Abstract

Progress Toward the Total Synthesis of Diazonamide A

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Diazonamide A (**3**) was isolated in 1991 from the colonial ascidian *Diazona angulata* and has been shown to be a potent cytotoxin with IC_{50} values of less than 15 ng/mL against HCT-116 human colon carcinoma and B-16 murine melanoma cancer cell lines. Due to its unique structure and promising biological activity, **3** has led to a Herculean effort by the synthetic community in recent years. Reported herein is a novel approach to this the new class of natural products.

Work in a model system has led to the development of two complementary approaches to the diazonamide bisaryl quaternary center C(10). The first approach involves the asymmetric cyclopropanation and subsequent ring opening of benzofuran **195**. The second strategy relies upon a more concise alkylation route ideal for material advancement (**198→210**).

In efforts directed toward fully functional diazonamide A, an efficient synthesis of benzofuranone **198** was developed utilizing a robust π-allyl alkylation/$Eu(fod)_3$ catalyzed Claisen rearrangement sequence (**198→210**). Alkylation of **198** with indole **262** affords advanced intermediate **275**, which is for advancement to diazonamide A (**3**).

Progress Toward the Total Synthesis of Diazonamide A

A Dissertation
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of
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by
Douglas Edward Fuerst

Dissertation Director: Professor John Louis Wood

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To Mom, Dad, and Scott

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Doug Fuerst

New Haven, Connecticut
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List of Abbreviations

$[\alpha]_D^{20}$	specific rotation at 20 °C and wavelength of sodium D line
AcOH	acetic acid
aq	aqueous
$BF_3 \cdot Et_2O$	boron trifloride diethyl etherate
Bn	benzyl
BnBr	benzyl bromide
BnOH	benzyl alcohol
Boc	*tert*-butyloxycarbonyl
br	broad
Bu	butyl
t-Bu	*tert*-butyl
BuLi	butyllithium
c	concentration in g/ml
C	carbon
°C	degrees Celsius
calc'd	calculated
C_2Cl_6	hexachloroethane
$CDCl_3$	chloroform-*d*
CH_3CO_3H	peracetic acid
CH_3CN	acetonitrile
$CHCl_3$	chloroform
CH_2Cl_2	methylene chloride
CI	chemical ionization
$ClCO_2Et$	ethyl chloroformate
Cs_2CO_3	cesium carbonate
m-CPBA	*meta*-chloroperoxybenzoic acid
δ	chemical shift in ppm downfield from Me_4Si

d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublets
ddd	doublet of doublets of doublets
DDQ	
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMF	dimethyl formamide
DMS	methyl sulfide
DMSO	dimethyl sulfoxide
dppb	diphenylphosphino butane
dt	doublet of triplets
EDC	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
EI	electron impact
equiv	equivalent
Et	ethyl
Et_2O	ethyl ether
EtOAc	ethyl acetate
Et_3N	triethylamine
FAB	fast atom bombardment
FTIR	Fourier transform infrared
g	gram(s)
h	hour(s)
H	hydrogen
Hz	hertz
HCl	hydrochloric acid
H_2O	water
HOBt	hydroxybenzotriazole hydrate
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum

H_2SO_4	sulfuric acid
J	coupling constant
K_2CO_3	otassium carbonate
K_3PO_4	potassium phosphate
L	liter(s)
LDA	lithium diisopropylamide
$LiBH_4$	lithium borohydride
LiHMDS	lithium hexamethyldisilazide
LiOH	lithium hydroxide
LiOMe	lithium methoxide
μ	micro
m	milli, medium (FTIR), multiplet (NMR)
M	moles per liter
Me	methyl
MeOH	methanol
Me_3OBF_4	trimethyloxonium tetrafloroborate
Me_2SO_4	methyl sulfate
MEPY	methyloxopyrrolidine
$MgSO_4$	magnesium sulfate
mp	melting point
MHz	megahertz
min	minute(s)
mol	mole(s)
mp	melting point
m/z	mass to charge ratio
NH_4Cl	ammonium chloride
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NaCl	sodium chloride
NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate

NaHMDS	sodium hexamethyldisilazide
NaOH	sodium hydroxide
NMR	nuclear magnetic resonance
O	oxygen
O_3	ozone
[O]	oxidation
OAc	acetate
p	para
p-TsOH	*para*-toluenesulfonic acid
PBr_3	phosphorus tribromide
PCC	pyridinium chlorochromate
$Pd(OAc)_2$	palladium acetate
$Pd_2(dba)_3$	
pH	hydrogen ion concentration
PPh_3	triphenylphosphine
ppm	parts per million
pyr	pyridine
q	quartet
$Rh_2(cap)_4$	rhodium (II) caprolactam
$Rh_2(OAc)_4$	rhodium(II) acetate dimer
$Rh_2(pfb)_4$	rhodium (II) perfluorobutyrate
rt	room temperature
s	singlet (NMR), strong (FTIR)
sat	saturated
t	triplet
td	triplet of doublets
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
w	weak

Chapter 1

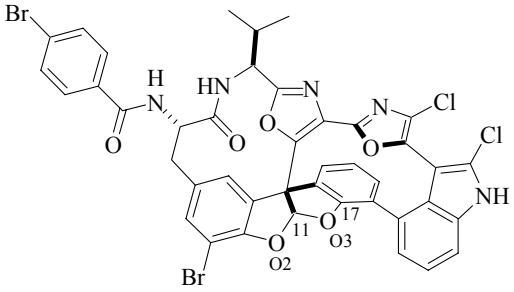
The Diazonamides: A Unique Class of Structurally and Biologically Interesting Natural Products

1.1 Background and Introduction to the Diazonamides

1.1.1 Isolation and Structural Elucidation

In 1991 Fenical and Clardy reported the isolation and structure of two unique secondary metabolites isolated from the colonial ascidian *Diazona chinesis*, which was later correctly identified as *Diazona angulata*.[1] This ascidian was collected from the ceilings of small caves along the northwest coast of the Siquijor Island, Philippines. Extraction of the lyophilized sample (256.2 g) followed by reverse phase HPLC purification yielded 54 mg and 132 mg of two unique compounds named diazonamide A (**3**, Figure 1.1.3) and diazonamide B (**2**, Figure 1.1.2), respectively.

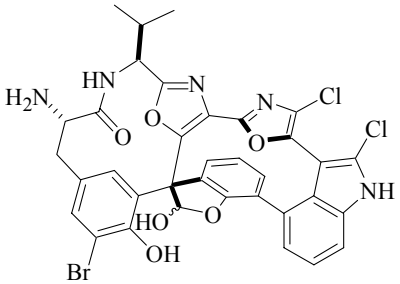
Extensive ^{1}H NMR, ^{13}C NMR, and HRFABMS studies of both compounds revealed several structural subunits, however, the complete structural assignment remained elusive. The final connectivities were established by single-crystal X-ray analysis of the *p*-bromobenzamide derivative of diazonamide B (**1**, Figure 1.1.1).



1

Figure 1.1.1 *p*-Bromobenzamide Diazonamide B.

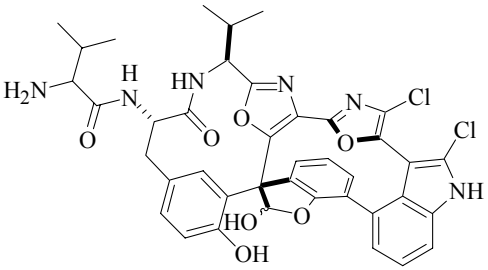
The complete structural assignment of diazonamide B from the crystal structure was straightforward in all but one respect. NMR coupling and correlation data indicated that diazonamide B was a hemiacetal at C(11). Therefore, it was assumed that upon derivatization to **1** the C(11) hemiacetal was converted to an acetal. Based on a three-bond correlation between the C(11) proton and C(17), the hemiacetal ring was assigned to involve O(3) rather than O(2). Additional molecular mechanics studies failed to resolve the stereochemistry at the C(11) hemiacetal. Based on the above considerations the structure of diazonamide B was ultimately assigned as compound **2** (Figure 1.1.2) below.



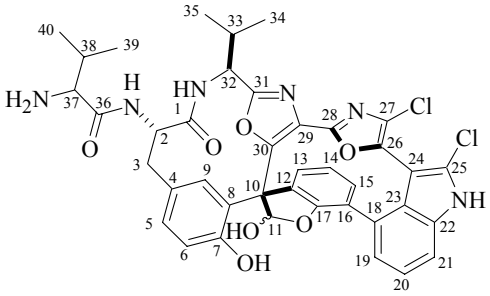
Diazonamide B (**2**)

Figure 1.1.2 Diazonamide B.

With the structure of diazonamide B in hand, diazonamide A (**3**, Figure 1.1.3) was determined to posses the same polycyclic core as diazonamide B except for replacement of the C(6) bromine with hydrogen based on the similarity of ^{1}H NMR, ^{13}C NMR, UV and IR data. Diazonamide A also contained an extra valine residue that was attached to N(1) via the valine carboxyl. The absolute stereochemistry of this valine residue was not determined.



Diazonamide A (**3**)



Diazonamide A (**3**)

Figure 1.1.3 Diazonamide A.

Taken together diazonamide A and B represent an entirely new class of natural products. Marine macrocycles possessing multiple oxazole fragments have been known for some time, however, the combination oxazole fragments with a bisaryl substituted quaternary center within a rigid macrocycle possessing two atropisomeric axes (about the C(16)-C(18) and C(24)-C(29) bonds) is unprecedented. Close examination of the diazonamides shows at least three common amino acids: a 3,4,5-trisubstituted L-tyrosine (C1-C9), a tryptophan substituted at the 2- and 4-positions of the indole (C18-C27), and an L-valine (C31-C35). The origins of C(28)-C(30) and C(10)-C(17) are not clear and their biosynthesis appears to require the ambiguous assembly of amino acid and aromatic polyketide fragments.

1.1.2 Biological Activity

In the original communication, Fenical and Clardy reported diazonamide A is a potent cytotoxin with IC_{50} values less than 15 ng/mL against HCT-116 human colon carcinoma and B-16 murine melanoma cancer cell lines. The activity of diazonamide B was only reported to be less than that of diazonamide A (no quantitative measurement was given).

Subsequent COMPARE analysis at the NCI showed diazonamide A to possess a mean GI_{50} = 4.9 nM against a standardized panel of human cancer cell lines, wherein it induced growth arrest in mitosis.[2]

Unfortunately, further biological testing has been prevented due to lack of the natural material.[1] Repeated trips to isolate more of the diazonamide producing ascidian have been unsuccessful. Thus, total synthesis is the only means available to access quantities necessary for biological screening and advanced testing.

1.2 Previous Synthetic Studies

1.2.1 Synthetic Efforts Toward Diazonamide A

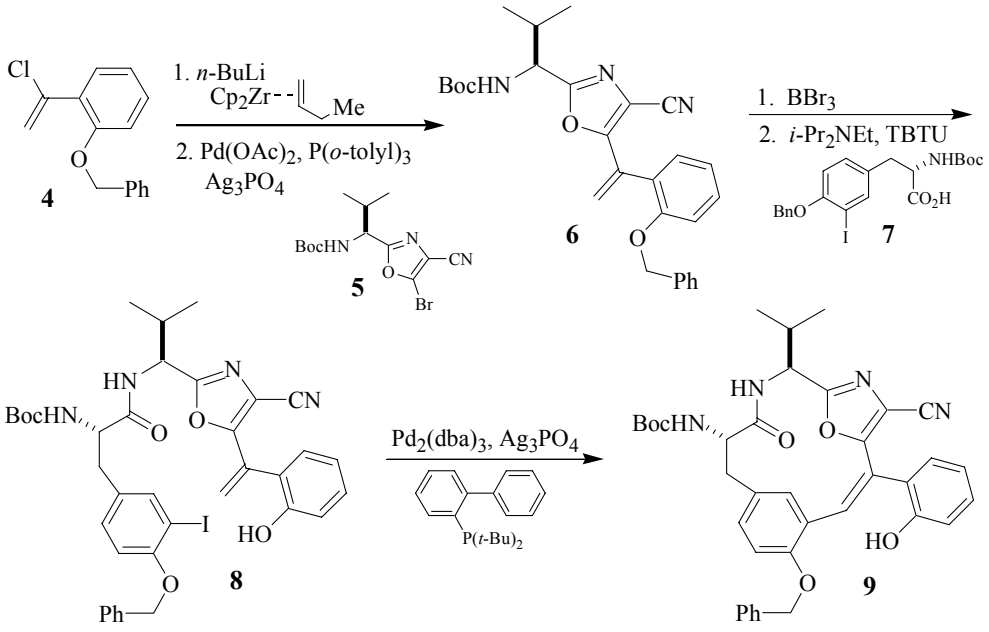
Due to its unique structure and promising biological activity, diazonamide A has led to a Herculean effort by the synthetic community in recent years.[3] This has resulted in two completed total synthesis to date, and a vast number of approaches, some of which are very advanced. Each approach is presented in detail in the following sections.

1.2.2 Completed Total Syntheses of Diazonamide A

1.2.2.1 Harran's Total Synthesis of Diazonamide A

In December of 2001 the Harran group at the University of Texas, Southwestern Medical Center at Dallas reported the first total synthesis of diazonamide A.[2,4-7] Their synthesis commenced with a modified Negishi coupling of vinyl chloride **4** with oxazole **5** to afford olefin **6**. Deprotection of **6** followed by coupling with iodo-tyrosine **7** provided modified dipeptide **8** which underwent smooth Heck endocyclization to generate cyclic triarylethylene **9**.

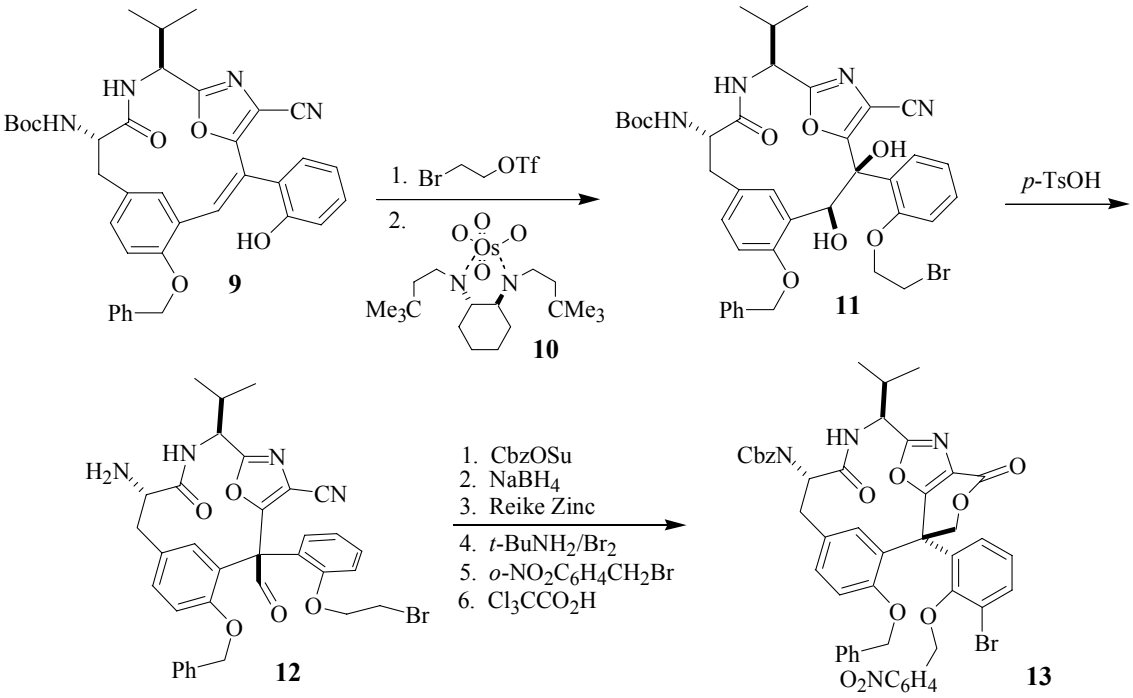
Scheme 1.2.1



Protection of the free phenol in **9** sets the stage for the key dihydroxylation which proceeded with stoichiometric chiral osmium reagent **10** in good 93:7 diastereoselectivity to afford diol **11**. The use of this osmium reagent is necessary to override the intrinsic bias of this molecule to undergo dihydroxylation with the opposite-face selectivity.

Treatment of **11** with excess *p*-TsOH initiated a ring-contracting pinacol rearrangement to set the critical bisaryl quaternary center as a single diastereomer. Subsequent functional group manipulation of aldehyde **12** furnished lactone **13**.

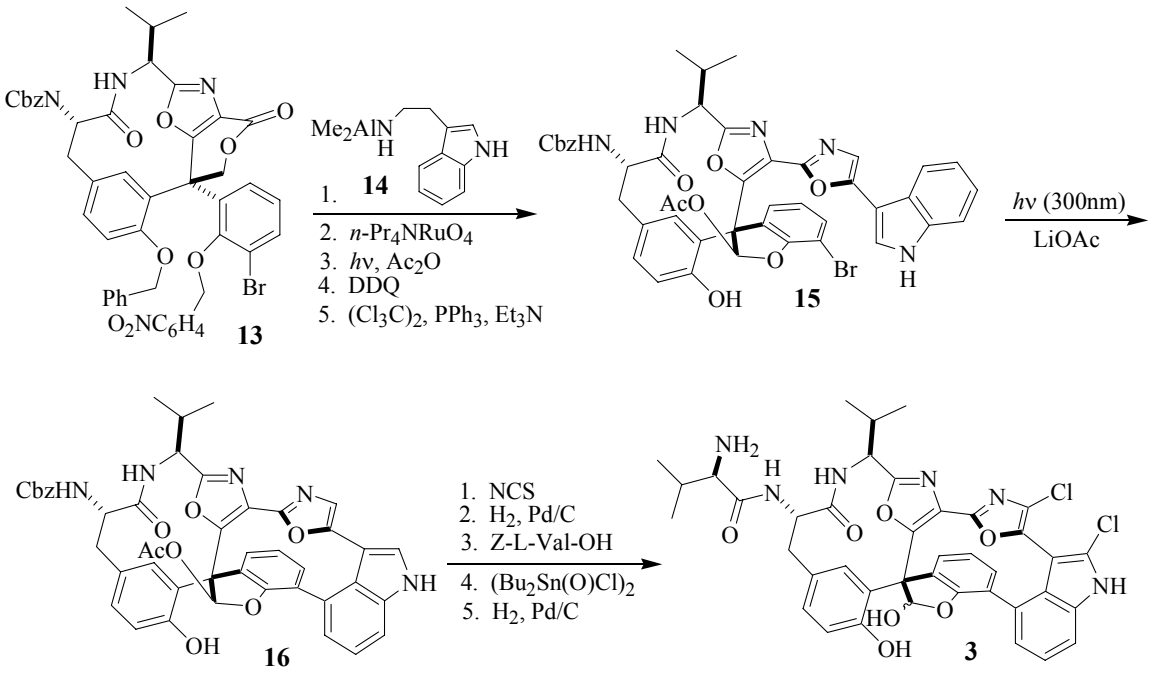
Scheme 1.2.2



Opening of lactone **13** with indole **14** followed by elaboration to the diazonamide hemiacetal and oxazole ring yielded biaryl bond precursor **15**. Remarkably, UV irradiation of **15** resulted in the loss of HBr and the formation of biaryl product **16** as a single atropdiastereomer. A plausible mechanism for this reaction involves an intramolecular photoinduced electron transfer from the indole chromophore to the adjacent bromoarene and biradical collapse to form the C(16)-C(18) bond. With **16** in hand, completion of diazonamide A proceeded by chlorination, valine homologation, and global deprotection. Surprisingly, this synthetically prepared material was different from

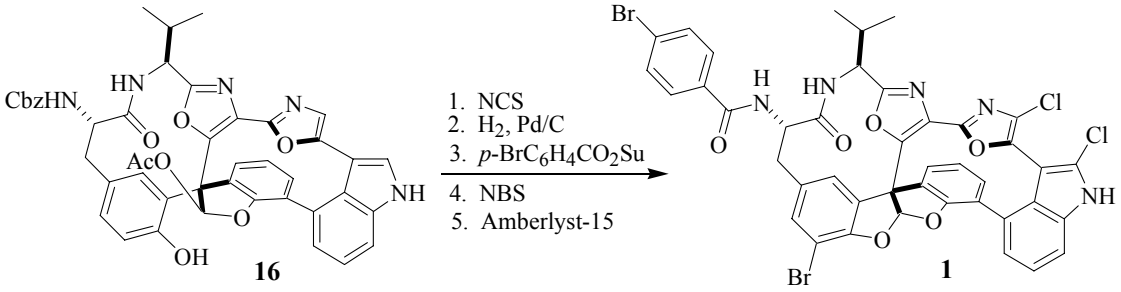
a sample of natural (-)-diazoanmide A in several respects, most notably its stability to handling and mobility on a thin-layer chromatography plate.

Scheme 1.2.3



In an effort to better understand the unexpected difference between their synthetically prepared material and natural diazonamide A, the Harran group also prepared the *p*-bromobenzamide derivative of diazonamide B (**1**) whose crystallographic characterization formed the basis of the initial diazonamide structural assignments. Conversion of **16** proceeded without incident to afford **1** via the five step sequence shown in Scheme 1.2.4. Once again, the synthetic material proved subtly different from the material derived from natural (-)-diazonamide B.[2]

Scheme 1.2.4



Now convinced that their synthetically prepared material of the originally reported diazonamide A structure was not consistent with the physical and spectroscopic data available for natural diazonamide A, Harran and co-workers began to carefully reexamine the original characterization procedure and data.[7] Most telling was that acid digest of diazonamide A did not produce valine as would be expected, suggesting that the C(2) diazonamide A side chain might have been misassigned. Careful inspection of NMR spectroscopic data of the natural material suggests that the C(2) side chain incorporates a hydroxyl group rather than an amino group as originally assigned.

In order to make this change from a NH_2 group to an OH group requires adjustment somewhere else in the molecule to account for the 1 Dalton increase in molecular mass. Returning to diazonamide B, Harran realized that the exact mass of 743.0340 for diazonamide B is more consistent with the formula $C_{35}H_{25}N_6O_4Cl_2Br$ ($[M^+ + H]$ = 743.0576) than the mass and formula $C_{35}H_{26}N_5O_6Cl_2Br$ ($[M+H]^+ - H_2O$ = 744.0416) originally assigned to diazonamide B by Fenical and Clardy. Therefore, Harran and co-workers reasoned that a protonated nitrogen must have been mistaken for an oxygen in the originally proposed structure.

The location of the misassigned atom became readily apparent upon examination of the X-ray crystallographic data of the original diazonamide B acetal moiety. Specifically, the observed length of the C(17)-O(3) bond (1.433Å) is significantly longer than the maximal value (1.409Å) observed for similar bond types. In addition, the O(3) atom displayed large thermal motion suggestive of an atom with fewer electrons and a larger covalent radius. Therefore, based on all the above data and a final conclusive ^{1}H-^{15}N correlation spectrum (HSQC) of diazonamide A, Harran et al. proposed the revised structures of diazonamide A (**18**) and B (**17**) shown in Figure 1.2.1.[7] In these revised structures the C(11) hemiacetal is assigned as a diaryl aminal and in diazonamide A the valine side chain is replaced by L-α-hydroxy isovaleric acid.

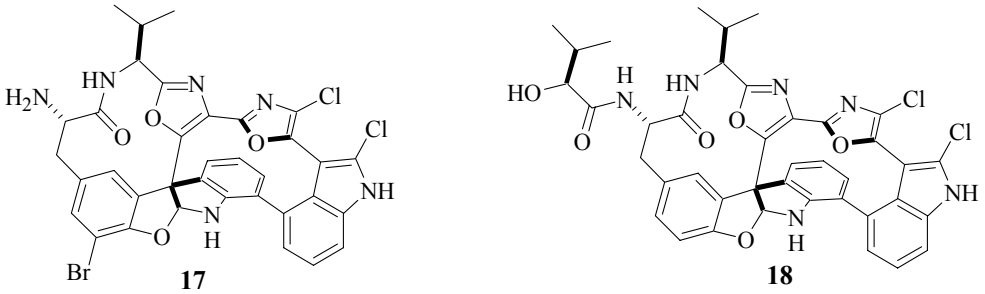


Figure 1.2.1 Harran's Revised Structures of Diazonamide A and Diazonamide B.

To further validate their structural assignment and gain additional insight into the biological activity of the diazonamides, Harran and co-workers prepared diazonamide analogs **19** and **20**.[7] In both molecules the newly revised diazonamide aminal is replaced with an acetal moiety and **19** is appended with L-valine whereas **20** is appended with L-α-hydroxy isovaleric acid. Alcohol **20** is > 50-fold more potent than amine **19** at inhibiting the growth of ovarian adenocarcinoma OVCAR-3 in vitro. Additionally, **20** is equipotent to natural diazonamide A in the same assay. Compound **20** was also shown to

be an antimitotic agent with potency similar to positive antimitotic controls Taxol and vinblastine. Further biological studies with diazonamide A functional equivalent **20** are currently ongoing in the Harran laboratories.

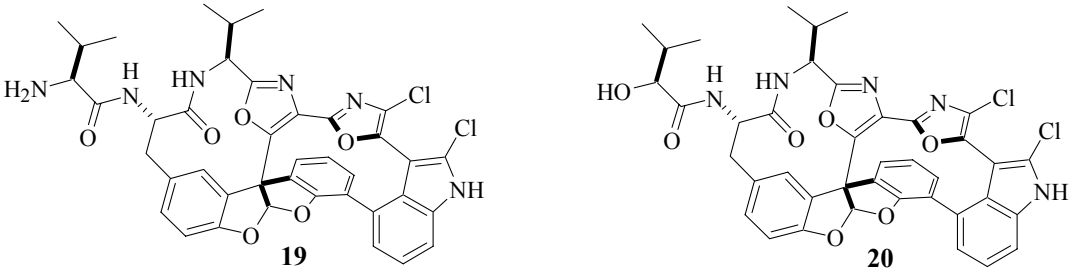


Figure 1.2.2 Harran's Synthetically Prepared Diazonamide A Analogs.

Finally, the Harran structural revision suggests a more plausible biosynthetic origin of the diazonamides.[7] It now appears that the diazonamide A polycyclic core is composed of four natural amino acids, wherein an oxidized 4,7-linked ditryptophan moiety is coupled to a tyrosine residue via an oxidative cyclization.

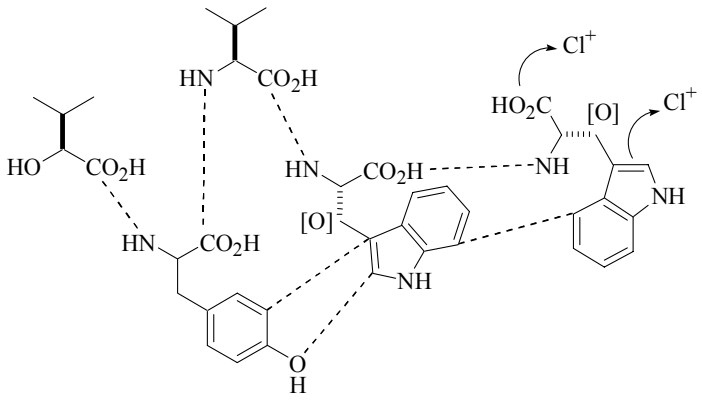
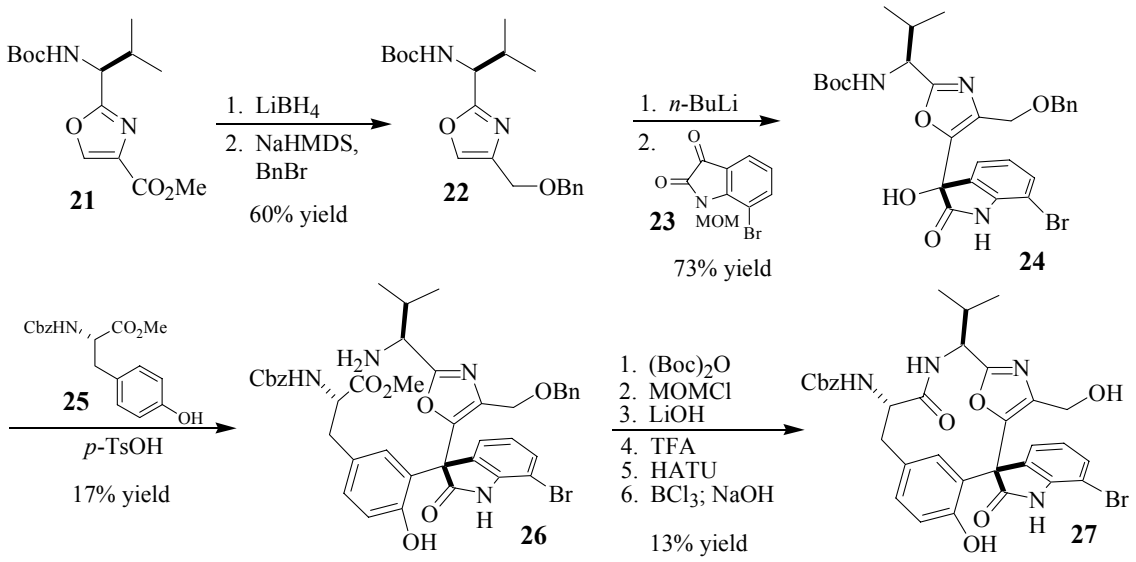


Figure 1.2.3 The Plausible Diazonamide A Biosynthetic Origin Proposed by Harran.

1.2.2.2 Nicolaou's Total Synthesis of Diazonamide A

Ten months after Harran published the revised structure of diazonamide A, the Nicolaou group at Scripps reported the first total synthesis of the revised diazonamide A structure.[8] Their synthesis commenced with reduction and protection of known oxazole **21** to afford benzyl ether **22**. Formation of the dianion of **22** followed by addition to isatin **23** furnished tertiary alcohol **24**. Construction of the diazonamide C(10) quaternary center was accomplished by refluxing **24** in the presence of tyrosine **25** under acidic conditions to furnish amine **26**. Subsequent functional group manipulations followed by macrolactamization provides the left hand diazonamide macrocycle (**27**).

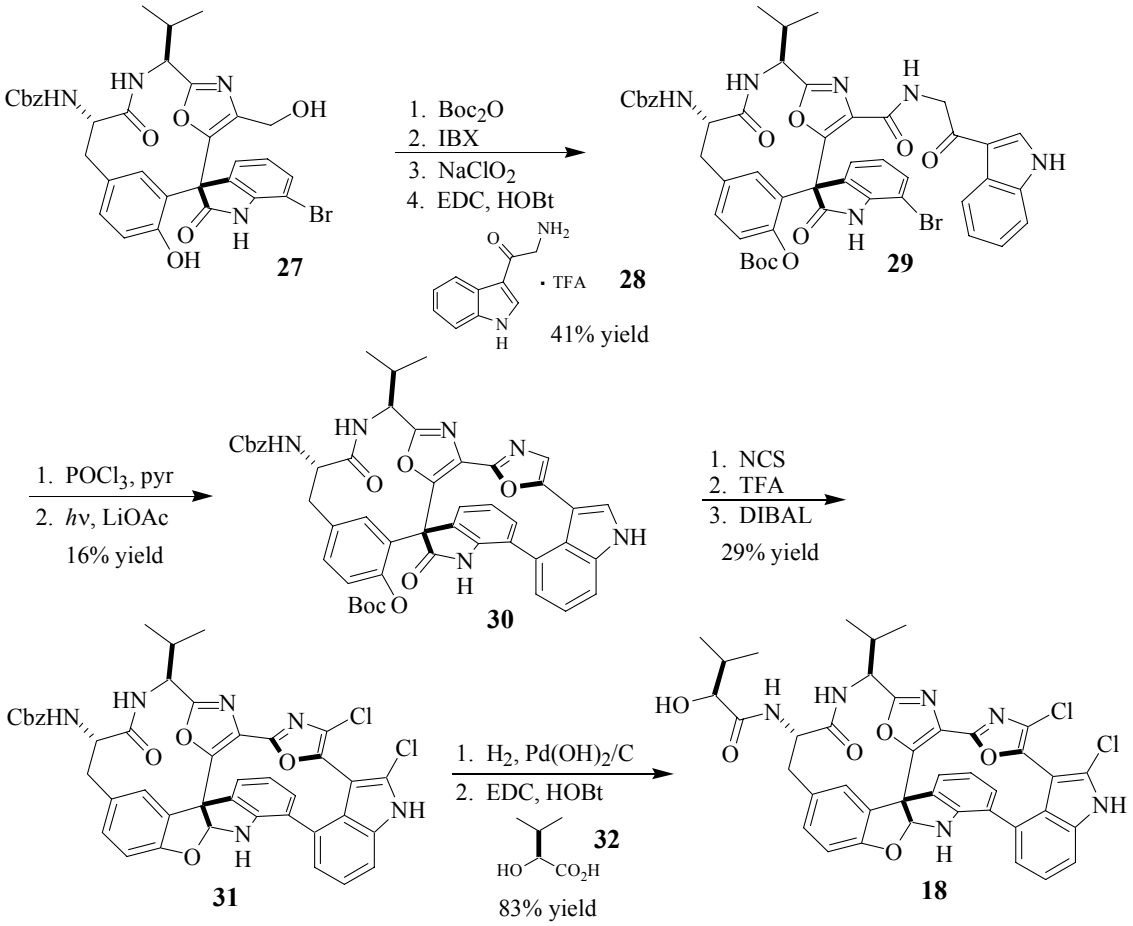
Scheme 1.2.5



At this point, completion of diazonamide A was straightforward based on the work of Harran. Boc protection, oxidation, and coupling of indole **28** to **27** yielded keto-amide **29**. Cyclodehydration and Witkop-type reation of **29** gave rise to biaryl **30**. Chlorination and phenol deprotection of **30** set the stage for aminal formation which was

accomplished with DIBAL reduction to afford the complete diazonamide core **31**. Finally, hydrogenolysis of the Cbz group and EDC mediated coupling of **31** and isovaleric acid **32** furnished diazonamide A. Importantly, the synthetic material prepared by Nicolaou and co-workers was identical in all respects to the natural material confirming the revised structural assignment of Harran.

Scheme 1.2.6



1.2.3. Approaches Toward Diazonamide A

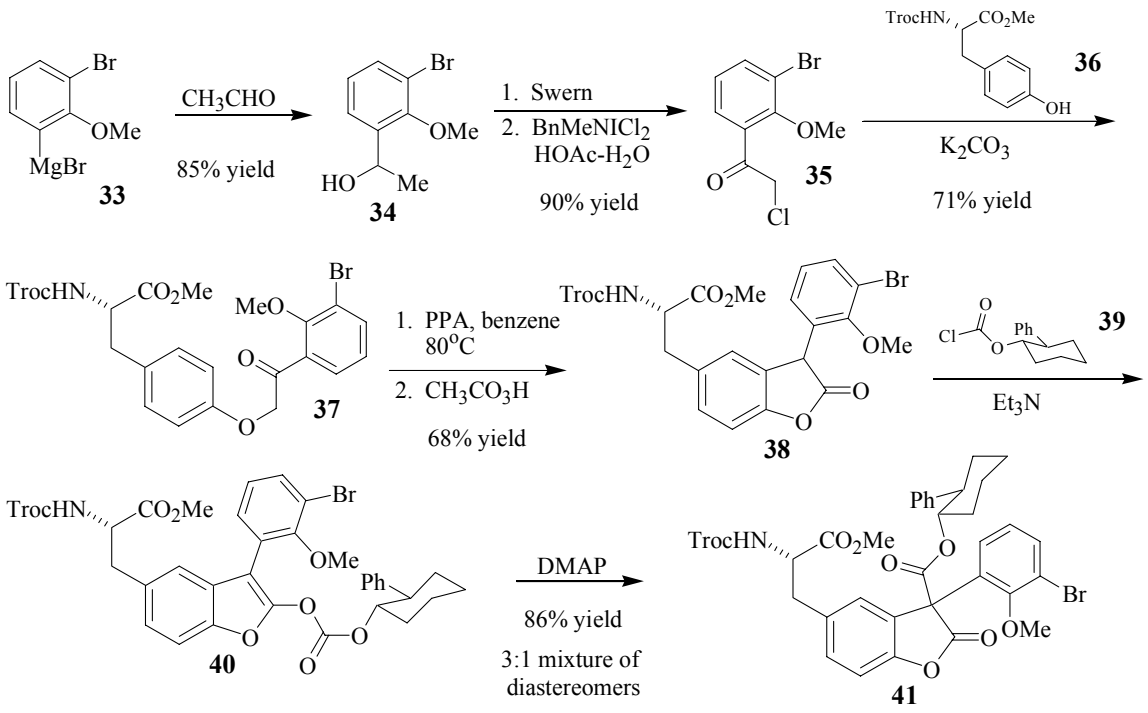
In addition to the recent total syntheses of Harran and Nicolaou numerous other synthetic groups have published approaches toward diazonamide A. All of these reported

efforts have been directed toward the initially reported structure of Fenical and Clardy and will be detailed below.

1.2.3.1 Vedejs's Approach Toward Diazonamide A

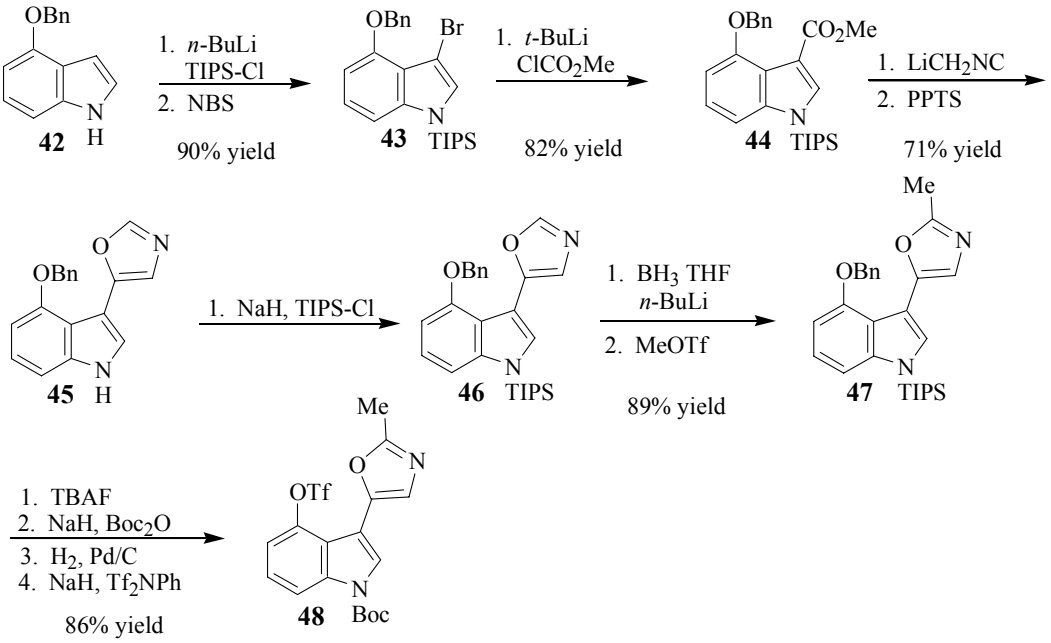
The Vedejs group, currently at the University of Michigan, has worked extensively on the synthesis of diazonamide A.[9-11] They have developed a unique approach to the diazonamide C(10) quaternary center detailed below. Addition of Grignard reagent **33** to acetaldehyde furnished alcohol **34** which was oxidized and chlorinated to provide α-chloro ketone **35**. Alkylation of **35** with tyrosine **36** gave ketone **37**. Benzofuran formation of **37** followed peracetic acid oxidation afforded benzofuranone **38**. Finally, formation of the quaternary center was achieved by acylation of **38** with chiral auxiliary **39** to yield carbonate **40** which underwent smooth O→C acyl migration to rearranged product **41** as a 3:1 mixture of diastereomers.

Scheme 1.2.7



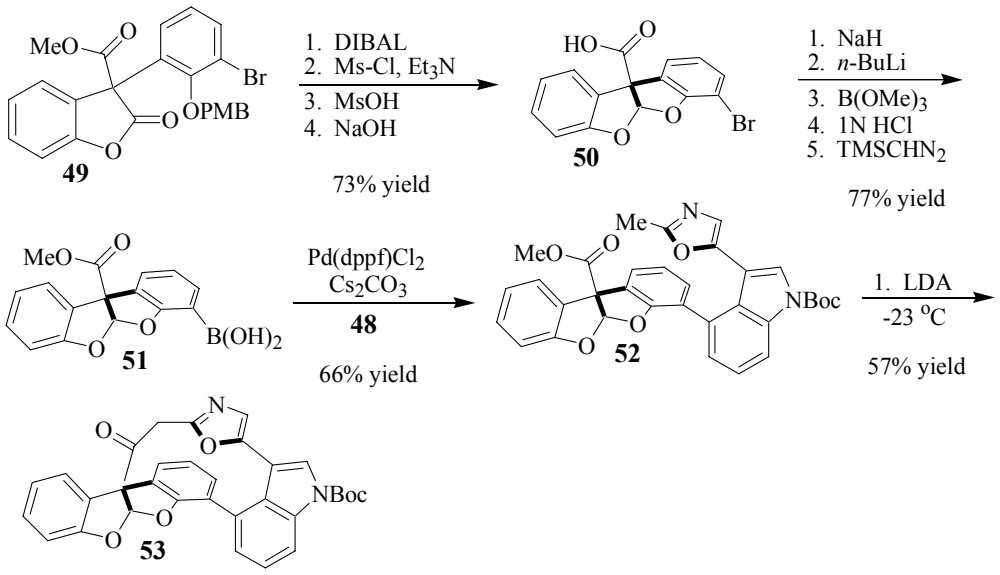
Vedejs and co-workers have also developed a unique synthesis of the indole oxazole portion of diazoanamide A. Protection of known indole **42** with TIPS-Cl and NBS mediated bromination provided bromide **43**. Transmetaltion of **43** and quenching of the anion with methyl chloroformate furnished ester **44**. Schollkopf reaction of **44** followed by mild acidic workup afforded oxazole **45**. Reprotection of **45** gave silylamine **46** which underwent smooth methylation to yield oxazole **47**. Subsequent functional group manipulation gave rise to triflate **48**.

Scheme 1.2.8



With **48** in hand, the Vedejs group investigated the construction of the right-hand macrocycle of diazonamide A. Lactone **49**, prepared as described previously, was first transformed to acetal **50**. Further functional group manipulation afforded boronic acid **51**. Palladium mediated Suzuki reaction of **51** with triflate **48** gave rise to macrocycle precursor **52**. Finally, treatment of **52** with LDA induced a Dieckmann-type cyclization to afford macrocylcic ketone **53** as a single atropdiasteremoer.

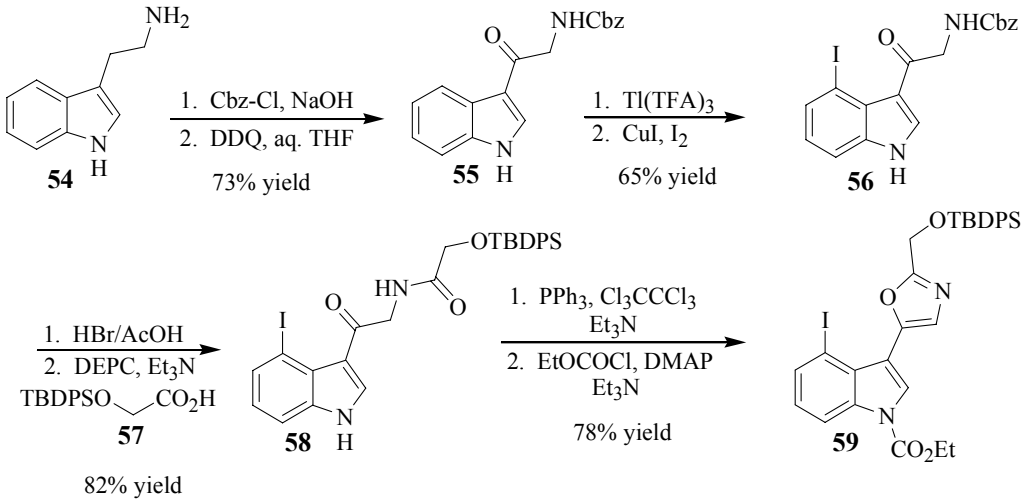
Scheme 1.2.9



1.2.3.2 Wipf's Approach Toward Diazonamide A

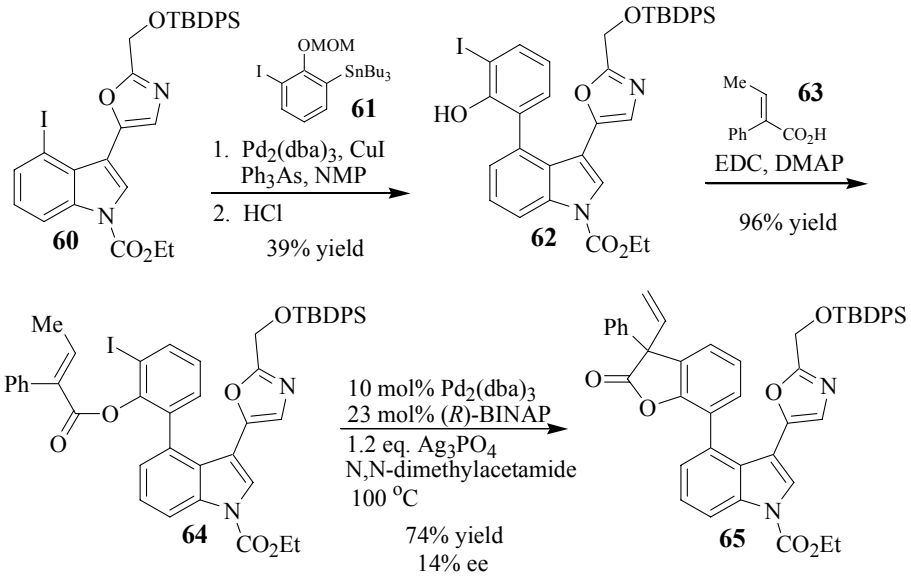
At the University of Pittsburgh, Peter Wipf and co-workers have also conducted research directed toward the total synthesis of diazonamide A.[12,13] Starting with tryptamine (**54**), DDQ oxidation and Cbz protection provided ketone **55**. Thallium mediated functionalization of the indole C(4) position of **55** ultimately furnished iodoindole **56**. Deprotection of **56** and coupling with acid **57** afforded amide **58**. Cyclodehydration of **58** using the robust procedure previously developed in Wipf labs yielded indole oxazole **59** after protection with ethyl chloroformate.[14]

Scheme 1.2.10



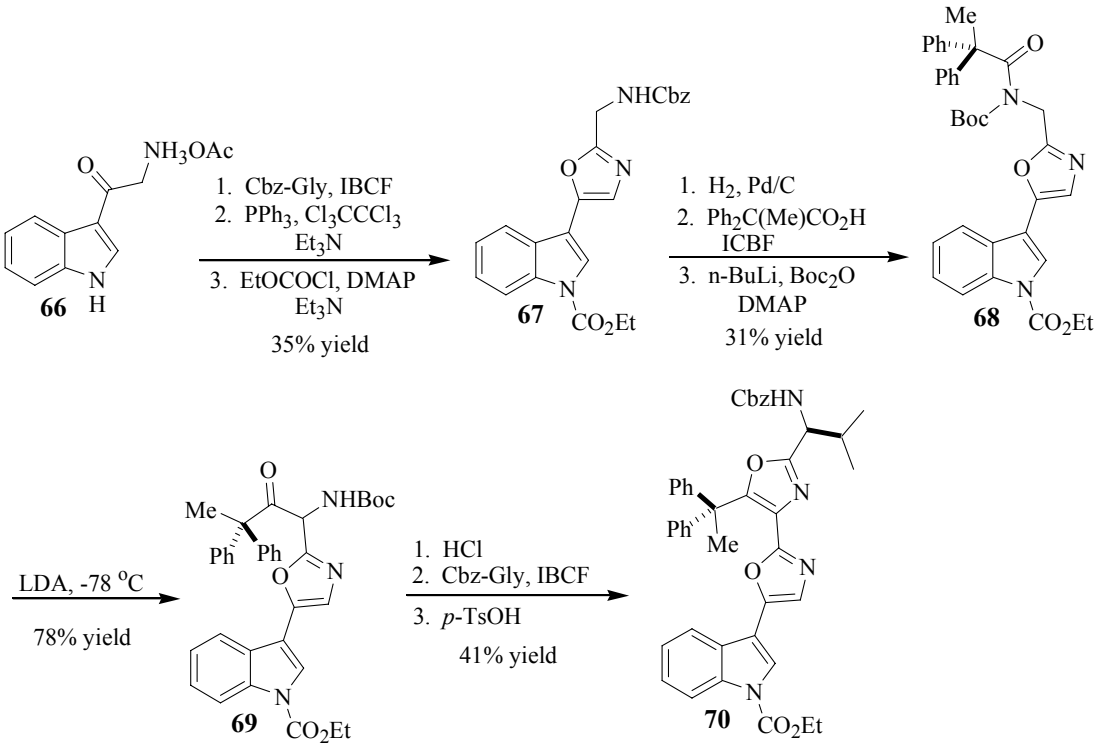
With **59** in hand, attention focused on construction of the diazonamide A quaternary center. Coupling of **60** with stannane **61** under palladium catalyzed conditions followed by MOM group deprotection furnished phenol **62**. Coupling of **62** to acid **63** afforded olefin **64** and set the stage for quaternary center formation. After considerable experimentation it was found that **64** underwent palladium mediated Heck cyclization to provide lactone **65** in good yield with poor enetioselectivity.

Scheme 1.2.11



Finally, the Wipf group has developed an approach to the diazonamide bisoxazole fragment. Synthesis of oxazole **67** from ketone **66** proceeded by the cyclodehydration sequence described previously. Hydrogenolysis and coupling to $Ph_2(Me)CCO_2H$, followed by amide protection yielded imide **68**. Treatment of **68** with LDA induced Chan rearrangement to aminoketone **69**. Conversion of **69** to bisoxazole **70** was accomplished by Boc group cleavage, coupling with N-Cbz-valine, and acid-mediated cyclodehydration.

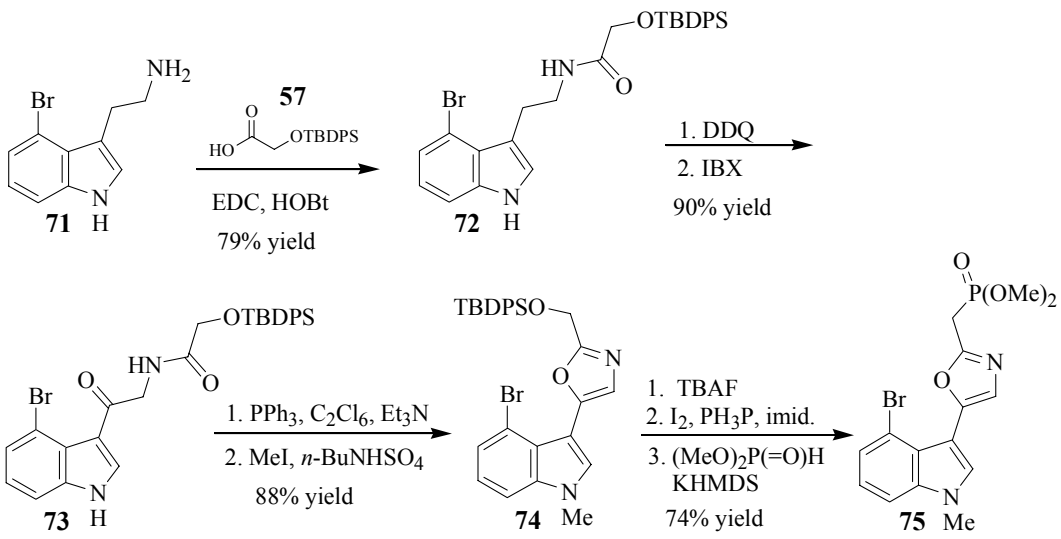
Scheme 1.2.12



1.2.3.3 Nicolaou's Approach Toward Diazonamide A

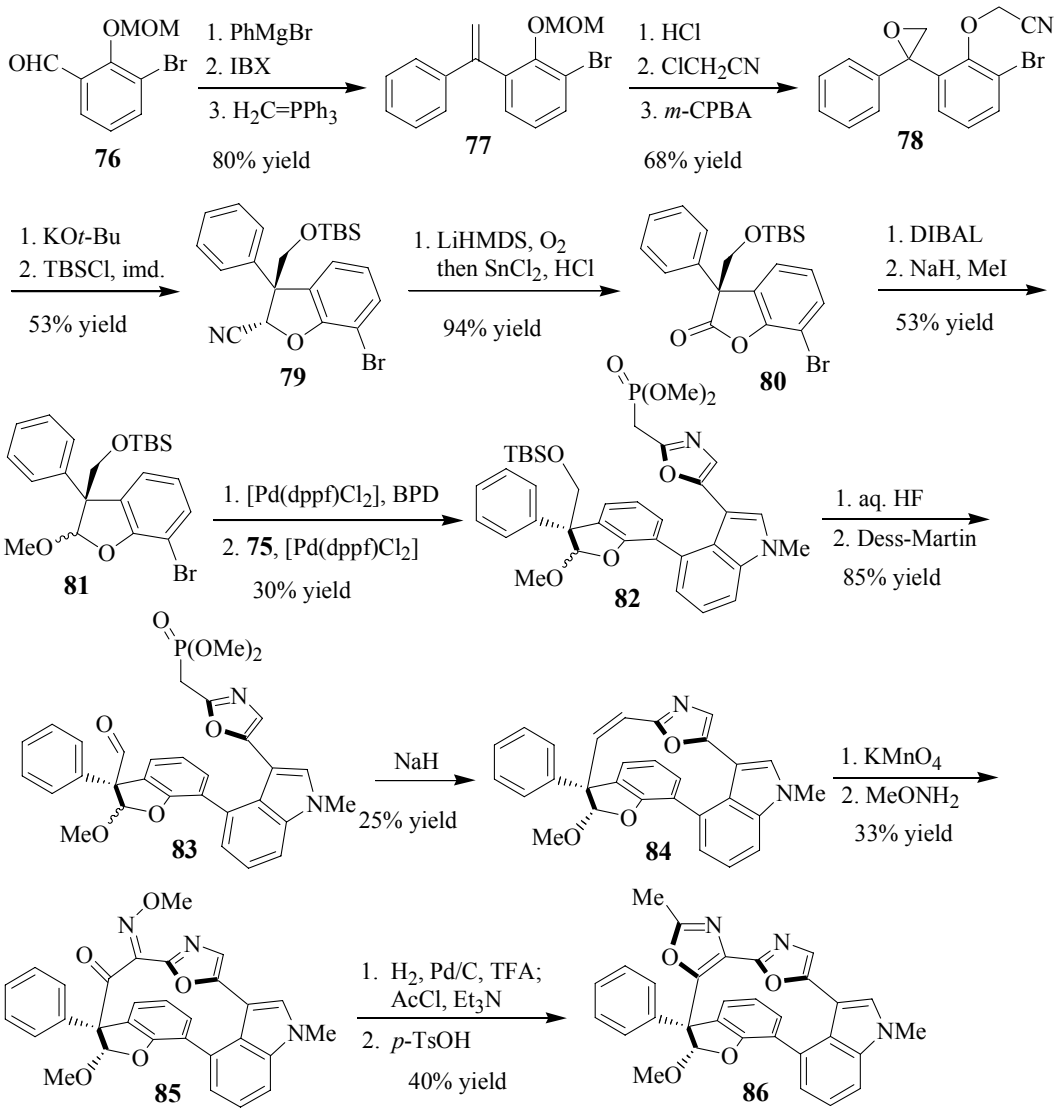
In addition to their previously described total synthesis Nicolaou and co-workers have reported on their approach to the initial diazonamide A structure.[15,16] The Nicolaou synthesis of the diazonamide indolyl oxazole segement closely mirrors the route published earlier by Wipf. Coupling of tryptamine **71** with acid **57** afforded amide **72** which underwent DDQ and IBX oxidation to ketone **73**. Cyclodehydration of **73** and methylation gave rise to oxazole **74**. Subsequent functional group manipulation of **74** yielded phosphonate **75** in three steps.

Scheme 1.2.13



Continuing with their approach, aldehyde **76** was converted to olefin **77** by phenyl Grignard addition, IBX oxidation, and Wittig olefination. Deprotection of **77**, epoxidation, and alkylation with chloroacetonitrile provided quaternary center precursor **78**. Treatment of **78** with KO*t*-Bu induced selective 5-exo-tet opening of the epoxide ring to afford dihydrobenzofurn **79** after protection of the primary alcohol. Oxidation of **79** to lactone **80** followed by DIBAL reduction and methylation provided hemi-acetal **81**. Formation of the diazonamide biaryl bond was next accomplished by sequential palladium catalyzed boronate ester formation and Suzuki coupling to afford intermediate **82**. Deprotection of **82** and Dess-Martin oxidation furnished aldehyde **83**. After considerable experimentation it was found that treatment of **83** with NaH smoothly led to the formation of macrocyclic olefin **84** as a single diastereomer. The final proof of principle in this approach is construction of the central diazonamide oxazole by conversion of **84** to ketone **85** which was successfully parlayed to bisoxazole **86** in two steps.

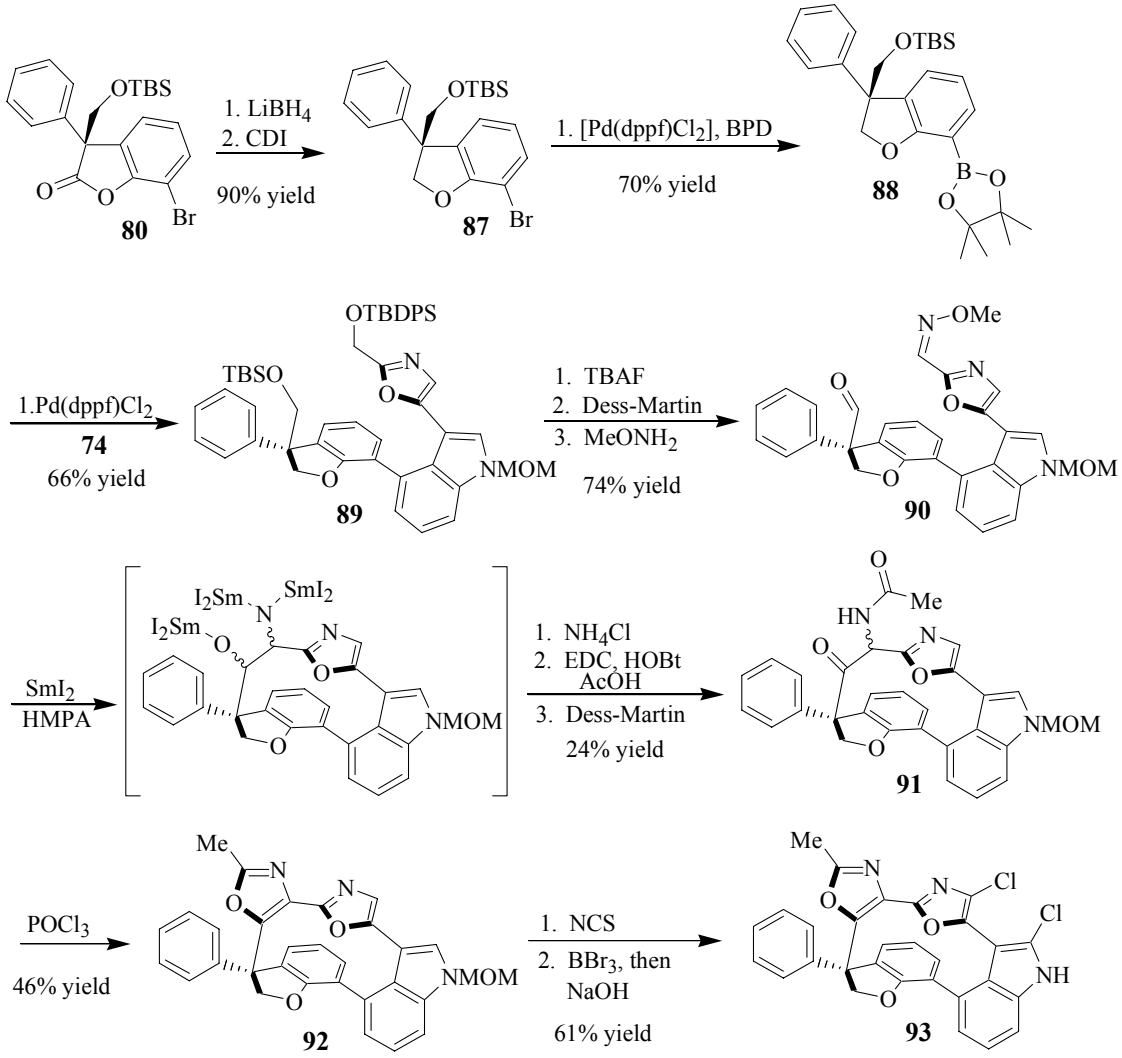
Scheme 1.2.14



Similar to the sequence described above, Nicolaou reported a complimentary approach to the diazonamide right-hand macrocycle. Elaboration of **80** to aldehyde-oxime **90** over seven steps sets the stage for a hetero pinacol macrocyclization. Treatment of **90** with a premixed complex of SmI_2 and HMPA, followed by quenching with aqueous NH_4Cl, peptide coupling with acetic acid, and Dess-Martin oxidation yielded amino ketone **91** in 24% overall yield. Formation of the central oxazole was

accomplished with $POCl_3$ to afford **92** which was finally chlorinated and MOM deprotected to ultimately provide advanced macrocycle **93**.

Scheme 1.2.15

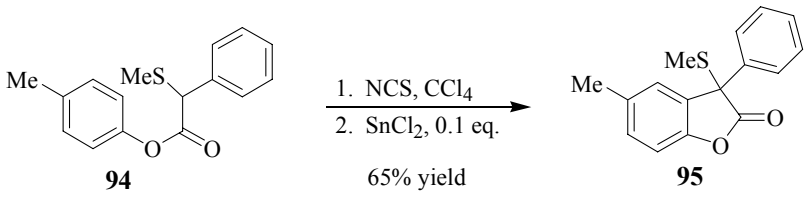


1.2.3.4 Magnus's Approach Toward Diazonamide A

The Magnus group at the University of Teaxas at Austin has published extensively on their approach to diazonamide A.[17-20] Their first paper deals with the construction of benzofuranones relevant to the initial diazonamide A structure with ionizable groups at the bisbenzylic position. Chlorination of ester **94** gave an

intermediate chloride that upon treatment with catalytic $SnCl_4$ afforded benzofuranone **95**. Importantly, the remaining thiomethyl group provides a handle to explore radical or cationic carbon-carbon bond forming reactions.

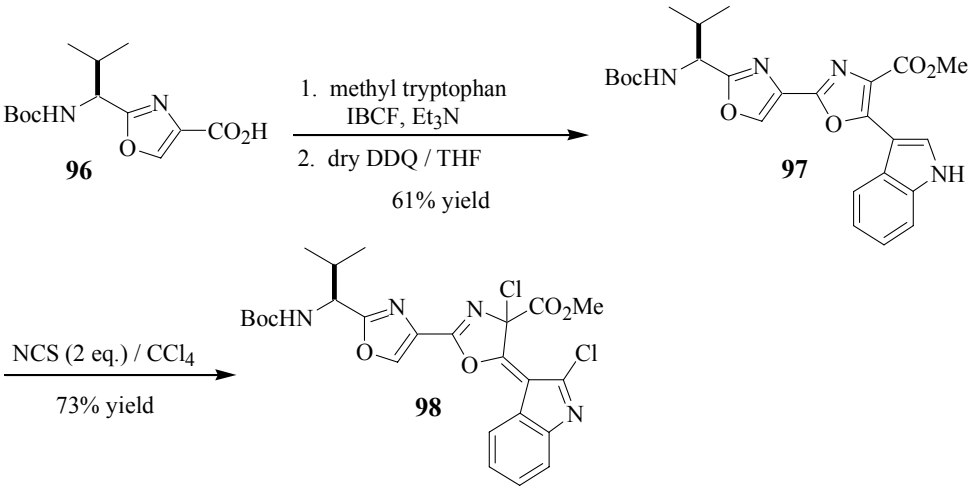
Scheme 1.2.16



94 **95**

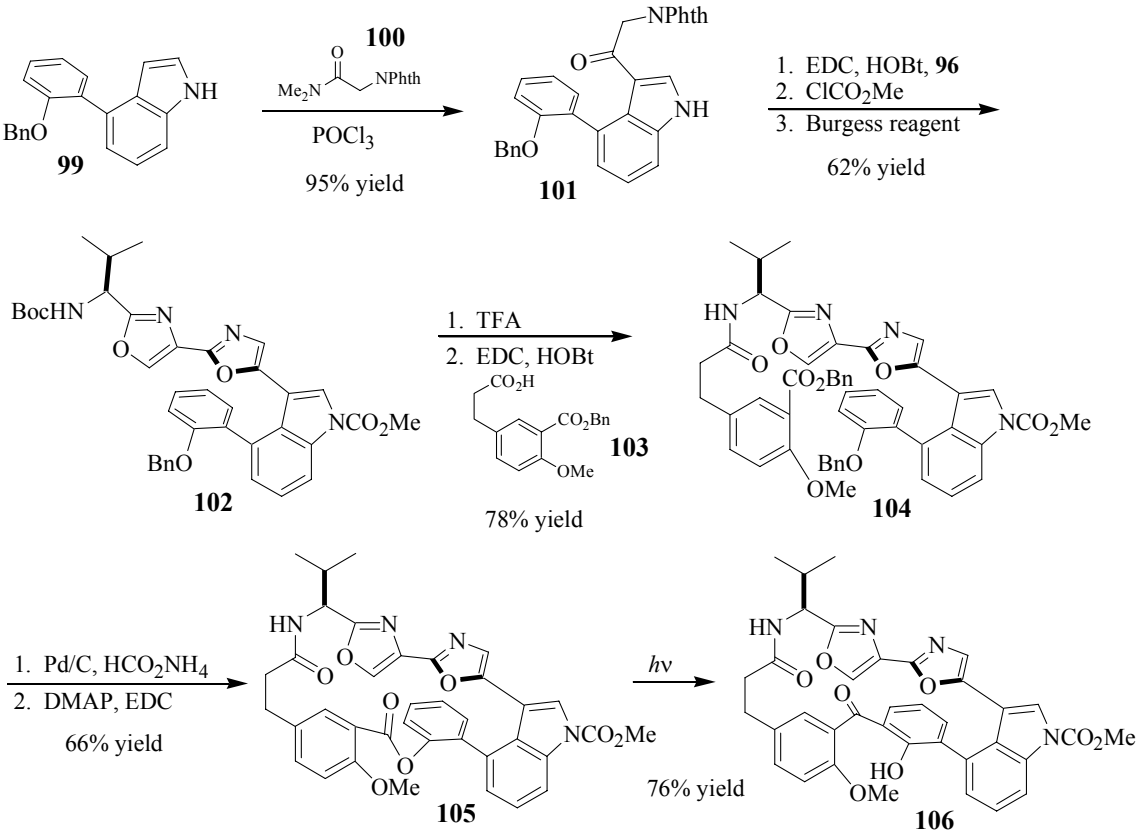
The synthesis of the indolyl oxazole portion of diazonamide A has been extensively published and by far the most used approach to this subunit has been the oxidation of a tryptamine amide followed by cyclodehydration. While Magnus and co-workers have also published on this approach, they first investigated a more efficient and perhaps biomimetic sequence. Coupling of oxazole **96** to methyl tryptophan and treatment with dry DDQ induced tandem oxidation and cyclodehydration in the same pot to furmish bisoxazole indole **97**. Unfortunately, chlorination of **97** led to indolenine **98** which could not be advanced to the desired aromatic system.

Scheme 1.2.17



The most recent report from the Magnus group describes the synthesis of macrocycle **106**. Indole **99** is first acylated under Vilsmeier-like condition with amide **100** to provide ketone **101**. Conversion of **101** proceeded without incident to afford bisoxazole iondole **102**. Deprotection of **102** and coupling to acid **103** gave amide **104** which, after deprotection, underwent smooth macrolactonization to macrolactone **105**. Irradiation of **105** with UV light induced photo-Fries rearrangement to furnish diazonamide core skeleton **106**.

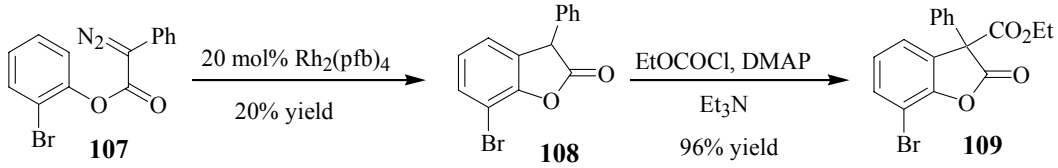
Scheme 1.2.18



1.2.3.5 Moody's Approach Toward Diazonamide A

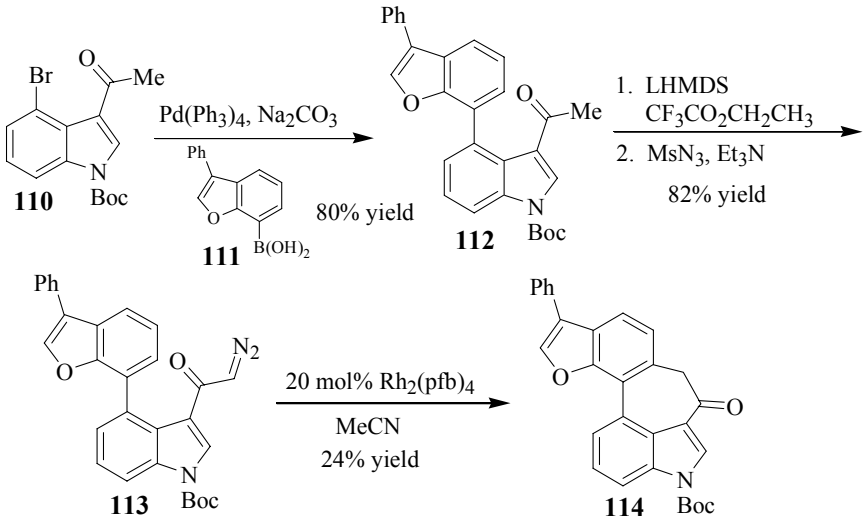
The Moody group at the University of Exeter in England has developed approaches to several diazonamide fragments.[21-25] Their first published report focused on the use of carbeniod chemistry wherein α-diazo ester **107** underwent rhodium (II) catalyzed C-H insertion to benzofuranone **108** in poor yield. Acylation of **108** and DMAP catalyzed rearrangement afforded ester **109** according to the procedure of Black.

Scheme 1.2.19



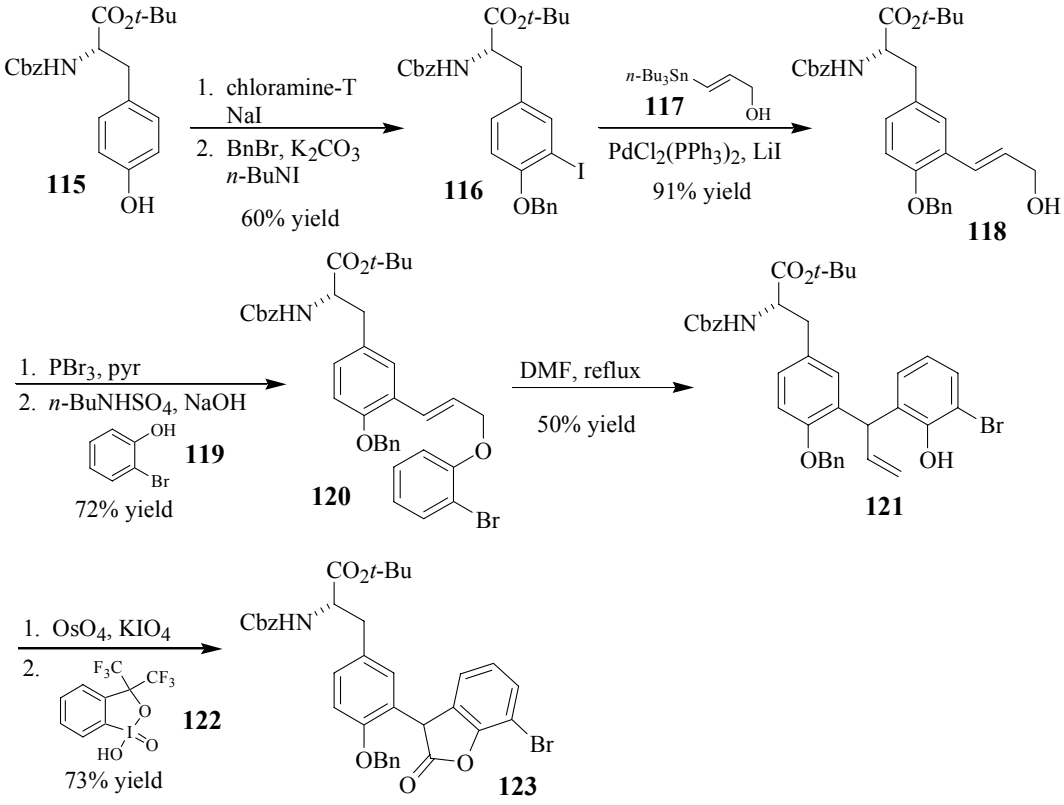
Suzuki coupling of bromide **110** with boronic acid **111** yielded biaryl **112** which was converted to α-diazo ketone **113** using Danheiser's modified diazo-transfer procedure. Unfortunately, treatment of **113** with $Rh_2(pfb)_4$ in acetonitrile solvent resulted in none of the desired oxazole, but instead resulted in aryl C-H insertion product **114**.

Scheme 1.2.20



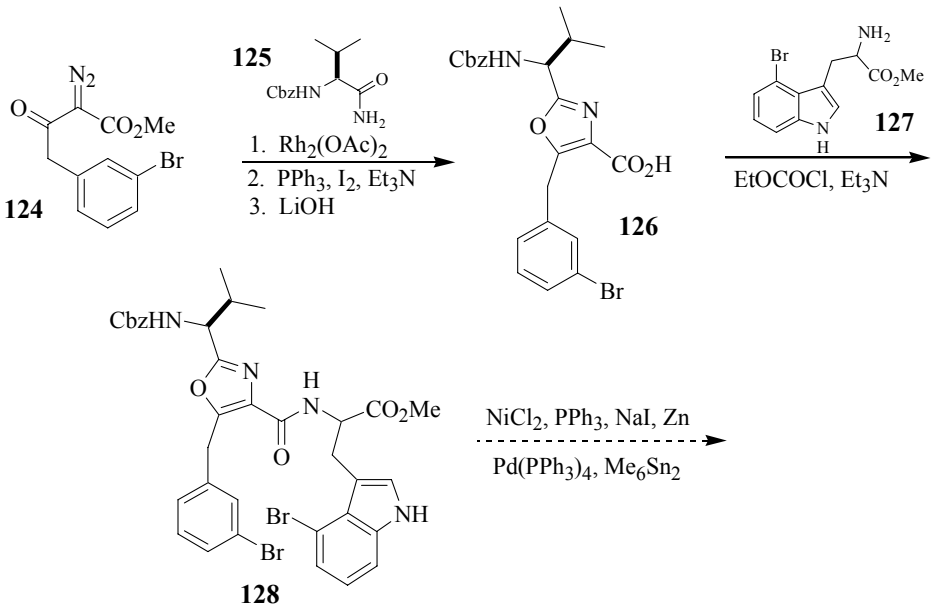
In an attempt to retool their synthesis, Moody and co-workers developed the following synthesis of the diazonamide tyrosine fragment. Iodination of **115** and protection of the free phenol furnished tyrosine **116** which participated in Stille coupling with stannane **117** to afford allylic alcohol **118**. Bromination of **118** and alkylation of 2-bromophenol (**119**) gave cinnamyl aryl ether **120** that underwent Claisen rearrangement to phenol **121**. Final oxidative cleavage of **121** and oxidation with iodinane oxide **122** yielded the desired lactone **123** in good yield.

Scheme 1.2.21



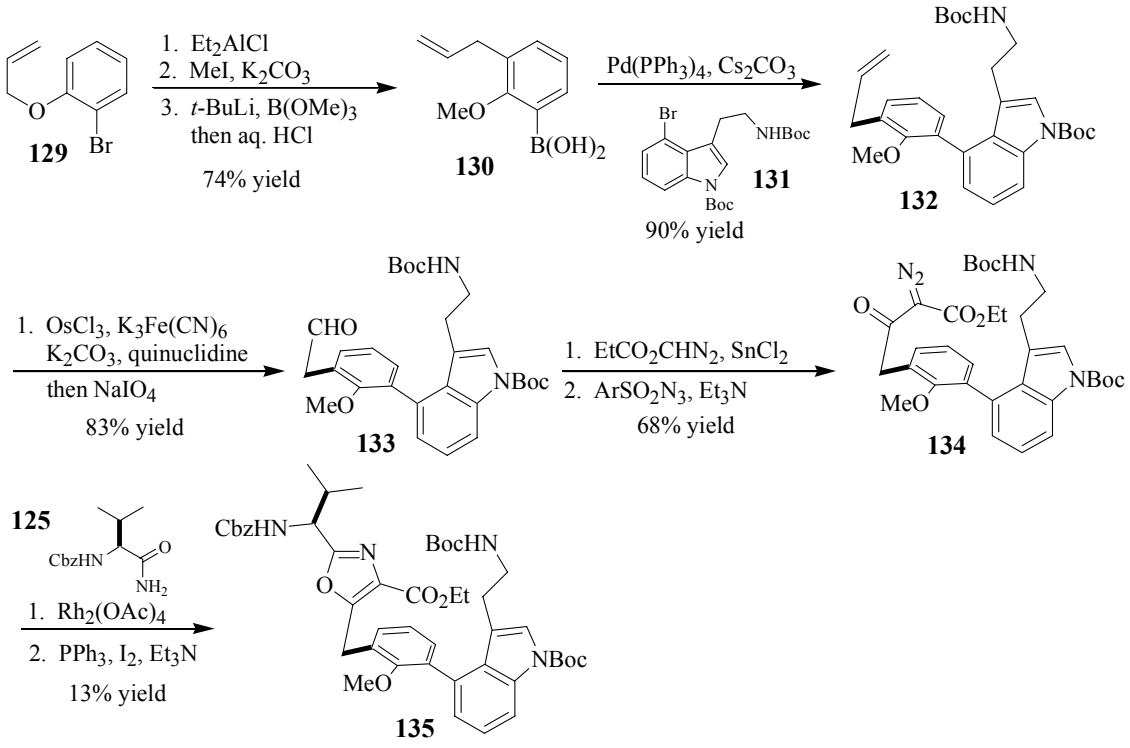
Shifting their attention to construction of the right-hand diazonamide macrocycle, α-diazo-β-ketoester **124** underwent rhodium (II) catalyzed N-H insertion into primary amide **125** followed by cyclodehydration and ester hydrolysis to provide acid **126**. Coupling of **126** with tryptophan **127** gave the dibromo compound **128**. Unfortunately, all attempts to effect the intramolecular biaryl coupling of **128** failed to give any of the desired macrocycle.

Scheme 1.2.22



Not deterred by their inability to construct the diazonamide biaryl bond in a intramolecular fashion, the Moody group focused on construction of this bond by an intermolecular cross coupling reaction. Toward this end, bromide **129** was converted to boronic acid **130**, which underwent facile Suzuki cross-coupling with indole **131** to form biaryl **132**. Subsequent functionalization of **132**, as described previously, ultimately gave the highly functionalized 4-aryltryptamine fragment of diazonamide **135**.

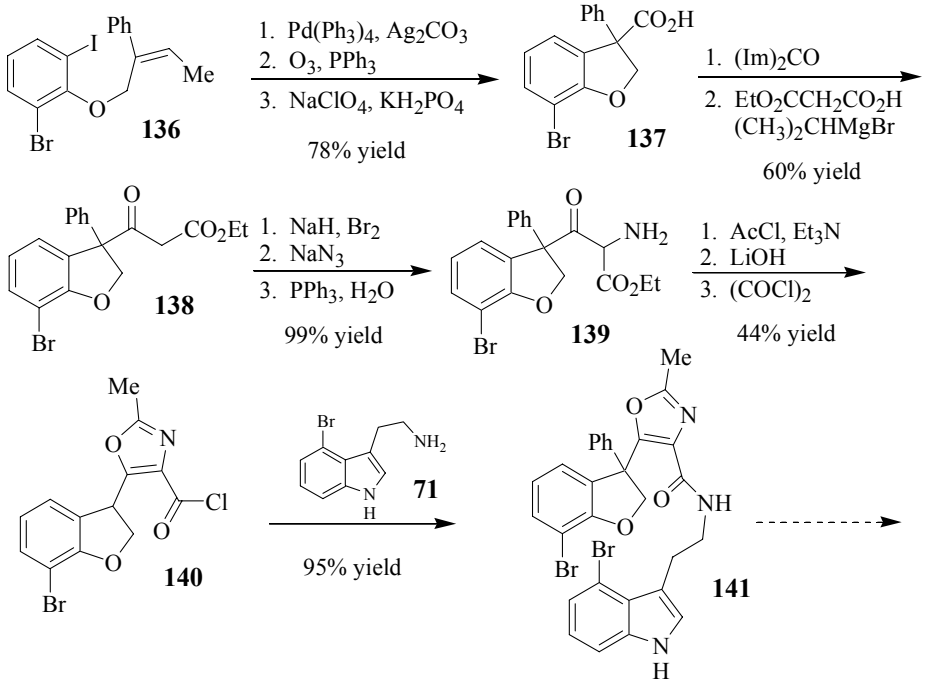
Scheme 1.2.23



1.2.3.6 Pattenden's Approach Toward Diazonamide A

In 1998 the Pattenden group at Nottingham University reported an approach to diazonamide A.[26] Their synthesis begins with Heck reaction and oxidative ozonolysis of **136** to afford acid **137**. Homologation of **137** to β-keto ester **138** followed amination gave rise to amine **139**. Acylation of **139** and *in situ* Hantzch cyclization furnished oxazole **140** after ester hydrolysis and acid chloride formation. Coupling of **140** to tryptamine **71** provided dibromo **141** which unfortunately failed to undergo biaryl coupling.

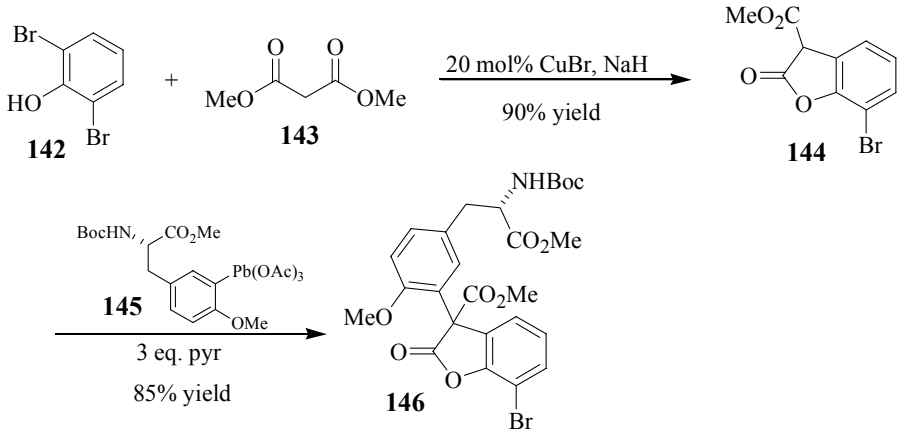
Scheme 1.2.24



1.2.3.7 Konopelski's Approach Toward Diazonamide A

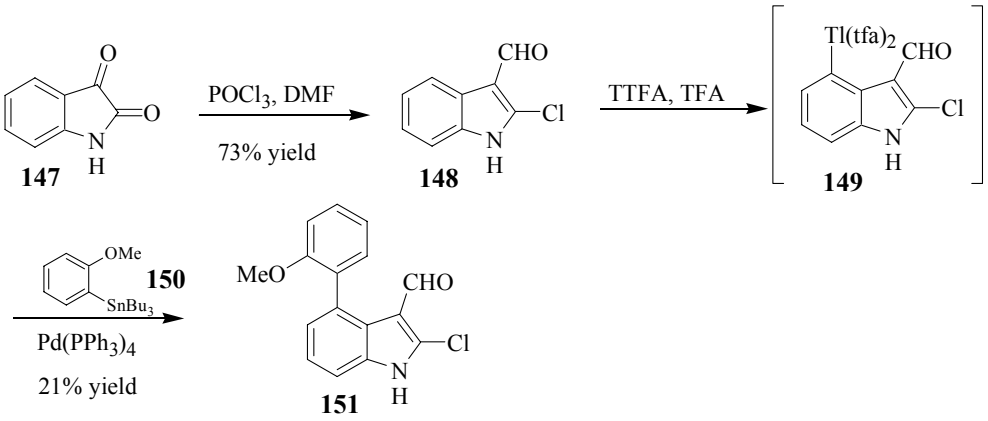
Konopelski and co-workers at the University of California, Santa Cruz have reported the approach to various diazonamide A fragments.[27] Treatment of phenol **142** and malonate **143** with NaH and catalytic copper bromide provides efficient access to benzofuranone **144**. Exposure of **144** to aryllead reagent **145** under basic conditions affords quaternary center containing lactone **146** in good yield as an unreported mixture of diastereomers.

Scheme 1.2.25



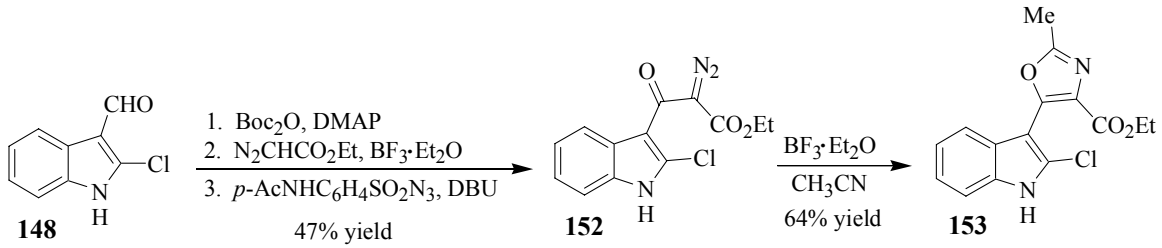
Investigation into the construction of the diazonamide biaryl bond begins with conversion of isatin (**147**) to indole **148** in good yield. Thalliation at the indole C(4) position furnishes intermediate **149** which undergoes palladium mediated coupling with stannane **150** to furnish biaryl **151**.

Scheme 1.2.26



Finally, Konopelski reported an approach to the oxazolylindole portion of diazonamide A starting by the synthesis of α-diazo-β-ketoester **152** from **148**. Treatment of **152** with $BF_3 \cdot Et_2O$ in acetonitrile solvent produced desired indole oxazole **153**.

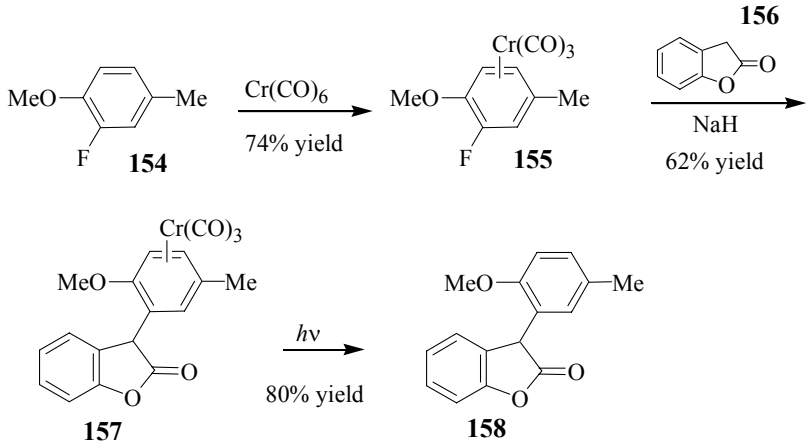
Scheme 1.2.27



1.2.3.8 Liebscher's Approach Toward Diazonamide A

One of the most recent diazonamide A literature reports has come from the Liebscher group in Germany.[28,29] Their approach begins with the treatment of **154** with hexacarbonylchromium to afford complex **155**. Reaction of **155** with the sodium enolate of lactone **156** furnished arylated product **157** wich was decomplexed to benzofuranone **158**.

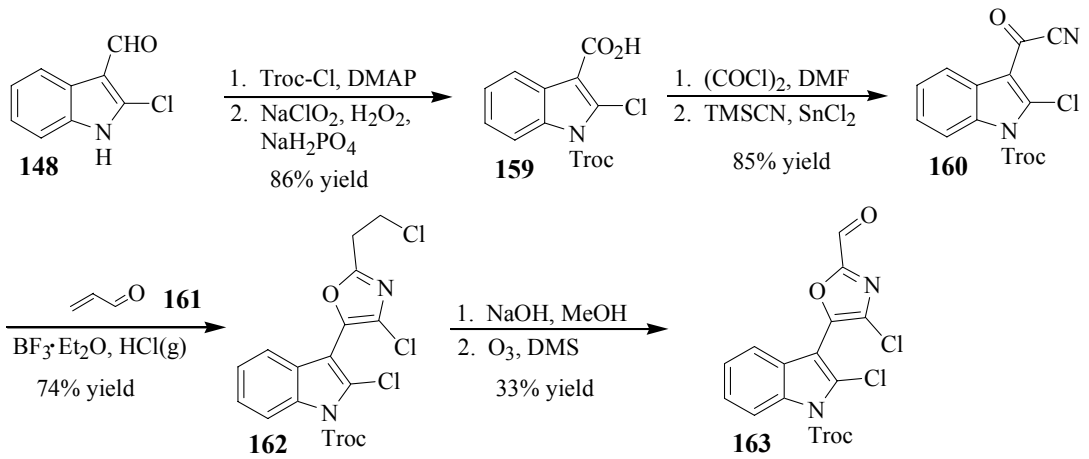
Scheme 1.2.28



Liebscher and co-workers also published their efforts toward the diazonamide indolyl oxazole fragment. Aldehyde **148** was first oxidized and Troc protected to yield acid **159**. Conversion of **159** to the corresponding acyl cyanide **160** followed by reaction

with acrolein (**161**) under strongly acidic conditions furnished oxazole **162**. Final functional group manipulation of **162** ultimately afforded aldehyde **163**.

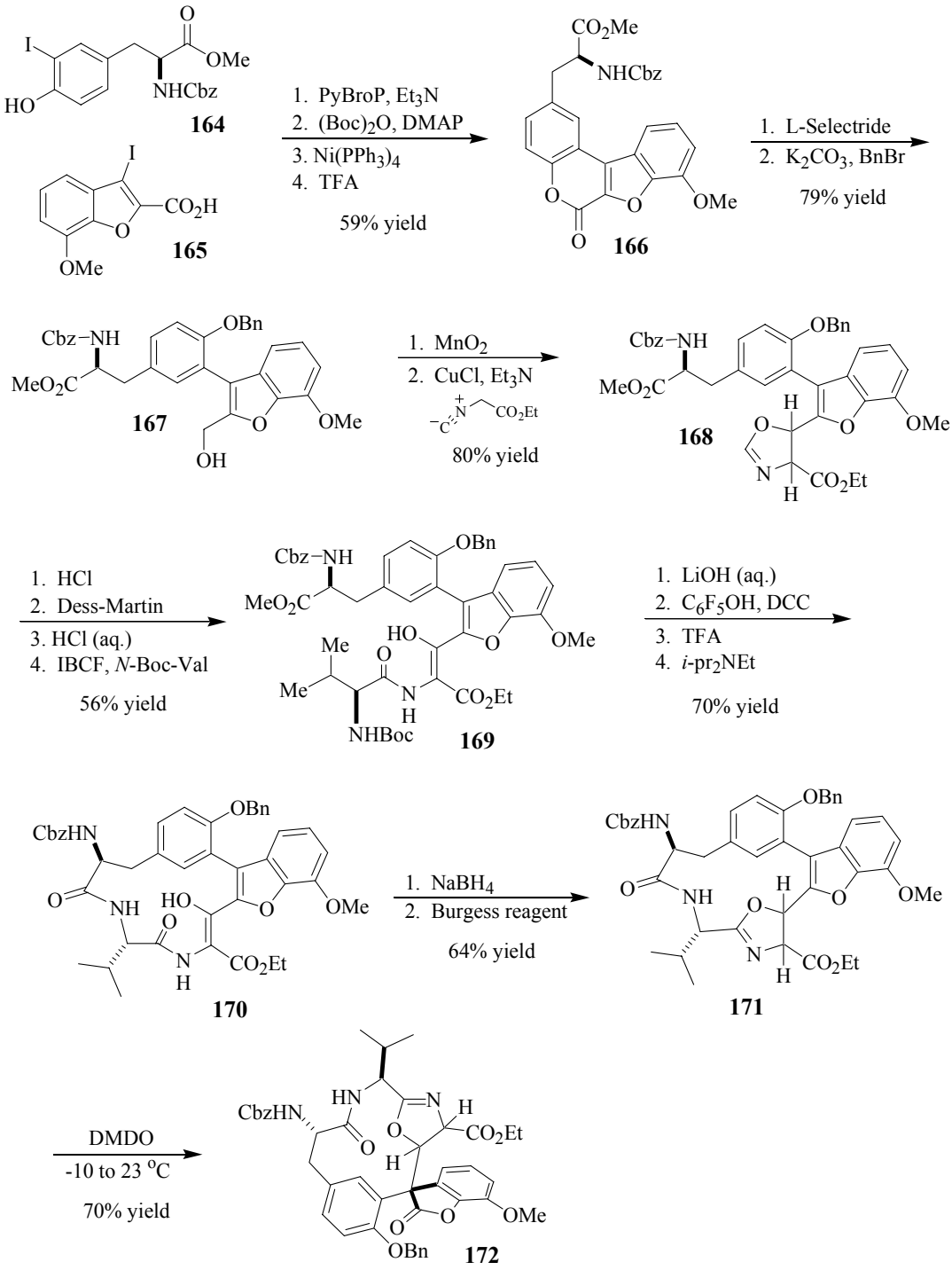
Scheme 1.2.29



1.2.3.9 Schreiber's Approach Toward Diazonamide A

While not published in the primary literature, the Schreiber group at Harvard University has revealed an approach toward diazonamide A in Timothy Jamison's doctoral thesis.[30] This approach begins with the union of tyrosine **164** and benzofuran **165** to provide lactone **166**. Reduction of **166** and selective phenol protection afforded alcohol **167** which was further elaborated to oxazoline **168**. Ring-opening and valine homologation furnished bis-amino acid **169,** that after a series of selective deprotections, smoothly underwent macrolactamization to yield macrocycle **170**. Reduction of **170** followed by reformation of the oxazoline gave rise to key intermediate **171**. Treatment of **171** with DMDO provided 3,3-disubstituted benzofuranone **172** as a single diastereomer. Unfortunately, all attempts to advance **172** by oxidation to the corresponding oxazole met with no success.

Scheme 1.2.30


1. PyBroP, Et3N
2. (Boc)2O, DMAP
3. Ni(PPh3)4
4. TFA
59% yield
1. L-Selectride
2. K2CO3, BnBr
79% yield
1. MnO2
2. CuCl, Et3N
80% yield
1. HCl
2. Dess-Martin
3. HCl (aq.)
4. IBCF, N-Boc-Val
56% yield
1. LiOH (aq.)
2. C6F5OH, DCC
3. TFA
4. i-pr2NEt
70% yield
1. NaBH4
2. Burgess reagent
64% yield
DMDO
-10 to 23 °C
70% yield
164
165
166
167
168
169
170
171
172

1.3 Notes and References

1. "Isolation and Structure Determination of Diazonamide-A and Diazonamide-B, Unusual Cytotoxic Metabolites from the Marine Ascidian Diazona-Chinensis", Lindquist N., Fenical W., Vanduyne G. D., Clardy J., *Journal of the American Chemical Society*, **1991**, *113*, 2303-2304.

2. "Total synthesis of nominal diazonamides - Part 1: Convergent preparation of the structure proposed for (-)-diazonamide A", Li J., Jeong S., Esser L., Harran P. G., *Angewandte Chemie-International Edition*, **2001**, *40*, 4765-4770.

3. "The diazonamides: The plot thickens", Ritter T., Carreira E. M., *Angewandte Chemie-International Edition*, **2002**, *41*, 2489.

4. "Macrocyclic triarylethylenes via Heck endocyclization: A system relevant to diazonamide synthesis", Jeong S., Chen X., Harran P. G., *Journal of Organic Chemistry*, **1998**, *63*, 8640-8641.

5. "Stereocontrol in pinacol ring-contraction of cyclopeptidyl glycols: The diazonamide C-10 problem", Chen X., Esser L., Harran P. G., *Angewandte Chemie-International Edition*, **2000**, *39*, 937.

6. "Synthetic seco forms of (-)-diazonamide A", Li J., Chen X., Burgett A. W. G., Harran P. G., *Angewandte Chemie-International Edition*, **2001**, *40*, 2682-2685.

7. "Total synthesis of nominal diazonamides - Part 2: On the true structure and origin of natural isolates", Li J., Burgett A. W. G., Esser L., Amezcua C., Harran P. G., *Angewandte Chemie-International Edition*, **2001**, *40*, 4770.

8. "Total synthesis of diazonamide A", Nicolaou K. C., Bella M., Chen D. Y. K., Huang X. H., Ling T. T., Snyder S. A., *Angewandte Chemie-International Edition*, **2002**, *41*, 3495-3499.

9. "A tyrosine-derived benzofuranone related to diazonamide A", Vedejs E., Wang J. B., *Organic Letters*, **2000**, *2*, 1031-1032.

10. "Progress toward synthesis of diazonamide A. Preparation of a 3- (oxazol-5-yl)-4-trifluoromethyl-sulfonyloxyindole and its use in biaryl coupling reactions", Vedejs E., Barda D. A., *Organic Letters*, **2000**, *2*, 1033-1035.

11. "Synthesis of the diazonamide A macrocyclic core via a Dieckmann-type cyclization", Vedejs E., Zajac M. A., *Organic Letters*, **2001**, *3*, 2451-2454.

12. "Synthetic studies toward diazonamide A. Preparation of the benzofuranone-indolyloxazole fragment", Wipf P., Yokokawa F., *Tetrahedron Letters*, **1998**, *39*, 2223-2226.

13. "Synthetic studies toward diazonamide A. A novel approach for polyoxazole synthesis", Wipf P., Methot J. L., *Organic Letters*, **2001**, *3*, 1261-1264.

14. "A New Synthesis of Highly Functionalized Oxazoles", Wipf P., Miller C. P., *Journal of Organic Chemistry*, **1993**, *58*, 3604-3606.

15. "Model studies towards diazonamide A: Synthesis of the heterocyclic core", Nicolaou K. C., Snyder S. A., Simonsen K. B., Koumbis A. E., *Angewandte Chemie-International Edition*, **2000**, *39*, 3473.

16. "Construction of the complete aromatic core of diazonamide A by a novel hetero pinacol macrocyclization cascade reaction", Nicolaou K. C., Huang X., Giuseppone N., Rao P. B., Bella M., Reddy M. V., Snyder S. A., *Angewandte Chemie-International Edition*, **2001**, *40*, 4705.

17. "Vilsmeier methodology for the synthesis of 3-(2-N- phthaloylacyl)indole derivatives, and its application to the synthesis of the GCDEF rings of diazonamide", Kreisberg J. D., Magnus P., McIver E. G., *Tetrahedron Letters*, **2001**, *42*, 627-629.

18. "Synthesis of benzofuranones related to diazonamide via an intramolecular Pummerer reaction", Magnus P., Kreisberg J. D., *Tetrahedron Letters*, **1999**, *40*, 451-454.

19. "Synthesis of the dichlorobisoxazole-indole portion of the antitumor agent diazonamide by a putative biogenetic strategy", Magnus P., McIver E. G., *Tetrahedron Letters*, **2000**, *41*, 831-834.

20. "Photo-Fries rearrangement for the synthesis of the diazonamide macrocycle", Magnus P., Lescop C., *Tetrahedron Letters*, **2001**, *42*, 7193-7196.

21. "Synthesis of Heterocyclic Natural-Products - Model Studies Towards Diazonamide-A", Moody C. J., Doyle K. J., Elliott M. C., Mowlem T. J., *Pure and Applied Chemistry*, **1994**, *66*, 2107-2110.

22. "Studies towards the synthesis of diazonamide A. Unexpected formation of a 3,4-bridged indole", Moody C. J., Doyle K. J., Elliott M. C., Mowlem T. J., *Journal of the Chemical Society-Perkin Transactions 1*, **1997**, 2413-2419.

23. "Studies towards the synthesis of diazonamide A. Synthesis of a tyrosine-derived benzofuranone", Lach F., Moody C. J., *Tetrahedron Letters*, **2000**, *41*, 6893-6896.

24. "Studies towards the synthesis of diazonamide A. Synthesis of the indole bis-oxazole fragment", Bagley M. C., Hind S. L., Moody C. J., *Tetrahedron Letters*, **2000**, *41*, 6897-6900.

25. "Studies towards the synthesis of diazonamide A. Synthesis of the 4-(oxazol-5-ylmethyl) aryltryptamine fragment", Bagley M. C., Moody C. J., Pepper A. G., *Tetrahedron Letters*, **2000**, *41*, 6901-6904.

26. "A synthetic approach towards the aromatic macrocyclic core of diazonamide A based on sp(2)-sp(2) coupling protocols", Boto A., Ling M., Meek G., Pattenden G., *Tetrahedron Letters*, **1998**, *39*, 8167-8170.

27. "Synthetic studies on diazonamide A. Benzofuranone-tyrosine and indole-oxazole fragment support studies", Konopelski J. P., Hottenroth J. M., Oltra H. M., Veliz E. A., Yang Z. C., *Synlett*, **1996**, 609.

28. "Synthesis of chlorooxazoles related to natural products", Radspieler A., Liebscher J., *Synthesis-Stuttgart*, **2001**, 745-750.

29. "Alpha-arylation of 2-arylacetates and benzofuran-2-one with tricarbonyl(fluoroarene)chromium complexes", Schley D., Radspieler A., Christoph G., Liebscher J., *European Journal of Organic Chemistry*, **2002**, 369-374.

30. Ph.D. Dissertation, Jamison T. F., Harvard University, Cambridge, MA , **1997**.

Chapter 2

Synthetic Studies Toward the Diazonamide Quaternary Center

2.1 Retrosynthetic Analysis of Diazonamide A

In August of 1999 efforts were initiated toward the total synthesis of diazonamide A. From the beginning it was felt that the focal point of the diazonamide problem and a successful synthesis would be controlling the absolute stereochemistry of the C(10) bisaryl quaternary center. It was envisioned that this difficult quaternary center would be forged by a catalytic asymmetric cyclopropanation/ring-opening process. Carbenoid reactions have been extensively utilized in organic synthesis and to date a number of excellent reviews have been published.[1,2] Recently, numerous catalytic asymmetric carbenoid methods have been developed: among the various types of carbeoid processes, cyclopropanation is one of the most reliable in terms of catalytic induction.[3] Cleavage of cyclopropanes by rupture of strained C-C bonds is also well precedented, however, the combination of an combining asymmetric cyclopropane synthesis with an efficient ring-opening protocol has received little attention. Furthermore, the utilization of such a strategy to form quaternary asymmetric centers possessing two aryl substituents is unprecedented.

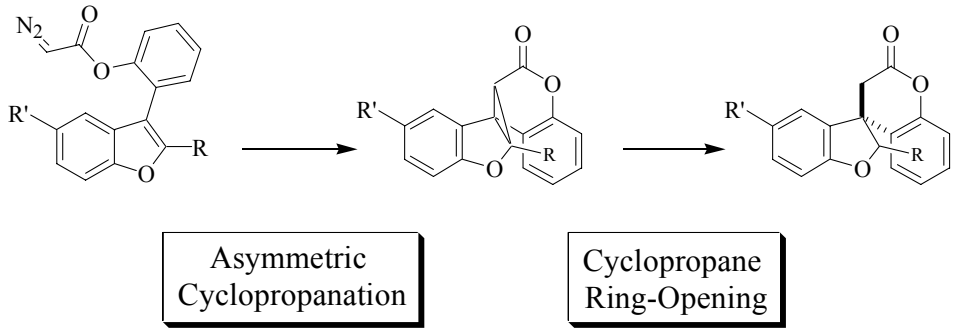
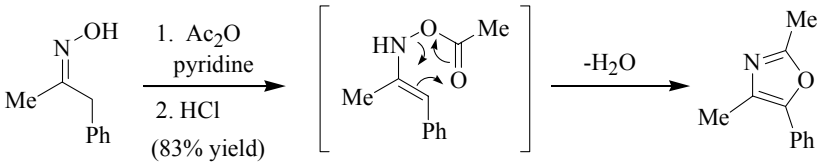


Figure 2.1.1 The Cyclopropanation/Ring-Oprning Appraoch Toward Diazonamide A

In addition to the C(10) quaternary center, another challenge posed by the synthesis of diazonamide A is the presence of the bis-oxazole moiety. The existence of numerous biologically active macrocyclic molecules possessing oxazole moieties makes a versatile method for their preparation attractive.[4-6] In general, known syntheses of macrocycles containing oxazole rings have been achieved by stitching an intact oxazole portion into the carbon framework. These methods rely on the manipulation of functional groups present on the pendent heterocycles. This convergent approach works well for large rings wherein a diverse array of functionality allows for incorporation of the requisite functional groups. However, a molecule such as diazonamide A, possessing two smaller rings comprised almost entirely of heterocycles, requires an alternative approach for oxazole incorporation.

In 1980, Bhatt reported a novel synthesis of oxazoles by rearrangement of an acyl oxime, followed by subsequent cyclodehydration.[7] Although the yields were good and the preparation of the starting materials was relatively trivial, this method has received little attention compared to other oxazole-forming reactions.

Scheme 2.1.1



An extension of this reaction is proposed herein for incorporation of the central macrocyclic oxazole present in diazonamide A. This approach will rely on tandem acylation of an oxime by well-precedented methods for macrolactonization, followed by [3,3]-sigmatropic rearrangement and cyclodehydration to furnish the oxazole in a ring-contracted macrocycle.

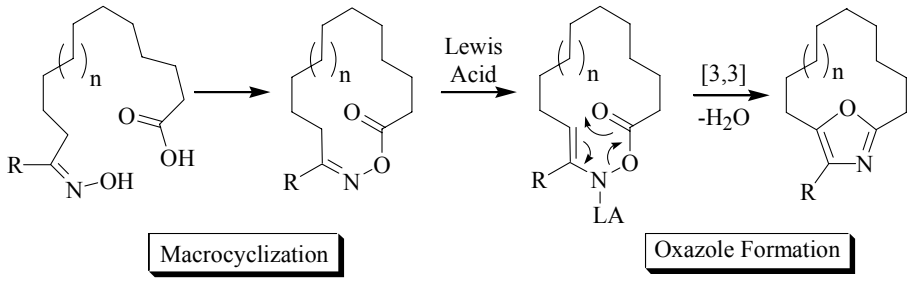
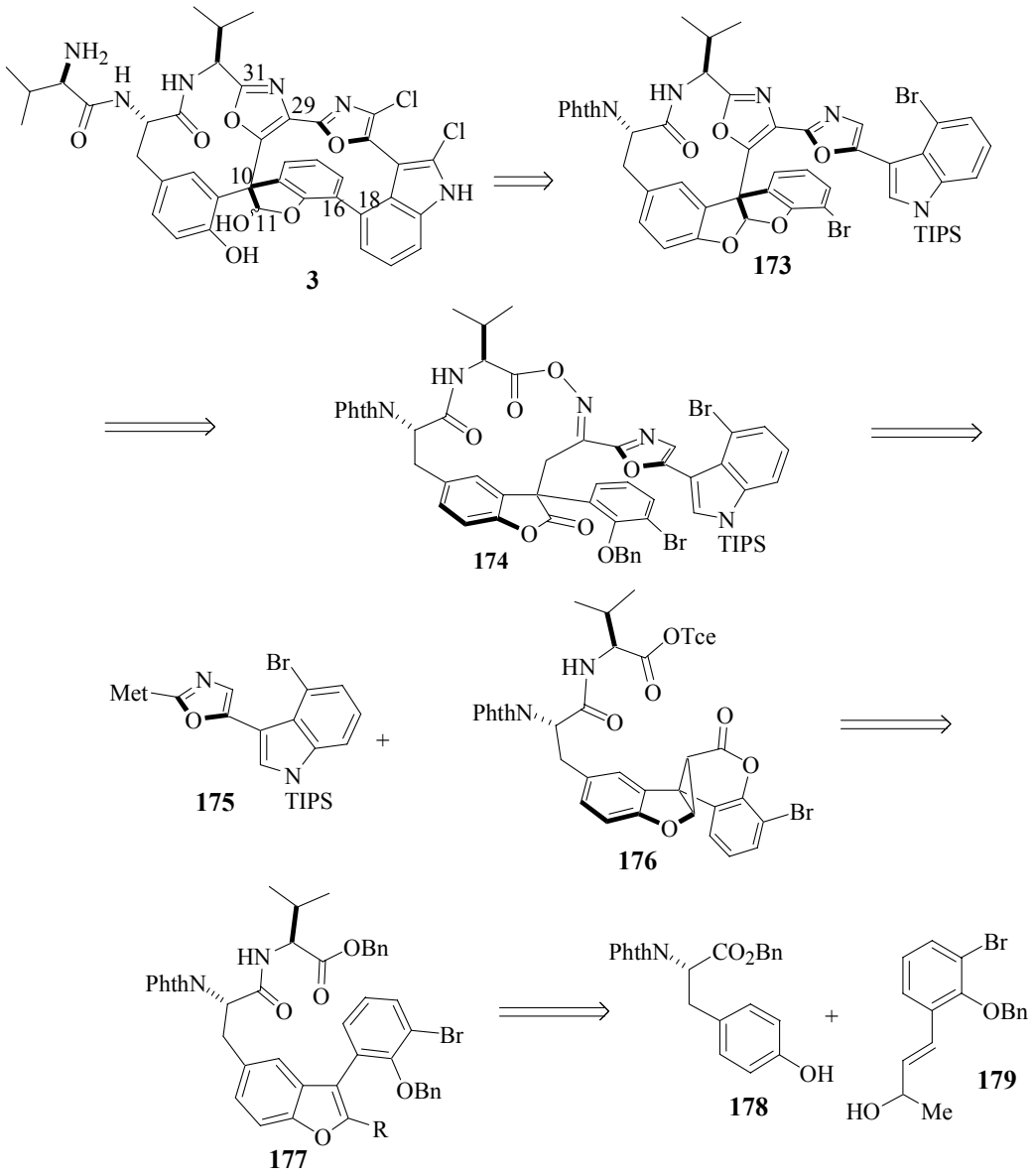


Figure 2.1.2 Approach to Macrocyclic Oxazole Formation

Guided by the above ideas, the retrosynthetic analysis illustrated in Scheme 2.1.2 evolved. It was envisioned that the atropisomerism about the C(16)-C(18) axis could be guided by the C(10) asymmetric quaternary center in conjunction with the benzhydrofuran. Therefore, cleavage of the biaryl bond is seen as a reasonable first disconnection. The sensitivity of the chloroheterocycles justifies their late-stage incorporation. Striking at the core of **173**, cleavage of the C(29)-C(31) oxazole provides acyl oxime macrocycle **174**. In the forward sense it is envisioned that oxazole formation

will occur via the Claisen-type rearrangement/cyclodehydration process described previously to furnish the ring-contracted macrocycle. Acyl oxime **174** will be prepared by well-precedented macro-lactonization techniques and will be available from the corresponding ketone which, in turn, will arise via coupling of the cyclopropyl lactone **176** with metallo-oxazole **175**. It is envisioned that directed ring opening of the strained cyclopropane in **176** will ultimately liberate the critical quaternary center. The key cyclopropyl intermediate (**176**) will be prepared by asymmetric cyclopropanation of benzofuran **177**. Classical disconnection of **177** by Claisen rearrangement reveals tyrosine **178** and allylic alcohol **179**.

Scheme 2.1.2



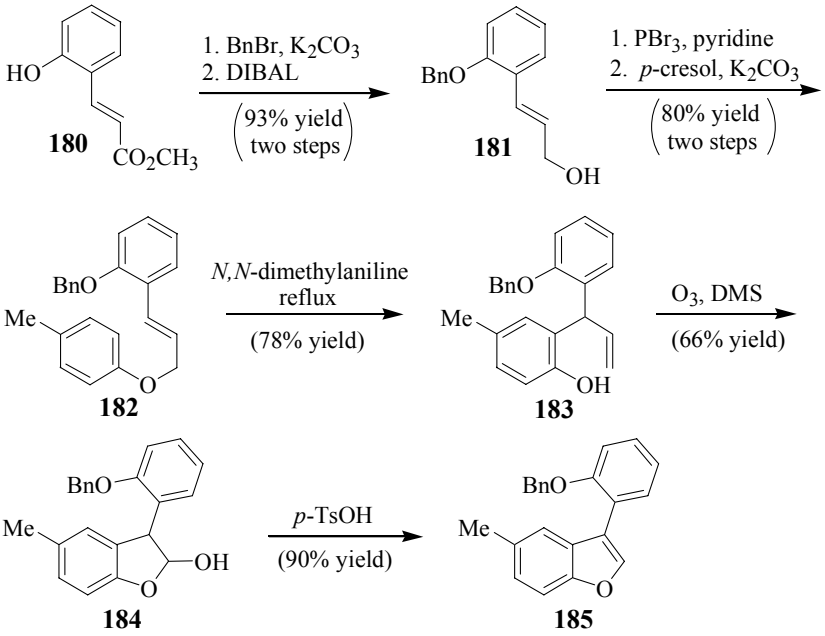
2.2 The First Generation Cyclopropanation Approach

2.2.1 Synthesis of the Benzofuran Core

Before embarking on the total synthesis of diazonamide A, work was initiated on a model system designed to study the construction of the diazonamide quaternary center via the proposed cyclopropanation/ring-opening process. In this model system the

diazonamide amino acid residues would be reduced to a methyl group. Work commenced with commercially available hydroxycinnamate **180**, which was converted to allylic alcohol **181** via formation of the benzyl ether and DIBAL reduction (Scheme 2.2.1). Subsequent bromination and alkylation of *p*-cresol furnished allyl ether **182**, which underwent smooth *ortho*-Claisen rearrangement to olefin **183**.[8] Reductive ozonolysis followed by dehydration of the resulting hemi-acetal **184** afforded benzofuran **185**, which proved to be a very versatile intermediate.

Scheme 2.2.1

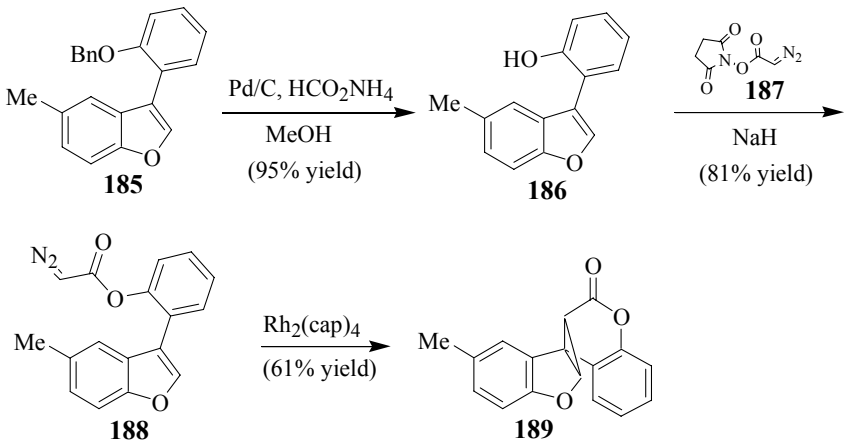


2.2.2 A Successful Cyclopopanation

With **185** in hand, work was directed toward formation of the quaternary center via our cyclopropanation/ring-opening approach (Scheme 2.2.2). To this end, benzyl deprotection of benzofuran **185** under transfer hydrogenation conditions proceeded in excellent yield to deliver phenol **186**. Notably, the transfer hydrogenation conditions

employed proceeded in quantitative yield after five minutes. In contrast, attempts to remove the benzyl group under more traditional conditions (H_2 balloon) were slow (>24 hours) and gave complex mixtures of debenzylation product along with benzofuran reduction. Treatment of **186** with the *N*-hydroxysuccinimide ester **187** and NaH afforded α-diazo ester **188**.[9] After much experimentation, it was ultimately found that cyclopropanation of **188** occurred with electroin-rich dirhodium (II) caprolactamate ($Rh_2(cap)_4$) in refluxing CH_2Cl_2 to give cyclopropane **189** accompanied with a small amount of presumed aryl C-H insertion product.[10]

Scheme 2.2.2

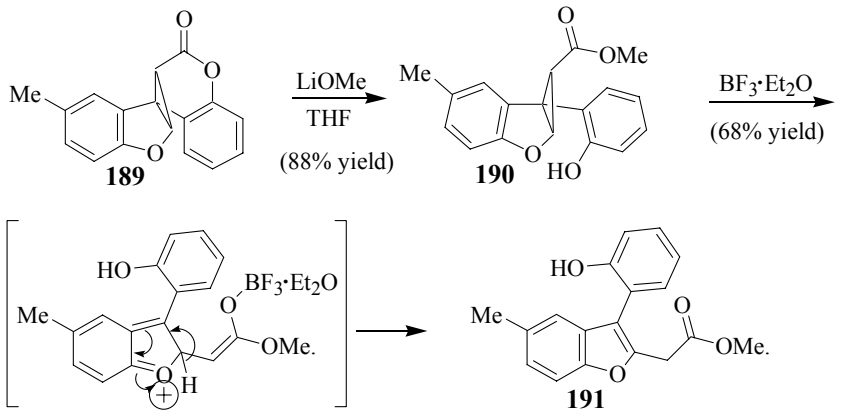


2.2.3 Undesired Cyclopropane Ring-Opening

Initial attempts to open the cyclopropane ring of **189** to unveil the desired bisaryl quaternary center met with no success. Treatment of **189** under a variety of acidic conditions resulted in either no reaction or decomposition of starting material. Undeterred, efforts focused on the cyclopropane ring-opening of ester **190** which could be conviently prepared by reaction of **189** with LiOMe (Scheme 2.2.3). Unfortunately, treatment of **190** with $BF_3{\cdot}Et_2O$ resulted in cleavage of the undesired cyclopropane bond

to furnish benzofuran **191**. It is believed that this reaction likely proceeds by through-ring scission of the cyclopropane followed by re-aromatization in a manner analogous to the known reactivity of indoles.[11]

Scheme 2.2.3

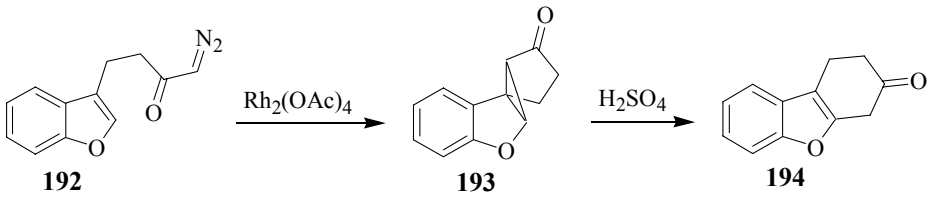


2.3 The Second Generation Cyclopropanation Approach

2.3.1 A Revised Cyclopropanation Substrate

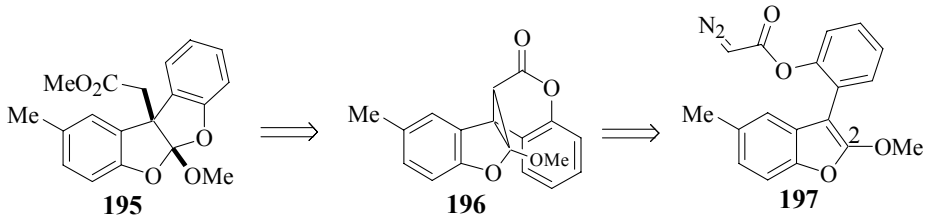
While the undesired cyclopropane ring-opeing was discouraging, it was not completely unexpected. Padwa and co-workers in 1989 reported a similar cyclopropanation/ring-opening sequence (Scheme 2.3.1).[12] In their system, the cyclopropanation of α-diazo ketone **192** afforded spirocycle **193**, which underwent acid-induced cyclopropane opening in a manner analogous to what was observed to furnish ketone **194**.

Scheme 2.3.1



In order to suppress this undesired mode of opening in the above system, a benzofuran with an additional alkoxy group at the benzofuran C(2) position (Scheme 2.3.2) was investigated. Installation of this alkoxy group was considered advantageous in at least two respects. First, the additional alkoxy group should improve the cyclopropanation reaction by making the benzofuran more electron-rich. More importantly, this change should result in cleavage of the desired cyclopropane bond due to the extra electron density residing at the C(2) carbon.

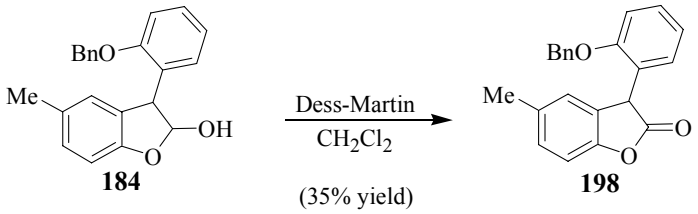
Scheme 2.3.2



2.3.2 Formation of the Alkoxy Substituted Benzofuran

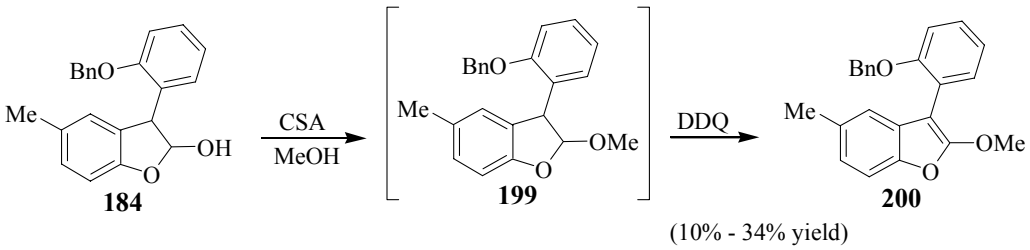
The initial attempt to install the benzofuran alkoxy group began with efforts directed toward the synthesis of benzofuranone **198,** which after O-alkylation would provide the desired alkoxy substituted product. Surprisingly, the oxidation of lactol **184** to **198** proved to be extremely problematic. Reaction of **184** with a wide variety of oxidizing reagents (i.e. PCC, PDC, Swern, TPAP, Ag_2CO_3) led to little or no desired product along with unreacted starting material and several unidentified side-products (Scheme 2.3.3). Ultimately, oxidation of lactol **184** under Dess-Martin conditions afforded the desired benzofuranone **198** in poor yield.

Scheme 2.3.3



Unable to oxidize **184** effectively, an alternative route in which to install an alkoxy group at the benzofuran C(2) position was sought. Toward this end, **184** was heated in refluxing methanol under acidic condition to afford acetal intermediate **199**, which underwent DDQ mediated oxidation to methoxy benzofuran **200** (Scheme 2.3.4). Unfortunately, this sequence was also low yielding and not reproducible on large scale (> 1g). The irreproducibility of this reaction sequence is presumably due to the acid generated during the course of the reaction, which leads to decomposition of the acetal moiety in **199**.

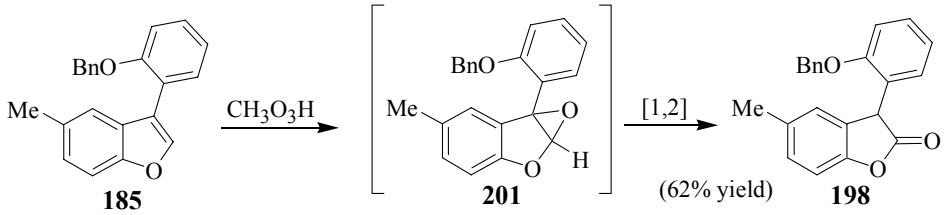
Scheme 2.3.4



In a final attempt to efficiently install the desired alkoxy group, attention was again directed toward the synthesis of benzofuranone **198**. There are several reports in the literature that epoxidation of benzofurans yield the corresponding benzofuranones after *in situ* [1,2] hydride shift of the transient epoxide intermediate. To this end,

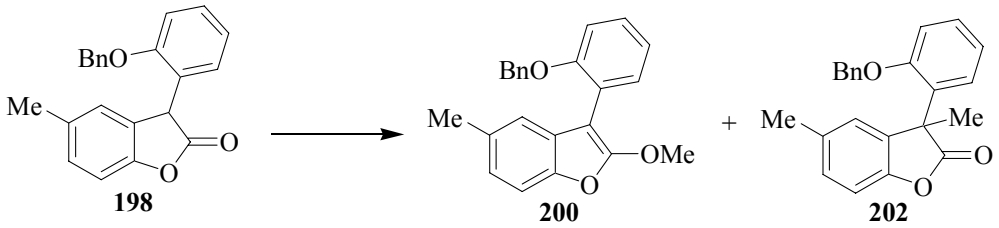
benzofuran **185** was reproducibly oxidized to lactone **198** with peracetic acid in good yield (Scheme 2.3.5).

Scheme 2.3.5



With an acceptable synthesis of **198** in hand, work focused on the O-alkylation of **198**. From the outset it was anticipated that O-alkylation should be favored due to the aromaticity of the product. Unfortunately, this proved untrue and initial attempts to alkylate **198** with Me_2SO_4 gave only an optimized 50:50 ratio of the desired *O*-alkylated benzofuran **200** and *C*-alkylated lactone **202**, respectively (Table 2.3.1). Similar results were seen with MeOTf as the source of methyl and various bases with different counterions. Alkylation with Meerwein's reagent (Me_3OBF_4) was more promising, wherein treatment of **198** with Me_3OBF_4 and NaH in DMF afforded a 71:29 ratio of products. The overall yield of this reaction was low, however, due to competing methylation of the DMF solvent. Finally, it was found that **198** could be methylated in high yield to furnish a 63:37 ratio of the desired *O*-alkylated benzofuran **200** and *C*-alkylated lactone **202**, respectively.

Table 2.3.1 **Survey of Various Methods for the Alkylation of Benzofuranone 198.**



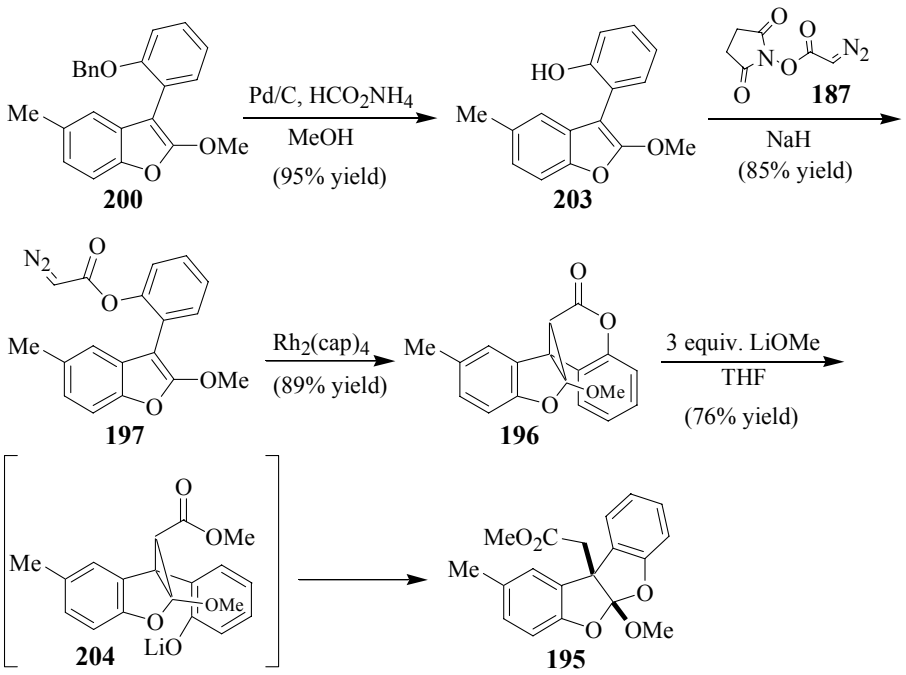
methyl source	base	solvent	% yield	**200: 202**
Me_2SO_4	NaH	THF	65	0 : 100
Me_2SO_4	NaH	DMF	72	50 : 50
Me_3OBF_4	Cs_2CO_3	CH_2Cl_2	35	50 : 50
Me_3OBF_4	NaH	DMF	40	71 : 29
Me_3OBF_4	NaH	THF	95	63 : 37

2.3.3 A Successful Cyclopropanation and Ring-Opening

Deprotection of **200** to **203** followed by acylation furnished α-diazo ester **197** (Scheme 2.3.6). Decomposition of **197** with $Rh_2(cap)_4$ gave rise to the desired cyclopropane **196** in excellent yield. Unlike the previous system, no aryl C-H product was dected. With **196** in hand, attention focused on the development of suitable conditions for cyclopropane ring-opening. Gratifyingly, treatment of **196** with 3 equivalents of LiOMe led directly to orthoester **195**.[13] This remarkable cascade reaction, which unmasks the desired quaternary center, likely proceeds via initial formation of ester **204** followed by opening of the cyclopropane. This mechanism is supported by the fact that on occasion the protonated form of **204** could be isolated and advanced independently to **195**. Overall, installation of the alkoxy group proved to be

advantageous by both improving the yield of the cyclopropanation reaction and directing the rupture of the correct cyclopropane bond.

Scheme 2.3.6



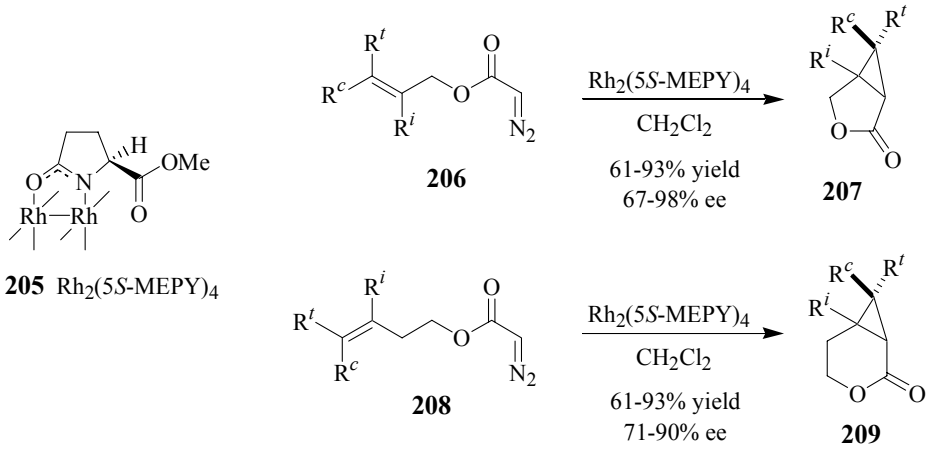
2.4 Development of an Asymmetric Cyclopropanation

2.4.1 Doyle and Martin's Work on the Asymmetric Cyclopropanation of α-Diazo Esters

Confident in the ability to affect the desired cyclopropanation and subsequent ring-opening, we began to investigate the utility of asymmetric catalysis in the key cyclopropanation step. Numerous literature reports describe the catalytic asymmetric cyclopropanation of α-diazo carbonyls with chiral transition metal catalysts. Among these reports, the work of Doyle and Martin dealing with the asymmetric cyclopropanation of α-diazo esters was especially appealing (Scheme 2.4.1).[3] Specifically, Doyle and Martin have published several elegant studies detailing the

asymmetric cyclopropanation of allylic α-diazo esters **206** and homoallylic α-diazo esters **208** to the corresponding cyclopropyl lactones **207** and **209**, respectively.[14-17]

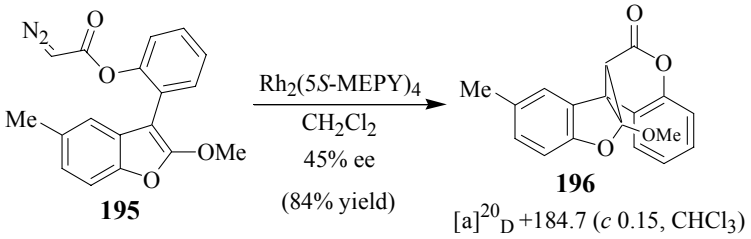
Scheme 2.4.1



2.4.2 Asymmetric Cyclopropanation of 195

Based on the work of Doyle and Martin described above, syringe pump addition of α-diazo ester **195** to a refluxing solution of Doyle's $Rh_2(5S\text{-MEPY})_4$ catalyst in methylene chloride gave rise to optically active cyclopropanated product **196** (α^{20}[D] = +184.7° (*c* 0.15, $CHCl_3$)). Subsequent analysis of **196** with the chiral shift reagent $Eu(hfc)_3$ determined the enantioselectivity of this cyclopropanation reaction to be 45% based on comparison to a racemic sample of **196** (Scheme 2.4.2). At this time the absolute sense of asymmetric induction in **196** is not known, **196** is only drawn as shown for illustrative purposes.

Scheme 2.4.2



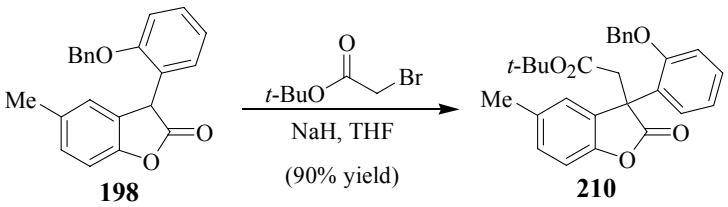
For the purpose of this model system, no attempts were made to optimize the enantioselectivity of this reaction. In the real system, however, there are many reactions parameters that can be manipulated in order to improve the asymmetric induction in this reaction.

2.5 An Alternative Approach to Diazonamide A

2.5.1 An Alkylation Appraoch to the Diazonamide Quaternary Center

Central to the success of the aforementioned cyclopropanation/ring-opening sequence was the recognition that the C(2) position of the benzofuran must be in the acid oxidation state. While not desired in the natural product, this increase in oxidation levels led to consideration of a complementary alkylation approach to the quaternary center (Scheme 2.5.1). During attempts to O-alkylate benzofuranone **198** the formation of the C-alkylation product **202** was never completely supressed. Therefore, it was reasoned that by using a different electrophile one might be able to take advantage of the propensity of this system to undergo C-alkylation. To this end, the enolate of lactone **198** was prepared as previously described and treated with *t*-butyl bromoacetate to afford C(3)-alkylated lactone **210** in excellent yield.

Scheme 2.5.1



Importantly, **210** contains the same carbon-carbon connectivity and oxidation states found in orthoester **195** (Figure 1.5.1). The convergent nature of both approaches described herein to the quaternary center should prove valuable in further studies directed toward diazonamide A. Whereas the alkylation approach is ideally suited for the advancement of material (4 fewer steps), the cyclopropanation/ring-opening sequence provides a means of introducing asymmetry into the synthesis.

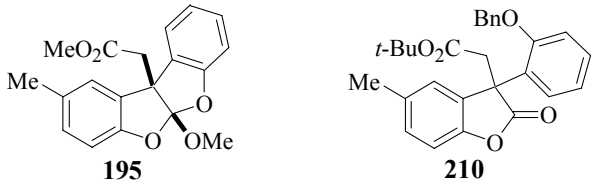


Figure 1.5.1 Side by Side Comparison of Orthoester 195 and Lactone 210

2.6 Experimental Section

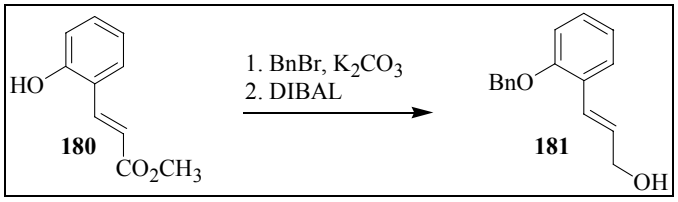
2.6.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly distilled solvents. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone. Methylene chloride (CH_2Cl_2), and benzene were distilled from calcium hydride. Methanol (MeOH) was distilled from magnesium. All other commercially obtained reagents were used as received. All reactions were

magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Column or flash chromatography was performed with the indicated solvents using silica gel (particle size 0.032-0.063 nm) purchased from Bodman. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance DPX-500 or Bruker Advance DPX-400 spectrometers. Chemical shifts are reported relative to internal chloroform (^{1}H, δ 7.27 ppm, ^{13}C δ 77.0 ppm), benzene (^{1}H, δ 7.30 ppm), dimethyl sulfoxide (^{13}C, δ 40.5 ppm), or methanol (^{13}C, δ 49.9 ppm). Melting points were obtained on a Gallenkamp variable temperature melting point apparatus and are uncorrected. Infrared spectra were recorded on a Midac M-1200 FTIR. High resolution mass spectra were acquired at The University of Illinois Mass Spectrometry Center.

2.6.2 Preparative Procedures

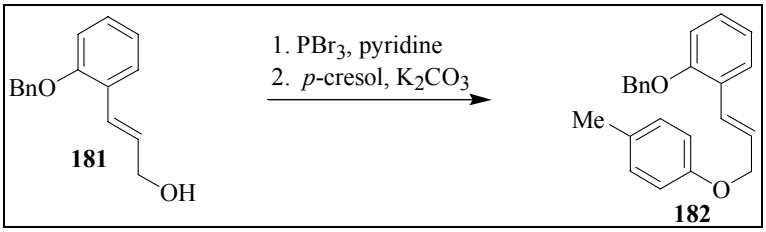
Preparation of allylic alcohol 181



To a solution of phenol **180** (27.0 g, 151.5 mmol) in acetone (250 mL) was added benzyl bromide (21.0 mL, 176.6 mmol) and K_2CO_3 (41.0 g, 296.7 mmol). The reaction mixture was heated to reflux for 12 h. After this time the reaction mixture was concentrated in vacuo and the crude mixture taken up in ether. Filtration of the residual solids and removal of the solvent in vacuo gave a light yellow oil that was taken up in THF (350

mL). This solution was cooled to –78 °C and treated with DIBAL (67.5 mL, 378.8 mmol). After 30 min. the reaction was carefully quenched with a saturated solution of Rochelle's salt (600 mL) and allowed to stir at room temperature for 2 h. The organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 (3 x 250 mL). The combined organic layers were washed with brine (250 mL) and dried ($MgSO_4$). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 6:1 then 3:1) to afford allylic alcohol **181** (34.0 g, 93% yield) as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50 (dd, *J*=1.5, 7.5 Hz, 1H), 7.47-7.35 (cm, 5H), 7.22 (m, 1H), 7.02 (d, *J*=16.0 Hz, 1H), 6.96 (m, 2H), 6.41 (dt, *J*=6.0, 16.0 Hz, 1H), 5.12 (s, 2H), 4.32 (dd, *J*=1.5, 5.5 Hz, 2H), 1.58 (br s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 155.9, 137.0, 129.2, 128.7, 128.5, 127.9, 127.3, 126.9, 126.2, 126.1, 121.0, 112.5, 70.4, 64.2; **IR** (thin film/NaCl) 3355 (br w), 3032 (w), 2918 (w), 2865 (w), 1487 (m), 1451 (m), 1381 (w), 1239 (s), 1013 (m), 750 (s) cm^{-1}; **HRMS** (EI) *m/z* found: 240.1147, [calc'd for $C_{16}H_{16}O_2$ (M+H): 240.1150].

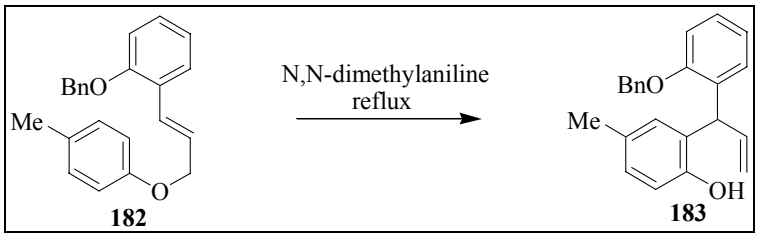
Preparation of allyl ether 182



To a solution of PBr_3 (10.3 mL, 108.3 mmol) and pyridine (4.4 mL, 54.0 mmol) in Et_2O (50 mL) was added allylic alcohol **181** (26.0 g, 108.3 mmol) in Et_2O (50 mL)over 1 h at –15 °C. After stirring for an additional 1 h the reaction mixture was carefully quenched

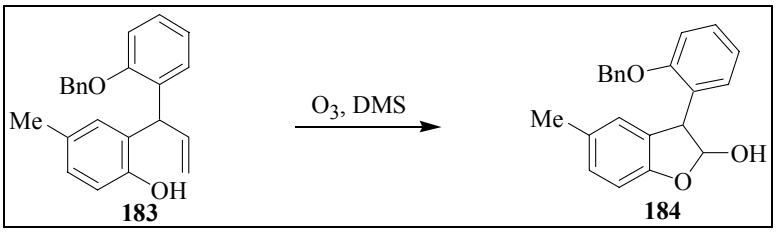
with distilled H_2O (100 mL). The organic layer was separated, and the aqueous layer extracted with Et_2O (50 mL) . The combined organic layers were washed with brine (100 mL) and dried ($MgSO_4$). After solvent removal in vacuo the crude pink residue was taken up in acetone (1000 mL) and treated with p-cresol (12.3 g, 113.6 mmol) and K_2CO_3 (26.2 g, 189.4 mmol). The reaction mixture was heated to reflux for 12 h. After this time the reaction mixture was concentrated in vacuo and the crude mixture taken up in ether. After filtration of the residual solids and removal of the solvent in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 10:1) to afford allyl ether **182** (36.2 g, 80% yield) as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53 (dd, *J*=1.5 Hz, 7.5H), 7.46-7.35 (cm, 5H), 7.23 (m, 1H), 7.15 (d, *J*=16.0 Hz, 1H), 7.10 (m, 2H), 6.96 (m, 2H), 6.88 (m, 2H), 6.47 (dt, *J*=6.0 Hz, 16.0H), 5.12 (s, 2H), 4.69 (dd, *J*=1.5. 6.0 Hz, 2H), 2.31 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 156.6, 155.9, 137.0, 129.9, 129.8, 128.5, 127.9, 127.8, 127.2, 127.1, 125.9, 125.3, 121.0, 114.7, 112.5, 70.3, 69.3, 20.5; **IR** (thin film/NaCl) 3031 (w), 2020 (w), 2862 (w), 1510 (s), 1452 (m), 1293 (m), 1241 (s), 1176 (w), 1015 (m), 750 (m) cm^{-1}; **HRMS** (FAB) *m/z* found: 330.1621, [calc'd for $C_{23}H_{22}O_2$ (M+): 330.1620].

Preparation of olefin 183



A solution of allyl ether **182** (400 mg, 1.20 mmol) in N,N-dimethylaniline (12 mL) was submersed into an oil bath preheated to 200 °C. The solution was refluxed for 16 hours, cooled and diluted with Et_2O (25 mL). The ethereal solution was washed with 1N HCl (6 x 10mL) and dried ($MgSO_4$). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 20:1 then 10:1) to afford olefin **183** (312 mg, 78% yield) as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40-7.33 (cm, 5H), 7.23 (m, 2H), 7.00-6.93 (cm, 4H), 6.74 (m, 1H), 6.36 (ddd, *J*=6.0, 10.0, 17.0 Hz, 1H), 5.42 (br s, 1H), 5.33 (d, *J*=6.0 Hz, 1H), 5.30 (dt, *J*=1.5, 10.5 Hz, 1H), 5.11 (s, 2H), 5.02 (dt, *J*=1.5, 17.0 Hz, 1H), 2.25 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.4, 154.7, 142.4, 139.8, 134.1, 131.8, 131.3, 131.3, 130.1, 129.9, 129.3, 129.2, 129.1, 129.0, 122.2, 116.7, 116.5, 114.2, 71.7, 43.3, 21.6; **IR** (thin film/NaCl) 3449 (w), 3031 (w), 2920 (w), 1598 (w), 1498 (s), 1451 (m), 1238 (s), 1103 (w), 918 (w), 753 (s) cm^{-1}; **HRMS** (FAB) *m/z* found: 330.1621, [calc'd for $C_{23}H_{22}O_2$ (M+): 330.1620].

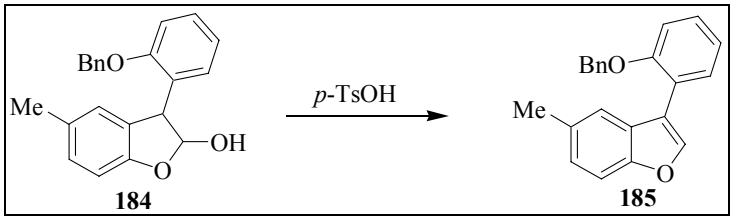
Preparation of hemi-acetal 184



A solution of **183** (8.8 g, 26.7 mmol) in MeOH (200 mL) was cooled to –78 °C and treated with O_3 until TLC showed the disappearance of starting material (about 30 min). The mixture was purged with nitrogen for 15 min at –78 °C, and dimethyl sulfide (27.0 mL) was added at that temperature. The dry ice bath was removed and the solution

allowed to stir at room temperature for 12 h. After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 20:1 then 10:1) to afford hemi-acetal **184** (5.86 g, 66% yield) as a viscous light yellow oil (2:1 mixture of diastereomers). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46-7.22 (cm, 6H), 7.02 (m, 2H), 6.95 (s, 1H), 6.90-6.80 (cm, 3H), 6.10 (d, *J*=7.0 Hz, 1H), 5.85 (d, *J*=2 Hz, 1H), 5.16 (s, 2H), 5.09 (d, *J*=11.5 Hz, 1H), 5.05 (s, 1H), 5.02 (d, *J*=11.5 Hz, 2H), 4.82 (d, *J*=1.0 Hz, 1H), 3.09 (br s, 1H), 2.30 (s, 3H), 2.29 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 156.8, 156.2, 156.1, 156.0, 136.8, 136.3, 130.6, 130.3, 129.1, 129.0, 128.8, 128.6, 128.5, 128.5, 128.3, 128.1, 128.0, 127.8, 127.4, 127.2, 127.1, 126.1, 125.7, 124.7, 121.3, 121.0, 112.3, 111.9, 109.6, 109.6, 107.0, 102.0, 70.4, 70.0, 50.7, 20.8; **IR** (neat) 3434 (w), 2862 (w), 1599 (w), 1490 (s), 1451 (m), 1240 (m), 1096 (w), 917 (w), 810 (w), 753 (m) cm^{-1}; **HRMS** (FAB) *m/z* found: 332.1411, [calc'd for $C_{22}H_{20}O_3$ (M+): 332.1412].

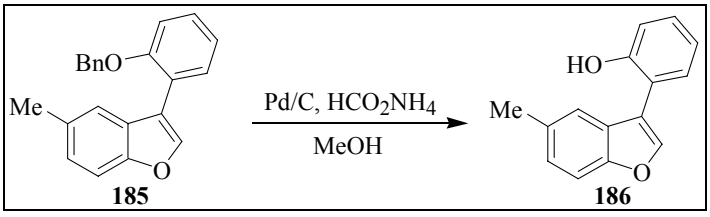
Preparation of benzofuran 185



To a solution of hemi-acetal **7** (465 mg, 1.40 mmol) in benzene (50 mL) was added *p*-toluenesulfonic acid (13.3 mg, 0.07 mmol). The reaction mixture was refluxed and the solvent passed through Å4 molecular sieves before returning to the flask for 3 h. After this time the reaction mixture was cooled, washed with sat. $NaHCO_3$ (3 x 25 mL), and dried ($MgSO_4$). After solvent removal in vacuo the residue was purified by silica gel

column chromatography (hexanes:EtOAc, 40:1) to afford benzofuran **8** (395 mg, 90% yield) as a clear colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.82 (dd, *J*=1.5, 7.5 Hz, 1H), 7.71 (s, 1H), 7.52 (d, *J*=8.5 Hz, 1H), 7.46-7.38 (cm, 6H), 7.22 (qd, *J*=1.0, 7.5 Hz, 2H), 7.18 (d, *J*=8.5 Hz, 1H), 5.20 (s, 2H), 2.55 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 155.9, 135.5, 144.2, 136.8, 132.0, 129.9, 128.4, 128.2, 127.8, 127.2, 127.2, 125.3, 121.6, 121.1, 120.9, 116.9, 112.9, 111.0, 70.5, 21.4; **IR** (thin film/NaCl) 3032 (w), 2919 (w), 1578 (w), 1494 (s), 1447 (m), 1241 (s), 1109 (m), 1023 (m), 855 (w), 750 (s) cm^{-1}; **HRMS** (FAB) *m/z* found: 314.1307, [calc'd for $C_{22}H_{18}O_2$ (M+): 314.1307].

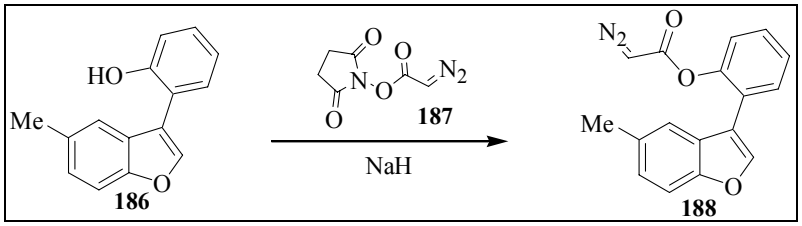
Preparation of phenol 186



To a solution of benzofuran **185** (455 mg, 1.45 mmol) in MeOH (25 mL) was added 10% Pd/C (290 mg) and HCO_2NH_4 (457 mg, 7.25 mmol). The reaction mixture was heated to reflux for 15 min. after which time TLC showed the complete disappearance of starting material. After cooling to room temperature the reaction mixture was filtered over a pad of celite and washed with ethyl acetate (150 mL). This solution was concentrated in vacuo, dissolved in ethyl acetate (50 mL), washed with H_2O (2 x 25 mL), and dried ($MgSO_4$). Solvent removal in vacuo afforded analytically pure phenol **186** (310 mg, 95% yield) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.48 (d, *J*=8.5

Hz, 1H), 7.44 (dd, *J*=1.5, 8.0 Hz, 1H), 7.41 (s, 1H), 7.33 (m, 1H), 7.21 (dd, *J*=1.5, 8.5 Hz, 1H), 7.07-7.04 (cm, 2H), 5.19 (s, 1H), 2.47 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 154.0, 1533, 143.0, 132.9, 130.4, 129.4, 126.7, 126.4, 120.8, 120.2, 117.8, 116.5, 111.4, 21.4; **IR** (thin film/NaCl) 3522 (br m), 1578 (m), 1471 (s), 1335 (m), 1279 (m), 1230 (s), 1186 (s), 1102 (s), 969 (w), 757 (s) cm^{-1}; **HRMS** (EI) *m/z* found: 224.0837, [calc'd for $C_{15}H_{12}O_2$ (M+): 224.0837].

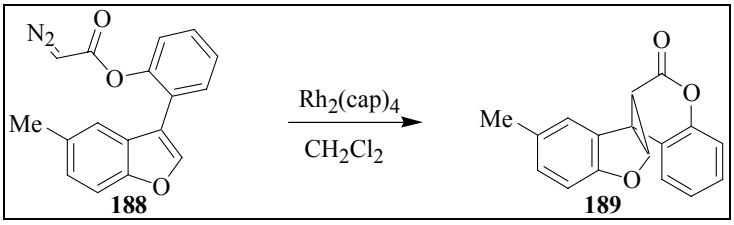
Preparation of α-diazo ester 188



To a solution of phenol **186** (200 mg, 0.893 mmol) in THF (10 mL) at 0°C was added succinimide **187** (172 mg, 0.938 mmol) in THF (5 mL) via cannula over 5 minutes. The reaction mixture was warmed to room temperature during which time a brown precipitate formed. After 15 min. the solvent was removed in vacuo and the crude mixture taken up ehtyl acetate. After filtration of the brown precipitate over a plug of cotton and solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 10:1) to afford α-diazo ester **188** (211 mg, 81% yield) as a clear bright yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.61 (dd, *J*=1.5, 7.5 Hz, 1H), 7.45-7.42 (cm, 3H), 7.37 (td, *J*=1.5, 7.5 Hz, 1H), 7.31 (m, 1H), 7.17 (m, 1H), 4.77 (br s, 1H), 2.46 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.6, 148.0, 142.8, 130.7, 128.6,

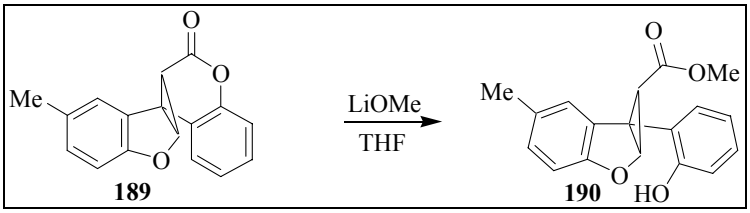
126.9, 126.4, 125.8, 125.3, 123.3, 120.4, 111.1, 21.4; **IR** (thin film/NaCl) 3115 (w), 2116 (s), 1707 (s), 1470 (w), 1366 (s), 1189 (s), 1145 (s), 1112 (m), 968 (w), 798 (m) cm^{-1}; **HRMS** (EI) *m/z* found: 293.0927, [calc'd for $C_{17}H_{13}N_2O_3$ (M+H): 240.1150].

Preparation of cyclopropyl lactone 189



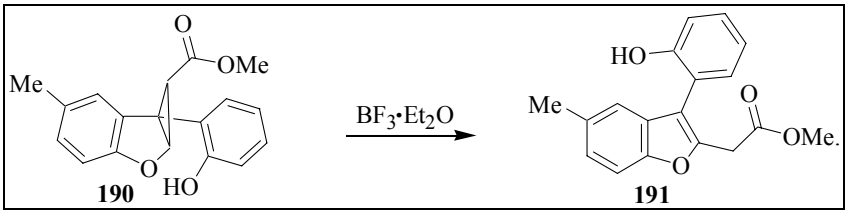
To a solution of α-diazo ester **188** (160 mg, 0.548 mmol) in CH_2Cl_2 (7.5 mL) was added $Rh_2(cap)_4$ (4.0 mg, 0.00548 mmol) in CH_2Cl_2 (7.5 mL) over 12 h via syringe pump. After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 20:1) to afford lactone **189** (88 mg, 61% yield) as a clear colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 (dd, *J*=1.5, 7.5 Hz, 1H), 7.39 (s, 1H), 7.34 (m, 1H), 7.22 (td, *J*=1.0, 7.5 Hz, 1H), 7.12 (dd, *J*=1.0, 8.0 Hz, 2H), 6.94 (d, *J*=8.0 Hz, 1H), 4.94 (d, *J*=1.0 Hz, 1H), 2.40 (s, 3H), 1.88 (d, *J*=1.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.0, 157.3, 150.3, 131.6, 129.7, 18.9, 126.4, 126.4, 124.7, 124.6, 117.7, 117.3, 111.3, 69.3, 38.1, 28.0, 21.0; **IR** (thin film/NaCl) 3065 (w), 2919 (w), 1754 (s), 1480 (m), 1265 (m), 1187 (s), 1077 (m), 1037 (w), 936 (m), 760 (m) cm^{-1}; HRMS (FAB) *m/z* found: 265.0866, [calc'd for $C_{17}H_{13}O_3$ (M+H): 265.0865].

Preparation of ester 190



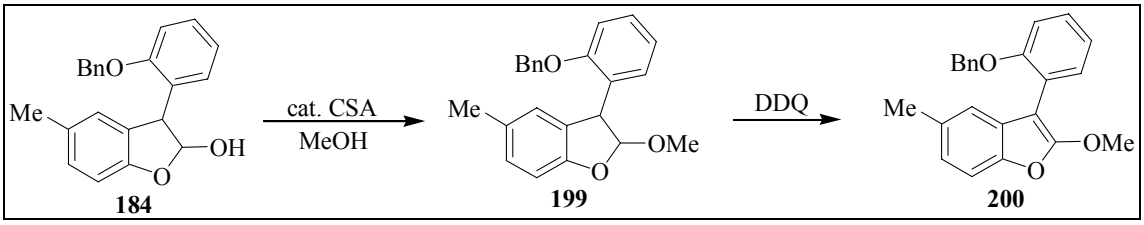
To a solution of lactone **189** (22 mg, 0.83 mmol) in THF (3 mL) at –78 °C was added LiOMe (2 mL, 0.0835M in MeOH). After 15 min. the reaction was quenched with sat. NH_4Cl (5 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (2 x 10 mL) and the combined organic layers dried (MgSO4). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 6:1) to afford ester **190** (22 mg, 88% yield) as a clear colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25-7.22 (cm, 2H), 7.00-6.93 (cm, 3H), 6.87-6.85 (cm, 2H), 5.45 (d, *J*=1.5 Hz, 1H), 5.11 (br s, 1H), 3.55 (s, 3H), 2.24 (s, 3H), 1.83 (d, *J*=1.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.3, 156.4, 154.8, 131.1, 131.1, 131.0, 129.5, 128.9, 124.4, 120.9, 119.6, 115.9, 110.4, 70.0, 51.9, 41.2, 29.2, 20.8; **IR** (thin film/NaCl) 3399 (br m), 2951 (w), 1701 (s), 1595 (w), 1483 (s), 1453 (s), 1277 (s), 1188 (s), 1079 (s), 911. m cm^{-1}; **HRMS** (EI) *m/z* found: 297.1127, [calc'd for $C_{18}H_{17}O_4$ (M+H): 297.1127].

Preparation of benzofuran 191



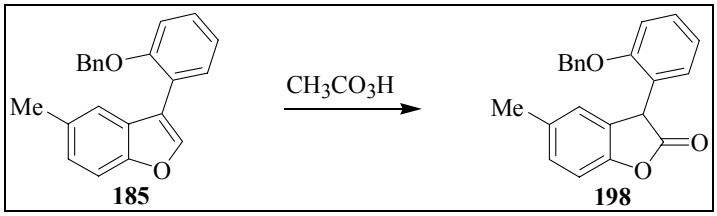
To a solution of ester 13 (5.0 mg, 0.017 mmol) in benzene (2 mL) at 0°C was added $BF_3 \cdot Et_2O$ (0.002 mL, 0.0170 mmol). After stirring for 15 min. the entire reaction mixture was poured onto a silica gel column and chromatographed (hexanes:EtOAc, 10:1 then 6:1) to afford benzofuran **14** (3.4 mg, 68% yield) as a clear colorless oil. **^{1}H NMR** (500 MHz, C_6D_6) δ 7.44-7.37 (cm, 2H), 7.30-7.28 (cm, 3H), 7.04-7.01 (cm, 2H), 6.31 (s, 1H), 3.52 (s, 2H), 3.26 (s, 3H), 2.26 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.4, 154.1, 153.2, 148.0, 132.8, 131.1, 129.9, 126.2, 120.5, 120.0, 112.0, 117.0, 116.4, 114.5, 110.8, 52.9, 33.1, 21.3; **IR** (thin film/NaCl) 3427 (br m), 2953 (m), 2923 (s), 1739 (s), 1602 (w), 1450 (s), 1199 (s), 1011 (w), 802 (w), 757 (m) cm^{-1}; **HRMS** (EI) *m/z* found: 296.1043, [calc'd for $C_{18}H_{16}O_4$ (M+): 296.1049].

Preparation of Benzofuran 200



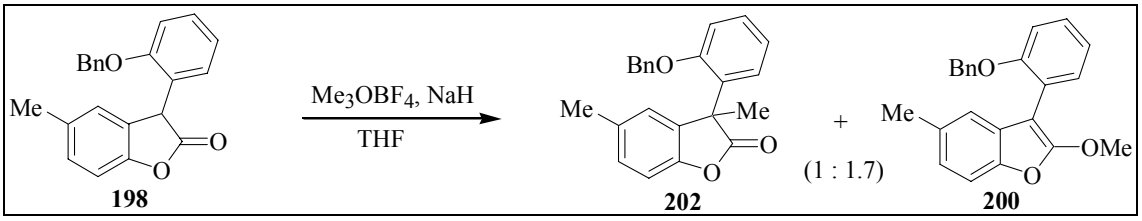
To a solution of hemi-acetal **184** (1.54 g, 4.64 mmol) in MeOH (100 mL) was added CSA (108 mg, 0.464 mmol). The reaction mixture was refluxed for 3 h and cooled to room temperature. After solvent removal in vacuo the residue was taken up in Et_2O (100 mL), washed with sat. $NaHCO_3$ (2 x 75 mL), and dried ($MgSO_4$). The crude product was suitable to be used directly in the next step. To a solution of acetal **xx** (0.430 mg, 1.24 mmol) in dioxane (15 mL) was added DDQ (0.704 mg, 3.1 mmol). The reaction mixture was refluxed for 5 h and cooled to room temperature. After solvent removal in vacuo the residue was taken up in Et_2O (50 mL), washed with sat. $NaHCO_3$ (2 x 25 mL), and dried ($MgSO_4$). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 20:1) to afford benzofuran **200** (146 mg, 34% yield) as a clear colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (dd, *J*=1.5, 8.0 Hz, 1H), 7.38-7.30 (cm, 7H), 7.25 (s, 1H), 7.13 (m, 2H), 7.03 (dd, *J*=1.5, 8.0 Hz, 1H), 5.16 (s, 2H), 4.02 (s, 3H), 2.43 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.4, 156.4, 146.7, 137.2, 132.1, 131.6, 130.2, 128.3, 128.3, 127.5, 127.1, 122.6, 120.9, 119.7, 113.1, 109.6, 91.2, 70.3, 58.3, 21.4; **IR** (thin film/NaCl) 2858 (w), 1640 (s), 1497 (s), 1366 (s), 1288 (m), 1241 (s), 1117 (w), 1038 (s), 945 (w), 752 (s) cm^{-1}; **HRMS** (FAB) *m/z* found: 344.1411, [calc'd for $C_{23}H_{20}O_3$ (M+): 344.1412].

Preparation of lactone 198



The procedure of Vedejs was used without modification. Peracetic acid (7.13 mL, 36.54 mmol, Aldrich) was gradually added to a solution of benzofuran **185** (387 mg, 1.23 mmol) in 72 mL of CH_2Cl_2. The mixture was stirred for 16 h and diluted with CH_2Cl_2 to a volume of 150 mL. The organic layer was washed with H_2O (75 ML), 10% $NaHSO_3$ (75 mL), 5% $NaHCO_3$ (75 mL), and dried (MgSO4). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 20:1) to afford lactone **198** (250 mg, 62% yield) as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32-7.28 (cm, 5H), 7.09 (m, 2H), 7.06 (m, 1H), 7.00 (td, *J*=1.0, 7.0 Hz, 1H), 6.93 (d, *J*=8.0 Hz, 1H), 6.86 (m, 2H), 5.00 (d, *J*=11.5 Hz, 1H), 4.93 (d, *J*=1.5 Hz, 1H), 4.93 (3, 1H), 2.29 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ 176.6, 156.2, 152.2, 137.1, 133.9, 132.6, 130.5, 129.5, 129.2, 129.0, 128.5, 128.1, 125.5, 125.2, 121.7, 113.5, 110.6, 70.0, 47.7, 21.4; **IR** (neat) 3033 (w), 2922 (w), 1815 (s), 1600 (m), 1486 (s), 1233 (s), 1065 (s), 1017 (m), 753 (s), 620 (w) cm^{-1}; **HRMS** (EI) *m/z* found: 330.1251, [calc'd for $C_{22}H_{18}O_3$ (M+): 330.1256].

Preparation of lactone 202 and benzofuran 200



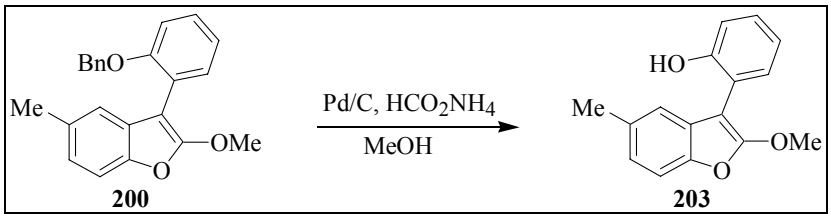
To a solution of lactone **198** (145 mg, 0.439 mmol) in THF (3 mL) at 0°C was added NaH (25 mg, 0.615 mmo; 60% dispersion in mineral oil, Aldrich) in one portion under N_2. The reaction was stirred at 0°C for 1 h before the granular NaH completely disappeared (the solution became dark yellow). Trimetyloxonium tetrafluoroborate (78 mg, 0.527 mmol) was added as a single portion and the mixture allowed to warm to room temperature. After stirring for 2 h the reaction was quenched with sat. NH_4Cl (5 mL) and diluted with ether (20 mL). The organic layer was washed with brine (2 x 10 mL) and dried ($MgSO_4$). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 40:1) to afford benzofuran **200** (87 mg, 58% yield) as a clear colorless oil and lactone **202** (51 mg, 34% yield) as a white solid.

The first compound to elute was benzofuran **200**, which was spectrally identical to the material prepared above.

The second compound to elute was lactone **202**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61 (dd, *J*=1.5, 8.0 Hz, 1H), 7.30-7.24 (cm, 4H), 7.07 (dt, *J*=0.5, 7.5 Hz, 1H), 7.00 (dd, *J*=1.0, 8.0 Hz, 1H), 6.95 (m, 2H), 6.82 (d, *J*=7.5 Hz, 1H), 6.74 (d, *J*=8.0 Hz, 1H), 6.69 (d, *J*=1.5 Hz, 1H), 4.92 (d, *J*=12.0 Hz, 1H), 4.78 (d, *J*=12.0 Hz, 1H), 2.27 (s, 3H), 1.83 (s, 3H); **^{13}C**

NMR (125 MHz, $CDCl_3$) δ 179.9, 155.3, 151.2, 135.7, 133.7, 133.2, 129.2, 128.2, 128.2, 127.7, 127.6, 127.0, 123.0, 120.7, 112.0, 109.9, 70.0, 48.3, 23.9, 21.0; **IR** (thin film/NaCl) 2917 (w), 1797 (s), 1488 (s), 1378 (w), 1261 (m), 1228 (m), 1145 (m), 1031 (s), 749 (m), 701 (w) cm^{-1}; **HRMS** (EI) *m/z* found: 345.1492, [calc'd for $C_{23}H_{21}O_3$ (M+H): 345.1491].

Preparation of phenol 203

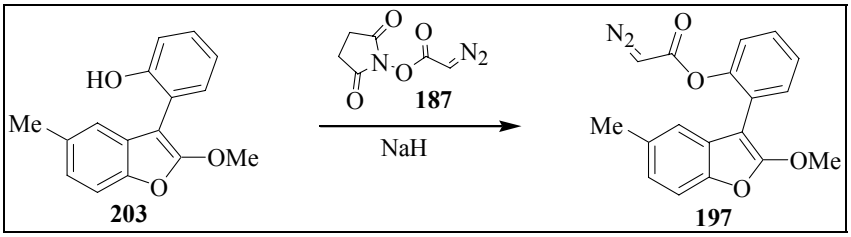


200 **203**

To a solution of benzofuran **200** (49 mg, 1.45 mmol) in MeOH (10 mL) was added 10% Pd/C (28 mg) and HCO_2NH_4 (45 mg, 0.71 mmol). The reaction mixture was heated to reflux for 15 min. after which time TLC showed the complete disappearance of starting material. After cooling to room temperature the reaction mixture was filtered over a pad of celite and washed with ethyl acetate (150 mL). This solution was concentrated in vacuo, dissolved in ethyl acetate (50 mL), washed with H_2O (2 x 25 mL), and dried ($MgSO_4$). Solvent removal in vacuo afforded analytically pure phenol **203** (34 mg, 95% yield) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 (dd, *J*=1.0, 7.5 Hz, 1H), 7.30 (d, *J*=8.0 Hz, 2H), 7.24 (m, 1H), 7.08 (dd, *J*=1.0, 8.0 Hz, 1H), 7.06-7.03 (cm, 2H), 5.58 (s, 1H), 4.12 (s, 3H), 2.42 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 157.6, 153.6, 147.2, 133.1, 130.5, 129.1, 129.0, 123.7, 120.7, 119.0, 117.3, 116.6, 110.1, 89.5, 59.0, 21.4; **IR** (thin film/NaCl) 3541 (br w), 2953 (w), 2926 (w), 1634 (m), 1611 (m), 1493

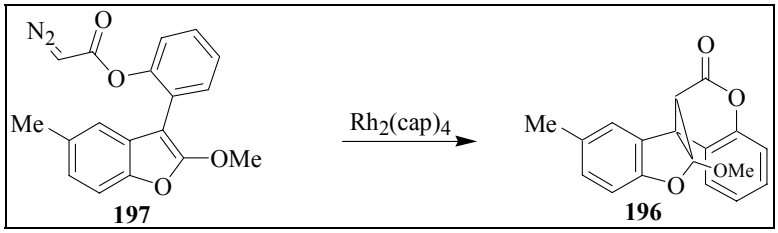
(m), 1371 (m), 1118 (w), 911 (s), 742 (s) cm^{-1}; **HRMS** (EI) *m/z* found: 254.0942, [calc'd for $C_{16}H_{14}O_3$ (M+): 254.0943].

Preparation of α-diazo ester 197



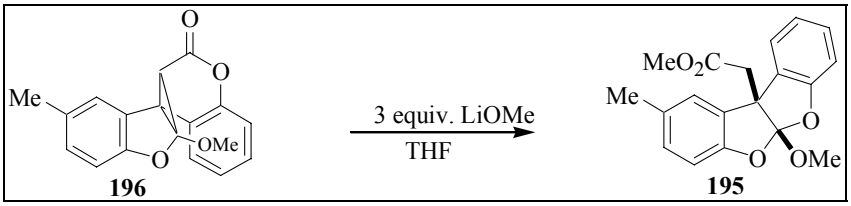
To a solution of phenol **203** (36 mg, 0.142 mmol) in THF (5 mL) at 0°C was added succinimide **187** (29 mg, 0.156 mmol) in THF (3 mL) via cannula over 5 minutes. The reaction mixture was warmed to room temperature during which time a brown precipitate formed. After 15 min. the solvent was removed in vacuo and the crude mixture taken up ethyl acetate. After filtration of the brown precipitate over a plug of cotton and solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 10:1) to afford α-diazo ester **197** (37 mg, 85% yield) as a clear bright yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 (dd, *J*=1.5, 7.5 Hz, 1H), 7.50-7.34 (cm, 5H), 7.09 (dd, *J*=1.0, 8.5 Hz, 1H), 4.78 (br s, 1H), 4.13 (s, 3H), 2.50 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.8, 148.3, 146.6, 132.6, 131.4, 129.3, 128.1, 126.0, 124.6, 123.1, 123.0, 119.1, 109.7, 90.2, 58.7, 21.4; **IR** (thin film/NaCl) 3112 (w), 2856 (w), 2114 (s), 1709 (s), 1493 (m), 1366 (s), 1287 (w), 1145 (s), 944 (m), 795 (m) cm^{-1}; **HRMS** (EI) *m/z* found: 322.0954, [calc'd for $C_{18}H_{14}N_2O_4$ (M+): 322.0954].

Preparation of lactone 196



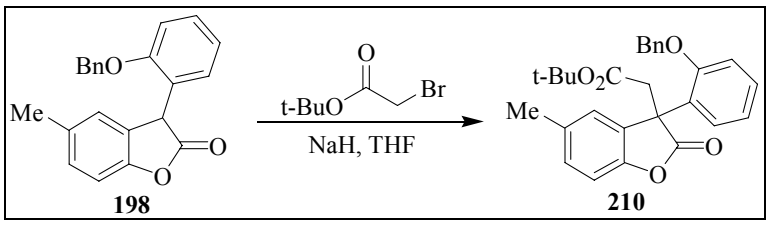
To a solution of α-diazo ester **197** (11 mg, 0.036 mmol) in CH_2Cl_2 (2 mL) was added $Rh_2(cap)_4$ (0.3 mg, 0.000458 mmol) in CH_2Cl_2 (2 mL) over 4 h via syringe pump. After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 20:1) to afford lactone **196** (9.4 mg, 89% yield) as a clear colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60 (dd, *J*=1.5, 7.5 Hz, 1H), 7.39-7.35 (cm, 2H), 7.24-7.13 (cm, 3H), 7.00 (d, *J*=8.0 Hz, 1H), 3.35 (s, 3H), 2.39 (s, 3H), 2.12 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.2, 155.4, 150.3, 131.6, 129.5, 129.0, 126.7, 126.6, 124.7, 124.5, 117.8, 114.0, 1109, 98.3, 56.4, 40.4, 32.2, 21.0; **IR** (thin film/NaCl) 2926 (w), 2857 (w), 1757 (s), 1481 (m), 1454 (m), 1375 (w), 1285 (m), 1205 (s), 1101 (m), 757 (w) cm^{-1}; **HRMS** (EI) *m/z* found: 295.0969, [calc'd for $C_{18}H_{15}O_4$ (M+H): 295.0970].

Preparation of orthoester 195



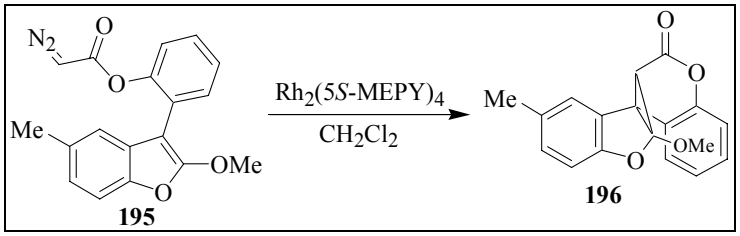
To a solution of lactone **196** (9.0 mg, 0.0306 mmol) in THF (4 mL) at 0 °C was added LiOMe (1 mL, 0.0917M in MeOH). After 30 min. the reaction was quenched with sat. NH_4Cl (5 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (2 x 10 mL) and the combined organic layers dried (MgSO4). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 20:1) to afford orthoester **195** (7.6 mg, 76% yield) as a clear colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 (dd, *J*=1.0, 7.5 Hz, 1H), 7.19-7.15 (cm, 2H), 6.97-6.94 (cm, 2H), 6.86 (d, *J*=8.0 Hz, 1H), 6.76 (d, *J*=8.0 Hz, 1H), 3.80 (s, 3H), 3.5 (s, 3H), 3.13 (s, 2H), 2.29 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.3, 156.1, 154.0, 131.5, 130.1, 129.9, 129.5, 129.0, 123.8, 123.4, 122.0, 110.1, 109.7, 57.0, 52.0, 51.6, 37.6, 29.7, 21.0; **IR** (thin film/NaCl) 2952 (m), 2924 (m), 1744 (s), 1492 (s), 1462 (m), 1268 (s), 1223 (s), 1043 (s), 936 (s), 811 (w) cm^{-1}; **HRMS** (EI) *m/z* found: 327.1233, [calc'd for $C_{19}H_{19}O_5$ (M+H): 327.1232].

Preparation of lactone 210



To a solution of lactone **198** (30 mg, 0.091 mmol) in THF (5 mL) at 0°C was added NaH (8.0 mg, 0.109 mmo; 60% dispersion in mineral oil, Aldrich) in one portion under N_2. The reaction was stirred at 0°C for 1 h before the granular NaH completely disappeared (the solution became dark yellow). *t*-butylbromo acetate (0.016 mL, 0.109 mmol) was added as a single portion and the mixture allowed to warm to room temperature. After stirring for 2 h the reaction was quenched with sat. NH_4Cl (5 mL) and diluted with ether (20 mL). The organic layer was washed with brine (2 x 10 mL) and dried ($MgSO_4$). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 20:1) to lactone **210** (35 mg, 90% yield) as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 (dd, *J*=1.0, 9.0 Hz, 1H), 7.27-7.24 (cm, 4H), 7.01-6.97 (cm, 4H), 6.79 (m, 2H), 6.68 (d, *J*=8.0 Hz, 1H), 4.95 (d, *J*=8.0 Hz, 1H), 4.80 (d, *J*=12. Hz, 1H), 3.38 (d, *J*=14.5 Hz, 1H), 3.33 (d, *J*=14.0 Hz, 1H), 2.25 (s, 3H), 1.2 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 178.3, 168.0, 155.5, 152.4, 135.7, 133.0, 130.0, 129.4, 128.8, 128.3, 127.8, 127.7, 127.7, 126.7, 123.9, 120.7, 112.6, 109.7, 81.8, 70.1, 50.5, 42.7, 27.5, 21.0; **IR** (thin film/NaCl) 2978 (w), 228 (w), 1807 (s), 1728 (s), 1597 (w), 1488 (s), 1368 (m), 1157 (s), 1127 (m), 844 (w) cm^{-1}; **HRMS** (EI) *m/z* found: 444.1928, [calc'd for $C_{28}H_{28}O_5$ (M+): 444.1937].

Preparation of enantioenriched cyclopropane 196



To a solution of α-diazo ester **195** (14 mg, 0.0434 mmol) in CH_2Cl_2 (2 mL) was added $Rh_2(cap)_4$ (0.4 mg, 0.000516 mmol) in CH_2Cl_2 (2 mL) over 4 h via syringe pump. After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 20:1) to afford lactone **196** (10.8 mg, 84% yield) as a clear colorless oil. Optically active xx was spectrally identical (^1H, ^{13}C, FT-IR) to racemic xx from $Rh_2(cap)_4$ with $\alpha^{20}[D] = +184.7°$ (*c* 0.15, $CHCl_3$). The enantioselectivity was determined by portion wise addition of the chiral shift reagent europium tris[3-(hepte-fluoropropylhydroxymethylene)-(+)camphorate (20 mg, 0.0168 mmol) to a solution of xx (6 mg, 0.02 mmol) in approximately 1 mL of $CDCl_3$. Sufficient resolution of the OMe peak for integration purposes was seen after the addition of the 4th portion (80 mg total) of the chiral shift reagent.

2.7 Notes and References

1. "Organic-Synthesis with Alpha-Diazocarbonyl Compounds", Ye T., McKervey M. A., *Chemical Reviews*, **1994**, *94*, 1091-1160.

2. Doyle M., McKervey M., Ye T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: from Cyclopropanes to Ylides*. New York: Wiley & Sons; 1998.

3. "Recent advances in asymmetric catalytic metal carbene transformations", Doyle M. P., Forbes D. C., *Chemical Reviews*, **1998**, *98*, 911-935.

4. "Total Synthesis of Bioactive Marine Macrolides", Norcross R. D., Paterson I., *Chemical Reviews*, **1995**, *95*, 2041-2114.

5. "Ulapualide-a and Ulapualide-B Extraordinary Antitumor Macrolides from Nudibranch Eggmasses", Roesener J. A., Scheuer P. J., *Journal of the American Chemical Society*, **1986**, *108*, 846-847.

6. "Phorboxazole-a and Phorboxazole-B - Potent Cytostatic Macrolides from Marine Sponge Phorbas Sp", Searle P. A., Molinski T. F., *Journal of the American Chemical Society*, **1995**, *117*, 8126-8131.

7. "A Convenient Synthesis of 2,4,5-Trisubstituted Oxazoles", Reddy G. S., Bhatt M. V., *Indian Journal of Chemistry Section B-Organic Chemistry Including Medicinal Chemistry*, **1981**, *20*, 322-323.

8. "Ortho-Claisen Rearrangement .4. Rearrangement of X-Cinnamyl Para-Tolyl Ethers", White W. N., Fife W. K., *Journal of the American Chemical Society*, **1961**, *83*, 3846.

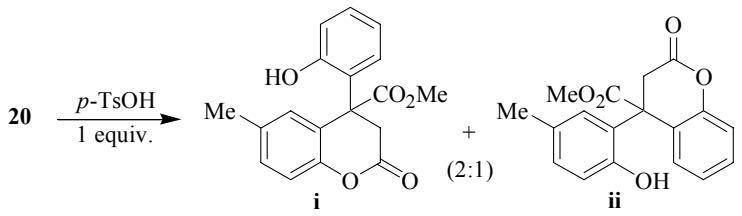
9. "A New Diazoacylating Reagent - Preparation, Structure, and Use of Succinimidyl Diazoacetate", Ouihia A., Rene L., Guilhem J., Pascard C., Badet B., *Journal of Organic Chemistry*, **1993**, *58*, 1641-1642.

10. "Ligand Effects on the Chemoselectivity of Transition-Metal- Catalyzed Reactions of Alpha-Diazo Carbonyl-Compounds", Padwa A., Austin D. J., *Angewandte Chemie-International Edition in English*, **1994**, *33*, 1797-1815.

11. For an excellent book on the chemistry of indoles, oxazole, and other heterocycles, see: Gilchrist T. L. *Heterocyclic Chemistry*. 2nd ed. ed. New York: Wiley.

12. "Intramolecular Cyclopropanation Reaction of Furanyl Diazo Ketones", Padwa A., Wisnieff T. J., Walsh E. J., *Journal of Organic Chemistry*, **1989**, *54*, 299-308.

13. Cyclopropane **196** can also be opened under acidic conditions (p-TsOH, 1 equiv.) to give a 2:1 mixture of i and ii, respectively.



14. "Enantioselective Intramolecular Cyclopropanations of Allylic and Homoallylic Diazoacetates and Diazoacetamides Using Chiral Dirhodium(Ii) Carboxamide Catalysts", Doyle M. P., Austin R. E., Bailey A. S., Dwyer M. P., Dyatkin A. B., Kalinin A. V., Kwan M. M. Y., Liras S., Oalmann C. J., Pieters R. J., Protopopova M. N., Raab C. E., Roos G. H. P., Zhou Q. L., Martin S. F., *Journal of the American Chemical Society*, **1995**, *117*, 5763-5775.

15. "Comparative evaluation of enantiocontrol for intramolecular cyclopropanation of diazoacetates with chiral Cu-I, Rh-II and Ru-II catalysts", Doyle M. P., Peterson C. S., Zhou Q. L., Nishiyama H., *Chemical Communications*, **1997**, 211-212.

16. "High Enantioselectivity in the Intramolecular Cyclopropanation of Allyl Diazoacetates Using a Novel Rhodium(Ii) Catalyst", Doyle M. P., Pieters R. J., Martin S. F., Austin R. E., Oalmann C. J., Muller P., *Journal of the American Chemical Society*, **1991**, *113*, 1423-1424.

17. "Enantioselective, Rhodium Catalyzed Intramolecular Cyclopropanations of Homoallytic Diazoacetates", Martin S. F., Oalmann C. J., Liras S., *Tetrahedron Letters*, **1992**, *33*, 6727-6730.

Appendix One: Spectra Relevant

To Chapter Two

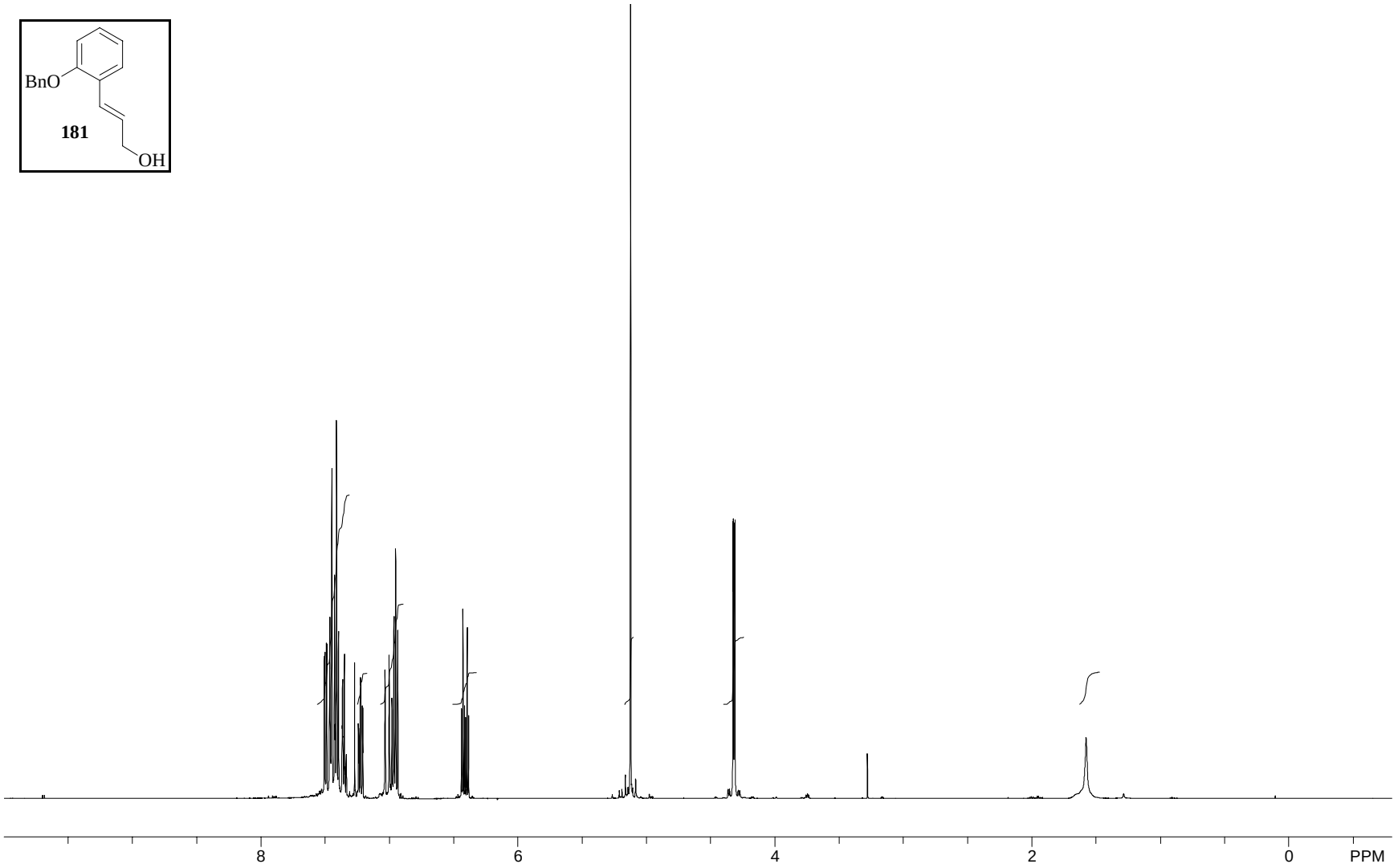


Figure A.1.1 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **181**.

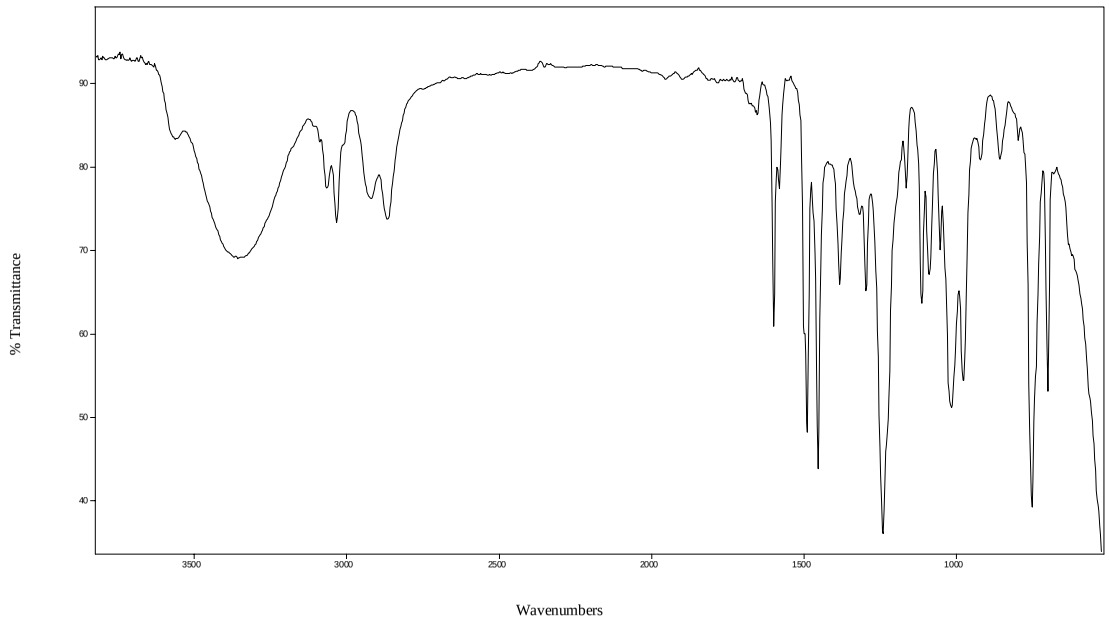


Figure A.1.2 FTIR Spectrum (thin film/NaCl) of Compound **181**.

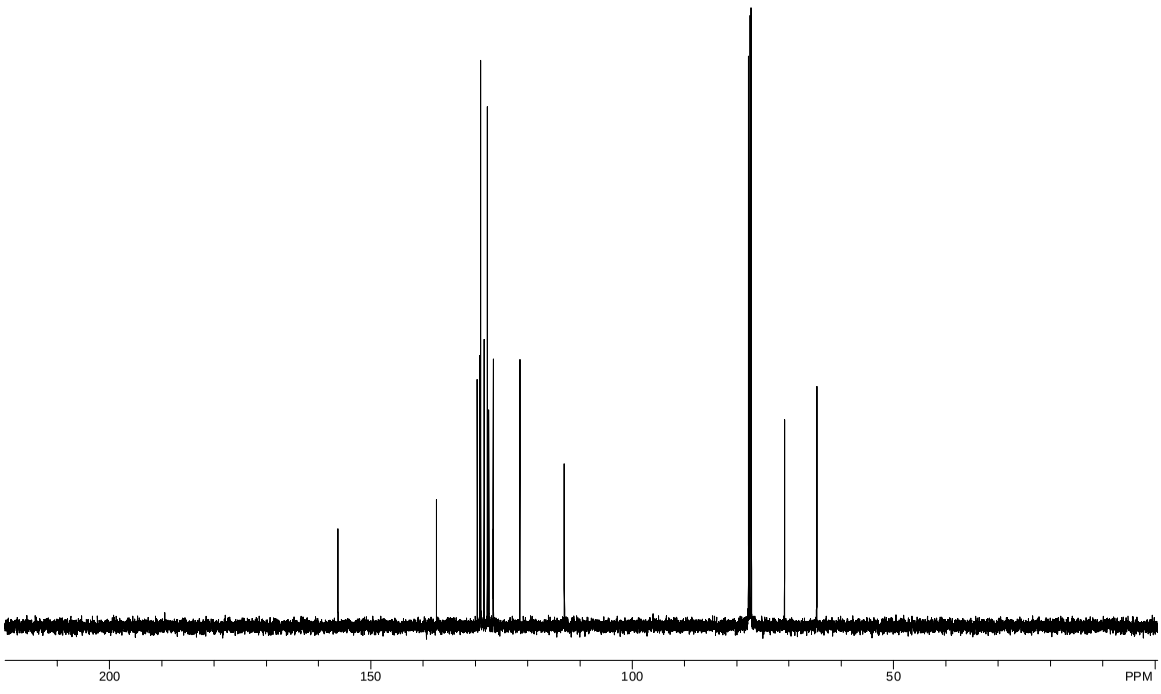


Figure A.1.3 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **181**.

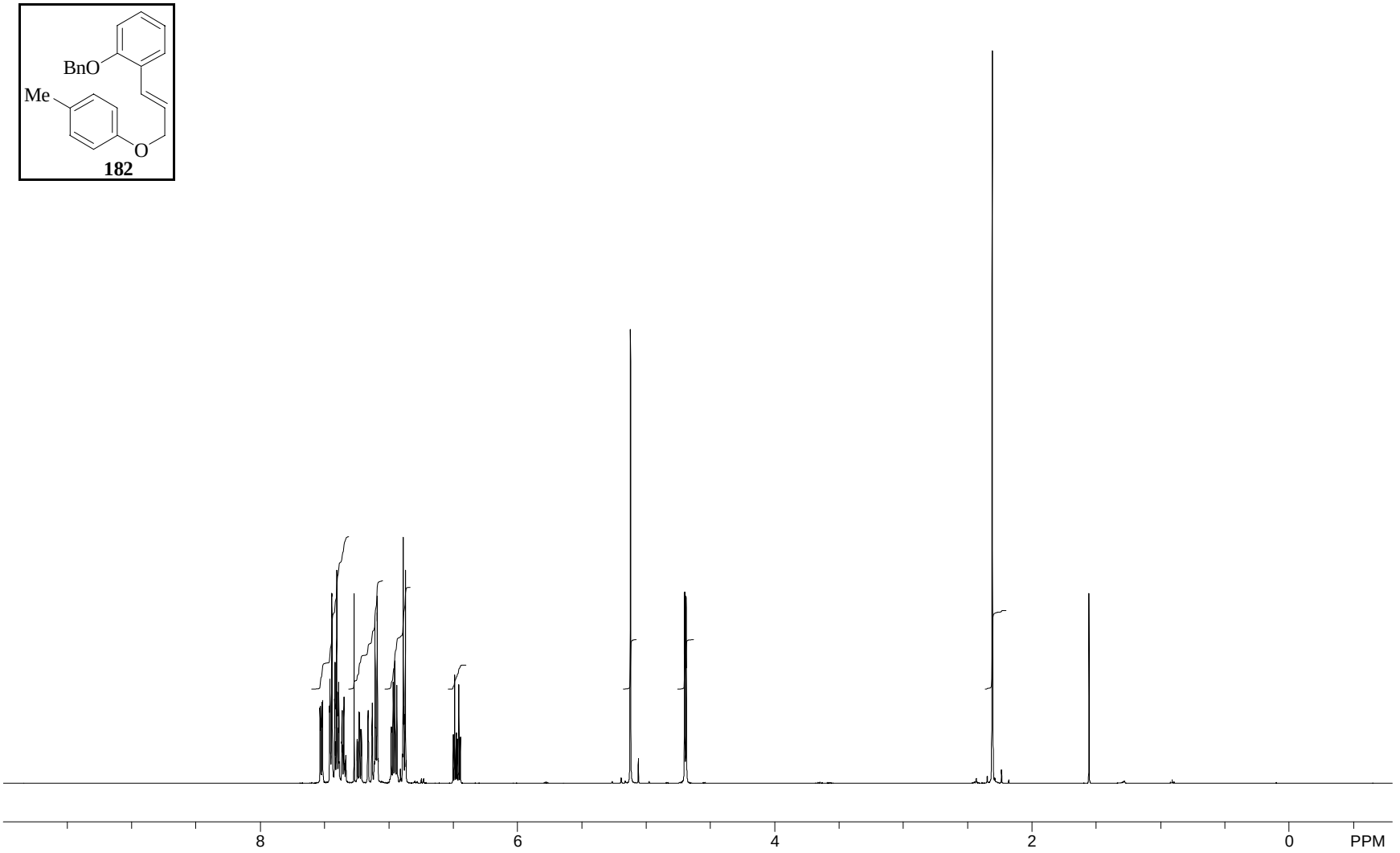


Figure A.1.4 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **182**.

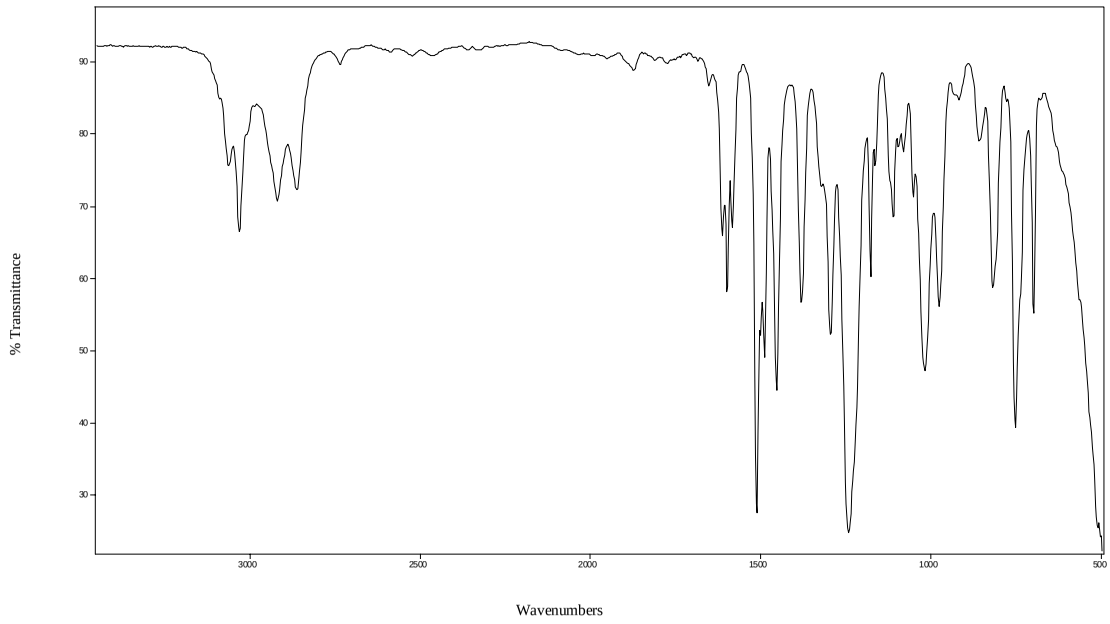


Figure A.1.5 FTIR Spectrum (thin film/NaCl) of Compound **182**.

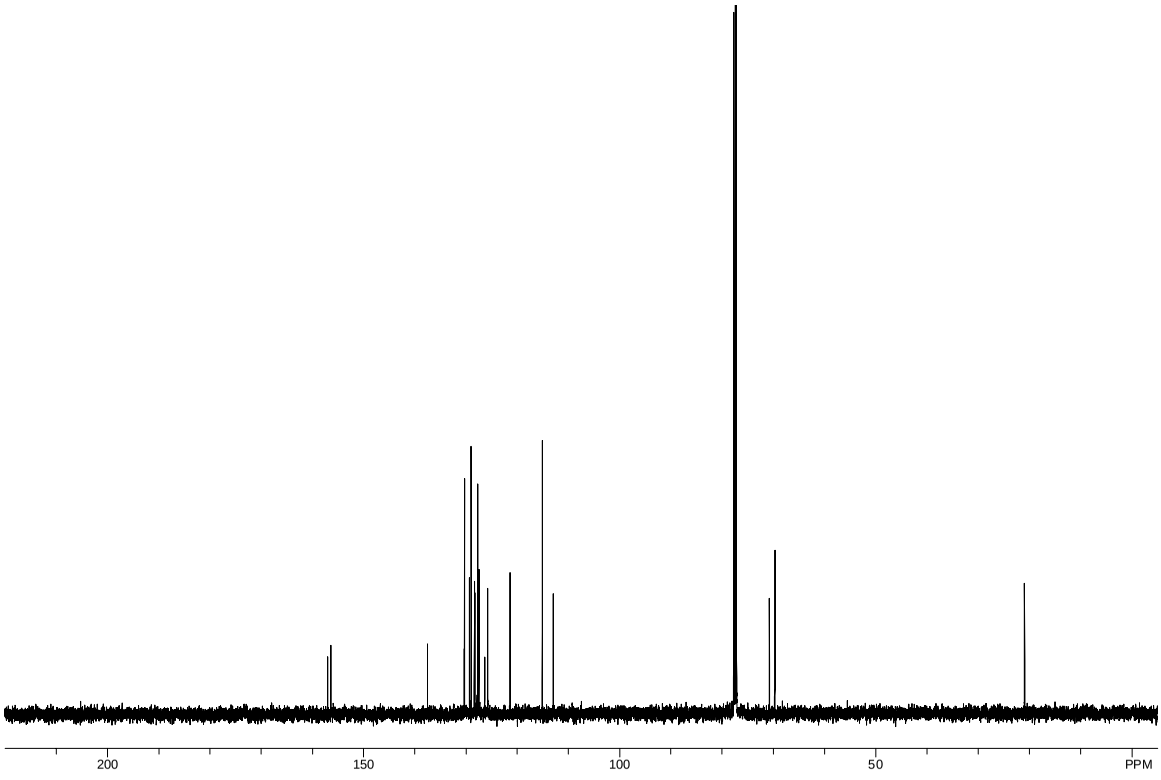


Figure A.1.6 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **182**.

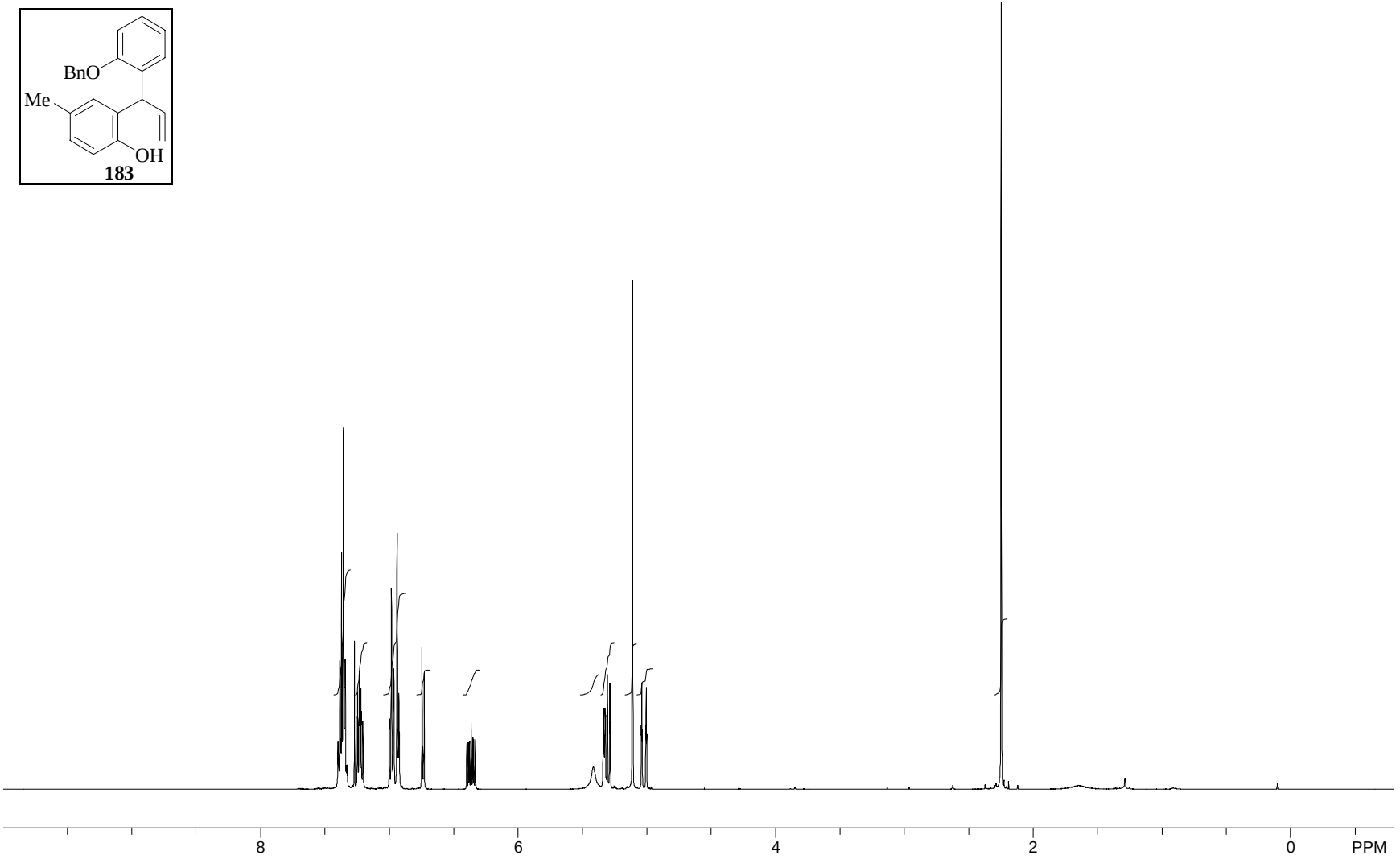


Figure A.1.7 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **183**.

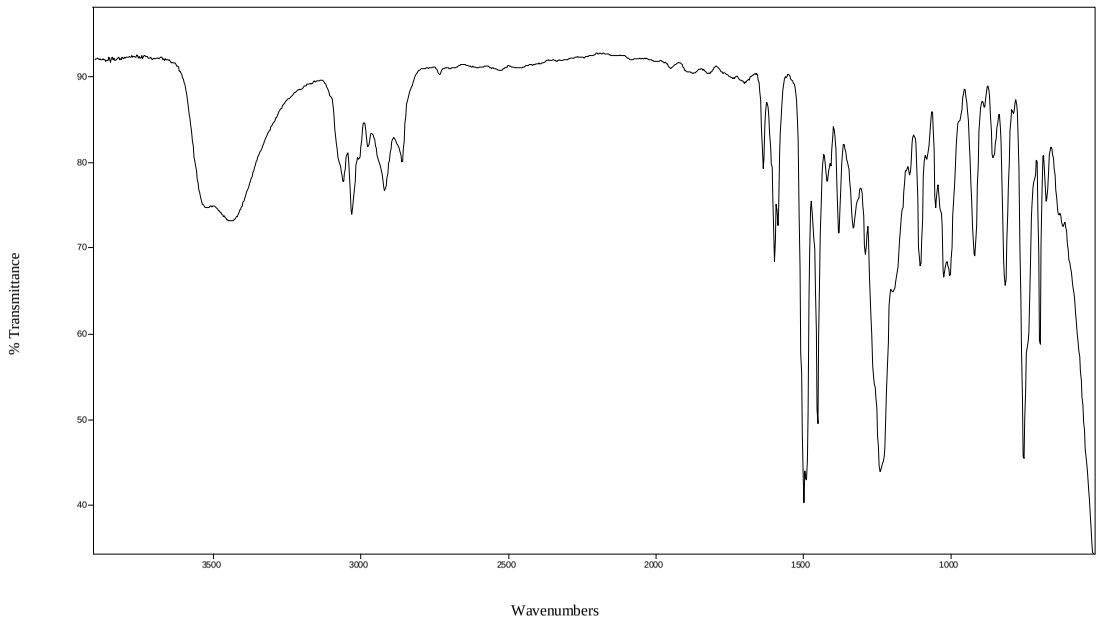


Figure A.1.8 FTIR Spectrum (thin film/NaCl) of Compound **183**.

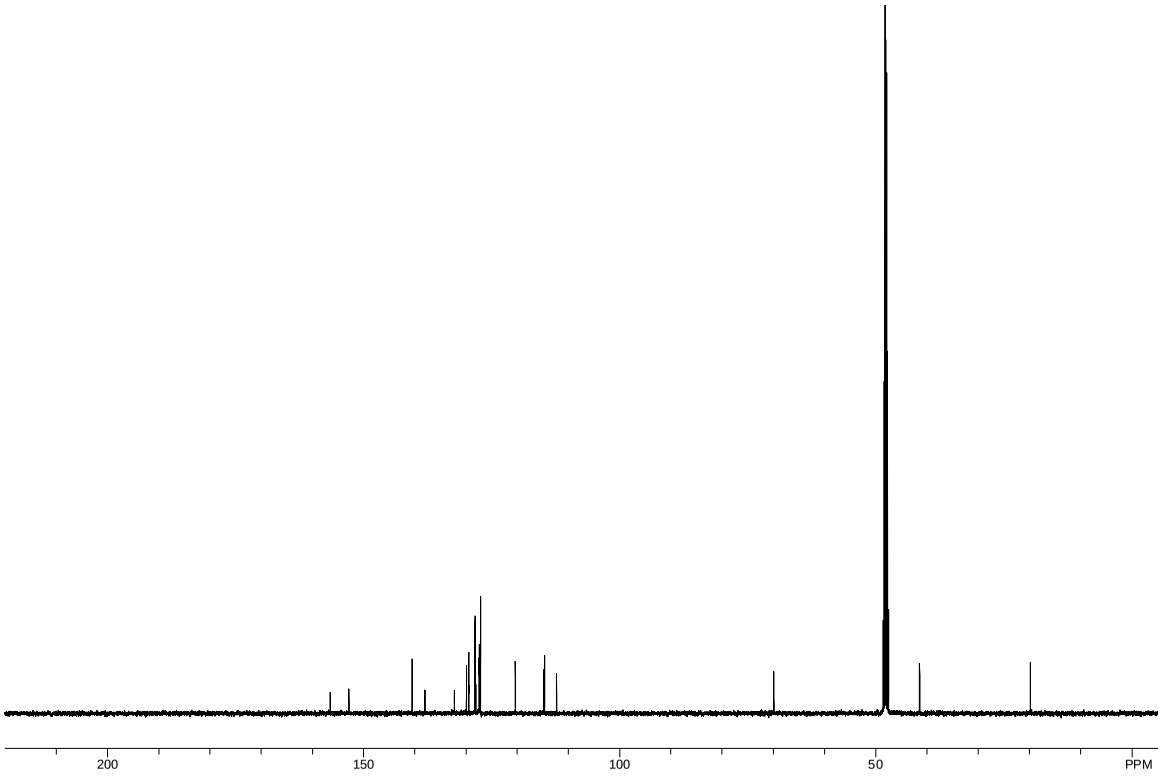


Figure A.1.9 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **183**.

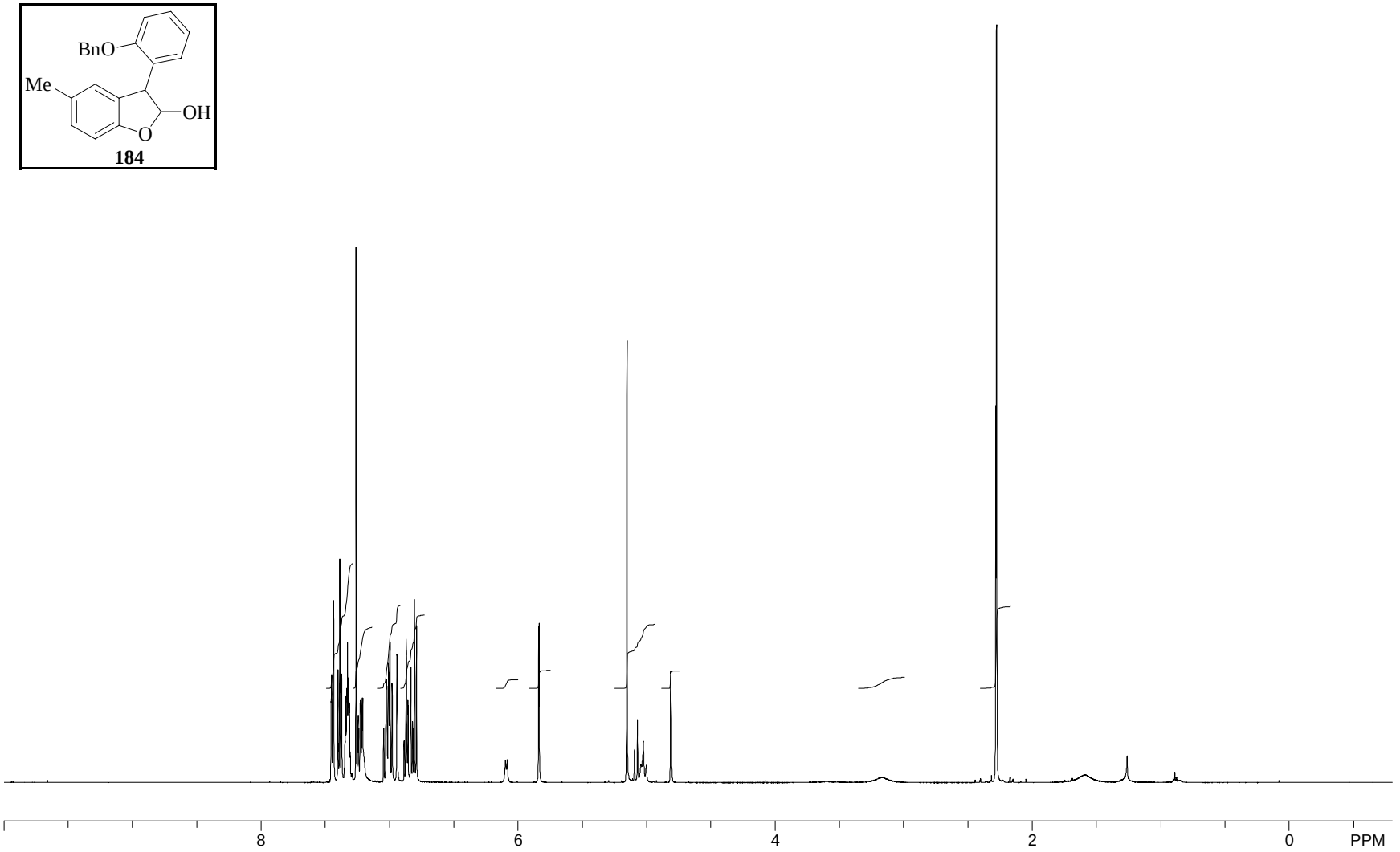


Figure A.1.10 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **184**.

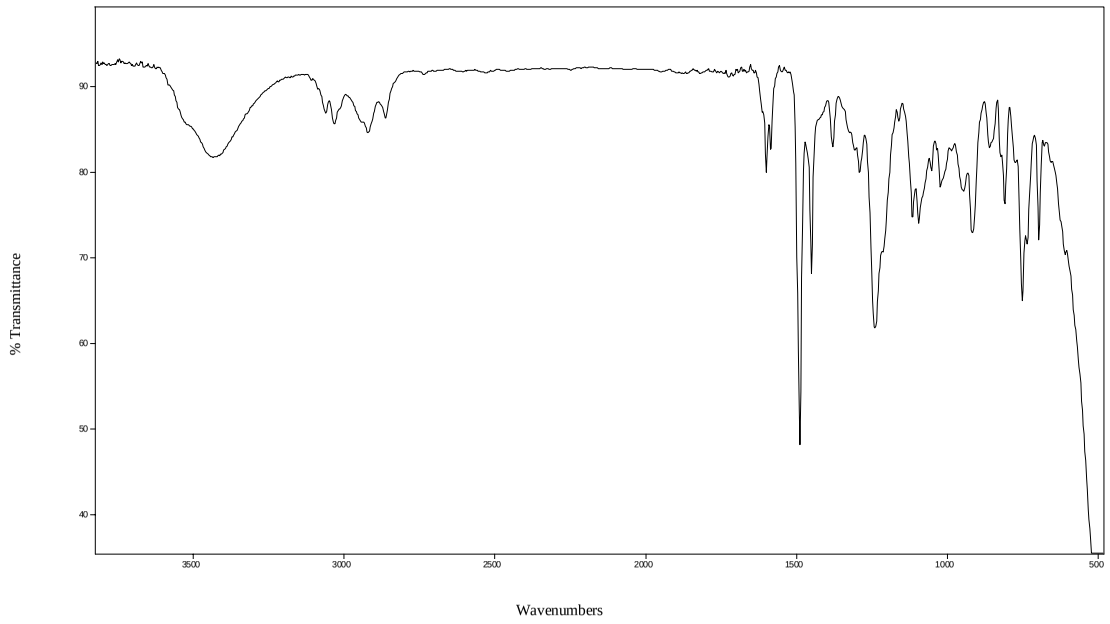


Figure A.1.11 FTIR Spectrum (thin film/NaCl) of Compound **184**.

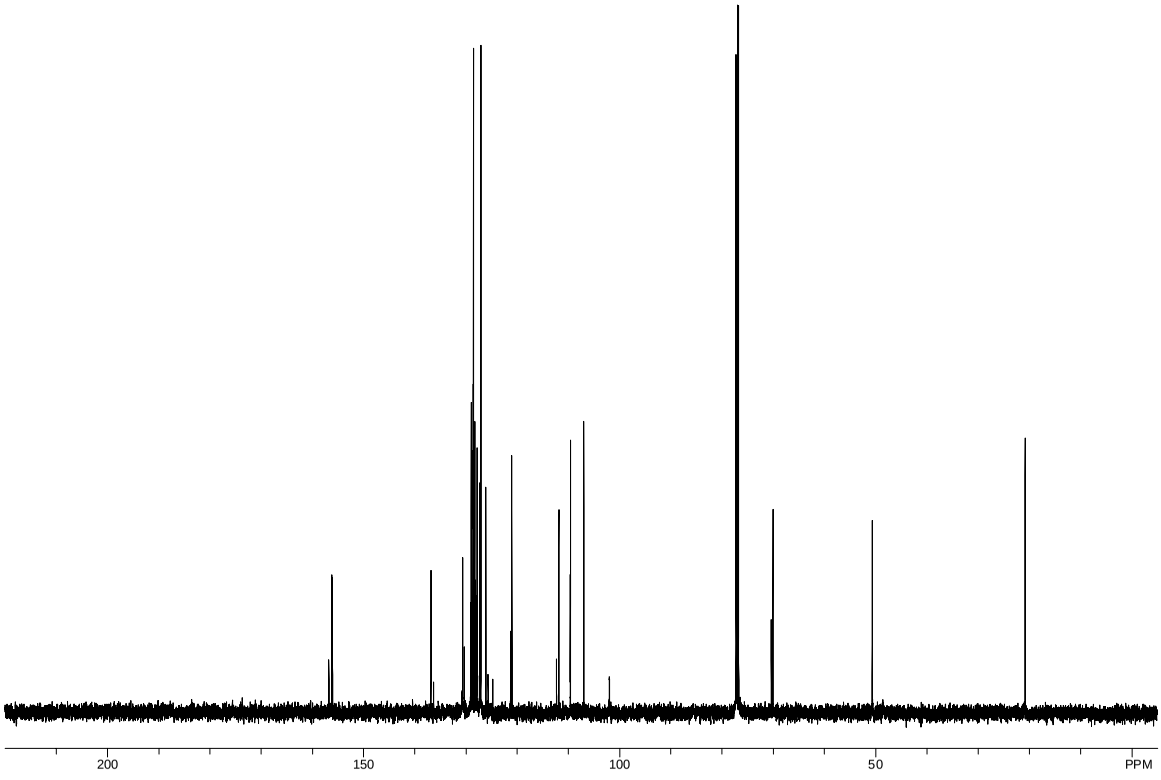


Figure A.1.12 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **184**.

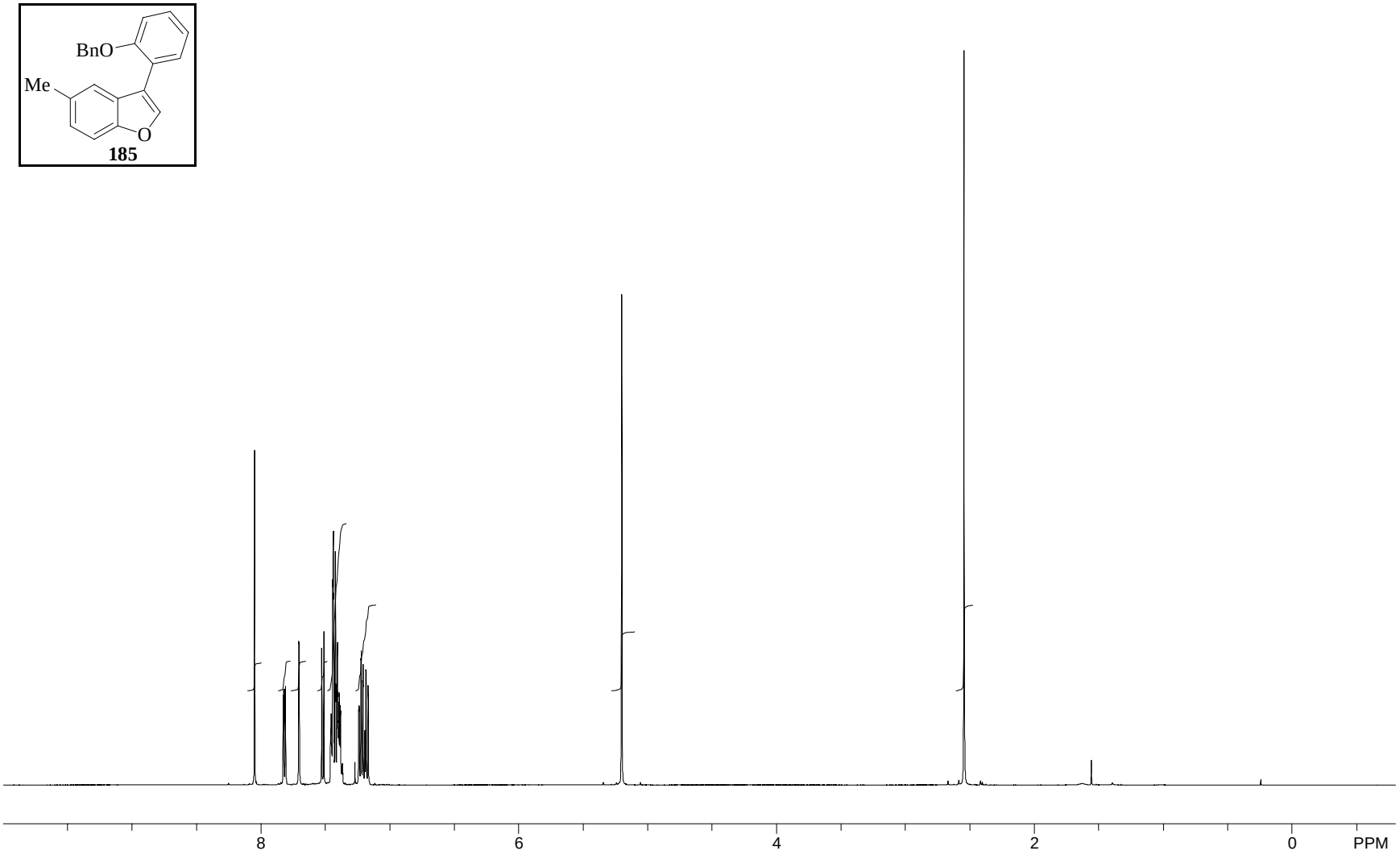


Figure A.1.13 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **185**.

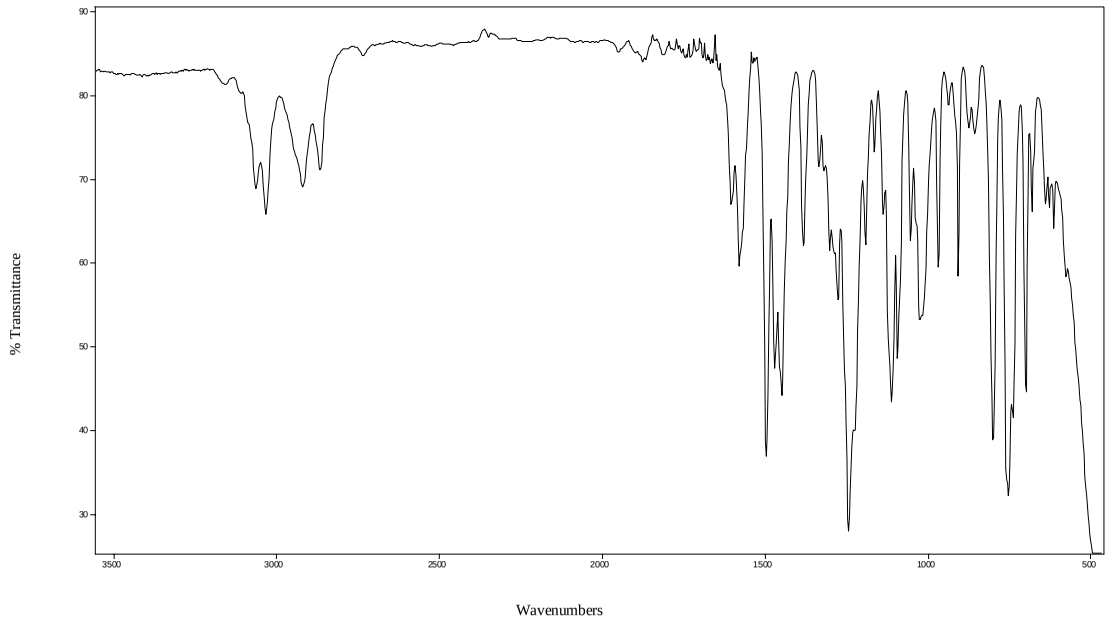


Figure A.1.14 FTIR Spectrum (thin film/NaCl) of Compound **185**.

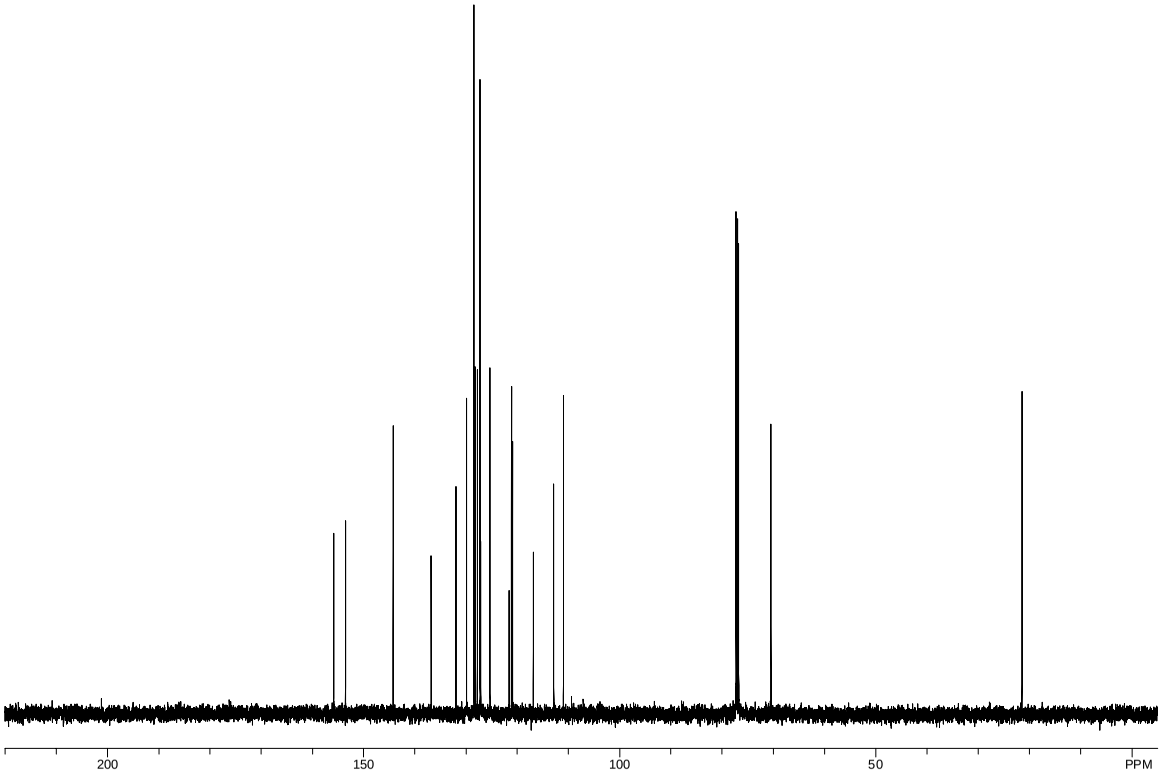


Figure A.1.15 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **185**.

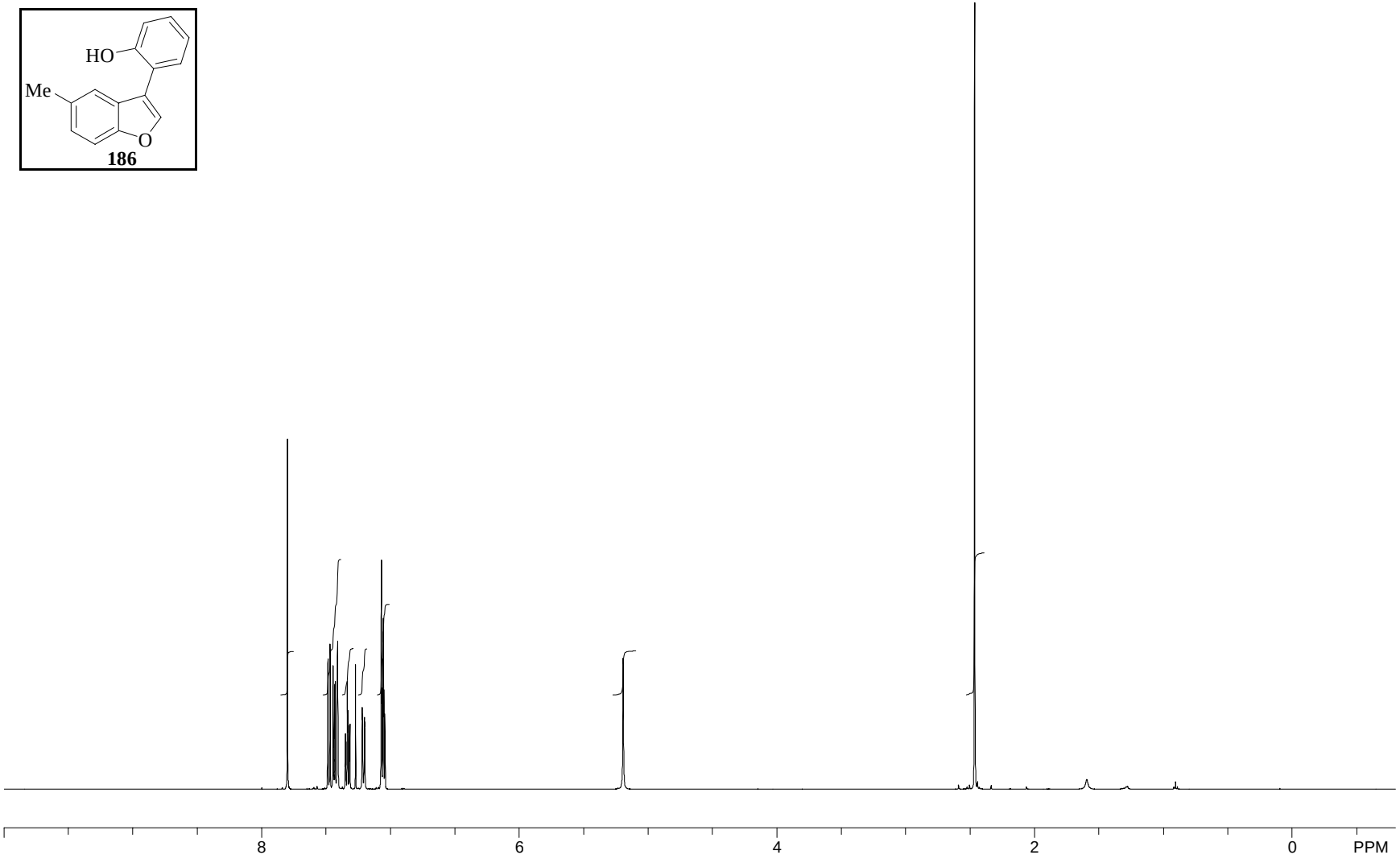


Figure A.1.16 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **186**.

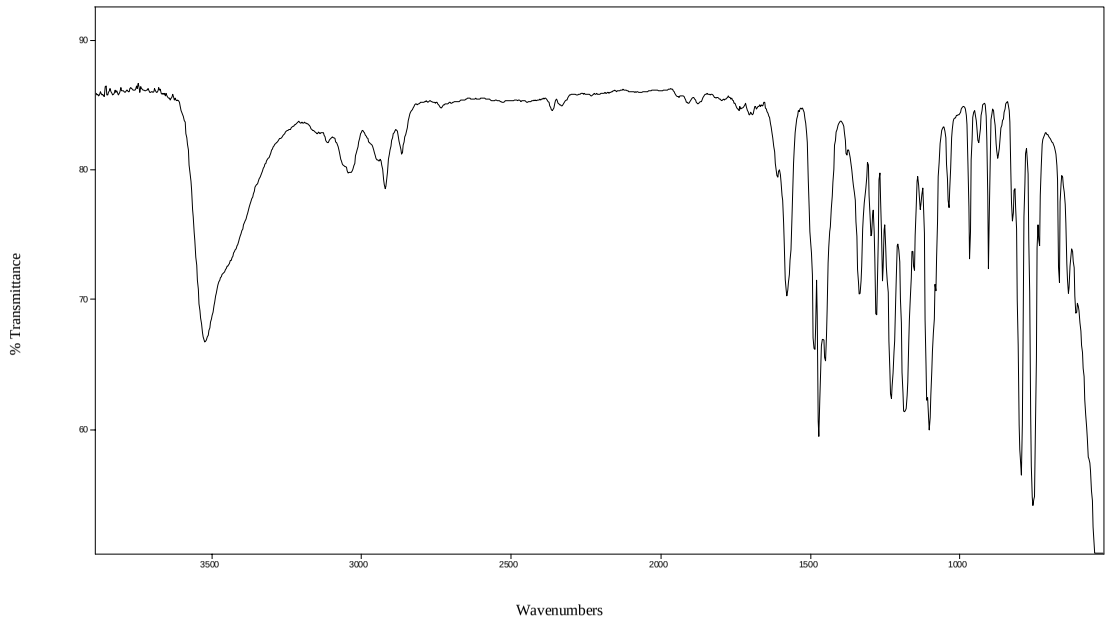


Figure A.1.17 FTIR Spectrum (thin film/NaCl) of Compound **186**.

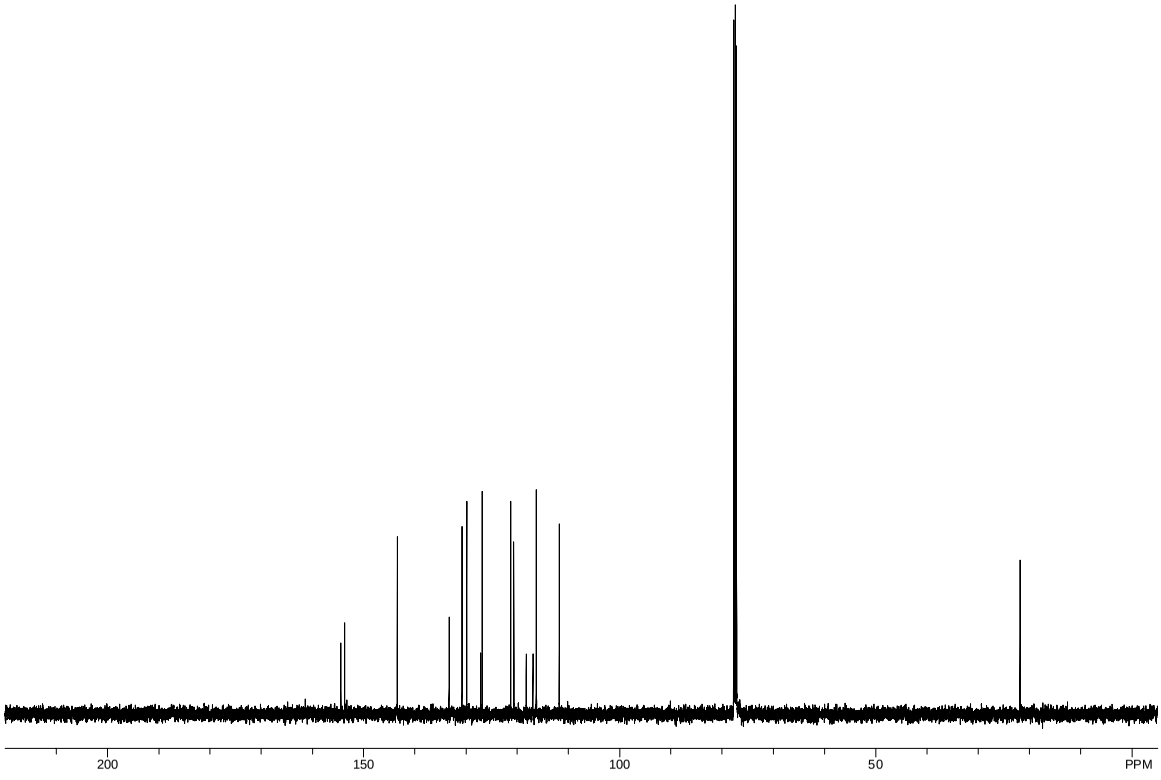


Figure A.1.18 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **186**.

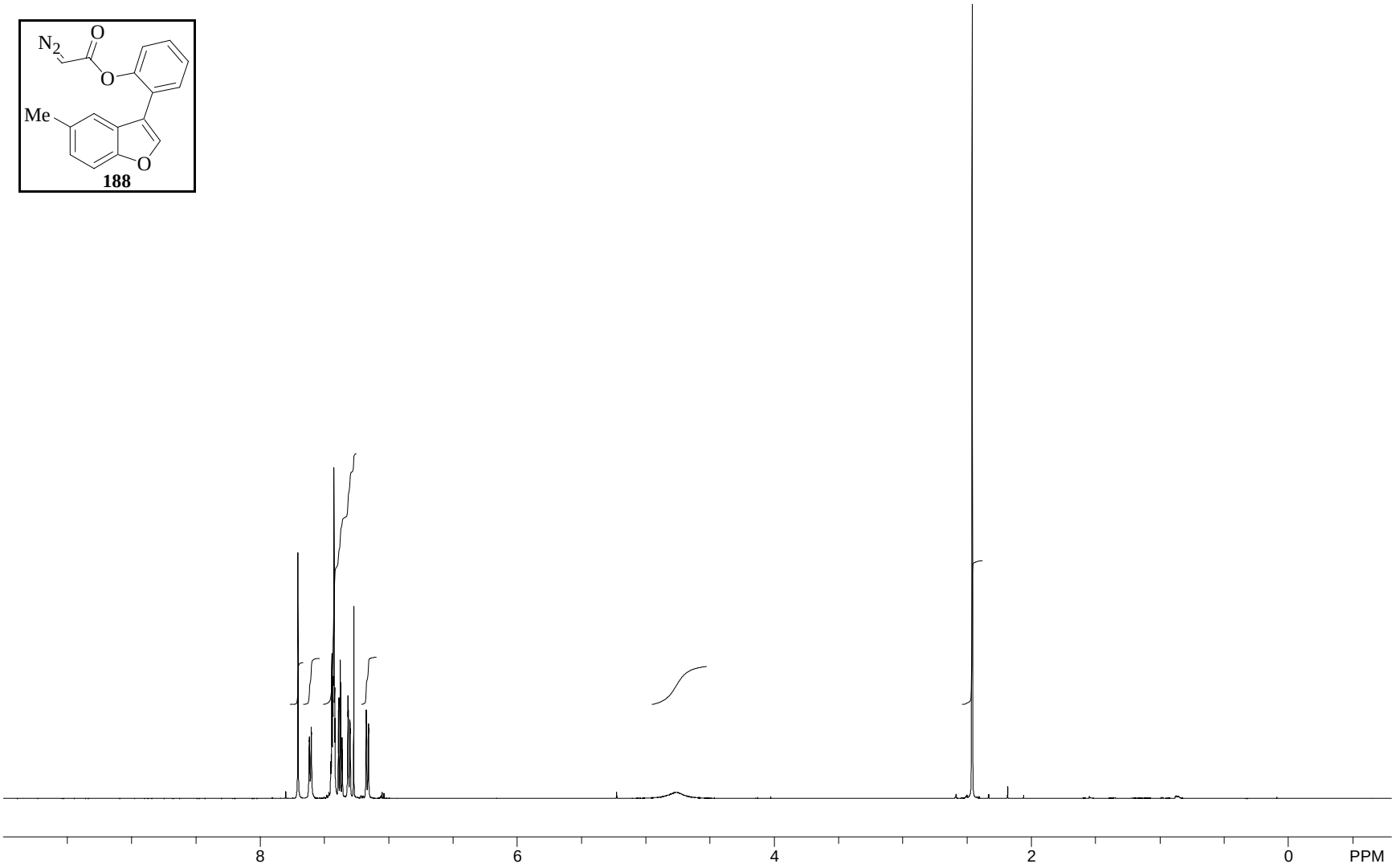


Figure A.1.19 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **188**.

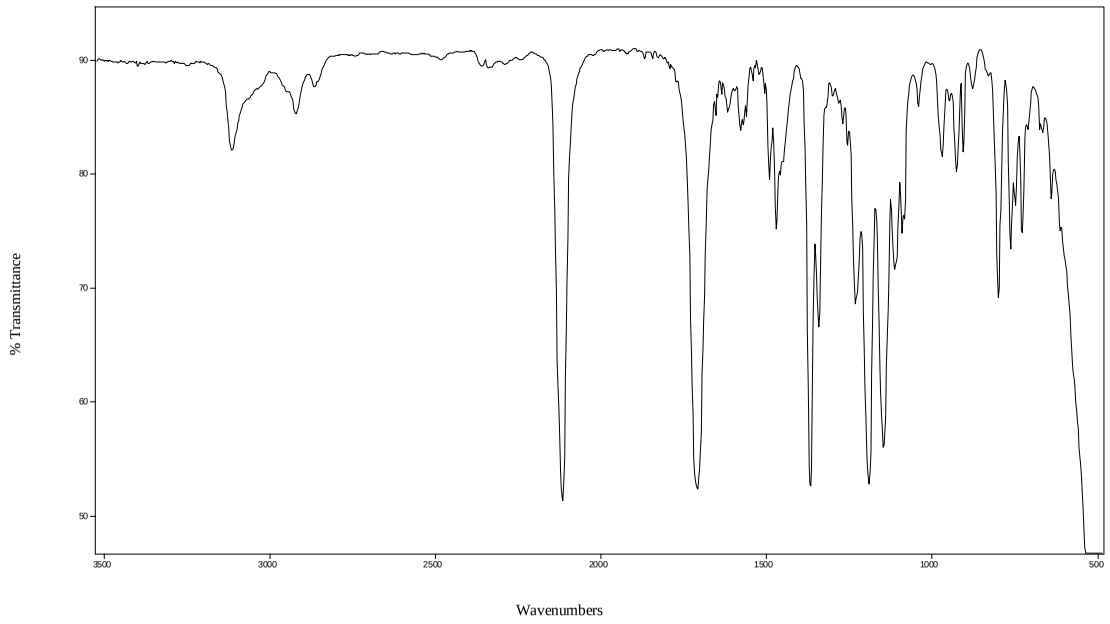


Figure A.1.20 FTIR Spectrum (thin film/NaCl) of Compound **188**.

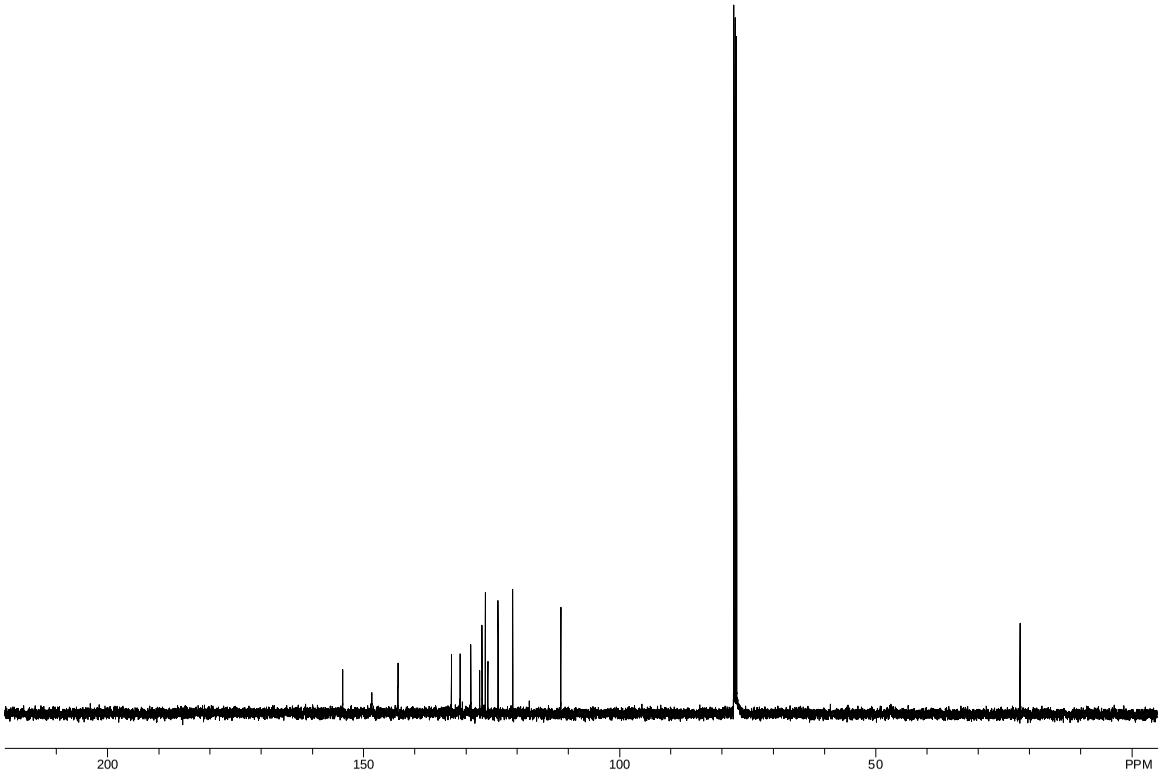


Figure A.1.21 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **188.**

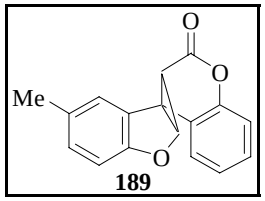


Figure A.1.22 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **189**.

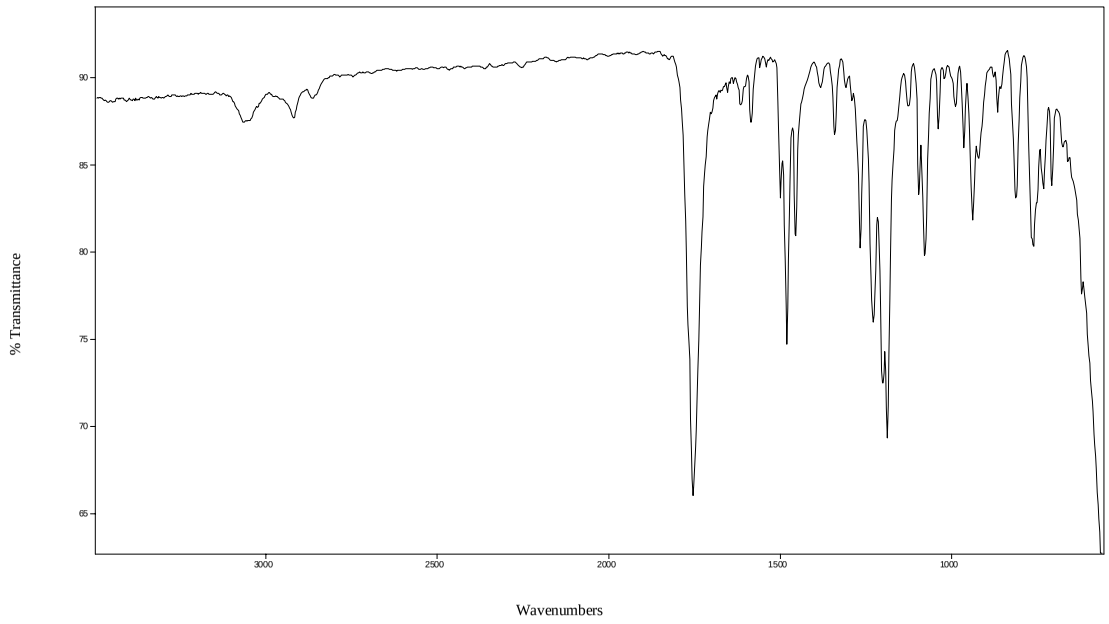


Figure A.1.23 FTIR Spectrum (thin film/NaCl) of Compound **189**.

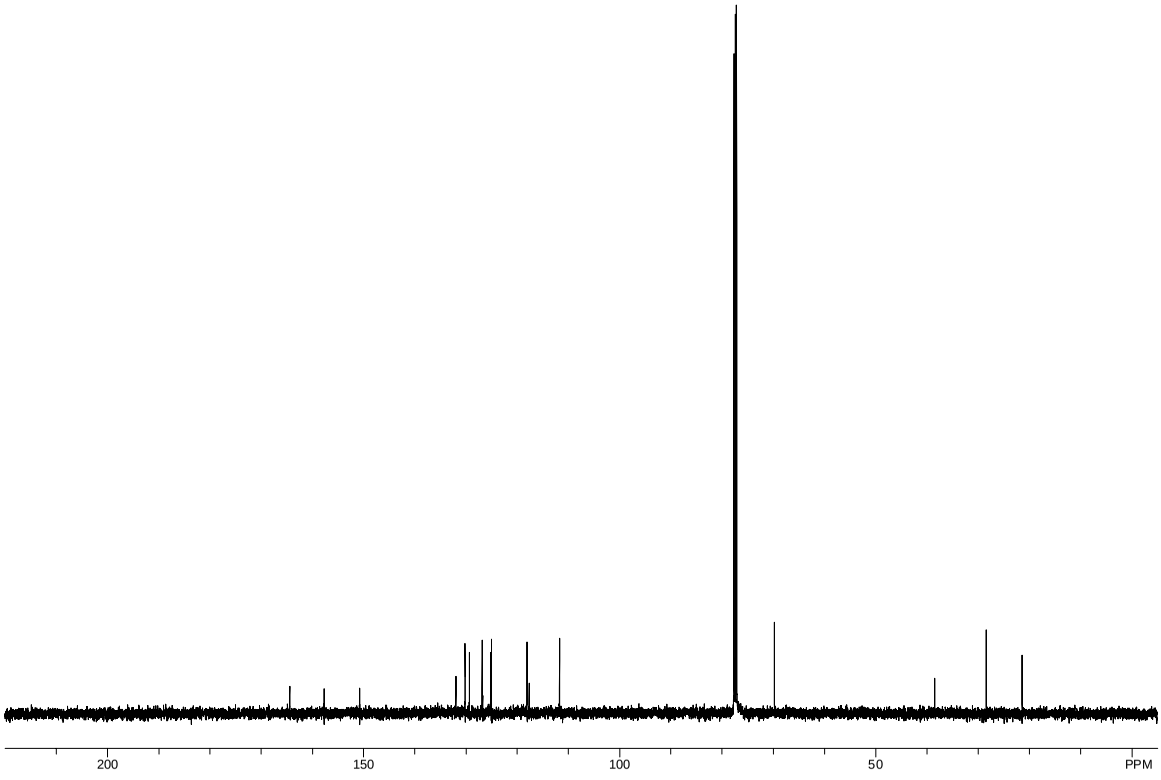


Figure A.1.24 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **189**.

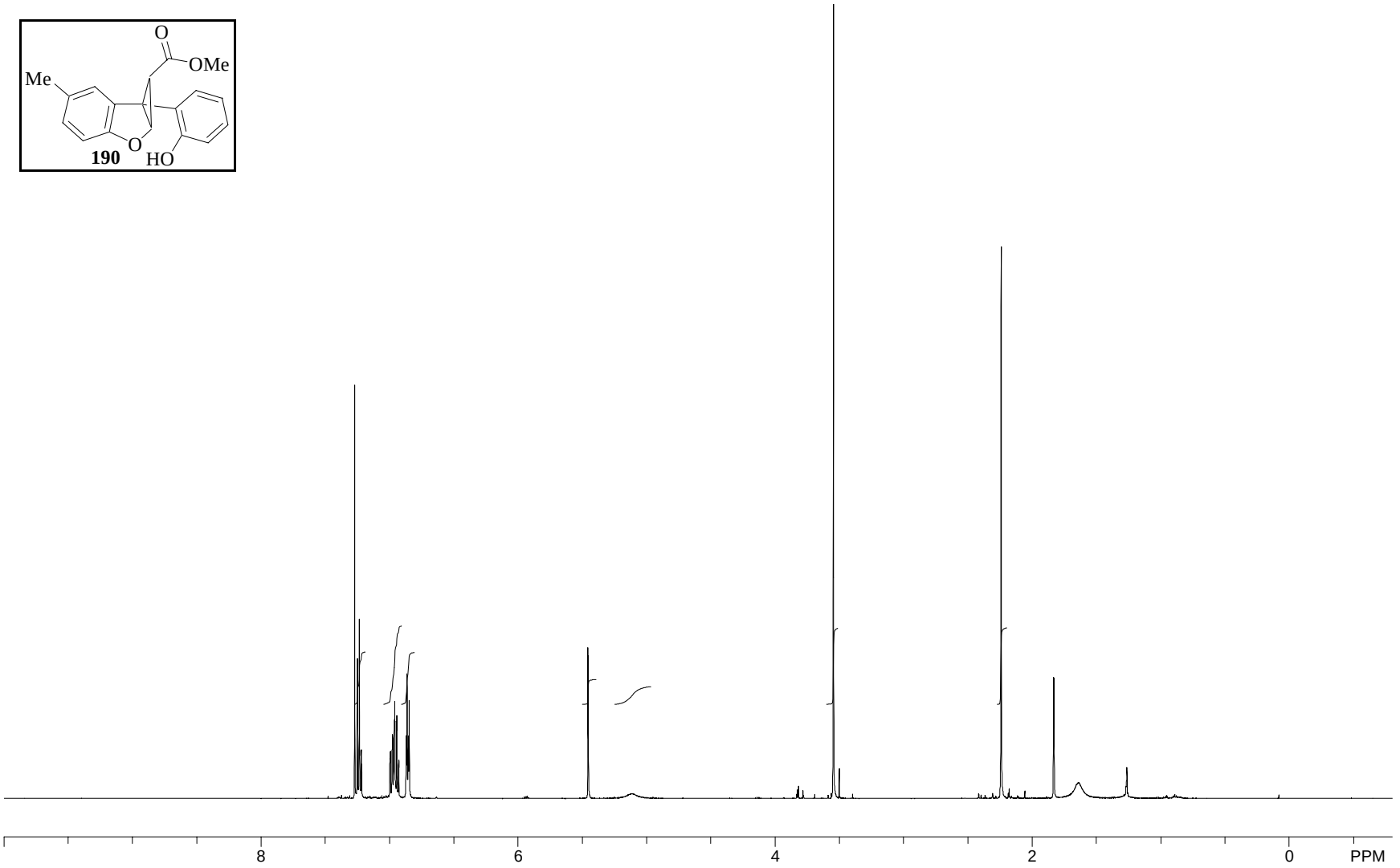


Figure A.1.25 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **190**.

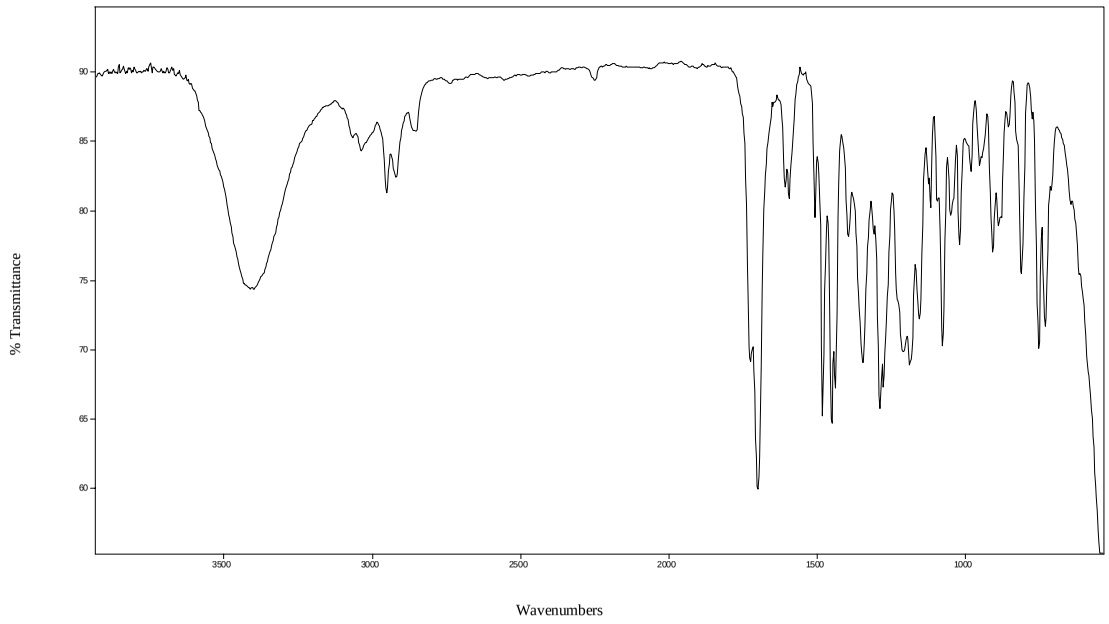


Figure A.1.26 FTIR Spectrum (thin film/NaCl) of Compound **190**.

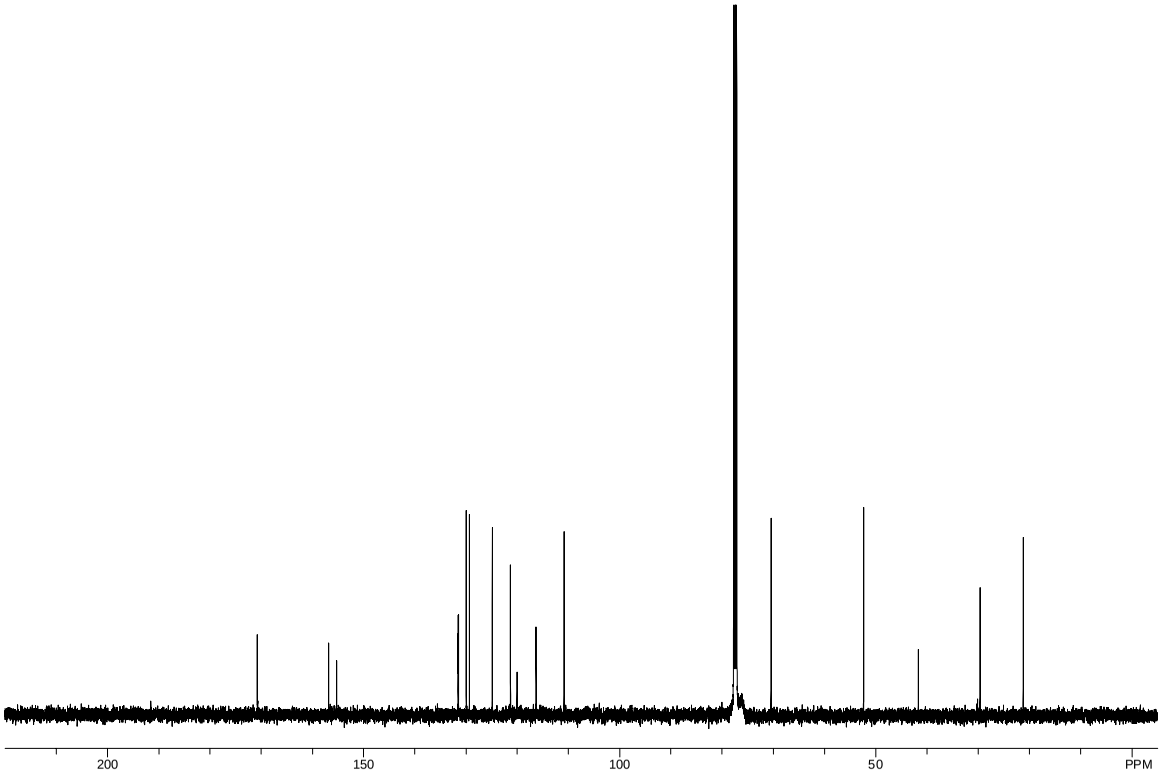


Figure A.1.27 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **190**.

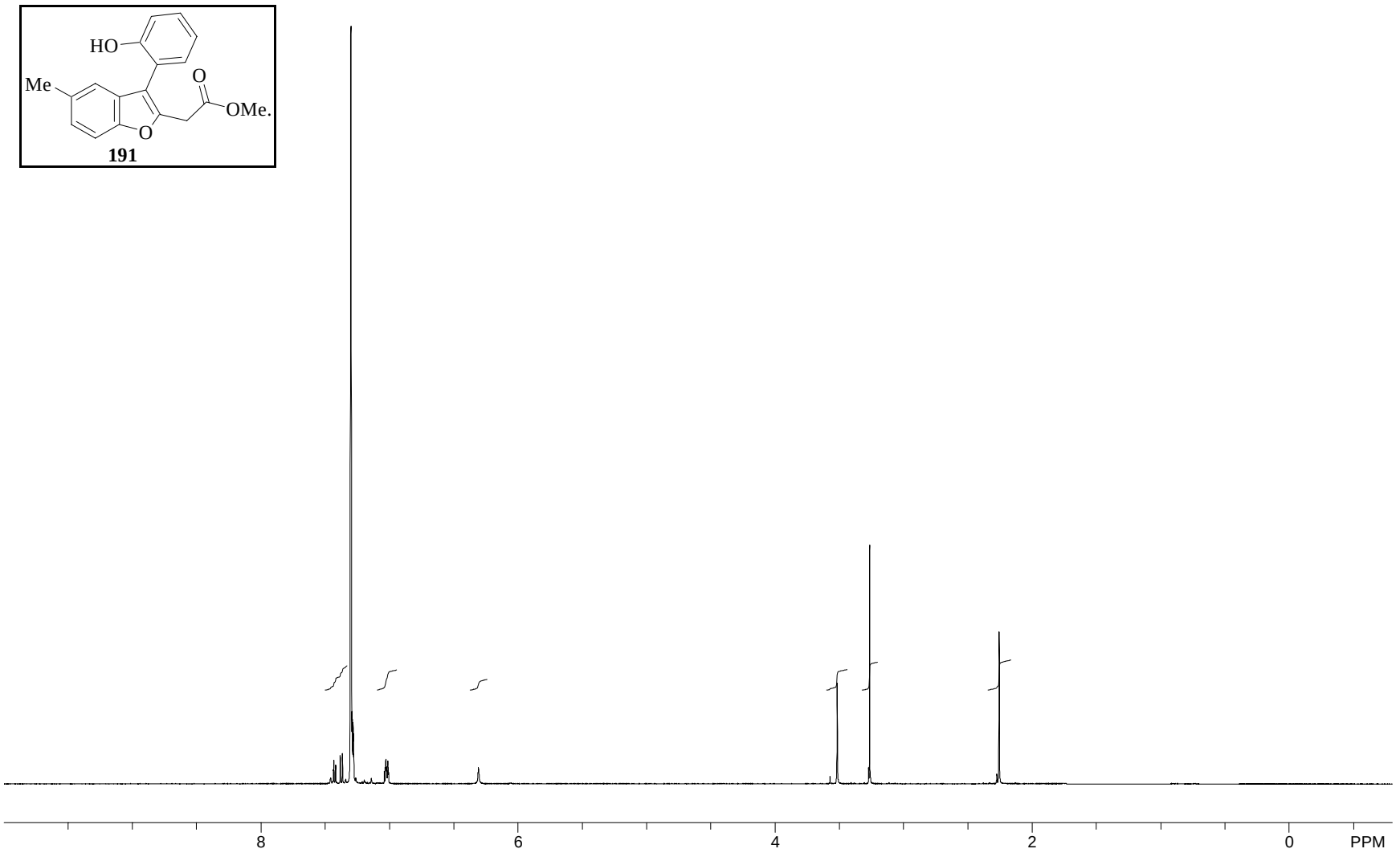


Figure A.1.28 ^{1}H NMR (500 MHz, C_6D_6) of Compound **191**.

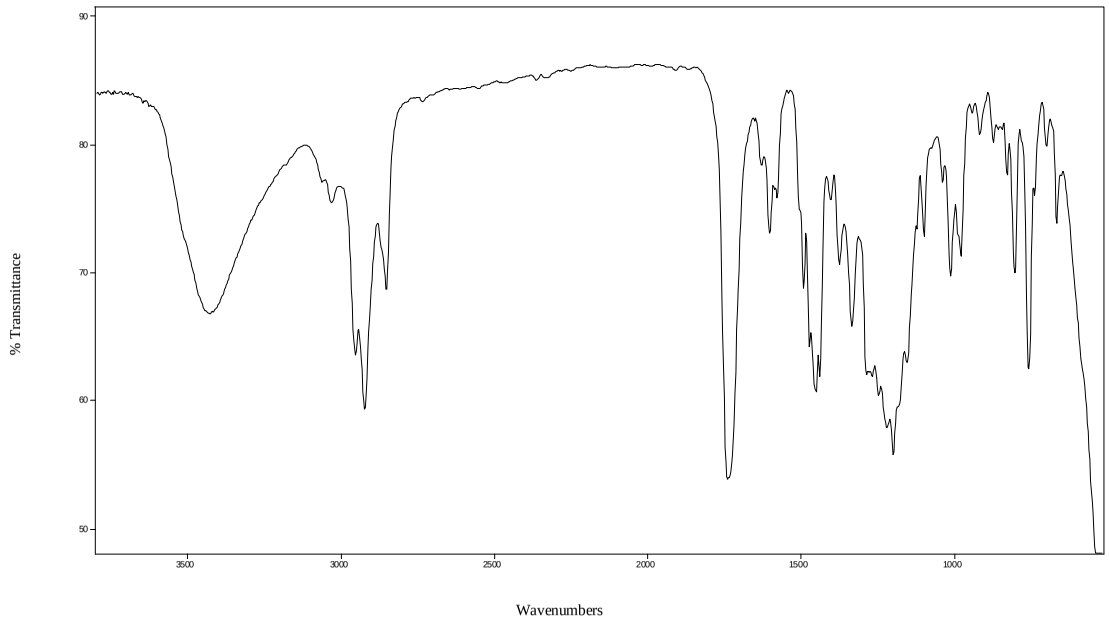


Figure A.1.29 FTIR Spectrum (thin film/NaCl) of Compound **191**.

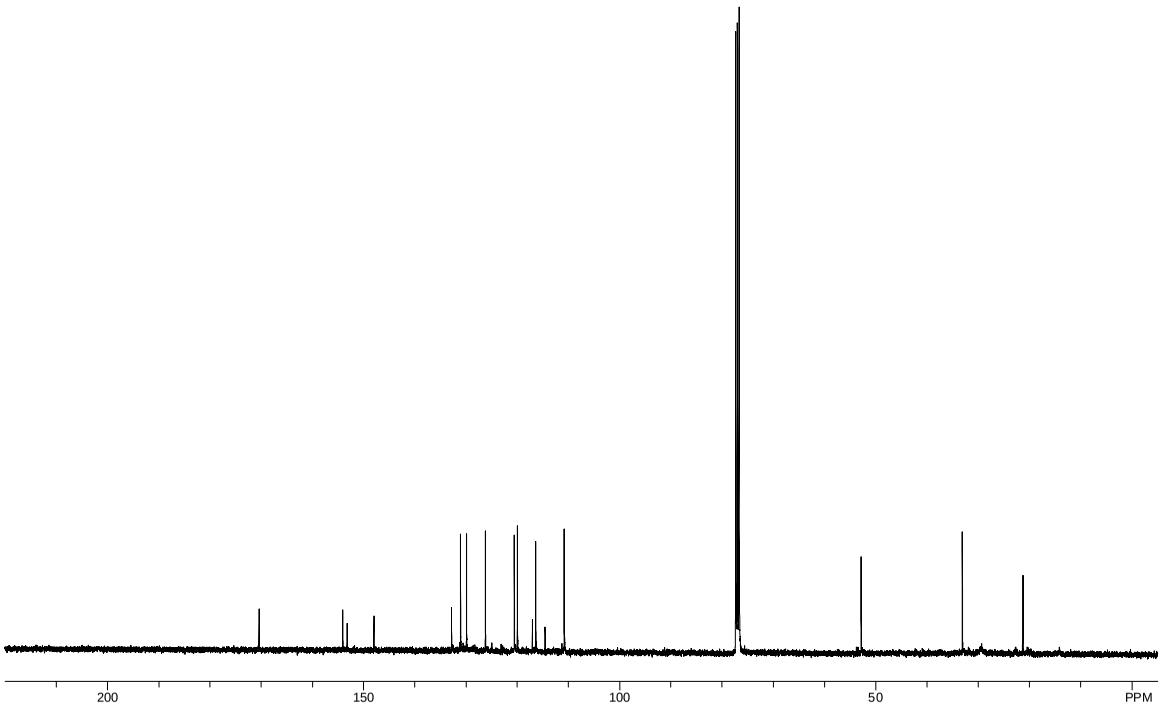


Figure A.1.30 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **191**.

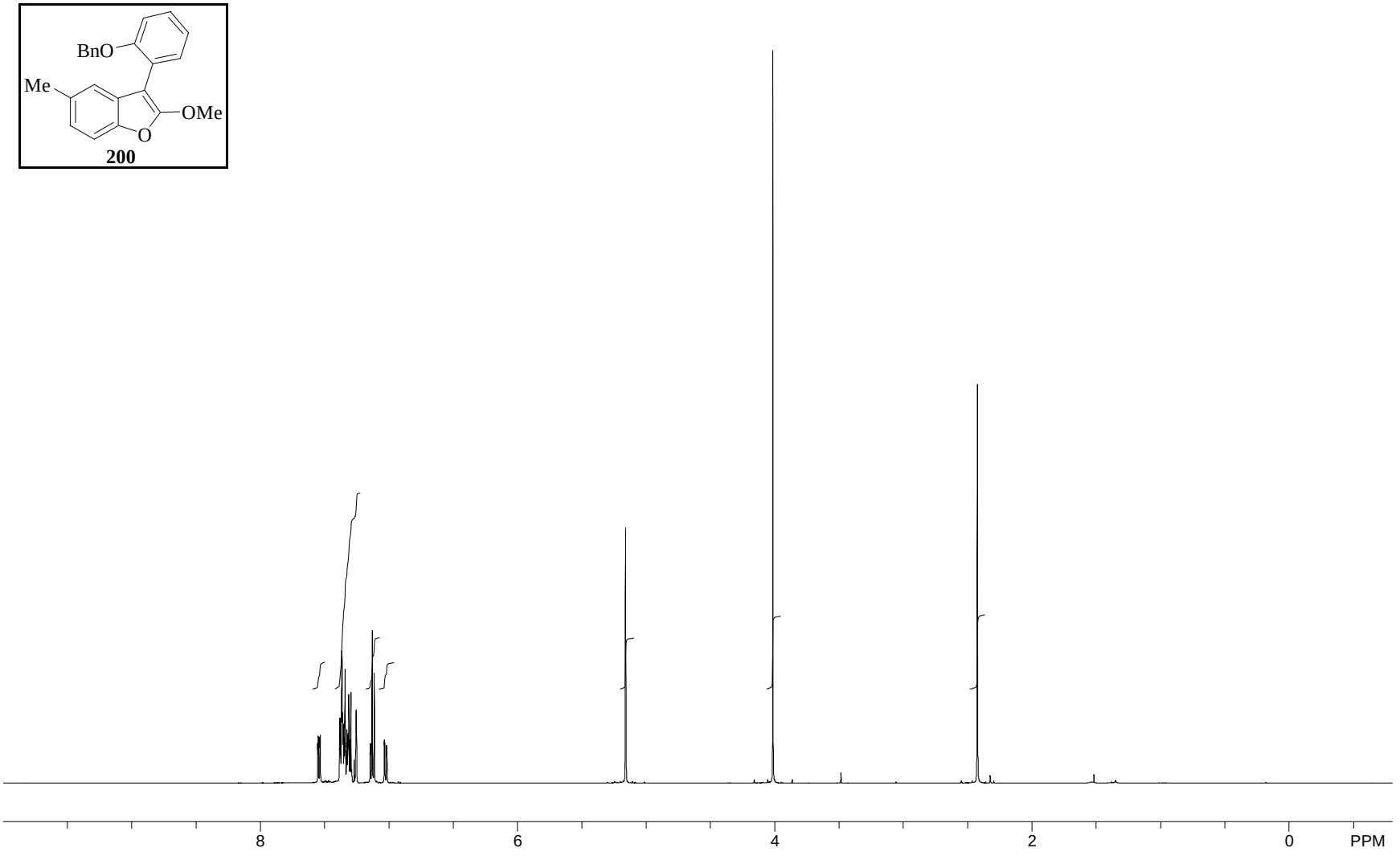


Figure A.1.31 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **200**.

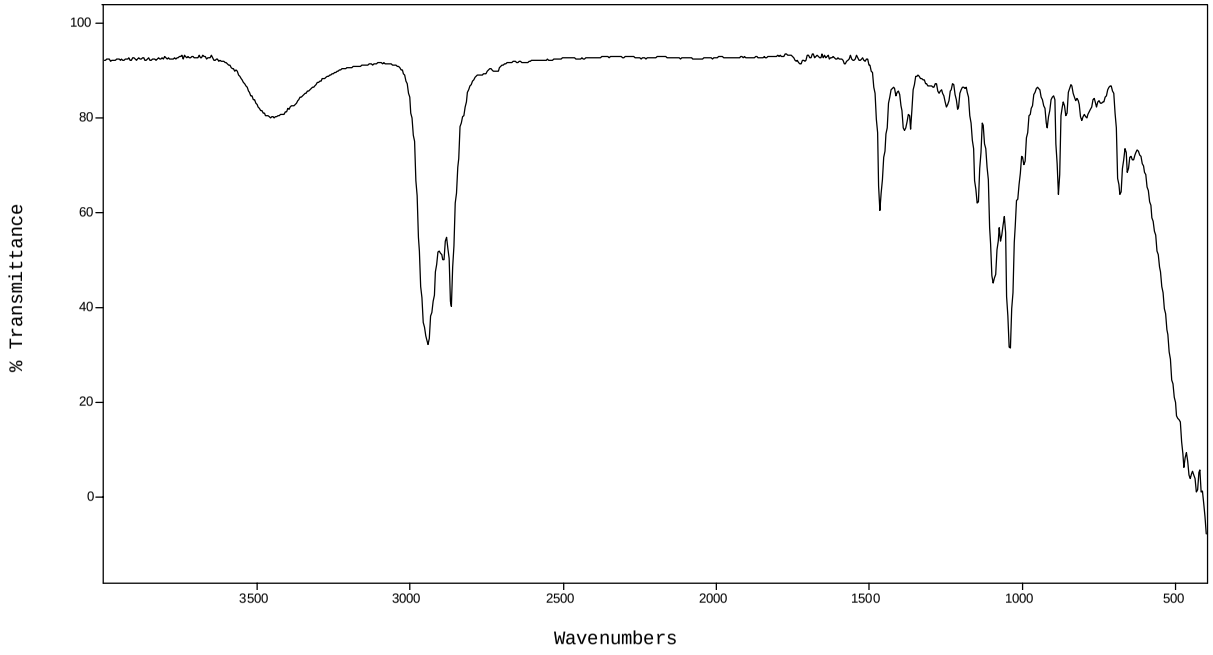


Figure A.1.32 FTIR Spectrum (thin film/NaCl) of Compound **200**.

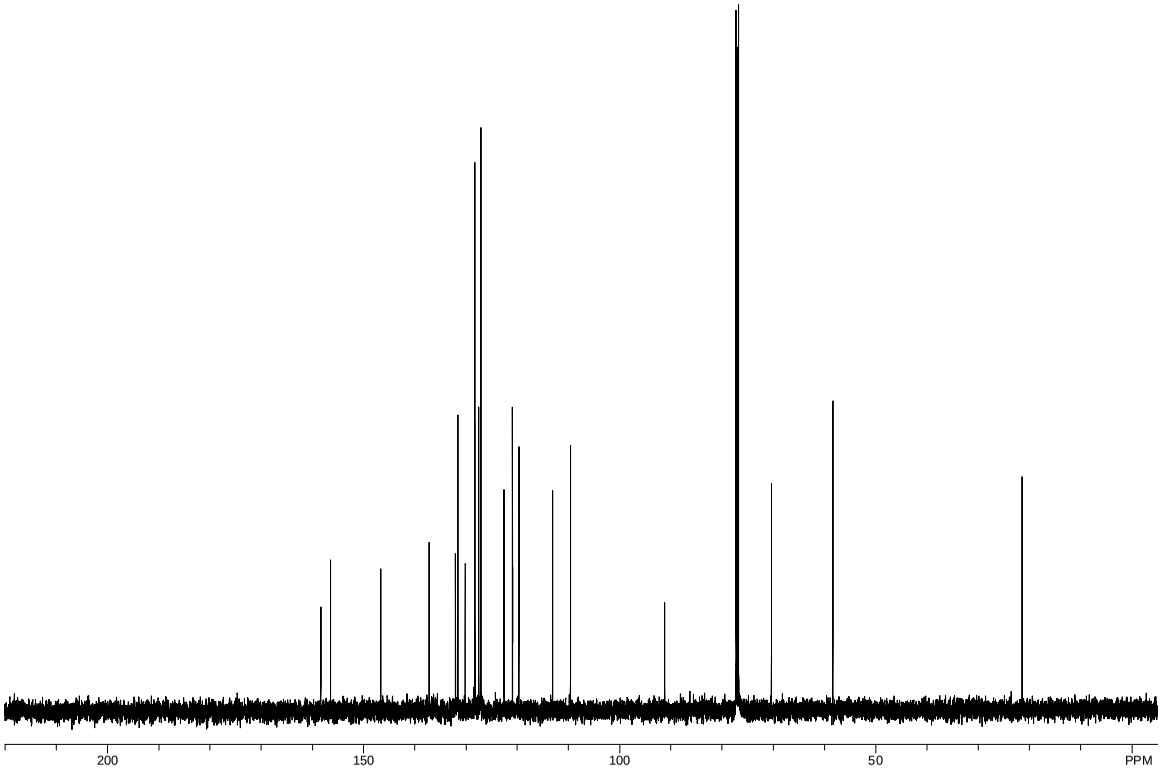


Figure A.1.33 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **200**.

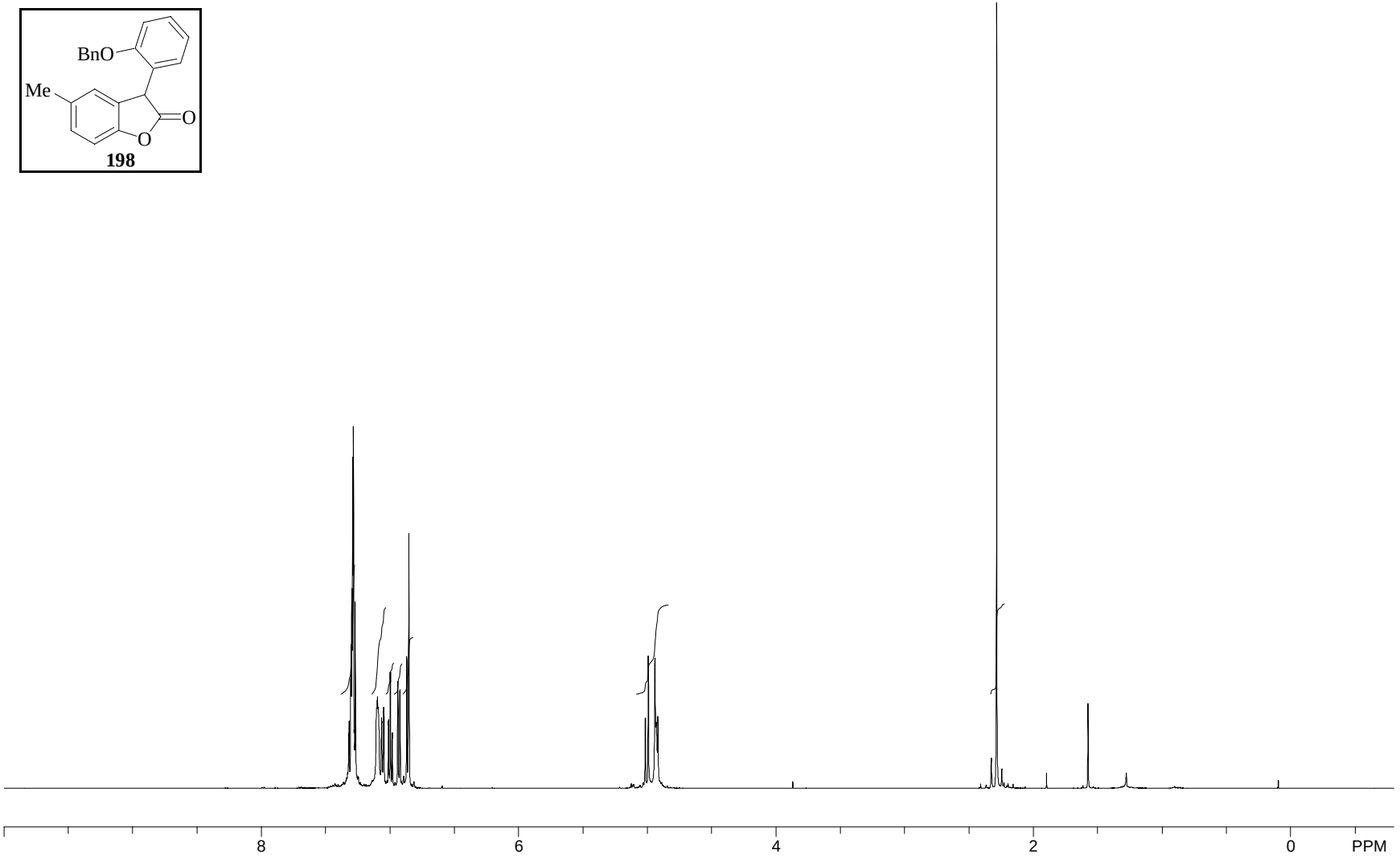


Figure A.1.34 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **198**.

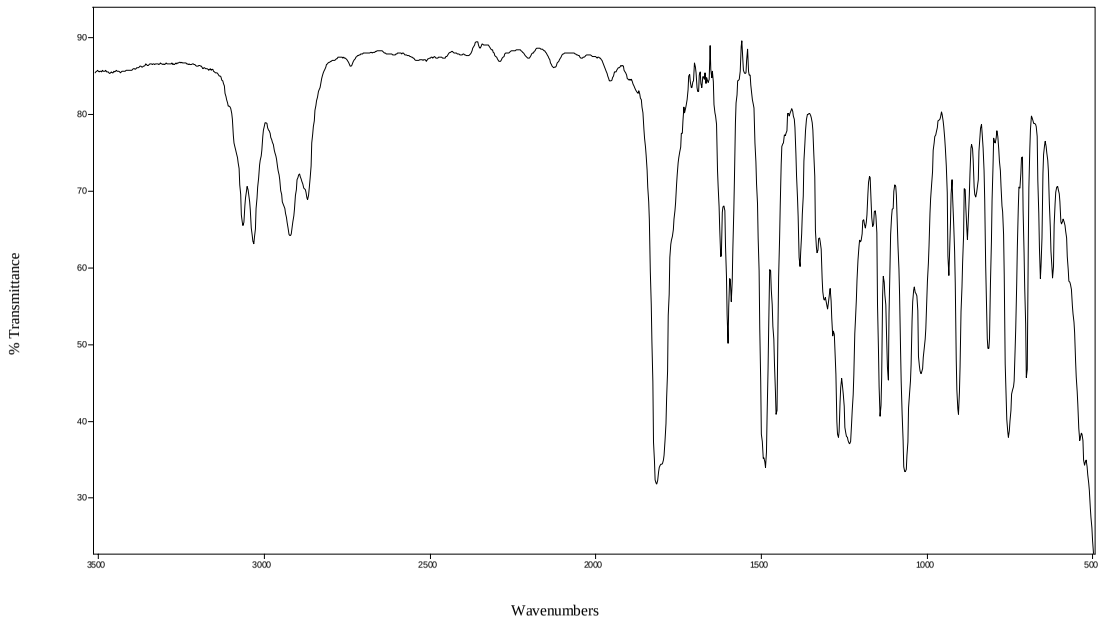


Figure A.1.35 FTIR Spectrum (thin film/NaCl) of Compound **198**.

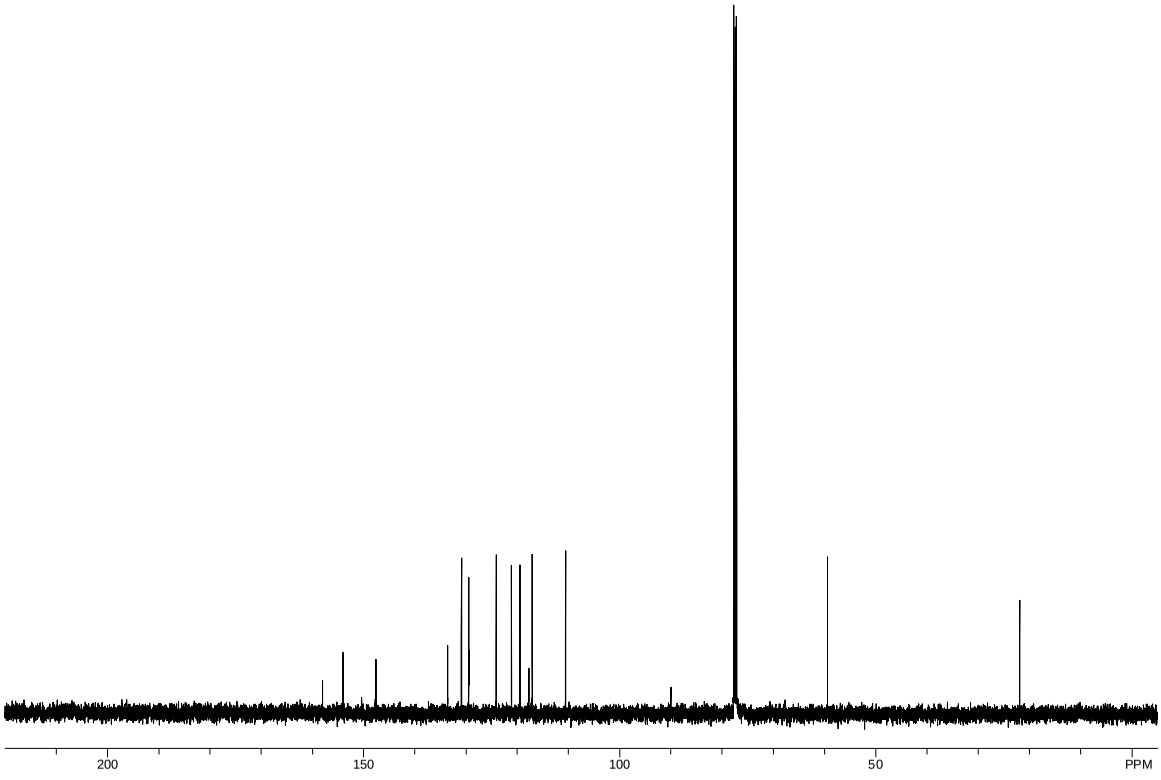


Figure A.1.36 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **198**.

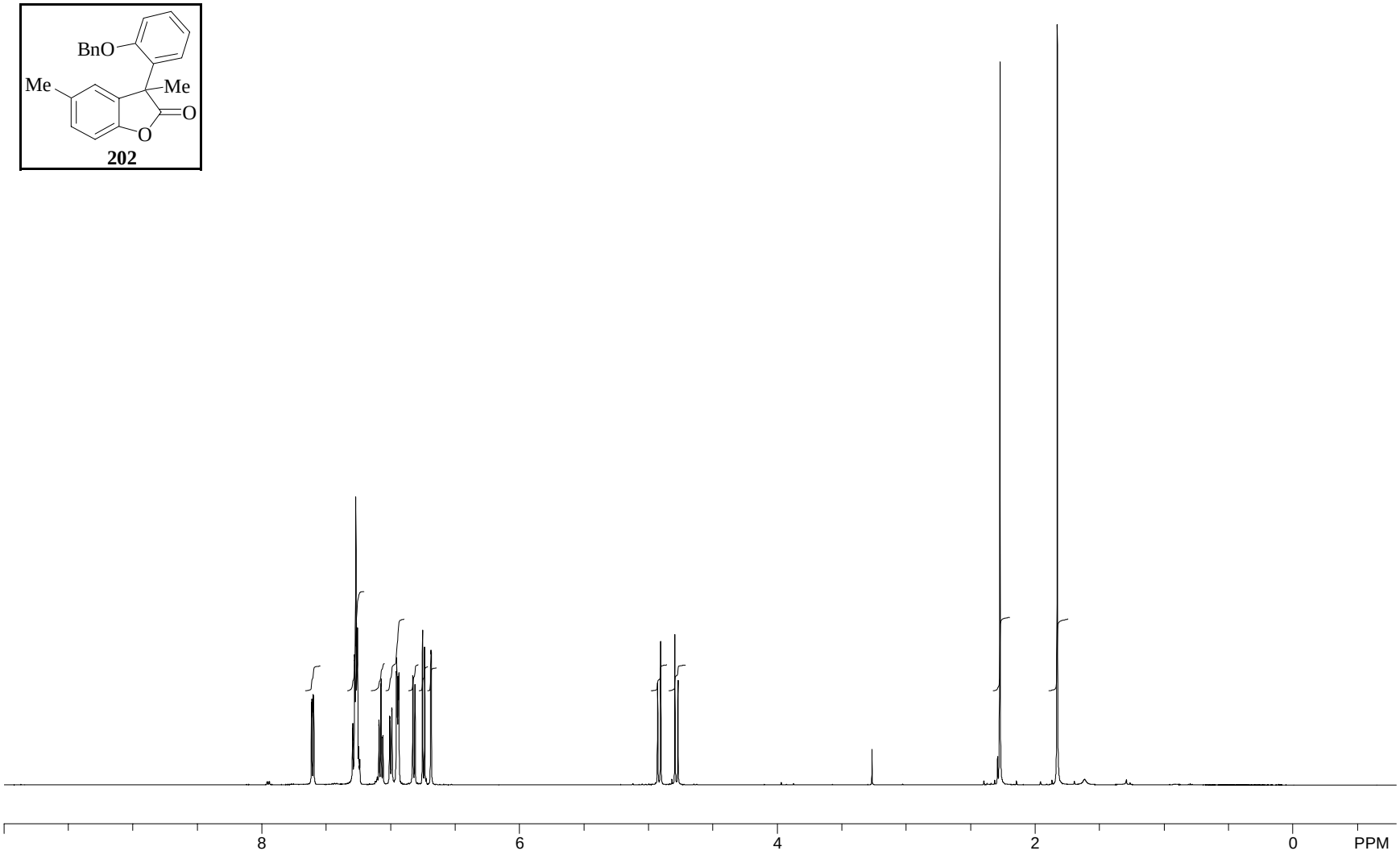


Figure A.1.37 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **202**.

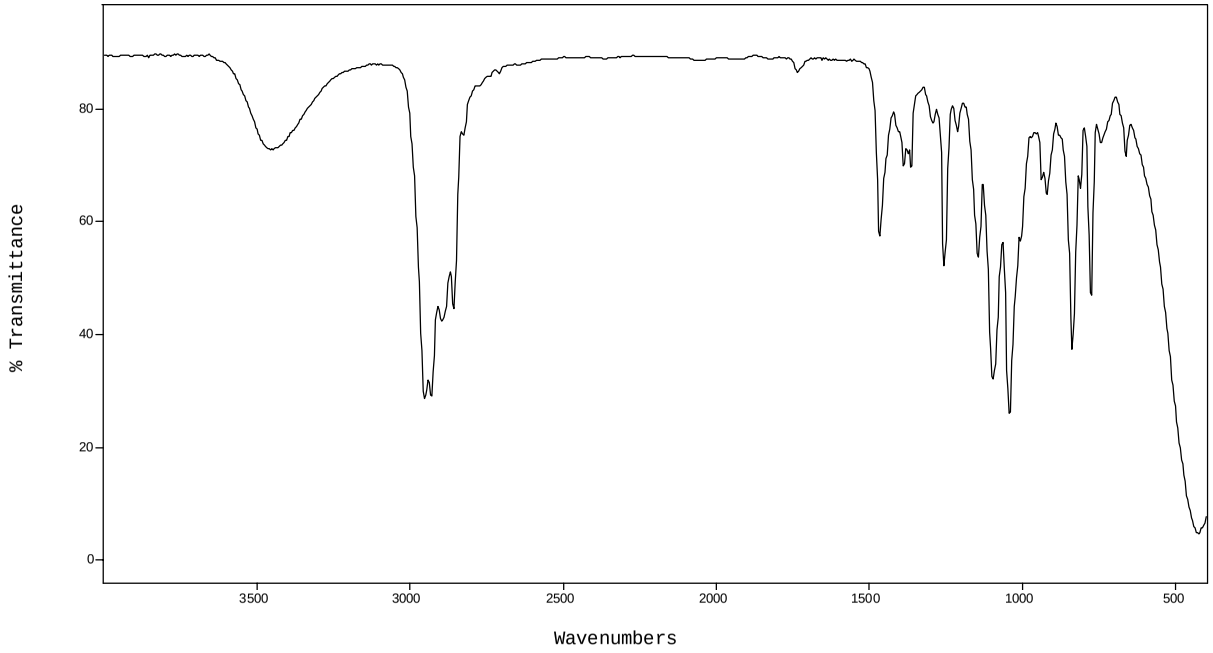


Figure A.1.38 FTIR Spectrum (thin film/NaCl) of Compound **202**.

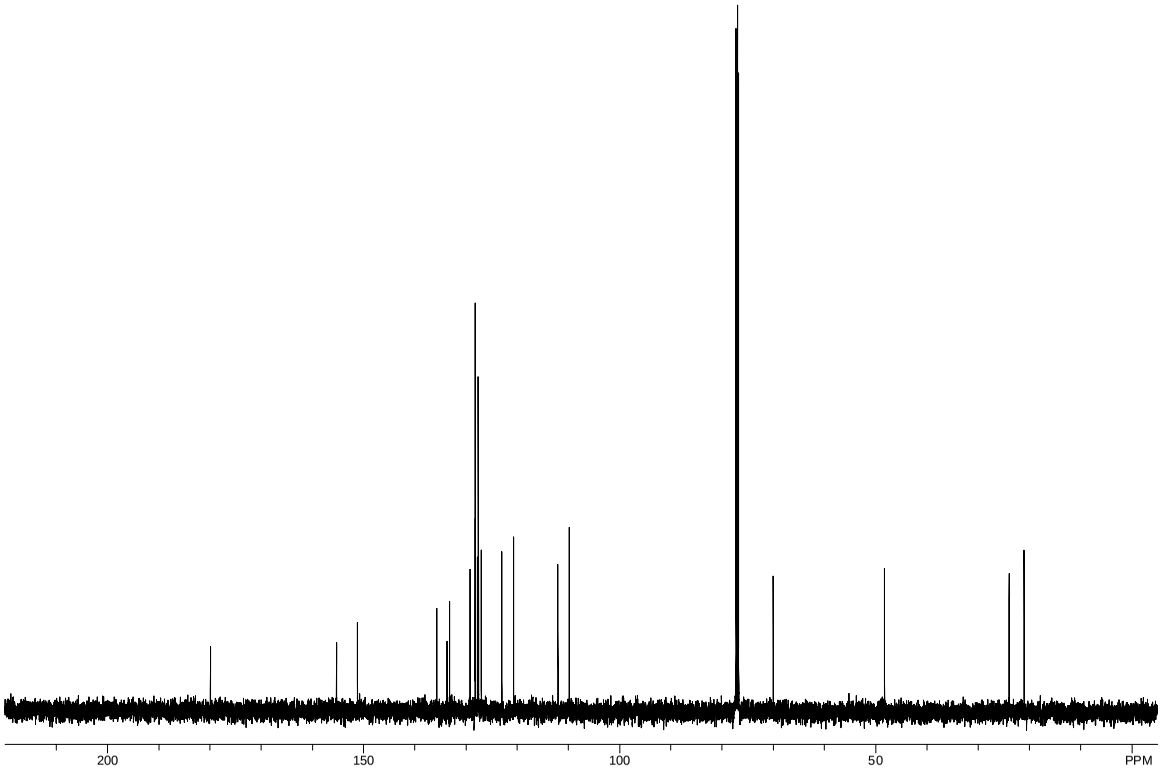


Figure A.1.39 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **202**.

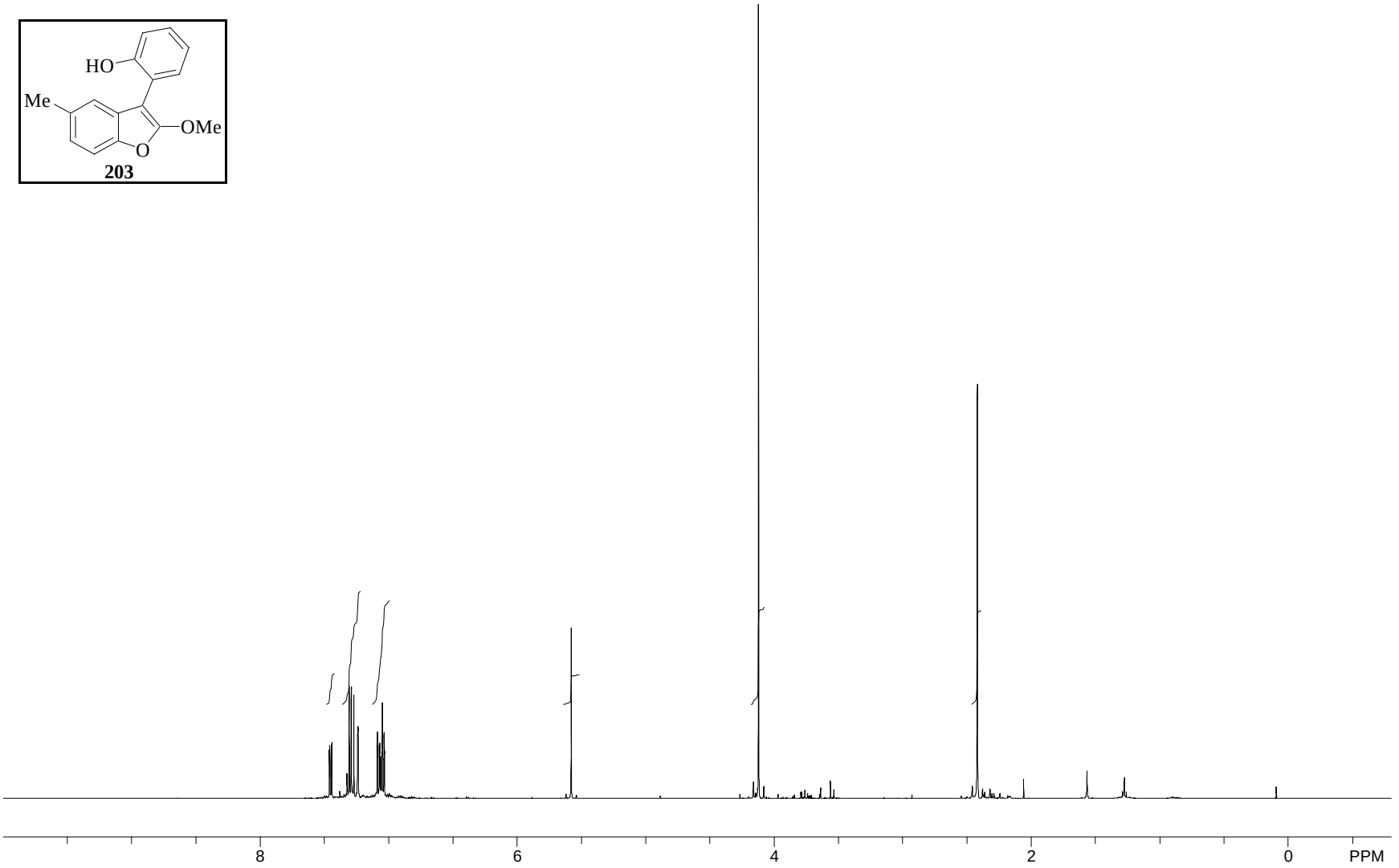


Figure A.1.40 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **203**.

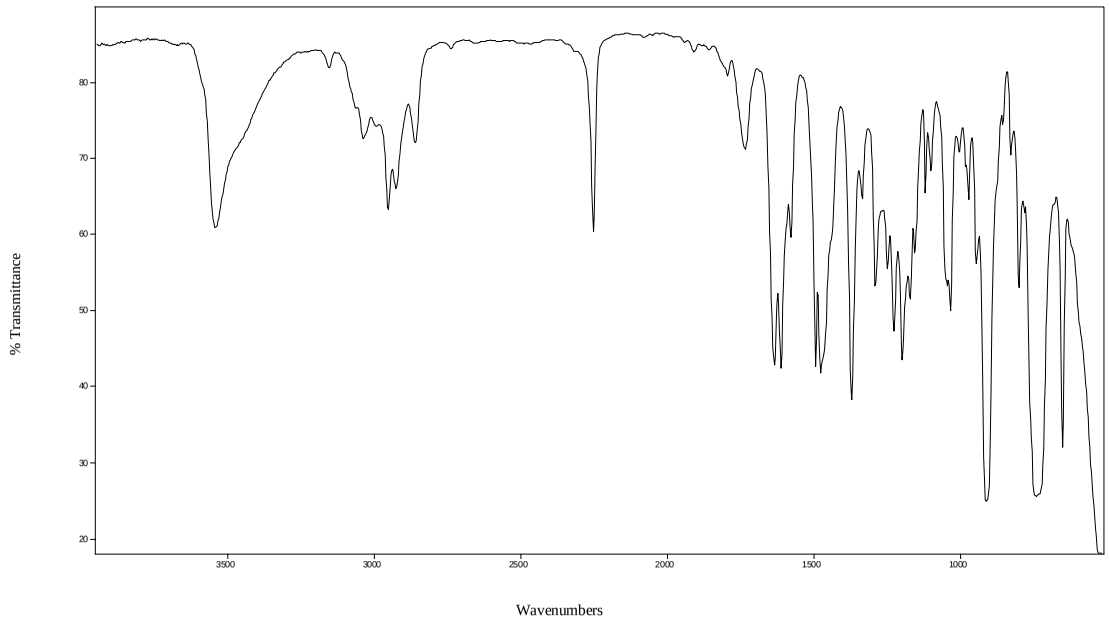


Figure A.1.41 FTIR Spectrum (thin film/NaCl) of Compound **203**.

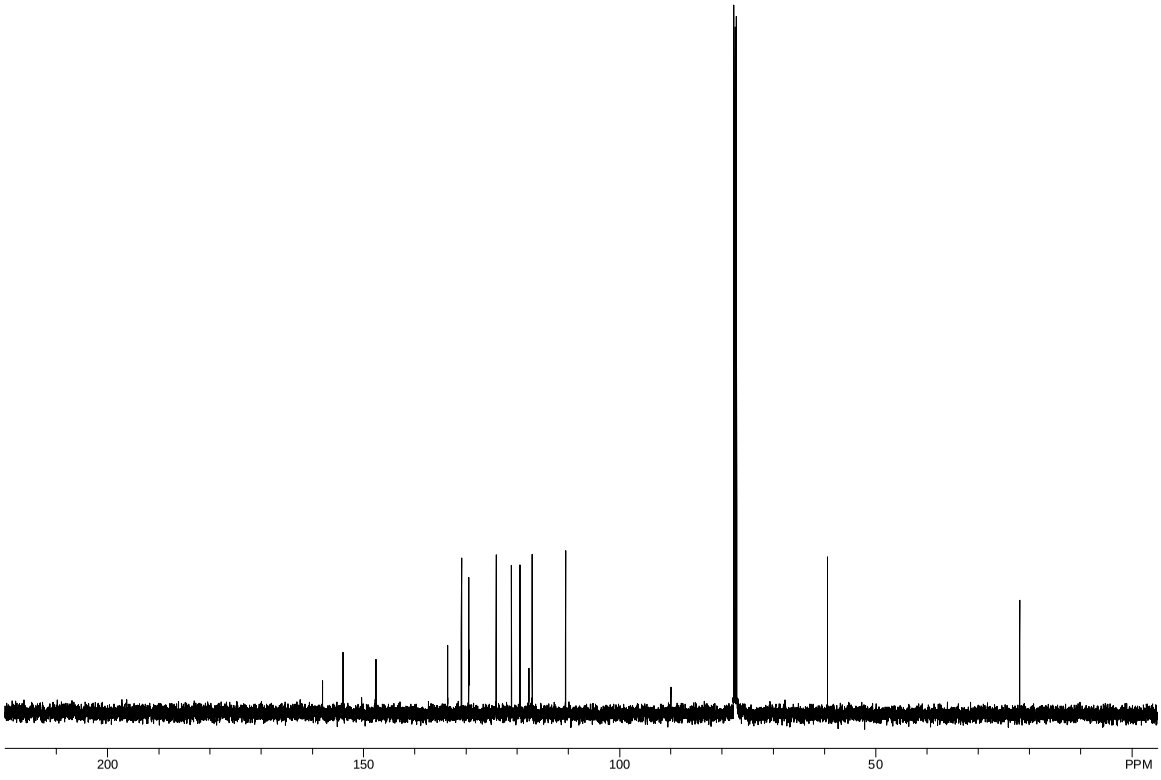


Figure A.1.42 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **203**.

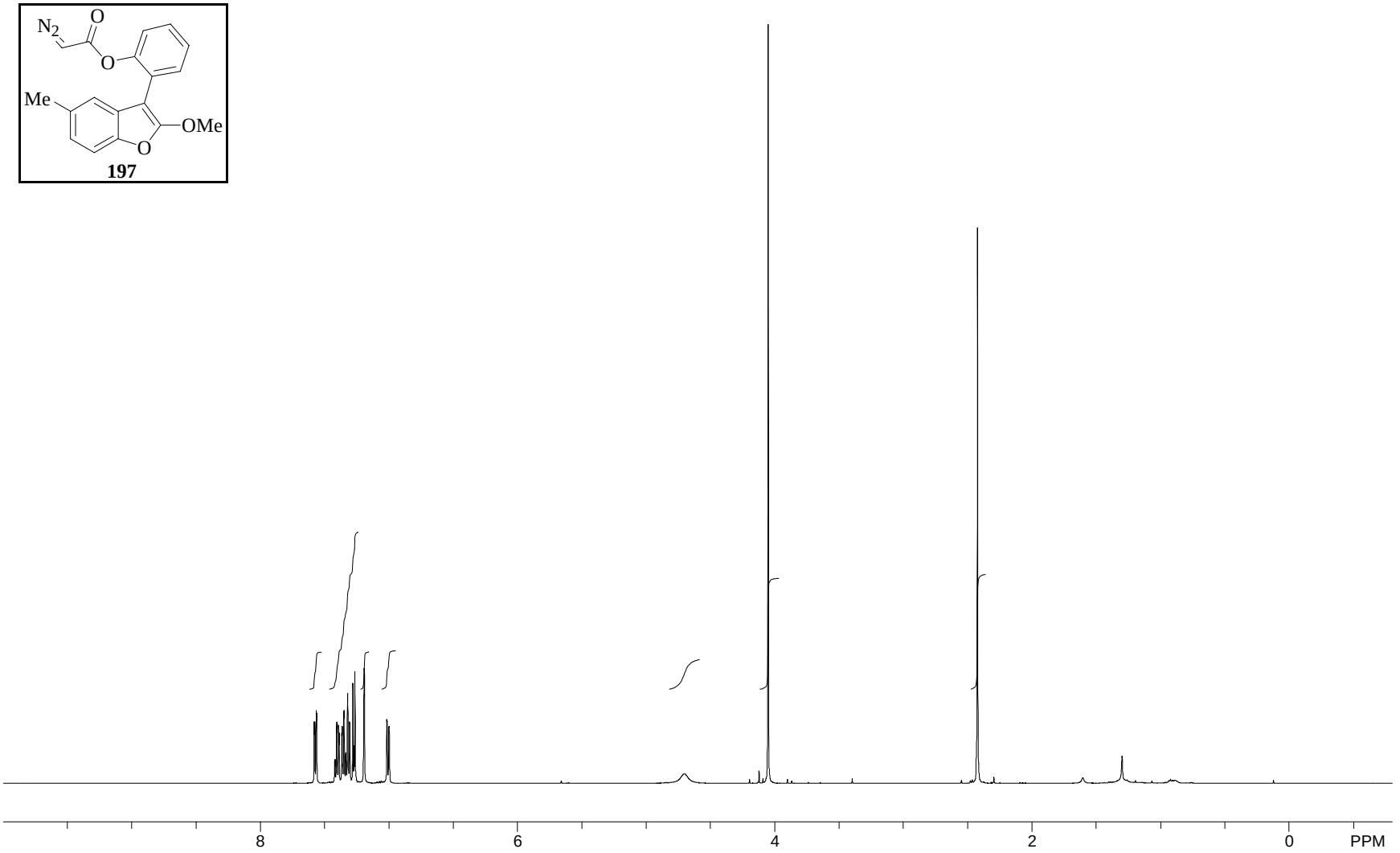


Figure A.1.43 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **197**.

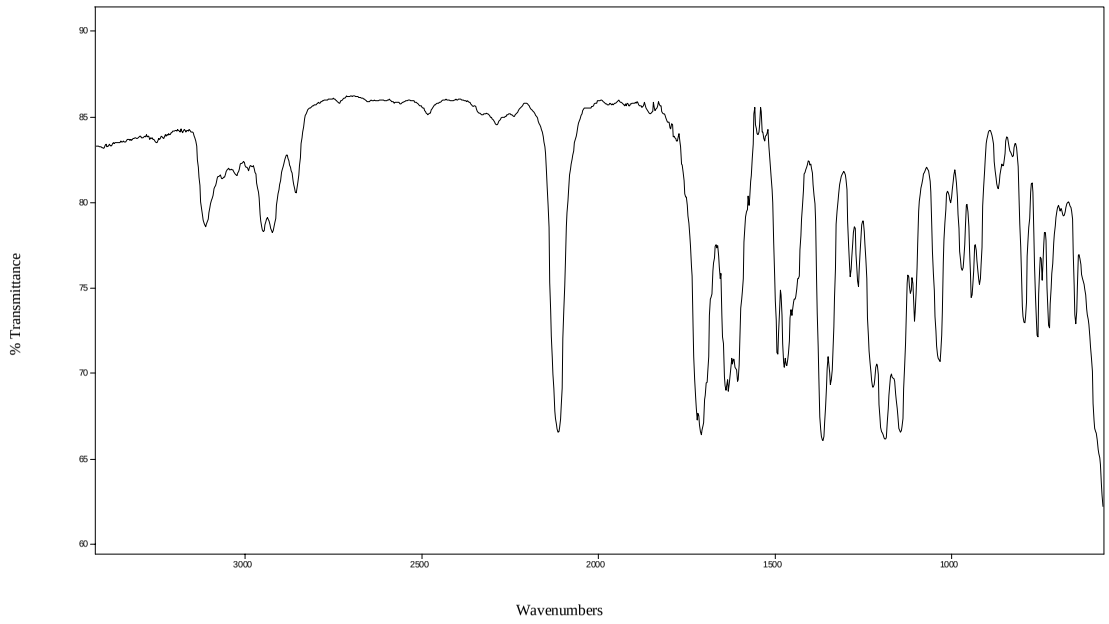


Figure A.1.44 FTIR Spectrum (thin film/NaCl) of Compound **197**.

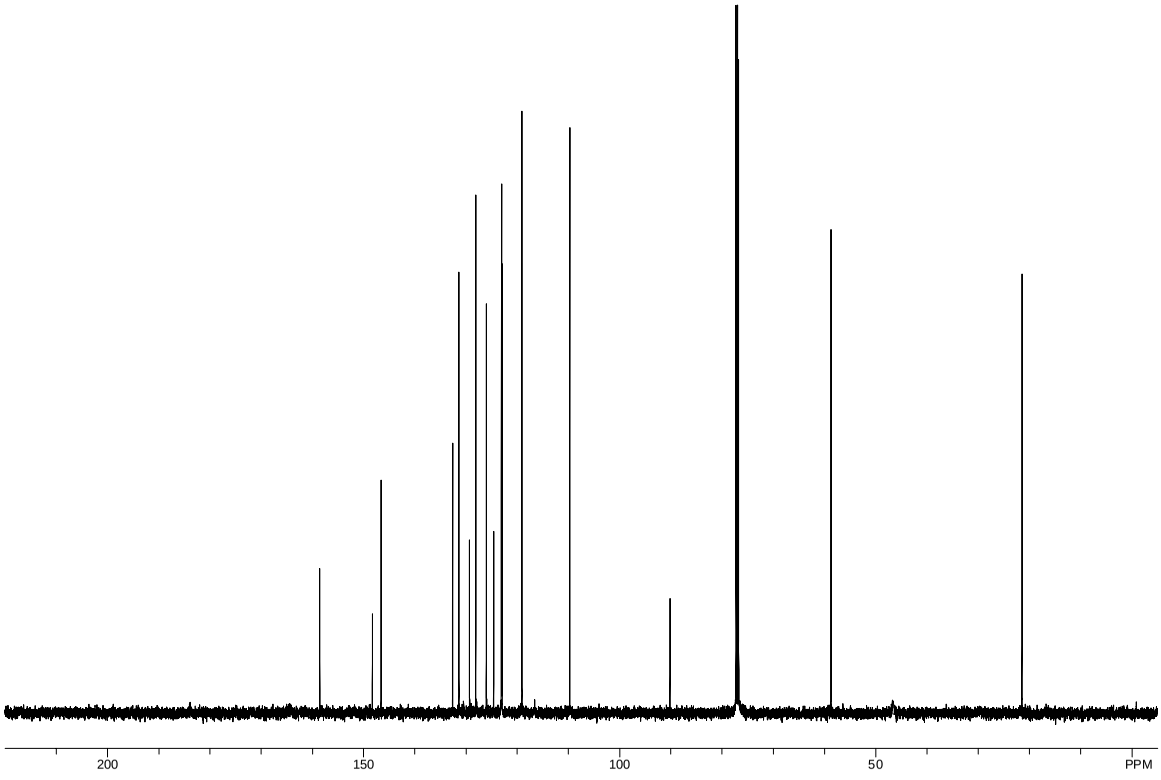


Figure A.1.45 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **197**.

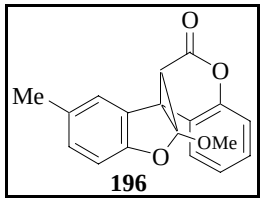


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Figure A.1.46 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **196.**

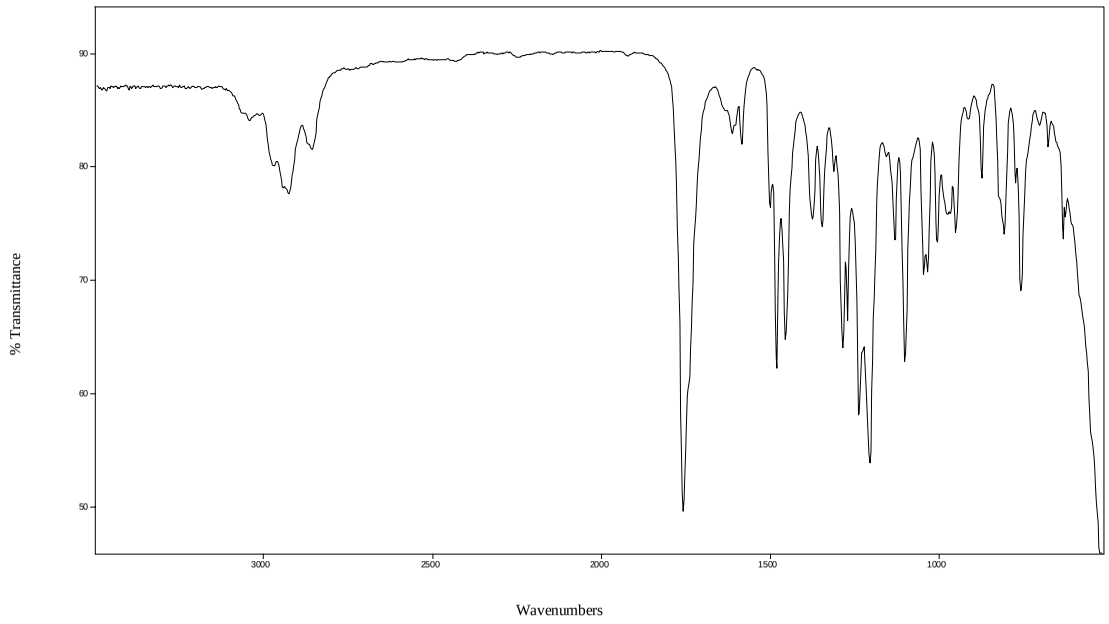

Figure A.1.47 FTIR Spectrum (thin film/NaCl) of Compound **196**.

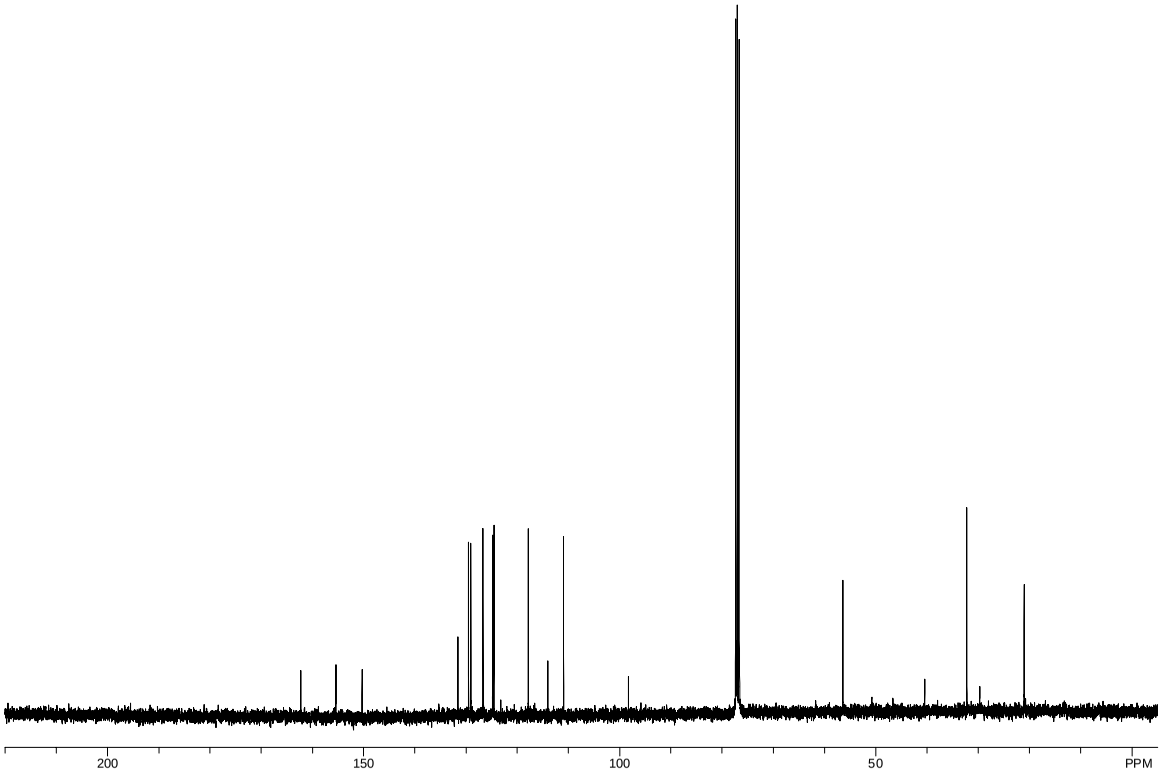

Figure A.1.48 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **196**.

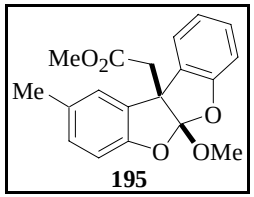

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Figure A.1.49 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **195**.

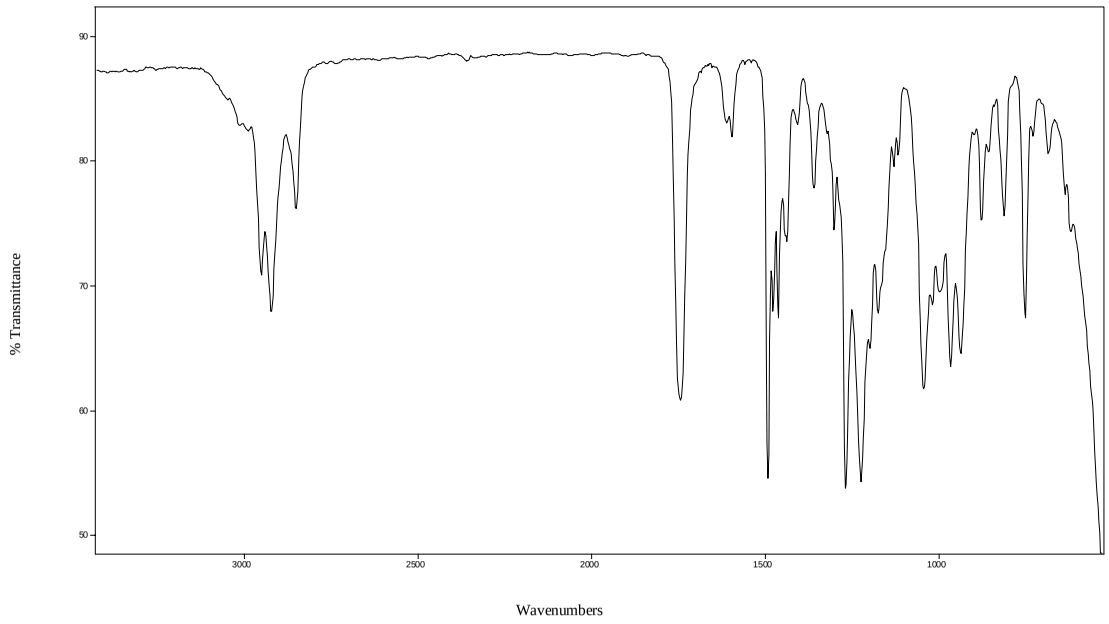


Figure A.1.50 FTIR Spectrum (thin film/NaCl) of Compound **195**.

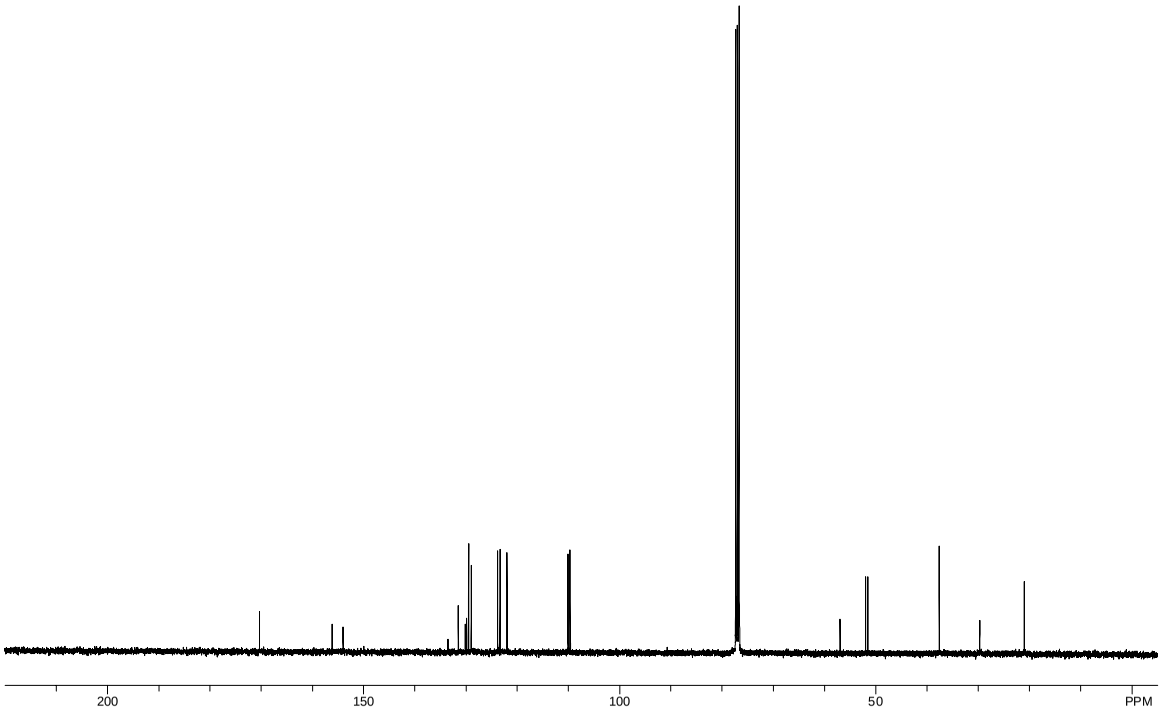


Figure A.1.51 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **195**.

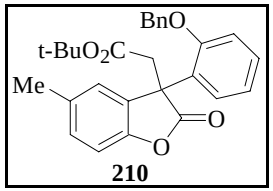


Figure A.1.52 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **210**.

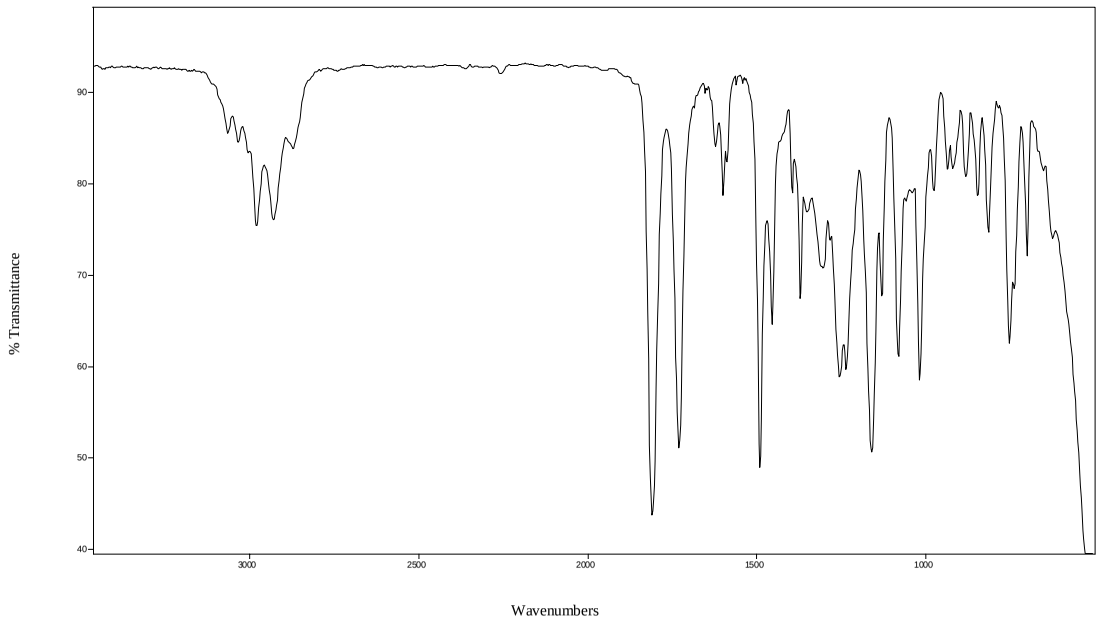


Figure A.1.53 FTIR Spectrum (thin film/NaCl) of Compound **210**.

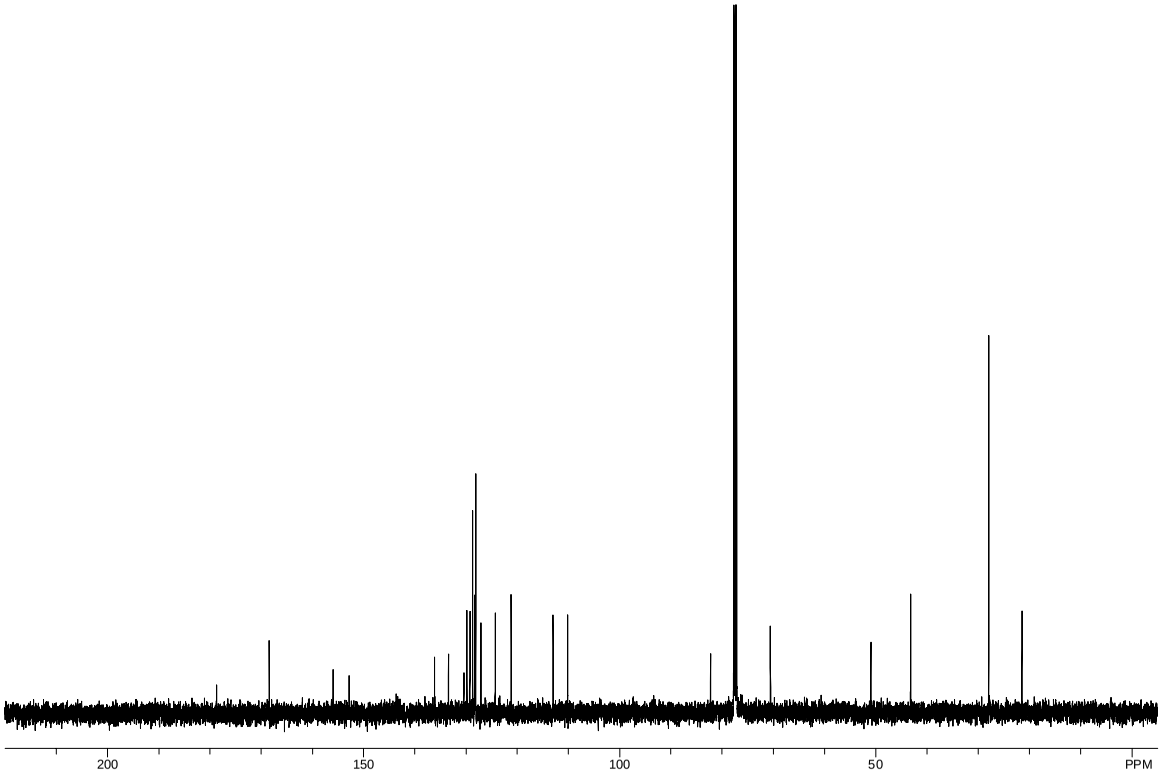


Figure A.1.54 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **210**.

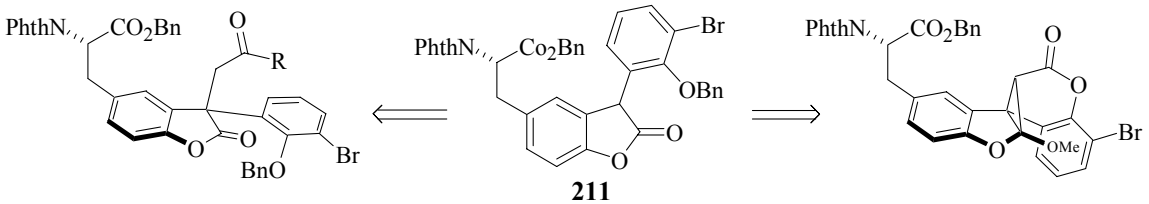
Chapter 3

Synthetic Studies Toward the Fully Elaborated Diazonamide A Structure

3.1 A Synthetic Strategy

Work in the diazonamide model system discussed in the previous chapter led to several key insights that would direct our approach to the fully elaborated diazonamide A structure. The most important insight was that the diazonamide C(11) must be in the acid oxidation state in order to insure opening of the correct cyclopropane bond in the cyclopropanation/ring-opening approach. This oxidation state also allows for a complimentary alkylation approach for construction of the diazonamide C(10) quaternary center core. Importantly, both the cyclopropanation/ring-opening and alkylation approach can be accessed through a common benzofuranone intermediate. Therefore, work in the real system began with the development of an efficient easily scalable synthesis of benzofuranone **211** (Scheme 3.1.1).

Scheme 3.1.1

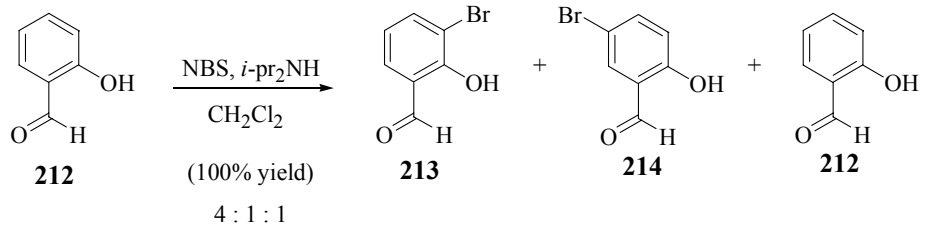


3.2 First Generation Approach to the Benzofuranone 211

3.2.1 Starting Material Preparation

Initial work directed toward benzofuranone **211** closely paralleled the synthetic route developed previously for the model system. Before this work could begin, however, the appropriately functionalized aromatic building blocks needed to be prepared. Toward this end, salicaldehyde (**212**) was ortho-brominated with NBS and catalytic *i*-pr$_2$NH to provide a mixture of desired bromide **213** along with para-brominated **214** and recovered starting material (Scheme 3.2.1). Fortunately, this mixture could be easily separated by fractional distillation allowing convient access to multi-gram quantities of **213**.

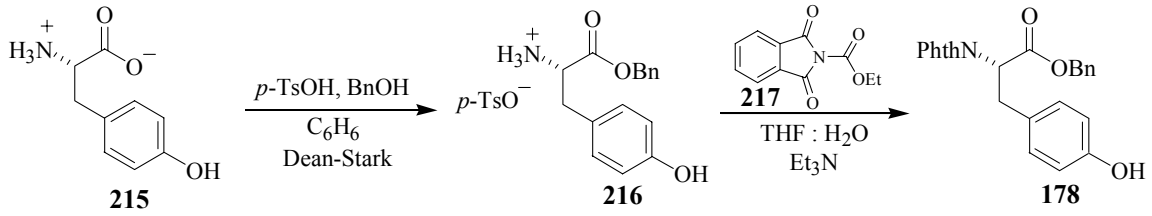
Scheme 3.2.1



The final building block that remained to be synthesized was an appropriately protected form of tyrosine. From the outset, it was realized that both protecting groups would need to be robust in order to survive the high temperature required for the planned aromatic Clasein rearrangement. Given the thermolytic instabilities of N-Boc and N-Cbz protesting groups, the tyrosine amine would be protected as the corresponding phthalimide. In addition, the tyrosine carboxyl would be protected as its benzyl ester due to its ease of deprotection under neutral conditions. Therefore, with the goal of synthesizing tyrosine **178** a careful literature search revealed that **178** was a known

compound. However, in this laboratory a modified route of the known synthesis provided convenient access to **178** (Scheme 3.2.2).[1] Benzyl protection of tyrosine (**215**) provided tosylate salt **216** which underwent smooth reaction with *N*-carbethoxyphthalimide (**217**) to afford **178**, which was identical in all respects to the reported literature data.

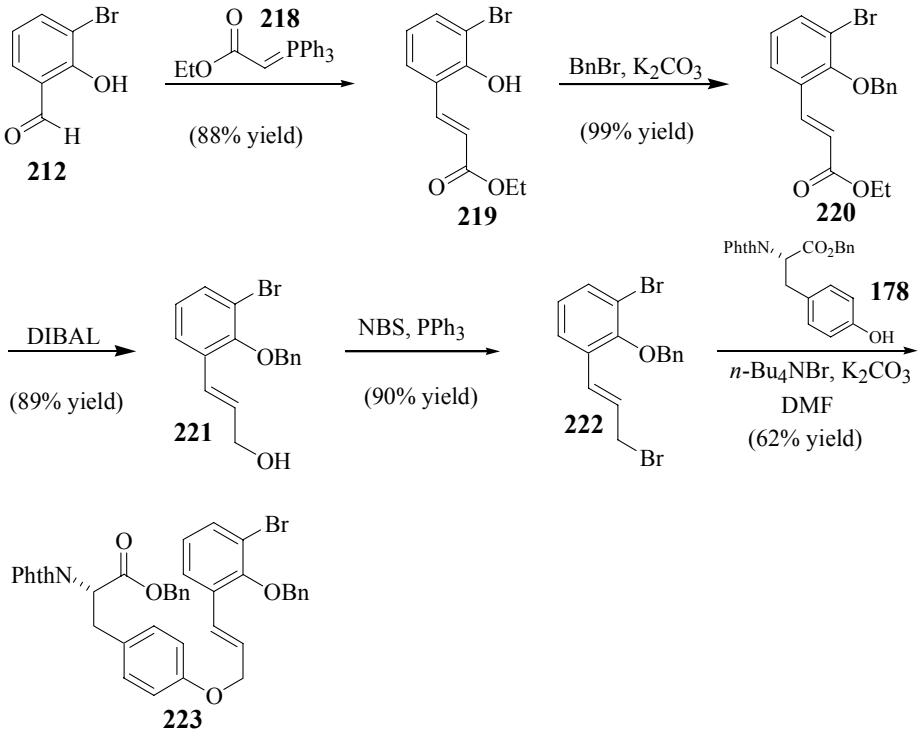
Scheme 3.2.2



3.2.2 Synthesis of a Claisen Rearrangement Substrate

With the appropriate starting materials in hand, salicaldehyde **212** underwent facile Wittig homologation at 0°C to afford α,β-unsaturated ester **219** (Scheme 3.2.3). Benzyl protection of **219** followed by DIBAL reduction of **220** yielded allylic alcohol **221**. Attempts to brominate **221** with PBr_3 as described previously were unsuccessful, however, it was ultimately discovered that **221** could be brominated with NBS and PPh_3 to furnish allylic bromide **222** in good yield. Final alkylation of tyrosine **178** with **222** under conditions that are known to prevent racimization of the amino acid gave rise to the desired Claisen rearrangement precursor **223**.

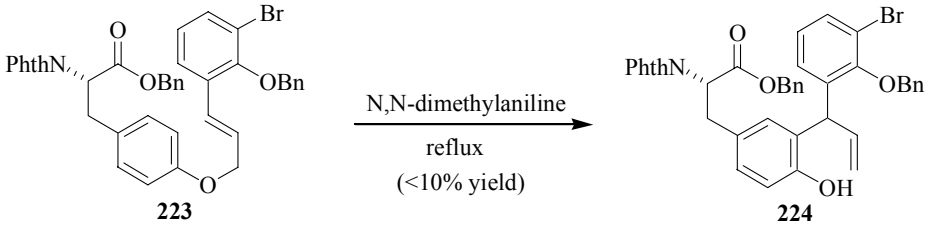
Scheme 3.2.3



3.2.3 Attempted Claisen Rearrangement

With **223** in hand, attention focused on Claisen rearrangement of this compound to furnish olefin **224** (Scheme 3.2.4). Unfortunately, refluxing **223** in *N,N*-dimethylaniline solvent for 24 hours afforded olefin **224** in less than 10% yield. The remaining reaction mixture was comprised of several unidentified byproducts and unreacted starting material. Efforts to drive the reaction toward completion by increasing the reaction time did not lead to an increase in yield. Furthermore, all attempts to perform the rearrangement at lower temperatures, in order to suppress the formation of unwanted byproducts, resulted in no reaction.

Scheme 3.2.4

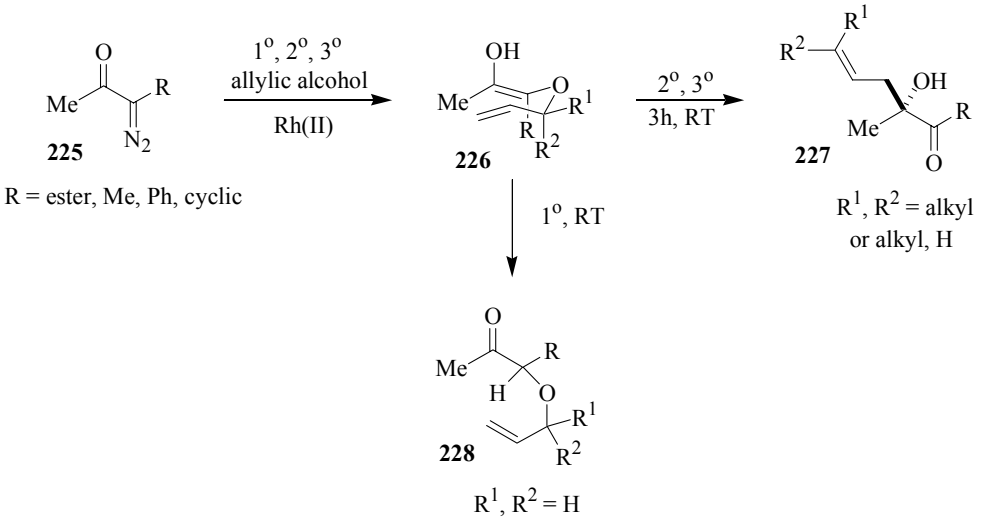


3.3 Second Generation Approach to Benzofuranone 211

3.3.1 Insights From the Rh(II)-Initiated Claisen Rearrangement

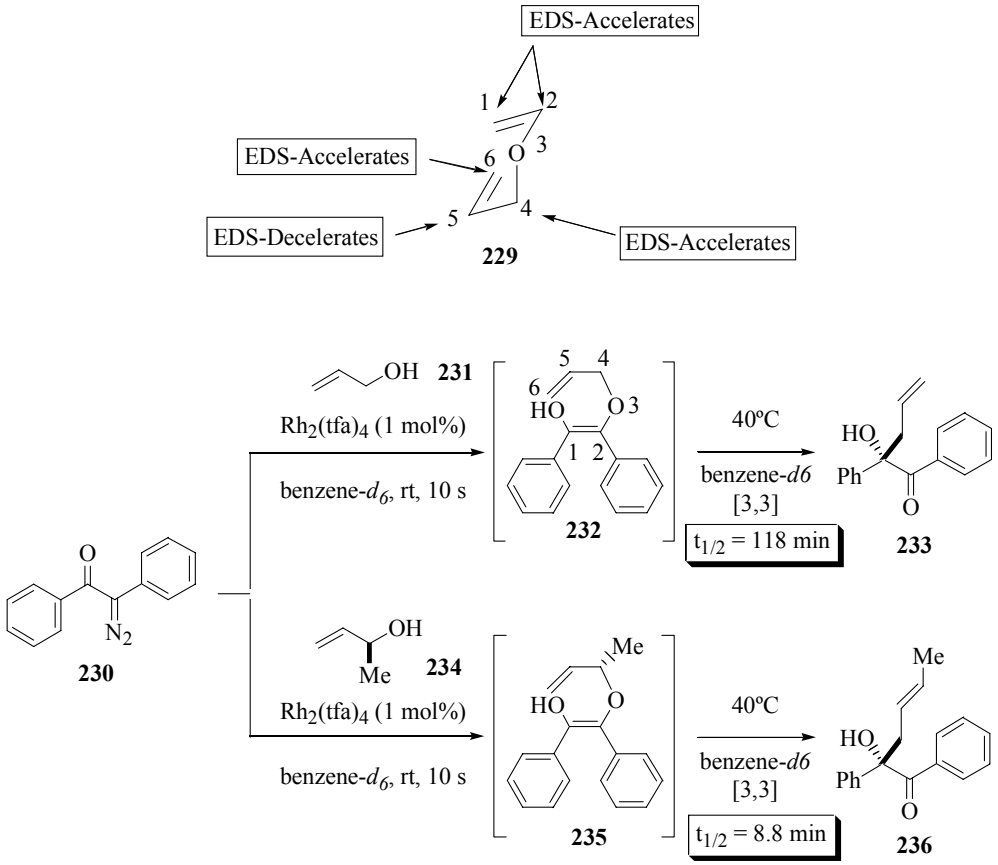
While the above result was discouraging, a potential solution to increasing the yield of the Claisen rearrangement was found from research concurrently being conducted in these laboratories. Since 1997 the Wood group has maintained a program aimed at studying the scope and mechanism of the Rh(II)-initiated Claisen rearrangement of α-diazoketones (**225**) and allylic alcohols (**226**) to furnish tertiary α-hydroxyketones (**227**).[2-4] Extensive work has shown that this novel reaction is quite general with regard to the diazo ketone and allylic alcohol, and that the postulated O-H insertion product (**228**) is not an intermediate in the reaction. In fact, the initial product arising from the coupling of an allylic alcohol and an α-diazoketone is an enol (e.g., compound **228**, Scheme 3.3.1). Futhermore, in the case of tertiary allylic alcohols, Claisen rearrangement of the resulting enols is fast and furnishes α-hydroxyketone products (e.g., **227**) in good yields. On the other hand, when coupled to primary allyic alcohols, Claisen rearrangement of the resulting enols is slow and tautomerization to the O-H insertion products (e.g., **228**) becomes a competitive process.

Scheme 3.3.1



These results concerning the rate of the Claisen rearrangement are consistent with literature reports wherein electron-donating groups on the C(4) position of the allylic enol ethers have been found to accelerate the rearrangement, and enol ethers which lack electron-donating substituents undergo rearrangement more slowly (see Scheme 3.3.2). Specific measurement of this phenomenon conducted in these laboratories determined that the substitution of a methyl group at the C(4) position in the Claisen rearrangement of α-diazoketone **230** with allylic alcohols leads to a more than 13 fold increase in reaction rate.

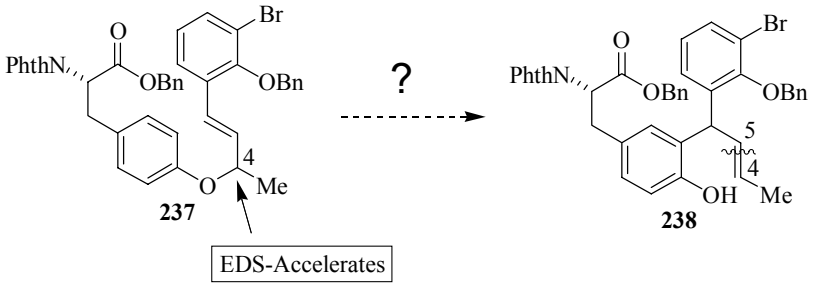
Scheme 3.3.2



3.3.2 A New Claisen Rearrangement Substrate

Armed with a better understanding of the Claisen rearrangement, work commenced to improve the poor rearrangement propensity of **223**. In accordance with the information detailed above, installation of a methyl group at the C(4) position was expected lead to an increase in reaction rate. It was hoped that an increase in the reaction rate would result in an improved yield of rearranged product and suppression of the undesired byproducts. Most importantly, after rearrangement the resulting 4,5-disubstituted olefin will be oxidatively cleaved removing C(4) and any substituent introduced at that position (Scheme 3.3.3).

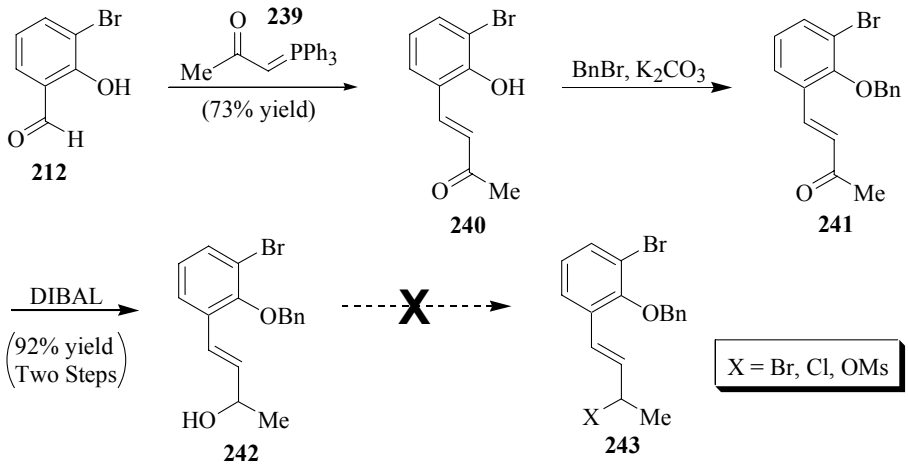
Scheme 3.3.3



3.3.3 Synthesis of a New Claisen Rearrangement Substrate

Synthesis of the new rearrangement substrate began as before from salicaldehyde **212** (Scheme 3.3.4). Wittig homologation of **212** with methyl ketone ylide **239** gave rise to α,β-unsaturated ketone **240**. Benzyl protection of **240** afforded ether **241**, which underwent smooth DIBAL reduction to furnish allylic alcohol **242**. Unfortunately, all attempts to functionalize **242** as the corresponding bromide were unsuccessful. Similarly, attempted chlorination and mesylate formation met with no success. In each of these reactions the major isolated product was recovered starting material along with a small amount of alcohol elimination product and desired product.

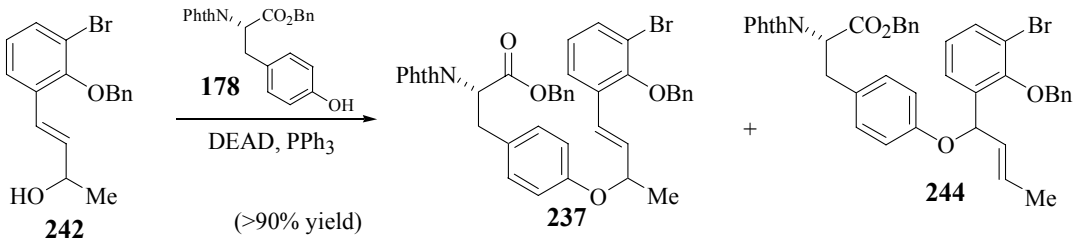
Scheme 3.3.4



3.3.4 Mitsunobu Approach to the Claisen Rearrangement Substrate

Unable to activate **242** as its corresponding halide or mesylate, attention shifted toward an alternative route for construction of the desired Claisen rearrangement substrate. It was felt that the Mitsunobu reaction would be an attractive alternative since it is a more direct approach and does not require isolation of the activated alcohol (Scheme 3.3.5). Therefore, treatment of **242** with DEAD and PPh_3 in the presence of tyrosine **178** afforded an irretractable mixture of desired S_N2 product **237** and undesired S_N2' product **244**. All attempts to suppress the formation of **244** by changing the dicarboxylate, phosphine, and solvent met with no success.

Scheme 3.3.5

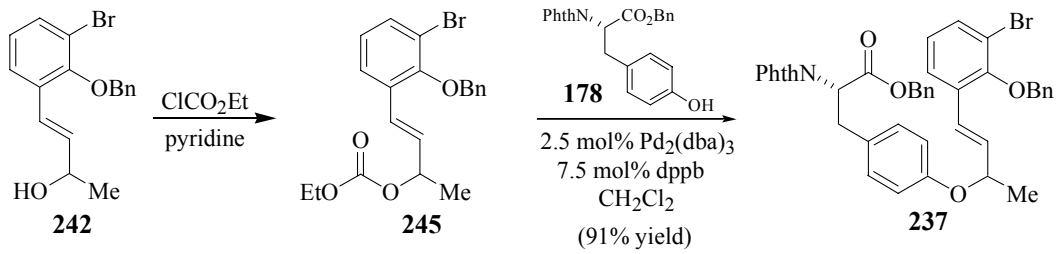


3.3.5 Palladium Catalyzed Alkylation Approach to the Claisen Rearrangement Substrate

Undeterred by the inability to efficiently prepare Claisen rearrangement substrate **237**, it was envisaged that palladium catalyzed π-allyl chemistry could be used for the construction of this key intermediate (Scheme 3.3.6).[5] Derivatization of **242** as the corresponding acetate was again unsuccessful. Acylation of **242** did occur, however, upon treatment with ethyl chloroforamte and pyridine to yield carbonate **245**. With **245** in hand, allylic alkylation of tyrosine **178** with **245** proceeded in <20% yield with

$Pd_2(dba)_3$ and dppb ligand in THF solvent. While the yield of this transformation was discouraging, all of the unreacted starting material could be isolated and no undesired S_N2' product was detected. Therefore, in an attempt to increase the conversion of the reaction an extensive amount of work was undertaken to optimize the catalytic system. All attempts at varying the palladium source, ligand source, and catalyst to ligand ratio were unsuccessful. Fortunately, performing the reaction in CH_2Cl_2 led to complete conversion and consumption of starting material in less than 2 hours. After further optimization of the catalyst system it was ultimately discovered that treatment of carbonate **245** and tyrosine **178** with 2.5 mol% $Pd_2(dba)_3$ and 7.5 mol% dppb in CH_2Cl_2 furnished the desired aryl ether **237** in 91% yield as a 1:1 mixture of diastereomers.

Scheme 3.3.6

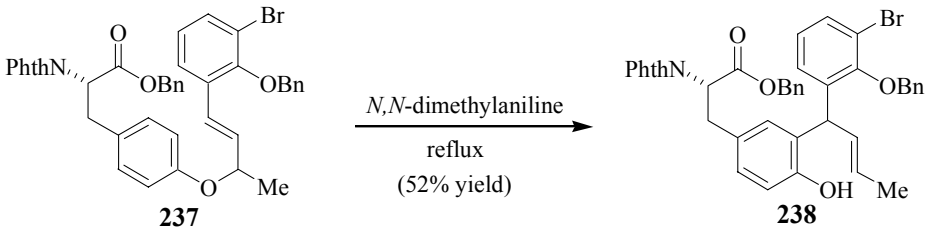


3.3.6 An Improved Claisen Rearrangement

With an efficient synthesis of **237** in hand, the reactivity of the modified Claisen rearrangement substrate could be examined. Gratifyingly, all expectations that the additional methyl group at C(4) would lead to an increase of reaction rate and yield were met (Scheme 3.3.7). Heating aryl ether **237** in refluxing *N,N*-dimethylaniline for 24 hours afforded a 52% yield of olefin **238** as a 1::1 mixture of diastereomers. While the reaction did proceed to completion, there was still the formation of unwanted byproducts

resulting from further reaction of the rearranged product. Nonetheless, significant quantities of olefin **238** could now be secured.

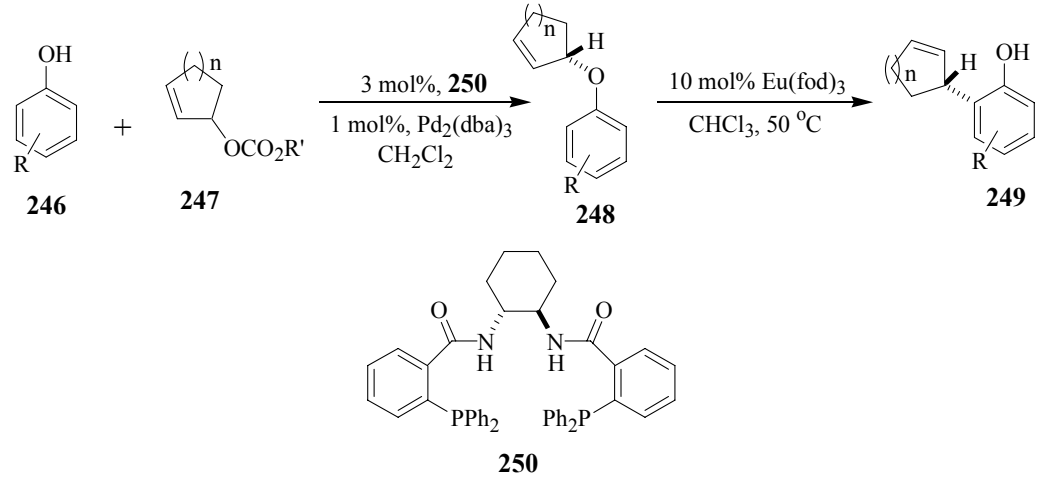
Scheme 3.3.7



3.3.7 Further Improvement of the Claisen Rearrangement

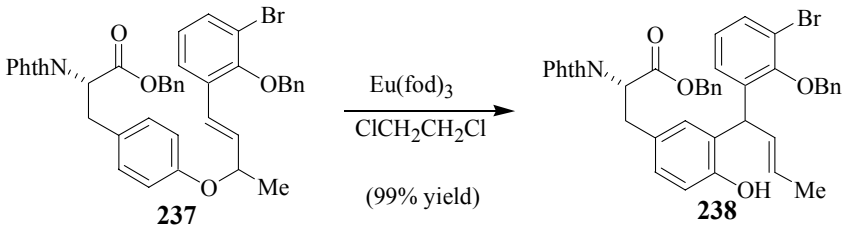
Concurrent with studies directed toward the synthesis of **238**, Trost and co-workers published a report on the asymmetric allylic alkylation of phenols followed by aromatic Claisen rearrangement (Scheme 3.3.8).[6] In this report, treatment of carbonates (**247**) and phenols (**246**) with $Pd_2(dba)_3$ and chiral ligand **250** furnished aryl ethers (**248**) as a single enantiomer. Refluxing the ether products in $CHCl_3$ with catalytic $Eu(fod)_3$ induced subsequent Claisen rearrangement to afford olefin products (**249**) in good yield with excellent transfer of chirality.

Scheme 3.3.8



Extension of the conditions developed by Trost for the Claisen rearrangement of aryl allyl ethers to the synthesis of **238** would have several practical benefits. Mainly, from the outset there was a great deal of concern that refluxing **237** for a prolonged period under basic conditions (*N,N*-dimethylaniline solvent) would result in racimization of the tyrosine stereocenter. The mild conditions of the Trost method should avoid this problem along with minimizing subsequent reaction of **238** to undesired byproducts. Application of the Trost conditions (refluxing $CHCl_3$ and 10% $Eu(fod)_3$) unfortunately resulted in no reaction after 7 days. But, careful examination of the experimental details in the Trost publication revealed that two substrates required refluxing $ClCH_2CH_2Cl$ in order for rearrangement to take place. Remarkably, refluxing **237** in $ClCH_2CH_2Cl$ with for 7 days led to essentially quantitative conversion of **237** to olefin **238** as a 1:1 mixture of diastereomers after simple removal of the catalyst over a plug of silica gel (Scheme 3.3.9).

Scheme 3.3.9

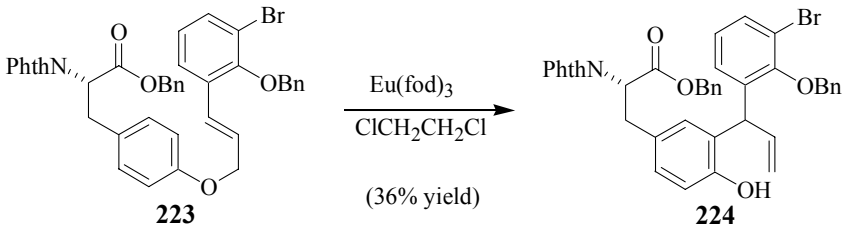


3.3.8 Reinvestigation of the Rearrangement of 223

Intrigued by the fascinating reaction of **237** with $Eu(fod)_3$ in refluxing $ClCH_2CH_2Cl$, attention again focused on the reactivity of **223**. Application of these new conditions to the rearrangement of **223** gave rise to **224** in 36% yield after two weeks

(Scheme 3.3.10). While the overall efficiency of the reaction was increased, the reaction was not as efficient as when applied to **223**, further confirmimg the beneficiary role of the C(4) methyl group.

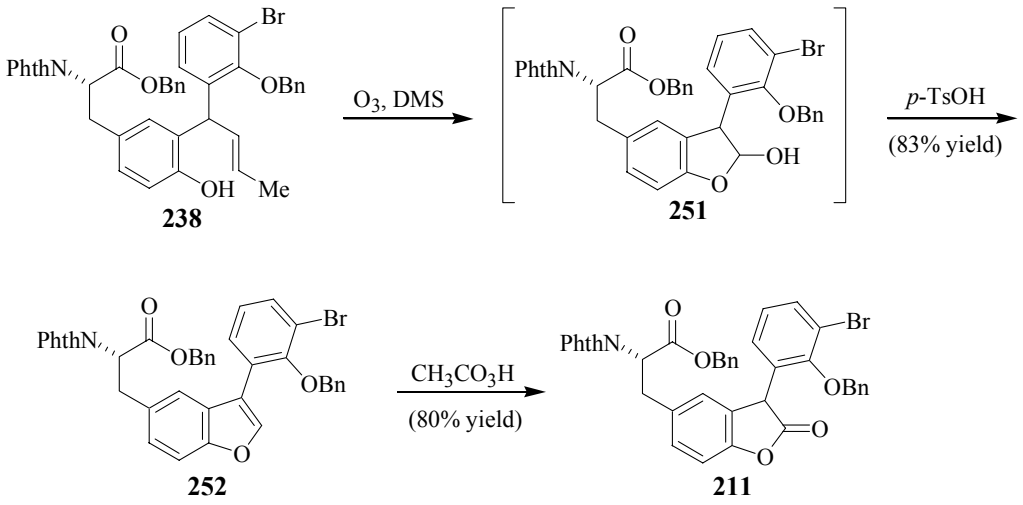
Scheme 3.3.10



3.3.9 Completion of Benzofuranone 211

With an extremely efficient and scalable route to **238** in hand, completion of the synthesis of benzofuranone **252** was straightforward (Scheme 3.3.11). Ozonolysis of **238** proceeded without event to furnish an intermediate hemi-acetal **251** which was eliminated under acidic conditions with concurrent removal of water to afford benzofuran **252**. Final oxidation of **252** according to the procedure of Vedejs yielded benzofuranone **211** in good yield.[7] Through the sequence detailed in this chapter, muti-gram quantities of **211** could be prepared and stored indefinitely without decomposition.

Scheme 3.3.11

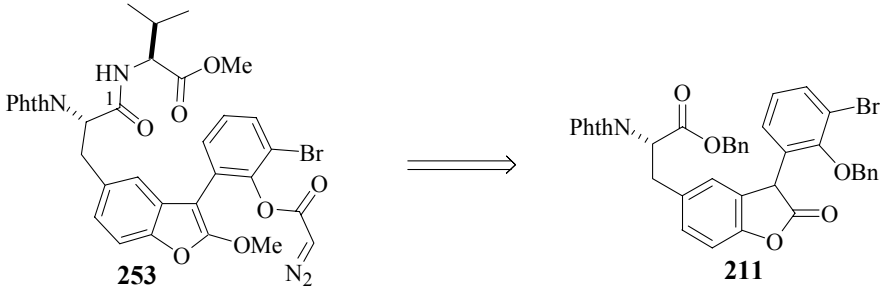


3.4 Investigation Into the Cyclopropanation Approach

3.4.1 Synthetic Plan

Once the synthetic route to **211** was secured, efforts were directed toward investigating the extsension of the cyclopropanation approach to the real system. As before, this would involve O-alkylation of lactone **211**, benzyl group deprotection, and diazoacylation to furnish the requisite cyclopropanation precursor. In addition, concurrent removal of the tyrosine benzyl group would afford the opportunity to study derivatization of the diazonamide C(1). As a result, α-diazo ester **253** was targeted as an attractive cyclopropanation substrate (Scheme 3.4.1).

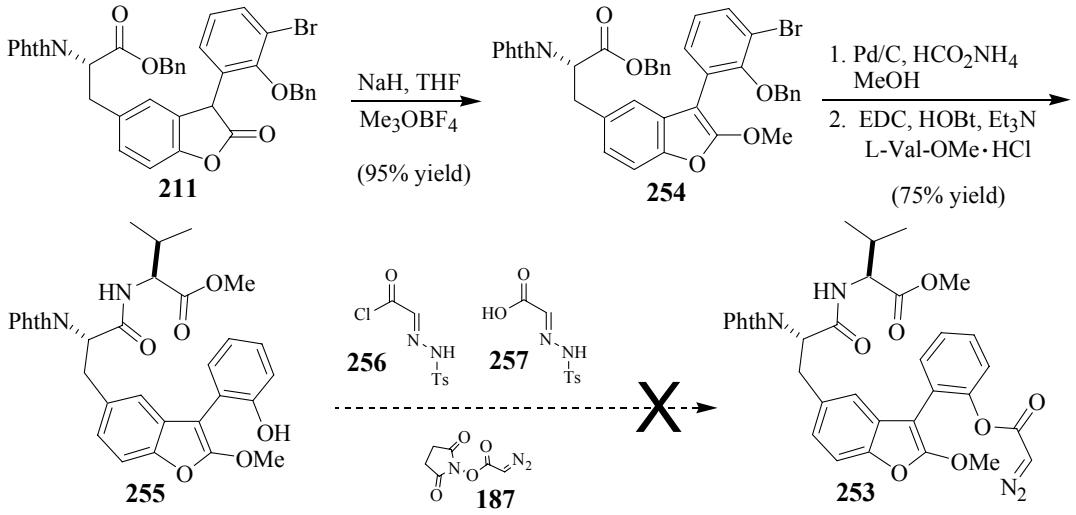
Scheme 3.4.1



3.4.2 Synthesis of Cyclopropanation Substrate 255

Synthetic studies directed at **253** began with O-alkylation of **211** under the optimal condition developed in the model system (Scheme 3.4.2). Therefore, deprotonation of **211** with NaH followed by treatment with Meerwein's reagent afforded O-alkylated product **254** exclusively. In stark contrast to the observations made in the model system, the product of C-alkylation was never observed in this reaction. With **254** in hand, exhaustive transfer hydrogenolysis furnished an intermediate acid that was coupled to L-Val-OMe with EDC and HOBt to furnish dipeptide **255**. Careful spectroscopic examination of **255** revealed that the C(16) bromide was hydrogenalytically removed along with both benzyl groups. In addition **255** was produced as a single diastereomer, confirming that the stereochemical integrity of the tyrosine stereocenter was maintained through this stage of the synthesis. Unfortunately, at this point all attempts to install the α-diazo ester functionality met with no success. Treatment of **255** with three different diazoacylation reagents (succinimide **187**, acid chloride **256**, and acid **257**) under various basic conditions resulted in only the isolation of unreacted starting material.[8,9]

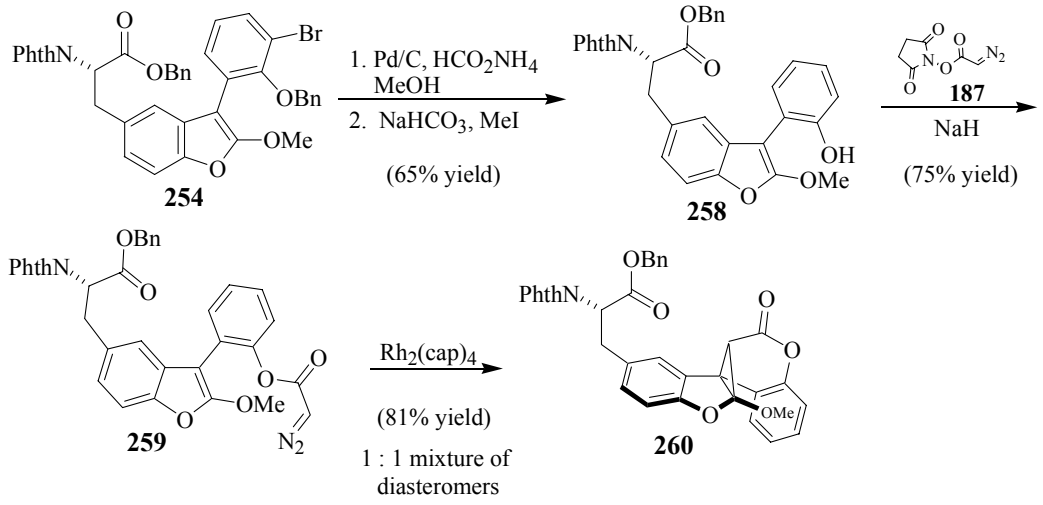
Scheme 3.4.2



3.4.3 A Revised Cyclopropanation Substrate

Due to the inability to diazoacylate **255**, α-diazo ester **259** was targeted as a revised cyclopropanation substrate (Scheme 3.4.3). Therefore, exhaustive transfer hydrogenation of benzofuran **254** as before yielded an intermediate acid that was selectively benzylated to afford ester **258**. Gratifyingly, diazoacylation of **258** proceeded smoothly and afforded α-diazo ester **259** upon treatment with succinimide **187**. With **259** in hand, cyclopropanation was straightforward. Treatment of **259** with $Rh_2(cap)_4$, as in the model system, furnished the desired cyclopropanated product **260** in good yield as a 1:1 mixture of diastereomers.[10]

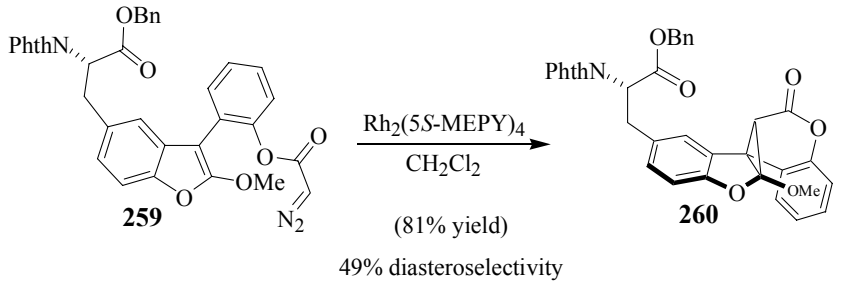
Scheme 3.4.3



3.4.4 Investigations into an Asymmetric Cyclopropanation

Pleased with the ability to successfully perform the cyclopropanation in a fully functional system, attention turned to increasing the level of diasteroselectivity in the formation of the quaternary center. While it was hoped that the tyrosine streocenter might influence the facial selectivity of the cyclopropanation, the results above show this not to be true. As a result, work again focused on the use of Doyle's $Rh_2(5S\text{-MEPY})_4$ catalyst to control the stereochemistry of the cyclopropanation reaction (Scheme 3.4.4). To this end, syringe pump addition of α-diazo ester **259** to a refluxing solution of Doyle's $Rh_2(5S\text{-MEPY})_4$ catalyst in CH_2Cl_2 gave rise to optically active cyclopropanated product **260** in 49% de. As before, the desired diastereomers is shown only for illustrative purposes. At this time the relative strerochemistry of the major diastereomer is not known.

Scheme 3.4.4

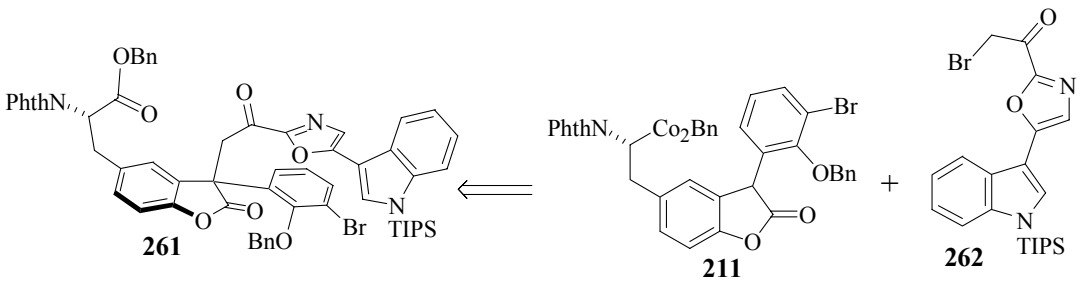


3.5 Investigation into the Alkylation Approach

3.5.1 Synthetic Plan

In an effort to gain more facile access to advanced diazonamide synthetic intermediates, it was decided to shift focus away from the cyclopropanation approach and concentrate on the alkylation approach. With benzofuranone **211** already in hand, work toward the alkylation approach would require the synthesis of an appropriate alkylation electrophile. Toward this end, indole **262** was indentified as an initial synthetic target (Scheme 3.5.1).

Scheme 3.5.1

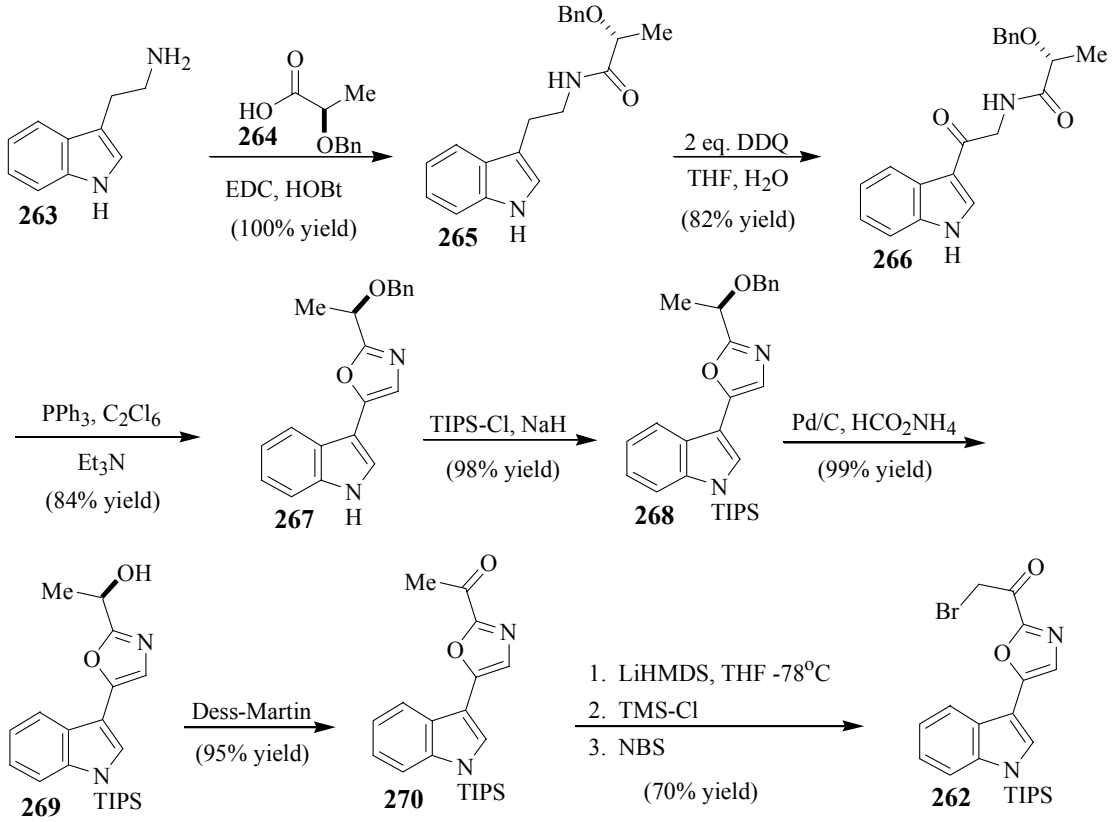


3.5.2 Synthesis of Alkylation Electrophile 262

Synthesis of the desired alkylation electrophile **262** began with coupling of protected lactic acid **264** to tryptamine (**263)** with EDC and HOBt to afford amide **265**

(Scheme 3.5.2). Subsequent DDQ oxidation under aqueous conditions provided intermediate ketone **266**. Cyclodehydration of **266** using Wipf's protocol furnished oxazole **267**.[11] At this stage indole protection of **267** with TIPS-Cl gave rise to oxazole **268**. The TIPS protecting group was chosen because of it is orthogonal to the protecting groups present in benzofuranone **211**. Benzyl deprotection of **268** afforded alcohol **269**, which was oxidized to ketone **270** with Dess-Martin periodinane. Finally, one pot α-bromination of **270** gave the desired α-bromo keton **262** in good yield.

Scheme 3.5.2

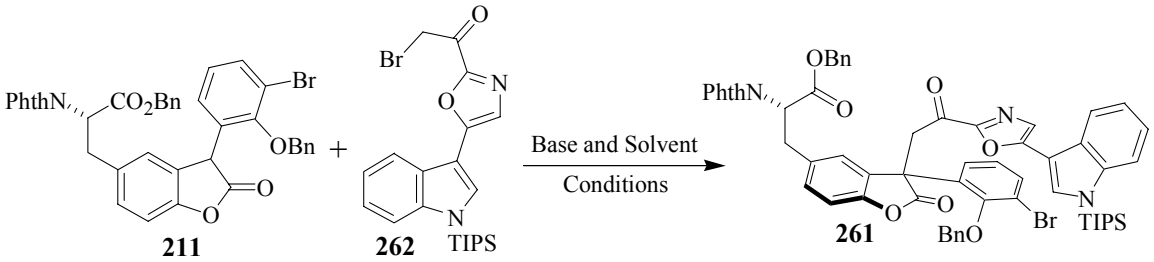


3.5.3 Attempts at Alkylation

With both alkylation partners in hand, work began in earnest to study the alkylative formation of the diazonamide C(10) quaternary center. Unfortunately, all

attempts toward this end met with no success. Formation of the enolate of **211** followed by addition of **262** invariably resulted in either decomposition of **262** and recovery of unreacted **211** or no reaction. All the conditions surveyed are summarized in Table 3.5.1.

Table 3.5.1 **Survey of Various Methods for the Alkylation of Benzofuranone 211 with α-Bromo Ketone 262.**

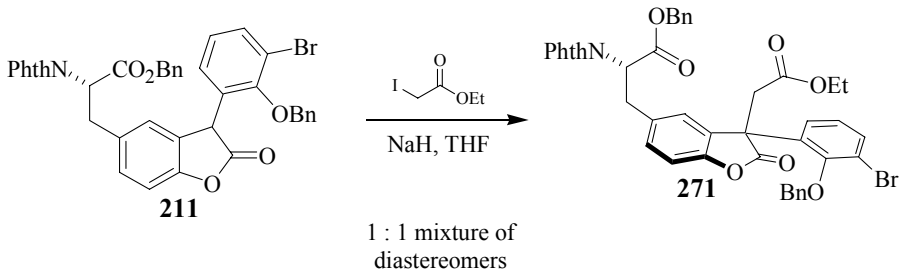


Entry	Alkylation Conditions	Product
1	NaH, THF, 0 °C	Indole **262** Decomposition
2	NaH, DMF, 0 °C	Indole **262** Decomposition
3	KO*t*-Bu, THF, 0 °C	Indole **262** Decomposition
4	KO*t*-Bu, DMF, 0 °C	Indole **262** Decomposition
5	LiHMDS, THF, -78 °C → 0 °C	Indole **262** Decomposition
6	LiHMDS, DMF, -78 °C → 0 °C	Indole **262** Decomposition
7	LiHMDS, THF, -78 °C → -20 °C	No reaction
8	LiHMDS, DMF, -78 °C → -20 °C	No reaction
9	LiHMDS, DMF, HMPA, -78°C → -20°C	Indole **262** Decomposition
10	K_2CO_3, *n*-Bu_4NBr, DMF, 25 °C	Indole **262** Decomposition
11	K_3PO_4, DMF, 25 °C	Indole **262** Decomposition

Disappointed in the inability to effect the desired alkylation under numerous conditions, attention turned to modification of the reaction substrates in hopes of improving the alkylation. In all attempted alkylations above -20 °C, indole **262**

underwent rapid decomposition to unidentifiable decomposition products. One plausible pathway for decomposition of **262** would involve removal of the TIPS group followed by decomposition of the α-bromo ketone moiety through participation of the aromatic system. Replacement of the TIPS group with a benzyl group on the indole nitrogen, however, had no benefical effect in suppressing decomposition under the reaction conditions. Interested if benzofuranone **211** was capable of undergoing alkylation with any α-halo carbonyl, the sodium enolate of **211** was prepared as before and subsequently treated with ethyl iodoacetate in THF to afford alkylated product **271** as a 1:1 mixture of diastereomers (Scheme 3.5.3). Pleased that **211** was finally alkylated, it was interesting to note that the reaction conditions required for alkylation of **211** were more forcing than the corresponding reaction of model benzofuranone **198**. In particular, the alkylation of **211** required 5 equivalents of α-iodo ester and 24 hours, whereas the alkylation of **198** required only 1 equivalent of α-bromo ester and 2 hours.

Scheme 3.5.3



3.5.4 Successful Alkylation of 211 with Indole 262

Based on the inability to alkylate benzofuranone **211** with indole **262** and the sluggish reactivity of **211** with ethyl iodoacetate, close examination of **211** was undertaken to determine if any structural changes could be made to improve its reactivity. Upon inspection of molecular models of **211**, it became clear that because of the adjacent

bromine substituent, the phenolic benzyl group could only adopt a conformation wherein the phenyl ring is blocking the benzofuranone C(3). This observation provides a reasonable explanation for the reduced reactivity of **211** and the model system relative to **198** (Figure 3.5.1). The phenolic benzyl group in model **198** is unsubstituted at the ortho-position and as a result it has more conformational freedom.

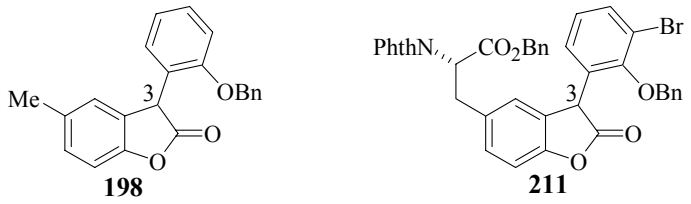
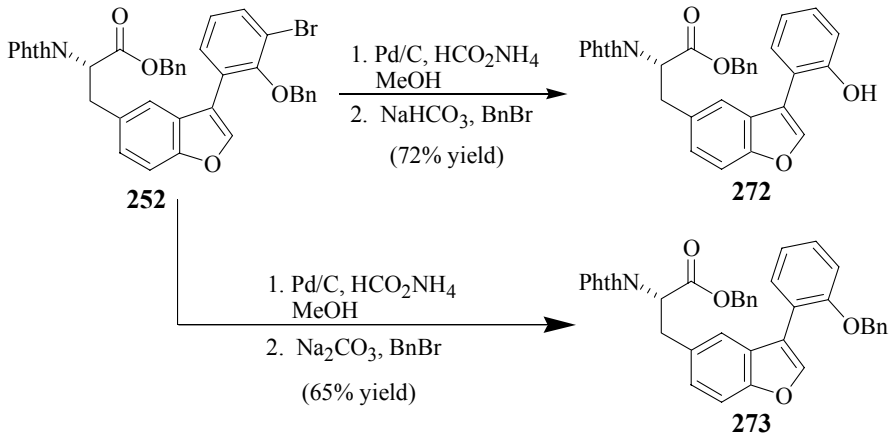


Figure 3.5.1 Side by Side Comparison of Benzofuranone 198 and 211.

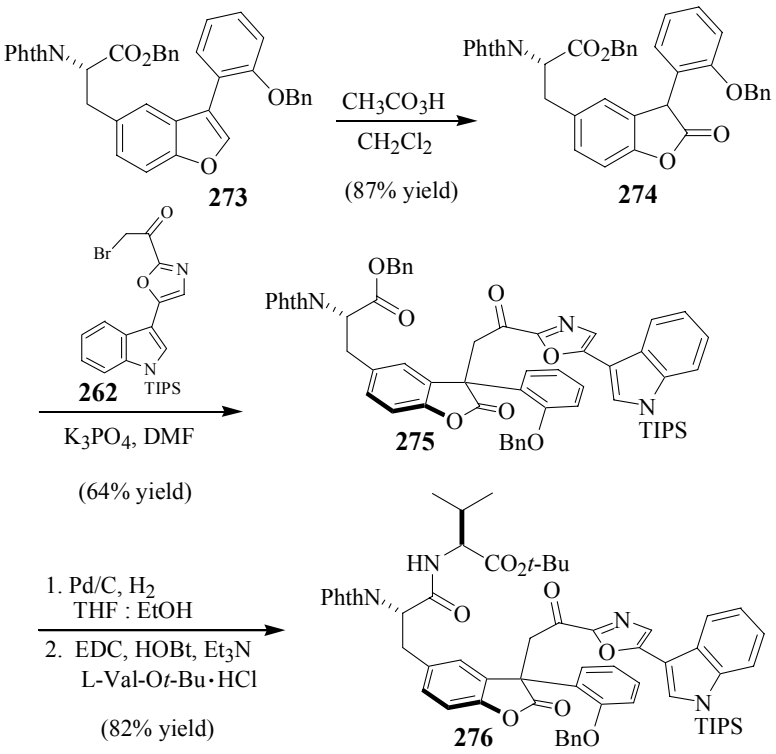
As a result of the above analysis, work began on preparation of a benzofuranone that is identical to **211** in all respects except for replacement of the aryl bromide with a hydrogen (Scheme 3.5.4). Toward this end, exhaustive transfer hydrogenolysis of benzofuran **252** followed by treatment with BnBr and $NaHCO_3$ at room temperature furnished phenol **272**. Similarly, exposure of the intermediate acid generated after hydrogenation to BnBr and Na_2CO_3 afforded benzyl ether **273**.

Scheme 3.5.4



With **273** in hand, oxidation proceeded smoothly to furnish the desired benzofuranone **274** lacking a bromine substituent ortho to the benzyl ether (Scheme 3.5.5). After much experimentation, it was discovered that simply mixing benzofuranone **274**, indole **262**, and K_3PO_4 at room temperature afforded ketone **275** as a 1:1 mixture of diastereomers. While concomitant decomposition of indole **262** was still a competing side reaction, removal of the aryl bromide was advantageous and led to the formation of the desired alkylation product in good yield. Unfortunately, all attempts to separate the diastereomers at this stage failed. Selective hydrogenolysis of **275** and coupling to L-Val-O*t*-Bu provided dipeptide **276** in excellent yield. Separation of the diasteromers at this stage was possible with silica gel chromatograaphy. But, all attempts to grow a single crystal of either diastereomer, in order to determine which diastereomer possess the correct relative stereochemistry, has been unsuccessful.

Scheme 3.5.5



3.6 Summary and Conclusions

Efforts directed toward the total synthesis of diazonamide A have been described. The synthetic route devised relies on the efficient construction of benzofuranone **211**, which was achieved via a robust π-allyl alkylation/$Eu(fod)_3$ catalyzed Claisen rearrangement sequence. Proceeding from benzofuranone **211**, an intramolecular cycloprpoanation reaction was utilized to construct the diazonamide C(10) bisaryl quaternary center in enantioenriched form. In addition, an alkylation based strategy was employed beginning with **211** to ultimately afford advanced peptide **276**.

While advanced intermediate **276** holds great promise for the sysnthesis of the originally proposed structure of diazonamide A, advancement of **276** toward the newly revised structure is not as encouraging. All attempts to convert the C(17) oxygen to the

newly revised nitrogen at this position in compounds **276** and **273** have met with no success. Therefore, based on the inability to install the diazonamide aminal nitrogen and the expertise gained in this lab for the cyclopropanation of heteroaromatic rings a revised synthesis of the reassigned diazonamide A structure is presented in the following section

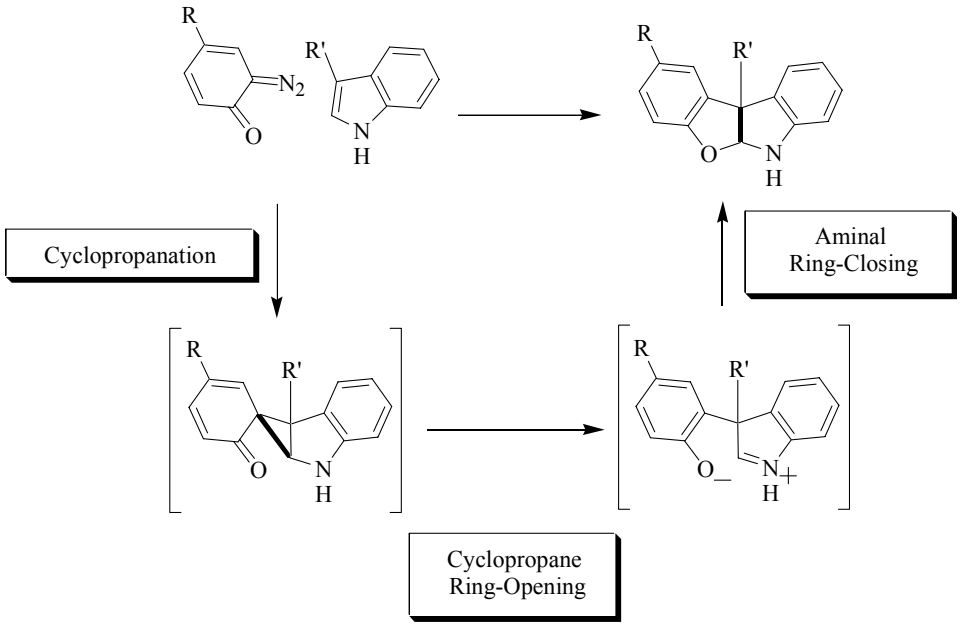
3.7 Future Studies

3.7.1 A Biomimetic Total Synthesis of Diazonamide A

3.7.1.1 Introduction

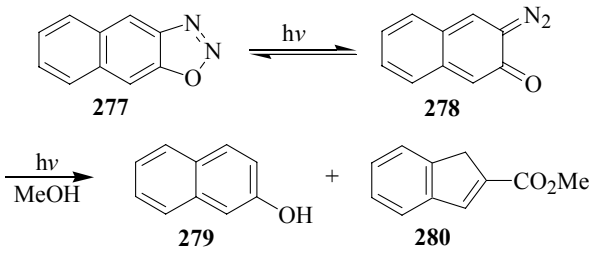
Inspired by the proposed biosynthetic origin of diazonamide A along this lab has become interested in pursuing an efficient biomimetic synthesis of this complex natural product. A biomimetic synthesis of diazonamide A offers the advantage of rapid construction of the diazonamide skeleton via standard peptide and oxazole synthesis from readily available amino acids. Realization of this approach, however, requires the development of a net oxidative cycloaddition of tyrosine and tryptophan. It is envisioned this difficult transformation can be realized by a catalytic cyclopropanation/cyclopropane ring-opening/aminal ring-closing process (Scheme 3.7.1).

Scheme 3.7.1



The existence and chemistry of 1,2,3-oxadiazoles has been the source of extensive research.[12] 1,2,3-Oxadiazoles (**227**) are stable isolatable compounds that upon irradiation with UV light exist in equilibrium with their corresponding valence isomer α-diazo ketones (**278**, Scheme 3.7.2).[12-14] Under prolonged exposure to UV light these compounds undergo subsequent reactions typically observed for α-diazo ketones (i.e. O-H insertion (**279**) and Wolff rearrangement (**280**)). [12,15]

Scheme 3.7.2

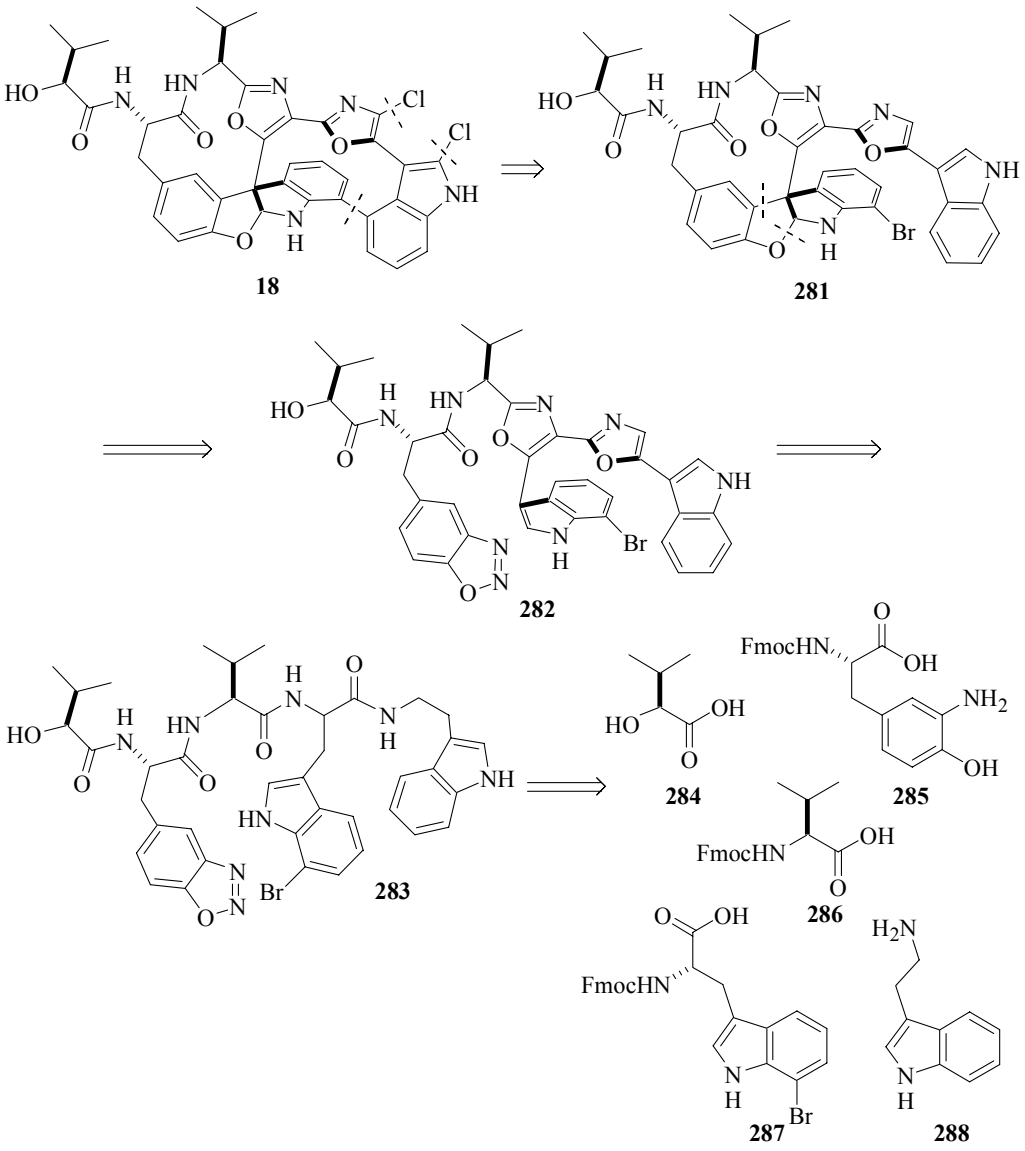


Taken together, the *in situ* formation of α-diazo ketones from 1,2,3 oxadiazoles and their subsequent carbenoid mediated cyclopropanation/ring-opening provides a truly novel method for the construction of the diazonamide A core.

3.7.1.2 Retrosynthetic Analysis

Guided by the interests to address the above issues, the retrosynthetic analysis illustrated in Scheme 3.7.3 is put forward. Cleavage of the biaryl bond and late stage introduction of both chlorines are seen as a reasonable first disconnection based on the work of Harran and Nicolaou. Striking at the core of **281**, cleavage of the C(10) and C(11) carbons provides oxadiazole **282**. In the forward sense it is envisioned that formation of these critical carbon centers will occur via the cyclopropanation/ring-opening/aminal-formation process described previously. Oxadiazole **282** will arise from peptide **283** by well-precedented oxidation/cyclodehydration conditions for the construction of oxazoles. Final disconnection of the four amide linkages in **283** reveals commercially available isovaleric acid **284**, aminotyrosine **285**, valine **286**, tryptophan **287**, and tryptamine (**288**).

Scheme 3.7.3

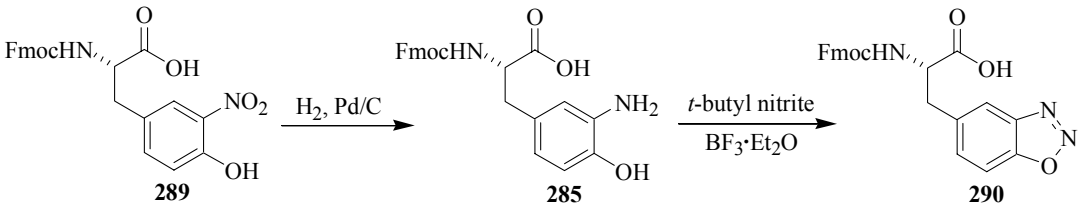


3.7.1.3 A Forward Synthetic Plan

As described previously in the retrosynthesis, diazonamide A can be broken into five commercially available building blocks. Of these building blocks, only aminotyrosine **285** needs to be manipulated before being incorporated into the diazonamide pentapeptide. Reduction of **289** with H_2 and Pd/C affords amino phenol

285,[16] which upon treatment with *t*-butyl nitrite under acidic conditions and purification with basic alumina will give rise to the desired oxadiazole **290** (Scheme 3.7.4).[12,17]

Scheme 3.7.4

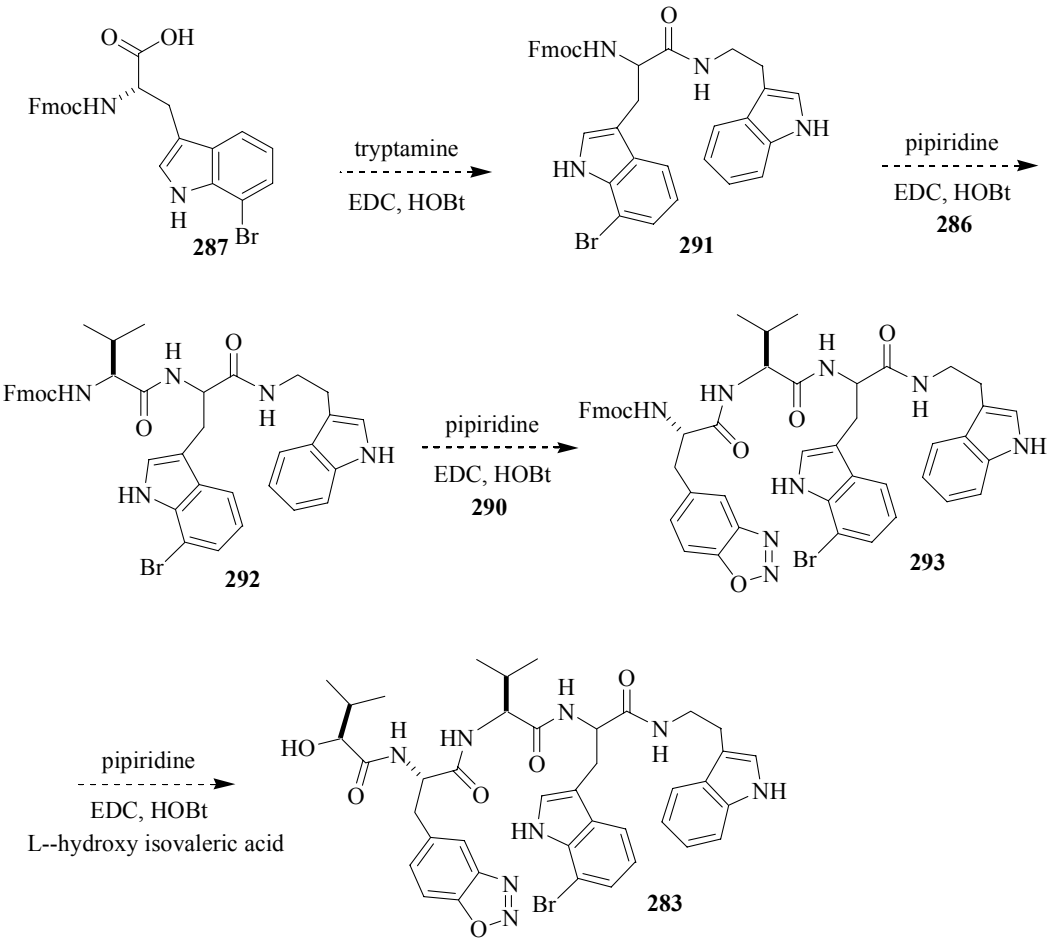


289 **285** **290**

Combination of the five building blocks requires the construction of four amide linkages. It is planed to form these bonds utilizing the standard C to N peptide coupling strategy. While this is not the most convergent approach, it does offer the advantage of easy adaptation to a solid supported synthesis that will become useful later for the rapid construction of diazonamide A analogs.

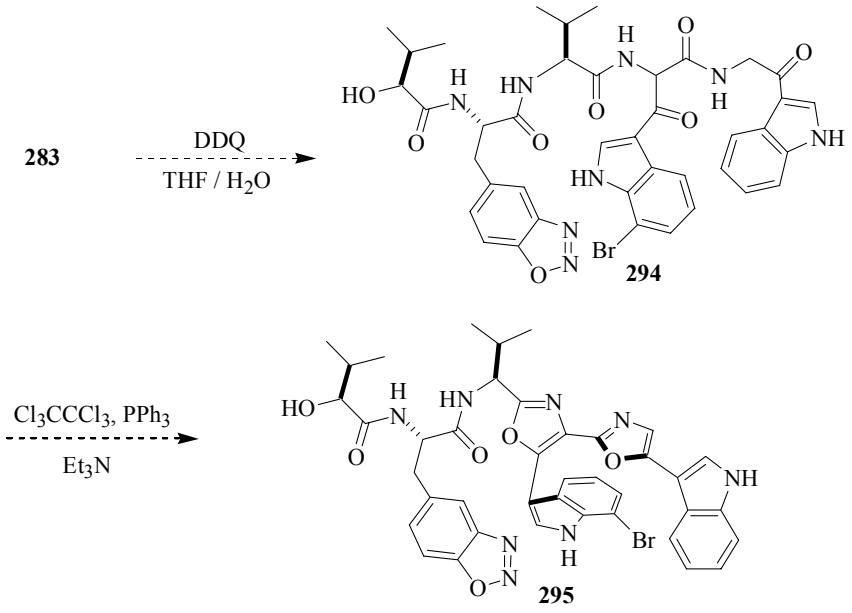
Work will commence with EDC/HOBt mediated coupling of tryptophan **287** with tryptamine (**288**) to provide bisindole **291** (Scheme 3.7.5). Deprotection of **291** with pipiridine followed by EDC/HOBt coupling with Fmoc-valine will provide peptide **292**. Reiteration of this deprotection/coupling sequence homologating the growing chain with **290** and L-α-hydroxy isovaleric acid is expected to give rise to the desired intermediate **283**.

Scheme 3.7.5



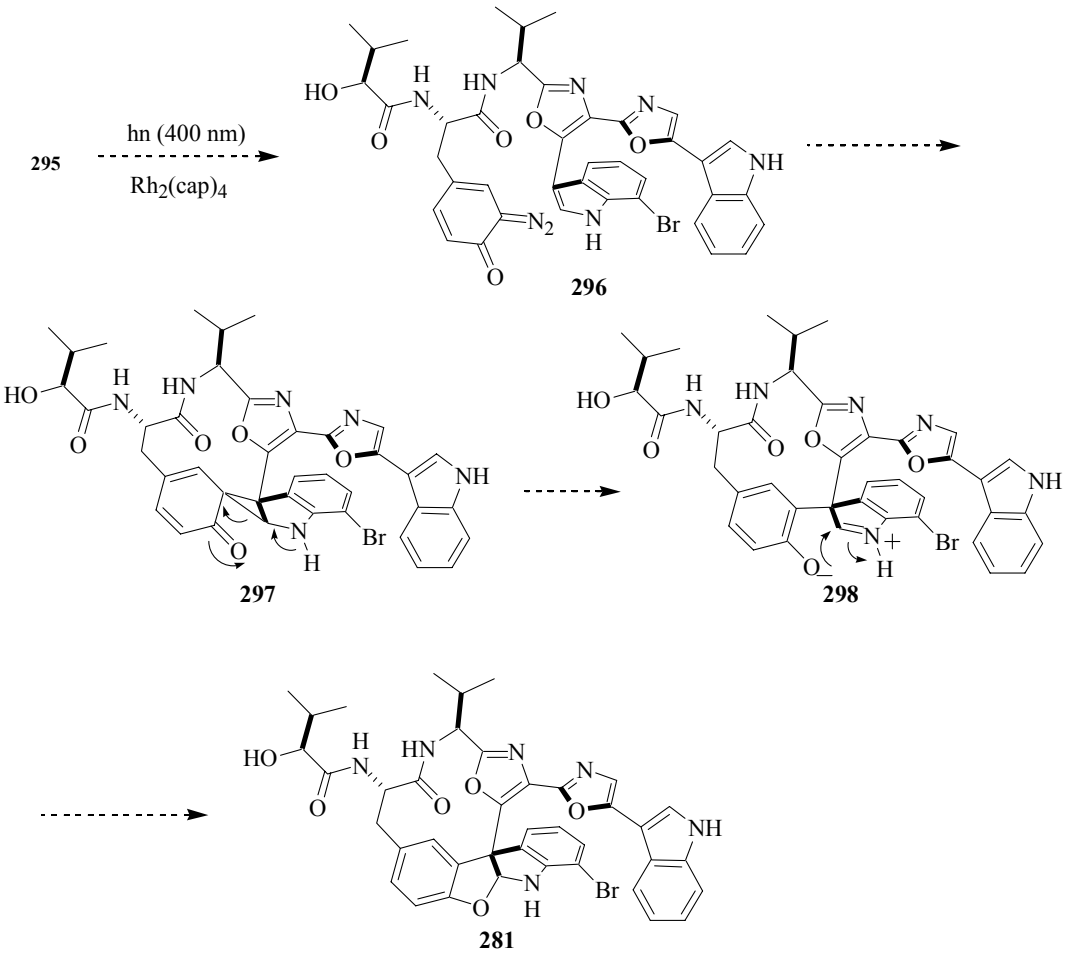
With **283** in hand, work will focus on the construction of the bisoxazole functionality present in diazonamide A. Treatment of **283** with DDQ will induce well-precedented indole oxidation to bisketone **294** (Scheme 3.7.6).[18] Cyclodehydration according to the procedure of Wipf,[11] utilized by six groups in their reported approached to diazonamide A, will afford bisoxazole **295**.

Scheme 3.7.6



The stage is now set for the crucial net oxidative cycloaddition of tyrosine and tryptophan to forge the diazonamide A C(10) quaternary center and C(11) aminal core (Scheme 3.7.7). Irradiation of oxadiazole **295** with 400 nm UV light in the presence of $Rh_2(cap)_4$ will first give rise to α-diazo ketone **296**. Following *in situ* decomposition with $Rh_2(cap)_4$, **296** is expected to undergo carbeniod mediated intramolecular cyclcopropanation to afford cyclopropane **297**. Subsequent nitrogen assisted ring-opening of **297** to afford imine **298** followed by aminal ring-closure will ultimately provide advanced intermediate **281**.

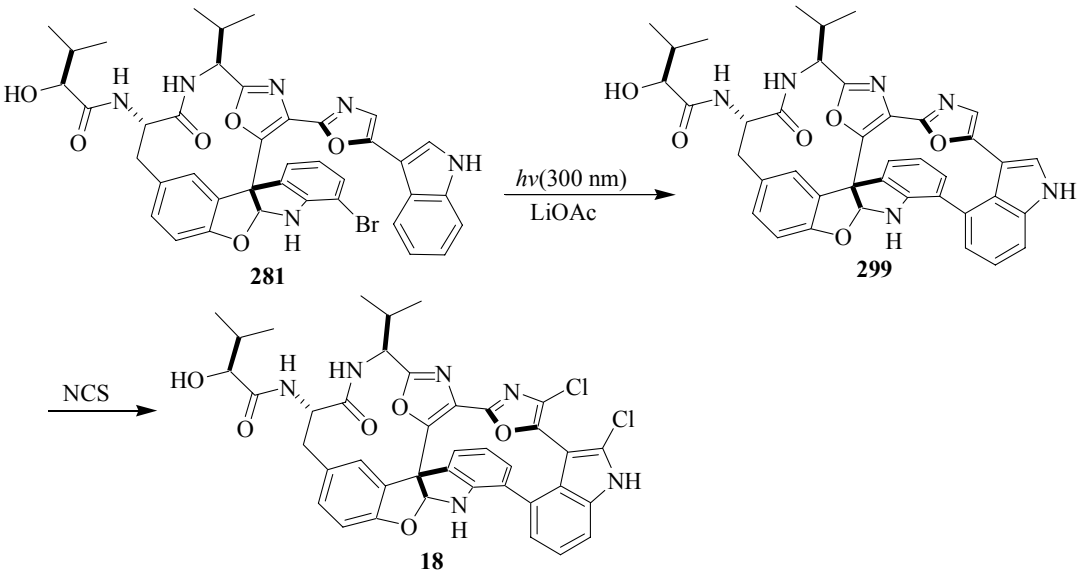
Scheme 3.7.7



In Scheme 3.7.7, the key stereochemistry determining cyclopropanation step is shown to provide exclusively the desired diastereomer **281**. However, two diastereomeric products could arise in the above step resulting from reaction on either face of the indole system. Control of the diastereoselectivity in this step should be possible based on the work of Doyle.[19-23] Doyle has extensively demonstrated that high enantiocontrol can be achieved in intramolecular cyclopropanations with chiral rhodium and copper catalysts to form *macrocycles*. Therefore the use of chiral cyclopropanation catalysts should allow for the selective synthesis of both diastereomers.

Completion of diazonamide A at this point will be straightforward in accordance with the literature precedence of Harran and Nicolaou (Scheme 3.7.8). Exposure of **281** to higher energy 300 nm UV light will induce a Witkop-type cyclization forming the C(16)-C(18) biaryl bond.[24] Chlorination of **299** with NCS at C(27) and C(25) will culminate in the total synthesis of diazonamide A.

Scheme 3.7.8

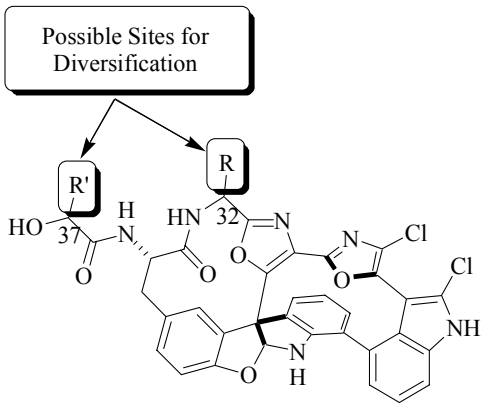


Diazonamide A

It is important to note at this point that two key sequential carbon-carbon bonding forming reactions (**295** to **181**, **281** to **299**) in this synthesis require photochemical conditions. Due to the known energetic requirements of these reactions, however, it is felt that they can be conducted independently. The Witkop-type reaction requires high energy 300 nm light for initiation.[24] Whereas the activation of oxadiazoles to the corresponding α-diazo ketones occurs with lower energy 400 nm light.[13] Therefore, utilizing a Rayonet benchtop photochemical apparatus, with interchangeable 419 nm and 300 nm bulbs, will allow selective oxadiazole activation without triggering Witkop cyclization.

In addition to providing natural diazonamide A this efficient modular synthesis will provide access to potentially valuable diazonamide analogs for biological testing (Scheme 3.7.9). The introduction of diversity at C(32) and C(37), in particular should be readily accessible via this route.

Scheme 3.7.9



3.8 Experimental Section

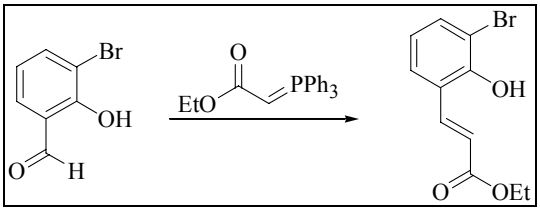
3.8.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly distilled solvents. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone. Methylene chloride (CH_2Cl_2), and benzene were distilled from calcium hydride. Methanol (MeOH) was distilled from magnesium. All other commercially obtained reagents were used as received. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Column or flash chromatography was performed with the indicated solvents using silica gel (particle size 0.032-0.063 nm) purchased from Bodman. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance

DPX-500 or Bruker Advance DPX-400 spectrometers. Chemical shifts are reported relative to internal chloroform (^{1}H, δ 7.27 ppm, ^{13}C δ 77.0 ppm), benzene (^{1}H, δ 7.30 ppm), dimethyl sulfoxide (^{13}C, δ 40.5 ppm), or methanol (^{13}C, δ 49.9 ppm). Melting points were obtained on a Gallenkamp variable temperature melting point apparatus and are uncorrected. Infrared spectra were recorded on a Midac M-1200 FTIR. High resolution mass spectra were acquired at The University of Illinois Mass Spectrometry Center.

3.8.2 Preparative Procedures

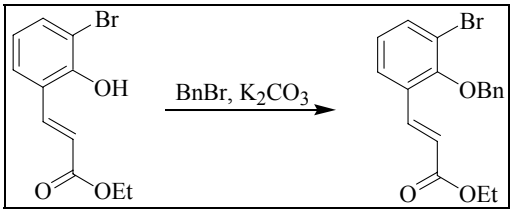
Preparation of olefin 219



To a solution of **212** (3.63 g, 18.10 mmol) in C_6H_6 (40 mL) at 0 °C was added a solution of (carbethoxymethylene)triphenyl-phosphorane (6.62 g, 19.01 mmol) in C_6H_6 (40 mL) over 10 min. Ater stirring for an additional 1 h the reaction was concentrated to half its original volume and purified by silica gel chromatography (hexanes:EtOAc, 6:1) to afford olefin **219** (4.30 g, 88% yield) as a white solid (m.p 104 °C). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94 (d, *J*=16.4 Hz, 1H), 7.45 (dd, J=1.2, 7.9 Hz, 2H), 7.41 (m, 1H), 6.81 (t, *J*=7.9 Hz, 1H), 6.55 (d, *J*=16.4 Hz, 1H), 6.29 (s, 1H), 4.27 (q, *J*=7.3, 2H), 1.43 (t, *J*=7.3 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.1, 151.1, 139.2, 133.3, 128.4, 122.9, 121.5, 120.1, 111.5, 60.514.3; **IR** (thin film/NaCl) 3304 (m), 2992 (w), 1694 (s), 1631

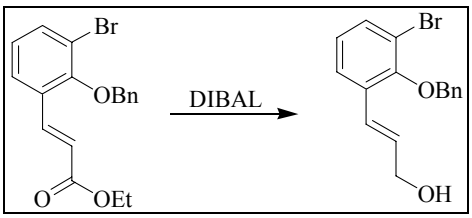
(m), 1447 (m), 11317 (s), 1193 (s), 996 (w), 778 (w), 627 (w) cm^{-1}; **HRMS** (FAB) *m/z* found: 270.9970, [calc'd for $C_{11}H_{12}O_3Br$(M+H): 270.9970].

Preparation of ether 220



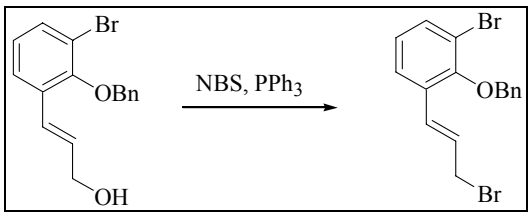
To a solution of phenol **219** (1.364 g, 5.03 mmol) in acetone (50 mL) was added benzyl bromide (0.72 mL, 6.03 mmol) and K_2CO_3 (1.60 g, 11.60 mmol). The reaction mixture was heated to reflux for 12 h. After this time the reaction mixture was concentrated in vacuo and the crude mixture taken up in ether. Filtration of the residual solids, removal of the solvent in vacuo, and purification by silica gel column chromatography (hexanes:EtOAc, 10:1) to afforded allylic benzyl ether **220** (1.80 g, 99% yield) as a white solid (m.p. 49-50 °C). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94 (d, *J*=16.3 Hz, 1H), 7.62 (dd, *J*=1.6, 7.8 Hz, 1H), 7.56-7.51 (dd, cm, 3H), 7.44-7.36 (cm, 3H), 7.06 (t, *J*=7.8 Hz, 1H), 6.42 (d, *J*=16.3 Hz, 1H), 7.96 (s, 1H), 4.26 (q, *J*=7.3 Hz, 2H), 1.35 (t, *J*=7.3 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.5, 154.5, 138.6, 135.9, 135.0, 130.6, 128.8, 128.5, 128.5, 126.8, 125.7, 120.5, 118.5, 60.5, 14.3; **IR** (thin film/NaCl) 3065 (w), 2981 (m), 1713 (s), 1636 (m), 1440 (s), 1263 (s), 1175 (s), 1038 (m), 788 (m), 556 (w) cm^{-1}; **HRMS** (FAB) *m/z* found: 361.0440, [calc'd for $C_{18}H_{18}O_3Br$(M+H): 361.0439].

Preparation allylic alcohol 221



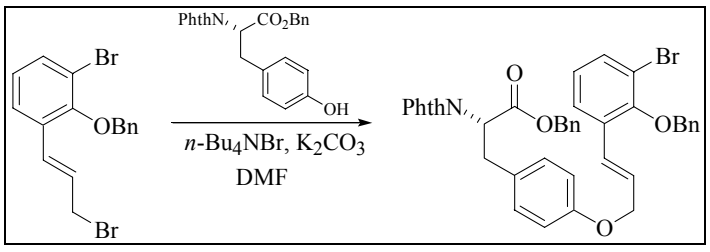
A solution of ester **220** (15.7 g, 43.5 mmol) in THF (300 mL) was cooled to –78 °C and treated with a 1.0 M CH_2Cl_2 solution of DIBAL (108.8 mL, 108.8 mmol). After 30 min. the reaction was carefully quenched with a saturated solution of Rochelle's salt (600 mL) and allowed to stir at room temperature for 2 h. The organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 (3 x 250 mL). The combined organic layers were washed with brine (250 mL) and dried ($MgSO_4$). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 6:1 then 3:1) to afford allylic alcohol **221** (12.3 g, 89% yield) as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53(m, 2H), 7.50 (dd, *J*=1.6, 8.0 Hz, 1H), 7.45-7.35 (cm, 4H), 7.00 (t, *J*=7.7 Hz, 1H), 6.81 (d, *J*=16.2 Hz, 1H), 6.33 (dt, *J*=5.6, 16.2 Hz, 1H), 4.95 (s, 2H), 4.26 (dd, J=1.6, 5.6 Hz, 1H), 1.50 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.1, 136.7, 132.7, 132.5, 131.0, 128.5, 128.3, 128.3, 125.9, 125.6, 125.1, 75.5, 63.7; **IR** (thin film/NaCl) 3352 (br m), 2867 (m), 1438 (s), 1373 (m), 1222 (s), 1077 (m), 975 (s), 864 (w), 753 (m), 559 (w) cm^{-1}; **HRMS** (FAB) *m/z* found: 316.0098, [calc'd for $C_{16}H_{13}O_2Br$(M-2H): 316.0099].

Preparation of bromide 222



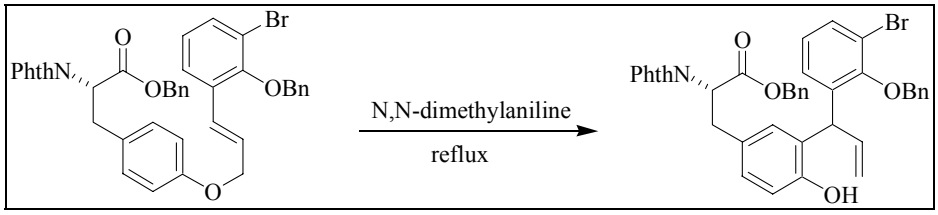
To a solution of alcohol **221** (2.12 g, 6.66 mmol) and PPh_3 (1.92 g, 7.31 mmol) in CH_2Cl_2 (50 mL) at -20 °C was added NBS (1.42 g, 7.97 mmol). After stirring for an additional 1 h the crude reaction mixture was diluted with hexanes (50 mL). Removal of the solids by filtration over a plug of silica gel afforded bromide **222** (2.28 g, 90% yield) as a light yellow solid (m.p. 41-42 °C). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58-7.51 (cm, 3H), 7.47-7.37 (cm, 4H), 7.02 (t, *J*=7.9 Hz, 1H), 6.85 (d, *J*=15.8 Hz, 1H), 6.42 (m, 1H), 4.94 (s, 2H), 4.10 (dd, *J*=1.0, 7.8 Hz, 2H; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.4, 136.4, 133.1, 131.8, 128.7, 128.5, 128.4, 128.3, 128.2, 127.6, 126.2, 125.5, 118.2, 75.6, 33.1; **IR** (thin film/NaCl) 3033 (w), 14336 (s), 1374 (m), 1216 (s), 1120 (w), 1073 (m), 971 (s), 750 (m), 697 (m), 461 (w) cm^{-1}; **HRMS** (EI) *m/z* found: 379.9408, [calc'd for $C_{16}H_{14}O_1Br$(M+): 379.9411].

Preparation of allyl ether 223



To a solution of bromide **222** (270 mg, 0.707 mmol) in DMF (3 mL) was added tyrosine **178** (280 mg, 0.700 mmol), K_2CO_3 (197 mg, 1.42 mmol), and *n*-Bu_4NI (26 mg, 0.070 mmol) at room temperature. After stirring for 16 h, the reaction was diluted with H_2O (20 mL) and extracted with Et_2O (3 x 15 mL) and the combined organic layers dried (MgSO4). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 5:1) to afford ether **223** (270 mg, 62% yield) as a clear colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.76 (m, 2H), 7.67 (m, 2H), 7.52-7.42 (cm, 4H), 7.39-7.30 (cm, 7H), 708 (m, 2H), 6.99 (t, *J*=7.9 Hz, 1H), 6.92 (d, *J*=16.1 Hz, 1H), 6.75 (m, 1H), 6.35 (dt, *J*=5.6, 16.1 Hz, 1H), 5.25 (d, *J*=12.4 Hz, 1H), 5.21 (d, *J*=12.4 Hz, 1H), 5.17 (m, 1H), 4.86 (s, 2H), 4.56 (dd, *J*=1.1, 5.6 Hz, 2H), 3.59-3.50 (cm, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.7, 167.4, 157.3, 153.2, 136.5, 135.2, 134.0, 132.7, 132.4, 131.6, 129.9, 128.9, 128.5, 128.5, 128.3, 128.3, 128.1, 127.0, 126.8, 126.0, 125.5, 123.4, 118.2, 114.8, 75.5, 68.3, 67.6, 53.6, 33.8; **IR** (thin film/NaCl) 3032 (w), 1776 (w), 1744 (m), 1716 (s), 1511 (m), 1387 (s), 1177 (m), 1072 (w), 911 (w), 720 (m) cm^{-1}; **HRMS** (FAB) *m/z* found: 702.1490, [calc'd for $C_{40}H_{30}N_1O_6Br$(M+H): 702.1491].

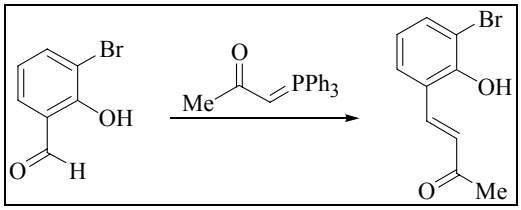
Preparation of olefin 224



A solution of allyl ether **223** (150 mg, 0.239 mmol) in *N,N*-dimethylaniline (4 mL) was submersed into an oil bath preheated to 200 °C. The solution was refluxed for 16 hours,

cooled and diluted with Et_2O (25 mL). The ethereal solution was washed with 1N HCl (6 x 10mL) and dried ($MgSO_4$). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 20:1 then 10:1) to afford olefin **224** (15 mg, 9.0% yield) as a clear oil (2:1 mixture of diastereomers). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.77-7.65 (cm, 4H), 7.48-7.29 (cm, 11H), 6.99-6.81 (cm, 3H), 6.76 (t, *J*=7.6 Hz, 1H), 6.59 (m, 1H), 6.10 (ddd, *J*=5.6, 10.2, 17.0 Hz, 1H), 65.91 (ddd, *J*=5.6, 10.2, 17.0 Hz, 1H), 5.61 (s, 1H), 5.54 (s, 1H), 5.29-5.08 (cm, 4H), 4.98 (d, *J*=10.2, 1H), 4.86 (m, 1H), 4.76-4.55 (cm, 2H), 3.50 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.7,167.4, 167.3, 152.9, 152.8, 152.4, 152.3, 138.7, 138.6, 137.2, 137.0, 136.4, 136.3, 135.1, 134.1, 134.1, 132.0, 131.8, 131.5, 131.3, 129.3, 129.2, 129.0, 128.8, 128.7, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.2, 128.2, 128.1, 128.1, 125.8, 125.5, 123.4, 117.6, 117.5, 117.2, 119.0, 116.4, 116.3, 75.5, 75.2, 67.6, 53.6, 53.5, 41.0, 41.0, 33.8; **IR** (neat) 3454 (br w), 3032 (w), 1775 (m), 1715 (s), 1509 (m), 1389 (s), 1247 (m), 1106 (m), 812 (w), 721 (s) cm^{-1}; **HRMS** (FAB) *m/z* found: 702.1490, [calc'd for $C_{40}H_{33}N_1O_6Br$ (M+H): 702.1491].

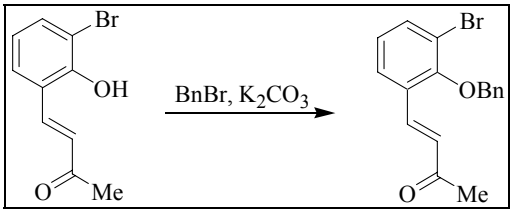
Preparation of olefin 240



To a solution of **212** (15.4 g, 76.6 mmol) in C_6H_6 (150 mL) at 0 °C was added a solution of ylide **239** (26.8 g, 84.3 mmol) in C_6H_6 (150 mL) over 30 min. Ater stirring for an additional 1 h the reaction was concentrated to half its original volume and purified by

silica gel chromatography (hexanes:EtOAc, 3:1) to afford olefin **240** (13.5 g, 73% yield) as white needles (m.p 119-120 °C). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.82 (d, *J*=16.2 Hz, 1H), 7.50 (dd, *J*=1.6, 8.3 Hz, 1H), 7.47 (dd, *J*=1.6, 8.3 Hz, 1H), 6.85 (t, *J*=8.1 Hz, 1H), 6.78 (d, *J*=16.2 Hz, 1H), 6.14 (s, 1H), 2.43 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.8, 151.1, 137.8, 133.6, 128.8, 128.0, 122.9, 121.7, 111.5, 27.3; **IR** (thin film/NaCl) 3190 (br w), 3060 (w), 1637 (s), 1589 (m), 1452 (s), 1364 (w), 1264 (s), 1112 (m), 1009 (w), 978 (m) cm^{-1}; **HRMS** (EI) *m/z* found: 239.9780, [calc'd for $C_{10}H_9O_2Br$(M+): 239.9786].

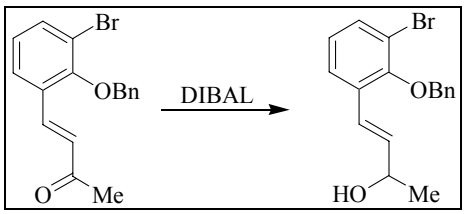
Preparation of ether 241



To a solution of phenol **240** (13.5 g, 56.0 mmol) in acetone (500 mL) was added benzyl bromide (8.0 mL, 67.2 mmol) and K_2CO_3 (18.6 g, 134.4 mmol). The reaction mixture was heated to reflux for 12 h. After this time the reaction mixture was concentrated in vacuo and the crude mixture taken up in ether. Filtration of the residual solids and removal of the solvent in vacuo afforded allylic benzyl ether **241** as an off-white solid (m.p. 71-72 °C). Typically this product was used directly in the next step, but analytical material could be obtained after purification by silica gel column chromatography (hexanes:EtOAc, 10:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64, (d, *J*=16.6 Hz, 1H), 7.64 (dd, *J*=1.6, 7.8 Hz, 1H), 7.51 (dd, *J*=1.6, 7.8 Hz, 1H), 7.47 (m, 2H), 7.43-7.35 (cm, 3H),

7.06 (dt, *J*=0.5, 7.8 Hz, 1H), 6.59 (d, *J*=16.6 Hz, 1H), 5.00 (s, 1H), 5.12 (s, 2H), 2.23 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.4, 154.6, 137.6, 135.9, 135.3, 130.6, 129.0, 128.6, 128.6, 126.5, 125.8, 118.4, 76.5, 26.8; **IR** (thin film/NaCl) 3073 (w), 2888 (w), 1668 (s), 1497 (w), 1440 (m), 1259 (m), 1222 (m), 1118 (w), 980 (m), 755 (m) cm^{-1}; **HRMS** (FAB) *m/z* found: 331.0335, [calc'd for $C_{17}H_{16}O_2Br$(M+H): 331.0333].

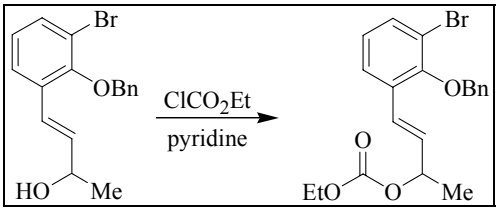
Preparation of allylic alcohol 242



A solution of crude ester **241** (18.5 g, 56.0 mmol) from the previous reaction in THF (450 mL) was cooled to –78 °C and treated with a 1.0 M CH_2Cl_2 solution of DIBAL (61.6 mL, 61.6 mmol). After 30 min. the reaction was carefully quenched with a saturated solution of Rochelle's salt (750 mL) and allowed to stir at room temperature for 2 h. The organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 (3 x 250 mL). The combined organic layers were washed with brine (250 mL) and dried ($MgSO_4$). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 6:1 then 3:1) to afford allylic alcohol **242** (17.2 g, 92% yield) as a clear oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55-7.49 (cm, 3H), 7.44-7.36 (cm, 4H), 6.99 (t, *J*=8.0 Hz, 1H), 6.77 (d, *J*=15.9 Hz, 1H), 6.25 (dd, *J*=6.3, 16.4 Hz, 1H), 4.94 (s, 2H), 4.41 (m, 1H), 1.63 (br s, 1H), 1.32 (d, *J*=6.3, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.1, 136.6, 135.9, 132.7, 132.5, 128.6, 128.5, 128.3, 125.8, 125.5, 123.5, 118.2, 75.5, 68.8,

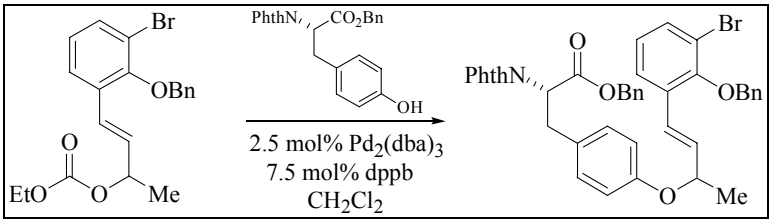
23.2; **IR** (thin film/NaCl) 3367 (br w), 3032 (w), 1497 (w), 1436 (s), 1222 (s), 1116 (m), 976 (s), 863 (w), 753 (s), 665 (w) cm^{-1}; **HRMS** (EI) *m/z* found: 240.1147, [calc'd for $C_{16}H_{16}O_2$ (M+H): 240.1150].

Preparation of carbonate 245



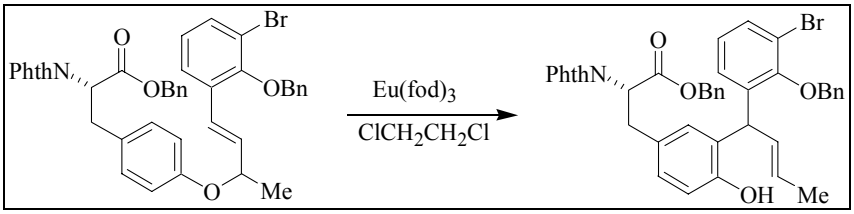
To a 0˚C solution of allylic alcohol **242** (4.50 g, 13.50 mmol) in CH_2Cl_2 (60 mL) was added pyridine (4.37 mL, 54.0 mmol). After 10 min ethyl chloroformate (2.59 mL, 27.0 mmol) was added and the reaction allowed to stir overnight. After this time the reaction was diluted with ether (150 mL) and washed with saturated $NaHCO_3$ (2 x 100 mL), saturated $CuSO_4$ (2 x 75 mL), brine (2 x 75 mL), and dried ($MgSO_4$). Typically this product was used directly in the next step, but analytical material could be obtained after purification by silica gel column chromatography (hexanes:EtOAc, 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.40 (dd, *J*=1.1, 8.2 Hz, 1H), 7.34-7.26 (cm, 4H), 6.89 (t, *J*=8.3 Hz, 1H), 6.86 (d, *J*=16.0 Hz, 1H), 6.16 (dd, *J*=6.5, 16.0 Hz, 2H), 5.28 (m, 1H), 4.82 (s, 2H), 4.10 (m, 2H), 1.35 (d, *J*=6.8 Hz, 3H), 1.21 (t, *J*=7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.2, 153.1, 136.3, 132.6, 131.9, 130.5, 128.3, 1228.3, 128.1, 126.0, 125.8, 125.3, 118.0, 75.3, 74.5, 63.5, 20.0, 14.0; **IR** (thin film/NaCl) 3064 (m), 2982 (s), 2872 (m), 1745 (s), 1559 (m), 1374 (s), 921 (m), 777 (s), 670 (m), 622 (w) cm^{-1}; **HRMS** (EI) *m/z* found: 407.0679, [calc'd for $C_{20}H_{22}O_4Br$(M+H): 407.0681].

Preparation of aryl allyl ether 237



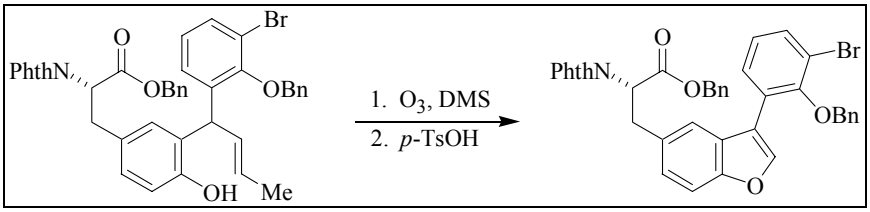
To a solution of $Pd_2(dba)_3$ (286 mg, 2.5 mol%) in CH_2Cl_2 (50 mL) was added dppb (399 mg, 7.5 mol%). After 10 min. tyrosine **178** (6.51 g, 16.2 mmol) was added followed by addition of carbonate **245** (5.06 g, 12.5 mmol) in CH_2Cl_2 (20 mL) via cannula. The reaction mixture was then allowed to stir at room temperature for 4 h. After this time the reaction was concentrated to half its original volume and purified by silica gel chromatography (hexanes:EtOAc, 4:1) to afford aryl allyl ether **237** (4.30 g, 91% yield) as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73 (m, 2H), 7.66 (m, 2H), 7.50 (dd, *J*=0.7, 6.9 Hz, 1H), 7.44-7.32 (cm, 11H), 7.05-6.97 (cm, 3H), 6.80 (dd, *J*=6.6, 16.6 Hz, 1H), 6.74 (m, 2H), 6.25 (m, 1H), 5.28-5.13 (cm, 3H), 4.86-4.74 (cm, 3H), 3.53 (m, 2H), 1.43 (dd, *J*=2.1, 6.6 Hz, 3H; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.8, 167.4, 156.7, 156.6, 153.2, 136.5, 136.5, 135.2, 134.0, 133.1, 133.1, 132.5, 132.4, 131.5, 131.5, 129.8, 128.9, 128.8, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 128.1, 126.0, 125.5, 125.0, 125.0, 123.3, 118.2, 118.2, 116.1, 116.1, 75.3, 74.3, 74.2, 67.6, 53.6, 53.5, 33.8, 21.5, 21.5; **IR** (thin film/NaCl) 3032 (w), 1777 (w), 1745 (m), 1717 (s), 1509 (m), 1388 (s), 1241 (m), 1117 (w), 910 (w), 720 (m) cm^{-1}.

Preparation of phenol 238



To a solution of aryl allyl ether **237** (4.30g, 6.0 mmol) in dichloroethane (6 mL) was added $Eu(fod)_3$ (623 mg, 0.60 mmol). The resulting solution was refluxed for 7 d after which time the reaction mixture was concentrated to half its original volume and purified by silica gel chromatography (hexanes:EtOAc, 3:1) to afford phenol **238** (4.21 g, 98% yield) as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 (m, 2H), 7.59 (m, 2H), 7.44-7.21 (cm, 11H), 6.92-6.80 (cm, 4H), 6.69 (m, 1H), 6.53 (m, 1H), 5.72 (s, 1H), 5.66 (m, 1H), 5.64-5.54 (cm, 1H), 5.21-5.07 (cm, 5H), 4.83 (d, *J*=10.4 Hz, 1H), 4.79 (d, *J*=10.4 Hz, 1H), 4.61 (d, *J*=10.7 Hz, 1H), 4.55 (d, *J*=10.7 Hz, 1H), 3.46 (m, 2H), 1.63 (d, *J*=6.3 Hz, 1H), 1.54 (d, *J*=6.3 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.7, 167.4,167.3, 152.7, 152.7, 152.4, 152.4, 138.3, 138.0, 136.4, 136.4, 135.1, 135.1, 134.1, 134.0, 134.0, 131.7, 131.6, 131.5, 131.5, 131.4, 131.3, 131.3, 129.5, 129.3, 129.2, 129.0, 128.8, 128.6, 128.5, 128.4, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 128.1, 128.1, 128.0, 128.0, 127.8, 127.7, 125.7, 125.5, 123.3, 117.5, 117.4, 116.3, 116.2, 75.4, 75.1, 67.5, 53.6, 53.6, 40.4, 40.2, 33.8, 33.8, 17.9; **IR** (thin film/NaCl) 3435 (br w), 3031 (w), 1775 (w), 1744 (m), 1715 (s), 1439 (m), 1389 (s), 1221 (m), 973 (w), 721 (m) cm^{-1}; **HRMS** (EI) *m/z* found: 715.1568, [calc'd for $C_{41}H_{34}NO_6Br$(M+): 715.1569].

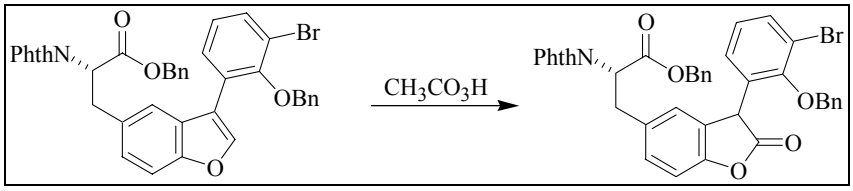
Preparation of benzofuran 252



A solution of **238** (6.4 g, 8.93 mmol) in MeOH (300 mL) and CH_2Cl_2 (100 mL) was cooled to –78 °C and treated with O_3 until TLC showed the disappearance of starting material (about 30 min). The mixture was purged with nitrogen for 15 min at –78 °C, and dimethyl sulfide (20.0 mL) was added at that temperature. The dry ice bath was removed and the solution allowed tostir at room temperature for 12 h. After solvent removal in vacuo the crude residue was dissolved in benzene (180 mL) and *p*-toluenesulfonic acid (84.8 mg, 0.07 mmol) was added. The reaction mixture was refluxed and the solvent passed through Å4 molecular sieves before returning to the flask for 3 h. After this time the reaction mixture was cooled, washed with sat. $NaHCO_3$ (3 x 50 mL), and dried ($MgSO_4$). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 4:1) to afford benzofuran **252** (5.08 g, 83% yield) as a clear colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.84 (s, 1H) 7.74 (m, 2H), 7.65 (m, 2H), 7.58 (dd, *J*=1.6, 8.1 Hz, 1H), 7.48 (d, *J*=1.2, 1H), 7.34 (d, *J*=8.5, 1H), 7.36-7.29 (cm, 6H), 7.23 (m, 3H), 7.16 (dd, *J*=2.0, 8.5 Hz, 1H), 7.13 (m, 2H), 7.04 (t, *J*=7.7 Hz, 1H), 5.28 (d, *J*=12.6, 1H), 5.23 (m, 1H), 5.23 (d, *J*=12.6, 1H), 4.60 (d, *J*=10.5, 1H), 4.58 (d, *J*=10.5, 1H), 3.70 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.7,167.4, 154.2, 153.1, 144.5, 136.2, 135.2, 134.1, 132.5, 131.5, 131.5, 129.2, 128.6, 128.5, 128.4, 128.2, 128.2, 128.1, 127.6, 126.8, 125.7, 125.5, 123.4, 120.8, 118.8, 116.5,

111.7, 74.6, 67.6, 53.9, 34.6; **IR** (thin film/NaCl) 3032 (w), 1776 (w), 1744 (m), 1716 (s), 1433 (w), 1388 (s), 1237 (m), 1108 (w), 911 (w), 720 (m) cm^{-1}; **HRMS** (FAB) *m/z* found: 686.1180, [calc'd for $C_{39}H_{29}NO_6Br$(M+H): 686.1178].

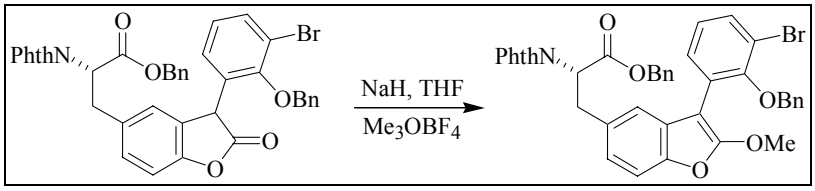
Preparation of benzofuranone 211



The procedure of Vedejs was used without modification. Peracetic acid (9.93 mL, 50.75 mmol, Aldrich) was gradually added to a solution of benzofuran **252** (1.16 g, 1.60 mmol) in 125 mL of CH_2Cl_2. The mixture was stirred for 16 h and diluted with CH_2Cl_2 to a volume of 250 mL. The organic layer was washed with H_2O (100 ML), 10% $NaHSO_3$ (100 mL), 5% $NaHCO_3$ (100 mL), and dried (MgSO4). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 3:1) to afford lactone **211** (953 mg, 80% yield) as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 (m, 4H), 7.61 (dd, *J*=1.5, 7.9 Hz, 1H), 7.44 (dd, *J*=1.5, 7.9 Hz, 1H), 7.35-7.29 (cm, 9H), 7.12 (d, *J*=8.5 Hz, 1H), 7.07 (d, *J*=8.5 Hz, 1H), 7.03 (t, *J*=7.9 Hz, 1H), 6.95-6.77 (cm, 3H), 5.20-4.96 (cm, 5H), 3.54 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.7, 174.6, 168.3, 168.3, 167.3, 167.3, 154.2, 153.9, 152.8, 152.7, 136.3, 136.2, 135.0, 134.3, 134.2, 134.0, 133.2, 133.2, 131.8, 131.6, 131.3, 131.2, 129.8, 129.8, 128.6, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.8, 127.5, 125.9, 125.6, 125.2, 125.0, 123.5, 123.4, 117.8, 117.5, 111.0, 110.8, 67.7, 67.7, 53.7, 53.3, 34.2, 34.0; **IR** (thin film/NaCl) 3033

(w), 1812 (m), 1776 (w), 1744 (m), 1716 (s), 1487 (m), 1388 (s), 1240 (m), 1061 (m), 780 (w) cm^{-1}; **HRMS** (FAB) *m/z* found: 702.1128, [calc'd for $C_{39}H_{29}NO_7Br$ (M+H): 702.1127].

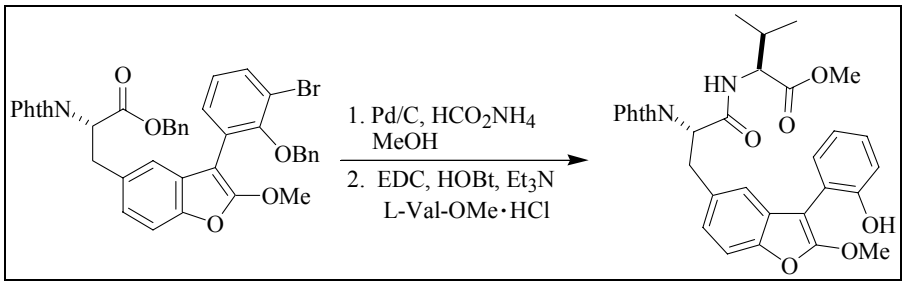
Preparation of benzofuran 254



To a solution of lactone **211** (355 mg, 0.505 mmol) in THF (7 mL) at 0°C was added NaH (25 mg, 0.606 mmol; 60% dispersion in mineral oil, Aldrich) in one portion under N_2. The reaction was stirred at 0°C for 1 h before the granular NaH completely disappeared (the solution became dark yellow). Trimetyloxonium tetrafluoroborate (90 mg, 0.606 mmol) was added as a single portion and the mixture allowed to warm to room temperature. After stirring for 2 h the reaction was quenched with sat. NH_4Cl (20 mL) and diluted with ether (30 mL). The organic layer was washed with brine (2 x 20 mL) and dried ($MgSO_4$). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 4:1) to afford benzofuran **254** (344 mg, 95% yield) as a clear colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (m, 2H), 7.61 (m, 2H), 7.55 (dd, *J*=1.5, 8.1 Hz, 1H), 7.33 (m, 5H), 7.20-7.11 (cm, 6H), 6.99 (m, 2H), 6.92 (m, 2H), 5.27 (d, *J*=12.1, 1H), 5.21 (d, *J*=12.1, 1H), 5.17 (t, *J*=5.5, 1H), 4.48 (s, 1H), 3.85 (s, 3H), 3.61 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.7, 167.4, 158.5, 154.1, 147.2, 136.4, 135.2, 134.0, 132.3, 131.6, 131.5, 130.6, 129.9, 128.5, 128.5, 128.3, 128.1, 128.0,

127.8, 127.0, 125.2, 123.3, 122.7, 119.3, 118.4, 110.1, 90.3, 75.0, 67.6, 54.0, 34.5; **IR** (thin film/NaCl) 3033 (w), 2948 (w), 1776 (w), 1745 (m), 1718 (s), 1612 (m), 1387 (s), 910 (m), 734 (s), 648 (w) cm^{-1}; **HRMS** (FAB) *m/z* found: 715.1207, [calc'd for $C_{40}H_{30}NO_7Br$ (M+): 715.1206].

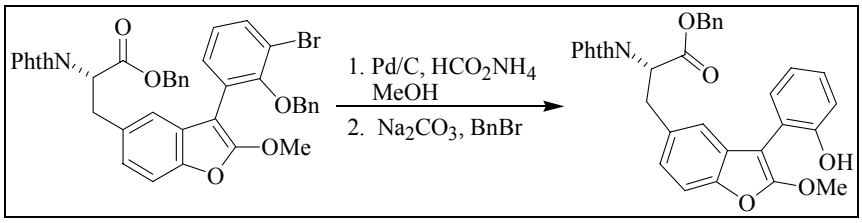
Preparartion of dipeptide 255



To a solution of benzofuran **254** (95 mg, 0.133 mmol) in MeOH (5 mL) and CH_2Cl_2 (5 mL) was added 10% Pd/C (53 mg) and HCO_2NH_4 (95 mg, 1.33 mmol). The reaction mixture was heated to reflux for 15 min. after which time TLC showed the complete disappearance of starting material. After cooling to room temperature the reaction mixture was filtered over a pad of celite and washed with ethyl acetate (125 mL). This solution was concentrated in vacuo, dissolved in ethyl acetate (50 mL), washed with H_2O (2 x 25 mL), and dried ($MgSO_4$). Solvent removal in vacuo afforded a crude acid that was taken up into CH_2Cl_2 (2 mL) and added via cannula to a solution of L-Val-OMe·HCl (34 mg, 0.200 mmol), HOBt (27 mg, 0.200 mmol), EDC (38 mg, 0.200 mmol) and Et_3N (0.037 mL, 0.266 mmol) in CH_2Cl_2 (2 mL). After stirring for 16 h the reaction was diluted with Et_2O (25 mL) and washed with 1M $NaHSO_4$ (25 mL), sat. $NaHCO_3$ (25 mL), brine (25 mL), and dried ($MgSO_4$). After solvent removal in vacuo the residue was

purified by silica gel column chromatography (hexanes:EtOAc, 2:1) to afford benzofuran **255** (57 mg, 75% yield) as a clear colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ d 7.77 (m, 2H), 7.68 (m, 2H), 7.24 (m, 2H), 7.16 (s, 1H), 7.11 (dd, *J*=1.5, 7.4, 1H), 7.05 (dd, *J*=1.5, 8.6, 1H), 7.10 (d, *J*=8.3, 1H), 6.93 (m, 1H), 6.72 (d, *J*=8.6 Hz, 1H), 5.55 (s, 1H), 5.14 (dd, *J*=5.9, 10.5, 1H), 4.58 (dd, *J*=4.9, 8.3, 1H), 4.06 (s, 3H), 3.67 (s, 3H), 3.60 (m, 2H), 2.16 (m, 1H), 0.93 (d, *J*=7.1, 3H), 0.85 (d, *J*=7.1, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.1, 168.3, 167.9, 157.5, 153.5, 147.8, 134.3, 132.0, 131.4, 130.2, 129.4, 129.0, 123.5, 123.4, 120.7, 119.3, 116.9, 116.7, 110.7, 89.7, 58.9, 57.4, 56.6, 52.1, 35.0, 31.3, 18.9, 17.7; **IR** (thin film/NaCl) 3373 (br w), 2959 (w), 1776 (w), 1717 (s), 1611 (w), 1383 (m), 1311 (w), 1219 (m), 910 (w), 723 (m) cm^{-1}; **HRMS** (FAB) *m/z* found: 569.1924, [calc'd for $C_{32}H_{29}N_2O_8$(M+H): 569.1924].

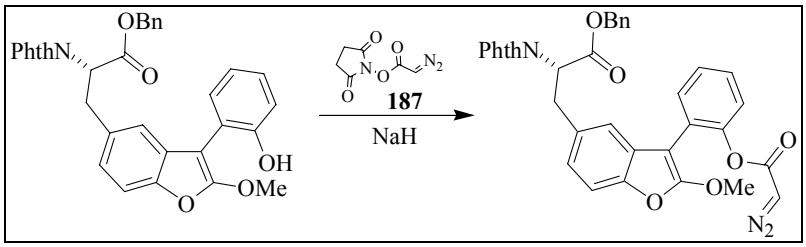
Preparation of phenol 258



To a solution of benzofuran **254** (547 mg, 0.763 mmol) in MeOH (25 mL) and CH_2Cl_2 (10 mL) was added 10% Pd/C (304 mg) and HCO_2NH_4 (1.09 g, 15.26 mmol). The reaction mixture was heated to reflux for 15 min. after which time TLC showed the complete disappearance of starting material. After cooling to room temperature the reaction mixture was filtered over a pad of celite and washed with ethyl acetate (300 mL). This solution was concentrated in vacuo, dissolved in ethyl acetate (50 mL), washed with

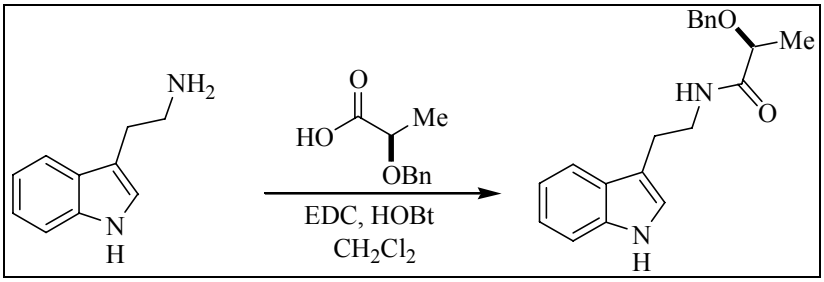
H_2O (2 x 25 mL), and dried ($MgSO_4$). Solvent removal in vacuo afforded a crude acid that was taken up in acetone (25 mL) was added benzyl bromide (0.091 mL, 0.763 mmol) and Na_2CO_3 (106 mg, 0.763 mmol). The reaction mixture was stirred at room temperature for 16 h. After this time the reaction mixture was concentrated in vacuo and the crude mixture taken up in ether. Filtration of the residual solids, removal of the solvent in vacuo, and purification by silica gel column chromatography (hexanes:EtOAc, 2:1) to afforded phenol **258** (257 mg, 65% yield) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ d 7.77 (m, 2H), 7.69 (m, 2H), 7.33 (m, 5H), 7.27-7.21 (cm, 2H), 7.17 (d, *J*=1.4 Hz, 1H), 7.11 (dd, *J*=1.8, 7.7 Hz, 1H), 7.02 (dd, *J*=1.4, 8.4 Hz, 1H), 7.00 (dd, *J*=1.1, 8.1 Hz, 1H), 6.91 (dt, *J*=1.4, 7.4 Hz, 1H), 5.48 (s, 1H), 5.27 (d, *J*=12.6, 1H), 5.22 (d, *J*=12.6, 1H), 5.18 (m, 1H), 4.06 (s, 3H), 3.62 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.6, 167.4, 157.4, 153.4, 147.8, 135.2, 134.1, 132.1, 131.6, 130.1, 129.3, 128.9, 128.5, 128.3, 128.1, 123.4, 123.4, 120.8, 120.7, 119.2, 116.7, 110.6, 89.7, 67.6, 58.9, 54.0, 34.6; **IR** (thin film/NaCl) 3466 (br m), 3033 (w), 1775 (w), 1744 (m), 1713 (s), 1609 (m), 1388 (s), 1101 (m), 980 (w), 720 (m) cm^{-1}; **HRMS** (FAB) *m/z* found: 518.1604, [calc'd for $C_{32}H_{24}NO_6$(M+H): 518.1604].

Preparation of α-diazo ester 259



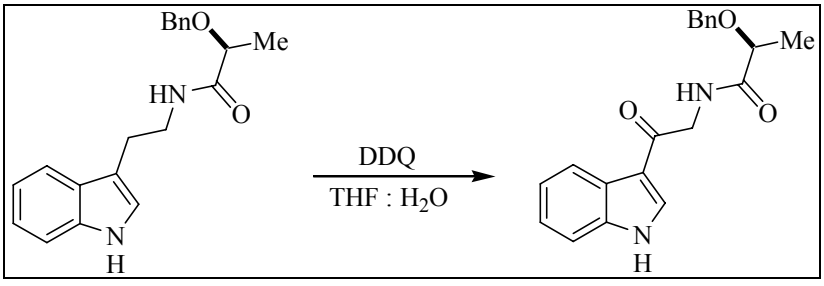
To a solution of phenol **258** (200 mg, 0.365 mmol) in THF (7 mL) at 0°C was added succinimide **187** (77 mg, 0.420 mmol) in THF (3 mL) via cannula over 5 minutes. The reaction mixture was warmed to room temperature during which time a brown precipitate formed. After 15 min. the solvent was removed in vacuo and the crude mixture taken up ethyl acetate. After filtration of the brown precipitate over a plug of cotton and solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 2:1) to afford α-diazo ester **259** (168 mg, 75% yield) as a clear bright yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ d 7.77 (m, 2H), 7.69 (m, 2H), 7.37-7.29 (cm, 6H), 7.25-7.20 (cm, 3H), 7.16 (m, 2H), 6.99 (dd, *J*=1.7, 8.2 Hz, 1H), 5.26 (d, *J*=12.5, 1H), 5.22 (d, *J*=12.5, 1H), 5.17 (m, 1H), 4.80 (br s, 1H), 3.98 (s, 3H), 3.63 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.7, 167.4, 158.7, 148.3, 147.3, 135.2, 134.1, 131.7, 131.6, 131.2, 129.7, 128.5, 128.3, 128.1, 128.1, 125.9, 124.2, 123.4, 123.1, 122.7, 119.3, 110.2, 90.2, 67.6, 58.7, 54.1, 34.6; **IR** (thin film/NaCl) 3112 (w), 2951 (w), 2116 (s), 1776 (w), 1743 (m), 1715 (s), 1610 (w), 1387 (s), 1148 (m), 911 (w) cm^{-1}; **HRMS** (FAB) *m/z* found: 615.1639, [calc'd for $C_{35}H_{25}N_3O_8$(M+): 615.1642].

Preparation of amide 265



To a solution of tryptamine (3.27 g, 20.43 mmol) in CH_2Cl_2 (100 mL) was added HOBt (3.16 g, 23.35 mmol) and EDC (4.48 g, 23.35 mmol) in that order. Carboxylic acid **264** (3.50 g, 19.46 mmol) was next added and the resulting mixture allowed to stir overnight. After this time the reaction was diluted with Et_2O (200 mL) and washed with 1M $NaHSO_4$ (150 mL), sat. $NaHCO_3$ (150 mL), brine (150 mL), and dried ($MgSO_4$). Solvent removal in vacuo afforded analytically pure amide **265** (6.27g, 100% yield) as an orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.55 (bs, 1H), 7.78 (d, *J*=7.8 Hz, 1H), 7.51 (d, *J*=8.0 Hz, 1H), 7.45 (m, 3H), 7.36 (m, 1H), 7.29 (m, 3H), 7.09 (d, *J*=2.3 Hz, 1H), 6.93 (m, 1H), 4.60 (d, *J*=11.4 Hz, 1H), 4.52 (d, *J*=11.4 Hz, 1H), 4.09 (q, *J*=6.6 Hz, 1H), 3.83 (m, 1H). 3.75 (m, 1H), 3.15 (m, 2H), 1.57 (d, *J*=7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.1, 137.2, 136.4, 128.4, 127.8, 127.6, 127.2, 122.1, 122.0, 119.3, 118.6, 112.4, 111.2, 71.7, 38.9, 25.2, 18.5; **IR** (thin film/NaCl) 3407 (br m), 3290 (br m), 1661 (s), 1530 (s), 1453 (m), 1363 (w), 1106 (m), 1046 (w), 912 (w), 743 (s) cm^{-1}; **HRMS** (FAB) *m/z* found: 323.1761, [calc'd for $C_{20}H_{23}N_2O_2$ (M+H): 323.1760].

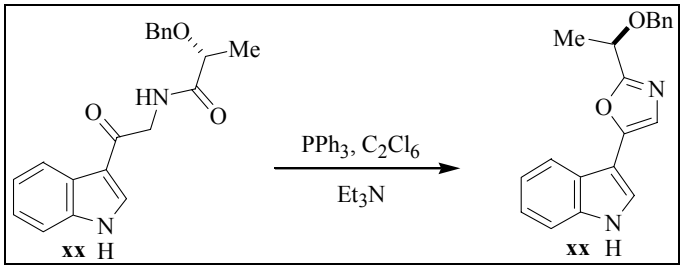
Preparation of ketone 266



To a solution of the amide **265** (6.27 g, 19.46 mmol) in THF (180 mL) and H_2O (20 mL) was added DDQ (9.22 g, 40.61 mmol) in one portion. This solution stirred at room

temperature for 2 hours and diluted with EtOAc (100 mL) and sat. $NaHCO_3$ (150 mL). After stirring for 30 min at ambient temperature the organic solution was washed with $NaHCO_3$ (3 x 100 mL), H_2O (100 mL), brine (100 mL), and dried ($MgSO_4$). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 1:1 then EtOAc 100%) to afford ketone **266** (5.38 g, 82% yield) as a light brown solid (m.p. = 137-138 °C). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.72 (bs, 1H), 8.33 (m, 1H), 7.87 (d, *J*=3.0 Hz, 1H), 7.78 (t, *J*=4.3 Hz, 1H), 7.45-7.38 (cm, 5H), 7.34-7.30 (cm, 4H), 4.72 (d, *J*=11.7 Hz, 1H), 4.64 (d, *J*=11.7 Hz, 1H), 4.62 (cm, 2H), 4.09 (q, *J*=6.6 Hz, 1H), 1.51 (d, *J*=6.6 Hz, 3H; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 188.6, 174.0, 137.3, 136.4, 131.4, 128.0, 128.0, 125.3, 123.9, 122.9, 122.0, 115.2, 111.8, 75.9, 72.1, 45.8, 18.7; **IR** (thin film/NaCl) 3243 (br w), 2928 (w), 1733 (w), 1638 (s), 1521 (s), 1436 (m), 1246 (w), 1111 (m), 1009 (w), 749 (m) cm^{-1}; **HRMS** (FAB) *m/z* found: 337.1551, [calc'd for $C_{20}H_{21}N_2O_3$ (M+H): 337.1552].

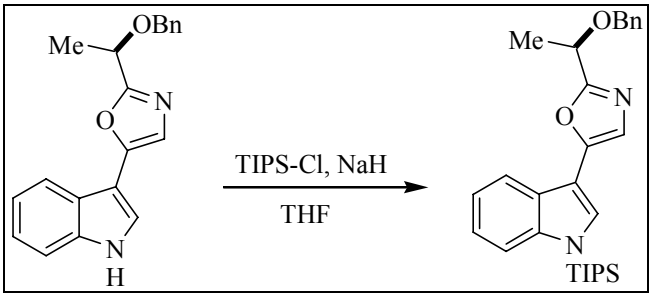
Preparation of oxazole 267



To a solution of PPh_3 (8.39 g, 32.00 mmol), C_2Cl_6 (7.58, 32.00 mmol) and Et_3N (8.92 mL, 64.00 mmol) in CH_2Cl_2 (200 mL) was added **266** (5.38 g, 16.00 mmol) in CH_2Cl_2 (50 mL) via cannula. After 2 h the dark reaction mixture was transferred to a seperatory

funnel, washed with sat. $Na_2S_2O_3$ (500 mL), and extracted with Et_2O (700 mL). The organic layer was washed with sat. $NaHCO_3$ (300 mL) dried ($MgSO_4$). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 3:1) to afford oxazole **267** (4.26 g, 84% yield) as an off-white solid (m.p. = 116-117 °C). (**^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.06 (bs, 1H), 7.90 (m, 1H), 7.57 (d, *J*=2.6 Hz, 1H), 7.42-7.40 (cm, 3H), 7.38-7.34 (cm, 2H), 7.32-7.26 (cm, 4H), 4.83 (q, *J*=6.6 Hz, 1H), 4.70 (d, *J*=11.7 Hz, 1H), 4.60 (d, *J*=11.7 Hz, 1H), 1.75 (d, *J*=6.6 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.5, 148.4, 137.6, 136.2, 128.4, 128.0, 127.8, 124.0, 122.9, 122.3, 120.8, 119.8, 119.6, 111.6, 105.3, 71.2, 70.2, 19.5; **IR** (thin film/NaCl) 3178 (br w), 1633 (s), 1564 (w), 1455 (s), 1217 (w), 1105 (s), 1052 (w), 1012 (m), 917 (m), 741 (s) cm^{-1}; **HRMS** (FAB) *m/z* found: 319.1447, [calc'd for $C_{20}H_{19}N_2O_2$ (M+H): 319.1447].

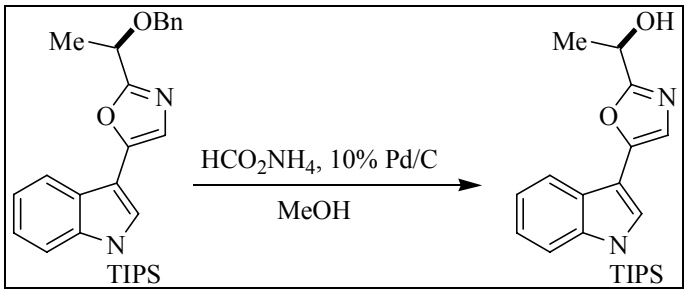
Preparation of protected indole 268



A solution of indole **267** (4.15 g, 13.04 mmol) in THF (100 mL) was cooled to 0˚C and treated with NaH (60% dispersion in mineral oil 0.626 g, 15.65 mmol) in 3 portions. After 10 min TIPS-Cl (3.07 mL, 14.34 mmol) was added via syringe and the reaction warmed to ambient temperature. After this time the reaction was poured into a solution

of 50% sat. $NaHCO_3$ (100 mL) and extracted with EtOAc (2 x 100 mL). The organic layers were then washed with brine (150 mL) and dried ($MgSO_4$). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 20:1) to afford indole **268** (6.07 g, 98% yield) as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.75 (m, 1H), 7.48 (s, 1H), 7.45 (m, 1H), 7.29-7.13 (cm, 8H), 4.67 (q, *J*=6.6 Hz, 1H), 4.54 (d, *J*=11.6 Hz, 1H), 4.45 (d, *J*=11.6 Hz, 1H), 1.68 (m, 3H), 1.60 (d, *J*=6.6 Hz, 3H), 1.07 (dd, *J*=1.0, 7.3 Hz, 18H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.5, 148.3, 141.3, 137.8, 129.0, 128.4, 128.0, 127.7, 127.4, 122.4, 120.9, 119.8, 119.7, 114.3, 107.5, 71.9, 70.1, 19.6, 18.0, 12.7; **IR** (thin film/NaCl) 2948 (s), 2868 (s), 1630 (m), 1452 (s), 1314 (w), 1241 (w), 1147 (s), 968 (s), 883 (m), 741 (s) cm^{-1}; **HRMS** (FAB) *m/z* found: 474.2701, [calc'd for $C_{29}H_{38}N_2O_2Si$ (M+): 474.2703].

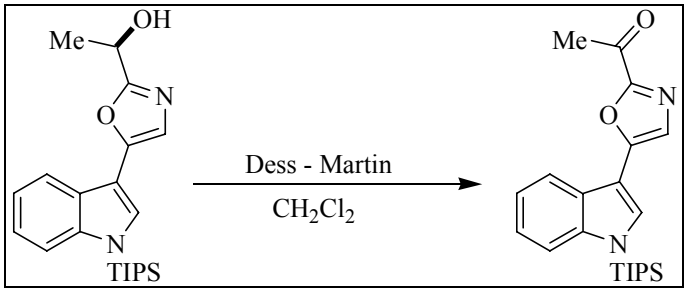
Preparation of alcohol 269



To a solution the indole **268** (6.07 g, 12.78 mmol) in MeOH (250 mL) was added 10% Pd/C (2.61 g) and HCO_2NH_4 (4.11 g, 65.2 mmol). The reaction mixture was heated to reflux for 5 hours after which time TLC showed the complete disappearance of starting material. After cooling to room temperature the reaction mixture was filtered over a pad of celite and washed with ethyl acetate (500 mL). This solution was concentrated in

vacuo, dissolved in ethyl acetate (200 mL), washed with H_2O (2 x 100 mL), and dried ($MgSO_4$). Solvent removal in vacuo afforded analytically pure alcohol **269** (4.88g, 99% yield) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81 (m, 1H), 7.55 (m, 2H), 7.27-7.22 (cm, 3H), 5.07 (m, 1H), 3.31 (d, *J*=4.9 Hz, 1H), 1.75 (m, 3H), 1.72 (d, *J*=6.6 Hz, 3H), 1.17 (d, *J*=7.3 Hz, 18H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.7, 148.1, 141.3, 128.9, 127.4, 122.4, 120.9, 119.7, 119.5, 114.3, 107.3, 63.9, 21.4, 18.1, 12.8; **IR** (thin film/NaCl) 3283 (br m), 2949 (s), 2869 (s), 1717 (w), 1633 (s), 1453 (s), 1173 (s), 967 (s), 796 (m), 515 (s) cm^{-1}; **HRMS** (FAB) *m/z* found: 385.2313, [calc'd for $C_{22}H_{33}N_2O_2Si$ (M+H): 385.2311].

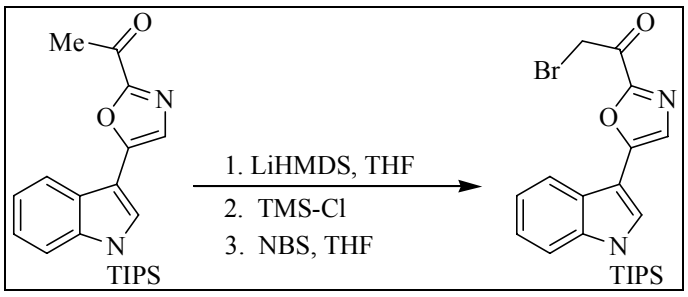
Preparation of ketone 270



To a solution of alcohol **269** (2.76 g, 7.18 mmol) in CH_2Cl_2 (75 mL) was added the Dess-Martin periodinane (3.35 g, 7.89 mmol). After 3 hours the reaction was quenched with sat. $Na_2S_2O_3$ (75 mL) and allowed to stir for an additional hour. The resulting organic layer was washed with sat. $NaHCO_3$ (2 x 75 mL), brine (75 mL), and dried ($MgSO_4$). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 20:1) to afford ketone **270** (2.61 g, 95% yield) as a light yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.86 (m, 1H), 7.75 (s, 1H), 7.54 (m,

1H), 7.47 (s, 1H), 7.25 (m,1H), 2.68 (s, 3H), 1.73 (m, 3H), 1.13 (d, *J*=7.5 Hz, 18H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 185.1, 155.8, 151.6, 141.4, 131.1, 127.2, 122.8, 121.9, 121.4, 119.6, 114.4, 106.5, 26.3, 17.9, 12.6; **IR** (thin film/NaCl) 3283 (br m), 2951 (s), 2868 (s), 1687 (s), 1611 (s), 1454 (s), 1388 (w), 1236 (s), 1071 (w), 740 (s) cm^{-1}; **HRMS** (FAB) *m/z* found: 383.2155, [calc'd for $C_{22}H_{31}N_2O_2Si$ (M+H): 383.2155].

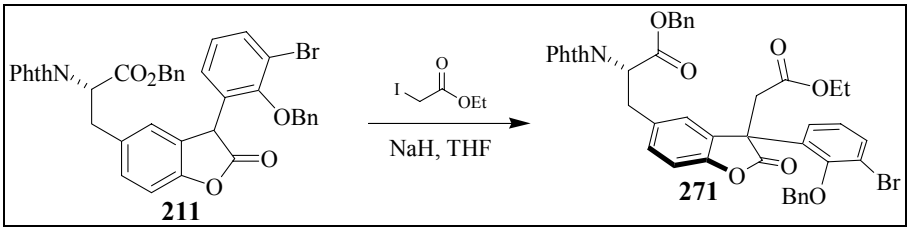
Preparation of α-bromo ketone 262



To a solution of ketone **270** (50 mg, 0.131 mmol) in THF (2 mL) at –78 °C was added LiHMDS (0.144 mL, 1.0 M in THF). After 30 min TMS-Cl (0.050 mL, 0.393 mmol) was added via syringe and allowed to stir for an additional 15 min still at –78 °C. After this time a solution of NBS (26 mg, 0.146 mmol) in THF (1 mL) was added via cannula. After 10 min. the reaction was quenched with sat. $NaHCO_3$, diluted with EtOAc (25 mL), washed with 1 N HCl (25 mL), brine (25mL), and dried ($MgSO_4$). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 20:1) to afford α-bromo ketone **262** (42 mg, 70% yield) as a bright yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 (m, 1H), 7.82 (m, 1H), 7.59 (m, 1H), 7.54 (s, 1H), 4.64 (s, 2H), 1.78 (m, 3H), 1.19 (d, *J*=7.6 Hz, 18H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 178.4, 153.6, 152.9, 141.4, 131.8, 127.1, 123.0, 122.4, 121.7, 119.7, 114.6,

106.3, 30.3, 18.0, 12.7; **IR** (thin film/NaCl) 2951 (s), 2869 (s), 1693 (s), 1607 (s), 1460 (s), 1384 (w), 1238 (m), 1111 (w), 968 (w), 743 (s) cm^{-1}; **HRMS** (EI) *m/z* found: 460.1187, [calc'd for $C_{22}H_{29}N_2O_2SiBr$ (M+): 460.1181].

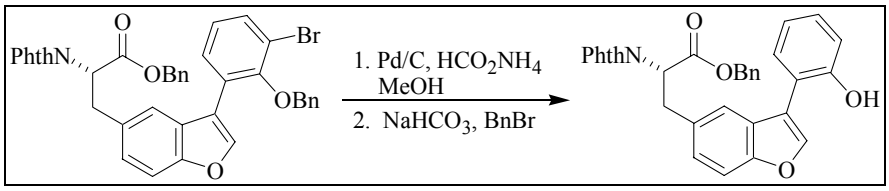
Preparation of ester 271



To a solution of lactone **211** (80 mg, 0.114 mmol) in THF (2 mL) at 0°C was added NaH (8 mg, 0.135 mmol; 60% dispersion in mineral oil, Aldrich) in one portion under N_2. The reaction was stirred at 0°C for 1 h before the granular NaH completely disappeared (the solution became dark yellow). Ethyl iodoacetate (0.067 ml, 0.570 mmol) was added as a single portion and the mixture allowed to warm to room temperature. After stirring for 24 h the reaction was quenched with sat. NH_4Cl (20 mL) and diluted with ether (30 mL). The organic layer was washed with brine (2 x 20 mL) and dried ($MgSO_4$). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 4:1) to afford ester **271** (67 mg, 74% yield) as a clear colorless oil (1:1 mixture of diastereomers). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71-7.59 (cm, 4H), 7.421 (dd, *J*=1.6, 8.1 Hz, 1H), 7.36-7.28 (cm, 7H), 7.23-7.09 (cm, 4H), 7.01-6.90 (cm, 2H), 6.73 (d, *J*=1.8 Hz, 1H), 6.63 (d, *J*=8.2 Hz, 1H), 6.58 (d, *J*=8.2 Hz, 1H), 5.21 (m, 2H), 5.09 (m, 1H), 4.58 (d, *J*=11.6 Hz, 1H), 6.49 (d, *J*=11.6 Hz, 1H), 3.90 (dq, *J*=2.0, 7.1 Hz, 2H), 3.84 (dq, *J*=2.0, 7.1 Hz, 2H), 3.62-3.48 (cm, 2H), 3.39-3.26 (cm, 2H), 3.03 (d, *J*=11.6 Hz,

1H), 1.02 (t, *J*=7.3 Hz, 3H), 1.00 (t, *J*=7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.1, 177.0, 168.3, 168.2, 168.1, 167.3, 167.2, 153.5, 153.1, 153.1, 153.0, 136.3, 136.2, 135.0, 135.0, 134.9, 134.6, 134.4, 134.3, 134.2, 132.7, 132.5, 131.3, 131.0, 130.9, 130.7, 130.0, 129.7, 128.6, 128.4, 128.1, 128.1, 128.0, 127.8, 127.3, 1276.3, 126.3, 126.2, 125.9, 125.2, 124.8, 124.0, 123.5, 123.4, 123.2, 117.7, 117.4, 111.3, 110.9, 73.4, 73.3, 70.6, 61.1, 53.7, 52.9, 50.1, 49.8, 41.7, 41.5, 34.0, 33.9, 13.7, 13.7; **IR** (thin film/NaCl) 2924 (w), 1809 (s), 1718 (s), 1610 (w), 1439 (m), 1385 (s), 1237 (s), 1016 (m), 881 (w), 729 (s) cm^{-1}.

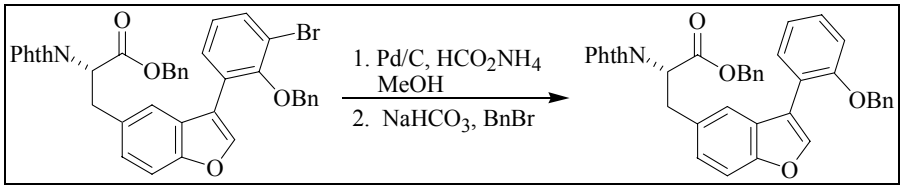
Preparation of phenol 272



To a solution of benzofuran **252** (728 mg, 0.728 mmol) in MeOH (25 mL) and CH_2Cl_2 (10 mL) was added 10% Pd/C (278 mg) and HCO_2NH_4 (1.25 g, 14.60 mmol). The reaction mixture was heated to reflux for 15 min. after which time TLC showed the complete disappearance of starting material. After cooling to room temperature the reaction mixture was filtered over a pad of celite and washed with ethyl acetate (300 mL). This solution was concentrated in vacuo, dissolved in ethyl acetate (50 mL), washed with H_2O (2 x 25 mL), and dried ($MgSO_4$). Solvent removal in vacuo afforded a crude acid that was taken up in acetone (25 mL) was added benzyl bromide (0.087 mL, 0.728 mmol) and $NaHCO_3$ (202 mg, 1.46 mmol). The reaction mixture was stirred at room

temperature for 16 h. After this time the reaction mixture was concentrated in vacuo and the crude mixture taken up in ether. Filtration of the residual solids, removal of the solvent in vacuo, and purification by silica gel column chromatography (hexanes:EtOAc, 2:1) to afforded phenol **272** (272 mg, 72% yield) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.71 (m, 2H), 7.62 (m, 2H), 7.37-7.27 (cm, 7H), 7.13 (td, *J*=1.5, 7.7 Hz, 1H), 7.15 (m, 2H), 6.91 (m, 2H), 5.32 (s, 1H), 5.25 (d, *J*=12.1, 1H), 5.20 (m, 1H), 5.20 (d, *J*=12.1, 1H), 3.66 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.6, 167.5, 154.5, 153.1, 143.3, 135.1, 134.1, 131.6, 131.5, 130.0, 129.1, 128.5, 128.3, 128.1, 127.0, 125.8, 123.4, 120.8, 120.8, 117.6, 117.7, 115.9, 111.7, 67.6, 54.0, 34.5; **IR** (thin film/NaCl) 3457 (br m), 3034 (w), 1775 (s), 1742 (s), 1713 (s), 1611 (m), 1389 (s), 979 (s), 959 (w), 722 (s) cm^{-1}; **HRMS** (FAB) *m/z* found: 518.1604, [calc'd for $C_{32}H_{24}NO_6$(M+H): 518.1604].

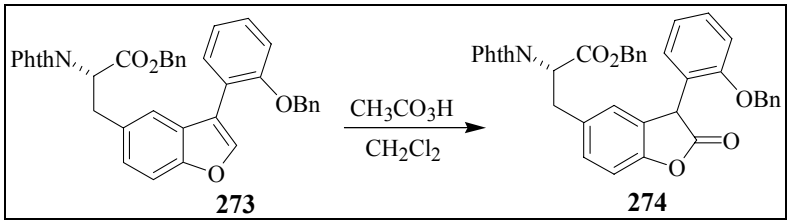
Preparation of benzofuran 273



To a solution of benzofuran **252** (1.00 g, 1.46 mmol) in MeOH (50 mL) and CH_2Cl_2 (20 mL) was added 10% Pd/C (556 mg) and HCO_2NH_4 (1.25 g, 14.60 mmol). The reaction mixture was heated to reflux for 15 min. after which time TLC showed the complete disappearance of starting material. After cooling to room temperature the reaction

mixture was filtered over a pad of celite and washed with ethyl acetate (300 mL). This solution was concentrated in vacuo, dissolved in ethyl acetate (50 mL), washed with H_2O (2 x 25 mL), and dried ($MgSO_4$). Solvent removal in vacuo afforded a crude acid that was taken up in acetone (25 mL) was added benzyl bromide (0.347 mL, 2.92 mmol) and K_2CO_3 (404 mg, 2.92 mmol). The reaction mixture was stirred at room temperature for 16 h. After this time the reaction mixture was concentrated in vacuo and the crude mixture taken up in ether. Filtration of the residual solids, removal of the solvent in vacuo, and purification by silica gel column chromatography (hexanes:EtOAc, 4:1) to afforded phenol **273** (571 mg, 65% yield) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.75 (m, 2H), 7.64 (m, 2H), 7.56 (d, *J*=1.8 Hz, 1H), 7.43 (dd, *J*=1.8, 7.7 Hz, 1H), 7.36-7.28 (cm, 11H), 7.13 (dd, *J*=1.8, 8.4 Hz, 1H), 7.06 (d, *J*=7.7 Hz, 1H), 7.01 (dt, *J*=0.7, 7.7 Hz, 1H), 5.26 (d, *J*=12.3, 1H), 5.24 (m, 1H), 5.23 (d, *J*=12.6, 1H), 5.10 (s, 2H), 3.60 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.8, 167.4, 155.8, 154.1, 144.5, 136.8, 135.2, 134.0, 132.6, 131.1, 129.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.3, 127.3, 125.0, 123.4, 121.2, 121.2, 116.7, 112.9, 111.5, 70.6, 67.6, 54.0, 34.7; **IR** (thin film/NaCl) 3033 (w), 1776 (w), 1744 (m), 1716 (s), 1443 (w), 1388 (s), 1239 (m), 1104 (w), 977 (w), 720 (m) cm^{-1}; **HRMS** (FAB) *m/z* found: 608.2074, [calc'd for $C_{39}H_{30}NO_6$(M+H): 608.2073].

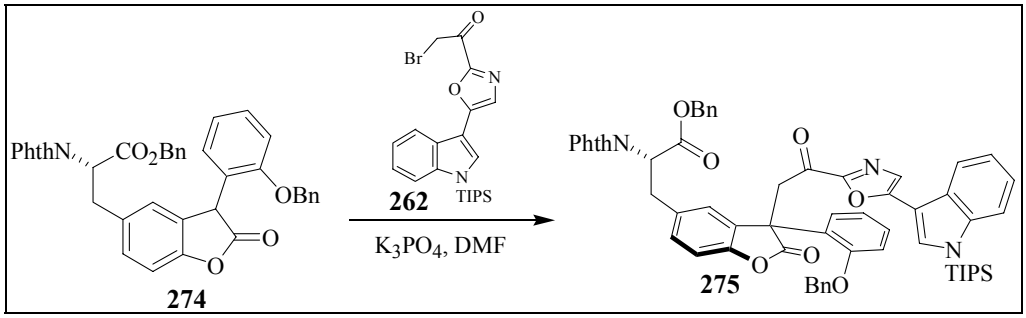
Preparation of benzofuranone 274



273 **274**

The procedure of Vedejs was used without modification. Peracetic acid (17.10 mL, 87.36 mmol, Aldrich) was gradually added to a solution of benzofuran **273** (1.77 g, 2.92 mmol) in 200 mL of CH_2Cl_2. The mixture was stirred for 16 h and diluted with CH_2Cl_2 to a volume of 500 mL. The organic layer was washed with H_2O (150 ML), 10% $NaHSO_3$ (150 mL), 5% $NaHCO_3$ (150 mL), and dried (MgSO4). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 3:1) to afford lactone **274** (1.58 g, 87% yield) as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.72-7.65 cm, 4H), 7.34-7.25 (cm, 5H), 7.17 (m, 2H), 7.01 (m, 2H), 6.93 (m, 1H), 6.85 (d, *J*=9.4 Hz, 11H), 6.70 (m, 2H), 5.20 (m, 2H), 5.08 (m, 1H), 5.10 (s, 2H), 4.90-4.61 (cm, 3H), 3.52 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.5, 175.4, 168.4, 168.4, 167.3, 167.3, 155.9, 155.7, 152.8, 135.8, 135.7, 135.0, 134.1, 132.4, 131.4, 131.3, 129.8, 129.6, 129.0, 128.9, 128.5, 128.4, 128.4, 128.3, 128.1, 128.1, 127.9, 127.8, 127.6, 127.4, 124.5, 124.5, 124.3, 124.1, 123.4, 121.0, 120.9, 112.3, 112.0, 110.3, 70.2, 70.1, 67.6, 67,6, 53.7, 53.4, 34.2, 34.1; **IR** (thin film/NaCl) 3033 (w), 1816 (m), 1775 (w), 1744 (m), 1715 (s), 1488 (m), 1387 (s), 1241 (m), 904 (m), 721 (m) cm^{-1}; **HRMS** (FAB) *m/z* found: 624.2025, [calc'd for $C_{39}H_{30}NO_7$(M+H): 624.2022].

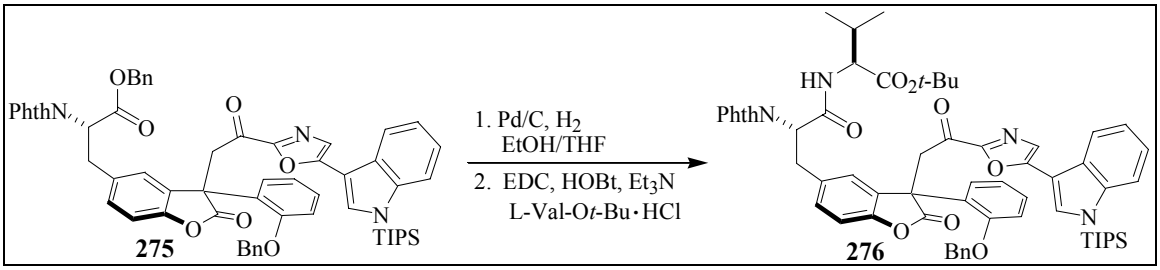
Preparation of ketone 275



To a solution of lactone **274** (100 mg, 0.160 mmol) in DMF (5 mL) at 0°C was added K_3PO_4 (41 mg, 0.192 mmol) and α-bromo ketone **262** (89 mg, 0.192 mmol) in DMF (5 mL). After stirring for 2 h the reaction was quenched with sat. NH_4Cl (5 mL) and diluted with ether (20 mL). The organic layer was washed with brine (2 x 10 mL) and dried ($MgSO_4$). After solvent removal in vacuo the residue was purified by silica gel column chromatography (hexanes:EtOAc, 4:1) to afford lactone **275** (102 mg, 64% yield) as a clear oil (1:1 Mixture of diastereomers). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (m, 1H), 7.85 (m, 1H), 7.69 (s, 1H), 7.61 (dd, *J*=3.1, 5.4 Hz, 1H), 7.56 (m, 2H), 7.49 (m, 2H), 7.41 (m, 3H), 7.30-7.20 (cm, 11H), 7.16 (m, 2H), 7.08 (m, 2H), 6.97 (m, 2H), 6.89 (dd, *J*=2.3, 7.7 Hz, 1H), 6.83 (m, 2H), 6.55 (d, *J*=8.5 Hz, 1H), 6.51 (d, *J*=8.5 Hz, 1H), 5.18-5.09 (cm, 2H), 5.01 (t, *J*=8.5 Hz, 1H), 4.92 (t, *J*=8.5 Hz, 1H), 4.86 (d, *J*=11.6, 1H), 4.82 (d, *J*=11.6, 1H), 4.78 (d, *J*=17.8, 1H), 4.61 (m, 1H), 4.49 (d, *J*=17.8, 1H), 4.49 (d, *J*=17.8, 1H), 3.98 (d, *J*=3.8, 1H), 3.95 (d, *J*=3.8, 1H), 3.40 (m, 2H), 1.72 (m, 3H), 1.14 (m, 18H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 182.1, 182.0, 178.5, 178.3, 168.5, 168.4, 167.1, 167.1, 155.7, 155.5, 155.1, 154.7, 153.7, 153.6, 151.9, 151.9, 141.4, 141.3, 135.5, 135.5, 135.1, 135.1, 133.8, 131.8, 131.5, 131.4, 131.3, 131.1, 131.1, 130.8, 130.6, 129.5, 129.4, 129.1, 129.0, 128.5, 128.3, 128.2, 128.1, 128.0, 128.0, 128.0, 127.9, 127.8, 127.5, 127.4, 127.1, 127.0,

127.0, 123.5, 123.3, 123.2, 123.0, 121.8, 121.7, 121.6, 121.6, 121.0, 120.8, 120.0, 119.7, 114.6, 114.5, 112.6, 112.3, 110.1, 110.0, 106.6, 106.4, 96.1, 70.4, 70.3, 67.5, 67.5, 53.3, 53.2, 49.7, 49.4, 44.6, 44.5, 34.1, 18.0, 18.0, 12.7, 12.7; **IR** (thin film/NaCl) 2948 (w), 1814 (s), 1776 (w), 1745 (m), 1716 (s), 1600 (w), 1488 (w), 1388 (s), 1061 (m), 697 (w) cm^{-1}; **HRMS** (FAB) *m/z* found: 1004.3945, [calc'd for $C_{61}H_{58}N_3O_9Si$ (M+H): 1004.3942].

Preparation of dipeptide 276



To a solution of lactone **275** (0.065 mg, 0.065 mmol) in THF (1 mL) and EtOH (3 mL) was added 10% Pd/C (20 mg). After stirring for 4 h under 1 atm of H_2 (g) the reaction mixture was filtered over a pad of celite and washed with ethyl acetate (50 mL). This solution was concentrated in vacuo, dissolved in ethyl acetate (25 mL), washed with H_2O (2 x 15 mL), and dried ($MgSO_4$). Solvent removal in vacuo afforded a crude acid that was taken up in CH_2Cl_2 (1 mL) and added via cannula to a solution of L-Val-O*t*-Bu·HCl (16 mg, 0.078 mmol), HOBt (11 mg, 0.078 mmol), EDC (15 mg, 0.078 mmol) and Et_3N (0.014 mL, 0.154 mmol) in CH_2Cl_2 (1 mL). After stirring for 16 h the reaction was diluted with Et_2O (25 mL) and washed with 1M $NaHSO_4$ (25 mL), sat. $NaHCO_3$ (25 mL), brine (25 mL), and dried ($MgSO_4$). After solvent removal in vacuo the residue was

purified by silica gel column chromatography (hexanes:EtOAc, 2:1) to afford peptide **276** (52 mg, 82% yield) as a clear colorless oil. The first diastereomers to elute was analytically pure allowing for characterization. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 (m, 1H), 7.72 (s, 1H), 7.62 (dd, *J*=1.1, 7.8 Hz, 1H), 7.57-7.52 (cm, 4H), 7.46 (m, 2H), 7.31-7.27 (cm, 5H), 7.20 (m, 1H), 7.09 (m, 2H), 7.01 (m, 1H), 6.86-6.82 (cm, 2H), 6.68 (d, *J*=7.8 Hz, 1H), 6.50 (cm, 1H), 4.93 (m, 1H), 4.83 (m, *2*H), 4.46 (d, *J*=4.4 Hz, 1H), 4.44 (d, *J*=4.4 Hz, 1H), 4.00 (d, 2H), 3.38 (m, 2H), 2.12 (m, 1H), 1.73 (m, 3H), 1.39 (s, 9H), 1.16 (dd, J=2.8, 7.8 Hz, 18H), 0.91 (d, *J*=6.8 Hz, 3H), 0.81 (d, *J*=6.8 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ; **IR** (thin film/NaCl) 3319 (w), 2927 (m), 1802 (m), 1715 (s), 1611 (w), 1457 (m), 1383 (w), 1170 (m), 1012 (w), 731 (s) cm^{-1}.

3.9 Notes and References

1. "Synthesis of N-Phthaloyl Amino-Acids and Amino-Acid Esters under Mild Conditions", Hoogwate D., Reinhoud D., Lie T. S., Gunneweg J. J., Beyerman H. C., *Recueil Des Travaux Chimiques Des Pays-Bas-Journal of the Royal Netherlands Chemical Society*, **1973**, *92*, 819-825.

2. "Rhodium carbenoid-initiated claisen rearrangement: Scope and mechanistic observations", Wood J. L., Moniz G. A., *Organic Letters*, **1999**, *1*, 371-374.

3. "Development of a rhodium carbenoid-initiated claisen rearrangement for the enantioselective synthesis of alpha- hydroxy carbonyl compounds", Wood J. L.,

Moniz G. A., Pflum D. A., Stoltz B. M., Holubec A. A., Dietrich H. J., *Journal of the American Chemical Society*, **1999**, *121*, 1748-1749.

4. "Catalyst-based control of 2,3 - and 3,3 -rearrangement in alpha-diazoketone-derived propargyloxy enols", Moniz G. A., Wood J. L., *Journal of the American Chemical Society*, **2001**, *123*, 5095-5097.

5. "Stereoselectivity and Regioselectivity in Palladium-Catalyzed Allylic Etherification", Goux C., Massacret M., Lhoste P., Sinou D., *Organometallics*, **1995**, *14*, 4585-4593.

6. "Asymmetric O- and C-alkylation of phenols", Trost B. M., Toste F. D., *Journal of the American Chemical Society*, **1998**, *120*, 815-816.

7. "A tyrosine-derived benzofuranone related to diazonamide A", Vedejs E., Wang J. B., *Organic Letters*, **2000**, *2*, 1031-1032.

8. "Efficient Synthesis and Intramolecular Cyclopropanation of Unsaturated Diazoacetic Esters", Corey E. J., Myers A. G., *Tetrahedron Letters*, **1984**, *25*, 3559-3562.

9. "A New Diazoacylating Reagent - Preparation, Structure, and Use of Succinimidyl Diazoacetate", Ouihia A., Rene L., Guilhem J., Pascard C., Badet B., *Journal of Organic Chemistry*, **1993**, *58*, 1641-1642.

10. Cyclopropanation product **260** could never be fully characterized, however, strong characterzation evidence for the corresponding amino acid methyl ester compound can be found in the Wood group archives.

11. "A New Synthesis of Highly Functionalized Oxazoles", Wipf P., Miller C. P., *Journal of Organic Chemistry*, **1993**, *58*, 3604-3606.

12. "Naphtho[2,3-D][1,2,3]Oxadiazole", Blocher A., Zeller K. P., *Angewandte Chemie-International Edition in English*, **1991**, *30*, 1476-1477.

13. "1,2,3-Benzoxadiazole - Detection in an Argon Matrix and in Solution", Schulz R., Schweig A., *Angewandte Chemie-International Edition in English*, **1984**, *23*, 509-511.

14. "Ir and Uv Matrix Photochemistry and Solvent Effects - the Isomerization of Diazocyclohexadienones (Ortho Quinone Diazides) Detection of Molecules with the 1,2,3-Benzoxadiazole Structure - a Uv Vis and Ir Absorption and Uv Photoelectron Spectroscopic Investigation", Schweig A., Baumgartl H., Schulz R., *Journal of Molecular Structure*, **1991**, *247*, 135-171.

15. "Photolysis of Napth[2,3-D]-1,2,3-Oxadiazole - A Contribution to the Oxirene Problem", Blocher A., Zeller K., *Chemische Berichte*, **1994**, *127*, 551-555.

16. "Synthesis of 6-azido-1-oxo-indan-4-oyl isoleucine; a photoaffinity approach to plant signaling", Schuler G., Wasternack C., Boland W., *Tetrahedron*, **1999**, *55*, 3897-3904.

17. "Alkyl Nitrite-Metal Halide Deamination Reactions .6. Direct Synthesis of Arenediazonium Tetrafluoroborate Salts from Aromatic-Amines, Tert-Butyl Nitrite, and Boron-Trifluoride Etherate in Anhydrous Media", Doyle M. P., Bryker W. J., *Journal of Organic Chemistry*, **1979**, *44*, 1572-1574.

18. "Synthesis of Pimprinine and Related Oxazolylindole Alkaloids from N-Acyl Derivatives of Tryptamine and Tryptophan Methyl-Ester by DDQ Oxidation", Oikawa Y., Yoshida T., Mohri K., Yonemitsu O., *Heterocycles*, **1979**, *12*, 1457-1462.

19. "Recent advances in asymmetric catalytic metal carbene transformations", Doyle M. P., Forbes D. C., *Chemical Reviews*, **1998**, *98*, 911-935.

20. "Macrocycle formation by catalytic intramolecular cyclopropanation. A new general methodology for the synthesis of macrolides", Doyle M. P., Peterson C.

S., Protopopova M. N., Marnett A. B., Parker D. L., Ene D. G., Lynch V., *Journal of the American Chemical Society*, **1997**, *119*, 8826-8837.

21. "Formation of macrocyclic lactones by enantioselective intramolecular cyclopropanation of diazoacetates catalyzed by chiral Cu-I and Rh-II compounds", Doyle M. P., Peterson C. S., Parker D. L., *Angewandte Chemie-International Edition in English*, **1996**, *35*, 1334-1336.

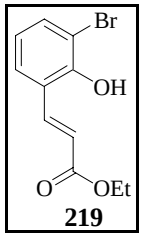
22. "Macrocyclic Lactones from Dirhodium(Ii)-Catalyzed Intramolecular Cyclopropanation and Carbon-Hydrogen Insertion", Doyle M. P., Protopopova M. N., Poulter C. D., Rogers D. H., *Journal of the American Chemical Society*, **1995**, *117*, 7281-7282.

23. Doyle M., McKervey M., Ye T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: from Cyclopropanes to Ylides*. New York: Wiley & Sons; 1998.

24. "Photoreductions and Photocyclizations of Tryptophan", Yonemits.O, Cerutti P., Witkop B., *Journal of the American Chemical Society*, **1966**, *88*, 3941.

Appendix Two: Spectra Relevant

To Chapter Three



219

Figure A.2.1 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **219**.

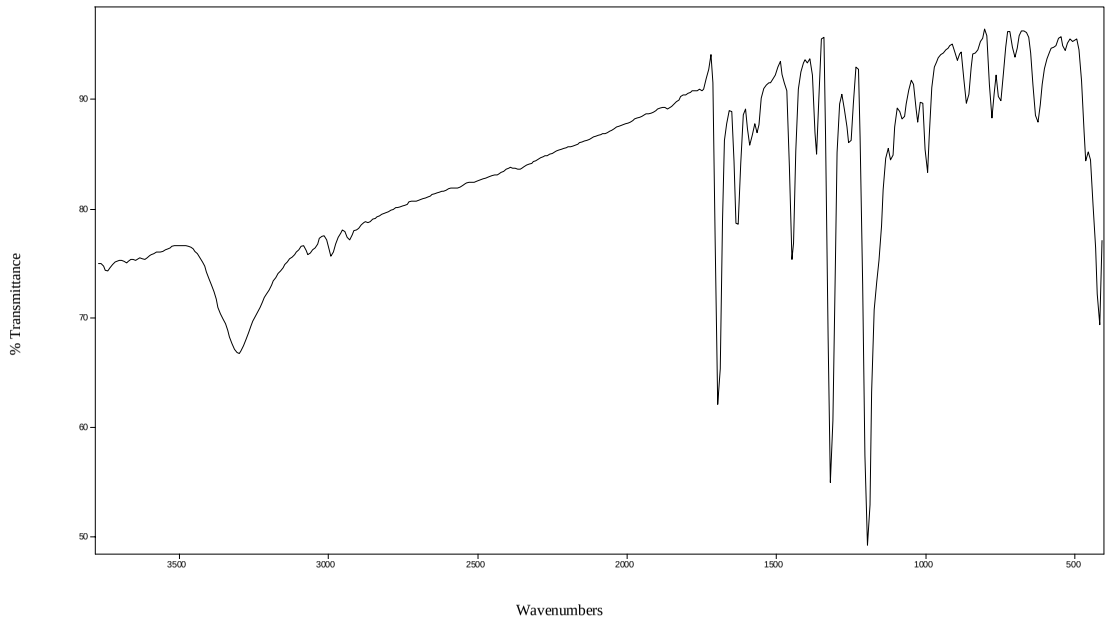


Figure A.2.2 FTIR Spectrum (thin film/NaCl) of Compound **219**.

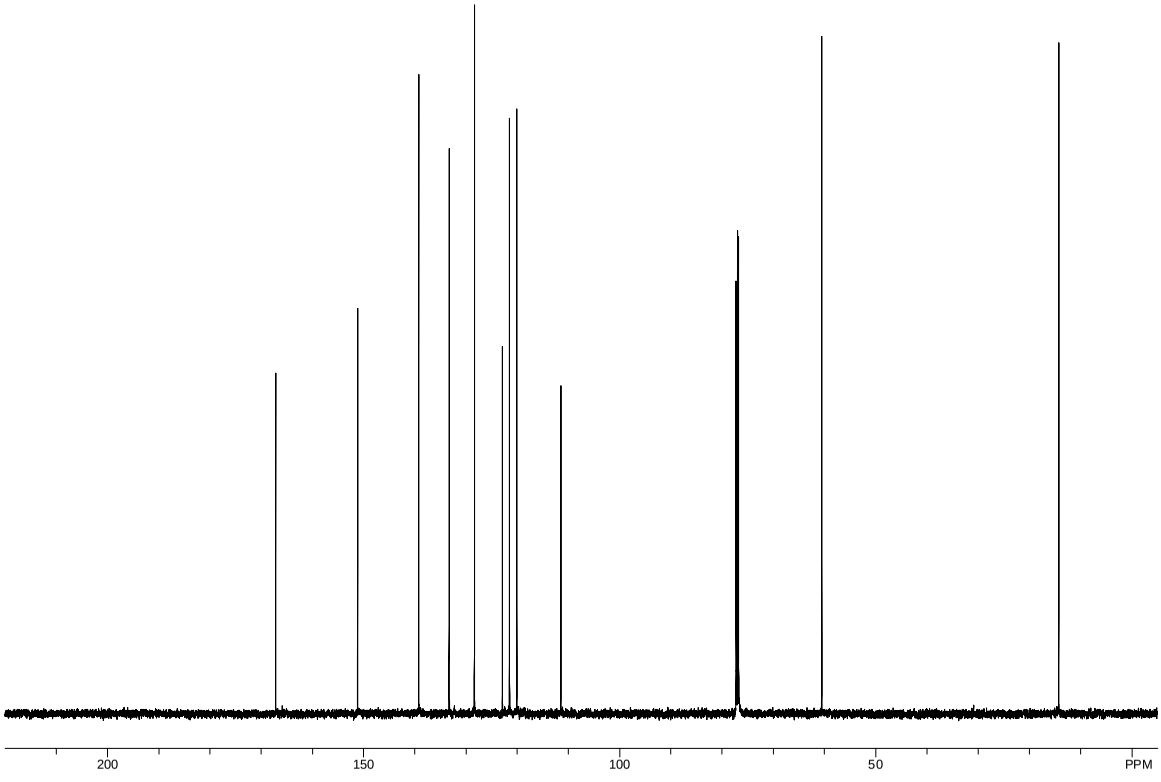


Figure A.2.3 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **219.**

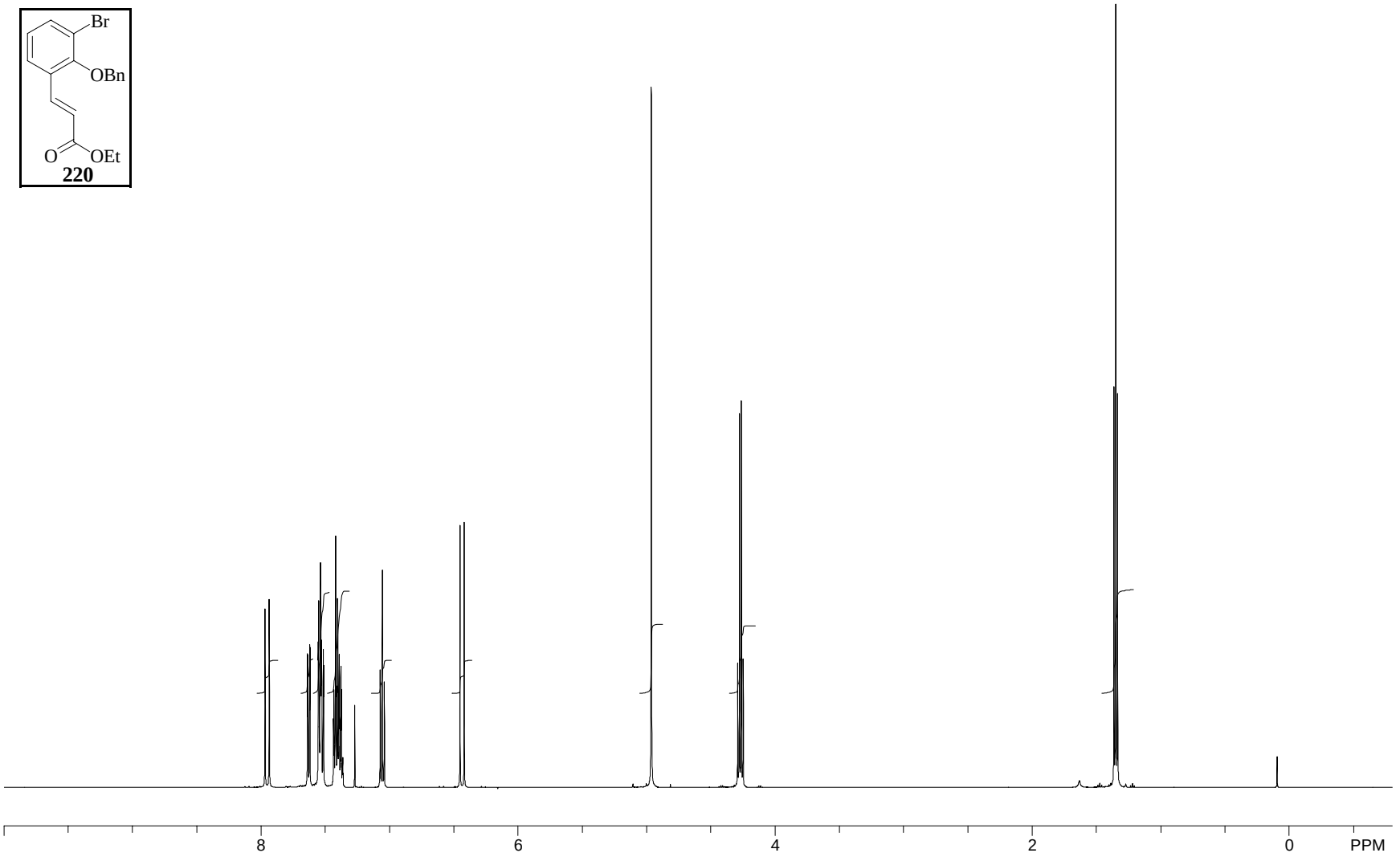


Figure A.2.4 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **220**.

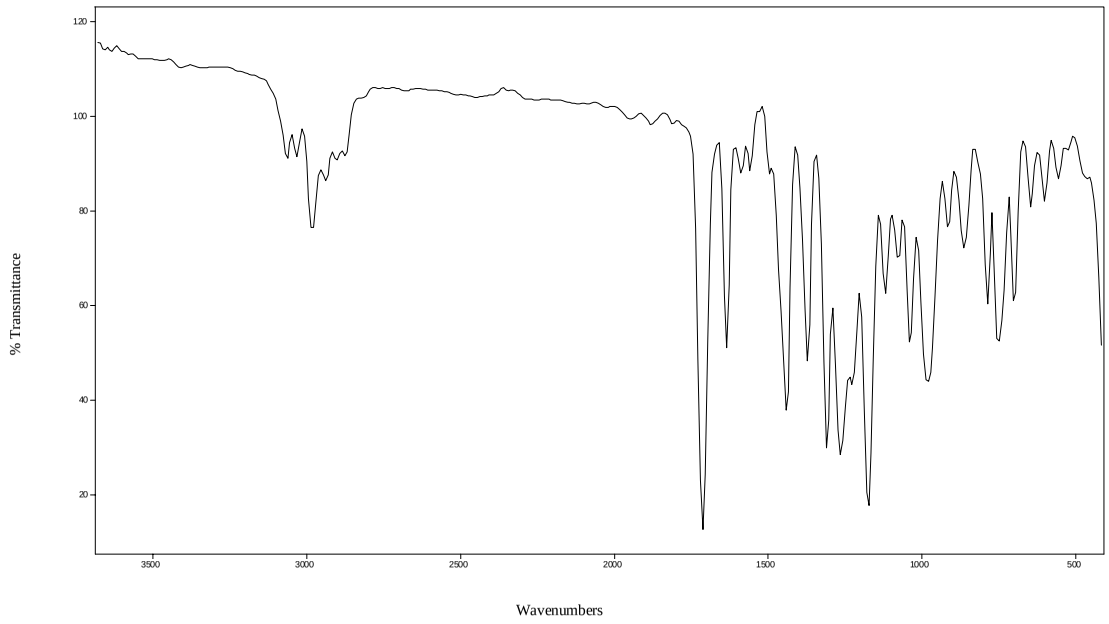


Figure A.2.5 FTIR Spectrum (thin film/NaCl) of Compound **220**.

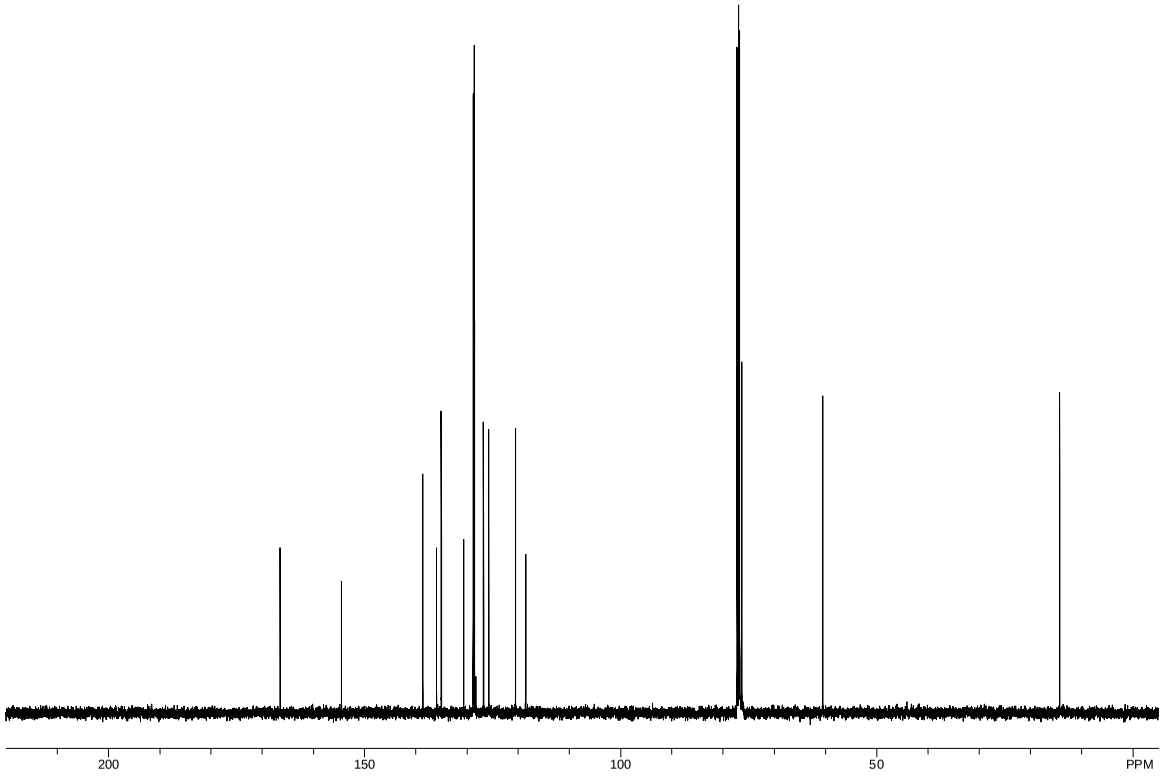


Figure A.2.6 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **220**.

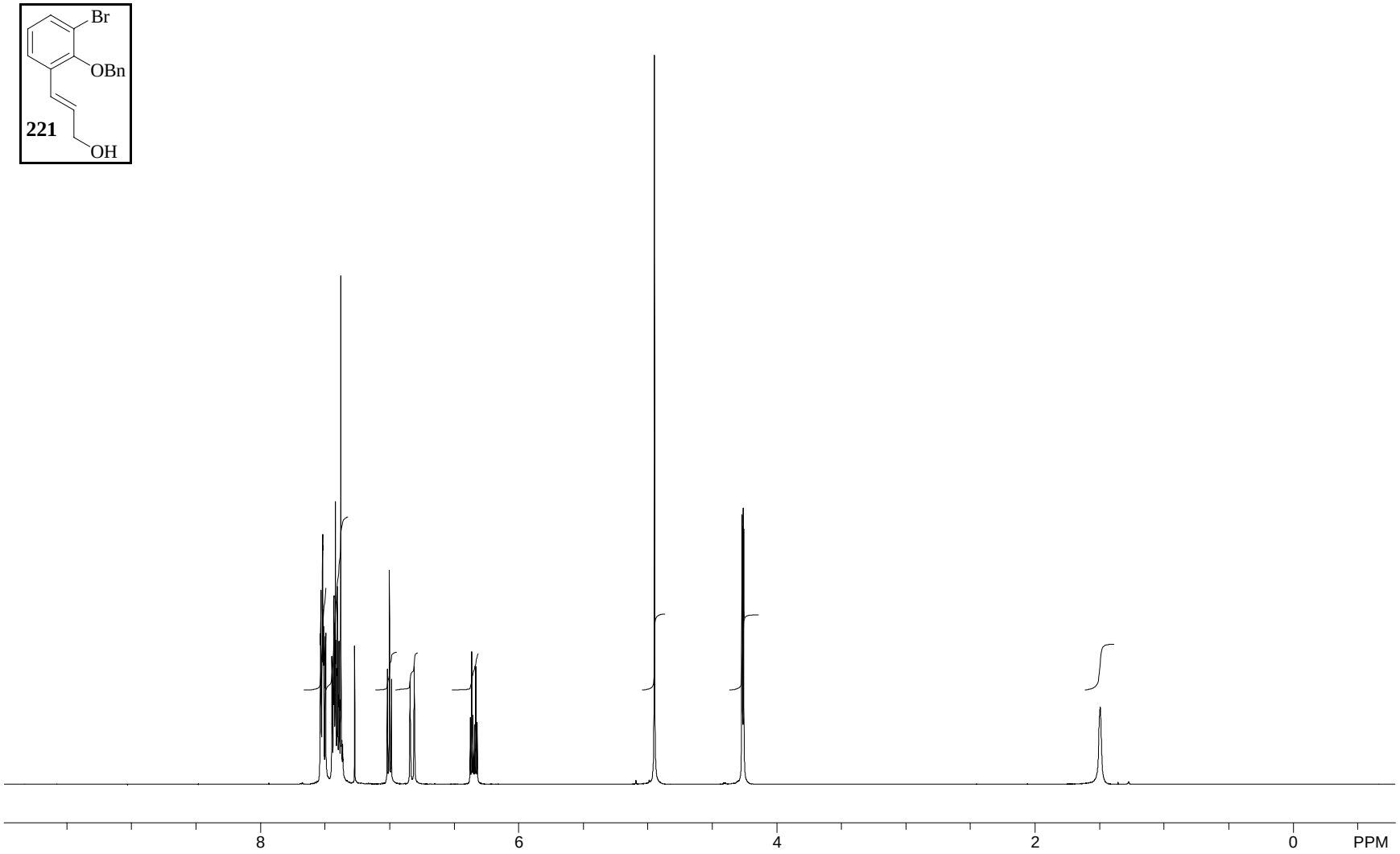


Figure A.2.7 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **221**.

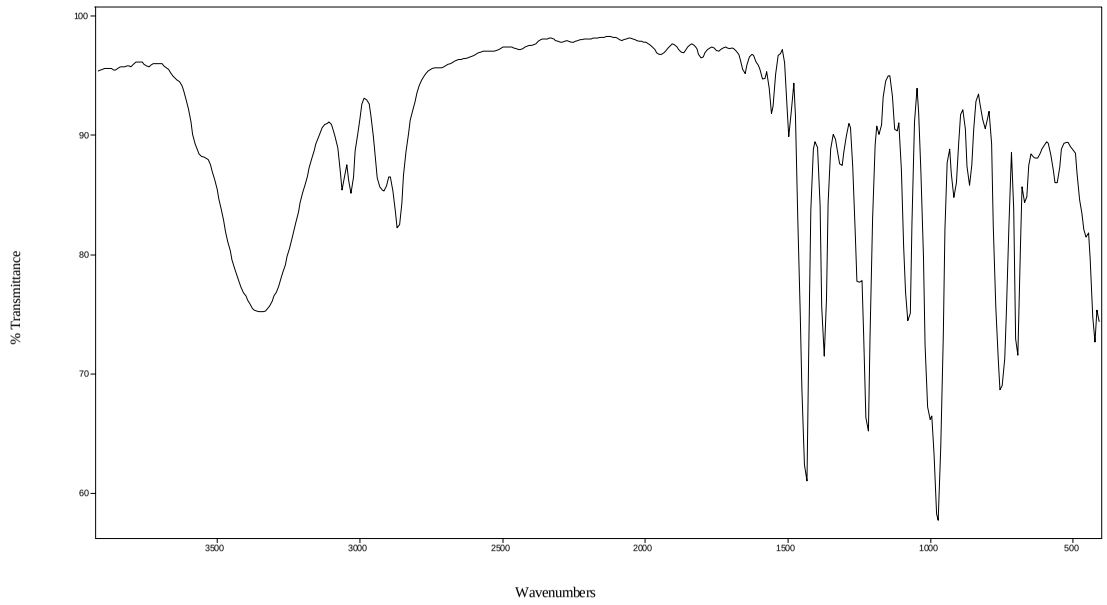


Figure A.2.8 FTIR Spectrum (thin film/NaCl) of Compound **221**.

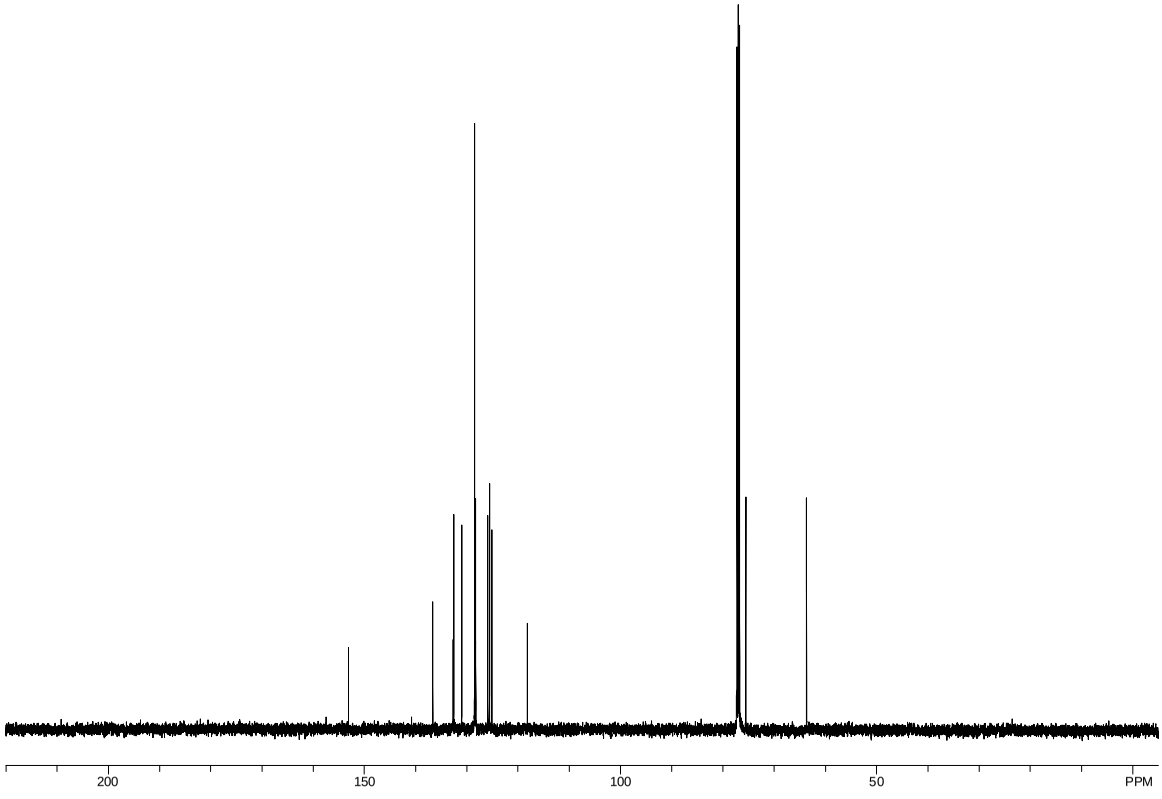


Figure A.2.9 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **221**.

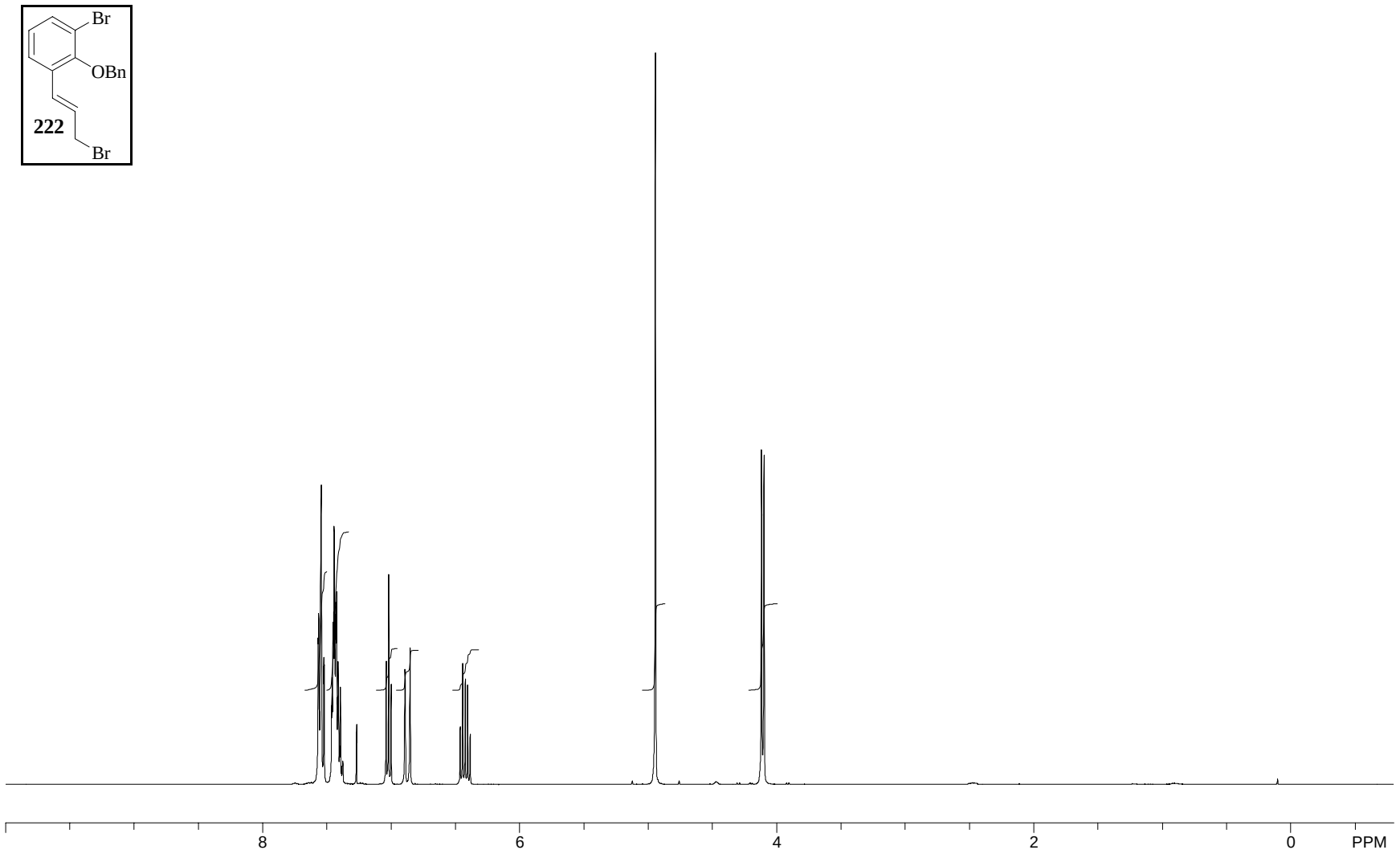


Figure A.2.10 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **222**.

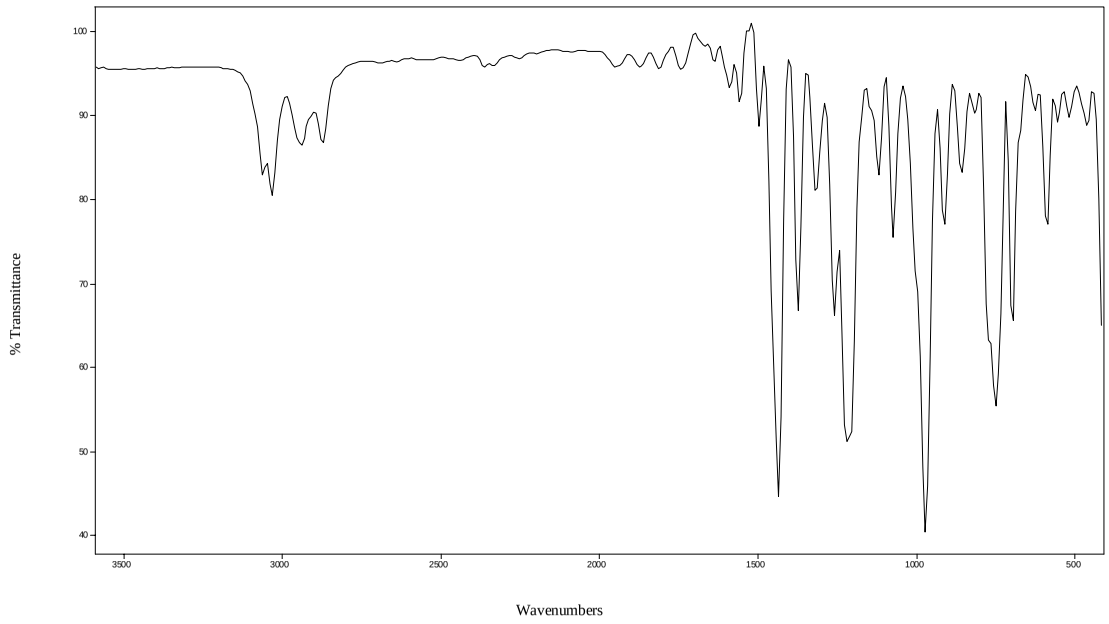


Figure A.2.11 FTIR Spectrum (thin film/NaCl) of Compound **222**.

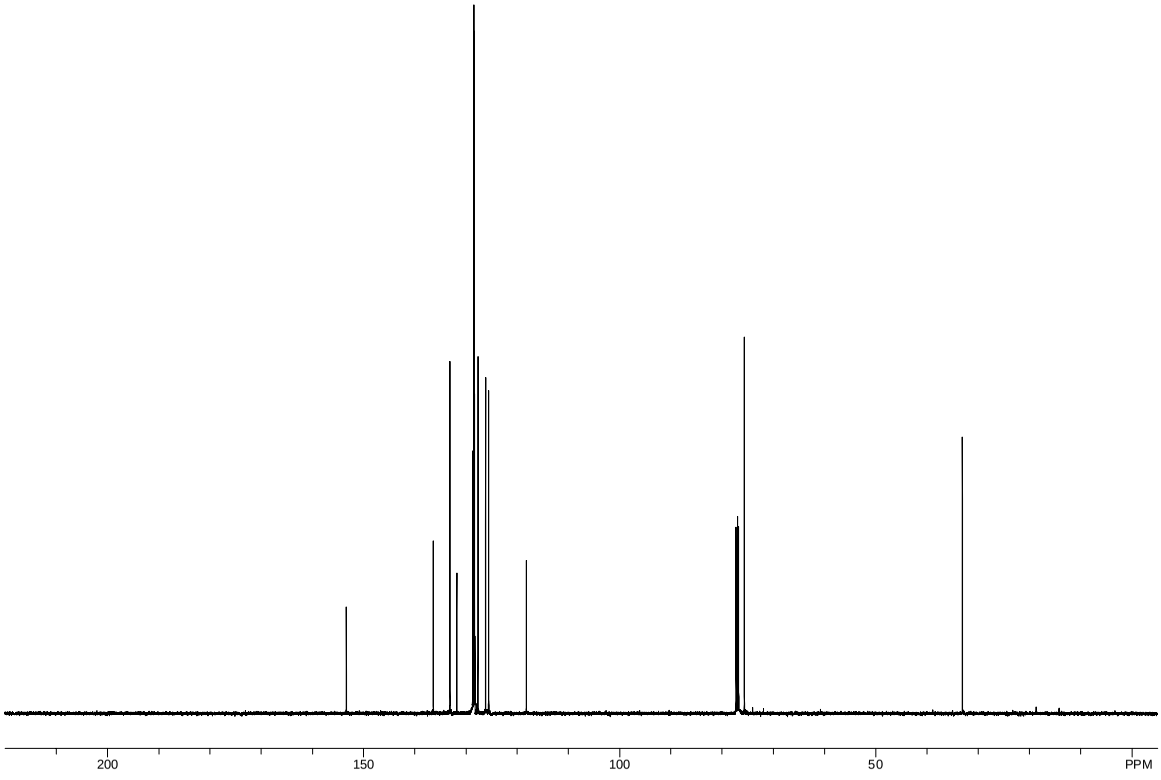


Figure A.2.12 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **222**.

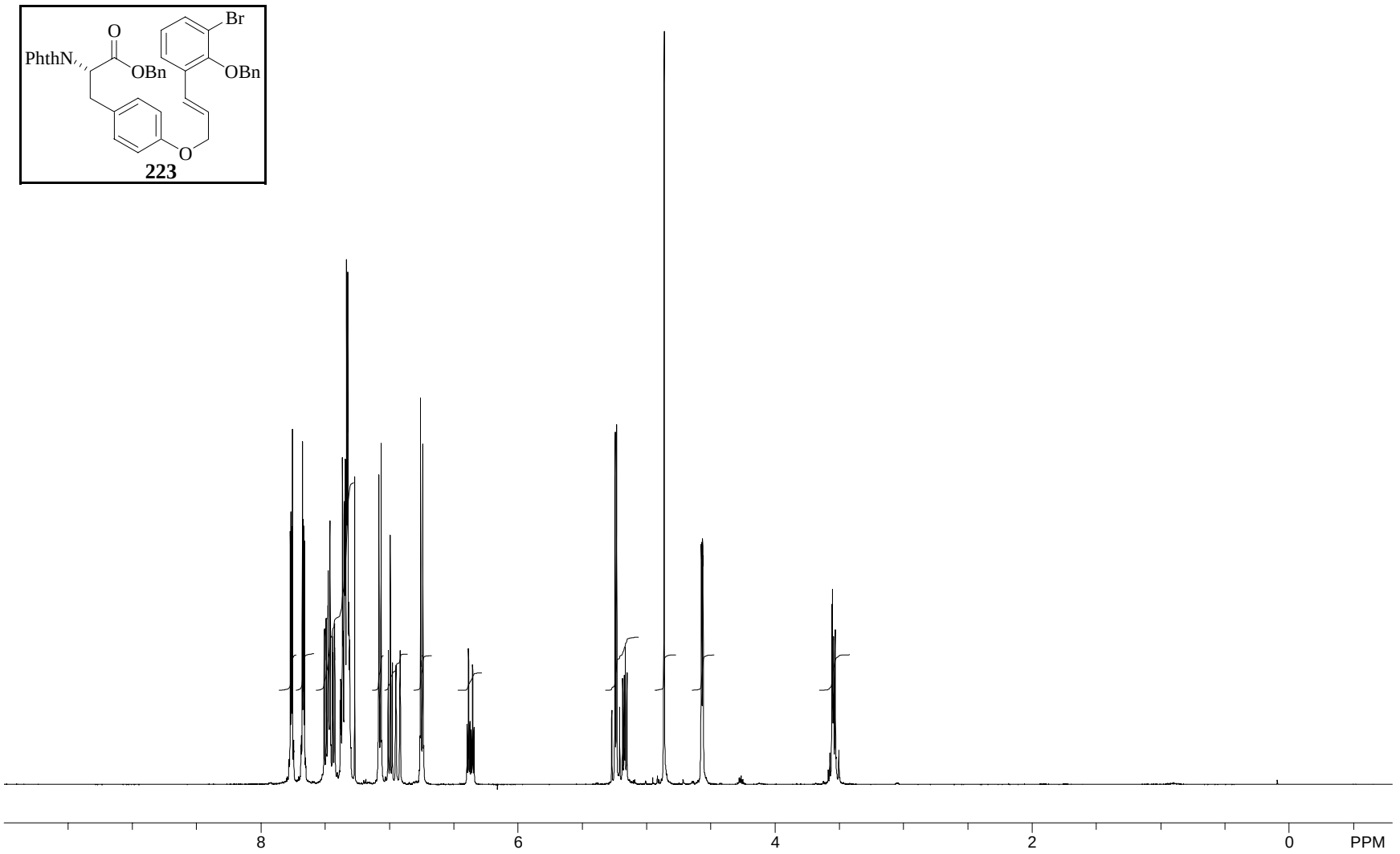


Figure A.2.13 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **223**.

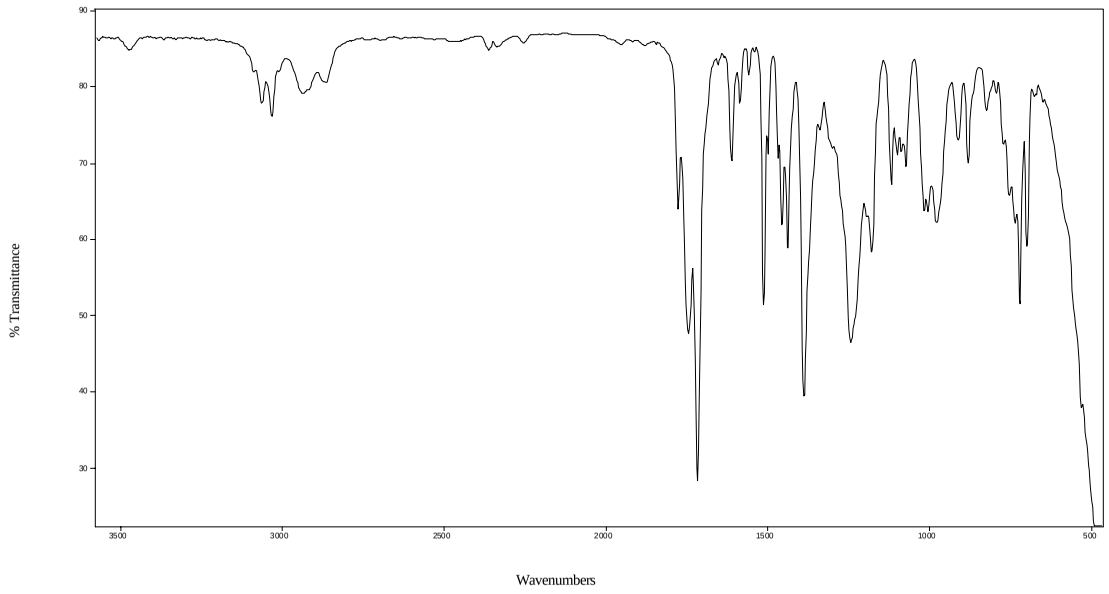


Figure A.2.14 FTIR Spectrum (thin film/NaCl) of Compound **223**.

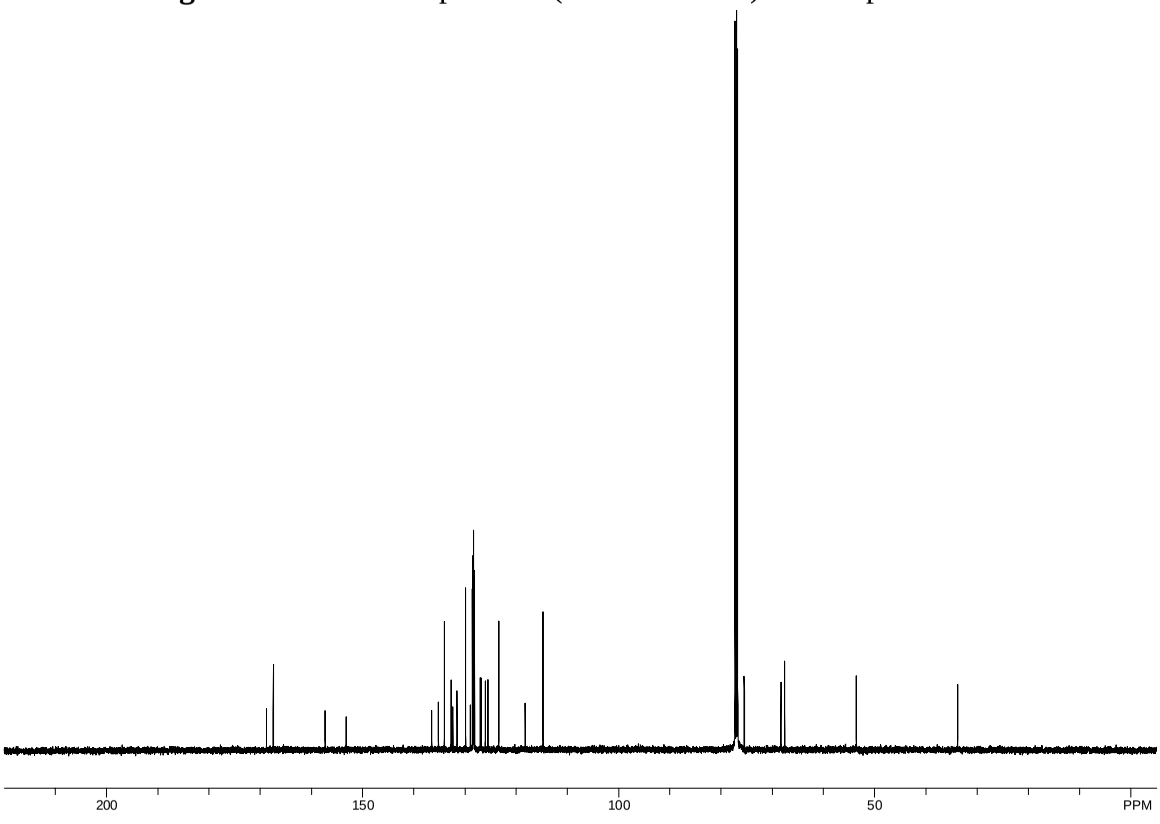


Figure A.2.15 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **223.**

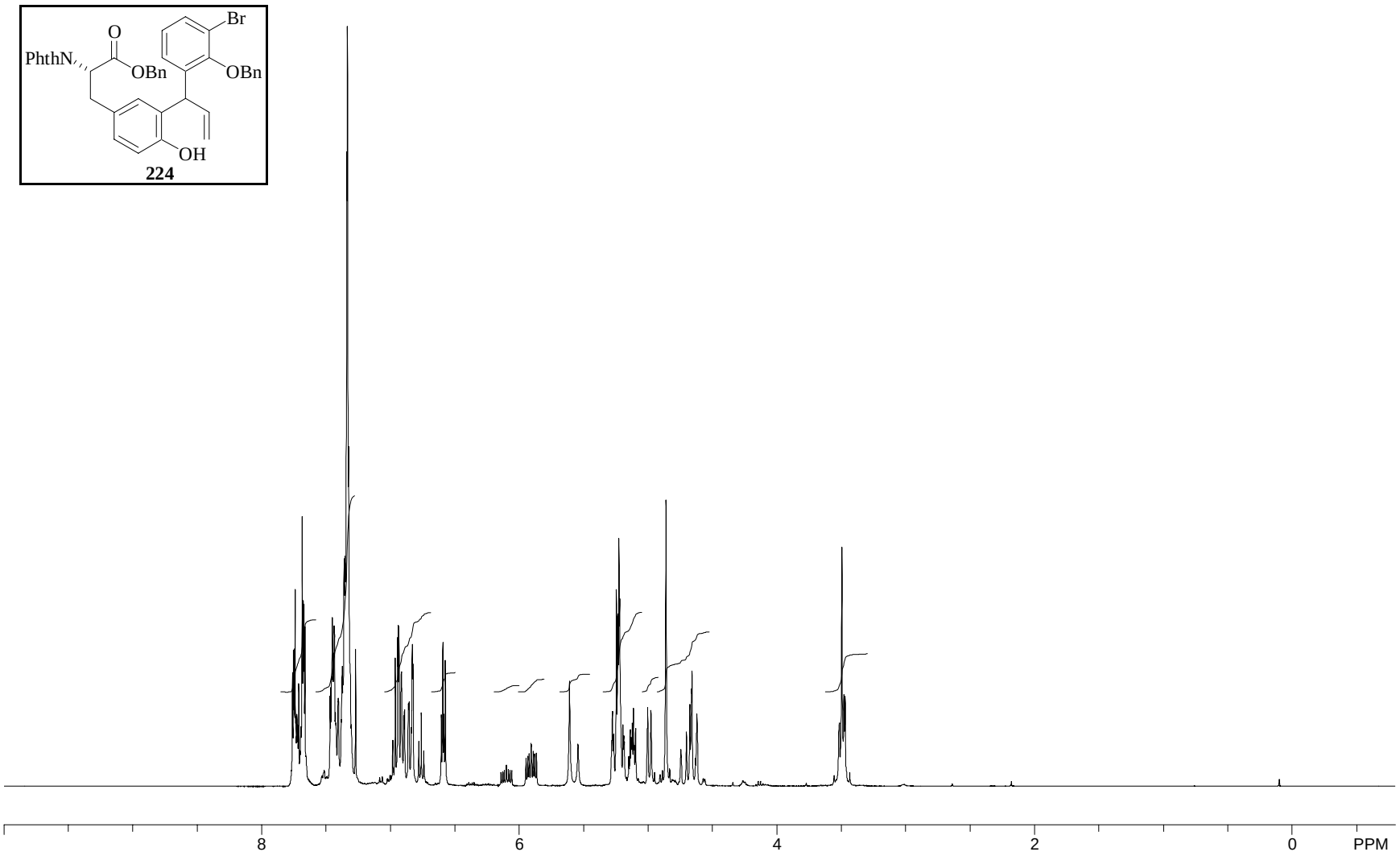


Figure A.2.16 ^{1}H NMR (400 MHz, C_6D_6) of Compound **224**.

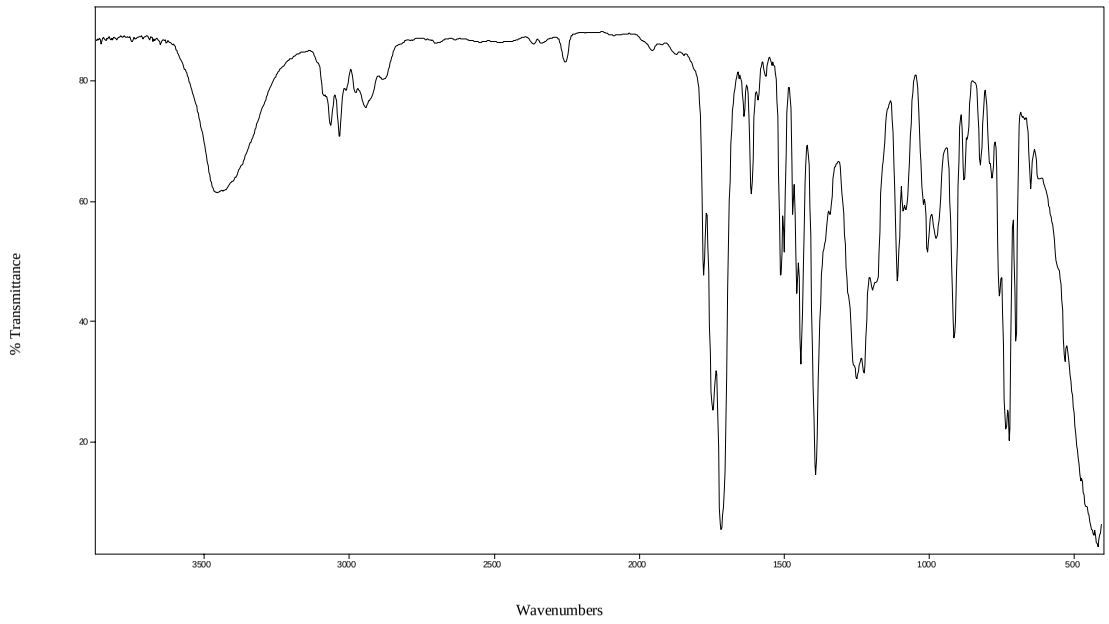


Figure A.2.17 FTIR Spectrum (thin film/NaCl) of Compound **224**.

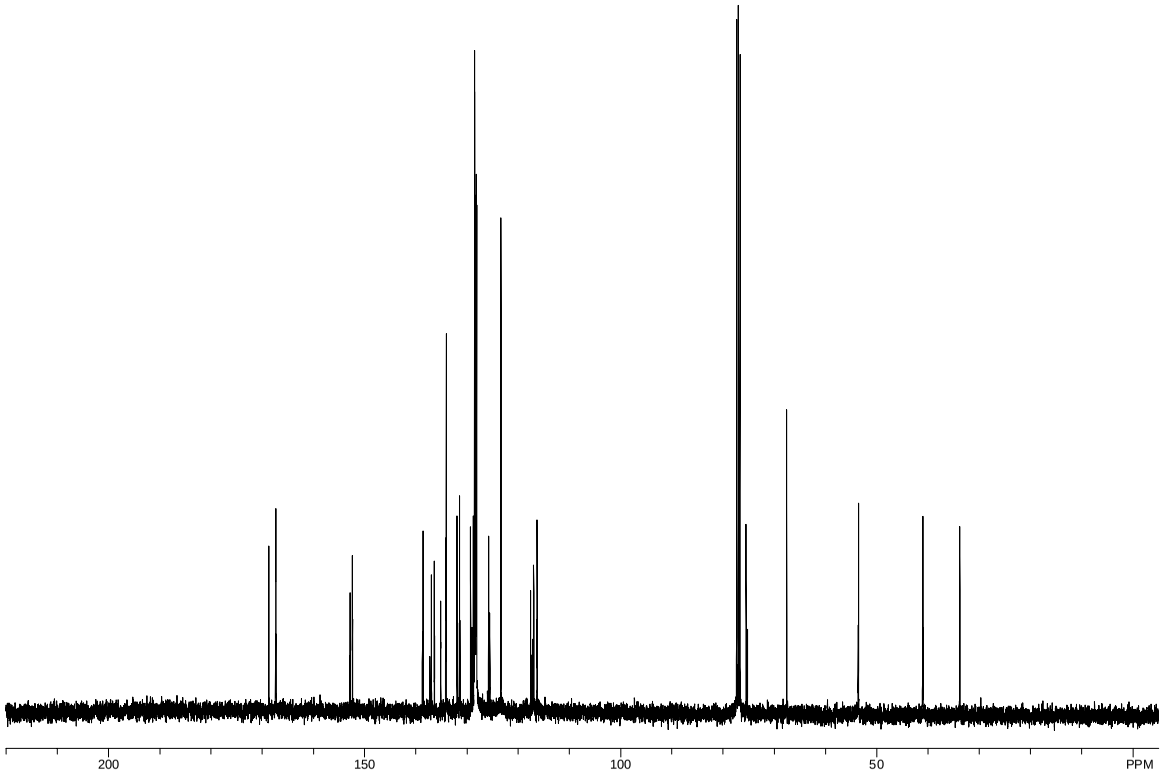
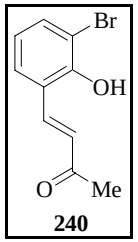


Figure A.2.18 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **224**.



240

Figure A.2.19 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **240**.

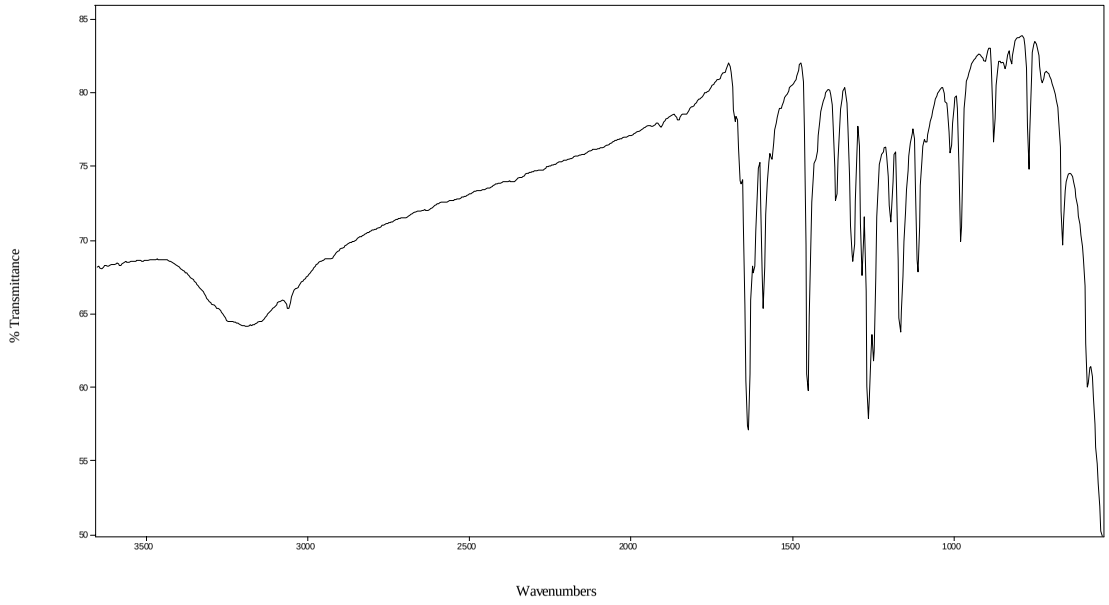


Figure A.2.20 FTIR Spectrum (thin film/NaCl) of Compound **240**.

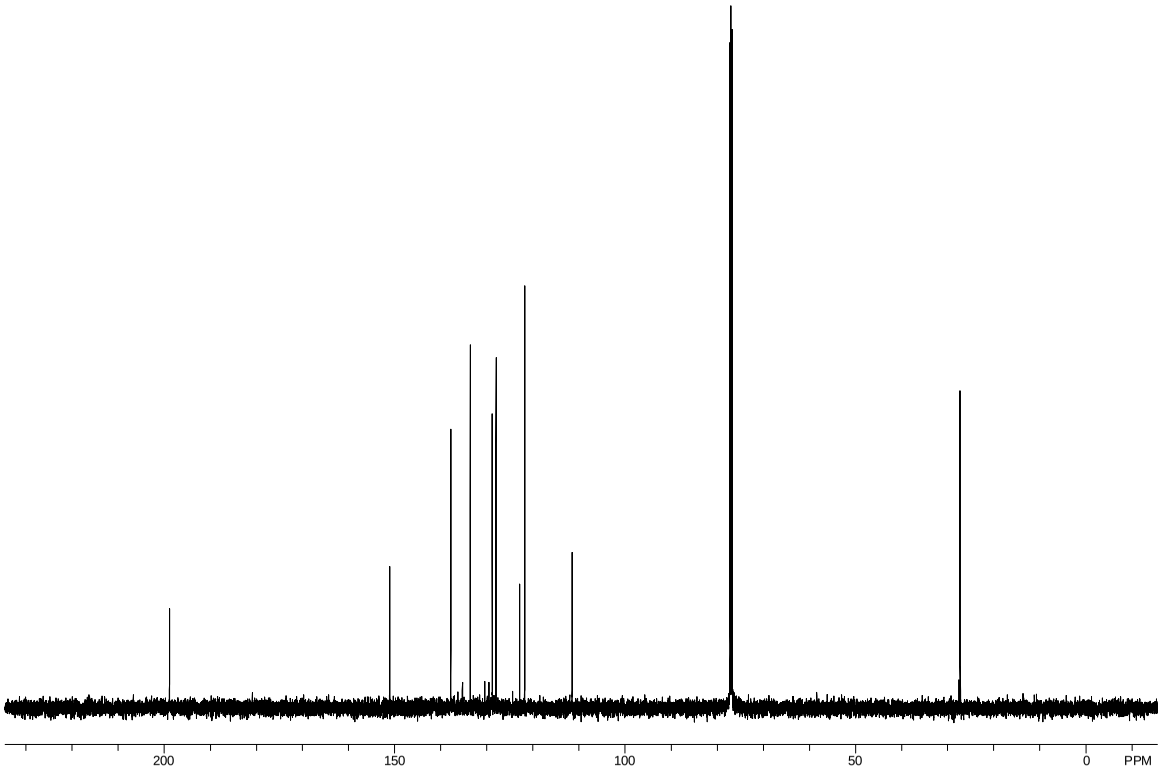
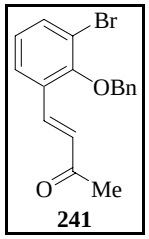


Figure A.2.21 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **240**.



241

Figure A.2.22 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **241**.

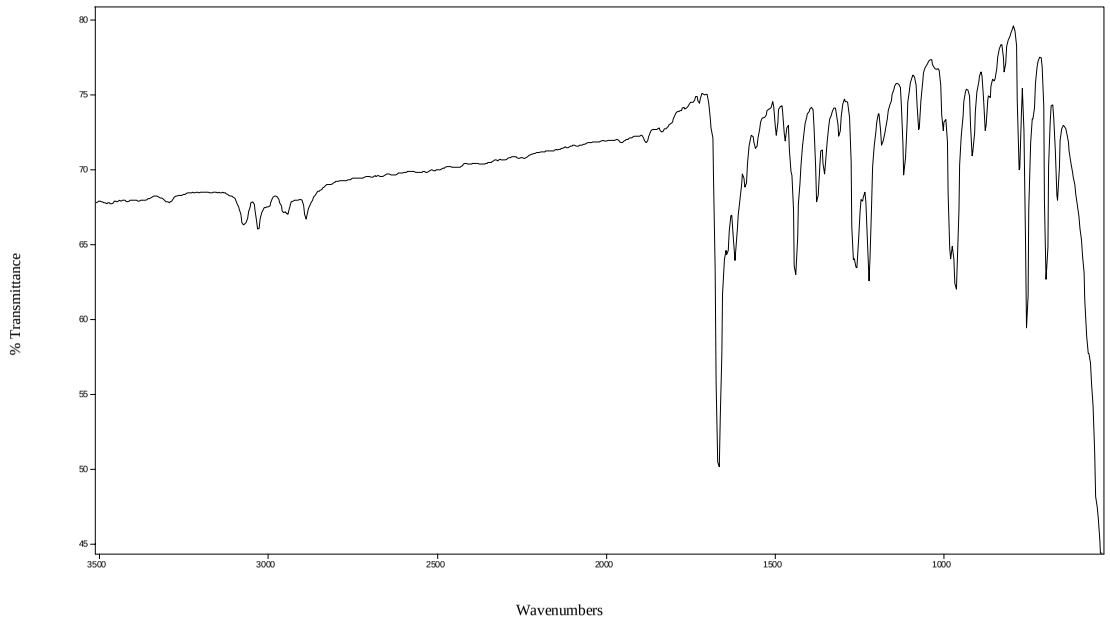


Figure A.2.23 FTIR Spectrum (thin film/NaCl) of Compound **241**.

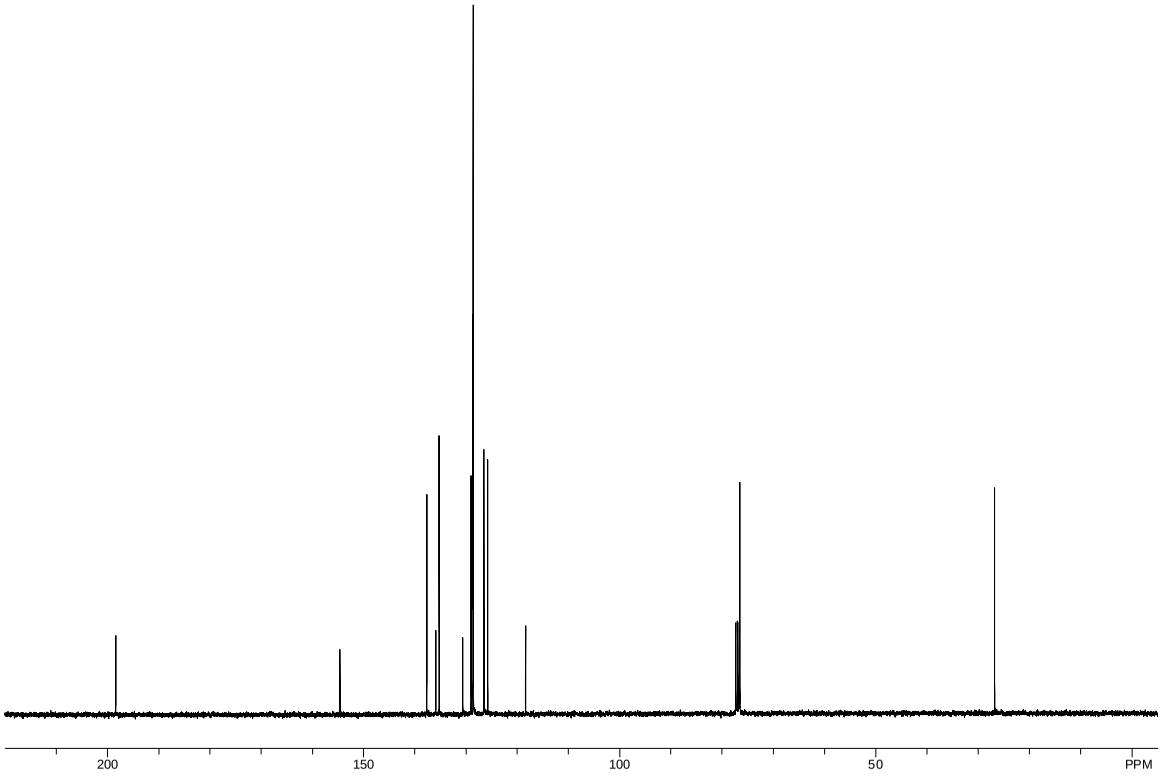


Figure A.2.24 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **241**.

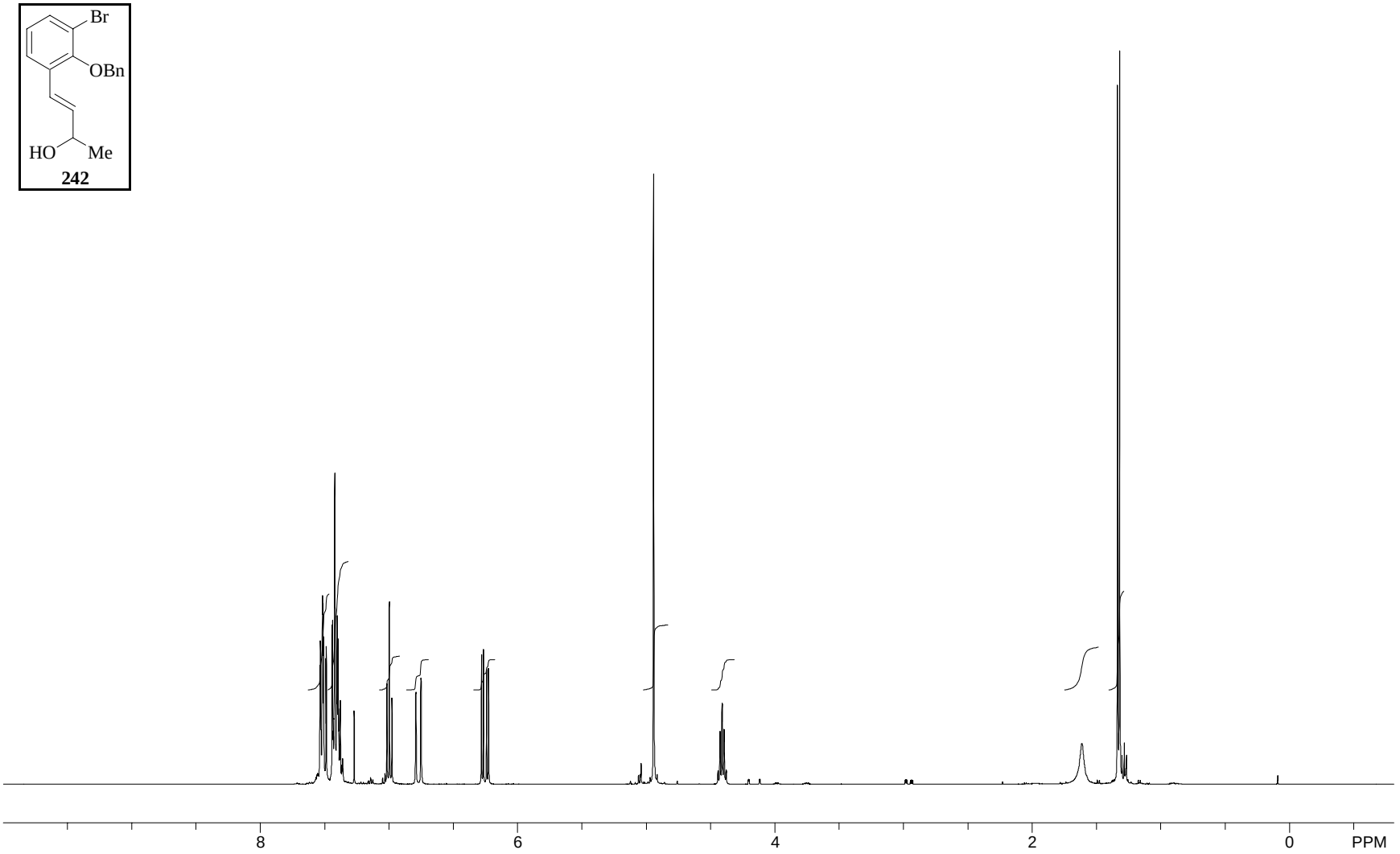


Figure A.2.25 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **242**.

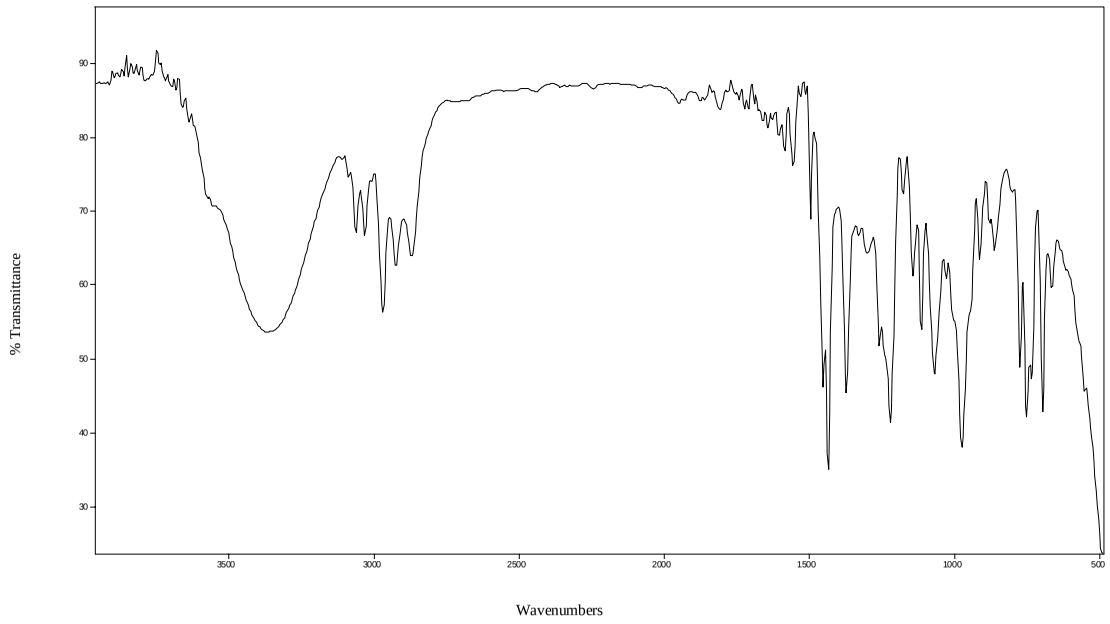


Figure A.2.26 FTIR Spectrum (thin film/NaCl) of Compound **242**.

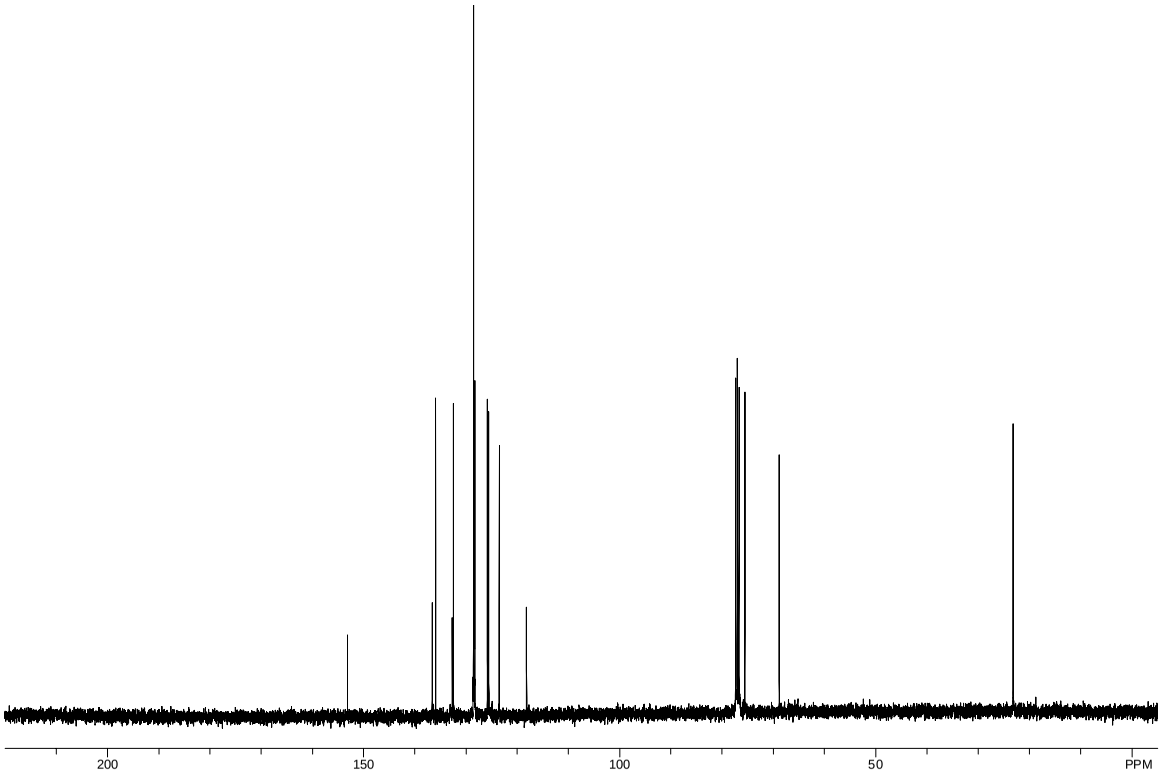


Figure A.2.27 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **242**.

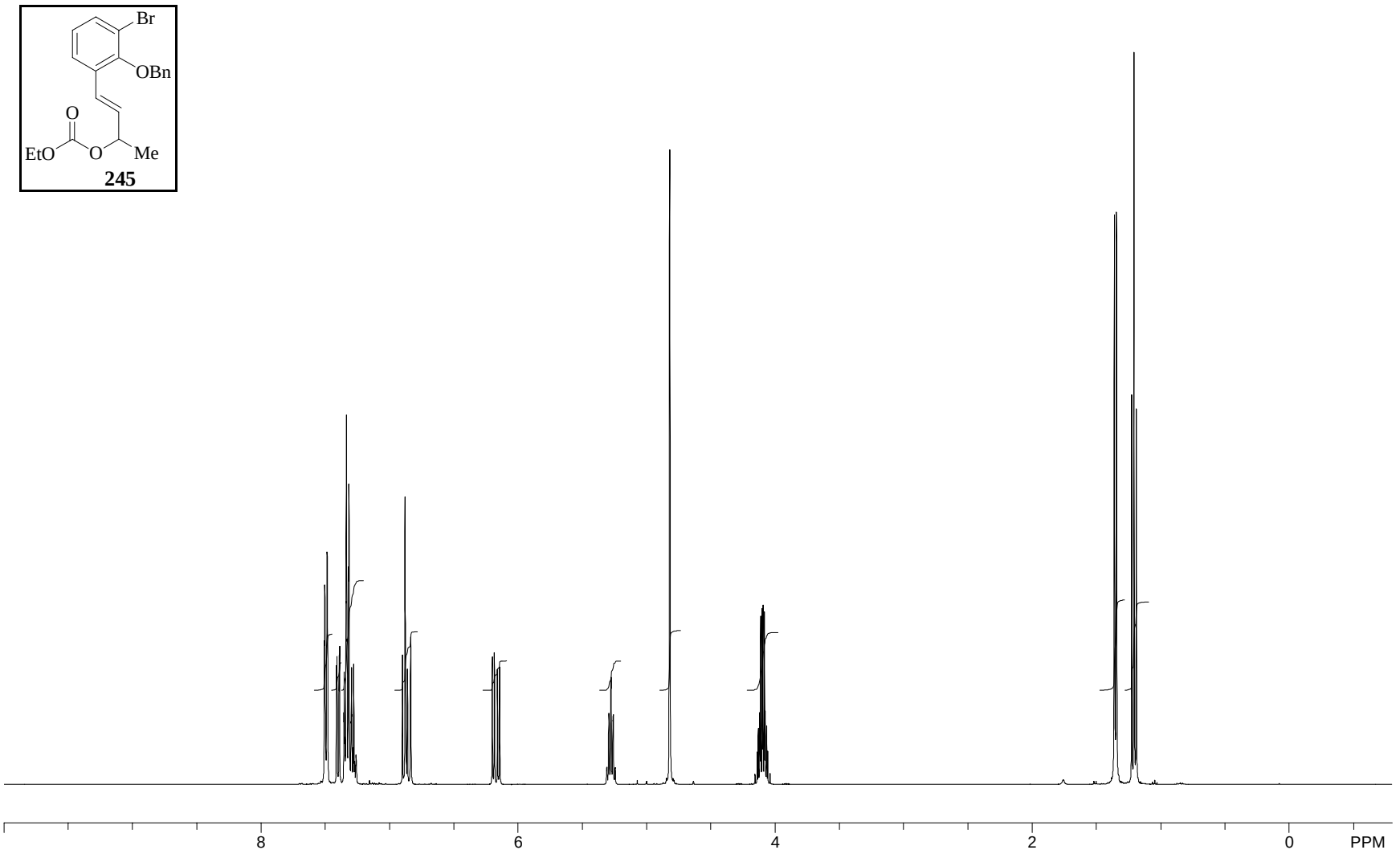


Figure A.2.28 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **245**.

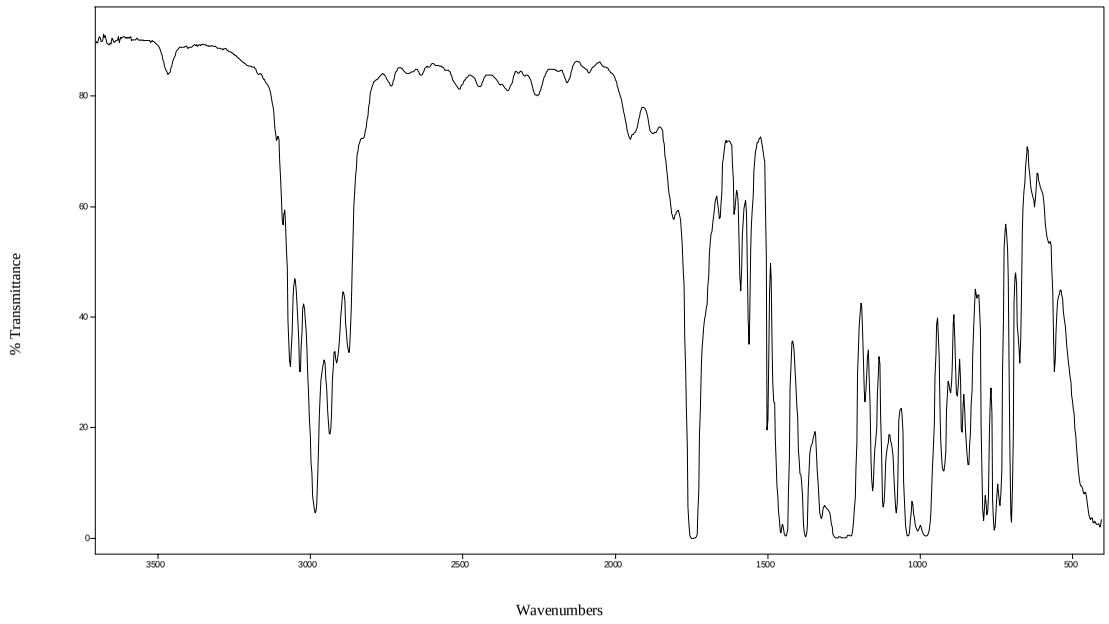


Figure A.2.29 FTIR Spectrum (thin film/NaCl) of Compound **245**.

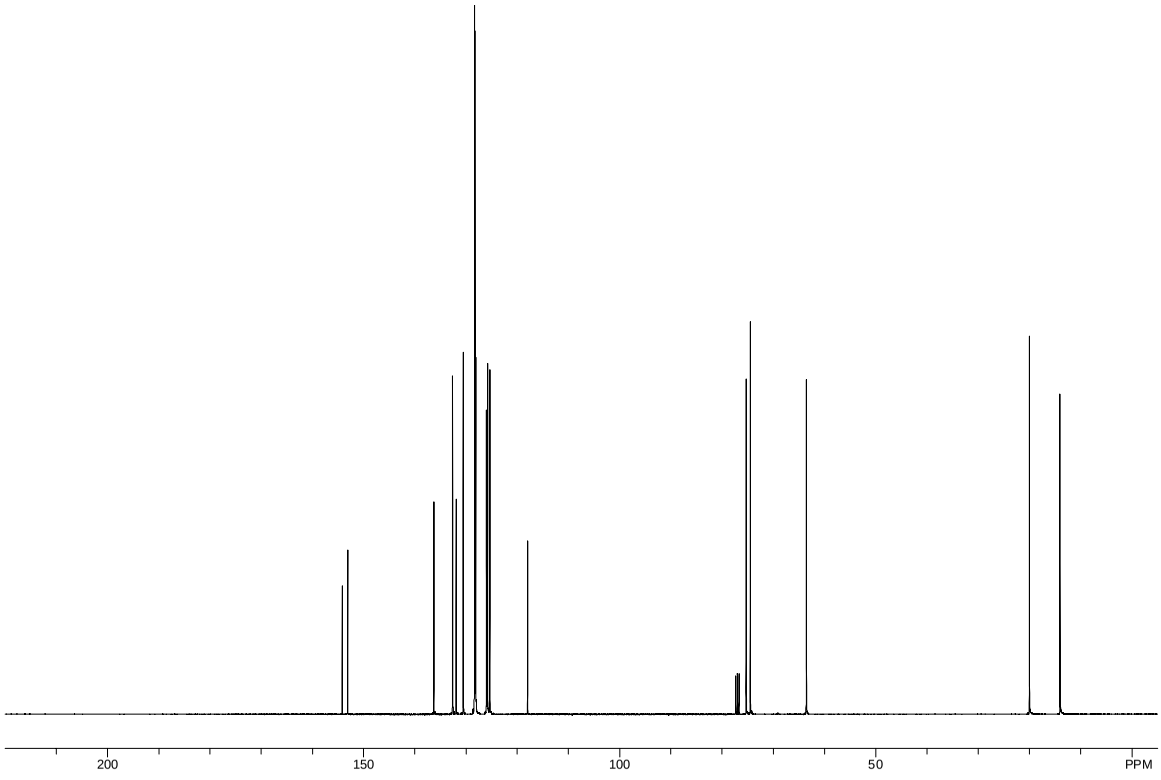


Figure A.2.30 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **245**.

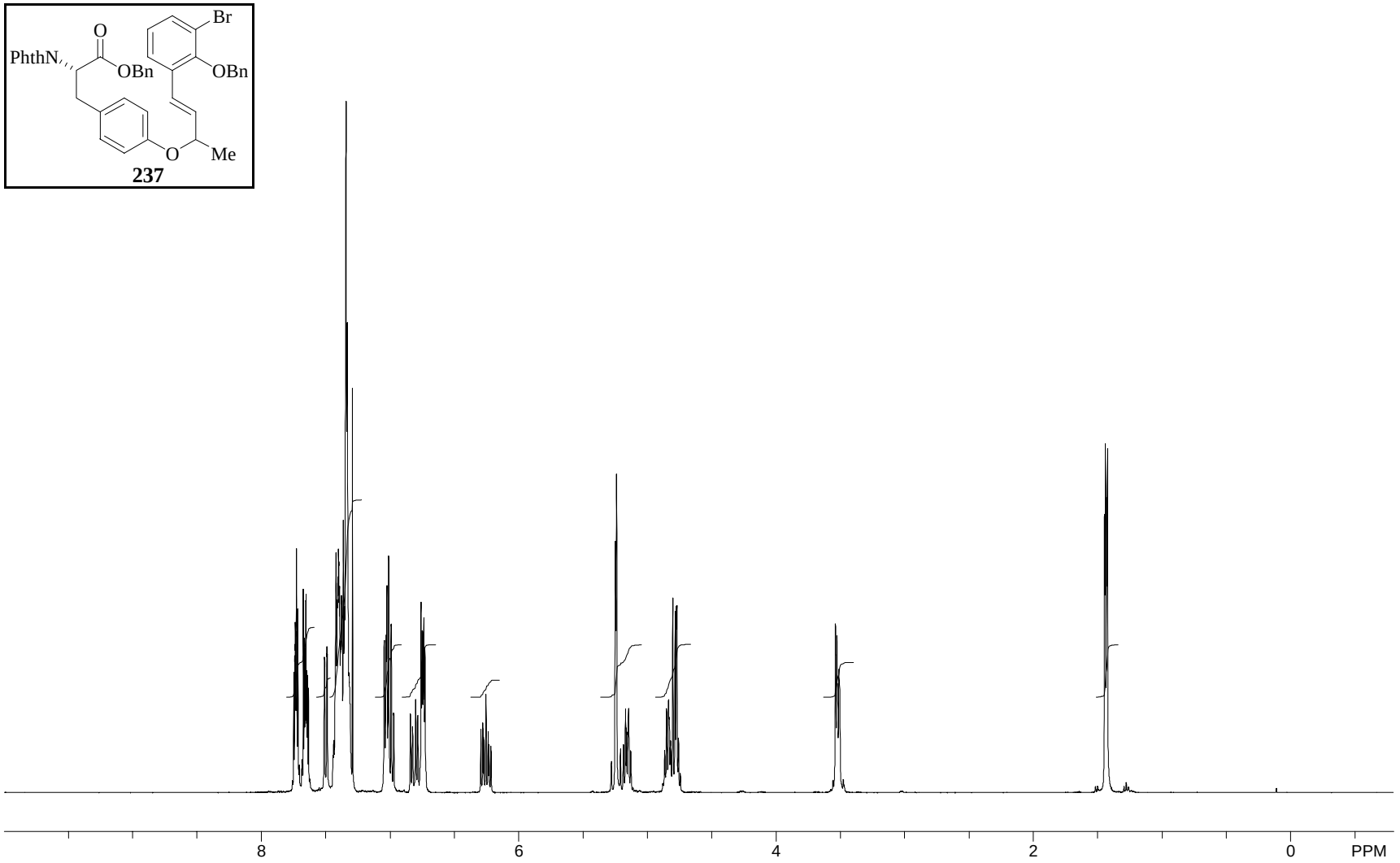


Figure A.2.31 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **237**.

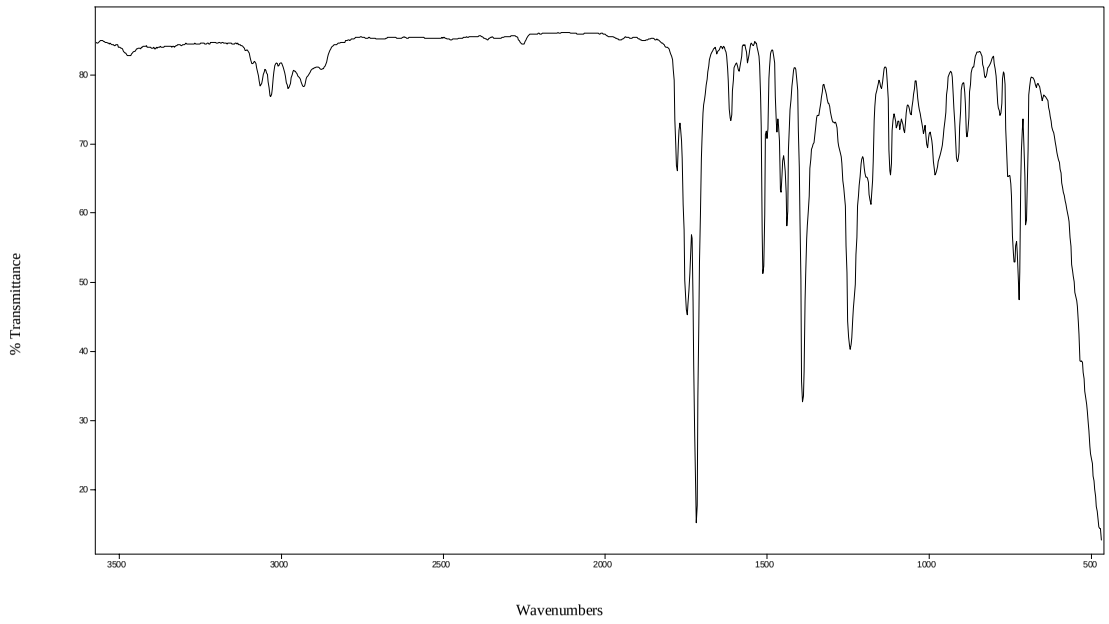


Figure A.2.32 FTIR Spectrum (thin film/NaCl) of Compound **237**.

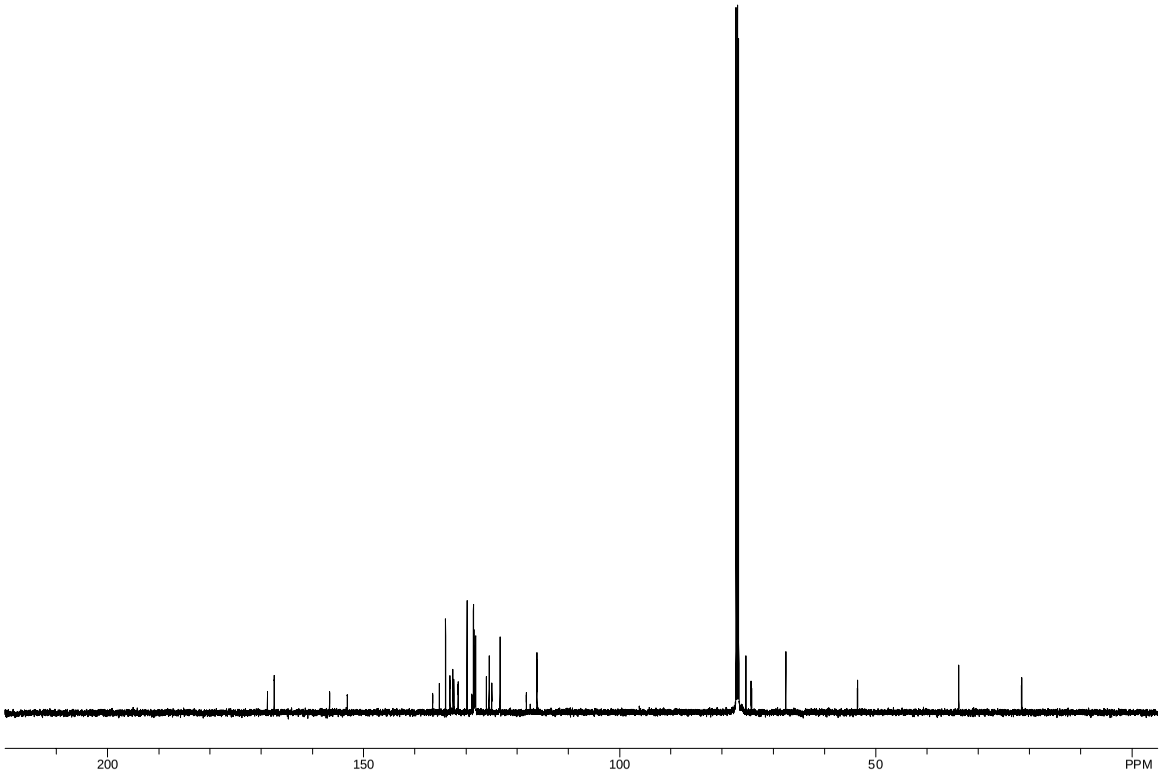


Figure A.2.33 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **237**.

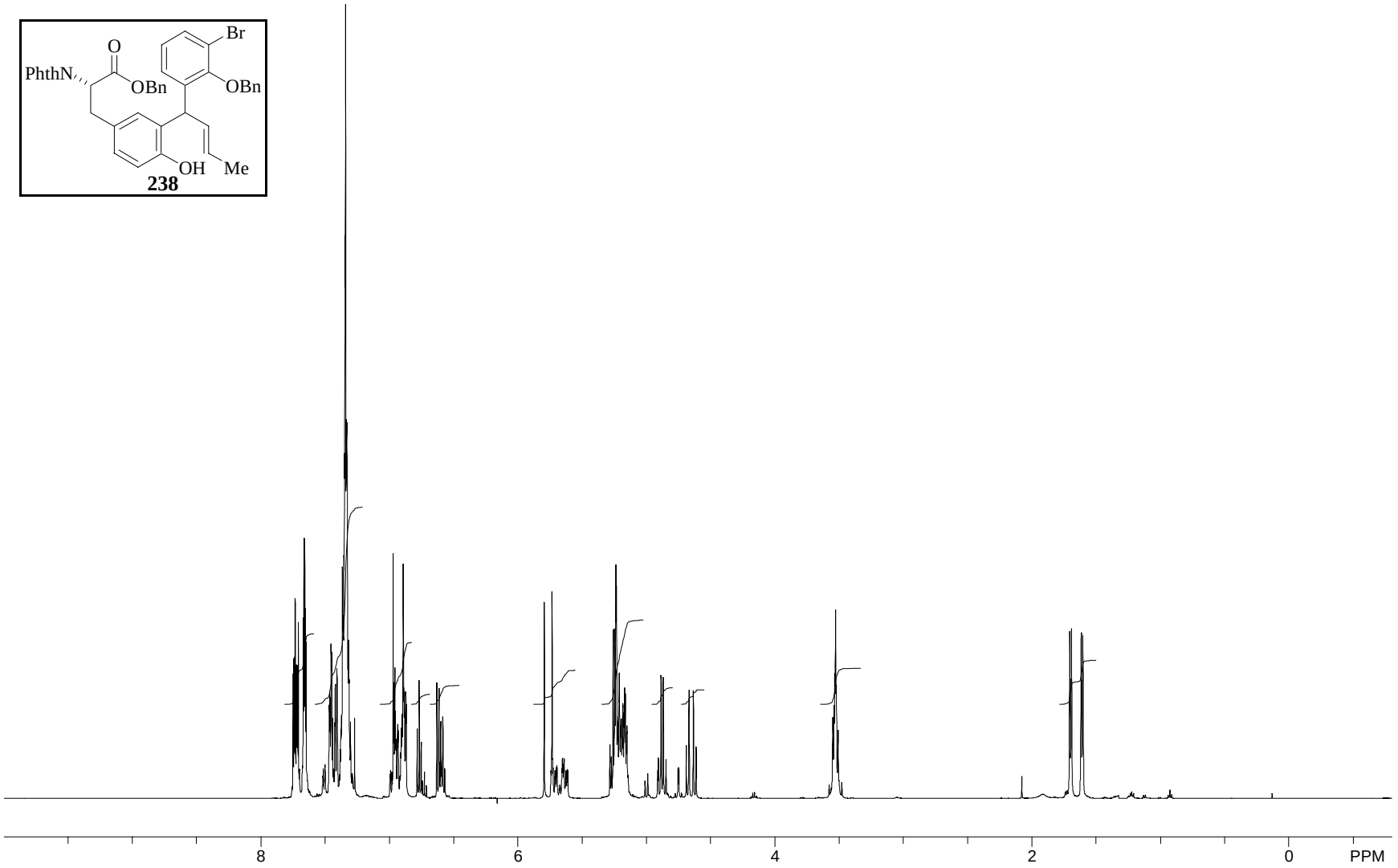


Figure A.2.34 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **238**.

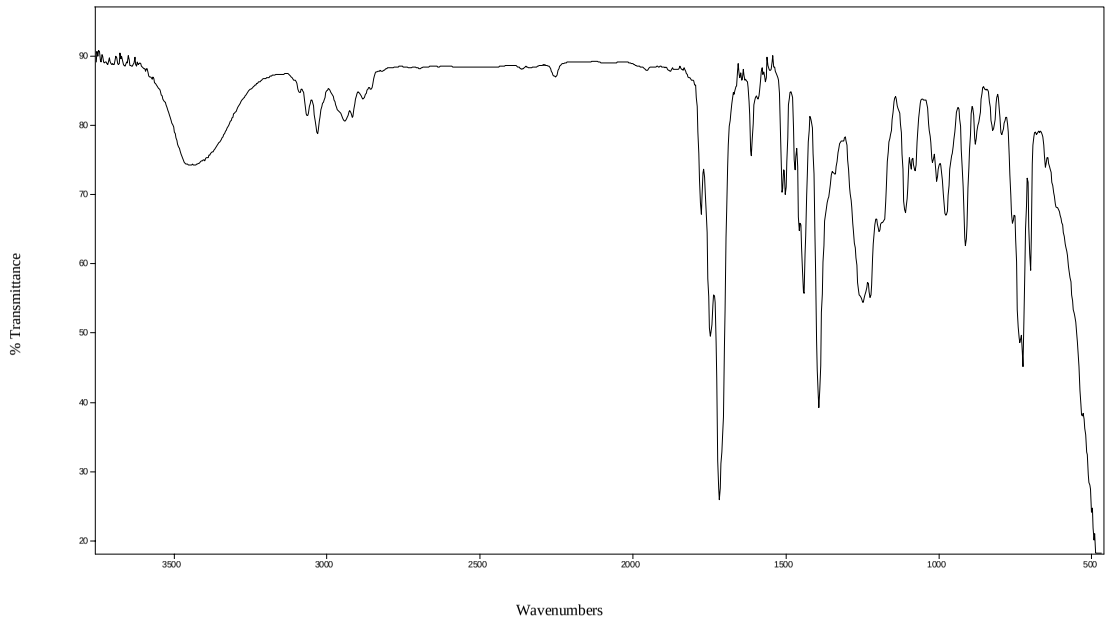


Figure A.2.35 FTIR Spectrum (thin film/NaCl) of Compound **238**.

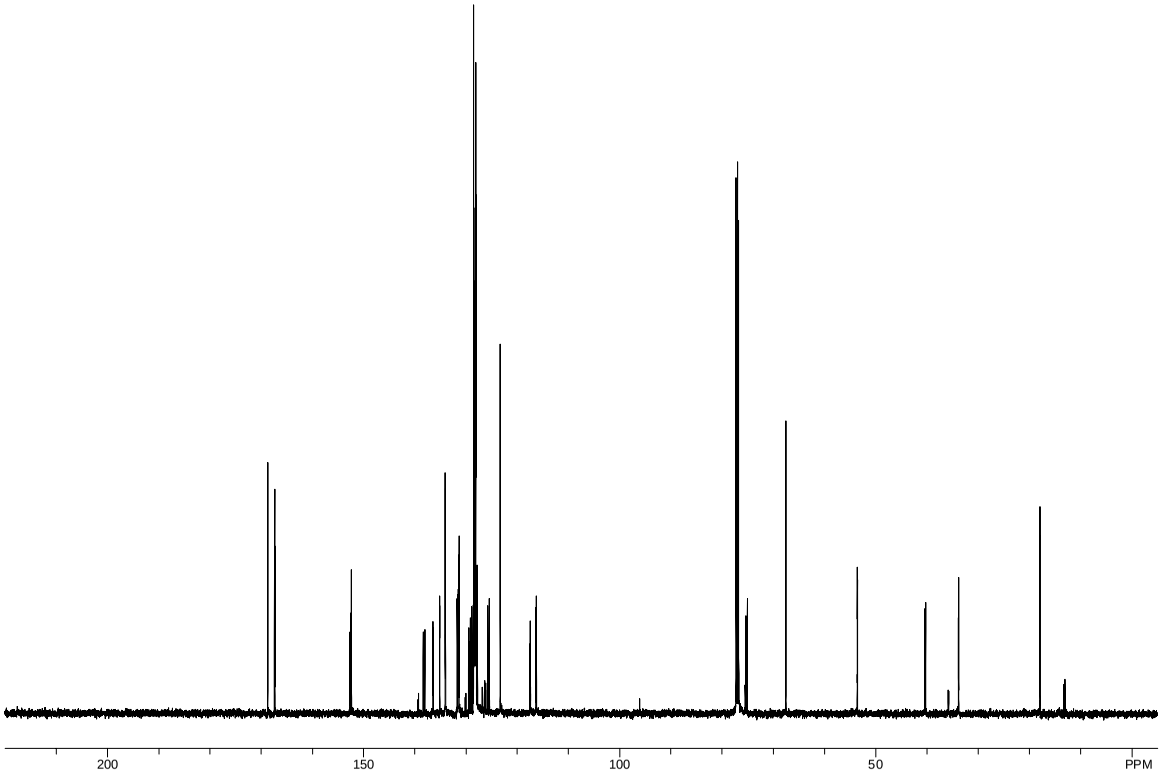


Figure A.2.36 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **238**.

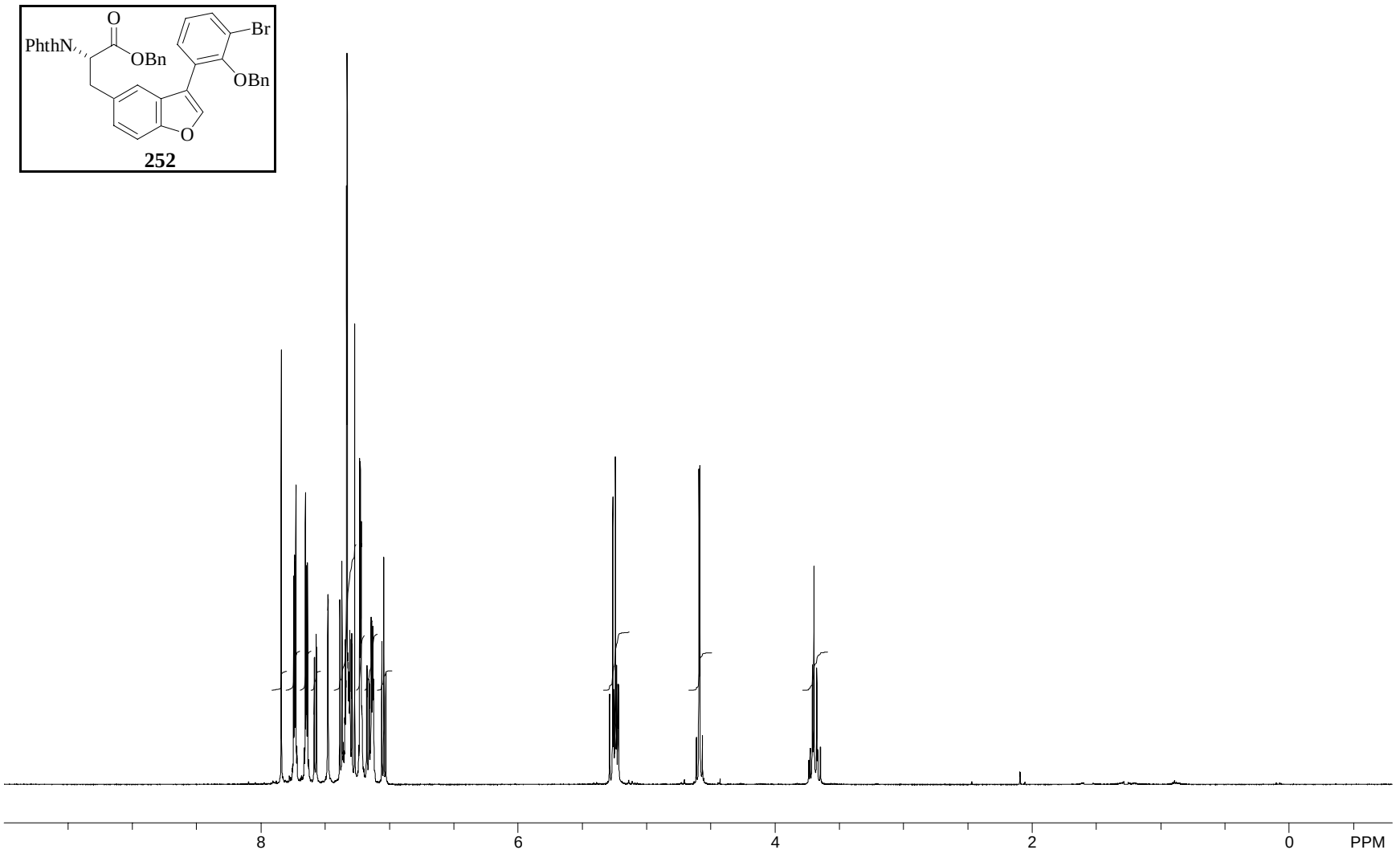


Figure A.2.37 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **252**.

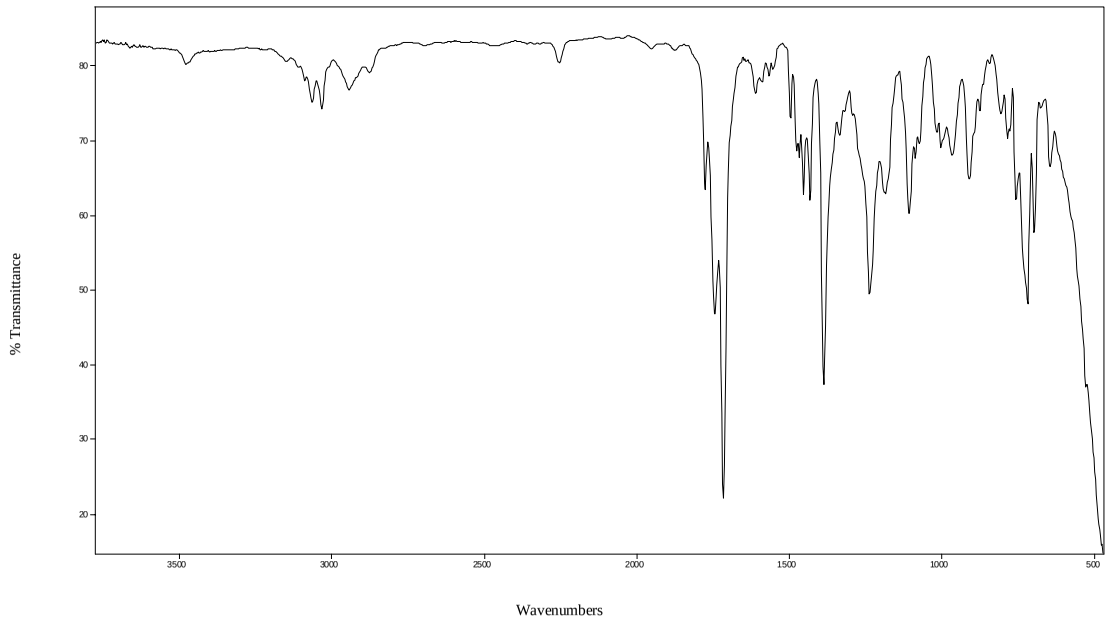


Figure A.2.38 FTIR Spectrum (thin film/NaCl) of Compound **252**.

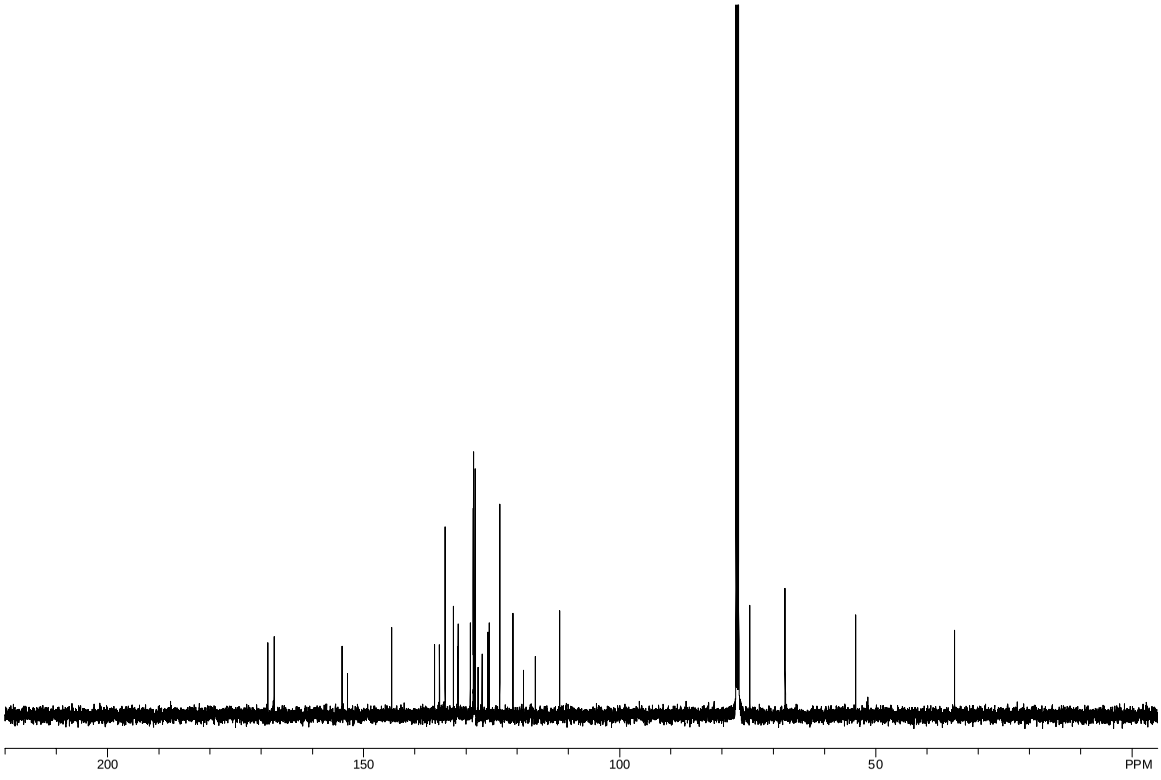


Figure A.2.39 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **252**.

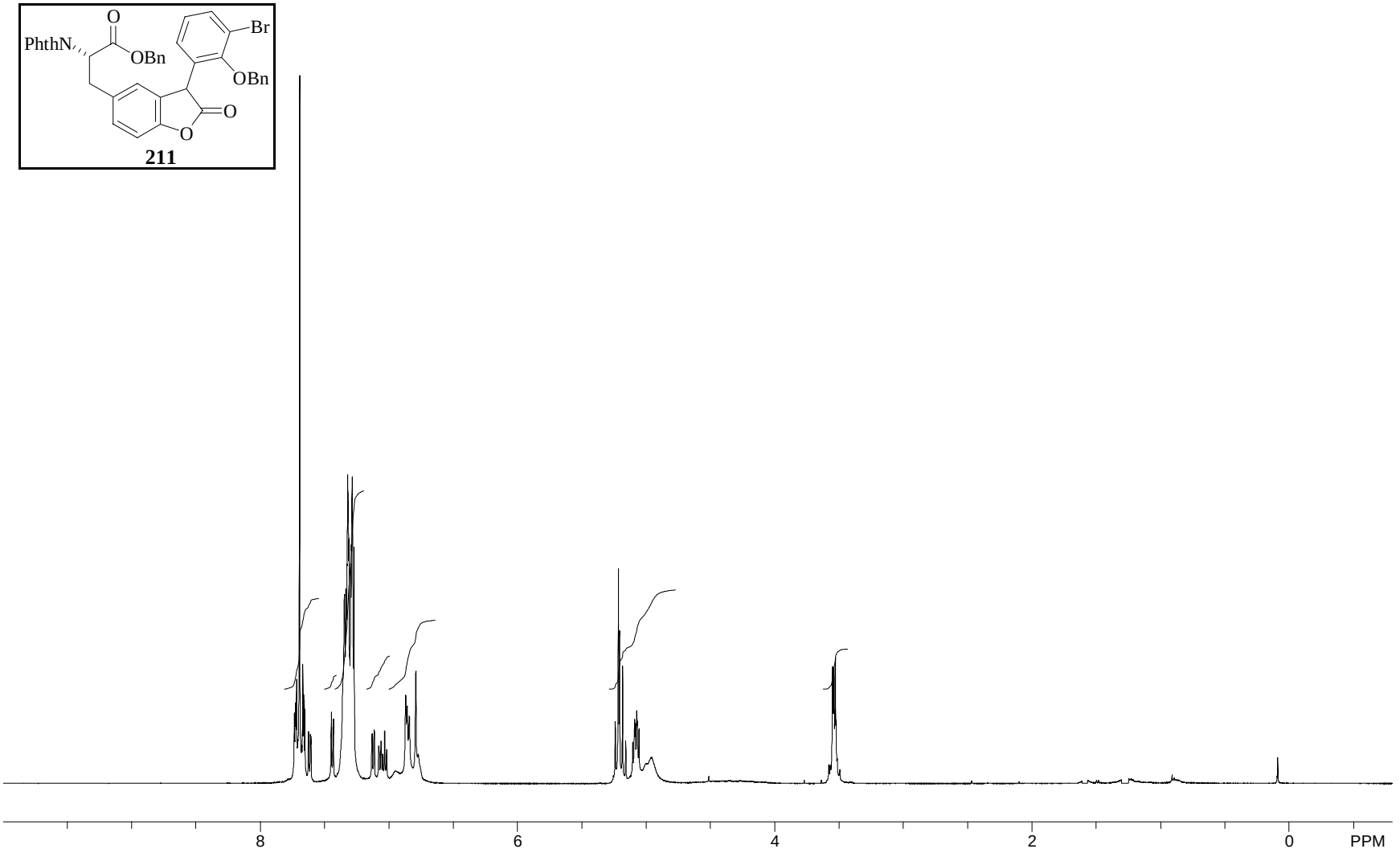


Figure A.2.40 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **211**.

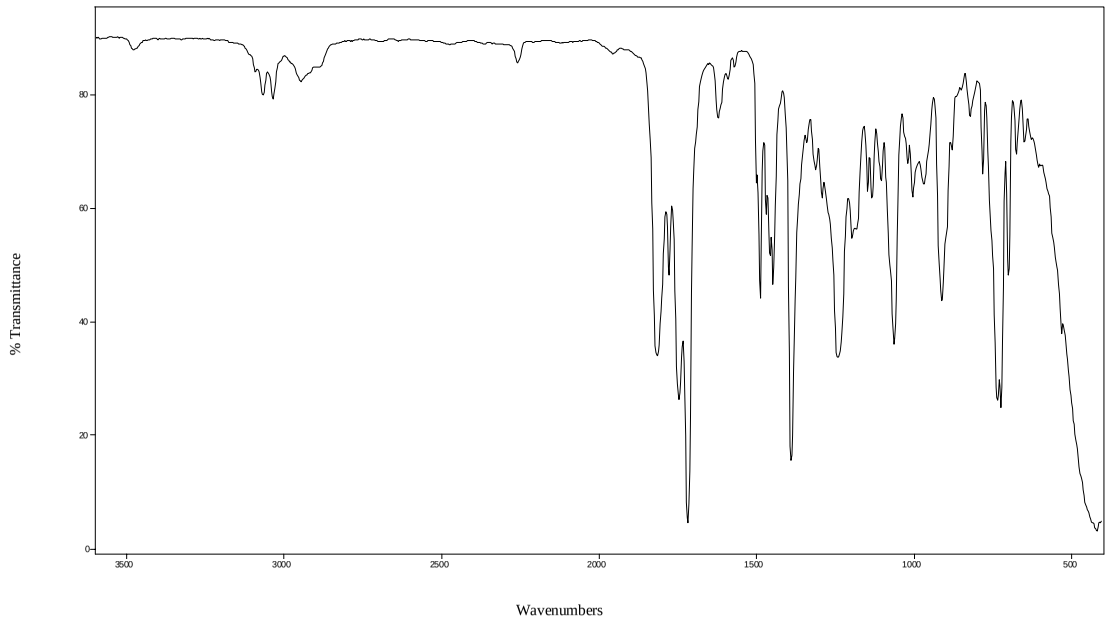


Figure A.2.41 FTIR Spectrum (thin film/NaCl) of Compound **211**.

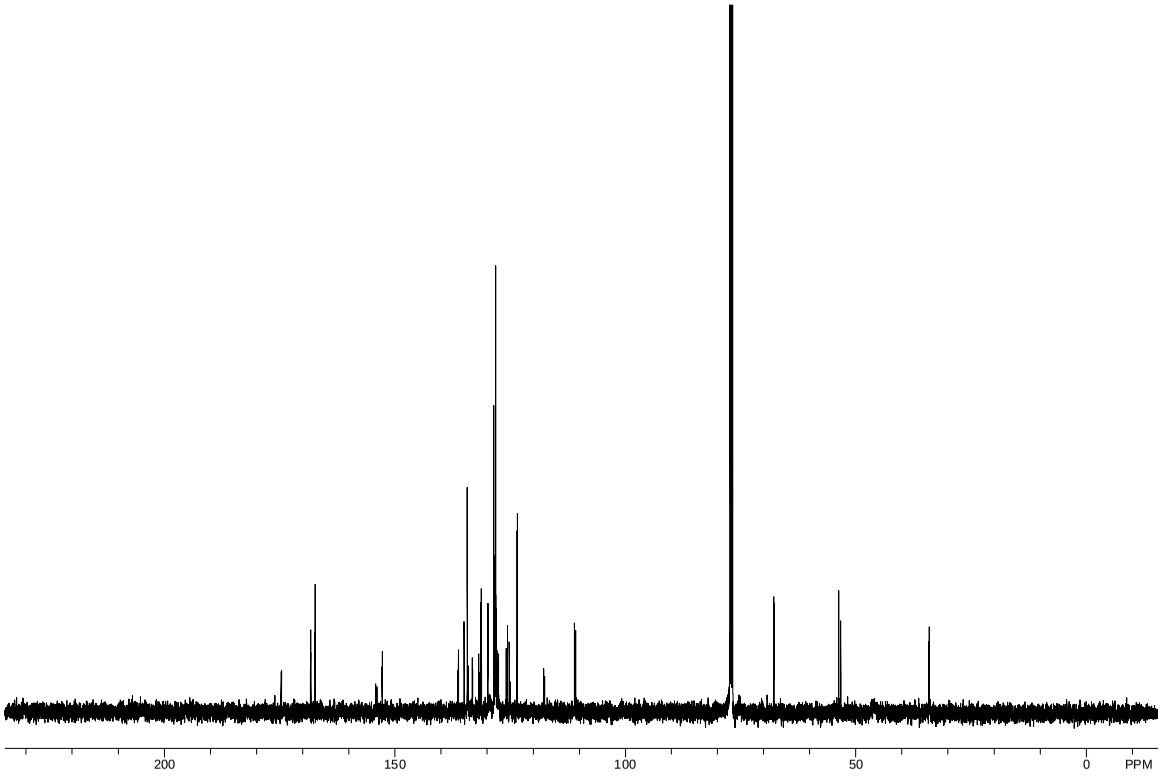


Figure A.2.42 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **211**.

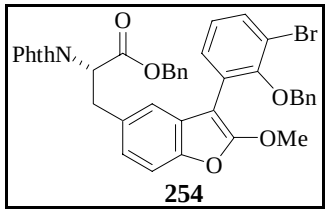


Figure A.2.43 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **254**.

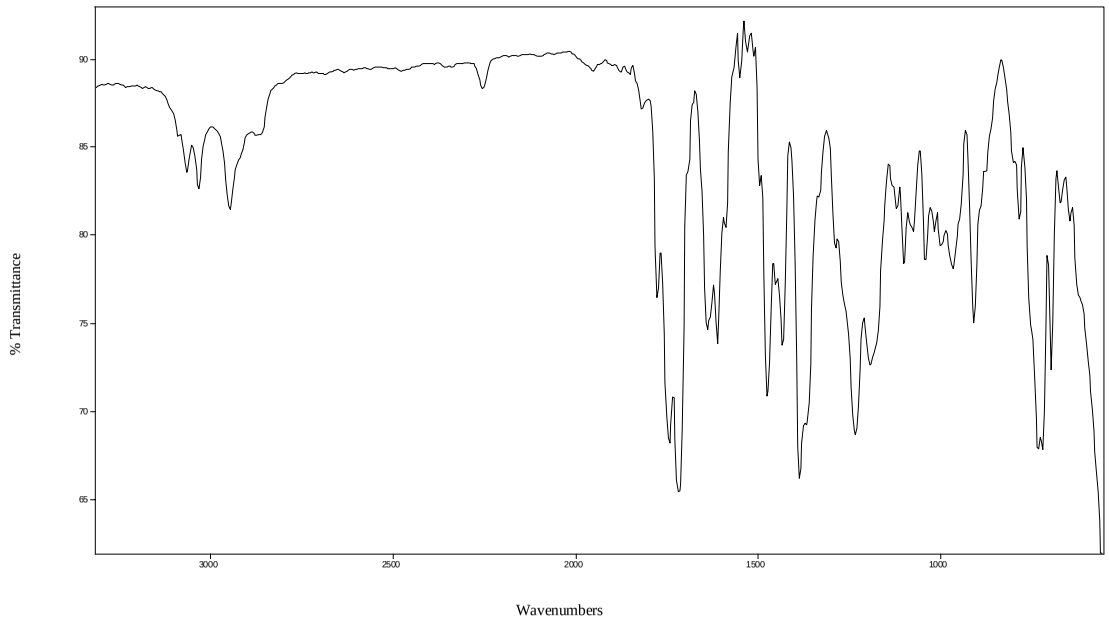


Figure A.2.44 FTIR Spectrum (thin film/NaCl) of Compound **254**.

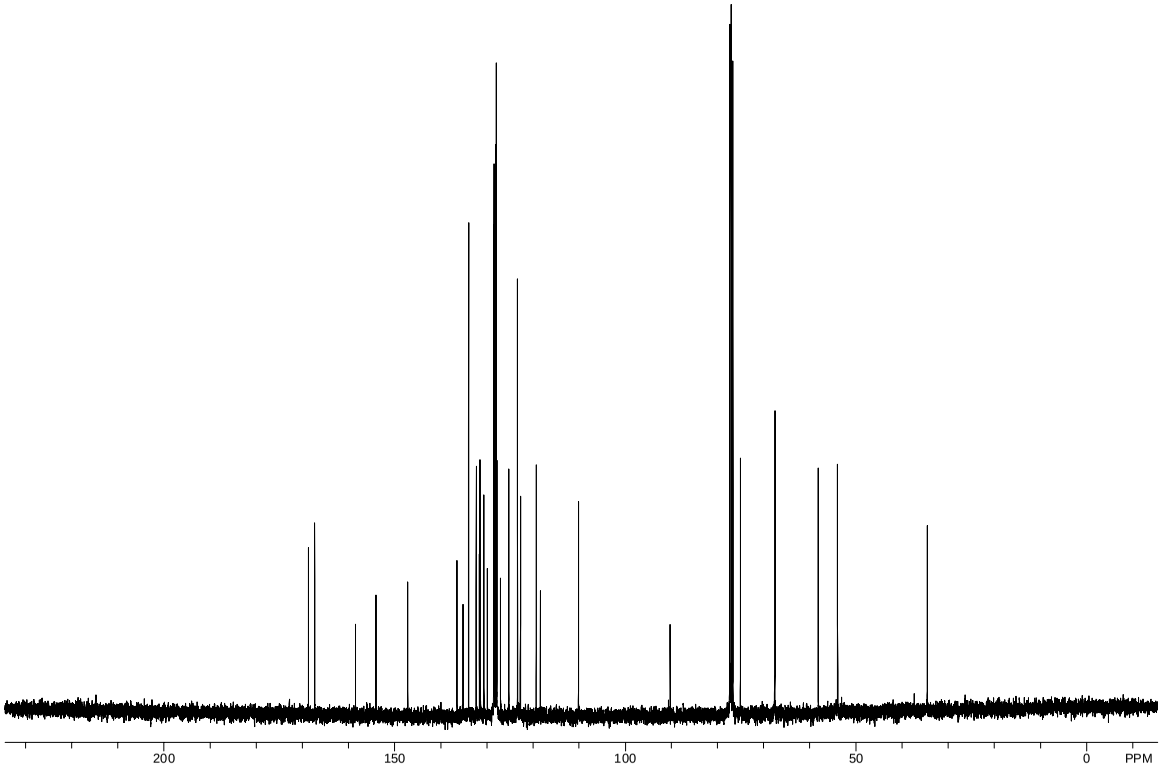


Figure A.2.45 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **254**.

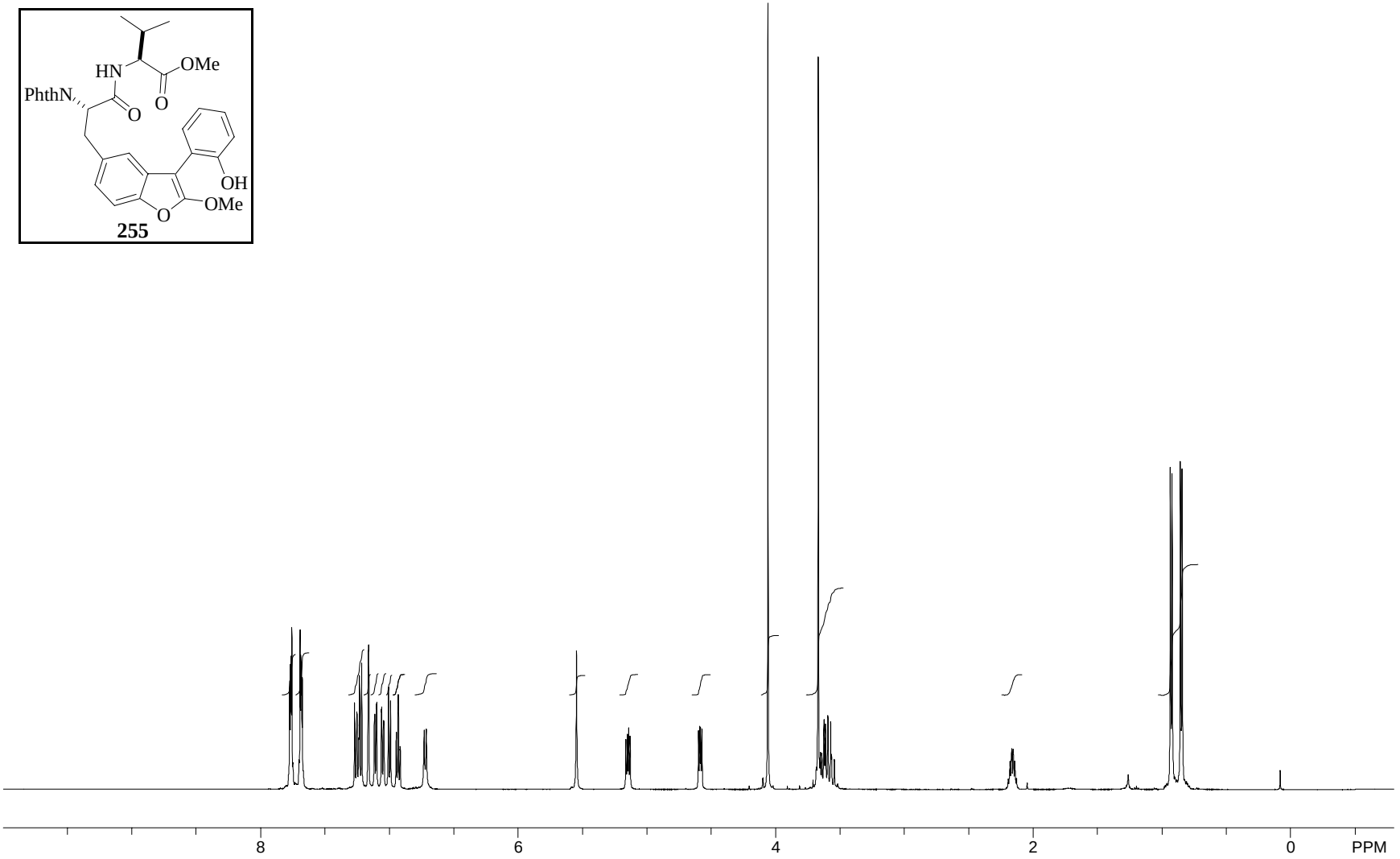


Figure A.2.46 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **255**.

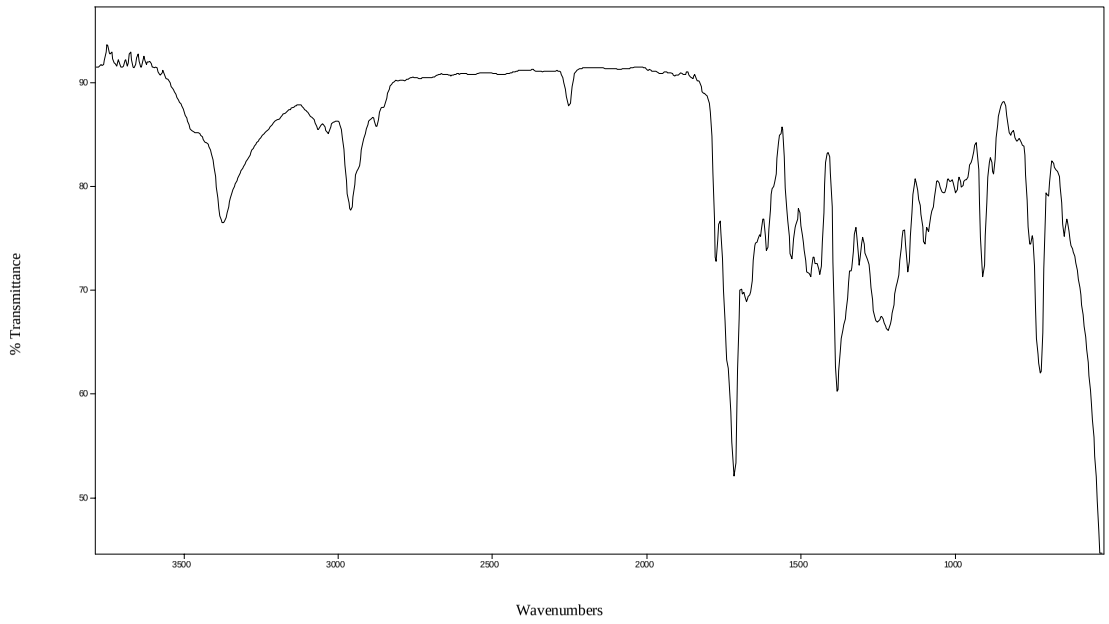


Figure A.2.47 FTIR Spectrum (thin film/NaCl) of Compound **255**.

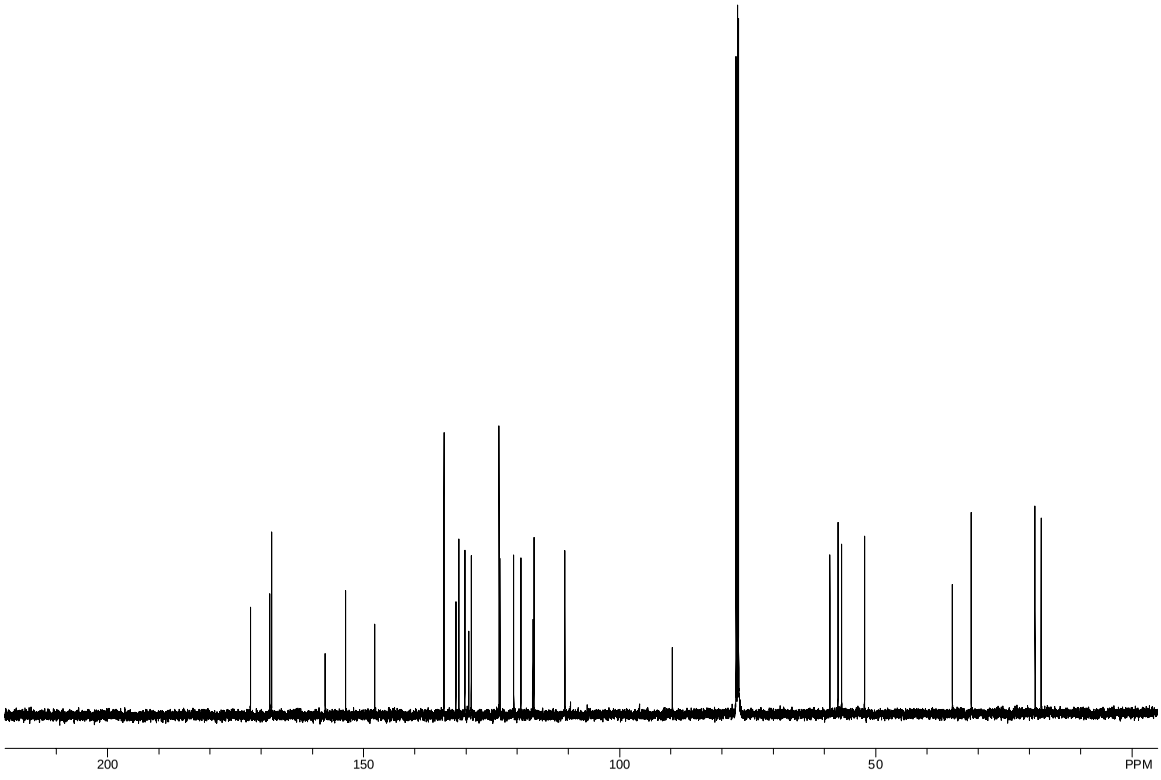


Figure A.2.48 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **255.**

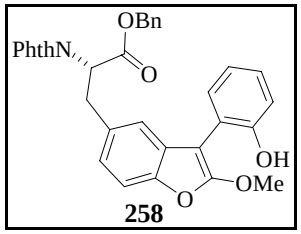


Figure A.2.49 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **258**.

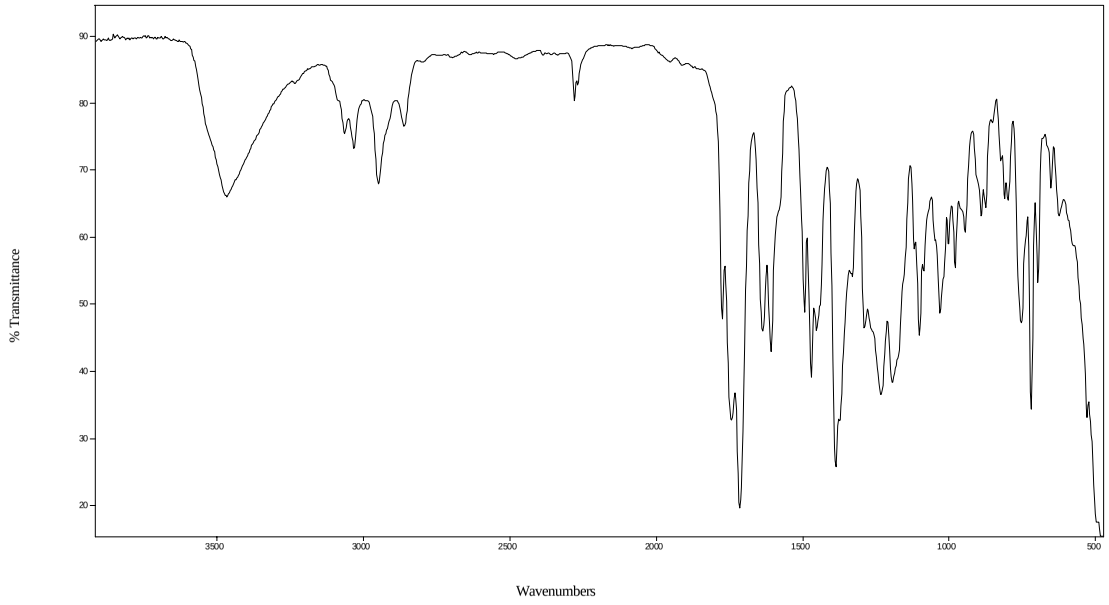


Figure A.2.50 FTIR Spectrum (thin film/NaCl) of Compound **258**.

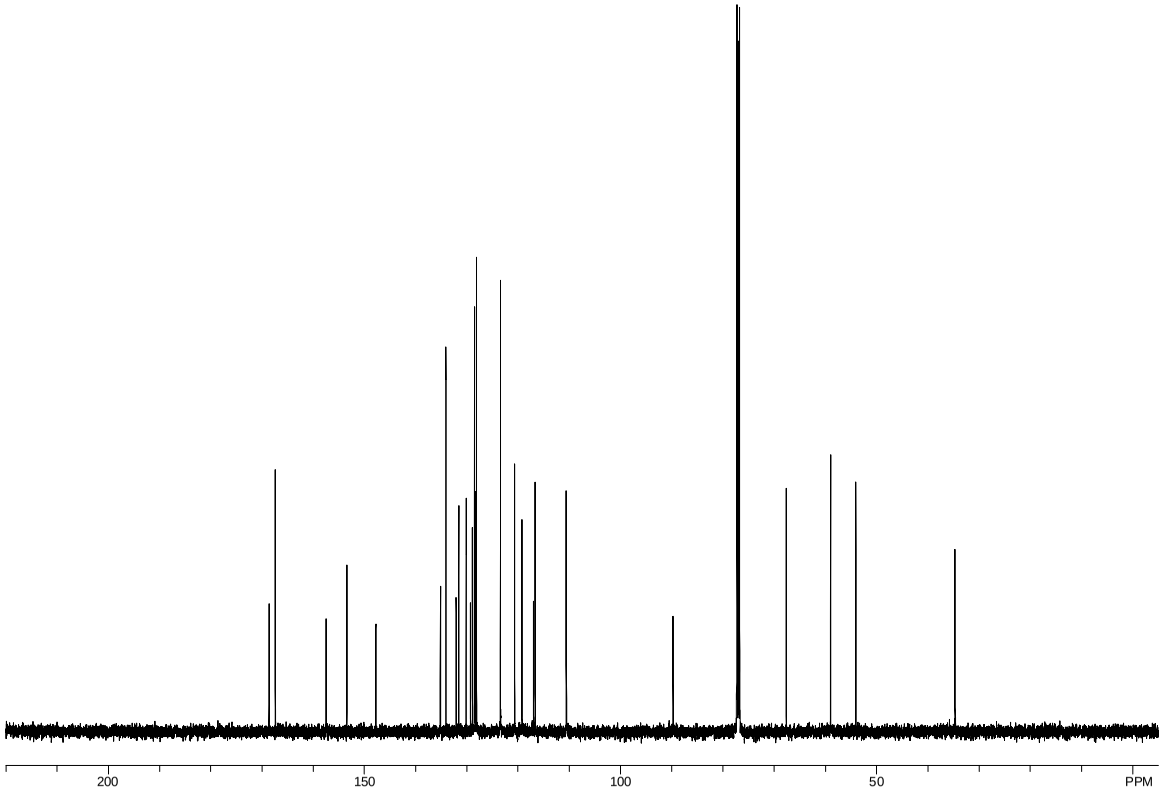


Figure A.2.51 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **258.**

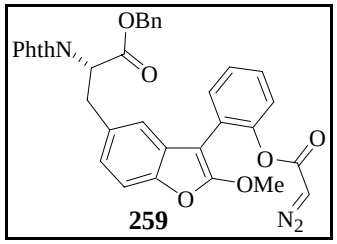


Figure A.2.52 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **259**.

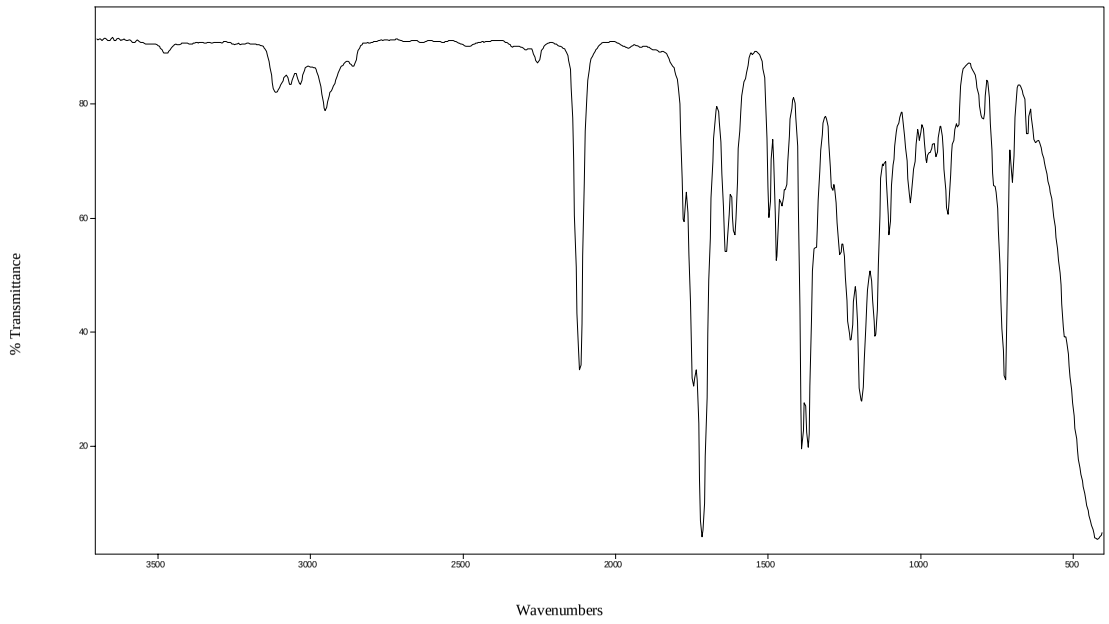


Figure A.2.53 FTIR Spectrum (thin film/NaCl) of Compound **259**.

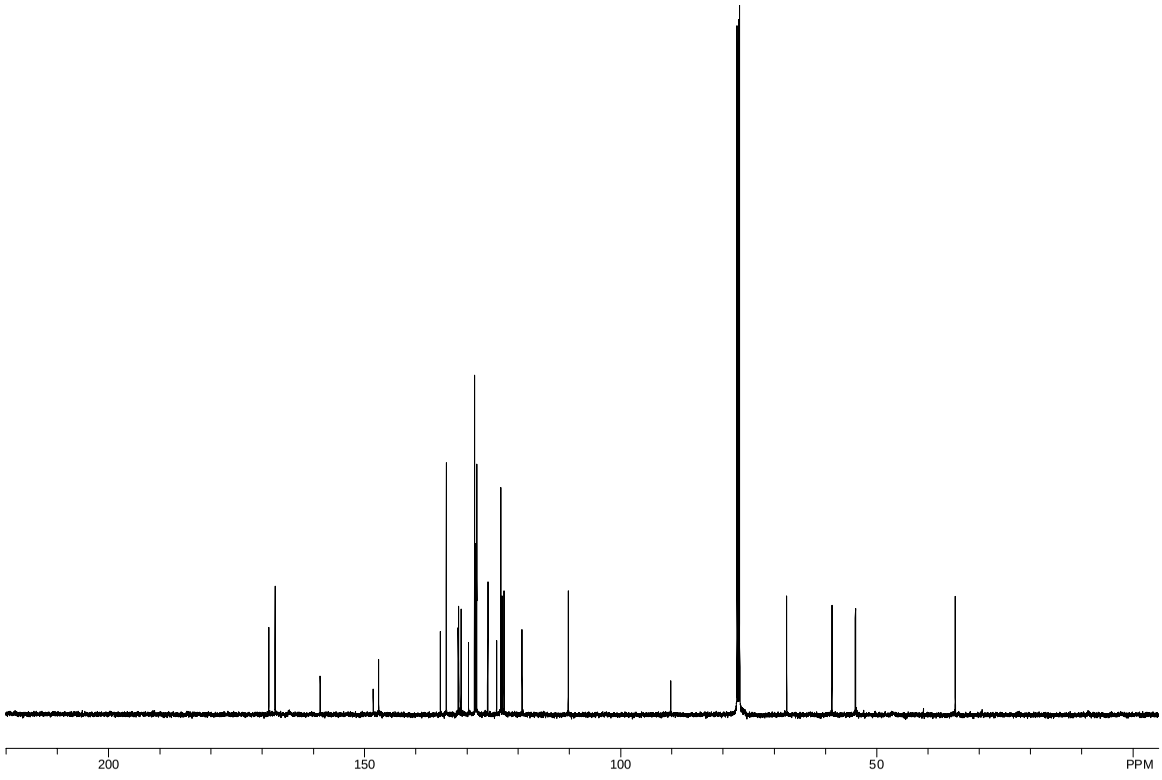


Figure A.2.54 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **259**.

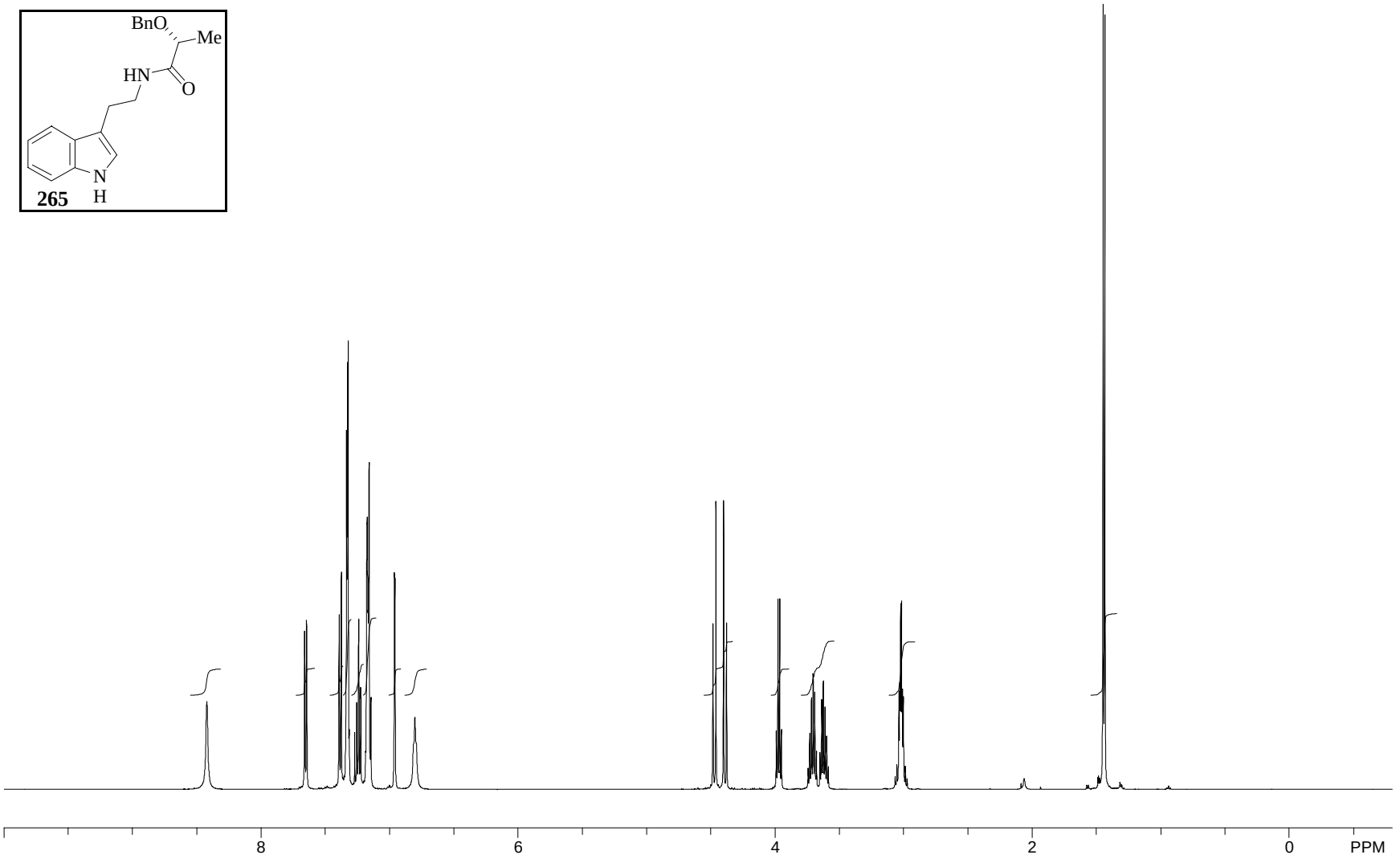


Figure A.2.55 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **265**.

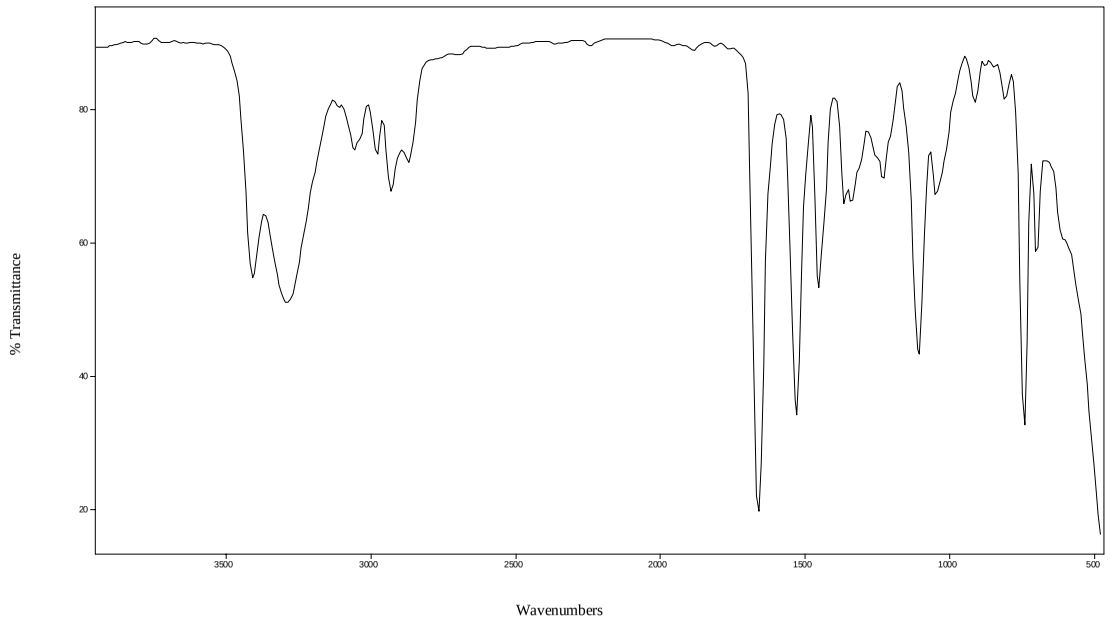


Figure A.2.56 FTIR Spectrum (thin film/NaCl) of Compound **265**.

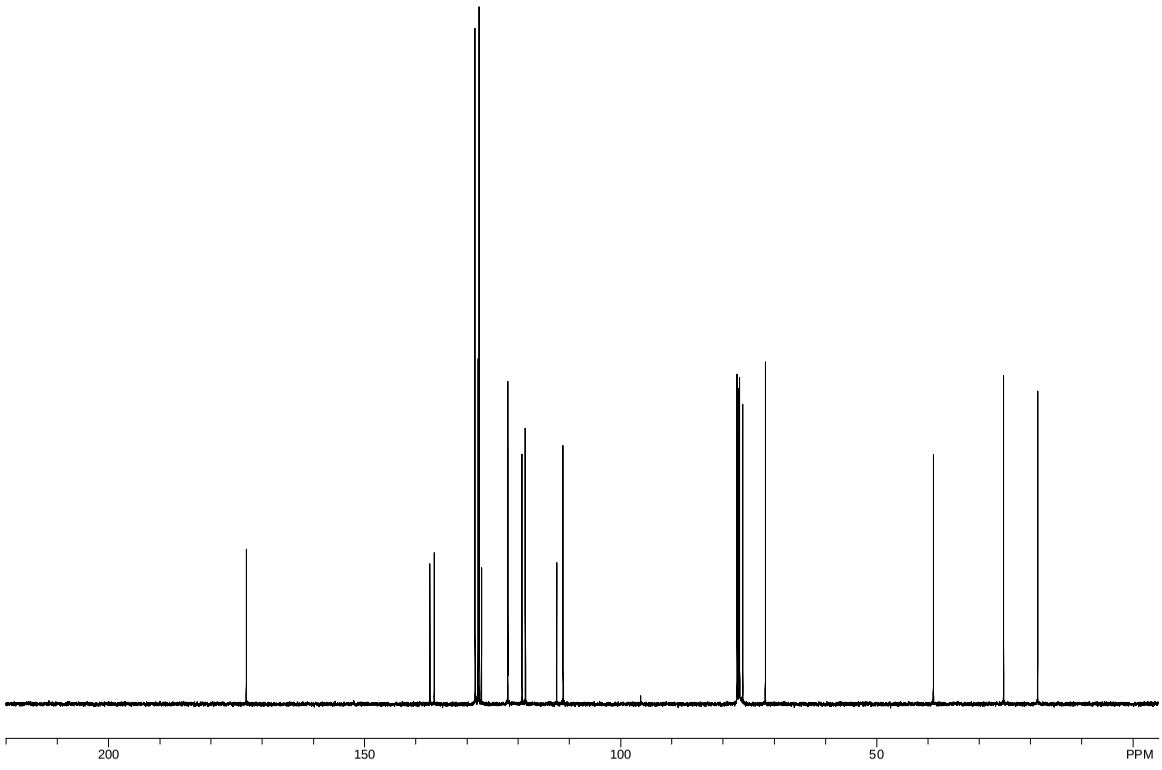


Figure A.2.57 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **265**.

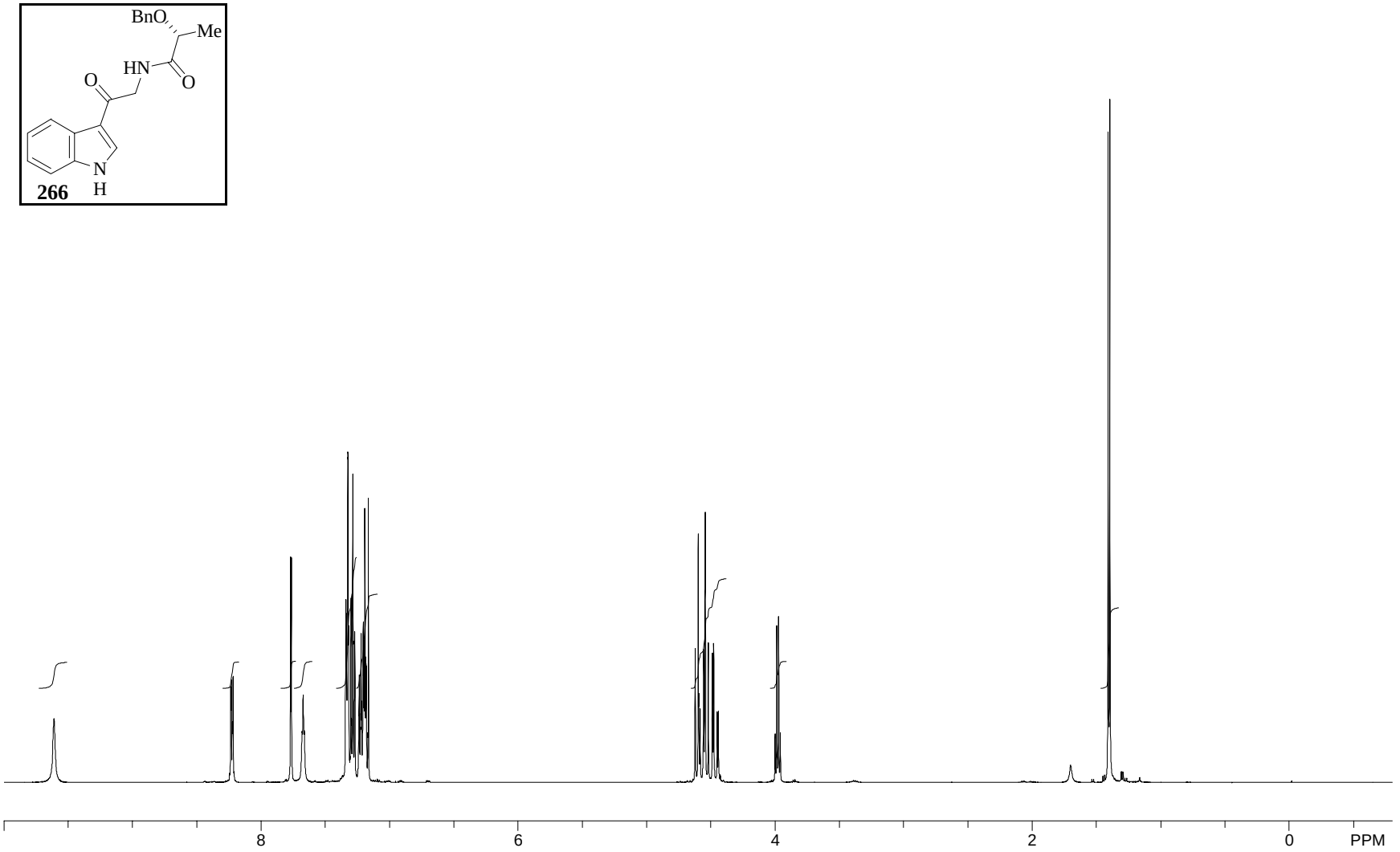


Figure A.2.58 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **266**.

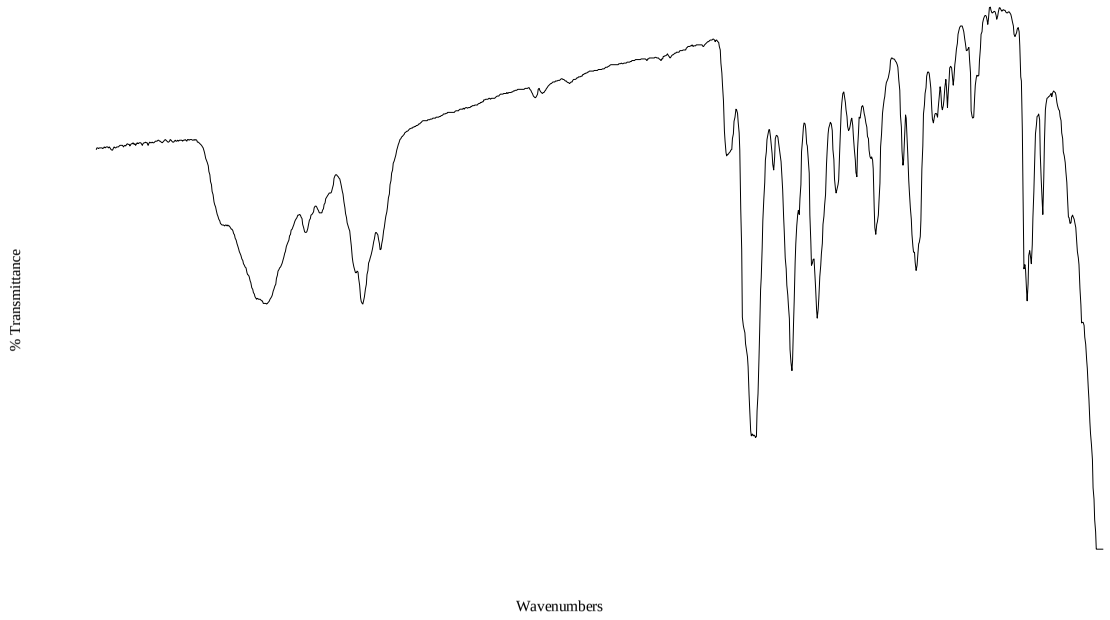


Figure A.2.59 FTIR Spectrum (thin film/NaCl) of Compound **266**.

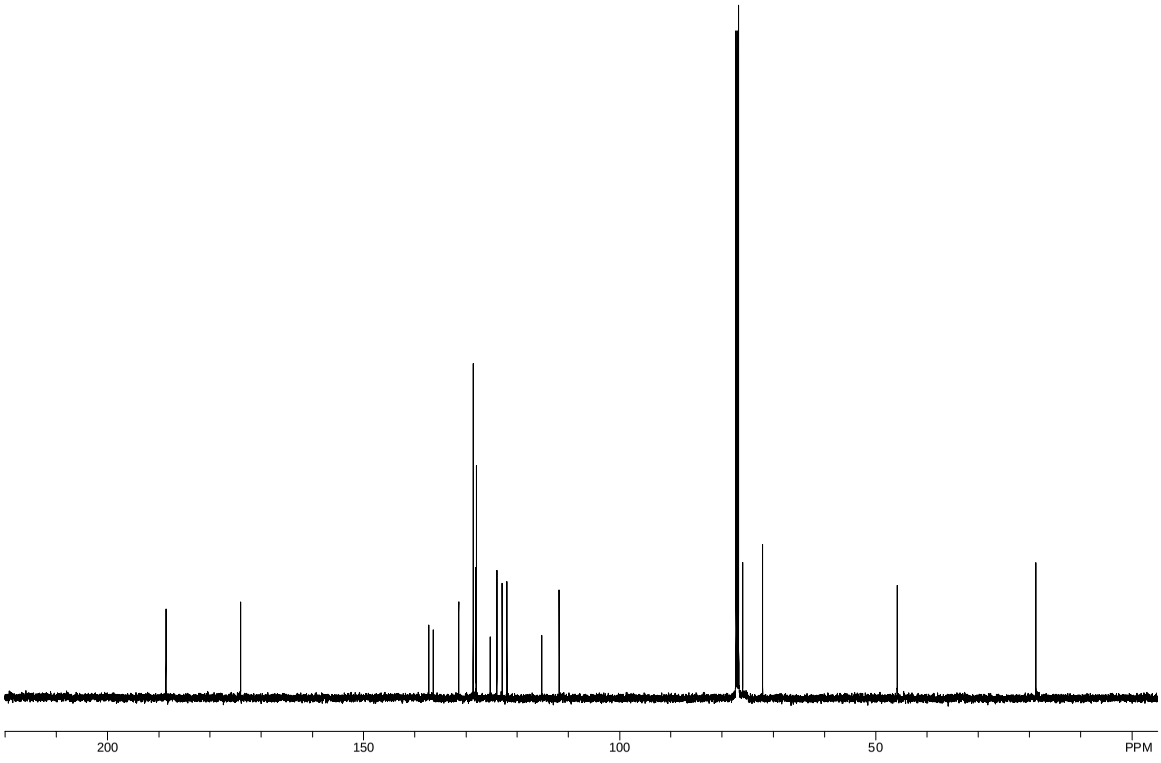


Figure A.2.60 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **266**.

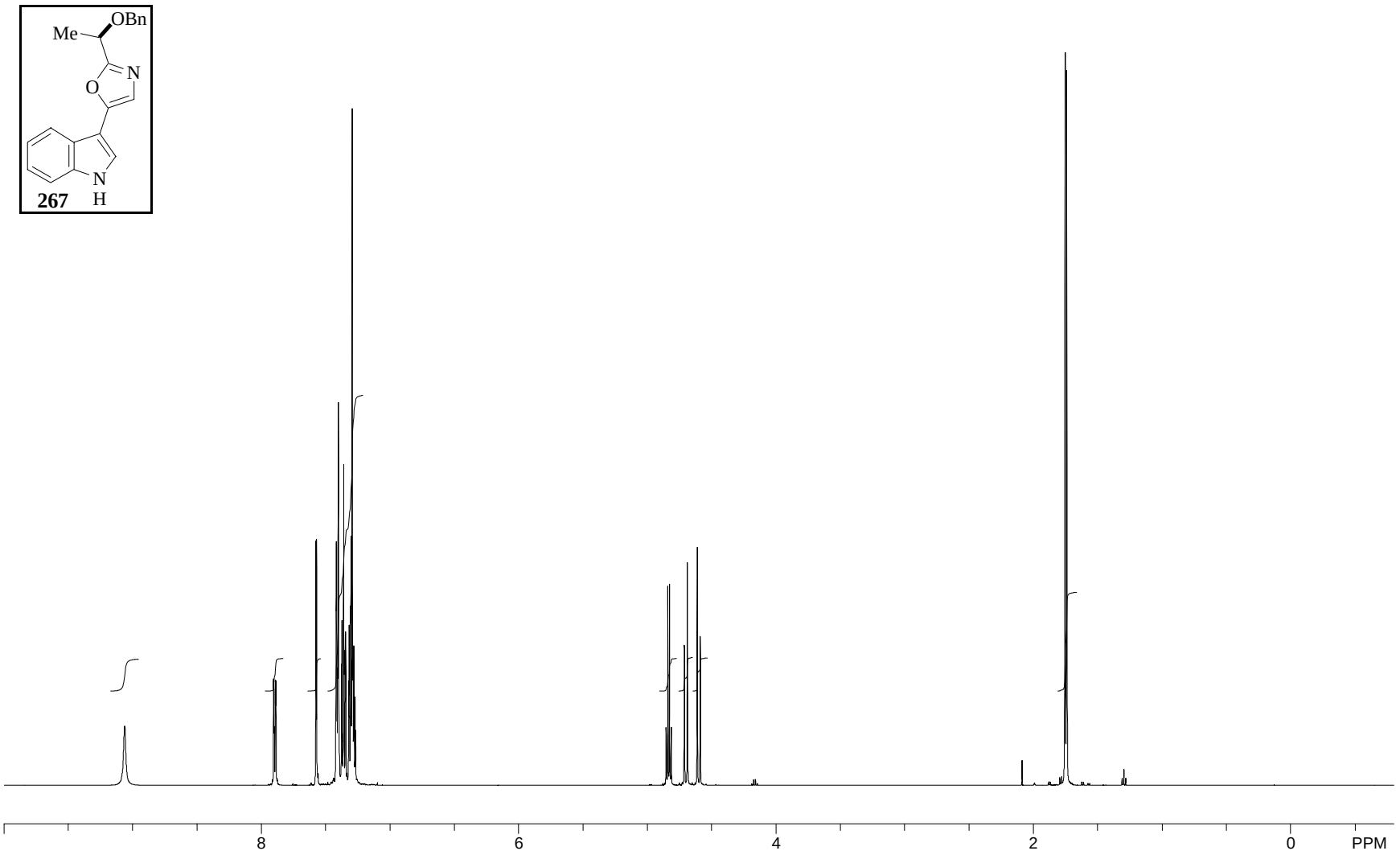


Figure A.2.61 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **267**.

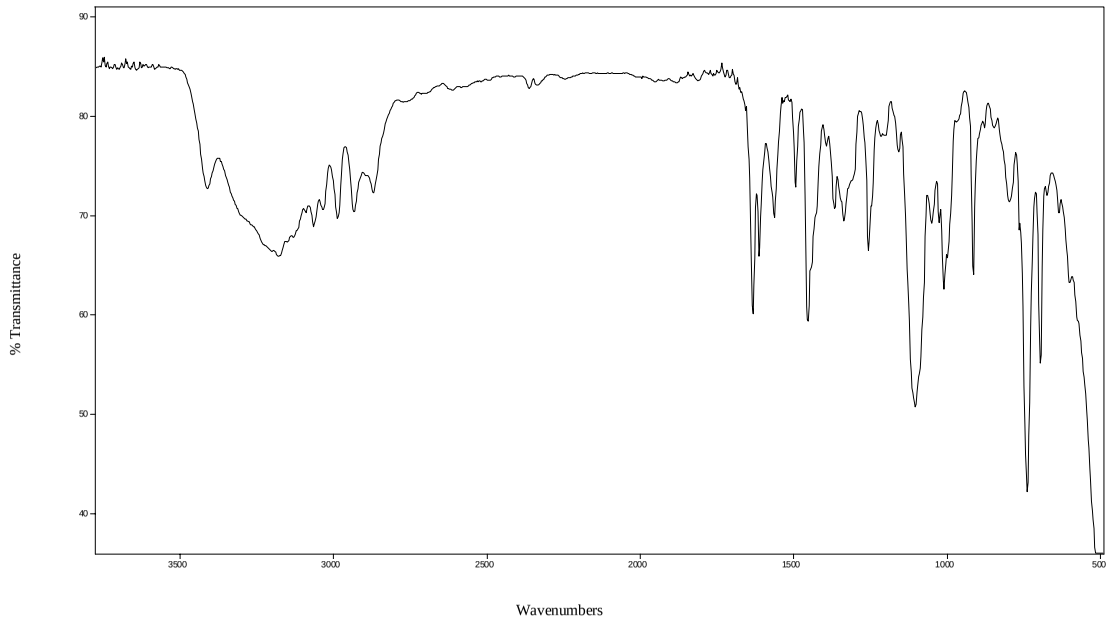


Figure A.2.62 FTIR Spectrum (thin film/NaCl) of Compound **267**.

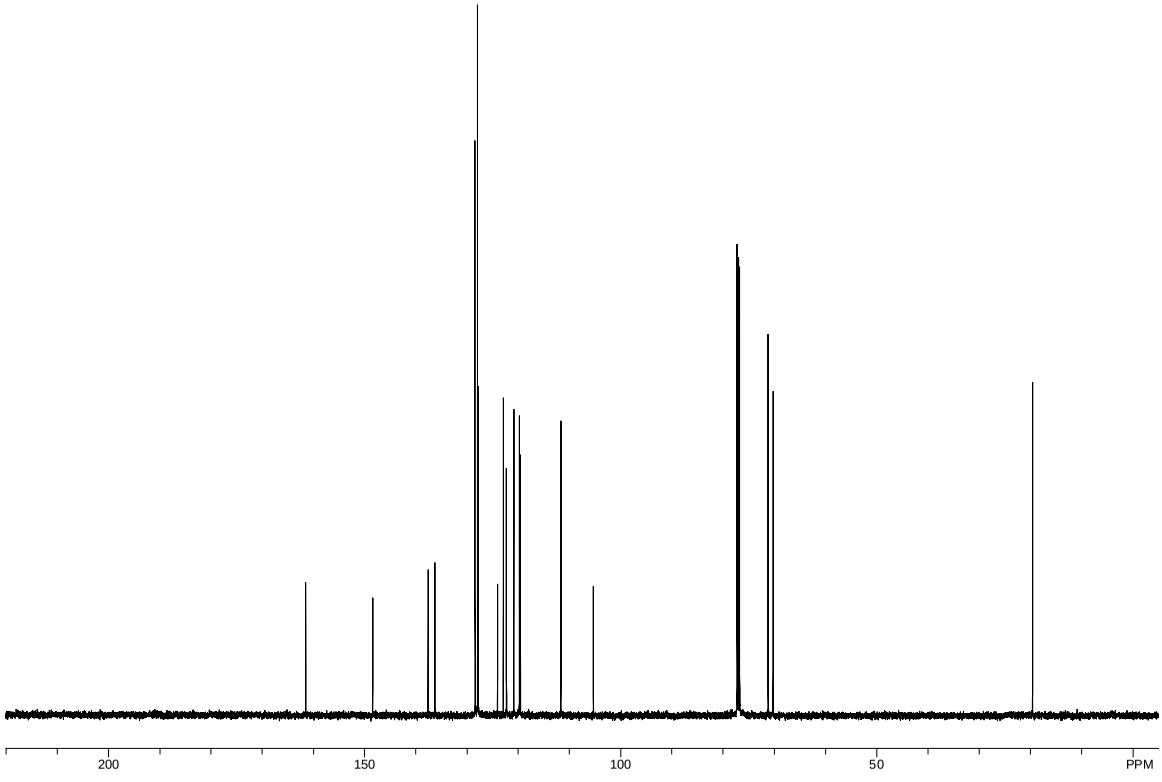


Figure A.2.63 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **267**.

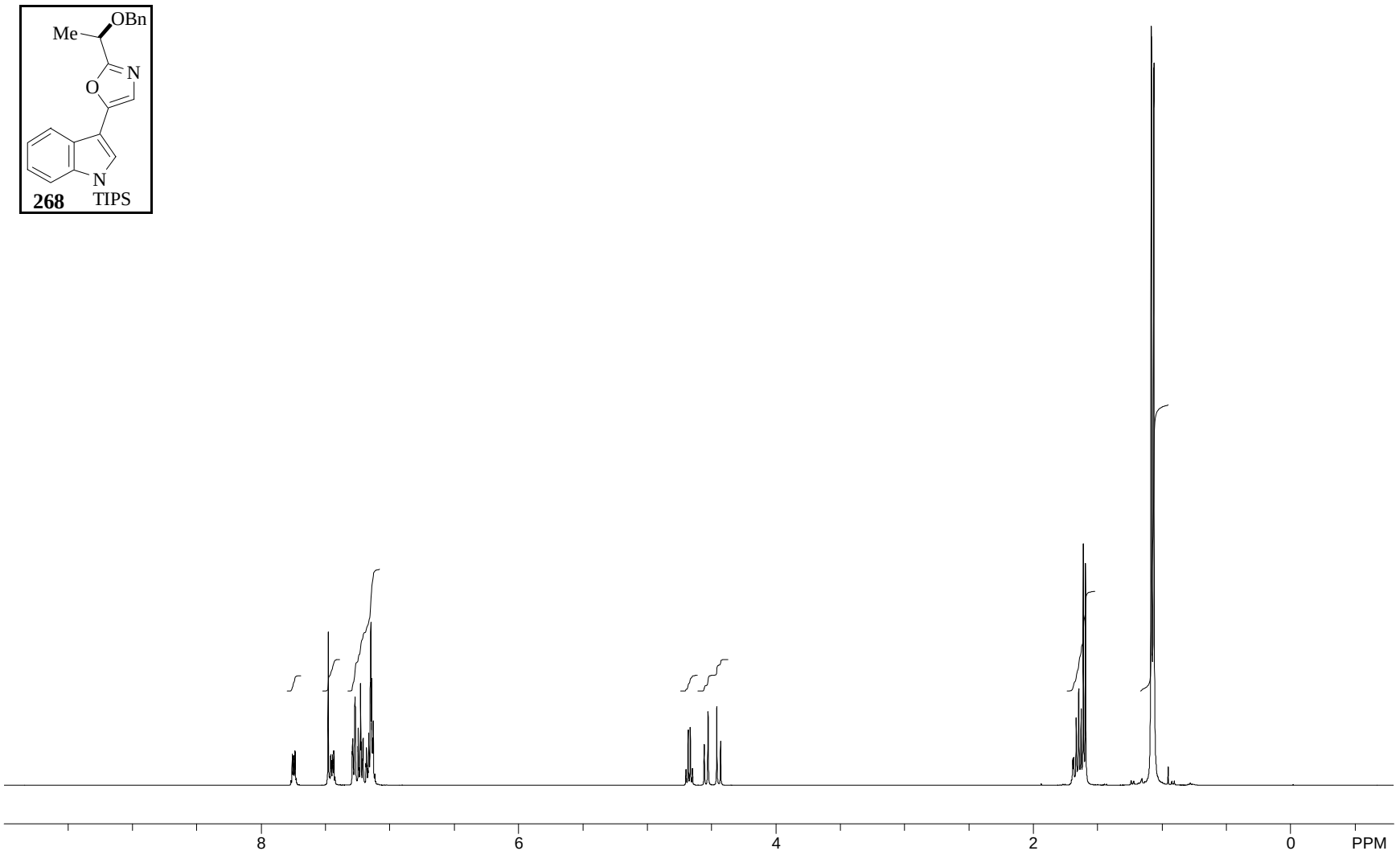


Figure A.2.64 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **268**.

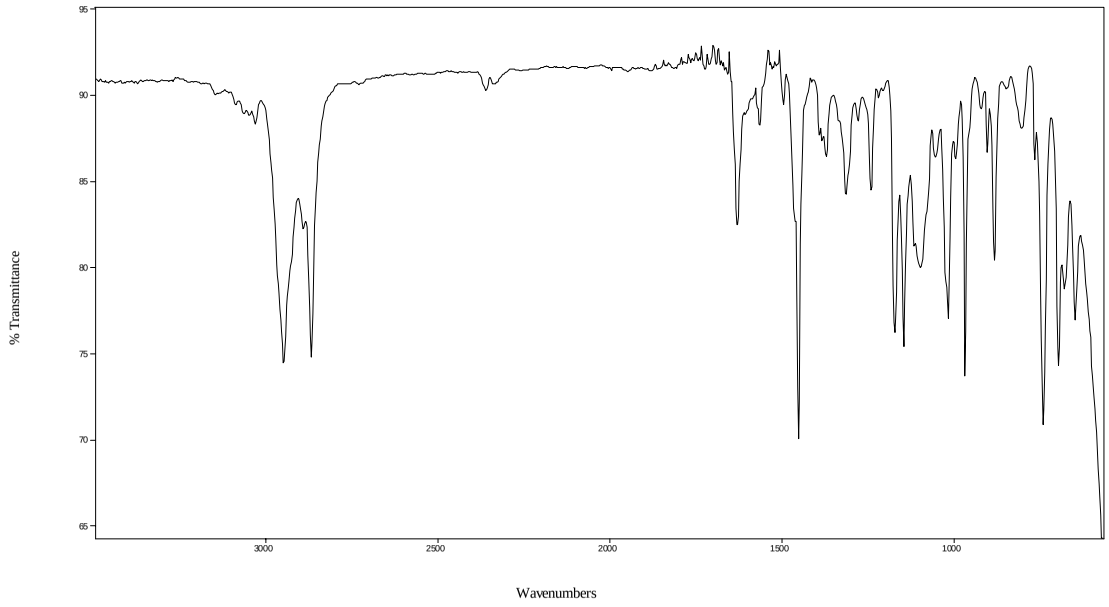


Figure A.2.65 FTIR Spectrum (thin film/NaCl) of Compound **268**.

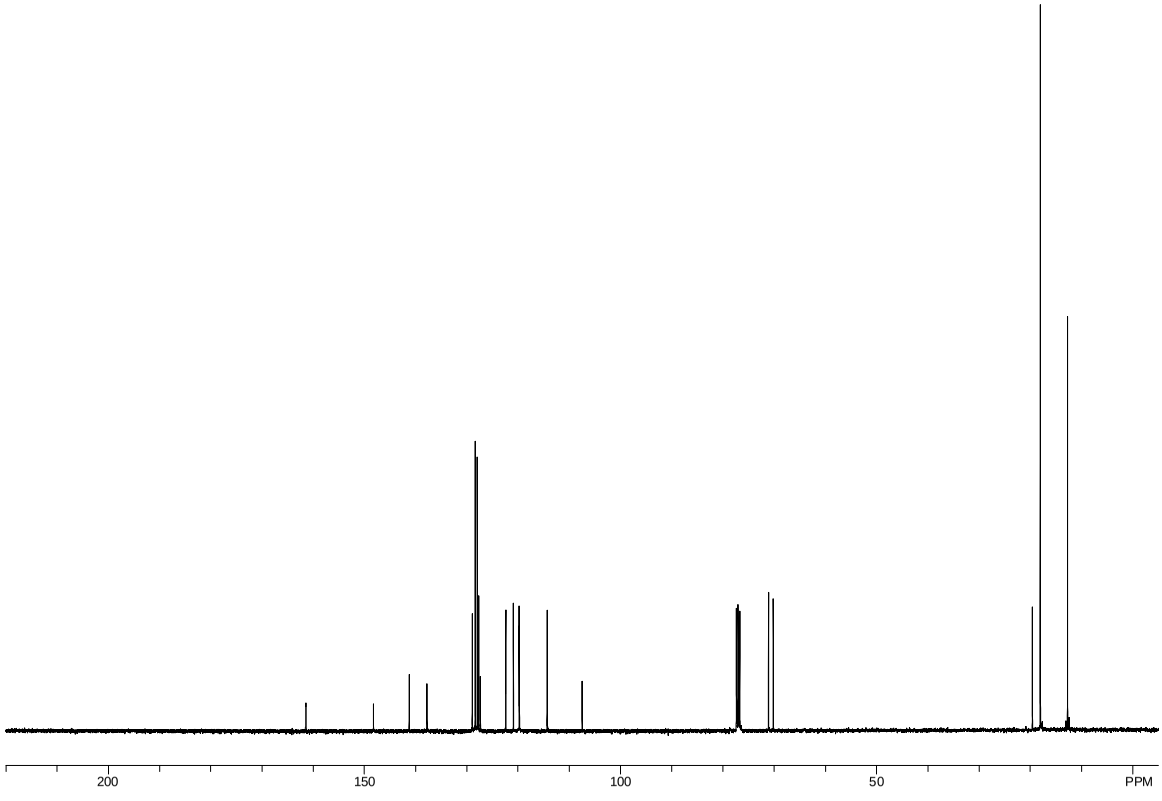


Figure A.2.66 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **268**.

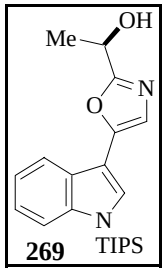


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Figure A.2.67 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **269**.

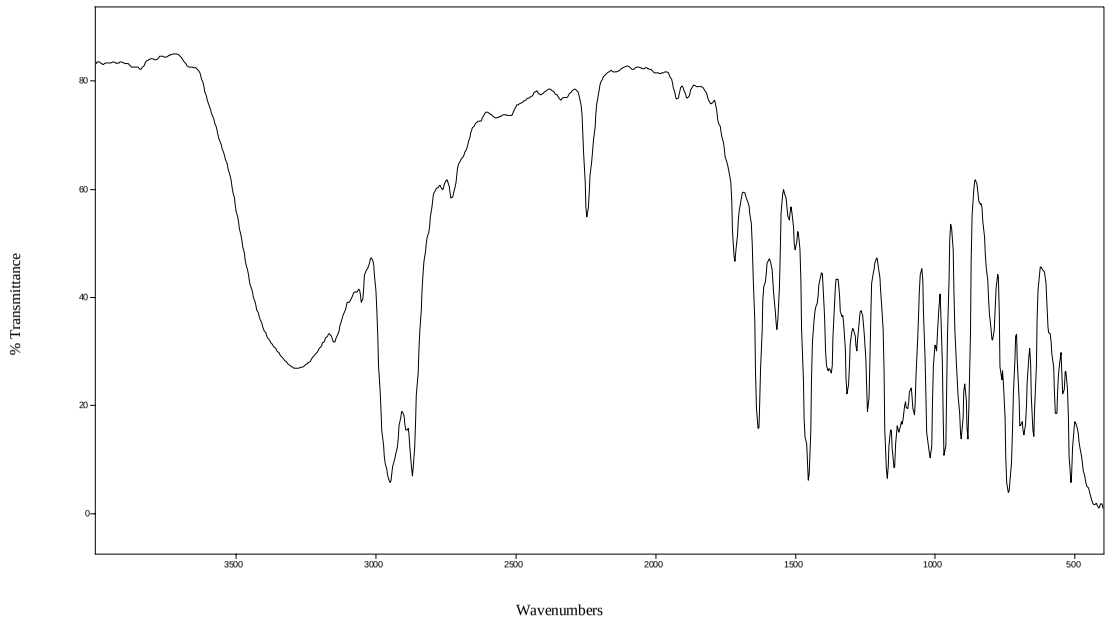


Figure A.2.68 FTIR Spectrum (thin film/NaCl) of Compound **269**.

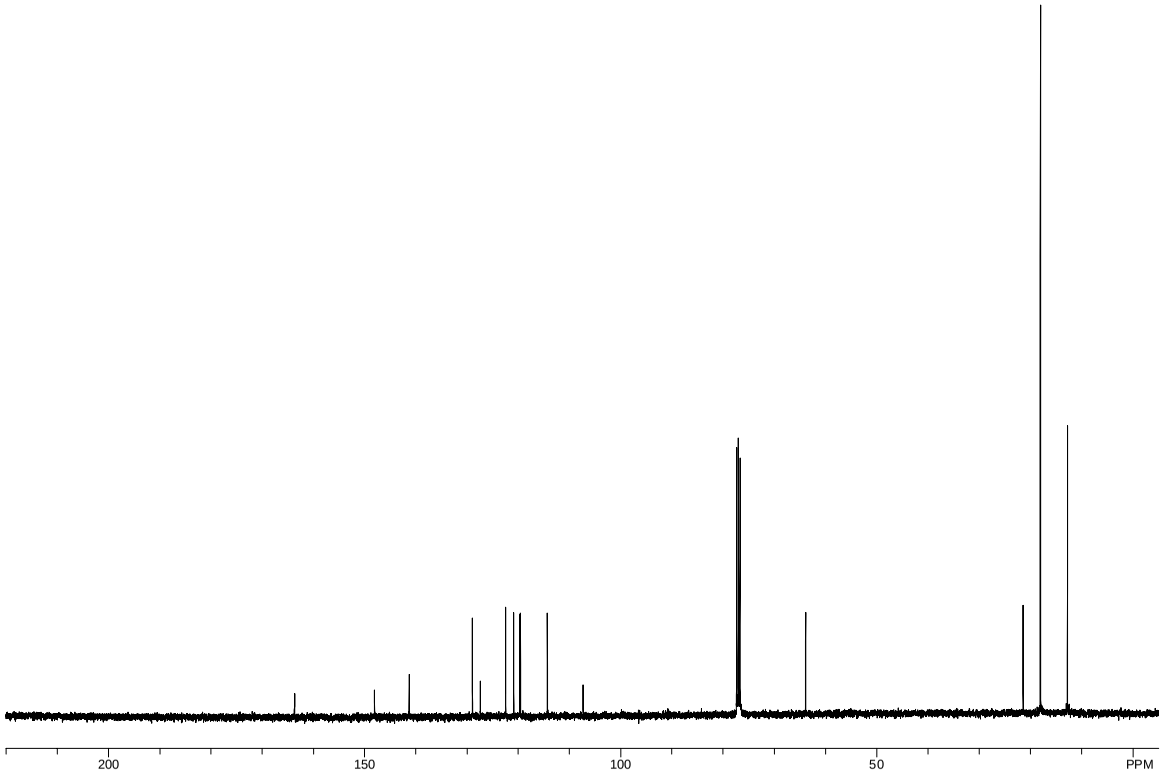
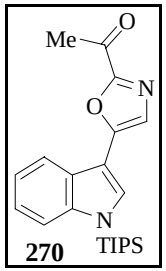


Figure A.2.69 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **269**.



270

Figure A.2.70 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **270**.

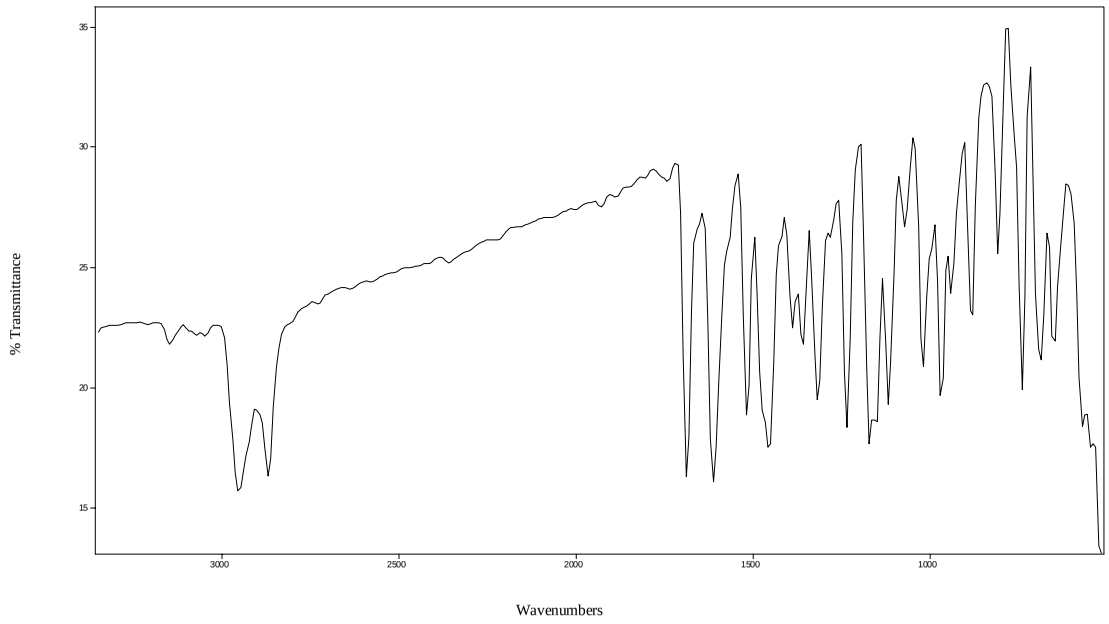


Figure A.2.71 FTIR Spectrum (thin film/NaCl) of Compound **270**.

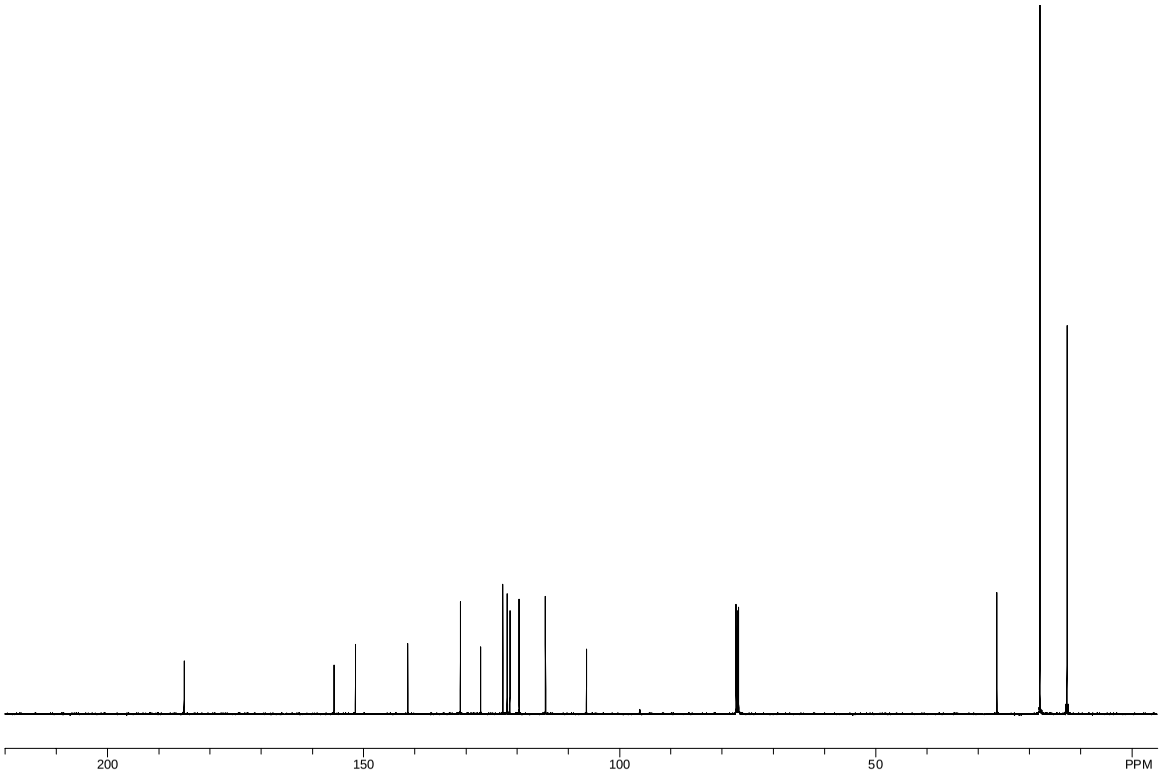


Figure A.2.72 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **270**.

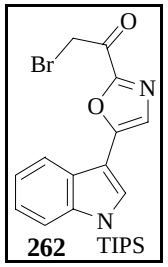


Figure A.2.73 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **262**.

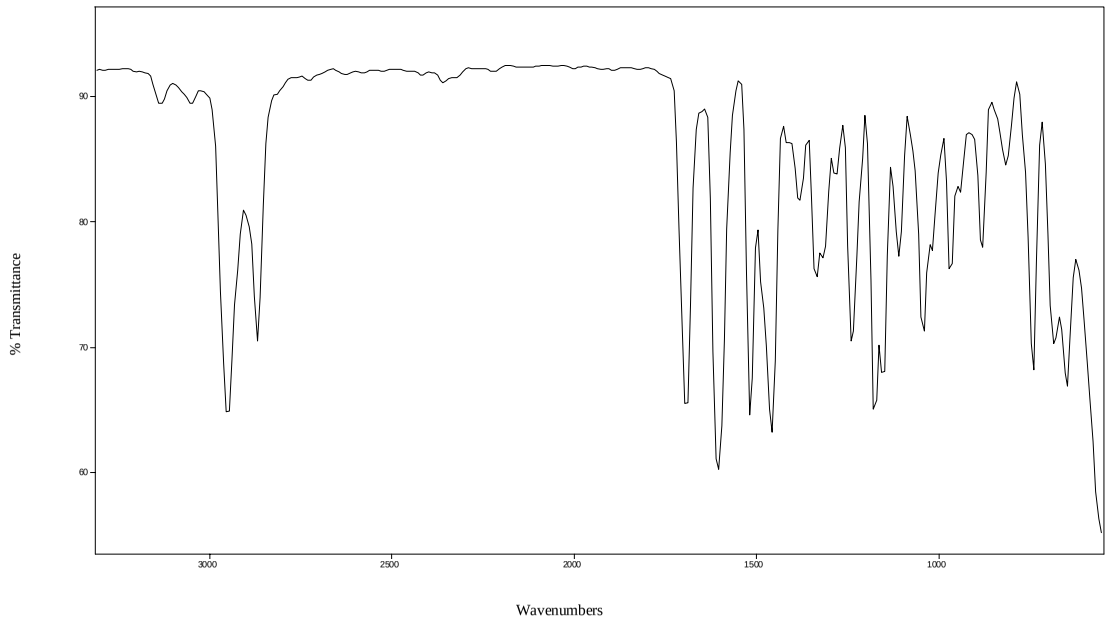


Figure A.2.74 FTIR Spectrum (thin film/NaCl) of Compound **262**.

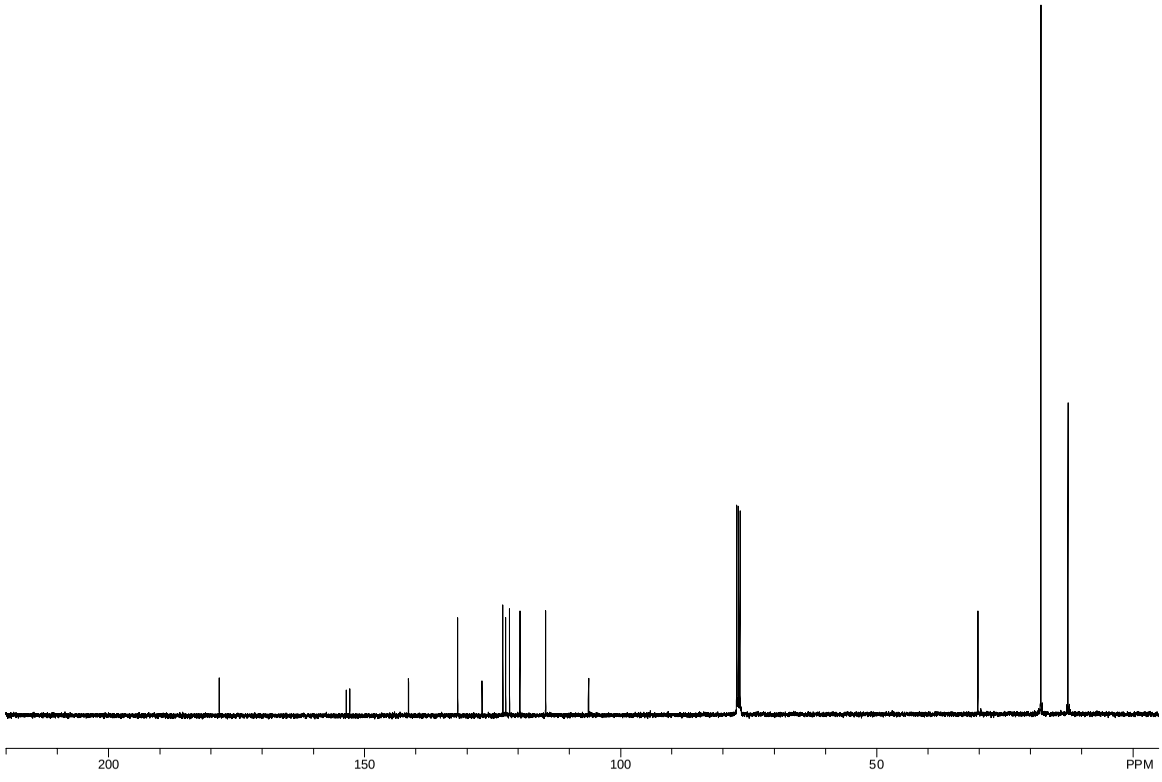


Figure A.2.75 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **262**.

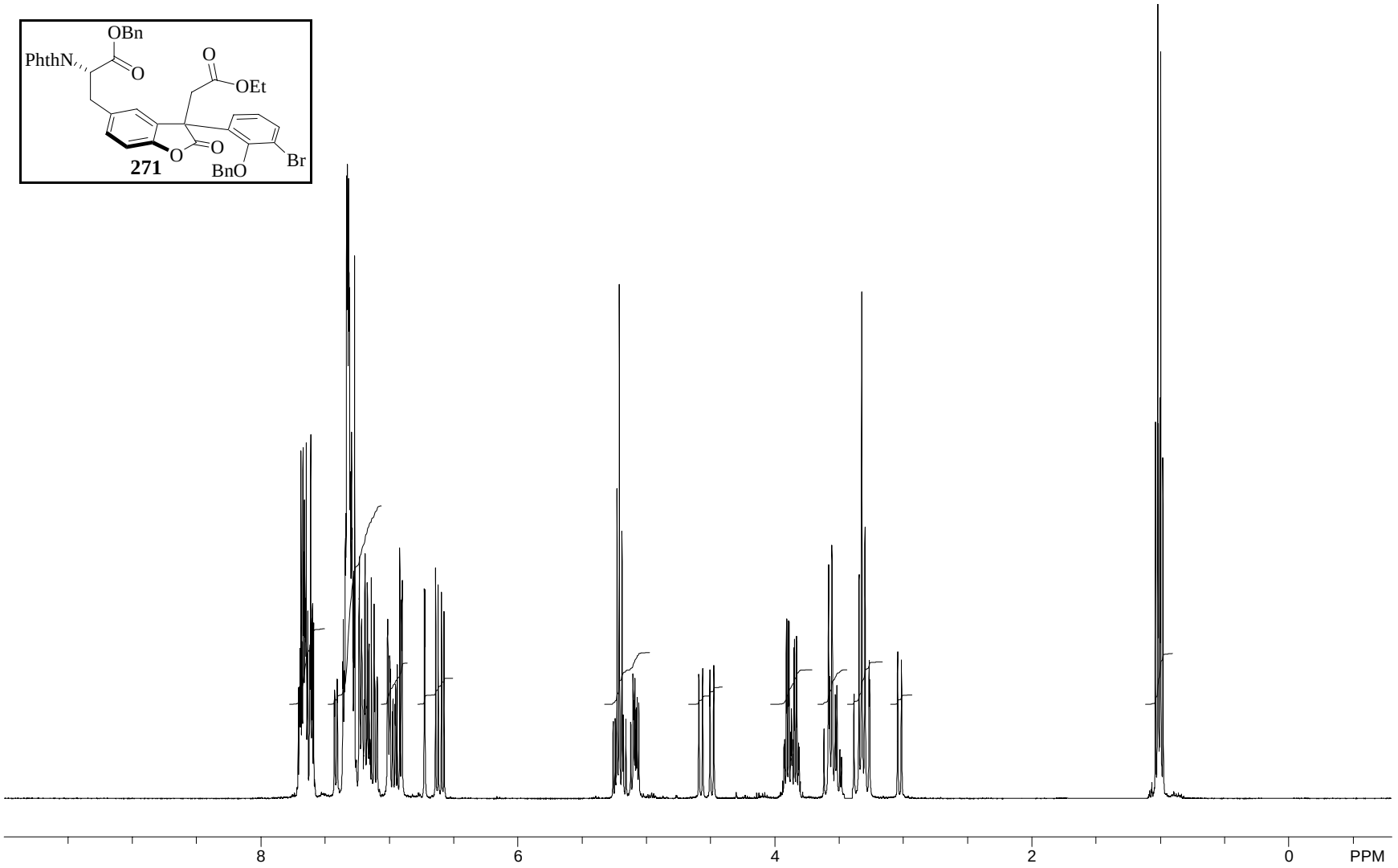


Figure A.2.76 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **271**.

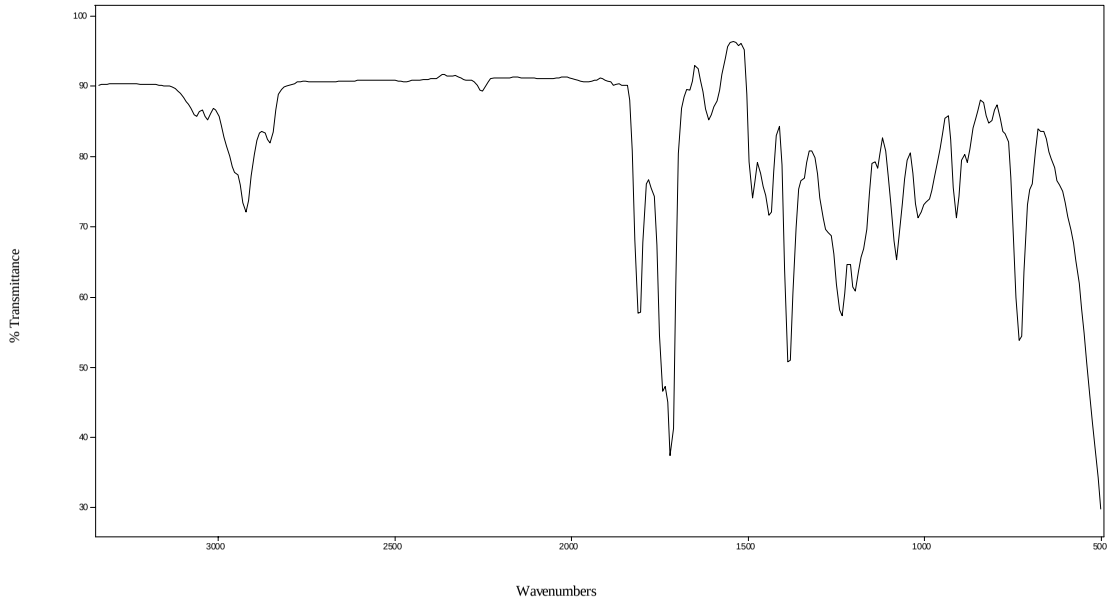


Figure A.2.77 FTIR Spectrum (thin film/NaCl) of Compound **271**.

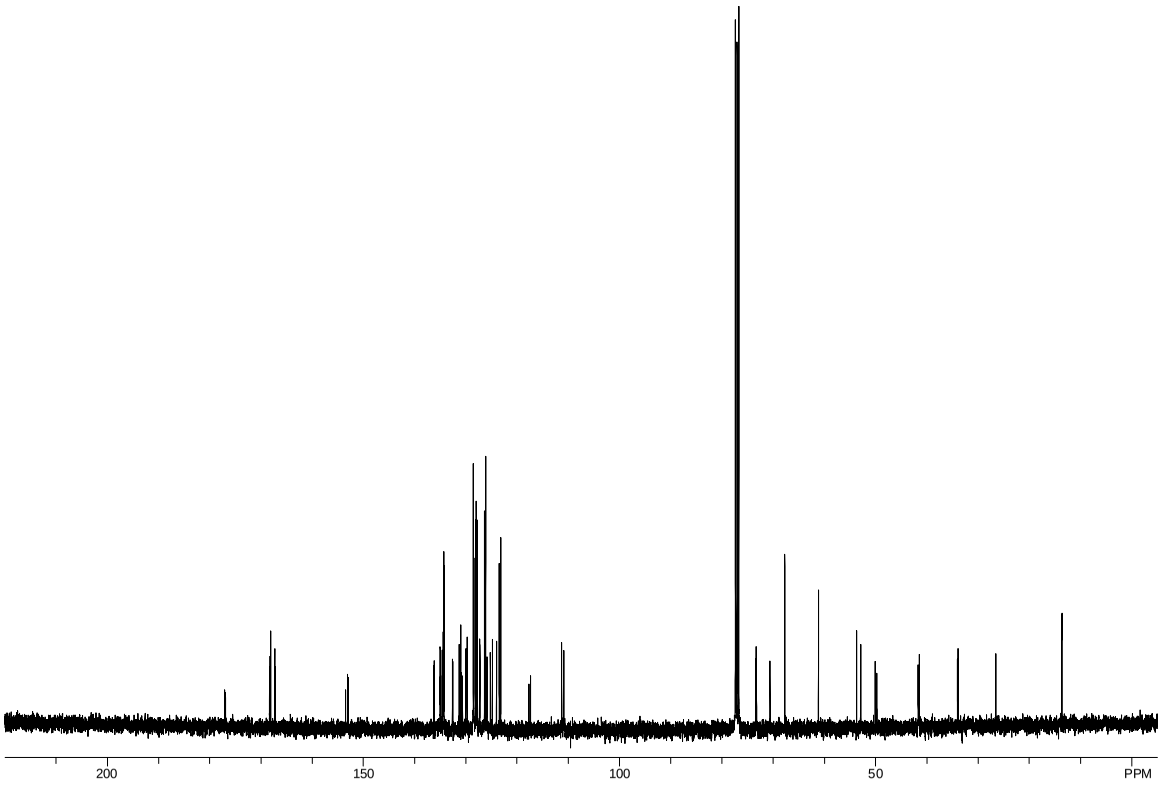


Figure A.2.78 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **271.**

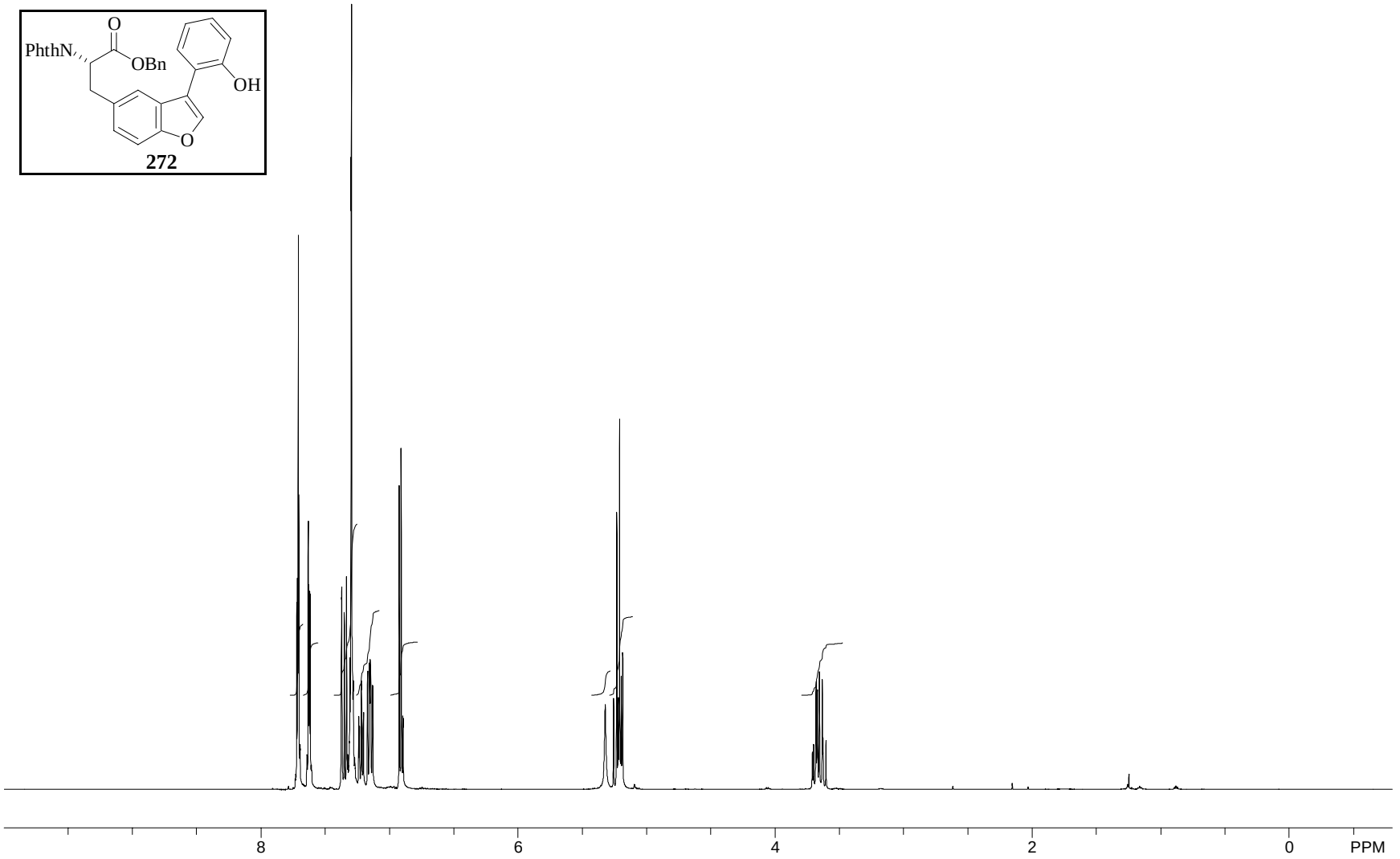


Figure A.2.79 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **272**.

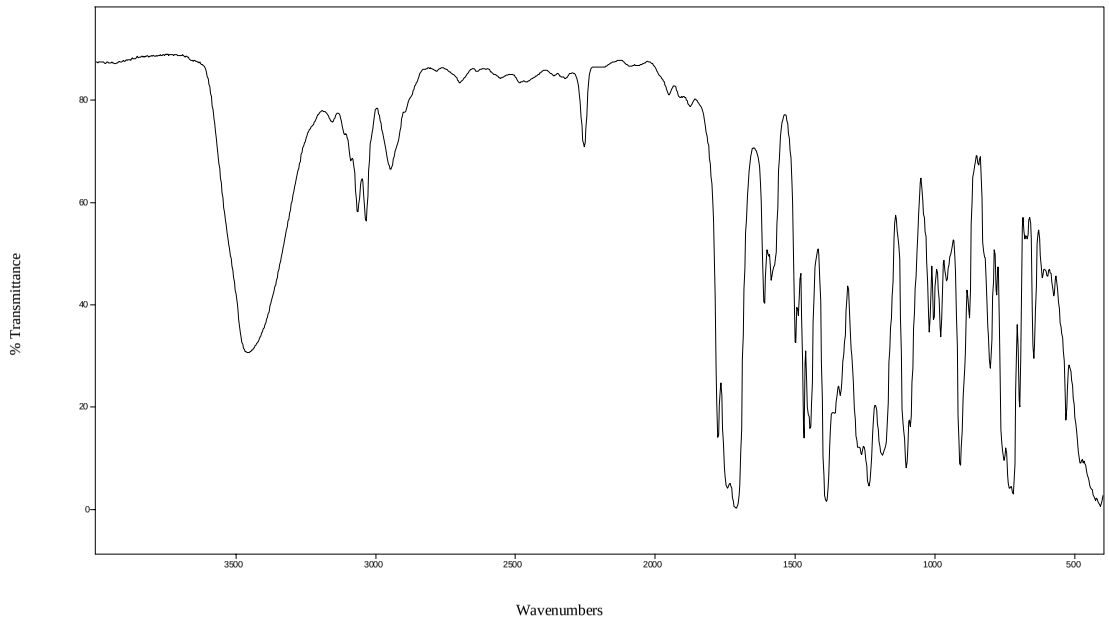


Figure A.2.80 FTIR Spectrum (thin film/NaCl) of Compound **272**.

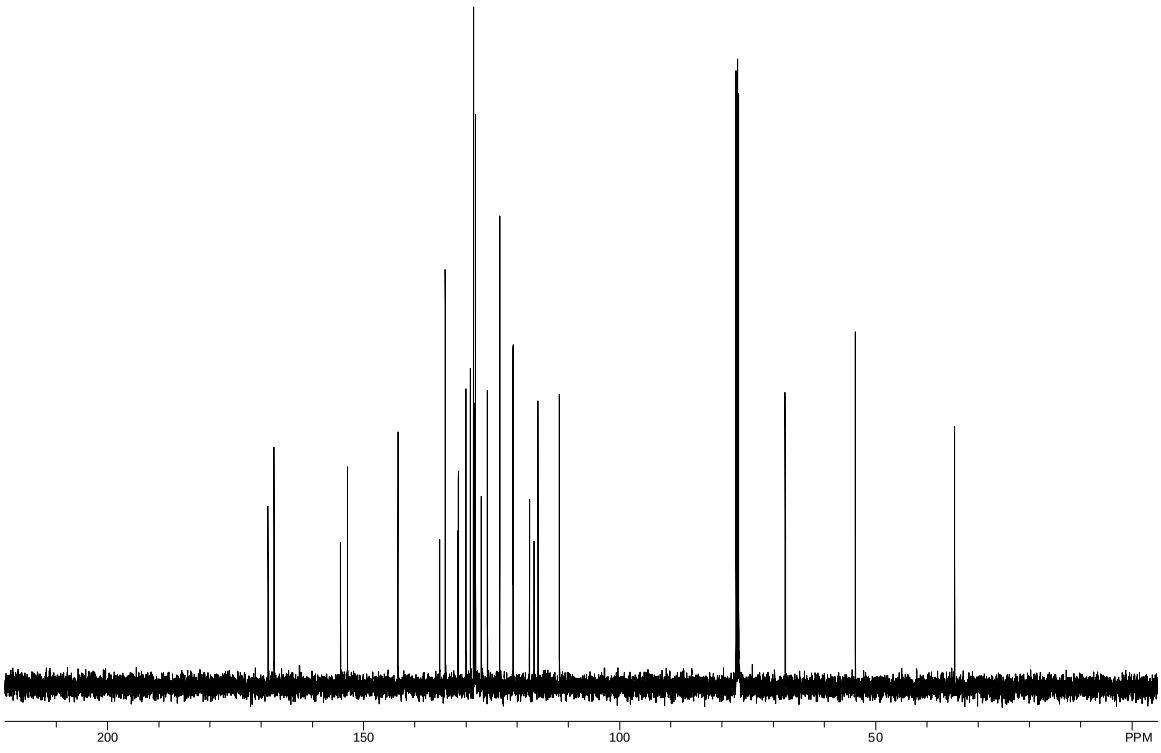


Figure A.2.81 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **272**.

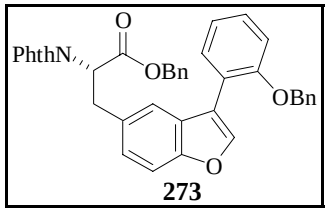


Figure A.2.82 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **273**.

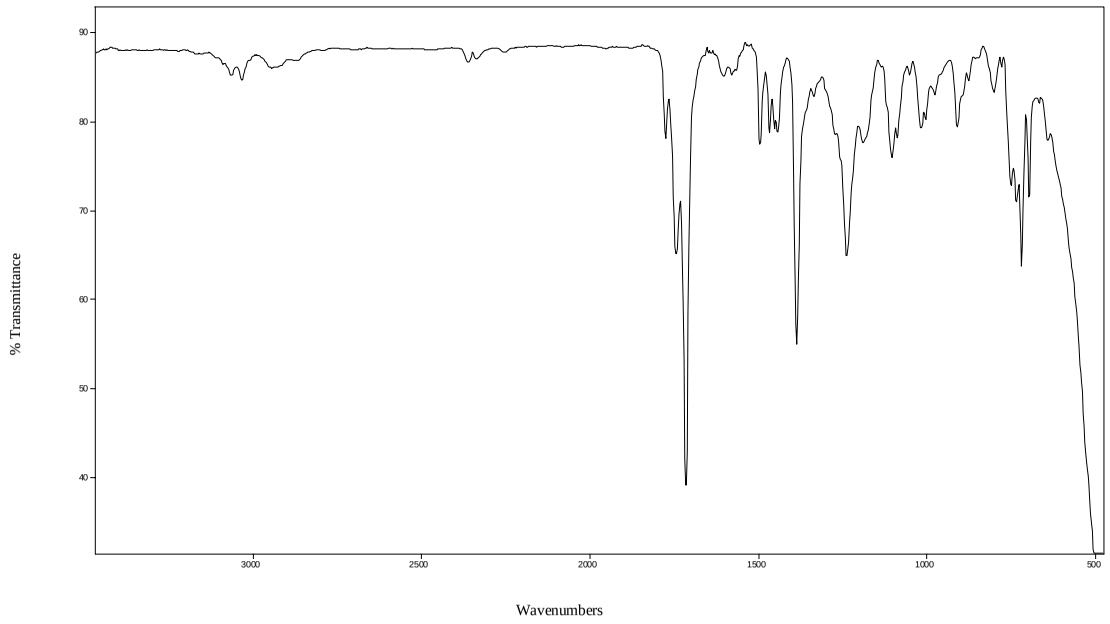


Figure A.2.83 FTIR Spectrum (thin film/NaCl) of Compound **273**.

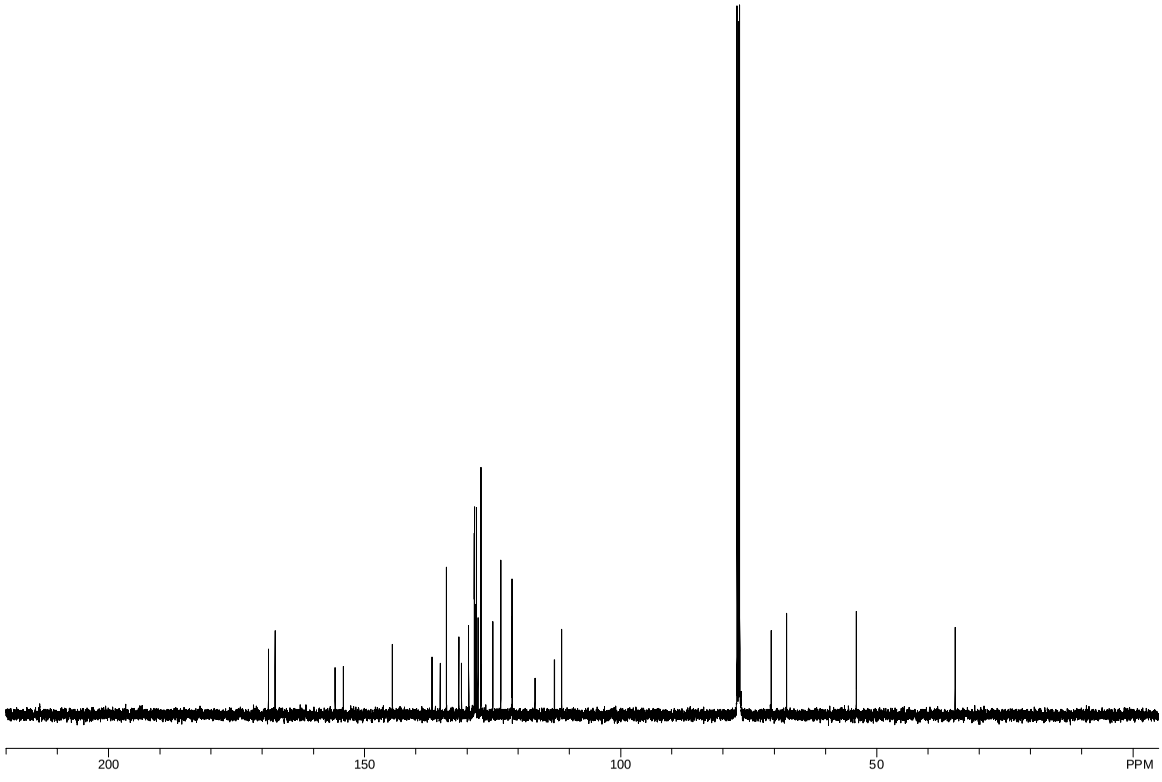


Figure A.2.84 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **273.**

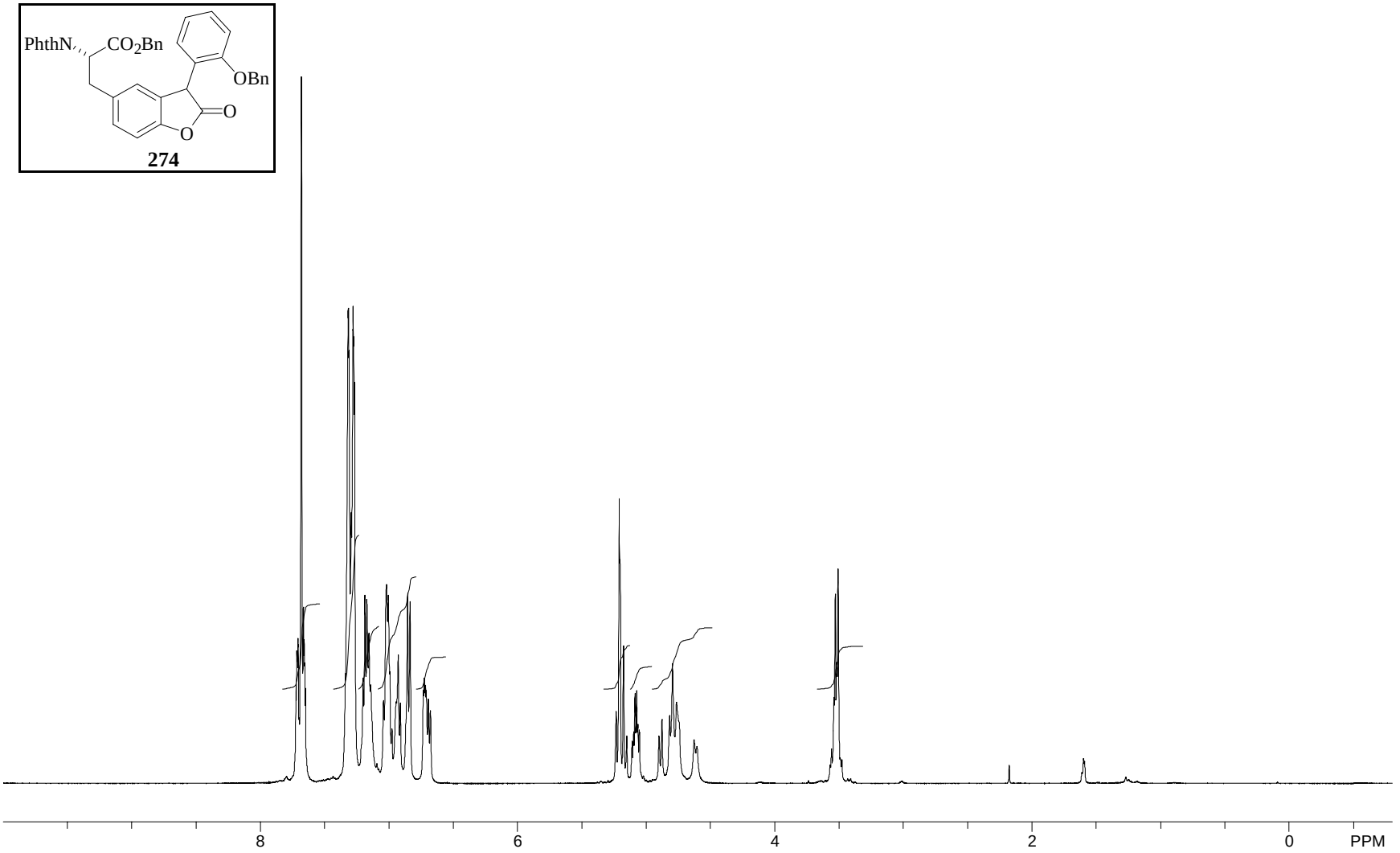


Figure A.2.85 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **274**.

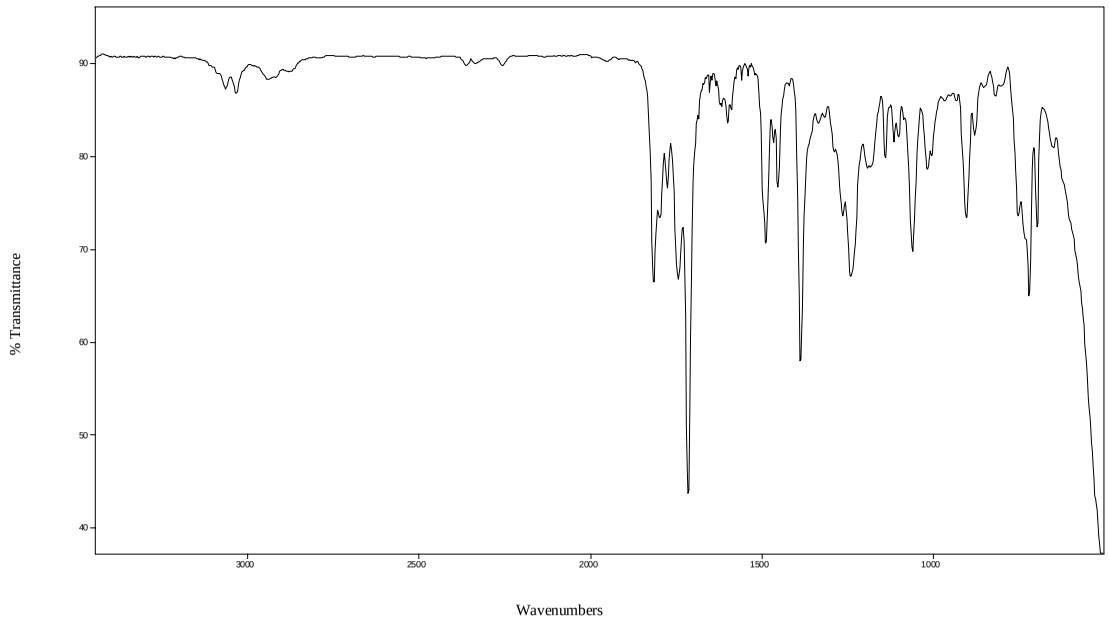


Figure A.2.86 FTIR Spectrum (thin film/NaCl) of Compound **274**.

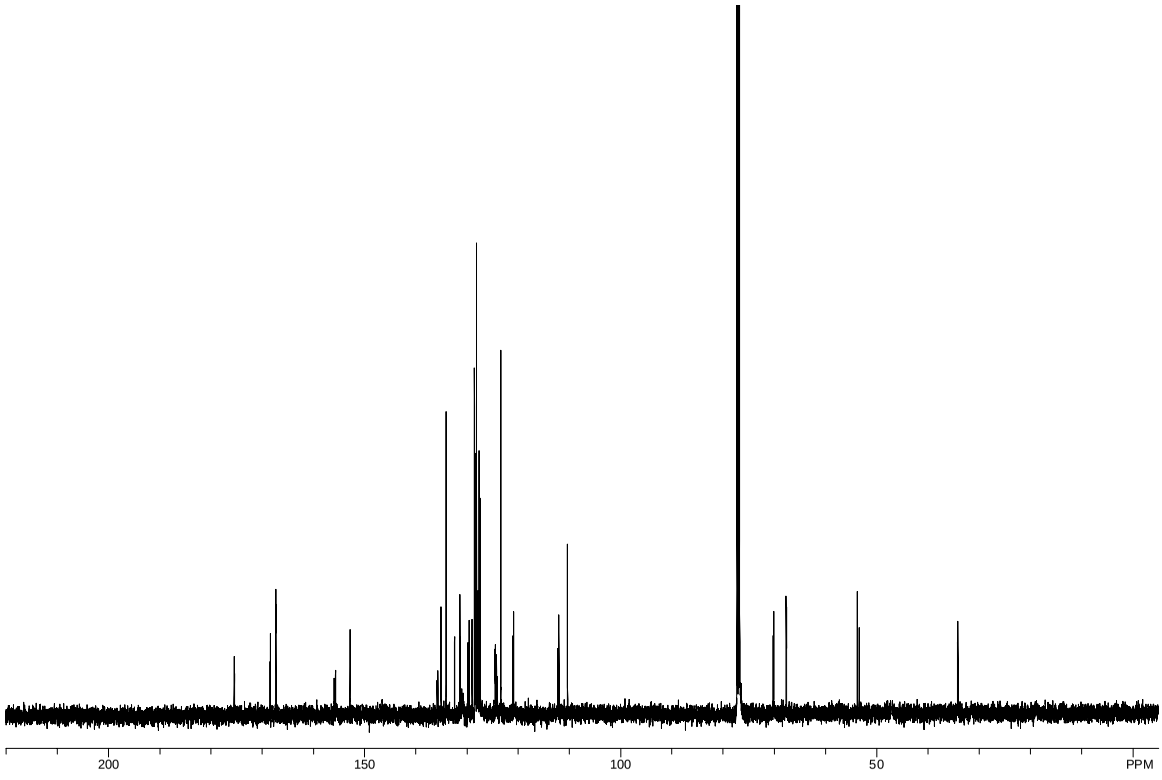
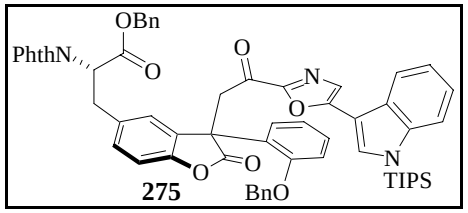


Figure A.2.87 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **274**.



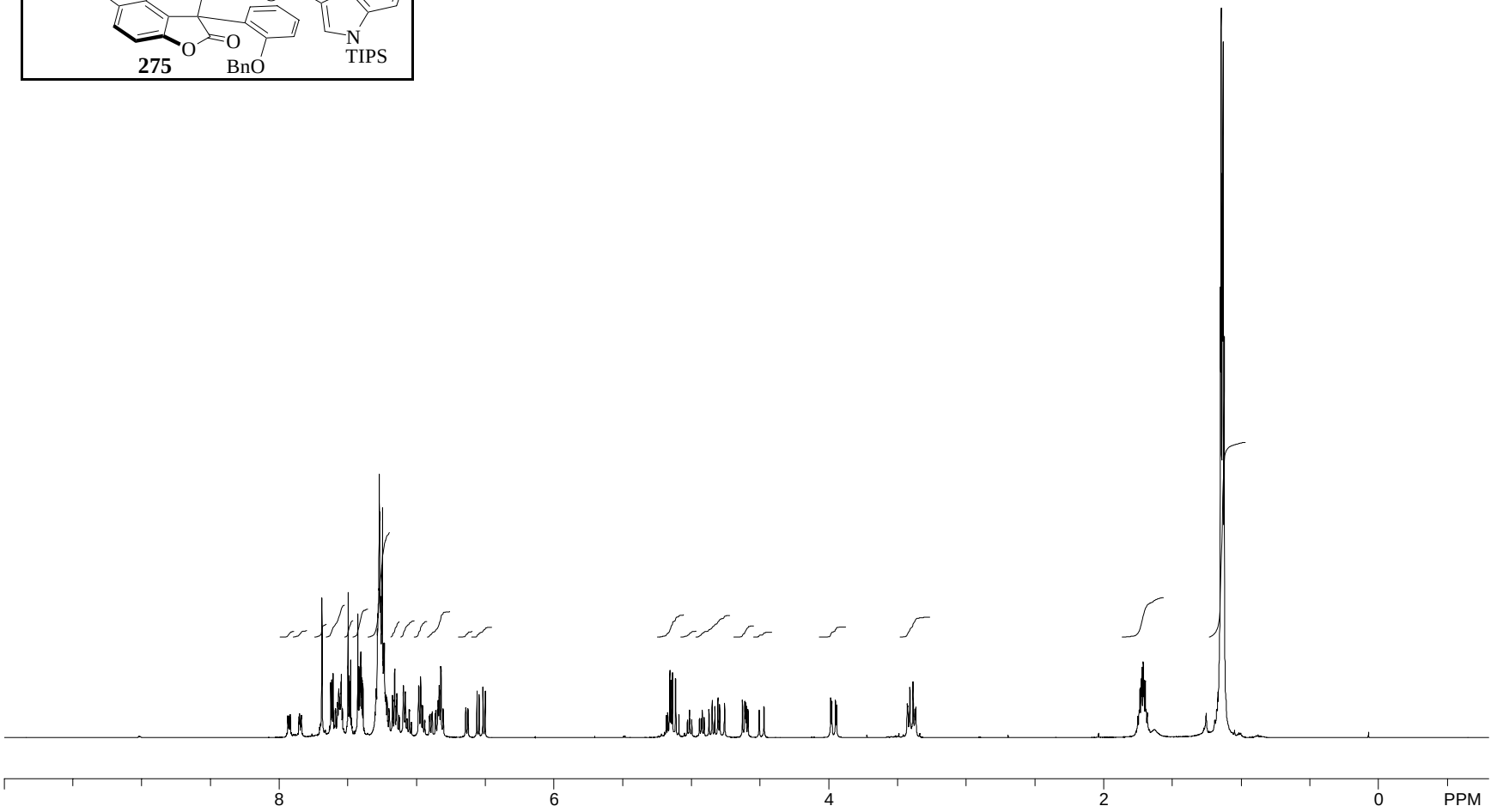


Figure A.2.88 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **275**.

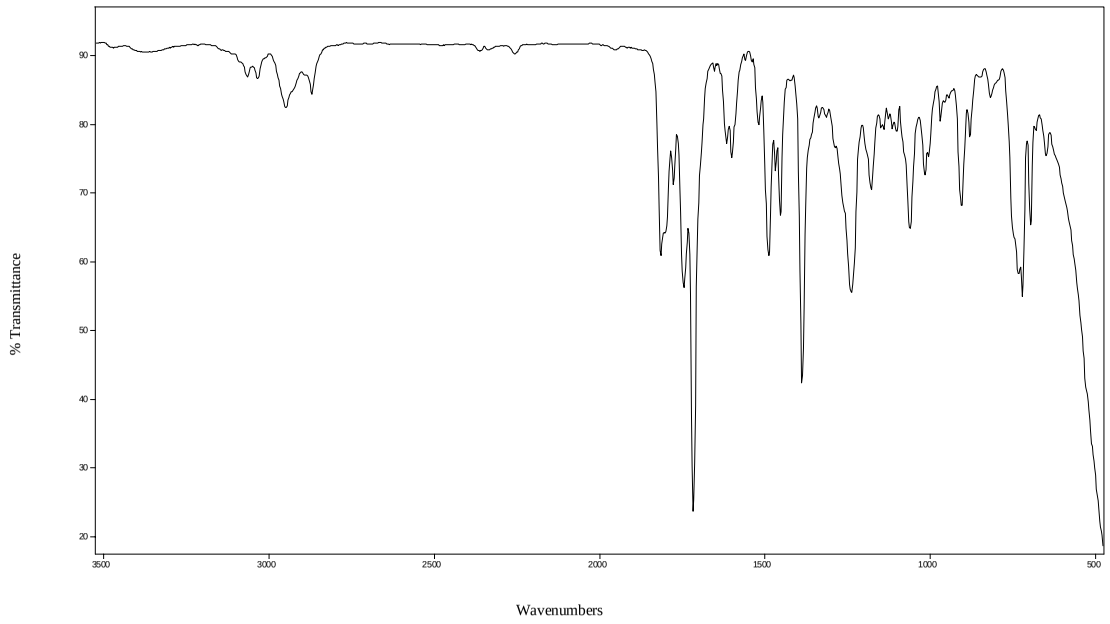


Figure A.2.89 FTIR Spectrum (thin film/NaCl) of Compound **275**.

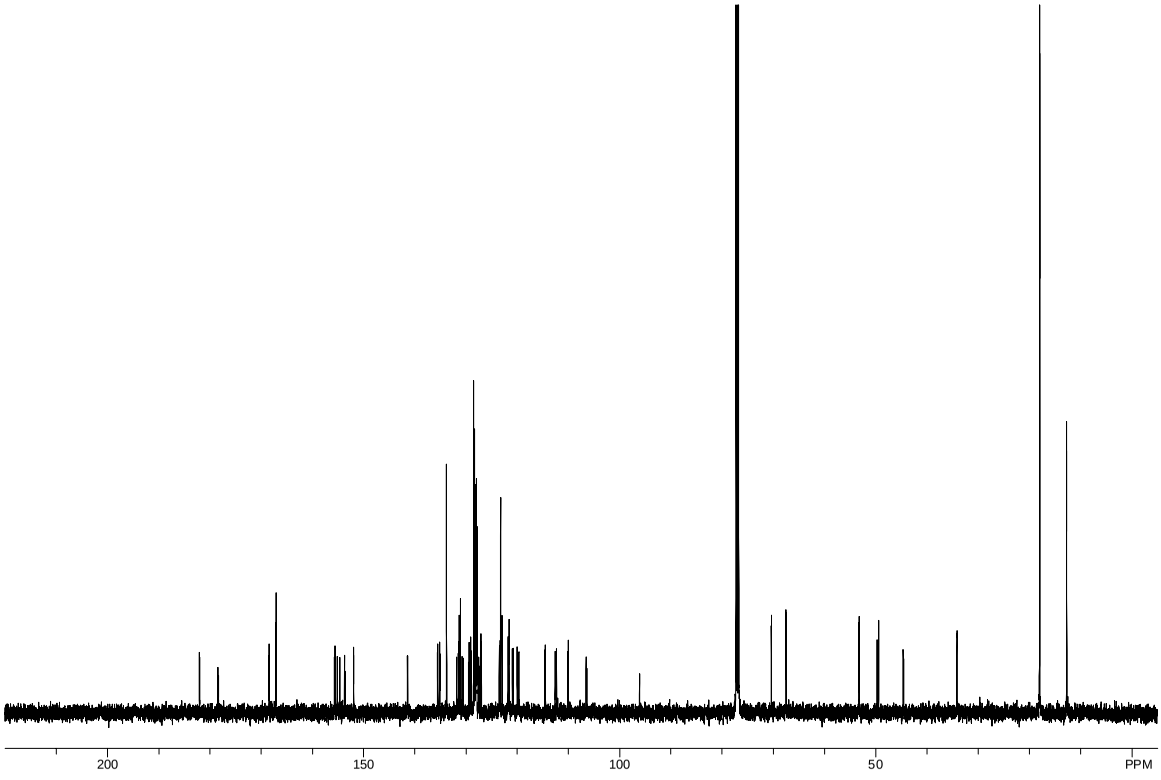


Figure A.2.90 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **275**.

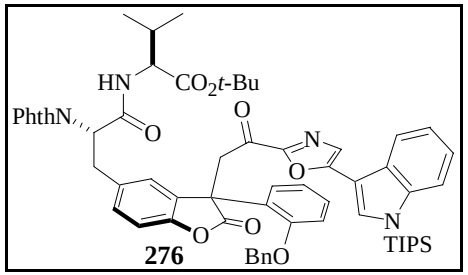


Figure A.2.91 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **276**.

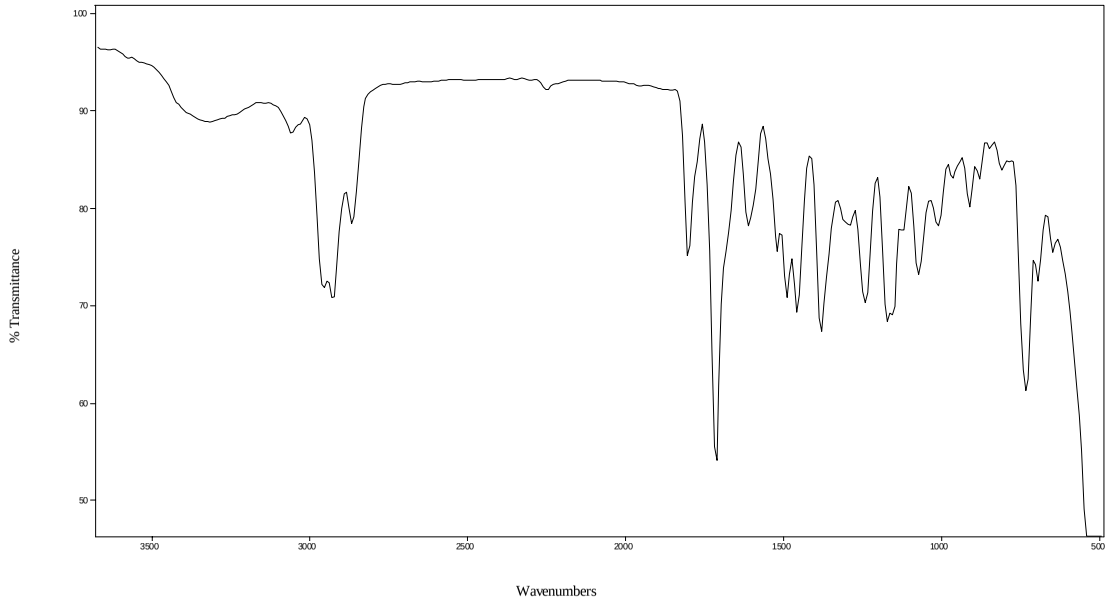


Figure A.2.92 FTIR Spectrum (thin film/NaCl) of Compound **276**.

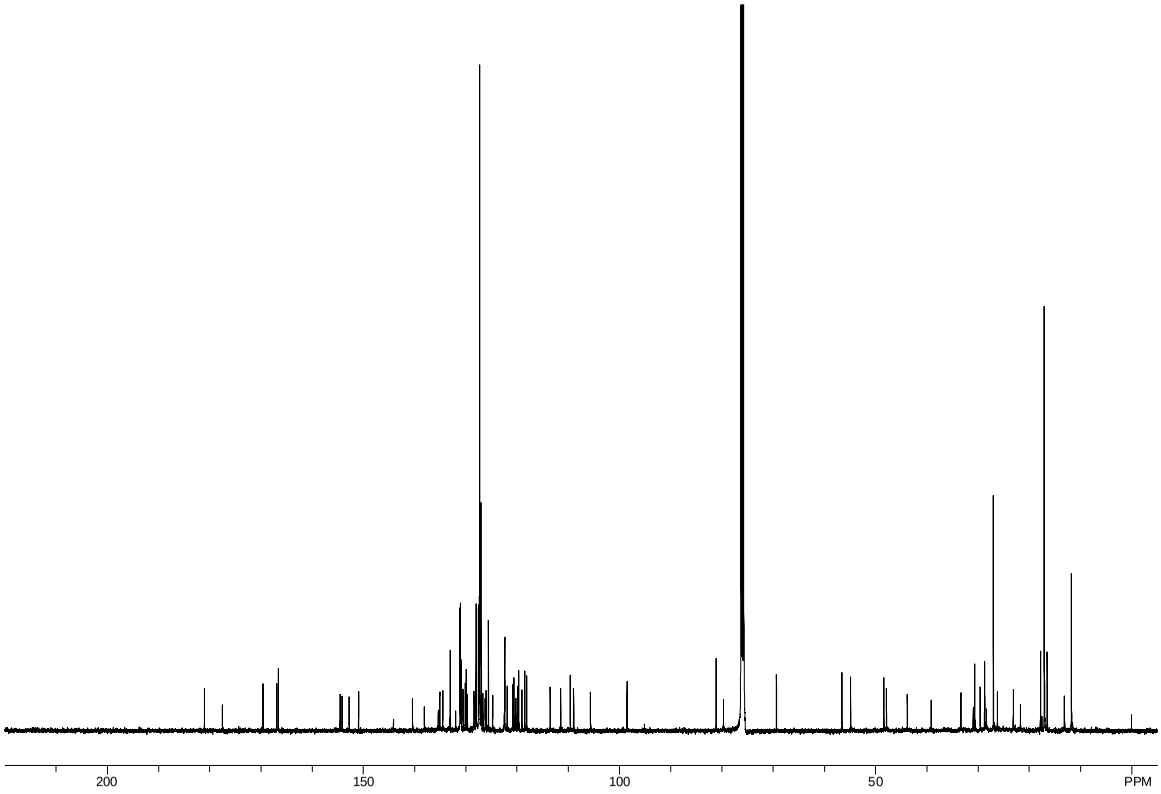


Figure A.2.93 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **276.**

Appendix Three: Note Book Cross-Reference

Appendix 3

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. DEF(II)-58) which corresponds to an archived characterization folder hard copy and folders stored on a CD. For each folder a characterization notebook number and page number (e.g. (III)-236) is given and for each spectrum a code (i.e. Proton for ^{1}H NMR, Carbon for ^{13}C NMR, and .spc for FTIR) is given. The characterization notebook, spectral data, and discs 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
181	DEF(II)-58	Proton	Carbon	Defii58.spc
182	DEF(II)-61	Proton	Carbon	Defii61.spc
183	DEF(II)-144	Proton	Carbon	Defii144.spc
184	DEF(II)-65	Proton	Carbon	Defii65.spc
185	DEF(II)-172	Proton	Carbon	Defii172.spc
186	DEF(II)-154	Proton	Carbon	Defii154.spc
188	DEF(II)-155	Proton	Carbon	Defii155.spc
189	DEF(II)-157	Proton	Carbon	Defii157.spc
190	DEF(II)-163	Proton	Carbon	Defii163.spc
191	DEF(II)-164	Proton	Carbon	Defii164.spc

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

195	DEF(II)-205	Proton	Carbon	Defii205.spc
196	DEF(II)-207	Proton	Carbon	Defii207.spc
197	DEF(II)-182	Proton	Carbon	Defii182.spc
198	DEF(II)-136	Proton	Carbon	Defii136.spc
200	DEF(II)-180A	Proton	Carbon	Defii180a.spc
202	DEF(II)-180B	Proton	Carbon	Defii180b.spc
203	DEF(II)-132	Proton	Carbon	Defii132.spc
210	DEF(II)-143	Proton	Carbon	Defii143.spc

Table A.4.2 Compounds Appearing in Chapter 3.

Compound	Folder	^{1}H NMR	^{13}C NMR	FTIR
211	DEF(V)-247	Proton	Carbon	Defv247.spc
219	TLH-204	Proton	Carbon	Tlh204.spc
220	TLH-205	Proton	Carbon	Tlh205.spc
221	TLH-208	Proton	Carbon	Tlh208.spc
222	TLH-209	Proton	Carbon	Tlh209.spc
223	TLH-221	Proton	Carbon	Tlh221.spc
224	TLH-218	Proton	Carbon	Tlh218.spc
237	TLH-217	Proton	Carbon	Tlh217.spc
238	DEF(IV)-85	Proton	Carbon	Defiv85.spc
240	DEF(V)-189	Proton	Carbon	Defv189.spc
241	DEF(V)-219	Proton	Carbon	Defv219.spc
242	DEF(V)-221	Proton	Carbon	Defv221.spc
245	TLH-215	Proton	Carbon	Tlh-215.spc

252	DEF(V)-243	Proton	Carbon	Defv243.spc
254	DEF(V)-187	Proton	Carbon	Defv187.spc
255	DEF(V)-195	Proton	Carbon	Defv195.spc
258	DEF(V)-281	Proton	Carbon	Defv281.spc
259	DEF(VI)-143	Proton	Carbon	Defvi143.spc
262	DEF(V)-105	Proton	Carbon	Defv105.spc
265	DEF(IV)-283	Proton	Carbon	Defiv283.spc
266	DEF(IV)-285	Proton	Carbon	Defiv285.spc
267	DEF(IV)-291	Proton	Carbon	Defiv291.spc
268	DEF(IV)-293	Proton	Carbon	Defiv293.spc
269	DEF(V)-33	Proton	Carbon	Defv33.spc
270	DEF(V)-35	Proton	Carbon	Defv35.spc
271	DEF(VI)-139	Proton	Carbon	Defvi139.spc
272	DEF(VI)-71A	Proton	Carbon	Defvi71a.spc
273	DEF(VI)-71B	Proton	Carbon	Defvi71b.spc
274	DEF(VI)-113	Proton	Carbon	Defvi113.spc
275	DEF(VI)-109	Proton	Carbon	Defvi109.spc
276	DEF(VI)-147	Proton	Carbon	Defvi147.spc

Bibliography

Bagley, M. C.; Moody, C. J.; Pepper, A. G. *Tetrahedron Letters* **2000**, *41*, 6901-6904.

Blocher, A.; Zeller, K. P. *Angewandte Chemie-International Edition in English* **1991**, *30*, 1476-1477.

Blocher, A.; Zeller, K. *Chemische Berichte* **1994**, *127*, 551-555.

Boto, A.; Ling, M.; Meek, G.; Pattenden, G. *Tetrahedron Letters* **1998**, *39*, 8167-8170.

Chen, X.; Esser, L.; Harran, P. G. *Angewandte Chemie-International Edition* **2000**, *39*, 937.

Corey, E. J.; Myers, A. G. *Tetrahedron Letters* **1984**, *25*, 3559-3562.

Doyle, M. P.; Bryker, W. J. *Journal of Organic Chemistry* **1979**, *44*, 1572-1574.

Doyle, M. P.; Pieters, R. J.; Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Muller, P. *Journal of the American Chemical Society* **1991**, *113*, 1423-1424.

Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q. L.; Martin, S. F. *Journal of the American Chemical Society* **1995**, *117*, 5763-5775.

Doyle, M. P.; Protopopova, M. N.; Poulter, C. D.; Rogers, D. H. *Journal of the American Chemical Society* **1995**, *117*, 7281-7282.

Doyle, M. P.; Peterson, C. S.; Parker, D. L. *Angewandte Chemie-International Edition in English* **1996**, *35*, 1334-1336.

Doyle, M. P.; Peterson, C. S.; Zhou, Q. L.; Nishiyama, H. *Chemical Communications* **1997**, 211-212.

Doyle, M. P.; Peterson, C. S.; Protopopova, M. N.; Marnett, A. B.; Parker, D. L.; Ene, D. G.; Lynch, V. *Journal of the American Chemical Society* **1997**, *119*, 8826-8837.

Doyle, M.; McKervey, M.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: from Cyclopropanes to Ylides*; Wiley & Sons: New York, 1998.

Doyle, M. P.; Forbes, D. C. *Chemical Reviews* **1998**, *98*, 911-935.

Fuerst, D. E.; Stoltz, B. M.; Wood, J. L. *Organic Letters* **2000**, *2*, 3521-3523.

Gilchrist, T. L. *Heterocyclic Chemistry*; 2nd ed. ed.; Wiley: New York.

Goux, C.; Massacret, M.; Lhoste, P.; Sinou, D. *Organometallics* **1995**, *14*, 4585-4593.

Harding, J. R.; Hughes, R. A.; Kelly, N. M.; Sutherland, A.; Willis, C. L. *Journal of the Chemical Society-Perkin Transactions 1* **2000**, 3406-3416.

Hoogwate, D.; Reinhoud, D.; Lie, T. S.; Gunneweg, J. J.; Beyerman, H. C. *Recueil Des Travaux Chimiques Des Pays-Bas-Journal of the Royal Netherlands Chemical Society* **1973**, *92*, 819-825.

Jamison, T. F., Ph.D. Dissertation, Harvard University, Cambridge, MA ,**1997**.

Jeong, S.; Chen, X.; Harran, P. G. *Journal of Organic Chemistry* **1998**, *63*, 8640-8641.

Konopelski, J. P.; Hottenroth, J. M.; Oltra, H. M.; Veliz, E. A.; Yang, Z. C. *Synlett* **1996**, 609.

Kreisberg, J. D.; Magnus, P.; McIver, E. G. *Tetrahedron Letters* **2001**, *42*, 627-629.

Lach, F.; Moody, C. J. *Tetrahedron Letters* **2000**, *41*, 6893-6896.

Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angewandte Chemie-International Edition* **2001**, *40*, 4765-4770.

Li, J.; Burgett, A. W. G.; Esser, L.; Amezcua, C.; Harran, P. G. *Angewandte Chemie-International Edition* **2001**, *40*, 4770.

Li, J.; Chen, X.; Burgett, A. W. G.; Harran, P. G. *Angewandte Chemie-International Edition* **2001**, *40*, 2682-2685.

Lindquist, N.; Fenical, W.; Vanduyne, G. D.; Clardy, J. *Journal of the American Chemical Society* **1991**, *113*, 2303-2304.

Magnus, P.; Kreisberg, J. D. *Tetrahedron Letters* **1999**, *40*, 451-454.

Magnus, P.; McIver, E. G. *Tetrahedron Letters* **2000**, *41*, 831-834.

Magnus, P.; Lescop, C. *Tetrahedron Letters* **2001**, *42*, 7193-7196.

Malamas, M. S.; Sredy, J.; Moxham, C.; Katz, A.; Xu, W. X.; McDevitt, R.; Adebayo, F. O.; Sawicki, D. R.; Seestaller, L.; Sullivan, D.; Taylor, J. R. *Journal of Medicinal Chemistry* **2000**, *43*, 1293-1310.

Martin, S. F.; Oalmann, C. J.; Liras, S. *Tetrahedron Letters* **1992**, *33*, 6727-6730.

Moniz, G. A.; Wood, J. L. *Journal of the American Chemical Society* **2001**, 5095-5097.

Moody, C. J.; Doyle, K. J.; Elliott, M. C.; Mowlem, T. J. *Pure and Applied Chemistry* **1994**, *66*, 2107-2110.

Moody, C. J.; Doyle, K. J.; Elliott, M. C.; Mowlem, T. J. *Journal of the Chemical Society-Perkin Transactions 1* **1997**, 2413-2419.

Nicolaou, K. C.; Snyder, S. A.; Simonsen, K. B.; Koumbis, A. E. *Angewandte Chemie-International Edition* **2000**, *39*, 3473.

Nicolaou, K. C.; Huang, X.; Giuseppone, N.; Rao, P. B.; Bella, M.; Reddy, M. V.; Snyder, S. A. *Angewandte Chemie-International Edition* **2001**, *40*, 4705.

Nicolaou, K. C.; Bella, M.; Chen, D. Y. K.; Huang, X. H.; Ling, T. T.; Snyder, S. A. *Angewandte Chemie-International Edition* **2002**, *41*, 3495-3499.

Oikawa, Y.; Yoshida, T., Mohri K.; Yonemitsu, O. *Heterocycles* **1979**, *12*, 1457-1462.

Ouihia, A.; Rene, L.; Guilhem, J.; Pascard, C.; Badet, B. *Journal of Organic Chemistry* **1993**, *58*, 1641-1642.

Padwa, A.; Wisnieff, T. J.; Walsh, E. J. *Journal of Organic Chemistry* **1989**, *54*, 299-308.

Padwa, A.; Austin, D. J. *Angewandte Chemie-International Edition in English* **1994**, *33*, 1797-1815.

Radspieler, A.; Liebscher, J. *Synthesis-Stuttgart* **2001**, 745-750.

Reddy, G. S.; Bhatt, M. V., *Indian Journal of Chemistry Section B-Organic Chemistry Including Medicinal Chemistry* **1981**, *20*, 322-323.

Ritter, T.; Carreira, E. M. *Angewandte Chemie-International Edition* **2002**, *41*, 2489.

Schuler, G.; Wasternack, C.; Boland, W. *Tetrahedron* **1999**, *55*, 3897-3904.

Schulz, R.; Schweig, A. *Angewandte Chemie-International Edition in English* **1984**, *23*, 509-511.

Schweig, A.; Baumgartl, H.; Schulz, R. *Journal of Molecular Structure* **1991**, *247*, 135-171.

Trost, B. M.; Toste, F. D. *Journal of the American Chemical Society* **1998**, *120*, 815-816.

Vedejs, E.; Monahan, S. D. *Journal of Organic Chemistry* **1996**, *61*, 5192-5193.

Vedejs, E.; Wang, J. B. *Organic Letters* **2000**, *2*, 1031-1032.

Vedejs, E.; Barda, D. A. *Organic Letters* **2000**, *2*, 1033-1035.

Vedejs, E.; Zajac, M. A. *Organic Letters* **2001**, *3*, 2451-2454.

White, W. N.; Fife, W. K. *Journal of the American Chemical Society* **1961**, *83*, 3846-&.

Wipf, P.; Miller, C. P. *Journal of Organic Chemistry* **1993**, *58*, 3604-3606.

Wipf, P.; Yokokawa, F. *Tetrahedron Letters* **1998**, *39*, 2223-2226.

Wipf, P.; Methot, J. L. *Organic Letters* **2001**, *3*, 1261-1264.

Wood, J. L.; Moniz, G. A. *Organic Letters* **1999**, *1*, 371-734.

Wood, J. L.; Moniz, G. A.; Pflum, D. A.; Stoltz, B. M.; Holubec, A. A.; Dietrich, H. J. *Journal of the American Chemical Society* **1999**, *121*, 1748-1749.

Ye, T.; McKervey, M. A. *Chemical Reviews* **1994**, *94*, 1091-1160.

Yonemits, O.; Cerutti, P.; Witkop, B. *Journal of the American Chemical Society* **1966**, *88*, 3941.

About the Author

Douglas E. Fuerst was born April 21, 1976, in Dayton, Ohio to Helen M. and Gordon L. Fuerst. A few years later, Douglas moved 60 miles north with his parents and baby brother Scott to Lima, Ohio. In 1988 the family moved again to neighboring Elida, Ohio. Douglas received his elementary, middle, and high school education in the Elida Local School District. In high school, Douglas spent the majority of his time playing golf earning three varsity letters. Douglas was the varsity golf team captain his senior year, earning 1st Team All-District honors along with Honorable Mention All-State honors for the state of Ohio.

After graduating from high school in 1994, Douglas moved to Indianapolis, Indiana were he attended Butler University to major in pharmacy. After two years in the pharmacy curriculum and being fully accepted into the pharmacy program, Douglas shifted his focus and changed his major to chemistry. This change was fueled by the de-emphasis of basic science in the pharmacy curriculum and his positive experience conducting original research in the laboratories of Professor Todd Hrubey. With Professor Hrubey, Douglas studied the inhibition of protein kinase CKII with synthetic polypeptides. Based on this work and previous work in the Hrubey labs, Douglas designed a bisubstrate inhbitor of CKII which he attempted to synthesize with the help of Professor O. LeRoy Salerni. It was Professor Salerni who inspired Douglas and developed his passion for organic chemistry by his tireless and enthusiastic devotion to teaching and research. Butler University was also where Douglas met his future wife, Joy Kruger. In May of 1998 Douglas graduated from Butler University with High Honors in chemistry and began an internship at Eli Lilly and Company. At Eli Lilly Douglas performed medicinal chemistry research in the Infectious Diseases division under the direction of Mohammad Zia-Ebrahimi.

In September of 1998, Douglas began graduate studies at Yale University. He received his Master's Degree in 2001 and his Doctorate in 2002 under the direction of Professor John L. Wood. Douglas will be moving to Massachusetts where he has accepted a post-doctoral position with Professor Eric N. Jacobsen at Harvard University.