DISSERTATION

PROGRESS TOWARD THE TOTAL SYNTHESIS OF CITRINADINS A AND B

Submitted by

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ABSTRACT

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In 2005 Kobayashi reported the isolation and absolute stereochemistry of Citrinadin A (**1**) and Citrinadin B (**2**), novel secondary metabolites of the marine fungus *Penicillium citrinum*. In addition to their interesting molecular architecture, the citrinadins are biologically active. Both exhibit cytotoxicity against murine leukemia L1210 (IC_{50} 6.2 and 10 μg/mL respectively), and **1** has shown activity against human epidermoid carcinoma KB cells (IC_{50} 6.2 μg/mL). Synthesis of **1** and **2** would allow for further testing of their biological activity and remains the best way to confirm their assigned structures. While, no total synthesis of either natural product has been reported to date, two synthetic approaches toward the citrinadins have been disclosed by Martin and Sorensen.

Efforts to synthesize **1** and **2** in the Wood laboratory are based upon a convergent (3+2) dipolar cycloaddition reaction between a spiro-oxindole dipolarophile and a nitrone, where two diastereomeric isoxazolidine cycloadducts are formed. Using the undesired cycloadduct, exploratory studies toward a synthesis of **2** were conducted, resulting in the synthesis of the C3-*epi*-Citrinadin Core (**±**)-**96**. Elaboration of the desired cycloadduct then led to a synthesis of the *ent*-Citrinadin Core (+)-**100**.

In order gain to access **2**, a C7-functionalized spiro-oxindole dipolarophile was employed in the cycloaddition; however, elaboration of the desired C7-functionalized cycloadduct to *ent*-**2** may result in a structural reassignment of **2**. Preliminary results suggest that spectral data for the C21-*epi*-*ent* diastereomer of **2** (**175**) match the data reported by Kobayashi for Citrinadin B (**2**) itself.

In an effort to gain access to **1**, a (3+2) cycloaddition strategy utilizing a C14-functionalized nitrone was explored. Following the synthesis of three nitrone precursors, a one-pot nitrone formation / (3+2) cycloaddition reaction was developed and one of the cycloadducts was successfully advanced to a key ring-fusion epoxide. Elaboration of this advanced intermediate is expected to eventually provide a total synthesis of Citrinadin A (**1**).

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BIOGRAPHY

The oldest of three children, Genessa was born in March of 1981 to Colorado natives George and Dianne Wood in Longmont, Colorado. While she was in elementary school, her family moved to Berthoud, Colorado where she later graduated from High School as one of five Valedictorians in her class.

Upon enrolling at Fort Lewis College (Durango, Colorado) in the fall of 1999, Genessa declared English as her major. However, she was later encouraged by her professors to consider changing her major to Chemistry. She followed their advice, and later discovered a strong inclination toward organic chemistry. Genessa did undergraduate research with Assistant Professor Cindy C. Browder in 2002 as well as an industrial internship at Boulder Scientific Company (Mead, CO) in 2003. She graduated *Summa Cum Laude* in 2004 with a BS in Chemistry and a minor in Writing.

Genessa married her college sweetheart, Ryan Smith, shortly after graduation, and the couple moved to Boston, Massachusetts where Ryan began working for IBM. During that time Genessa explored her interest in the pharmaceutical industry, first working for Momenta Pharmaceuticals, and later for Cetek Pharmaceuticals, functioning as an integral part of a small medicinal chemistry group. When Cetek went out of business in 2006, she was hired by Absolute Science, where she remained until returning to school in Colorado in 2007.

Genessa was a Roche Excellence in Chemistry awardee in May 2011 and was also invited to participate in the ACS Organic Division Graduate Research Symposium (Santa Barbara, CA) in July of the same year. In March 2012, she received her PhD for her contributions to the total synthesis of Citrinadins A and B. She has accepted a position as an Assistant Professor at the University of Tennessee at Martin and is expected to start teaching in August 2012.

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LIST OF ABBREVIATIONS

Ac	acetyl
AIBN	azoisobutyronitrile
Ar	aryl
aq	aqueous
BHT	butylated hydroxytoluene
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
Bn	benzyl
Boc	tert-butoxycarbonyl
bp	boiling point
Bu	butyl
Bz	benzoyl
CAN	cerium(IV) ammonium nitrate
Cbz	benzyloxycarbonyl
CE	Cotton effect
CSA	camphorsulfonic acid
cy	cyclohexyl
d.e. (de)	diastereomeric excess
d.r. (dr)	diastereomeric ratio
DABCO	1,4-diazabicyclo[2.2.2]-octane
dba	dibenzylidene acetone
DBU	1,8-diazabicyclo[5.4.0-undec-7ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano benzoquinone
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DIBAL	diisobutylaluminum hydride

DIPA	diisopropylamine
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DME	dimethoxyethane, glyme
DMF	*N*,*N*-dimethylformamide
DMI	1,3-dimethylimidazolidin-2-one
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
dppf	diphenylphosphinoferrocene
e.e. (ee)	enantiomeric excess
e.r. (er)	enantiomeric ratio
Et	ethyl
hν	irradiation with light
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
IBX	*o*-iodoxybenzoic acid
Imid	imidazole
IR	infrared spectroscopy
KHMDS	potassium bis(trimethylsilyl)amide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamine
LiHMDS	lithium hexamethyldisilazide
M.S.	mass spectrometry
m-CPBA	*m*-chloroperbenzoic acid
Me	methyl
Mes	mesityl
Ms	methanesulfonyl
MS	molecular sieves
MTBE	methyl-*tert*-butylether
MVK	methyl vinyl ketone
mw (μw)	microwave
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine oxide

NMP (MPD)	*N*-methyl-2-pyrrolidinone
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
piv	pivaloyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium toluenesulfonate
Pr	propyl
PTSA	(*p*-TSA, TsOH) *p*-toluenesulfonic acid
Py	pyridine
Rf	retention factor
RT	room temperature
TBAF	tetra-*n*-butylammonium fluoride
TBAT	tetra-*n*-butylammonium difluorotriphenylsilicate
TBDPS	*tert*-butyl-diphenyl silyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyl-dimethyl silyl
TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
Th	2-thienyl
THF	tetrahydrofuran
TIPS	triisopropyl silyl
TMS	trimethyl silyl
Tr	trityl
Ts	*p*-toluenesulfonyl

CHAPTER 1

Introduction To the Citrinadins and Related Natural Products

1.1 Isolation, Structural Characterization, and Biological Activity

1.1.1 The Citrinadins and PF1270s

In 2004, Kobayashi and coworkers reported the isolation of Citrinadin A (**1**), a novel secondary metabolite of the marine fungus *Penicillium citrinum* (Figure 1.1).[1] The fungus was cultured from the marine red alga *Actinotrichia fragilis*, which was collected from the Hedo Cape of Okinawa Island

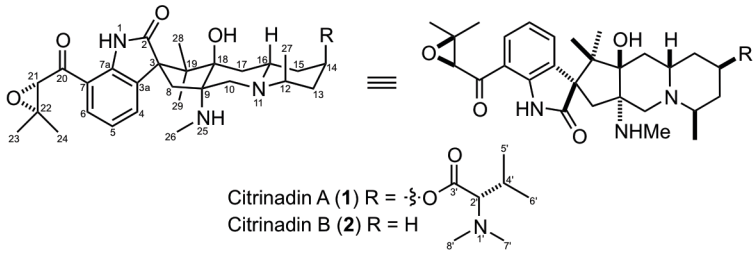


Figure 1.1

in Japan. Extensive NMR analysis of naturally isolated material revealed that **1** contains a highly functionalized cyclopenta[*b*]quinolizidine moiety and a spiro-fused oxindole. It is capped on one end with a rare *N*,*N*-dimethylvaline ester, and on the other, with a unique epoxycarbonyl side chain. Similar to **1**, Citrinadin B (**2**), was isolated by Kobayashi in 2005 and shares the same basic structure but lacks the C14

ester.[2] PF1270A (**3**), PF1270B (**4**), and PF1270C (**5**)—three alkaloids recently isolated by Kushida et al. from the fungus, *Penicillium waksmanii* (strain PF1270)—also bear a strong resemblance to the citrinadins (Figure 1.2).[3]

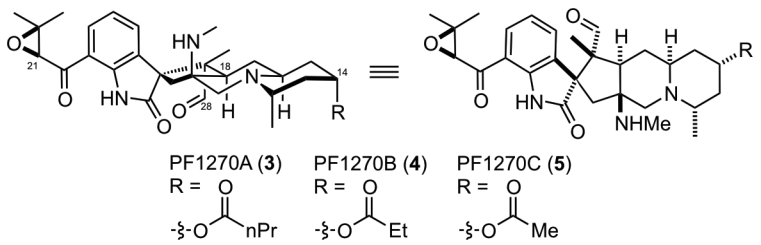


Figure 1.2

The relative stereochemistry of the citrinadin pentacyclic core was determined using standard NOE correlation data and $^{1}H–^{1}H$ coupling constants.[2] The absolute configuration of the *N*,*N*-dimethylvaline ester was unambiguously established via comparison of the hydrolysate of **1** with authentic D- and L-*N*,*N*-dimethylvaline chiral HPLC traces. The absolute configuration of the epoxycarbonyl side chain was determined using comparative VCD spectroscopy. Model epoxides **6** and **7** were synthesized and found to display mirror image, weak Cotton effects at *c.* 1230 cm^{-1} (Figure 1.3). Analogous to model epoxide **7**, VCD analysis of **1** revealed a Cotton curve of negative sign at 1245 cm^{-1}, suggesting the corresponding (*S*)-configuration at C21.

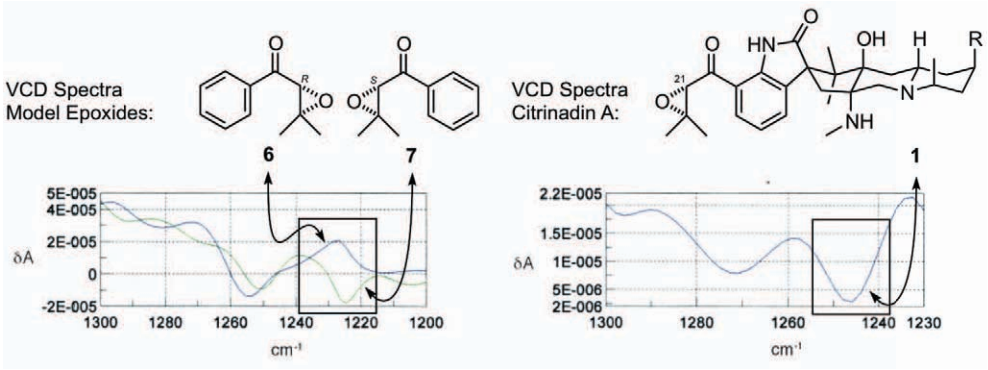
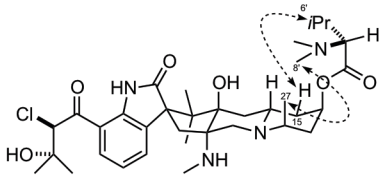


Figure 1.3

The absolute stereochemistry of **1** was extrapolated from ROESY and ECD spectra.[2] ROESY correlations between the (*S*)-*N*,*N*-dimethylvaline side chain and the quinolizidine ring system of a chlorohydrin derivative (**8**) of **1** were used to assign the (*S*)-configuration to C14 (Figure 1.4).[4] Analysis of

ECD spectra for the uncarine spiro-oxindole alkaloids resulted in a conclusion that like Undecarine E and D (**11** and **12**), the negative first Cotton curve seen at λ_{ext} 340 nm for **1** was consistent with an (*S*)-configuration at the oxindole spirocenter (Figure 1.5).[5]



8

Figure 1.4

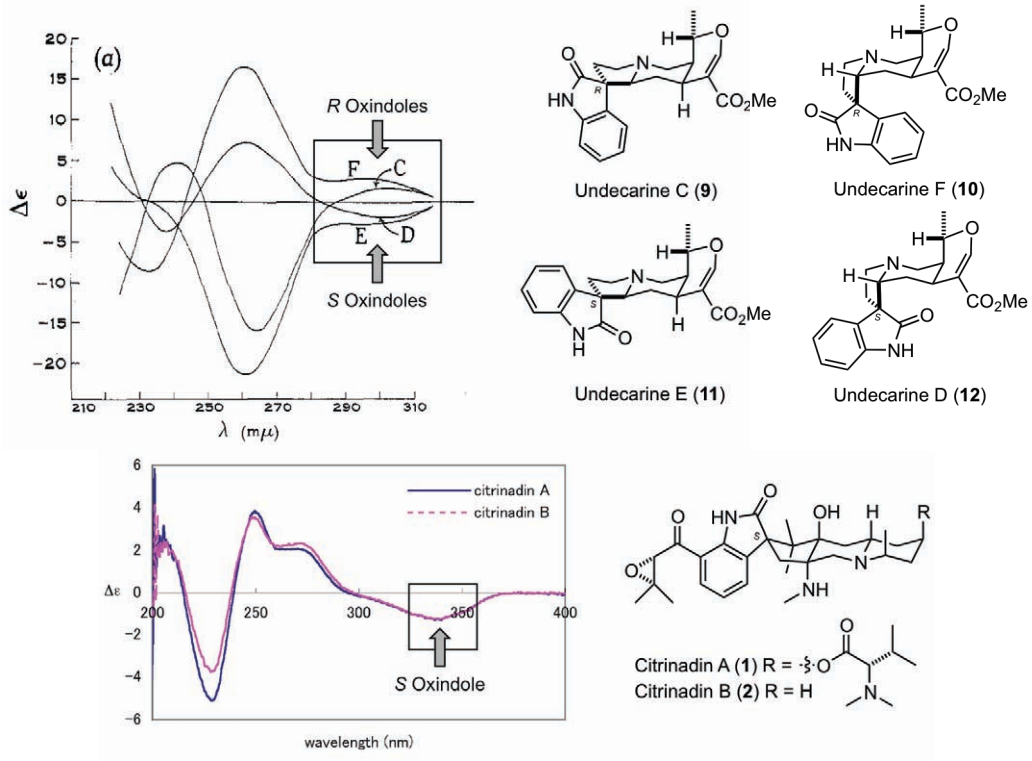


Figure 1.5

It is significant to note that alternate orientations of the flexible (*S*)-*N*,*N*-dimethylvaline side chain might support a different stereochemical assignment of C14. Furthermore, it has been demonstrated that not all spiro-oxindoles conform to the usual Cotton Effect (CE) trends. In one example, Hemmingway et al. have demonstrated that CD spectra for the rhynchophylline oxindole alkaloids Corynoxine and Corynoxine B and their 9-phenolic counterparts, Mitrafoline and Isomitrafoline display CEs of *opposite sign* for spiro-oxindoles of the *same* configuration (Figure 1.6).[6]

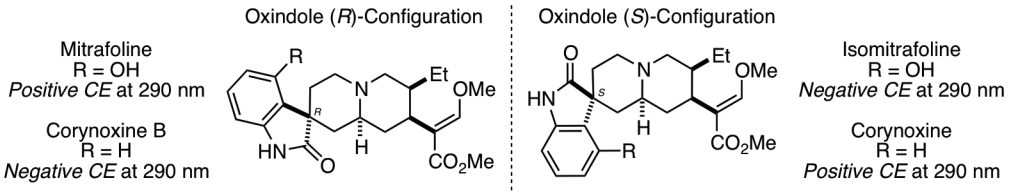


Figure 1.6

Unlike the citrinadins, the relative stereochemistry of PF1270A (**3**) was established not only by standard spectroscopic analysis but also by using X-ray crystallographic data.[3] PF1270A–C (**3**–**5**) each display a simple alkyl ester side chain instead of the *N*,*N*-dimethylvaline ester of citrinadin A, and the degree of oxidation at C18 and C28 also differs from the citrinadins. Particularly intriguing, however, is the fact that the relative stereochemistry of the epoxyketone side chain in PF1270A-C (as arbitrarily depicted in the isolation paper by Kushida) is opposite that assigned to **1** and **2** by Kobayashi.[7] Because Kushida does not establish absolute stereochemistry, an alternate interpretation of the data would imply that the epoxide configuration seen in the PF1270s is the same as the citrinadins while the PF1270 core is enantiomeric to the citrinadins (Figure 1.2).

1.1.2 Citrinadin Biological Activity

In addition to their interesting molecular architecture, the citrinadin natural products possess noteworthy biological activity. Both **1** and **2** have demonstrated cytotoxicity against murine leukemia L1210 cells (IC_{50} 6.2 μg/mL and 10 μg/mL respectively), and **1** has demonstrated activity against human epidermoid carcinoma KB cells (IC_{50} 10 μg/mL).[1,2]

PF1270A–C (**3**–**5**) have shown high affinity for both rat and human histamine H3 receptor (H3R) ligands and function as potent agonists therein (EC_{50} 0.12 μM, 0.15 μM, and 0.20 μM respectively).[3] Because H3Rs play a role in the release of neurotransmitters such as serotonin, noradrenalin and dopamine, it is believed that H3R ligands may hold potential for the treatment of diabetes, obesity and central nervous system (CNS) disorders. Although structurally similar to **3**–**5**, the citrinadins (**1** and **2**) have not been tested for analogous H3R biological activity. Indeed, in the absence of a total synthesis of **1** or **2**, lack of any remaining authentic samples precludes further analysis of citrinadin biological activity.

1.1.3 Other Structurally Relevant Natural Products

Many alkaloids which contain spiroindolinone moieties similar to **1** and **2** have been isolated from *Penicillium* and *Aspergillus* fungi. Some of these include the brevianamides[8] (**13**), paraherquamides[9] (**14**), marcfortines[10] (**15**), asperparalines[11] (**16**), and sclerotiamide[12] (**17**) (Figure 1.7).

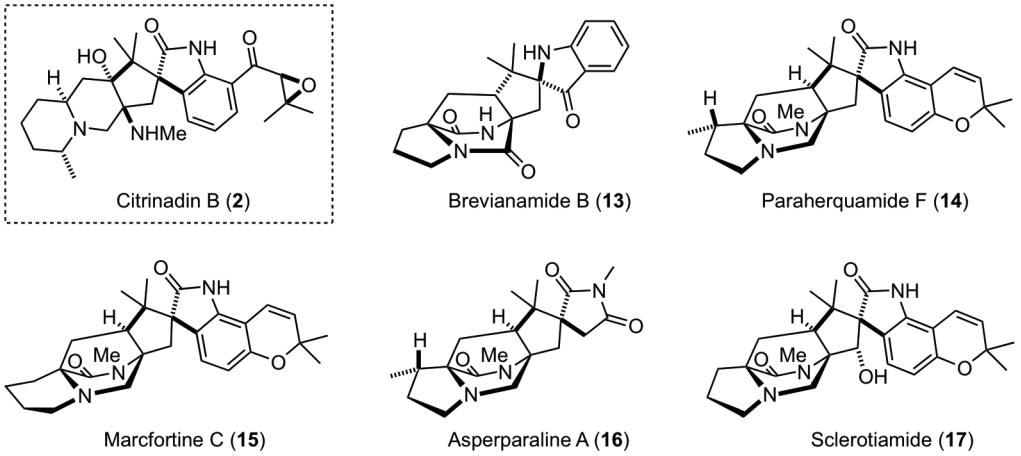


Figure 1.7

However, reports of natural products which contain the *N*,*N*-dimethylvaline residue are limited to 14-(*N*,*N*-dimethyl-L-valyloxy)paspaline (**18**), isolated[13] from *Aspergillus nominus*, and dolastatin 10 (**19**), isolated[14] from the sea hare *Dolabella auricularia* (Figure 1.8).

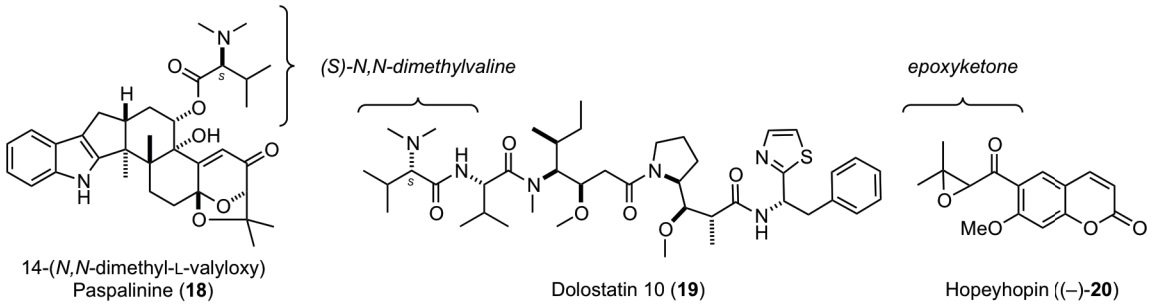


Figure 1.8

Likewise, examples of the epoxyketone unit are rare. C7-prenylated indoles have been isolated from *Aspergillus* fungi[15] as well as some containing a more oxidized epoxy isoprene substitution at C4.[16] But, other than **1**–**5**, the only other structure containing an epoxyketone moiety is hopeyhopin (**20**), a coumarin isolated from the *Amris madrensis* shrub in northeast Mexico (Figure 1.8).[17]

1.1.4 Biosynthesis of the Citrinadins

Kobayashi and coworkers have suggested two plausible biosynthetic pathways for the citrinadin core.[2] One possibility is that the citrinadin skeleton arose from modifications to a marcfortine-type structure, including loss of the bridging amide carbonyl, oxidation of C14 and C18, and methylation of C12. (Figure 1.9, Path A). Alternatively, the citrinadins may have derived from a dipeptide intermediate requiring the oxidation of C18 and C14 as well as the reduction of C27. (Figure 1.9, Path B). In either case, it appears that the natural building blocks of the citrinadins are L-pipecolic acid, L-tryptophan, and isoprene.[18]

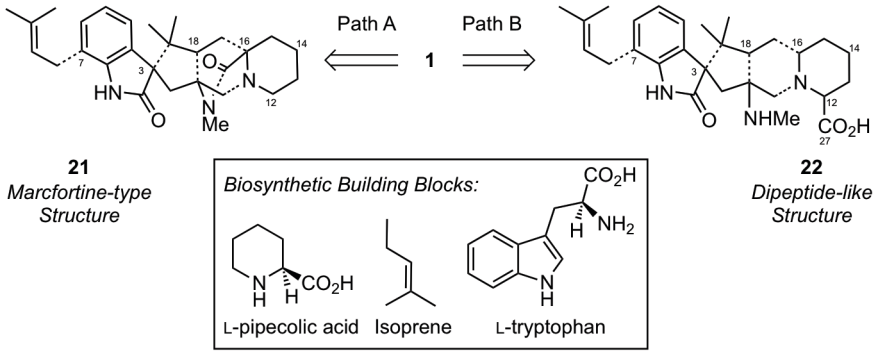


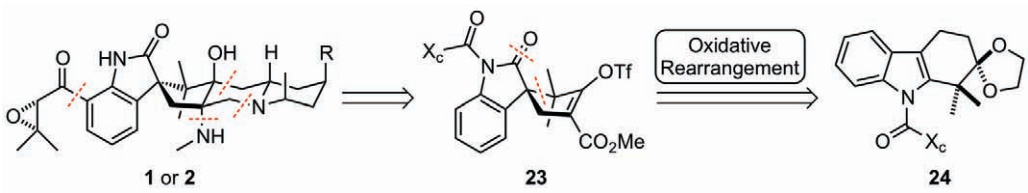
Figure 1.9

1.2 Previous Synthetic Efforts

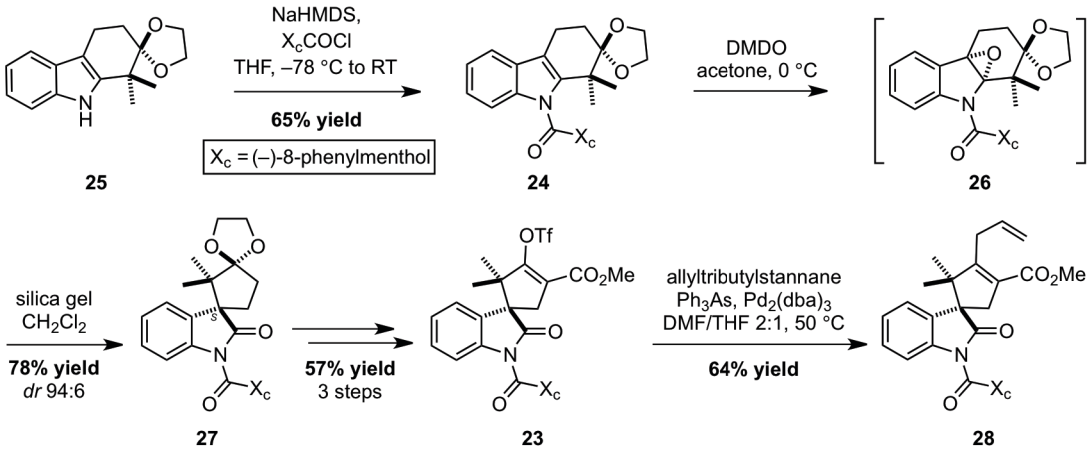
1.2.1 Martin Group Spiro-oxindole Synthesis

Martin and coworkers were the first to publish progress toward the synthesis of **1**.[19] Their approach highlights the oxidative rearrangement of an indole (**24**) to provide a spiro-oxindole (**23**) in stereoselective fashion (Scheme 1.1).

Scheme 1.1



Scheme 1.2



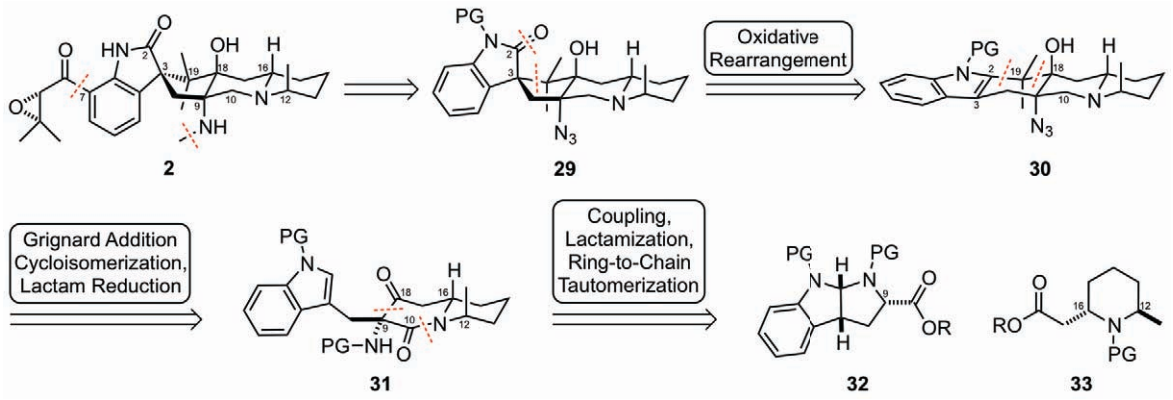
Exploration of the oxidative rearrangement revealed that treatment of a chiral, non-racemic *N*-acyl indole **24** with DMDO produced 2,3-epoxyindole **26**, which spontaneously rearranged to the desired spiro-oxindole **27** (78% yield, *dr* 94:6) in the presence of silica gel (Scheme 1.2). The newly generated quaternary center was found to possess the correct (*S*)-stereochemistry for the synthesis of **1**. The ABC-tricycle **27** was further elaborated to the ABC-triflate **23**. Subsequent cross-coupling of **23** with allyltribulylstannane served as a model reaction for an anticipated coupling to a piperidine fragment. While research in the Martin group is ongoing, details regarding their recent progress toward **1** have not yet been published.

1.2.2 Sorensen Group Synthesis of the Citrinadin Core.

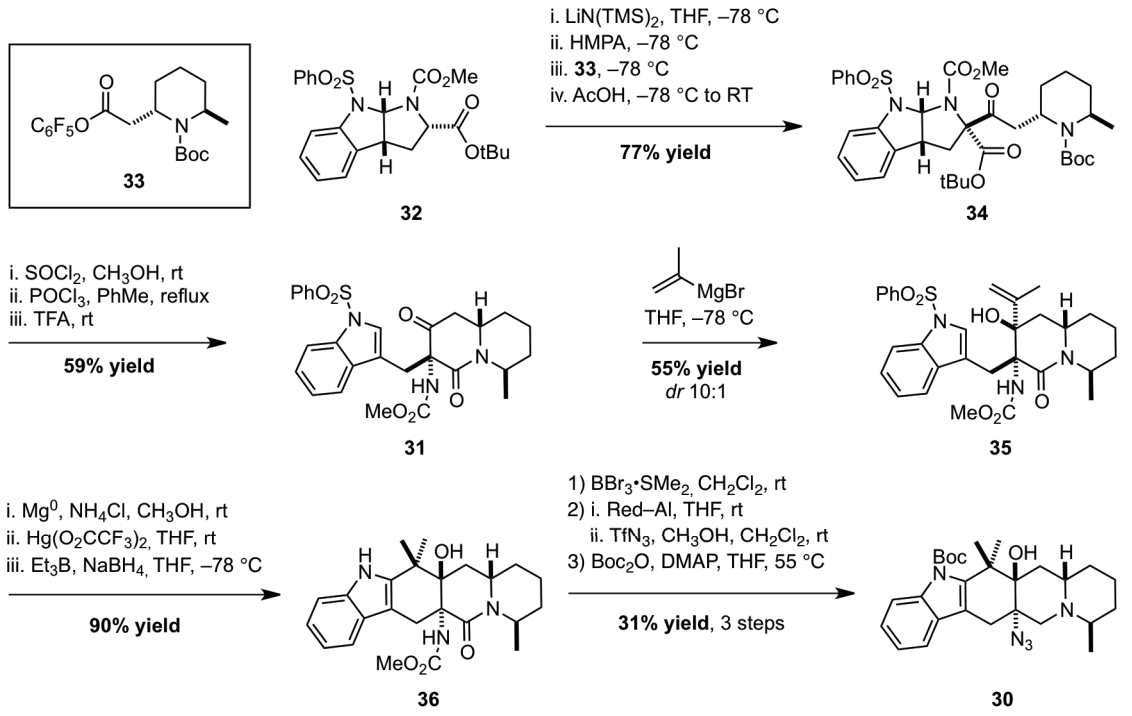
Reminiscent of Kobayashi's proposed citrinadin biosyntheses, Sorensen and Guerrero strategized that coupling a tryptophan-type fragment (**32**) and a piperdine fragment (**33**) might result in an intermediate that could be elaborated to tethered lactam **31** following a ring-to-chain tautomerization reaction (Scheme 1.3).[20] Elaboration of **31** to the pentacyclic indole **30** would provide an advanced substrate amenable to oxidative rearrangement, thus installing the C3 spiro-oxindole stereocenter similar to Martin et al.

Indeed, exposure of coupled product **34** to in situ generated hydrochloric acid facilitated Boc-removal (Scheme 1.4). Subsequent treatment with phosphorus oxychloride at elevated temperatures

Scheme 1.3



Scheme 1.4



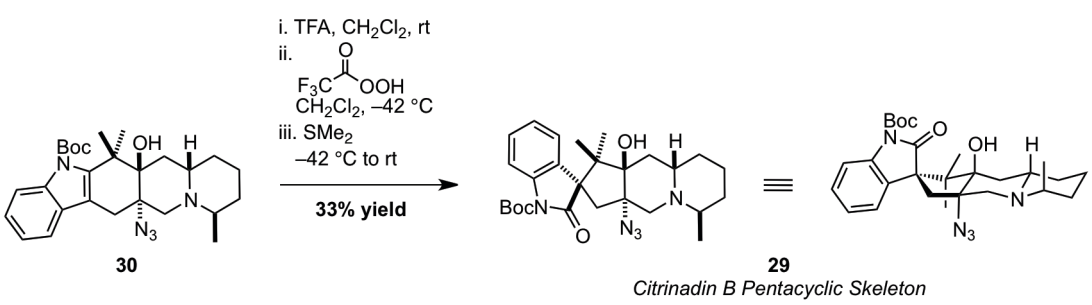
induced lactamization, and ring-to-chain tautomerisation of the pyrroloindoline moiety was accomplished using trifluoroacetic acid. Addition of iso-propenylmagnesium bromide to the ketocarbonyl of lactam **31** could be accomplished at low temperature (55% yield, *dr* 10:1 at –78 °C) to provide **35** diastereoselectively. Subsequent reductive deprotection of **35**, followed by mercury-assisted cyclization and reductive demercuration, gave the desired pentacyclic indole **36**. To avoid unwanted azetidine or cyclic imidate products during the key oxidative rearrangement, the angular nitrogen was masked as the

azide. Thus, removal of the carbamate was followed by reduction of the lactam and aziridination to provide azido alcohol **30**.

Successful oxidative rearrangement of the boc-protected substrate **30** was accomplished using a three-step protocol involving protonation of the tertiary amine with trifluoroacetic acid, oxidation of the indole with trifluoroperacetic acid, and addition of dimethyl sulfide to quench remaining unreacted oxidant (Scheme 1.5). Neutralization, workup, and purification of the reaction mixture provided the desired oxindole **29** as the major product**.**

In addition to converting the azide to the corresponding methyl amine, elaboration of **29** to **2** would require a non-trivial functionalization of the oxindole at C7. Nevertheless, the published synthesis of **29** constitutes a significant step toward the total synthesis of **1** and **2**.

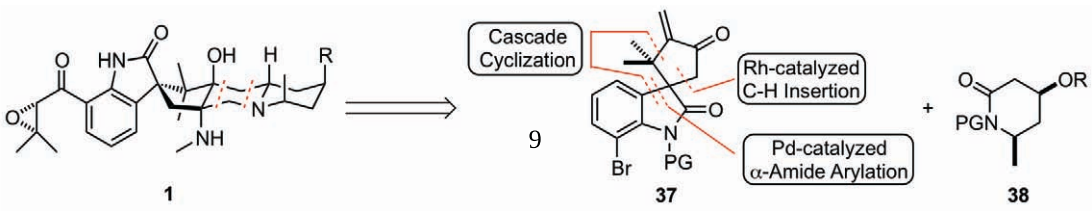
Scheme 1.5



1.2.3 Previous Wood Group Efforts.

Pursuit of the total synthesis of **1** and **2** in the Wood group was the result of a long-standing interest in the preparation of oxygenated indoles such as Welwitindolinones A and C and Diazonamide A.[21,22] Initial retrosynthetic analysis of **1** suggested a division of the molecule into two fragments: a lactam (**38**) and a spiro-oxindole (**37**) (Scheme 1.6). This led to the exploration of four synthetic strategies to access the more complex spiro-oxindole: rhodium-mediated C-H insertion, palladium-catalyzed α-amide arylation, radical cascade cyclization, and a reductive Heck cascade

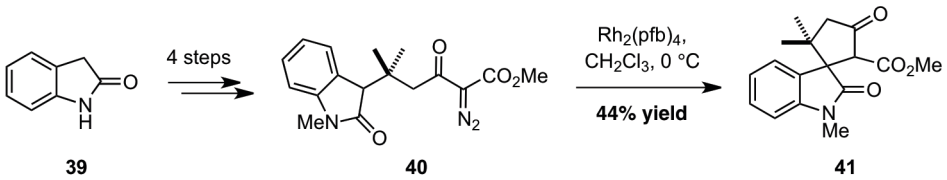
Scheme 1.6



cyclization.[23]

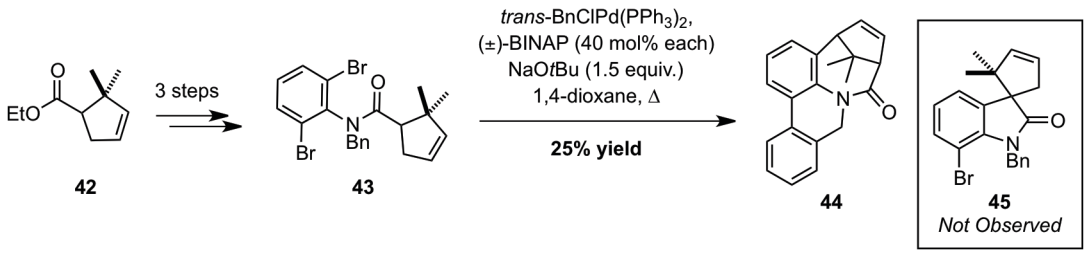
Previously developed group chemistry revealed that exposure of **40** to rhodium-mediated C-H insertion conditions resulted in the formation of spiro-oxindole **41** as one of two products (Scheme 1.7). Further exploration of reaction conditions revealed that the use of catalytic rhodium pentafluoroborate dimer could provide **41** as the sole product. Unfortunately, the C-H insertion strategy was abandoned owing to the difficulty of preparing more elaborated substrates.

Scheme 1.7



A revised strategy suggested that spiro-oxindole **45** could be formed using a palladium catalyzed α-amide arylation (Scheme 1.8). Dibromoanilide **43**, synthesized in three steps from known ester **42**, was used as a substrate to explore potential arylation conditions. Classic α-amide arylation conditions resulted exclusively in the recovery of starting material, and an increase in catalyst loading merely provided the bridged pentacycle **44**. This side product was speculated to be the result of both an undesired Heck coupling and a biaryl coupling to the benzyl protecting group. In an effort to overcome this undesired Heck pathway, the reactive olefin of **43** was first oxidized to the diol, then protected as the acetonide and subjected to α-amide arylation conditions. However, none of the desired arylation product was obtained.

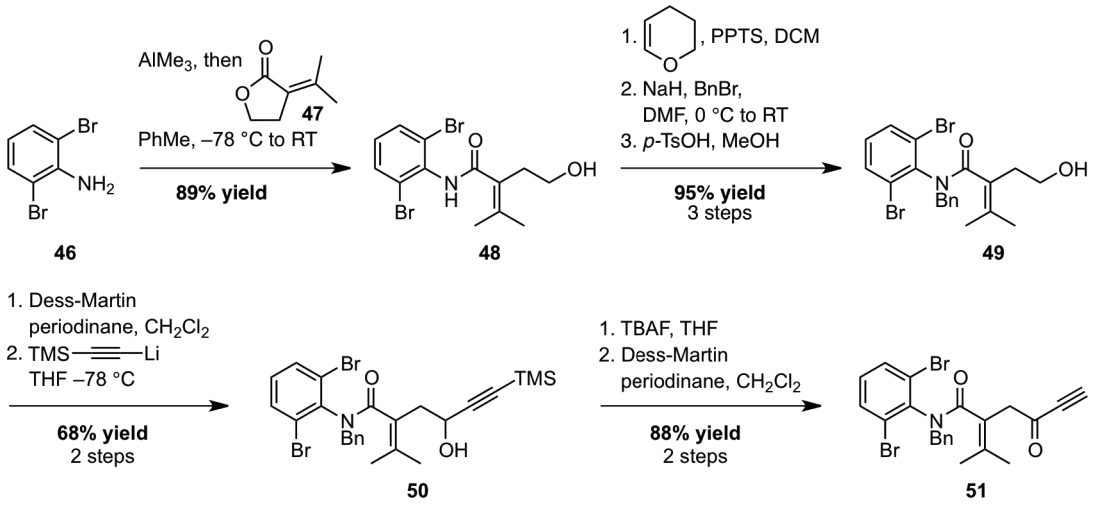
Scheme 1.8



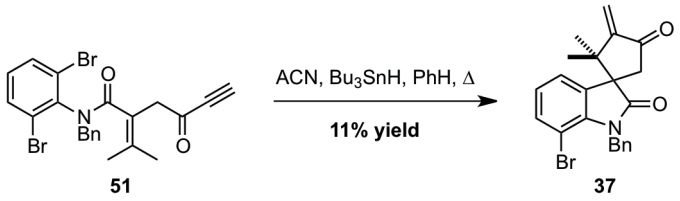
Hypothesizing that the desired spiro-oxindole might be accessible via a radical cascade cyclization, propargyl ketone **51** was synthesized in eight steps from dibromoanaline **46** (Scheme 1.9). Gratifyingly, when treated with the radical initiator, 1,1'-azobis-1-cyclohexanenitrile (ACHN) in the

presence of tributyltin hydride, **51** successfully underwent the desired cyclization to provide spiro-oxindole

Scheme 1.9



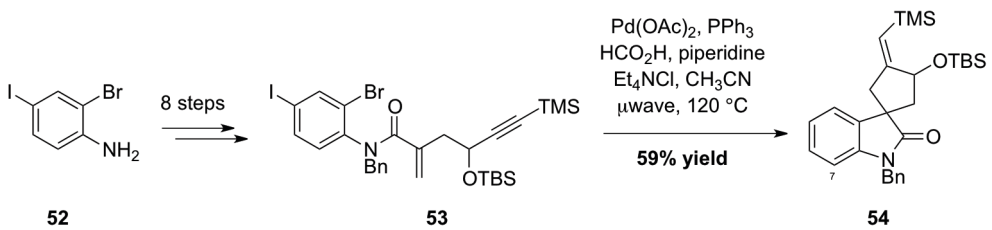
Scheme 1.10



37 (Scheme 1.10). Unfortunately, attempts to increase the yield of this reaction using other radical initiators, hydride sources, or solvent combinations were not effective. Thus, a modified strategy incorporating a reductive Heck reaction was investigated.

Reductive Heck cyclization substrate **53** was synthesized in eight steps from 2-bromo-4-iodoaniline (Scheme 1.11). Because, aniline **52** was initially misassigned as its 2-bromo-6-iodoaniline counterpart, the reductive cyclization of anilide **53** was expected to yield a C7-brominated spiro-oxindole. In practice, anilide **53** underwent reductive deiodination first, followed by reductive cyclization, to yield spiro-oxindole **54**. Utilization of microwave-mediated conditions provided **54** in high yield.

Scheme 1.11



1.3 Conclusions

Marine derived fungi continue to act as a primary source for structurally intriguing and biologically relevant secondary metabolites including **1** and **2**. Synthesis of the citrinadins would allow for further testing of their biological activity, in particular as H3R ligands, which are known to play an important role in the release of neurotransmitters. Additionally, the synthesis of complex natural products remains the best way to confirm their assigned structures.

While, no total synthesis of **1** or **2** has been reported to date, two synthetic approaches toward the citrinadins have been disclosed. Martin et al. have detailed the ability to use an oxidative rearrangement of an *N*-acyl indole to stereoselectively provide the spiro-oxindole moiety of the citrinadins. Sorensen and Guerrero have outlined an efficient, stereoselective route for the construction of the pentacyclic skeleton of **1** and **2**.

In the Wood group, a number of synthetic strategies targeting the formation of the citrinadin spiro-oxindole have been explored including: rhodium-mediated C-H insertion, palladium-catalyzed α-amide arylation, radical cascade cyclization, and reductive Heck cascade cyclization. Of these, the most promising approach proved to be a reductive cyclization strategy.

1.4 Notes and References

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CHAPTER 2

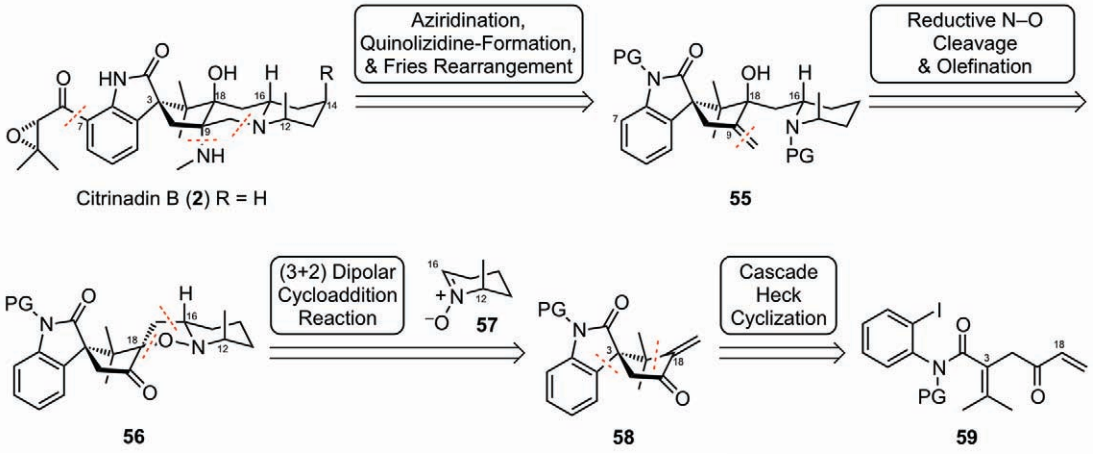
Accessing the C3-*epi*-Citrinadin B Core

2.1 Developing a Retrosynthetic Strategy

In developing a synthesis of the citrinadin natural products (**1** and **2**), we chose to focus on strategies that would provide access to either natural product congener; however initial efforts were devoted to a route leading to the simpler of the two, Citrinadin B (**2**).

In a retrosynthetic sense, removal of the epoxyketone-containing side-chain and rupture of the central ring produced the tethered piperdine **55** as a potential synthetic precursor to **2.** In the forward sense, aziridination of the exocyclic olefin of **55** would set the stage for an intramolecular nucleophilic opening. This would directly provide the requisite amine and alcohol moieties at the angular positions while

Scheme 2.1



simultaneously establishing the core quinolizidine ring-system (Scheme 2.1). Late stage incorporation of the C7-epoxycarbonyl side chain was envisioned to occur intramolecularly via a Fries-type rearrangement of an *N*-acylated intermediate or through a C–H activation process.

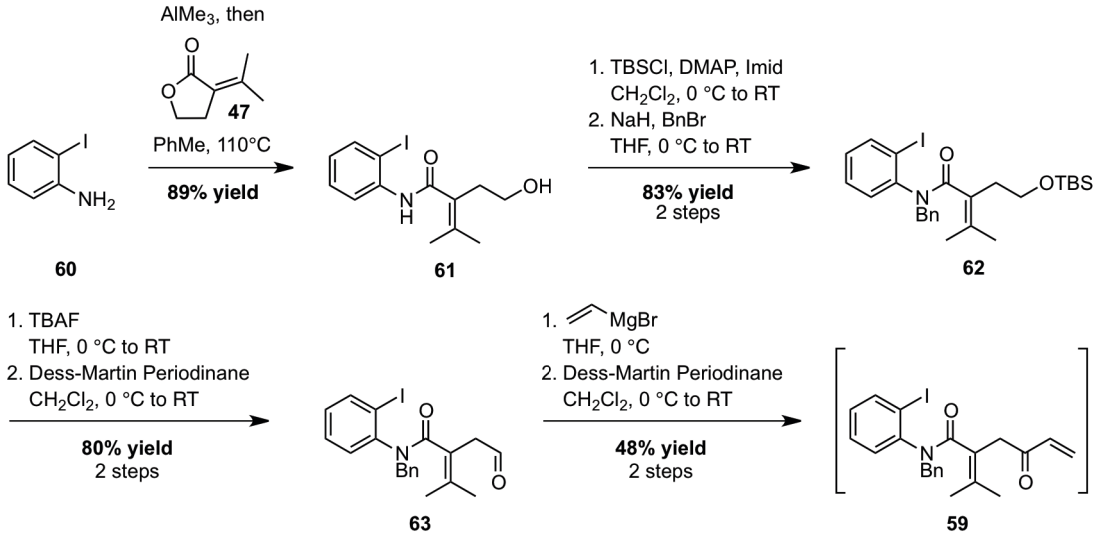
Tethered piperdine **55** was envisioned to arise from the reductive opening of an isoxazolidine scaffold **56**, itself the product of a key (3+2) dipolar cycloaddition reaction[1] between a spiro-oxindole dipolarophile (**58**) and a nitrone[2] (**57**). Although the number of possible regio– and stereo– chemical outcomes of the proposed cycloaddition was daunting, the convergency of this approach was nevertheless attractive. The possibility of nitrone **57** approaching dipolarophile **58** from the opposite face of the C12 methyl group bolstered our confidence in regard to achieving the desired diastereoselectivity, and it was further recognized that reduction of **58** to the corresponding allylic alcohol might allow for the use of beneficial steric or directing effects in the reaction. Spiro-oxindole dipolarophile **58** was expected to arise from a stereoselective cascade Heck cyclization of anilide **59**.

2.2 Spiro-oxindole Synthesis

2.2.1 Cascade Heck Cyclization Strategy

The successful cascade Heck cyclization of aryl bromide **53** to form spiro-oxindole (±)-**54** (See Chapter 1) inspired initial efforts to synthesize spiro-oxindole **58** from aryl iodide **59**. To that end, 2-

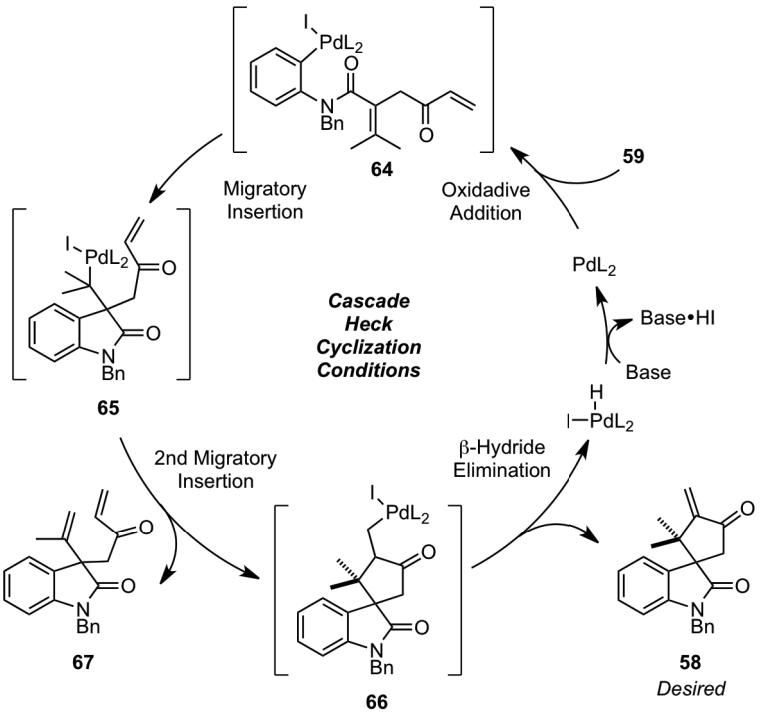
Scheme 2.2



iodoaniline **60** was smoothly coupled with lactone[3] **47** in the presence of trimethylaluminum to furnish alcohol **61** (Scheme 2.2). Routine functional group manipulations were employed to provide aldehyde **63**, where addition of vinylmagnesium bromide and subsequent Dess–Martin oxidation resulted in the formation of enone[4] **59,** which was carried directly into the next step.

Multiple conditions for the projected tandem cyclization of **59** to form **58** were explored (Scheme 2.3). Ideally, oxidative addition of palladium to aryl iodide **59** followed by olefin insertion would furnish oxindole-containing intermediate **65**, poised for a second migratory insertion that would deliver spirocycle **66**, an intermediate from which β-hydride elimination was expected to furnish **58**. In practice, under cationic Heck conditions using silver phosphate, none of the desired spiro-oxindole product **58** was formed. Neutral conditions resulted in the formation of oxindole **67**, an interrupted product arising from facile β-hydride elimination of **65**. Reasoning that lower reaction temperatures might suppress the unwanted

Scheme 2.3



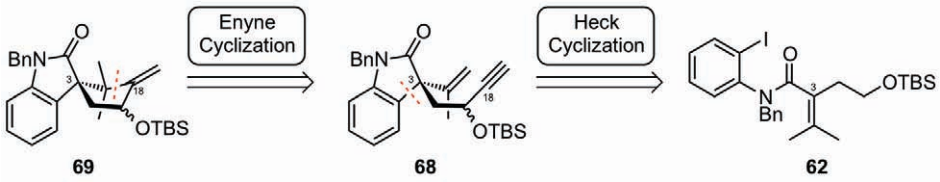
Conditions	*Yield*
$Pd_2(dba)_3$, (+)-BINAP, Ag_3PO_4, DMA, 90 °C	decomp.
$Pd(OAc)_2$, (+)-BINAP, PMP, PhMe, 95 °C	10% **67**
$Pd(OAc)_2$, nBu_4NCl, K_2CO_3, DMF, RT	33% **67**
$Pd(OAc)_2$ (1 equiv.), DMF, RT	62% **67**

β-hydride elimination, Jeffery's conditions were employed at room temperature.[5] Although these conditions successfully promoted Heck cyclization, oxindole **67** remained as the only isolable product. Indeed, premature β-hydride elimination resulting in the formation of **67** could not be suppressed even in the presence of a stoichiometric amount of palladium acetate ($Pd(OAc)_2$) and the exclusion of exogenous base.

2.2.2 Stepwise Cyclization Strategy

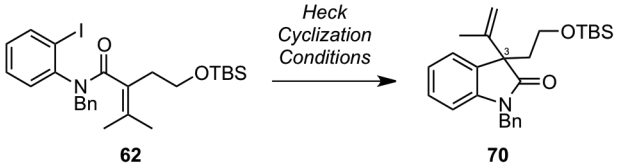
Although the undesired β-hydride elimination proved insurmountable, we were mindful that the informative synthesis of **67** could yet be applied to a synthesis of **58**; thus, a revised strategy was devised. An asymmetric Heck cyclization[6] of **62** would be followed by a deprotection/oxidation/alkylation sequence that would furnish enyne **68** and set the stage for a second palladium-mediated cyclization to give allylic alcohol **69** (Scheme 2.4).[7]

Scheme 2.4



Using standard Heck conditions ($Pd(OAc)_2$, PPh_3, PhMe), **62** was found to undergo smooth transformation to oxindole (±)-**70** in quantitative yield (Scheme 2.5). Disappointingly, attempts to effect this transformation with asymmetric catalysts were met with low yields. Nevertheless, these latter efforts provided some insight in that both palladium dibenzylideneacetone ($Pd_2(dba)_3$) and $Pd(OAc)_2$ were acceptable precatalysts in the presence of (+)-BINAP, although $Pd(OAc)_2$ provided oxindole **70** with

Scheme 2.5

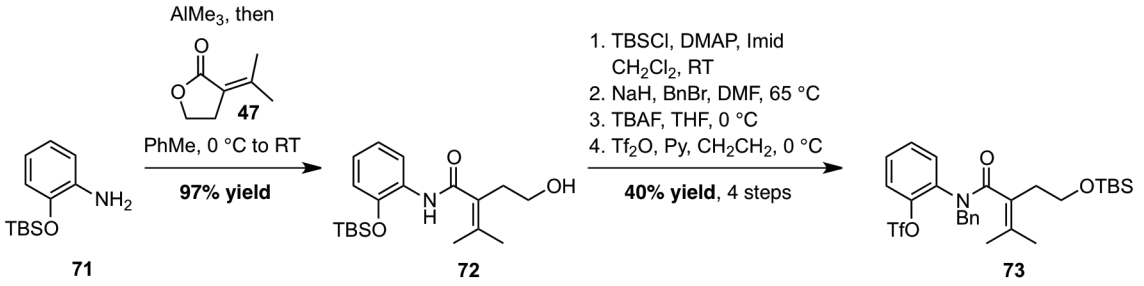


Conditions	*Yield*	*ee*
$Pd(OAc)_2$, PPh_3, NEt_3, PhMe, 110 °C	96%	N/A
$Pd_2(dba)_3$, (+)-BINAP, PMP, DMA, 80 °C	24%	18%
$Pd(OAc)_2$, (+)-BINAP, PMP, DMA, 80 °C	25%	24%
$Pd_2(dba)_3$, (+)-BINAP, Ag_3PO_4, DMA, 80 °C	65%	16%

slightly improved enantioexcess. Furthermore, a screen of various solvents revealed that polar solvents had a beneficial effect on the enantioenrichment of **70** (toluene: 43% yield, 0% ee; CH_3CN: 15% yield, 8% ee; THF: 37% yield, 1% ee; NMP: 35% yield, 15% ee). Upon switching to cationic conditions (Pd_2dba_3, Ag_3PO_4, DMA), yields of **70** increased but the enantioselectivity was worse. These results suggested that an increase in the lability of the Pd–X bond might facilitate better bidentate coordination of the chiral ligand, and thus result in better enantioenrichment.[8] To that end, a pursuit of aryl triflate **73** ensued.

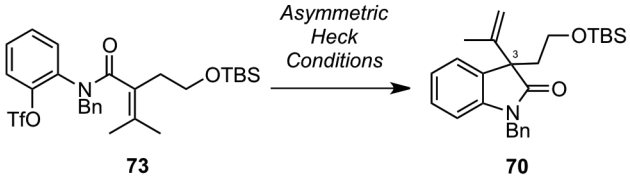
Similar to **60**, synthesis of **73** began with the trimethylaluminum-mediated coupling of lactone **47** and *tert*-butyldimethylsilyloxy aniline **71**, followed by protection of the primary alcohol and amide (Scheme 2.6). Selective cleavage of the phenolic silyl ether required treatment with one equivalent of TBAF,[9] whereupon conversion to the corresponding triflate **73** provided the desired substrate for investigation of an asymmetric Heck cyclization.

Scheme 2.6



Gratifyingly, aryl triflate **73** proved to be superior to aryl iodide **62** in the asymmetric Heck cyclization (Scheme 2.7). The choice of solvent once again proved integral to enantioenrichment, and among the solvents screened, DMA was found to be optimal. Unlike the cyclization of aryl iodide **62**, however, the use of $Pd(OAc)_2$ proved inferior to $Pd_2(dba)_3$. The use of (+)- or (–)-BINAP allowed for the preparation of both antipodes of **70**.[10,11]

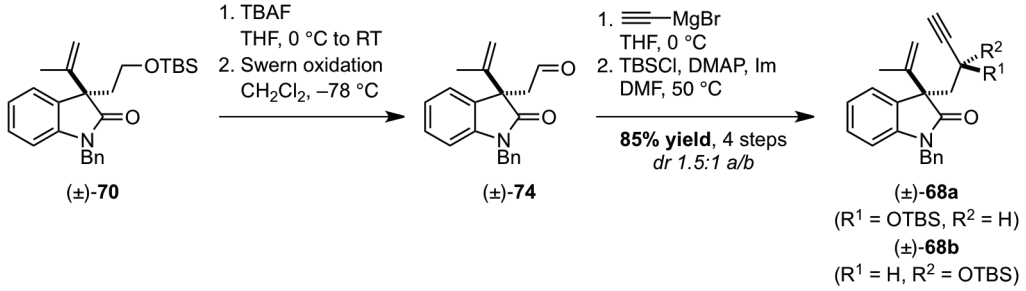
Scheme 2.7



Conditions	*Yield*	*ee*
$Pd_2(dba)_3$, (+)-BINAP, PMP DMA, 110 °C , 20 h	85% (–)-**70**	65%
$Pd_2(dba)_3$, (–)-BINAP, PMP DMA, 110 °C , 20 h	96% (+)-**70**	80%

With an eye toward the proposed reductive enyne cyclization of **68**, silyl ether (±)-**70** was treated with TBAF and oxidized to provide aldehyde (±)-**74** (Scheme 2.2.8). This was subjected to ethynylmagnesium bromide resulting in two diasteromeric propargylic alcohols (*dr* 1.5:1), which were masked as the corresponding silyl ethers (±)-**68a/b**.[12]

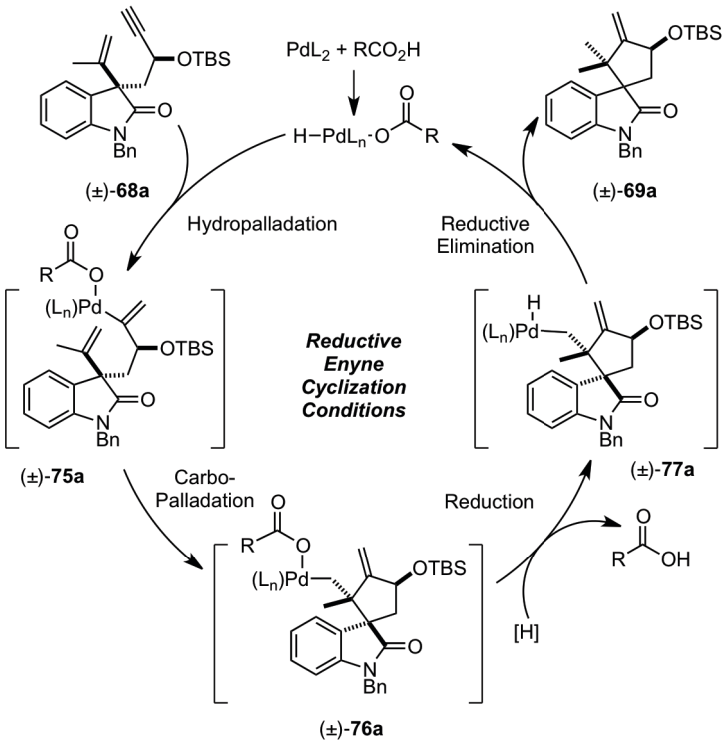
Scheme 2.8



(±)-**70** (±)-**74** (±)-**68a** (R^1 = OTBS, R^2 = H) (±)-**68b** (R^1 = H, R^2 = OTBS)

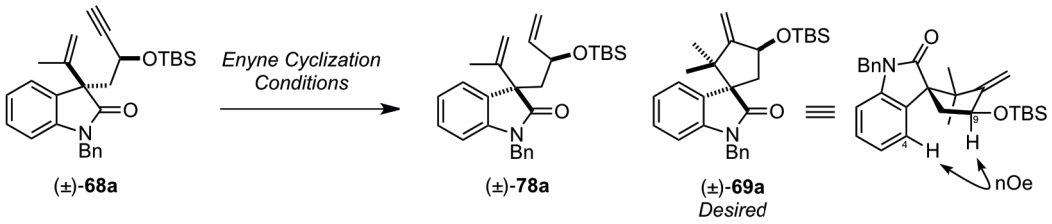
The subsequent palladium-catalyzed reductive cyclization of (±)-**68a** was expected to occur via hydropalladation of the akyne (i.e., (±)-**75a**) followed by carbo-palladation (i.e., (±)-**76a**) to form the desired carbon–carbon bond (Scheme 2.9). Exogenous reduction of palladium (i.e., (±)-**77a**) and reductive elimination would generate the desired carbocycle (±)-**69a** and regenerate the palladium catalyst.

Scheme 2.9



In practice, Trost's conditions[13] ($Pd_2(dba)_3$, (*o*-tol)$_3$P, PMHS, AcOH, PhMe) only resulted in the formation of an uncyclized allylic alcohol (±)-**78a**, the product of a direct, premature reduction of the hydropalladation intermediate (±)-**75a** (Scheme 2.10). Our understanding of the mechanism suggested that the use of a less potent reducing reagent at higher dilution would discourage the unwanted formation of (±)-

Scheme 2.10

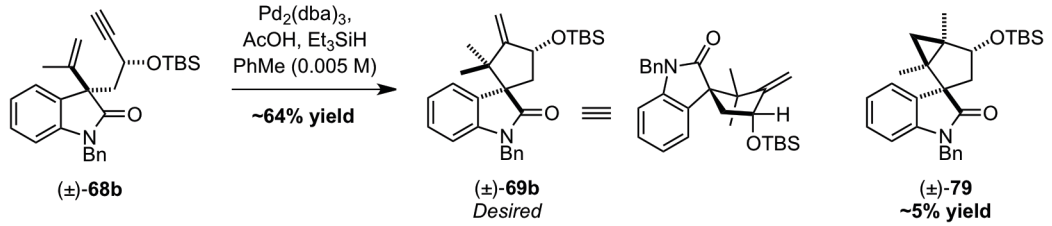


Conditions	*Result*
$Pd_2(dba)_3$, (*o*-Tol)$_3$P, AcOH, PMHS, PhMe (0.02 M)	63% yield (±)-**78a**
$Pd_2(dba)_3$, AcOH, Et_3SiH, PhMe (0.005 M)	~60% yield (±)-**69a**

78a, and this indeed proved to be the case.[14] Modified conditions ($Pd_2(dba)_3$, Et_3SiH, AcOH, 0.005 M PhMe)—where the omission of the phosphine ligand also proved beneficial[15]—resulted in isolation of the desired cyclic alylic alcohol (±)-**69a** as the major product, the relative stereochemistry of which was assigned based on NOE correlations.

Analagously, (±)-**68b** could be advanced to the cyclic alylic alcohol (±)-**69b** (Scheme 2.11). Interestingly, a cyclopropane by-product ((±)-**79**) was also observed in the reaction mixture and presumed to be the result *two* consecutive carbopalladations.[16]

Scheme 2.11

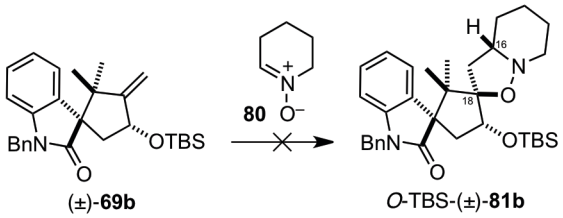


2.3 The (3+2) Cycloaddition Reaction

*2.3.1 Using Model Nitrone **80***

Eager to investigate the postulated (3+2) cycloaddition reaction, our initial investigations began with the newly formed dipolarophiles (**±**)-**69a/b** and model nitrone **80**—readily synthesized[17] by the selenium oxide catalyzed oxidation of piperidine. Unfortunately, heating a mixture of silyl ether (±)-**69b** and nitrone **80** in a variety of solvents did not provide the desired cycloaddition product *O*-TBS-(±)-**81** (Scheme 2.12).

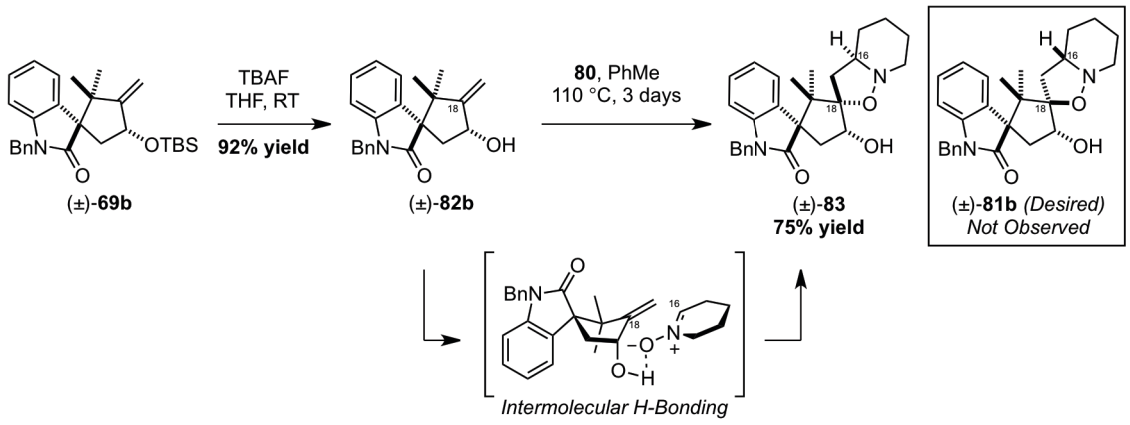
Scheme 2.12



Conditions	*Results*
PhMe, 130 °C, 24h	66% recovered (±)-**69b**
1,2-dichlorobenzene, 190 °C, 10h	61% recovered (±)-**69b**
Nitrobenzene, 240 °C, 4h	decomposition

Suspecting that the bulky silyl group on dipolarophile (±)-**69b** might be the cause of the sluggish reactivity, it was removed with TBAF (Scheme 2.13). Gratifyingly, under the cycloaddition reaction conditions, allylic alcohol (±)-**82b** proved much more reactive and provided isoxazolidine (±)-**83** in good yield. Unfortunately, extensive NMR analysis of isoxazolidine (±)-**83** indicated the *opposite* stereochemistry at C16 and C18 relative to Citrinadin B (**2**). It was reasoned that during the dipolar cycloaddition reaction, nitrone **80** was approaching olefin (±)-**82b** from the same face as the free hydroxyl

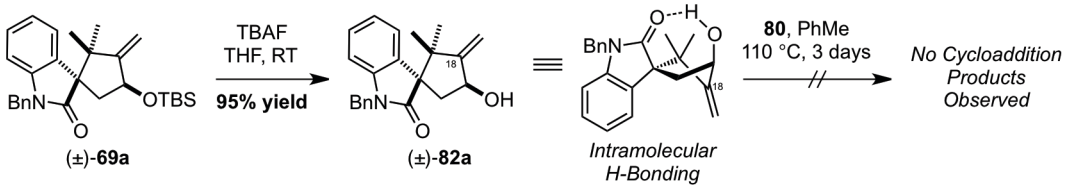
Scheme 2.13



group, implying that intramolecular hydrogen bonding might be directing the process.[18] The possibility of a hydrogen bond in the cycloaddition was further supported by the observation that the methyl ether of allylic alcohol (±)-**82b** was nonreactive under identical conditions, presumably due to the removal of its hydrogen bonding capability.

The implications of hydrogen bonding during the cycloaddition reaction prompted us to employ dipolarophile (±)-**69a** in the hope that the opposite alcohol stereochemistry would direct the incoming nitrone to the desired olefin face (Scheme 2.14). Surprisingly however, allylic alcohol (±)-**82a** was reluctant to participate in the cycloaddition at all under thermal conditions. Lewis acid ($MgBr_2$•Et_2O), Brönsted acid (TFA), and the combination of EtMgBr/*i*PrOH were each explored as additives to promote the cycloaddition reaction. Unfortunately, only recovered starting material was obtained. A plausible explanation for the marked difference in reactivity between allylic alcohols (±)-**82a** and (±)-**82b** was the presence of an *intramolecular* hydrogen bond between the hydroxyl group of (±)-**82a** and the neighboring oxindole carbonyl (i.e., Scheme 2.14). This hypothesis was supported by the relatively low IR stretch of the oxindole carbonyl (1687 cm^{-1}) of (±)-**82a** compared with that of (±)-**82b** (1701 cm^{-1}), as well as a downfield OH shift in the ^1H NMR of (±)-**82a** (4.51 ppm). Such hydrogen bonding might serve to disrupt any pre-association of the hydroxyl group of (±)-**82a** with the incoming nitrone **80**, thereby disabling the reaction.

Scheme 2.14

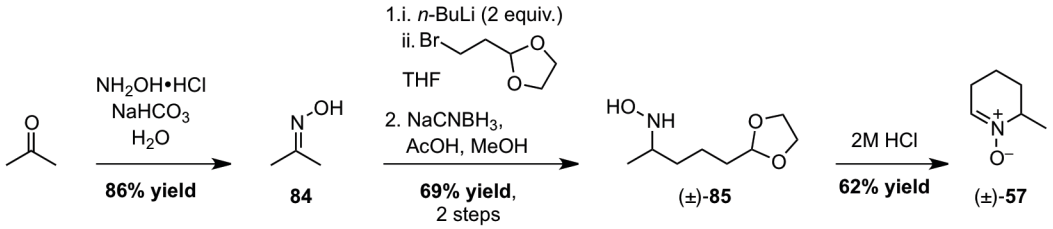


At this stage, preliminary studies using the model nitrone **80** had inspired confidence in the feasibility of the dipolar cycloaddition reaction, but issues of stereochemical control remained unsolved. The synthesis of a more functionalized and stereogenic nitrone (i.e., **57** in Scheme 2.15) that would be better suited for the synthesis of **2** became the next objective. Of particular importance was the ability of the stereocenter resident in **57** to impart some stereocontrol into the (3+2) process.

2.3.2 Using Methyl-Substituted Nitrone 57

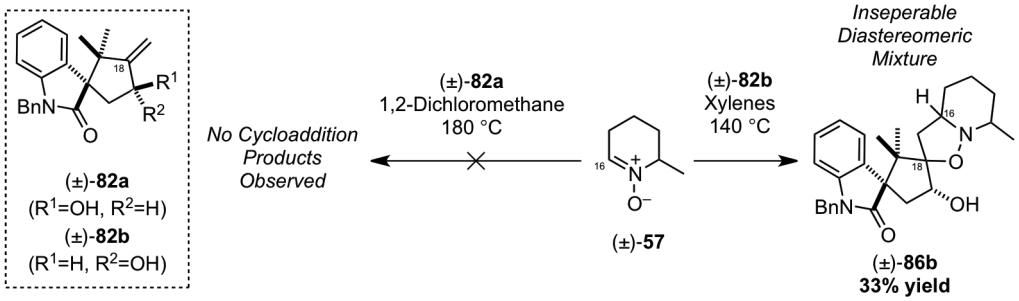
The synthesis of nitrone (±)-**57** was achieved in 4 steps. Alkylation of oxime **84,** derived from acetone, was followed by a sodium cyanoborohydride reduction to give **85** (Scheme 2.15).[19] Exposure to acidic conditions unmasked the aldehyde allowing intramolecular condensation to furnish nitrone (**±**)-**57**. Not surprisingly, nitrone (±)-**57** displayed reactivity similar to nitrone **80** in the (3+2) cycloaddition reaction (Scheme 2.16). Heating a mixture of (±)-**57** and racemic allylic alcohol (±)-**82b** provided an inseparable mixture of diastereomeric isoxazolidines, whereas no reaction was observed between (±)-**57** and (±)-**82a**.

Scheme 2.15

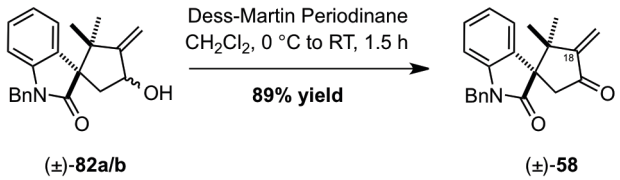


At this stage an alternate dipolarophile was explored as a potential substrate for the cycloaddition. Enone (**±**)-**58** was readily prepared from (±)-**82a** or (±)-**82b** upon Dess–Martin oxidation (Scheme 2.17). To our delight, enone (**±**)-**58** participated readily in a cycloaddition with nitrone (±)-**57** at ambient

Scheme 2.16

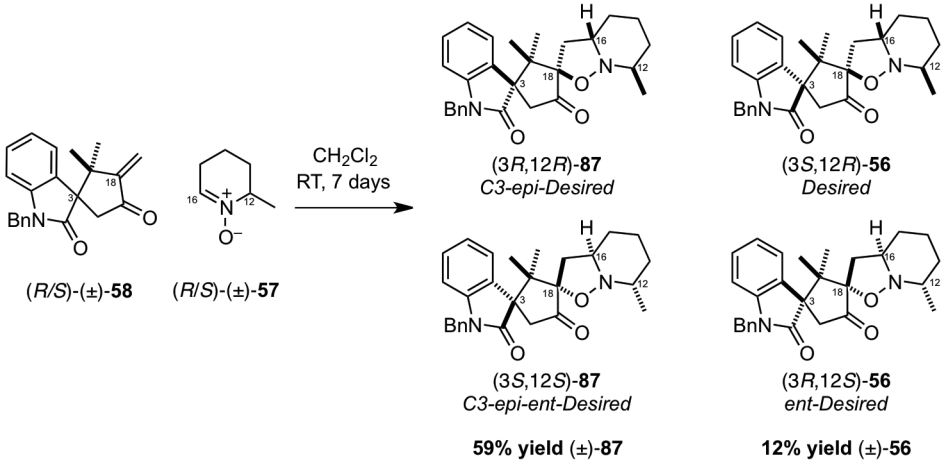


Scheme 2.17

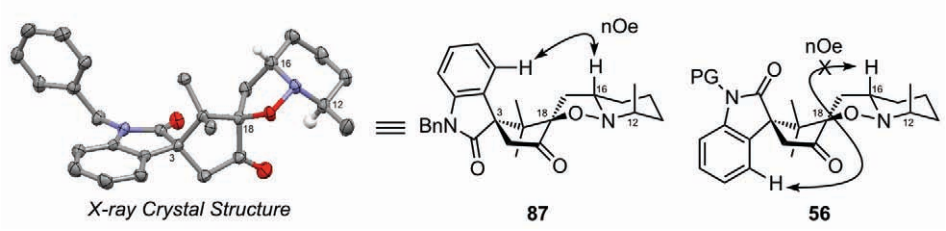


temperature, giving rise to two isoxazolidine adducts (Scheme 2.18). A Comparison of the NOE correlations for both products confirmed that the minor diastereomer (±)-**56** possessed the requisite stereochemistry for a synthesis of Citrinadin B (**2**), and the stereochemistry of the major isoxazolidine diastereomer (±)-**87** was unambiguously established through X-ray crystallographic analysis (Scheme 2.19).

Scheme 2.18



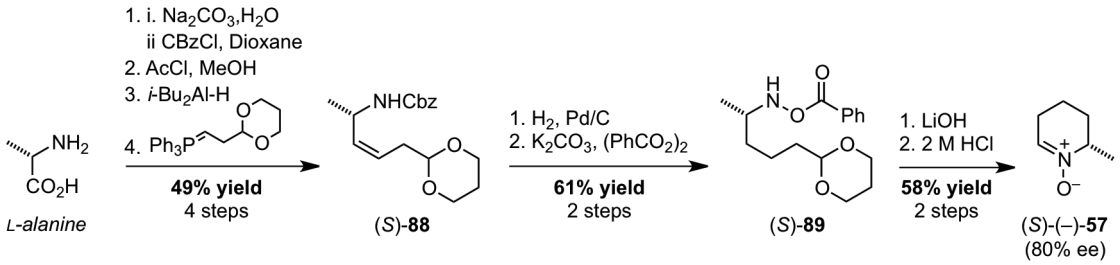
Scheme 2.19



In contrast to the cycloadditions employing allylic alcohol (±)-**82b** as the dipolarophile, the stereochemical outcome of the racemic cycloaddition reaction of enone (**±**)-**58** and nitrone (±)-**57** demonstrated that the chiral center in the nitrone was now the dominant stereocontrolling element of the reaction. Specifically, the stereochemistry of C16 and C18 in both isoxazolidine diastereomers (±)-**56** and (±)-**87** derived from the enone approaching the nitrone from the *face opposite to the methyl substituent*.

It was recognized that a cycloaddition of nonracemic enone **58** and nitrone **57** should provide the desired isoxazolidine **56** as the major product. The nonracemic enones (3*S*)-(+)-**58** and (3*R*)-(–)-**58** were accessible by advancing the enantioenriched oxindoles, (+)-**70** and (–)-**70** respectively.[10] Enantioenriched nitrone (12*S*)-(–)-**57**, on the other hand, had to be prepared following a known procedure[20] starting from L-

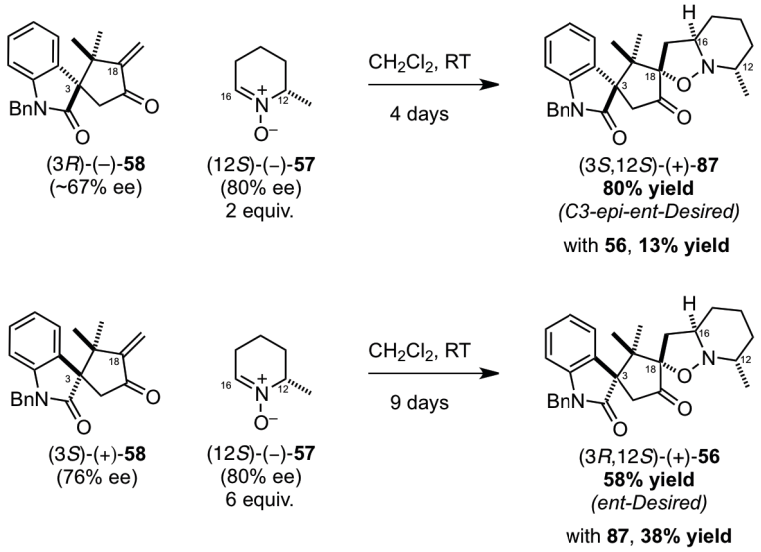
Scheme 2.20



alanine (>98% ee) (Scheme 2.20).[21] In the event, Cbz-L-alanine methyl ester was carefully reduced to the aldehyde, which was then subjected to a Wittig olefination to provide the (Z)-alkene (*S*)-**88**. Reduction of the double bond, as well as cleavage of the Cbz group, was achieved in a single operation. The derived primary amine was oxidized with benzyl peroxide to afford *O*-hydroxyl amine ester (*S*)-**89**. Generation of the chiral nitrone (12*S*)-(–)-**57** occurred following saponification of the ester and treatment with aq. HCl. Using chiral HPLC analysis of an *N*-acylated hydroxylamine derivative of (12*S*)-(–)-**57**, the ee of the nitrone was determined to be 80%. Unfortunately, partial racemization, most likely occurring during the DIBAL reduction or Wittig olefination step, prevented isolation of enantiopure nitrone.

Cycloadditions between nitrone (12*S*)-(–)-**57** and either antipode of enone **58** were subsequently explored (Scheme 2.21).[10] The reaction between enone (–)-**58** (67% ee) and nitrone (12*S*)-(–)-**57** (76% ee) expediently provided two isoxazolidine products with (3*S*,12*S*)-(+)-**87** being the predominant stereoisomer. In accord with observations using racemic substrates, the cycloaddition between enone (+)-**58** and nitrone

Scheme 2.21



(12*S*)-(–)-**57** was more sluggish but nevertheless furnished a predominant product, (3*R*,12*S*)-(+)-**56,** that was diastereomeric to **87** at C3.

Taken together, the cycloaddition between (3*R*)-(–)-**58** and (12*S*)-(–)-**57** to form (+)-**87** in 80% yield reflects the *matched* nature of the cycloaddition substrates. On the other hand, the cycloaddition of (3*S*)-(+)-**58** and (12*S*)-(–)-**57** to form (3*R*,12*S*)-(+)-**56** in 58% yield, appears to be *mismatched*.[22] Quite remarkably, even in the mismatched case, **56** and **87** were the only products formed in the reaction.

2.4 Synthesis of the C3-*epi*-Citrinadin Core

2.4.1 The Challenge of Wittig Olefination

Having successfully coupled spiro-oxindole **58** and nitrone **57** together through a dipolar cycloaddition that furnished pentacyclic **56**, the next task was to rupture the superfluous N–O bond (Scheme 2.22). For the purpose of exploratory studies, the readily available isoxazolidine diastereomer (±)-**87** was used as a model substrate in the subsequent reactions. Initially a reductive cleavage of the N–O bond of isoxazolidine (±)-**87** followed by olefination of the C9 carbonyl was explored. Unfortunately this approach was not successful, resulting in attempts to access **90** by inducing olefination prior to N–O bond cleavage.

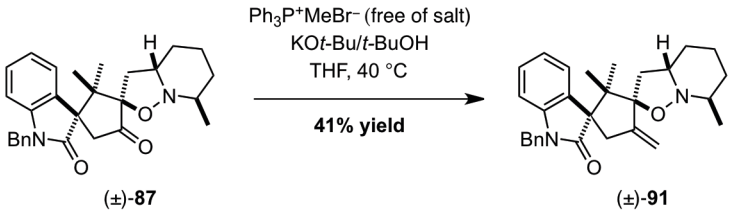
Scheme 2.22

Olefination of ketone (±)-**87** proved to be extremely difficult. Wittig and Peterson olefination[23] conditions only returned starting material. The low reactivity of ketone (±)-**87** was attributed to the highly enolizable nature of the carbonyl moiety under basic conditions. This hypothesis was supported by the result of an experiment where D_2O quench of a Wittig olefination resulted in significant deuterium incorporation at the α position.

Other attempts to accomplish the desired olefination were also met with difficulty. For example, the use of Takai and Utimoto's olefination protocol (CH_2I_2, Zn, $TiCl_4$, $PbBr_2$)[24], known to be effective for highly enolizable ketones, only resulted in an intractable mixture. Tebbe olefination[25] afforded no reaction, and Petasis conditions regrettably facilitated retro-dipolar cycloaddition (±)-**87**.[26]

Continued investigation of the Wittig conditions eventually revealed that isoxazolidine (±)-**87** could be successfully homologated using a methylenephosphorane solution *free of salt* (Scheme 2.23).[27] Further optimization demonstrated that mild heating (40 ºC) functioned to accelerate the reaction without encouraging the retro (3+2) cycloaddition. Under these conditions, the desired olefin was finally isolated in 41% yield along with 35% of recovered starting material.

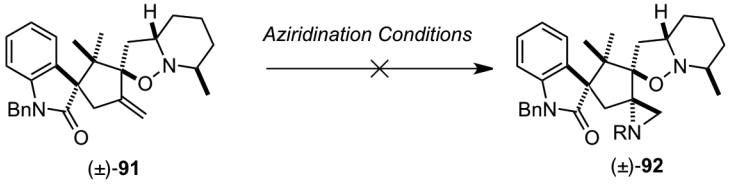
Scheme 2.23



2.4.2 Unsuccessful Aziridination Strategy

With the alkene in hand, our next goal was to stereoselectively aziridinate the exocyclic olefin of (±)-**91** in preparation for subsequent quinolizidine ring formation (Scheme 2.1).[28] A wide variety of conditions were employed to attempt the conversion of (±)-**91** to (±)-**92**, but to no avail (Scheme 2.24). In one case, attempted aziridination of (±)-**91** focused on the use of popular *N*-*p*-toluenesulfonylimine phenyliodinane (PhI=NTs)[29] as the nitrene source in the presence of various copper catalysts such as

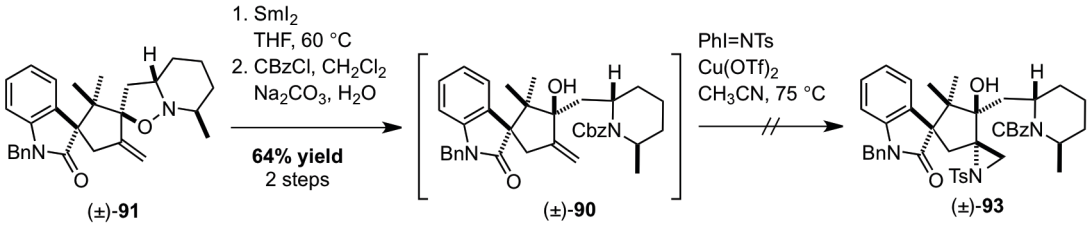
Scheme 2.24



$Cu(OTf)_2$,[30] CuOTf, and IPrCuCl[31]. Regrettably, none of these conditions yielded fruitful results. Even DuBois' conditions ($Rh_2(pfm)_4$, $H_2NSO_3CH_2CCl_3$, $PhI(OAc)_2$, MgO)[32] only led to decomposition of the starting material. The instability of the isoxazolidine ring to Lewis acidic conditions appears to be at least partially responsible for the failure of these aziridination attempts.

In an attempt to obviate the difficulty of aziridination, cleavage of the N–O bond was attempted prior to aziridination. Reduction of the isoxazolidine (±)-**91** took place smoothly in the presence of SmI_2 to provide an amino alcohol, which was then capped as the carbamate[33] (Cbz-(±)-**90**) (Scheme 2.25). Unfortunately, even though this substrate proved to be more stable than isoxazolidine (±)-**91**, a brief exploration of aziridination conditions still failed to provide any positive results.

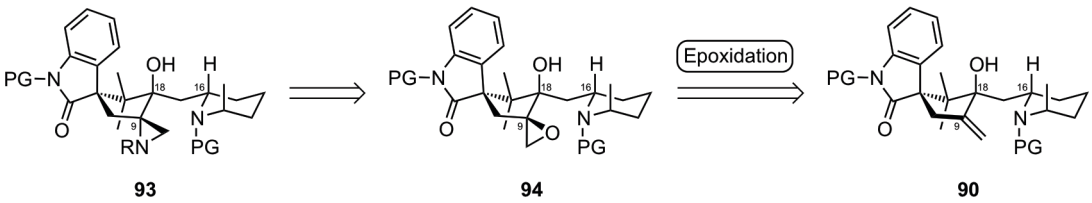
Scheme 2.25



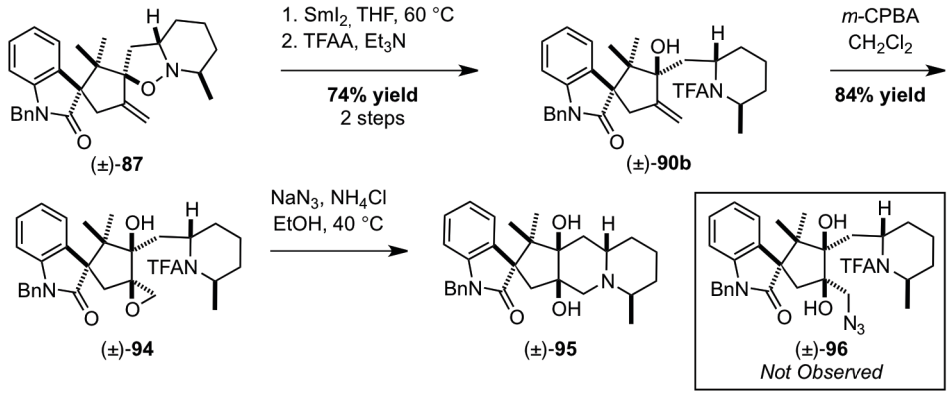
2.4.3 Successful Epoxide Opening Strategy

After concluding that direct aziridination might not be viable, we reasoned that an indirect approach to the incorporation of the angular nitrogen would garner more success. A logical choice was to proceed through the intermediacy of an epoxide, with the intention of employing a method for epoxide to aziridine conversion (Scheme 2.26).

Scheme 2.26



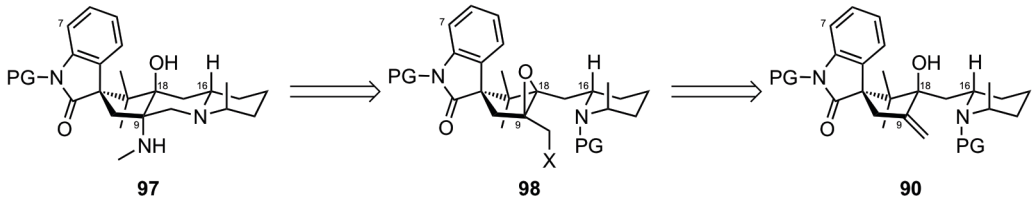
Scheme 2.27



In the event, epoxidation of the allylic alcohol (±)-**90b** with *m*-CPBA provided the hydroxy epoxide *N*-TFA-(±)-**94** in good yield (Scheme 2.27). However attempted ring opening of the epoxide with sodium azide under slightly acidic conditions (NaN_3, NH_4Cl, EtOH)[34] did not provide azido alcohol (±)-**96**. Instead, under the influence of NaN_3, the trifluoroacetamide group was cleaved and the newly released amine intramolecularly opened the epoxide to provide diol (±)-**95**.

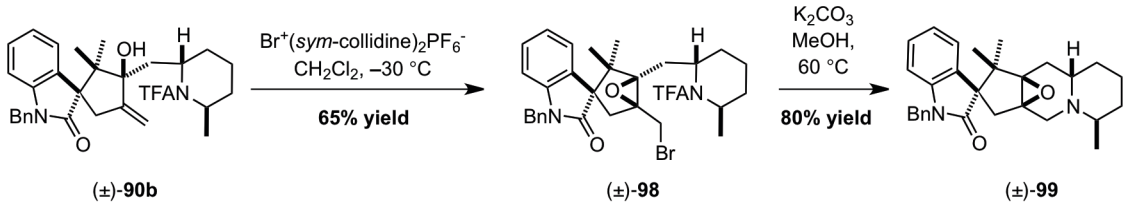
Serendipitous formation of (±)-**95** from (**±**)-**94** inspired us to investigate an alternate approach to the construction of the desired amino alcohol moiety. To this end we reasoned that **90** could serve as precursor to a ring-fusion epoxide (**98**), capable of participating in an intermolecular opening to provide the antiperiplanar 1,2-amino alcohol **97** (Scheme 2.28).

Scheme 2.28



Towards that goal, (±)-**90b** was subjected to a halo-etherification[35] with bis (*sym*-collidine)bromine(I) hexafluorophosphate ($Br^+(sym\text{-collidine})_2PF_6^-$)[36] to provide the desired bromide[37] (±)-**98** (Scheme 2.29). The reaction was plagued with a significant amount of electrophilic aromatic bromination, even with careful control of the reaction stoichiometry. Fortunately, lowering the reaction temperature to –30 ºC enhanced the selectivity and yield. Cleavage of the trifluoroacetamide (TFA) group

Scheme 2.29

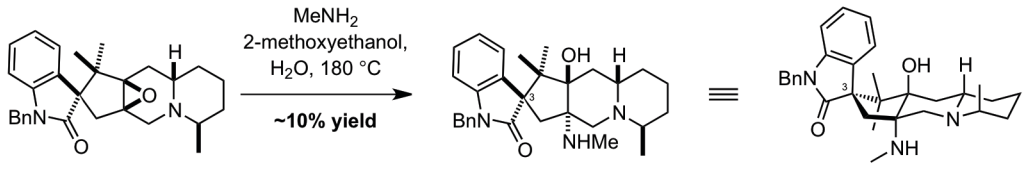


(±)-**90b** (±)-**98** (±)-**99**

was carried out under standard conditions (K_2CO_3, MeOH, 84 ºC) and followed by spontaneous displacement of the bromide by the newly released secondary amine to give (**±**)-**99**. Conducting the reaction at lower temperatures (60 ºC) minimized the formation of other reaction byproducts.

With epoxide (±)-**99** in hand, we faced a difficult epoxide opening reaction. From the outset, this transformation presented numerous challenges, many of which we related to the substrate's steric congestion. Amazingly however, epoxide (**±**)-**99** was found to undergo ring opening in the presence of methylamine, directly providing the desired amino alcohol (±)-**97**, albeit in rather low yield (Scheme 2.30). The structure of (±)-**97** was confirmed by X-ray analysis and represents the synthesis of the core structure of C3-*epi* citrinadin B (**2**). Although optimization of this reaction was attempted, using different Lewis acids ($LiClO_4$, $Yb(OTf)_3$, $Mg(ClO_4)_2$), and/or other nucleophiles ($BnNH_2$, H_2NNH_2, $BnONH_2$, $BnNHAlMe_2$), failed to provide any improvement.

Scheme 2.30



(±)-**99** C3-*epi*-Citrinadin B Core (±)-**97**

2.5 Conclusions

This chapter describes efforts toward the total synthesis of Citrinadin B (**2**) based upon a (3+2) dipolar cycloaddition strategy. In order to explore the cycloaddition reaction, spiro-oxindole dipolarophile (**±**)-**58**, was synthesized in 10 steps from aryl iodide **62**, via sequential Heck and reductive

enyne cyclization. Similarly, both (3*R*)-(–)- and (3*S*)-(+)-**58** could be accessed starting from aryl triflate **73**.

Impressively, only two isoxazolidine cycloadducts were formed in a (3+2) cycloaddition reaction between **57** and **58**. The minor, mismatched, cycloadduct **56** was found to possess all of the requisite stereochemistry for a synthesis of Citrinadin B (**2**). The major, matched, cycloadduct (±)-**87** was epimeric to (±)-**56** at the C3 spirocenter. Importantly, cycloadduct **56** could be isolated as the major product when nonracemeic nitrone (12*S*)-(–)-**57** and spiro-oxindole (3*S*)-(+)-**58** were employed.

Using the isoxazolidine cycloadduct (±)-**87**, exploratory studies toward the synthesis of Citrinadin B (**2**) were conducted. A challenging Wittig olefination and reduction of the N–O bond provided tethered piperdine (±)-**90** which was successfully elaborated to the ring fusion epoxide (±)-**99**. Direct nucleophilic opening of (±)-**99** with methylamine provided the C3-*epi*-Citrinadin B core ((±)-**97**).

2.6 Experimental

2.6.1 Materials and Methods

General. Unless otherwise stated, reactions were magnetically stirred in flame- or oven-dried glassware under an atmosphere of nitrogen. Triethylamine, diisopropylamine, and methanol were dried over calcium hydride and freshly distilled. Benzene, tetrahydrofuran, dichloromethane, toluene, and diethyl ether were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. Anhydrous CH_3CN, DMF, DMSO, acetone, and 1,2-dichloroethane were supplied by Fischer Scientific and purchased from the Colorado State Chemistry Stockroom and kept under a nitrogen atmosphere. All other commercially available reagents were used as received.

Unless otherwise stated, all reactions were monitored by thin-layer chromatography (TLC) using Silicycle glass-backed extra hard layer, 60 Å plates (indicator F-254, 250 μm). Column or flash chromatography was performed with the indicated solvents using Silicycle SiliaFlash. P60 (230-400 mesh) silica gel as the stationary phase. All melting points were obtained on a Gallenkamp capillary melting point apparatus (model: MPD350.BM2.1) and are uncorrected. Infrared spectra were obtained using a Nicolet

Avatar 320 FTIR or Bruker Tensor 27 FTIR. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500, Varian Inova 400, Varian Inova 400 autosampler, or Varian Inova 300 spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to internal residual solvent peaks from indicated deuterated solvents. Coupling constants (*J*) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent, par = partial. High resolution mass spectra were performed at the Central Instrument Facility by Donald L. Dick of Colorado State University. Single-crystal X-ray analyses were performed by Susie Miller, Brian Newell, and Stephanie Fielder of Colorado State University.

2.6.2 Preparative Procedures

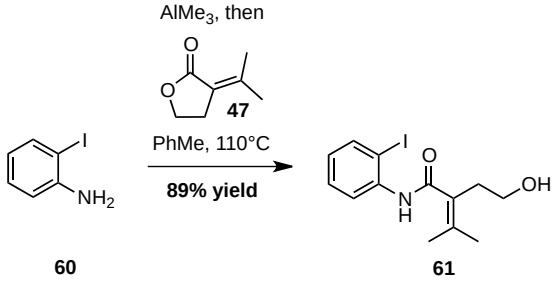
Preparation of Butyrolactone 47

A mixture of α-bromo-γ-butyrolactone (180 ml, 1.95 mol) and triethylphosphite (386 ml, 2.15 mol) was heated to 140 °C for 3 days, concentrated, and placed under vacuum to provide the crude product (416 g, 96% yield) which was used directly in the next step.

To a solution of the β-phosphonate ester (416 g, 1.87 mol) in THF (1500 ml) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 74 g, 1.85 mol) in portions. After stirring for 30 minutes, acetone (275 mL, 3.74 mol) was added to the orange mixture. The reaction was stirred at room temperature for 44 hours, quenched with water (250 ml), extracted with EtOAc (250 ml x 5), washed with water (150 ml) and brine (150 ml), concentrated and purified by distillation (0.6 mmHg; first fraction 60 °C (impurities), second fraction 75~80 °C (the desired) to provide butyrolactone **47** as a light yellow oil (100 g, 41% yield).

Known compound; CAS 24186-31-0. Characterization data matched literature reports.

Preparation of Iodoanilide 61

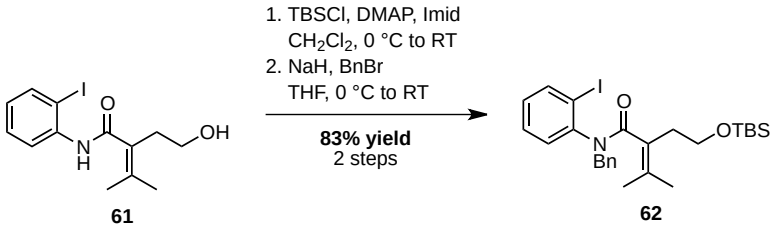


60 **61**

To a solution of 2-iodoaniline **60** (8.73 g, 39.9 mmol) in toluene (100 ml) at 0 ºC was slowly added $AlMe_3$ (2.0 M in heptanes, 30 ml). The reaction mixture was stirred at room temperature for 20 min, cooled to 0 ºC and γ-butyrolactone (7.54 g, 59.8 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 20 min, 110 ºC for 2.5 h, re-cooled to 0 ºC and quenched carefully with 1 N HCl solution (60 ml). The mixture was stirred at room temperature for 30 min, and the aqueous layer was extracted with EtOAc (60 ml × 3), and the combined organic layers were washed with water, brine, concentrated and purified by flash chromatography (30→40%→50% EtOAc/hexanes) to provide alcohol **61** as a yellowish solid (12.3g, 89% yield).

R_f = 0.33 (60% EtOAc/hexanes); m.p. 95–97 ºC (heptanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (br s, 1H, N**H**), 8.02 (d, *J* = 8.1 Hz, 1H, **Ar**), 7.73 (dd, *J* = 1.2 Hz, 8.1 Hz, 1H, **Ar**), 7.27 (dd, *J* = 7.2 Hz, 7.5 Hz, 1H, **Ar**), 6.80 (ddd, *J* = 1.2 Hz, 7.2 Hz, 8.1 Hz, 1H, **Ar**), 4.03 (app t, 1H, O**H**), 3.71 (dd, *J* = 5.7 Hz, 5.7 Hz, 2H, $CH_2C\mathbf{H_2}OH$), 2.52 (t, *J* = 5.7 Hz, 2H, $C\mathbf{H_2}CH_2OH$), 1.91 (s, 3H, $C{=}CC\mathbf{H_3}$), 1.52 (s, 3H, $C{=}CC\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 138.8, 138.2, 137.1, 129.4, 128.8, 126.2, 123.2, 91.0, 61.2, 32.9, 22.8, 20.2; IR (thin film): 3370 (br m), 3227 (br m), 1657 (s), 1581 (s), 1513 (s), 1431 (s), 1302 (s), 748 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{13}H_{17}INO_2$ [M+H]: 346.0304. Found: 346.0301.

Preparation of Bis-Protected Anilide 62



TBS Protection:

To a solution of alcohol **61** (12.3 g, 35.6 mmol) in CH_2Cl_2 (150 ml) at 0 ºC was added imidazole (3.6 g, 53.5 mmol), DMAP (436 mg, 0.356 mmol) and TBSCl (5.4 g, 35.6 mmol). The reaction mixture was stirred at room temperature for 1.5 h and quenched by saturated $NaHCO_3$ solution (40 ml). The aqueous layer was extracted with CH_2Cl_2 (30 ml × 2), and the combined organic layers were washed with water (30 ml), brine (30 ml), dried ($MgSO_4$), and concentrated to provide 16.7 g of the crude silyl ether as a yellowish oil. For characterization purposes, the oil could be purified by flash chromatography (5→10%→15% EtOAc/hexanes) to provide the silyl alcohol as a colorless oil.

R_f = 0.40 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.5 Hz, 1H, **Ar**), 8.02 (br s, 1H, N**H**), 7.77 (d, *J* = 7.8 Hz, 1H, **Ar**), 7.33 (dd, *J* = 7.5 Hz, 7.8 Hz, 1H, **Ar**), 6.83 (dd, *J* = 7.5 Hz, 7.8 Hz, 1H, **Ar**), 3.80 (t, *J* = 6.6 Hz, 2H, $CH_2C\mathbf{H_2}OTBS$), 2.64 (t, *J* = 6.6 Hz, 2H, $C\mathbf{H_2}CH_2OTBS$), 1.97 (s, 3H, $C{=}CC\mathbf{H_3}$), 1.81 (s, 3H, $C{=}CC\mathbf{H_3}$), 0.85 (s, 9H, $SiC(C\mathbf{H_3})_3$), 0.03 (s, 6H, $Si(C\mathbf{H_3})_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 138.8, 138.4, 136.9, 129.4, 128.9, 126.0, 123.1, 91.0, 62.1, 33.4, 25.8, 22.7, 20.5, 18.2, –5.4; IR (thin film): 3380 (m), 3273 (br m), 1682 (s), 1584 (s), 1504 (s), 1471 (s), 1428 (s), 1297 (s), 1255 (s), 1088 (s), 836 (s), 777 (s), 749 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{19}H_{31}INO_2Si$ [M+H]: 460.1169. Found: 460.1168.

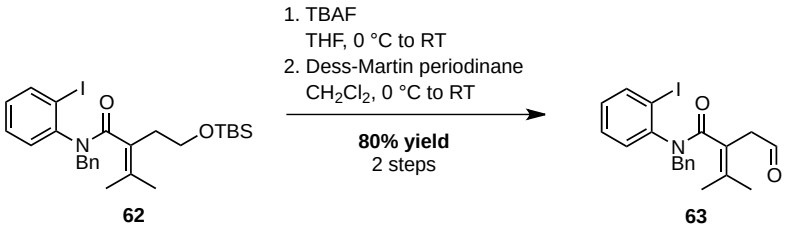
Benzyl Protection:

The crude silyl alcohol (16.7 g) was dissolved in THF (150 ml), cooled to 0 ºC, and treated with NaH (60 % in mineral oil, 2.18 g) in portions. After stirring at 0 ºC for 5 min, BnBr (6.5 ml, 54.5 mmol) was added. The reaction mixture was stirred at room temperature for 40 min and another 2 ml of BnBr was added. After stirring for 20 min, the orange/red colored solution was quenched with saturated NH_4Cl

solution (50 ml). The aqueous layer was extracted with EtOAc (50 ml × 2), and the combined organic layers were concentrated and purified by flash chromatography (5→10%→15% EtOAc/hexanes) to provide the protected amide **62** as a pale yellowish oil, which solidified upon standing at ambient temperature (16.2 g, 83% yield, two steps).

R_f = 0.22 (10% EtOAc/hexanes); m.p. 54–56 ºC (heptanes); ^{1}H NMR (400 MHz, $CDCl_3$) (two rotamers in 2.3 : 1 ratio) For major rotamer: δ 7.94 (dd, *J* = 2.0 Hz, 10.8 Hz, 1H, **Ar**), 7.27 (m, 5H, CH_2**Ph**), 7.13 (ddd, *J* = 1.6 Hz, 10.4 Hz, 10.4 Hz, 1H, **Ar**), 7.00 (ddd, *J* = 2.0 Hz, 10.0 Hz, 10.4 Hz, 1H, **Ar**), 6.60 (dd, *J* = 2.0 Hz, 10.4 Hz, 1H, **Ar**), 5.82 (d, *J* = 13.8 Hz, 1H, C**H$_2$**Ph), 4.07 (d, *J* = 13.8 Hz, 1H, C**H$_2$**Ph), 3.73 (m, 1H, C**H$_2$**OTBS), 3.58 (m, 1H, C**H$_2$**OTBS), 2.15 (m, 2H, C**H$_2$**CH_2OTBS), 1.71 (br s, 3H, C=CC**H$_3$**), 1.52 (br s, 3H, C=CC**H$_3$**), 0.94 (s, 9H, SiC(C**H$_3$**)$_3$), 0.11 (s, 3H, SiC**H$_3$**), 0.10 (s, 3H, SiCC**H$_3$**); ^{1}H NMR (300 MHz, C_6D_6, 60 ºC) δ 7.61 (d, *J* = 7.8 Hz, 1H, **Ar**), 7.24 (br m, 2H, CH_2**Ph**), 7.04 (br m, 2H, CH_2**Ph**), 6.61 (m, 2H, **Ar**), 6.43 (dd, *J* = 6.6 Hz, 7.5 Hz, 1H, **Ar**), 6.00 (d, *J* = 13.8 Hz, 1H, C**H$_2$**Ph), 4.12 (d, *J* = 13.8 Hz, 1H, C**H$_2$**Ph), 3.95 (m, 1H, C**H$_2$**OTBS), 3.82 (m, 1H, C**H$_2$**OTBS), 2.29 (br s, 2H, C**H$_2$**CH_2OTBS), 1.72 (br s, 3H, C=CC**H$_3$**), 1.34 (br s, 3H, C=CC**H$_3$**), 1.00 (s, 9H, SiC(C**H$_3$**)$_3$), 0.14 (s, 6H, Si(C**H$_3$**)$_2$); ^{13}C NMR (75 MHz, C_6D_6, 60 ºC) δ 171.6, 144.7, 140.8, 138.5, 134.0, 132.5, 130.4, 129.6, 129.1, 128.88, 128.81, 128.5, 100.0, 62.7, 51.9, 34.3, 26.6, 23.6, 19.6, 18.8, –4.7; IR (thin film): 1646 (s), 1469 (s), 1089 (m) cm^{-1}; HRMS (ESI) Calcd. for $C_{26}H_{37}INO_2Si$ [M+H]: 550.1638. Found: 550.1626.

Preparation of Aldehyde 63



Alcohol Deprotection:

To a solution of silyl ether **62** (1.15 g, 2.09 mmol) in THF (20 ml) at 0 ºC was added TBAF (1.0 M in THF, 3.14 ml, 3.14 mmol). The reaction mixture was stirred at room temperature for 2 h and quenched by saturated NH_4Cl solution. The aqueous layer was extracted with EtOAc and the combined

organic layers were concentrated and purified by flash chromatography (40→60%→100% EtOAc/hexanes) to provide the alcohol as a colorless gum (788 mg, 87% yield).

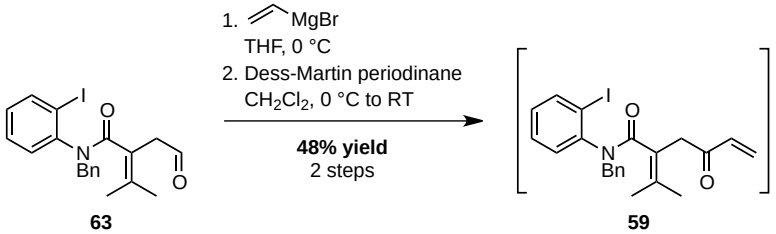
R_f = 0.43 (80% EtOAc/hexanes).

Dess-Martin Oxidation:

To a solution of the alcohol (788 mg, 1.81 mmol) in CH_2Cl_2 (24 ml) at 0 ºC was added Dess-Martin periodinane (950 mg, 2.24 mmol). The reaction mixture was stirred at room temperature for 3 h and quenched by saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc and the combined organic layers were concentrated and purified by flash chromatography (20→40% →60% EtOAc/hexanes) to provide aldehyde **63** as a colorless oil (710 mg, 73% yield), which solidified after storing at –15 ºC.

R_f = 0.48 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 2.0 Hz, 1H, C**H**O), 7.86 (d, *J* = 8.0 Hz, 1H, **Ar**), 7.22 (m, 5H, CH_2**Ph**), 7.09 (dd, *J* = 7.2 Hz, 8.0 Hz, 1H, **Ar**), 6.95 (dd, *J* = 7.2 Hz, 8.0 Hz, 1H, **Ar**), 6.55 (d, *J* = 8.0 Hz, 1H, **Ar**), 5.76 (dd, *J* = 2.0 Hz, 14.0 Hz, 1H, C**H**$_2$Ph), 4.03 (d, *J* = 2.0 Hz, 14.0 Hz, 1H, C**H**$_2$Ph), 3.05 (d, *J* = 17.6 Hz, 1H, C**H**$_2$CHO), 2.92 (d, *J* = 17.6 Hz, 1H, C**H**$_2$CHO), 1.77 (s, 3H, C=CC**H**$_3$), 1.39 (s, 3H, C=CC**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 170.9, 142.6, 140.3, 138.9, 136.6, 131.6, 129.9, 129.3, 128.6, 128.3, 127.6, 122.3, 99.2, 51.4, 44.0, 23.1, 19.9; IR (thin film): 1721 (s), 1642 (s), 1469 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{20}H_{21}INO_2$ [M+H]: 434.0617. Found: 434.0612.

Preparation of Enone 59



63 **59**

Grignard Addition:

To a solution of aldehyde **63** (723 mg, 1.67 mmol, azeotropically dried with toluene) in THF (24 ml) at 0 ºC was added vinylmagnesium bromide (1.0 M in THF, 2.0 ml). The reaction mixture was stirred at 0 ºC for 10 min and quenched by saturated NH_4Cl solution. The aqueous layer was extracted with EtOAc

and the combined organic layers were concentrated and purified by flash chromatography (30→40% →50% EtOAc/hexanes) to provide the allylic alcohol as a colorless oil (540 mg, 70% yield).

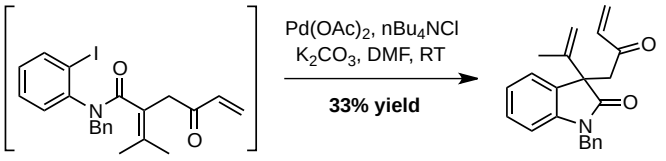
R_f = 0.43 (50% EtOAc/hexanes). ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.13 (d, *J* = 8.1 Hz, 1H), 8.02 (s, 1H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 6.83 (t, *J* = 7.7 Hz, 1H), 3.80 (t, *J* = 6.6 Hz, 2H), 2.64 (td, *J* = 6.4, 0.3 Hz, 2H), 1.97 (s, 3H), 1.81 (s, 3H), 0.85 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.82, 138.92, 138.57, 137.04, 129.50, 129.05, 126.18, 123.29, 91.20, 62.23, 33.58, 26.01, 22.90, 20.65, 18.37, -5.23; IR (thin film): 3370 (br, m), 3227 (br, m), 1657 (s), 1581 (s), 1513 (s), 1431 (s), 1302 (s), 748 (s) cm^{-1}. HRMS (ESI) Calcd. for $C_{13}H_{17}INO_2$ [M+H]: 346.0301. Found: 346.0304.

Dess-Martin Oxidation:

To a solution of the allylic alcohol (494 mg, 1.07 mmol) in CH_2Cl_2 (24 ml) at 0 ºC was added Dess-Martin periodinane (545 mg, 1.28 mmol). The reaction mixture was stirred at room temperature for 1 h and quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc and the combined organic layers were concentrated and purified by flash chromatography (30%→40% EtOAc/hexanes) to provide enone **59** as a pale yellowish oil (340 mg, 69% yield).

R_f = 0.52 (50% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.9 (d, 1H), 7.4~6.8 (m, 7H), 6.8 (d, 1H), 6.56 (dd, 1H), 6.47 (d, 1H), 6.23 (dd, 1H), 5.80 (d, 1H), 5.73 (dd, 1H), 4.07 (d, 1H), 3.27 (d, 1H), 3.02 (d, 1H), 1.8 (s, 3H), 1.4 (s, 3H); HRMS (ESI) Calcd. for $C_{28}H_{23}INO_2$ [M+H]: 460.0773. Found: 460.0767.

Preparation of Enone 67



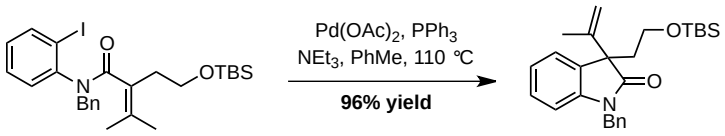
59 **67**

To a solution of iodo anilide **59** (21 mg, azeotropically dried with toluene) in DMF (2 ml, degassed through freeze-pump-thaw processes) was added $Pd(OAc)_2$ (3.1 mg, 0.0137 mmol), anhydrous K_2CO_3 (15.8 mg, 0.114 mmol) and *n*Bu_4NCl (12.7 mg, 0.0457 mmol). The reaction mixture was stirred at

room temperature for 16 h, quenched with water and extracted with EtOAc. The combined organic layers were washed with water, brine, dried ($MgSO_4$), concentrated and purified by flash chromatography (20%→30%→40% EtOAc/hexanes) to provide enone **67** as a colorless oil (5 mg, 33% yield).

R_f = 0.54 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H, CH_2**Ph**), 7.15 (ddd, *J* = 1.2 Hz, 7.5 Hz, 7.5 Hz, 1H, **Ph**), 7.09 (dd, *J* = 1.2 Hz, 7.5 Hz, 1H, **Ph**), 6.97 (ddd, *J* = 0.9 Hz, 7.5 Hz, 7.5 Hz, 1H, **Ph**), 6.73 (d, *J* = 7.5 Hz, 1H, **Ph**), 6.23 (d, *J* = 9.6 Hz, 1H, CH_2=C**H**), 6.20 (d, *J* = 2.1 Hz, 1H, CH=C**H$_2$**), 5.77 (dd, *J* = 2.1 Hz, 9.6 Hz, 1H, CH=C**H$_2$**), 5.15 (d, *J* = 15.6 Hz, 1H, C**H$_2$**Ph), 5.02 (d, *J* = 0.9 Hz, 1H, C=C**H$_2$**), 4.97 (br s, 1H, C=C**H$_2$**), 4.85 (d, *J* = 15.6 Hz, 1H, C**H$_2$**Ph), 3.54 (s, 1H, C**H$_2$**CO), 3.53 (s, 1H, C**H$_2$**CO), 1.69 (s, 3H, CH_2=C**CH$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1, 177.8, 143.9, 143.3, 136.2, 135.9, 131.0, 128.7, 128.6, 128.1, 127.4, 127.3, 123.1, 122.3, 113.3, 109.2, 77.2, 54.5, 44.3, 19.3; IR (thin film): 1713 (s), 1612 (m), 1489 (m), 1357 (m) cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{21}NNaO_2$ [M+Na]: 354.1470. Found: 354.1464.

Preparation of Oxindole 70



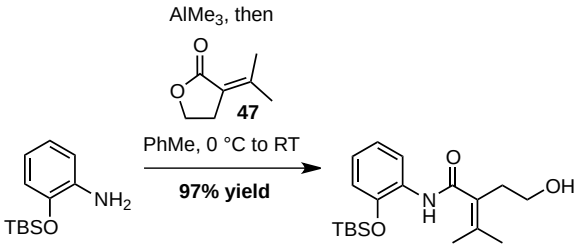
62 **70**

To a solution of the iodo anilide **62** (3.19 g, 5.80 mmol) in toluene (84 ml, degassed through freeze-pump-thaw processes, three times) at room temperature was added $Pd(OAc)_2$ (130 mg, 0.58 mmol), PPh_3 (457 mg, 1.74 mmol) and Et_3N (4.05 ml, 29.0 mmol) successively. The reaction mixture was stirred at room temperature for 20 min, 110 ºC for 4 h, directly concentrated *in vacuo* and purified by flash chromatography (5% →10% EtOAc/hexanes) to provide oxindole **70** as a colorless oil (2.35g, 96% yield).

R_f = 0.37 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H, CH_2**Ph**), 7.17 (m, 2H, **Ar**), 7.06 (dd, *J* = 7.5 Hz, 7.5 Hz, 1H, **Ar**), 6.77 (d, *J* = 7.5 Hz, 1H, **Ar**), 5.09 (br s, 1H, C=C**H$_2$**), 5.06 (br s, 1H, C=C**H$_2$**), 5.01 (d, *J* = 15.6 Hz, 1H, C**H$_2$**Ph), 4.90 (d, *J* = 15.6 Hz, 1H, C**H$_2$**Ph), 3.48 (ddd, *J* = 6.6 Hz, 9.3 Hz, 9.3 Hz, 1H, C**H$_2$**OTBS), 3.30 (ddd, *J* = 4.8 Hz, 9.0 Hz, 9.3 Hz, 1H, C**H$_2$**OTBS), 2.55 (ddd, *J* = 6.6 Hz, 9.3 Hz, 13.2 Hz, 1H, C**H$_2$**CH_2OTBS), 2.30 (ddd, *J* = 4.8 Hz, 9.0 Hz, 13.2 Hz, 1H, C**H$_2$**CH_2OTBS),

1.61 (s, 3H, **CCH$_3$**), 0.90 (s, 9H, SiC(C**H$_3$**)$_3$), –0.93 (s, 3H, SiC**H$_3$**), –0.96 (s, 3H, SiC**H$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 143.3, 142.6, 135.7, 130.9, 128.4, 127.6, 127.2, 127.0, 123.5, 122.1, 112.7, 108.6, 59.2, 55.6, 43.5, 37.1, 25.5, 19.1, 17.9, –5.82, –5.87; IR (thin film): 1713 (s), 1466 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{26}H_{35}NNaO_2Si$ [M+Na]: 444.2335. Found: 444.2335.

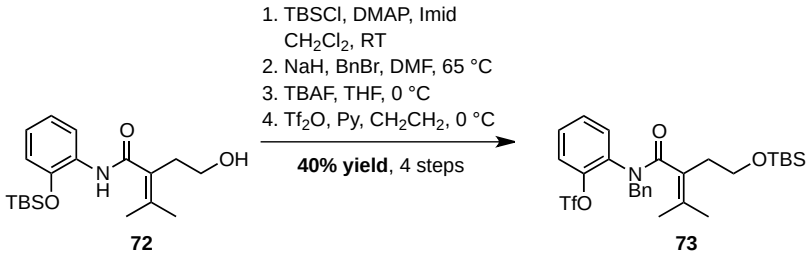
Phenol-alcohol 69



To a solution of the aniline **71** (2.82 g, 12.6 mmol) in toluene (50 ml) at 0 ºC was added $AlMe_3$ (2.0 M in toluene, 12.6 ml, 25.2 mmol). After stirring at room temperature for 20 min, the solution was cooled to 0 ºC and treated with the γ-lactone (2.4 g, 18.9 mmol). The reaction mixture was stirred at room temperature for 3.5 h, cooled to 0 ºC, and slowly quenched with saturated $NaHCO_3$ solution (40 ml) and saturated Rochelle solution (40 ml). The mixture was stirred for 1 h, extracted with EtOAc, and the combined organic layers were washed with brine, and concentrated *in vacuo*. The crude material was triturated with 20% EtOAc/hexanes (40 ml). The white precipitate was collected on a fritted funnel to provide the first crop of the product. The mother liquid was concentrated and purified by flash chromatography (20→30%→40% EtOAc/hexanes) to provide the second crop of **72**. (4.3 g, 97% yield).

R_f = 0.14 (30% EtOAc/hexanes); mp 82–87 ºC (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (m, 1H, **Ar**), 7.94 (br s, 1H, N**H**), 6.89 (m, 2H, **Ar**), 6.84 (m, 1H, **Ar**), 3.77 (dt, *J* = 5.7 Hz, 5.7 Hz, 2H, $CH_2C\mathbf{H}_2OH$), 3.44 (t, *J* = 5.4 Hz, 1H, O**H**), 2.56 (t, *J* = 5.7 Hz, 2H, CC**H$_2$**), 1.92 (s, 3H, C=CC**H$_3$**), 1.81 (s, 3H, C=CC**H$_3$**), 1.01 (s, 9H, SiC(C**H$_3$**)$_3$), 0.28 (s, 6H, Si(C**H$_3$**)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 143.9, 135.1, 130.3, 129.2, 123.6, 121.5, 120.0, 117.3, 61.4, 33.2, 25.6, 22.6, 19.8, 18.1, –4.3; IR (thin film): 3411 (s), 3273 (br s), 1649 (s), 1596 (s), 1521 (s), 1451 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{19}H_{32}NO_3Si$ [M+H]: 350.2152. Found: 350.2151.

Preparation of Aryl Triflate 73



72 **73**

TBS Protection:

To a solution of alcohol **72** (14.4 g, 41.2 mmol) in CH_2Cl_2 (150 ml) at room temperature was added imidazole (4.21 g, 61.8 mmol), DMAP (252 mg, 2.06 mmol) and TBSCl (6.21 g, 41.2 mmol). The reaction mixture was stirred at room temperature for 45 min and quenched with saturated $NaHCO_3$ solution (80 ml). The mixture was extracted with EtOAc (60 ml×2), concentrated *in vacuo* and purified by flash chromatography (5%→7.5% EtOAc/hexanes) to provide the desired product as a colorless oil (17.7 g, 93% yield).

R_f = 0.37 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (m, 1H, **Ar**), 7.84 (br s, 1H, N**H**), 6.96 (m, 2H, **Ar**), 6.83 (m, 1H, **Ar**), 3.73 (t, *J* = 7.2 Hz, 2H, CH_2CH_2OH), 2.59 (t, *J* = 7.2 Hz, 2H, CCH_2), 1.89 (s, 3H, C=CC**H$_3$**), 1.80 (s, 3H, C=CC**H$_3$**), 1.02 (s, 9H, $SiC(CH_3)_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.28 (s, 6H, $Si(CH_3)_2$), 0.04 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 143.8, 134.5, 130.1, 129.6, 123.2, 121.5, 120.0, 117.2, 61.9, 33.9, 25.7, 25.5, 22.4, 19.9, 18.1, 17.9, –4.5, –5.5; IR (thin film): 3426 (s), 1678 (s), 1596 (s), 1514 (s), 1448 (s), 1257 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{25}H_{46}NO_3Si_2$ [M+H]: 464.3016. Found: 464.3024.

Benzyl Protection:

To a solution of the anilide (2.3 g, 4.96 mmol) in THF (50 ml) at 0 ºC was added NaH (60% in mineral oil, 375 mg, 9.38 mmol). After stirring at 0 ºC for 10 min, benzyl bromide (1.18 ml, 9.92 mmol) was added. The reaction mixture was stirred at 65 ºC for 40 min, cooled to 0 ºC, and carefully quenched with saturated $NaHCO_3$ solution. The mixture was extracted with EtOAc, and the combined organic layers were concentrated in vacuo and purified by flash chromatography (5%→10%→15%→20% EtOAc/hexanes) to provide the benzyl amide as a pale yellow oil (1.7 g, 62% yield).

R_f = 0.32 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 7.42 (m, 2H, CH_2**Ph**), 7.08 (m, 3H, CH_2**Ph**), 6.86 (ddd, *J* = 1.8 Hz, 7.5 Hz, 7.8 Hz, 1H, **Ar**), 6.75 (m, 2H, **Ar**), 6.51 (ddd, *J* = 1.2 Hz, 7.5 Hz, 7.5 Hz, 1H, **Ar**), 6.22 (d, *J* = 13.8 Hz, 1H, C**H**$_2$Ph), 4.17 (d, *J* = 13.8 Hz, 1H, C**H**$_2$Ph), 4.00 (app q, *J* = 8.1 Hz, 1H, CH_2C**H**$_2$OTBS), 3.80 (br s, 1H, CH_2C**H**$_2$OTBS), 2.31 (t, *J* = 7.8 Hz, 2H, CC**H**$_2$$CH_2$OTBS), 1.76 (br s, 3H, C=CC**H**$_3$), 1.35 (br s, 3H, C=CC**H**$_3$), 1.09 (s, 9H, SiC(C**H**$_3$)$_3$), 1.00 (s, 9H, SiC(C**H**$_3$)$_3$), 0.31 (s, 3H, SiC**H**$_3$), 0.23 (s, 3H, SiC**H**$_3$), 0.10 (s, 3H, SiC**H**$_3$), 0.09 (s, 3H, SiC**H**$_3$); ^{13}C NMR (75 MHz, C_6D_6) δ 172.2, 151.8, 139.3, 133.0, 132.8, 132.1, 130.0, 129.3, 128.9, 127.9, 120.9, 119.0, (one aromatic carbon overlapping with C_6D_6), 62.6, 51.3, 34.1, 26.6, 26.3, 23.1, 19.3, 18.8, 18.7, –3.5, –4.0, –4.8; IR (thin film): 1644 (s), 1498 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{32}H_{52}NO_3Si_2$ [M+H]: 554.3485. Found: 554.3487.

Phenol Deprotection:

To a solution of the silylated phenol (2.7 g, 4.88 mmol) in THF (60 ml) at 0 ºC was added TBAF (1.0 M in THF, 4.88 ml). The reaction mixture was stirred at 0 ºC for 3 min and quenched with saturated NH_4Cl solution. The mixture was extracted with EtOAc and the combined organic layers were concentrated *in vacuo* and purified by flash chromatography (10%→20%→30% EtOAc/hexanes) to provide the desired product as a slightly yellowish oil (1.7g, 79% yield).

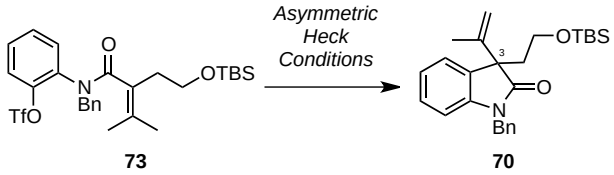
R_f = 0.32 (10% EtOAc/hexanes); mp 149–152 (20% EtOAc/Hexanes); ^{1}H NMR (300 MHz, C_6D_6) (two rotamers in 3 : 1 ratio) For major rotamer: δ 8.30 (br s, 1H, O**H**), 7.38 (d, *J* = 6.6 Hz, 1H, **Ar**), 7.07 (m, 5H, CH_2**Ph**), 6.92 (dd, *J* = 7.2 Hz, 7.8 Hz, 1H, **Ar**), 6.61 (d, 1H, *J* = 7.2 Hz, **Ar**), 6.45 (ddd, *J* = 1.2 Hz, 7.8 Hz, 7.8 Hz, 1H, **Ar**), 5.96 (d, *J* = 13.2 Hz, 1H, C**H**$_2$Ph), 4.18 (br s, 1H, C**H**$_2$Ph), 3.94 (m, 2H, CH_2C**H**$_2$OTBS), 2.32 (m, 2H, C**H**$_2$$CH_2$OTBS), 1.79 (br s, 3H, C=CC**H**$_3$), 1.29 (br s, 3H, C=CC**H**$_3$), 1.03 (br s, 9H, SiC(C**H**$_3$)$_3$), 0.22 (br s, 6H, Si(C**H**$_3$)$_2$); ^{13}C NMR (100 MHz, C_6D_6) (two rotamers in 3 : 1 ratio) For major rotamer: δ 173.6, 153.8, 138.9, 133.2, 131.0, 130.1, 129.9, 129.4, 129.0, 128.3, 128.0, 119.8, 118.0, 63.4, 51.7, 33.3, 26.7, 23.3, 19.5, 19.2, –4.6, –4.9; IR (thin film): 3165 (br s), 1614 (s), 1584 (s), 1460 (s), 1089 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{26}H_{38}NO_3Si$ [M+H]: 440.2621. Found: 440.2623.

Phenol Triflation:

To a solution of the phenol (2.1g, 4.78 mmol) in CH_2Cl_2 (45 ml) at 0 ºC was added pyridine (1.16 ml, 14.3 mmol) and triflic anhydride (1.21 ml, 7.16 mmol). The dark reaction mixture was stirred at room temperature for 25 min and quenched with saturated NH_4Cl solution. The mixture was extracted with EtOAc, the combined organic layers were concentrated *in vacuo* and purified by flash chromatography (10%→15% EtOAc/hexanes) to provide **73** as a pale yellow oil (2.4 g, 88% yield).

R_f = 0.37 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 7.31 (m, 2H, CH_2**Ph**), 7.12~6.95 (m, 3H, CH_2**Ph**), 6.68 (m, 1H, **Ar**), 6.57 (m, 2H, **Ar**), 6.46 (m, 1H, **Ar**), 6.12 (d, *J* = 14.4 Hz, 1H, C**H**$_2$Ph), 4.05 (d, *J* = 14.4 Hz, 1H, C**H**$_2$Ph), 3.92 (t, *J* = 8.1 Hz, 2H, CH_2C**H$_2$**OTBS), 2.37 (m, 2H, C**H$_2$**CH_2OTBS), 1.65 (br s, 3H, C=CC**H$_3$**), 1.29 (br s, 3H, C=CC**H$_3$**), 1.02 (s, 9H, SiC(C**H$_3$**)$_3$), 0.15 (s, 6H, Si(C**H$_3$**)$_2$); ^{13}C NMR (75 MHz, C_6D_6) (two rotamers in 2.3:1 ratio) For major rotamer: δ 171.6, 145.5, 138.3, 135.1, 131.6, 129.5, 129.1, 128.8, 128.6, 128.2, 127.9, 125.28 (*C*F_3), 121.03 (*C*F_3), 116.80 (*C*F_3), 112.55 (*C*F_3, *J* = 319 Hz), 121.9, 121.2, 62.4, 52.0, 34.4, 26.1, 22.9, 19.3, 18.4, –5.2; IR (thin film): 1652 (s), 1414 (s), 1249 (s), 1217 (s), 1140 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{27}H_{37}F_3NO_5SSi$ [M+H]: 572.2114. Found: 572.2120.

Preparation of Asymmetric Oxindoles (+)- and (–)-70



73 **70**

Conditions	*Yield*	*ee*
$Pd_2(dba)_3$, (+)-BINAP, PMP DMA, 110 °C , 20 h	85% (–)-**70**	65%
$Pd_2(dba)_3$, (–)-BINAP, PMP DMA, 110 °C , 20 h	96% (+)-**70**	80%

(–)-70 From (+)-BINAP:

To a solution of the aryl triflate **73** (81 mg, 0.142 mmol) in DMA (4 ml, degassed through freeze-pump-thaw processes, three times) was added $Pd_2(dba)_3$·$CHCl_3$ (7.3 mg, 0.00708 mmol), (+)-BINAP (13.2 mg, 0.0213 mmol) and 1,2,2,5,5-pentamethylpiperidine (120 µl, 0.708 mmol). The orange mixture was stirred at room temperature for 40 minutes, 110 °C for 19 h, cooled to room temperature and quenched with water. The mixture was extracted with EtOAc, the combined organic layers were washed with brine, concentrated *in vacuo* and purified by flash chromatography (5%→7.5% EtOAc/hexanes) to provide (–)-**70** as a colorless oil (51 mg, 85% yield).

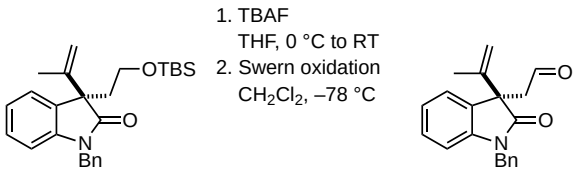
$^{1}H/^{13}C$ NMR data matched the racemic sample. $[\alpha]_D$ = not determined. 67% ee by HPLC.

(+)-70 From (–)-BINAP:

To a solution of the aryl triflate **73** (425 mg, 0.743 mmol) in DMA (12 ml, degassed through freeze-pump-thaw processes, three times) was added $Pd_2(dba)_3$ (34 mg, 0.0372 mmol), (–)-BINAP (51 mg, 0.0818 mmol) and 1,2,2,5,5-pentamethylpiperidine (672 µl, 3.72 mmol). The reaction flask was evacuated and refilled with N_2 for three times. The dark reaction mixture was stirred at room temperature for 40 min, 110 °C for 20 h, cooled to room temperature and quenched with water. The mixture was extracted with EtOAc, the combined organic layers were washed with brine, concentrated *in vacuo* and purified by flash chromatography (5%→7.5% EtOAc/hexanes) to provide (+)-**70** as a colorless oil (300 mg, 96% yield).

$^{1}H/^{13}C$ NMR data matched the racemic sample. $[\alpha]_D^{23}$ = +9.0 (c 2.2, $CHCl_3$). 80% ee by HPLC.

Preparation of Aldehyde 74



(±)-**70** (±)-**74**

Alcohol Deprotection:

To a solution of the silyl ether **70** (2.35 g, 5.57 mmol) in THF (40 ml) at 0 ºC was added TBAF (1.0 M in THF, 8.4 ml). The reaction mixture was stirred at room temperature for 75 min and quenched with saturated NH_4Cl solution (15 ml). The volatile was evaporated in vacuo and the residue was extracted with EtOAc (25 ml × 3), washed with brine, dried ($MgSO_4$) and concentrated to provide the alcohol as a yellowish oil (3.07 g), which was used in the next step without further purification. For characterization purpose, the crude mixture was purified by flash chromatography (30% →50% EtOAc/hexanes) to provide the pure alcohol as a colorless oil, which solidifies to colorless crystals upon standing at ambient temperature.

R_f = 0.20 (40% EtOAc/hexanes); mp 89–91 ºC (CH_2Cl_2/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 5H, CH_2**Ph**), 7.14 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H, **Ph**), 7.09 (d, *J* = 7.6 Hz, 1H, **Ph**), 7.00 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H, **Ph**), 6.72 (d, *J* = 7.6 Hz, 1H, **Ph**), 5.04 (br s, 1H, C=**CH$_2$**), 5.02 (br s, 1H, C=**CH$_2$**), 4.96 (d, *J* = 15.6 Hz, 1H, **CH$_2$**Ph), 4.81 (d, *J* = 15.6 Hz, 1H, **CH$_2$**Ph), 3.41 (m, 2H, **CH$_2$**OTBS), 2.50 (ddd, *J* = 7.2 Hz, 7.2 Hz, 14.0 Hz, 1H, C**CH$_2$**CH_2), 2.33 (br s, 1H, **OH**), 2.20 (ddd, *J* = 6.4 Hz, 6.4 Hz, 14.0 Hz, 1H, C**CH$_2$**CH_2), 1.60 (s, 3H, C**CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 143.0, 142.8, 135.8, 131.2, 128.7, 128.1, 127.5, 127.3, 123.6, 122.6, 113.4, 109.2, 59.1, 56.3, 43.9, 37.2, 19.5; IR (thin film): 3421 (br, s), 1707 (s), 1610 (s), 1487 (s), 1466 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{20}H_{22}NO_2$ [M+H]: 308.1651. Found: 308.1649. (+)-**70** → (+)-**Alcohol :** $[\alpha]_D^{23}$ = +25.9 (c 1.8, $CHCl_3$); ~80% ee.

Swern Oxidation:

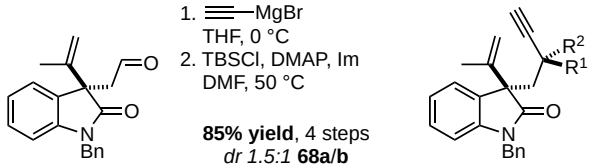
To a solution of DMSO (2.51 ml, 35.4 mmol) in CH_2Cl_2 (80 ml) at –78 ºC was added oxalyl chloride (1.50 ml, 17.7 mmol) dropwise. After stirring at –78 ºC for 20 min, a solution of the crude alcohol (2.72 g) in CH_2Cl_2 (20 ml) was added (plus 20 ml of rinse) followed by the addition of Et_3N (6.2 ml, 44.2 mmol). The reaction mixture was stirred at –78 ºC for 1 h, warmed to room temperature over 40 min and quenched with saturated $NaHCO_3$ solution (40 ml). The aqueous layer was extracted with CH_2Cl_2 (40 ml × 2), and the combined organic layers were washed with water (20 ml), brine (20 ml), dried (Na_2SO_4) and concentrated to give the crude aldehyde as a yellowish oil (2.4 g). This crude mixture was used in the next step without further purification. For characterization purpose, the crude mixture was purified by flash chromatography (20% →30% EtOAc/hexanes) to provide pure aldehyde **74** as a pale yellow oil.

R_f = 0.50 (20% EtOAc/benzene); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (m, 1H, C**H**O), 7.35-7.22 (m, 5H, CH_2**Ph**), 7.16 (ddd, *J* = 1.2 Hz, 7.6 Hz, 7.6 Hz, 1H, **Ph**), 7.09 (d, *J* = 7.2 Hz, 1H, **Ph**), 7.00 (ddd, *J* = 1.2 Hz, 7.6 Hz, 7.6 Hz, 1H, **Ph**), 6.75 (d, *J* = 7.6 Hz, 1H, **Ph**), 5.06 (br s, 1H, C=C**H$_2$**), 5.03 (AB system, d, *J* = 16.0 Hz, 1H, C**H$_2$**Ph), 4.99 (br s, 1H, C=C**H$_2$**), 4.86 (AB system, d, *J* = 16.0 Hz, 1H, C**H$_2$**Ph), 3.22 (dd, *J* = 1.2 Hz, 16.8 Hz, 1H, C**H$_2$**CHO), 3.12 (dd, *J* = 1.2 Hz, 16.8 Hz, 1H, C**H$_2$**CHO), 1.62 (s, 3H, CC**H$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 177.1, 143.0, 142.4, 135.7, 130.4, 128.7, 128.5, 127.6, 127.3, 123.5, 122.8, 113.9, 109.4, 54.2, 47.7, 44.1, 19.2; IR (thin film): 1715 (s), 1705 (s), 1609 (s), 1488

(s), 1466 (s), 1359 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{20}H_{20}NO_2$ [M+H]: 306.1494. Found: 306.1489.

(+)-**Alcohol** → (+)-**74 :** $[\alpha]_D^{23}$ = +4.0 (c 2.3, $CHCl_3$), ~80% ee.

Preparation of Enynes 68a/b



(±)-**74**

(±)-**68a**
(R^1 = OTBS, R^2 = H)
(±)-**68b**
(R^1 = H, R^2 = OTBS)

Grignard Addition:

To a solution of the crude aldehyde (±)-**74** (2.4 g, azeotropically dried with toluene) in THF (50 ml) at 0 ºC was added ethynylmagnesium bromide (0.5 M in THF, 31 ml). The reaction mixture was stirred at 0 ºC for 30 min and quenched by saturated NH_4Cl solution (30 ml). The aqueous layer was extracted with EtOAc (30 ml × 2), and the combined organic layers were washed with brine (20 ml), dried ($MgSO_4$) and concentrated to provide the crude propargylic alcohol (2.0 g) as a mixture of diastereomers (dr = 1.5:1), which was used in the next step without further purification. For characterization purposes, the crude mixture was purified by flash chromatography (20%→25%→30% EtOAc/hexanes) to provide the β-OH diastereomer (**a**) as a colorless solid and α-OH diastereomer (**b**) as a colorless oil.

β-OH diastereomer (**a**): R_f = 0.40 (20% EtOAc/benzene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H, CH_2**Ph**), 7.19 (ddd, *J* = 1.5 Hz, 7.5 Hz, 7.5 Hz, 1H, **Ph**), 7.12 (dd, *J* = 1.5 Hz, 7.5 Hz, 1H, **Ph**), 7.04 (ddd, *J* = 0.9 Hz, 7.2 Hz, 7.5 Hz, 1H, **Ph**), 6.74 (d, *J* = 8.1 Hz, 1H, **Ph**), 5.03 (br s, 1H, C=C**H$_2$**), 5.01 (br s, 1H, C=C**H$_2$**), 5.00 (d, *J* = 15.6 Hz, 1H, C**H$_2$**Ph), 4.82 (d, *J* = 15.6 Hz, 1H, C**H$_2$**Ph), 3.99 (m, 1H, C**H**OH), 2.84 (dd, *J* = 11.1 Hz, 14.4 Hz, 1H, CC**H$_2$**CH), 2.47 (dd, *J* = 3.0 Hz, 14.4 Hz, 1H, CC**H$_2$**CH), 2.40 (d, *J* = 2.1 Hz, 1H, C≡C**H**), 1.80 (d, *J* = 8.1 Hz, 1H, O**H**), 1.67 (s, 3H, CC**H$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 143.64, 143.60, 135.9, 129.8, 128.6, 128.3, 127.4, 127.3, 123.9, 122.4, 113.2, 109.4, 84.5, 72.7, 59.5, 55.9, 44.1, 42.3, 19.4; IR (thin film): 3406 (s), 1701 (s), 1610 (s), 1488 (s), 1466 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{22}NO_2$ [M+H]: 332.1651. Found: 332.1652.

α-OH diastereomer (**b**): R_f = 0.33 (20% EtOAc/benzene); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.25 (m, 6H, **Ph**, CH_2**Ph**), 7.20 (dd, *J* = 6.8 Hz, 6.8 Hz, 1H, **Ph**), 7.06 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H, **Ph**), 6.77 (d, *J* = 8.0 Hz, 1H, **Ph**), 5.12 (br s, 2H, C=C**H$_2$**), 5.08 (d, *J* = 15.6 Hz, 1H, C**H$_2$**Ph), 4.80 (d, *J* = 15.6 Hz, 1H, C**H$_2$**Ph), 4.62 (m, 1H, C**H**OH), 3.62 (d, *J* = 4.0 Hz, 1H, O**H**), 2.72 (dd, *J* = 3.6 Hz, 14.4 Hz, 1H, CC**H$_2$**CH), 2.41 (d, *J* = 1.6 Hz, 1H, C≡C**H**), 2.29 (dd, *J* = 8.4 Hz, 14.4 Hz, 1H, CC**H$_2$**CH), 1.72 (s, 3H, CC**H$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 142.2, 141.9, 135.4, 131.4, 128.8, 128.4, 127.7, 127.3, 123.7, 122.9, 114.4, 109.5, 84.3, 72.8, 59.7, 56.7, 44.0, 42.3, 19.7; IR (thin film): 3406 (br m), 3293 (br m), 1705 (s), 1610 (s). HRMS (ESI) not obtained.

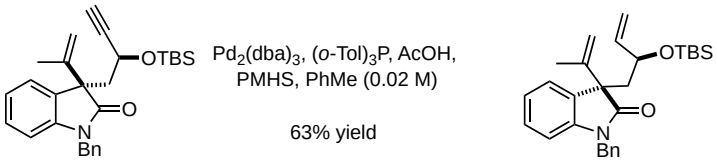
TBS Protection:

A mixture of the crude propargylic alcohol (2.0 g), imidazole (822 mg, 12.1 mmol) and DMAP (369 mg, 3.02 mmol) was azeotropically dried with toluene (3 ml), dissolved in DMF (50 ml) and treated with TBSCl (1.09 g, 7.24 mmol). The reaction mixture was stirred at 50 ºC for 15 h and quenched with water (20 ml). The mixture was extracted with EtOAc (50 ml × 3) and the combined organic layers were washed with water, brine, concentrated in vacuo and purified by flash chromatography (hexanes→2.5%→5%→10% EtOAc/hexanes) to provide the β-OTBS diastereomer **68a** (1.12 g) as a colorless oil and α-OH diastereomer **68b** (748 mg) as a colorless oil (85% combined yield, four steps).

β-OTBS diastereomer (**68a**): R_f = 0.38 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32~7.18 (m, 7H, CH_2**Ph**, **Ph**), 7.01 (ddd, *J* = 0.9 Hz, 7.5 Hz, 7.5 Hz, 1H, **Ph**), 6.71 (d, *J* = 7.8 Hz, 1H, **Ph**), 5.20 (d, *J* = 15.6 Hz, 1H, C**H$_2$**Ph), 4.97 (br s, 1H, C=C**H$_2$**), 4.93 (br s, 1H, C=C**H$_2$**), 4.61 (d, *J* = 15.6 Hz, 1H, C**H$_2$**Ph), 4.24 (ddd, *J* = 2.1 Hz, 6.3 Hz, 7.2 Hz, 1H, C**H**OTBS), 2.79 (dd, *J* = 7.5 Hz, 13.8 Hz, 1H, CC**H$_2$**CH), 2.45 (dd, *J* = 6.3 Hz, 13.8 Hz, 1H, CC**H$_2$**CH), 2.11 (d, *J* = 1.8 Hz, 1H, C≡C**H**), 1.70 (s, 3H, CC**H$_3$**), 0.84 (s, 9H, SiC**(CH$_3$)$_3$**), 0.03 (s, 3H, SiC**H$_3$**), –0.07 (s, 3H, SiC**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 144.1, 143.3, 135.9, 130.3, 128.5, 127.9, 127.3, 127.2, 124.6, 122.0, 112.9, 108.9, 84.6, 73.2, 60.1, 55.8, 43.8, 42.7, 25.9, 19.5, 18.2, -4.4, -4.7; IR (thin film): 1716 (s), 1488 (s), 1466 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{28}H_{36}NO_2Si$ [M+H]: 446.2515. Found: 446.2567. (+)-**74** → (–)-**68a:** $[\alpha]_D^{23}$ = –2.2 (c 1.8, $CHCl_3$), ~80% ee.

α-OTBS diastereomer (**68b**): R_f = 0.29 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5H, CH_2**Ph)**, 7.18 (ddd, *J* = 1.2 Hz, 7.5 Hz, 7.5 Hz, 1H, **Ph**), 7.13 (dd, *J* = 1.2 Hz, 7.5 Hz, 1H, **Ph**), 7.03 (ddd, *J* = 1.5 Hz, 7.5 Hz, 7.5 Hz, 1H, **Ph**), 6.75 (d, *J* = 7.8 Hz, 1H, **Ph**), 5.15 (d, *J* = 15.6 Hz, 1H, **CH$_2$**Ph), 5.00 (br s, 1H, C=**CH$_2$**), 4.97 (br s, 1H, C=**CH$_2$**), 4.61 (d, *J* = 15.6 Hz, 1H, **CH$_2$**Ph), 4.04 (ddd, *J* = 2.1 Hz, 5.4 Hz, 7.8 Hz, 1H, **CH**OTBS), 2.74 (dd, *J* = 7.8 Hz, 13.8 Hz, 1H, C**CH$_2$**CH), 2.48 (dd, *J* = 5.4 Hz, 13.8 Hz, 1H, C**CH$_2$**CH), 2.27 (d, *J* = 2.1 Hz, 1H, C≡**CH**), 1.68 (s, 3H, C**CH$_3$**), 0.80 (s, 9H, SiC**(CH$_3$)$_3$**), –0.01 (s, 3H, Si**CH$_3$**), –0.13 (s, 3H, Si**CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 143.9, 143.2, 136.0, 130.6, 128.6, 128.1, 127.51, 127.48, 124.2, 122.3, 113.0, 109.1, 84.6, 73.4, 60.0, 55.8, 43.9, 42.9, 25.7, 19.5, 18.0, –4.7, –5.2; IR (thin film): 2105 (w), 1715 (s), 1611 (s), 1488 (s), 1466 (s), 1080 (s) cm^{-1}. HRMS (ESI) Not Obtained. (+)-**74** → (–)-**68b:** $[\alpha]_D^{23}$ = –12.4 (c 2.2, $CHCl_3$), ~80% ee

Preparation of Silyl-Allylic Alcohol 78a



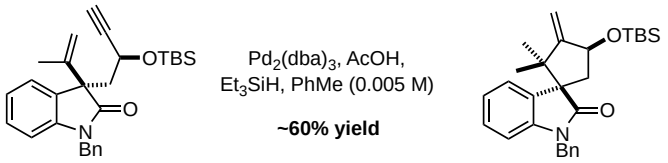
(±)-**68a** (±)-**78a**

A mixture of $Pd_2(dba)_3$ (4.5 mg, 0.005 mmol) and tri(o-tolyl)phosphine (3 mg, 0.010 mmol) was dissolved in toluene (1 ml, degassed through freeze-pump-thaw process). After stirring at ambient temperature for 2 minutes, PMHS (~15 μl) and acetic acid (2.8 μl) was added. After 2 minutes, a solution of enyne **68a** (11 mg, 0.0247 mmol, azeotroped in PhMe) in PhMe (1 ml) was added. The reaction mixture was stirred at ambient temperature for 80 minutes, concentrated, and purified by flash chromatography (5% 7.5% 10% EtOAc/hexanes). Only the reduced alkyne **78a** was obtained (7 mg, 63% yield).

^{1}H NMR (300 MHz; $CDCl_3$) δ 7.35-7.24 (m, 6H), 7.14 (td, *J* = 7.6, 1.4 Hz, 1H), 7.07 (ddd, *J* = 7.4, 1.4, 0.5 Hz, 1H), 6.98 (td, *J* = 7.4, 1.0 Hz, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 5.27 (ddd, *J* = 17.2, 10.0, 7.3 Hz, 1H), 5.14 (d, *J* = 15.4 Hz, 1H), 4.96 (m, 2H), 4.64 (d, *J* = 15.4 Hz, 1H), 4.55 (ddd, *J* = 12.2, 1.7, 0.8 Hz, 1H), 4.51 (ddd, *J* = 5.3, 1.7, 0.8 Hz, 1H), 3.91 (m, 1H), 2.63 (dd, *J* = 13.6, 5.8 Hz, 1H), 2.22 (dd, *J* =

13.6, 7.4 Hz, 1H), 1.65 (s, 3H), 0.83 (s, 9H), -0.08 (s, 3H), -0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.60, 144.72, 143.48, 141.08, 136.41, 131.39, 128.81, 127.98, 127.81, 127.72, 124.62, 122.22, 113.79, 112.90, 108.94, 72.18, 55.99, 43.96, 43.09, 26.05, 19.54, 18.26, -4.07, -4.49; IR (thin film): 1713 (s), 1487 (s), 1466 (s), 835 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{28}H_{37}NNaO_2Si$ [M+Na]: 470.2491. Found: 470.2481.

Preparation of Spiro-oxindole 69a



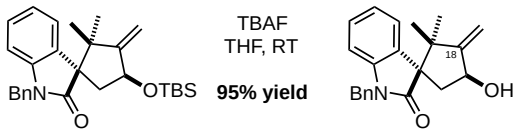
(±)-**68a** (±)-**69a**

To a solution of $Pd_2(dba)_3$ (220 mg, 0.240 mmol) in toluene (200 ml) at room temperature was added Et_3SiH (319 µl, 1.99 mmol) and acetic acid (228 µl, 3.99 mmol). After stirring at room temperature for 4 min, a solution of enyne **68a** (889 mg, 1.99 mmol) in toluene (100 ml) was added plus 200 ml of rinse, resulting in a final substrate concentration of 0.005 M. The reaction mixture was stirred for 70 min, concentrated and purified by flash chromatography (5%→7.5% EtOAc/hexanes) to provide 956 mg of semi-pure product as a pale yellow oil, which was used in the next step without further purification. For characterization purpose, the semi-pure product was further purified by flash chromatography (0%→0.25%→0.5% acetone/$CHCl_3$) to provide spiro-oxindole **69a** as a colorless oil, which solidified upon standing at ambient temperature.

R_f = 0.40 (10% EtOAc/hexanes), 0.17 ($CHCl_3$); m.p. 97-100 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5H, CH_2**Ph**), 7.13 (ddd, *J* = 0.9 Hz, 7.5 Hz, 7.5 Hz, 1H, **Ph**), 7.05 (d, *J* = 7.2 Hz, 1H, **Ph**), 6.94 (dd, *J* = 7.5 Hz, 7.5 Hz, 1H, **Ph**), 6.71 (d, *J* = 7.8 Hz, 1H, **Ph**), 5.24 (br s, 1H, C=**CH$_2$**), 5.11 (d, *J* = 15.6 Hz, 1H, **CH$_2$**Ph), 5.03 (br s, 1H, C=**CH$_2$**), 5.00 (m, 1H, **CH**OTBS), 4.73 (d, *J* = 15.6 Hz, 1H, **CH$_2$**Ph), 2.47 (dd, *J* = 7.2 Hz, 13.2 Hz, 1H, C**CH$_2$**CH), 2.26 (dd, *J* = 8.4 Hz, 13.2 Hz, 1H, C**CH$_2$**CH), 1.39 (s, 3H, C**CH$_3$**), 0.95 (s, 9H, SiC**(CH$_3$)$_3$**), 0.79 (s, 3H, C**CH$_3$**), 0.16 (s, 3H, Si**CH$_3$**), 0.12 (s, 3H, Si**CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 161.4, 142.3, 136.2, 132.9, 128.7, 127.52, 127.47, 127.2, 123.9, 121.9, 108.7, 108.0, 73.3, 58.3, 48.4, 43.8, 42.6, 26.3, 25.8, 23.8, 18.1, –4.4, –4.6; IR (thin film): 1713 (s), 1610 (m),

1488 (s), 1466 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{28}H_{38}NO_2Si$ [M+H]: 448.2672. Found: 448.2662. (–)-**68a** → (–)-**69a**: $[\alpha]_D^{23}$ = –11.4 (c 1.6, $CHCl_3$); ~80% ee.

Preparation of Allylic Alcohol 82a

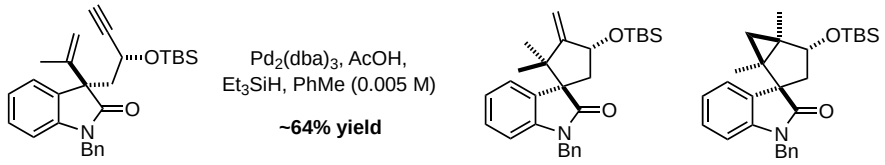


(±)-**69a** (±)-**82a**

To a solution of the semi-pure silyl ether **69a** (956 mg) in THF (25 ml) at 0 ºC was added TBAF (1.0 M in THF, 5 ml). The reaction mixture was stirred at room temperature for 1 h and quenched by saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc and the combined organic layers were concentrated and purified by flash chromatography (10%→20% acetone/hexanes) to provide the allylic alcohol **82a** as a colorless oil (390 mg, 59% yield over two steps).

R_f = 0.18 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 6H, CH_2**Ph**, **Ph**), 7.21 (dd, *J* = 7.2 Hz, 7.2 Hz, 1H, **Ph**), 7.05 (dd, *J* = 7.2 Hz, 8.0 Hz, 1H, **Ph**), 6.79 (d, *J* = 8.0 Hz, 1H, **Ph**), 5.53 (d, *J* = 1.6 Hz, 1H, C=**CH$_2$**), 5.14 (d, *J* = 1.6 Hz, 1H, C=**CH$_2$**), 5.05 (d, *J* = 15.6 Hz, 1H, **CH$_2$**Ph), 4.82 (m, 1H, **CH**OH), 4.74 (d, *J* = 15.6 Hz, 1H, **CH$_2$**Ph), 4.52 (d, *J* = 11.6 Hz, 1H, **OH**), 2.66 (dd, *J* = 8.0 Hz, 14.8 Hz, 1H, C**CH$_2$**CH), 2.06 (d, *J* = 14.8 Hz, 1H, C**CH$_2$**CH), 1.18 (s, 3H, C**CH$_3$**), 0.96 (s, 3H, C**CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.7, 163.0, 143.5, 135.6, 128.7, 128.6, 128.2, 127.6, 127.3, 125.2, 122.2, 109.8, 109.2, 72.3, 60.6, 50.1, 43.8, 41.2, 27.8, 21.8; IR (thin film): 3432 (br, s), 1687 (s), 1611 (s), 1466 (s), 1367 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{24}NO_2$ [M+H]: 334.1807. Found: 334.1812. (–)-**69a** → (–)-**82a**: $[\alpha]_D$ = –13.3 (c 2.7, $CHCl_3$), ~80% ee}

Preparation of Spiro-oxindole 69b and Cyclopropane 79



(±)-**68b** (±)-**69b** (±)-**79**

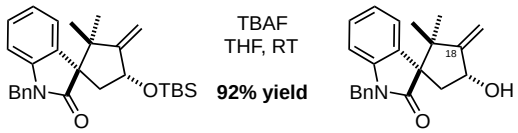
To a solution of $Pd_2(dba)_3$ (143 mg, 0.156 mmol) in toluene (100 ml) at room temperature was added Et_3SiH (166 µl, 1.04 mmol) and acetic acid (119 µl, 2.08 mmol). After stirring at room temperature for 4 min, a solution of the enyne **68b** (463 mg, 1.04 mmol) in toluene (50 ml) was added plus 50 ml of rinse, resulting in a final substrate concentration of 0.005 M. The reaction mixture was stirred for 70 min, concentrated and purified by flash chromatography (30%→50%→70% $CHCl_3$/hexanes) to provide spiro-oxindole **69b** as a pale yellow oil (297 mg, 64% yield) and byproduct cyclopropane **79** (25 mg, 5%) as a colorless oil.

Spiro-oxindole 69b: R_f = 0.42 (10% EtOAc/hexanes), 0.50 ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36~7.24 (m, 6H, CH_2**Ph**, **Ph**), 7.16 (app dd, *J* = 7.5 Hz, 7.8 Hz, 1H, **Ph**), 6.99 (app dd, *J* = 7.5 Hz, 7.5 Hz, 1H, **Ph**), 6.71 (d, *J* = 7.8 Hz, 1H, **Ph**), 5.24 (br s, 1H, C=**C**$\mathbf{H_2}$), 5.21 (m, 1H, **CH**OTBS), 5.12 (d, *J* = 15.6 Hz, 1H, **C**$\mathbf{H_2}$Ph), 5.00 (br s, 1H, C=**C**$\mathbf{H_2}$), 4.64 (d, *J* = 15.6 Hz, 1H, **C**$\mathbf{H_2}$Ph), 2.59 (dd, *J* = 8.1 Hz, 13.5 Hz, 1H, C**C**$\mathbf{H_2}$CH), 2.05 (dd, *J* = 5.7 Hz, 13.5 Hz, 1H, C**C**$\mathbf{H_2}$CH), 1.07 (s, 6H, C(**C**$\mathbf{H_3}$)$_2$), 0.95 (s, 9H, SiC(**C**$\mathbf{H_3}$)$_3$), 0.17 (s, 3H, Si**C**$\mathbf{H_3}$), 0.12 (s, 3H, Si**C**$\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.4, 161.8, 143.0, 136.2, 130.8, 128.7, 127.7, 127.5, 127.4, 125.5, 121.9, 108.5, 107.3, 72.3, 59.0, 48.5, 43.7, 42.1, 26.2, 25.9, 24.1, 18.1, –4.5, –4.7; IR (thin film): 1711 (s), 1611 (m), 1488 (m), 1466 (m) cm^{-1}. HRMS (ESI) not obtained. (–)-**68b** → (+)-**69b**: $[\alpha]_D$ = +37.4 (c 2.2, $CHCl_3$), ~80% ee.

Cyclopropane 79: R_f = 0.35 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 1.2 Hz, 7.2 Hz, 1H, **Ph**), 7.28 (m, 4H, CH_2**Ph**), 7.22 (m, 1H, CH_2**Ph**), 7.08 (ddd, *J* = 1.2 Hz, 7.6 Hz, 7.6 Hz, 1H, **Ph**), 6.95 (ddd, *J* = 1.2 Hz, 7.6 Hz, 7.6 Hz, 1H, **Ph**), 6.68 (d, *J* = 7.6 Hz, 1H, **Ph**), 5.02 (d, *J* = 15.6 Hz, 1H, **C**$\mathbf{H_2}$Ph), 4.75 (d, *J* = 15.6 Hz, 1H, **C**$\mathbf{H_2}$Ph), 4.39 (d, *J* = 5.6 Hz, 1H, **CH**OTBS), 2.25 (dd, *J* = 5.6 Hz, 14.8 Hz, 1H, C**C**$\mathbf{H_2}$CH), 1.64 (d, *J* = 14.8 Hz, 1H, C**C**$\mathbf{H_2}$CH), 1.32 (d, J = 5.6 Hz, 1H, C**C**$\mathbf{H_2}$C), 1.20 (s, 3H, CHC**C**$\mathbf{H_3}$), 0.92 (s, 9H, SiC(**C**$\mathbf{H_3}$)$_3$), 0.68 (s, 3H, CHCC**C**$\mathbf{H_3}$), 0.11 (m, 4H, Si**C**$\mathbf{H_3}$, C**C**$\mathbf{H_2}$C), 0.00 (s, 3H, Si**C**$\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.4, 142.0, 136.4, 133.3, 128.7, 127.5, 127.3, 127.2,

126.7, 122.1, 108.4, 78.7, 57.4, 43.8, 43.1, 37.2, 33.3, 25.9, 18.3, 18.2, 14.4, 14.0, –4.6, –4.9; IR (thin film): 1712 (s), 1611 (m), 1487 (s), 1466 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{28}H_{38}NO_2Si$ [M+H]: 448.2672. Found: 448.2668.

Preparation of Allylic Alcohol 82b



To a solution of silyl ether **69b** (207 mg, 0.462 mmol) in THF (5 ml) at 0 ºC was added TBAF (1.0 M in THF, 925 µl). The reaction mixture was stirred at room temperature for 2.5 h and another 100 µl of TBAF was added. After stirring for 30 min, the reaction was quenched by saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc and the combined organic layers were concentrated and purified by flash chromatography (30%→40%→50% EtOAc/hexanes) to provide the allylic alcohol **82b** as a white solid (142 mg, 92% yield).

R_f = 0.07 (20% EtOAc/hexanes); m.p. 113–119 ºC ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 6H, CH_2**Ph**, **Ph**), 7.15 (ddd, *J* = 0.8 Hz, 7.6 Hz, 8.0 Hz, 1H, **Ph**), 6.99 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H, **Ph**), 6.70 (d, *J* = 8.0 Hz, 1H, **Ph**), 5.33 (d, *J* = 2.0 Hz, 1H, C=**CH$_2$**), 5.26 (br dd, *J* = 7.2 Hz, 8.0 Hz, 1H, **CH**OH), 5.08 (d, *J* = 2.0 Hz, 1H, C=**CH$_2$**), 5.04 (d, *J* = 15.6 Hz, 1H, **CH$_2$**Ph), 4.62 (d, *J* = 15.6 Hz, 1H, **CH$_2$**Ph), 2.52 (dd, *J* = 8.4 Hz, 13.6 Hz, 1H, C**CH$_2$**CH), 2.15 (dd, *J* = 6.8 Hz, 13.6 Hz, 1H, C**CH$_2$**CH), 1.20 (s, 3H, C**CH$_3$**), 0.96 (s, 3H, C**CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0, 162.1, 143.2, 135.9, 129.3, 128.6, 127.9, 127.4, 127.3, 125.4, 121.8, 108.6, 108.0, 72.1, 59.4, 48.1, 43.5, 41.0, 27.7, 23.1; IR (thin film): 3432 (br, s), 1701 (s), 1610 (s), 1488 (s), 1466 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{23}NNaO_2$ [M+Na]: 356.1627. Found: 356.1635.

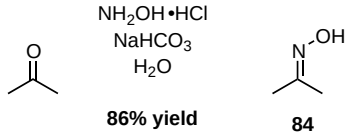
Preparation of Unsubstituted Nitrone 80

To a solution of piperdine (2.26 g, 26.5 mmol) in acetone (51 ml) at 0 °C was added SeO_2 (147 mg, 1.33 mmol) and H_2O_2 (30% by wt in H_2O, 5.6 ml, 58.4 mmol) dropwise. The reaction mixure was

stirred at rt for 3 h. Acetone was removed *in vacuo* and the resulting residue was extracted with CH_2Cl_2 (100 ml), concentrated, and purified by flash chromatography (basic Al_2O_3, 2.5%→5%→7.5% MeOH/CH_2Cl_2) to provide nitrone **80** as a yellow oil (1.1 g, 42% yield)

Known compound; CAS 34418-91-2. Characterization data matched literature reports.

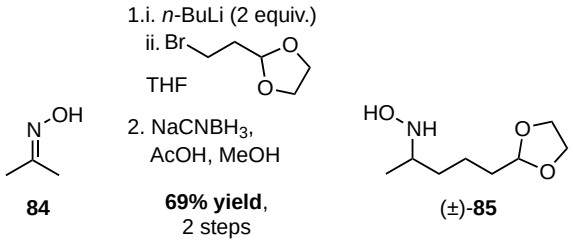
Preparation of Acetone Oxime 84



To a solution of hydroxylamine hydrochloride (5.0 g, 72.0 mmol) in H_2O (55 ml) at room temperature was added solid $NaHCO_3$ (7.25 g, 86.3 mmol). Following the evolution of gas, acetone (5.28 ml, 72.0 mmol) was added. The reaction was stirred at room temperature for 2 h, extracted with Et_2O, dried ($MgSO_4$), and concentrated to provide the desired oxime **84** as a white powder (4.5 g, 86% yield).

R_f = 0.41 (50% EtOAc/Hexanes, $KMnO_4$). Known compound; CAS 127-06-0. Characterization data matched literature reports.

Preparation of Oxime 85



Alkylation:

To a solution of the oxime **84** (1.55 g, 21.2 mmol) in THF (75 ml) at 0 °C was added *n*-butyl lithium (1.6 M in hexanes, 26.6 ml, 42.4 mmol) dropwise. The reaction mixture turned cloudy before turning clear again. This mixture was stirred at room temperature for 30 min and then was cooled to –78 °C. A solution of 2-(2-bromoethyl)-1,3-dioxolane (2 ml, 17 mmol) in THF (75 ml) was added slowly via

cannula. The reaction was allowed to stir at –78 °C for 1 h, then at room temperature for 3 h. This was quenched with water, extracted with EtOAc, concentrated, dried (Na_2SO_4) and purified by flash chromatography (10% →20%→30%→40%→50% EtOAc/Hexanes) to provide the desired oxime as a pale yellow oil (2.56 g, 85% yield).

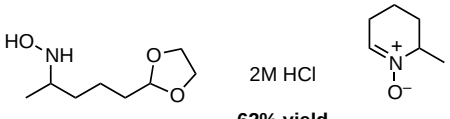
R_f = 0.29 (50% EtOAc/Hexanes, $KMnO_4$).

Oxime Reduction:

To a solution of the oxime (831 mg, 4.8 mmol) in methanol (32 ml), cooled to 0 °C in an ice bath, were added glacial acetic acid (2.8 ml, 48 mmol) and sodium cyanoborohydride (a freshly opened bottle, 1.5 g, 24 mmol). The ice bath was removed and the clear solution stirred for 6 h at room temperature. At that time, the reaction mixture was basified with aqueous sodium hydroxide solution (2 M, 25 ml). The reaction was extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (0.5%→1%→2%→3% MeOH/CH_2Cl_2) to provide the hydroxylamine **85** as a white solid (689 mg, 82% yield).

R_f = 0.23 (10% MeOH/CH_2Cl_2, $KMnO_4$). Known compound; CAS (*S*)-(–) 900780-42-9 / (*R*)-(+) 900780-55-4. Characterization data matched literature reports.

Preparation of Nitrone (±)-57

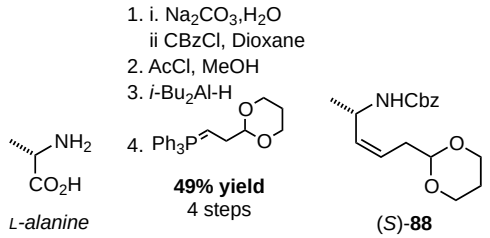


(±)-**85** (±)-**57**

To a flask containing the hydroxylamine **85** (100 mg, 0.57 mmol) was added aqueous HCl solution (2 M, 1 ml). The reaction was stirred at room temperature for 25 minutes, diluted with water (3 ml), and basified to pH 11 with Na_2CO_3 (approx. 150 mg Na_2CO_3). This was extracted with $CHCl_3$, dried ($MgSO_4$), concentrated. The residue was purified by flash chromatography (basic Al_2O_3, 5%→10% MeOH / CH_2Cl_2) to provide the nitrone **57** as a yellow-greenish oil (40 mg, 62%).

R_f = 0.37 (10% MeOH/CH_2Cl_2, TLC pre-treated with NH_3, UV & $KMnO_4$). Known compound; CAS (±) 106130-14-7. Characterization data matched literature reports.

Preparation of Olefin 88



CBz Protection:

L-alanine (4 g, 44.9 mmol) and anhydrous Na_2CO_3 (14.3 g, 135 mmol) were dissolved in water (150 ml). At 0 °C a solution of benzyl chloroformate (7.05 ml, 49.4 mmol) in dioxane (40 ml) was added slowly. The milky mixture was stirred at 0 °C for 30 min, then at room temperature for 20 h. The reaction mixture was washed with Et_2O, and the aqueous layer was acidified to pH 2 using concentrated HCl (~10 ml). This was extracted with EtOAc, dried ($MgSO_4$), and concentrated to provide the desired product as a white gummy solid (7.3 g, 73% yield).

R_f = 0.22 (40% EtOAc/Hexanes, CAM).

Esterification:

A solution of *N*-CBz-L-alanine (3.7 g, 16.6 mmol) in methanol (40 ml) was cooled to 0 °C in an ice bath. To this was added dropwise acetyl chloride (2.4 ml, 33.1 mmol). The reaction mixture was stirred at room temperature for 1 h, then quenched slowly with saturated $NaHCO_3$ solution (10 ml) and solid $NaHCO_3$. The mixture was extracted with EtOAc, washed with water and brine, and dried ($MgSO_4$) to provide the desired ester as a pale yellow oil (3.7 g, 94% yield).

R_f = 0.52 (40% EtOAc/Hexanes, CAM). Known compound; CAS (*S*)-(–) 28819-05-8. Characterization data matched literature reports.

DIBAl-H Reduction:

A solution of the ester (4.06 g, 17.1 mmol) in CH_2Cl_2 (120 ml) was cooled to –78 °C. To this was added a solution of diisobutylaluminum hydride (6.1 ml, 34.2 mmol) in CH_2Cl_2 (30 ml) by syringe pump over 3 hours. The reaction mixture was stirred at –78 °C for 6 h. The reaction was quenched with aqueous HCl solution (1 N, 40 ml) and saturated Rochelle's salt solution (50 ml) at which point it was stirred for another 1.5 h. The layers were separated, and the organic layer was washed with 1 N HCl (40 ml) and water (40 ml), concentrated and purified by flash chromatography (20%→30%→40% EtOAc/Hexanes) to provide the aldehyde as a colorless oil (2.85 g, 80% yield).

R_f = 0.29 (40% EtOAc/Hexanes, CAM). Known compound; CAS (*S*)-(–) 111955-03-4. Characterization data matched literature reports.

Wittig Reagent:

A solution of 2-(2-bromoethyl)-1,3-dioxane (8.8 g, 45.1 mmol) and triphenylphosphine (18.7 g, 71.3 mmol) in cyclohexane (23 ml) was heated to 87 °C for 24 h, cooled to room temperature, then filtered. The solid was washed with Et_2O (90 ml) and pentane (90 ml), collected, then dried under vacuum to provide the desired product as a white powder (9 g, 44% yield).

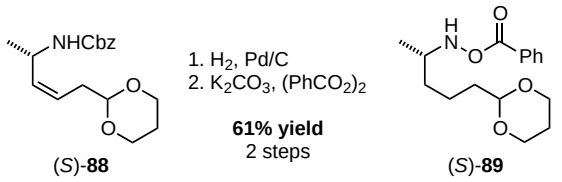
Known compound; CAS 69891-57-2. Characterization data matched literature reports.

Wittig Reaction

To a slurry of phosphonium bromide (14.3 g, 31.3 mmol) in THF (150 ml) at 0 °C was added KO*t*Bu (3.51 g, 31.3 mmol). The orange mixture was stirred at room temperature for 1 h before a solution of the aldehyde (5.4 g, 26.1 mmol) in THF (50 ml) was added followed by 40 ml of rinse. The reaction mixure was stirred at room temperatre for 14 h, quenched with saturated NH_4Cl solution, extracted with EtOAc, concentrated and purified by flash chromatography (5%→10%→15%→20% acetone/hexanes, then 40% EtOAc/Hexanes) to provide the olefin (*S*)-**88** as a colorless oil (7.1 g, 89% yield).

R_f = 0.29 (25% acetone/hexanes, CAM). Known compound; CAS (*S*)-(+) 195372-68-0. Characterization data matched literature reports.

Preparation of Benzyloxyamine 89



(*S*)-**88** (*S*)-**89**

Hydrogenation:

A solution of the alkene (*S*)-**88** (7.1 g, 23.3 mmol) in ethyl acetate / ethanol (2:1, 108 ml) containing 10 wt% palladium on carbon (866 mg, 0.814 mmol) was bubbled with H_2 for 1 minute and stirred under H_2 (balloon pressure) for 6 days, filtered through a pad of celite, washed with CH_2Cl_2, and concentrated to provide the amine as a pale yellow oil (4 g, 99% yield).

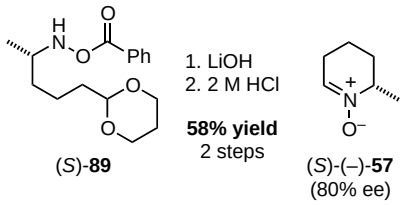
R_f = baseline (30% EtOAc/hexanes, CAM). Known compound; CAS (S)-(+) 195372-69-1. Characterization data matched literature reports.

Oxidation:

Solid $NaHCO_3$ (5.95 g, 71 mmol) was dissolved in H_2O (94 ml) and mixed with NaOH solution (1.5 M in H_2O, 10 ml, 15 mmol). This solution was added to a flask containing the amine (3.2 g, 18.5 mmol) followed by the addition of a solution of benzoyl peroxide (6.7 g, 27.7 mmol) in CH_2Cl_2 (94 ml). The mixture was vigorously stirred at room temperature for 25 hours, the layers separated, and the aqueous portion extracted with EtOAc. Following concentration of the organic layers, the residue was triturated with 10% EtOAc/hexanes. The resulting organic solution was concentrated and purified by flash chromatography (10%→20%→30%→40% EtOAc/Hexanes) to provide the desired benzyloxyamine (*S*)-**89** as a colorless oil (3.3 g, 61% yield).

R_f = 0.27 (30% EtOAc/hexanes, CAM). Known compound; CAS (S)-(–) 195372-70-4. Characterization data matched literature reports.

Preparation of Nitrone (*S*)-(–)-57

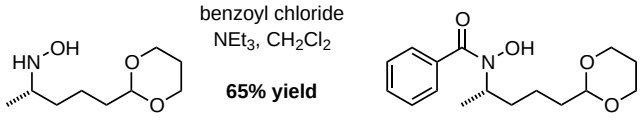


Saponification:

To a solution of the benzyloxyamine (*S*)-**89** (15.2 g, 51.8 mmol) in THF/MeOH 1:1 (160 ml) at room temperature was added LiOH solution (2M, 160 ml). After stirring at room temperature for 4 minutes, the mixture was extracted with EtOAc, concentrated, and purified by flash chromatography (60%→80%→100% EtOAc/hexanes to 10% MeOH/CH_2Cl_2) to provide the desired hydroxylamine (6.6 g, 67% yield).

R_f = 0.43 (10% MeOH/CH_2Cl_2, TLC pre-treated with NH_3). Known compound; CAS (S)-(+) 195372-71-5. Characterization data matched literature reports.

Determination of the ee:



To determine the ee of the hydroxylamine: A solution of the hydroxylamine (23 mg, 0.122 mmol) in CH_2Cl_2 (4 ml) at 0 °C was added NEt_3 (34 μL, 0.243 mmol) and benzoyl chloride (13 μL, 0.109 mmol). The reaction was stirred at room temperature for 30 minutes, quenched with saturated $NaHCO_3$ solution, extracted with EtOAc, concentrated, and purified by flash chromatography (30%→40%→50%→60% EtOAc/hexanes) to provide the *N*-acylated product (23 mg, 65% yield) for HPLC assay.

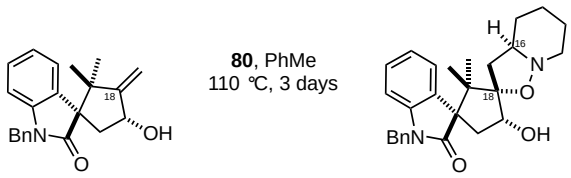
R_f = 0.52 (10% MeOH/CH_2Cl_2, $KMnO_4$); Racemic HPLC conditions: 90:10 hexanes/*i*-PrOH, rate = 1 ml/minute, Chiralpak AD–H, t = 12.58 min (45.174%), 14.5 min (54.826%); Enantioenriched HPLC conditions: 90:10 hexanes/*i*-PrOH, rate = 0.8 ml/minute, Chiralpak AD–H, 254 nm, t = 16.07 min (9.469%), 18.36 min (90.531%). ee = 81%.

Acid-Mediated Nitrone Condensation:

The hydroxylamine (53 mg, 0.280 mmol) was treated with aqueous HCl solution (2 M, 2 ml). After 15 minutes, the reaction was diluted with water (3 ml) and basified to pH 11 with solid Na_2SO_3. The solution was extracted with $CHCl_3$ (5 x 8 ml) and concentrated to provide (*S*)-(–)-**57** which was used directly in the cycloaddition reaction.

Known compound; CAS (*S*)-(–) 195372-72-6. Characterization data matched literature reports.

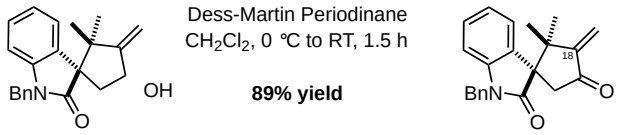
Preparation of Isoxazolidine 83



A mixture of the allylic alcohol **82b** (36 mg, 0.108 mmol) and nitrone **80** (21 mg, 0.216 mmol) in toluene (1 mL) was heated to 110 °C for 1.5 days. At that time a second portion of nitrone **80** (21 mg, 0.216 mmol) was added. The reaction mixture was stirred for another 2.5 days, and directly purified by flash chromatography (10%→20%→30% acetone/hexanes) to afford the isoxazolidine cycloadduct **83** as a white foam (35 mg, 75% yield).

R_f = 0.35 (60% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, 1H, **Ph**), 7.19~6.89 (m, 7H, CH_2**Ph**, **Ph**), 6.43 (d, 1H, **Ph**), 5.03 (d, *J* = 16.3 Hz, 1H, **C**$\mathbf{H_2}$Ph), 4.79 (br t, *J* = 8.5 Hz, 1H, C**H**OH), 4.25 (d, *J* = 16.3 Hz, 1H, **C**$\mathbf{H_2}$Ph), 3.15 (m, 1H, R_2N**C**$\mathbf{H_2}$), 2.91 (dd, *J* = 7.6 Hz, 13.2 Hz, 1H, **C**$\mathbf{H_2}$CHOH), 2.53 (dd, *J* = 9.1 Hz, 13.2 Hz, 1H, **C**$\mathbf{H_2}$CHOH), 2.09 (m, 1H, R_2N**C**$\mathbf{H_2}$), 1.91 (m, 2H, R_2NCH**C**$\mathbf{H_2}$), 1.76 (m, 1H, N**CH**), 1.46 (br d, *J* = 12.4, 1H, R_2NCH**CH2**), 1.39~1.12 (m, 7H, $R_2NCH_2\mathbf{CH_2}$, C**C**$\mathbf{H_3}$) 0.77 (s, 3H, C**C**$\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.0, 143.9, 137.6, 134.7, 129.3, 128.9, 127.9, 127.7, 127.6, 122.2, 108.8, 92.0, 79.5, 68.4, 58.9, 55.1, 47.3, 44.1, 43.4, 38.9, 29.6, 27.4, 25.1, 24.2, 22.4; IR (thin film): 3396 (br, s), 2938 (s), 2274 (s), 1709 (s), 1609 (s), 1487 (s), 1466 (s), 1349 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{27}H_{33}N_2O_3$ [M+H]: 433.2491. Found: 433.2485.

Preparation of Enone 58



(±)-**82a/b** (±)-**58**

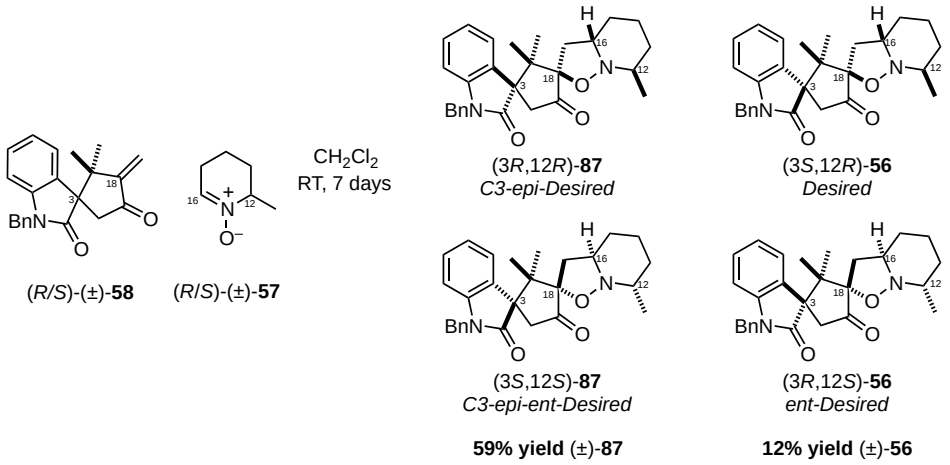
To a solution of the alcohol **82a/b** (830 mg, 2.49 mmol) in CH_2Cl_2 (25 ml) at 0 ºC was added Dess–Martin periodinane (1.58 g, 3.73 mmol). The reaction mixture was stirred at room temperature for 1.5 h and was quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc and the combined organic layers were concentrated and purified by flash chromatography (10%→20%→30% EtOAc/hexanes) to provide enone **58** as a white powder (734 mg, 89% yield).

R_f = 0.37 (30% EtOAc/hexanes); m.p. 99–102 ºC (EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30~7.15 (m, 7H, CH_2**Ph**, **Ph**), 6.99 (ddd, *J* = 0.8 Hz, 7.6 Hz, 7.6 Hz, 1H, **Ph**), 6.77 (d, *J* = 8.0 Hz, 1H, **Ph**), 6.16 (s, 1H, C=**CH$_2$**), 5.25 (s, 1H, C=**CH$_2$**), 5.04 (d, *J* = 15.2 Hz, 1H, **CH$_2$**Ph), 4.66 (d, *J* = 15.2 Hz, 1H, **CH$_2$**Ph), 2.74 (s, 2H, C**CH$_2$**C=O), 1.18 (s, 3H, C**CH$_3$**), 1.13 (s, 3H, C**CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 178.4, 152.7, 143.4, 135.7, 128.7, 128.5, 128.2, 127.6, 127.3, 124.7, 122.2, 116.2, 109.2, 55.1, 47.2, 44.2, 43.7, 26.7, 23.1; IR (thin film): 1730 (s), 1708 (s), 1611 (s), 1466 (s), 1365 cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{22}NO_2$ [M+H]: 332.1651. Found: 332.1642.

Prepared from (–)-**70**: $[\alpha]_D$ = –1.5 (c 1.4, $CHCl_3$); ~67% ee.

Prepared from (+)-**70**: $[\alpha]_D$ = +3.1 (c 1.5, $CHCl_3$); 76% ee by HPLC.

Preparation of Isoxazolidines (±)-87 and (±)-56

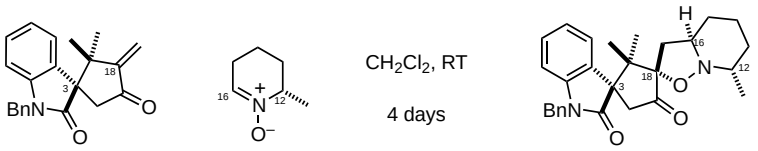


A solution of the racemic enone (**±**)-**58** (1.02 g, 3.07 mmol) and the racemic nitrone (**±**)-**57** (173 mg, 1.53 mmol) in CH_2Cl_2 (8 ml) was stirred at room temperature for 41 h. More nitrone (**±**)-**57** (173 mg, 1.53 mmol) in CH_2Cl_2 (5 ml) was added. After stirring for an additional 48 h, the reaction mixture was concentrated in vacuo and purified by flash chromatography (10%→20%→30%→40%→50% EtOAc/hexanes) to provide the minor cycloadduct (**±**)-**56** as a colorless oil (165 mg, 12% yield), the major cycloadduct (**±**)-**87** as a colorless solid (803 mg, 59% yield) and recovered enone (**±**)-**58** (284 mg, 28%).

Isoxazolidine (±)-87: R_f = 0.48 (40% EtOAc/hexanes); m.p. 177–179 ºC (THF/pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.6 Hz, 1H, **Ar**), 7.28~7.18 (m, 5H, CH_2**Ph**), 7.11 (dd, *J* = 7.6 Hz, 8.0 Hz, 1H, **Ar**), 6.96 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H, **Ar**), 6.67 (d, *J* = 8.0 Hz, 1H, **Ar**), 5.06 (d, *J* = 15.6 Hz, 1H, C**H**$_2$Ph), 4.54 (d, *J* = 15.6 Hz, 1H, C**H**$_2$Ph), 3.46 (m, 1H, CCH_2C**H**N), 3.18 (m, 1H, NC**H**CH_3), 2.81 (d, *J* = 18.8 Hz, 1H, CC**H**$_2$C=O), 2.70 (d, *J* = 18.8 Hz, 1H, CC**H**$_2$C=O), 2.59 (dd, *J* = 13.2 Hz, 13.2 Hz, 1H, CC**H**$_2$CHN), .2.42 (dd, *J* = 5.6 Hz, 13.2 Hz, 1H, CC**H**$_2$CHN), 1.88 (m, 2H, NCHC**H**$_2$**H**$_2$CH$_2$), 1.59 (m, 1H, NCHCH$_2$C**H**$_2$), 1.42 (m, 2H, NCHCH$_2$C**H**$_2$, NCH(CH_3)C**H**$_2$), 1.14 (m, 1H, NCH(CH_3)C**H**$_2$), 1.10 (d, *J* = 6.0 Hz, 3H, CHC**H**$_3$), 1.03 (s, 3H, CC**H**$_3$), 0.95 (s, 3H, CC**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.2, 180.0, 143.5, 135.8, 129.6, 128.8, 128.4, 127.7, 127.2, 126.6, 122.3, 108.8, 93.3, 61.9, 55.3, 55.2, 48.1, 44.0, 43.2, 37.5, 32.9, 25.4, 20.9, 20.8, 20.4, 18.8; IR (thin film): 1748 (s), 1708 (s), 1610 (s), 1466 (s), 1365 cm^{-1}; HRMS (ESI) Calcd. for $C_{28}H_{33}N_2O_3$ [M+H]: 445.2491. Found: 445.2468. X-ray quality crystals were obtained by slow diffusion of pentane into a THF solution of the substrate.

Isoxazolidine (±)-56: R_f = 0.27 (40% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H, CH_2**Ph**), 7.19 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H, **Ar**), 7.04 (d, *J* = 7.6 Hz, 1H, **Ar**), 6.98 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H, **Ar**), 6.75 (d, *J* = 7.6 Hz, 1H, **Ar**), 5.25 (d, *J* = 15.6 Hz, 1H, C**H**$_2$Ph), 4.54 (d, *J* = 15.6 Hz, 1H, C**H**$_2$Ph), 3.51 (m, 1H, CCH_2C**H**N), 3.26 (d, *J* = 18.8 Hz, 1H, CC**H**$_2$C=O), 3.25 (m, 1H, NC**H**CH_3), 2.56 (dd, *J* = 12.0 Hz, 12.0 Hz, 1H, CC**H**$_2$CHN), 2.55 (d, *J* = 18.8 Hz, 1H, CC**H**$_2$C=O), 2.25 (dd, *J* = 6.0 Hz, 12.0 Hz, 1H, CC**H**$_2$CHN), 2.00 (m, 1H, NCHC**H$_2$**CH_2), 1.91 (m, 1H, NCHC**H$_2$**CH_2), 1.72 (m, 2H, $NCHCH_2$C**H**$_2$, $NCH(CH_3)$C**H**$_2$), 1.50 (m, 2H, $NCHCH_2$C**H**$_2$, $NCH(CH_3)$C**H**$_2$), 1.27 (s, 3H, CC**H$_3$**), 1.20 (d, *J* = 5.6 Hz, 3H, CHC**H$_3$**), 0.83 (s, 3H, CC**H$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.8, 178.0, 143.5, 136.0, 131.4, 128.8, 128.5, 127.7, 127.4, 124.2, 121.5, 108.9, 92.8, 61.7, 55.7, 54.6, 48.8, 44.3, 42.9, 39.0, 32.8, 25.3, 20.7, 20.6, 20.2, 18.9; IR (thin film): 1745 (s), 1716 (s), 1610 (s), 1466 (s), 1349 cm^{-1}; HRMS (ESI) Calcd. for $C_{28}H_{33}N_2O_3$ [M+H]: 445.2491. Found: 445.2468.

Preparation of Enantioenriched Isoxazolidine 87



(3*R*)-(–)-**58** (~67% ee)

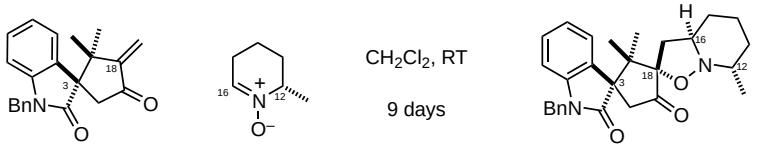
(12*S*)-(–)-**57** (80% ee) 2 equiv.

(3*S*,12*S*)-(+)-**87** **80% yield** *(C3-epi-ent-Desired)*

To a vial containing the enone (3*R*)-(–)-**58** (77 mg, 0.232 mmol) was added a solution of the freshly prepared nitrone (12*S*)-(–)-**57** (~26 mg, 0.232 mmol) in CH_2Cl_2 (2 ml). The reaction mixture was stirred at ambient temperature for 44 hours. At that time, another aliquot of the nitrone (~26 mg, 0.232 mmol) in CH_2Cl_2 (1 ml) was added. The reaction was stirred or 36 hours, concentrated, and purified by flash chromatography (100% $CHCl_3$ →2.5%→50% acetone/$CHCl_3$) to provide (3*S*,12*S*)-(+)-**87** (83 mg, 80% yield) and **56** (13 mg, 13% yield).

Isoxazolidine (3*S*,12*S*)-(+)-87: $[\alpha]_D^{23}$ = +27.1 (c 0.93, $CHCl_3$); Other characterization data matched that of (±)-87.

Preparation of Enantioenriched Isoxazolidine 56



(3*S*)-(+)-**58** (76% ee)

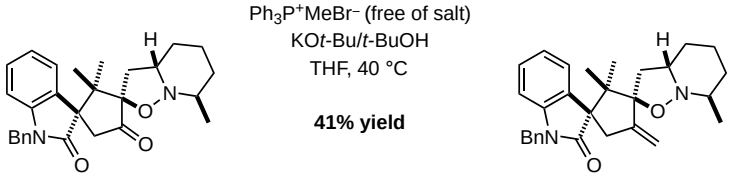
(12*S*)-(–)-**57** (80% ee) 6 equiv.

(3*R*,12*S*)-(+)-**56** **58% yield** *(ent-Desired)*

To a solution of the enone (3*S*)-(+)-**58** (78 mg, 0.235 mmol) in CH_2Cl_2 (1 ml) at ambient temperature was added a solution of freshly prepared nitrone (12*S*)-(–)-**57** (~27 mg, 0.235) in CH_2Cl_2 (0.5 ml). The reaction stirred for a total of 9 days, with the addition of fresh nitrone (~27 mg, 0.235) in CH_2Cl_2 (0.5 ml) every 36 hours. After that time, the reaction mixture was concentrated and purified by flash chromatography (100% $CHCl_3$ →2.5%→50% acetone/$CHCl_3$). Only partial separation was realized. The mixture was further purified by flash chromatography (10%→15%→20%→30% EtOAc/benzene) to provide (3*R*,12*S*)-(+)-**56** (40 mg, 38% yield) and **87** (61 mg, 58% yield).

Isoxazolidine (3*R*,12*S*)-(+)-56: $[\alpha]_D^{22}$ = +145 (c 1.1, $CHCl_3$). Other characterization data matched that of (±)-**56**.

Preparation of Exomethylene 91



(±)-**87**

(±)-**91**

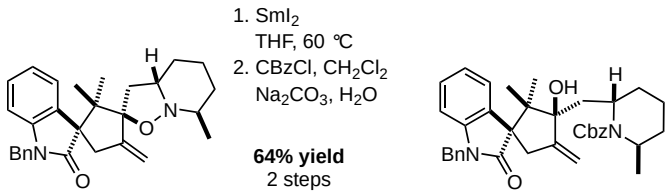
To a slurry of methyltriphenylphosphonium bromide (300 mg, 0.840 mmol) in toluene (9 ml) was added KO*t*Bu (1.0 M in *t*-BuOH, 0.84 ml). The resulting orange mixture was stirred for 1.5 h and allowed to settle for 3 h before use.

To a solution of the ketone **87** (120 mg, 0.270 mmol) in THF (2 ml) was added the ylide solution (the supernatant layer, 4 ml). The reaction was stirred at 40 ºC for 24 h and treated with another 4 ml of the ylide solution (the supernatant layer). After stirring at 40 ºC for an additional 24 h, the reaction was

quenched with sat. NH_4Cl solution. The aqueous layer was extracted with EtOAc and the combined organic layers were concentrated and purified by flash chromatography (10%→20%→30%→40% EtOAc/hexanes) to provide exomethylene **91** as a colorless oil (49 mg, 41% yield) and recovered starting material (55 mg).

R_f = 0.41 (40% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.2 Hz, 1H), 7.30~7.22 (m, 5H), 7.07 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H), 6.94 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 5.20 (br s, 1H), 5.12 (d, *J* = 15.6 Hz, 1H), 5.02 (br s, 1H), 4.52 (d, *J* = 15.6 Hz, 1H), 3.63 (m, 1H), 3.01 (d, *J* = 16.0 Hz, 1H), 3.00 (m, 1H), 2.91 (dd, *J* = 2.0 Hz, 13.2 Hz, 1H), 2.72 (d, *J* = 16.0 Hz, 1H), 2.71 (dd, *J* = 13.2 Hz, 13.2 Hz, 1H), 1.92 (m, 2H), 1.63 (m, 1H), 1.45 (m, 2H), 1.23 (d, *J* = 5.6 Hz, 3H), 1.19 (m, 1H), 1.00 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.2, 154.4, 142.9, 136.2, 133.3, 128.7 (2 carbons), 127.5, 127.2, 126.7, 122.0, 108.2, 105.6, 95.1, 61.1, 56.6, 55.4, 49.9, 43.9, 40.3, 36.3, 32.9, 25.7, 23.0, 22.0, 20.7, 18.8; IR (thin film): 1708 (s), 1609 (s), 1466 (s), 1360 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{29}H_{35}N_2O_2$ [M+H]: 443.2699. Found: 443.2698.

Preparation of Cbz-Protected Piperdine 90 and TFA-Protected Piperdine 90b



(±)-**91** (±)-**90**

Samarium Iodide-Mediated Ring Opening:

To a solution of the isoxazolidine **91** (41 mg, 0.0926 mmol, azeotropically dried with toluene) in THF (3 ml, degassed by purging with N_2 for 10 min) was added SmI_2 (0.1 M in THF, 3 ml). The reaction was heated at 60 ºC for 3 h and quenched with half sat. $Na_2S_2O_3$ solution. The aqueous layer was extracted with EtOAc and the combined organic layers were concentrated and purified by flash chromatography (40% EtOAc/hexanes→5%→10% MeOH/CH_2Cl_2) to provide the desired product as a white solid (40 mg, 98% yield).

R_f = 0.30 (10% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (br s, 1H, –NH), 7.95 (br s, 1H, –OH), 7.29~7.20 (m, 6H), 7.08 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H), 6.93 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H), 6.63 (d,

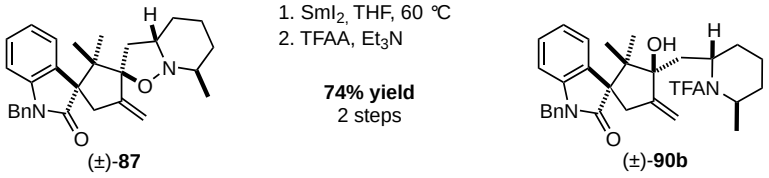
J = 7.6 Hz, 1H), 5.52 (br s, 1H), 5.23 (br s, 1H), 5.08 (d, *J* = 15.6 Hz, 1H), 4.51 (d, *J* = 15.6 Hz, 1H), 3.92 (m, 1H), 3.85 (m, 1H), 3.05 (dt, *J* = 2.8 Hz, 17.6 Hz, 1H), 2.89 (dd, *J* = 10.4 Hz, 16.0 Hz, 1H), 2.73 (d, *J* = 17.6 Hz, 1H), 2.52 (dd, *J* = 2.0 Hz, 16.0 Hz, 1H), 2.08 (m, 2H), 1.90 (m, 1H), 1.71 (m, 3H), 1.45 (d, *J* = 6.4 Hz, 3H), 1.00 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6, 154.4, 142.7, 135.7, 132.2, 128.7, 127.9, 127.5, 127.1, 126.4, 122.1, 110.0, 108.6, 83.7, 57.8, 51.7, 50.3, 48.5, 43.9, 39.2, 36.5, 28.5, 28.3, 24.0, 21.4, 17.7, 17.3; IR (thin film): 3375 (br s), 1697 (s), 1609 (s), 1466 (s), 1366 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{29}H_{37}N_2O_2$ [M+H]: 445.2850. Found: 445.2855.

Cbz-Protection:

To a solution of the piperdine (14 mg, 0.0315 mmol) in CH_2Cl_2 (0.7 ml) was added H_2O (0.7 ml), Na_2CO_3 (21 mg, X mmol) and benzyl chloroformate (9 μl, 0.0630 mmol). The mixture was vigorously stirred for 12 h, diluted with sat. $NaHCO_3$ solution, extracted with EtOAc, concentrated and purified by flash chromatography (10%→20%→30% EtOAc/Hexanes) to provide the Cbz-protected piperdine **90** (12 mg, 65% yield).

Cbz-Protected Piperdine 90: R_f = 0.37 (30% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.8 (d, 1H), 7.4~7.2 (m, 10H), 7.1 (t, 1H), 7.0 (t, 1H), 6.6 (d, 1H), 5.18 (d, 1H), 5.17 (d, 1H), 5.1 (d, 1H), 4.85 (d, 2H), 4.71 (d, 1H), 4.54 (d, 1H), 4.38 (m, 1H), 4.03 (m, 1H), 2.8 (s, 2H), 2.4 (dd, 1H), 2.1 (m, 2H), 1.8~1.7 (m, 5H), 1.3 (d, 3H), 1.0 (s, 3H), 0.7 (s, 3H). ^{13}C NMR not obtained. IR not obtained. HRMS not obtained.

TFA-Protection:

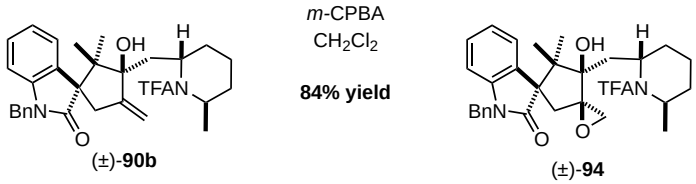


To a solution of the piperdine (40 mg, 0.0900 mmol) in CH_2Cl_2 (5 ml) at 0 °C was added Et_3N (25 μl, 0.180 mmol) and trifluoroacetic anhydride (15 μl, 0.108 mmol). After stirring at 0 °C for 10 minutes, another portion of Et_3N (25 μl, 0.180 mmol) and TFAA (15 μl, 0.108 mmol) were added. After stirring for

10 minutes longer, the reaction was quenched with sat. $NaHCO_3$ solution, extracted with EtOAc, concentrated and purified by flash chromatography (10%→20%→30% EtOAc/Hexanes) to provide the TFA-protected piperdine **90b** as a colorless oil (37 mg, 76% yield).

TFA-Protected Piperdine 90b: R_f = 0.28 (20% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.6 Hz, 1H), 7.34-7.24 (m, 5H), 7.11 (dt, *J* = 7.7, 1.1 Hz, 1H), 6.95 (dt, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 5.34 (d, *J* = 1.9 Hz, 1H), 5.21 (d, *J* = 1.9 Hz, 1H), 5.17 (d, *J* = 15.7 Hz, 1H), 4.57 (d, *J* = 15.7 Hz, 1H), 3.72 (m, 2H), 3.11 (dt, *J* = 17.3, 2.2 Hz, 1H), 2.84 (dt, *J* = 17.3, 1.8 Hz, 1H), 2.63 (dd, *J* = 15.8, 11.1 Hz, 1H), 2.11-2.03 (m, 2H), 1.88-1.63 (m, 5H), 1.33 (d, *J* = 7.0 Hz, 3H), 1.15 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (100 MHz, CDCl3): δ 180.02, 156.50, 154.17, 142.86, 136.38, 133.53, 128.91, 127.76, 127.69, 127.41, 127.32, 122.17, 109.90, 108.36, 83.25, 59.04, 52.04, 49.52, 47.85, 44.14, 40.10, 38.10, 30.17, 27.83, 23.65, 22.53, 17.60, 16.15; IR (thin film): 3503 (br s), 1694 (s), 1609 (s), 1487 (s), 1466 (s), 1348 (s), 1194 (s), 1142 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{31}H_{35}F_3N_2O_3$ [M+H]: 541.2678. Found: 541.2666.

Preparation of Spiro-epoxide 94

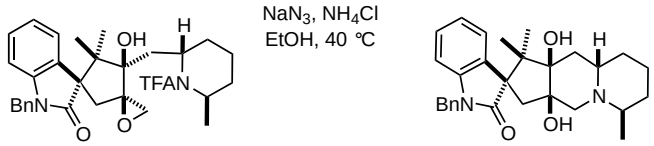


To a solution of the allylic alcohol **90b** (37 mg, 0.0684 mmol) in CH_2Cl_2 (2 ml) was added *m*-CPBA (70%, 34 mg, 0.137 mmol). The reaction was stirred at room temperature for 10 hours and quenched with sat. $NaHCO_3$ solution and sat. $Na_2S_2O_3$ solution, extracted with EtOAc, concentrated, and purified by flash chromatography (10%→20%→30% EtOAc/Hexanes) to provide the desired epoxide **94** (32 mg, 84% yield).

R_f = 0.52 (30% EtOAc/Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, 55 °C) δ 7.45 (d, *J* = 7 Hz, 1H), 7.32~7.25 (m, 5H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.64 (d, *J* = 8 Hz, 1H), 5.15 (d, *J* = 8 Hz, 1H), 4.54 (d, *J* = 8 Hz, 1H), 4.33 (br s, 1H), 4.15 (br s, 1H), 4.14 (m, 1H), 3.13 (d, *J* = 15 Hz, 1H), 3.09 (s, 2H), 2.73 (d, *J* = 14 Hz, 1H), 2.43 (s, 1H), 2.19 (m, 2H), 1.92~1.7 (m, 6H), 1.43 (d, *J* = 6 Hz, 3H),

1.05 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 55 °C) δ 180.6, 157.3 (*C*OCF_3), 157.0 (*C*OCF_3), 156.7 (*C*OCF_3), 156.4 (*C*OCF_3, *J* = 35 Hz), 143.0, 136.3, 133.7, 128.7, 127.7, 127.5, 127.3, 127.1, 121.9, 120.3 (*C*F_3), 118.0 (*C*F_3), 115.7 (*C*F_3), 113.4 (*C*F_3, *J* = 287 Hz), 108.5, 79.8, 67.2, 57.2, 51.8, 50.0 (br s), 49.4 (br s), 48.3 (br s), 44.2, 39.2, 35.6 (br s), 27.6 (br s), 25.3 (br s), 24.6, 21.8, 21.2, 14.18 (br s). IR (thin film): not obtained. HRMS (ESI): not obtained.

Preparation of Diol 95

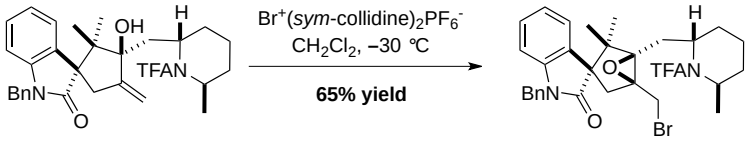


(±)-**94** (±)-**95**

To a solution of the epoxide **94** (3 mg, X mmol) in EtOH (0.5 ml) was added solid NH_4Cl (~3 mg) and NaN_3 (~3 mg). The mixture was stirred at room temperature for 12 hours, heated to 40 °C for 23 hours, then concentrated. The residue was purified by flash chromatography (40%→80% EtOAc/Hexanes→10%→15%→20% MeOH/CH_2Cl_2) to provide the diol **95** as the major product (yield not determined).

R_f = 0.39 (10% MeOH/CH_2Cl_2, TLC plate pre-treated with NH_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.6 Hz, 1H), 7.31 (m, 5H), 7.11 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H), 6.99 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 5.11 (d, *J* = 8.0 Hz, 1H), 4.59 (d, *J* = 15.6 Hz, 1H), 3.12 (d, *J* = 14.4 Hz, 1H), 3.03 (m, 1H), 2.55 (m, 4H), 1.87 (d, *J* = 14.4 Hz, 1H), 1.81 (m, 1H), 1.65~1.57 (m, 3H), 1.52 (m, 2H), 1.34 (m, 1H), 1.08 (s, 3H), 1.03 (d, *J* = 6.4 Hz, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.3, 142.6, 136.3, 134.6, 128.7, 127.7, 127.45, 127.38, 127.2, 121.8, 108.2, 80.6, 80.3, 58.2, 57.6, 53.5, 50.9, 48.8, 43.9, 43.7, 40.4, 33.3, 32.2, 27.5, 22.2, 18.4, 9.7; IR (thin film): 3453 (br, s), 1704 (s), 1608 (s), 1486 (s), 1466 (s), 1367 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{29}H_{37}N_2O_3$ [M+H]: 461.2801. Found: 461.2804.

Preparation of Epoxybromide 98

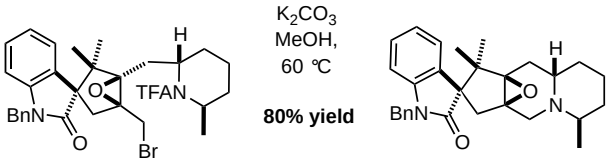


(±)-**90b** (±)-**98**

To a solution of the allylic alcohol **90b** (73 mg, 0.135 mmol) in CH_2Cl_2 (5 ml) at –30 ºC was added a solution of bis (sym-collidine)bromine(I) hexafluorophosphate (70 mg, 0.135 mmol) in CH_2Cl_2 (1.5 ml). After 10 min, another equivalent of bis (sym-collidine)bromine(I) hexafluorophosphate in CH_2Cl_2 (1.5 ml) was added. After 10 min, a third equivalent of bis (sym-collidine)bromine(I) hexafluorophosphate in CH_2Cl_2 (1.5 ml) was added. The reaction was stirred for an additional 5 min and quenched with sat. $Na_2S_2O_3$ solution. The aqueous solution was extracted with EtOAc and the combined organic layers were concentrated and purified by flash chromatography (5%→10%→15%→20% EtOAc/hexanes) to provide the epoxybromide **98** as a white solid (54 mg, 65% yield).

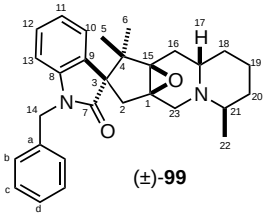
R_f = 0.38 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 6.8 Hz, 1H), 7.30 (m, 5H), 7.12 (ddd, *J* = 1.2 Hz, 7.6 Hz, 7.6 Hz, 1H), 7.01 (dd, *J* = 6.8 Hz, 7.6 Hz, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 5.14 (d, *J* = 15.6 Hz, 1H), 4.63 (d, *J* = 15.6 Hz, 1H), 4.19 (m, 2H), 4.03 (m, 1H), 3.95 (d, *J* = 10.8 Hz, 1H), 2.78 (d, *J* = 14.4 Hz, 1H), 2.44 (d, *J* = 14.4 Hz, 1H), 2.21 (d, *J* = 13.2 Hz, 1H), 2.12~1.70 (m, 7H), 1.41 (d, *J* = 6.8 Hz, 3H), 1.20 (s, 3H), 0.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 157.7 (*C*$COCF_3$), 157.4 (*C*OCF_3), 157.0 (*C*OCF_3), 156.7 (*C*OCF_3, *J* = 35 Hz), 143.3, 136.5, 133.7, 129.1, 128.8, 127.9, 127.8, 127.4, 122.5, 121.2 (*C*F_3), 118.3 (*C*F_3), 115.4 (*C*F_3), 112.6 (*C*F_3, *J* = 287 Hz), 108.7, 75.1, 68.7, 57.0, 50.4, 49.8, 49.1, 44.3, 39.1, 31.5, 26.8, 26.2, 23.5, 22.4, 22.0, 20.6, 13.4; IR (thin film): 1709 (s), 1671 (s), 1466 (m), 1204 (s), 1146 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{32}H_{35}BrF_3N_2O_3$ [M+H]: 619.1783. Found: 619.1781.

Preparation of Ring-Fusion Epoxide 99



(±)-**98** (±)-**99**

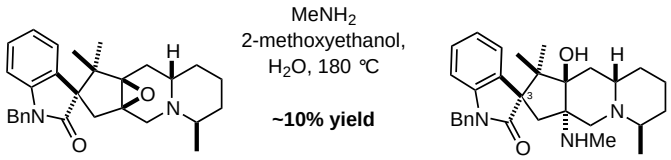
To a slurry of the trifluoroacetamide **98** (54 mg, 0.0872 mmol) in MeOH (6 ml) was added solid K_2CO_3 (44 mg, 0.318 mmol). The mixture was stirred at 60 ºC for 3 d, concentrated and purified by flash chromatography (40% EtOAc/hexane→5%→10%→15% MeOH/CH_2Cl_2) to provide epoxide **99** as a pale yellow oil (31 mg, 80% yield).



(±)-**99**

R_f = 0.23 (10% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.6 Hz, 1H**,** H**10**), 7.34–7.24 (m, 5H, **Ph**), 7.09 (ddd, *J* = 0.8 Hz, 7.6 Hz, 7.6 Hz, 1H, H**12**), 6.97 (ddd, *J* = 0.8 Hz, 7.2 Hz, 8.0 Hz, 1H, H**11**), 6.64 (d, *J* = 7.6 Hz, 1H, H**13**), 5.17 (d, *J* = 15.6 Hz, 1H, H**14a**), 4.59 (d, *J* = 15.6 Hz, 1H, H**14b**), 3.39 (d, *J* = 14.4 Hz, 1H, H**23a**), 3.22 (d, *J* = 14.4 Hz, 1H, H**23b**), 2.98 (m, 1H, H**21**), 2.82 (m, 1H, H**17**), 2.66 (d, *J* = 14.0 Hz, 1H, H**2a**), 2.30 (d, *J* = 14.0 Hz, 1H, H**2b**), 2.02 (m, 1H, H**16a**), 1.76 (m, 3H, H**16b**, H**18a**, H**20a**), 1.58 (m, 2H, H**19**), 1.46 (m, 1H, H**20b**), 1.34 (m, 1H, H**18b**), 1.29 (s, 3H, H**5**), 1.10 (d, *J* = 6.4 Hz, 3H, H**22**), 0.69 (s, 3H, H**6**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 143.0, 136.2, 134.0, 128.8, 128.6, 127.5, 127.2, 127.0, 122.0, 108.1, 70.7, 65.4, 58.2, 50.4, 49.4, 48.3, 46.8, 43.9, 41.3, 33.5, 32.1, 27.2, 24.6, 21.3, 18.8, 14.5; IR (thin film): 1710 (s), 1608 (s), 1484 (s), 1466 (s), 1360 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{29}H_{35}N_2O_2$ [M+H]: 443.2699. Found: 443.2693.

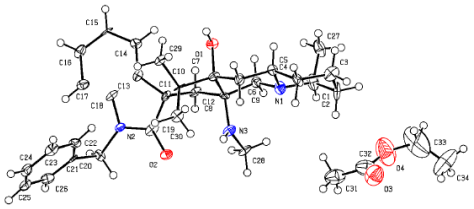
Preparation of C3-Epi-Citrinadin B Core 97



(±)-**99** (±)-**97**

To a solution of epoxide **99** (4 mg, 0.009 mmol) in 2-methoxyethanol (1 ml) was added $MeNH_2$ (40 wt% in H_2O, 4 drops). The mixture was stirred at 170 °C for 8 hours, 180 °C for 12 hours, concentrated and purified by flash chromatography (5% 10% 15% 20% MeOH/CH_2Cl_2) to provide a trace amount of the desired amino alcohol **97**.

R_f = 0.28 (15% MeOH/CH_2Cl_2, $KMnO_4$/CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4 (d, 1H), 7.3 (m, 5H), 7.2 (t, 1H), 7.13 (t, 1H), 6.68 (d, 1H), 5.25 (d, 1H), 4.6 (d, 1H), 3.8 (s, 2H), 3.5 (m, 2H), 3.2 (m, 2H), ~3-1.5 (m, 12H), 1.3 (s, 3H), 1.2 (s, 3H), 0.9 (s, 3H). An X-ray crystal structure was obtained:



2.7 Notes and References

[1] For a review of (1,3)-dipolar cycloaddition reactions, see: Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–909.

[2] For a review of enantiopure cyclic nitrones in asymmetric synthesis, see: Revuelta, J.; Cicchi, S.; Goti, A.; Brandi, A. *Synthesis* **2007**, *4*, 485–504.

[3] Murphy, J. A.; Rasheed, F.; Roome, S. J.; Scott, K. A.; Lewis, N. *J. Chem. Soc., Perkin. Trans. 1*, **1998**, 2331–2339.

[4] This compound was not subjected to complete characterization.

[5] Jeffery, T. *Tetrahedron* **1996**, *52*, 10113–10130.

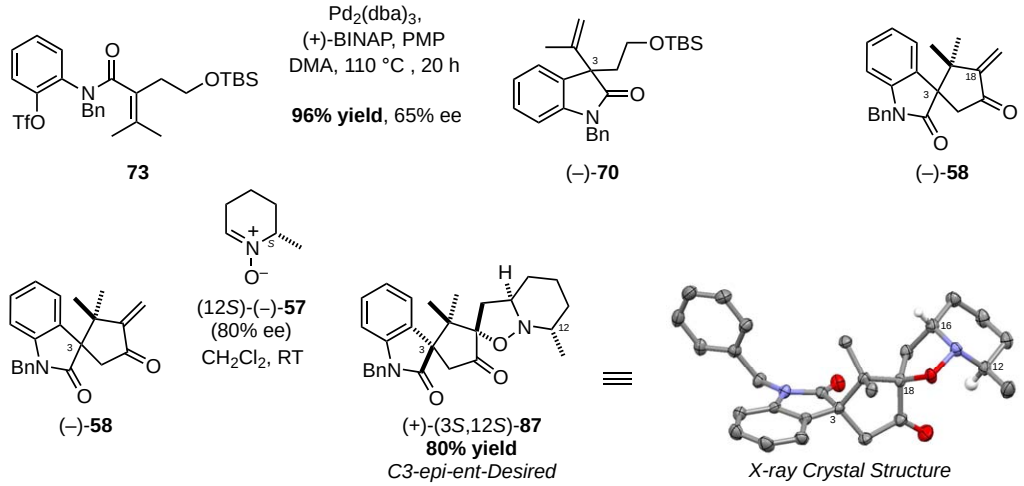
[6] For a review of the asymmetric Heck cyclization, see: Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945-2963.

[7] For a review of metal-catalyzed enyne cyclization, see: Michelet, V.; Toullec, P. Y.; Genêt, J-P. *Angew. Chem. Int. Ed.* **2008**, *47*, 4268–4315.

[8] For a related example, see: Maddaford, S. P.; Andersen, N. G.; Cristofoli, W. A.; Keay, B. A. *J. Am. Chem. Soc.* **1996**, *118*, 10766–10773.

[9] Collington, E. W.; Finch, H.; Smith, I. J. *Tetrahedron Lett.* **1985**, *26*, 681–684.

[10] The absolute stereochemical assignments of the oxindoles (–)-**70** and (+)-**70** were not made until later in the synthesis. A dipolar cycloaddition between (–)-**58** (derived from (–)-**70**, the product of an asymmetric Heck reaction using (+)-BINAP as the chiral ligand) and (*S*)-(–)-**57** results predominantly in the formation of (3*S*,12*S*)-(+)-**87**, the same diastereomer for which an x-ray crystal structure was obtained in the racemic series.



[11] Differences in the enantioenrichment of the two oxindoles (–)-**70** and (+)-**70** are believed to be the result of batch-variation in the $Pd_2(dba)_3$ catalyst and BINAP ligand.

[12] The relative stereochemistry of propargyl alcohols (±)-**68a** and (±)-**68b** was based on NOE data obtained from (±)-**69a** and (±)-**69b** following reductive enyne cyclization.

[13] a) Trost, B. M.; Rise, F. *J. Am. Chem. Soc.* **1987**, *109*, 3161–3163; b) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34–42.

[14] For a scale of reducing ability of silane reagents, see: Hayashi, K.; Iyoda, J.; Shiihara, I. *J. Organomet. Chem*. **1967**, *10*, 81–94.

[15] For a similar finding, see: Wender, P. A.; D'Angelo, N.; Elitzin, V. I.; Ernst, M.; Jackson-Ugueto, E. E.; Kowalski, J. A.; Mckendry, S.; Rehfeuter, M.; Sun, R.; Voigtlaender, D. *Org. Lett*. **2007**, *9*, 1829–1832.

[16] For a related reaction: Oh, C. H.; Kang, J. H.; Rhim, C. Y.; Kim, J. H. *Chem. Lett*. **1998**, 375-376.

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[18] For hydroxyl group directed nitrile oxide–olefin cycloadditions, see: a) Kanemasa, S.; Nishiuchi, M.; Kamimura, A.; Hori, K. *J. Am. Chem. Soc*. **1994**, *116*, 2324–2339; b) Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. *Angew. Chem. Int. Ed*. **2001**, *40*, 2082–2085.

[19] Adams, D. R.; Carruthers, W.; Williams, M. J.; Crowley, P. J. *J. Chem. Soc., Perkin Trans, 1* **1989**, 1507–1513.

[20] Chackalamannil, S.; Wang, Y. *Tetrahedron* **1997**, *53*, 11203.

[21] The use of the less expensive L-alanine enantiomer was expected to provide a total synthesis of *ent*-Citrinadin B (*ent*-**2**).

[22] Particularly in the mismatched case, erosion in the diastereoselectivity of the reaction may be the result of using a super-stoichiometric excess of the enantioenriched (but not enantiopure) nitrone. The resulting rapid cycloaddition of the (3*R*)-(+)-**58** enone with the minor (12*R*)-(–)-**57** nitrone enantiomer could result in substantial amounts of the undesired (3*R*,12*R*)-(–)-**87** isoxazolidine diastereomer being formed.

[23] Peterson, D. J. *J. Org. Chem*. **1968**, *33*, 780–784.

[24] Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem*. **1994**, *59*, 2668–2670.

[25] (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc*. **1978**, *100*, 3611–3613. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc*. **1980**, *102*, 3270–3272.

[26] Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc*. **1990**, *112*, 6392–6394.

[27] The term "salt free" generally refers to a Wittig reagent wherein the counteranion derived from base is not lithium. To avoid confusion, the term "free of salt" is used to refer to a Wittig reagent in which the inorganic salt has been deliberately removed.

[28] Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev*. **1997**, *97*, 2341–2372.

[29] Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, 361–362.

[30] Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Chem*. **1994**, *116*, 2742–2753.

[31] Trost, B. M.; Dong, G. *J. Am. Chem. Soc*. **2006**, *128*, 6054–6055.

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[33] This compound was not subjected to complete characterization.

[34] Behrens, C. H.; Sharpless. K. B. *J. Org. Chem*. **1985**, *50*. 5696–5704.

[35] Evans, R. D.; Magee, J. W.; Schauble, J. H. *Synthesis* **1988**, 862–868.

[36] *Org. Syn*. **2000**, *77*, 206.

[37] This compound was not subjected to complete characterization.

CHAPTER 3

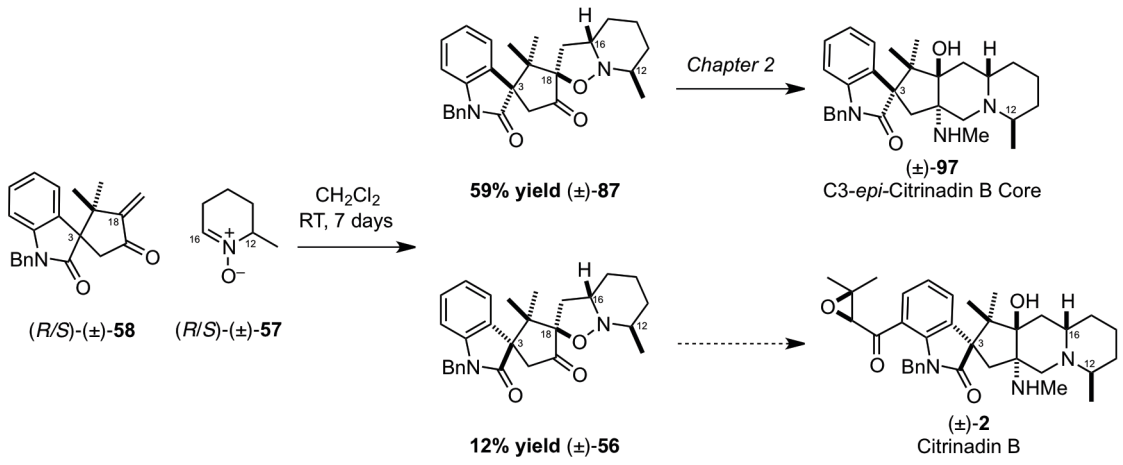
Accessing *ent*-Citrinadin B

3.1 Synthesis of the *ent*-Citrinadin Core

3.1.1 Revising the C3-epi-Citrinadin B Approach

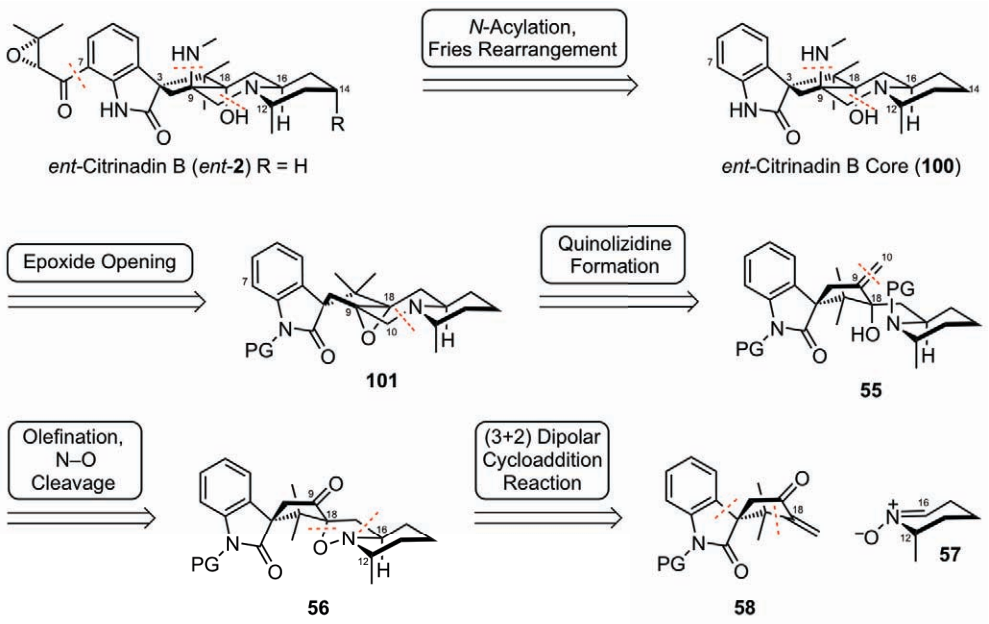
Having identified a method to access the C3-*epi* Citrinadin B core (**97**) from isoxazolidine **87**, it was strategized that a similar sequence of transformations might be utilized to synthesize Citrinadin B (**2**) from the diastereomeric (3+2) cycloaddition product (**56**)—the C3-epimer of **87—**which shares the correct relative stereochemistry at C3, C16, and C12 with respect to **2**, as proposed by Kobayashi (Scheme 3.1).[1]

Scheme 3.1



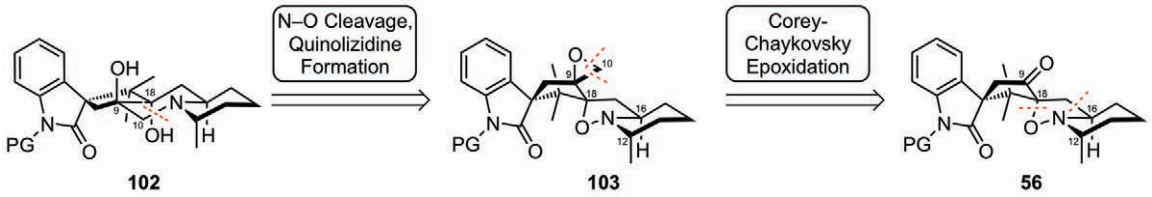
Given that **87** had previously been established to be the predominant diastereomer formed in the cycloaddition of racemic substrates, enantioenriched substrates **58** and **57** would be required to obtain sufficient amounts of the mismatched (3+2) adduct (**56**). Based on the absolute stereochemistry assigned to Citrinadin B (**2**) by Kobayashi, access to the natural product would be expected to result from using nitrone (*R*)-(+)-**57**—derived from D-alanine—however, initial studies began with the less expensive L-stereoisomer, and were expected to provide *the enantiomer* of Citrinadin B (*ent*-**2**) (Scheme 3.2). Akin to the synthesis of the C3-*epi*-Citrinadin Core **97**, a Wittig olefination and N–O cleavage were proposed to provide **55**, setting the stage for subsequent quinolizidine formation and epoxide opening to furnish the *ent*-Citrinadin Core (**100**). A late stage functionalization of the aromatic ring, possibly via a Fries rearrangement or C-H activation, was envisioned for the incorporation of the epoxyketone moiety.

Scheme 3.2



Unfortunately, from the outset the pronounced instability of isoxazolidine **56**—compared with its diastereomeric counterpart **87**—made attempts at a Wittig olefination futile. Thus, an alternative approach was proposed wherein installation of the C10 carbon would be achieved via an epoxidation to provide **103** (Scheme 3.3). Importantly, the spiro-epoxide was expected to not only provide the requisite carbon atom—C10—but also enable subsequent ring closure upon unmasking of the nucleophilic nitrogen by reductive

Scheme 3.3

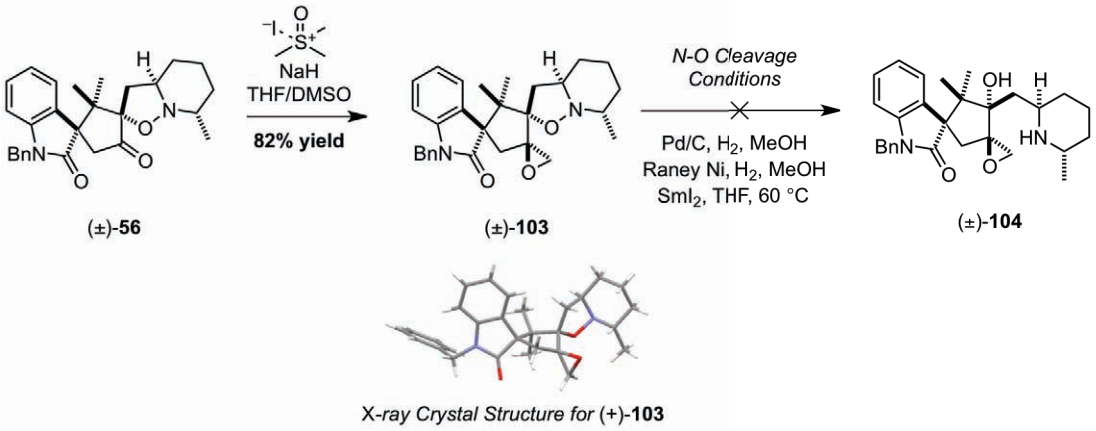


cleavage of the isoxazolidine N–O bond. The diol (**102**) derived from this latter event would serve as a precursor to the desired ring-fusion epoxide **101**.

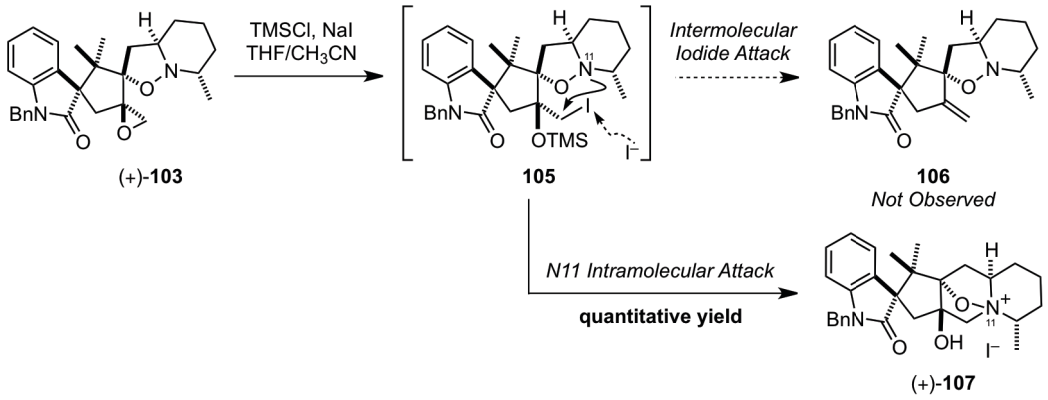
3.1.2 Synthesis of the ent-Citrinadin Tetrasubstituted Epoxide

To implement the spiro-epoxidation strategy, (±)-**56** was exposed to the Corey–Chaykovsky conditions[2] (NaH, $[(CH_3)_3S{=}O]^+I^-$) to provide the desired epoxide (±)-**103** as a single diastereomer, the structure and relative stereochemistry of which were secured by X-ray crystallographic analysis (Scheme 3.4). Although the stereochemical outcome of this reaction was not necessarily critical to the success of subsequent chemistry, the observed diastereomer correlates to addition to the least encumbered face of ketone **56**. Upon ring opening, **103** was expected to lead to an antiperiplaner relationship of the alcohol moieties (e.g., **102** in Scheme 3.3), potentially facilitating the installation of a ring-fused epoxide **101**. Unfortunately, reductive cleavage of the N–O bond in (±)-**103** to provide (±)-**104** proved problematic, resulting in either over-reduction (H_2/Raney Ni) or a complex mixture (SmI_2).

Scheme 3.4



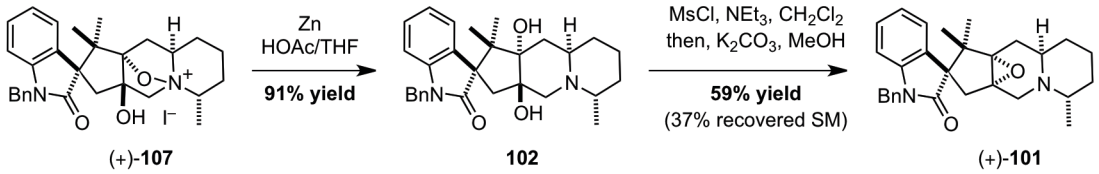
Scheme 3.5



Given our previous success with N-O cleavage on an exomethylene-containing substrate (e.g. **87**, Scheme 2.27) it was clear that further manipulation of **103** would be required prior to reduction. To this end a report from Caputo and coworkers, which described the deoxygenation of spiro-epoxides to furnish the corresponding exomethylenes, was intriguing (Scheme 3.5, intermolecular pathway).[3] Conveniently, this two-step reaction sequence to access **106** from **103** would intercept the original retrosynthetic plan to synthesize the Citrinadin B core (**100**). In practice however, when epoxide (+)-**103** was treated with TMSCl/NaI under the conditions described by Caputo and coworkers,[3] a new adduct was isolated in high yield that was subsequently identified as the isoxazolidinium salt (+)-**107** (Scheme 3.5, intramolecular pathway). Although unexpected, it was recognized that ammonium salt (+)-**107** not only possessed the requisite C–N bond and desired diol but also an N–O bond that was activated toward reductive cleavage. Indeed, when (+)-**107** was treated with activated zinc in acetic acid,[4] it underwent a smooth reduction to provide diol **102**, the direct precursor to tetrasubstituted epoxide **101** (Scheme 3.6).

Ensuing attempts at forming the epoxide (**101**) were initially thwarted by a lack of reactivity of the sterically hindered diol **102**. Under Mitsunobu's conditions (PPh_3/DEAD),[5] Mukaiyama's conditions (2-

Scheme 3.6

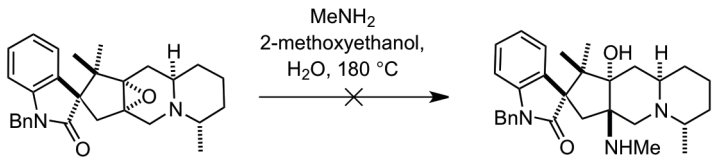


fluoro-1-methylpyridium p-toluenesulfonate/Et_3N),[6] or Vorbrüggen's conditions (perfluorobutanesulfonyl fluoride/DBU),[7] only recovered starting material was found. Eventually, it was discovered that treatment of diol **102** with Martin's sulfurane[8] produced the desired epoxide (+)-**101** as did exposure of **102** to MsCl/Et_3N followed by K_2CO_3; the latter furnishing more synthetically useful yields and some recoverable starting material (Scheme 3.6).

3.1.3 Advancing to the Benzyl Protected ent-Citrinadin Core

Preparation of epoxide **101** set the stage for installation of the angular methyl amine moiety Unfortunately, attempts to employ reaction conditions developed for the C3-epimer (i.e., **99** → **97**, Scheme 2.30) proved unsuccessful for (±)-**101** and only decomposition was observed under these forcing conditions (Scheme 3.7). Attempts to promote the reaction by the addition of Lewis acids, including $LiClO_4$,[9] $Mg(OTf)_2$,[9] $Yb(OTf)_3$,[10] and neutral Al_2O_3,[11] also failed to produce even a trace amount of the desired amino alcohol ((±)-**108**). Screening of other *N*-based nucleophiles including allylamine/$LiClO_4$,[12] BnNHMe/$Mg(OTf)_2$,[9] BocNHMe/$Mg(OTf)_2$,[9] and $Me_2AlNHMe$[13] proved fruitless with no sign of the ring opened product.

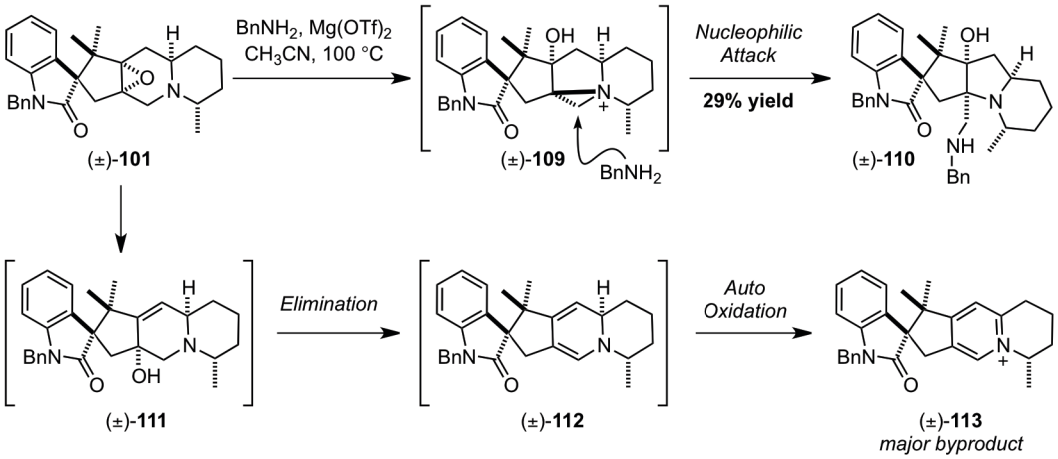
Scheme 3.7



(±)-**101** (±)-**108**

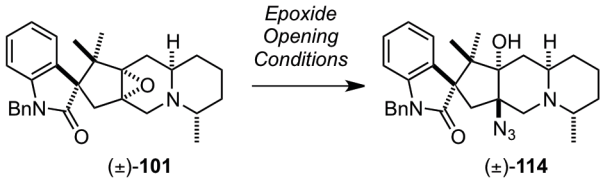
Eventually, epoxide (±)-**101** would undergo reaction when benzylamine was employed as the nucleophile in the presence of magnesium triflate (Scheme 3.8); however, spectroscopic analysis of the derived product revealed that the ring opening reaction under these conditions was the result of intramoleuclar attack by the resident nitrogen and subsequent attack of benzyl amine onto an intermediate aziridinium (±)-**109** to furnish the skeletally rearranged indolizidine (±)-**110**. Also isolated from the reaction was significant amount of the pyridinium ion (±)-**113**, which likely arises from an elimination of allylic alcohol (±)-**111** and subsequent oxidative aromatization of (±)-**112**.

Scheme 3.8



Screening of other potential nucleophiles and various Lewis acids revealed that sodium azide in the presence of $LiClO_4$ in CH_3CN at elevated temperature, conditions reported by Crotti,[9] delivered a small amount of azido alcohol (**±**)-**114** without the concomitant skeleton rearrangement (Scheme 3.9). Other Lewis Acids, such as $Ti(OiPr)_2N_3$,[14] Et_2AlCl,[15] and $CeCl_3$[16] failed to promote the ring opening; however, switching to $Mg(ClO_4)_2$[9] allowed for reaction at much lower temperatures (80 ºC)—but the yields under these conditions were variable. Other magnesium-based Lewis acids such as $MgCl_2$, $MgBr_2$, and $Mg(OTf)_2$ proved more effective and eventually, $MgCl_2$ was deemed the best overall Lewis acid based on both reproducibility and yield.

Scheme 3.9

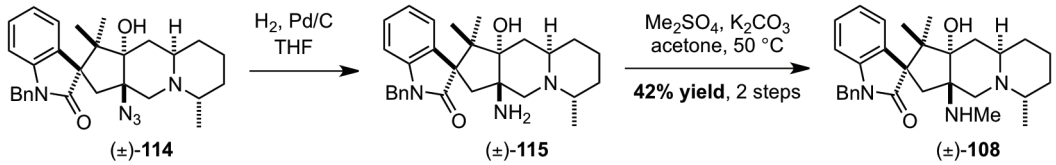


Conditions	*Yield*
NaN_3, $LiClO_4$, CH_3CN, 160 °C	10% yield
NaN_3, $Mg(ClO_4)_2$, CH_3CN, 80 °C	variable yield
NaN_3, $MgBr_2$, CH_3CN, 80 °C	32% yield
NaN_3, $Mg(OTf)_2$, CH_3CN, 60 °C	60% yield
NaN_3, $MgCl_2$, CH_3CN, 60 °C	68% yield

With the azido alcohol **114** in hand, only four obstacles stood in the way of accessing Citrinadin B (**2**): azide reduction, *N*-methylation, debenzylation, and introduction of the epoxyketone side-chain. The first task was readily accomplished by hetereogeneous hydrogenation that provided amino alcohol (**±**)-**115** (Scheme 3.10).[17] Reductive alkylation of (**±**)-**115** under standard conditions failed ($NaCNBH_3$, HCHO, AcOH). Nevertheless, switching to a more electrophilic methylating reagent (Me_2SO_4), in the presence of

excess potassium carbonate and at slightly elevated temperature, provided *N*-methylamine (±)-**108** in reasonable yield with no sign of over-methylation.

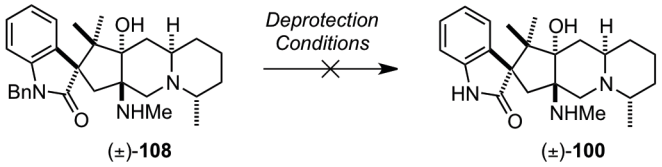
Scheme 3.10



3.1.4 Overcoming A Problematic Debenzylation

The final hurdle to overcome in obtaining the core structure of Citrinadin B was a projected debenzylation of oxindole **108**. In spite of the moderate risk associated with using the *N*-Bn protecting group, the initial choice was guided by the known stability of *N*-Bn oxindoles under the most common synthetic manipulations. Additionally, the lability of this protecting group, particularly under dissolving metal reduction conditions, had been routinely exploited for its late stage removal in other successful total syntheses (e.g., strychnofoline).[18] Quite disappointingly, however, subjecting *N*-Bn oxindole (±)-**108** to dissolving metal conditions only provided a trace amount of the free oxindole (±)-**100** at best (Scheme 3.11). It was of further dissapointment to find that exposure of (±)-**108** to either oxidative conditions (DDQ[19] and NBS/N-methylacetamide[20]) or conc. HBr resulted only in decomposition of the starting material or aromatic bromination products, respectively.

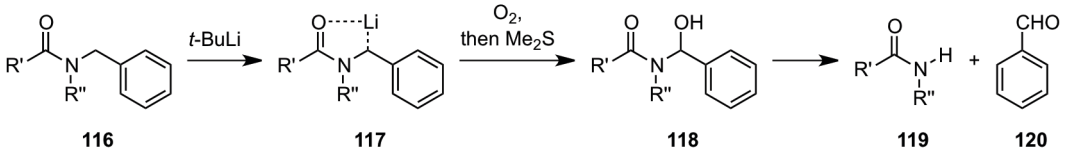
Scheme 3.11



The failure of traditional benzyl deprotection conditions, prompted an attempt to use the oxidative conditions developed by Williams and coworkers.[21] In this reaction, treatment of *N*-benzyl amide **116** with *t*-BuLi is believed to form a dipole stabilized carbanion **117**, which can undergo peroxide formation and

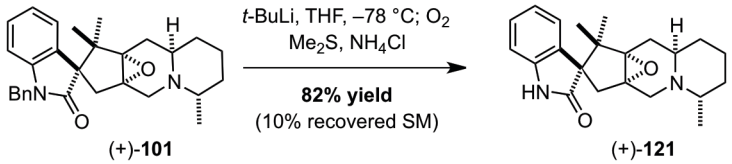
subsequent reduction, to arrive at a hemi-aminal intermediate **118**, which then collapses to release the free amide **119** and benzaldehyde (**120**) as a side product (Scheme 3.12).

Scheme 3.12



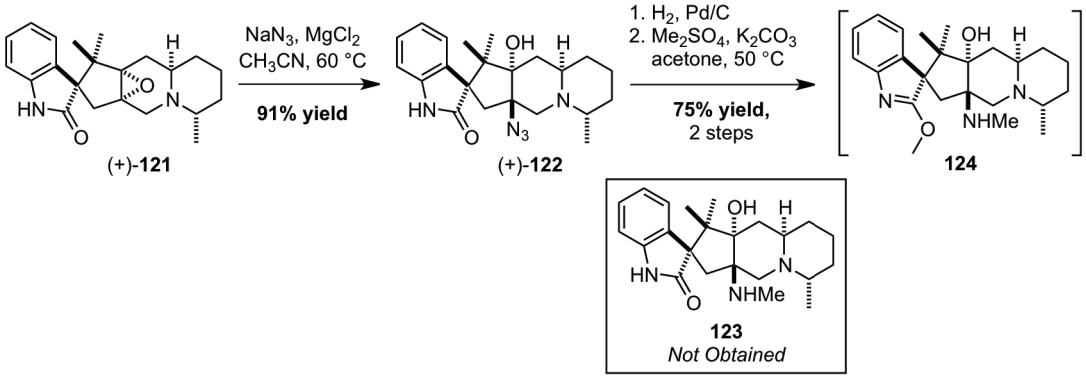
Not surprisingly, amino alcohol **108** was not compatible with the strongly basic conditions of the reaction. However, treating *N*-Bn substrate (+)-**101** with a slight excess of *t*-BuLi at low temperature, followed by oxidation with O_2 and reduction with dimethylsulfide, provided the desired debenzylated oxindole (+)-**121** in excellent yield (Scheme 3.13). Epoxide (+)-**101** represents the most advanced intermediate that could be deprotected using the Williams' protocol.

Scheme 3.13



Thankfully, epoxide (+)-**121** could be opened intermolecularly, using the previously optimized conditions ($MgCl_2$, NaN_3), to arrive at the azido alcohol (+)-**122** (Scheme 3.14); however, the subseqeunt hydrogenation/methylation sequence did not provide the desired methylamine **123**. In addition to methylation of the amine, it appeared that an unwanted methylation of the electron-rich oxindole was also

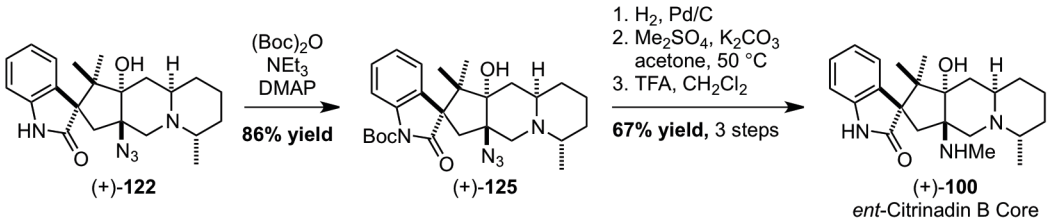
Scheme 3.14



occurring to form the corresponding imidate **124**[22], which to our chagrin, failed to undergo hydrolysis to furnish **123**.

Unable to overcome the undesired methylation, protection of the oxindole prior to *N*-methylation was required. To this end, (+)-**122** was converted to the corresponding the *N*-tertbutylcarbonyl (+)-**125**. Hydrogenation of **125**, followed by methylation of the resulting amine (K_2CO_3, Me_2SO_4), and hydrolysis of the *N*-tertbutylcarbonyl group using acidic conditions, finally delivered (+)-**100**, structurally consistent with the core of *ent*-Citrinadin B (Scheme 3.15).

Scheme 3.15

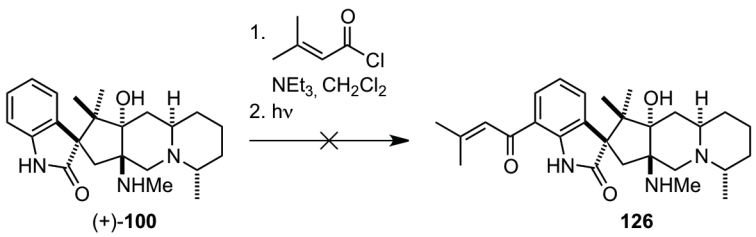


3.2 Attempts at Late-Stage Side Chain Homologation

3.2.1 An Attempted Fries Rearrangement

With the core of *ent*-Citrinadin B (**100**) assembled, the final obstacle—installation of the epoxyketone side-chain—became the focus. Based upon the inherent tendency of the aromatic ring to undergo electrophilic aromatic substitution *para* to the electron-donating oxindole amide, a Fries rearrangement was viewed as a convenient way to enforce *ortho*-acylation selectivity. Taddei and coworkers have reported the Fries rearrangement of aromatic amides to form *ortho*-substituted anilines via photochemical homolysis of the nitrogen–carbon bond.[23] Unfortunately, *N*-acylation of the citrinadin core

Scheme 3.16

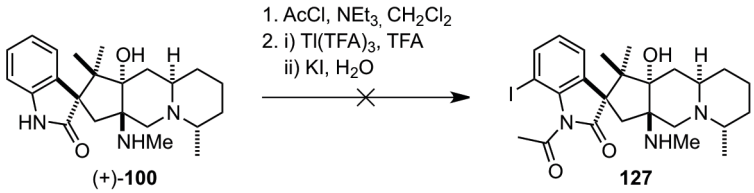


(+)-**100**, followed by exposure to ultraviolet light (450 W Hanovia lamp, equipped with either a quartz or pyrex filter) in a variety of solvents (CH_3CN, PhH, and *i*-PrOH) did not result in the formation of any of the desired *ortho*-acylated oxindole product **126** (Scheme 3.16); only deacylated oxindole was recovered. Although attempts were made to promote the reaction using Lewis acids (TiC_4, $AlCl_3$, or $Sc(OTf)_3$), these also proved ineffective at promoting the rearrangement.

3.2.2 Investigating A Possible Lithium Halogen Exchange

Unable to induce a Fries rearrangement, an alternate strategy was explored wherein halogenation at C7 would be followed by either a cross-coupling or a lithium-halogen exchange reaction to provide access to *ent*-Citrinadin B (**2**). Regiocontrol in the former was expected based on a known procedure involving electrophilic aromatic thallation followed by treatment with aqueous potassium iodide.[24] Aromatic substrates which furnish the products of *ortho*-thallation are believed to do so via pre-complexation of the $Tl(TFA)_3$ electrophile to a directing group (e.g. the carboxylic acid of benzoic acid). Regrettably, however, attempts to synthesize aryl iodide **127** through the intermediacy of an *ortho*-thallated oxindole did not result in the formation of any desired product (Scheme 3.17). Only starting material was recovered.

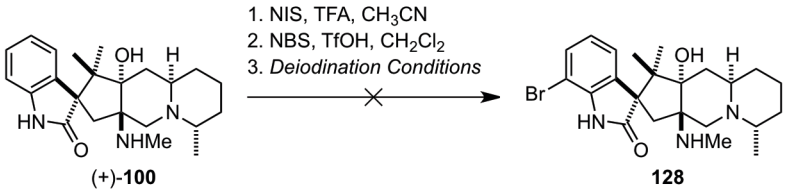
Scheme 3.17



Returning to the idea that electrophilic aromatic substitution of the oxindole should be favored *para* to the amide, a two-step bis-substitution was performed where a proposed deiodination might provide aryl bromide **128**. In the event, oxindole **100** was first treated with *N*-iodosuccinimide, and then with *N*-bromosuccinimide, to provide the *p*-iodo-*o*-bromo oxindole (Scheme 3.18). Unfortunately, attempts to selectively cleave the superfluous carbon–iodine bond using radical chemistry (AIBN, $(n\text{-Bu})_3SnH$) or

palladium-catalyzed reductive dehalogenation conditions ($Pd(OAc)_2$ or $Pd(PPh_3)_4$ with $(n\text{-}Bu)_3SnH$) only resulted in decomposition of the starting material.

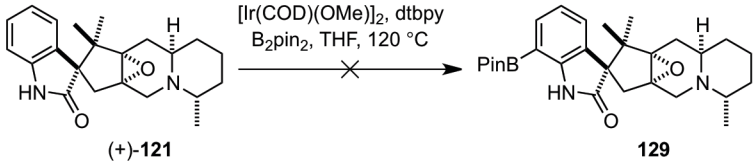
Scheme 3.18



3.2.3 Toward a Metal Catalyzed Cross Coupling

Aware that C7-selective borylations of indoles had been reported by Maleczka and Smith using iridium catalysis, one final attempt was made to introduce C7-functionalization to oxindole (+)-**121** (Scheme 3.19).[25] Unfortunately, this too only resulted in the decomposition of starting material.

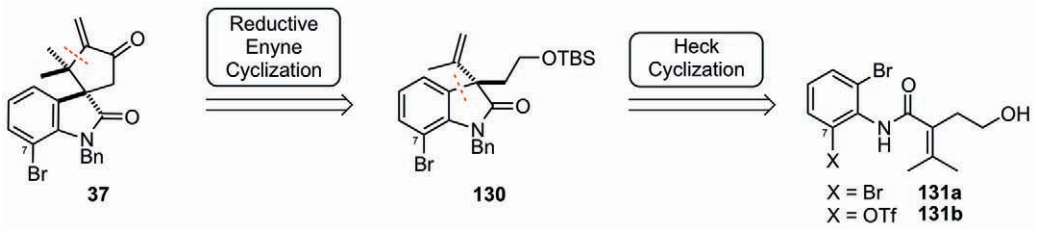
Scheme 3.19



3.3 Synthesis of a C7 Pre-Functionalized Enone

Given the considerable challenge associated with the late stage functionalization of oxindole **100**, incorporation of a C7 functional handle at an earlier stage of the synthesis was considered essential. To that end, a synthesis of bromoenone **37** via oxindole **130** ensued (Scheme 3.20). It was

Scheme 3.20

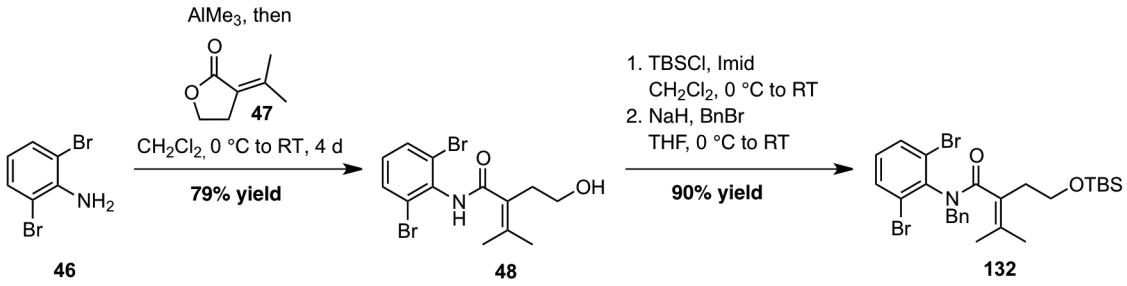


recognized that Heck cyclization of 2,6-dibromoanilide **131a** would allow for the construction of **130**. Although previous studies suggested that preparing **130** from **131a** would be effective for the preparation of racemic material, a substrate containing a triflate (e.g., **131b**) would likely be required to access enantioenriched **130**. Given the commercial availability of dibromoanaline, initial studies began in the racemic series.

3.5.1 Synthesis of a Racemic C7-Bromo-oxindole

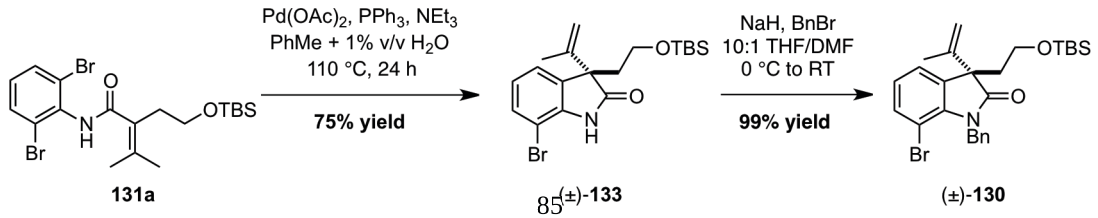
In a manner analogous to our previous efforts we turned to a trimethylaluminum-mediated coupling of 2,6-dibromoaniline **49** with lactone **47** (Scheme 3.21). Although this reaction was initially performed at reflux in toluene, optimization efforts revealed that CH_2Cl_2 as a solvent and ambient reaction temperature resulted in higher yields and allowed for the use of fewer equivalents of lactone **47**. Protection of the primary alcohol **48** as its tertbutyldimethylsilyl ether proceeded smoothly, as did a subsequent benzyl protection.[26]

Scheme 3.21



Unfortunately, Heck cyclization of anilide **132** ($Pd(OAc)_2$, PPh_3, Et_3N, PhMe, 110 °C) was remarkably poor yielding in comparison with previous substrates (i.e., **62** and **73**, Schemes 2.5 and 2.7). Attempts to improve the yield by using other pre-catalysts ($Pd(dba)_3$), bases (K_2CO_3), additives (*n*-Bu_4NCl), and solvents (DMF, THF, NMP) were ineffective. What proved more beneficial was to perform

Scheme 3.22

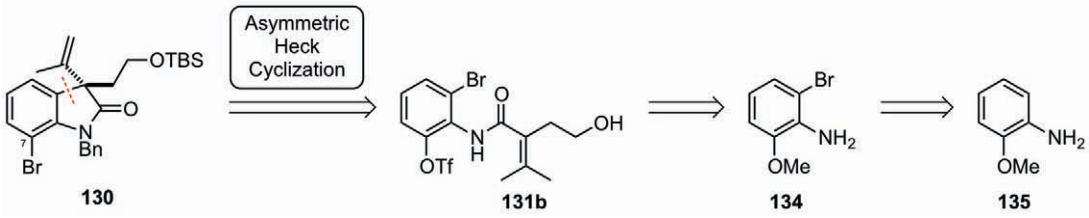


the Heck reaction prior to benzyl protection. Apparently the added steric bulk of the bis-substituted anilide **132** was prohibitively affecting the cyclization. The addition of a small amount of water (1% v/v) to the reaction proved crucial both in terms of yield and reproducibility. Benzyl protection of the resulting oxindole (±)-**133** conveniently provided the desired *N*-Bn oxindole (±)-**130**.

3.5.2 Attempted Asymmetric Synthesis of a C7-Bromo-oxindole

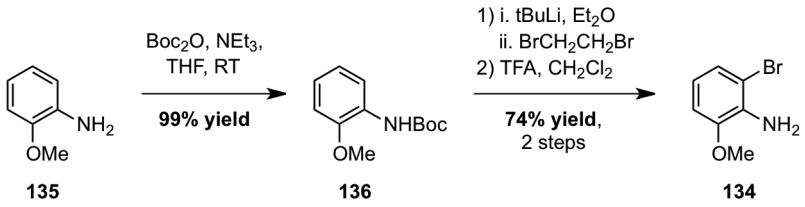
In a similar sense, it was envisioned that nonracemic oxindole **130** could arise from the asymmetric Heck cyclization of aryl triflate **131b** (Scheme 3.23). Although 2-bromo-6-methoxyaniline **134** was not commercially available, it was accessible from a directed bromination of the corresponding 2-methoxyaniline **135**.

Scheme 3.23



Following a modified literature procedure[27], conversion of the aniline (**135**) to its *N*-Boc carbamate (**136**) was followed by treatment with *t*-butyllithium resulting in a directed lithiation of the aromatic ring (Scheme 3.24). Exposure to electrophilic bromine (1,2-dibromoethane) subsequently provided the desired aryl bromide, whereupon a final trifluoroacetic acid-mediated removal of the carbamate yielded 2-bromo-6-methoxyaniline **134**.

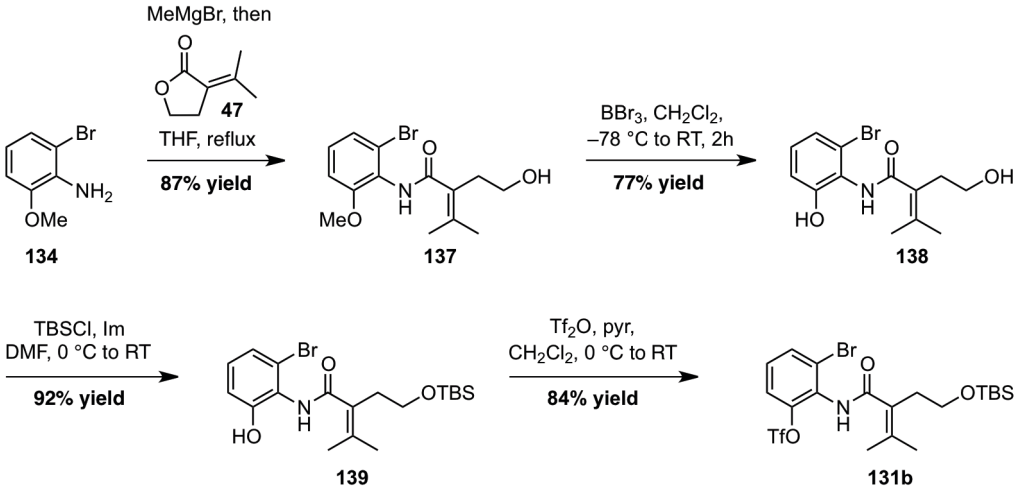
Scheme 3.24



Coupling of the aniline **134** to lactone **47** via the corresponding magnesium amide was found to proceed smoothly, and de-methylation of the derived anisole to the phenol (**138**) was then

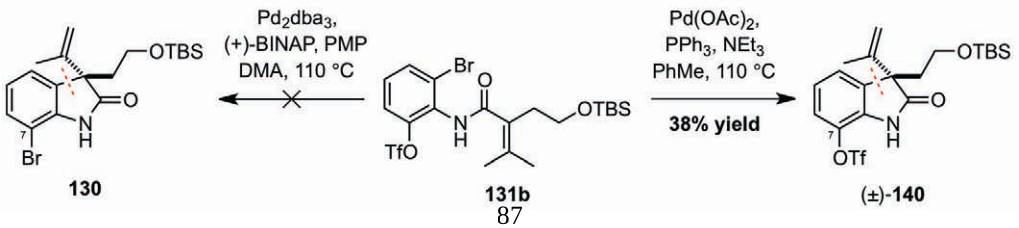
accomplished via treatment with a solution of boron tribromide in CH_2Cl_2 (Scheme 3.25). Although, bis-silyl protection of the primary alcohol and phenol was problematic under standard silylation conditions (TBSCl, imidazole, CH_2Cl_2, RT), selective protection of primary alcohol **138** could be realized via portionwise addition of the silyl chloride to a cold solution of the alcohol in DMF. Subsequent conversion of phenol **139** to its triflic ester **131b** under standard conditions provided the desired substrate for the asymmetric Heck cyclization.

Scheme 3.25



Unfortunately, when triflate **131b** was exposed to asymmetric Heck conditions previously optimized for triflate **73** ($Pd_2(dba)_3$, (+)-BINAP, PMP, DMA), no reaction took place (Scheme 3.26). Aware that the unprotected amide might be incompatible with the asymmetric conditions, attempts were also made to induce the cyclization of *N*-Bn and *N*-Boc variants of **131b.** However, these reactions were also ineffective. Surprisingly, when the substrate was tested under the racemic conditions used for dibromoanilide **131a**, the desired aryl bromide (±)-**130** was not produced. Instead, aryl triflate (±)-**140** was the only isolated product, albeit in low yield. This stands in contrast to conventional trends, which predict that oxidative insertion of palladium into the C–O triflate bond should be preferable to insertion into the

Scheme 3.26

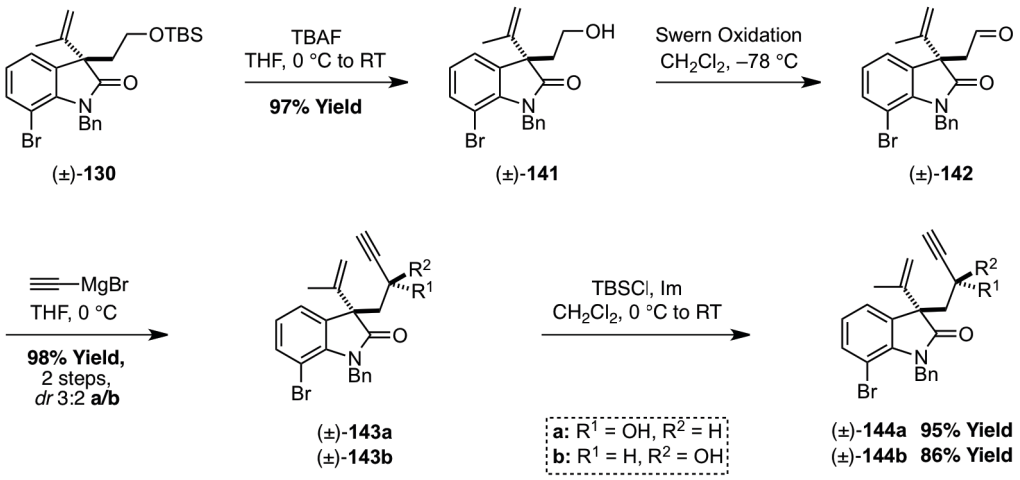


C–Br bond.[28] Faced with these unexpected complications, and eager to test the ability of a brominated enone **37** to participate in the (3+2) cycloaddition reaction, development of the asymmetric reaction was discontinued.

3.5.2 Synthesis of the Bromoenone

In anticipation of the ensuing enyne cyclization, the silyl ether (±)-**130** was cleaved and the alcohol (**±**)-**141** was oxidized using Swern oxidation conditions (Scheme 3.27). The resulting aldehyde (±)-**142** was used without purification in the subsequent Grignard addition, where optimization of the reaction revealed that a nearly quantitative yield of the propargyl alcohols (±)-**143a/b** could be achieved via addition of the aldehyde to a solution of the Grignard reagent. Yields of (±)-**143a/b** resulting from the reverse order of addition were inferior, and undesirable homo-Aldol side products and recovered starting material were prevalent in the reaction mixture. Silyl protection of the propargyl alcohols (±)-**143a/b** provided the substrates (±)-**144a/b** necessary for enyne cyclization.

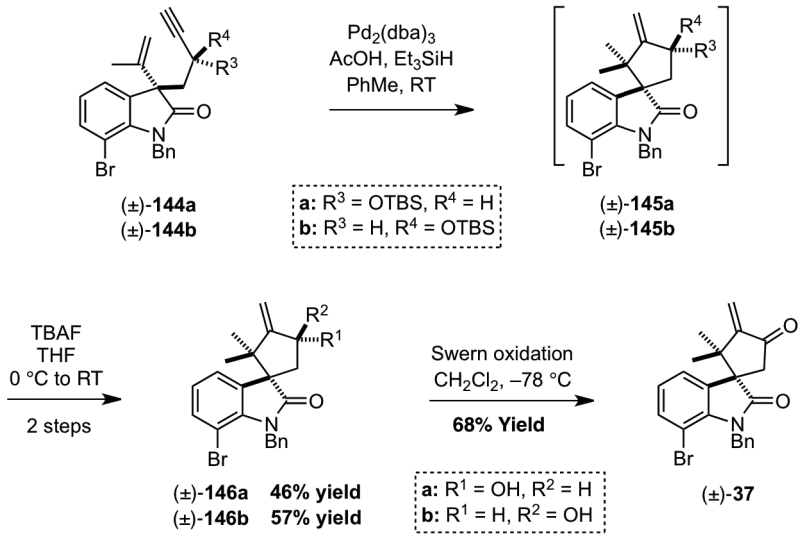
Scheme 3.27



Initial attempts at inducing the palladium-catalyzed reductive enyne cyclization of (±)-**144a** to (±)-**145a** (followed by removal of the silyl protecting group) resulted in poor yields of the desired tricycle (±)-**146a**. As this appeared to be the result of a particularly facile alkyne reduction—precluding cyclization of the substrate—slow syringe pump addition of the triethysilane reducing agent was conducted

and found to provide nearly double the amount of subsequent tricycle (±)-**146a** (Scheme 3.28). Interestingly, enyne diastereomer (±)-**144b** proved to be a slightly superior substrate for the cyclization and was amenable to decreased catalyst loadings and more concentrated reaction mixtures. Regrettably, access to (±)-**144b** was limited by the more favorable formation of (±)-**143a** in the preceding Grignard reaction. Nevertheless, oxidation of the combined allylic alcohols (±)-**146a/b** was accomplished via Swern oxidation to yield the desired C7-functionalized bromoenone (±)-**37**.

Scheme 3.28



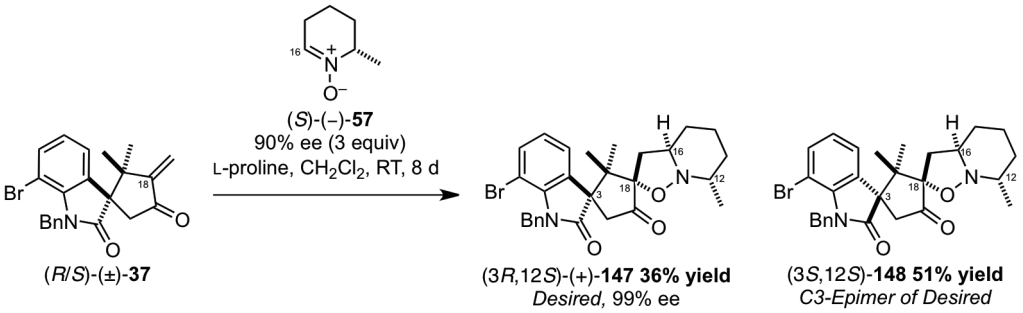
3.4 Synthesis of *ent*-Citrinadin B

3.4.1 The (3+2) Cycloaddition Reaction

With bromoenone (±)-**37** in hand, the ability of the newly synthesized dienophile to undergo the desired (3+2) cycloaddition reaction was explored. Similar to the synthesis of **56**, it was found the reaction of nitrone (–)-**57** with bromoenone (**±**)-**37** resulted in the formation of two diastereomeric isoxazolidines (3*R*,12*S*)-(+)-**147** and (3*S*,12*S*)-**148** (Scheme 3.29). Importantly, the use of excess nitrone in the cyclization enabled the isolation of synthetically useful amounts of the desired diastereomer ((3*R*,12*S*)-(+)-**147**), the mismatched of the two diastereomeric products. Interestingly, the addition of proline to the

reaction resulted in highly enantioenriched isoxazolidine **147**; however at this stage, the factors leading to this improved stereoselectivity have yet to be fully delineated.

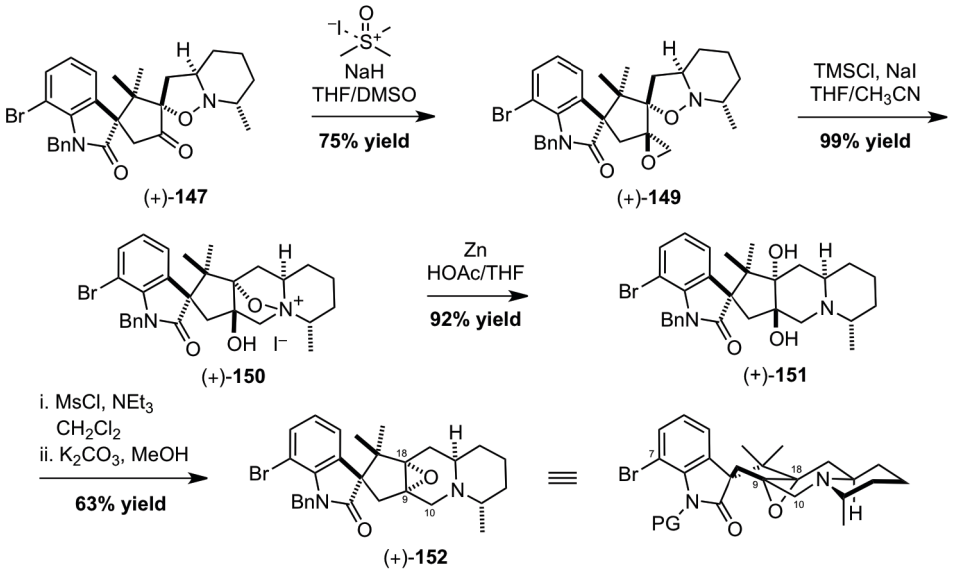
Scheme 3.29



3.4.2 Advancing to the Tetrasubstituted Epoxide

With the desired isoxazolidine (3*R*,12*S*)-(+)-**147** in hand, efforts construct a tetrasubstituted epoxide (analogous to **101**) began with Corey-Chaykovsky epoxidation of the ketone followed by intramolecular opening of the derived epoxide ((+)-**149**) to give the ammonium salt (+)-**150** (Scheme 3.30). Reductive cleavage of the N–O bond in (+)-**150** set the stage for mesylation, and treatment with base to furnish the ring-fusion epoxide (+)-**152**.

Scheme 3.30



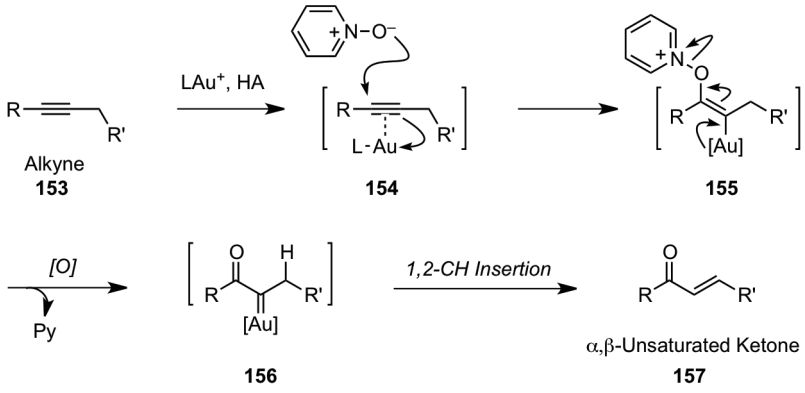
At this stage, efforts to advance **152** via a route mirroring that employed for **101** became complicated by the unusually harsh conditions that proved necessary for removal of the benzyl protecting group (*t*-BuLi, O_2). Clearly, these conditions would not be compatible with the aryl bromide due to the well known ability of such functionality to undergo metal halogen exchange. Likewise, installation of the fully functionalized and somewhat labile epoxyketone side chain prior to opening of the tetrasubstituted epoxide with sodium azide did not seem prudent. The only perceived way forward was to advance **152** to an intermediate that could withstand the harsh benzyl deprotection conditions, be advanced through the azide opening of the epoxide, and remain poised for introduction of the epoxyketone.

3.4.3 Attaching the Side Chain

Governed by the above constraints, a recent publication by Zhang and coworkers describing the gold-catalyzed regioselective oxidation of alkynes (e.g., **153**) to α,β-unsaturated ketones (e.g., **157**) was quite intriguing (Scheme 3.31).[29] In this reaction, an alkyne is activated by exposure to a gold catalyst (e.g., $(Ph_3P)AuNTf_2$) which facilitates reaction of the intermediate complex (**154**) with pyridine *N*-oxide at the least hindered position. Subsequent expulsion of pyridine from he derived intermediate (**155**) provides an α-oxo gold carbene (**156**) which is proposed to undergo formal 1,2-C–H insertion to deliver an enone (**157**).

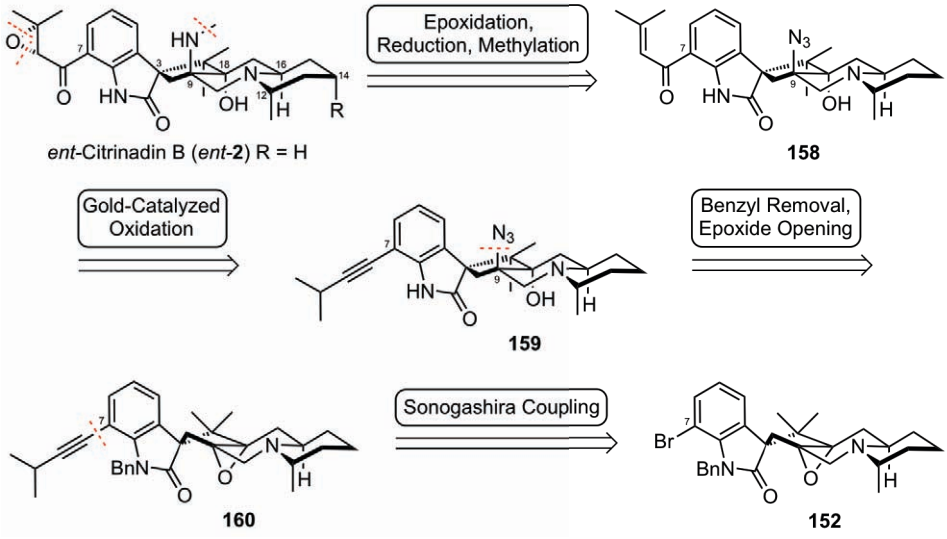
Based on this method, a plan was developed wherein alkyne **160** would derive from **152** and serve as a masked α,β-unsaturated ketone capable of withstanding the conditions required for both benzyl

Scheme 3.31



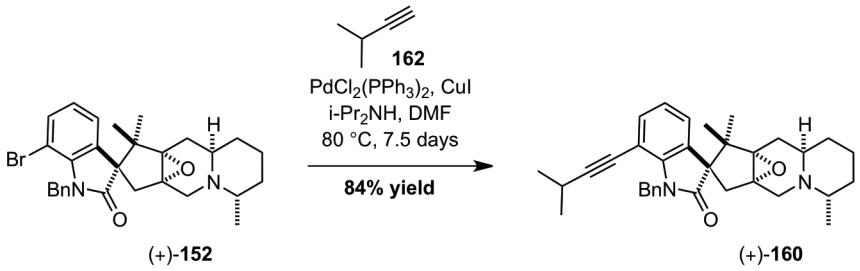
deprotection and epoxidation. Finally, conversion of the alkyne **159** to the enone (**158**) in accord with Zhang's protocol would set the stage for the epoxidation, reduction, and methylation reactions that would provide *ent*-Citrinadin B (*ent*-**2**) (Scheme 3.32).

Scheme 3.32



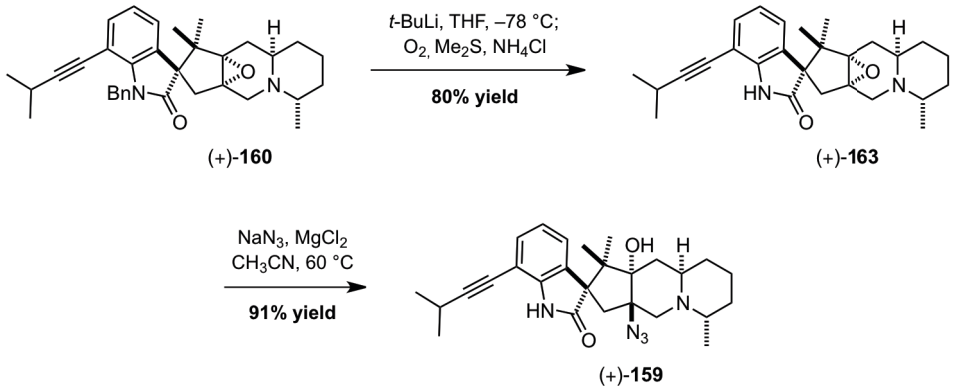
Implementation of the plan began with exploration of the Sonogashira coupling of aryl bromide (+)-**152** with alkyne **162** (Scheme 3.33). After considerable experimentation it was determined that Pd(II) catalysis employing $PdCl_2(PPh_3)_2$ at elevated temperatures and long reaction times (80 °C for 7 days) were required to obtain high yields of (+)-**160**.

Scheme 3.33



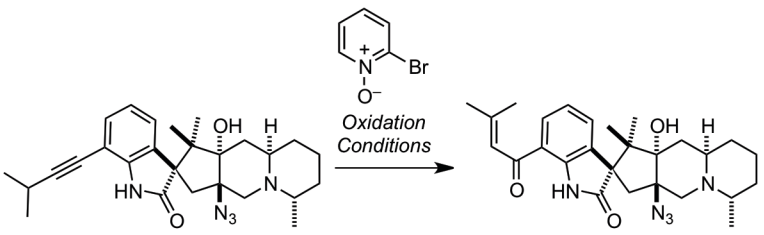
With this alkyne in hand, the critical benzyl deprotection and epoxide opening reactions were at hand. Thankfully, exposure of (+)-**160** with t-BuLi/O_2 proceeded smoothly to deliver the free amide (+)-**163** which, in turn, proved to be and excellent substrate for the regioselective opening of the ring-fusion epoxide with azide. (Scheme 3.34).

Scheme 3.34



Eager to attempt the conversion of alkyne (+)-**159** to enone **158**, Zhang's oxidation protocol[29] ($(PPh_3)AuNTf_2$, *N*-oxide, THF, RT) was employed (Scheme 3.35). Unfortunately, initial results were disappointing. Only recovered starting material was obtained and attempts to heat the reaction were not beneficial. Questions arose concerning the compatibility of the tertiary amine with the reaction conditions. Examples of amines—including pyridine—acting as gold ligands have been noted in the literature.[30] This suggested that an attempt to mask the tertiary amine in situ as the methanesulfonic acid or trifluoroacetic acid salt might be helpful. However, these attempts were equally ineffective. On the other hand, increasing the amount of $(PPh_3)AuNTf_2$ in the reaction solution was quite beneficial. This provided the desired enone (+)-**158** in excellent yield and suggested that one equivalent of the gold species may indeed be occupied in an unproductive ligation during the reaction.

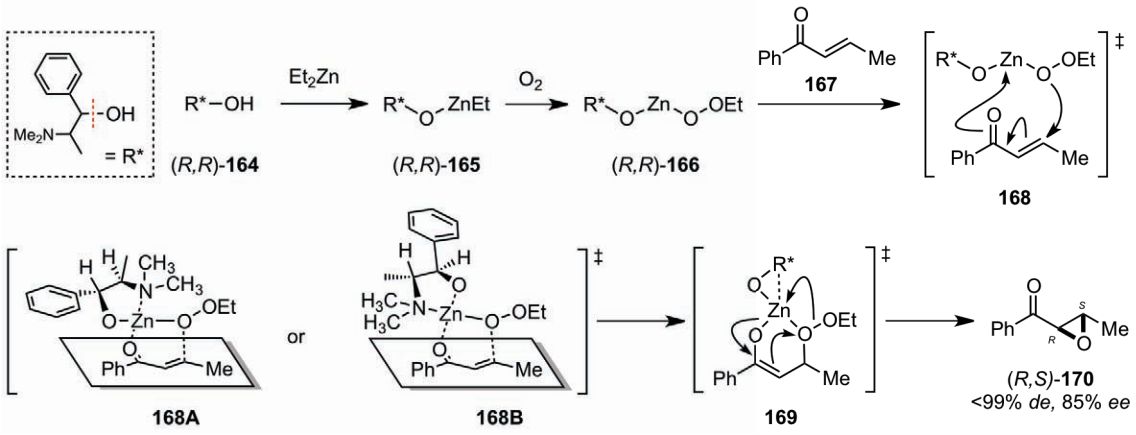
Scheme 3.35



Conditions	*Result*
$(PPh_3)AuNTf_2$ (0.1 equiv) THF, RT or 60°C, 24h	*no reaction*
i. MsOH or TFA ii. $(PPh_3)AuNTf_2$ (0.1 equiv) THF, RT to 60 °C, 24h	*no reaction*
$(PPh_3)AuNTf_2$ (1.1 equiv) THF, RT, 12h	**79% yield**

Having successfully traversed the benzyl deprotection and introduced the enone, it was time to begin considering methods for introducing the epoxide. In 1989, K. Yamamoto and N. Yamamoto published the susceptibility of α,β-unsaturated ketones to undergo epoxidation in the presence of

Scheme 3.36

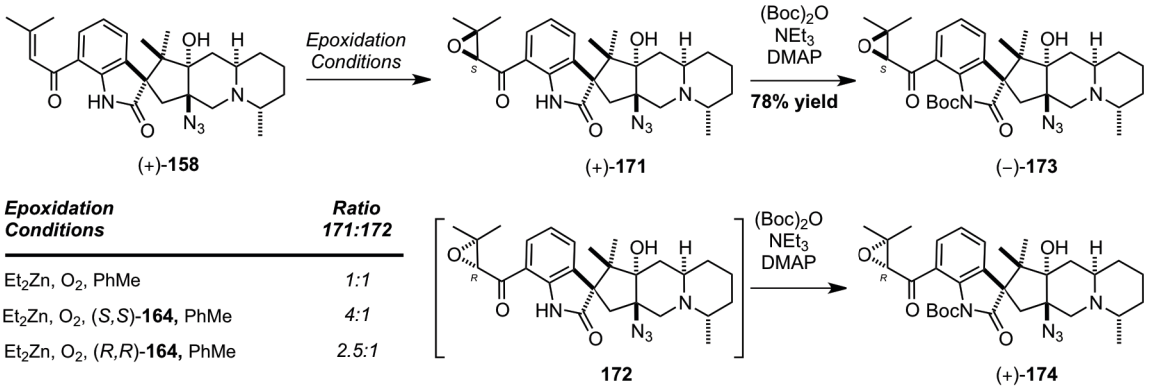


dialkylzinc and oxygen.[31] Enders and coworkers later demonstrated that this epoxidation could be rendered highly stereoselective via the addition of a chiral methylpseudophedrine ligand.[32] Mechanistically, addition of the chiral alcohol (*R*,*R*)-**164** to diethylzinc is believed to form a chiral zinc alkoxide (*R*,*R*)-**165**. Exposure of this species to molecular oxygen results in the insertion of O_2 into the remaining Zn–C bond to form an alkoxy(ethylperoxy)zinc species (*R*,*R*)-(**166**) (Scheme 3.36). When (*R*,*R*)-**166** reacts with an α,β-unsaturated ketone such as **167**, the minimization of negative steric interactions between the phenyl group of **167** and the phenyl group of the ligand on (*R*,*R*)-**166** is proposed to result in a highly diastereoselective and enantioselective epoxidation via the intermediacy of transition state **168A** or **168B**. Selective formation of the epoxide (*R*,*S*)-**170** via **169** results.

The use of Enders' zinc-mediated epoxidation conditions for the synthesis of the epoxide of ent-**2** was attractive based on the reported chemoselectivity and enantioselectivity of the transformation. Review of the transition state models suggested that ligand (*R*,*R*)-**164** should provide the desired *R*-epoxide.

In practice, the ability of the α,β-unsaturated ketone **158** to participate in the epoxidation was first evaluated using racemic conditions (Et_2Zn, O_2). This resulted in a 1:1 mixture of two epoxide diastereomers (Scheme 3.37, entry 1). Next, an experiment using the commercially available chiral ligand (*S*,*S*)-**164** was conducted. As expected, this resulted in a mixture of diastereomers (*dr* 4:1) where the major diastereomer ((+)-**171**) was tentatively assigned the *S*-configuration based on the Enders model. In order to conduct the analogous non-racemic reaction, the ligand (*R*,*R*)-**164** was synthesized from (*R*,*R*)-pseudoephedrine according to a literature procedure.[33] The subsequent Enders' epoxidation with (*R*,*R*)-**164**

Scheme 3.37



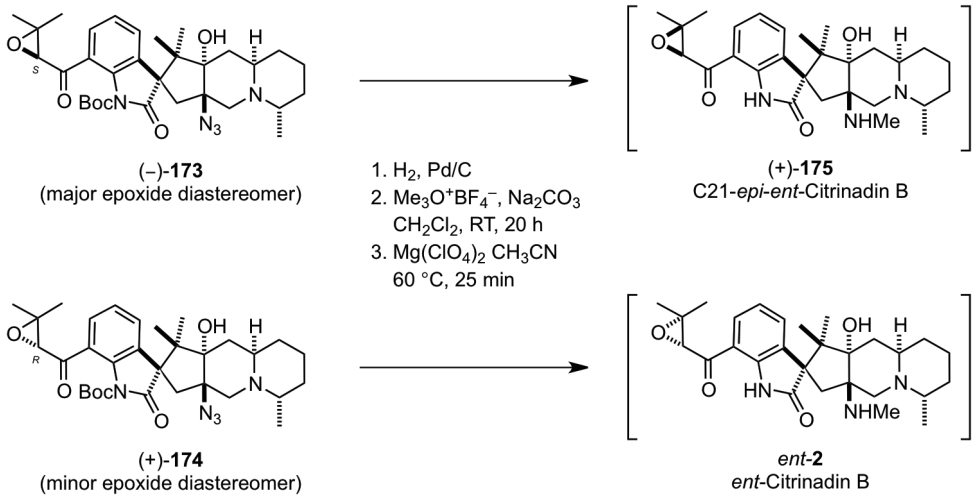
resulted in another mixture of diastereomers; however, it appeared that the major diastereomeric product was the *same* as that isolated using the opposite antipode of the chiral ligand. Investigation of the reaction revealed that pre-incubation of the ligand (*R*,*R*)-**164** and diethylzinc with O_2 had some effect on the diastereomeric ratio, but only to the benefit of the same major diastereomer ((+)-**171)**, resulting in an average diastereomeric ratio of 2.5:1 (**171**/**172**). Attempts to obtain significant amounts of the minor epoxide diastereomer (**172**)—tentatively assigned the *R*-configuration—from reactions containing the chiral ligand were plagued by low yields and difficult chromatographic separation, and it appeared that these conditions were actually facilitating a decomposition of the minor diastereomer. Consequently, the best yields of **172** were obtained from the racemic epoxidation. Elaboration of the epoxyketone diastereomeric mixtures to the corresponding Boc-protected products (–)-**173** and (+)-**174** prior to separation provided more optimal overall yields.

3.4.4 Synthesis of ent-Citrinadin B and the C21 *Epimer*

Ever advancing toward the natural product, both epoxide diastereomers (–)-**173** and (+)-**174** were subjected to the remaining reaction conditions, expected to result in the synthesis of *ent*-Citrinadin B (*ent*-**2**) and C21-*epi*-*ent*-Citrinadin B (**175**). For each substrate, reduction to the amine was followed by *N*-methylation with $Me_3O^+BF_4^-$ (Scheme 3.38). Unlike *des*-epoxyketone substrate (+)-**125**, methylation of the epoxyketone substrates with Me_2SO_4 provided poor yields of the desired methylamine, possibly the result of the insufficient stability of the intermediate amine combined with extended reaction

times. A final Boc-deprotection using magnesium perchlorate at elevated temperatures provided two products believed to be *ent*-**2** and C21-*epi*-*ent*-Citrinadin B (**175**).

Scheme 3.38



3.4.5 A Possible Structural Revision

Unfortunately, comparison of the ^{1}H spectra for the two products (+)-**175** and *ent*-**2** to natural Citrinadin B (**2**) did not reveal an immediate match. As an alternate means of comparison, the CD spectra of (+)-**175** and *ent*-**2** were obtained. Surprisingly, the CD spectrum of *ent*-**2**—originating from the

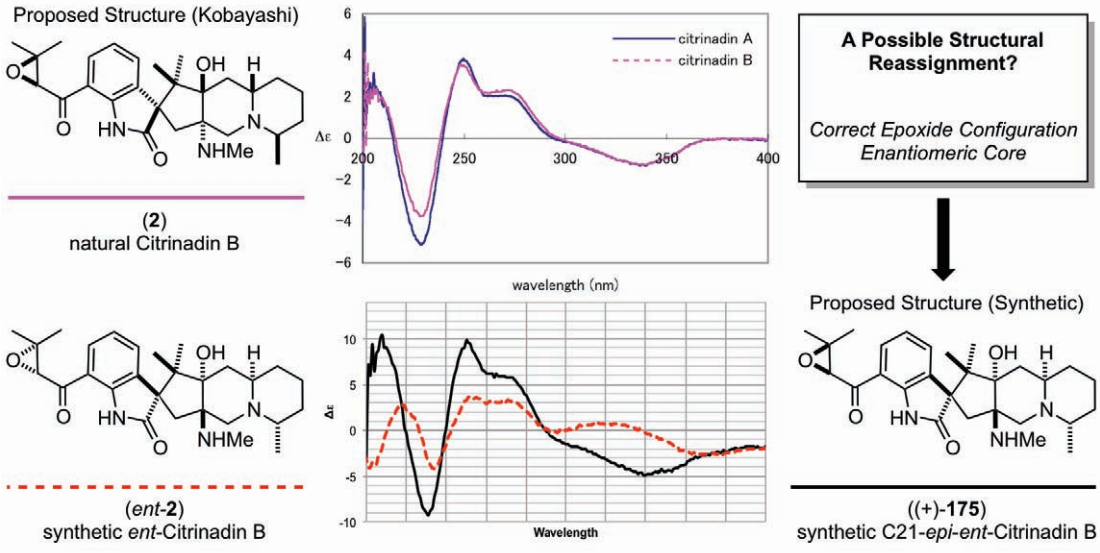


Figure 3.1

minor epoxide diastereomer and believed to be *ent*-Citrinadin B—did not match the CD spectra for **2** (Figure 3.1). But even more unexpected, the CD spectrum of (+)-**175**—originating from the major epoxide diastereomer and believed to be C21-*epi*-*ent*-Citrinadin B—was a nearly exact match to **2**, even in terms of sign. By definition, the CD spectrum for *ent*-**2** should match that of **2** but be opposite in terms of sign. One interpretation of these results suggests that (+)-**175** is an *identical match* to the natural product, and suggests that a structural revision of **2** may be in order. Additional data to support this assertion was obtained in the optical rotation for **175** (+36.7 (*c* 0.03, MeOH)), which is a match in terms of sign to the natural product (+8 (*c* 1.0, MeOH)).

The possibility of a structural reassignment of Citrinadin B raised questions regarding the certainty of Kobayashi's stereochemical assignments to begin with. The assignment of the (*S*)-configuration to the epoxyketone appeared reasonable, being based on the comparison of VCD curves obtained for synthetic model epoxides of known absolute configuration (See Chapter 1). However, the assignment of the absolute stereochemistry of the core inspired less confidence. Although the assignment of the C3 oxindole center aligned with literature trends that correlate negative cotton curves to the (*S*)-configuration, it is known that some oxindoles do not conform to these trends. Of even greater concern was the fact that the absolute stereochemistry of C14 in Citrinadin A (**1**) was assigned via ROESY correlations between the core and the flexibly appended ester side chain. Additional evidence to support a structural reassignment of **2** to (+)-**175** is provided by way of the PF compounds[34] (**3**-**5**). For **3**, the relative stereochemical relationship between the epoxide and the core—assigned via X-ray crystallography—is the *same* as the relative stereostructure suggested in the proposed structural revision (i.e., (+)-**175**, Figure 3.2).

Although the matching CD data was encouraging and interpretable via stereochemical revision, the lack of agreement between the published NMR data of the natural product and that obtained

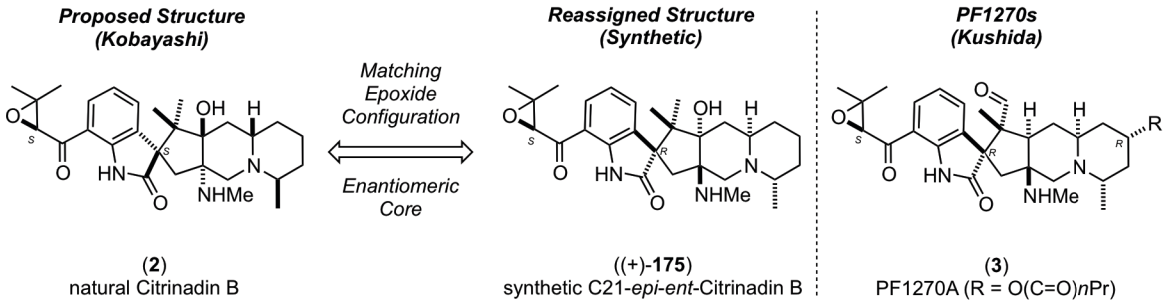


Figure 3.2

via synthesis was troubling. ^{1}H NMR spectra derived from both the free base of (+)-**175** (obtained by passing the sample through a plug of basic alumina) or the TFA salt of (+)-**175** (obtained by brief exposure to TFA) did not precisely match the data published for the natural product; although, in the latter case the spectra did become more like that reported for the natural product.

In this regard, it is worth noting that similar difficulties in matching experimental NMR data to isolation NMR data have been reported previously in the literature. In one instance, the Overman group demonstrated that the ^{1}H NMR of Nankakurine A (**176**)—also isolated by Kobayashi in 2004—is highly pH dependent (Figure 3.3).[35] More significantly, the published isolation ^{1}H NMR spectrum for **176** does not reflect either the free base or the TFA salt of **176** but instead, something halfway between the two. In order to obtain a matching ^{1}H NMR of **176**, Overman et al. found it necessary to obtain multiple ^{1}H NMR spectra corresponding to the incremental addition of TFA to the synthetic **176**. Similar systematic evaluation of **175** may eventually provide a spectrum that more closely mirrors that of the natural product.

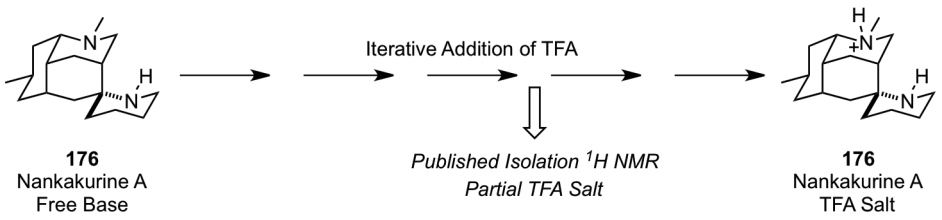


Figure 3.3

3.5 Conclusions

This chapter describes a synthesis of (+)-**100**—the core of *ent*-Citrinadin B (*ent*-**2**)—and outlines late stage attempts to functionalize the aromatic ring in order to access the enantiomer of the natural product (*ent*-**2**). The synthesis of (+)-**100** capitalized on a Corey-Chaykovsky spiro-epoxidation reaction as an alternative to Wittig olefination. Also key to the synthesis was the identification of an effective means of debenzylation. Unfortunately, attempts at a Fries rearrangement, thallium assisted iodination, stepwise bromination, or borylation of the aromatic ring were unproductive.

This prompted the development of a pre-functionalized C7-bromo-oxindole **37** for use in the key (3+2) cycloaddition reaction. Starting from 2,6-dibromoaniline (**46**), a racemic synthesis of

oxindole (±)-**130** was developed. By analogy, an asymmetric synthesis of **130** was also attempted, starting from 2-bromo-6-methoxyaniline (**134**) and arriving at the Heck cyclization precursor **131b**. However, Heck cyclizations of **131b** were prohibitively low yielding and unexpectedly resulted in the C7-trifluorosulfonate oxindole (±)-**140** rather than the desired C7-bromo-oxindole. Nevertheless subsequent transformations of oxindole (±)-**130** provided the desired C7-bromoenone (±)-**37** for use in the cycloaddition.

Reaction of the pre-functionalized bromoenone dipolarophile (±)-**37** with nitrone (*S*)-(–)-**57** effectively provided the desired isoxazolidine (3*R*,12*S*)-(+)-**147** and its C3-epimer (3*S*,12*S*)-**148** in 36% and 51% yields respectively. Elaboration of **147** to the tetrasubstituted epoxide was followed by the installation of a side chain surrogate, which proved stable to the debenzylation conditions and could be advanced to the epoxyketones (+)-**171** and **172** via a gold-mediated oxidation and an Enders' asymmetric epoxidation.

Advancement of both epoxide diastereomers—whose configurations were tentatively assigned using Enders' models—resulted in a synthesis of two products believed to be *ent*-Citrinadin B (*ent*-**2**) and C21-*epi*-*ent*-Citrinadin B (**176**). Surprisingly, the characterization data obtained from *ent*-**2** and **176** do not align with the characterization data provided by Kobayashi for **2**. Current evidence suggests that a structural reassignment of **2** (to **176**) may be forthcoming provided the requisite matching ^{1}H and ^{13}C NMR spectra—or an X-ray crystal structure—of **176** can be obtained. The reassignment of **2** would serve to bring the Citrinadin natural products (**1** and **2**) into better alignment with PF1270A-C (**3**-**5**), for which definitive X-ray crystal data has already been obtained.

3.6 Experimental

3.6.1 Materials and Methods

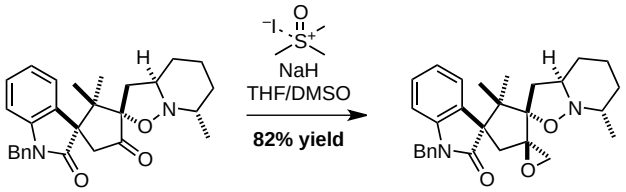
General. Unless otherwise stated, reactions were magnetically stirred in flame- or oven-dried glassware under an atmosphere of nitrogen. Triethylamine, diisopropylamine, and methanol were dried over calcium hydride and freshly distilled. Benzene, tetrahydrofuran, dichloromethane, toluene, and diethyl ether were

dried using a solvent purification system manufactured by SG Water U.S.A., LLC. Anhydrous CH_3CN, DMF, DMSO, acetone, and 1,2-dichloroethane were supplied by Fischer Scientific and purchased from the Colorado State Chemistry Stockroom and kept under a nitrogen atmosphere. All other commercially available reagents were used as received.

Unless otherwise stated, all reactions were monitored by thin-layer chromatography (TLC) using Silicycle glass-backed extra hard layer, 60 Å plates (indicator F-254, 250 μm). Column or flash chromatography was performed with the indicated solvents using Silicycle SiliaFlash. P60 (230-400 mesh) silica gel as the stationary phase. All melting points were obtained on a Gallenkamp capillary melting point apparatus (model: MPD350.BM2.1) and are uncorrected. Infrared spectra were obtained using a Nicolet Avatar 320 FTIR or Bruker Tensor 27 FTIR. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500, Varian Inova 400, Varian Inova 400 autosampler, or Varian Inova 300 spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to internal residual solvent peaks from indicated deuterated solvents. Coupling constants (*J*) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent, par = partial. High resolution mass spectra were performed at the Central Instrument Facility by Donald L. Dick of Colorado State University. Single-crystal X-ray analyses were performed by Susie Miller, Brian Newell, and Stephanie Fielder of Colorado State University. CD Spectra were obtained using an Aviv model 202 circular dichroism spectrometer.

3.6.2 Preparative Procedures

Preparation of Spiro-epoxide 103

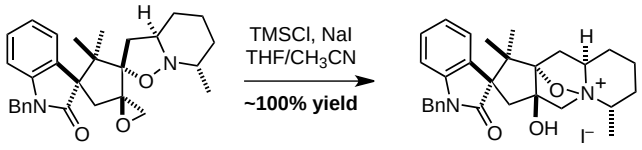


(±)-**56** (±)-**103**

To a mixture of trimethylsulfoxonium iodide (1.05 g, 4.77 mmol) and NaH (60% in mineral oil, 188 mg, 4.70 mmol) was added DMSO (8 ml). After stirring for 30 min, to the resulting homogenous solution was added a solution of ketone **56** (696 mg, 1.57 mmol, azeotropically dried with toluene) in THF (10 ml) followed by 5 ml of rinse. The reaction mixture was stirred at ambient temperature for 23 h, cooled to 0 ºC, and quenched with saturated $NaHCO_3$ solution (10 ml). The mixture was diluted with H_2O (20 ml) and the aqueous layer was extracted with EtOAc (25 ml, 4 times). The combined organic layers were concentrated in vacuo and purified by flash chromatography (10%→20%→30%→40% EtOAc/hexanes) to provide spiro-epoxide **103** as a white solid (586 mg, 82% yield). Slow evaporation of the white solid from CH_2Cl_2/hexanes (1:1) provided colorless crystals suitable X-ray analysis.

R_f = 0.46 (50% EtOAc/hexanes); m.p. 177–179 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39~7.27 (m, 6H), 7.15 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H), 7.01 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 5.21 (d, *J* = 15.6 Hz, 1H), 4.48 (d, *J* = 15.6 Hz, 1H), 3.51 (m, 1H), 3.27 (d, *J* = 5.6 Hz, 1H), 3.04 (d, *J* = 5.6 Hz, 1H), 2.75 (m, 1H), 2.57 (dd, *J* = 12.0 Hz, 12.8 Hz, 1H), 2.44 (m, 2H), 2.29 (d, *J* = 14.4 Hz, 1H), 1.91 (m, 2H), 1.64 (m, 1H), 1.47 (m, 2H), 1.29 (br s, 3H), 1.25 (m, 1H), 1.13 (d, *J* = 5.6 Hz, 3H), 0.71 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 143.5, 136.1, 133.1, 128.8, 128.0, 127.6, 127.2, 124.5, 121.5, 108.7, 91.6, 65.6, 60.1, 55.9, 55.7, 55.6, 49.3, 44.1, 36.0, 35.5, 32.9, 25.7, 23.7, 21.4, 20.8, 18.6; IR (thin film): 1717 (s), 1610 (m), 1487 (m), 1466 (m) cm^{-1}; HRMS (ESI) Calcd. for $C_{29}H_{35}N_2O_3$ [M+H]: 459.2648. Found: 459.2649. From (+)-**56** (91% ee): $[\alpha]_D^{23}$ = +171 (c 1.3, $CHCl_3$); ~91% ee.

Preparation of Ammonium Salt 107

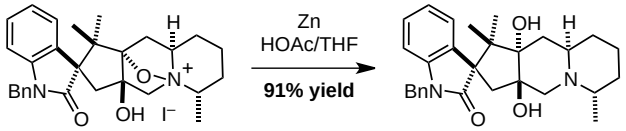


(+)-**103** (+)-**107**

To a solution of epoxide **103** (566 mg, 1.23 mmol) in CH_3CN/THF (5:1, 30 ml) at ambient temperature was added NaI (900 mg, 6.00 mmol) and TMSCl (0.39 ml, 3.07 mmol). After stirring for 1.5 h, to the yellowish mixture was added another 900 mg of NaI and 0.39 ml of TMSCl. After stirring for 1 h, the reaction was quenched with saturated $NaHCO_3$ solution (10 ml) and saturated $Na_2S_2O_3$ solution (10 ml). The aqueous layer was extracted with EtOAc/CH_2Cl_2 (9:1, 20 ml, 4 times). The combined organic layers were concentrated in vacuo and purified by flash chromatography (50% EtOAc/hexanes→5%→ 7.5%→10% MeOH/CH_2Cl_2) to provide 418 mg of the ammonium salt **107** as a pale yellow solid. The recovered starting material (contaminated with an unidentified product) was placed under vacuum overnight, dissolved in CH_2Cl_2 (15 ml), and washed with $NaHCO_3$ solution (10 ml) and saturated $Na_2S_2O_3$ solution (10 ml). The aqueous layer was extracted with EtOAc/CH_2Cl_2 (9:1, 20 ml, 3 times) and the combined organic layers were concentrated in vacuo and purified by flash chromatography (50% EtOAc/hexanes→5%→7.5%→10% MeOH/CH_2Cl_2) to provide another crop of 180 mg of **170**. (598 mg, ~100% yield)

R_f = 0.15 (10% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.2 Hz, 1H), 7.33~7.25 (m, 5H), 7.12 (dd, *J* = 7.6 Hz, 8.0 Hz, 1H), 6.98 (dd, *J* = 7.2 Hz, 8.0 Hz, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 5.94 (br s, 1H, –OH), 5.34 (d, *J* = 11.6 Hz, 1H), 5.04 (d, *J* = 15.6 Hz, 1H), 4.61 (d, *J* = 15.6 Hz, 1H), 4.18 (m, 1H), 4.09 (m, 1H), 4.04 (d, *J* = 11.6 Hz, 1H), 2.97 (d, *J* = 14.4 Hz, 1H), 2.84 (d, *J* = 14.4 Hz, 1H), 2.80 (d, *J* = 12.4 Hz, 1H), 2.50 (m, 1H), 2.35 (m, 2H), 2.12 (m, 1H), 1.91 (m, 2H), 1.85 (m, 1H), 1.63 (d, *J* = 6.8 Hz, 3H), 1.12 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 142.5, 135.8, 131.1, 128.8, 128.2, 127.8, 127.6, 127.2, 122.4, 108.6, 107.7, 86.1, 73.9, 69.5, 66.3, 62.0, 50.9, 45.7, 44.0, 27.3, 26.5, 26.3 (2 carbons), 20.6, 17.5, 12.6; IR (thin film): 3260 (br, s), 2194 (w), 1711 (s), 1609 (m), 1487 (m), 1466 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{29}H_{35}N_2O_3$ [M^+]: 459.2648. Found: 459.2645. From (+)-**103** (~91% ee): $[\alpha]_D^{23}$ = +74.7 (c 1.0, $CHCl_3$); ~91% ee.

Preparation of Diol 102

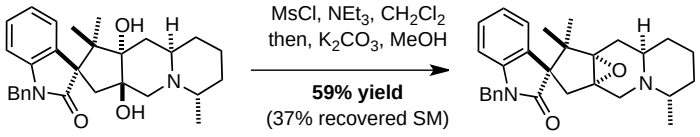


(+)-**107** **102**

To a solution of ammonia salt **107** (418 mg, 0.881 mmol) in THF/MeOH/CH_2Cl_2/AcOH (6 : 1 : 5 : 6, 18 ml) was added activated zinc powder (358 mg, 5.47 mmol). The reaction mixture was vigorously stirred for 22 h at ambient temperature, filtered through a pad of Celite, rinsed with CH_2Cl_2, and concentrated in vacou. The resulting yellowish oil was dissolved in CH_2Cl_2 (2 ml), added saturated $NaHCO_3$ solution and extracted with EtOAc/CH_2Cl_2. The combined organic layers were concentrated and purified by flash chromatography (basic Al_2O_3, 5% MeOH/CH_2Cl_2) to provide diol **102** as a white solid (420 mg, 91% yield).

R_f = 0.48 (10% MeOH/CH_2Cl_2, TLC plate pretreated with NH_3); ^{1}H NMR (400 MHz, $CDCl_3$) (Note: ^{1}H NMR of this compound is highly dependent on the acidity of purification media. To ensure reproducibility, it is recommended to pass through a pad of basic Al_2O_3 before taking ^{1}H NMR) δ 7.46 (d, *J* = 7.6 Hz, 1H), 7.36 (m, 5H), 7.19 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H), 7.09 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.07 (d, *J* = 2.0 Hz, 1H, –OH), 5.09 (d, *J* = 15.6 Hz, 1H), 4.68 (d, *J* = 15.6 Hz, 1H), 4.07 (m, 1H), 3.86 (d, *J* = 11.2 Hz, 1H), 3.85 (m, 1H), 3.69 (d, *J* = 11.2 Hz, 1H), 2.63 (m, 1H), 2.57 (d, *J* = 14.8 Hz, 1H), 2.36 (ddd, *J* = 2.0 Hz, 13.6 Hz, 13.6 Hz, 1H), 2.25 (d, *J* = 14.8 Hz, 1H), 1.93 (m, 2H), 1.81 (m, 3H), 1.69 (dd, *J* = 3.6 Hz, 13.6 Hz, 1H),, 1.43 (d, *J* = 7.2 Hz, 3H), 1.28 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.7, 142.4, 135.1, 131.4, 128.9, 128.2, 127.9, 127.5, 127.4, 123.4, 109.3, 81.5, 81.2, 61.1, 57.7, 55.3, 52.9, 51.1, 47.1, 44.4, 32.8, 31.5, 29.9, 26.4, 21.2, 17.2, 11.5; IR (thin film): 3307 (br, s), 1675 (s), 1609 (s), 1466 (m), 1380 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{29}H_{37}N_2O_3$ [M+H]: 461.2804. Found: 461.2805. $[\alpha]_D^{23}$ = not obtained.

Preparation of Ring-Fusion Epoxide 101

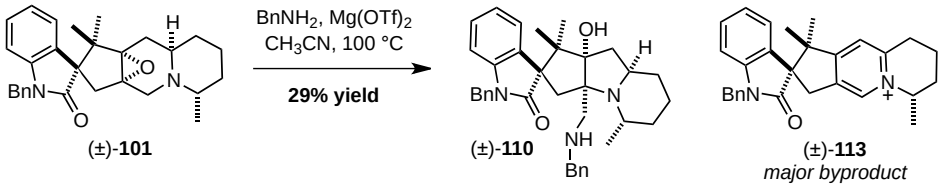


102 (+)-**101**

To a solution of diol **102** (49 mg, 0.106 mmol) in CH_2Cl_2 (2 ml) at room temperature was added triethylamine (148 μl, 1.06 mmol) and MsCl (25 μl, 0.319 mmol). After stirring for 45 minutes, another portion of triethylamine (148 μl, 1.06 mmol) and MsCl (25 μl, 0.319 mmol) were added. After 45 minutes, solid K_2CO_3 (50 mg) and MeOH (2 ml) were added. The reaction mixture was stirred at room temperature for 13 hours, quenched with saturated $NaHCO_3$ solution, extracted with EtOAc/CH_2Cl_2, concentrated and purified by flash chromatography (5%→7.5%→10%→15% MeOH/CH_2Cl_2) to provide epoxide **101** as a pale yellow oil (28 mg, 59% yield) with some recovered starting material (18 mg, 37% recovered).

R_f = 0.41 (10% MeOH/CH_2Cl_2, TLC plate pretreated with NH_3); ^{1}H NMR (400 MHz, $CDCl_3$) (Note: ^{1}H NMR of this compound is highly dependent on the acidity of purification media. To ensure reproducibility, it is recommended to pass through a pad of basic Al_2O_3 before taking ^{1}H NMR) δ 7.33~7.24 (m, 5H, **Ph**), 7.12 (dd, *J* = 7.6 Hz, 8.0 Hz, 1H, **Ar**), 7.09 (d, *J* = 7.6 Hz, 1H, **Ar**), 6.95 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H, **Ar**), 6.65 (d, *J* = 7.6 Hz, 1H, **Ar**), 5.10 (d, *J* = 15.6 Hz, 1H, **CH_2**Ph), 4.53 (d, *J* = 15.6 Hz, 1H, **CH_2**Ph), 3.26 (dd {AB system}, *J* = 14.4 Hz, 2H, N**CH_2**), 3.02 (m, 1H, N**CH**CH_3), 2.77 (m, 1H, N**CH**CH_2), 2.61 (d, *J* = 14.4 Hz, 1H, **CH_2**CO), 2.22 (d, *J* = 14.4 Hz, 1H, **CH_2**CO), 1.87 (m, 2H, **CH_2**CO), 1.74 (m, 2H, **CH_2**CHN), 1.64~1.48 (m, 3H, **CH_2**CH_2, **CH_2**CHN), 1.24 (m, 1H, **CH_2**CHN), 1.09 (s, 3H, **CH_3**), 1.07 (d, *J* = 6.4 Hz, 3H, **CH_3**CHN), 1.03 (s, 3H, **CH_3**). ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 143.2, 136.5, 130.7, 128.6, 127.9, 127.7, 127.4, 126.2, 121.2, 108.3, 70.0, 64.6, 58.9, 51.4, 49.8, 47.5, 45.9, 44.0, 40.5, 33.3, 29.7, 26.1, 20.1, 18.6, 12.4; IR (thin film): 1715 (s), 1609 (s), 1489 (s), 1466 (s), 1344 (s) $cm^{=1}$; HRMS (ESI) Calcd. for $C_{29}H_{34}N_2O_2$ [M+H]: 443.2696. Found: 443.2699. From (+)-**107** (~91% ee): $[\alpha]_D^{23}$ = +92.2 (c 1.0, $CHCl_3$); ~91% ee.

Preparation of Benzylamine 110 and Pyridinium Salt 113



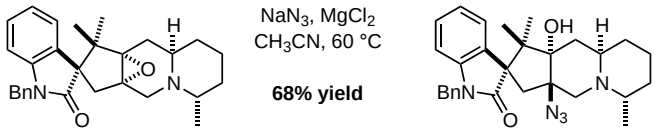
A mixture of epoxide **101** (14 mg, 0.0316 mmol) and benzylamine (28 mg, 0.254 mmol, azeotropically dried with toluene) were taken up in CH_3CN (1.5 ml) and treated with $Mg(OTf)_2$ (~25 mg, 0.775 mmol). The reaction mixture was stirred at 120 °C for 20 hours, concentrated, and purified by flash chromatography (10%→20%→30% EtOAc/Hexanes→5%→10%→15% MeOH/CH_2Cl_2) to provide the benzyl amine **110** as a colorless oil (5 mg, 29% yield) with the pyridinium salt **113** as a major byproduct.

Benzylamine: R_f = 0.07 (10% EtOAc/hexanes, TLC plate pretreated with NH_3); ^{1}H NMR (400 MHz, $CDCl_3$) (Note: ^{1}H NMR of this compound is highly dependent on the acidity of purification media. To ensure reproducibility, it is recommended to pass through a pad of basic Al_2O_3 before taking ^{1}H NMR) δ 7.38~7.26 (m, 10H, **Ar** & **Ph**), 7.22 (t, *J* = 7.25 Hz, 1H, **Ph**), 7.15 (dt, *J* = 1.03 Hz, 7.68 Hz, 1H, **Ar**), 7.04 (dt, *J* = 0.90 Hz, 7.56 Hz, 1H, **Ar**), 6.70 (d, *J* = 7.73 Hz, 1H, **Ar**), 5.12 (d, *J* = 15.63 Hz, 1H, **CH$_2$**Ph), 4.64 (d, *J* = 15.63 Hz, 1H, **CH$_2$**Ph), 4.07 (m, 1H N**CH**), 3.75 (d, *J* = 13.14 Hz, 1H, **CH$_2$**Ph), 3.67 (d, *J* = 13.14 Hz, 1H, **CH$_2$**Ph), 3.41 (d, *J* = 12.51 Hz, 1H, NH**CH$_2$**), 3.28 (m, 1H, N**CH**CH_3), 2.73 (d, *J* = 12.51 Hz, 1H, NH**CH$_2$**), 2.20 (d, *J* = 14.08 Hz, 1H, $NHCH_2C$**CH$_2$**), 1.97 (dd, *J* = 5.55 Hz, 14.10 Hz, 1H, NCH**CH$_2$**), 1.88 (dd, *J* = 9.54 Hz, 14.10 Hz, 1H, NCH**CH$_2$**), 1.79 (d, *J* = 14.08 Hz, 1H, $NHCH_2C$**CH$_2$**), 1.72~1.55 (m, 4H, NCH**CH$_2$CH$_2$CH$_2$**), 1.45 (m, 4H, **CH$_3$** & NCH**CH$_2$**), 1.32 (m, 1H, NCH**CH$_2$**), 1.22 (d, *J* = 6.42 Hz, 3H, CH**CH$_3$**), 0.79 (s, 3H, **CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.8, 142.6, 141.5, 135.5, 131.0, 128.8, 128.1, 128.0, 127.9, 127.7, 127.3, 126.8, 126.4, 122.3, 109.0, 94.6, 77.3, 65.1, 56.8, 54.8, 53.5, 51.7, 45.9, 44.8, 43.9, 41.2, 34.5, 31.9, 28.0, 20.1, 19.6, 13.9; IR (thin film): 3323 (br s), 1675 (s), 1609 (s), 1489 (m), 1466 (m), 1374 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{36}H_{44}N_3O_2$ [M+H]: 550.3434. Found: 550.3429.

Pyridinium Salt: R_f = 0.11 (10% MeOH/CH_2Cl_2, TLC plate pretreated with NH_3); ^{1}H NMR (400 MHz, $CDCl_3$) (Note: ^{1}H NMR of this compound is highly dependent on the acidity of purification media. To ensure reproducibility, it is recommended to pass through a pad of basic Al_2O_3 before taking ^{1}H NMR)

δ 8.56 (s, 1H, **Ar**), 7.41 (s, 1H, **Ar**), 7.34~7.25 (m, 7H, **Ph** & **Ar**), 7.09 (t, *J* = 7.6 Hz, 1H, **Ar**), 6.83 (d, *J* = 7.8 Hz, 1H, **Ar**), 5.00 (m, 1H, N**CH**), 4.98 (d, *J* = 15.6 Hz, 1H, **CH$_2$**Ph), 4.69 (d, *J* = 15.6 Hz, 1H, **CH$_2$**Ph), 3.67 (d, *J* = 17.0 Hz, 1H, NCOC**CH$_2$**), 3.40 (d, *J* = 17.0 Hz, 1H, NCOC**CH$_2$**), 3.37 (m, 1H, NC**CH$_2$**), 3.28 (dt, *J* = 18.6, 4.8 Hz, 1H, NC**CH$_2$**), 2.37 (m, 1H, NCCH$_2$**CH$_2$**), 2.05 (m, 3H, NCCH$_2$**CH$_2$CH$_2$**), 1.71 (d, J = 6.8 Hz, 3H, CH**CH$_3$**), 1.35 (s, 3H, **CH$_3$**), 1.24 (s, 3H, **CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 170.0, 155.0, 143.3, 139.9, 138.6, 135.3, 129.4, 128.9, 127.9, 127.3, 126.1, 125.8, 123.1, 122.2, 109.6, 61.5, 61.0, 51.6, 43.8, 37.1, 29.0, 27.5, 26.8, 22.4, 20.9, 14.3; IR (thin film): 3059 (s), 2934 (s), 1706 (s), 1466 (s), 1289 (s), 1247 (s), 1161 (s), 1029 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{29}H_{31}N_2O^+$ [M+]: 423.2431. Found: 423.2438.

Preparation of Azide 114



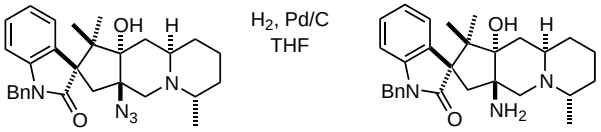
(±)-**101** (±)-**114**

To a solution of epoxide **101** (27 mg, 0.0610 mmol, azeotropically dried with toluene) in CH_3CN (2.2 ml) was added $MgCl_2$ (35 mg, 0.368 mmol) and NaN_3 (25 mg, 0.385 mmol). The reaction mixture was stirred at 63 °C for 40 h and quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc/CH_2Cl_2 (4:1) and the combined organic layers were concentrated and purified by flash chromatography (30%→50%→70%→90% EtOAc/hexanes) to provide 20 mg (68% yield) of azide **114** as a pale yellow oil.

R_f = 0.64 (30% MeOH/CH_2Cl_2, TLC plate pretreated with NH_3); ^{1}H NMR (400 MHz, $CDCl_3$) (Note: ^{1}H NMR of this compound is highly dependent on the acidity of purification media. To ensure reproducibility, it is recommended to pass through a pad of basic Al_2O_3 before taking ^{1}H NMR) δ 7.50 (d, *J* = 7.2 Hz, 1H), 7.35-7.28 (m, 5H), 7.17 (ddd, *J* = 0.8 Hz, 7.6 Hz, 7.6 Hz, 1H), 7.09 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 5.34 (d, *J* = 2.4 Hz, 1H, –OH), 5.10 (d, *J* = 15.6 Hz, 1H), 4.67 (d, *J* = 15.6 Hz, 1H), 3.56 (d, *J* = 11.2 Hz, 1H), 3.10 (m, 1H), 3.01 (m, 1H), 2.68 (d, *J* = 11.2 Hz, 1H), 2.53 (d, *J* = 14.4 Hz, 1H), 2.08 (d, *J* = 14.4 Hz, 1H), 1.82 (m, 1H), 1.68-1.58 (m, 4H), 1.57-1.48 (m, 2H), 1.29 (m, 1H), 1.25

(s, 3H), 1.07 (d, J = 6.4 Hz, 3H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.6, 142.6, 135.4, 132.4, 128.8, 127.8 (two carbons), 127.4, 127.2, 122.9, 109.1, 83.2, 73.9, 61.0, 54.6, 54.5, 51.9, 46.8, 45.8, 44.3, 36.1, 33.9, 32.3, 26.6, 21.8, 18.9, 9.9; IR (thin film): 3349 (br, s), 2117 (s), 1682 (s), 1609 (s), 1487 (m), 1466 (s), 1373 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{29}H_{36}N_5O_2$ [M+H]: 485.2869. Found: 486.2876.

Preparation of Amine 115

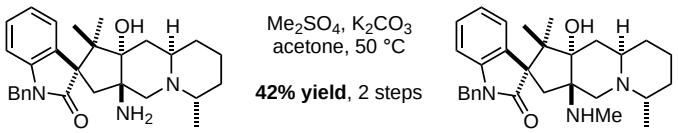


(±)-**114** (±)-**115**

To a solution of azide **114** (27 mg, 0.0556 mmol) in THF (2 ml) was added Pd/C (10 wt%, 15 mg). The mixture was purged with H_2 for 1 min and stirred under H_2 atmosphere (balloon) for 11 h. The mixture was filtered through a pad of Celite, washed with CH_2Cl_2, and concentrated in vacuo to provide the crude amine (26 mg). For characterization purposes, the crude product was purified by flash chromatography (5%→10%→15%→20% MeOH/CH_2Cl_2) to give pure amine **115** as a colorless oil.

R_f = 0.43 (10% MeOH/CH_2Cl_2, TLC plate pretreated with NH_3); ^{1}H NMR (400 MHz, $CDCl_3$) (Note: ^{1}H NMR of this compound is highly dependent on the acidity of purification media. To ensure reproducibility, it is recommended to pass through a pad of basic Al_2O_3 before taking ^{1}H NMR) δ 7.62 (d, J = 7.6 Hz, 1H), 7.35-7.28 (m, 5H), 7.14 (dd, J = 7.6 Hz, 7.6 Hz, 1H), 7.05 (dd, J = 7.6 Hz, 7.6 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 5.12 (d, J = 15.6 Hz, 1H), 4.90 (d, J = 2.4 Hz, 1H, –OH), 4.68 (d, J = 15.6 Hz, 1H), 3.50 (d, J = 9.6 Hz, 1H), 3.00 (m, 1H), 2.92 (m, 1H), 2.53 (d, J = 14.0 Hz, 1H), 2.00 (d, J = 9.6 Hz, 1H), 1.86-1.74 (m, 3H), 1.68-1.47 (m, 6H), 1.45 (s, 3H), 1.19 (m, 1H), 1.08 (d, J = 6.8 Hz, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.1, 142.7, 135.7, 133.5, 128.8, 127.7, 127.4 (two carbons), 127.3, 122.5, 108.8, 83.6, 63.9, 61.6, 60.7, 55.1, 52.3, 48.5, 47.2, 44.2, 35.8, 34.7, 32.7, 28.2, 22.3, 19.0, 10.3; IR (thin film): 3351 (br, s), 1683 (s), 1609 (s), 1371 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{29}H_{38}N_3O_2$ [M+H]: 460.2964. Found: 460.2960.

Preparation of Methylamine 108

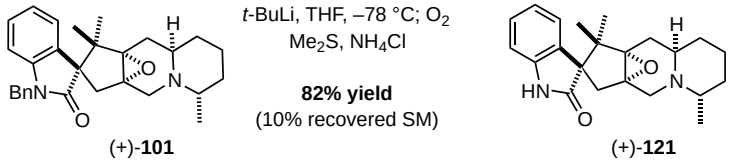


(±)-**115** (±)-**108**

The crude amine (**115**) was dissolved in acetone (1.5 ml) and treated with K_2CO_3 (25 mg) and Me_2SO_4 (16 µl, 0.167 mmol). The mixture was stirred at 50 °C for 28 h and quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc/CH_2Cl_2 (4:1) and the combined organic layers were concentrated in vacuo and purified by flash chromatography (5%→7.5%→10%→12.5%→15% MeOH/CH_2Cl_2) to provide 11 mg (42% yield, two steps) of the methylamine (**108**) as a colorless oil.

R_f = 0.54 (10% MeOH/CH_2Cl_2, TLC plate pretreated with NH_3); ^{1}H NMR (400 MHz, $CDCl_3$) (Note: ^{1}H NMR of this compound is highly dependent on the acidity of purification media. To ensure reproducibility, it is recommended to pass through a pad of basic Al_2O_3 before taking ^{1}H NMR) δ 7.50 (d, *J* = 7.2 Hz, 1H), 7.31 (m, 5H), 7.13 (dd, *J* = 7.6 Hz, 8.0 Hz, 1H), 7.05 (dd, *J* = 7.2 Hz, 7.6 Hz, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 5.11 (d, *J* = 15.6 Hz, 1H), 4.95 (d, *J* = 2.0 Hz, 1H, –OH), 4.69 (d, *J* = 15.6 Hz, 1H), 3.10 (d, *J* = 10.8 Hz, 1H), 3.01 (m, 1H), 2.90 (m, 1H), 2.53 (d, *J* = 10.8 Hz, 1H), 2.31 (s, 3H), 2.21 (br s, 1H, –NH), 2.12 (s, 2H), 1.76 (m, 1H), 1.65-1.47 (m, 5H), 1.39 (s, 3H), 1.36 (m, 1H), 1.15 (m, 1H), 1.08 (d, *J* = 6.4 Hz, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.1, 142.7, 135.8, 133.6, 128.8, 127.8, 127.6, 127.4, 127.2, 122.5, 108.8, 84.0, 68.6, 61.8, 55.2, 51.7, 50.5, 46.9, 44.2, 41.2, 35.5, 34.8, 32.8, 29.8, 28.2, 22.3, 19.0, 10.4; IR (thin film): 3384 (br, m), 1683 (s), 1609 (s), 1486 (m), 1466 (m), 1371 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{30}H_{40}N_3O_2$ [M+H]: 474.3121. Found: 474.3106.

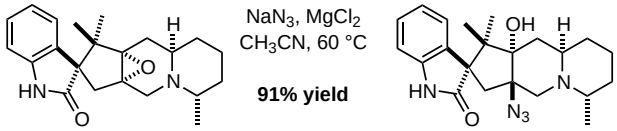
Preparation of *des*-Benzyl Oxindole (+)-121



To a solution of benzylamide **101** (61 mg, 0.138 mmol, azeotroped with toluene) in THF (3 ml) at –78 °C was added *t*-BuLi (1.5 M in pentane, 140 µl, 0.207 mmol). After stirring for 5 minutes, a stream of oxygen was passed through the dark reaction mixture for 10 minutes. The resulting pale yellow solution was quenched with Me_2S (2 drops) and NH_4Cl (110 mg). The mixture was warmed to room temperature and stirred for 1 hour. The reaction mixture was washed with saturated $NaHCO_3$ solution, extracted with EtOAc/CH_2Cl_2, concentrated, and purified by flash chromatograpy (5%→7.5%→10%→12.5%→15%→20% MeOH/CH_2Cl_2) to provide the *des*-Benzyl oxindole **121** (40 mg, 82% yield) and recovered starting material (6 mg, 10% recovered).

R_f = 0.25 (10% MeOH/CH_2Cl_2, TLC plate pretreated with NH_3); ^{1}H NMR (400 MHz, $CDCl_3$) (Note: ^{1}H NMR of this compound is highly dependent on the acidity of purification media. To ensure reproducibility, it is recommended to pass through a pad of basic Al_2O_3 before taking ^{1}H NMR) δ 8.62 (br s, 1H, **NH**), 7.12 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H, **Ar**), 7.02 (d, *J* = 7.2 Hz, 1H, **Ar**), 6.91 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H, **Ar**), 6.83 (d, *J* = 7.6 Hz, 1H, **Ar**), 3.24 (s, 2H, N**CH$_2$**), 3.01 (m, 1H, N**CH**), 2.74 (m, 1H, N**CH**), 2.57 (d, *J* = 14.4 Hz, 1H, **CH$_2$**COC), 2.19 (d, *J* = 14.4 Hz, 1H, **CH$_2$**COC), 1.86 (m, 2H, **CH$_2$**COC), 1.71 (m, 2H, **CH$_2$CH$_2$**CHN), 1.60~1.44 (m, 3H, **CH$_2$CH$_2$**CHN), 1.22 (m, 1H, **CH$_2$**CHN), 1.10 (s, 3H, **CH$_3$**), 1.04 (d, *J* = 6.4 Hz, 3H, **CH$_3$**CH), 0.99 (s, 3H, **CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.8, 141.2, 131.1, 127.9, 126.3, 121.0, 109.2, 70.0, 64.5, 59.4, 51.4, 49.6, 47.3, 46.0, 39.8, 33.0, 29.7, 25.9, 19.7, 18.4, 12.3; IR (thin film): 3272 (br m), 1719 (s), 1472 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{29}N_2O_2$ [M+H]: 353.2218. Found: 353.2229. From (+)-**101** (~91% ee): $[\alpha]_D^{23}$ = +76.9 (c 0.75, $CHCl_3$); ~91% ee.

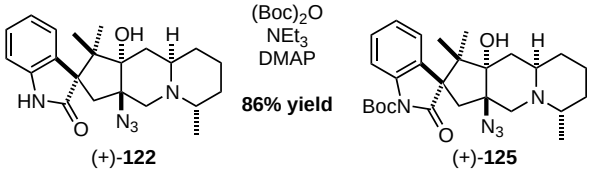
Preparation of *des*-Benzyl Azide (+)-122



To a solution of epoxide **121** (40 mg, 0.113 mmol, azeotropically dried with toluene) in CH_3CN (5 ml) was added $MgCl_2$ (44 mg, 0.454 mmol) and NaN_3 (50 mg, 0.769 mmol). The mixture was stirred at 63 °C for 67 h and quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with $EtOAc/CH_2Cl_2$ (4:1) and the combined organic layers were concentrated and purified by flash chromatography (30%→50%→70% EtOAc/hexanes) to provide azide **122** as a white film (41 mg, 91% yield).

R_f = 0.30 (30% EtOAc/hexanes, TLC plate pretreated with NH_3); ^{1}H NMR (400 MHz, $CDCl_3$) (Note: ^{1}H NMR of this compound is highly dependent on the acidity of purification media. To ensure reproducibility, it is recommended to pass through a pad of basic Al_2O_3 before taking ^{1}H NMR) δ 9.22 (br s, 1H, **NH**), 7.44 (d, *J* = 7.6 Hz, 1H, **Ar**), 7.22 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H, **Ar**), 7.09 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H, **Ar**), 6.93 (d, *J* = 7.6 Hz, 1H, **Ar**), 5.25 (s, 1H, **OH**), 3.53 (d, *J* = 11.2 Hz, 1H, **CH$_2$**N), 3.13 (m, 1H, **CH**N), 3.00 (m, 1H, **CH**N), 2.69 (d, *J* = 11.2 Hz, 1H, **CH$_2$**N), 2.49 (d, *J* = 14.4 Hz, 1H, **CH$_2$**CN_3), 2.06 (d, *J* = 14.4 Hz, 1H, **CH$_2$**CN_3), 1.82 (m, 1H, **CH$_2$**CHN), 1.68~1.48 (m, 6H, **CH$_2$CH$_2$**CHN), 1.30 (m, 1H, **CH$_2$**CHOH), 1.24 (s, 3H, **CH$_3$**), 1.07 (d, *J* = 6.8 Hz, 3H, **CH$_3$**CH), 1.02 (s, 3H, **CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.1, 140.7, 132.8, 127.9, 127.3, 122.8, 109.9, 83.2, 73.8, 61.6, 54.5, 54.4, 51.8, 46.9, 45.2, 35.9, 33.9, 32.2, 26.5, 21.5, 18.8, 9.9; IR (thin film): 3211 (br m), 2111 (s), 1686 (s), 1472 (s), 1267 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{30}N_5O_2$ [M+H]: 396.2398. Found: 396.2400. From (+)-**121** (~91% ee): $[\alpha]_D^{23}$ = +65.3 (c 0.9, $CHCl_3$); ~91% ee.

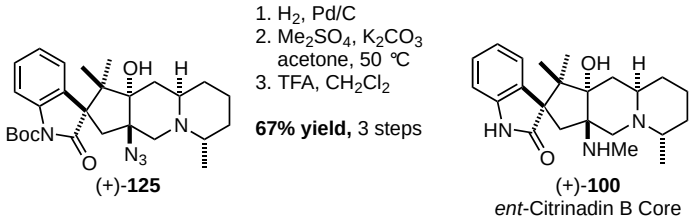
Preparation of Boc-Protected Oxindole (+)-125



A solution of oxindole **122** (62 mg, 0.157 mmol) and Boc_2O (51 mg, 0.235 mmol) in CH_2Cl_2 (4 ml) was added DMAP (19 mg, 0.157 mmol) and triethylamine (70 μl, 0.502 mmol). The reaction was stirred at room temperature for 50 minutes, quenched with saturated $NaHCO_3$ solution, extracted with EtOAc/CH_2Cl_2, concentrated and purified by flash chromatography (5%→10%→20%→ 30% EtOAc/ hexanes) to provide the Boc-protected oxindole **125** as a white solid (67 mg, 86% yield).

R_f = 0.67 (30% EtOAc/hexanes, TLC plate pretreated with NH_3); ^{1}H NMR (400 MHz, $CDCl_3$) (Note: ^{1}H NMR of this compound is highly dependent on the acidity of purification media. To ensure reproducibility, it is recommended to pass through a pad of basic Al_2O_3 before taking ^{1}H NMR) δ 7.77 (d, 8.4 Hz, 1H, **Ar**), 7.55 (d, 7.6 Hz, 1H, **Ar**), 7.30 (ddd, 1.2 Hz, 7.6 Hz, 8.0 Hz, 1H, **Ar**), 7.21 (dd, 7.6 Hz, 8.0 Hz, 1H, **Ar**), 4.53 (d, 2.4 Hz, 1H, **OH**), 3.52 (d, 11.2 Hz, 1H, **CH$_2$**NH), 3.08 (m, 1H, **CH**N), 2.98 (m, 1H, **CH**N), 2.67 (d, 11.2 Hz, 1H, **CH$_2$**NH), 2.55 (d, 14.4 Hz, 1H, **CH$_2$**CN_3), 2.07 (d, 14.4 Hz, 1H, **CH$_2$**CN_3), 1.80 (m, 1H, **CH$_2$**CHN), 1.63 (s, 9H, **Boc**), 1.60~1.50 (m, 6H, **CH$_2$CH$_2$**CHN), 1.26 (m, 1H, **CH$_2$**CHN), 1.13 (s, 3H, **CH$_3$**), 1.05 (d, 6.8 Hz, **CH$_3$**CH), 0.98 (s, 3H, **CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.5, 148.5, 139.2, 130.9, 128.1, 127.1, 124.4, 114.4, 84.8, 83.5, 73.7, 61.7, 54.53, 54.45, 53.4, 46.7, 46.2, 36.1, 33.9, 32.3, 28.0, 26.2, 21.4, 18.8, 9.8; IR (thin film): 3402 (br m), 2115 (s), 1736 (s), 1465 (m), 1370 (m), 1287 (m), 1149 (m) cm^{-1}; HRMS (ESI) Calcd. for $C_{27}H_{38}N_5O_4$ [M+H]: 496.2919. Found: 496.2924. From (+)-**122** (~91% ee): $[\alpha]_D^{23}$ = +97.9 (c 1.4, $CHCl_3$); ~91% ee.

Preparation of the *ent*-Citrinadin Core (+)-100



Azide Reduction:

A solution of azide **125** (67 mg, 0.135 mmol) in THF (5 ml) containing Pd/C (10 wt%, 29 mg, 0.0270 mmol) was purged with H_2 for 1 minute and stirred under H_2 atmosphere (balloon) for 24 hours. Another portion of Pd/C was added (30 mg, 0.0270 mmol). The reaction mixture was stirred for another 24 hours, filtered through a pad of celite, rinsed with CH_2Cl_2, concentrated, and purified by flash chromatography (30% EtOAc/hexanes 5%→7.5%→10%→15% MeOH/CH_2Cl_2) to provide the desired amine as a pale yellow oil (62 mg, 98% yield).

R_f = 0.24 (20% EtOAc/hexanes, TLC plate pretreated with NH_3).

Methylation:

To a solution of the amine (60 mg, 0.128 mmol) in acetone (2.5 ml) was added K_2CO_3 (60 mg) and Me_2SO_4 (50 μl, 0.528 mmol). The reaction mixture was stirred at 60 °C for 40 hours, quenched with saturated $NaHCO_3$ solution, extracted with EtOAc/CH_2Cl_2, concentrated, and purified by flash chromatography (30%→50%→70% EtOAc/hexanes) to provide the methylamine as a white solid (48 mg, 78% yield).

R_f = 0.56 (20% EtOAc/hexanes, TLC plate pretreated with NH_3); ^{1}H NMR (400 MHz, $CDCl_3$) (Note: ^{1}H NMR of this compound is highly dependent on the acidity of purification media. To ensure reproducibility, it is recommended to pass through a pad of basic Al_2O_3 before taking ^{1}H NMR) δ 7.76 (d, *J* = 8.1 Hz, 1H, **Ar**), 7.54 (d, *J* = 7.5 Hz, 1H, **Ar**), 7.26 (t, *J* = 7.1 Hz, 1H, **Ar**), 7.17 (t, *J* = 7.5 Hz, 1H, **Ar**), 4.26 (d, *J* = 2.6 Hz, 1H, **OH**), 3.05 (d, *J* = 10.7 Hz, 1H, NHC**CH$_2$**), 3.00 (m, 1H, N**CH**), 2.88 (t, *J* = 10.8 Hz, 1H, N**CH**), 2.53 (d, *J* = 10.7 Hz, 1H, NHC**CH$_2$**), 2.31 (s, 3H, NH**CH$_3$**), 2.12 (q, *J* = 11.5 Hz, 2H, NHC**CH$_2$**), 2.12 (m, 1H, NCH**CH$_2$**), 1.76 (m, 1H, NCH**CH$_2$**), 1.64 (s, 9H, **Boc**), 1.59~1.47 (m, 4H,

NCH**CH$_2$**), 1.4 (m, 1H, NCHCH$_2$**CH$_2$**), 1.27 (s, 3H, **CH$_3$**), 1.13 (m, 1H, NCHCH$_2$**CH$_2$**), 1.06 (d, *J* = 6.7 Hz, 3H, CH**CH$_3$**), 0.96 (s, 3H, **CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.09, 148.95, 139.38, 132.28, 127.93, 127.60, 124.29, 114.29, 84.60, 84.38, 68.63, 62.53, 55.30, 53.30, 50.38, 46.99, 41.70, 35.55, 34.82, 32.87, 29.79, 28.20, 27.87, 22.11, 19.11, 10.51; IR (thin film): not obtained; HRMS (ESI) not obtained. From (+)-**125** (~91% ee): $[\alpha]_D^{23}$ = +94.6 (c 1.0, $CHCl_3$); ~91% ee.

Boc-Removal:

To a solution of the Boc amide (12 mg, 0.025 mmol) in CH_2Cl_2 (1 ml) at room temperature was added TFA (100 μl). The reaction was stirred at room temperature for 30 minutes, carefully quenched with saturated $NaHCO_3$ solution and solid $NaHCO_3$, extracted with EtOAc/CH_2Cl_2, concentrated and purified by flash chromatography (50% 80% EtOAc/hexanes 5% → 10% → 15% MeOH/CH_2Cl_2) to provide **100** as a white foam (11 mg, 88% yield).

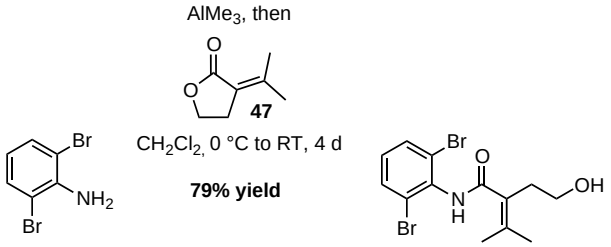
R_f = 0.37 (30% EtOAc/hexanes, TLC plate pretreated with NH_3); IR (thin film): 3332 (br), 3203 (br), 1691 (s), 1672 (s), 1202 (s); HRMS (ESI) Calcd. for $C_{23}H_{34}N_3O_2$ [M+H]: 384.2651. Found: 384.2651.

TFA salt: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.66 (br s, 1H, **NH**), 8.20 (br s, 1H, **NH**), 7.39 (d, *J* = 7.6 Hz, 1H, **Ar**), 7.20 (t, *J* = 7.7 Hz, 1H, **Ar**), 7.06 (t, *J* = 7.6 Hz, 1H, **Ar**), 6.88 (d, *J* = 7.7 Hz, 1H, **Ar**), 5.54 (s, 1H, **OH**), 3.79-3.63 (m, 3H, **CH$_2$**N**CH**), 3.27 (d, *J* = 11.3 Hz, 1H, NHC**CH**), 2.53 (s, 1H, **NH**CH_3), 2.40 (m, 1H, NCH**CH$_2$**), 2.39 (s, 3H, NH**CH$_3$**), 2.30 (m, 1H, NCH**CH$_2$**), 2.22 (d, *J* = 14.1 Hz, 1H, NHC**CH$_2$**), 2.09 (d, *J* = 14.1 Hz, 1H, NHC**CH$_2$**), 2.02 (m, 1H, NCH**CH$_2$**), 1.75-1.63 (m, 4H, **CH$_2$**NCH**CH$_2$CH$_2$**), 1.40 (d, *J* = 6.9 Hz, 3H, CH**CH$_3$**), 1.37 (s, 3H, **CH$_3$**), 0.98 (s, 3H, **CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.64, 140.54, 132.74, 128.23, 128.05, 123.20, 109.91, 82.63, 67.81, 62.04, 58.06, 52.32, 50.98, 50.81, 41.72, 31.69, 29.94, 29.56, 29.30, 28.10, 21.89, 17.48, 12.12. $[\alpha]_D^{22}$ (TFA salt) = +50.7 (c 0.9, $CHCl_3$).

Freebase: ^{1}H NMR (400 MHz, $CDCl_3$) (Note: ^{1}H NMR of this compound is highly dependent on the acidity of purification media. To ensure reproducibility, it is recommended to pass through a pad of basic Al_2O_3 before taking ^{1}H NMR) δ 8.32 (s, 1H, **NH**), 7.46 (d, *J* = 7.6 Hz, 1H, **Ar**), 7.18 (t, *J* = 8 Hz, 1H, **Ar**), 7.06 (t, *J* = 7.6 Hz, 1H, **Ar**), 6.89 (d, *J* = 8 Hz, 1H, **Ar**), 4.80 (d, *J* = 2.8 Hz, 1H, **OH**), 3.07 (d, *J* = 10.8 Hz, 1H, NHC**CH$_2$**), 3.01 (p, *J* = 5.2 Hz, 1H, N**CH**), 2.88 (tt, *J* = 10.8 Hz, 2.8 Hz, 1H, N**CH**), 2.53 (d,

J = 10.8 Hz, 1H, NHC**H**$_2$), 2.31 (s, 3H, NH**CH**$_3$), 2.18 (br s, 1H, **NH**CH$_3$), 2.09 (AB q, J_{AB} = 12 Hz, 2H, NHC**H**$_2$), 1.76 (m, 1H, NCH**CH**$_2$), 1.64~1.46 (m, 4H, NCH**CH**$_2$**CH**$_2$), 1.38 (s, 3H, **CH**$_3$), 1.38 (m, 1H, NCH**CH**$_2$), 1.15 (m, 1H, NCH**CH**$_2$), 1.07 (d, *J* = 6.4 Hz, 3H, CH**CH**$_3$), 0.99 (s, 3H, **CH**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.3, 140.6, 134.1, 128.1, 127.3, 122.4, 109.4, 84.1, 68.5, 62.4, 55.2, 51.6, 50.5, 46.9, 40.7, 35.4, 34.7, 32.8, 29.8, 28.1, 22.0, 19.0, 10.4; $[\alpha]_D^{22}$ (free base) = +58.7 (c 1.2, $CHCl_3$).

Preparation of Dibromoanilide 48



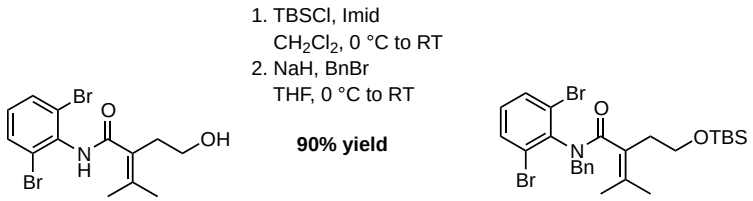
46 **48**

Dibromoaniline **46** (24.9 g, 100 mmol) was dissolved in CH_2Cl_2 (400 mL), cooled to 0 ºC, and treated with trimethylaluminum (2.0 M in toluene, 100 mL, 200 mmol). The reaction mixture was stirred at room temperature for 30 minutes. Next was added γ-butyrolactone **47** (15 g, 120 mmol) to produce a yellow solution, which was stirred for an additional 72 hours. The resulting dark green reaction solution was quenched by the slow addition of 0.5 mL potassium sodium tartrate solution (1 M in H_2O) every 15 minutes for one hour. The slurry was poured into a large Erlenmeyer flask containing potassium sodium tartrate solution (1 M in H_2O, 398 mL), and the reaction vessel was thoroughly rinsed with a combination of CH_2Cl_2 (400 mL) and water (200 mL). The biphasic mixture was vigorously stirred for 4 hours. Upon separation, the aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were subsequently washed with 1 M HCl, saturated $NaHCO_3$ solution, and brine. After drying over sodium sulfate, the solvent was removed in vacuo to yield the crude alcohol as a yellow solid. This residue was purified by triteration in Et_2O (150 mL) to provide the pure alcohol **48** as a cream colored solid (29.8 g, 79%).

R_f = 0.2 (50% EtOAc/Hexane); mp 156-158 ºC (ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (br s, 1H, N**H**), 7.60 (d, *J* = 8.1 Hz, 2H, **Ar**), 7.03 (dd, *J* = 8.1 Hz, 8.1 Hz, 1H, **Ar**), 3.89 (q, *J* = 5.4, 2H,

C**H$_2$**OH), 2.73 (t, *J* = 4.9 Hz, 1H, O**H**), 2.67 (t, *J* = 5.6 Hz, 2H, C**H$_2$**CH$_2$OH), 2.09 (s, CH$_3$, CC**H$_3$**), 1.83 (s, CH$_3$, CC**H$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 139.2, 135.1, 132.4, 129.5, 128.8, 124.0, 62.3, 32.9, 23.0, 20.8; IR (thin film): 3212 (br, s), 1654 (s), 1049 (m) cm^{-1}; HRMS (ESI) Calcd. for $C_{13}H_{15}Br_2NO_2Na$ [M+Na+2]: 399.9347. Found: 399.9332.

Preparation of bis-Protected Dibromoanilide 132



TBS-Protection:

To a reaction flask containing alcohol **48** (29.8 g, 79 mmol) and imidazole (8.1 g, 118.5 mmol) was added CH_2Cl_2 (200 mL). The light yellow solution was cooled to 0 ºC in an ice bath before adding TBSCl (13.1 g, 86.9 mmol). The reaction was allowed to warm to room temperature overnight (12 h) and a white precipitate emerged. The reaction was diluted with CH_2Cl_2 (200 mL) and quenched with saturated NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with saturated $NaHCO_3$ solution, water, and brine; dried over sodium sulfate; and concentrated. This provided the silyl ether as a light yellow oil (38.7 g, 99%), which was dried under high vacuum and used without further purification.

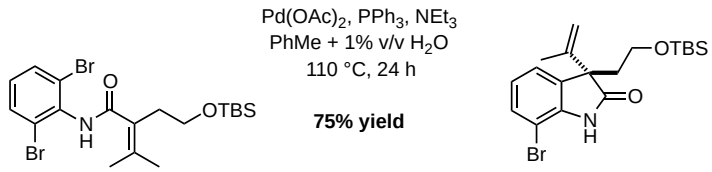
R_f = 0.13 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (br s, 1H, N**H**), 7.59 (d, *J* = 8.1 Hz, 2H, **Ar**), 7.01 (dd, *J* = 8.1 Hz, 8.1 Hz, 1H, **Ar**), 3.91 (t, *J* = 5.6 Hz, 2H, C**H$_2$**OTBS), 2.72 (t, *J* = 5.6 Hz, 2H, C**H$_2$**CH$_2$OTBS), 2.05 (s, 3H, CC**H$_3$**), 1.80 (s, 3H, CC**H$_3$**), 0.84 (s, 9H, SiC(C**H$_3$**)$_3$), 0.06 (s, 6H, Si(C**H$_3$**)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 140.1, 135.4, 132.3, 129.3, 128.9, 124.6, 63.8, 53.5, 32.8, 26.0, 22.6, 20.9, 18.5, -5.4; IR (thin film): 3232 (br, s), 1663.5 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{19}H_{30}Br_2NO_2Si$ [M+H+2]: 492.0392. Found: 492.0394.

Benzyl-Protection:

To the amide (477 mg, 0.97 mmol) in DMF (10 ml) at 0 °C in an ice bath was added NaH (120 mg, 3 mmol) to produce a yellow solution. Benzyl bromide (178 µl, 1.5 mmol) was subsequently added and the reaction was allowed to warm to room temperature. Upon completion (as determined by TLC) the reaction was quenched with a saturated NH_4Cl solution. The aqueous portion was extracted with EtOAc; and the combined organic layers were washed with H_2O and brine, dried over sodium sulfate, concentrated, and purified by flash chromatography to provide the benzyl amide (447 mg, 80% yield).

R_f = 0.5 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.48 (d, *J* = 8.0 Hz, 2H, **Ar**), 7.26-7.14 (m, 3H, **Ph**), 7.03-7.00 (m, 2H, **Ph**), 6.95 (t, *J* = 8.0 Hz, 1H, **Ar**), 4.84 (d, *J* = 6.5 Hz, 2H, **C**$\mathbf{H_2}$Ph), 3.94 (td, *J* = 9.7, 5.6 Hz, 1H, **C**$\mathbf{H_2}$OTBS), 3.77 (td, *J* = 9.5, 6.6 Hz, 1H, **C**$\mathbf{H_2}$OTBS), 2.84 (m, 1H, **C**$\mathbf{H_2}$$CH_2$OTBS), 2.58 (m, 1H, **C**$\mathbf{H_2}$$CH_2$OTBS), 2.01 (s, 3H, **C**$\mathbf{H_3}$), 1.90 (s, 3H, **C**$\mathbf{H_3}$), 0.91 (s, 9H, SiC(**C**$\mathbf{H_3}$)$_3$), 0.08 (s, 6H, Si(**C**$\mathbf{H_3}$)$_2$). ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.62, 143.60, 139.43, 139.39, 137.95, 135.72, 135.11, 133.29, 133.23, 131.97, 67.03, 58.56, 39.43, 31.27, 31.20, 28.12, 24.83, 23.60, 0.10; IR (thin film): 2925 (s), 2850 (s), 1658 (s), 1441 (s), 1083 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{26}H_{36}Br_2NO_2Si$ [M+H+2]: 582.0882. Found: 582.0857.

Preparation of C7-Bromo-Oxindole 133



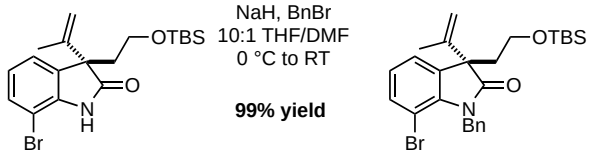
131a (±)-**133**

To the Dibromoanilide **131a** (13.5 g, 27 mmol) dissolved in toluene (270 mL) was added $Pd(OAc)_2$ (306 mg, 1.35 mmol), PPh_3 (1.1 g, 4.05 mmol), and NEt_3 (18.8 mL, 135 mmol). The subsequent addition of water (2.7 mL) formed a dispersion on the surface of the glass. This was stirred at room temperature for 15 minutes, during which time the clear solution became cloudy. The reaction was heated to reflux for 24 h. The solution was cooled and the toluene was removed in vacuo. The residue was

purified by flash chromatography (1→5% EtOAc/hexanes) to provide oxindole **133** as a white solid (8.3 g, 75% yield).

R_f = 0.31 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (br s, 1H, N**H**), 7.34 (d, *J* = 8.1, 1H, **Ar**), 6.98 (d, *J* = 7.4 Hz, 1H, **Ar**), 6.93 (dd, *J* = 7.7 Hz, 7.7 Hz, 1H, **Ar**), 5.00 (s, 1H, C=C**H**), 4.98 (s, 1H, C=C**H**), 3.41 (m, 2H, C**H$_2$**OTBS), 2.51 (ddd, *J* = 7.8 Hz, 7.8 Hz, 13.5 Hz, 1H, C**H$_2$**CH_2OTBS), 2.15 (ddd, *J* = 4.6 Hz, 6.3 Hz, 13.5 Hz, 1H, C**H$_2$**CH_2OTBS), 1.67 (s, 3H, CH_2=CC**H$_3$**), 0.78 (s, 9H, SiC(C**H$_3$**)$_3$), -0.12 (s, 3H, SiC**H$_3$**), -0.14 (s, 3H, SiC**H$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 143.4, 140.9, 133.1, 130.8, 123.5, 123.2, 113.4, 103.0, 59.6, 58.1, 37.1, 25.9, 19.4, 18.3, -5.6; IR (thin film): 1717 (s), 1089 (m) cm^{-1}; HRMS (ESI) Calcd. for $C_{19}H_{29}BrNO_2Si$ [M+H+2]: 412.1151. Found: 412.1129.

Preparation of Benzyl-Protected Oxindole 130



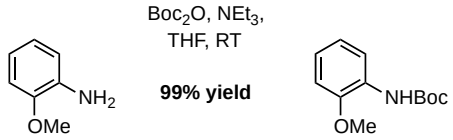
(±)-**133** (±)-**130**

Oxindole **133** (8.4 g, 20.5 mmol) was dissolved in a 10:1 solution of THF/DMF (110 mL). The solution was cooled to 0 ºC and treated with NaH (60% in mineral oil, 1.6 g, 41 mmol) in portions. After stirring at 0 ºC for 5 min, the reaction was allowed to warm to room temperature. To this was added BnBr (3.6 mL, 30.8 mmol). The reaction was stirred for an additional 4 h, at which time THF was removed in vacuo, and the residue was taken up in EtOAc (100 mL). This solution was quenched with saturated NH_4Cl solution, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over sodium sulfate, and concentrated. The residue was purified by flash chromatography (0→4% EtOAc/hexanes) to afford the benzylamide **130** as a colorless oil (10.2 g, 99% yield).

R_f = 0.27 (5% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (dd, *J* = 1.2 Hz, 8.2 Hz, 1H, **Ar**), 7.42 (m, 5H, CH_2**Ph**), 7.08 (dd, *J* = 1.2 Hz, 7.3 Hz, 1H, **Ar**), 6.92 (dd, *J* = 7.4 Hz, 8.1 Hz, 1H, **Ar**), 5.40 (AB q, J_{AB} = 16.3 Hz, 2H, C**H$_2$**Ph), 5.02 (s, 1H, C=C**H$_2$**), 4.99 (s, 1H, C=C**H$_2$**), 3.41 (ddd, *J* = 6.8 Hz,

8.2 Hz, 10.1 Hz, 1H, C**H**$_2$OTBS), 3.33 (ddd, *J* = 5.1 Hz, 8.5 Hz, 10.1 Hz, 1H, C**H**$_2$OTBS), 2.54 (ddd, *J* = 6.8 Hz, 8.4 Hz, 13.3 Hz, 1H, C**H**$_2$CH$_2$OTBS), 2.21 (ddd, *J* = 5.1 Hz, 8.2 Hz, 13.3 Hz, 1H, C**H**$_2$CH$_2$OTBS), 1.64 (s, 3H, C=CC**H**$_3$), 0.81 (s, 9H, SiC(C**H**$_3$)$_3$), -0.08 (s, 3H, SiC**H**$_3$), -0.09 (s, 3H, SiC**H**$_3$); ^{13}C NMR (100 MHz) δ 178.5, 143.8, 140.8, 138.0, 134.8, 134.1, 128.6, 127.1, 126.7, 123.8, 123.3, 113.6, 102.4, 59.6, 55.8, 44.6, 37.7, 26.0, 19.6, 18.4, -5.4; IR (thin film): 2954 (m), 2928 (m), 2856 (m), 1724 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{26}H_{35}BrNO_2Si$ [M+H+2]: 502.1600. Found: 502.1603.

Preparation of *N*-Boc Methoxyaniline 136

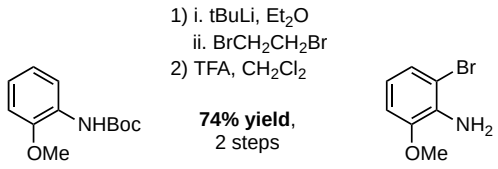


135 **136**

To a solution of 2-aminophenol **135** (5 g, 45.9 mmol) in THF (100 ml) was added Boc_2O (10.5 g, 48.7 mmol) in portions. The reaction was stirred at room temperature fro 36 hours before removing the THF. The remaining solids were dissolved in Et_2O, washed with citric acid solution and brine, dried (Na_2SO_4), and concentrated to yield the *N*-Boc methoxyaniline **136** as a light pink solid (9.5g, 99% yield).

Known compound; CAS 154150-18-2. Characterization data matched literature reports.

Preparation of 2-Bromo-6-Methoxyaniline 134



136 **134**

Directed Bromination:

To a solution of *N*-Boc methoxyaniline **136** (9 g, 40.4 mmol, azeotroped from toluene) in Et_2O (90 ml) at –30 °C was added *t*-BuLi (1.64 M in pentanes, 54 ml, 88.9 mmol). The reaction was

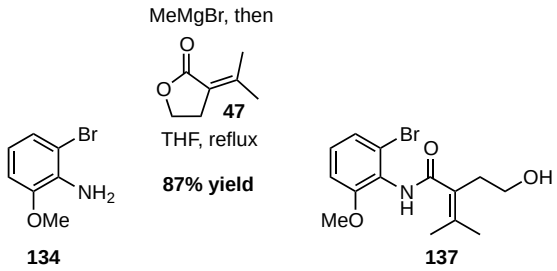
transferred to a salt/ice bath and allowed to stir for 3 hours, maintaining a bath temperature between –10 and 0 °C. Next, a solution of 1,2-dibromoethane (11.4 g, 60.6 mmol) in Et_2O (90 ml) was added to the reaction at –78 °C. This was allowed to warm to room temperature gradually. The reaction was quenched with saturated NH_4Cl solution, extracted with EtOAc, washed with water and brine, dried (Na_2SO_4), and concentrated to provide a crude solid that was triterated with hexanes to provide the desired aryl bromide as a white solid (6.5 g, 53% yield).

Boc Removal:

To a solution of the carbamate (6.5 g, 21 mmol) in CH_2Cl_2 (75 ml) cooled to 0 °C was added trifluoroacetic acid (7.8 ml, 105 mmol). This was stirred at room temperature for 24 hours. The reaction was quenched with saturated $NaHCO_3$ solution, extracted with CH_2Cl_2, washed with water and brine, dried (Na_2SO_4), concentrated, and purified by flash chromatography (10% EtOAc/hexanes) to provide the pure aniline **134** as a light yellow oil (4.0 g, 95% yield)

Known compound; CAS 5473-01-8. Characterization data matched literature reports.

Preparation of 2-Bromo-6-Methoxyanilide 137

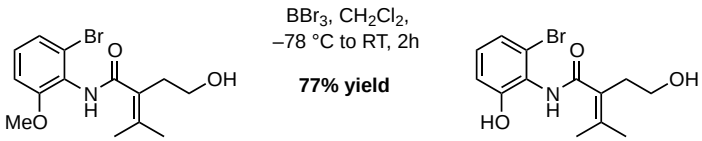


To a solution of 2-bromo-6-methoxyaniline **134** (2.4 g, 11.9 mmol, azeotroped with toluene) in THF (225 ml) cooled to 0 °C was added methylmagnesium bromide (3 M in diethyl ether, 9 ml, 26.9 mmol). The resulting solution was stirred at room temperature for 30 minutes before adding the lactone (2.28 g, 17.9 mmol). The reaction was heated to reflux for 2 hours and then stirred at room temperature for 24 hours. Another portion of methylmagnesium bromide (3 ml, 8.97 mmol) was added at that time, followed by another portion of lactone (250 mg, 1.79 mmol). This was refluxed for another 2

hours and stirred at room temperature for another 24 hours. The reaction was quenched with saturated $NaHCO_3$ solution, extracted with EtOAc, washed with water and brine, dried (Na_2SO_4), and concentrated. The resulting brown solids were purified by flash chromatography (30%→40%→50%→60%→70% EtOAc/hexanes) to provide anilide **137** as a white solid (3.4 g, 87% yield).

R_f = 0.08 (60% EtOAc/hexanes); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.82 (s, 1H, **NH**), 7.11 (dd, *J* = 8.0, 0.8 Hz, 1H, **Ar**), 7.03 (t, *J* = 8.0 Hz, 1H, **Ar**), 6.79 (dd, *J* = 7.2, 0.8 Hz, 1H, **Ar**), 3.89 (t, *J* = 5.2 Hz, 1H, **OH**), 3.75 (s, 3H, O**CH$_3$**), 3.73 (t, *J* = 5.6 Hz, 2H, **CH$_2$**OH), 2.51 (t, *J* = 5.2 Hz, 2H, **CH$_2$**CH$_2$OH), 1.96 (s, 3H, **CH$_3$**), 1.70 (s, 3H, **CH$_3$**); ^{13}C NMR (100 MHz; $CDCl_3$): δ 171.4, 156.4, 136.7, 129.4, 129.0, 124.9, 124.7, 123.5, 110.7, 61.6, 56.2, 33.5, 22.7, 20.4; IR (thin film): 3225 (br, s), 2939 (s), 1629 (s), 1516 (s), 1267 (m), 1038 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{14}H_{19}BrNO_3$ [M+H+2]: 330.0528. Found: 330.0526.

Preparation of Phenol 138



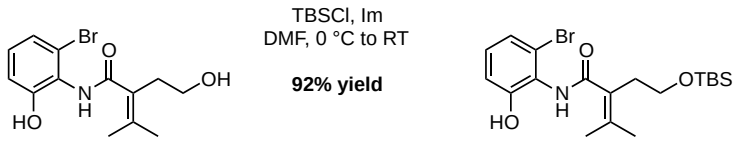
137 **138**

A solution of methoxyphenol **137** (300 mg, 0.9 mmol, azeotroped with toluene) in CH_2Cl_2 (9 ml) was cooled to –78 °C. To this was added boron tribromide (20% v/v solution in CH_2Cl_2, 0.750 ml, 1.58 mmol) dropwise. After stirring at –78 °C for 10 minutes, the resulting reaction mixture—an orange solution containing a gummy white solid—was transferred to a salt/ice bath to allow the solid to dissolve and stirring to resume. This was stirred cold for two hours, then quenched with saturated $NaHCO_3$ solution. The aqueous layer was basified to pH 11 with 5% NaOH solution and extracted with CH_2Cl_2. The aqueous layer was then acidified to pH 7 using 10% aqueous HCl solution and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na_2SO_4), and concentrated to provide **138** as a white solid which was used without further purification (220 mg, 77% yield).

R_f = 0.16 (40% EtOAc/hexanes); ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.80 (s, 1H, Ar**OH**), 9.19 (s, 1H, **NH**), 7.07 (dd, *J* = 8.0, 1.6 Hz, 1H, **Ar**), 7.03 (t, *J* = 8.0 Hz, 1H, **Ar**), 6.86 (dd, *J* = 7.6, 1.6 Hz,

1H, **Ar**), 4.74 (br s, 1H, **OH**), 3.56 (t, *J* = 7.2 Hz, 2H, **CH$_2$**OH), 2.44 (t, *J* = 7.2 Hz, 2H, **CH$_2$**CH$_2$OH), 1.91 (s, 3H, **CH$_3$**), 1.72 (s, 3H, **CH$_3$**); ^{13}C NMR (100 MHz; DMSO): δ 169.9, 155.2, 132.6, 129.5, 128.7, 124.4, 123.6, 122.5, 115.3, 60.0, 33.9, 22.3, 19.8; IR (thin film): 3230 (br, s), 1629 (s), 1586 (s), 1521 (s), 1448 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{13}H_{16}BrNO_3$ [M+H]: 314.0392. Found: 314.0392.

Preparation of *O*-TBS-Protected Alcohol 139

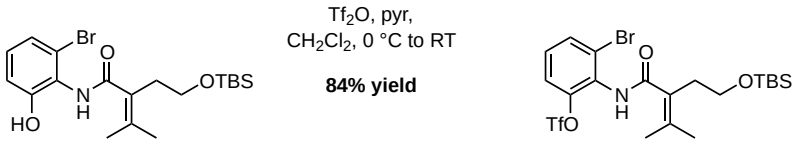


138 **139**

To a solution of diol **138** (484 mg, 1.54 mmol) in DMF (20 ml) was added imidazole (304 mg, 4.62 mmol). After cooling to 0 °C in an ice bath, tertbutyldimethylsilyl chloride (254.7 mg, 1.69 mmol) was added to the reaction. This stirred for 30 minutes at room temperature, was recooled to 0 °C in an ice bath, and a second portion of tertbutyldimethylsilyl chloride (70 mg, 0.462 mmol) was added. This was allowed to stir for another 30 minutes at room temperature, cooled again to 0 °C, and a final portion of tertbutyldimethylsilyl chloride (70 mg, 0.462 mmol) was added. The reaction was quenched cold with water and extracted with Et_2O. The Et_2O extracts were washed with water and brine, dried (Na_2SO_4), concentrated, and purified by flash chromatography (1%→2%→4%→6%→8% EtOAc/hexanes) to provide **139** as a light yellow oil (605 mg, 92% yield).

R_f = 0.33 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.26 (s, 1H, Ar**OH**), 8.95 (br s, 1H, **NH**), 7.14 (t, *J* = 4.7 Hz, 1H, **Ar**), 7.02-7.01 (m, 2H, **Ar**), 3.86 (t, *J* = 6.0 Hz, 2H, **CH$_2$**O), 2.71 (t, *J* = 6.0 Hz, 2H, **CH$_2$**CH$_2$O), 2.04 (s, 3H, **CH$_3$**), 1.85 (s, 3H, **CH$_3$**), 0.84 (s, 9H, SiC**(CH$_3$)$_3$**), 0.02 (s, 6H, Si**(CH$_3$)$_2$**); ^{13}C NMR (100 MHz; $CDCl_3$) δ 172.1, 151.8, 142.1, 128.0, 127.7, 125.2, 124.5, 120.0, 117.6, 62.6, 33.3, 26.0, 23.2, 21.4, 18.6, -5.3; IR (thin film): 3250 (br, w), 2929 (s), 1647 (m), 1468 (s), 1312 (m), 1256 (m), 1086 (m), cm^{-1}; HRMS (ESI) Calcd. for $C_{19}H_{30}BrNO_3Si$ [M+H]: 430.1233. Found: 430.1239.

Preparation of Triflate 131b

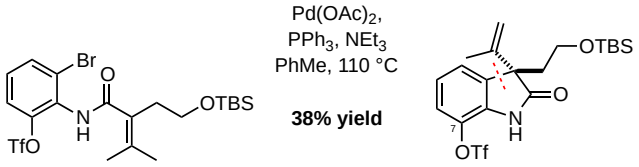


139 **131b**

A solution of phenol **139** (560 mg, 1.3 mmol, azeotroped with toluene) in CH_2Cl_2 (50 ml) was cooled to 0 °C in an ice bath. To this was added pyridine (0.315 ml, 3.9 mmol) and trifluoromethanesulfonic anhydride (0.328 ml, 1.95 mmol). A white precipitate emerged briefly and then disappeared. The solution was stirred at 0 °C for 30 minutes and then at room temperature for another 15 minutes. The reaction was quenched in an ice bath with saturated NH_4Cl solution and extracted with CH_2Cl_2. The organic extracts were washed with water and brine, dried (Na_2SO_4) and concentrated. The orange residue was purified by column chromatograpy (1%→2%→3%→4%→6% EtOAc/Hexanes) to provide **131b** as a white solid (614 mg, 84% yield).

R_f = 0.13 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.18 (s, 1H, **NH**), 7.63 (dd, *J* = 8.0, 1.4 Hz, 1H, **Ar**), 7.29 (dd, *J* = 8.3, 1.1 Hz, 1H, **Ar**), 7.21 (t, *J* = 8.2 Hz, 1H, **Ar**), 3.92 (t, *J* = 5.4 Hz, 2H, OC**H$_2$**), 2.69 (t, *J* = 5.4 Hz, 2H, OCH$_2$**CH$_2$**), 2.01 (s, 3H, **CH$_3$**), 1.80 (s, 3H, **CH$_3$**), 0.86 (s, 9H, **TBS**), 0.05 (s, 6H, **TBS**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.65, 146.76, 141.51, 132.86, 130.75, 128.91, 128.27, 124.25, 121.27, 120.21, 117.02, 64.10, 32.67, 26.12, 22.49, 21.02, 18.63, -5.55; IR (thin film): 3233 (br, m), 2931 (s), 1682 (s), 1427 (s), 1214 (s), 1142 (s), 918 (s), 837 (m) cm^{-1}; HRMS (ESI) Calcd. for $C_{20}H_{30}BrF_3NO_5SSi$ [M+H+2]: 562.0749. Found: 562.0721.

Preparation of C7-Triflate-Oxindole 140

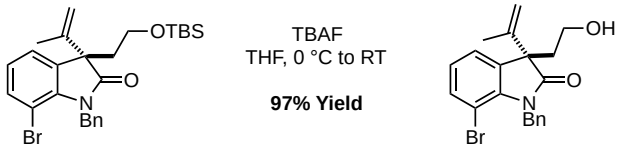


131b (±)-**140**

To a solution of aryl bromide **131b** (50 mg, 0.0892 mmol, azeotroped with toluene) in toluene (1.5 ml) was added $Pd(OAc)_2$ (1 mg, 0.0045 mmol, 5 mol%), PPh_3 (3.5 mg, 0.0134 mmol, 15 mol%), and Et_3N (62 μl, 0.446 mmol). This stirred at room temperature for 30 minutes and was then heated to reflux for 24 hours. After cooling to room temperature, the reaction was concentrated and purified by flash chromatography (0.5%→1%→2%→3%→4% EtOAc/hexanes) to provide the aryl triflate **140** (14 mg, 38% yield).

R_f = 0.36 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.78 (br s, 1H, **NH**), 7.20 (dd, *J* = 6.9, 2.6 Hz, 1H, **Ar**), 7.09 (m, 2H, **Ar**), 5.03 (d, *J* = 1.1 Hz, 1H, **CH$_2$**Ph), 4.99 (s, 1H, **CH$_2$**Ph), 3.41 (d, *J* = 5.7 Hz, 1H, OC**H$_2$**), 3.39 (d, *J* = 5.7 Hz, 1H, OC**H$_2$**), 2.52 (dt, *J* = 13.5, 7.7 Hz, 1H, OCCH$_2$**CH$_2$**), 2.19 (dt, *J* = 13.5, 5.7 Hz, 1H, OCCH$_2$**CH$_2$**), 1.66 (s, 3H, **CH$_3$**), 0.77 (s, 9H, ***t*-Bu**), -0.12 (s, 3H, **CH$_3$**), -0.13 (s, 3H, **CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.40, 142.86, 135.25, 133.74, 132.45, 124.40, 123.20, 121.11, 120.36, 113.91, 59.50, 57.08, 37.21, 25.94, 19.37, 18.37, -5.58, -5.62; IR (thin film): 2930 (m), 1727 (s), 1635 (m), 1419 (s), 1205 (s), 1136 (s), 803 (m) cm^{-1}; HRMS (ESI) Calcd. for $C_{20}H_{29}F_3NO_5SSi$ [M+H]: 480.1488. Found: 480.1475.

Preparation of Alcohol 141



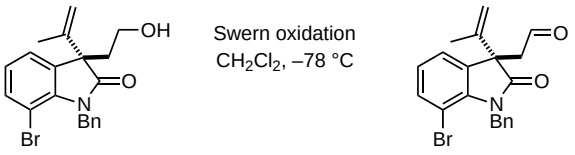
(±)-**130** (±)-**141**

To a solution of silyl ether **130** (12.6 g, 25 mmol) in THF (125 mL) at 0 ºC was added TBAF (1.0 M in THF, 30 mL, 30 mmol). The reaction mixture was stirred at room temperature for 4 h and

quenched by saturated NH_4Cl solution. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with water and brine, dried, and concentrated. The residue was purified by flash chromatography (10→50% EtOAc/hexanes) to provide alcohol **141** as a colorless oil which solidified upon standing (9.4 g, 97%).

R_f = 0.13 (30% EtOAc/hexanes); m.p. 84-87 ºC ($CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 1.2 Hz, 8.1 Hz, 1H, **Ar**), 7.27 (m, 5H, CH_2**Ph**), 7.08 (dd, *J* = 1.2 Hz, 7.3 Hz, 1H, **Ar**), 6.93 (dd, *J* = 7.3 Hz, 8.1 Hz, 1H, **Ar**), 5.40 (s, 2H, C**H**$_2$Ph), 5.06 (s, 1H, C=C**H**$_2$), 5.02 (s, 1H, C=C**H**$_2$), 3.52 (m, 1H, C**H**$_2$OH), 3.42 (m, 1H, C**H**$_2$OH), 2.55 (ddd, *J* = 6.9 Hz, 6.9 Hz, 13.9 Hz, 1H, C**H**$_2$$CH_2$OH), 2.19 (ddd, *J* = 5.7 Hz, 6.2 Hz, 13.9 Hz, 1H, C**H**$_2$$CH_2$OH), 1.63 (s, 3H, H_2C=CC**H**$_3$); ^{13}C NMR (100 MHz) δ 179.5, 143.1, 140.7, 137.7, 134.7, 134.3, 128.5, 127.1, 126.6, 124.0, 123.0, 113.9, 102.6, 59.1, 56.0, 44.9, 37.6, 19.6; IR (thin film): 3430 (br s), 1717 (s), 1450 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{20}H_{21}BrNO_2$ [M+H]: 386.0756. Found: 386.0748.

Preparation of Aldehyde 142

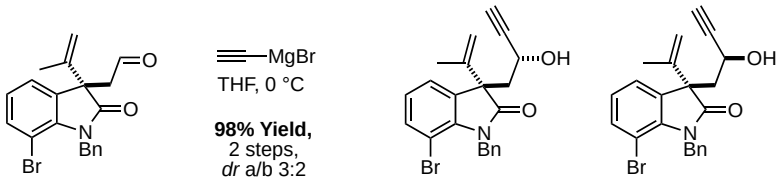


(±)-**141** (±)-**142**

To a solution of DMSO (17.9 mL, 344.8 mmol) in CH_2Cl_2 (300 mL) at –78 ºC was added oxalyl chloride (19.9 mL, 172.4 mmol) dropwise. Over the course of one hour, a solution of the alcohol (**141**) (33.3 g, 86.2 mmol) in CH_2Cl_2 (400 mL) was added plus 100 mL of rinse. Then, NEt_3 (60 mL, 431 mmol) was added. This stirred for an additional 30 minutes at –78 ºC, then at room temperature for another 2 h. The reaction was quenched with saturated $NaHCO_3$ solution and the aqueous was extracted with CH_2Cl_2. The combined organics were washed with water and brine, dried (Na_2SO_4), and concentrated to give the crude aldehyde as a light yellow oil (33.1 g). The aldehyde was used in the next step without further purification. For characterization purposes, purification by flash chromatography (10→30% EtOAc/hexanes) provided pure **142** as a colorless oil.

R_f = 0.24 (20% EtOAc/hexane; stains blue-green w/ anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H, C**H**O), 7.39 (dd, *J* = 1.1 Hz, 8.2 Hz, 1H **Ar**), 7.34-7.23 (m, 5H, CH_2**Ph**), 7.06 (dd, *J* = 0.8 Hz, 7.4 Hz, 1H, **Ar**), 9.92 (dd, *J* = 7.8 Hz, 7.8 Hz, 1H, **Ar**), 5.44 (AB q, J_{AB} = 16.4 Hz, 2H, C**H$_2$**Ph), 5.08 (s, 1H, C=C**H$_2$**), 4.96 (s, 1H, C=C**H$_2$**), 3.31 (dd, *J* = 0.7 Hz, 17.4 Hz, 1H, C**H$_2$**CHO), 3.13 (dd, *J* = 1.9 Hz, 17.4 Hz, 1H, C**H$_2$**CHO), 1.65 (s, 3H, C=CC**H$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 178.0, 142.3, 141.0, 137.7, 134.7, 133.9, 128.6, 127.2, 126.7, 124.1, 122.8, 114.5, 102.8, 53.9, 48.1, 45.1, 19.4; IR (thin film): 1727 (s), 1424 (s), 1345 (s), 1163 (s), cm^{-1}; HRMS (ESI) Calcd. for $C_{20}H_{19}BrNO_2$ [M+H+2]: 386.0599. Found: 386.0578.

Preparation of Alkynes 143a and 143b



(±)-**142** (±)-**143a** (±)-**143b**

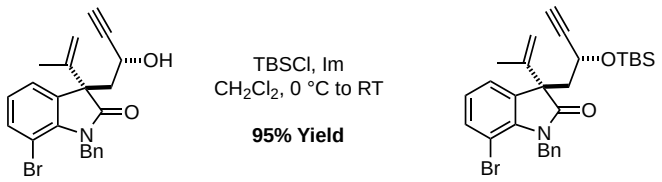
A reaction flask was charged with ethynylmagnesium bromide (0.5 M in THF, 375 mL, 187.5 mmol) and cooled to 0 ºC. A solution of crude **142** (36.2 g, 94 mmol, azeotropically dried with toluene) dissolved in THF (550 mL), was added to the flask using an addition funnel over the course of 2 h. Following the addition, the reaction was stirred for an additional 2 h at room temperature. This was quenched with saturated NH_4Cl solution and the aqueous portion extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (5%→15%→40% Et_2O/hexanes) to provide the β-OH diastereomer (**143a**) (24.5 g, 63% yield), as a colorless solid (which could be triterated in 20% EtOAc/hexanes to provide a free-flowing solid) and the α-OH diastereomer (**143b**) (13.6 g, 35% yield), as a colorless foam.

β-OH diastereomer 143a: R_f = 0.27 (10% EtOAc/toluene; stains purple w/ anisaldehyde); m.p.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 1.2 Hz, 8.1 Hz, 1H, **Ar**), 7.28–7.17 (m, 5H, CH_2**Ph**), 7.03 (dd, *J* = 1.2 Hz, 7.3 Hz, 1H, **Ar**), 6.91 (dd, *J* = 7.4 Hz, 8.1 Hz, 1H, **Ar**), 5.32 (AB q, J_{AB} = 16.9 Hz, 2H, C**H$_2$**Ph), 4.99 (s, 1H, C=C**H$_2$**), 4.92 (s, 1H, C=C**H$_2$**), 3.97 (dddd, *J* = 2.2 Hz, 3.5 Hz, 8.3 Hz,

10.6 Hz, 1H, C**H**OH), 2.80 (dd, *J* = 10.7 Hz, 14.2 Hz, 1H, C**H**$_2$CHOH), 2.38 (dd, *J* = 3.5 Hz, 14.2 Hz, 1H, C**H**$_2$CHOH), 2.33 (d, *J* = 2.2 Hz, 1H, C≡C**H**), 2.08 (d, *J* = 8.3, 1H, O**H**), 1.63 (s, 3H, C=CC**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 143.5, 141.5, 138.0, 134.5, 133.4, 128.4, 127.0, 126.7, 123.7, 123.4, 113.8, 102.8, 84.3, 73.2, 59.5, 55.6, 45.1, 42.6, 19.5; IR (thin film): 3435 (br m), 3296 (m), 1708 (s), 1452 (s), 1347 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{20}BrNNaO_2$ [M+Na+2]: 434.0575. Found: 434.0549.

α-OH diastereomer 143b: R_f = 0.2 (10% EtOAc/toluene); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 1.0 Hz, 8.1 Hz, 1H, **Ar**), 7.33–7.23 (m, 5H, CH_2**Ph**), 7.12 (dd, *J* = 1.0 Hz, 7.4 Hz, 1H, **Ar**), 6.94 (dd, *J* = 7.5 Hz, 8.1 Hz, 1H, **Ar**), 5.42 (AB q, J_{AB} = 16.4 Hz, 2H, C**H**$_2$Ph), 5.12 (s, 1H, C=C**H**$_2$), 5.06 (s, 1H, C=C**H**$_2$), 4.56 (m, 1H, C**H**OH), 3.02 (d, *J* = 4.3 Hz, 1H, O**H**), 2.70 (dd, *J* = 3.9 Hz, 14.6 Hz, 1H, C**H**$_2$COH) 2.41 (d, *J* = 2.1, 1H, C≡C**H**), 2.29 (dd, *J* = 8.1 Hz, 14.6 Hz, 1H, C**H**$_2$COH), 1.67 (s, 3H, C=CC**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.4, 142.2, 140.2, 137.3, 134.8, 134.5, 128.6, 127.2, 126.6, 124.2, 123.1, 114.7, 102.7, 84.2, 73.4, 59.6, 56.1, 44.9, 42.7, 19.8; IR (thin film): 3423 (br m), 3295 (m), 1712 (s), 1451 (s), 1355 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{20}BrNNaO_2$ [M+Na]: 432.0575. Found: 432.0566.

Preparation of Enyne 144a

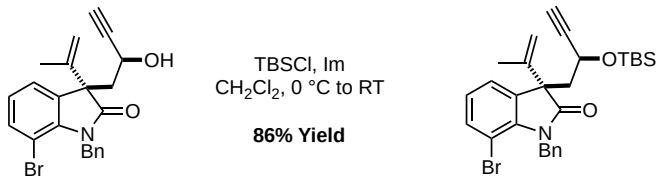


(±)-**143a** (±)-**144a**

To a solution of **143a** (24.5 g, 60 mmol) in CH_2Cl_2 (300 mL) was added imidazole (6.1 g, 89.6 mmol). The solution was cooled to 0 ºC in an ice bath before adding TBSCl (9.9 g, 65.7 mmol). The reaction was allowed to warm to room temperature overnight (12 h) and a white precipitate emerged. The reaction was diluted with CH_2Cl_2 and quenched with saturated NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with saturated $NaHCO_3$ solution, water, and brine; dried (Na_2SO_4); and concentrated. The residue was purified by flash chromatography (2%→10%→25%→50% EtOAc/hexanes) to provide the pure silyl alcohol (**144a**) as a colorless oil which solidified upon standing (29.7 g, 95%).

R_f = 0.52 (5% EtOAc/toluene); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 1.1 Hz, 8.1 Hz, 1H, **Ar**), 7.21–7.31 (m, 5H, CH_2**Ph**), 7.10 (dd, *J* = 1.1 Hz, 7.3 Hz, 1H, **Ar**), 6.92 (dd, *J* = 7.7 Hz, 7.7 Hz, 1H, **Ar**), 5.41 (AB q, J_{AB} = 16.5 Hz, 2H, C**H$_2$**Ph), 5.98 (s, 1H, C=C**H$_2$**), 4.87 (s, 1H, C=C**H$_2$**), 4.17 (ddd, *J* = 2.1 Hz, 6.0 Hz, 7.9 Hz, 1H, C**H**OTBS), 2.84 (dd, *J* = 7.9 Hz, 13.7 Hz, 1H, C**H$_2$**COTBS), 2.40 (dd, *J* = 6.0 Hz, 13.7 Hz, 1H, C**H$_2$**COTBS), 2.22 (d, *J* = 2.1, 1H, C≡C**H**), 1.73 (s, 3H, C=CC**H$_3$**), 0.85 (s, 9H, SiC(C**H$_3$**)$_3$), 0.03 (s, 3H, Si(C**H$_3$**)$_2$), -0.07 (s, 3H, Si(C**H$_3$**)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 144.3, 141.2, 138.0, 134.2, 133.7, 128.5, 127.1, 126.7, 124.1, 123.4, 113.6, 102.7, 84.6, 73.6, 60.1, 55.5, 44.5, 43.0, 25.9, 19.3, 18.2, -4.4, -4.8; IR (thin film): 1725 (s), 1453 (s), 1119 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{28}H_{34}BrNO_2Si$ [M+H+2]: 526.1620. Found: 526.1598.

Preparation of Enyne 144b



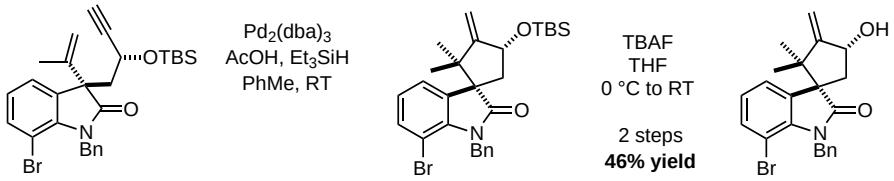
(±)-**143b** (±)-**144b**

To a solution of **143b** (13.6 g, 33 mmol) in CH_2Cl_2 (165 mL) was added imidazole (3.4 g, 49.7 mmol). The solution was cooled to 0 ºC in an ice bath before adding TBSCl (5.5 g, 36.5 mmol). The reaction was allowed to warm to room temperature overnight (12 h) and a white precipitate emerged. The reaction was diluted with CH_2Cl_2 and quenched with saturated NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with saturated $NaHCO_3$ solution, water, and brine; dried (Na_2SO_4); and concentrated. The residue was purified by flash chromatography (2%→10%→25%→50% EtOAc/hexanes) to provide the pure silyl alcohol (**144b**) as a colorless oil which solidified upon standing (14.8 g, 86%).

R_f = 0.45 (5% EtOAc/toluene); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 1.1 Hz, 8.1 Hz, 1H, **Ar**), 7.30–7.19 (m, 5H, CH_2**Ph**), 7.08 (dd, *J* = 1.1 Hz, 7.3 Hz, 1H, **Ar**), 6.90 (dd, *J* = 7.5 Hz, 8.1 Hz, 1H, **Ar**), 5.35 (s, 2H, C**H$_2$**Ph), 4.97 (s, 1H, C=C**H$_2$**), 4.90 (s, 1H, C=C**H$_2$**), 4.13 (ddd, *J* = 2.1 Hz, 6.1 Hz, 7.1 Hz, 1H, C**H**OTBS), 2.71 (dd, *J* = 7.1 Hz, 13.7 Hz, 1H, C**H$_2$**COTBS), 2.44 (dd, *J* = 6.1 Hz, 13.7 Hz, 1H,

C**H**$_2$COTBS), 2.28 (d, *J* = 2.1, 1H, C≡C**H**), 1.6 (s, 3H, C=CC**H**$_3$), 0.80 (s, 9H, SiC(C**H**$_3$)$_3$), 0.00 (s, 3H, Si(C**H**$_3$)$_2$), -0.01 (s, 3H, Si(C**H**$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 144.0, 140.9, 137.9, 134.3, 134.2, 128.5, 127.1, 126.9, 123.7, 113.7, 102.6, 84.6, 73.8, 60.2, 55.6, 44.7, 43.1, 25.9, 19.6, 18.2, -4.4, -4.9; IR (thin film): 1720 (s), 1451 (s), 1161 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{28}H_{34}BrNO_2Si$ [M+H+2]: 526.1620. Found: 526.1593.

Preparation of Spiro-oxindole 146a



(±)-**144a** (±)-**145a** (±)-**146a**

Enyne Cyclization:

To a solution of the β-*O*-TBS enyne diastereomer **144a** (22.1 g, 42.1 mmol) dissolved in toluene (2.1 L) was added $Pd_2(dba)_3$ (1.65 g, 1.6 mmol) and acetic acid (4.8 mL, 84.2 mmol) to produce a deep purple colored solution. Next was added Et_3SiH (6.7 mL, 42.1 mmol), dropwise over the course of 15 h, using a syringe pump. The color of the solution gradually changed from purple to red and then back to purple. At this time the solution was filtered through a silica plug which was subsequently rinsed with 1% EtOAc/hexanes. The filtrate was concentrated to provide the crude β-silyl alcohol (16.5 g) as a colorless oil, used in the next step without further purification.

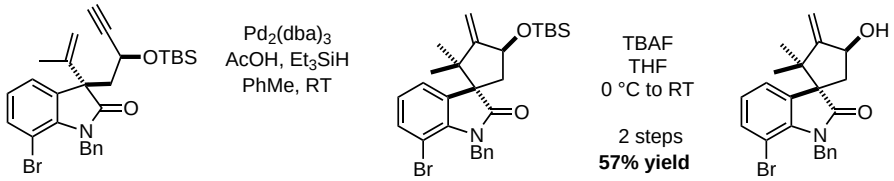
TBS-Removal:

To a solution of the β-silyl alcohol (16.5 g, 31.3 mmol) in THF (150 mL) at 0 ºC was added TBAF (1 M in THF, 37.6 mL, 37.6 mmol). The reaction was allowed to stir at room temperature for 5 hours. The solution was diluted with EtOAc (100 mL) and quenched with saturated NH_4Cl solution. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography

(1%→5%→8% EtOAc/toluene) to provide the pure β-alcohol **146a** as a colorless solid (8 g, 46% yield over 2 steps).

R_f = 0.22 (20% EtOAc/hexane, stains pink with anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.2 Hz, 1H, **Ar**), 7.29–7.17 (m, 5H, CH_2**Ph**), 7.14 (d, *J* = 7.4 Hz, 1H, **Ar**), 6.91 (dd, *J* = 7.7 Hz, 7.7 Hz, 1H, **Ar**), 5.46 (d, *J* = 1.6 Hz, 1H, C=C**H$_2$**), 5.36 (AB q, J_{AB} = 16.4 Hz, 2H, C**H$_2$**Ph), 5.07 (d, *J* = 1.9, 1H, C=C**H$_2$**), 4.77 (m, 1H, C**H**OH), 4.22 (d, *J* = 11.9, 1H, O**H**), 2.61 (dd, *J* = 8.0 Hz, 14.8 Hz, 1H, C**H$_2$**COH), 2.04 (d, *J* = 14.8 Hz, 1H, C**H$_2$**COH), 1.10 (s, 3H, CC**H$_3$**), 0.88 (s, 3H, CC**H$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.7, 162.6, 141.1, 137.3, 134.4, 132.2, 128.6, 127.2, 126.6, 124.4, 123.4, 110.2, 102.6, 72.3, 60.1, 50.8, 44.7, 41.7, 27.8, 21.9; IR (thin film): 3454 (br s), 1695 (s), 1452 (s) 1123 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{23}BrNO_2$ [M+H]: 412.0912. Found: 412.0903.

Preparation of Spiro-oxindole 146b



(±)-**144b** (±)-**145b** (±)-**146b**

Enyne Cyclization:

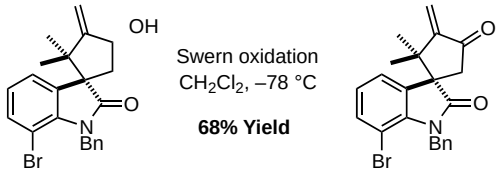
To a solution of the α-*O*-TBS enyne diastereomer **144b** (14.8 g, 28 mmol) dissolved in toluene (2.8 L) was added $Pd_2(dba)_3$ (725 mg, 0.7 mmol) and acetic acid (3.2 mL, 56 mmol) to produce a deep purple colored solution. Next was added Et_3SiH (4.5 mL, 28 mmol), dropwise over the course of 4 h, using a syringe pump. The color of the solution gradually changed from purple to red to orange. At this time the toluene was removed in vacuo, and the crude residue was filtered through a silica plug (1%→2% EtOAc/hexanes) to provide the α-silyl alcohol (10.7 g) as a colorless oil, used in the next step without further purification.

TBS-Removal:

To a solution of the α-silyl alcohol (10.7 g, 20.3 mmol) in THF (100 mL) at 0 ºC was added TBAF (1 M in THF, 24.4 mL, 24.4 mmol). The reaction was allowed to stir at room temperature over night (12 h). The red solution was diluted with EtOAc (100 mL) and quenched with saturated NH_4Cl solution. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (5%→10%→20%→25% EtOAc/hexanes) to provide the pure α-alcohol **146b** as a colorless foam (6.6 g, 57% yield over 2 steps).

R_f = 0.13 (20% EtOAc/hexane, stains pink with anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.36 (dd, *J* = 0.9 Hz, 8.2 Hz, 1H, **Ar**), 7.30–7.2 (m, 6H, CH_2**Ph** and **Ar**), 6.90 (dd, *J* = 7.9 Hz, 7.9 Hz, 1H, **Ar**), 5.39 (AB q, J_{AB} = 16.4 Hz, 2H, C$\mathbf{H_2}$Ph), 5.33 (d, *J* = 1.7 Hz, 1H, C=C$\mathbf{H_2}$), 5.22 (ddd, *J* = 1.7 Hz, 6.5 Hz, 8.3 Hz, 1H, C**H**OH), 5.06 (d, *J* = 2.0, 1H, C=C$\mathbf{H_2}$), 2.59 (dd, *J* = 8.4 Hz, 13.8 Hz, 1H, C$\mathbf{H_2}$COH), 2.48 (br s, 1H, O**H**), 2.13 (dd, *J* = 6.5 Hz, 13.8 Hz, 1H, C$\mathbf{H_2}$COH), 1.14 (s, 3H, CC$\mathbf{H_3}$), 0.97 (s, 3H, CC$\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 161.8, 140.8, 137.8, 134.1, 133.3, 128.5, 127.1, 126.7, 124.6, 123.2, 108.4, 102.2, 72.2, 59.0, 49.0, 44.5, 41.6, 27.2, 23.7; IR (thin film): 3439 (br s), 1712 (s), 1450 (s), 1121 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{23}BrNO_2$ [M+H]: 412.0912. Found: 412.0906.

Preparation of Bromoenone 37



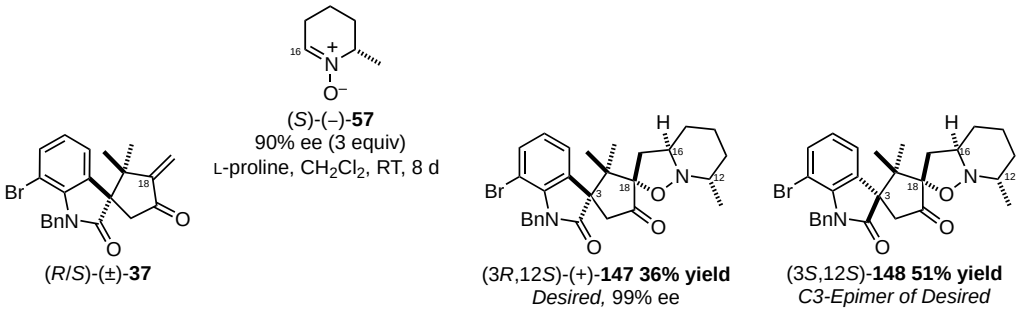
(±)-**146a/b** (±)-**37**

To a solution of DMSO (16.8 mL, 236 mmol) in CH_2Cl_2 (300 mL) at –78 ºC was added oxalyl chloride (10 mL, 118 mmol) dropwise. To this was added a solution containing the β-OH diastereomer **146a** (17.7 g, 43 mmol) and the α-OH diastereomer **146b** (6.6 g, 16 mmol) in CH_2Cl_2 (500 mL) over the course of one hour. Then, NEt_3 (41 mL, 295 mmol) was added. This stirred for an additional 30 minutes at –78 ºC, then at room temperature for another 2 h. The reaction was quenched with saturated NH_4Cl solution and the aqueous layer was extracted with CH_2Cl_2. The combined organics were washed

with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by recrystallization from EtOAc to provide the pure ketone as a light yellow solid (16.4 g, 68% yield).

R_f = 0.34 (20% EtOAc/hexane, does not stain with anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 1.1 Hz, 8.2 Hz, 1H, **Ar**), 7.32–7.22 (m, 5H, CH_2**Ph**), 7.11 (dd, *J* = 1.1 Hz, 7.5 Hz, 1H, **Ar**), 6.91 (dd, *J* = 7.8 Hz, 7.8 Hz, 1H, **Ar**), 6.18 (s, 1H, C=**C**$\mathbf{H_2}$), 5.39 (AB q, J_{AB} = 16.3 Hz, 2H, **C**$\mathbf{H_2}$Ph), 5.27 (s, 1H, C=**C**$\mathbf{H_2}$), 2.81 (AB q, J_{AB} = 18.2 Hz, 2H, **C**$\mathbf{H_2}$CO), 1.15 (s, 6H, C**C**$\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 179.2, 152.6, 141.0, 137.4, 134.7, 132.2, 128.6, 127.2, 126.7, 123.8, 123.6, 116.7, 102.7, 54.7, 47.9, 44.8, 44.7, 26.4, 23.8; IR (thin film): 1729 (s), 1451 (s), 1122 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{21}BrNO_2$ [M+H+2]: 412.0756. Found: 412.0729.

Preparation of Bromo-Isoxazolidines (+)-147 and 148



To a flask containing non-racemic nitrone hydroxylamine precursor (1.2 g, 6.34 mmol) was added 2M HCl solution (12 ml). The mixture was vigorously stirred at room temperature for 25 min, diluted with 12 ml of H_2O and slowly quenched with solid Na_2CO_3 (1.3 g). The solution was extracted with $CHCl_3$ (25 ml, five times) and the combined organic layers were dried (Na2SO4) and concentrated to yield the nitrone (*S*)-(–)-**57**, which was immediately used in the cycloaddition reaction.

To a solution of racemic enone (2.6 g, 6.34 mmol) in CH_2Cl_2 (18 ml) was added L-proline (730 mg, 6.34 mmol) and a solution of freshly prepared nitrone in CH_3CN (18 ml). After stirring for 3.5 d, another portion of nitrone (prepared in the same manner) in CH_3CN (3 ml) was added. After stirring for 3.5 d, another portion of nitrone (freshly prepared form 600 mg of the hydroxylamine precursor) in CH_2Cl_2 (3 ml) was added. After stirring for 2 d, the reaction was quenched with saturated NaHCO3 solution, extracted with EtOAc, concentrated and purified by flash chromatography (10%→20%→30%→40%

EtOAc/hexanes) to provide 1.7 g of the undesired diastereomer (51% yield) and the more polar diastereomer, which was purified by a second flash chromatography (5%→10%→15%→20% EtOAc/ CH_2Cl_2) to provide 1.2 g (36% yield) of the desired diastereomer.

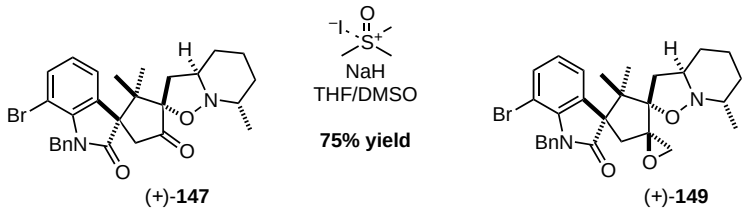
Isoxazolidine (+)-**147:** R_f = 0.27 (40% EtOAc/hexanes); $[\alpha]_D^{22}$ +160.4 (*c* 1.8, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.4 Hz, 1H, **Ar**), 7.27~7.17 (m, 5H, CH_2**Ph**), 6.92 (d, *J* = 7.2 Hz, 1H, **Ar**), 6.81 (dd, *J* = 7.2 Hz, 8.4 Hz, 1H, **Ar**), 5.34 (AB system, *J* = 16.4 Hz, 2H, **CH_2**Ph), 3.44 (m, 1H, N**CH**), 3.22 (d, *J* = 18.8 Hz, 1H, **CH_2**C=O), 3.18 (m, 1H, N**CH**), 2.52 (d, *J* = 12.0 Hz, 1H, NCH**CH_2**), 2.50 (d, *J* = 18.8 Hz, 1H, CC**H**$_2$C=O), 2.12 (dd, *J* = 6.0 Hz, 12.0 Hz, 1H, NCH**CH_2**), 1.94 (m, 1H, NCH**CH2**), 1.85 (m, 1H, NCH**CH2**), 1.63 (m, 1H, NCHCH_2**CH_3**), 1.44 (m, 2H, NCH**CH2**), 1.18 (m, 1H, NCHCH_2**CH_3**), 1.15 (s, 3H, C**CH_3**), 1.12 (d, *J* = 5.6 Hz, 3H, CH**CH_3**), 0.77 (s, 3H, C**CH_3**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.1, 178,6, 140.9, 137.4, 134.7, 134.4, 128.4, 127.0, 126.6, 123.2, 122.5, 102.3, 92.5, 61.7, 55.6, 54.2, 49.3, 44.9, 43.1, 39.0, 32.7, 25.2, 20.7 (two carbons), 20.1, 18.8; IR (thin film): 1724 (s), 1450 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{28}H_{32}BrN_2O_3$ [M+H]: 525.1576. Found: 525.1563.

The ee of the product was analyzed by chiral HPLC. Analytic chiral HPLC was performed on a Chiralpak AD-H column (250×4.6 mm), λ = 220 nm, hexane/2-propanol = 95/5, flow rate = 1.0 ml/min. Under these conditions, the racemic mixture gave the following peaks: R_t = 12.44 min and R_t = 19.02 min. Racemic sample was prepared by reacting (±)-enone with (±)-nitrone (prepared according to the literature procedure).

Isoxazolidine 148: R_f = 0.55 (50% EtOAc/hexanes); $[\alpha]_D^{22}$ = not obtained; ^{1}H NMR (400 MHz; CDCl3) δ 7.48 (d, *J* = 7.5 Hz, 1H, **Ar**), 7.38 (d, *J* = 8.2 Hz, 1H, **Ar**), 7.33~7.21 (m, 5H, CH_2**Ph**), 6.93 (t, *J* = 7.9 Hz, 1H, **Ar**), 5.41 (d, *J* = 16.4 Hz, 1H, C**H**$_2$Ph), 5.37 (d, *J* = 16.4 Hz, 1H, C**H**$_2$Ph), 3.51 (m, 1H, N**CH**), 3.22 (m, 1H, N**CH**), 2.89 (d, *J* = 19.0 Hz, 1H, O=C**CH_2**), 2.80 (d, *J* = 19.0 Hz, 1H, O=C**CH_2**), 2.65 (t, *J* = 13.1 Hz, 1H, NCH**CH_2**), 2.36 (dd, *J* = 13.4, 5.9 Hz, 1H, NCH**CH_2**), 2.03-1.89 (m, 2H, NCH**CH_2**), 1.67 (d, *J* = 13.9 Hz, 1H, NCH**CH_2**), 1.49 (m, *J* = 7.2, 3.5 Hz, 2H, NCH**CH_2CH_3**), 1.24 (m, 1H, NCHCH-$_2$**CH_3**), 1.17 (d, *J* = 5.8 Hz, 3H, CH**CH_3**), 1.06 (s, 3H, C**CH_3**), 0.98 (s, 3H, C**CH_3**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.52, 180.85, 141.08, 137.53, 134.58, 133.34, 128.66, 127.27, 126.58, 125.85, 123.52, 102.27, 93.39, 62.11, 55.28, 54.93, 48.61, 44.96, 43.65, 37.29, 33.04, 25.58, 21.55, 20.81, 20.52, 18.92; IR (thin

film): 2934 (s), 1716 (s), 1601 (m), 1450 (s), 1348 (m), 1120 (m), 754 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{28}H_{32}BrN_2O_3$ [M+H]: 525.1576. Found: 525.1575.

Preparation of Spiro-epoxide (+)-149

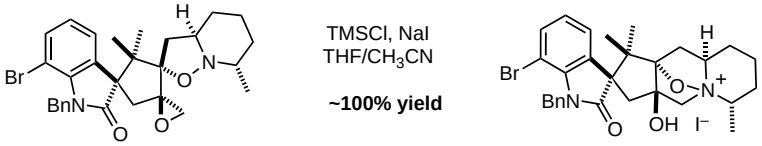


(+)-**147** (+)-**149**

To a mixture of trimethylsulfoxonium iodide (1.46 g, 6.65 mmol) and NaH (60% in mineral oil, 266 mg, 6.65 mmol) was added DMSO (15 ml). After stirring for 45 min, to the resulting homogenous solution was added a solution of the ketone (1.16 g, 2.22 mmol, azeotropically dried with toluene) in THF (10 ml) followed by 8 ml of rinse. The reaction mixture was stirred at ambient temperature for 30 h, cooled to 0 ºC, and quenched with saturated $NaHCO_3$ solution (30 ml). The mixture was diluted with H_2O (20 ml) and the aqueous layer was extracted with EtOAc (30 ml×3). The combined organic layers were concentrated in vacuo and purified by flash chromatography (10%→20%→30%→40% EtOAc/hexanes) to provide 880 mg (75% yield) of the desired product as a white foam.

R_f = 0.29 (40% EtOAc/hexanes); $[\alpha]_D^{22}$ +165.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35~7.20 (m, 7H), 6.90 (dd, *J* = 8.0 Hz, 8.0 Hz, 1H), 5.35 (s, 2H), 3.51 (m, 1H), 3.25 (d, *J* = 5.2 Hz, 1H), 3.03 (d, *J* = 5.2 Hz, 1H), 2.75 (m, 1H), 2.55 (dd, *J* = 12.4 Hz, 12.8 Hz, 1H), 2.43 (d, *J* = 14.8 Hz, 1H), 2.35 (dd, *J* = 6.0 Hz, 12.0 Hz, 1H), 2.28 (d, *J* = 14.8 Hz, 1H), 1.91 (m, 2H), 1.62 (m, 1H), 1.47 (m, 2H), 1.27 (m, 1H), 1.20 (br s, 3H), 1.12 (d, *J* = 5.6 Hz, 3H), 0.73 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6, 140.9, 137.5, 136.3, 133.9, 128.4, 126.9, 126.4, 123.6, 122.5, 102.1, 91.3, 65.3, 60.0, 55.57, 55.45, 55.38, 49.7, 44.6, 36.4, 35.6, 32.8, 25.6, 23.7, 21.3, 20.9, 18.5; IR (thin film): 1722 (s), 1601 (m), 1451 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{29}H_{34}BrN_2O_3$ [M+H]: 537.1753. Found: 537.1747.

Preparation of Ammonium Salt (+)-150

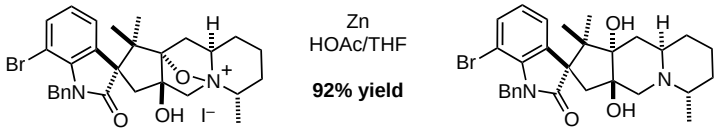


(+)-**149** (+)-**150**

To a solution of the epoxide (880 mg, 1.64 mmol) in CH_3CN/THF (4:1, 20 ml) at ambient temperature was added NaI (1.2 g, 8.00 mmol) and TMSCl (0.50 ml, 3.94 mmol). After stirring for 1 h, to the yellowish mixture was added another 1.2 g of NaI and 0.50 ml of TMSCl. After stirring for 1 h, the reaction was quenched with saturated $Na_2S_2O_3$ solution (10 ml). and saturated $NaHCO_3$ solution (10 ml). The aqueous layer was extracted with EtOAc/CH_2Cl_2 (9:1, 20 ml, 4 times). The combined organic layers were concentrated in vacuo and purified by flash chromatography (50% EtOAc/hexanes→5% →7.5%→10% MeOH/CH_2Cl_2) to provide 800 mg of the desired product as a pale yellow solid. The recovered starting material (contaminated with an unidentified product) was placed under high vacuum overnight, dissolved in CH_2Cl_2 (15 ml), and washed with $NaHCO_3$ solution (10 ml) and saturated $Na_2S_2O_3$ solution (10 ml). The aqueous layer was extracted with EtOAc/CH_2Cl_2 (9:1, 20 ml, 3 times) and the combined organic layers were concentrated in vacuo and purified by flash chromatography (50% EtOAc/hexanes→5%→7.5%→10% MeOH/CH_2Cl_2) to provide another crop of 200 mg of the desired product (1 g combined, ~100% yield).

R_f = 0.15 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{22}$ +57.4 (*c* 1.1, 5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.6 Hz, 1H), 7.34~7.21 (m, 5H), 7.17 (d, *J* = 7.2 Hz, 1H), 6.90 (ddd, *J* = 1.2 Hz, 7.6 Hz, 8.0 Hz, 1H), 6.13 (br s, 1H, –OH), 5.44 (d, *J* = 12.4 Hz, 1H), 5.35 (AB system, *J* = 16.4 Hz, 2H), 4.14 (m, 1H), 4.01 (d, *J* = 12.4 Hz, 1H), 3.97 (m, 1H), 2.98 (d, *J* = 14.8 Hz, 1H), 2.89 (d, *J* = 14.8 Hz, 1H), 2.87 (dd, *J* = 8.0 Hz, 12.4 Hz, 1H), 2.60 (m, 1H), 2.31 (m, 2H), 2.14 (m, 1H), 1.95 (m, 2H), 1.81 (m, 1H), 1.60 (d, *J* = 6.8 Hz, 3H), 1.07 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 139.9, 137.2, 134.5, 134.1, 128.4, 127.03, 126.99, 126.3, 123.5, 107.4, 101.8, 86.1, 73.4, 69.5, 66.4, 61.4, 50.9, 46.2, 44.8, 27.3, 26.4, 26.3, 26.1, 20.6, 17.4, 12.6; IR (thin film): 3248 (br, s), 1718 (s), 1601 (m), 1450 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{29}H_{34}BrN_2O_3$ [M^+]: 537.1747. Found: 537.1750.

Preparation of Diol (+)-151

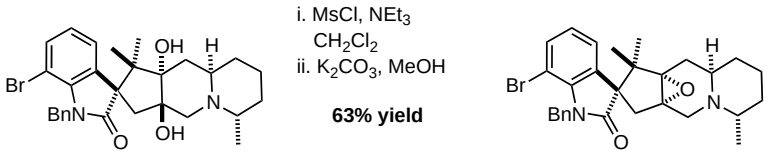


(+)-**150** (+)-**151**

To a solution of the ammonia salt (1.0 g) in THF/AcOH (2:1, 15 ml) was added activated zinc powder (643 mg, 5.47 mmol). The reaction mixture was vigorously stirred at ambient temperature for 25 h, filtered through a pad of Celite, rinsed with CH_2Cl_2, and concentrated in vacuo. The resulting yellowish oil was taken up in CH_2Cl_2 (5 ml), treated with saturated $NaHCO_3$ solution and extracted with EtOAc/CH_2Cl_2 (9:1, 20 ml×4). The combined organic layers were concentrated in vacuo and purified by flash chromatography (basic Al_2O_3, 5% MeOH/CH_2Cl_2) to provide 810 mg (92% yield, two steps) of the desired product as a pale yellow solid.

R_f = 0.36 (10% MeOH/CH_2Cl_2, TLC plate pretreated with NH_3); m.p. = 231~234 C (CH_2Cl_2, decomp.); $[\alpha]_D^{22}$ +56.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) (Note: ^{1}H NMR of this compound is highly dependent on the acidity of the purification media. To ensure reproducibility, it is recommended to pass through a pad of basic Al_2O_3 before taking ^{1}H NMR) δ 7.54 (dd, *J* = 0.8 Hz, 7.6 Hz, 1H), 7.37~7.23 (m, 6H), 6.97 (dd, *J* = 7.6 Hz, 8.0 Hz, 1H), 5.41 (s, 2H), 4.95 (d, *J* = 1.6 Hz, 1H, –OH), 4.51 (br s, 1H, –OH), 3.41 (d, *J* = 10.4 Hz, 1H), 3.05 (m, 1H), 2.89 (m, 1H), 2.56 (d, *J* = 14.4 Hz, 1H), 2.28 (d, *J* = 10.4 Hz, 1H), 2.09 (d, *J* = 14.4 Hz, 1H), 1.82~1.50 (m, 7H), 1.27 (s, 3H), 1.18 (m, 1H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.1, 140.0, 137.2, 136.5,133.4, 128.4, 127.1, 126.7, 126.4, 123.8, 102.0, 83.1, 81.7, 60.8, 57.0, 54.9, 52.4, 47.1, 45.9, 45.0, 36.3, 34.3, 32.5, 27.0, 21.5, 18.5, 10.8; IR (thin film): 3392 (br, s), 1688 (s), 1451 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{29}H_{36}BrN_2O_3$ [M+H]: 539.1904. Found: 539.1907.

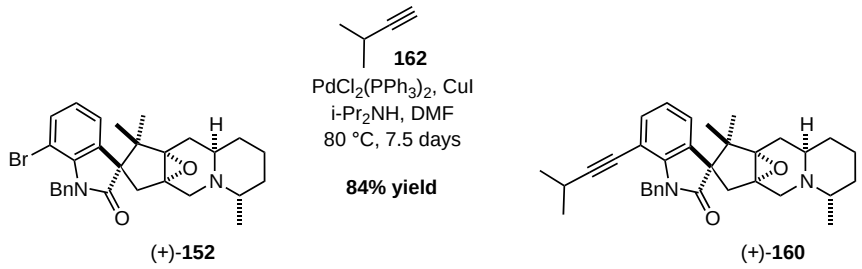
Preparation of Ring-Fusion Epoxide (+)-152



A parallel of five reactions were set up side by side. To a solution of the diol (60 mg) in CH_2Cl_2 (2 ml) was added Et_3N (150 µl) and MsCl (25 µl). After 40 min, another 150 µl of Et_3N and 25 µl of MsCl were added. After 40 min, solid K_2CO_3 (50 mg) was added followed by MeOH (2 ml). The yellowish reaction mixture was stirred at ambient temperature for 15 h. The five reactions were combined and quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc/CH_2Cl_2 (5:1, 20 ml×4). The organic layers were combined, concentrated in vacuo and purified by flash chromatography (5%→7.5%→10→15%→20% MeOH/CH_2Cl_2) to provide 195 mg (63% yield) of the desired product as a white foam and 101 mg of recovered starting material (34%).

R_f = 0.57 (10% MeOH/CH_2Cl_2, TLC plate pretreated with NH_3); $[\alpha]_D^{22}$ +94.0 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) (Note: ^{1}H NMR of this compound is highly dependent on the acidity of the purification media. To ensure reproducibility, it is recommended to pass through a pad of basic Al_2O_3 before taking ^{1}H NMR) δ 7.26 (dd, *J* = 0.8 Hz, 8.4 Hz, 1H), 7.20 (m, 5H), 7.01 (d, *J* = 6.8 Hz, 1H), 6.79 (dd, *J* = 7.6 Hz, 8.0 Hz, 1H), 5.27 (s, 2H), 3.19 (AB system, *J* = 14.0 Hz, 2H), 2.96 (m, 1H), 2.68 (m, 1H), 2.59 (d, *J* = 14.4 Hz, 1H), 2.16 (d, *J* = 14.4 Hz, 1H), 1.77 (m, 2H), 1.68 (m, 2H), 1.58~1.42 (m, 3H), 1.19 (m, 1H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.99 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.4, 140.6, 137.9, 134.1, 133.9, 128.2, 126.9, 126.8, 125.1, 122.2, 101.6, 70.0, 64.7, 58.5, 51.4, 49.8, 47.9, 45.8, 44.4, 40.8, 33.23, 33.17, 29.9, 25.9, 20.1,18.5, 12.1; IR (thin film): 2248 (w), 1725 (s), 1601 (m), 1453 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{29}H_{34}BrN_2O_2$ [M+H]: 521.1798. Found: 521.1792.

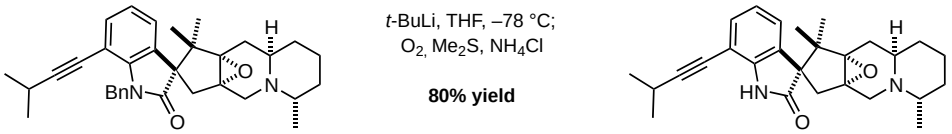
Preparation of Alkyne (+)-160



To a solution of the aryl bromide (196 mg, 0.376 mmol) in DMF (4 ml) was added $PdCl_2(PPh_3)_2$ (26 mg, 0.0376 mmol), CuI (11 mg, 0.0564 mmol), *i*Pr_2NH (105 µl, 0.752 mmol) and 3-methyl-1-butyne (200 µl, 1.88 mmol). The reaction mixture was stirred in a sealed tube at 80 °C for 7.5 d and quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with H_2O, brine and concentrated in vacuo. The residue was dried under high vacuum at 50 °C for 4 h, and purified by flash chromatography (40%→100% EtOAc/hexanes→2.5%→5%→7.5%→10% MeOH/CH_2Cl_2) to provide 160 mg (84% yield) of the desired product as a pale yellow foam.

R_f = 0.57 (10% MeOH/CH_2Cl_2, TLC plate pretreated with NH_3); $[\alpha]_D^{22}$ +94.0 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) (Note: ^{1}H NMR of this compound is highly dependent on the acidity of the purification media. To ensure reproducibility, it is recommended to pass through a pad of basic Al_2O_3 before taking ^{1}H NMR) δ 7.26 (dd, *J* = 0.8 Hz, 8.4 Hz, 1H), 7.20 (m, 5H), 7.01 (d, *J* = 6.8 Hz, 1H), 6.79 (dd, *J* = 7.6 Hz, 8.0 Hz, 1H), 5.27 (s, 2H), 3.19 (AB system, *J* = 14.0 Hz, 2H), 2.96 (m, 1H), 2.68 (m, 1H), 2.59 (d, *J* = 14.4 Hz, 1H), 2.16 (d, *J* = 14.4 Hz, 1H), 1.77 (m, 2H), 1.68 (m, 2H), 1.58~1.42 (m, 3H), 1.19 (m, 1H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.99 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.4, 140.6, 137.9, 134.1, 133.9, 128.2, 126.9, 126.8, 125.1, 122.2, 101.6, 70.0, 64.7, 58.5, 51.4, 49.8, 47.9, 45.8, 44.4, 40.8, 33.23, 33.17, 29.9, 25.9, 20.1,18.5, 12.1; IR (thin film): 2248 (w), 1725 (s), 1601 (m), 1453 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{29}H_{34}BrN_2O_2$ [M+H]: 521.1798. Found: 521.1792.

Preparation of *des*-Benzyl Oxindole (+)-163

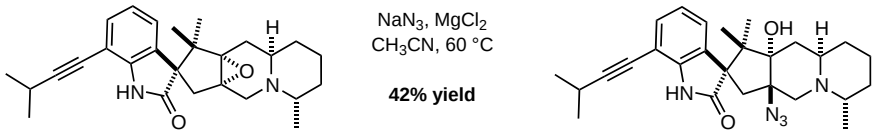


(+)-**160** (+)-**163**

To a solution of the benzyl oxindole (62 mg, 0.122 mmol, azeotropically dried with toluene) in THF (3 ml) at –78 °C was added *t*-BuLi (1.2 M in pentane, 200 µl). After stirring at –78 °C for 5 min, O_2 was bubbled through the dark reaction solution for 10 min. The resulting light yellow solution was then treated with Me_2S (100 µl) and solid NH_4Cl (100 mg). The reaction mixture was warmed to room temperature, stirred for an additional 3 h, and quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were concentrated in vacuo and purified by flash chromatography (40% EtOAc/hexanes→2.5%→5%→7.5%→10% MeOH/CH_2Cl_2) to provide 41 mg (80% yield) of the desired product as a pale yellow oil.

R_f = 0.45 (10% MeOH/CH_2Cl_2, TLC plate pretreated with NH_3); $[\alpha]_D^{22}$ +57.6 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) (Note: ^{1}H NMR of this compound is highly dependent on the acidity of the purification media. To ensure reproducibility, it is recommended to pass through a pad of basic Al_2O_3 before taking ^{1}H NMR) δ 7.31 (br s, 1H, -NH), 7.17 (dd, *J* = 1.2 Hz, 7.6 Hz, 1H), 6.95 (d, *J* = 7.2 Hz, 1H), 6.89 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H), 3.24 (AB system, *J* = 14.0 Hz, 2H), 3.00 (m, 1H), 2.79 (septet, *J* = 6.8 Hz, 1H), 2.74 (m, 1H), 2.60 (d, *J* = 14.8 Hz, 1H), 2.18 (d, *J* = 14.8 Hz, 1H), 1.87 (m, 2H), 1.73 (m, 2H), 1.61~1.48 (m, 3H), 1.26 (d, *J* = 6.8 Hz, 6H), 1.21 (m, 1H), 1.11 (s, 3H), 1.05 (d, *J* = 6.4 Hz, 3H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 142.5, 130.5, 130.3, 125.7, 121.0, 105.0, 101.0, 74.2, 70.0, 64.6, 60.0, 51.5, 49.6, 47.5, 45.8, 39.8, 33.3, 33.2, 29.9, 25.8, 23.0 (two carbons), 21.2, 19.8, 18.5, 12.1; IR (thin film): 3199 (br, m), 1718 (s), 1614 (m), 1593 (m), 1452 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{27}H_{34}N_2O_2$ [M+H]: 419.2699. Found: 419.2697.

Preparation of Azide (+)-159

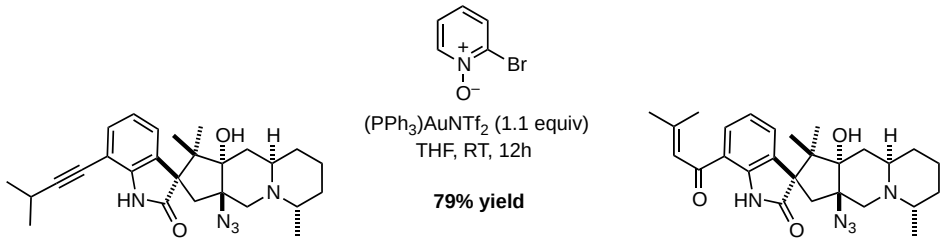


(+)-**163** (+)-**159**

To a solution of the epoxide (120 mg, 0.287 mmol, azeotroped with PhMe) in CH_3CN (5 ml) was added $MgCl_2$ (136 mg, 1.43 mmol) and NaN_3 (93 mg, 1.43 mmol). The reaction mixture was stirred at 63 °C for 2.5 days. Another aliquot of $MgCl_2$ (136 mg, 1.42 mmol) and NaN_3 (93 mg, 1.43 mmol) were added. The reaction was stirred for 3 more days, quenched with saturated $NaHCO_3$ solution, extracted with EtOAc/CH_2Cl_2, concentrated and purified by flash chromatography (10%→30%→50% EtOAc/hexanes→ 10%→15% MeOH/CH_2Cl_2) to provide the desired azide (55 mg, 42% yield) with some recovered starting material.

R_f = 0.43 (20% EtOAc/hexanes, TLC plate pretreated with NH_3); $[\alpha]_D^{22}$ +31.7 (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) (Note: ^{1}H NMR of this compound is highly dependent on the acidity of the purification media. To ensure reproducibility, it is recommended to pass through a pad of basic Al_2O_3 before taking ^{1}H NMR) δ 8.01 (br s, 1H, -NH), 7.36 (d, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.2 Hz, 1H), 7.01 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H), 5.02 (d, *J* = 2.0 Hz, 1H, -OH), 3.52 (d, *J* = 11.6 Hz, 1H), 3.08 (m, 1H), 2.97 (m, 1H), 2.84 (septet, *J* = 6.8 Hz, 1H), 2.66 (d, *J* = 11.6 Hz, 1H), 2.47 (d, *J* = 14.4 Hz, 1H), 2.03 (d, *J* = 14.4 Hz, 1H), 1.81 (m, 1H), 1.64≈1.46 (m, 6H), 1.29 (d, *J* = 7.2 Hz, 6H), 1.25 (m, 1H), 1.21 (s, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.8, 142.0, 132.2, 130.3, 126.7, 122.6, 106.0, 101.2, 83.2, 74.1, 73.8, 62.3, 54.6, 54.4, 52.0, 46.8, 45.3, 36.1, 33.9, 32.3, 26.5, 23.0 (two carbons), 21.5, 21.2, 18.9, 9.8; IR (thin film): 3366 (br m), 3209 (br, m), 2116 (s), 1686 (s), 1447 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{27}H_{36}N_5O_2$ [M+H]: 462.2869. Found: 462.2866.

Preparation of Enone (+)-158

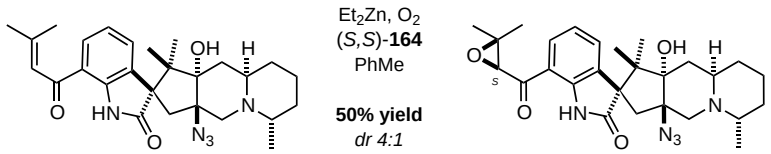


(+)-**159** (+)-**158**

To a solution of the aryl alkyne (48 mg, 0.104 mmol) in THF (0.5 ml) was added a solution of $(Ph_3P)AuNTf_2$ (85 mg, 0.114 mmol) and 2-bromopyridine *N*-oxide (27 mg, 0.156 mmol) in THF (1 ml) plus 1 ml of rinse with THF. After stirring at ambient temperature for 12 h, the reaction was quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc/CH_2Cl_2 (5:1) and the combined organic layers were concentrated in vacuo. The residue was taken up in CH_2Cl_2, passed through a pad of basic Al_2O_3, rinsed with 5% MeOH/CH_2Cl_2, and concentrated in vacuo. The residue was purified by flash chromatography (10%→30%→50%→70% EtOAc/hexanes) to provide 35 mg (73% yield) of the desired product as a pale yellow oil.

R_f = 0.33 (20% EtOAc/hexanes, TLC plate pretreated with NH_3); $[\alpha]_D^{22}$ +35.3 (*c* 0.45, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) (Note: ^{1}H NMR of this compound is highly dependent on the acidity of the purification media. To ensure reproducibility, it is recommended to pass through a pad of basic Al_2O_3 before taking ^{1}H NMR) δ 9.84 (br s, 1H, -NH), 7.73 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.13 (dd, *J* = 7.6 Hz, 8.0 Hz, 1H), 6.79 (s, 1H), 5.05 (d, *J* = 2.4 Hz, 1H, -OH), 3.53 (d, *J* = 11.2 Hz, 1H), 3.09 (m, 1H), 2.99 (m, 1H), 2.67 (d, *J* = 11.2 Hz, 1H), 2.49 (d, *J* = 14.4 Hz, 1H), 2.21 (s, 3H), 2.05 (s, 3H), 2.02 (d, *J* = 14.4 Hz, 1H), 1.81 (m, 1H), 1.64≈1.45 (m, 6H), 1.24 (m, 1H), 1.22 (s, 3H), 1.06 (d, *J* = 6.4 Hz, 3H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 185.3, 157.8, 143.1, 134.6, 131.3, 127.8, 121.8, 120.4, 120.2, 83.3, 73.9, 60.2, 54.7, 54.5, 52.0, 46.8, 45.4, 36.1, 33.9, 32.3, 28.1, 26.7, 21.6, 21.2, 18.9, 9.9; IR (thin film): 3381 (br s), 2115 (s), 1702 (s), 1609 (s), 1450 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{27}H_{36}N_5O_3$ [M+H]: 478.2818. Found: 478.2811.

Preparation of Epoxyketone (+)-171

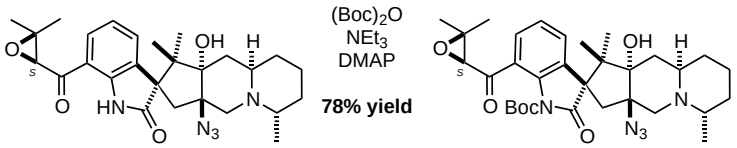


(+)-**158** (+)-**171**

To a solution of (*S*,*S*)-*N*-methylpseudoephedrine (36 mg) in toluene (1 ml) at 0 C was added Et_2Zn (1.0 M in heptanes, 80 ul). After 90 min, the reaction vial was attached to a balloon of oxygen and the reaction was stirred at 0 C under O_2 atmosphere for 6 h, at which point a solution of the enone (10 mg, azeotropically dried with toluene) in toluene (1 ml) plus 0.5 ml of rinse. The resulting brightly yellowish solution was stirred under O_2 atmosphere for 3 h and room temperature for 9 h. The reaction was quenched by saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc/CH_2Cl_2 (5:1) and the combined organic layers were concentrated in vacuo. The residue was taken up in CH_2Cl_2, passed through a pad of basic Al_2O_3, rinsed with 5% MeOH/CH_2Cl_2, and concentrated in vacuo. The residue was purified by flash chromatography (10%→30%→50%→70% EtOAc/hexanes) to provide 5 mg (50% yield) of an inseparable mixture of two diastereomers (dr = 4 :1) in favor of the desired product.

R_f = 0.28 (30% EtOAc/hexanes, TLC plate pretreated with NH_3); $[\alpha]_D^{22}$ +3.1 (*c* 0.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) (Note: ^{1}H NMR of this compound is highly dependent on the acidity of the purification media. To ensure reproducibility, it is recommended to pass through a pad of basic Al_2O_3 before taking ^{1}H NMR) δ 9.55 (br s, 1H, -NH), 7.80 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.20 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H), 4.89 (d, *J* = 1.6 Hz, 1H, -OH), 4.05 (s, 1H), 3.54 (d, *J* = 11.6 Hz, 1H), 3.09 (m, 1H), 2.99 (m, 1H), 2.68 (d, *J* = 11.6 Hz, 1H), 2.49 (d, *J* = 14.4 Hz, 1H), 2.02 (d, *J* = 14.4 Hz, 1H), 1.81 (m, 1H), 1.65≈1.48 (m, 6H), 1.61 (s, 3H), 1.30 (s, 3H), 1.29 (m, 1H), 1.24 (s, 3H), 1.06 (d, *J* = 6.4 Hz, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 185.3, 142.8, 135.0, 132.7, 127.6, 122.2, 117.5, 83.3, 73.8, 64.1, 61.6, 60.2, 54.7, 54.5, 52.3, 46.8, 45.6, 36.2, 33.9, 32.3, 26.7, 24.3, 21.6, 18.9, 18.7, 9.9; IR (thin film): 3391 (br s), 2115 (s), 1707 (s), 1672 (s), 1604 (s), 1452 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{27}H_{36}N_5O_4$ [M+H]: 494.2767. Found: 494.2765.

Preparation of Boc-Protected Epoxyketone (+)-173

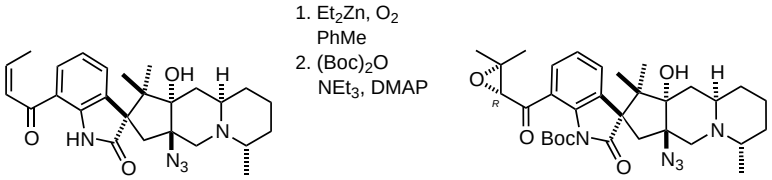


(+)-**171** (–)-**173**

To a solution of the oxindole (3 mg, a mixture of diastereomers in a ratio of 4 : 1) and $(Boc)_2O$ (3 mg) in CH_2Cl_2 (1 ml) was added DMAP (one crystal) and Et3N (10 ul). After 20 min, the reaction was quenched with saturated solution. The aqueous layer was extracted with EtOAc/CH_2Cl_2 (5:1) and the combined organic layers were concentrated in vacuo. The residue was taken up in CH_2Cl_2, passed through a pad of basic Al_2O_3, rinsed with 5% MeOH/CH_2Cl_2, and concentrated in vacuo. The residue was purified by flash chromatography (10%→20%→30%→40%→50% EtOAc/hexanes) to provide 2.8 mg (78% yield) of the desired product as white solid.

R_f = 0.43 (20% EtOAc/hexanes, TLC plate pretreated with NH_3); $[\alpha]_D^{22}$ –21.9 (*c* 0.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) (Note: ^{1}H NMR of this compound is highly dependent on the acidity of the purification media. To ensure reproducibility, it is recommended to pass through a pad of basic Al_2O_3 before taking ^{1}H NMR) δ 7.70 (dd, *J* = 1.2 Hz, 7.6 Hz, 1H), 7.48 (dd, *J* = 1.2 Hz, 8.0 Hz, 1H), 7.27 (overlapped with $CHCl_3$, 1H), 4.34 (s, 1H, -OH), 3.70 (s, 1H), 3.53 (d, *J* = 11.6 Hz, 1H), 3.09 (m, 1H), 2.98 (m, 1H), 2.70 (d, *J* = 11.6 Hz, 1H), 2.57 (d, *J* = 14.4 Hz, 1H), 2.11 (d, *J* = 14.4 Hz, 1H), 1.80 (m, 1H), 1.60 (s, 9H), 1.58≈1.50 (m, 6H), 1.48 (s, 3H), 1.25 (m, 1H), 1.13 (s, 3H), 1.07 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 183.0, 149.5, 137.5, 133.2, 130.2, 127.9, 124.04, 124.01, 85.7, 83.7, 73.6, 66.1, 62.2, 61.4, 54.7, 54.5, 53.7, 46.7, 46.0, 36.1, 33.9, 32.3, 27.8, 26.2, 24.9, 21.5, 18.9, 18.6, 9.8; IR (thin film): 3427 (br s), 2117 (s), 1736 (s), 1687 (s), 1440 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{32}H_{44}N_5O_6$ [M+H]: 594.3292. Found: 594.3286.

Preparation of Boc-Protected Epoxyketone (+)-174



(+)-**158** (+)-**174**

Epoxidation:

To a solution of the enone (2.1 mg, azeotroped with PhMe) in toluene (1.0 ml) at –78 °C was added Et_2Zn (1.0 M in hexanes, 40 μl). An O_2 balloon was attached to the reaction vial and the light yellowish solution was stirred at –78 °C for 30 minutes, room temperature for 17 hours, then quenched with saturated $NaHCO_3$ solution. The mixture was extracted with $EtOAc/CH_2Cl_2$, concentrated, and purified by flash chromatography (10%→30%→50%→70% EtOAc/hexanes) to provide a mixture of the two epoxide diastereomers (1 mg, *dr* 1:1).

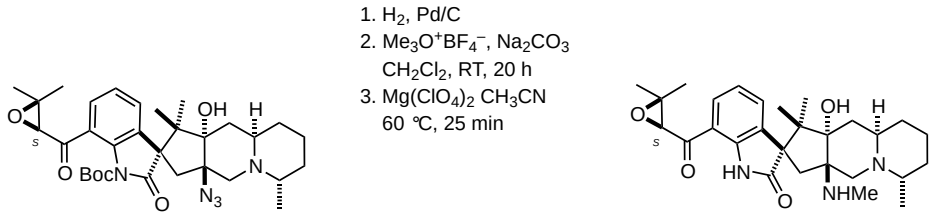
Boc-Protection:

To a solution of the oxindole (6 mg, 0.012 mmol) and Boc_2O (6 mg) in CH_2Cl_2 (1 ml) was added DMAP (one crystal) and Et_3N (two drops). After 20 minutes, the reaction was quenched with saturated $NaHCO_3$ solution, extracted with $EtOAc/CH_2Cl_2$, concentrated and purified by flash chromatography (10%→20%→30%→40%→50% EtOAc/hexanes) to provide the less polar diastereomer (–)-**173** (2 mg), the more polar diastereomer (+)-**174** (2 mg), and 1 mg of a mixture of both diastereomers.

R_f = 0.35 (20% EtOAc/hexanes, TLC plate pretreated with NH_3); $[\alpha]_D^{22}$ +117 (*c* 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) (Note: ^1H NMR of this compound is highly dependent on the acidity of the purification media. To ensure reproducibility, it is recommended to pass through a pad of basic Al_2O_3 before taking ^1H NMR) δ 7.74 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.48 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 5.31 (s, 1H), 4.47 (d, *J* = 2.1 Hz, 1H), 3.82 (s, 1H), 3.53 (d, *J* = 11.3 Hz, 1H), 3.09 (m, 1H), 2.97 (m, 1H), 2.68 (d, *J* = 11.4 Hz, 1H), 2.56 (d, *J* = 14.5 Hz, 1H), 2.01 (s, 2H), 1.79 (m, 2H), 1.60 (s, 3H), 1.59 (s, 9H), 1.23 (s, 3H), 1.16 (s, 3H), 1.06 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.03, 182.27, 148.49, 137.38, 132.77, 130.46, 127.63, 124.50, 124.35, 85.61, 83.51, 73.65, 65.50, 62.10, 61.69, 54.58,

54.44, 53.79, 46.68, 45.42, 36.18, 33.86, 32.22, 27.87, 26.33, 24.67, 21.20, 18.80, 18.65, 9.80. IR (thin film): not obtained; HRMS (ESI) not obtained.

Preparation of Synthetic C21-*epi*-*ent*-Citrinadin B (+)-175



(–)-**173** (+)-**175**

Azide Reduction:

To a solution of the azide (1.3 mg, R_f = 0.86, 70% EtOAc/hexanes, TLC plate pretreated with NH_3) in THF (0.5 ml) was added Pd/C (10 wt%, 3 mg). The mixture was purged with H_2 for 1 min (from a balloon of H_2) and stirred under H_2 atmosphere for 12h, filtered through a pad of Celite, rinsed with CH_2Cl_2, concentrated and purified by flash chromatography (5%→10%→15% MeOH/ CH_2Cl_2) to provide 1.2 mg of the desired primary amine (R_f = 0.18, 70% EtOAc/hexanes, TLC plate pretreated with NH_3).

Methylation:

To a solution of the amine (1.0 mg, azeotropically dried with toluene) in CH_2Cl_2 (0.5 ml) was added Na_2CO_3 (10 mg) and $Me_3O^+BF_4^-$ (6 mg). The reaction mixture was vigorously stirred at for 36 h and quenched with saturated NaHCO3 solution. The aqueous layer was extracted with EtOAc/ CH_2Cl_2 (5:1) and the combined organic layers were concentrated in vacuo. The residue was purified by flash chromatography (5%→10%→12.5%→15 MeOH/ CH_2Cl_2) to provide 0.8 mg (63% yield, two steps) of the desired product as white solid.

Rf = 0.45 (70% EtOAc/hexanes, TLC plate pretreated with NH_3); $[\alpha]_D^{22}$ –26.0 (c 0.05, CHCl3); ^{1}H NMR (400 MHz, $CDCl_3$) (Note: 1H NMR of this compound is highly dependent on the acidity of the purification media. To ensure reproducibility, it is recommended to pass through a pad of basic Al_2O_3 before taking 1H NMR) δ 7.67 (dd, J = 1.2 Hz, 7.6 Hz, 1H), 7.45 (dd, J = 1.2 Hz, 8.0 Hz, 1H), 7.24 (dd, J =

7.6 Hz, 8.0 Hz, 1H), 4.06 (d, J = 2.8 Hz, 1H, -OH), 3.72 (s, 1H), 3.06 (d, J = 10.4 Hz, 1H), 3.01 (m, 1H), 2.88 (m, 1H), 2.55 (d, J = 10.4 Hz, 1H), 2.33 (s, 3H), 2.16 (dd, AB system, J = 14.4 Hz, 2H), 1.75 (m, 1H), 1.60 (s, 9H), 1.62≈1.50 (m, 5H), 1.48 (s, 3H), 1. 38≈1.28 (m, 2H), 1.19 (s, 3H), 1.15 (s, 3H), 1.05 (d, J = 6.8 Hz, 3H), 1.02 (s, 3H); 13C NMR (100 MHz, $CDCl_3$) δ 196.3, 183.4, 150.8, 137.7, 134.5, 131.0, 127.2, 123.81, 123.78, 85.4, 84.3, 68.5, 66.0, 62.14, 62.10, 55.2, 53.5, 50.2, 46.9, 41.4, 35.3, 34.6, 32.7, 29.6, 27.9, 27.6, 24.9, 22.0, 19.0, 18.6, 10.3; IR (thin film): 3449 (br s), 1734 (s), 1686 (m), 1438 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{33}H_{48}N_3O_6$ [M+H]: 582.3543. Found: 582.3541.

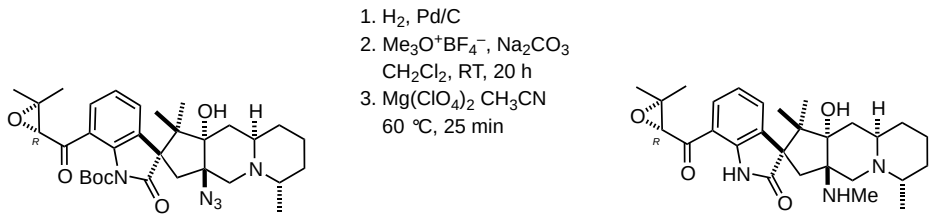
Boc-Removal:

To a solution of Boc oxindole (0.4 mg) in CH_3CN (0.2 ml) was added a solution of $Mg(ClO_4)_2$ (0.4 mg) in CH_3CN (0.2 ml). After stirring at 65 ºC for 25 min, the reaction was quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc/CH_2Cl_2 (5:1) and the combined organic layers were concentrated in vacuo. The residue was purified by flash chromatography (5%→10%→15 MeOH/CH_2Cl_2) to provide 0.3 mg of the desired product as white solid. R_f = 0.28 (70% EtOAc/hexanes, TLC plate pretreated with NH_3)

Freebase: (The solid was dissolved in 5% MeOH/CH_2Cl_2 and passed through a pad of basic Al_2O_3 to provide the free base); $[\alpha]_D^{22}$ + 36.7 (c 0.03, CHCl3); ^{1}H NMR: See Appendix to Chapter 3; HRMS (ESI) Calcd. for $C_{28}H_{40}N_3O_4$ [M+H]: 482.3019. Found: 482.3018.

TFA Salt: (To a vial containing the free base (0.2 mg) was added 0.8 ml of a solution of 0.5% of TFA in CH_3CN (prepared by adding 5 ul of TFA to 1 ml of CH_3CN). The solution was immediately concentrated on rotvap (ca. 10 min) and dried under vacuo for 4 h.) ^{1}H NMR: See Appendix to Chapter 3.

Preparation of ent-2



174 *ent*-**2**

Azide Reduction:

To a solution of the azide **174** (2 mg) in THF (0.5 ml) was added Pd/C (10 wt%, ~3 mg). The mixture was purged with H_2 for 1 minute and stirred under H_2 atmosphere (balloon) for 10 hours, filtered through a pad of celite, rinsed with CH_2Cl_2, concentrated and purified by flash chromatography (5%→10%→15% MeOH/CH_2Cl_2) to provide 1.5 mg of the desired product.

Boc-Removal:

To a vial containing the methylated Boc-oxindole (0.5 mg) was added a solution of $Mg(ClO_4)_2$ (0.5 mg) in CH_3CN (0.5 ml). After stirring at 60 °C for 20 minutes, the reaction was quenched with saturated $NaHCO_3$ solution, extracted with EtOAc/CH_2Cl_2, concentrated and purified by flash chromatography (5%→10%→12.5%→15% MeOH/CH_2Cl_2) to provide a trace amount of ent-**2**.

R_f = 0.38 (70% EtOAc/Hexanes, TLC pre-treated with NH_3). HRMS (ESI) Calcd. for $C_{28}H_{40}N_3O_4$ [M+H]: 482.3019. Found: 482.3015. ^{1}H NMR: See Appendix to Chapter 3.

3.7 Notes and References

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[26] One could ask, given the difficulties with benzyl deprotection of **108**, why a change was not made at this stage. In reality, the limited methods available to introducing the C7 side-chain in (+)-**100** had led to the initiation of the efforts described in this section *prior to* the deprotection difficulties becoming fully apparent.

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CHAPTER 4

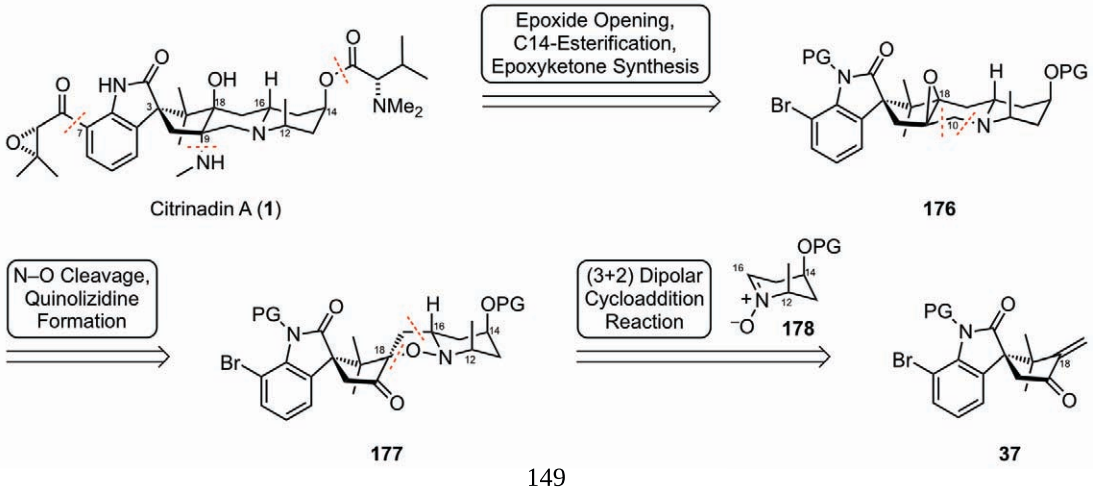
Progress Toward Citrinadin A

4.1 Developing a Synthetic Approach Toward Citrinadin A

4.1.1 Retrosynthetic Strategies Toward a C14-functionalized Nitrone

The successful application of the (3+2) cycloaddition reaction toward a number of citrinadin B analogues (most notably, *ent*-**2** and **175**) is expected to lead to a structural reassignment of Citrinadin B (**2**) and left us increasingly intrigued by a synthesis of Citrinadin A (**1**). As proposed by Kobayashi, **1** differs from **2** by the presence of an oxygen atom at C14, which is acylated as the corresponding *N*,*N*-dimethylvaline ester. Importantly, the strategy we developed for accessing **2** was also

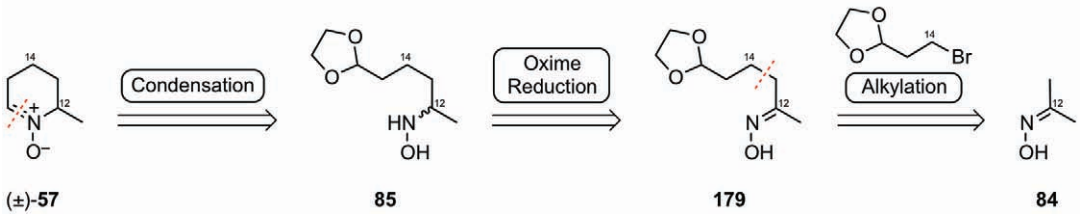
Scheme 4.1



designed to provide access to **1** by simply altering the structure of the nitrone employed in the key cycloaddition step. Although there was no guarantee that the more heavily functionalized nitrone required for the synthesis of **1** (i.e., **178**) would provide identical reactivity, attempting to extend our previous efforts was the logical next step. Key to implementing this strategy was the preparation of **178** and the study of its ability to engage the previously prepared dipolarophile (**37**) to furnish isoxazolidine (**177**) (Scheme 4.1). Elaboration of **177** to the ring-fusion epoxide **176** would leave us poised for late stage installation an *N*,*N*-dimethylvaline ester and completion of **1**.

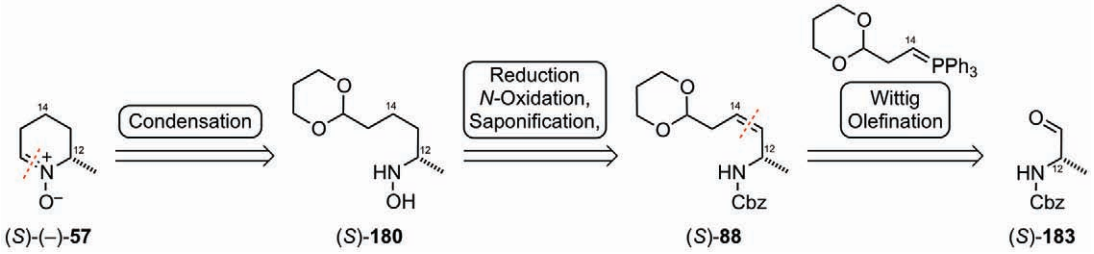
Insights gained as a result of our previous preparations of (±)-**57** and (*S*)-(–)-**57** proved influential in planning synthetic access to nitrone **178**.[1] For example, the synthesis of (±)-**57** from acetone oxime **84** (Scheme 4.2) suggested an initial synthetic design for **178**, involving nucleophilic attack on a C14-*aldehyde* or *ester* (as opposed to an *alkyl halide*) to provide the requisite oxidation of C14. The ubiquity of stereoselective aldol reactions and ketone reductions would selectively provide access to the desired C14 antipode.

Scheme 4.2



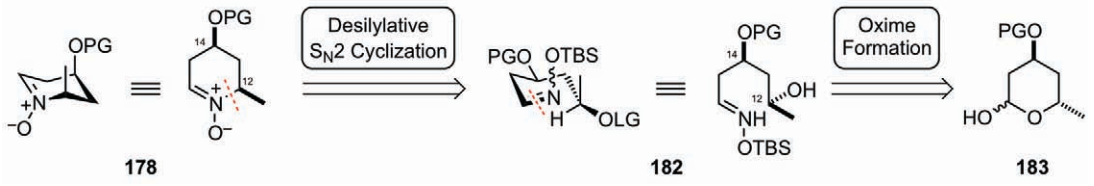
Reflecting on the preparation of (*S*)-(–)-**57**, the utility of a fixed configuration of the C12 stereocenter—incorporated at the outset from commercially available starting material—became apparent (Scheme 4.3).[2] This approach provided enantioenriched (*S*)-(–)-**57** (80% ee) and made the syntheses of *ent*-**2** and **175** possible. Unfortunately, the synthesis also demonstrated poor scalability. Erosion of the enantiopurity was observed during the reduction and olefination reactions used to access (*S*)-**88**. The *N*-oxidation and saponification reactions leading to (*S*)-**180** were poor yielding upon scale up and difficult to purify. Moreover, the hydroxylamine ((*S*)-**180**) demonstrated a limited shelf life, necessitating on demand synthesis. Thus, the limitations inherent to the synthesis of (*S*)-(–)-**57** underscored the need for robust, scalable chemistry to access **178**.

Scheme 4.3



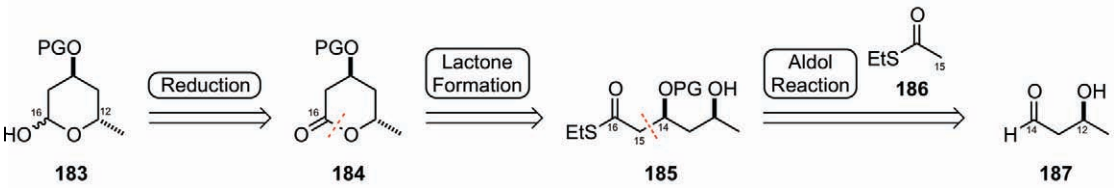
Based on these observations, an attractive strategy emerged. Synthesis of nitrone **178** would arise from an intramolecular, desilylative S_N2 reaction of **182** to form the N11–C12 bond (Scheme 4.4). Unlike the syntheses of nitrones (±)- and (*S*)-(–)-**57** which relied on the formation of the N11–C16 bond, this approach would obviate the need for stereoselective reduction of an oxime or an operationally difficult *N*-oxidation/saponification sequence; the C12 stereoconfiguration of **178** would be set by a stereospecific inversion of **182**. Similar to a procedure reported by Goti et al., the silyl oxime (**182**) could arise from condensation of hydroxylamine onto the aldehyde tautomer of lactol **183**.[3]

Scheme 4.4



Straightforward access to **183** was expected to result from the lactonization of a thioester (**185**) followed by a reduction (Scheme 4.5). The next key retrosynthetic intermediate, *syn*-diol **185**, would be accessible from **187** via an aldol reaction between thioacetate **186** and an aldehyde (**187**).

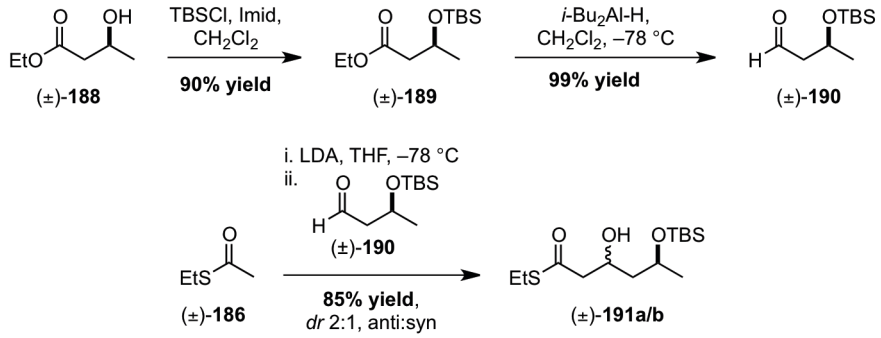
Scheme 4.5



4.1.2 Synthesis of a C14-O-TBDPS Nitrone Precursor

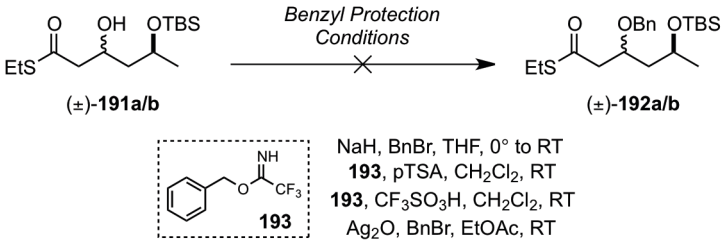
At the exploratory stage of the synthesis, quick access to a diol such as **185** was anticipated to result from a non-selective aldol reaction. Commercially available β-hydroxybutanoate (±)-**188** was protected as the corresponding tertbutyldimethylsilyl (TBS) ether and reduced to the aldehyde according to a known procedure (Scheme 4.6).[4] An aldol reaction between thioacetate **186** and aldehyde (±)-**190** generated the β-hydroxyketones (±)-**191a/b** in a 2:1 diastereomeric mixture with the *anti*-diol being the major stereoisomer.[5] Owing to the difficulty encountered in separation of the diastereomers, (±)-**191a/b** was carried into subsequent reactions as a mixture.

Scheme 4.6



Initially, it was considered desirable to protect the C14 alcohol as the benzyl ether.[6] However, attempts to induce the reaction under standard conditions (NaH, BnBr) did not yield any of the desired product (±)-**192a/b** (Scheme 4.7). Instead, an α,β-unsaturated ester resulted, most likely the result of facile elimination of benzyl alcohol. To circumvent the unwanted elimination reaction, acidic conditions (pTSA, $BnCH_2OC(NH)CF_3$) were alternatively employed; but, only recovered starting material was obtained. The use of a stronger acid (TfOH)[7], appeared to provide some of the desired benzyl alcohol but

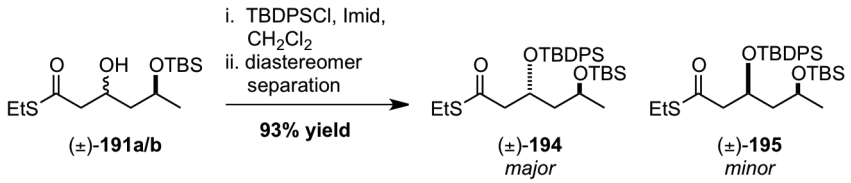
Scheme 4.7



this rapidly converted to the elimination product during work up. In a final attempt, conditions for silver-mediated benzyl protection (Ag_2O, BnBr) were employed but to no avail.[8]

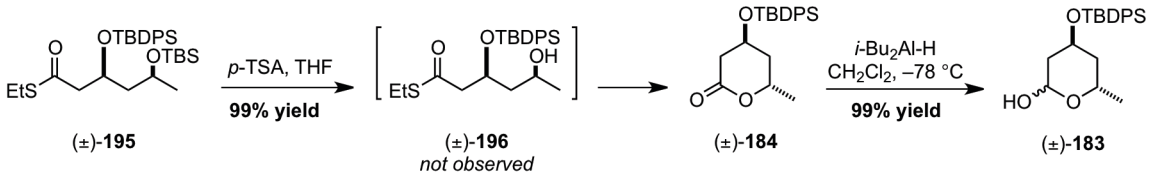
In light of these difficulties, an alternate silyl protection of the C14 alcohol was attempted.[9] Gratifyingly, conversion of the diastereomeric alcohol mixture (±)-**191a/b** to the corresponding tertbutyldiphenylsilyl (TBDPS) ether products (±)-**194** and (±)-**195** was straightforward, and the two diastereomers could be successfully separated via flash chromatography using a nonpolar solvent mixture of toluene and hexanes (Scheme 4.8).[10]

Scheme 4.8



Keeping with the retrosynthetic plan, TBDPS ether (±)-**195** was exposed to *p*-toluenesulfonic acid (*p*TSA) to cleave the more labile TBS ether. Conveniently, the deprotection was accompanied by concomitant cyclization to provide lactone (±)-**184** which participated in the subsequent partial reduction using diisobutylaluminum hydride (DIBAl-H) to effectively provide lactol (±)-**183**

Scheme 4.9

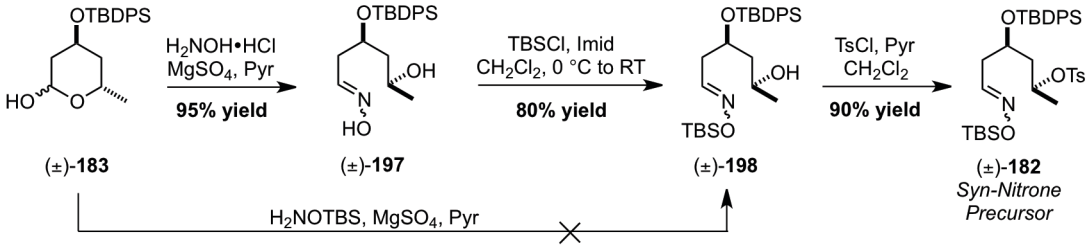


(Scheme 4.9).

With lactol (±)-**183** in hand, exploratory studies toward the synthesis of nitrone (±)-**178** ensued. Inspired by Goti's efficiency,[3] formation of the protected silyl oxime (±)-**198** from lactol (±)-**183** in a single synthetic operation was attempted (Scheme 4.10). Unfortunately, when lactol (±)-**183** was exposed to *O*-TBS hydroxylamine, yields of the corresponding TBS silyl oxime (±)-**198** were prohibitively low. As a result, stepwise installation the silyl oxime was employed. In the event, exposure of lactol (±)-

183 to hydroxylamine hydrochloride in a concentrated pyridine solution over anhydrous magnesium sulfate

Scheme 4.10

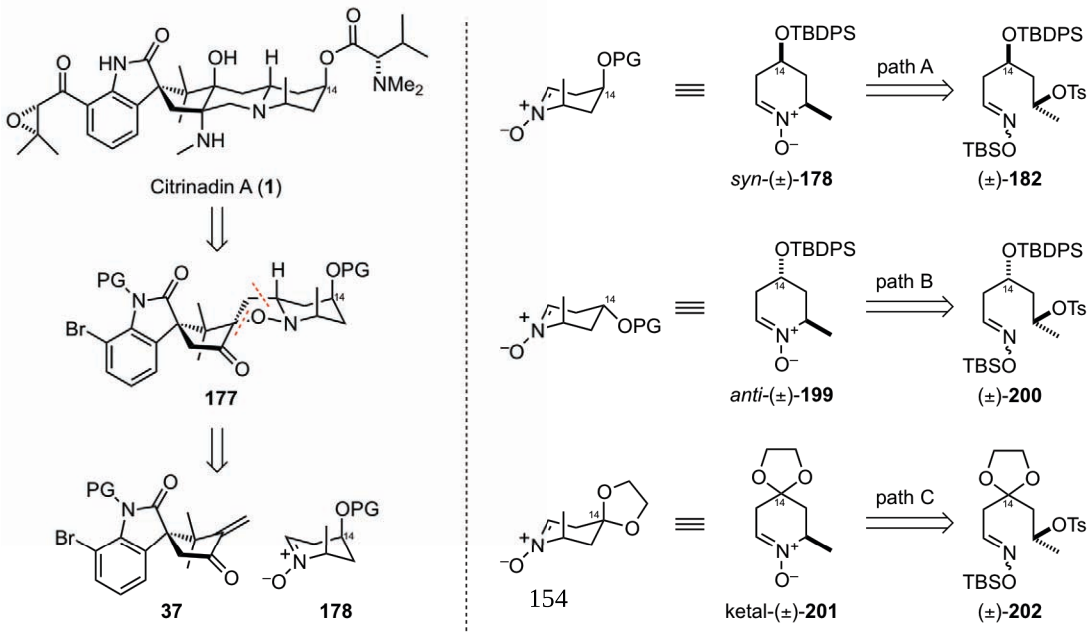


resulted in conversion to the oxime (**±**)-**197**, which was readily converted to the TBS ether (**±**)-**198**. Careful control of the reaction stoichiometry and temperature were essential to avoid bis-silyl protection of the oxime and the secondary alcohol. Activation of the secondary alcohol as the tosylate afforded (**±**)-**182** the desired target for exploration of the anticipated desilylative cyclization.

4.1.4 Synthesis of Alternate Nitrone Precursors

Although the C14 stereochemistry of *syn*-nitrone **178** arising from precursor **182** (path A, Scheme 4.11) was consistent with the desired cycloaddition product **177** (and hence, **1**), we endeavored to synthesize two other nitrone precursors, recognizing that the stereochemistry at C14 (or lack thereof) could potentially impact the sense and degree of stereochemical induction imparted by C12 in the subsequent

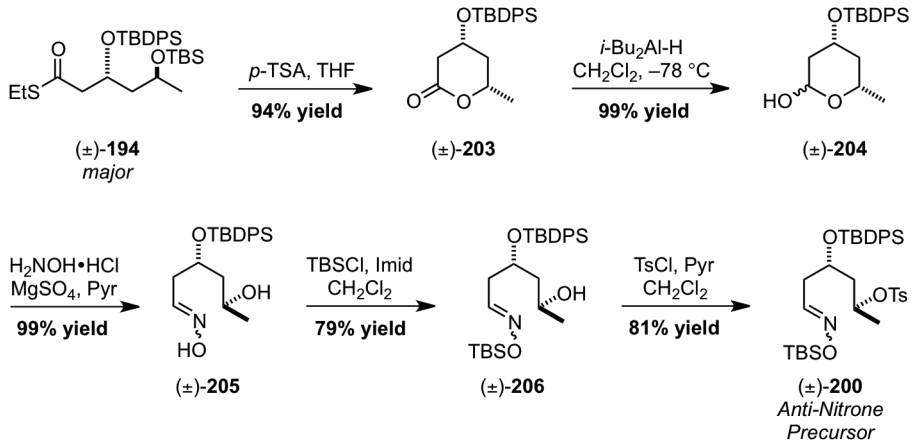
Scheme 4.11



cycloaddition reaction. The readily available bis-protected *anti*-diol (i.e., **192**, scheme 4.7) was expected to lead to nitrone precursor **200** which could undergo desilylative cyclization to give *anti*-nitrone **199** (path B, Scheme 4.11). Alternately, the synthesis of *ketal*-nitrone **201** from precursor **202** (path C, Scheme 4.11) would provide a C14 ketone.

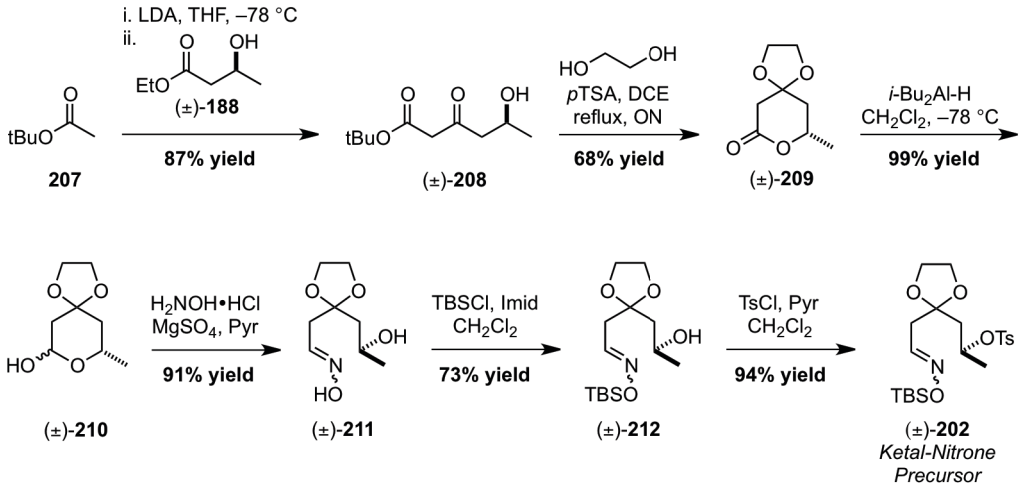
The synthesis of the *anti*-nitrone precursor (±)-**200** proceeded analogously to the synthesis of the *syn*-nitrone precursor (i.e., (±)-**182**, Scheme 4.10). Lactonization of *anti*-diol (±)-**194** was followed by reduction to provide lactol (±)-**204** (Scheme 4.12). Condensation with hydroxylamine, silyl protection, and tosylation subsequently led to (±)-**200**.

Scheme 4.12



In order to obtain the ketal nitrone precursor (±)-**202**, a synthesis of the ketal-lactol (±)-**210** ensued (Scheme 4.13). Following a series of procedures published by Anderson et al., a successful

Scheme 4.13



Claisen condensation of *tert*-butylacetate (±)-**207** and β-hydroxybutanoate (±)-**189** provided β-hydroxyketone (±)-**208**.[11] Lactonization and ketalization of (±)-**208** with 1,2-ethanediol and *p*TSA in dichloromethane was not reproducible; however, substituting 1,2-dichloroethane for dichloromethane was effective to gain access to the lactone (±)-**209**. DIBAl-H reduction provided the desired lactol (±)-**210** wherein conversion to the nitrone precursor (±)-**202** via hydroxylamine condensation, oxime protection, and alcohol activation was straightforward.

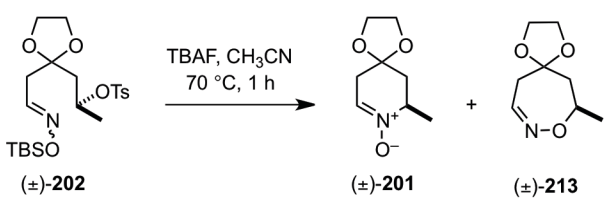
4.2 Citrinadin A Cycloadditions

4.2.1 Employing the C14-Ketal Nitrone Precursor

Having procured access to three different nitrone precursors (i.e., **182**, **200**, and **202**) efforts to synthesize the corresponding nitrones—and apply them in the subsequent (3+2) cycloadditon reaction—ensued. Unfortunately initial attempts to form nitrone **178** from nitrone precursor **182** only resulted in complex reaction mixtures for which the results were difficult to interpret. As a result, we chose to first explore the desilylative cyclization of the less complex ketal nitrone precursor **202**, recognizing that it wouldn't require selective desilylation of the silyl oxime in the presence of an *O*-TBDPS silyl alcohol.

Using conditions similar to those described by Chevrier et al. (TBAF, dry CH_3CN, 80 °C, 1 hour), the desired desilylative cyclization of (±)-**202** to (±)-**201** was attempted (Scheme 4.14).[12] Complete desilylation of (±)-**202** rapidly following the addition of tetrabutylammonium fluoride (TBAF) was observed. After heating the solution to 70 °C for one hour, two products were identified in the reaction mixture. Gratifyingly, one of these corresponded to the desired nitrone ((±)-**201**). The other appeared to be

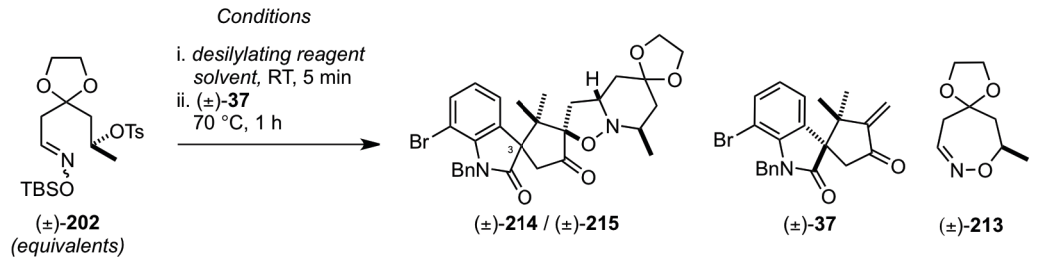
Scheme 4.14

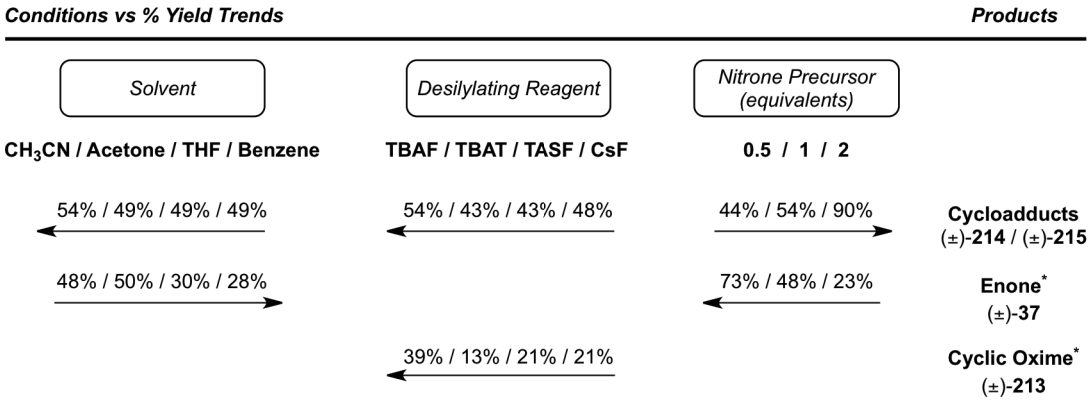


an undesired cyclic oxime ((±)-**213**).[13] Although spectroscopic data for the two compounds was similar, they were easily distinguished by the significantly increased polarity of (±)-**201** relative to (±)-**213** by TLC.

Unfortunately, isolated yields of (±)-**201** were very low (<25% yield), even when TLC and NMR analysis of crude reaction mixtures implied otherwise. Unsure of the stability of (±)-**201** and aware that enone (±)-**37** should be compatible with the nitrone-forming reaction conditions, a one-pot, nitrone-formation and (3+2) cycloaddition reaction was attempted. Impressively, desilylation of the nitrone precursor (±)-**202** (TBAF, CH_3CN, RT, 5 minutes), followed by immediate addition of the dipolarophile (±)-**37,** provided the combined cycloaddition isoxazolidines (±)-**214** and (±)-**215** in a 54% yield (*dr* 3:1) after only one hour (Scheme 4.15). Recovered enone ((±)-**37**) (~48%) and cyclic oxime ((±)-**213**) (~39%) were also obtained.[14]

Scheme 4.15



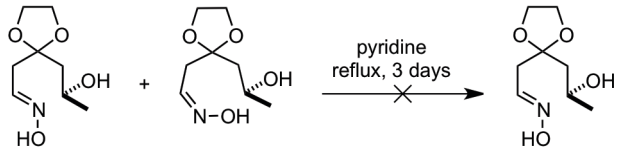


Our hope to improve the yields of (±)-**214** and (±)-**215** prompted optimization of the reaction via a series of experiments designed to explore the effect of solvent polarity, fluoride source, order of addition, temperature, and reactant stoichiometry (Scheme 4.15). A screen of solvents (CH_3CN,

acetone, THF, and benzene) revealed that solvent polarity did not have a substantial impact upon the amount of (±)-**214** and (±)-**215** generated; however, the recovery of enone (±)-**37** was slightly improved with polar solvents. The fluoride source (TBAF, TBAT, TASF, or CsF) showed little effect on cycloadduct yields; but, TBAF generated significant amounts of the cyclic oxime byproduct (±)-**213**. Comparable amounts of the cycloadducts were obtained with and without heating. On the other hand, the reaction stoichiometry demonstrated a dramatic effect. When two equivalents of the nitrone precursor (±)-**202** were added to the reaction, the yield of the combined cycloadducts (±)-**214** and (±)-**215** increased from 54% (*dr* 3:1) to 90% (*dr* 3:1).

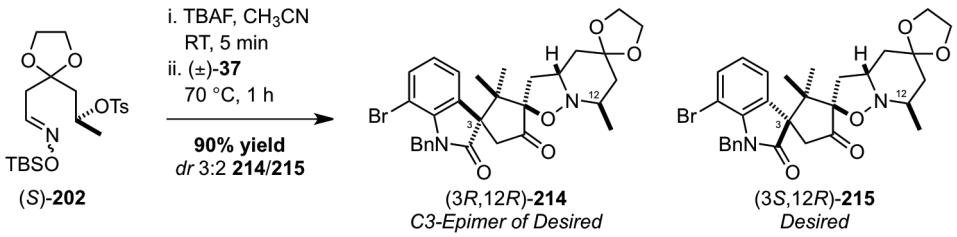
Collectively, these results suggested that the *E/Z* stereoisomers of the silyloxime were not equally competent at forming the nitrone ((±)-**201**). Perhaps optimistically, attempts were made to shift the *E/Z* ratio observed for (±)-**211** by isomerizing the higher energy (*Z*)-conformation to the lower energy (*E*)-conformation.[15] However, when a solution of (E/Z)-**211** was heated to 100 °C in pyridine for several days, no significant change in the diastereomeric ratio could be seen (Scheme 4.16). Thus, in the absence of *E*-enriched oxime (±)-**211**, it was determined that super-stoichiometric amounts of the nitrone precursor would be required for the cycloaddition reaction to reach completion.

Scheme 4.16



In an effort to explore the effect of enantioenriched nitrone on the diastereomeric ratio of cycloaddition products, the synthesis of enantioenriched nitrone precursor (*S*)-**202** was pursued. Starting from the commercially available (*S*)-β-hydroxybutyrate (*S*)-**188** the enantioenriched precursor (*S*)-**202** was

Scheme 4.17



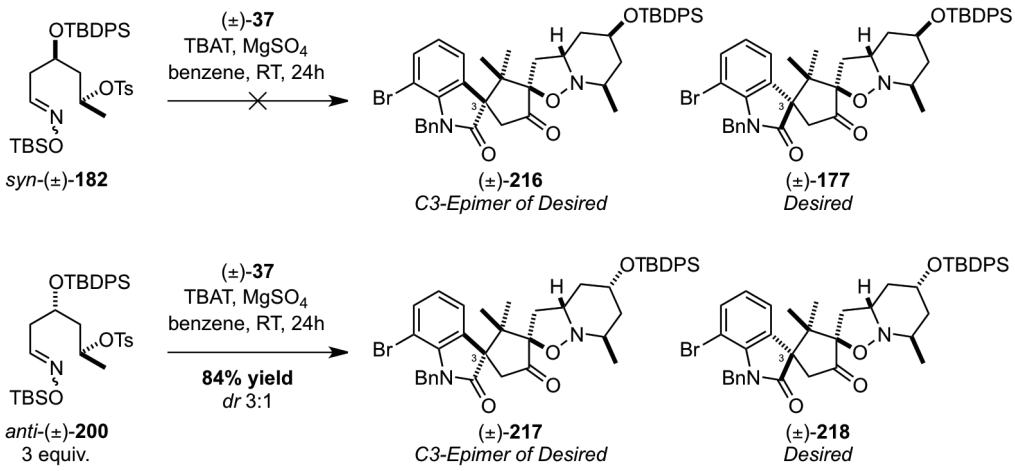
synthesized in the same fashion as (±)-**202** (see Scheme 4.13). As expected, resolution of the enone (±)-**37** with two equivalents of (*S*)-**202** under the desilylative cyclization conditions (TBAF, CH_3CN, 70 °C, 1 h) resulted in the isolation of the cycloadducts (3*R*,12*R*)-**214** and (3*S*,12*R*)-**215** in comparable yields, but with more of the desired isoxazolidine diastereomer (*dr* ~3:2) (Scheme 4.17).

4.2.2 Employing the C14-O-TBDPS Nitrone Precursors

Having established the utility of the desilylative cyclization to form nitrone **201,** which was capable of participating in a one-pot (3+2) cycloaddition reaction, we decided to revisit the C14-*O*-TBDPS nitrone precursors (±)-**182** and (±)-**200**. Unfortunately, the TBAF-mediated desilylative cyclization conditions did not prove compatible with the *O*-TBDPS alcohol protecting group and resulted in complex reaction mixtures. Seeking a more selective desilylation, Ishibashi's tetrabutylammonium triphenyldifluorosilicate (TBAT)[16] emerged as ideal reagent. Preliminary results using TBAT indicated that both (±)-**182** and (±)-**200** were competent in the nitrone-forming reaction, and led to investigations of the one-pot nitrone-formation / (3+2) cycloaddition protocol.

Unfortunately when (±)-**182** was exposed to enone (±)-**37** under the desilylative cyclization conditions (TBAT, benzene, $MgSO_4$, RT), no appreciable amounts of the desired cycloaddition products could be identified (Scheme 4.18). On the other hand, when two equivalents of (±)-**200** were exposed to

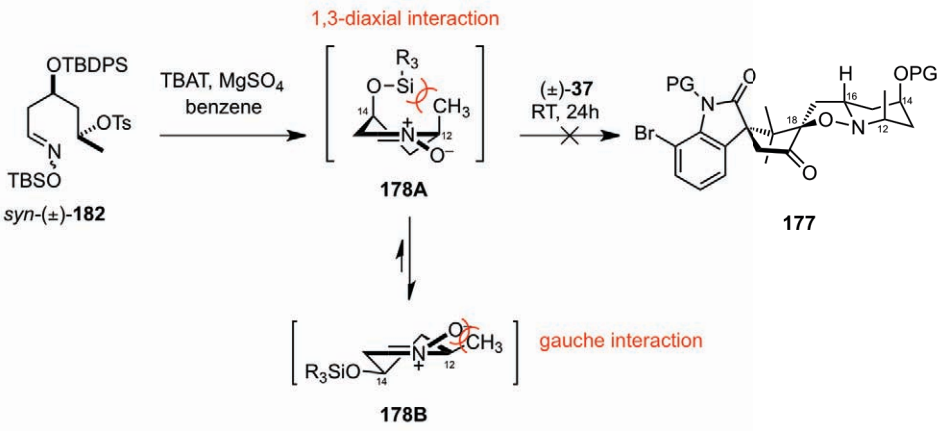
Scheme 4.18



the same conditions, the desired cycloadducts were isolated in 74% yield (*dr* ~3:1). Employing three equivalents of (±)-**200** provided a slight improvement in the yield (84% yield, *dr* ~3:1).

In order to rationalize the difference in reactivity between the *syn*-nitrone precursor (**182**) and the *anti*-nitrone precursor (**200**) we turned to conformational analysis. Analysis of the two half-chair conformations of *syn*-nitrone **178**, suggested that conformation **178A**—where both nitrone substituents are

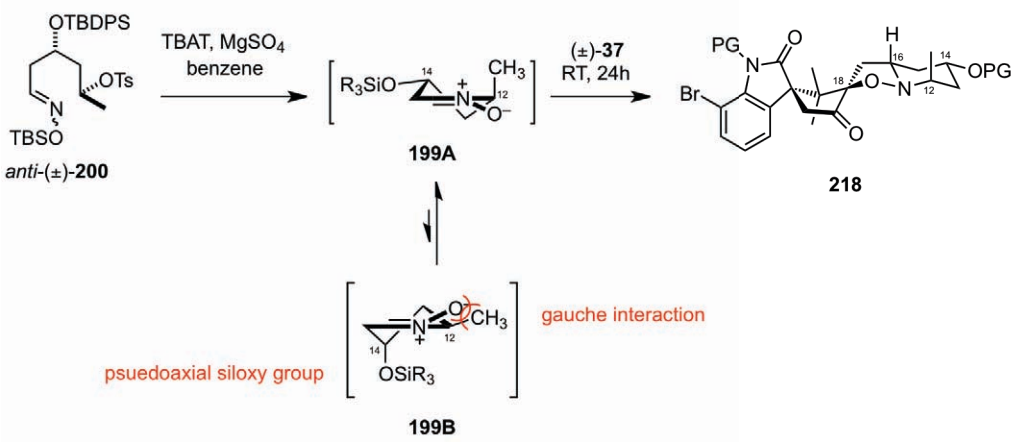
Scheme 4.19



pseudoaxial—would be higher in energy due to 1,3-diaxial interactions (Scheme 4.19). Regrettably, the more stable conformation **178B** would place the C12 methyl group gauche to the nitrone, perhaps disfavoring the approach of the dienophile in the (3+2) cycloaddition reaction or facilitating the reverse reaction.

In contrast, the more stable half-chair conformation of *anti*-nitrone **199** could favor the (3+2) cycloaddition reaction. Conformation **199B**—containing a psuedoaxially orientated C14-siloxy group and

Scheme 4.20

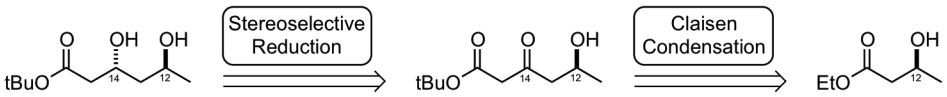


the deleterious gauche interaction—would be higher in energy than **199A** (Scheme 4.20). Most significantly, the favorable pseudoequatioal orientation of the silyloxy moiety in nitrone **199** suggested that this nitrone should participate *more readily* in the (3+2) cycloaddition relative to the C14-unsubstituted nitrone **57**. Experimental data support this supposition. Whereas (3+2) cycloaddition reactions with **57** required lengthy reaction times (7-10 days), cycloadditions with *anti*-nitrone precursor (±)-**200** were complete in less than 24 hours.

4.2.3 Synthesis of an Enantioenriched Anti-Nitrone

While the (3+2) cycloaddition of (±)-**200** and (±)-**37** enabled the synthesis of (±)-**217** and (±)-**218** in high overall yield (84% yield, *dr* 1:3), it was recognized that enantioenriched *anti*-nitrone **199** would be required to obtain greater yields of the desired, minor isoxazolidine **218**. Retrosynthetically, **200** was accessible from a non-racemic *anti*-diol (e.g., **194**); however, our desire to selectively synthesize the *anti*-diol to the exclusion of the *syn*-diol (i.e., **195**, Scheme 4.8) prompted us to pursue an alternate, stereoselective reduction of ketone **208**, readily accessible from (*S*)-**188** (Scheme 4.21).

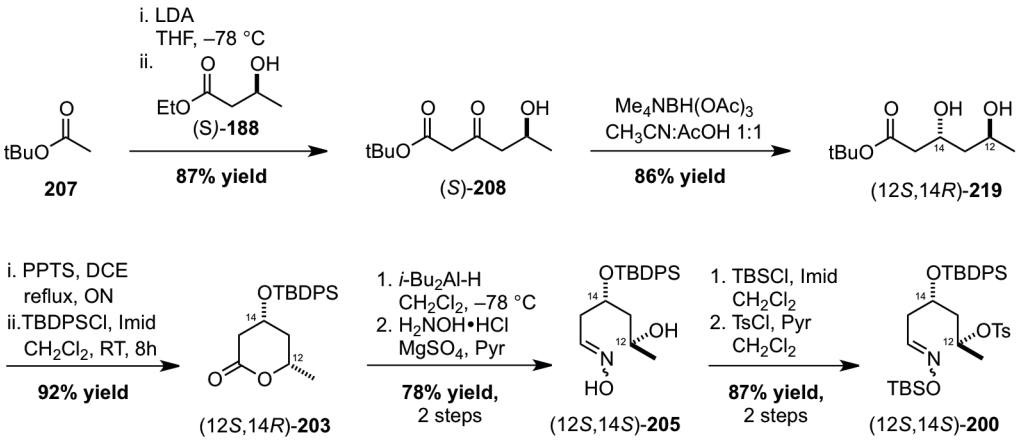
Scheme 4.21



(12*S*,14*R*)-**219** (*S*)-**208** (*S*)-**188**

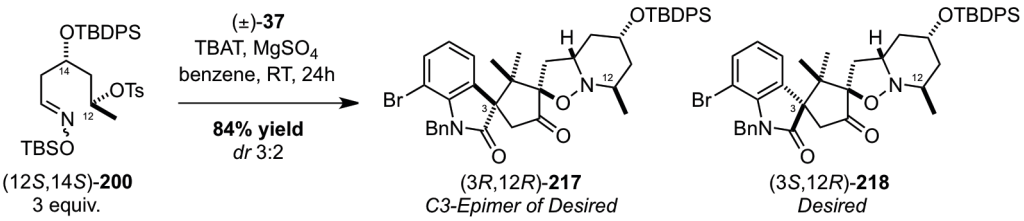
Following a literature procedure, (*S*)-**188** was synthesized from the Claisen condensation of t-butyl acetate **207** and hydroxybutyrate (*S*)-**188** (Scheme 4.22).[17] Subjection of the hydroxyketone (*S*)-**208** to an Evans' reduction ($Me_4NBH(OAc)_3$, CH_3CN/AcOH 1:1) provided the desired diol (12*S*,14*R*)-**219** in high yield and good diastereoselectivity.[18] Lactonization of (12*S*,14*R*)-**219** using pyridinium *p*-toluenesulfonic acid in dichloroethane was immediately followed with protection of the secondary alcohol to provide (12*S*,14*R*)-**203**. Reduction and condensation with hydroxylamine were followed with silyl protection of the oxime and tosylation to provide the non-racemic nitrone precursor (12*S*,14*S*)-**200**.

Scheme 4.22



As expected, when (12*S*,14*S*)-**200** was exposed to enone (±)-**37** under the desilylative cyclization conditions (TBAT, benzene, $MgSO_4$, RT), the desired cycloadducts (3*R*,12*R*)-**217** and (3*S*,12*R*)-**218** were isolated in high yield, but with improved diastereoselectivity (*dr* ~3:2) (Scheme 4.23).

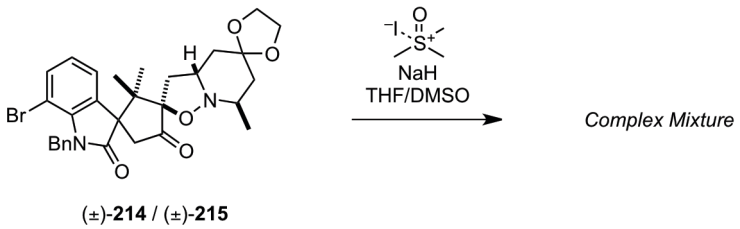
Scheme 4.23



4.3 Beyond the Cycloaddition

With two sets of C14-substituted isoxazolidines in hand, we began efforts to advance toward a ring-fusion epoxide (e.g., **176**, Scheme 4.1). Unfortunately, chromatographic separation of the

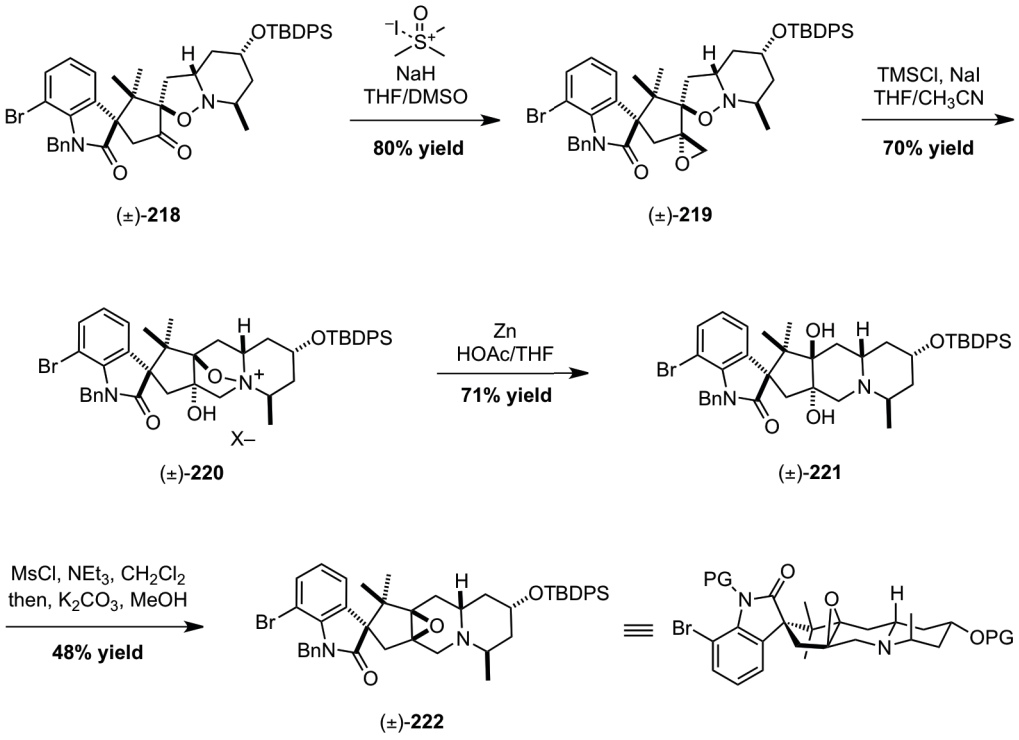
Scheme 4.24



isoxazolidines (±)-**214** and (±)-**215** proved prohibitively difficult. Attempts were made to employ Corey-Chakovsky epoxidation conditions on the mixture with the hope that the resulting diastereomers might be separated following work up (Scheme 4.24). In practice, however, this did not prove to be fruitful and a complex mixture was obtained.

Isoxazolidine (±)-**218**, more easily isolated from the (3+2) cycloaddition reaction, readily participated in the Corey-Chakovsky epoxidation reaction to give the desired spiro-epoxide (±)-**219** (Scheme 4.25). Exposure to Caputo's conditions (TMSCl, NaI, THF/CH_3CN) enabled the intramolecular opening of spiro-epoxide (±)-**219** to provide the corresponding ammonium iodide salt (±)-**220**.[19] Interestingly, the counterion of the ammonium salt appeared to be susceptible to exchange. When a brine wash of the reaction mixture was conducted, the resulting product—believed to be the ammonium chloride salt—was not reactive toward reductive cleavage of the N-O bond. Omission of the brine wash, however, provided a product ((±)-**220**) that was susceptible to the reductive zinc and acetic acid conditions necessary to furnish diol (±)-**221**. Diol (±)-**221** was successfully advanced to the ring-fusion epoxide (±)-**222** following mesylation and exposure to base.

Scheme 4.25



4.4 Conclusions

Endeavoring toward a total synthesis of Citrinadin A (**1**) using the (3+2) cycloaddition strategy outlined for Citrinadin B (**2**) (See Chapters 2 and 3) led to the design of a desilylative cyclization reaction for the synthesis of C14-substituted nitrones.

In total, three nitrone precursors were explored: a ketal-nitrone **202**, a *syn*-*O*-TBDPS-nitrone **182**, and an *anti*-*O*-TBDPS nitrone **200**. Desilylative cyclization of **202** revealed that the corresponding ketal-nitrone **201** could be isolated, but in low yield. On the other hand, in-situ nitrone formation in the presence of the enone dipolarophile (±)-**37** resulted in high combined yields of the desired ketal cycloadducts **214** and **215**. Optimal yields required at least two equivalents of the nitrone precursor **202**.

Desilylative cyclization of the *syn*-*O*-TBDPS-nitrone precursor (±)-**182** in the presence of enone (±)-**37** did not result in the isolation of any (3+2) cycloaddition products. However, desilylative cyclization of the *anti*-*O*-TBDPS nitrone precursor **200** provided the combined cycloadducts ((±)-**217** and (±)-**218**) in high overall yield (84% yield). The synthesis of an enantioenriched nitrone precursor **200** improved the yield of the minor, desired cycloadduct ((3*S*,12*R*)-**218**) from 25% to 40% yield.

Advancing toward a synthesis of Citrinadin A (**1**), isoxazolidine (±)-**218** was subjected to reaction conditions resulting in the formation of ring-fusion expoxide (±)-**222**, analogous to epoxide (+)-**152** (e.g. Scheme 3.34) used in the total synthesis of *ent*-**2** and **175**.

Elaboration of **222** to access **1** would require incorporation of the 1,2 amino alcohol moiety, installation of the epoxyketone side-chain, and installation of the *N*,*N*-dimethylvaline ester. Although the latter necessitates an inversion of the C14 stereochemistry, this should be readily accomplished using a Mitsunobu esterification.[20] Forthcoming efforts to access **1** will be reported in due course.

4.5 Experimental

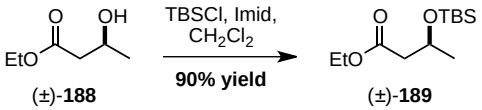
4.5.1 Materials and Methods

General. Unless otherwise stated, reactions were magnetically stirred in flame- or oven-dried glassware under an atmosphere of nitrogen. Triethylamine, diisopropylamine, and methanol were dried over calcium hydride and freshly distilled. Benzene, tetrahydrofuran, dichloromethane, toluene, and diethyl ether were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. Anhydrous CH_3CN, DMF, DMSO, acetone, and 1,2-dichloroethane were supplied by Fischer Scientific and purchased from the Colorado State Chemistry Stockroom and kept under a nitrogen atmosphere. All other commercially available reagents were used as received.

Unless otherwise stated, all reactions were monitored by thin-layer chromatography (TLC) using Silicycle glass-backed extra hard layer, 60 Å plates (indicator F-254, 250 μm). Column or flash chromatography was performed with the indicated solvents using Silicycle SiliaFlash. P60 (230-400 mesh) silica gel as the stationary phase. All melting points were obtained on a Gallenkamp capillary melting point apparatus (model: MPD350.BM2.1) and are uncorrected. Infrared spectra were obtained using a Nicolet Avatar 320 FTIR or Bruker Tensor 27 FTIR. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500, Varian Inova 400, Varian Inova 400 autosampler, or Varian Inova 300 spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to internal residual solvent peaks from indicated deuterated solvents. Coupling constants (*J*) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent, par = partial. High resolution mass spectra were performed at the Central Instrument Facility by Donald L. Dick of Colorado State University. Single-crystal X-ray analyses were performed by Susie Miller, Brian Newell, and Stephanie Fielder of Colorado State University.

4.5.2 Preparative Procedures

Preparation of Silyl Alcohol 189

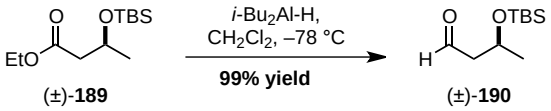


(±)-**188** (±)-**189**

To a solution of ethyl-3-hydroxybutyrate (6.5 ml, 50 mmol) in CH_2Cl_2 (125 ml) was added imidazole (3.7 g, 55 mmol). The solution was cooled to 0 °C in an ice bath and tertbutyldimethylsilyl chloride was added (11.3 g, 75 mmol). The reaction was allowed to stir at room temperature over night (17 h) before adding a 50% saturated NH_4Cl solution. The layers were separated and the aqueous portion was extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated, and subjected to flash chromatography (0.5%→1%→2%→4%→6% EtOAc/hexanes) to provide the silyl alcohol as a light yellow oil (11.1 g, 90% yield).

Known compound; CAS 81327-43-7. Characterization data matched literature reports.

Preparation of Aldehyde 190

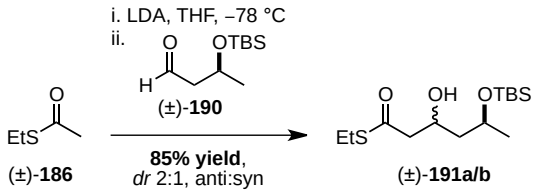


(±)-**189** (±)-**190**

A solution of the ester (12.1 g, 49 mmol, azeotroped with toluene) in CH_2Cl_2 (450 ml) was cooled to –78 °C in a three-neck flask. To this was added diisobutylaluminum hydride (1 M in hexanes, 54 ml, 54 mmol) dropwise via addition funnel. This stirred cold for another hour, at which time the reaction was quenched at –78 °C with MeOH (50 ml) and allowed to warm to room temperature. The resulting reaction solution was vigorously stirred with an added solution of Rochelle's salt (50 g in 200 ml H_2O) for one hour. Following separation of the layers, the aqueous portion was extracted with CH_2Cl_2 (200 ml), and the combined organics were washed with water and brine, dried (Na_2SO_4), and concentrated to provide the aldehyde (9.9 g, 100% yield) as a clear oil, used in the next step without further purification.

Known compound; CAS 92775-37-6. Characterization data matched literature reports.

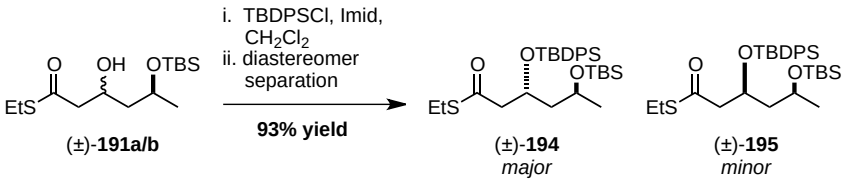
Preparation of the β-Hydroxyketones 191a and 191b



To a solution of diisopropylamine (8.9 ml, 63.6 mmol) in THF (125 ml) at 0 °C was added *n*-BuLi (1.47 M in hexanes, 38 ml, 56.1 mmol). This was stirred at 0 °C for 30 minutes, then cooled to –78 °C before adding EtSAc (6 ml, 56.1 mmol, as a solution in THF (75 ml), dried over molecular sieves). After 30 minutes, the aldehyde (9.4 g, ~85% pure, ~37.4 mmol, as a solution in THF (125 ml), dried over molecular sieves) was added. The reaction was allowed to stir for 3 hours at –78 °C before quenching the reaction with a 50% saturated NH_4Cl solution at –78 °C. Upon warming to room temperature, the layers were separated and the THF removed in vacuo. The aqueous portion was extracted with EtOAc and the combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated, and subjected to flash chromatography (2%→4%→6%→8%→10% EtOAc/hexanes) to provide the diol as a light yellow oil (8.5 g, *dr* 2:1 anti/syn, 74% yield) and some less pure product fractions (2.4 g, *dr* 7:3, ~2:3 diol/aldehyde, ~11% yield).

R_f = 0.12 (5% EtOAc/hexanes); ^{1}H NMR (300 MHz; $CDCl_3$; *dr* 2:1 anti/syn mixture) δ 4.40 (dddt, *J* = 10.0, 7.5, 4.9, 2.5 Hz, 0.7 H, O**CH**), 4.27~4.13 (m, 0.3 H, O**CH**), 4.18 (td, *J* = 6.3, 3.5 Hz, 0.7 H, O**CH**), 4.12~4.03 (m, 0.3 H, O**CH**), 3.62 (d, *J* = 1.8 Hz, 0.3 H, **OH**), 3.59 (d, *J* = 2.6 Hz, 0.7 H, **OH**), 2.94~2.86 (m, 1.4 H + 0.6 H, S**CH$_2$**), 2.79~2.61 (m, 1.4 H + 0.6 H, OCH**CH$_2$**), 1.70~1.59 (m, 1.4 H, OCH**CH$_2$**), 1.51 (ddd, *J* = 14.1, 6.3, 2.5 Hz, 0.6 H, OCH**CH$_2$**), 1.25 (tx2, *J* = 7.5 Hz, 2.1 H + 0.9 H, SCH_2**CH$_2$**), 1.20 (dx2, *J* = 6.2 Hz, 2.1 H + 0.9 H, **CH$_3$**), 0.89 (sx2, 6.3 H + 2.7 H, **TBS**), 0.10 (d, *J* = 3.7 Hz, 1.8 H, **TBS**), 0.08 (d, *J* = 3.4 Hz, 4.2 H, **TBS**). ^{13}CNMR (100 MHz, $CDCl_3$) δ 198.63, 198.39, 68.91, 68.00, 66.84, 65.71, 51.57, 51.26, 45.35, 44.32, 24.33, 23.45, 23.43, 23.30, 18.05, 18.01, 14.73, 14.70, -3.90, -4.38, -4.67, -4.88; IR (thin film): cm^{-1}; HRMS (ESI) Calcd. for $C_{12}H_{25}NaO_3Si$ [M+Na]: 329.1581. Found: 329.1583.

Preparation of the Bis-Protected Diols 194 and 195



To a solution of the alcohol (6:4 anti/syn, 8.4 g, 27.4 mmol) in CH_2Cl_2 (100 ml) was added imidazole (3.7 g, 54.8 mmol) and then tertbutyldiphenylsilyl chloride (7.8 g, 30.1 mmol) at room temperature. The reaction was allowed to stir for 24 hours before adding a 50% saturated NH_4Cl solution. The layers were separated, and the aqueous portion was extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated, and subjected to flash chromatography. To obtain the best separation of diastereomers, the residue was adsorbed onto silica gel (1 column volume) and loaded onto a bed of silica (3 column volumes) (0%→2.5%→5% (Hold until 2nd diastereomer starts to elute)→7.5%→10%→80% Toluene/hexanes). This provided the pure bis-protected *anti*-diol (5 g), enriched *anti*-diol (2.5 g), and enriched *syn*-diol (6 g) for a total yield of 13.5 g (93% yield).

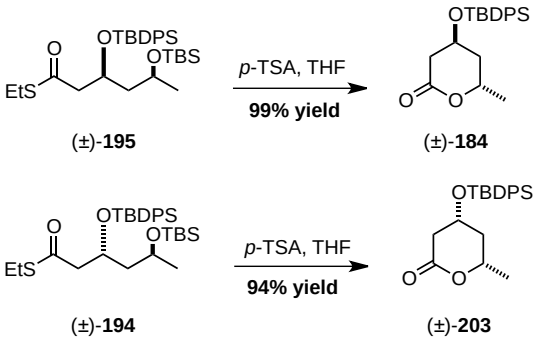
Anti Diol 194: R_f = 0.53 (40% Toluene/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (m, 4H, **TBDPS**), 7.40 (m, 6H, **TBDPS**), 4.26 (m, 1H, O**CH**), 3.56 (m, 1H, O**CH**), 2.84 (qd, *J* = 7.4 Hz, 1.4 Hz, 2H, S**CH$_2$**CH$_3$), 2.76 (dd, *J* = 14.4 Hz, 6.9 Hz, 1H, SC**CH$_2$**), 2.70 (dd, *J* = 14.4 Hz, 5.3 Hz, 1H, SC**CH$_2$**), 1.69 (dt, *J* = 14.0 Hz, 7.1 Hz, 1H, OC**CH$_2$**CO), 1.53 (ddd, *J* = 13.8 Hz, 5.5 Hz, 4.8 Hz, 1H, OC**CH$_2$**CO), 1.23 (t, *J* = 7.4 Hz, 3H, SCH$_2$**CH$_3$**), 1.03 (s, 9H, ***t*-Bu**), 0.84 (d, *J* = 6.1 Hz, 3H, CH**CH$_3$**), 0.82 (s, 9H, ***t*-Bu**), -0.04 (s, 3H, **CH$_3$**), -0.06 (s, 3H, **CH$_3$**); ^{13}C-NMR (100 MHz, CDCl3) δ 14.80, 18.13, 19.51, 23.45, 24.12, 26.01, 27.06, 47.84, 52.44, 66.39, 69.57, 127.69, 129.73, 129.80, 133.94, 134.30, 135.71, 136.06, 136.09, 197.28, -4.08, -4.51; IR (thin film): 2930 (s), 2857 (s), 1691 (s), 1112 (s), 703 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{28}H_{43}NaO_3Si_2$ [M+Na]: 567.2760. Found: 567.2760.

Syn Diol 195: R_f = 0.37 (40% Toluene/hexanes); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.71~7.66 (m, 4H, **TBDPS**), 7.43~7.34 (m, 6H, **TBDPS**), 4.33 (quintet, *J* = 6.2 Hz, 1H, O**CH**), 3.84 (dt, *J* = 12.1, 6.1 Hz, 1H, O**CH**), 2.81 (q, *J* = 7.4 Hz, 2H, S**CH$_2$**), 2.73 (dd, *J* = 5.7, 4.3 Hz, 2H, OC**CH$_2$**), 1.68 (dt, *J* = 13.4, 6.6 Hz, 1H, OC**CH$_2$**), 1.56 (m, 1H, OC**CH$_2$**), 1.21 (t, *J* = 7.4 Hz, 3H, SCH$_2$**CH$_2$**), 1.03 (s, 9H, ***t*-Bu**), 0.86 (d, *J* = 6.1 Hz, 3H, CH**CH$_3$**), 0.80 (s, 9H, ***t*-Bu**), -0.03 (s, 6H, **CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.94,

140.70, 138.77, 138.55, 134.37, 134.36, 132.30, 132.27, 73.20, 70.34, 56.03, 51.27, 31.74, 30.61, 28.22, 28.06, 24.15, 22.71, 19.38, 18.89, 0.47, -0.00; IR (thin film): 2931 (s), 2857 (s), 1691 (s), 1111 (s), 703 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{28}H_{43}NaO_3Si_2$ [M+Na]: 567.2760. Found: 567.2747.

Preparation of Lactones 184 and 203

(Representative Procedure)



To a solution of the silyl alcohol (5 g, 9.2 mmol) in THF (100 ml) at room temperature was added *p*-toluenesulfonic acid (5.2 g, 27.5 mmol). The reaction was allowed to stir overnight (12 h). The reaction was cooled to 0 °C in an ice bath and basified with a 50% saturated $NaHCO_3$ solution (200 ml). To the biphasic mixture was added hydrogen peroxide (30% w/w H_2O_2, 1 ml, 9.2 mmol) and this was stirred vigorously for two hours. Water was added to dissolve any residual salts, and the layers were separated. The aqueous portion was extracted with EtOAc, and the combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated, and purified by flash chromatography (2%→4%→6%→10%→20% EtOAc/hexanes) to yield the lactone as a viscous oil (3.2 g, 94%).

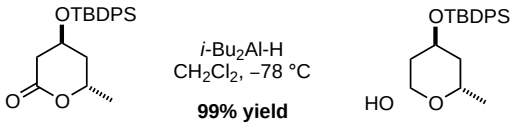
***syn*-Lactone 184:** Known compound. CAS 136786-47-5. Characterization data matched literature reports.

***anti*-Lactone 203:** Characterization data matched literature reports for the (+)-(R,R)-stereoisomer, CAS 263369-05-7.

Preparation of Lactols 183 and 204

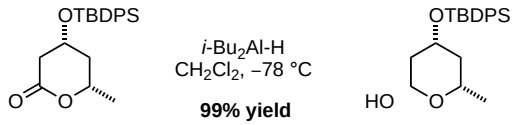
(Representative Procedure)

Lactone (3.2 g, 8.7 mmol) in CH_2Cl_2 (90 ml) was cooled to –78 °C for the addition of diisobutylaluminum hydride solution (1 M in hexanes, 9.6 ml, 9.6 mmol). This stirred cold for two hours at which time the reaction was quenched at –78 °C with MeOH (9 ml) and allowed to warm to room temperature. The resulting reaction solution was vigorously stirred with an added solution of Rochelle's salt (9 g in 100 ml H_2O) for one hour. Following separation of the layers, the aqueous portion was extracted with Et_2O, and the combined organics were washed with brine, dried (Na_2SO_4), and concentrated to provide the lactol as a 1:1 mixture of anomers (3.2 g, 100% yield), which was used in the next step without further purification.



(±)-**184** (±)-**183**

***anti*-Lactol 183:** Characterization data matched literature reports for the (+)-(R,R)-stereoisomer, CAS 263369-06-8.



(±)-**203** (±)-**204**

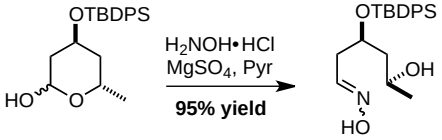
syn*-Lactol 204:* R_f = 0.29~0.44 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.68 (m, 8H, **TBDPS**), 7.46-7.36 (m, 12H, **TBDPS**), 5.30 (br t, 1H, O**CH**O), 4.50 (ddd, *J* = 9.7, 6.6, 2.1 Hz, 1H, O**CH**O), 4.22 (m, 1H, O**CH**), 3.91 (m, 2H, O**CH** & **OH**), 3.79 (tt, *J* = 10.9, 4.8 Hz, 1H, O**CH**), 3.31 (dqd, *J* = 11.6, 5.9, 1.9 Hz, 1H, O**CH**), 3.01 (t, *J* = 2.6 Hz, 1H, **OH**), 2.09 (ddt, *J* = 12.2, 4.4, 2.1 Hz, 1H, O_2C**C**$\mathbf{H_2}$CH), 1.98 (ddt, *J* = 12.8, 4.7, 1.7 Hz, 1H, O_2C**C**$\mathbf{H_2}$CH), 1.76 (m, 2H, O_2C**C**$\mathbf{H_2}$CH & OC**CH**-$_2$CH), 1.60 (dddd, *J* = 12.9, 11.0, 3.6, 2.0 Hz, 1H, O_2C**C**$\mathbf{H_2}$CH), 1.48~1.26 (m, 3H, OC**C**$\mathbf{H_2}$CH), 1.19 (d, *J* = 6.2 Hz, 3H, **C**$\mathbf{H_3}$), 1.11 (d, *J* = 6.3 Hz, 3H, **C**$\mathbf{H_3}$), 1.08 (s, 9H, **TBDPS**), 1.07 (s, 9H, **TBDPS**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.83, 134.60, 134.48, 134.24, 134.13, 129.84, 129.82, 129.70, 129.69, 127.76, 127.74, 127.67, 127.65, 94.39, 92.93, 68.28, 68.16, 65.14, 64.16, 43.30, 42.61, 42.29, 39.51, 27.07, 27.01,

21.51, 21.27, 19.24, 19.19; IR (thin film): 3398 (br, m), 2932 (m), 2858 (m), 1428 (m), 1112 (s), 702 (s) $cm^{=1}$; HRMS (ESI) Calcd. for $C_{22}H_{30}NaO_3Si$ [M+Na]: 393.1858. Found: 393.1862.

Preparation of Oximes 197, 205, and 211

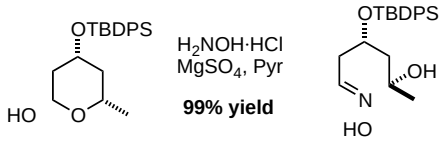
(Representative Procedure)

Lactol **183** (2.8 g, 7.6 mmol) was taken up in pyridine (15 ml). To this was added anhydrous magnesium sulfate (1.8 g, 15.2 mmol) and hydroxylamine hydrochloride (791 mg, 11.4 mmol). This was allowed to stir at room temperature for 36 hours. To work up, the reaction mixture was filtered through Celite, which was subsequently washed with 1:1 CH_2Cl_2/hexanes and then CH_2Cl_2. The resulting solution was concentrated, azeotroped with hexanes, and subjected to column chromatography (5%→10%→15%→30%→50% EtOAc/hexanes) to provide oxime **197** as an oil in a 1:1 mixture of *E*/Z isomers (2.9 g, 100%).



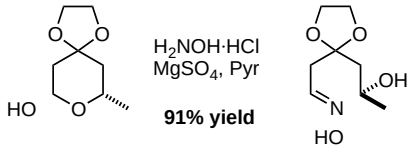
(±)-**183** (±)-**197**

Oxime 197: R_f = 0.18 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H, N**OH**), 8.35 (s, 1H, N**OH**), 7.71~7.67 (m, 7H, **TBDPS**), 7.64 (d, *J* = 7.1 Hz, 1H, **TBDPS**), 7.47-7.36 (m, 12H, **TBDPS**), 7.31 (t, *J* = 6.3 Hz, 1H, N**CH**), 6.77 (t, *J* = 5.5 Hz, 1H, N**CH**), 4.16 (m, 2H, O**CH**), 3.90 (m, 2H, O**CH**), 2.57 (ddd, *J* = 15.9, 5.8, 4.4 Hz, 1H, NCH**CH$_2$**), 2.46 (dt, *J* = 15.9, 5.6 Hz, 1H, NCH**CH$_2$**), 2.36 (dt, *J* = 14.6, 6.3 Hz, 1H, NCH**CH$_2$**), 2.28 (ddd, *J* = 14.6, 6.8, 4.2 Hz, 1H, NCH**CH$_2$**), 2.14 (s, 1H), 1.67 (m, 2H, OC**CH$_2$**), 1.57 (m, 2H, OC**CH$_2$**), 1.073 (s, 9H, **TBDPS**), 1.069 (s, 9H, **TBDPS**), 1.04 (2 x d, *J* = 6.2 Hz, 6H, **CH$_3$**). ^{13}C NMR (100 MHz, CDCl3) δ 149.67, 149.50, 136.49, 136.33, 134.28, 134.27, 134.08, 134.03, 130.52, 128.36, 70.69, 70.11, 66.32, 66.11, 46.37, 46.36, 46.01, 45.99, 37.40, 32.89, 27.62, 24.42, 24.38, 19.88; IR (thin film): 3281 (br, m), 2932 (m), 1428 (m), 1111 (s), 738 (m), 703 (s) $cm^{=1}$; HRMS (ESI) Calcd. for $C_{22}H_{31}NNaO_3Si$ [M+Na]: 408.1969. Found: 408.1970.



(±)-**204** (±)-**205**

Oxime 205: R_f = 0.12 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (br s, 1H, N**OH**), 8.81 (br s, 1H, N**OH**), 7.71~7.66 (m, 8H, **TBDPS**), 7.45~7.35 (m, 12H, **TBDPS**), 7.26 (t, *J* = 6.3 Hz, 1H, N**CH**), 6.67 (t, *J* = 5.5 Hz, 1H, N**CH**), 4.15 (m, 2H, O**CH**), 3.94 (m, 2H, O**CH**), 2.63 (ddd, *J* = 15.8 Hz, 6.8 Hz, 5.5 Hz, 1H, NCH**CH$_2$**), 2.55 (ddd, *J* = 15.8 Hz, 5.3 Hz, 4.9 Hz, 1H, NCH**CH$_2$**), 2.45 (ddd, *J* = 14.6 Hz, 7.1 Hz, 6.2 Hz, 1H, NCH**CH$_2$**), 2.30 (ddd, *J* = 14.6 Hz, 6.6 Hz, 4.4 Hz, 1H, NCH**CH$_2$**), 1.66-1.52 (m, 4H, OC**CH$_2$**), 1.069 (s, 9H, **TBDPS**), 1.065 (s, 9H, **TBDPS**), 1.05 (d, *J* = 6.2 Hz, 6H, **CH$_3$**); ^{13}C NMR (100 MHz, CDCl3) δ 149.54, 148.81, 148.64, 136.02, 135.99, 133.48, 133.47, 133.38, 133.33, 130.09, 127.89, 69.73, 69.24, 64.60, 64.52, 45.08, 44.63, 36.70, 32.38, 27.11, 23.78, 19.35; IR (thin film): 3268 (br, m), 2931 (m), 2858 (m), 1428 (m), 1112 (s), 738 (m), 703 (s) cm$^{=1}$; HRMS (ESI) Calcd. for $C_{22}H_{31}NNaO_3Si$ [M+Na]: 408.1969. Found: 408.1971.



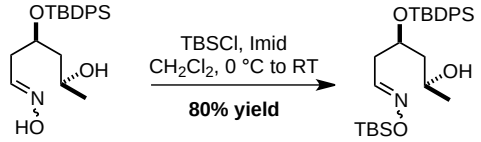
(±)-**210** (±)-**211**

Oxime 211: R_f = 0.15 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H, N**OH**), 7.43 (s, 1H, N**OH**), 7.40 (t, *J* = 6.5 Hz, 1H, N**CH**), 6.80 (t, *J* = 5.5 Hz, 1H, N**CH**), 4.13-4.00 (m, 10H, **CH-$_2$CH$_2$** & O**CH**), 3.38 (d, *J* = 10.0 Hz, 2H, **OH**), 2.80 (qd, *J* = 17.6, 5.5 Hz, 2H, NCH**CH$_2$**), 2.58 (m, 2H, NCH**CH$_2$**), 1.82 (m, 4H, OCH**CH$_2$**), 1.17 (d, *J* = 6.3 Hz, 6H, CH**CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.22, 146.88, 110.19, 110.05, 65.08, 64.97, 64.78, 64.67, 63.97, 63.86, 44.99, 44.93, 37.78, 32.99, 23.18, 23.14; IR (thin film): 3313 (br s), 2970 (s), 1416 (m), 1143 (m), 1065 (m), 948 (m) cm$^{=1}$; HRMS (ESI) Calcd. for $C_8H_{16}NO_4$ [M+H]: 190.1079. Found: 190.1076.

Preparation of Silyl-Protected Oximes 198, 206, and 212

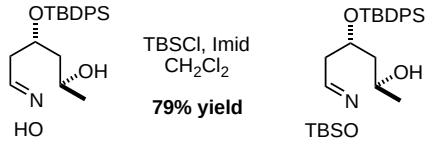
(Representative Procedure)

To a solution of oxime **205** (2.9 g, 7.6 mmol, azeotroped in toluene) in CH_2Cl_2 (75 ml) was added imidazole (1 g, 15.2 mmol). The solution was cooled to 0 °C in an ice bath and tertbutylsilyl chloride (0.6 g, 4 mmol) was added. The reaction was stirred cold for 45 minutes. Then, another portion of tertbutylsilyl chloride (0.6 g, 4 mmol) was added and the reaction was allowed to gradually come to room temperature overnight. The reaction was extracted with a 50% saturated NH_4Cl solution and the aqueous was extracted with Et_2O. The organic extracts were washed with brine, dried (Na_2SO_4), concentrated, and purified by flash chromatography (0%→2%→4%→8%→15% EtOAc/Hexanes) to yield the TBS-protected oxime **206** as an oil (3 g, 79% yield).



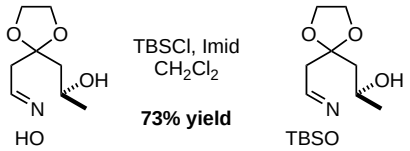
(±)-**197** (±)-**198**

***O*-TBS Oxime 198:** R_f = 0.21 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71~7.68 (m, 8H, **TBDPS**), 7.47~7.36 (m, 13H, **TBDPS** & N**CH**), 6.95 (t, *J* = 5.4 Hz, 1H, N**CH**), 4.17 (m, 2H, O**CH**), 3.88 (dtd, *J* = 13.2, 7.0, 3.5 Hz, 2H, O**CH**), 2.62 (ddd, *J* = 15.7, 5.9, 4.1 Hz, 1H, NCH**CH$_2$**), 2.43 (m, 1H, NCH**CH$_2$**), 2.36 (d, *J* = 6.4 Hz, 1H, NCH**CH$_2$**), 2.30 (ddt, *J* = 14.5, 6.8, 3.6 Hz, 1H, NCH**CH$_2$**), 2.13 (d, *J* = 3.8 Hz, 1H, **OH**), 1.95 (d, *J* = 4.0 Hz, 1H, **OH**), 1.66 (m, 3H, OCH**CH$_2$**), 1.55 (ddd, *J* = 14.3, 6.4, 3.5 Hz, 1H, OCH**CH$_2$**), 1.079 (m, 18H + 3H + 3H, **TBDPS** & CH**CH$_3$**), 0.91 (s, 9H, **TBS**), 0.89 (s, 9H, **TBS**), 0.127 (s, 6H, **TBS**), 0.123 (s, 6H, **TBS**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.51, 152.44, 135.98, 133.87, 133.84, 133.62, 133.51, 130.05, 130.01, 129.99, 127.89, 127.88, 127.85, 127.84, 70.57, 70.09, 66.04, 65.88, 45.97, 45.47, 37.01, 32.87, 27.14, 27.12, 26.23, 26.15, 23.99, 23.96, 19.39, 19.38, 18.30, 18.21, -5.12, -5.16; IR (thin film): 3440 (br, m), 2931 (s), 1428 (m), 1252 (m), 1111 (s), 703 (s) cm$^{=1}$; HRMS (ESI) Calcd. for $C_{28}H_{46}NO_3Si2$ [M+H]: 500.3020. Found: 500.3017.



(±)-**205** (±)-**206**

***O*-TBS Oxime 206:** R_f = 0.72 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73~7.68 (m, 8H, **TBDPS**), 7.47~7.37 (m, 12H, **TBDPS**), 7.33 (t, *J* = 6.3 Hz, 1H, N**CH**), 6.85 (t, *J* = 5.4 Hz, 1H, N**CH**), 4.17 (m, 2H, O**CH**), 4.01 (ddqt, *J* = 18.1 Hz, 9.1 Hz, 6.1 Hz, 3.0 Hz, 2H, O**CH**), 2.70 (ddd, *J* = 15.6 Hz, 7.1 Hz, 5.5 Hz, 1H NCH**CH$_2$**), 2.57 (ddd, *J* = 15.7 Hz, 9.9 Hz, 5.1 Hz, 1H, NCH**CH$_2$**), 2.53 (dt, *J* = 14.5 Hz, 6.6 Hz, 1H, NCH**CH$_2$**), 2.5 (d, *J* = 3.0 Hz, 1H, **OH**), 2.31 (ddd, *J* = 14.5 Hz, 5.9 Hz, 4.3 Hz, 1H, NCH**CH$_2$**), 2.27 (d, *J* = 3.2 Hz, 1H, **OH**), 1.61 (m, 4H, OCH**CH$_2$**), 1.093 (d, *J* = 6.0 Hz, 3H, CH**CH$_3$**), 1.09 (s, 18H, **TBDPS**), 1.07 (d, *J* = 6.4, 3H, CH**CH$_3$**), 0.92 (s, 9H, **TBS**), 0.91 (s, 9H, **TBS**), 0.14 (s, 6H, **TBS**), 0.13 (s, 6H, **TBS**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.31, 152.10, 136.06, 136.01, 133.53, 133.46, 133.38, 133.25, 130.13, 130.11, 127.93, 127.90, 69.99, 69.48, 64.49, 64.31, 44.99, 44.03, 36.52, 32.86, 27.14, 26.23, 26.16, 23.82, 19.39, 19.34, 18.29, 18.23, -5.14, -5.16; IR (thin film): 3452 (br, m), 2931 (s), 2858 (s), 1472 (m), 1112 (s), 703 (s) cm$^{=1}$; HRMS (ESI) Calcd. for $C_{28}H_{46}NO_3Si2$ [M+H]: 500.3020. Found: 500.3016.



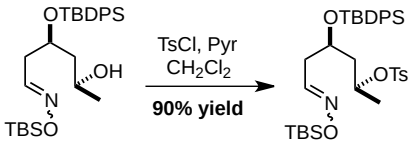
(±)-**211** (±)-**212**

***O*-TBS Oxime 212:** R_f = 0.33 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (t, *J* = 6.5 Hz, 1H, N**CH**), 6.92 (t, *J* = 5.4 Hz, 1H, N**CH**), 4.13-3.99 (m, 10H, **CH$_2$CH$_2$** & O**CH**), 3.40 (d, *J* = 11.7 Hz, 2H, **OH**), 2.80 (qd, *J* = 15.9, 5.7 Hz, 2H, NCH**CH$_2$**), 2.58 (d, *J* = 6.5, 2H, NCH**CH$_2$**), 1.85~1.75 (m, 4H, OCH**CH$_2$**), 1.16 (d, *J* = 6.2 Hz, 6H, CH**CH$_3$**), 0.93 (d, *J* = 2.1, 18H, **TBS**), 0.16 (d, *J* = 3.9, 12H, **TBS**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.12, 150.68, 110.54, 110.45, 65.20, 65.16, 64.87, 64.81, 63.98, 63.86, 45.19, 37.94, 33.56, 26.21, 26.16, 23.41, 23.37, 18.33, 18.27, -5.14; IR (thin film): 3541 (br s), 2930 (s), 2858 (s), 1473 (m), 1252 (m), 1143 (w), 1065 (w), 927 (m), 838 (m) cm$^{=1}$; HRMS (ESI) Calcd. for $C_{15}H_{29}NO_4Si$ [M+H]: 304.1944. Found: 304.1935.

Preparation of Nitrone Precursors 182, 200, and 202

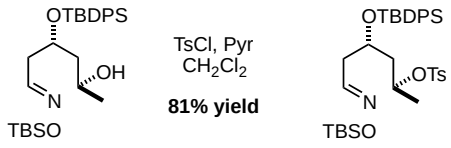
(Representative Procedure)

A solution of alcohol **206** (1.1 g, 3.6 mmol) and pyridine (10 ml) in CH_2Cl_2 (30 ml) was cooled to 0 °C in an ice bath. To this was added tosyl chloride (2.7 g, 14.4 mmol). The solution was allowed to gradually warm to room temperature overnight (20 h). The reaction was washed with 10% $CuSO_4$ solution and the aqueous layer was extracted with Et_2O. The combined organics were washed with water and brine, dried (Na_2SO_4), and concentrated. The crude oil was purified by flash chromatography (1%→2%→3% EtOAc/hexanes) to provide tosyl alcohol **200** (1.3 g, 81% yield), which was either used immediately or temporarily stored as a solution (1 M in benzene, over molecular sieves) in the freezer.



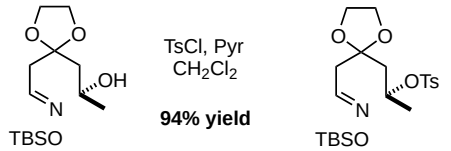
(±)-**198** (±)-**182** *Syn-Nitrone Precursor*

Tosyl Alcohol 182: R_f = 0.35 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.62-7.55 (m, 12H, **Ph**), 7.47-7.35 (m, 12H, **Ph**), 7.30 (dd, *J* = 7.1, 5.3 Hz, 1H, N**CH**), 7.19 (dd, *J* = 18.8, 8.2 Hz, 4H, **Ph**), 6.84 (dd, *J* = 6.7, 4.2 Hz, 1H, N**CH**), 4.53 (m, 2H, O**CH**), 3.79 (m, 2H, O**CH**), 2.46 (dq, *J* = 12.1, 3.6 Hz, 1H, NCH**CH$_2$**), 2.40 (d, *J* = 8.6 Hz, 6H, **Ts**), 2.12 (dt, *J* = 14.8, 5.6 Hz, 1H, NCH**CH$_2$**), 2.04 (ddd, *J* = 14.8, 7.2, 4.1 Hz, 1H, NCH**CH$_2$**), 1.95 (dt, *J* = 15.8, 4.8 Hz, 1H, NCH**CH$_2$**), 1.87 (ddt, *J* = 13.9, 8.5, 5.3 Hz, 1H, OCH**CH$_2$**), 1.63 (ddd, *J* = 14.1, 7.1, 5.7 Hz, 1H, OCH**CH$_2$**), 1.53 (m, 2H, OCH**CH$_2$**), 1.11 (d, *J* = 6.2 Hz, 3H, CH**CH$_3$**), 1.08 (d, *J* = 6.2 Hz, 3H, CH**CH$_3$**), 1.02 (s, 18H, ***t*-Bu**), 0.91 (s, 9H, ***t*-Bu**), 0.90 (s, 9H, ***t*-Bu**), 0.13 (d, *J* = 3.4 Hz, 6H, **CH$_3$**), 0.12 (s, 6H, **CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.10, 151.99, 144.57, 144.55, 136.01, 135.97, 134.27, 134.14, 133.69, 133.56, 130.04, 130.02, 129.99, 129.85, 129.79, 127.90, 127.86, 127.83, 77.45, 77.39, 67.87, 67.47, 43.72, 43.30, 35.93, 31.46, 27.10, 26.26, 26.20, 21.77, 21.38, 21.14, 19.37, 19.35, 18.32, 18.28, -5.09, -5.13; IR (thin film): 2931 (m), 1365 (m), 1177 (s), 1111 (m), 899 (m), 703 (m) cm^{-1}; HRMS (ESI) Calcd. for $C_{35}H_{52}NO_5SSi_2$ [M+H]: 654.3105. Found: 654.3087.



(±)-**206** (±)-**200** *Anti-Nitrone Precursor*

Tosyl Alcohol 200: R_f = 0.56 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55~7.49 (m, 12H, **Ph**), 7.34~7.21 (m, 12H, **Ph**), 7.16 (t, *J* = 6.2 Hz, 1H, N**CH**), 7.13 (d, *J* = 7.4 Hz, 4H, **Ph**), 6.70 (t, *J* = 5.2 Hz, 1H, N**CH**), 4.46 (m, 2H, O**CH**), 3.75 (quintet, *J* = 5.7 Hz, 2H, O**CH**), 2.30 (dt, *J* = 16.0 Hz, 5.4 Hz, 1H, NCH**CH$_2$**), 2.29 (s, 6H, **Ts**), 2.26 (dt, *J* = 16.0 Hz, 5.6 Hz, 1H, NCH**CH$_2$**), 2.13 (dt, *J* = 14.6 Hz, 6.3 Hz, 1H, NCH**CH$_2$**), 2.06 (ddd, *J* = 14.6 Hz, 6.2 Hz, 4.9 Hz, 1H, NCH**CH$_2$**), 1.74 (ddd, *J* = 14.5 Hz, 7.5 Hz, 6.1 Hz, 1H, OCH**CH$_2$**), 1.68 (dd, *J* = 14.0 Hz, 7.2 Hz, 1H, OCH**CH$_2$**), 1.49 (tt, *J* = 14.0 Hz, 5.7 Hz, 2H, OCH**CH$_2$**), 0.93 (d, *J* = 6.3 Hz, 3H, CH**CH$_3$**), 0.90 (s, 18H, ***t*-Bu**), 0.89 (d, *J* = 3.0 Hz, 3H, CH**CH$_3$**), 0.79 (s, 9H, ***t*-Bu**), 0.77 (s, 9H, ***t*-Bu**), 0.005 (d, *J* = 2.5 Hz, 6H, **CH$_3$**), 0.00 (s, 6H, **CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.20, 18.25, 19.35, 19.39, 21.27, 21.47, 21.74, 26.15, 26.22, 27.08, 33.09, 37.22, 44.25, 44.62, 68.30, 68.71, 77.88, 77.96, 127.70, 127.72, 127.81, 127.83, 127.85, 129.81, 129.93, 129.97, 133.64, 133.70, 133.77, 134.81, 134.87, 135.93, 135.95, 135.98, 144.46, 144.49, 152.09, 152.18, -5.11, -5.15; IR (thin film): 2931 (m), 2858 (m), 1363 (m), 1177 (s), 1111 (m), 919 (m), 703 (m) cm^{-1}; HRMS (ESI) Calcd. for $C_{35}H_{52}NO_5SSi_2$ [M+H]: 654.3105. Found: 654.3113.

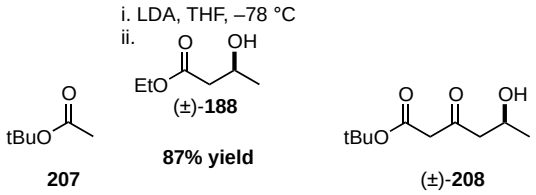


(±)-**212** (±)-**202** *Ketal-Nitrone Precursor*

Tosyl Alcohol 202: R_f = 0.39 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.79 (dd, *J* = 8.3, 1.5 Hz, 4H, **Ts**), 7.36 (t, *J* = 6.5 Hz, 1H, N**CH**), 7.31 (dd, *J* = 8.0, 1.2 Hz, 4H, **Ts**), 6.80 (t, *J* = 5.3 Hz, 1H, N**CH**), 4.87 (septet, *J* = 6.0 Hz, 2H, O**CH**), 3.91 (d, *J* = 8.3 Hz, 8H, **CH$_2$CH$_2$**), 2.72 (dd, *J* = 16.1, 5.5 Hz, 1H, NCH**CH$_2$**), 2.61 (dd, *J* = 16.1, 5.2 Hz, 1H, NCH**CH$_2$**), 2.43 (s, 6H, **Ts**), 2.42 (m, 2H, NCH**CH$_2$**), 2.08 (ddd, *J* = 15.0, 5.6, 1.7 Hz, 2H, OCH**CH$_2$**), 1.84 (dd, *J* = 15.0, 6.1 Hz, 2H, OCH**CH$_2$**), 1.31 (d, *J* = 6.3 Hz, 6H, CH**CH$_3$**), 0.92 (s, 18H, **TBS**), 0.15 (d, *J* = 6.5 Hz, 12H, **TBS**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.06, 150.65, 144.50, 134.93, 129.79, 127.86, 127.84, 108.31, 108.16, 76.53, 76.50, 64.98, 64.95, 64.93,

64.87, 43.89, 43.73, 38.12, 33.77, 26.20, 26.15, 22.45, 22.40, 21.75, 18.31, 18.24, -5.13, -5.15; IR (thin film): 2930 (m), 1362 (m), 1189 (m), 1177 (s), 920 (m) $cm^{=1}$; HRMS (ESI) Calcd. for $C_{21}H_{36}NO_6SSi$ [M+H]: 458.2033. Found: 458.2034.

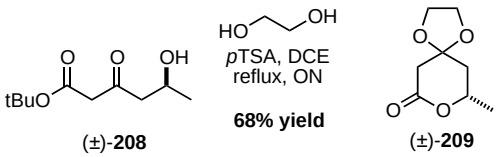
Preparation of β-hydroxyketone 208



To a solution of diisopropylamine (13.3 ml, 95 mmol) in THF (50 ml) at 0 °C was added *n*-BuLi (1.6 M in hexanes, 47.5 ml, 76 mmol). This was stirred at 0 °C for 30 minutes, then cooled to –78 °C before adding tertbutylacetate (10.2 ml, 76 mmol, as a solution in THF (20 ml), dried over molecular sieves). After 30 minutes, *S*-hydroxybutyrate (2.46 ml, 19.0 mmol, as a solution in THF (50 ml), dried over molecular sieves) was added followed by a THF rinse (30 ml). The reaction was allowed to stir cold for 1.25 hours at –78 °C, then above the cold bath for 30 minutes, and finally at room temperature for 15 minutes (The glass was still frosty). The reaction was quenched with water, the layers separated, and the organic portion concentrated. The aqueous portion was extracted with EtOAc, and the combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated, and subjected to flash chromatography (5%→7.5%→10%→20%→30% EtOAc/hexanes) to provide the pure product as a light yellow oil (3.29 g, 87% yield).

Known compound; CAS 125404-65-1. Characterization data matched literature reports.

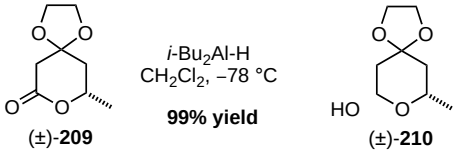
Preparation of Ketal Lactone 209



To a solution of β-hydroxyketone **208** (3.2 g, 14.5 mmol) in 1,2-dichloroethane (100 ml) was added *p*-toluenesufonic acid (552 mg, 2.9 mmol) and 1,2-ethanediol (8.1 ml, 145 mmol). The resulting heterogenous solution was heated to 100 °C for 30 hours. The reaction was cooled and directly adsorbed onto silica gel. Flash chromatography (10%→15%→20%→30%→40% EtOAc/hexanes) provided **209** as a white crystalline solid (1.7 g, 68% yield).

Characterization data matched literature reports for the known (S)-(–) stereoisomer; CAS 1202377-91-0.

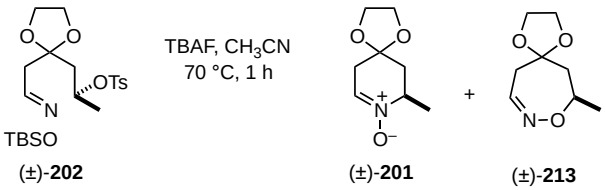
Preparation of Ketal Lactol 210



Lactone **209** (1.6 g, 8.7 mmol) in CH_2Cl_2 (90 ml) was cooled to –78 °C for the addition of diisobutylaluminum hydride solution (1 M in hexanes, 10.2 ml, 10.2 mmol). This stirred cold for one hour at which time the reaction was quenched at –78 °C with MeOH (9 ml) and allowed to warm to room temperature. The resulting reaction solution was vigorously stirred with an added solution of Rochelle's salt (9 g in 100 ml H_2O) for one hour. Following separation of the layers, the aqueous portion was extracted with Et_2O, and the combined organics were washed with brine, dried (Na_2SO_4), and concentrated to provide lactol **210** as a 1:1 mixture of anomers (1.6 g, 100% yield), used in the next step without further purification.

Characterization data matched literature reports for the known (*S*) stereoisomer; CAS 1202377-94-3.

Preparation of Ketal Nitrone 201 and Ketal Cyclic Oxime 213

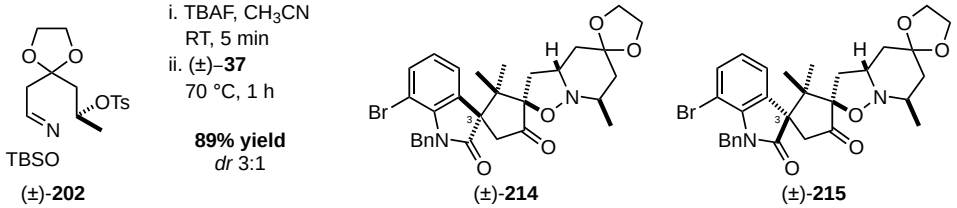


To the activated alcohol (110 mg, 0.28 mmol) in THF (3 ml) was added TBAF (1 M, 320 µl, 0.32 mmol). The reaction was stirred at ambient temperature for 1 hour, then heated to 70 °C for 1 hour. After cooling to room temperature, the reaction was filtered through celite and the solution was adsorbed onto celite and subjected to flash chromatography (cyclic oxime: 5%→10%→15%→20%→100% acetone/ hexanes. Nitrone: 0%→1%→2%→10% MeOH/acetone; then a second purification 0%→1%→2%→10% MeOH/CH_2Cl_2) to afford both products as clear oils.

Nitrone 201: R_f = 0.44 (10% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.97 (t, *J* = 3.4 Hz, 1H, N**CH**), 4.08-3.95 (m, 5H, **CH_2CH_2** & O**CH**), 2.68 (d, *J* = 19.6 Hz, 1H, NCH**CH_2**), 2.57 (d, *J* = 19.3 Hz, 1H, NCH**CH_2**), 2.17 (ddd, *J* = 13.7, 5.4, 2.3 Hz, 1H, OCH**CH_2**), 1.97 (dd, *J* = 13.7, 9.3 Hz, 1H, OCH**CH_2**), 1.56 (d, *J* = 6.8 Hz, 3H, CH**CH_3**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.91, 103.67, 65.05, 64.78, 62.60, 39.48, 36.70, 18.89; IR (thin film): 3200 (br m), 2887 (s), 1375 (m), 1210 (s), 1047 (s), 949 (m) $cm^{=1}$; HRMS (ESI) Calcd. for $C_8H_{14}NO_3$ [M+H]: 172.0974. Found: 172.0968.

Cyclic Oxime 213: R_f = 0.27 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.52 (dd, *J* = 6.0, 4.1 Hz, 1H, N**CH**), 3.95 (m, 5H, **CH_2CH_2** & O**CH**), 3.10 (dd, *J* = 13.2, 3.8 Hz, 1H, NCH**CH_2**), 2.34 (ddd, *J* = 13.2, 6.6, 2.4 Hz, 1H, NCH**CH_2**), 2.10 (dd, *J* = 14.0, 11.6 Hz, 1H, OCH**CH_2**), 1.92 (dt, *J* = 14.0, 2.2 Hz, 1H, OCH**CH_2**), 1.33 (d, *J* = 6.5 Hz, 3H, CH**CH_3**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.69, 105.97, 73.41, 65.03, 64.74, 48.05, 37.39, 21.75; IR (thin film): 2970 (s), 1373 (s), 1130 (s), 1054 (s), 948 (s) $cm^{=1}$; HRMS (ESI) Calcd. for $C_8H_{14}NO_3$ [M+H]: 172.0974. Found: 172.0966.

Preparation of Ketal Cycloadducts 214 and 215



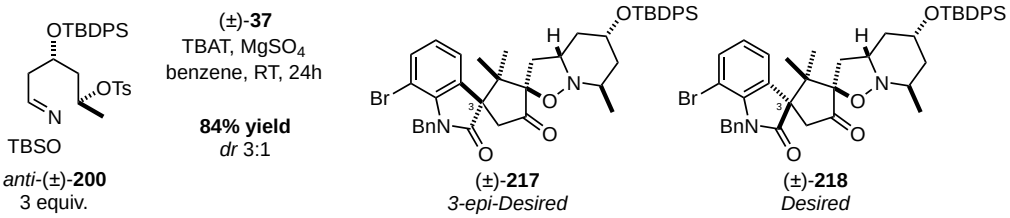
To a solution of the tosyl nitrone precursor (54 mg, 0.12 mmol) in acetonitrile (600 μl) was added a solution of tetrabutylammonium fluoride (1 M in THF, 128 μl, 0.128 mmol). After stirring at room temperature for 5 minutes, the enone (24.5 mg, 0.06 mmol) was added and the reaction stirred at 70 °C for 1 hour. The reaction mixture was diluted with CH_2Cl_2 (to dissolve any residual enone), directly adsorbed onto silica gel and purified by flash chromatography (0%→2.5%→5%→20% Acetone/hexanes) to provide a mixture of two isoxazolidine diastereomers (31 mg, 89% yield, *dr* 3:1). (The diastereomers could be chromatographically separated for purification purposes, but were too close in polarity for total separation.)

Isoxazolidine 214: R_f = 0.14 (20% acetone/pentane); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.39 (d, *J* = 7.3 Hz, 2H, **Ar**), 7.39 (d, *J* = 7.3 Hz, 2H, **Ar**), 7.32-7.20 (m, 5H, **Ph**), 6.93 (t, *J* = 7.8 Hz, 1H, **Ar**), 5.40 (d, *J* = 16.4 Hz, 1H, **CH$_2$**Ph), 5.37 (d, *J* = 16.4 Hz, 1H, **CH$_2$**Ph), 4.00-3.84 (m, 4H, **CH$_2$CH$_2$**), 3.63-3.50 (m, 2H, N**CH** & N**CH**), 3.00 (t, *J* = 13.3 Hz, 1H, NCH**CH$_2$**), 2.82 (d, *J* = 3.9 Hz, 2H, O=C**CH$_2$**), 2.50 (dd, *J* = 13.6, 5.8 Hz, 1H, NCH**CH$_2$**), 2.19 (dd, *J* = 14.1, 6.3 Hz, 1H, NCH**CH$_2$**), 1.97 (d, *J* = 13.5 Hz, 1H, NCH**CH$_2$**), 1.70 (d, *J* = 13.6 Hz, 1H, NCH**CH$_2$**), 1.57 (m, 1H, NCH**CH$_2$**), 1.19 (d, *J* = 6.0 Hz, 3H, CH**CH$_3$**), 1.07 (s, 3H, **CH$_3$**), 0.96 (s, 3H, **CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.24, 180.93, 141.15, 137.49, 134.64, 133.04, 128.66, 127.27, 126.54, 125.73, 123.46, 106.35, 102.33, 93.92, 77.36, 64.89, 64.15, 61.93, 54.82, 52.90, 48.52, 43.45, 40.76, 38.46, 33.77, 21.09, 20.91, 20.07; IR (thin film): 3401 (br m), 2932 (s), 1750 (s), 1716 (s), 1451 (s), 1350 (s), 1124 (s), 729 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{30}H_{34}BrN_2O_5$ [M+H+2]: 583.1651. Found: 583.1633.

Isoxazolidine 215: R_f = 0.19 (20% acetone/pentane); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.38 (d, *J* = 8.1 Hz, 1H, **Ar**), 7.31 (m, 2H, **Ph**), 7.20 (m, 3H, **Ph**), 7.00 (d, *J* = 7.4 Hz, 1H, **Ar**), 6.88 (t, *J* = 7.8 Hz, 1H, **Ar**), 5.40 (d, *J* = 16.6 Hz, 1H, **CH$_2$**Ph), 5.38 (d, *J* = 16.6 Hz, 1H, **CH$_2$**Ph), 4.01 (t, *J* = 6.2 Hz, 2H, **CH$_2$**CH$_2$), 3.91 (t, *J* = 6.2 Hz, 2H, **CH$_2$**CH$_2$), 3.55 (m, 2H, N**CH** & N**CH**), 3.24 (d, *J* = 19.0 Hz, 1H,

O=C**CH$_2$**), 2.91 (t, *J* = 12.4 Hz, 1H, NCH**CH$_2$**), 2.56 (d, *J* = 19.0 Hz, 1H, O=C**CH$_2$**), 2.26 (m, 2H, NCH**CH$_2$**), 1.94 (d, *J* = 14.5 Hz, 1H, NCH**CH$_2$**), 1.73 (d, *J* = 13.2 Hz, 1H, NCH**CH$_2$**), 1.56 (m, 1H, NCH**CH$_2$**), 1.20 (m, 6H, **CH$_3$** & CH**CH$_3$**), 0.81 (s, 3H, **CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.86, 141.10, 137.59, 134.68, 128.67, 127.30, 126.80, 126.56, 123.51, 122.82, 106.42, 102.60, 98.84, 93.26, 77.36, 64.97, 64.07, 61.80, 54.45, 53.30, 49.35, 45.13, 43.19, 40.32, 39.80, 33.94, 21.10, 20.70, 19.89; IR (thin film): 3279 (br m), 2930 (s), 1725 (s), 1450 (s), 1103 (s), 734 (s), 703 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{30}H_{34}BrN_2O_5$ [M+H+2]: 583.1651. Found: 583.1623.

Preparation of *O*-TBDPS Cycloadducts 217 and 218



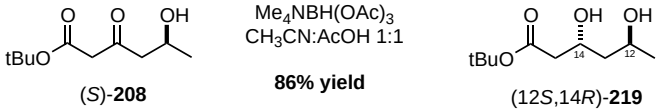
To a solution of the tosyl nitrone precursor (118 mg, 0.18 mmol) in benzene (900 μl) was added $MgSO_4$ (43 mg, 0.36 mmol) and the enone (24.5 mg, 0.06 mmol). Lastly, tetrabutylammonium difluorotriphenylsilicate (97 mg, 0.18 mmol) was added in two portions. This stirred at ambient temperature overnight (17 hours). At that time the heterogeneous mixture was diluted with CH_2Cl_2 (1 ml) and filtered through a celite plug. The filtrate was directly adsorbed onto silica gel and purified by flash chromatography (0%→2.5%→5%→→20% EtOAc/hexanes) to provide two isoxazolidine diastereomers (39 mg total, 84% yield, *dr* 7:3), the desired isoxazolidine (12 mg) and the C3-epimer (27 mg), both as white foams.

Isoxazolidine 217: R_f = 0.42 (15% EtOAc/toluene); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.70 (m, *J* = 1.5 Hz, 4H, **Ph**), 7.57 (dd, *J* = 7.6, 0.9 Hz, 1H, **Ar**), 7.44-7.27 (m, 10H, **Ph** & **Ar**), 7.23 (d, *J* = 7.2 Hz, 2H, **Ph**), 6.91 (t, *J* = 7.9 Hz, 1H, **Ar**), 5.42 (d, *J* = 16.4 Hz, 1H, **CH$_2$**Ph), 5.38 (d, *J* = 16.5 Hz, 1H, **CH$_2$**Ph), 3.98 (br s, 1H, O**CH**), 3.79 (br m, 1H, N**CH**), 3.42 (br m, 2H, N**CH** & NCH**CH$_2$**), 2.90 (s, 2H, O=C**CH$_2$**), 2.44 (br m, 1H, NCH**CH$_2$**), 2.02 (d, *J* = 14.4 Hz, 1H, NCH**CH$_2$**), 1.91 (dt, *J* = 14.4, 3.7 Hz, 1H, NCH**CH$_2$**), 1.55 (m, 1H, NCH**CH$_2$**), 1.25 (m, 1H, NCH**CH$_2$**), 1.13 (m, 12H, Si***t*Bu** & CH**CH$_3$**), 1.01 (s, 3H, **CH$_3$**), 0.97 (s,

3H, **CH_3**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.35, 19.24, 19.99, 20.62, 22.44, 27.10, 32.31, 38.16, 39.59, 43.70, 44.96, 48.24, 48.67, 55.01, 61.28, 65.67, 77.36, 93.73, 102.10, 123.49, 125.97, 126.57, 127.20, 127.78, 128.65, 129.80, 129.86, 133.98, 134.02, 134.40, 136.01, 136.06, 137.78, 141.04, 180.54, 213.66; IR (thin film): 2930 (s), 1751 (s), 1718 (s), 1450 (m), 1104 (s), 733 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{44}H_{49}BrN_2O_4Si$ [M+H+2]: 779.2723. Found: 779.2707.

Isoxazolidine 218: R_f = 0.37 (15% EtOAc/toluene); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.72-7.67 (m, 4H, **Ph**), 7.46-7.39 (m, 6H, **Ph**), 7.37 (dd, *J* = 8.2, 0.9 Hz, 1H, **Ar**), 7.33-7.29 (m, 2H, **Ph**), 7.26-7.22 (m, 3H, **Ph**), 6.82 (d, *J* = 7.4 Hz, 1H, **Ar**), 6.71 (t, *J* = 7.8 Hz, 1H, **Ar**), 5.42 (d, *J* = 16.3 Hz, 1H, **CH_2**Ph), 5.39 (d, *J* = 16.3 Hz, 1H, **CH_2**Ph), 4.03 (br m, 1H, N**CH**), 3.93 (br m, 1H, N**CH**), 3.37 (m, 2H, O**CH** & NCH**CH_2**), 3.29 (d, *J* = 18.9 Hz, 1H, O=C**CH_2**), 2.53 (d, *J* = 18.9 Hz, 1H, O=C**CH_2**), 2.26 (br m, 1H, NCH**CH_2**), 1.88 (br s, 2H, NCH**CH_2**), 1.68 (d, *J* = 14.2 Hz, 1H, NCH**CH_2**), 1.31 (t, *J* = 12.7 Hz, 1H, NCH**CH_2**), 1.23 (s, 3H, **CH_3**), 1.19 (d, *J* = 5.7 Hz, 3H, CH**CH_3**), 1.14 (s, 9H, Si***t*Bu**), 0.78 (s, 3H, **CH_3**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.00, 178.69, 141.09, 137.59, 135.97, 135.92, 135.19, 134.59, 134.00, 133.80, 130.02, 129.90, 128.64, 127.88, 127.82, 127.28, 126.84, 123.46, 122.43, 102.48, 93.00, 66.02, 60.98, 54.39, 49.61, 49.56, 45.10, 43.08, 42.08, 39.62, 32.07, 27.08, 20.84, 19.93, 19.76, 19.43; IR (thin film): 3278 (br w), 2963 (m), 1748 (s), 1722 (s), 1450 (m), 1125 (s), 1068 (s), 729 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{44}H_{49}BrN_2O_4Si$ [M+H+2]: 779.2723. Found: 779.2703.

Preparation of Enantioenriched *anti*-Diol (12*S*,14*R*)-219



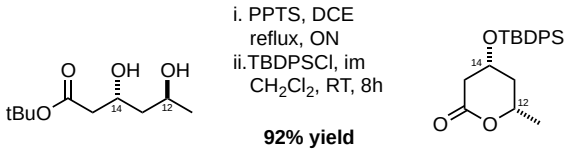
(*S*)-**208** (12*S*,14*R*)-**219**

A solution of tetramethylammonium triacetoxyborohydride (6 g, 22.8 mmol) in acetonitrile (15 ml) and acetic acid (20 ml) was cooled to –40 °C. To this was added a solution of the *S*-β-hydroxyketone (768 mg, 3.8 mmol) in acetonitrile (5 ml). The resulting icy slurry was sealed and placed in a cryocool for 5 days and mixed by hand every 24 hours. At this time, the reaction was allowed to warm to 0 °C in an ice bath and stirred for an additional 5 hours. The reaction mixture was diluted with CH_2Cl_2, quenched via addition to a solution of Rochelle's salt (30 g) in water (100 ml), and carefully basified via

the addition of solid Na_2CO_3 (~20g). The addition of water produced a clear solution, and the layers were separated. The aqueous portion was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated. This provided the diol as an oil (666 mg, 86% yield).

Known compound; (racemic) CAS 139209-89-5. Characterization data matched literature reports.

Preparation of Enantioenriched Lactone (12S,14R)-203



(12*S*,14*R*)-**219** (12*S*,14*R*)-**203**

Lactonization:

To a solution of the diol (666 mg, 3.26 mmol) in 1,2-dichloroethane (15 ml) was added pyridinium *p*-toluenesulfonic acid (83 mg, 0.33 mmol), and the reaction was heated to reflux overnight (17 h). At that time, the reaction mixture was filtered through a plug of silica gel using EtOAc as an eluent. The resulting solution was concentrated to provide the crude product as a light yellow oil (430 mg).

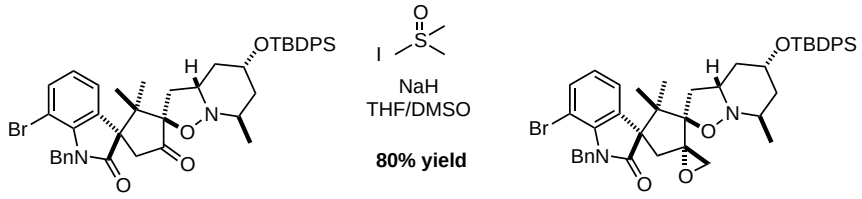
Known compound; (racemic) CAS 121843-08-1. Characterization data matched literature reports.

TBDPS Protection:

To a solution of the crude alcohol (424 mg, 3.26 mmol) in CH_2Cl_2 (15 ml) was added imidazole (666 mg, 9.78 mmol). The solution was cooled to 0 °C in an ice bath, and tertbutyldiphenylsilyl chloride (0.94 ml, 3.6 mmol) was added. This was allowed to stir at room temperature for 8 hours, then placed in the freezer overnight. The next day, the reaction was quenched with saturated NH_4Cl solution, extracted with Et_2O, washed with water and brine, dried (Na_2SO_4), and concentrated. Flash chromatography of the resulting residue provided the product as a clear oil (1.1 g, 92% yield over 2 steps).

Characterization data matched racemic silyl alcohol (±)-**203**.

Preparation of Spiro-epoxide 219

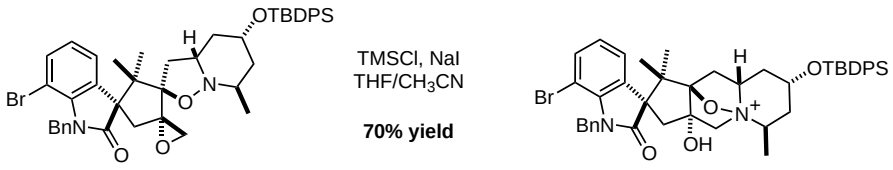


(±)-**218** (±)-**219**

To a solution of trimethylsulfoxonium iodide (145.3 mg, 0.66 mmol) in DMSO (2.2 ml) was added NaH (60% in mineral oil, 26.4 mg, 0.66 mmol). After stirring at room temperature for 4 hours, the resulting homogenous solution was added a solution of the ketone (170 mg, 0.22 mmol) in THF (4.4 ml) cooled to 0 °C in an ice bath to produce an opaque white solution. This was stirred at ambient temperature for 36 h, cooled to 0 ºC, and quenched with saturated $NaHCO_3$ solution. The mixture was diluted with H_2O and the aqueous layer was extracted with EtOAc. The combined organic portions were washed with brine solution, dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash chromatography (4%→8%→12%→30% EtOAc/hexanes) to provide the desired product as a white foam (140 mg, 80% yield).

R_f = 0.36 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.72 (m, 4H, **Ph**), 7.42 (m, 6H, **Ph**), 7.34 (d, *J* = 8.3 Hz, 1H, **Ar**), 7.30 (m, 3H, **Ph**), 7.24 (d, *J* = 7.1 Hz, 1H, **Ar**), 7.21 (m, 2H, **Ph**), 6.87 (t, *J* = 7.8 Hz, 1H, **Ar**), 5.35 (s, 2H, **C**$\mathbf{H_2}$Ph), 3.96 (s, 1H, N**CH**), 3.34 (br s, 1H, O**CH**), 3.33 (d, *J* = 5.5 Hz, 2H, CH_2C–O–**C**$\mathbf{H_2}$), 3.29 (m, 1H, **C**$\mathbf{H_2}$C–O–CH_2) 3.05 (s, 1H, N**CH**), 2.55 (d, *J* = 14.6 Hz, 1H, NCH**C**$\mathbf{H_2}$), 2.43 (br s, 1H, **C**$\mathbf{H_2}$C–O–CH_2), 2.20 (d, *J* = 14.6 Hz, 1H, NCH**C**$\mathbf{H_2}$), 1.90 (m, 1H, NCH**C**$\mathbf{H_2}$), 1.84 (m, 1H, NCH**C**$\mathbf{H_2}$), 1.62 (m, 1H, NCH**C**$\mathbf{H_2}$), 1.28~1.09 (m: 9H, ***t*Bu**; 3H, **C**$\mathbf{H_3}$; 3H, CH**C**$\mathbf{H_3}$; 1H, NCH**C**$\mathbf{H_2}$), 0.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.69, 141.14, 137.82, 136.56, 136.00, 134.11, 134.00, 129.87, 128.60, 127.78, 127.14, 126.68, 124.07, 122.57, 102.19, 91.85, 77.36, 65.72, 65.57, 59.19, 56.05, 55.21, 50.44, 49.64, 44.88, 39.55, 38.26, 36.92, 36.21, 34.81, 34.66, 32.45, 31.72, 29.20, 27.12, 27.06, 25.42, 23.48, 22.79, 21.00, 20.85, 19.32, 18.91, 14.26, 11.57; IR (thin film): 2930 (s), 1723 (s), 1450 (s), 1105 (s), 734 (s), 703 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{45}H_{52}BrN_2O_4Si$ [M+H+2]: 793.2880. Found: 793.2870.

Preparation Ammonium Salt 220

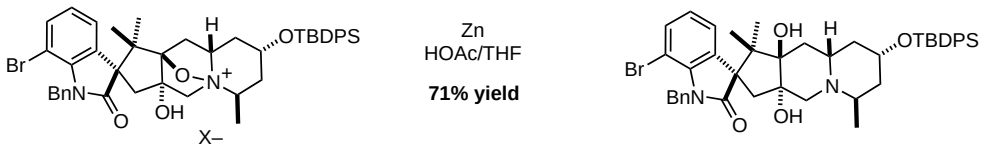


(±)-**219** (±)-**220**

To a solution of the epoxide (30 mg, 0.04 mmol) in CH_3CN/THF (3:1, 0.6 ml) cooled to 0 °C in an ice bath was added NaI (30 mg, 0.2 mmol) and TMSCl (12.5 ml, 0.1 mmol). The clear solution became yellow and a precipitate formed. After stirring for 4 hours, the reaction was diluted with Et_2O and washed with saturated $Na_2S_2O_3$ solution. (Note: DO NOT wash with brine solution.) The aqueous layer was extracted with EtOAc. The combined organic extracts were concentrated in vacuo and purified by flash chromatography (20%→40%→60%→ 80%→100% EtOAc/hexanes →5%MeOH/CH_2Cl_2) to provide the desired product as a clear glass (26 mg, 70% yield).

R_f = 0.10 (80% EtOAc/hexanes); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.66 (m, *J* = 1.6 Hz, 4H, **Ph**), 7.54 (dd, *J* = 7.6, 1.1 Hz, 1H, **Ar**), 7.50-7.40 (m, 7H, **Ph**), 7.31 (dd, *J* = 8.2, 1.1 Hz, 1H, **Ar**), 7.28 (m, 1H, **Ph**), 7.22 (m, 1H, **Ph**), 7.13 (m, 2H, **Ph**), 6.89 (dd, *J* = 8.2, 7.6 Hz, 1H, **Ar**), 5.31 (s, 2H, **CH$_2$**Ph), 5.16 (d, *J* = 11.9 Hz, 1H, N**CH$_2$**), 4.10 (d, *J* = 11.9 Hz, 1H, N**CH$_2$**), 4.01 (m, 2H, N**CH** & O**CH**), 3.82 (m, 1H, N**CH**), 2.99 (q, *J* = 13.3 Hz, 2H, HOC**CH$_2$**), 2.81 (dd, *J* = 12.4, 8.0 Hz, 1H, NCH**CH$_2$**), 2.49 (dd, *J* = 14.7, 10.5 Hz, 1H, , NCH**CH$_2$**), 2.41 (m, 1H, NCH**CH$_2$**), 2.21 (m, 1H, NCH**CH$_2$**), 2.15 (dt, *J* = 15.6, 5.4 Hz, 1H, NCH**CH$_2$**), 1.84 (dd, *J* = 15.1, 4.6 Hz, 1H, NCH**CH$_2$**), 1.24 (d, 3H, CH**CH$_2$**), 1.07 (s, 9H, Si***t*Bu**), 1.04 (s, 3H, **CH$_3$**), 1.00 (s, 3H, **CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.83, 180.27, 140.10, 137.40, 135.83, 134.43, 132.87, 132.76, 130.50, 130.48, 128.71, 128.24, 128.21, 127.40, 127.22, 126.40, 123.95, 108.64, 102.07, 98.63, 86.22, 77.36, 75.58, 68.75, 65.64, 64.58, 61.68, 51.33, 46.51, 45.11, 36.22, 35.10, 29.86, 26.95, 26.35, 26.28, 20.70, 19.15, 13.36; IR (thin film): not obtained; HRMS (ESI) Calcd. for $C_{45}H_{52}BrN_2O_4Si$ [M+H+2]: 793.2874. Found: 793.2861.

Preparation of Diol 221

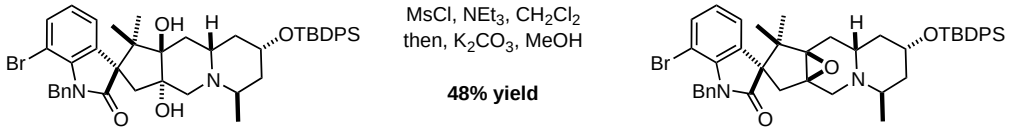


(±)-**220** (±)-**221**

To a solution of the ammonium salt (8 mg, 0.009 mmol) in THF/AcOH (180 μl / 240 μl) was added activated zinc powder (4 mg, ~0.05 mmol). The reaction mixture was vigorously stirred under nitrogen for 18 h at ambient temperature, after which time the solvent had evaporated. The solvent mixture THF/AcOH (180 μl / 240 μl) was added again, and the reaction was stirred in a sealed flask for 2 more days. This was filtered through a pad of Celite, rinsed with CH_2Cl_2, and concentrated in vacuo. The resulting yellowish oil was dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$ solution and the aqueous portion extracted with EtOAc/CH_2Cl_2. The combined organic layers were concentrated and purified by flash chromatography (basic Al_2O_3, 0%→1%→2% MeOH/CH_2Cl_2) to provide the desired product as a clear oil (5 mg, 71% yield).

R_f = 0.50 (5% MeOH/CH_2Cl_2, TLC plate pretreated with NH_3); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.65 (m, 4H, **Ph**), 7.48 (dd, *J* = 7.5, 1.1 Hz, 1H, **Ar**), 7.39 (m, 6H, **Ph**), 7.32 (dd, *J* = 8.1, 1.1 Hz, 1H, **Ar**), 7.28 (m, 2H, **Ph**), 7.21 (m, 3H, **Ph**), 6.93 (dd, *J* = 8.1, 7.5 Hz, 1H, **Ar**), 5.36 (s, 2H, **CH$_2$**Ph), 4.90 (d, *J* = 2.7 Hz, 1H, **OH**), 4.31 (s, 1H, **OH**), 3.92 (tt, *J* = 11.0, 4.5 Hz, 1H, O**CH**), 3.23 (d, *J* = 10.2 Hz, 1H, N**CH$_2$**), 2.98 (m, 1H, N**CH**), 2.75 (tt, *J* = 11.1, 2.8 Hz, 1H, N**CH**), 2.47 (d, *J* = 14.4 Hz, 1H, HOC**CH$_2$**), 2.22 (d, *J* = 10.2 Hz, 1H, N**CH$_2$**), 2.02 (d, *J* = 14.4 Hz, 1H, HOC**CH$_2$**), 1.82 (ddt, *J* = 12.2, 4.5, 2.4 Hz, 1H, NCH**CH$_2$**), 1.74 (td, *J* = 11.7, 4.7 Hz, 1H, NCH**CH$_2$**), 1.63 (ddt, *J* = 10.3, 4.9, 2.6 Hz, 1H, NCH**CH$_2$**), 1.57 (m, 1H, NCH**CH$_2$**), 1.45 (dd, *J* = 13.0, 3.4 Hz, 1H, NCH**CH$_2$**), 1.32 (m, 1H, NCH**CH$_2$**), 1.22 (s, 3H, **CH$_3$**), 1.05 (s, 9H, Si***t*Bu**), 0.87 (s, 3H, **CH$_3$**), 0.75 (d, *J* = 6.9 Hz, 3H, CH**CH$_3$**). ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.31, 140.15, 137.31, 136.57, 135.89, 135.84, 134.76, 134.54, 133.70, 129.74, 129.72, 128.66, 127.71, 127.68, 127.27, 126.87, 126.59, 124.01, 102.23, 82.93, 81.97, 77.36, 66.16, 61.05, 56.35, 55.56, 52.49, 46.38, 46.06, 45.22, 43.74, 41.96, 36.13, 29.86, 27.19, 27.14, 21.68, 19.27, 11.79; IR (thin film):; HRMS (ESI) Calcd. for $C_{45}H_{53}BrN_2O_4Si$ [M+H+2]: 795.3036. Found: 795.3028.

Preparation of Epoxide 222



(±)-**221** (±)-**222**

To a solution of the diol (10 mg, 0.13 mmol) in CH_2Cl_2 (250 μl) at room temperature was added triethylamine (175 μl, 0.123 mmol) and MsCl (3 μl, 0.039 mmol). After stirring for 3 hours, another portion of triethylamine (175 μl, 0.123 mmol) and MsCl (3 μl, 0.039 mmol) were added. After 3 hours, the gummy orange reaction mixture was dissolved in MeOH (250 μl) and solid K_2CO_3 (7 mg, 0.052 mmol) was added. The reaction mixture was stirred at room temperature overnight (17 hours), quenched with saturated $NaHCO_3$ solution, extracted with $EtOAc/CH_2Cl_2$, concentrated and purified by flash chromatography (5% 10% 15% 20% 30% EtOAc/Hexanes) to provide the epoxide (5 mg, 48% yield) and some recovered starting material (5 mg, 50% recovered).

R_f = 0.25 (60% EtOAc/hexanes, TLC plate pretreated with NH_3); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.59 (m, 4H, **Ph**), 7.37~7.28 (m, 6H, **Ph**), 7.23 (dd, *J* = 8.3, 0.8 Hz, 1H, **Ar**), 7.17~7.09 (m, 5H, **Ph**), 7.00 (dd, *J* = 7.6, 0.8 Hz, 1H, **Ar**), 6.77 (t, *J* = 7.8 Hz, 1H, **Ar**), 5.23 (s, 2H, **CH$_2$**Ph), 3.82 (tt, *J* = 10.0, 4.8 Hz, 1H, O**CH**), 3.05 (d, *J* = 13.5 Hz, 1H, N**CH$_2$**), 3.01 (d, *J* = 13.5 Hz, 1H, N**CH$_2$**), 2.94 (tt, *J* = 6.8, 3.3 Hz, 1H, N**CH**), 2.54~2.44 (m, 2H, HOC**CH$_2$** & N**CH**), 2.11 (d, *J* = 14.6 Hz, 1H, HOC**CH$_2$**), 1.81 (dd, *J* = 14.1, 3.6 Hz, 1H, NCH**CH$_2$**), 1.72 (dd, *J* = 14.1, 10.1 Hz, 1H, NCH**CH$_2$**), 1.61 (td, *J* = 11.4, 4.3 Hz, 1H, NCH**CH$_2$**), 1.52 (ddd, *J* = 16.2, 6.8, 4.1 Hz, 1H, NCH**CH$_2$**), 1.24 (q, *J* = 11.6 Hz, 2H, NCH**CH$_2$**), 0.98 (s, 9H, Si***t*Bu**), 0.93 (s, 3H, **CH$_3$**), 0.86 (s, 3H, **CH$_3$**), 0.63 (d, *J* = 6.6 Hz, 3H, CH**CH$_3$**); ^{13}C NMR (contains trace EtOAc & MsOH) (100 MHz, $CDCl_3$) δ 193.64, 179.49, 140.73, 138.10, 135.90, 135.85, 134.64, 134.50, 134.45, 134.14, 129.78, 129.75, 128.43, 127.73, 127.68, 127.09, 127.00, 125.29, 125.26, 122.53, 101.89, 77.37, 70.17, 65.96, 65.58, 59.10, 52.49, 49.57, 47.96, 45.00, 44.69, 43.35, 43.13, 42.18, 40.85, 31.92, 31.69, 27.13, 25.98, 20.37, 19.26, 11.47; IR (thin film): ; HRMS (ESI) Calcd. for $C_{45}H_{52}BrN_2O_3Si$ [M+H+2]: 777.2931. Found: 777.2910.

4.6 Notes and References

[1] For a helpful review on the synthesis of asymmetric nitrones see: Revuelta, J.; Cicchi, S.; Goti, A.; and Brandi, A. *Synthesis* **2007** *4*, 485–504.

[2] Chackalamannil, S.; Wang, Y. *Tetrahedron* **1997** *53*, 11203.

[3] a) Cicchi, S.; Marradi, M.; Vogel, P.; Goti, A. *J. Org. Chem.* **2006** *71*, 1614–1619. b) Cicchi, S.; Corsi, M.; Brandi, A.; Goti, A. *J. Org. Chem.* **2002** *67*, 1678-1681.

[4] Amans, D.; Bareille, L.; Bellosta V.; Cossy, J. *J. Org. Chem.* **2009** *74*, 7665-7674.

[5] For a relevant example, see: Schuler, M.; Silva, F.; Bobbio, C.; Tessier, A.; Gouverneur, V.; *Angew Chem Int Ed* **2008**, *47*, 7927–7930.

[6] Difficulties encountered in the benzyl deprotection of **108** (Scheme 3.11) had not yet been established; thus, a late-stage global benzyl deprotection was viewed as an efficient means of generating the C14 alcohol later in the synthesis.

[7] For a relevant example, see: Sugimura, T.; Sato, Y.; Im, C.-Y.; Okuyama T. *Org Lett* **2004** *6*, 4439–4741.

[8] For a relevant example, see: Dehoux, C.; Gorrichon, L.; Baltas, M. *Eur. J. Org. Chem.* **2001** 1105–1113.

[9] For a related example see: Amans, D.; Bareille, L.; Bellosta, V.; and Cossy, J. *J. Org. Chem.* **2009** *74*, 7665–7674.

[10] Substantial amounts of the pure bis-protected *anti*-diol could be obtained via a single chromatographic separation, however, to obtain the pure bis-protected *syn*-diol, multiple purifications were generally required.

[11] Anderson, K. R.; Atkinson, S. L. G.; Fujiwara, T.; Giles, M. E.; Matsumoto, T.; Merifield, E.; Singleton, J. T.; Saito, T.; Sotoguchi, T.; Tornos, J. A.; Way, E. L. *Org. Proc. Res. & Devel.* **2010** *14*, 58–71.

[12] Chevrier, C.; LeNouen, D.; Neuburger, M.; Defoin, A.; Tarnus, C. *Tet. Lett.* **2004** *45*, 5363–5366.

[13] Chevrier et al. (see reference 12) report the isolation of a similar cyclic oxime as a minor byproduct in a similar, desilylative cyclization to form a 5-membered nitrone.

[14] Enone **37** and cyclic oxime **213** were co-isolated from the reaction mixture. Yields were estimated based upon relative ratios of the two compounds as determined by ^{1}H NMR.

[15] O'Ferrall, R. A. M.; O'Brien, Deirdre. *J. Phys. Org. Chem.* **2004** *17*, 631–640.

[16] Tamura, O.; Toyao, A.; Ishibashi, H. *Synlett* **2002** *8*, 1344–1346.

[17] Nakamura, R.; Tanino, K.; Miyashita, M. *Org. Lett.* **2005** *7*, 2929–2932.

[18] Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988** *110*, 3560–3578.

[19] Caputo, R.; Mangoni, L.; Nerl, O.; Palumbo, G. *Tetrahedron Lett.* **1981** *22*, 3551–3552.

[20] For a review of the Mitsunobu esterification, see: Hughes, D. L. *Org. Prep. & Proc. Int.* **1996** *28*, 127–164.

APPENDIX I: SPECTRA RELEVANT TO CHAPTER 2

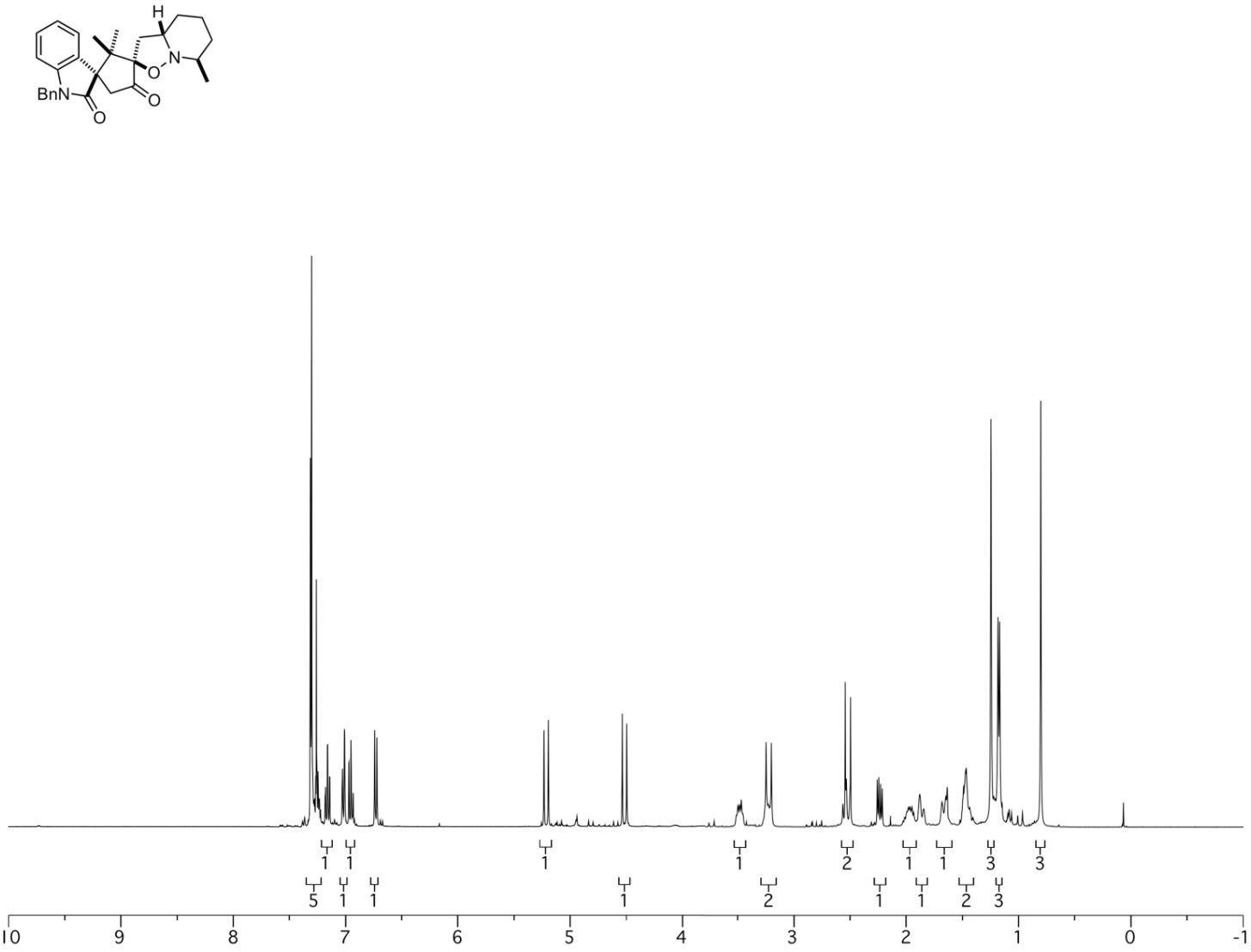


Figure A.1.1a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **56**

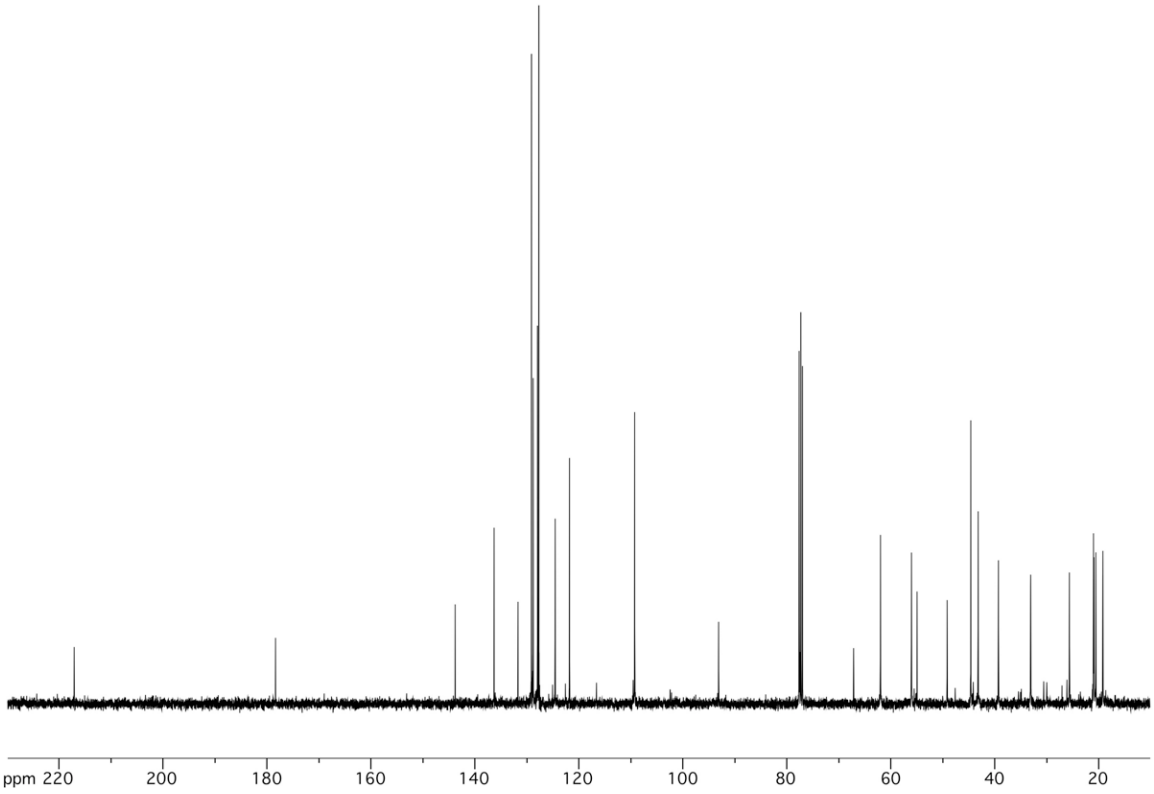


Figure A.1.1b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **56**

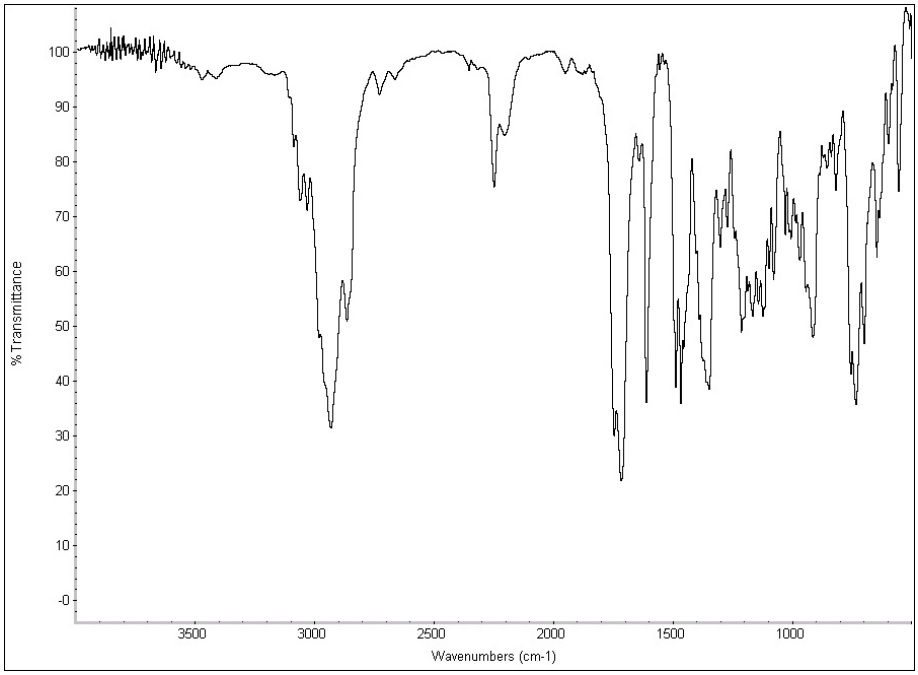


Figure A.1.1c IR spectrum (thin film/NaCl) of compound **56**

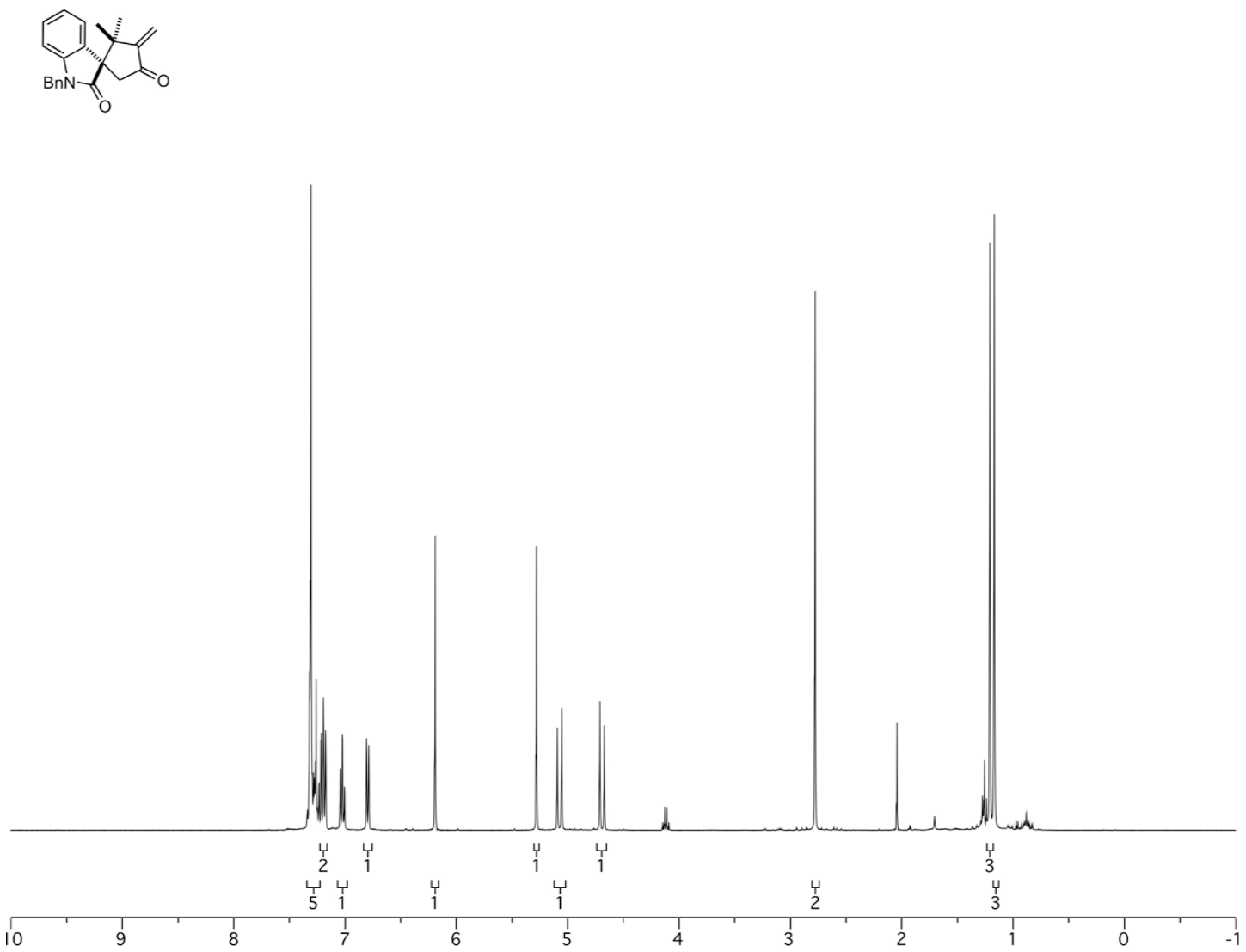


Figure A.1.2a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **58**

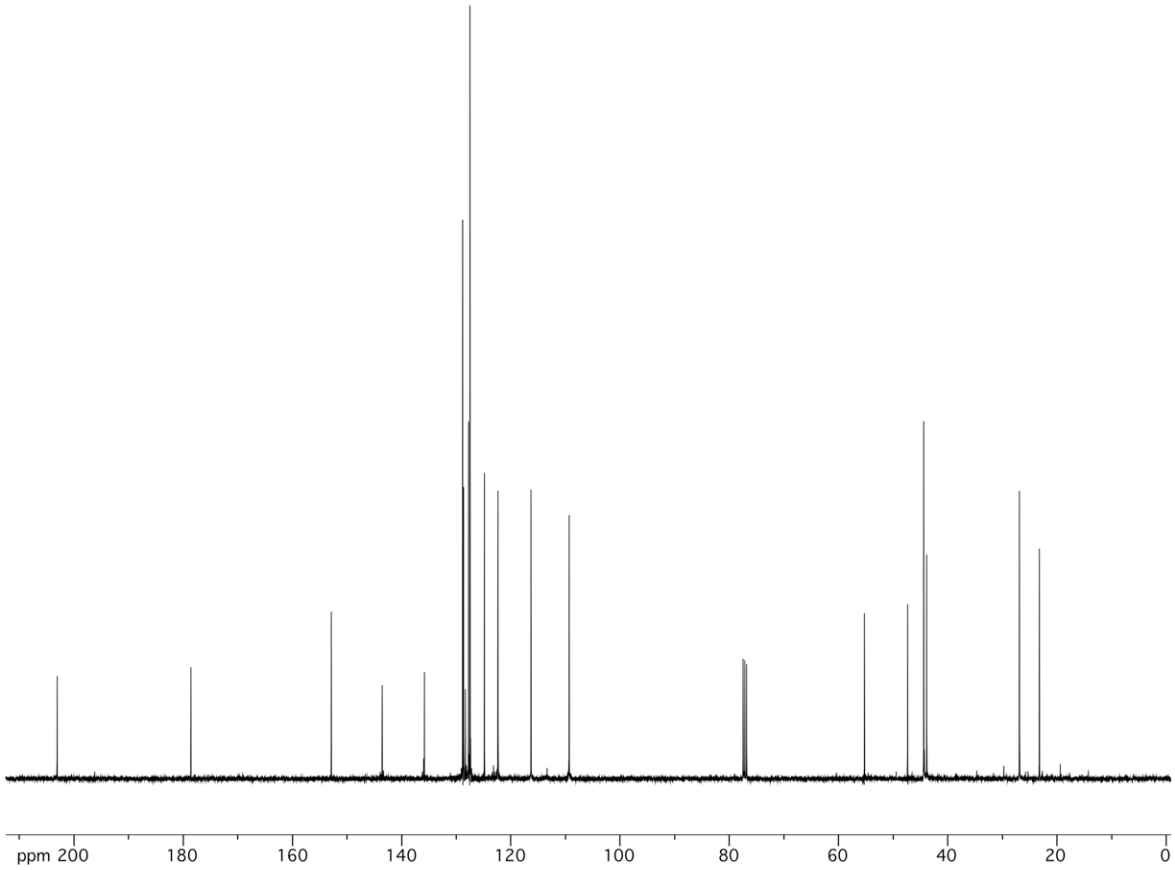


Figure A.1.2b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **58**

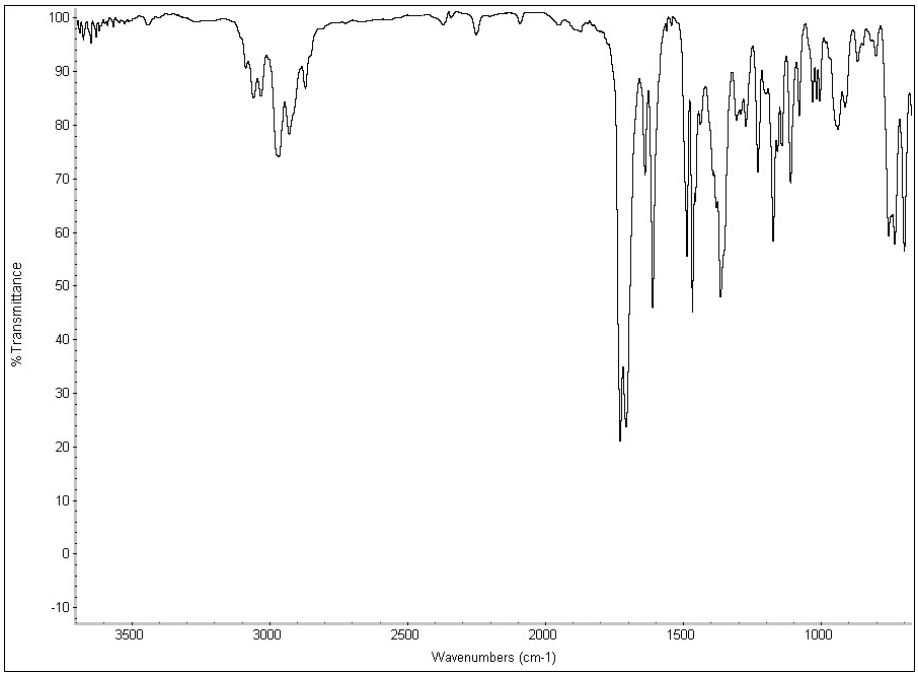


Figure A.1.2c IR spectrum (thin film/NaCl) of compound **58**

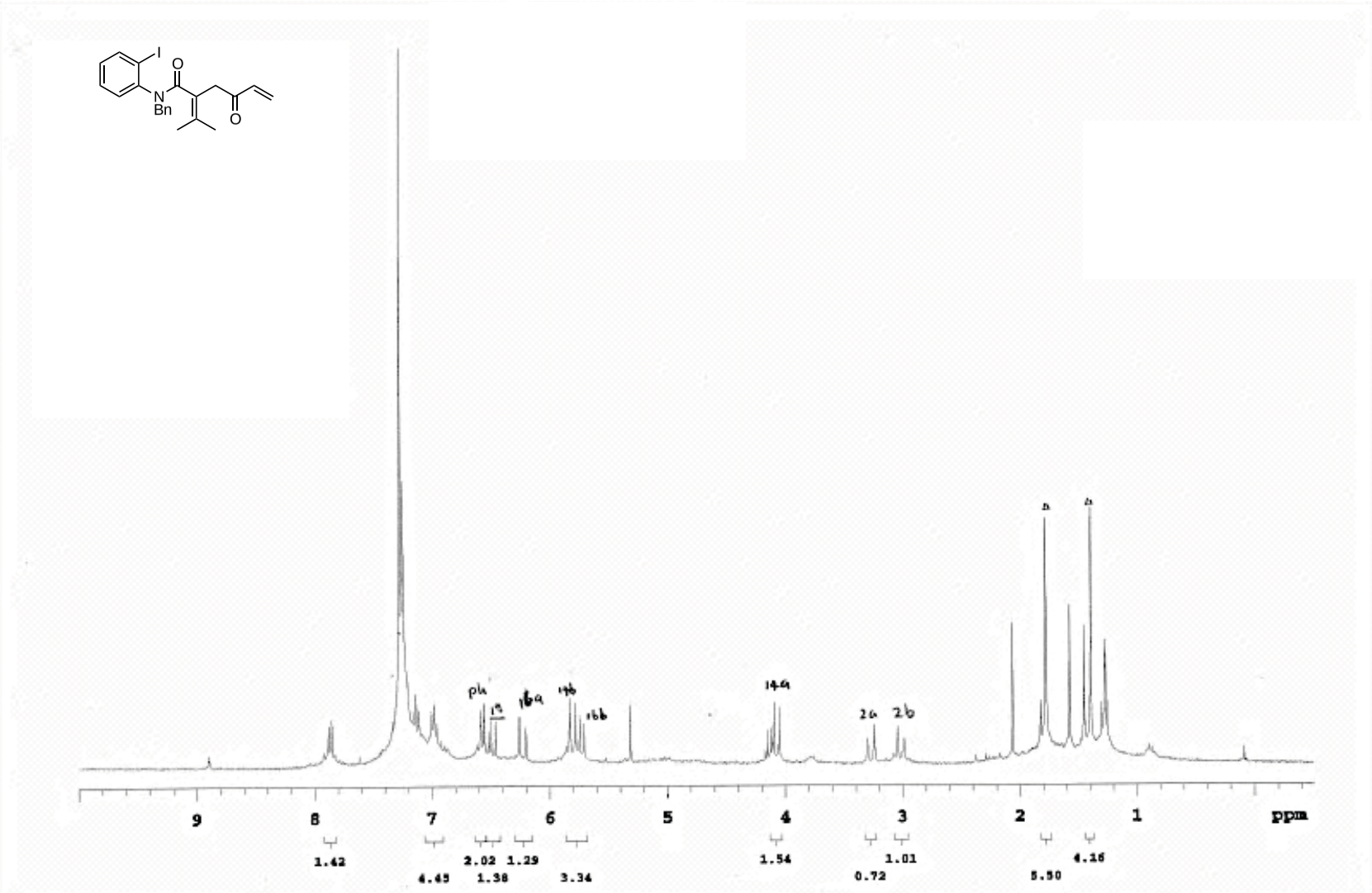
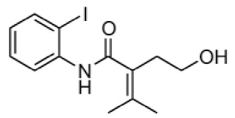


Figure A.1.3a ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **59**



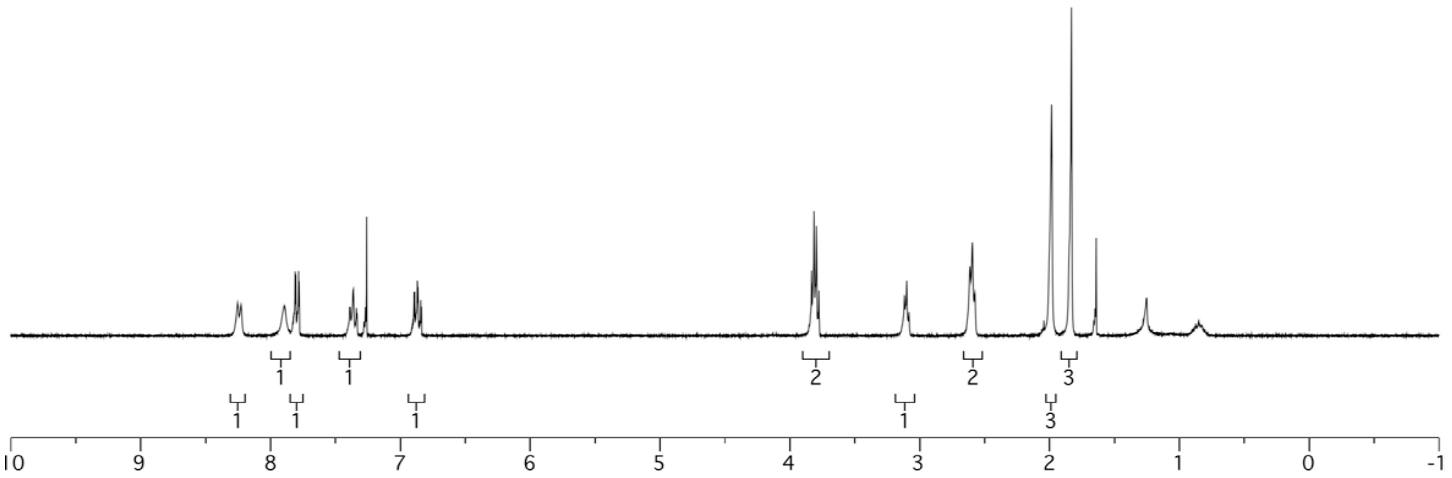


Figure A.1.4a ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **61**

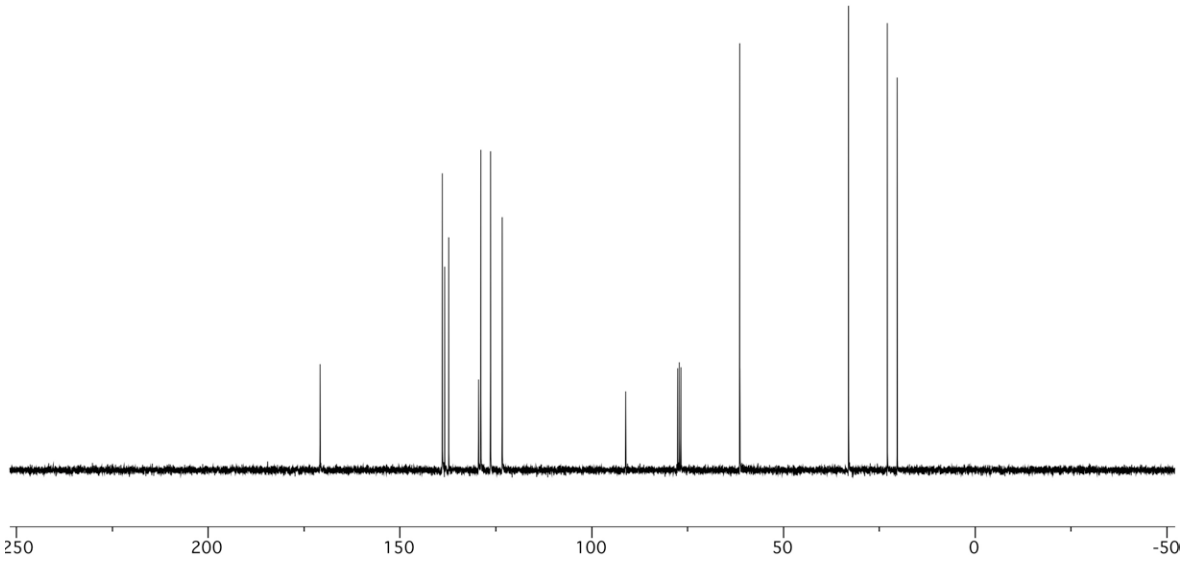


Figure A.1.4b ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **61**

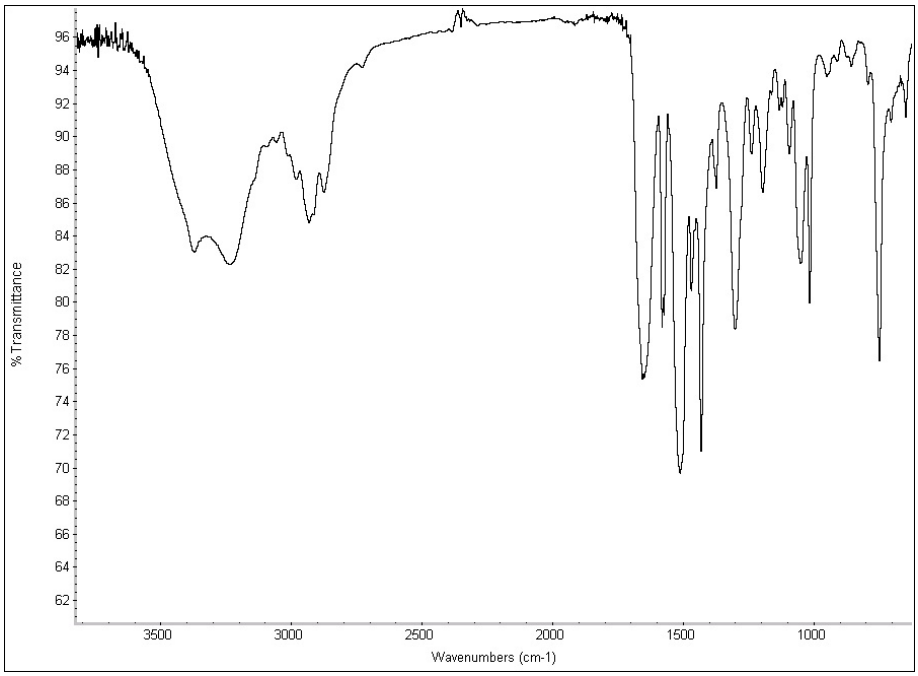


Figure A.1.4c IR spectrum (thin film/NaCl) of compound **61**

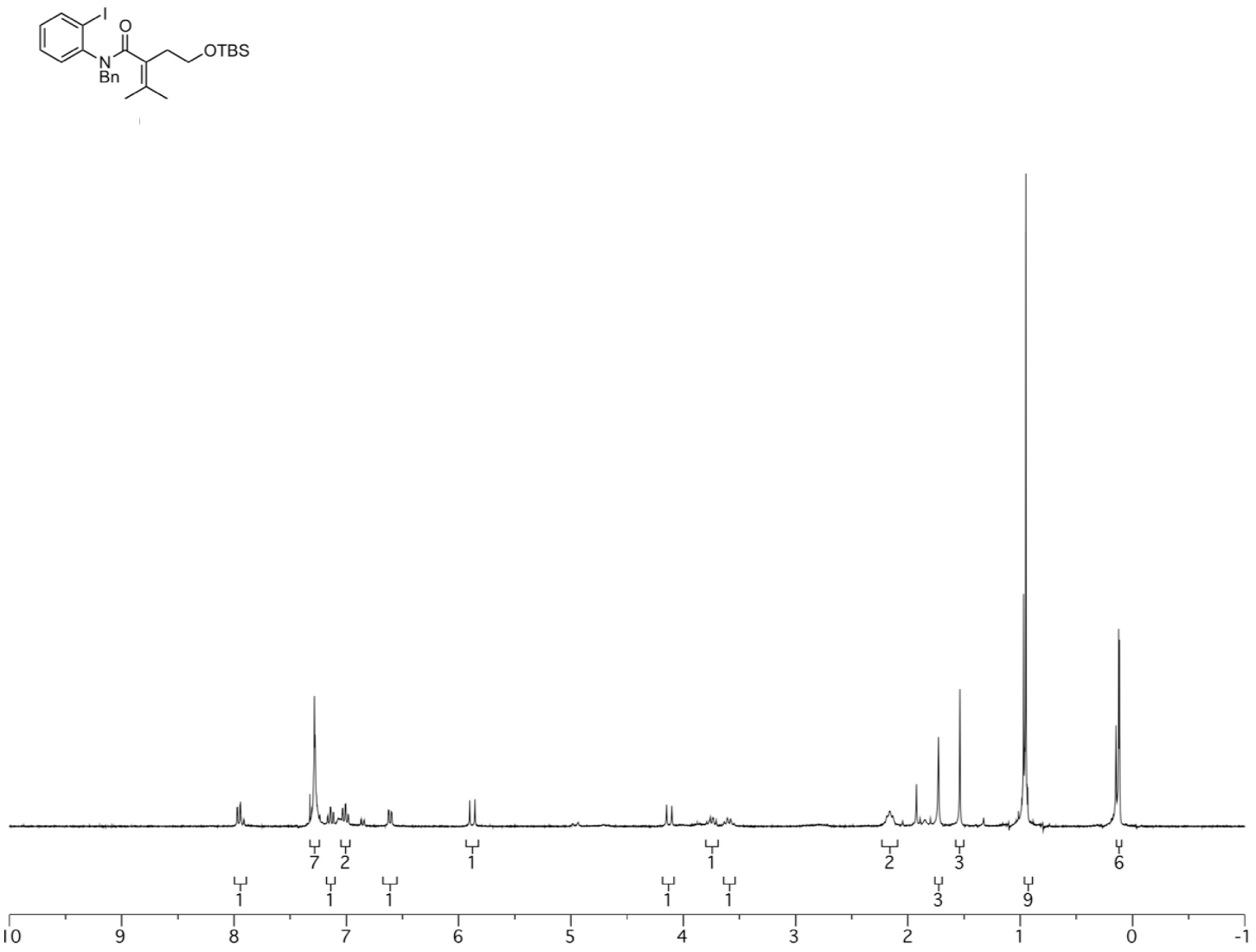


Figure A.1.5a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **62**

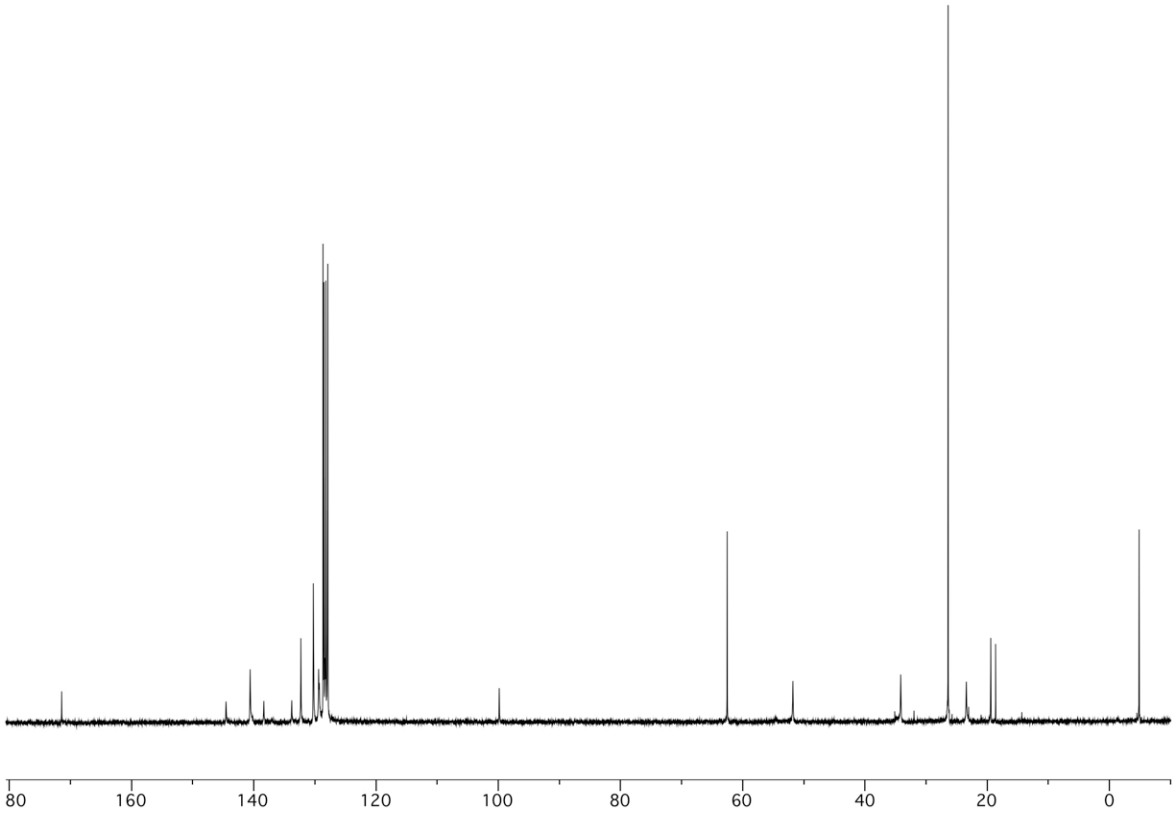


Figure A.1.5b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **62**

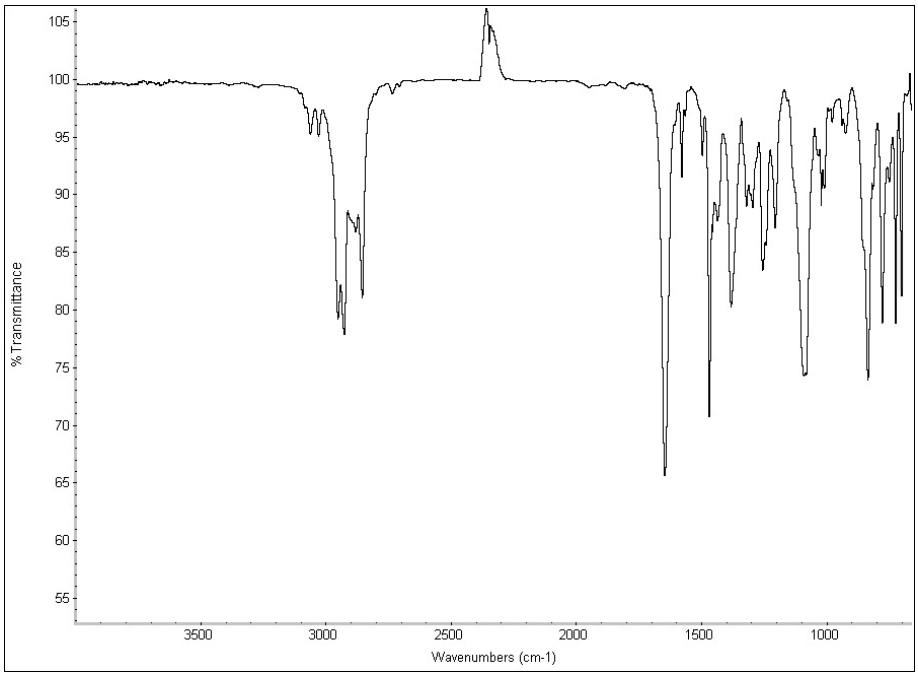


Figure A.1.5c IR spectrum (thin film/NaCl) of compound **62**

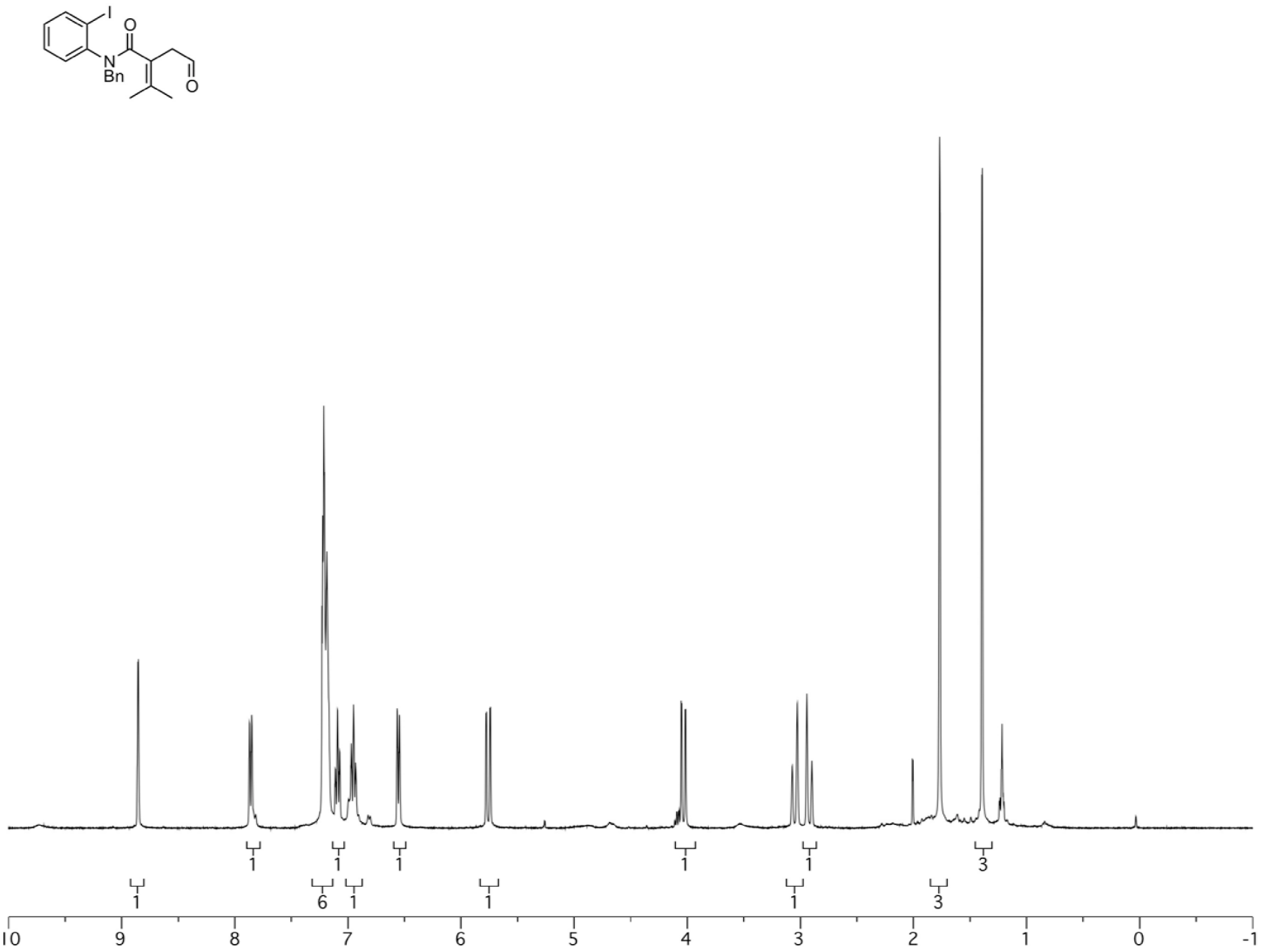


Figure A.1.6a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **63**

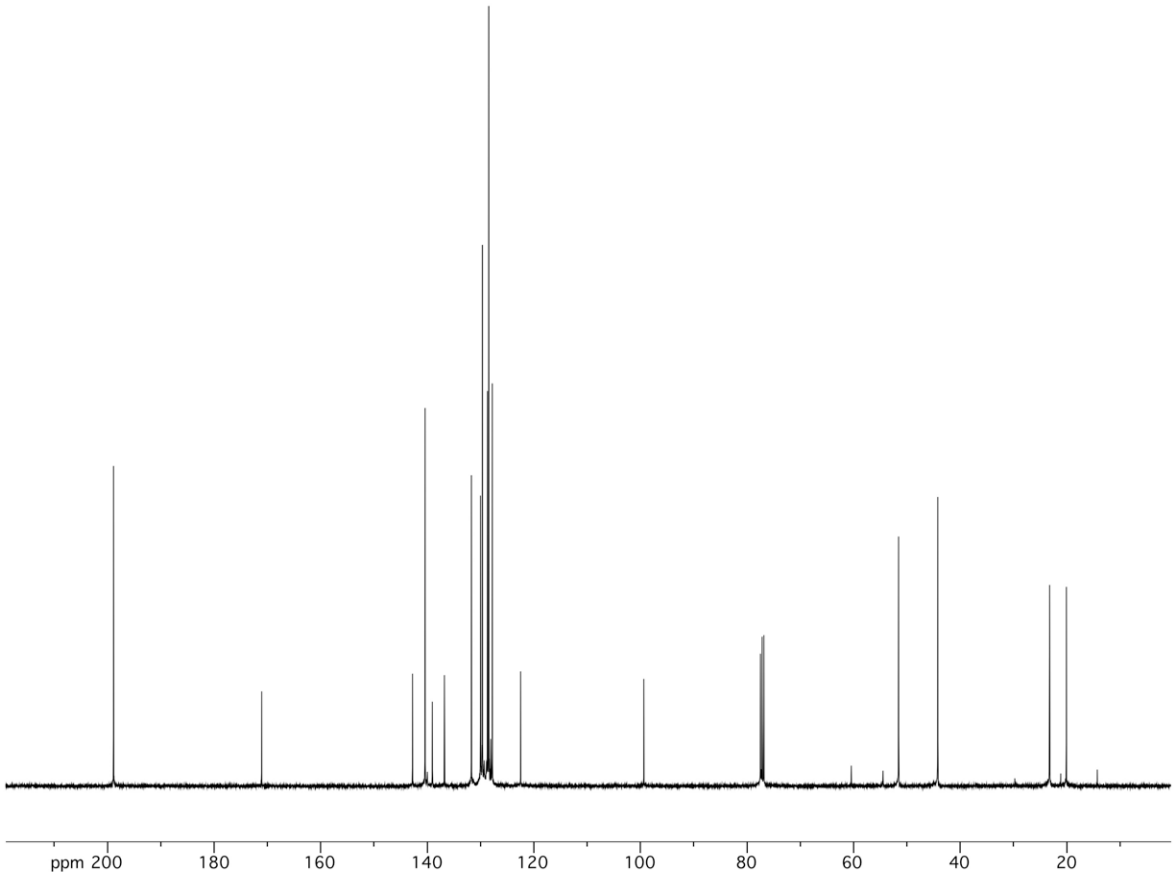


Figure A.1.6b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **63**

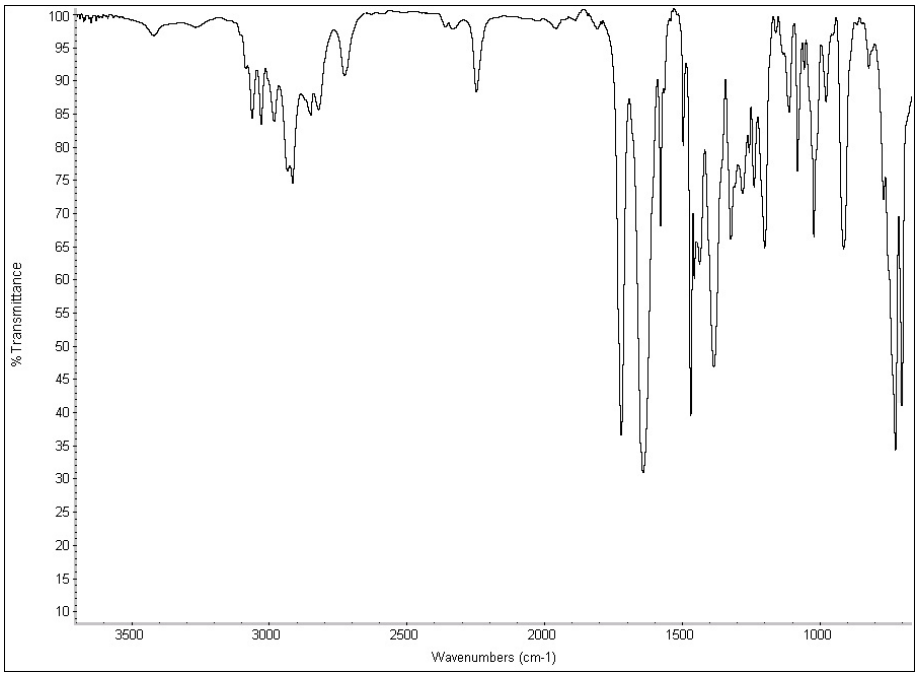


Figure A.1.6c IR spectrum (thin film/NaCl) of compound **63**

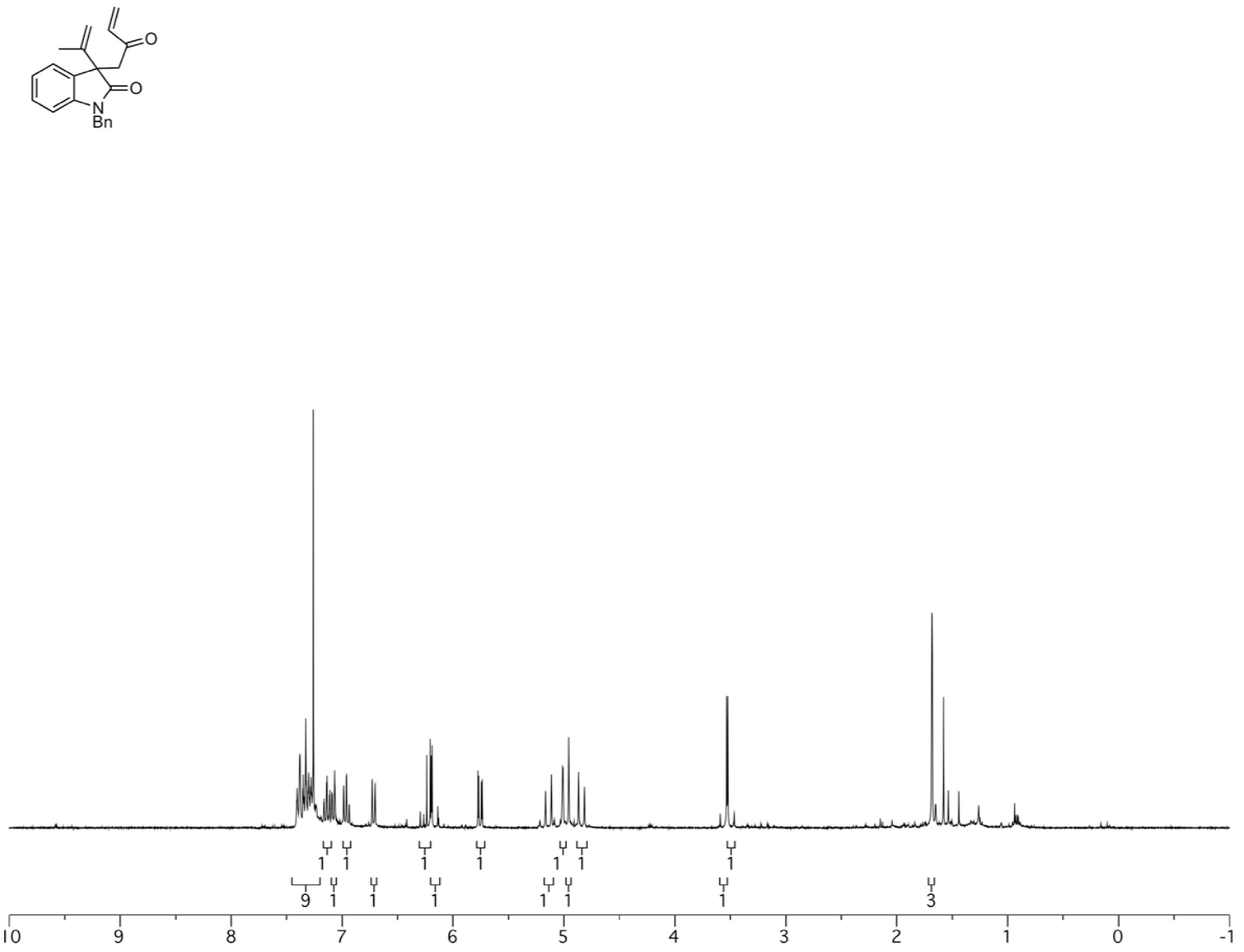


Figure A.1.7a ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **67**

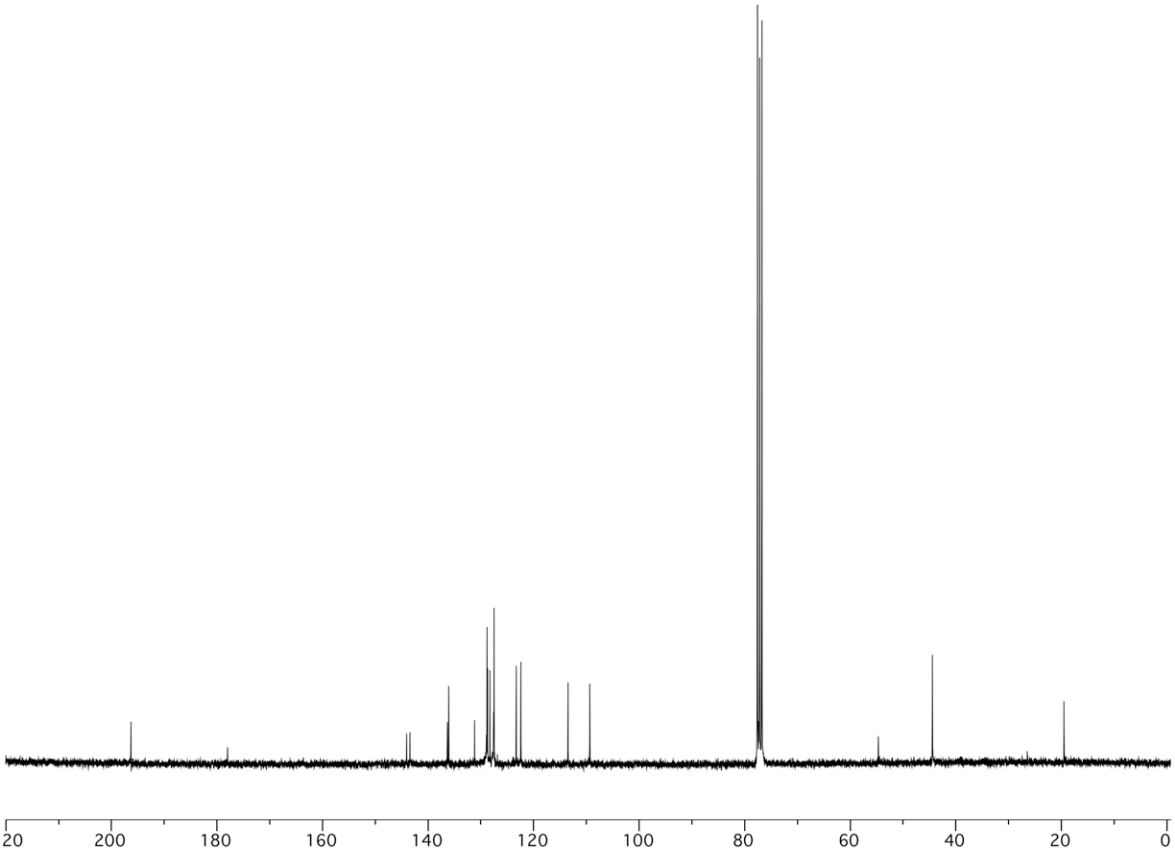


Figure A.1.7b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **67**

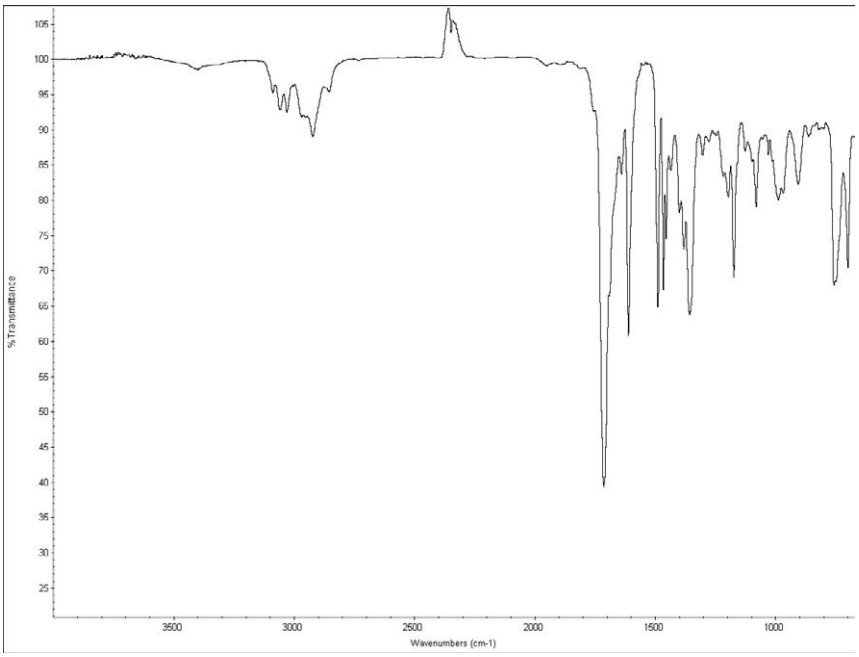


Figure A.1.7c IR spectrum (thin film/NaCl) of compound **67**

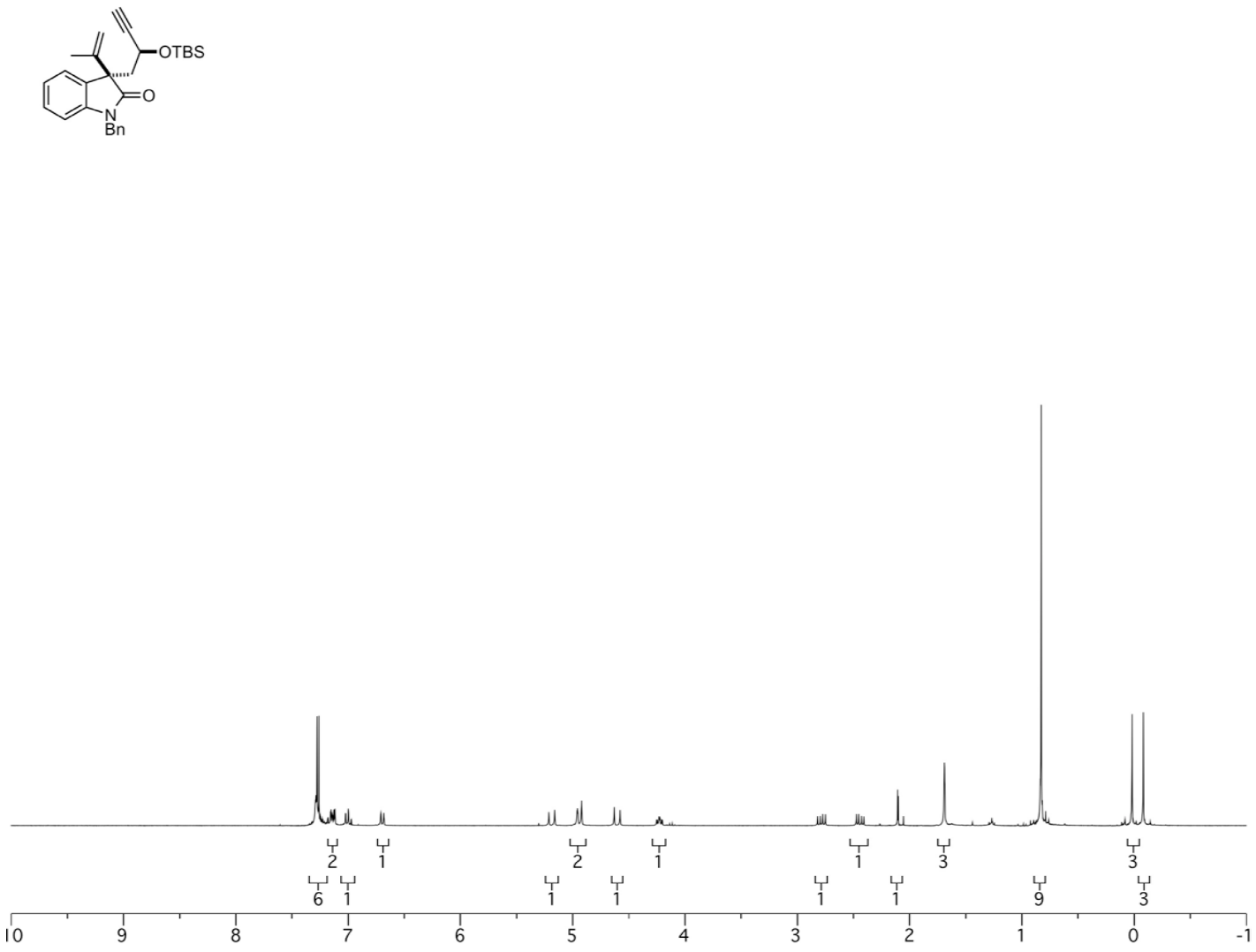


Figure A.1.8a ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **68a**

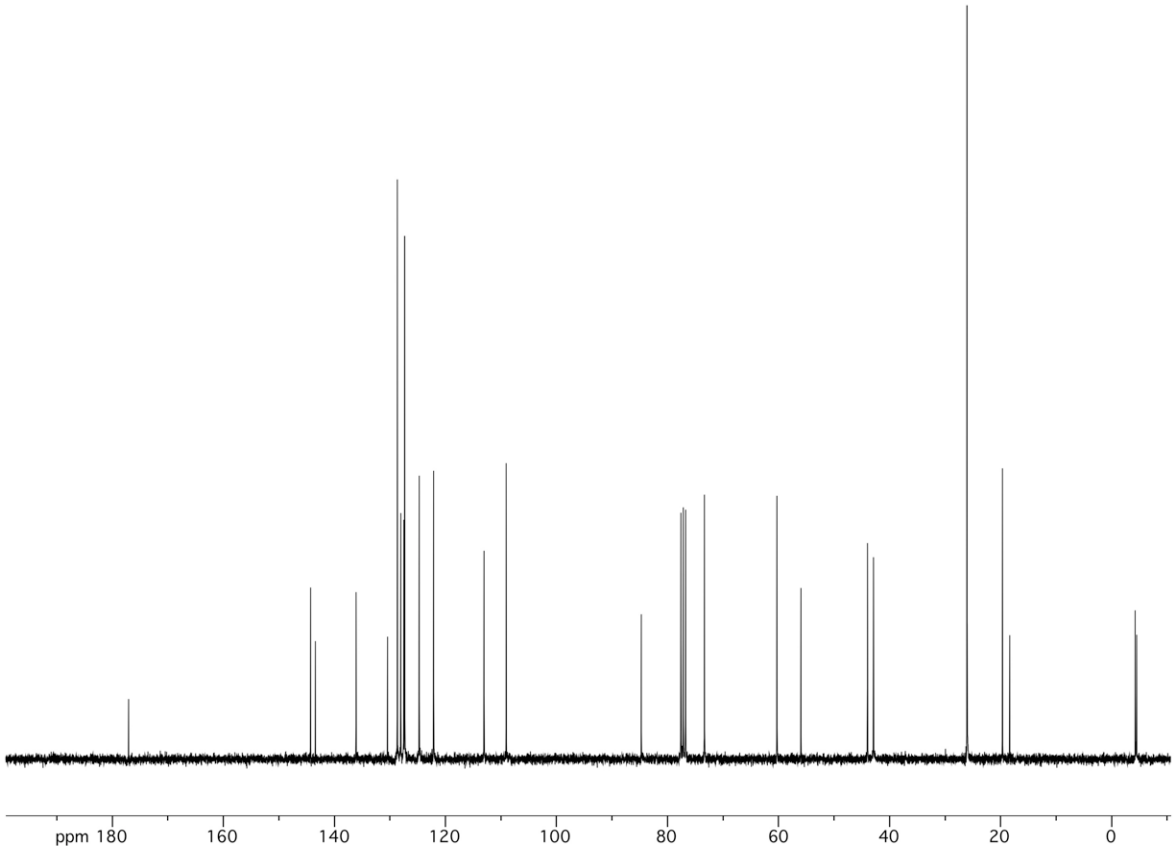


Figure A.1.8b ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **68a**

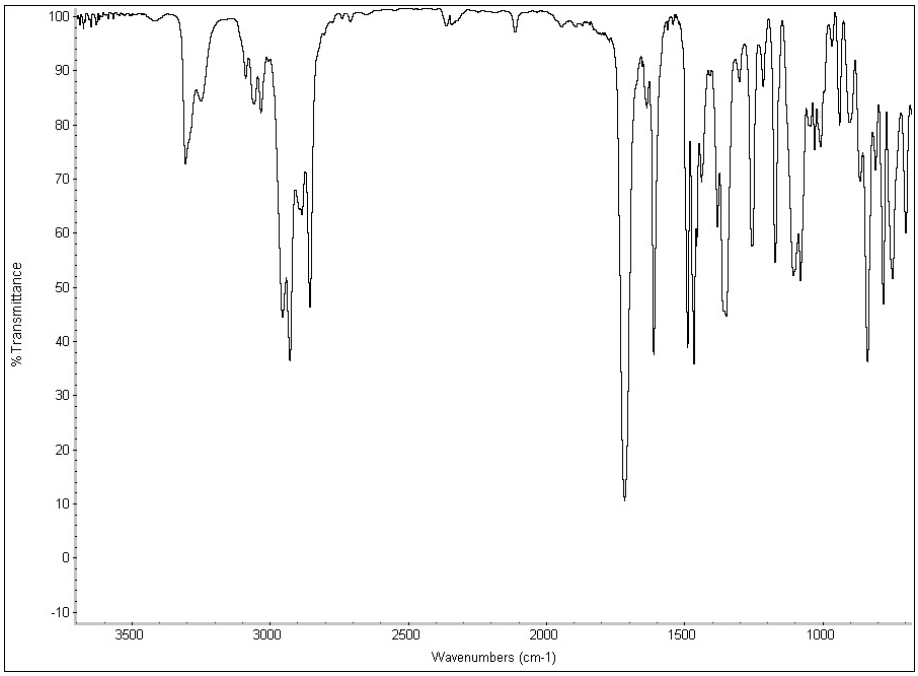
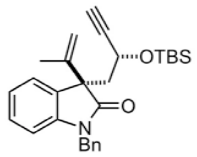


Figure A.1.8c IR spectrum (thin film/NaCl) of compound **68a**



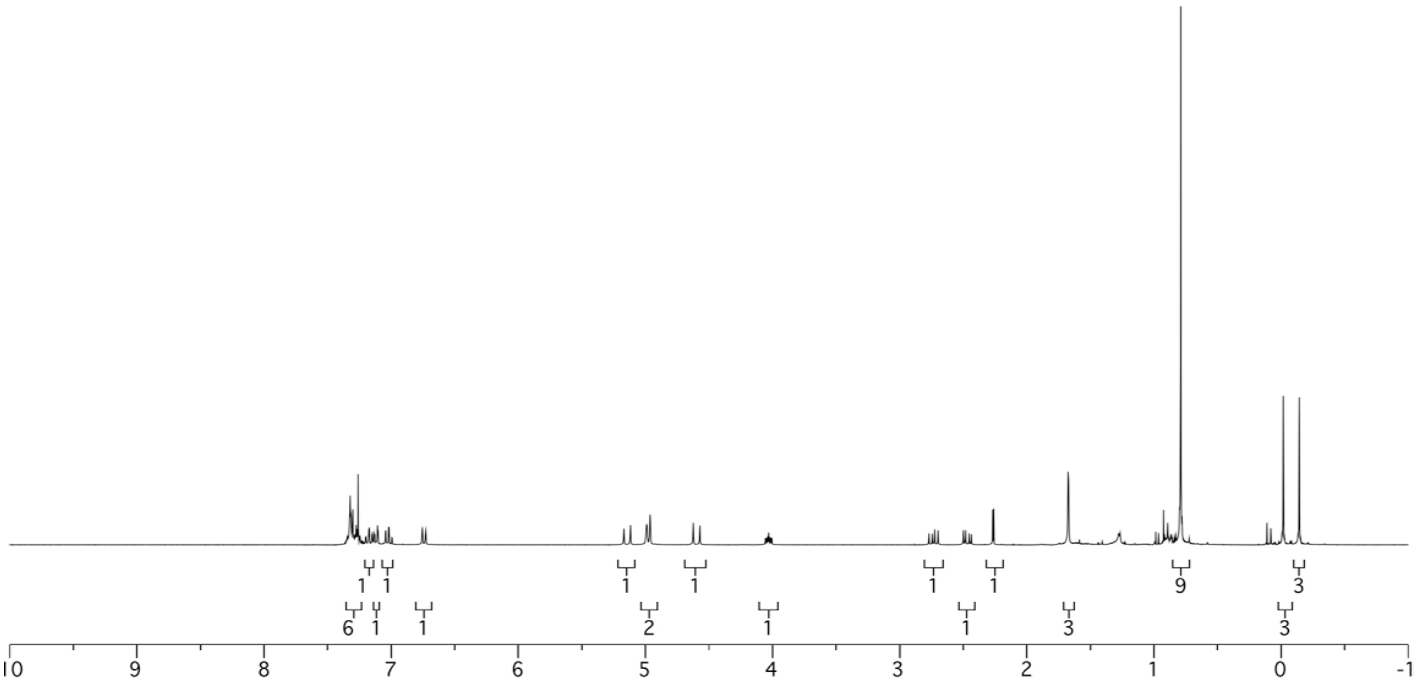


Figure A.1.9a ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **68b**

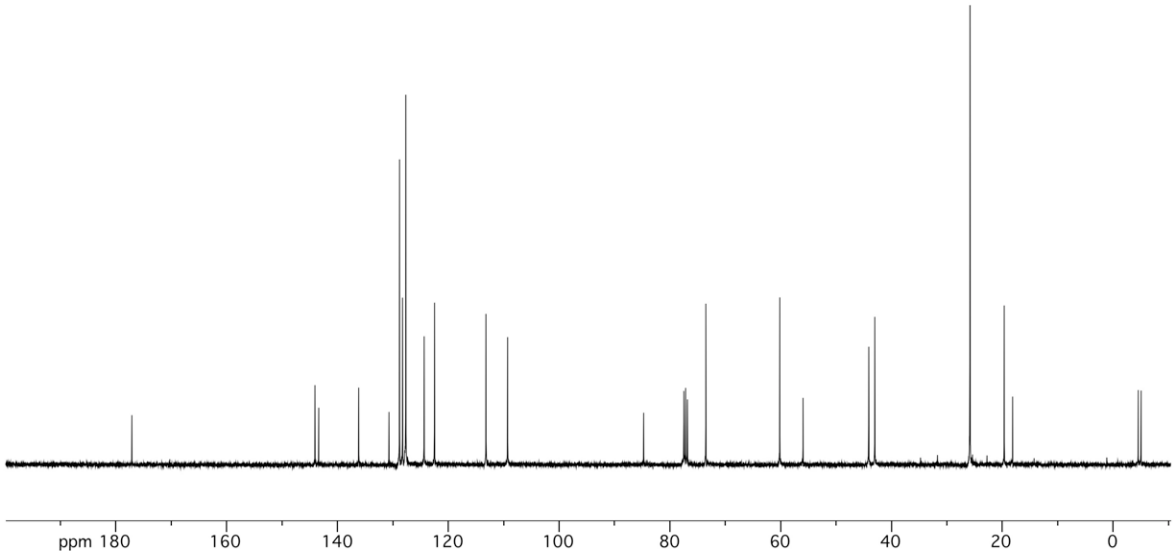


Figure A.1.9b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **68b**

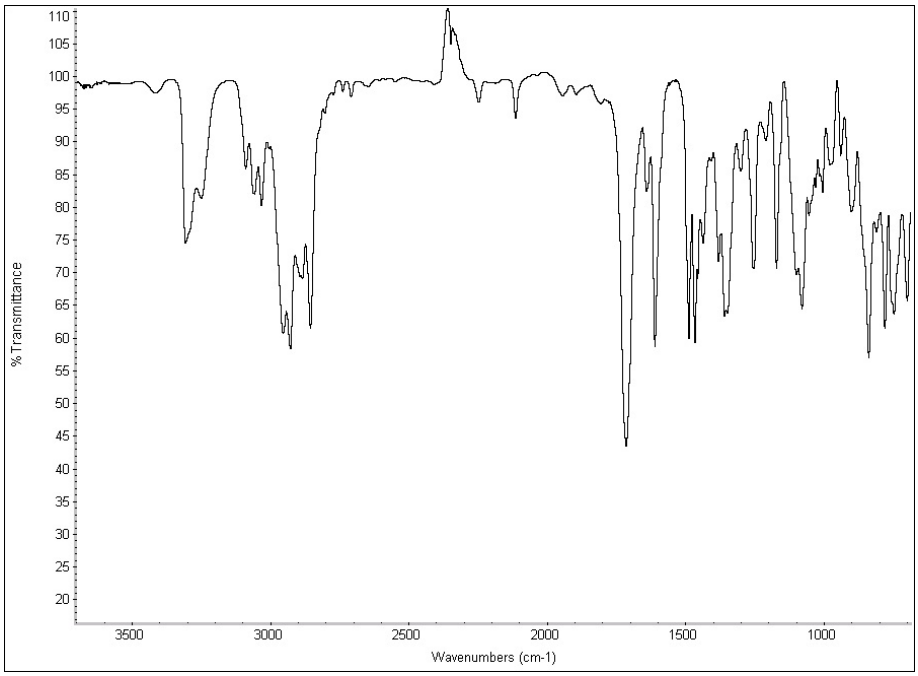


Figure A.1.9c IR spectrum (thin film/NaCl) of compound **68b**

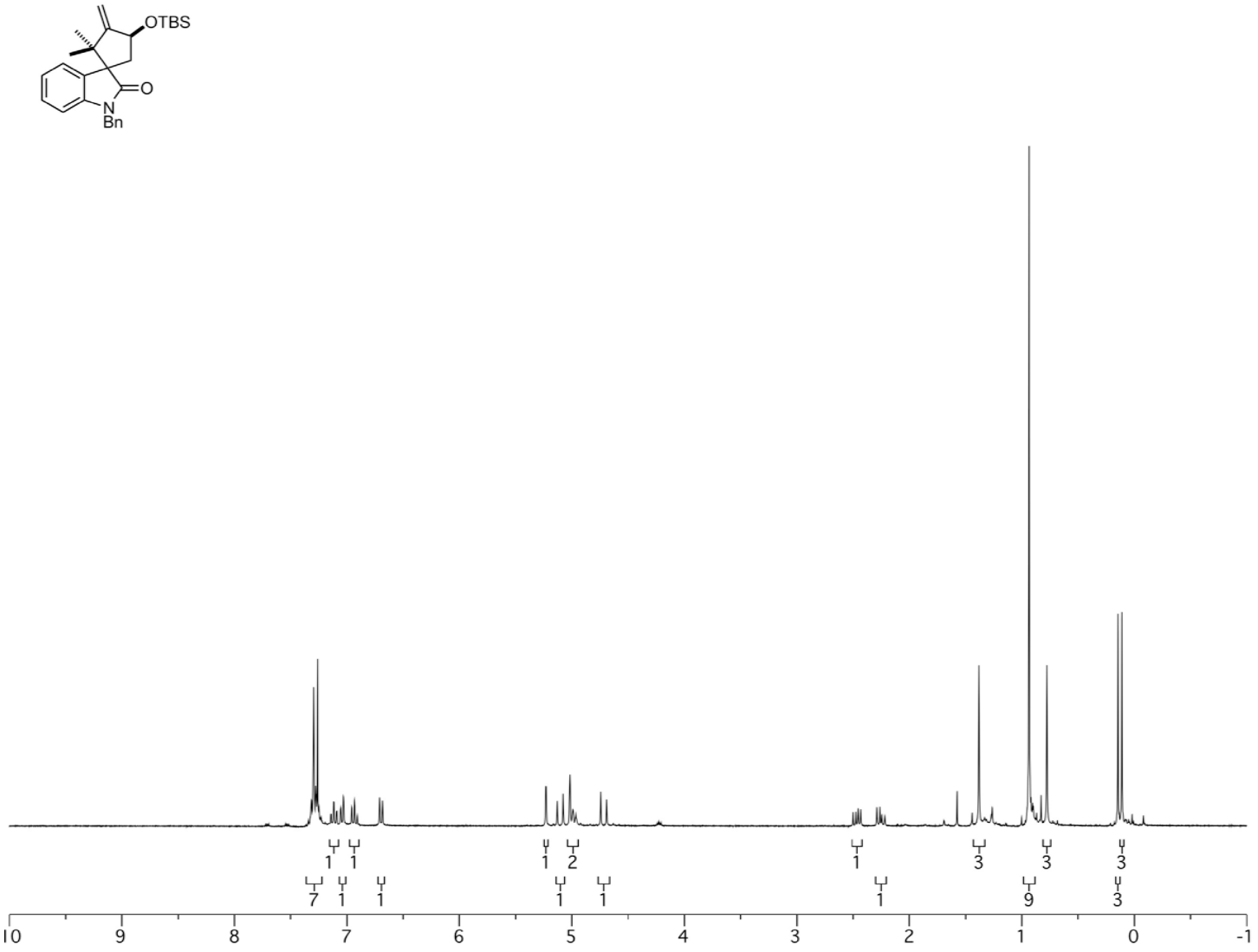


Figure A.1.10a ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **69a**

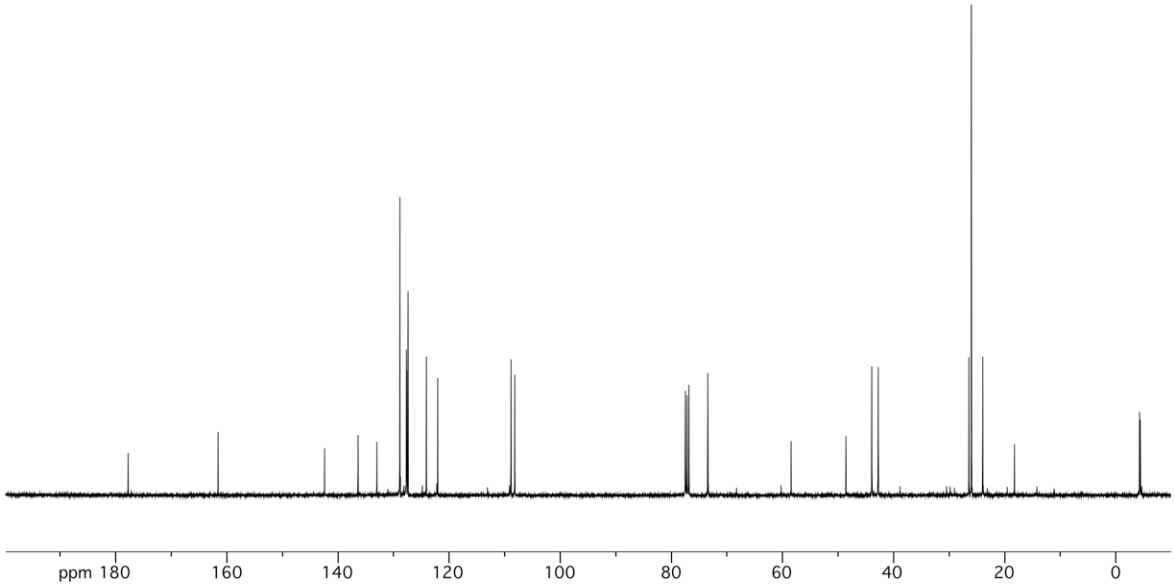


Figure A.1.10b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **69a**

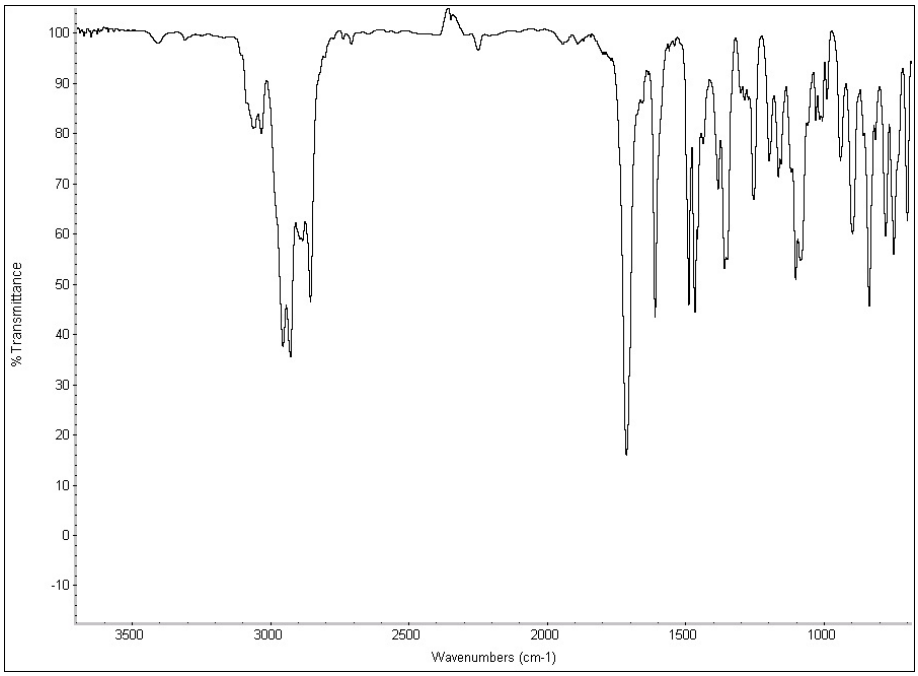


Figure A.1.10c IR spectrum (thin film/NaCl) of compound **69a**

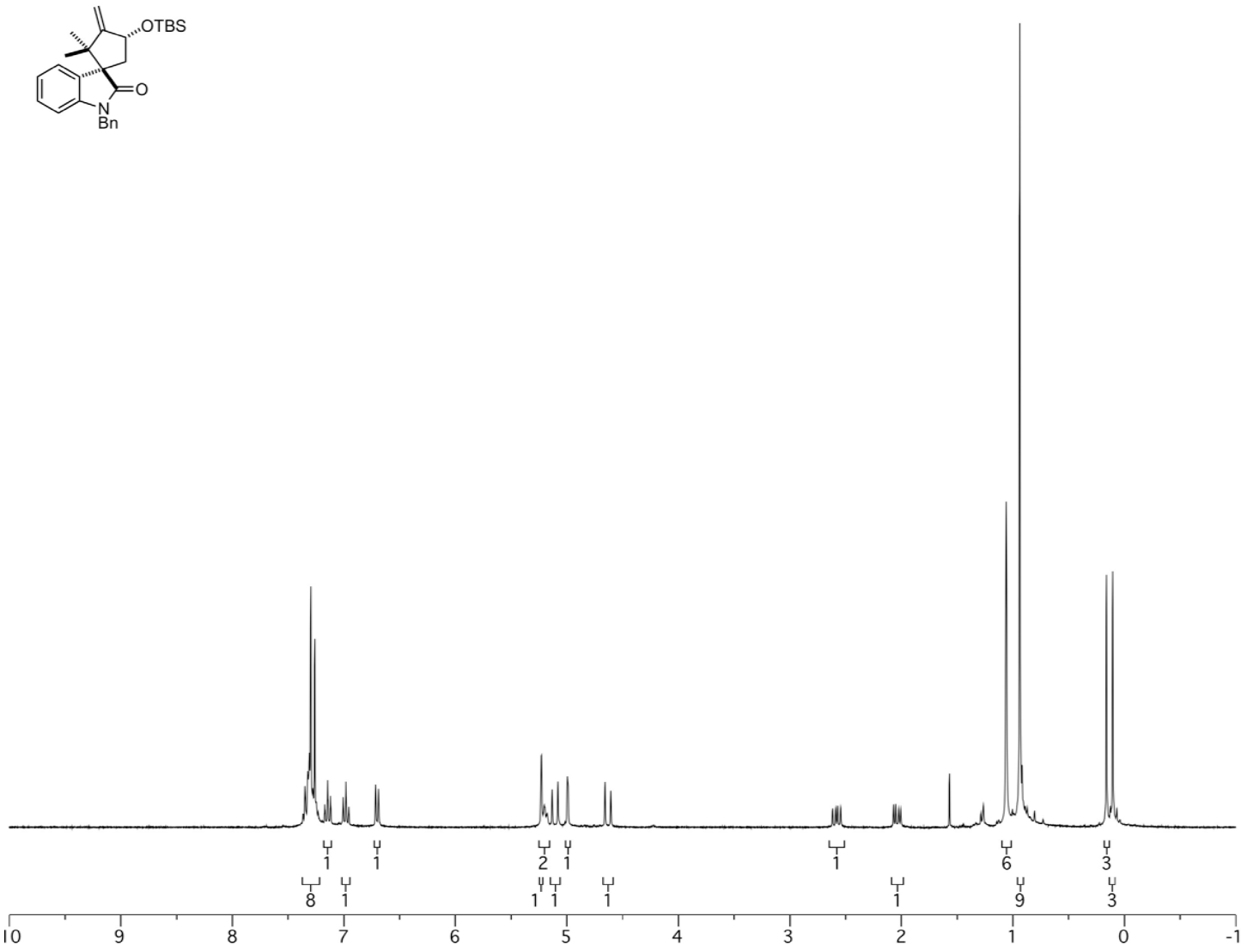


Figure A.1.11a ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **69b**

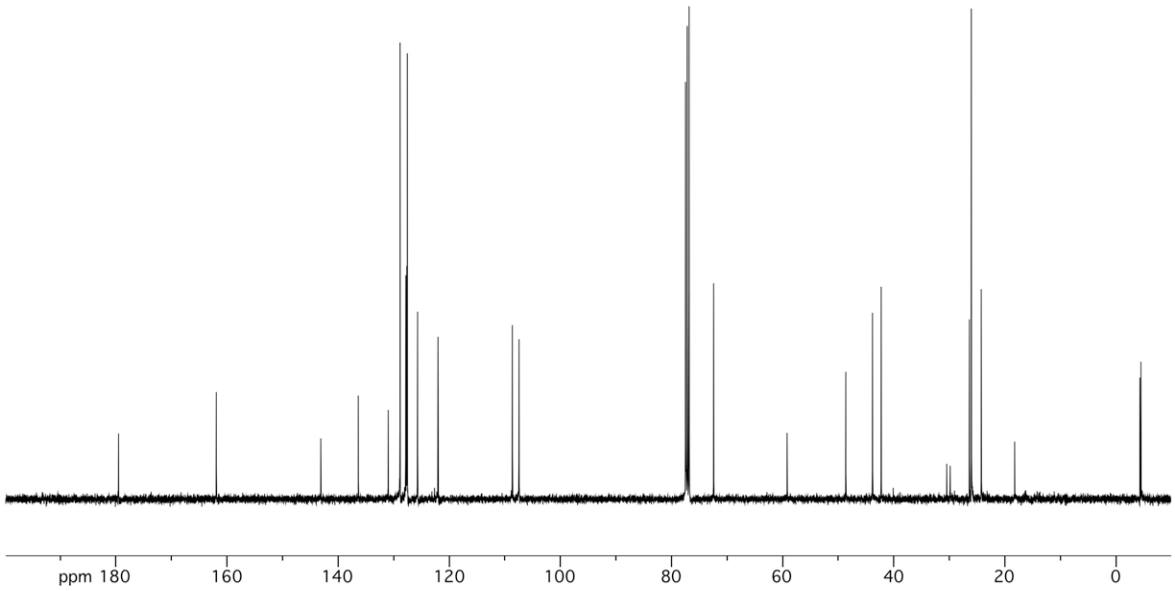


Figure A.1.11b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **69b**

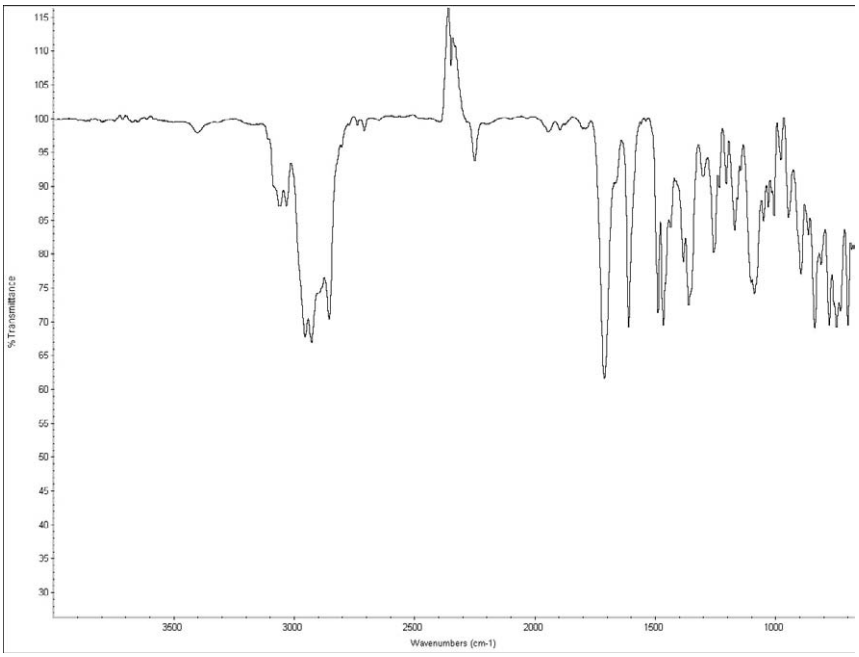


Figure A.1.11c IR spectrum (thin film/NaCl) of compound **69b**

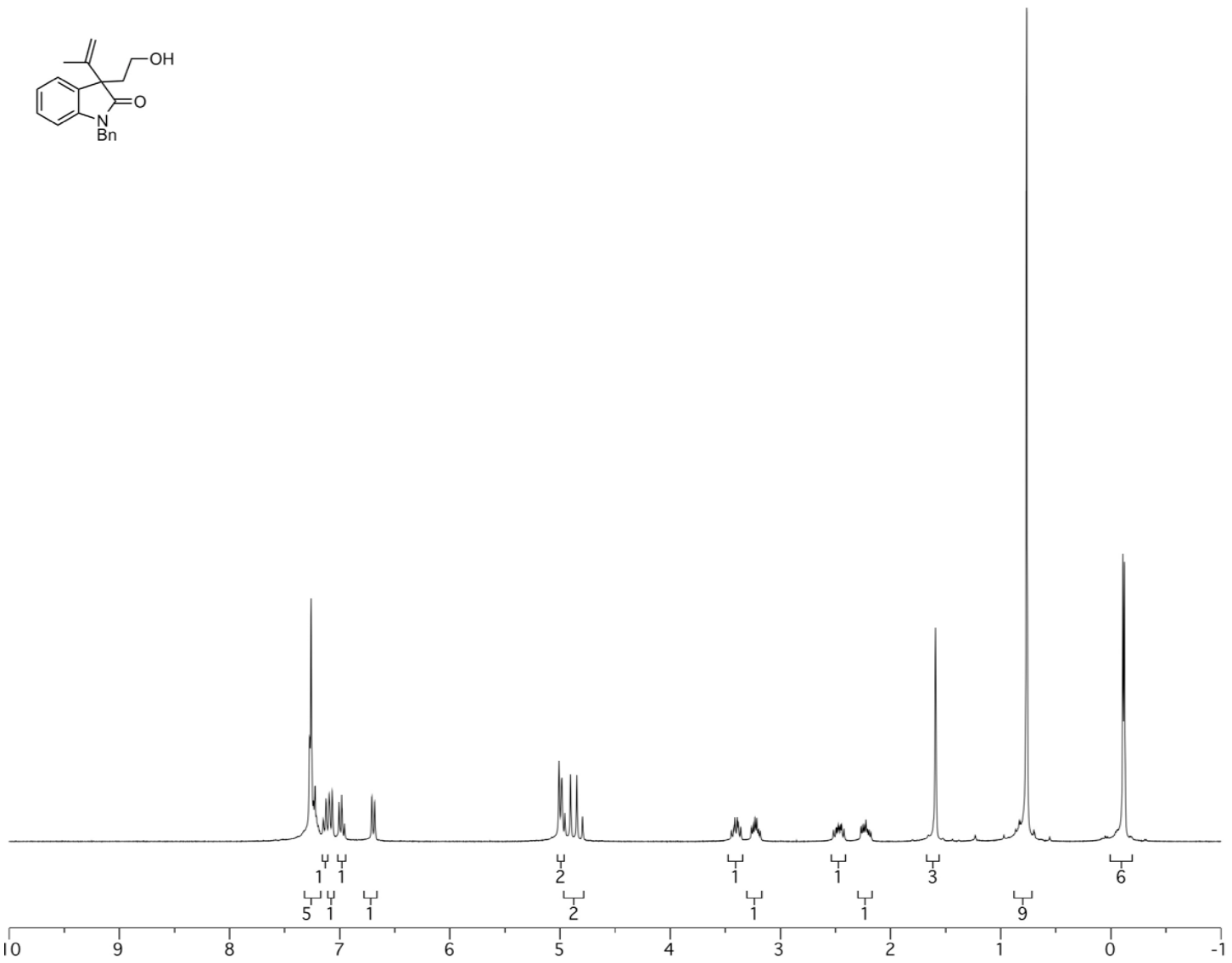


Figure A.1.12a ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **70**

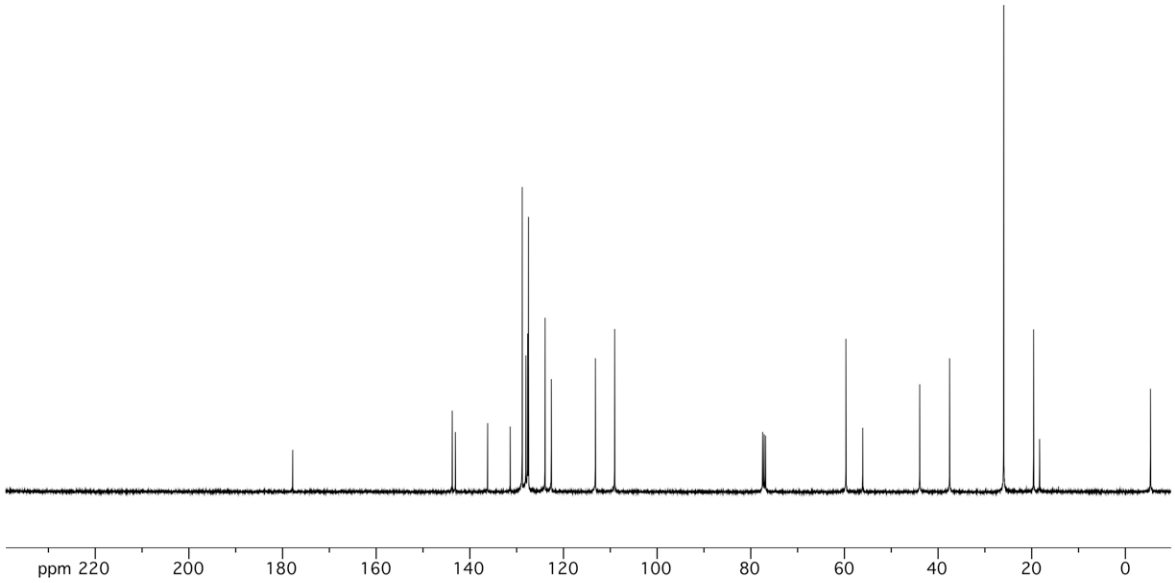


Figure A.1.12b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **70**

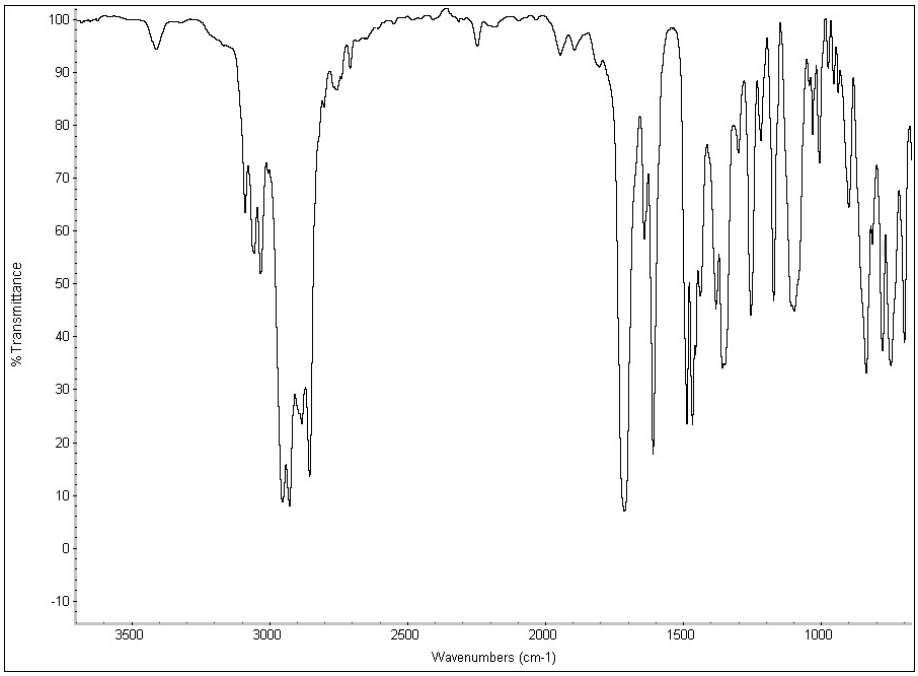


Figure A.1.12c IR spectrum (thin film/NaCl) of compound **70**

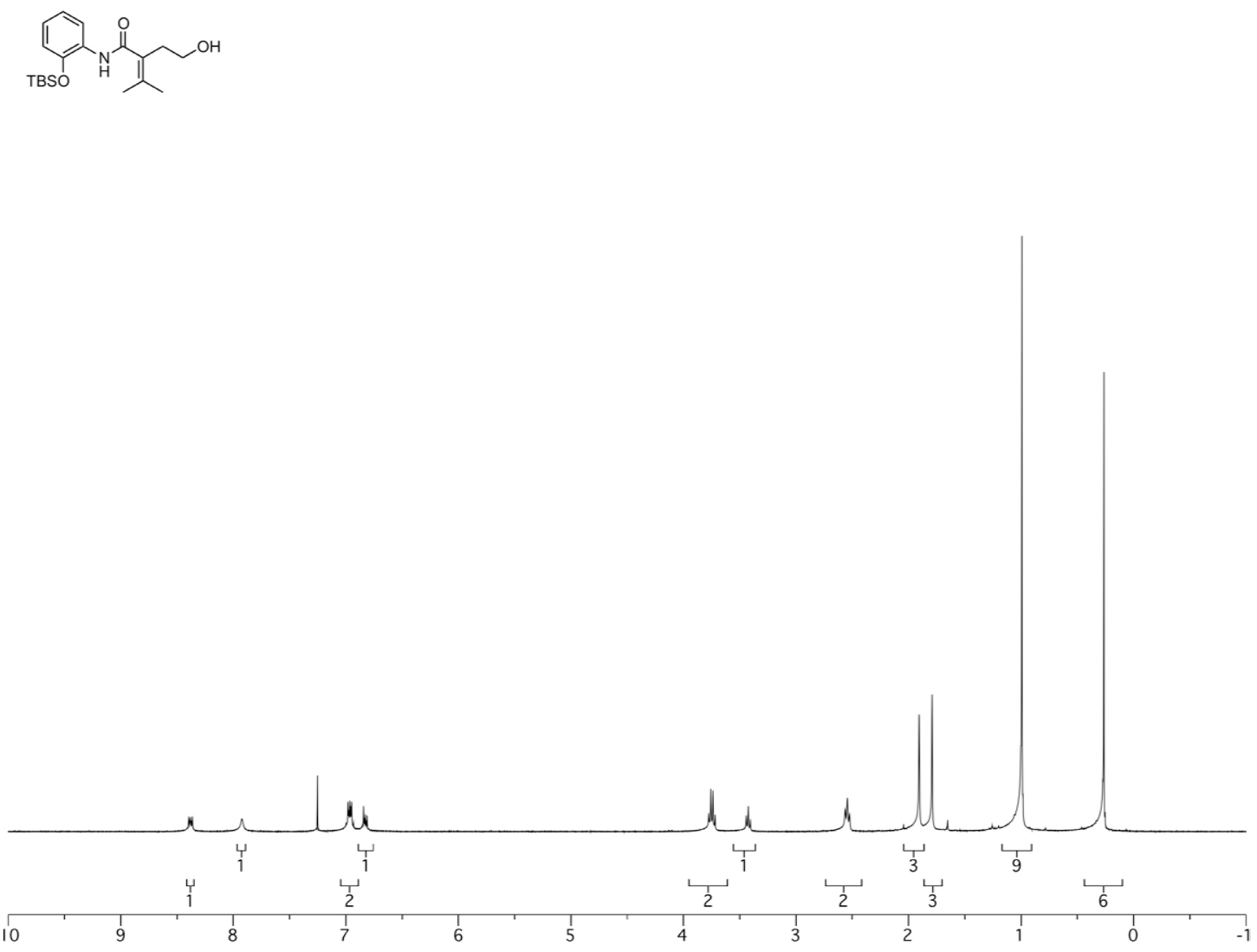


Figure A.1.13a ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **72**

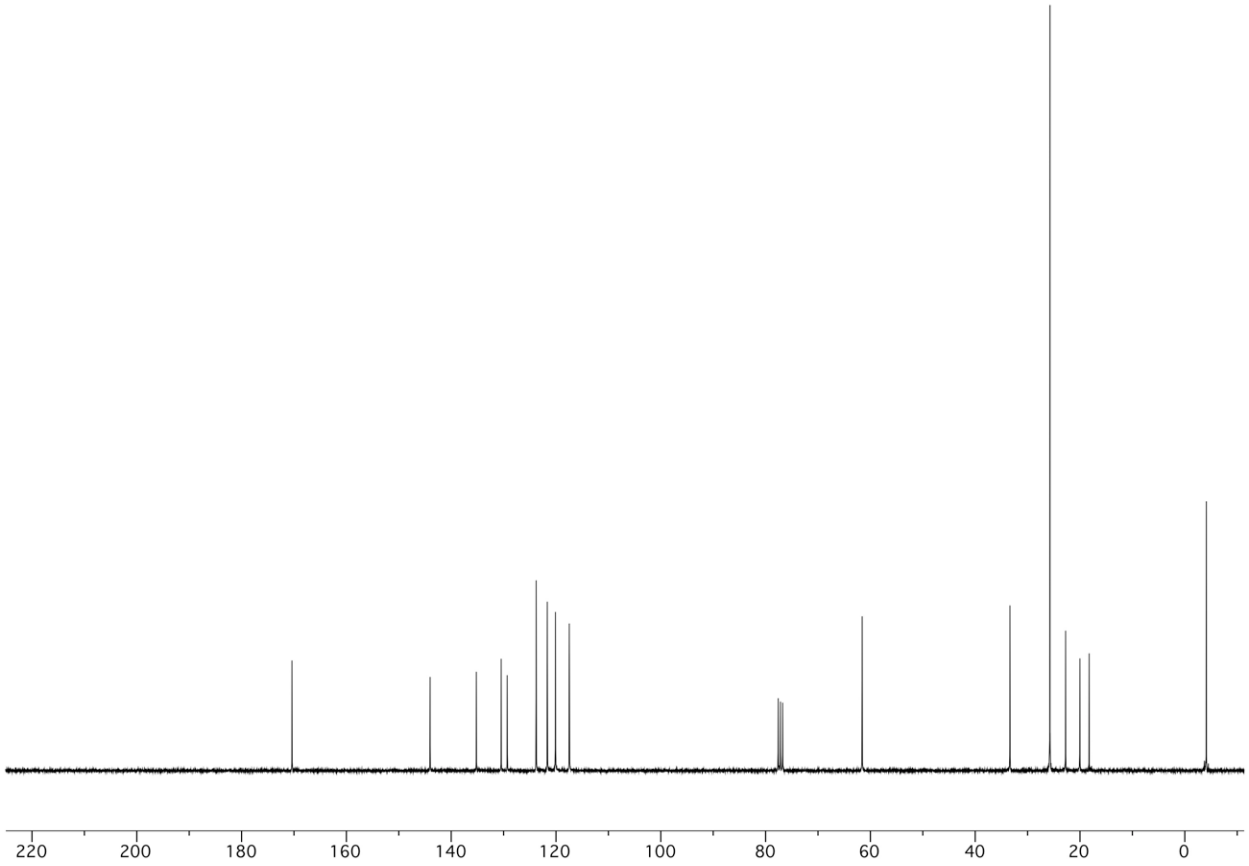


Figure A.1.13b ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **72**

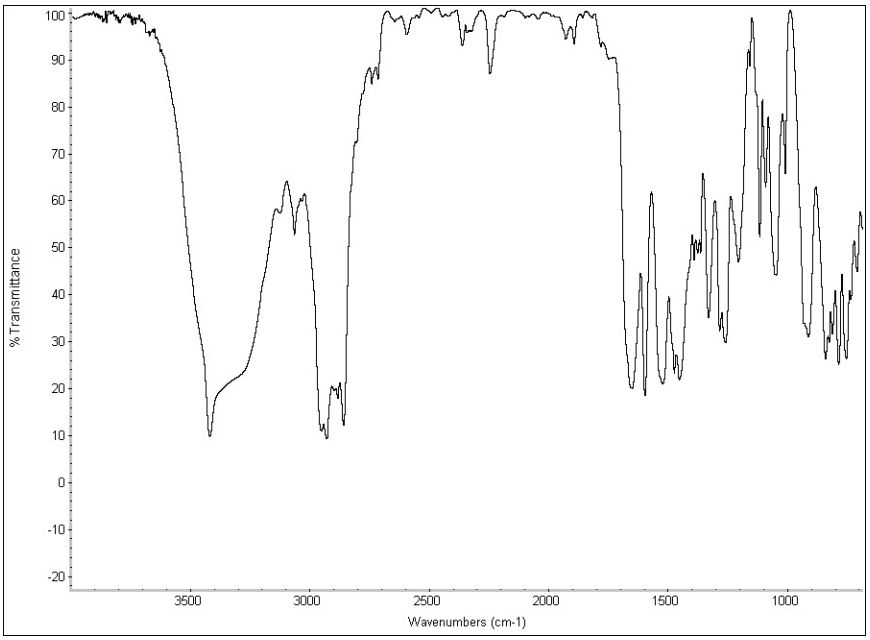


Figure A.1.13c IR spectrum (thin film/NaCl) of compound **72**

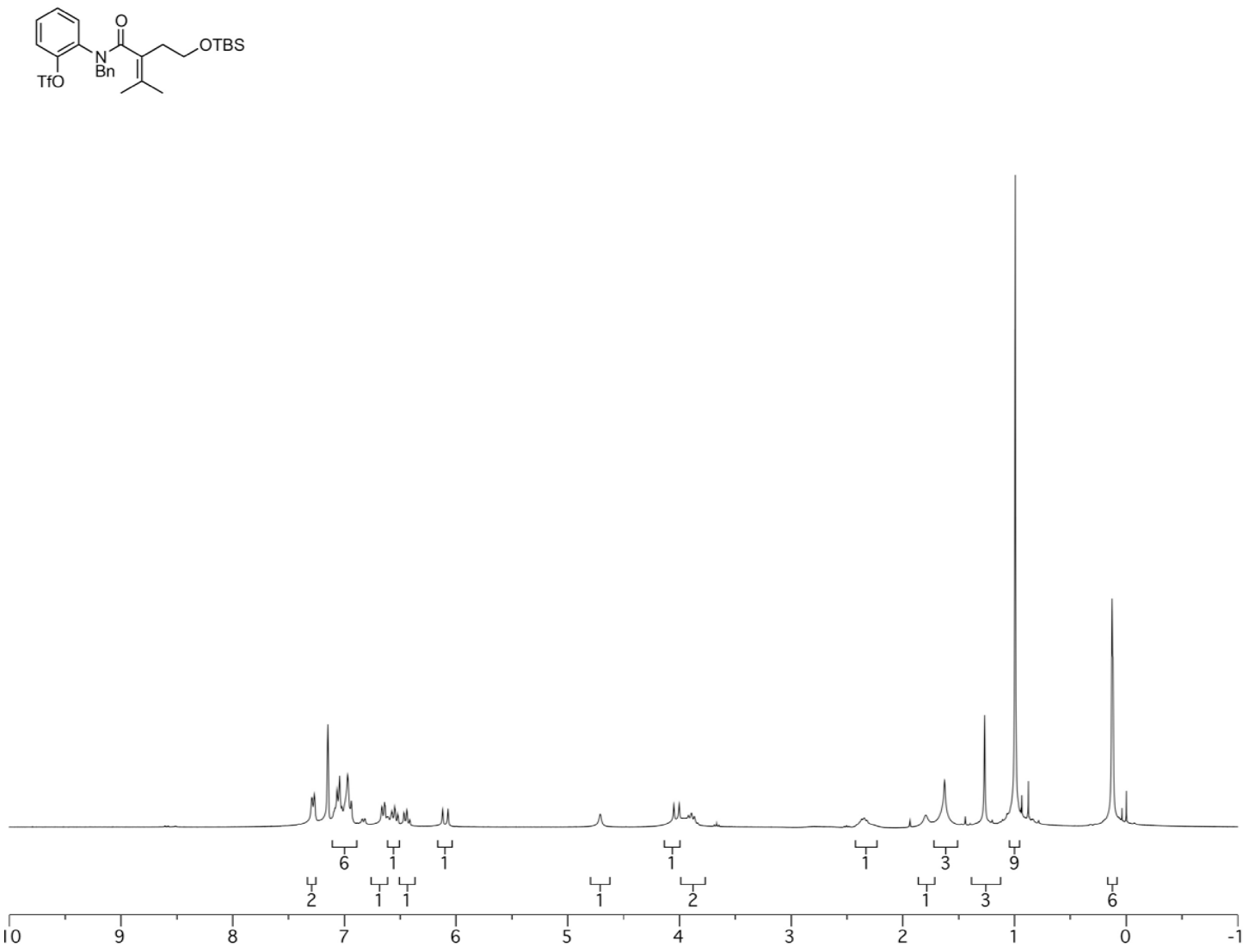


Figure A.1.14a ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **73**

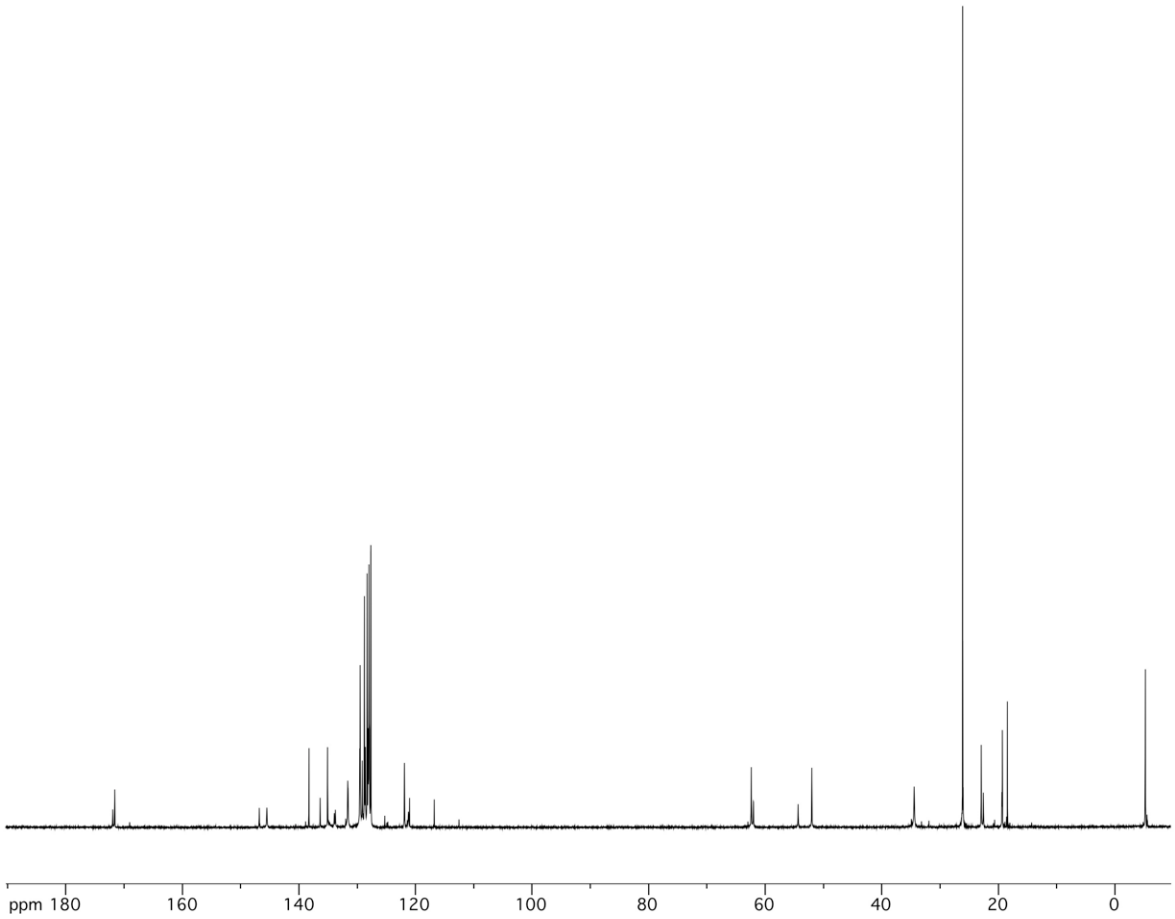


Figure A.1.14b ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **73**

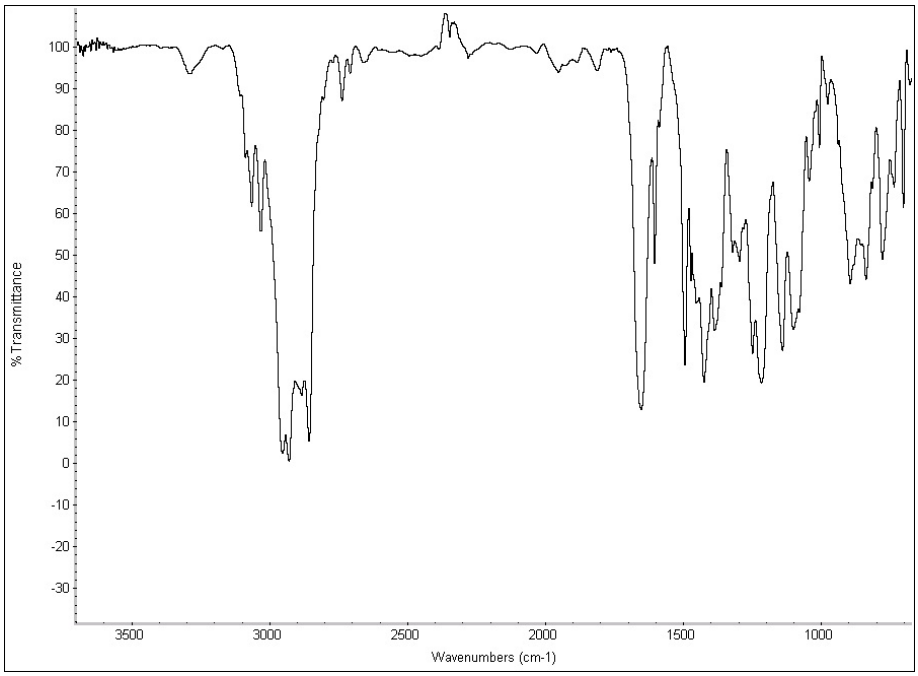
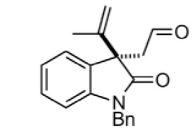


Figure A.1.14c IR spectrum (thin film/NaCl) of compound **73**



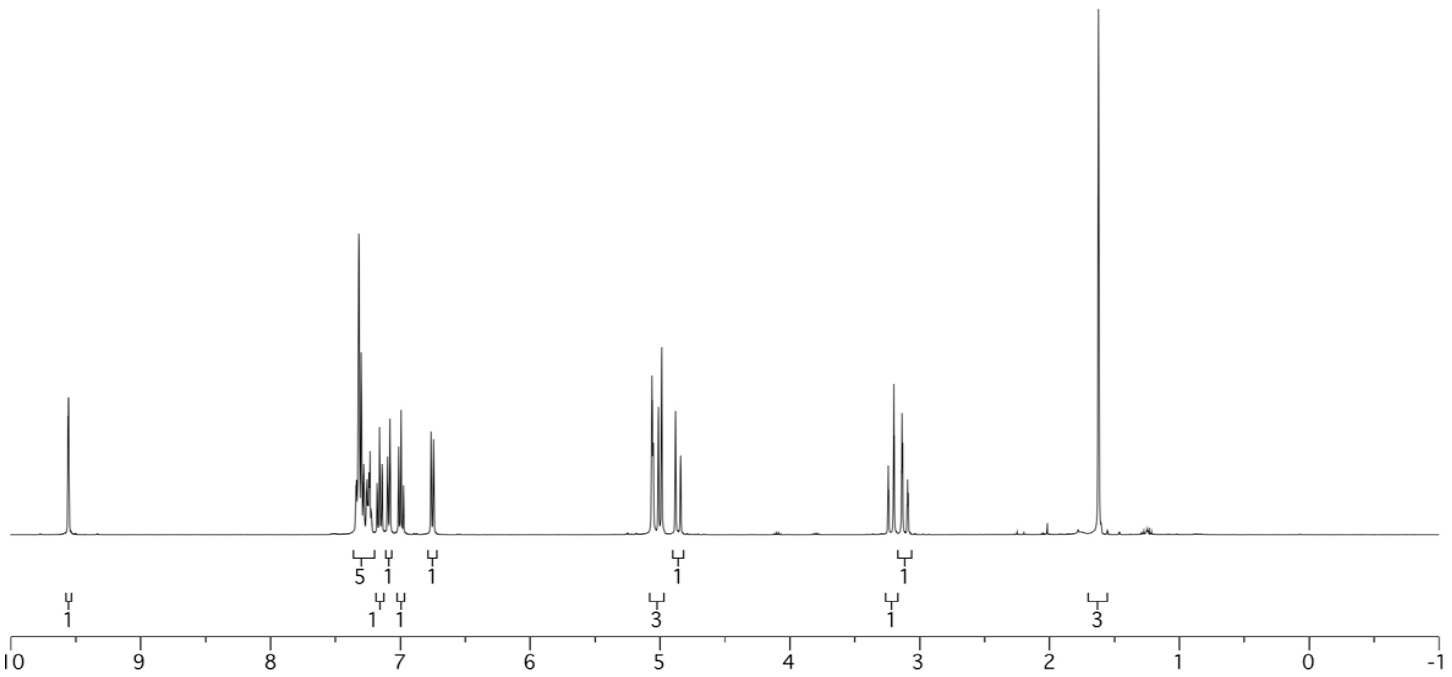


Figure A.1.15a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **74**

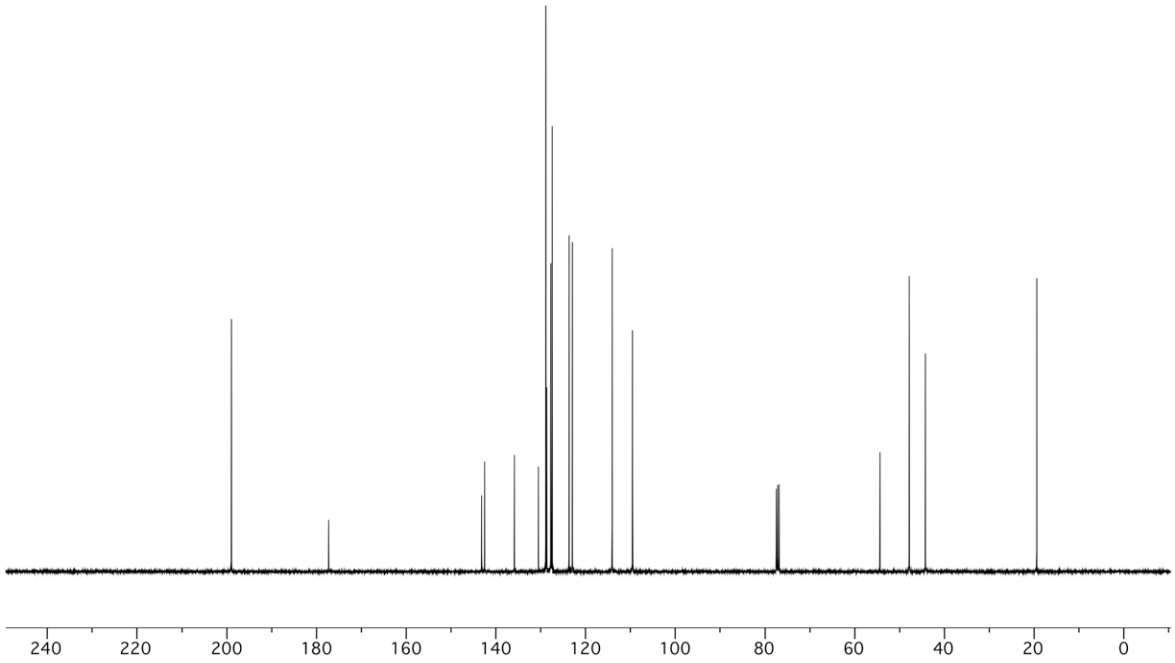


Figure A.1.15b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **74**

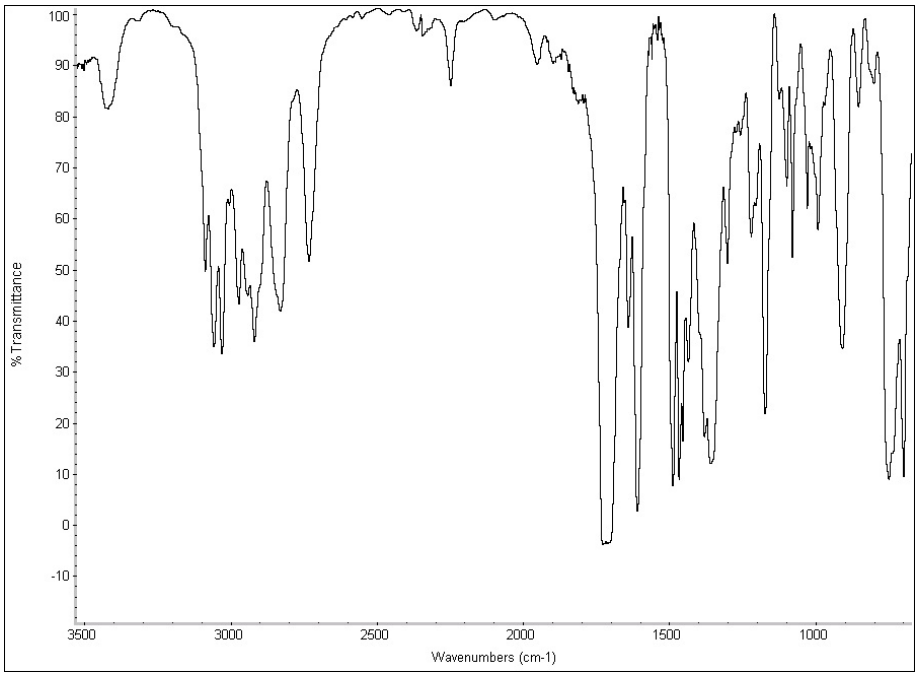


Figure A.1.15c IR spectrum (thin film/NaCl) of compound **74**

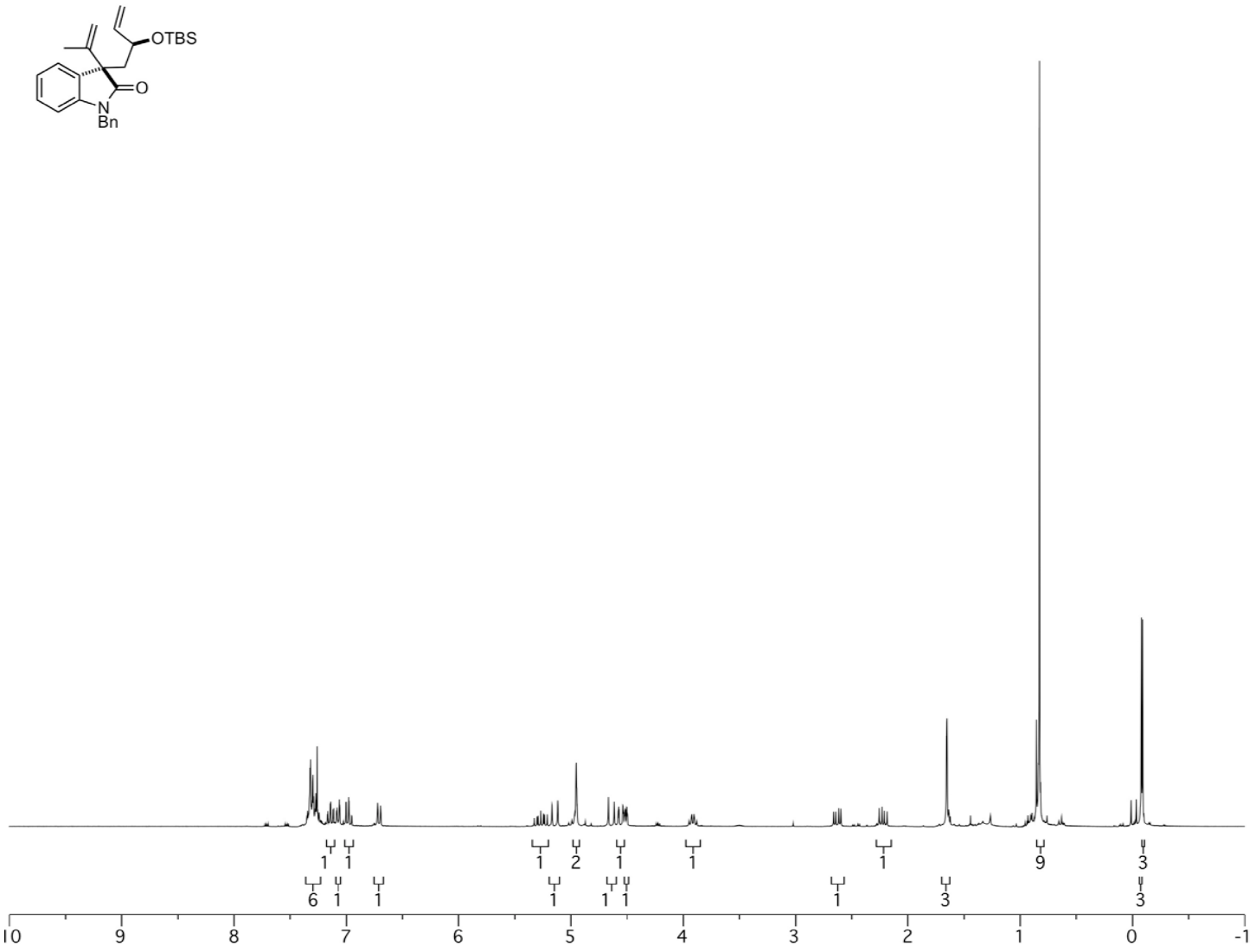


Figure A.1.16a ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **78a**

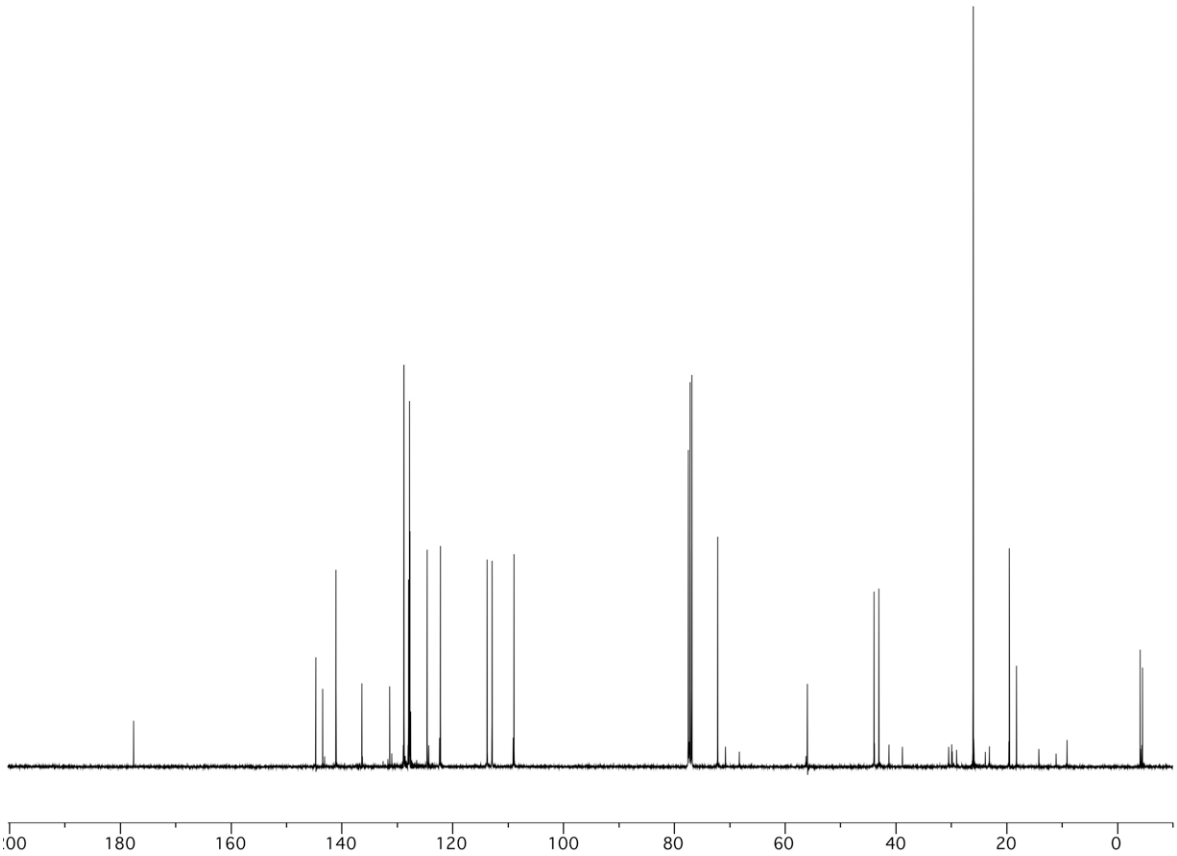


Figure A.1.16b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **78a**

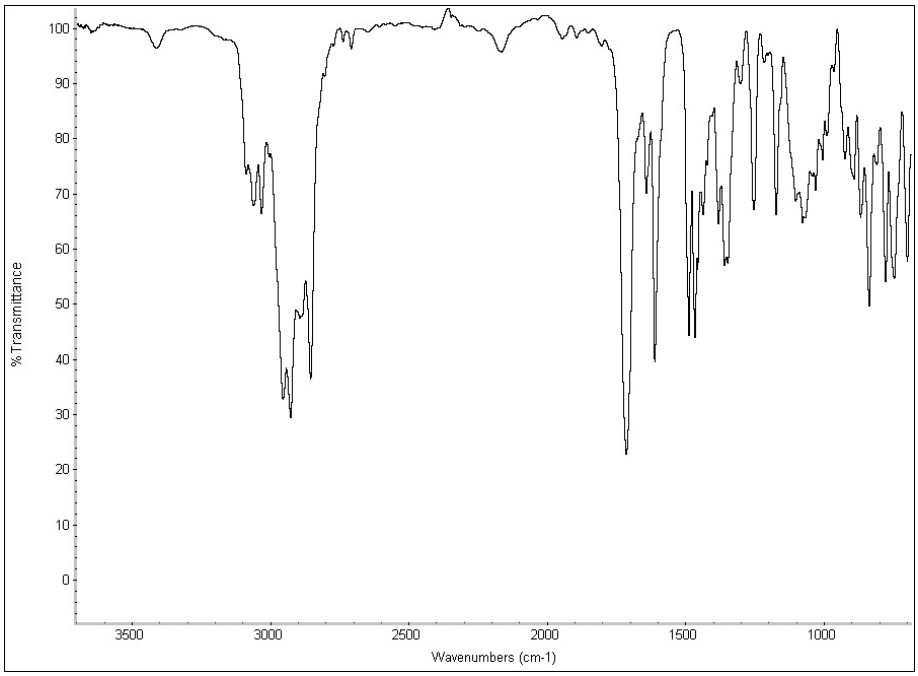


Figure A.1.16c IR spectrum (thin film/NaCl) of compound **78a**

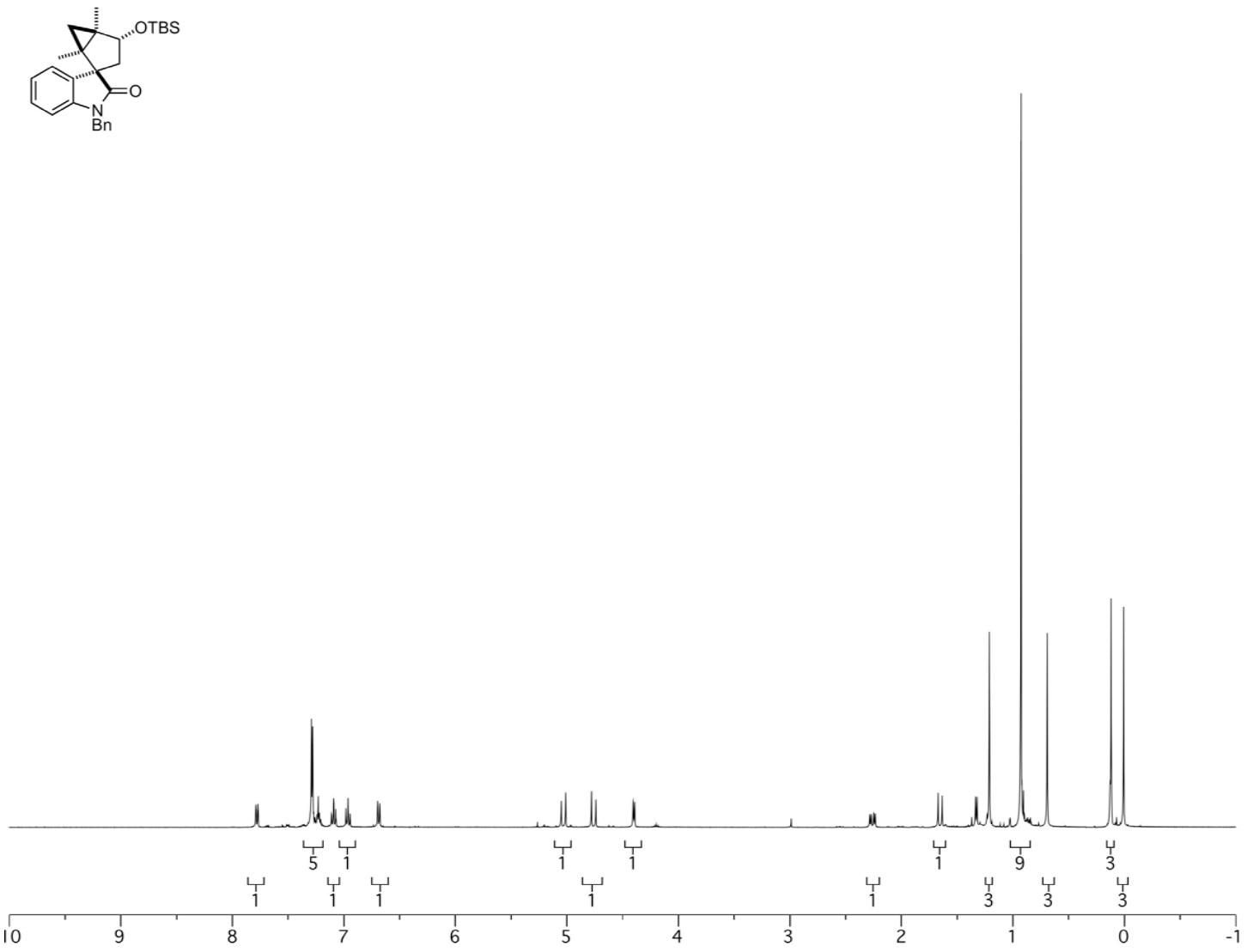


Figure A.1.17a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **79**

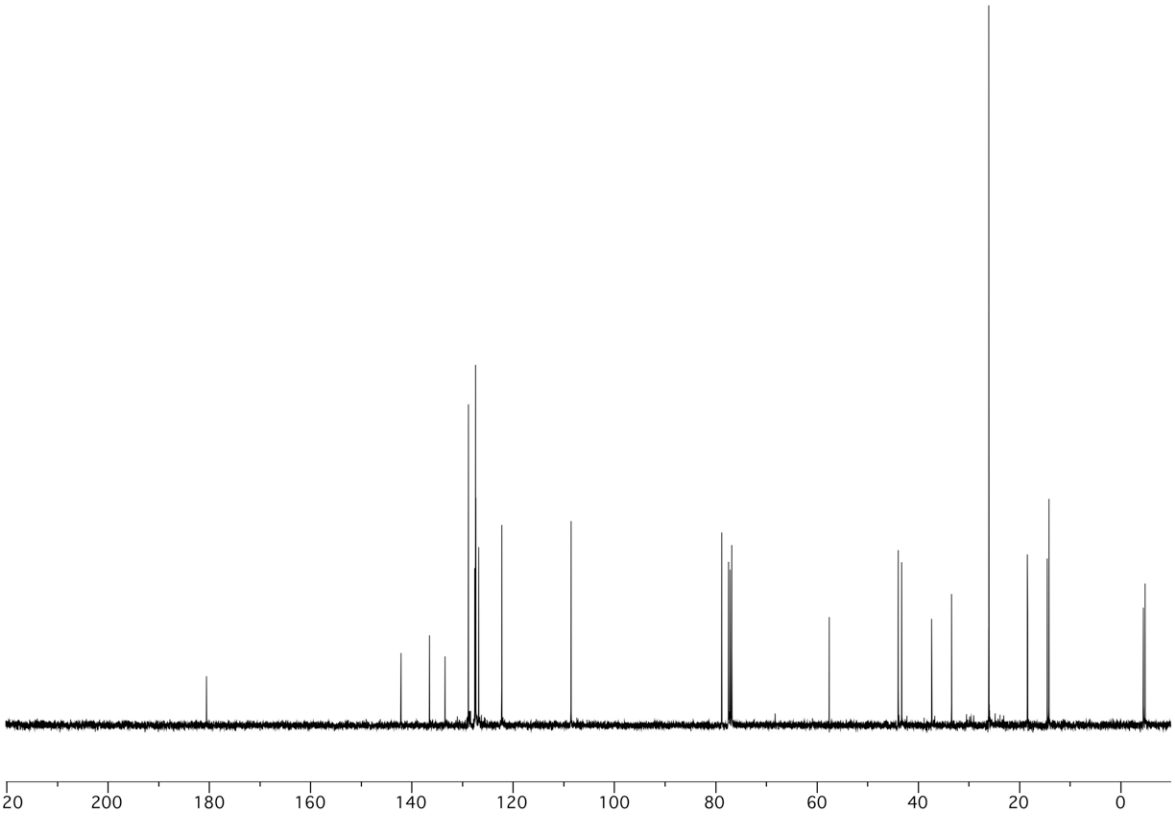


Figure A.1.17b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **79**

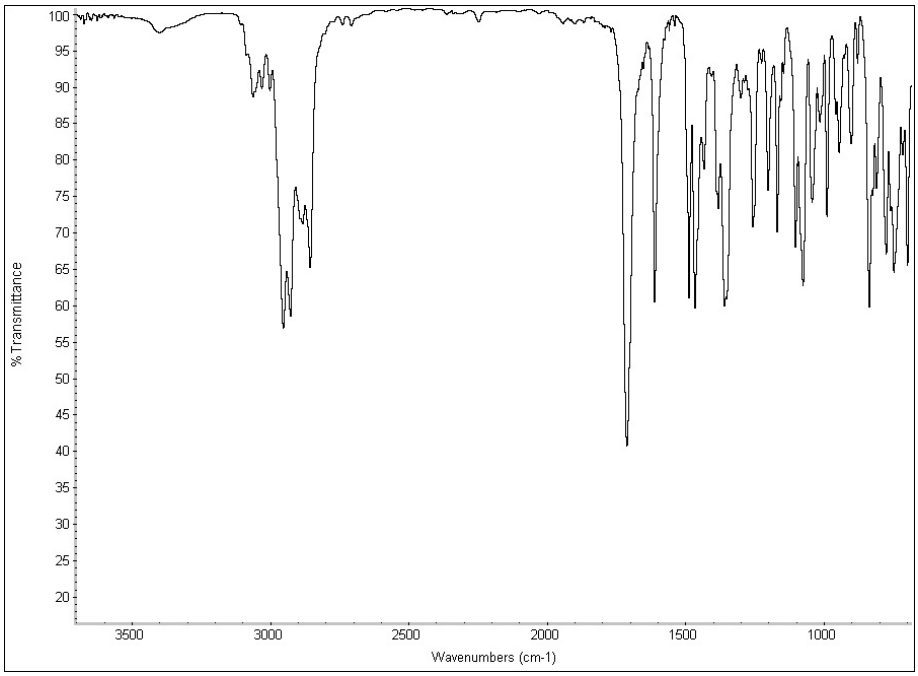


Figure A.1.17c IR spectrum (thin film/NaCl) of compound **79**

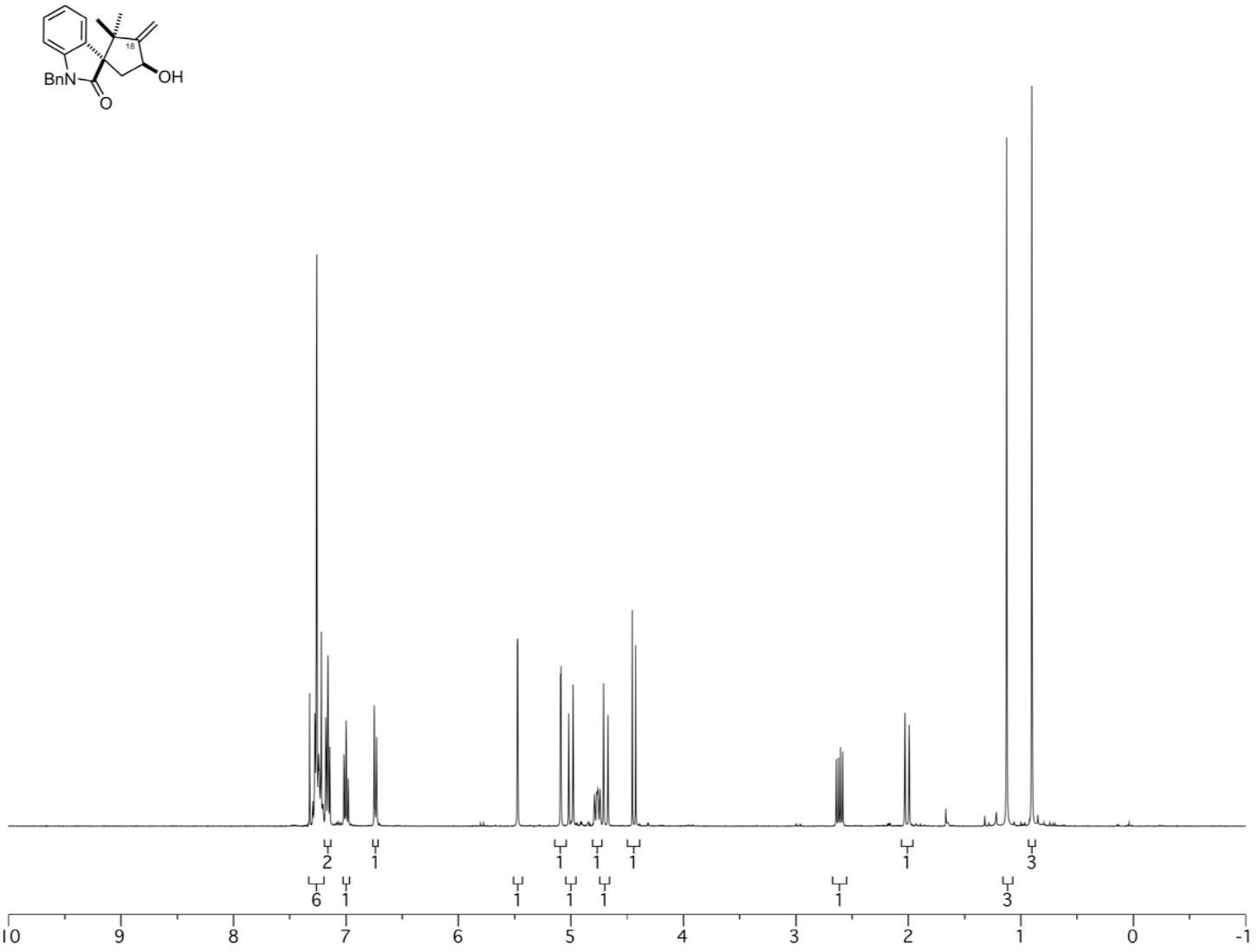


Figure A.1.18a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **82a**

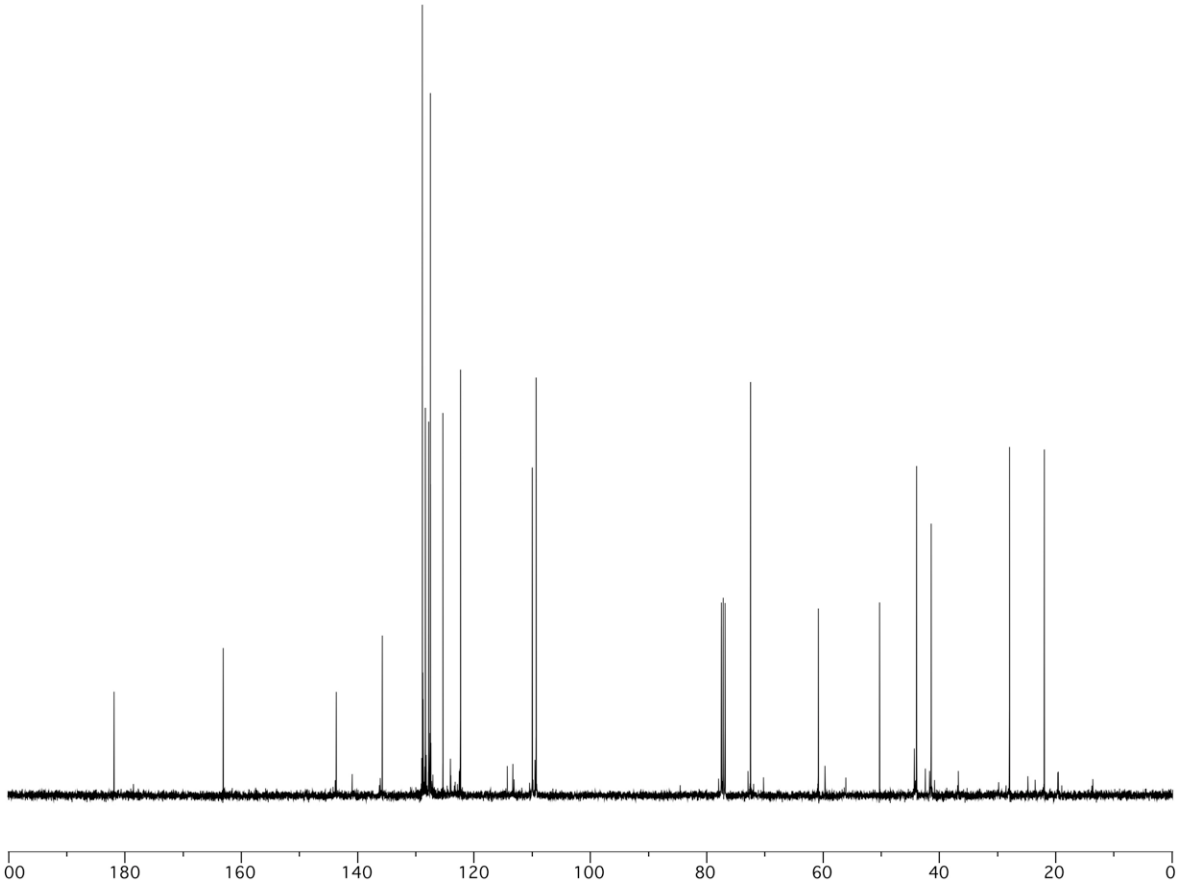


Figure A.1.18b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **82a**

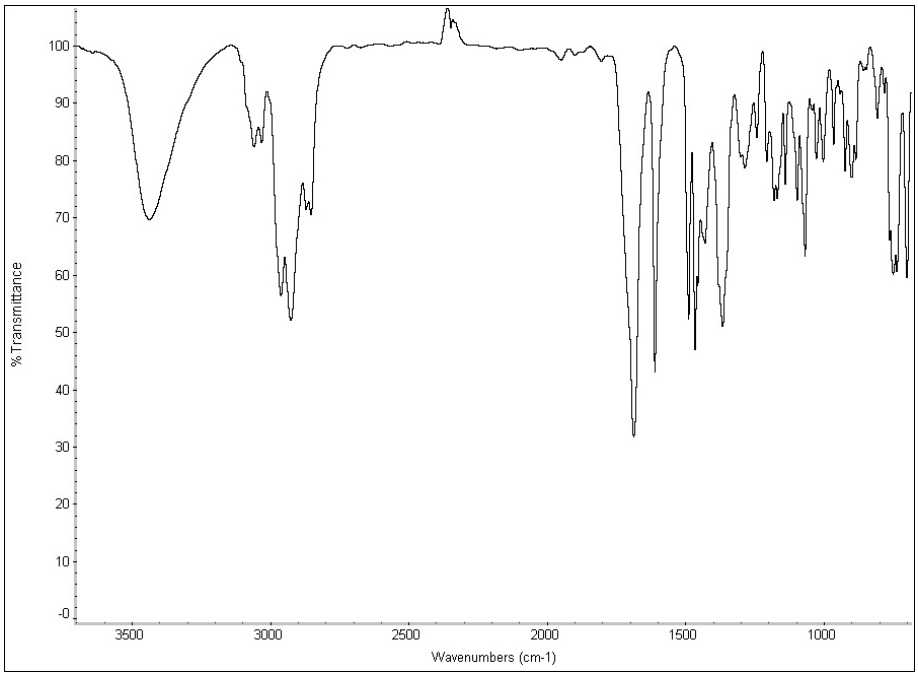


Figure A.1.18c IR spectrum (thin film/NaCl) of compound **82a**

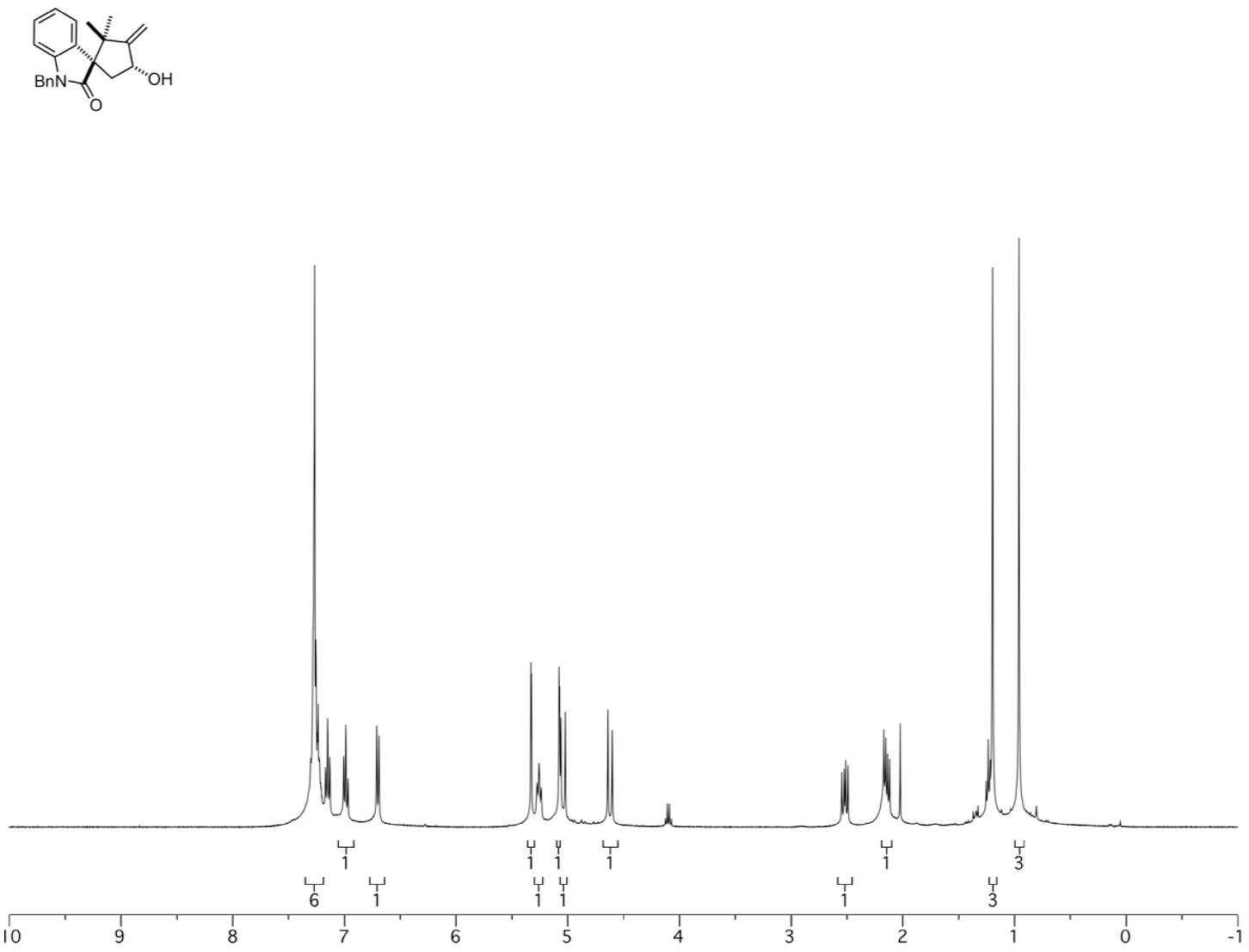


Figure A.1.19a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **82b**

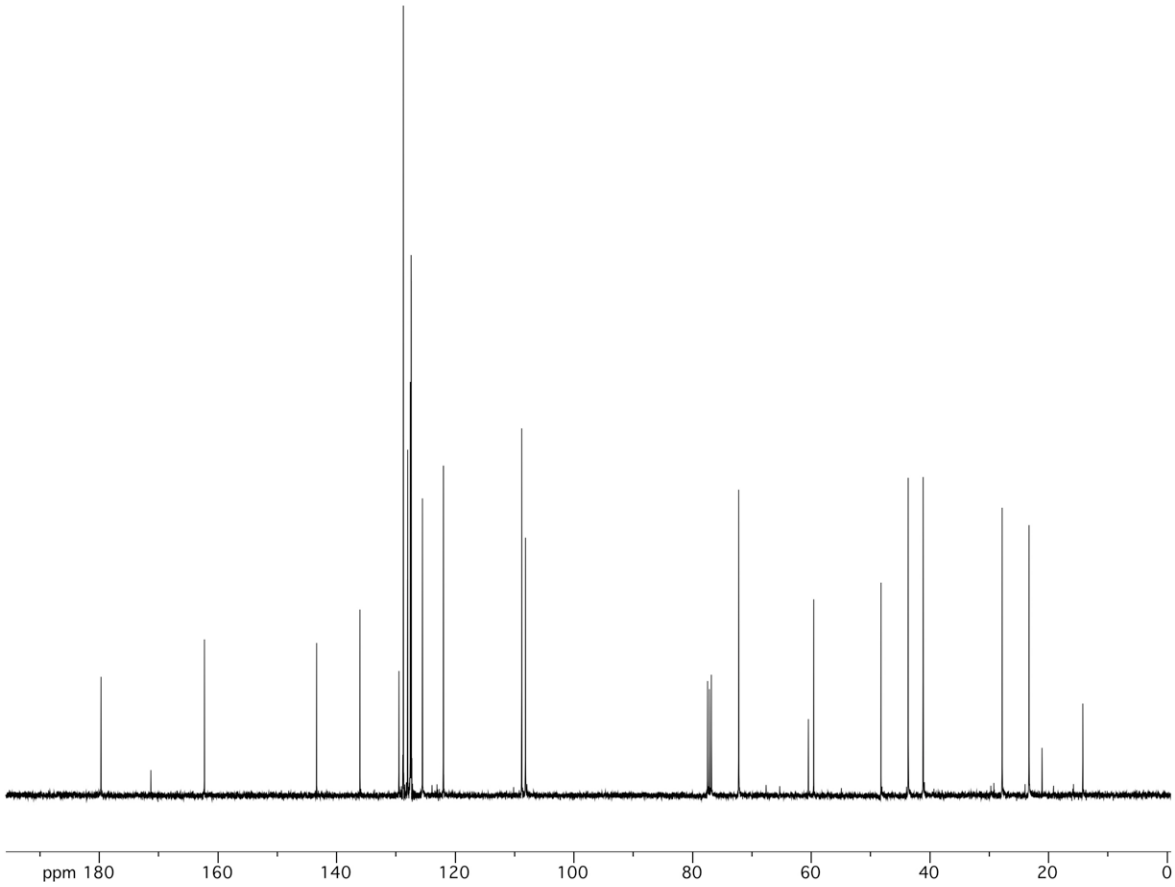


Figure A.1.19b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **82b**

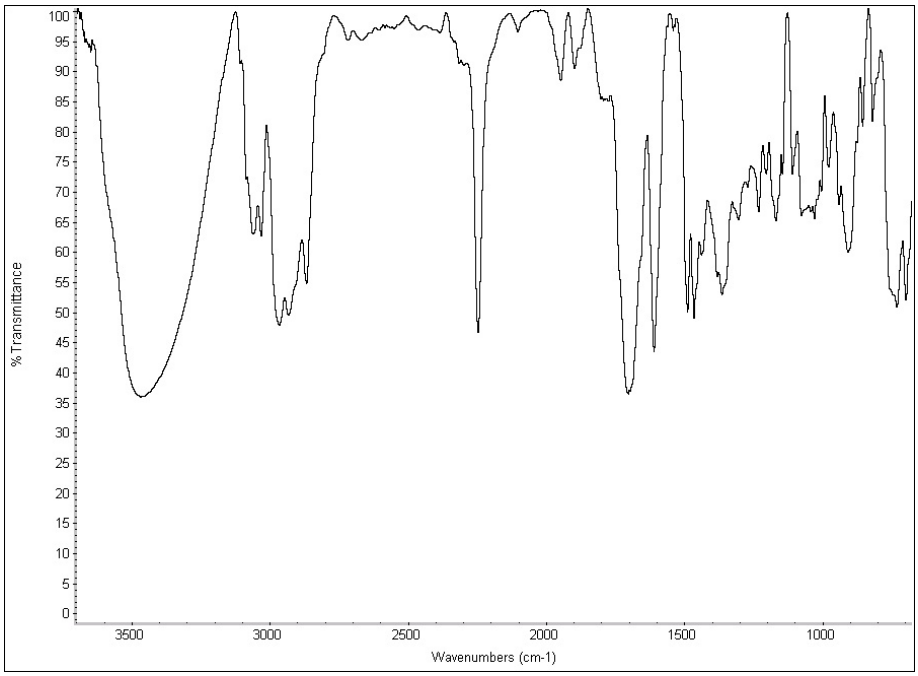


Figure A.1.19c IR spectrum (thin film/NaCl) of compound **82b**

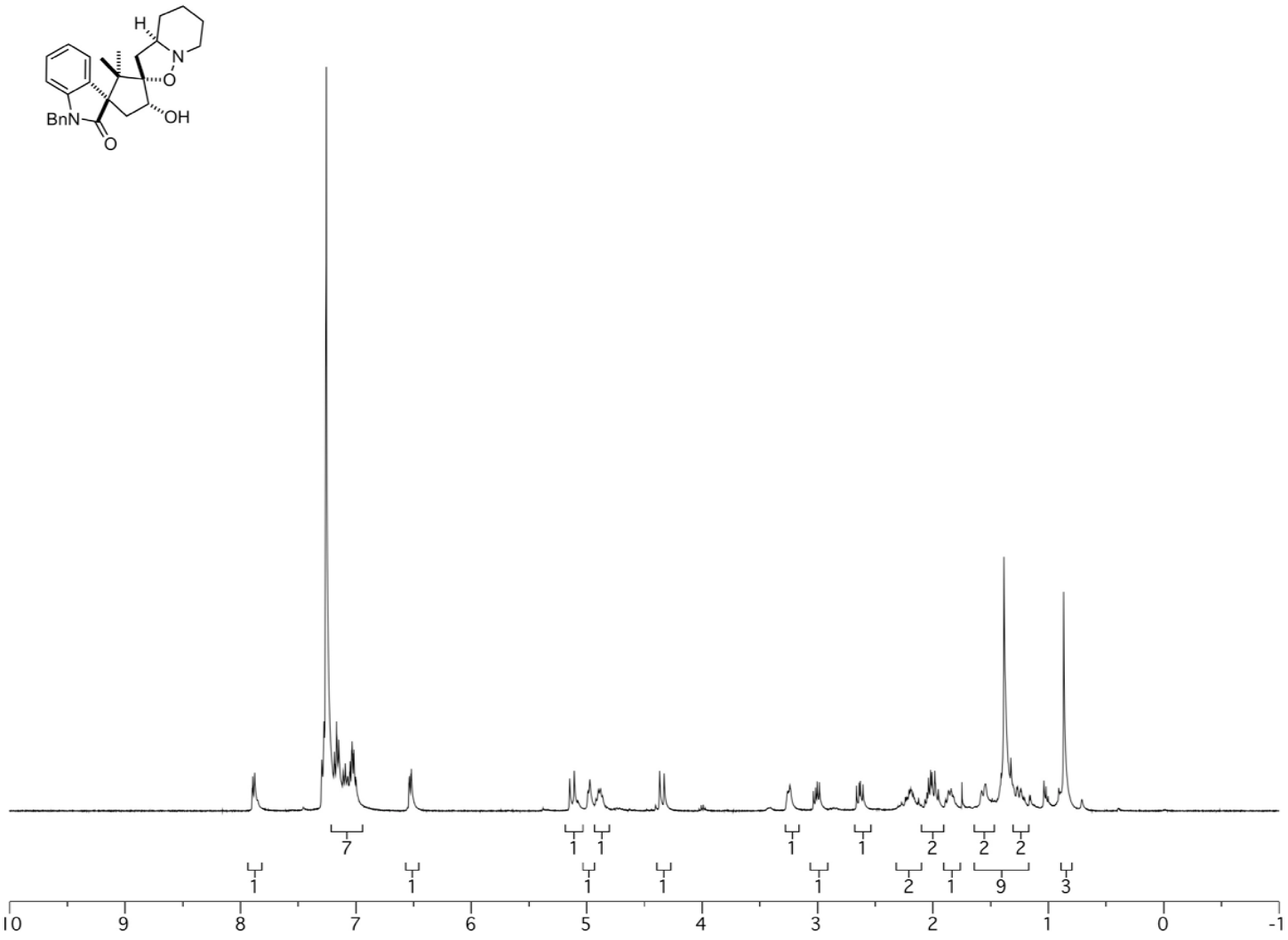


Figure A.1.20a ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **83**

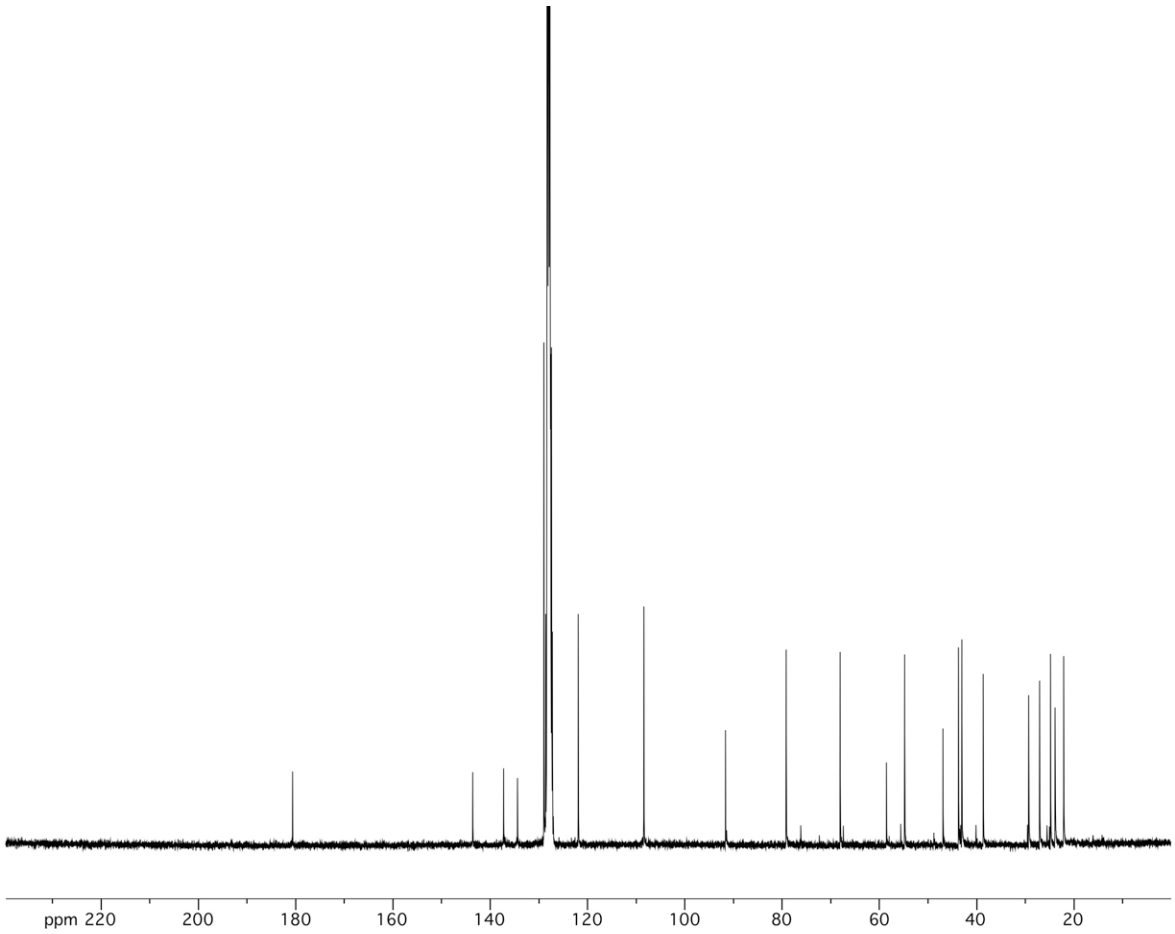


Figure A.1.20b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **83**

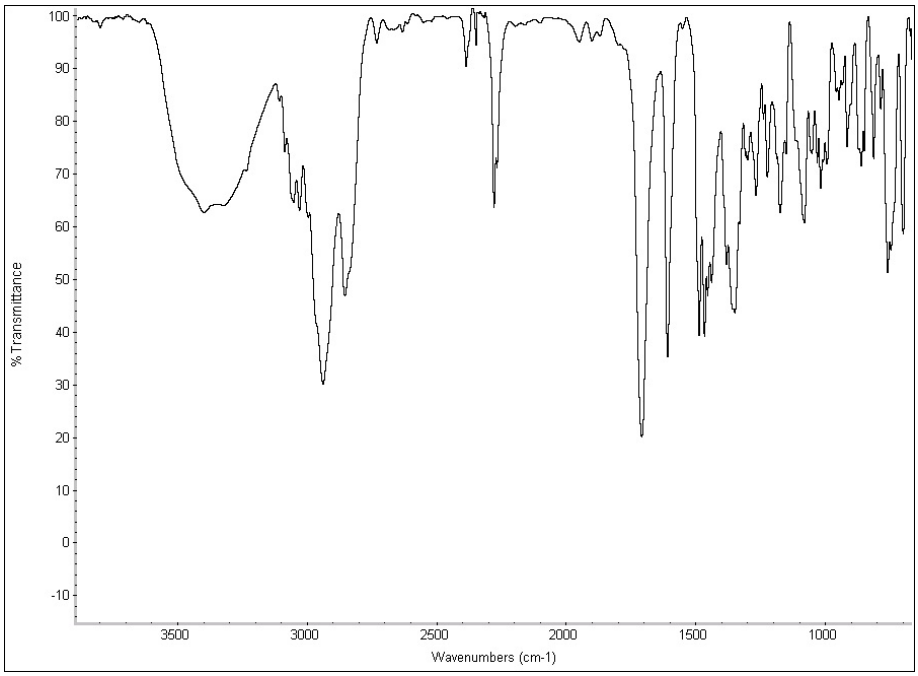


Figure A.1.20c IR spectrum (thin film/NaCl) of compound **83**

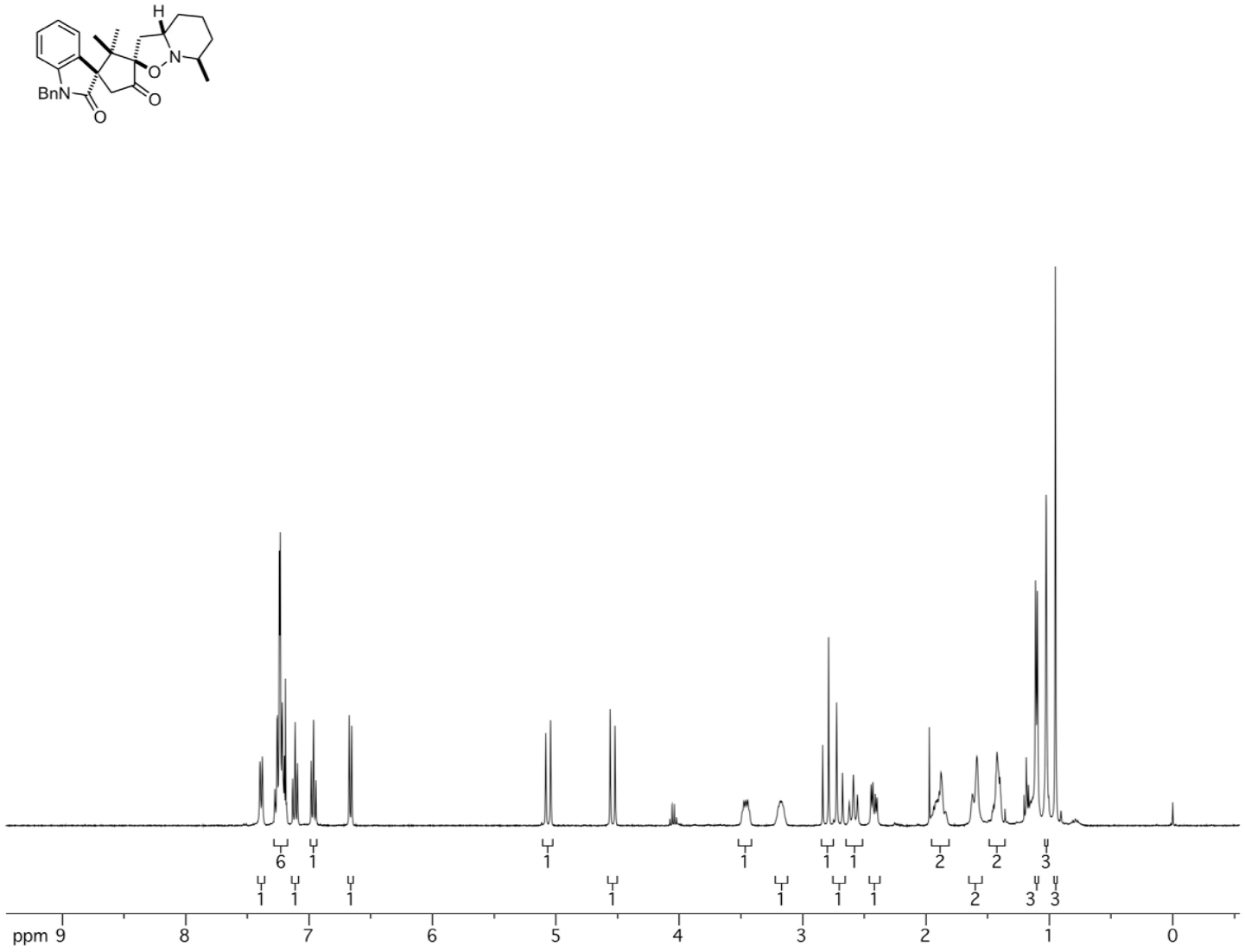


Figure A.1.21a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **87**

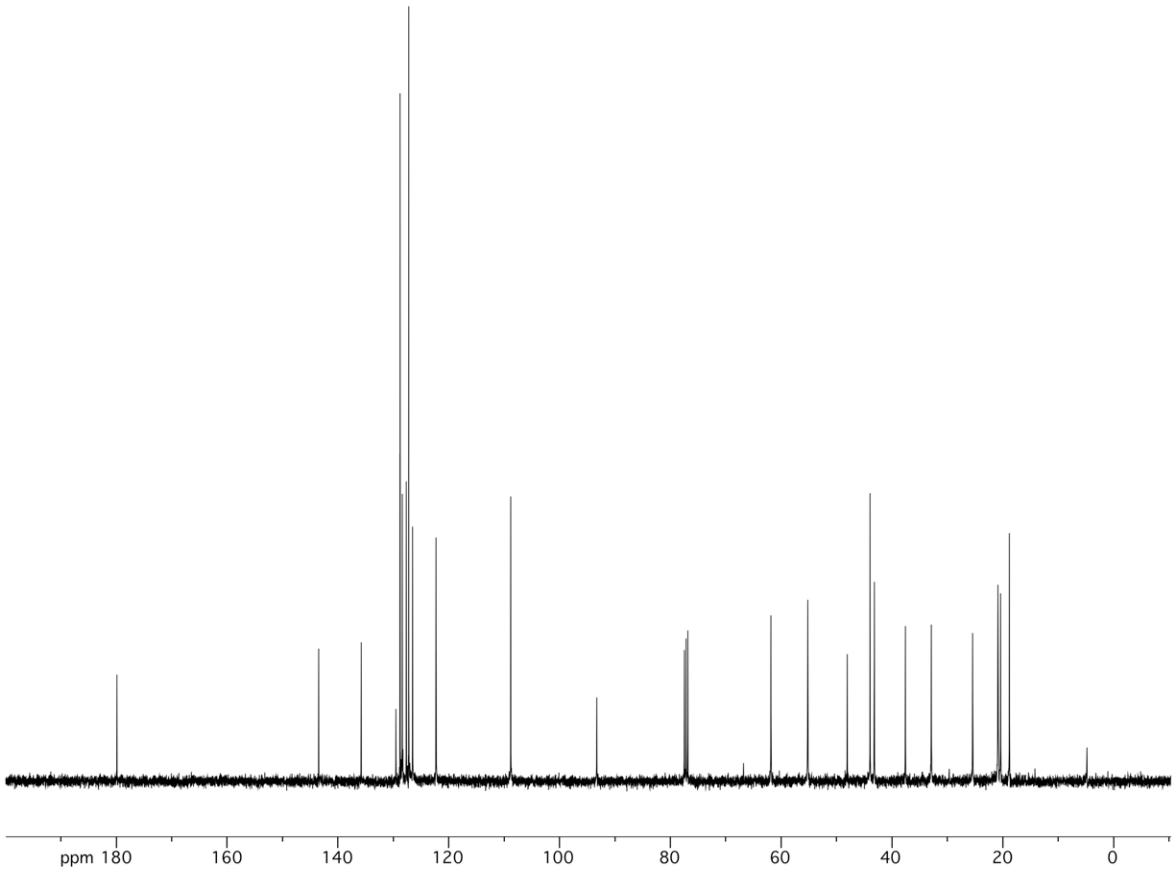


Figure A.1.21b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **87**

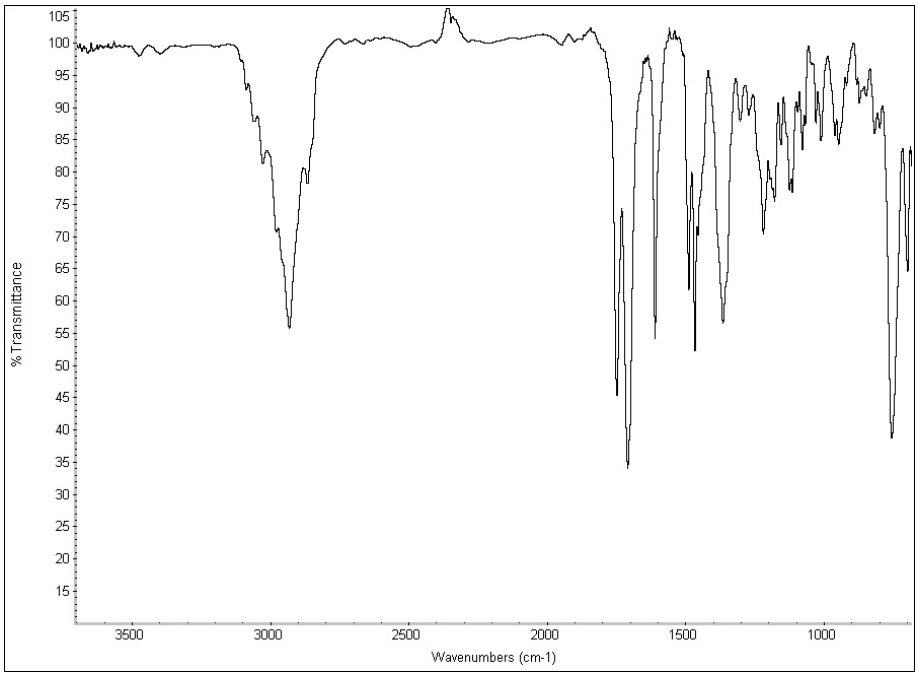


Figure A.1.21c IR spectrum (thin film/NaCl) of compound **87**

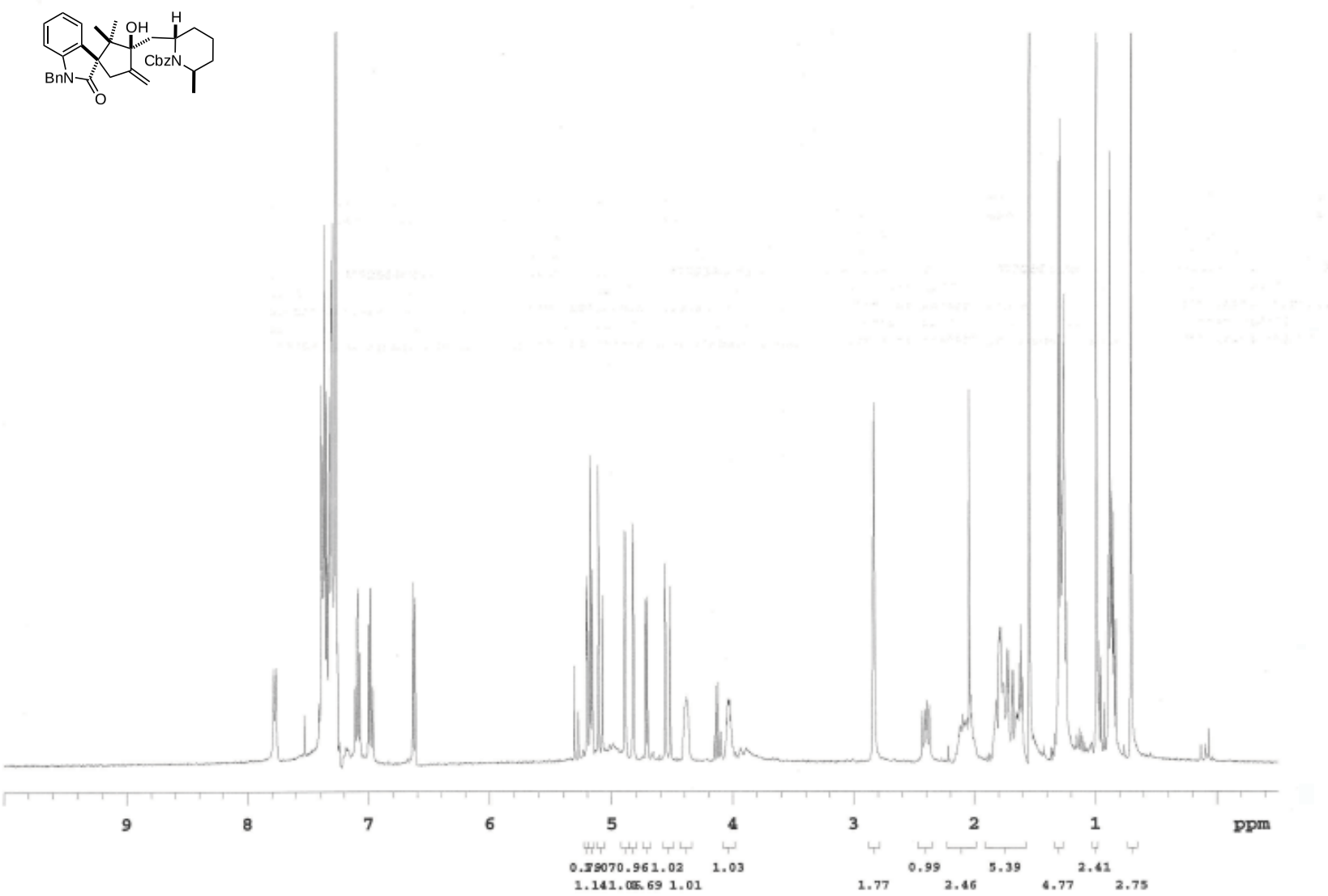


Figure A.1.22a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **90**

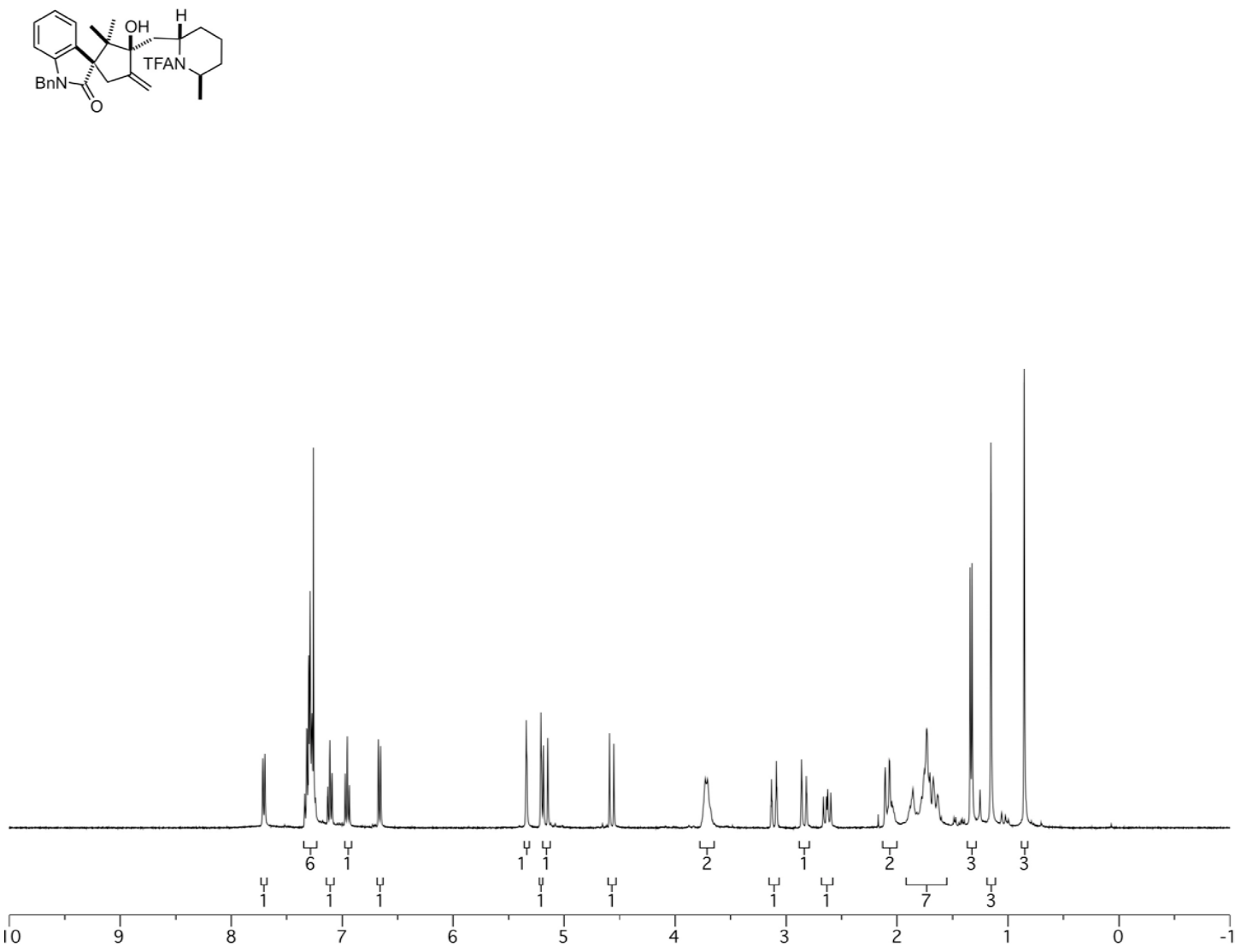


Figure A.1.23a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **90b**

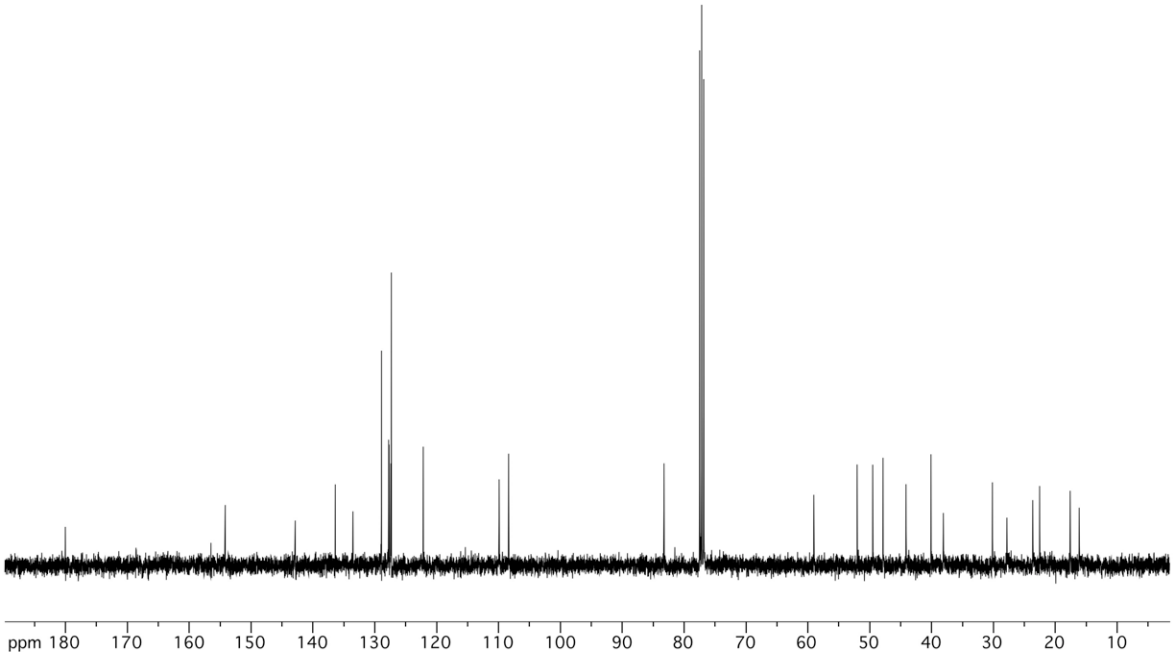


Figure A.1.23b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **90b**

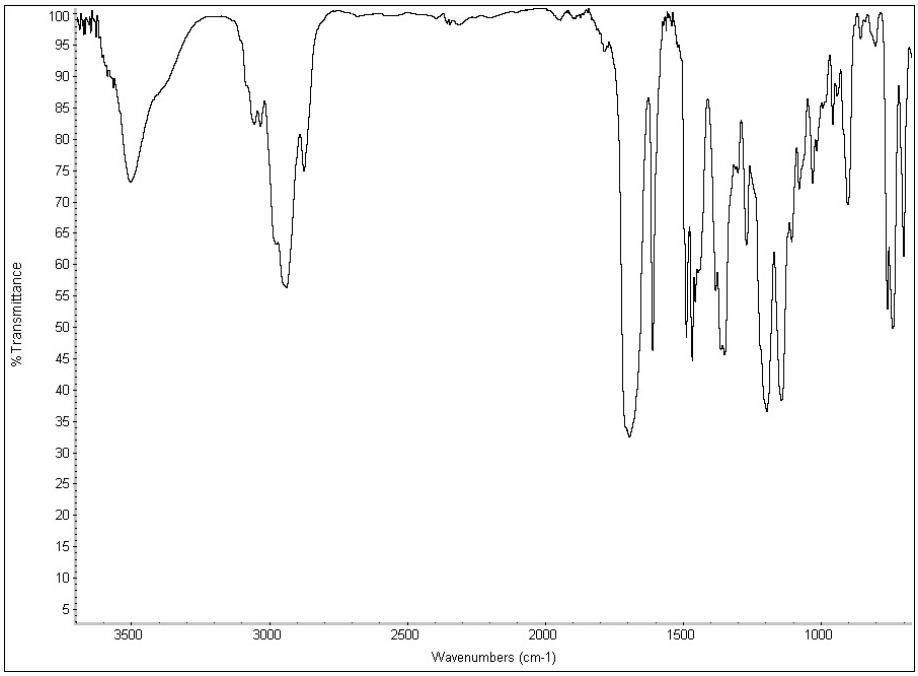


Figure A.1.23c IR spectrum (thin film/NaCl) of compound **90b**

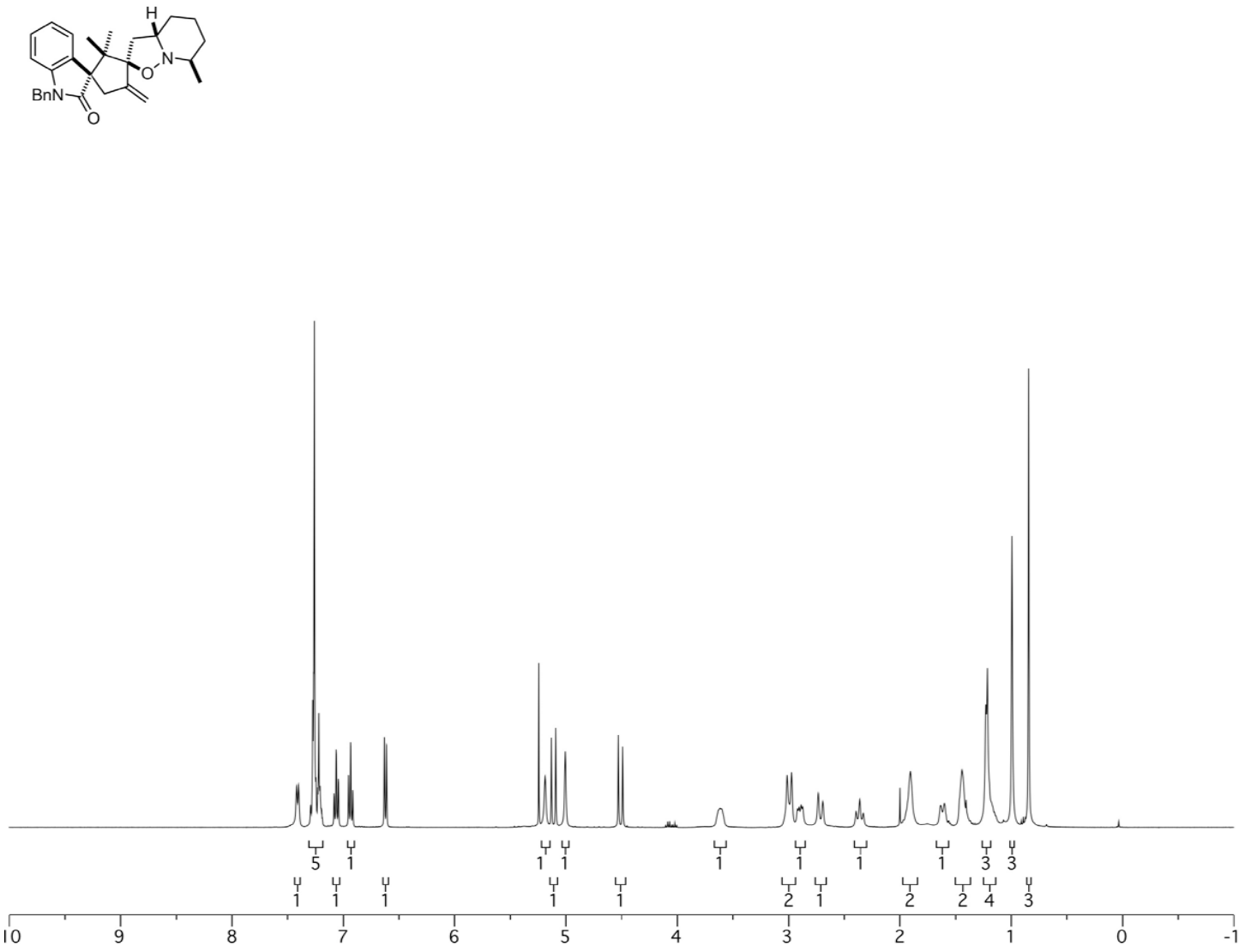


Figure A.1.24a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **91**

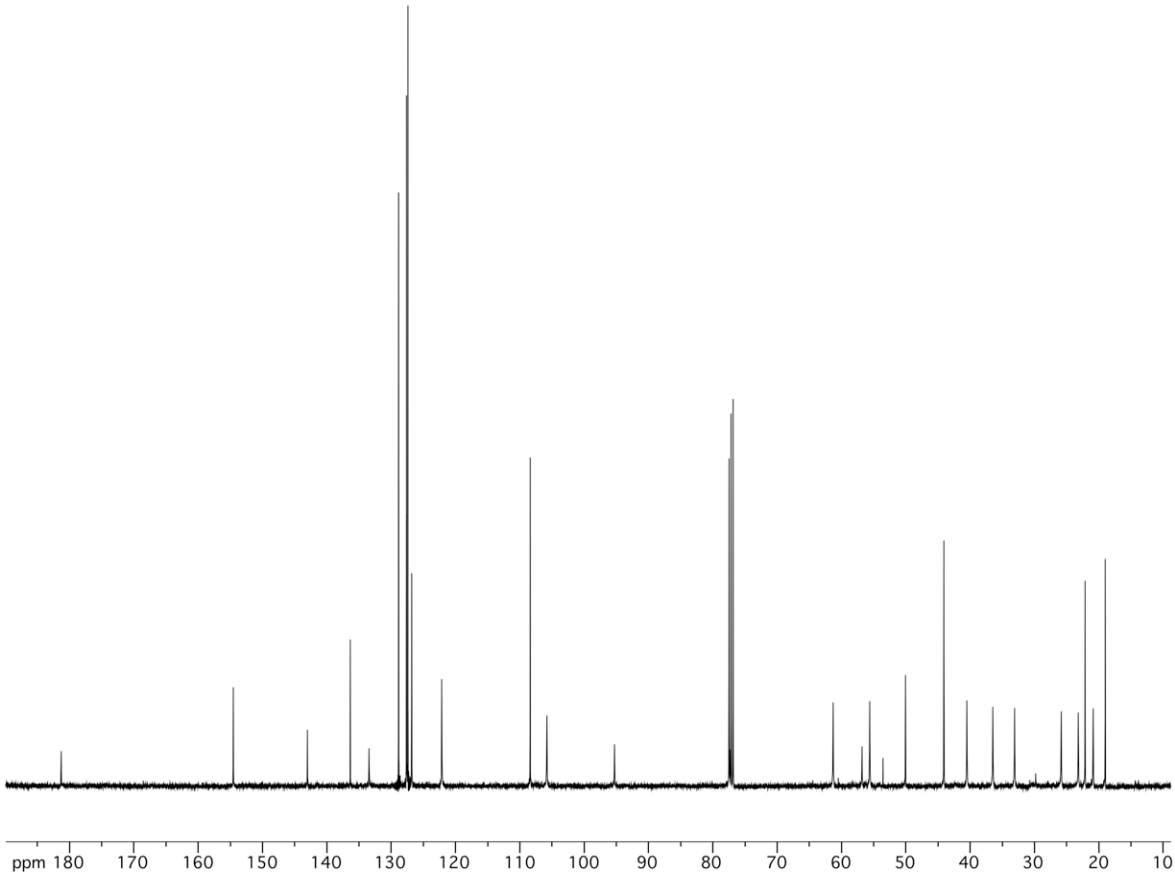


Figure A.1.24b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **91**

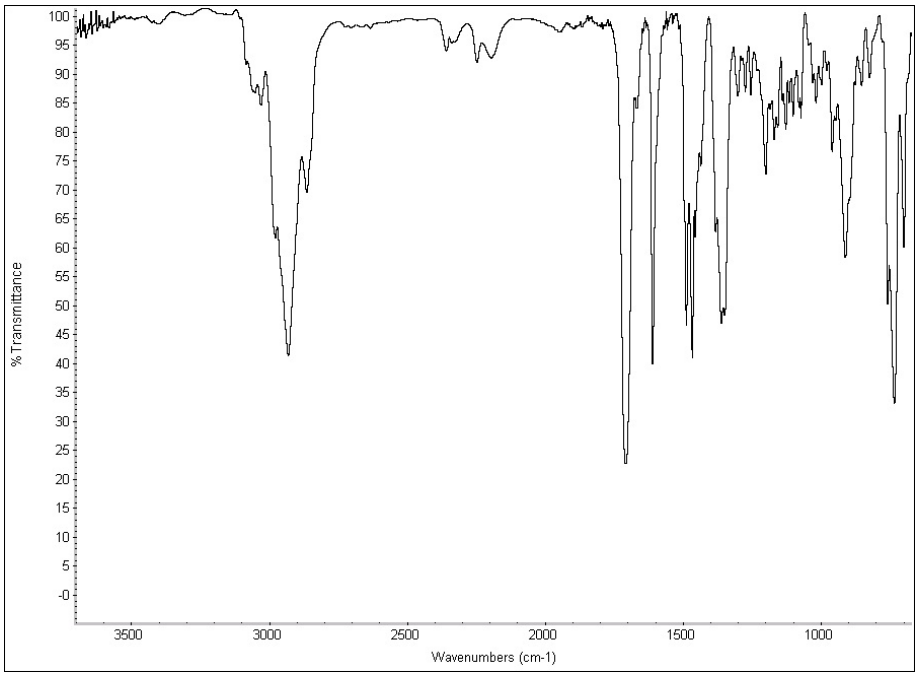


Figure A.1.24c IR spectrum (thin film/NaCl) of compound **91**

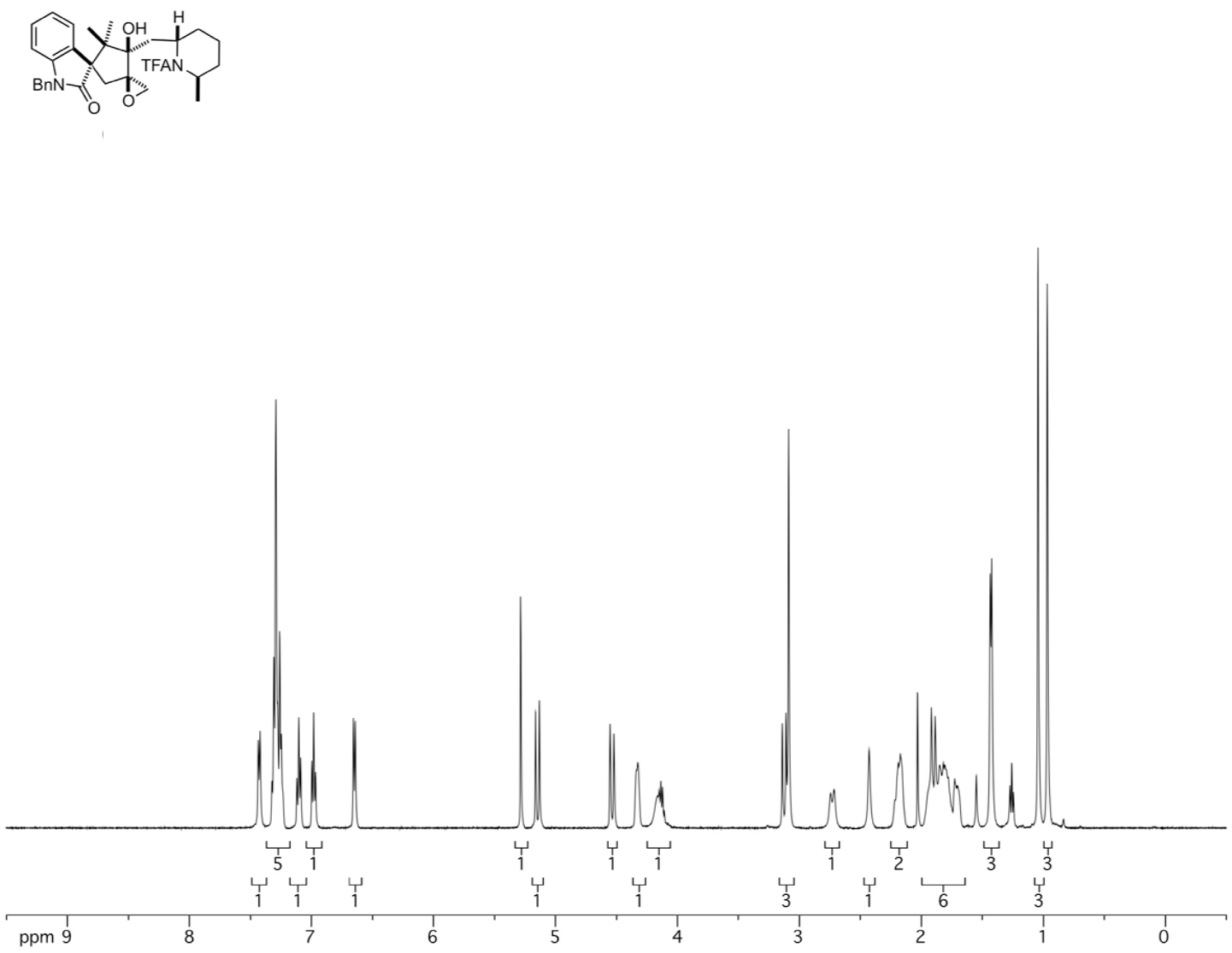


Figure A.1.25a ^{1}H NMR spectrum (500 MHz, $CDCl_3$, 55 ℃) of compound **94**

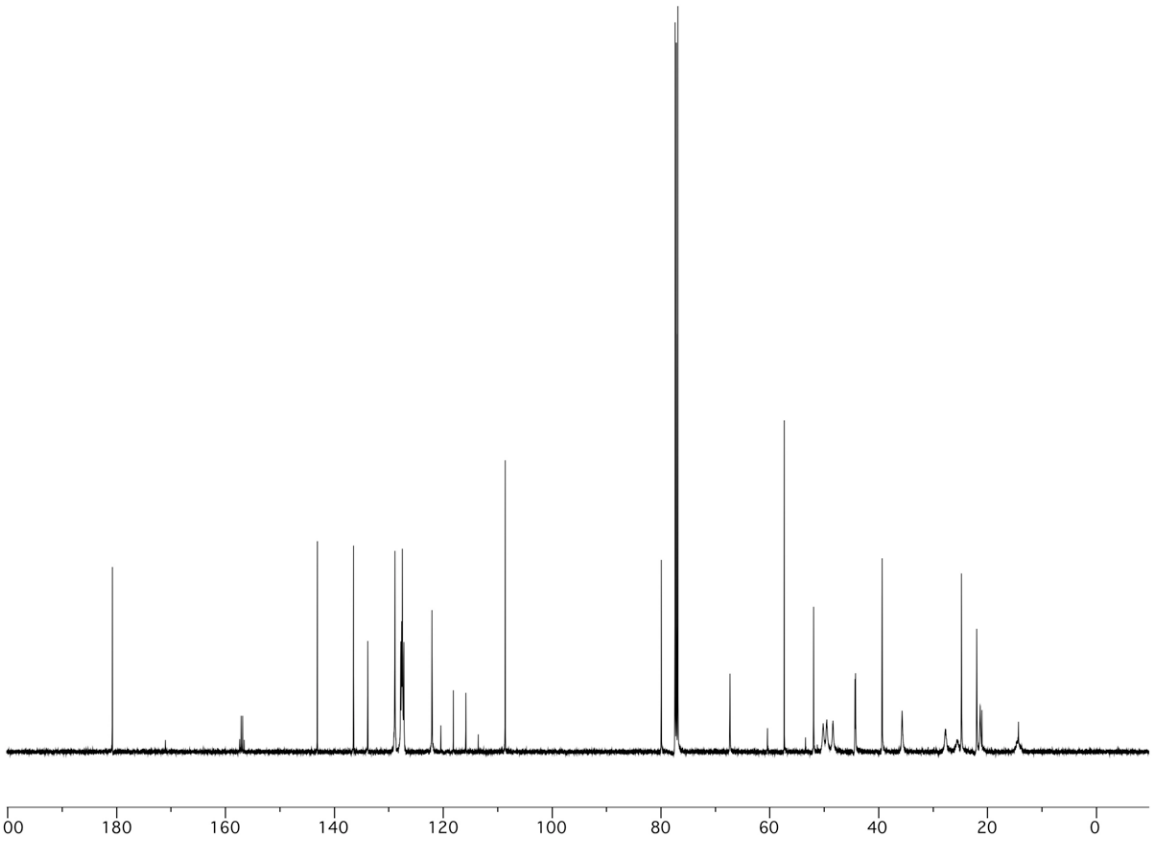


Figure A.1.25b ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **94**

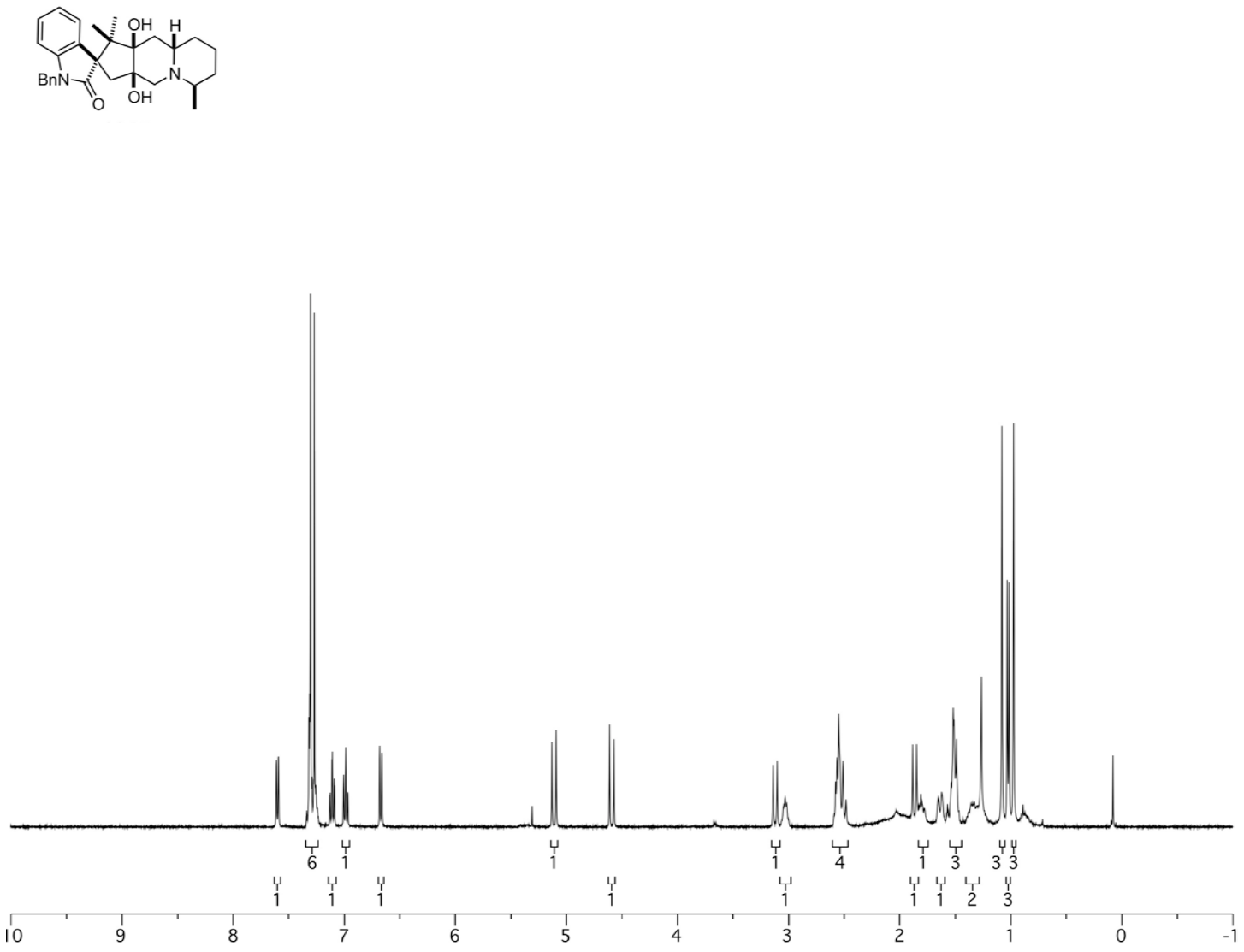


Figure A.1.26a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **95**

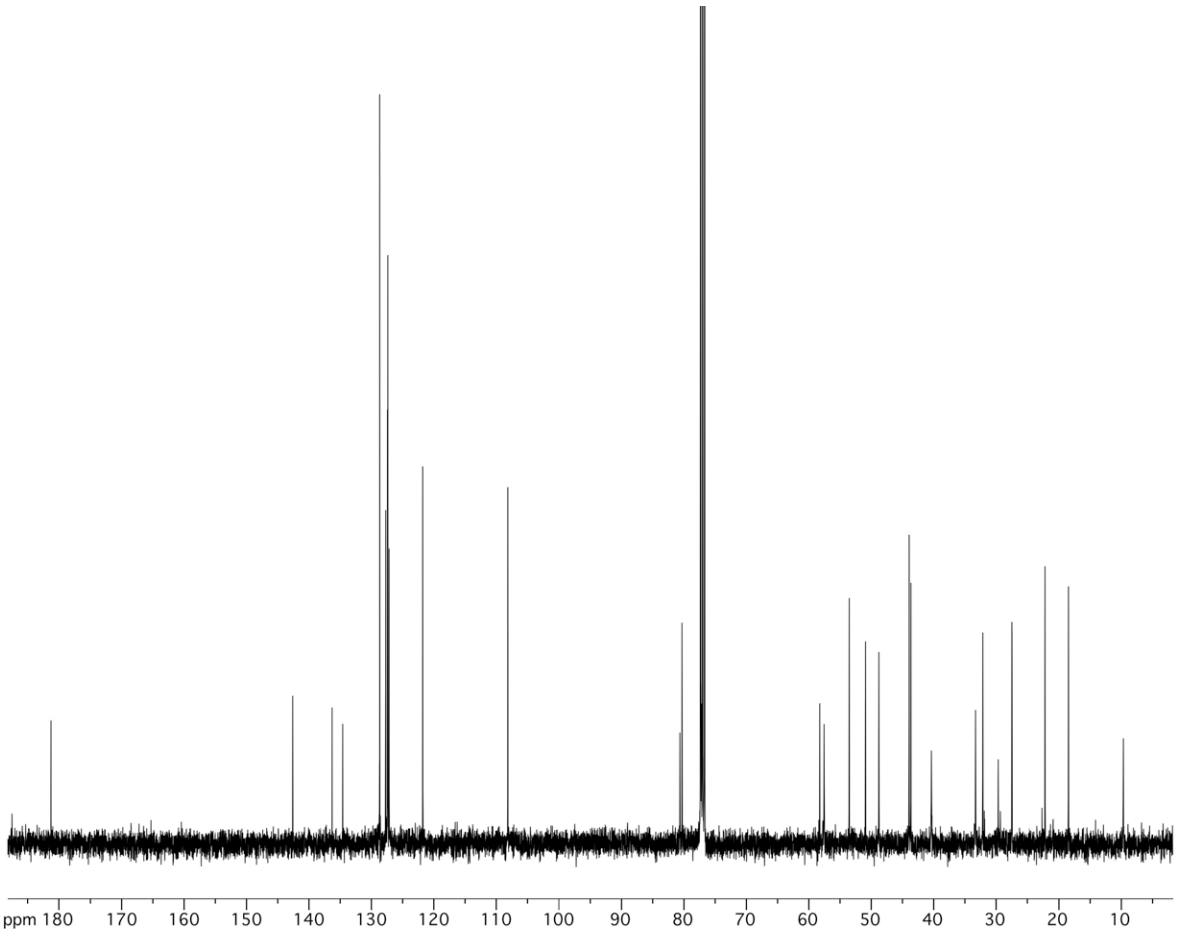


Figure A.1.26b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **95**

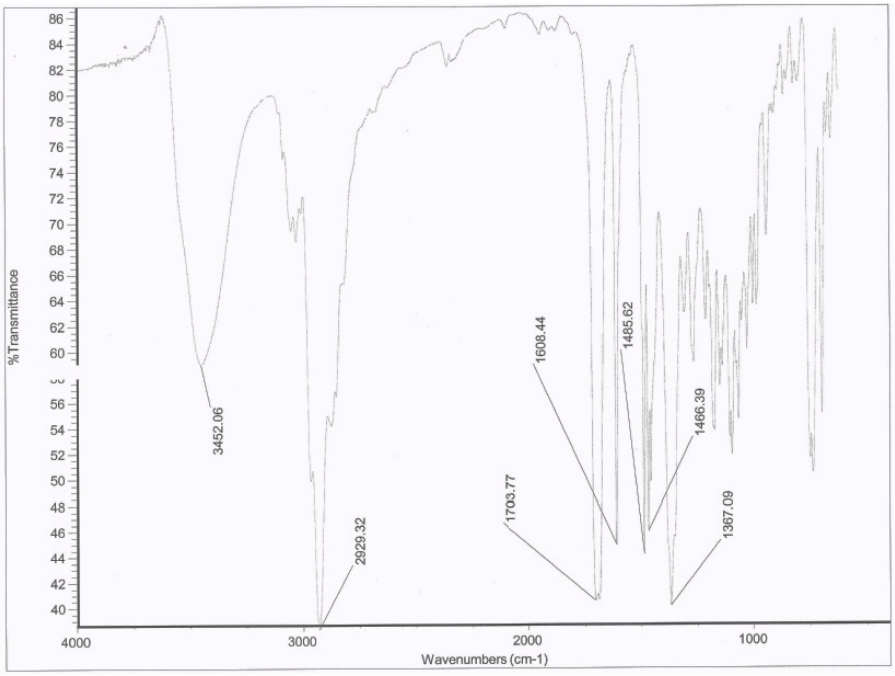


Figure A.1.26c IR spectrum (thin film/NaCl) of compound **95**

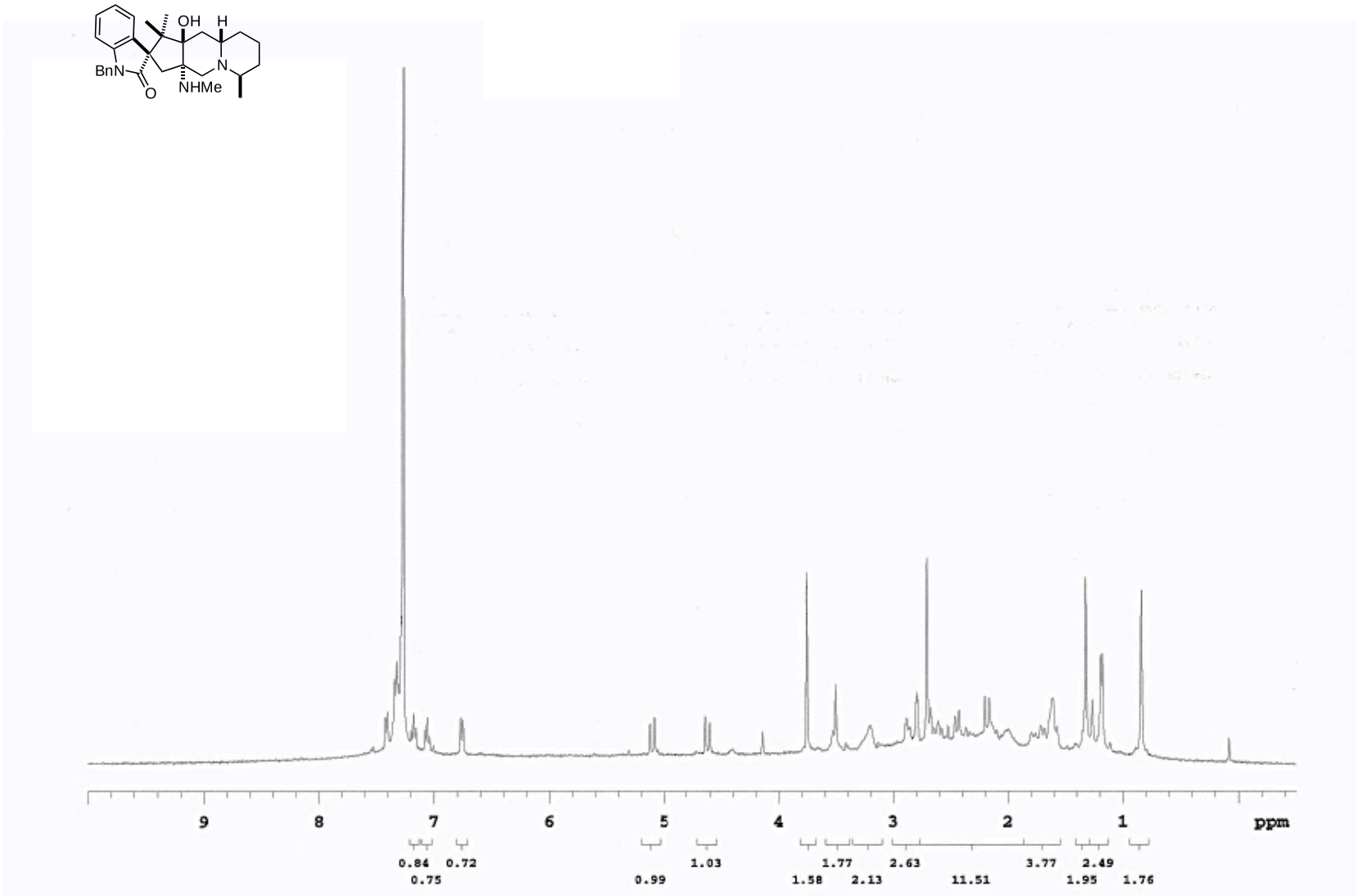


Figure A.1.27a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **97**

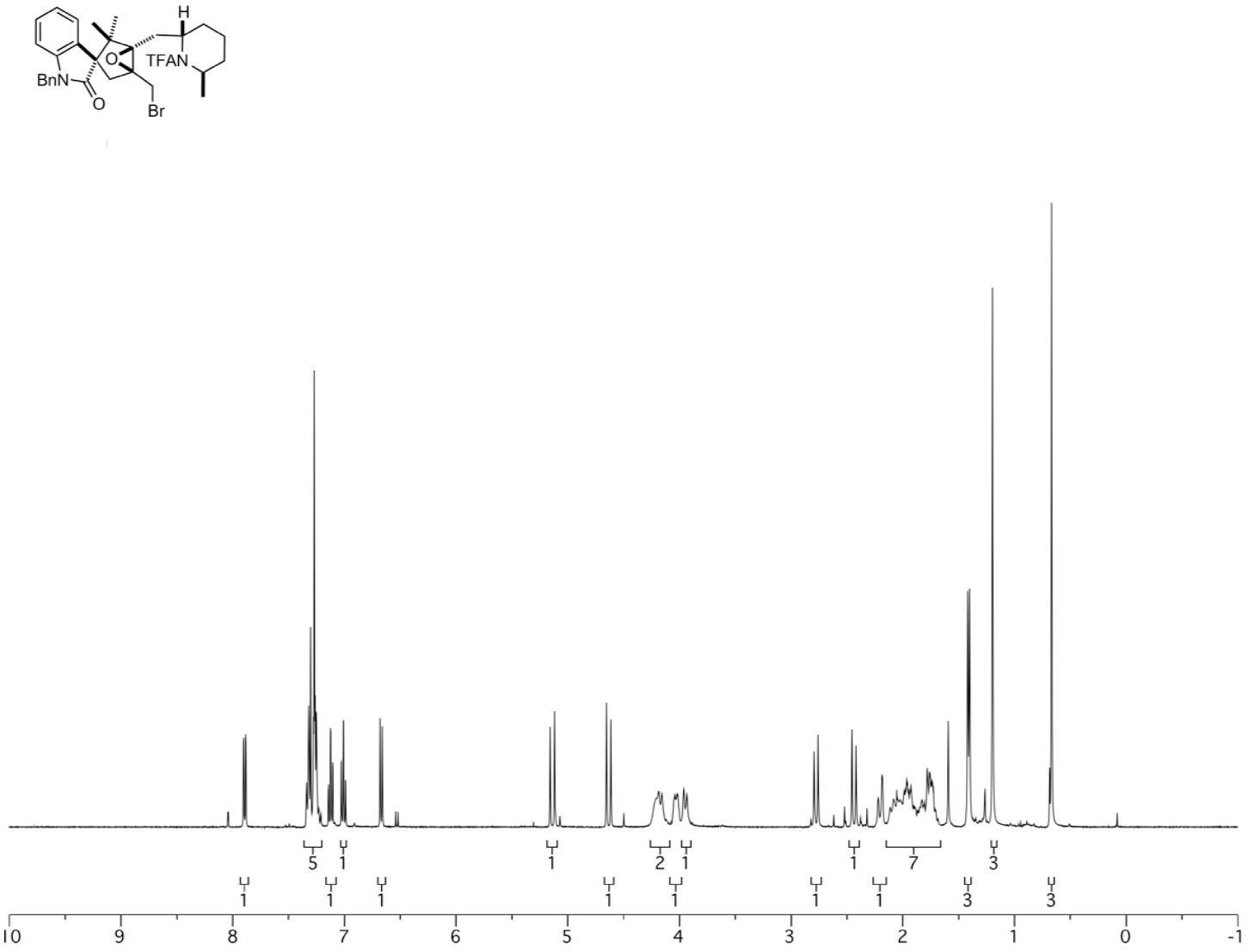


Figure A.1.28a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **98**

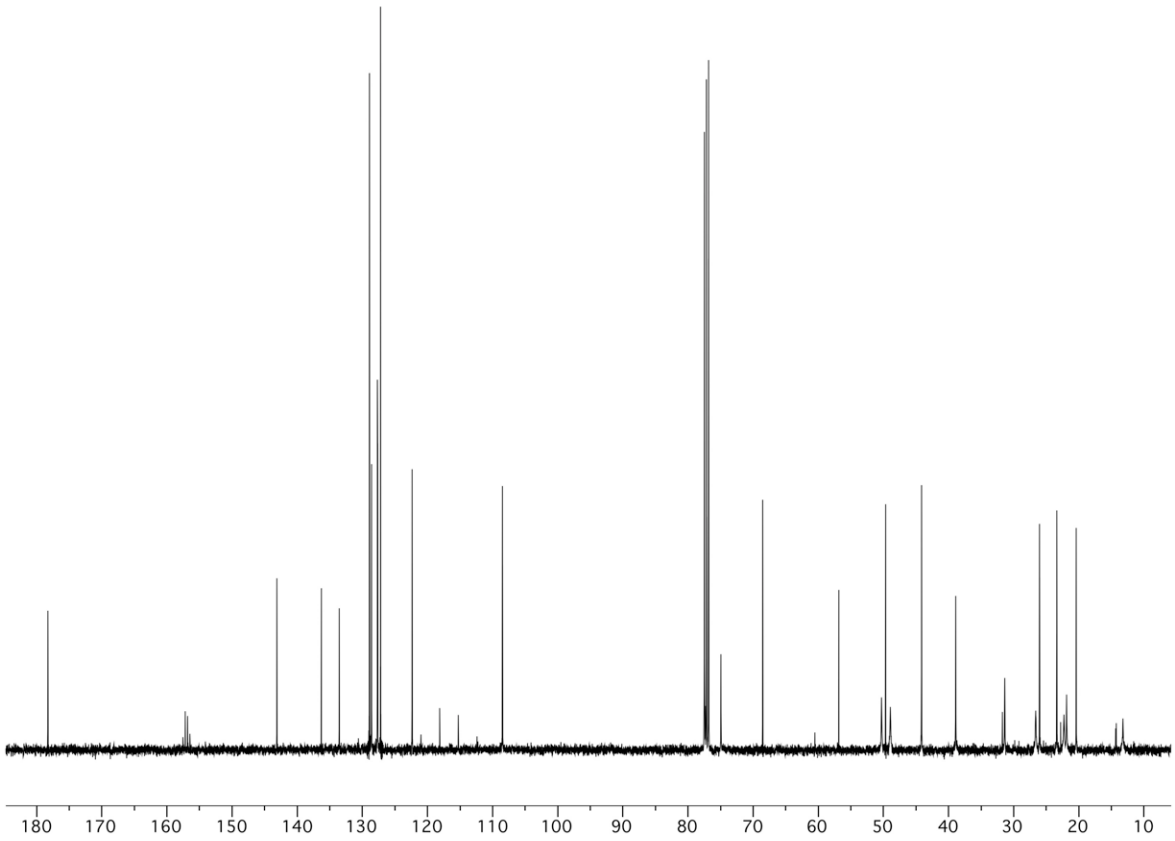


Figure A.1.28b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **98**

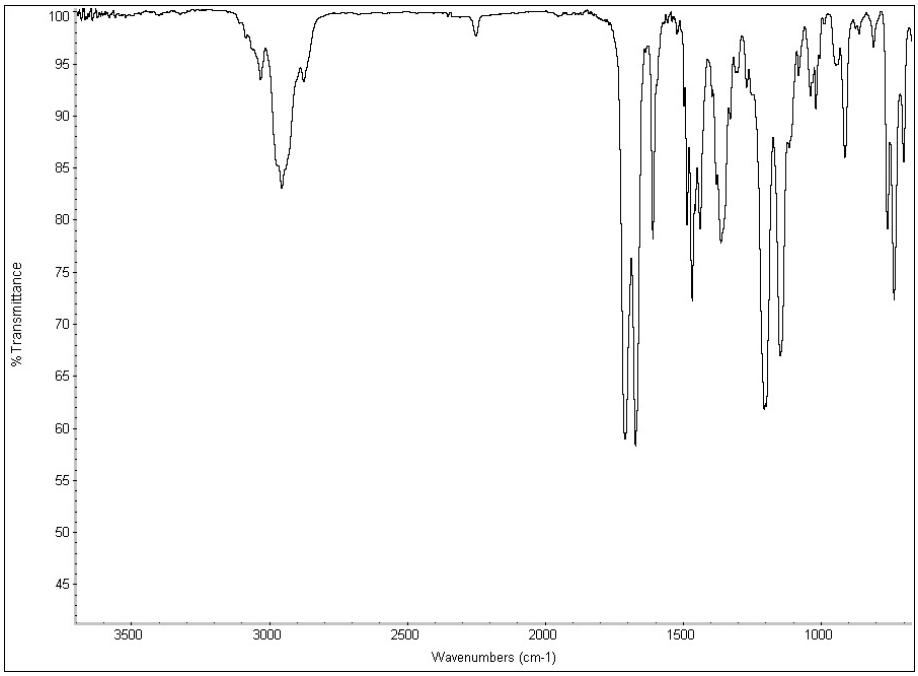


Figure A.1.28c IR spectrum (thin film/NaCl) of compound **98**

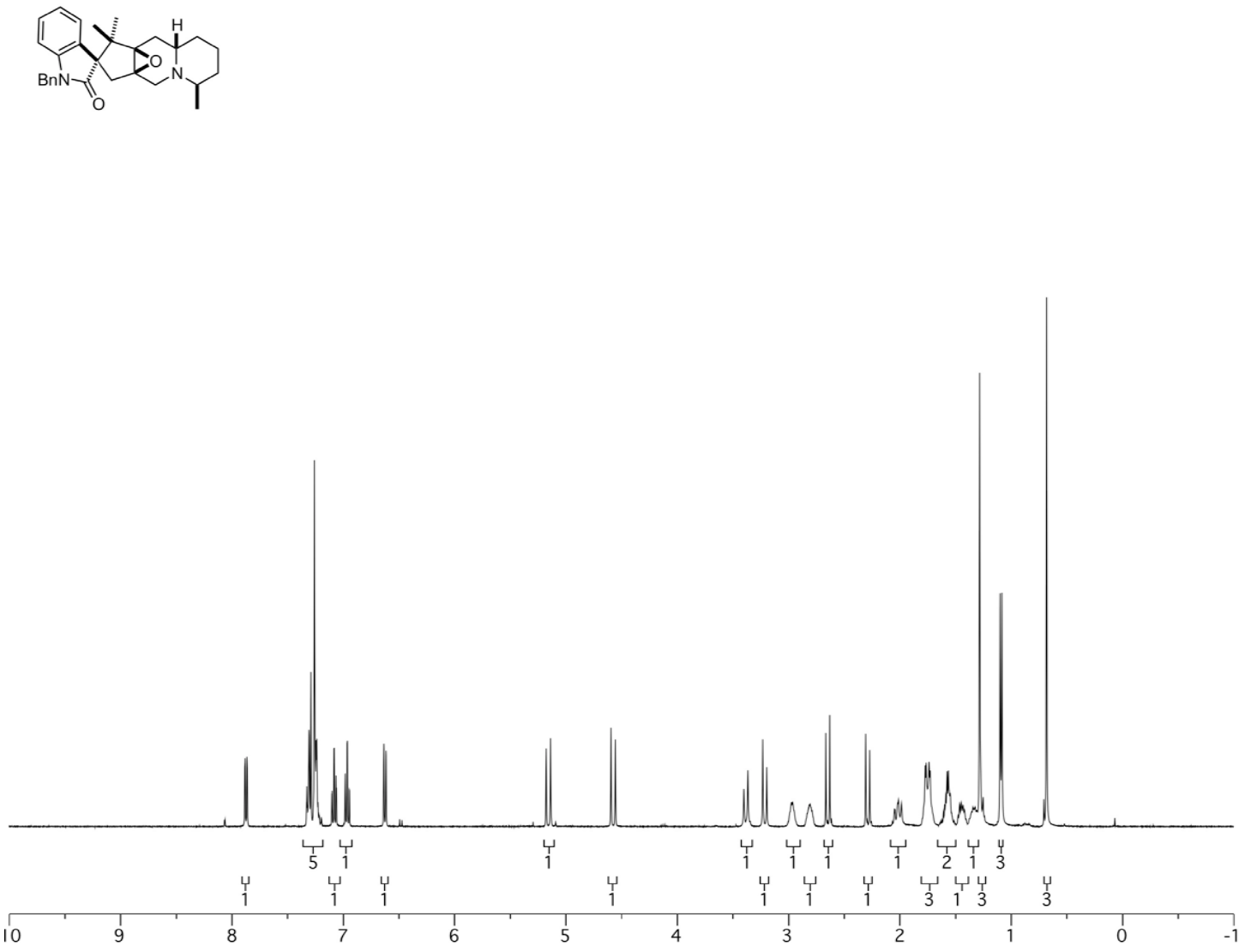


Figure A.1.29a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **99**

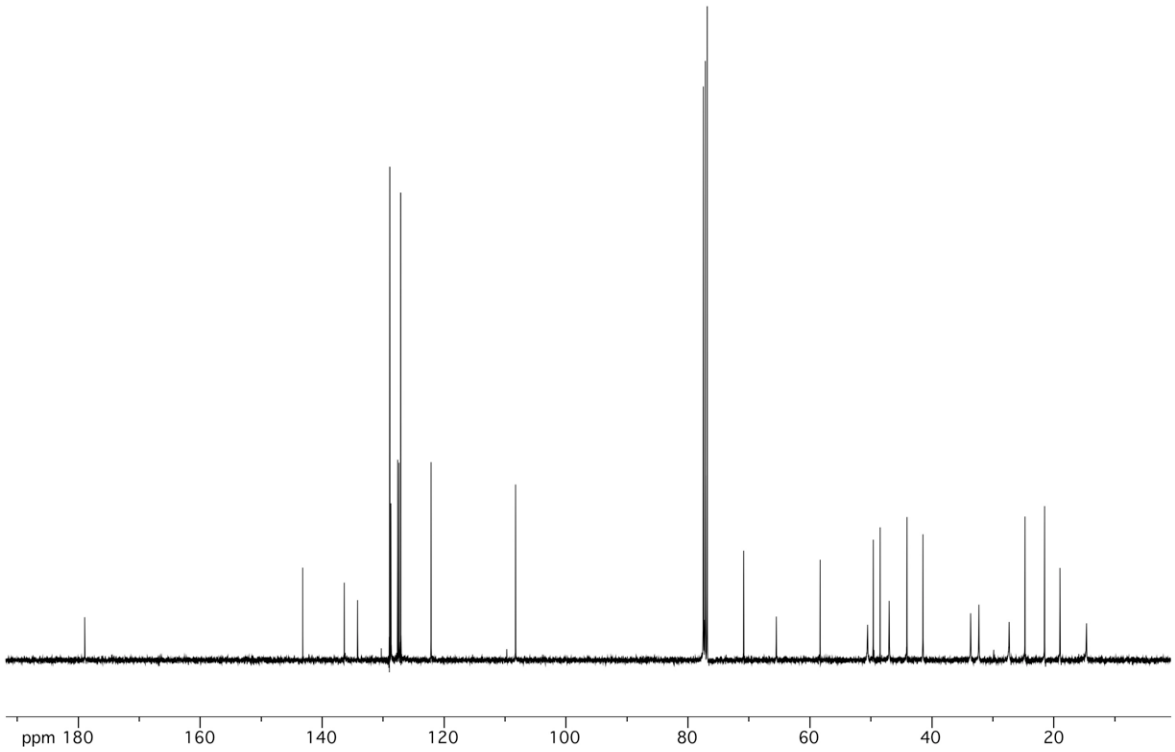


Figure A.1.29b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **99**

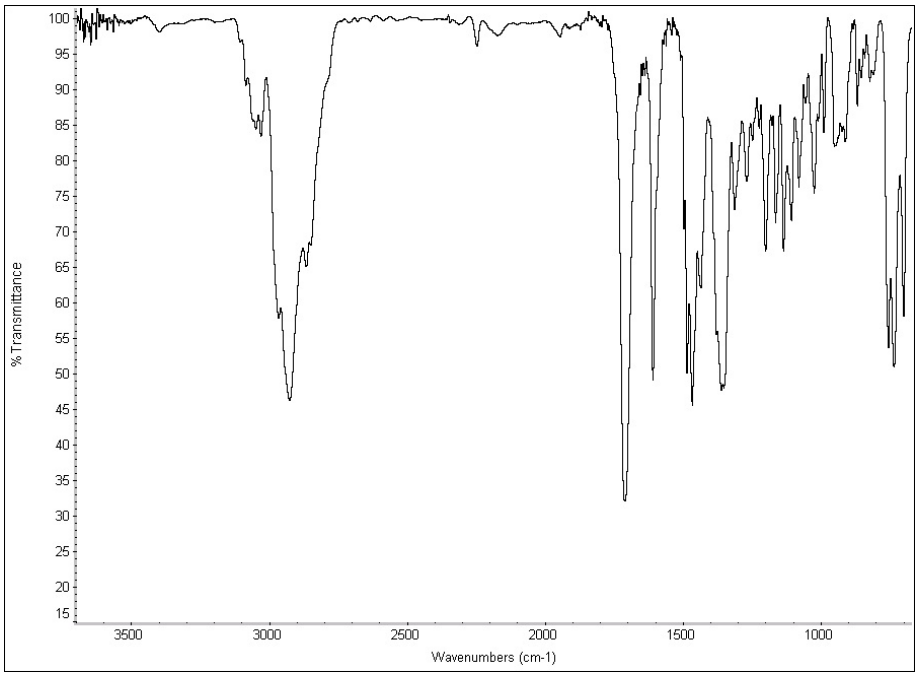


Figure A.1.29c IR spectrum (thin film/NaCl) of compound **99**

APPENDIX II: SPECTRA RELEVANT TO CHAPTER 3

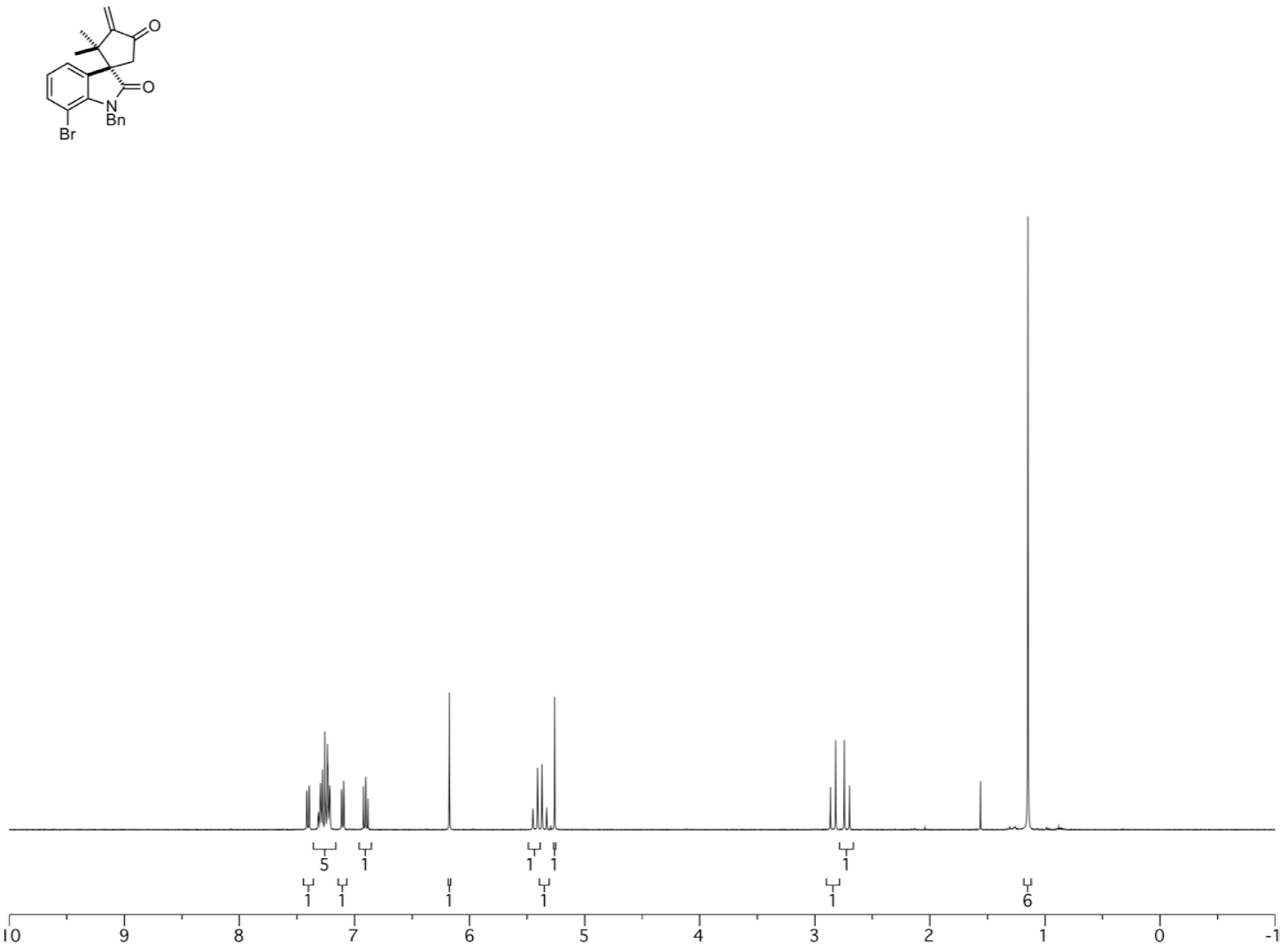


Figure A.2.1a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **37**

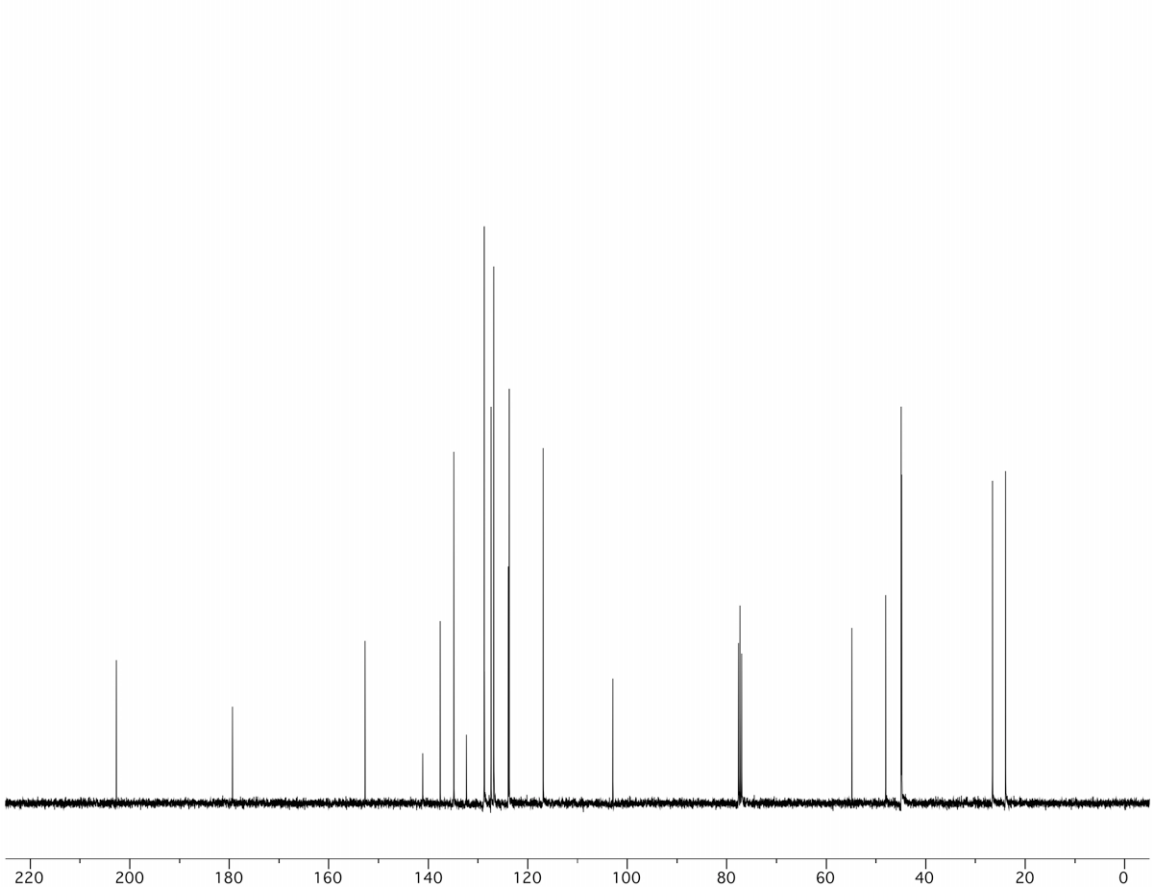


Figure A.2.1b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **37**

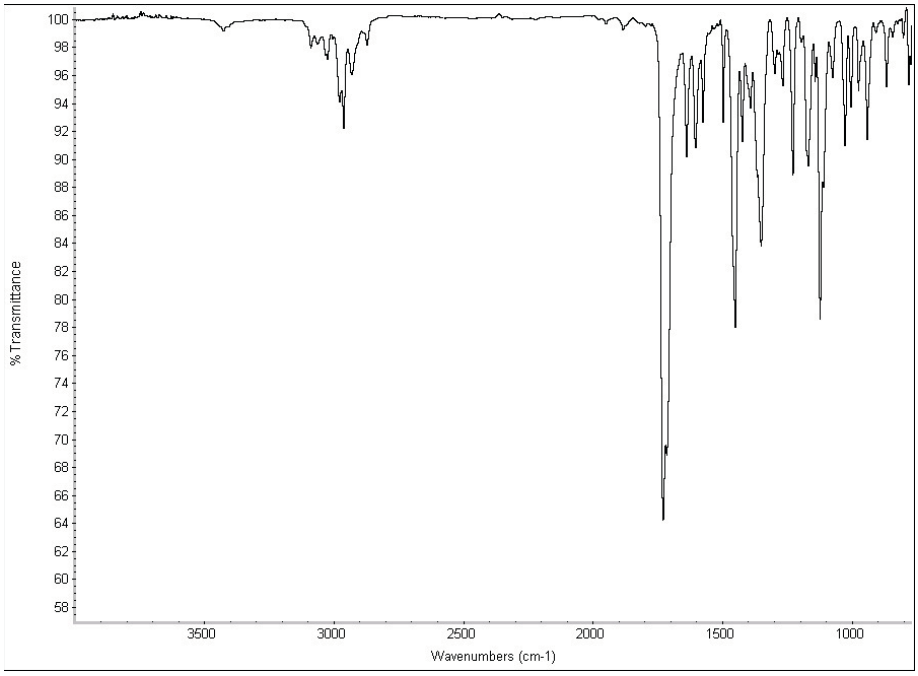


Figure A.2.1c. IR spectrum (thin film/NaCl) of compound **37**

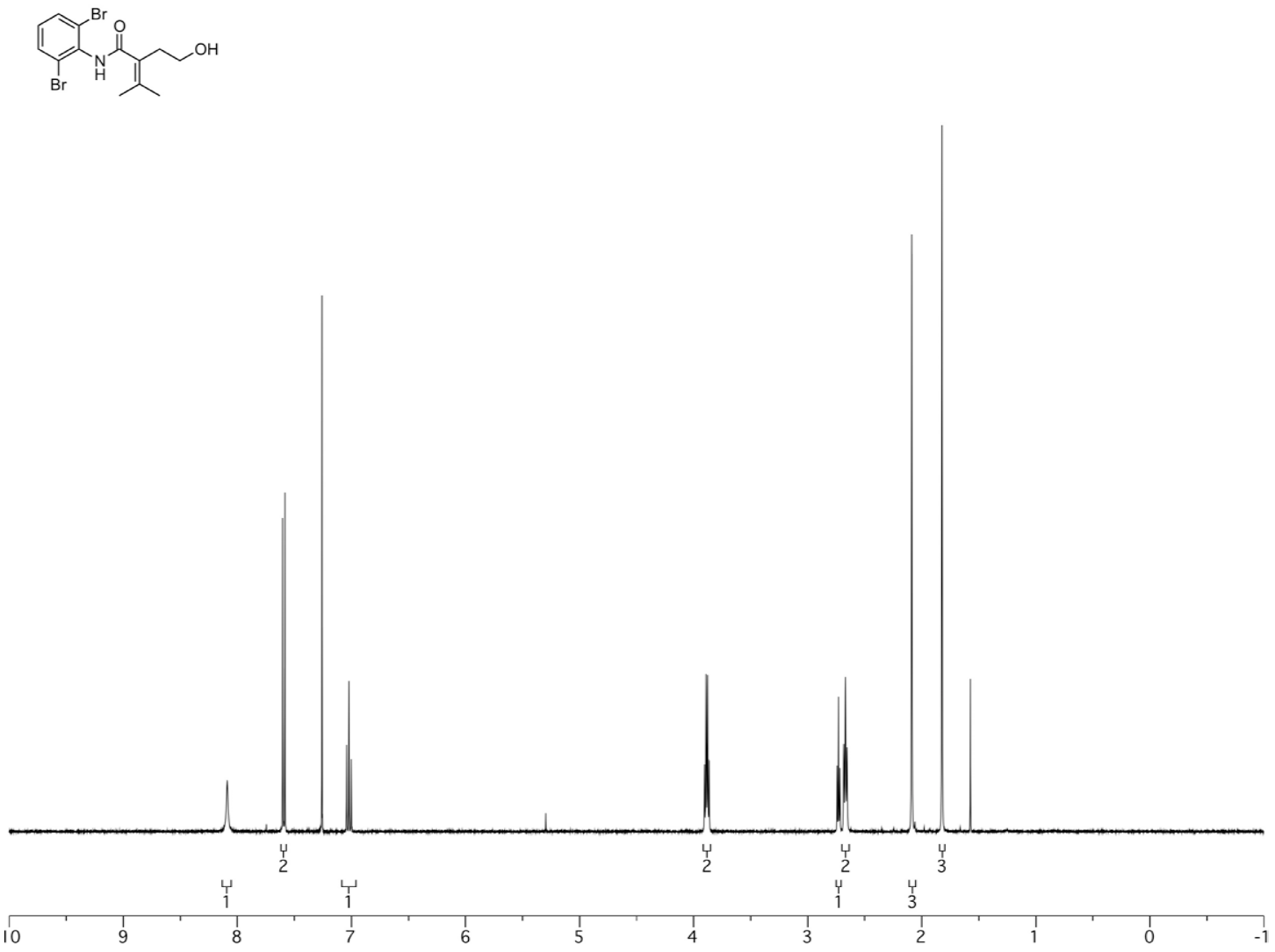


Figure A.2.2a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **48**

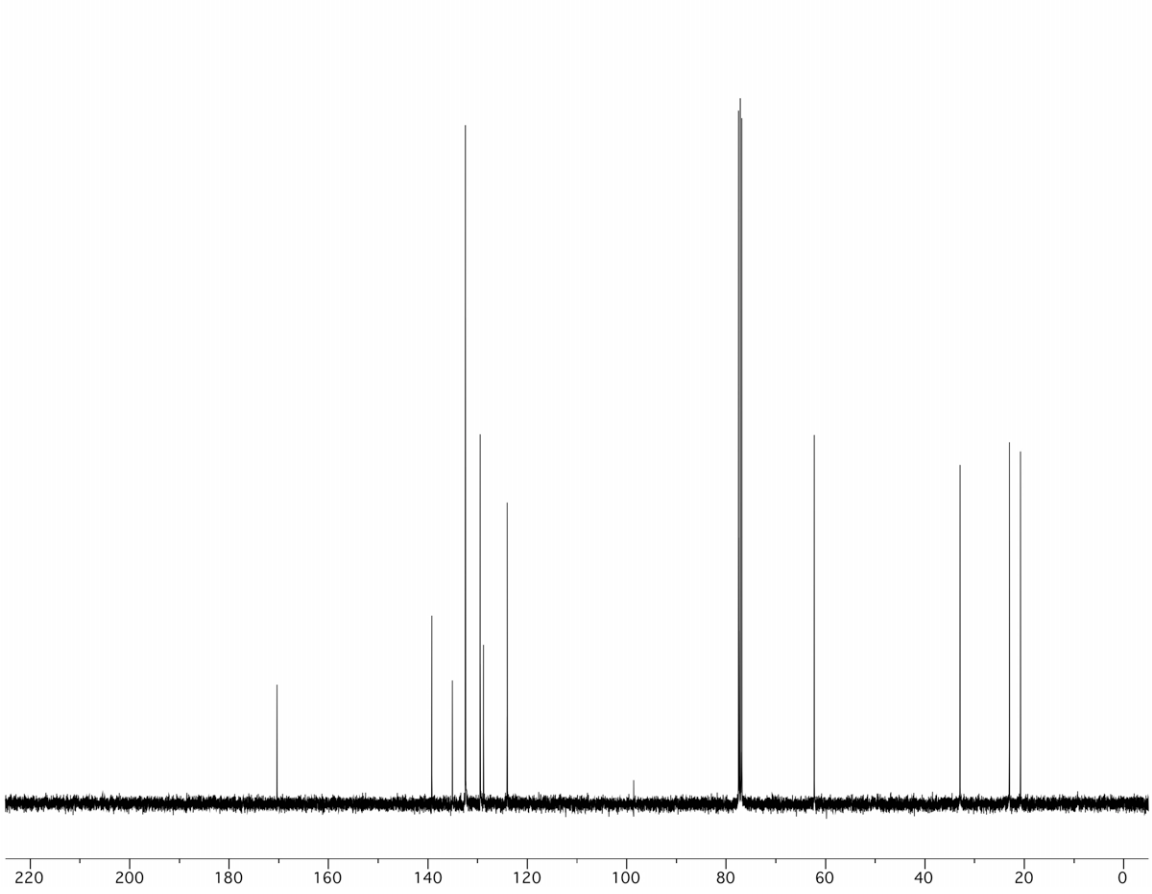


Figure A.2.2b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **48**

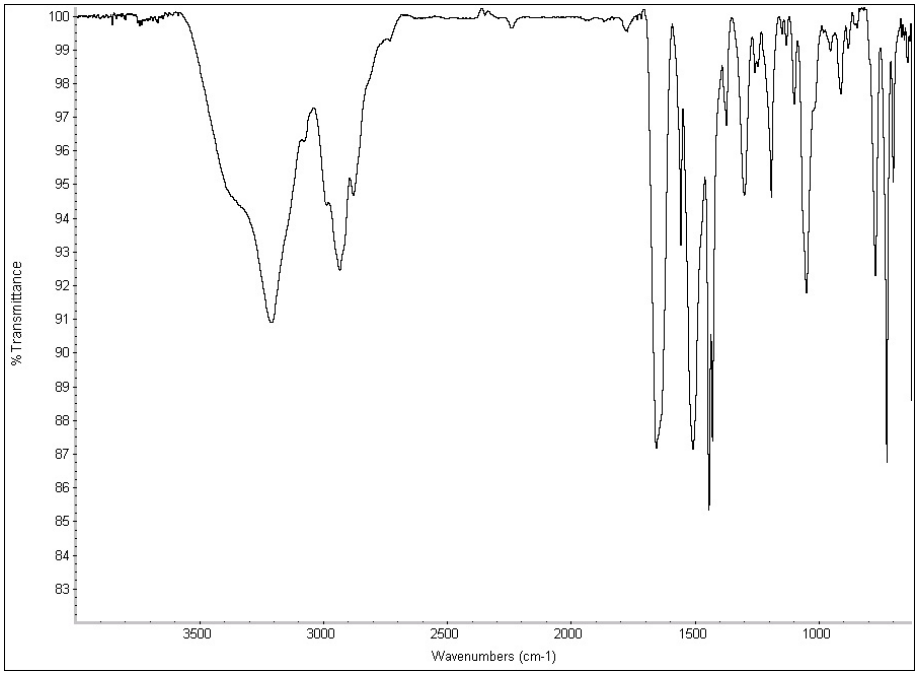


Figure A.2.2c. IR spectrum (thin film/NaCl) of compound **48**

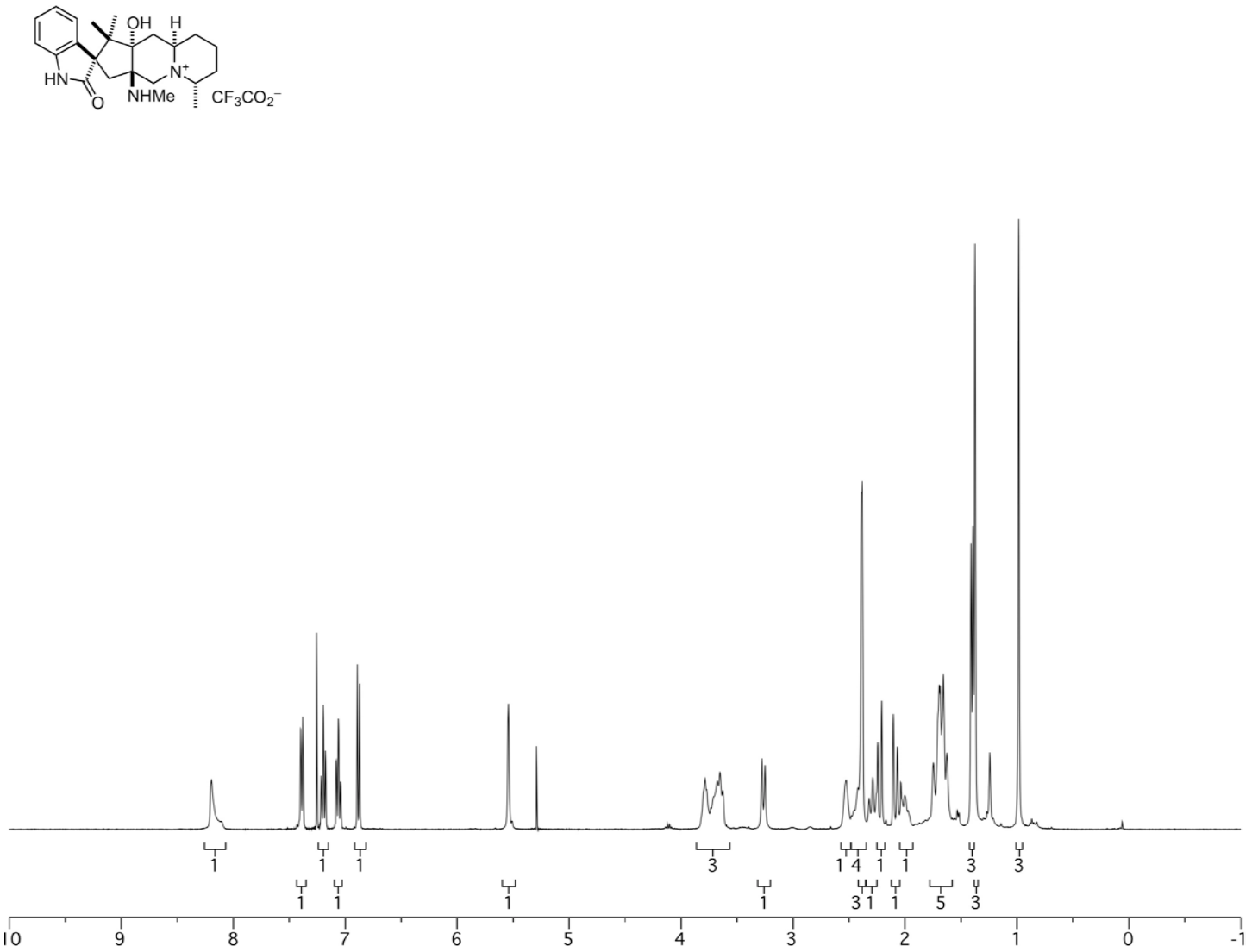


Figure A.2.3a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **100** (TFA Salt)

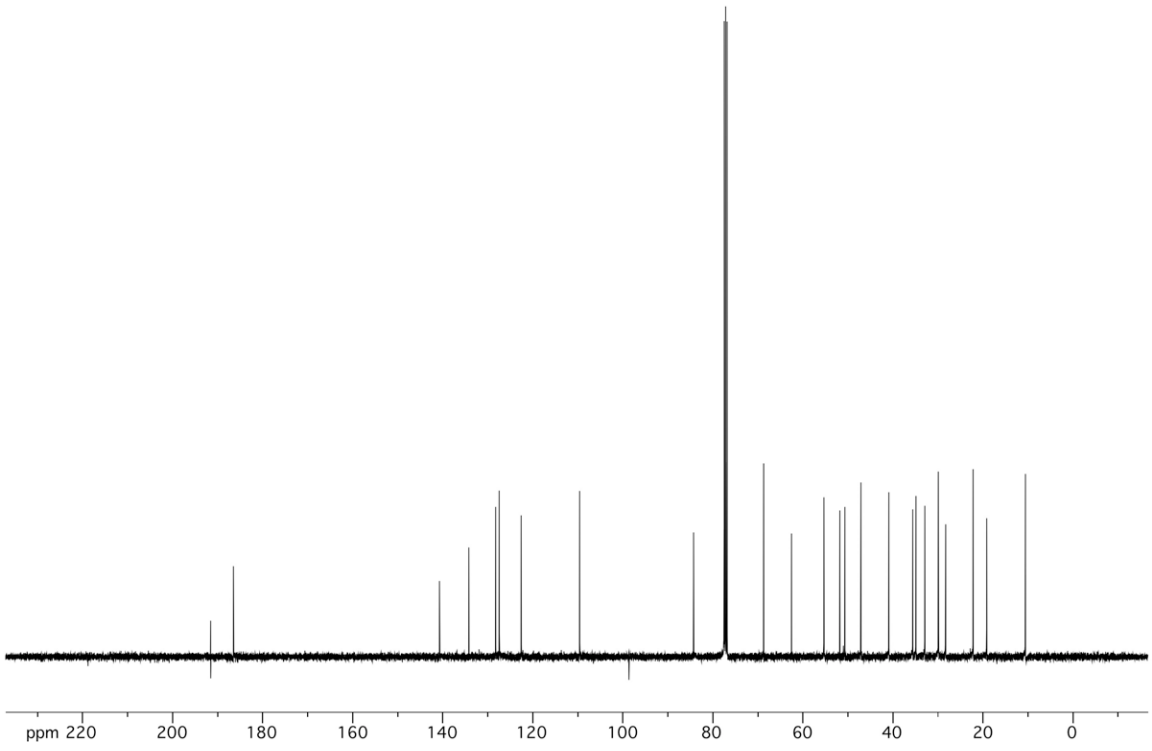


Figure A.2.3b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **100** (Free Base)

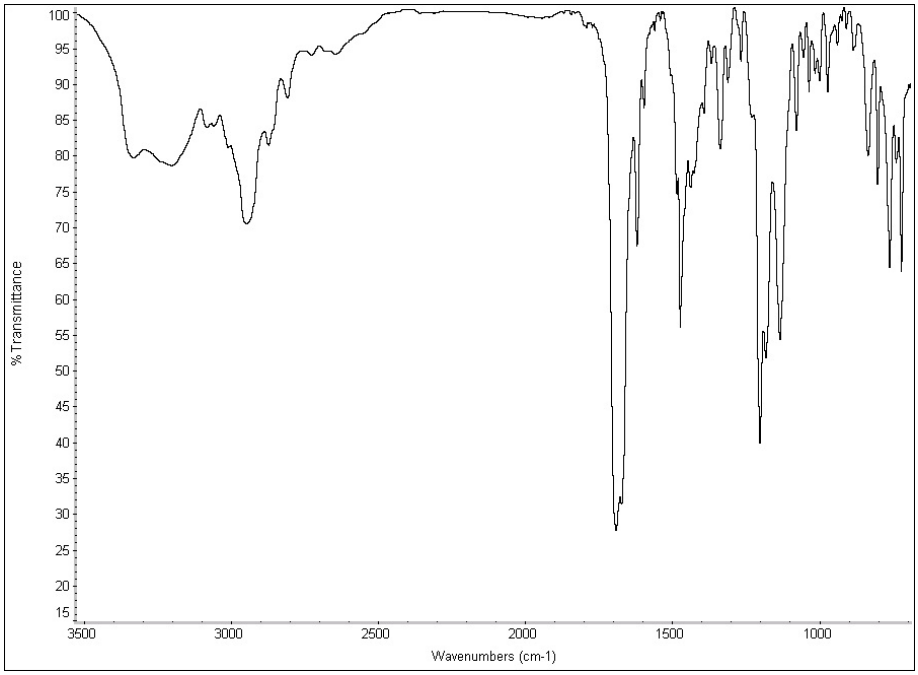


Figure A.2.3c. IR spectrum (thin film/NaCl) of compound **100** (TFA salt)

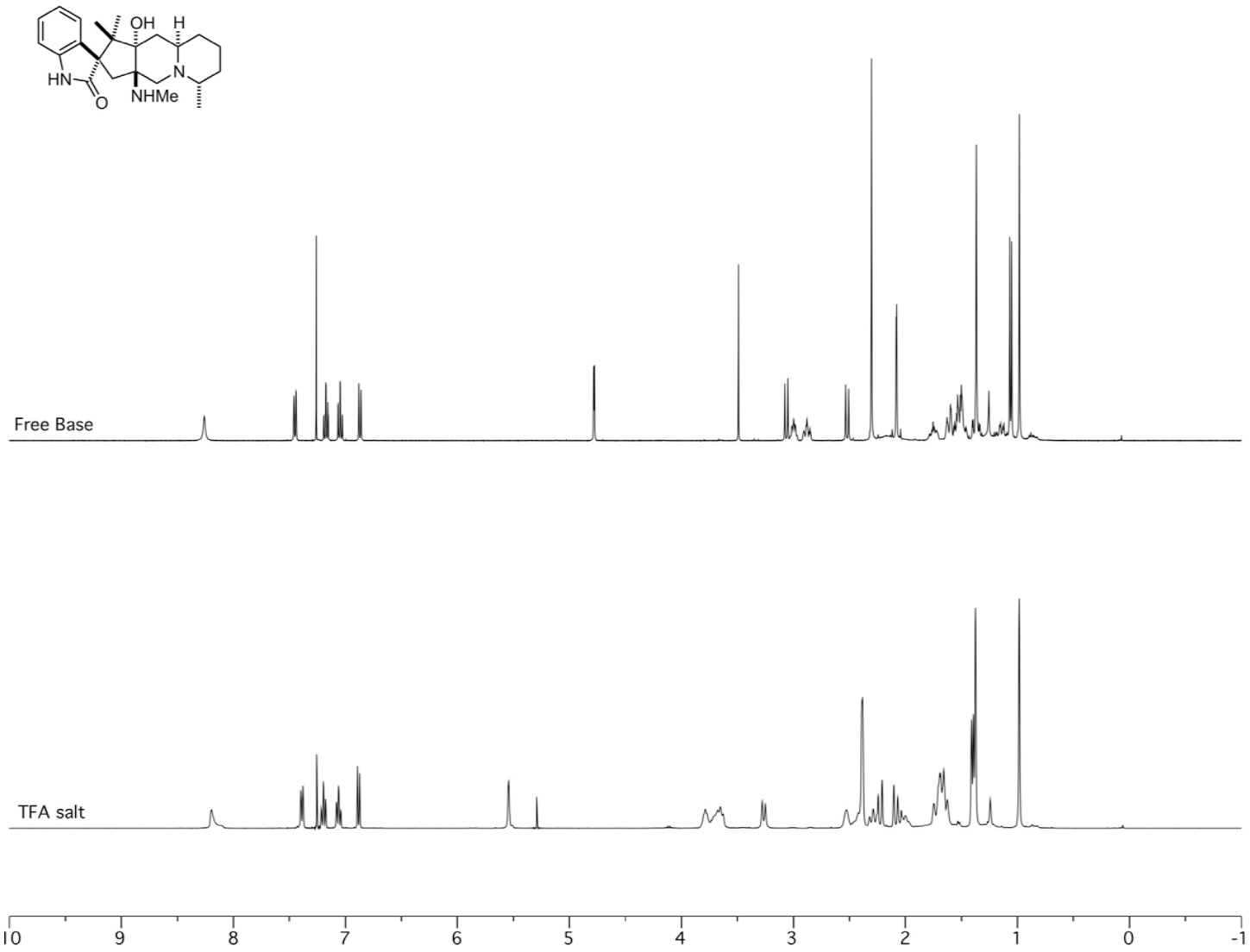
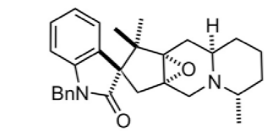


Figure A.2.3d. ^{1}H NMR overlay of compound **100** (Free Base & TFA Salt)



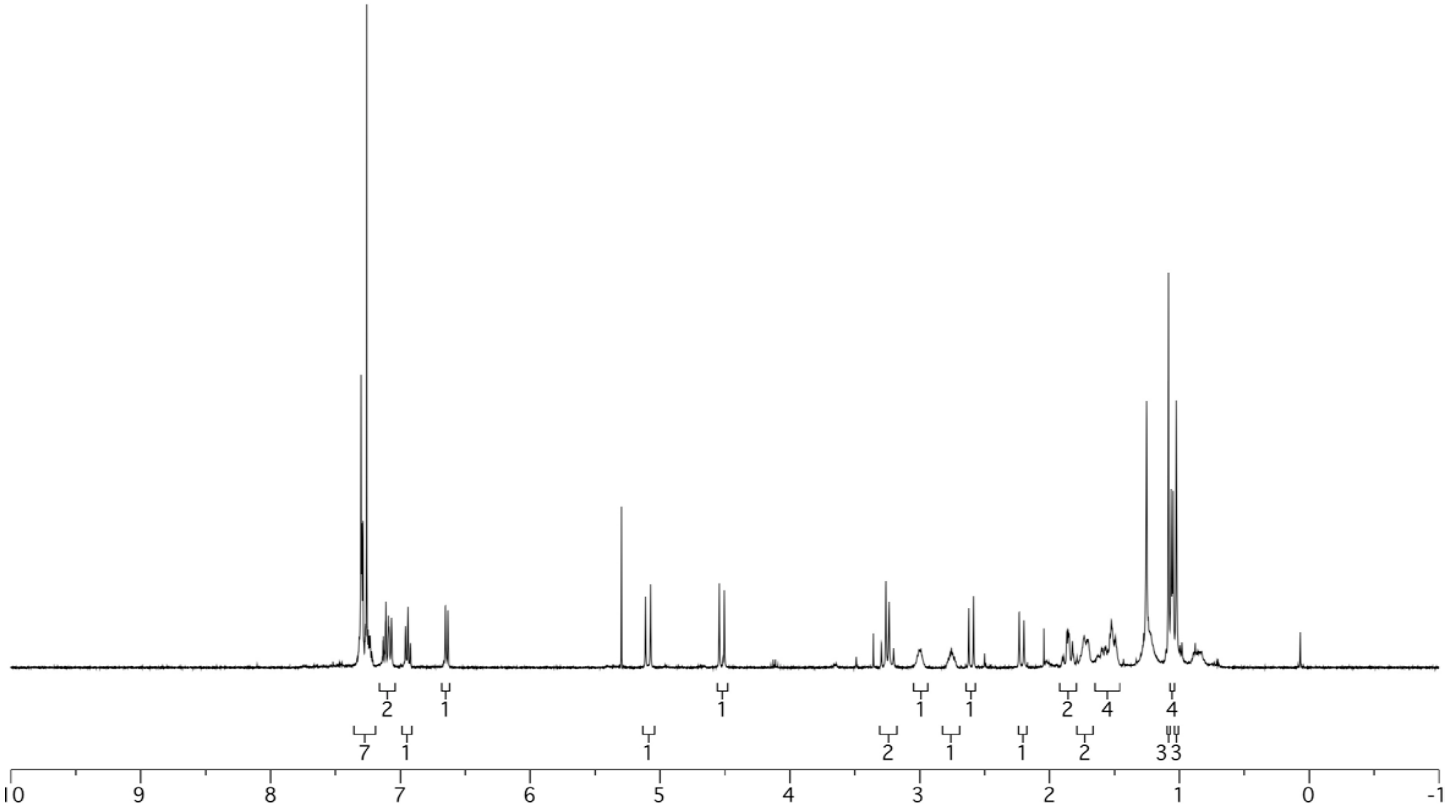


Figure A.2.4a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **101**

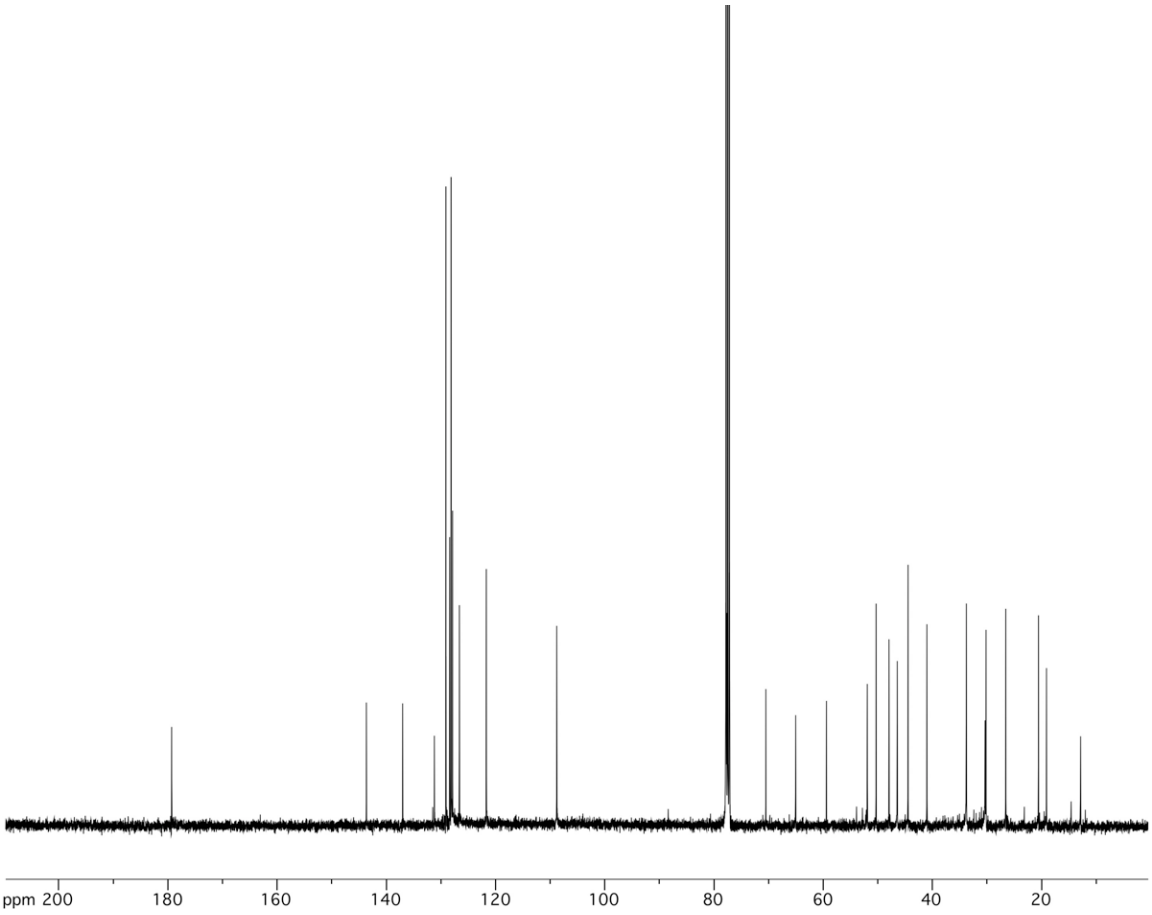


Figure A.2.4b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **101**

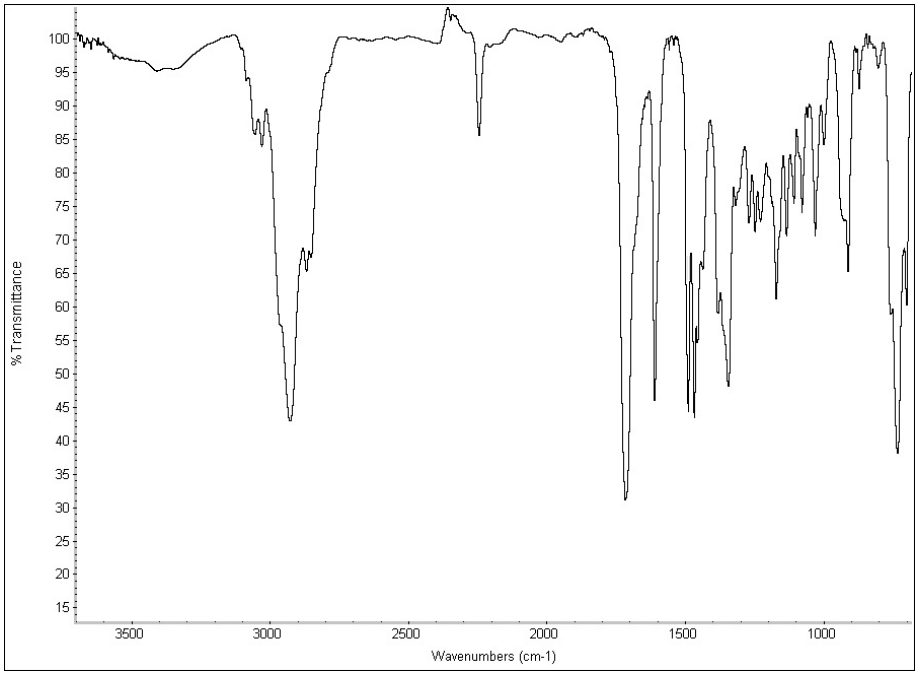
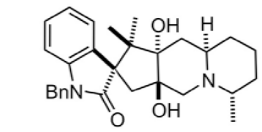


Figure A.2.4c. IR spectrum (thin film/NaCl) of compound **101**



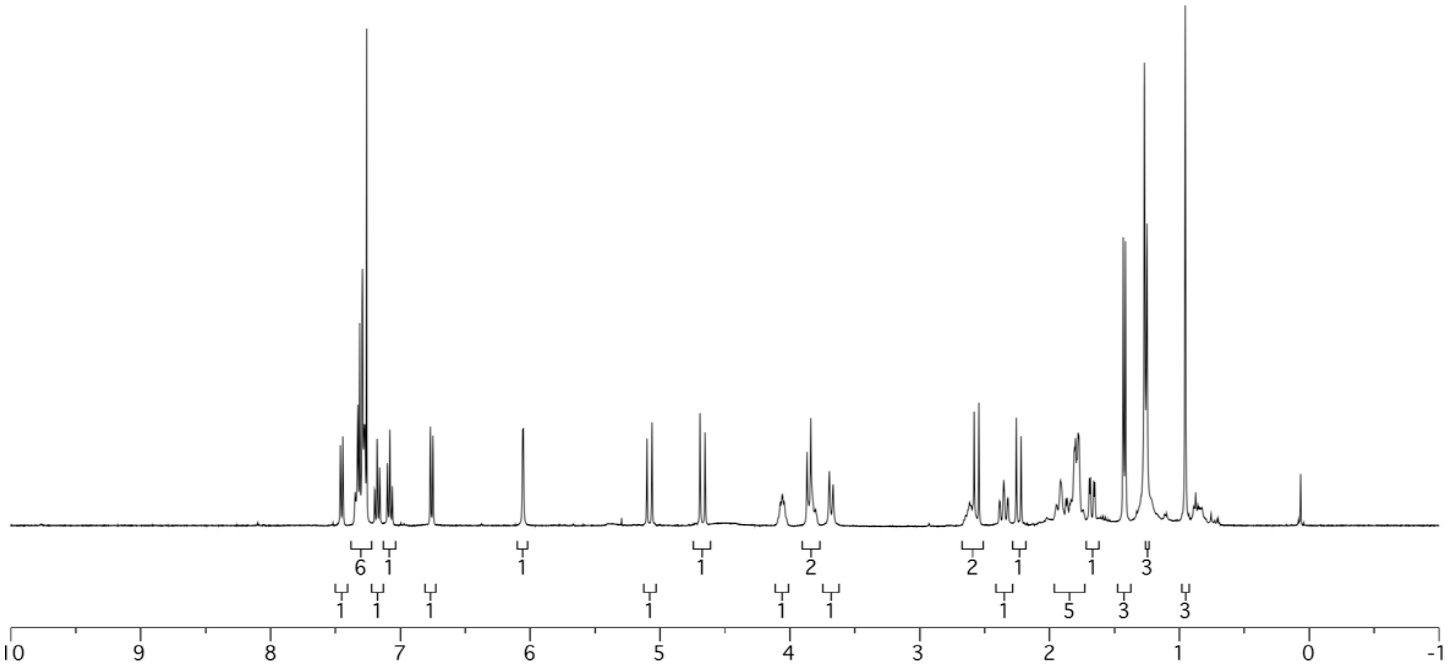


Figure A.2.5a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **102**

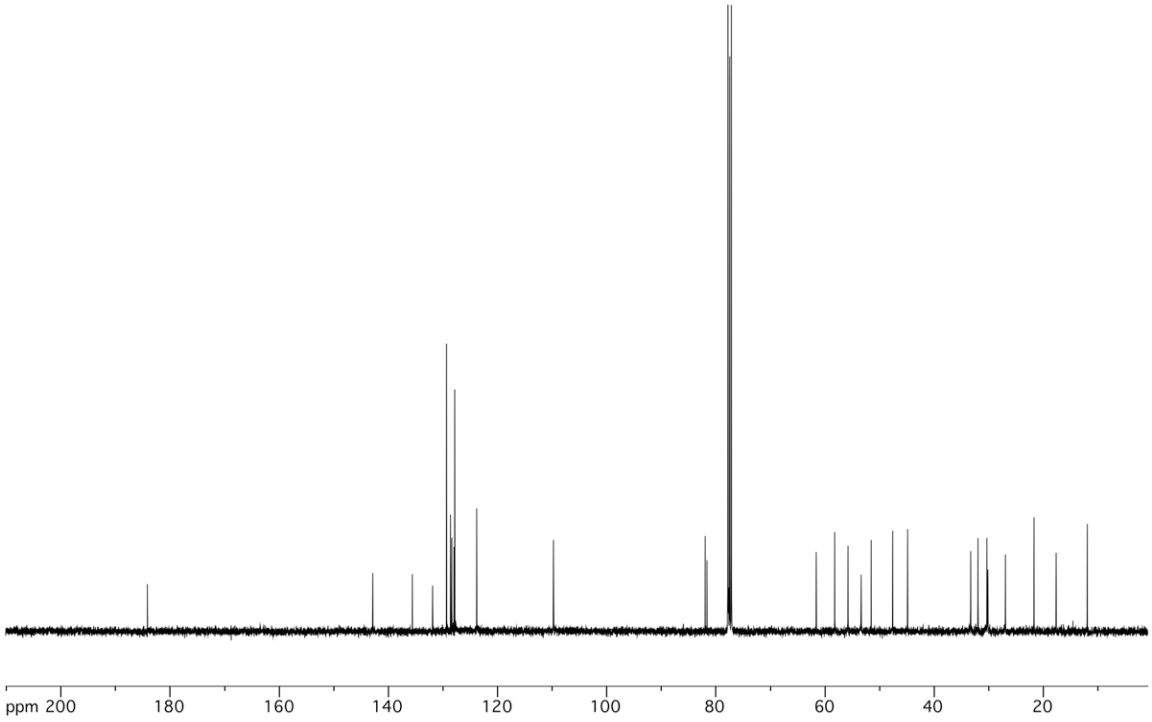


Figure A.2.5b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **102**

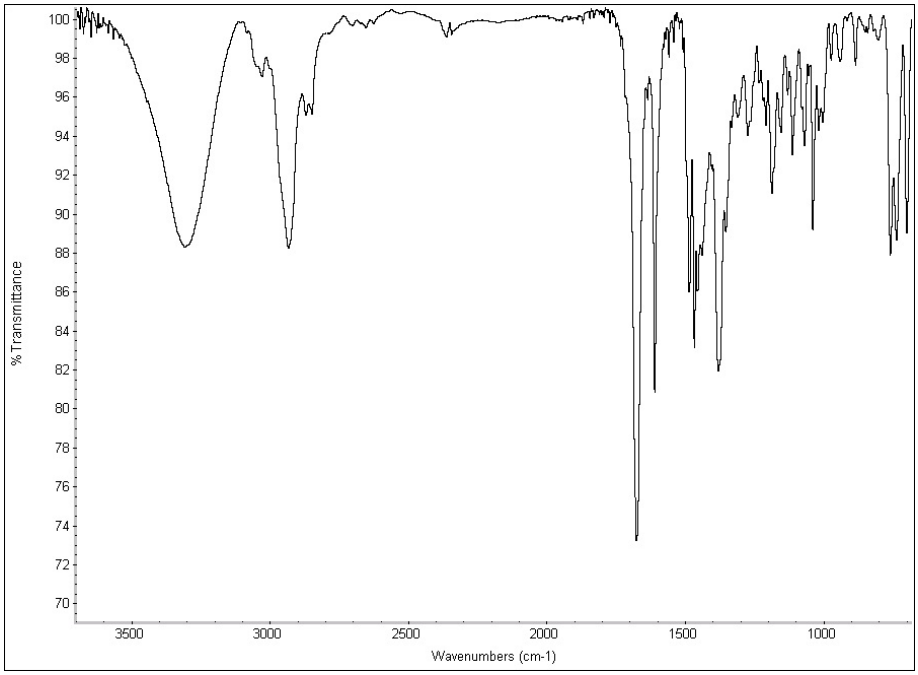
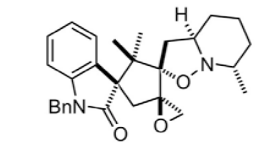


Figure A.2.5c. IR spectrum (thin film/NaCl) of compound **102**



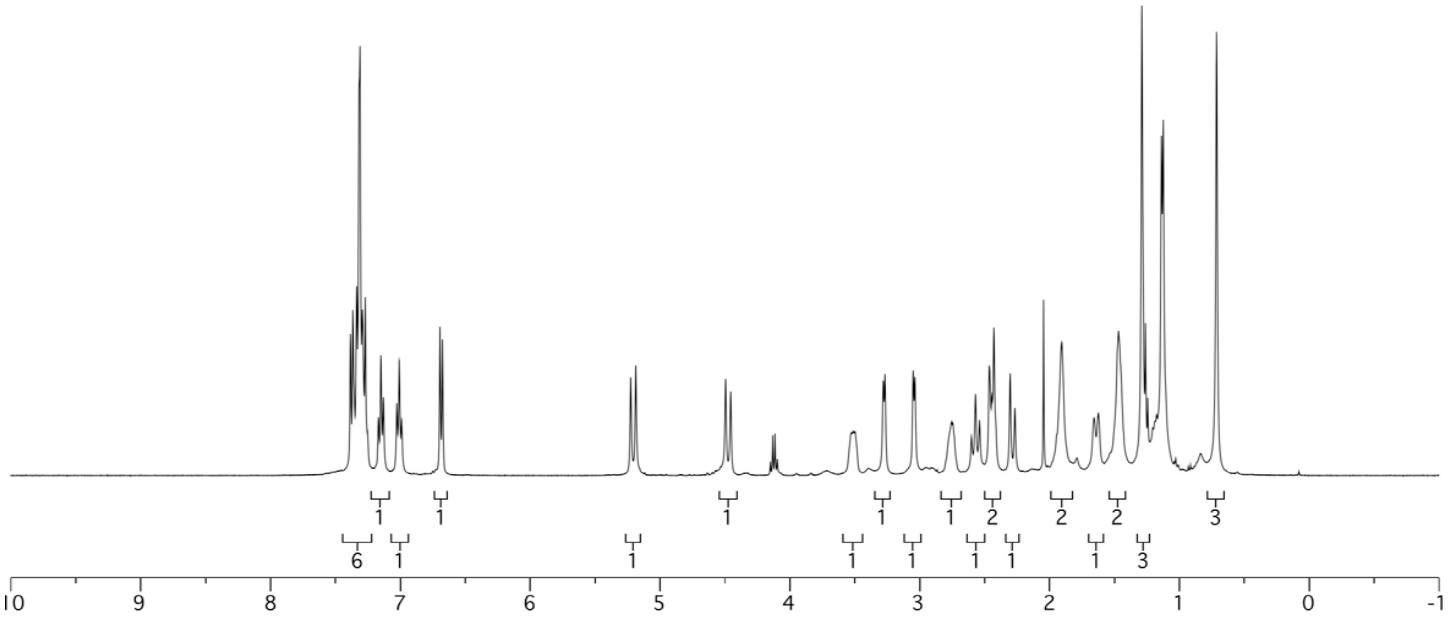


Figure A.2.6a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **103**

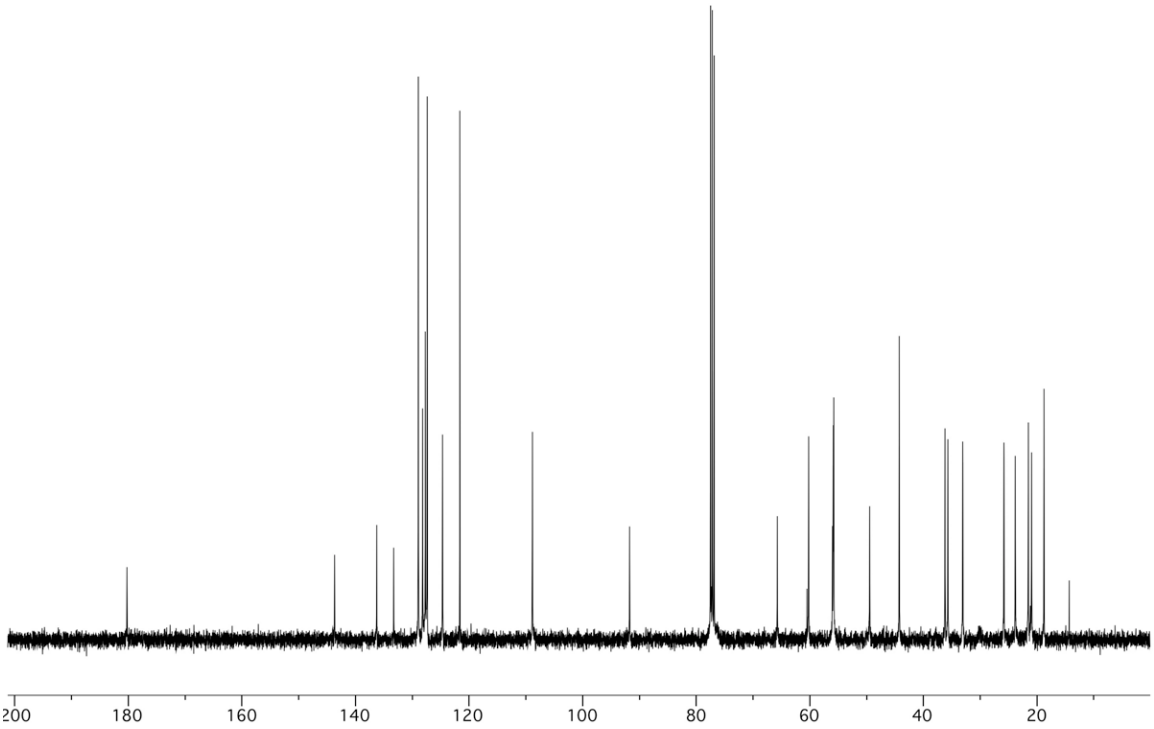


Figure A.2.6b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **103**

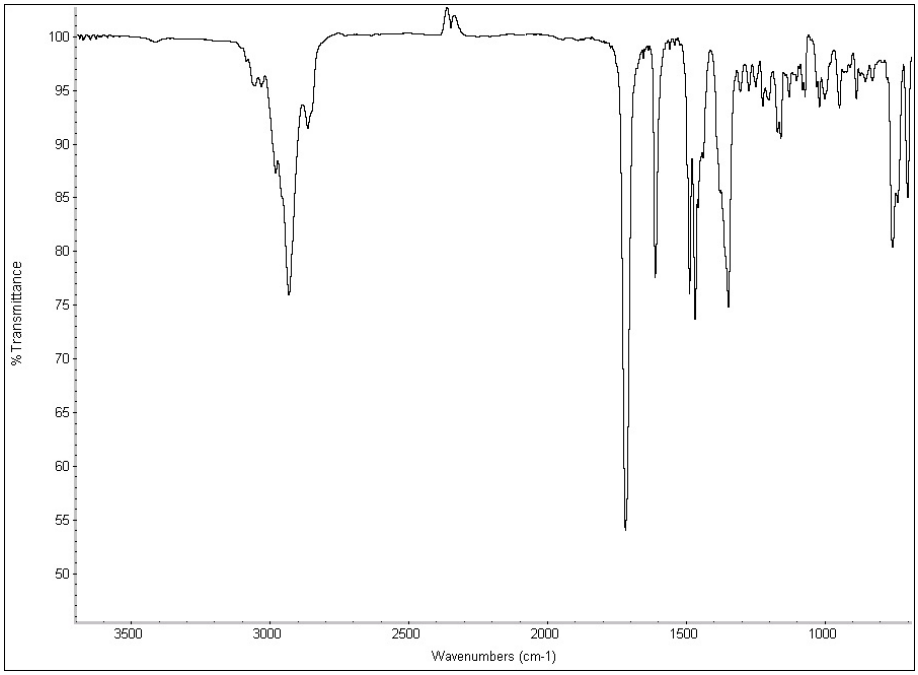
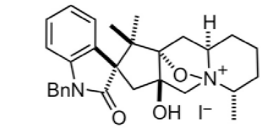


Figure A.2.6c. IR spectrum (thin film/NaCl) of compound **103**



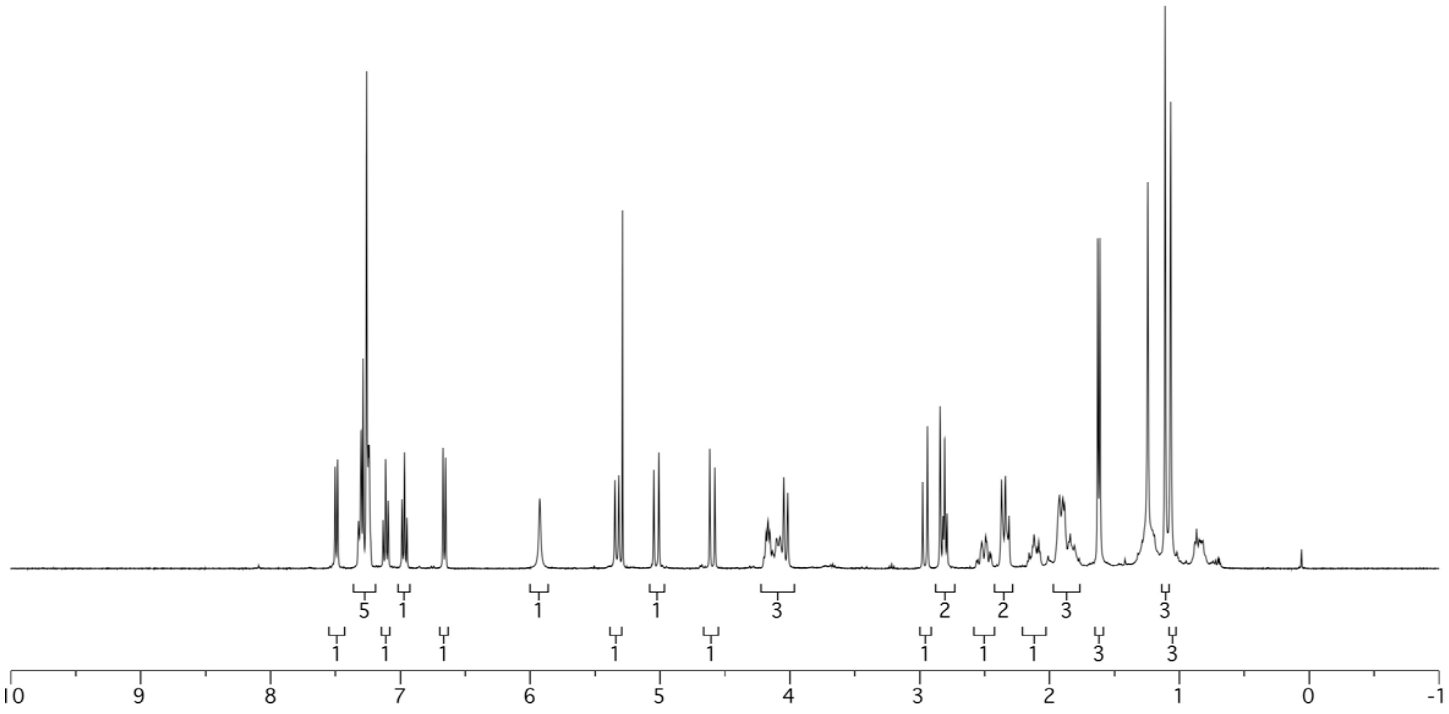


Figure A.2.7a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **107**

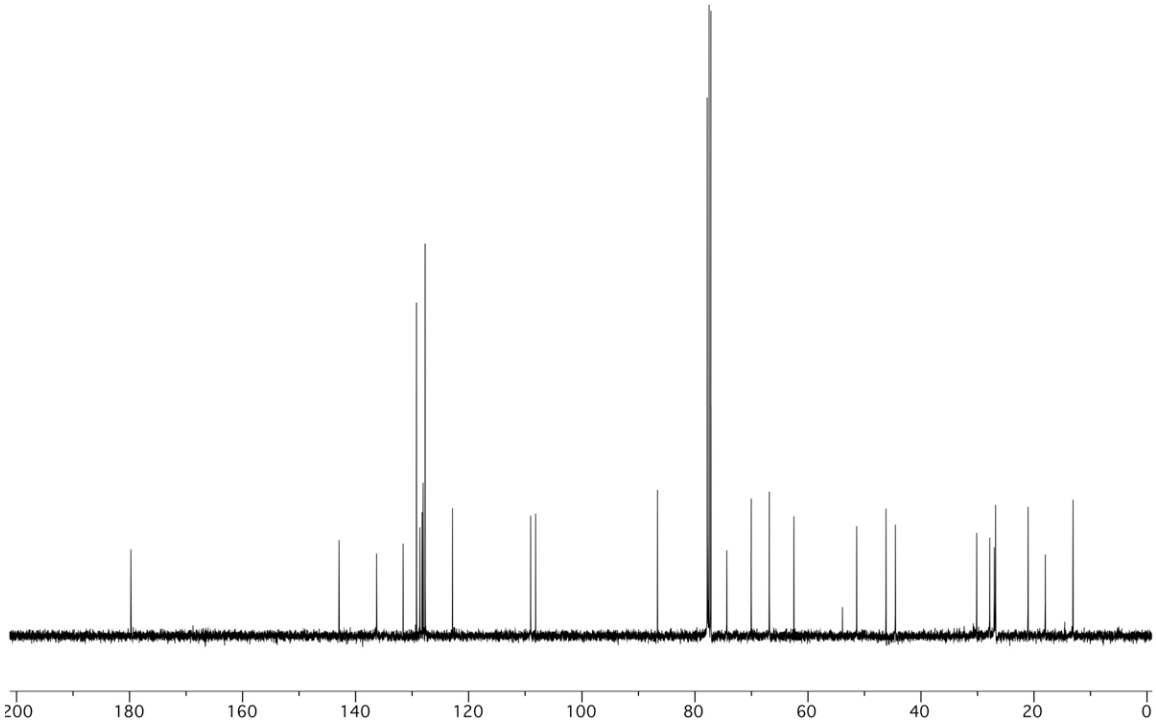


Figure A.2.7b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **107**

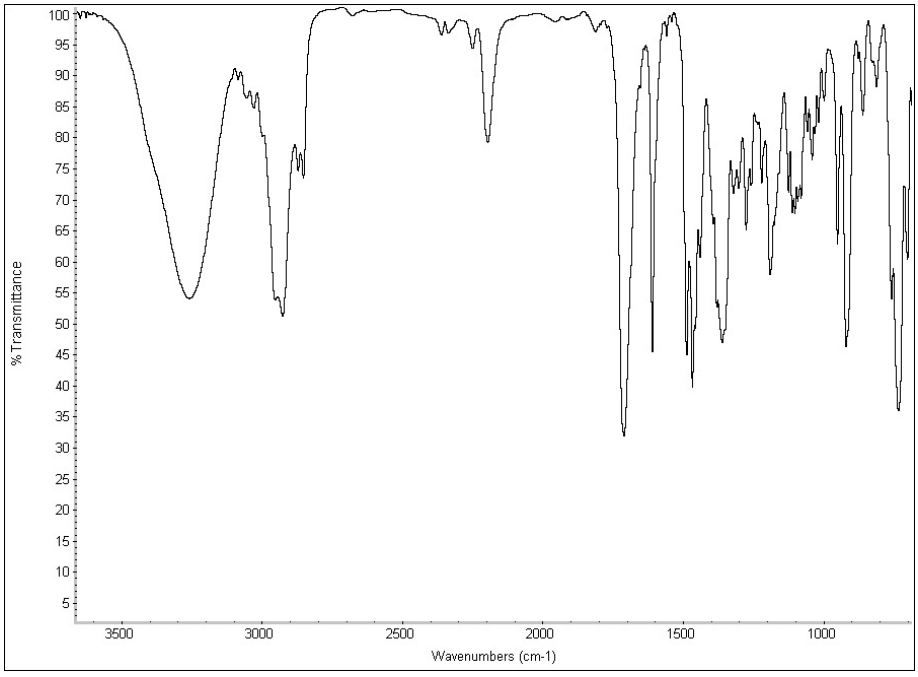


Figure A.2.7c. IR spectrum (thin film/NaCl) of compound **107**

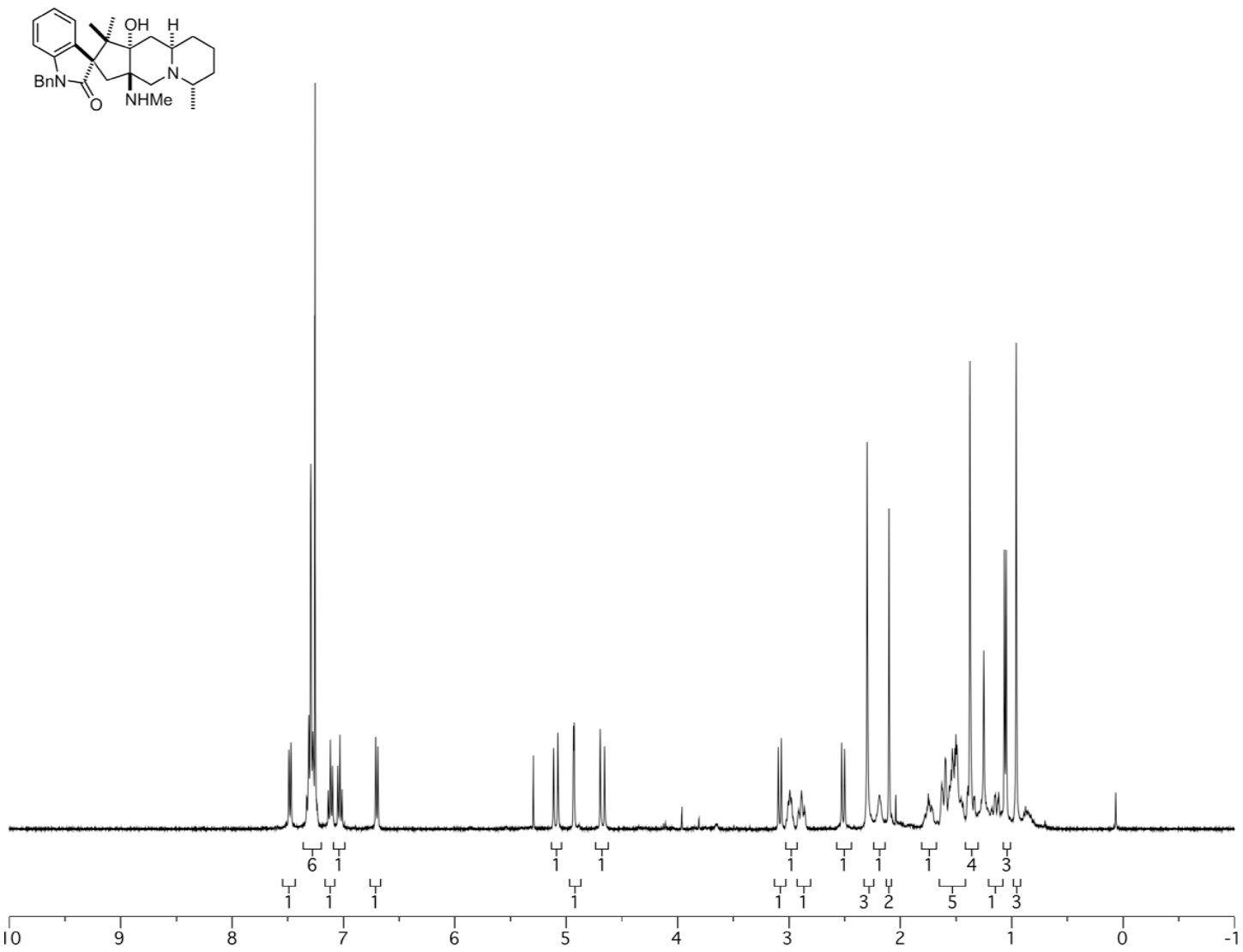


Figure A.2.8a. H NMR spectrum (400 MHz, $CDCl_3$) of compound **108**

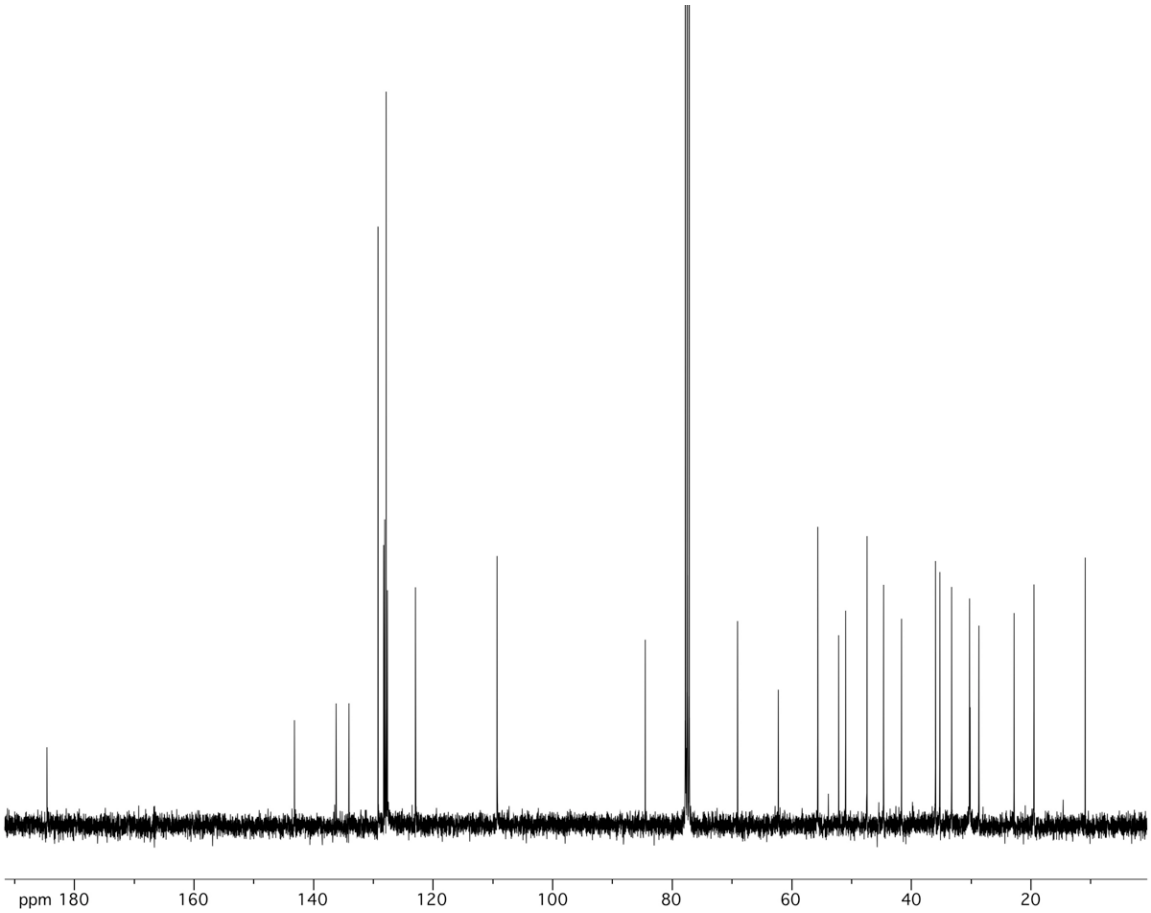


Figure A.2.8b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **108**

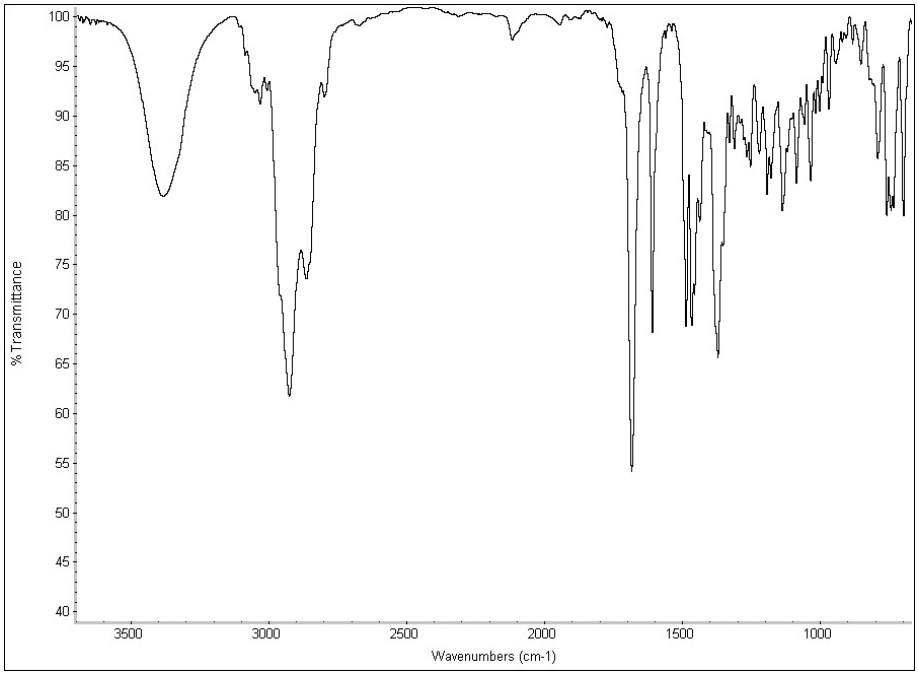
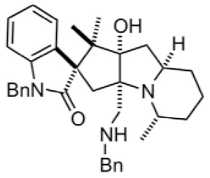


Figure A.2.8c. IR spectrum (thin film/NaCl) of compound **108**



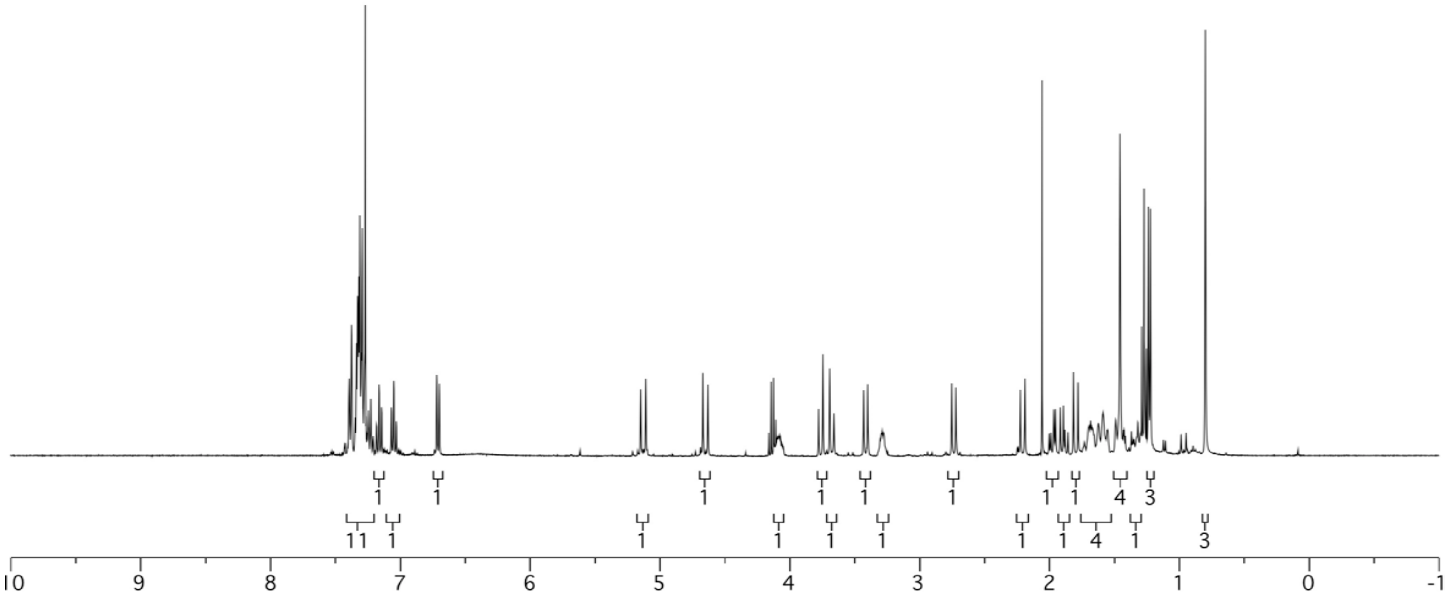


Figure A.2.9a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **110**

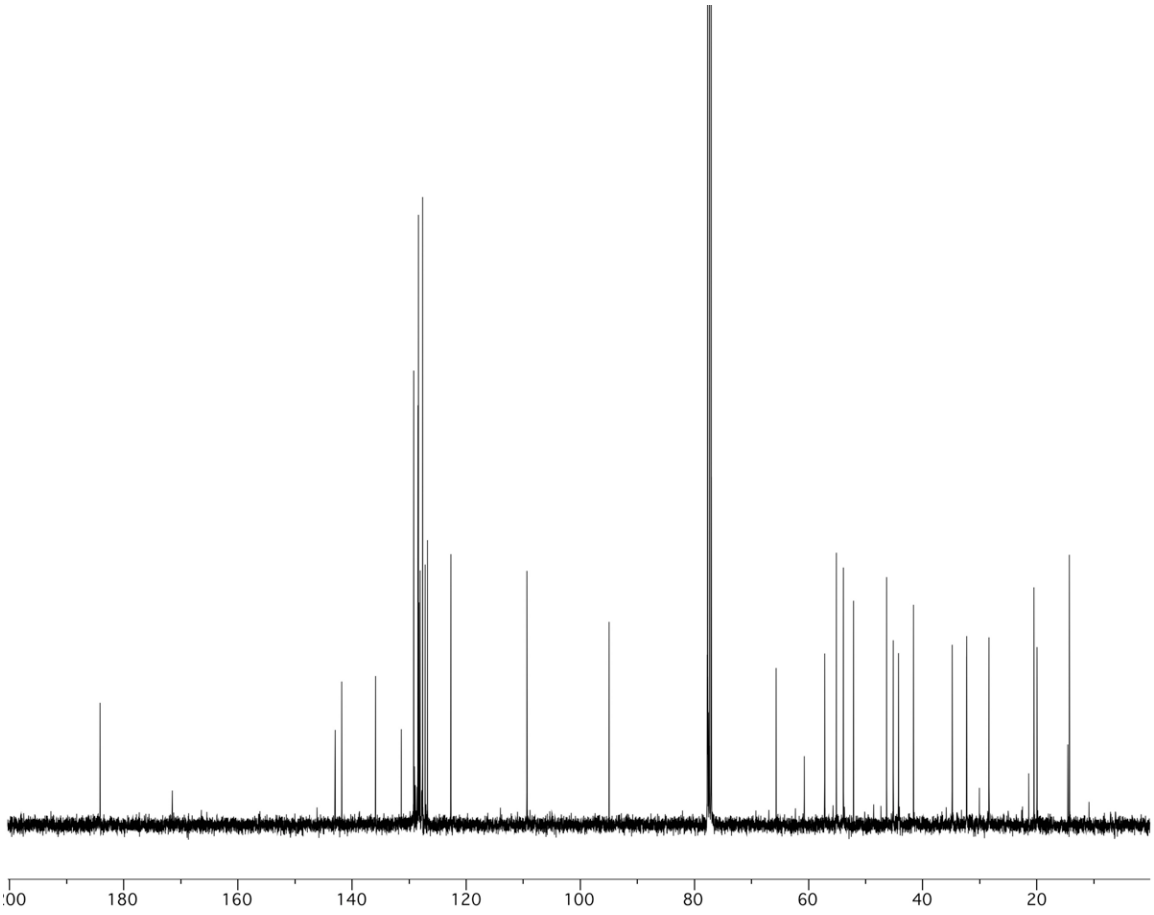


Figure A.2.9b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **110**

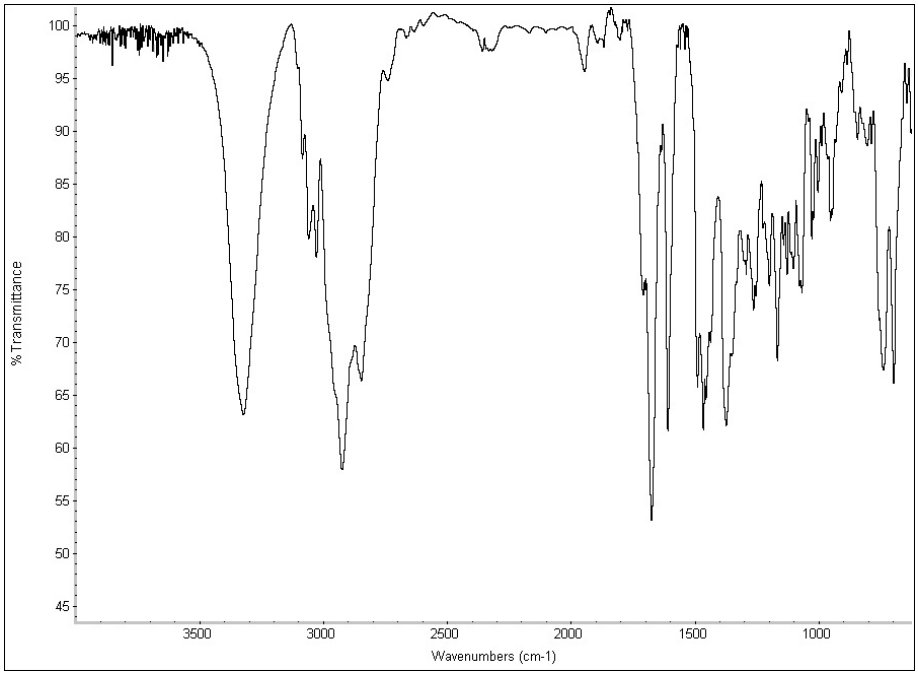


Figure A.2.9c. IR spectrum (thin film/NaCl) of compound **110**

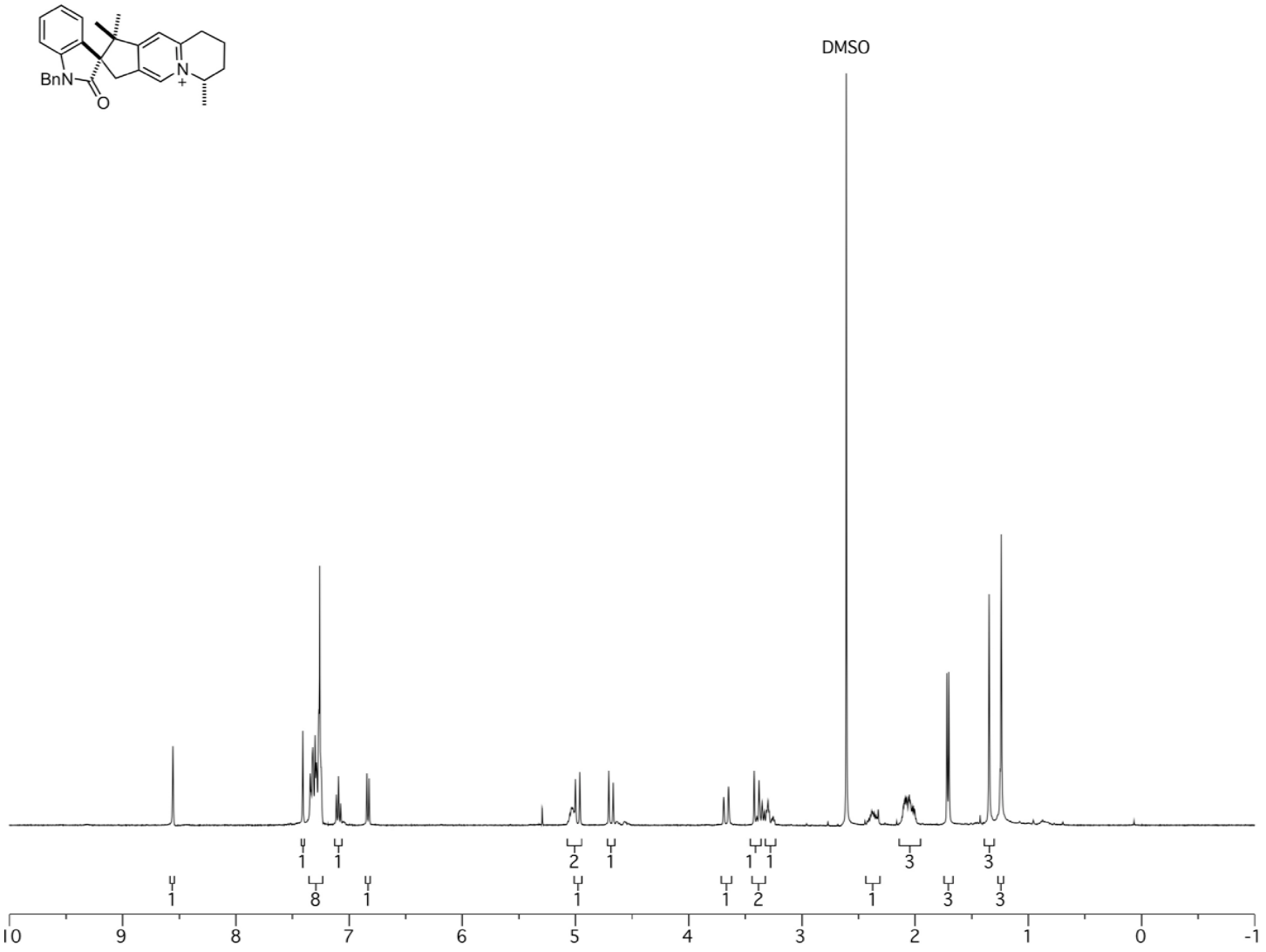


Figure A.2.10a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **113**

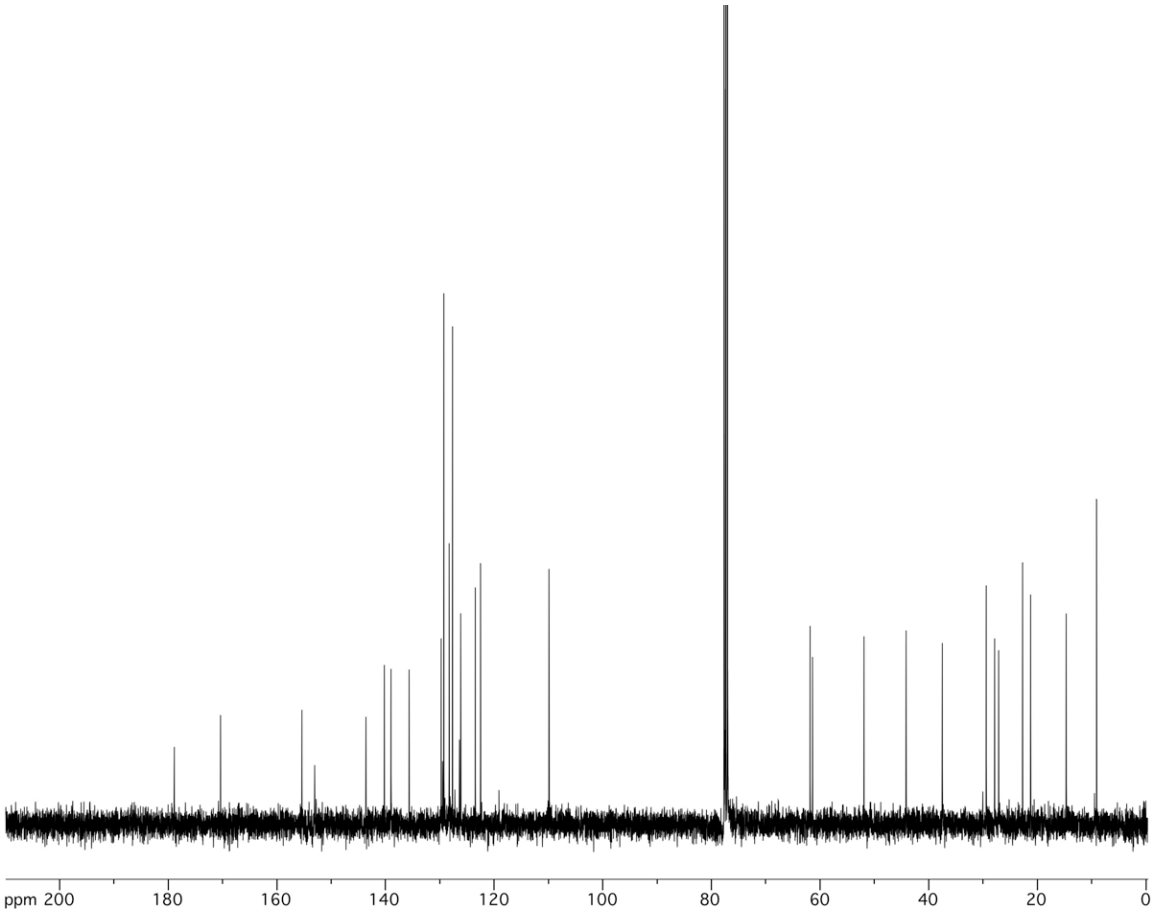


Figure A.2.10b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **113**

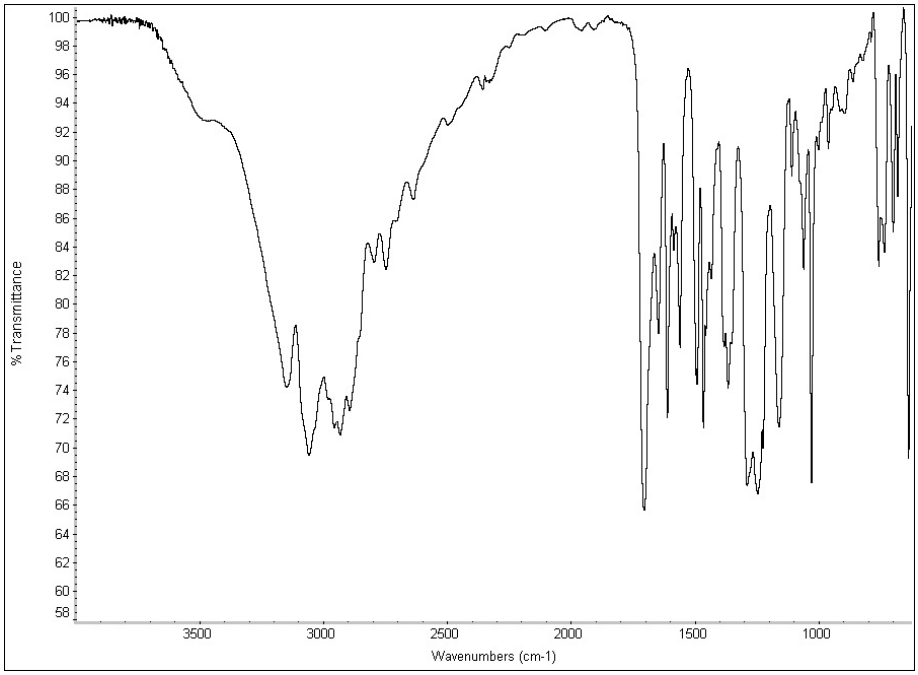


Figure A.2.10c. IR spectrum (thin film/NaCl) of compound **113**

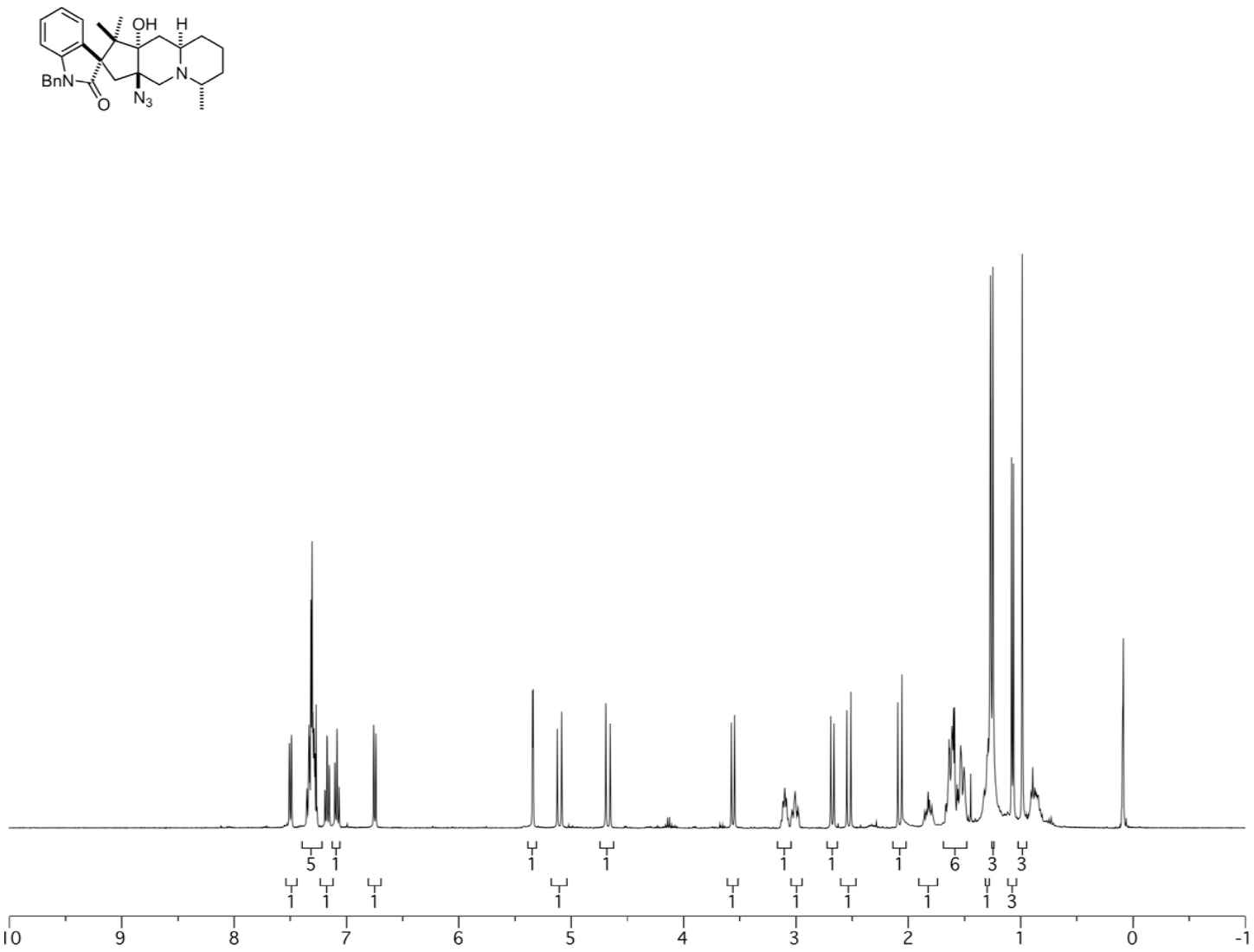


Figure A.2.11a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **114**

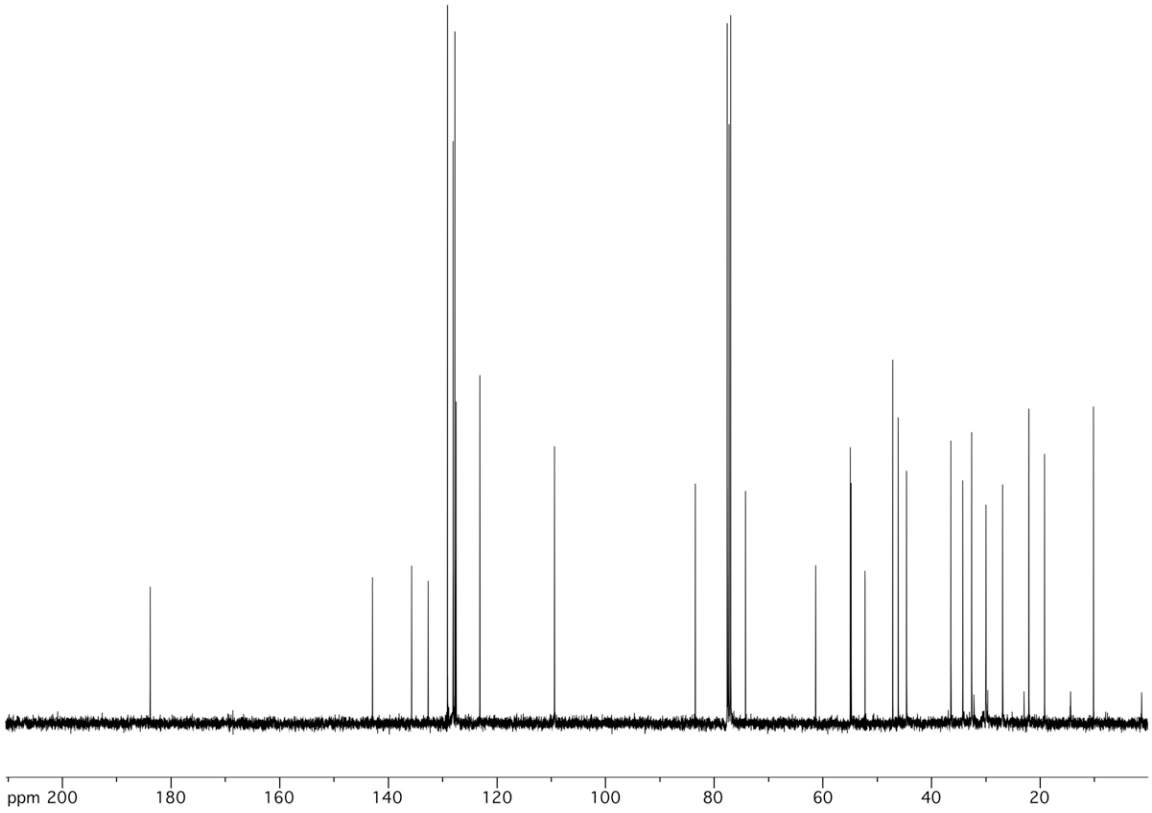


Figure A.2.11b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **114**

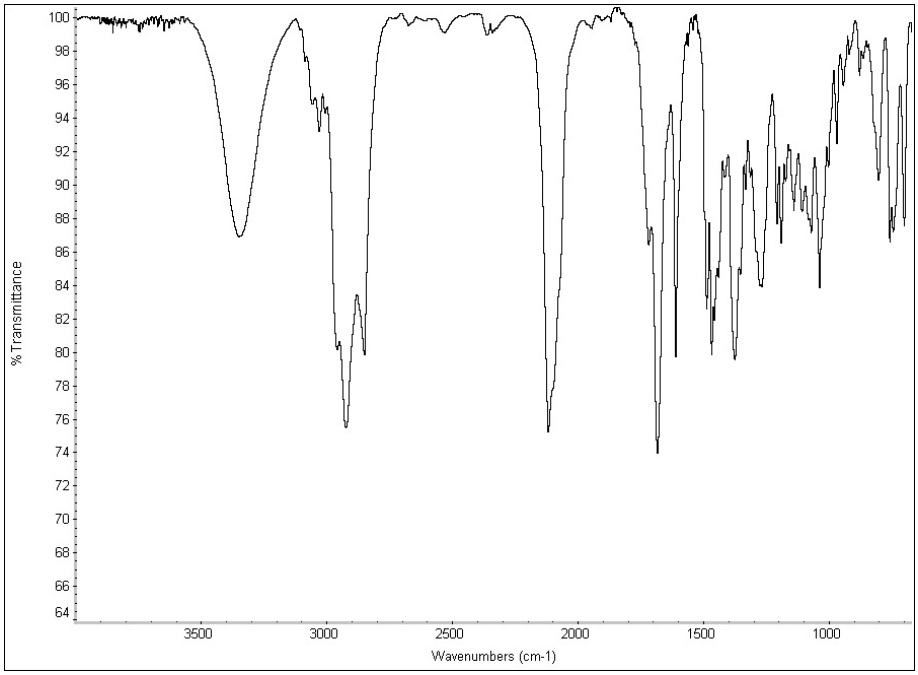
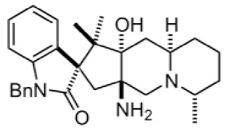


Figure A.2.11c. IR spectrum (thin film/NaCl) of compound **114**



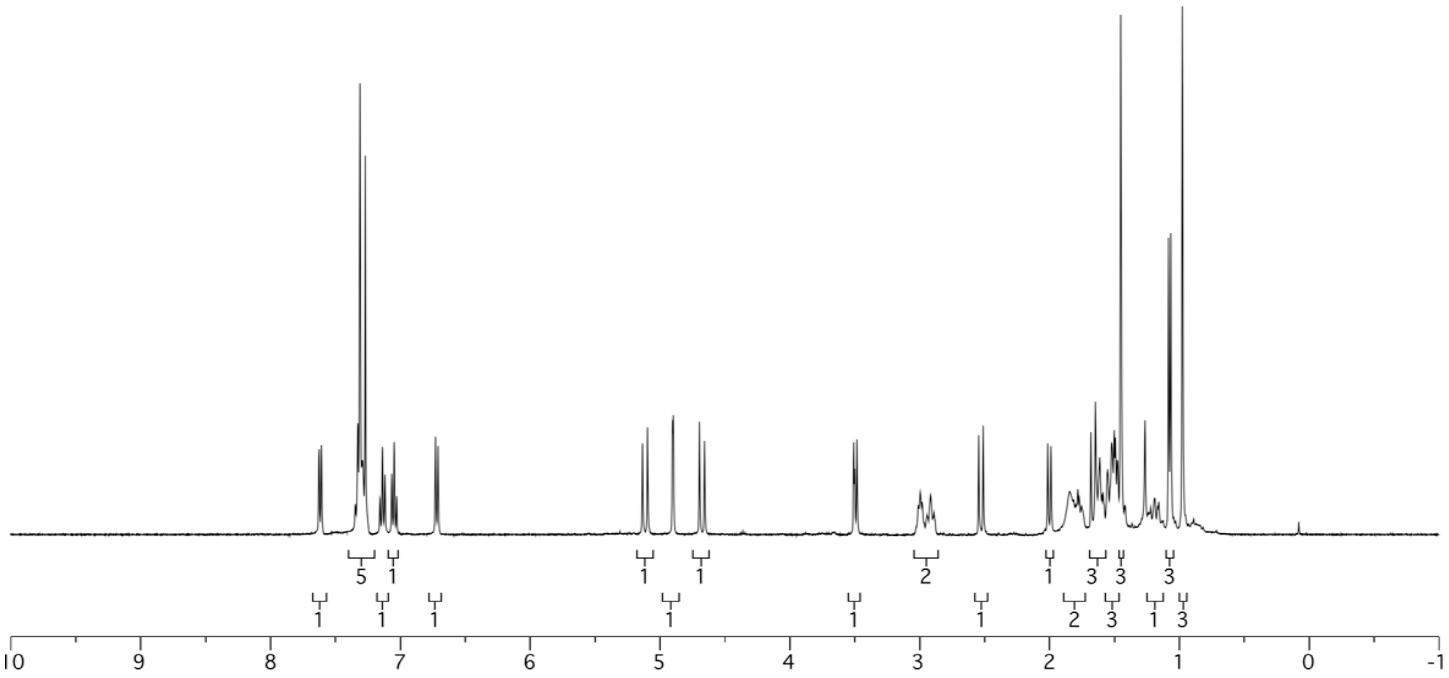


Figure A.2.12a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **115**

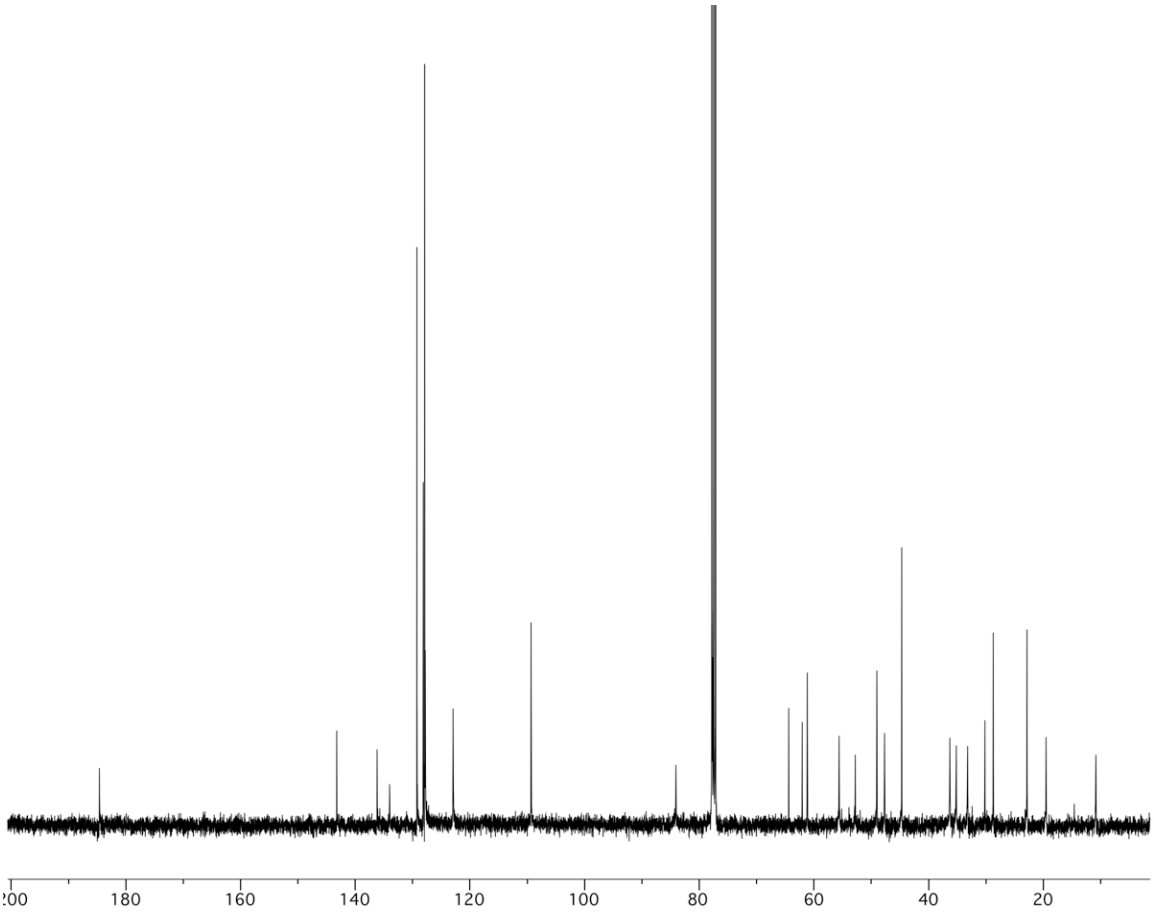


Figure A.2.12b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **115**

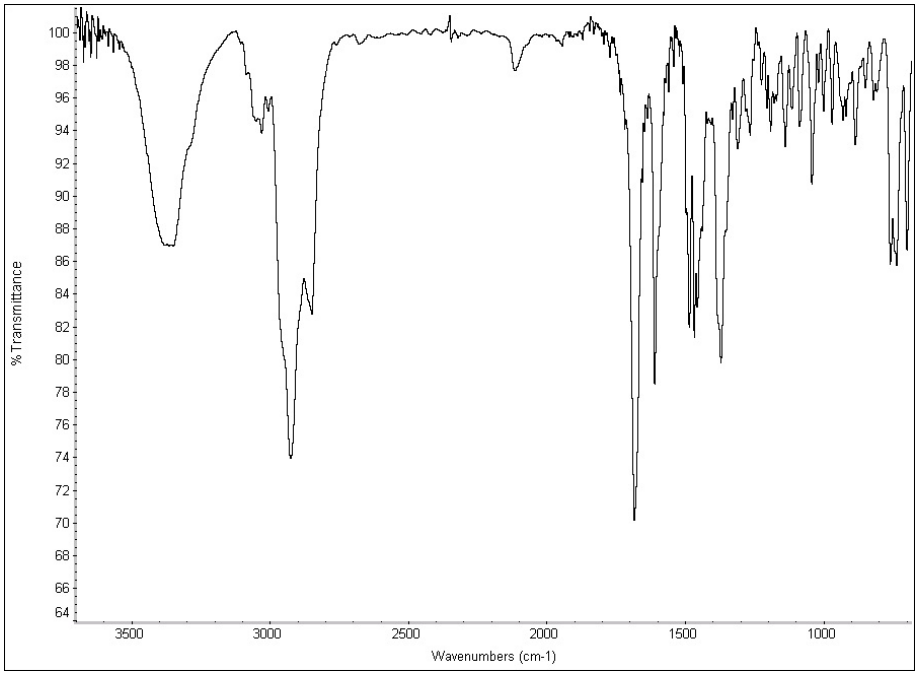


Figure A.2.12c. IR spectrum (thin film/NaCl) of compound **115**

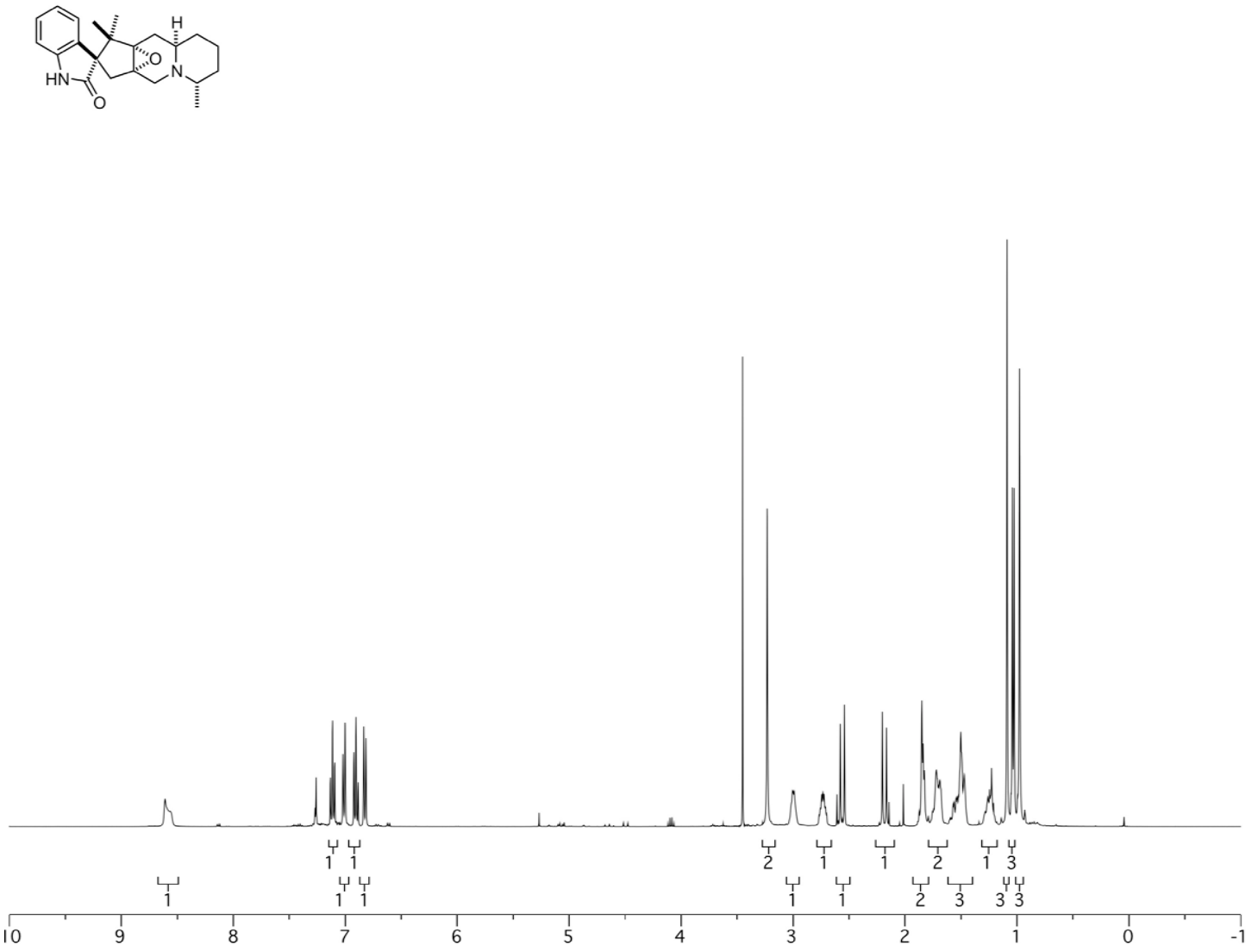


Figure A.2.13a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **121**

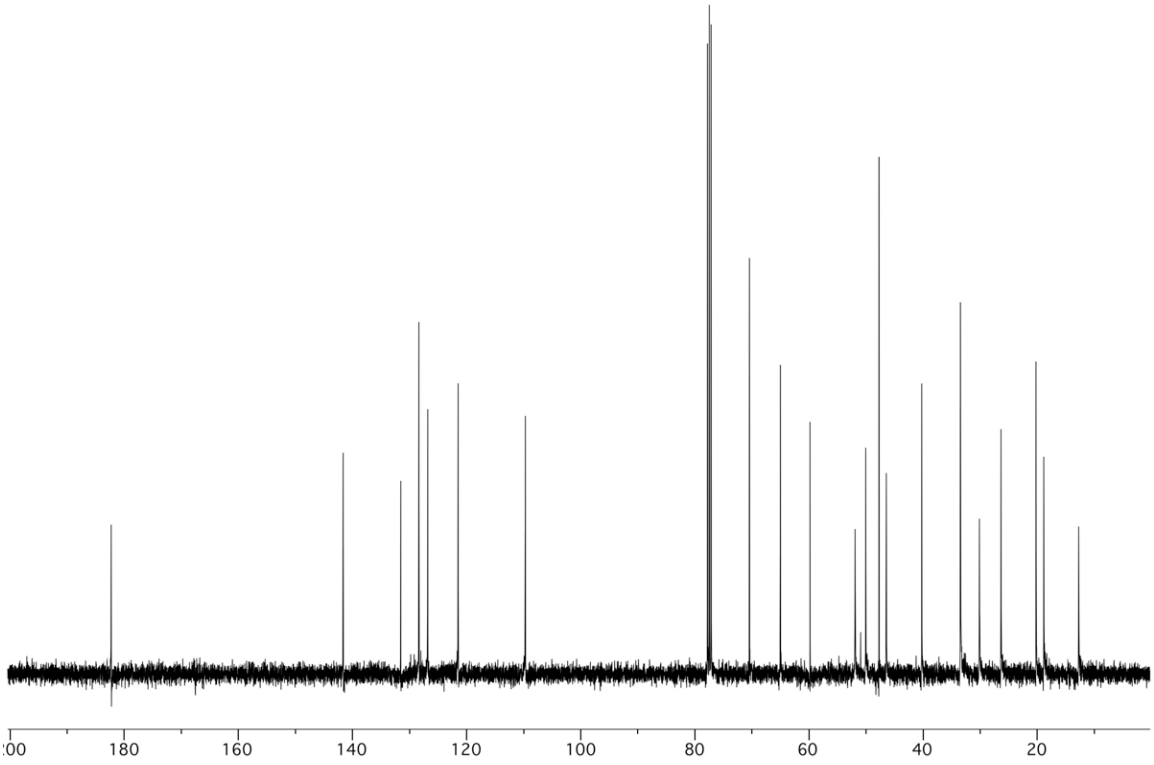


Figure A.2.13b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **121**

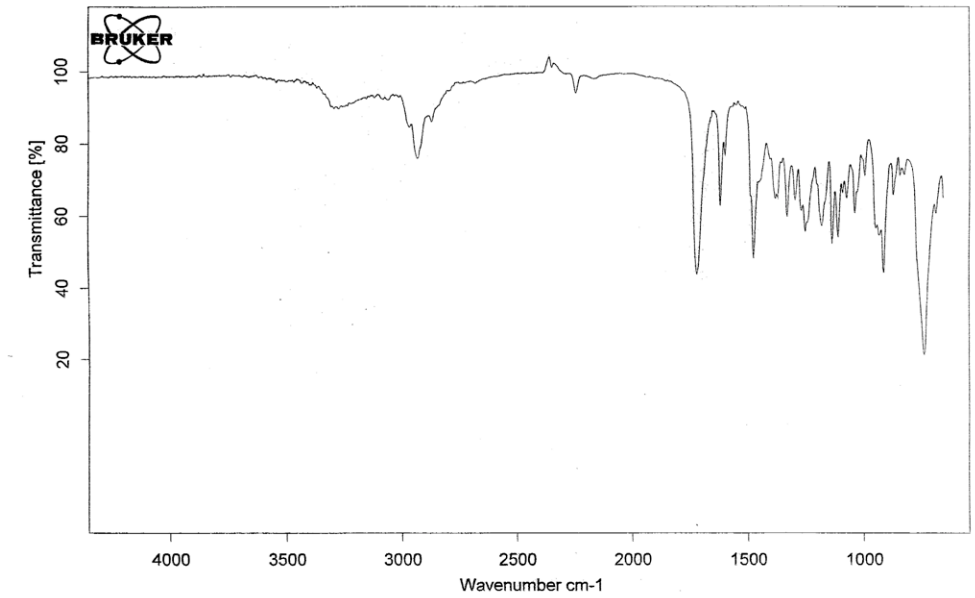
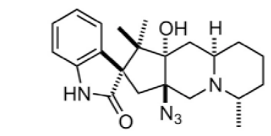


Figure A.2.13c. IR spectrum (thin film/NaCl) of compound **121**



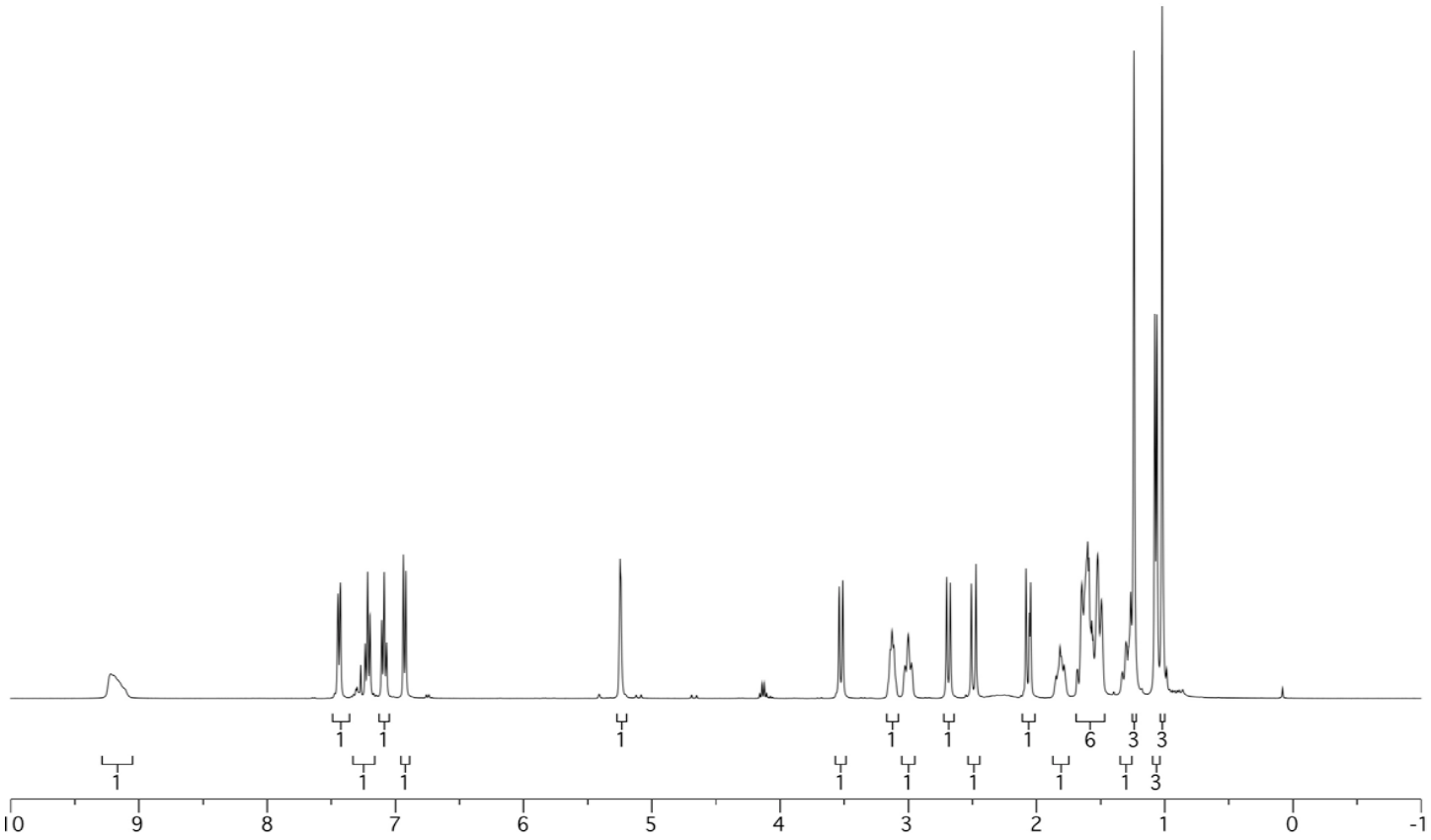


Figure A.2.14a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **122**

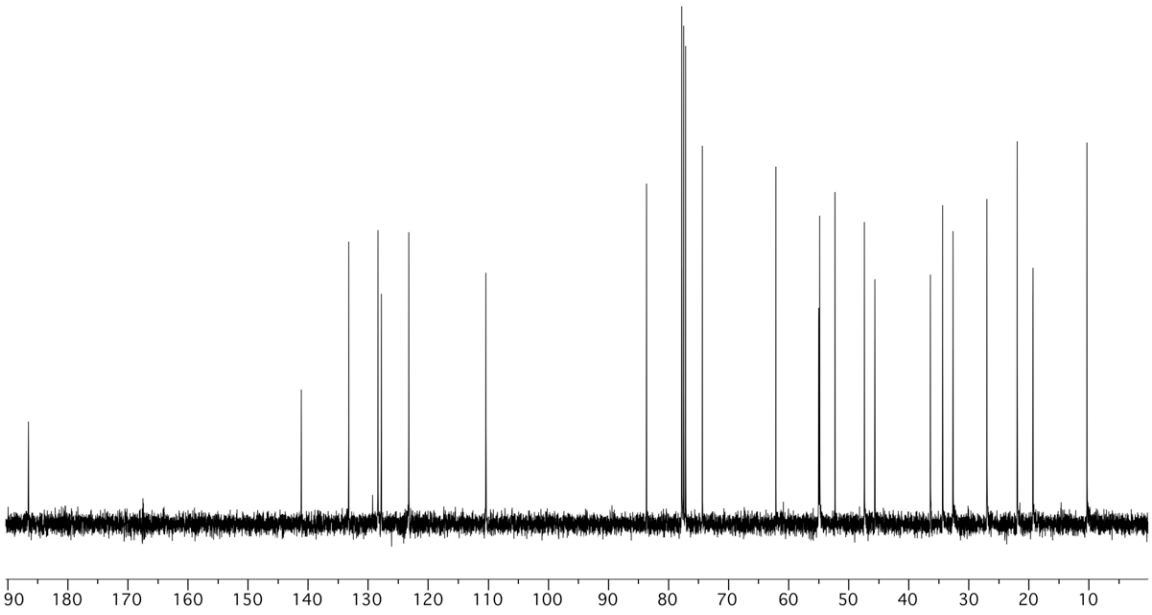


Figure A.2.14b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **122**

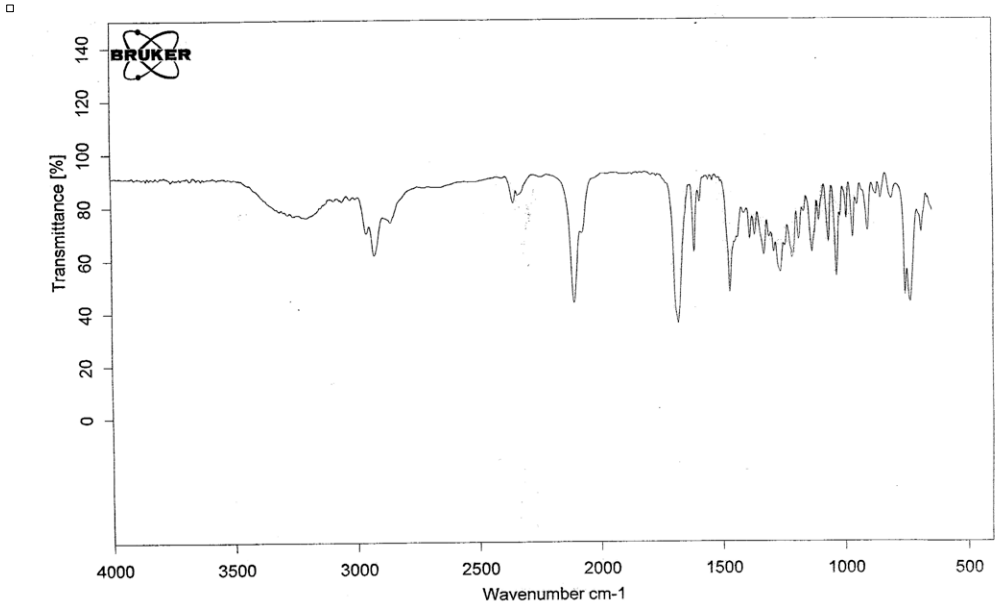


Figure A.2.14c. IR spectrum (thin film/NaCl) of compound **122**

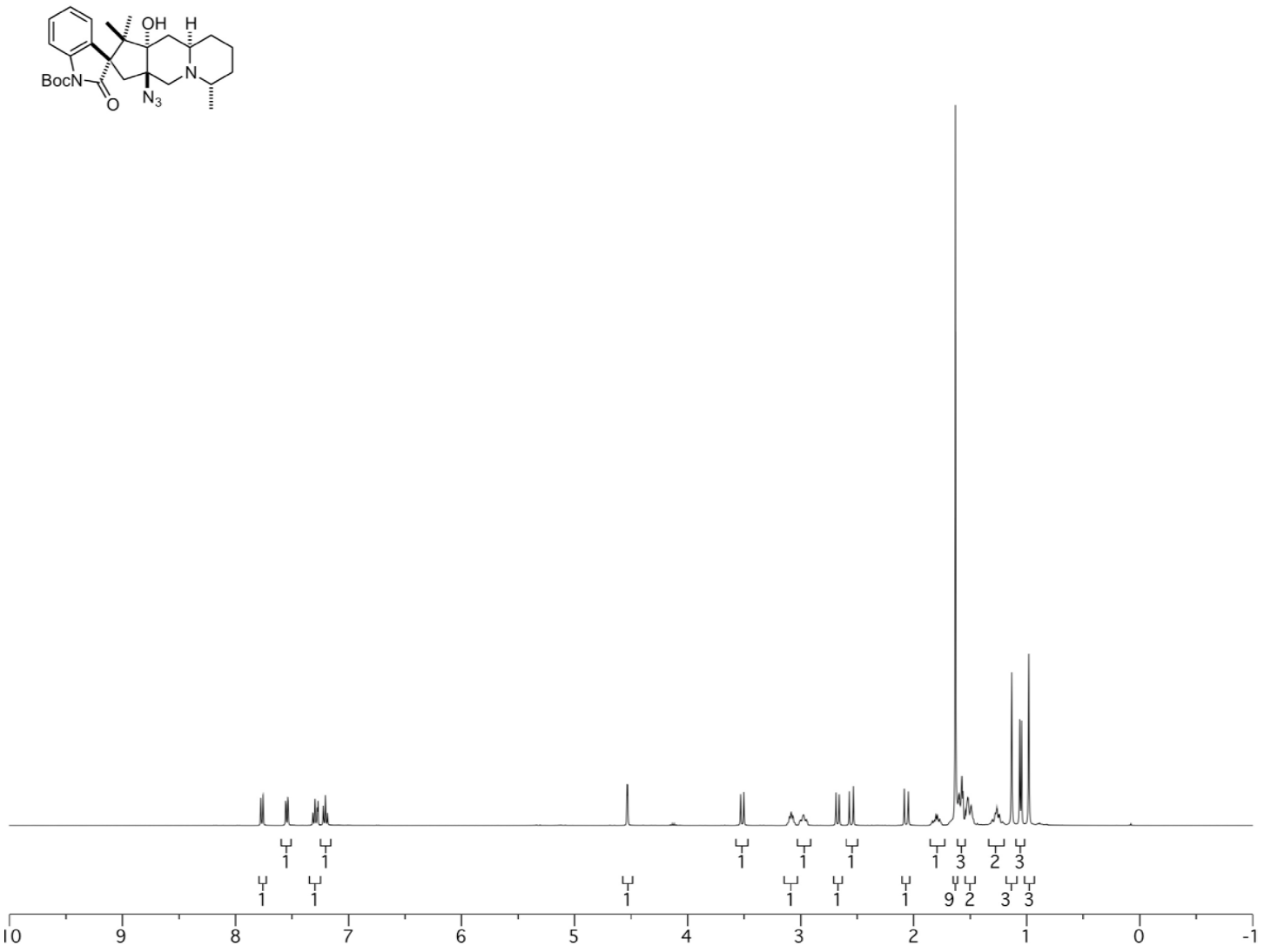


Figure A.2.15a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **125**

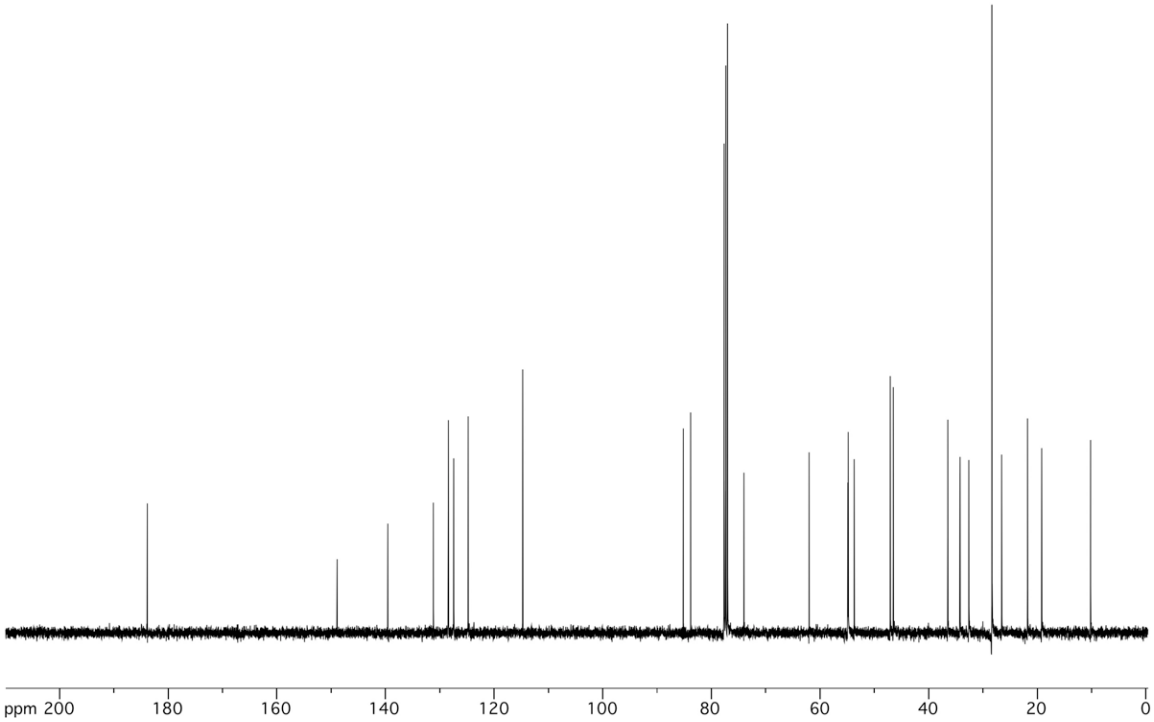


Figure A.2.15b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **125**

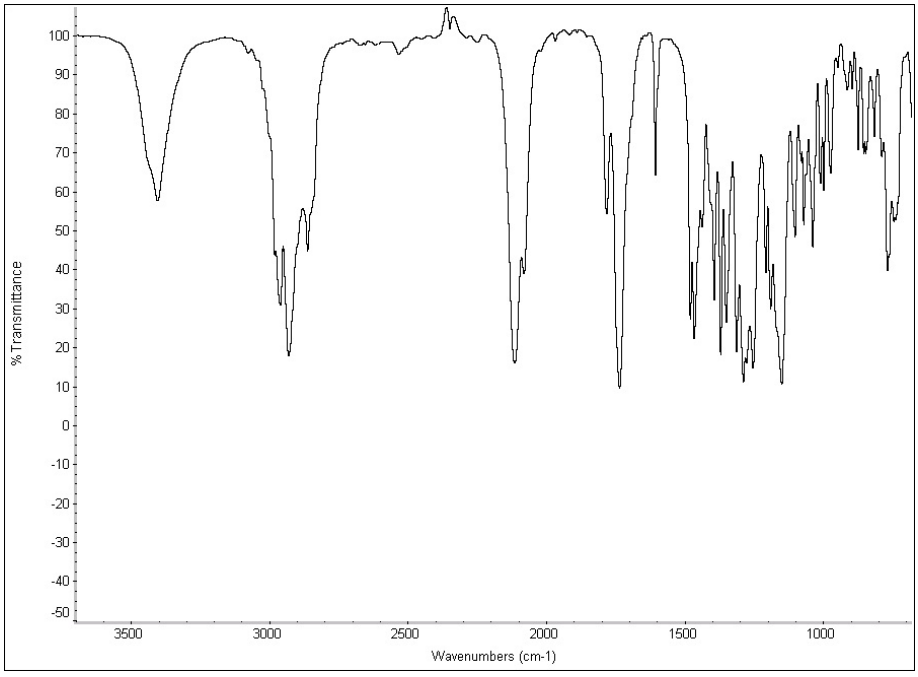


Figure A.2.15c. IR spectrum (thin film/NaCl) of compound **125**

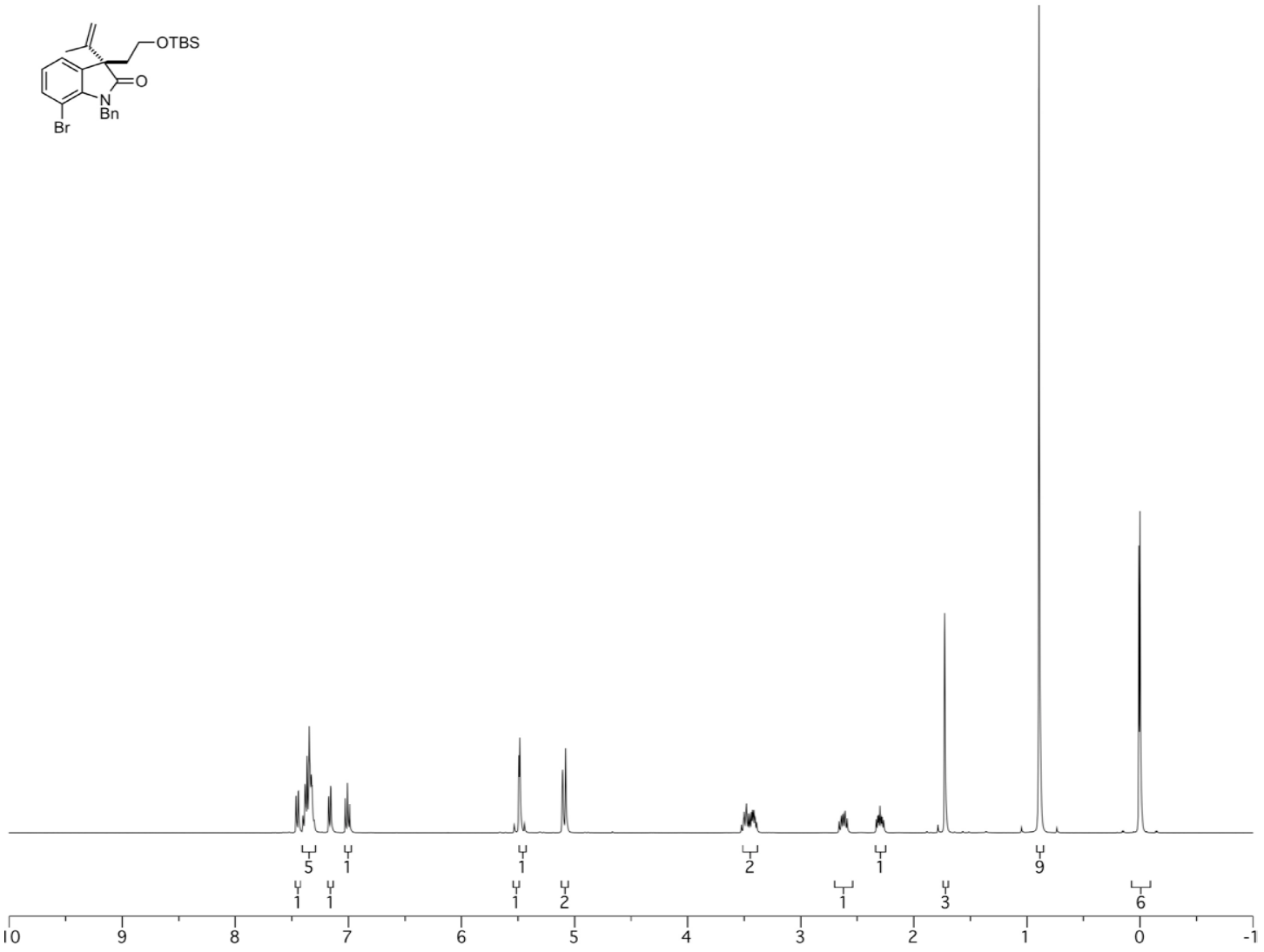


Figure A.2.16a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **130**

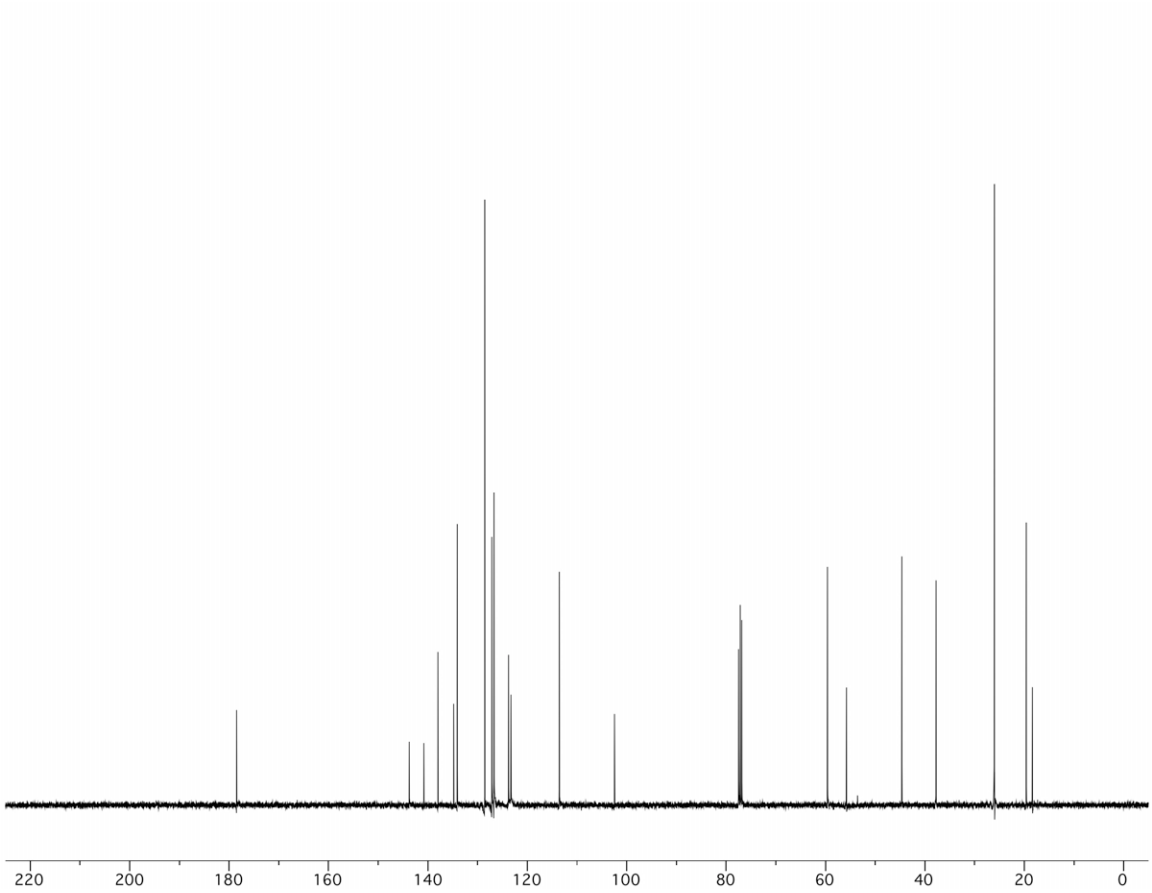


Figure A.2.16b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **130**

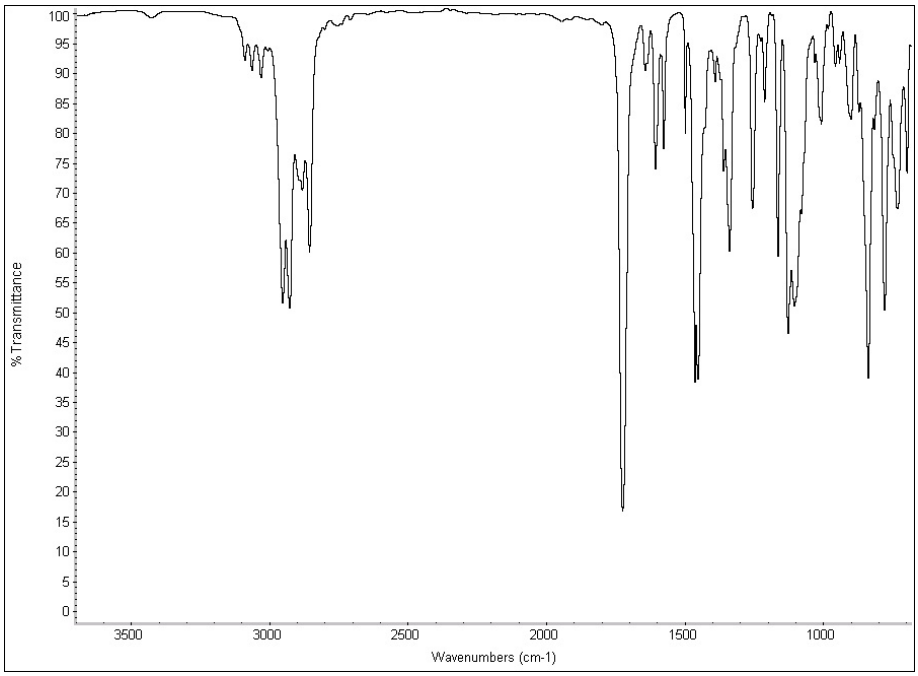


Figure A.2.16c. IR spectrum (thin film/NaCl) of compound **130**

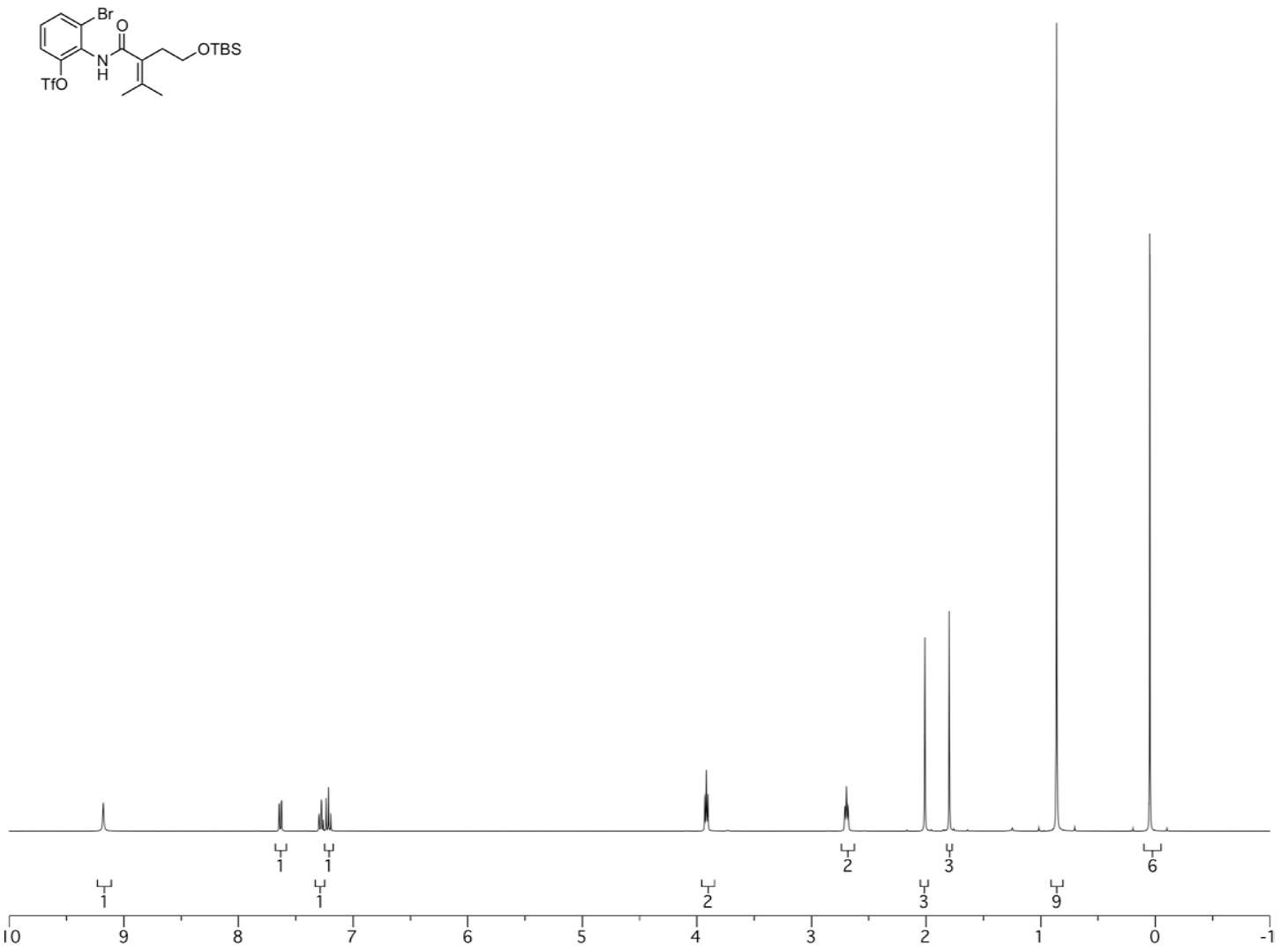


Figure A.2.17a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **131b**

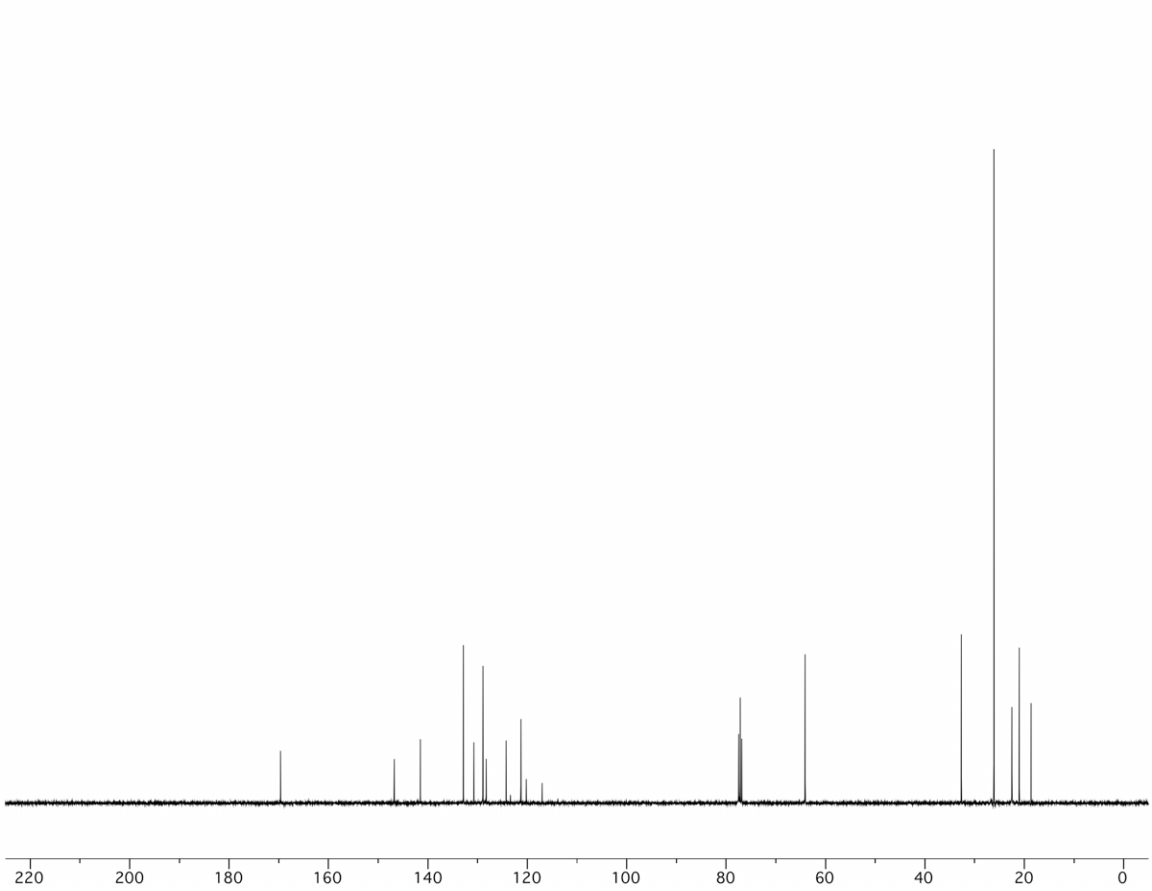


Figure A.2.17b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **131b**

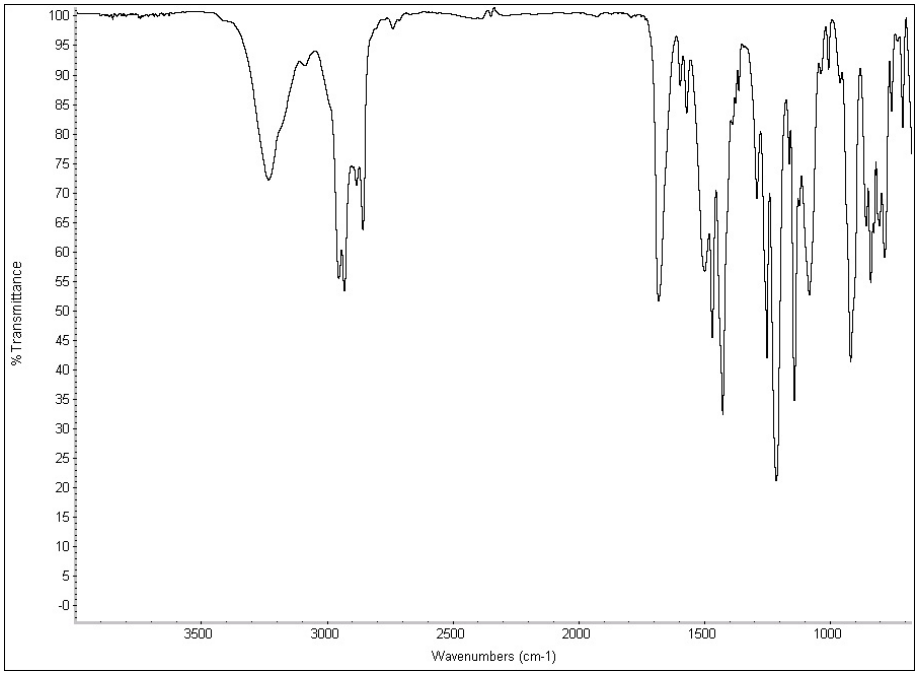


Figure A.2.17c. IR spectrum (thin film/NaCl) of compound **131b**

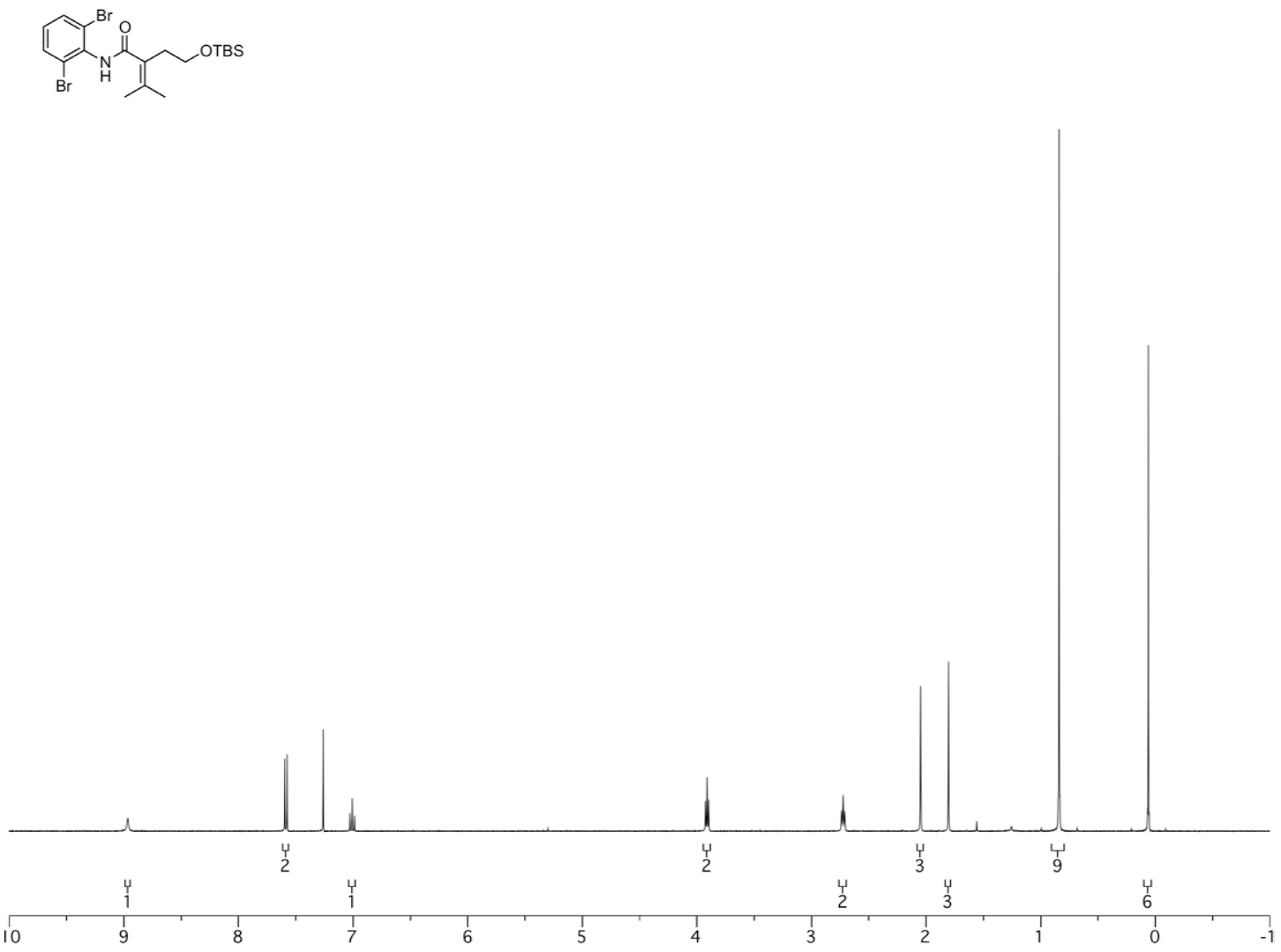


Figure A.2.18a. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **132**

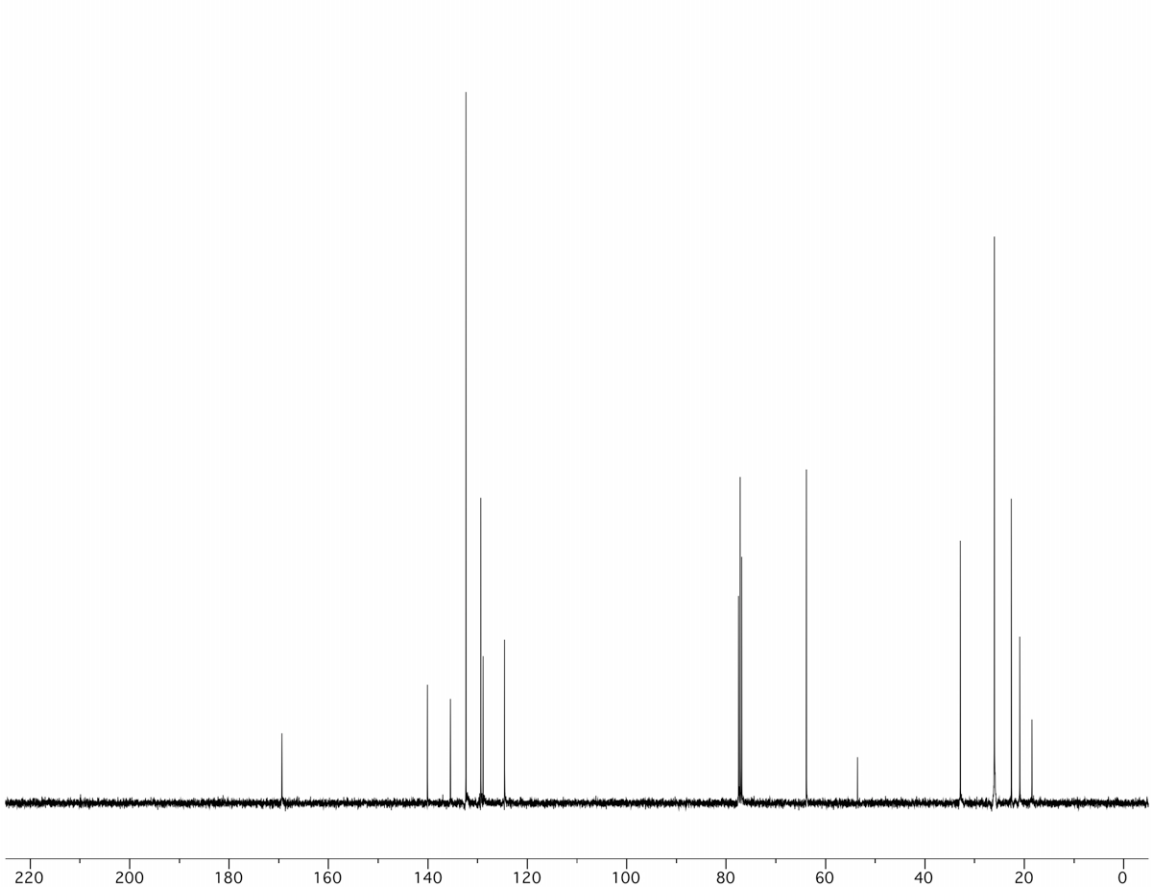


Figure A.2.18b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **132**

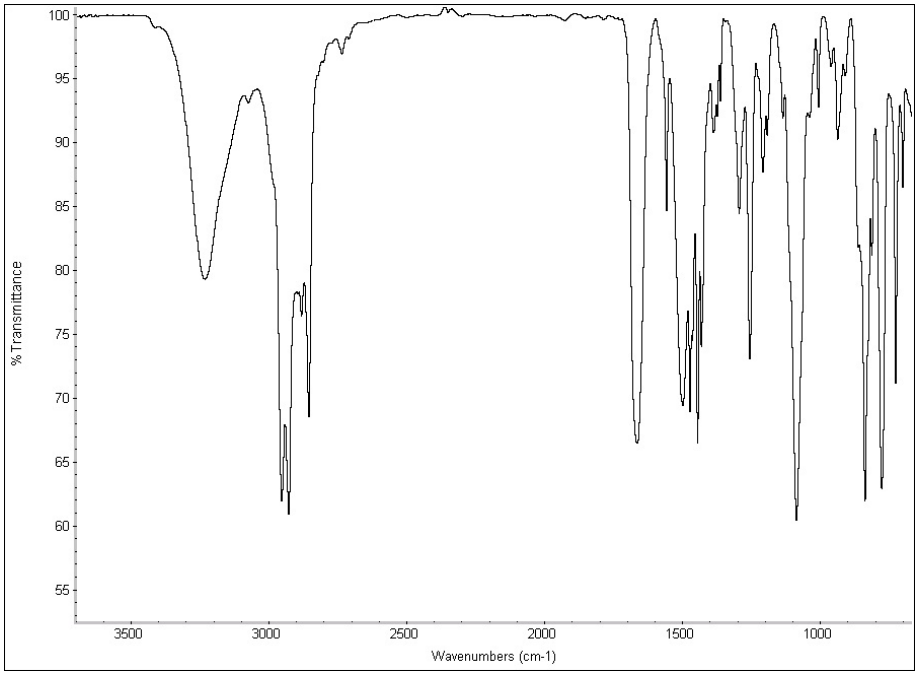


Figure A.2.18c. IR spectrum (thin film/NaCl) of compound **132**

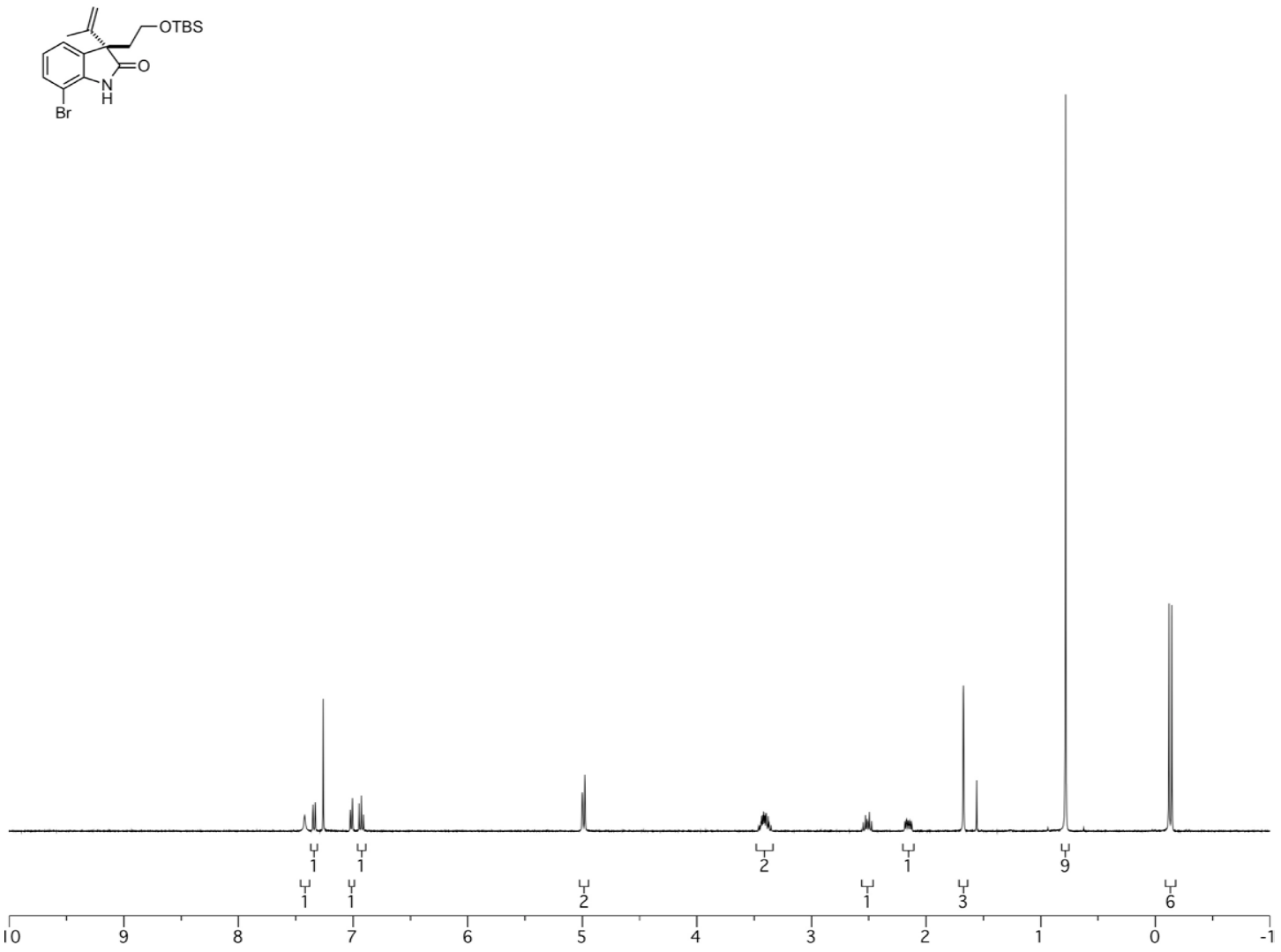


Figure A.2.19a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **133**

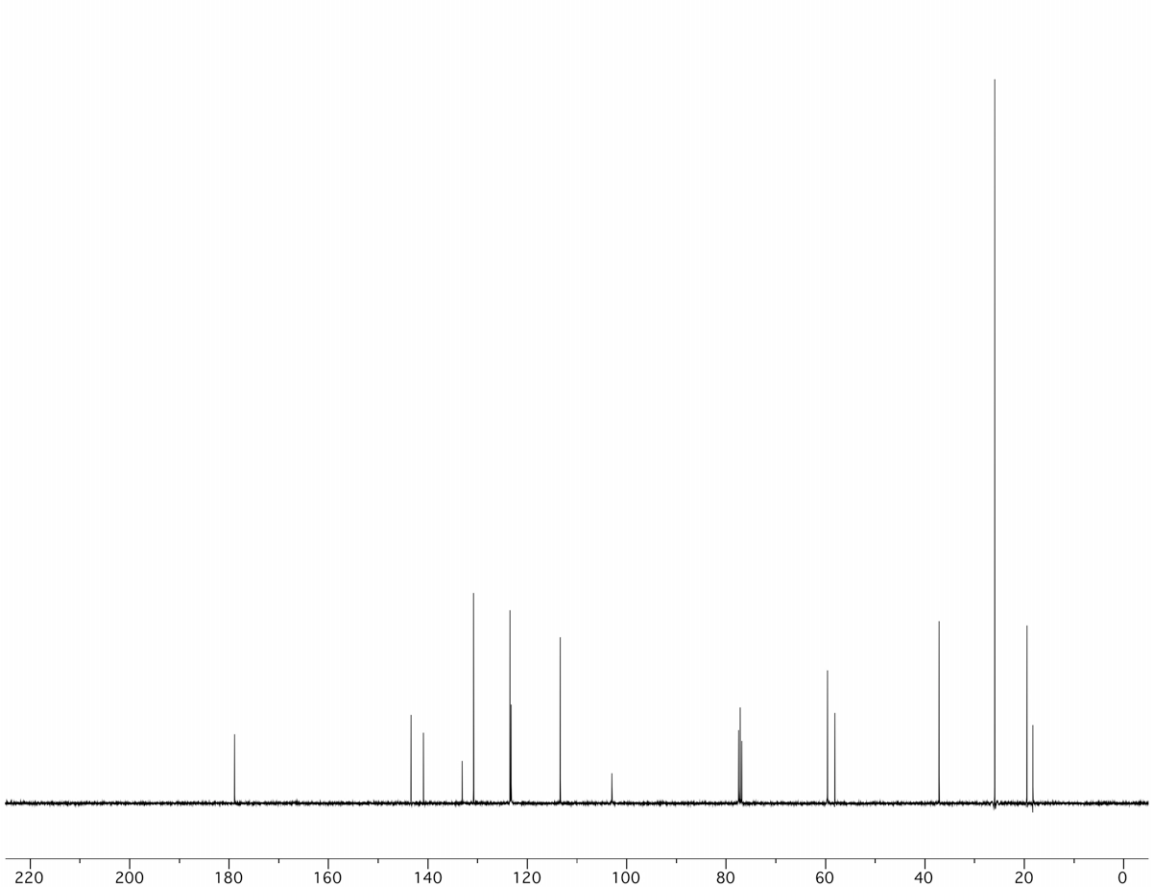


Figure A.2.19b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **133**

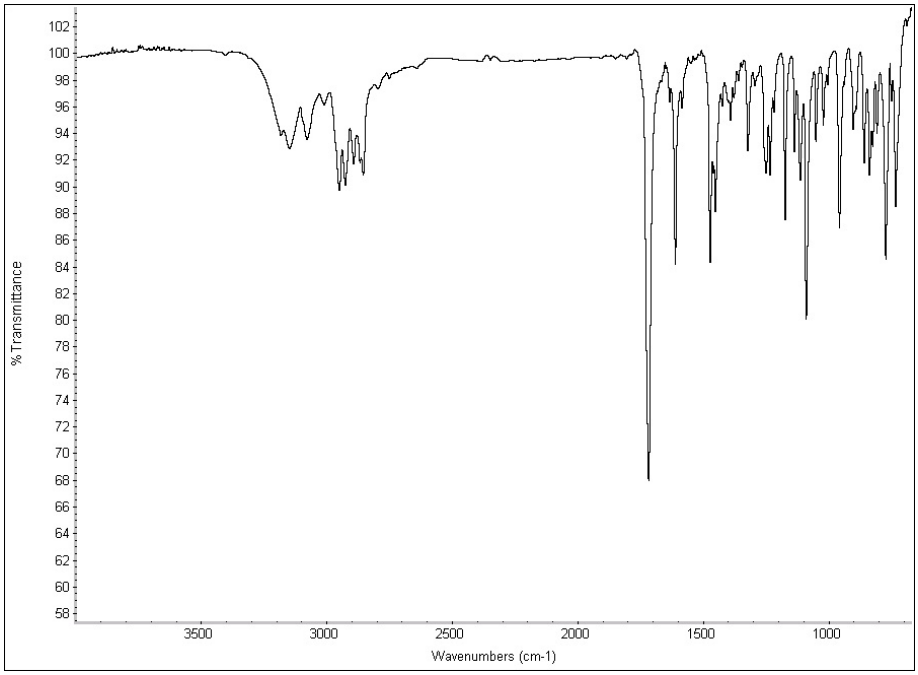


Figure A.2.19c. IR spectrum (thin film/NaCl) of compound **133**

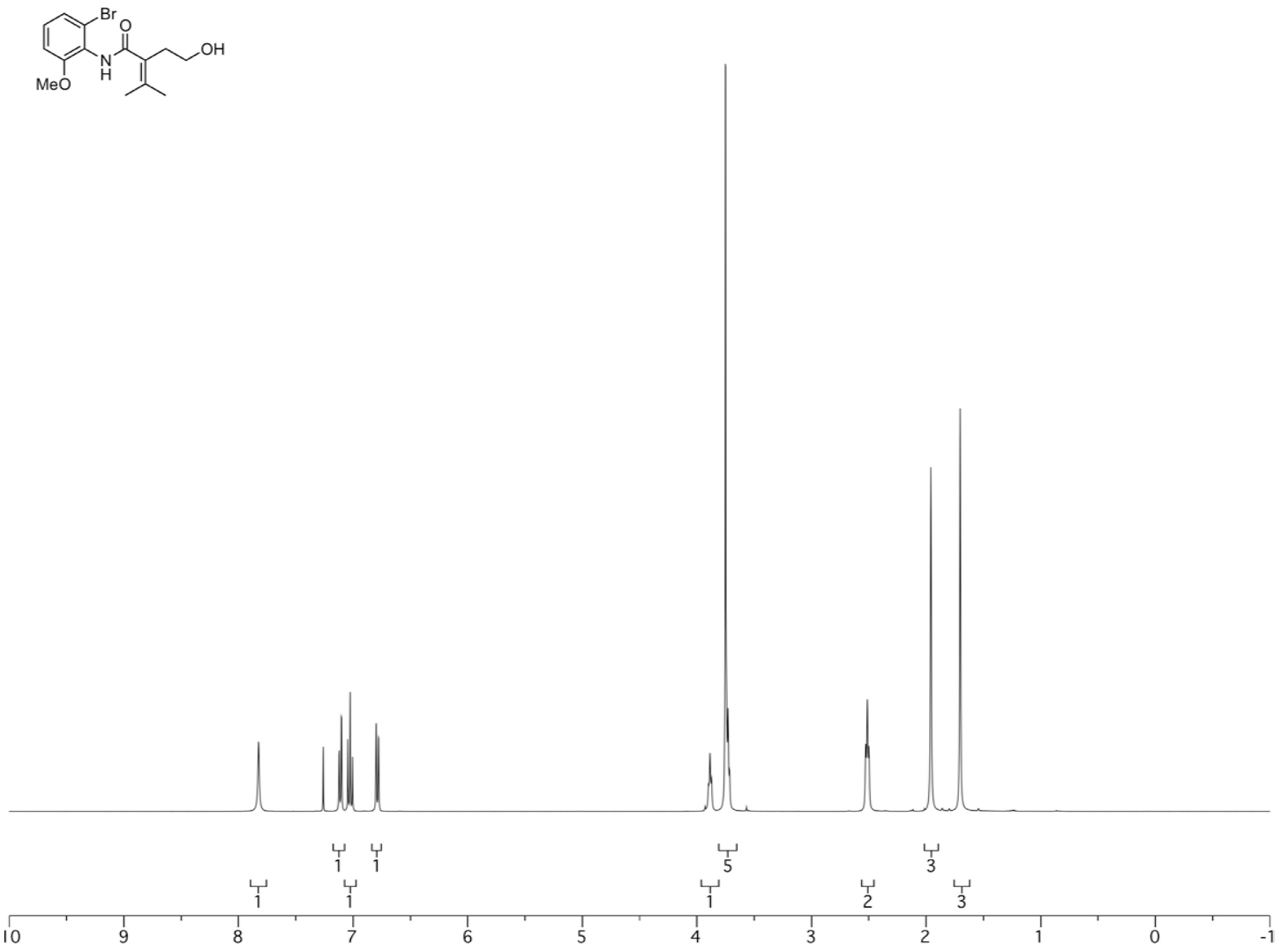


Figure A.2.20a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **137**

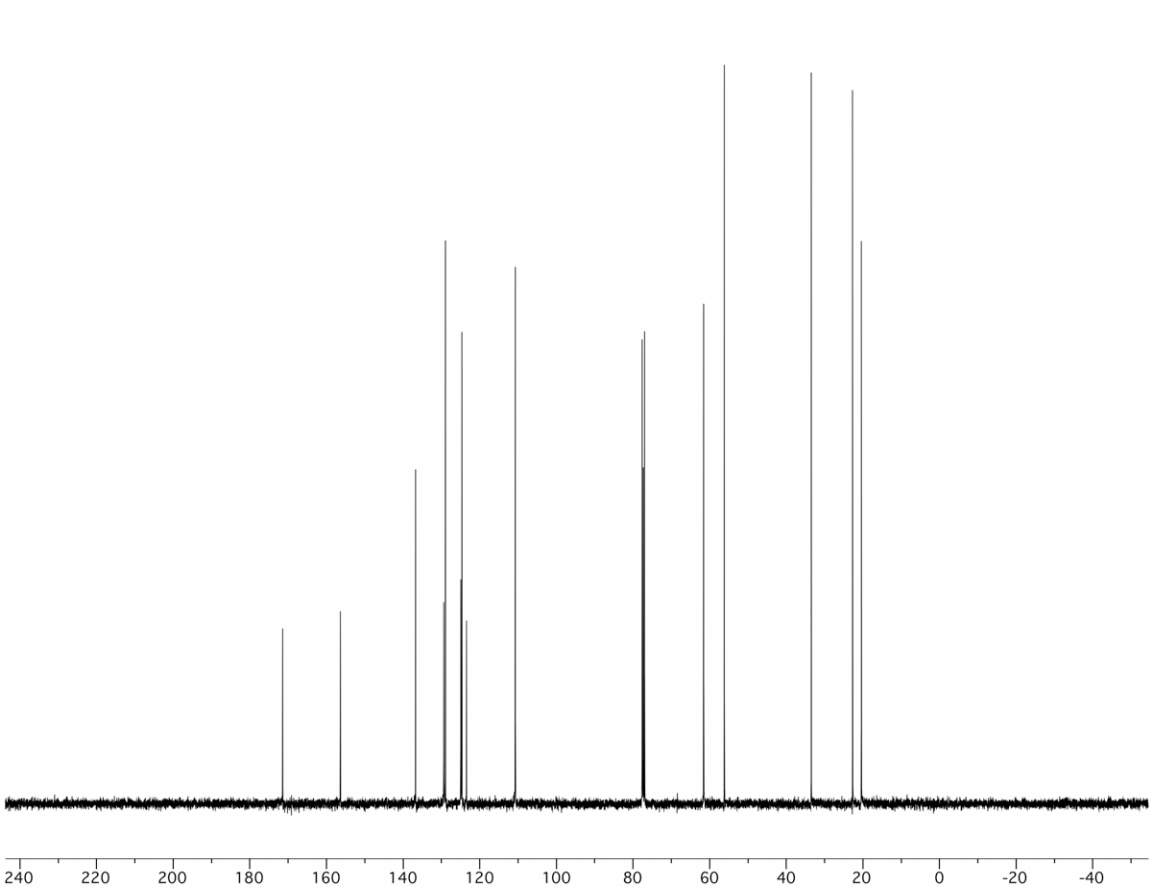


Figure A.2.20b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **137**

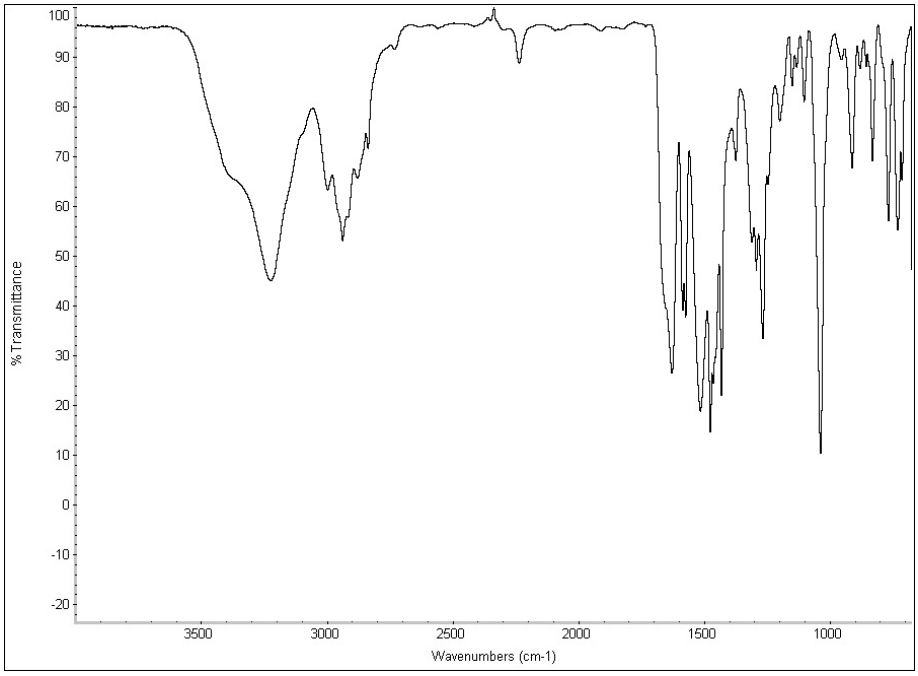


Figure A.2.20c. IR spectrum (thin film/NaCl) of compound **137**

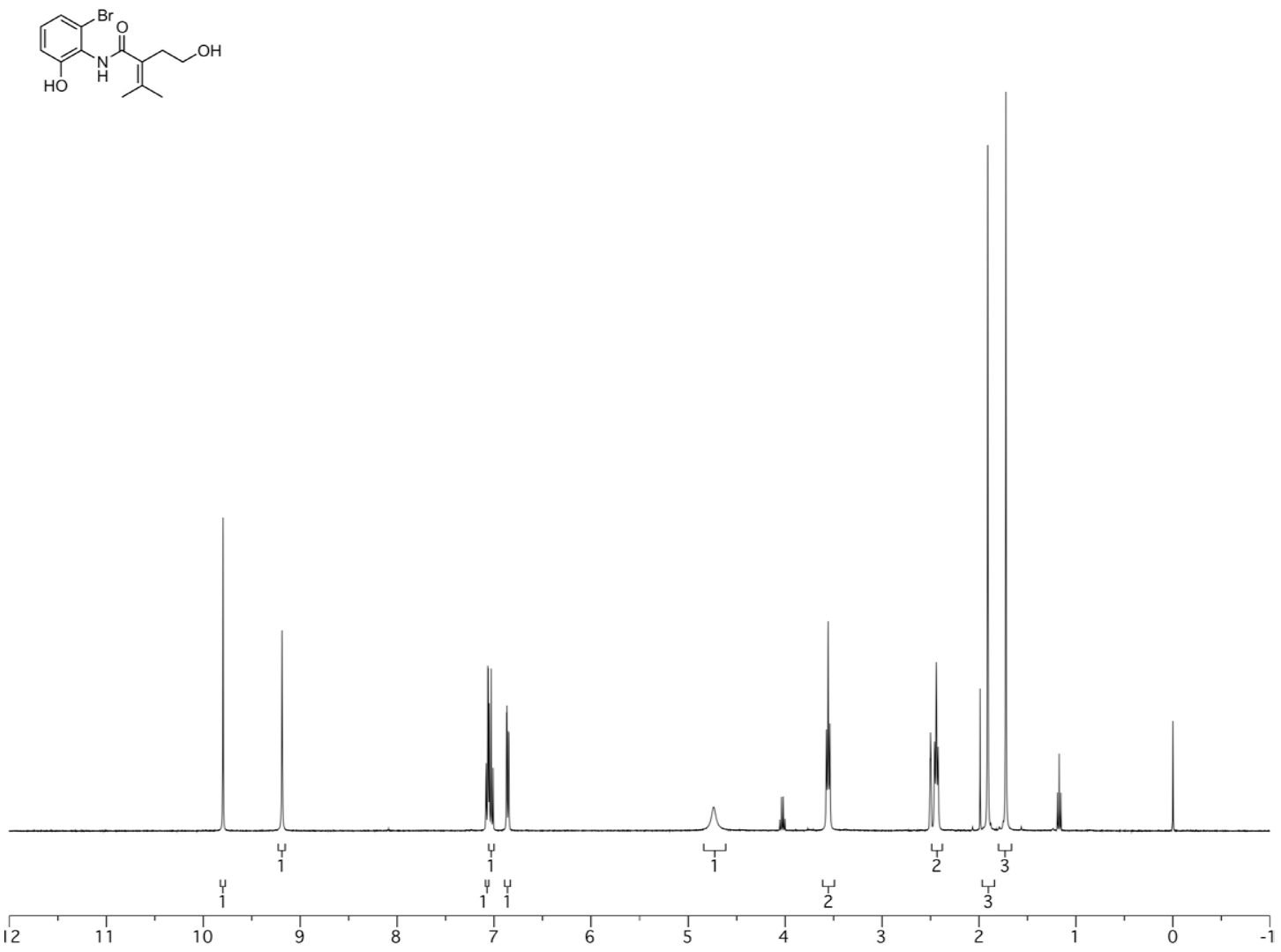


Figure A.2.21a. ^{1}H NMR spectrum (400 MHz, DMSO-d6) of compound **138**

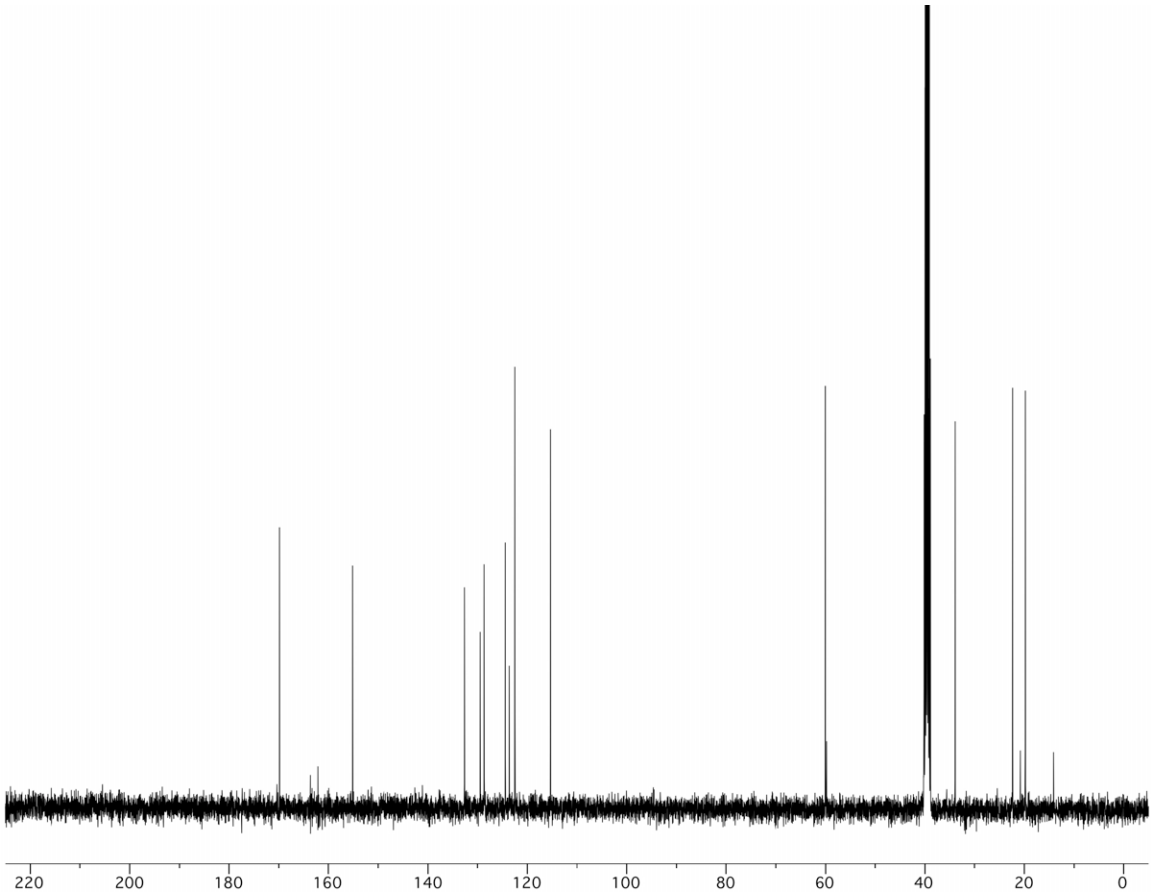


Figure A.2.21b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **138**

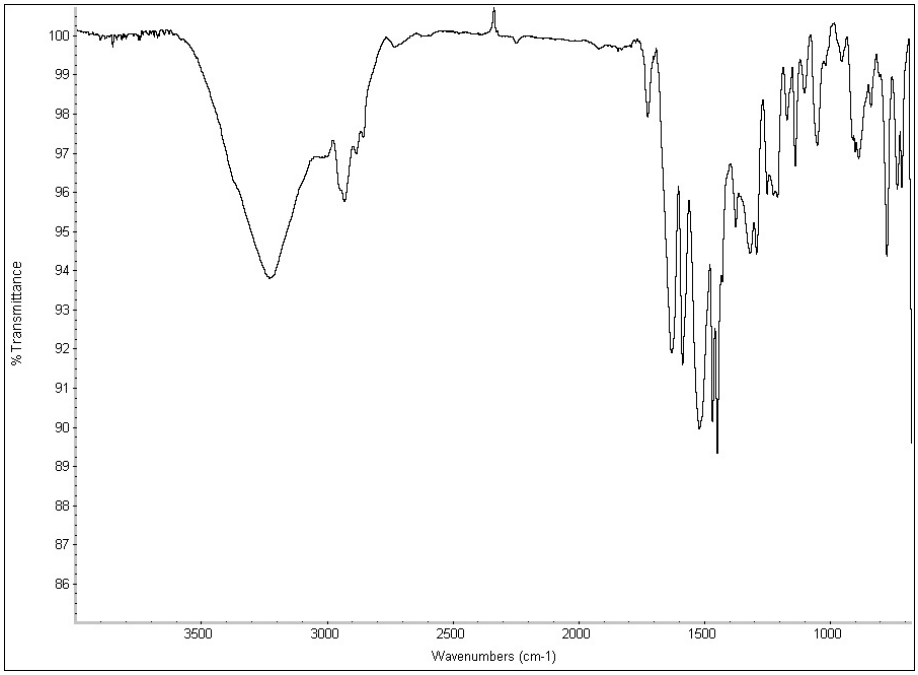


Figure A.2.21c. IR spectrum (thin film/NaCl) of compound **138**

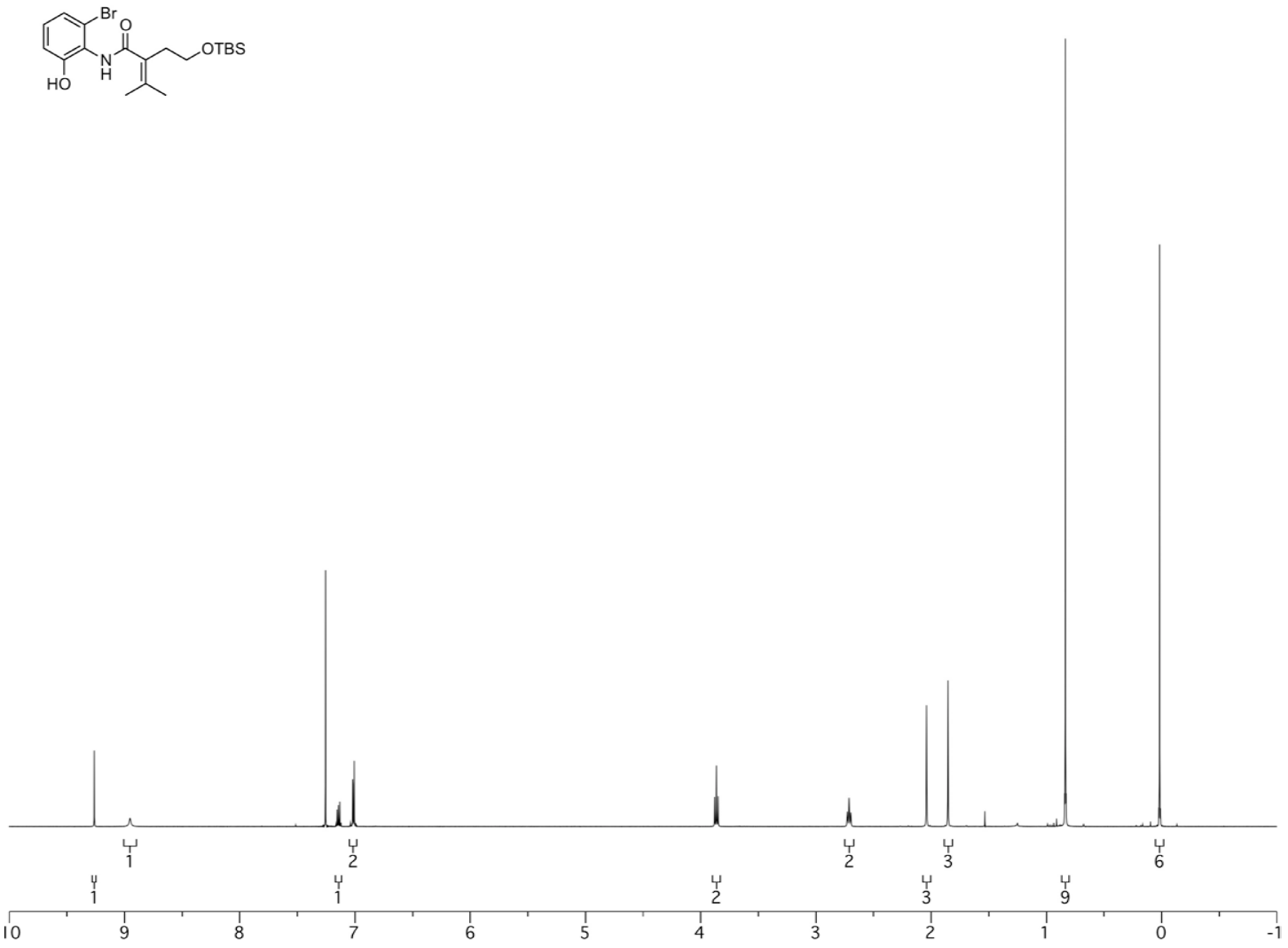


Figure A.2.22a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **139**

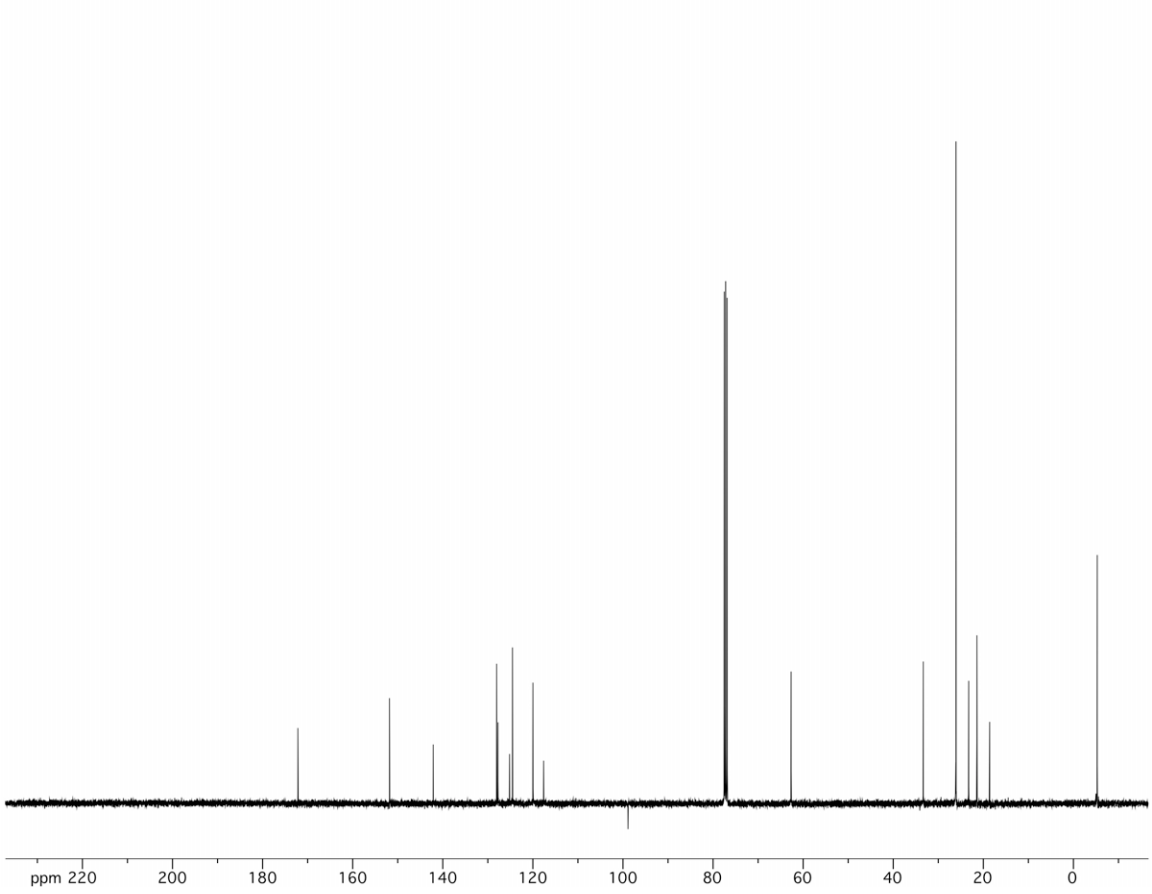


Figure A.2.22b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **139**

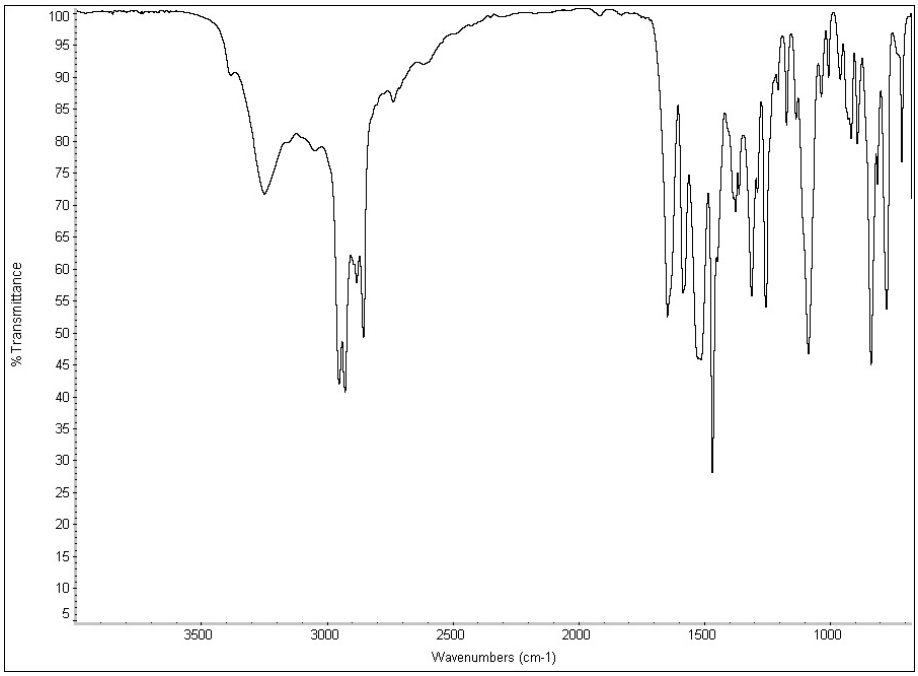


Figure A.2.22c. IR spectrum (thin film/NaCl) of compound **139**

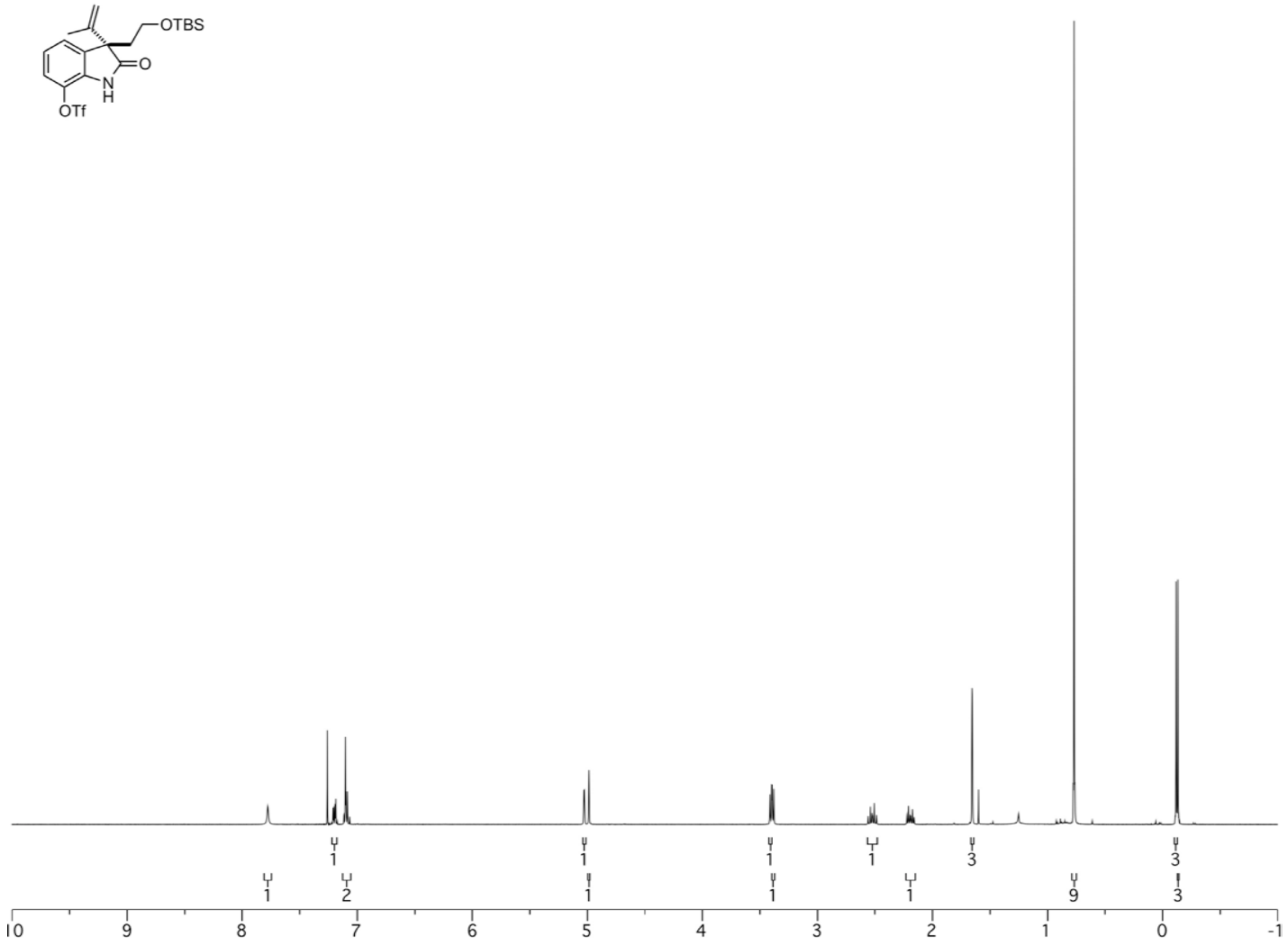


Figure A.2.23a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **140**

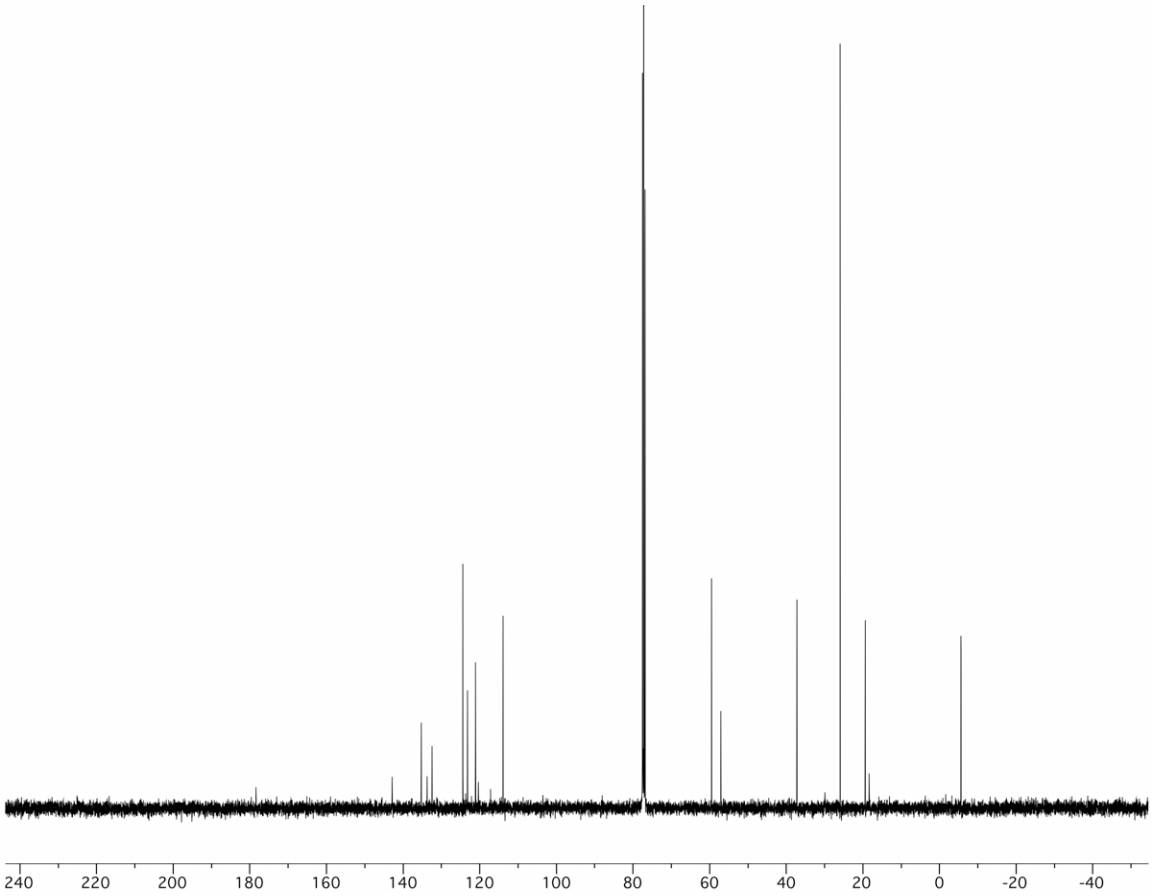


Figure A.2.23b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **140**

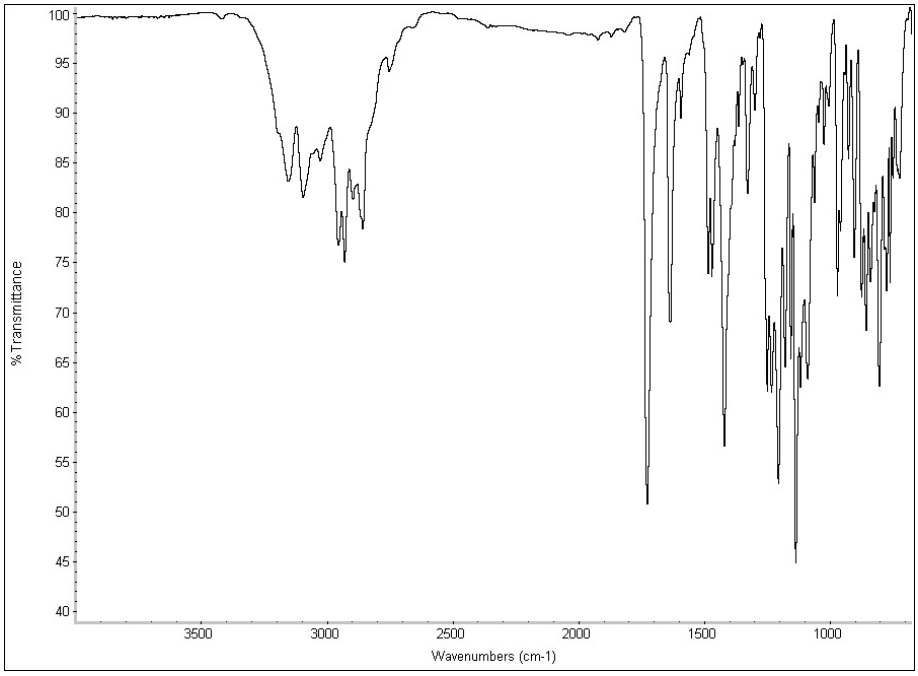


Figure A.2.23c. IR spectrum (thin film/NaCl) of compound **140**

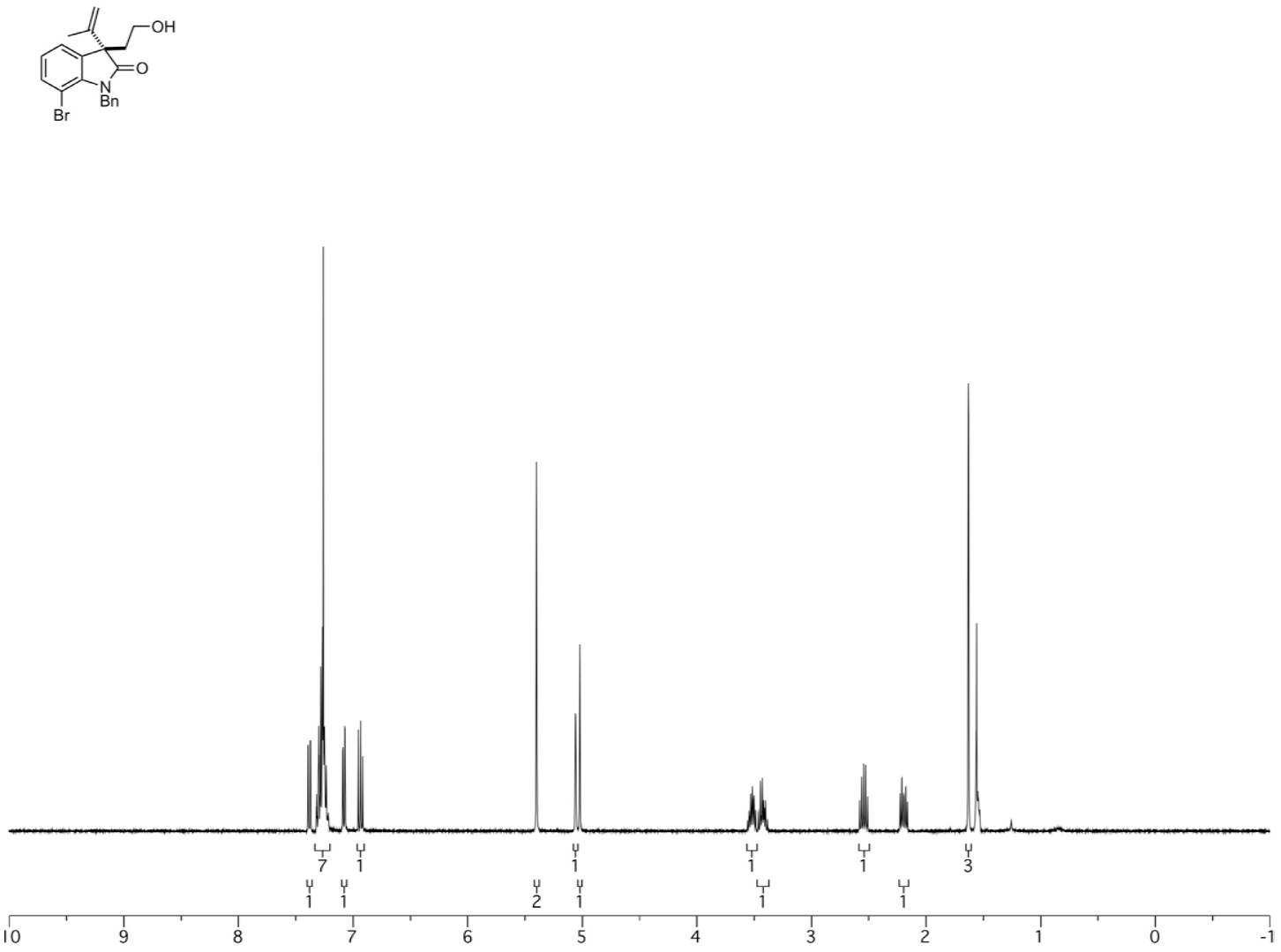


Figure A.2.24a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **141**

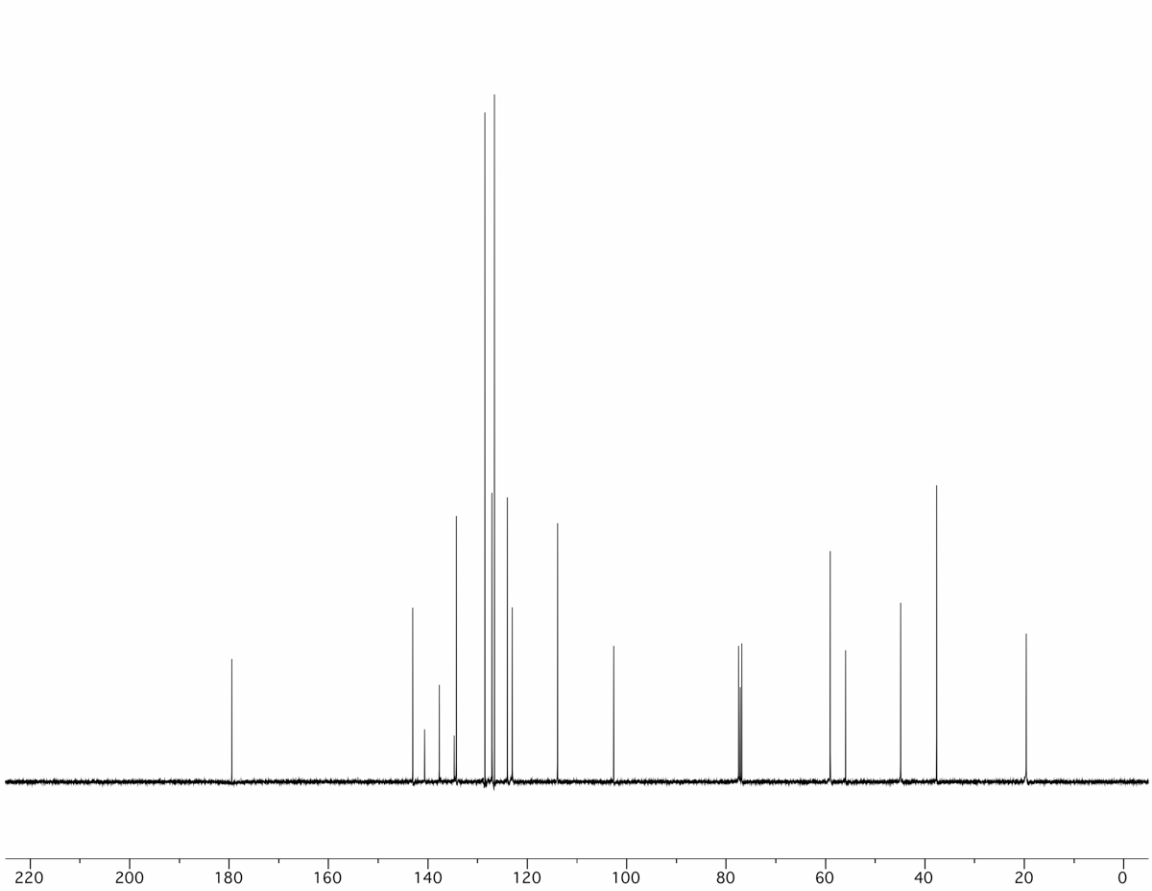


Figure A.2.24b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **141**

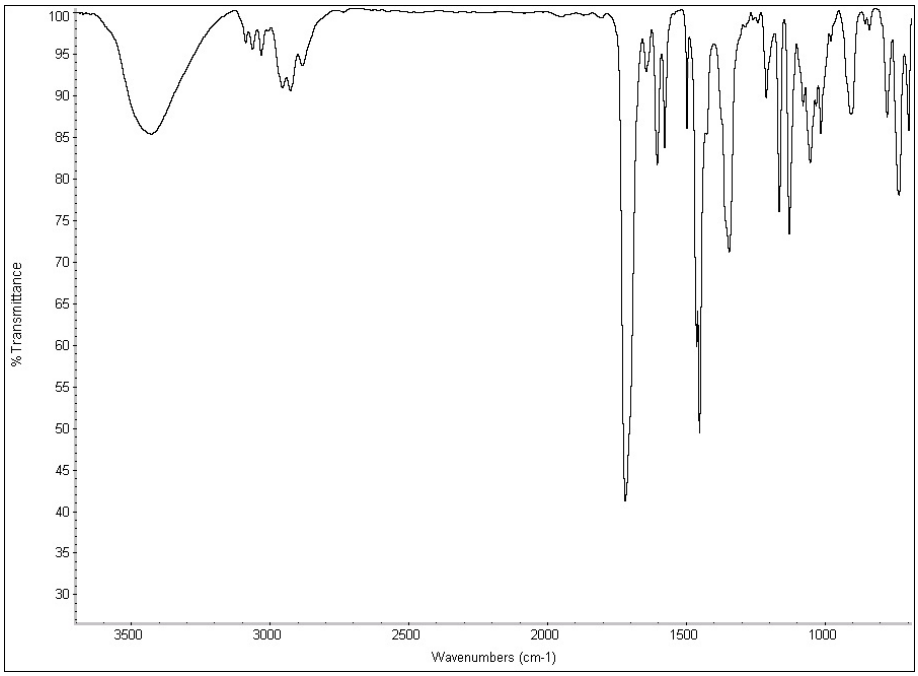


Figure A.2.24c. IR spectrum (thin film/NaCl) of compound **141**

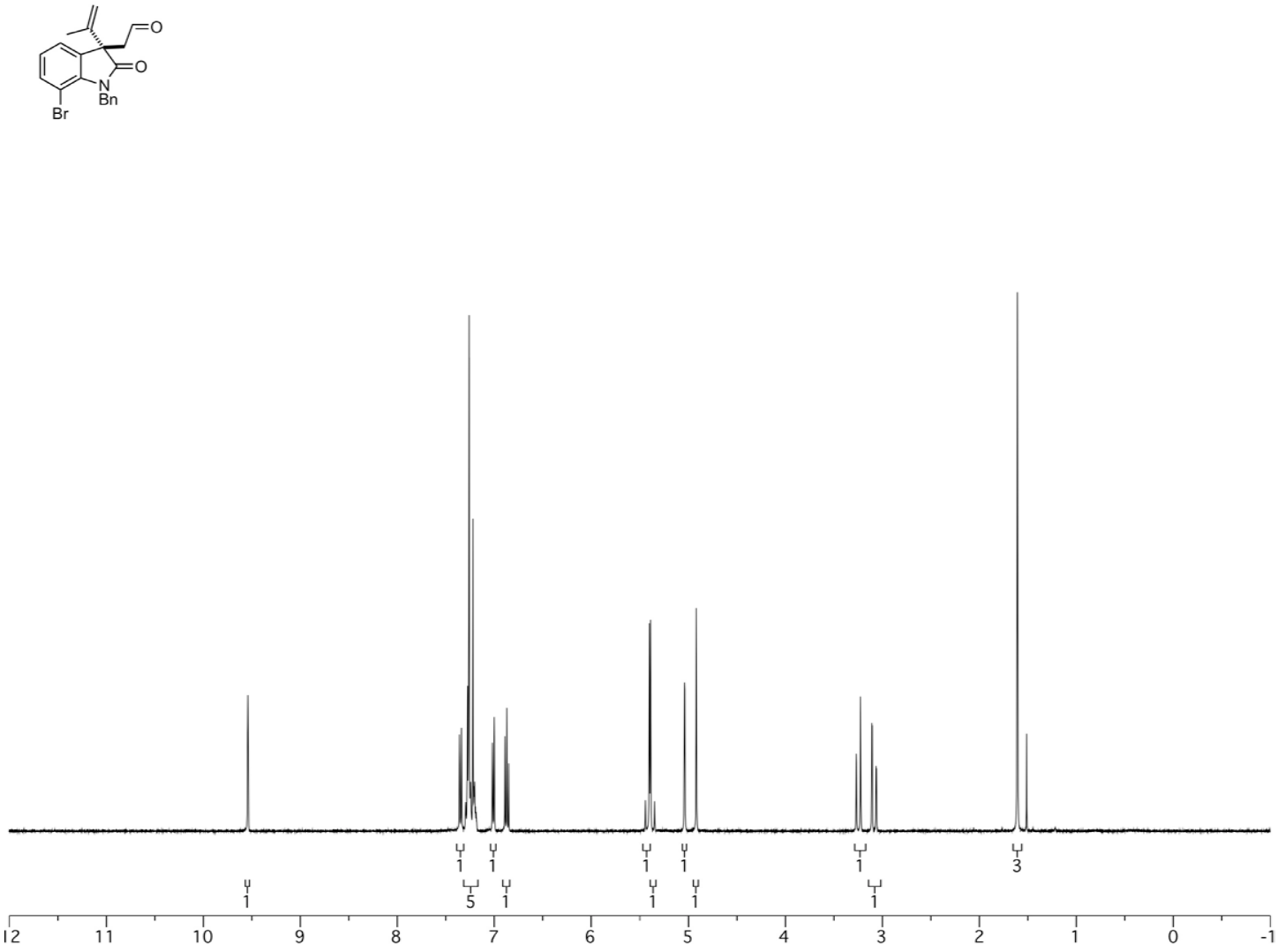


Figure A.2.25a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **142**

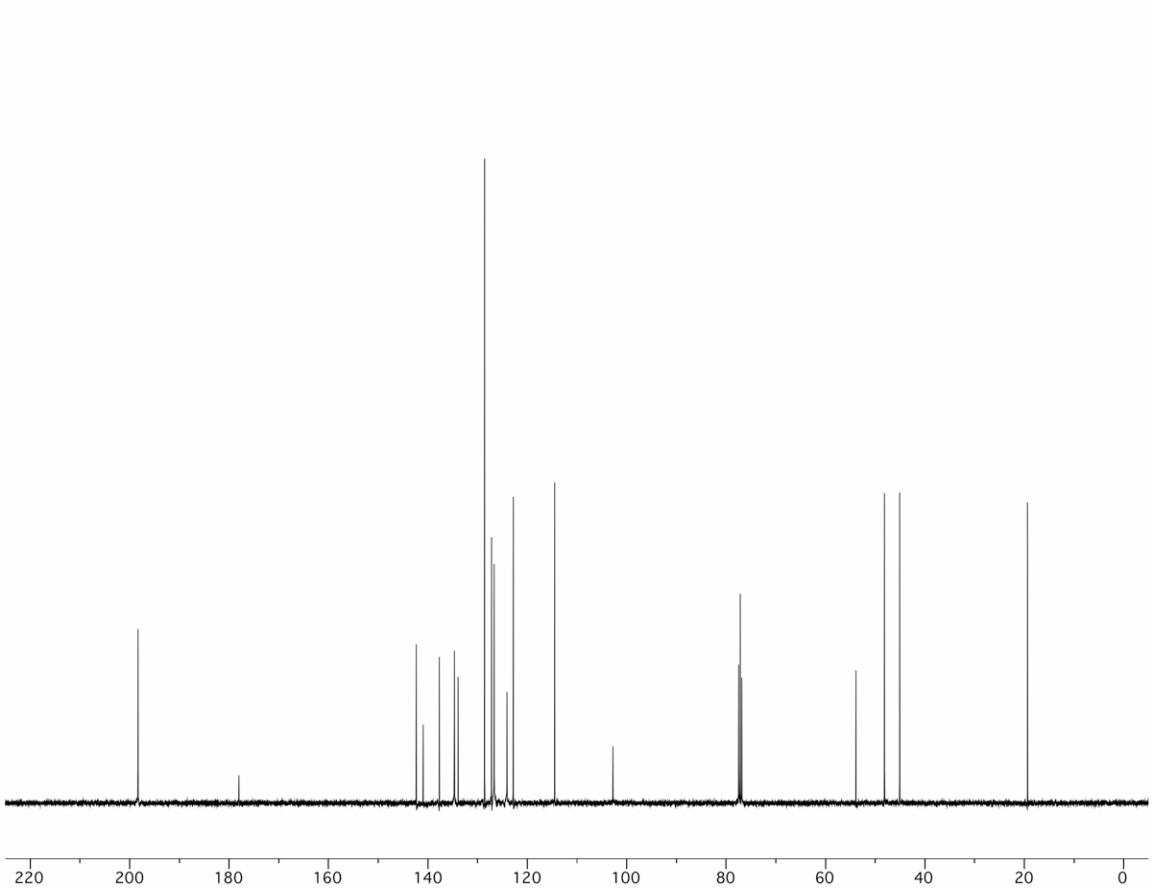


Figure A.2.25b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **142**

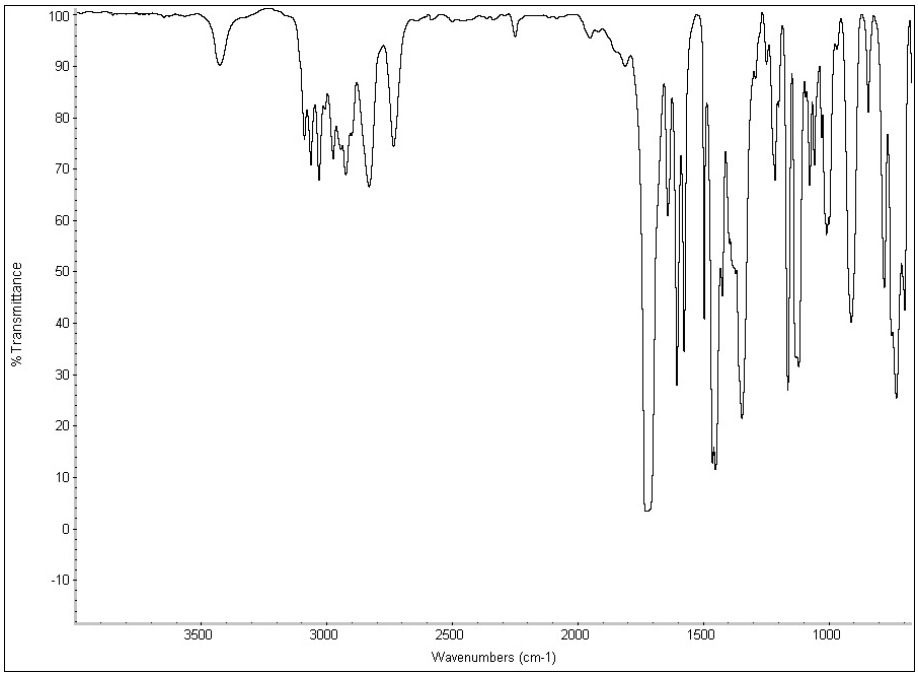


Figure A.2.25c. IR spectrum (thin film/NaCl) of compound **142**

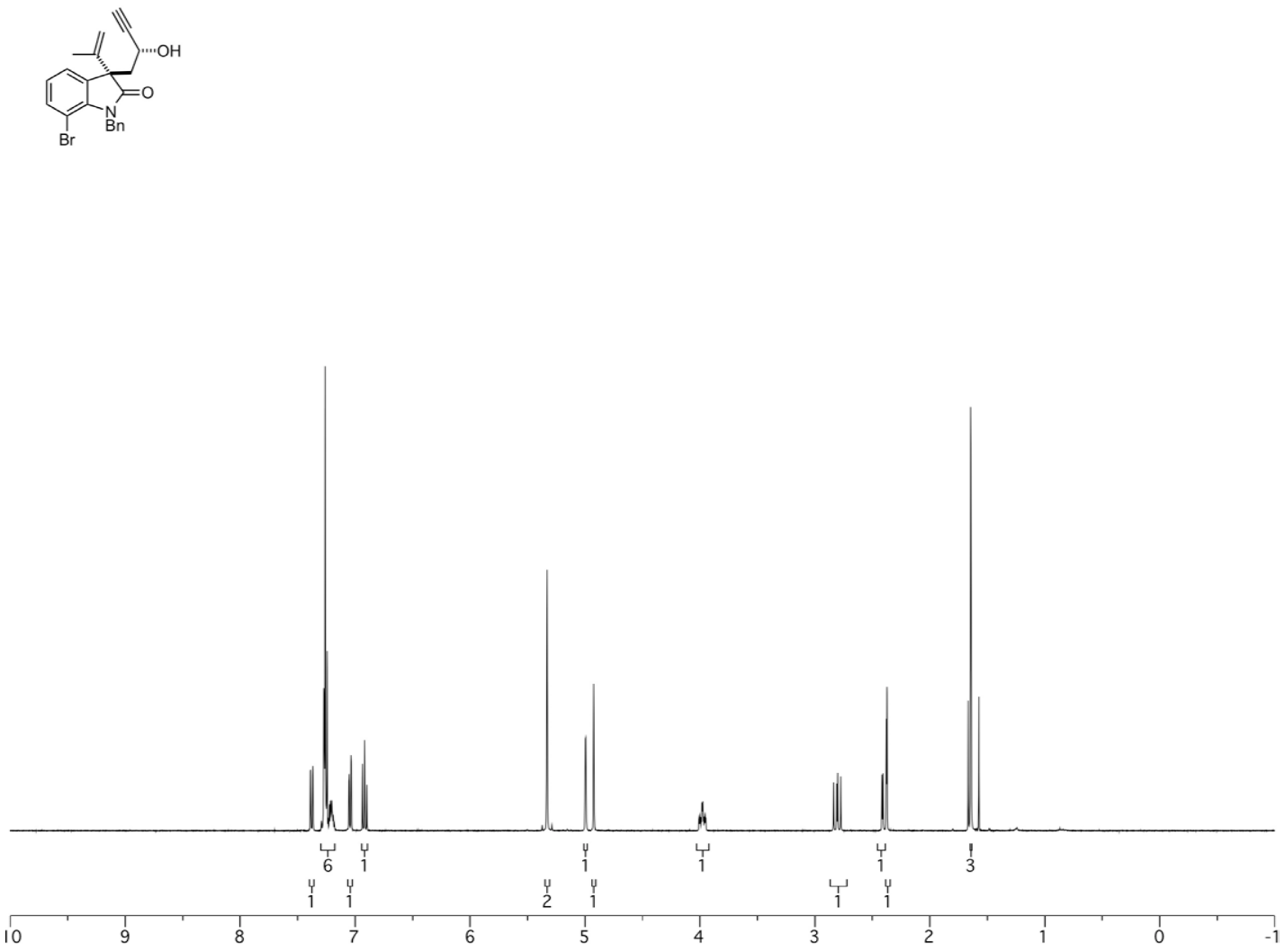


Figure A.2.26a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **143a**

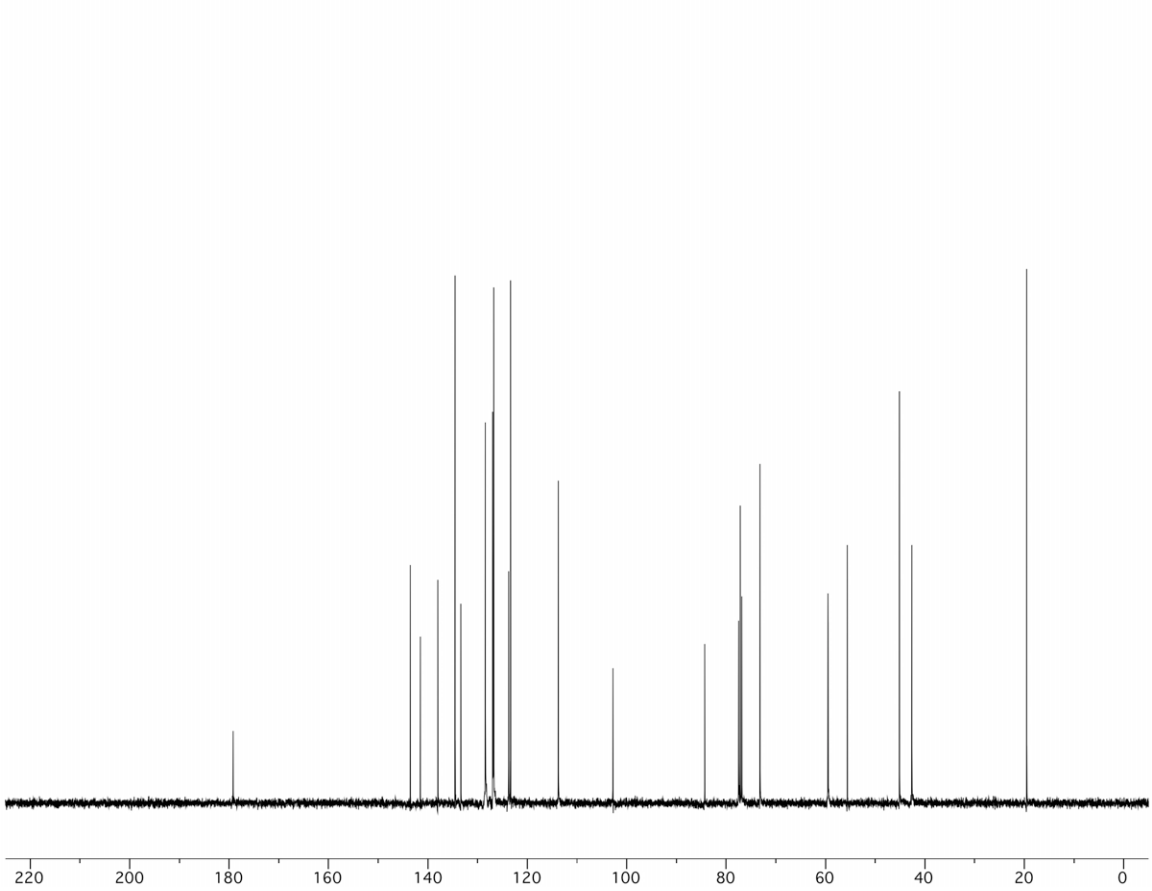


Figure A.2.26b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **143a**

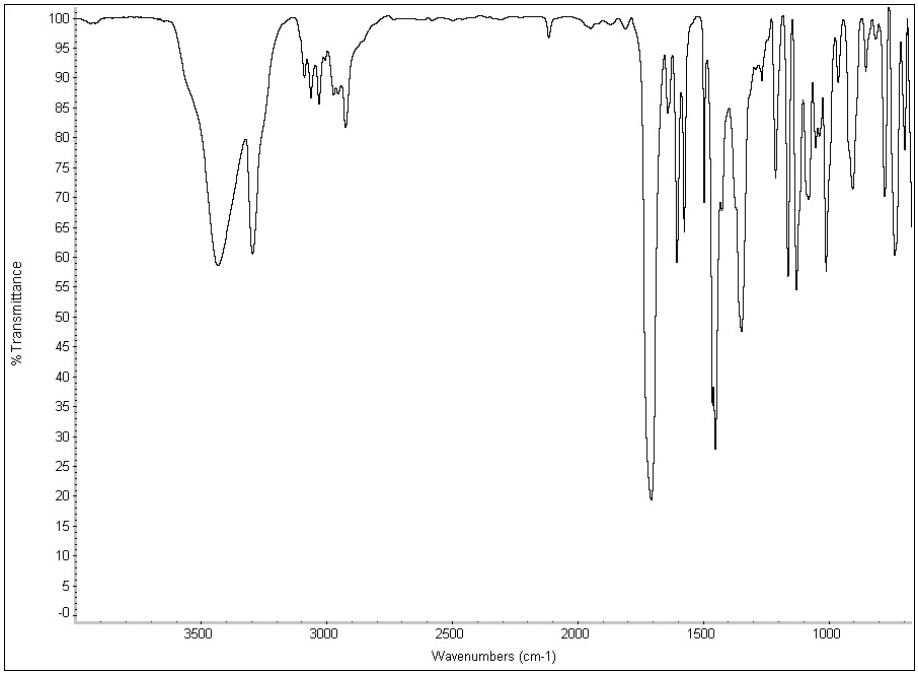


Figure A.2.26c. IR spectrum (thin film/NaCl) of compound **143a**

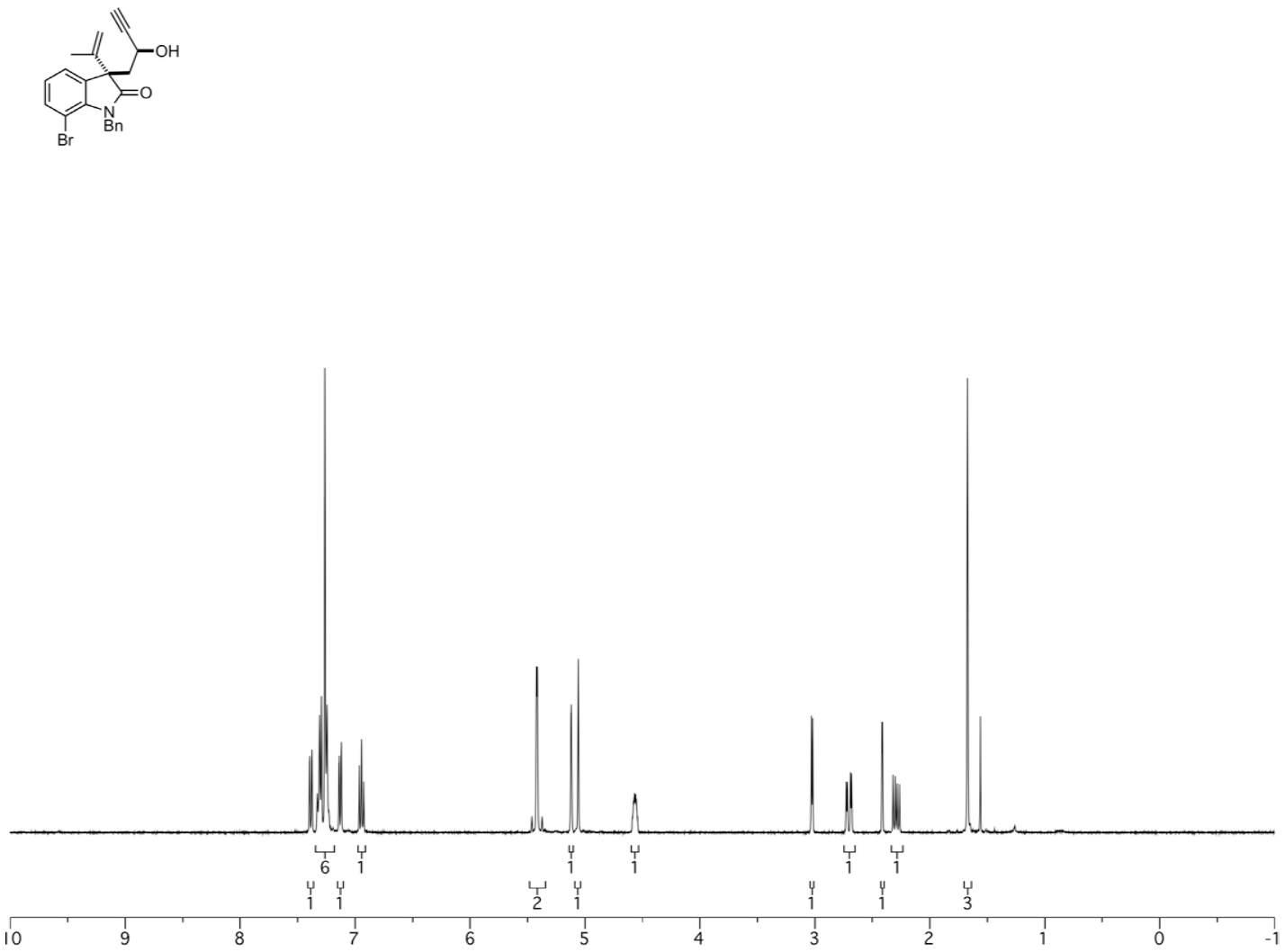


Figure A.2.27a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **143b**

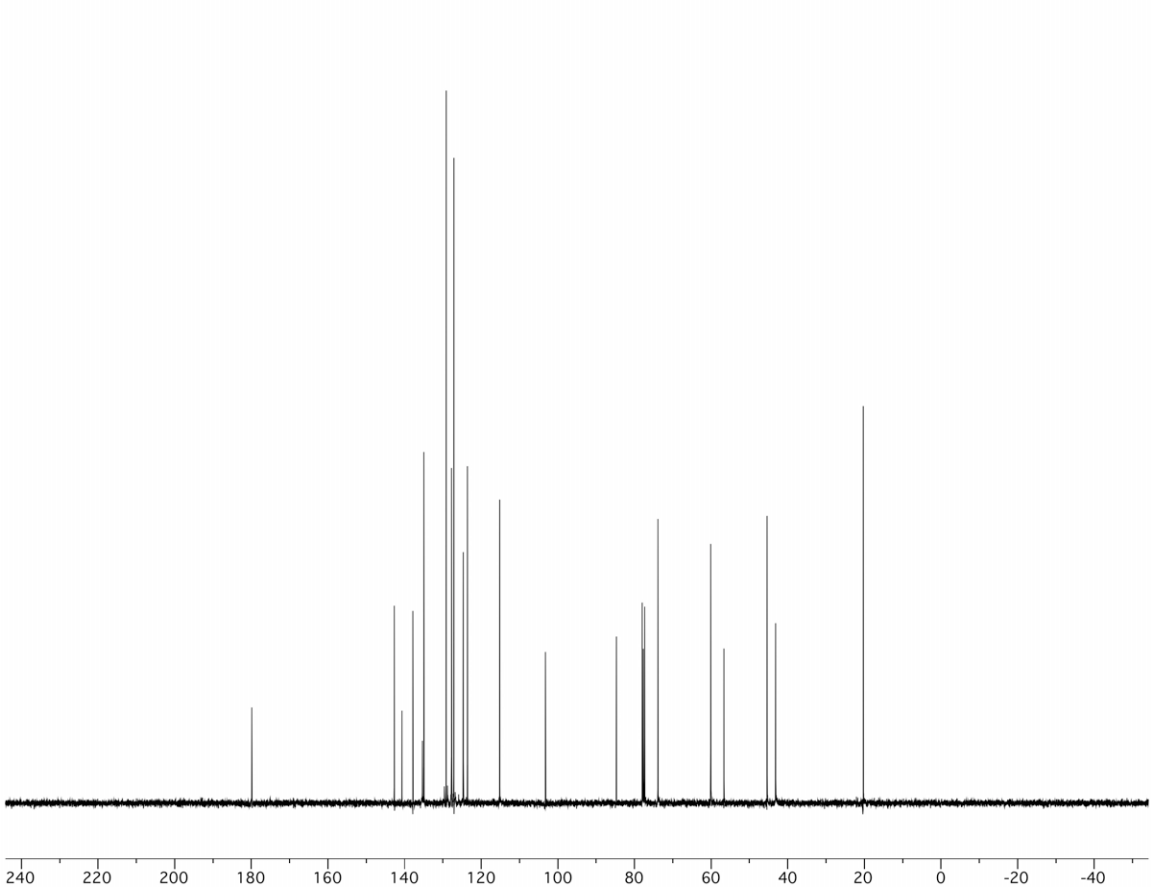


Figure A.2.27b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **143b**

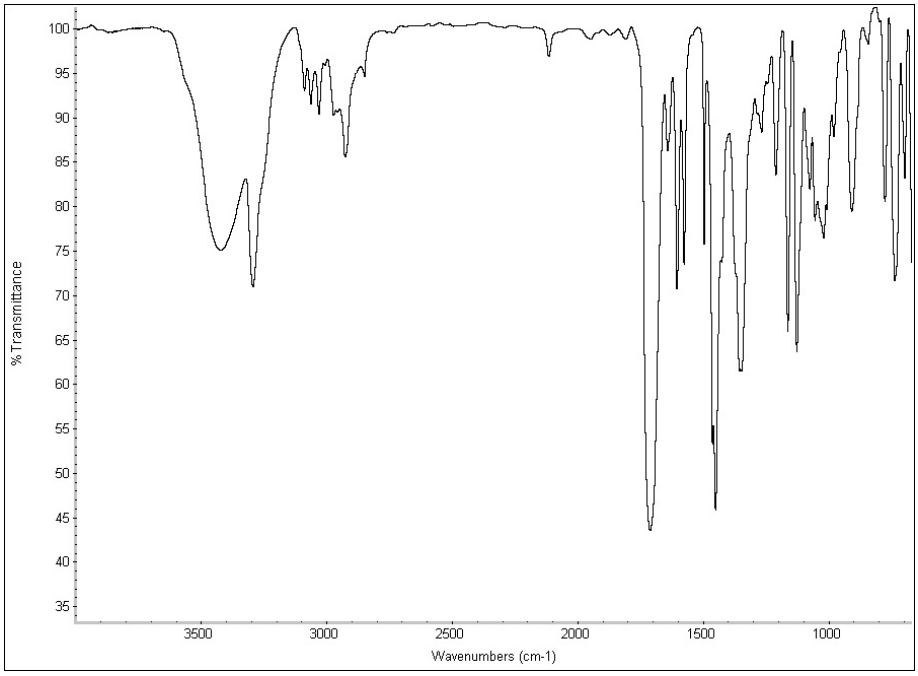


Figure A.2.27c. IR spectrum (thin film/NaCl) of compound **143b**

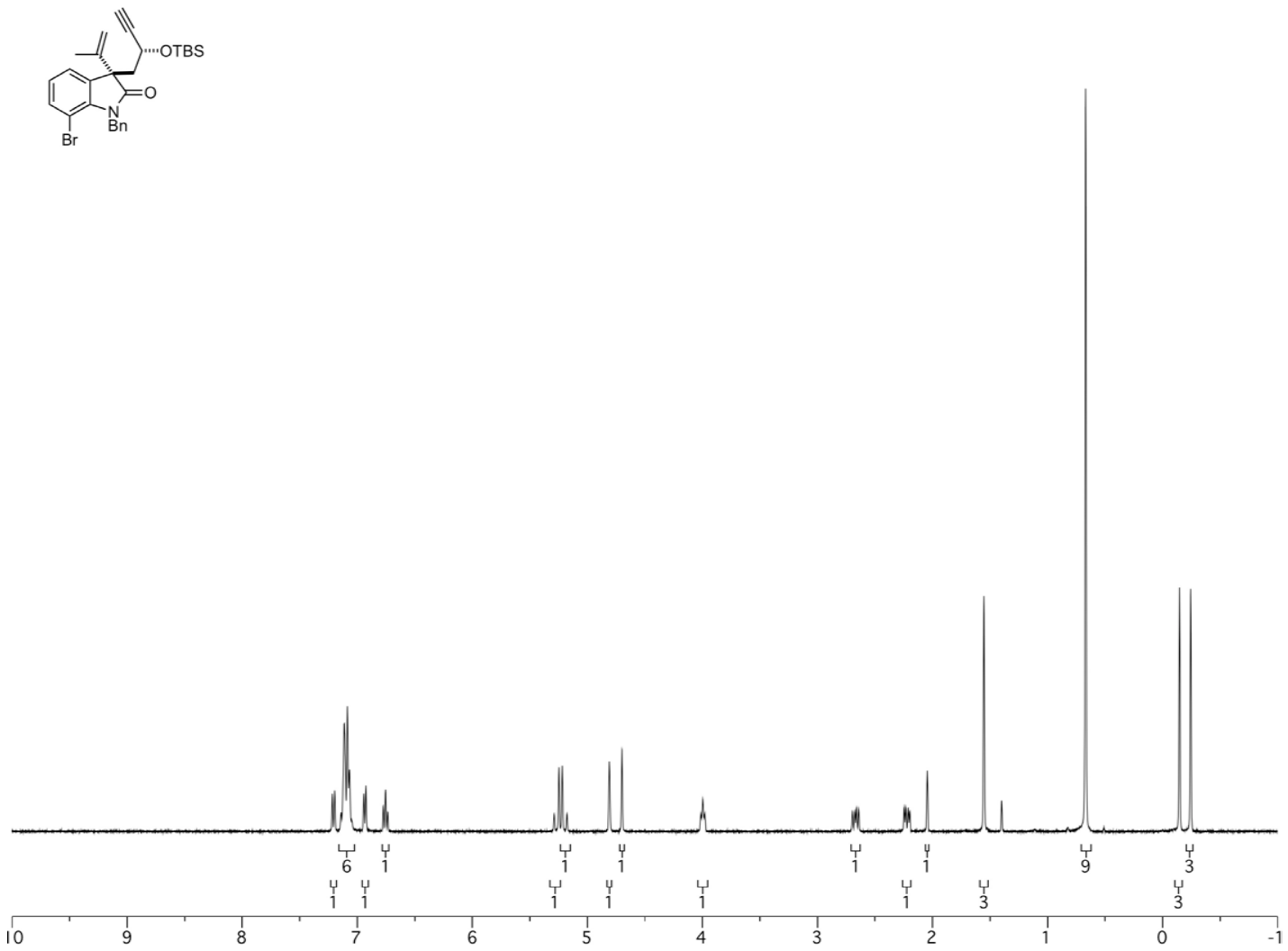


Figure A.2.28a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **144a**

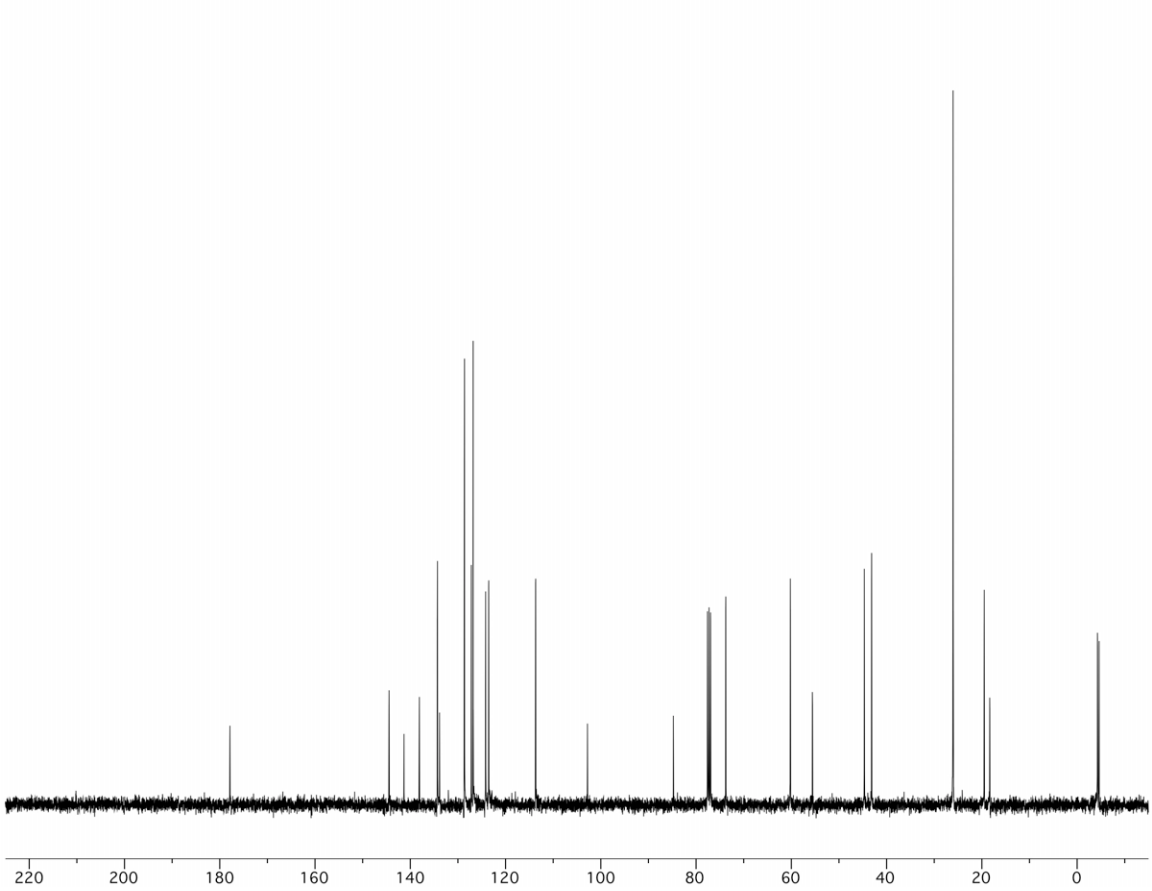


Figure A.2.28b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **144a**

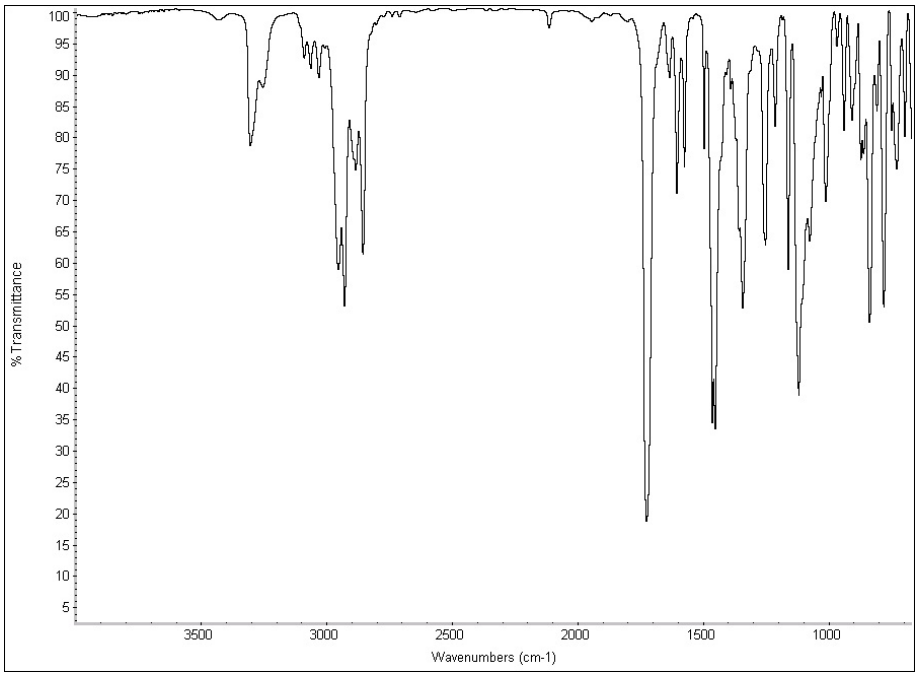


Figure A.2.28c. IR spectrum (thin film/NaCl) of compound **144a**

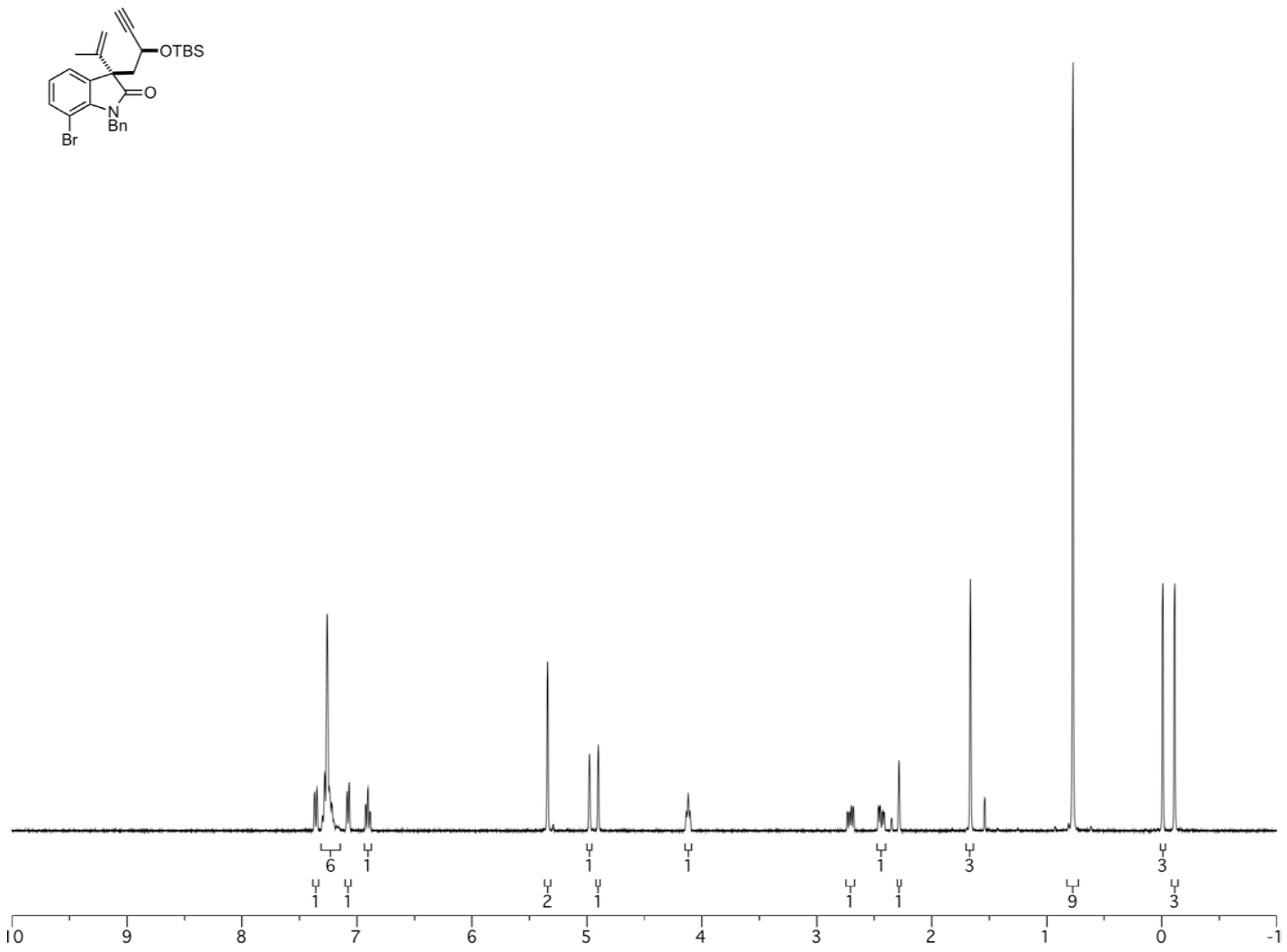


Figure A.2.29a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **144b**

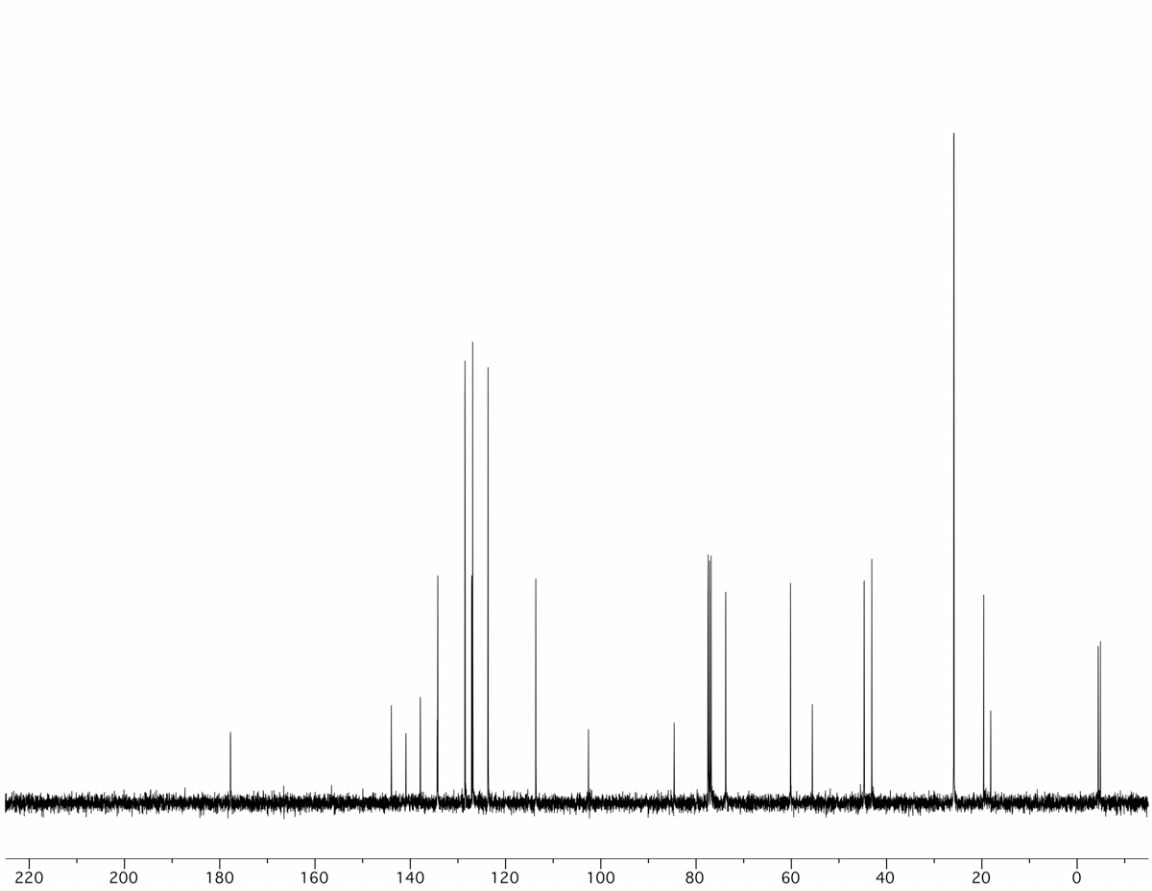


Figure A.2.29b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **144b**

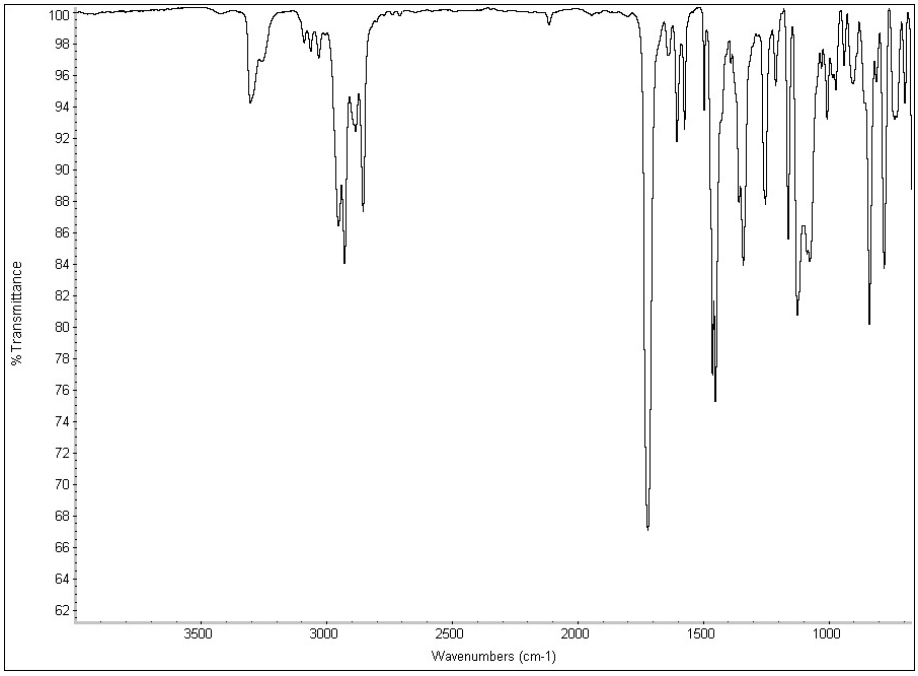


Figure A.2.29c. IR spectrum (thin film/NaCl) of compound **144b**

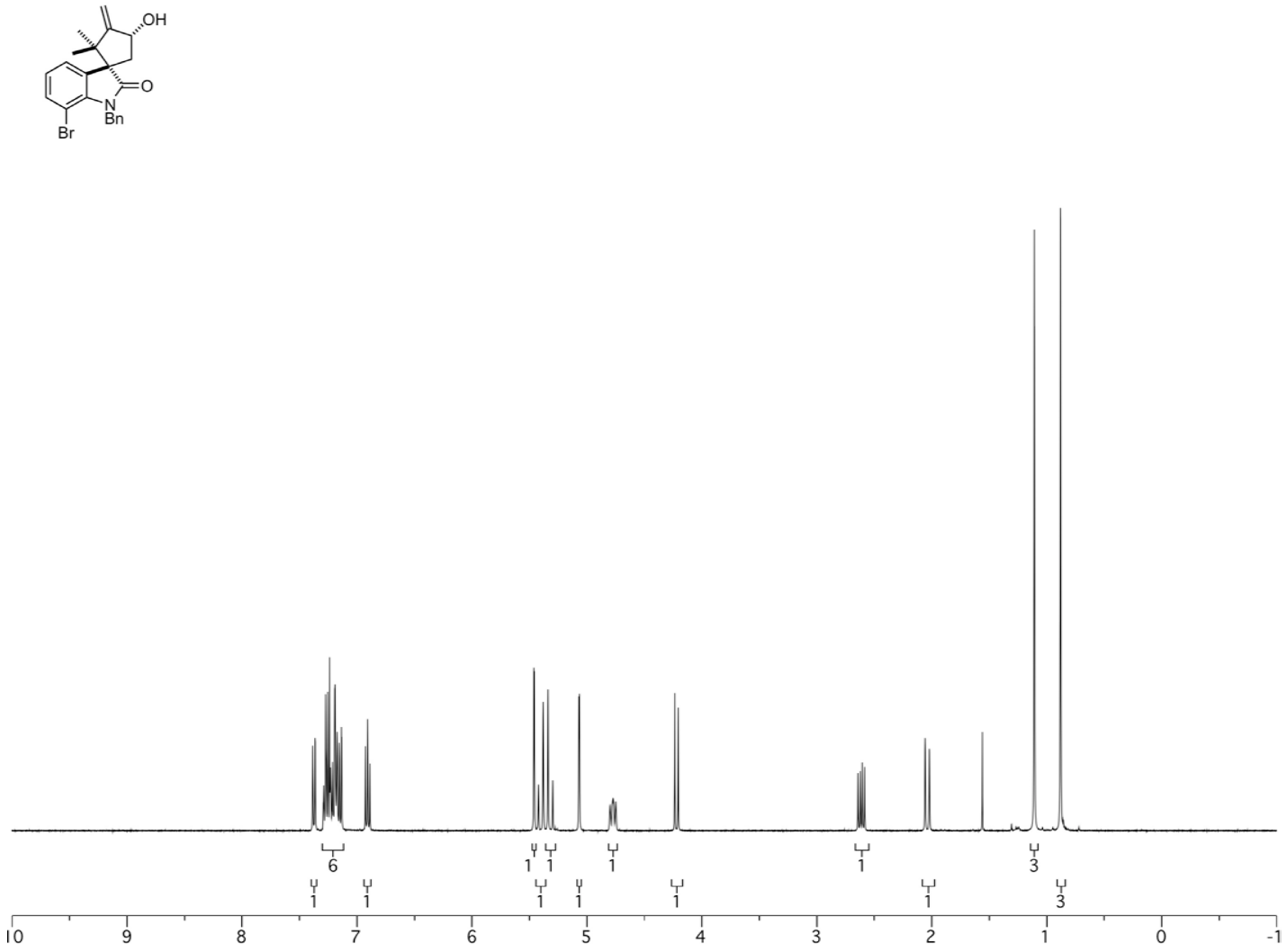


Figure A.2.30a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **146a**

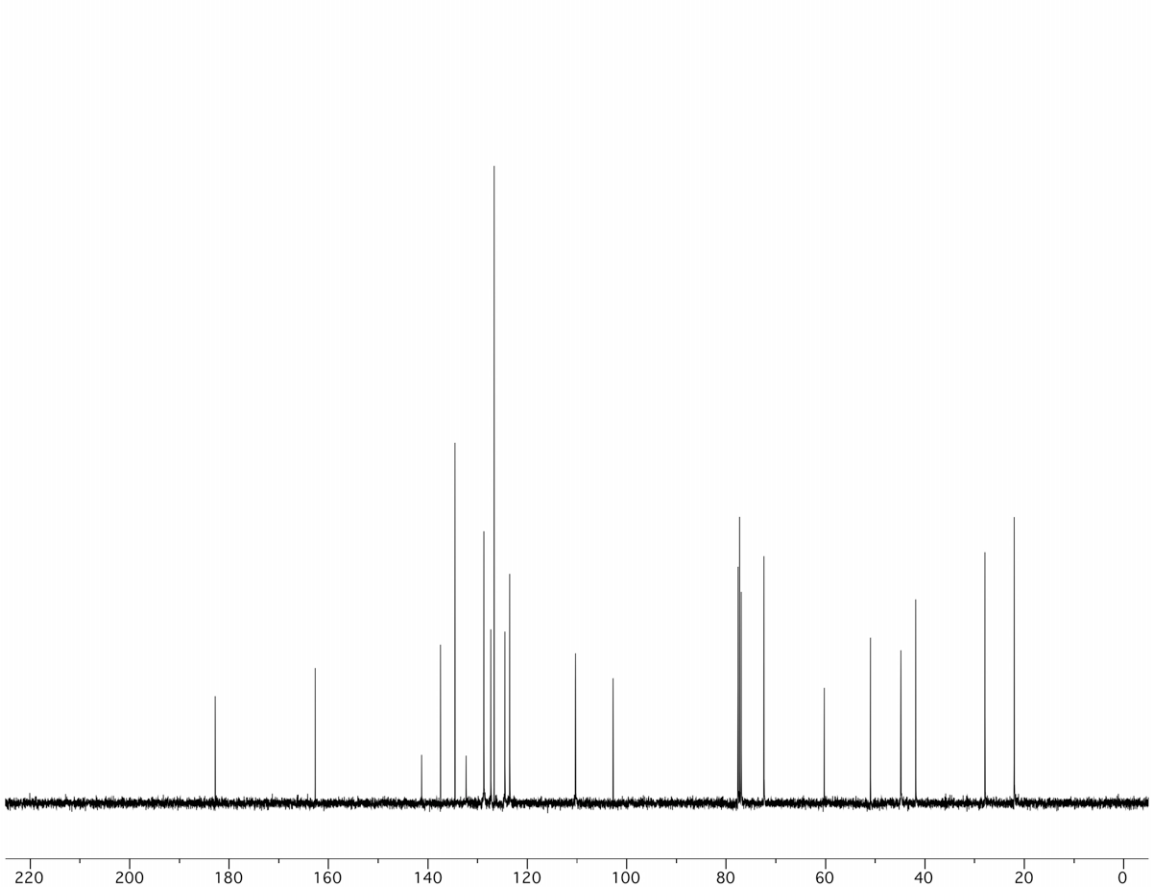


Figure A.2.30b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **146a**

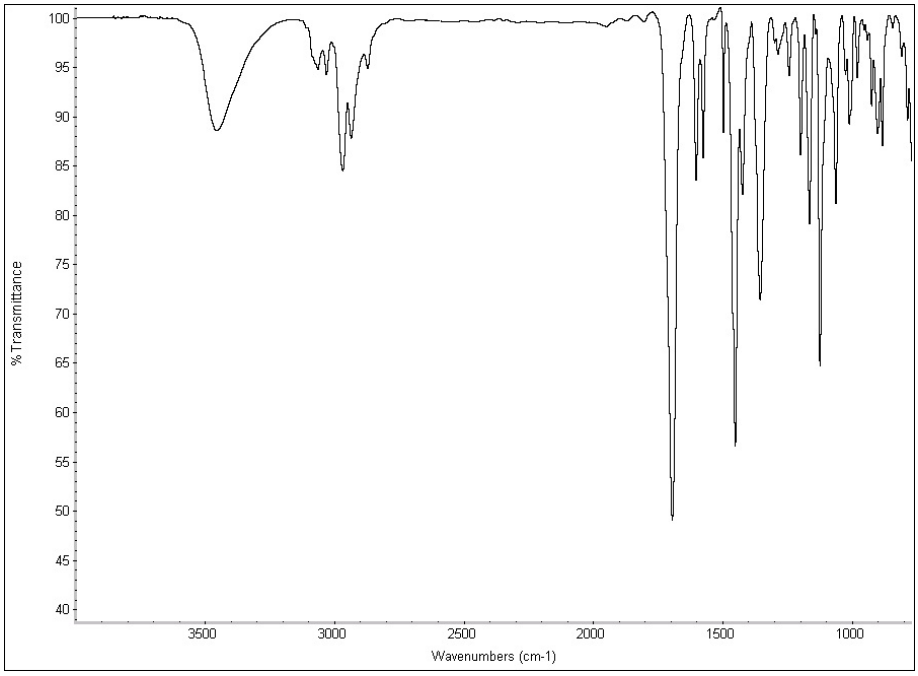


Figure A.2.30c. IR spectrum (thin film/NaCl) of compound **146a**

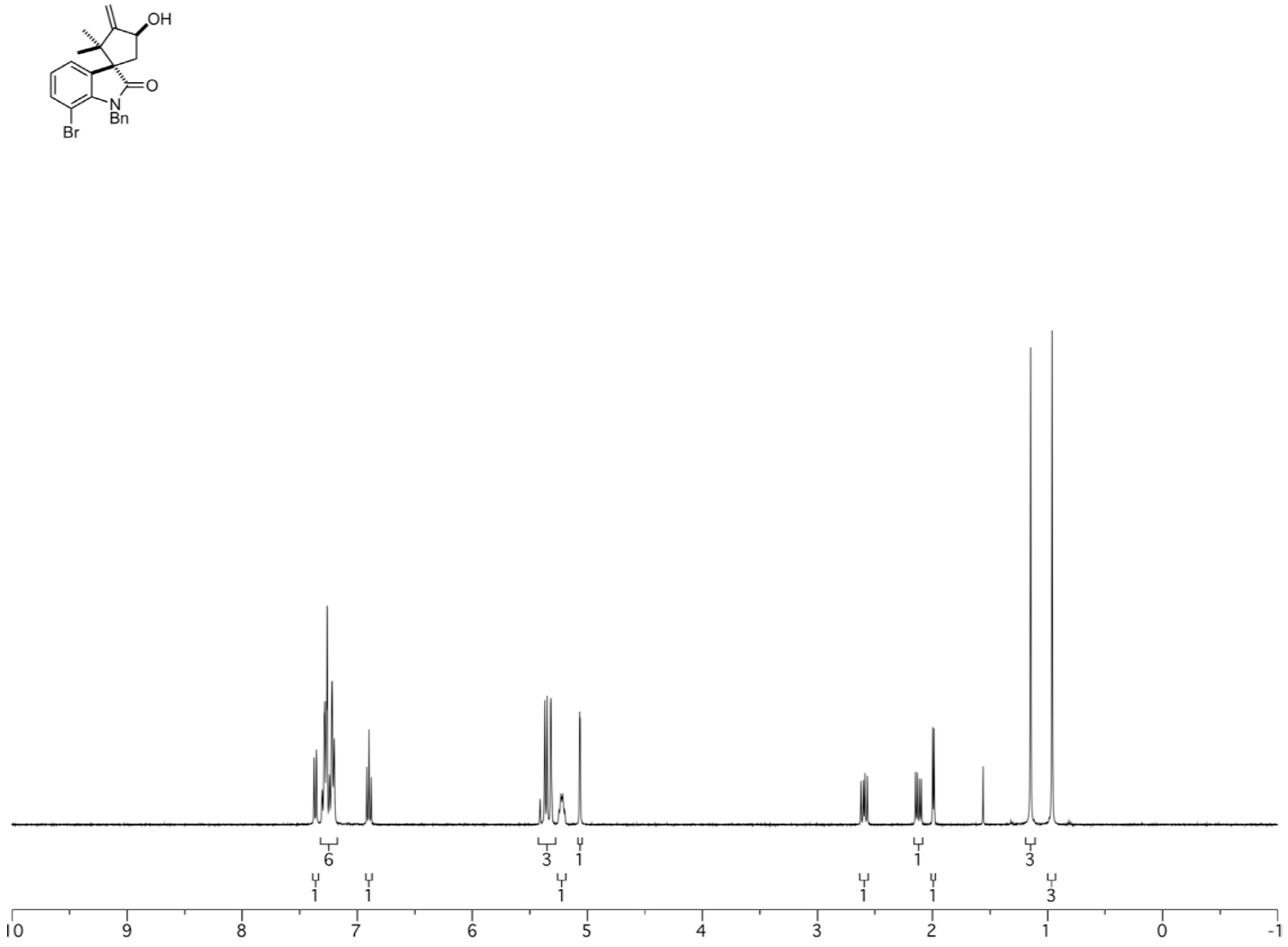


Figure A.2.31a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **146b**

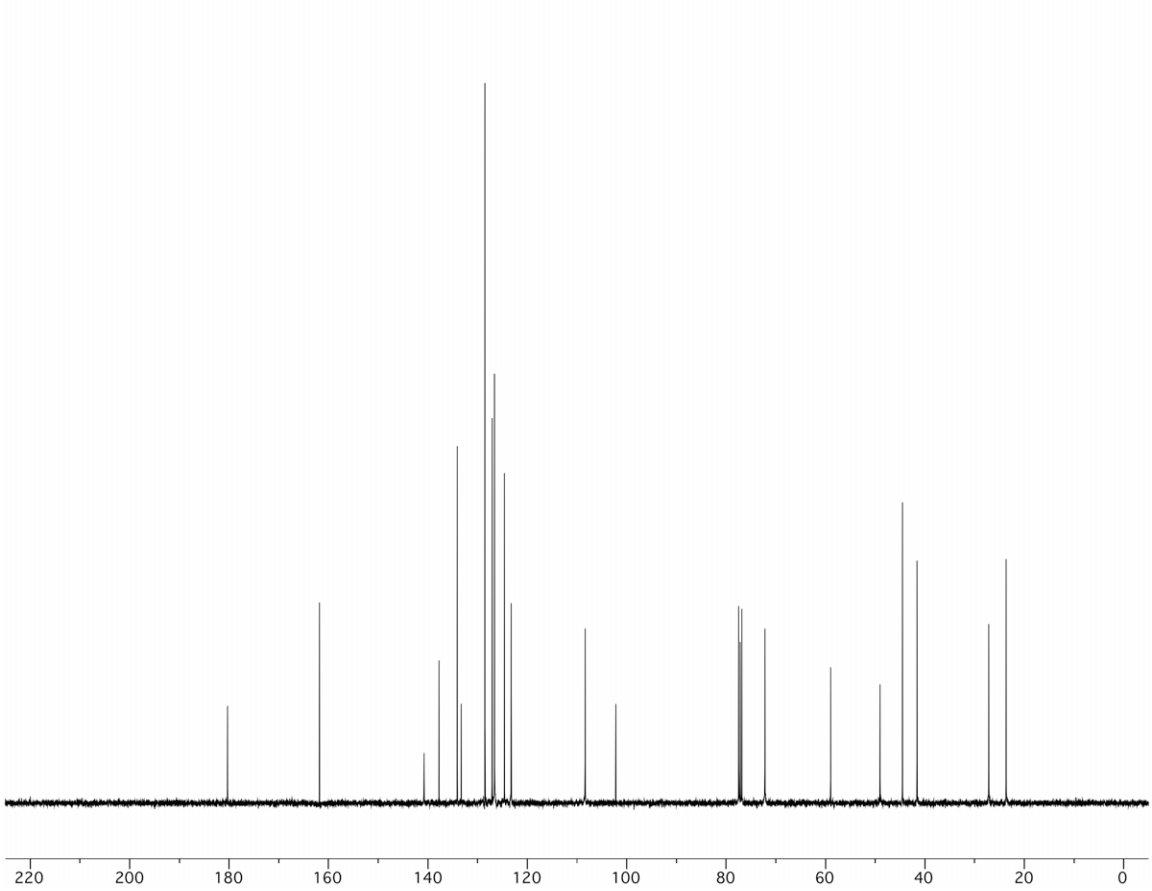


Figure A.2.31b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **146b**

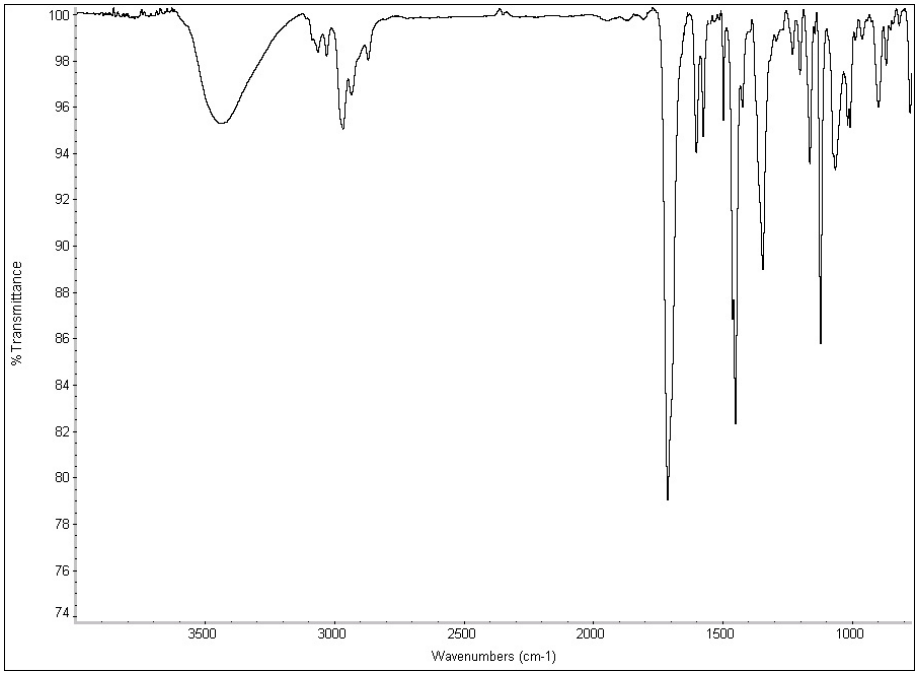


Figure A.2.31c. IR spectrum (thin film/NaCl) of compound **146b**

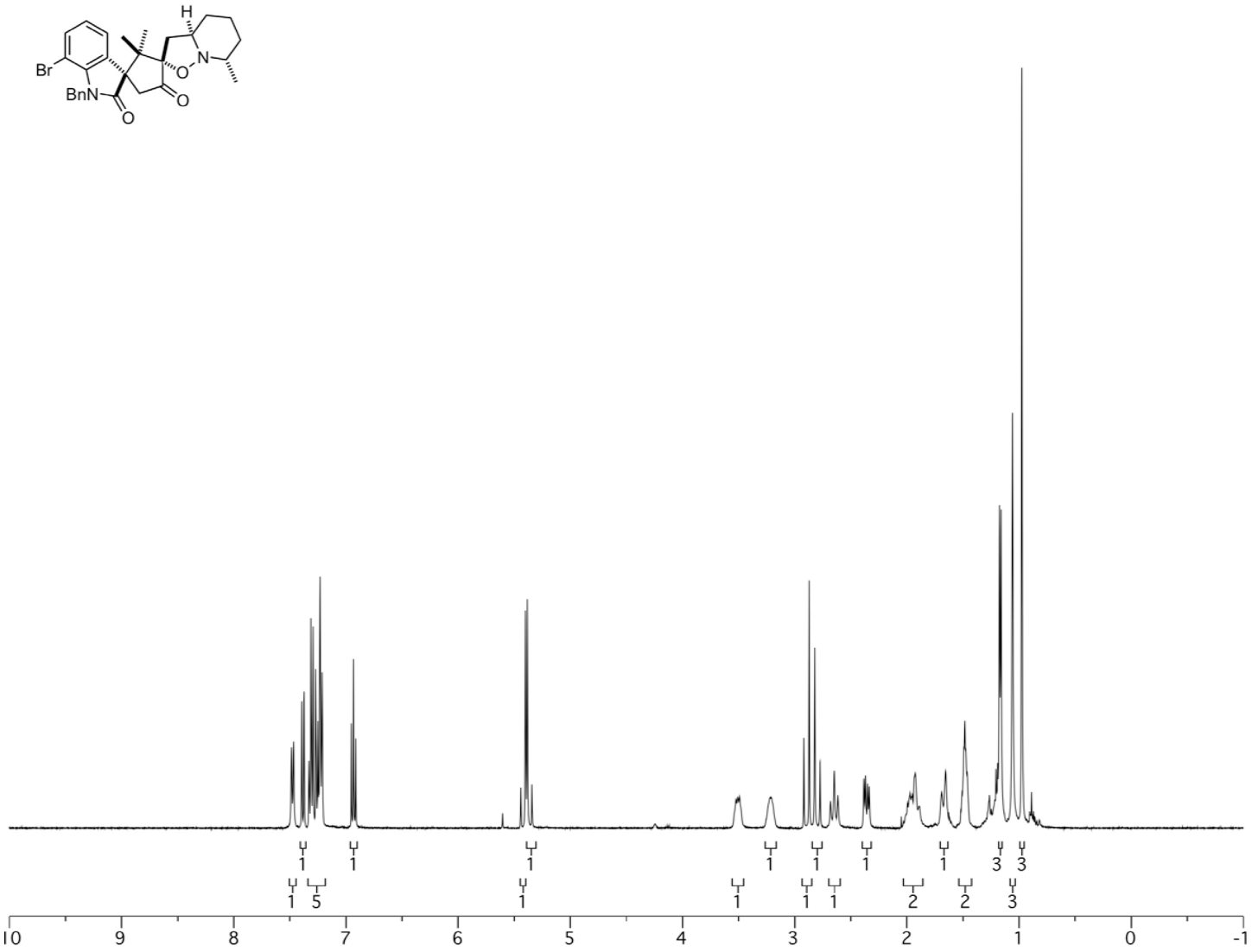


Figure A.2.32a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **147**

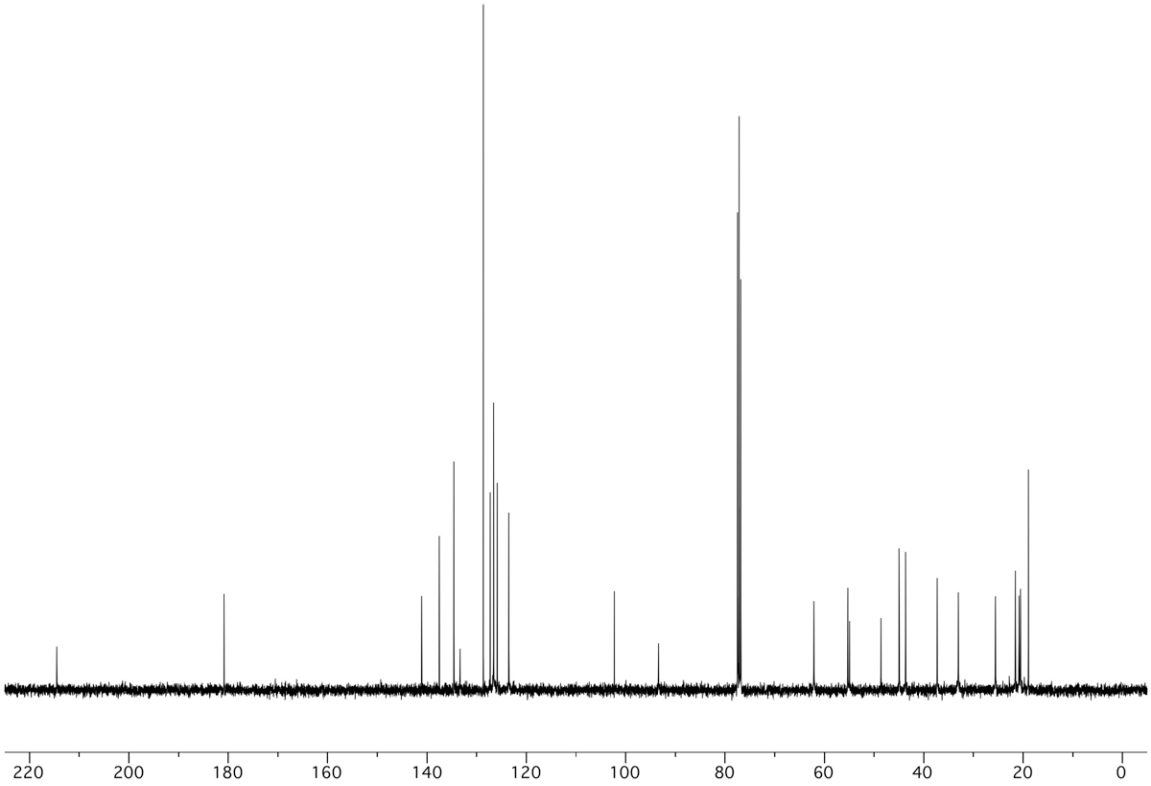


Figure A.2.32b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **147**

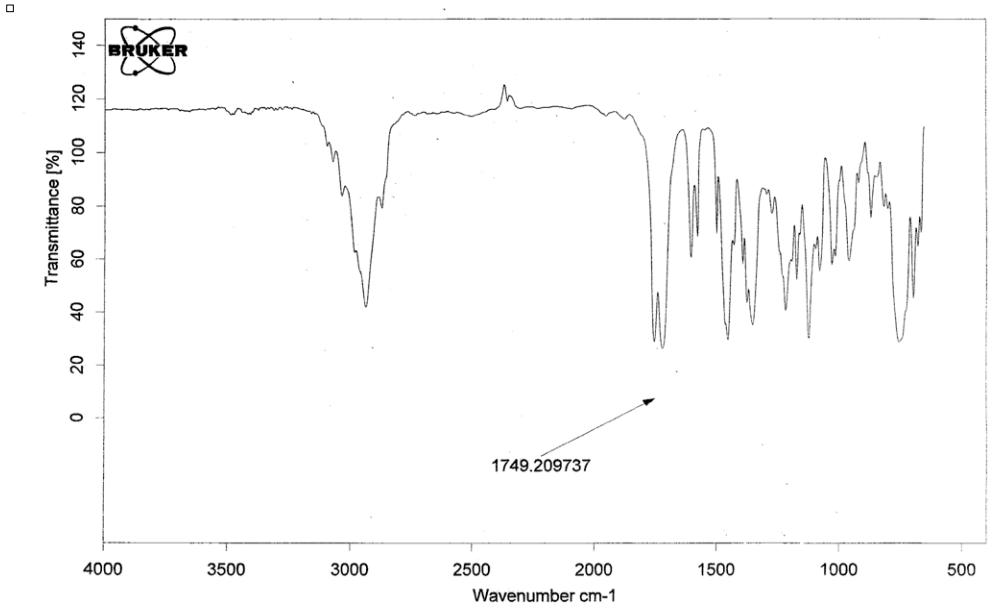


Figure A.2.32c. IR spectrum (thin film/NaCl) of compound **147**

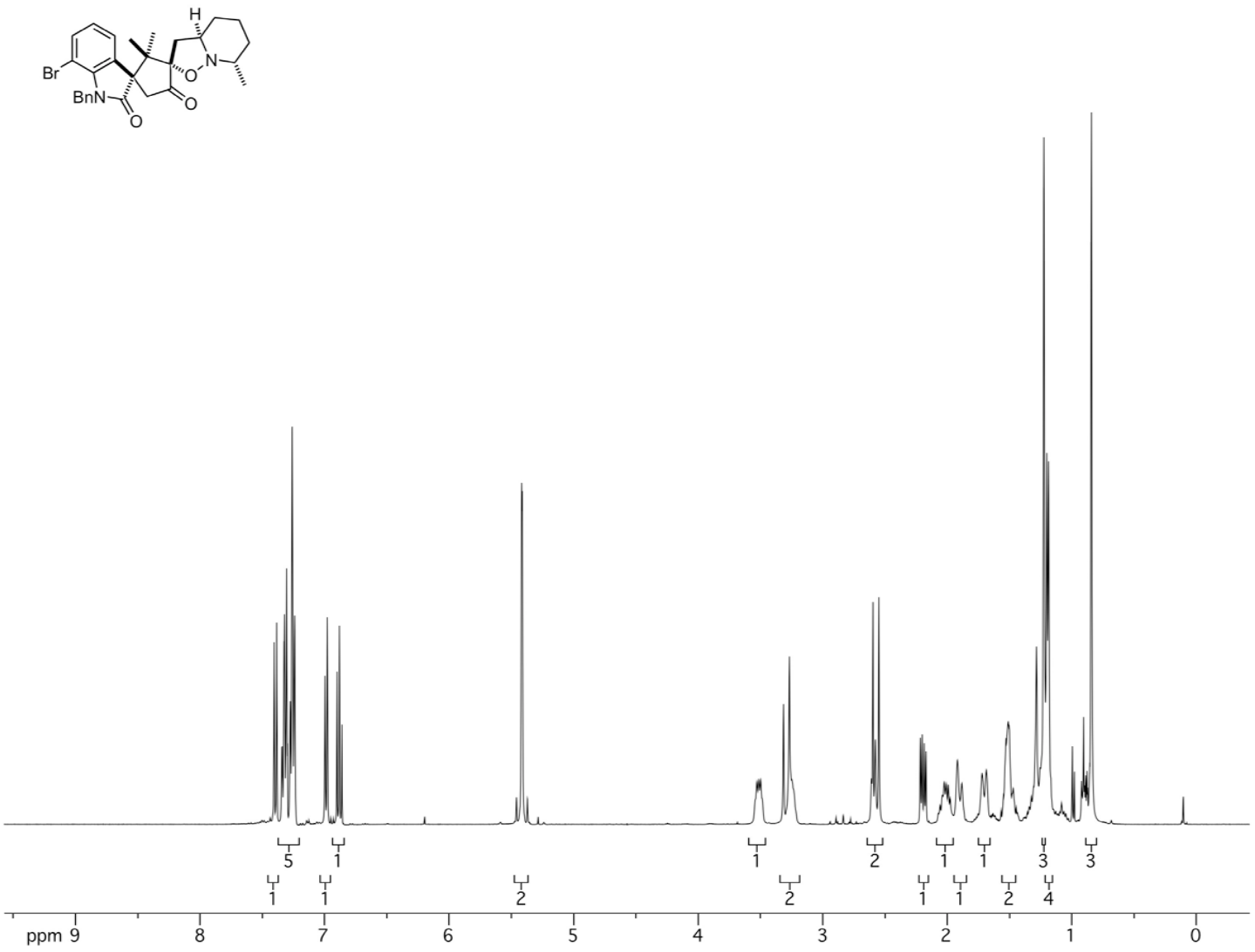


Figure A.2.33a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **148**

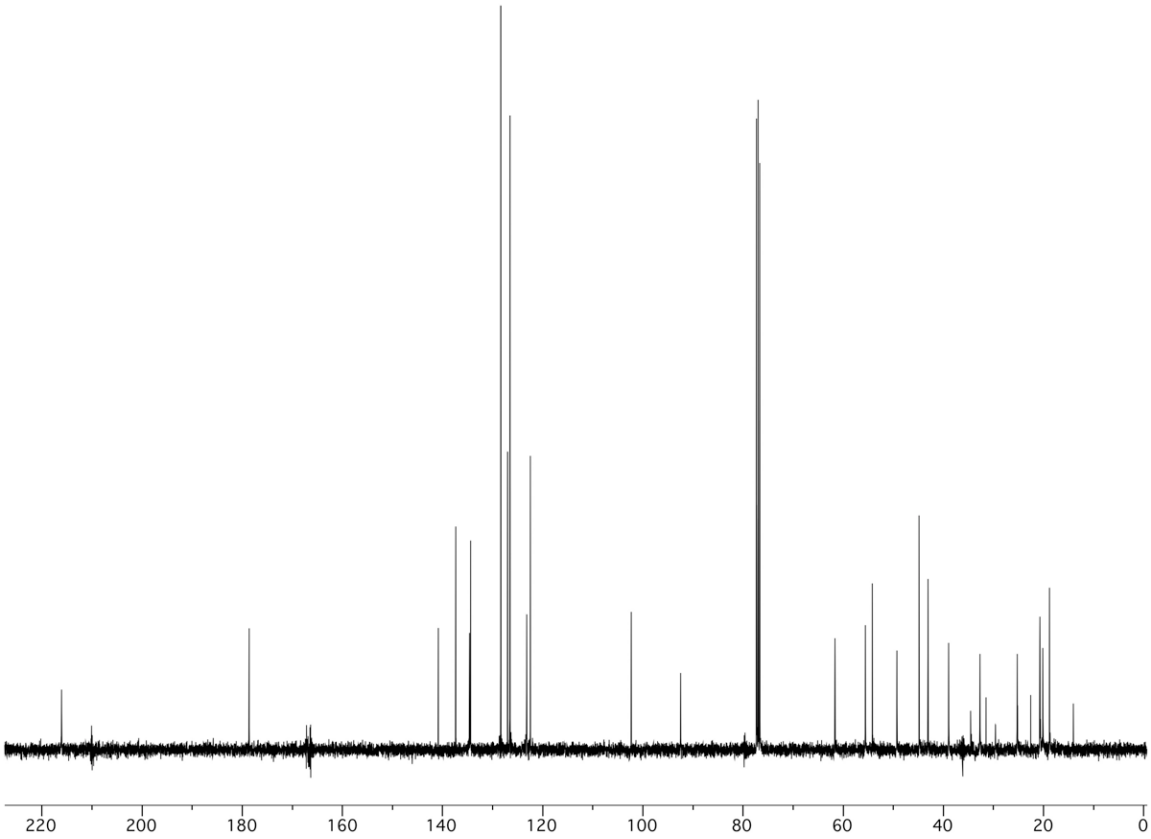


Figure A.2.33b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **148**

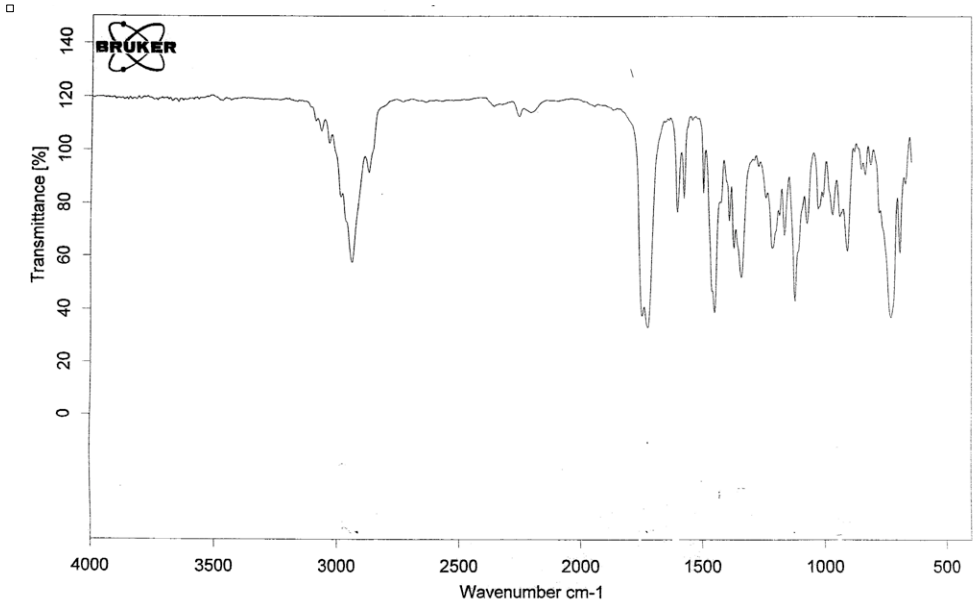


Figure A.2.33c. IR spectrum (thin film/NaCl) of compound **148**

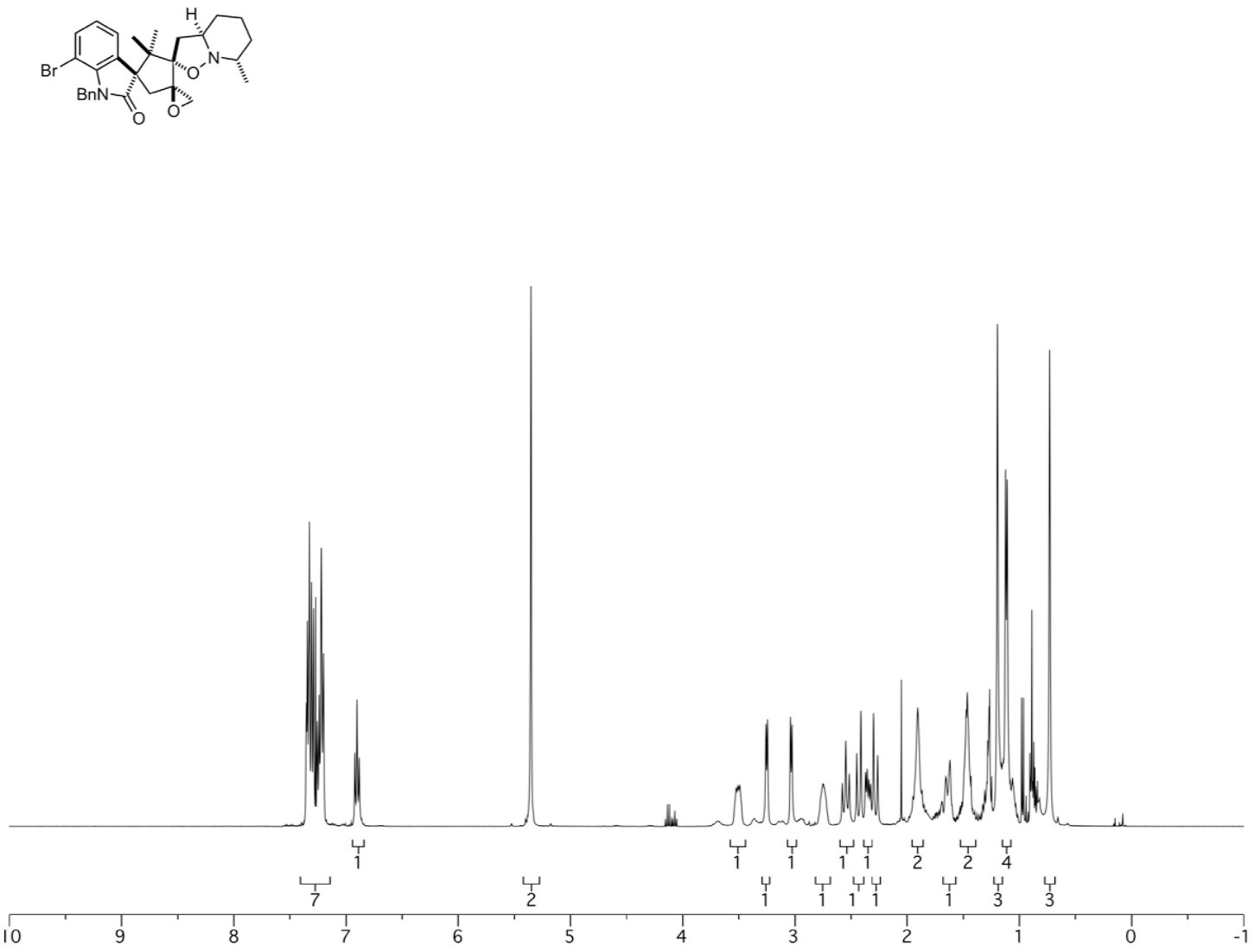


Figure A.2.34a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **149**

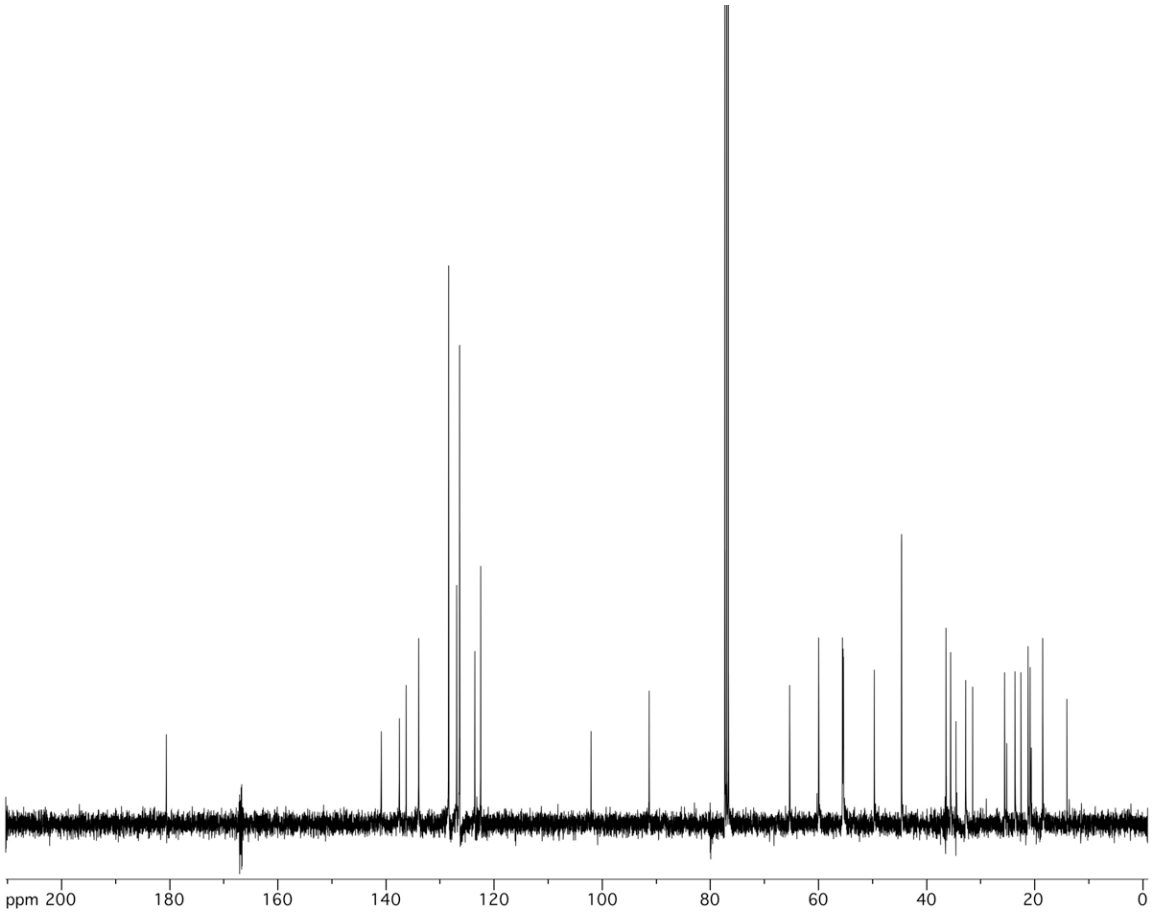


Figure A.2.34b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **149**

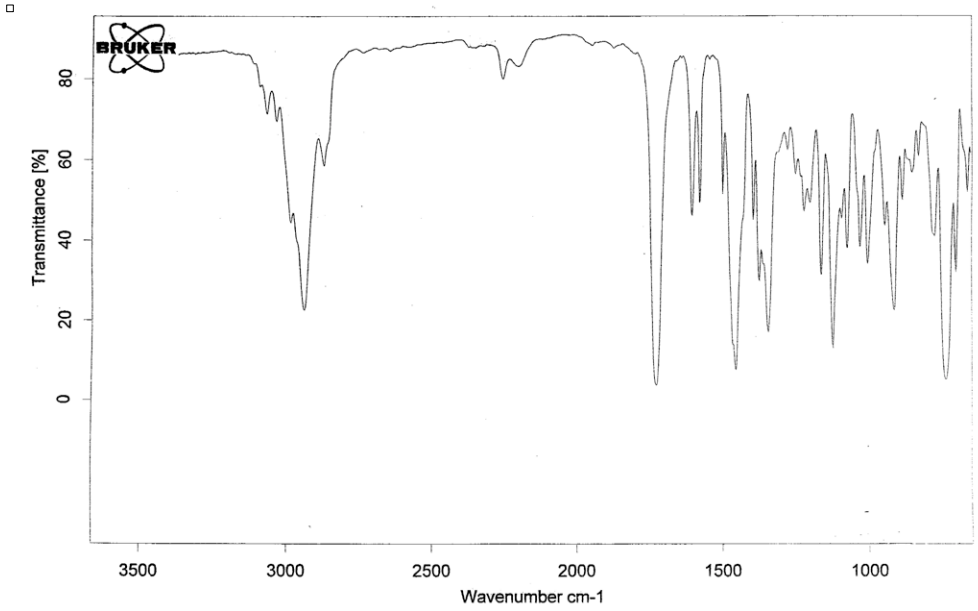


Figure A.2.34c. IR spectrum (thin film/NaCl) of compound **149**

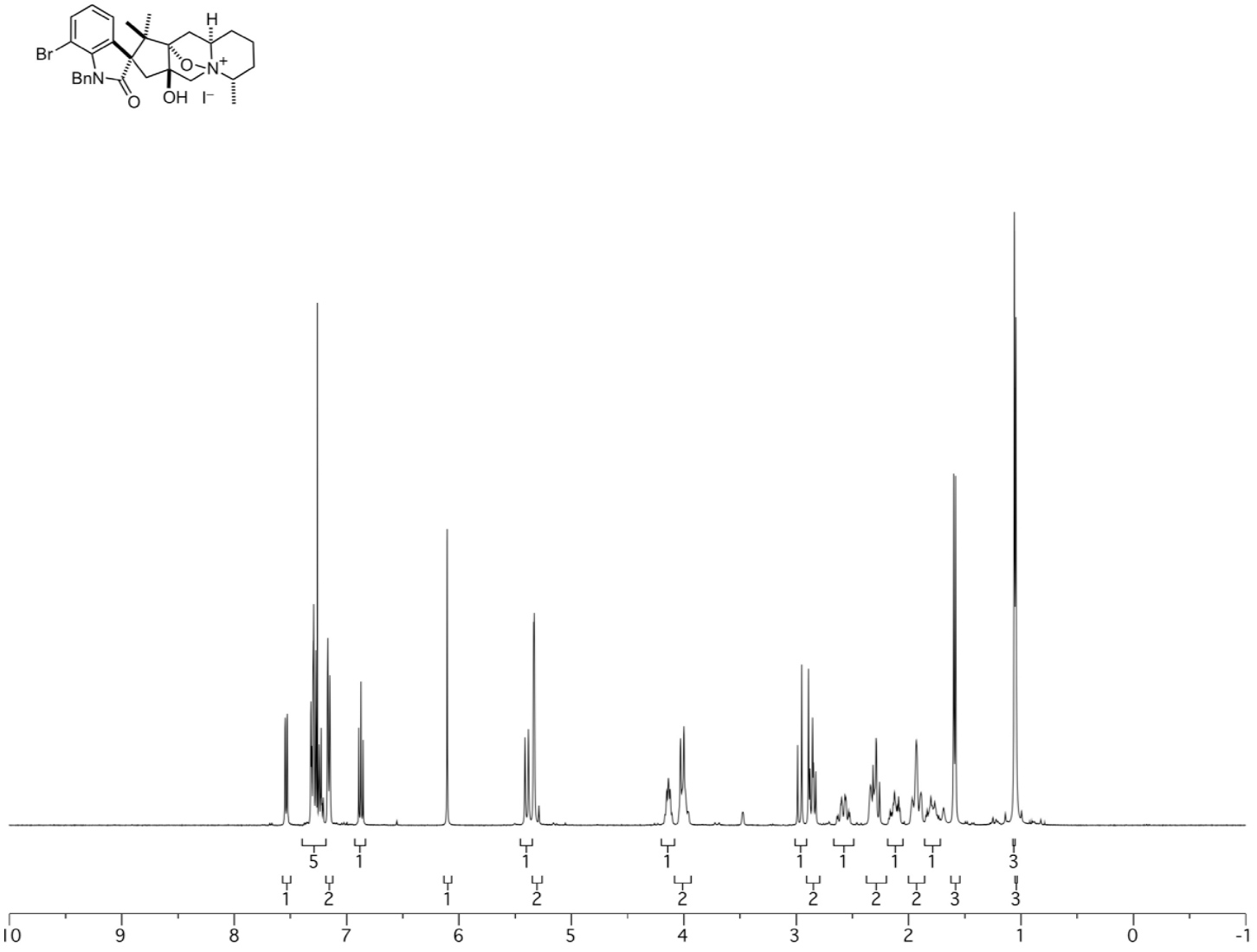


Figure A.2.35a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **150**

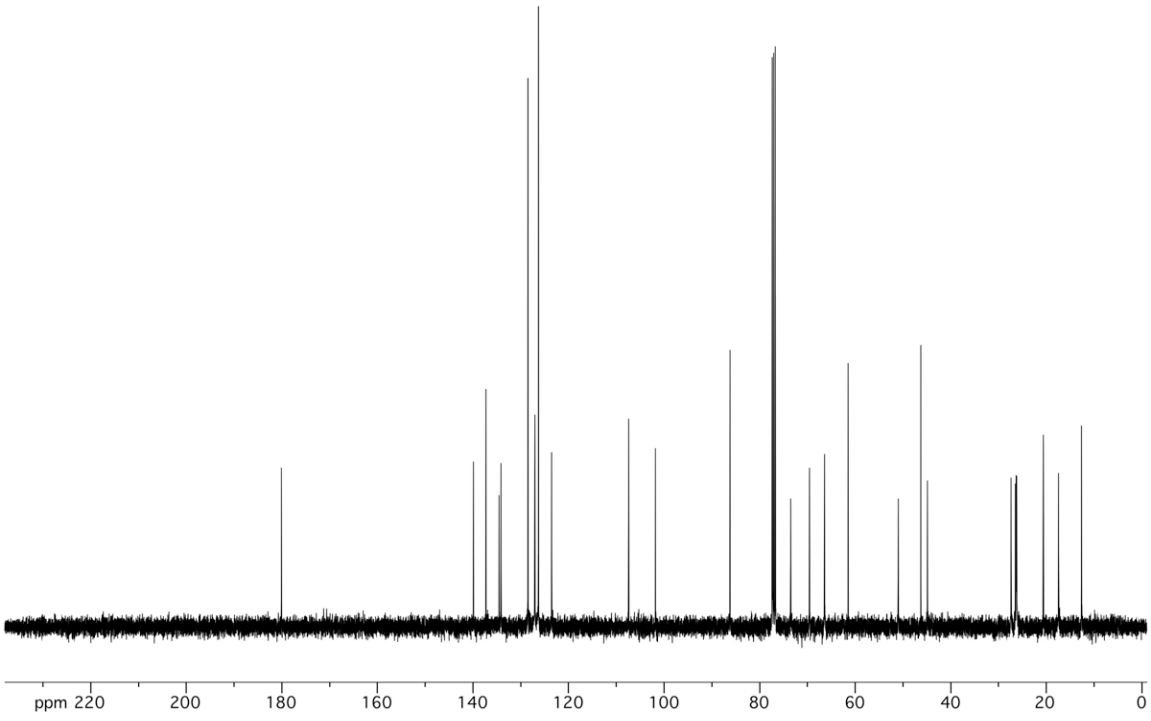


Figure A.2.35b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **150**

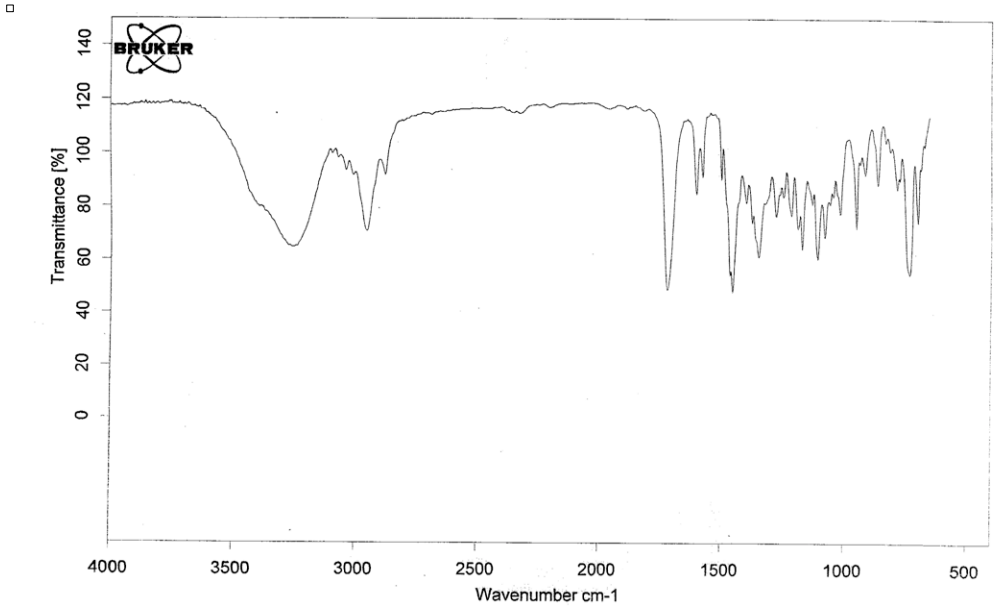


Figure A.2.35c. IR spectrum (thin film/NaCl) of compound **150**

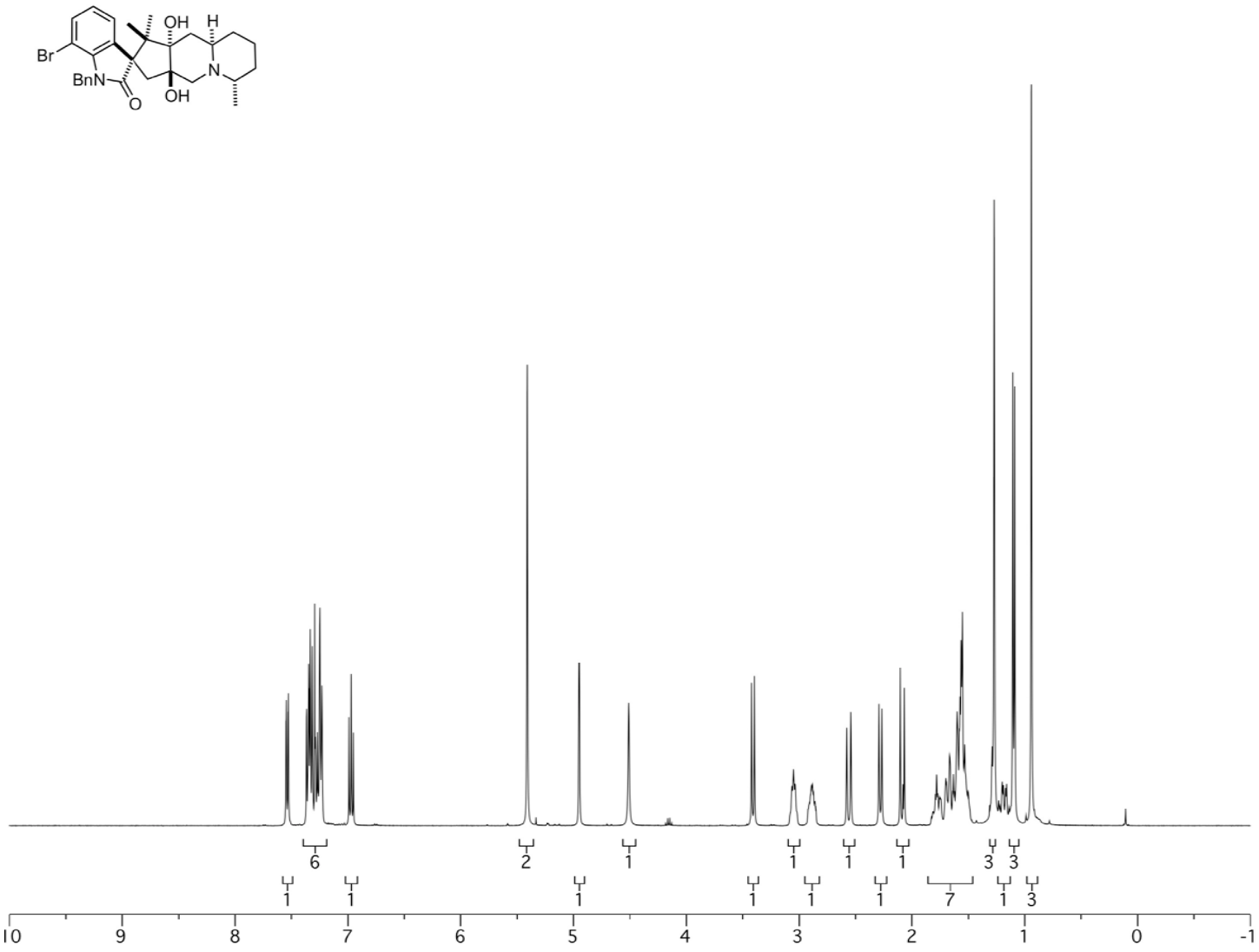


Figure A.2.36a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **151**

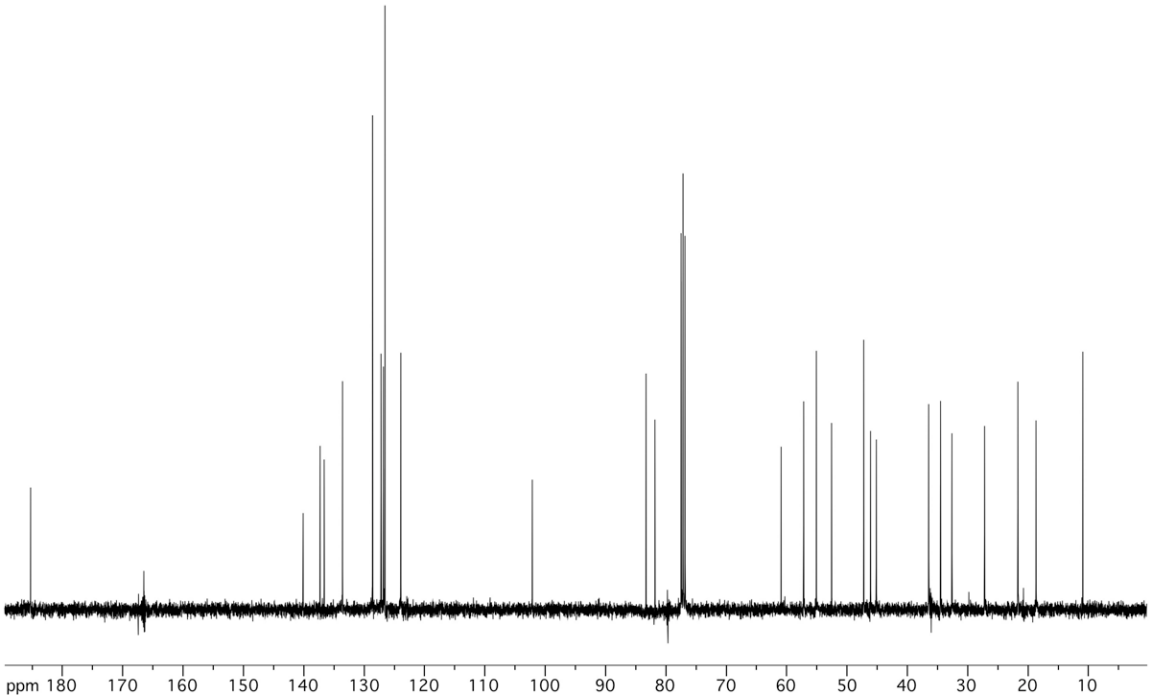


Figure A.2.36b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **151**

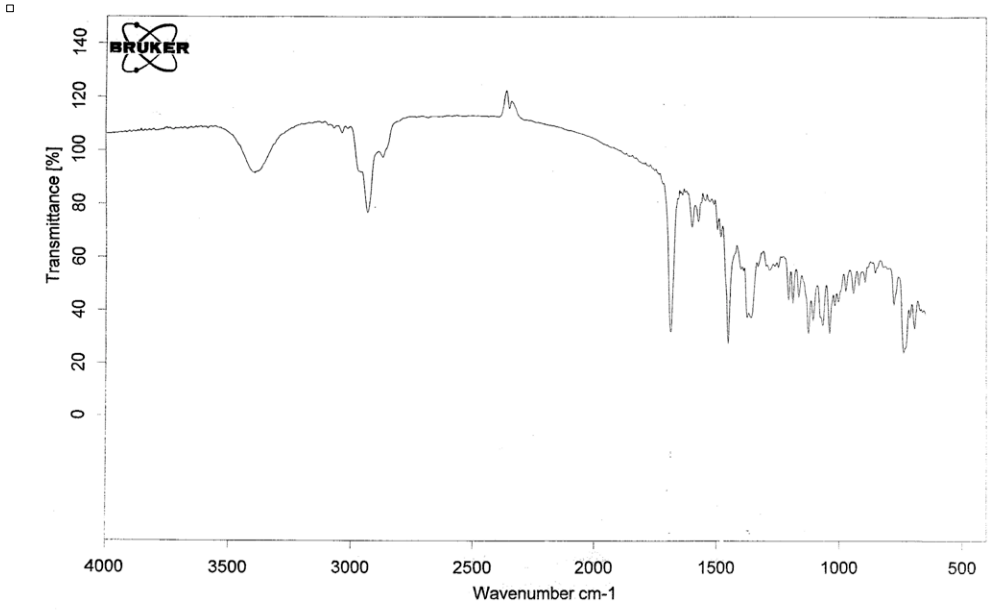


Figure A.2.36c. IR spectrum (thin film/NaCl) of compound **151**

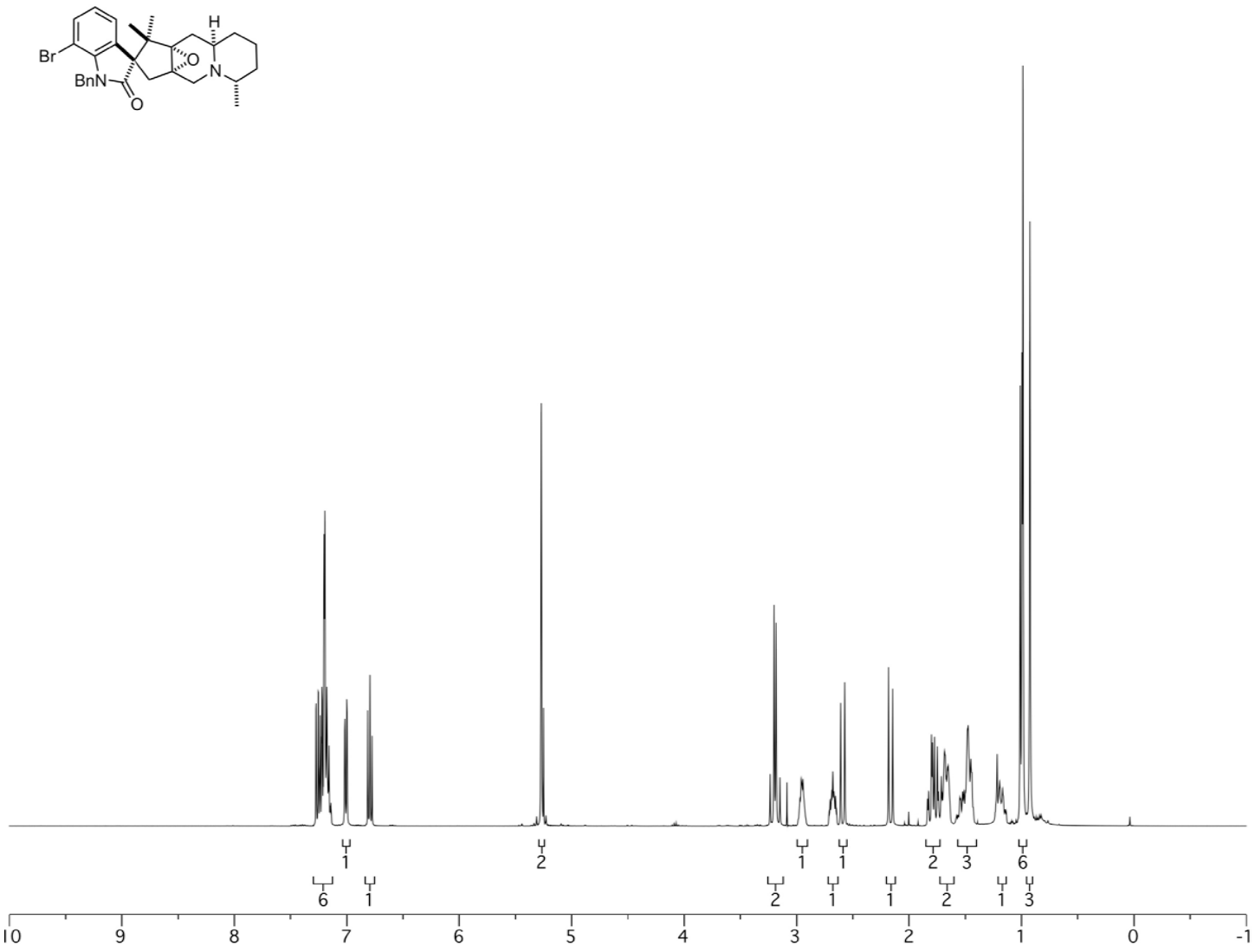


Figure A.2.37a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **152**

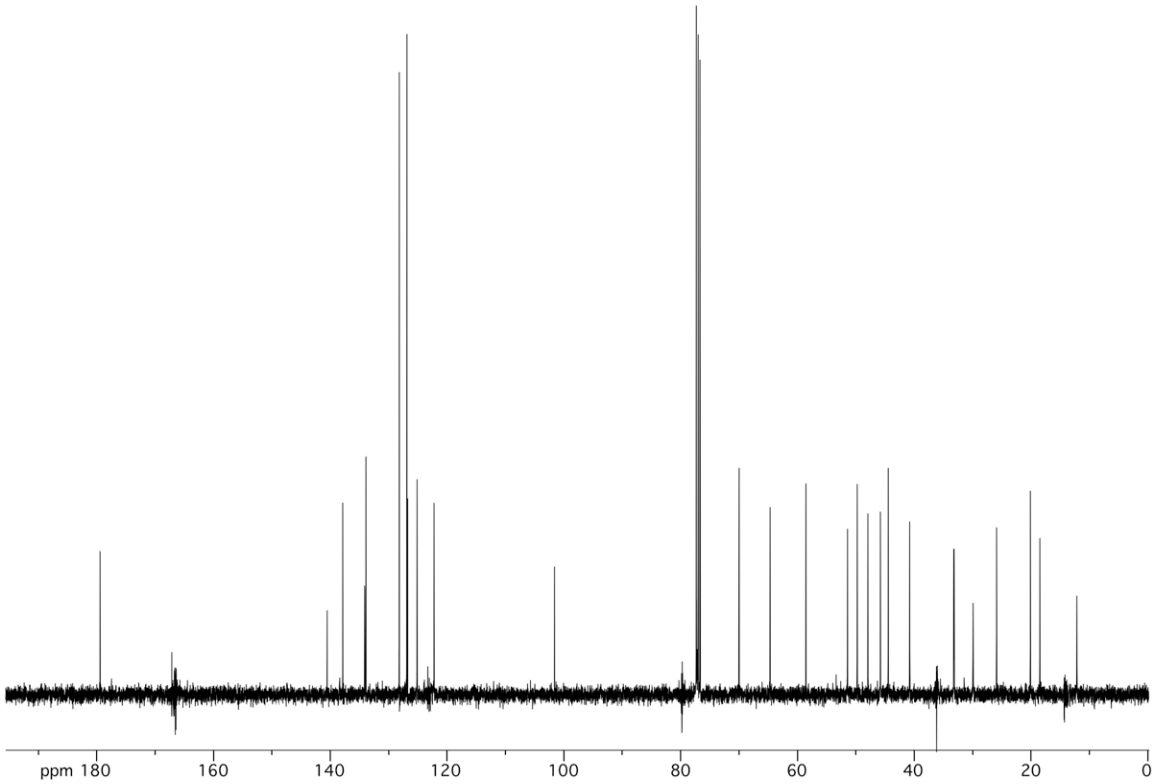


Figure A.2.37b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **152**

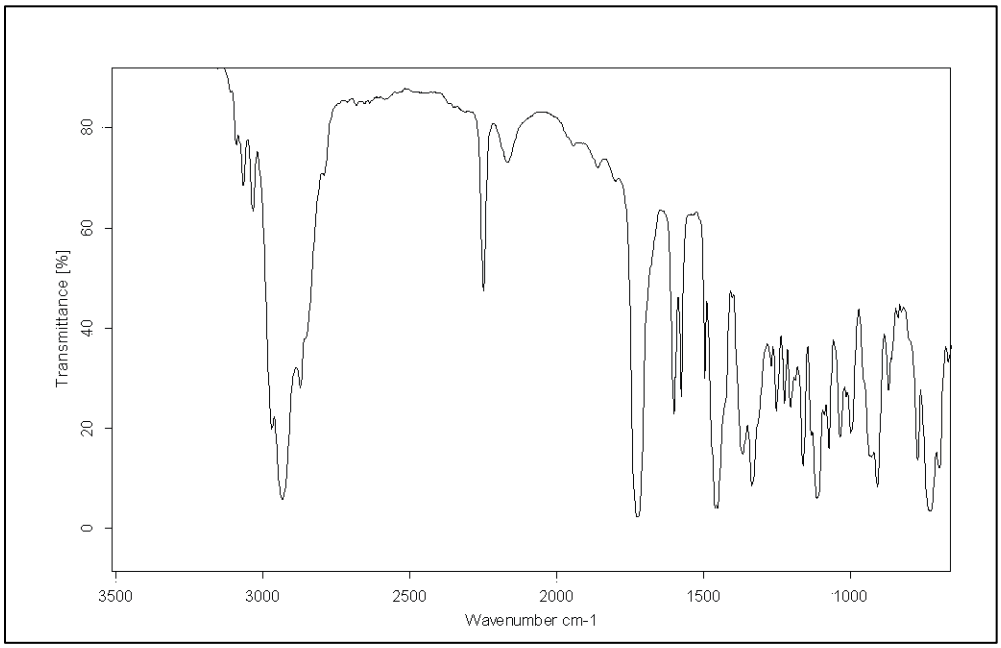


Figure A.2.37c. IR spectrum (thin film/NaCl) of compound **152**

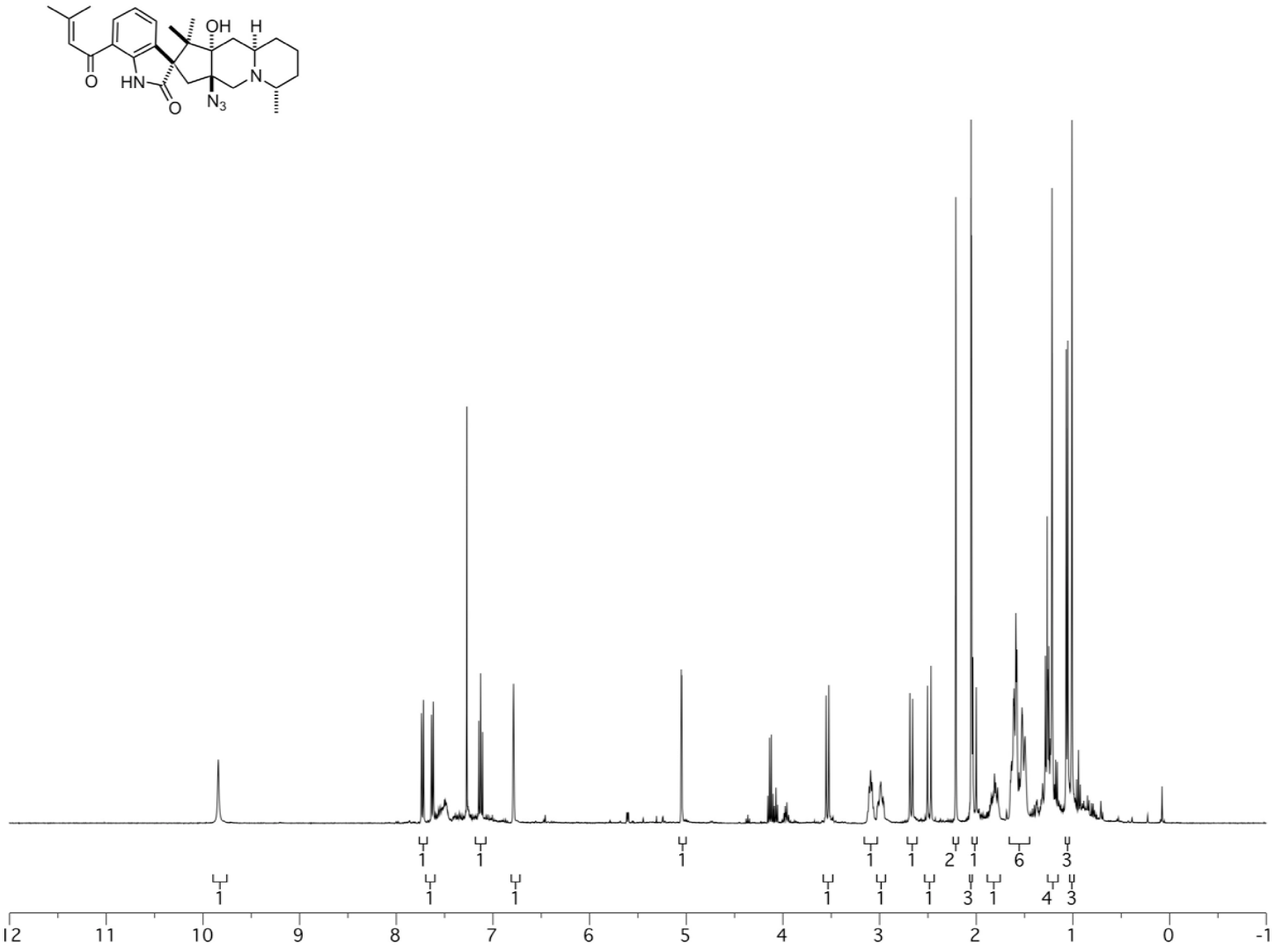


Figure A.2.38a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **158**

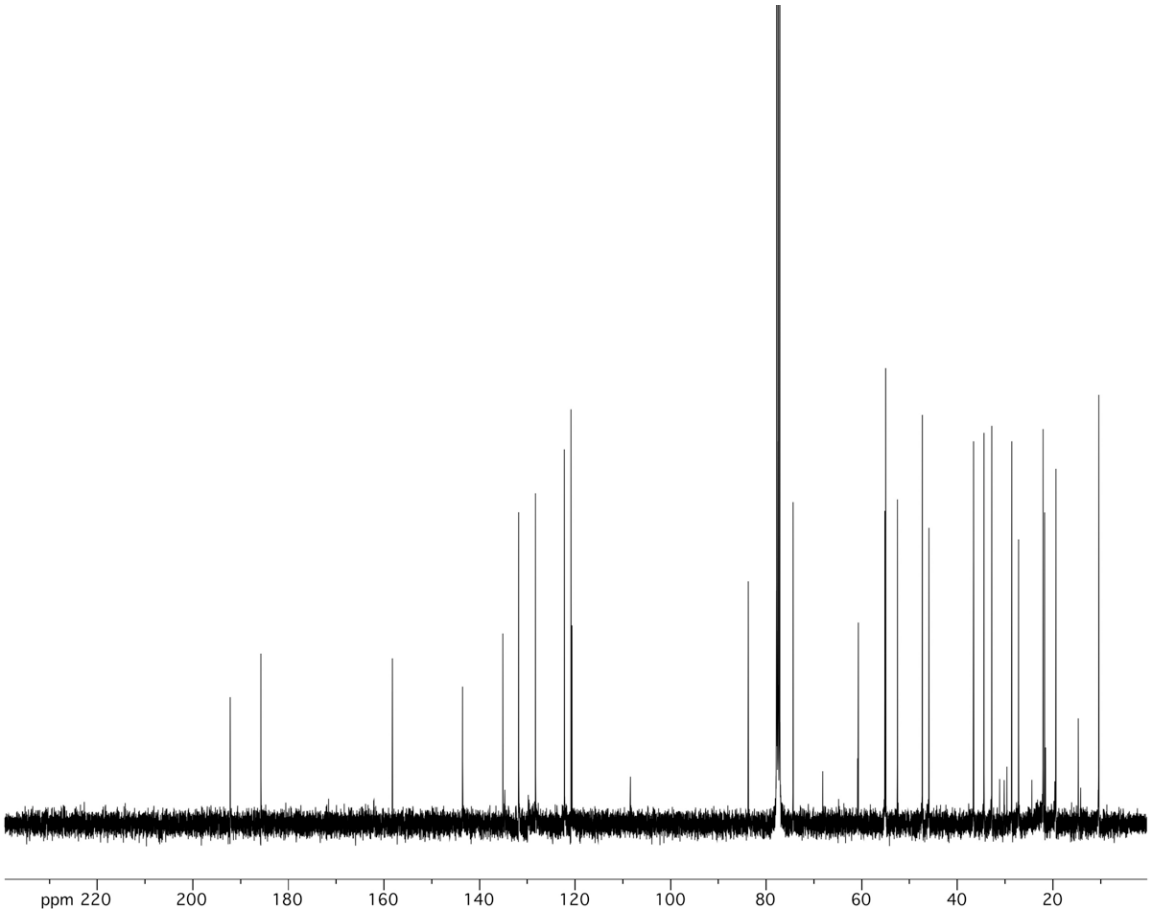


Figure A.2.38b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **158**

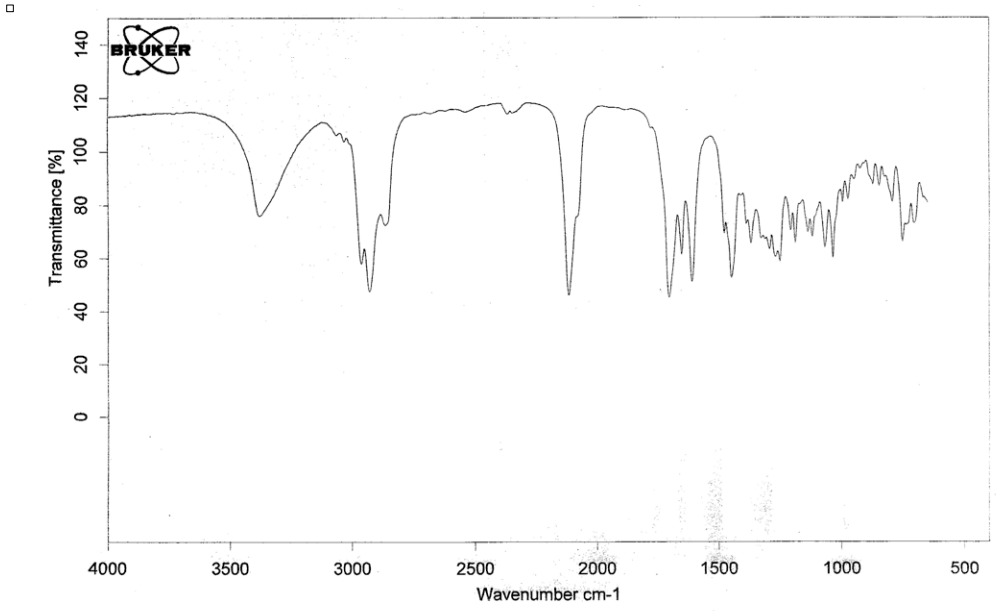
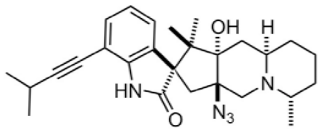


Figure A.2.38c. IR spectrum (thin film/NaCl) of compound **158**



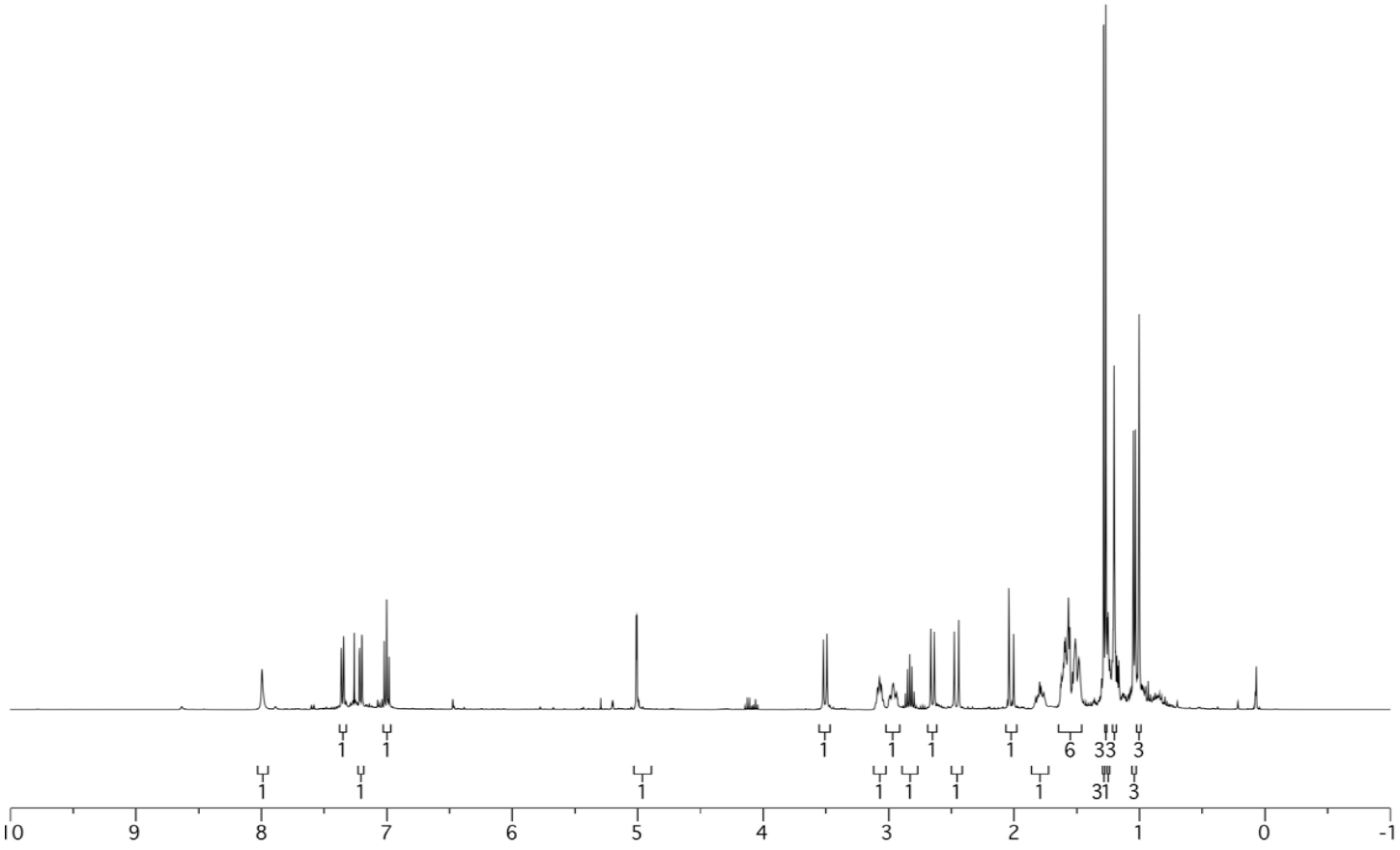


Figure A.2.39a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **159**

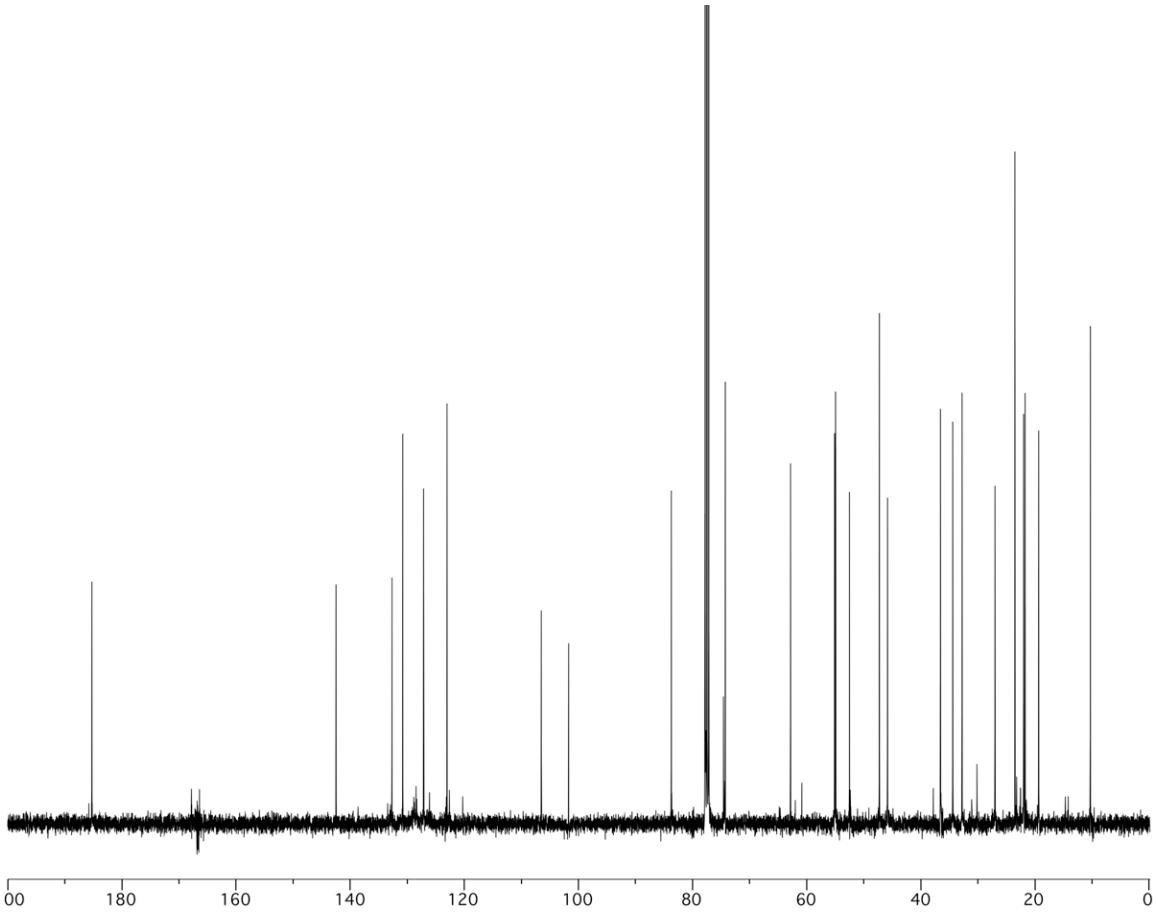


Figure A.2.39b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **159**

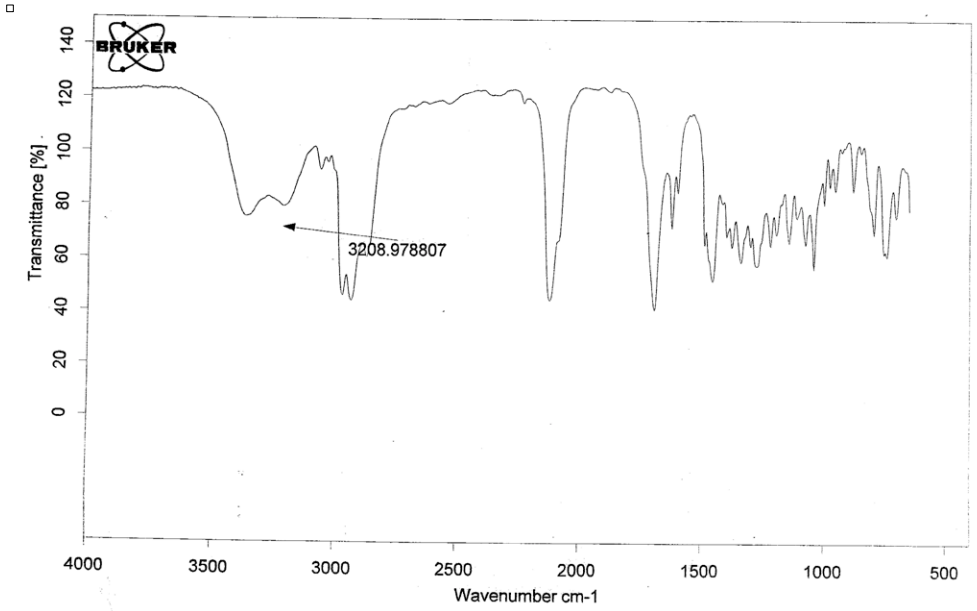


Figure A.2.39c. IR spectrum (thin film/NaCl) of compound **159**

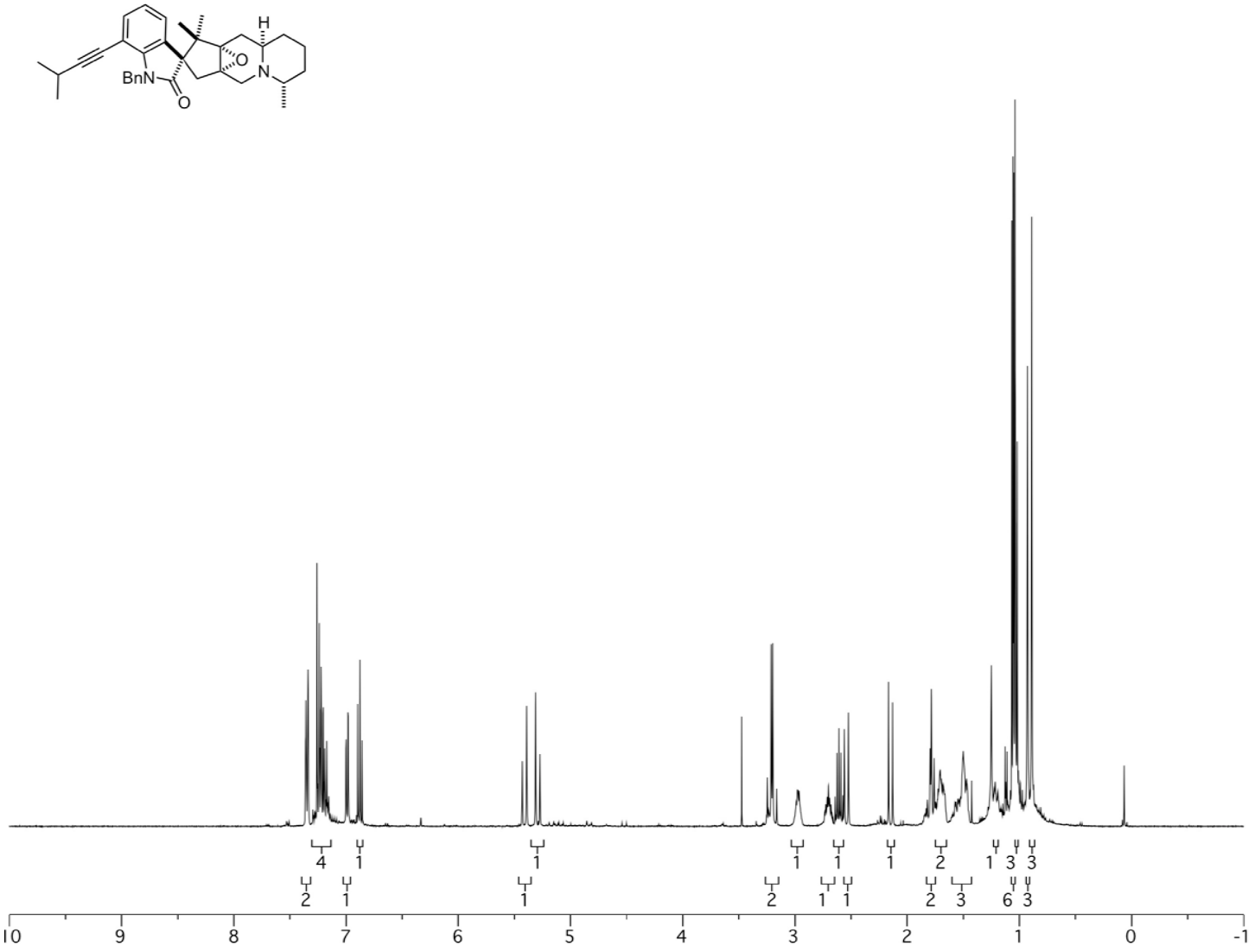


Figure A.2.40a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **160**

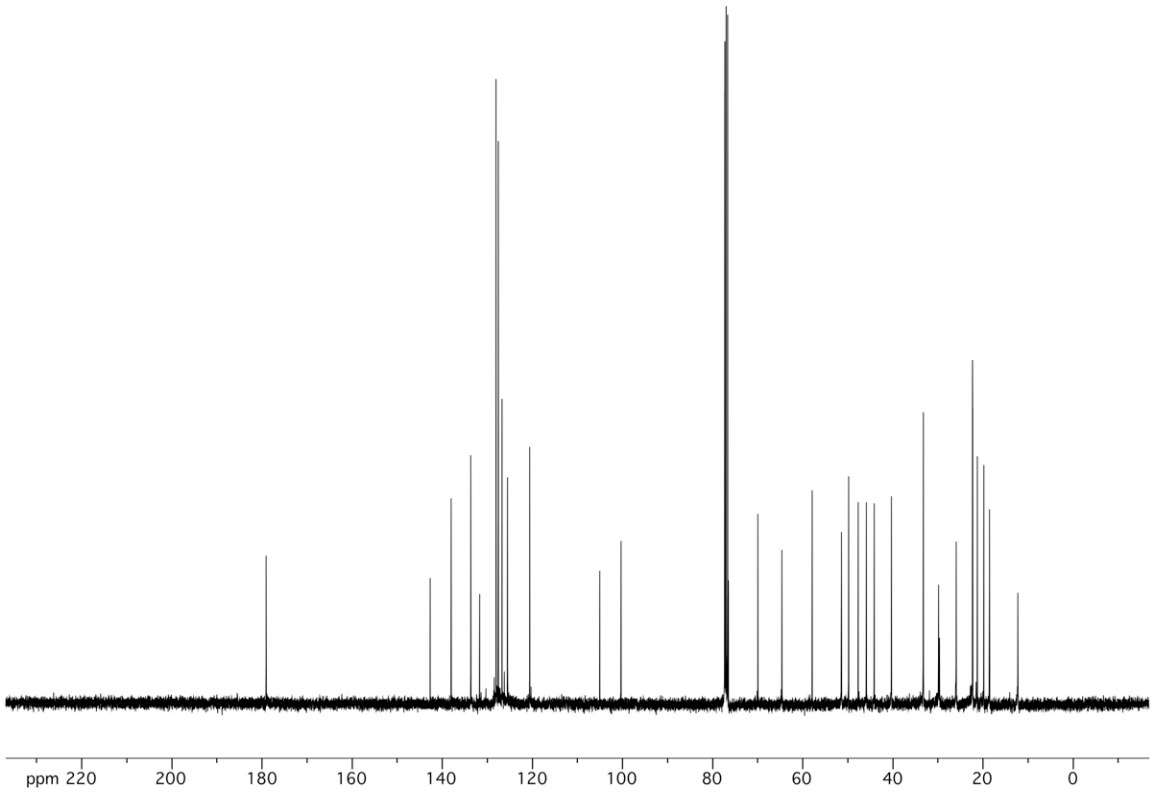


Figure A.2.40b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **160**

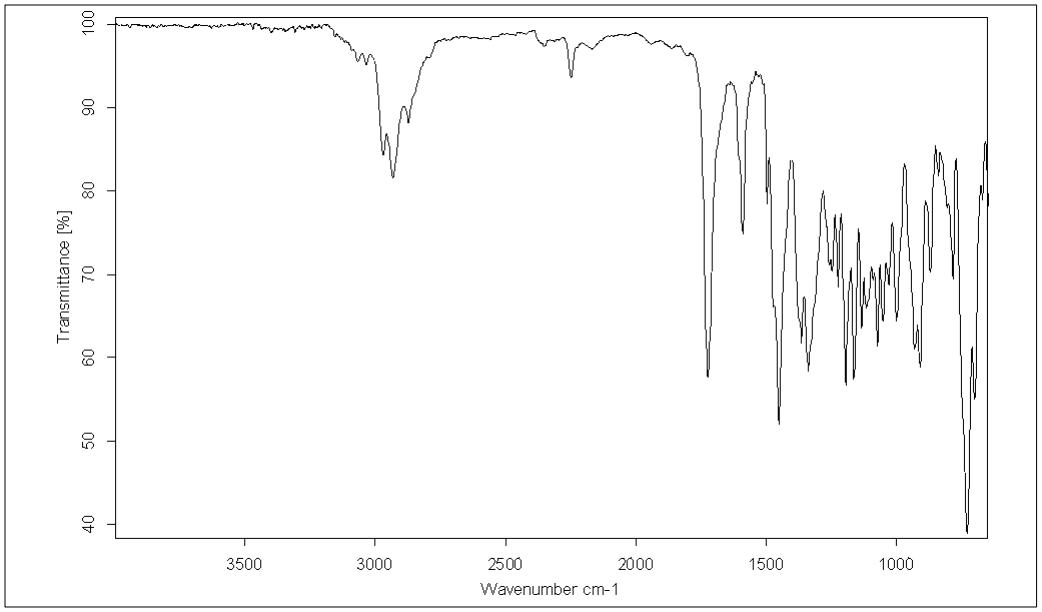


Figure A.2.40c. IR spectrum (thin film/NaCl) of compound **160**

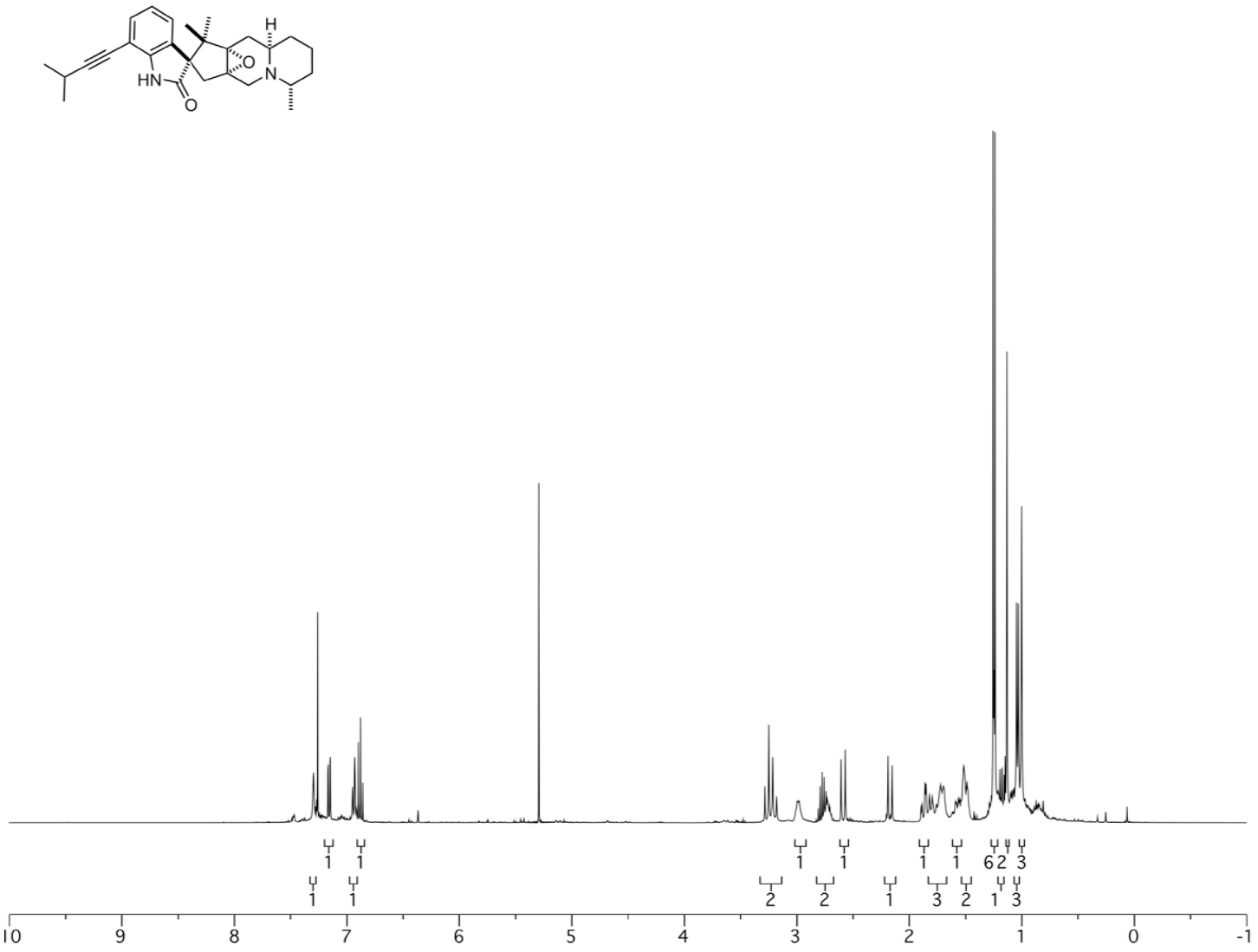


Figure A.2.41a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **163**

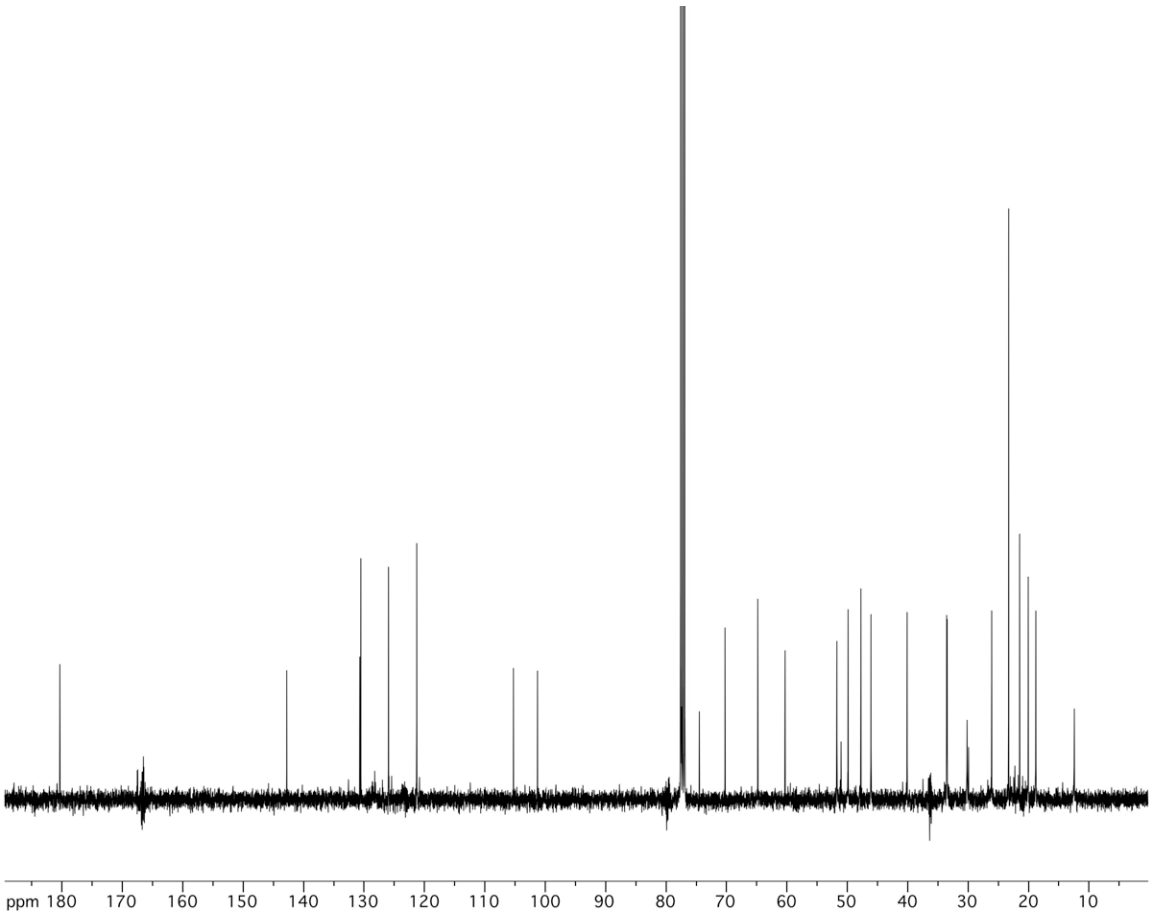


Figure A.2.41b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **163**

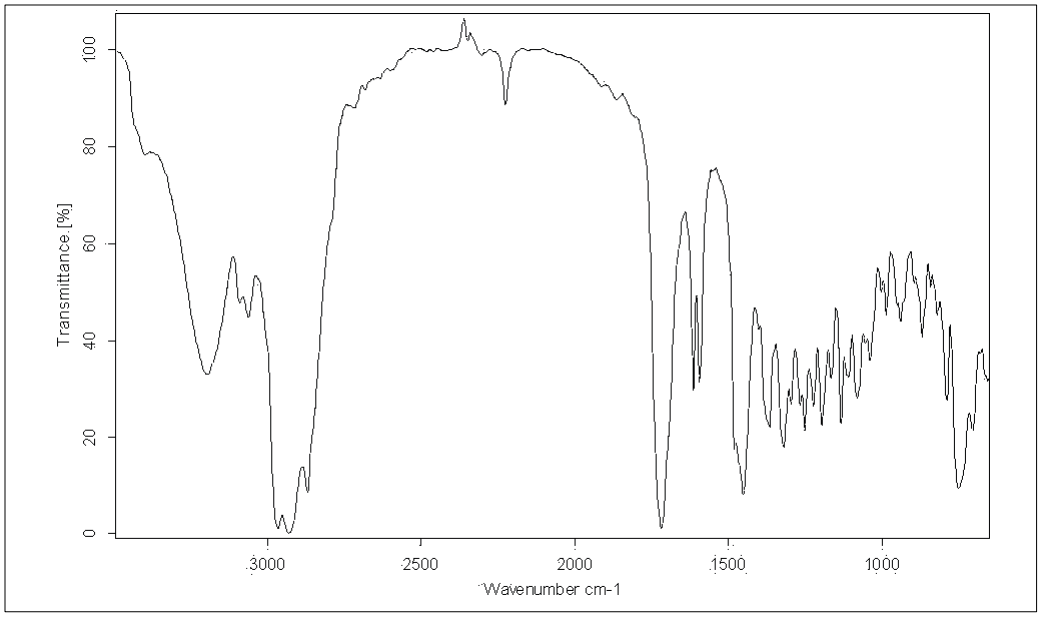


Figure A.2.41c. IR spectrum (thin film/NaCl) of compound **163**

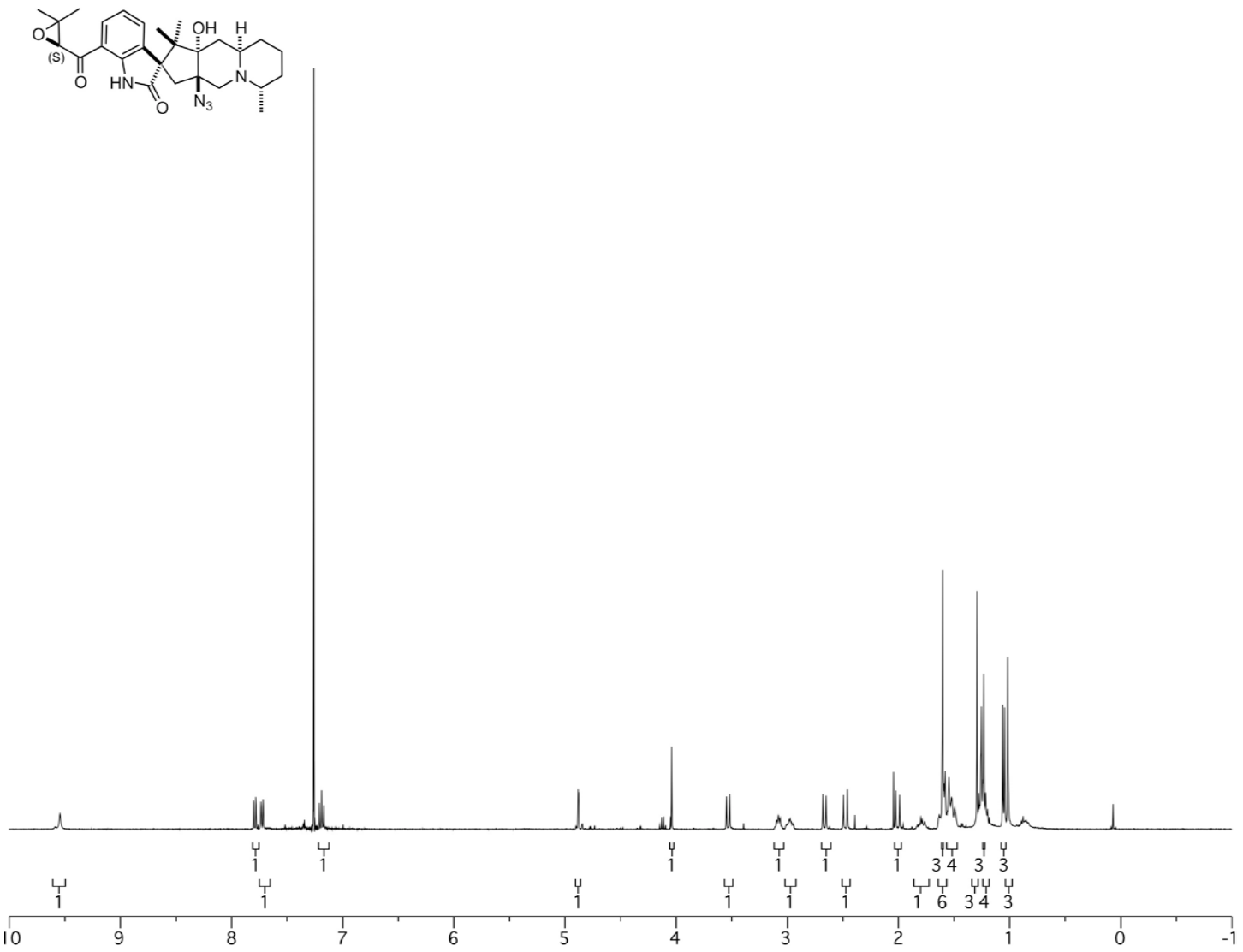


Figure A.2.42a. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **171**

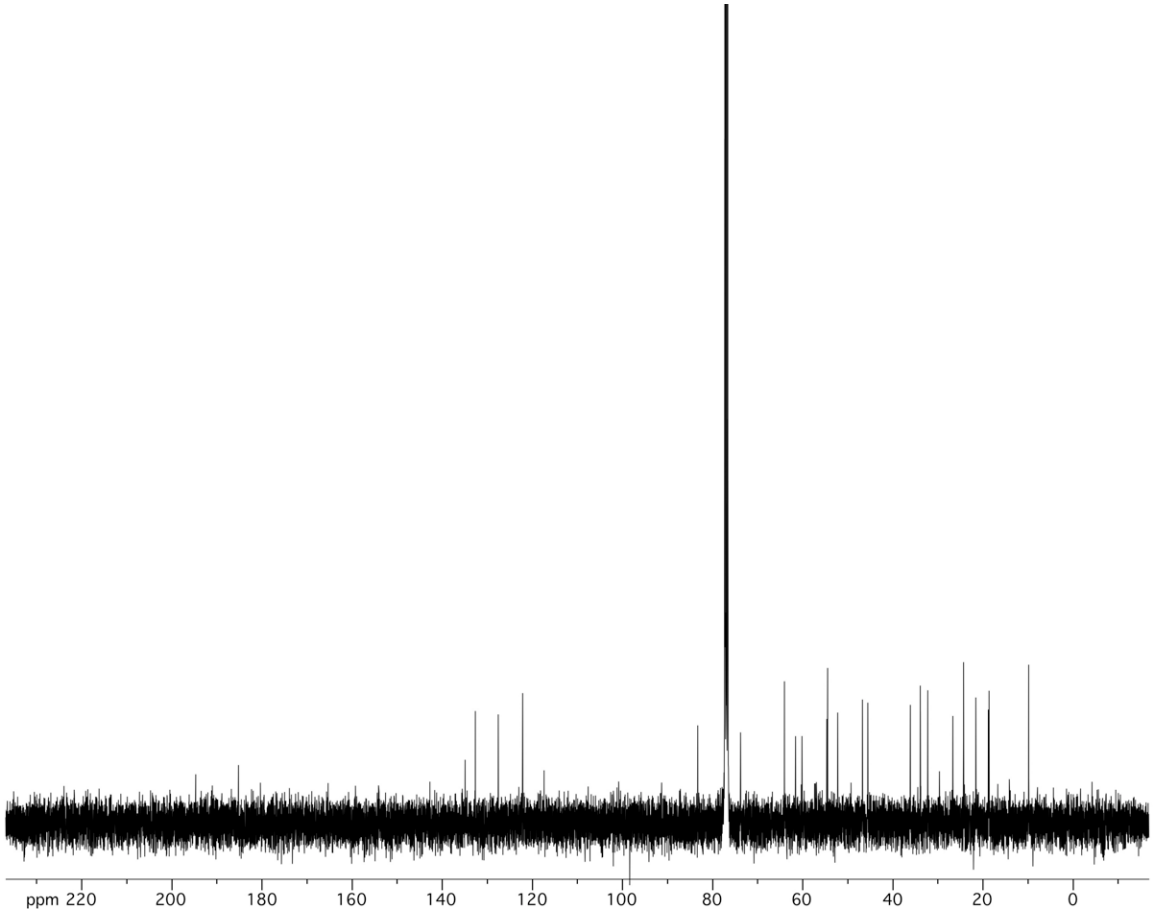


Figure A.2.42b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **171**

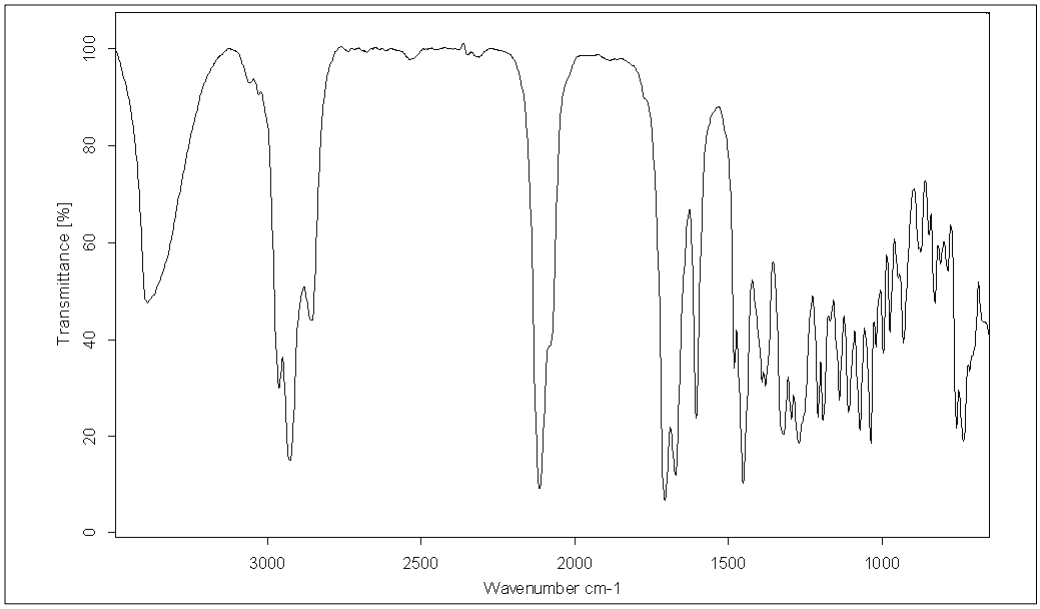


Figure A.2.42c. IR spectrum (thin film/NaCl) of compound **171**

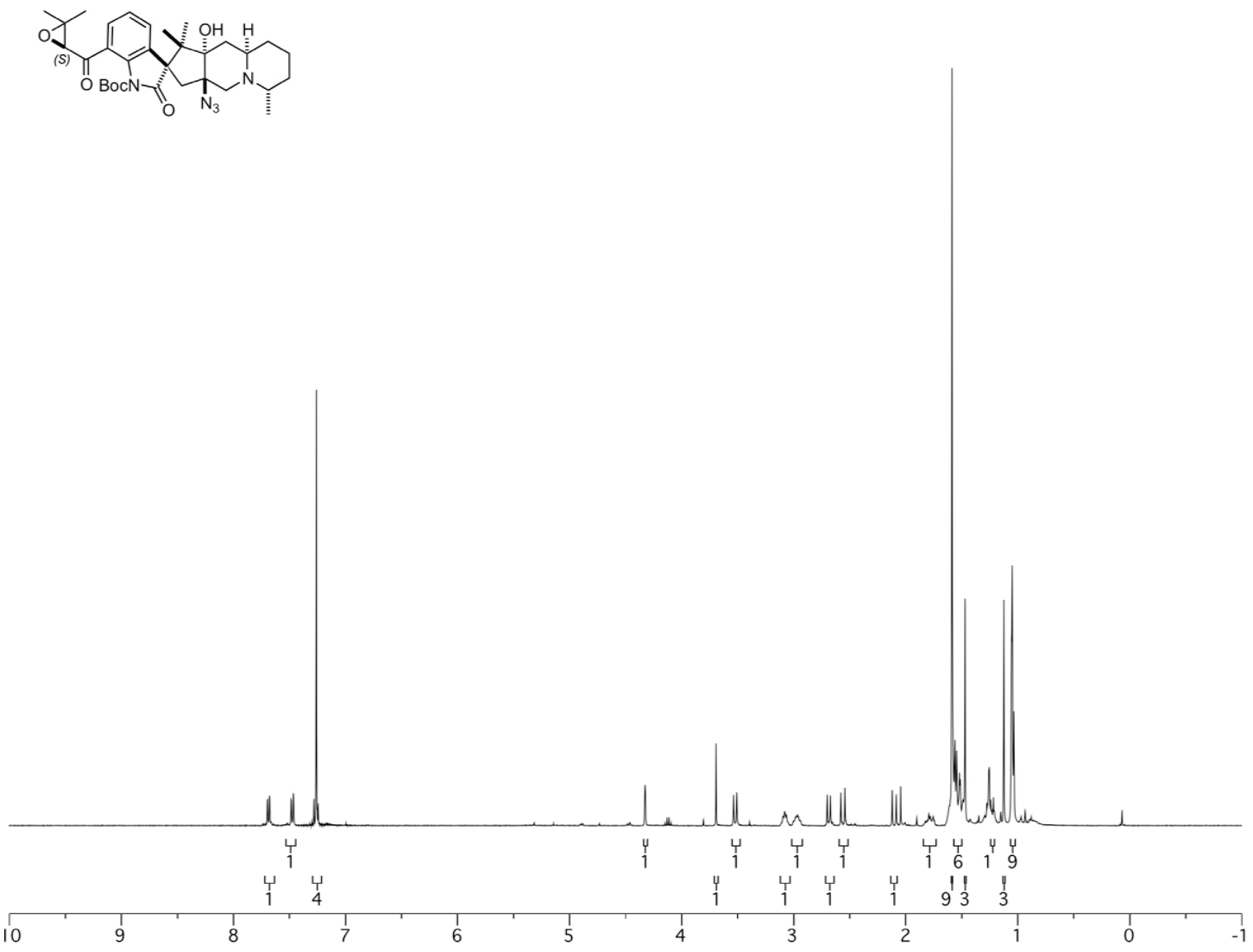


Figure A.43a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **173**

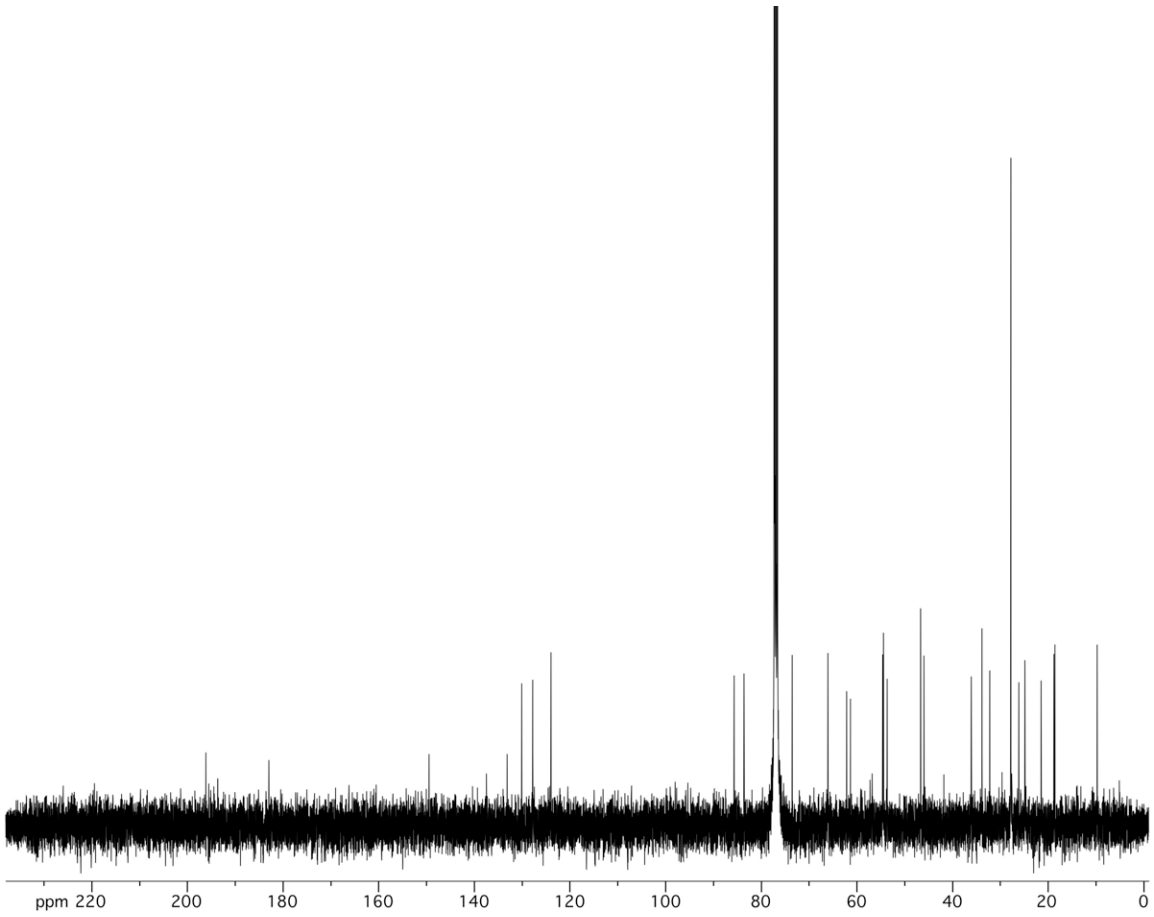


Figure A.2.43b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **173**

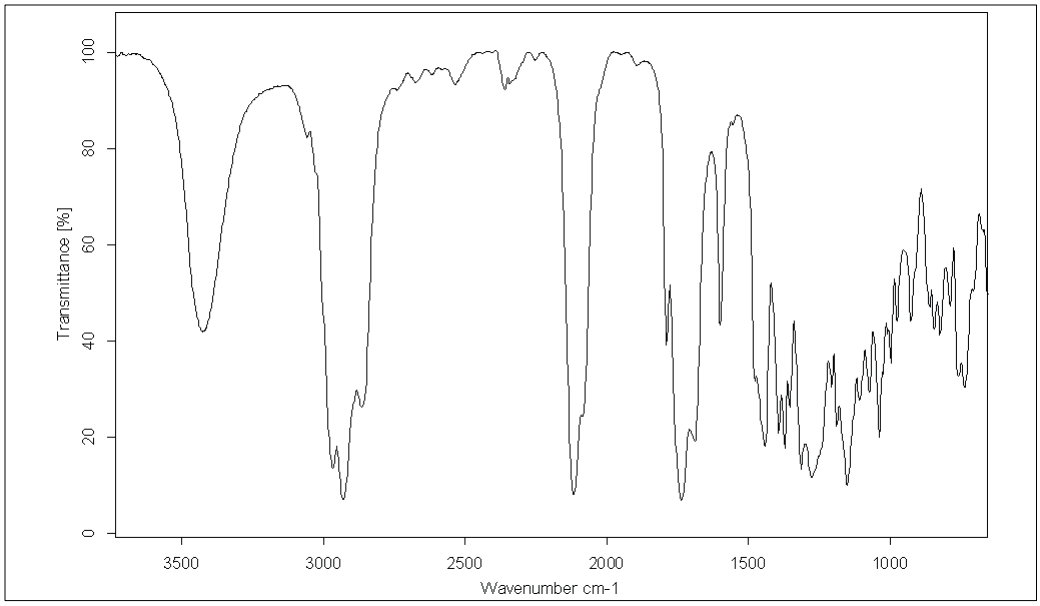


Figure A.2.43c. IR spectrum (thin film/NaCl) of compound **173**

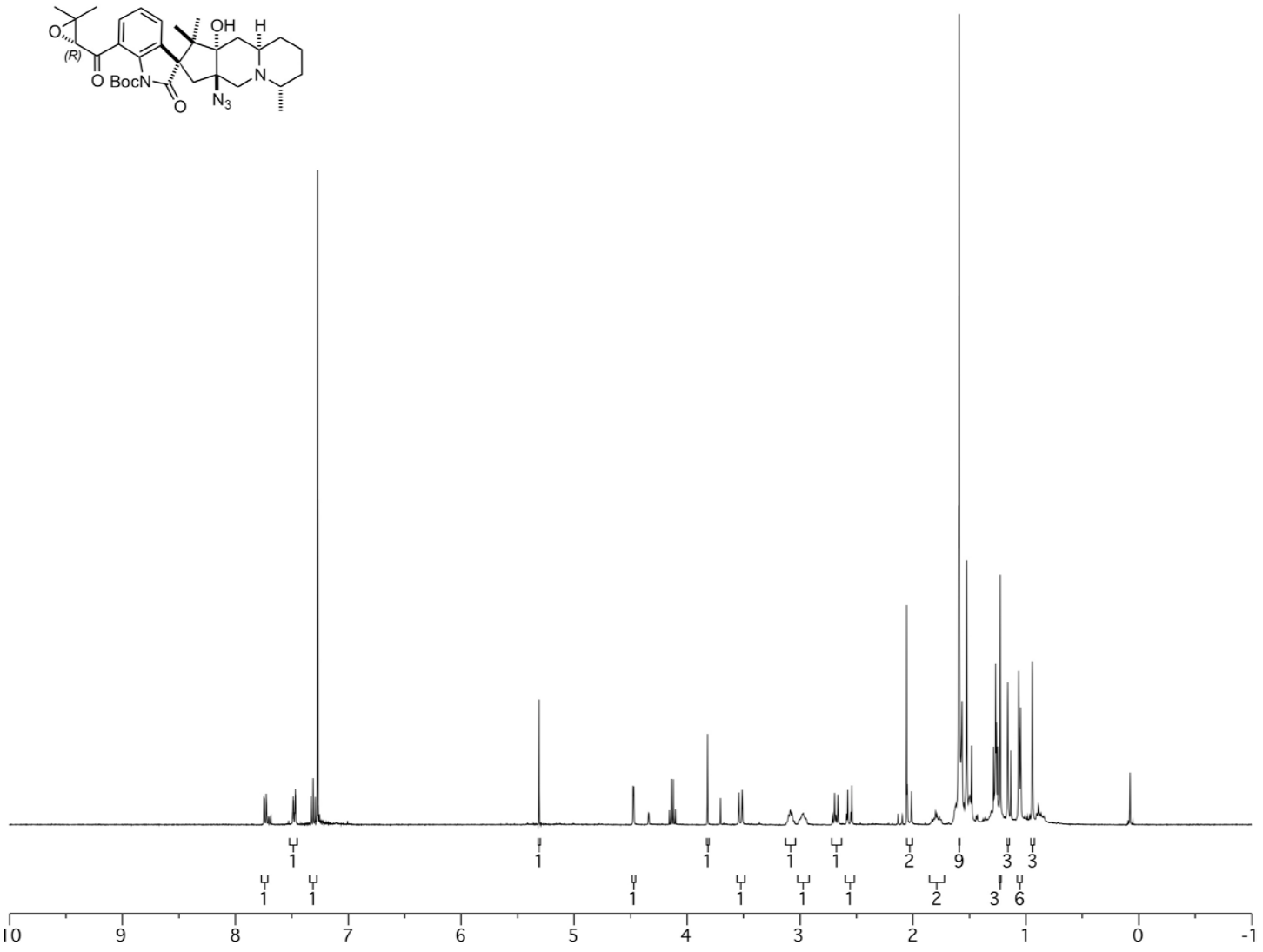


Figure A.44a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **174**

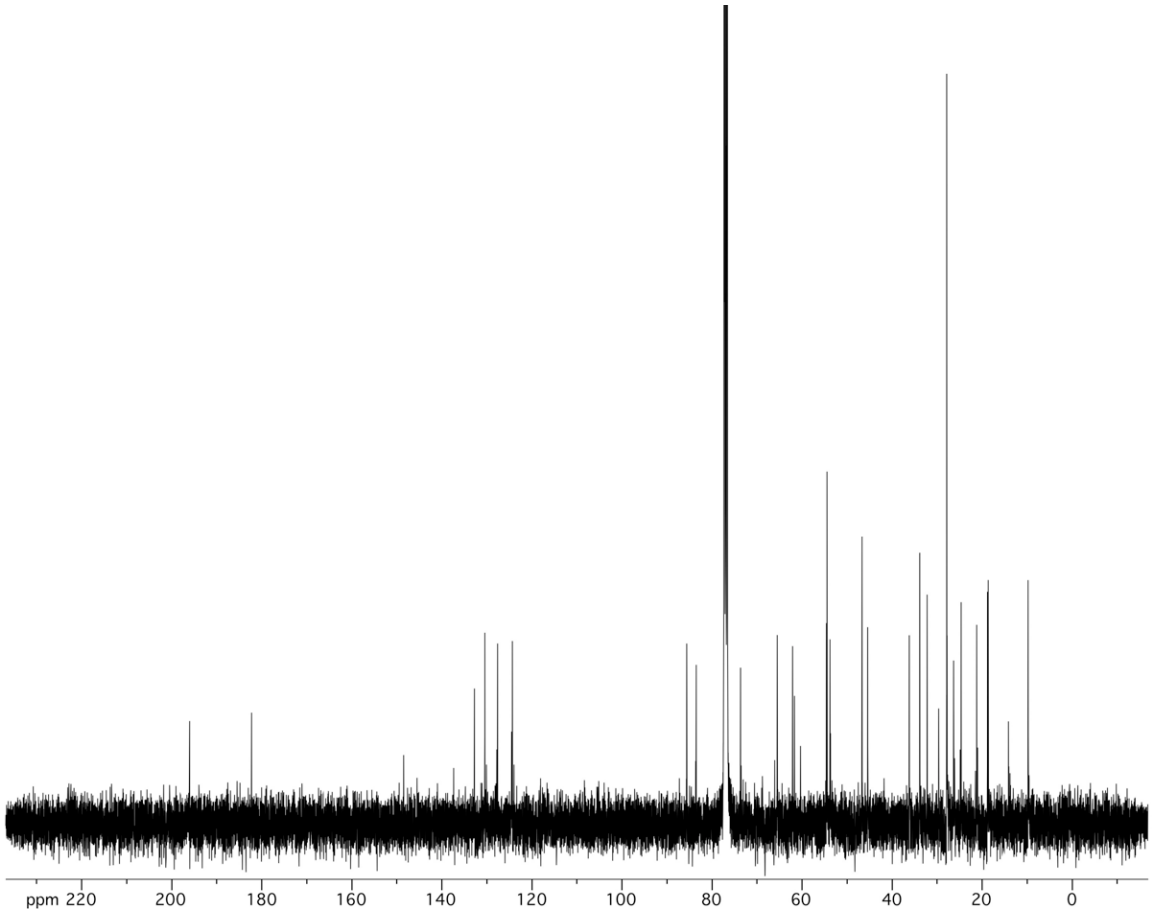


Figure A.2.44b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **174**

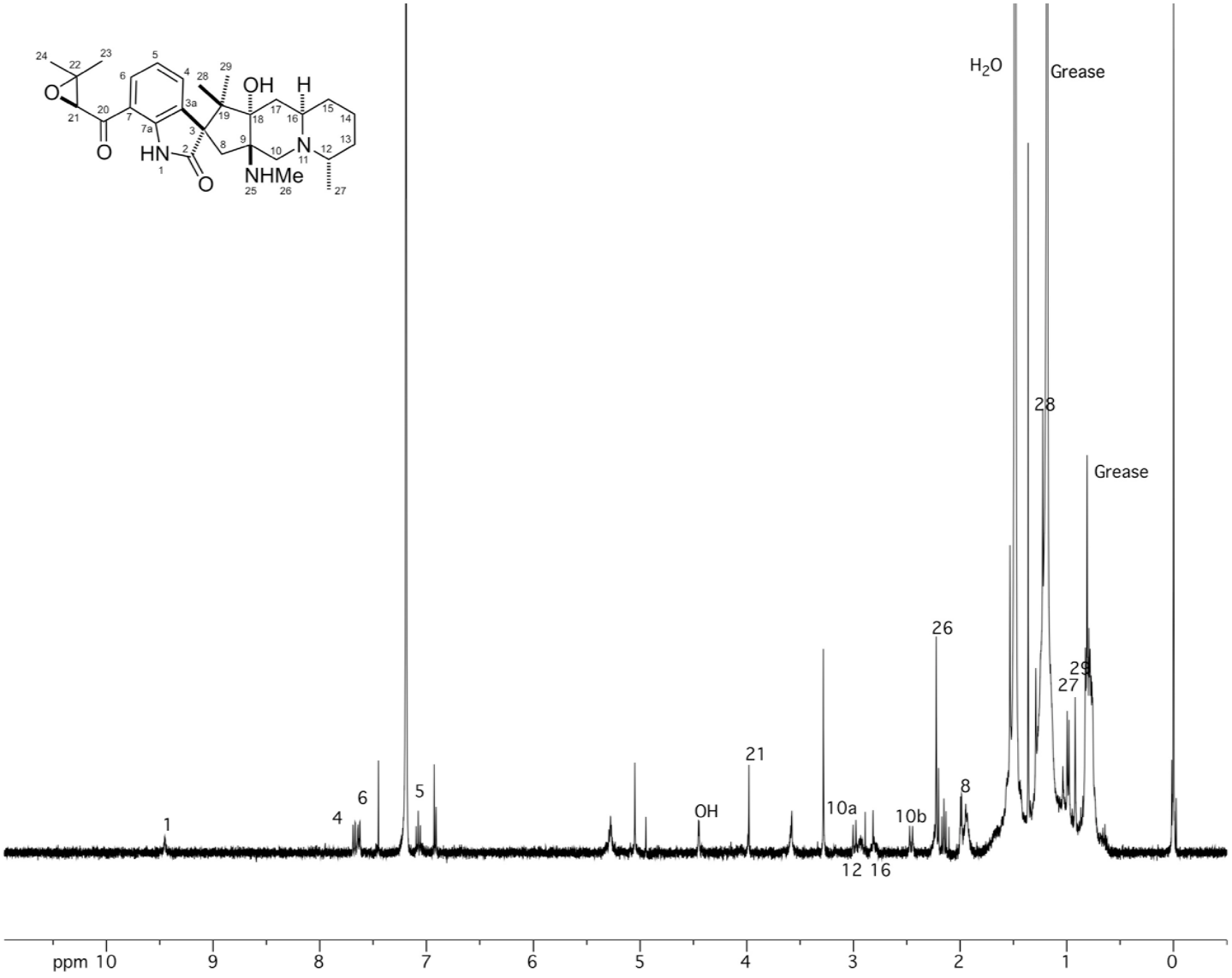


Figure A.2.45a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **175** (Free Base)

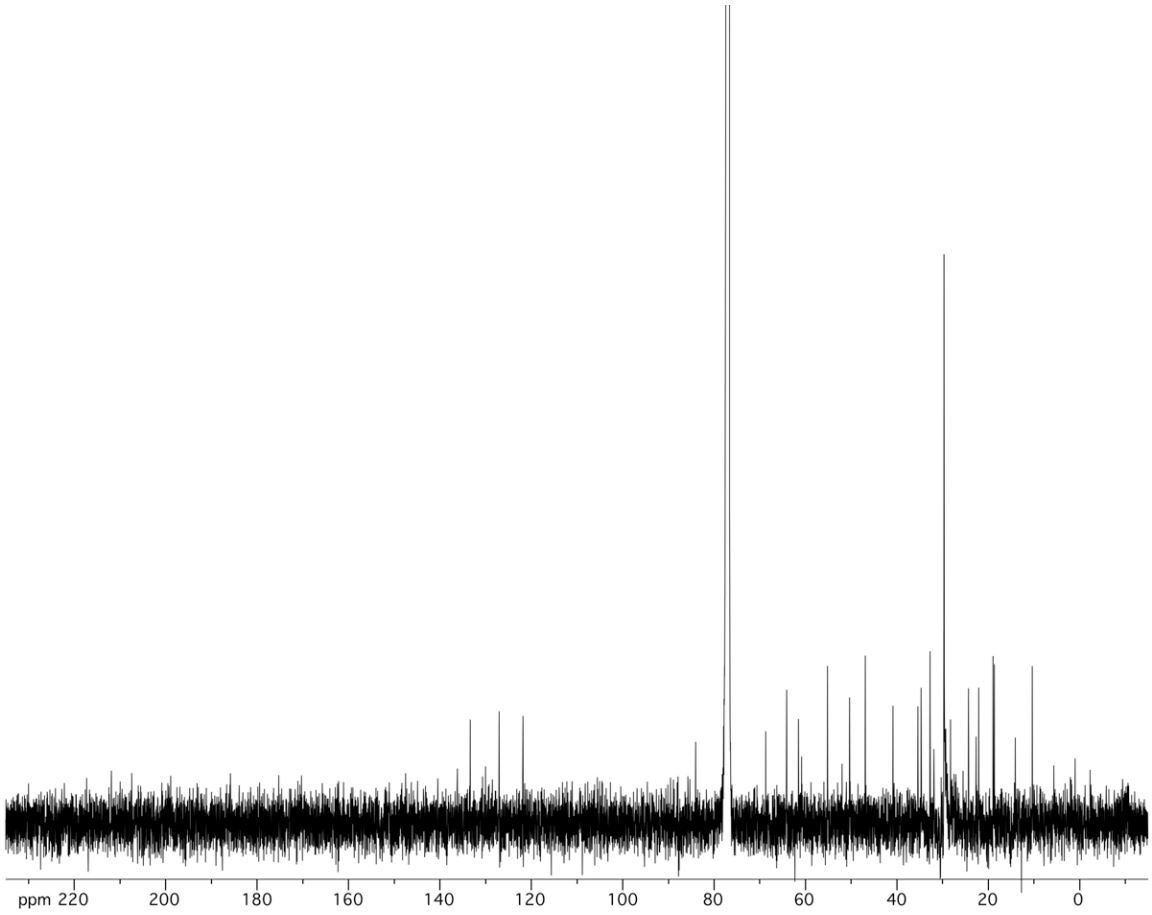


Figure A.2.45b. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **175** (Free Base)

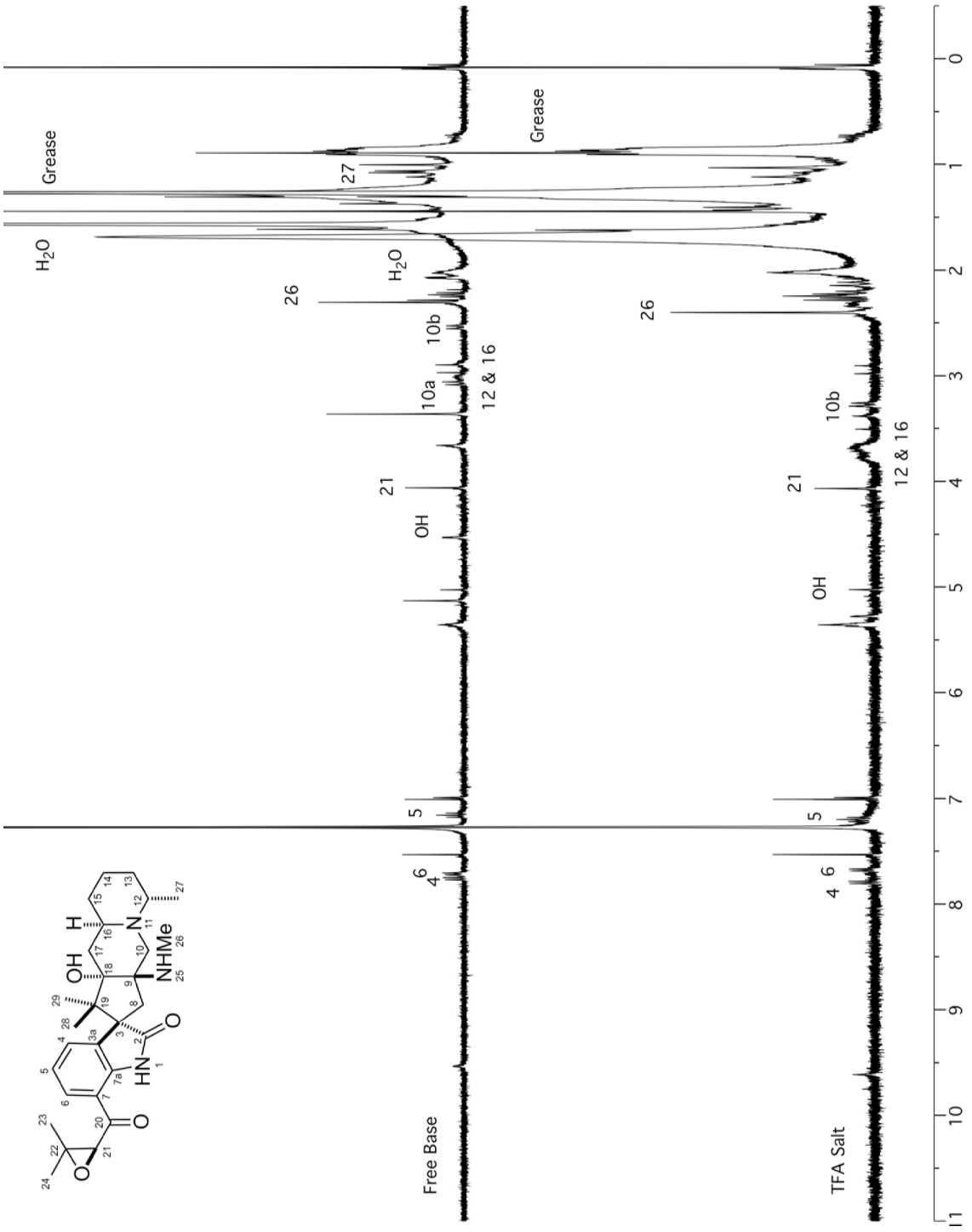


Figure A.2.45d. ^{1}H NMR (400 MHz, $CDCl_3$) overlay of **175** (Free Base) and **175** (TFA salt)

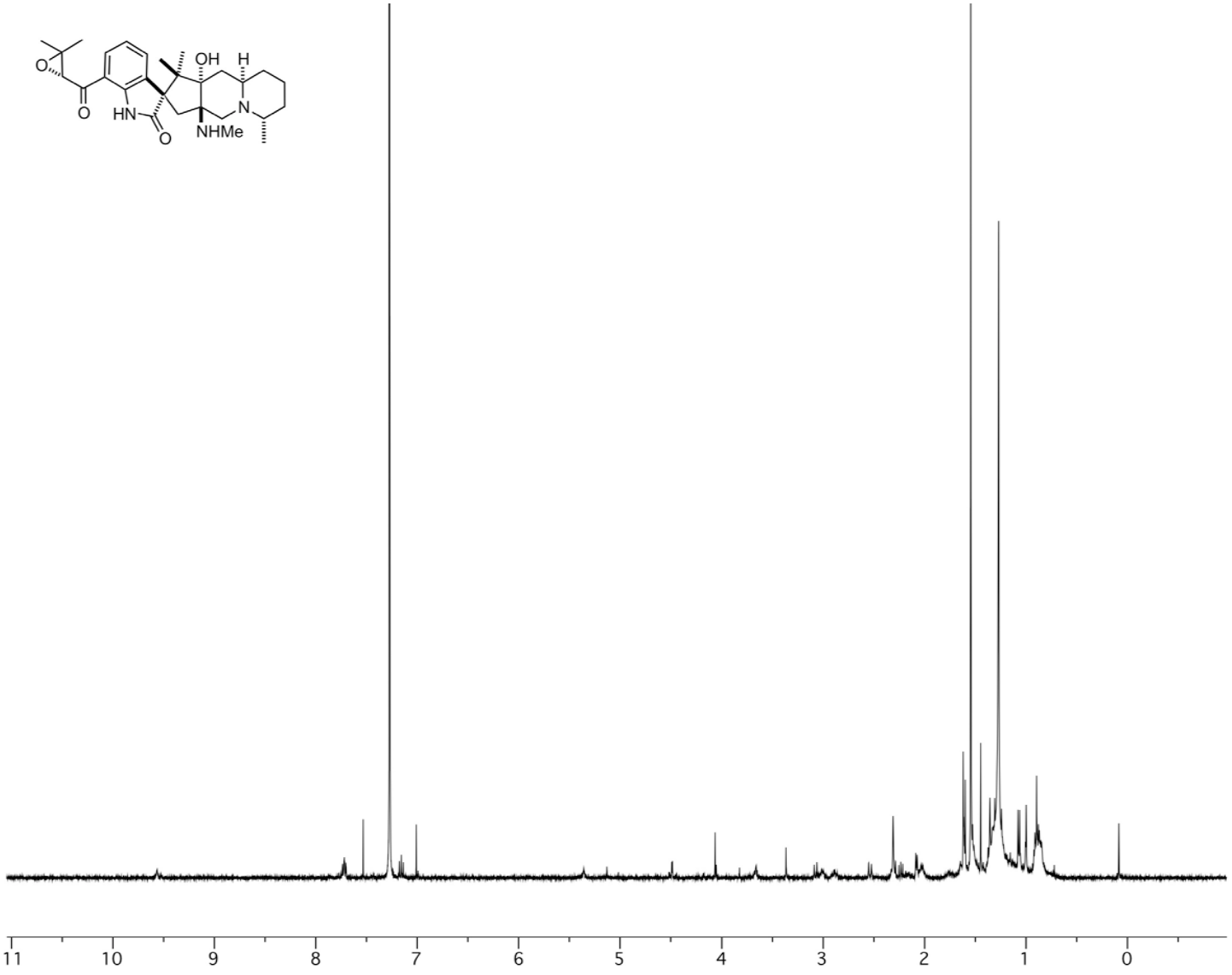


Figure A.2.46a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **ent-2**

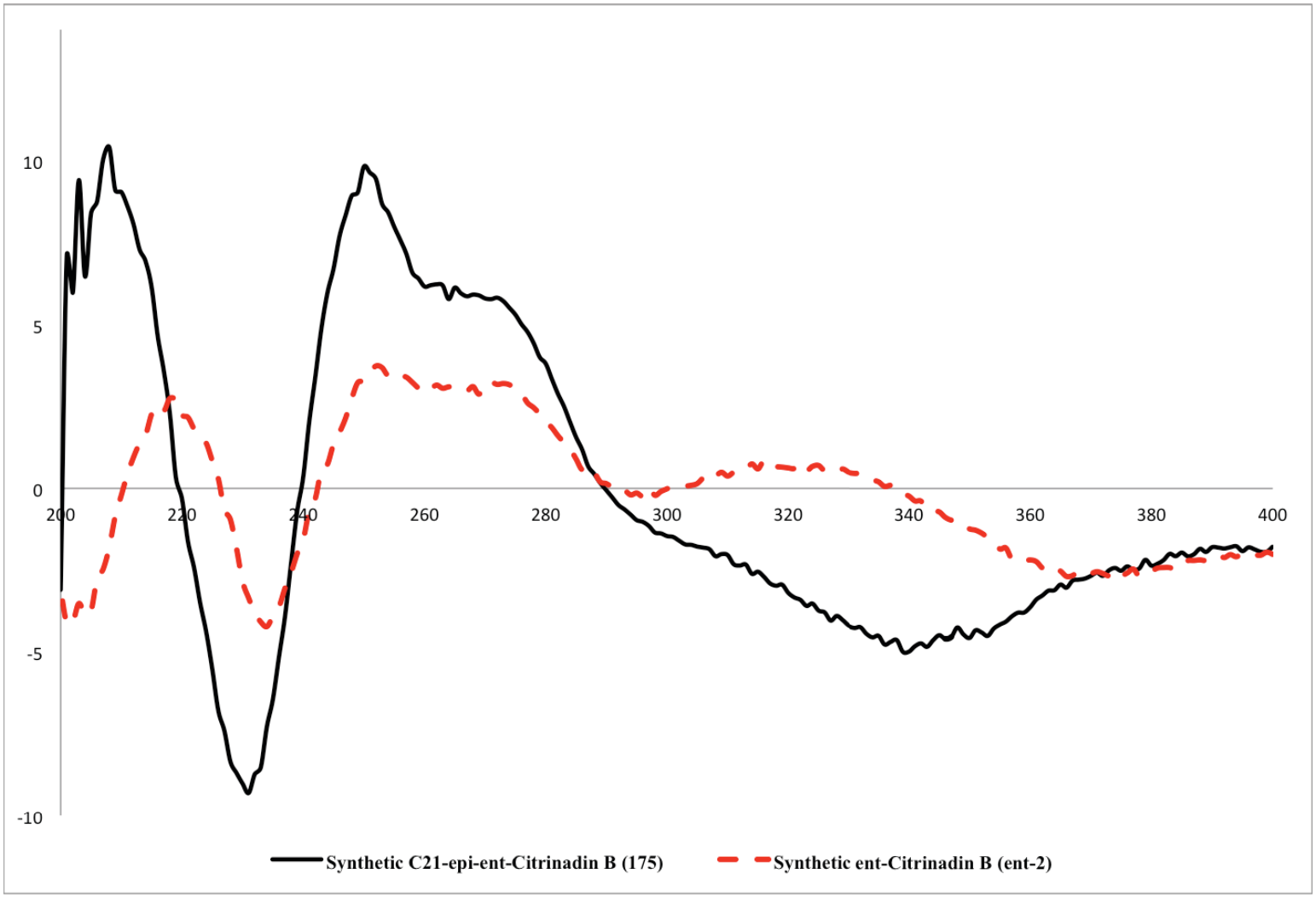


Figure A.2.47 CD Spectra for compounds **175** and **ent-2** in MeOH

APPENDIX III: SPECTRA RELEVANT TO CHAPTER 4

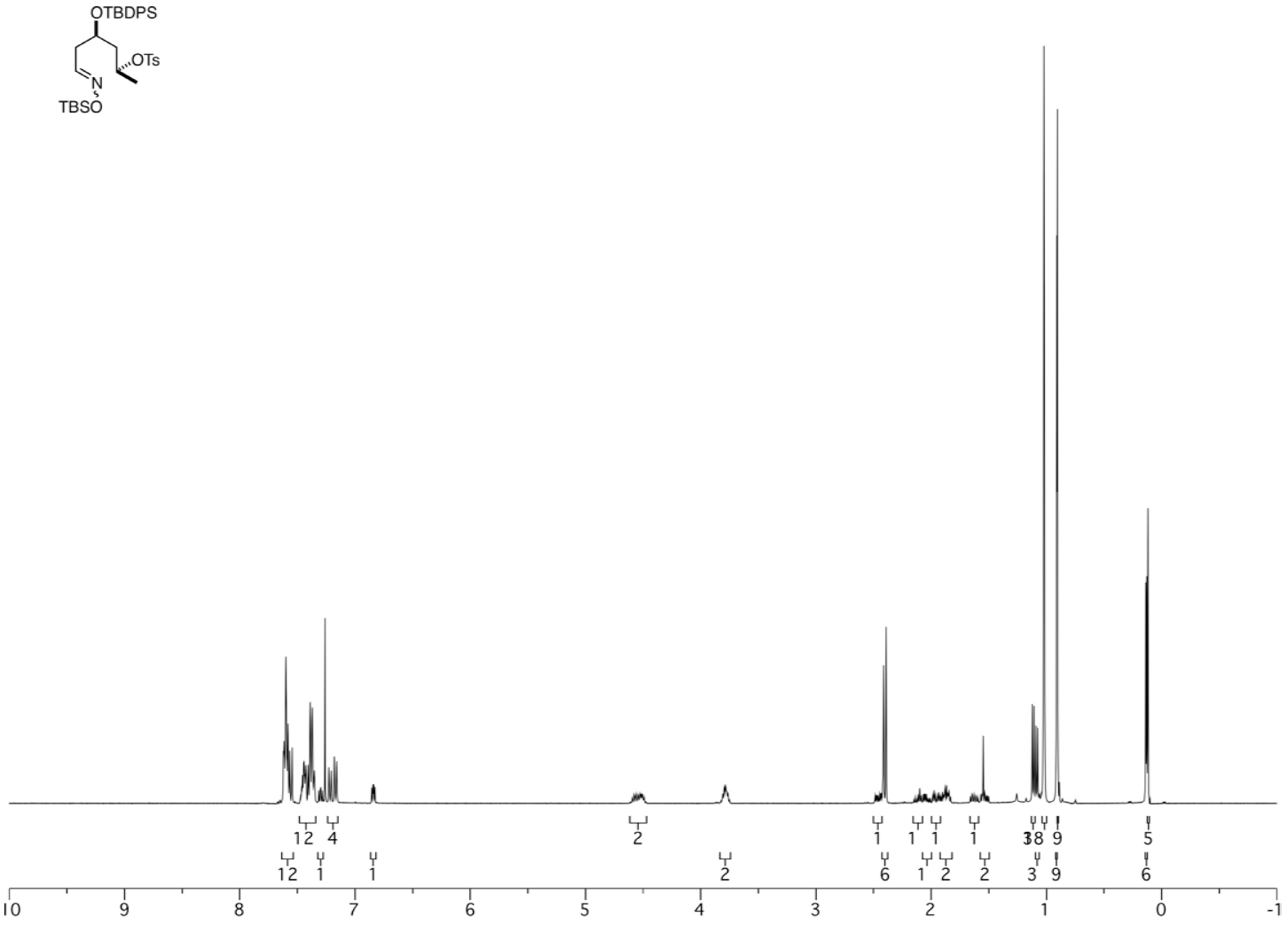


Figure A.3.1a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **182**

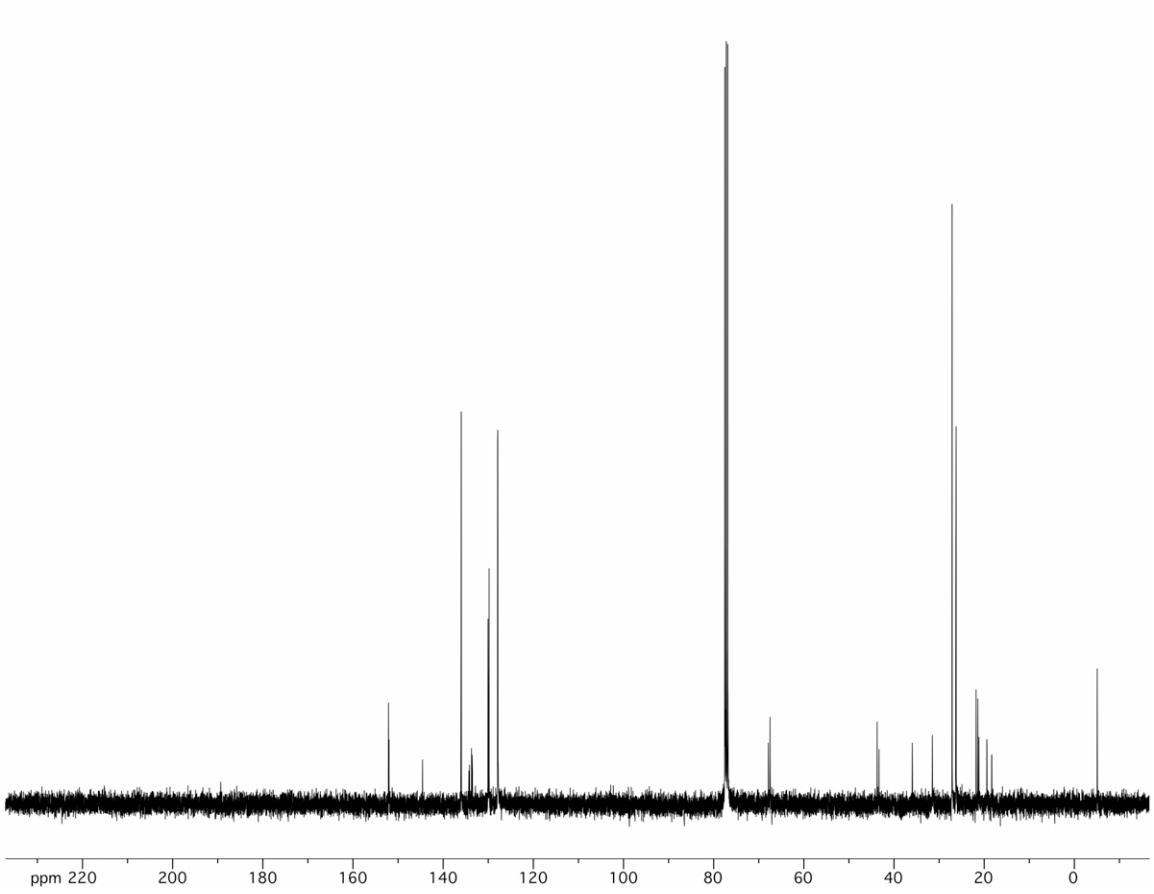


Figure A.3.1b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **182**

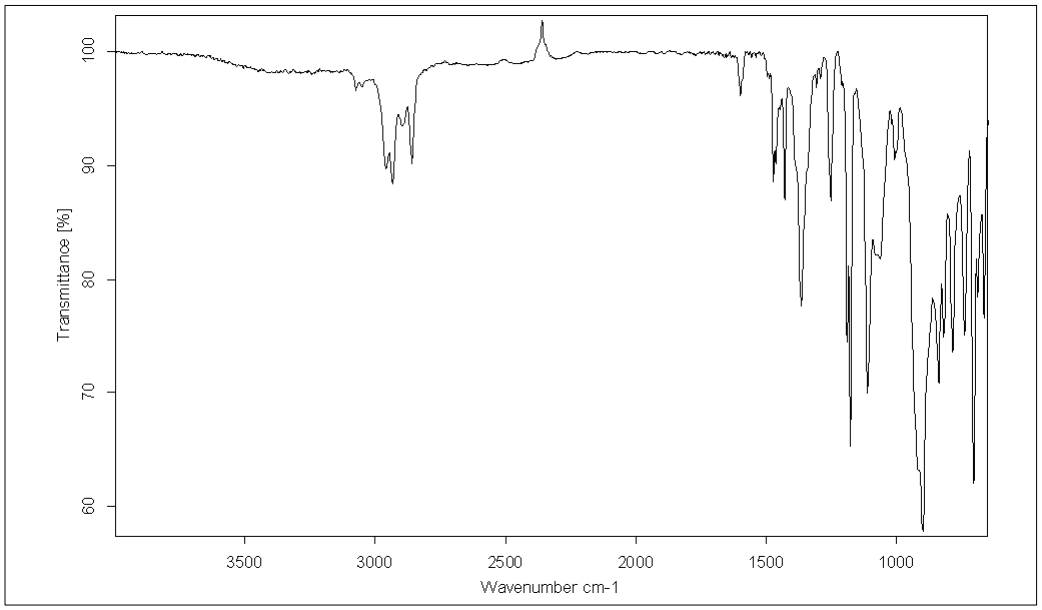


Figure A.3.1c IR spectrum (thin film/NaCl) of compound **182**

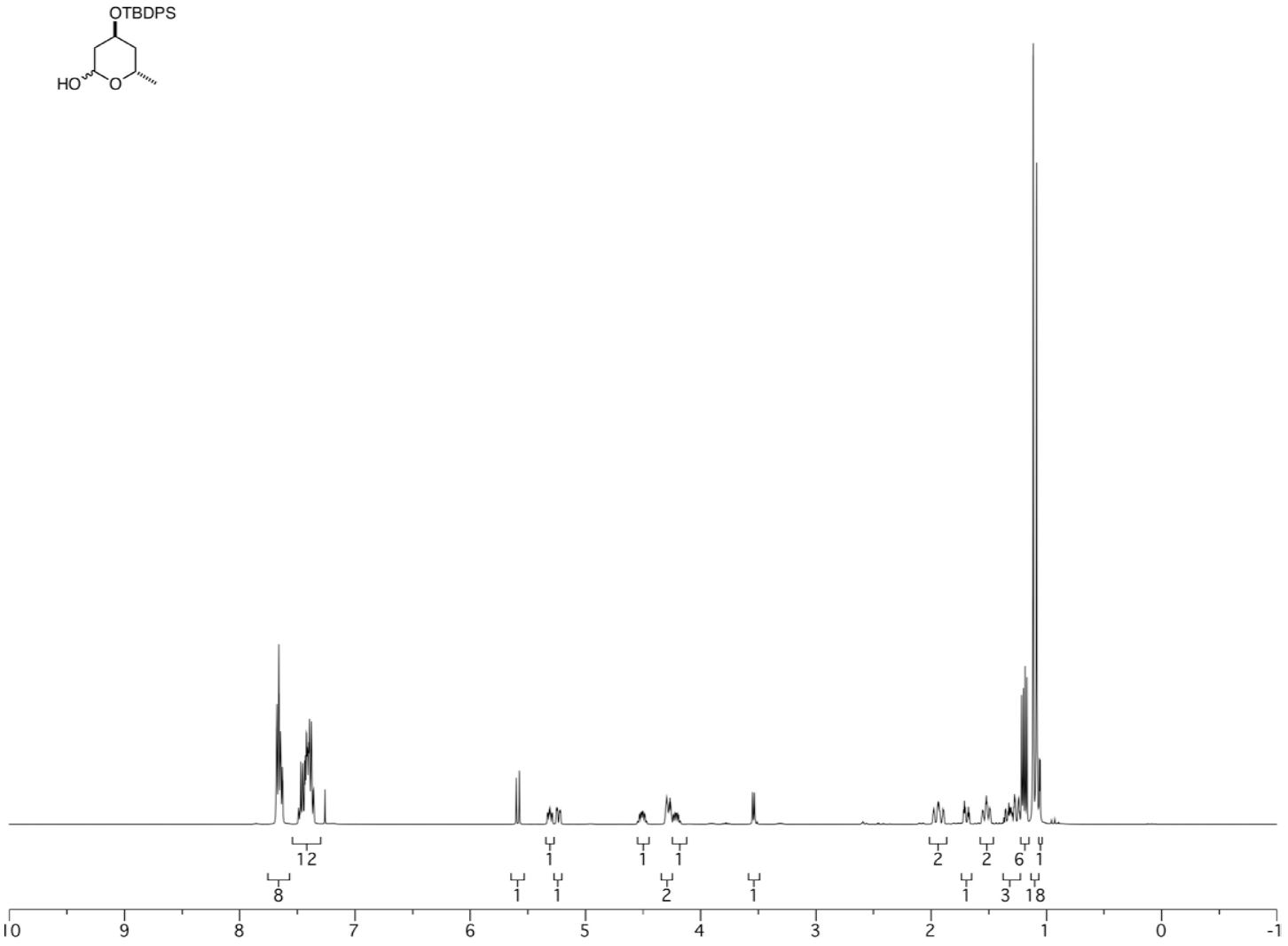


Figure A.3.2a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **183**

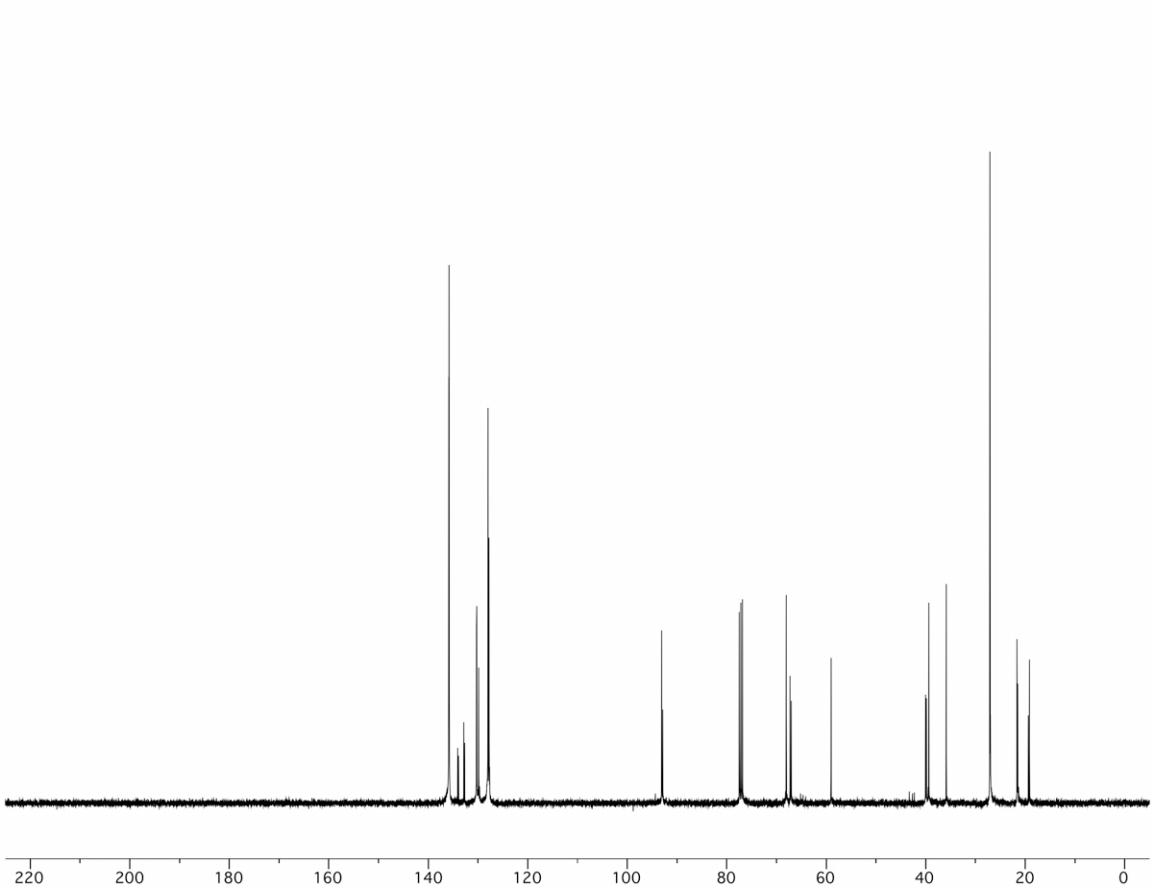


Figure A.3.2b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **183**

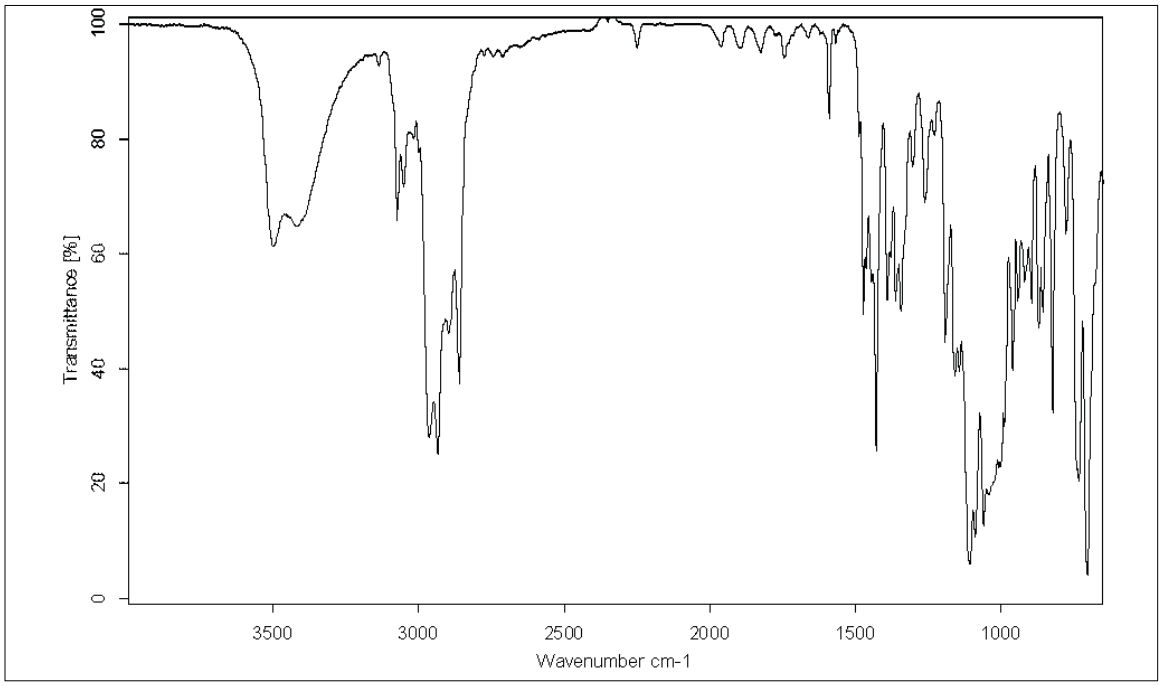


Figure A.3.2c IR spectrum (thin film/NaCl) of compound **183**

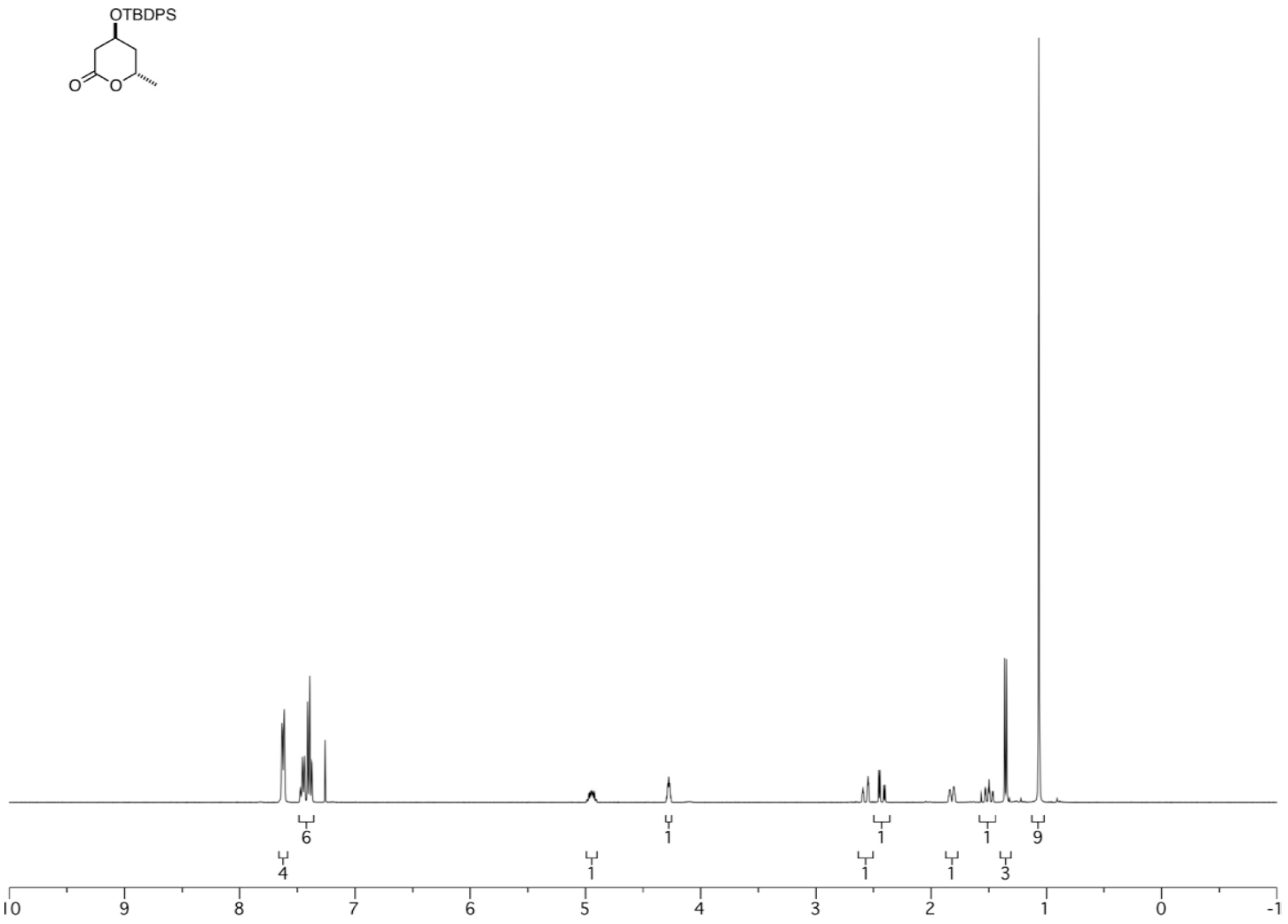


Figure A.3.3a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **184**

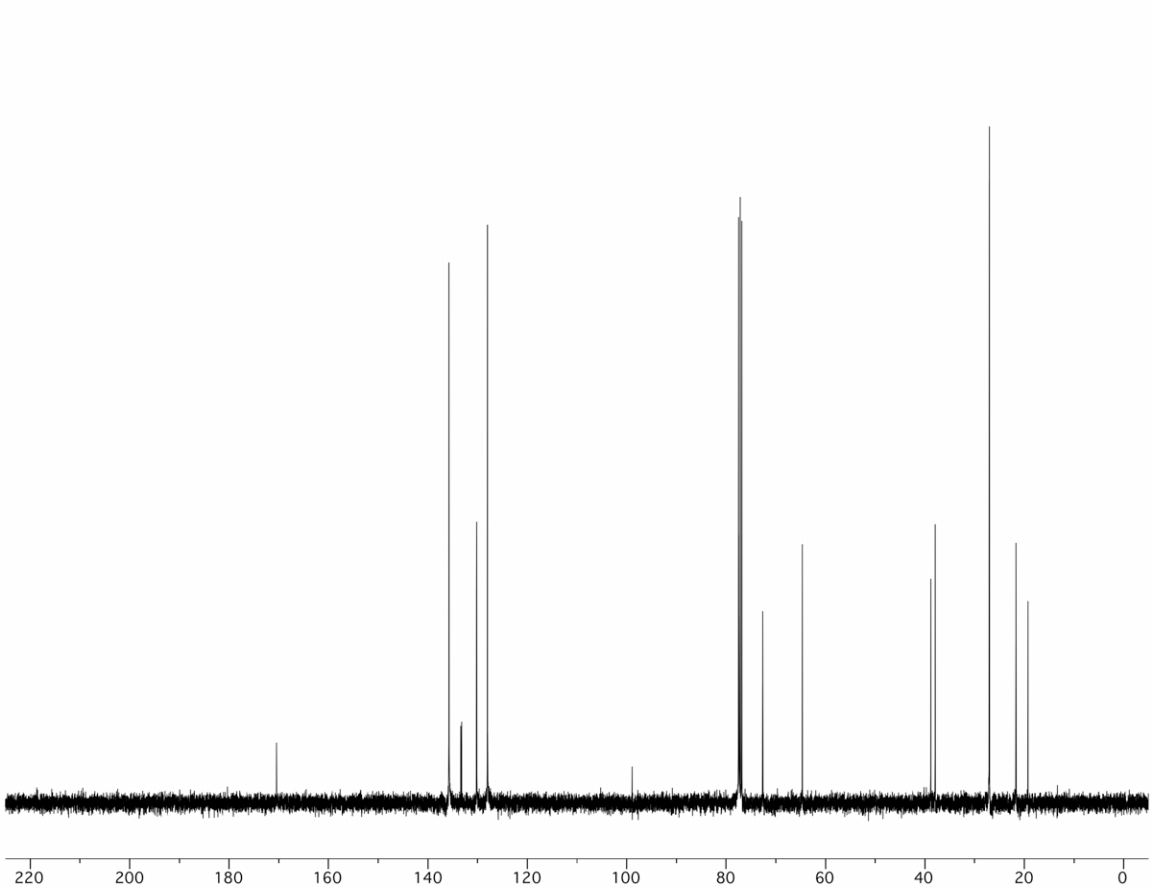


Figure A.3.3b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **184**

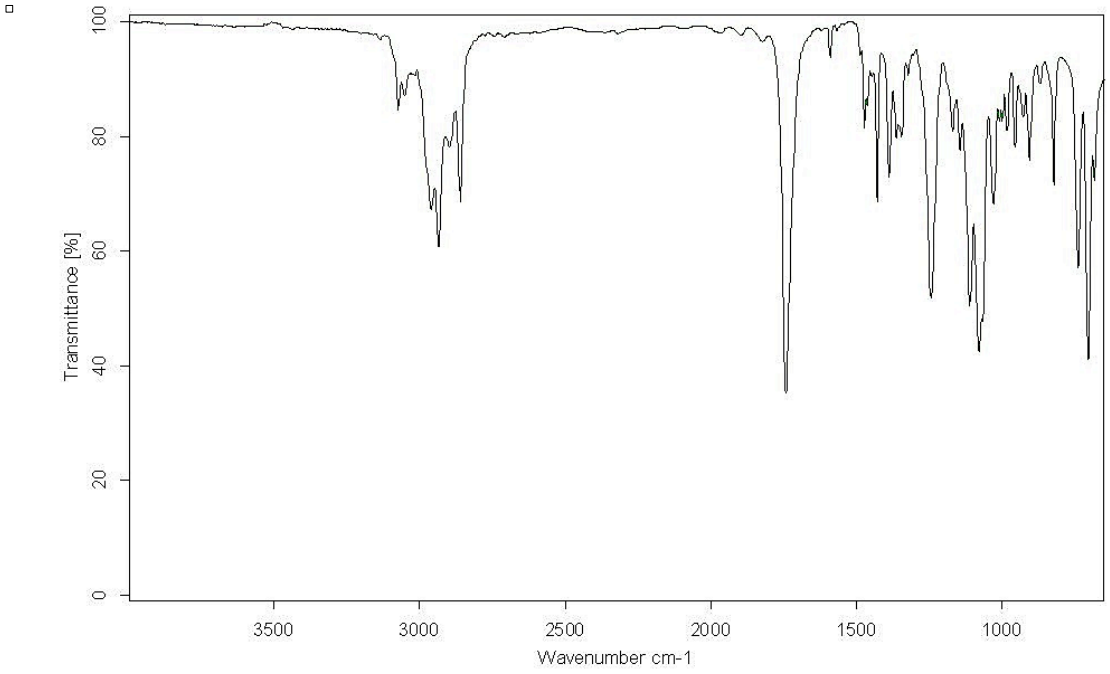


Figure A.3.3c IR spectrum (thin film/NaCl) of compound **184**

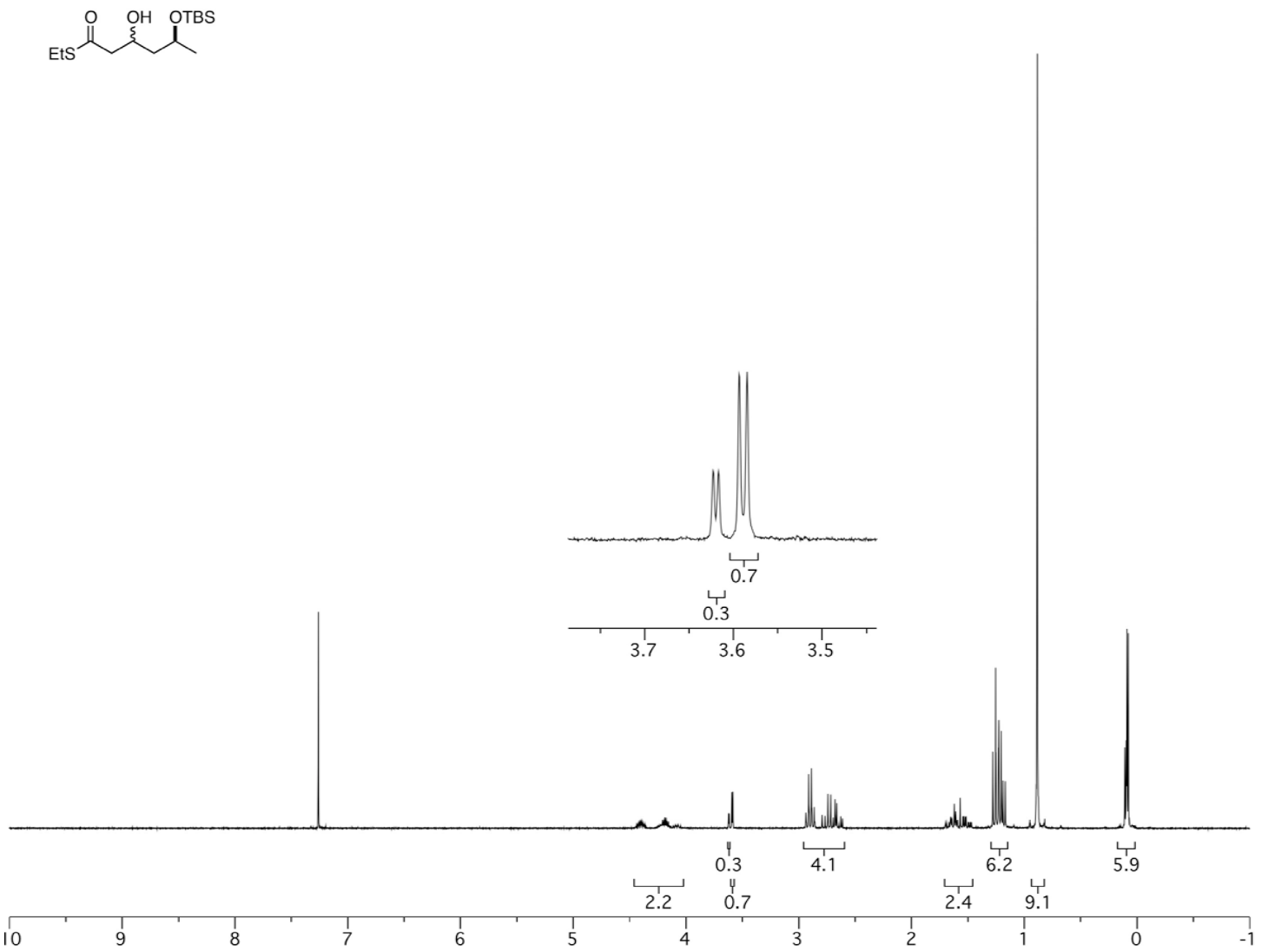


Figure A.3.4a ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **191**

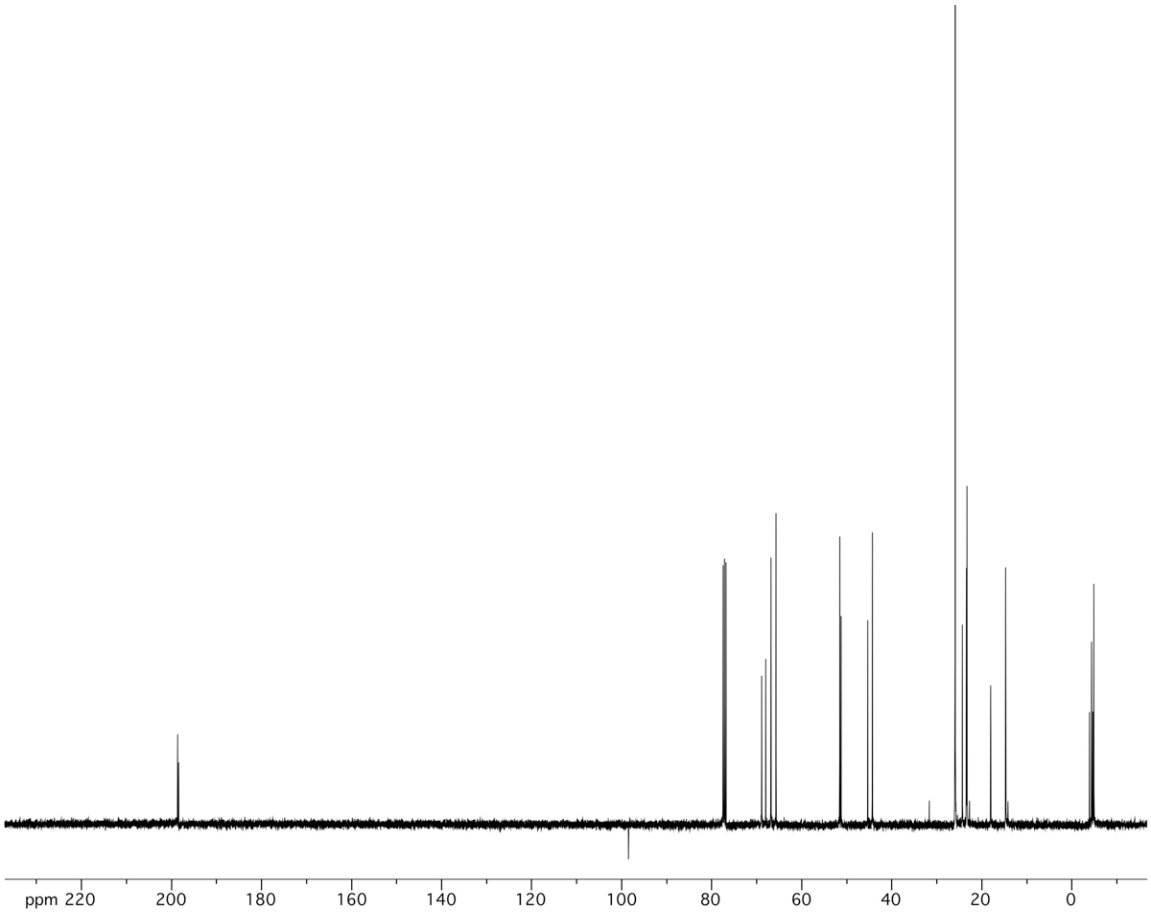


Figure A.3.4b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **191**

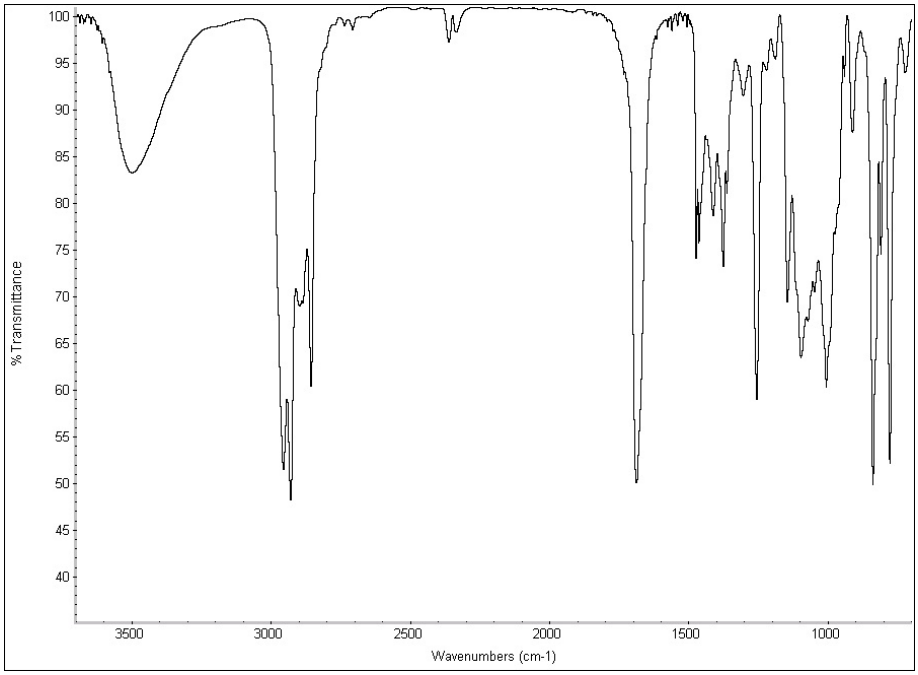


Figure A.3.4c IR spectrum (thin film/NaCl) of compound **191**

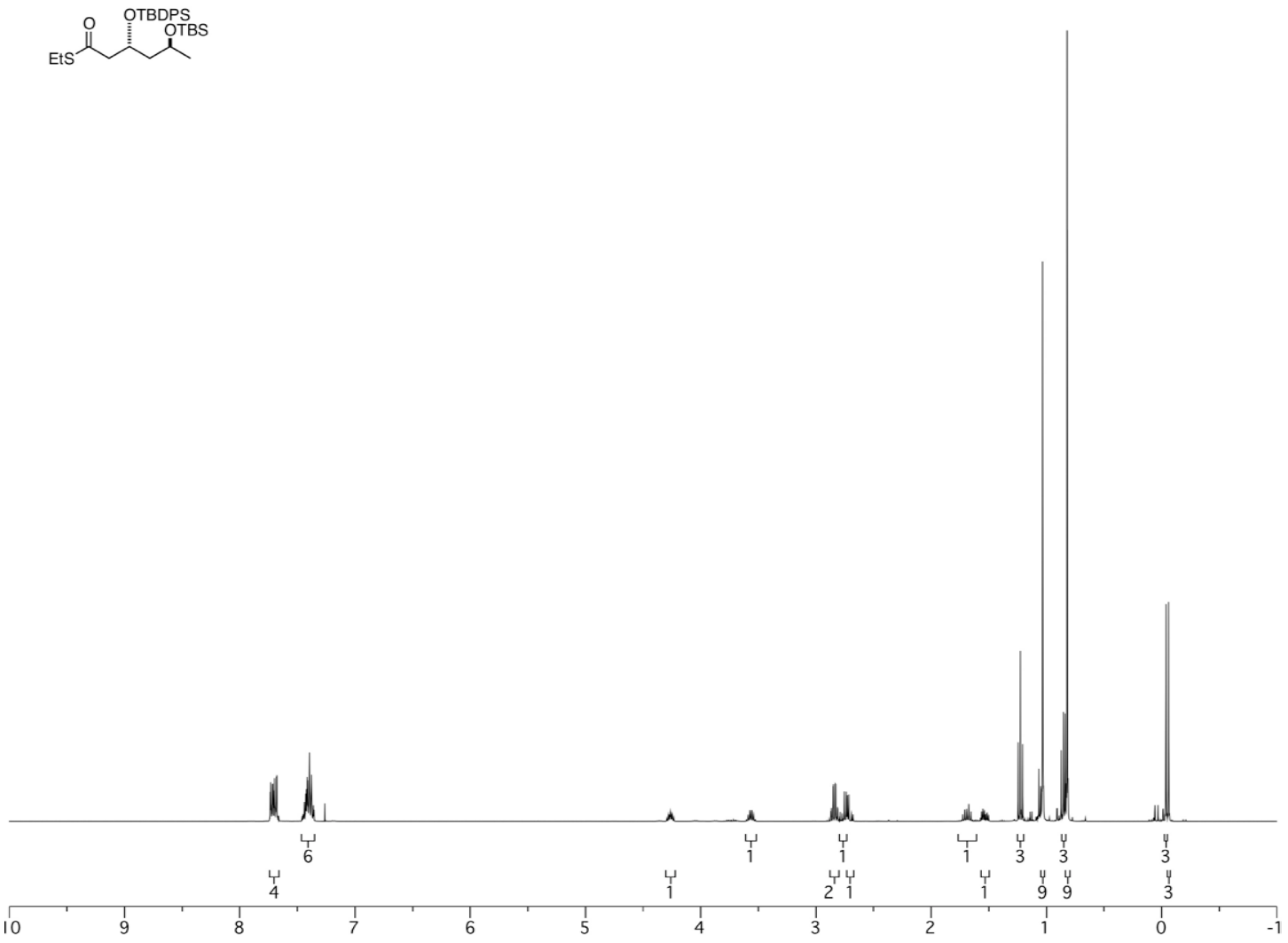


Figure A.3.5a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **194**

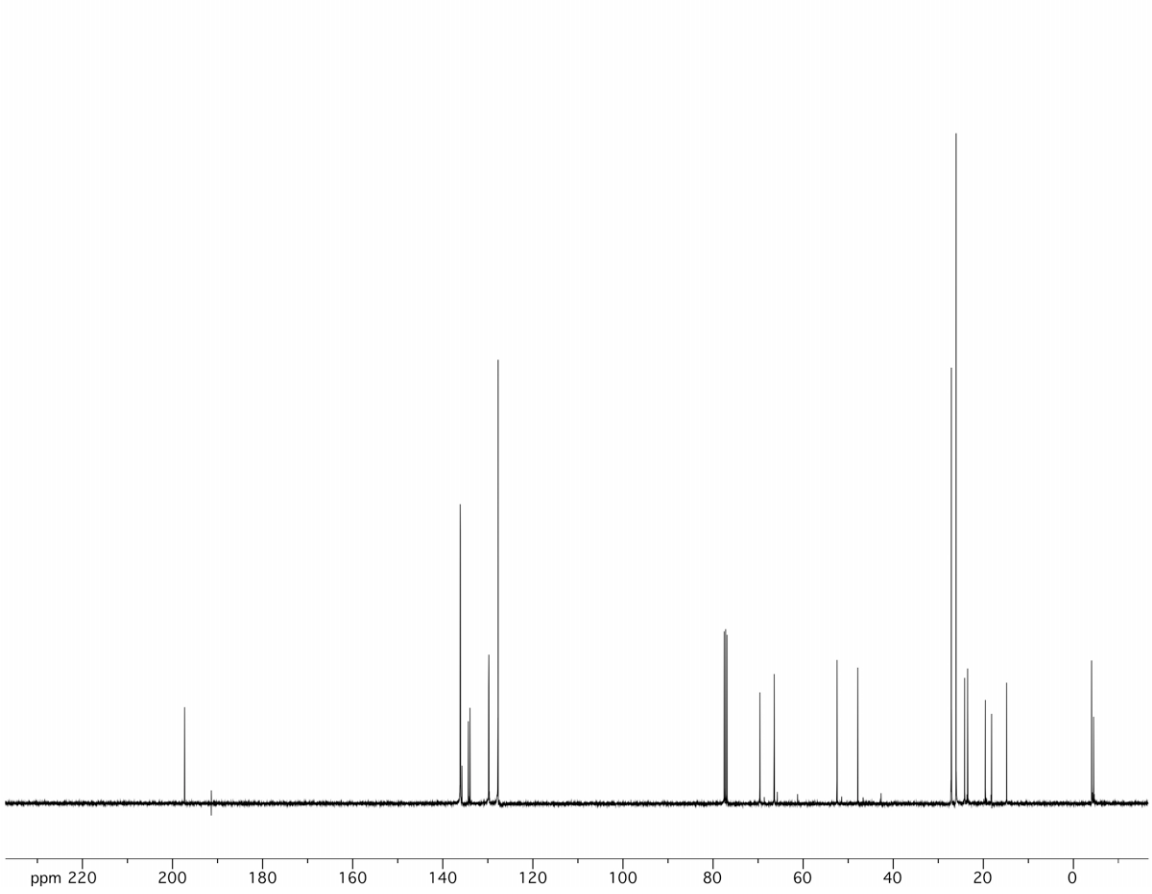


Figure A.3.5b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **194**

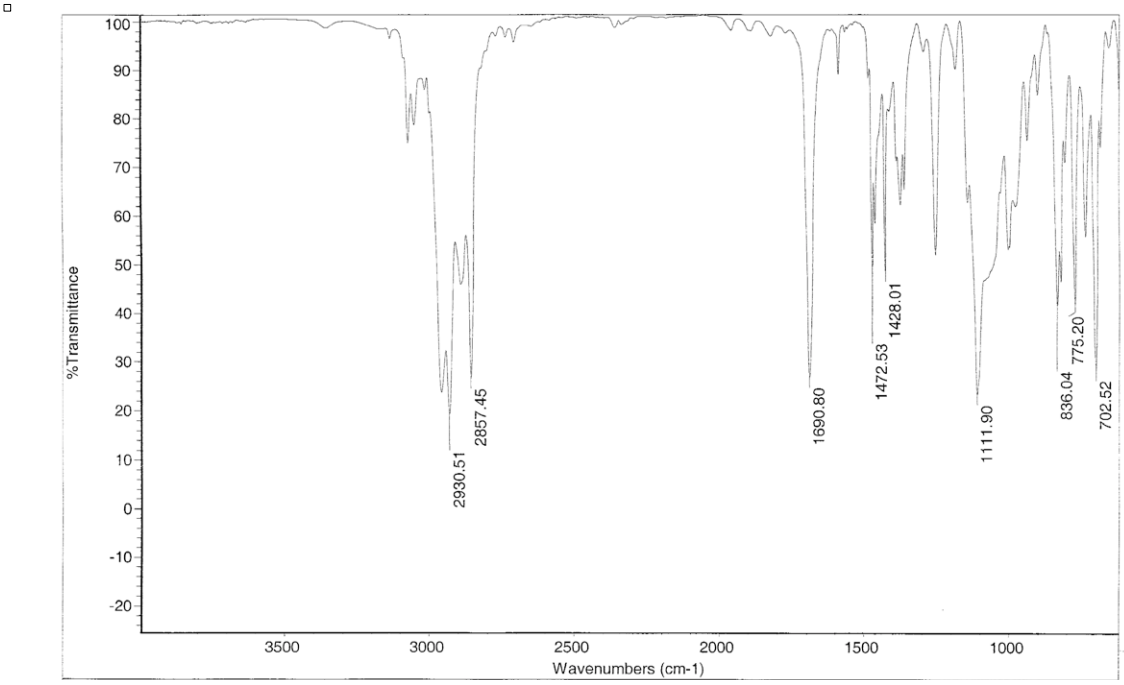


Figure A.3.5c IR spectrum (thin film/NaCl) of compound **194**

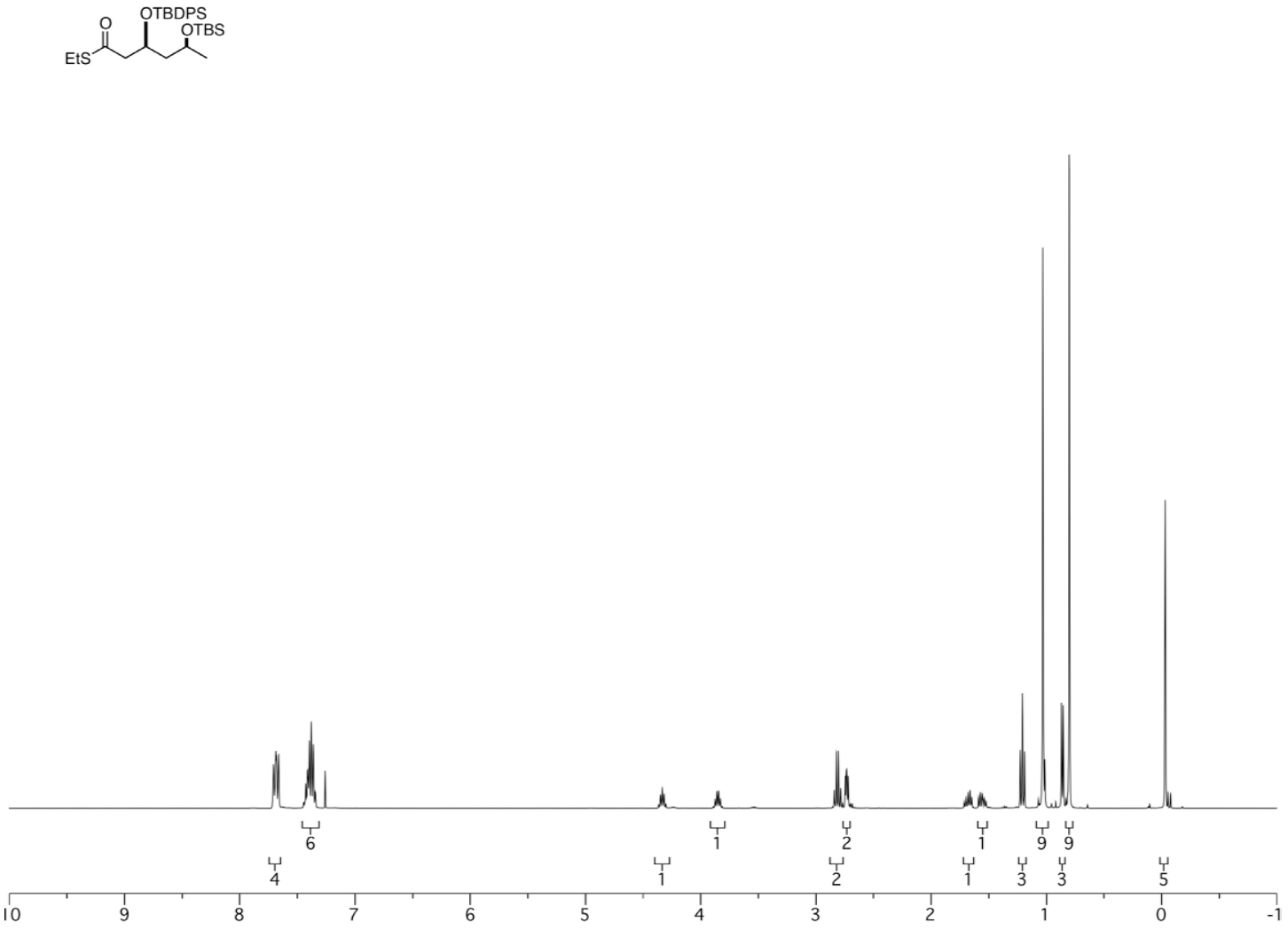


Figure A.3.6a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **195**

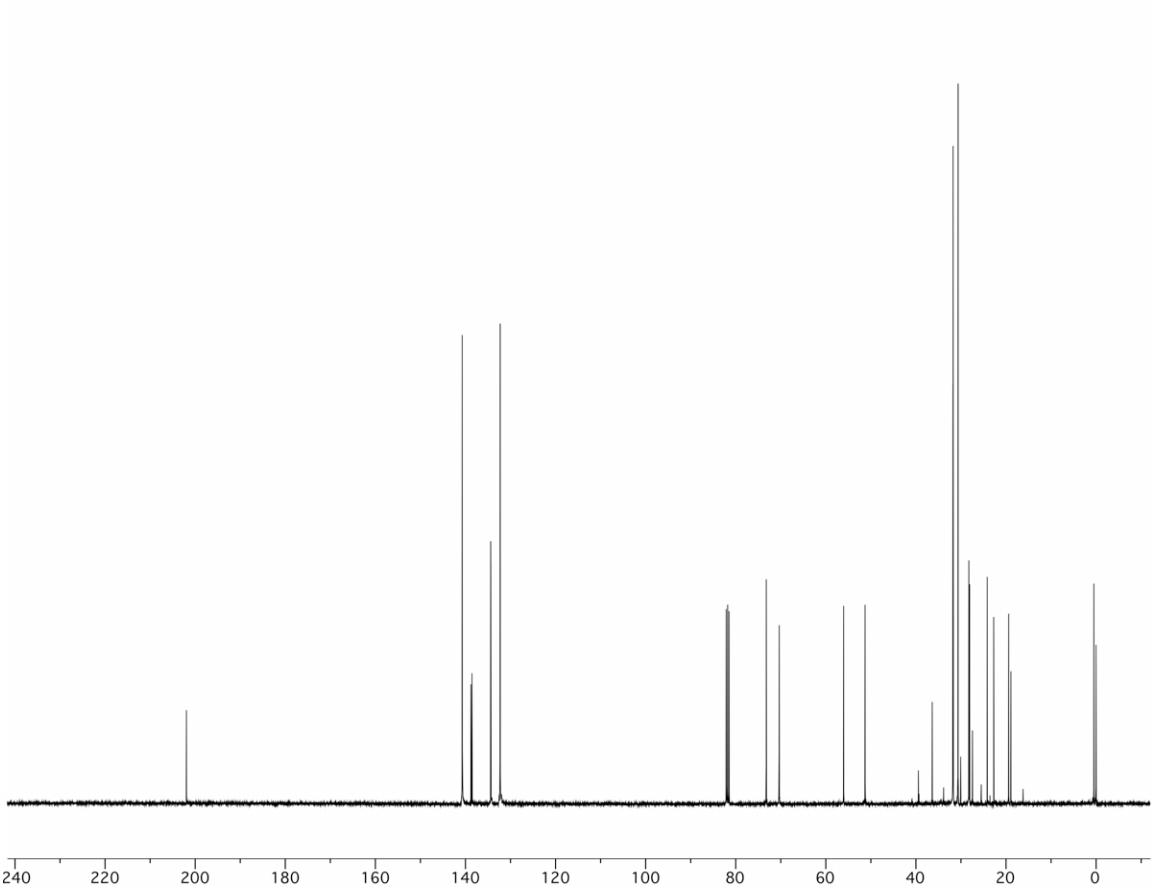


Figure A.3.6b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **195**

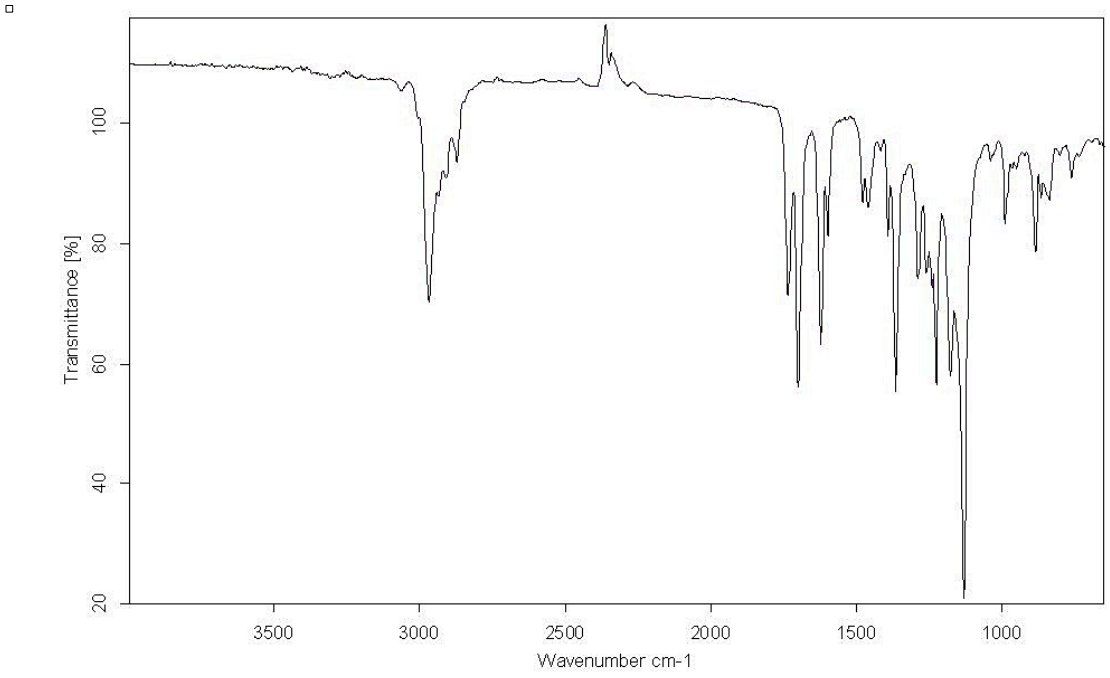


Figure A.3.6c IR spectrum (thin film/NaCl) of compound **195**

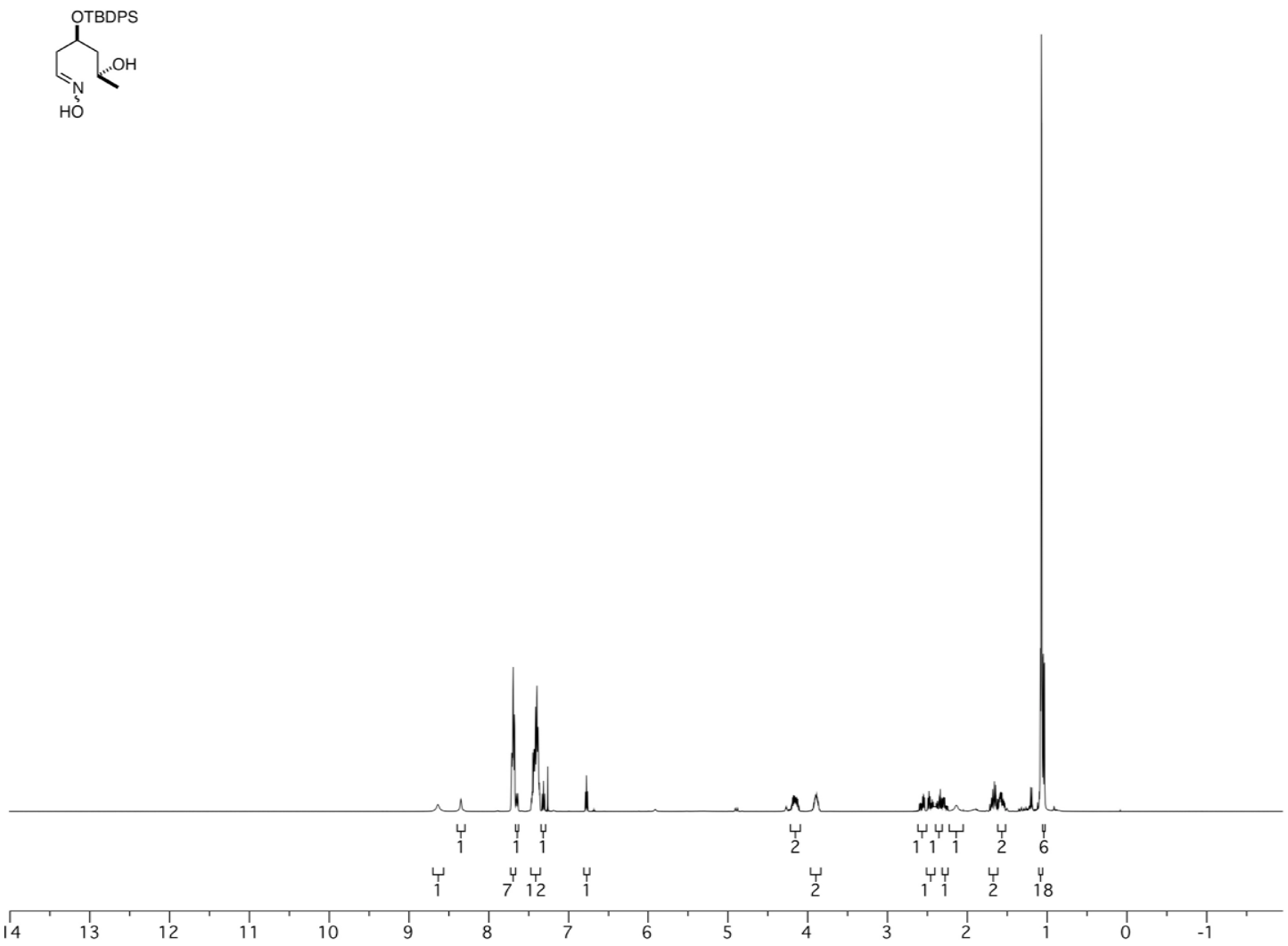


Figure A.3.7a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **197**

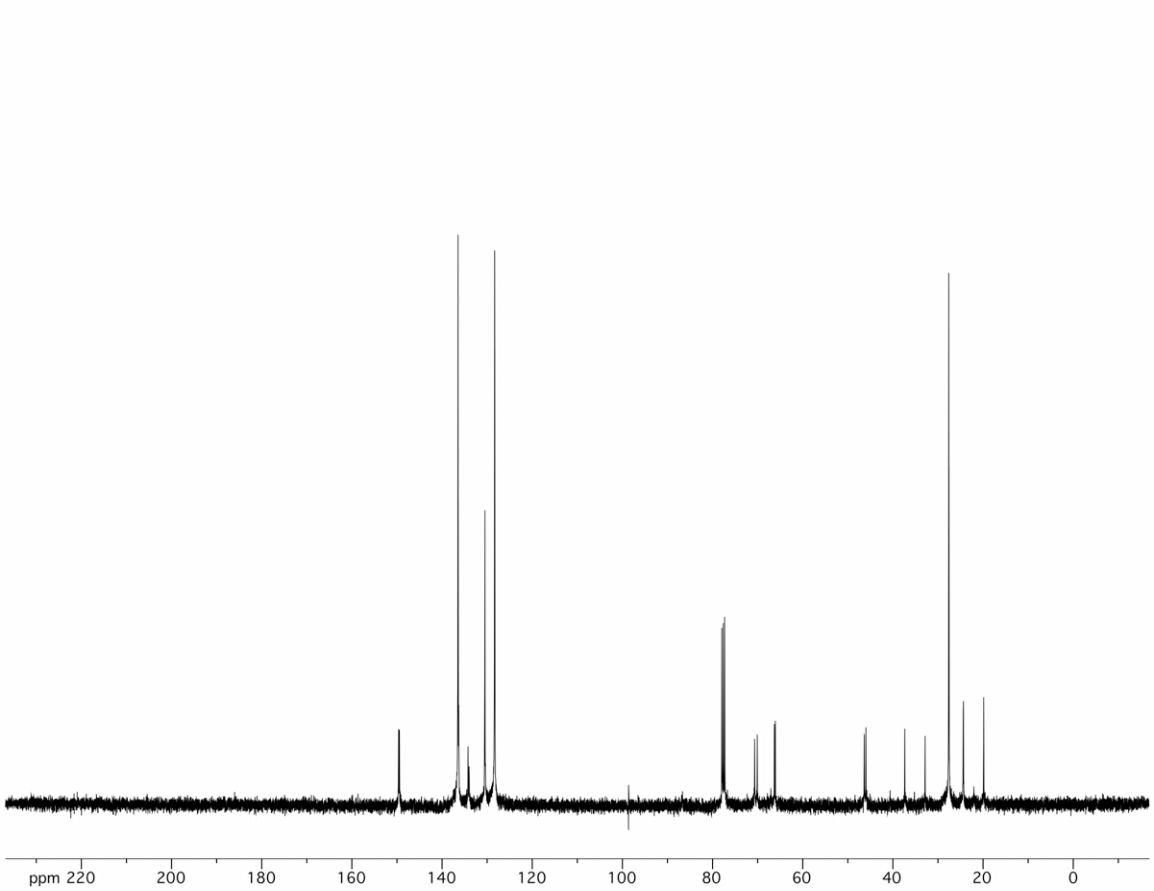


Figure A.3.7b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **197**

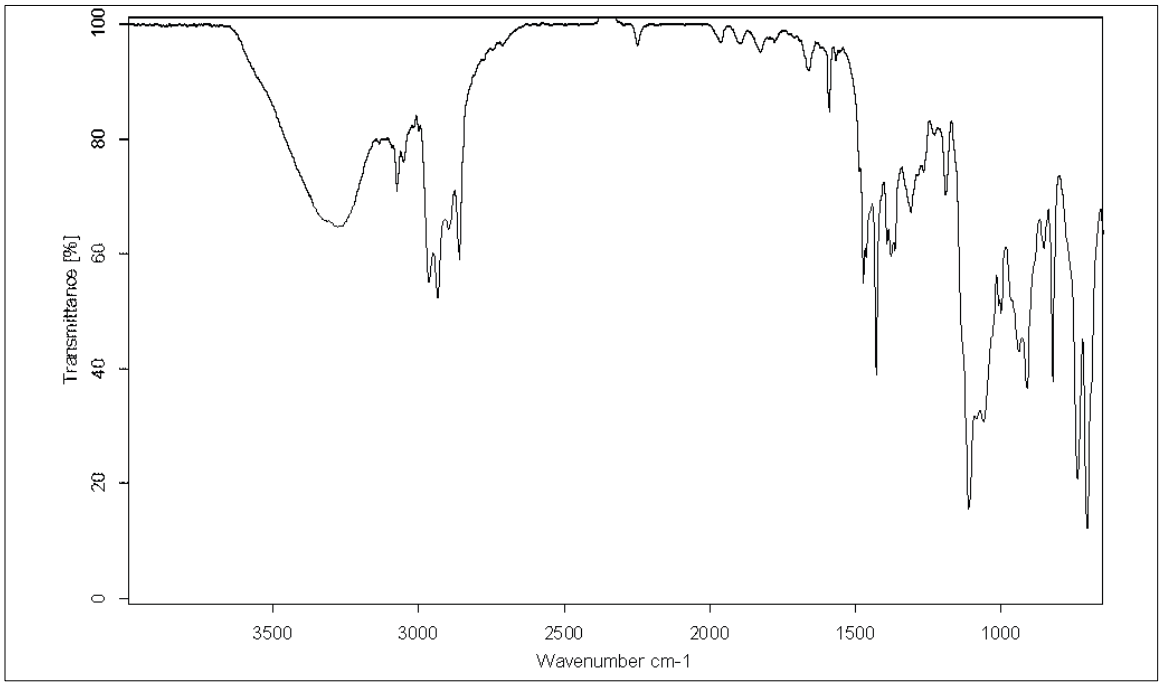


Figure A.3.7c IR spectrum (thin film/NaCl) of compound **197**

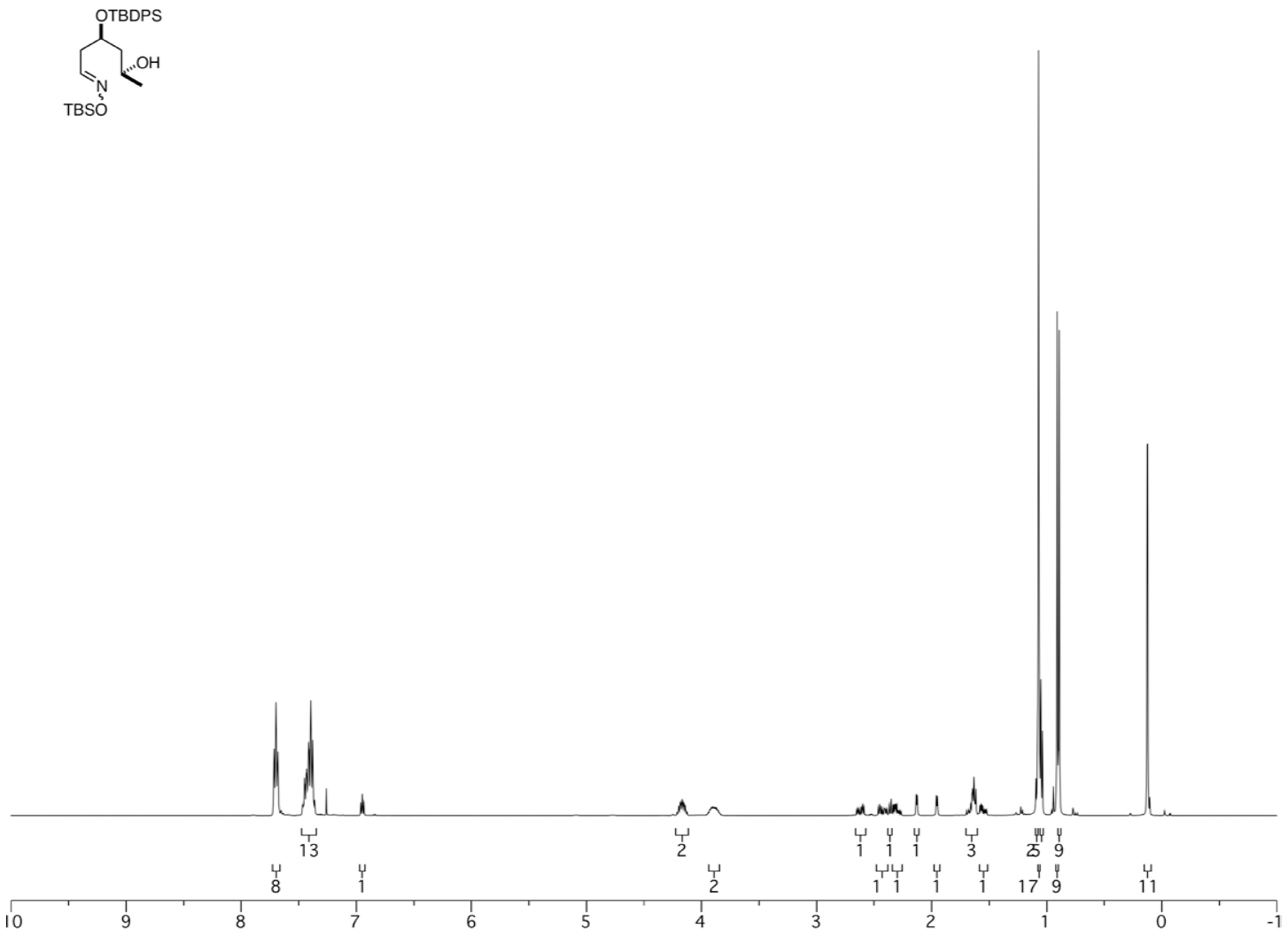


Figure A.3.8a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **198**

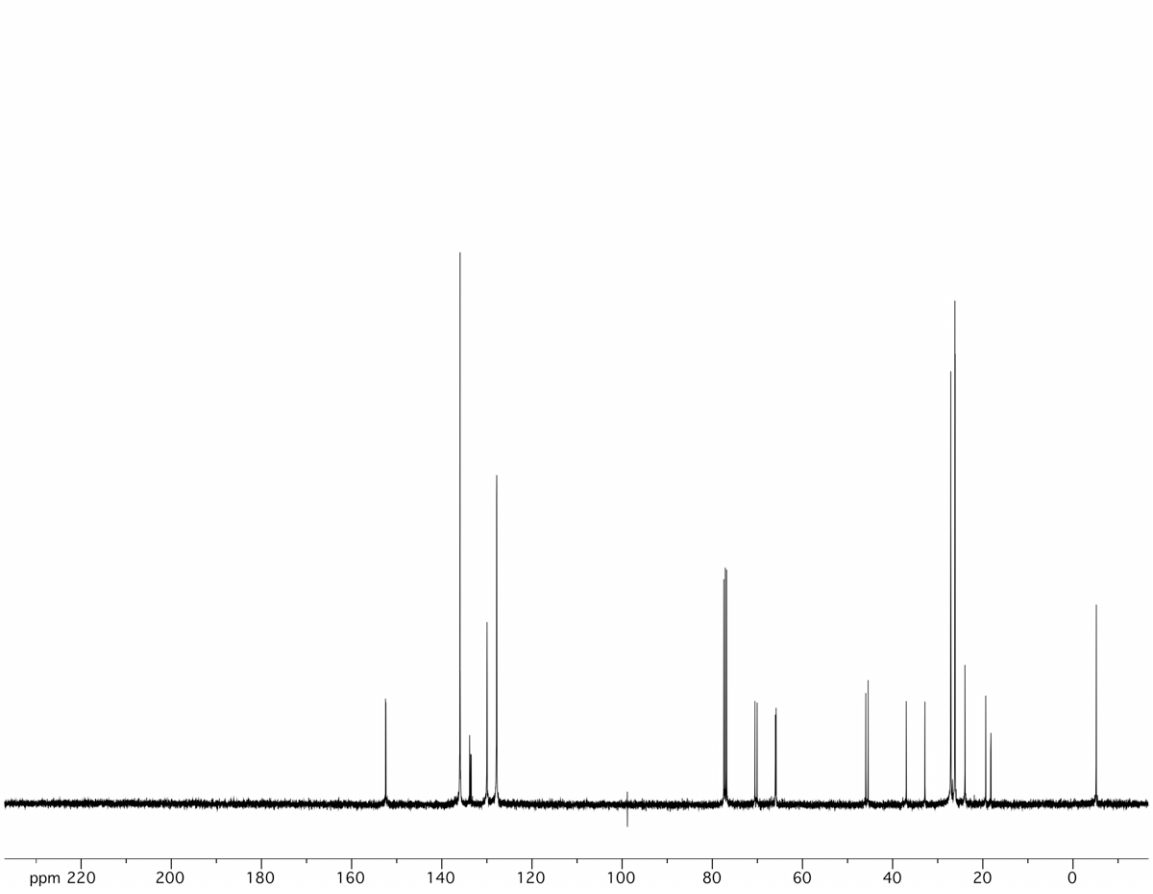


Figure A.3.8b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **198**

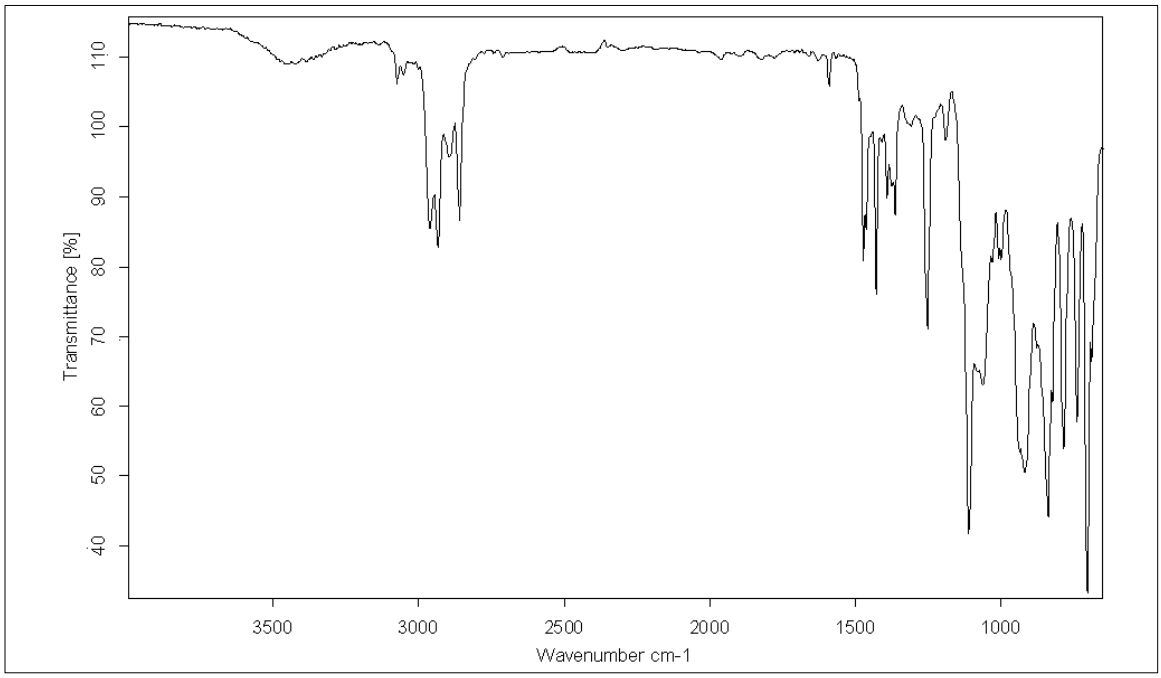


Figure A.3.8c IR spectrum (thin film/NaCl) of compound **198**

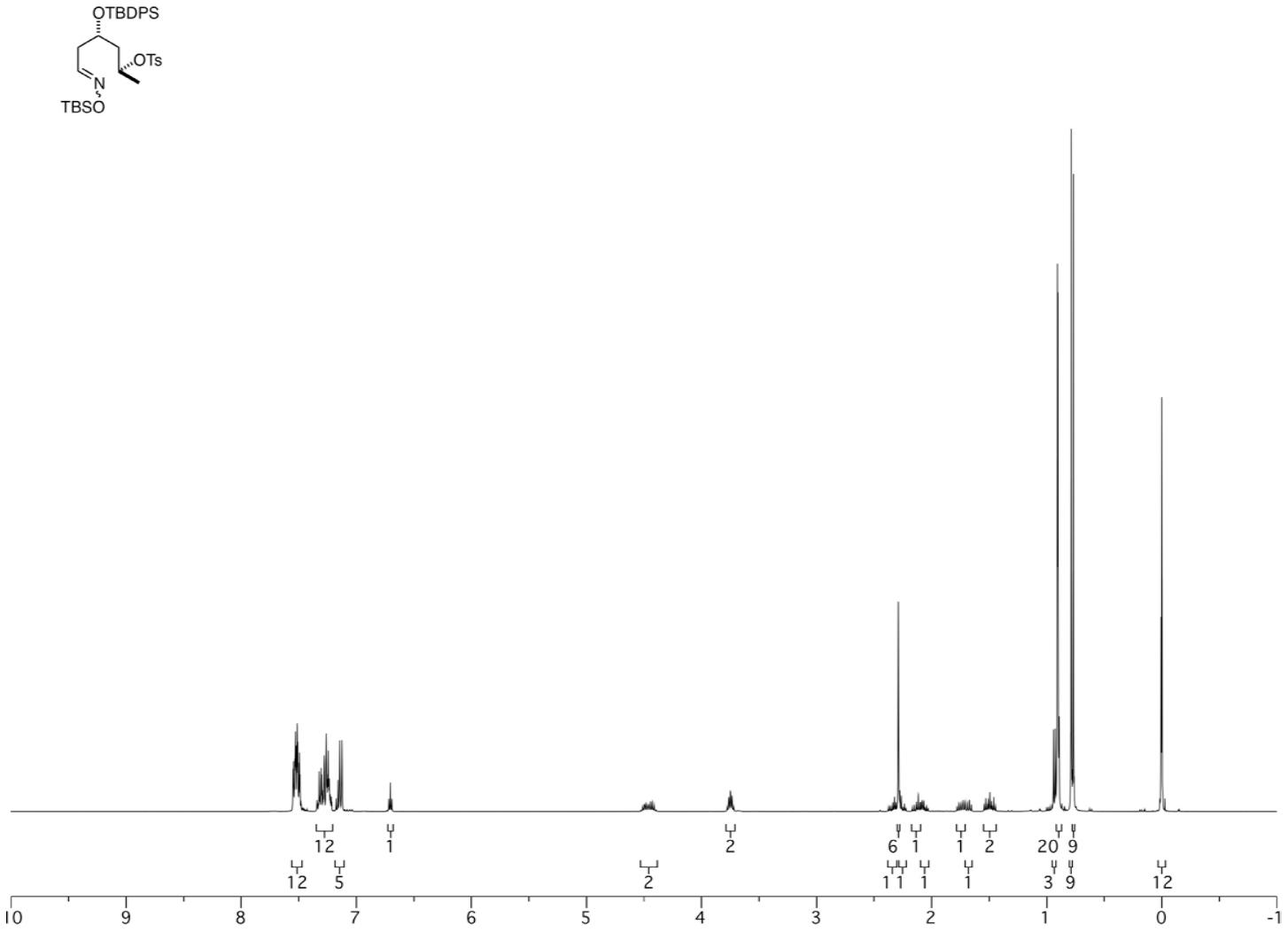


Figure A.3.9a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **200**

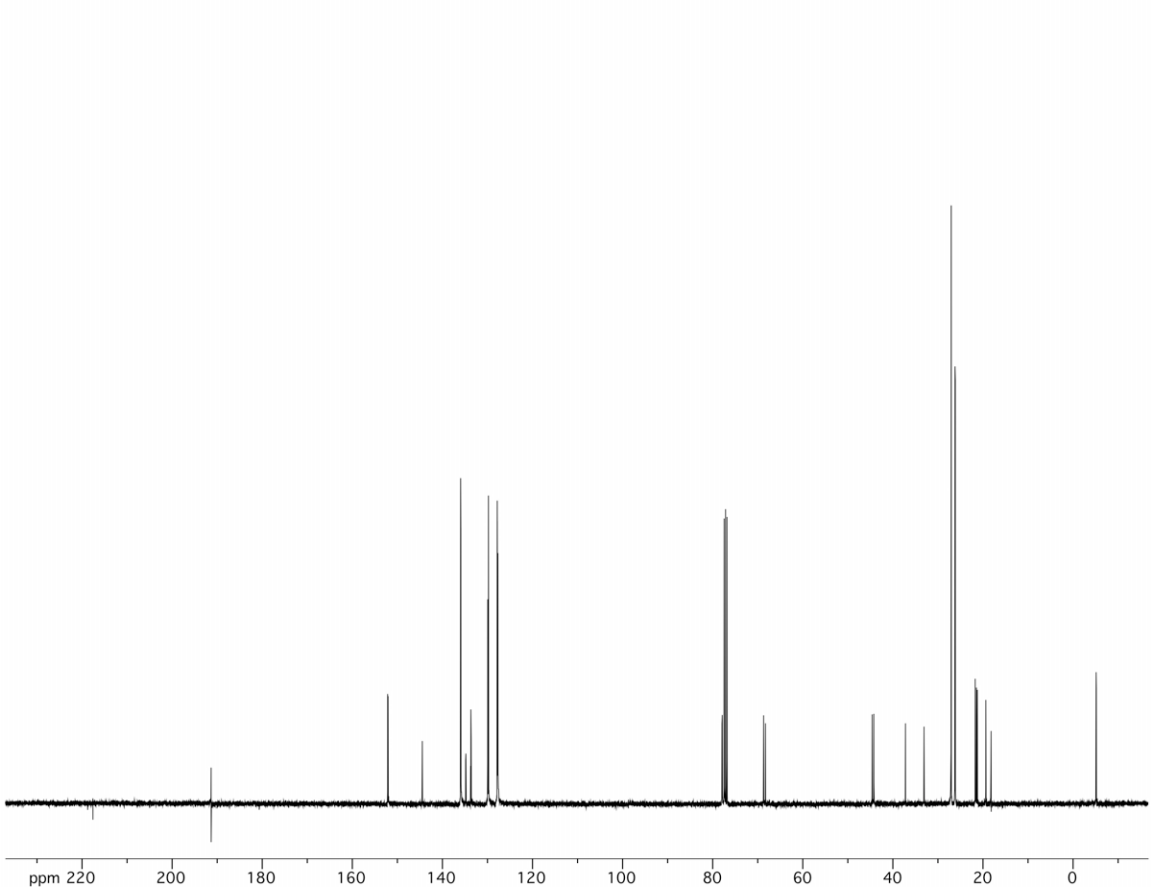


Figure A.3.9b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **200**

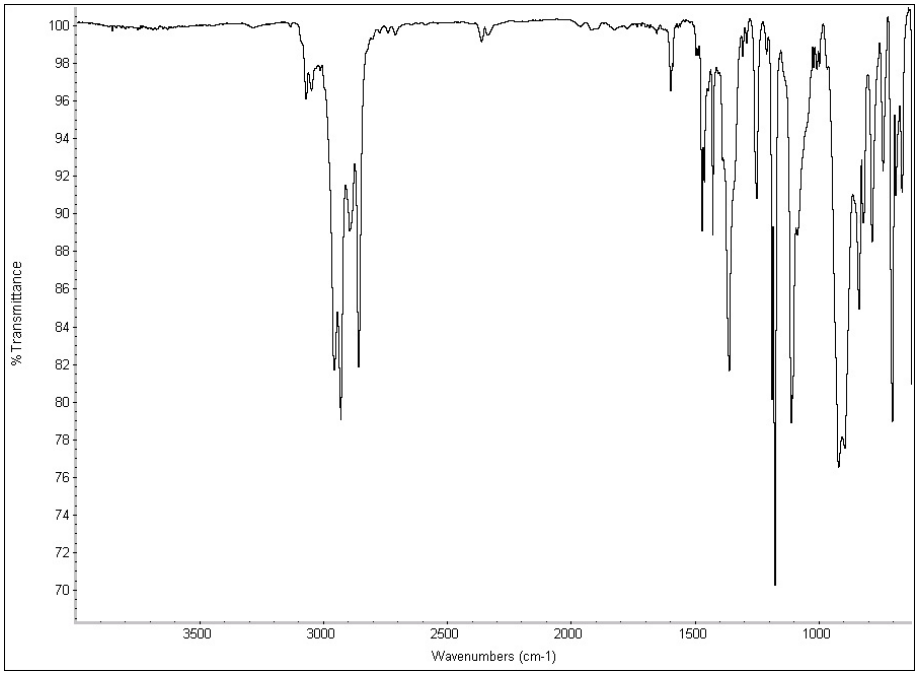


Figure A.3.9c IR spectrum (thin film/NaCl) of compound **200**

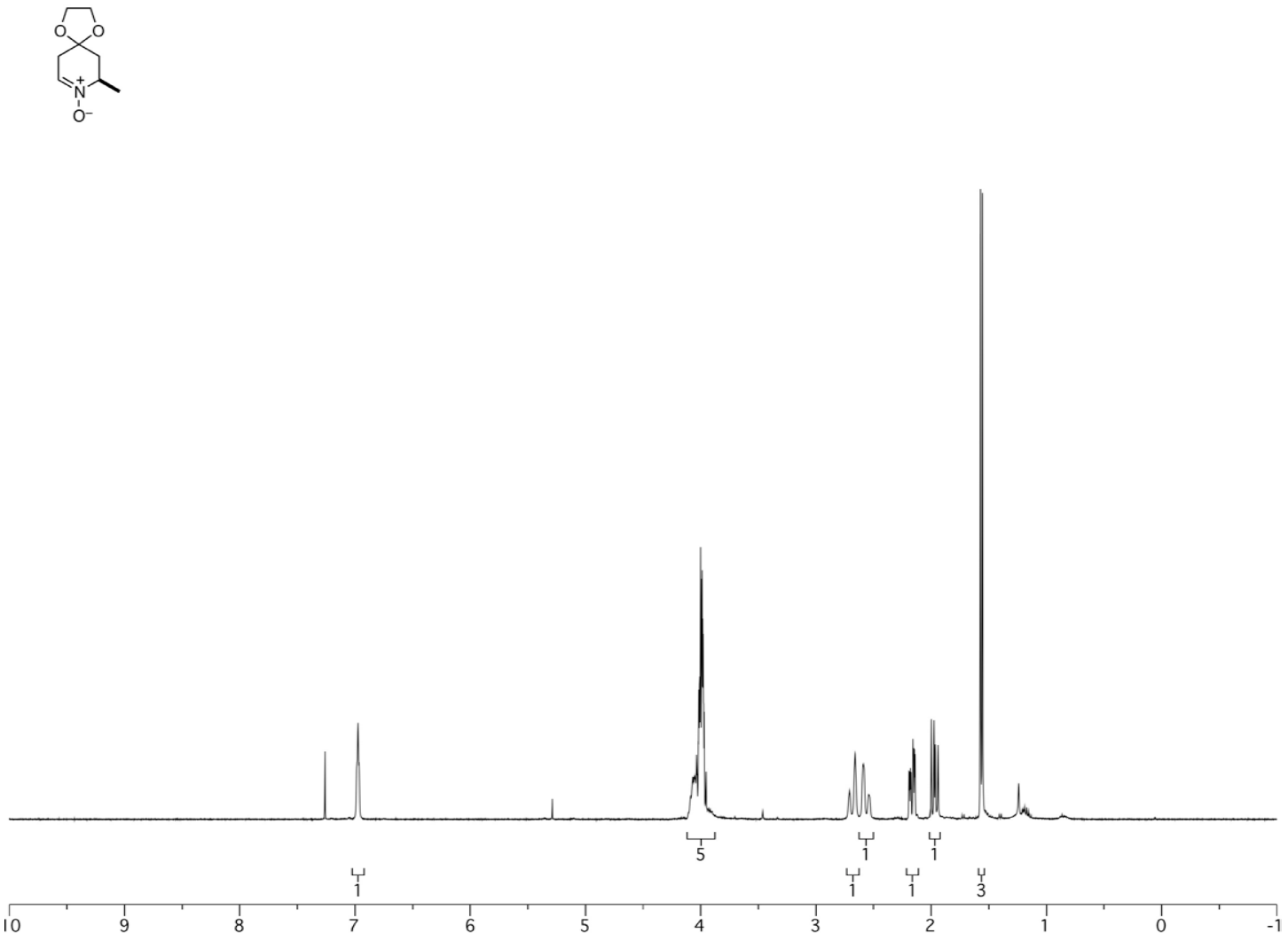


Figure A.3.10a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **201**

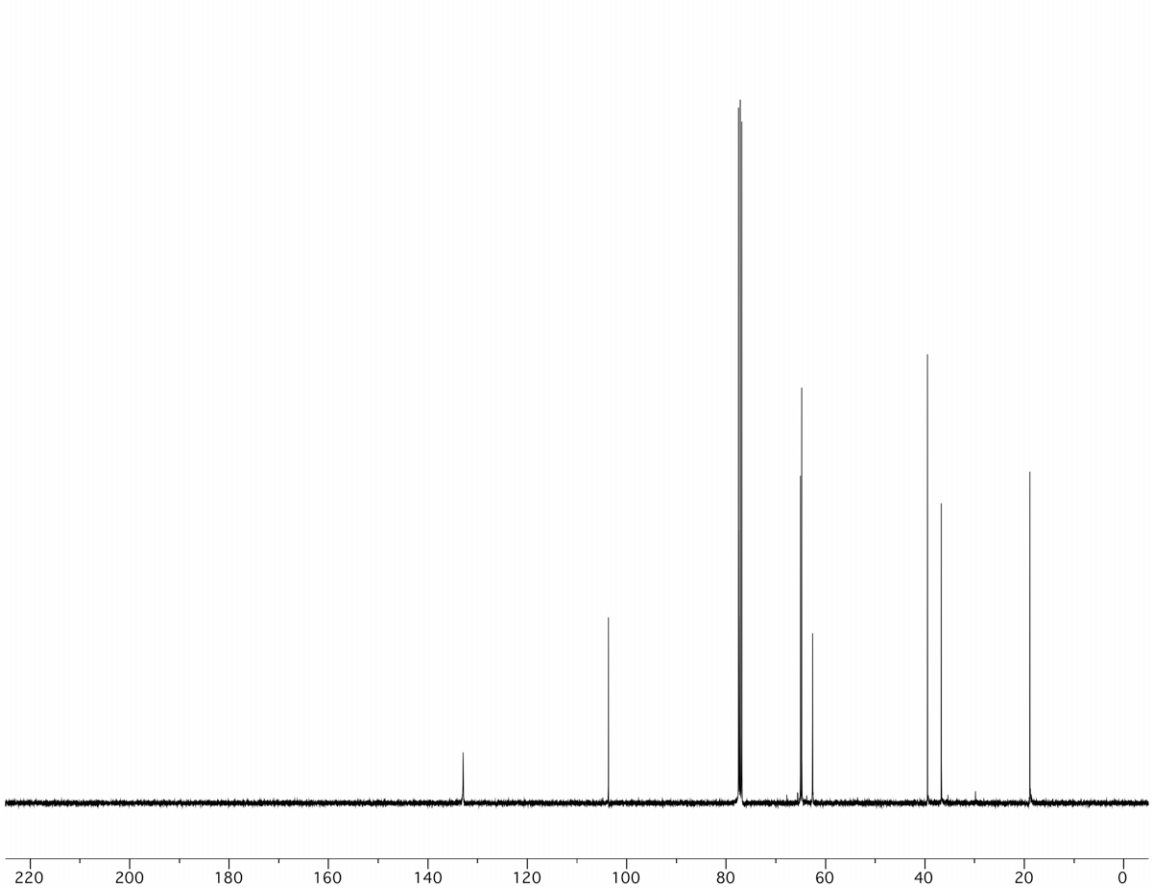


Figure A.3.10b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **201**

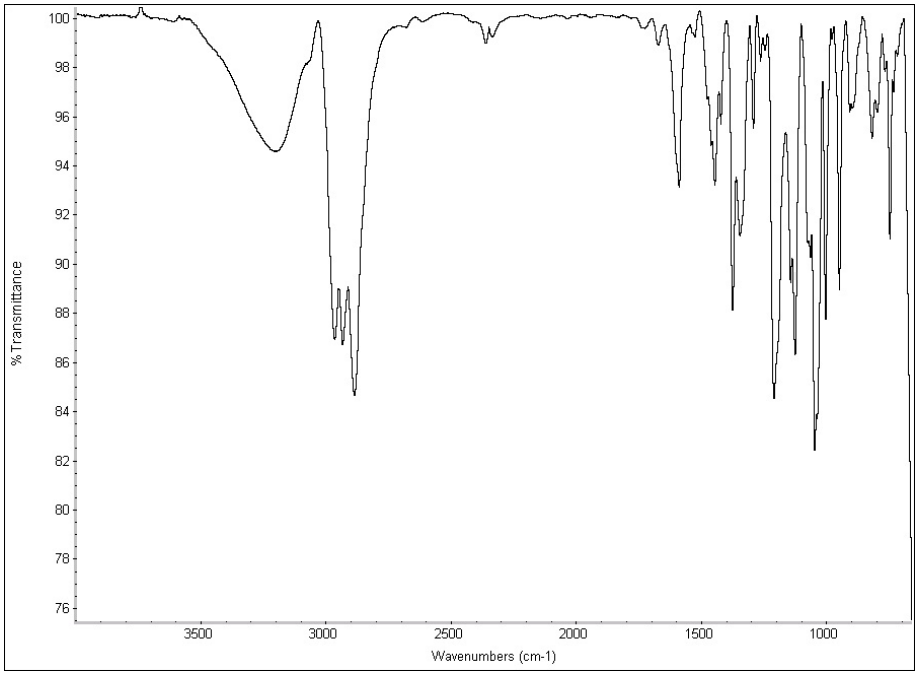


Figure A.3.10c IR spectrum (thin film/NaCl) of compound **201**

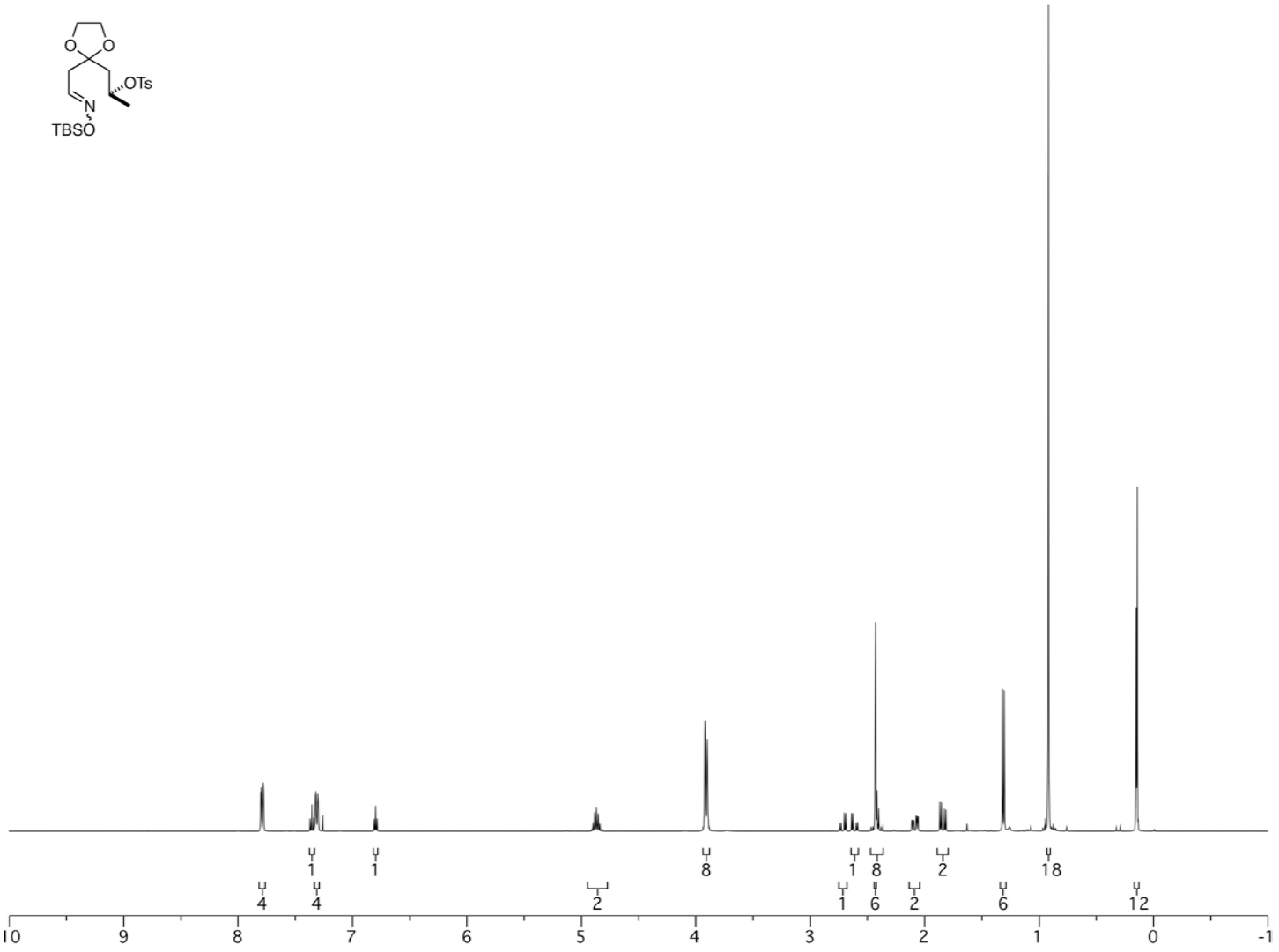


Figure A.3.11a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **202**

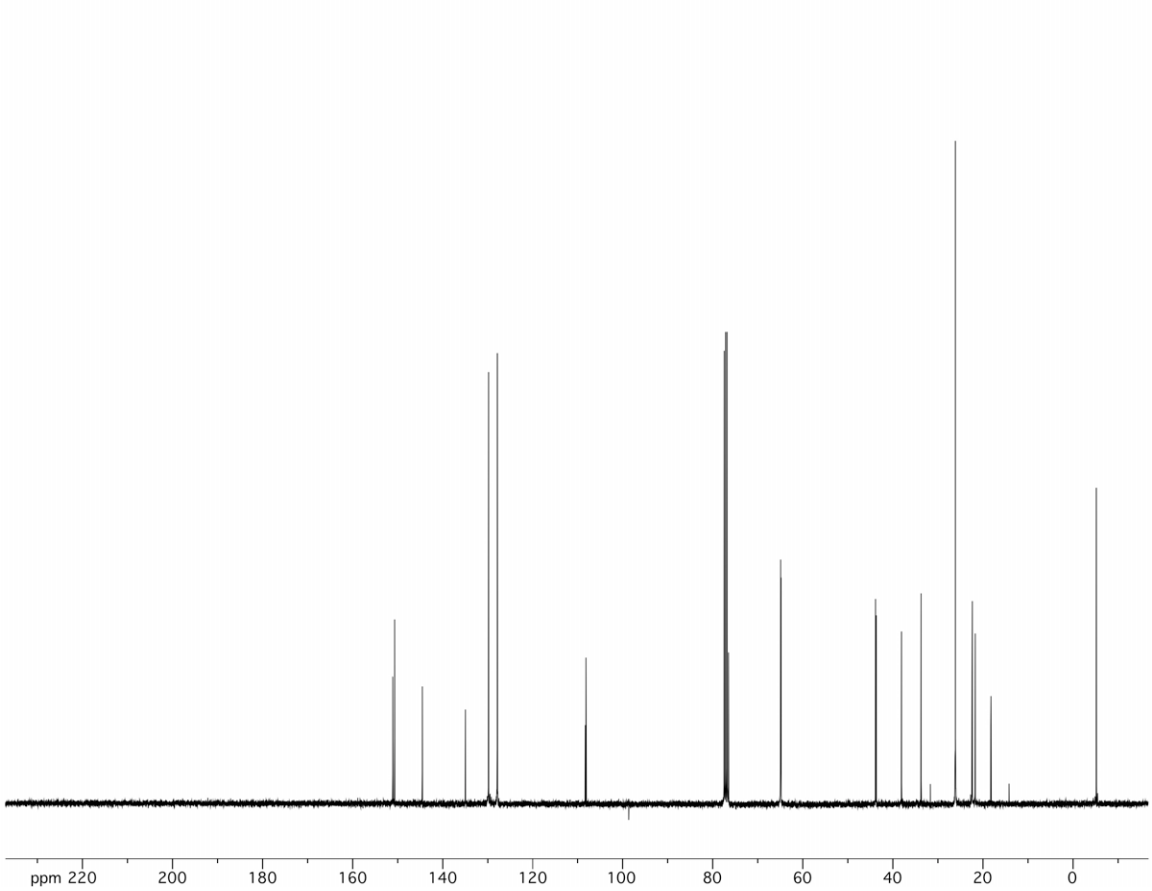


Figure A.3.11b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **202**

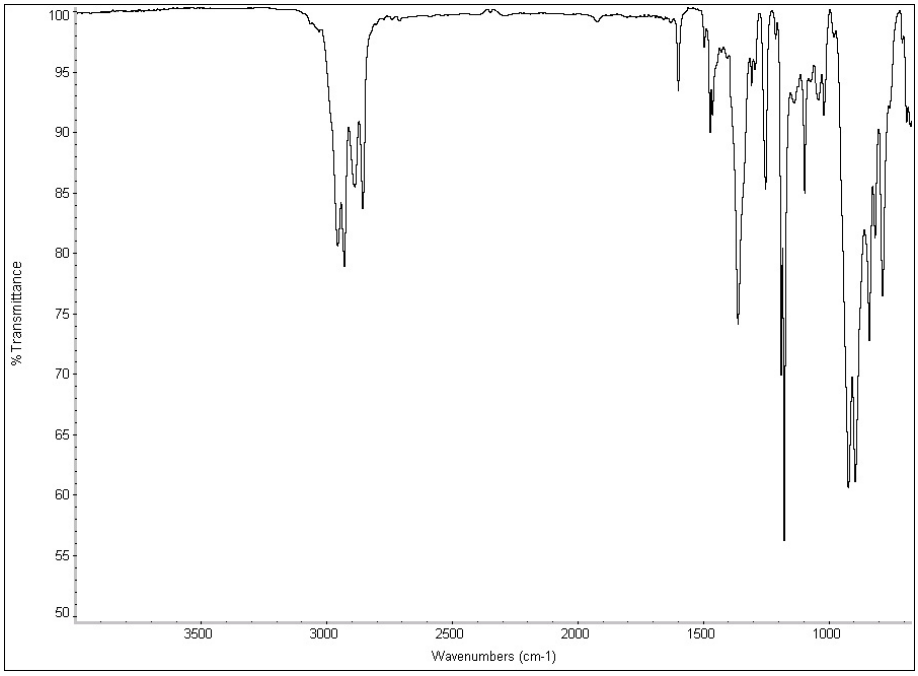


Figure A.3.11c IR spectrum (thin film/NaCl) of compound **202**

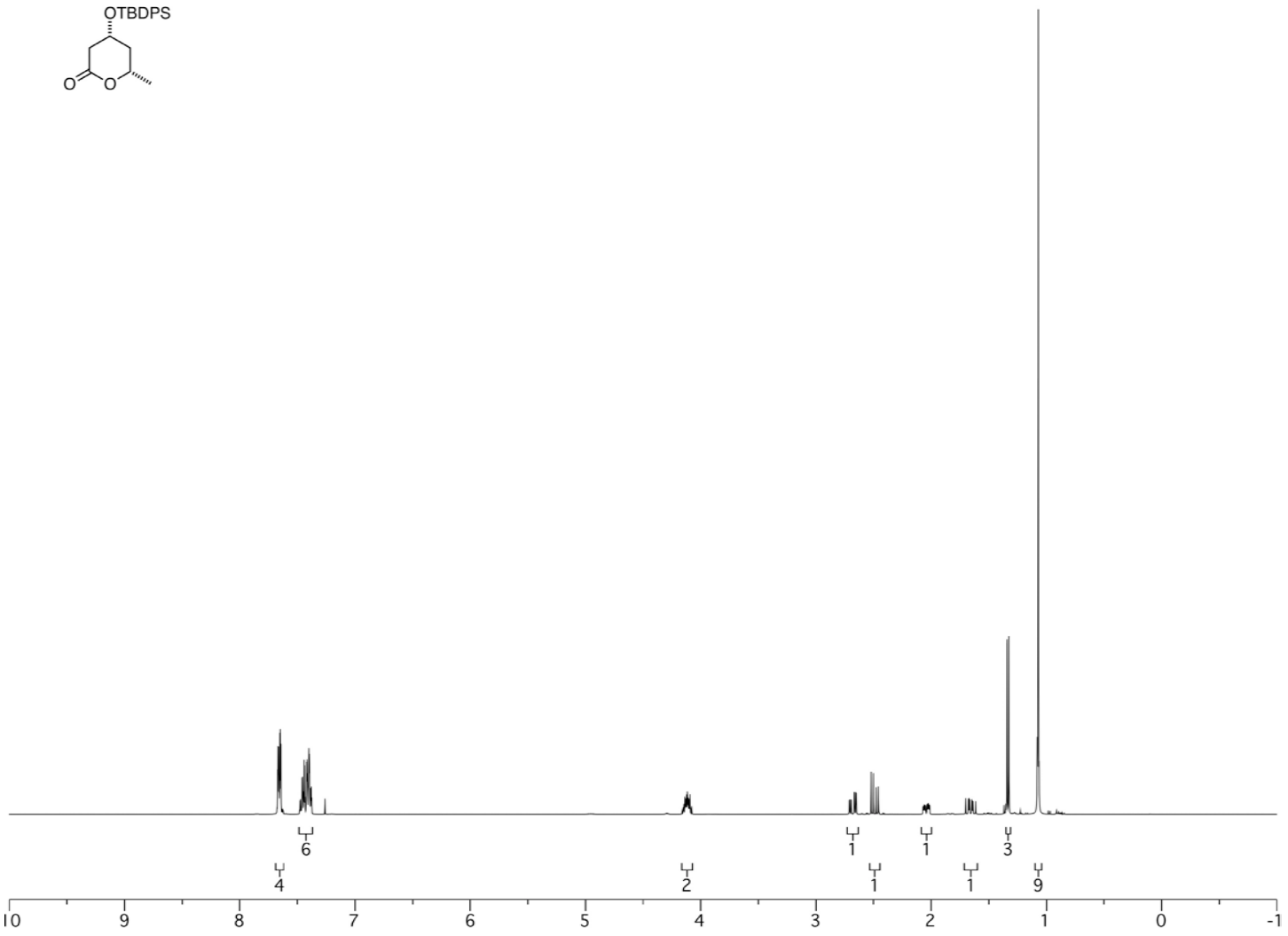


Figure A.3.12a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **203**

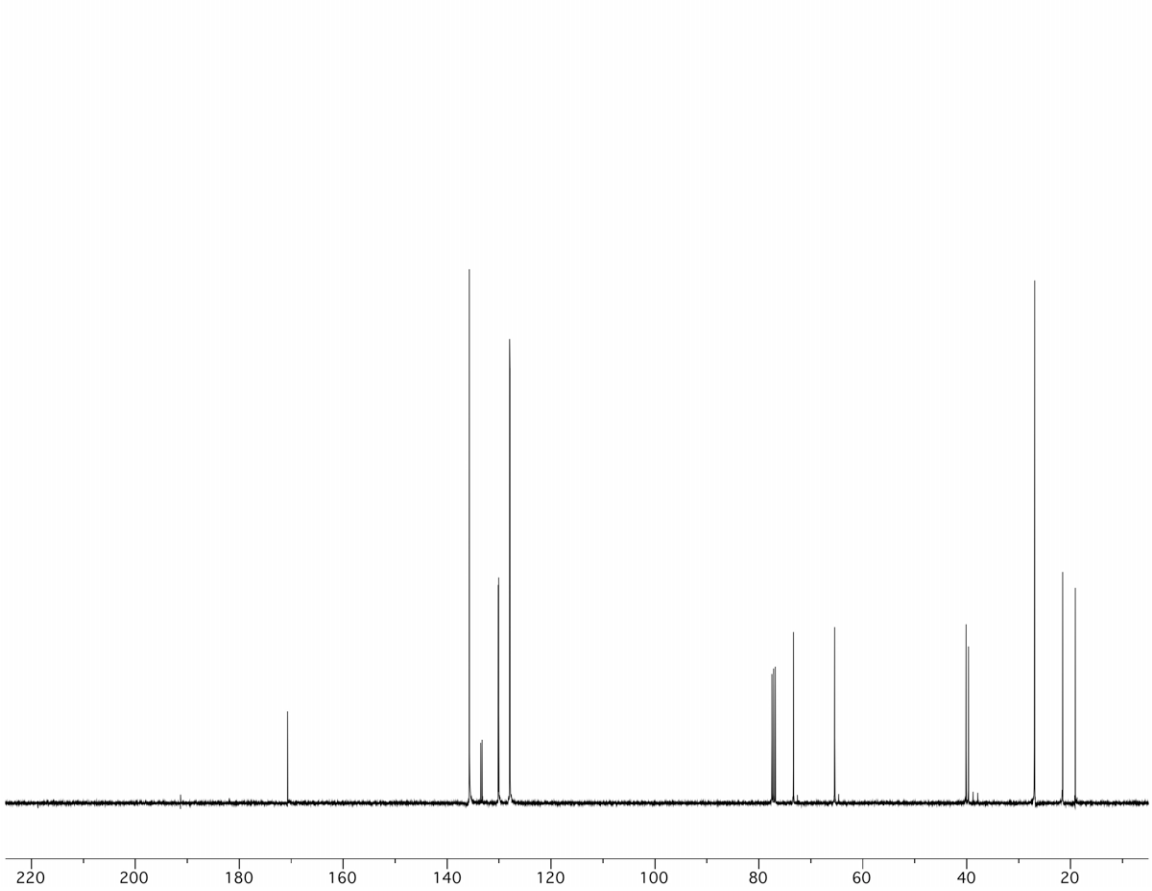


Figure A.3.12b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **203**

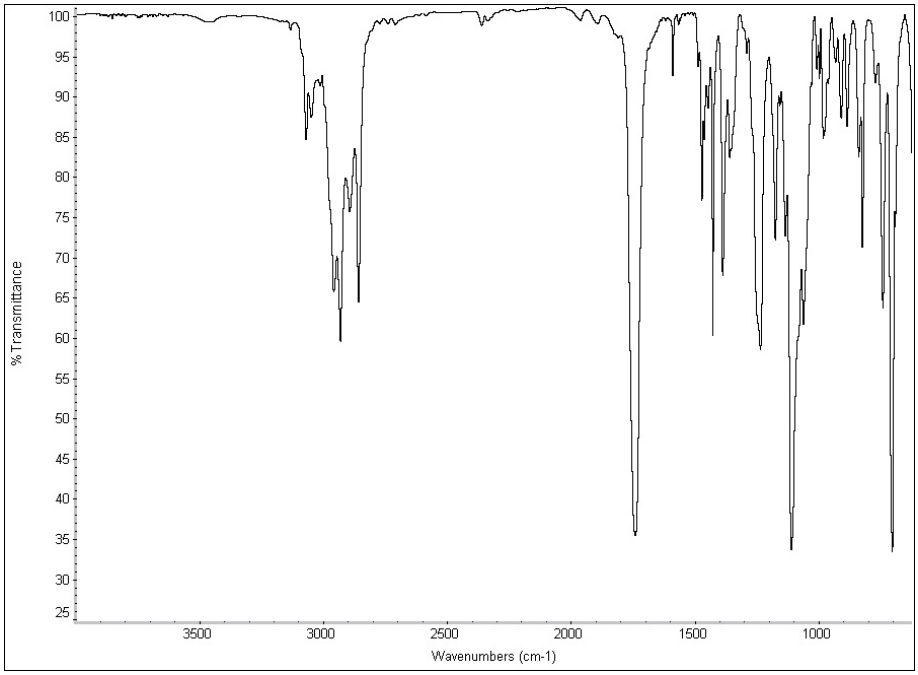


Figure A.3.12c IR spectrum (thin film/NaCl) of compound **203**

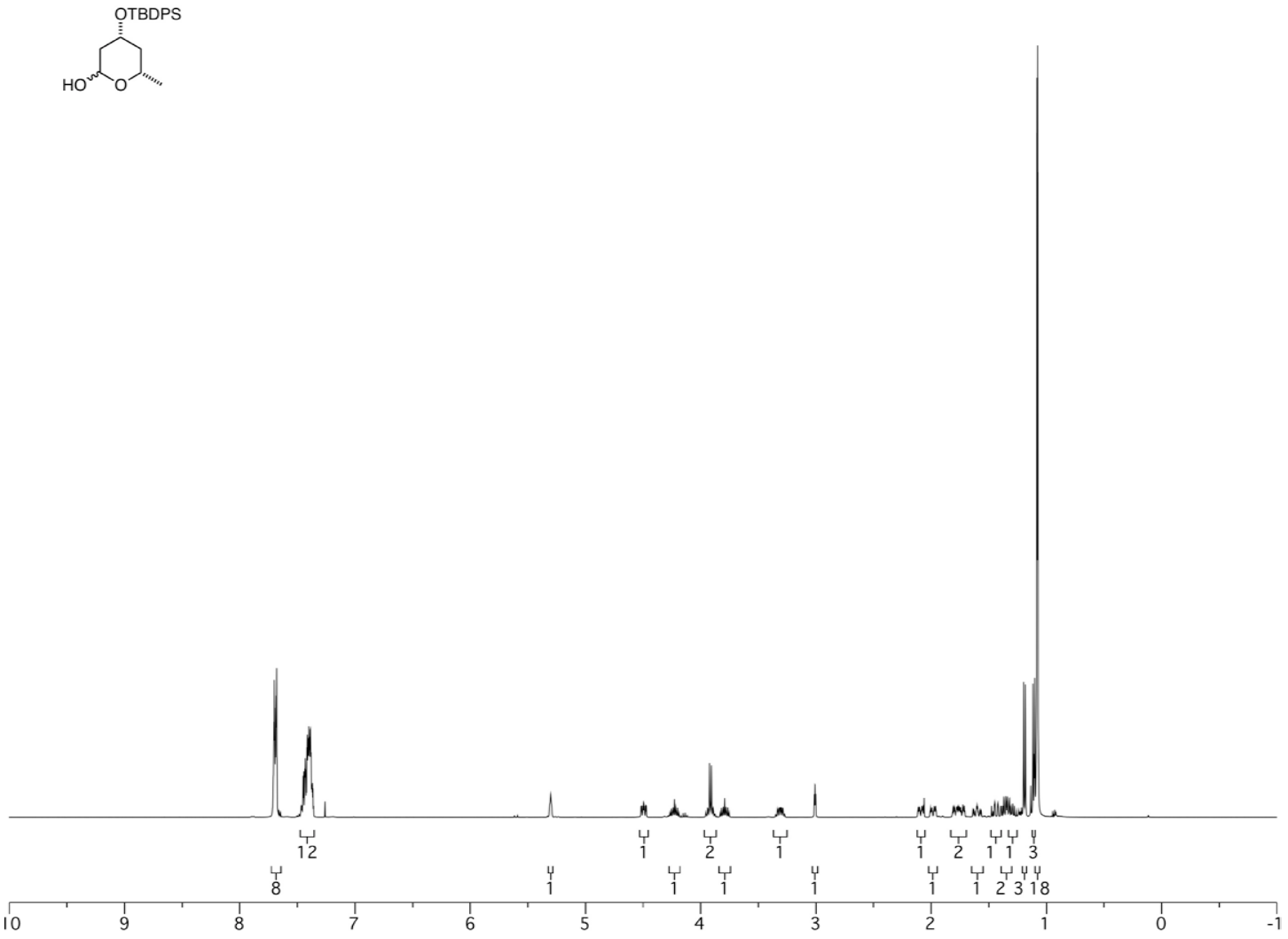


Figure A.3.13a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **204**

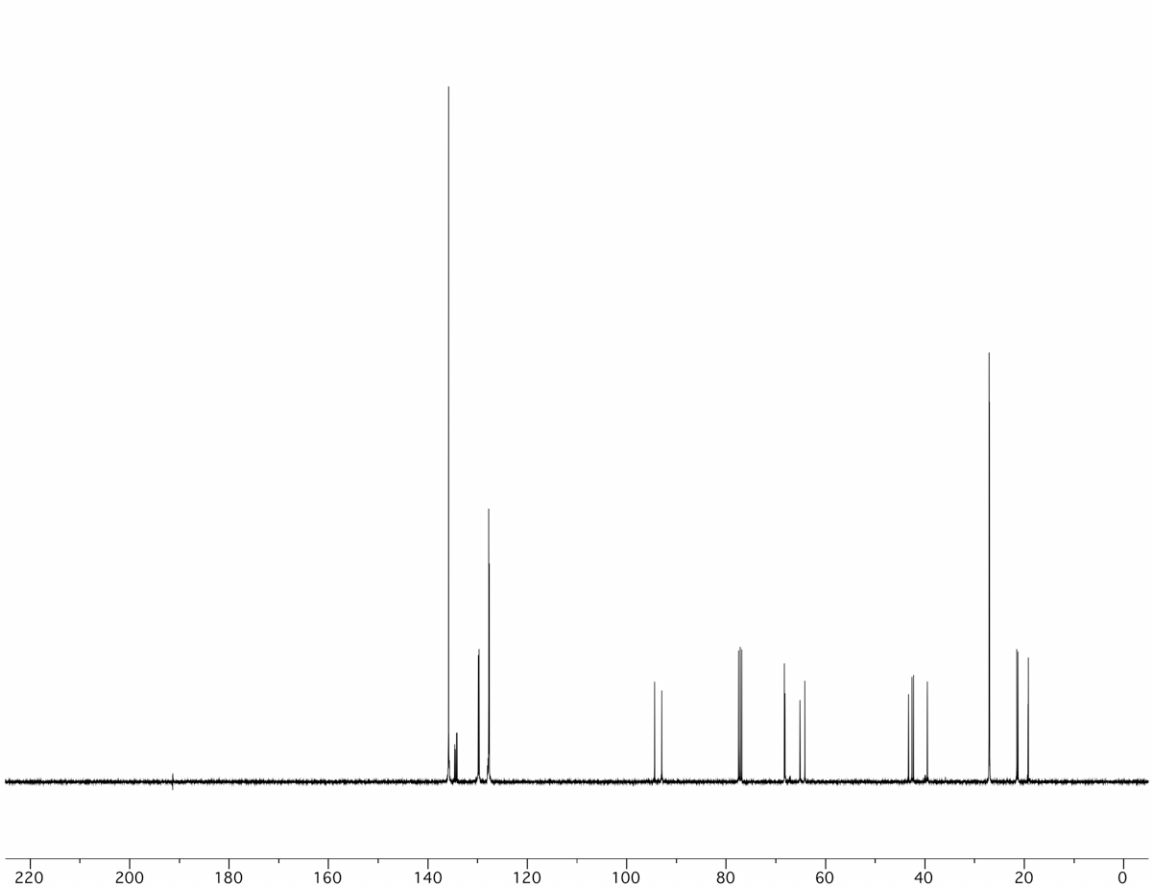


Figure A.3.13b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **204**

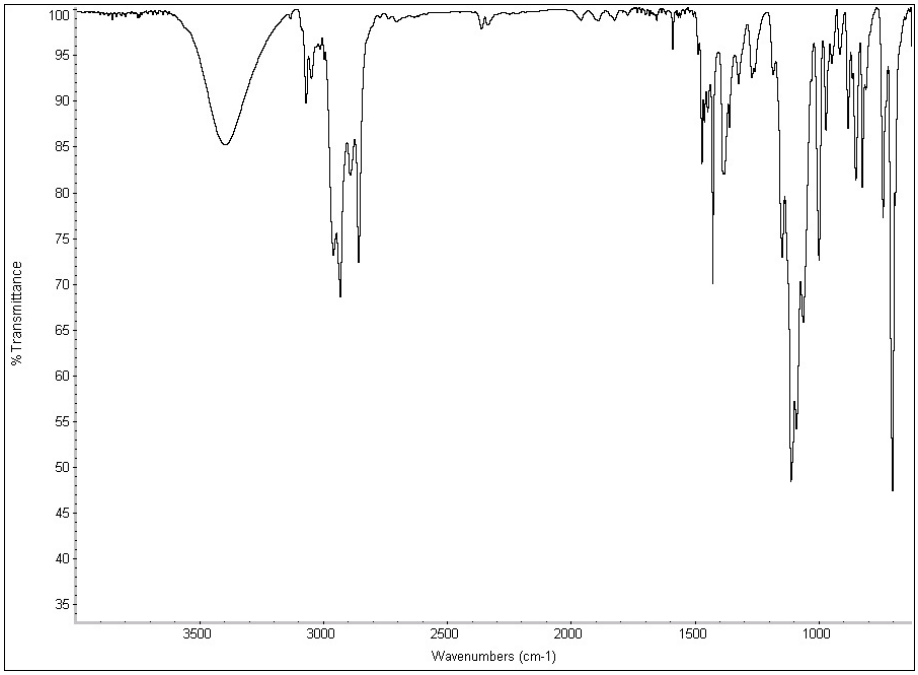


Figure A.3.13c IR spectrum (thin film/NaCl) of compound **204**

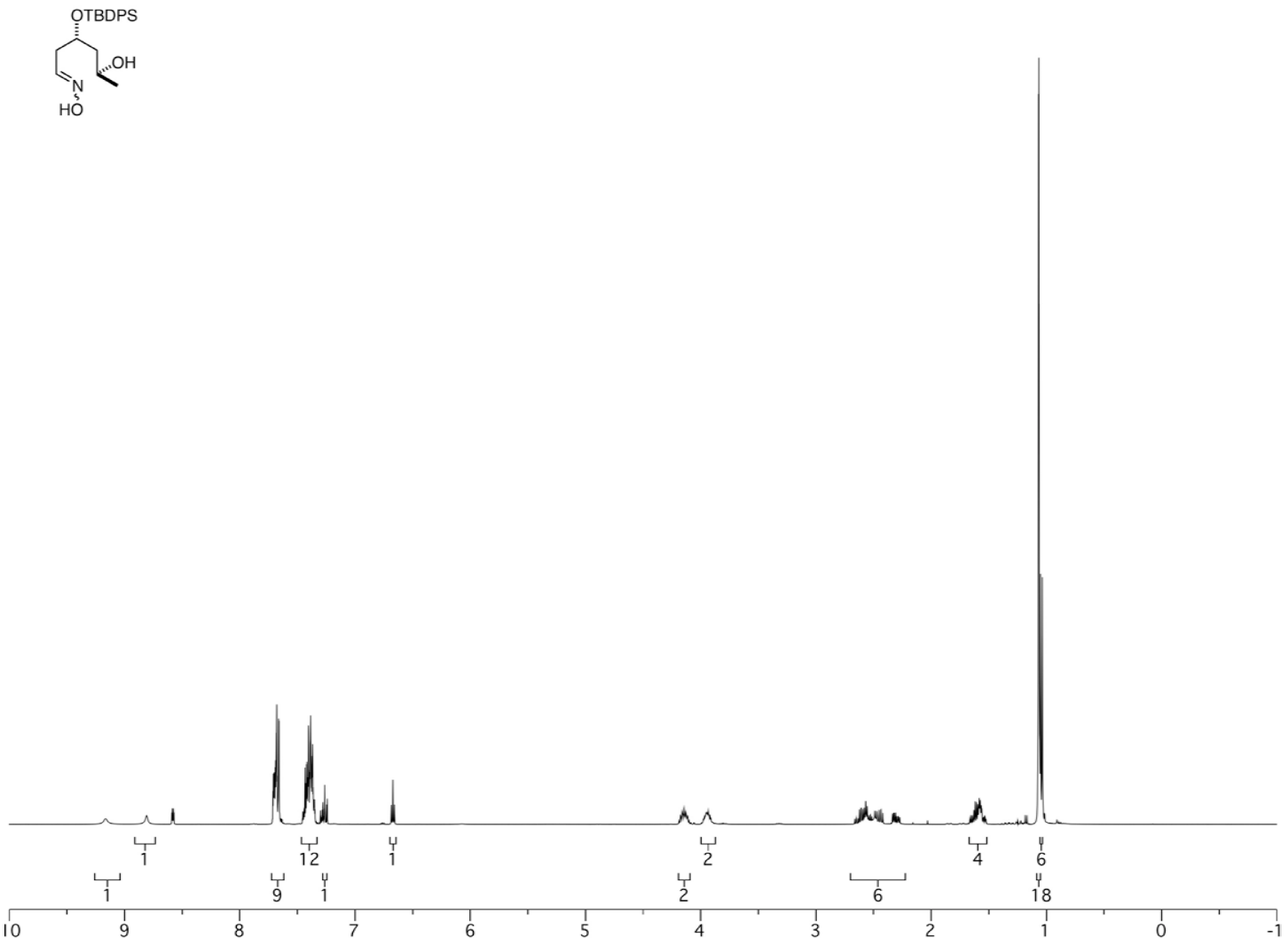


Figure A.3.14a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **205**

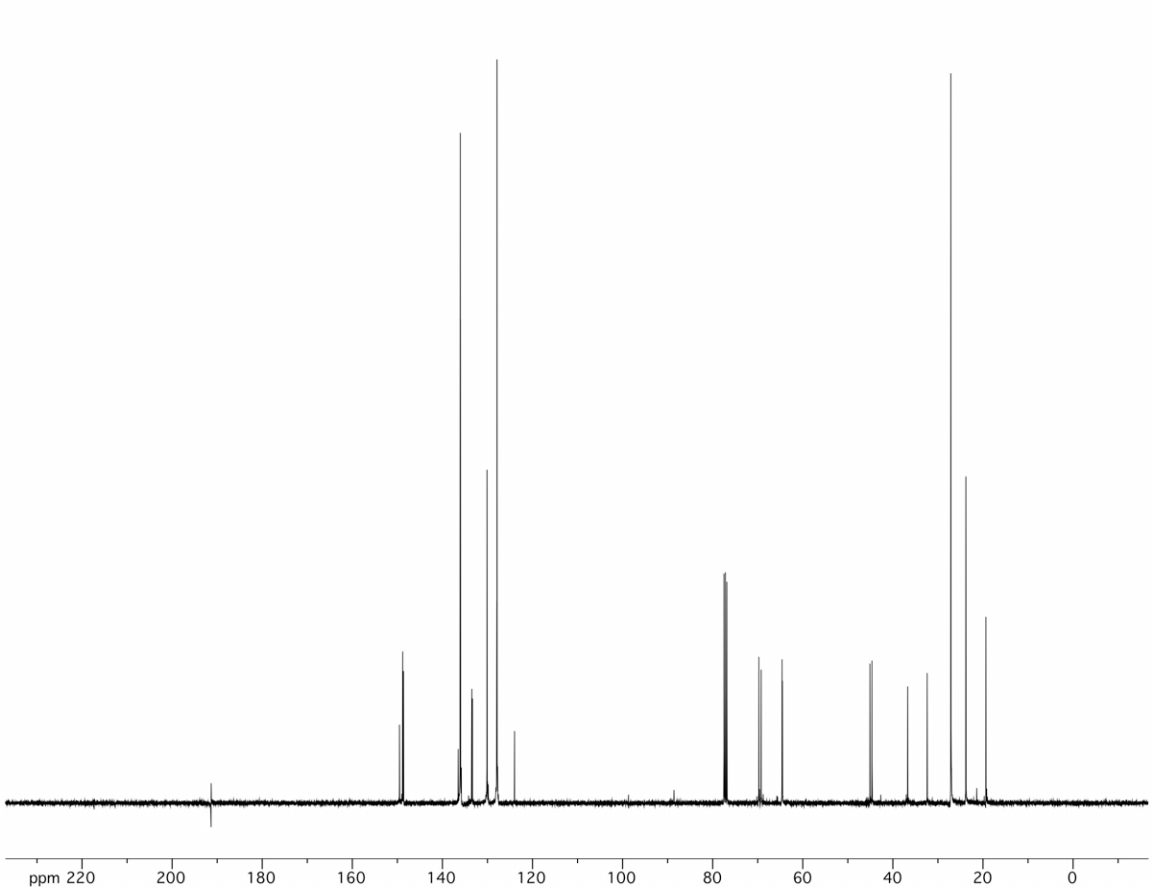


Figure A.3.14b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **205**

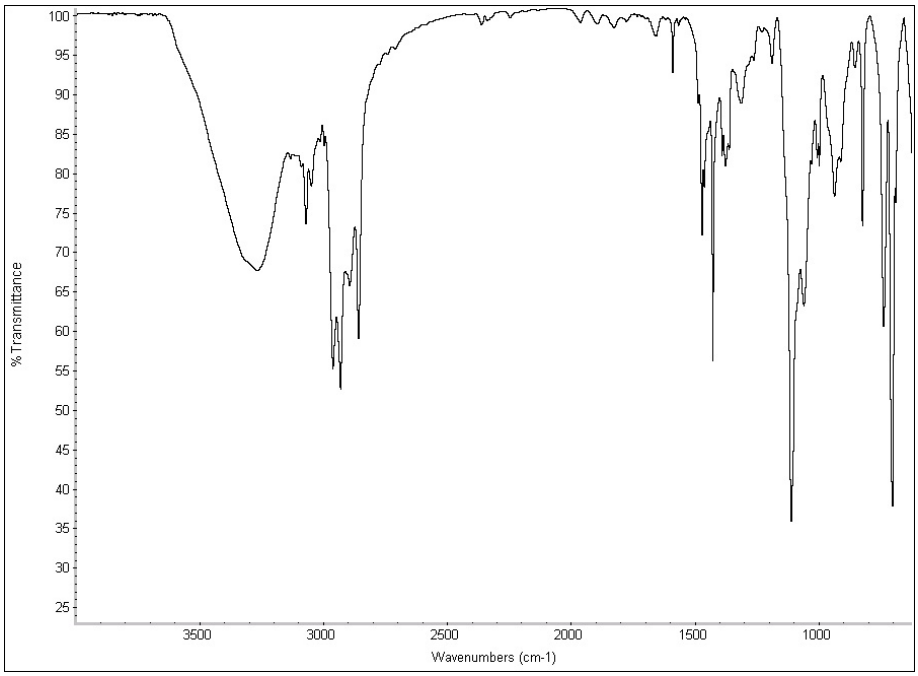


Figure A.3.14c IR spectrum (thin film/NaCl) of compound **205**

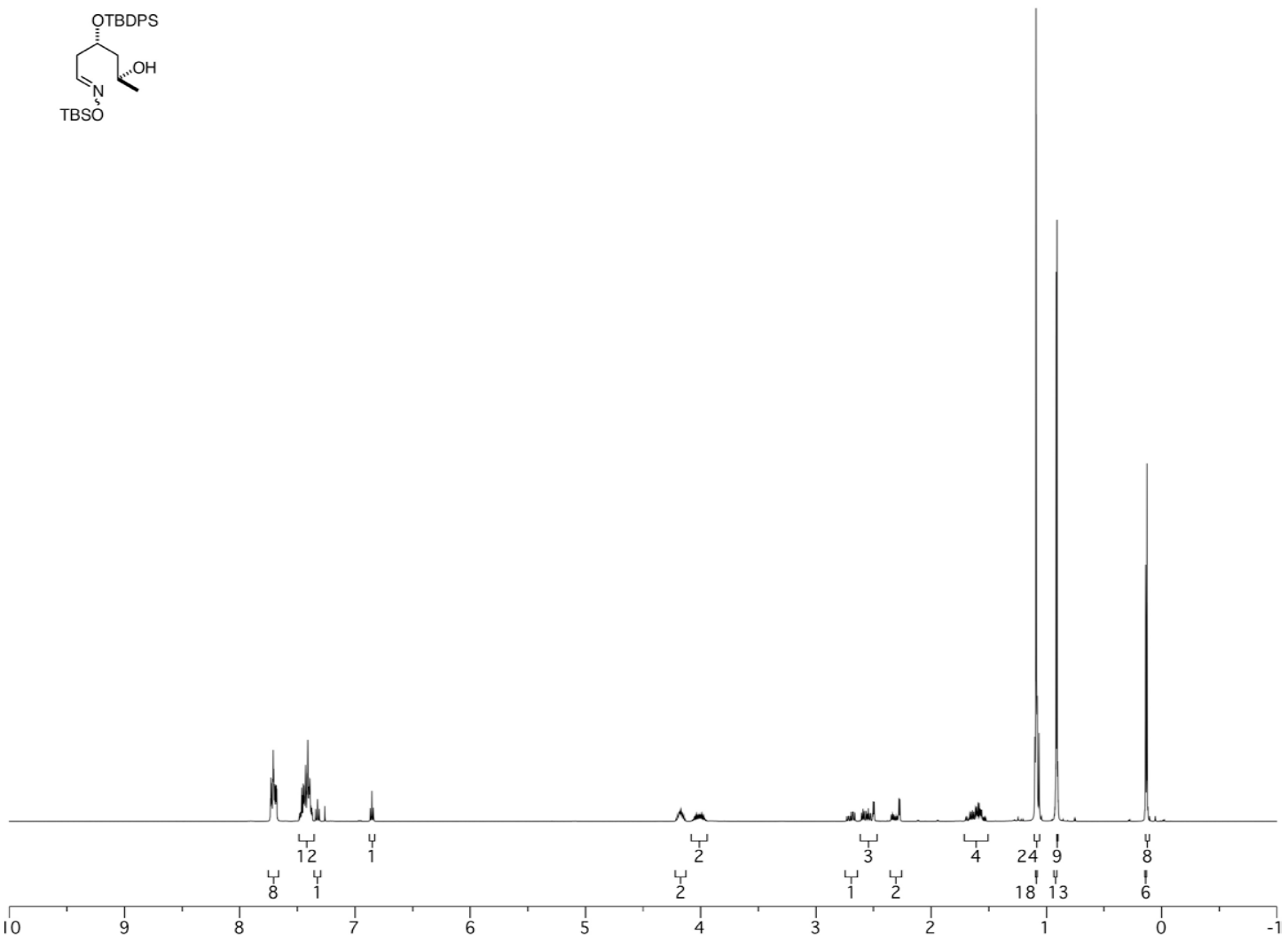


Figure A.3.15a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **206**

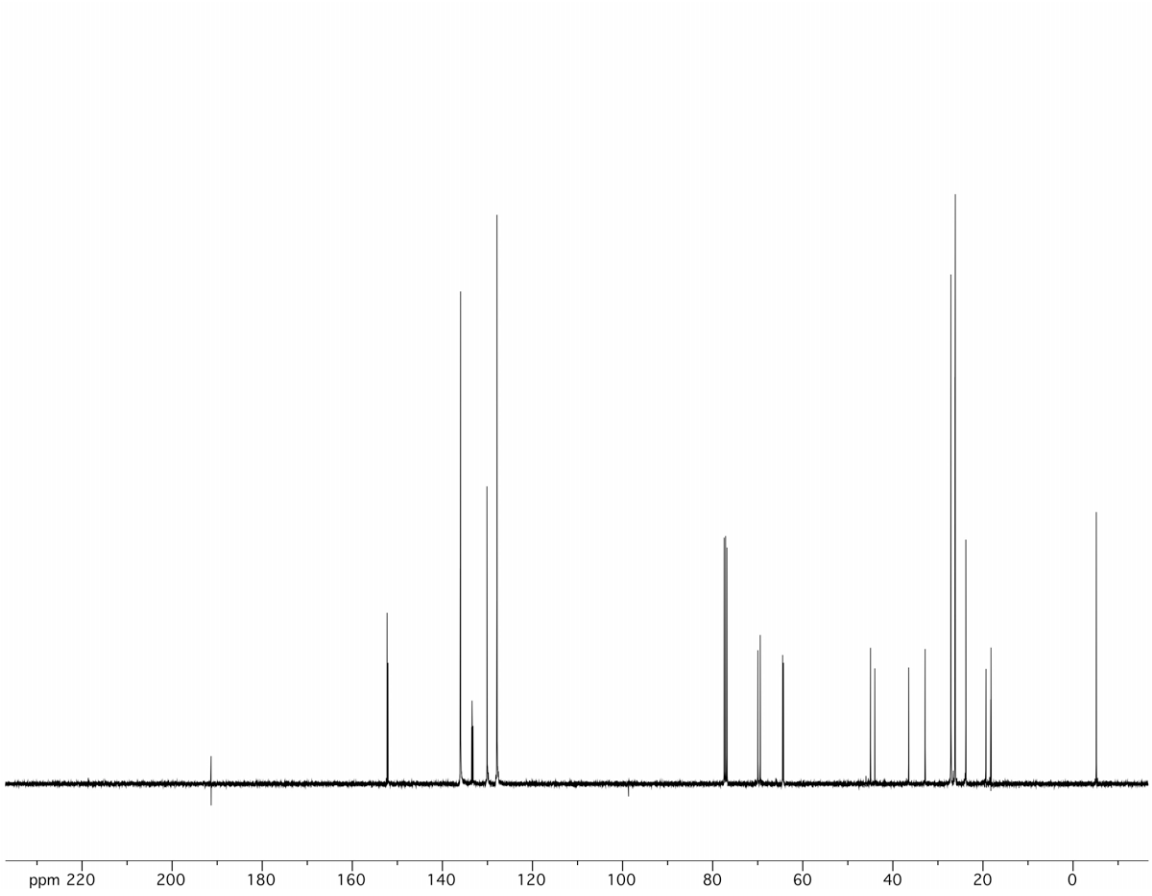


Figure A.3.15b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **206**

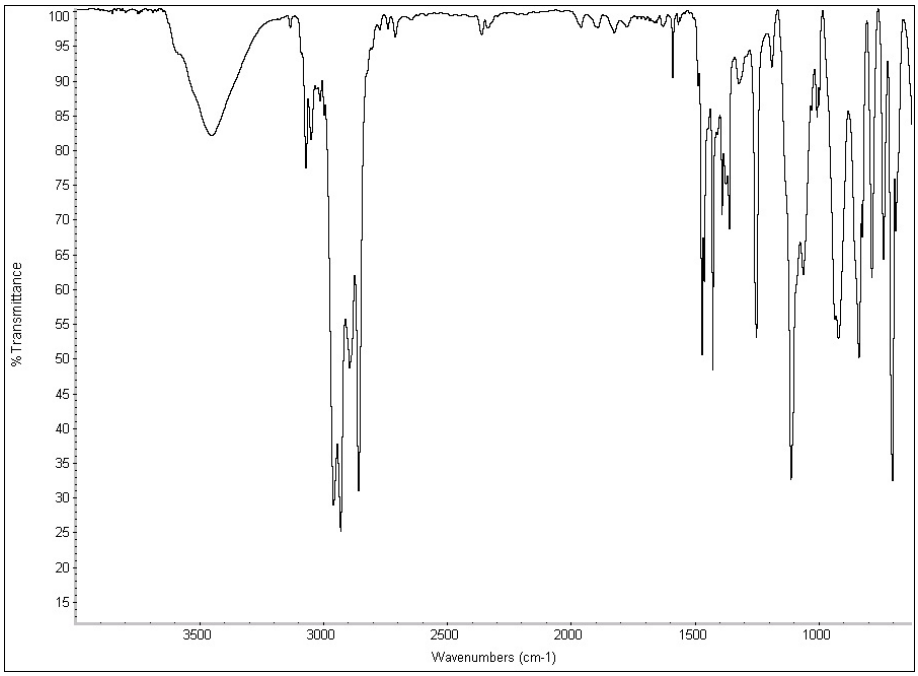


Figure A.3.15c IR spectrum (thin film/NaCl) of compound **206**

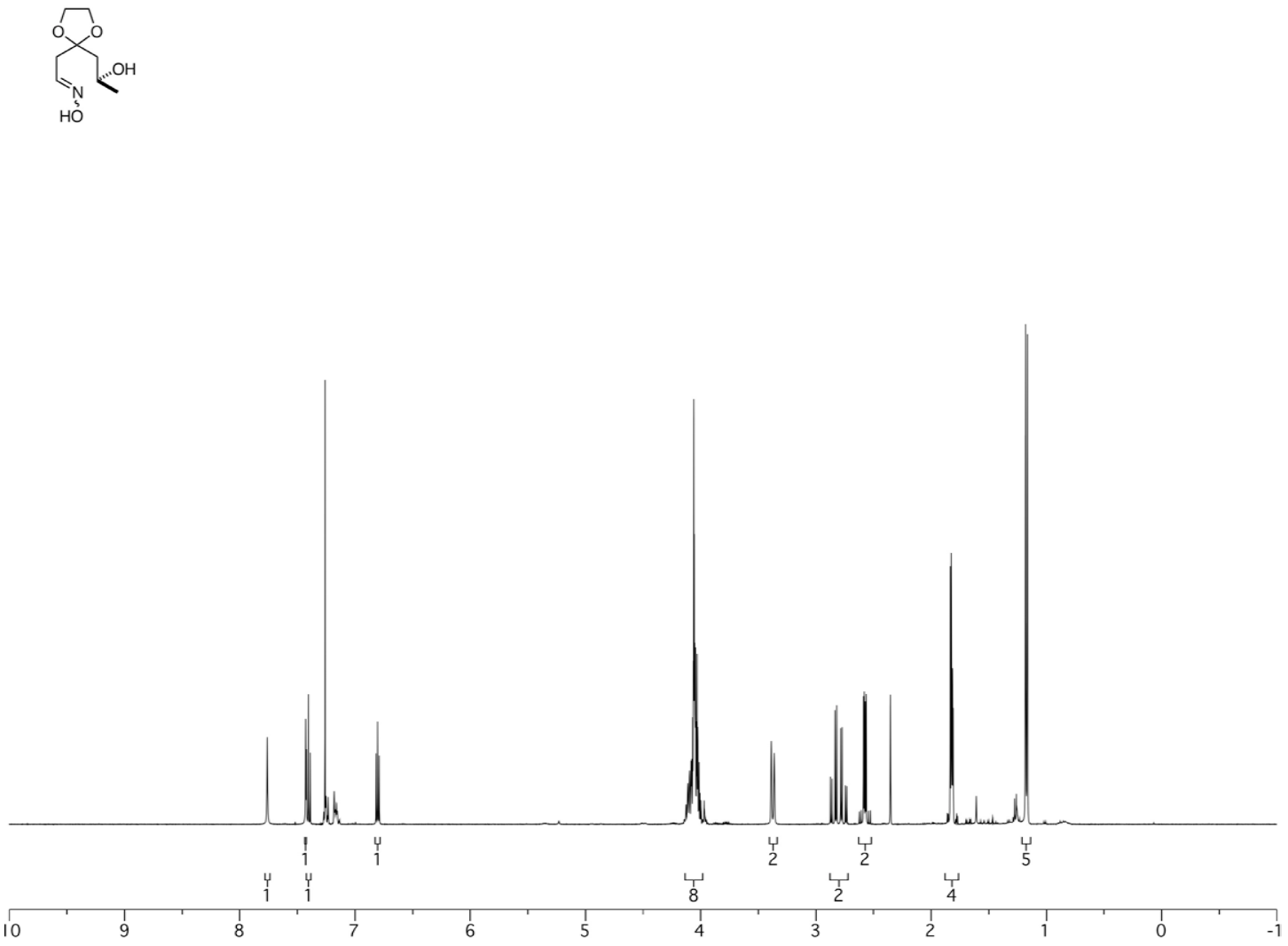


Figure A.3.16a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **211**

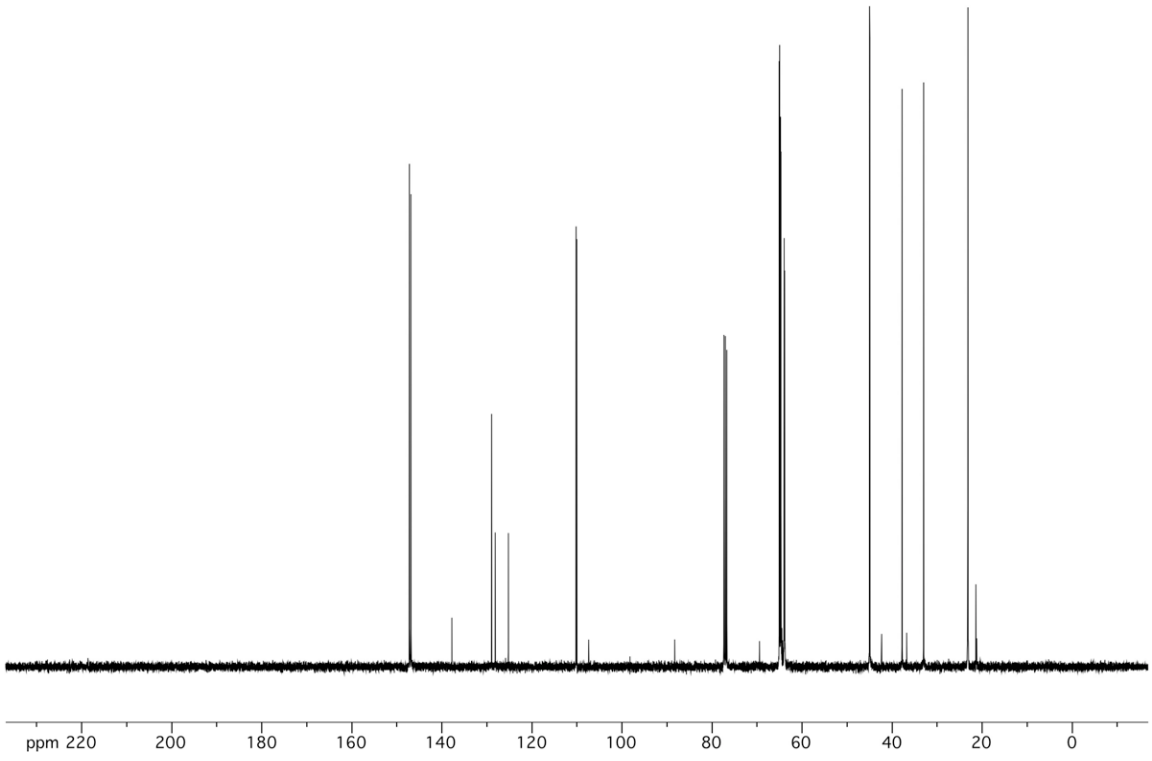


Figure A.3.16b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **211**

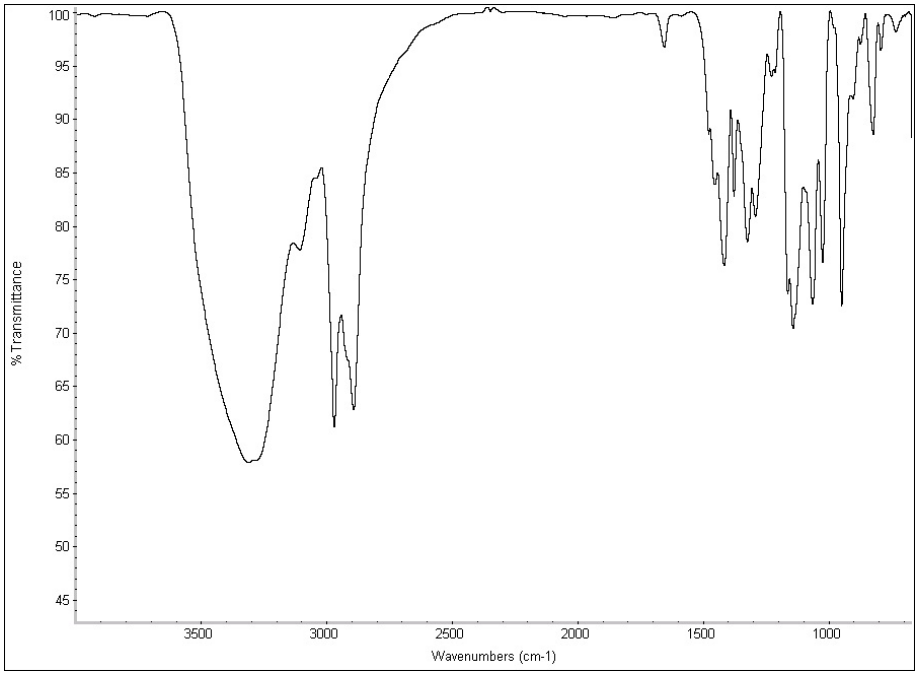


Figure A.3.16c IR spectrum (thin film/NaCl) of compound **211**

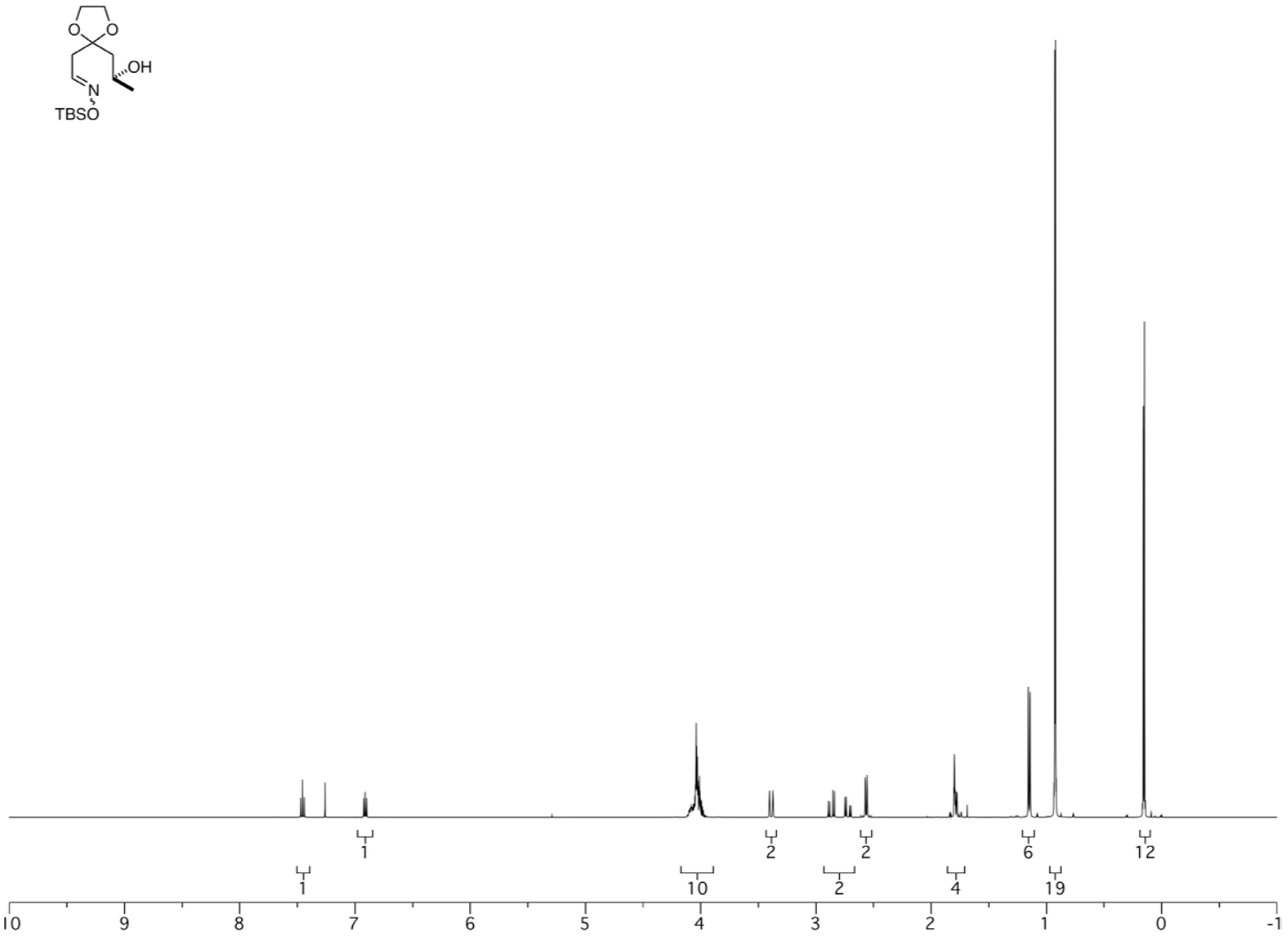


Figure A.3.17a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **212**

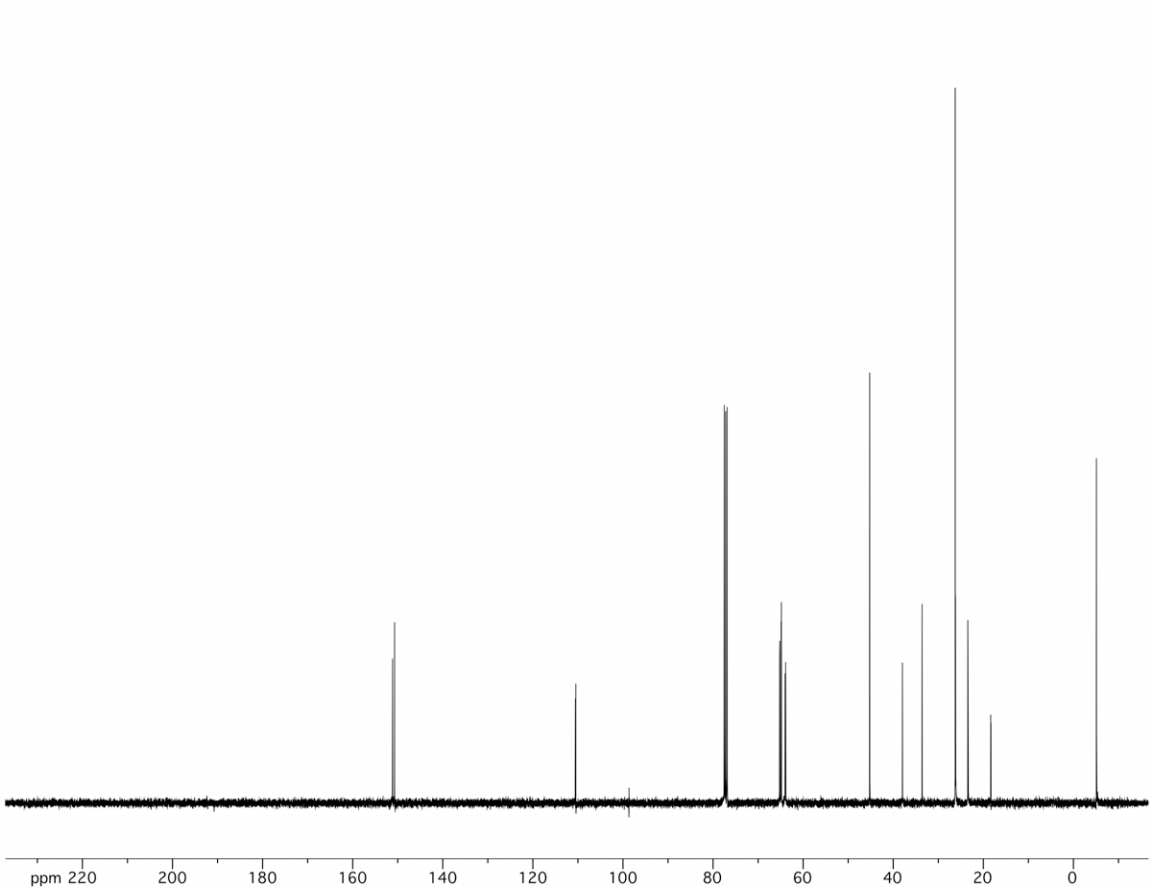


Figure A.3.17b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **212**

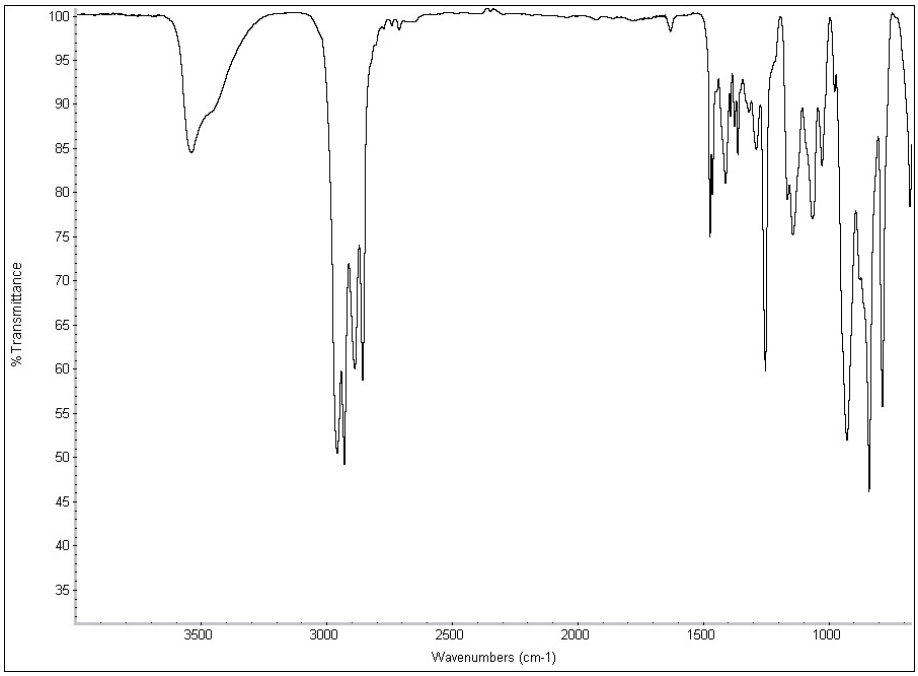


Figure A.3.17c IR spectrum (thin film/NaCl) of compound **212**

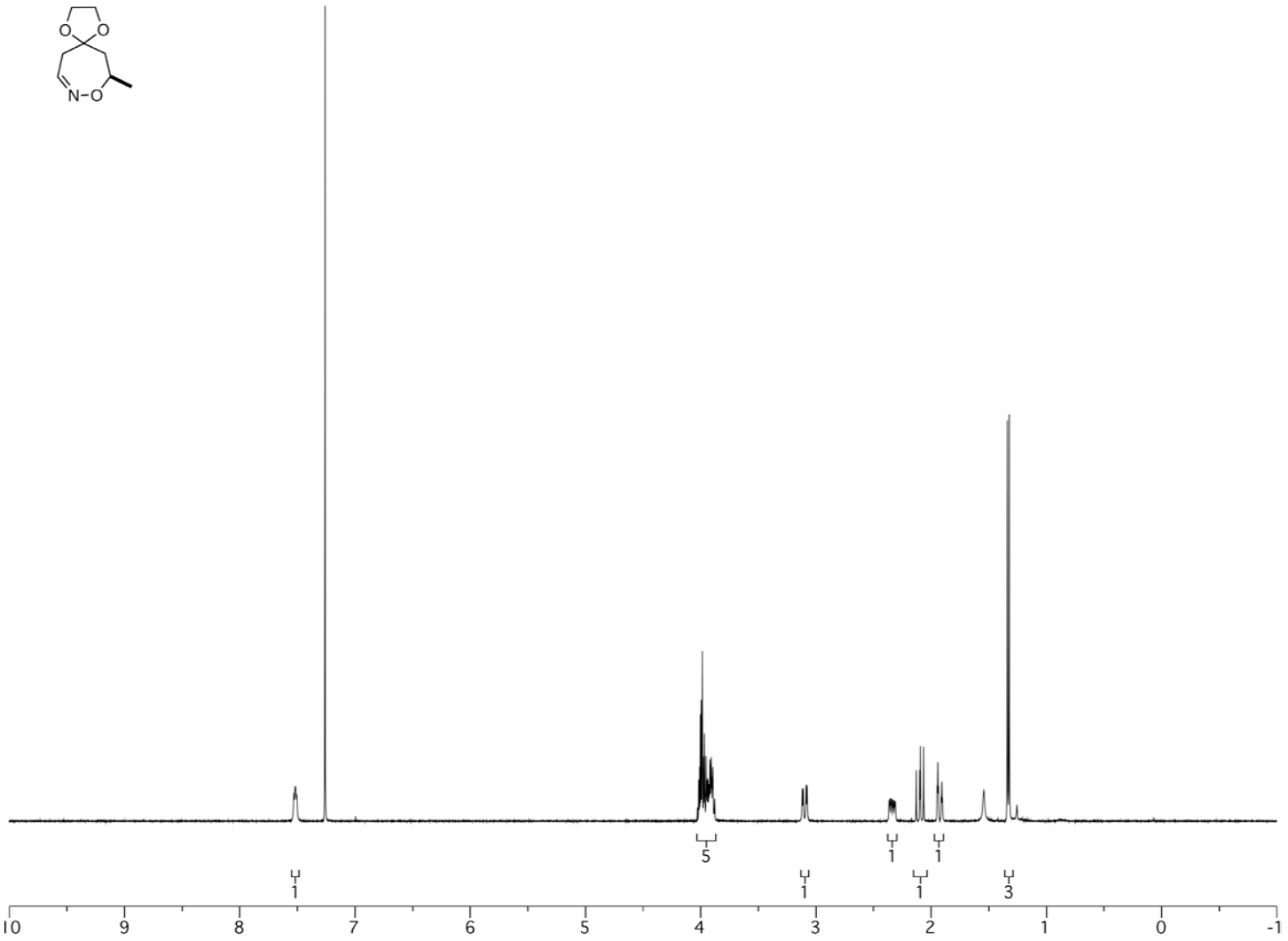


Figure A.3.18a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **213**

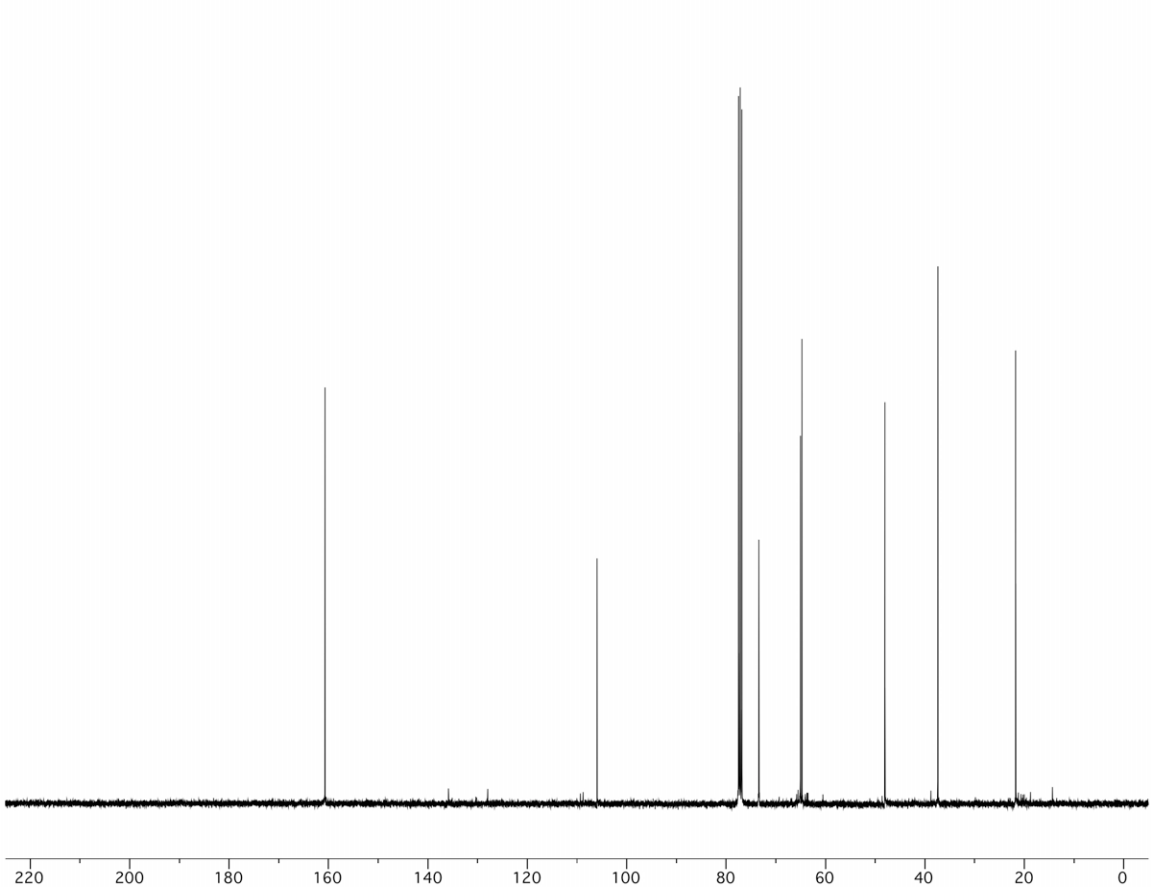


Figure A.3.18b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **213**

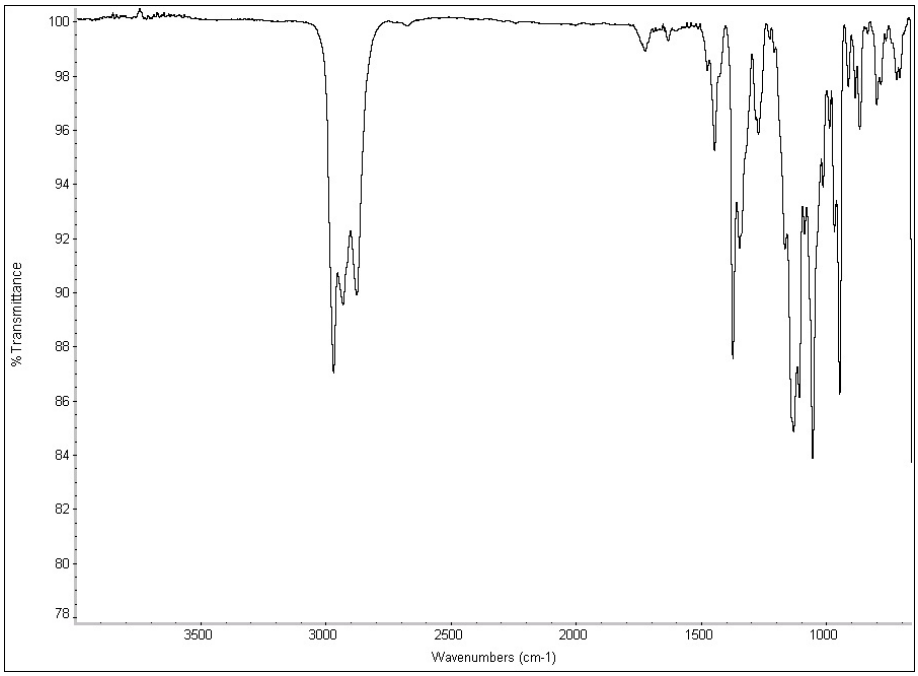


Figure A.3.18c IR spectrum (thin film/NaCl) of compound **213**

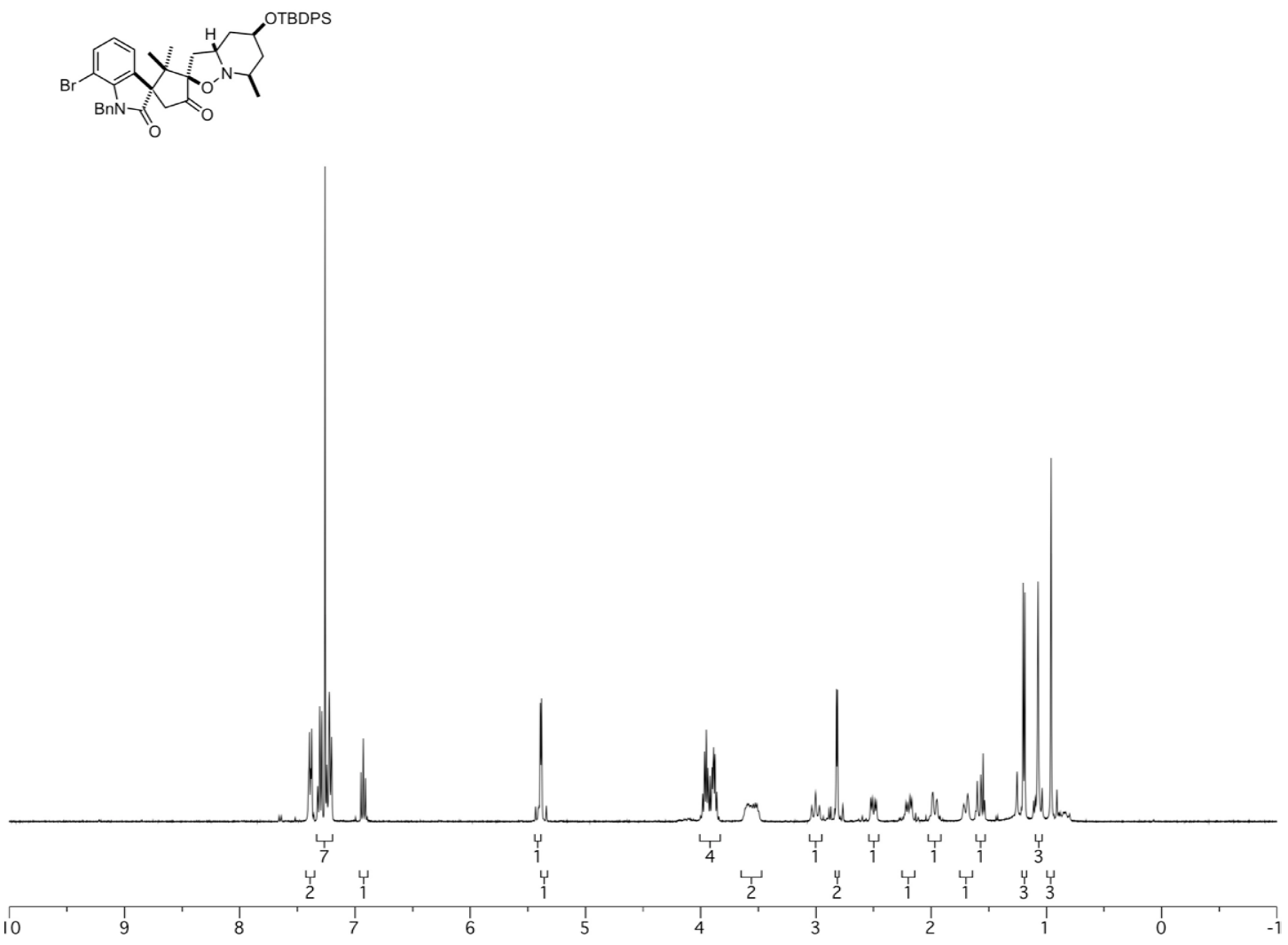


Figure A.3.19a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **214**

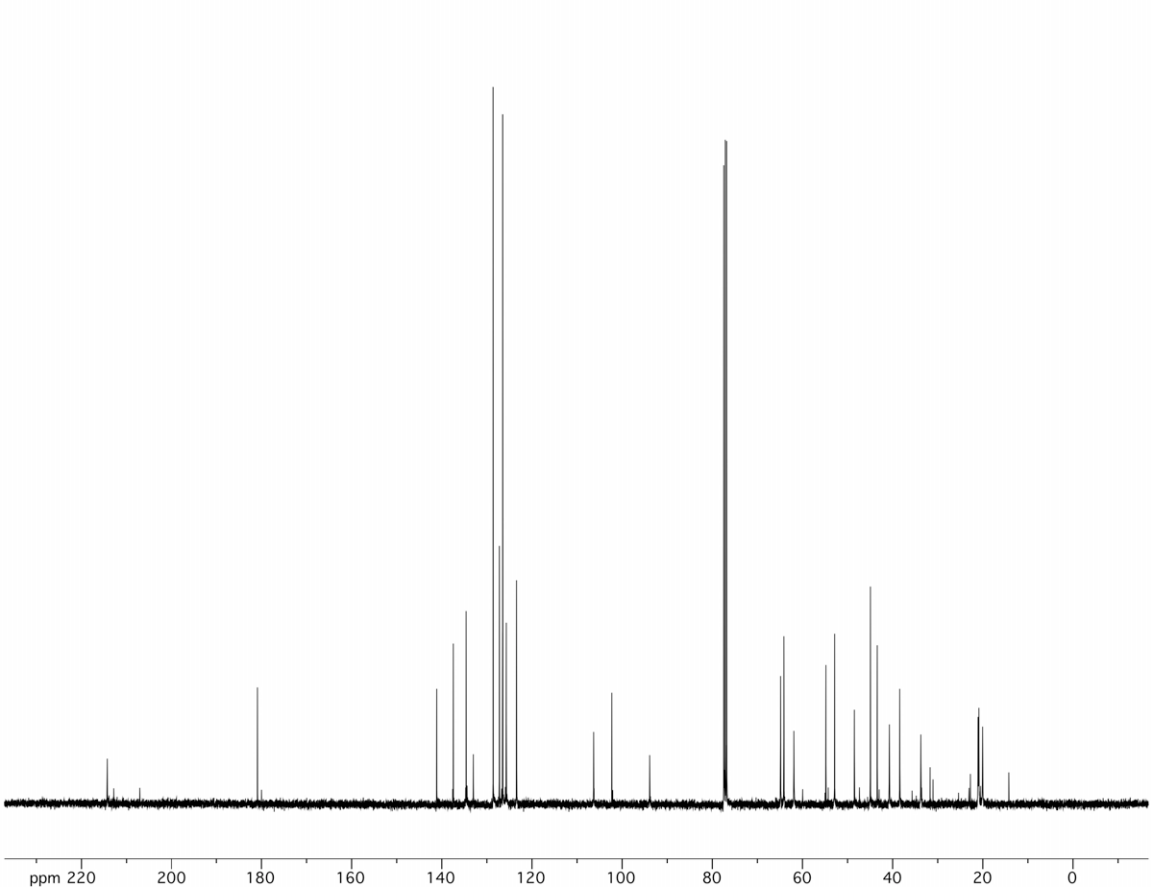


Figure A.3.19b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **214**

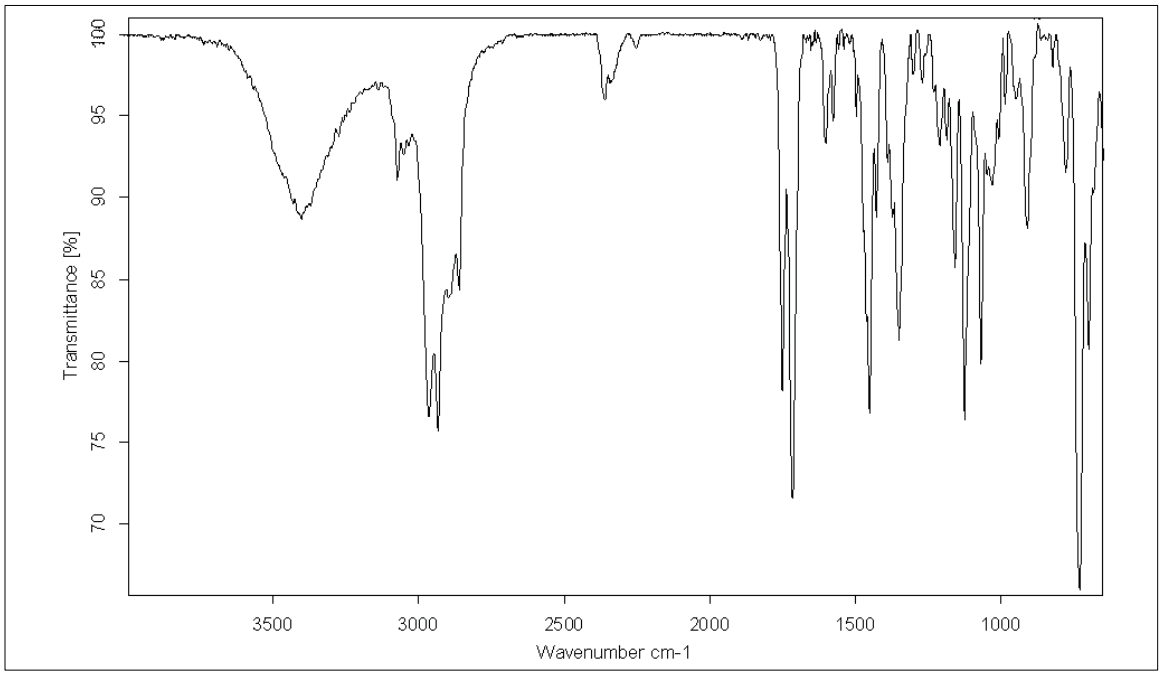


Figure A.3.19c IR spectrum (thin film/NaCl) of compound **214**

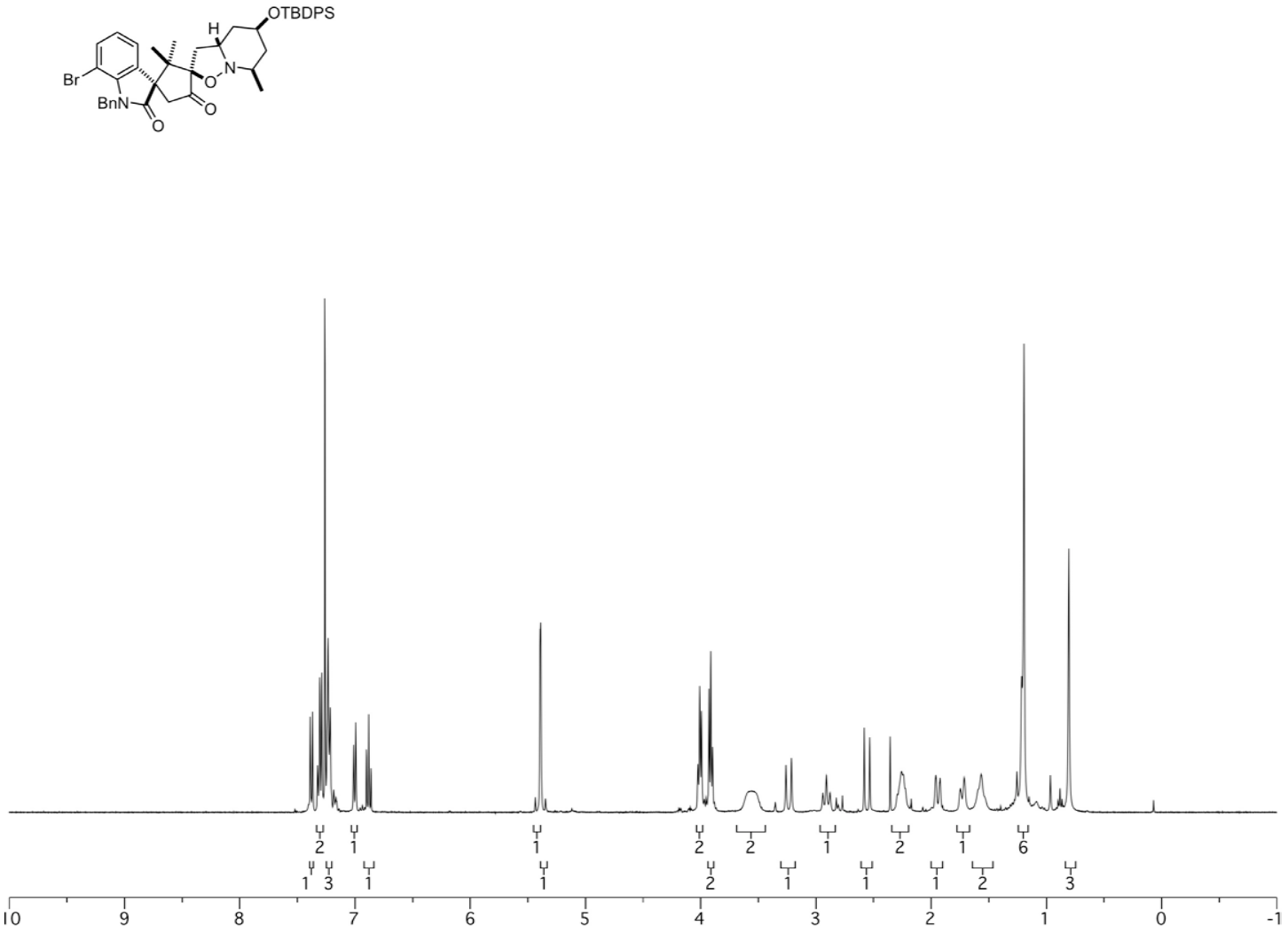


Figure A.3.20a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **215**

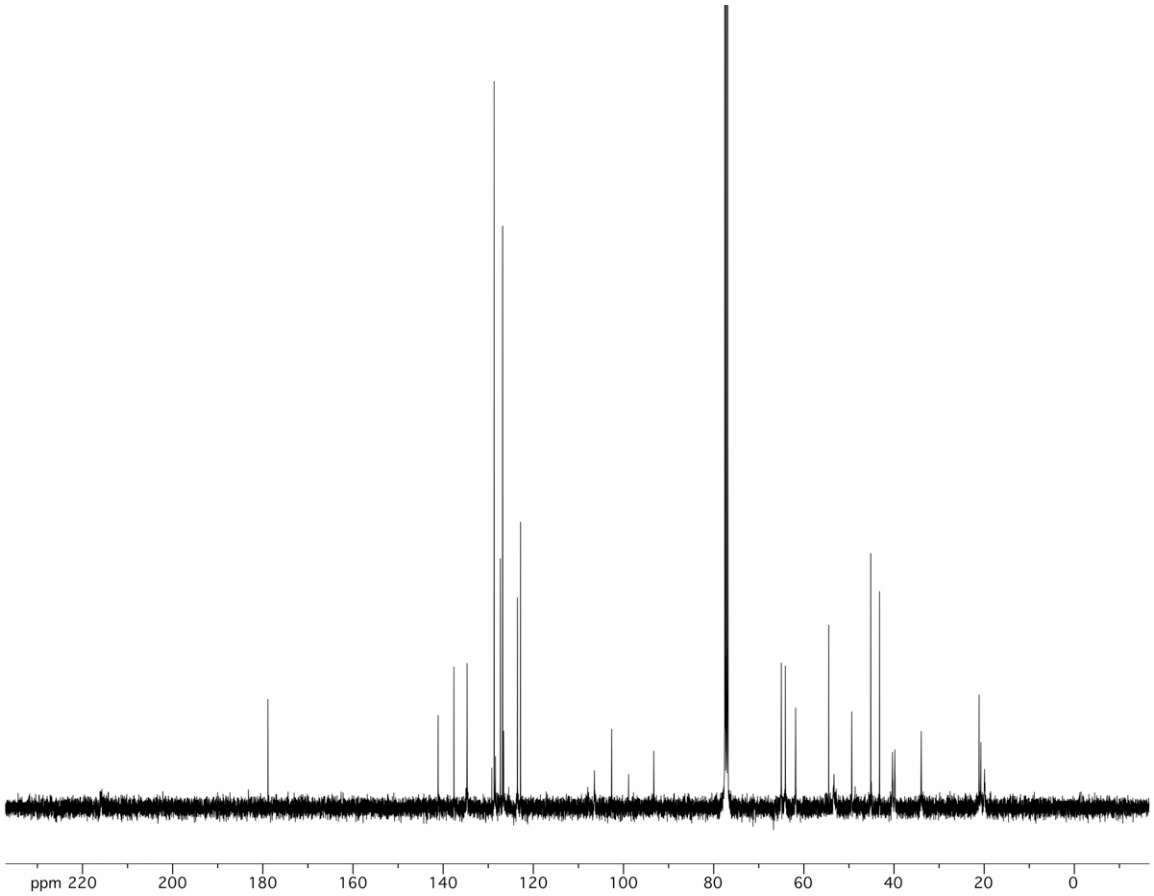


Figure A.3.20b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **215**

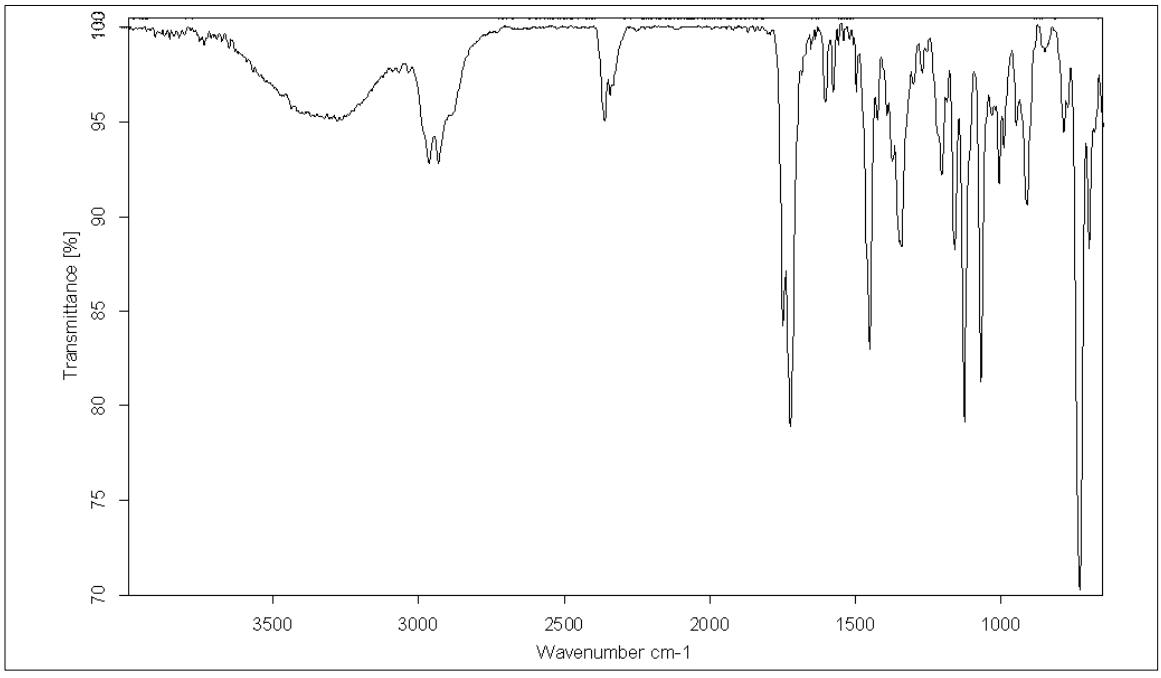


Figure A.3.20c IR spectrum (thin film/NaCl) of compound **215**

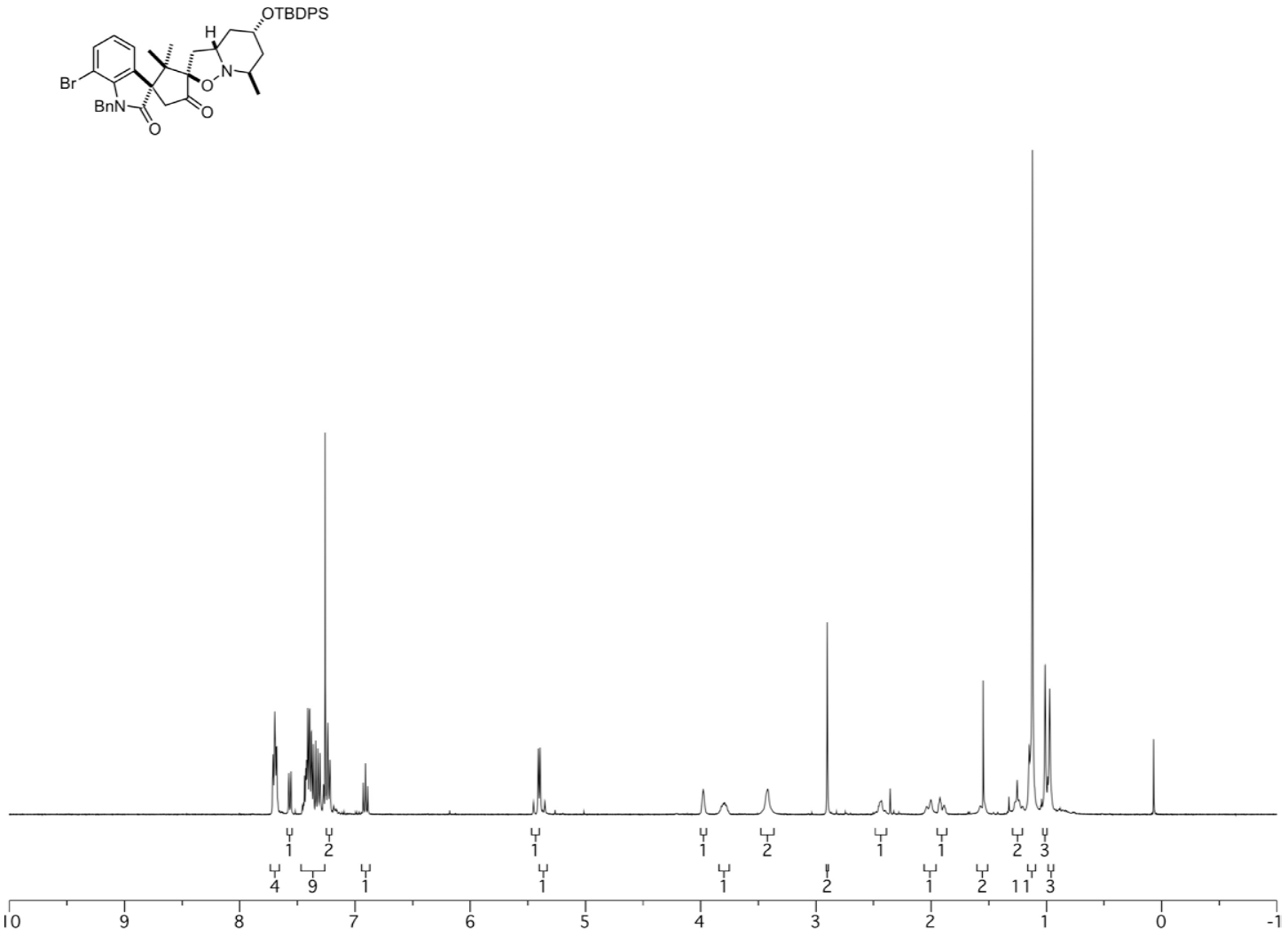


Figure A.3.21a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **217**

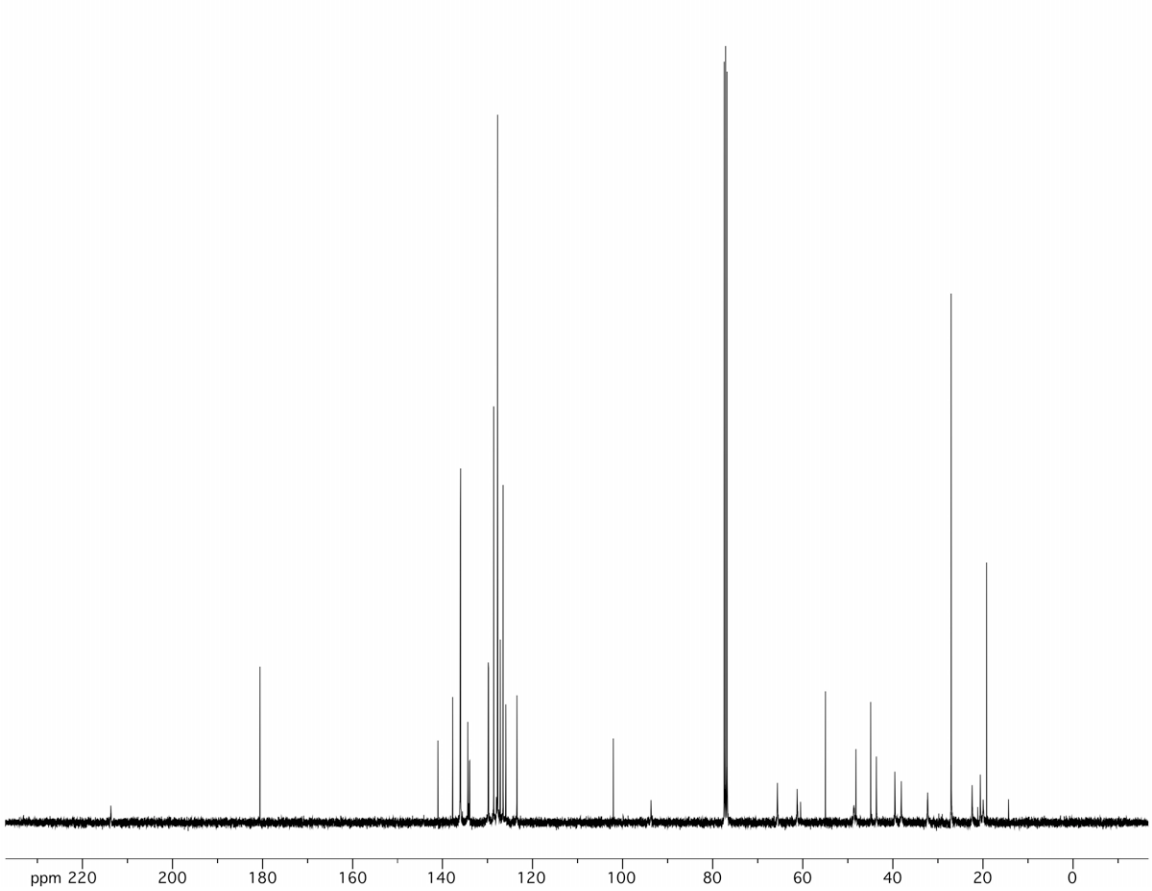


Figure A.3.21b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **217**

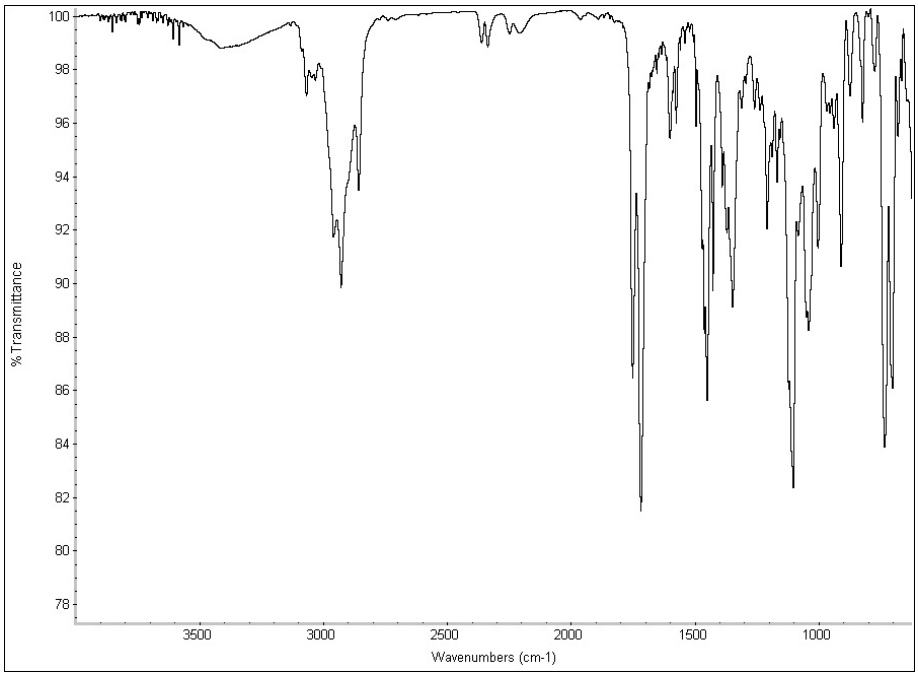


Figure A.3.21c IR spectrum (thin film/NaCl) of compound **217**

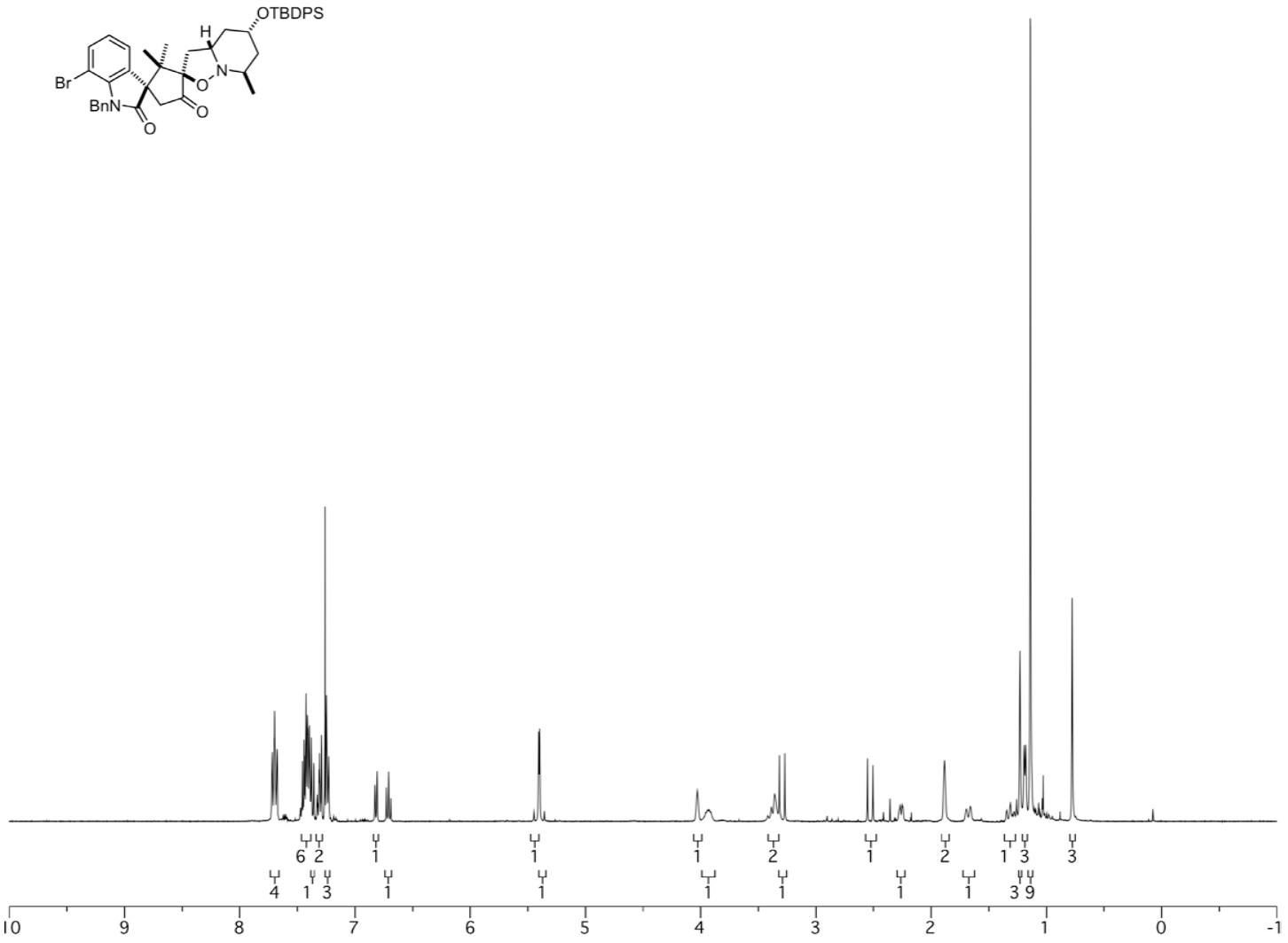


Figure A.3.22a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **218**

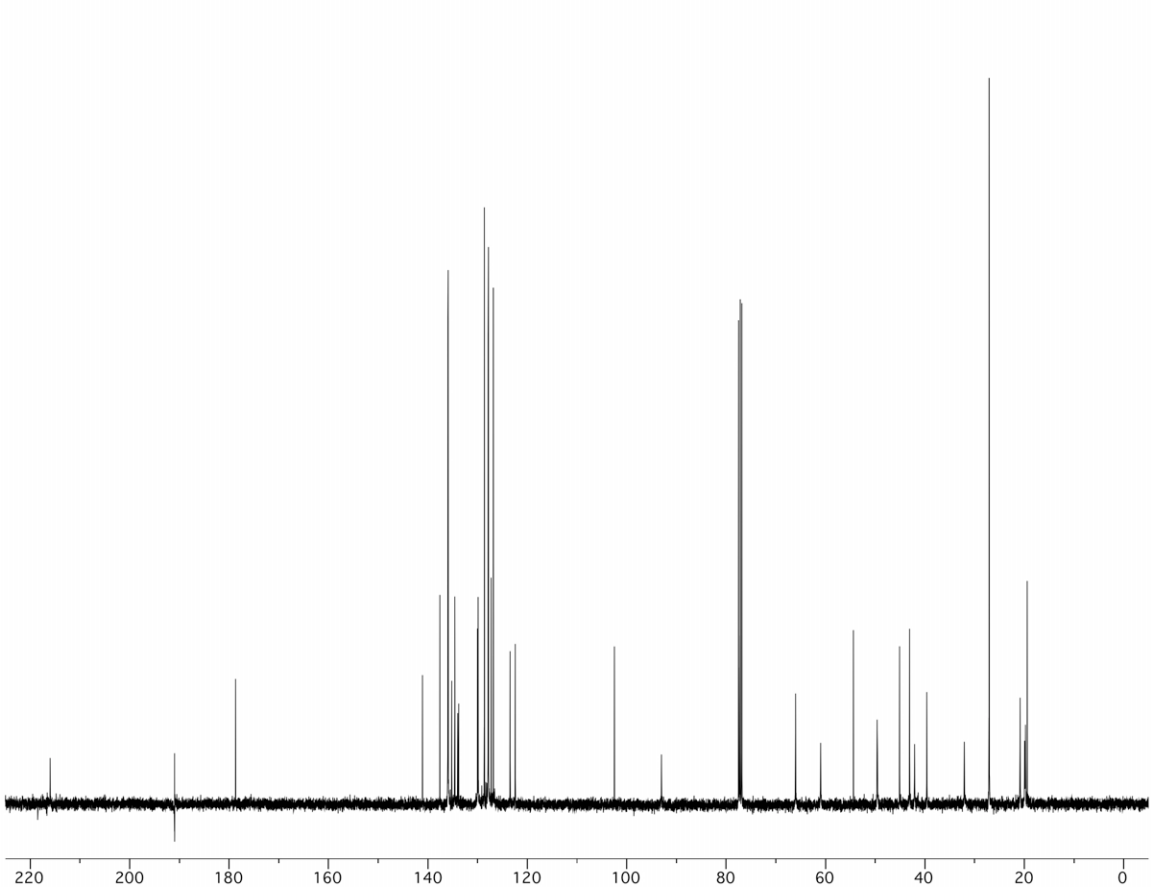


Figure A.3.22b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **218**

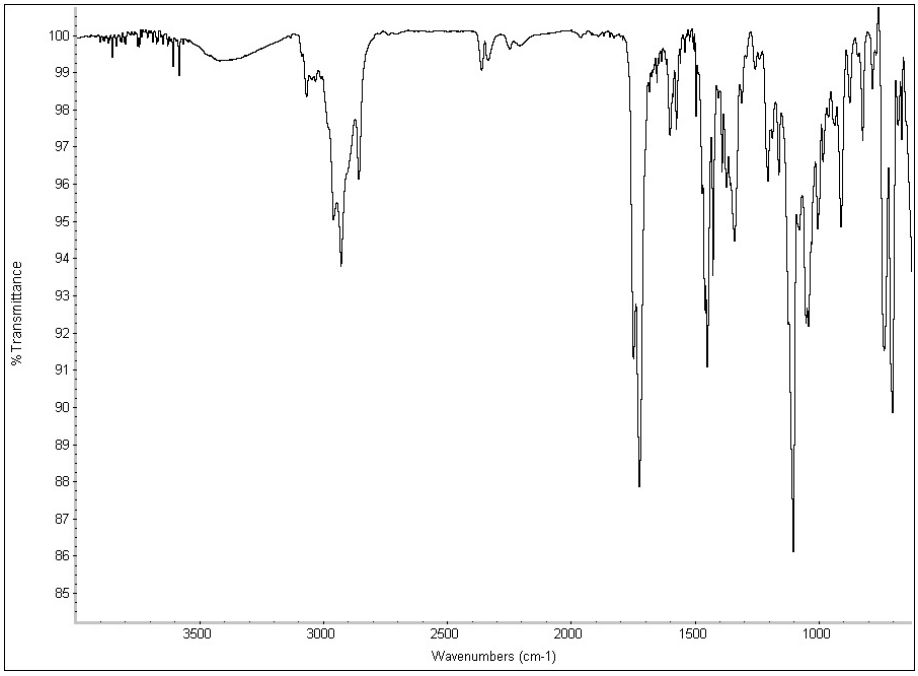


Figure A.3.22c IR spectrum (thin film/NaCl) of compound **218**

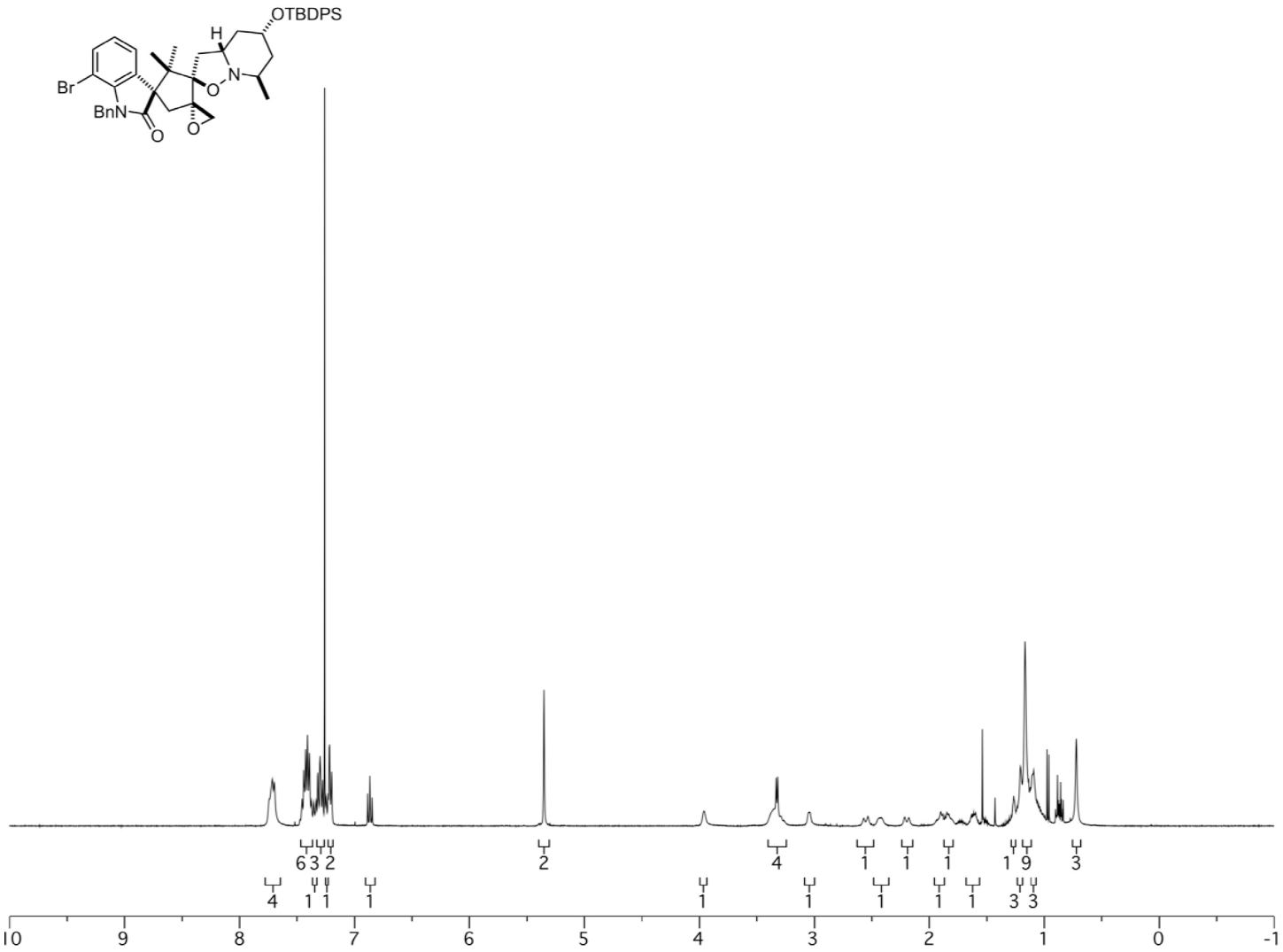


Figure A.3.23a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **219**

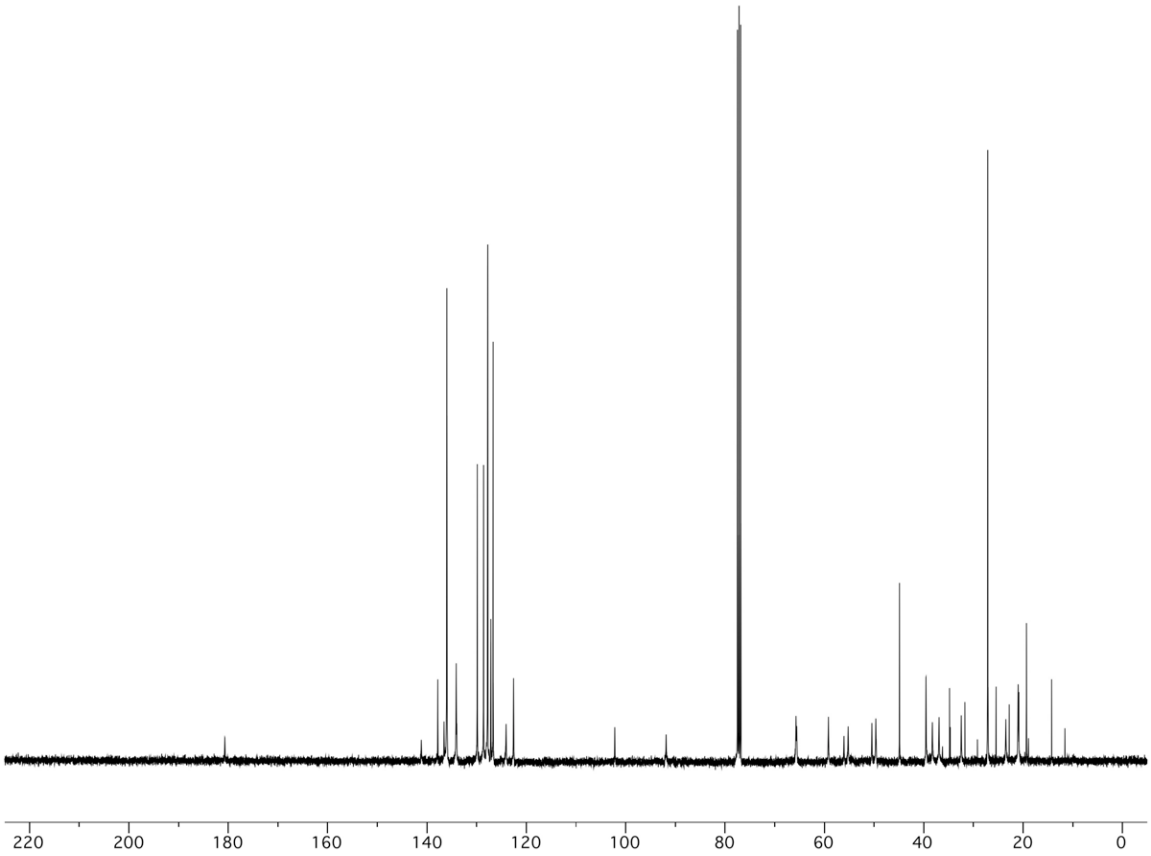


Figure A.3.23b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **219**

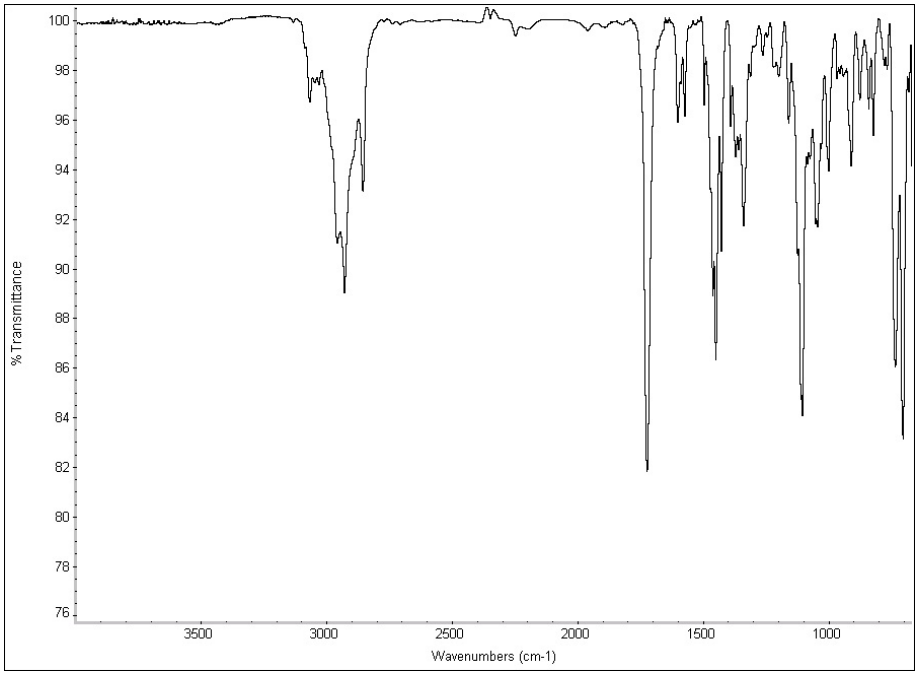


Figure A.3.23c IR spectrum (thin film/NaCl) of compound **219**

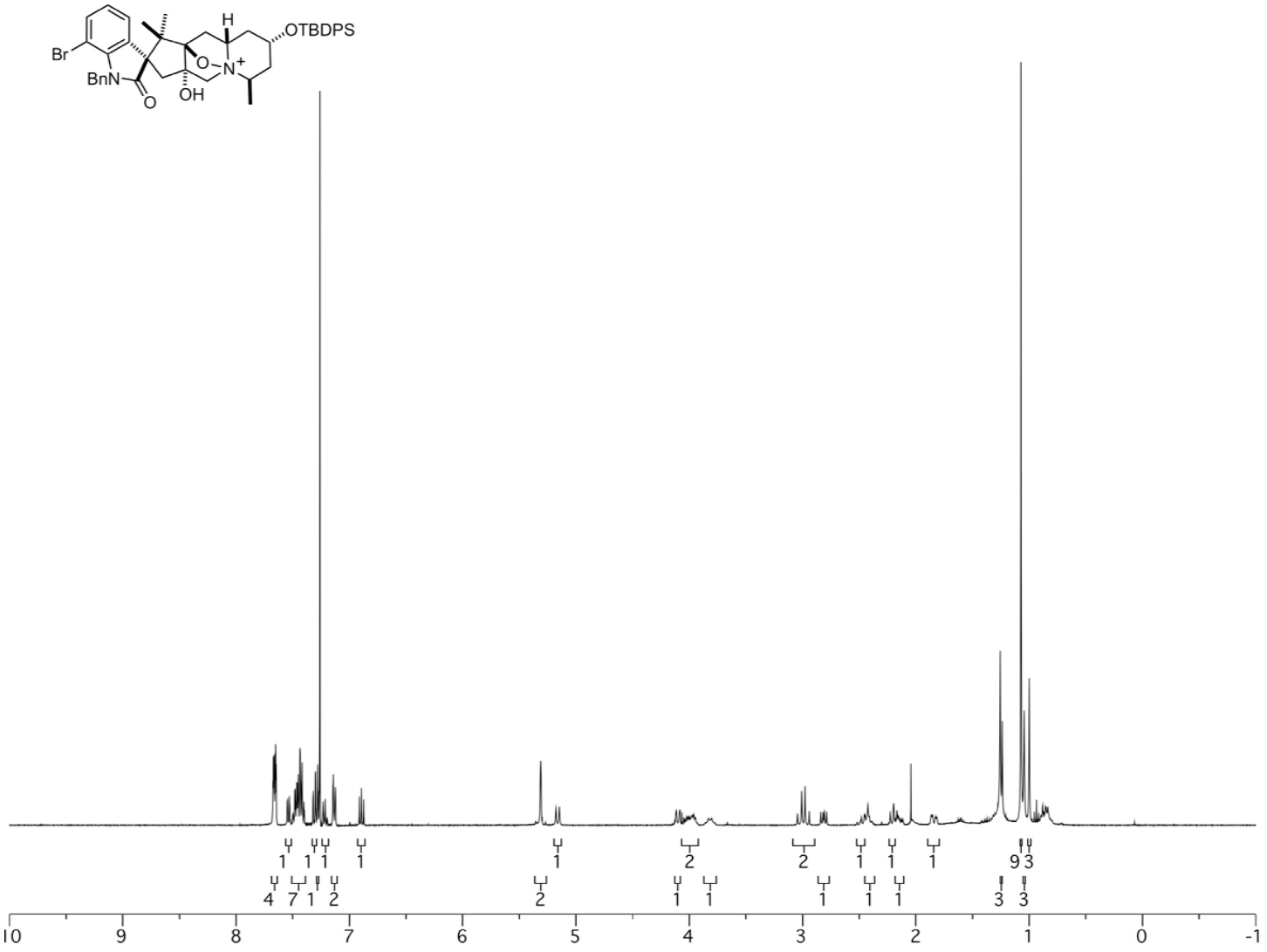


Figure A.3.24a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **220**

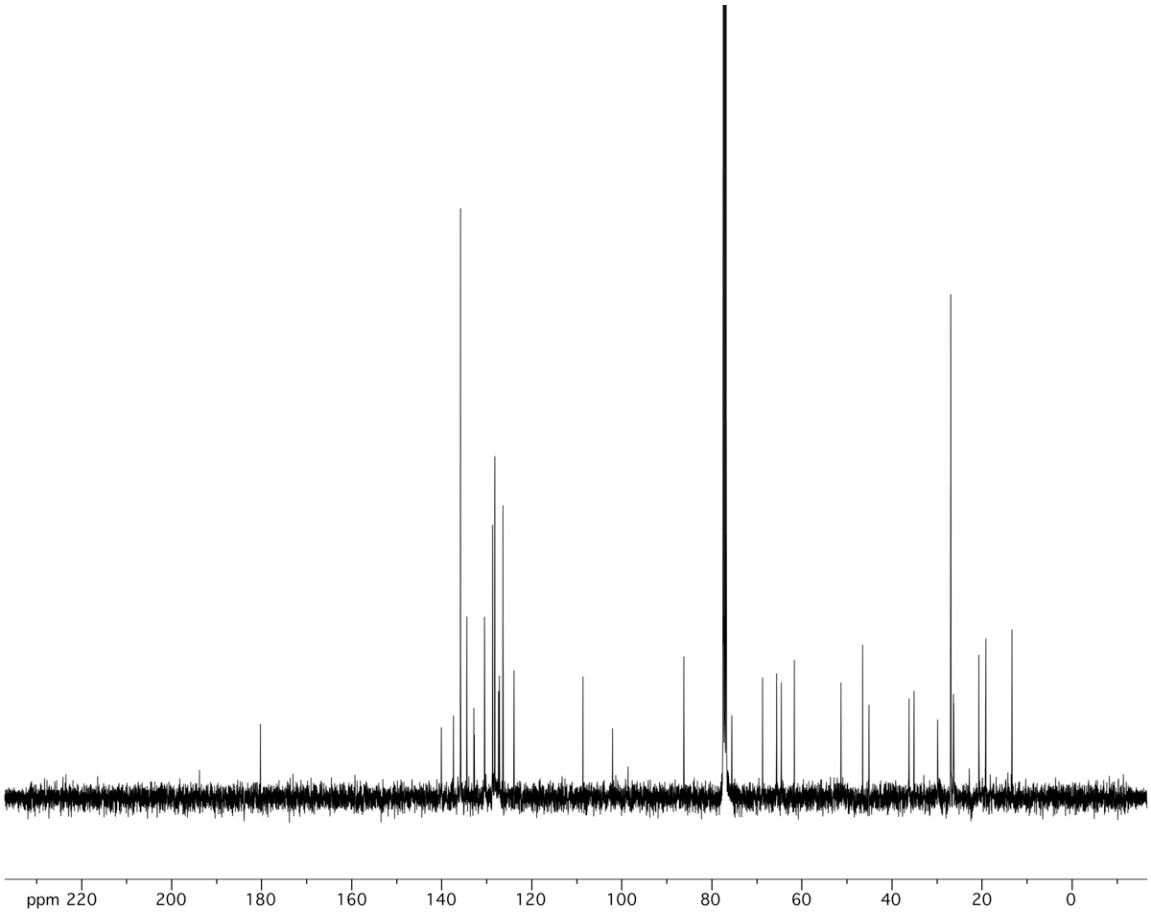


Figure A.3.24b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **220**

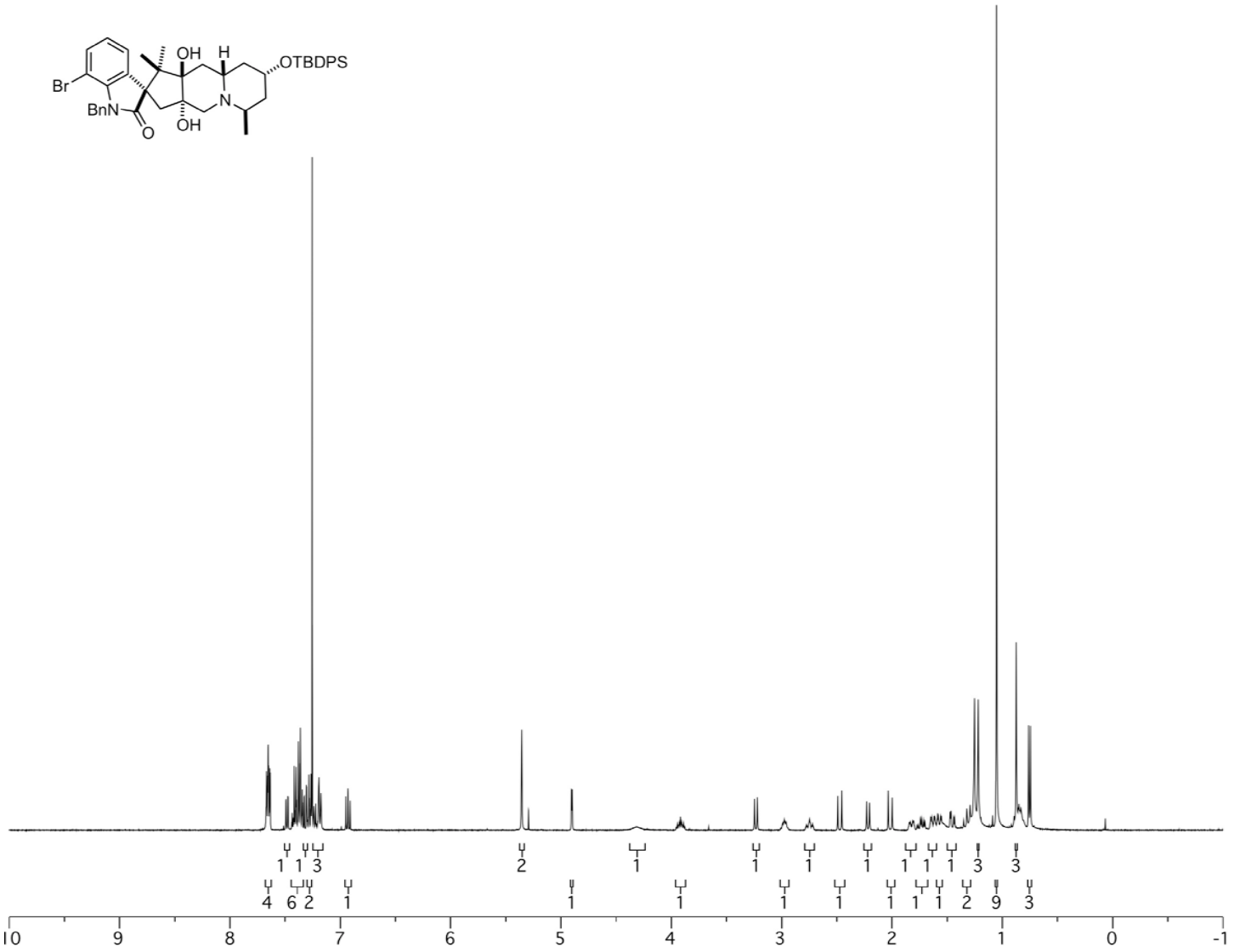


Figure A.3.25a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **221**

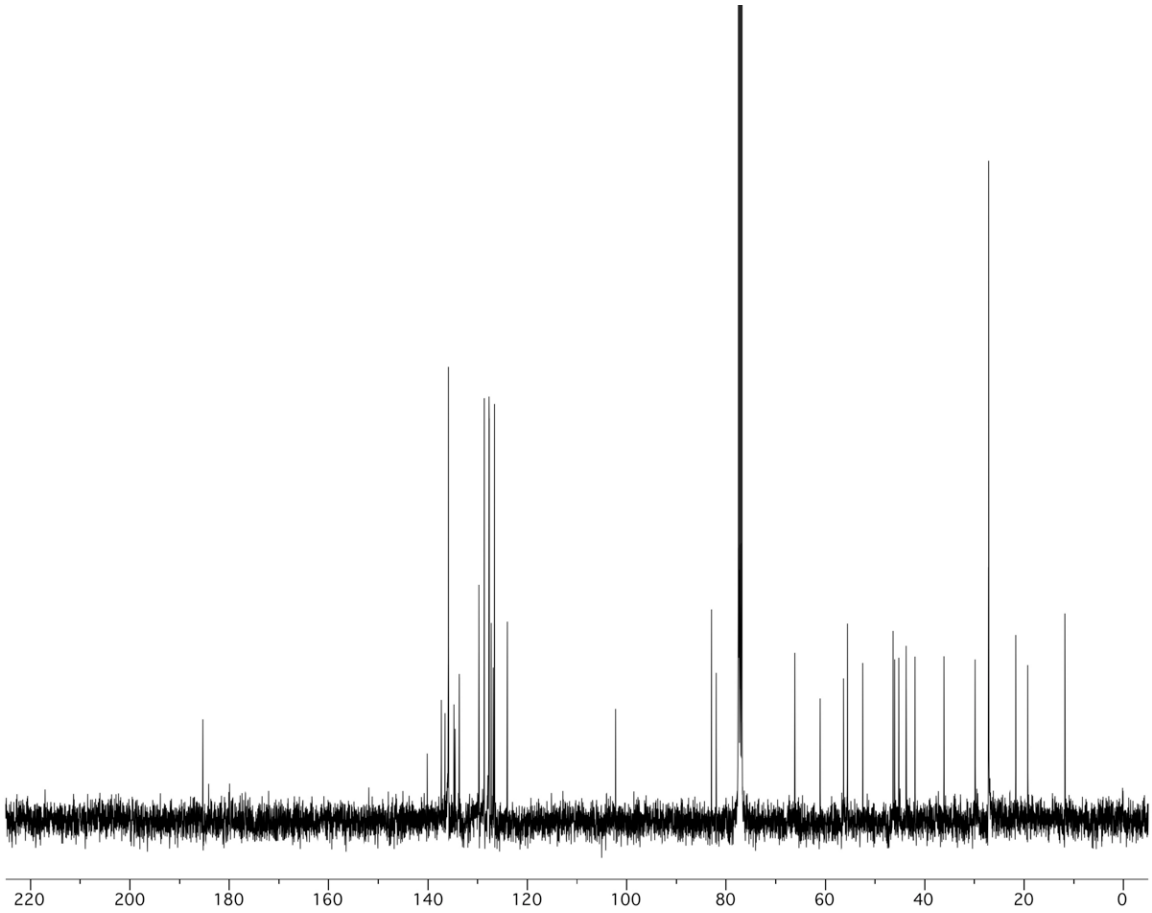


Figure A.3.25b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **221**

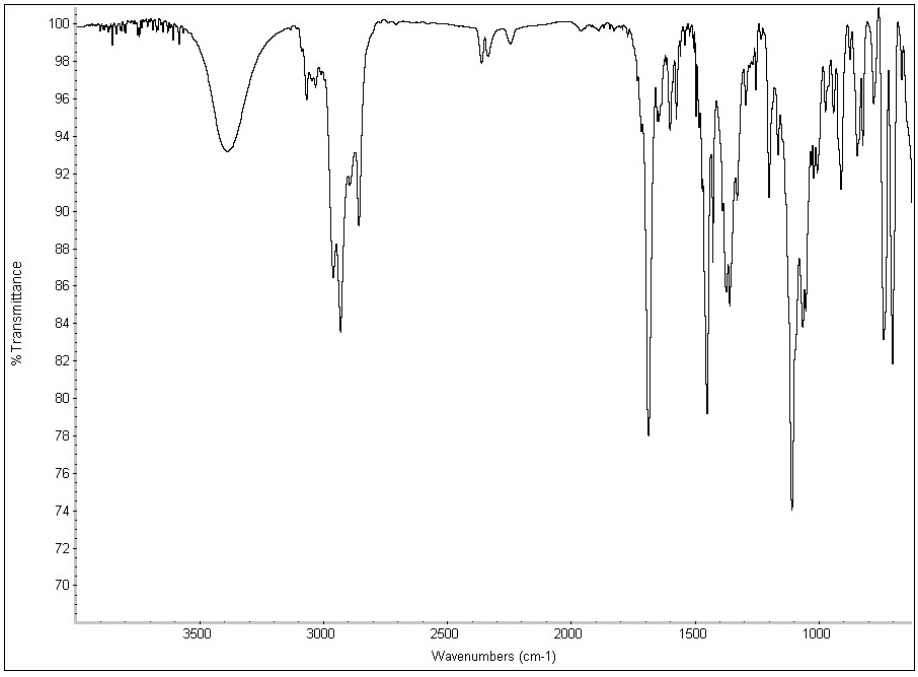


Figure A.3.25c IR spectrum (thin film/NaCl) of compound **221**

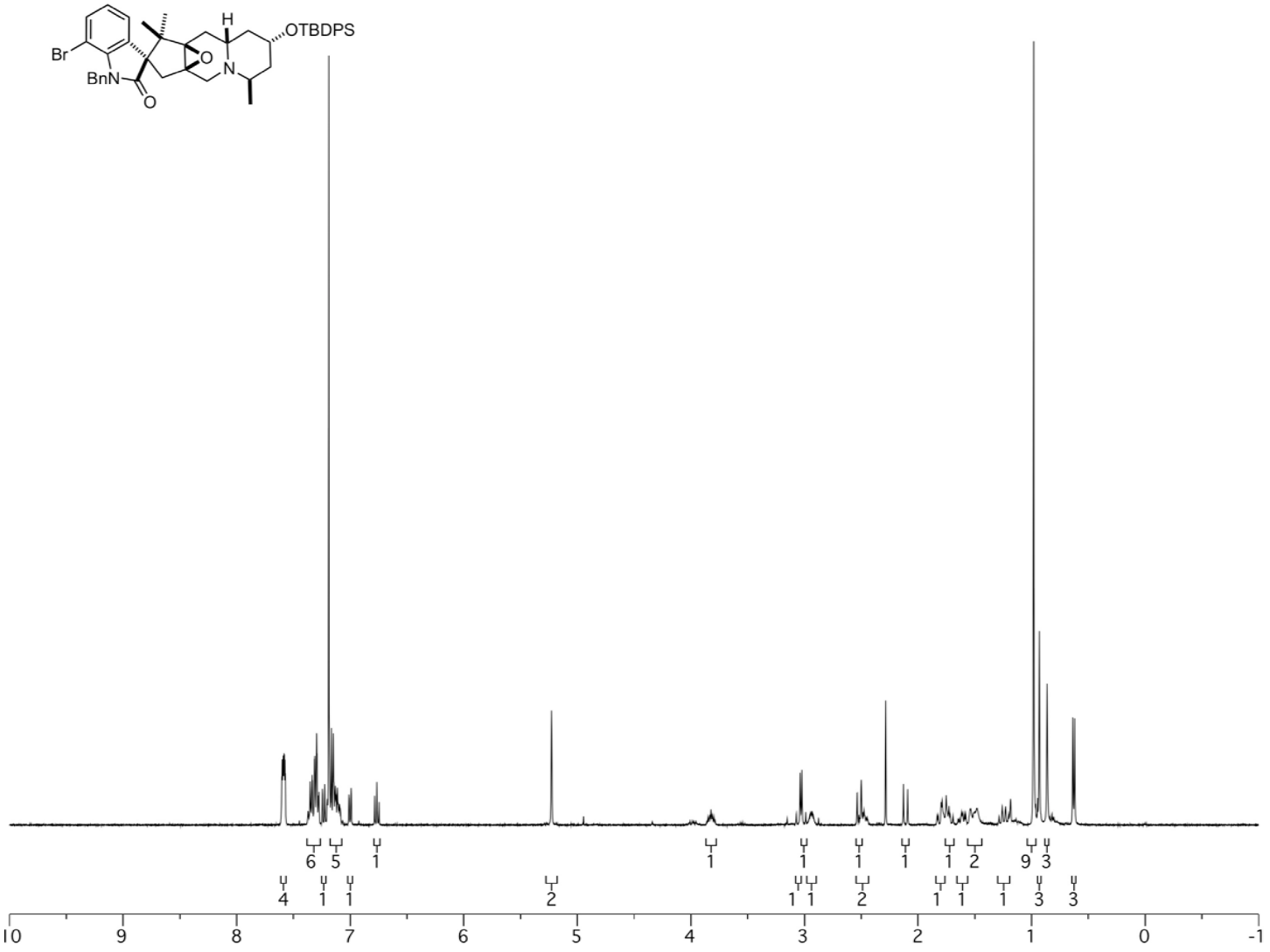


Figure A.3.26a ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **222**

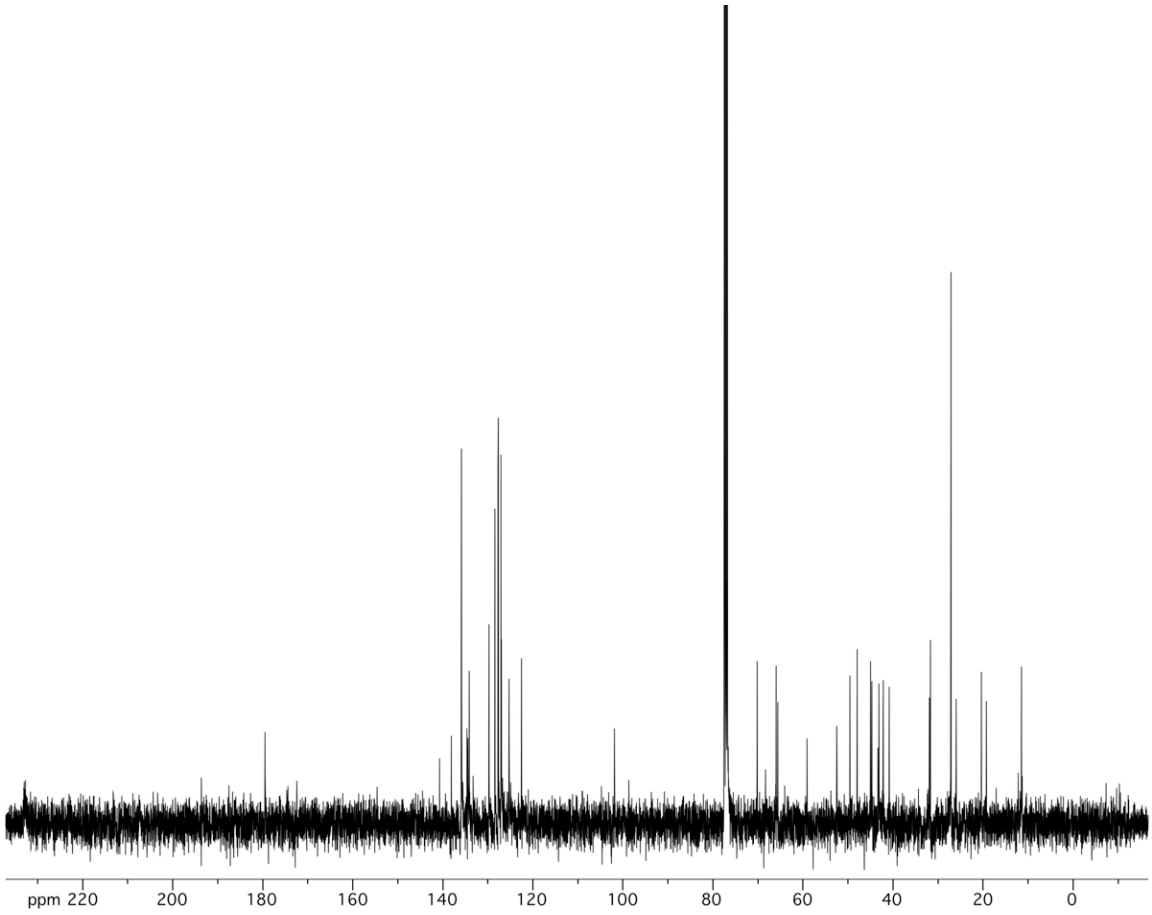


Figure A.3.26b ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **222**

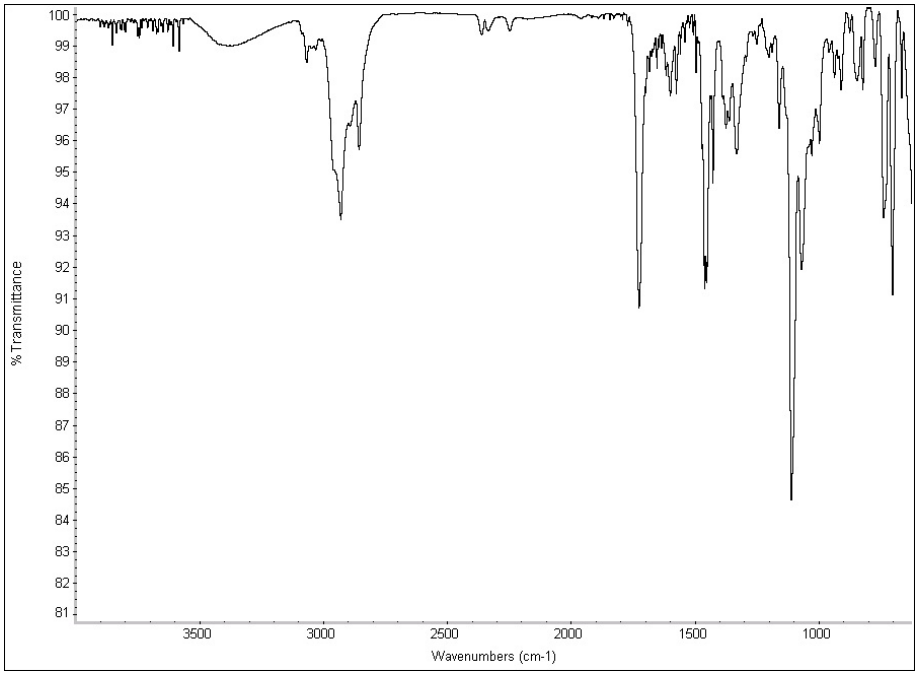


Figure A.3.26c IR spectrum (thin film/NaCl) of compound **222**

NOTEBOOK CROSS-REFERENCE

Butyrolactone **47** KK-VII-57, KK-VII-69

Iodoanilide **61** KK-III-123, GSA13

Bis-Protected Anilide **62**

- TBS Protection KK-III-129
- Benzyl Protection KK-II-9, KK-III-131

Aldehyde **63**

- Alcohol Deprotection KK-II-39
- Dess-Martin Oxidation KK-II-25, KK-II-49

Enone **59**

- Grignard Addition KK-II-51
- Dess-Martin Oxidation KK-II-23, KK-II-57

Enone **67** KK-II-83, KK-II-89

Oxindole **70** KK-II-33, KK-II-199

Phenol-alcohol **69** KK-III-225

Aryl Triflate **73**

- TBS Protection KK-III-267, KK-VI-223
- Benzyl Protection KK-III-257, KK-III-291
- Phenol Deprotection KK-III-293
- Phenol Triflation KK-III-261, KK-IV-177

Asymmetric Oxindoles (+)- and (–)-**70**

- (–)-**70** From (+)-BINAP KK-IV-21
- (+)-**70** From (–)-BINAP KK-VI-235, KK-VI-241

Aldehyde **74**

- Alcohol Deprotection KK-II-115, KK-II-209, KK-VI-245
- Swern Oxidation KK-II-249, KK-VI-247

Enynes **68a**/**b**

- Grignard Addition KK-II-121, KK-II-253

TBS Protection KK-II-255, KK-VI-253
Silyl-Allylic Alcohol **78a** KK-II-109-I, KK-II-179
Spiro-oxindole **69a** KK-II-223, KK-III-23, KK-VI-255
Allylic Alcohol **82a** KK-II-191, KK-III-27, KK-VI-259
Spiro-oxindole **69b** and Cyclopropane **79** KK-II-213, KK-II-273, KK-VI-257
Allylic Alcohol **82b** KK-II-267, KK-II-281
Unsubstituted Nitrone **80** KK-III-69
Acetone Oxime **84** KK-IV-137, KK-IV-143
Oxime **85**
Alkylation KK-IV-139, GSC105
Oxime Reduction KK-IV-141, GSC119
Nitrone (±)-**57** KK-IV-145, GSC123
Olefin **88**
CBz Protection KK-IV-43
Esterification KK-IV-55
DIBAl-H Reduction KK-IV-125, KK-IX-213
Wittig Reagent KK-IV-57, KK-IX-235
Wittig Reaction KK-V-261, KK-IX-215, KK-IX-239
Benzyloxyamine **89**
Hydrogenation KK-V-271, KK-IX-247
Oxidation KK-VI-187, KK-IX-249
Nitrone (S)-(–)-**57**
Saponification KK-VI-199, KK-VI-251, KK-IX-251
Determination of the ee KK-VI-213
Acid-Mediated Nitrone Condensation KK-VI-191
Isoxazolidine **83** KK-II-277, KK-III-17
Enone **58** KK-II-215, KK-V-63, KK-VI-263
Isoxazolidines (±)-**87** and (±)-**56** KK-IV-153, KK-V-67
Enantioenriched Isoxazolidine **87** KK-VI-189
Enantioenriched Isoxazolidine **56** KK-VI-265
Exomethylene **91** KK-VII-265, KK-VII-287
Cbz-Protected Piperdine **90** & TFA-Protected Piperdine **90b**
Samarium Iodide-Mediated Ring Opening KK-VII-277, KK-VIII-53
Cbz-Protection KK-VII-189, KK-VII-253
TFA-Protection KK-VII-283, KK-VII-291, KK-VIII-15
Spiro-epoxide **94** KK-VII-285, KK-VII-297
Diol **95** KK-VIII-11, KK-VIII-13

Epoxybromide **98** KK-VIII-17, KK-VIII-57
Ring-Fusion Epoxide **99** KK-VIII-27, KK-VIII-61
C3-*epi*-Citrinadin B Core **97** KK-VIII-77
Spiro-epoxide **103** KK-VIII-213, KK-VIII-261, KK-IX-285
Ammonium Salt **107** KK-VIII-217, KK-VIII-295, KK-IX-299
Diol **102** KK-VIII-227, KK-VIII-297, KK-IX-301
Ring-Fusion Epoxide **101** KK-VIII-239, KK-IX-137, KK-X-89
Benzylamine **110** KK-IX-119
Pyridinium Salt **113** KK-VIII-287
Azide **114** KK-VIII-291, KK-IX-279
Amine **115** KK-IX-79, KK-IX-261
Methylamine **108** KK-IX-135, KK-IX-261
des-Benzyl Oxindole (+)-**121** KK-X-111
des-Benzyl Azide (+)-**122** KK-X-113
Boc-Protected Oxindole (+)-**125** KK-X-145, KK-X-163
ent-Citrinadin Core (+)-**100**
Azide Reduction KK-X-167
Methylation KK-X-173
Boc-Removal KK-X-155
Dibromoanilide **48** GSB197, GSB207, GSC33
Bis-Protected Dibromoanilide **132**
TBS-Protection GSB221, GSC41
Benzyl-Protection GSA100
C7-Bromo-Oxindole **133** GSB217, GSB293
Benzyl-Protected Oxindole **130** GSB223, GSC11
N-Boc Methoxyaniline **136** GSA137
2-Bromo-6-Methoxyaniline **134**
Directed Bromination GSA160
Boc Removal GSA118
2-Bromo-6-Methoxyanilide **137** GSA154, GSA168, GSA124
Phenol **138** GSA158, GSA175
O-TBS-Protected Alcohol **139** GSA176
Triflate **131b** GSA177, GSA187
C7-Triflate-Oxindole **140** GSA179
Alcohol **141** GSB225, GSC13
Aldehyde **142** GSC15, GSB227, GSC79
Alkynes **143a** and **143b** GSB229, GSC81

Enyne **144a** GSB237a, GSC91
Enyne **144b** GSB237b, GSC93
Spiro-oxindole **146a**
Enyne Cyclization GSC145
TBS-Removal GSB243, GSC147
Spiro-oxindole **146b**
Enyne Cyclization GSC113
TBS-Removal GSB245, GSC115
Bromoenone **37** GSB247, GSC149
Bromo-Isoxazolidines (+)-**147** and **148** KK-X-285-I/II, KK-XI-141
Spiro-epoxide (+)-**149** KK-X-297, KK-XI-161
Ammonium Salt (+)-**150** KK-X-287, KK-XI-169
Diol (+)-**151** KK-X-303, KK-XI-173
Ring-Fusion Epoxide (+)-**152** KK-X-291, KK-XI-179
Alkyne (+)-**160** KK-XI-183
des-Benzyl Oxindole (+)-**163** KK-XI-139, KK-XI-191
Azide (+)-**159** KK-XI-131, KK-XI0193
Enone (+)-**158** KK-XI-133, KK-XII-271
Epoxyketone (+)-**171** KK-XI-135, KK-XII-273
Boc-Protected Epoxyketone (+)-**173** KK-XI-157
Boc-Protected Epoxyketone (+)-**174**
Epoxidation KK-XI-103, KK-XI-209
Boc-Protection KK-XI-213
C21-*epi*-*ent*-Citrinadin B (+)-**175**
Azide Reduction KK-XI-159
Methylation KK-XI-185
Boc-Removal ..... KK-XI-203 (Free Base), KK-XI-221 (Salt)
ent-Citrinadin B (**2**)
Azide Reduction KK-XI-217
Methylation KK-XI-237
Boc-Removal KK-XI-239
Silyl Alcohol **189** GSD27
Aldehyde **190** GSE213
β-Hydroxyketones **191a** and **191b** GSC177, GSD87
Bis-Protected Diols **194** and **195** GSC105, GSD89
Lactone **184** GSD149
Lactone **203** GSE107, GSD93

Lactol **183** GSD155
Lactol **204** GSD95, GSE109
Oxime **197** GSD153
Oxime **205** GSD113, GSE111
Oxime **211** GSE35
Silyl-Protected Oxime **198** GSD157
Silyl-Protected Oxime **206** GSE115
Silyl-Protected Oxime **212** GSE39
Nitrone Precursor **182** GSD159
Nitrone Precursor **200** GSE117
Nitrone Precursor **202** GSE43
β-hydroxyketone **208** GSD19, GSE123
Ketal Lactone **209** GSE135
Ketal Lactol **210** GSE137
Ketal Nitrone **201** GSD291, GSE45, GSE47
Ketal Cyclic Oxime **213** GSD265, GSD293, GSE11, GSE45, GSE47
Ketal Cycloadducts **214** and **215** GSD293, GSE155
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