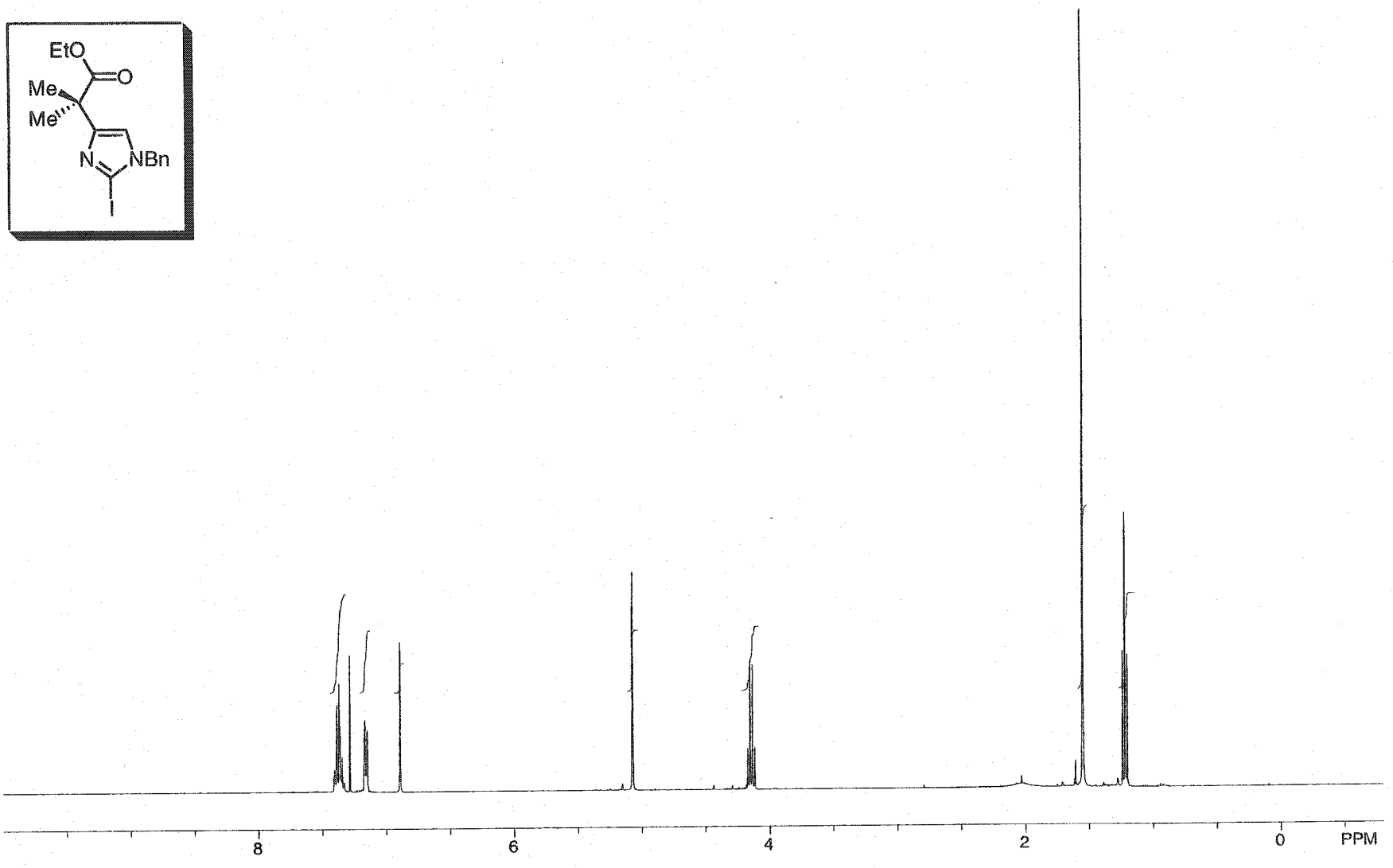


Figure A.1.1 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **128**.

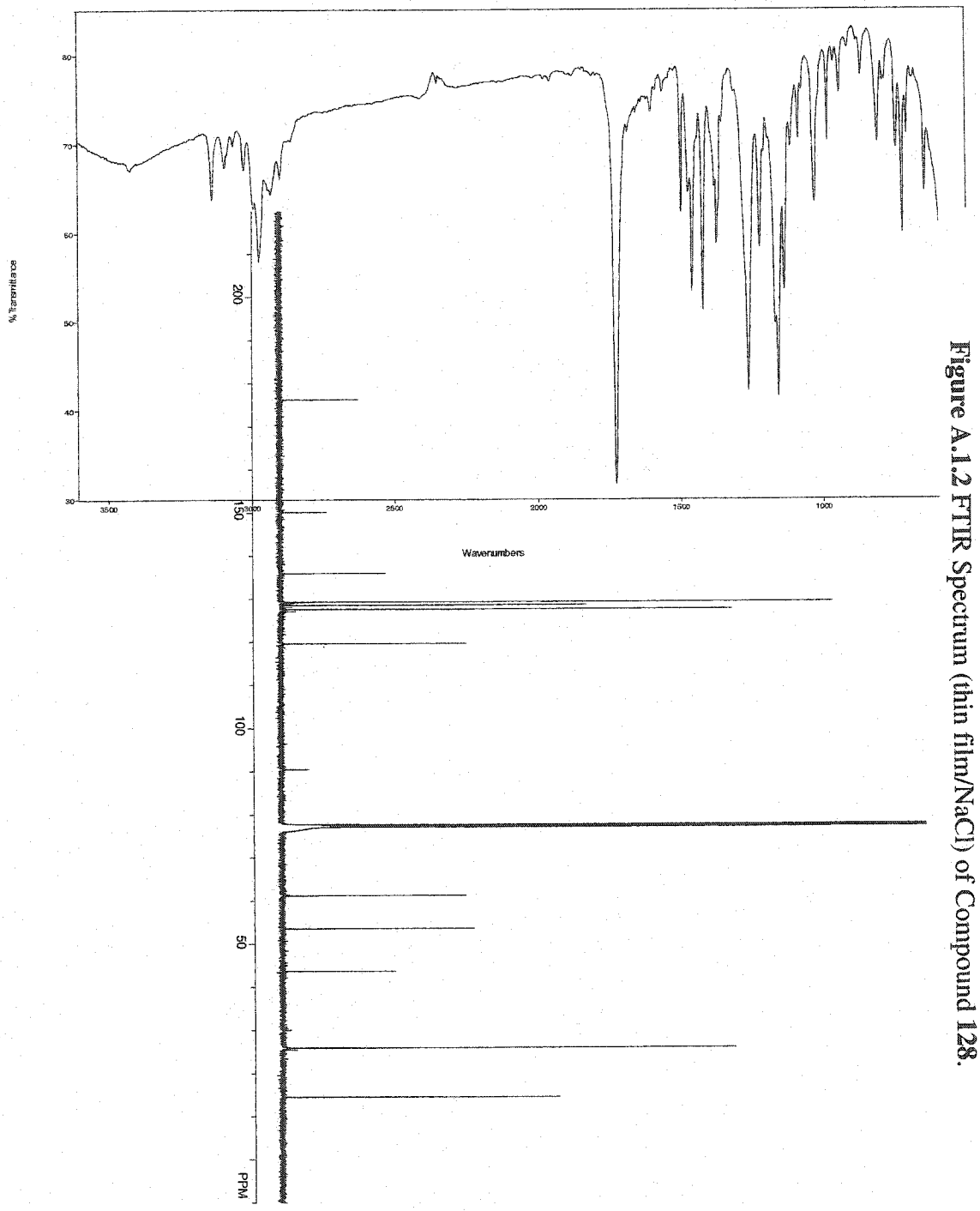


Figure A.1.2 FTIR Spectrum (thin film/NaCl) of Compound **128**.

Figure A.1.3 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **128**.

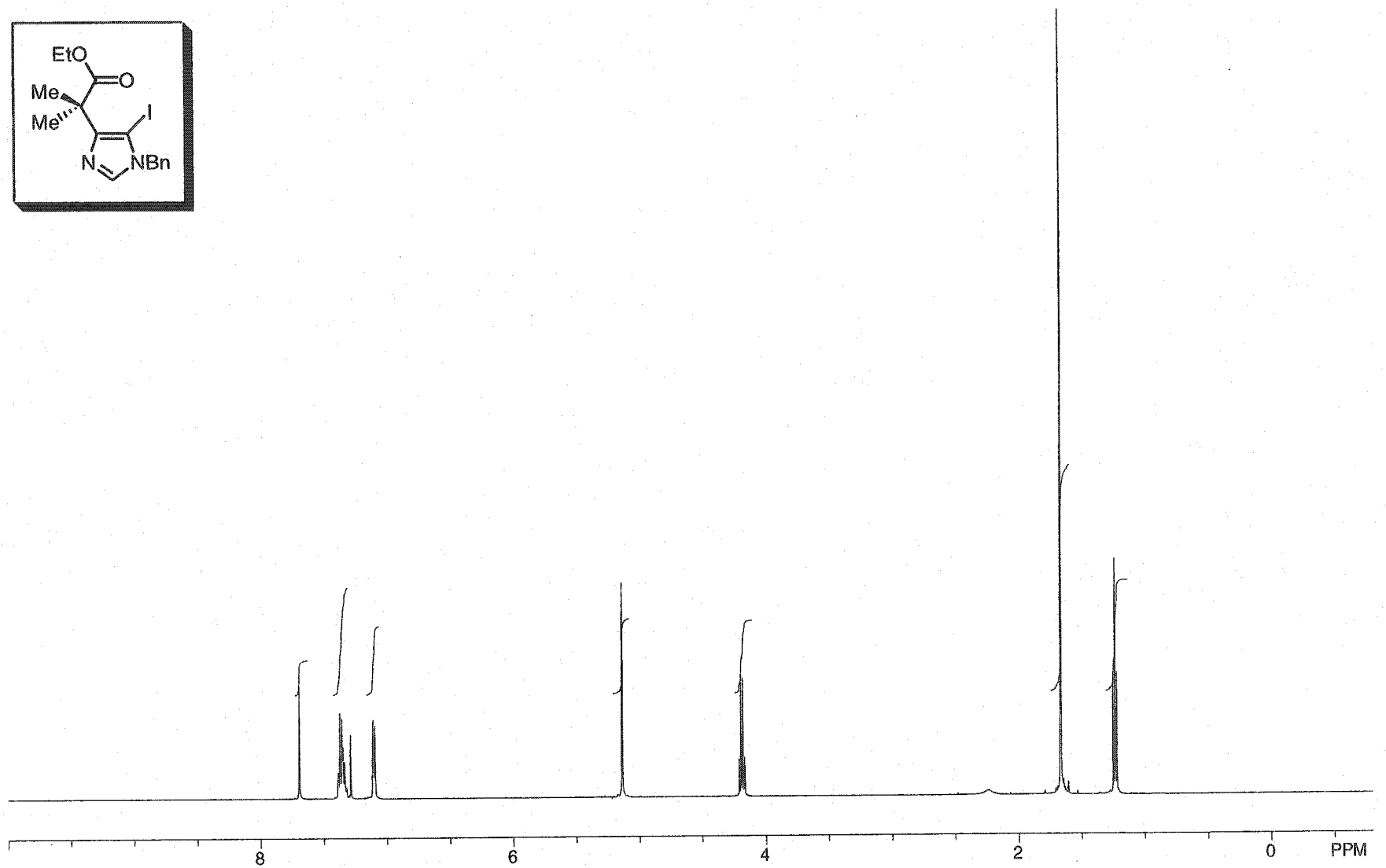


Figure A.1.4 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **127.**

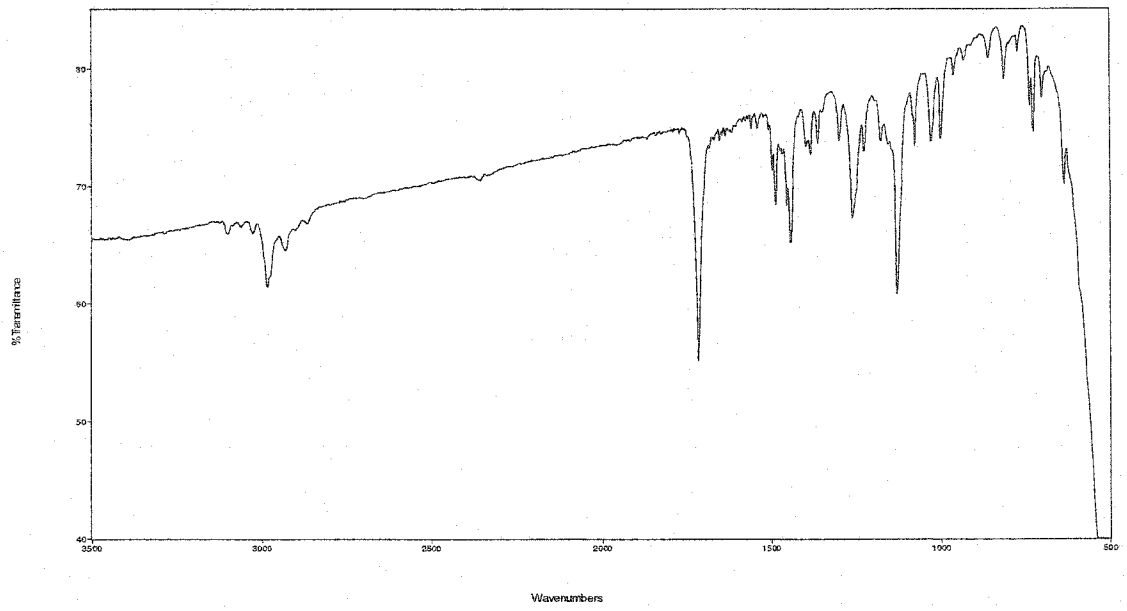


Figure A.1.5 FTIR Spectrum (thin film/NaCl) of Compound **127**.

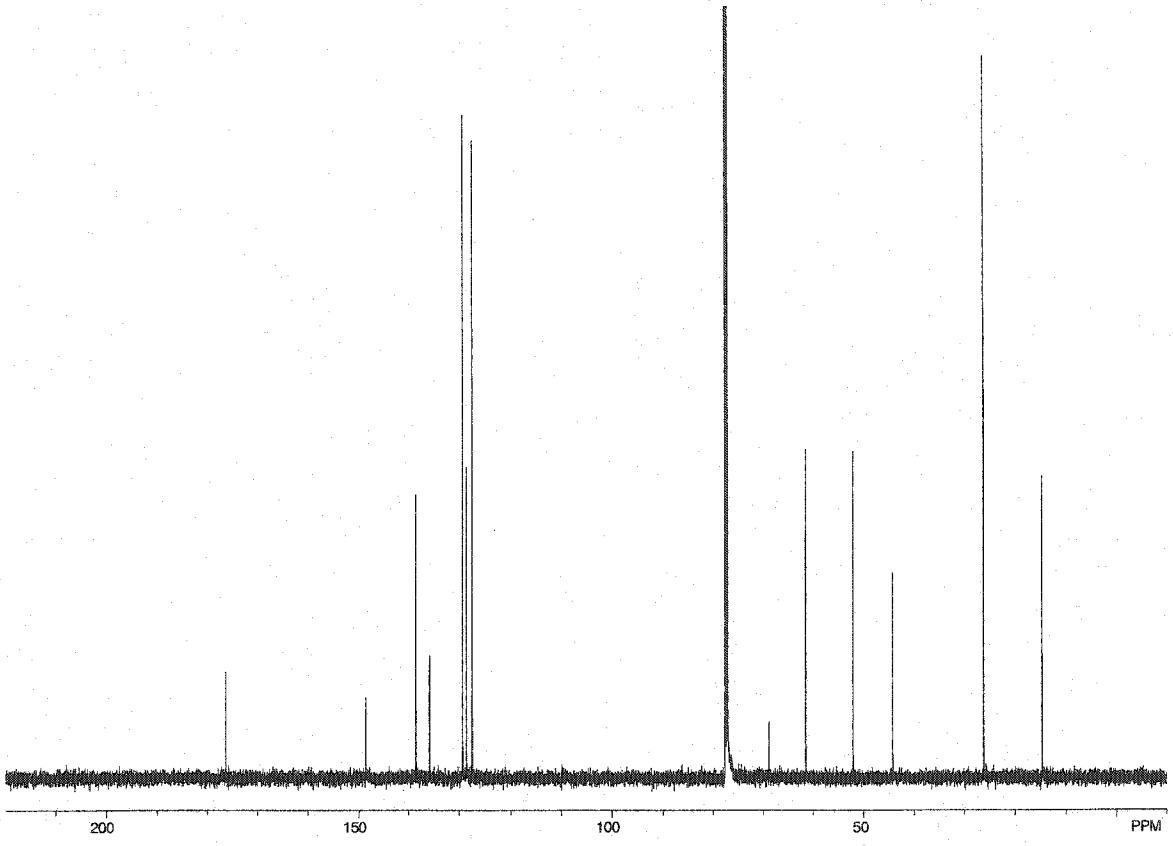


Figure A.1.6 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **127**.

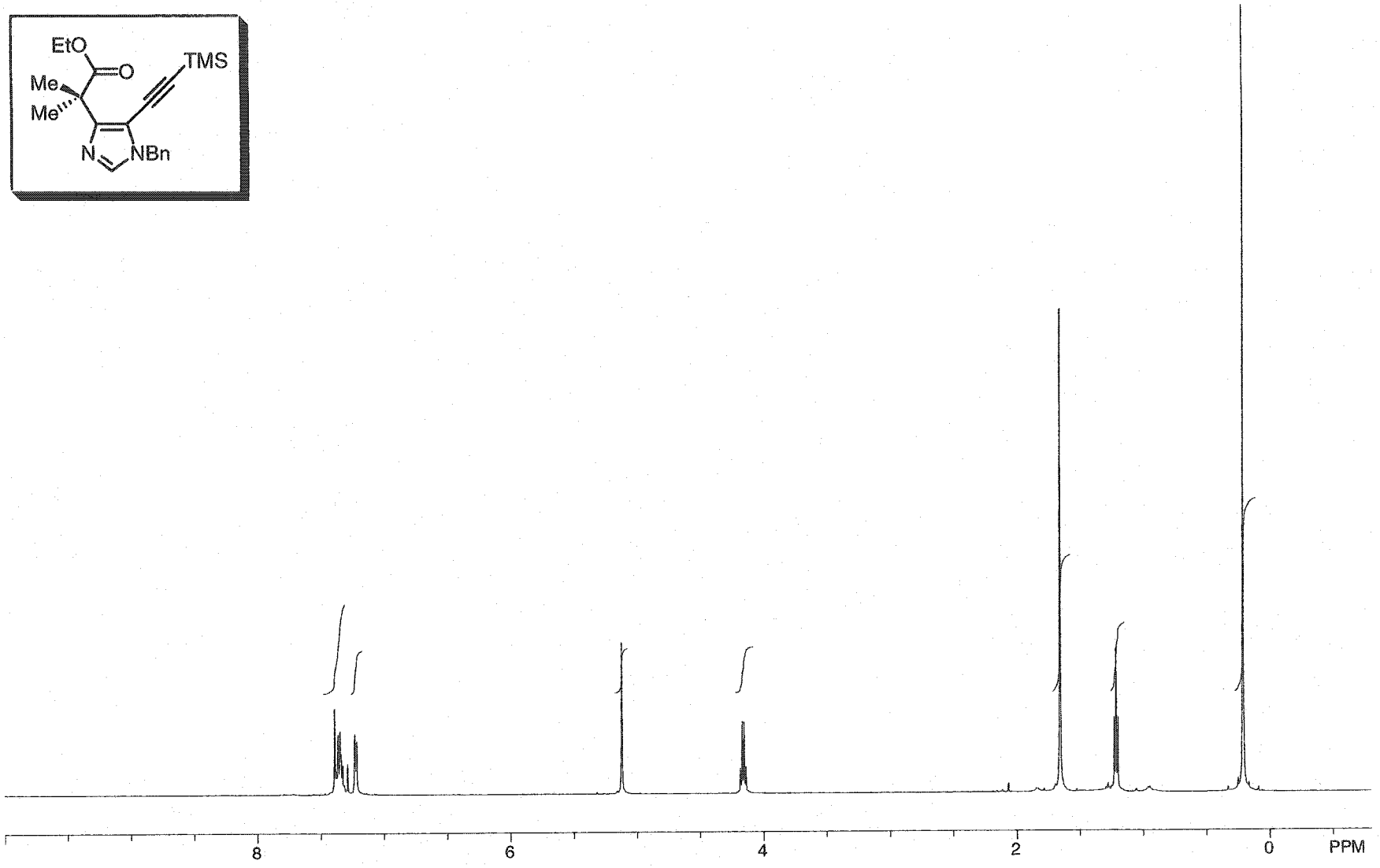


Figure A.1.7 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **129**.

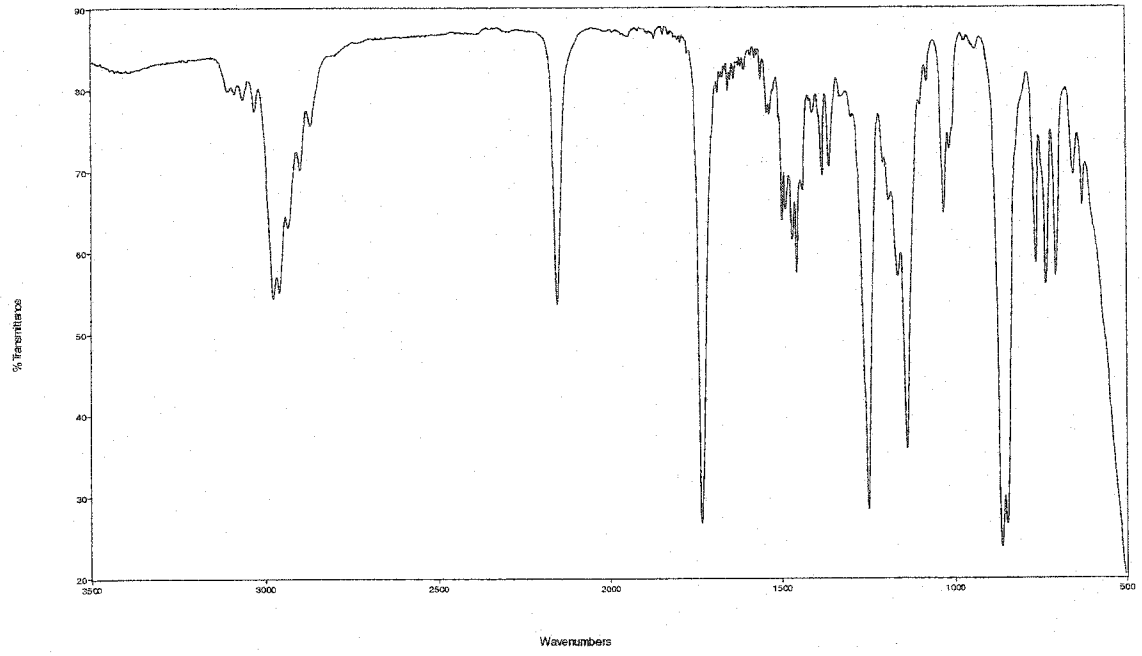


Figure A.1.8 FTIR Spectrum (thin film/NaCl) of Compound **129**.

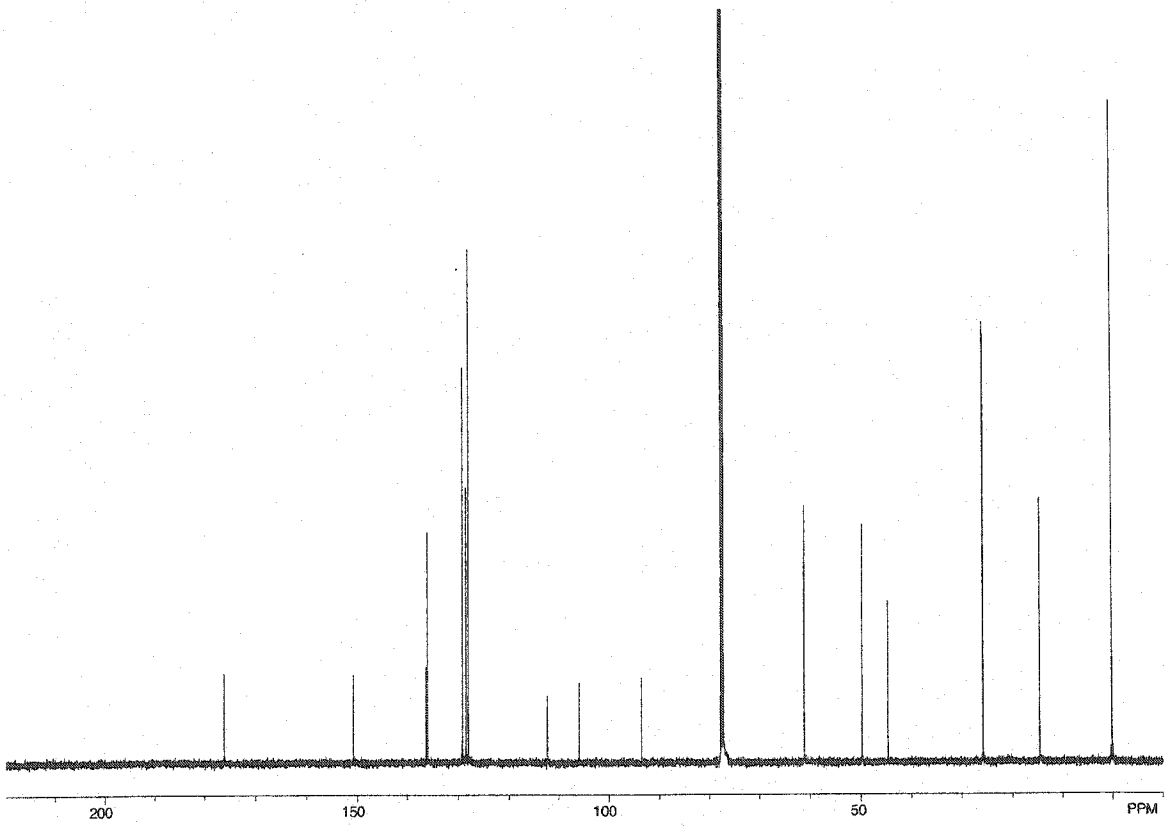


Figure A.1.9 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **129**.

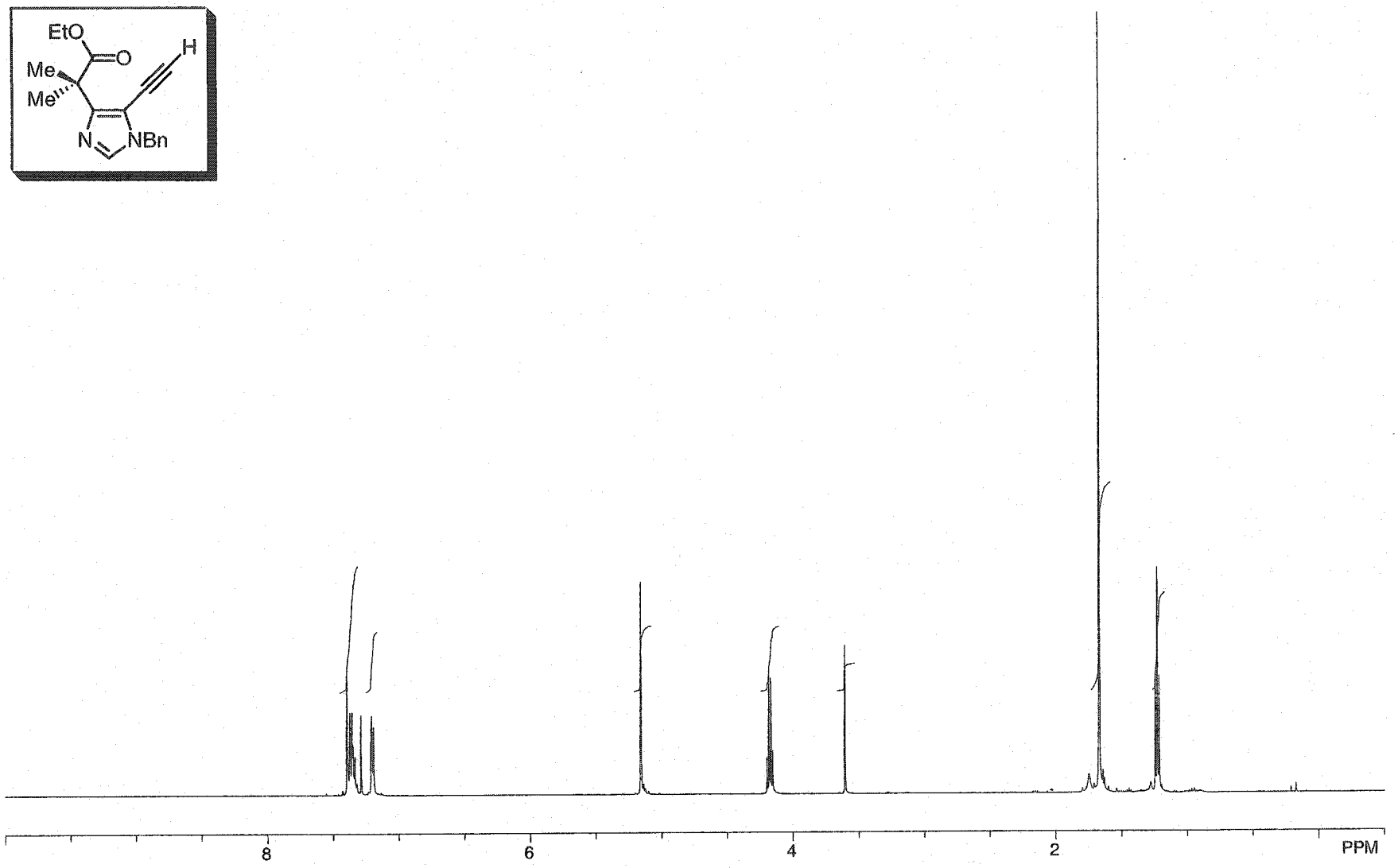


Figure A.1.10 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **130**.

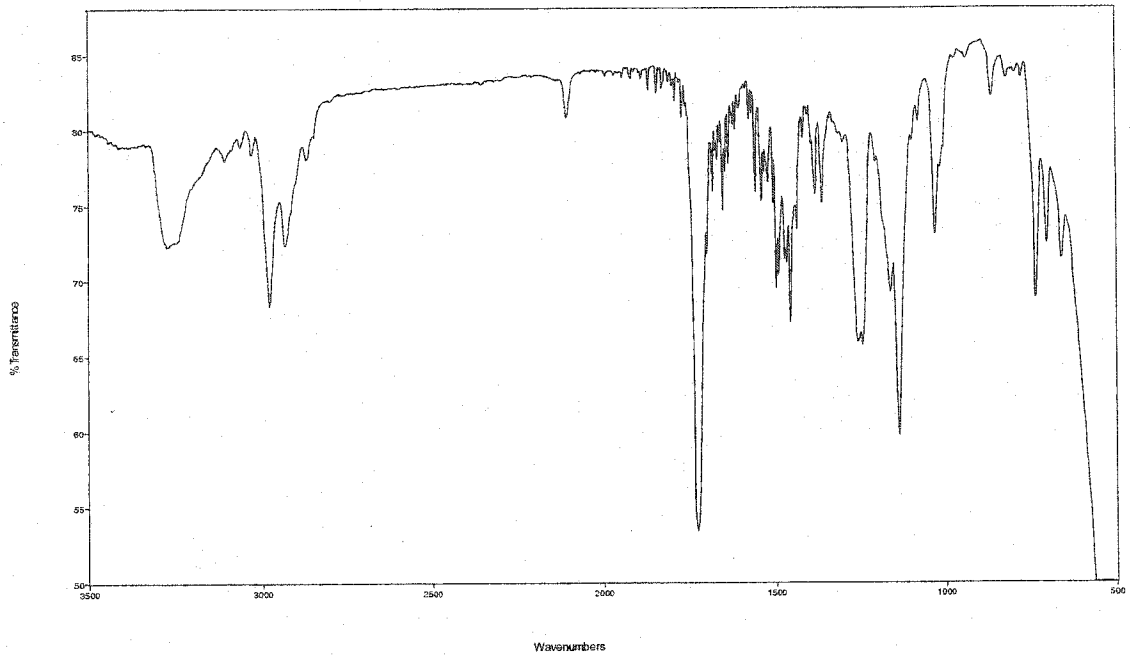


Figure A.1.11 FTIR Spectrum (thin film/NaCl) of Compound **130**.

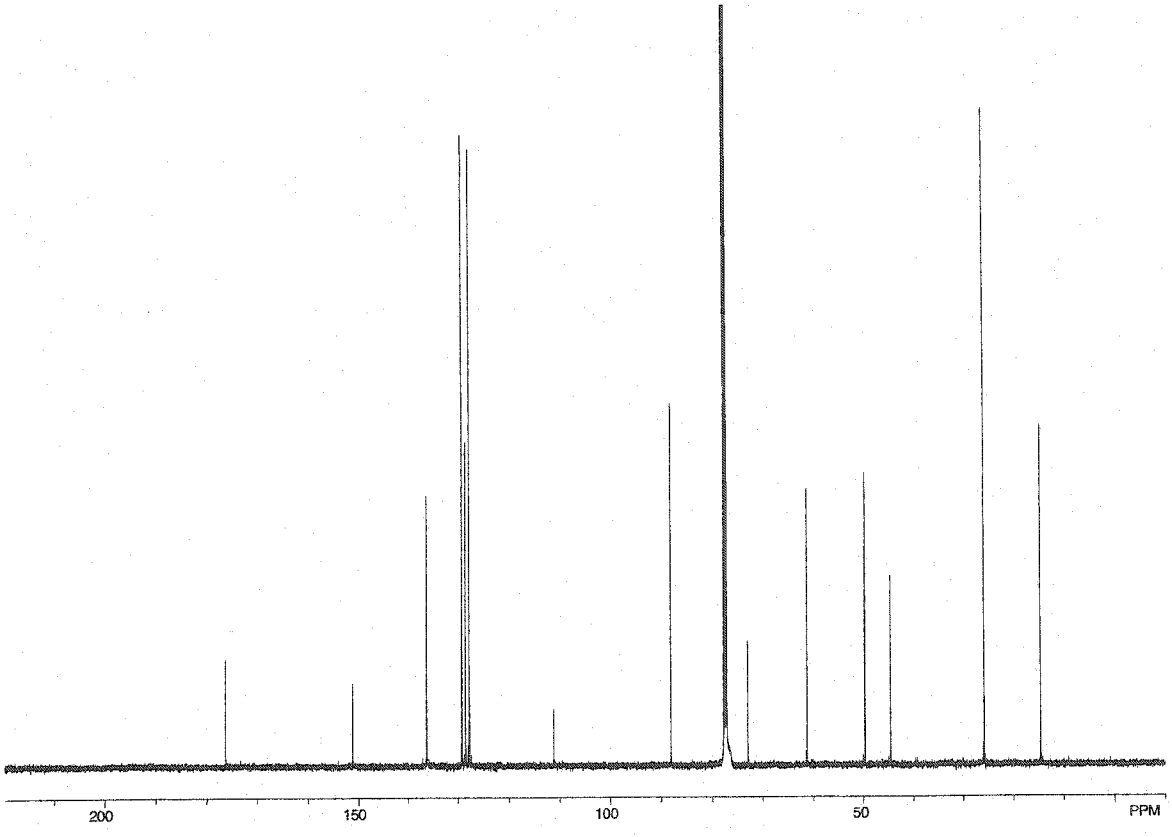


Figure A.1.12 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **130**.

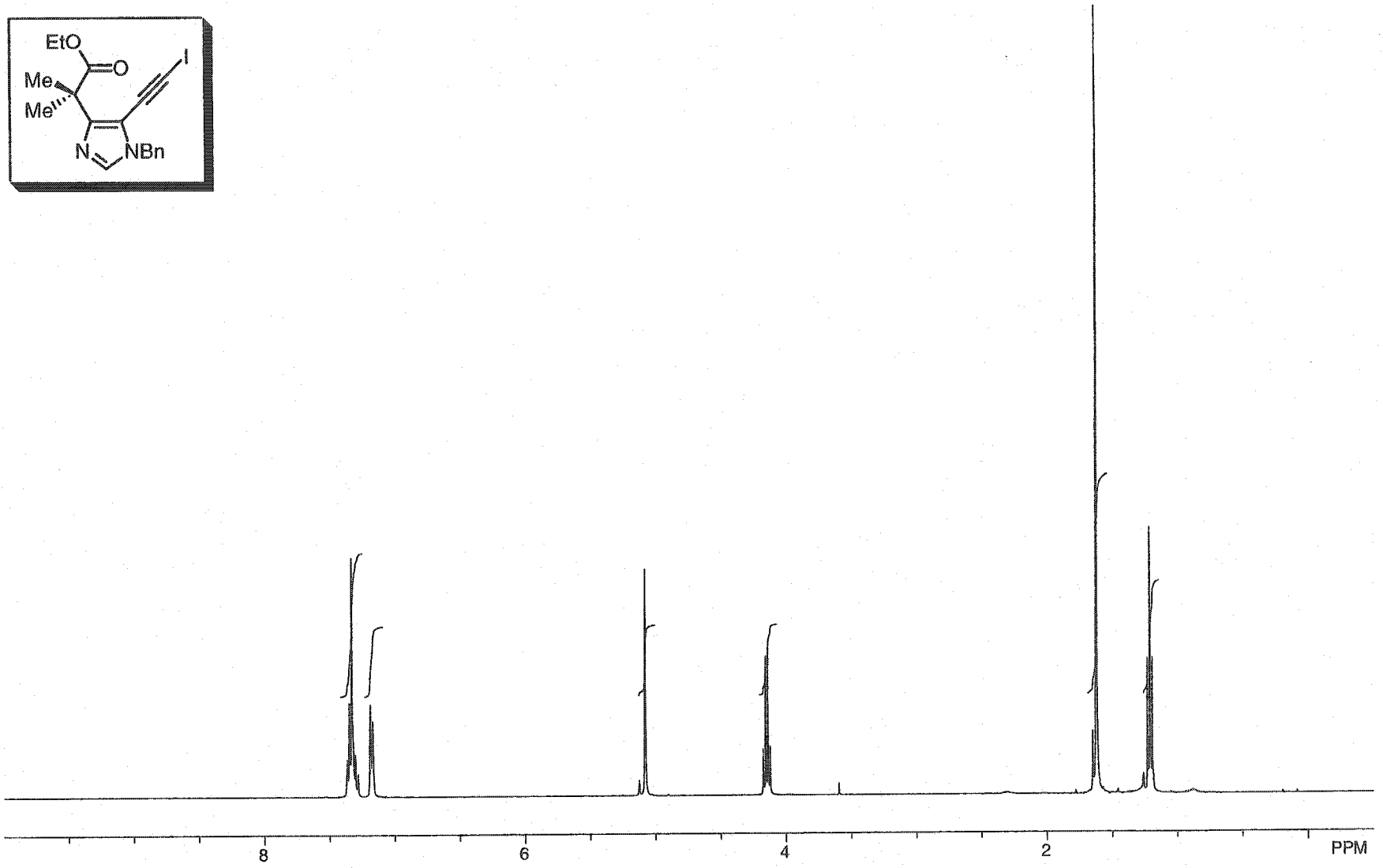


Figure A.1.13 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **131**.

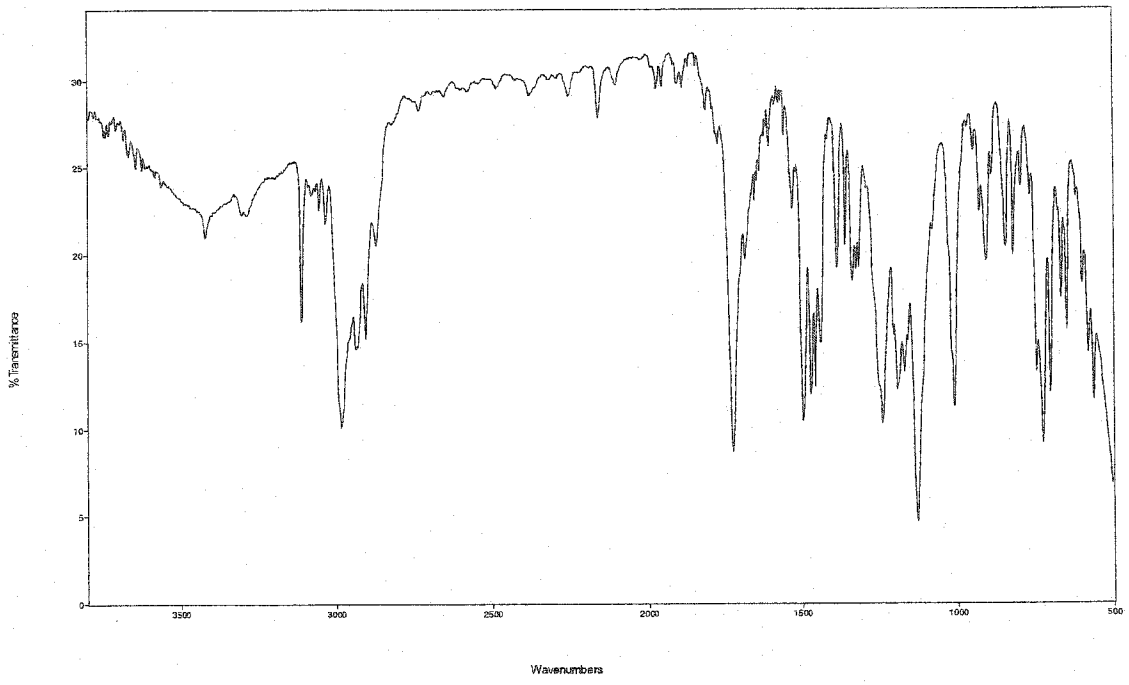


Figure A.1.14 FTIR Spectrum (thin film/NaCl) of Compound **131**.

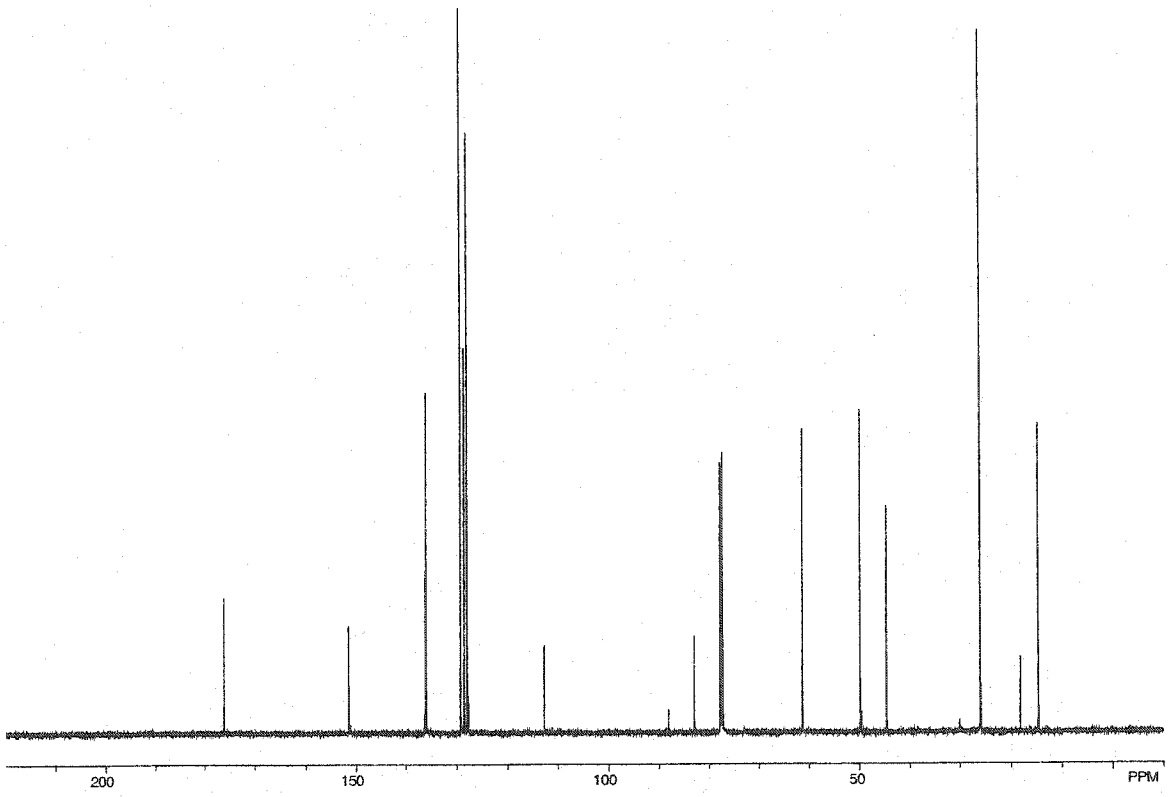


Figure A.1.15 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **131**.

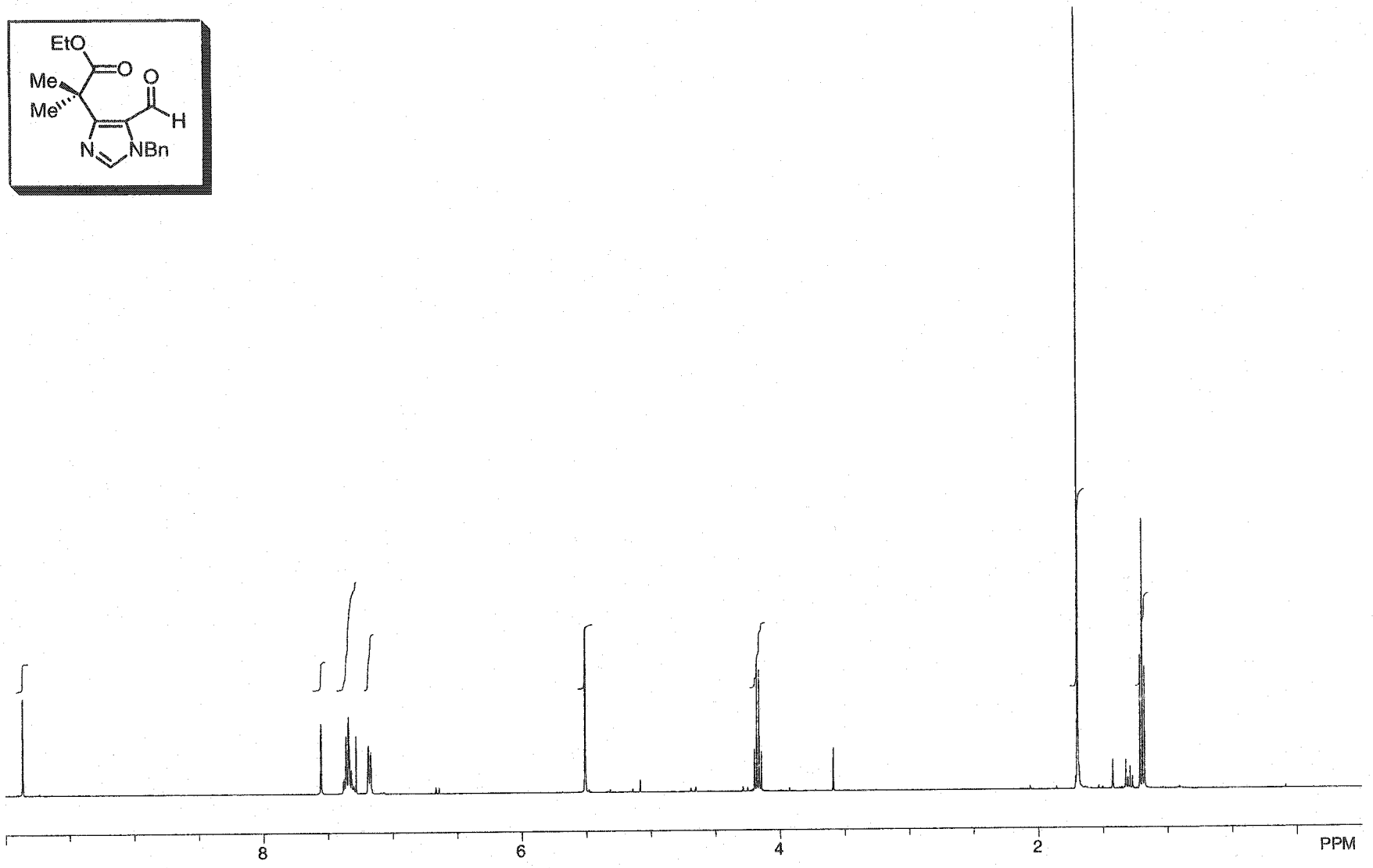


Figure A.1.16 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **133**.

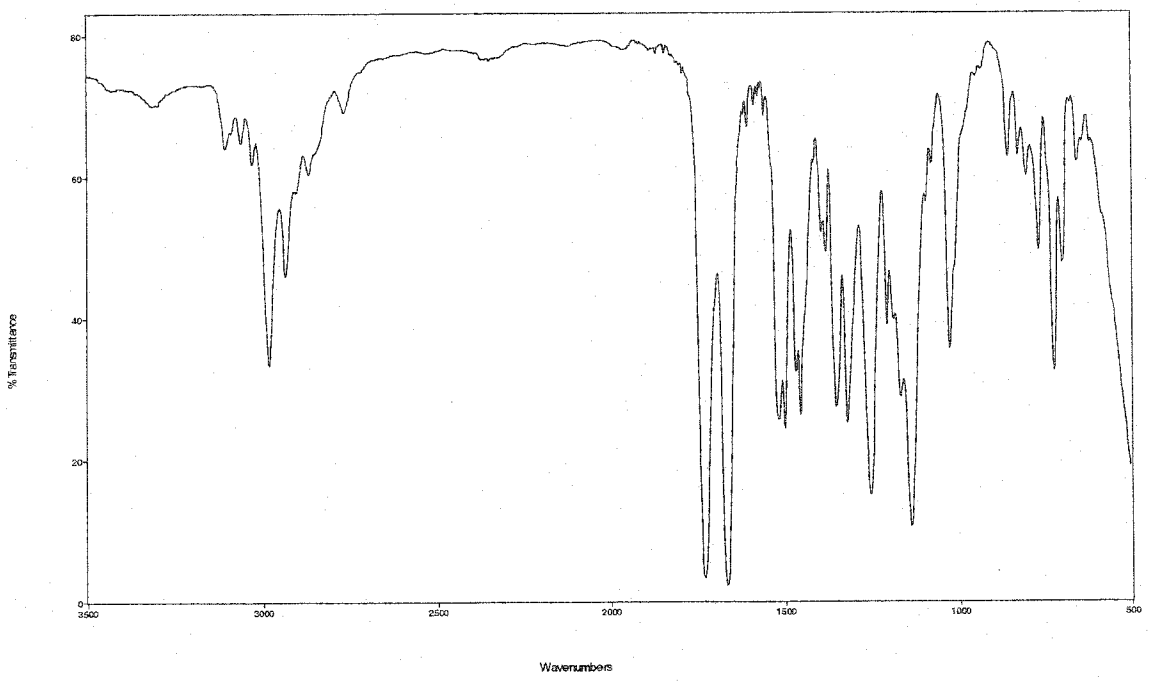


Figure A.1.17 FTIR Spectrum (thin film/NaCl) of Compound **133**.

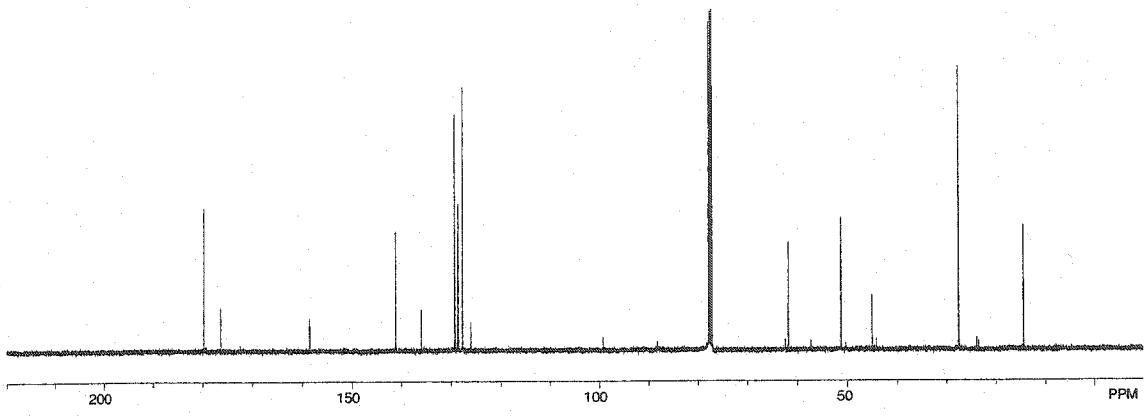
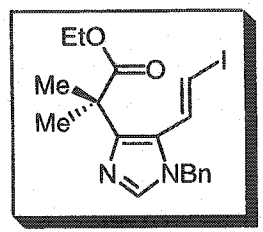


Figure A.1.18 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **133**.



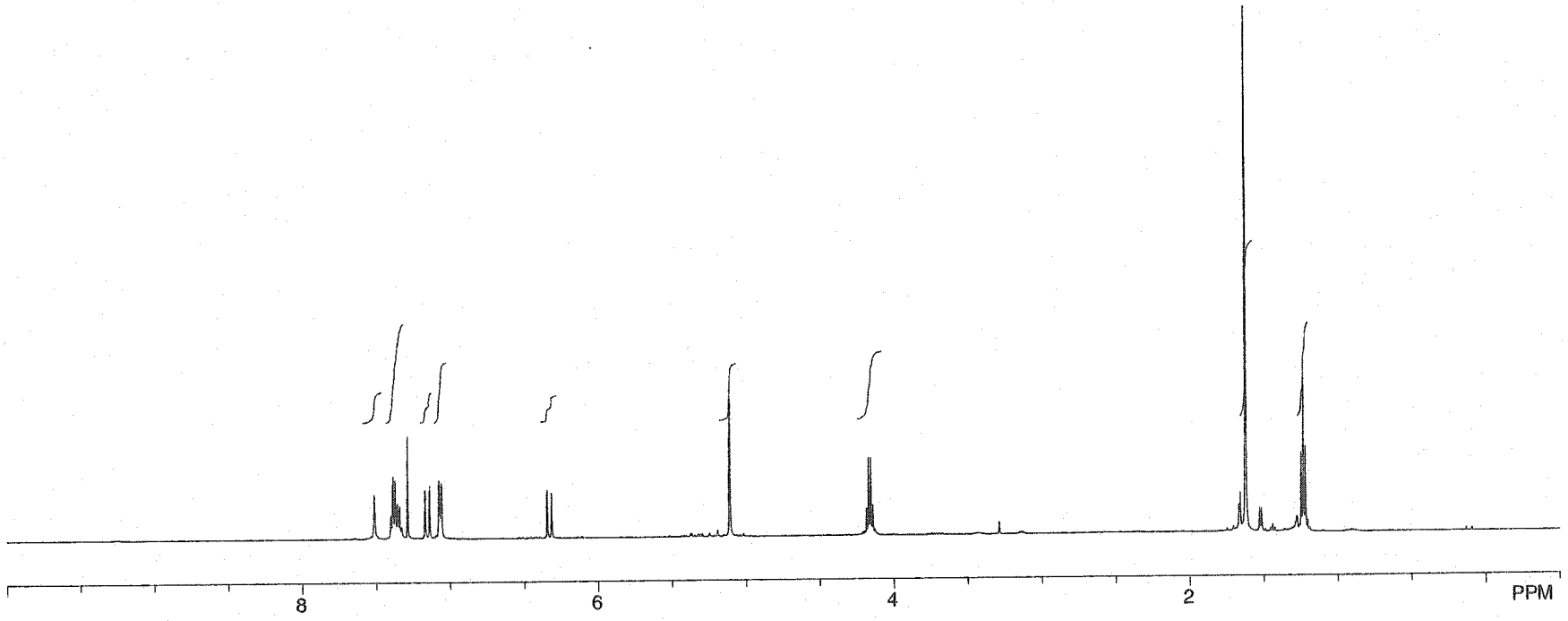


Figure A.1.19 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **134**.

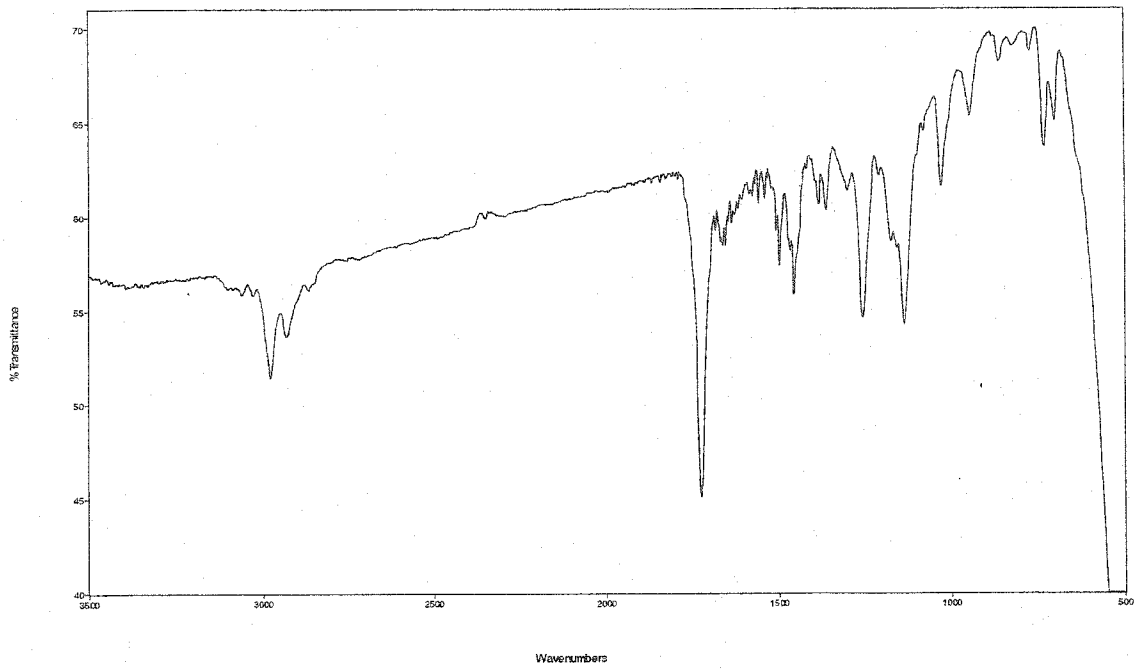


Figure A.1.20 FTIR Spectrum (thin film/NaCl) of Compound **134**.

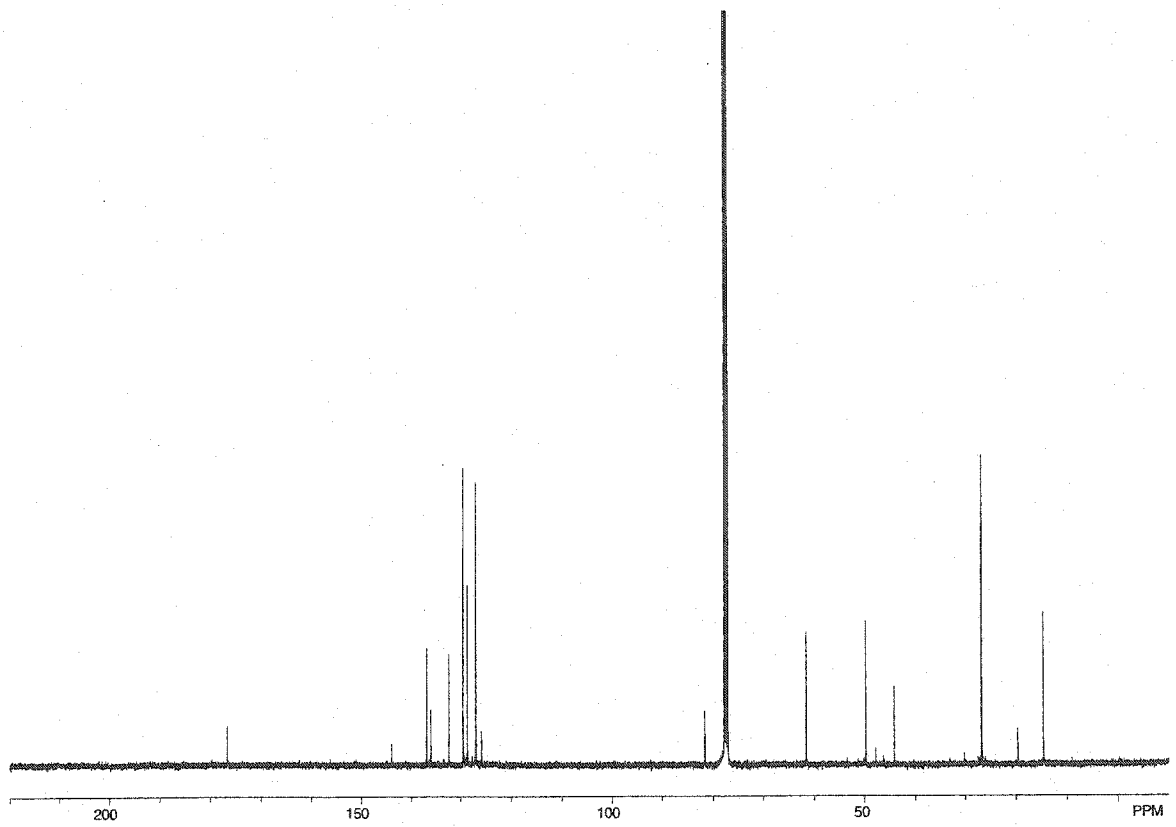
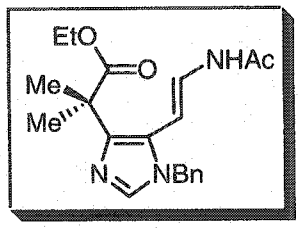


Figure A.1.21 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **134**.



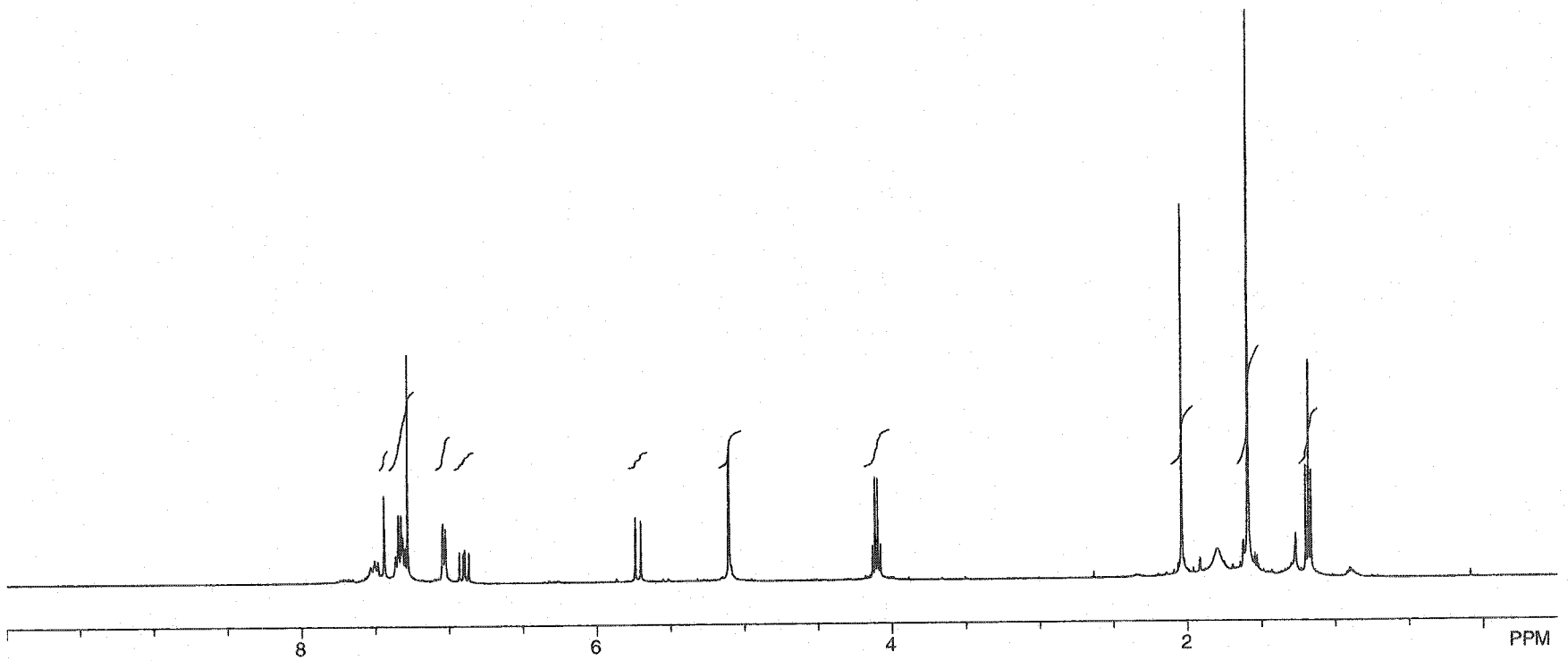


Figure A.1.22 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **135**.

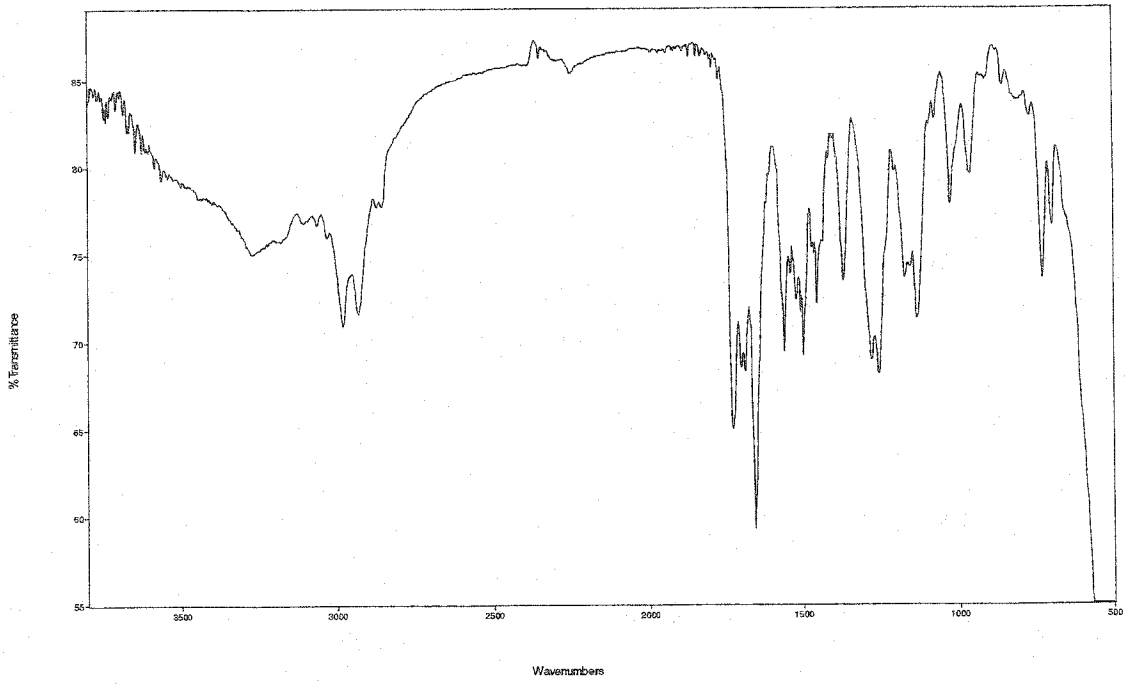


Figure A.1.23 FTIR Spectrum (thin film/NaCl) of Compound **135**.

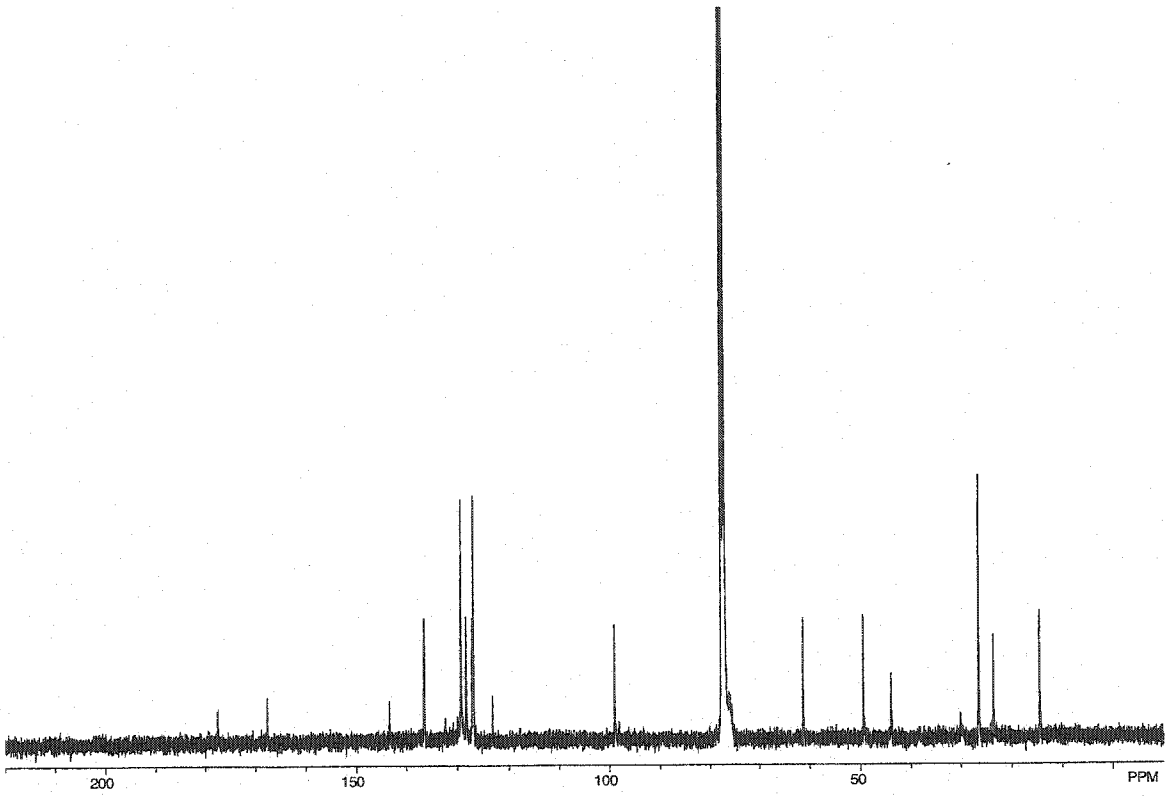


Figure A.1.24 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **135**.

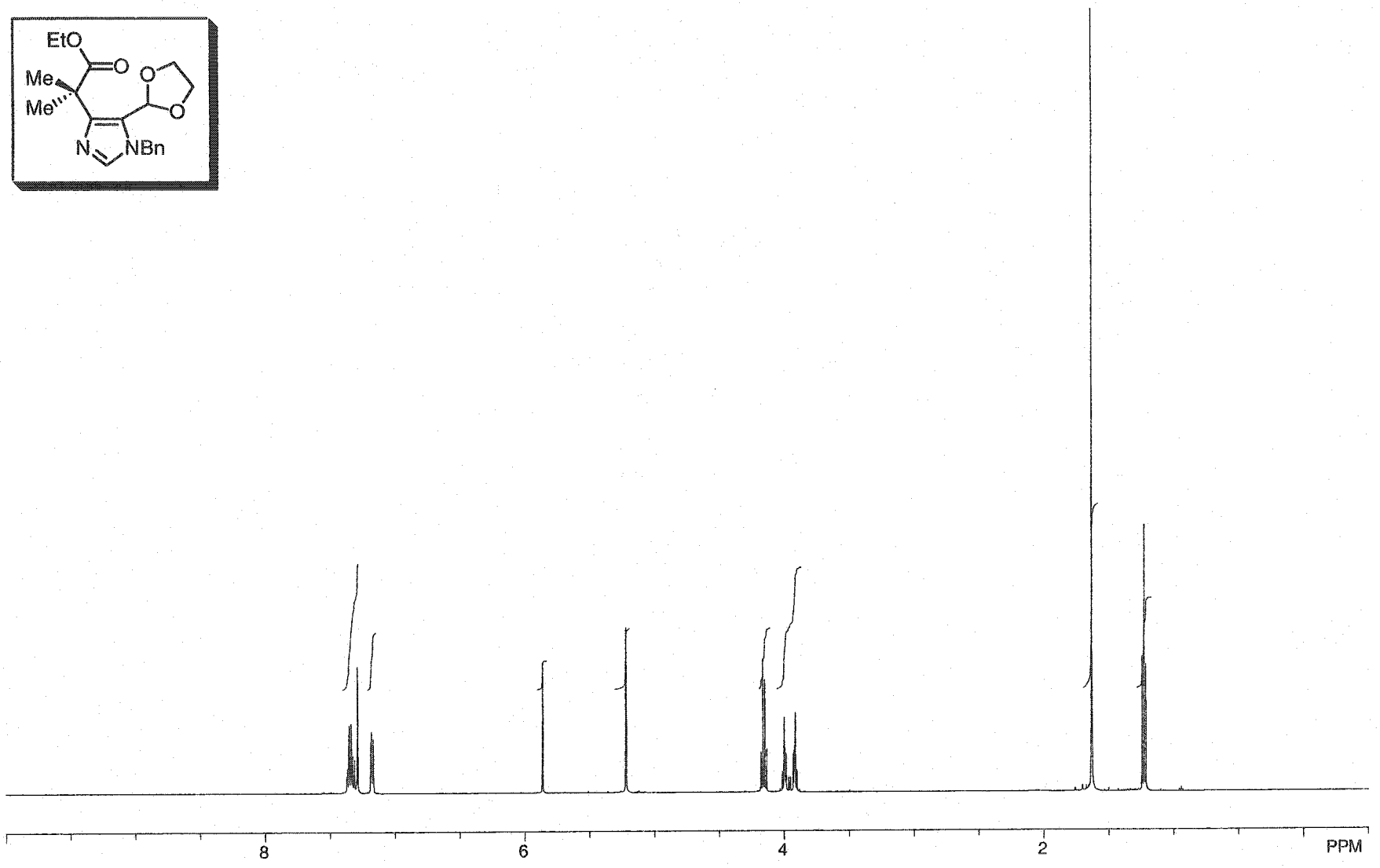


Figure A.1.25 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **139**.

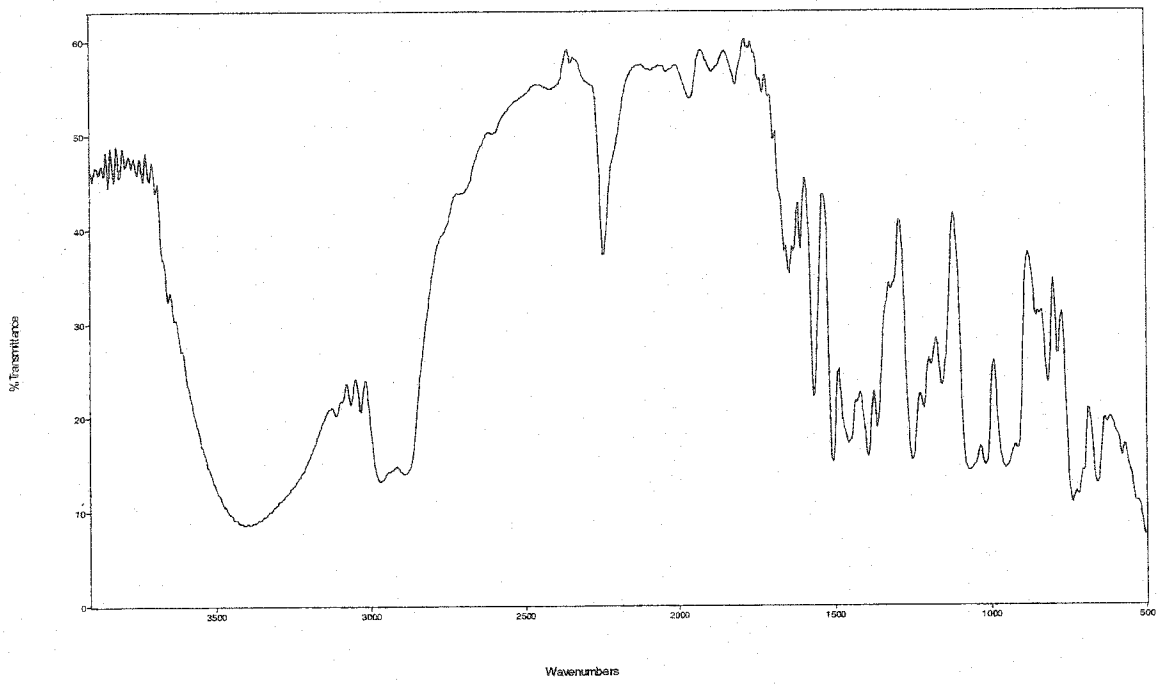


Figure A.1.26 FTIR Spectrum (thin film/NaCl) of Compound **139**.

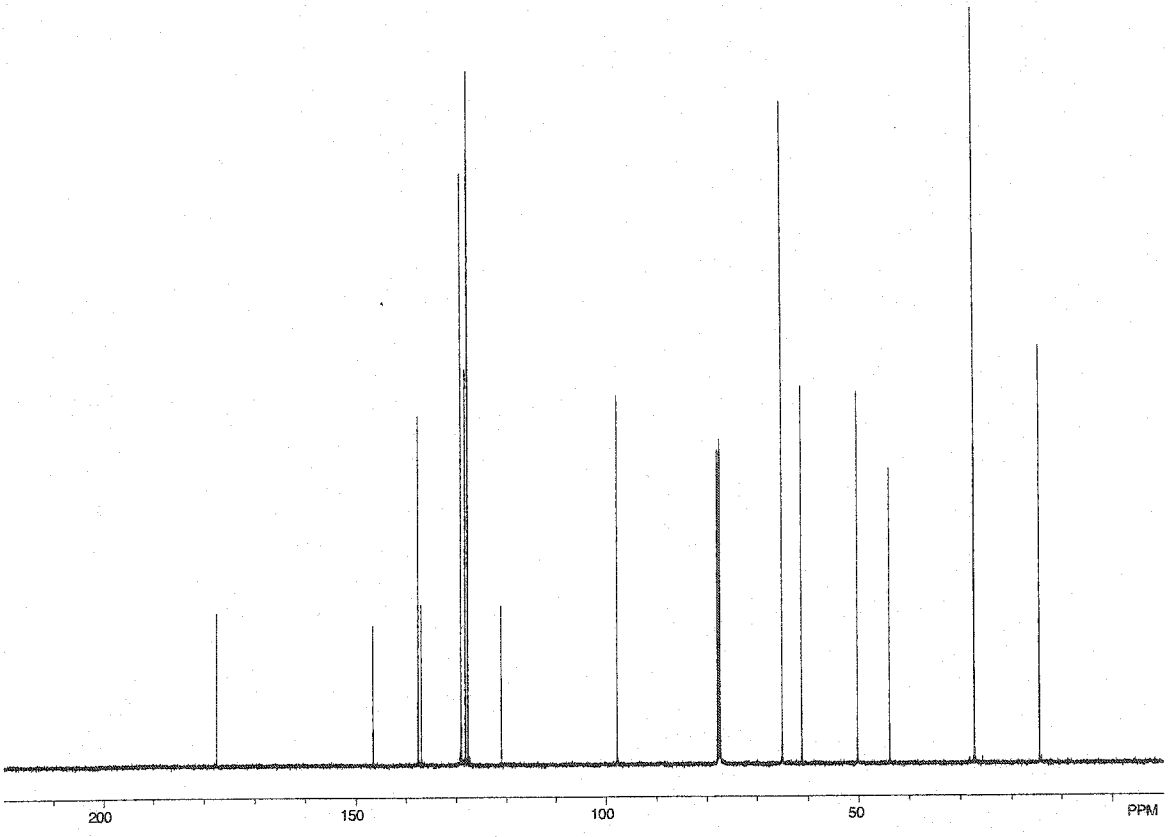


Figure A.1.27 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **139**.

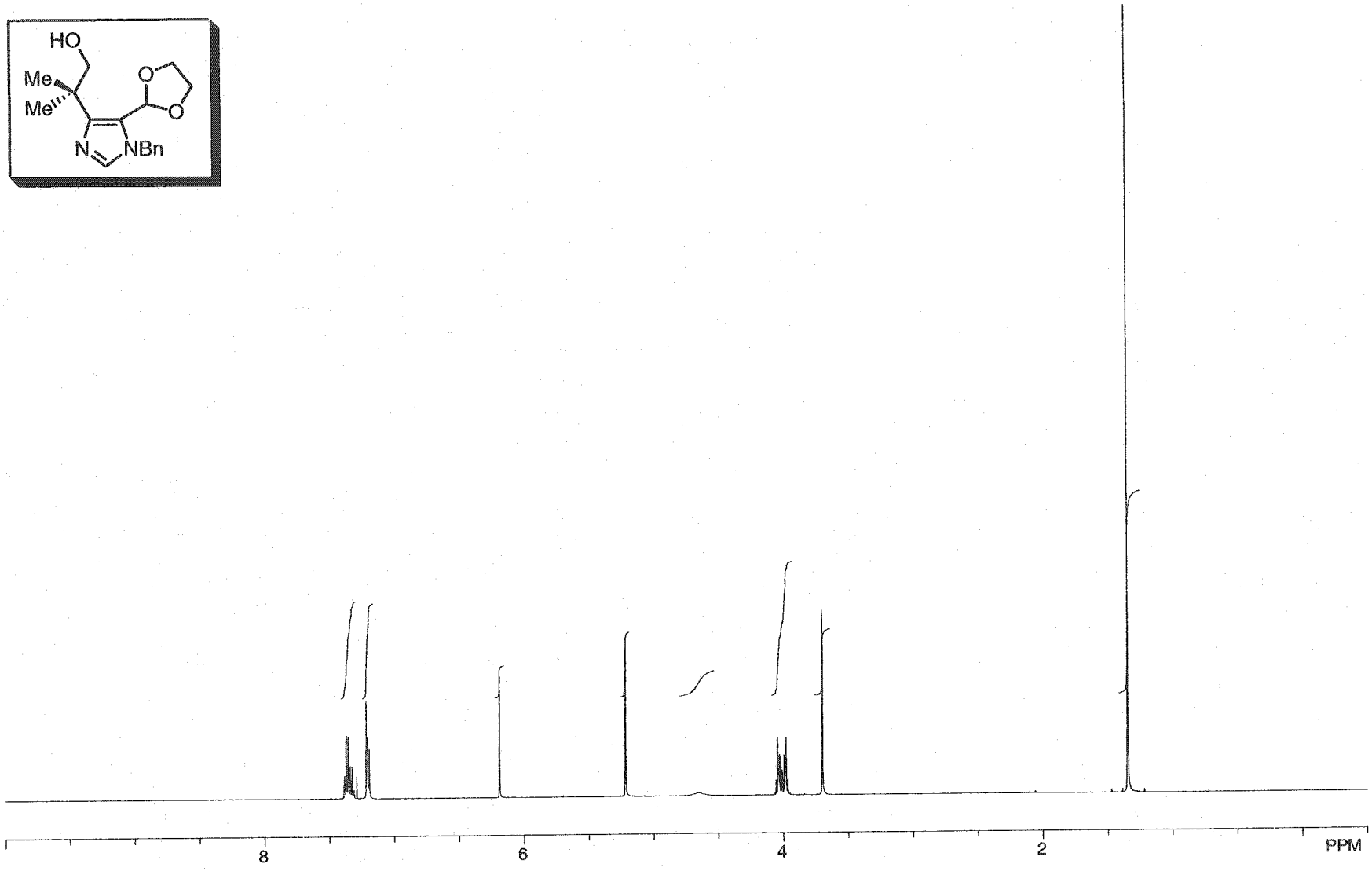


Figure A.1.28 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **140**.

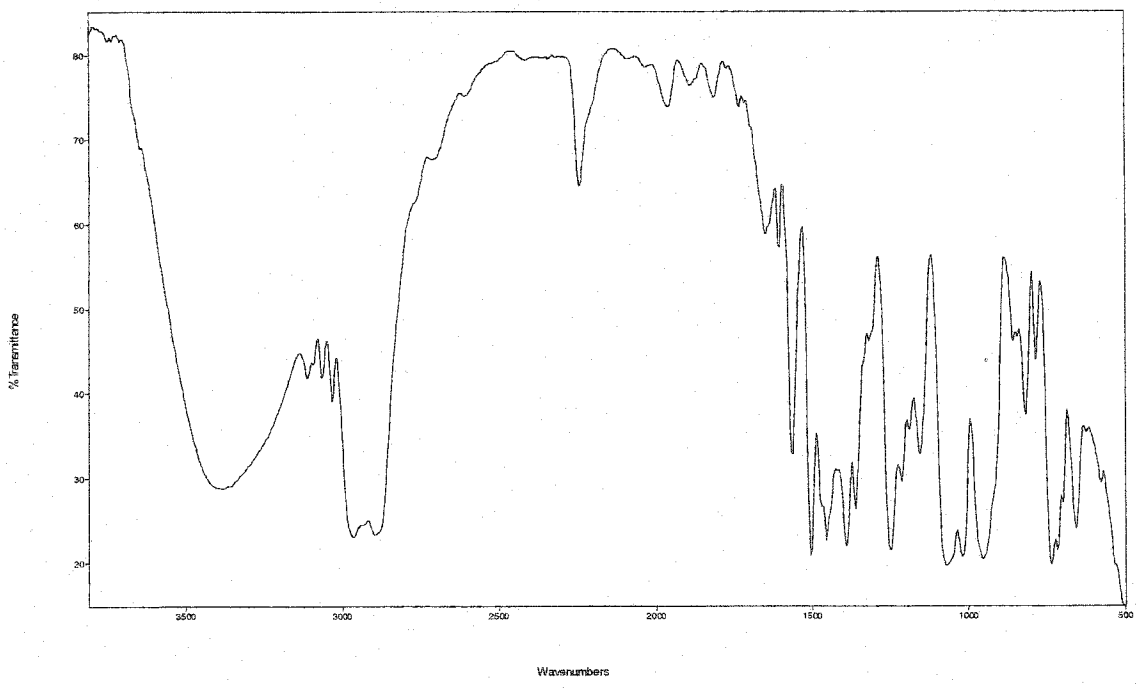


Figure A.1.29 FTIR Spectrum (thin film/NaCl) of Compound **140**.

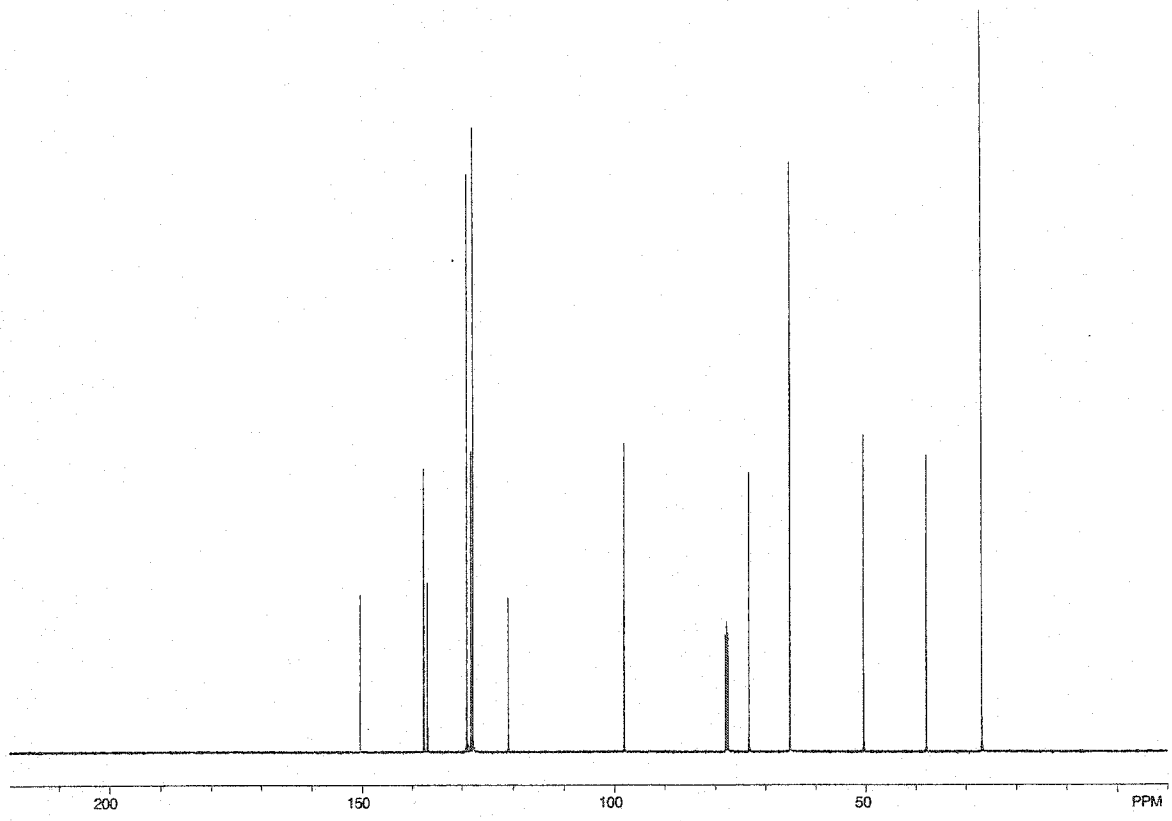


Figure A.1.30 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **140**.

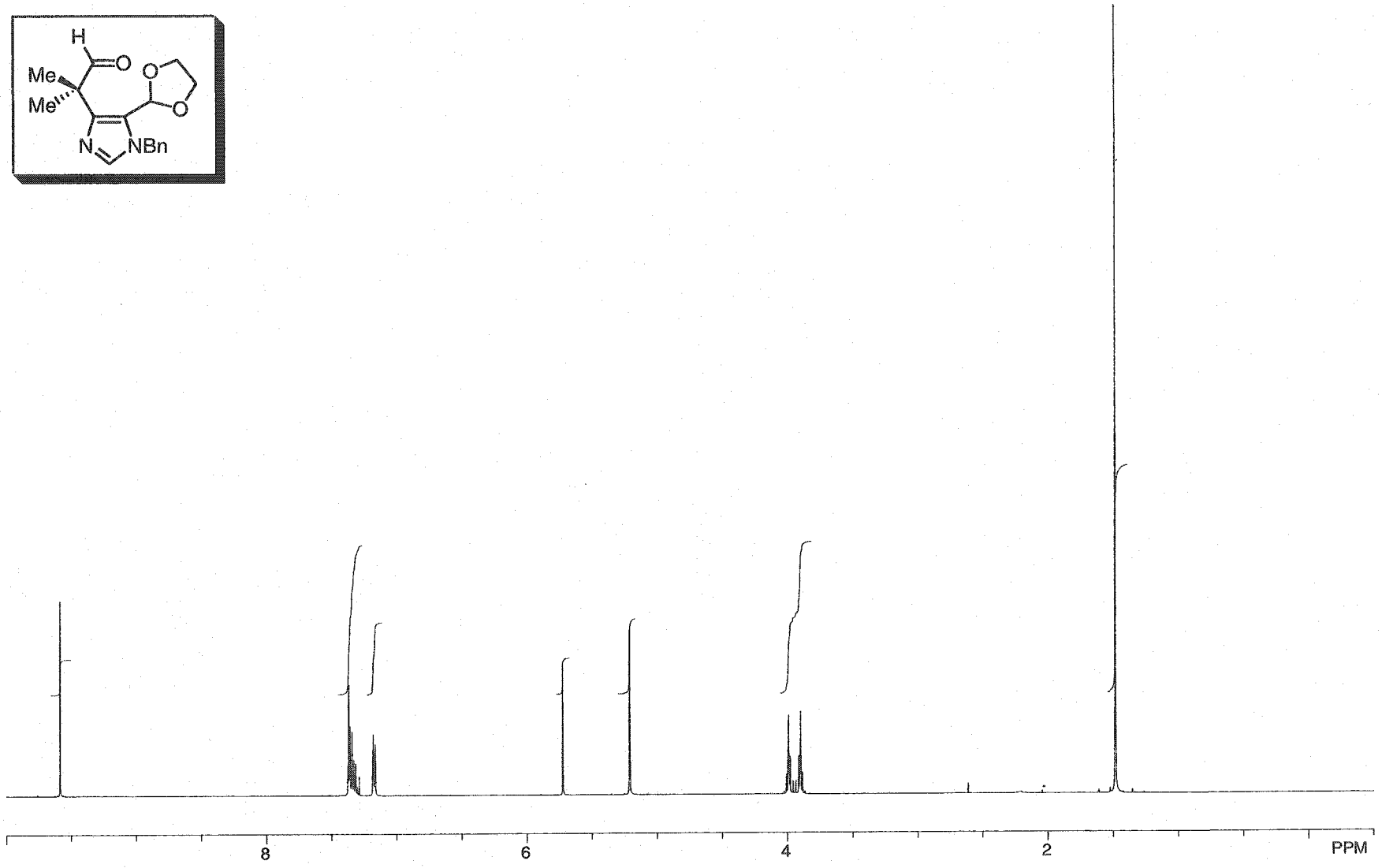


Figure A.1.31 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **141**.

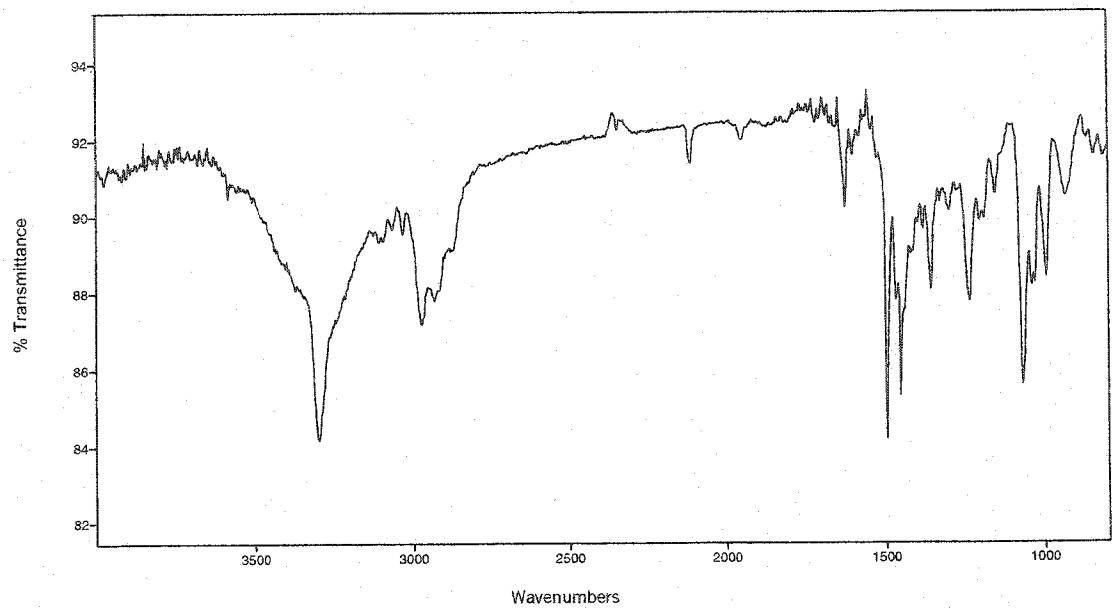


Figure A.1.32 FTIR Spectrum (thin film/NaCl) of Compound **141**.

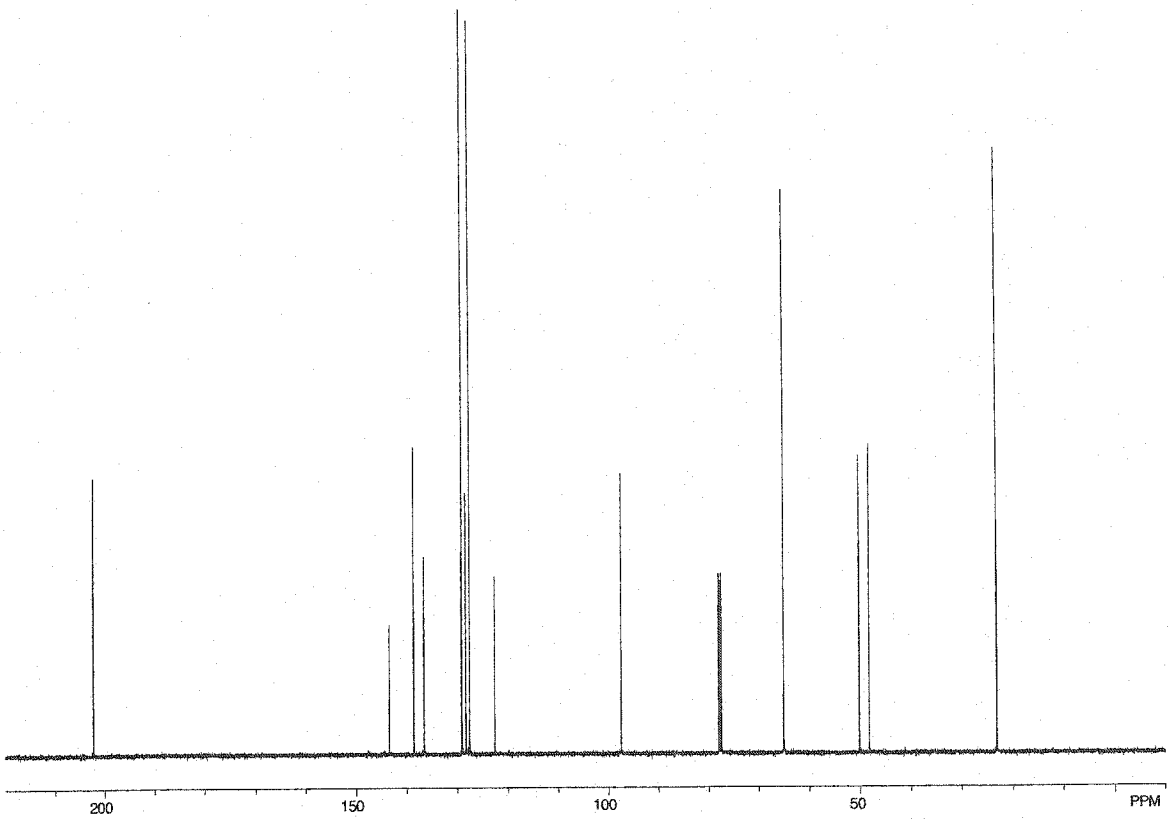


Figure A.1.33 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **141**.

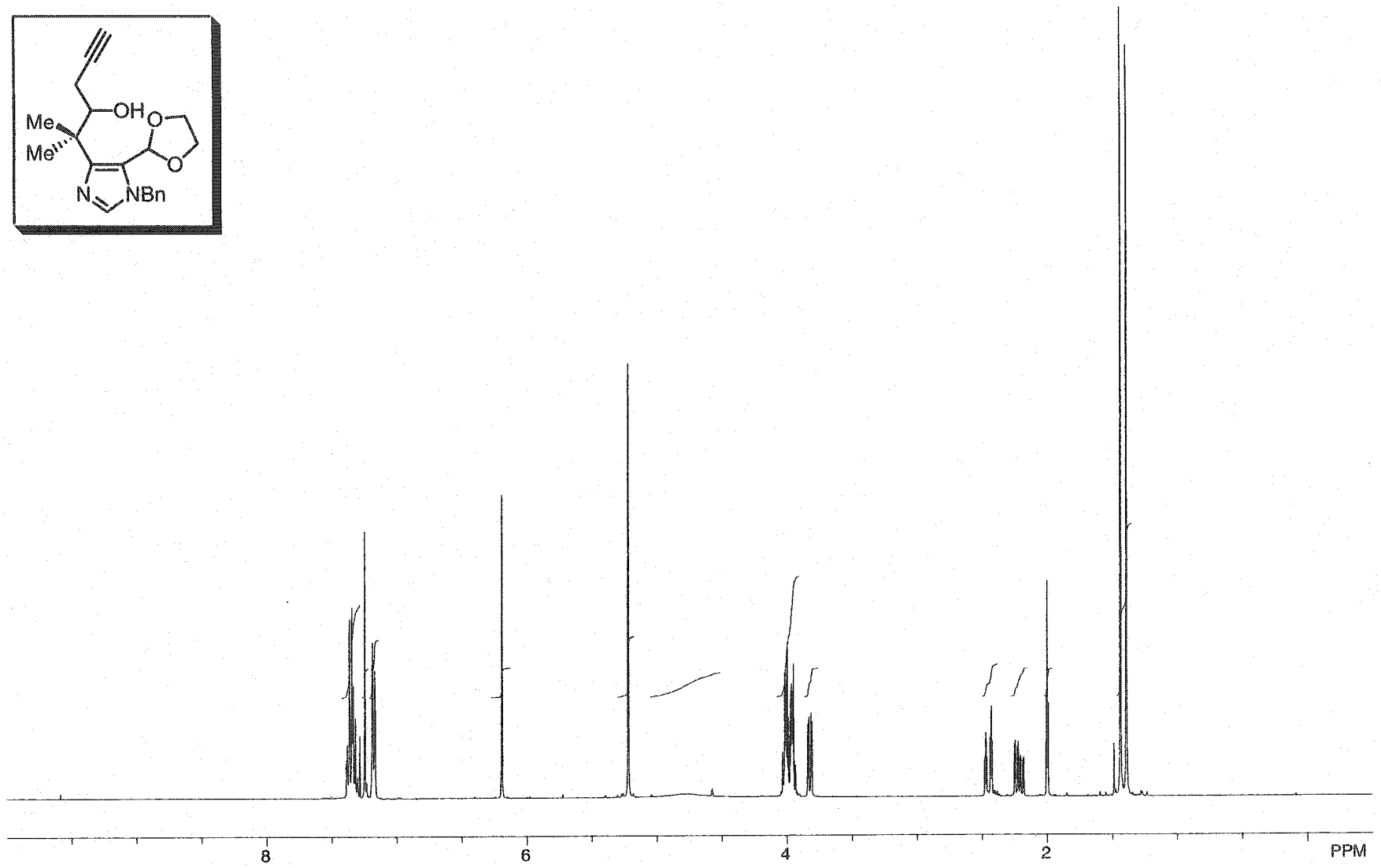


Figure A.1.34 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **142**.

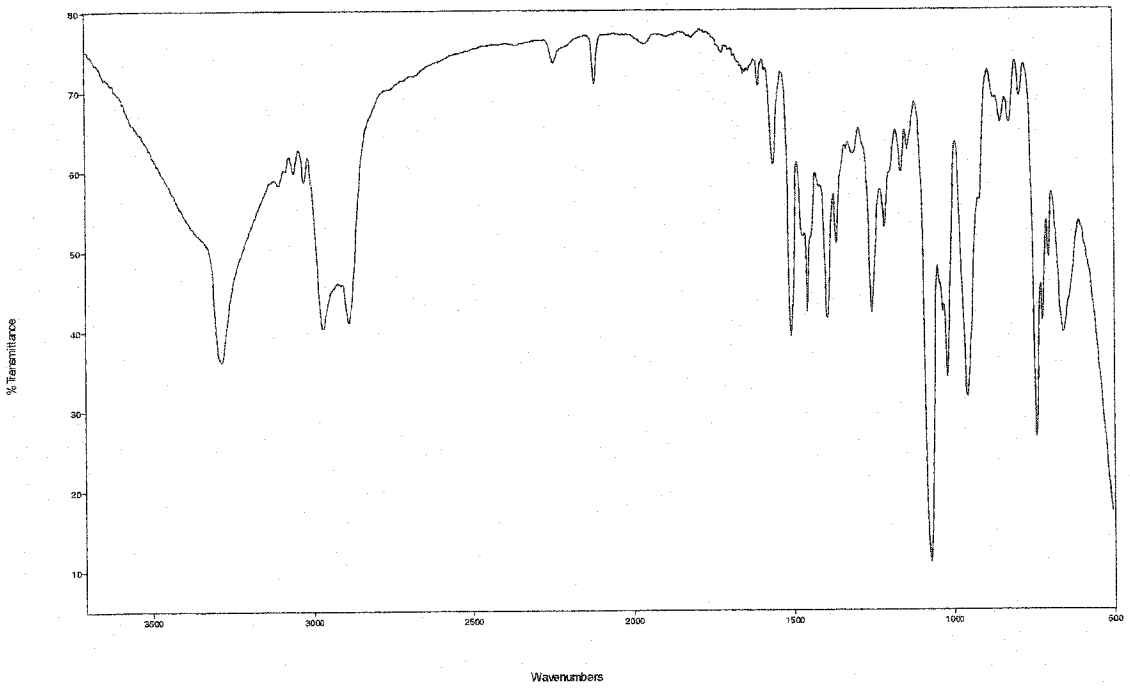


Figure A.1.35 FTIR Spectrum (thin film/NaCl) of Compound **142**.

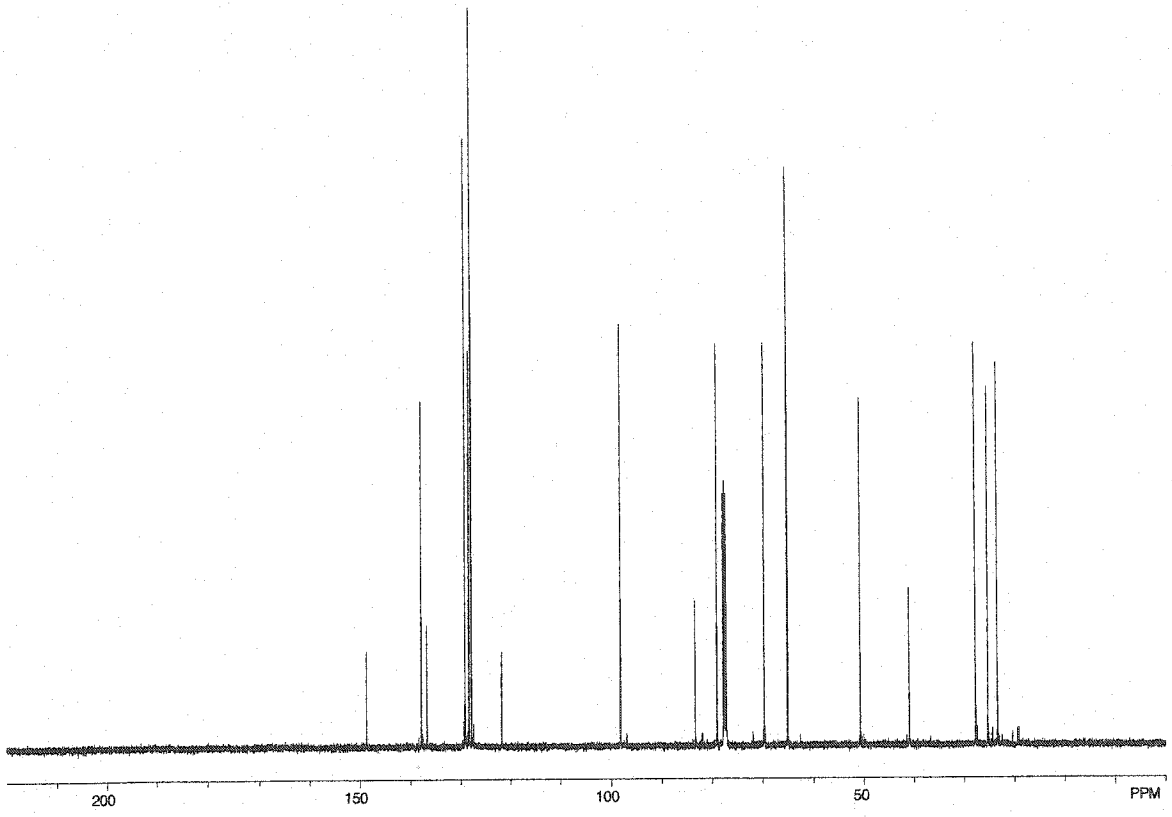


Figure A.1.36 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **142**.

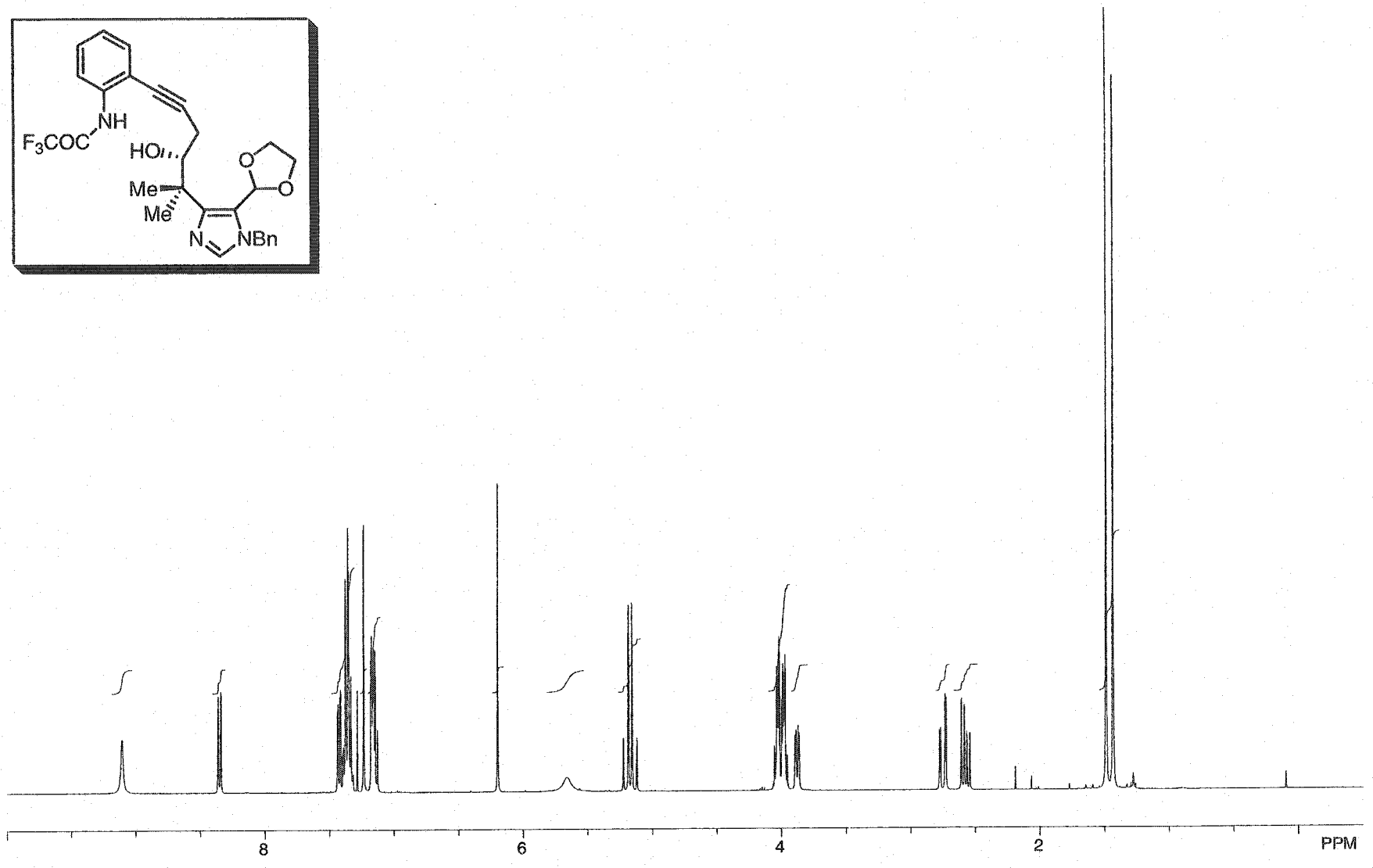


Figure A.1.37 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **143**.

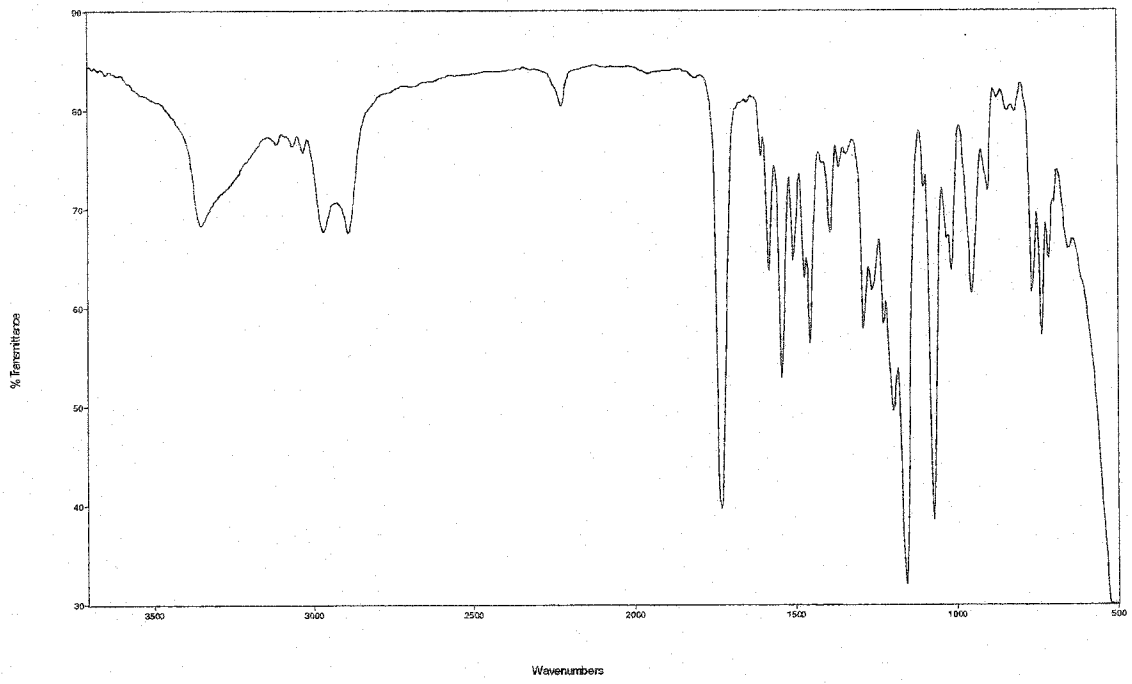


Figure A.1.38 FTIR Spectrum (thin film/NaCl) of Compound **143**.

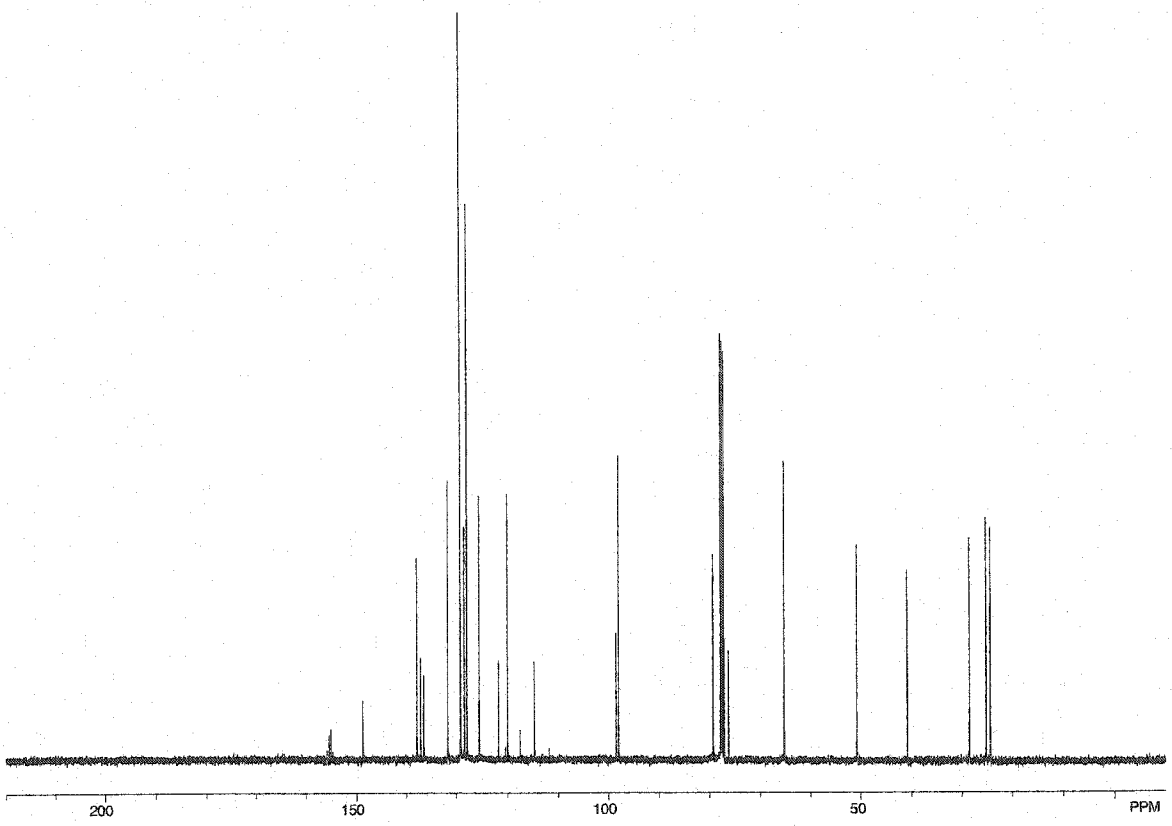


Figure A.1.39 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **143**.

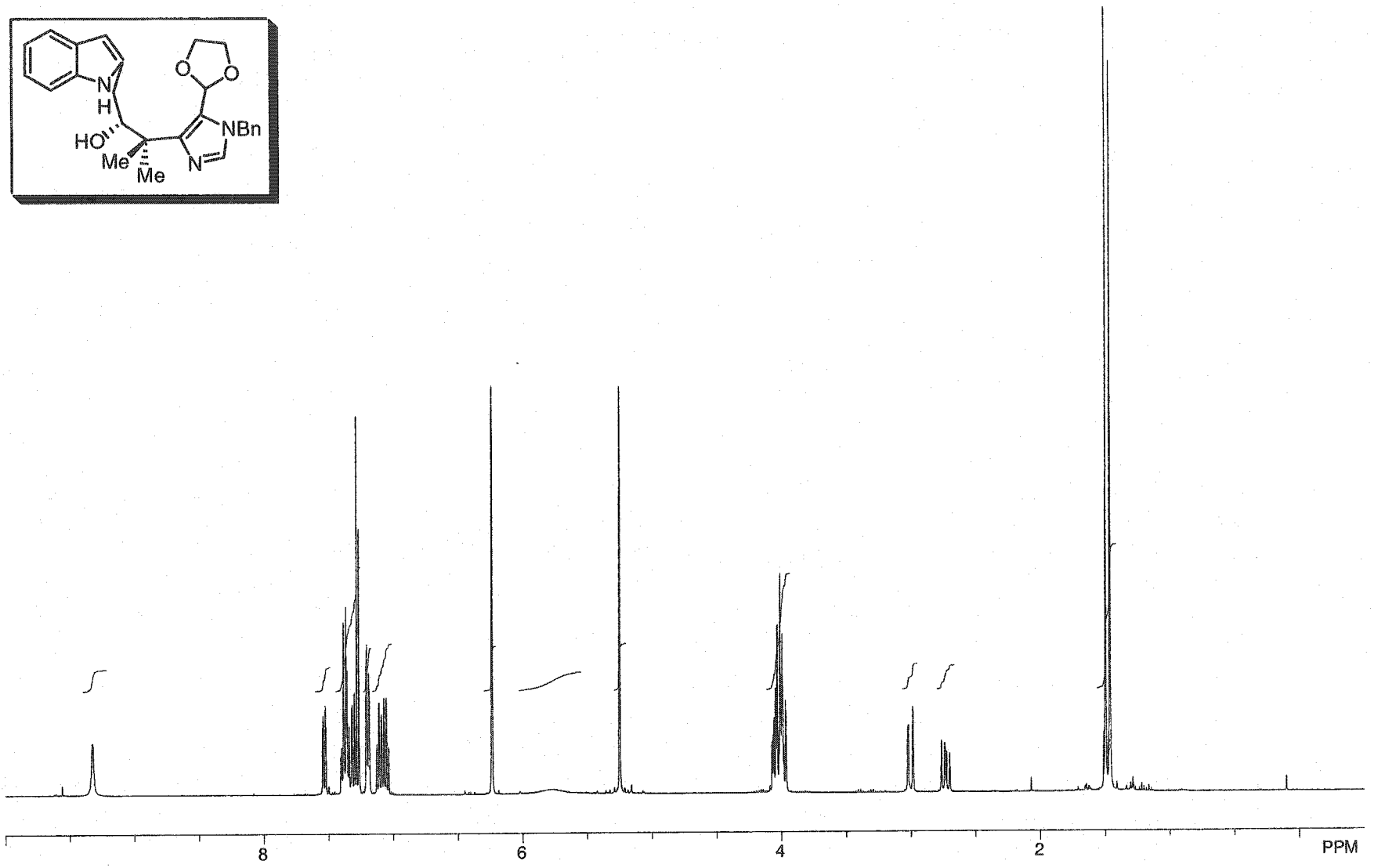


Figure A.1.40 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **144**.

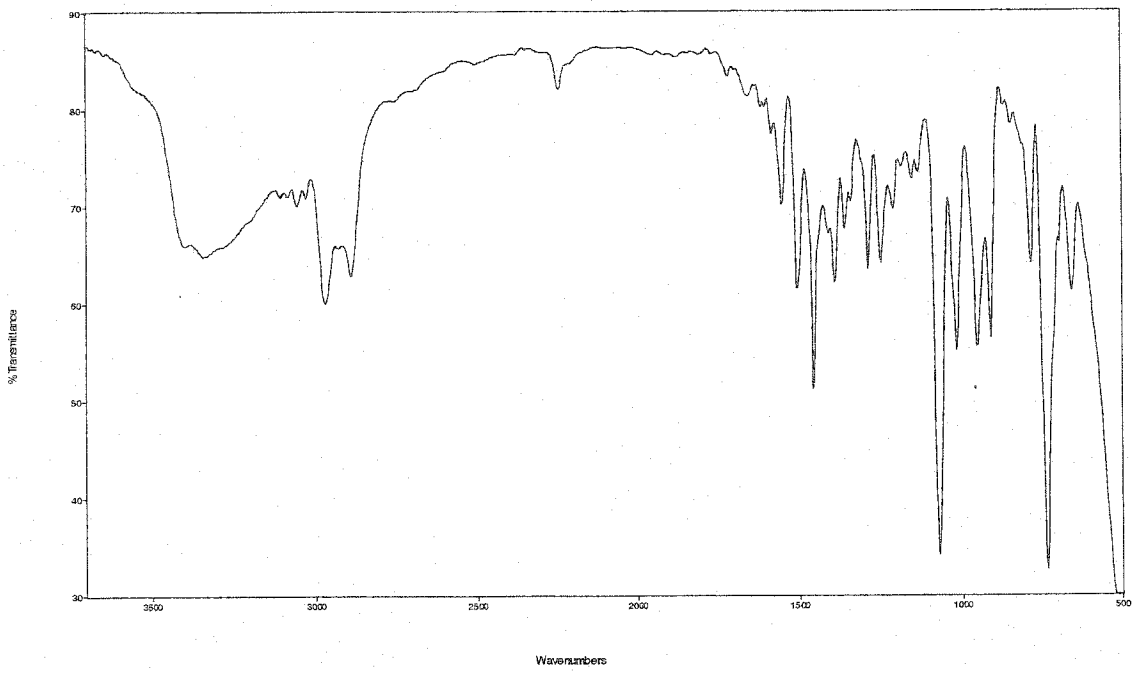


Figure A.1.41 FTIR Spectrum (thin film/NaCl) of Compound **144**.

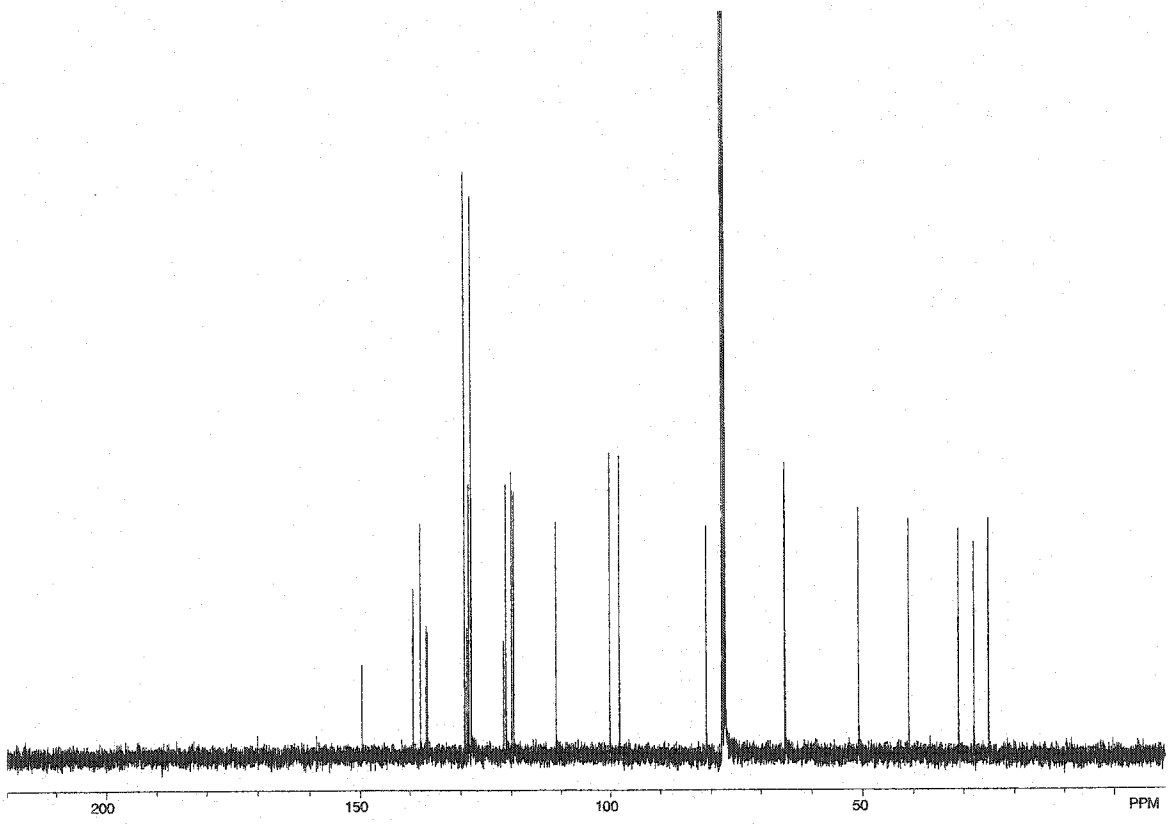
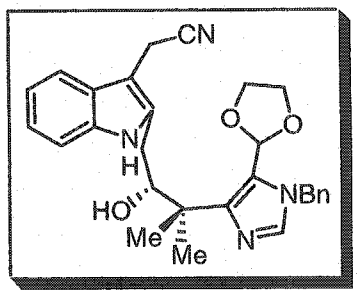


Figure A.1.42 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **144**.



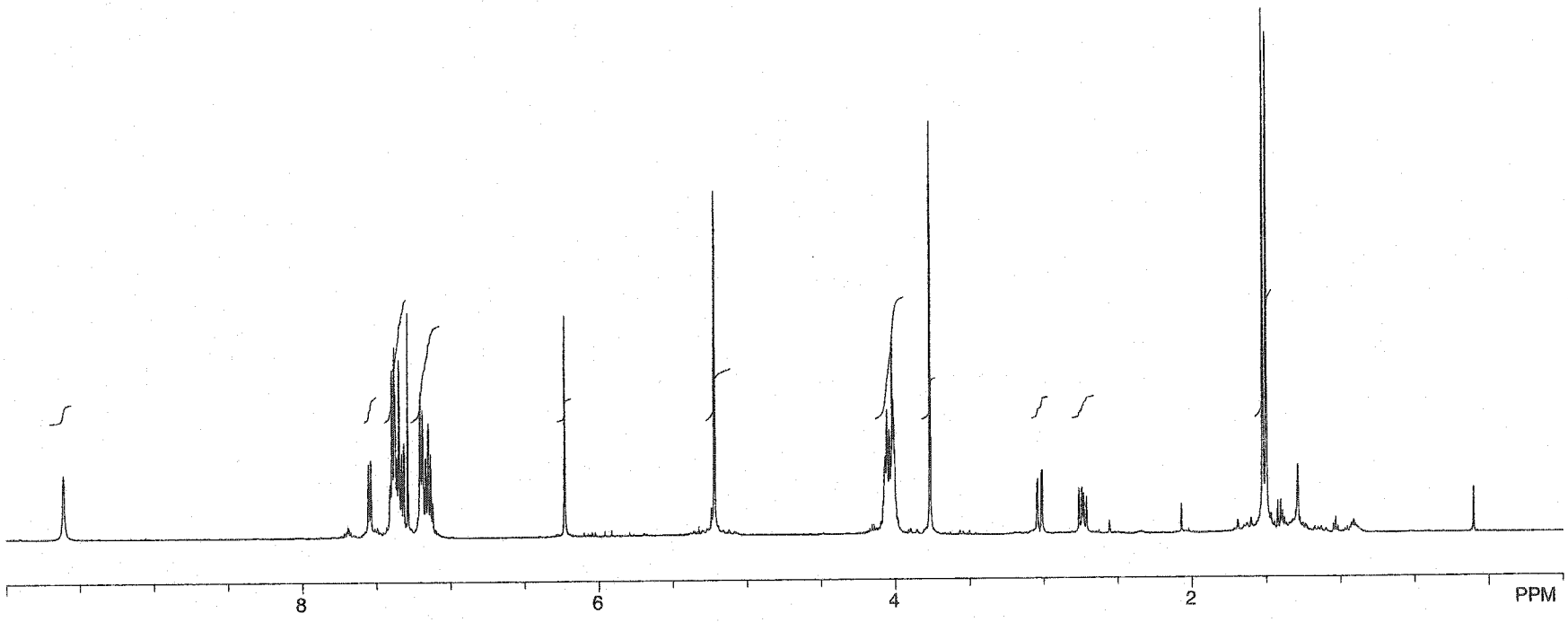


Figure A.1.43 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **145**.

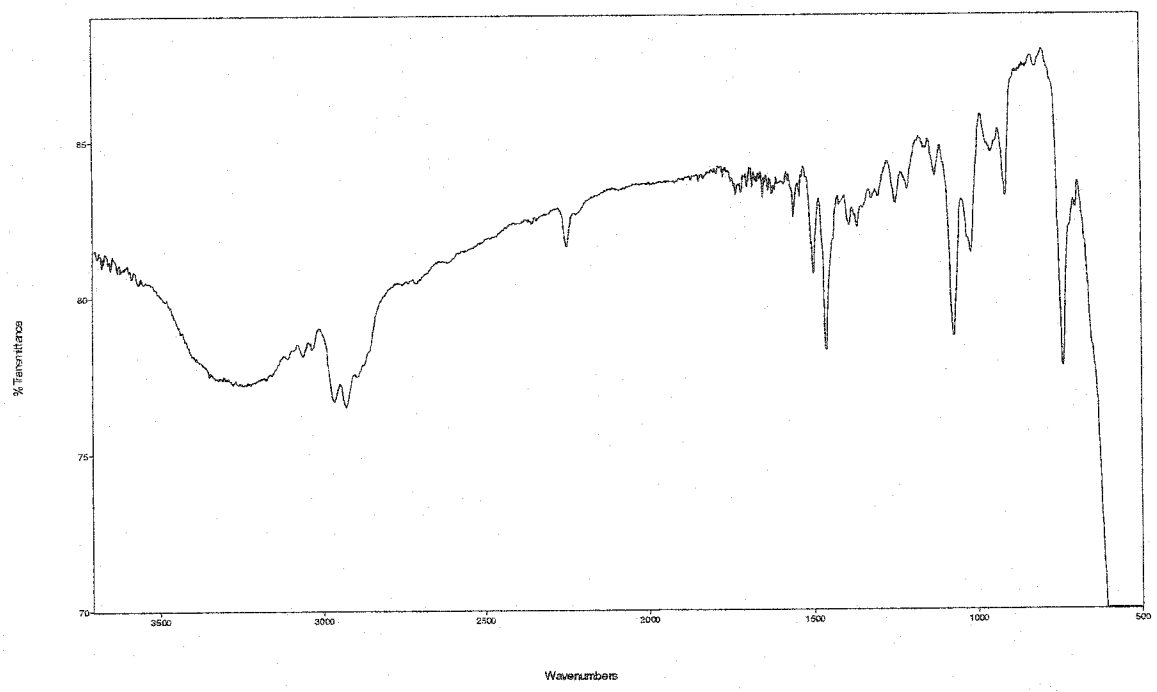


Figure A.1.44 FTIR Spectrum (thin film/NaCl) of Compound **145**.

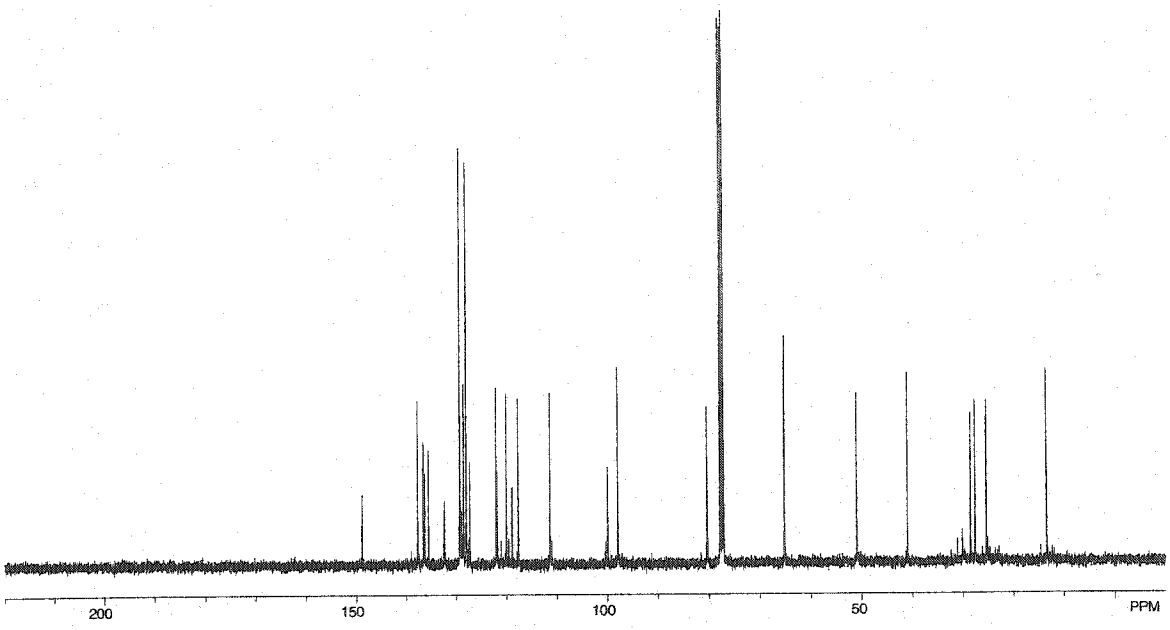
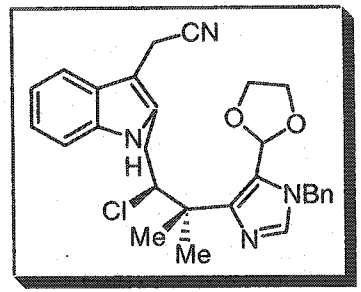


Figure A.1.45 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **145**.



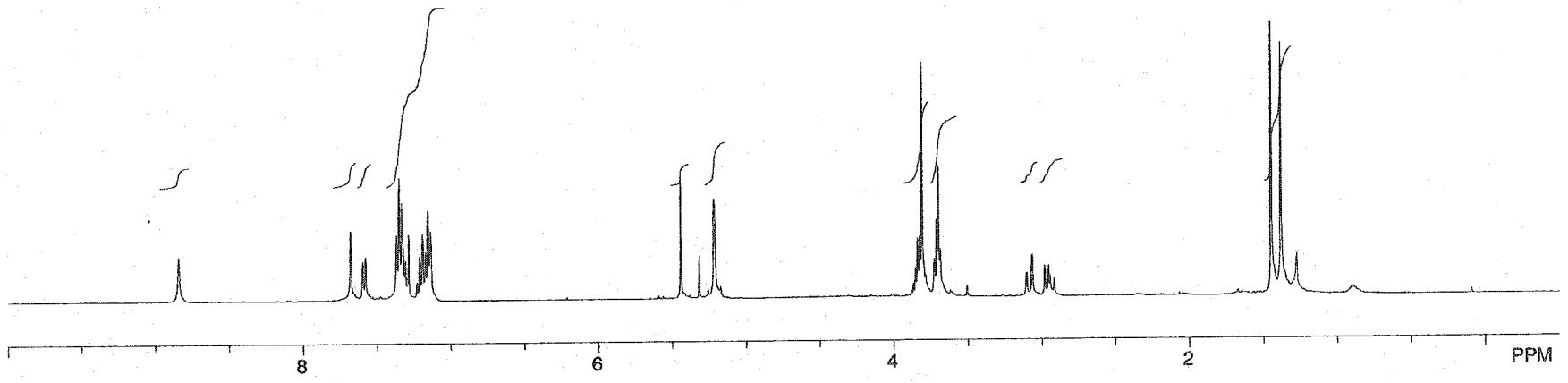


Figure A.1.46 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **146**.

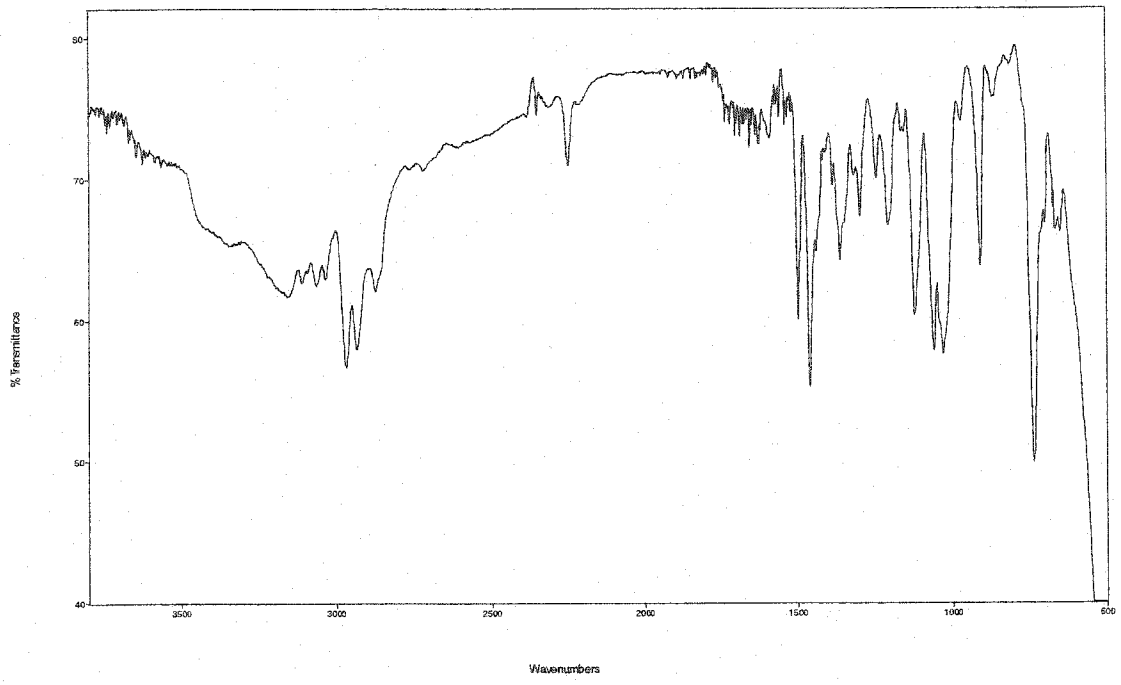


Figure A.1.47 FTIR Spectrum (thin film/NaCl) of Compound **146**.

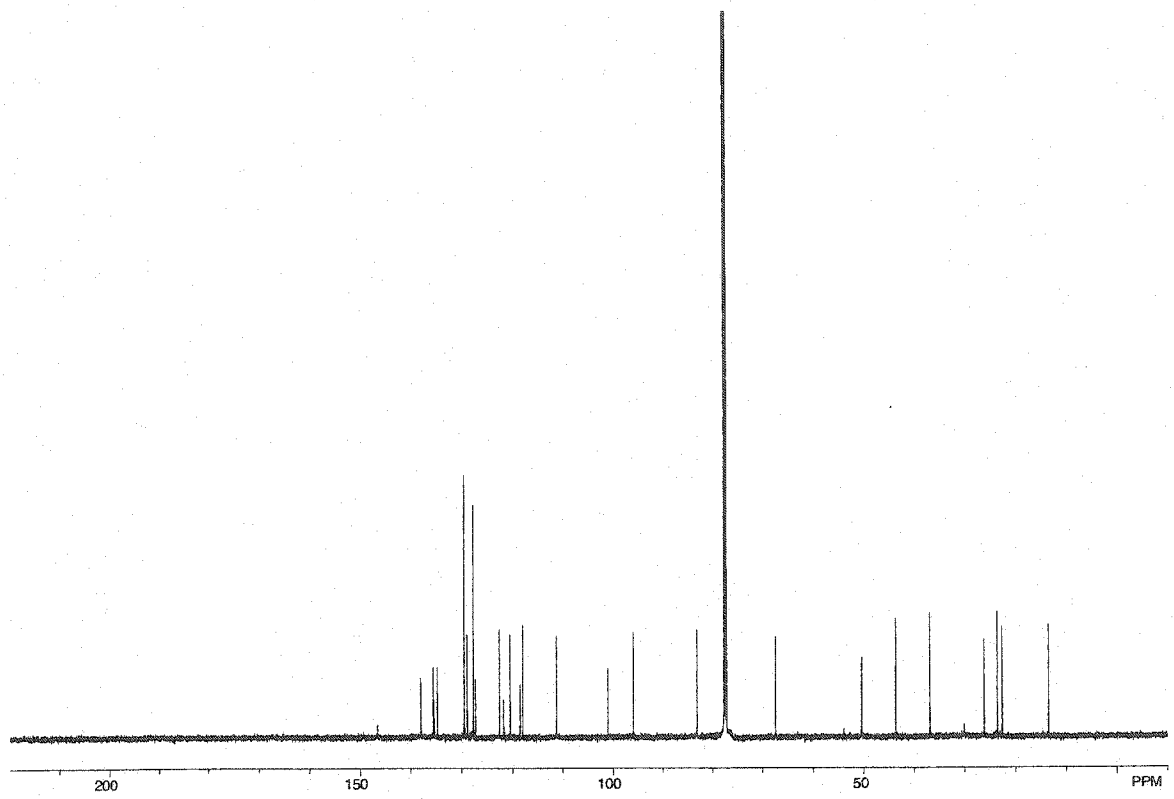


Figure A.1.48 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **146**.

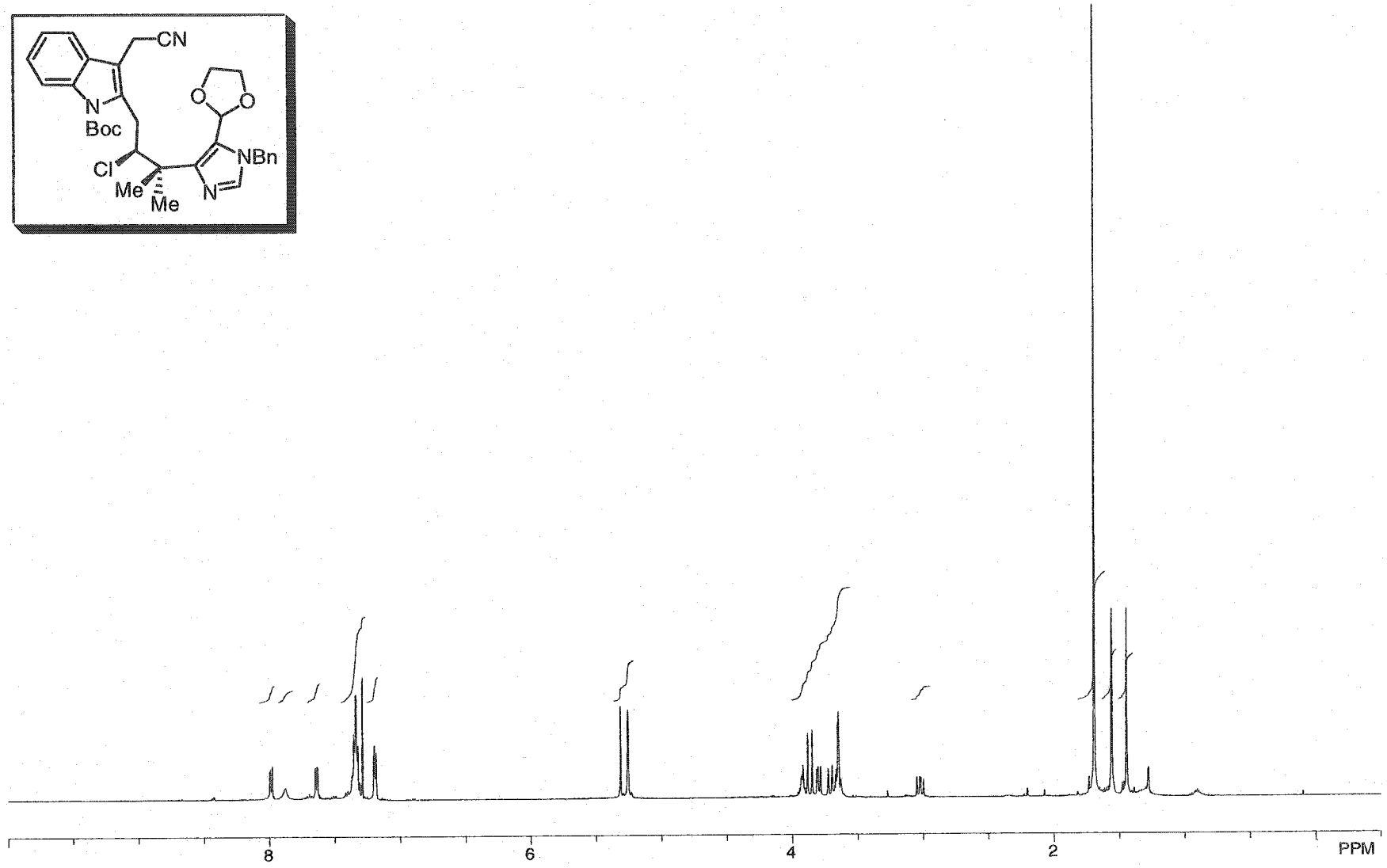


Figure A.1.49 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **147**.

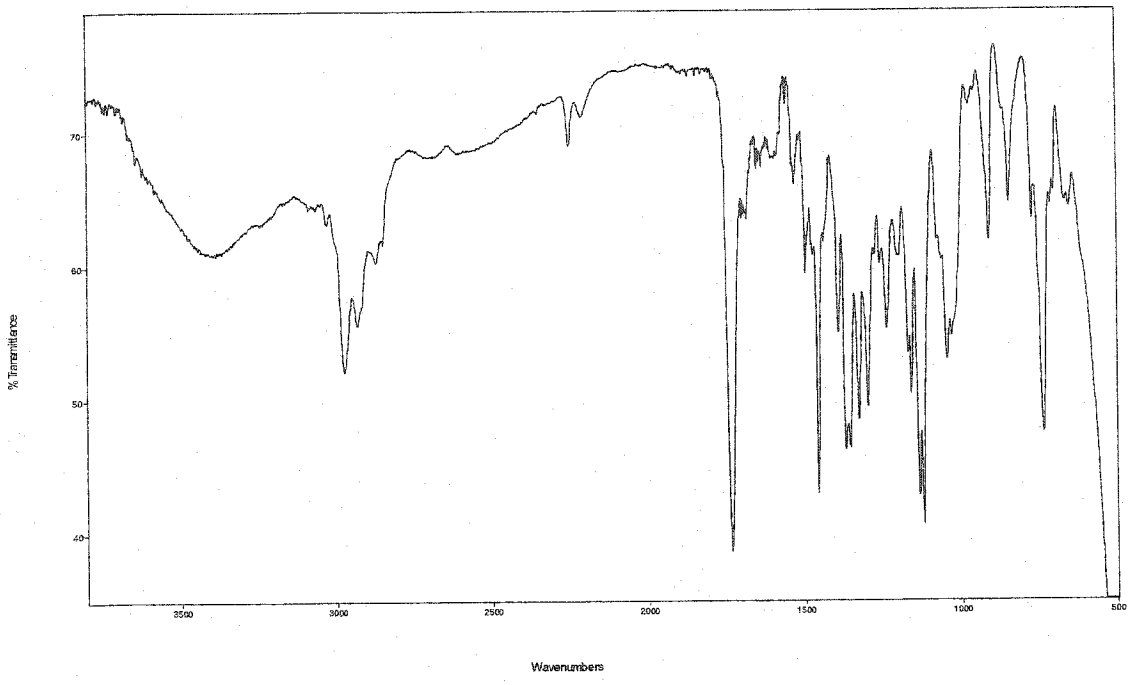


Figure A.1.50 FTIR Spectrum (thin film/NaCl) of Compound **147**.

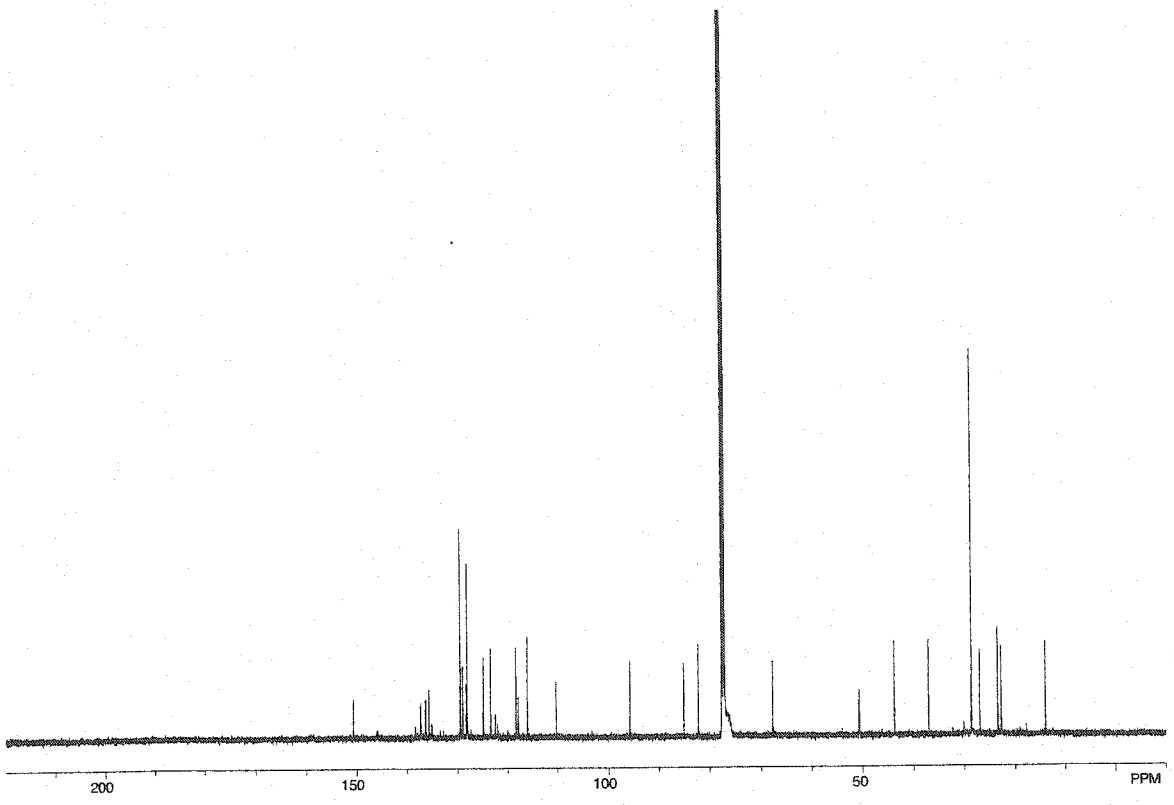


Figure A.1.51 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **147**.

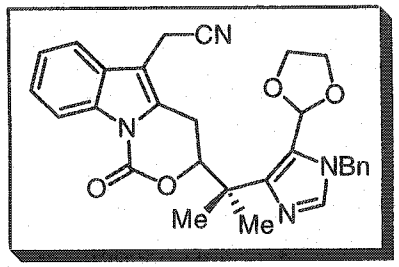


Figure A.1.52 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **149**.

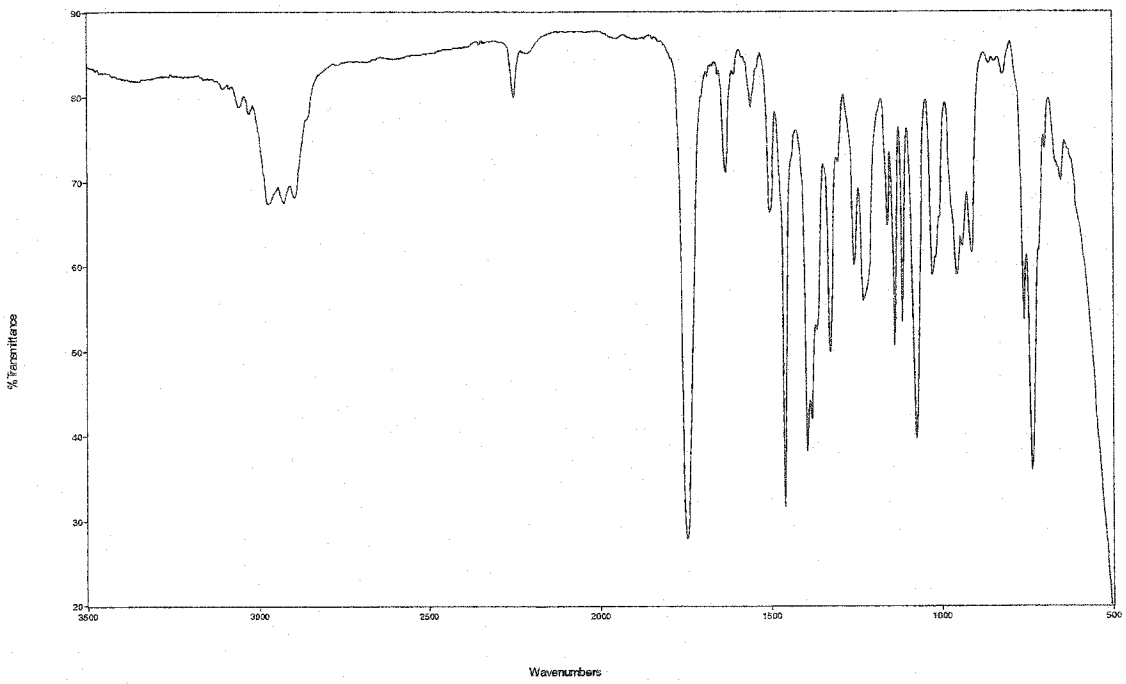


Figure A.1.53 FTIR Spectrum (thin film/NaCl) of Compound **149**.

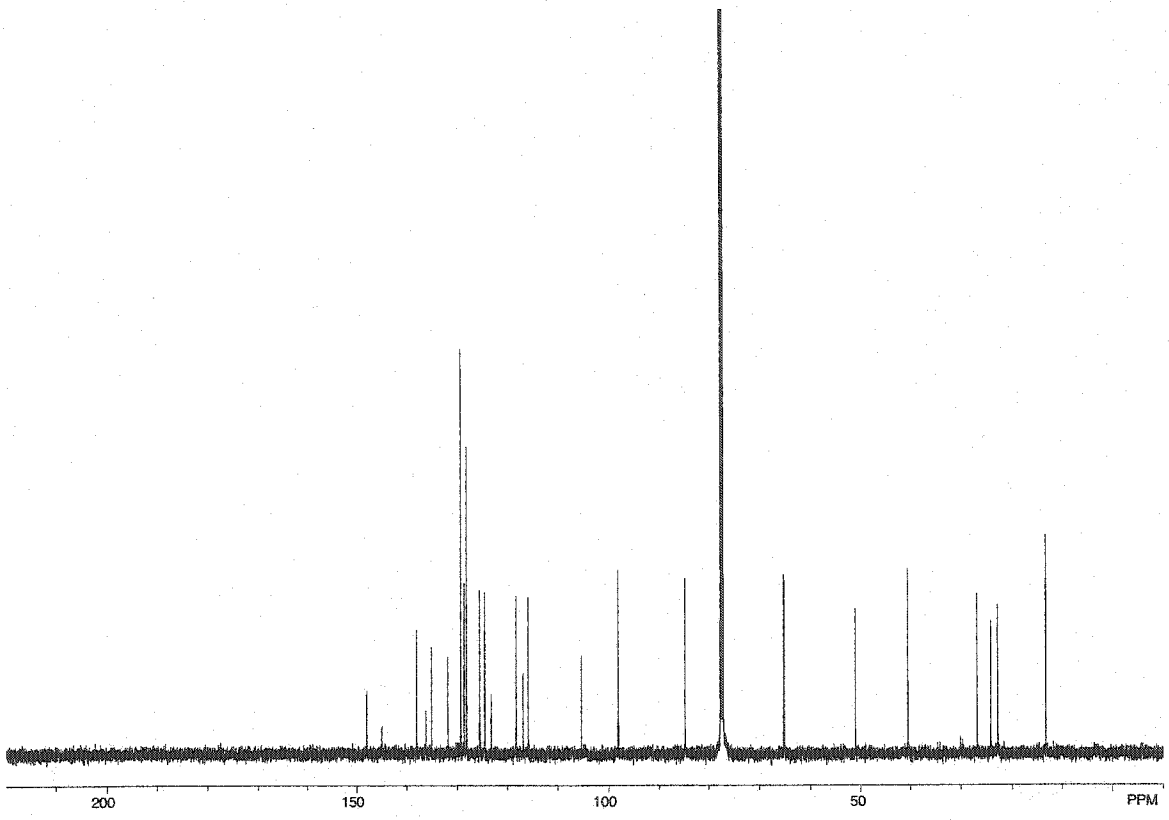


Figure A.1.54 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **149**.

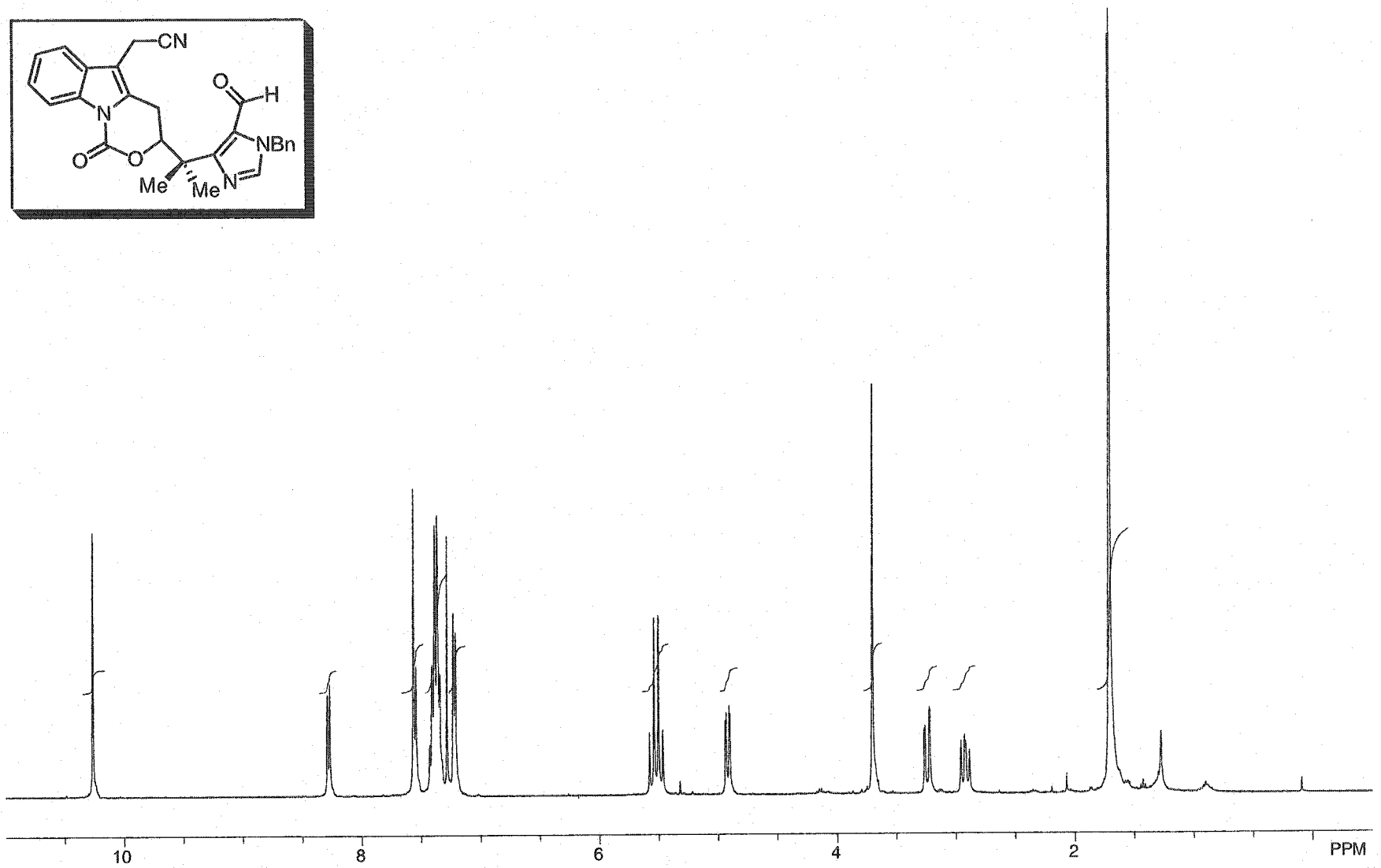


Figure A.1.55 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **150**.

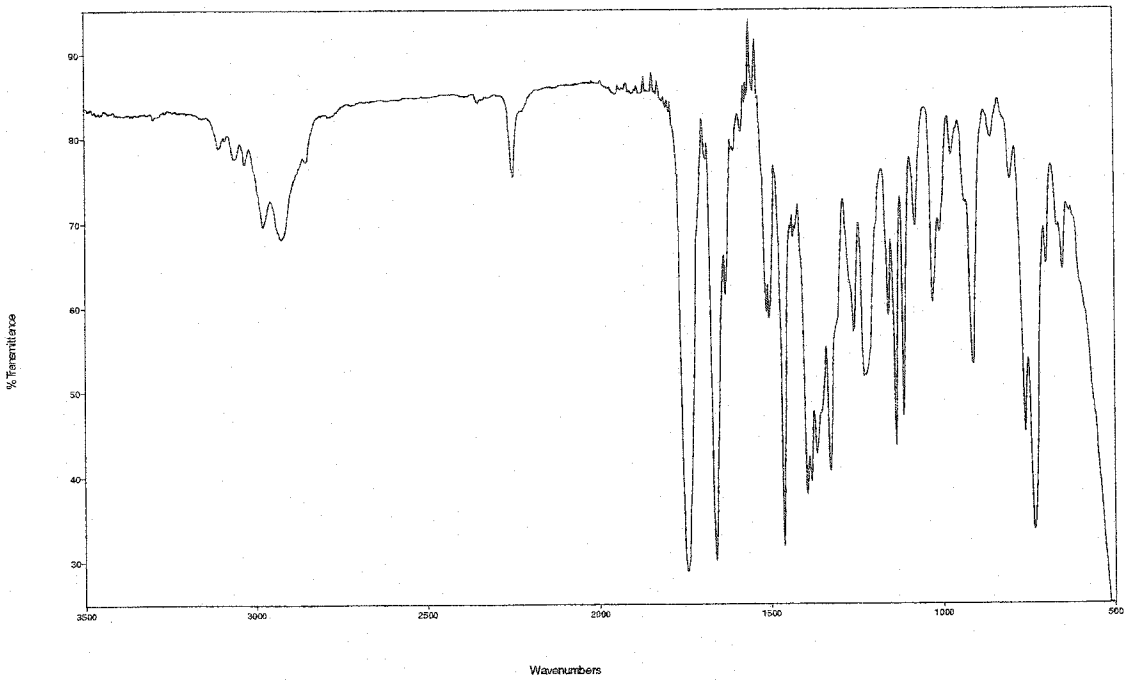


Figure A.1.56 FTIR Spectrum (thin film/NaCl) of Compound **150**.

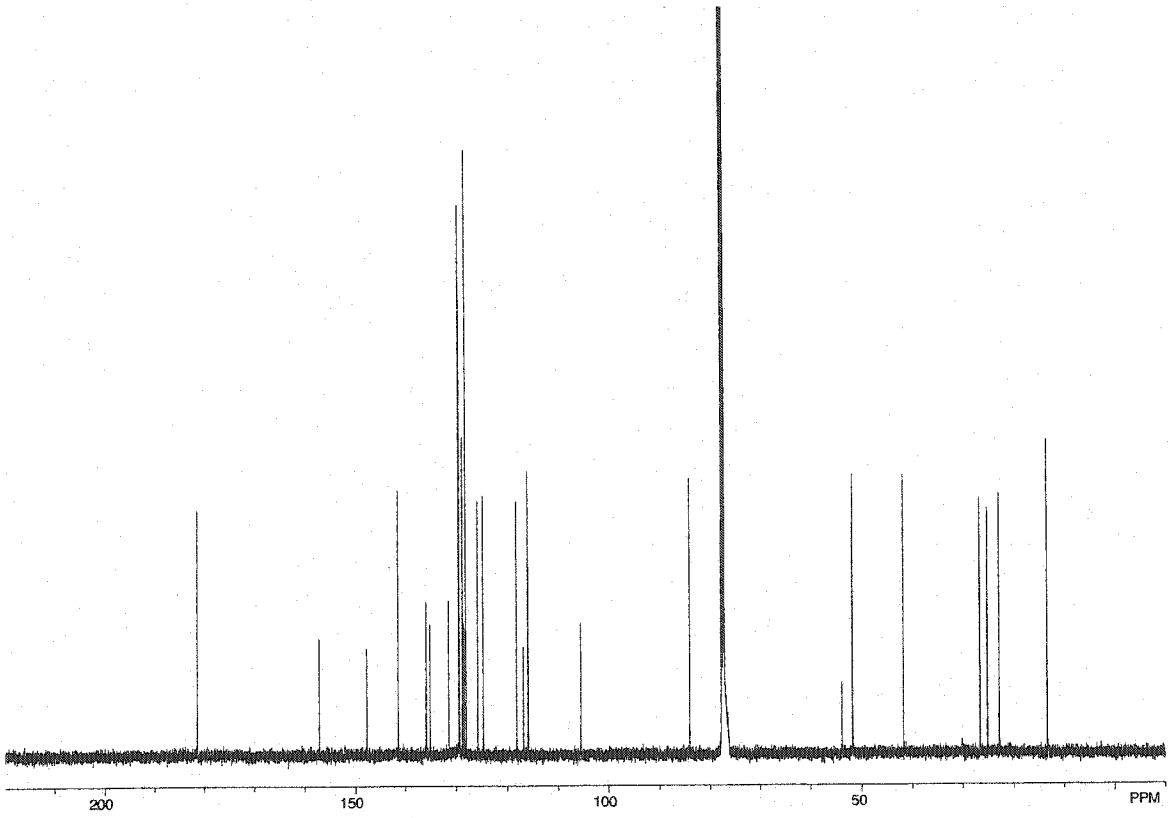


Figure A.1.57 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **150**.

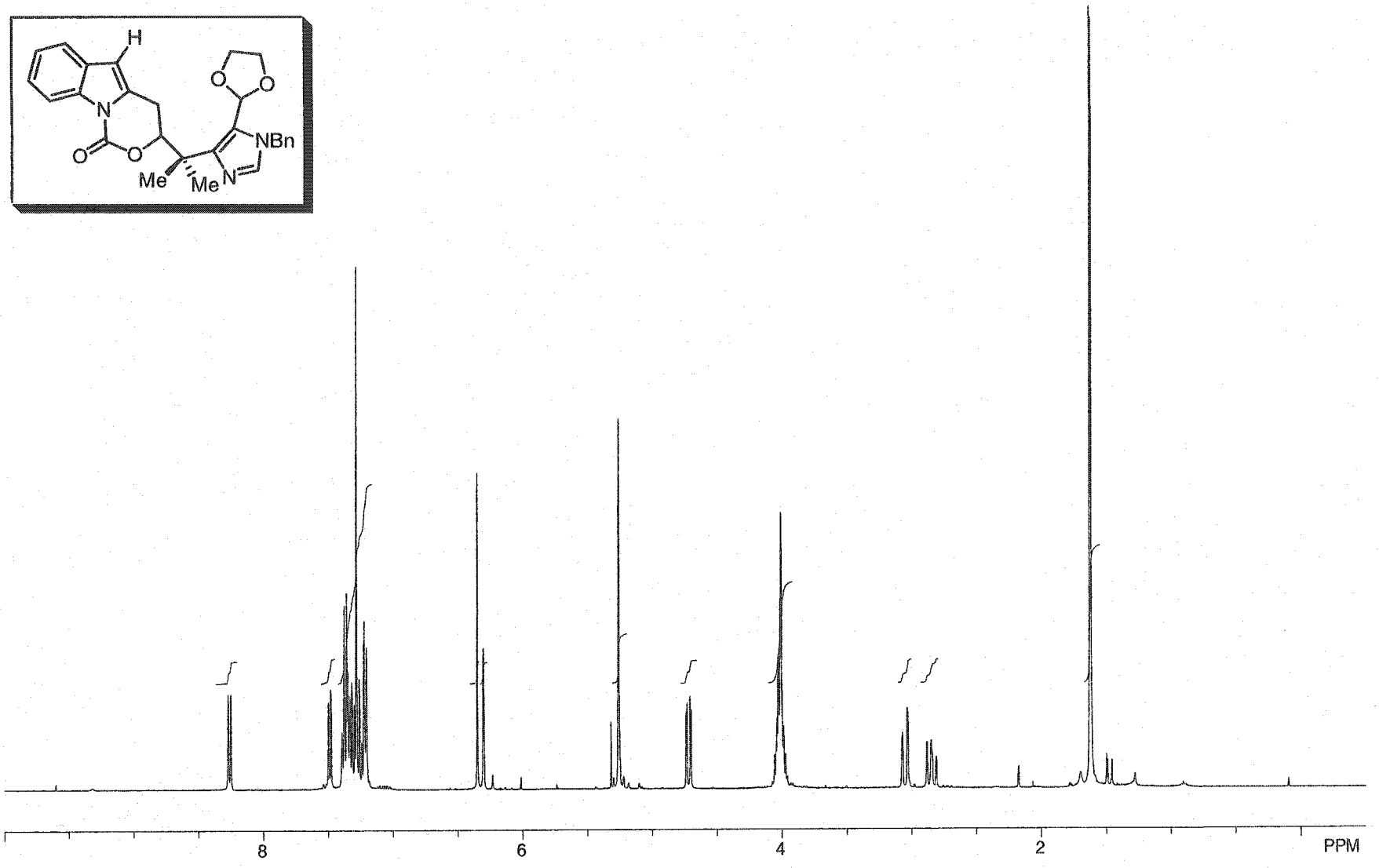


Figure A.1.58 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **152**.

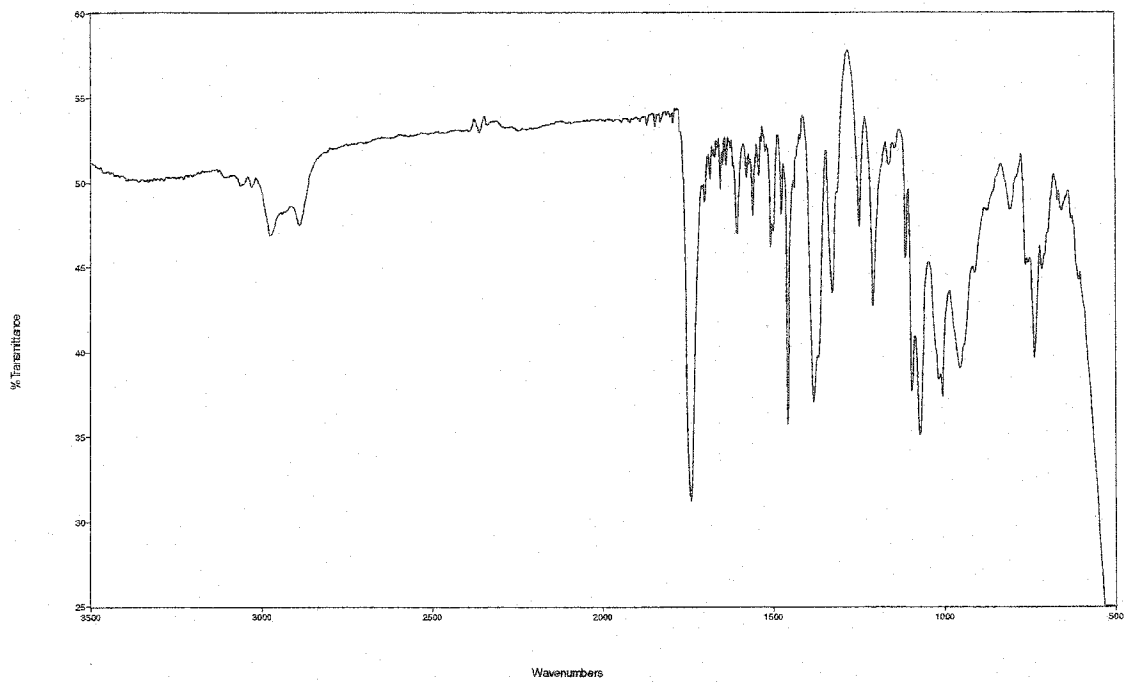


Figure A.1.59 FTIR Spectrum (thin film/NaCl) of Compound **152**.

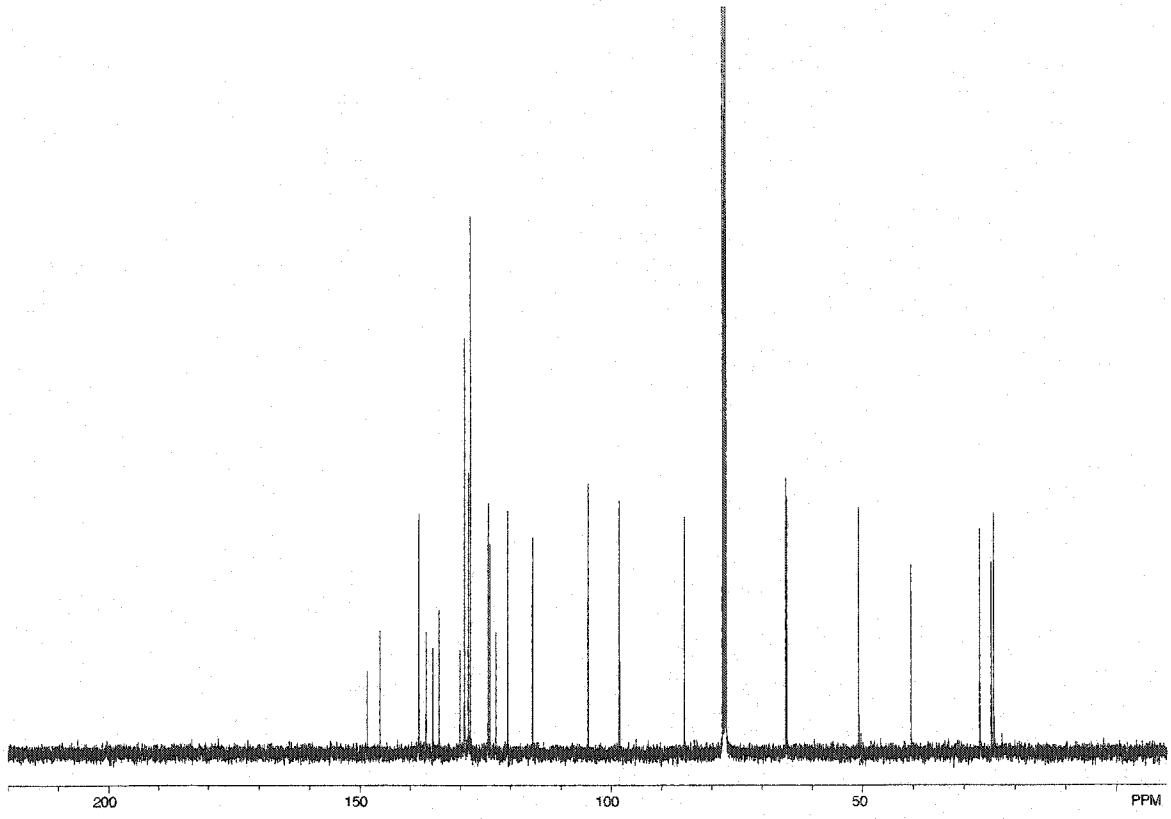


Figure A.1.60 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **152**.

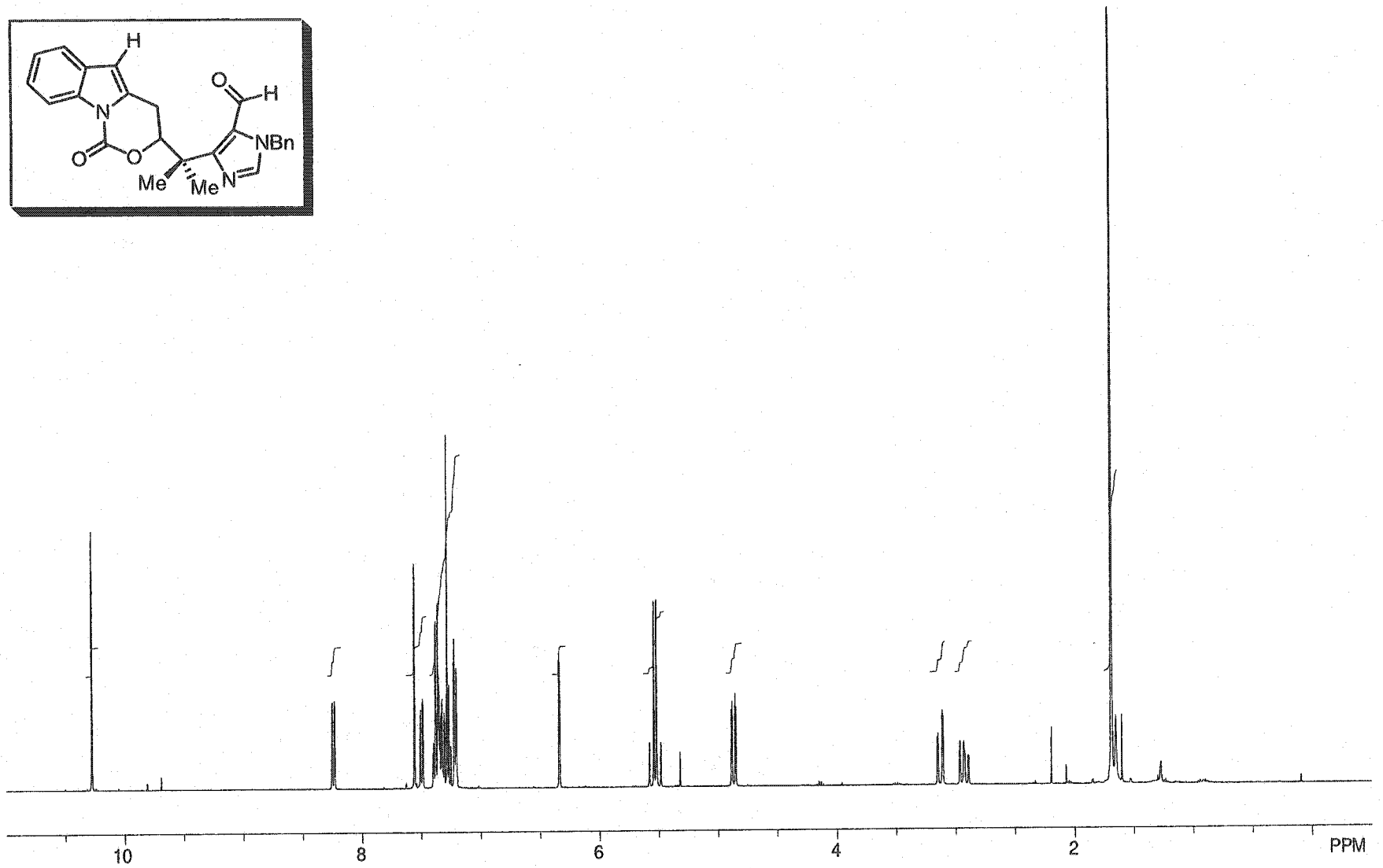


Figure A.1.61 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **153**.

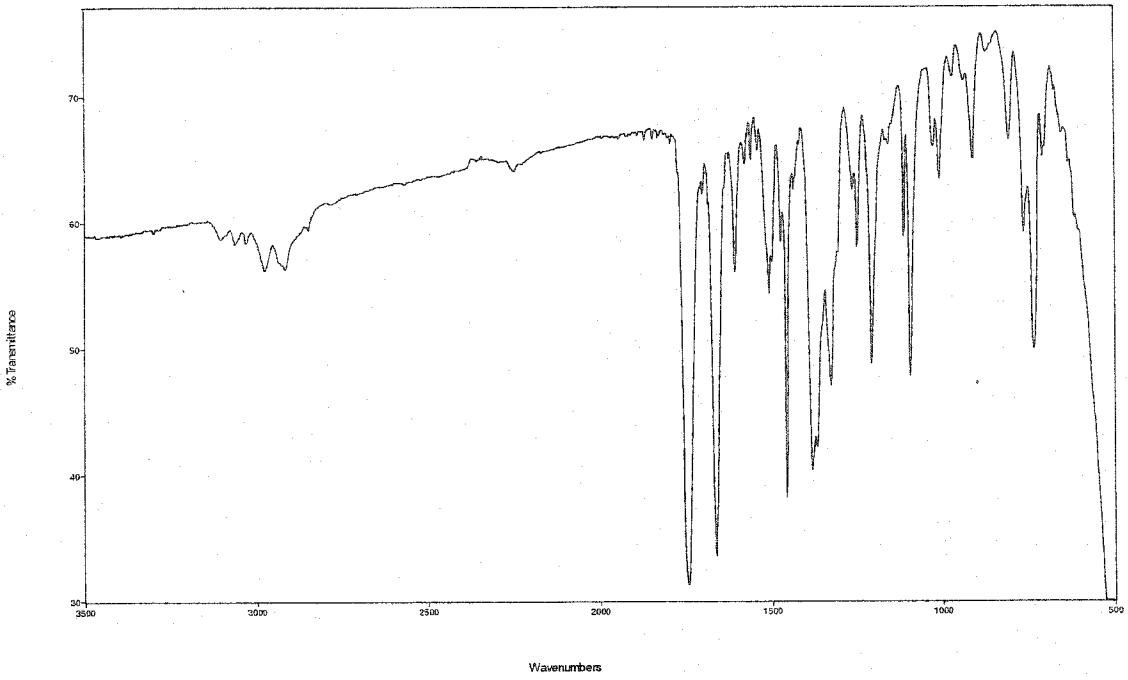


Figure A.1.62 FTIR Spectrum (thin film/NaCl) of Compound **153**.

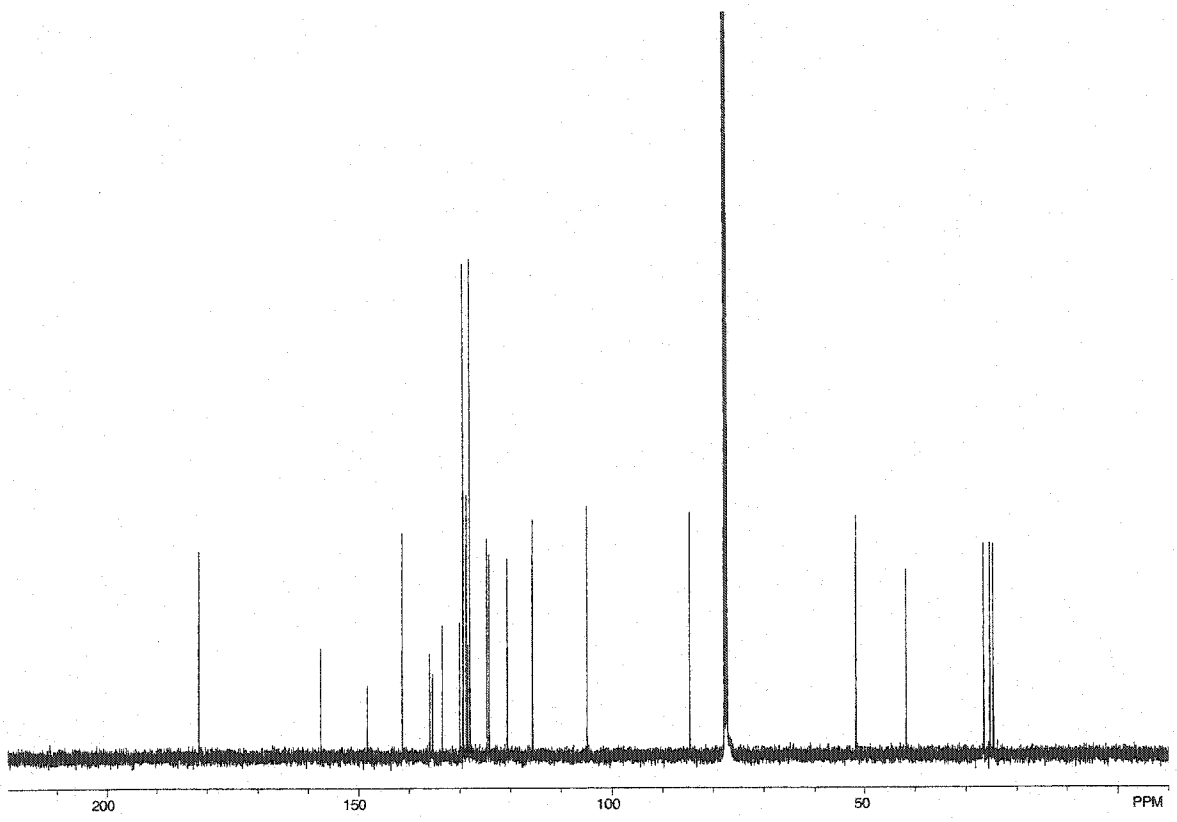
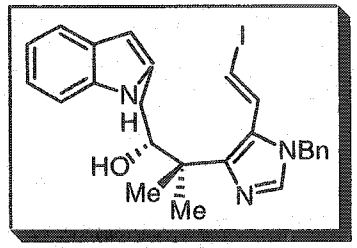


Figure A.1.63 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **153**.



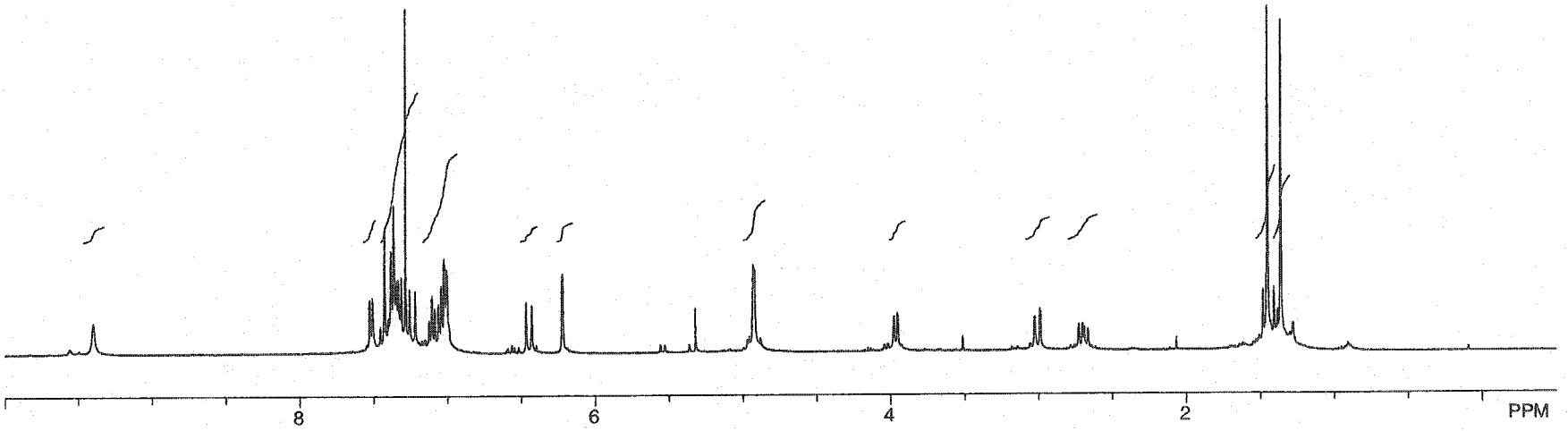


Figure A.1.64 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **156**.

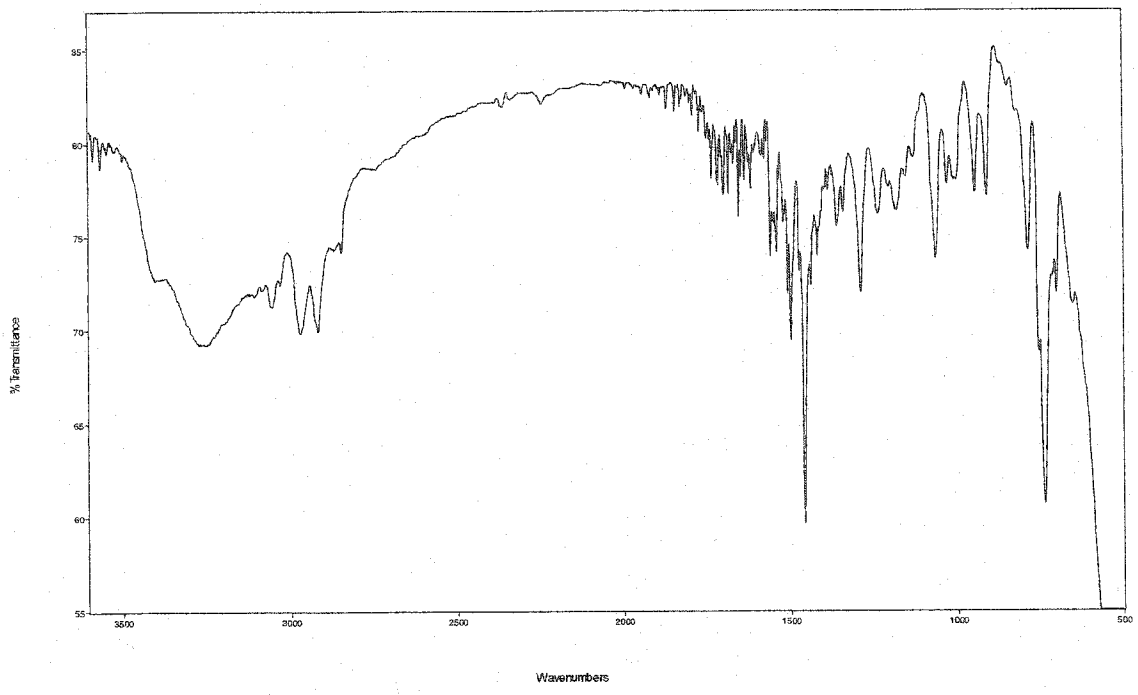


Figure A.1.65 FTIR Spectrum (thin film/NaCl) of Compound **156**.

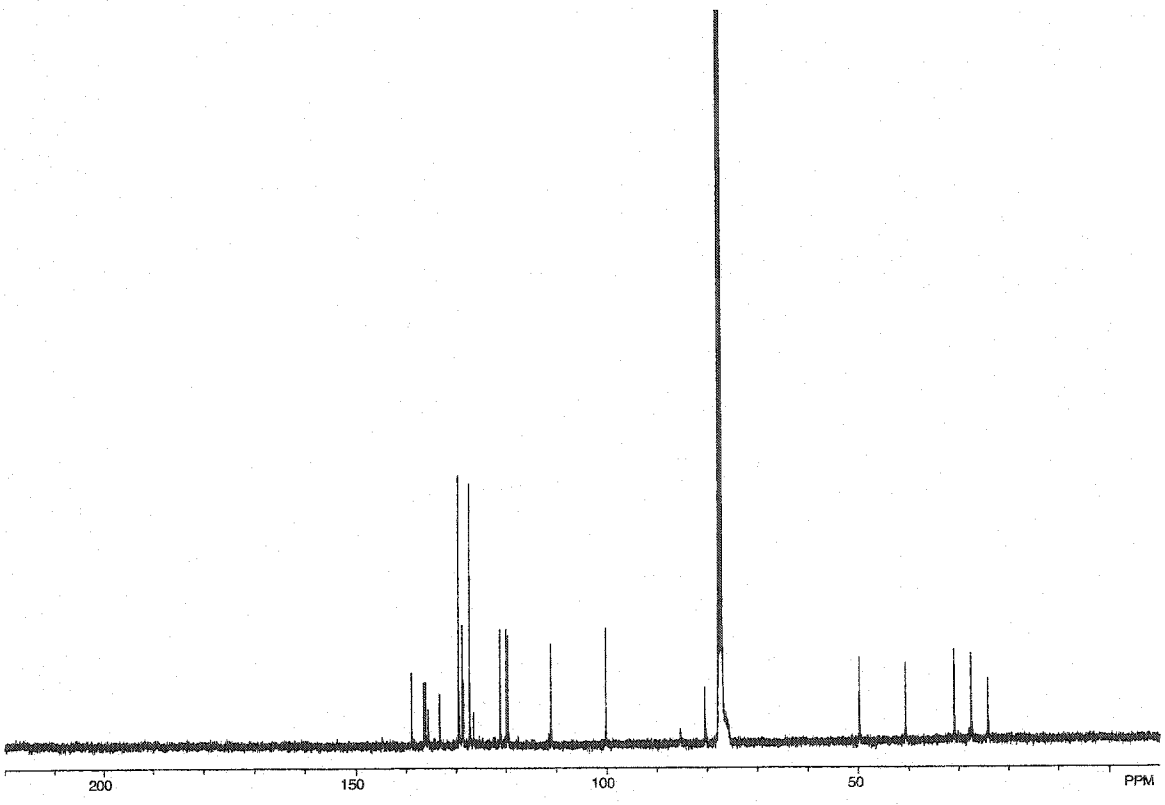


Figure A.1.66 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **156**.

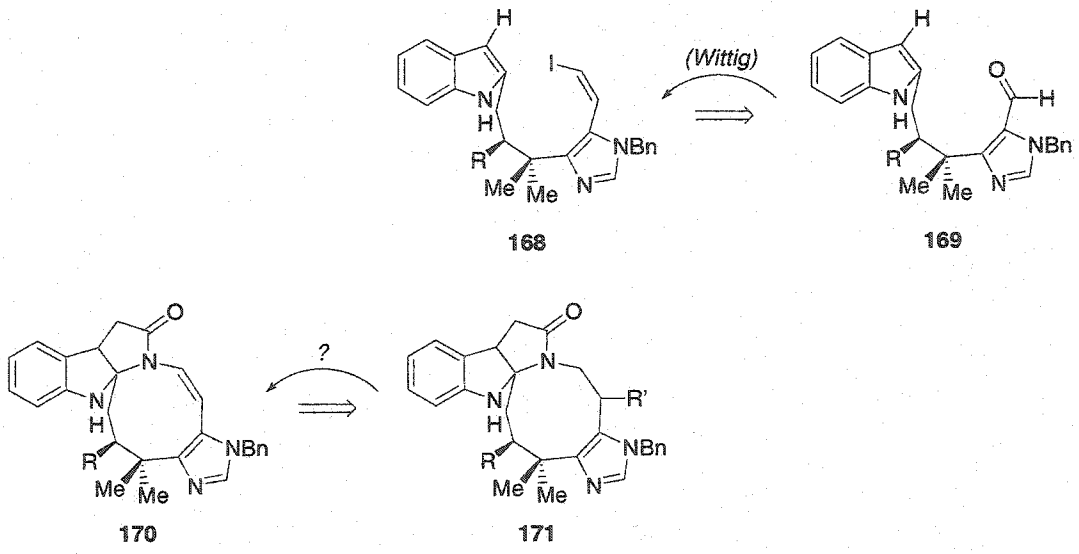
Chapter Three

Construction of the Securamine A Macrocycle

3.1 A New Synthetic Strategy

Unable to advance the previous synthetic approach to the key cross-coupling step, a new strategy was devised toward securamine A. In the previous sequence most problems centered around the selectivity and yield of the Wittig olefination. Preferential formation of the (*Z*)-olefin was viewed as a prerequisite for incorporation of the correct macrocyclic enamide bond geometry. It therefore seemed prudent to install the olefinic portion of the enamide after macrolactamization (Figure 3.1.1).[1-8]

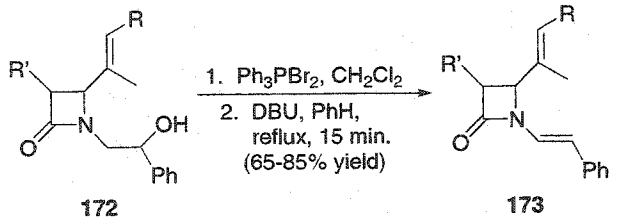
Figure 3.1.1



3.1.1 A Well-Precedented Enamide Formation

A variety of literature reports describe the generation of acyclic and macrocyclic enamides from the corresponding amido alcohols. One protocol developed by Cossio and coworkers describes the conversion of amido alcohol **172** to the corresponding bromide using triphenylphosphonium bromide (Scheme 3.1.1).[9] Subsequent basic elimination of the bromide provided desired enamide **173**.

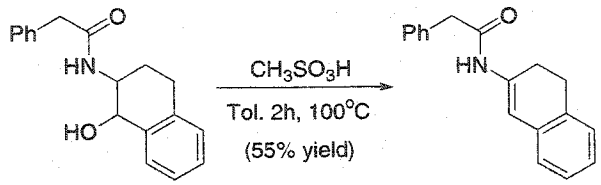
Scheme 3.1.1



172 **173**

In a more recent protocol developed by Nichols and coworkers simple exposure of amido alcohol **174** to methanesulfonic acid at 100°C in toluene accomplished the desired transformation to generate **175** in moderate yield (Scheme 3.1.2).[10]

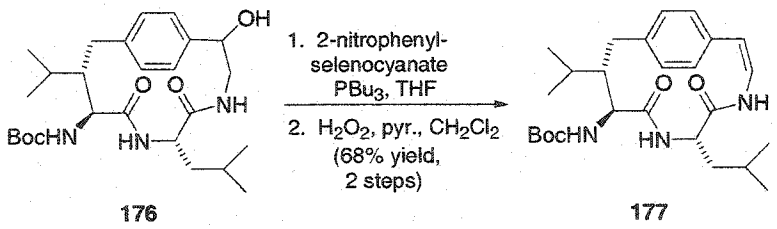
Scheme 3.1.2



174 **175**

The most encouraging and recently developed protocol was provided by Jouliee and coworkers at the University of Pennsylvania.[11] First, access to macrolactam **176** is accomplished by simple intramolecular coupling of the corresponding amino acid (Scheme 3.1.3). This amido alcohol (**176**) is then treated with a Greico procedure to convert the alcohol to the corresponding selenide. Immediate oxidation with hydrogen peroxide followed by elimination provided exclusively the (*Z*)-enamide (**177**) embedded in a 14-membered cyclopeptidyl ring. A notable feature of all three protocols is that the hydroxyl portion of the amido alcohol substrate is benzylic which seemed encouraging.

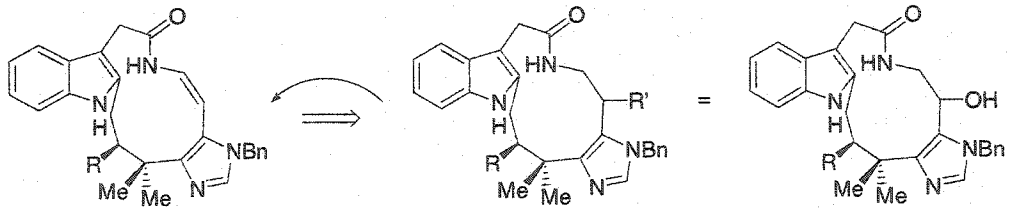
Scheme 3.1.3



176 **177**

Confident a variety of methods would prove suitable for the conversion of a macrocyclic amidoalcohol to the corresponding enamide, we turned toward a modification of our synthetic route to allow access to key amido alcohol synthon **179** (Figure 3.1.2).

Figure 3.1.2

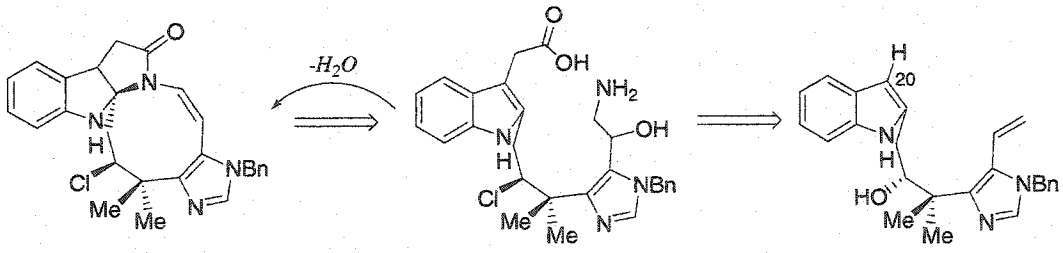


170 178 R'= OH, Br, Cl 179

3.2 Retrosynthetic Analysis

As stated before, the desired enamide macrocycle could arise from coupling of amino acid **180** followed by dehydration (Scheme 3.2.1). The resulting amino alcohol side chain is envisioned to arise from a vinyl moiety. The carboxylic acid at the indole 3-position could be arrived at via alkylation at C20 with ethyl iodoacetate as before.

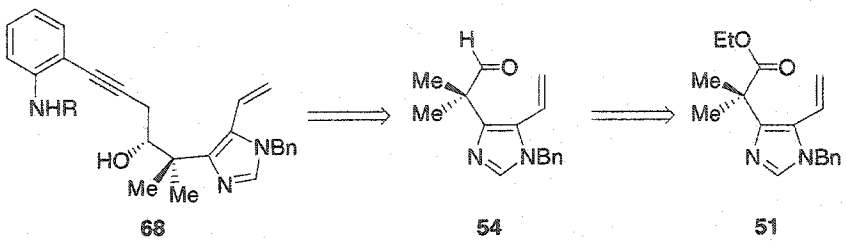
Scheme 3.2.1



98 180 173

At this point most of the previously developed chemistry should hold true with the vinyl side chain.[12] The indole core should once again be provided by palladium cyclization of aniline **68** (Scheme 3.2.2). This protected aniline derivative will arise via addition of a propargyl anion into aldehyde **54.**

Scheme 3.2.2



However, before attempting to install the necessary amino alcohol side chain onto the fully elaborated system it was thought wise to test the regiochemical preference of it's installation using model olefin **51**.

3.3 Early Model Studies

3.3.1 Installation Via Aminohydroxylation

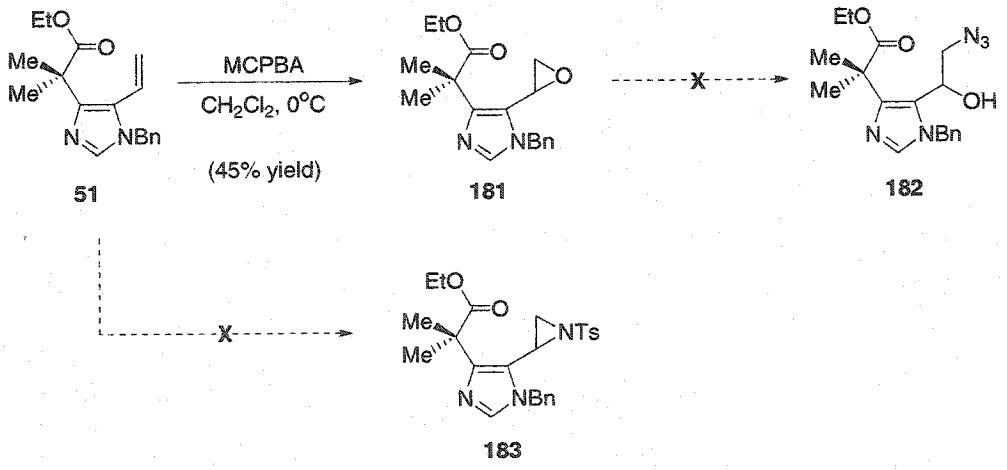
The first method explored for installation of the amino alcohol side chain was that of Sharpless' aminohydroxylation methodology. Unfortunately efforts to employ this methodology turned out to be more complicated than originally anticipated. The first issue faced was that of the regioselective nature of the aminohydroxylation chemistry. The majority of the published protocols are known to provide the undesired regioiosmer in similar benzylic (styrene) systems.[13]

Two protocols were found that provided the desired regioisomeric selectivity on styrenyl systems.[14,15] Unfortunately, exposure of this methodology to **51** met with little to no success in achieving the desired transformation.

3.3.2 Installation Via Epoxidation

It was subsequently believed that installation of the desired amino alcohol side chain could take place by reduction of corresponding azido alcohol **182**. Therefore treatment of vinyl imidazole **51** with MCPBA in CH_2Cl_2 provided the desired epoxide (**181**) in good yield (Scheme 3.3.1). Unfortunately, all attempts at opening of this epoxide proved fruitless. Along these same lines, it was also found that aziridination of the same vinyl imidazole led to only extensive decomposition.

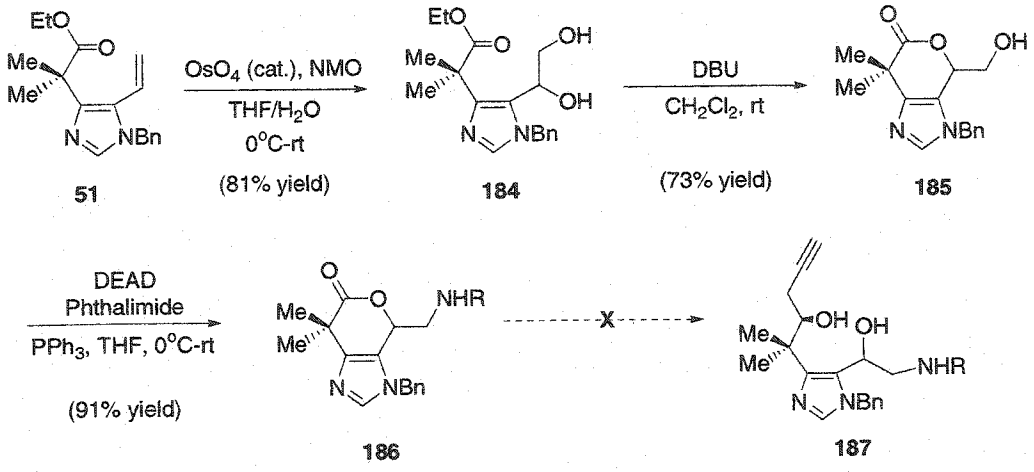
Scheme 3.3.1



3.3.3 Installation Via Dihydroxylation

Exposure of **51** to catalytic osmium tetroxide and NMO afforded the anticipated diol (**184**) possessing readily differentiable hydroxyl moieties in excellent yield (Scheme 3.3.2).[16] Hydrolysis of the ethyl ester in **184** followed by lactonization provided primary alcohol **185**. Substitution of the primary alcohol using phthalamide via a Mitsonobu protocol subsequently proved fruitful to afford lactone **186** in good yield.

Scheme 3.3.2

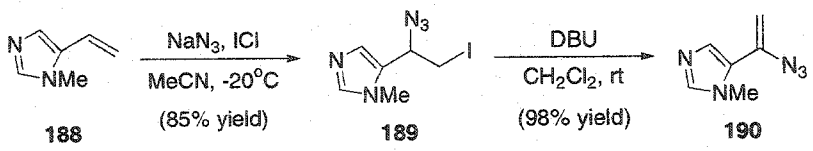


Unfortunately all attempts to add nucelophilic reagents (DIBAL, propargyl magnesium bromide, Weinreb's amine) into the (**184**) lactone carbonyl led to only extensive decomposition.

3.3.4 Installation Using ICl Chemistry

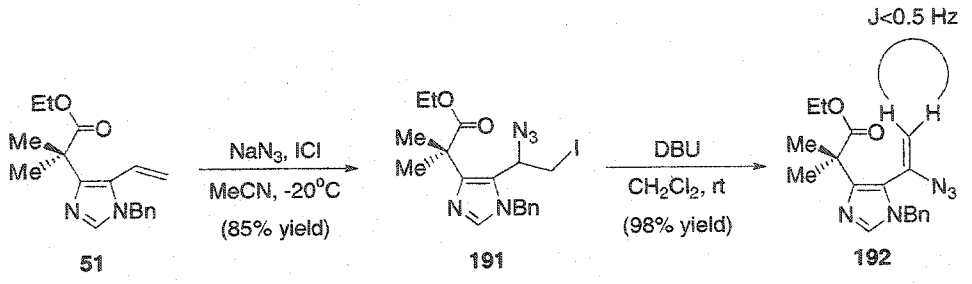
Twenty years ago, Khuong-Hu and coworkers reported the smooth functionalization of vinyl imidazole **188** with ICl and NaN_3. Premixture of NaN_3 and ICl in CH_3CN for one hour was followed by addition of methylated vinyl imidazole **188** (Scheme 3.3.3).[17] After workup this provided **189** possessing an iodine at the terminal position and a 2° azide at the allylic position, presumably arising from attack of the azide anion onto the corresponding iodonium ion at the allylic center. A notable feature of this methodology is that the ICl reacts exclusively with the vinyl side chain and yielded none of the expected byproduct resulting from reaction with the imidazole 2-position.

Scheme 3.3.3



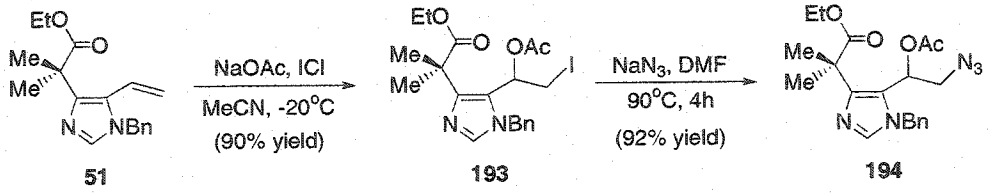
Indeed upon testing this chemistry on the more heavily functionalized imidazole **51**, it was found that iodide **191** was generated (Scheme 3.3.4). Regiochemical addition of the azide was confirmed by simple treatment of **191** with DBU to provide olefin **192**.

Scheme 3.3.4



Unfortunately, direct addition of **51** to NaN_3/ICl gives the undesired regiochemical outcome with respect to the desired amino alcohol side chain. It was postulated that substitution of a suitably protected oxygen nuclephile in place of sodium azide would provide the alcohol portion of the desired side chain at the benzylic position. The terminal iodine would then leave a nice handle to install the nitrogen equivalent of the amino alcohol side chain via direct displacement with NaN_3. Indeed, it was found that treatment of vinyl imidazole **51** with a mixture of NaOAc and ICl in acetonitrile provided the acetylated iodohydrin **193** (Scheme 3.3.5). Displacement of the primary iodide using sodium azide in DMF provided **194** in an excellent 80% yield over two steps.

Scheme 3.3.5



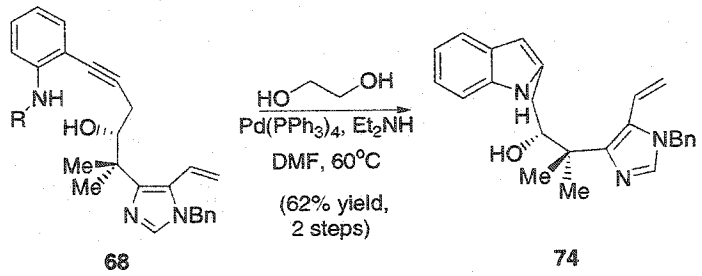
With suitable methodology to functionalize the vinyl side chain now in hand, attention was refocused on the previously developed chemistry in hopes that installation of the amino alcohol side chain could take place on a more advanced indole containing system.

3.4 Indole Core Construction

3.4.1 Advancing to an Unalkylated Indole System

Using chemistry previously developed in the Wood labs access of aniline derivative **68** was accomplished by the same procedure described in chapter one. [12] Transformation of **68** was carried out smoothly once again using the slightly modified indole cyclization conditions described in chapter two to provide indole **74** in 75% yield (Scheme 3.4.1).

Scheme 3.4.1

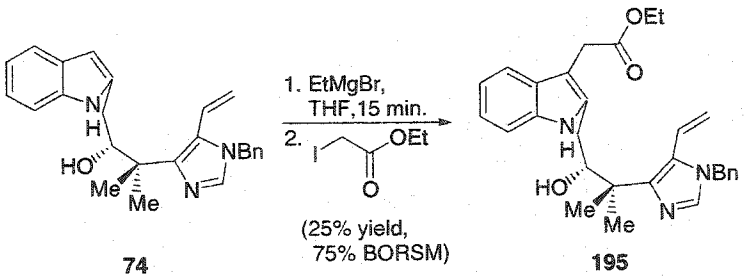


68 **74**

3.4.2 Problems With the Alkylation Chemistry

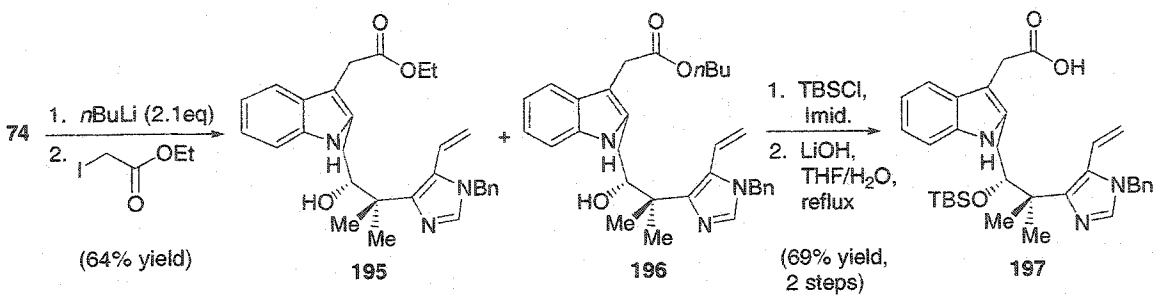
It was found that treatment of unalkylated indole **74** with an ethyl Grignard base followed by an ethyl iodoacetate electrophile worked in only 25% conversion to provide the 2,3-disubstituted indole containing the desired ethyl ester side chain at the indole 3-position (Scheme 3.4.2). Usable quantities of **195** for further elaboration could not be accessed using this protocol.

Scheme 3.4.2



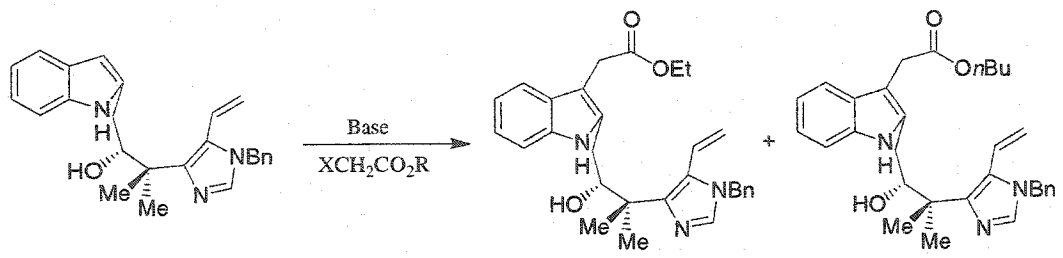
Of major concern was the low conversion rate. It was found that upon substitution of *n*-butyl lithium for ethyl magnesium bromide there was complete conversion of unalkylated indole **74** observed to generate a mixture of esters **195** and **196** (Scheme 3.4.3). The latter presumably having come about by a transesterification reaction with a possible butoxide contaminant. This was confirmed by protection of the neopentyl alcohol and subsequent hydrolysis of the mixture to generate carboxylic acid **197**.

Scheme 3.4.3



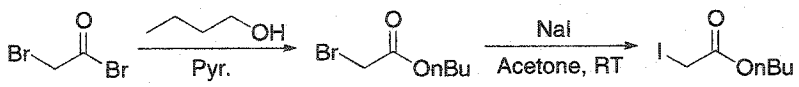
An extensive empirical effort was made to optimize this alkylation protocol, including an exploration of the impact of base (LDA, *n*BuLi, NaH, EtMgBr), solvent (THF, Et_2O), additive (HMPA, DMPU), temperature, and order of addition (Scheme 3.4.4). Use of freshly opened *n*BuLi from a variety of sources failed to alleviate this problem. It was found that use of *t*BuLi provided exclusively desired ethyl ester **195** without any of the *n*-butyl ester byproduct (**196**). However, this reaction unfortunately worked in only moderate yields. Therefore, the solution to this transesterfication problem was to use an *n*-butyl iodoacetate (**200**) for alkylation. This electrophile was prepared using standard procedures. Ultimately, alkylation of indole **74** was accomplished using *n*-butyl lithium as base followed by *n*-butyl iodoacetate **200** to provide exclusively *n*-butyl ester **196** in a very good 85% yield.

Scheme 3.4.4



A: 74 **B: 195** **C: 196**

X, R (eq.)	Base	Result (A:B:C)	Yield
I, Et (5 eq.)	EtMgBr (5eq.)	2:1:0	75%
I, Et (1 eq.)	*n*BuLi (2.1eq.)	0:3:1	64%
I, Et (1 eq.)	*t*BuLi (2.1eq.)	0:1:0	44%
Br, *n*Bu (1 eq.)	*n*BuLi (2.1eq.)	1:0:1	75%
I, *n*Bu (1 eq.)	*n*BuLi (2.1eq.)	0:0:1	85%

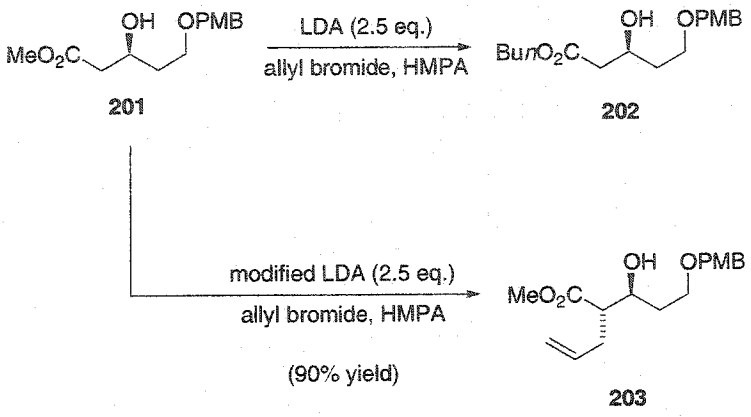


198 **199** **200**

3.4.3 Transesterfication Precedent

Others have observed systems extremely sensitive to contaminants in commercially available *n*BuLi.[18] The same transesterification problem in the presence of LDA was cited in Schreiber's FK-506 synthesis. Upon subjection of hydroxyl ester **201** to 2.5 equivalents of LDA and subsequent exposure to allyl bromide one would expect to generate alkylation product **203** (Scheme 3.4.5). However, little to no alkylation product was formed. Instead, the corresponding *n*-butyl ester **202** was isolated.

Scheme 3.4.5



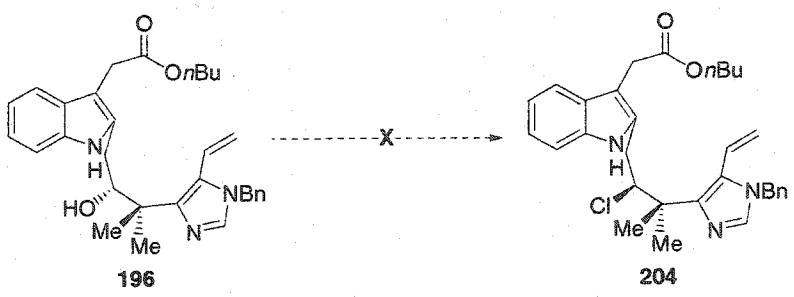
It was later found that this was due to the method used to prepare the LDA. Under the usual preparation conditions (diisopropyl amine and *n*BuLi in THF) the transesterification product was formed almost exclusively. However, when the LDA is prepared via a newer protocol using diisopropyl amine, lithium metal and α-methyl styrene, alkylation product **203** is isolated in an excellent 90% yield. Schreiber goes on to state that various attempts were made at LDA preparation using various bottles of *n*-BuLi from different suppliers all with the same unfortunate results.

3.4.4 First Attempts at Chlorine Installation

With the securamine indole core properly functionalized, focus was shifted to installation of the neopentyl chlorine center. However, it was found that treatment of alcohol **196** with the previously successful chlorination conditions effected only extensive decomposition apparently from reaction with the vinyl side chain (Scheme

3.4.6). Moreover, exposure to a variety of other chlorination conditions also met with failure.

Scheme 3.4.6



Because a variety of successful of chlorination conditions had been observed in previous systems (**55, 88, 145**) it was anticipated that failure of **196** to undergo smooth chlorination was substrate dependent. Anticipating alternative C2-C3 substitution patterns would be generated it was decided that chlorination be put off until the installation of the appropriate side chain was complete.

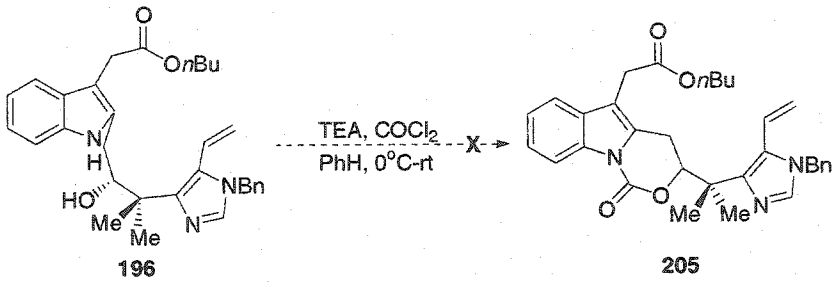
3.5 Protecting Group Problems

Exposure of *n*-butyl ester **196** to the ICl protocol led only to extensive decomposition of the starting material, presumably due to reaction with the free indole moiety. Moreover protection of the indole had to be preceded by masking of the neopentyl hydroxyl due to it's more reactive nature with suitable protection methods.

Even more unfortunate is that upon exposure of **196** to phosgene in the presence of TEA in benzene none of the desired carbamate (**205**) could be isolated (Scheme 3.5.1).

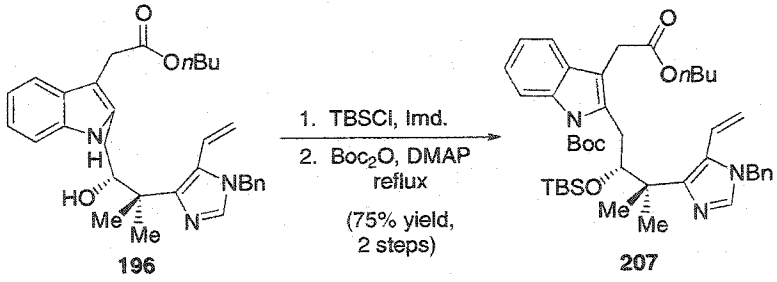
Due to this result it was obvious that rethinking the protecting group strategy was necessary.

Scheme 3.5.1



The solution to this problem turns out to be protecting the two heteroatoms separately. Therefore treatment of alcohol **196** with TBS-Cl in the presence of imidazole base masks the hydroxyl as it's TBS derivative (Scheme 3.5.2). This is followed by exposure of **196** to Boc_2O in the presence of TEA and DMAP. These two protection steps successfully masked both heteroatoms in an excellent 75% yield over two steps.

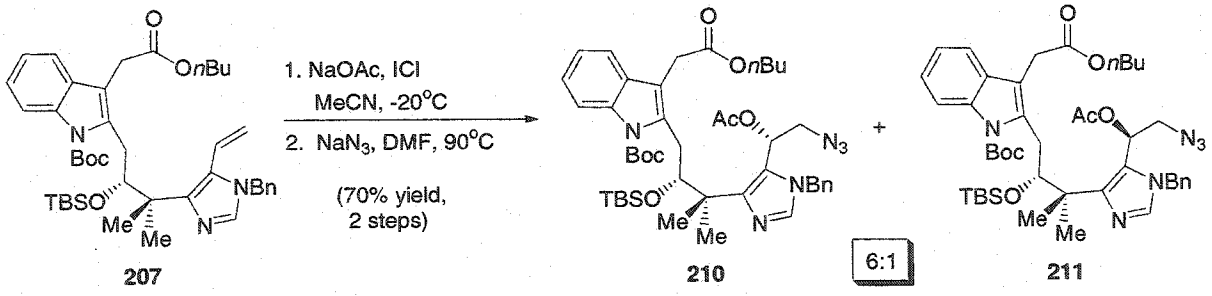
Scheme 3.5.2



3.6 Incorporation of the ICl Methodology

With a suitably protected substrate (**207**) in hand, attention was now focused on incorporating the previously tested ICl methodology to install the amino alcohol side chain. Vinyl imidazole **207** was added to a mixture of ICl and NaOAc in acetonitrile to effect a transformation that furnished the corresponding acetylated iodohydrins as a 6:1 mixture of diastereomers (Scheme 3.6.1). Displacement of the primary iodide then proceeded smoothly to provide azides **210** and **211** in excellent yield.

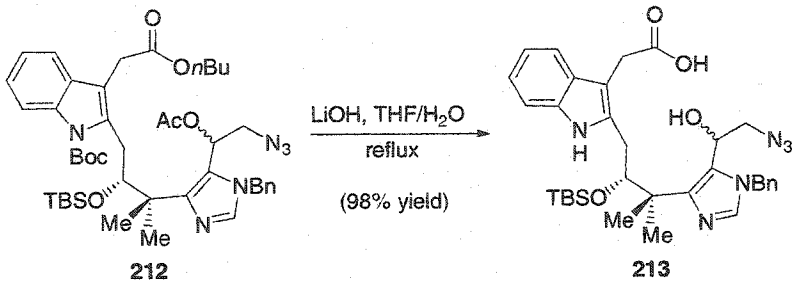
Scheme 3.6.1



A C2-C3 hydroxy-azide had now been installed on the advanced system with the correct regiochemical preference. With this exciting result, attention was immediately focused on macrolactamization. Exposure of azides **210** and **211** to refluxing LiOH in a mixture of THF and water accomplished three transformations: hydrolysis of the n-butyl ester, removal of the acetate protecting group, and unmasking of the free indole N-H by deprotection of the Boc group to provide acid **213** in a very good 98% yield (Scheme

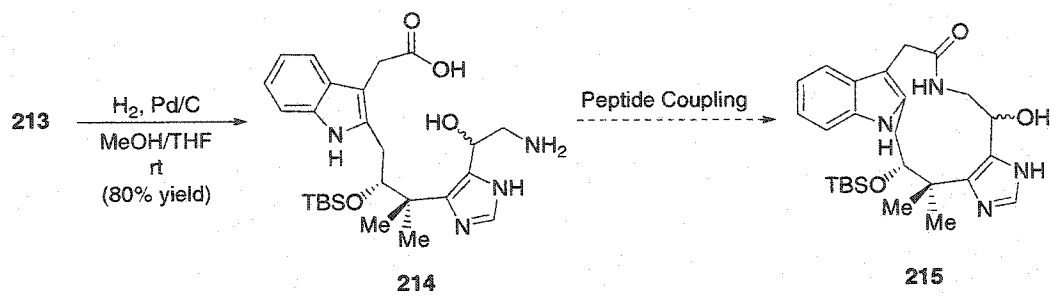
3.6.2). This important intermediate proved extremely difficult to purify and was therefore used crude.

Scheme 3.6.2



Treatment of the primary azide with H_2 in the presence of Pd/C not only effected a reduction to the primary amine but also deprotected the imidazole ring to generate amino acid **214** (Scheme 3.6.3). Unfortunately, this compound was extremely polar and difficult to handle. Moreover, purification of this compound has never been accomplished and all attempts at a peptide coupling of this particular amino acid have failed to date. However, a solution to this problem seemed to have presented itself earlier on in some model study work.

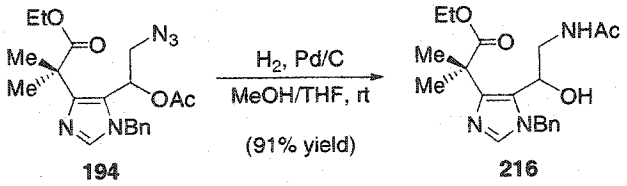
Scheme 3.6.3



3.7 Construction of the Macrolactam

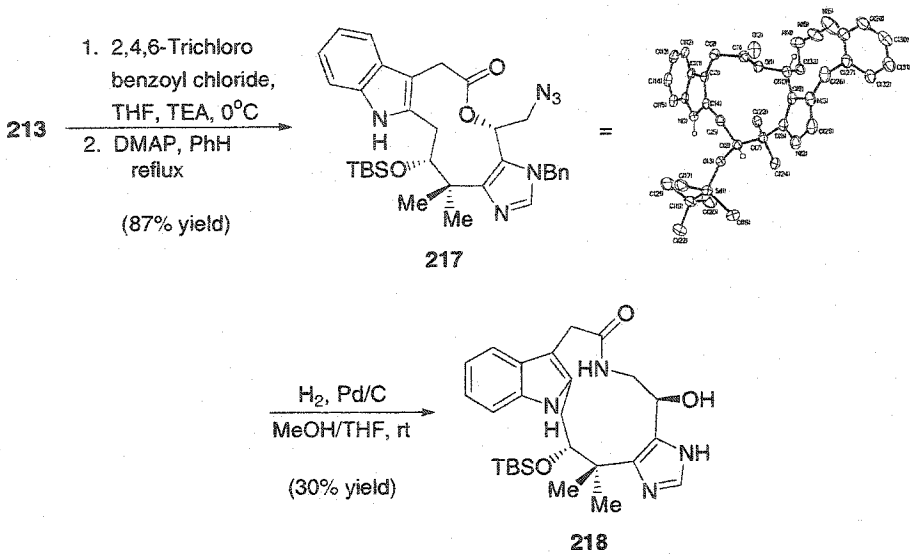
Earlier in the ICl model study some interesting results were discovered. It was found that upon treatment of **194** to azide reduction conditions not only was there a reduction observed but also a migration of the acetate protecting group onto the newly formed primary amine to provide amido alcohol **216** in very good yield (Scheme 3.7.1).[19-23]

Scheme 3.7.1



It was hoped that this migration could be exploited and so treatment of the aforementioned acid **213** with Yamaguchi lactonization conditions provided cleanly, lactone **217** in good yield (Scheme 3.7.2).[24] Interestingly, the rate of this macrolactonization was found to be much greater with one diastereomer over the other to provide exclusively lactone **217**. The relative configuration was confirmed by x-ray crystallography. Exposure of **217** to hydrogenation conditions then accomplished two transformations; reduction and migration of the primary azide to form the Securine macrolactam, and deprotection of the benzyl group unmasking the free imidazole. This macrolactam (**218**) was now beginning to look a lot like the desired natural product.

Scheme 3.7.2

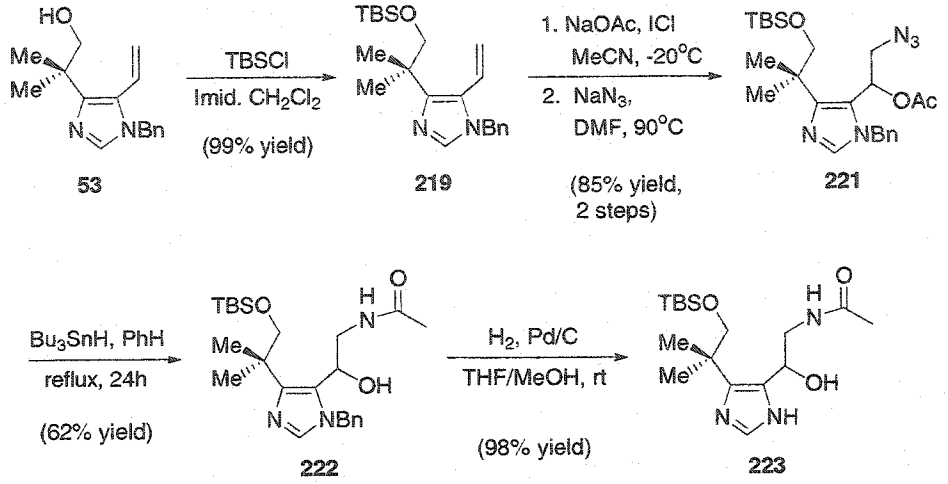


3.8 Model Studies for Enamide Formation

With methodology in hand to form the amide macrocycle attention could now be focused on installation of that elusive enamide bond. Vinyl imidazole **53** was adopted as a model substrate for the investigation of dehydration protocols.

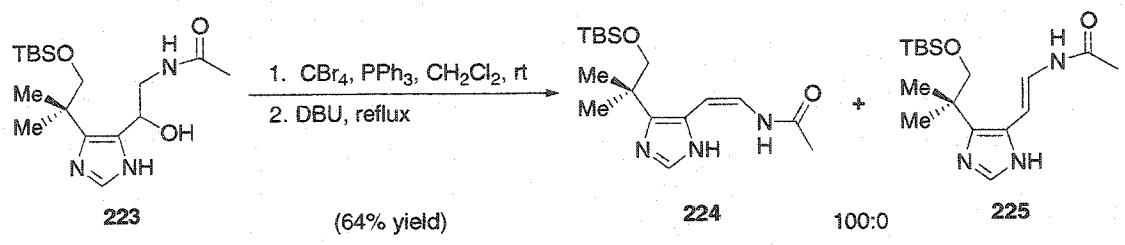
First treatment of **53** with TBS-Cl in the presence of imidazole base successfully masked the primary alcohol (Scheme 3.8.1). At this point **219** was treated with the ICl methodology to provide the corresponding iodide. This was followed immediately by displacement with NaN_3 in DMF to generate **221**. Exposure of the primary azide to tirbutyltin hydride in refluxing benzene provided amide **222**.[25,26] This was followed by hydrogenation to remove the benzyl protecting group.

Scheme 3.8.1



After the usual methods for dehydration on amido alcohol **223** failed (Acid, Martin Sulferane, Burgess reagent, Grieco protocol) it was apparent that perhaps the best route would be an elimination pathway to access the enamide. Fortunately, treatment of **223** with CBr_4 and PPh_3 followed by addition of DBU base effected a tandem bromination/elimination in one pot to provide the desired enamide (**224**) (Scheme 3.8.2). Moreover, (*Z*)-enamide **224** was isolated exclusively with none of the expected (*E*) byproduct (**225**). This is illustrated in the ^1H NMR by the 9.4 Hz coupling constant of the vinyl protons.

Scheme 3.8.2



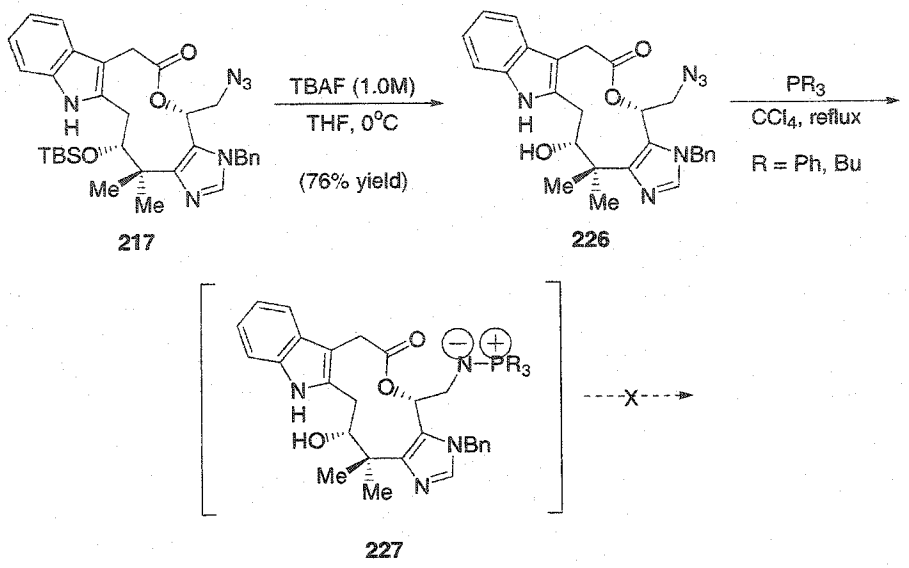
With a working model system now in hand, attention could be focused on dehydration of the fully elaborated system.

3.9 Advancement of the Lactam Macrocycle

3.9.1 Attempts at Chlorine Installation

With lactone **217** in hand, installation of the neopentyl chlorine functionality was attempted prior to elimination of the allylic alcohol. After further consideration it was envisioned that installation of the neopentyl chlorine could be accomplished in tandem with reduction of the azide and migration to the lactam via a Staudinger type protocol. Deprotection of the neopentyl alcohol using TBAF afforded key alcohol **226** in 76% yield (Scheme 3.9.1). Exposure of alcohol **226** to the previously successful chlorination conditions led to a single product. Spectroscopic data (^{1}H nmr and LRMS,) are consistent with nitrogen ylide **227**. A known intermediate in Staudinger type reductions of azides. Unfortunately, incorporation of PBu_3 led only to the corresponding tributyl ylide. Moreover, ylide **227** was resistant to all hydrolysis conditions including treatment with HCl.

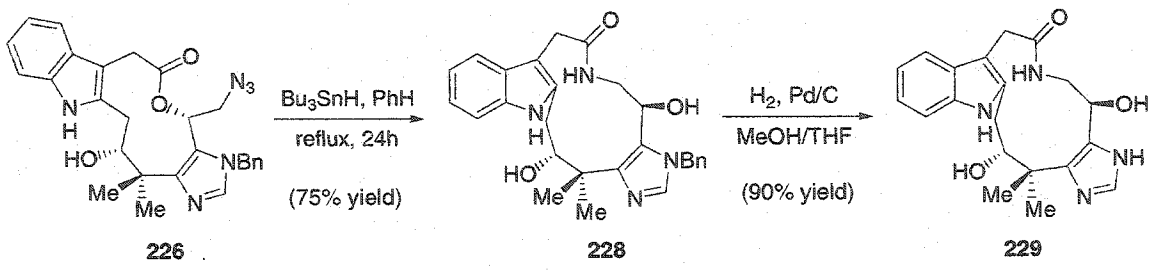
Scheme 3.9.1



3.9.2 Construction of the Lactam Macrocycle

At this point, postponement of chlorine installation until after reduction of the primary azide seemed the most logical course of events. Therefore, treatment of lactone **226** with tributyltin hydride in refluxing benzene yielded the desired macrolactam (**228**) in a much improved 75% yield (Scheme 3.9.2). Exposure of lactam **228** to hydrogenation conditions in MeOH/THF removed the benzyl protecting group to provide free imidazole **229**.

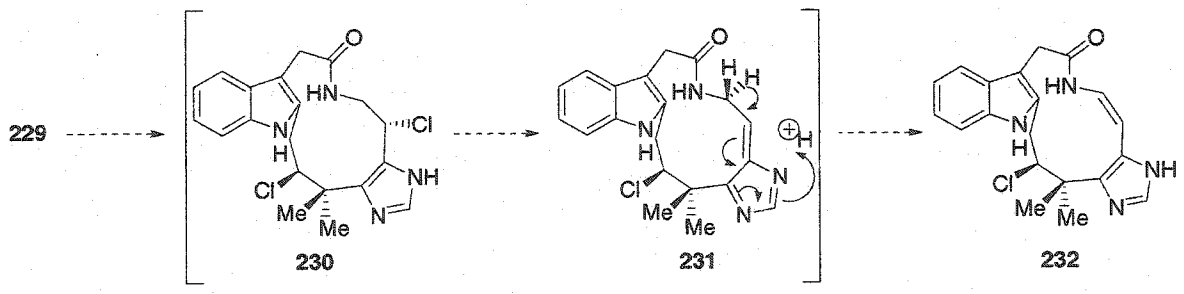
Scheme 3.9.2



226 228 229

Chlorination once again seemed the obvious next step in the synthetic sequence. However, with two free alcohols present it was believed that chlorination of both the neopentyl alcohol would take place along with chlorination of the allylic alcohol and subsequent treatment with DBU would provide the elusive enamide functionality in one pot to provide des-bromo securine A (**232**) (Scheme 3.9.3).

Scheme 3.9.3

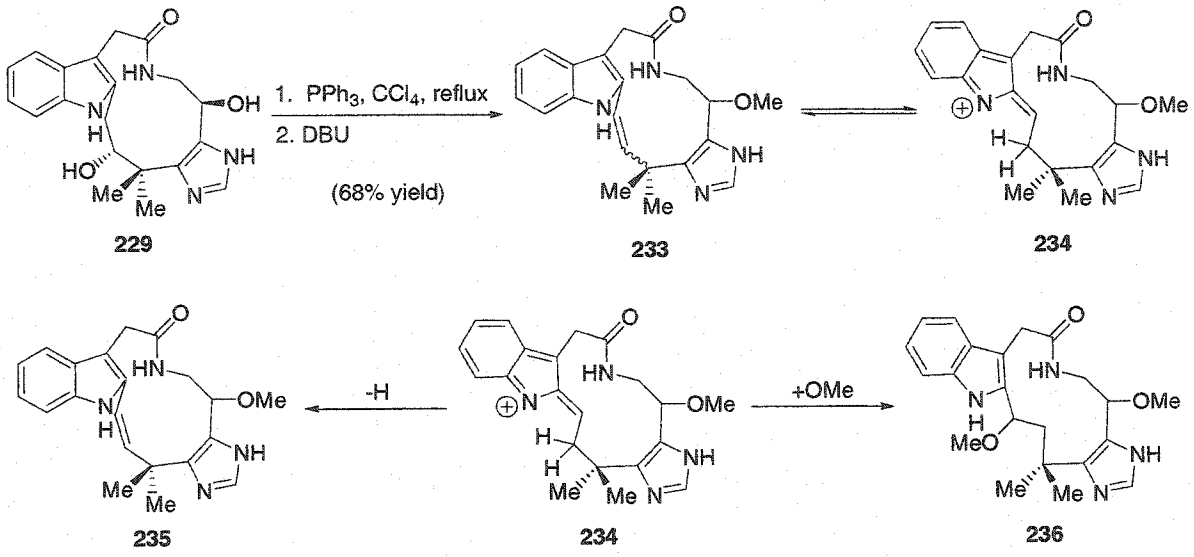


230 231 232

Exposure of diol **229** to triphenyl phosphine chlorination conditions followed by DBU provided one product which was eventually identified after silica gel chromatography to be macrocycle **233** (Scheme 3.9.4). This result presumably arises from elimination of the activated neopentyl alcohol (which is in conjugation with the indole ring) along with chlorination of the allylic alcohol followed by displacement with

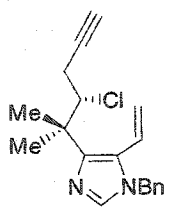
methanol due to the composition of the eluent used in chromatography. Prolonged dissolution in methanol or attempted purification lead to olefin isomerization and dimethyl ether formation, all presumably via iminium ion **234.**

Scheme 3.9.4

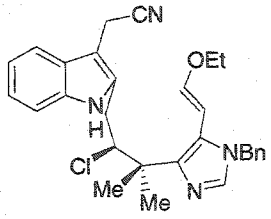


This was certainly a very unexpected result due to the fact that other compounds containing the neopentyl chlorine have been exposed to strongly basic conditions without observance of any elimination product (Figure 3.9.1). It was now clear that installation of the enamide and neopentyl alcohol would have to take place in a stepwise fashion to avoid this elimination problem.

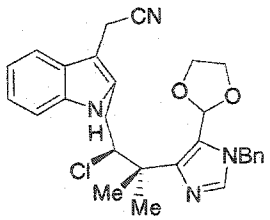
Figure 3.9.1



55



88

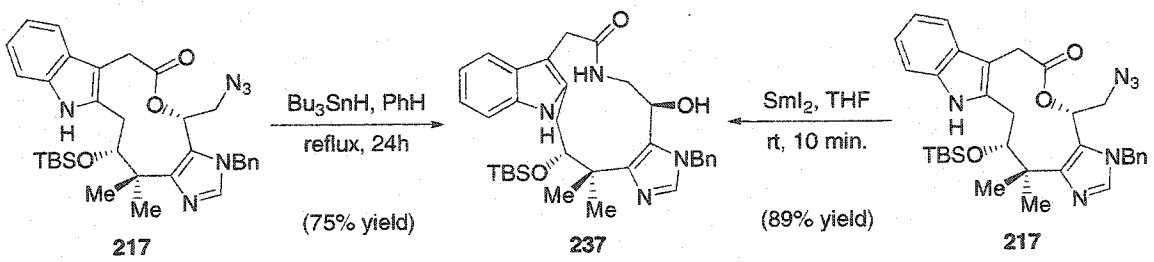


145

3.9.3 Reordering of Events

Taking a few steps backward, lactone **217** was first treated with Bu_3SnH before removal of the TBS protecting group to provide lactam **237** in 75% yield (Scheme 3.9.5). At this point it was also discovered that a much quicker way of accomplishing this transformation with similar efficiency was to simply treat lactone **217** with SmI_2 in THF for 10 minutes at room temperature.[27] This also provided lactam **237** in a more efficient 89% yield. It is presumed that this reaction takes place so quickly because of the Sm(III) acting as a lewis acid with respect to the lactone carbonyl allowing the amine to migrate in a more facile fashion. This SmI_2 protocol proved fruitless with both the model system and the macrolactone containing the free neopentyl alcohol in prior experimentation.

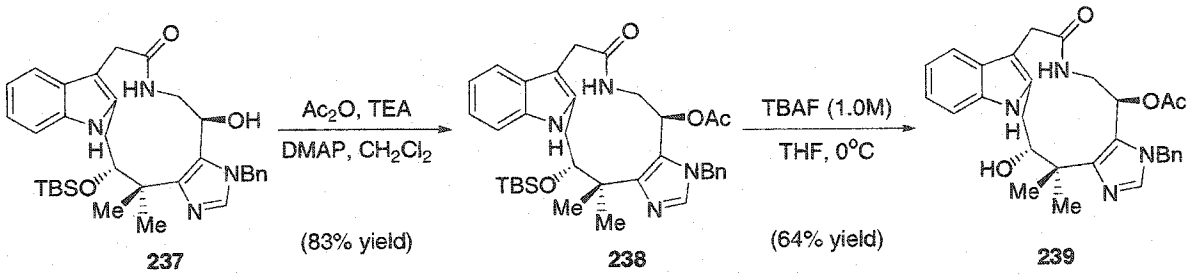
Scheme 3.9.5



217 237 217

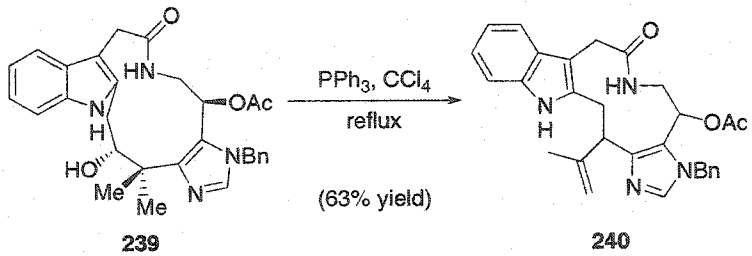
Treatment of lactam **237** with acetic anhydride in the presence of DMAP and Et_3N orthogonally protected the allylic alcohol with respect to the neopentyl hydroxyl to furnish acetate **238** in very good yield (Scheme 3.9.6). Exposure of **238** to TBAF removed the silyl protecting group to provide alcohol **239**.

Scheme 3.9.6



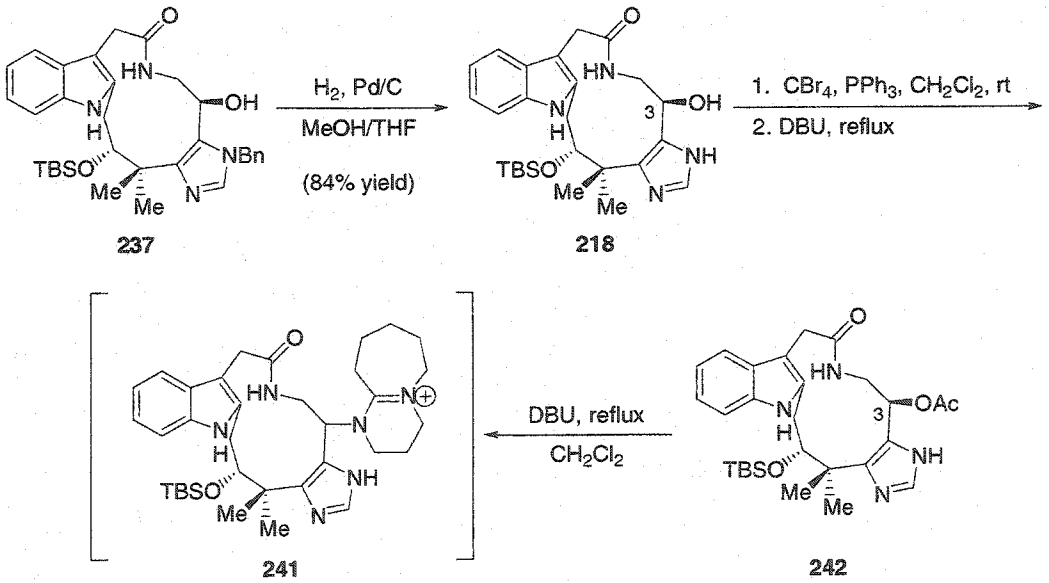
At this point attention was once again focused on installation of the elusive neopentyl chlorine. Unfortunately, exposure of alcohol **239** to the previously mentioned chlorination conditions gave exclusively olefin **240** having arisen via the imidazole assisted rearrangement observed in previous systems (Scheme 3.9.7). The presence or absence of an N(4) benzyl group had no impact on the observed course of this reaction.

Scheme 3.9.7



With this disappointing result in hand, it would appear that there was no choice left but to install the enamide first and then attempt to install the neopentyl chlorine. Debenzylation of lactam **237** using the same hydrogenation conditions as previously discussed provided the free imidazole (**218**) in good yield (Scheme 3.9.8). Using previously developed methodology from the model system discussed in section 3.8, lactam **218** was exposed to CBr_4 and PPh_3 followed by addition of DBU. This reaction led to one product which has been confirmed by ^1H nmr and mass spectrometry to be that of a DBU adduct **241** wherein the amine base has substituted at the allylic position rather than eliminate as hoped. Moreover, this same result has been reproduced with a variety of potential leaving groups at that allylic position (Ac, Cl) and a variety of bases.

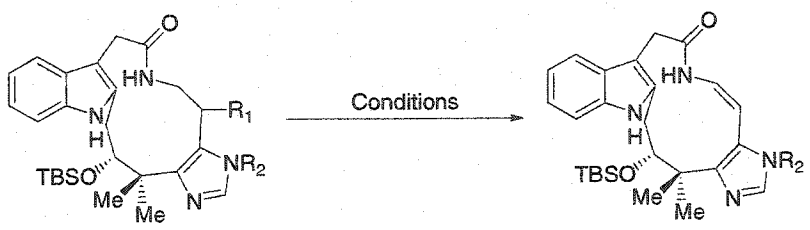
Scheme 3.9.8



Frustrated with the inability to eliminate the C3 hydroxyl an all out effort was put forth to screen conditions in hopes that either elimination or dehydration to the desired

enamide would take place (Figure 3.9.2). The results of these experiments are listed below.

Figure 3.9.2



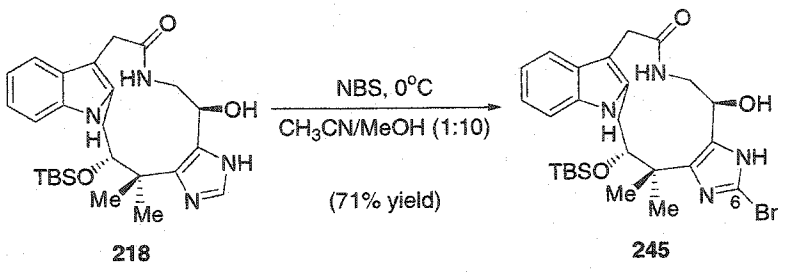
243 **244**

R_1, R_2	Conditions	Result
OH, H	1. PPh_3, MeCN/CCl_4 2. DBU	Adduct **241**
OH, H	1. PPh_3, MeCN/CCl_4 2. Proton Sponge	Decomposition
OH, H	1. PPh_3, MeCN/CCl_4 2. TEA	Decomposition
OH, H	1. PPh_3, MeCN/CCl_4 2. Amberlite resin	Decomposition
OH, H	1. PBu_3, MeCN/CCl_4 2. DBU	Adduct **241**
OH, H	1. PPh_3, CBr_4, CH_2Cl_2 2. DBU	No Reaction
OAc, H	Toluene, reflux	Decomposition
OH, H	MsCl, TEA, DMAP, CH_2Cl_2	Decomposition
OH, H	1. PPh_3, MeCN/CCl_4 2. Ag_2CO_3	Decomposition
OH, H	PPTS, PhH, reflux	Diol **229**
OH, H	pTSA, MeOH, Sealed Tube, 70°C	No Reaction
OH, H	Mol. Sieves 4A, CCl_4, reflux	No Reaction
OAc, H	DBU, CH_2Cl_2, 0°C	Adduct **241**

Installation of the bromine at the imidazole 2-position proceeded by treatment of lactam **218** with one equivalent of NBS in an acetonitrile/methanol mixture (Scheme

3.9.9). Unfortunately bromide **245** is a fairly unstable molecule that has not been advanced further in the synthetic sequence to date, cementing the intuitive idea that installation of a C6 bromide is not necessarily the ultimate step.

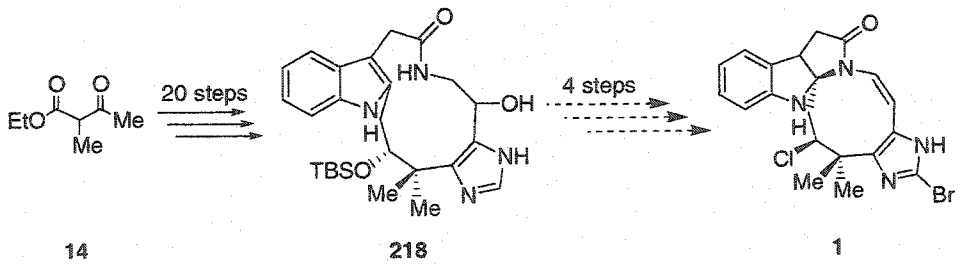
Scheme 3.9.10



3.10 Conclusions

Using a previously discussed synthetic sequence, this lab has been able to advance a simple, commercially available starting material (**43**) and in an efficient 20-step sequence successfully construct **218** which contains the complete the securamine A (**1**) macrocyclic core (Scheme 3.10.1).

Scheme 3.10.1



With numerous possible sequences in mind for completion of the natural product, this lab set out on three different pathways to complete construction of **1**. The first was to introduce the elusive neopentyl chlorine and enamide moieties in one step by treatment of diol **229** with previously successful chlorination/elimination conditions (Scheme 3.9.4).

Upon failure of this first attempt it was believed that both of these functionalities could be installed sequentially. Unfortunately, after protection of the C3 alcohol and treatment of the neopentyl chlorine with the previously successful chlorination conditions, olefin **240** is isolated exclusively (Scheme 3.9.7).

With two failed endgame sequences in hand, it was hoped that a reordering of events would prove fruitful. However, this final strategy would also ultimately prove ineffective as exposure of a variety of suitable substrates to various elimination conditions failed providing none of the desired enamide (**244**) (Scheme 3.9.9)

Therefore work on the most advanced substrates (**245, 242**) currently stands at a maximum four synthetic steps away from the desired natural product. It is hoped that one of these pathways may soon be advanced to Securamine A (**1**).

3.11 Experimental Section

3.11.1 Materials and Methods.

Unless stated otherwise, reactions were performed in flame dried glassware under a nitrogen atmosphere using freshly distilled solvents. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methylene chloride (CH_2Cl_2), benzene (PhH), toluene (PhMe), triethylamine (Et_3N), pyridine, and piperidine were distilled from calcium hydride. Methyl sulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF) were either purchased from the Aldrich Chemical Company in Sure/Seal™ containers and used as received or stored over molecular sieves. All other commercially obtained reagents were used as received.

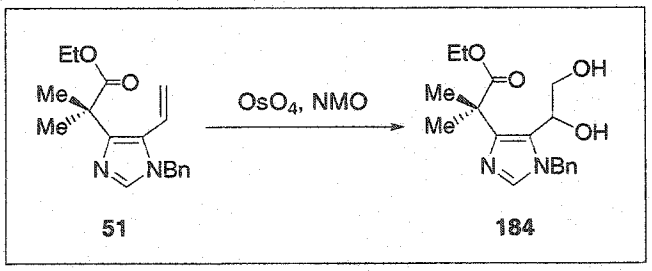
Unless stated otherwise, all reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm). Column or flash chromatography was performed with the indicated solvents using silica gel (230-400 mesh) purchased from Bodman. Concentration *in vacuo* refers to the removal of solvent with a Buchi R-3000 rotary evaporator at normal aspirator pressure followed by further evacuation with a two stage mechanical pump. When reactions were adsorbed onto silica gel, the amount of silica gel used was equal to two times the weight of the reagents.

All melting points were obtained on a Gallenkamp variable temperature capillary melting point apparatus (model: MPD350.BM2.1) and are uncorrected. Infrared spectra were recorded on a Midac M1200 FTIR. ^1H and ^{13}C NMR spectra were recorded on a

Bruker AM-500, Bruker Avance DPX-500, or Bruker Avance DPX-400 spectrometer. Chemical shifts are reported relative to internal chloroform (^{1}H, δ 7.27 ppm; ^{13}C, δ 77.0 ppm), methanol (^{1}H, δ 3.31 ppm; ^{13}C, δ 49.0 ppm), or DMSO (^{1}H, δ 2.50 ppm; ^{13}C, δ 39.50 ppm). High resolution mass spectra were performed at the University of Illinois Mass Spectrometry Center. High performance liquid chromatography (HPLC) was performed on a Waters 510 solvent delivery system using a Rainin Microsorb 80-199-C5 column, or a Rainin Dynamax SD-200 solvent delivery system using a Rainin Microsorb 80-120-C5 column. Single crystal X-ray analyses were performed by Dr. Christopher Incarvito of Yale University.

3.11.2 Preparative Procedures.

Preparation of Diol 184:



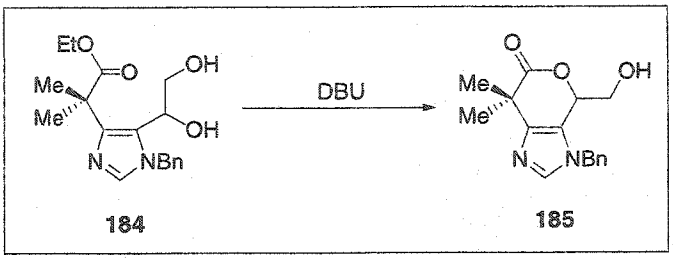
51 184

Diol 184. To a solution of vinyl imidazole **51** (2.0 g, 6.80 mmol, 1.0 equiv.) in a 4:1 mixture of THF (35 mL) and H_2O (18 mL) was added OsO_4 (4% aq.) (300 μL) and N-methylmorpholine-N-Oxide (1.13 g, 8.40 mmol, 1.24 equiv.). The mixture was allowed to slowly warm to room temperature and monitored by TLC. Upon consumption

of the starting material (as indicated by TLC) the reaction mixture was diluted with Et_2O (50 mL), washed with brine (50 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The resulting residue was chromatographed on silica gel (70% EtOAc/Hexanes) to afford **184** (1.8 g, 81% yield) as a off-white solid.

Diol 184. FTIR (thin film/NaCl) 3361 (s), 2980 (s), 2934 (s), 2873 (m), 2248 (w), 1955 (w), 1869 (w), 1723 (s), 1558 (m), 1505 (m), 1455 (m), 1385 (m), 1363 (m), 1257 (s), 1140 (s), 1078 (m), 1029 (m), 999 (m), 911 (m), 886 (m), 860 (m), 774 (m), 730 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (m, 4H), 7.07 (d, *J*=6.8 Hz, 2H), 5.35 (s, 2H), 5.00 (dd, *J*=4.1 Hz, 9.5 Hz, 1H), 4.24-4.08 (m, 2H), 3.65 (dd, *J*=9.5 Hz, 11.3 Hz, 1H), 3.50 (dd, *J*=4.1 Hz, 11.3 Hz, 1H), 3.23 (bs, 1H), 2.56 (bs, 1H), 1.64 (s, 3H), 1.62 (s, 3H), 1.26 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 142.6, 137.5, 137.3, 129.2, 128.3, 127.2, 125.5, 67.6, 65.5, 61.6, 44.0, 27.4, 27.0, 14.4; HRMS (EI) *m/z* 333.1814 [calculated for $C_{18}H_{25}N_2O_4$ (M^+) 333.1814].

Preparation of Lactone 185:

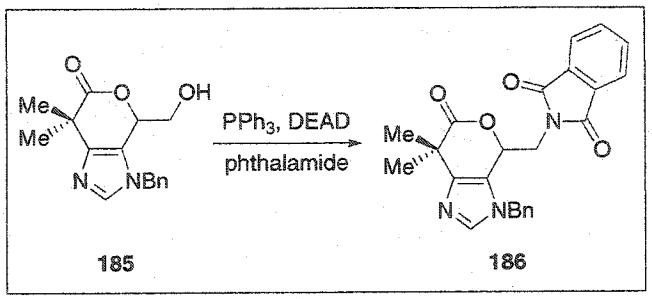


184 **185**

Lactone 185. To a stirred solution of diol **184** (520 mg, 1.59 mmol, 1.0 equiv.) in CH_2Cl_2 (15 mL) was added DBU (2.20 mL, 15.00 mmol, 9.43 equiv.). The reaction was allowed to stir at room temperature and monitored by TLC. Upon consumption of the starting material (as indicated by TLC) the solvent was removed *in vacuo*. The resulting oil was chromatographed on silica gel (50% EtOAc/Hexanes) to afford **185** (330 mg, 73% yield) as a white solid.

Lactone 185. m.p. 152-155°C; FTIR (thin film/NaCl) 3112 (m), 3033 (m), 2979 (m), 2932 (m), 2870 (m), 2250 (w), 2210 (w), 1729 (s), 1501 (s), 1453 (m), 1386 (m), 1358 (m), 1307 (w), 1229 (s), 1196 (m), 1166 (m), 1116 (s), 1080 (m), 1049 (m), 975 (w), 911 (m), 836 (m), 732 (s), 697 (m), 647 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.42-7.32 (m, 3H), 7.11 (d, *J*=7.0 Hz, 2H), 5.19 (t, *J*=3.9 Hz, 1H), 5.16 (d, *J*=15.7 Hz, 1H), 5.10 (d, *J*=15.7 Hz, 1H), 3.82 (dd, *J*=3.4 Hz, 12.3 Hz, 1H), 3.69 (dd, *J*=4.4 Hz, 12.3 Hz, 1H), 1.60 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 142.1, 140.0, 135.3, 129.7, 129.1, 127.3, 118.5, 78.7, 65.1, 50.1, 41.1, 28.8, 27.2; HRMS (EI) *m/z* 287.1395 [calculated for $C_{16}H_{19}N_2O_3$ (M^+) 287.1396].

Preparation of Phthalamide 186:

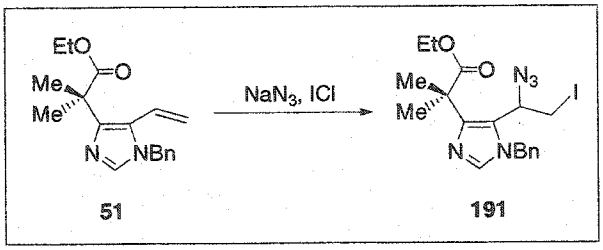


Phthalamide 186. To a solution of lactone **185** (232 mg, 0.81 mmol, 1.0 equiv.) in THF (10 mL) at 0°C was added triphenylphosphine (PPh_3) (263 mg, 1.01 mmol, 1.25 equiv.), diethyl azodicarboxylate (DEAD) (222 μL, 1.41 mmol, 1.75 equiv.) and phthalimide (147 mg, 1.01 mmol, 1.25 equiv.). The reaction was allowed to warm to room temperature and stirred for 2 hours at which time the solvent was removed *in vacuo*. The resulting viscous oil was chromatographed on silica gel (70% EtOAc/Hexanes) to afford **186** (305 mg, 91% yield) as a white solid.

Phthalamide 186. m.p. 201-204°C; FTIR (thin film/NaCl) 3476 (w), 3109 (w), 3063 (w), 3032 (w), 2977 (m), 2935 (m), 2871 (w), 2255 (w), 2215 (w), 1773 (m), 1738 (s), 1719 (s), 1613 (w), 1499 (m), 1419 (s), 1395 (s), 1365 (m), 1316 (m), 1227 (m), 1192 (m), 1171 (m), 1102 (s), 1058 (m), 1007 (m), 978 (w), 950 (w), 908 (m), 851 (w), 794 (w), 724 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (dd, *J*=3.2 Hz, 5.2 Hz, 2H), 7.73 (dd, *J*= 3.2 Hz, 5.2 Hz, 2H), 7.60 (s, 1H), 7.44-7.33 (m, 3H), 7.27 (d, *J*=7.0 Hz, 2H), 5.50 (dd, *J*=2.6 Hz, 8.7 Hz, 1H), 5.27 (s, 2H), 3.92 (dd, *J*=9.0 Hz, 14.5 Hz, 1H), 3.76 (dd, *J*=2.6 Hz, 14.5 Hz, 1H), 1.62 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 168.0, 142.4, 140.1, 135.2, 134.7, 132.2, 129.8, 129.2, 127.7, 124.0, 118.3, 72.8, 50.1,

43.6, 41.2, 29.4, 26.4; HRMS (EI) *m/z* 416.1610 [calculated for $C_{24}H_{22}N_3O_4$ (M^+) 416.1610].

Preparation of Azide 191:

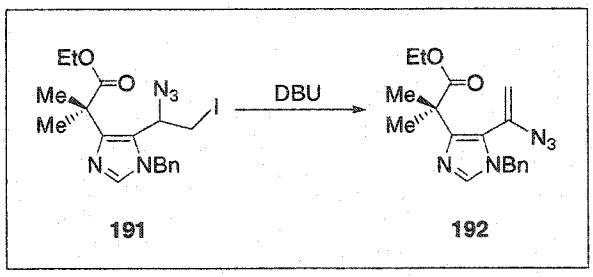


Azide 191. To a stirred solution of sodium azide (NaN_3) (22 mg, 0.39 mmol, 2.0 equiv.) in CH_3CN (1 mL) at -20°C was added dropwise iodine monochloride as a 1.0M solution in CH_2Cl_2 (350 μL, 2.1 equiv.). The reaction mixture was stirred for 1.5 hours at -20°C at which time vinyl imidazole **51** (50 mg, 0.17 mmol, 1.0 equiv.) was added. The reaction mixture was then allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was then washed with $Na_2S_2O_4$ (sat., aq.) (5 mL), brine (5 mL) and dried with $MgSO_4$. The solvent was removed *in vacuo* and the resulting oil chromatographed on silica gel (50% EtOAc/Hexanes) to afford **191** (65 mg, 82% yield) as a colorless oil.

Azide 191. FTIR (thin film/NaCl) 3107 (w), 3064 (w), 3031 (w), 2980 (m), 2935 (m), 2871 (w), 2107 (s), 1722 (s), 1498 (m), 1453 (m), 1413 (w), 1384 (w), 1353 (w), 1330 (w), 1253 (s), 1210 (w), 1182 (m), 1160 (m), 1137 (s), 1027 (m), 926 (m), 851 (w), 772 (w), 727 (m), 695 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.41-7.31

(m, 3H), 7.09 (d, *J*=7.2 Hz, 2H), 5.32 (d, *J*=15.9 Hz, 1H), 5.27 (d, *J*=15.9 Hz, 1H), 5.14 (dd, *J*=3.6 Hz, 11.1 Hz, 1H), 4.23 (dq, *J*=2.2 Hz, 7.1 Hz, 2H), 3.12 (dd, *J*=4.1 Hz, 10.6 Hz, 1H), 3.05 (t, *J*=10.9 Hz, 1H), 1.68 (s, 3H), 1.66 (s, 3H), 1.30 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 144.5, 138.3, 136.2, 129.6, 128.8, 127.0, 123.0, 61.9, 60.2, 50.3, 44.0, 27.5, 14.5, 5.2; HRMS (EI) *m/z* 468.0896 [calculated for $C_{18}H_{23}N_5O_2I$ (M^+) 468.0897].

Preparation of Olefin 192:



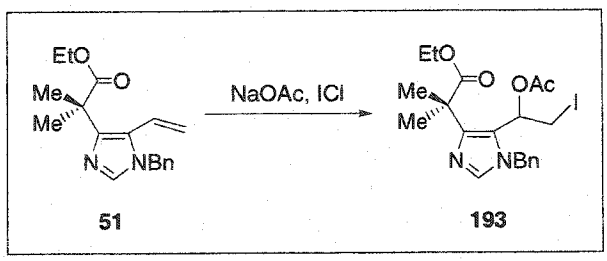
191 **192**

Olefin 192. To a stirred solution of azide **191** (25 mg, 0.05 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) was added DBU (40 µL, 0.27 mmol, 5.00 equiv.). The reaction was allowed to stir at room temperature and monitored by TLC. Upon consumption of the starting material (as indicated by TLC) the solvent was removed *in vacuo*. The resulting oil was chromatographed on silica gel (50% EtOAc/Hexanes) to afford **192** (15 mg, 83% yield) as a colorless oil.

Olefin 192. FTIR (thin film/NaCl) 3111 (w), 3066 (w), 3033 (w), 2981 (m), 2936 (m), 2871 (w), 2100 (s), 1729 (s), 1640 (m), 1542 (w), 1489 (m), 1469 (m), 1382 (m), 1361 (m), 1320 (m), 1255 (s), 1194 (w), 1136 (s), 1029 (m), 735 (m), 698 (m), 688 (m)

cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.40-7.30 (m, 3H), 7.15 (d, *J*=7.7 Hz, 2H), 5.18 (s, 1H), 5.07 (s, 2H), 4.74 (s, 1H), 4.13 (q, *J*=7.1 Hz, 2H), 1.62 (s, 6H), 1.24 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 145.3, 136.9, 136.0, 135.7, 129.3, 128.6, 127.7, 121.7, 109.2, 61.1, 49.5, 44.3, 26.6, 14.4; HRMS (EI) *m/z* 340.1774 [calculated for $C_{18}H_{22}N_5O_2$ (M^+) 340.1774].

Preparation of Iodide 193:

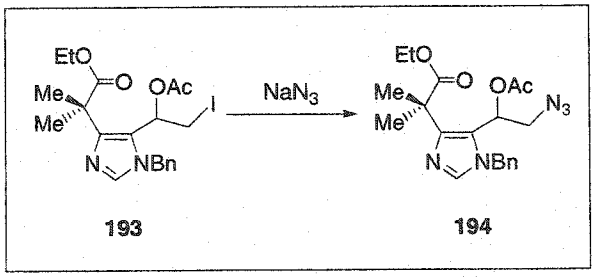


51 **193**

Iodide 193. To a stirred solution of sodium acetate (NaOAc) (413 mg, 5.04 mmol, 2.0 equiv.) in CH_3CN (12 mL) at -20°C was added dropwise iodine monochloride as a 1.0M solution in CH_2Cl_2 (5.30 mL, 2.1 equiv.). The reaction mixture was stirred at -20°C for 1.5 hours at which time vinyl imidazole **51** (750 mg, 2.52 mmol, 1.0 equiv.) was added. The reaction mixture was then allowed to warm to 0°C and stirred for 2 hours. The reaction mixture was then washed with $Na_2S_2O_4$ (sat., aq.) (25 mL), brine (25 mL) and dried with $MgSO_4$. The solvent was removed *in vacuo* and the resulting oil chromatographed on silica gel (50% EtOAc/Hexanes) to afford **193** (1.22 mg, 99% yield) as a colorless oil.

Iodide 193. m.p. 84-87°C; FTIR (thin film/NaCl) 3090 (w), 3064 (w), 3030 (w), 2979 (m), 2935 (m), 2872 (w), 1748 (s), 1723 (s), 1497 (m), 1466 (m), 1455 (m), 1370 (m), 1301 (w), 1227 (s), 1180 (m), 1134 (m), 1052 (m), 1022 (m), 952 (m), 920 (m), 859 (w), 772 (w), 730 (m), 695 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (bs, 1H), 7.40-7.29 (m, 3H), 6.97 (d, *J*=7.1 Hz, 2H), 6.20 (dd, *J*=3.8 Hz, 10.6 Hz, 1H), 5.31 (s, 2H), 4.31-4.15 (m, 2H), 3.38-3.24 (m, 2H), 1.74 (s, 3H), 1.70 (s, 3H), 1.68 (s, 3H), 1.30 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 169.4, 144.5, 138.1, 137.1, 129.4, 128.4, 126.2, 122.8, 81.6, 67.9, 50.1, 44.3, 27.0, 26.9, 20.4, 14.4, 4.7; HRMS (EI) *m/z* 485.0940 [calculated for $C_{15}H_{28}N_5O_5I$ (M^+) 485.0937].

Preparation of Azide 194:

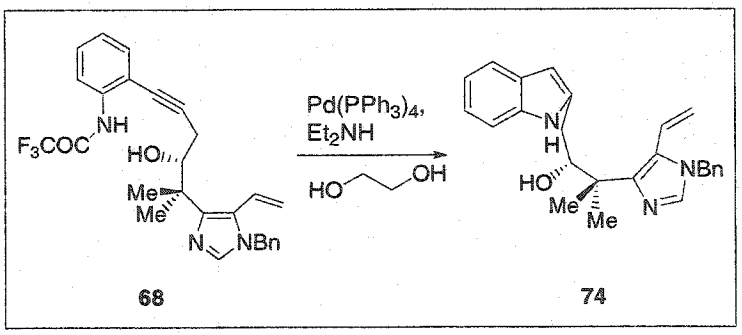


193 **194**

Azide 194. To a stirred solution of iodide **193** (500mg, 1.03 mmol, 1.0 equiv.) in DMF (10 mL) was added sodium azide (NaN_3) (500 mg, 7.54 mmol, 7.5 equiv.). The mixture was stirred at 90°C for 4 hours, then cooled to room temperature, diluted with Et_2O (50 mL) and washed with H_2O (2 x 25 mL). The organic layer was then dried with $MgSO_4$, reduced *in vacuo* and chromatographed on silica gel (50% EtOAc/Hexanes) to afford **194** (300 mg, 72% yield) as a colorless oil.

Azide 194. m.p. 77-79°C; FTIR (thin film/NaCl) 3108 (w), 3064 (w), 3031 (w), 2981 (m), 2936 (m), 2873 (w), 2101 (s), 1748 (s), 1723 (s), 1498 (m), 1453 (m), 1371 (m), 1299 (m), 1256 (s), 1220 (s), 1137 (m), 1030 (m), 942 (m), 842 (w), 811 (w), 773 (w), 730 (m), 695 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.38-7.28 (m, 3H), 6.94 (d, *J*=7.4 Hz, 2H), 6.21 (dd, *J*=3.3 Hz, 9.3 Hz, 1H), 5.39 (d, *J*=16.4 Hz, 1H), 5.30 (d, *J*=16.4 Hz, 1H), 4.26-4.11 (m, 2H), 3.49 (dd, *J*=9.5 Hz, 13.3 Hz, 1H), 3.27 (dd, *J*=3.6 Hz, 13.3 Hz, 1H), 1.70 (s, 3H), 1.68 (s, 3H), 1.27 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 169.6, 144.6, 138.4, 137.5, 129.5, 128.4, 126.2, 121.9, 67.0, 61.5, 53.6, 50.4, 44.3, 28.8, 27.0, 20.6, 14.5; HRMS (EI) *m/z* 400.1984 [calculated for $C_{20}H_{26}N_5O_4$ (M^+) 400.1985].

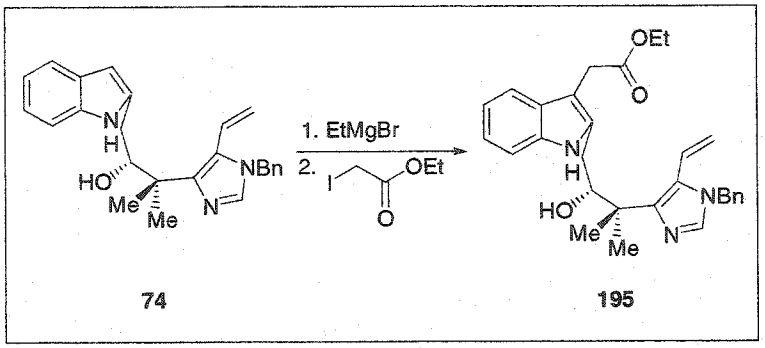
Preparation of Indole 74:



Indole 74. To a stirred solution of **68** (10.4 g, 21.6 mmol, 1.0 equiv.) in DMF (75 mL) and ethylene glycol (30 mL) was added Et_2NH (15.0 mL, 205 mmol, 9.5 equiv.) and $Pd(PPh_3)_4$ (1.24 g, 1.08 mmol, 0.05 equiv.). The mixture was heated to 60°C for 12 hours and then poured into Et_2O (500 mL). The reaction was washed with H_2O (3 x 200

mL), brine (200 mL), and dried with $MgSO_4$. The solvent was removed *in vacuo* and the crude mixture chromatographed on silica gel (40% EtOAc/Hexanes) to afford **74** (6.1 g, 73% yield) as a yellow foam.

Preparation of Ester 195:

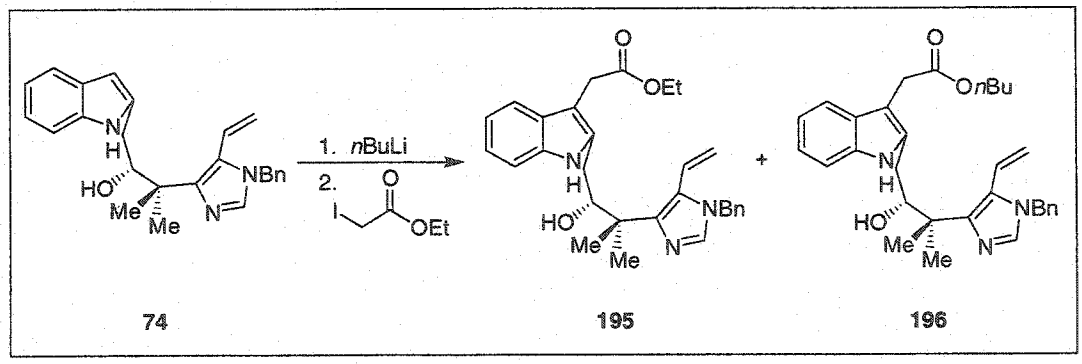


Ester 195. To a stirred solution of EtMgBr (1.0 M) (2.90 mL, 2.90 mmol, 8.0 equiv.) in THF (5 mL) at room temperature was added **74** (140 mg, 0.36 mmol, 1.0 equiv.) in THF (5 mL) dropwise. The mixture was stirred for 30 minutes at room temperature. After 30 minutes ethyl iodoacetate (300 μL, 2.52 mmol, 7.0 equiv.) was added. The reaction was stirred for another 30 minutes and then quenched by addition of NH_4Cl (sat. aq.) (5.0 mL). H_2O (10 mL) was added and the reaction was extracted with EtOAc (3 x 25 mL). The organic layers were combined, washed with brine (50 mL) and dried with $MgSO_4$. Silica gel chromatography (40% EtOAc/Hexanes) afforded **74** (58 mg, 38% yield) and **195** (27 mg, 17% yield) as yellow foams.

Esters 195. FTIR (thin film/NaCl) 3261 (s), 3111 (m), 3061 (m), 2976 (s), 2931 (s), 2873 (m), 2247 (w), 1731 (s), 1634 (m), 1498 (s), 1463 (s), 1359 (m), 1310 (m), 1241

(m), 1161 (s), 1103 (m), 1063 (m), 1031 (m), 996 (m), 910 (m), 736 (s), 697 (m), 648 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.46 (bs, 1H), 7.57 (d, *J*=7.6 Hz, 1H), 7.44 (s, 1H), 7.42-7.27 (m, 4H), 7.19-7.08 (m, 2H), 7.06 (d, *J*=7.6 Hz, 1H), 6.67 (dd, *J*=11.4 Hz, 17.8 Hz, 1H), 5.48 (dd, *J*=1.3 Hz, 11.7 Hz, 1H), 5.28 (dd, *J*=1.6 Hz, 18.1 Hz, 1H), 5.11 (s, 2H), 4.12 (q, *J*=7.0 Hz, 2H), 3.98 (d, *J*=10.5 Hz, 1H), 3.71 (d, *J*=15.4 Hz, 1H), 3.67 (d, *J*=15.4 Hz, 1H), 3.11 (dd, *J*=1.4 Hz, 15.4 Hz, 1H), 2.65 (dd, *J*=10.5 Hz, 15.1 Hz, 1H), 1.49 (s, 3H), 1.44 (s, 3H), 1.23 (t, *J*=7.3 Hz ,3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 145.6, 137.0, 136.8, 135.6, 135.5, 129.4, 128.4, 127.0, 126.3, 126.1, 121.5, 121.4, 119.4, 118.4, 111.1, 104.2, 80.8, 61.1, 49.3, 40.6, 31.1, 31.0, 28.6, 27.2, 24.8, 14.7; HRMS (EI) *m/z* 472.2600 [calculated for $C_{29}H_{34}N_3O_3$ (M^+) 472.2600].

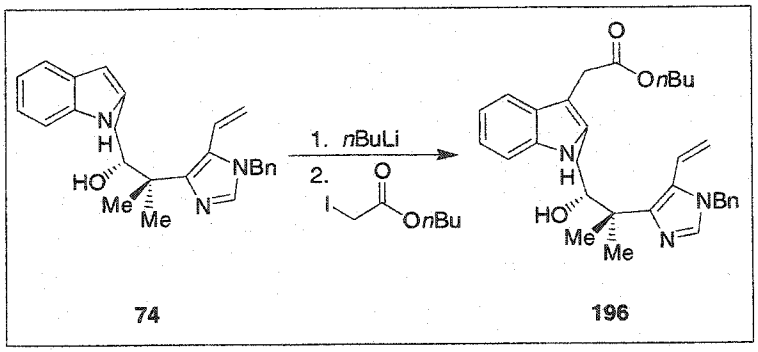
Preparation of Esters 195 and 196:



Esters 195 and 196. To a stirred solution of **74** (500 mg, 1.30 mmol, 1.0 equiv.) in THF (10 mL) at -78°C was added *n*-BuLi (1.6M) (1.31 mL, 2.1 equiv.) dropwise. The reaction mixture was stirred at -78°C for 45 minutes at which time ethyl iodoacetate (154 μL, 1.30 mmol, 1 equiv.) was added dropwise. The reaction was warmed to 0°C and

allowed to stir for 1 hour and then quenched by addition of NH_4Cl (sat. aq.) (10 mL). H_2O (20 mL) was added and the reaction was extracted with EtOAc (3 x 25 mL). The organic layers were combined, washed with brine (50 mL) and dried with $MgSO_4$. Silica gel chromatography (30% EtOAc/Hexanes) afforded an inseparable mixture of **195** (98 mg, 16% yield) and **196** (311 mg, 48% yield) as white foams.

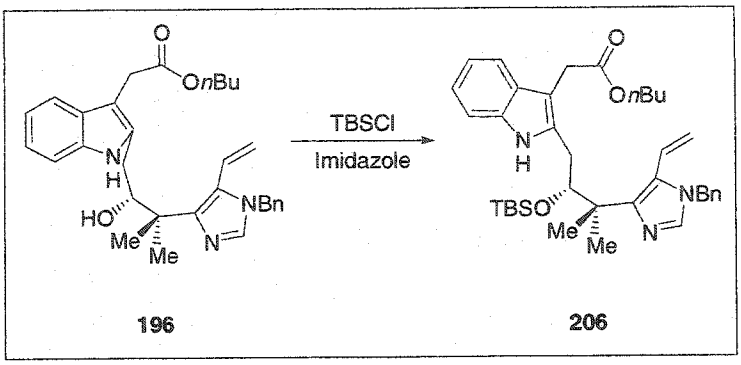
Preparation of Ester 196:



Ester 196. To a stirred solution of **74** (75 mg, .195 mmol, 1.0 equiv.) in THF (5 mL) at -78°C was added *n*-BuLi (1.6M) (250 µL, 2.05 equiv.) dropwise. The reaction mixture was stirred at -78°C for 45 minutes at which time *n*-butyl iodoacetate (**200**) (28 µL, .195 mmol, 1.0 equiv.) was added dropwise. The reaction was warmed to 0°C and allowed to stir for 1 hour and then quenched by addition of NH_4Cl (sat. aq.) (5 mL). H_2O (10 mL) was added and the reaction was extracted with EtOAc (3 x 25 mL). The organic layers were combined, washed with brine (25 mL) and dried with $MgSO_4$. Silica gel chromatography (30% EtOAc/Hexanes) afforded **196** (87 mg, 89% yield) as white foams.

Ester 196. FTIR (thin film/NaCl) 3271 (s), 3058 (m), 2978 (s), 2929 (m), 1732 (s), 1663 (m), 1644 (m), 1550 (w), 1498 (m), 1457 (s), 1358 (w), 1302 (w), 1239 (w), 1184 (s), 1061 (m), 1030 (m), 946 (w), 853 (m), 780 (m), 736 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.51 (bs, 1H), 9.45 (bs, 1H), 7.55 (d, *J*=7.5 Hz, 1H), 7.52 (d, *J*=7.9 Hz, 1H), 7.46 (s, 1H), 7.44 (s, 1H), 7.38-7.28 (m, 8H), 7.13-7.01 (m, 8H), 6.32 (d, *J*=13.0 Hz, 1H), 6.29 (d, *J*=13.0 Hz, 1H), 6.20 (s, 1H), 5.37 (d, *J*=13.0 Hz, 1H), 5.35 (d, *J*=13.0 Hz, 1H), 5.00 (s, 2H), 4.98 (s, 2H), 4.10 (q, *J*=7.0 Hz, 2H), 3.92 (m, 2H), 3.80 (m, 4H), 3.70 (d, *J*=15.3 Hz, 1H), 3.65 (d, *J*=15.3 Hz, 1H), 3.09 (dd *J*=1.5 Hz, 15.3 Hz, 1H), 3.00 (dd, *J*=1.6 Hz, 15.1 Hz, 1H), 2.67 (dd, *J*=10.3 Hz, 15.2 Hz, 1H), 2.61 (dd, *J*=10.3 Hz, 15.2 Hz, 1H), 1.46 (s, 3H), 1.45 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.31 (t, *J*=7.0 Hz, 3H), 1.30 (t, *J*=7.0 Hz, 3H), 1.21 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 153.0, 152.9, 145.0, 144.9, 136.7, 136.6, 136.2, 136.1, 135.2, 135.1, 135.0, 128.9, 128.3, 128.0, 127.9, 126.7, 126.6, 122.9, 122.8, 120.9, 120.6, 119.4, 119.1, 118.9, 117.9, 110.7, 110.6, 103.7, 99.4, 92.4, 80.8, 80.5, 65.5, 65.4, 60.6, 48.4, 48.4, 40.1, 40.1, 30.6, 30.5, 28.2, 27.4, 27.1, 24.5, 24.3, 14.7, 14.2; HRMS (EI) *m/z* 472.2600 [calculated for $C_{29}H_{34}N_3O_3$ (M^+) 472.2600].

Preparation of TBS-Alcohol 196:



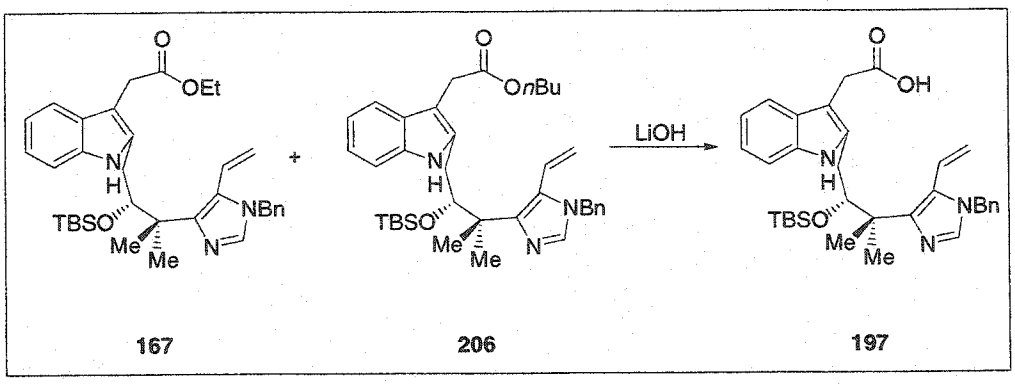
196 206

TBS-Alcohol 206. To a stirred solution of alcohol **196** (3.55 g, 6.50 mmol, 1.0 equiv.) in DMF (40 mL) at room temperature was added imidazole (1.60 g, 23.0 mmol, 3.5 equiv.) and TBSCl (1.50 g, 9.70 mmol, 1.5 equiv.). The mixture was stirred for 24 hours, at which time it was diluted with Et_2O (100 mL) and washed with H_2O (2 x 100 mL). The organic layer was separated, washed with brine (100 mL) and dried with $MgSO_4$. Silica gel chromatography (50% EtOAc/Hexanes) afforded **206** (3.94 g, 91% yield) as a colorless, viscous oil.

TBS-Alcohol 206. FTIR (thin film/NaCl) 3377 (m), 3197 (m), 3089 (m), 3059 (m). 3032 (m), 2957 (s), 2930 (s), 2895 (m), 2856 (m), 1731 (s), 1630 (s), 1497 (m), 1463 (s), 1382 (m), 1359 (m), 1306 (m), 1251 (s), 1160 (s), 1076 (s), 1040 (m), 1005 (m), 995 (m), 928 (m), 836 (s), 810 (m), 776 (s), 736 (s), 697 (m), 668 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.55 (d, J=7.6 Hz, 1H), 7.47 (s, 1H), 7.36-7.24 (m, 4H), 7.15-7.01 (m, 4H), 6.70 (dd, J=11.6 Hz, 17.9 Hz, 1H), 5.39 (dd, J=1.5 Hz, 11.6 Hz, 1H), 5.19 (dd, J=1.5 Hz, 17.9 Hz, 1H), 5.02 (s, 2H), 4.68 (dd, J=4.0 Hz, 5.3 Hz, 1H), 4.08 (t, J=6.7 Hz, 2H), 3.68 (d, J=15.3 Hz, 1H), 3.58 (d, J=15.3 Hz, 1H), 2.94 (dd, J=4.0 Hz,

15.5 Hz, 1H), 2.87 (dd, *J*=5.5 Hz, 15.5 Hz, 1H), 1.60 (q, *J*=6.9 Hz, 2H), 1.42-1.29 (m, 2H), 1.40 (s, 3H), 1.36 (s, 3H), 0.99 (s, 9H), 0.91 (t, *J*=7.4 Hz, 3H), 0.05 (s, 3H), -0.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 146.6, 137.2, 137.0, 136.5, 135.8, 129.3, 128.9, 128.2, 127.1, 126.8, 126.4, 121.3, 120.0, 119.3, 118.7, 110.6, 105.1, 79.2, 64.7, 49.2, 42.8, 31.9, 31.1, 28.9, 28.5, 21.3, 19.4, 18.5, 13.9, -4.1, -4.3; HRMS (EI) *m/z* 614.3780 [calculated for $C_{37}H_{53}N_3O_3Si$ (M^+) 614.3778].

Preparation of Carboxylic Acid 197:

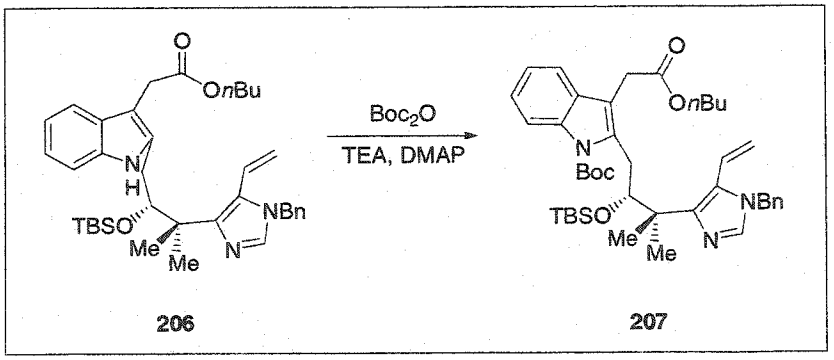


Carboxylic Acid 197. To a solution of esters **167** and **206** (35 mg, .057 mmol, 1.0 equiv.) in a mixture of THF (2 mL) and H_2O (1 mL) was added LiOH (15 mg, 0.6 mmol, 10 equiv.). The reaction mixture was heated to 80°C and stirred for 24 hours. The reaction was cooled to room temperature diluted with Et_2O (5 mL) and washed with NH_4Cl (sat. aq.) (5 mL). The organic layer was dried with $MgSO_4$ and chromatographed on silica gel (80% EtOAc/Hexanes) to afford **197** (25 mg, 76% yield) as a white solid.

Carboxylic Acid 197. FTIR (thin film/NaCl) 3194 (m), 3060 (m), 2954 (s), 2929 (s), 2895 (m), 2855 (s), 1722 (m), 1713 (m), 1549 (m), 1462 (m), 1390 (m), 1362 (w),

1303 (w), 1255 (m), 1087 (m), 1008 (w), 986 (w), 911 (m), 838 (m), 778 (m), 734 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.06 (bs, 1H), 7.87 (s, 1H), 7.46 (d, *J*=7.4 Hz, 1H), 7.39-7.30 (m, 4H), 7.09-6.96 (m, 4H), 6.46 (dd, *J*=11.6 Hz, 17.8 Hz, 1H), 5.72 (d, *J*=11.3 Hz, 1H), 5.39 (d, *J*=17.8 Hz, 1H), 4.90 (t, *J*=5.3 Hz, 1H), 4.79 (d, *J*=14.8 Hz, 1H), 4.73 (d, *J*=14.8 Hz, 1H), 3.68 (d, *J*=15.7 Hz, 1H), 3.62 (d, *J*=15.7 Hz, 1H), 2.86 (dd, *J*=6.3 Hz, 15.6 Hz, 1H), 2.77 (d, *J*=5.6 Hz, 15.5 Hz, 1H), 1.35 (s, 3H), 1.32 (s, 3H), 0.89 (s, 9H), -0.01 (s, 3H), -0.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 138.1, 135.9, 134.4, 133.7, 132.7, 129.8, 129.7, 128.8, 128.2, 127.3, 127.4, 123.6, 121.7, 119.5, 118.3, 111.5, 104.8, 76.5, 51.0, 41.9, 31.0, 30.8, 27.2, 26.4, 22.1, 18.4, -4.0, -4.6; HRMS (EI) *m/z* 558.3103 [calculated for $C_{33}H_{46}N_2O_2Si$ (M^+) 558.3098].

Preparation of Boc-Indole 207:

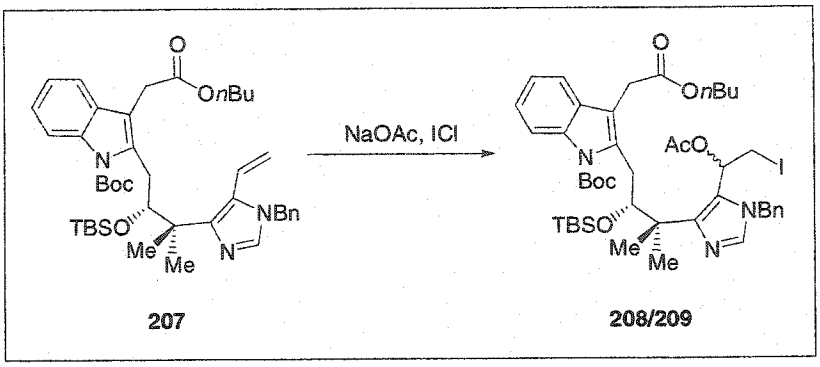


Boc-Indole 207. To a stirred solution of **206** (3.94 g, 5.93 mmol, 1.0 equiv.) in CH_2Cl_2 (100 mL) at room temperature was added Et_3N (4.13 mL, 29.7 mmol, 5.0 equiv.) and DMAP (724 mg, 29.7 mmol, 5.0 equiv.) followed by di-*t*-butyl dicarbonate (6.48 g, 2.88 mmol, 10 equiv.). The solution was heated to reflux and stirred for 24 hours, at

which time the reaction was poured into H_2O (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, washed with brine (100 mL) and dried with $MgSO_4$. The resulting oil was chromatographed on silica gel (30% EtOAc/Hexanes) to afford **207** (3.67 g, 85% yield) as a colorless oil.

Boc-Indole 207. FTIR (thin film/NaCl) 2958 (m), 2931 (m), 2855 (m), 1733 (s), 1628 (w), 1607 (w), 1577 (w), 1497 (w), 1456 (m), 1359 (m), 1324 (m), 1253 (m), 1157 (m), 1136 (m), 1117 (m), 1077 (m), 1005 (w), 990 (w), 913 (w), 837 (m), 807 (w), 774 (m), 732 (m), 696 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98-7.93 (m, 1H), 7.46-7.41 (m, 6H), 7.34-7.16 (m, 6H), 7.02 (d, *J*=7.6 Hz, 2H), 6.80 (dd, *J*=11.7 Hz, 17.7 Hz, 1H), 5.29 (d, *J*=11.7 Hz, 1H), 5.12 (d, *J*=17.7 Hz, 1H), 4.86-4.70 (m, 2H), 4.65 (dd, *J*=4.6 Hz, 8.1 Hz, 1H), 4.08 (t, *J*=6.6 Hz, 2H), 3.73 (d, *J*=16.2 Hz, 1H), 3.68 (d, *J*=16.2 Hz, 1H), 3.38 (dd, *J*=8.1 Hz, 14.7 Hz, 1H), 3.17 (dd, *J*=5.1 Hz, 14.7 Hz, 1H), 1.72 (s, 9H), 1.63-1.56 (m, 2H), 1.53 (s, 3H), 1.46 (s, 3H), 1.39-1.31 (m, 2H), 0.91 (t, *J*=7.1 Hz, 3H), 0.86 (s, 9H), -0.04 (s, 3H), -0.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 150.8, 146.8, 137.9, 136.8, 136.0, 130.4, 129.1, 128.0, 127.1, 127.0, 125.7, 123.5, 122.6, 118.4, 117.8, 115.8, 114.1, 83.7, 78.0, 64.9, 49.0, 42.5, 31.4, 31.1, 31.0, 28.7, 27.8, 26.7, 22.1, 19.4, 18.5, 13.8, -4.3; HRMS (EI) *m/z* 714.4303 [calculated for $C_{42}H_{60}N_3O_5Si$ (M^+) 714.4302].

Preparation of Iodides 208, 209:

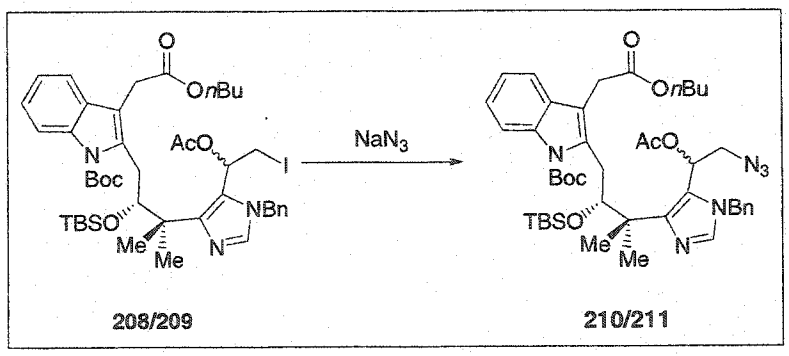


Iodides 208, 209. To a stirred solution of sodium acetate (NaOAc) (385 mg, 4.68 mmol, 3.0 equiv.) in CH_3CN (15 mL) at -20°C was added dropwise iodine monochloride as a 1.0M solution in CH_2Cl_2 (2.75 mL, 1.75 equiv.). The reaction mixture was stirred at -20°C for 1.5 hours at which time vinyl imidazole **207** (1.07 g, 1.56 mmol, 1.0 equiv.) was added. The reaction mixture was then allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was then washed with $Na_2S_2O_4$ (sat., aq.) (25 mL), brine (25 mL) and dried with $MgSO_4$. The solvent was removed *in vacuo* and the resulting oil chromatographed on silica gel (50% EtOAc/Hexanes) to afford **208** and **209** (1.30 mg, 93% yield) as a white foam.

Iodides 208, 209. FTIR (thin film/NaCl) 3583 (w), 2957 (m), 2930 (m), 2855 (w), 1734 (s), 1456 (m), 1369 (m), 1324 (w), 1229 (m), 1157 (m), 1137 (w), 1116 (w), 1078 (w), 947 (w), 920 (w), 837 (m), 807 (w), 775 (w), 729 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J*=7.7 Hz, 1H), 7.45 (d, *J*=7.2 Hz, 1H), 7.41-7.26 (m, 5H), 7.24-7.16 (m, 2H), 7.08-7.00 (m, 2H), 6.73 (dd, *J*=3.3 Hz, 10.5 Hz, 0.3H), 6.68 (dd, *J*=3.3 Hz, 10.5 Hz, 0.7H), 5.30-5.17 (m, 2H), 4.72 (d, *J*=10.5 Hz, 0.7H), 4.66 (d, *J*=10.5 Hz, 0.3H),

4.17-4.02 (m, 2H), 3.85-3.70 (m, 2H), 3.61-3.37 (m, 2H), 3.31 (dd, *J*=4.4 Hz, 11.1 Hz, 1H), 3.03-2.92 (m, 1H), 1.88 (s, 2H), 1.82 (s, 1H), 1.73 (s, 9H), 1.65-1.55 (m, 5H), 1.54-1.45 (m, 3H), 1.39-1.30 (m, 2H), 0.91 (t, *J*=7.2 Hz, 3H), 0.83 (s, 9H), -0.01 (s, 1H), -0.02 (s, 2H), -0.71 (s, 2H), -0.74 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 169.3, 169.1, 150.9, 150.8, 148.2, 147.9, 138.6, 138.6, 137.9, 137.7, 137.5, 137.3, 136.4, 136.2, 130.4, 130.2, 129.4, 129.4, 129.4, 128.3, 128.2, 126.7, 126.6, 123.6, 123.1, 123.0, 122.6, 122.5, 118.4, 115.8, 115.7, 114.7, 114.2, 83.9, 83.9, 78.8, 78.6, 68.3, 68.0, 64.8, 50.3, 43.3, 43.1, 31.1, 31.1, 31.0, 31.0, 30.3, 30.3, 28.8, 28.8, 28.7, 28.4, 28.3, 26.8 26.7, 26.6, 21.5, 20.6, 20.5, 19.4, 18.6, 18.5, 13.8, 5.8, 5.3, -3.9, -3.9, -4.6, -4.6; HRMS (EI) *m/z* 900.3477 [calculated for $C_{47}H_{61}N_6O_4I$ (M^+) 900.3799].

Preparation of Azides 210, 211:

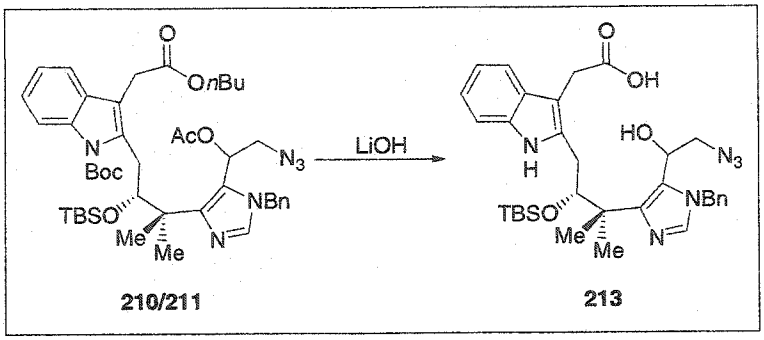


Azides 210, 211. To a stirred solution of iodides **208** and **209** (4.23 mg, 4.70 mmol, 1.0 equiv.) in DMF (80 mL) was added NaN_3 (3.4 g, 50.0 mmol, 10.0 equiv.). The mixture was stirred at 90°C for 4 hours, then cooled to room temperature, diluted with Et_2O (200 mL) and washed with H_20 (2 x 200 mL). The organic layer was then

dried with $MgSO_4$, reduced *in vacuo,* and chromatographed on silica gel (50% EtOAc/Hexanes) to afford **210/211** (3.77 g, 98% yield) as a colorless oil.

Azides 210, 211. FTIR (thin film/NaCl) 2959 (s), 2931 (s), 2885 (m) ,2856 (m), 2101 (s), 1735 (s), 1499 (m), 1456 (s), 1369 (s), 1325 (s), 1252 (s), 1227 (s), 1158 (s), 1137 (s), 1117 (s), 1080 (s), 1030 (m), 981 (m), 940 (m), 838 (s), 807 (m), 756 (s), 695 (w), 667 (w), 632 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.0-7.95 (m, 1H), 7.48-7.43 (m, 1H), 7.42 (s, 1H), 7.39-7.26 (m, 4H), 7.25-7.17 (m, 2H), 7.08-7.01 (m, 2H), 6.75-6.66 (m, 1H), 5.39-5.23 (m, 3H), 4.69 (dd, *J*=3.9 Hz, 10.5 Hz, 1H), 4.14-4.03 (m, 2H), 3.85-3.70 (m, 2H), 3.63-3.46 (m, 2H), 3.38 (dd, *J*=3.9 Hz, 13.2 Hz, 1H), 3.03-2.94 (m, 1H), 1.85 (s, 2H), 1.81 (s, 1H), 1.72 (s, 9H), 1.65-1.54 (m, 5H), 1.50 (s, 3H), 1.39-1.31 (m, 2H), 0.91 (t, *J*=7.2 Hz, 3H), 0.83 (s, 9H), -0.02 (s, 2H), -0.03 (s, 1H), -0.71 (s, 2H), -0.73 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 169.4, 169.2, 150.9, 150.8, 148.1, 138.9, 138.8, 137.9, 137.7, 137.7, 137.7, 136.4, 136.2, 130.4, 130.2, 129.4, 129.4, 128.3, 128.2, 126.7, 126.6, 126.6, 123.6, 123.6, 122.6, 122.6, 122.2, 118.4, 118.4, 115.8, 115.7, 114.7, 114.3, 83.7, 83.6, 78.8, 78.5, 67.2, 64.8, 54.5, 50.5, 43.3, 43.1, 31.1, 31.0, 31.0, 30.4, 30.3, 28.8, 28.7, 28.6, 26.8, 26.7, 21.8, 20.6, 20.5, 19.4, 18.6, 18.5, 13.8, -4.0, -4.0, -4.6; HRMS (EI) *m/z* 815.4530 [calculated for $C_{44}H_{63}N_6O_7Si$ (M^+) 487.2709].

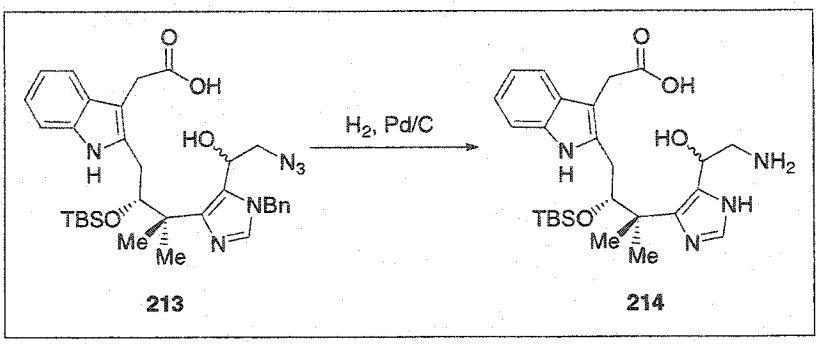
Preparation of Acid 213:



210/211 213

Acid 217. To a solution of esters **210** and **211** (550 mg, 0.675 mmol, 1.0 equiv.) in THF (15 mL) and H_2O (15 mL) is added LiOH (800 mg, 19.0 mmol, 28 equiv.). The reaction mixture was heated and stirred at reflux. After 3 days the reaction was cooled, diluted with THF (50 mL), washed with NH_4Cl (sat. aq.) (50 mL), brine (50 mL), and dried with $MgSO_4$. Removal of the solvent *in vacuo* afforded **213** (410 mg, 99% yield) as a pale yellow solid.

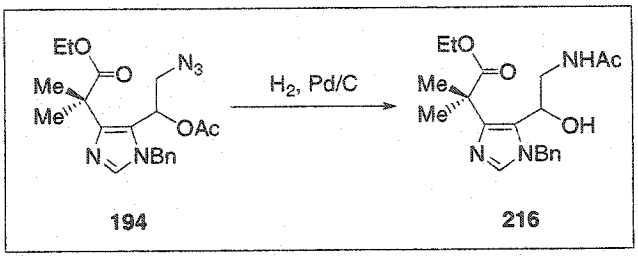
Preparation of Amine 214:



213 214

Amine 214. To azide **213** (8 mg, 0.013 mmol, 1.0 equiv.) in EtOAc (2 mL) was added palladium (10 wt. % on activated carbon) (25 mg). The reaction mixture was then stirred under an atmosphere of hydrogen and monitered by TLC. Upon consumption of the starting material (as indicated by TLC) the reaction mixture was filtered through a celite plug which was then washed with 10% MeOH/CH_2Cl_2. Removal of the solvent *in vacuo*, afforded **214** (5 mg, 80% yield) as a white solid.

Preparation of Amide 216:

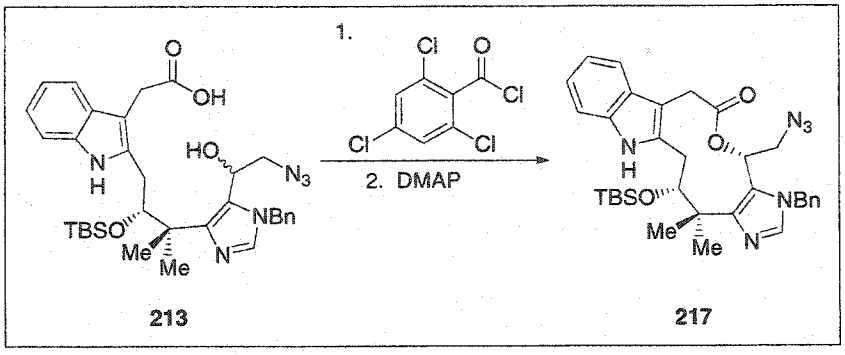


194 216

Amide 216. To azide **194** (15 mg, 0.031 mmol, 1.0 equiv.) in EtOAc (2 mL) was added palladium (10 wt. % on activated carbon) (15 mg). The reaction mixture was then stirred under an atmosphere of hydrogen and monitered by TLC. Upon consumption of the starting material (as indicated by TLC) the reaction mixture was filtered through a celite plug which was then washed with 10% $MeOH/CH_2Cl_2$. Removal of the solvent *in vacuo*, afforded **216** (10 mg, 71% yield) as a white solid.

Amide 216. FTIR (thin film/NaCl) 3270 (m), 3090 (m), 3067 (m), 3033 (m), 2980 (m), 2934 (m), 2872 (m), 2245 (w), 1724 (s), 1654 (s), 1549 (m), 1502 (m), 1455 (m), 1368 (m), 1297 (m), 1256 (s), 1208 (m), 1140 (s), 1085 (m), 1029 (m), 1003 (m), 919 (w), 859 (w), 773 (w), 731 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.26 (m, 4H), 7.09 (d, *J*=6.8 Hz, 2H), 6.08 (t, *J*=5.5 Hz, 1H), 5.44 (d, *J*=16.1 Hz, 1H), 5.33 (d, *J*=16.1 Hz, 1H), 4.97 (dd, *J*=4.2 Hz, 9.0 Hz, 1H), 4.16 (dq, *J*=3.0 Hz, 7.1 Hz, 2H), 3.98 (bs, 1H), 3.42-3.24 (m, 2H), 1.95 (s, 3H), 1.63 (s, 6H), 1.26 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 171.8, 143.1, 137.6, 137.3, 129.4, 128.4, 127.1, 126.1, 67.1, 61.6, 50.1, 45.7, 44.2, 27.5, 27.1, 23.4, 14.5; HRMS (EI) *m/z* 374.2082 [calculated for $C_{20}H_{28}N_3O_4$ (M^+) 374.2080].

Preparation of Lactone 217:

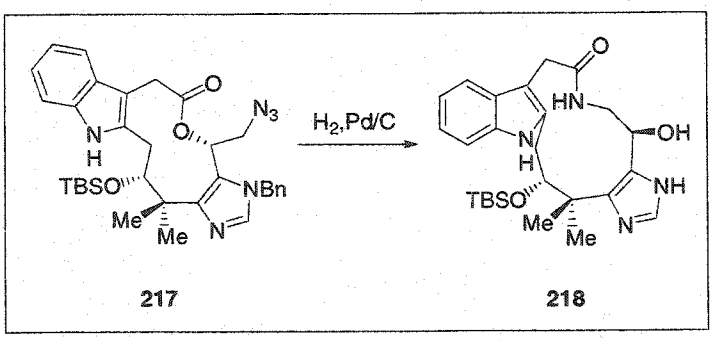


Lactone 217. To a solution of acid **213** (700 mg, 0.95 mmol, 1.0 equiv.) in THF (15 mL) and Et_3N (415 mL, 3.0 mmol, 3.0 equiv.) at 0°C was added trichloro acetylchloride (238 mL, 1.50 mmol, 1.5 equiv.). The reaction mixture was allowed to stir at 0°C for 1 hour at which time the ice bath was removed and the reaction mixture was cannulated into a solution of DMAP (50 mg, 0.41 mmol, 0.4 equiv.) in refluxing PhH (10 mL). After 1 hour of heating the reaction was cooled to room temperature and the solvent removed *in vacuo*. The resulting oil was diluted with Et_2O (50 mL), washed with NH_4Cl (sat., aq.) (25 mL), $NaHCO_3$ (sat., aq.) (25 mL), brine (25 mL), and dried with $MgSO_4$. The solvent was removed *in vacuo* once again and the resulting oil chromatographed on silica gel to afford **217** (500 mg, 74% yield) as a clear solid.

Lactone 217. m.p. 193-196°C; FTIR (thin film/NaCl) 3438 (s), 3059 (w), 3029 (w), 2954 (m), 2930 (m), 2898 (m), 2857 (m), 2102 (s), 1731 (s), 1620 (w), 1582 (w), 1562 (w), 1530 (w), 1463 (m), 1255 (m), 1228 (m), 1175 (m), 1063 (m), 1000 (m), 935 (m), 917 (w), 864 (w), 832 (m), 778 (m), 736 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ

9.62 (s, 1H), 7.64 (s, 1H), 7.47 (d, *J*=7.5 Hz, 1H), 7.45-7.33 (m, 3H), 7.30 (d, *J*=7.5 Hz, 1H), 7.22-7.08 (m, 4H), 5.83 (dd, *J*=3.1 Hz, 10.3 Hz, 1H), 5.37 (s, 2H), 4.42 (d, *J*=5.6 Hz, 1H), 4.05 (d, *J*=17.8 Hz, 1H), 3.63-3.52 (m, 2H), 2.81 (dd, *J*=5.9 Hz, 16.3 Hz, 1H), 1.43 (s, 3H), 1.17 (s, 9H), 0.97 (s, 3H), 0.37 (s, 3H), 0.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 137.2, 136.2, 135.9, 135.1, 129.7, 129.1, 128.0, 127.6, 123.5, 121.5, 119.6, 117.5, 110.8, 103.8, 79.7, 67.6, 52.8, 50.5, 43.8, 30.7, 30.6, 28.2, 26.7, 20.4, 18.8, -3.3, -4.2; HRMS (EI) *m/z* 599.3166 [calculated for $C_{33}H_{43}N_6O_3Si$ (M^+) 599.3166].

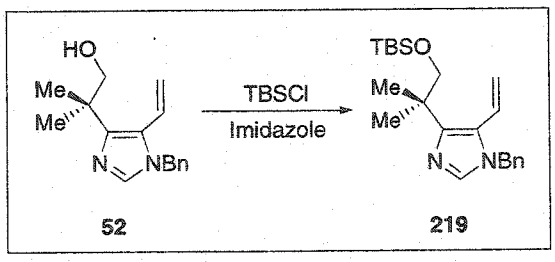
Preparation of Lactam 218:



Lactam 218. To azide **217** (100 mg, 0.17 mmol, 1.0 equiv.) in a mixture of THF (2 mL) and MeOH (2 mL) was added palladium (10 wt. % on activated carbon) (50 mg). The reaction mixture was then stirred under an atmosphere of hydrogen and monitored by TLC. Upon consumption of the starting material (as indicated by TLC) the reaction mixture was filtered through a celite plug which was then washed with 10% MeOH/CH_2Cl_2 (50 mL). Removal of the solvent *in vacuo*, afforded **218** (24 mg, 30% yield) as a white solid.

Lactam 218. m.p. 234-237°C; FTIR (thin film/NaCl) 3337 (s), 2953 (s), 2929 (s), 2886 (m), 2857 (s), 2561 (m), 1733 (w), 1645 (s), 1460 (s), 1413 (m), 1361 (w), 1334 (w), 1316 (w), 1259 (m), 1191 (w), 1152 (w), 1132 (w), 1071 (m), 1011 (w), 994 (w), 923 (w), 834 (m), 778 (m), 740 (m) cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 8.04 (s, 1H), 7.50 (d, *J*=7.5 Hz, 1H), 7.27 (d, *J*=7.1 Hz, 1H), 7.13-7.02 (m, 2H), 6.77 (bt, 1H), 4.94 (dd, *J*=5.0 Hz, 11.0 Hz, 1H), 4.78 (dd, *J*=1.7 Hz, 6.5 Hz, 1H), 3.82-3.70 (m, 1H), 3.65 (d, *J*=16.6 Hz, 1H), 3.25 (d, *J*=16.6 Hz, 1H), 3.01 (dd, *J*=6.7 Hz, 16.5 Hz, 1H), 2.65 (dd, *J*=1.8 Hz, 16.6 Hz, 1H), 1.36 (s, 3H), 1.16 (s, 9H), 1.08 (s, 3H), 0.39 (s, 3H), 0.31 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.8, 135.6, 135.0, 134.7, 128.2, 121.4, 119.6, 117.5, 110.3, 104.8, 77.7, 63.6, 43.6, 31.1, 30.2, 28.3, 25.7, 19.9, 18.2, -4.7, -5.7; HRMS (EI) *m/z* 483.2793 [calculated for $C_{26}H_{39}N_4O_3Si$ (M^+) 483.2791].

Preparation of TBS-Alcohol 219:



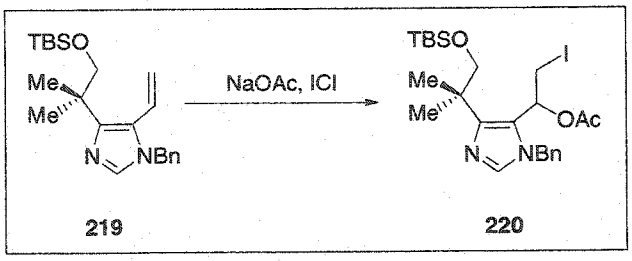
52 219

TBS-Alcohol 219. To a stirred solution of alcohol **52** (3.85 g, 15.0 mmol, 1.0 equiv.) in DMF (30 mL) at room temperature was added imidazole (3.06 g, 45.0 mmol, 3.0 equiv.) and TBSCl (4.50 g, 30.0 mmol, 1.5 equiv.). The mixture was stirred at room temperature, at which time it was diluted with Et_2O (100 mL) and washed with H_20 (2 x

100 mL). The organic layer was separated, washed with brine (100 mL) and dried with $MgSO_4$. Silica gel chromatography (30% EtOAc/Hexanes) afforded **219** (5.46 g, 99% yield) as a pale yellow oil.

TBS-Alcohol 219. FTIR (thin film/NaCl) 3090 (w), 3066 (w), 3032 (w), 2955 (s), 2928 (s), 2896 (m), 2855 (s), 2737 (w), 2709 (w), 1948 (w), 1860 (w), 1808 (w), 1631 (m), 1497 (m), 1471 (m), 1455 (m), 1388 (m), 1360 (m), 1250 (s), 1092 (s), 1005 (m), 994 (m), 938 (m), 915 (m), 836 (s), 776 (s), 731 (m), 697 (m), 668 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.38-7.26 (m, 3H), 7.04 (d, J=7.0 Hz, 2H), 6.73 (dd, J=11.6 Hz, 17.9 Hz, 1H), 5.32 (dd, J=1.4 Hz, 11.5 Hz, 1H), 5.15 (dd, J=1.3 Hz, 17.9 Hz, 1H), 5.14 (s, 2H), 3.67 (s, 2H), 1.35 (s, 6H), 0.87 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 137.0, 129.2, 128.1, 127.0, 126.8, 126.0, 119.0, 72.1, 49.1, 39.1, 26.3, 25.6, 18.7, -5.0; HRMS (EI) *m/z* 371.2518 [calculated for $C_{22}H_{35}N_2OSi$ (M^+) 371.2519].

Preparation of Iodide 220:

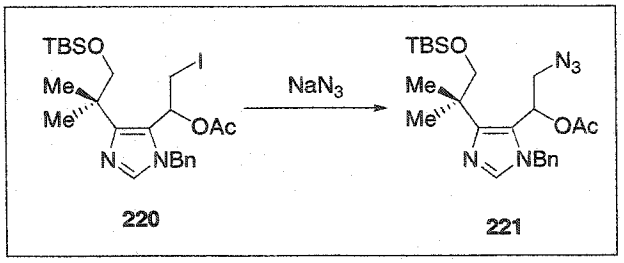


219 220

Iodide 220. To a stirred solution of sodium acetate (NaOAc) (2.30 mg, 28.4 mmol, 3.5 equiv.) in CH_3CN (35 mL) at -20°C was added dropwise iodine monochloride

as a 1.0M solution in CH_2Cl_2 (16.2 mL, 2.0 equiv.). The reaction mixture was stirred at -20°C for 1.5 hours at which time vinyl imidazole **219** (3.00 g, 8.10 mmol, 1.0 equiv.) was added. The reaction mixture was then allowed to warm to room temperature and stirred for 2 hours, washed with $Na_2S_2O_4$ (sat., aq.) (50 mL), brine (50 mL) and dried with $MgSO_4$. The solvent was removed *in vacuo* and the resulting oil chromatographed on silica gel (30% EtOAc/Hexanes) to afford **220** (4.50 mg, 99% yield) as a pale yellow foam.

Preparation of Azide 221:



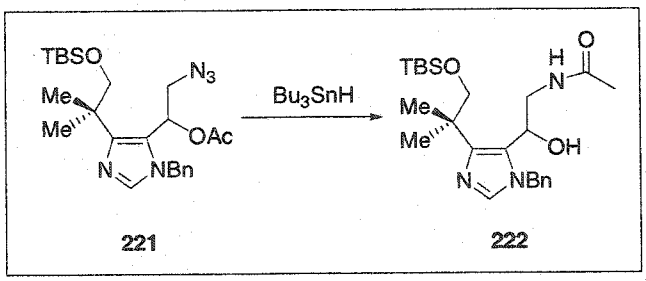
220 **221**

Azide 221. To a stirred solution of iodide **220** (4.50 g, 8.03 mmol, 1.0 equiv.) in DMF (40 mL) was added NaN_3 (5.2 g, 80.0 mmol, 10.0 equiv.). The mixture was stirred at 90°C for 4 hours, then cooled to room temperature, diluted with Et_2O (100 mL) and washed with H_2O (2 x 100 mL). The organic layer was then dried with $MgSO_4$ and chromatographed on silica gel (30% EtOAc/Hexanes) to afford **221** (3.33 g, 86% yield) as a white foam.

Azide 221. FTIR (thin film/NaCl) 3065 (w), 3032 (w), 2955 (m), 2929 (m), 2857 (m), 2101 (s), 1750 (s), 1662 (w), 1607 (w), 1558 (w), 1499 (m), 1472 (m), 1454 (m),

1371 (m), 1249 (s), 1221 (s), 1089 (s), 1036 (m), 1007 (m), 940 (m), 837 (s), 777 (m), 728 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.39-7.29 (m, 3H), 6.94 (d, *J*=6.8 Hz, 2H), 6.58 (dd, *J*=3.5 Hz, 9.5 Hz, 1H), 5.35 (q, *J*=16.5 Hz, 2H), 3.74 (d, *J*=9.5 Hz, 1H), 3.71 (d, *J*=9.5 Hz, 1H), 3.53 (dd, *J*=9.3 Hz, 13.1 Hz, 1H), 3.26 (dd, *J*=3.3 Hz, 13.1 Hz, 1H), 1.70 (s, 3H), 1.40 (s, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 147.3, 138.8, 137.9, 129.4, 128.3, 126.1, 122.1, 72.5, 67.5, 54.4, 50.4, 39.4, 26.4, 26.1, 25.5, 20.6, 18.8, -4.9. -4.9; HRMS (EI) *m/z* 472.2742 [calculated for $C_{24}H_{38}N_5O_3Si$ (M^+) 472.2744].

Preparation of Amide 222:

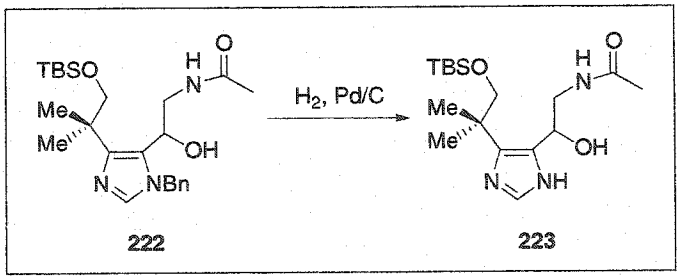


221 **222**

Amide 222. To a stirred solution of azide **221** (1.40 g, 2.95 mmol, 1.0 equiv.) in PhH (1 mL) was added tributyltin hydride (Bu_3SnH) (1.60 mL, 5.90 mmol, 2.0 equiv.) and 2,2'-azobisisobutyronitrile (AIBN) (70 mg, 0.43 mmol, 0.15 equiv.). The reaction mixture was stirred at reflux for 24 hours, at which time the solvent was removed *in vacuo*. Silica gel chromatography of the resulting oil afforded **222** (810 mg, 62% yield) as a white foam.

Amide 222. m.p. 53-55°C; FTIR (thin film/NaCl) 3269 (m), 3066 (w), 3033 (w), 2955 (m), 2928 (m), 2855 (m), 1653 (m), 1558 (m), 1506 (m), 1471 (m), 1456 (m), 1388 (w), 1372 (w), 1361 (m), 1289 (w), 1250 (m), 1156 (w), 1087 (m), 911 (w), 838 (s), 778 (m), 734 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.37-7.29 (m, 3H), 7.08 (d, *J*=6.9 Hz, 2H), 5.96 (bt, 1H), 5.41 (d, *J*=16.2 Hz, 1H), 5.28 (d, *J*=16.4 Hz, 1H), 5.19 (dd, *J*=3.5 Hz, 9.8 Hz, 1H), 3.63 (d, *J*=9.5 Hz, 1H), 3.60 (d, *J*=9.5 Hz, 1H), 3.48 (ddd, *J*=3.5 Hz, 7.5 Hz, 14.0 Hz, 1H), 3.26 (ddd, *J*= 4.3 Hz, 9.8 Hz, 14.0 Hz, 1H), 1.98 (s, 3H), 1.44 (s, 3H), 1.38 (s, 3H), 0.86 (s. 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 144.9, 137.5, 137.5, 129.3, 128.3, 127.1, 126.9, 73.2, 66.7, 49.9, 46.3, 38.9, 26.7, 26.4, 26.2, 23.6, 18.9, -5.0, -.5.1; HRMS (EI) *m/z* 446.2839 [calculated for $C_{24}H_{40}N_3O_3Si$ (M^+) 446.2839].

Preparation of Imidazole 223:

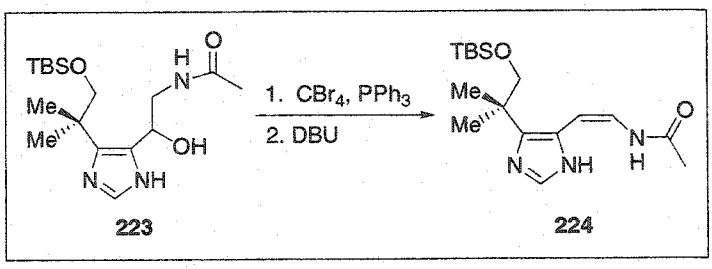


Imidazole 223. To benzimidazole **222** (140 mg, 0.32 mmol, 1.0 equiv.) in a mixture of THF (3 mL) and MeOH (3 mL) was added palladium (10 wt. % on activated carbon) (180 mg). The reaction mixture was then stirred under an atmosphere of hydrogen and monitored by TLC. Upon consumption of the starting material (as

indicated by TLC) the reaction mixture was filtered through a celite plug which was then washed with 10% MeOH/CH_2Cl_2 (50 mL). Removal of the solvent *in vacuo*, afforded **223** (110 mg, 98% yield) as a white solid.

Imidazole 223. m.p. 49-52°C; FTIR (thin film/NaCl) 3264 (s), 2955 (s), 2930 (s), 2885 (m), 2857 (s), 2241 (w), 1653 (s), 1559 (m), 1497 (m), 1472 (m), 1464 (m), 1373 (m), 1293 (w), 1256 (m), 1097 (s), 1006 (m), 911 (m), 838 (s), 778 (m), 734 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (bs, 1H), 6.91 (bt, 1H), 5.08 (dd, *J*=3.9 Hz, 7.6 Hz, 1H), 3.78 (ddd, *J*=3.9 Hz, 7.1 Hz, 13.7 Hz, 1H), 3.64 (s, 2H), 3.46-3.37 (m, 1H), 2.00 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 0.93 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 134.3, 133.9, 133.2, 73.0, 65.9, 46.6, 37.1, 26.3, 25.8, 25.5, 23.5, 18.6, -5.1, -5.1; HRMS (EI) *m/z* 356.2369 [calculated for $C_{17}H_{34}N_3O_3Si$ (M^+) 356.2369].

Preparation of Enamide 224:



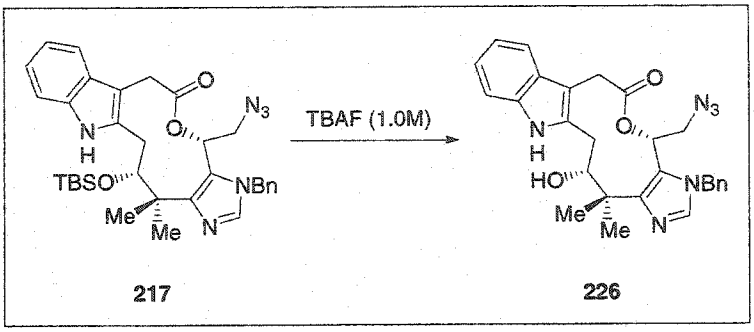
223 **224**

Enamide 224. To a stirred solution of amide **223** (10 mg, 0.028 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) was added CBr_4 (28 mg, 0.085 mmol, 3.0 equiv.) and polymer supported PPh_3 (3mmol/g) (20 mg, 2.0 equiv.). The reaction mixture was allowed to stir at room temperature and monitored by TLC. Upon consumption of the starting material

(as indicated by TLC) DBU (15 μL, 0.09 mmol, 3.0 equiv.) was added and the mixture was stirred an additional 3 hours. The reaction was then allowed to cool to room temperature and filtered through a celite plug. The plug was subsequently washed with CH_2Cl_2 (10 mL) and the solvent removed *in vacuo*. The resulting oil was chromatographed on silica gel (10% MeOH/CH_2Cl_2 + 1% Et_3N) to afford **224** (6 mg, 64% yield) as a colorless oil.

Enamide 224. FTIR (thin film/NaCl) 3232 (m), 3117 (m), 2955 (m), 2929 (m), 2896 (m), 2856 (m), 1652 (s), 1559 (m), 1541 (w), 1496 (m), 1489 (m), 1472 (m), 1436 (m), 1397 (m), 1363 (m), 1281 (m), 1257 (m), 1220 (w), 1096 (m), 1049 (w), 984 (w), 946 (w), 838 (m), 776 (m), 719 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.52 (d, *J*=9.1 Hz, 1H), 10.07 (s, 1H), 7.50 (s, 1H), 6.93 (dd, *J*=9.4 Hz, 10.2 Hz, 1H), 5.71 (d, *J*=9.4 Hz, 1H), 3.64 (s, 2H), 2.16 (s, 3H), 1.35 (s, 6H), 0.95 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 134.3, 132.7, 131.9, 121.2, 100.4, 73.3, 36.8, 26.3, 25.8, 24.2, 18.6, -5.1; HRMS (EI) *m/z* 338.2263 [calculated for $C_{17}H_{32}N_3O_2Si$ (M^+) 338.2264].

Preparation of Alcohol 226:

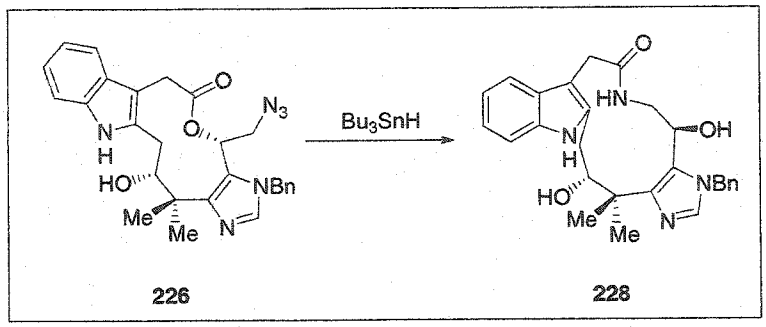


Alcohol 226. To a stirred solution of lactone **217** (150 mg, .25 mmol, 1.0 equiv.) in THF (5 mL) at 0°C was added TBAF (1.0 M) (315 μL, 1.25 equiv.). The reaction mixture was allowed to stir at 0°C and monitored by TLC. Upon consumption of the starting material (as indicated by TLC) the solvent was removed *in vacuo*. The resulting oil was then chromatographed on silica gel to afford **226** (89 mg, 73% yield) as a white solid.

Alcohol 226. FTIR (thin film/NaCl) 3412 (m), 3059 (w), 3030 (w), 2973 (m), 2932 (m), 2103 (s), 1729 (s), 1506 (m), 1498 (m), 1483 (m), 1463 (m), 1393 (w), 1354 (m), 1341 (m), 1260 (m), 1226 (m), 1175 (m), 1131 (m), 1064 (m), 1042 (m), 997 (m), 947 (w), 909 (m), 832 (w), 736 (s), 648 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.66 (s, 1H), 7.48 (d, *J*=7.7 Hz, 1H), 7.45-7.32 (m, 4H), 7.24-7.08 (m, 4H), 5.85 (dd, *J*=2.5 Hz, 10.2, Hz, 1H), 5.37 (s, 2H), 4.44 (bs, 1H), 4.07 (d, *J*=17.5 Hz, 1H), 3.60 (d, *J*=17.5 Hz, 1H), 3.58 (d, *J*=10.2 Hz, 1H), 3.34 (bs, 1H), 2.95 (dd, *J*=5.7 Hz, 16.1 Hz, 1H), 2.35 (d, *J*=12.3 Hz, 1H), 2.28 (d, *J*=15.9 Hz, 1H), 1.51 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 137.2, 135.9, 135.7, 135.2, 129.7, 129.2, 128.0, 127.7,

123.6, 121.5, 119.5, 117.4, 111.1, 103.5, 78.8, 67.6, 52.9, 50.6, 43.1, 30.9, 29.7, 27.7, 19.9; HRMS (EI) *m/z* 485.2303 [calculated for $C_{27}H_{29}N_6O_3$ (M^+) 485.2301].

Preparation of Lactam 228:



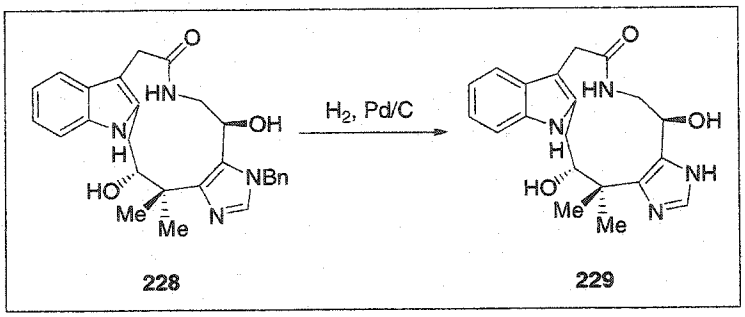
226 228

Lactam 228. To a stirred solution of azide **226** (35 mg, 0.074 mmol, 1.0 equiv.) in PhH (1 mL) was added tributyltin hydride (Bu_3SnH) (45 mL, 0.17 mmol, 2.25 equiv.) and 2,2'-azobisisobutyronitrile (AIBN) (10 mg, 0.061 mmol, 0.82 equiv.). The reaction mixture was stirred at reflux for 24 hours, at which time the solvent was removed *in vacuo*. Silica gel chromatography of the resulting oil afforded **228** (18 mg, 55% yield) as a white foam.

Lactam 228. FTIR (thin film/NaCl) 3408 (w), 2726 (w), 1541 (w), 1461 (s), 1308 (w), 1270 (w), 1154 (w), 1075 (w), 1043 (w), 722 (w) cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 8.13 (d, *J*=10.0 Hz, 1H), 7.45-7.34 (m, 5H), 7.35 (d, *J*=7.7 Hz, 1H), 7.30 (d, *J*=7.7 Hz, 1H), 7.15 (s, 1H), 7.06 (dt, *J*=1.0 Hz, 7.1 Hz, 1H), 7.00 (dt, *J*=1.0 Hz, 7.1 Hz, 1H), 5.91 (dd, *J*=6.4 Hz, 11.2 Hz, 1H), 5.72 (d, *J*=14.2 Hz, 1H), 5.35 (d, *J*=14.2 Hz, 1H), 4.45-4.34 (m, 1H), 4.14 (dd, *J*=5.8 Hz, 10.3 Hz, 1H), 3.62 (d, *J*=18.2 Hz, 1H), 3.33 (quint., *J*=1.6 Hz, 1H), 3.14 (d, *J*=18.2 Hz, 1H), 3.09 (dd, *J*=6.5 Hz, 13.0 Hz, 1H), 2.99

(dd, *J*=6.0 Hz, 14.6 Hz, 1H), 2.40 (dd, *J*=10.1 Hz, 14.6 Hz, 1H), 1.48 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 172.9, 143.3, 137.0, 136.6, 136.5, 136.3, 129.0, 128.9, 128.5, 128.5, 128.2, 121.0, 118.9, 116.9, 110.6, 104.5, 76.0, 63.7, 50.5, 42.8, 42.6, 31.0, 28.3, 26.4; HRMS (EI) *m/z* 459.2395 [calculated for $C_{27}H_{31}N_4O_3$ (M^+) 459.2396].

Preparation of Imidazole 229:



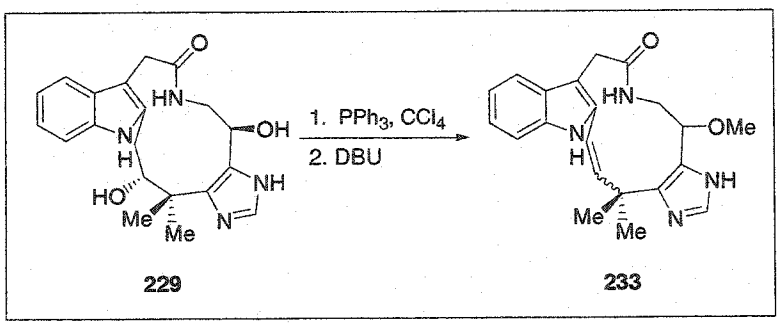
228 **229**

Imidazole 229. To benzimidazole **228** (56 mg, 0.12 mmol, 1.0 equiv.) in a mixture of THF (2 mL) and MeOH (2 mL) was added palladium (10 wt. % on activated carbon) (100 mg). The reaction mixture was then stirred under an atmosphere of hydrogen and monitored by TLC. Upon consumption of the starting material (as indicated by TLC) the reaction mixture was filtered through a celite plug which was then washed with 10% MeOH/CH_2Cl_2 (50 mL). Removal of the solvent *in vacuo*, afforded **229** (35 mg, 77% yield) as a white solid.

Imidazole 229. FTIR (thin film/NaCl) 3397 (w), 3261 (w), 2922 (w), 1632 (m), 1544 (m), 1462 (m), 1345 (w), 1290 (w), 1259 (w), 1077 (w), 1016 (w), 923 (w), 759 (w) cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.95 (s, 1H), 7.34 (d, *J*=7.9 Hz, 1H), 7.30 (d, *J*=7.9 Hz, 1H), 7.05 (t, *J*=7.5 Hz, 1H), 6.98 (t, *J*=7.5 Hz, 1H), 5.62 (dd, *J*=5.3 Hz, 10.6 Hz, 1H),

4.14 (dd, *J*=5.3 Hz, 10.1 Hz, 1H), 4.07 (t, *J*=11.9 Hz, 1H), 3.57 (d, *J*=18.1 Hz, 1H), 3.33 (quint., *J*=1.7 Hz, 1H), 3.16 (dd, *J*=5.6 Hz, 12.5 Hz, 1H), 3.15 (d, *J*=18.1 Hz, 1H), 2.99 (dd, *J*=5.6 Hz, 14.7 Hz, 1H), 2.30 (dd, *J*=10.3 Hz, 14.7 Hz, 1H), 1.52 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 171.4, 135.6, 134.9, 133.9, 132.1, 130.1, 126.9, 119.4, 117.3, 115.4, 108.9, 103.0, 74.3, 61.9, 42.6, 40.2, 29.4, 26.8, 24.7, 23.6; HRMS (EI) *m/z* 369.1926 [calculated for $C_{20}H_{25}N_4O_3$ (M^+) 369.1927].

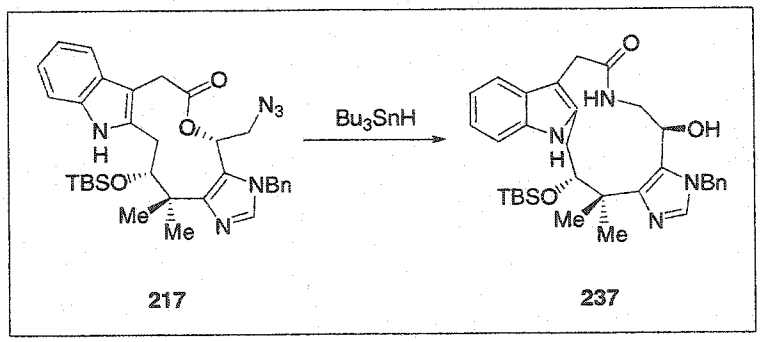
Preparation of Methyl Ether 233:



Methyl Ether 233. To a stirred solution of amide **229** (32 mg, 0.028 mmol, 1.0 equiv.) in CCl_4 (2 mL) and MeCN (2 mL) was added polymer supported-PPh_3 (3mmol/g) (130 mg, 3.0 equiv.). The reaction mixture was allowed to stir at reflux and monitored by TLC. Upon consumption of the starting material (as indicated by TLC), the reaction was allowed to cool to room temperature and filtered through a celite plug. The plug was subsequently washed with 10% MeOH/CH_2Cl_2 (10 mL) and the solvent removed *in vacuo*. The resulting oil was chromatographed on silica gel (10% MeOH/CH_2Cl_2) to afford **233** (21 mg, 68% yield) as a white solid.

Methyl Ether 233. FTIR (thin film/NaCl) 3446 (m), 2954 (m), 2929 (m), 2856 (m), 1653 (s), 1559 (m), 1540 (m), 1258 (w), 1199 (w), 1108 (m), 1101 (w), 921 (w), 835 (m), 780 (w), 744 (w) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 8.05 (bt, 1H), 7.61 (s, 1H), 7.35 (d, *J*=8.1 Hz, 1H), 7.17 (d, *J*=8.1 Hz, 1H), 6.96 (dt, *J*=1.0 Hz, 8.1 Hz, 1H), 6.88 (dt, 0.9 Hz, 7.9 Hz, 1H), 6.31 (d, *J*=16.1 Hz, 1H), 6.10 (d, *J*=16.1 Hz, 1H), 4.44 (dd, *J*=4.2 Hz, 10.5 Hz, 1H), 3.93-3.86 (m, 1H), 3.60 (d, *J*=15.7 Hz, 1H), 3.43-3.33 (m, 2H), 3.26-3.08 (m, 5H), 1.49 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.4, 140.8, 136.3, 134.1, 133.2, 129.6, 121.7, 119.0, 118.0, 117.5, 110.7, 106.9, 72.6, 55.5, 42.6, 38.1, 31.4, 29.7, 29.0, 28.7; HRMS (EI) *m/z* 365.1977 [calculated for $C_{21}H_{25}N_4O_2$ (M^+) 365.1978].

Preparation of Lactam 237:

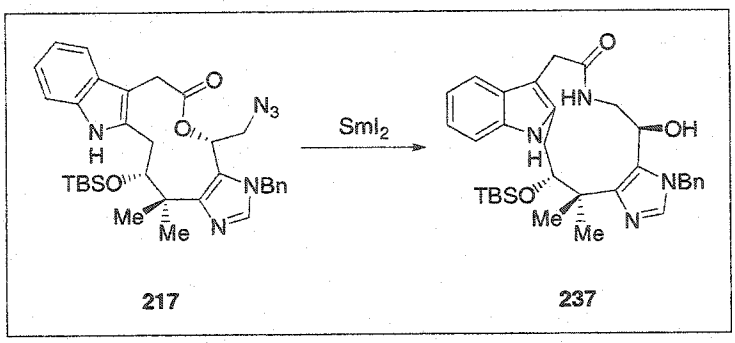


Lactam 237. To a stirred solution of azide **217** (820 mg, 1.37 mmol, 1.0 equiv.) in PhH (25 mL) was added tributyltin hydride (Bu_3SnH) (560 μL mL, 2.75 mmol, 2.00 equiv.) and 2,2'-azobisisobutyronitrile (AIBN) (60 mg, 0.37 mmol, 0.27 equiv.). The reaction mixture was stirred at reflux for 24 hours, at which time the solvent was

removed *in vacuo*. Silica gel chromatography of the resulting oil (80% EtOAc/Hexanes) afforded **237** (630 mg, 81% yield) as a white foam.

Lactam 237. m.p. 139-141°C; FTIR (thin film/NaCl) 3436 (m), 2953 (m), 2928 (m), 2855 (m), 2358 (w), 1653 (m), 1558 (w), 1521 (m), 1463 (m), 1418 (w), 1361 (w), 1256 (m), 1245 (m), 1152 (w), 1132 (w), 1070 (m), 1017 (w), 988 (w), 932 (w), 862 (w), 834 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.71 (bs, 1H), 7.48 (d, *J*=7.3 Hz, 1H), 7.36-7.24 (m, 5H), 7.18 (bs, 2H), 7.12-6.98 (m, 3H), 5.85 (bs, 1H), 5.50 (d, *J*=14.9 Hz, 1H), 5.38 (d, *J*=14.9 Hz, 1H), 5.27 (dd, *J*=5.6 Hz, 10.9 Hz, 1H), 5.08 (d, *J*=6.7 Hz, 1H), 3.80 (bs, 1H), 3.56 (d, *J*=16.9 Hz, 1H), 3.39-3.27 (m, 1H), 3.23 (d, *J*=16.9 Hz, 1H), 2.92 (dd, *J*=7.1 Hz, 16.2 Hz, 1H), 2.75 (d, *J*=15.8 Hz, 1H), 1.26 (s, 3H), 1.13 (s, 9H), 1.05 (s, 3H), 0.31 (s, 3H), 0.29 (s, 3H); ^{13}C NMR (100 MHz, d^6-Acetone) δ 171.2, 145.1, 138.0, 137.8, 136.5, 135.8, 129.0, 128.5, 128.4, 127.9, 126.1, 121.3, 119.6, 117.8, 110.9, 105.0, 78.1, 64.4, 50.0, 43.0, 42.6, 32.0, 31.6, 26.2, 20.6, 18.4, -4.1, -4.9; HRMS (EI) *m/z* 573.3264 [calculated for $C_{33}H_{45}N_4O_3Si$ (M^+) 573.3261].

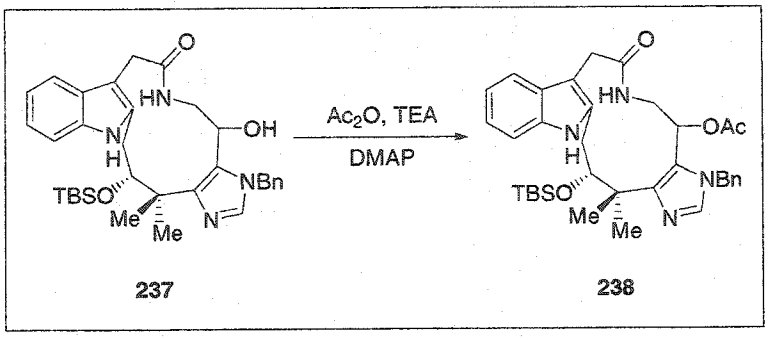
Preparation of Lactam 237:



217 237

Lactam 237. To a stirred solution of **217** (135 mg, 0.225 mmol, 1.0 equiv.) in THF (4 mL) at room temperature was added SmI_2 as a 0.1M solution in THF (10 mL, 1.0 mmol, 4.44 equiv.). The reaction was stirred at room temperature for 15 minutes, at which time it was quenched by addition of NH_4Cl (sat. aq.) (10 mL). The mixture was then extracted with CH_2Cl_2 (3 x 25 mL), the organic layers combined and dried with MgSO4. The solvent was then removed in vacuo and the resulting residue chromatographed on silica gel (80% EtOAC/Hexanes) to afford **237** (97 mg, 89% yield) as a white foam.

Preparation of Acetate 238:



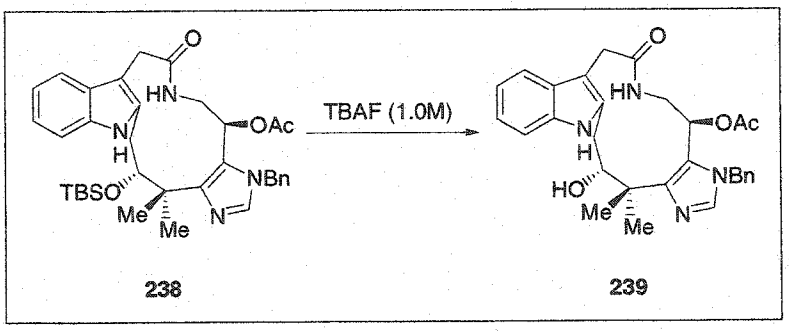
237 238

Acetate 238. To a stirred solution of **237** (70 mg, 0.13 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) at room temperature was added Et_3N (210 µL, 1.50 mmol, 10.0 equiv.) and DMAP (20 mg, 0.16 mmol, 1.23 equiv.) followed by acetic anhydride (150 µL, 1.50 mmol, 10 equiv.). The solution was stirred at room temperature for 2 hours, at which time the reaction was poured into H_2O (25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The organic layers were combined, washed with brine (25 mL) and dried with $MgSO_4$. The resulting oil was chromatographed on silica gel (50% EtOAc/Hexanes) to afford **238** (62 mg, 83% yield) as a white foam.

Acetate 238. FTIR (thin film/NaCl) 3437 (s), 3059 (w), 3030 (w), 2953 (s), 2929 (s), 2895 (m), 2856 (m), 1740 (s), 1672 (s), 1513 (s), 1462 (s), 1364 (m), 1320 (w), 1231 (s), 1152 (w), 1133 (w), 1067 (s), 1021 (s), 966 (m), 933 (m), 862 (w), 834 (s), 778 (m0, 734 (m), 697 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.54 (bs, 1H), 7.48 (d, *J*=7.8 Hz, 1H), 7.43-7.33 (m, 4H), 7.31 (d, *J*=7.8 Hz, 1H), 7.21 (t, *J*=7.3 Hz, 1H), 7.15 (t, *J*=7.3 Hz, 1H), 7.06 (d, *J*=6.9 Hz, 1H), 6.10 (dd, *J*=5.6 Hz, 12.1 Hz, 1H), 5.57 (d, *J*=9.9 Hz, 1H), 5.47 (d, *J*=15.9 Hz, 1H), 5.41 (d, *J*=15.9 Hz, 1H), 4.97 (d, *J*=4.7 Hz, 1H), 4.56-4.41 (m,

1H), 3.68 (d, *J*=18.1 Hz, 1H), 3.31 (d, *J*=18.1 Hz, 1H), 2.94 (dd, *J*=5.6 Hz, 15.9 Hz, 1H), 2.75 (d, *J*=15.9 Hz, 1H), 1.50 (s, 3H), 1.35 (s, 3H), 1.17 (s, 9H), 1.02 (s, 3H), 0.35 (s, 3H), 0.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 169.8, 148.0, 139.6, 137.9, 137.4, 135.5, 129.5, 129.3, 128.1, 127.7, 127.1, 126.9, 122.0, 121.1, 120.2, 117.5, 111.,3 104.4, 78.5, 65.9, 50.5, 43.2, 42.5, 40.1, 31.9, 31.6, 28.4, 26.8, 26.7, 20.8, 20.4, 18.7, -3.2, -4.4; HRMS (EI) *m/z* 615.3350 [calculated for $C_{35}H_{47}N_4O_4Si$ (M^+) 615.3367].

Preparation of Alcohol 239:

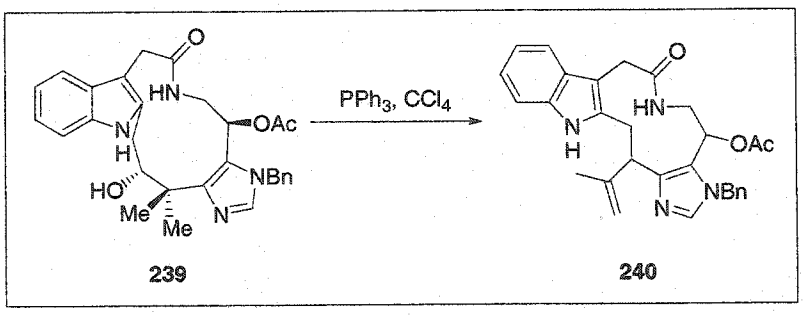


Alcohol 239. To a stirred solution of **238** (65 mg, .11 mmol, 1.0 equiv.) in THF (5 mL) at 0°C was added TBAF (1.0 M) (150 μL, 1.37 equiv.). The reaction mixture was allowed to stir at 0°C and monitored by TLC. Upon consumption of the starting material (as indicated by TLC) the solvent was removed *in vacuo*. The resulting oil was then chromatographed on silica gel to afford **239** (33 mg, 64% yield) as a white solid.

Alcohol 239. FTIR (thin film/NaCl) 3269 (m), 2927 (m), 2853 (m), 1745 (s), 1638 (s), 1546 (m), 1537 (m), 1499 (m), 1466 (m), 1454 (m), 1440 (m), 1409 (w), 1371 (m), 1323 (w), 1287 (w), 1227 (s), 1078 (w), 1056 (m), 1027 (m), 968 (m), 921 (w), 850

(w), 730 (m), 698 (m) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 8.17 (d, *J*=10.6 Hz, 1H), 7.52 (w, 1H), 7.42-7.27 (m, 5H), 7.11-7.03 (m, 3H), 7.02-6.92 (m, 2H), 5.61 (d, *J*=16.5 Hz, 1H), 5.48 (d, *J*=16.5 Hz, 1H), 4.52-4.41 (m, 1H), 4.17 (dd, *J*=5.9 Hz, 10.0 Hz, 1H), 3.64 (d, *J*=18.2 Hz, 1H), 3.15 (d, *J*=18.2 Hz, 1H), 3.04 (dt, *J*=6.5 Hz, 14.1 Hz, 1H), 2.39 (dd, *J*=10.0 Hz, 14.1 Hz, 1H), 1.52 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 173.1, 170.1, 145.8, 138.5, 138.4, 136.6, 136.3, 128.9, 128.5, 127.7, 126.7, 124.3, 121.0, 118.9, 116.9, 110.6, 104.4, 76.0, 65.7, 50.5, 43.1, 39.9, 30.9, 28.3, 26.4, 26.0, 19.1; HRMS (EI) *m/z* 501.2504 [calculated for $C_{29}H_{33}N_4O_4$ (M^+) 501.2502].

Preparation of Olefin 240:

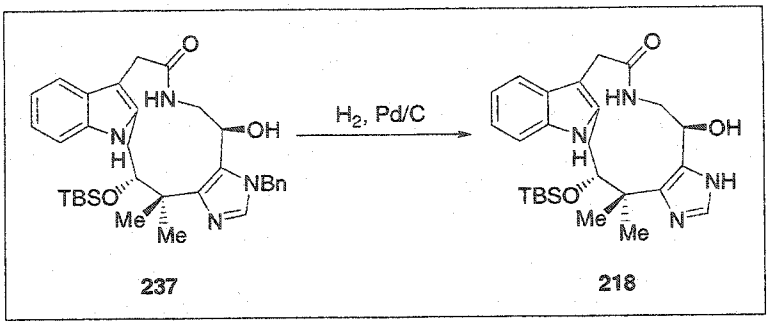


Olefin 240. To a stirred solution of alcohol **239** (5 mg, 0.012 mmol, 1.0 equiv.) in CH_2Cl_2 (1 mL) was added polymer supported-PPh_3 (3mmol/g) (40 mg, 4.0 equiv.). The reaction mixture was heated to reflux and allowed to stir while being monitored by TLC. Upon consumption of the starting material (as indicated by TLC) LiCl (25 mg, 0.60 mmol, 50.0 equiv.) was added and the mixture was stirred an additional 3 hours. The reaction mixture was filtered through a silica gel plug (10% MeOH/CH_2Cl_2). The resulting oil was redissolved in EtOAc (5 mL), and washed with H_2O (2 x 5 mL). The

organic layer was dried with $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was chromatographed on silica gel (10% MeOH/CH_2Cl_2) to afford **240** (3 mg, 63% yield) as a colorless oil.

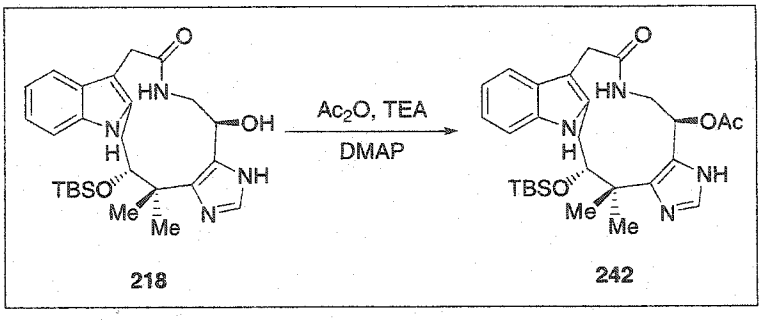
Olefin 240. FTIR (thin film/NaCl) 3379 (m), 2917 (m), 2849 (w), 1734 (m), 1669 (s), 1559 (m), 1507 (m), 1497 (m), 1457 (m), 1370 (m), 1231 (m), 1064 (m), 1023 (w), 909 (w), 732 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.88 (bs, 1H), 7.46 (s, 1H), 7.43 (d, *J*=8.1 Hz, 1H), 7.34 (d, *J*=8.1 Hz, 1h), 7.20 (t, *J*=7.4 Hz, 1H), 7.15 (t, *J*=7.4 Hz, 1H), 6.87 (t, *J*=7.9 Hz, 1H), 6.52 (d, *J*=7.9 Hz, 1H), 5.71 (d, *J*=3.0 Hz, 1H), 5.40 (d, *J*=10.4 Hz, 1H), 5.05 (d, *J*=16.4 Hz, 1H), 4.92 (d, *J*=16.4 Hz, 1H), 4.87 (s, 1H), 4.70 (s, 1H), 4.01 (dd, *J*=5.5 Hz, 12.4 Hz, 1H), 3.94 (dd, *J*=11.4 Hz, 14.4 Hz, 1H), 3.83 (d, *J*=17.9 Hz, 1H), 3.70 (d, *J*=17.9 Hz, 1H), 3.54-3.43 (m, 1H), 3.38 (dd, *J*=5.5 Hz, 14.4 Hz, 1H), 2.03 (s, 3H), 1.93 (s, 3H), 1.90 (bs, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 170.5, 147.6, 137.7, 137.1, 136.0, 135.0, 129.6, 126.2, 123.1, 122.1, 120.1, 117.9, 112.7, 111.2, 105.1, 68.6, 49.3, 44.9, 40.2, 32.6, 31.4, 21.7, 21.3; HRMS (EI) *m/z* 483.2395 [calculated for $C_{29}H_{31}N_4O_3$ (M^+) 483.2396].

Preparation of Imidazole 218:



Imidazole 218. To benzimidazole **237** (182 mg, 0.32 mmol, 1.0 equiv.) in a mixture of THF (8 mL) and MeOH (8 mL) was added palladium (10 wt. % on activated carbon) (150 mg). The reaction mixture was then stirred under an atmosphere of hydrogen and monitored by TLC. Upon consumption of the starting material (as indicated by TLC) the reaction mixture was filtered through a celite plug which was then washed with 10% MeOH/CH_2Cl_2 (50 mL). Removal of the solvent *in vacuo*, afforded **218** (128 mg, 84% yield) as a white solid.

Preparation of Acetate 242:



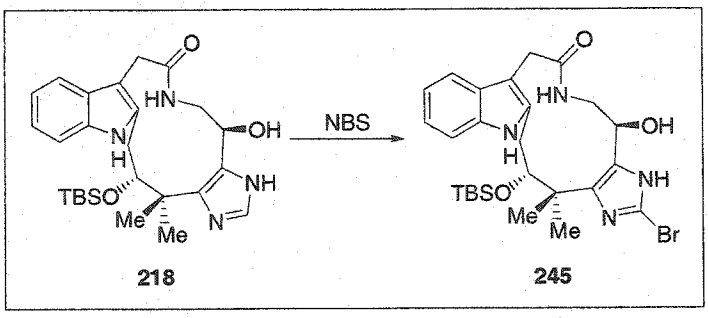
218 242

Acetate 242. To a stirred solution of **218** (80 mg, 0.17 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) at room temperature was added Et_3N (241 μL, 1.70 mmol, 10.0 equiv.) and DMAP (37 mg, 0.16 mmol, 1.82 equiv.) followed by acetic anhydride (180 μL, 1.70 mmol, 10.0 equiv.). The reaction mixture was allowed to stir at room temperature for 2 hours, at which time the reaction was poured into H_2O (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, washed with brine (50 mL) and dried with $MgSO_4$. The resulting oil was chromatographed on silica gel (50% EtOAc/Hexanes) to afford **242** (82 mg, 94% yield) as a white foam.

Acetate 242. FTIR (thin film/NaCl) 3439 (s), 3391 (m), 2953 (s), 2930 (s), 2895 (m), 2857 (m), 2246 (w), 1734 (s), 1653 (s), 1533 (m), 1463 (s), 1437 (m), 1239 (s), 1132 (w), 1075 (m), 1019 (m), 968 (w), 932 (m), 911 (m), 861 (w), 836 (s), 779 (m), 733 (s), 679 (w), 647 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.67 (bs, 1H), 7.68 (bs, 1H), 7.45 (d, *J*=7.9 Hz, 1H), 7.36 (d, *J*=7.9 Hz, 1H), 7.20 (t, *J*=7.5 Hz, 1H), 7.15 (t, *J*=7.5 Hz, 1H), 5.94 (bs, 1H), 5.60 (d, *J*=8.7 Hz, 1H), 4.95 (bs, 1H), 3.64 (d, *J*=17.8 Hz, 1H), 3.30 (d, *J*=17.8 Hz, 1H), 3.03 (bs, 1H), 2.98 (dd, *J*=5.4 Hz, 16.2 Hz, 1H), 2.64 (d, *J*=16.2 Hz, 1H), 2.01 (s, 3H), 1.37 (s, 3H), 1.15 (s, 9H), 1.11 (bs, 3H), 0.35 (s, 3H), 0.28 (s, 3H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 172.6, 169.9, 136.1, 135.5, 127.6, 122.1, 120.3, 117.3, 111.3, 104.2, 66.4, 42.6, 41.3, 31.8, 31.3, 26.7, 26.6, 21.3, 18.7, -3.3, -4.4; HRMS (EI) *m/z* 525.2895 [calculated for $C_{28}H_{41}N_4O_4Si$ (M^+) 525.2897].

Preparation of Bromoimidazole 245:



Bromoimidazole 245. To a stirred solution of **218** (50 mg, 0.103 mmol, 1.0 equiv.) in CH_3CN (500 μL) and MeOH (5 mL) at 0°C was added NBS (29 mg, 0.103 mmol, 1.0 equiv). The reaction was stirred at 0°C and monitored by TLC. Upon consumption of starting material (as indicated by TLC), the solvent was removed *in vacuo*. Silica gel chromatography of the resulting oil afforded **245** (40 mg, 71% yield) as a white solid.

Bromoimidazole 245. ^1H NMR (400 MHz, d^6-Acetone) δ 8.05 (bs, 1H), 7.55 (d, J=7.3 Hz, 1H), 7.40 (bs, 1H), 7.33-7.18 (m, 3H), 5.15 (dd, J=4.5 Hz, 10.6 Hz, 1H), 4.99 (dd, J=1.6 Hz, 6.9 Hz, 1H), 3.44 (bs, 1H), 3.38-3.18 (m, 4H), 3.13-3.00 (m, 2H), 1.55 (s, 6H), 0.96 (s, 9H), 0.21 (s, 3H), 0.08 (s, 3H).

3.12 Notes and References

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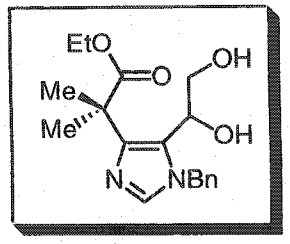
Appendix Two: Spectra Relevant to Chapter Three



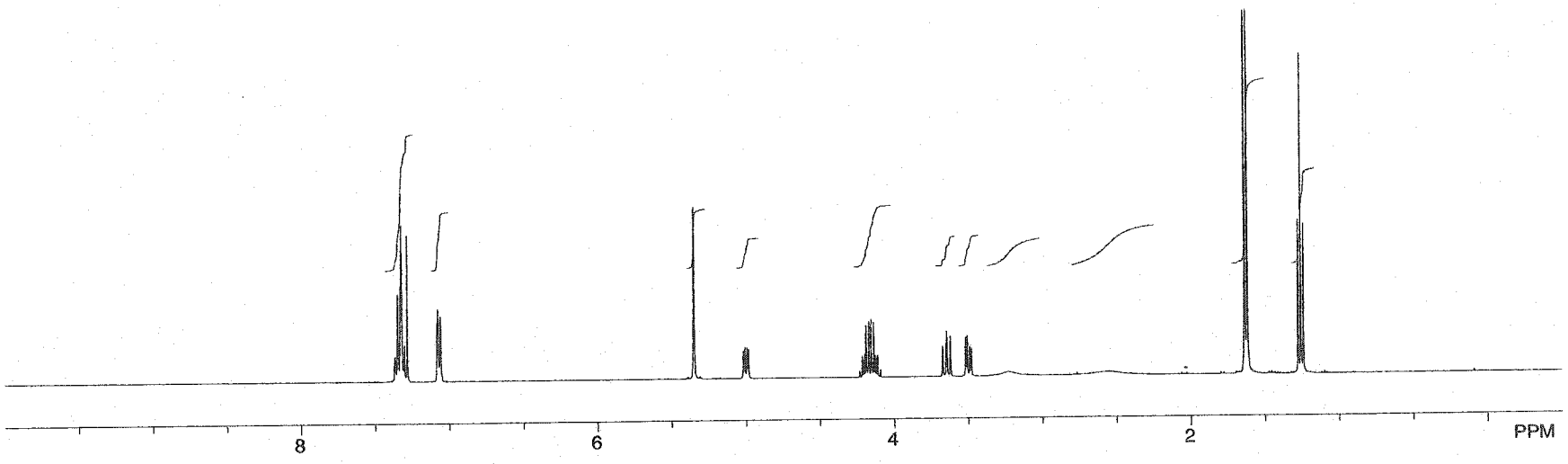


Figure A.2.1 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **184**.

Figure A.2.2 FTIR Spectrum (thin film/NaCl) of Compound **184**.

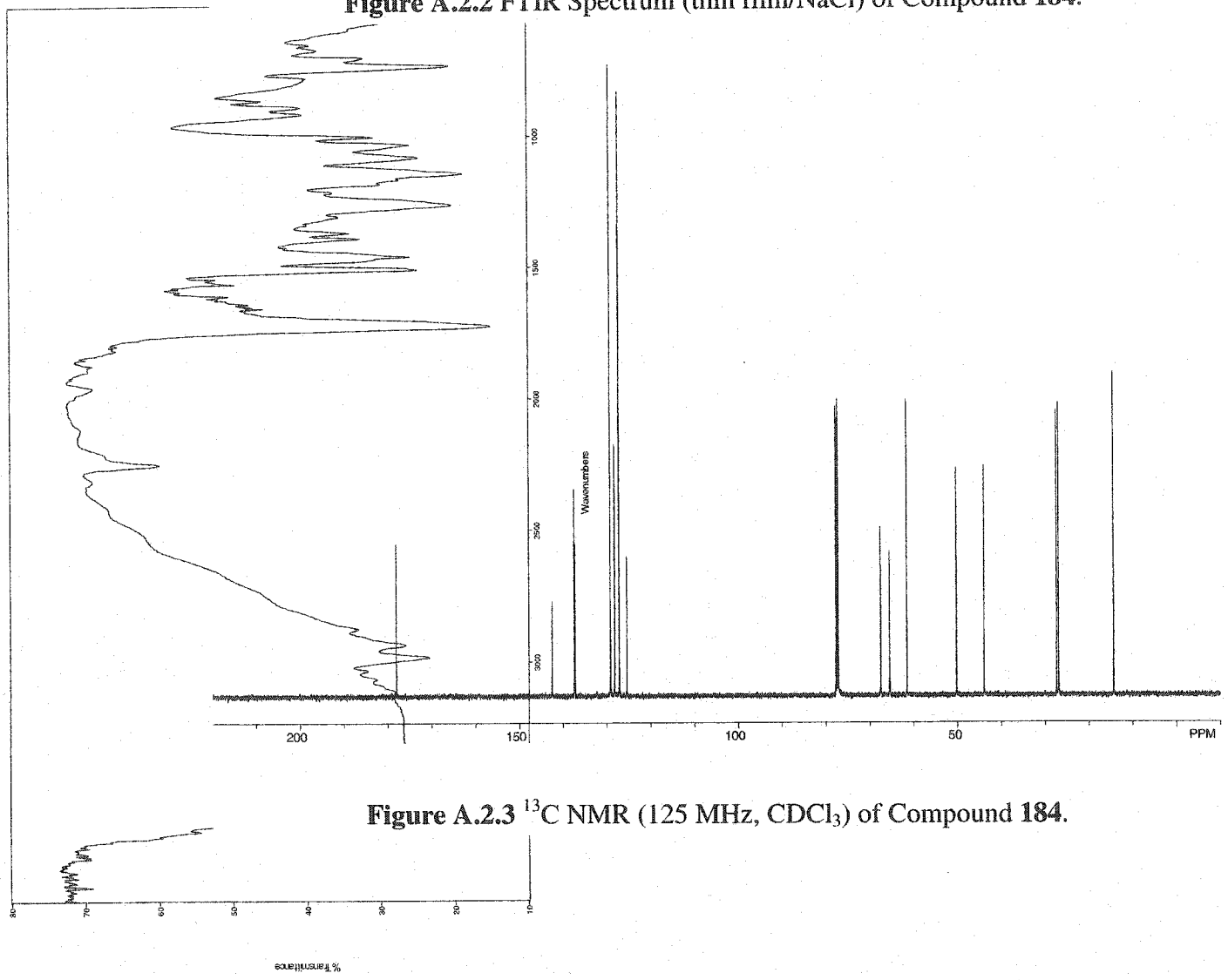


Figure A.2.3 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **184**.

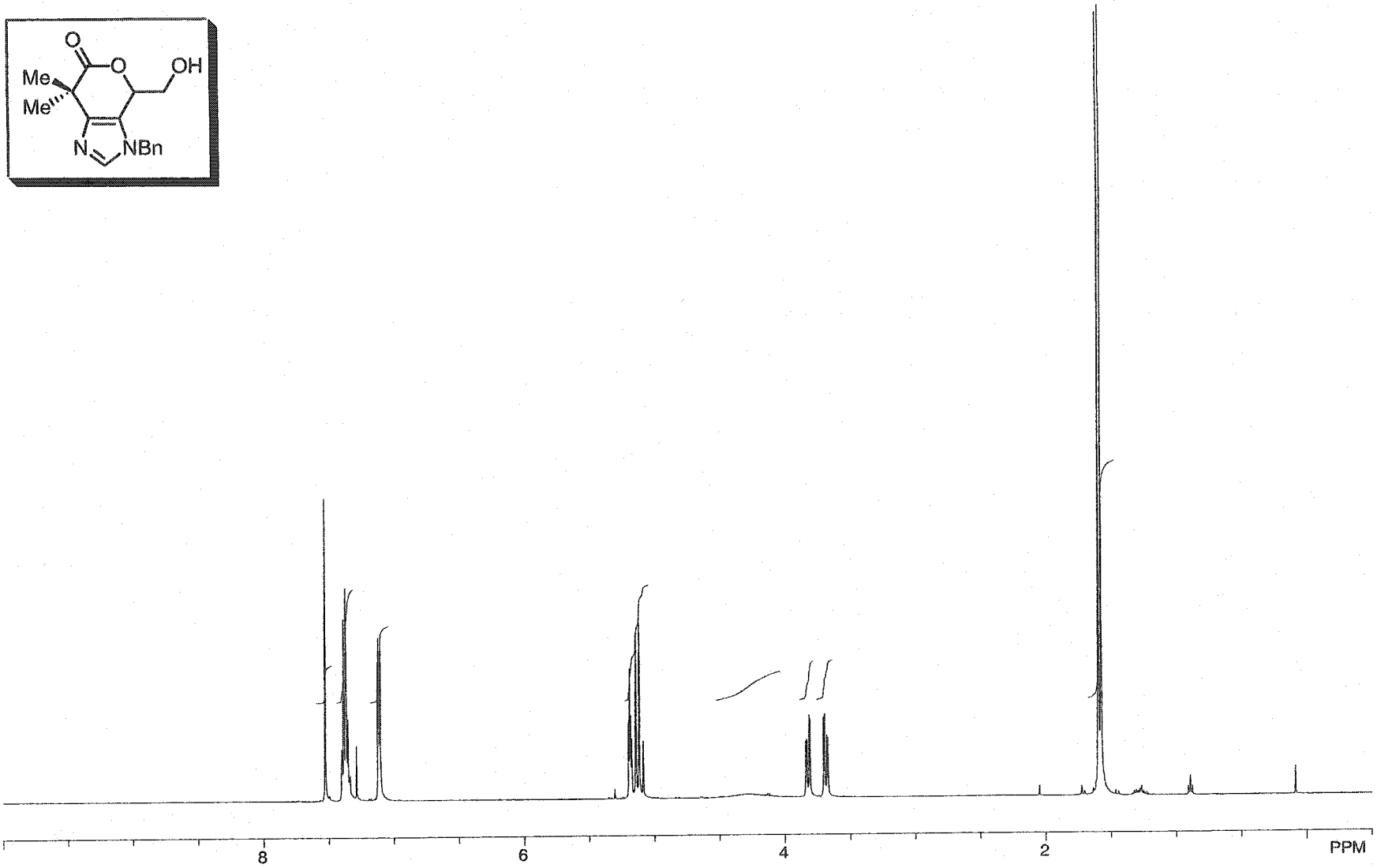


Figure A.2.4 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **185**.

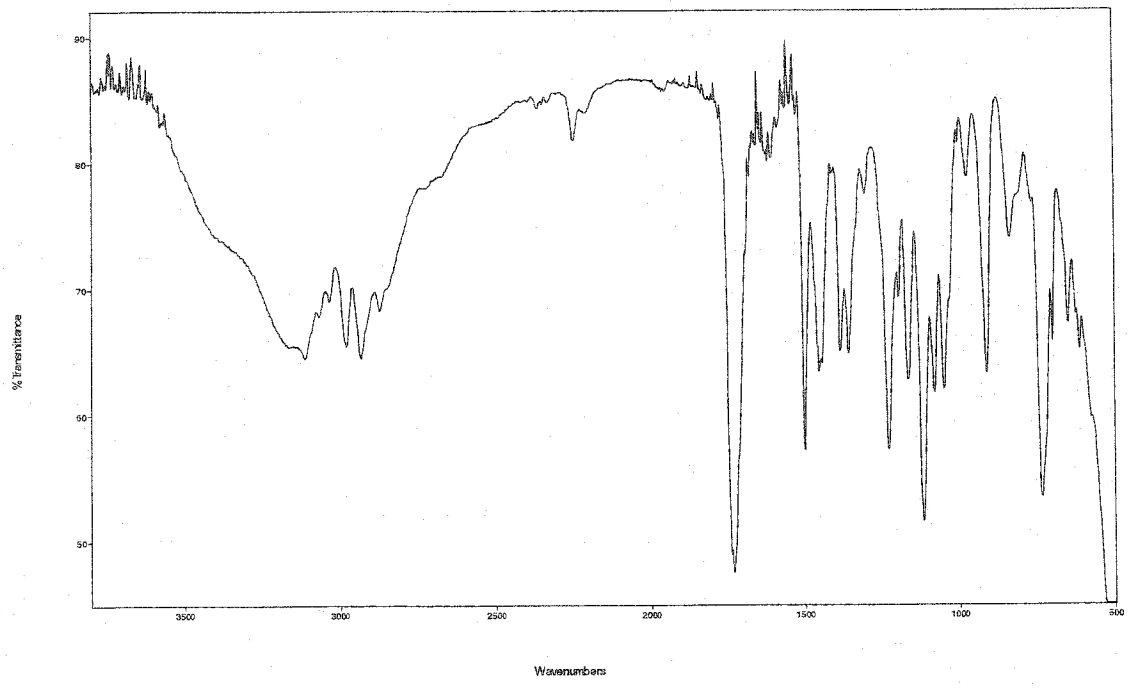


Figure A.2.5 FTIR Spectrum (thin film/NaCl) of Compound **185**.

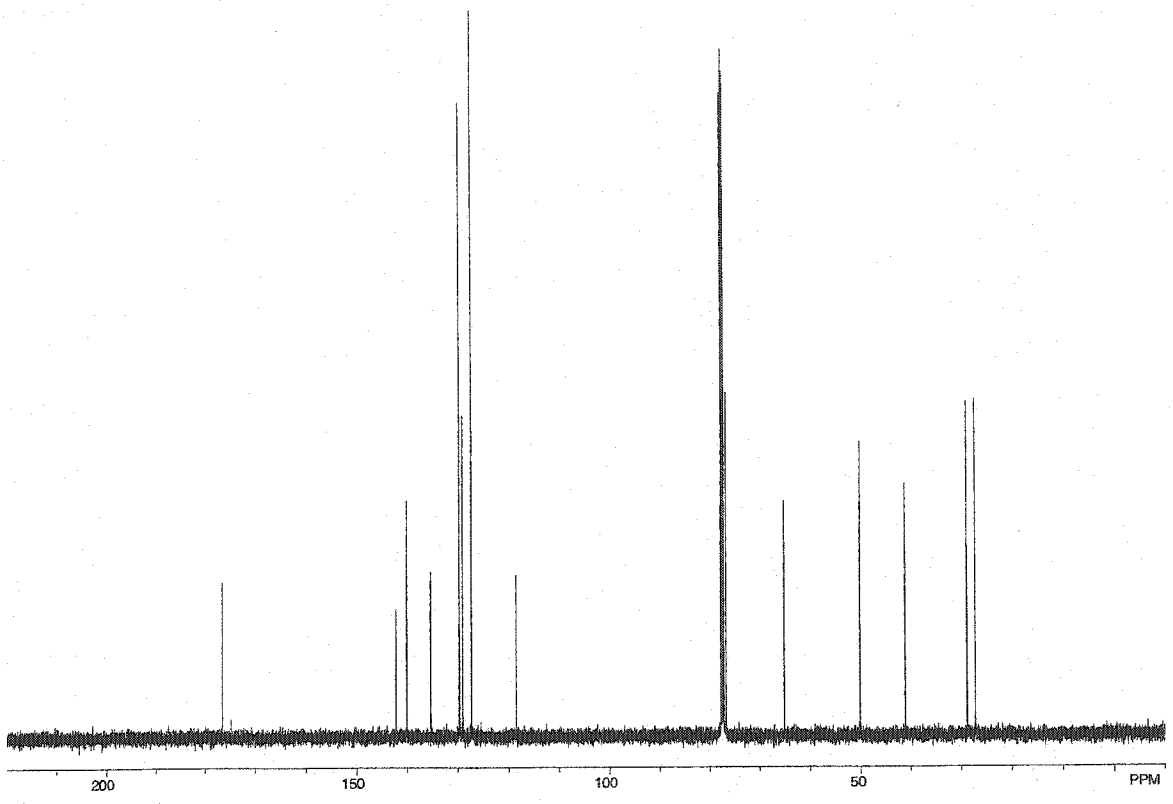


Figure A.2.6 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **185**.

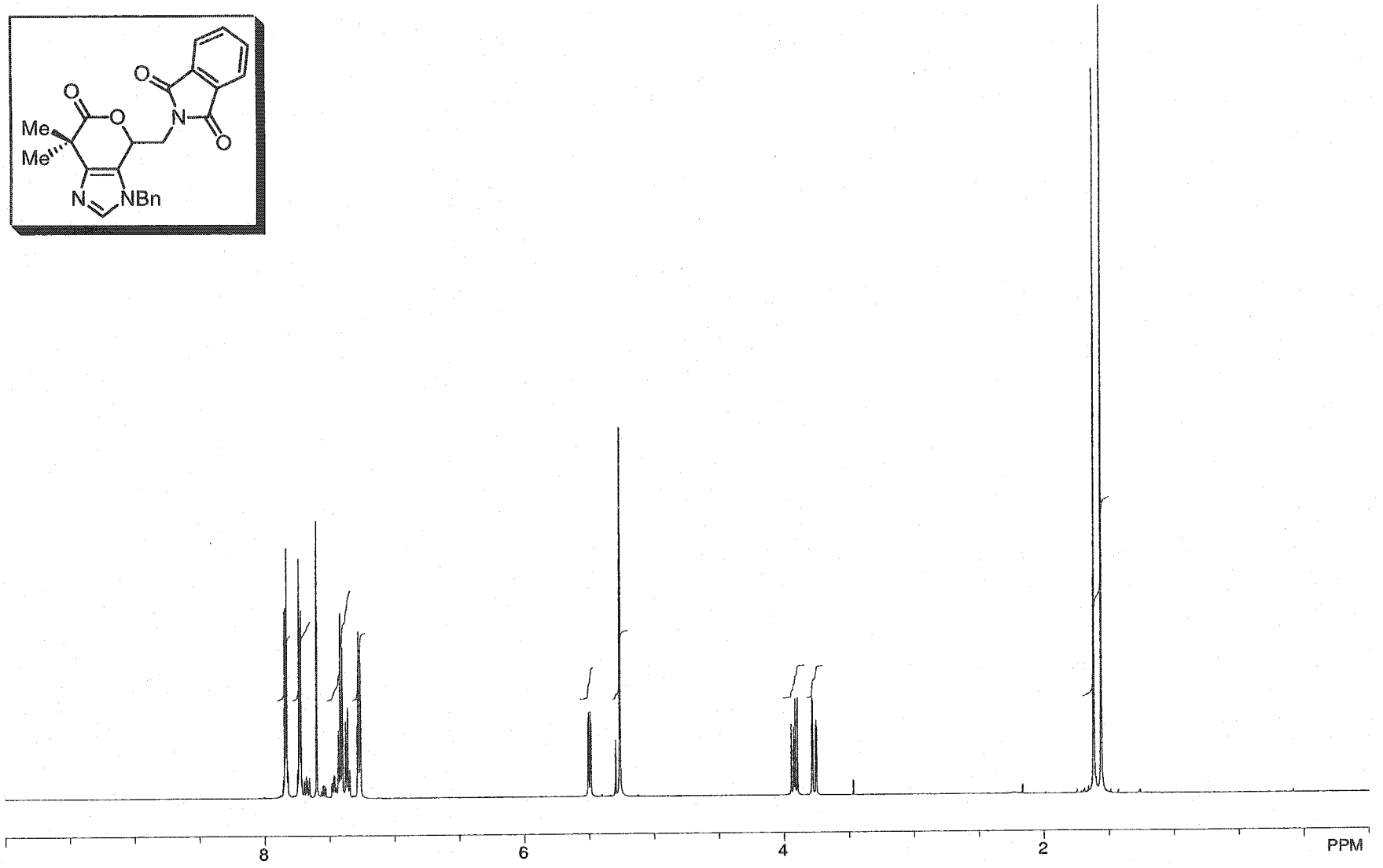


Figure A.2.7 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **186**.

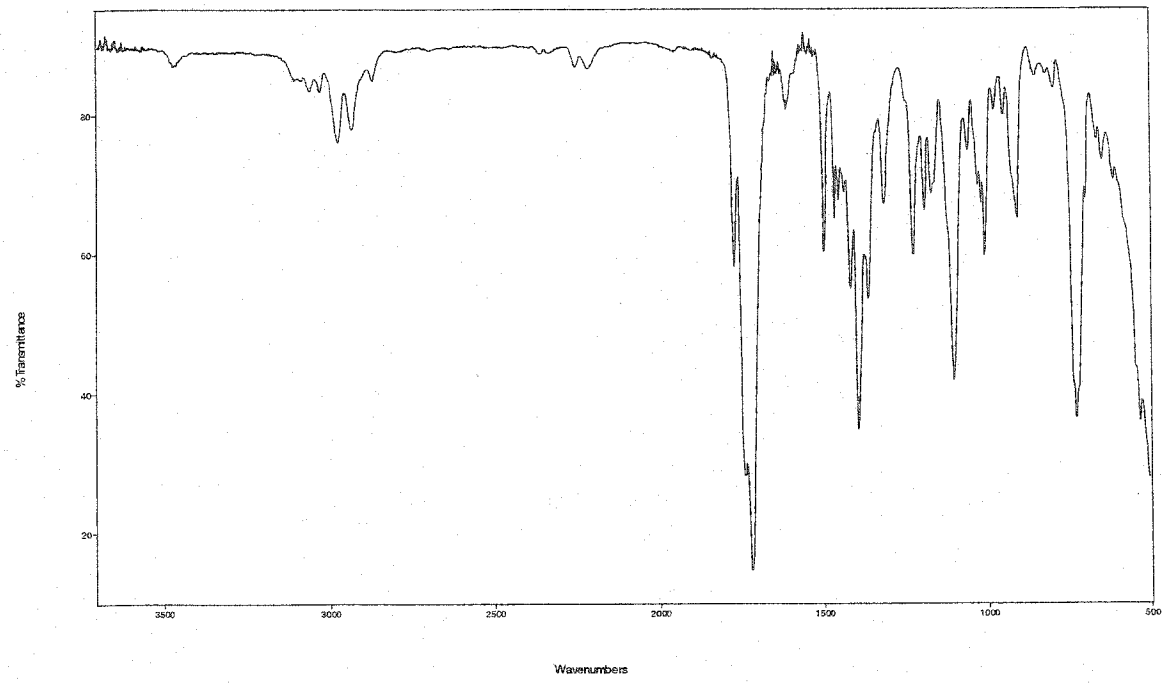


Figure A.2.8 FTIR Spectrum (thin film/NaCl) of Compound **186**.

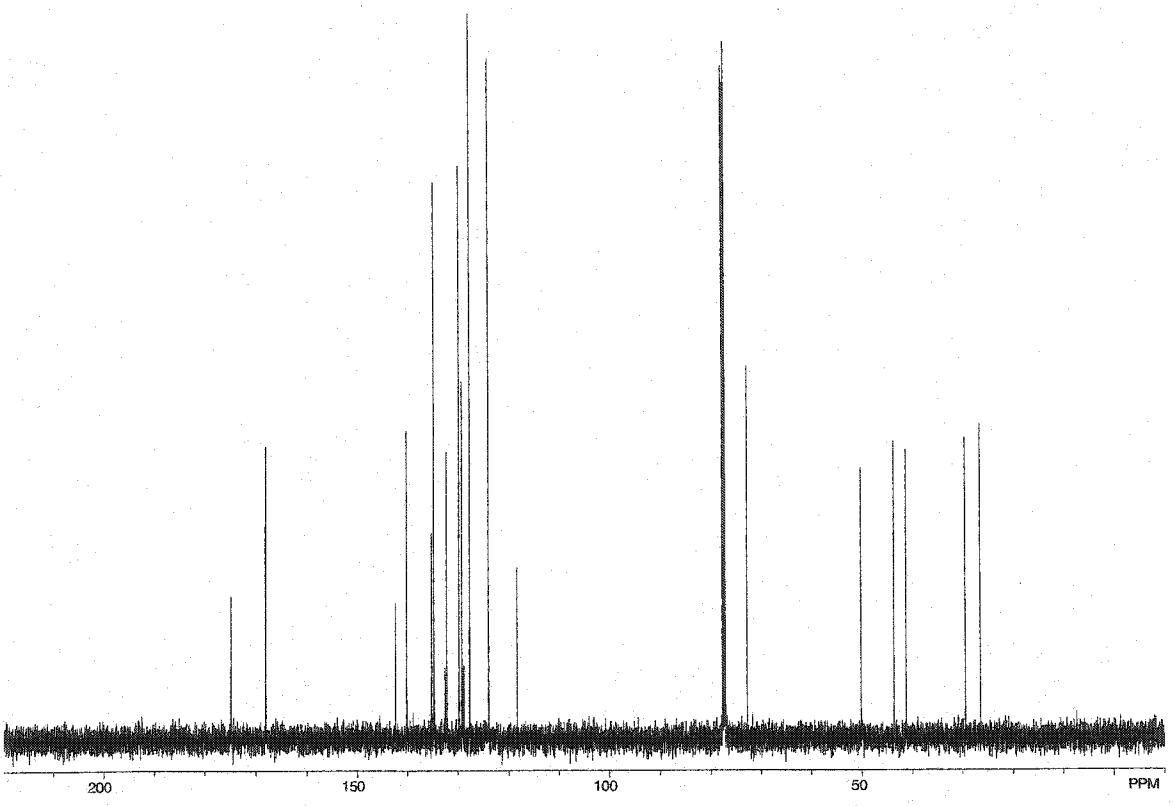


Figure A.2.9 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **186**.

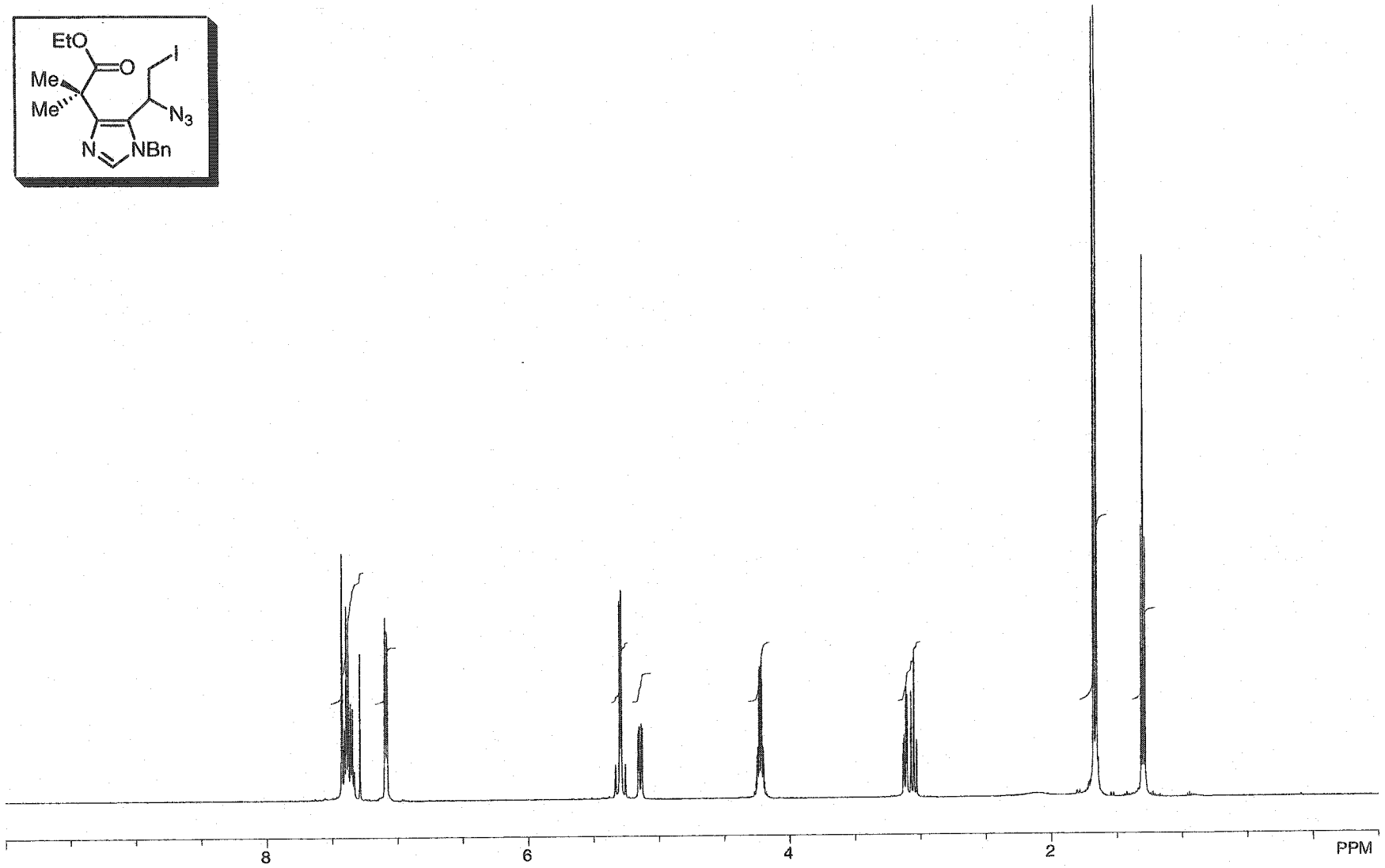


Figure A.2.10 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **191**.

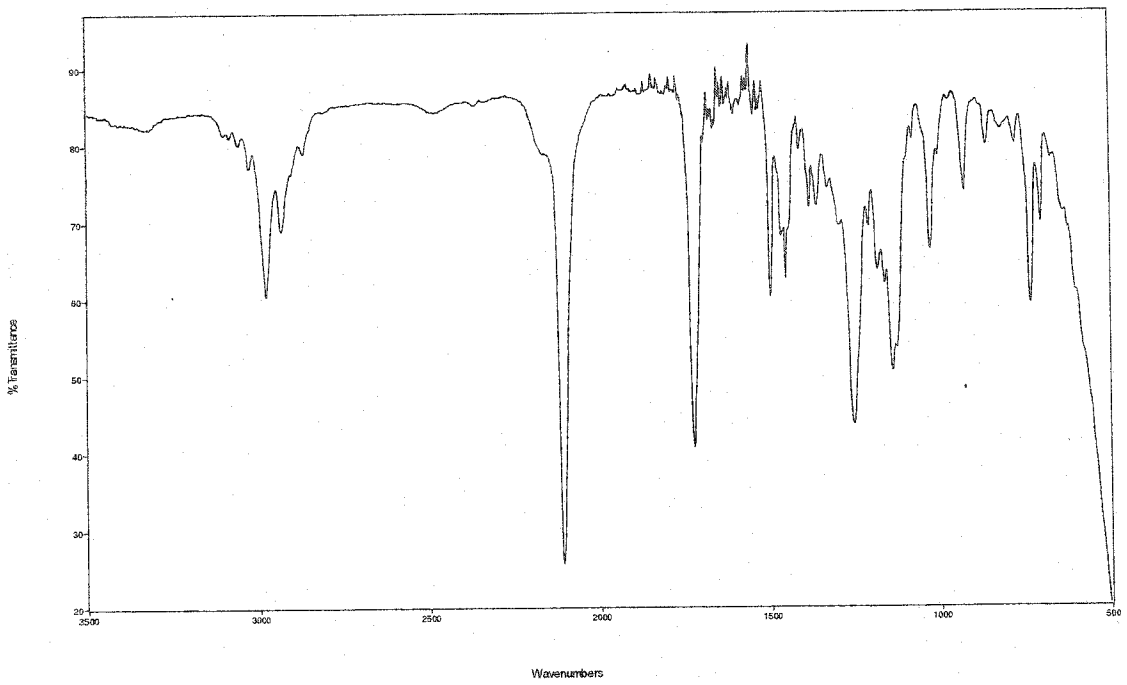


Figure A.2.11 FTIR Spectrum (thin film/NaCl) of Compound **191**.

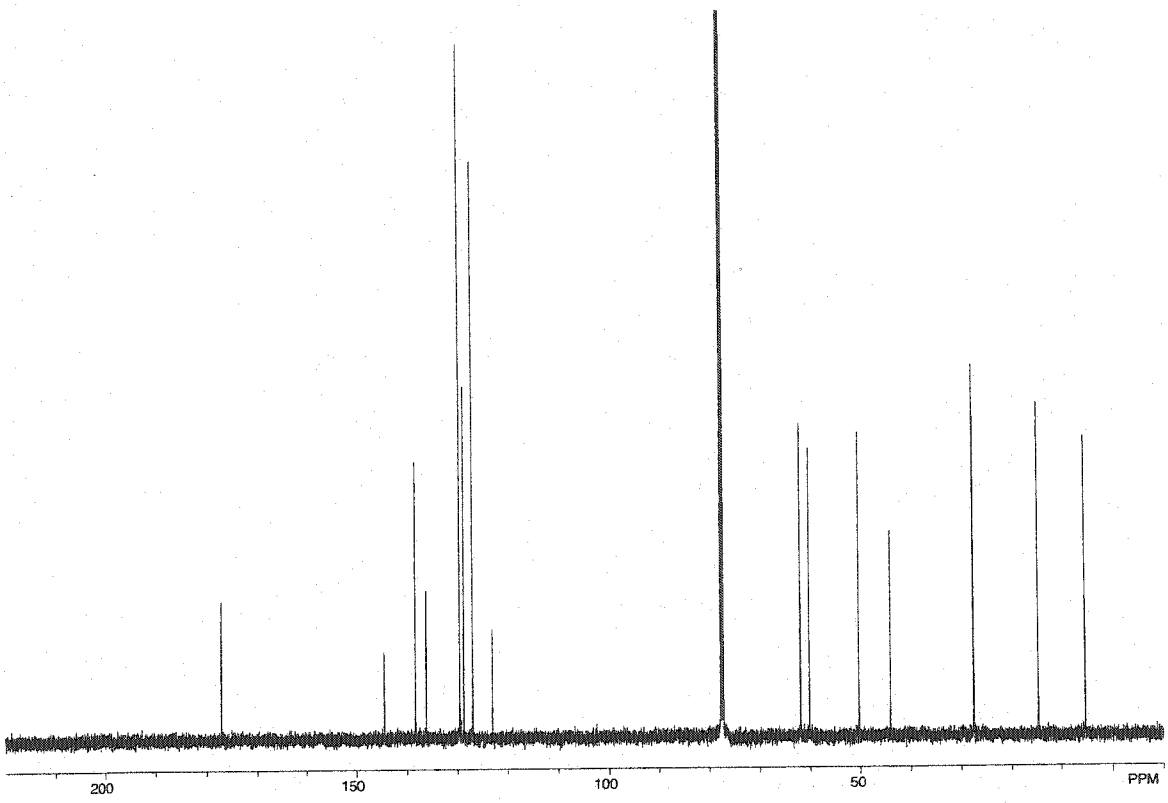


Figure A.2.12 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **191**.

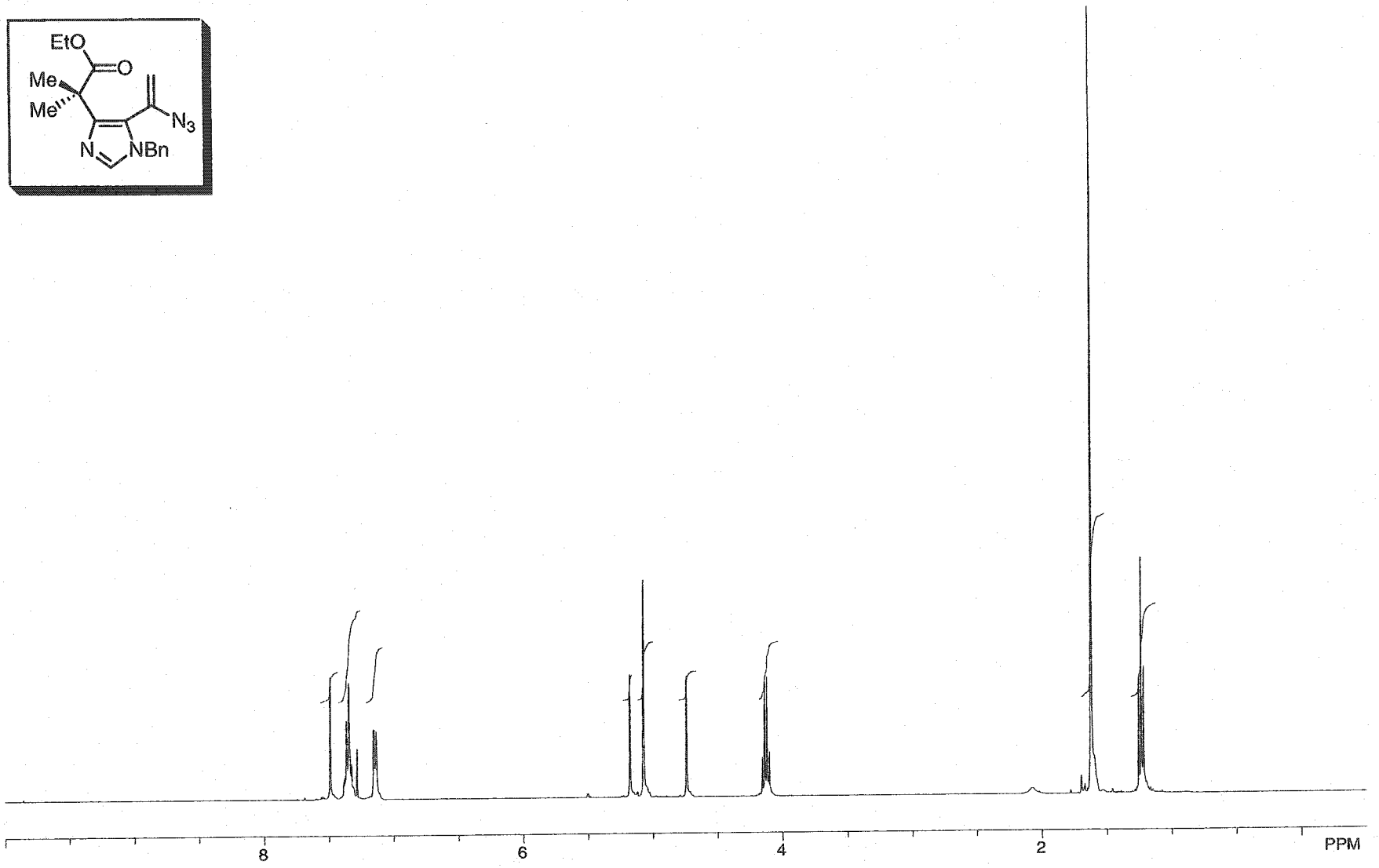


Figure A.2.13 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **192**.

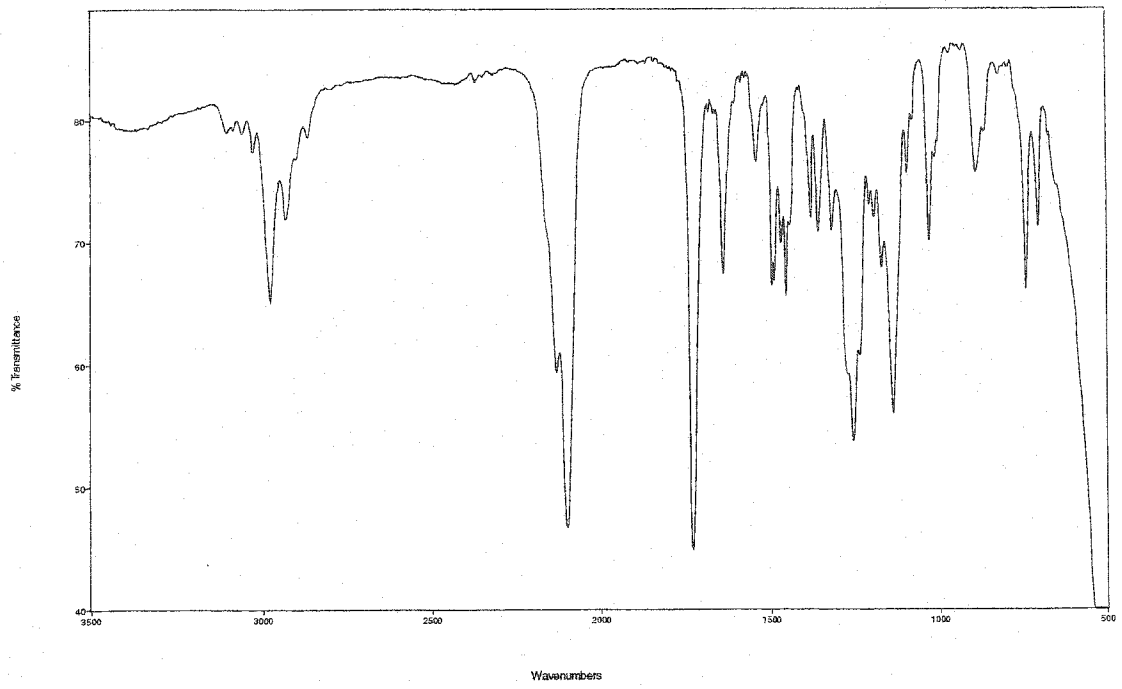


Figure A.2.14 FTIR Spectrum (thin film/NaCl) of Compound **192**.

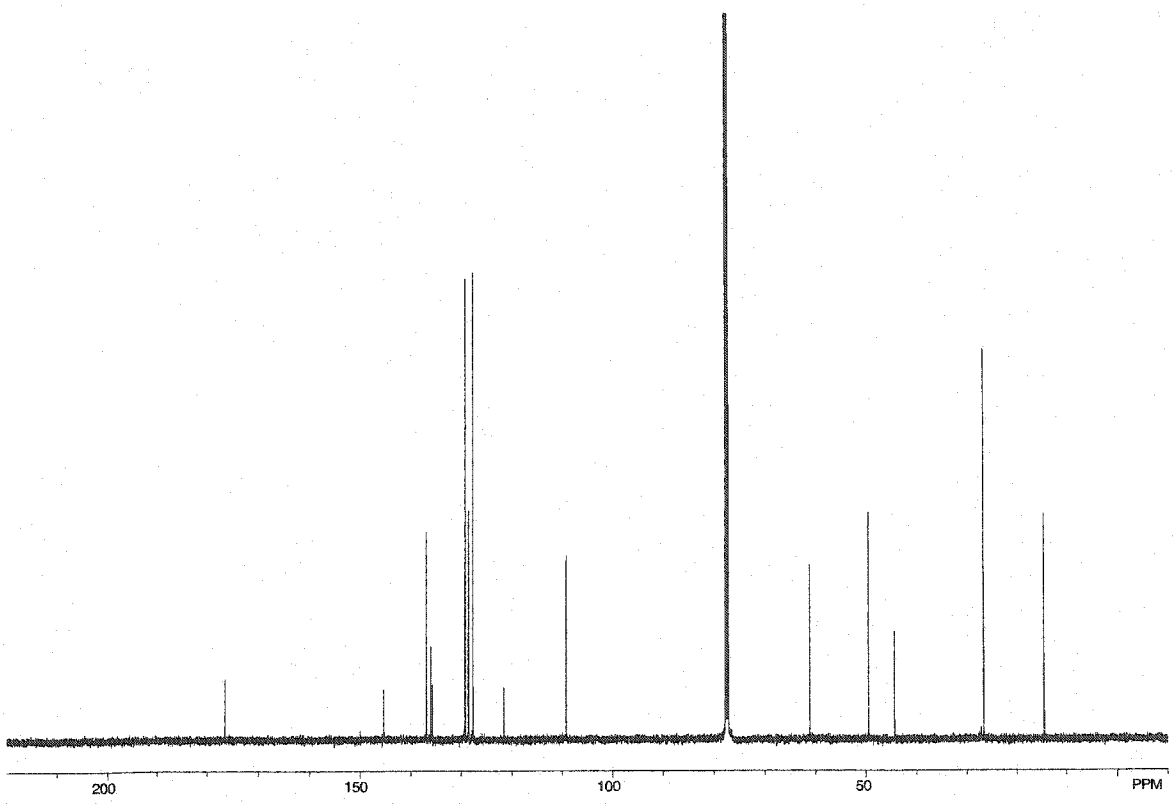


Figure A.2.15 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **192**.

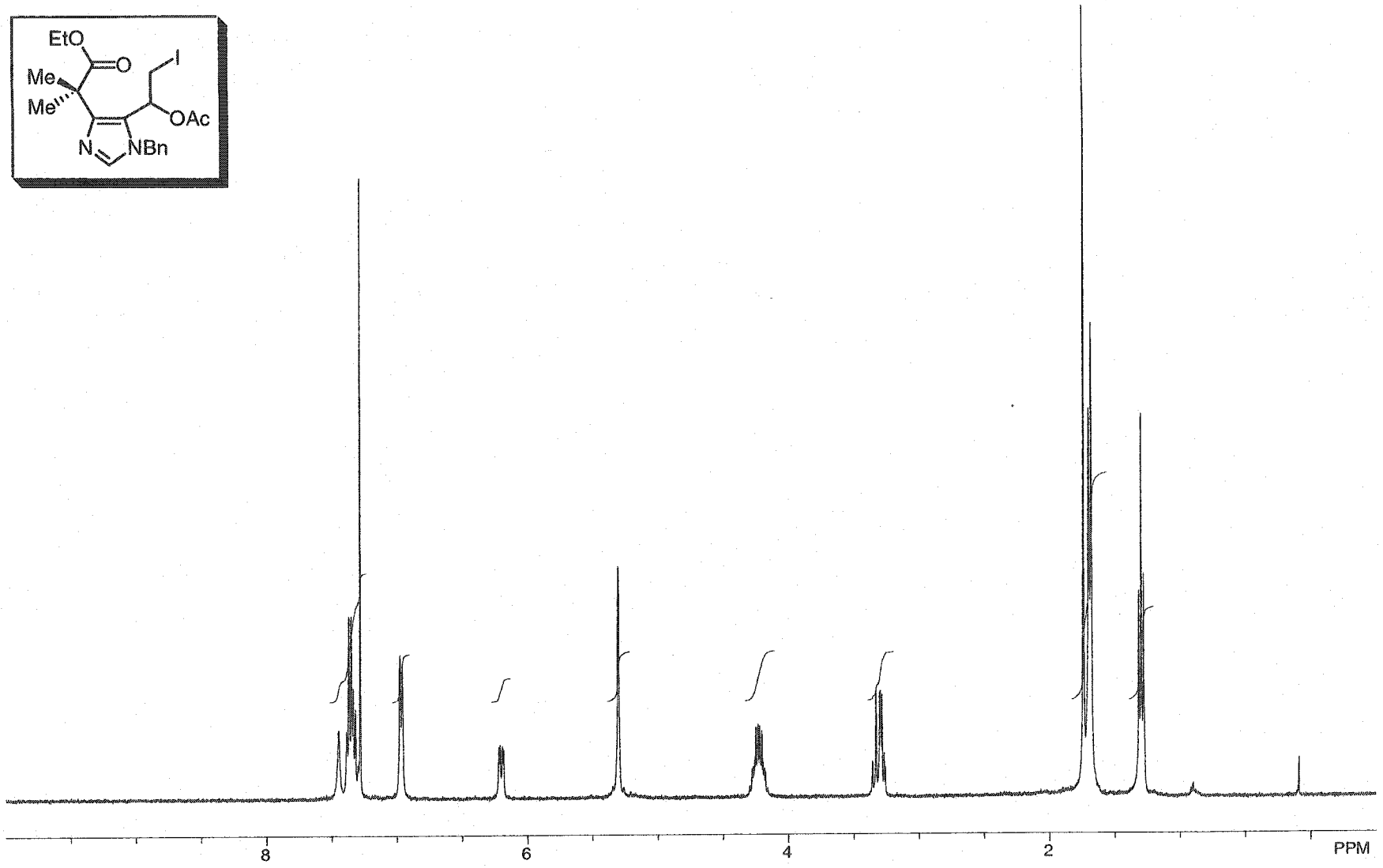


Figure A.2.16 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **193**.

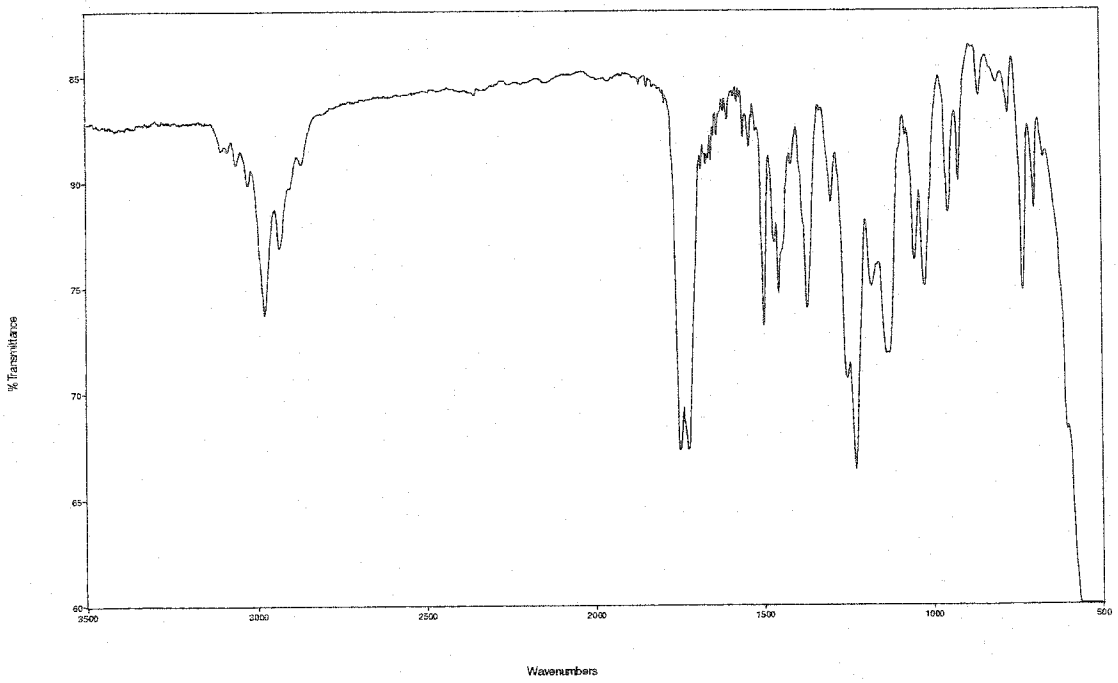


Figure A.2.17 FTIR Spectrum (thin film/NaCl) of Compound **193**.

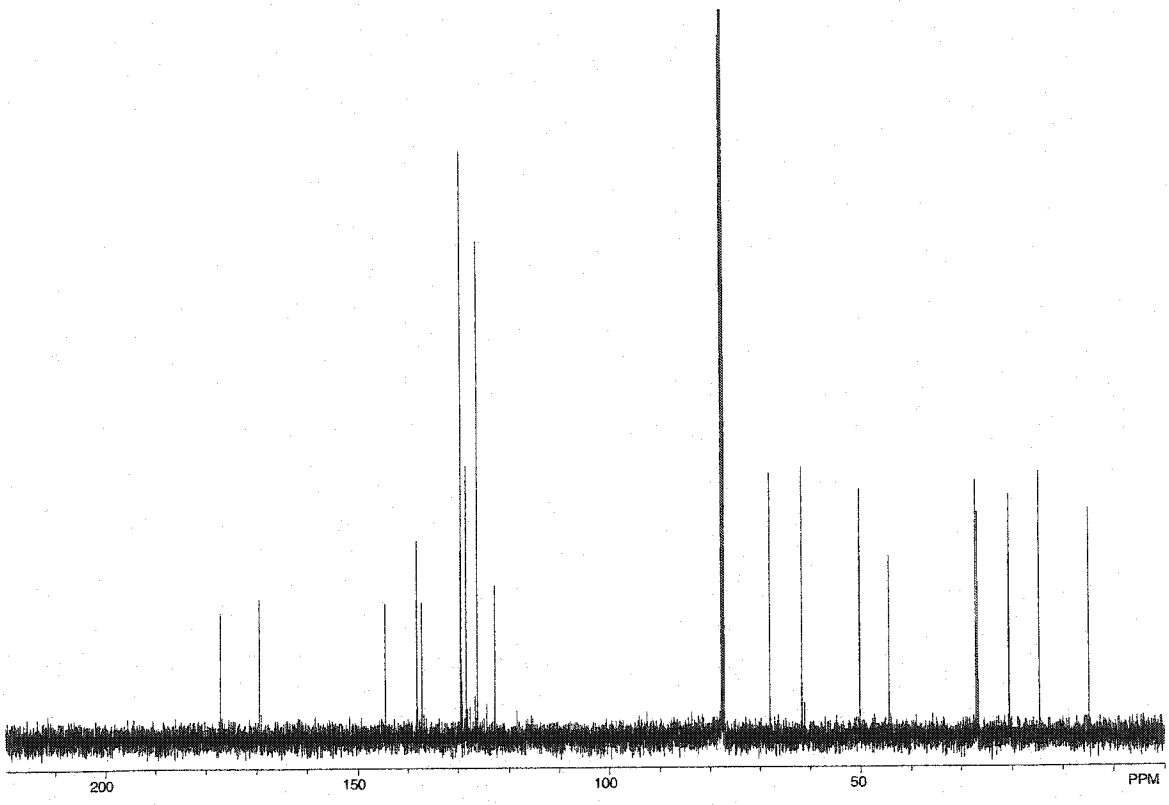


Figure A.2.18 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **193**.

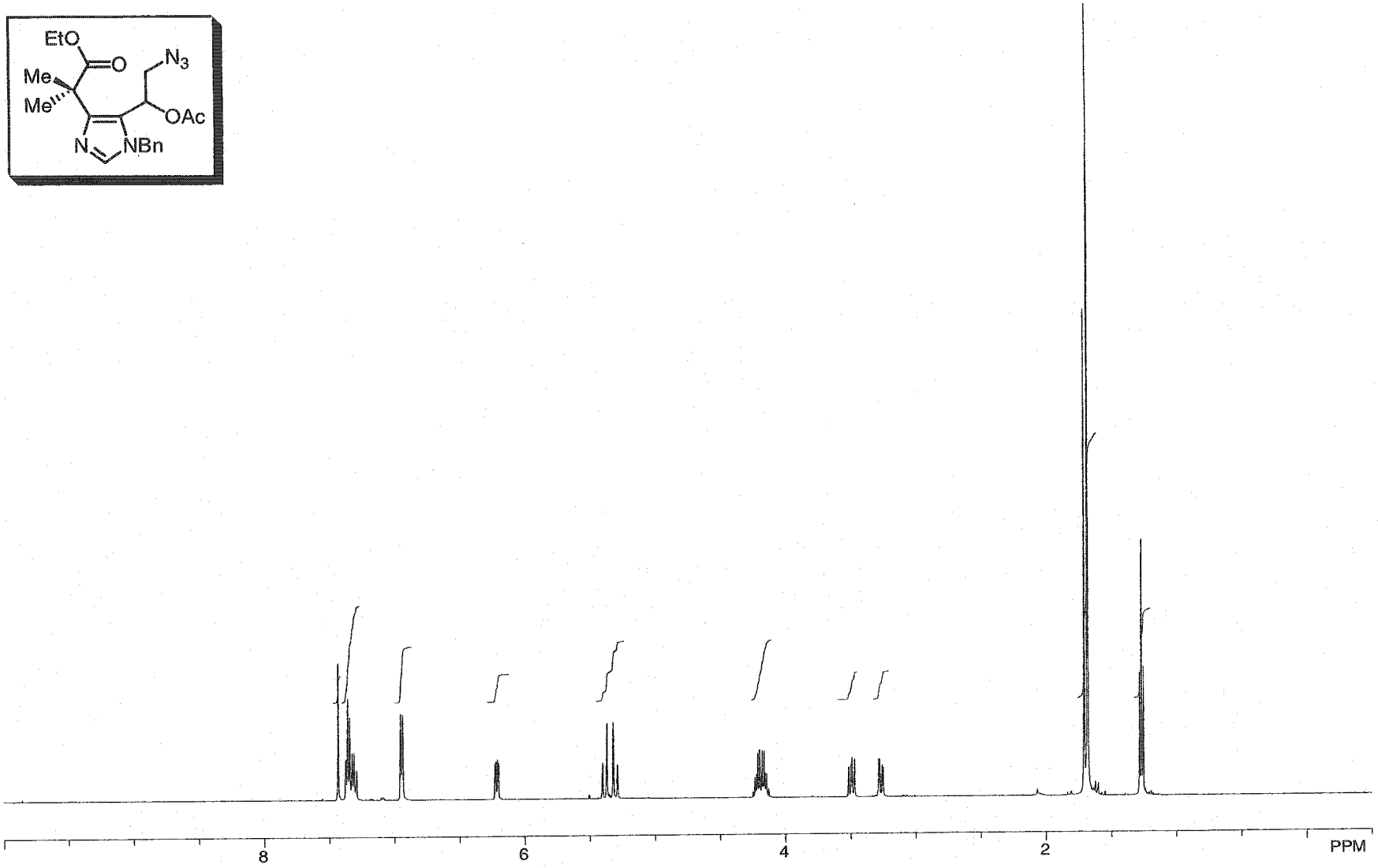


Figure A.2.19 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **194**.

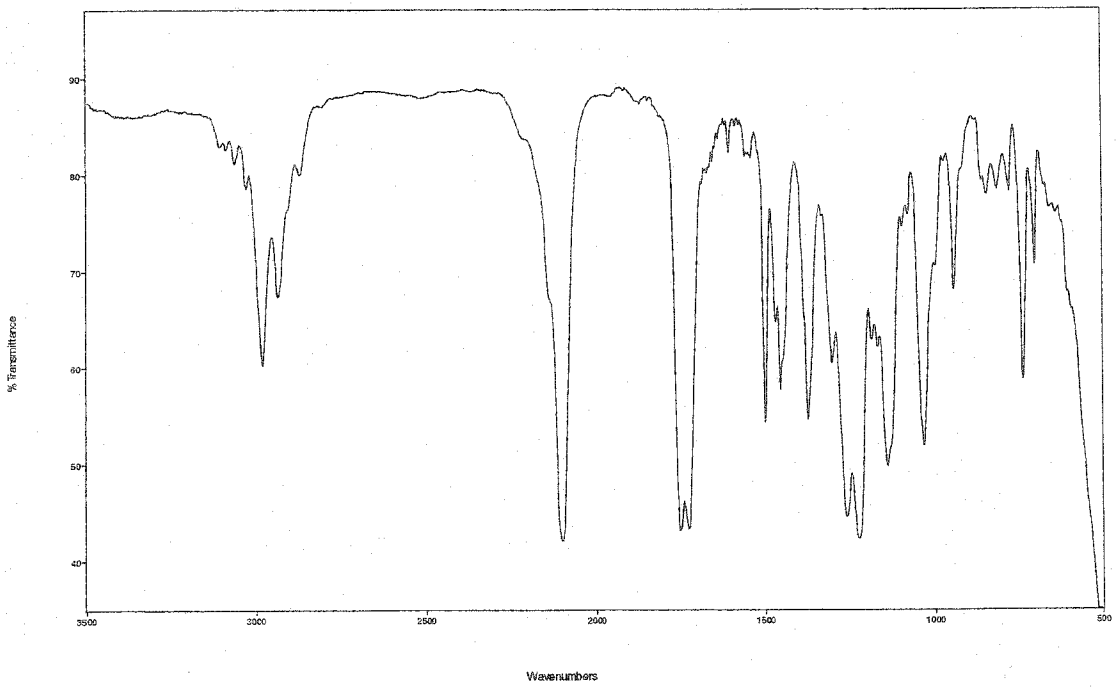


Figure A.2.20 FTIR Spectrum (thin film/NaCl) of Compound **194**.

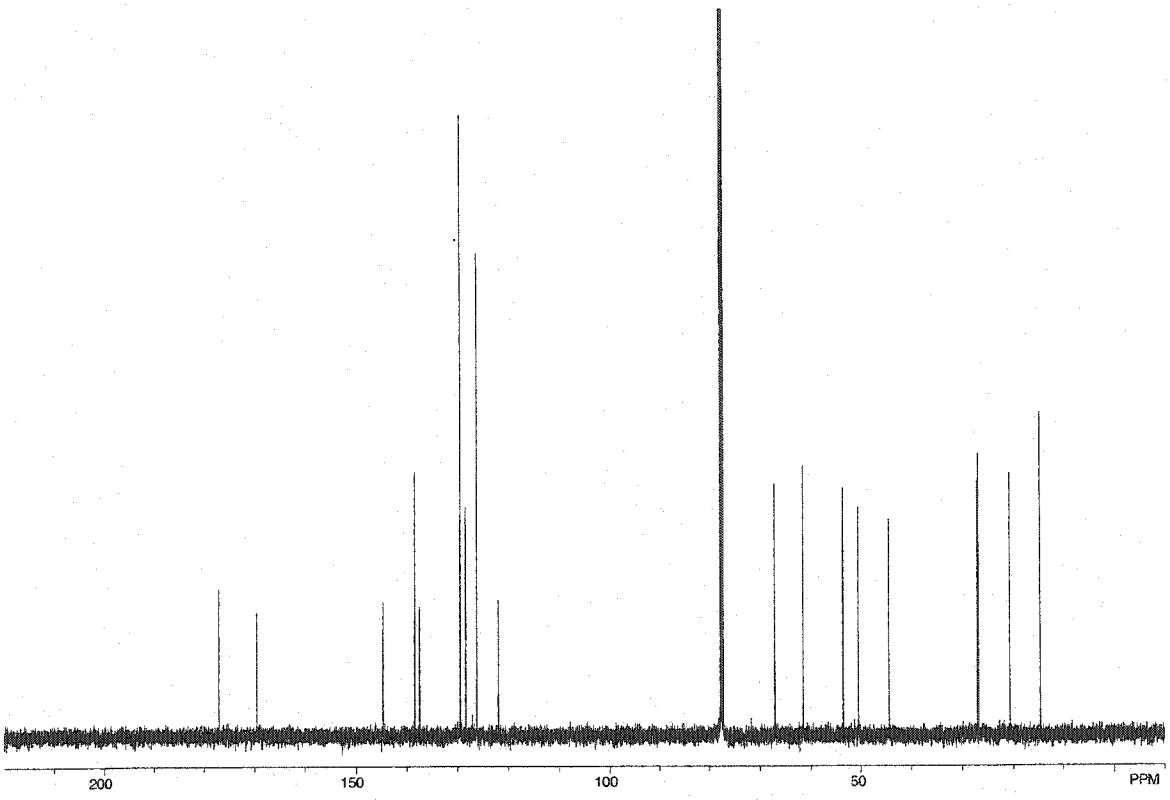
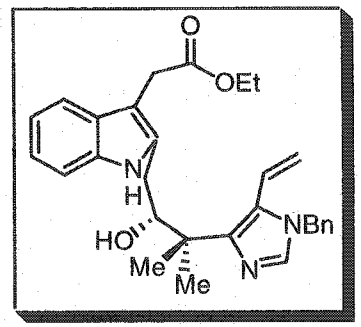


Figure A.2.21 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **194**.



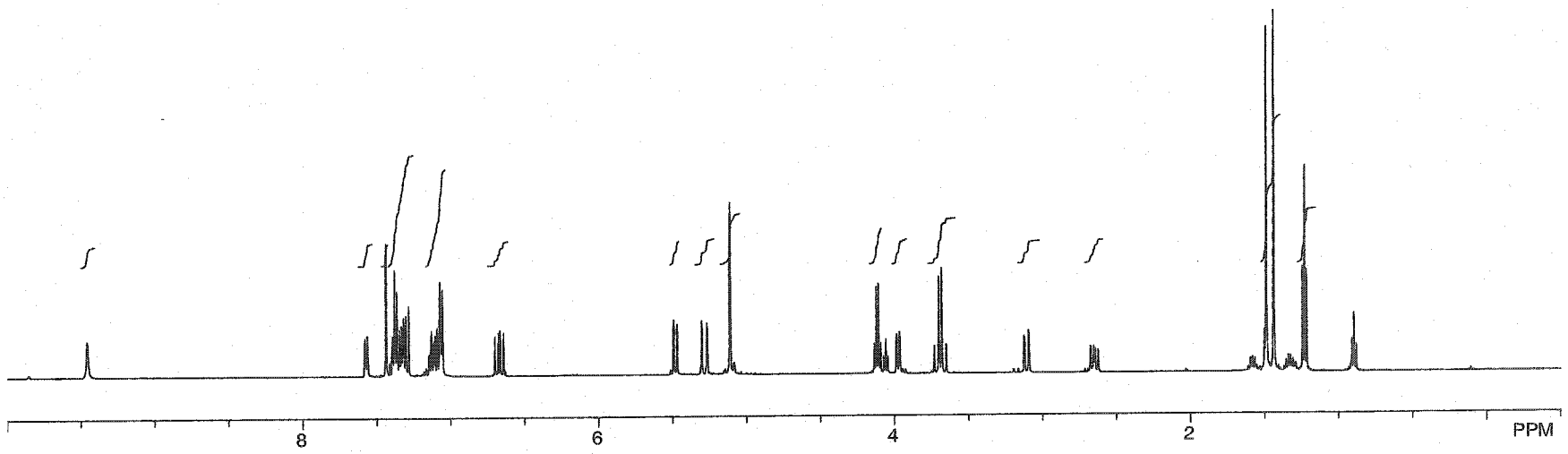


Figure A.2.22 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **195**.

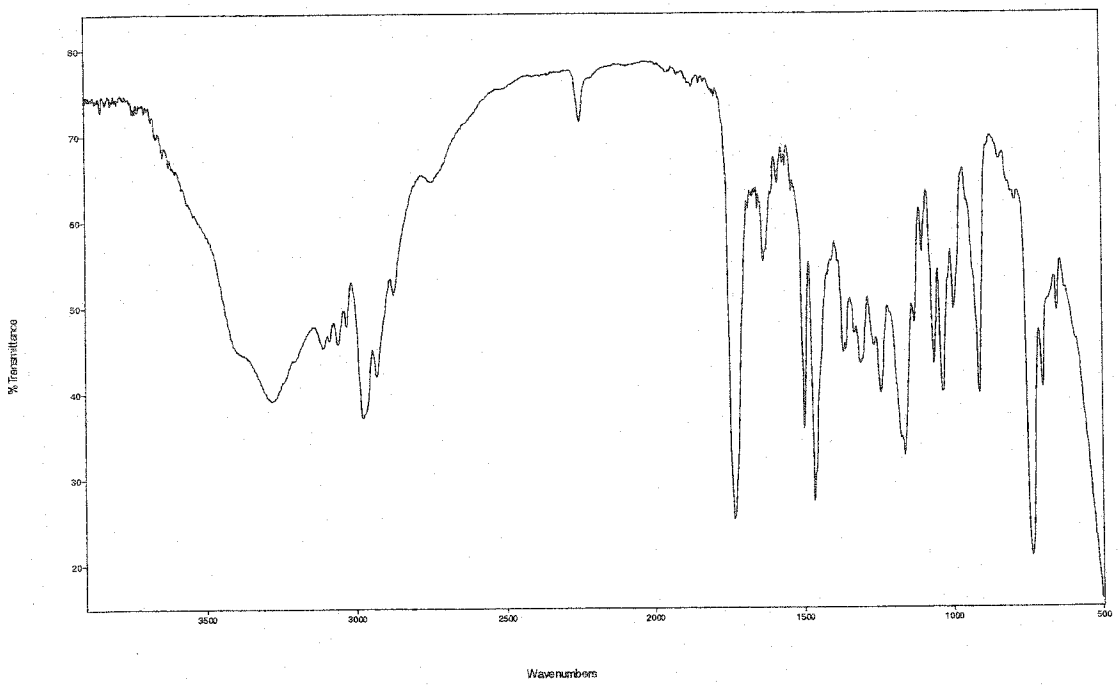


Figure A.2.23 FTIR Spectrum (thin film/NaCl) of Compound **195**.

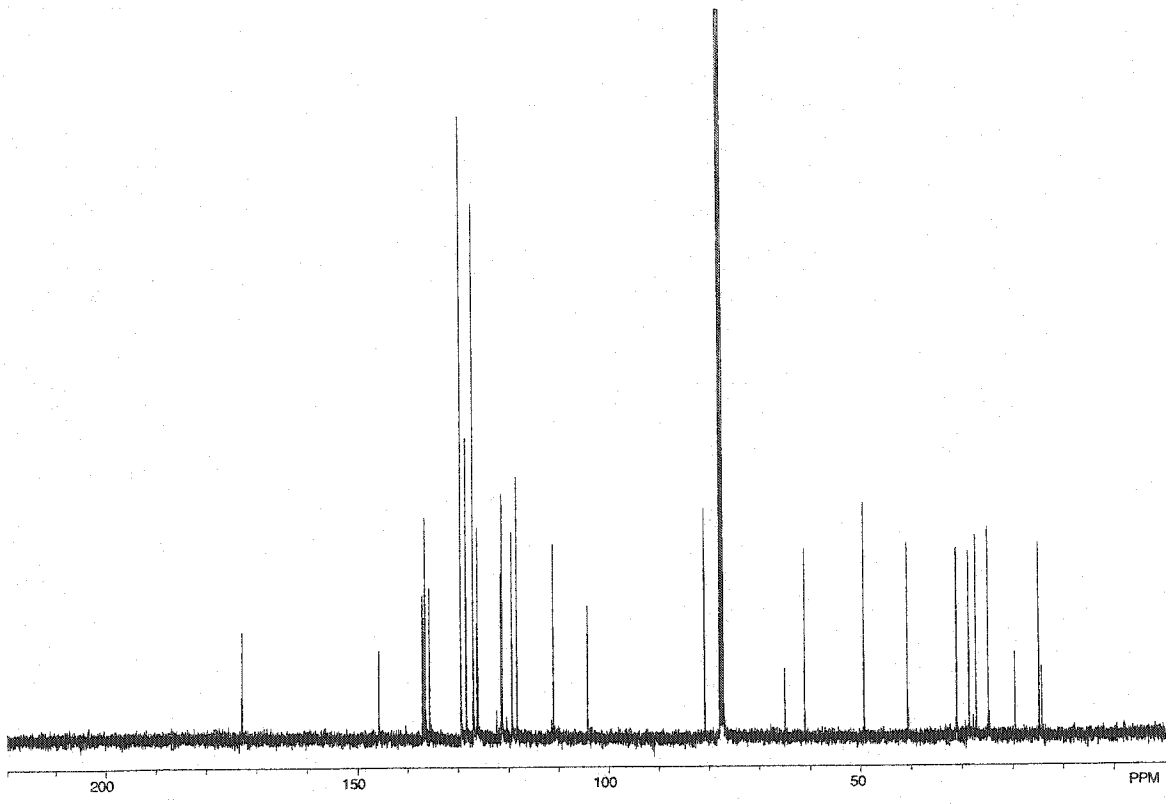


Figure A.2.24 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **195**.

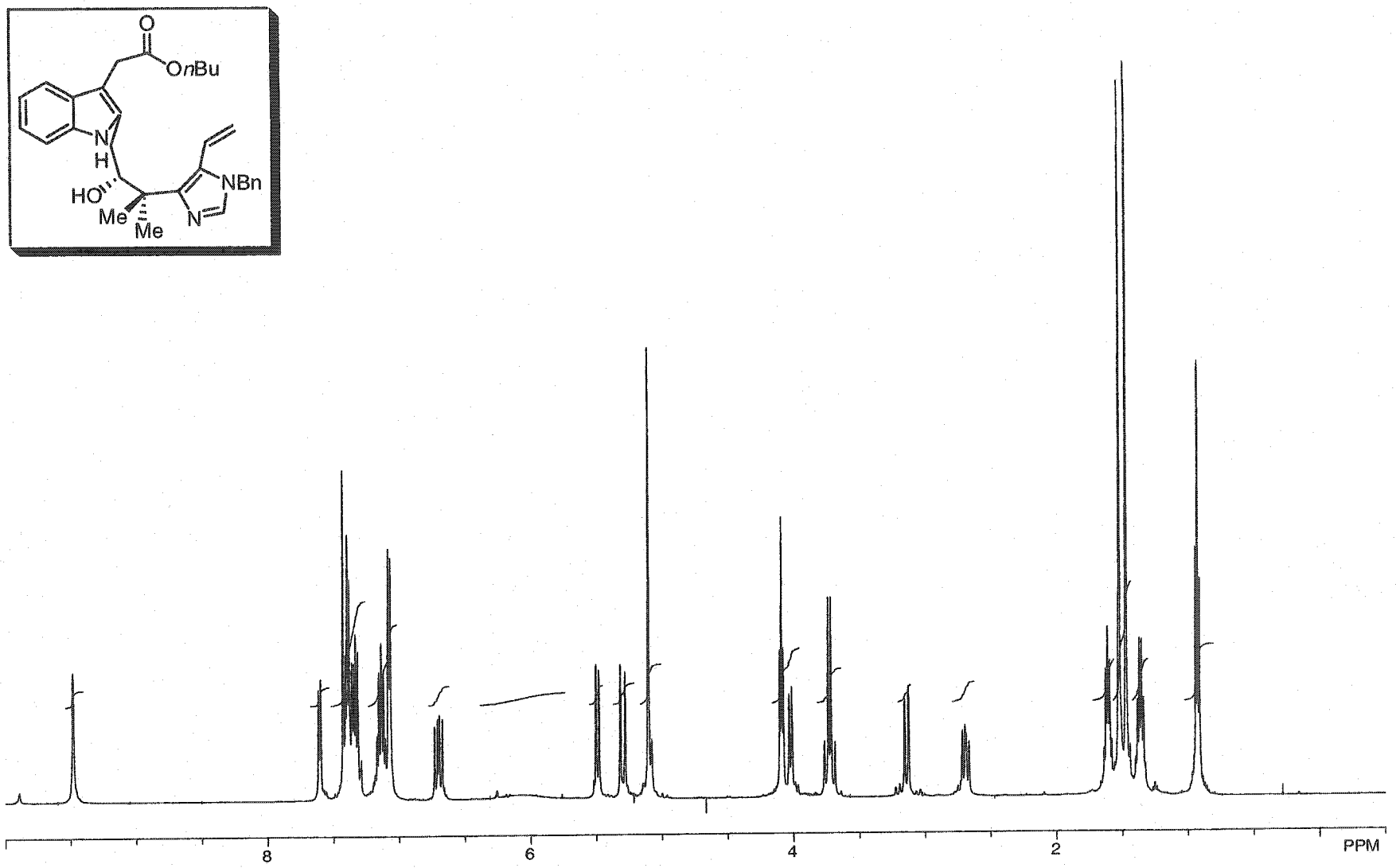


Figure A.2.25 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **196**.

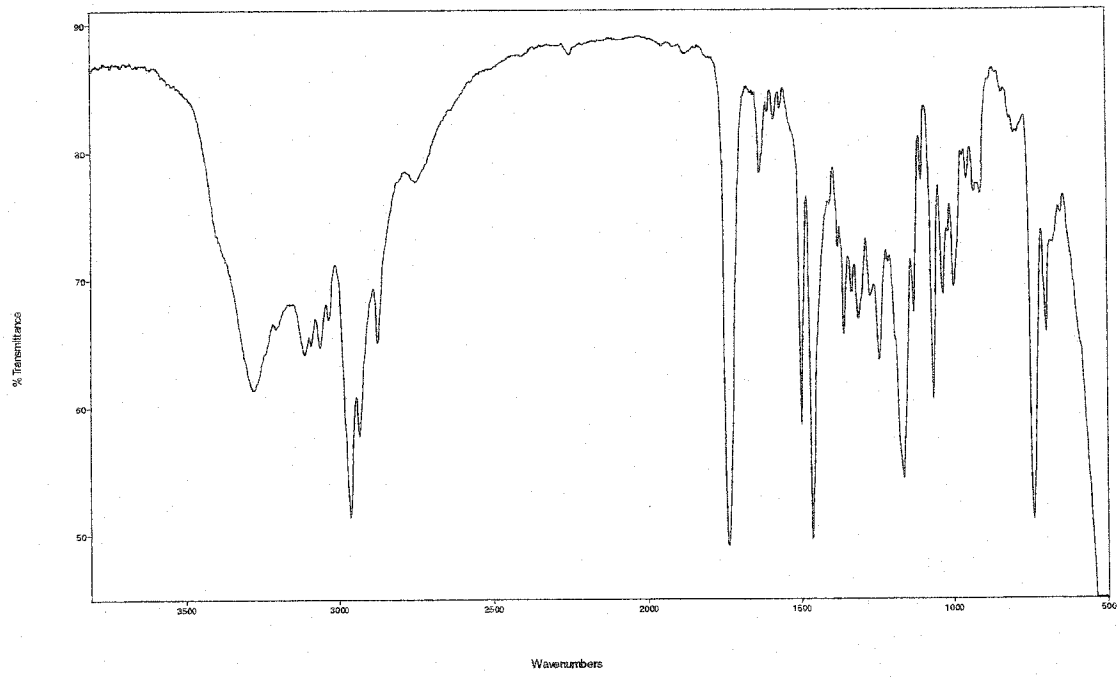


Figure A.2.26 FTIR Spectrum (thin film/NaCl) of Compound **196**.

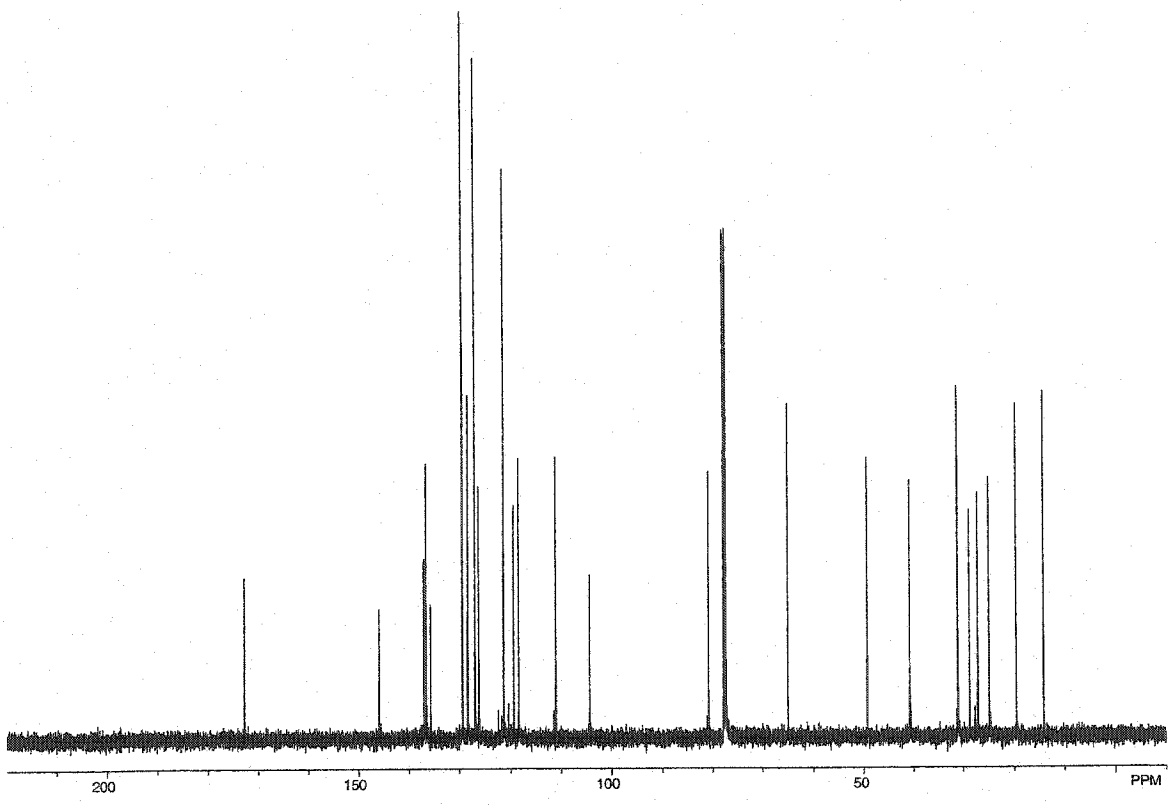


Figure A.2.27 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **196**.

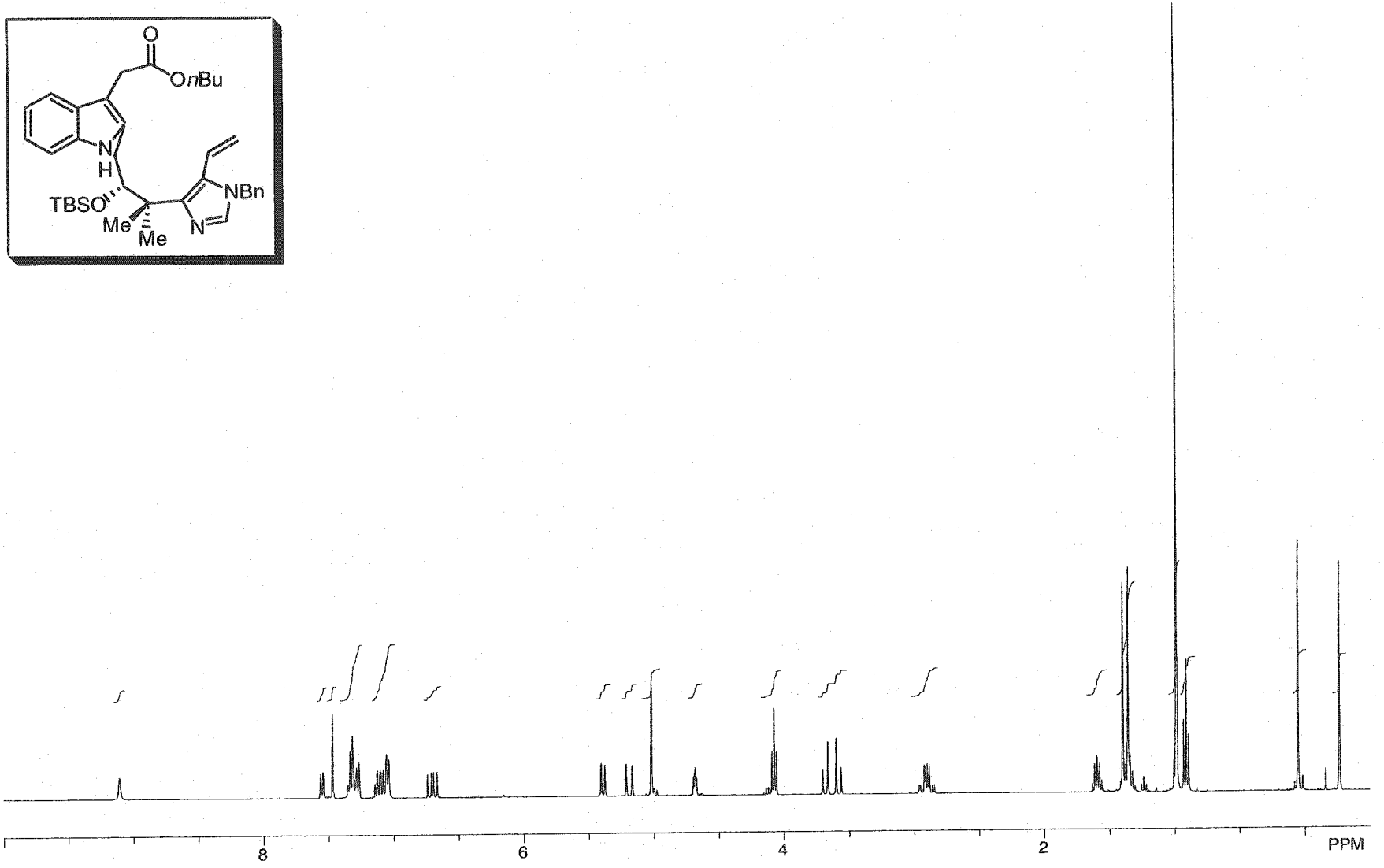


Figure A.2.28 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **206**.

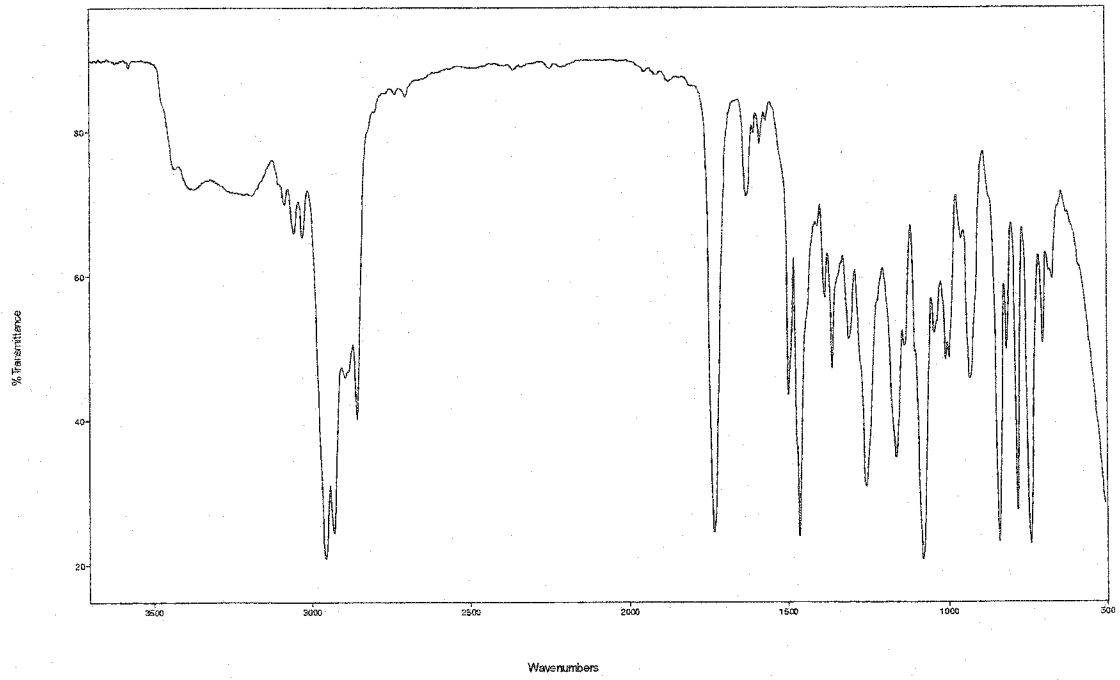


Figure A.2.29 FTIR Spectrum (thin film/NaCl) of Compound **206**.

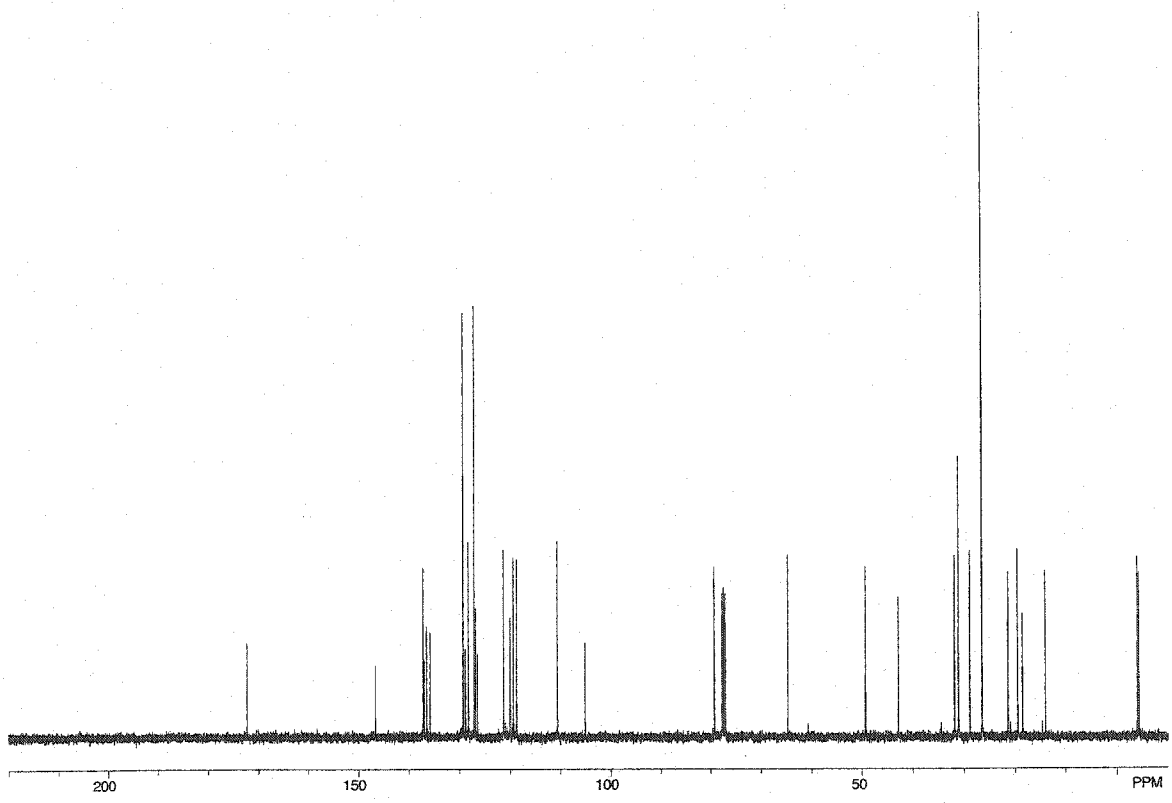


Figure A.2.30 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **206**.

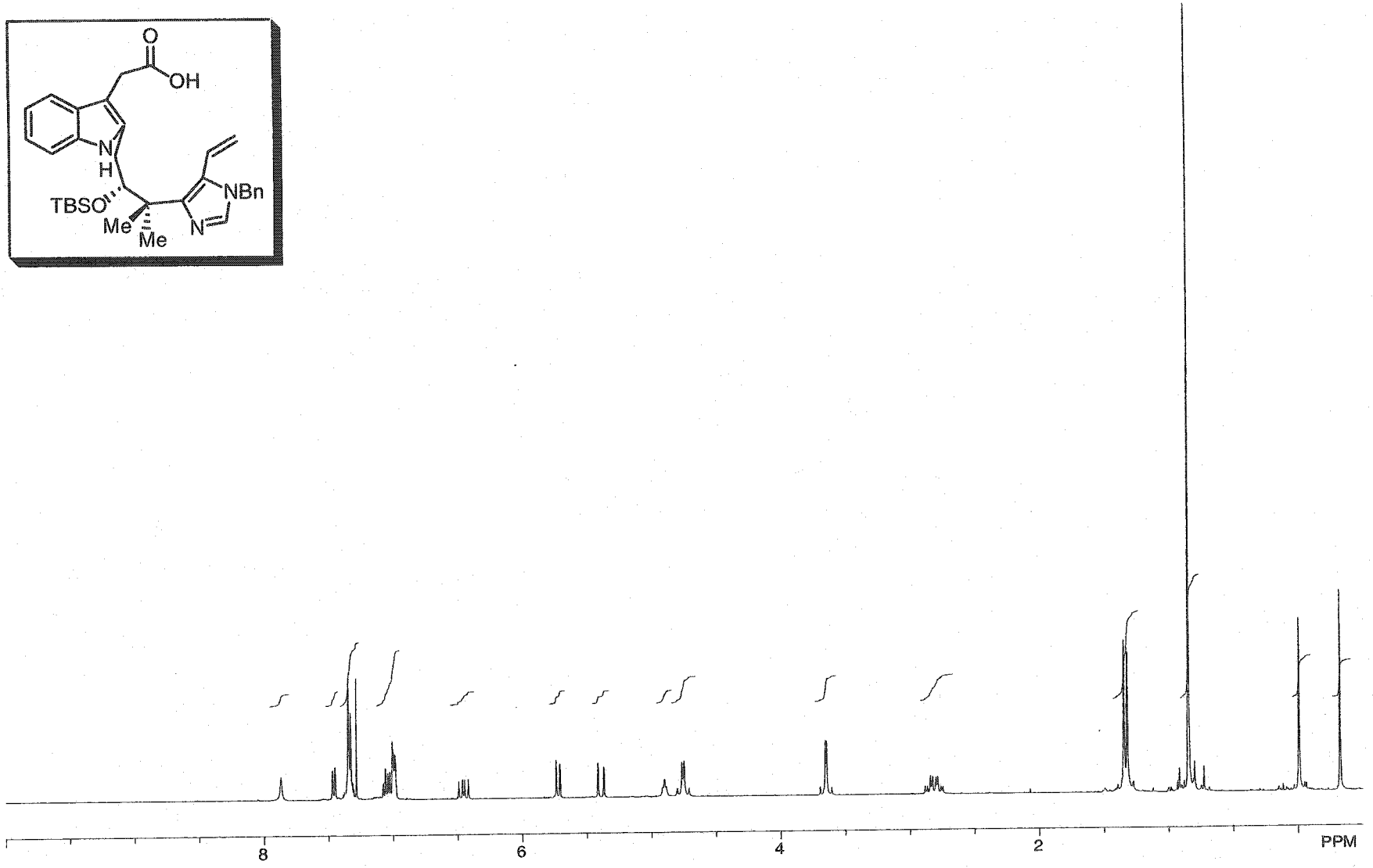


Figure A.2.31 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **197**.

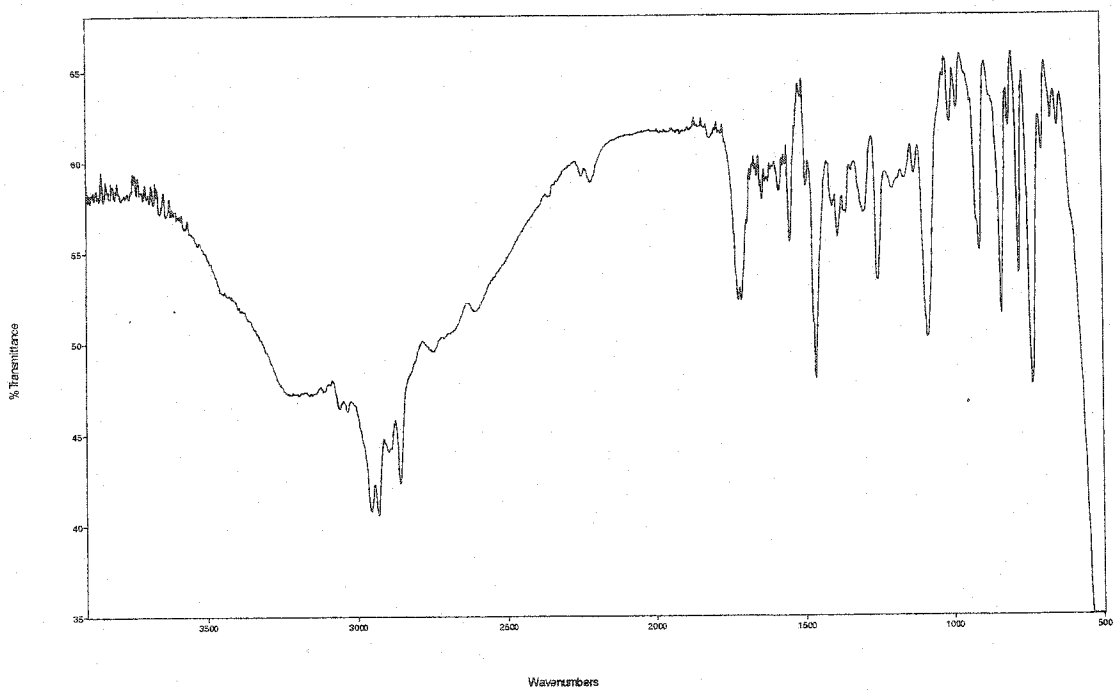


Figure A.2.32 FTIR Spectrum (thin film/NaCl) of Compound **197**.

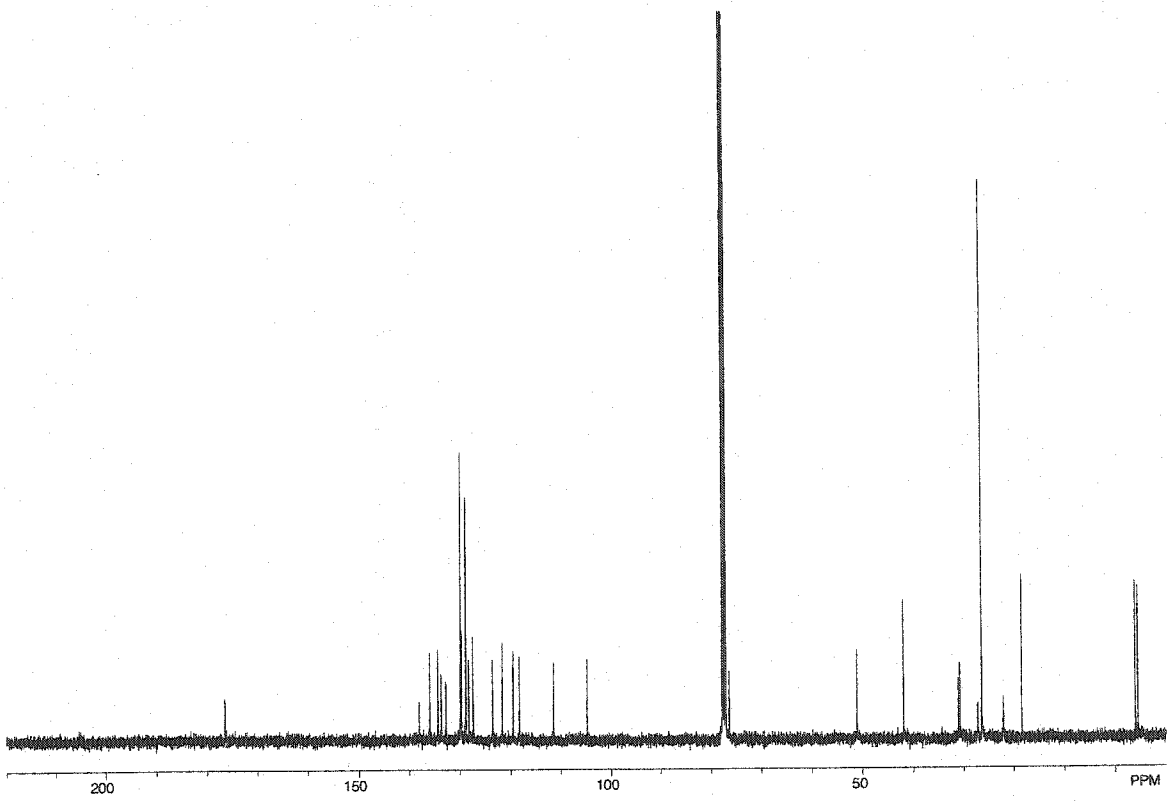


Figure A.2.33 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **197**.

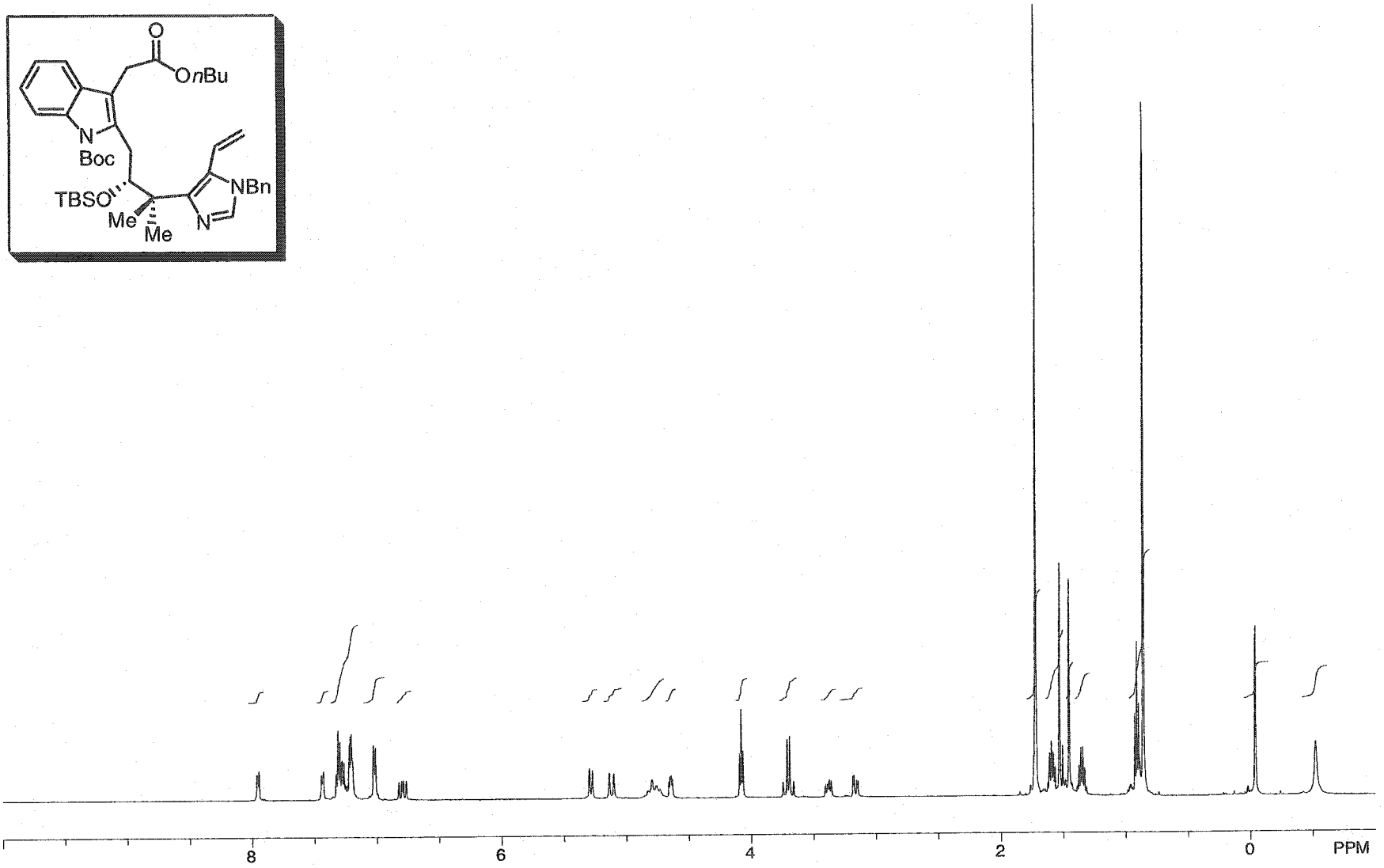


Figure A.2.34 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **207**.

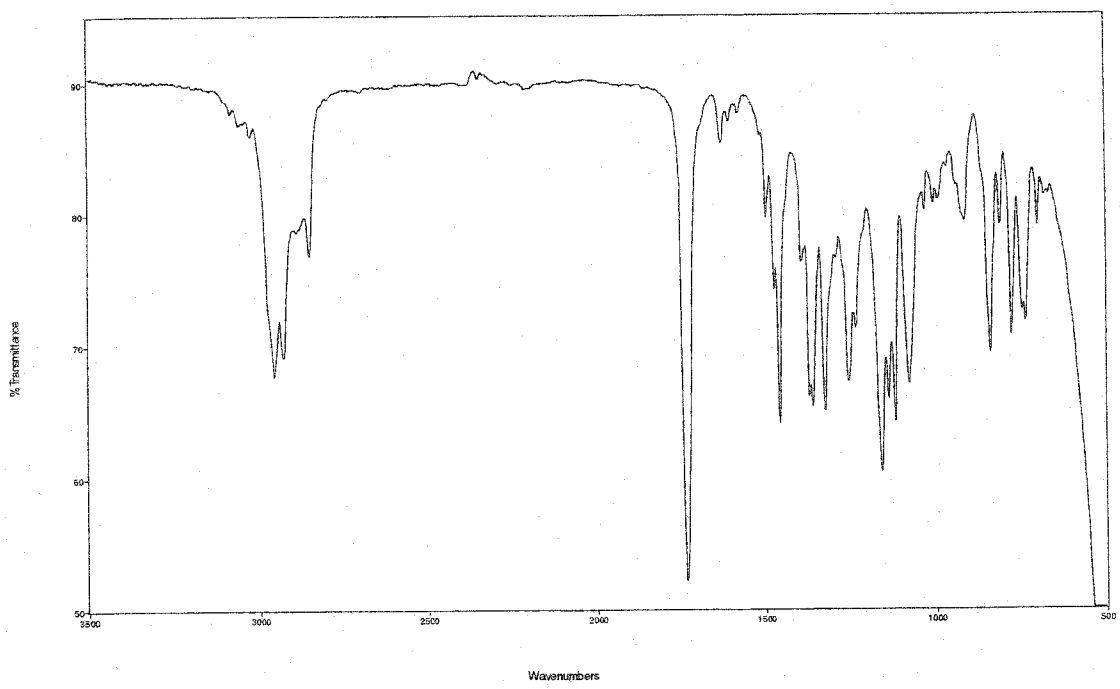


Figure A.2.35 FTIR Spectrum (thin film/NaCl) of Compound **207**.

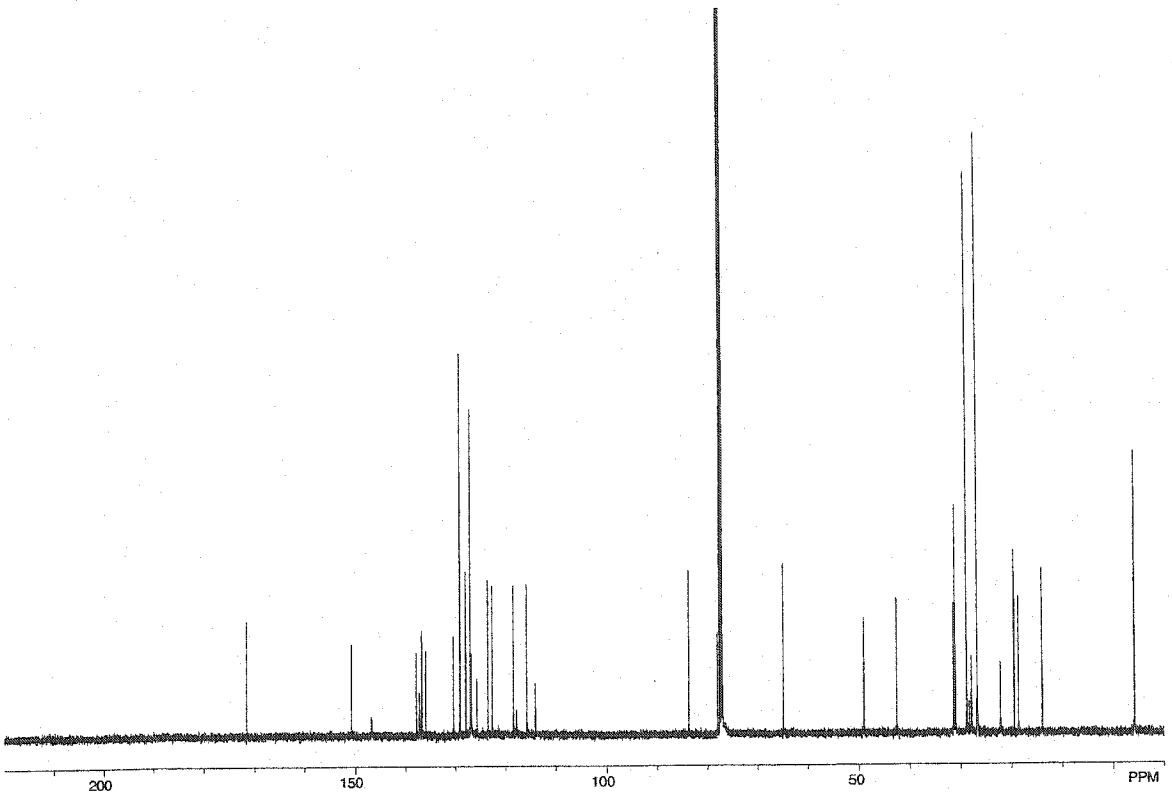


Figure A.2.36 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **207**.

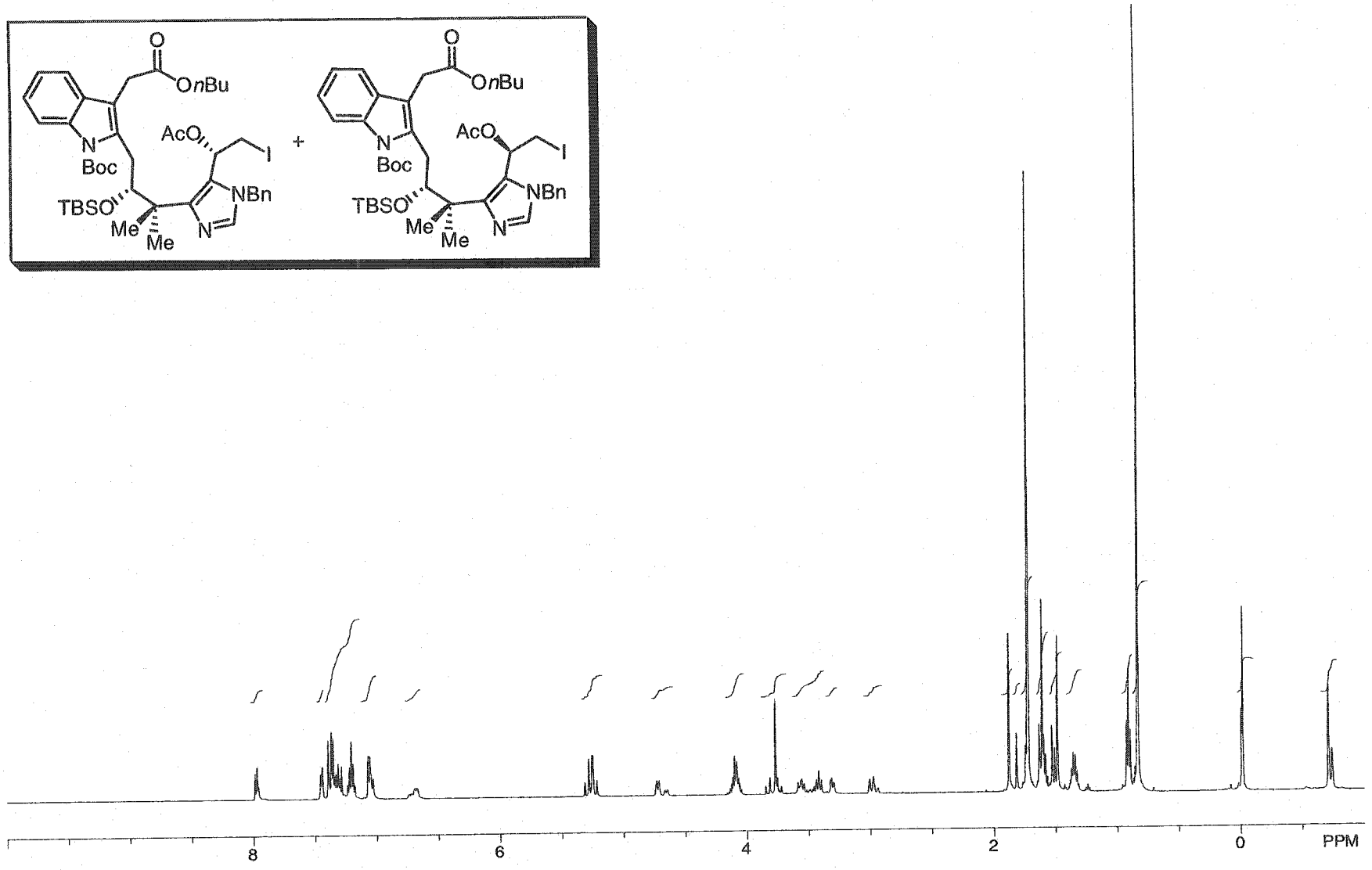


Figure A.2.37 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **208** and **209**.

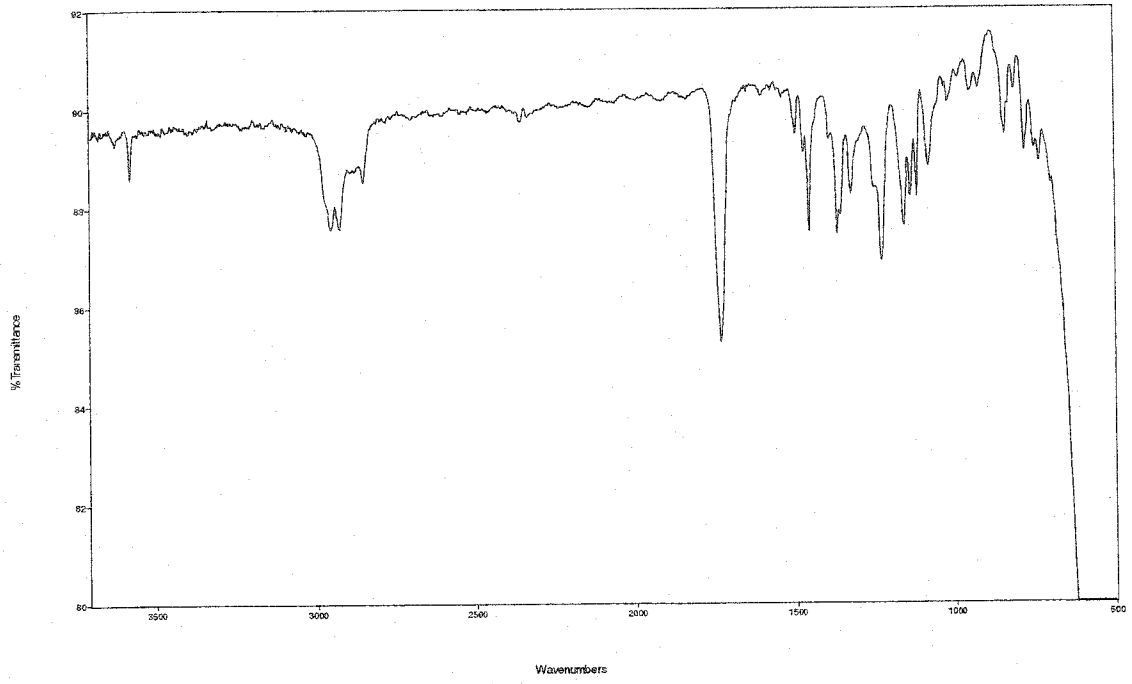


Figure A.2.38 FTIR Spectrum (thin film/NaCl) of Compound **208** and **209**.

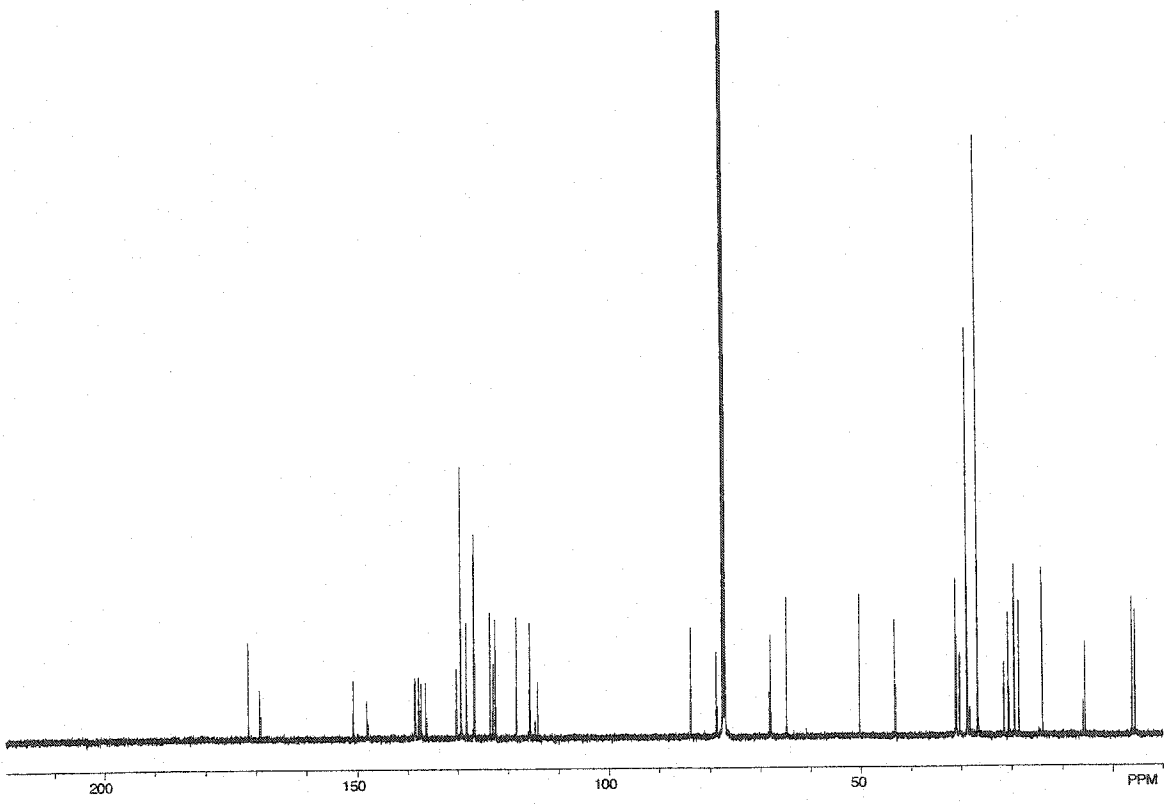


Figure A.2.39 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **208** and **209**.

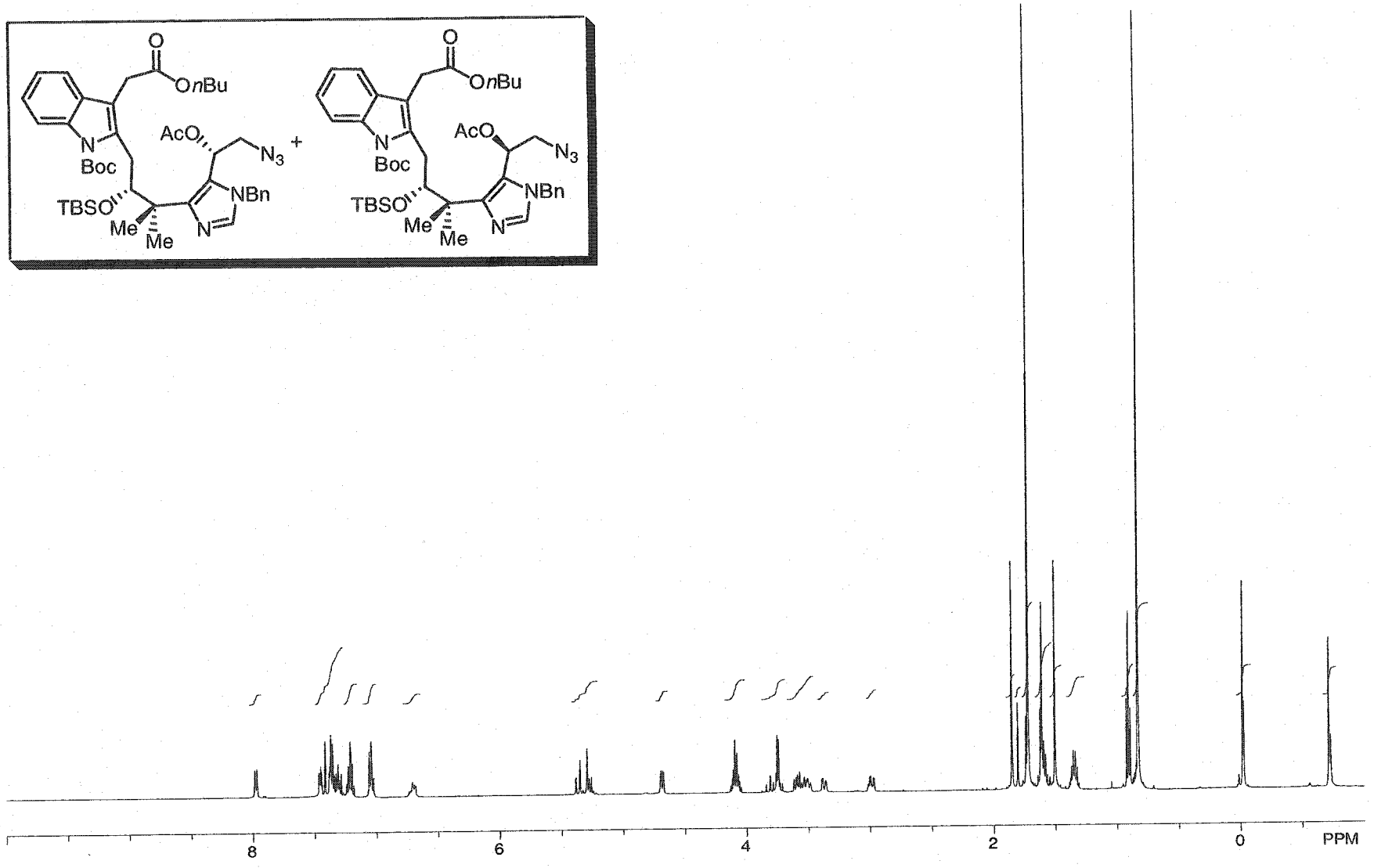


Figure A.2.40 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **210** and **211**.

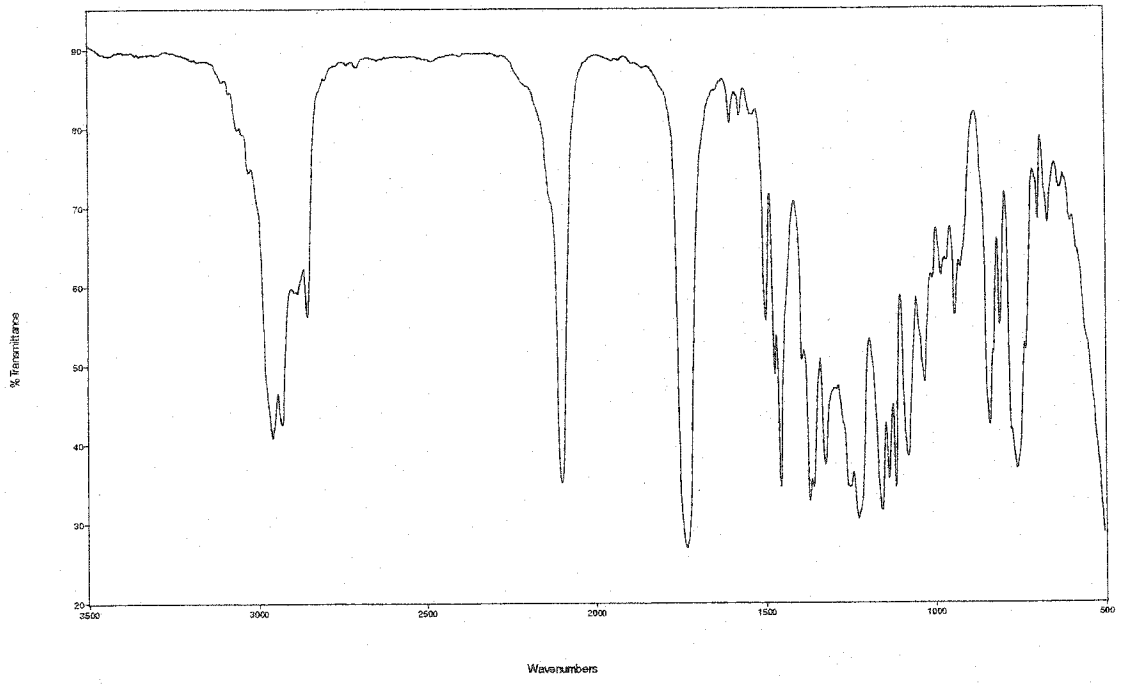


Figure A.2.41 FTIR Spectrum (thin film/NaCl) of Compound **210** and **211**.

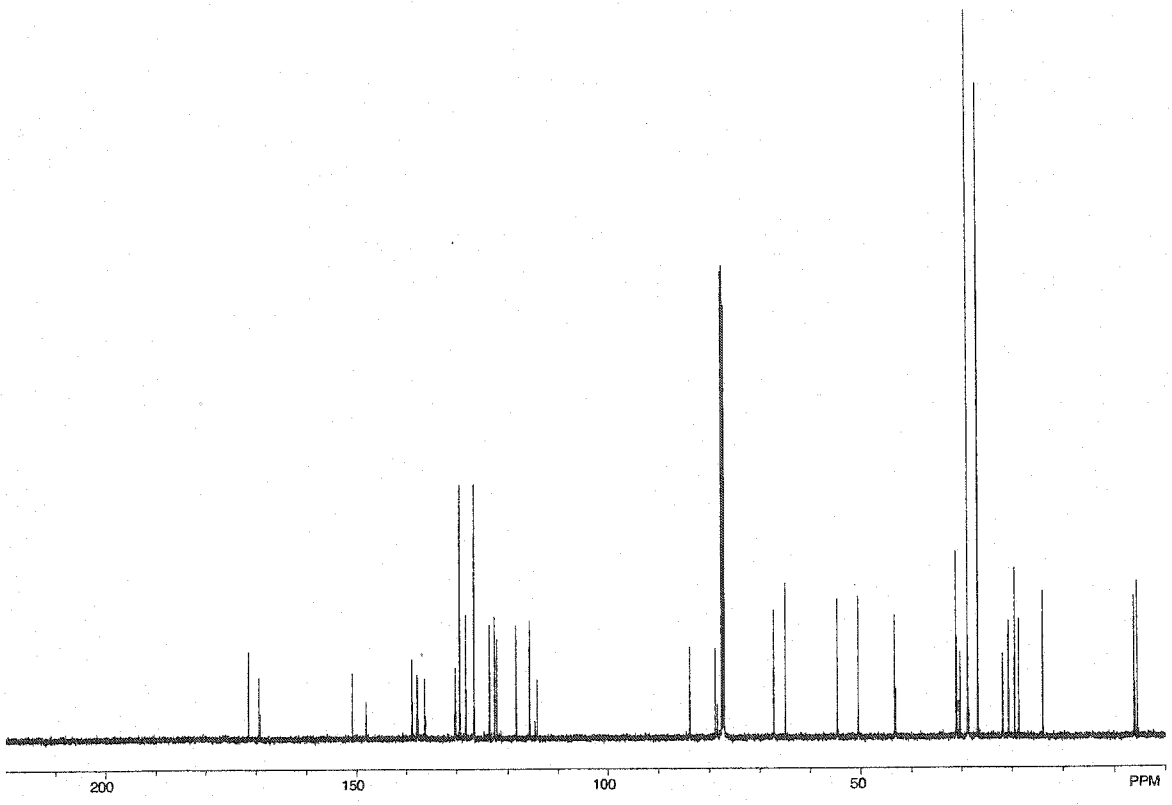


Figure A.2.42 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **210** and **211**.

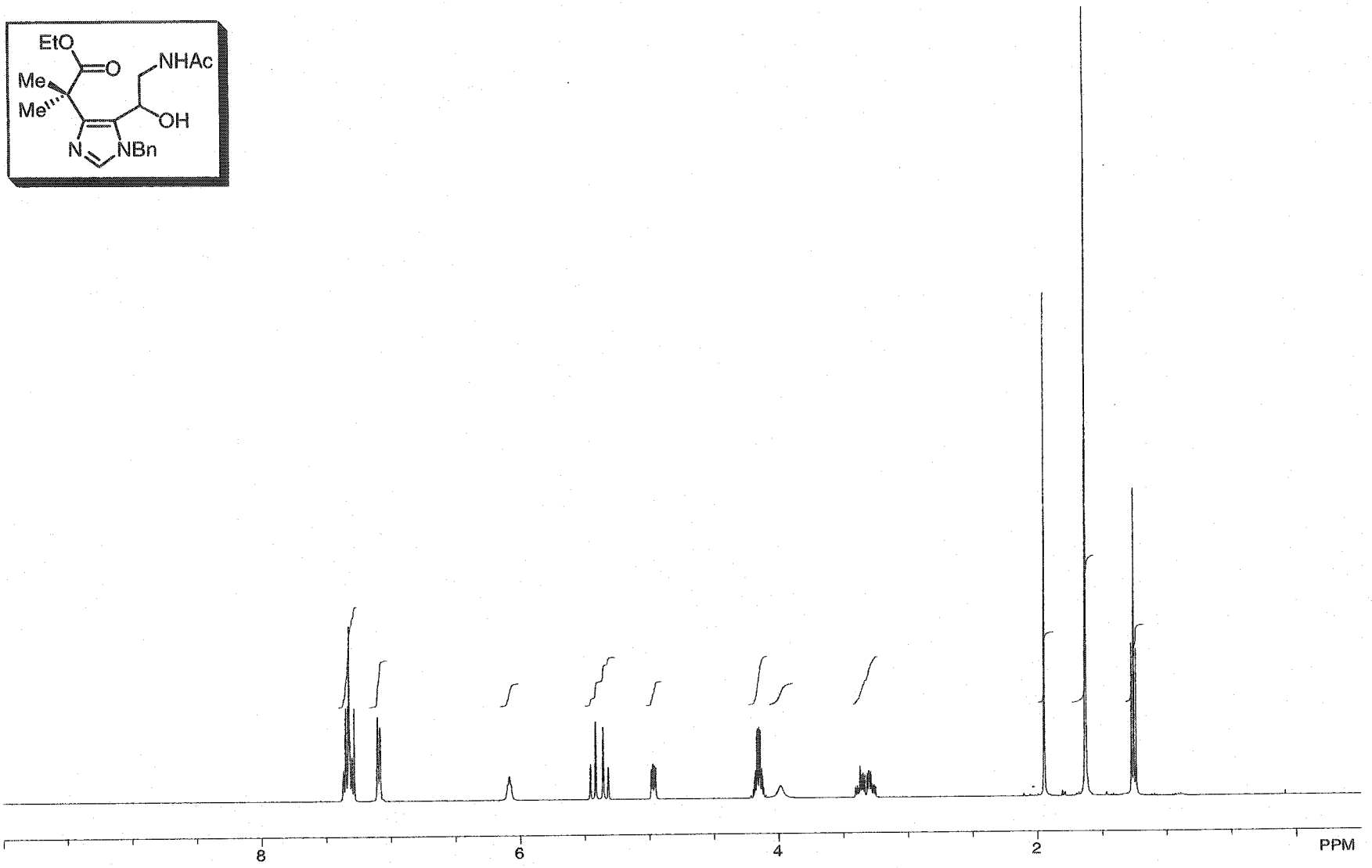


Figure A.2.43 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **216**.

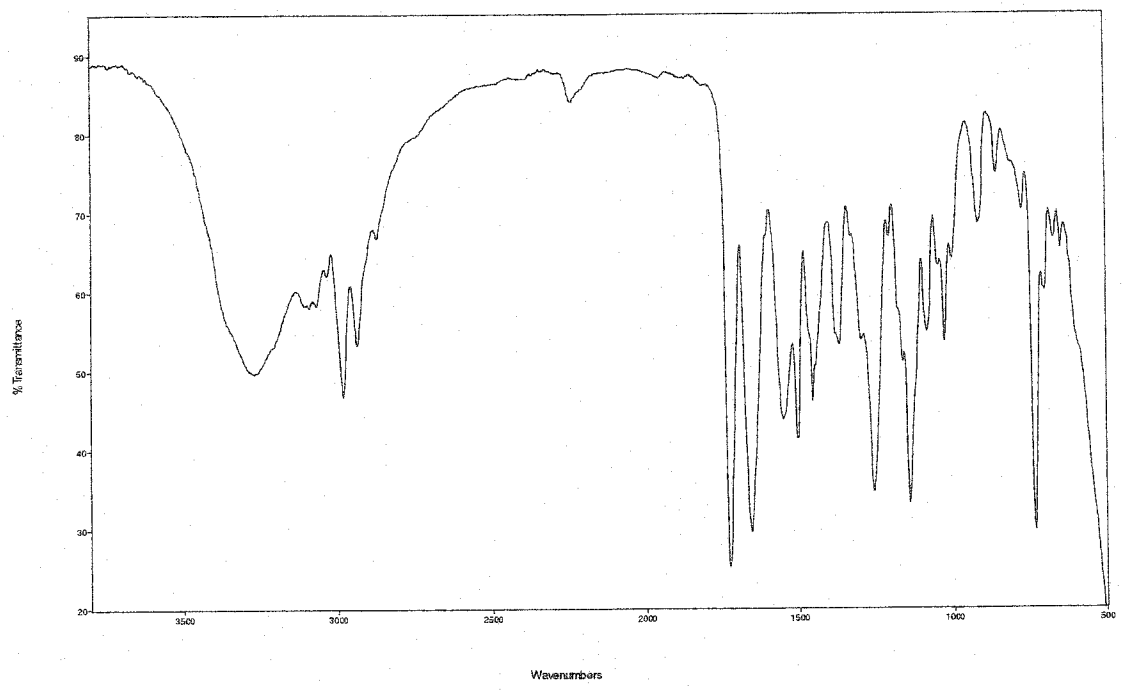


Figure A.2.44 FTIR Spectrum (thin film/NaCl) of Compound **216**.

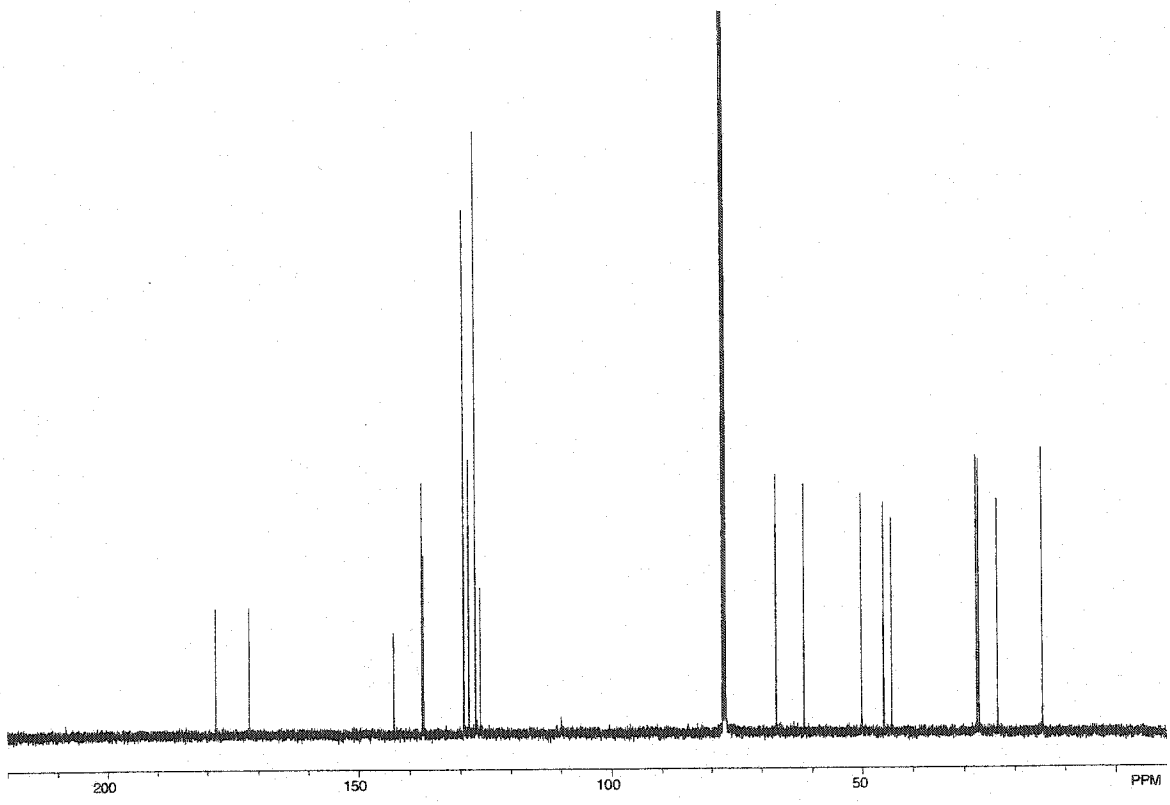


Figure A.2.45 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **216**.

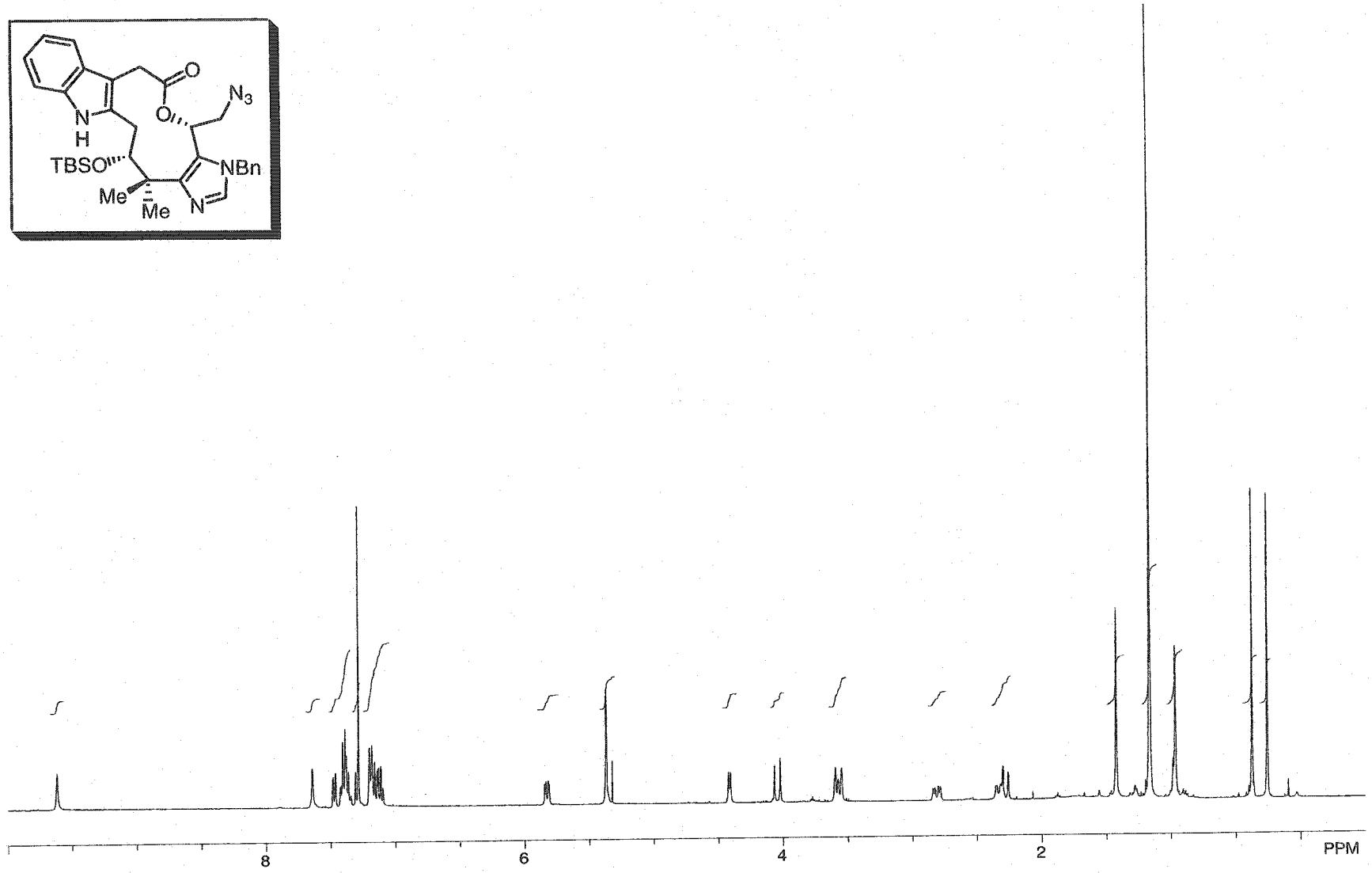


Figure A.2.46 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **217**.

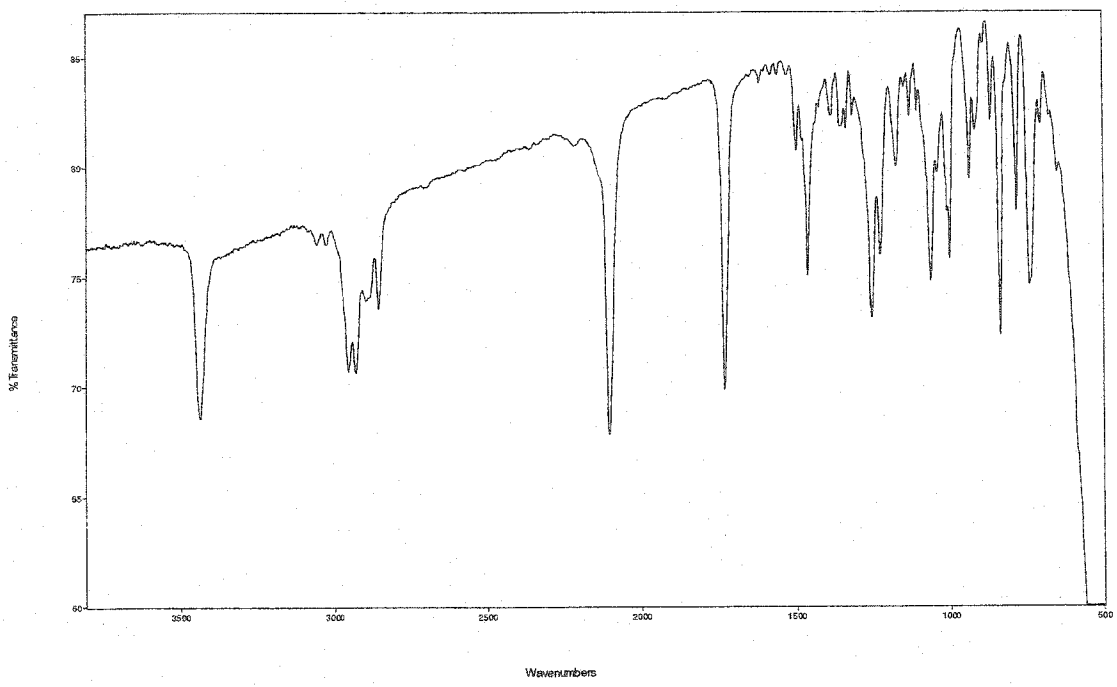


Figure A.2.47 FTIR Spectrum (thin film/NaCl) of Compound **217**.

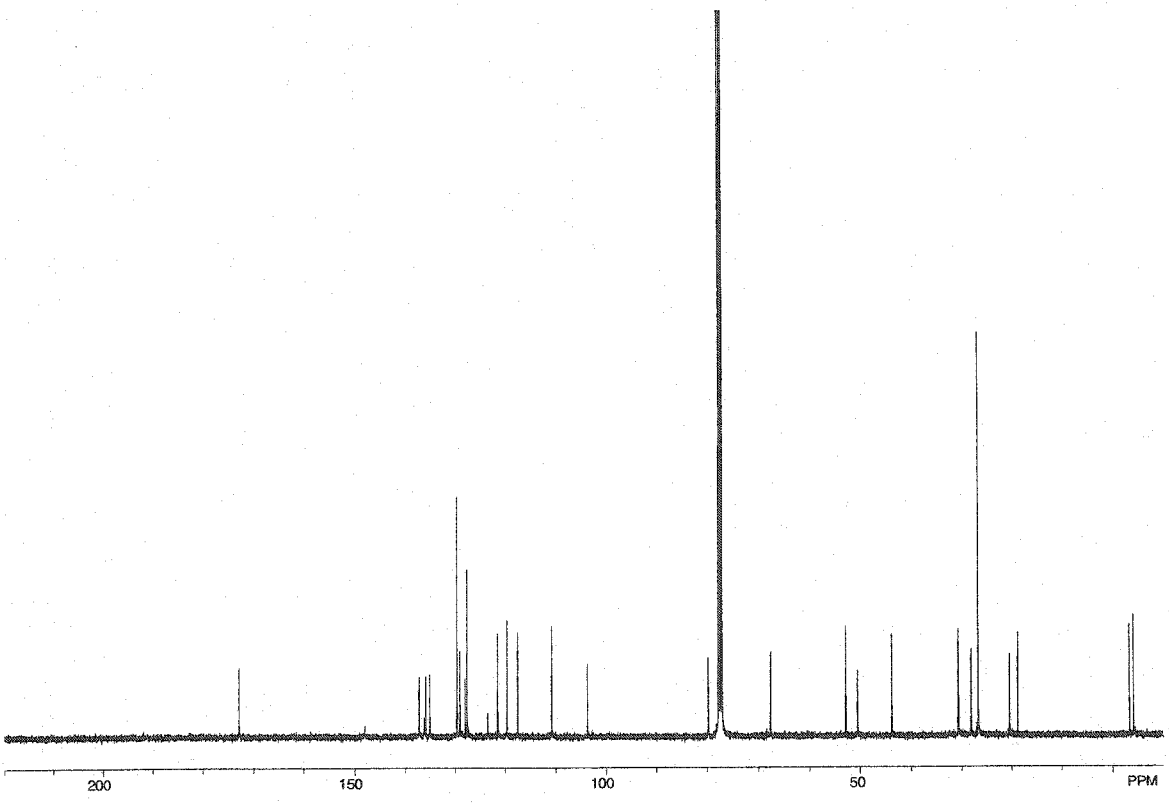


Figure A.2.48 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **217**.

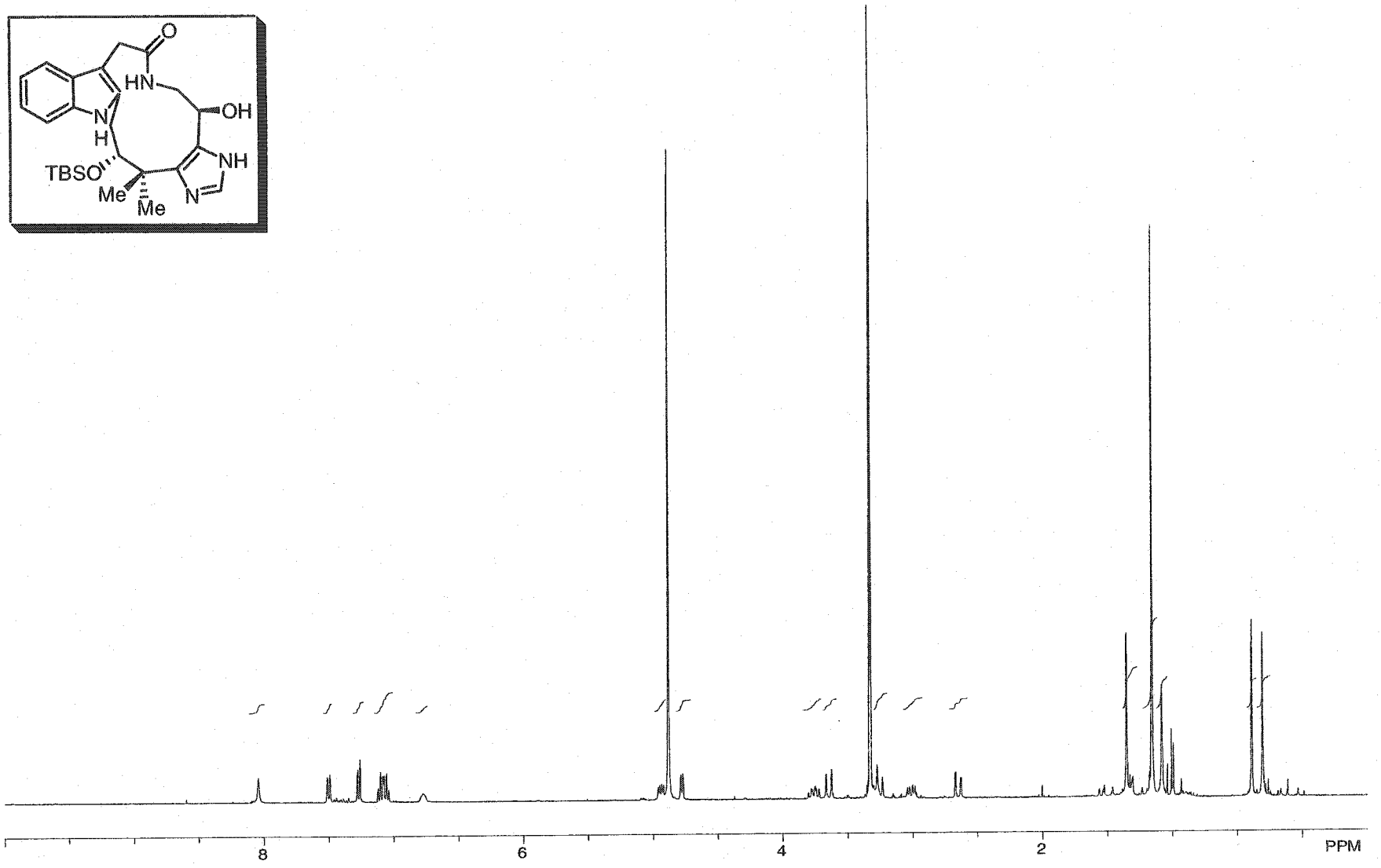


Figure A.2.49 ^{1}H NMR (400 MHz, CD_3OD) of Compound **218**.

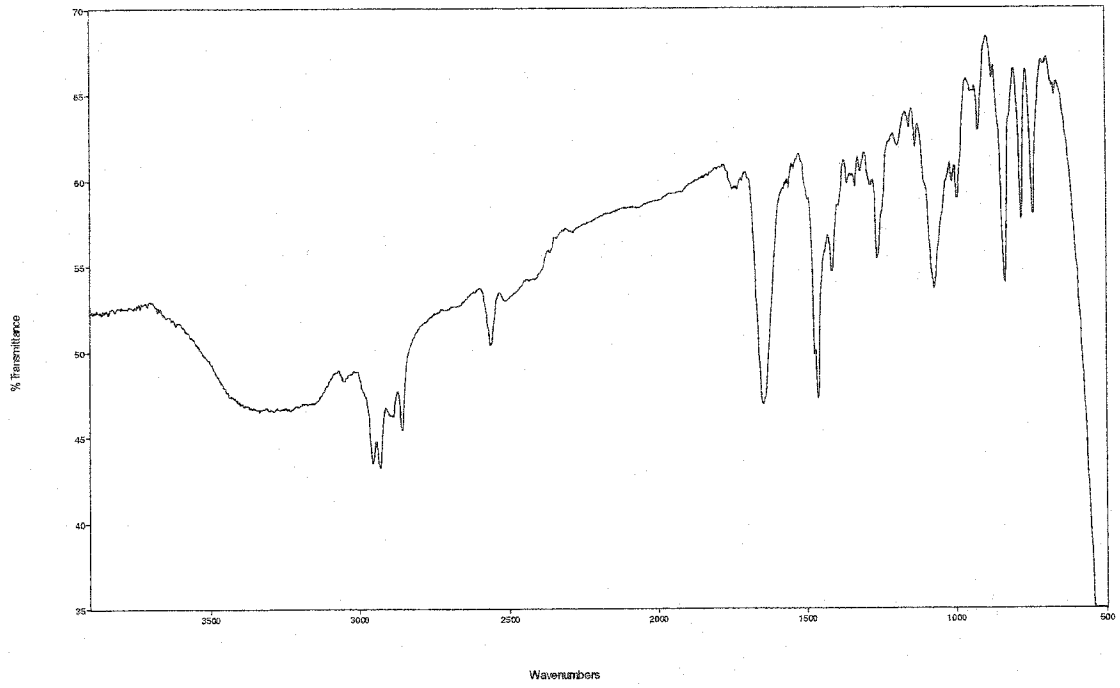


Figure A.2.50 FTIR Spectrum (thin film/NaCl) of Compound **218**.

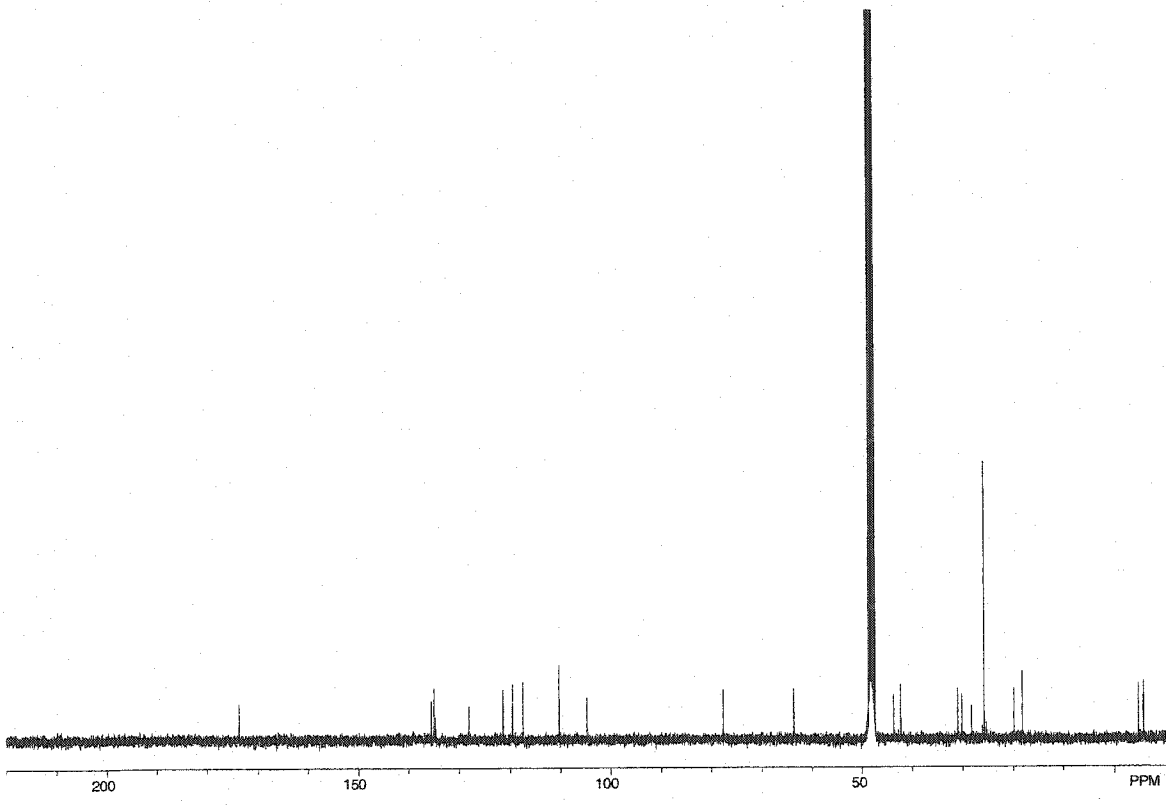


Figure A.2.51 ^{13}C NMR (100 MHz, CD_3OD) of Compound **218**.

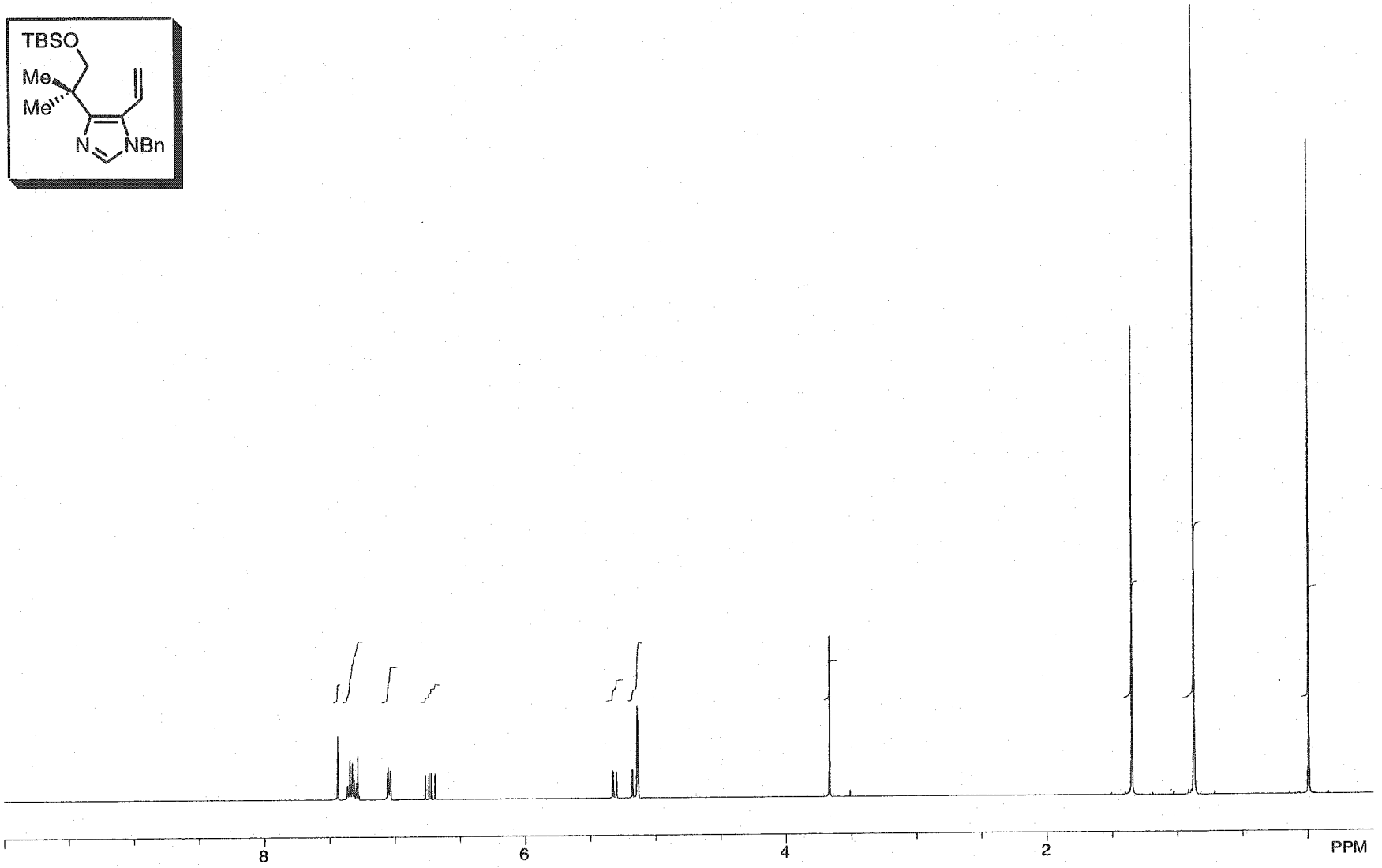


Figure A.2.52 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **219**.

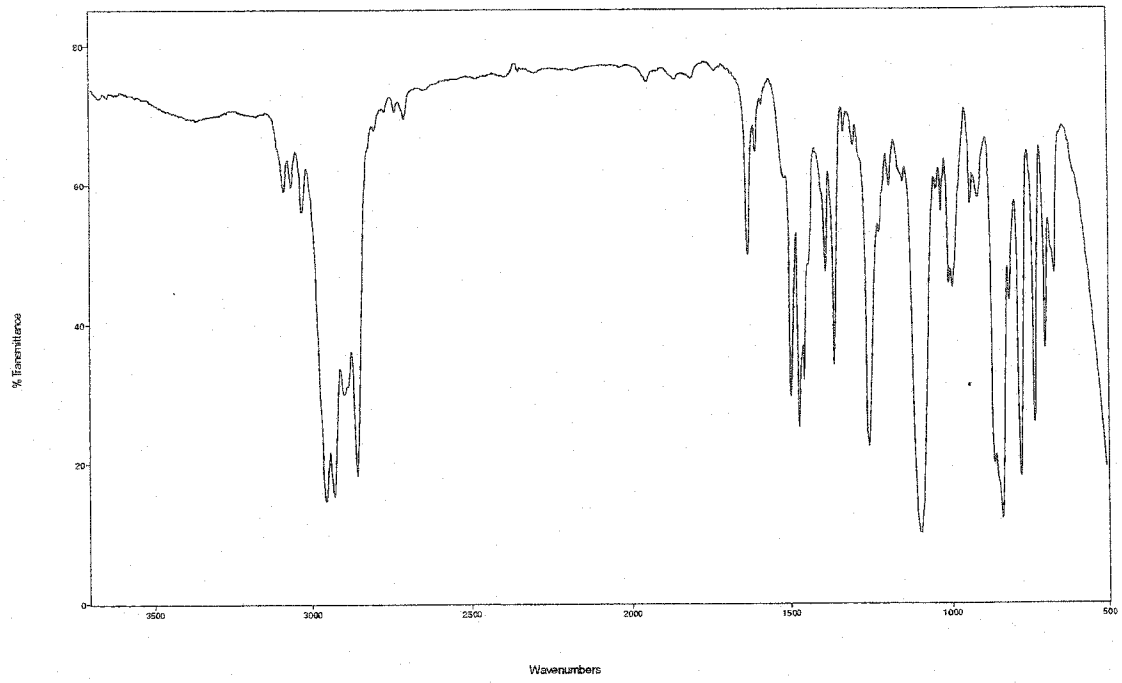


Figure A.2.53 FTIR Spectrum (thin film/NaCl) of Compound **219**.

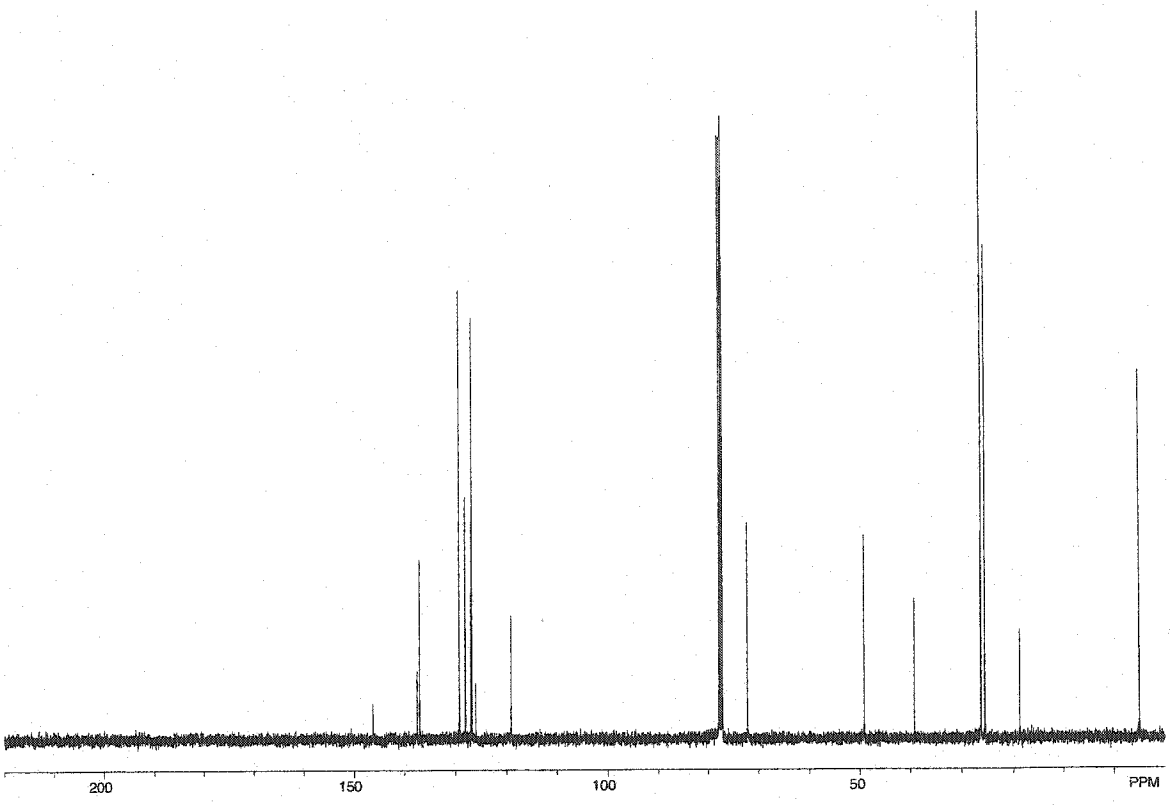


Figure A.2.54 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **219**.

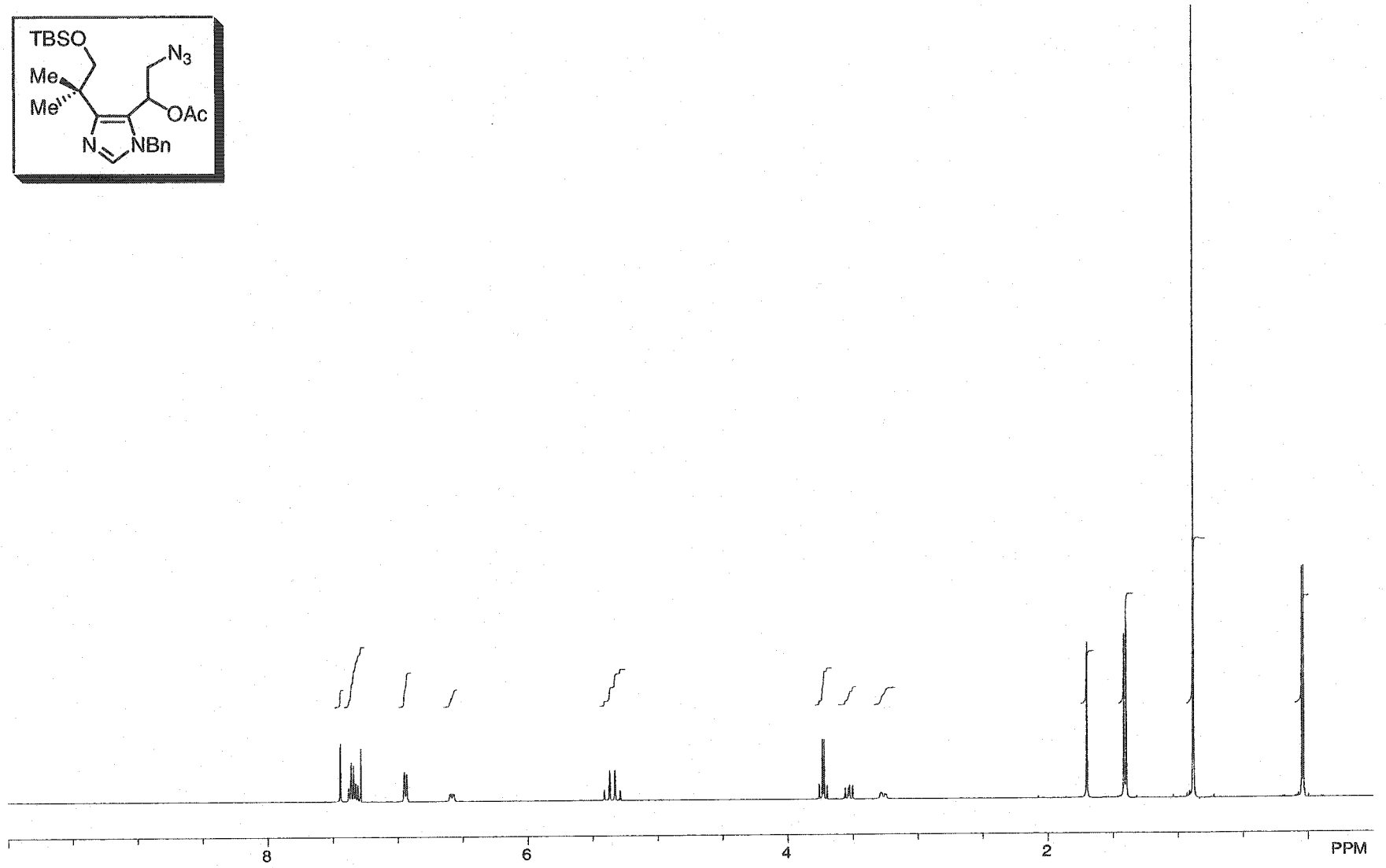


Figure A.2.55 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **221**.

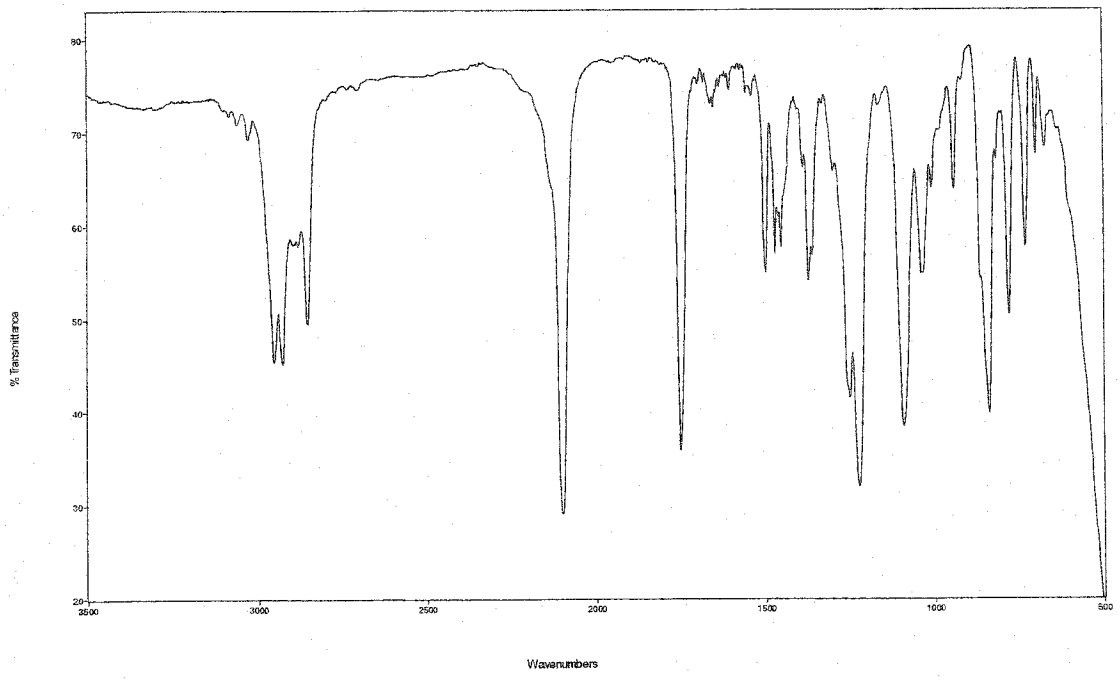


Figure A.2.56 FTIR Spectrum (thin film/NaCl) of Compound **221**.

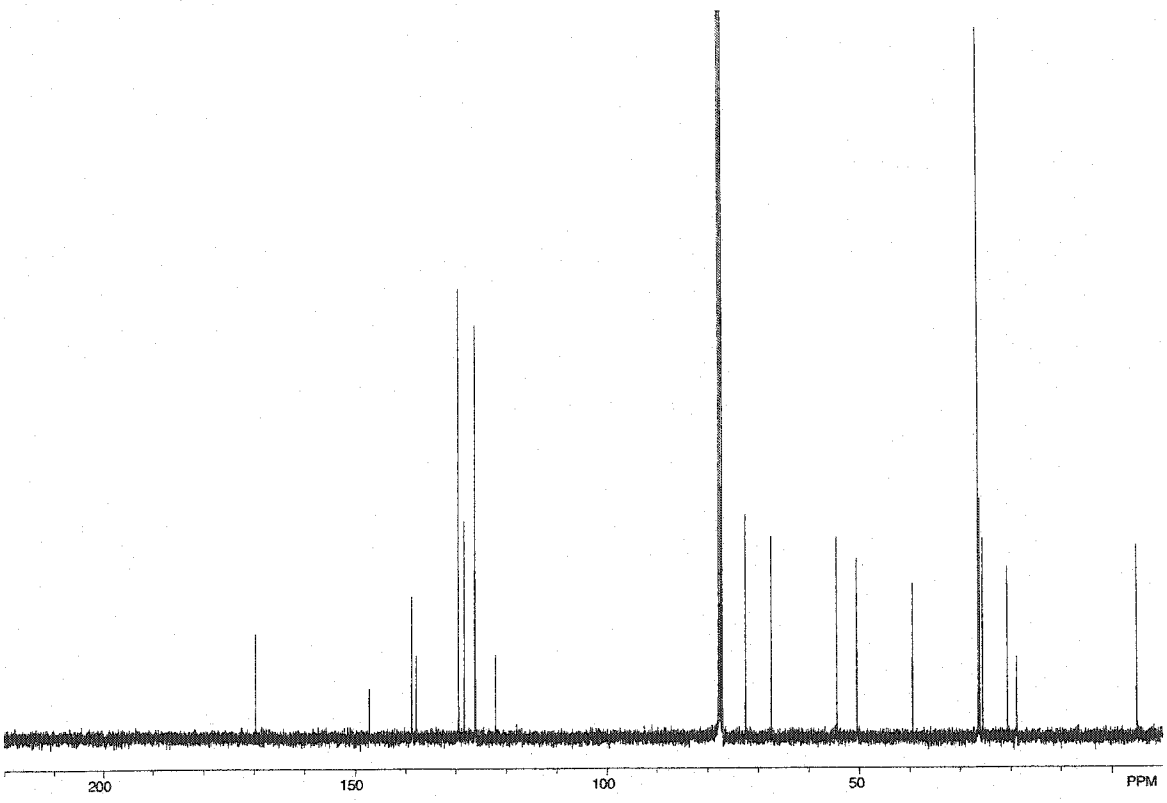


Figure A.2.57 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **221**.

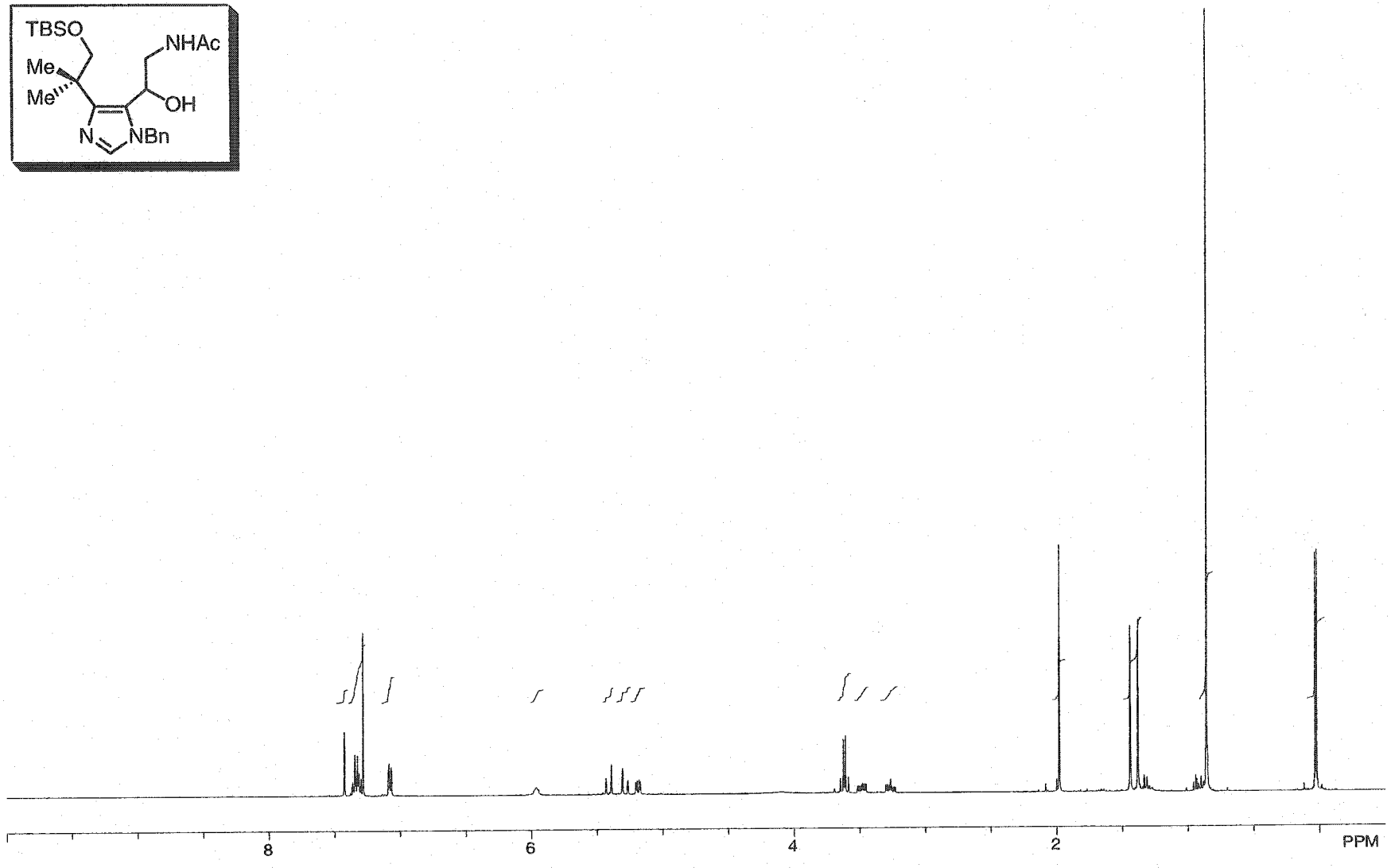


Figure A.2.58 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **222**.

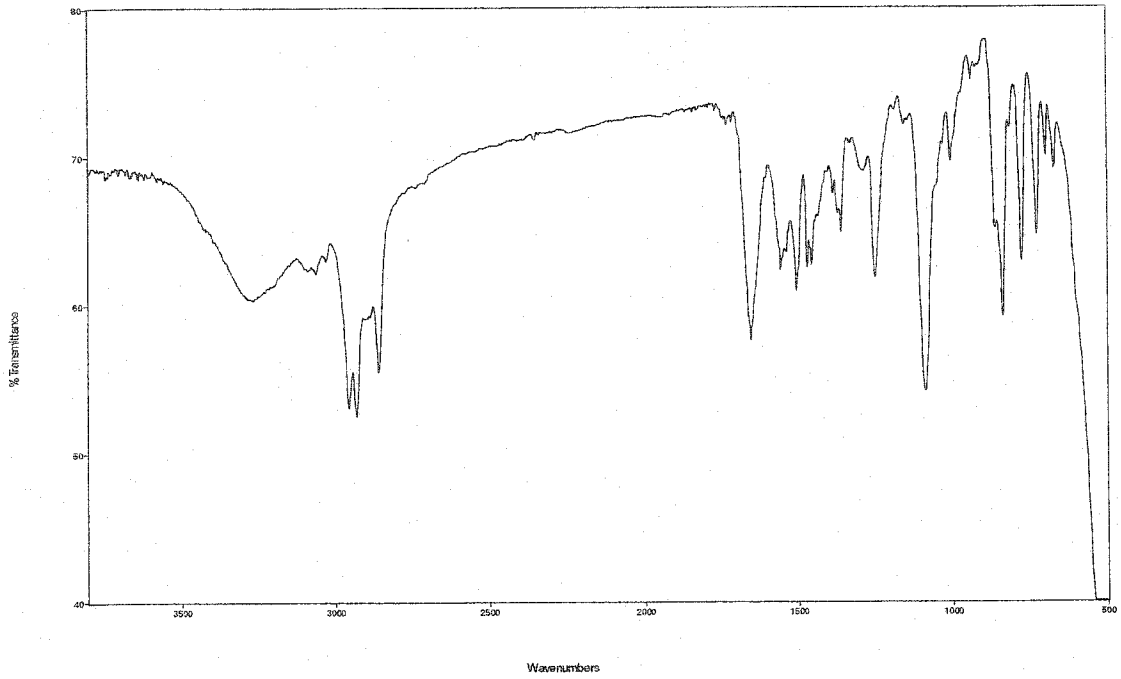


Figure A.2.59 FTIR Spectrum (thin film/NaCl) of Compound **222**.

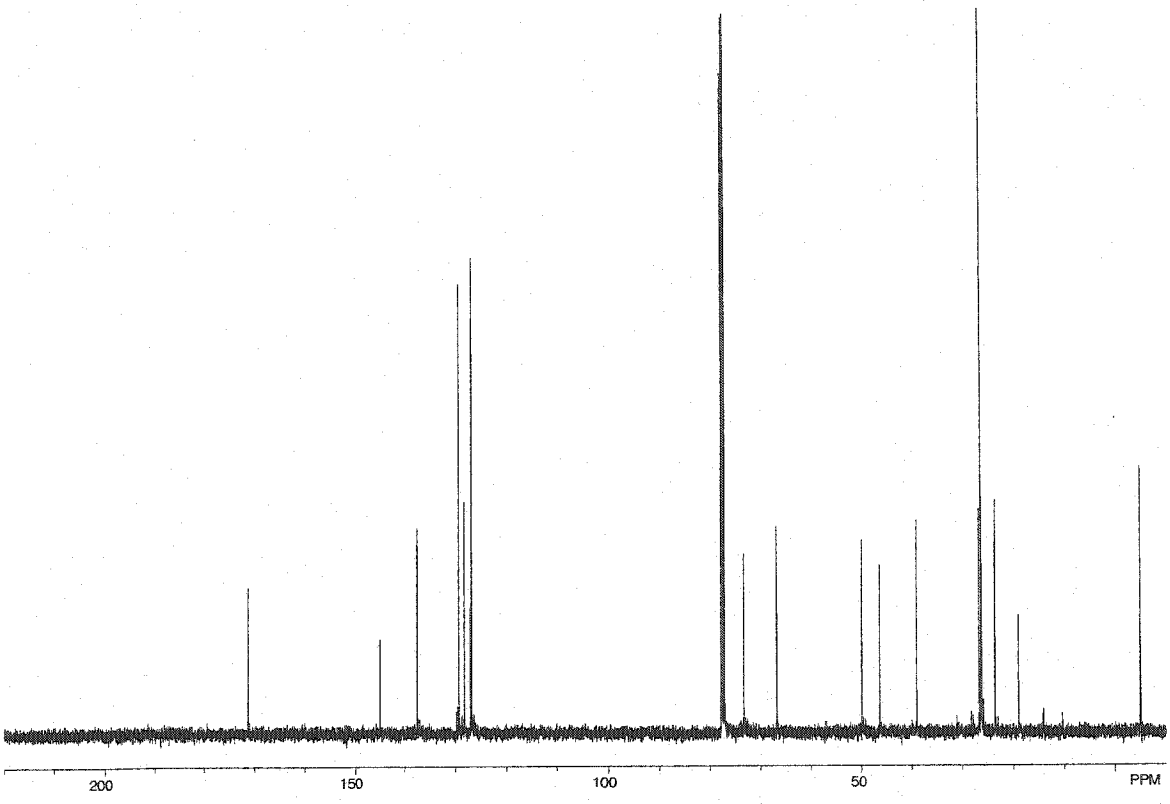


Figure A.2.60 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **222**.

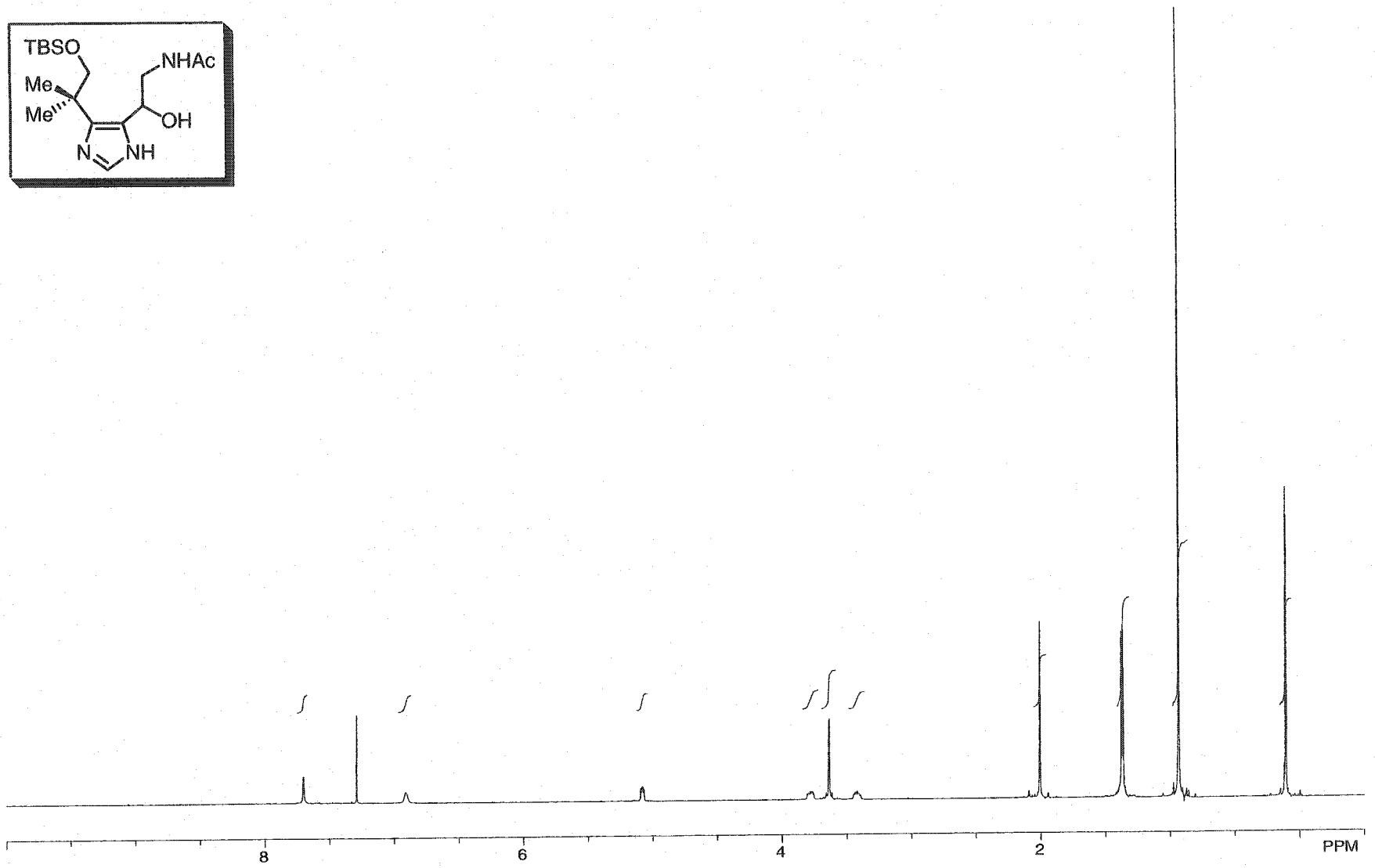


Figure A.2.61 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **223**.

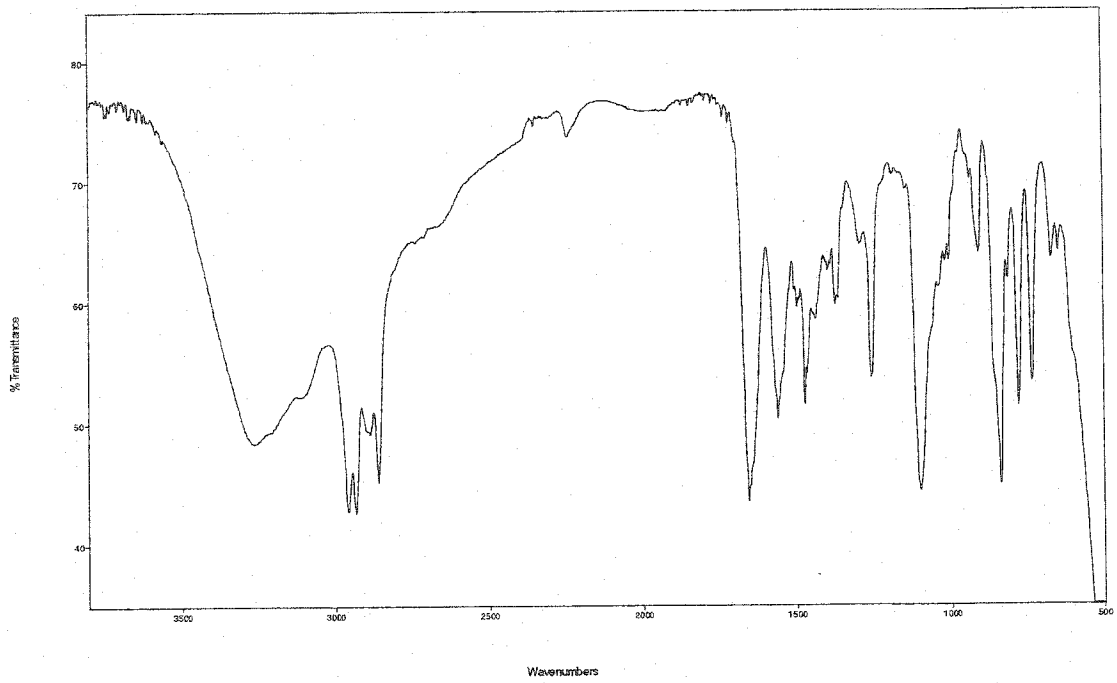


Figure A.2.62 FTIR Spectrum (thin film/NaCl) of Compound **223**.

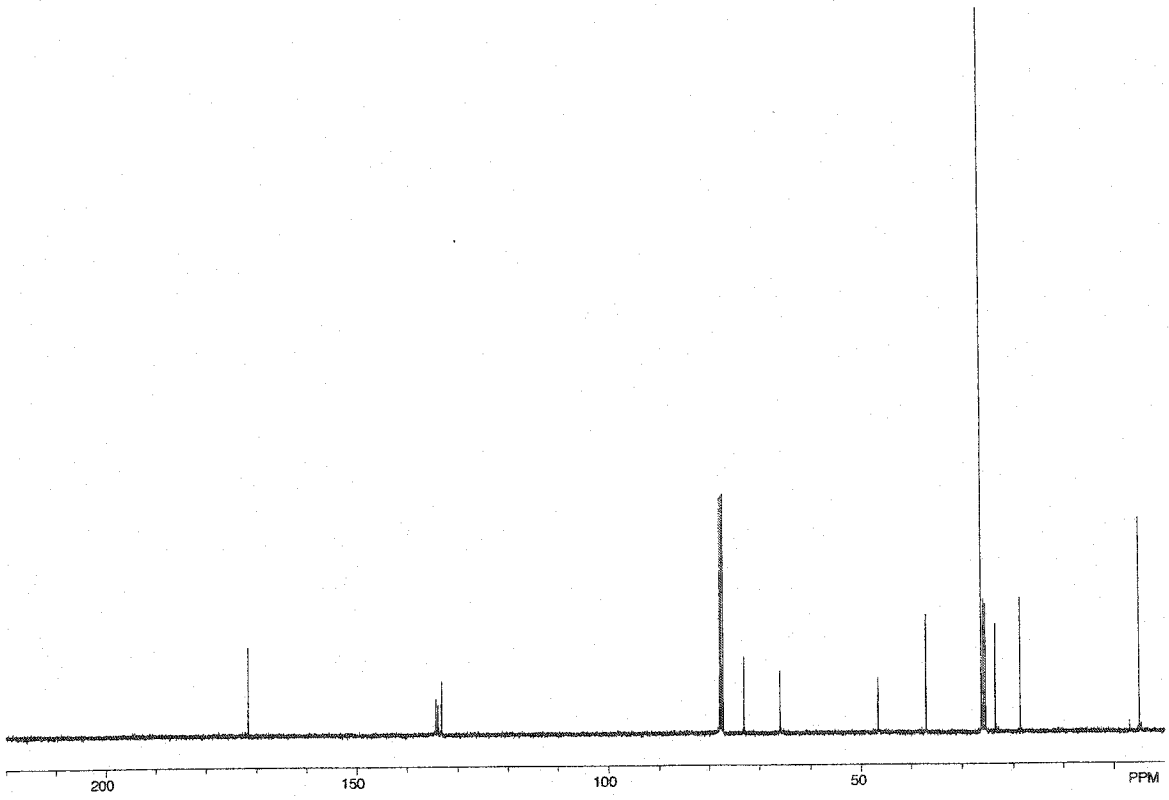


Figure A.2.63 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **223**.

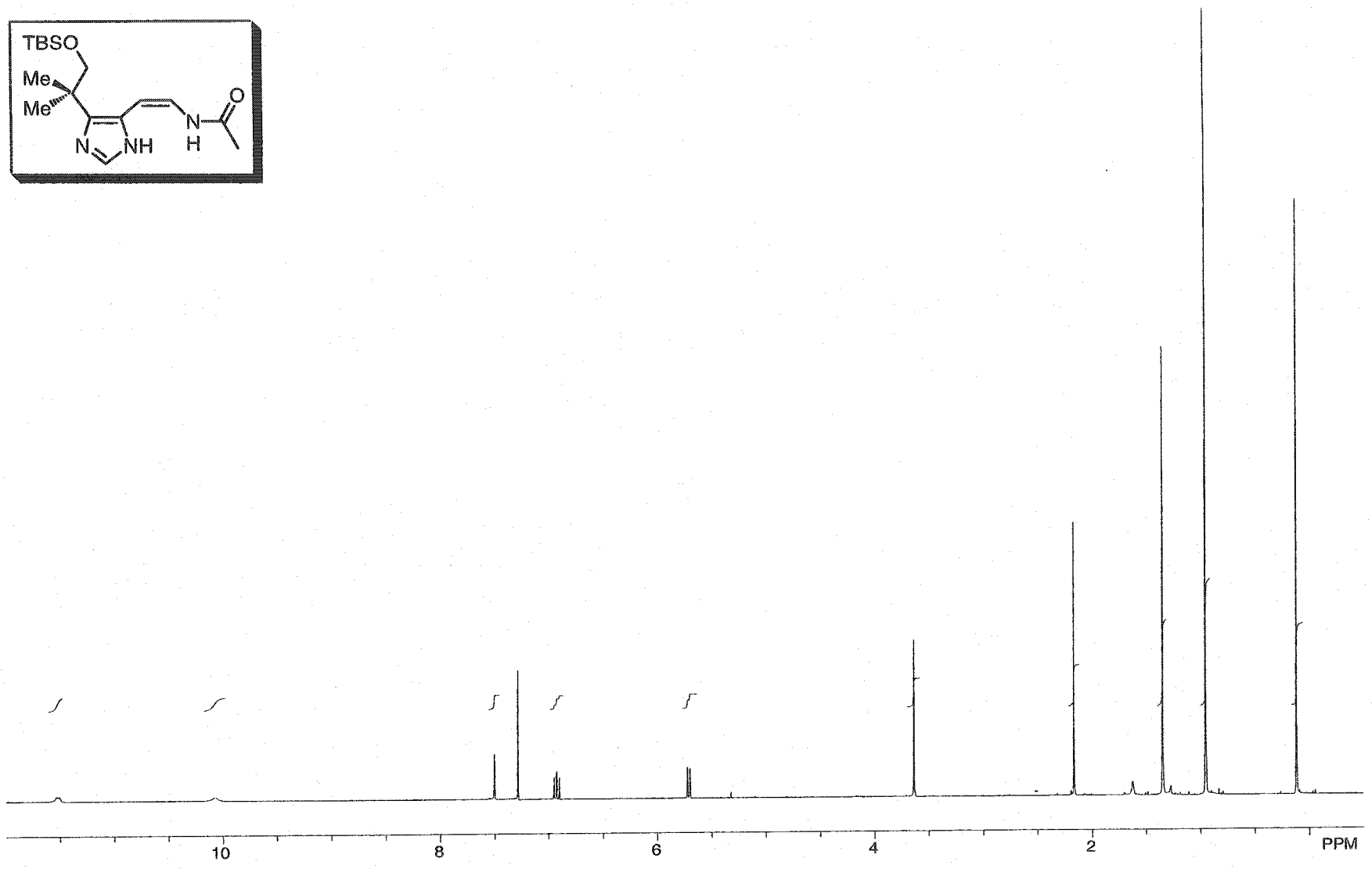


Figure A.2.64 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **224**.

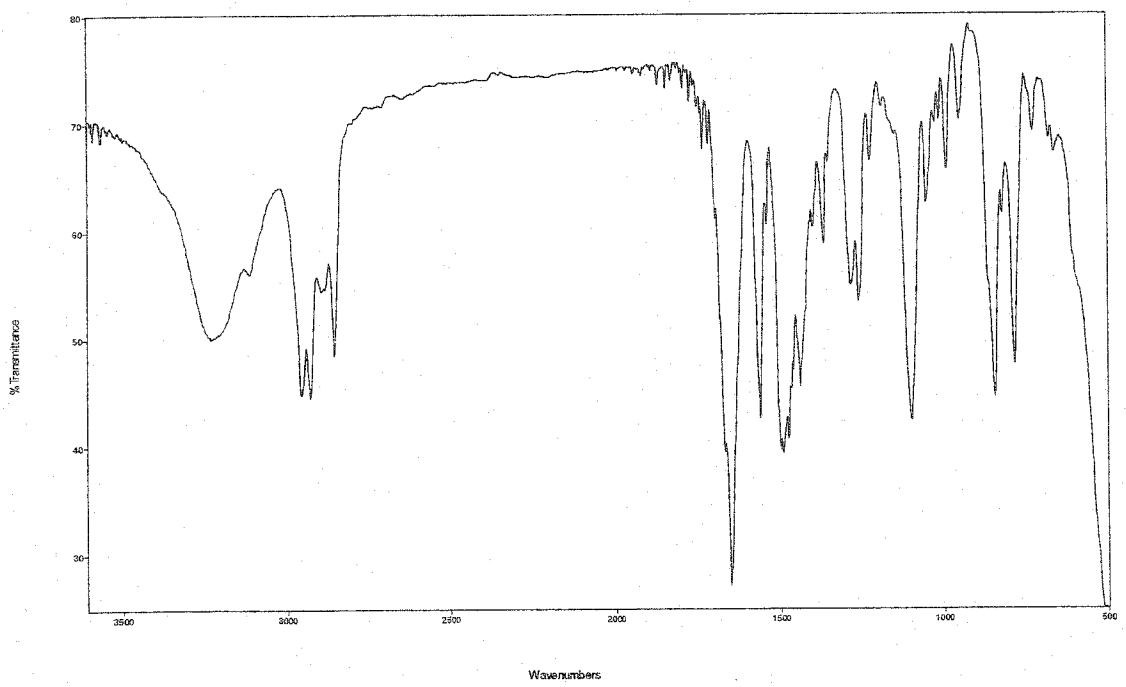


Figure A.2.65 FTIR Spectrum (thin film/NaCl) of Compound **224**.

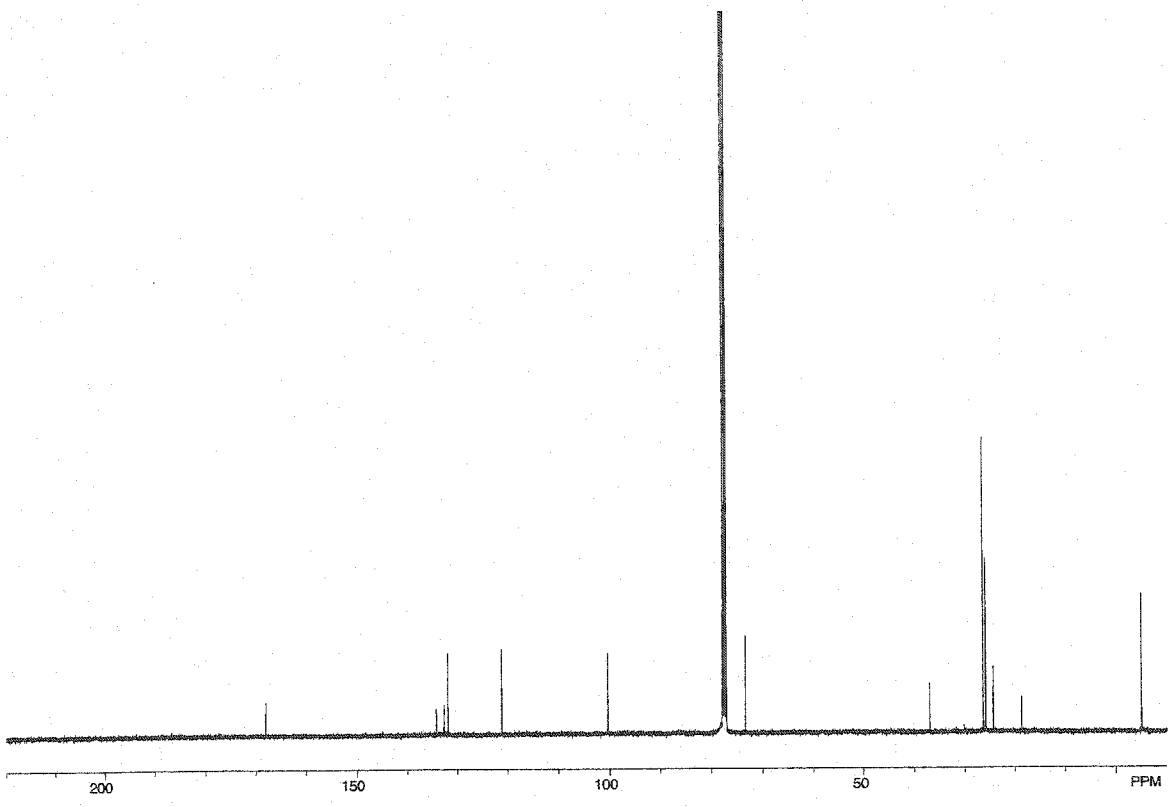
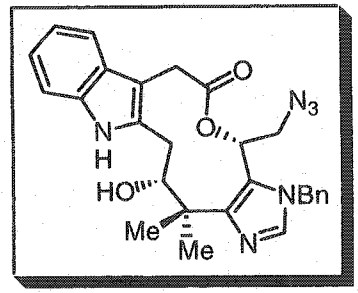


Figure A.2.66 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **224**.



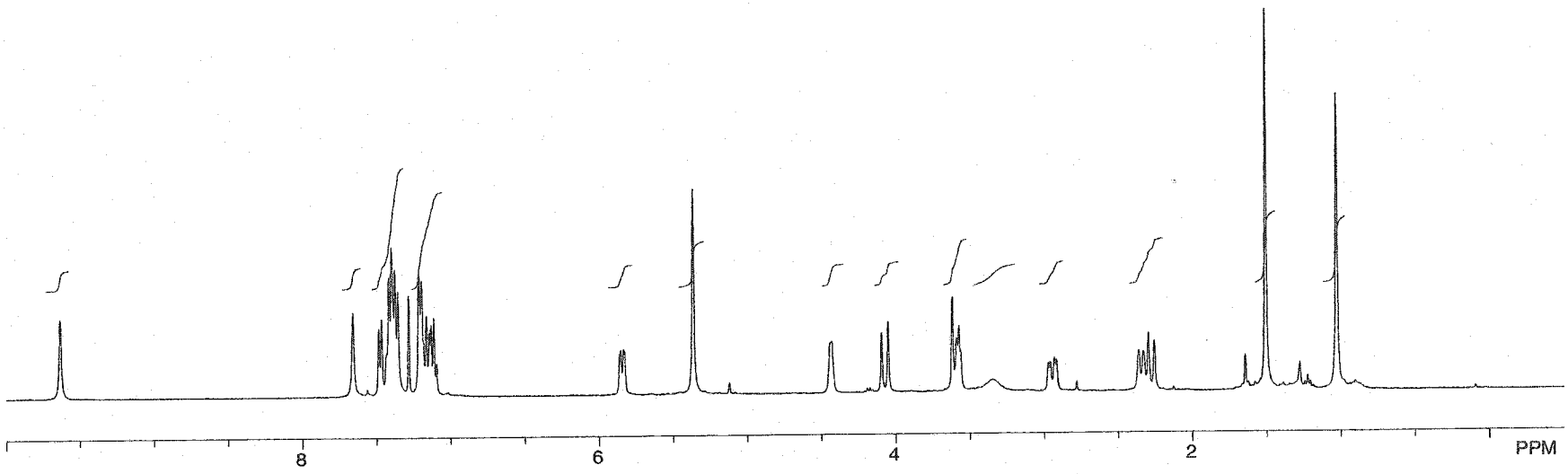


Figure A.2.67 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **226**.

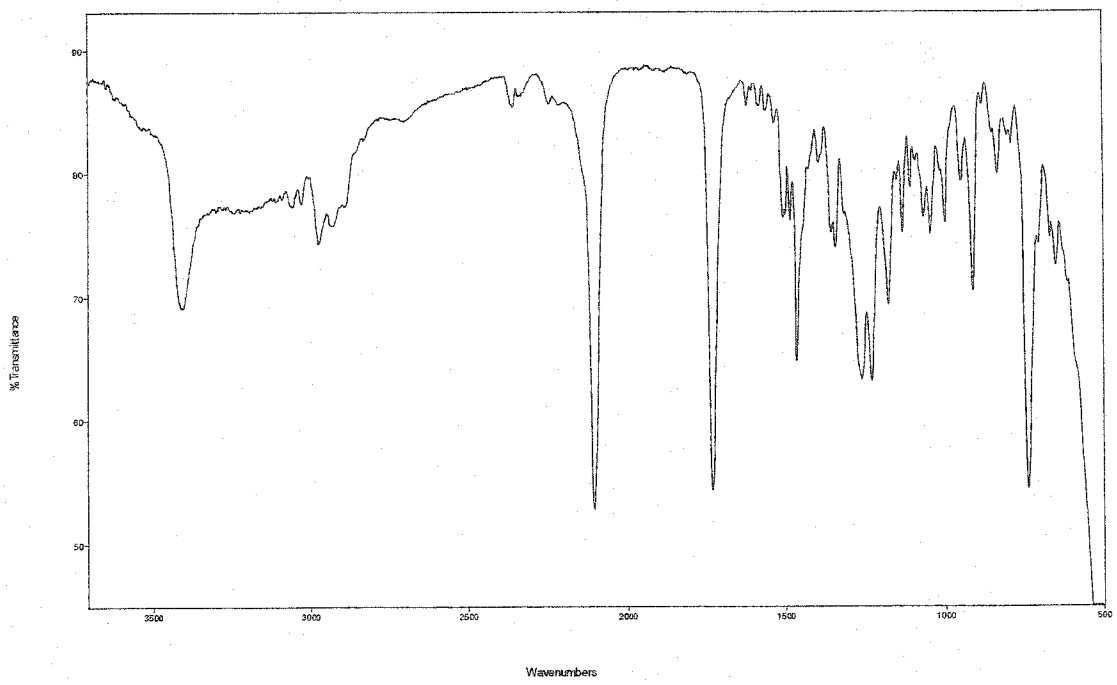


Figure A.2.68 FTIR Spectrum (thin film/NaCl) of Compound **226**.

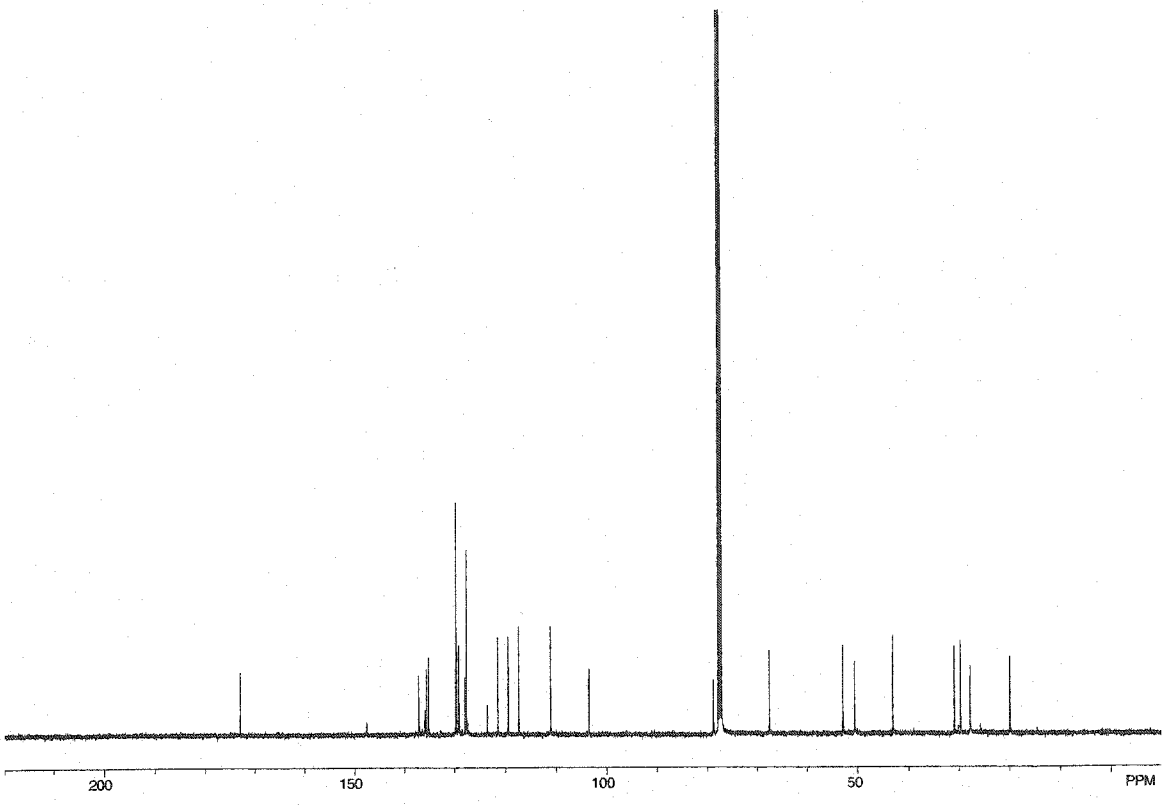


Figure A.2.69 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **226**.

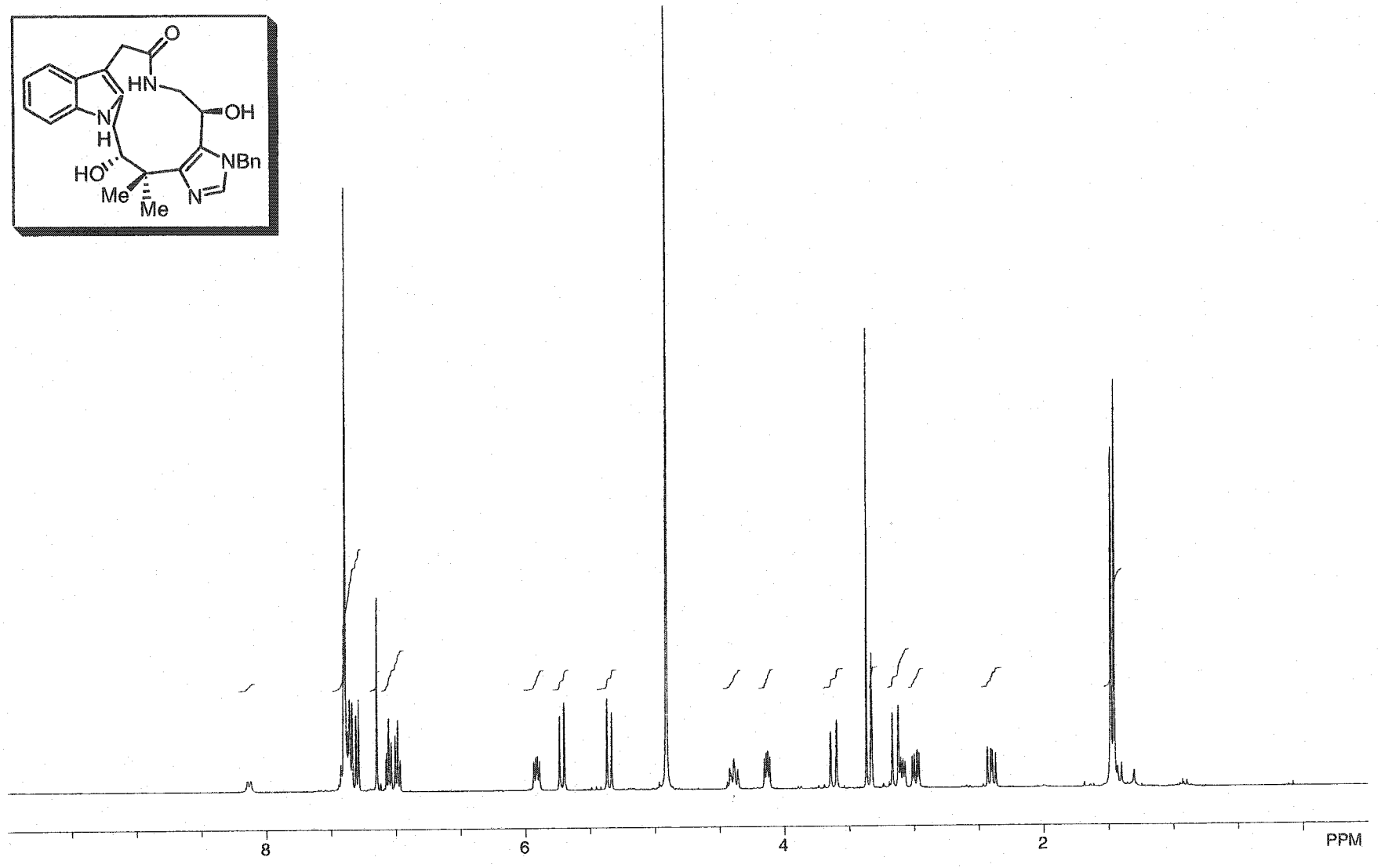


Figure A.2.70 ^{1}H NMR (400 MHz, CD_3OD) of Compound **228**.

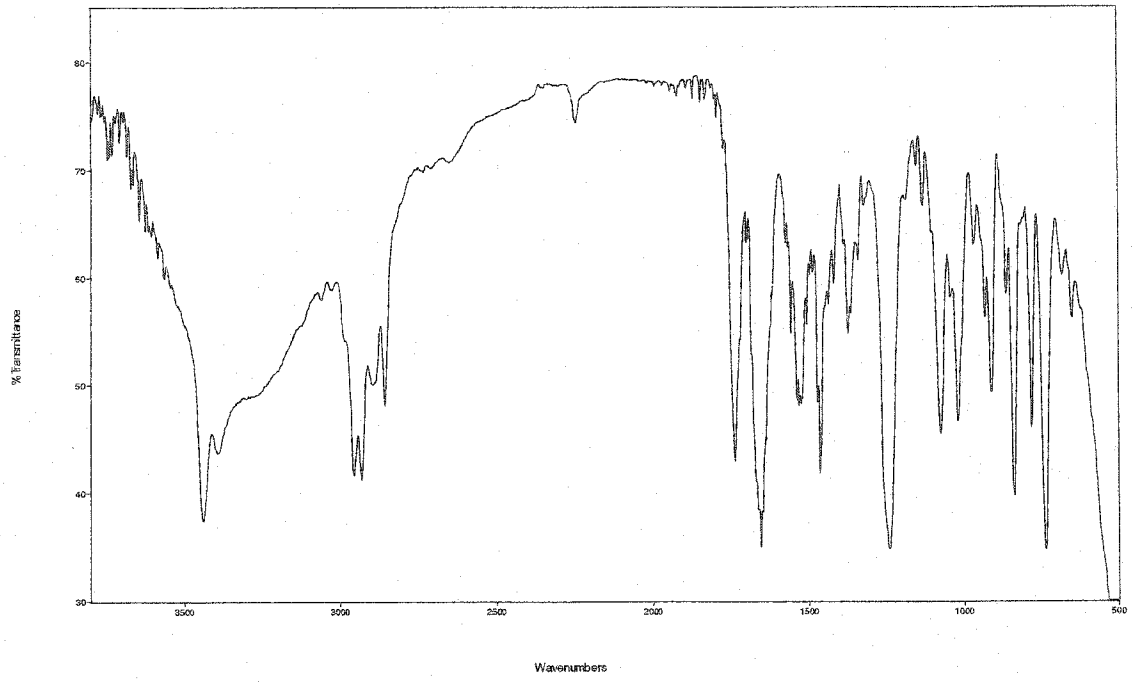


Figure A.2.71 FTIR Spectrum (thin film/NaCl) of Compound **228**.

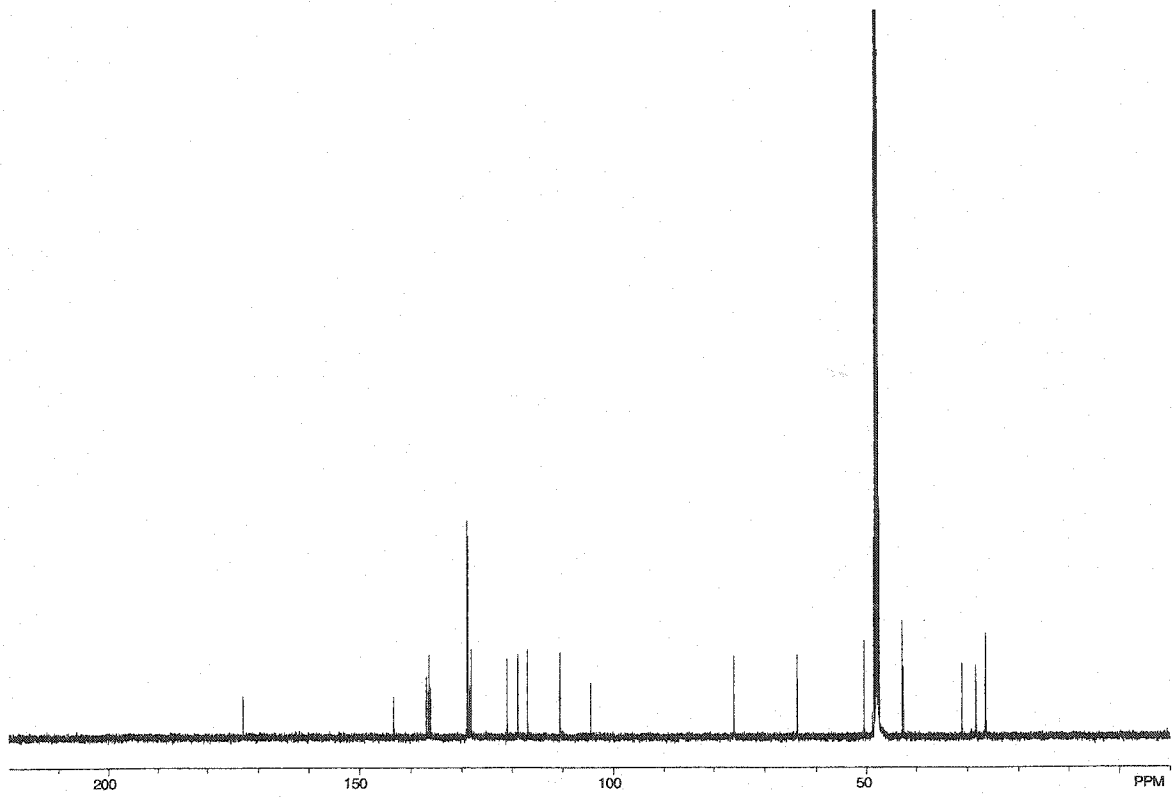


Figure A.2.72 ^{13}C NMR (125 MHz, CD_3OD) of Compound **228**.

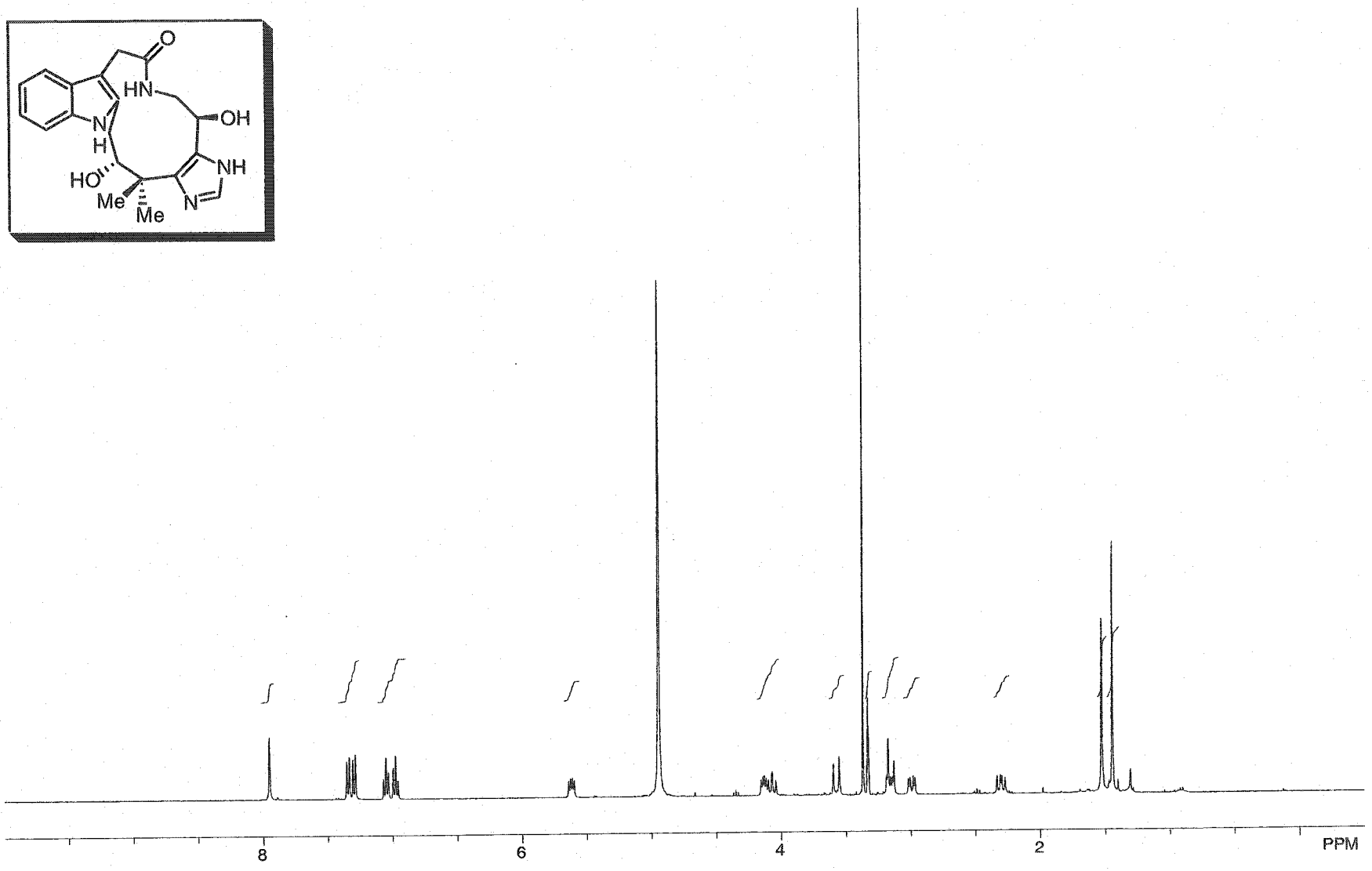


Figure A.2.73 ^{1}H NMR (400 MHz, CD_3OD) of Compound **229**.

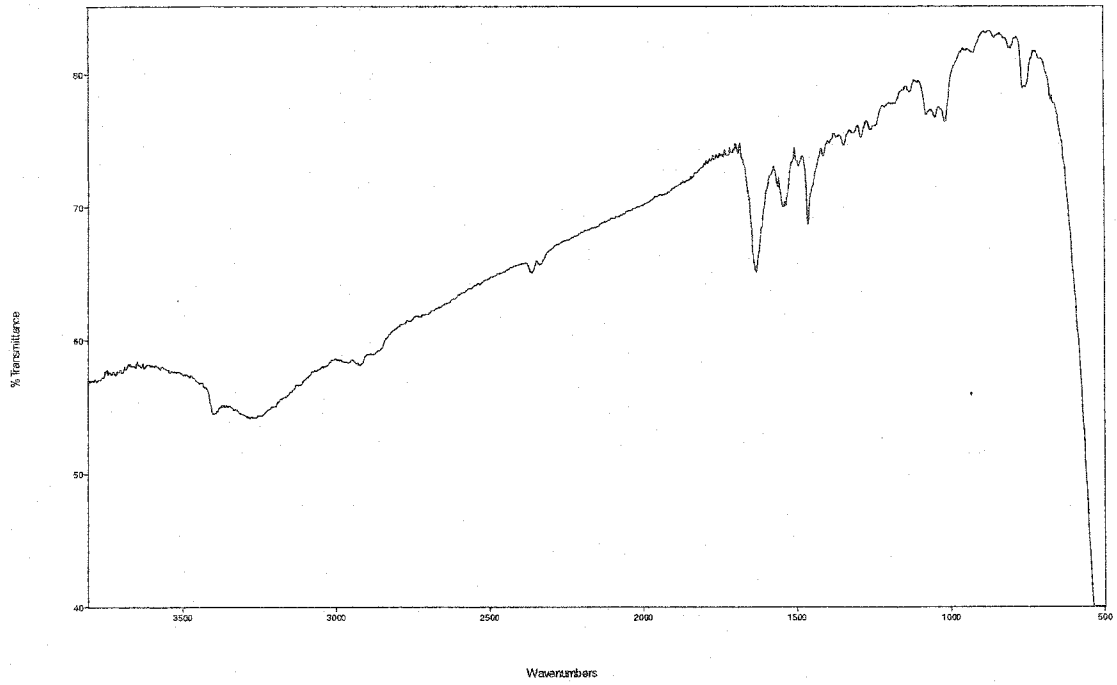


Figure A.2.74 FTIR Spectrum (thin film/NaCl) of Compound **229**.

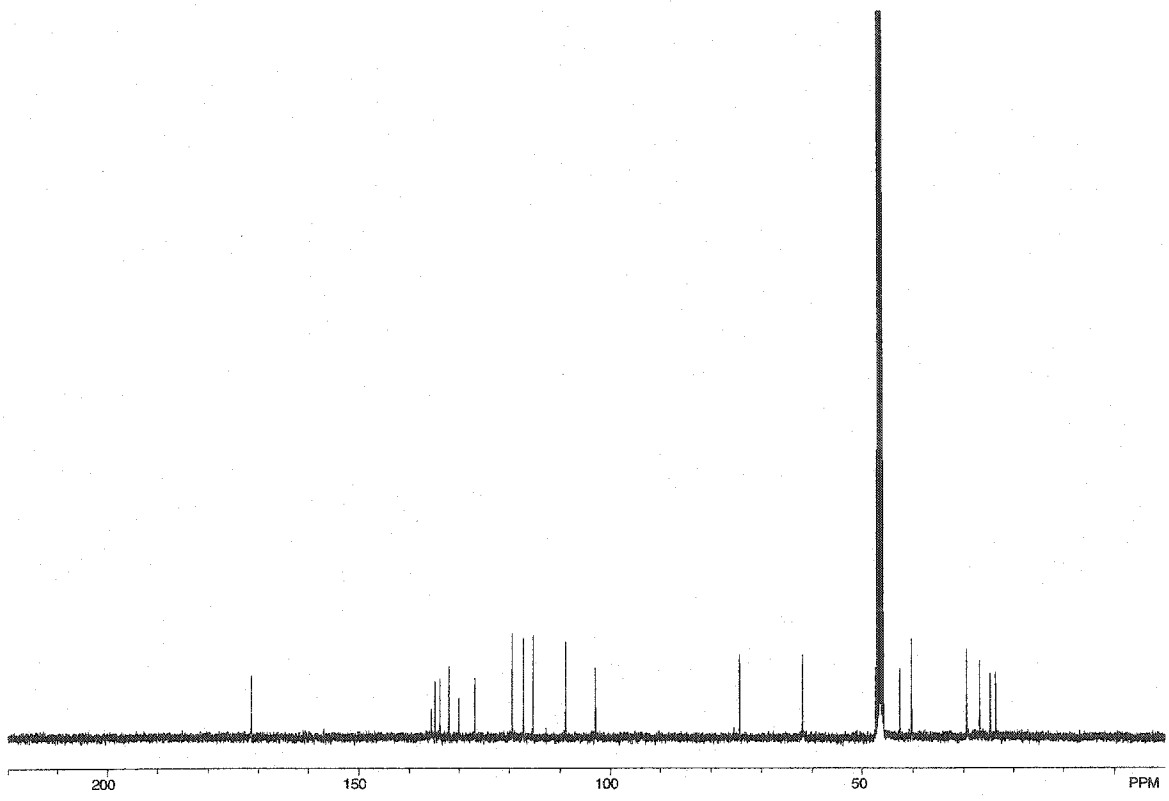


Figure A.2.75 ^{13}C NMR (125 MHz, CD_3OD) of Compound **229**.

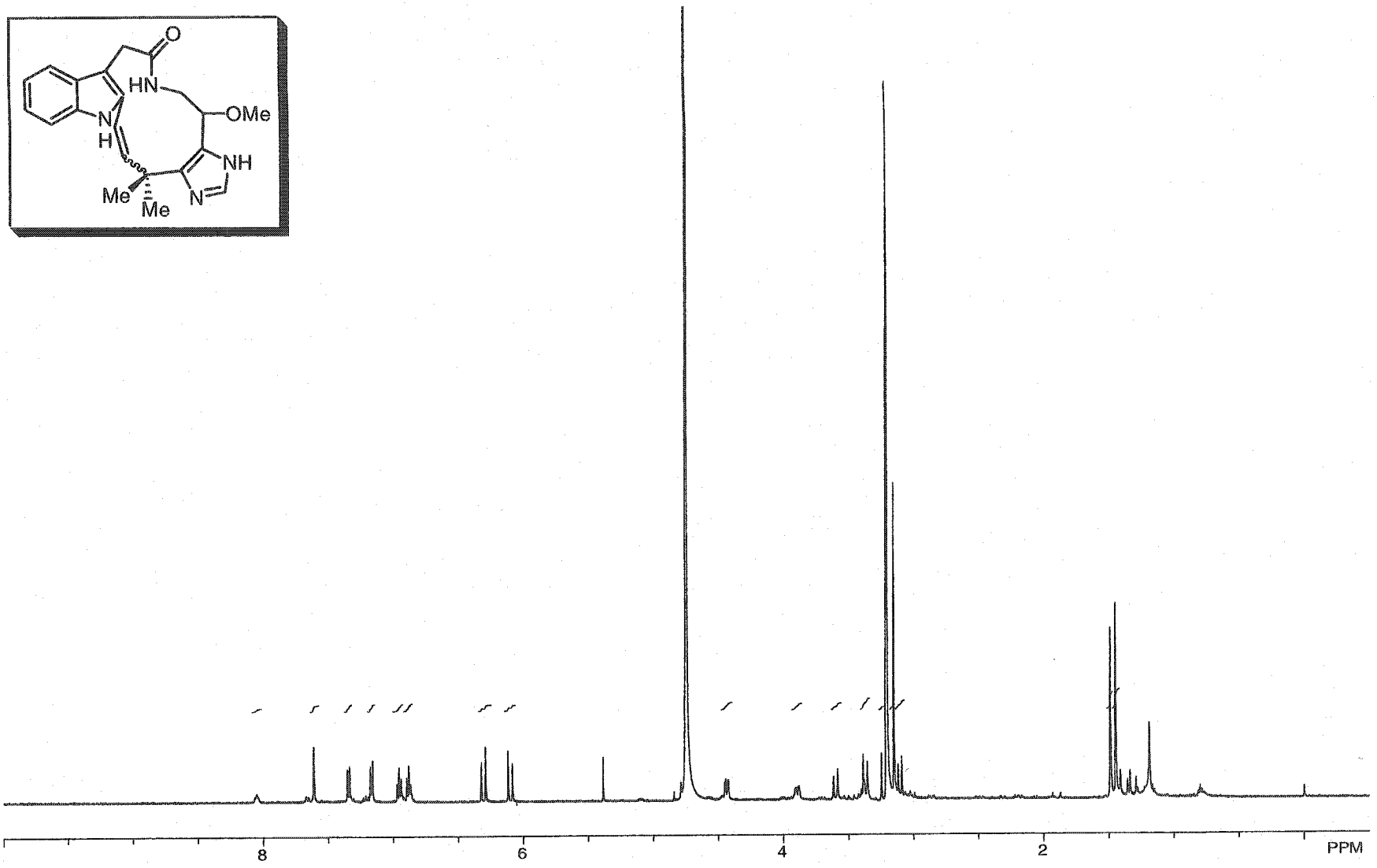


Figure A.2.76 ^{1}H NMR (500 MHz, CD_3OD) of Compound **233**.

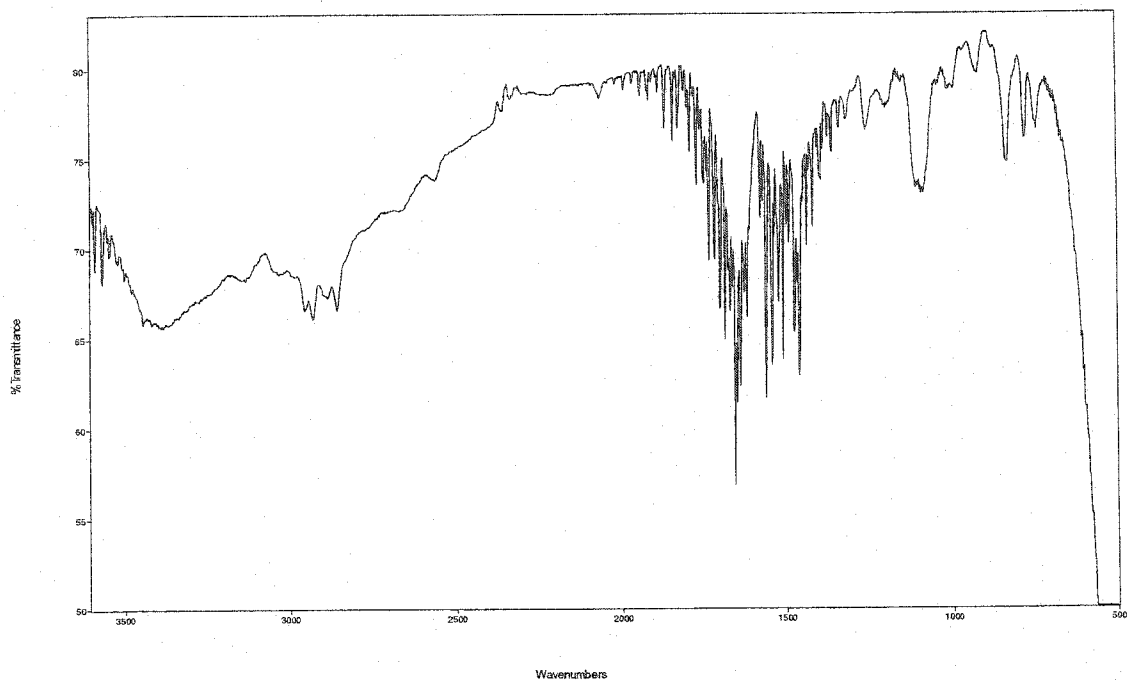


Figure A.2.77 FTIR Spectrum (thin film/NaCl) of Compound **233**.

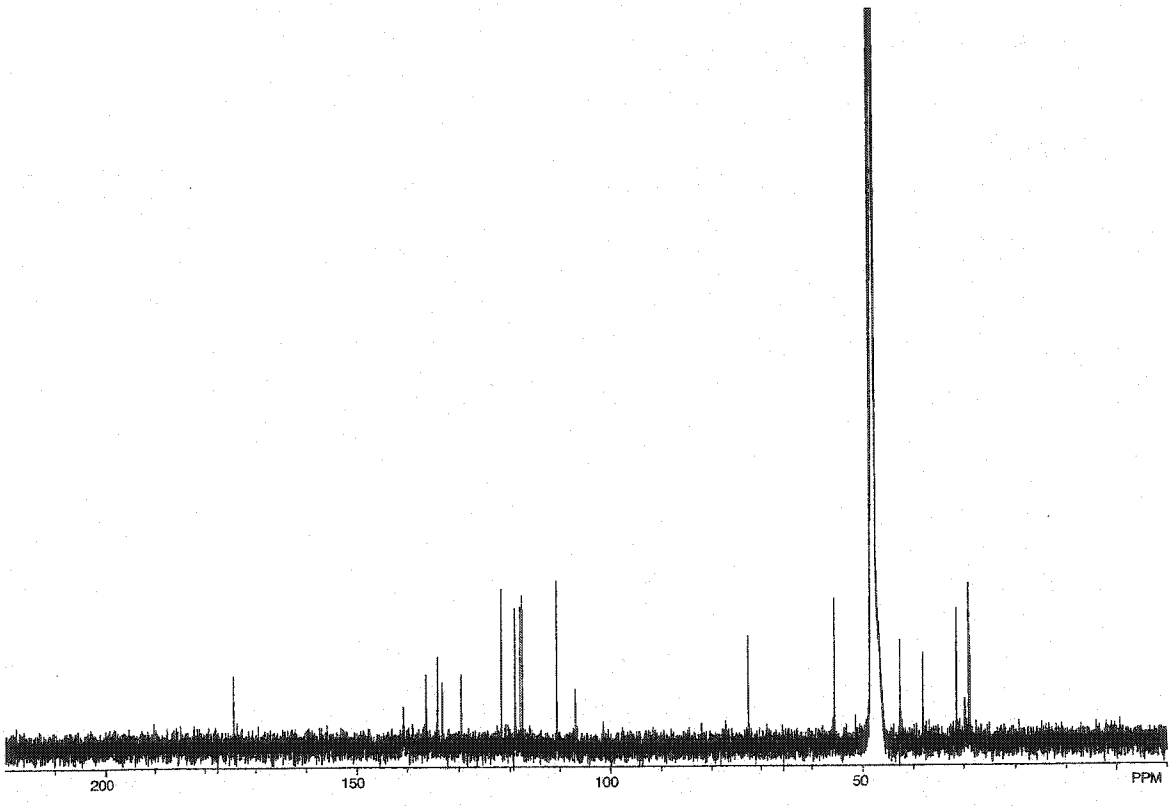


Figure A.2.78 ^{13}C NMR (125 MHz, CD_3OD) of Compound **233**

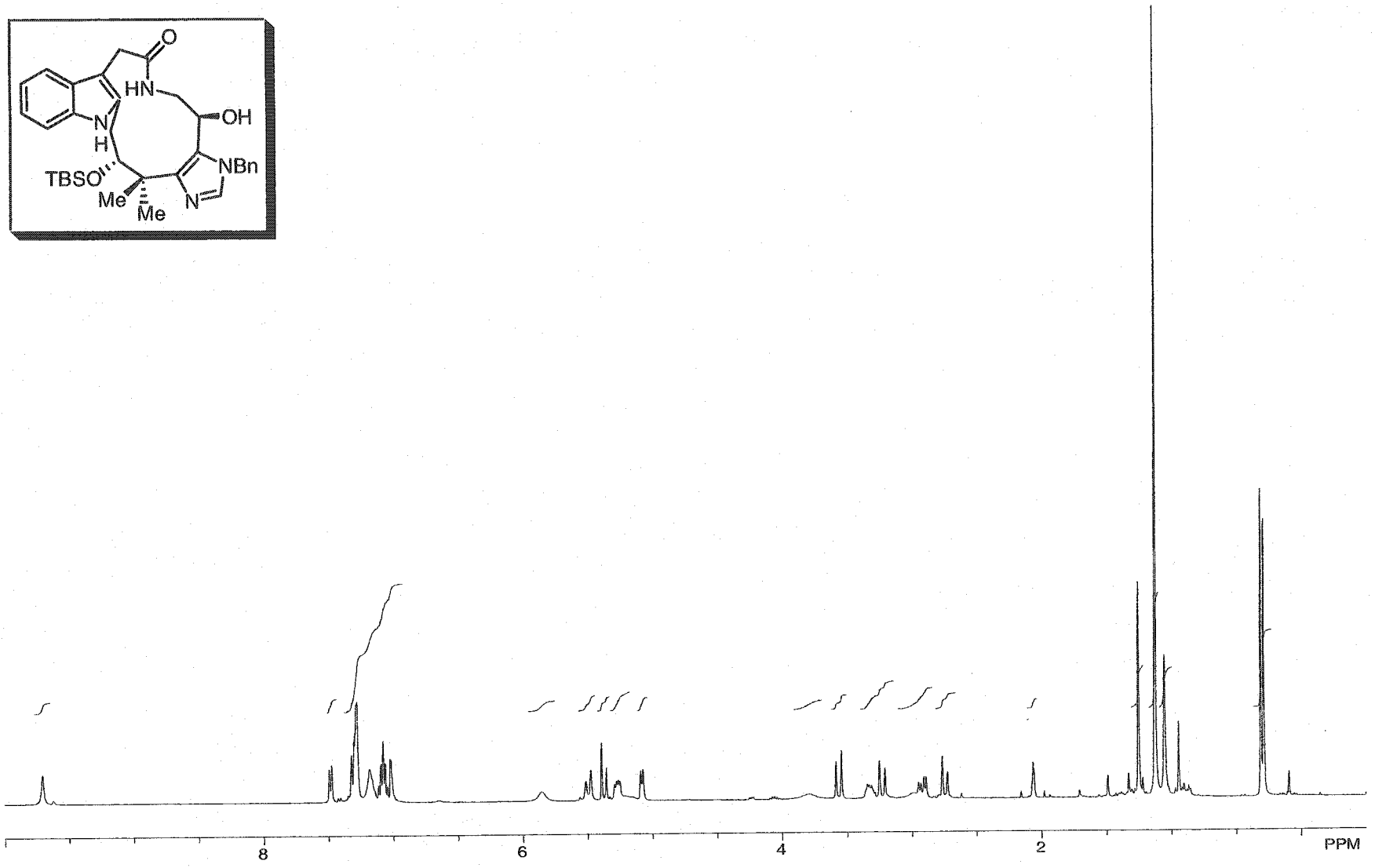


Figure A.2.79 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **236**.

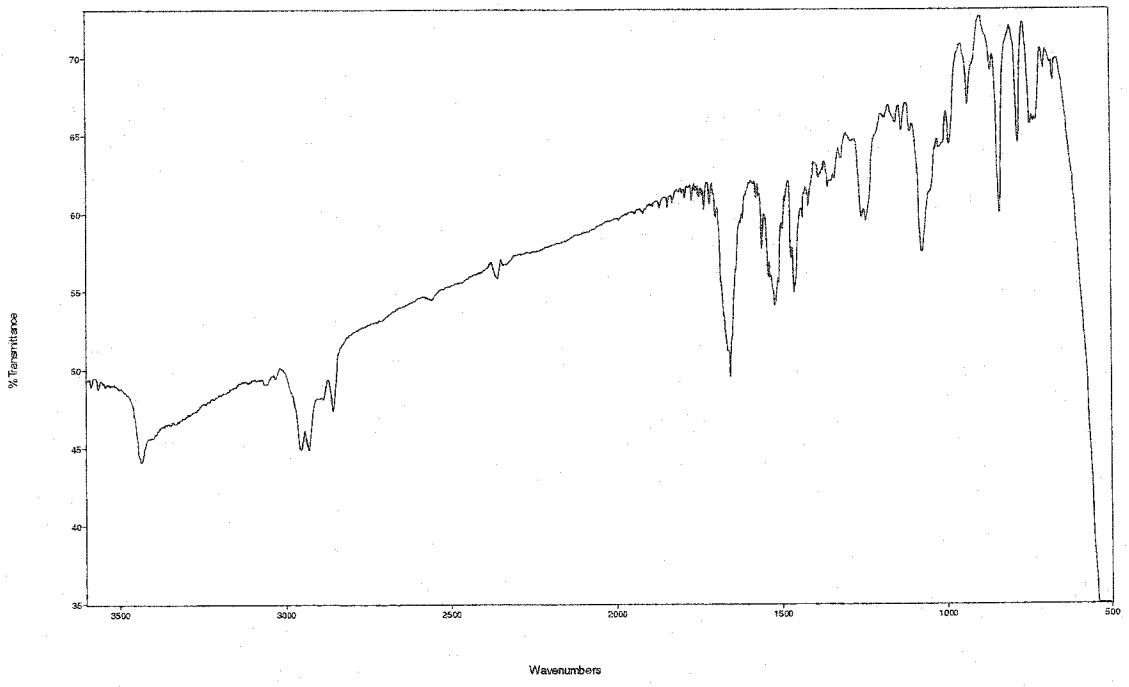


Figure A.2.80 FTIR Spectrum (thin film/NaCl) of Compound **236**.

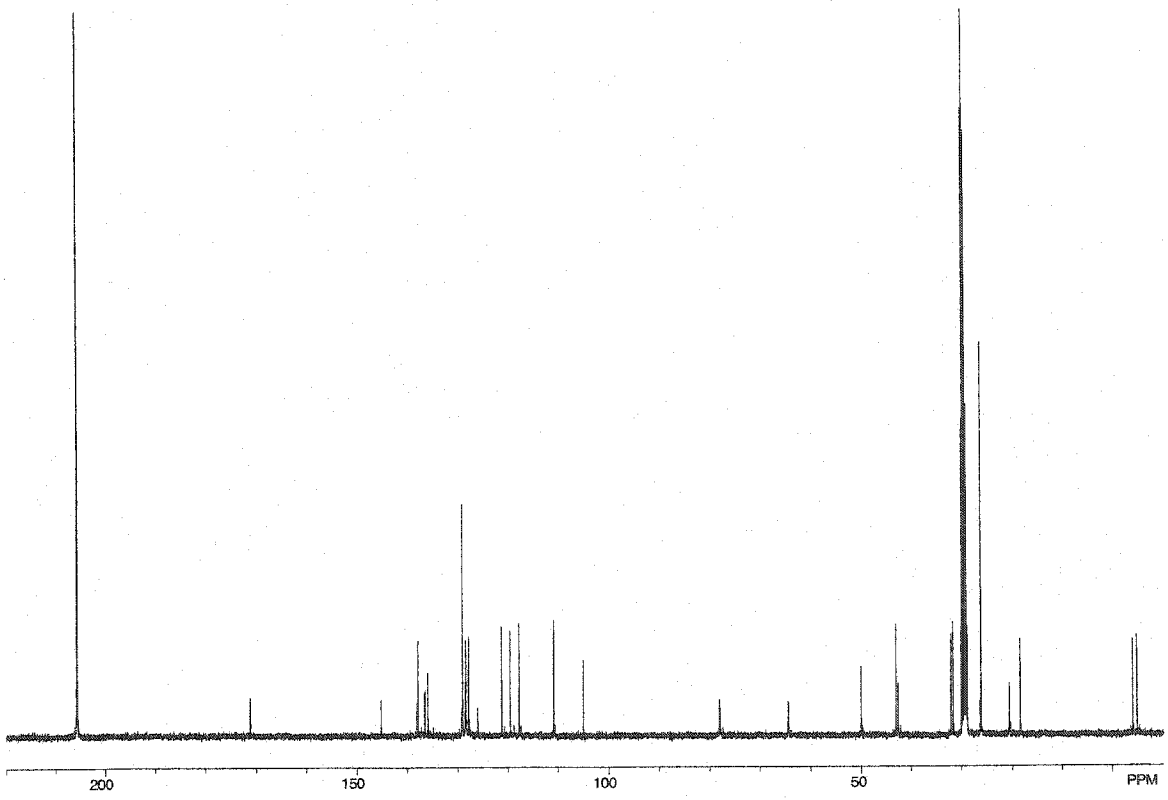


Figure A.2.81 ^{13}C NMR (100 MHz, d^6-Acetone) of Compound **236**.

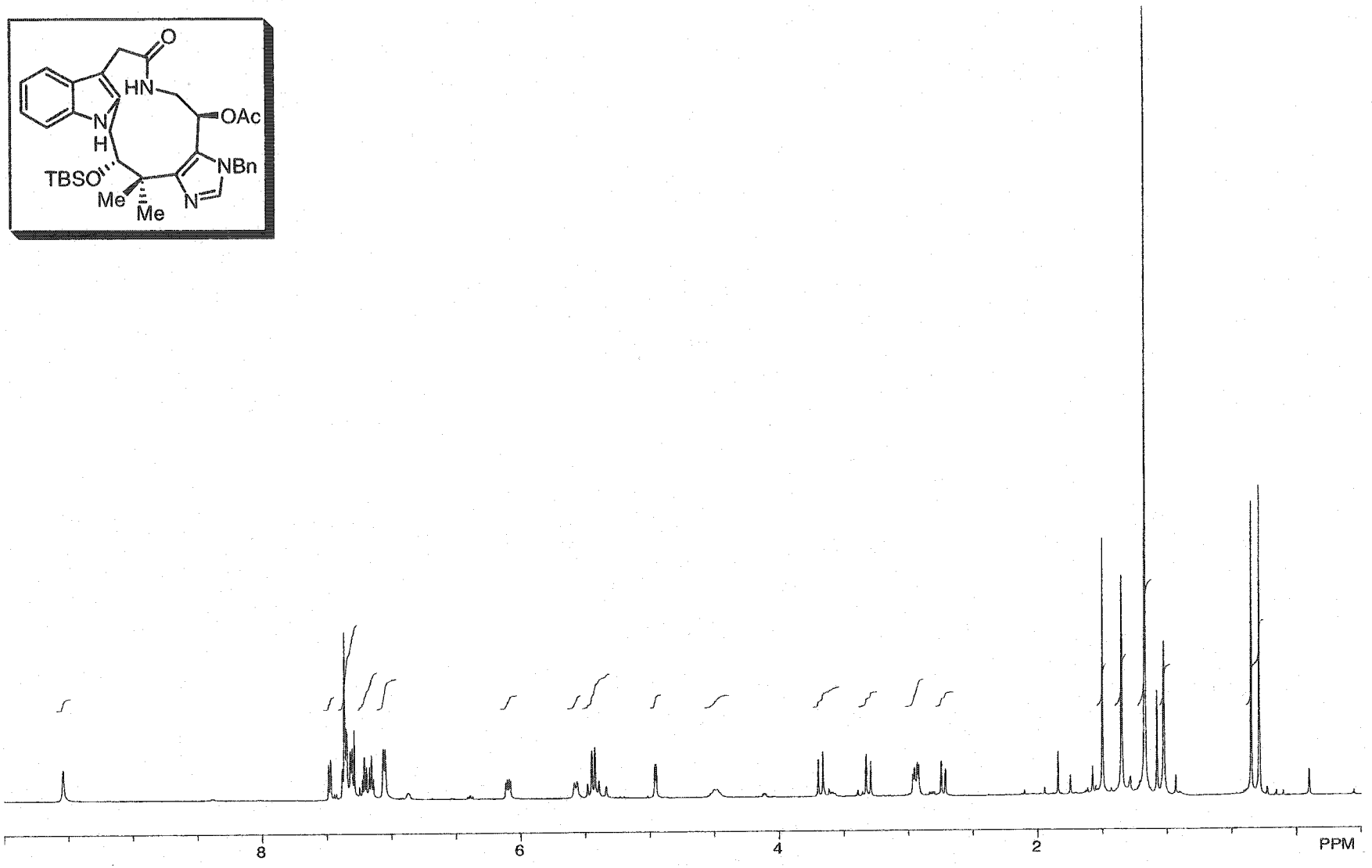


Figure A.2.82 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **237**.

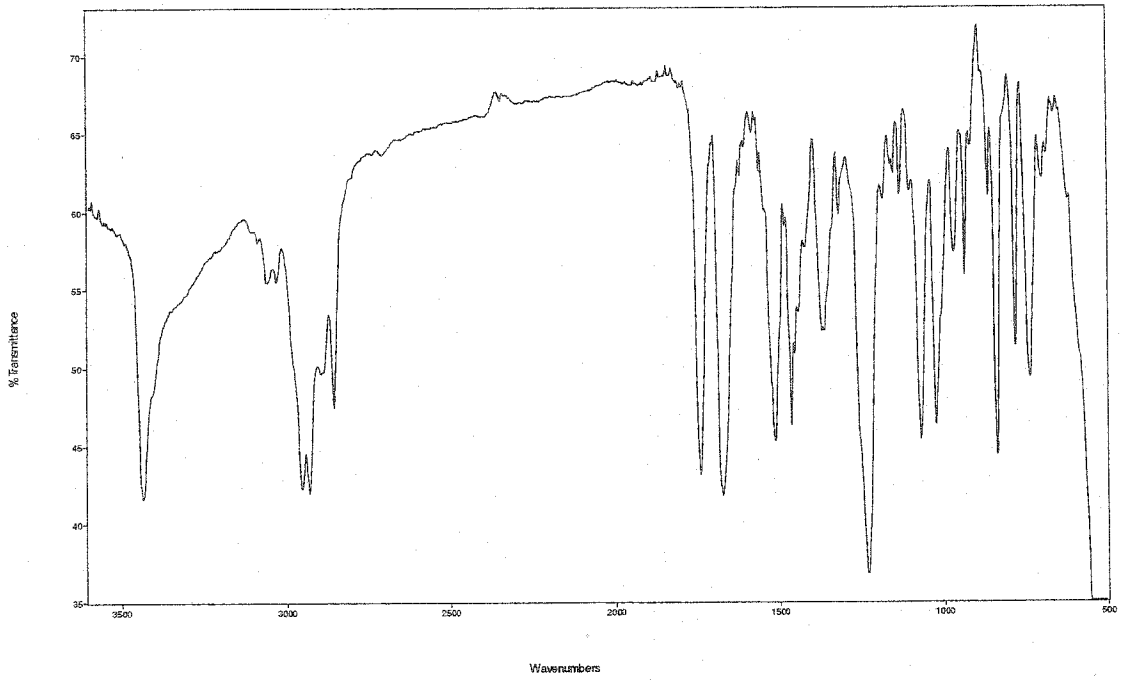


Figure A.2.83 FTIR Spectrum (thin film/NaCl) of Compound **237**.

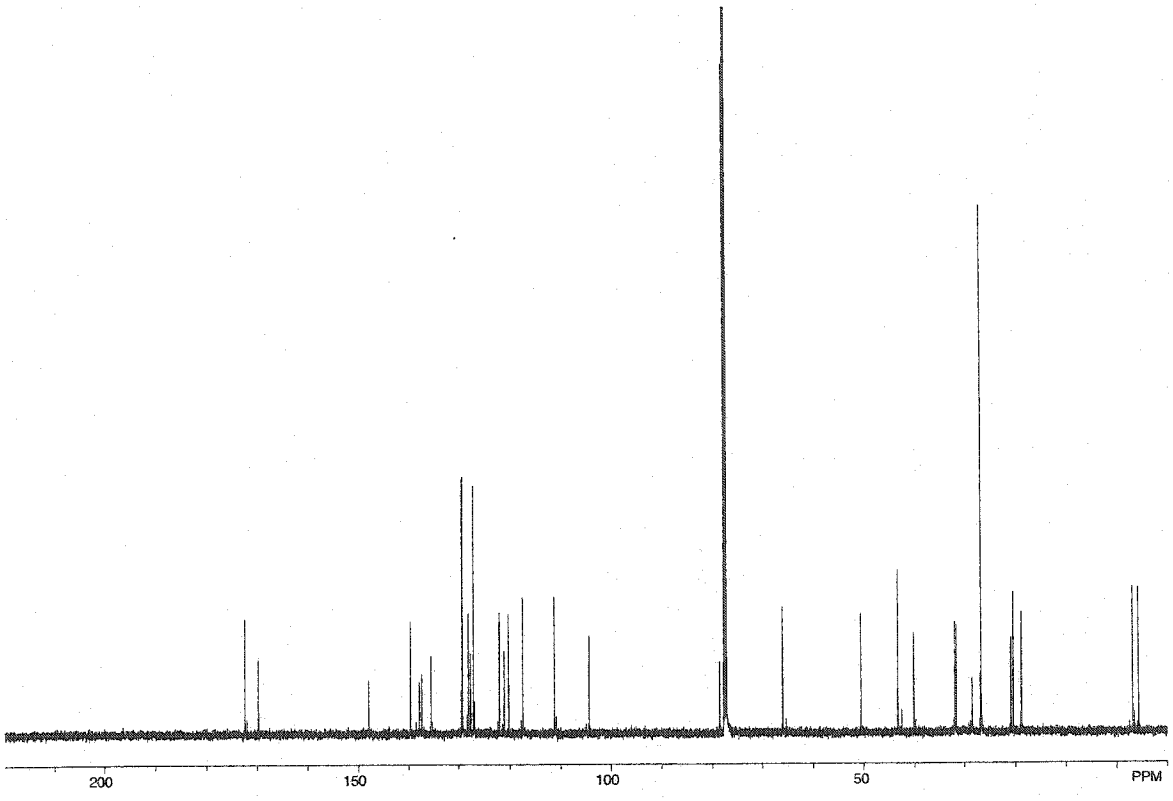


Figure A.2.84 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **237**.

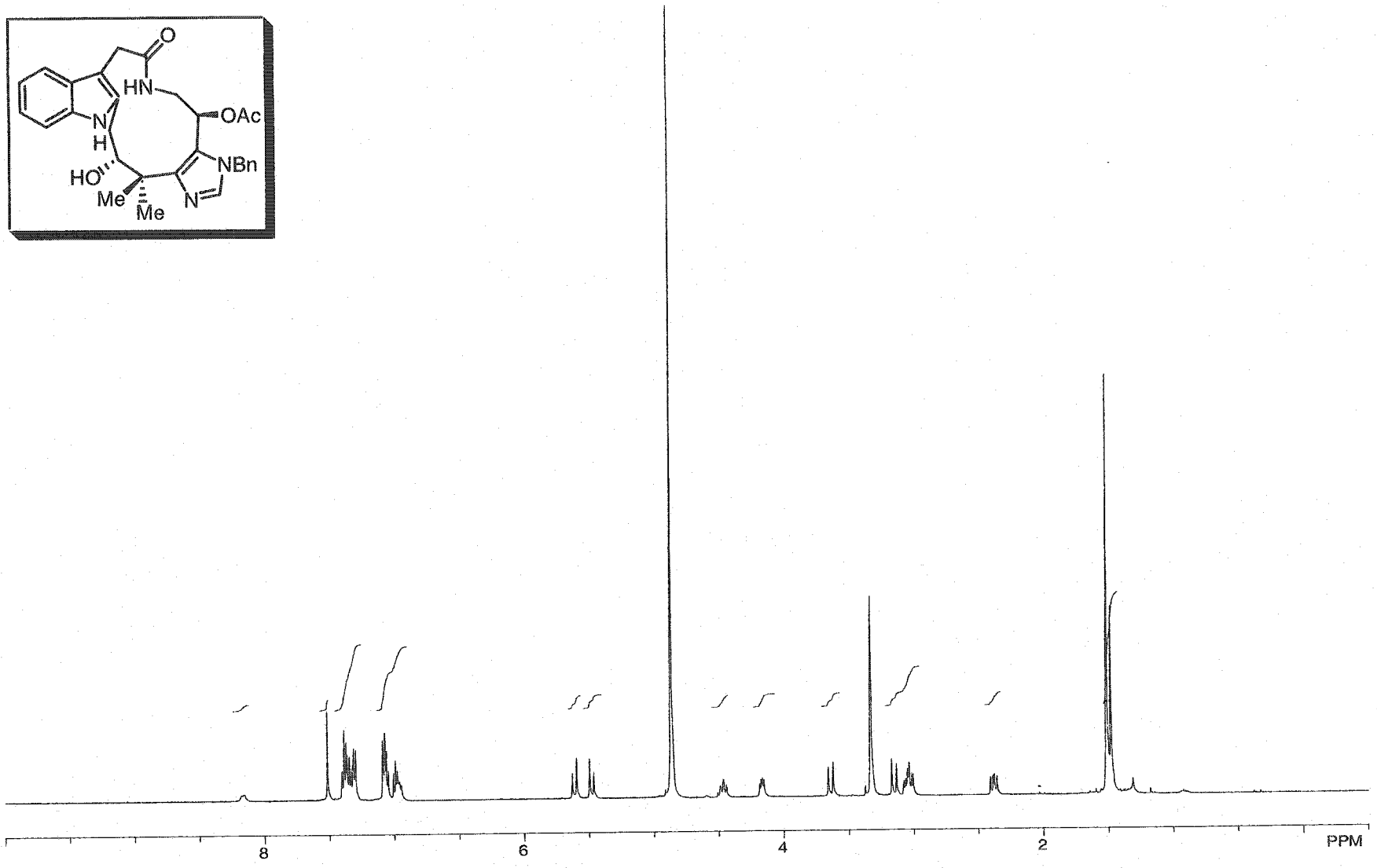


Figure A.2.85 ^{1}H NMR (500 MHz, CD_3OD) of Compound **238**.

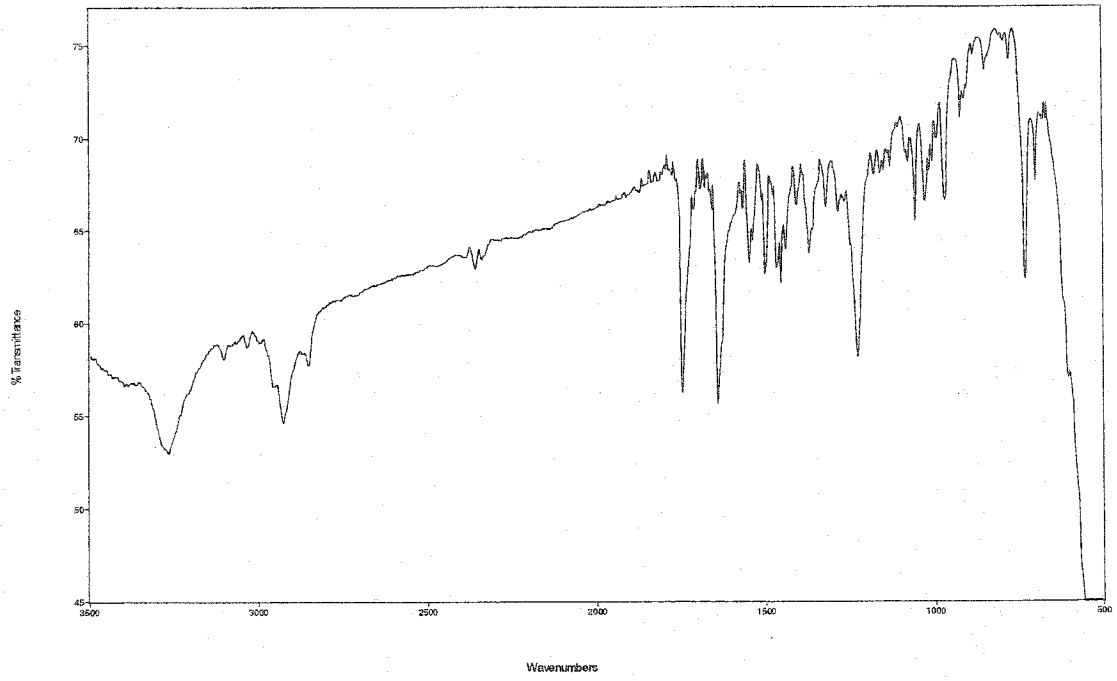


Figure A.2.86 FTIR Spectrum (thin film/NaCl) of Compound **238**.

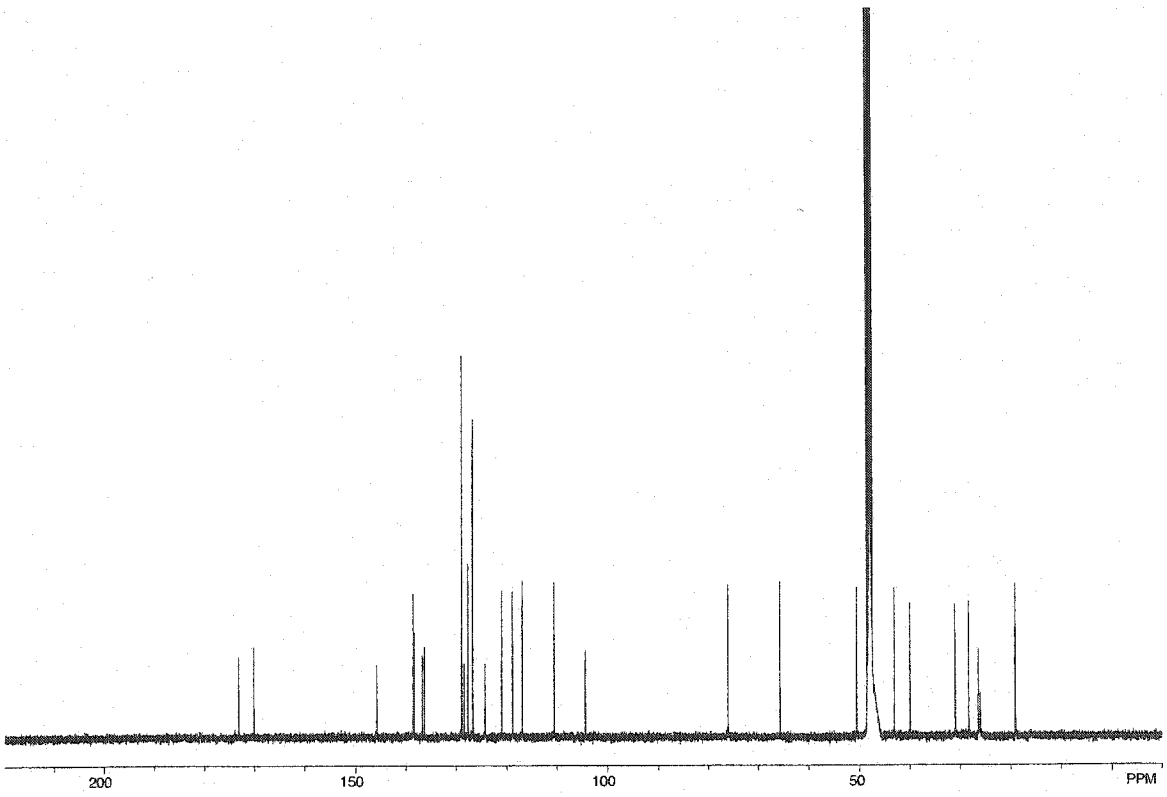


Figure A.2.87 ^{13}C NMR (125 MHz, CD_3OD) of Compound **238**.

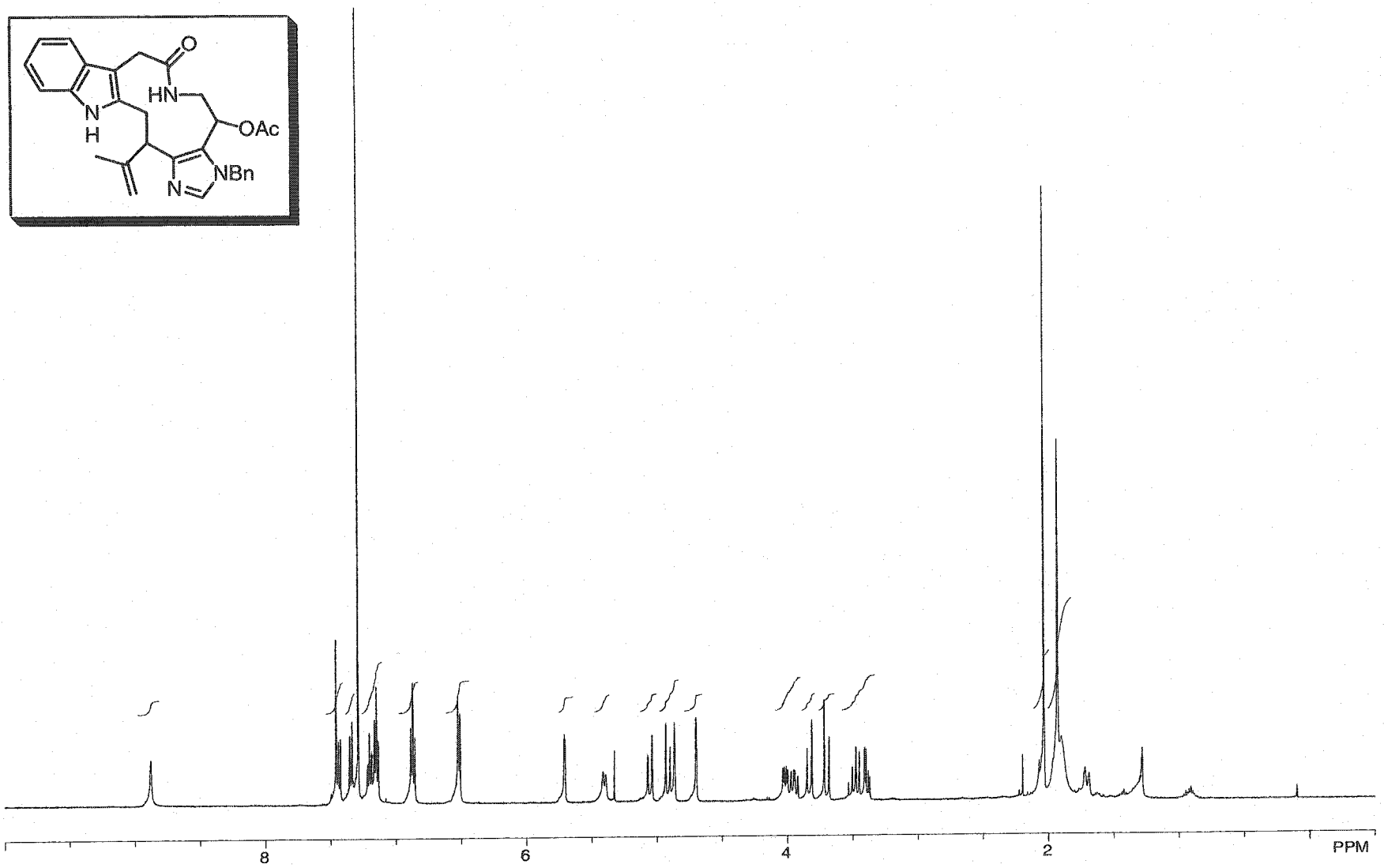


Figure A.2.88 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **239**.

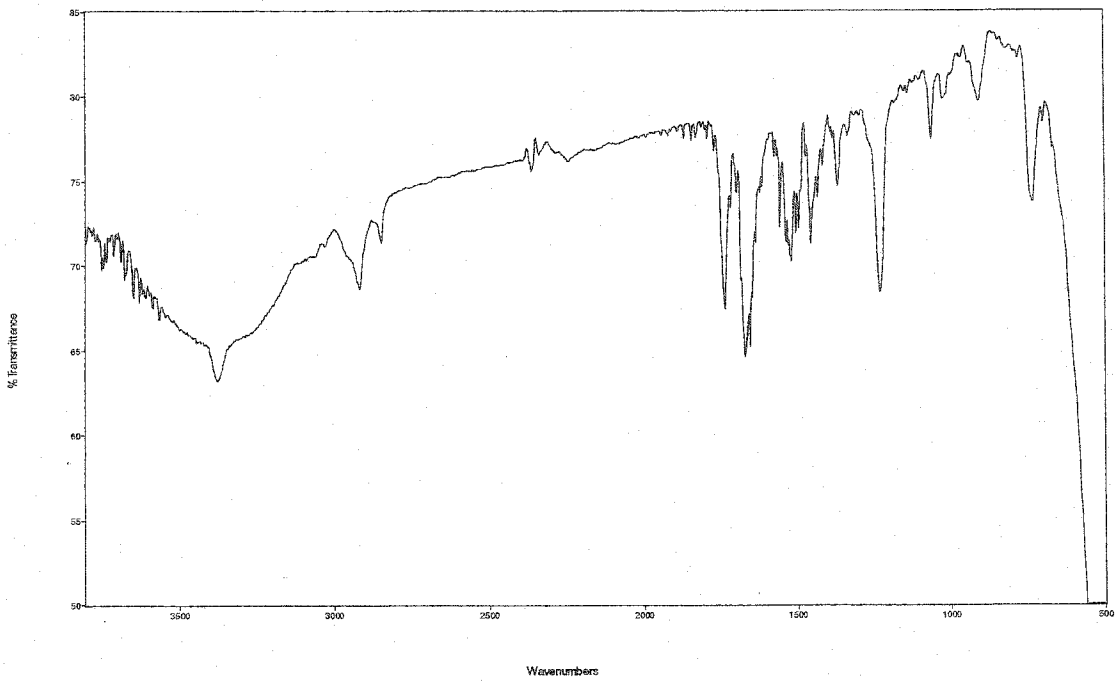


Figure A.2.89 FTIR Spectrum (thin film/NaCl) of Compound **239**.

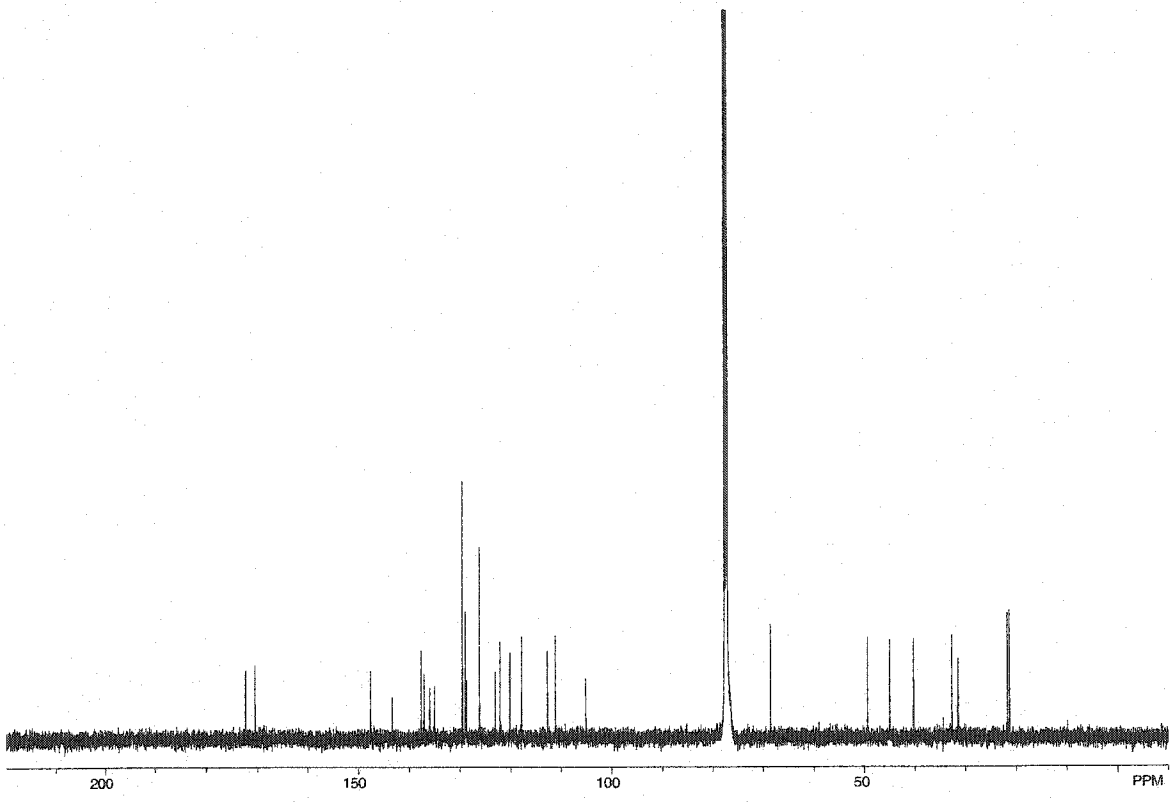


Figure A.2.90 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **239**.

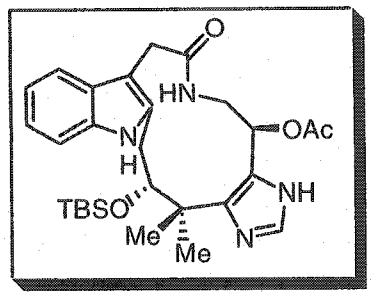


Figure A.2.91 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **241**.

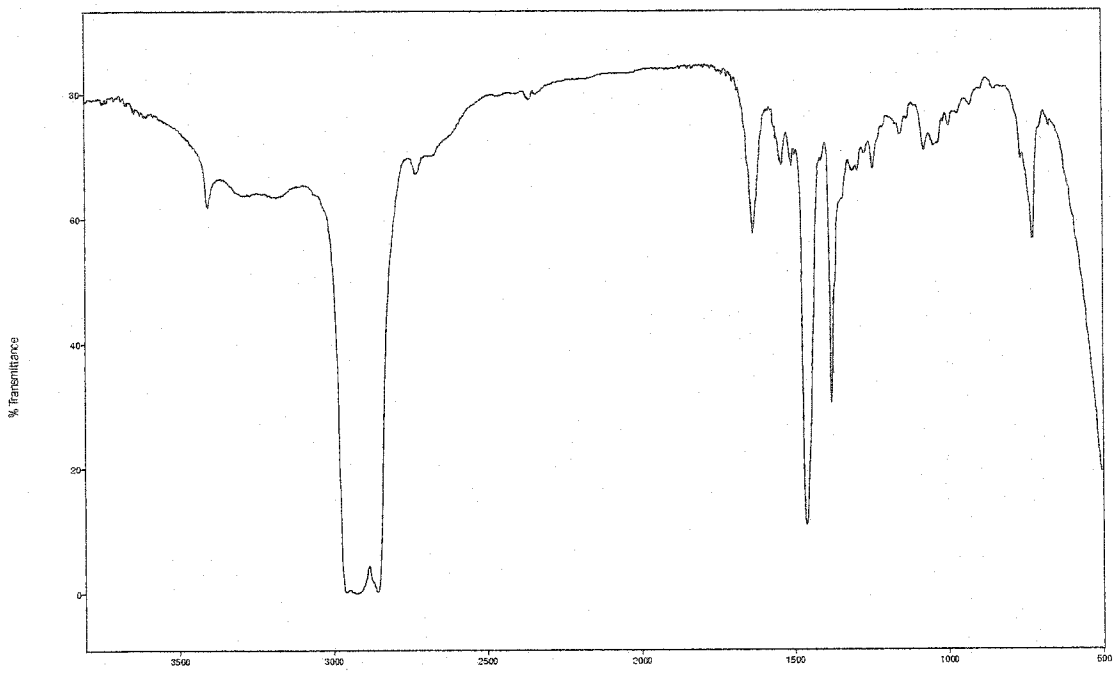


Figure A.2.92 FTIR Spectrum (thin film/NaCl) of Compound **241**.

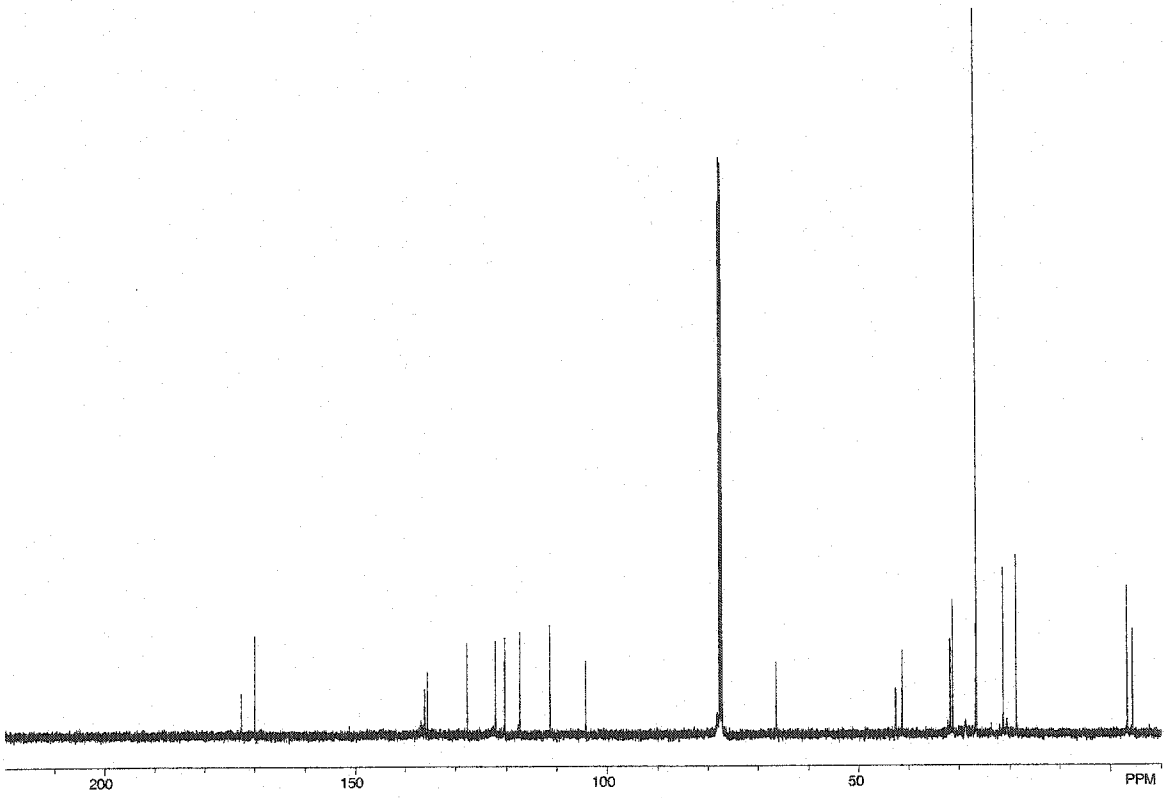


Figure A.2.93 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **241.**

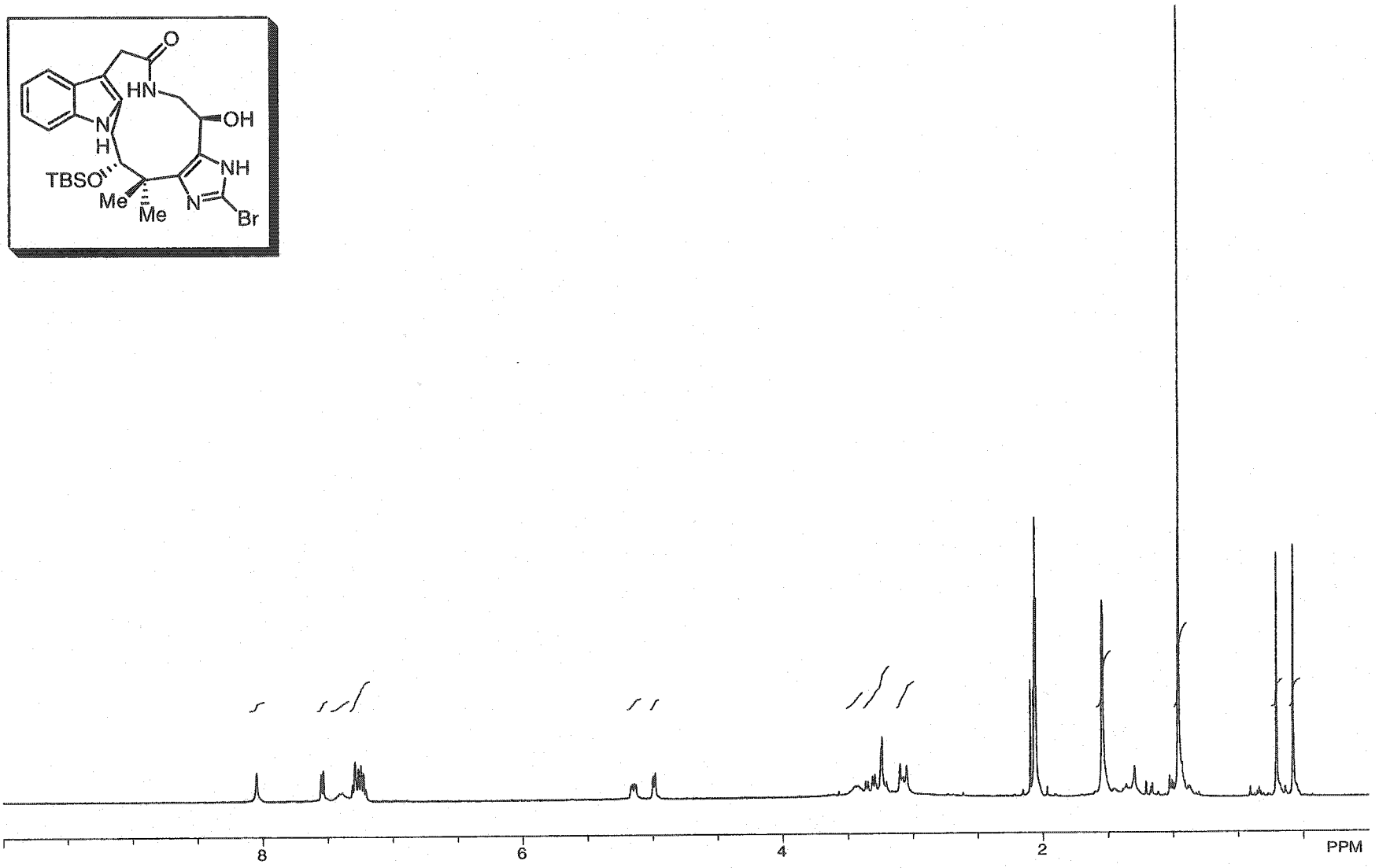
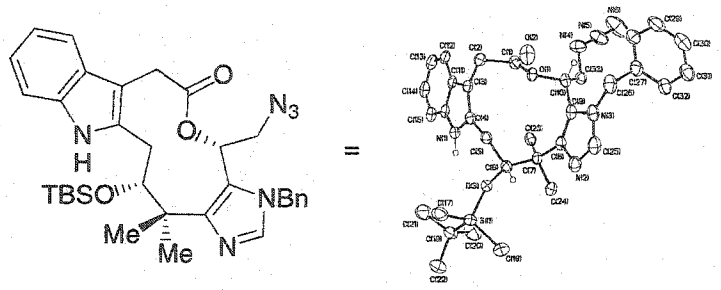


Figure A.2.94 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **242**.

Appendix Three: X-ray Crystallography Reports Relevant to Chapter Three

Figure A.3.1.1 X-Ray Crystallography Report for Lactone 217



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A.3.1.1 Crystal Data and Structure Refinement

Identification code	wood_js01	
Empirical formula	$C_{33}\ H_{42}\ N_6\ O_3\ Si$	
Formula weight	598.82	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 12.430(3) Å	α= 90°.
	b = 20.623(4) Å	β= 91.53(3)°.
	c = 13.004(3) Å	γ = 90°.
Volume	3332.5(12) $Å^3$	
Z	4	
Density (calculated)	1.194 g/cm^3	
Absorption coefficient	1.12 cm^{-1}	
F(000)	1280	

Crystal size	0.20 x 0.15 x 0.15 mm^3
Theta range for data collection	2.45 to 26.00°.
Index ranges	-15<=h<=15, -25<=k<=25, -16<=l<=16
Reflections collected	11509
Independent reflections	6453 [R(int) = 0.0853]
Completeness to theta = 26.00°	98.7 %
Absorption correction	None
Max. and min. transmission	0.9834 and 0.9780
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6453 / 0 / 392
Goodness-of-fit on F^2	1.069
Final R indices [I>2sigma(I)]	R1 = 0.0647, wR2 = 0.1635
R indices (all data)	R1 = 0.1011, wR2 = 0.1846
Largest diff. peak and hole	0.258 and -0.290 e.$Å^{-3}$

A.3.1.2 Atomic Coordinates and U(eq)

Table A.3.1.1.

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

	x	y	z	U(eq)
Si(1)	1130(1)	1604(1)	9646(1)	50(1)
O(1)	6444(1)	2048(1)	9396(1)	41(1)
O(2)	6905(2)	2019(1)	11064(1)	74(1)
O(3)	2356(1)	1699(1)	9190(1)	44(1)
N(1)	3839(2)	717(1)	8858(1)	42(1)
N(2)	3891(2)	3408(1)	10320(2)	59(1)
N(3)	5639(2)	3504(1)	10640(2)	53(1)
N(4)	7906(2)	2743(1)	8181(2)	67(1)
N(5)	8458(2)	3100(2)	7691(2)	82(1)
N(6)	9053(3)	3400(2)	7262(3)	150(2)
C(1)	6632(2)	1742(1)	10290(2)	45(1)
C(2)	6441(2)	1028(1)	10203(2)	49(1)
C(3)	5505(2)	831(1)	9532(2)	40(1)
C(4)	4465(2)	1053(1)	9576(2)	40(1)
C(5)	3979(2)	1557(1)	10247(2)	41(1)
C(6)	3207(2)	2049(1)	9729(2)	43(1)
C(7)	3709(2)	2554(1)	8999(2)	43(1)
C(8)	4421(2)	2992(1)	9676(2)	44(1)
C(9)	5522(2)	3045(1)	9857(2)	43(1)
C(10)	6522(2)	2749(1)	9447(2)	43(1)
C(11)	5536(2)	365(1)	8725(2)	43(1)
C(12)	6358(2)	3(1)	8280(2)	54(1)
C(13)	6111(2)	-394(1)	7463(2)	65(1)

C(14)	5069(2)	-458(1)	7078(2)	62(1)
C(15)	4224(2)	-105(1)	7491(2)	53(1)
C(16)	4479(2)	304(1)	8311(2)	42(1)
C(17)	1214(2)	1126(2)	10855(2)	72(1)
C(18)	488(2)	2399(1)	9907(3)	77(1)
C(19)	380(2)	1149(1)	8606(2)	66(1)
C(20)	471(3)	1491(2)	7574(3)	95(1)
C(21)	810(2)	452(2)	8497(3)	89(1)
C(22)	-821(2)	1104(2)	8876(3)	89(1)
C(23)	4279(2)	2240(1)	8096(2)	45(1)
C(24)	2789(2)	2971(1)	8524(2)	60(1)
C(25)	4639(2)	3700(1)	10867(2)	62(1)
C(26)	6632(2)	3709(1)	11184(2)	62(1)
C(27)	7375(2)	4103(1)	10544(2)	55(1)
C(28)	8381(2)	3878(1)	10312(2)	71(1)
C(29)	9058(2)	4244(2)	9719(3)	92(1)
C(30)	8733(3)	4842(2)	9374(3)	83(1)
C(31)	7743(3)	5076(2)	9603(2)	74(1)
C(32)	7055(2)	4711(1)	10178(2)	60(1)
C(33)	6814(2)	2981(1)	8389(2)	46(1)

A.3.1.3 Bond Lengths and Angles

Table A.3.1.2. Bond lengths [Å] and angles [°]

Si(1)-O(3)	1.6620(16)	N(1)-H(1)	0.89(2)
Si(1)-C(17)	1.855(3)	N(1)-C(16)	1.376(3)
Si(1)-C(18)	1.859(3)	N(1)-C(4)	1.385(3)
Si(1)-C(19)	1.874(3)	N(2)-C(25)	1.303(3)
O(1)-C(1)	1.338(3)	N(2)-C(8)	1.378(3)
O(1)-C(10)	1.452(3)	N(3)-C(25)	1.347(3)
O(2)-C(1)	1.199(3)	N(3)-C(9)	1.396(3)
O(3)-C(6)	1.447(3)	N(3)-C(26)	1.467(3)

N(4)-N(5)	1.201(3)	O(3)-Si(1)-C(19)	104.13(10)
N(4)-C(33)	1.476(3)	C(17)-Si(1)-C(19)	111.17(14)
N(5)-N(6)	1.124(4)	C(18)-Si(1)-C(19)	111.46(14)
C(1)-C(2)	1.494(3)	C(1)-O(1)-C(10)	114.86(17)
C(2)-C(3)	1.492(3)	C(6)-O(3)-Si(1)	123.46(13)
C(3)-C(4)	1.374(3)	H(1)-N(1)-C(16)	128.8(14)
C(3)-C(11)	1.424(3)	H(1)-N(1)-C(4)	120.8(14)
C(4)-C(5)	1.496(3)	C(16)-N(1)-C(4)	109.56(18)
C(5)-C(6)	1.539(3)	C(25)-N(2)-C(8)	105.8(2)
C(6)-C(7)	1.551(3)	C(25)-N(3)-C(9)	106.5(2)
C(7)-C(8)	1.529(3)	C(25)-N(3)-C(26)	125.3(2)
C(7)-C(23)	1.531(3)	C(9)-N(3)-C(26)	128.1(2)
C(7)-C(24)	1.545(3)	N(5)-N(4)-C(33)	115.7(2)
C(8)-C(9)	1.386(3)	N(6)-N(5)-N(4)	173.6(4)
C(9)-C(10)	1.496(3)	O(2)-C(1)-O(1)	122.9(2)
C(10)-C(33)	1.510(3)	O(2)-C(1)-C(2)	125.1(2)
C(11)-C(12)	1.402(3)	O(1)-C(1)-C(2)	112.0(2)
C(11)-C(16)	1.411(3)	C(3)-C(2)-C(1)	115.65(18)
C(12)-C(13)	1.371(4)	C(4)-C(3)-C(11)	107.37(19)
C(13)-C(14)	1.383(4)	C(4)-C(3)-C(2)	127.2(2)
C(14)-C(15)	1.396(4)	C(11)-C(3)-C(2)	125.41(19)
C(15)-C(16)	1.391(3)	C(3)-C(4)-N(1)	108.58(19)
C(19)-C(20)	1.524(4)	C(3)-C(4)-C(5)	130.6(2)
C(19)-C(21)	1.541(4)	N(1)-C(4)-C(5)	120.81(18)
C(19)-C(22)	1.546(4)	C(4)-C(5)-C(6)	117.40(18)
C(26)-C(27)	1.499(4)	O(3)-C(6)-C(5)	108.82(17)
C(27)-C(28)	1.374(4)	O(3)-C(6)-C(7)	109.80(17)
C(27)-C(32)	1.395(4)	C(5)-C(6)-C(7)	117.00(17)
C(28)-C(29)	1.381(5)	C(8)-C(7)-C(23)	114.75(18)
C(29)-C(30)	1.369(5)	C(8)-C(7)-C(24)	108.18(18)
C(30)-C(31)	1.362(5)	C(23)-C(7)-C(24)	106.4(2)
C(31)-C(32)	1.376(4)	C(8)-C(7)-C(6)	106.27(18)
		C(23)-C(7)-C(6)	112.82(18)
O(3)-Si(1)-C(17)	109.53(10)	C(24)-C(7)-C(6)	108.23(18)
O(3)-Si(1)-C(18)	111.28(11)	N(2)-C(8)-C(9)	109.5(2)
C(17)-Si(1)-C(18)	109.19(15)	N(2)-C(8)-C(7)	116.03(19)

C(9)-C(8)-C(7)	134.3(2)	C(20)-C(19)-C(21)	108.5(3)
C(8)-C(9)-N(3)	105.10(19)	C(20)-C(19)-C(22)	108.8(2)
C(8)-C(9)-C(10)	137.2(2)	C(21)-C(19)-C(22)	107.8(2)
N(3)-C(9)-C(10)	117.7(2)	C(20)-C(19)-Si(1)	110.9(2)
O(1)-C(10)-C(9)	111.55(17)	C(21)-C(19)-Si(1)	111.5(2)
O(1)-C(10)-C(33)	106.93(17)	C(22)-C(19)-Si(1)	109.3(2)
C(9)-C(10)-C(33)	114.65(18)	N(2)-C(25)-N(3)	113.1(2)
C(12)-C(11)-C(16)	118.5(2)	N(3)-C(26)-C(27)	114.3(2)
C(12)-C(11)-C(3)	134.2(2)	C(28)-C(27)-C(32)	118.8(3)
C(16)-C(11)-C(3)	107.34(18)	C(28)-C(27)-C(26)	121.1(3)
C(13)-C(12)-C(11)	119.2(2)	C(32)-C(27)-C(26)	120.1(3)
C(12)-C(13)-C(14)	121.7(2)	C(27)-C(28)-C(29)	120.6(3)
C(13)-C(14)-C(15)	121.3(2)	C(30)-C(29)-C(28)	119.7(3)
C(16)-C(15)-C(14)	116.9(2)	C(31)-C(30)-C(29)	120.6(3)
N(1)-C(16)-C(15)	130.4(2)	C(30)-C(31)-C(32)	120.2(3)
N(1)-C(16)-C(11)	107.07(19)	C(31)-C(32)-C(27)	120.1(3)
C(15)-C(16)-C(11)	122.5(2)	N(4)-C(33)-C(10)	107.80(18)

Symmetry transformations used to generate equivalent atoms:

A.3.1.4 Anisotropic Displacement Parameters

Table A.3.1.3. Anisotropic displacement parameters ($Å^2 x\ 10^3$).

The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si(1)	40(1)	48(1)	62(1)	4(1)	9(1)	3(1)
O(1)	56(1)	36(1)	31(1)	4(1)	-1(1)	-4(1)
O(2)	116(2)	67(1)	37(1)	6(1)	-18(1)	-17(1)

O(3)	41(1)	42(1)	50(1)	3(1)	4(1)	-2(1)
N(1)	43(1)	38(1)	46(1)	3(1)	2(1)	-2(1)
N(2)	71(1)	43(1)	65(1)	-9(1)	21(1)	-6(1)
N(3)	73(1)	45(1)	43(1)	-8(1)	8(1)	-15(1)
N(4)	49(1)	98(2)	56(1)	24(1)	11(1)	4(1)
N(5)	57(1)	128(2)	59(2)	5(2)	9(1)	-21(2)
N(6)	107(2)	220(5)	125(3)	2(3)	52(2)	-73(3)
C(1)	51(1)	47(1)	37(1)	8(1)	-2(1)	-6(1)
C(2)	50(1)	47(1)	51(1)	13(1)	-1(1)	1(1)
C(3)	43(1)	34(1)	44(1)	11(1)	3(1)	-1(1)
C(4)	46(1)	35(1)	39(1)	8(1)	3(1)	-4(1)
C(5)	45(1)	40(1)	40(1)	3(1)	7(1)	-4(1)
C(6)	42(1)	40(1)	45(1)	1(1)	8(1)	-3(1)
C(7)	47(1)	34(1)	49(1)	5(1)	5(1)	-3(1)
C(8)	59(1)	33(1)	42(1)	1(1)	11(1)	-4(1)
C(9)	62(1)	33(1)	35(1)	-2(1)	6(1)	-8(1)
C(10)	53(1)	38(1)	37(1)	2(1)	1(1)	-10(1)
C(11)	51(1)	30(1)	49(1)	12(1)	7(1)	2(1)
C(12)	62(1)	35(1)	64(2)	11(1)	14(1)	8(1)
C(13)	85(2)	38(1)	72(2)	5(1)	26(2)	11(1)
C(14)	102(2)	33(1)	51(2)	-2(1)	16(2)	-4(1)
C(15)	76(2)	37(1)	46(1)	5(1)	3(1)	-6(1)
C(16)	58(1)	28(1)	41(1)	7(1)	8(1)	-2(1)
C(17)	53(1)	93(2)	71(2)	21(2)	20(1)	3(1)
C(18)	60(2)	66(2)	107(3)	-4(2)	18(2)	14(1)
C(19)	45(1)	74(2)	79(2)	5(2)	2(1)	-6(1)
C(20)	90(2)	120(3)	74(2)	8(2)	-15(2)	-26(2)
C(21)	72(2)	78(2)	118(3)	-28(2)	0(2)	-7(2)
C(22)	48(2)	99(2)	121(3)	6(2)	-2(2)	-11(2)
C(23)	53(1)	45(1)	35(1)	5(1)	1(1)	-9(1)
C(24)	59(1)	46(1)	75(2)	16(1)	1(1)	1(1)
C(25)	88(2)	46(1)	53(2)	-12(1)	25(1)	-8(1)
C(26)	93(2)	50(1)	43(1)	-5(1)	-7(1)	-15(1)
C(27)	66(2)	50(1)	48(1)	-10(1)	-14(1)	-11(1)
C(28)	62(2)	62(2)	89(2)	-14(2)	-23(2)	-8(1)
C(29)	56(2)	100(3)	120(3)	-33(2)	-4(2)	-19(2)

C(30)	75(2)	99(3)	75(2)	-1(2)	-3(2)	-35(2)
C(31)	81(2)	72(2)	67(2)	10(2)	-18(2)	-22(2)
C(32)	69(2)	53(2)	57(2)	-2(1)	-6(1)	-13(1)
C(33)	48(1)	45(1)	44(1)	10(1)	3(1)	-5(1)

A.3.1.4 Hydrogen Coordinates

Table A.3.1.4. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10 ^{3})

	x	y	z	U(eq)
H(1)	3151(18)	826(11)	8735(17)	42(6)
H(2A)	7098	824	9935	59
H(2B)	6334	853	10901	59
H(5A)	4573	1802	10587	50
H(5B)	3585	1332	10793	50
H(6A)	2864	2298	10293	51
H(10A)	7133	2860	9932	51
H(12A)	7077	34	8542	64
H(13A)	6671	-632	7153	78
H(14A)	4924	-746	6522	75
H(15A)	3508	-144	7224	64
H(17A)	1611	1374	11384	108
H(17B)	1588	716	10729	108
H(17C)	486	1035	11089	108
H(18A)	444	2654	9271	116
H(18B)	919	2634	10427	116
H(18C)	-238	2328	10161	116
H(20A)	72	1246	7043	143

H(20B)	1230	1520	7393	143
H(20C)	169	1929	7622	143
H(21A)	398	226	7953	134
H(21B)	736	221	9149	134
H(21C)	1571	466	8318	134
H(22A)	-1214	864	8335	134
H(22B)	-1122	1542	8929	134
H(22C)	-890	878	9534	134
H(23A)	4572	2579	7655	67
H(23B)	3765	1976	7696	67
H(23C)	4867	1965	8360	67
H(24A)	3090	3293	8058	90
H(24B)	2410	3193	9074	90
H(24C)	2284	2691	8139	90
H(25A)	4495	4017	11374	74
H(26A)	7021	3318	11433	74
H(26B)	6438	3966	11793	74
H(28A)	8614	3467	10563	85
H(29A)	9747	4081	9550	110
H(30A)	9201	5095	8971	100
H(31A)	7528	5493	9365	88
H(32A)	6361	4873	10327	72
H(33A)	6293	2811	7867	55
H(33B)	6797	3461	8361	55

Appendix 4

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 (e.g., SCCC.079.H) which corresponds to an archived characterization folder hard copy and folders stored on a compact disk. For each folder a characterization notebook page number (e.g., 099) is given and for each spectrum a code (i.e.: H for ^{1}H NMR, C for ^{13}C NMR and I for FTIR) and a number (e.g., 099) are given. The characterization notebook, spectral data and disks are stored in the Wood Group archives.

Table A.4.1 Compounds Appearing in Chapter 2.

Compound	Folder	^{1}H NMR	^{13}C NMR	FTIR
127	PKVIII269A	PKVIII269AH	PKVIII269AC	PKVIII269I
128	PKVIII269B	PKVIII269BH	PKVIII269BC	PKVIII269BI
129	PKVIII279	PKVIII279H	PKVIII279C	PKVIII279I
130	PKVIII281	PKVIII281H	PKVIII281C	PKVIII281I
131	PKIX029	PKIX029H	PKIX029C	PKIX029I
133	PKVIII117	PKVIII117H	PKVIII117C	PKVIII117I
134	PKVIII213	PKVIII213H	PKVIII213C	PKVIII213I
135	SCCC.094	SCCC.094.H	SCCC.094.C	SCCC.094.I
139	PKVII085	PKVII085H	PKVII085C	PKVII085I
140	PKVII087	PKVII087H	PKVII087C	PKVII087I

Table A.4.1 Compounds Appearing in Chapter 2 (Continued)

141	PKVII089	PKVII089H	PKVII089C	PKVII089I
142	PKVIII237	PKVIII237H	PKVIII237C	PKVIII237I
143	PKVII103	PKVII103H	PKVII103C	PKVII103I
144	PKVII263	PKVII263H	PKVII263C	PKVII263I
145	PKVIII249	PKVIII249H	PKVIII249C	PKVIII249I
146	PKVIII287	PKVIII287H	PKVIII287C	PKVIII287I
147	PKVIII289	PKVIII289H	PKVIII289C	PKVIII289I
149	PKVIII251	PKVIII251H	PKVIII251C	PKVIII251I
150	PKVIII253	PKVIII253H	PKVIII253C	PKVIII253I
152	PKVIII177	PKVIII177H	PKVIII177C	PKVIII177I
153	PKVIII193	PKVIII193H	PKVIII193C	PKVIII193I
156	PKIX039	PKIX039H	PKIX039C	PKIX039I

Table A.4.2 Compounds Appearing in Chapter 3.

Compound	Folder	^{1}H NMR	^{13}C NMR	FTIR
184	PKVIII271	PKVIII271H	PKVIII271C	PKVIII271I
185	JBSXIII143	JBSXIII143H	JBSXIII143C	JBSXIII143I
186	JBSXIII149	JBSXIII149H	JBSXIII149C	JBSXIII149I
191	PKVIII273	PKVIII273H	PKVIII273C	PKVIII273I
192	PKVIII275	PKVIII275H	PKVIII275C	PKVIII275I
193	JBSXIV195	JBSXIV195H	JBSXIV195C	JBSXIV195I
194	JBSXIV217	JBSXIV217H	JBSXIV217C	JBSXIV217I
195	PKVII293	PKVII293H	PKVII293C	PKVII293I
196	JBSXIV243	JBSXIV243H	JBSXIV243C	JBSXIV243I
197	PKXI043	PKIX043H	PKIX043C	PKXI043I
206	JBSXIV241	JBSXIV241H	JBSXIV241C	JBSXIV241I
207	JBSXV113	JBSXV113H	JBSXV113C	JBSXV113I
208&209	JBSXV035	JBSXV035H	JBSXV035C	JBSXV035I
210&211	JBSXV037	JBSXV037H	JBSXV037C	JBSXV037I
216	PKVII277	PKVII277H	PKVII277C	PKVII277I
217	JBSXV257	JBSXV257H	JBSXV257C	JBSXV257I
218	PKVIII225	PKVIII225H	PKVIII225C	PKVIII225I
219	JBSXV273	JBSXV273H	JBSXV273C	JBSXV273I
221	JBSXV277	JBSXV277H	JBSXV277C	JBSXV277I
222	JBSXV283	JBSXV283H	JBSXV283C	JBSXV283I
223	JBSXV287	JBSXV287H	JBSXV287C	JBSXV287I
224	PKVIII205	PKVIII205H	PKVIII205C	PKVIII205I
226	JBSXV159	JBSXV159H	JBSXV159C	JBSXV159I
228	JBSXVI201	JBSXVI201H	JBSXVI201C	JBSXVI201I

229	JBSXVI089	JBSXVI089H	JBSXVI089C	JBSXVI089I
233	JBSXVI207	JBSXVI207H	JBSXVI207C	JBSXVI207I
237	PKVIII197	PKVIII197H	PKVIII197C	PKVIII197I
239	PKIX019	PKIX019H	PKIX019C	PKIX019I
240	PKIX021	PKIX021H	PKIX021C	PKIX021I
242	PKIX023	PKIX023H	PKIX023C	PKIX023I
245	JBSXVI193	JBSXVI193H	JBSXVI193C	JBSXVI193I

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About the Author

Peter Korakas was born in Concord, NH on August 19th, 1977 to Doreen and Alex Korakas. After spending the first five years of his life in Allenstown, NH he and his family moved further north to the small town of Franklin, NH. It is there that Peter would begin his education first attending St. Mary's private grade school. In the fifth grade Peter's parents opted out of private school and enrolled him in the Franklin public school system.

He spent his fifth grade year at Rowell Elementary school followed by completing sixth grade at "Sisters of the Holy Cross" (Franklin's middle school was still under construction therefore sixth grade was moved to a rented site 10 minutes outside of town). After completion of Franklin Middle School, Peter and his enrolled in Franklin High School. It was there that he first took an interest in chemistry.

After graduating high school, Peter decided to attend college at Sacred Heart University in Fairfield, Connecticut. It was there that his interest in chemistry was strengthened by Dr. James P. Louey. It was under Dr. Louey's tutelage that Peter became interested in synthetic organic chemistry and decided to take on an undergraduate

research project in Dr. Louey's lab. He completed his undergraduate thesis entitled "o-Substituent Effects in the Radical Conjugate Addition Reactions of Aryl Triazenes to α,β-Unsaturated Ketones" and graduated *summa cum laude* from Sacred Heart in May, 1999.

Later that fall, Peter began graduate studies in organic chemistry at Yale University. After showing a genuine interest in synthetic chemistry, he joined the laboratories of Professor John L. Wood and began working on an existing project with fellow graduate student Stuart Chaffee directed toward the total synthesis of Securamine A. Upon Stuart's departure in 2001 , Peter would take control of the project and spend the next three years attempting to complete the synthesis. In the spring of 2003, Peter accepted a position as a senior scientist with Schering-Plough Research Institute located in Kenilworth, NJ.